Health Canada / Santé Canada

Health Products and Food Branch / Direction générale des produits de santé et des aliments

Biologic and Radiopharmaceutical Drugs Directorate
100 Eglantine Driveway
LCDC Building
Tunney's Pasture, A.L. 0601C
Ottawa, Ontario
K1A 0K9

January 29, 2021

[redacted] Regulatory Affairs
Novavax Inc. c/o
PPD Development, LP
13900 Paramount Parkway
Morrisville, North Carolina 27560-7200
United States
Email: PPD-HCsubmissions@ppd.com

Dossier ID: [redacted]
Control #: [redacted]
Document #: [redacted]

ACKNOWLEDGMENT LETTER

Dear Mrs. [redacted]:

This is to acknowledge receipt of the information and material for Novavax COVID-19 Vaccine (SARS-CoV-2 rS with Matrix-M1 Adjuvant), submitted on January 29, 2021. This COVID-19 Interim Order Application proposes the use of Novavax COVID-19 Vaccine for active immunization for the prevention of mild, moderate, and severe coronavirus diseases 2019 (COVID-19) caused by SARS-CoV-2 [redacted]

You are requested to refer to the dossier ID and control number in any communications relating to this submission.

Enquiries regarding the status of your application may be obtained at any time by contacting the Office of Regulatory Affairs (ORA). In addition, you can obtain the status of your application by accessing the Drug Submission Tracking System (DSTS).

Sincerely,

This document has been signed electronically using the Health Canada docuBridge system.

Shalu Patel
Senior Regulatory Affairs Officer
Office of Regulatory Affairs
Tel: 613-462-8129
Fax: 613-946-9520

Canada

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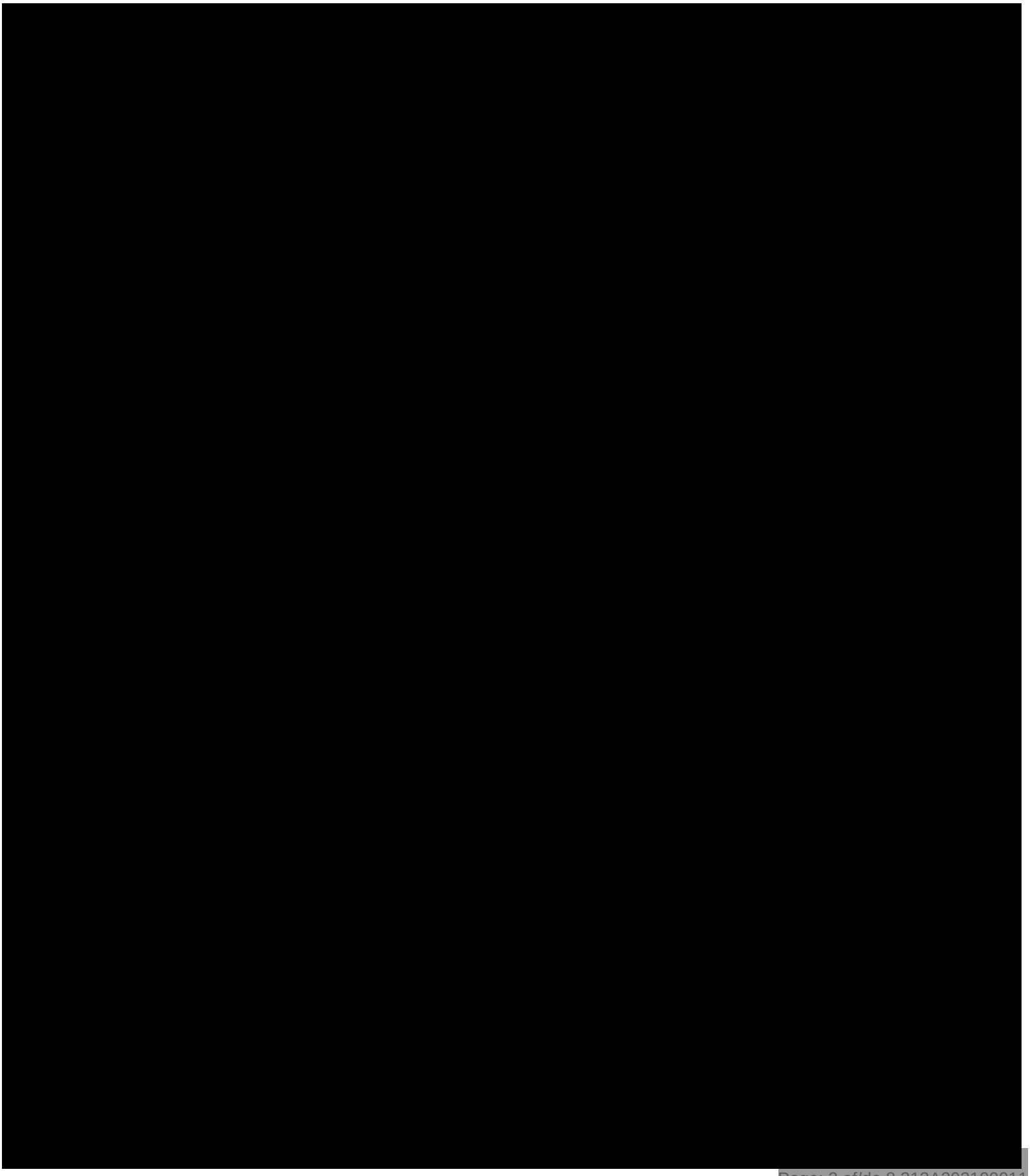

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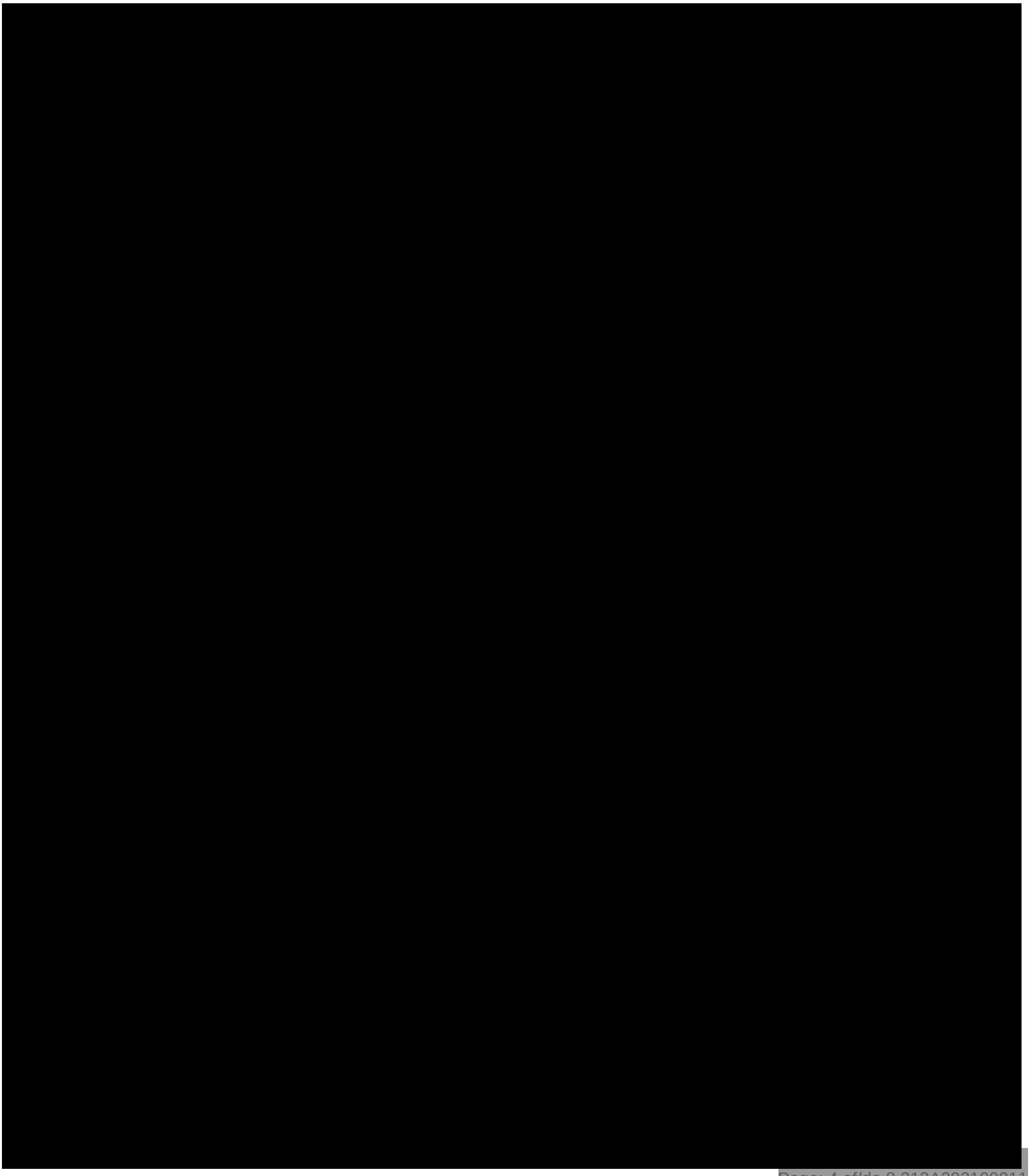

Interim Order Application
Dossier ID: [redacted]
Control [redacted]
Document [redacted]
Response to Screening Clarifax of February 01, 2021

The comments outlined below must be addressed within 15 Days of this facsimile

Question 1:

Provide a completed detailed copy of the rolling application plan (Industry Rolling Submission Plan – Template.xlsx) outlining the expected dates for clinical, non-clinical, CMC, RMP and labelling information. The plan should also describe the studies to be completed and the anticipated timing of when this information will be available for submission to Health Canada. It should contain (as per *Information and application requirements for drugs authorized under the Interim Order: Guidance document*):

- list of study data (planned and in progress) and when data will be available
- detailed information on when each component of the application can be expected (for example, quality)
- commitment to market the drug should Health Canada authorize the sale under the Interim Order and marketing plans
- dates of filing in other foreign jurisdictions (for example, European Medicines Agency, US Food and Drug Administration)

Response 1:

[redacted]

Interim Order Application
Dossier ID: [redacted]
Control [redacted]
Document [redacted]
Response to Screening Clarifax of February 01, 2021

Question 2:

Provide consent to share regulatory information from Novavax Inc. (Consent to share regulatory information.docx). Please note Health Canada will be providing the information on a confidential basis to the members of the ACCESS Consortium, EMA and the USFDA, and on the understanding that any information provided by HC staff will not be disclosed by the receiving participant, except as provided for under those arrangements.

Response 2:

[redacted]

Ridgen, Patrick (HC/SC)

From: Patel, Shalu (HC/SC)
Sent: 2021-03-11 4:54 PM
To: [redacted]
Cc: [redacted] Antonio, Christopher (HC/SC); Panetta, Vincent (HC/SC); Akel, Sereen H (HC/SC); Eassa, Samar (HC/SC)
Subject: RE: Novavax-COVID-19 Vaccine-[redacted]

Dear [redacted]

[redacted]

Please do not hesitate to contact us again if you have any further questions.

Kind regards,
Shalu

From: [redacted]
Sent: 2021-03-08 11:57 AM
To: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Cc: [redacted] Antonio, Christopher (HC/SC) <christopher.antonio@canada.ca>; Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>; Akel, Sereen H (HC/SC) <sereenh.akel@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Eassa, Samar (HC/SC) <samar.eassa@canada.ca>
Subject: Novavax-COVID-19 Vaccine-[redacted]

Dear Shalu,

Hope you and the rest of the team are doing great.

We have a question regarding the second dose reminder card and Health Canada's feedback would be greatly appreciated.

Currently, Novavax commercial team is preparing Recipient Reminder cards for recipients to receive after their first dose and to track their 2nd dose. Below is an example from the UK. Would you please advise if the AE reporting site should be included on the Canadian reminder card (similar to VAERS in the US or Yellow Card in the UK)? If yes, would you please advise for the site that should be added?

Regards

[redacted] REGULATORY AFFAIRS
REGULATORY AFFAIRS

PPD
929 North Front Street
Wilmington, NC 28401-3331
[redacted]
www.ppdi.com
www.ppd.com/regulatory-affairs

Early Development | Clinical Development | Laboratories | Post-Approval | Consulting

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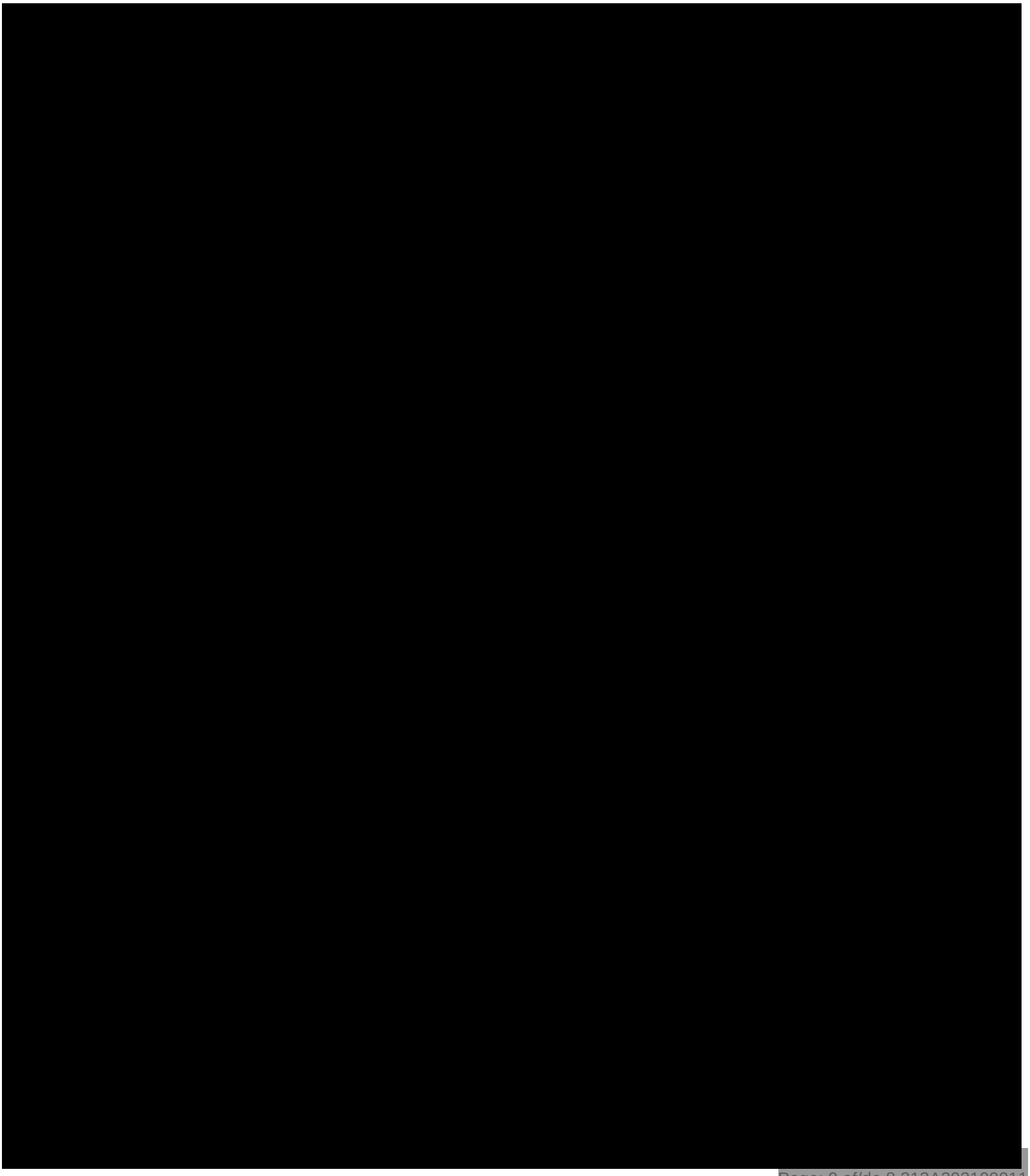

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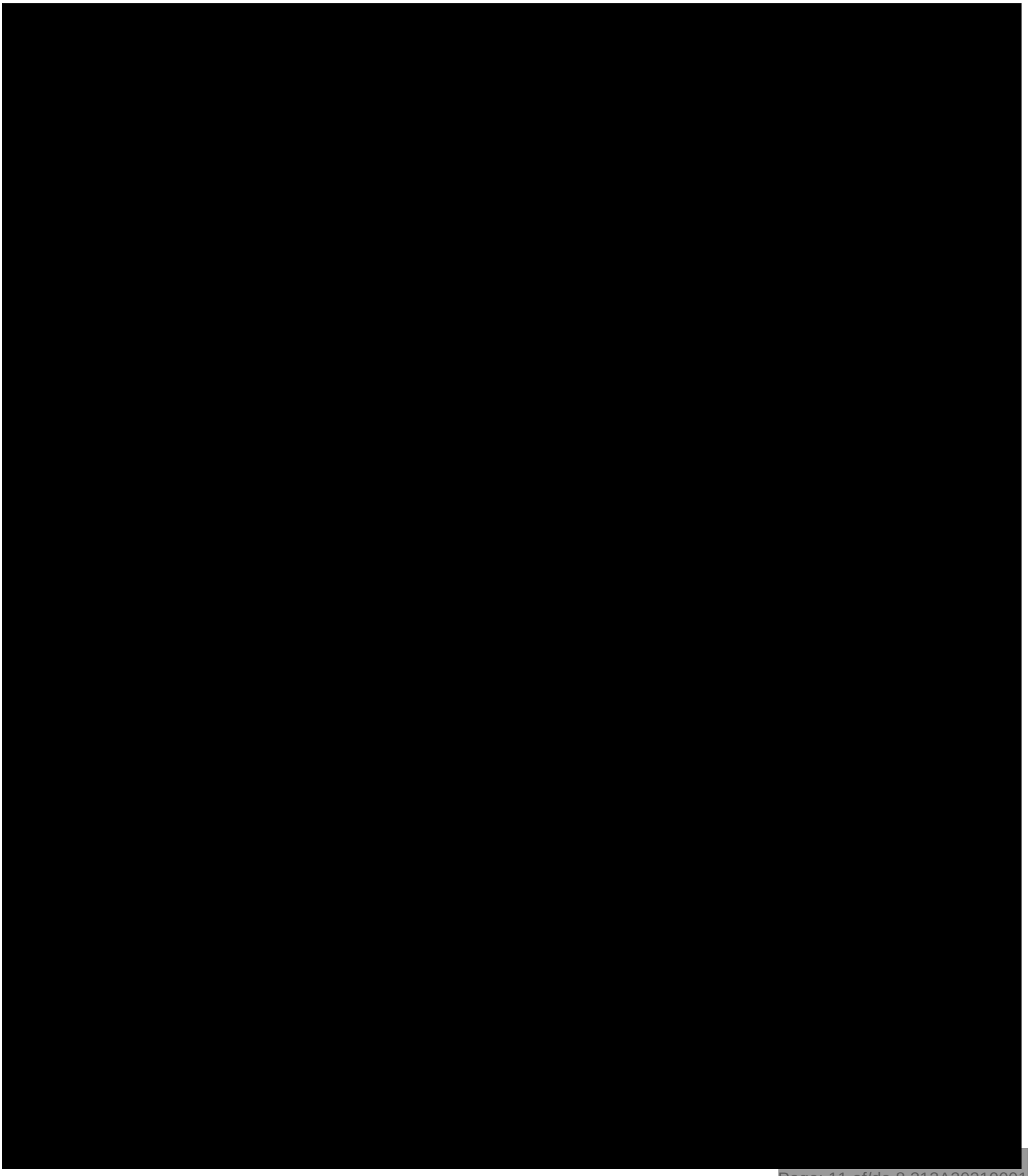

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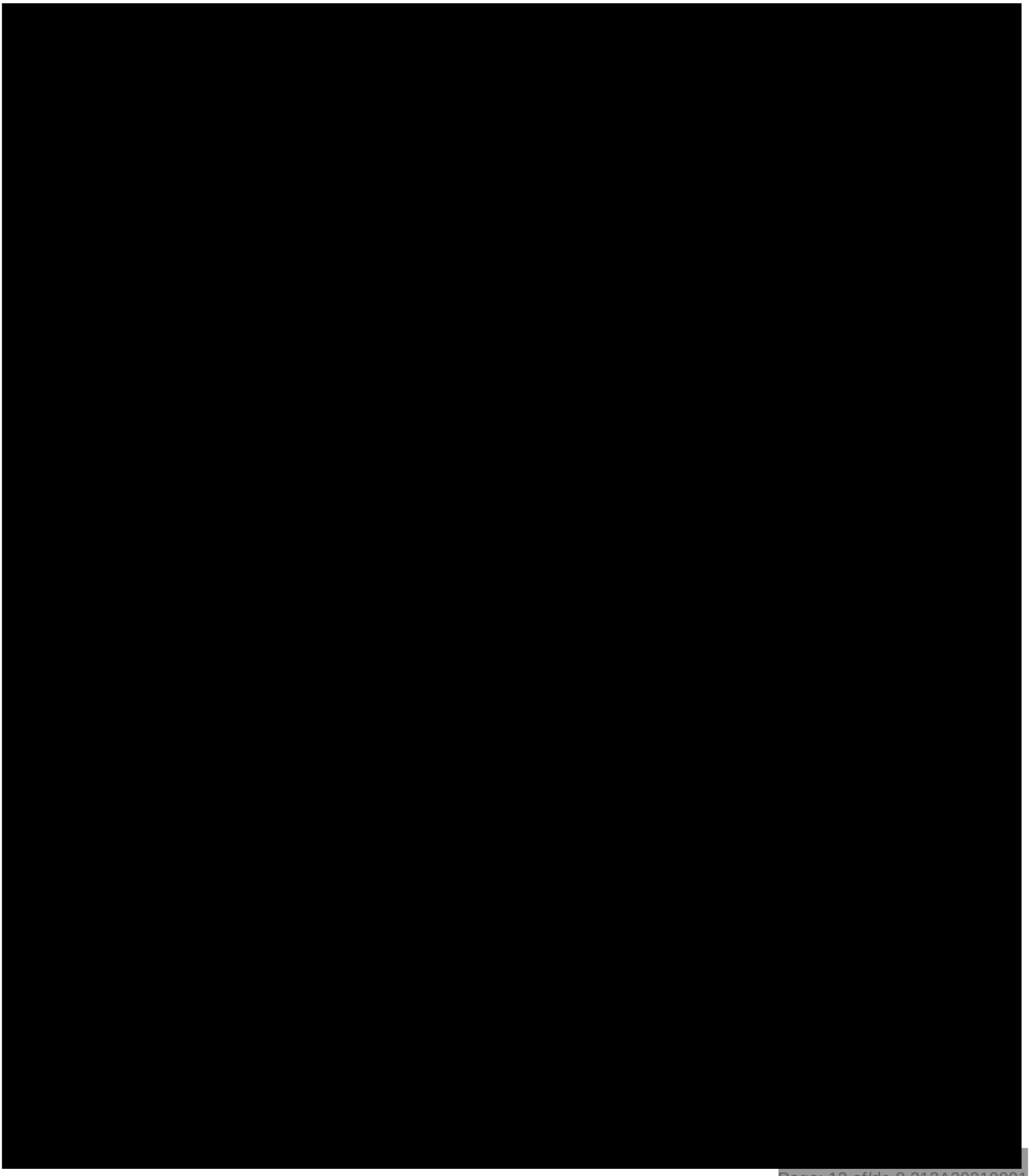

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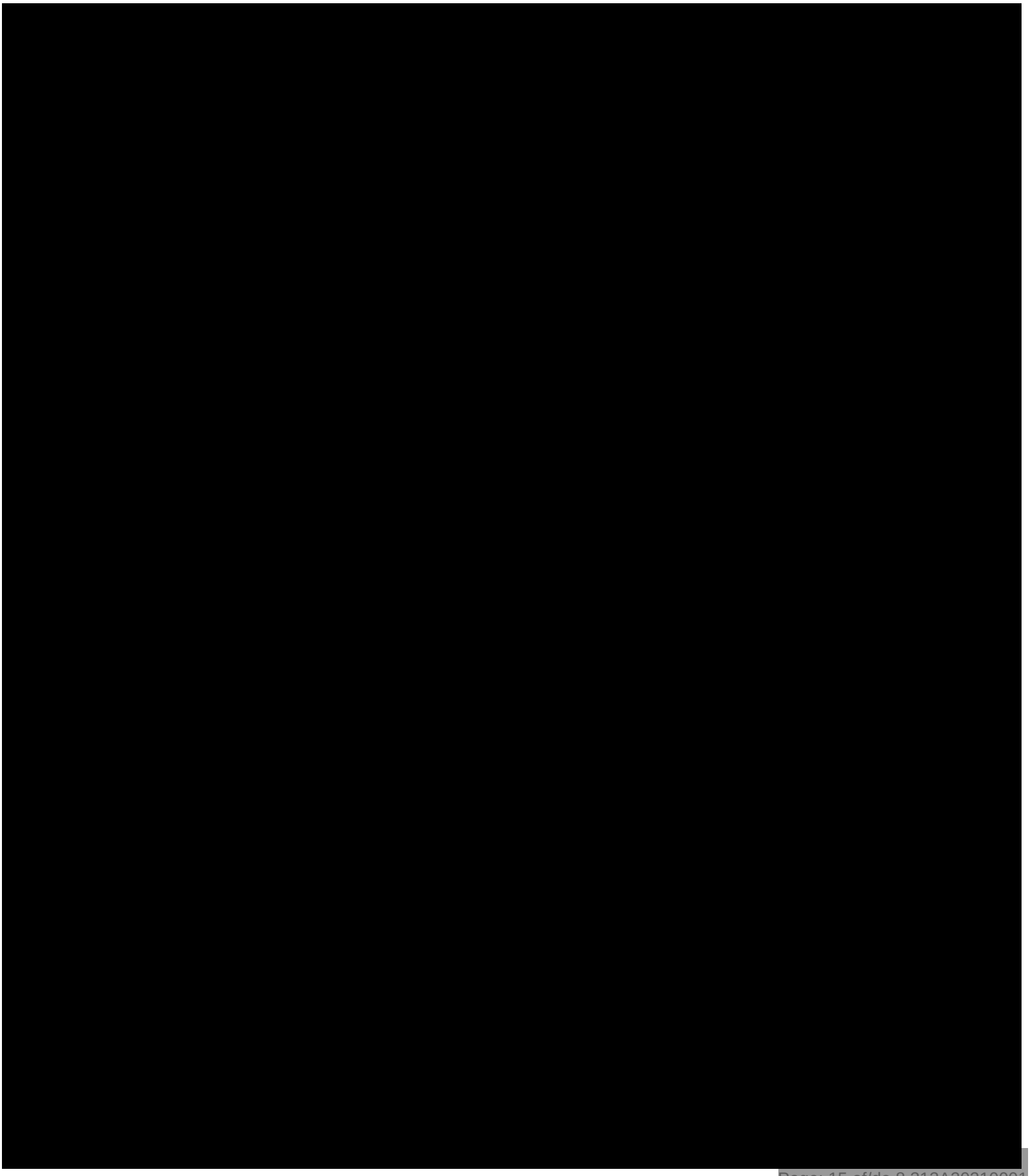

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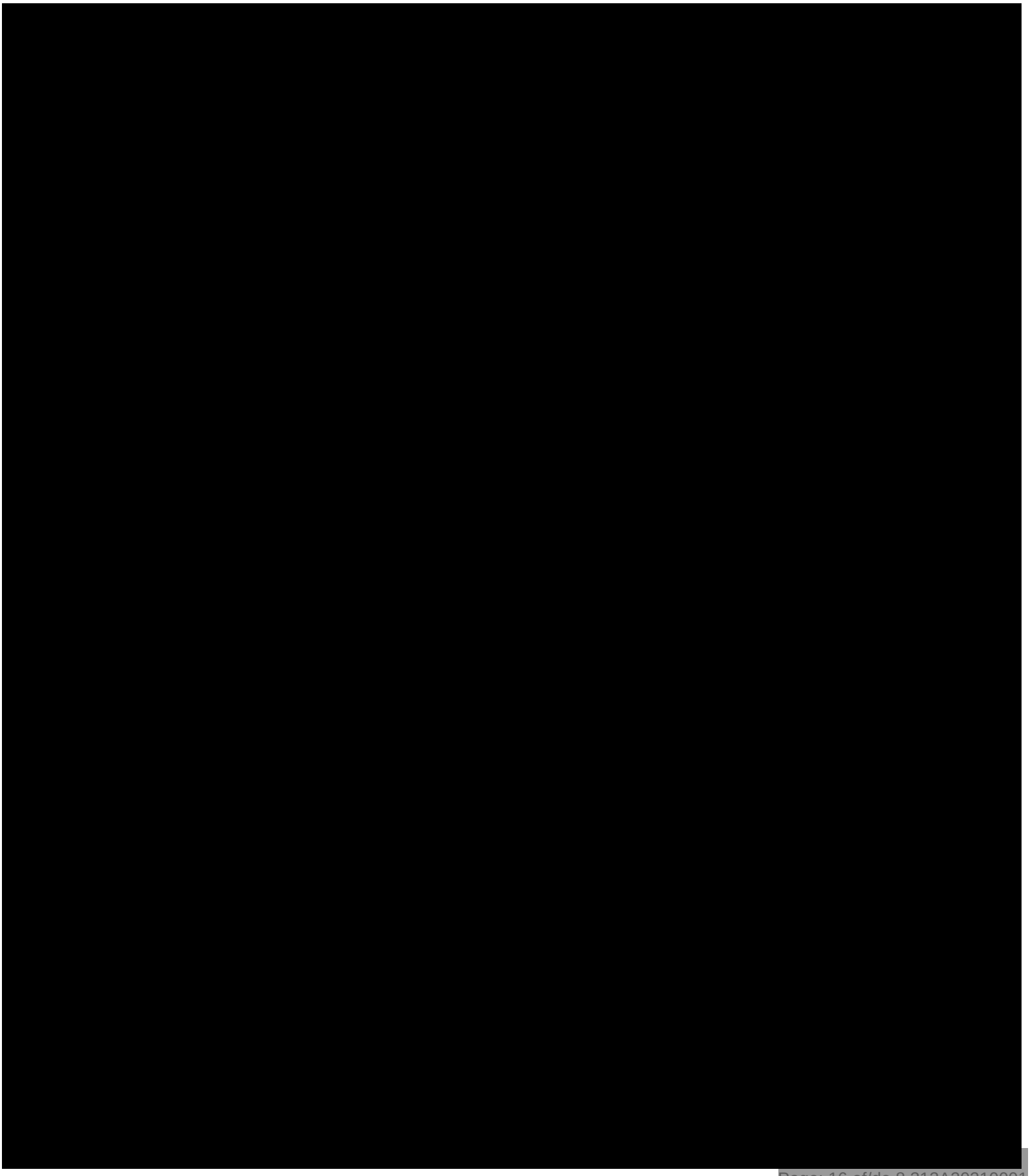

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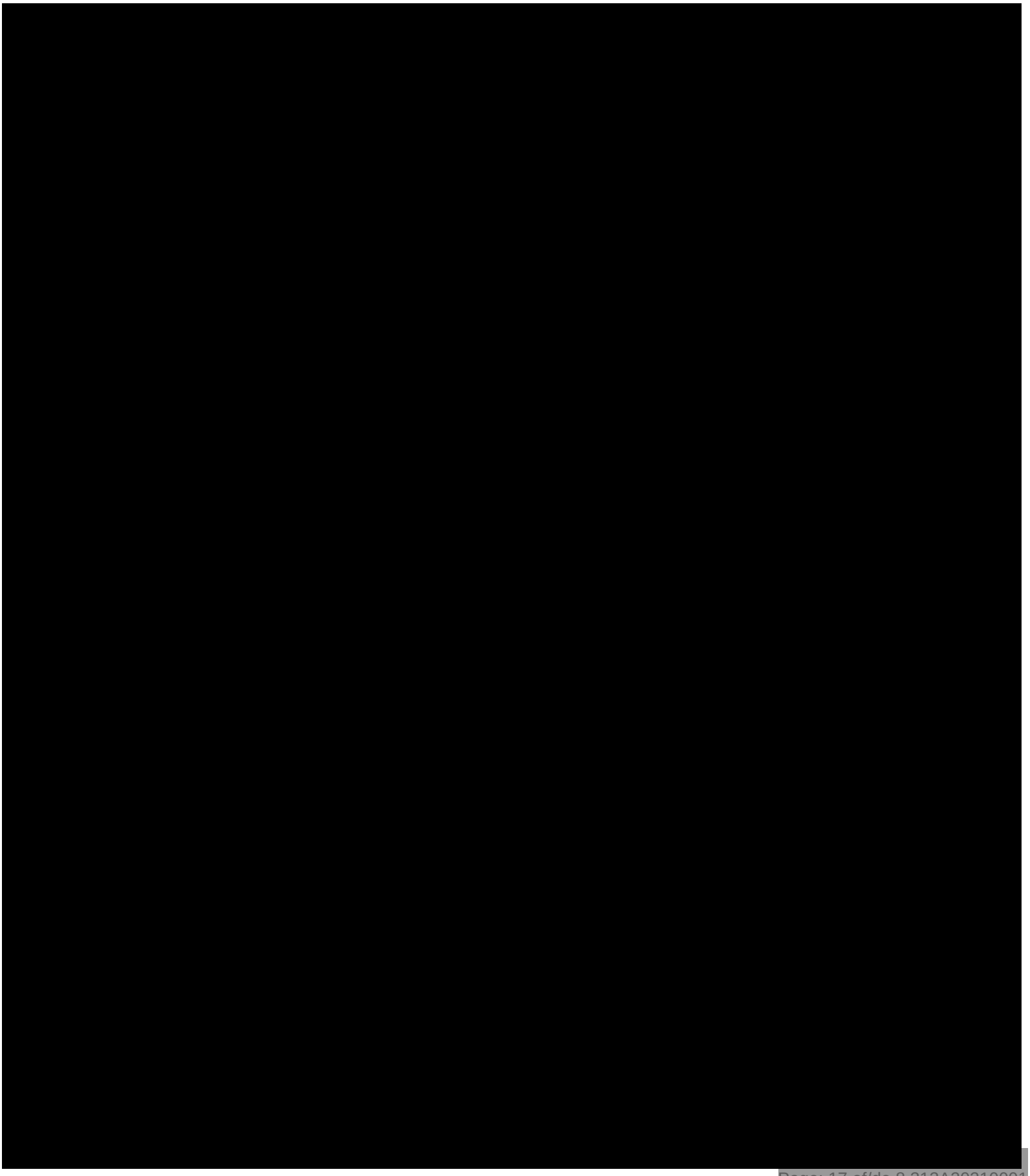

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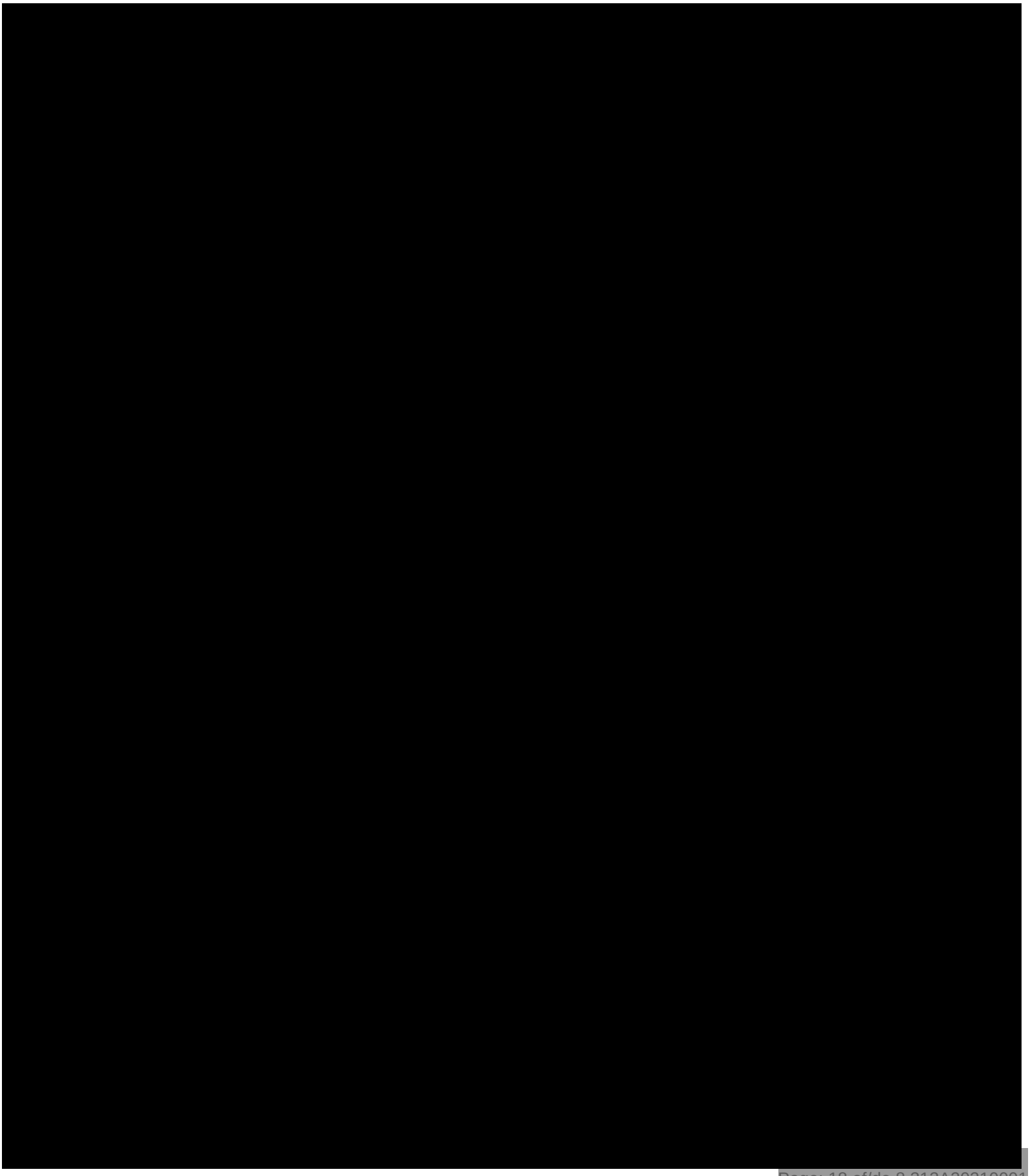

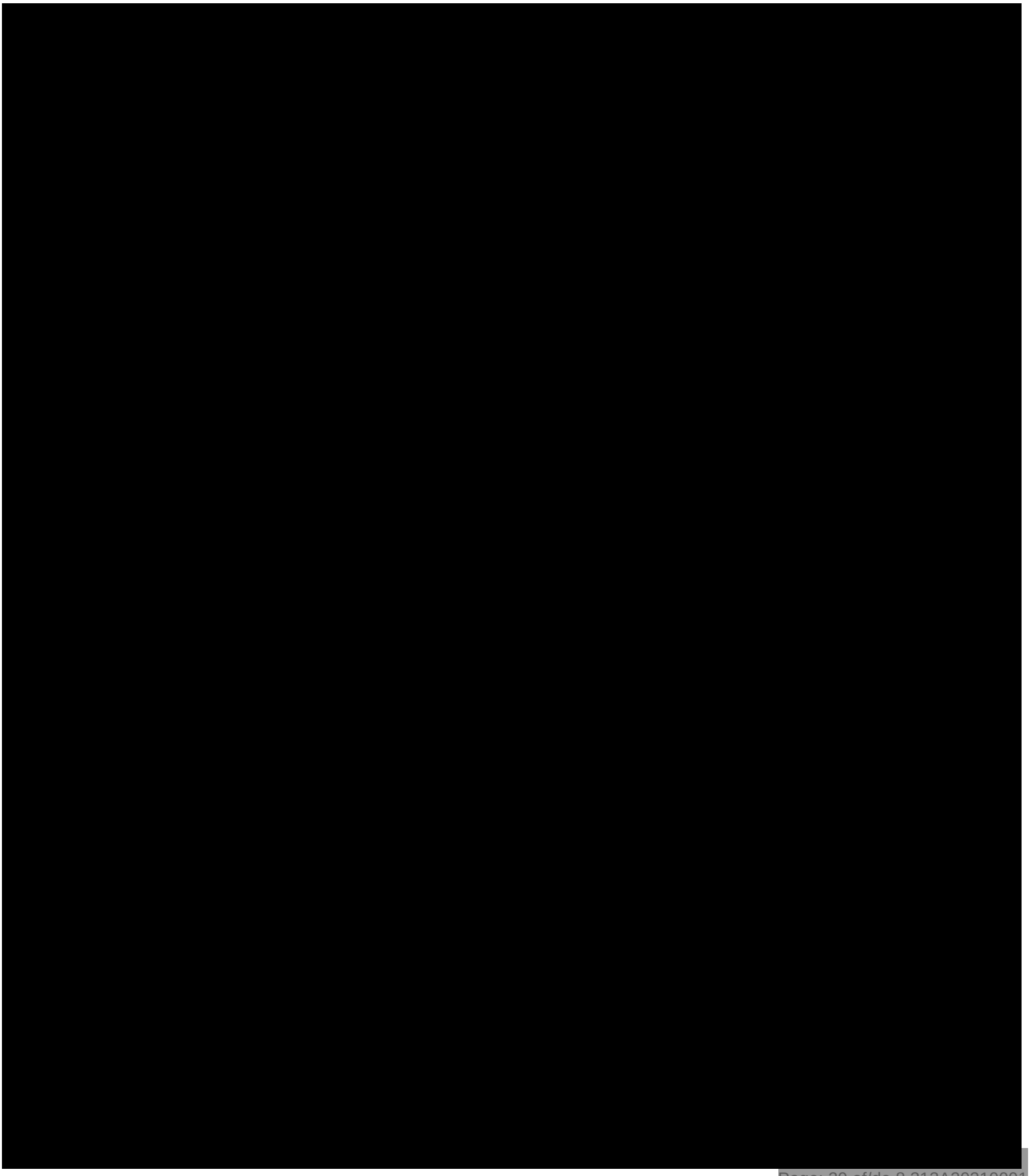

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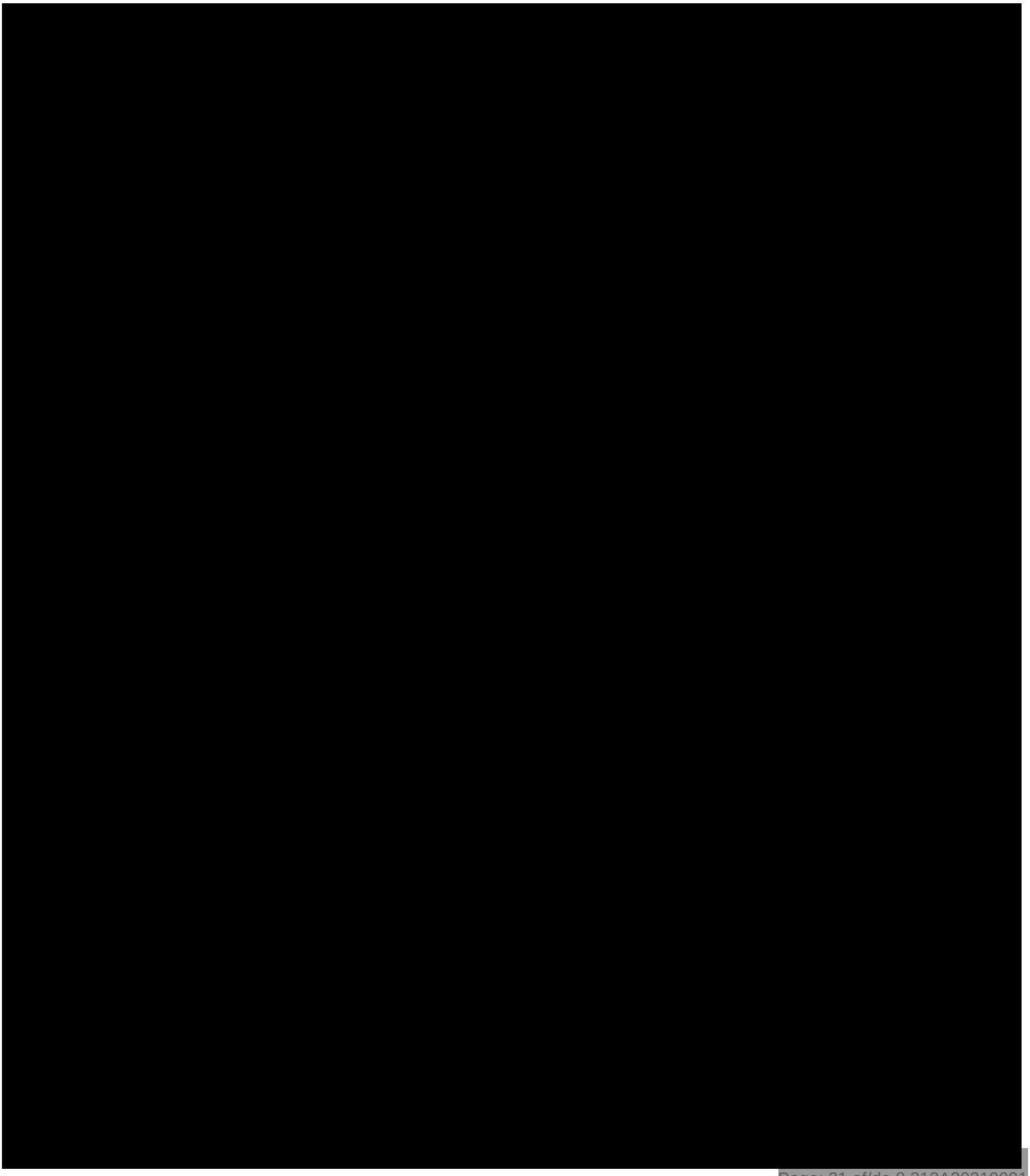

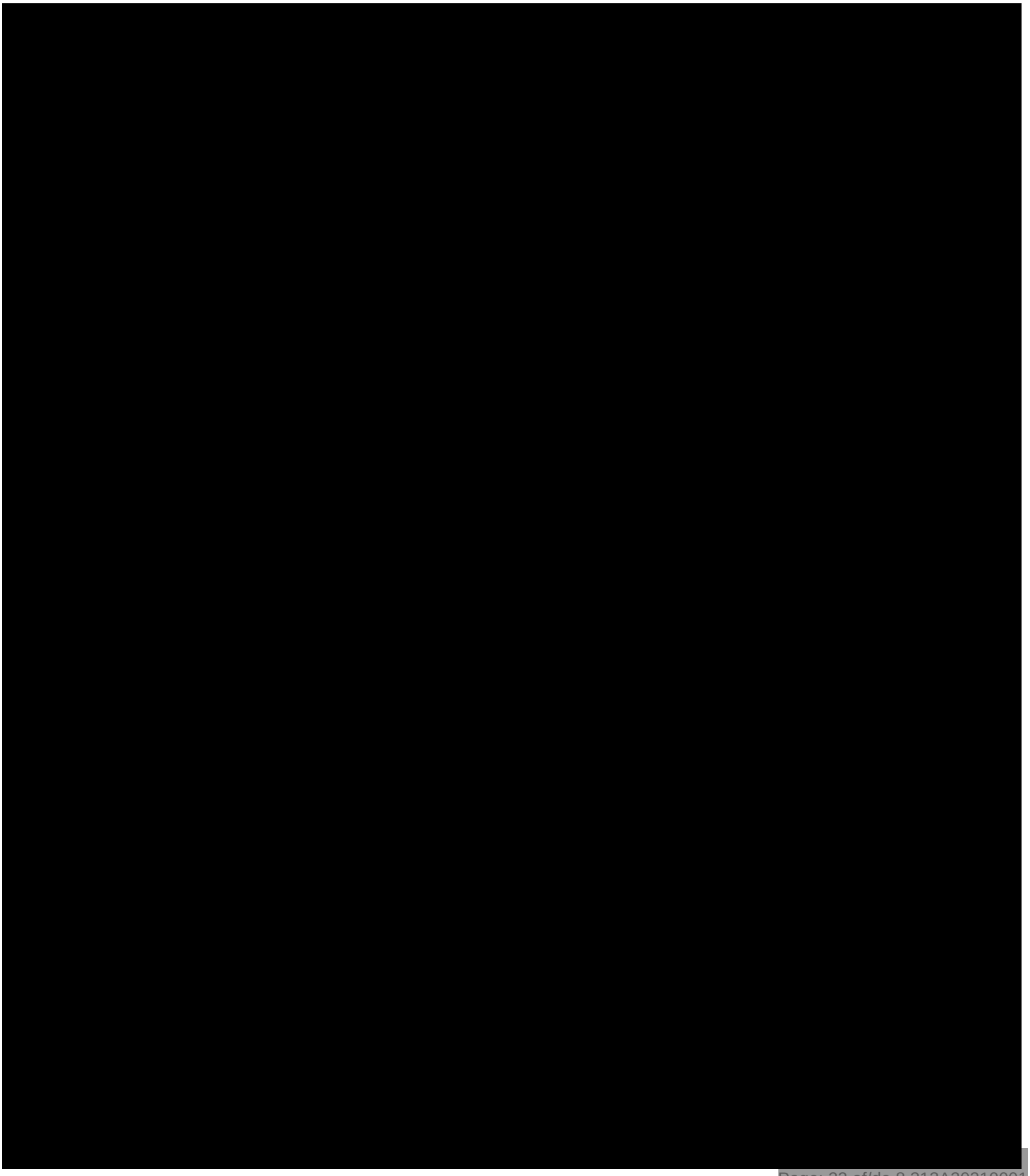

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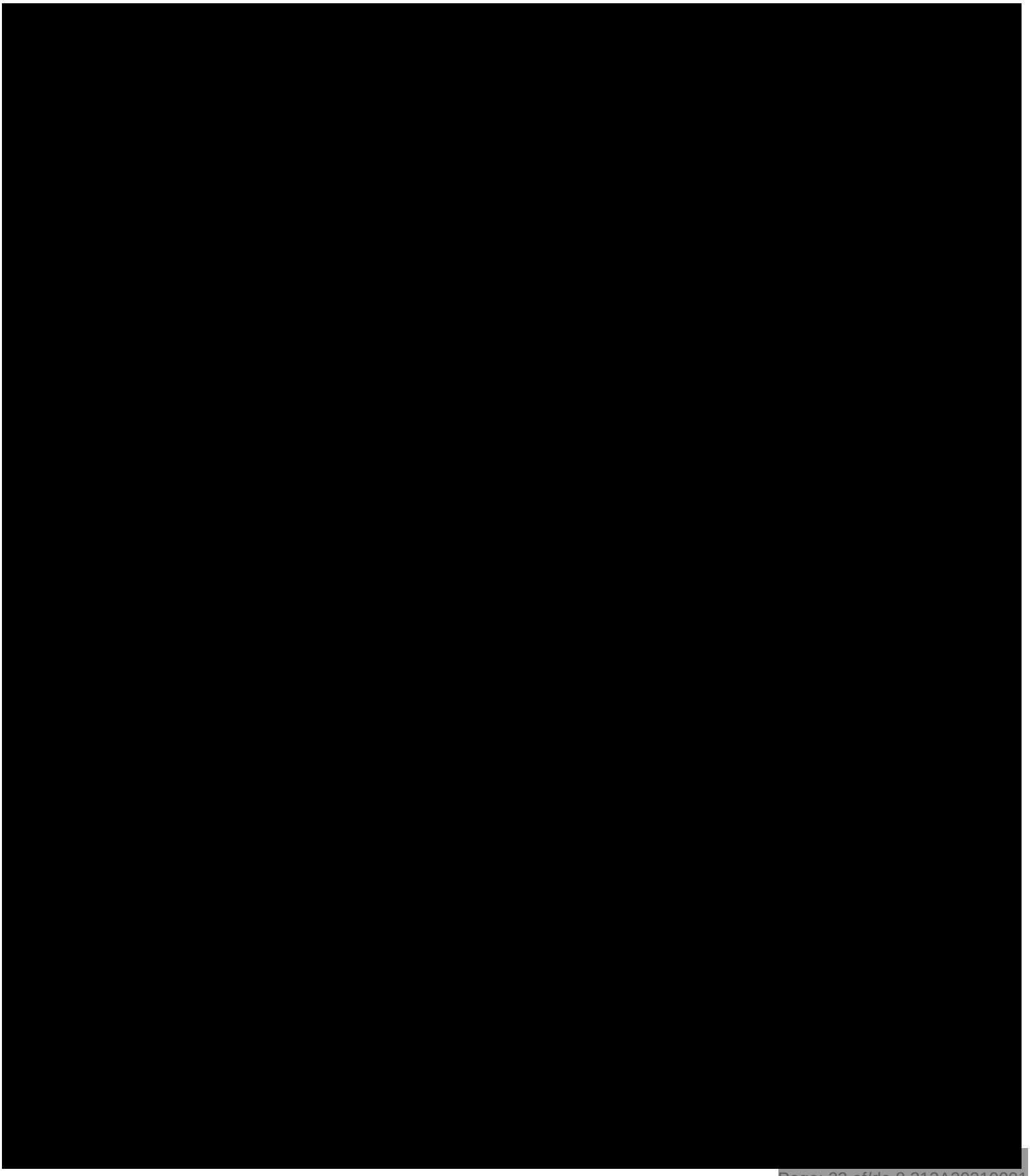

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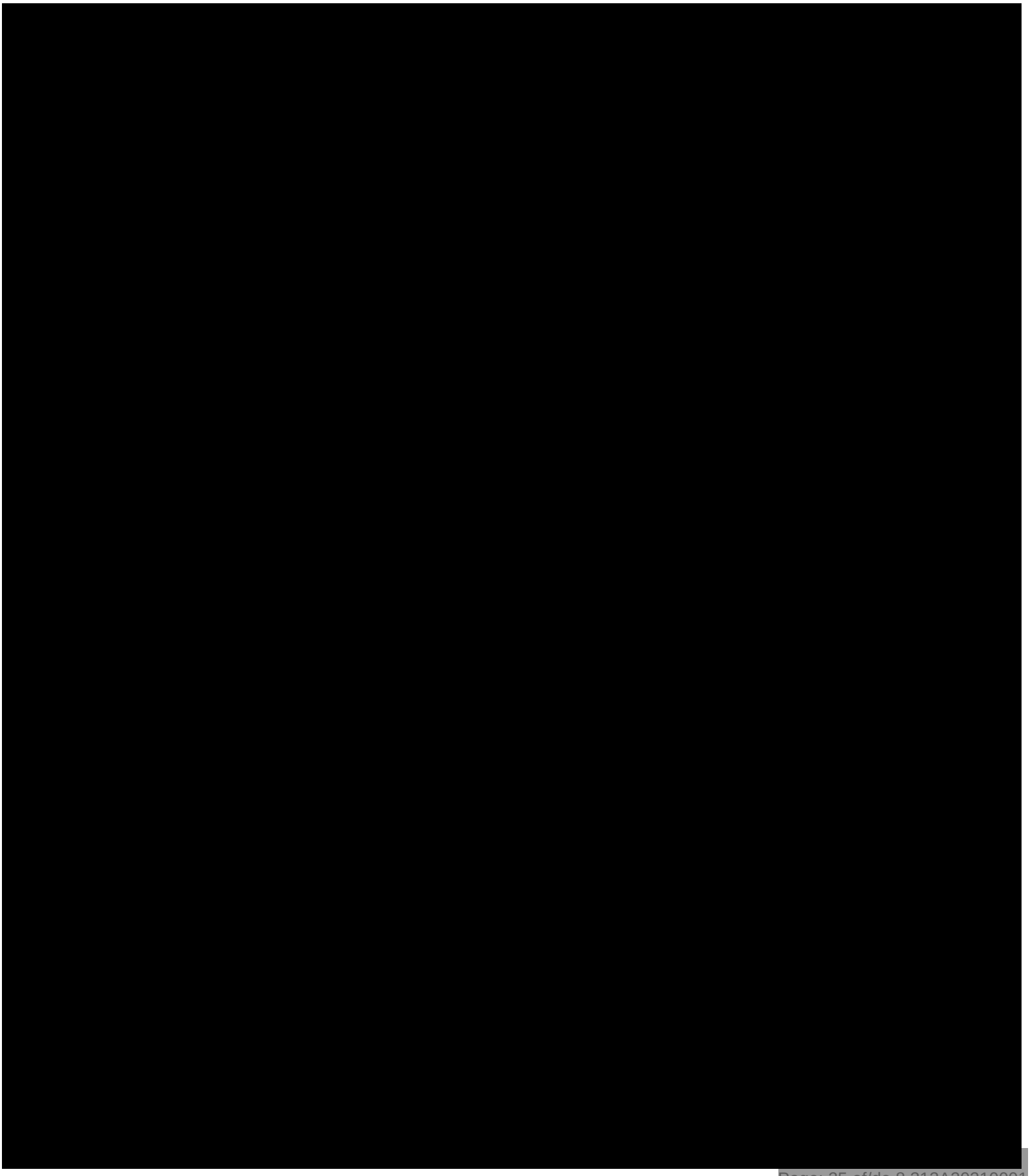

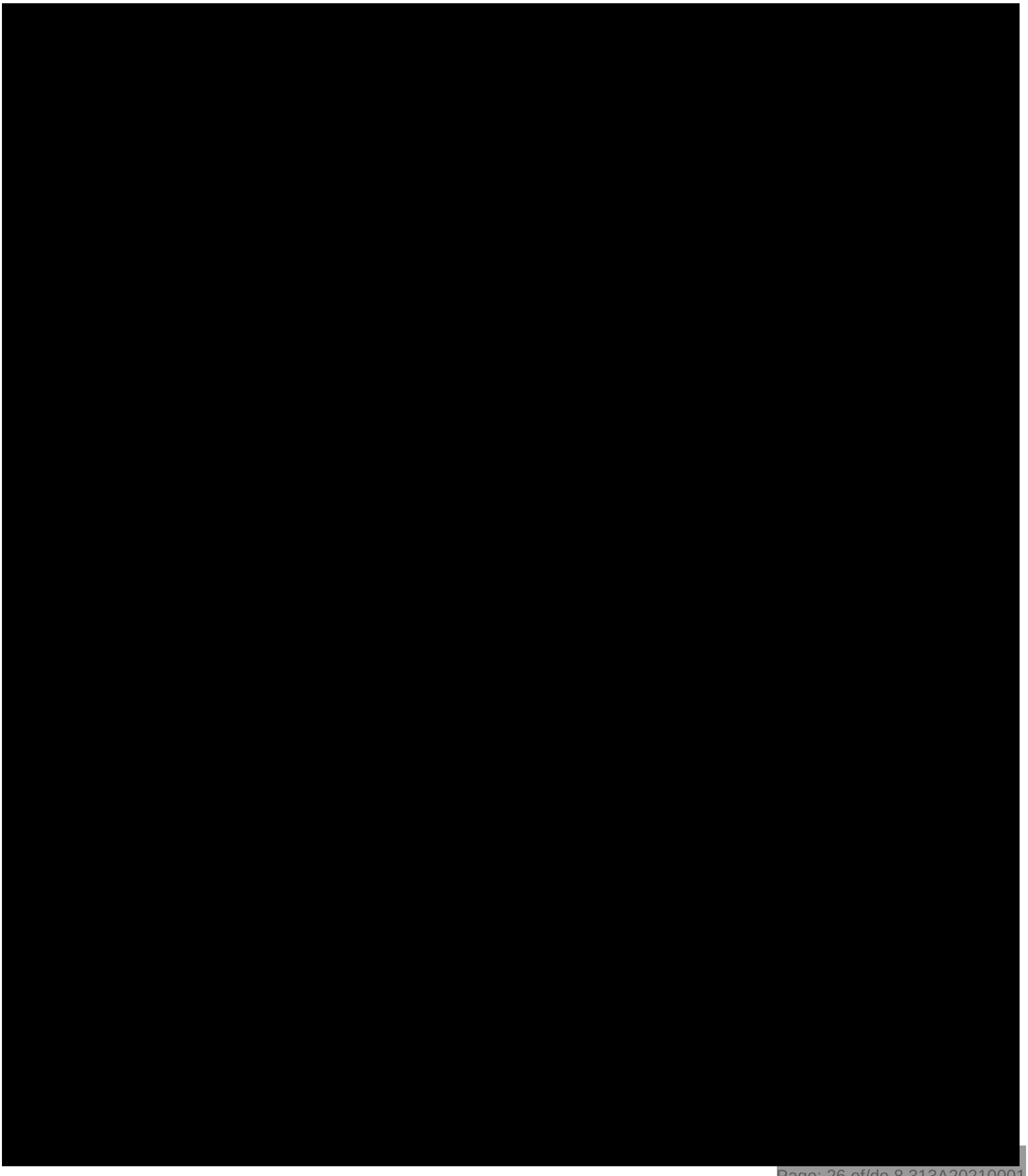

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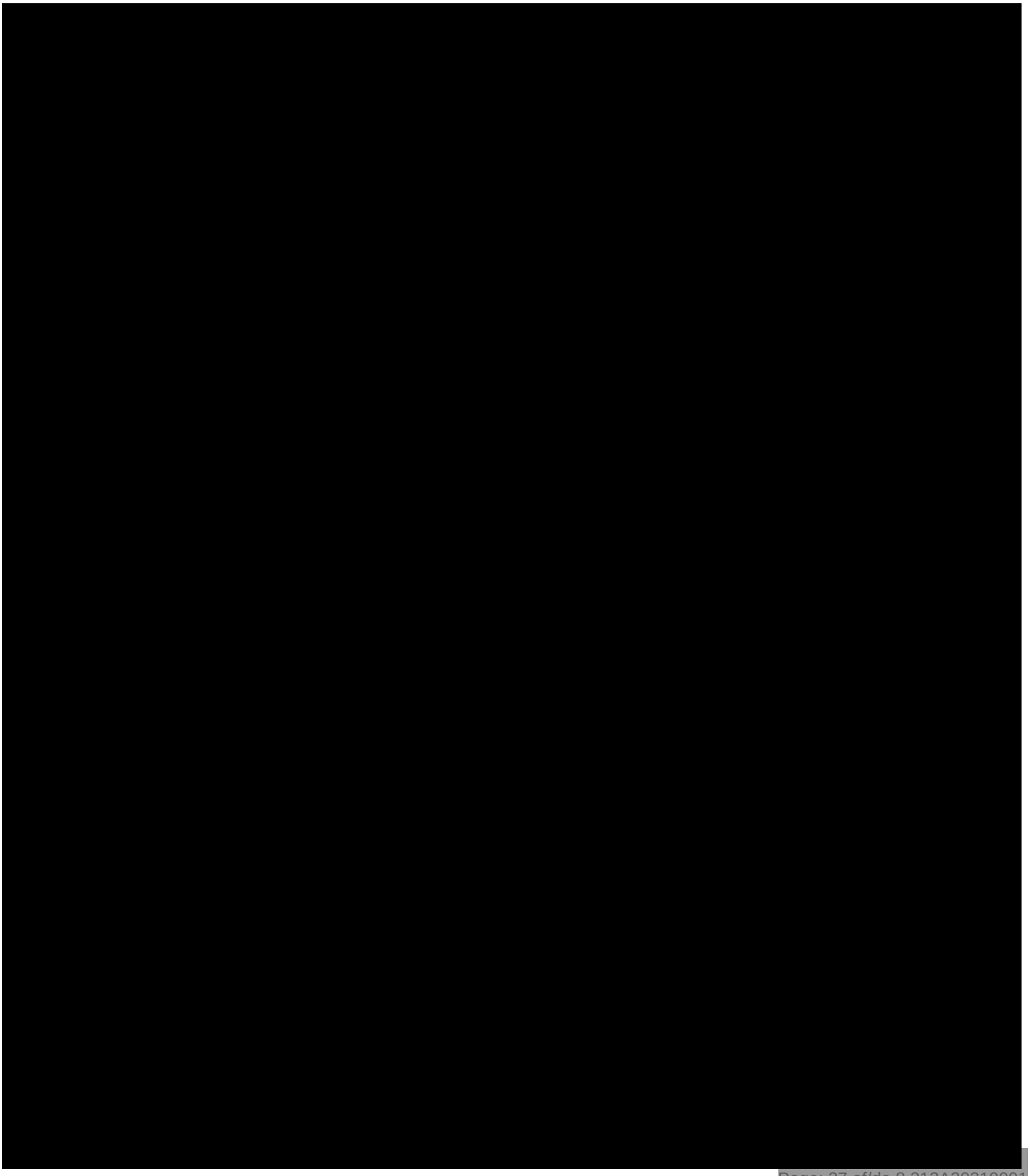

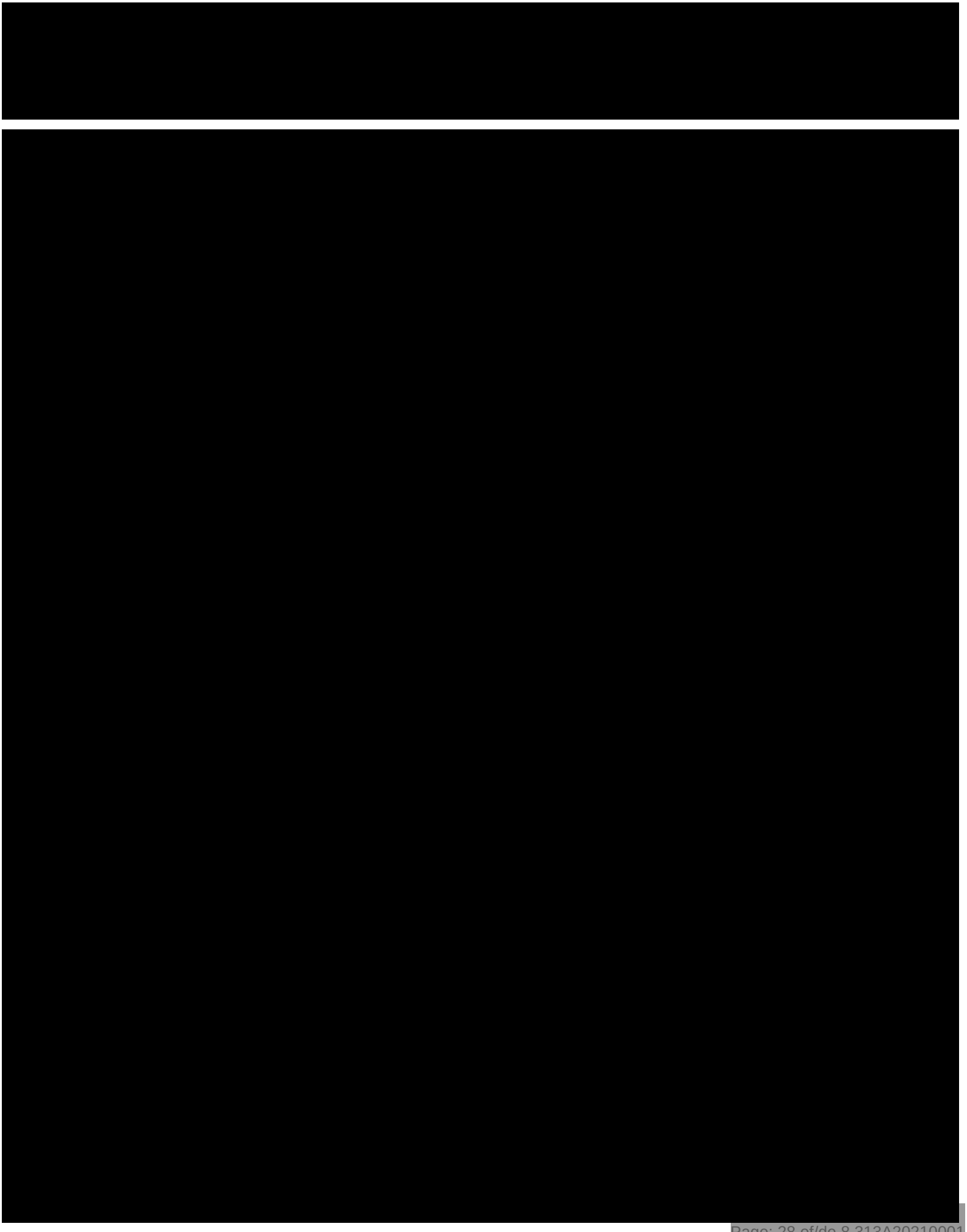

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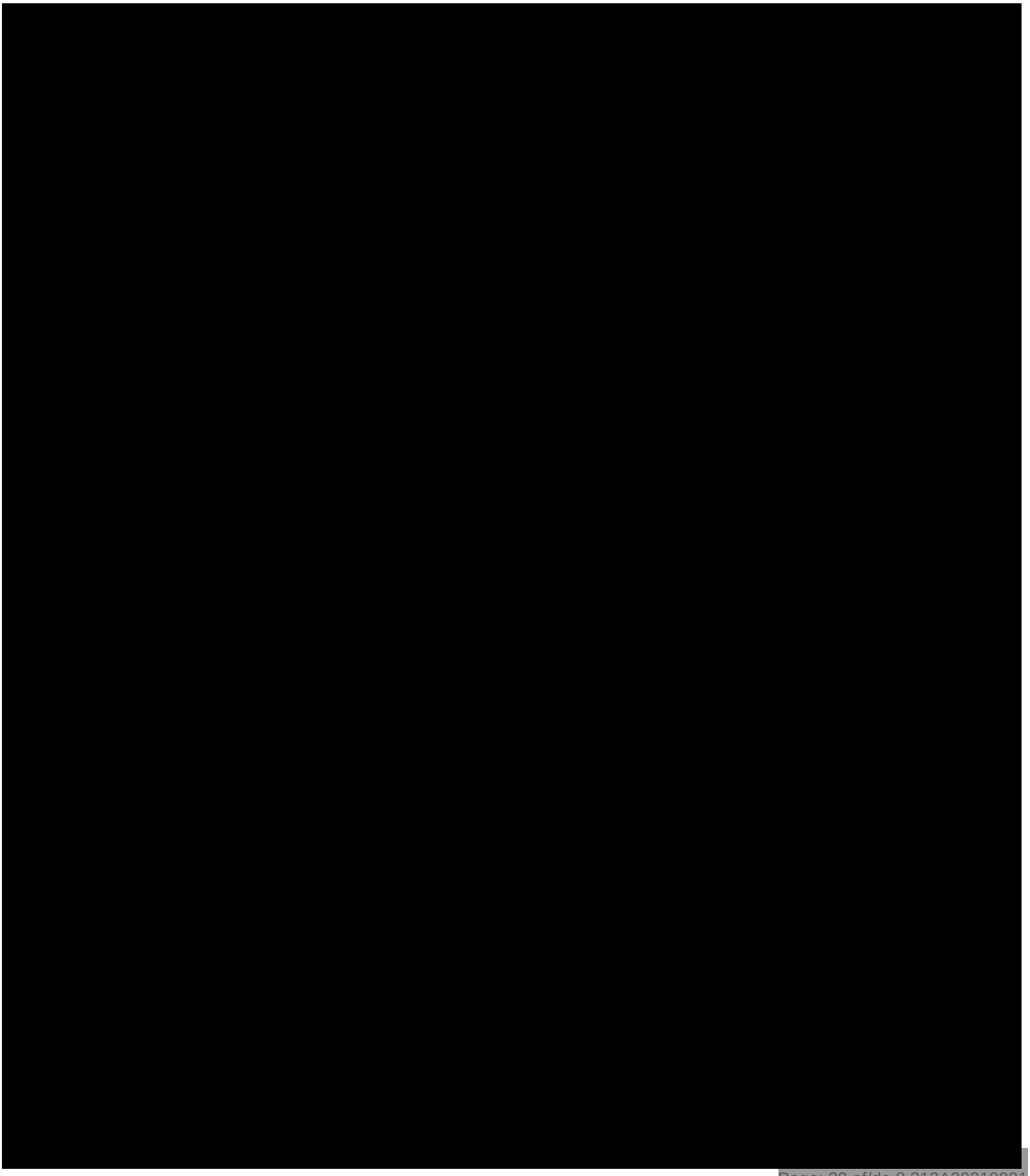

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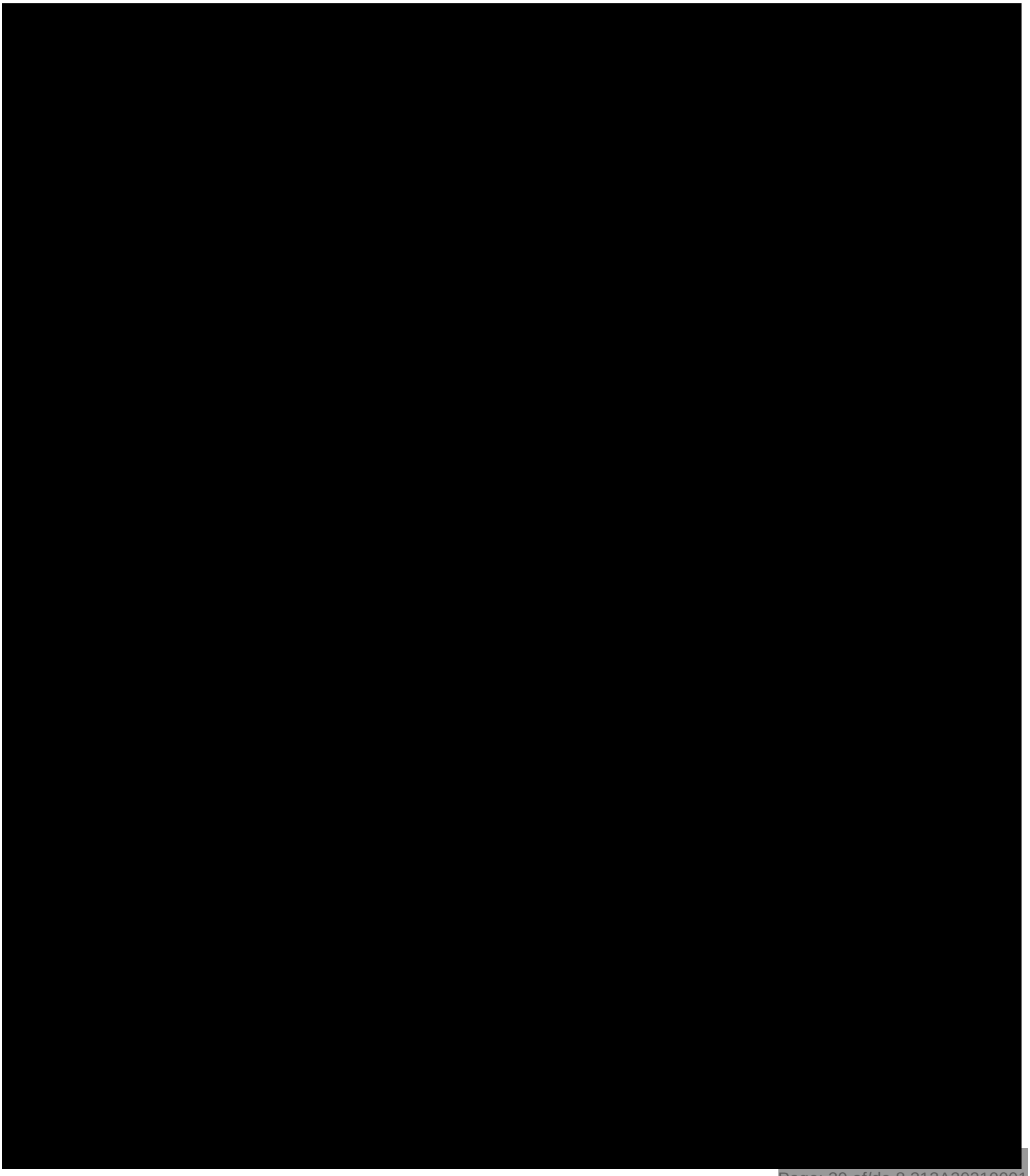

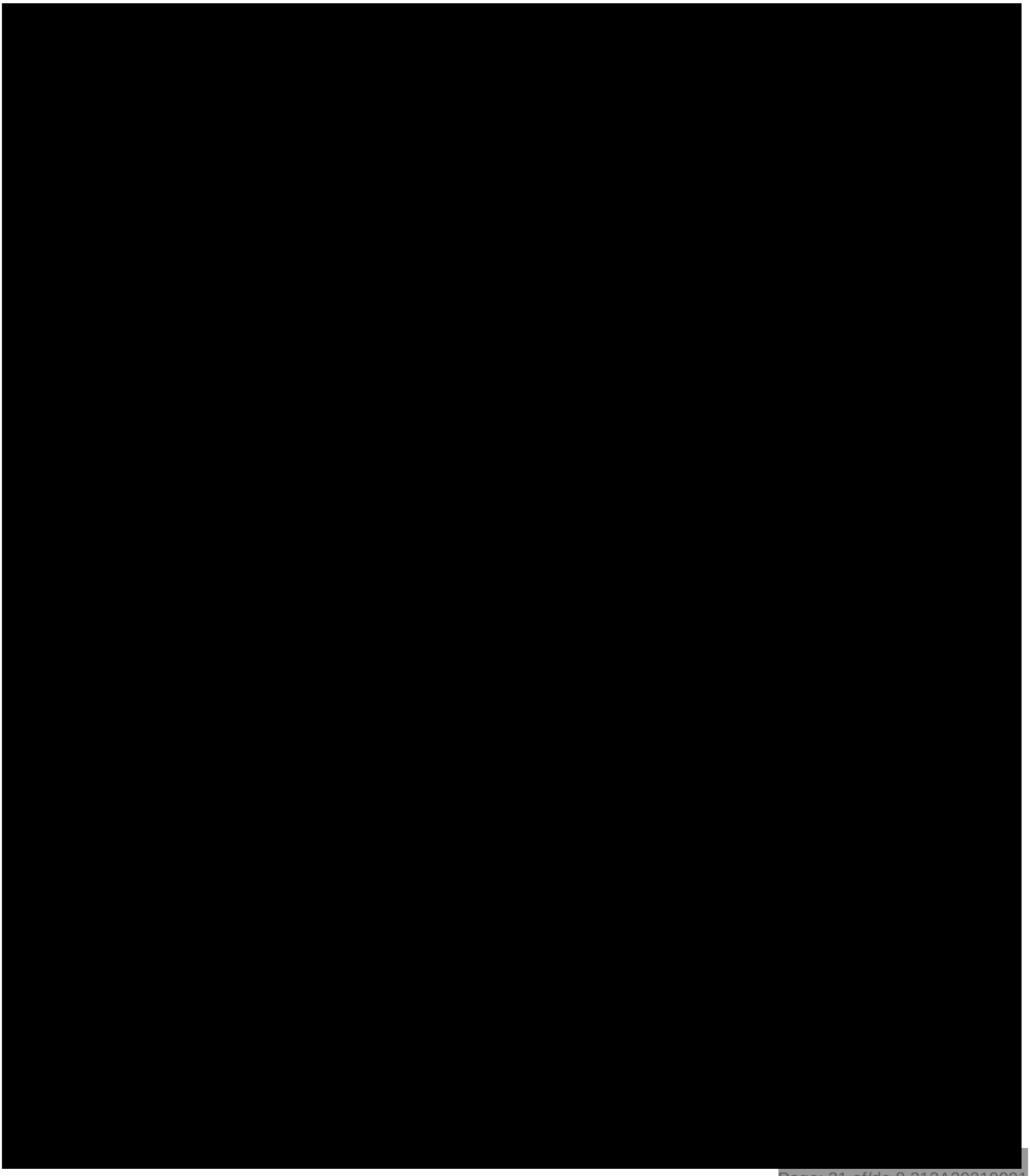

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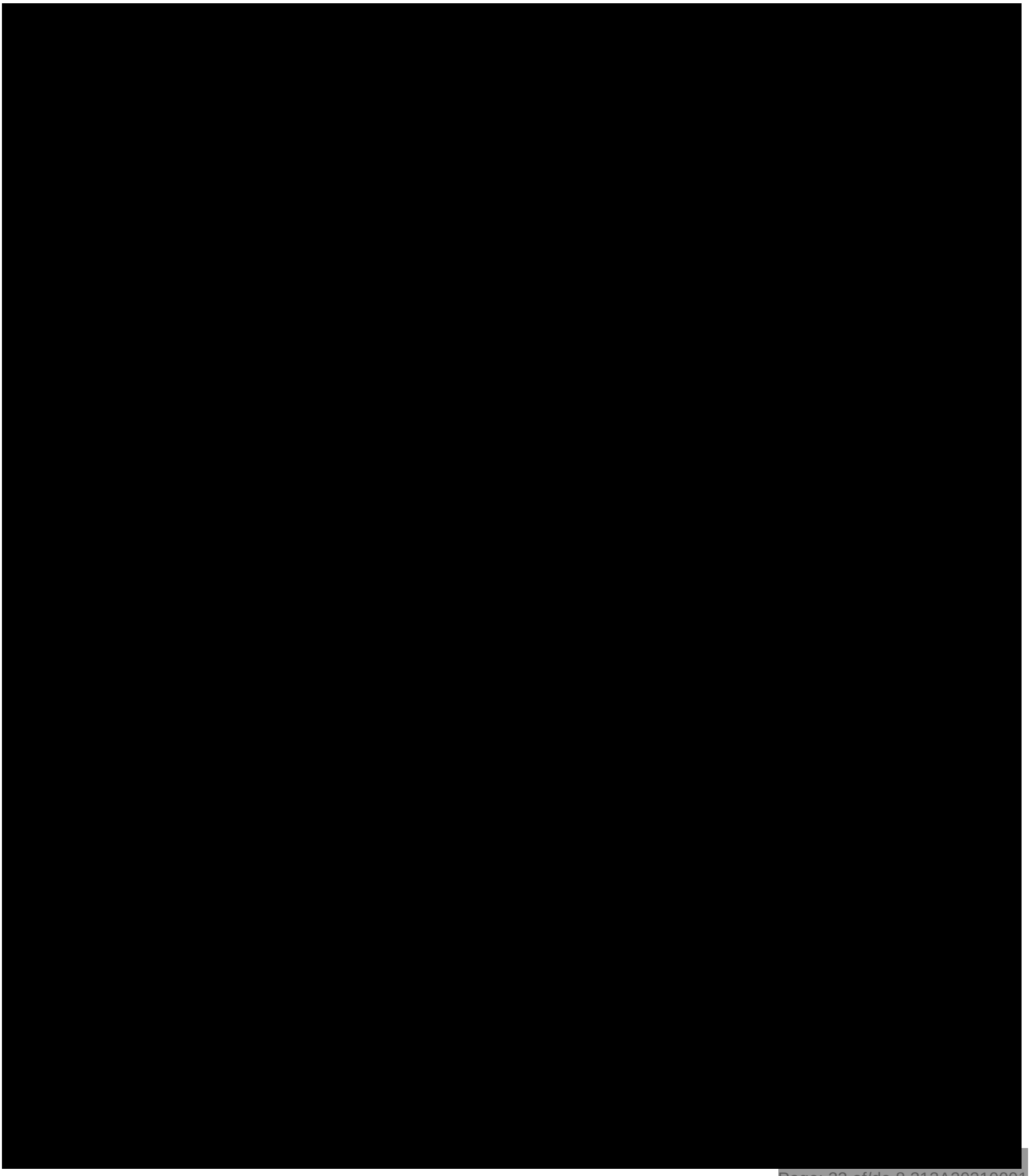

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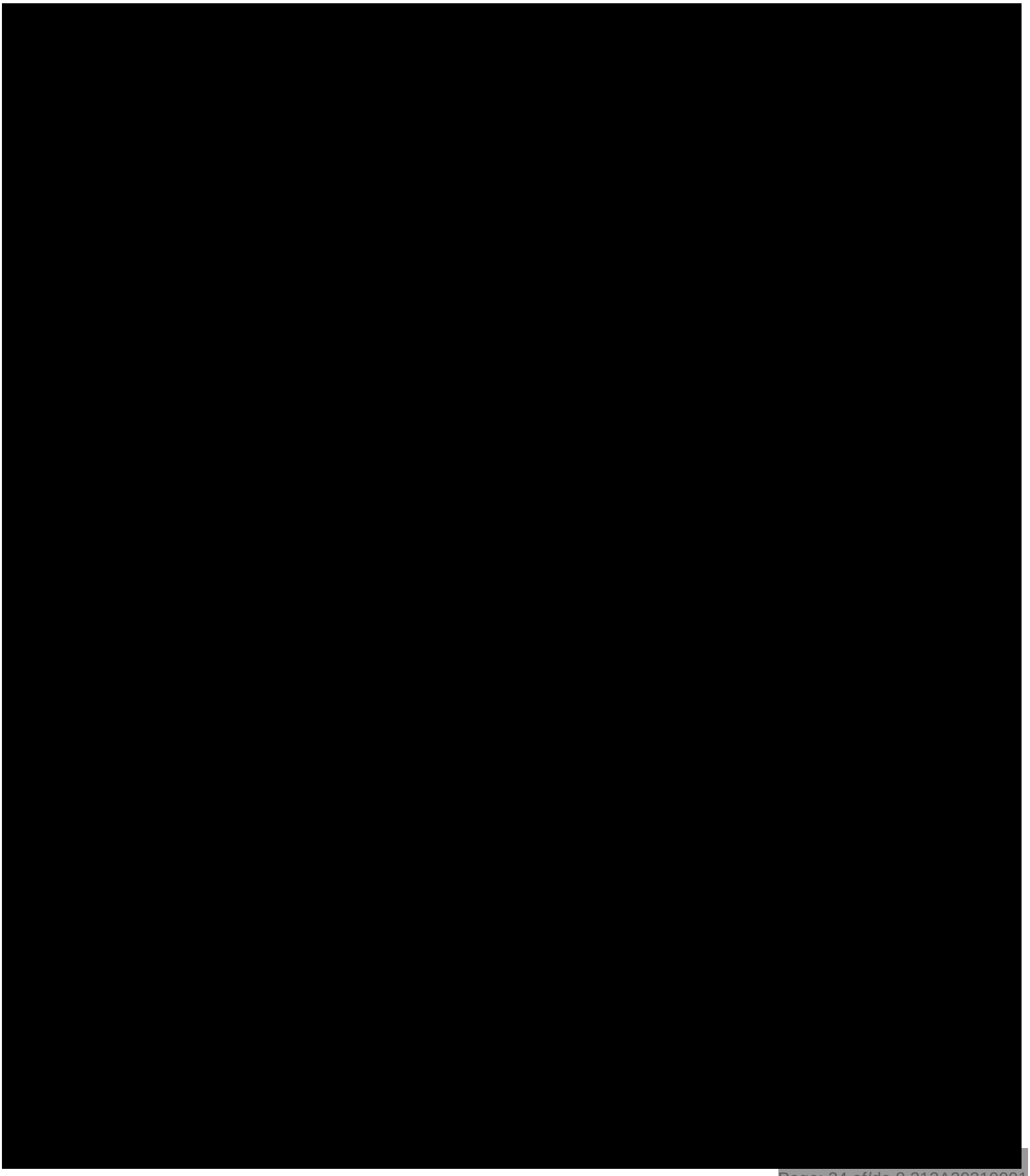

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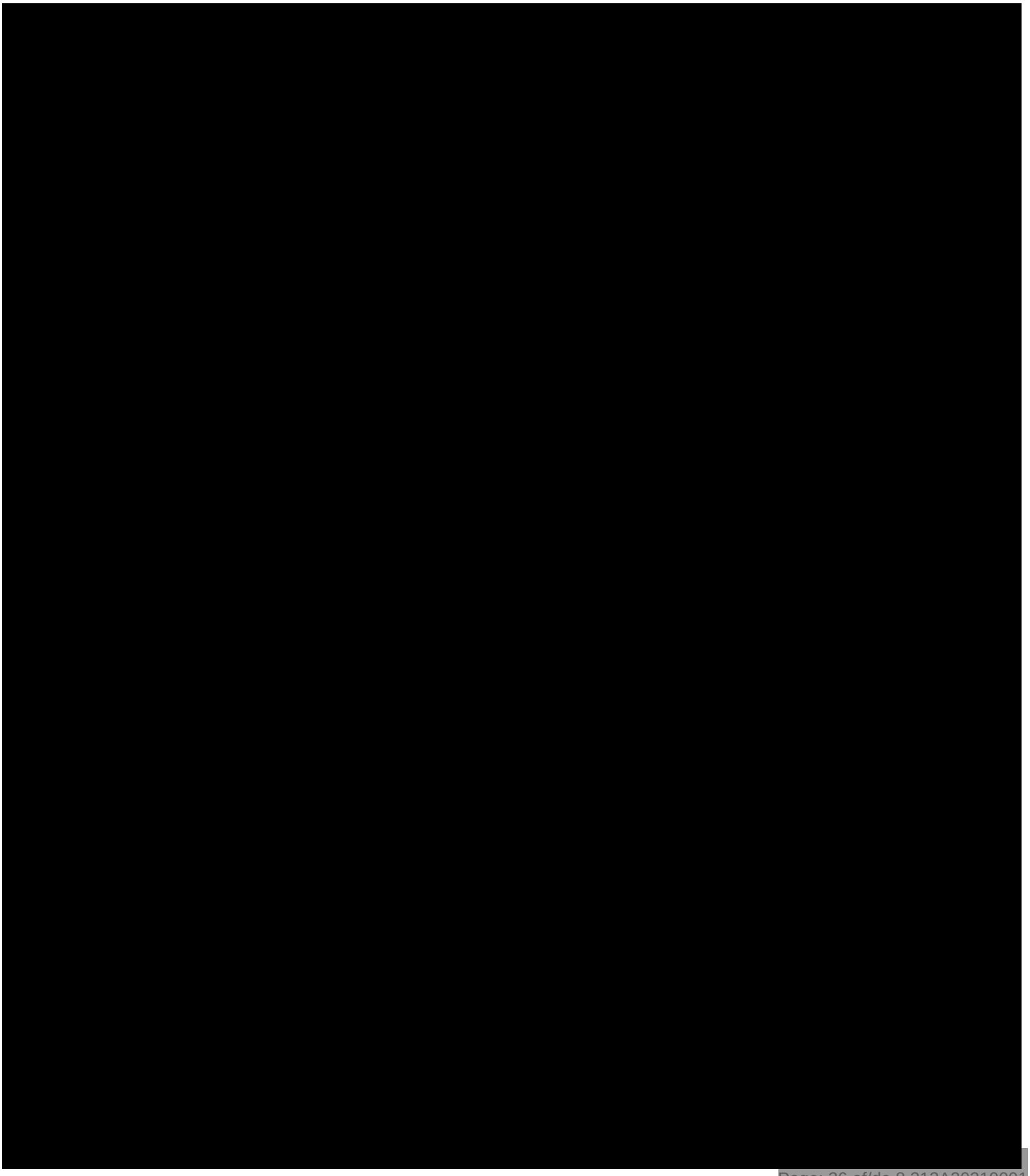

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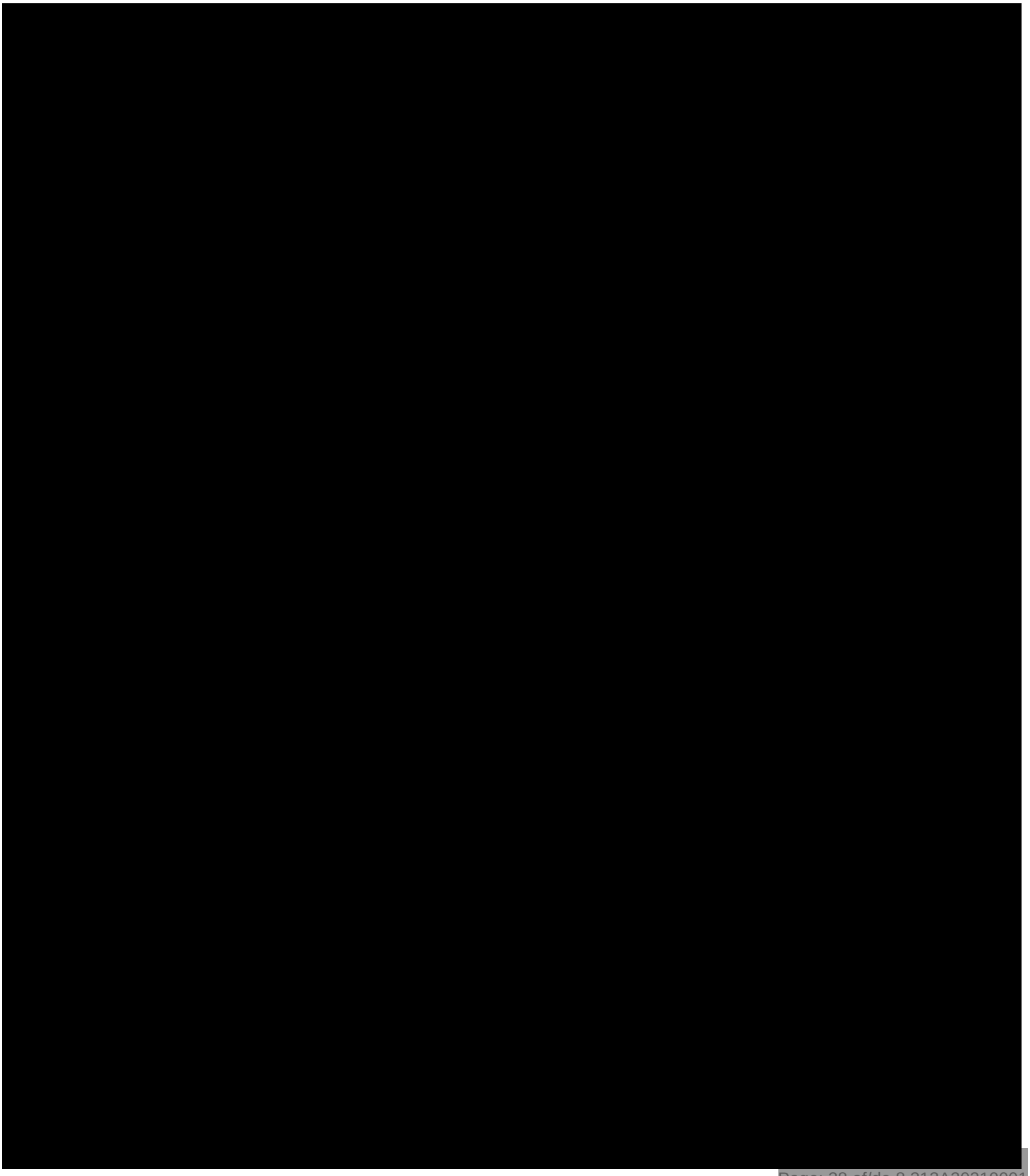

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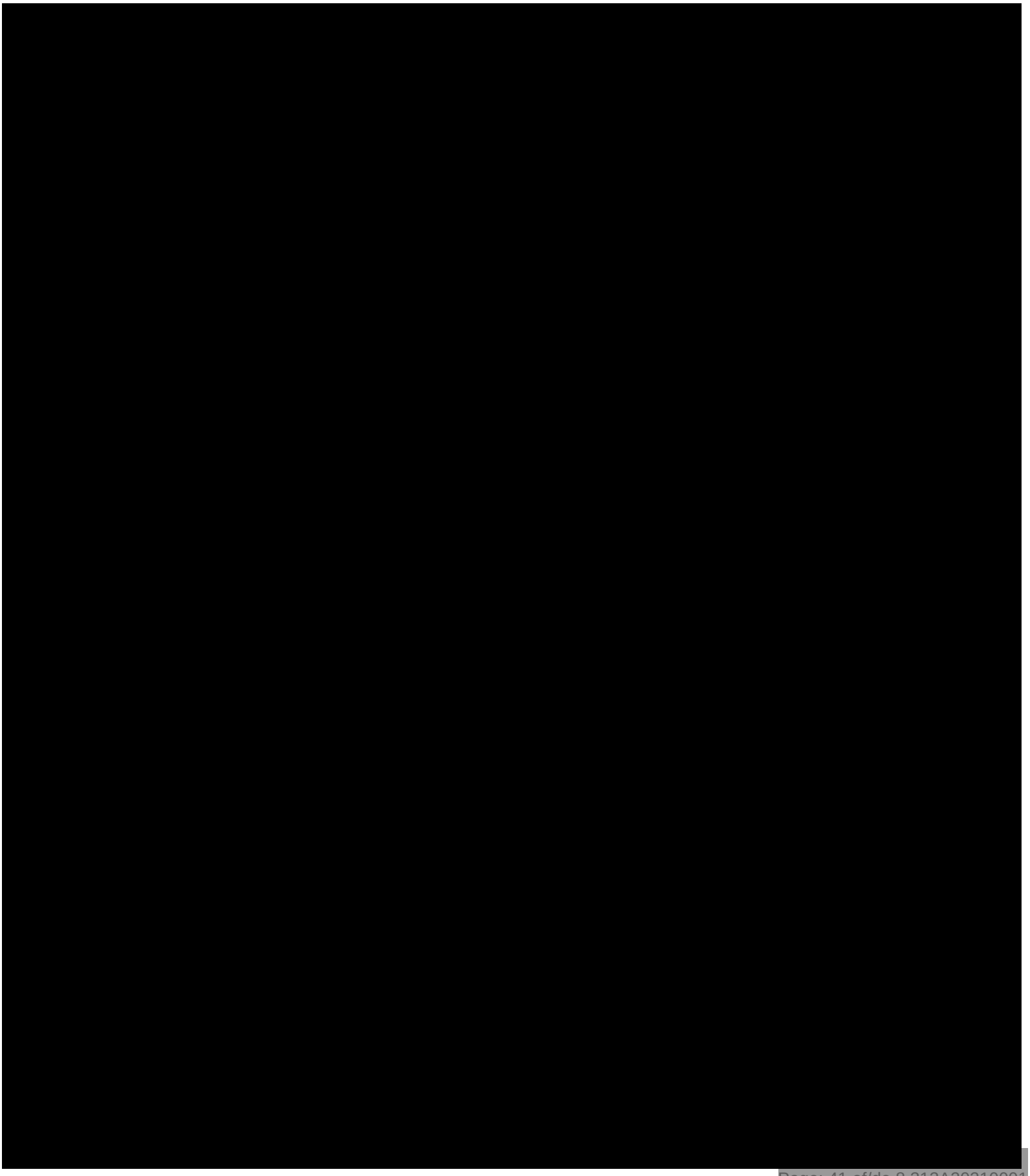

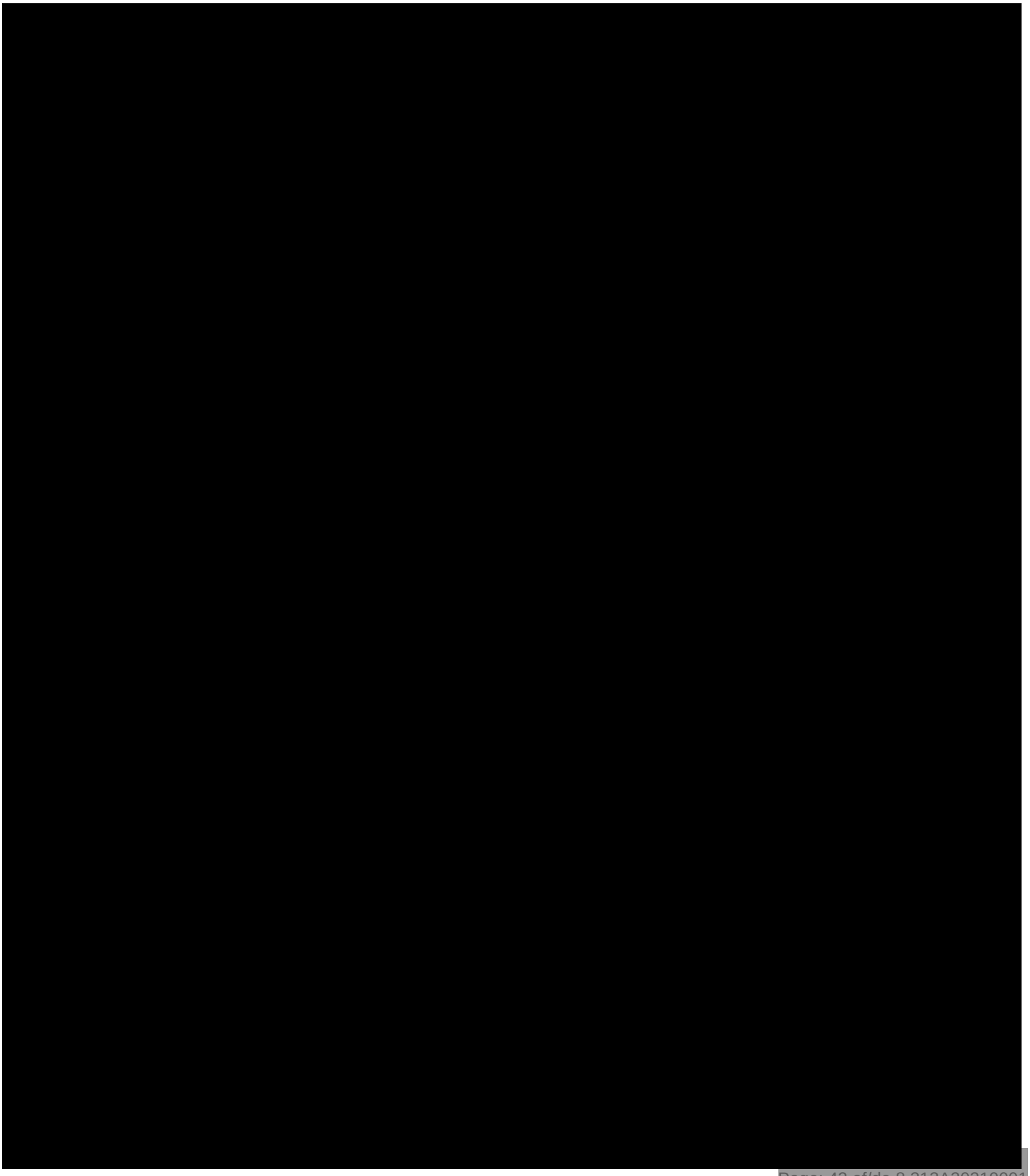

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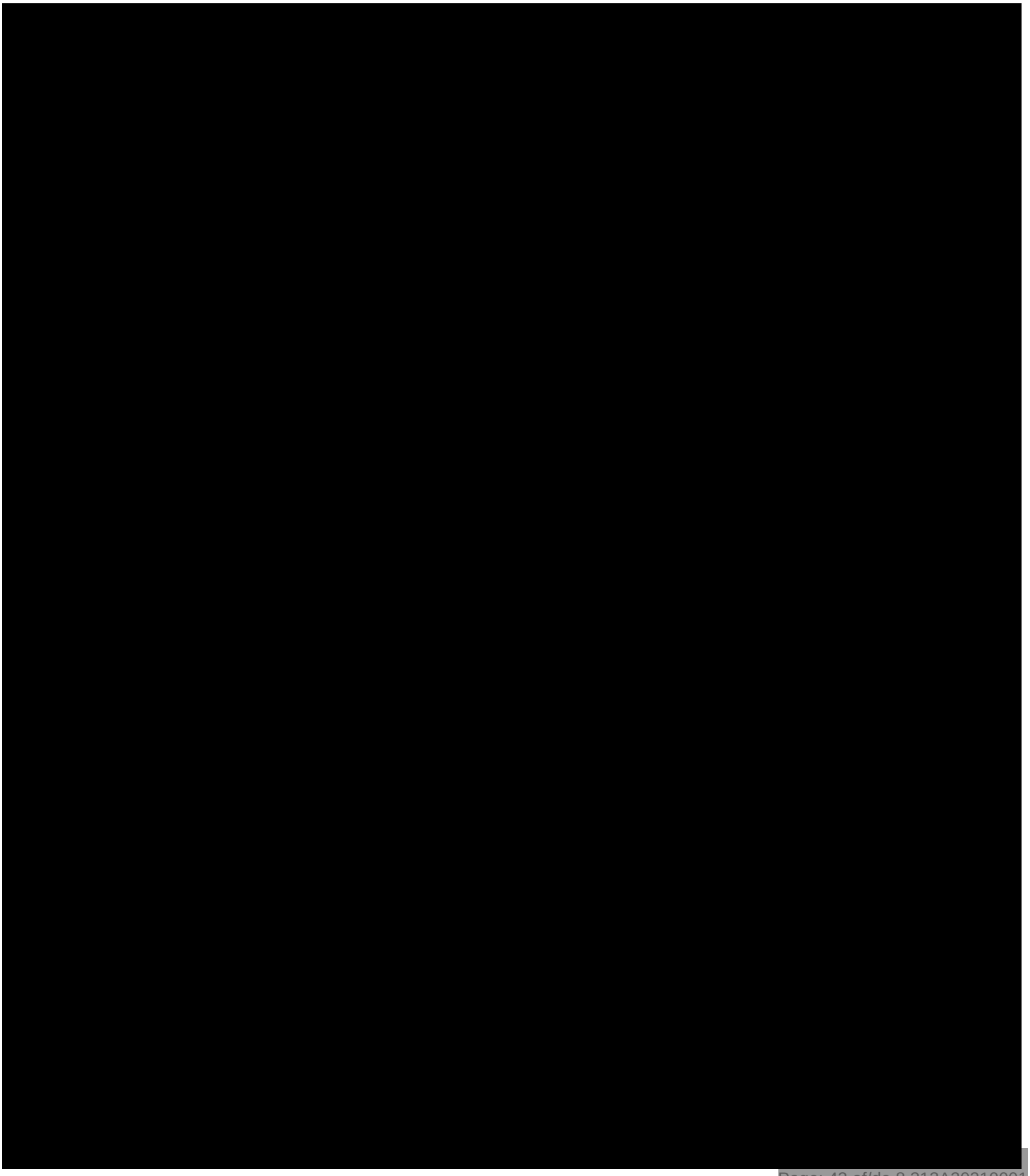

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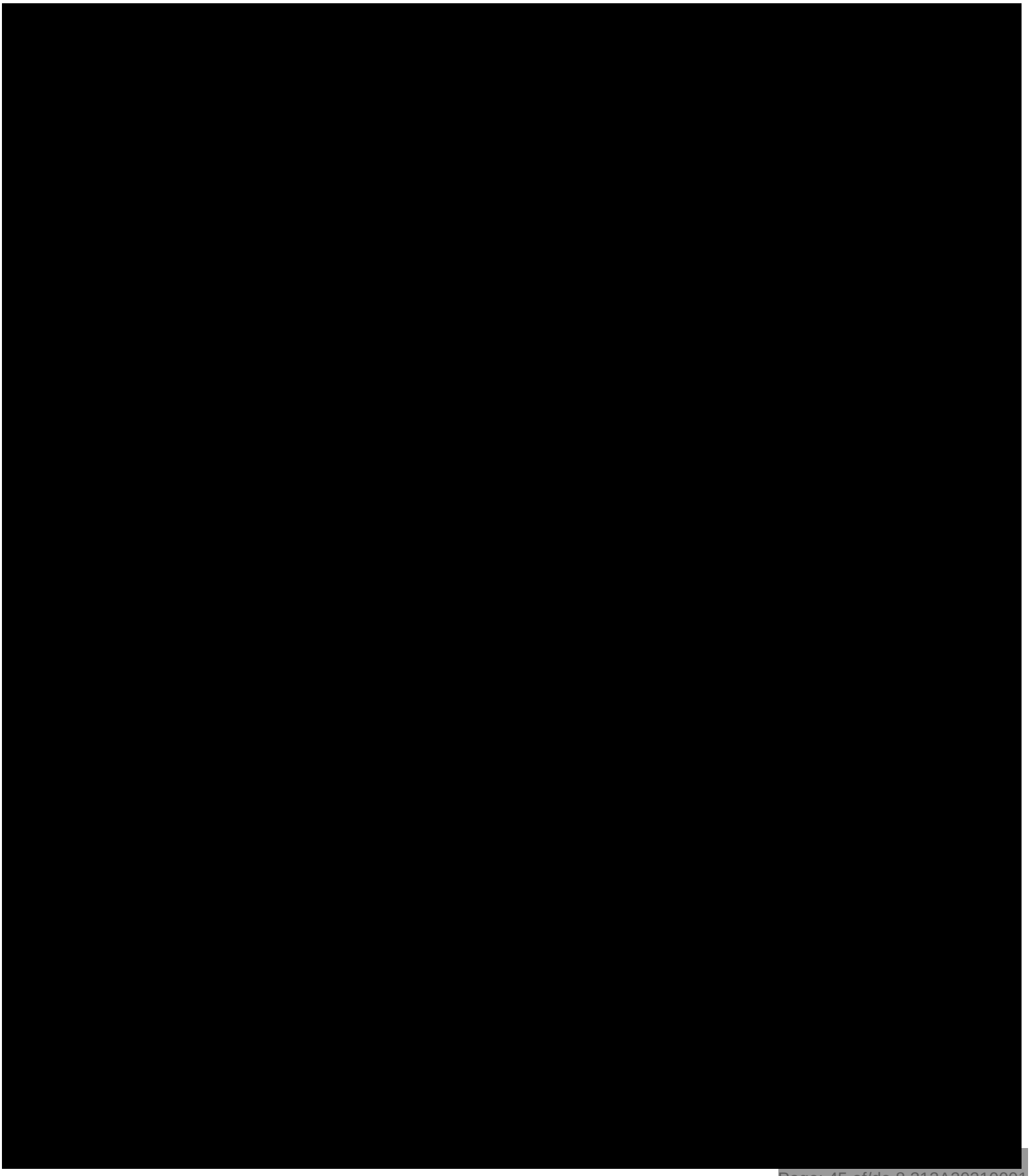

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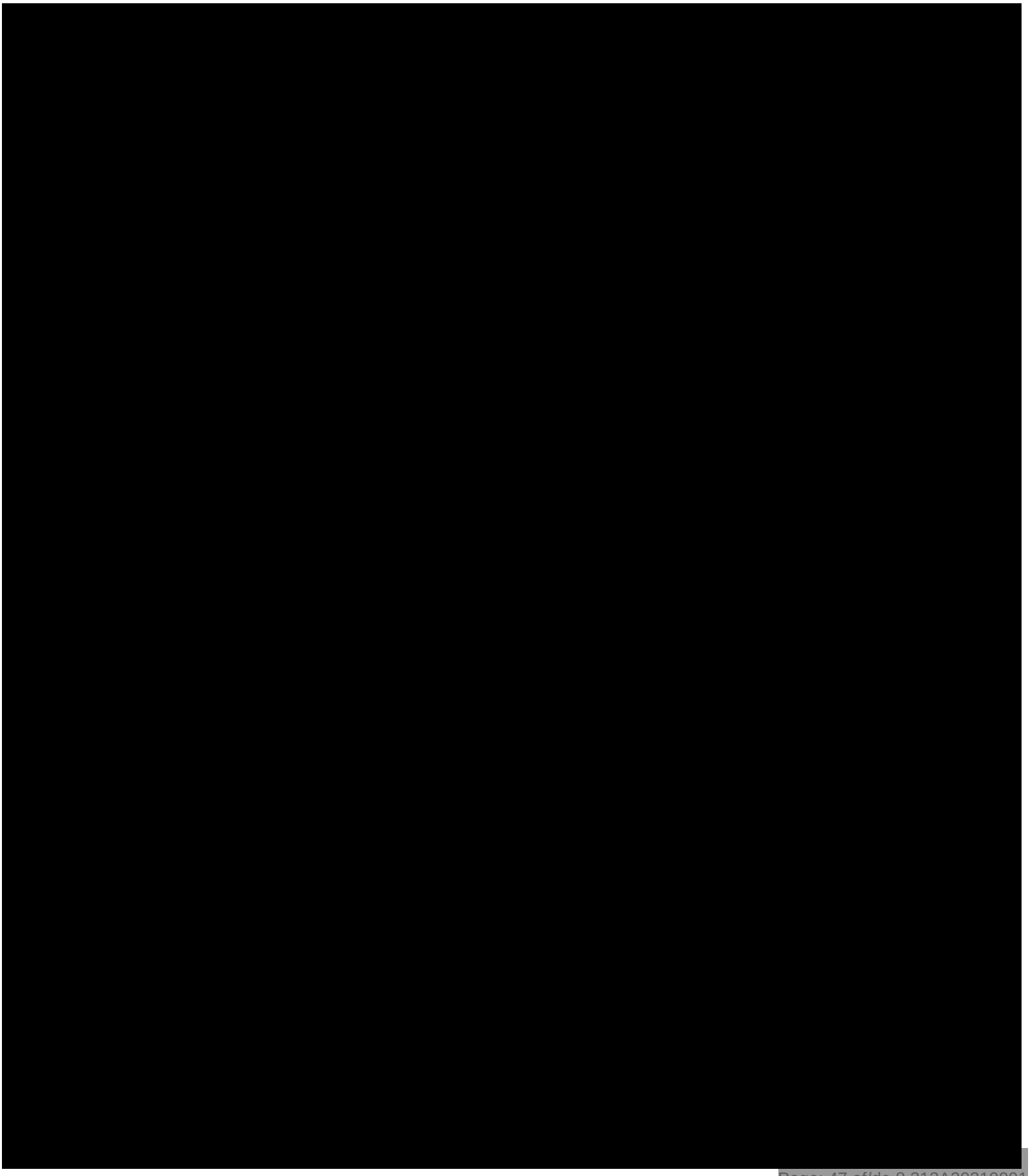

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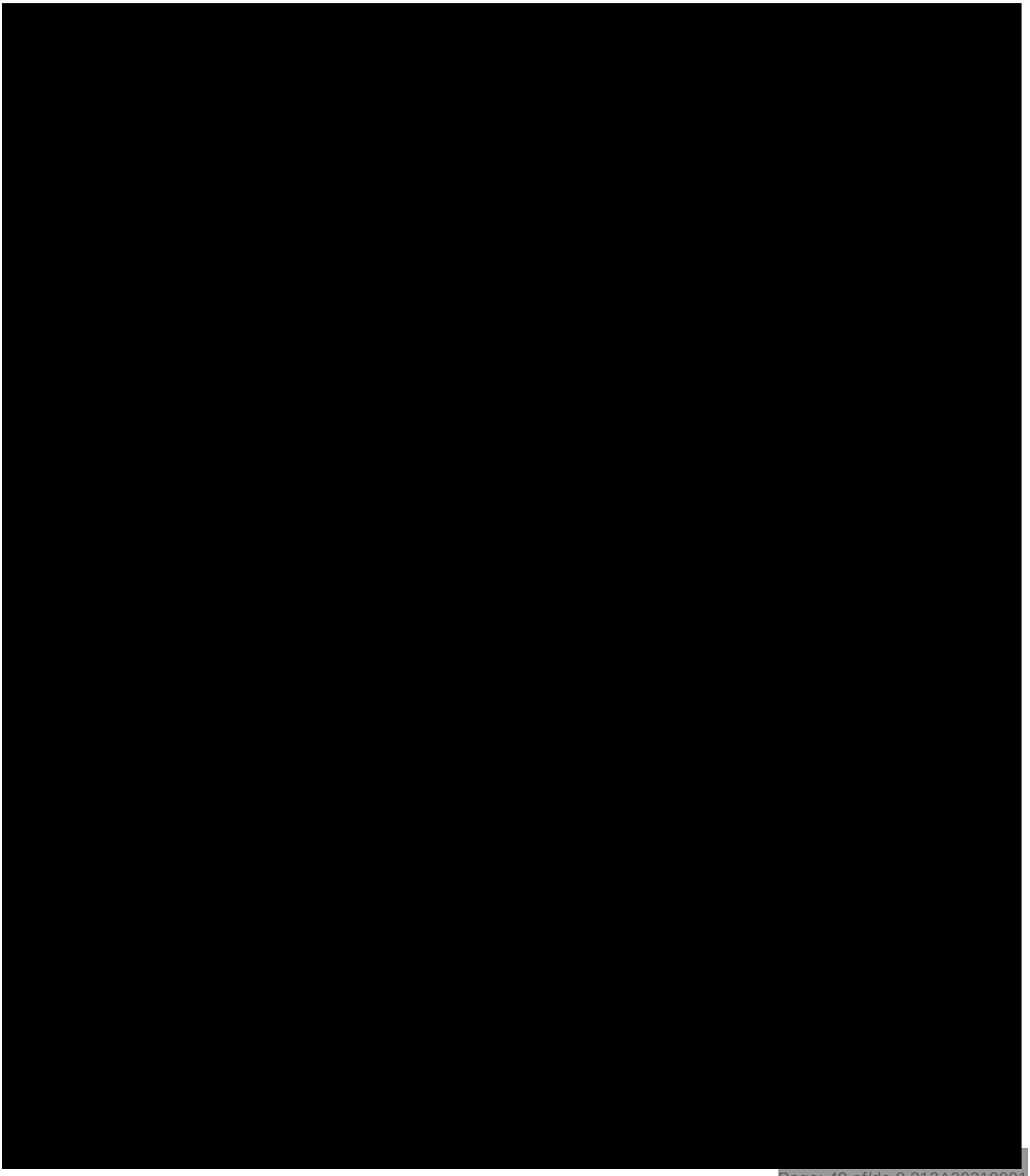

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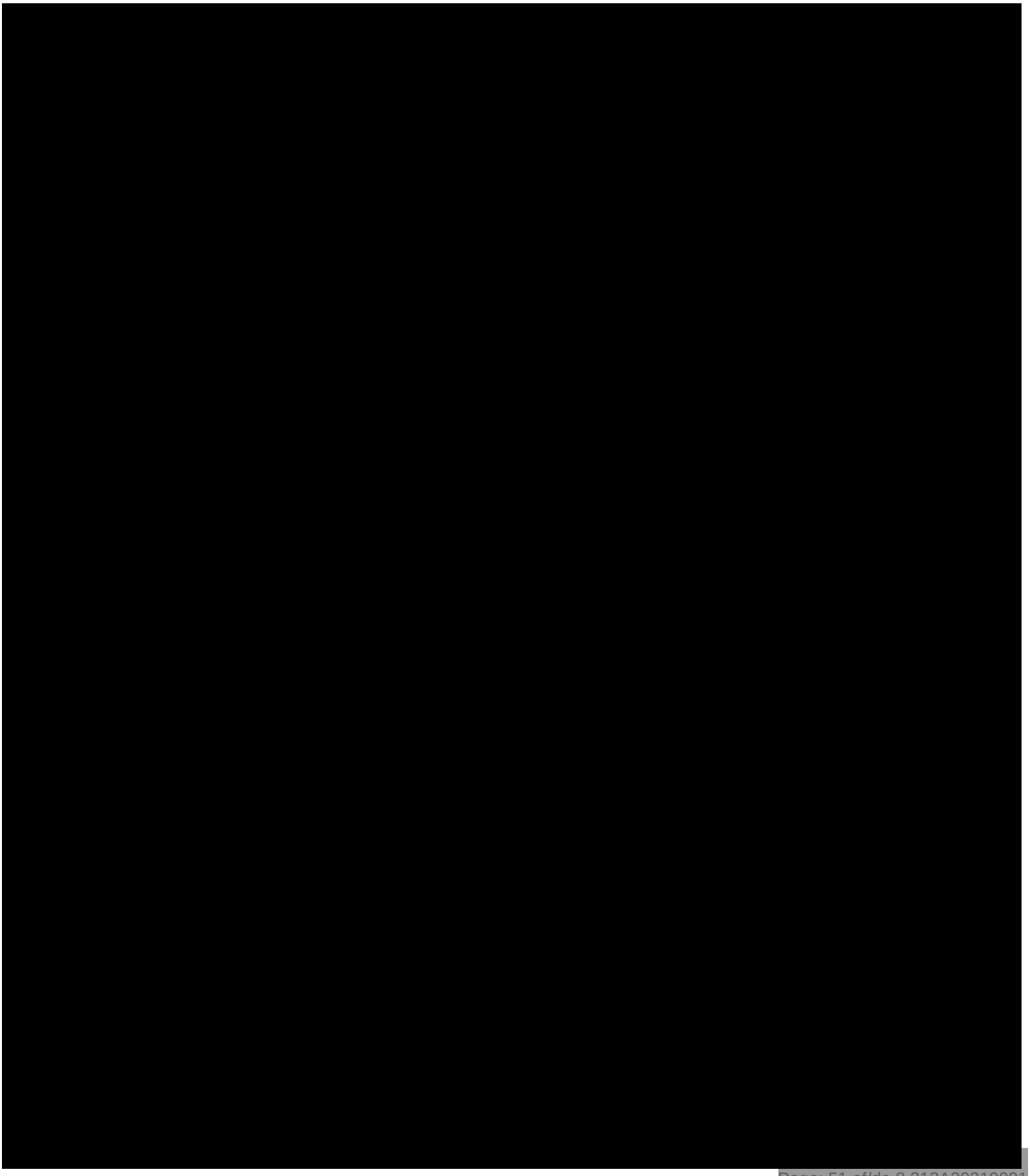

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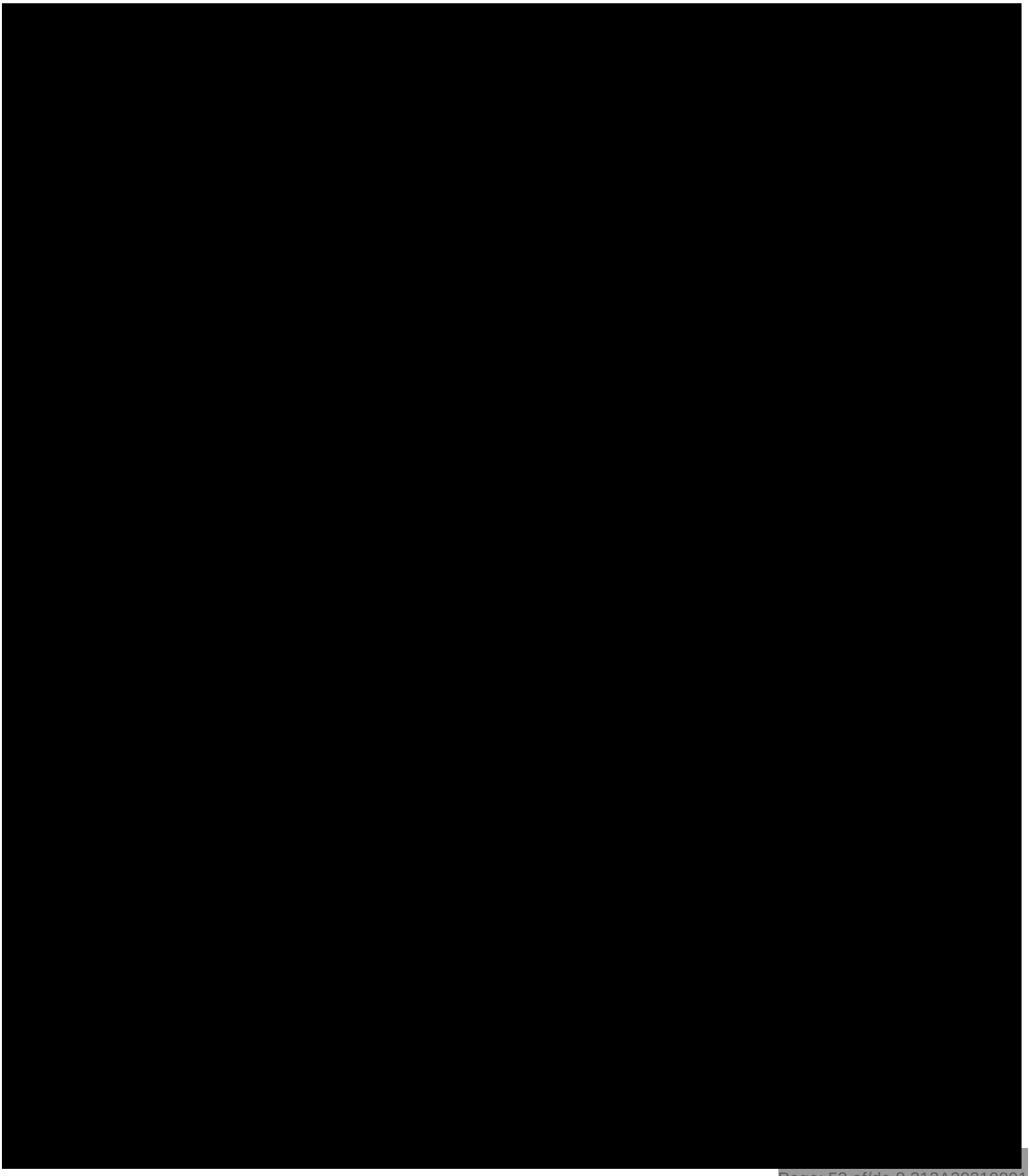

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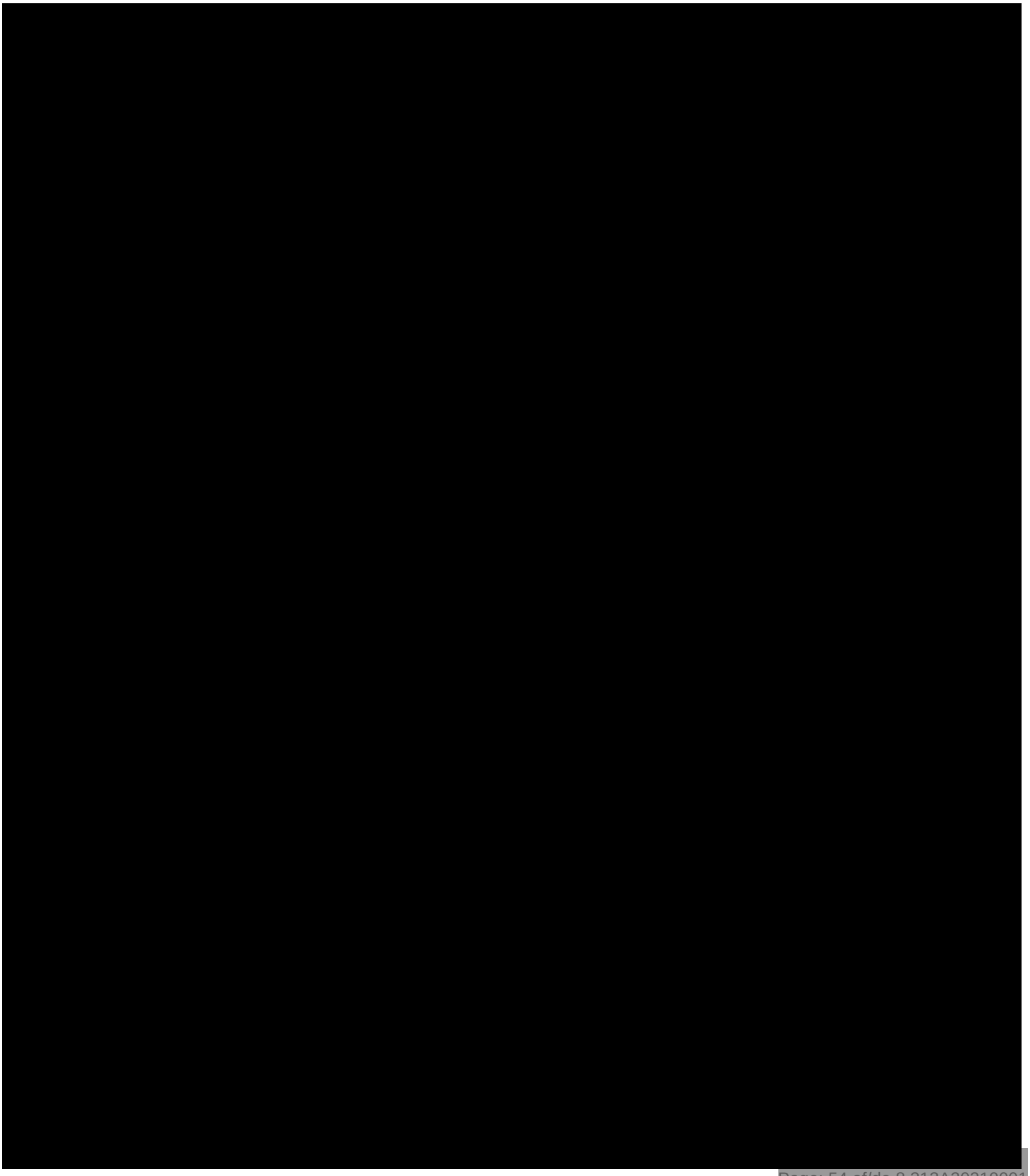

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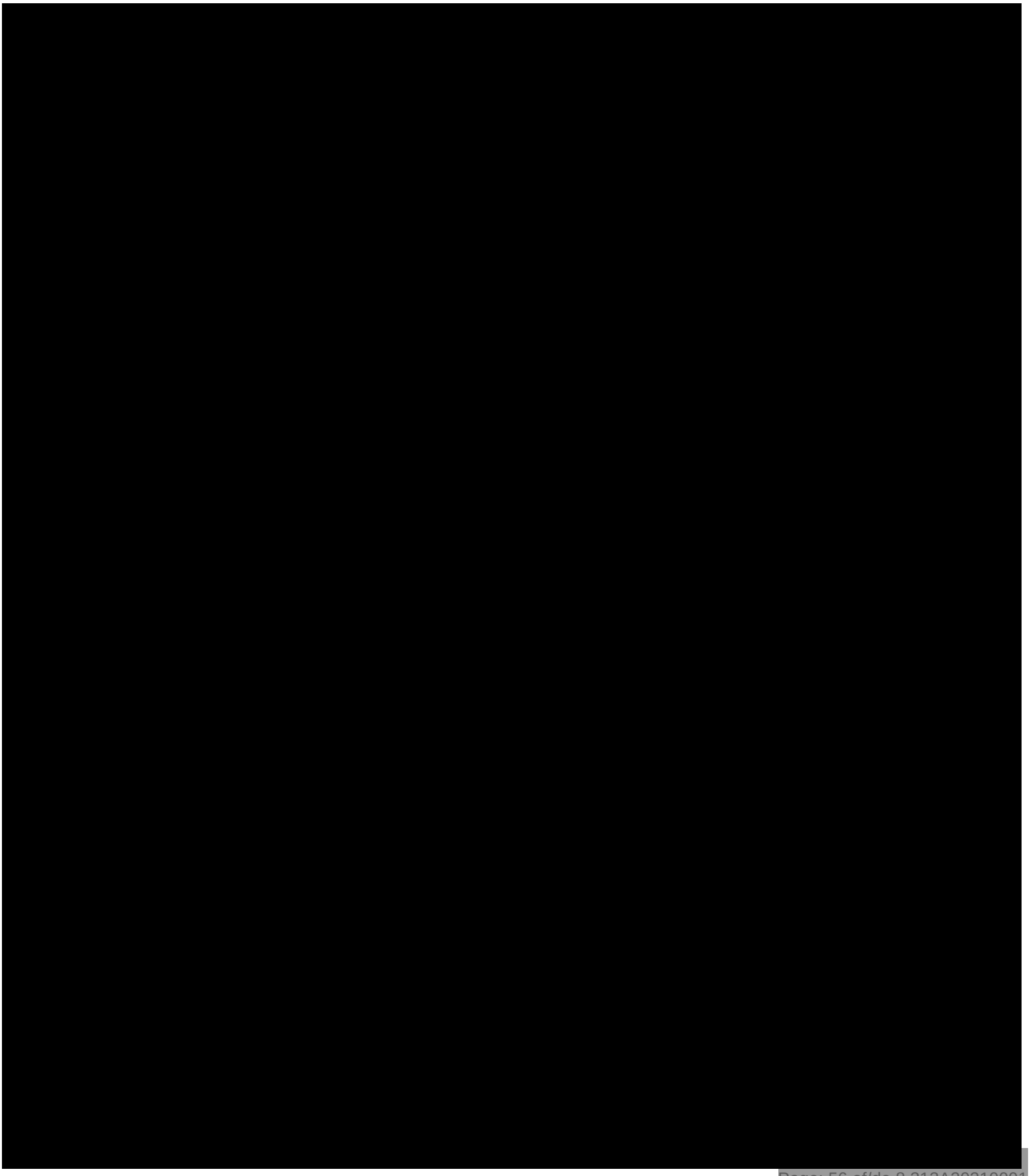

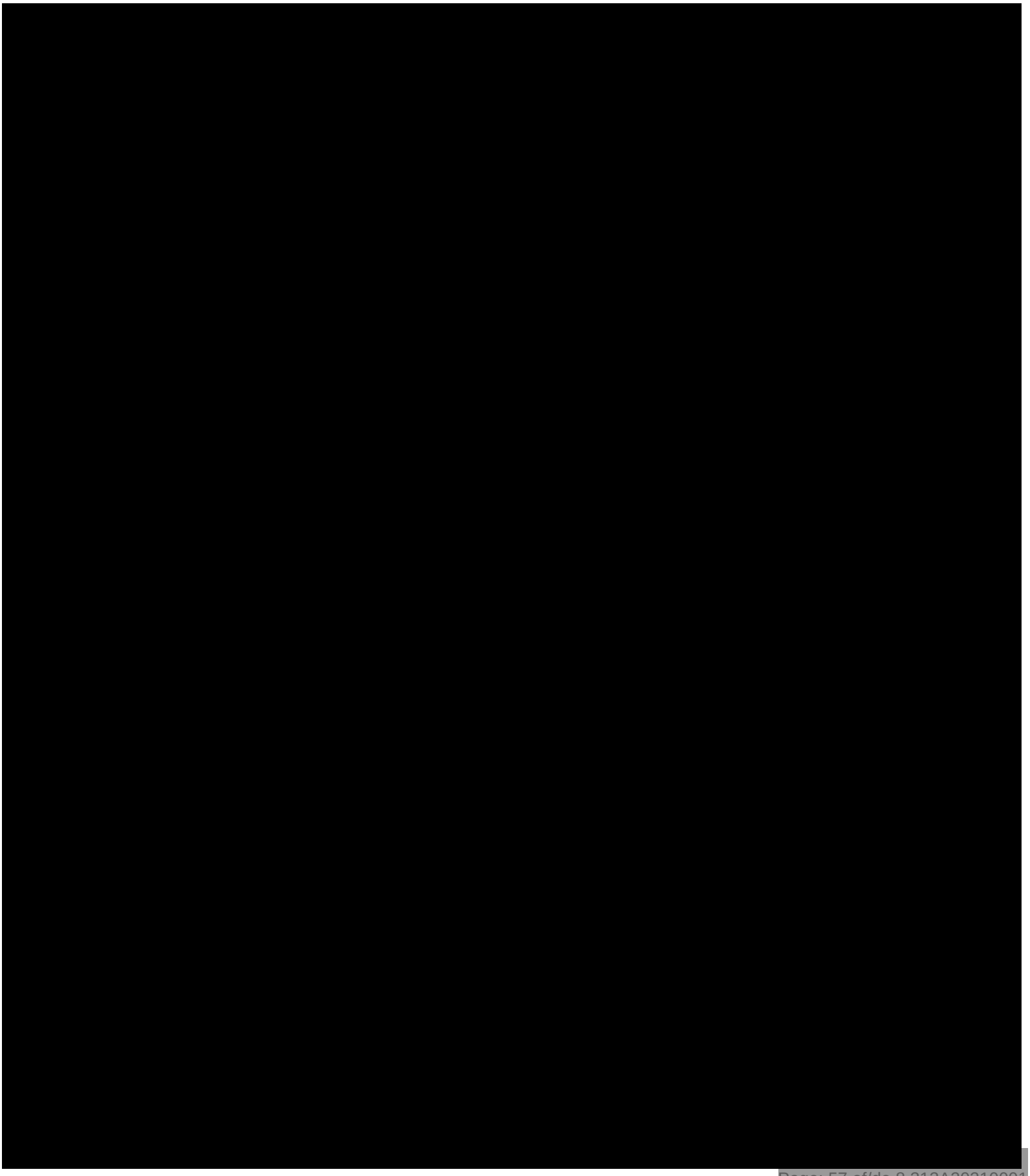

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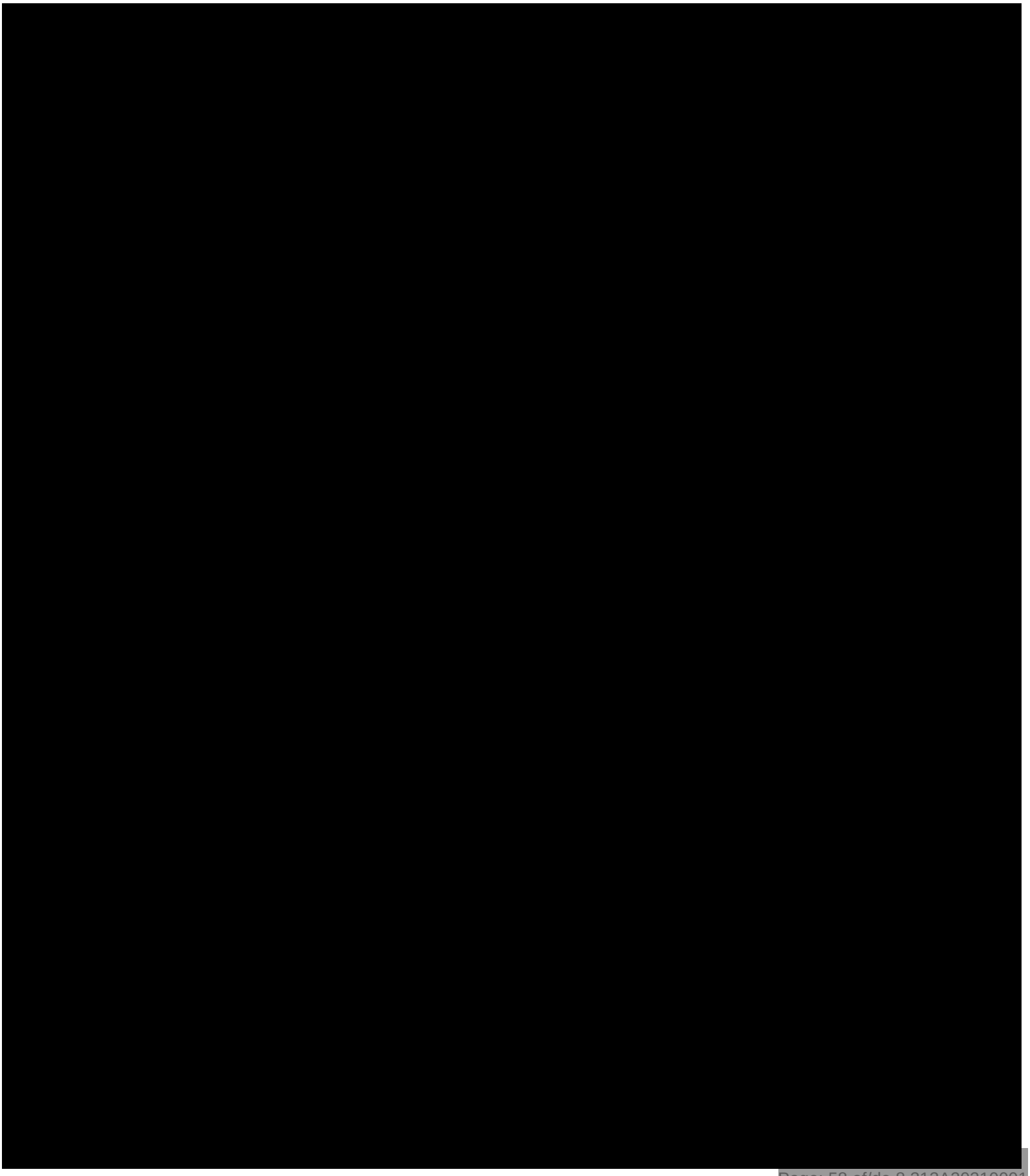

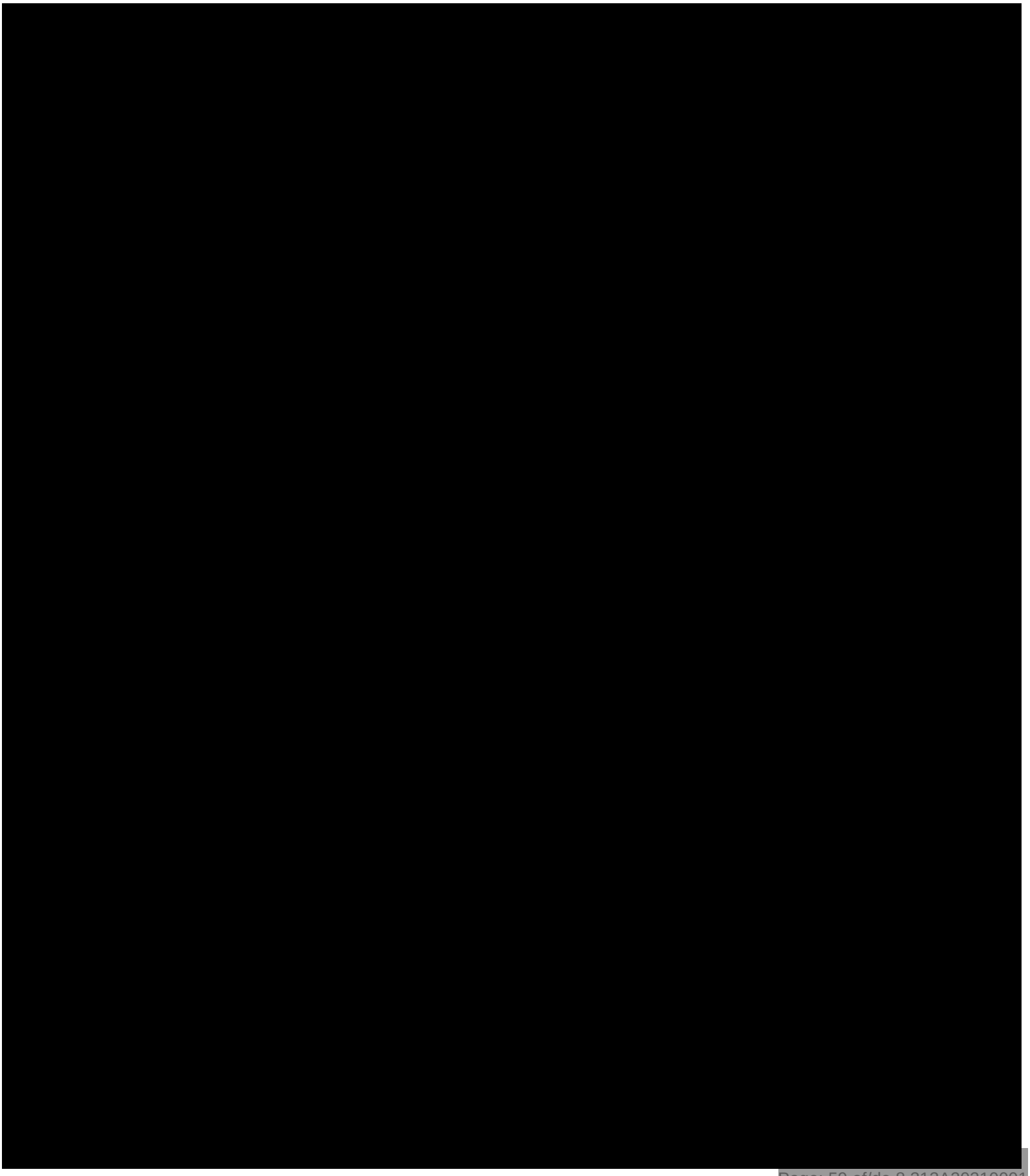

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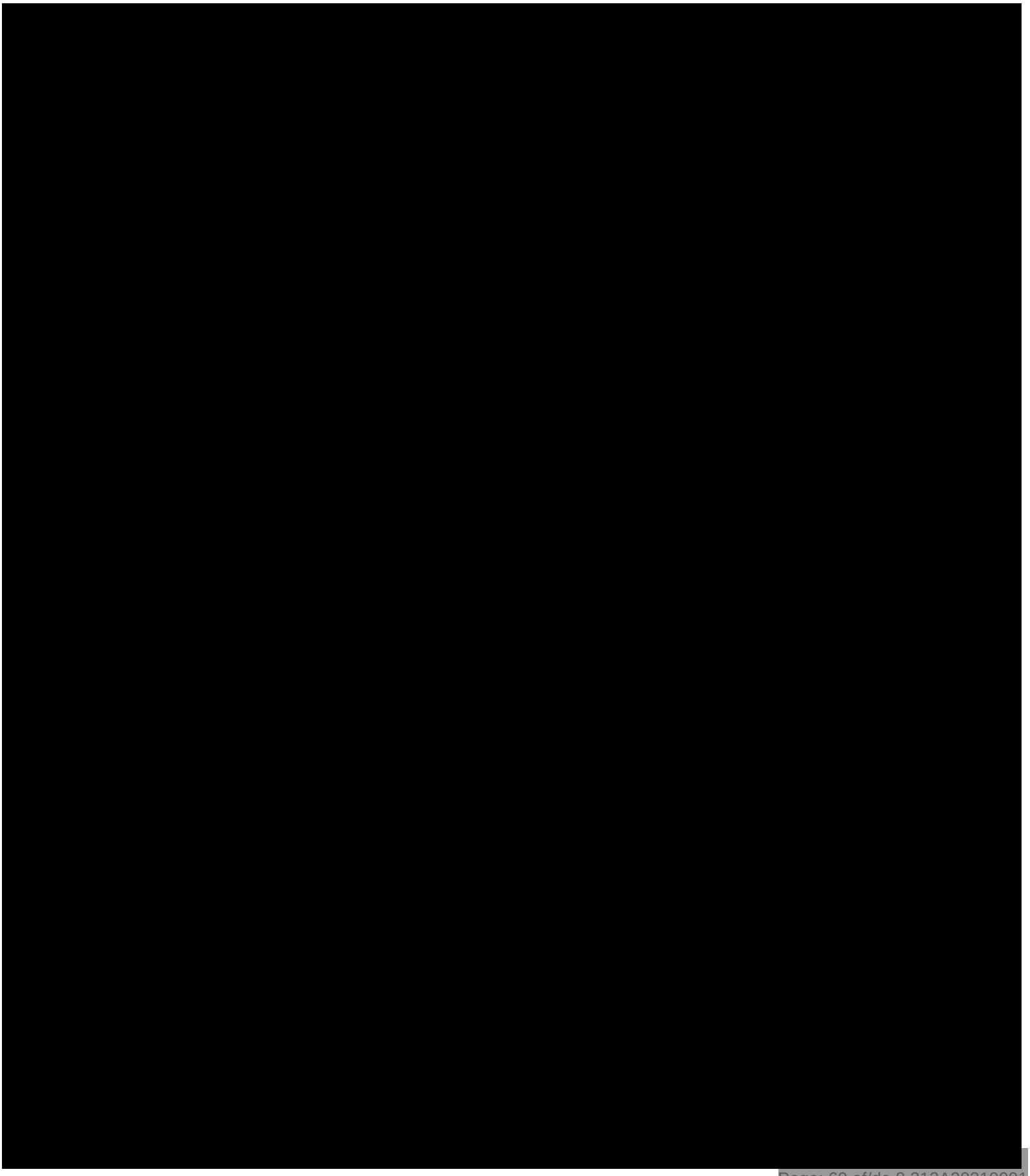

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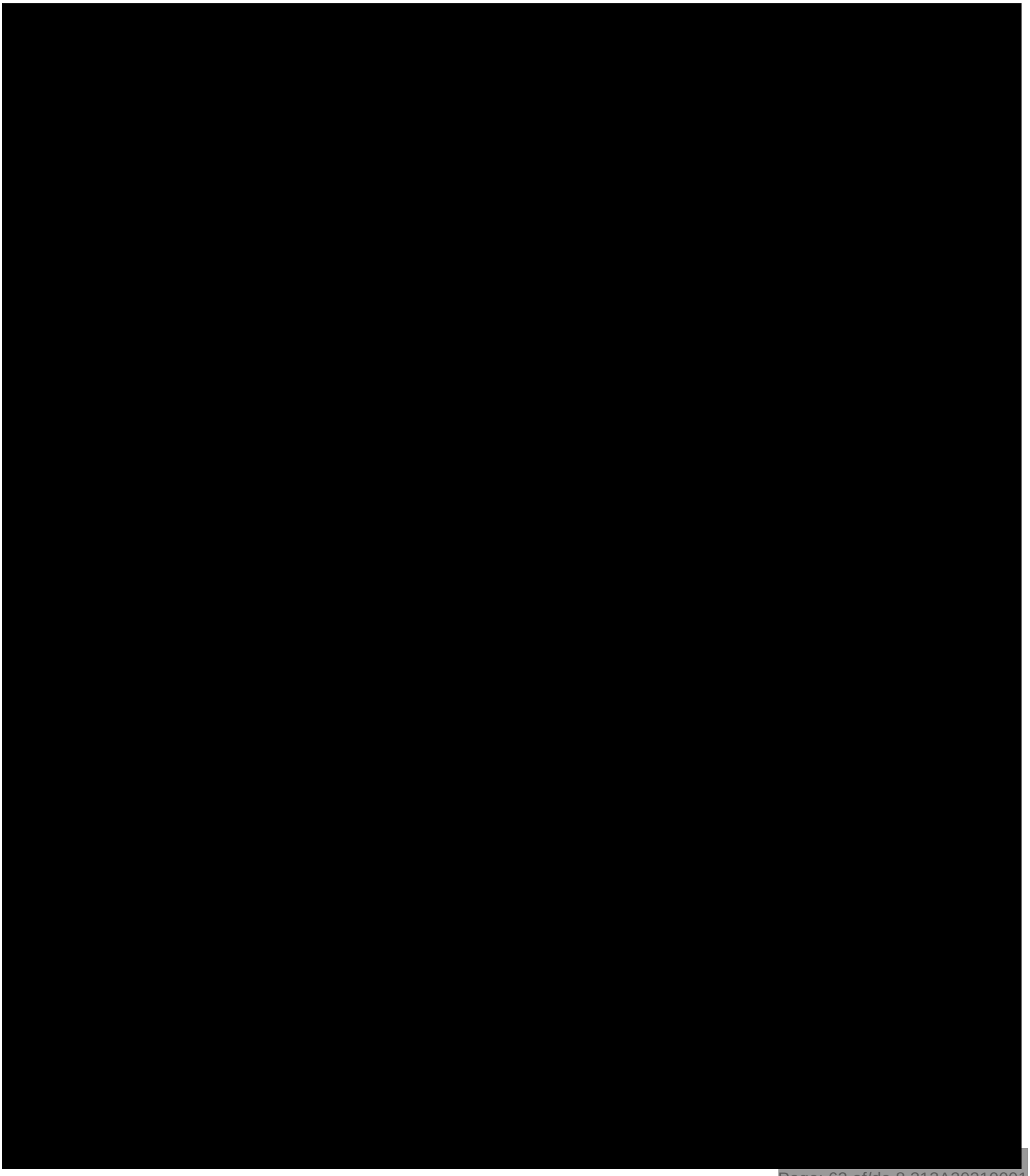

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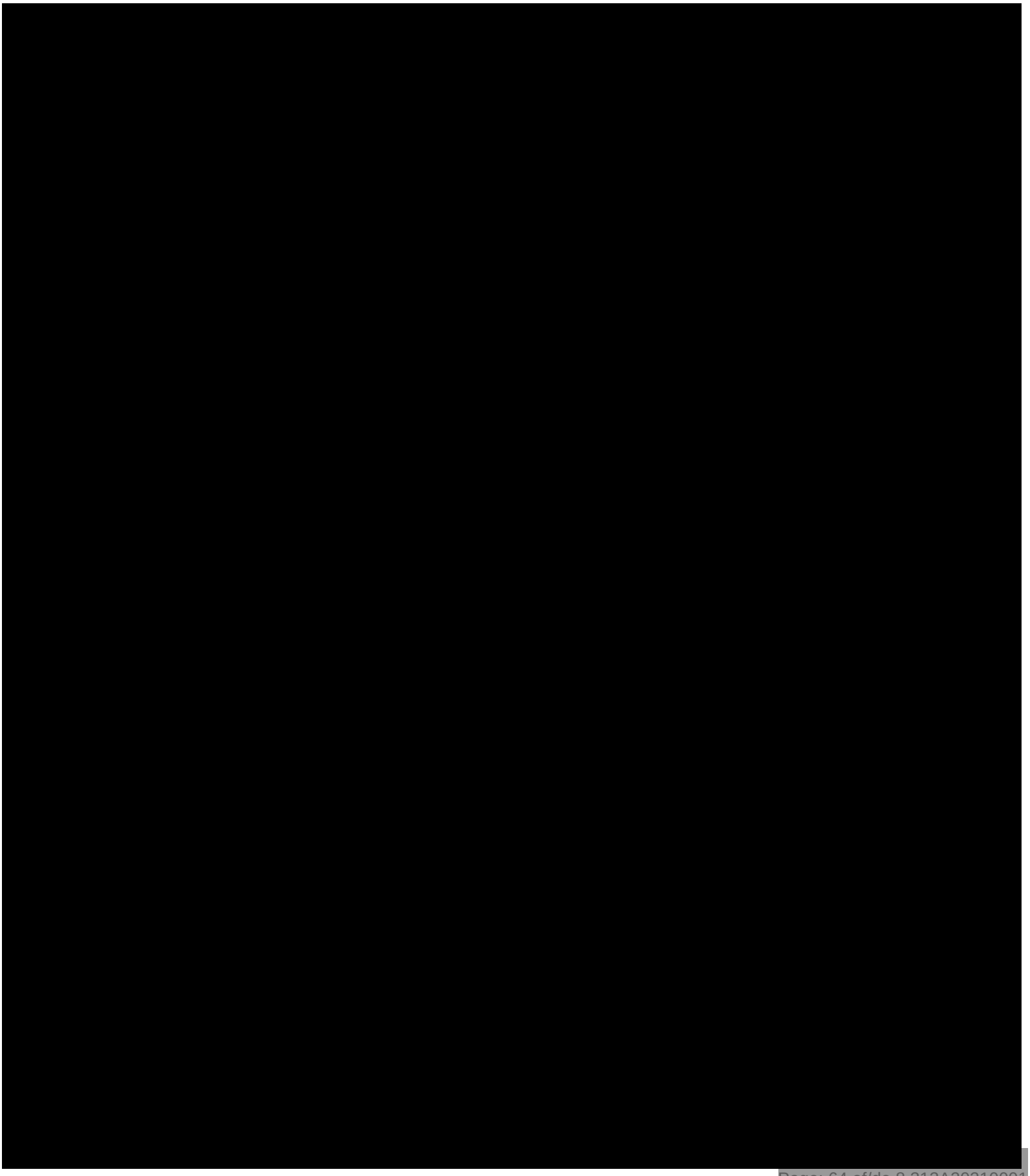

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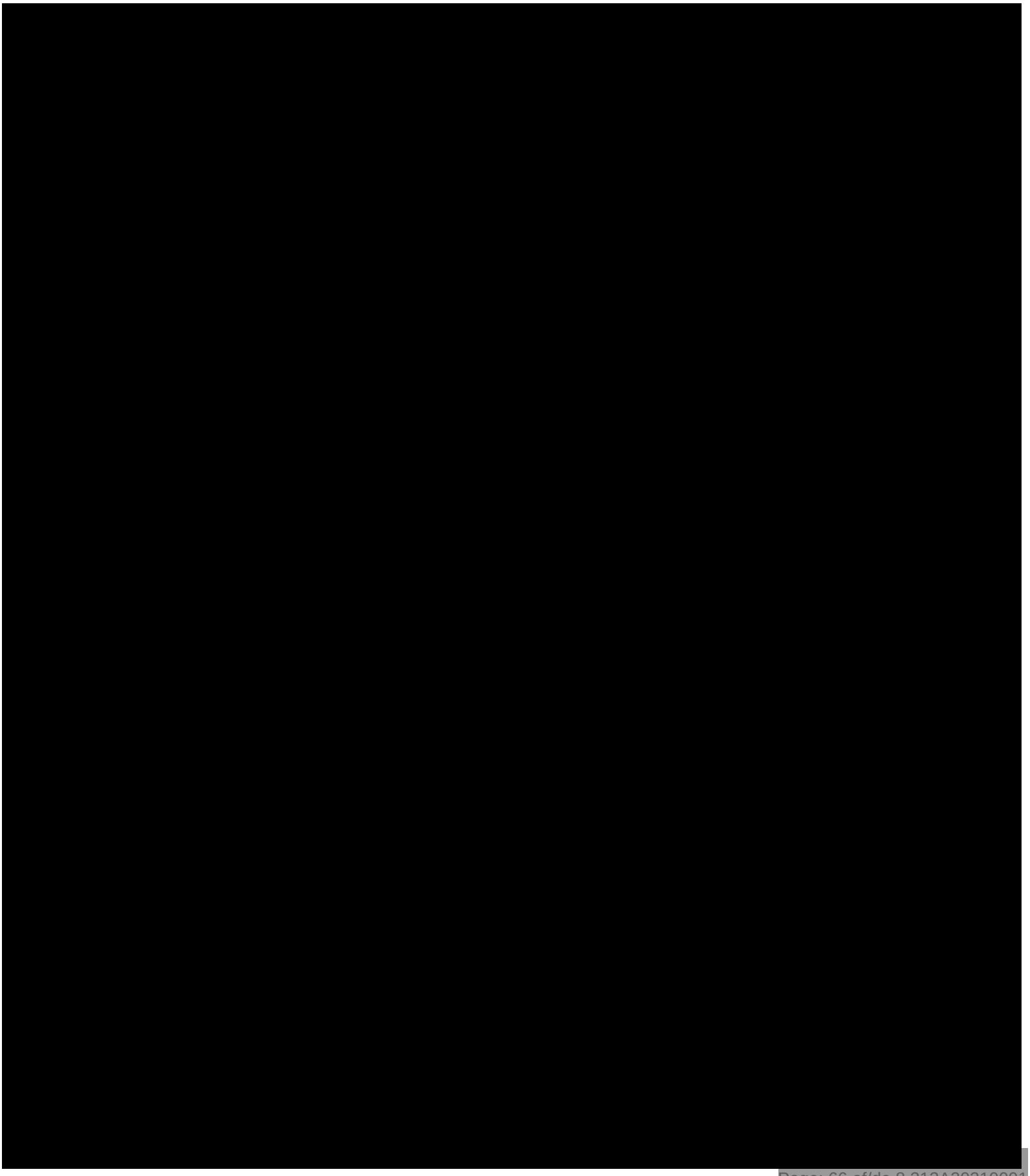

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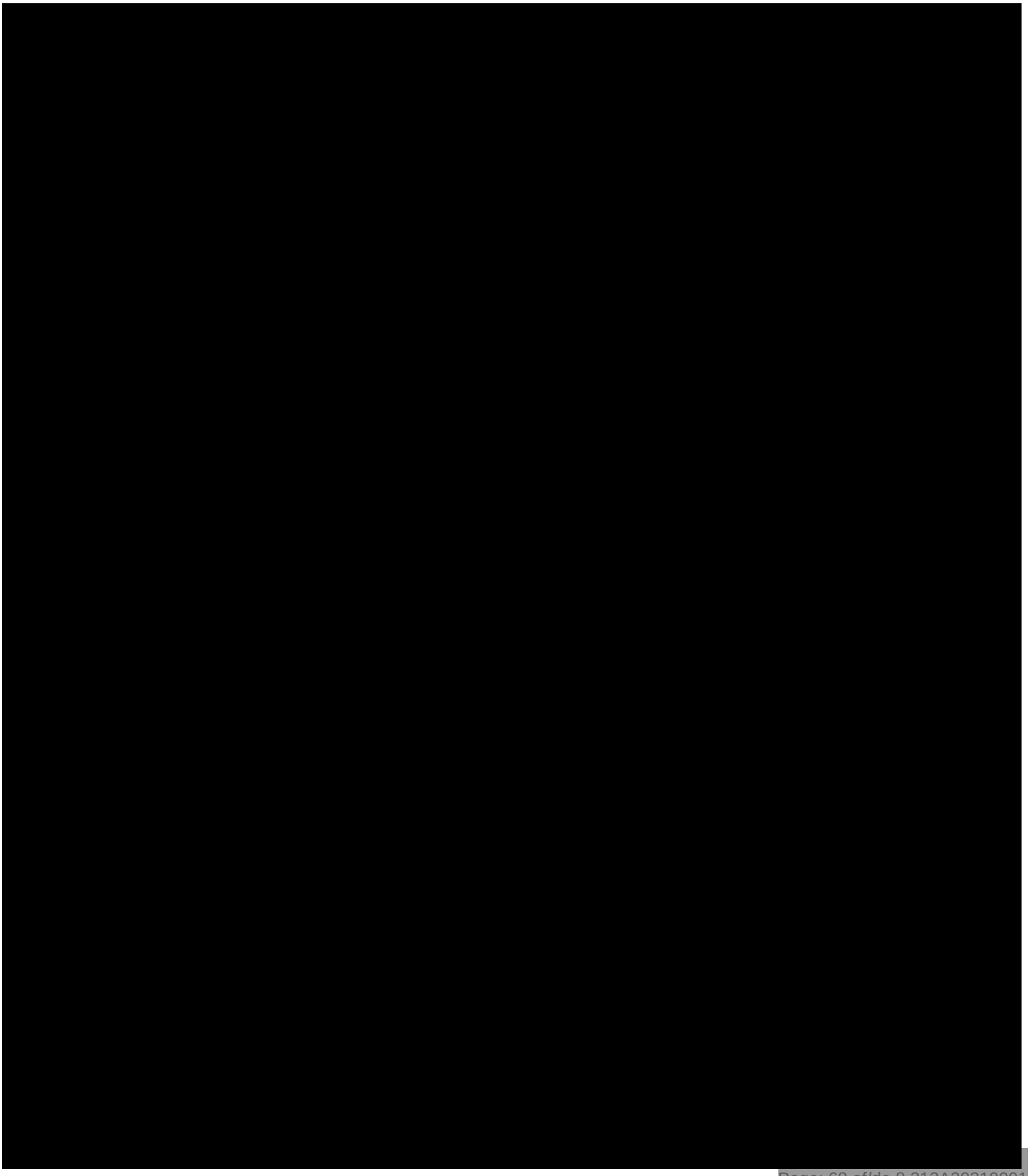

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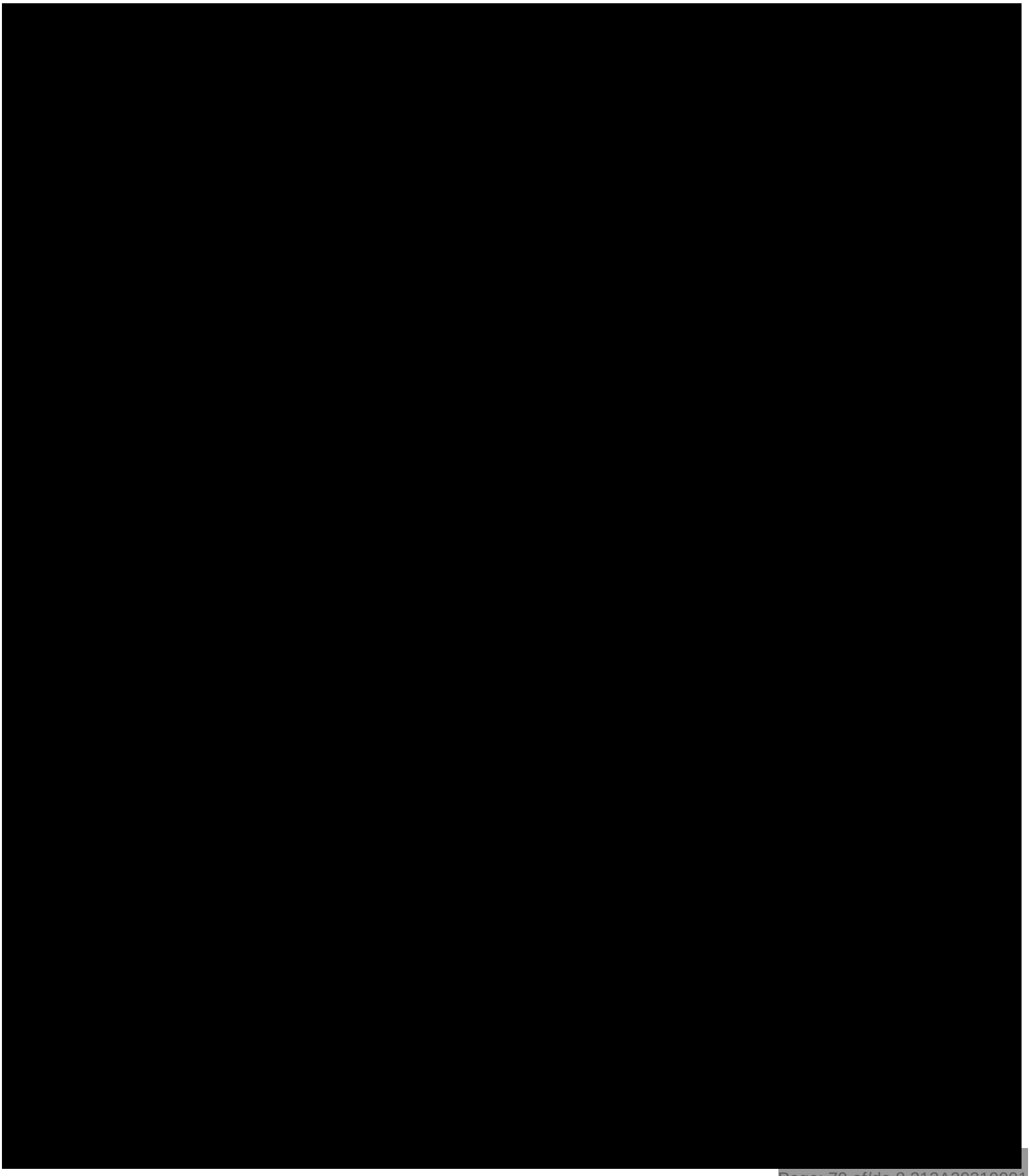

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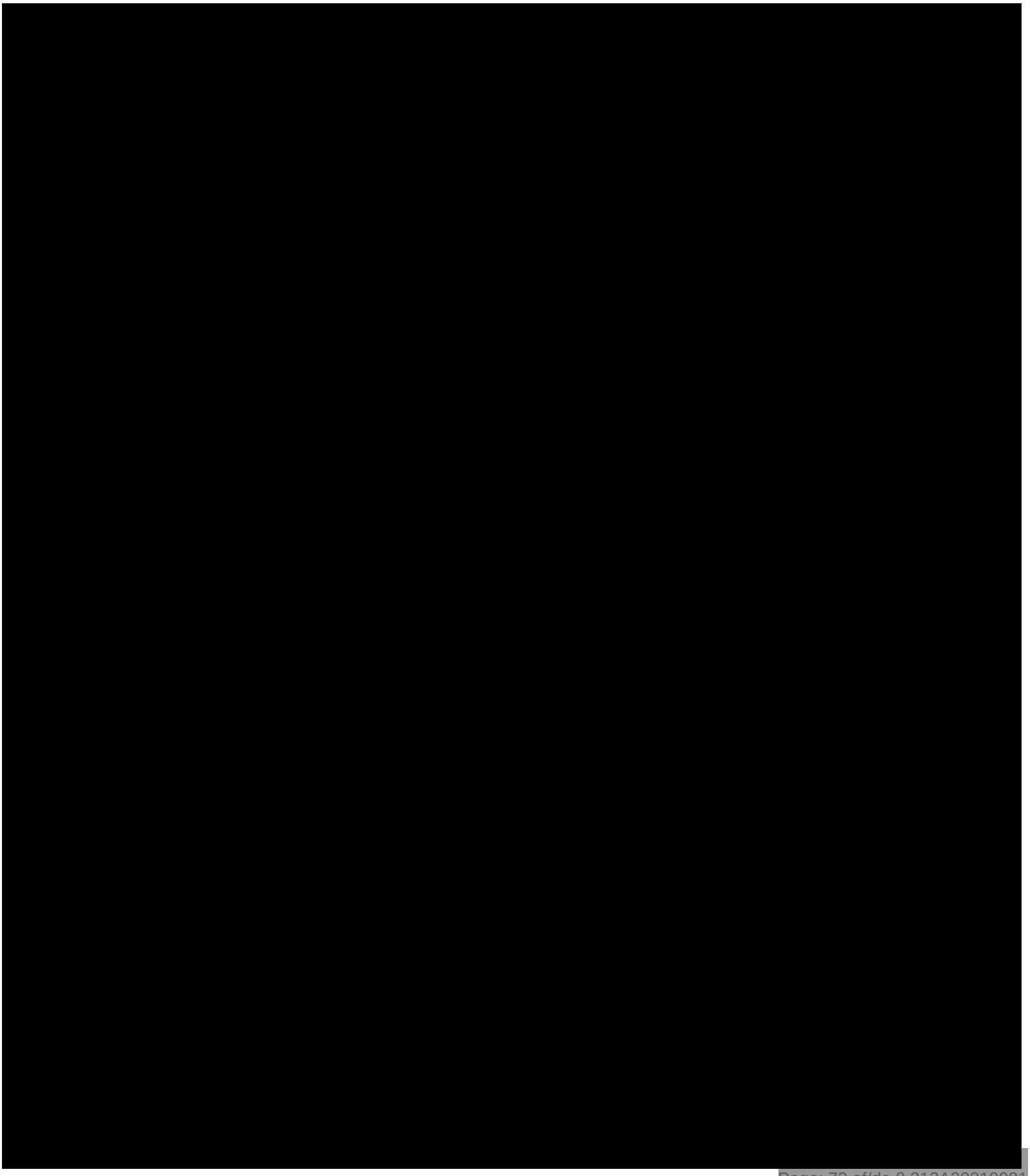

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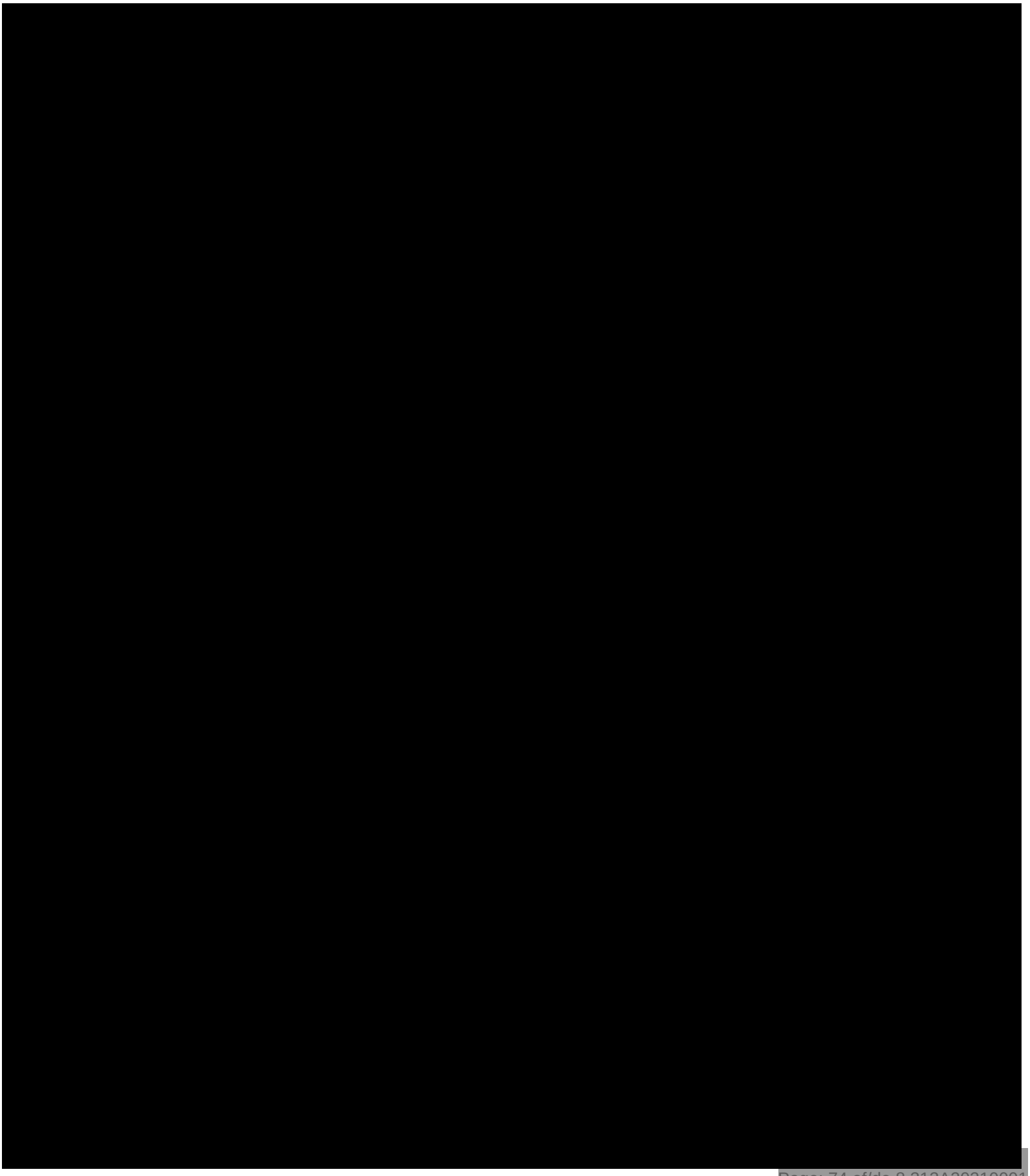

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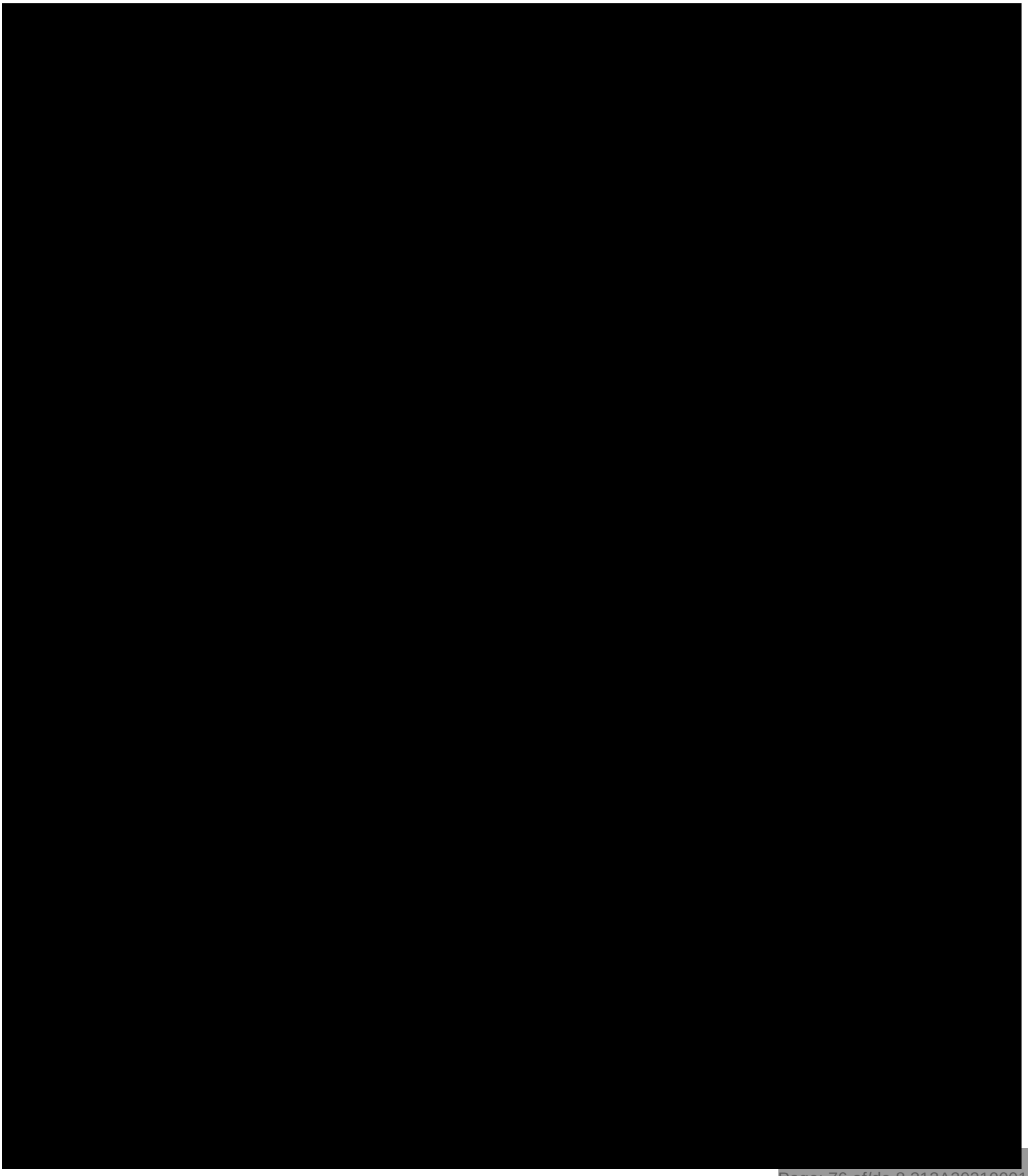

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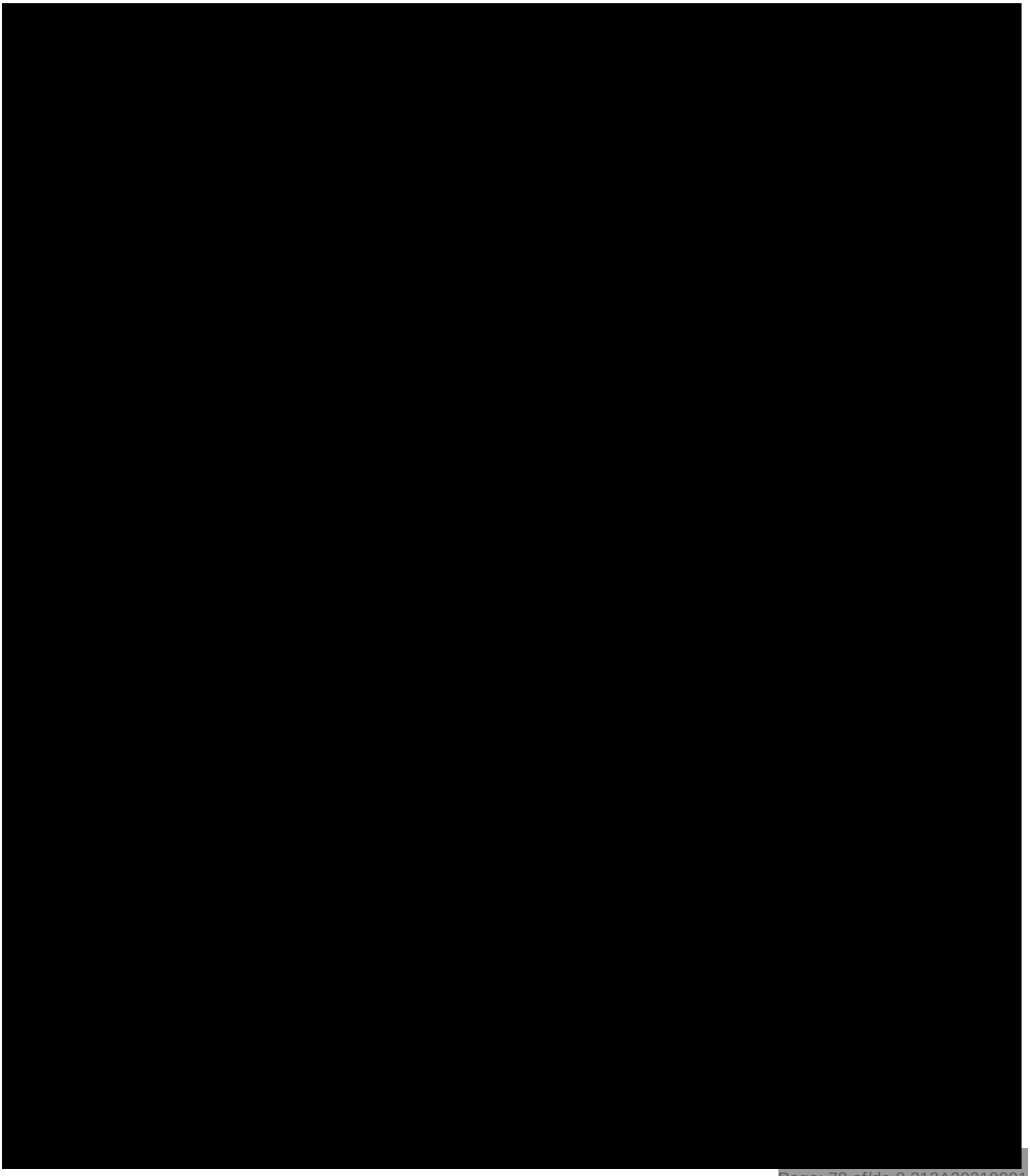

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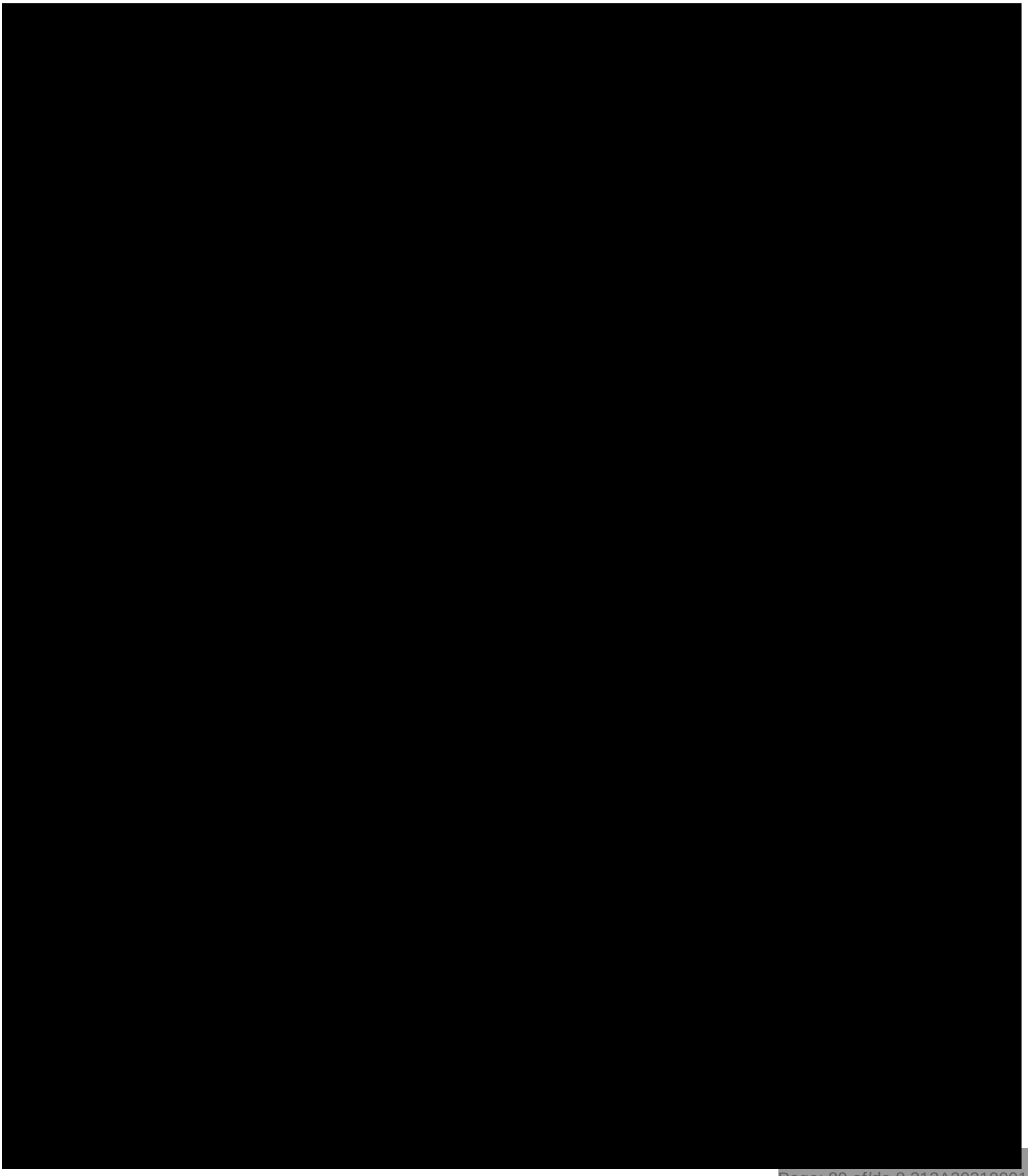

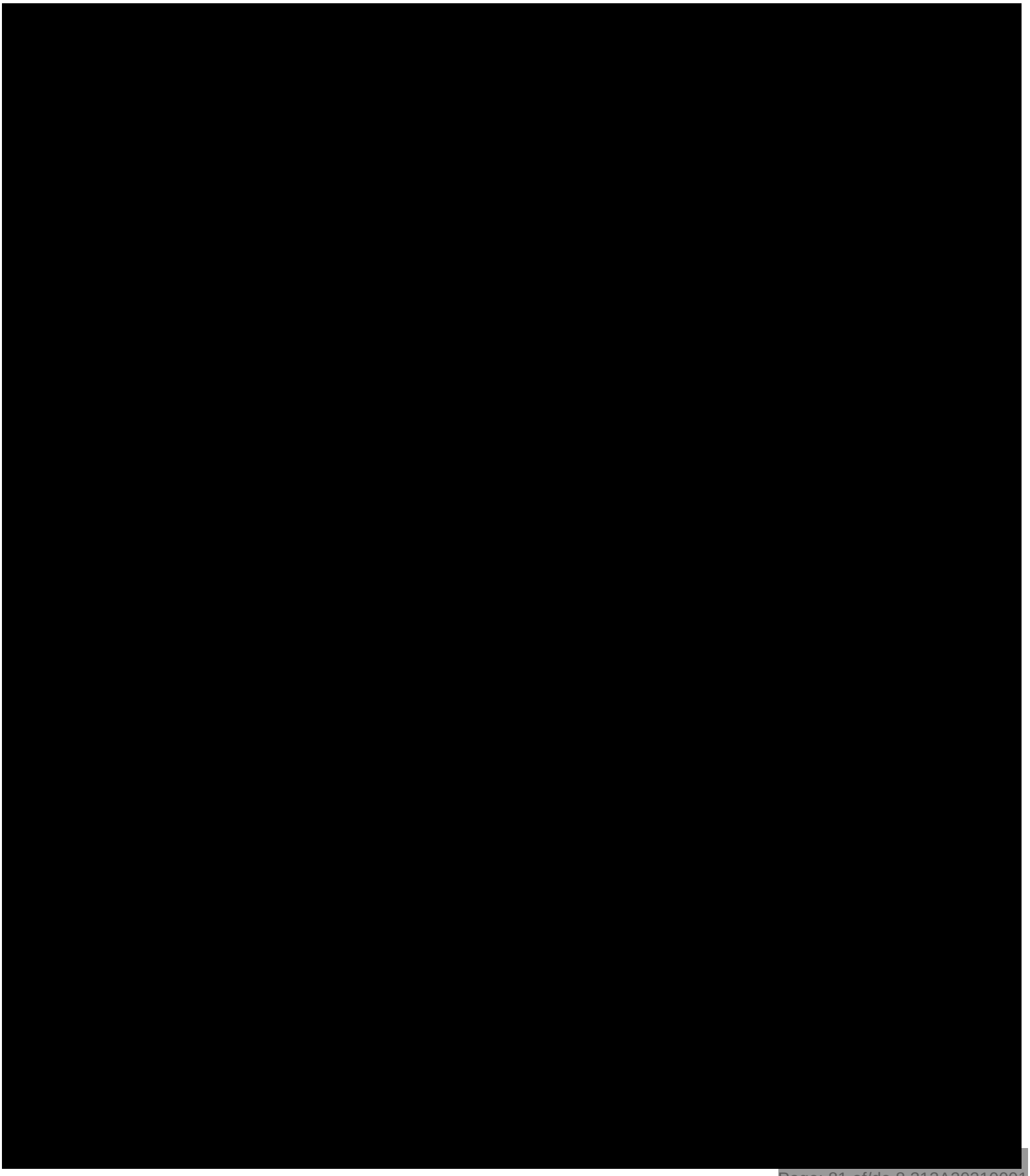

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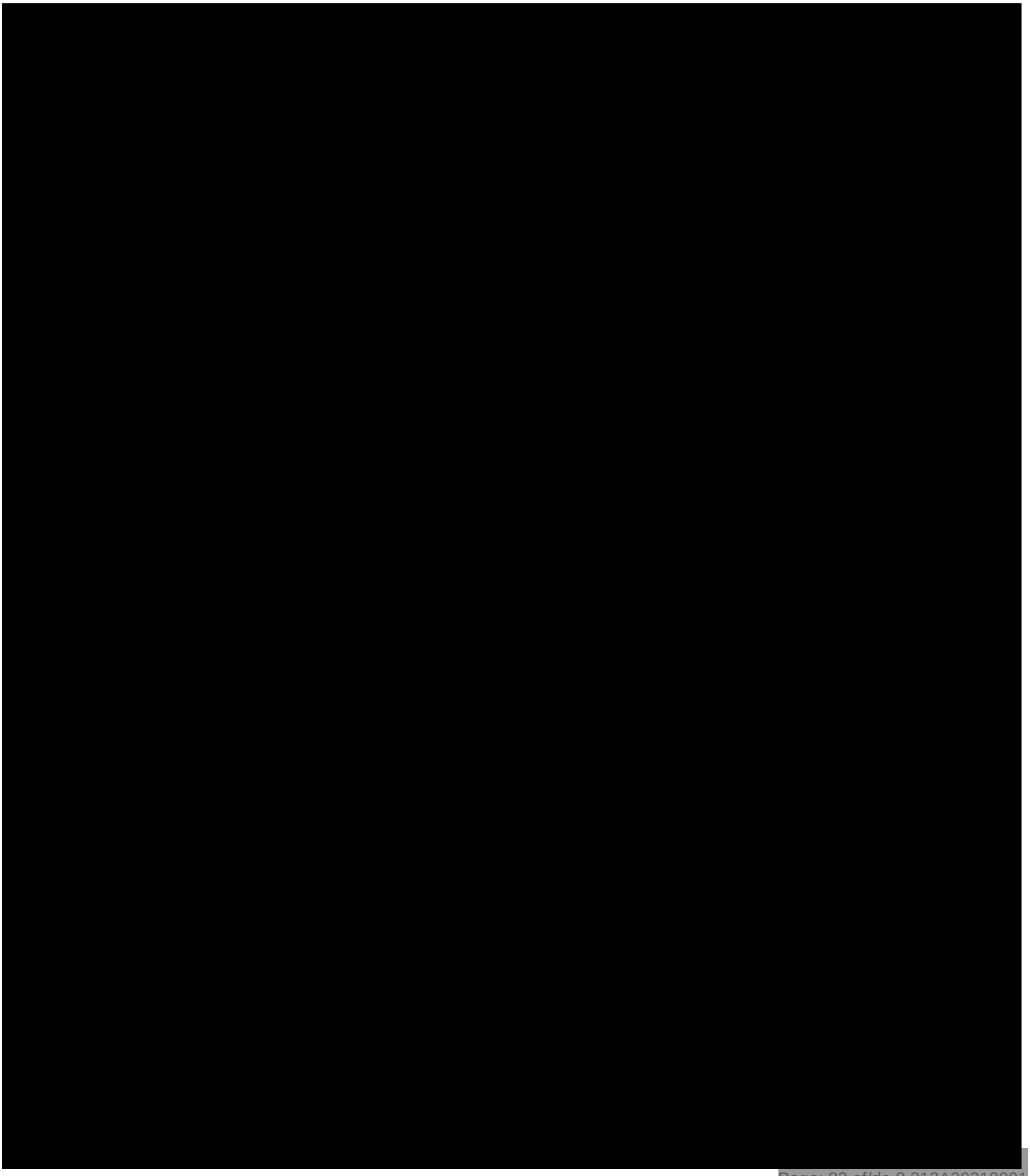

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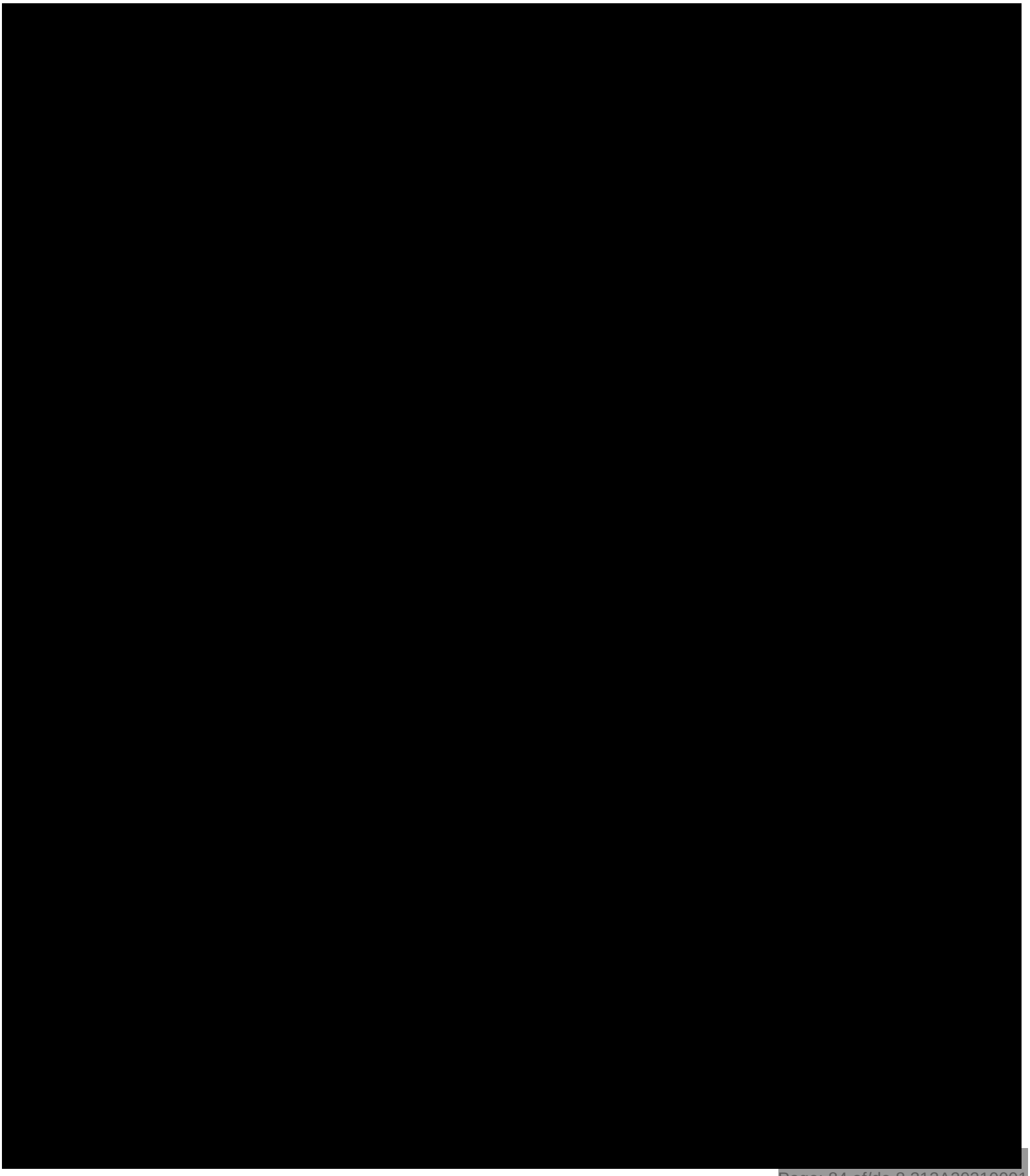

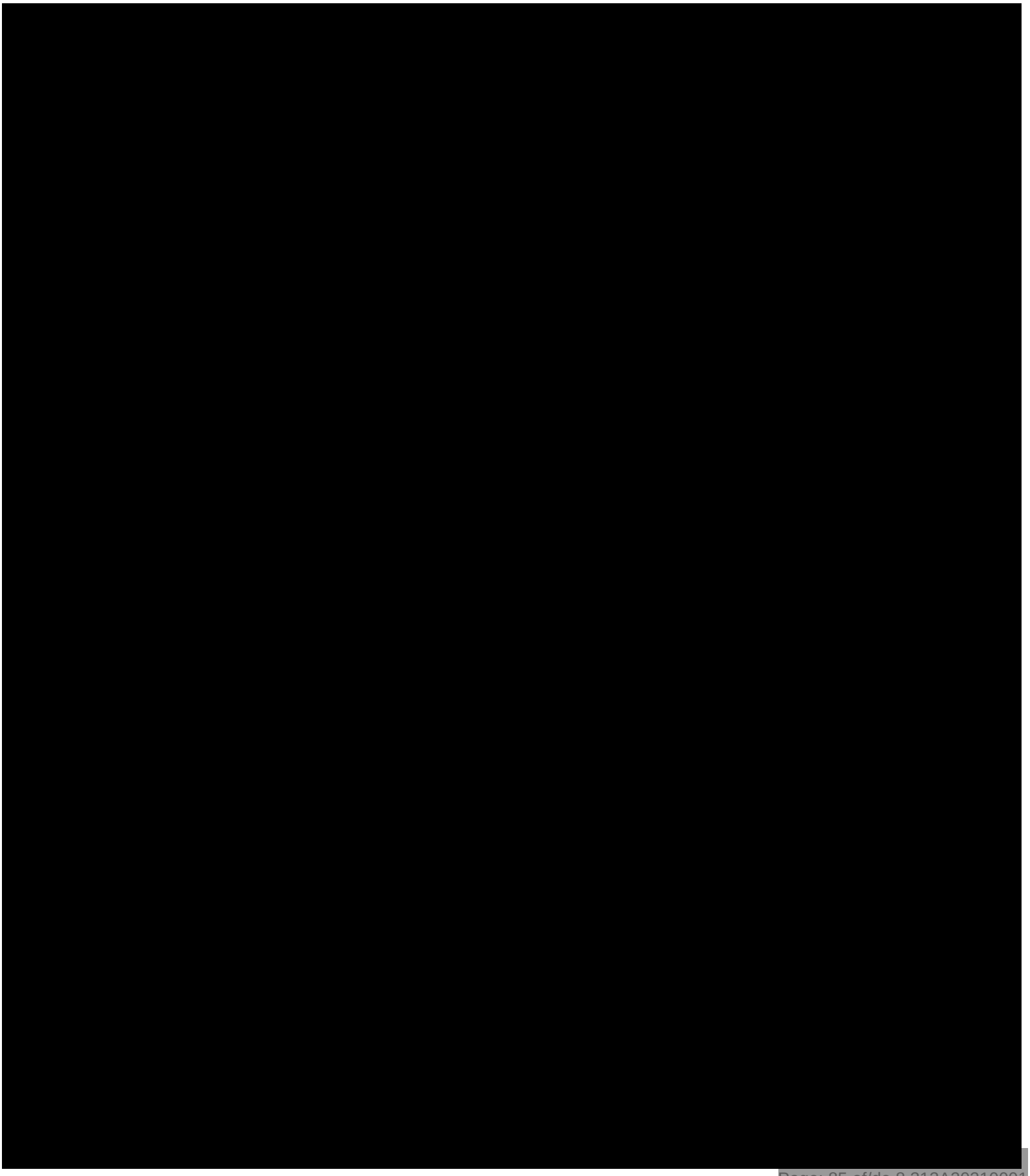

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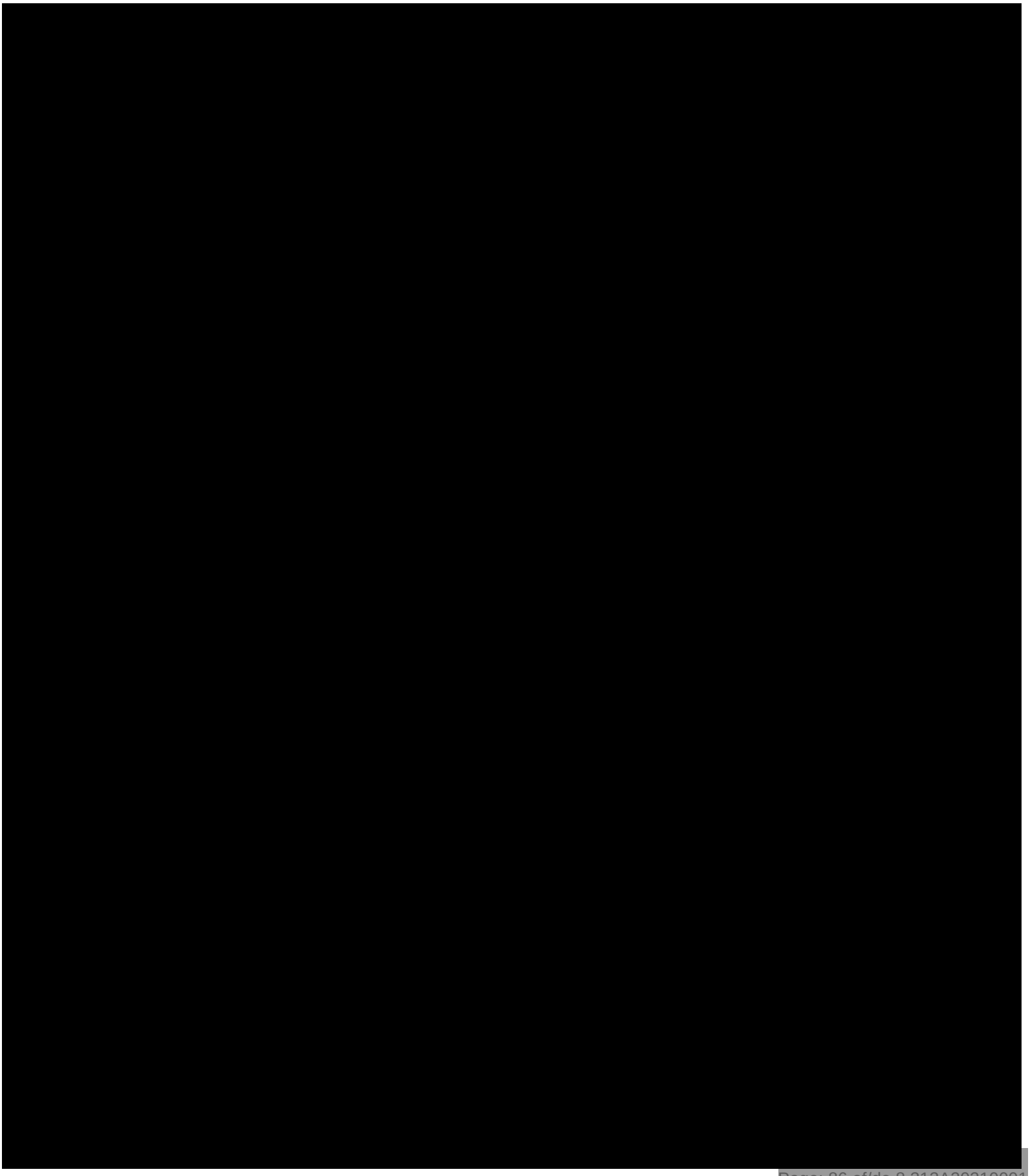

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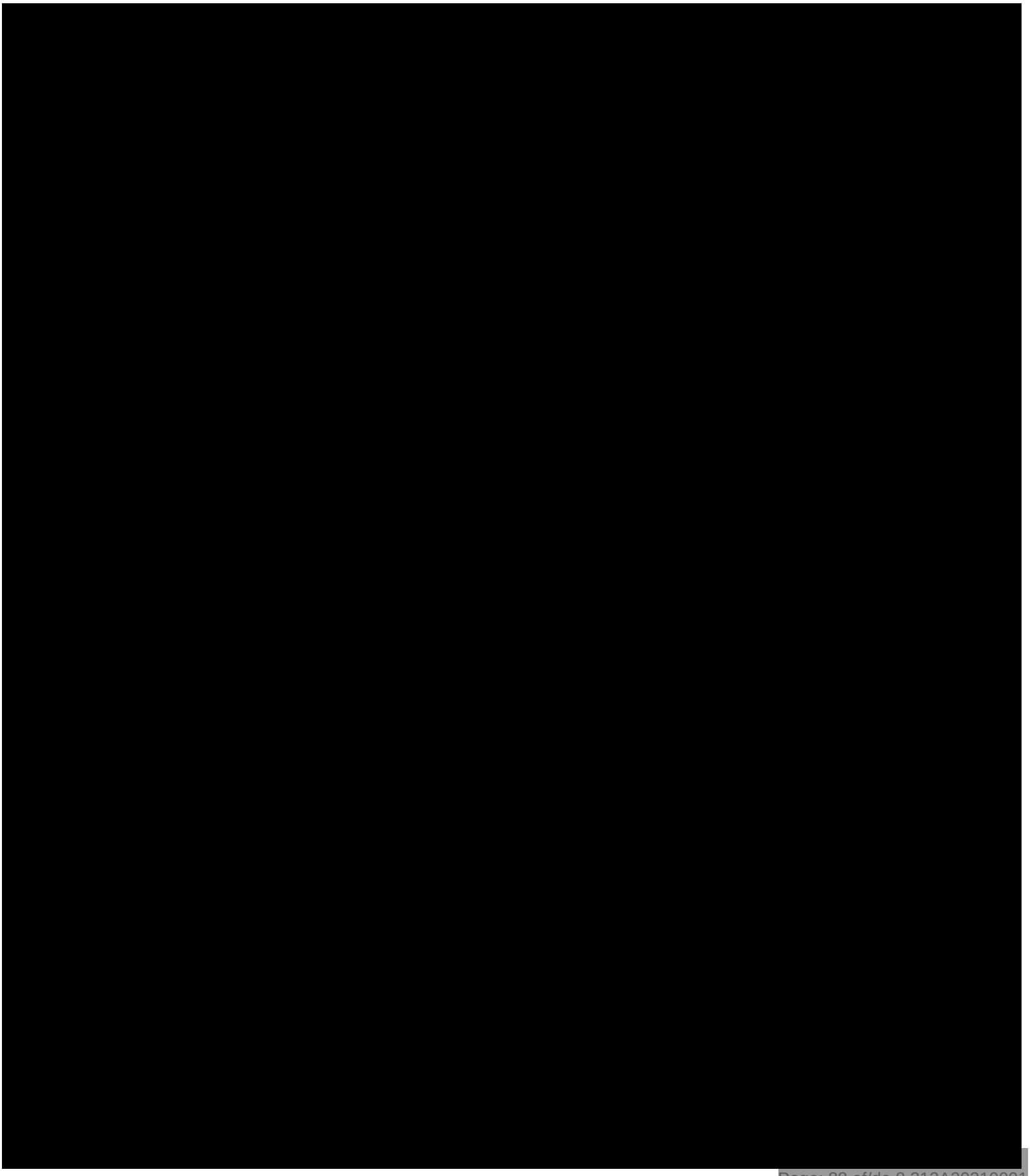

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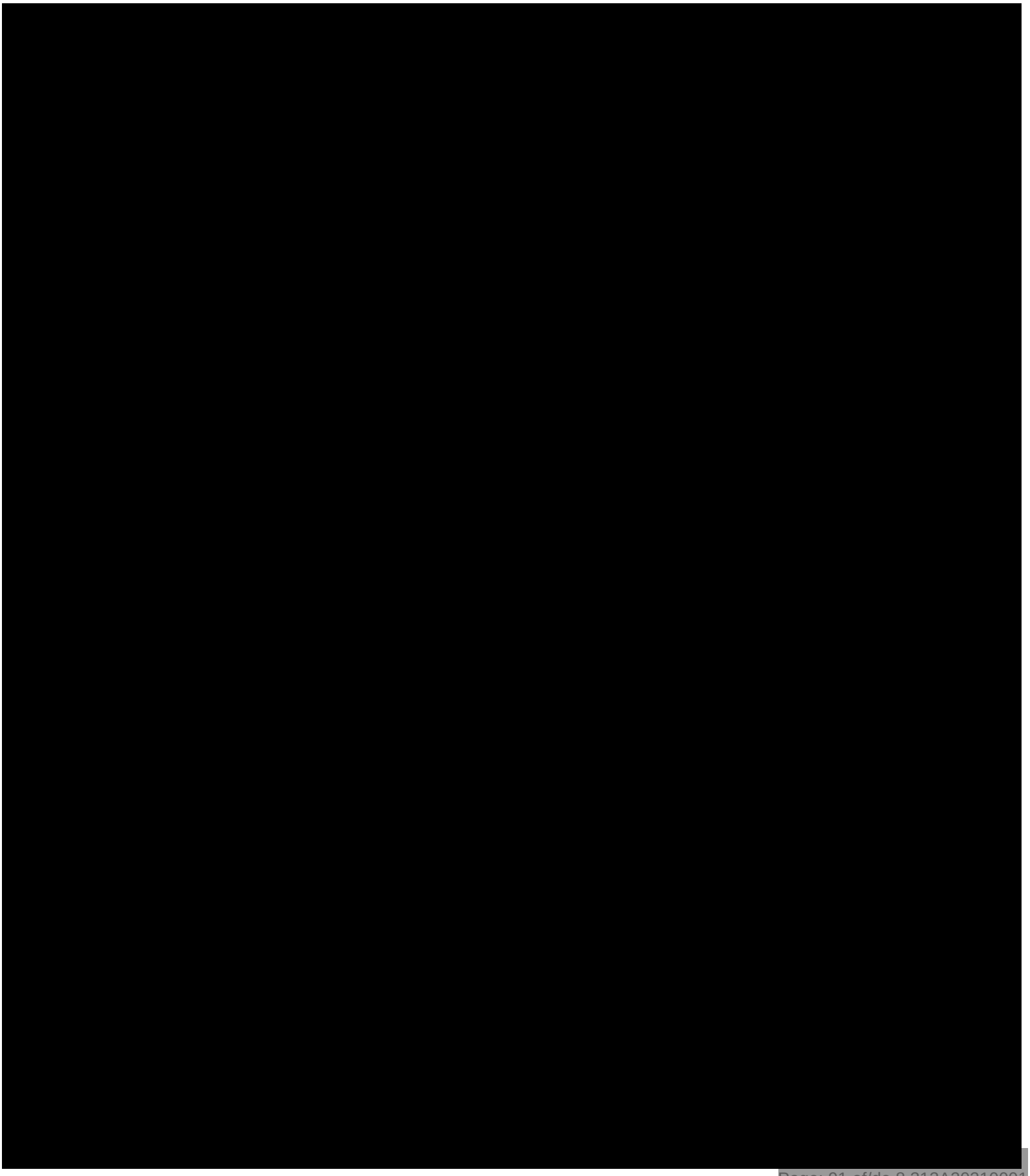

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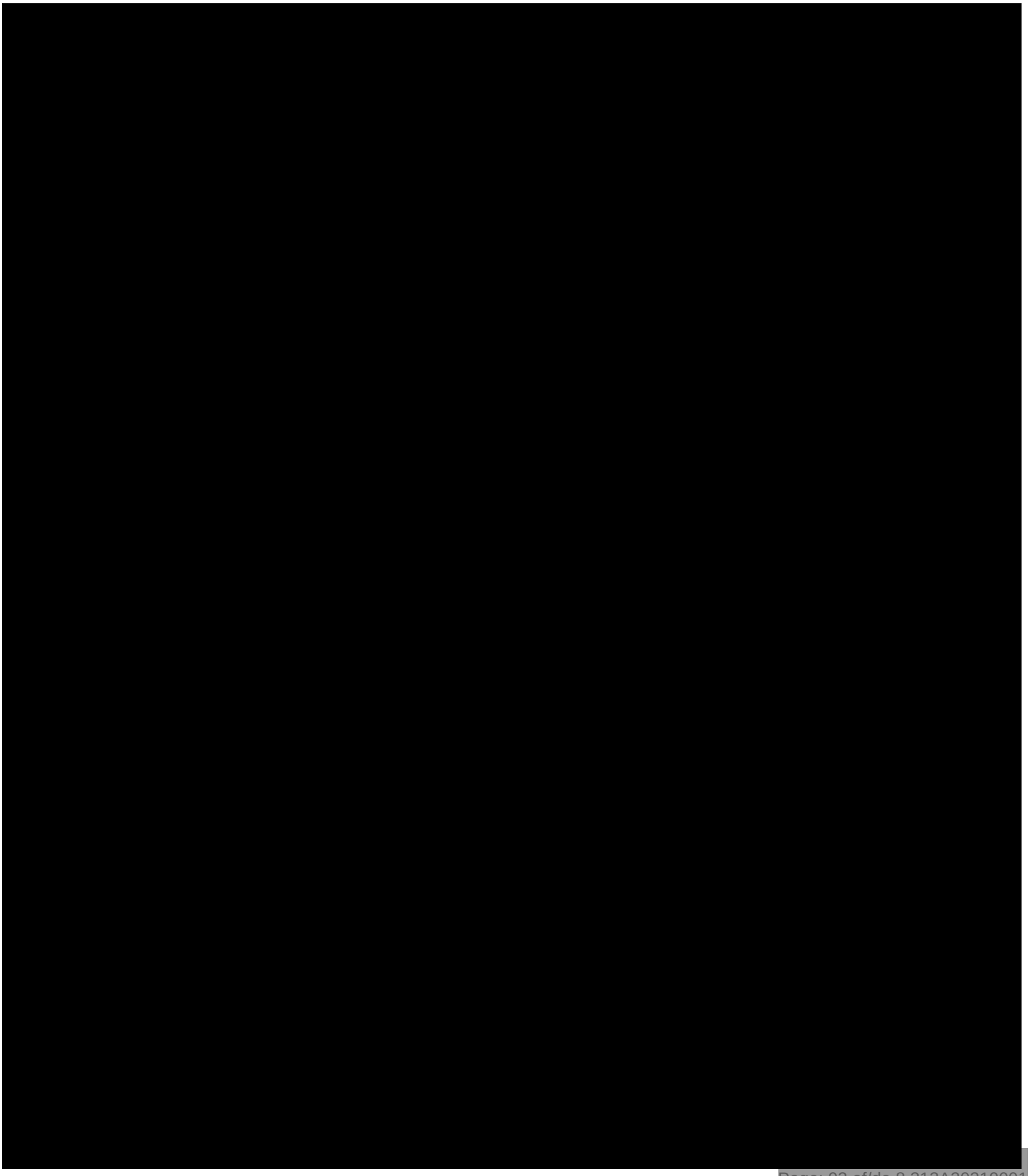

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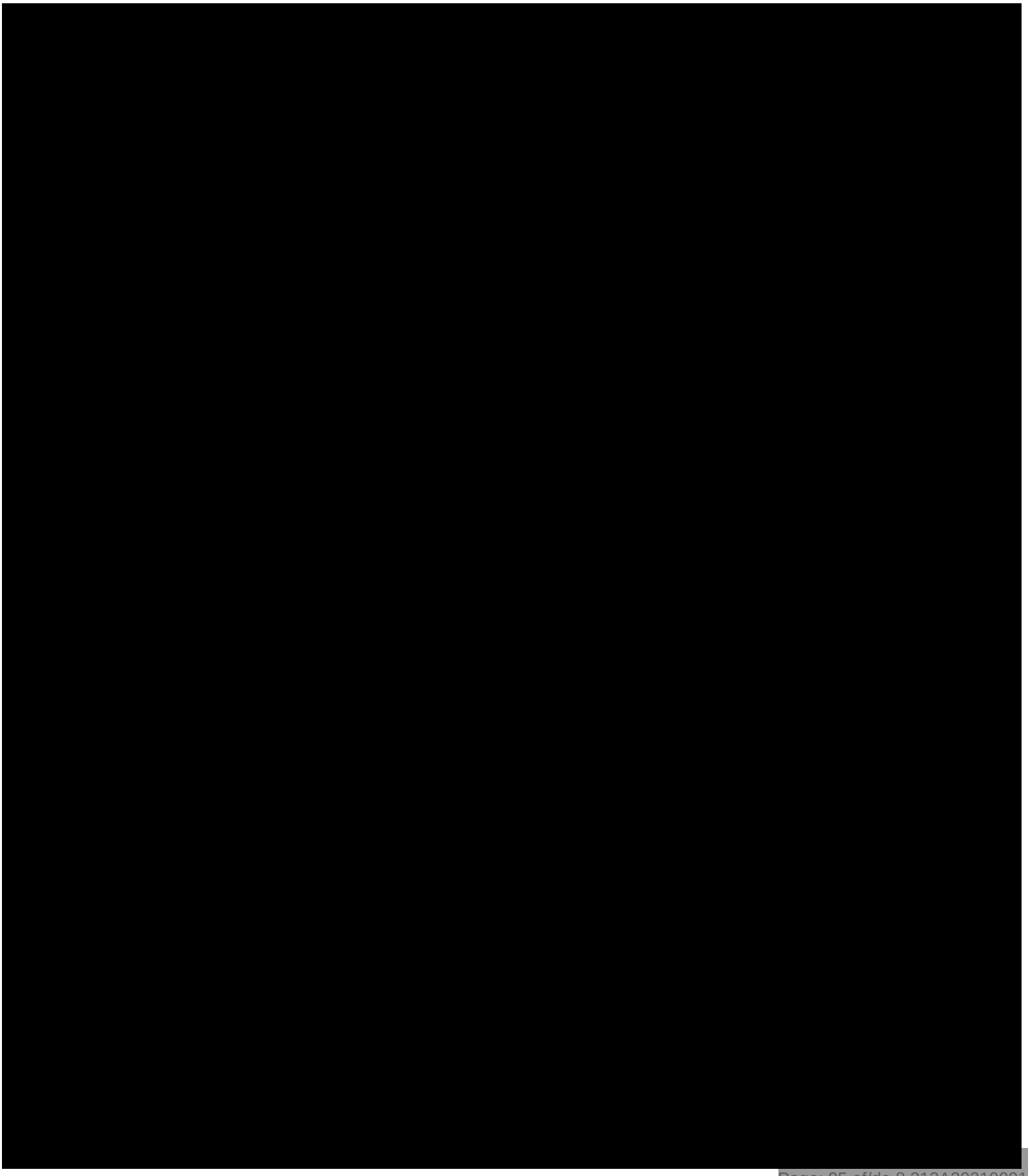

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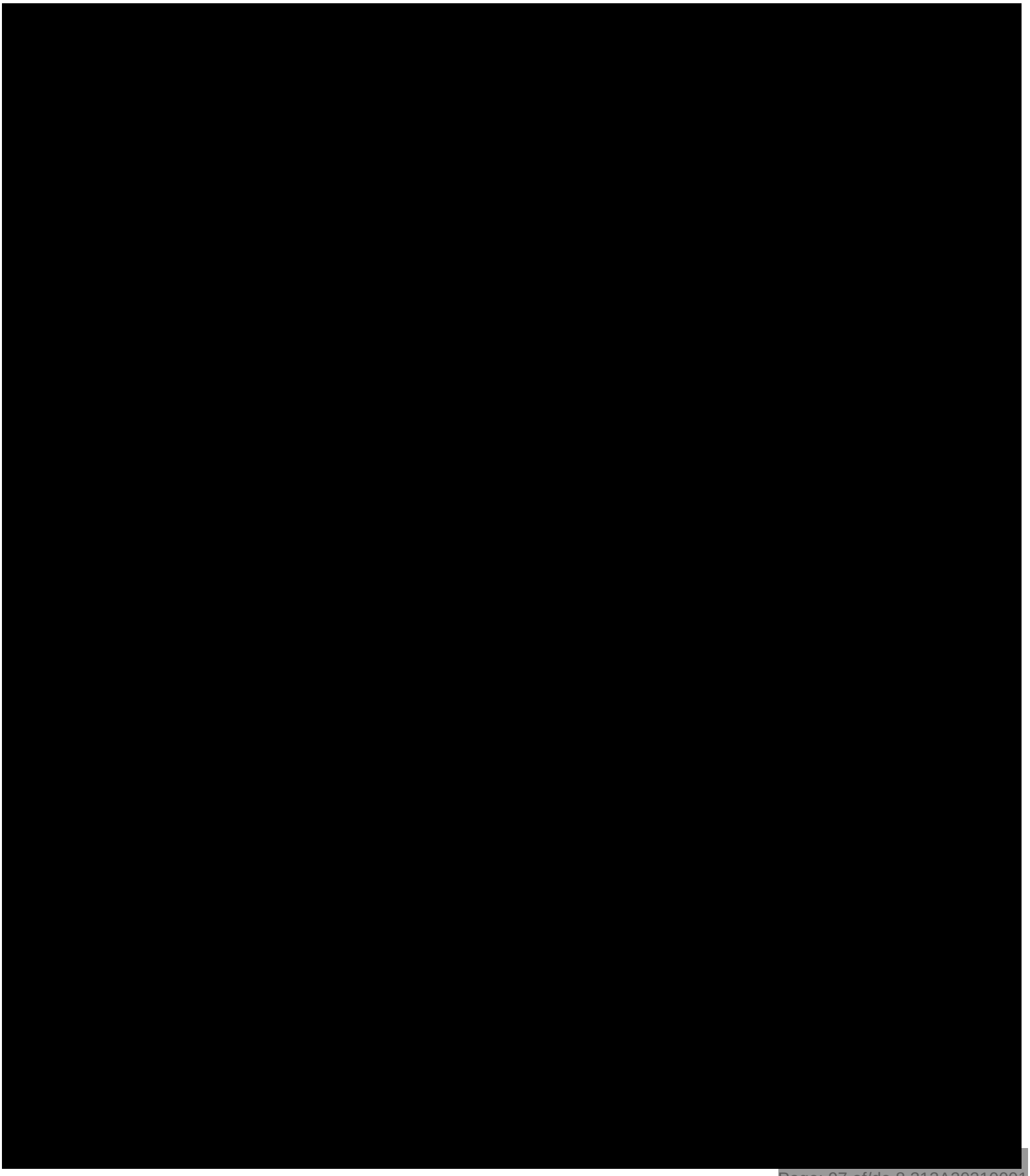

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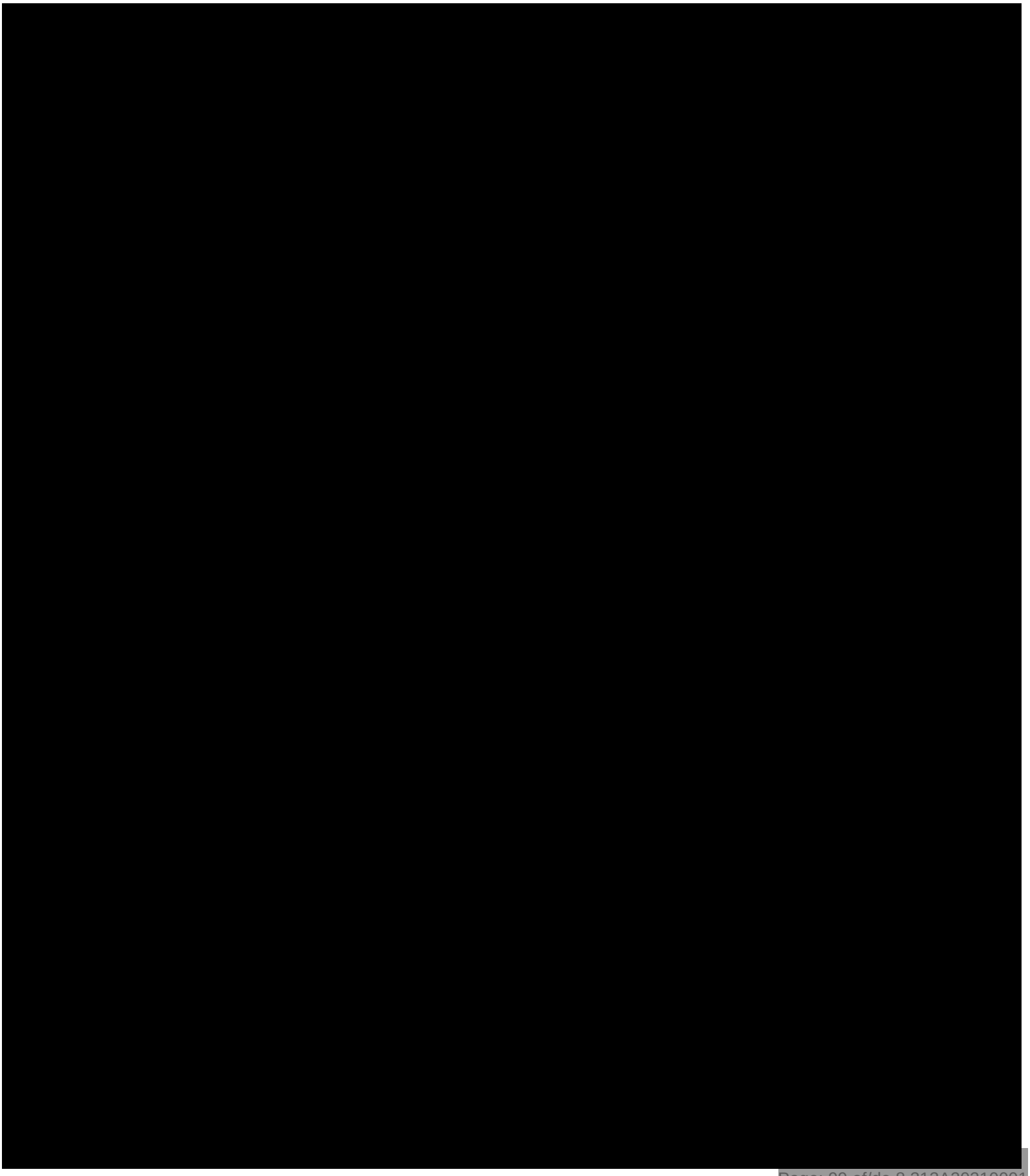

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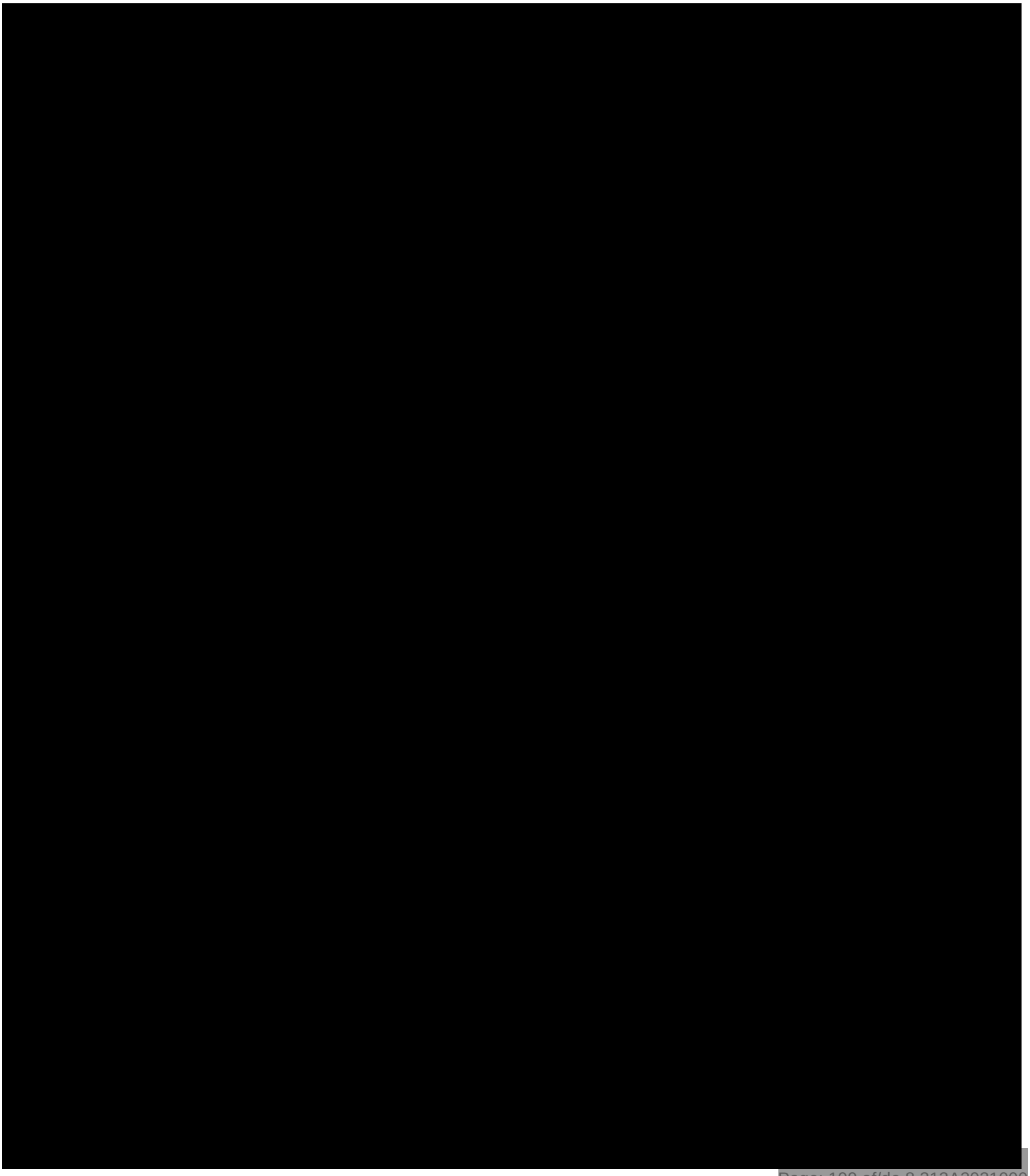

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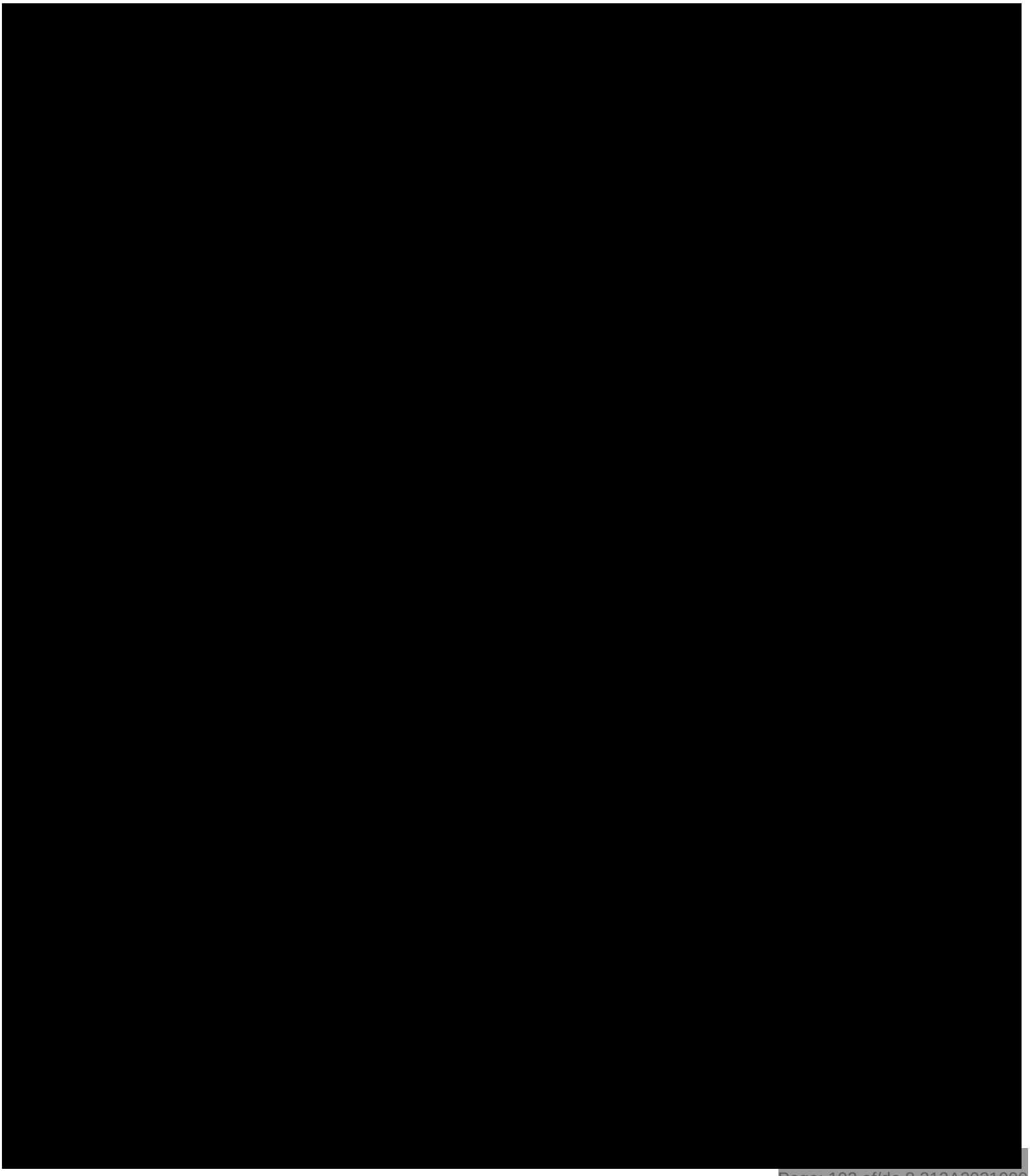

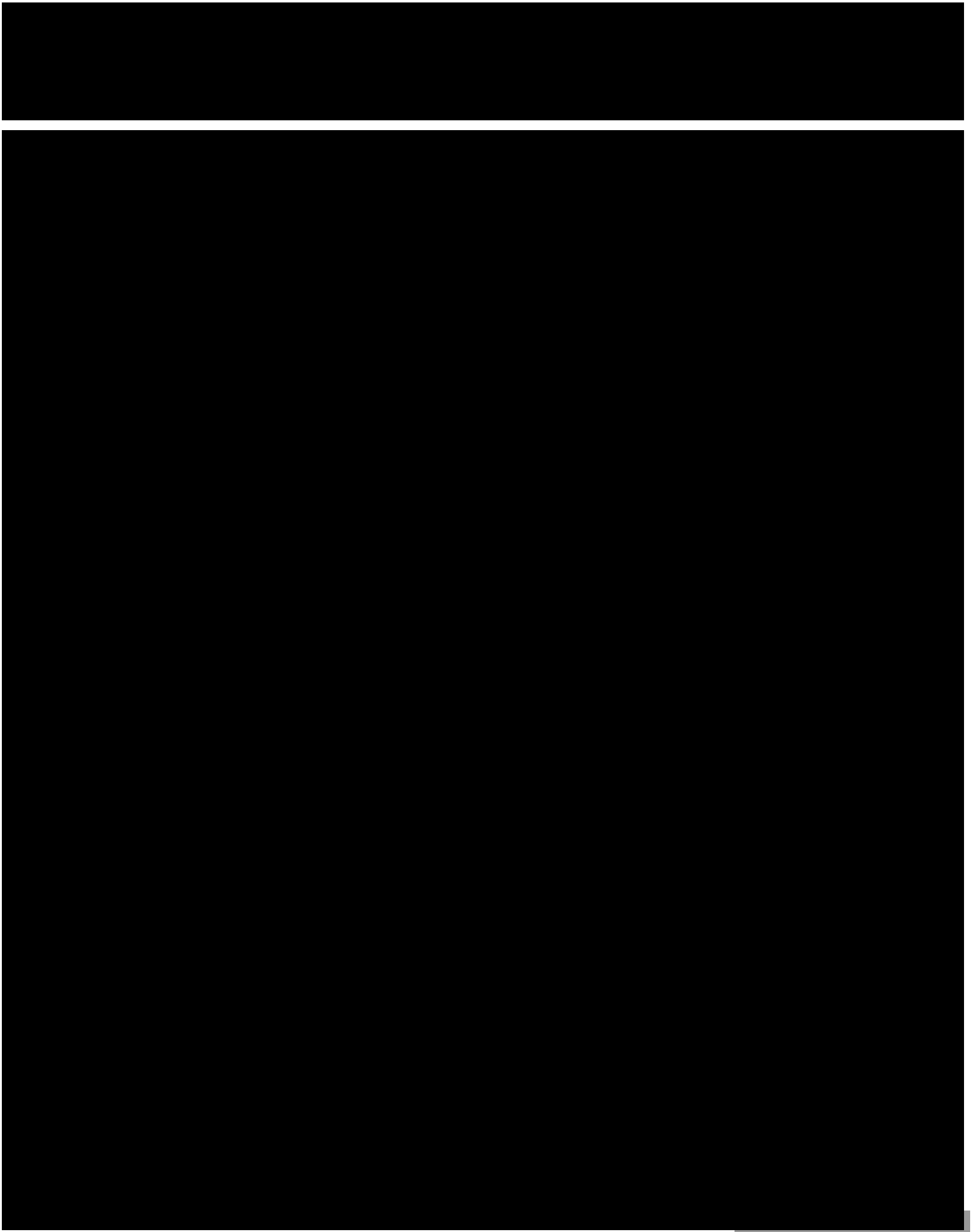

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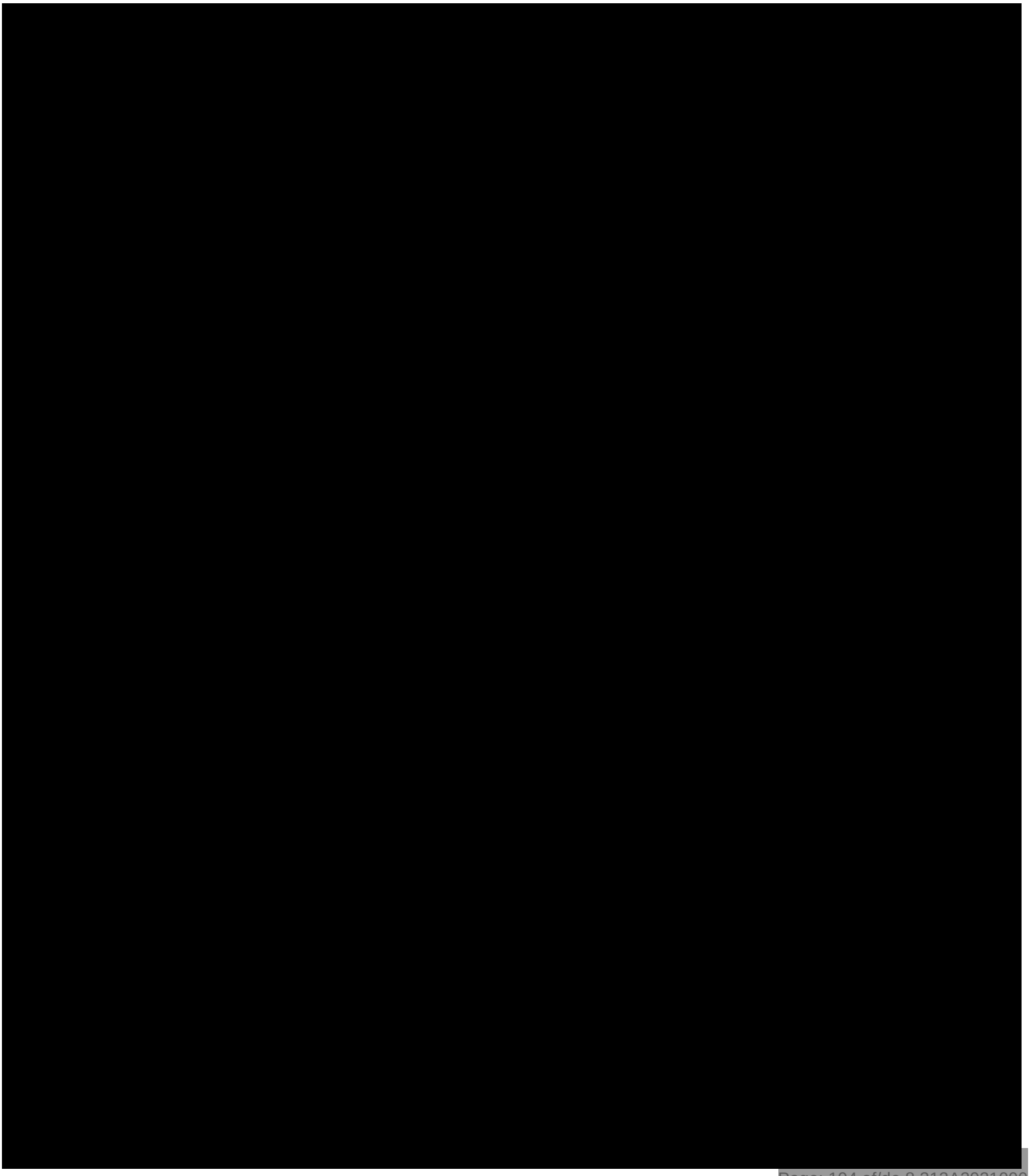

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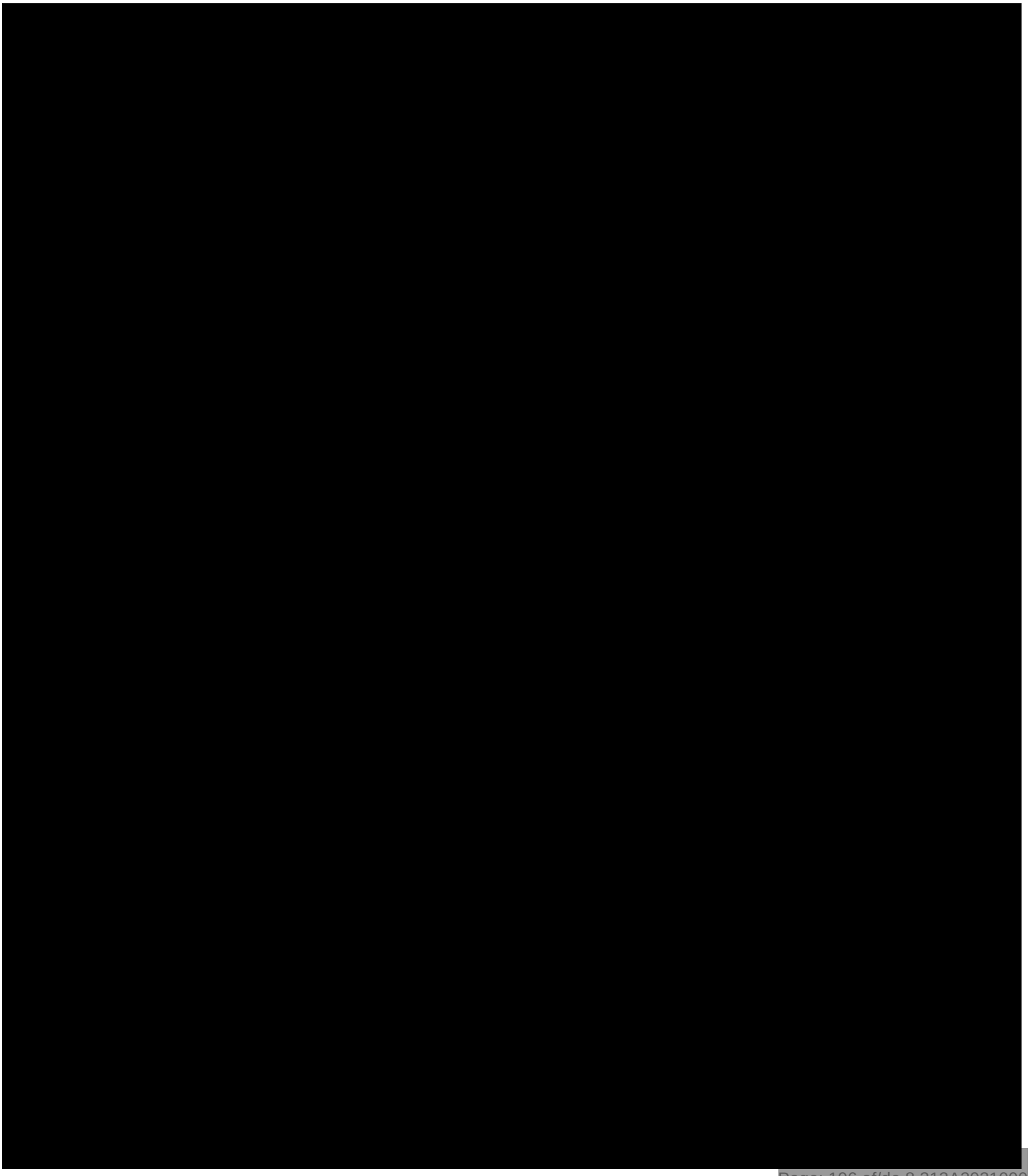

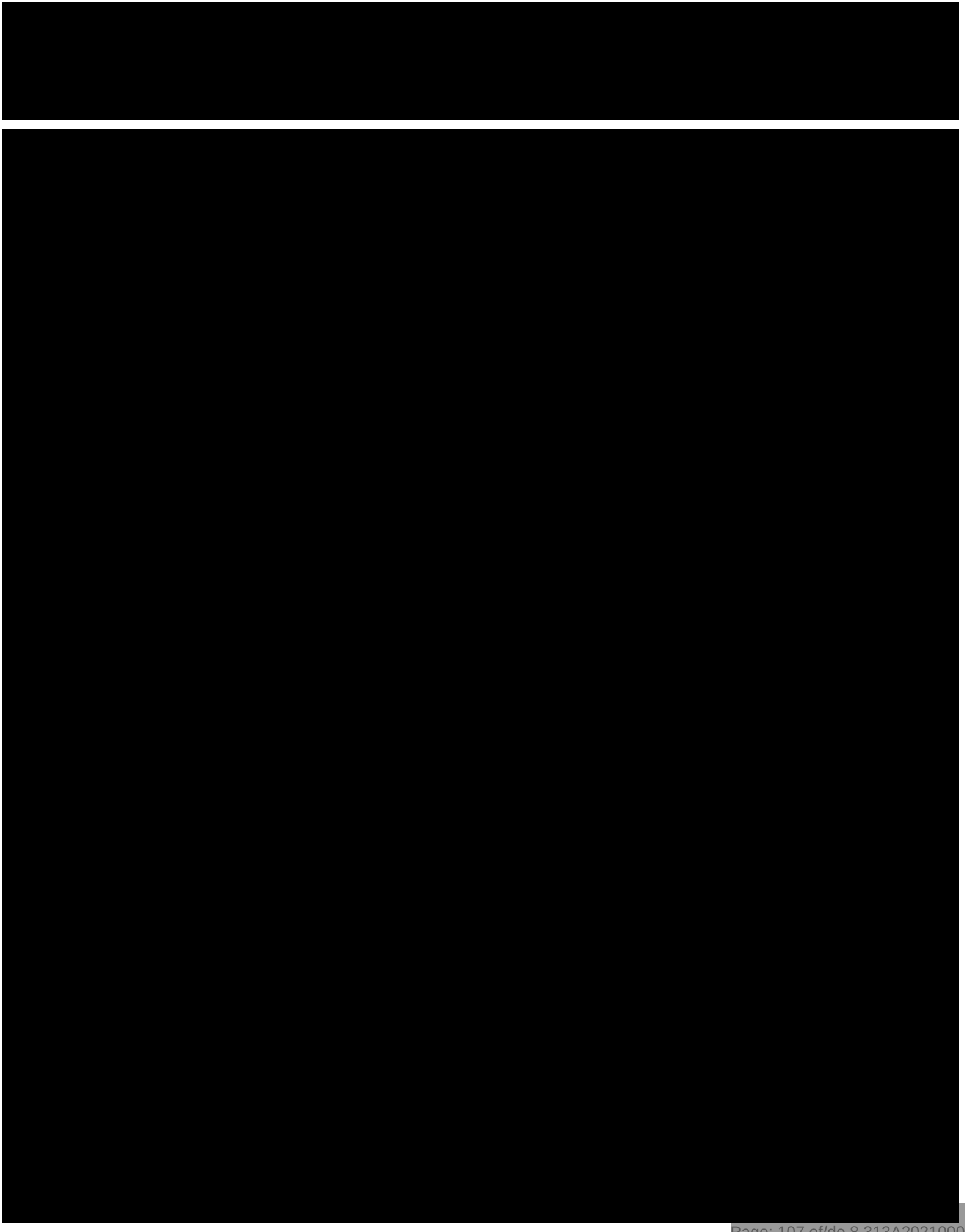

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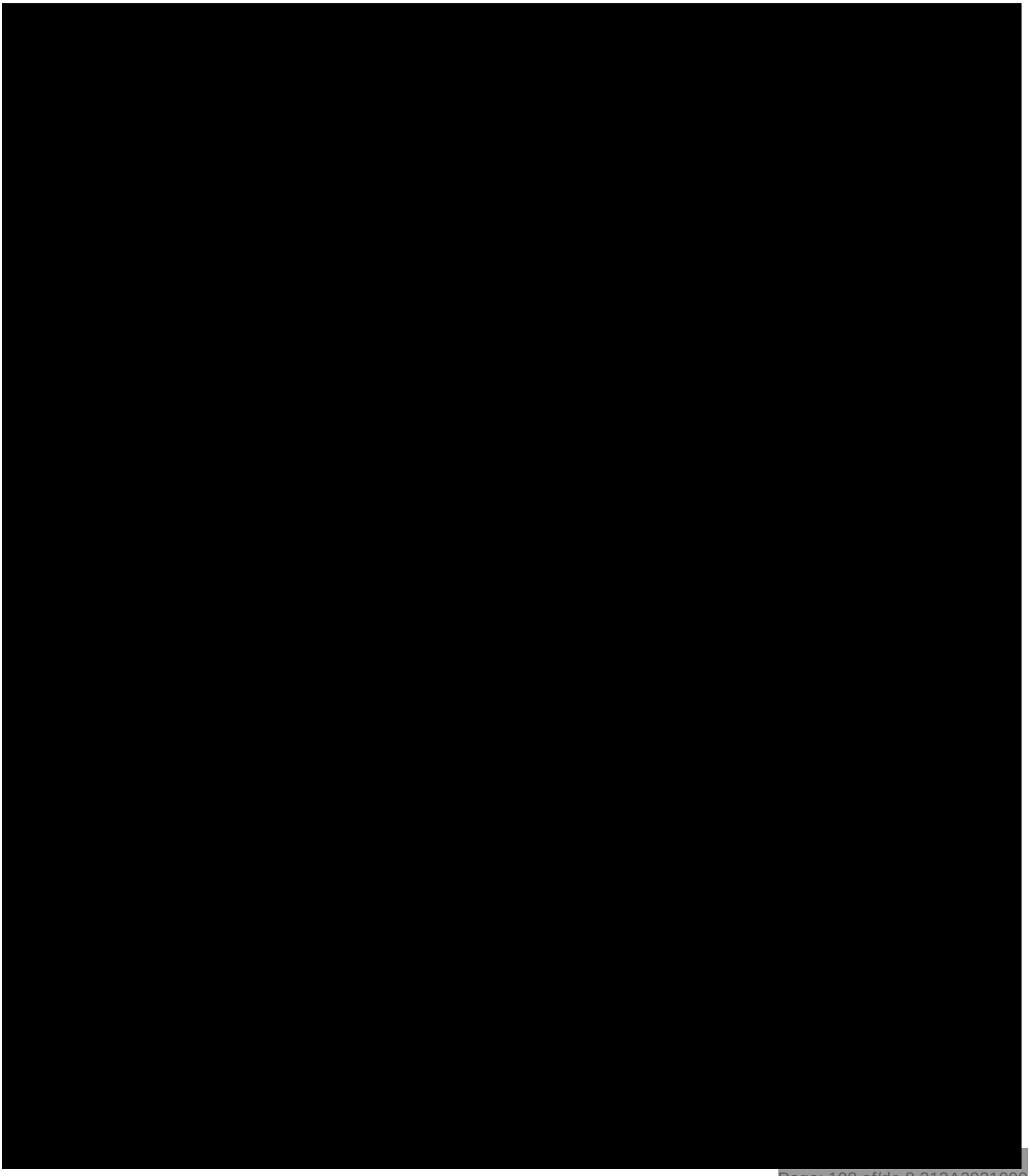

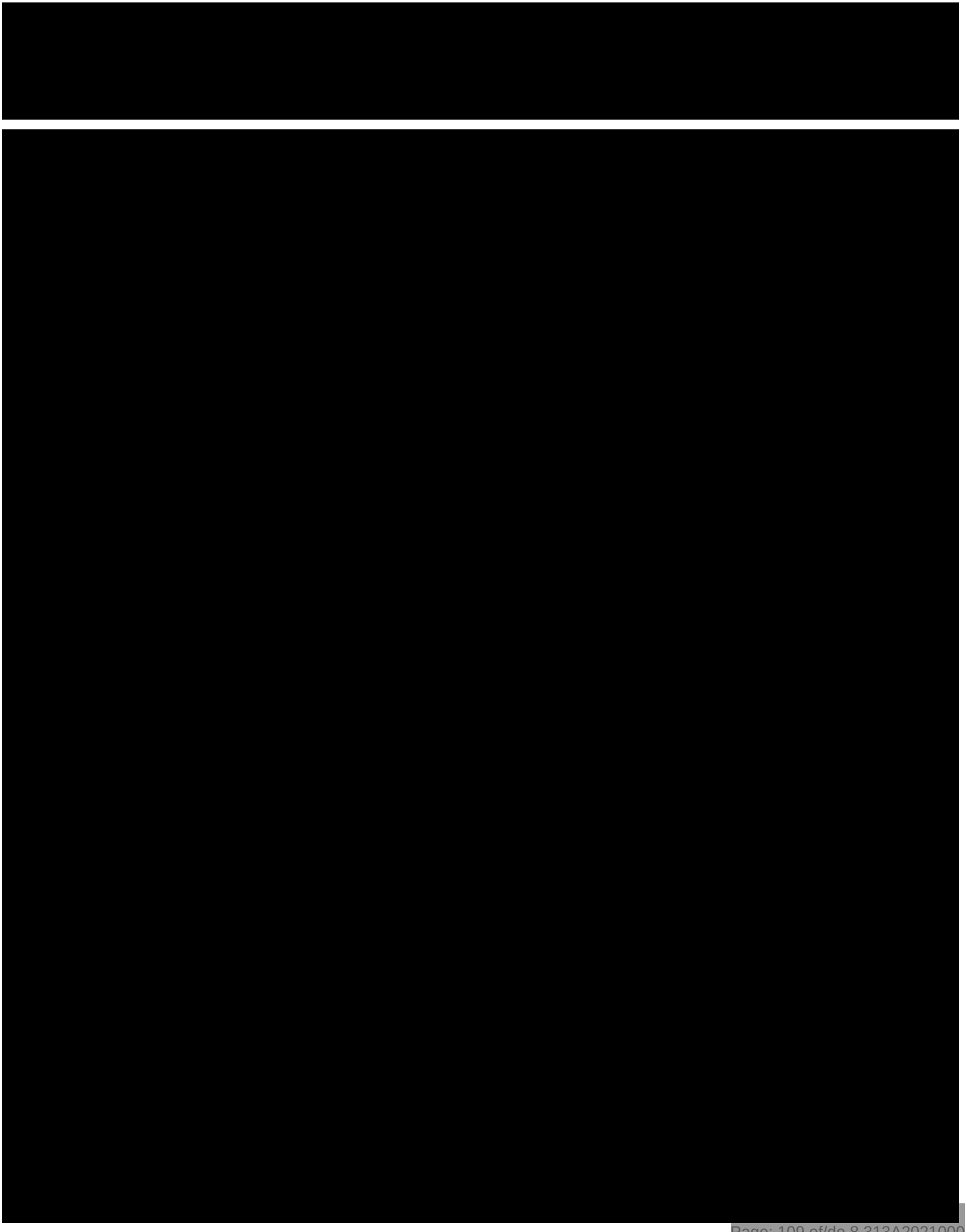

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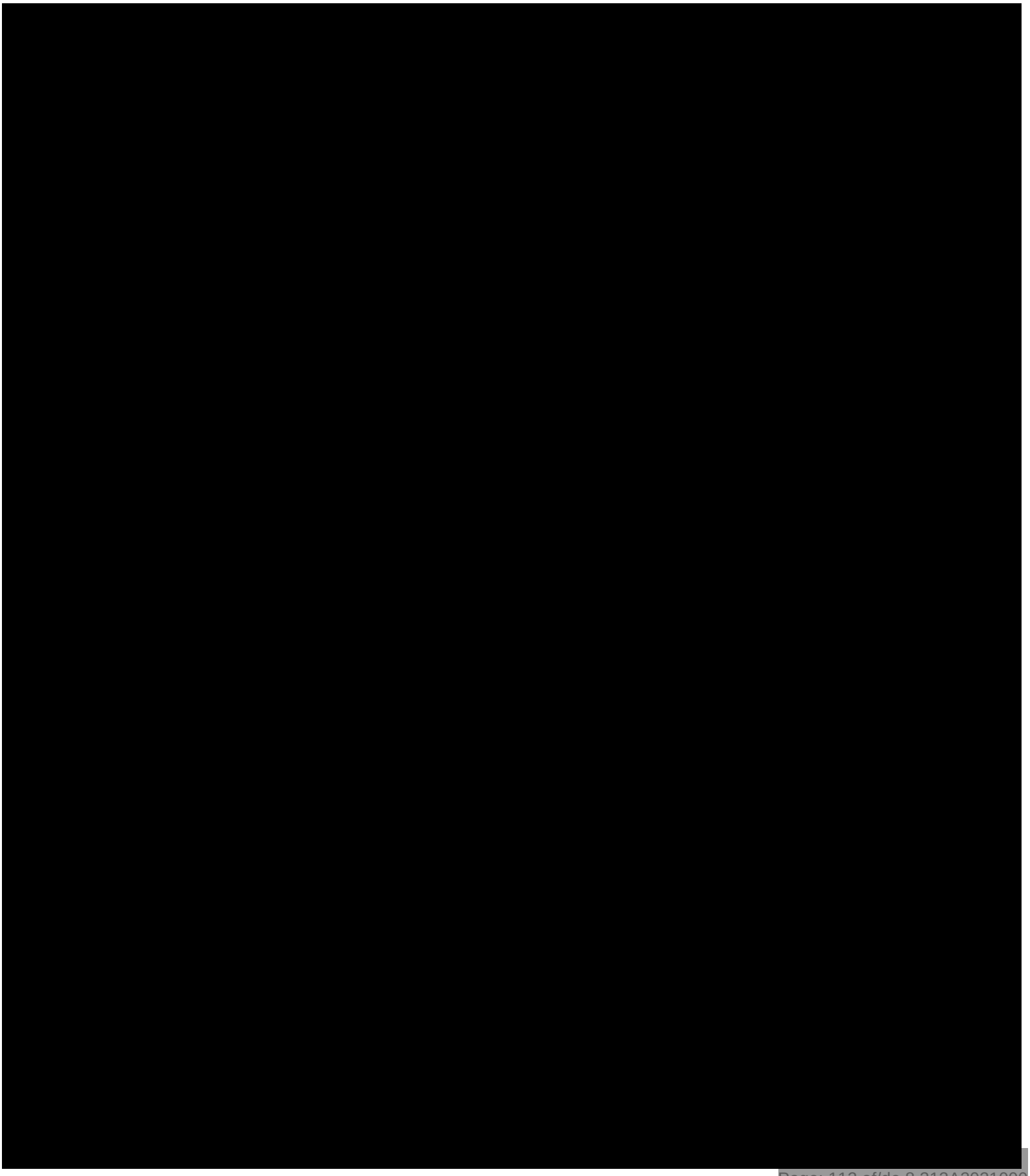

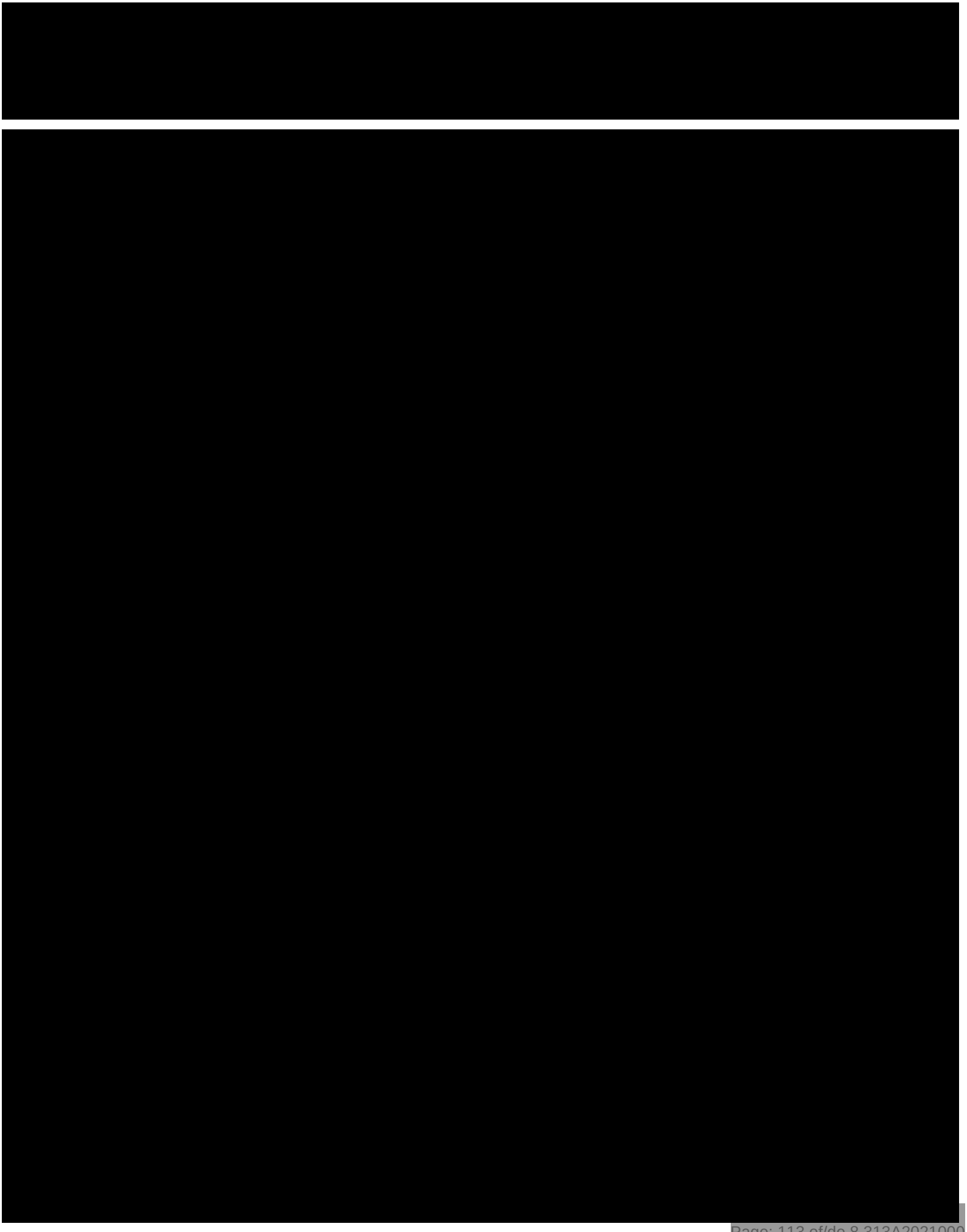

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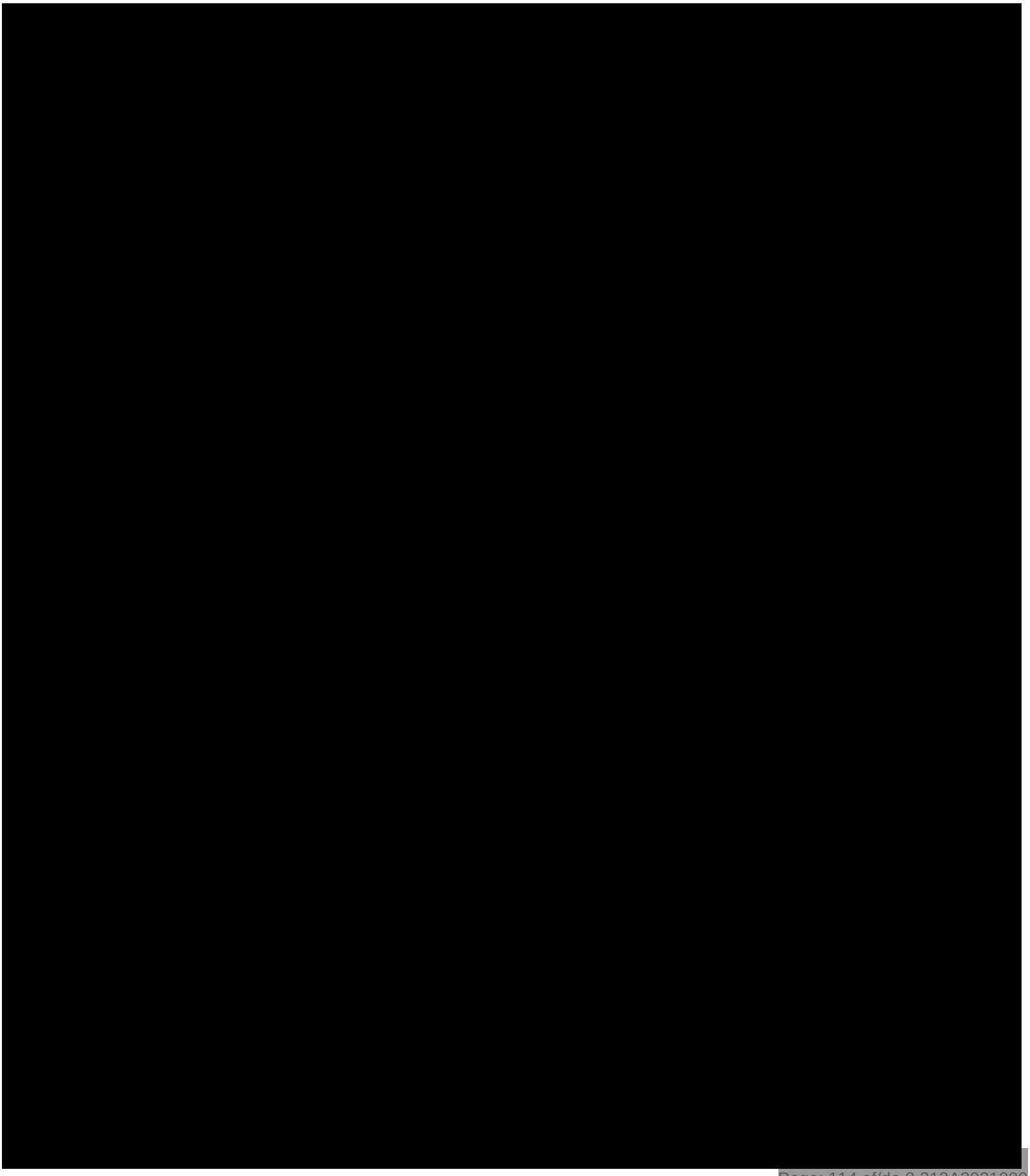

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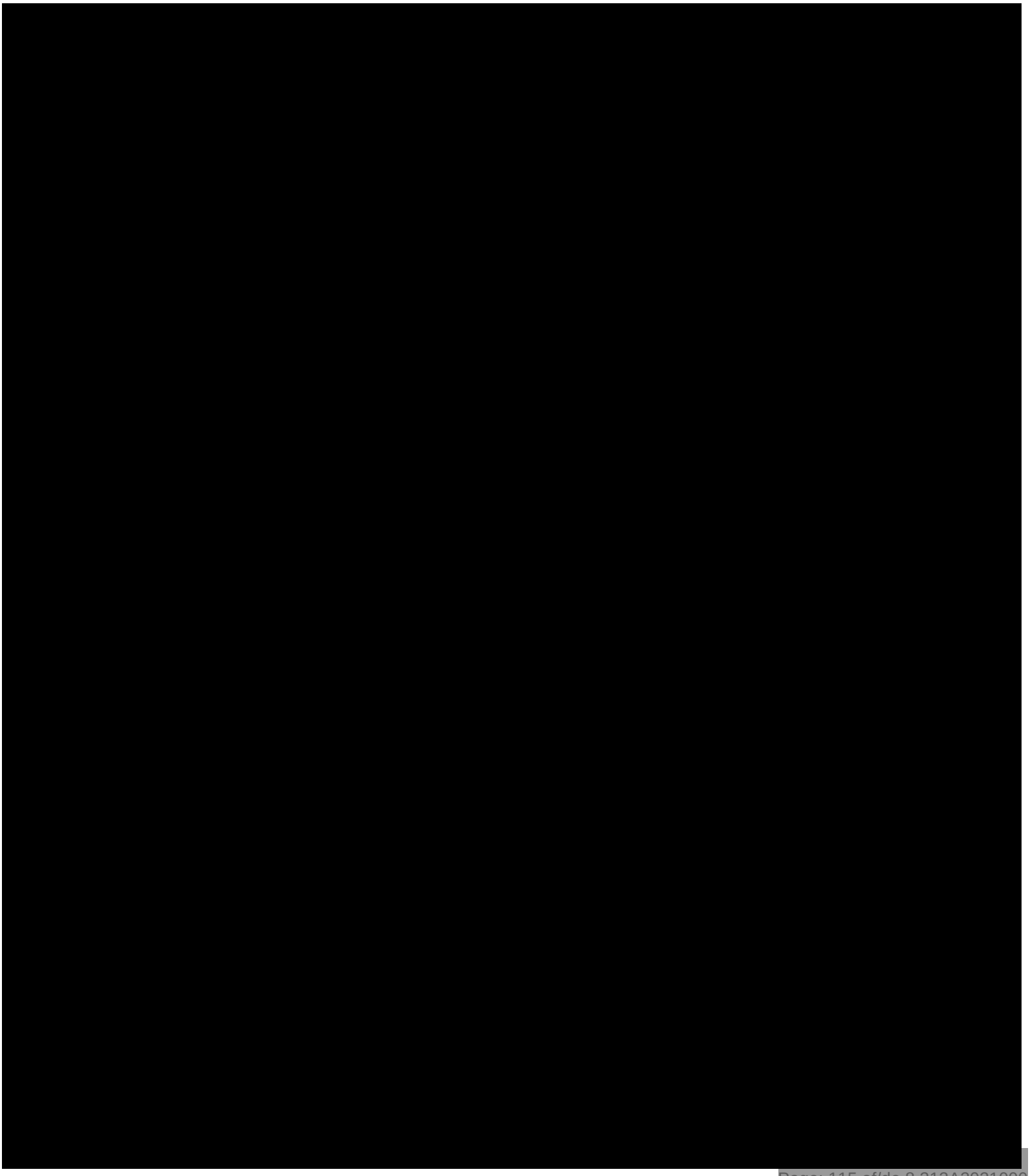

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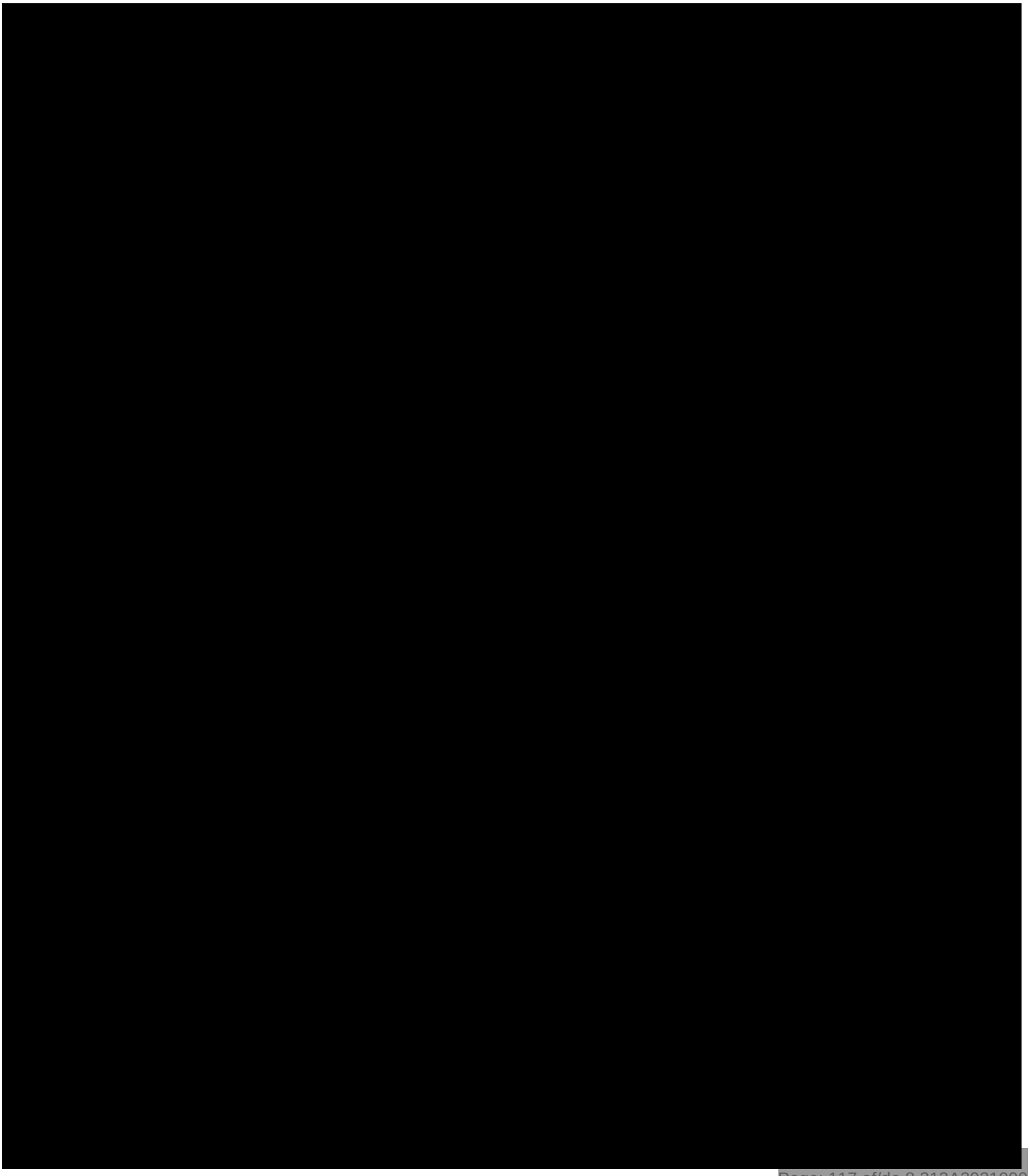

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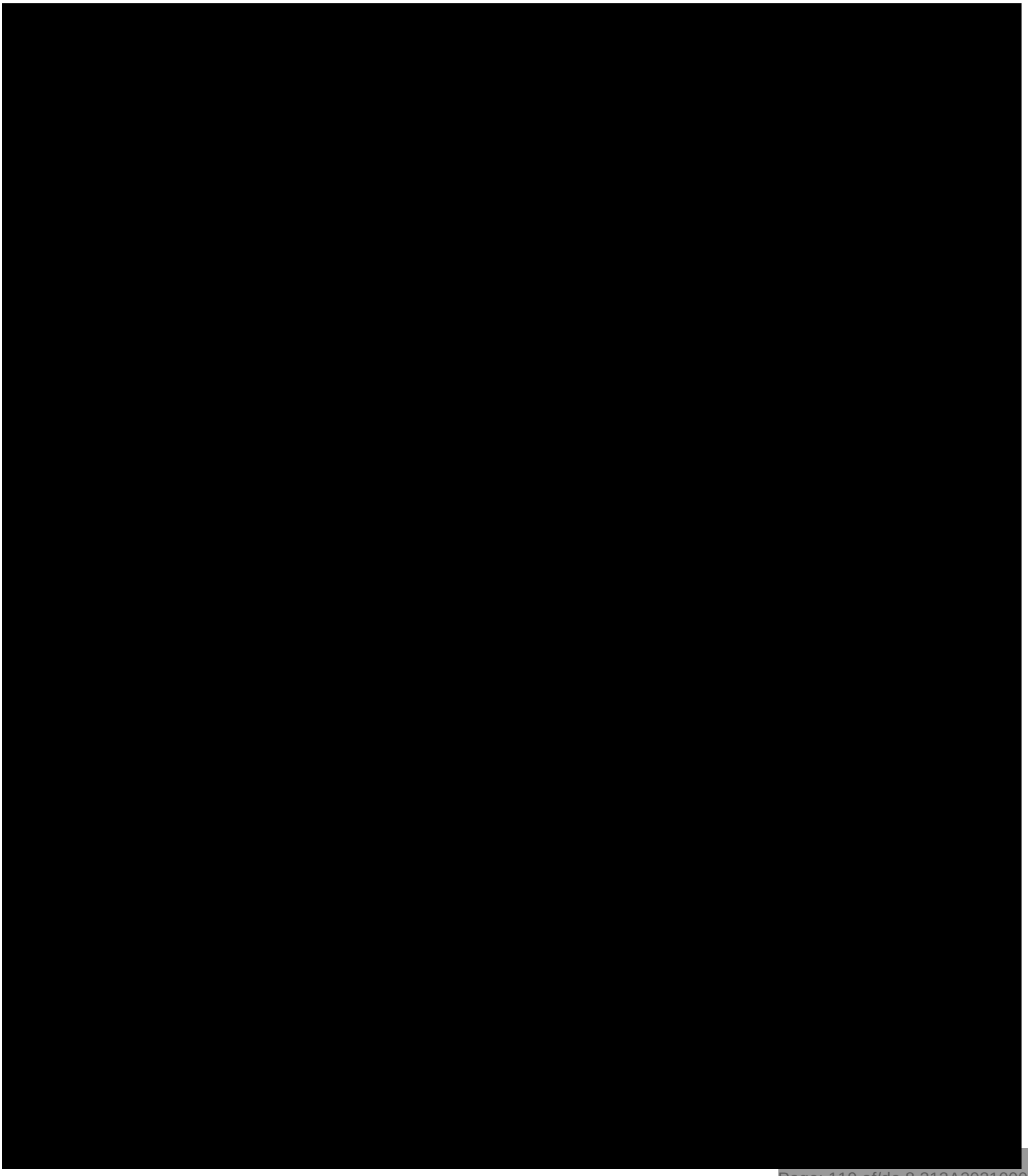

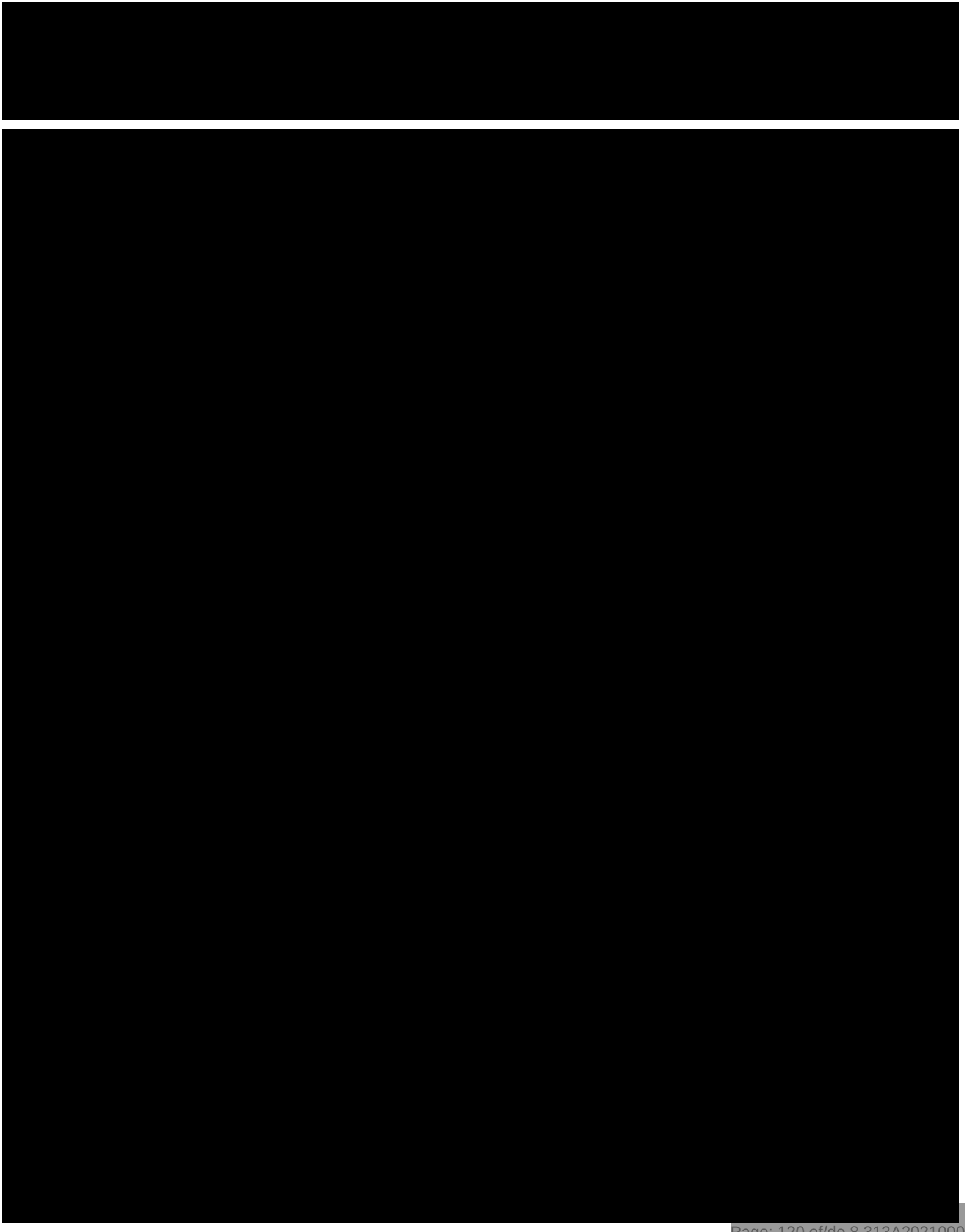

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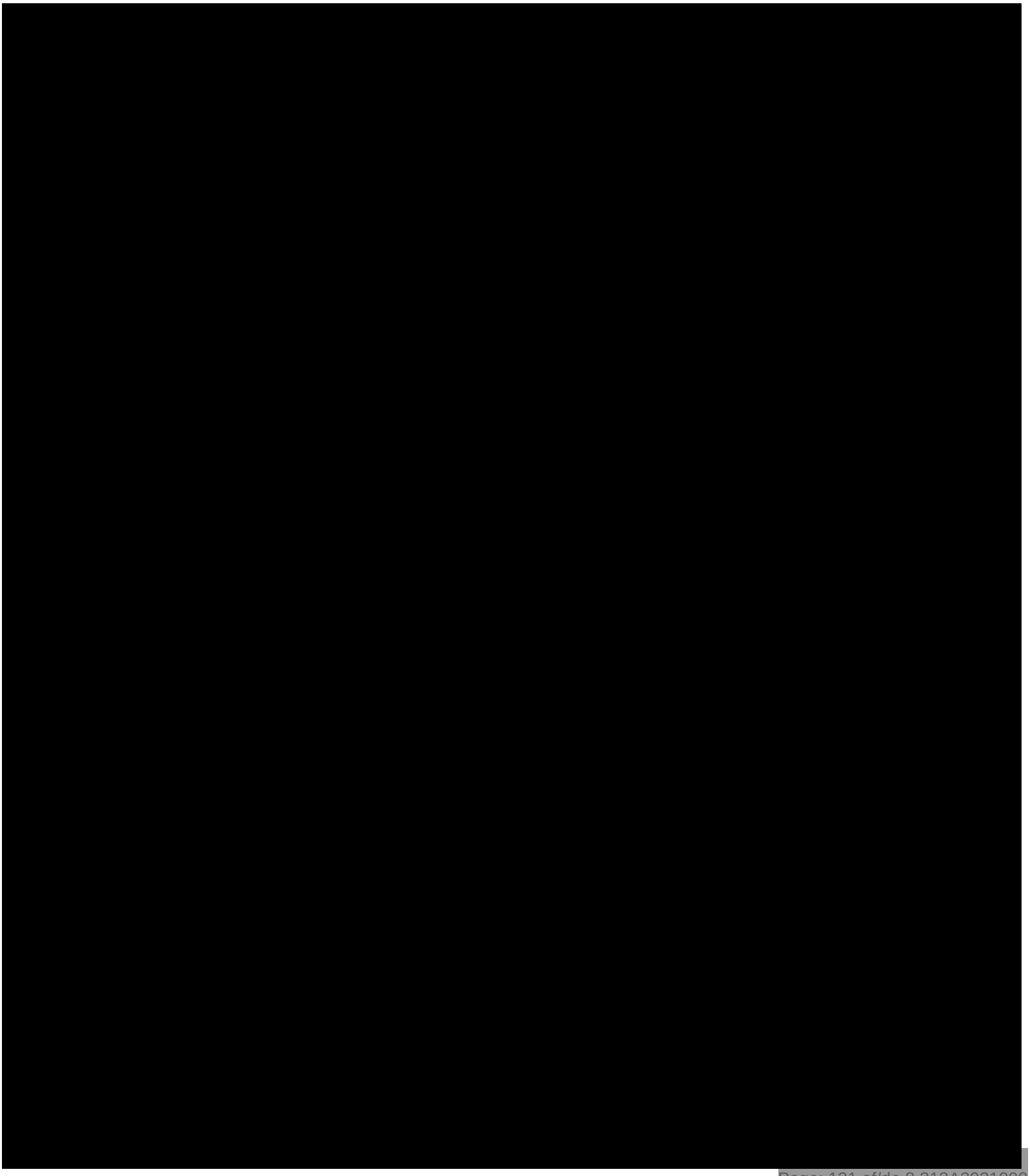

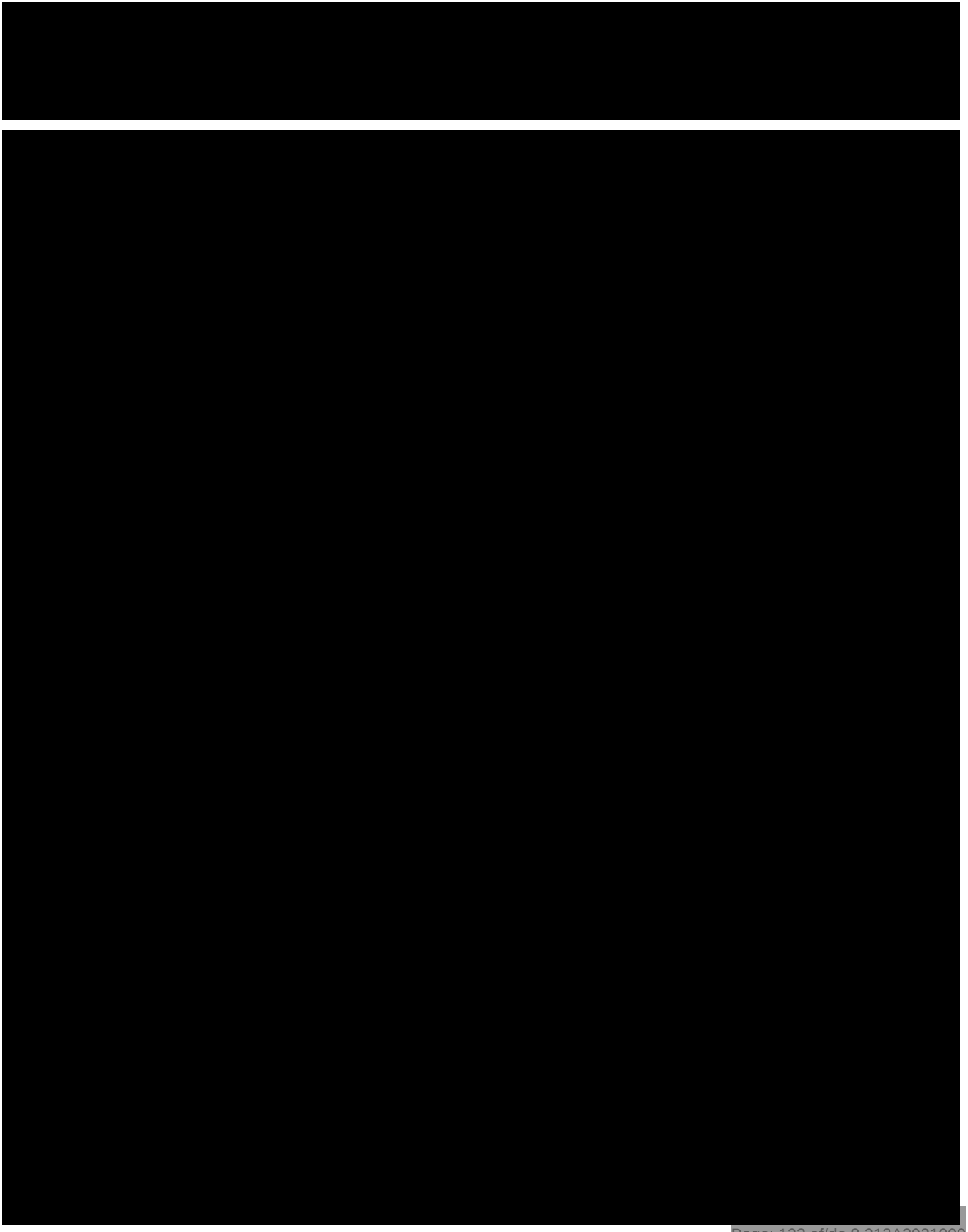

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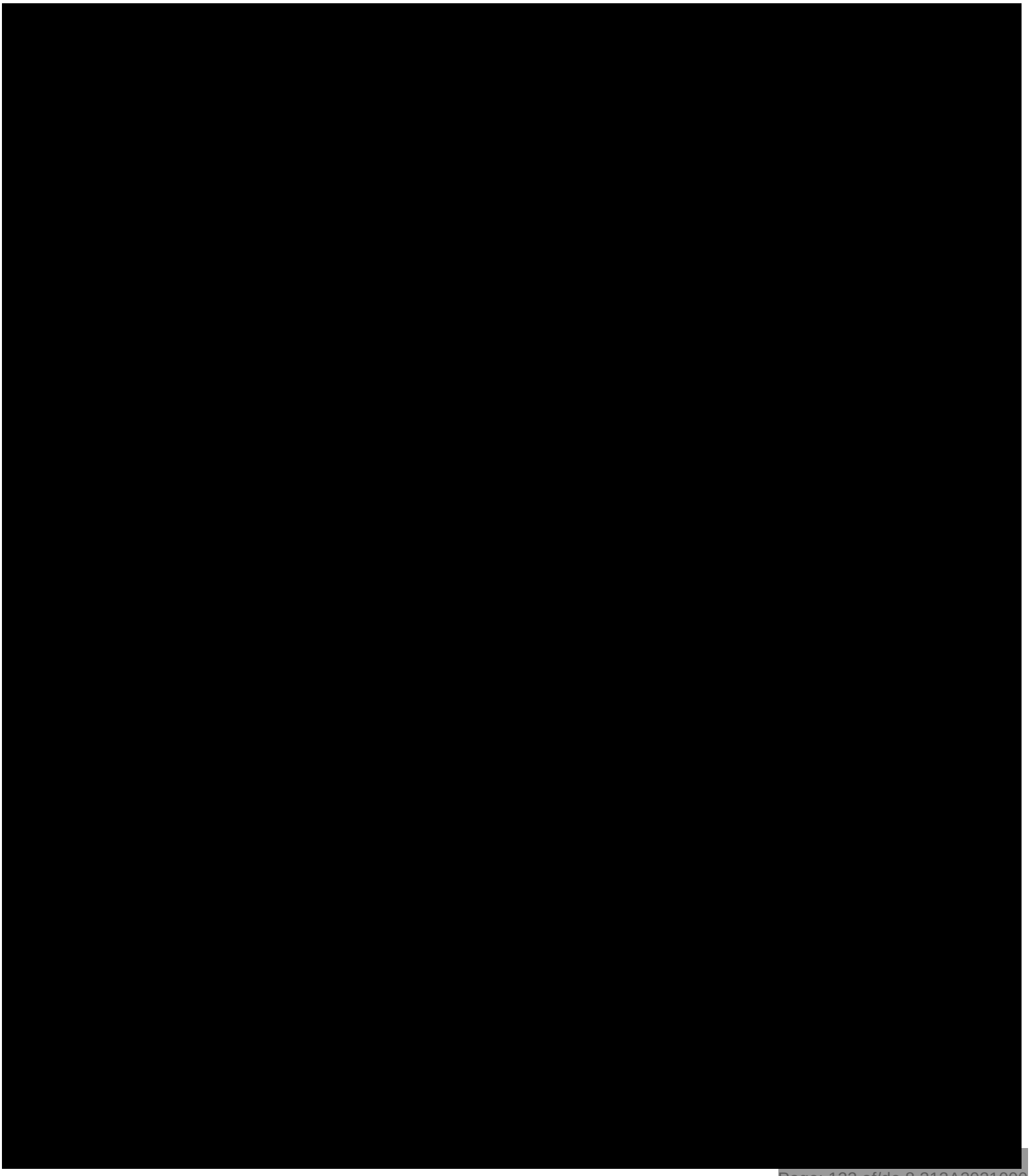

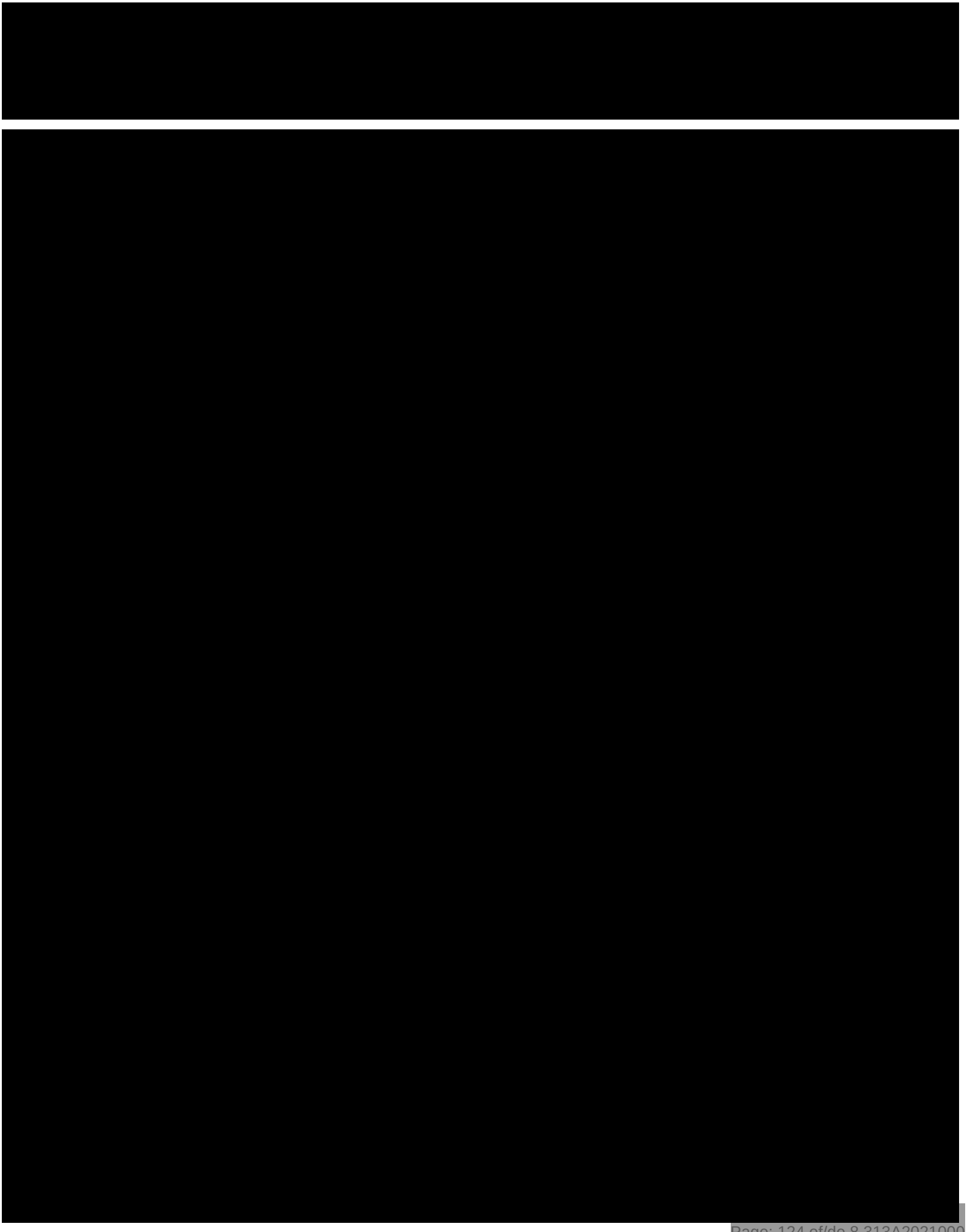

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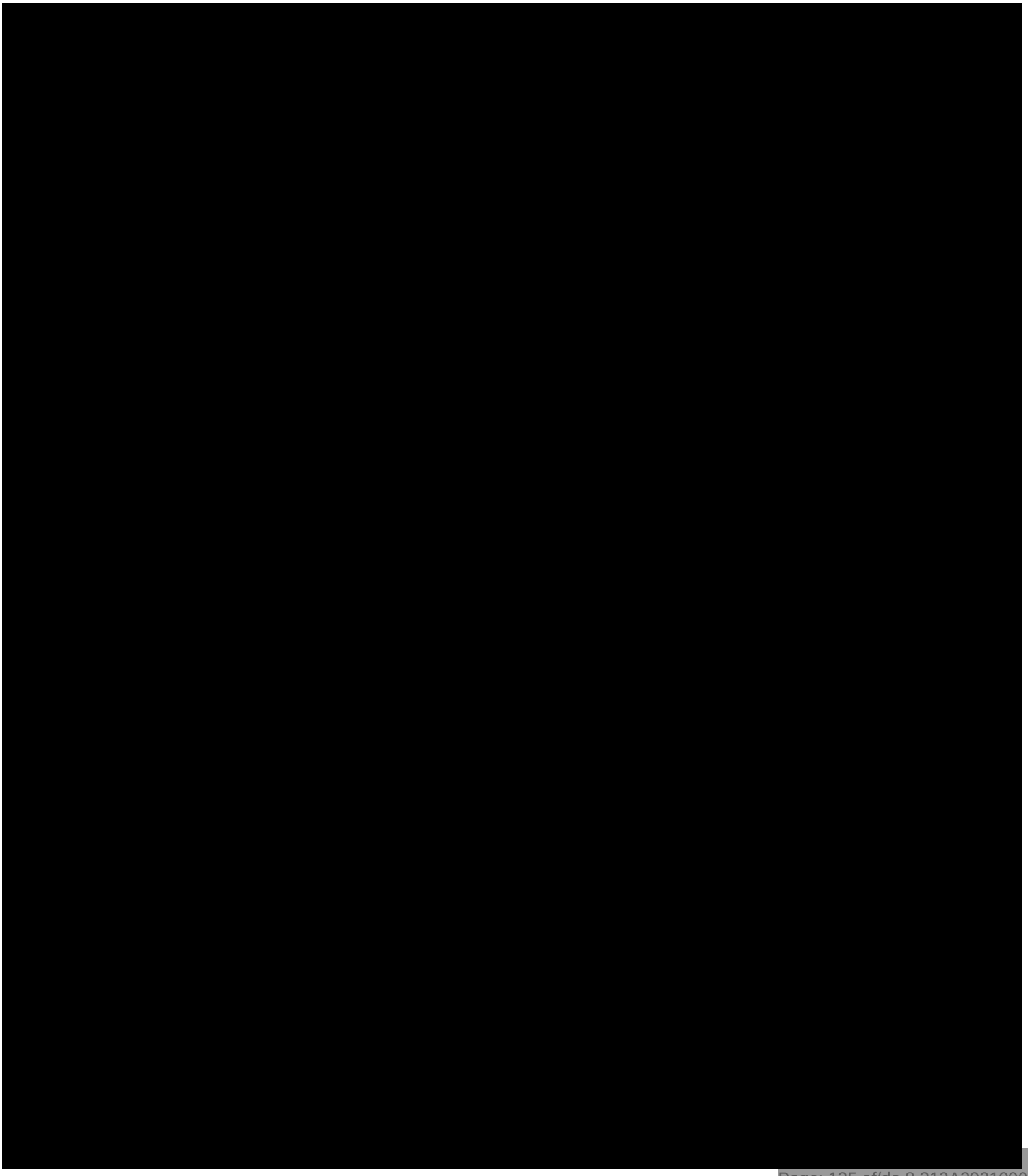

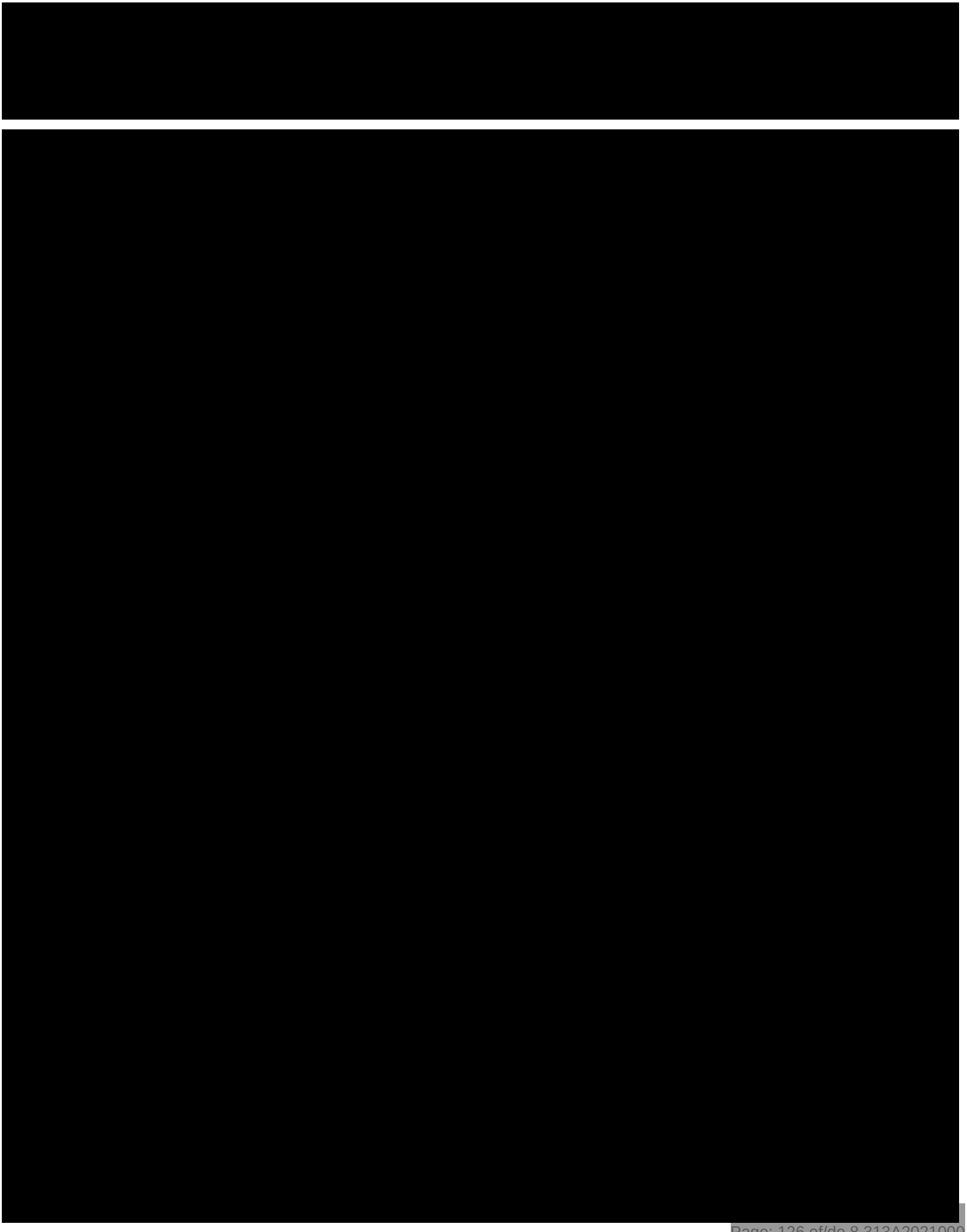

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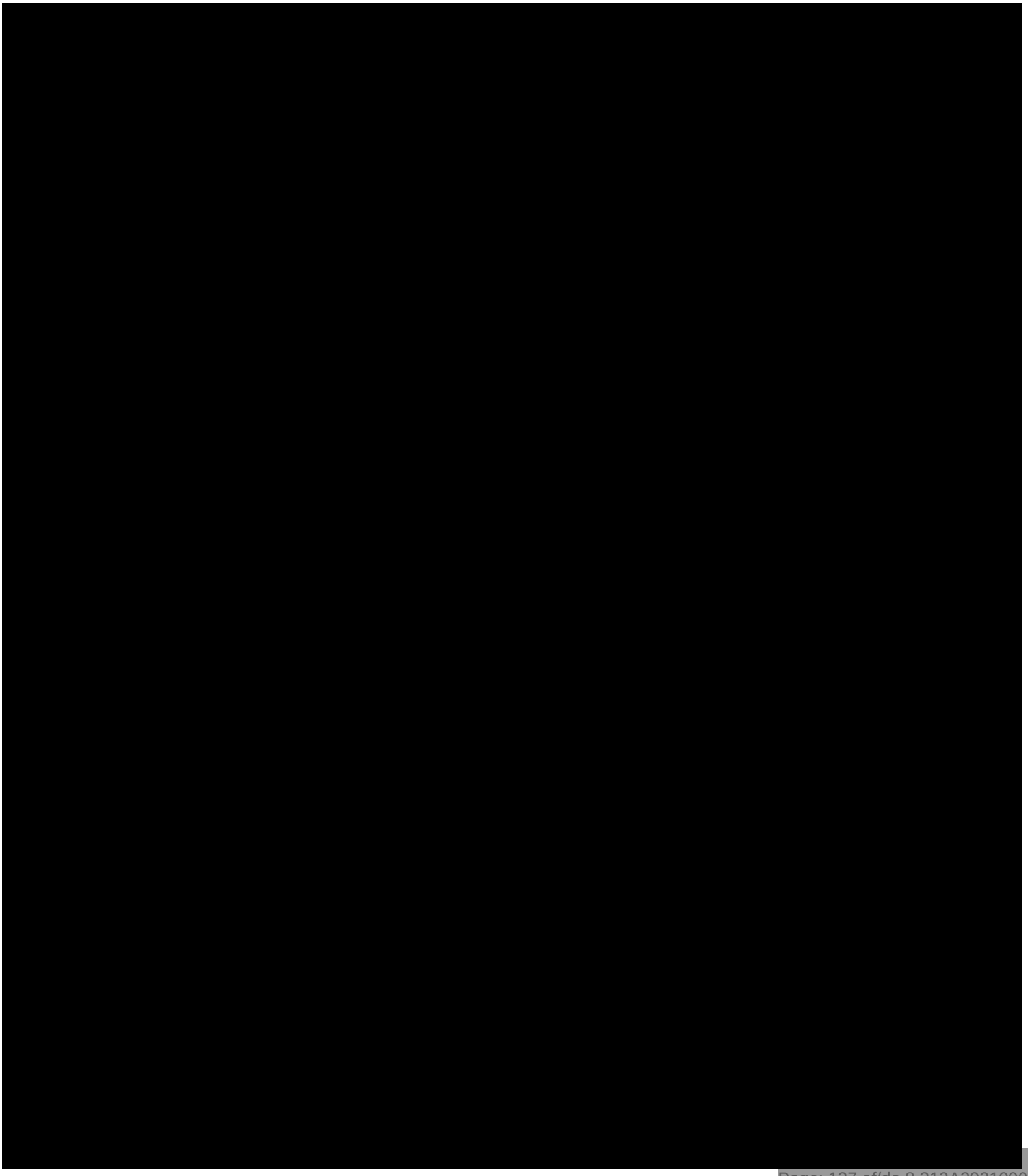

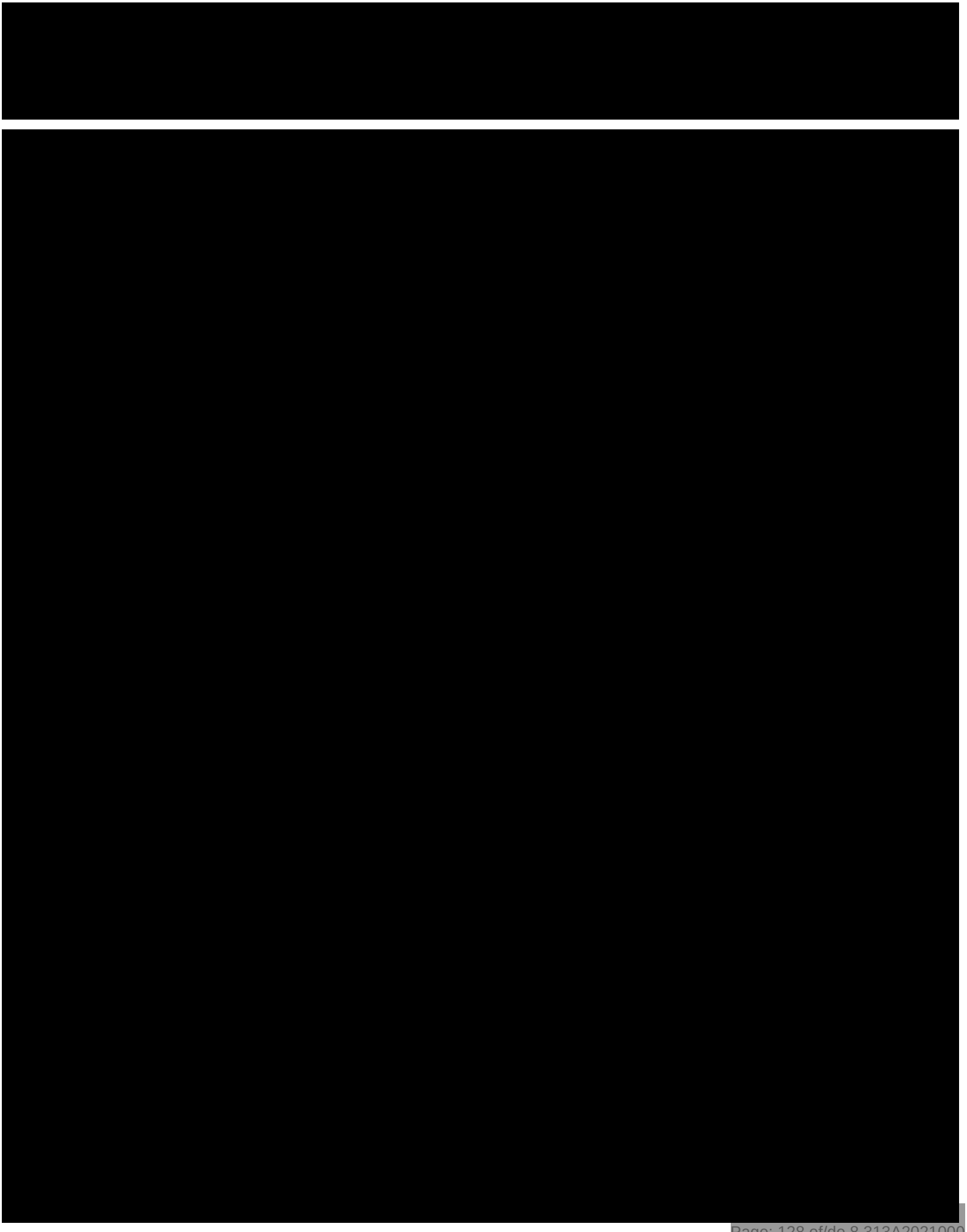

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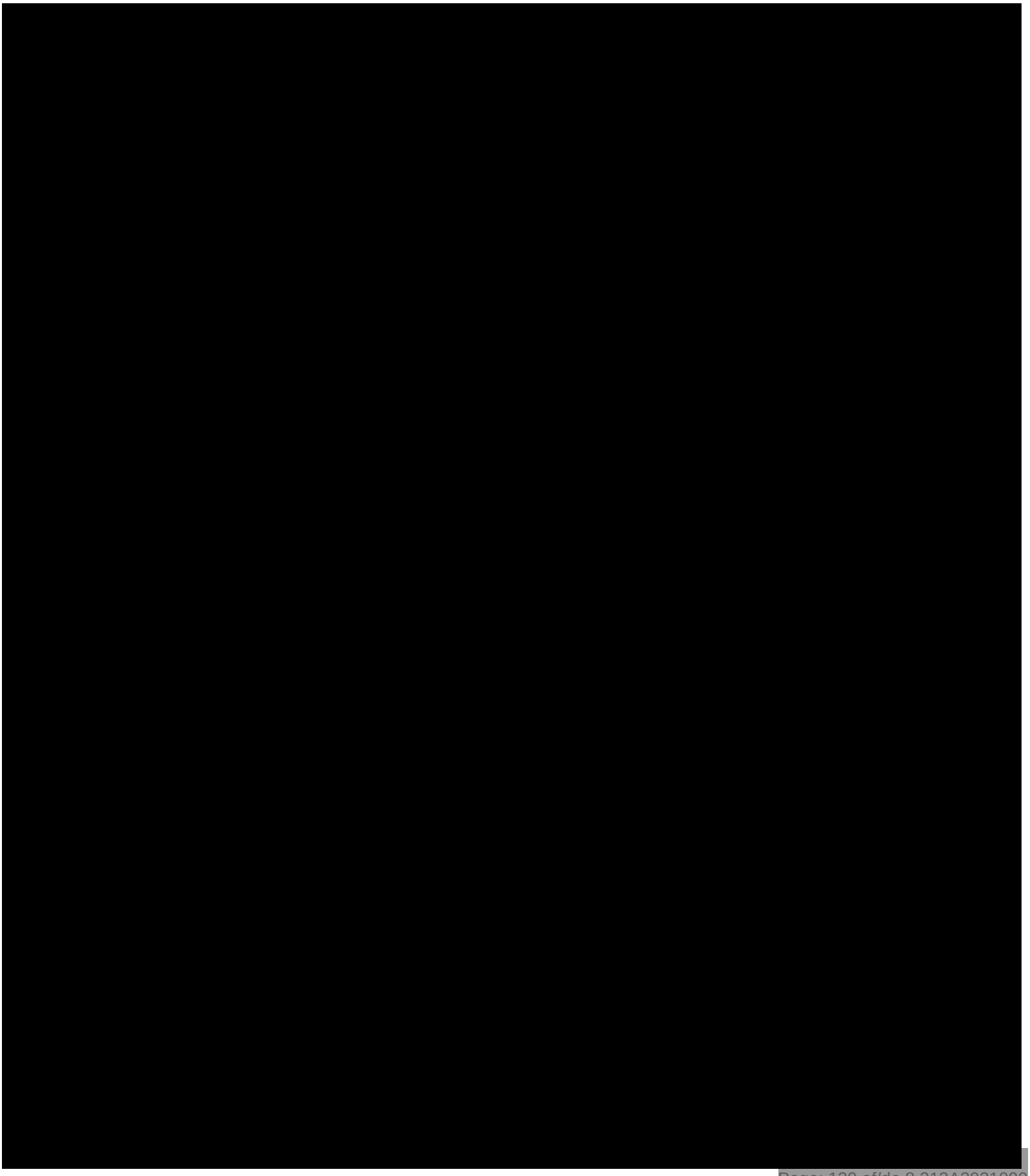

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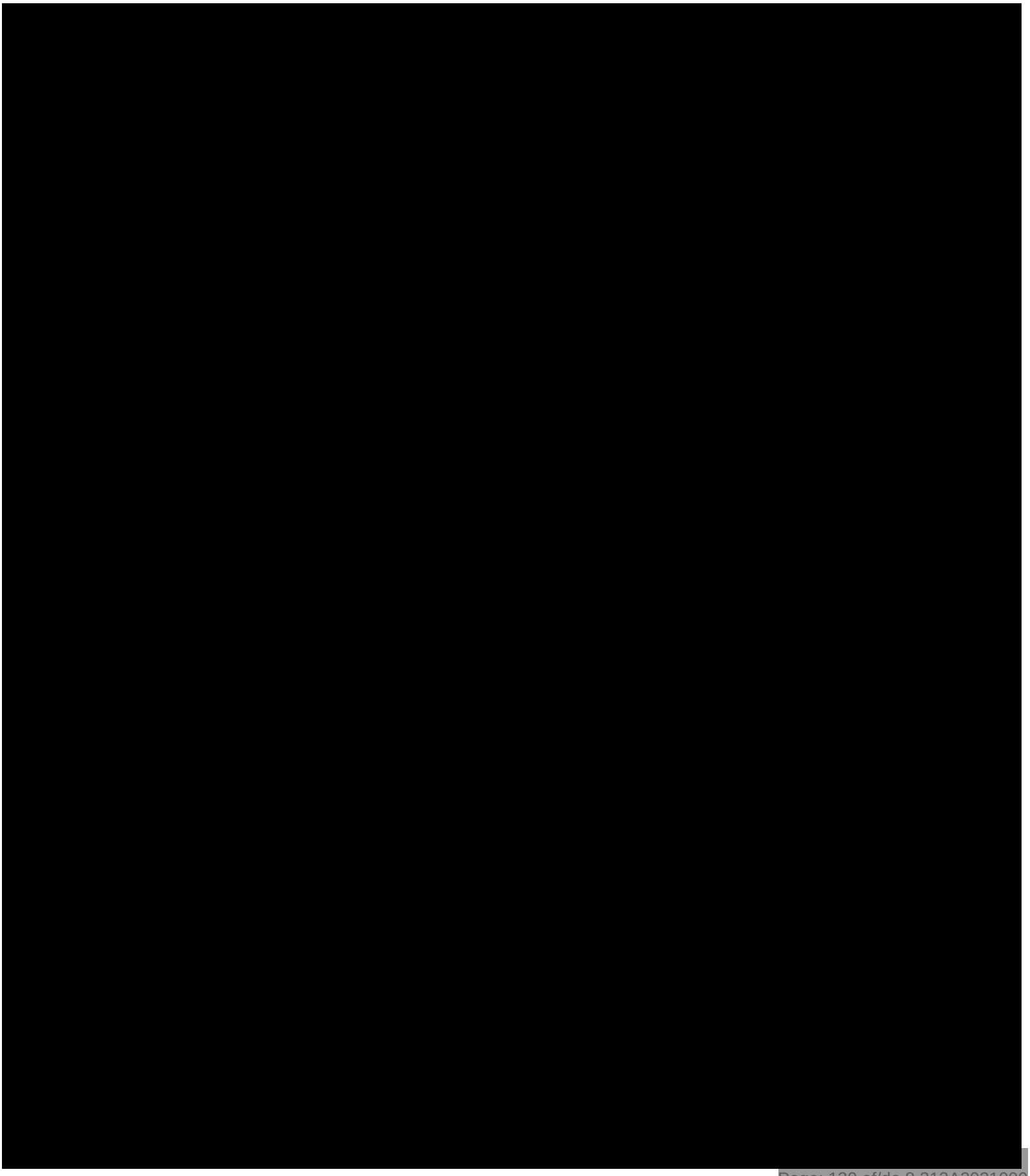

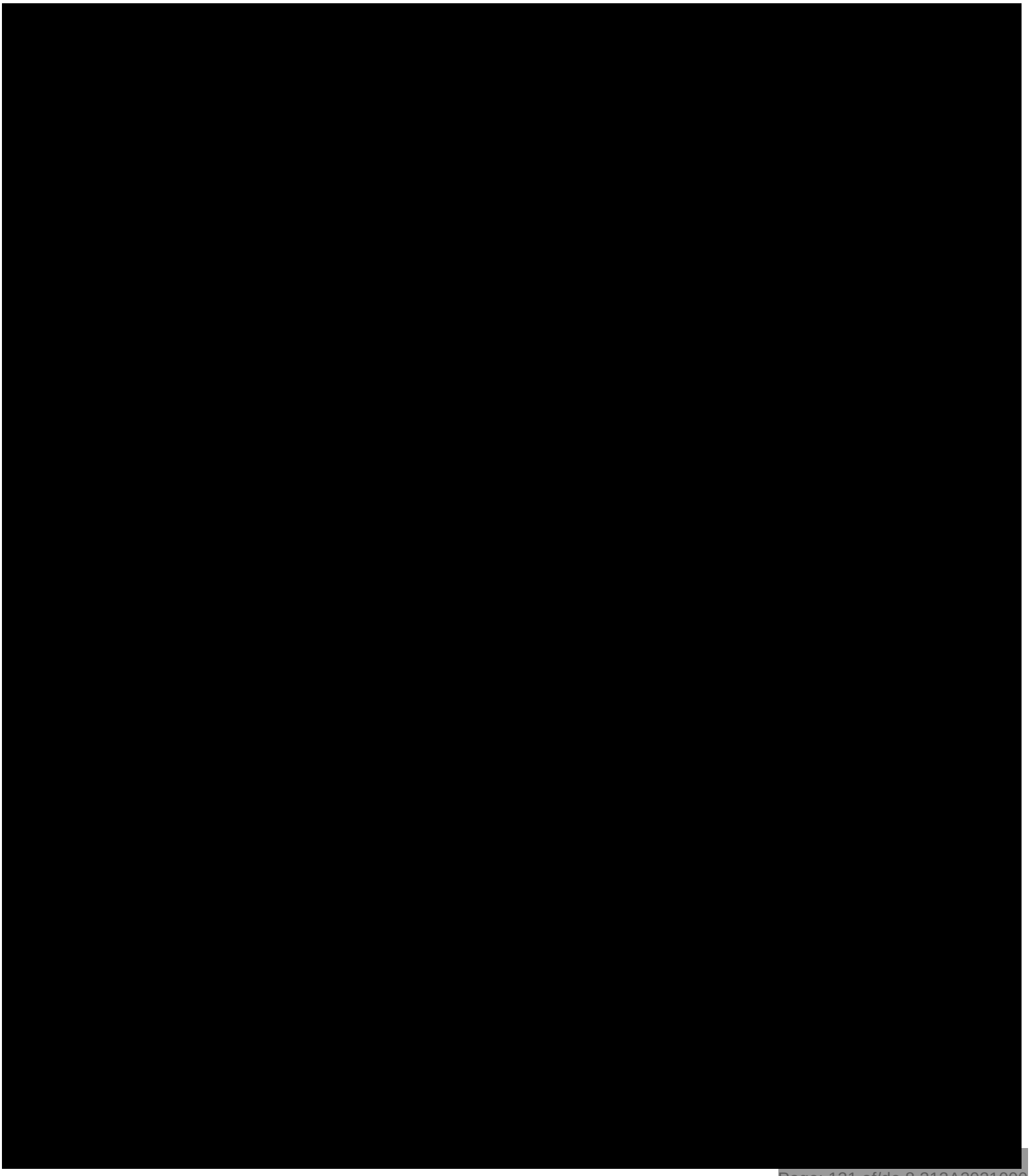

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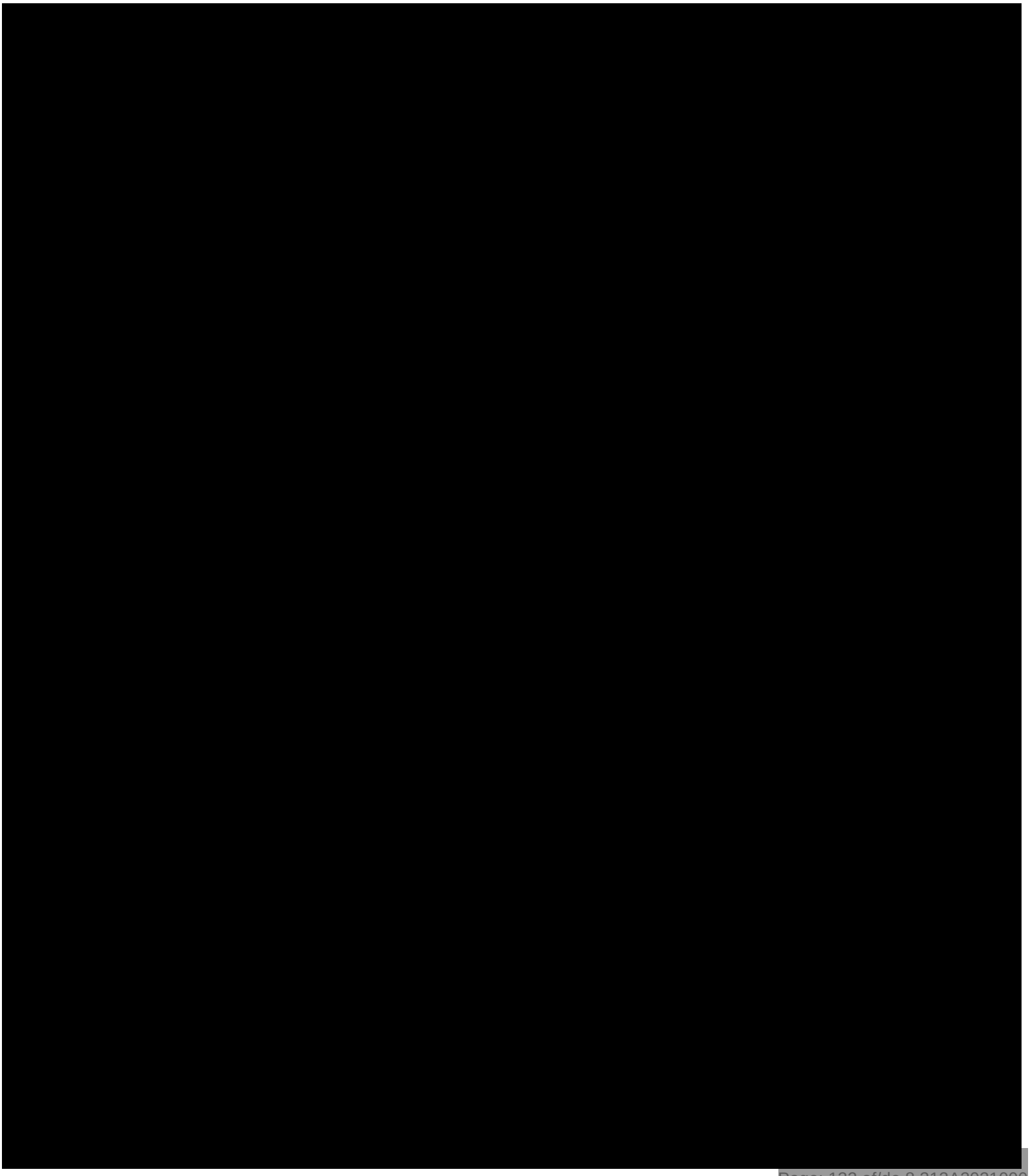

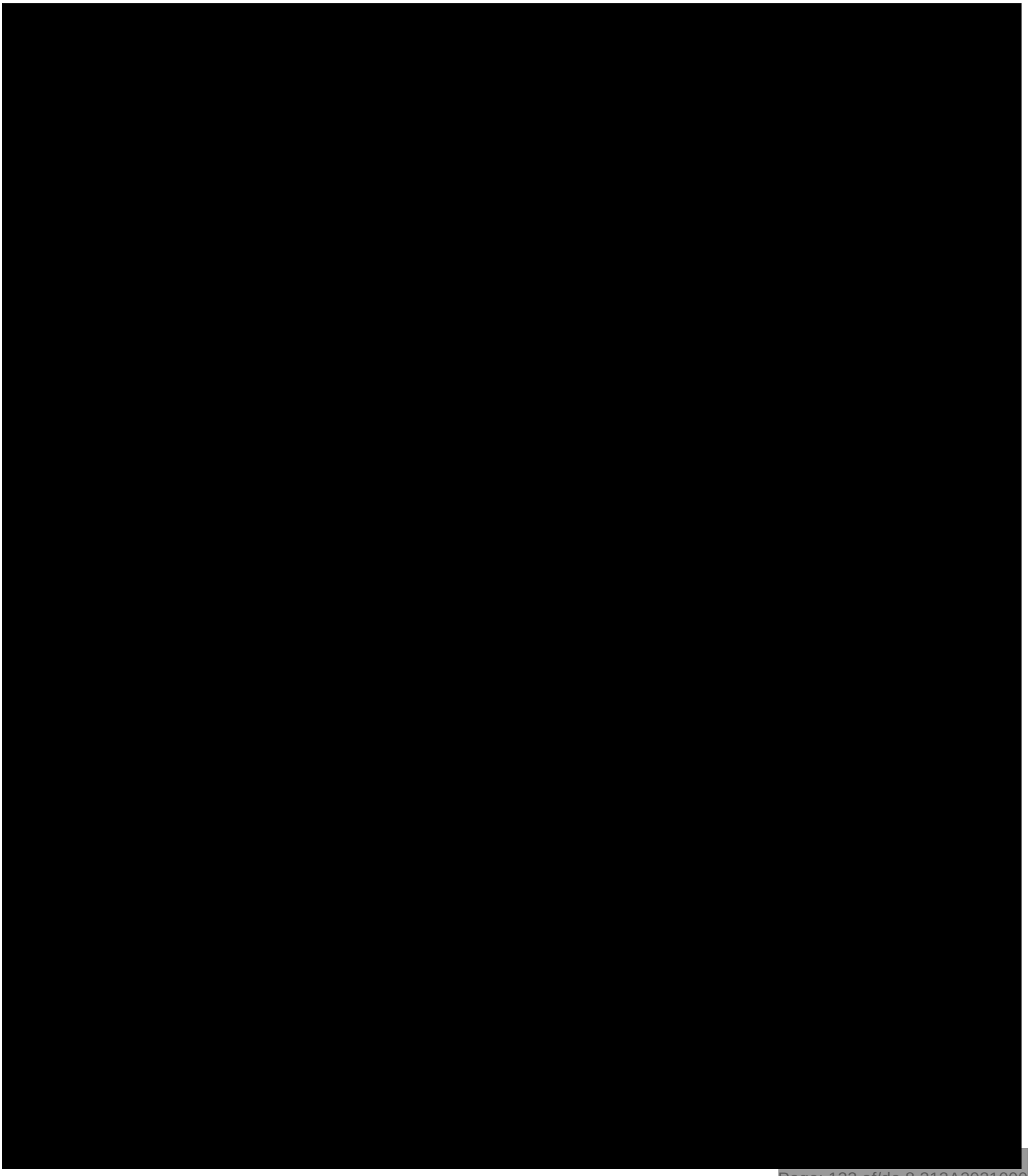

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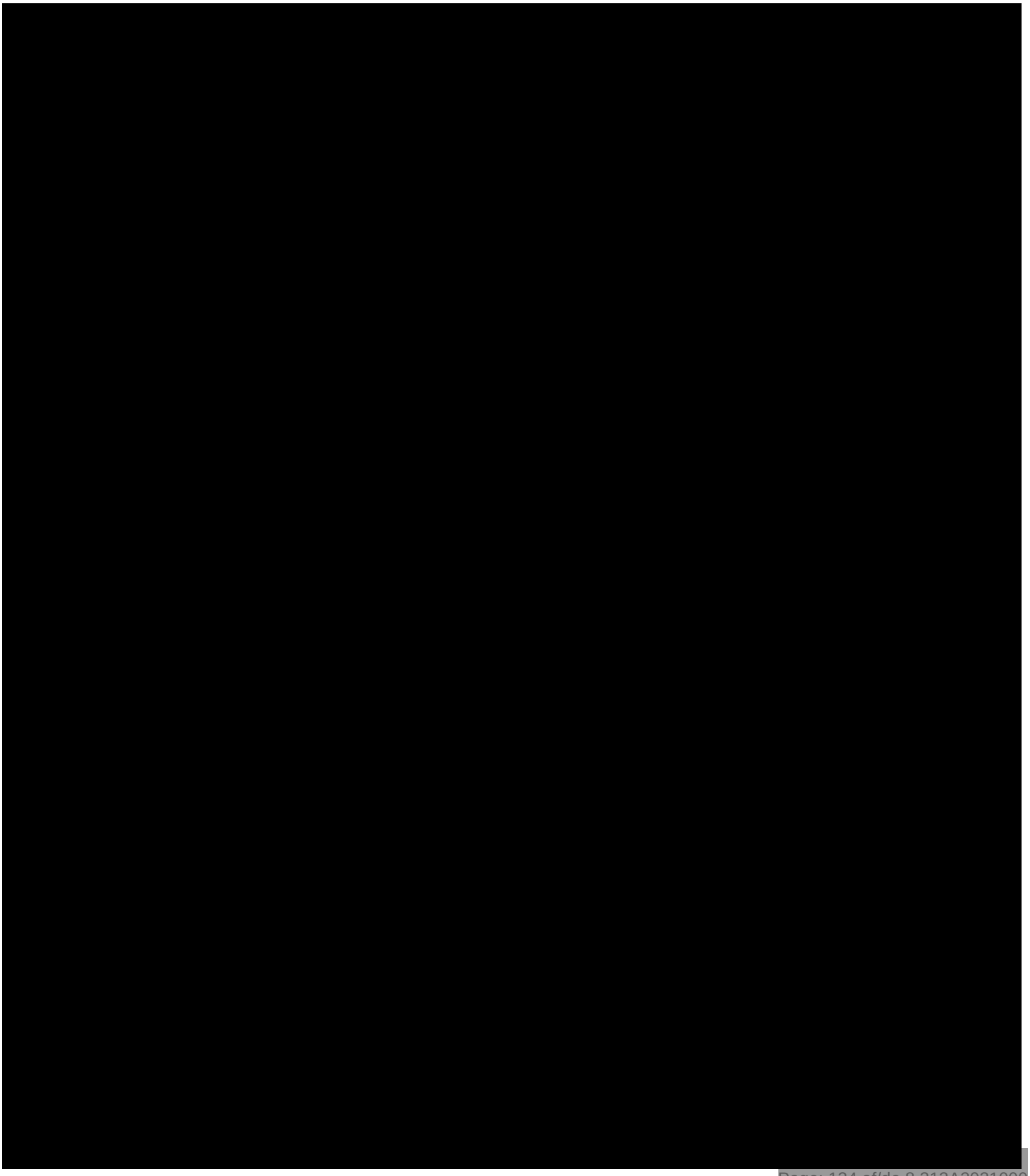

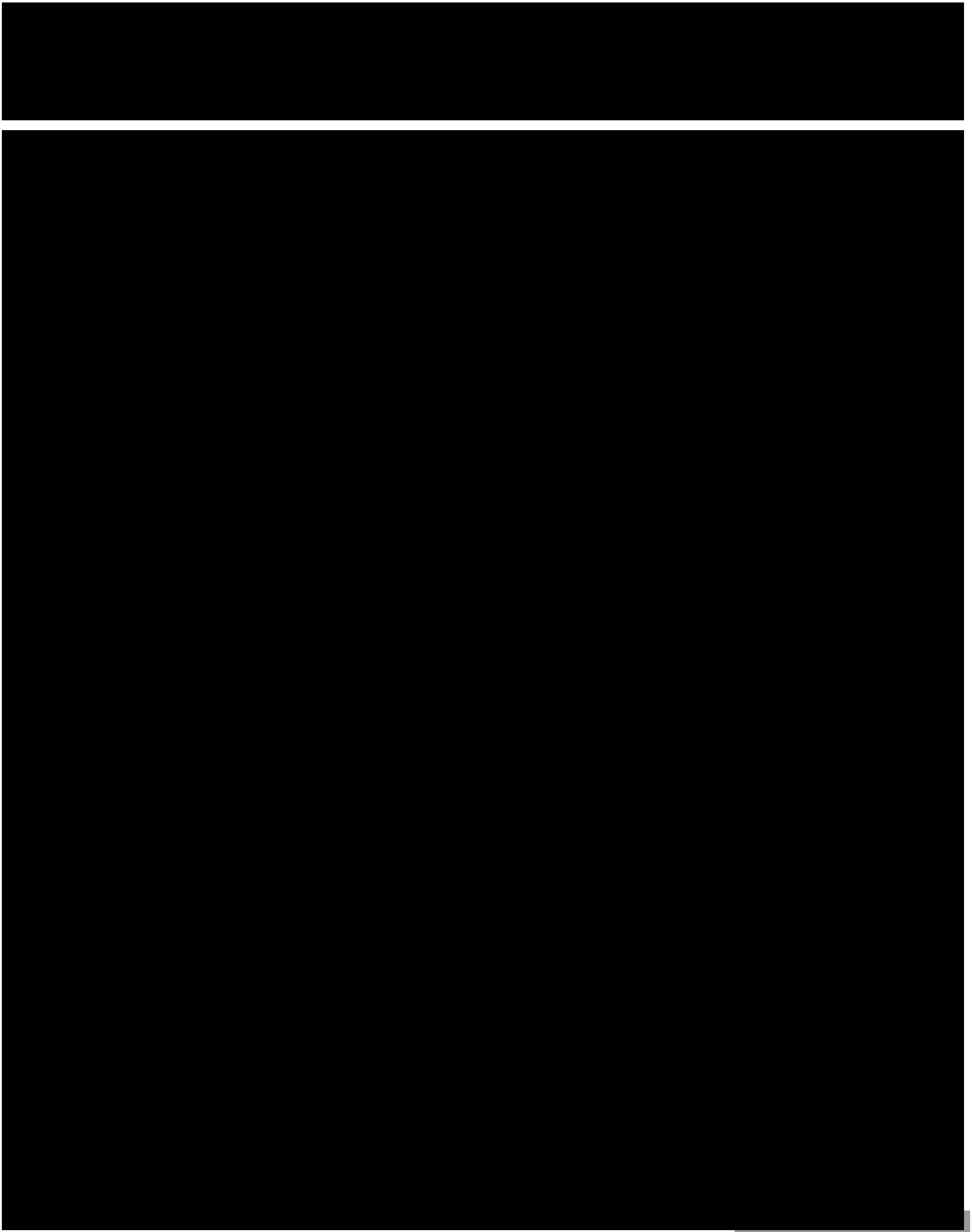

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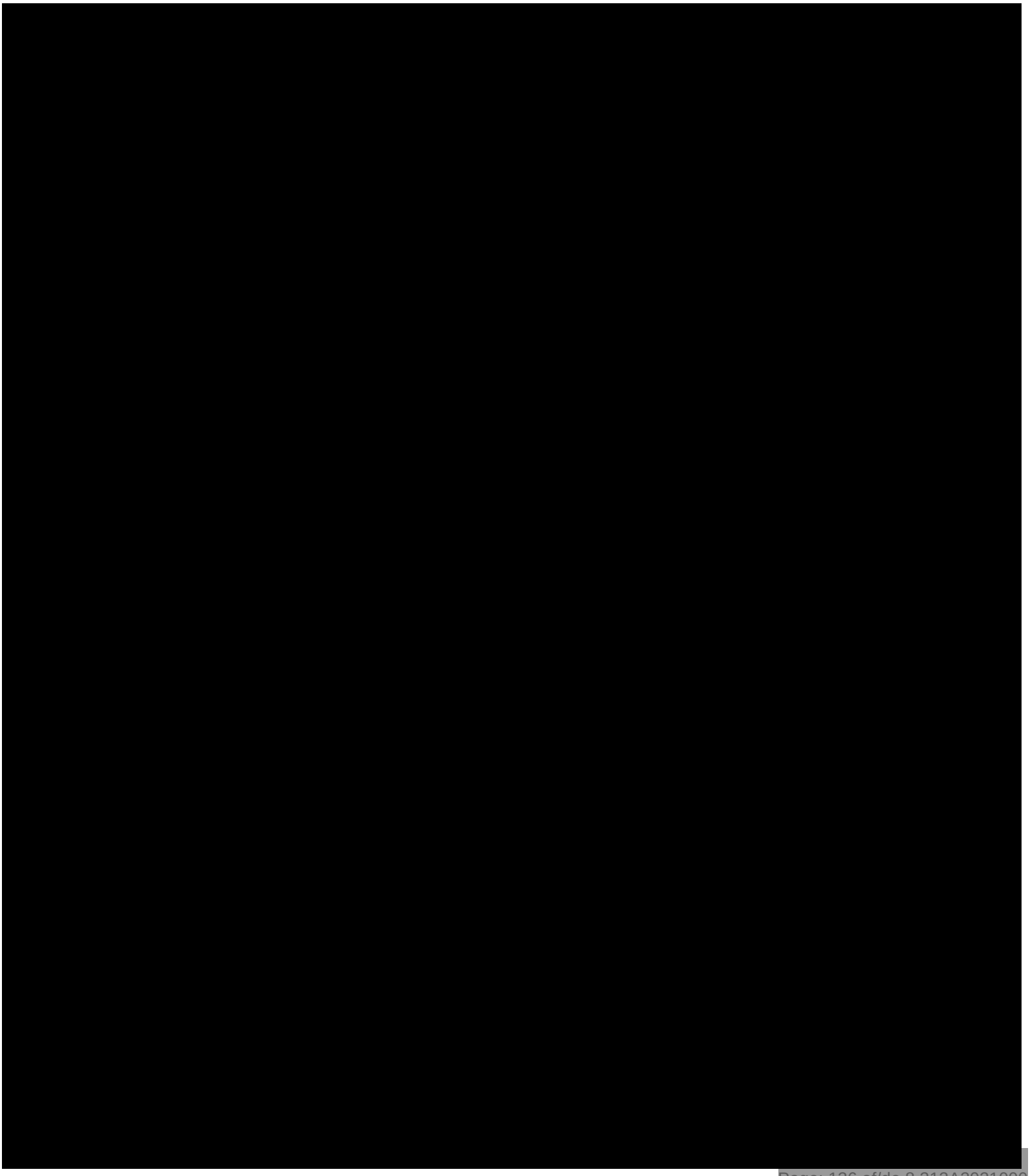

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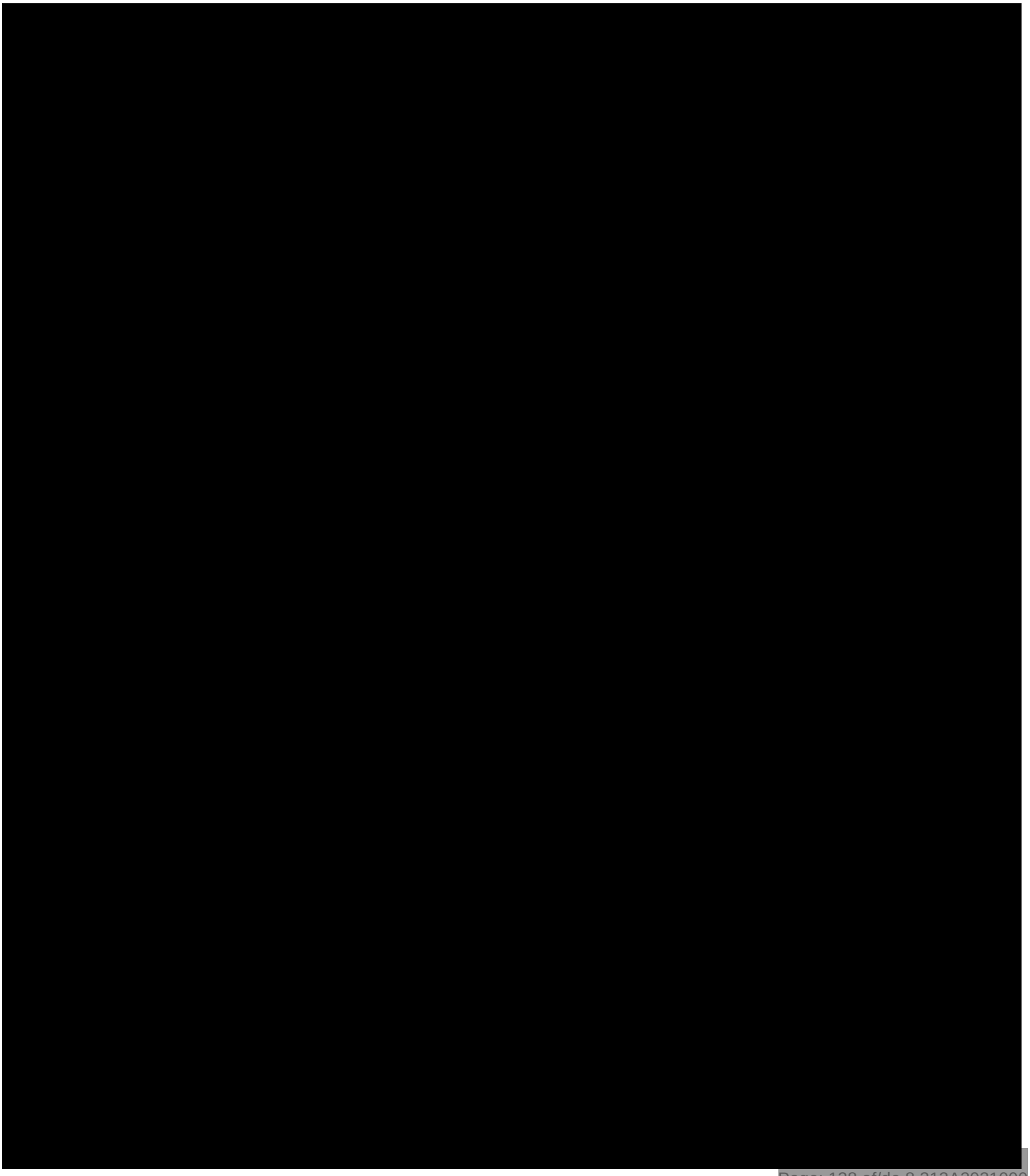

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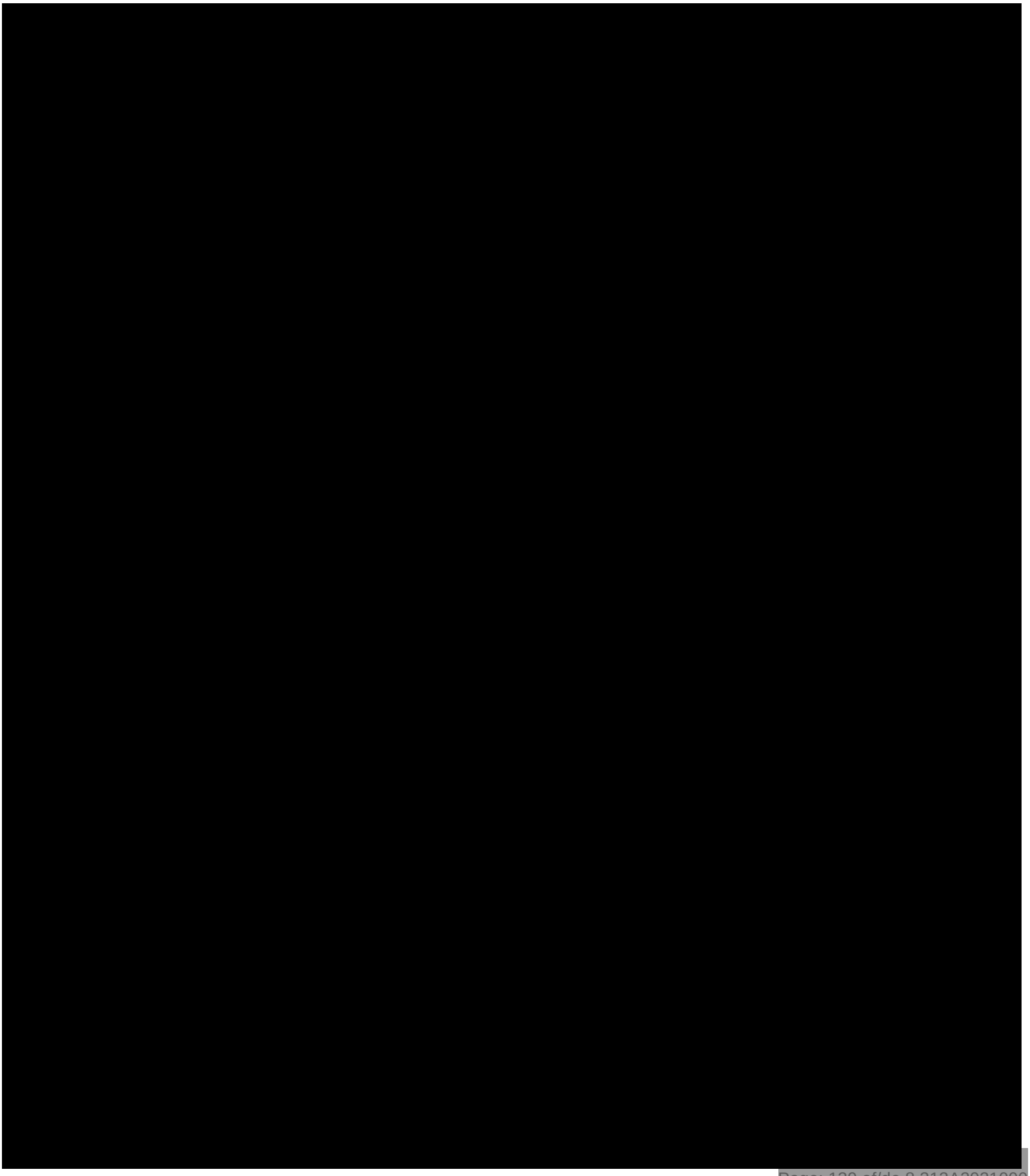

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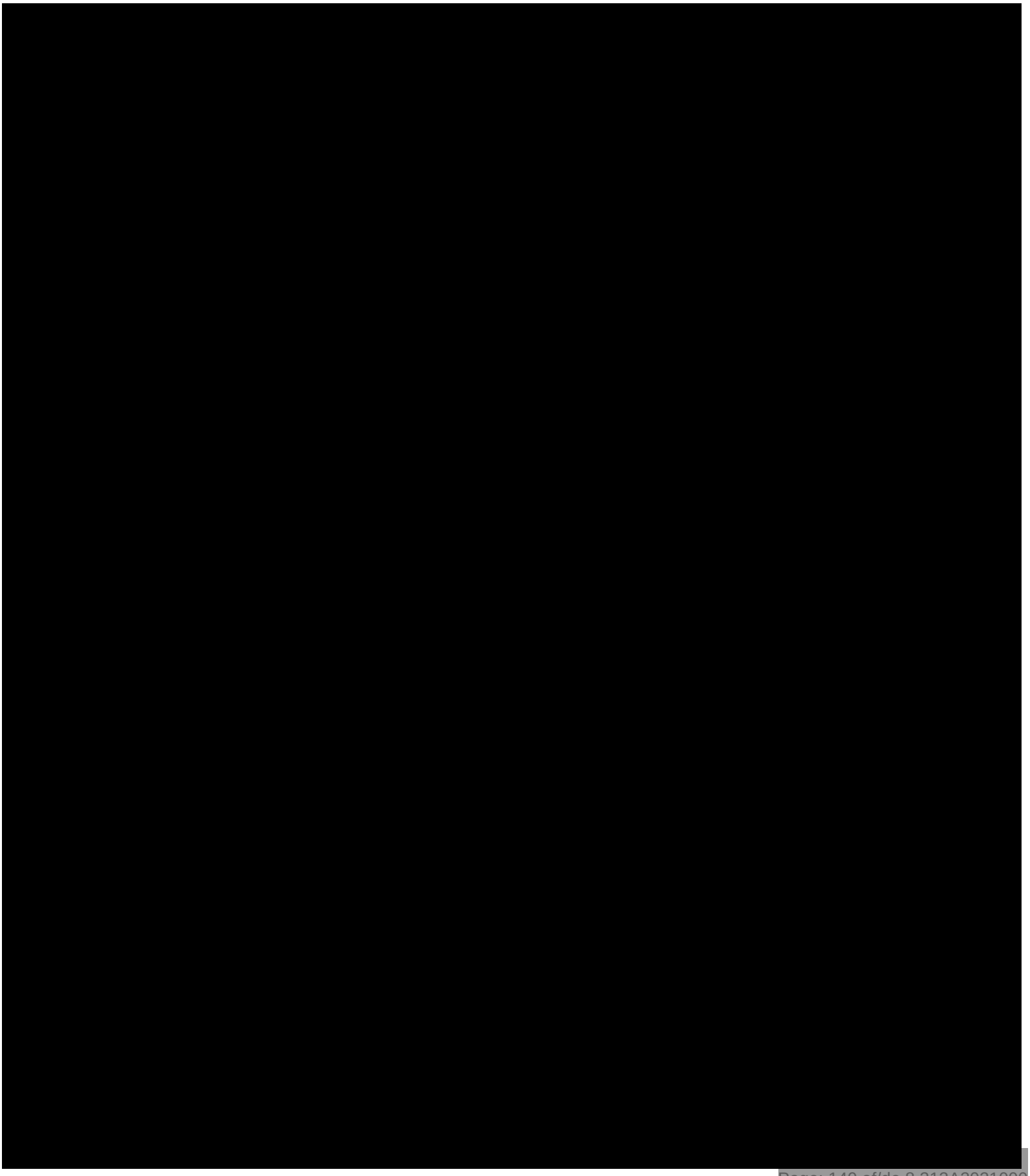

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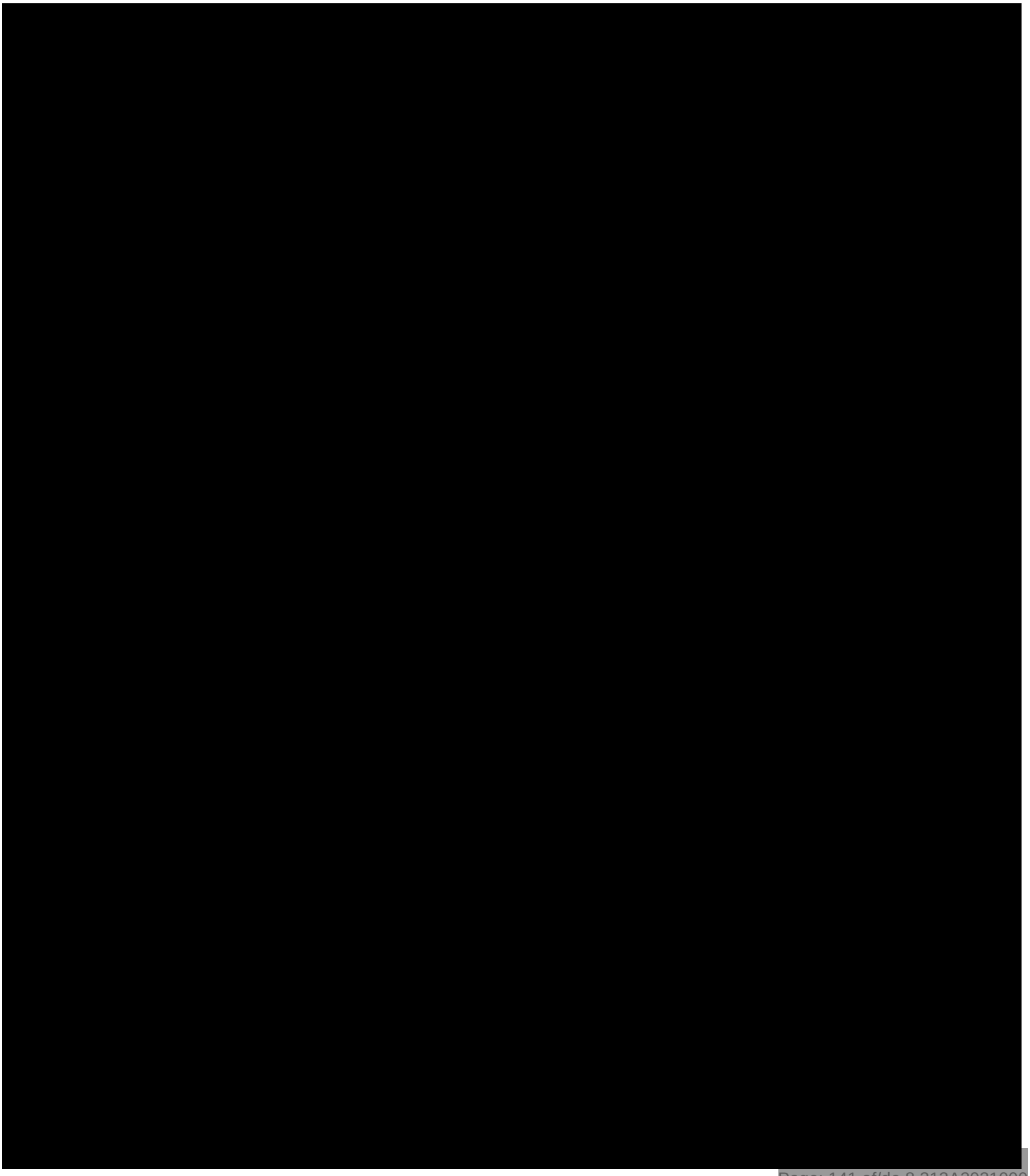

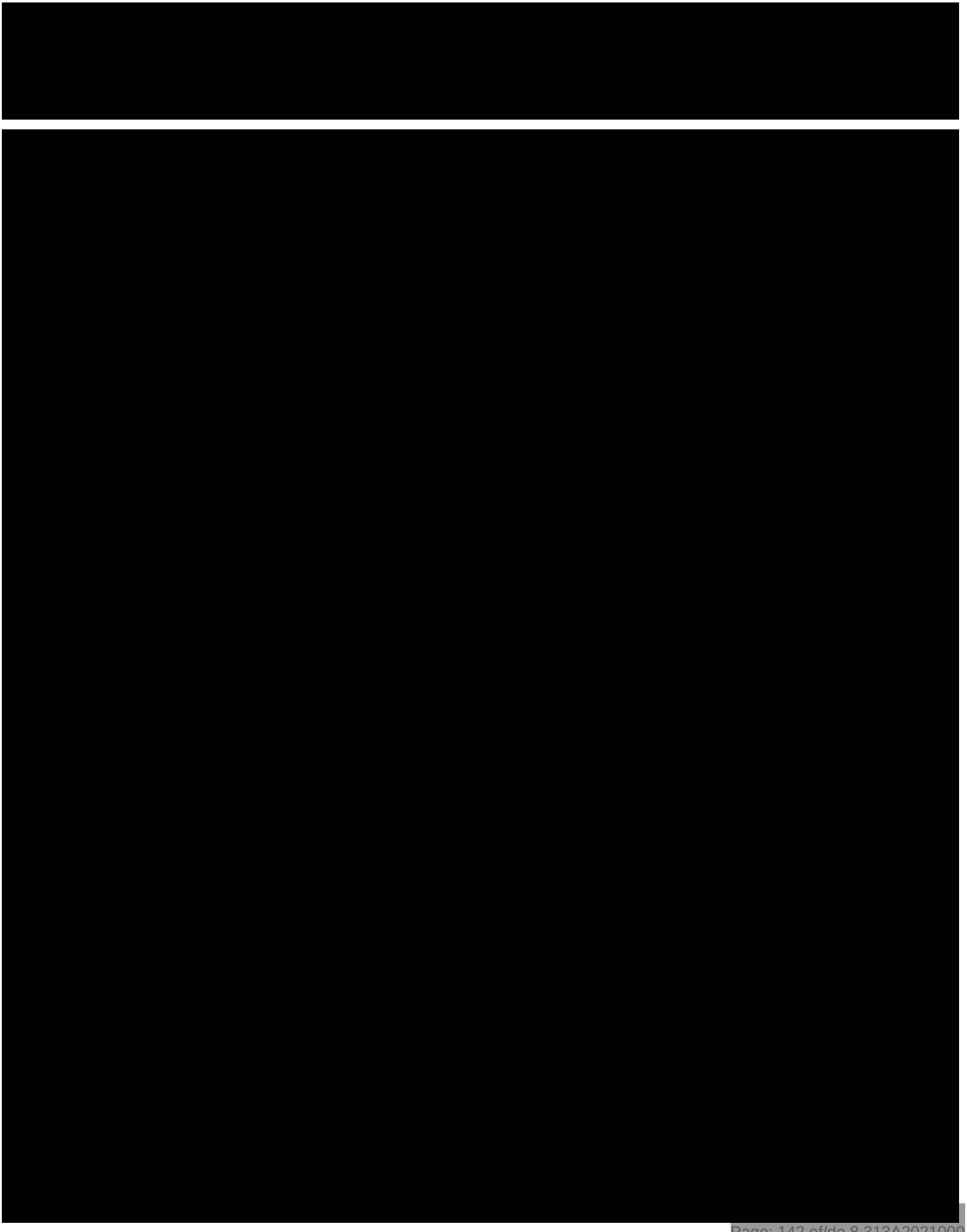

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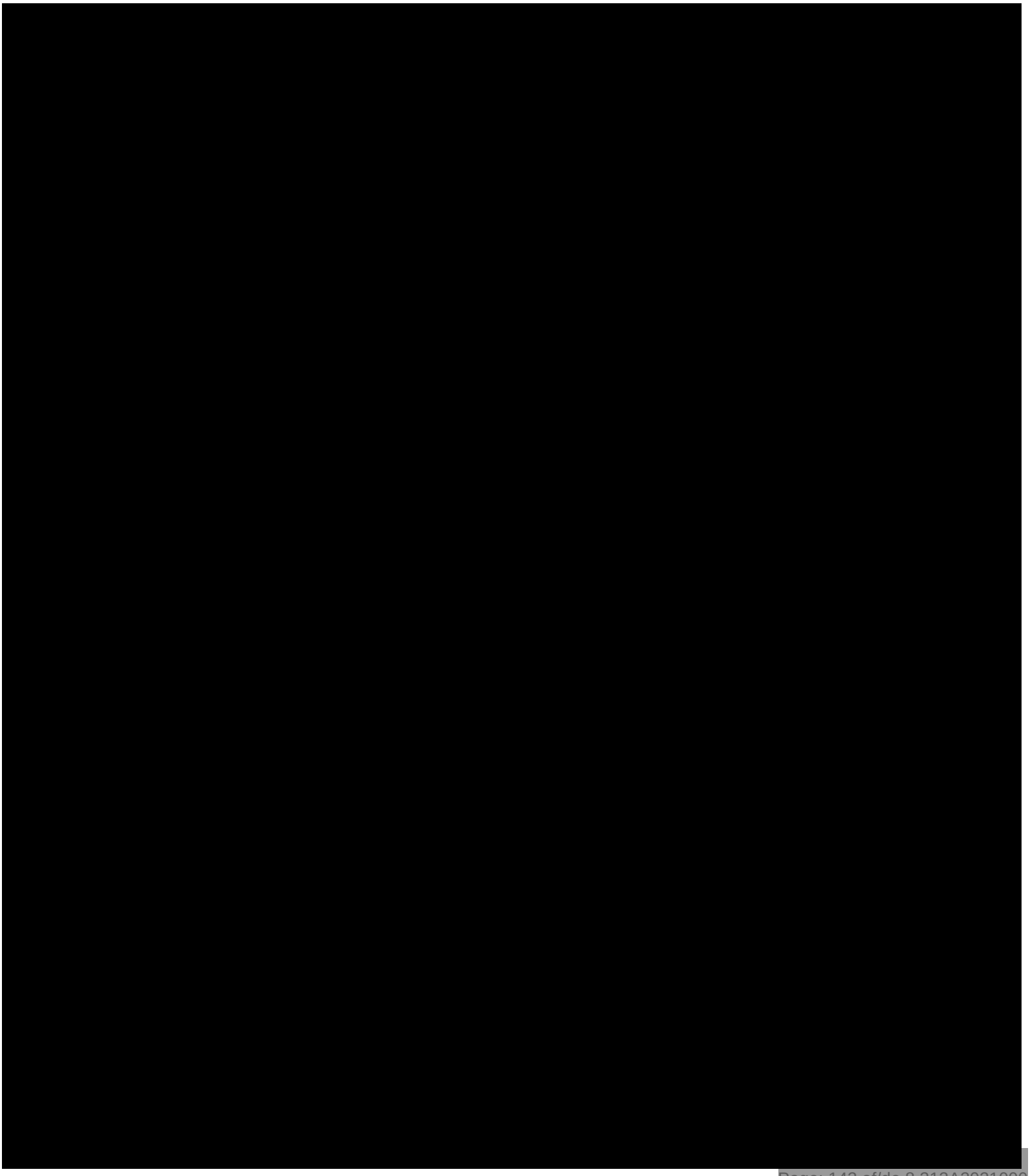


Meeting Minutes with Health Canada

Meeting Date and Time	January 20, 2021 (5:30 pm EST)
Product	SARS-CoV-2 rS Vaccine with Matrix-M1 Adjuvant (Novavax COVID-19 Vaccine)
Meeting Scope	Regulatory Strategy Overview

LIST OF ATTENDEES

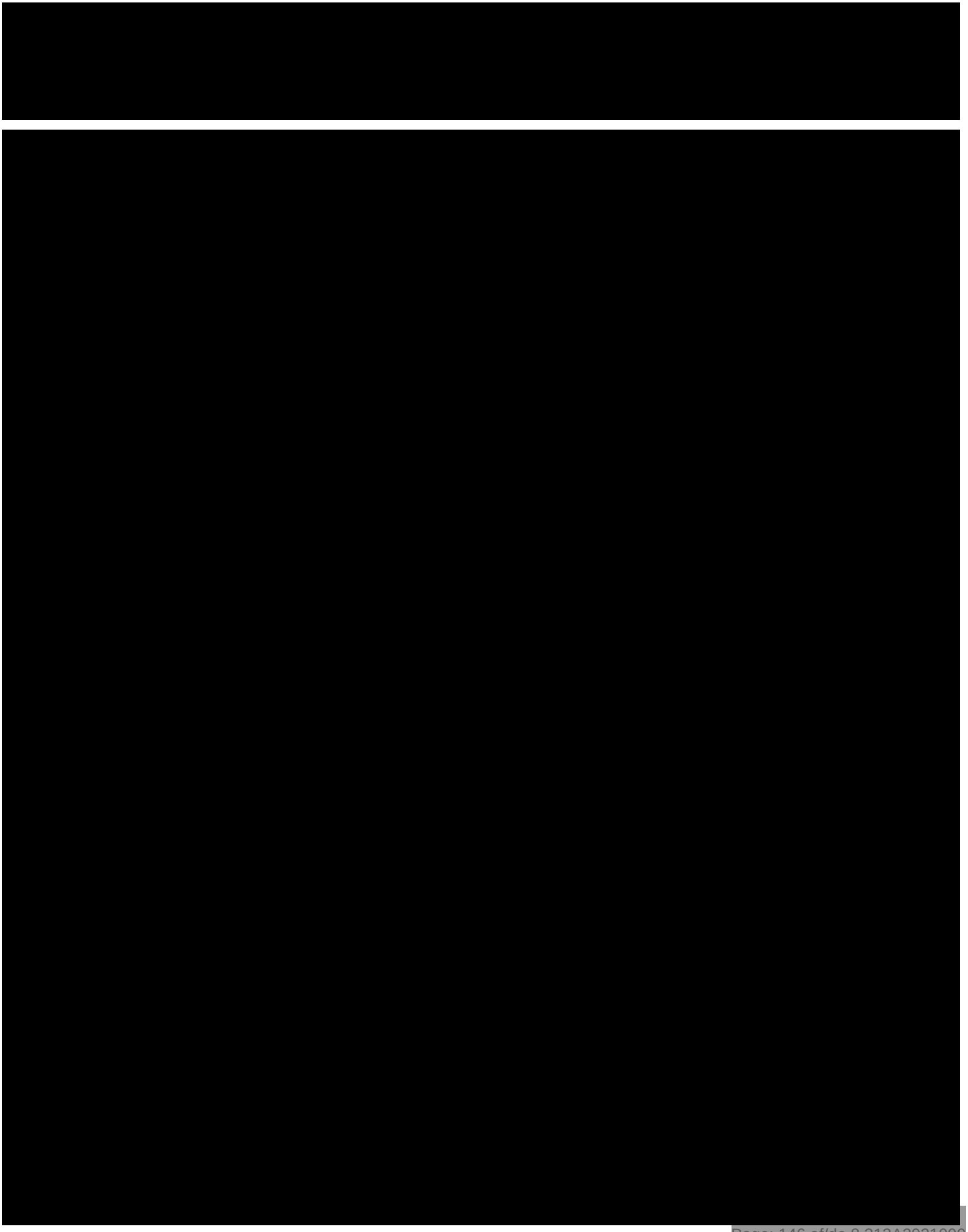
Sponsor's Attendees	Health Canada's Attendees
• [redacted]	• Dr. Celia Lourenco, Director, Biologic and Radiopharmaceutical Drugs Directorate (BRDD) • Stephanie Hardy, Executive Director, BRDD • Dr. Michael Rosu-Myles, Director, Centre of Biologics Evaluation (CBE) • Dr. Leo Bouthillier, Director, CBE

BACKGROUND SUMMARY

Novavax is developing a severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M1 adjuvant for active immunization for the prevention of mild, moderate, and severe coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in adults ≥[redacted]

INTRODUCTION AND MEETING OBJECTIVES

[redacted]



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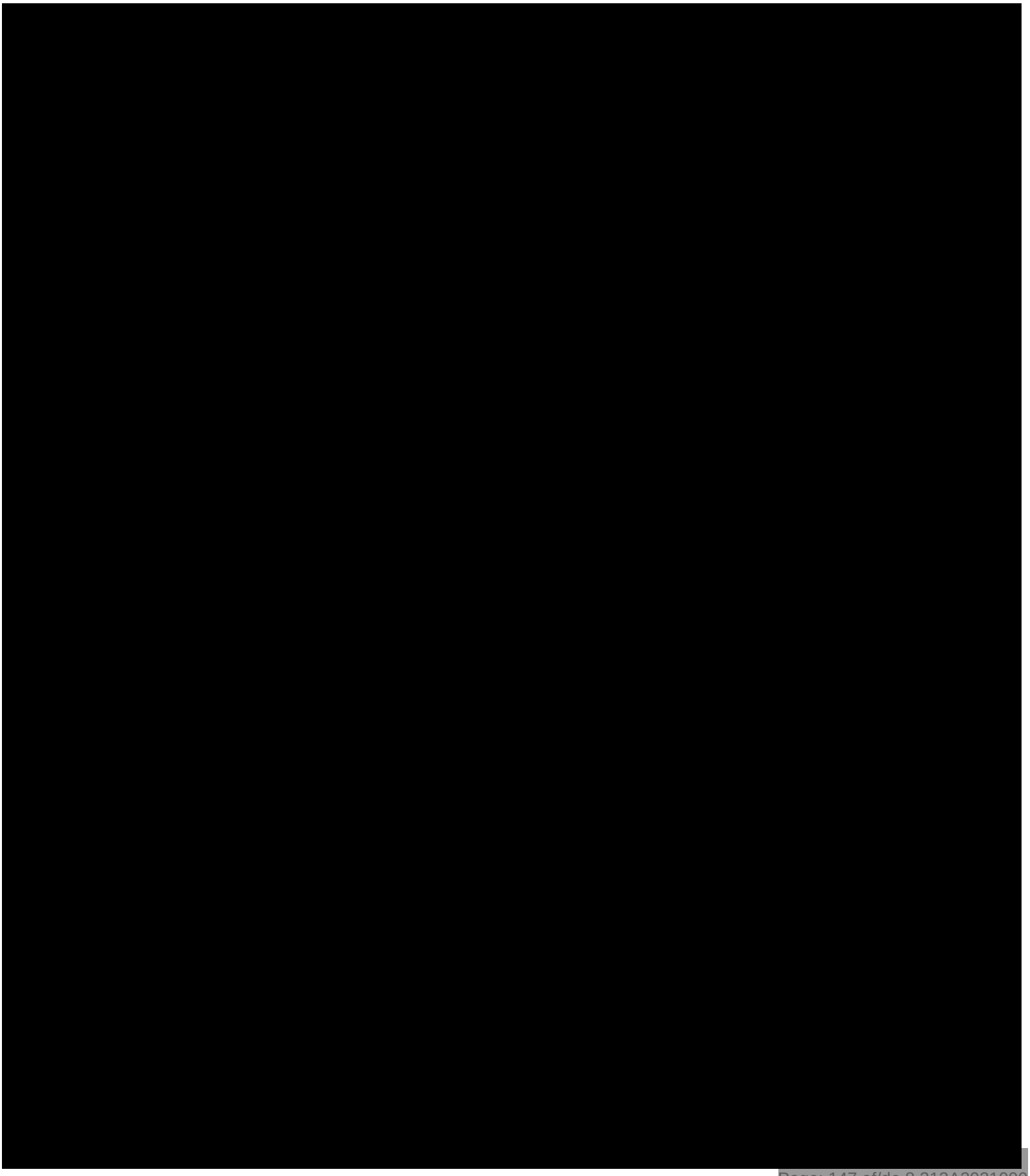

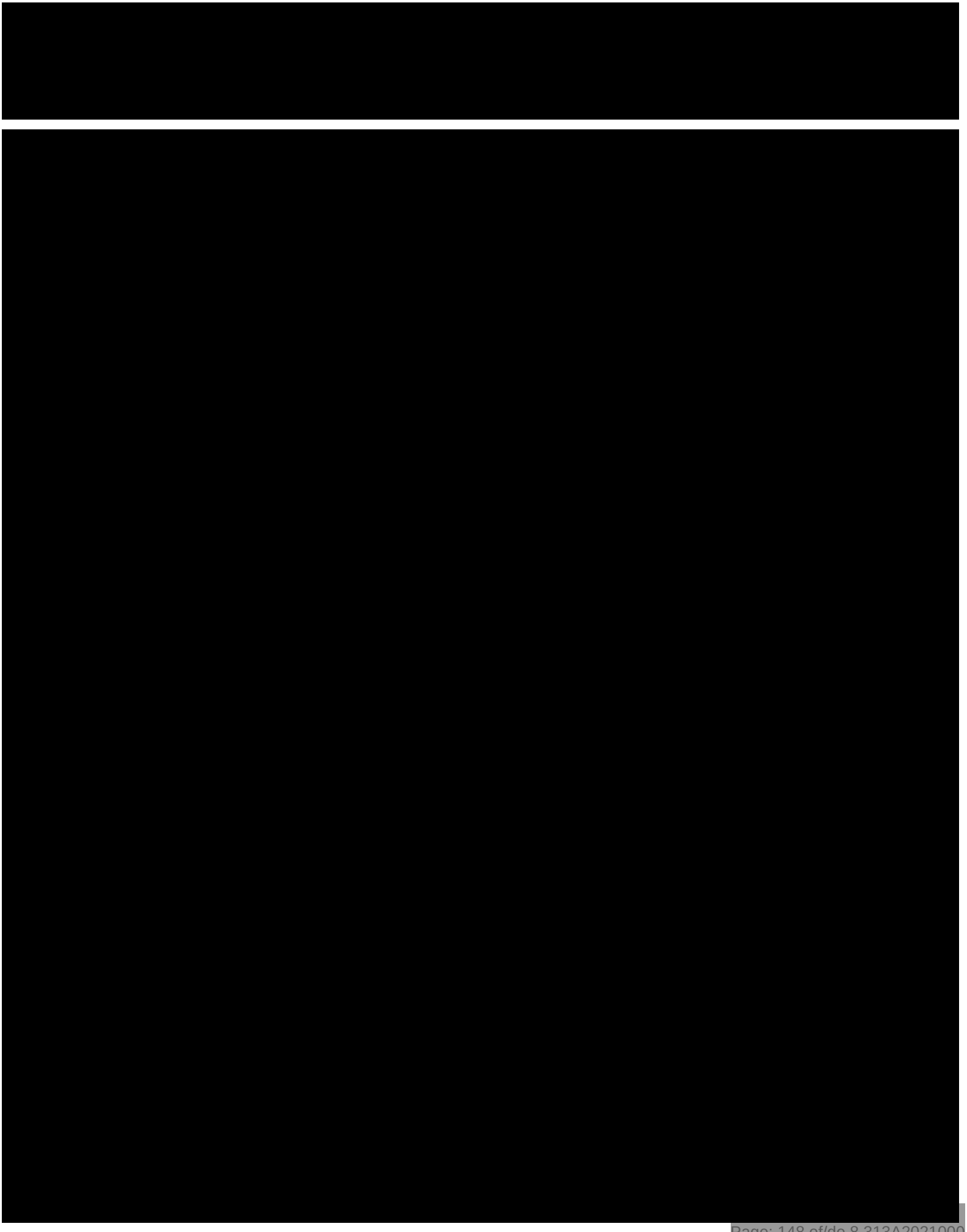

From: [redacted]
To: Hashem, Nesma (HC/SC); [redacted] Health Canada Communications
Cc: Patel, Shalu (HC/SC); Finlayson, Sarah (HC/SC); Panetta, Vincent (HC/SC)
Subject: RE: URGENT: [redacted] Novavax COVID-19 Vaccine - COVID-19 Interim Order (Control [redacted]
Date: 2021-06-18 11:53:06 AM
Attachments: image001.png
image002.png
image003.png
image004.png
image005.png

Dear Nesma

On Behalf of [redacted], I do confirm the receipt of the [redacted] Novavax COVID-19 Vaccine.

Regards

[redacted]
PRINCIPAL SPECIALIST, REGULATORY AFFAIRS
REGULATORY AFFAIRS

PPD
929 North Front Street
Wilmington, NC 28401-3331
[redacted]
www.ppdi.com
www.ppd.com/regulatory-affairs

Early Development | Clinical Development | Laboratories | Post-Approval | Consulting

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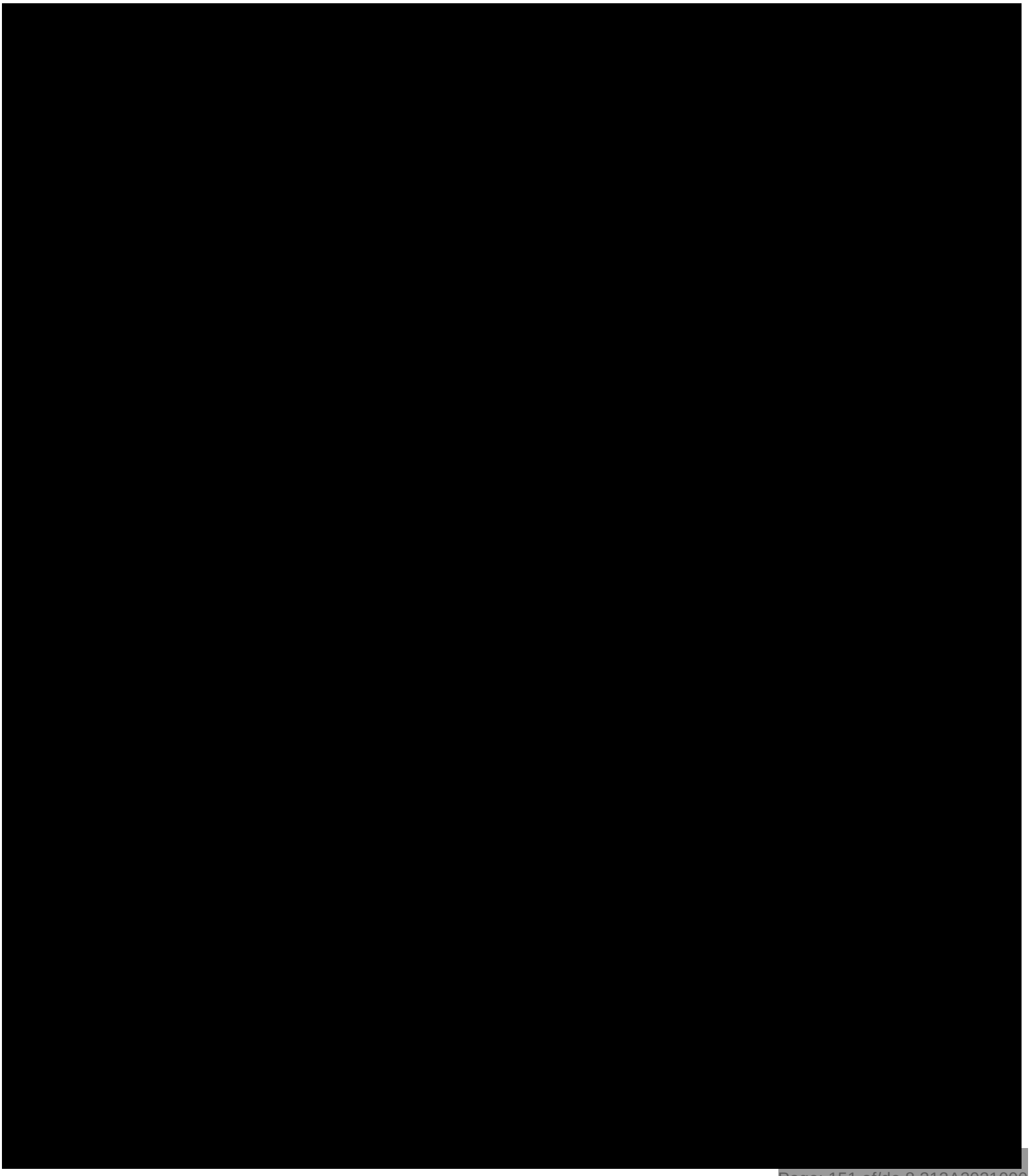
From: Hashem, Nesma (HC/SC) <nesma.hashem@canada.ca>
Sent: Friday, June 18, 2021 11:41 AM
To: [redacted] Health Canada Communications <PPD-HCsubmissions@ppd.com>; [redacted]
Cc: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>; Finlayson, Sarah (HC/SC) <sarah.finlayson@canada.ca>; Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: URGENT: [redacted] Novavax COVID-19 Vaccine - COVID-19 Interim Order (Control [redacted]
Importance: High

Dear [redacted]
Enclosed is the [redacted] for the above-mentioned submission.
Please confirm receipt of this email and its attachments.
Thank you,
Nesma

Nesma Hashem, MESc., RAQC
Senior Regulatory Affairs Officer
Biologic and Radiopharmaceutical Drugs Directorate
Health Canada / Health Products and Food Branch / Government of Canada
nesma.hashem@canada.ca / Tél. : 613-355-7315 / Fax: 613-946-9520



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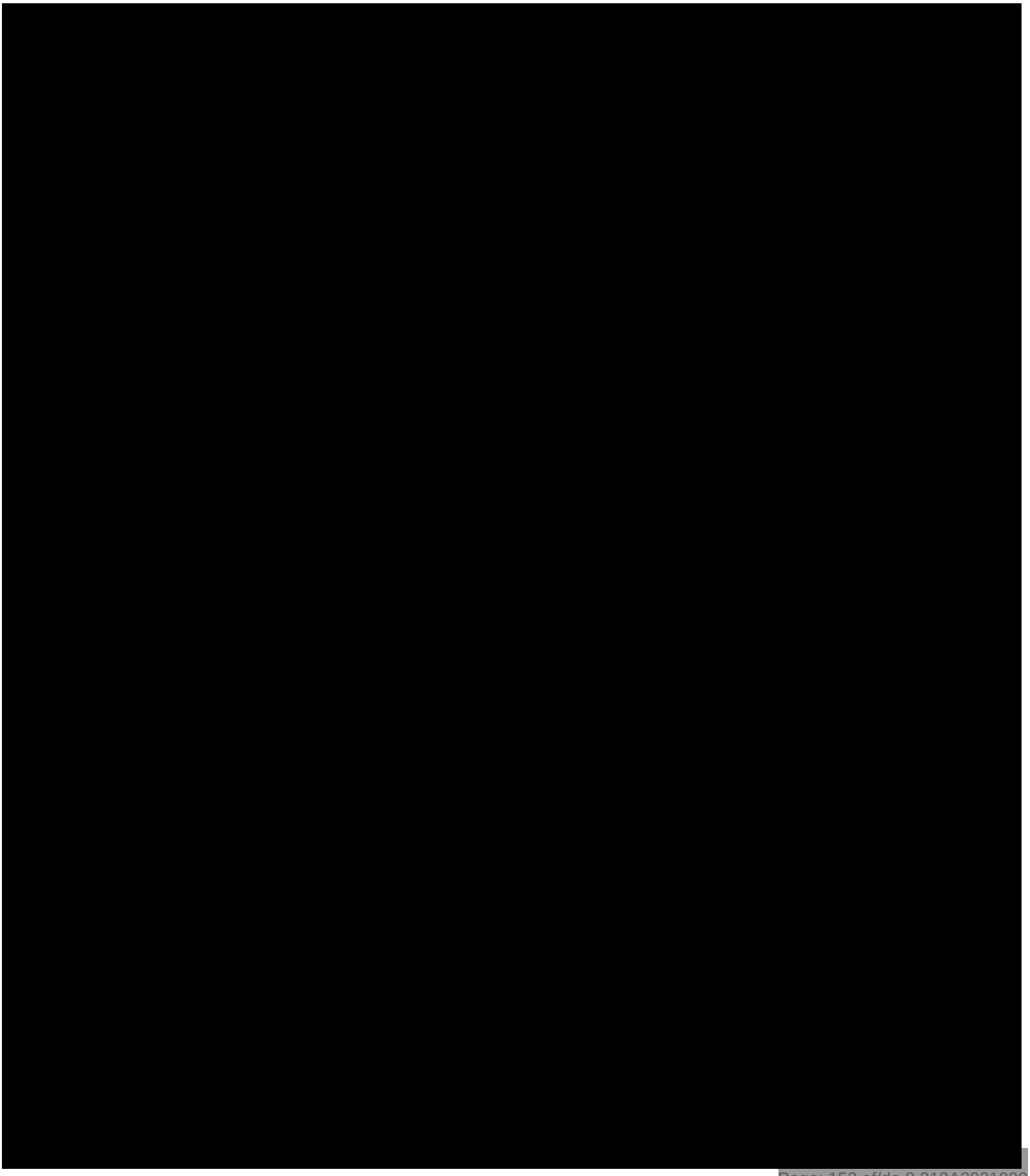

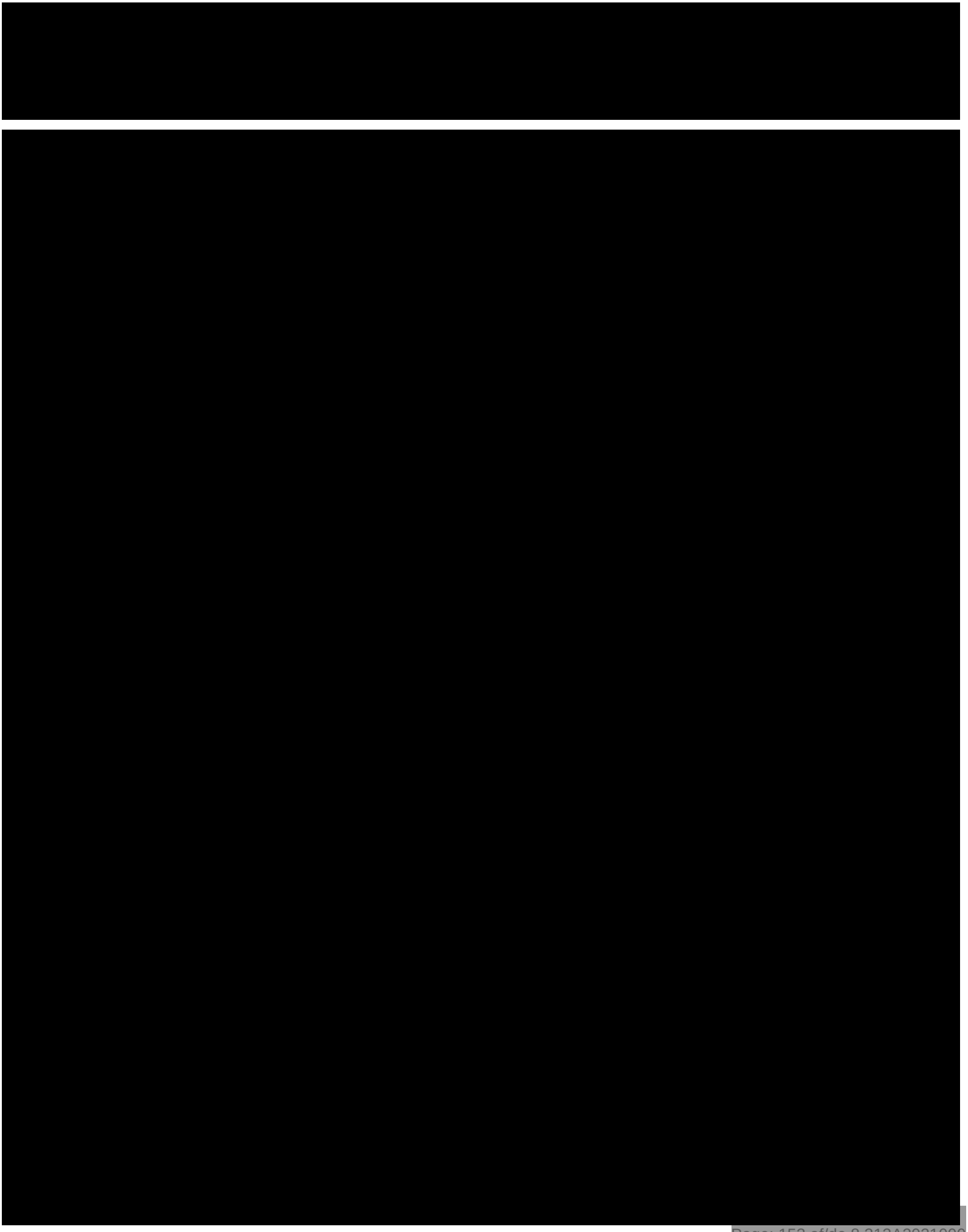

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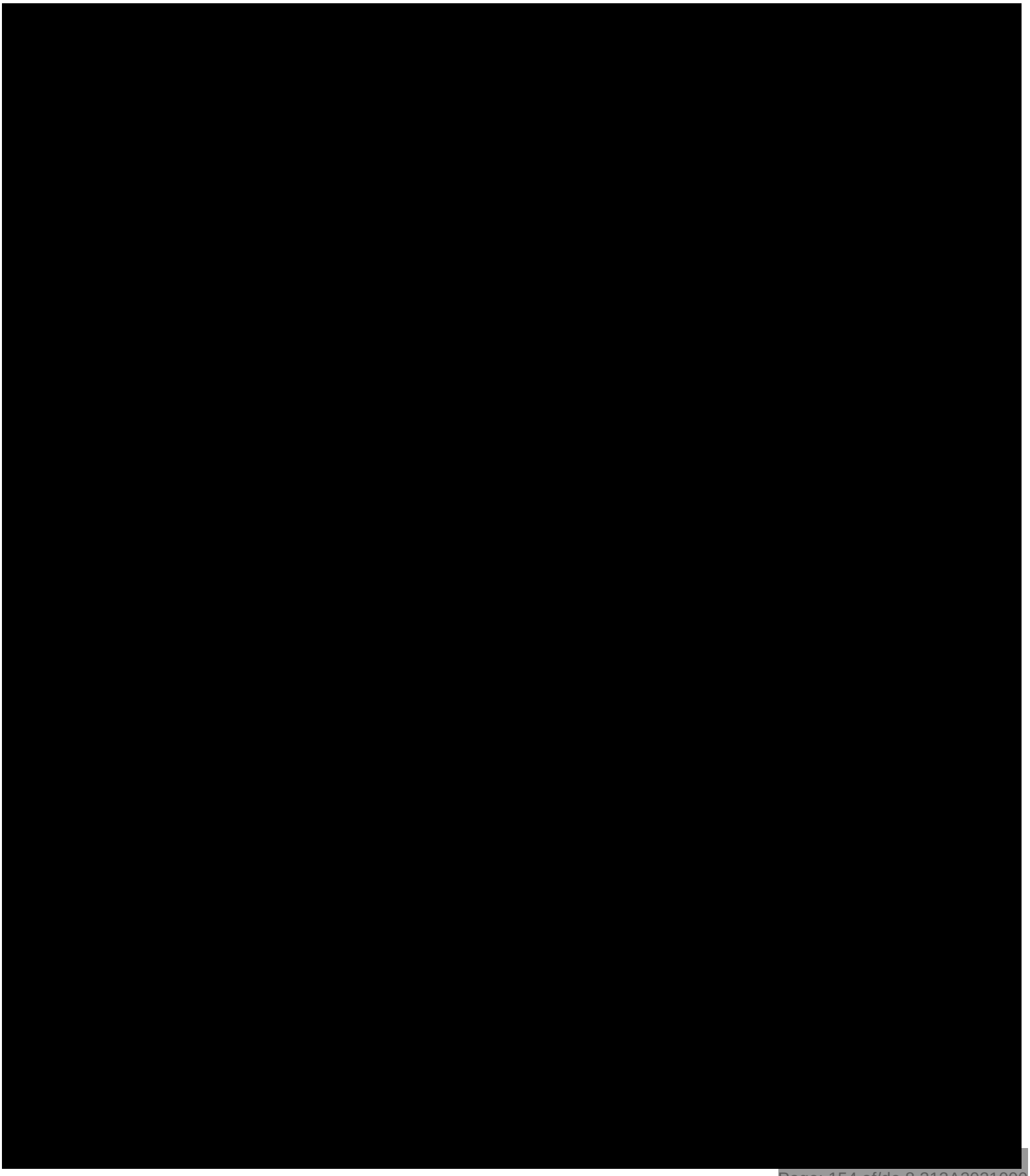

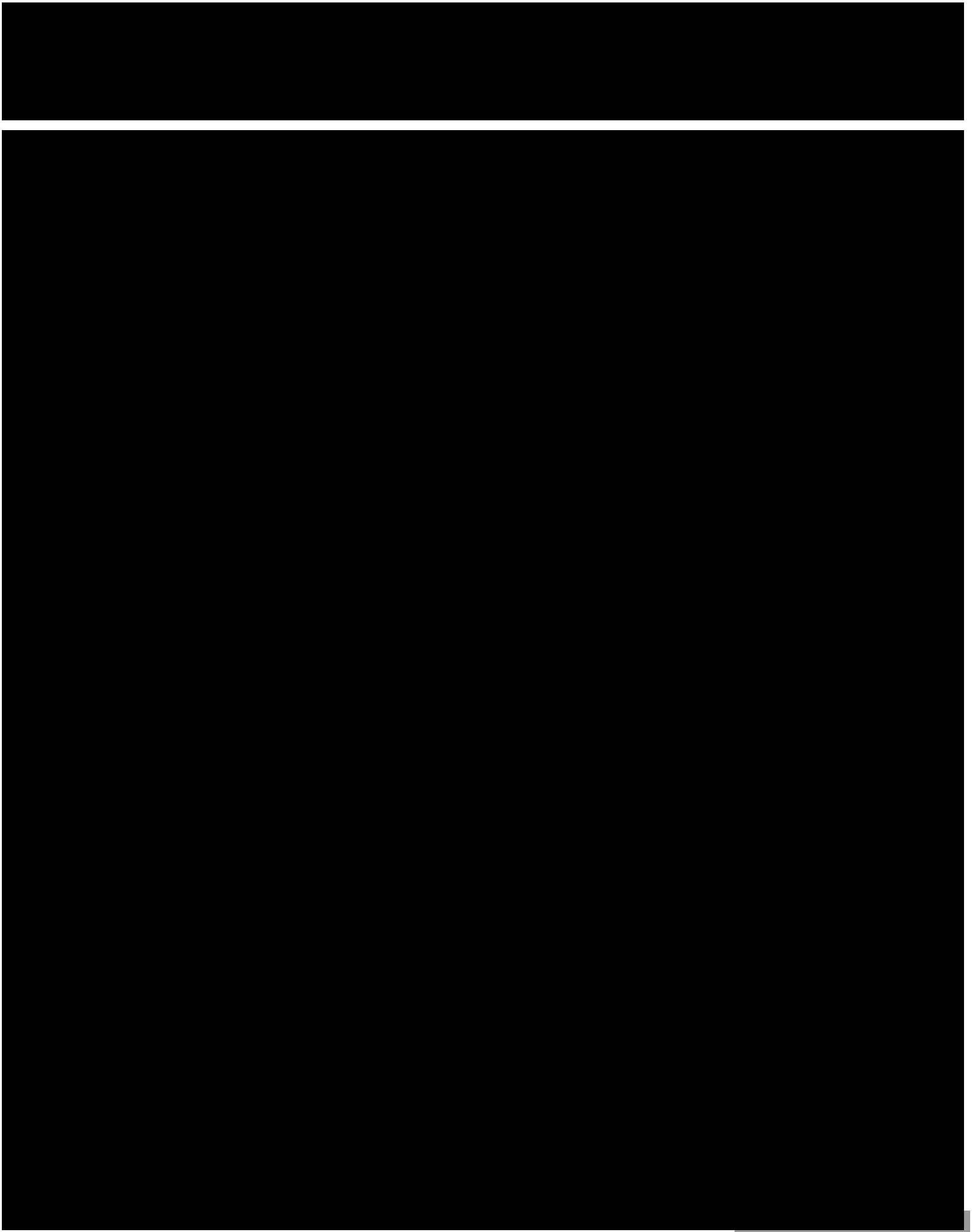

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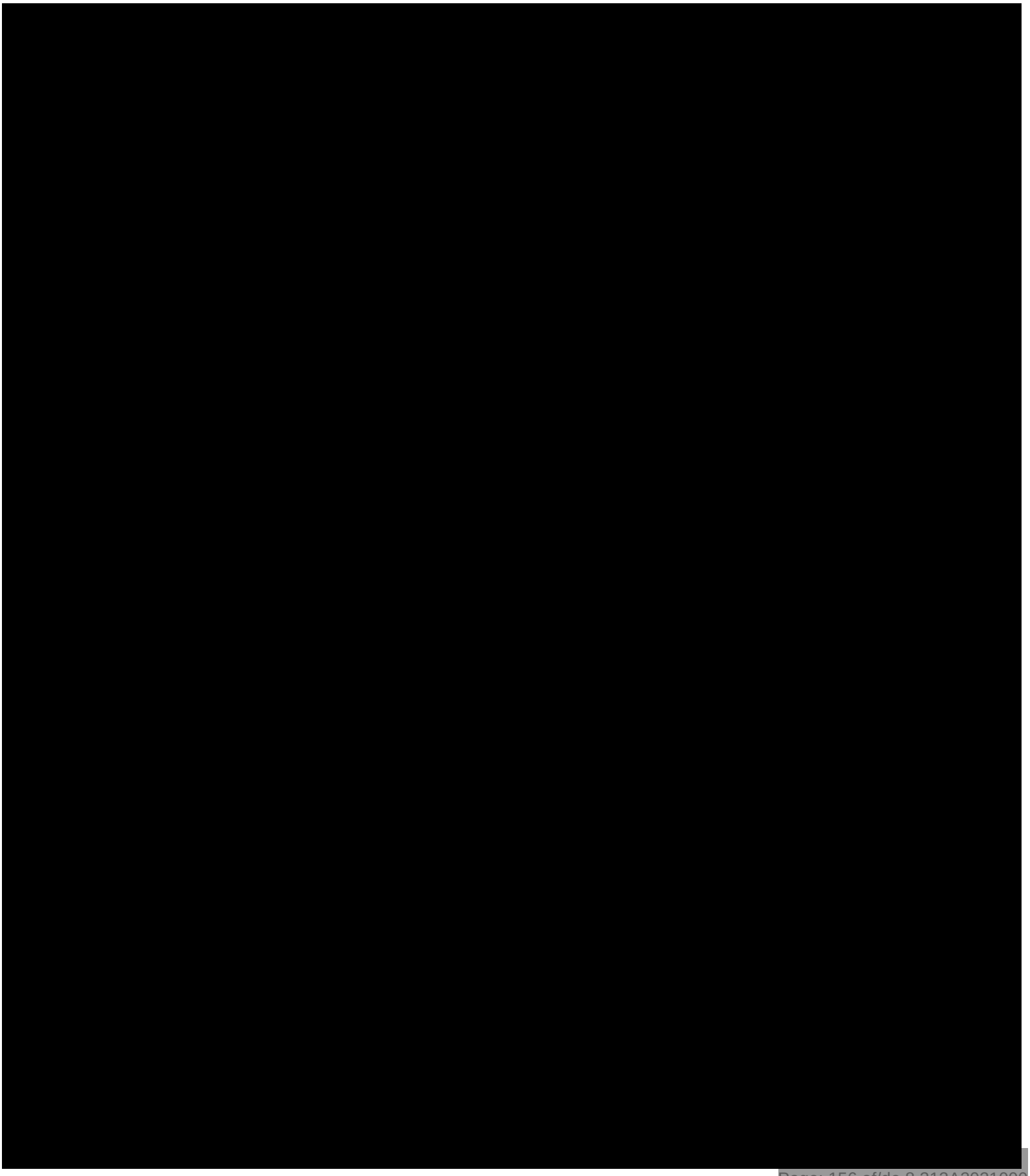

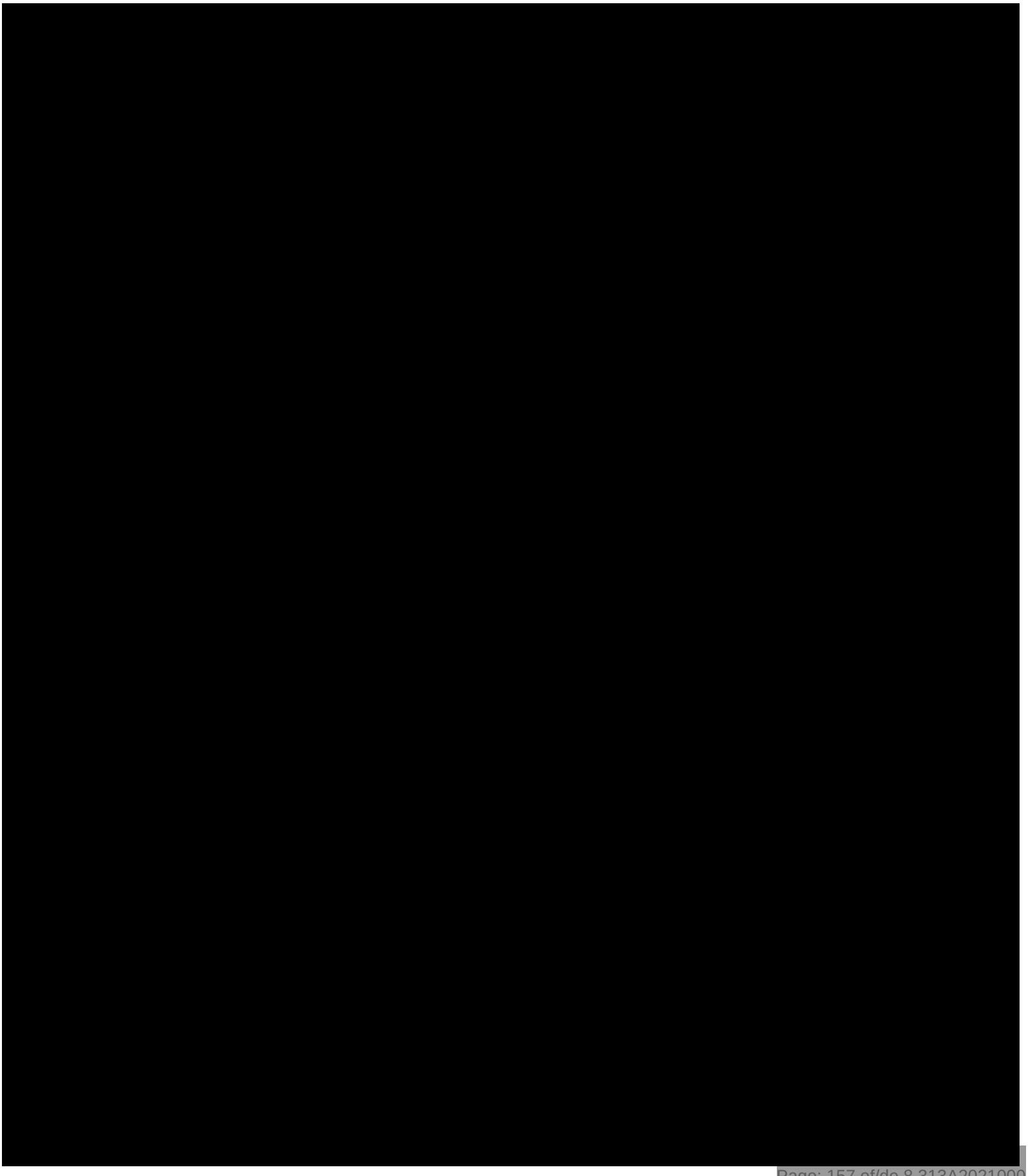

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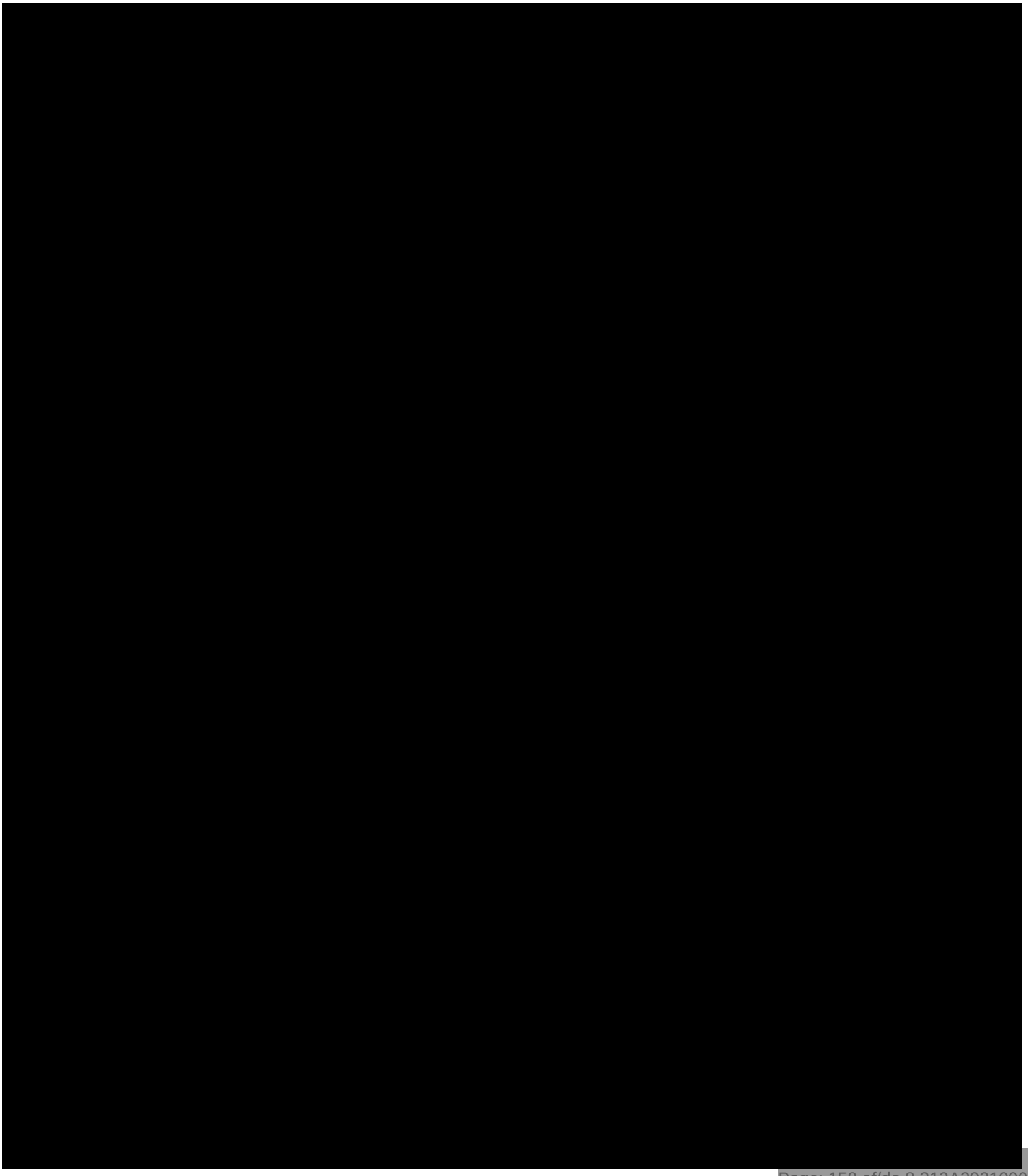

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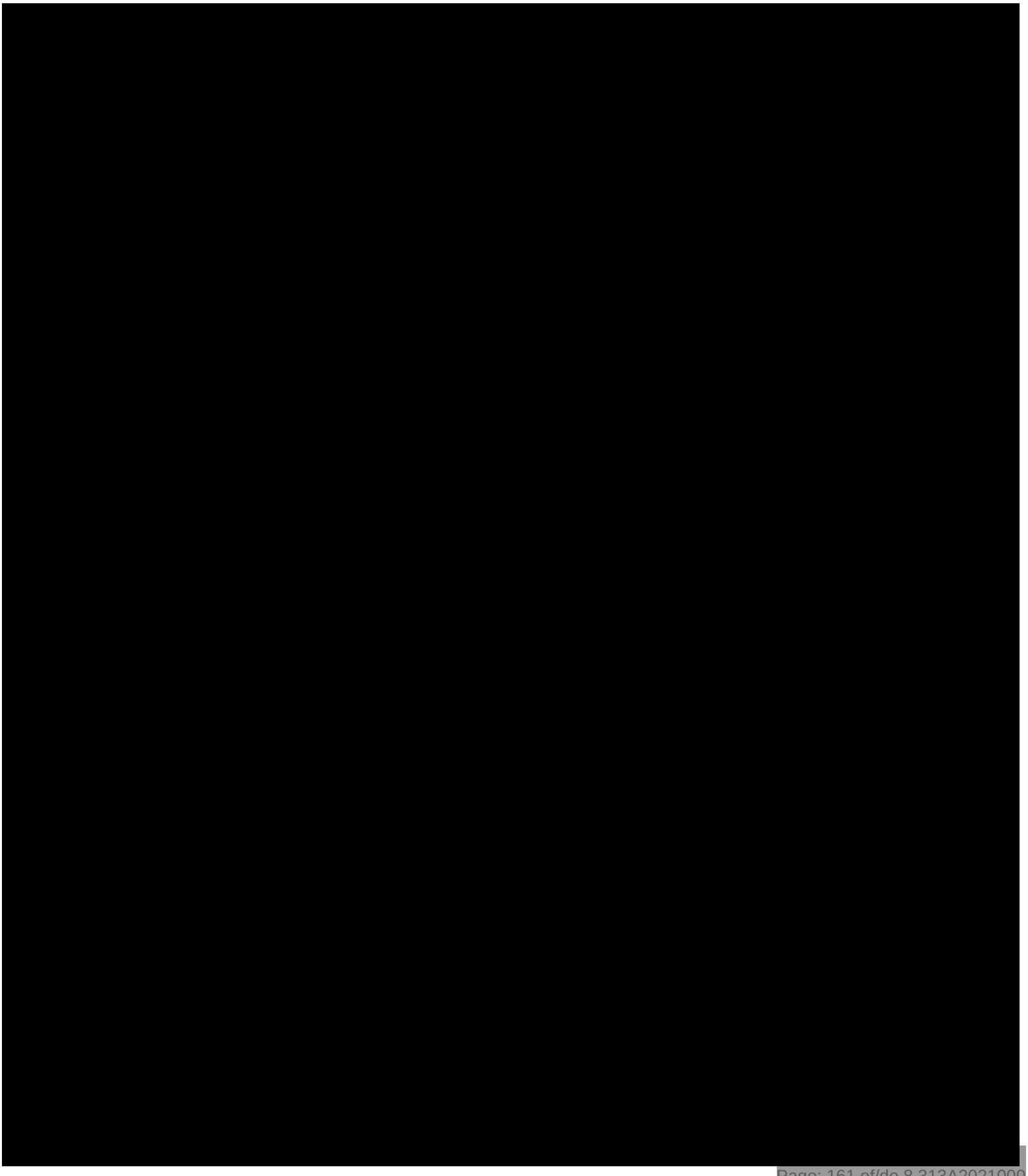

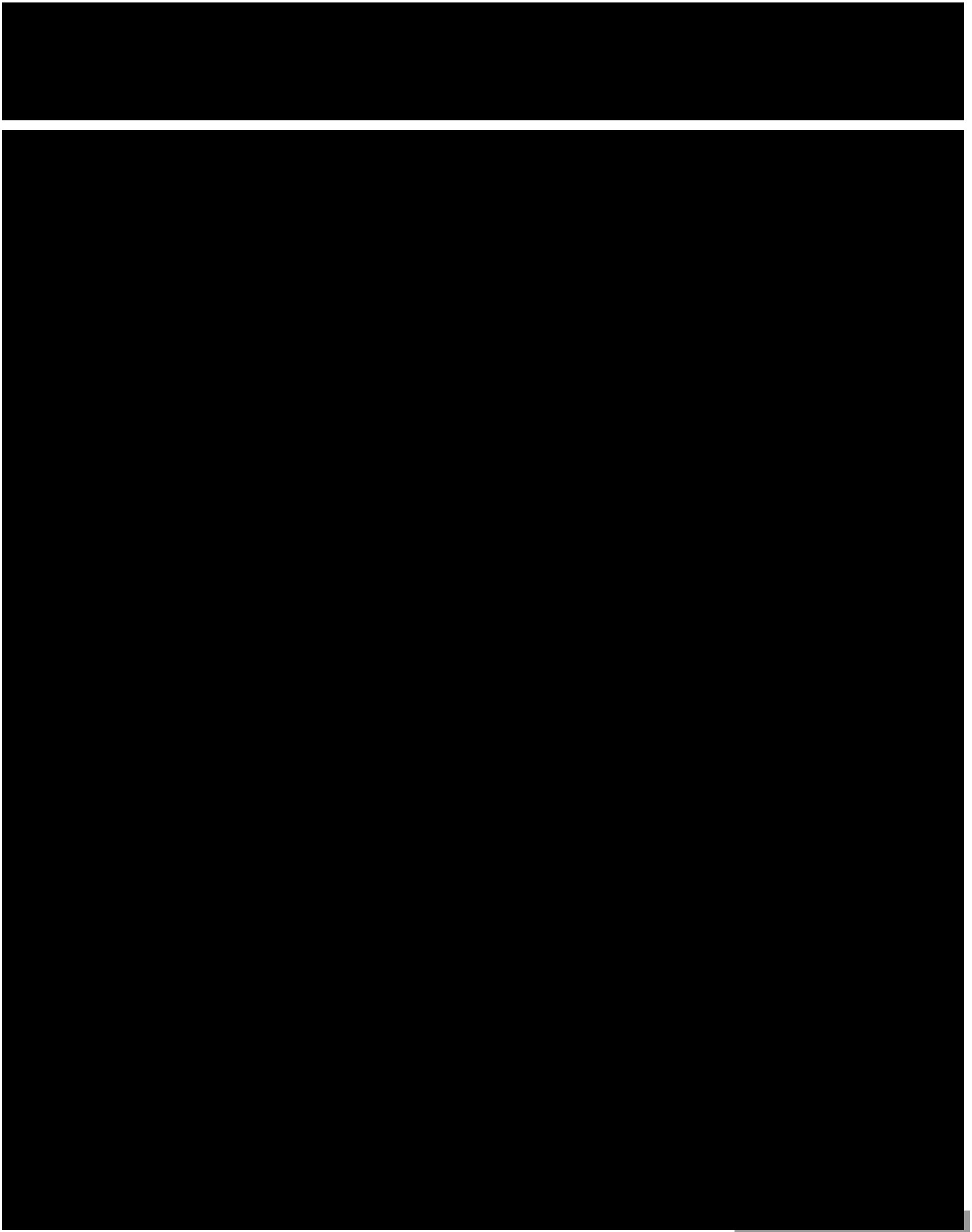

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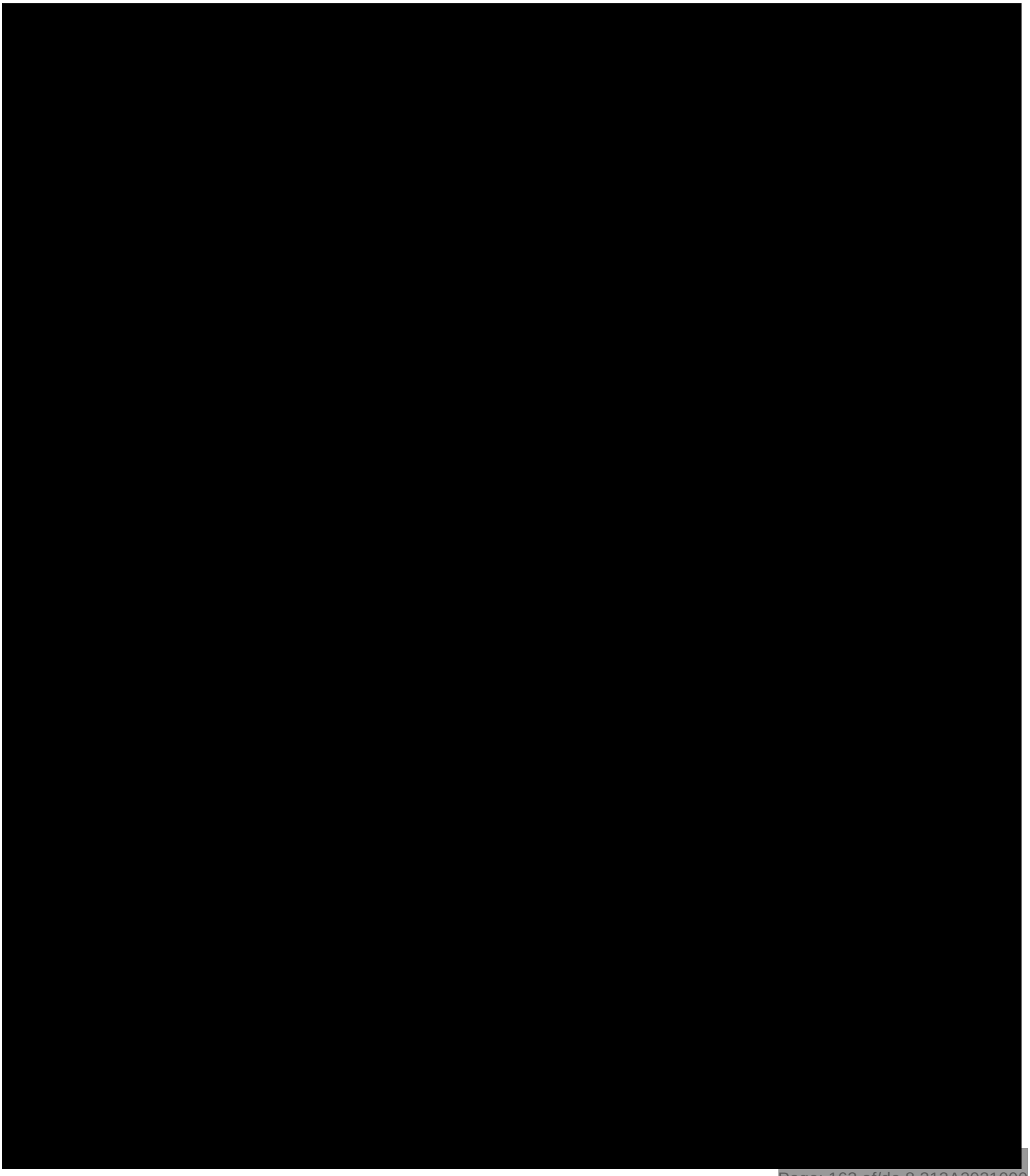

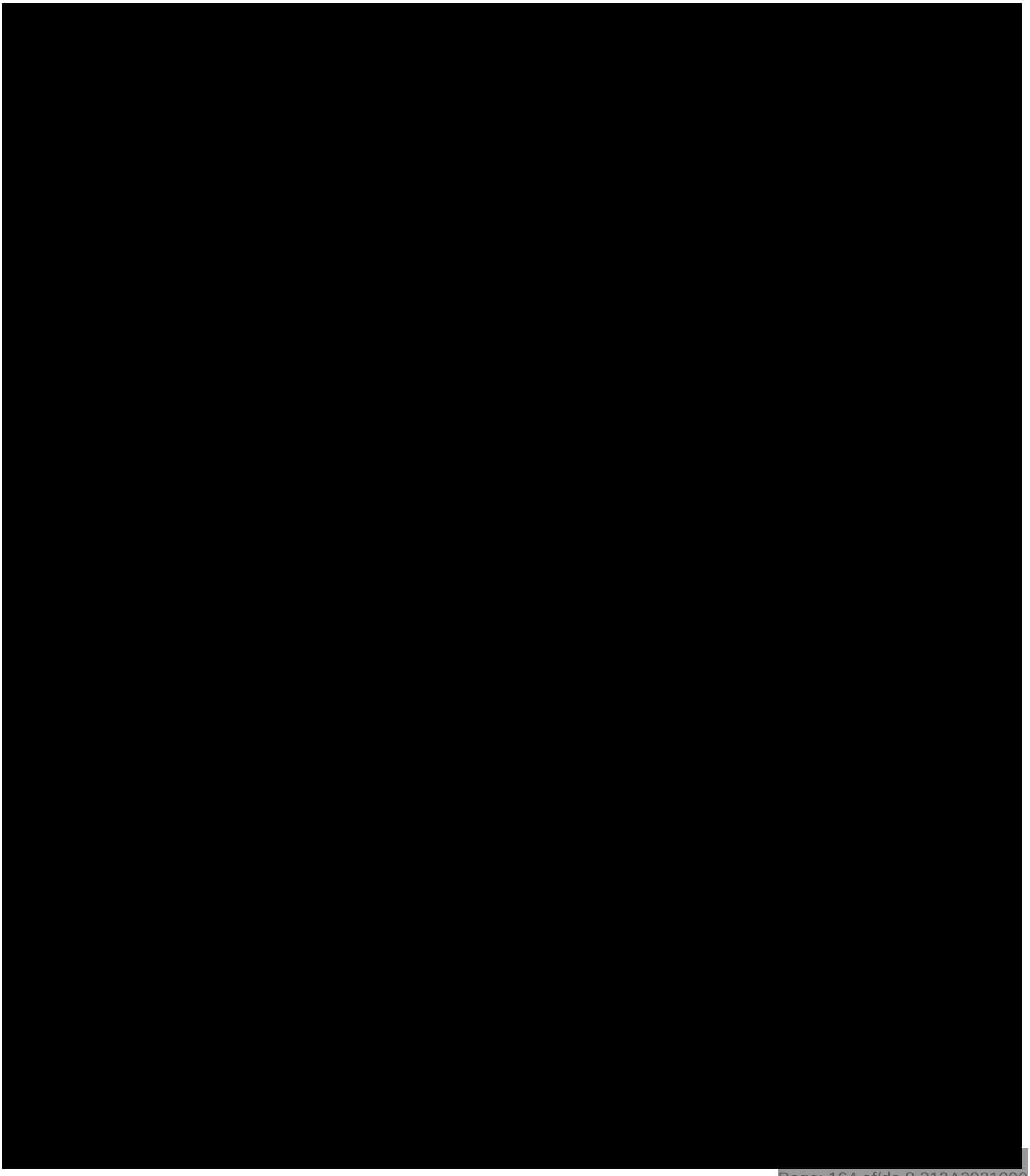

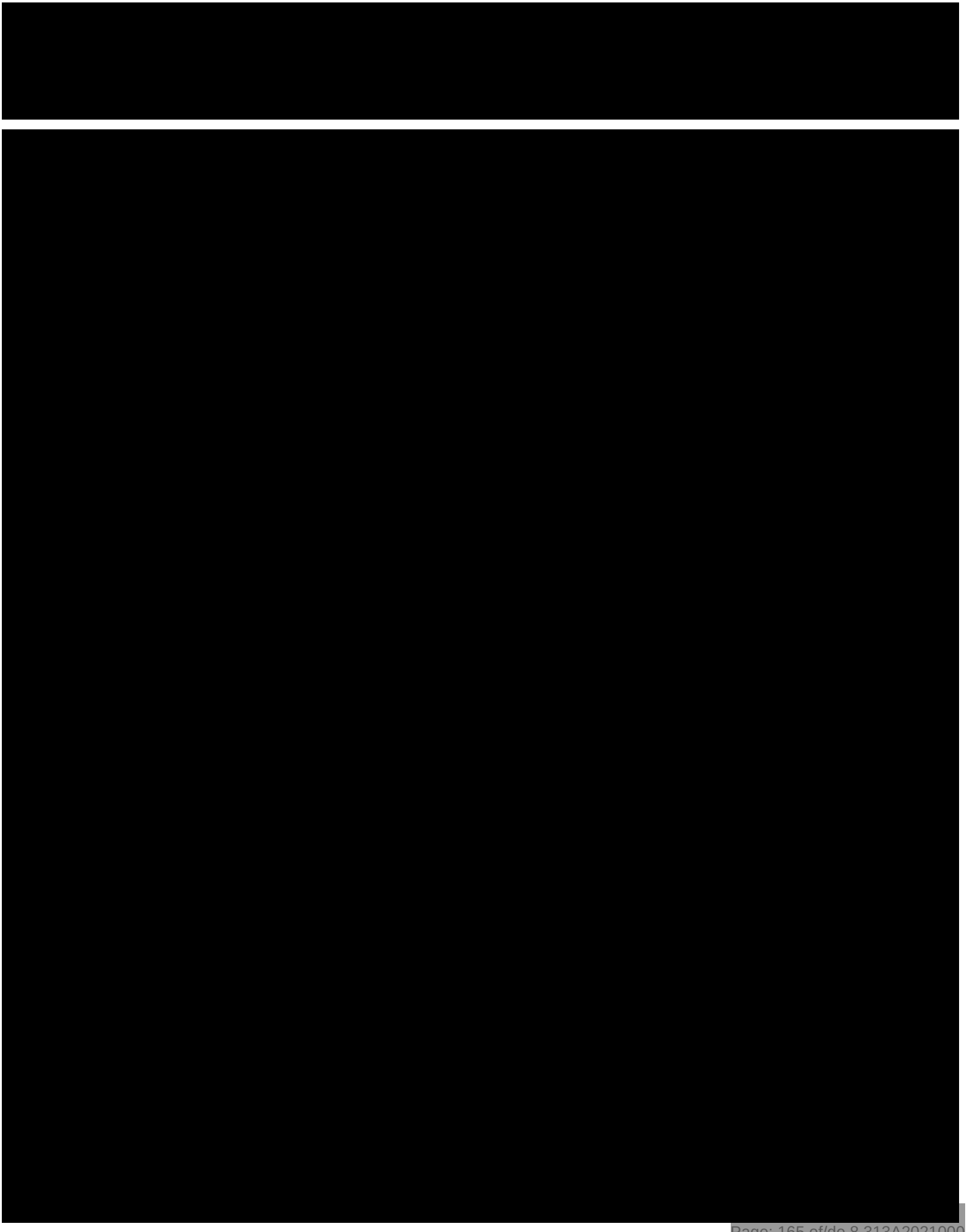

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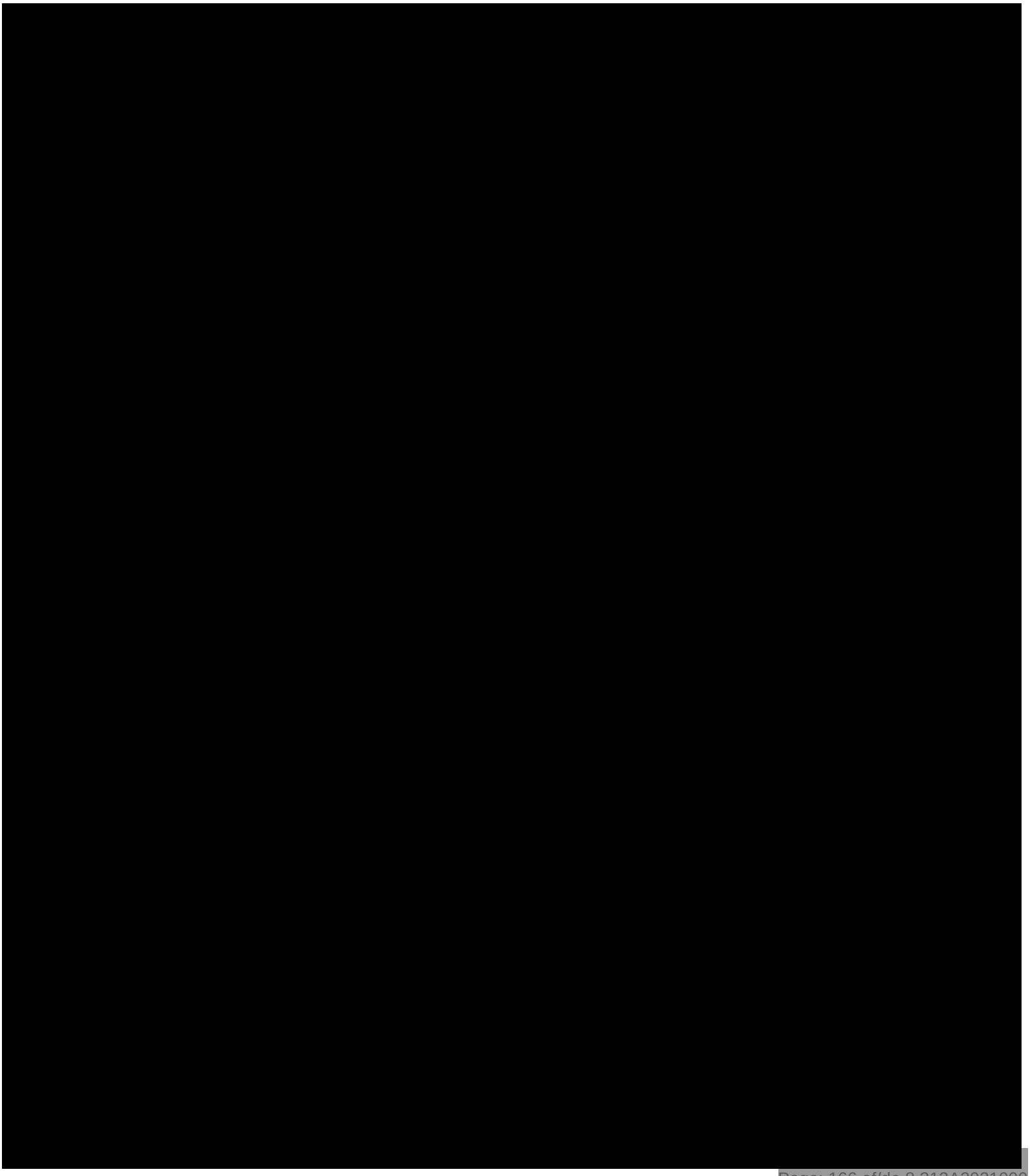

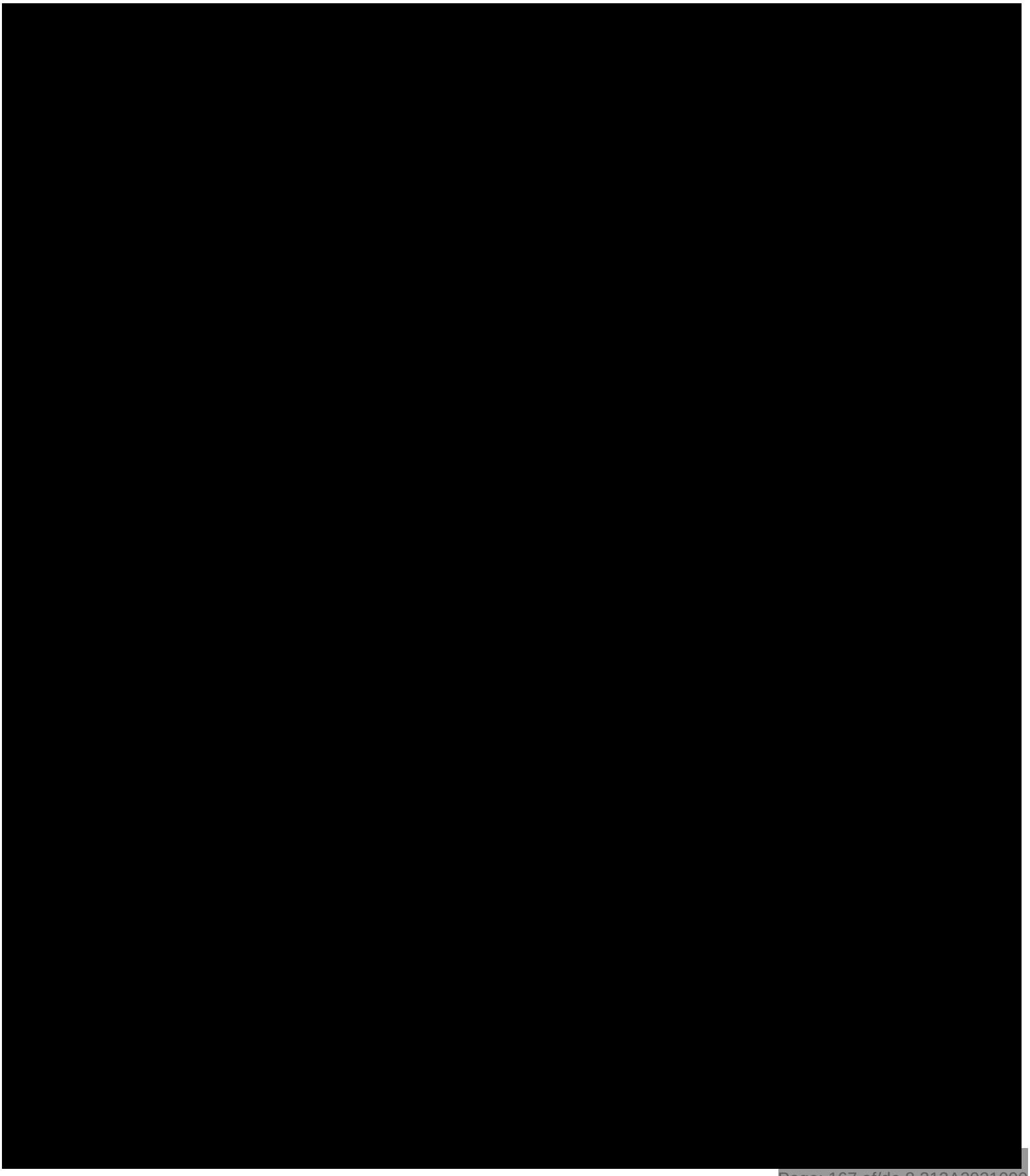

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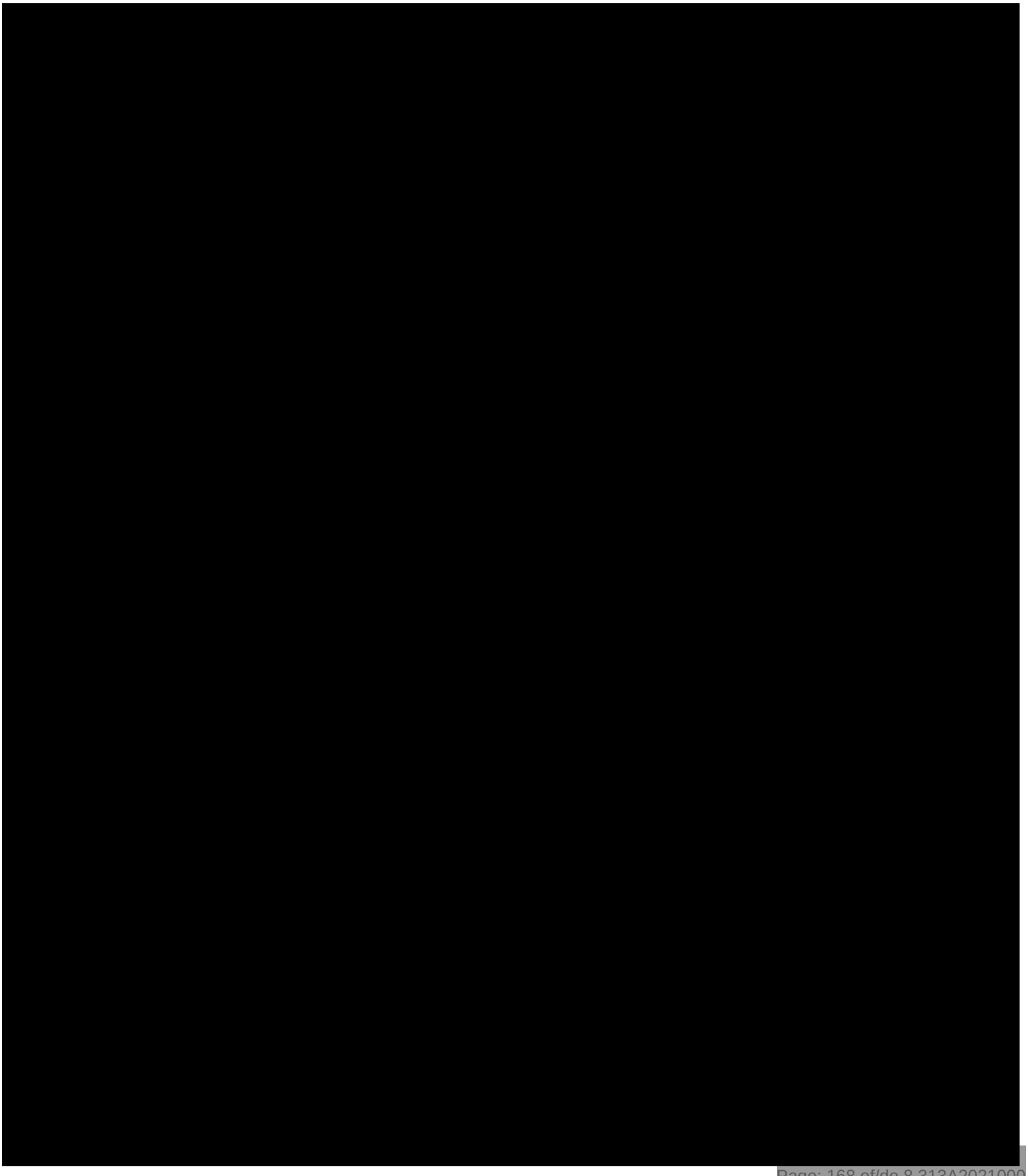

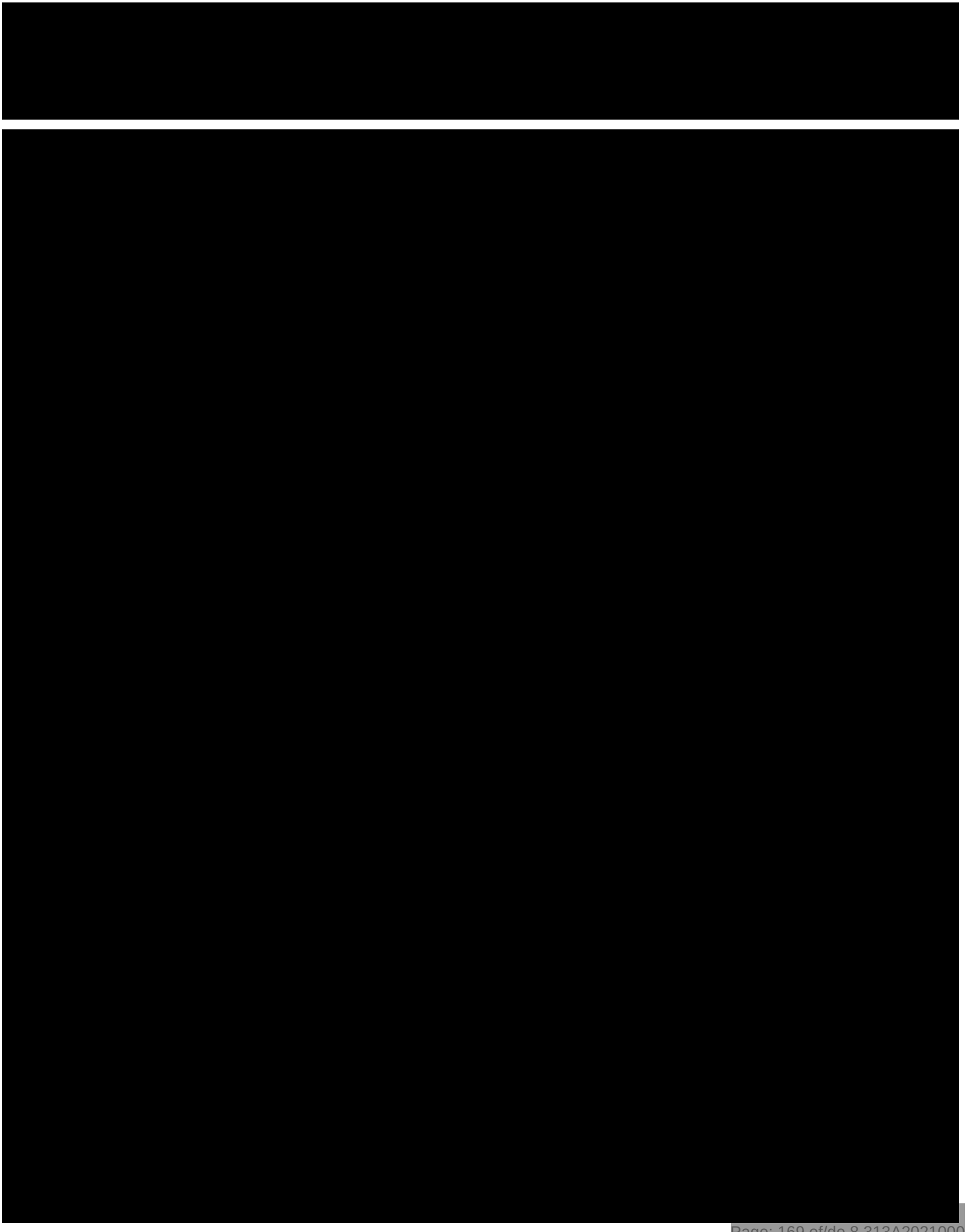

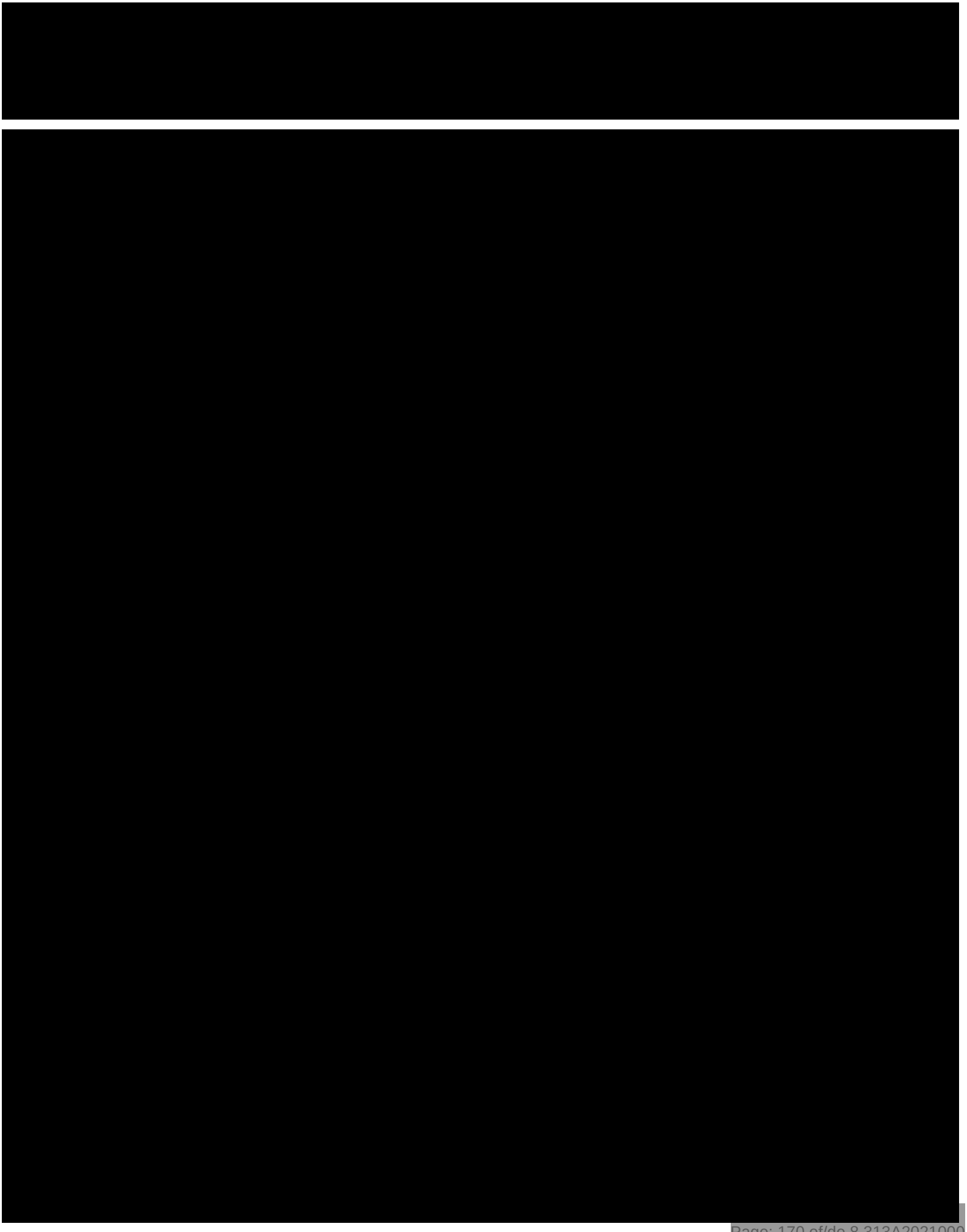

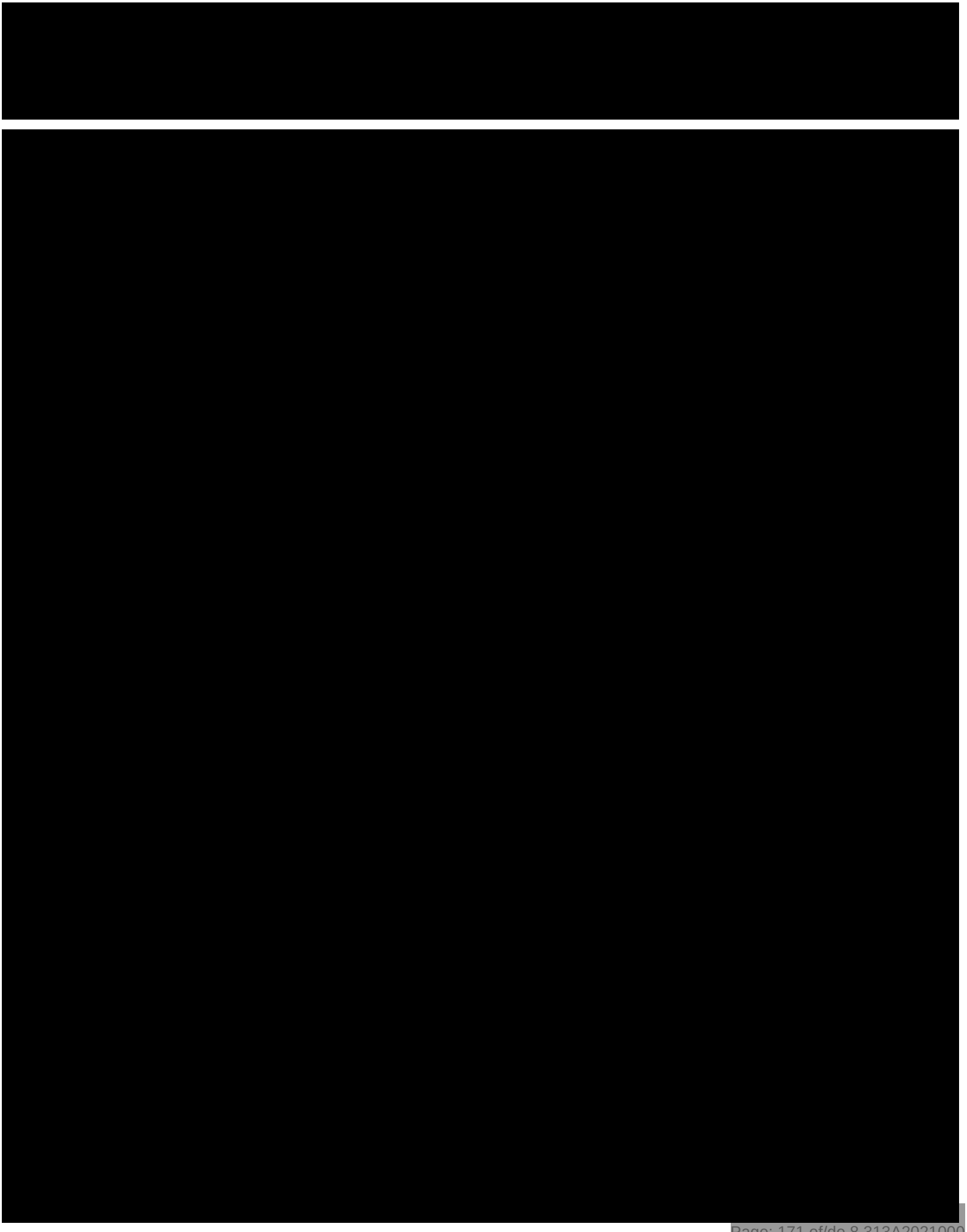

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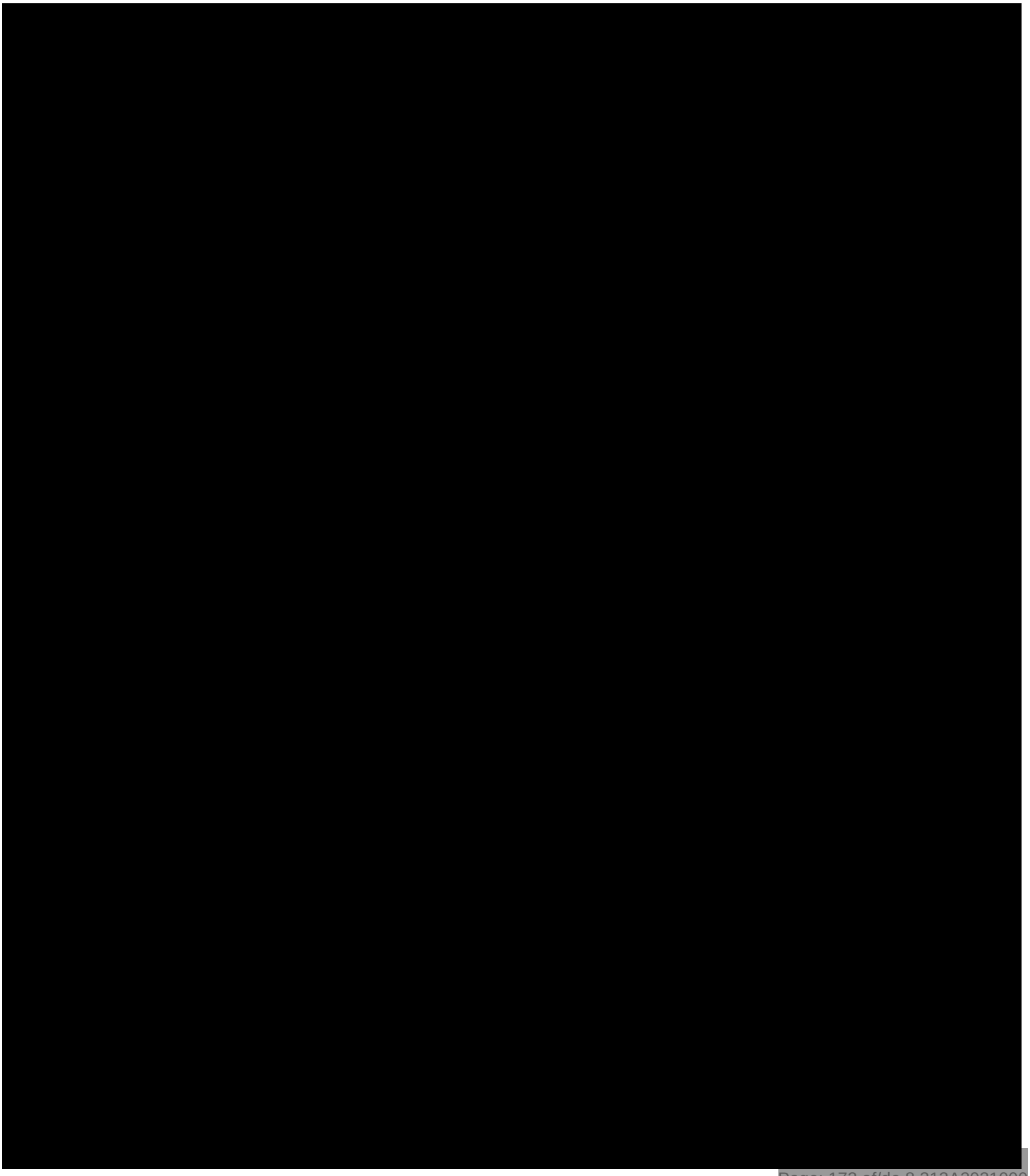

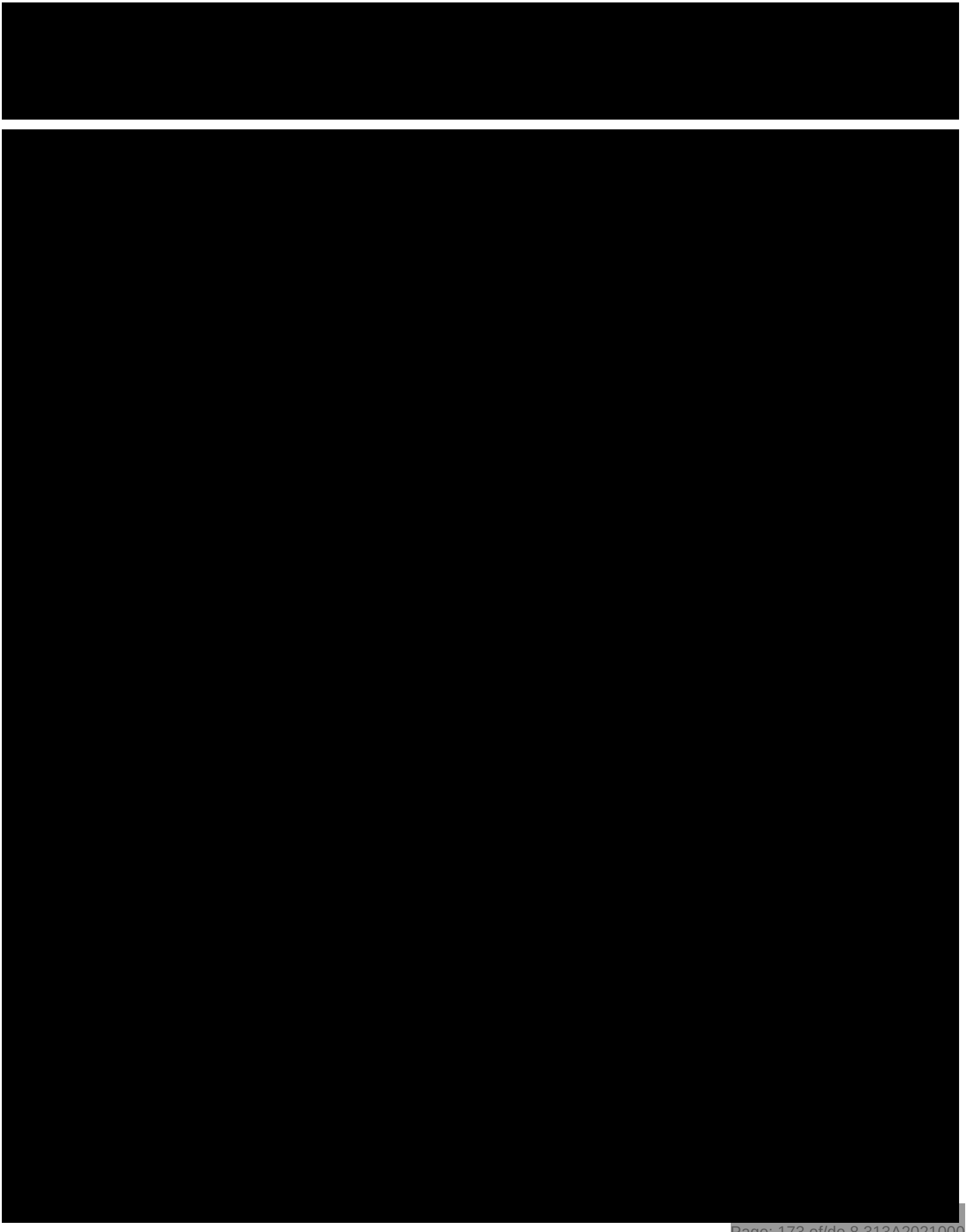

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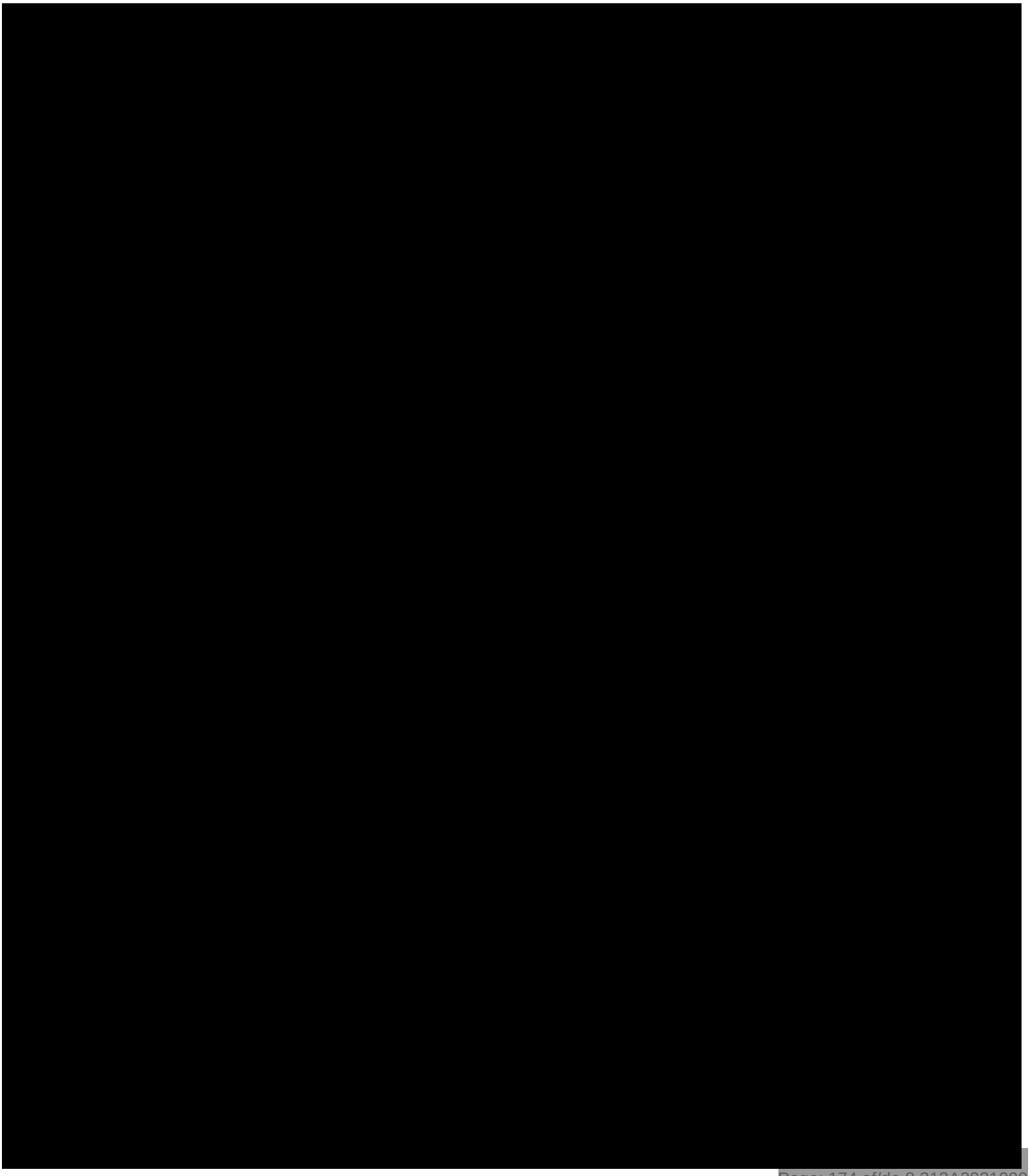

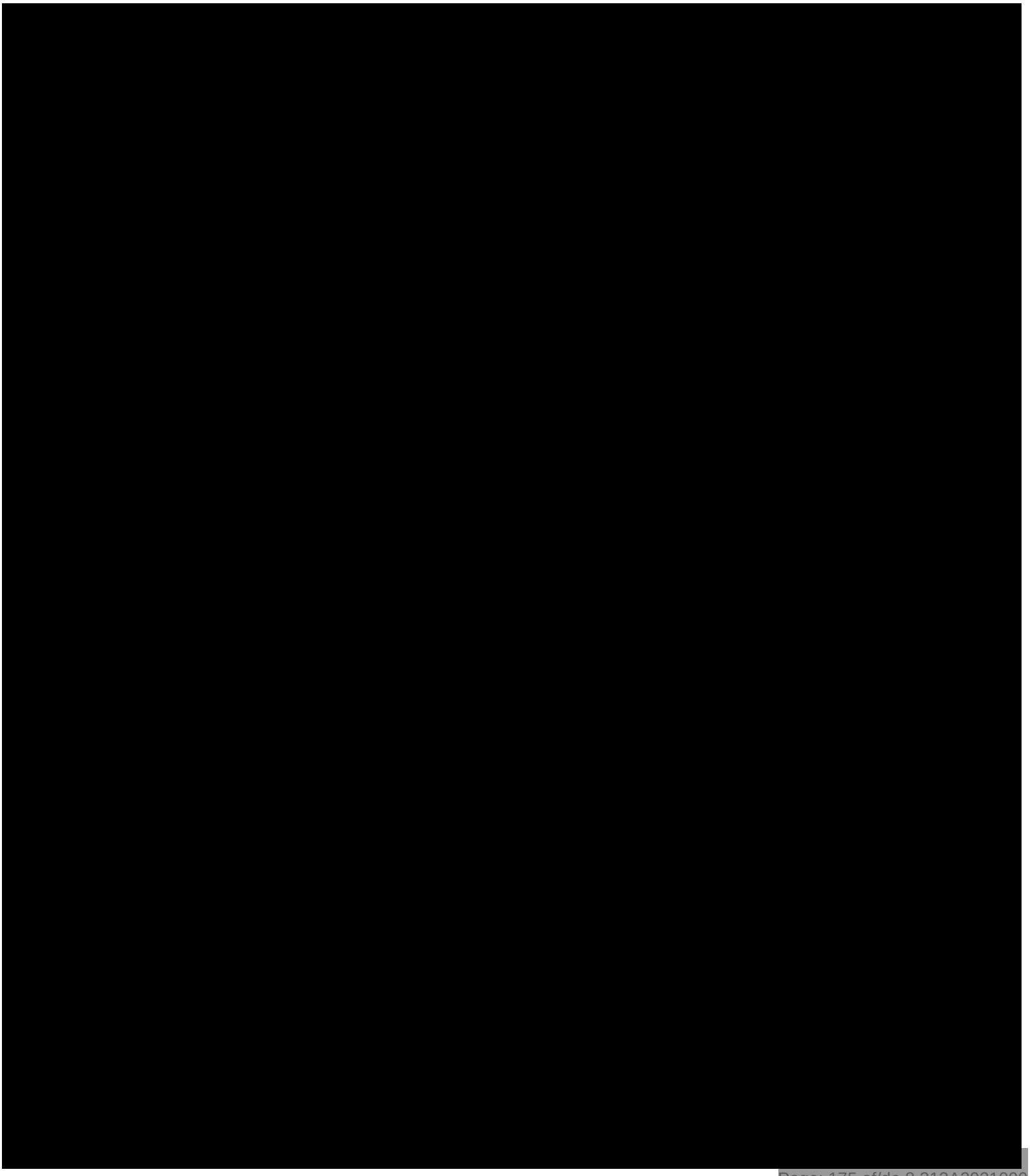

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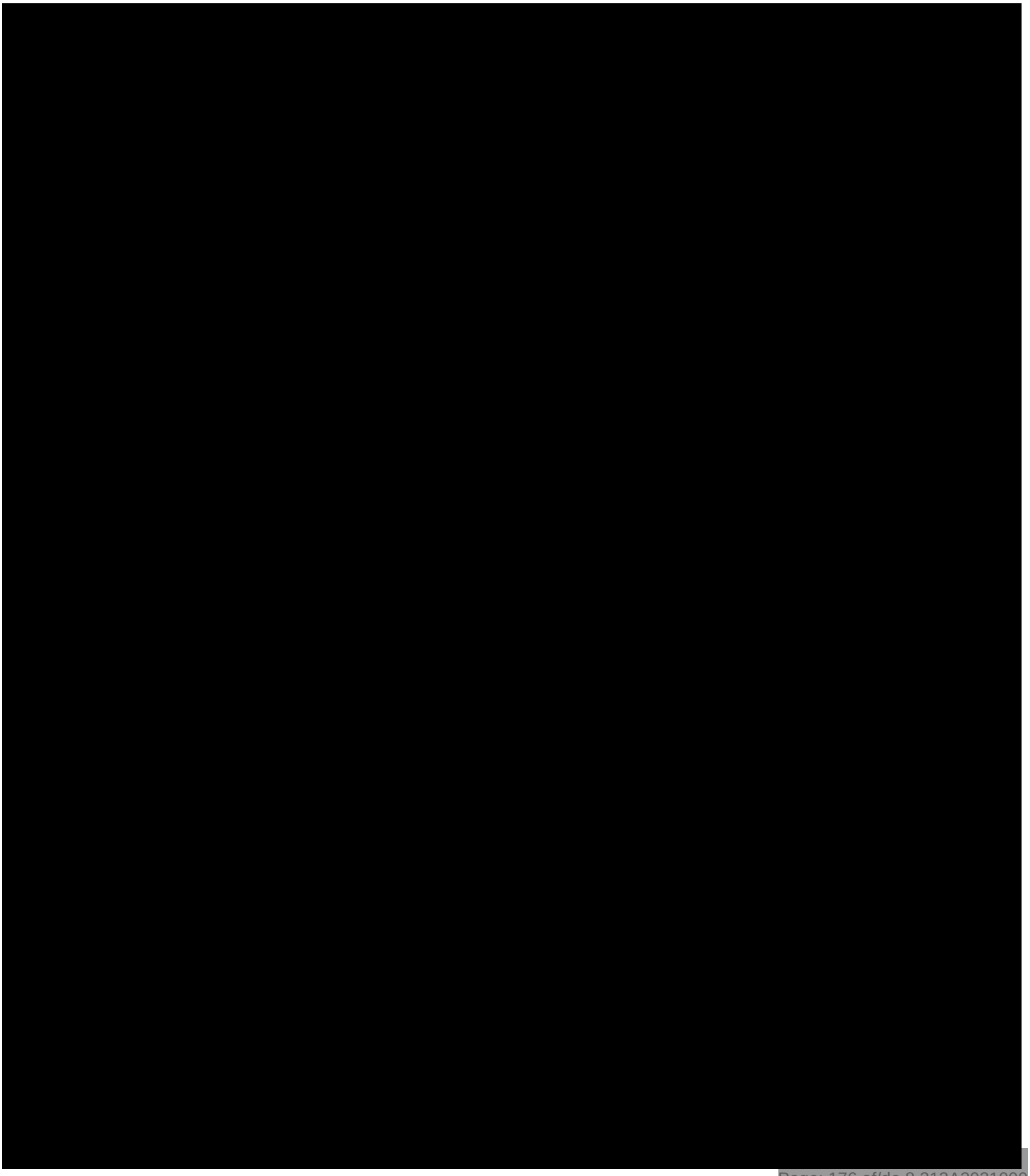

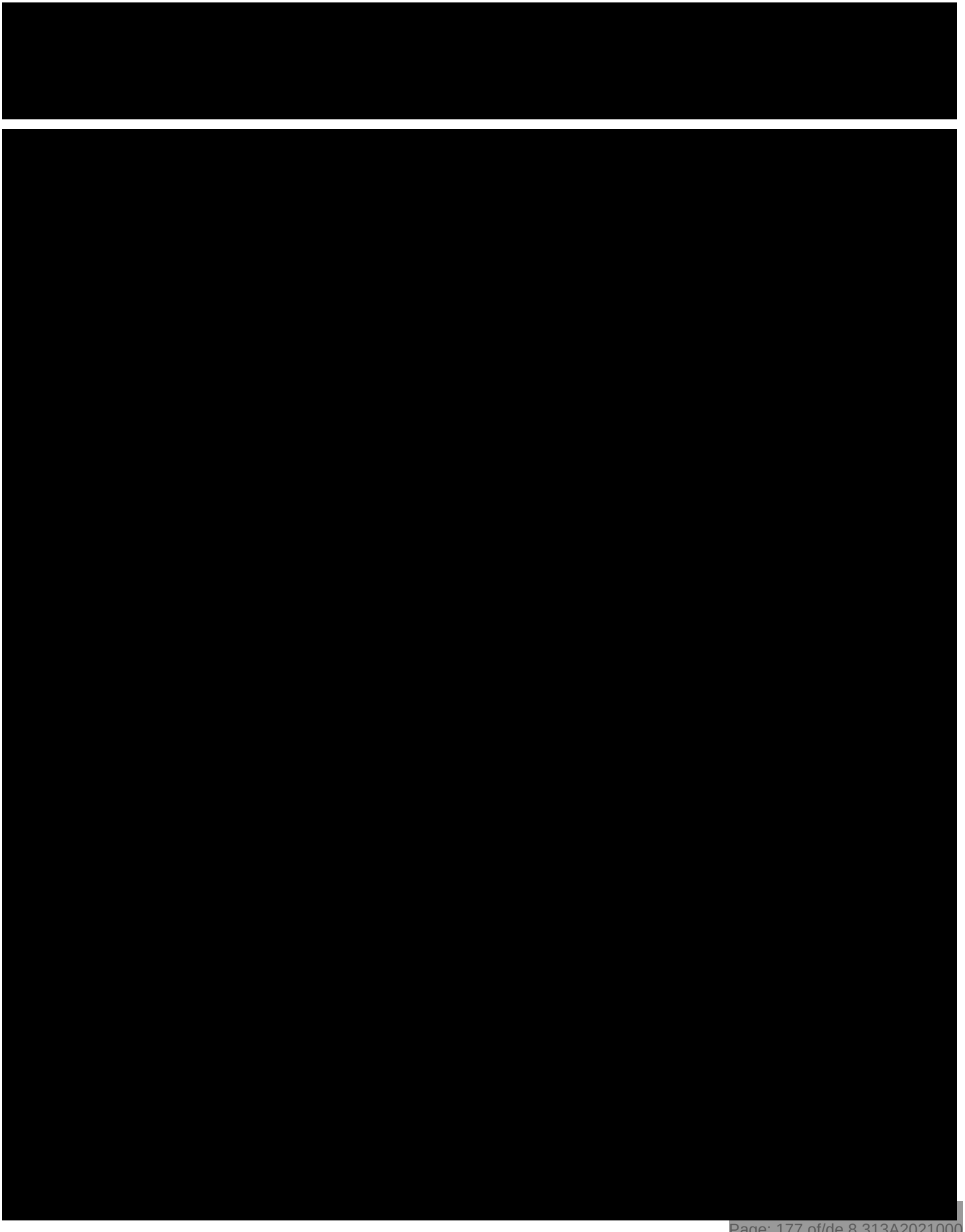

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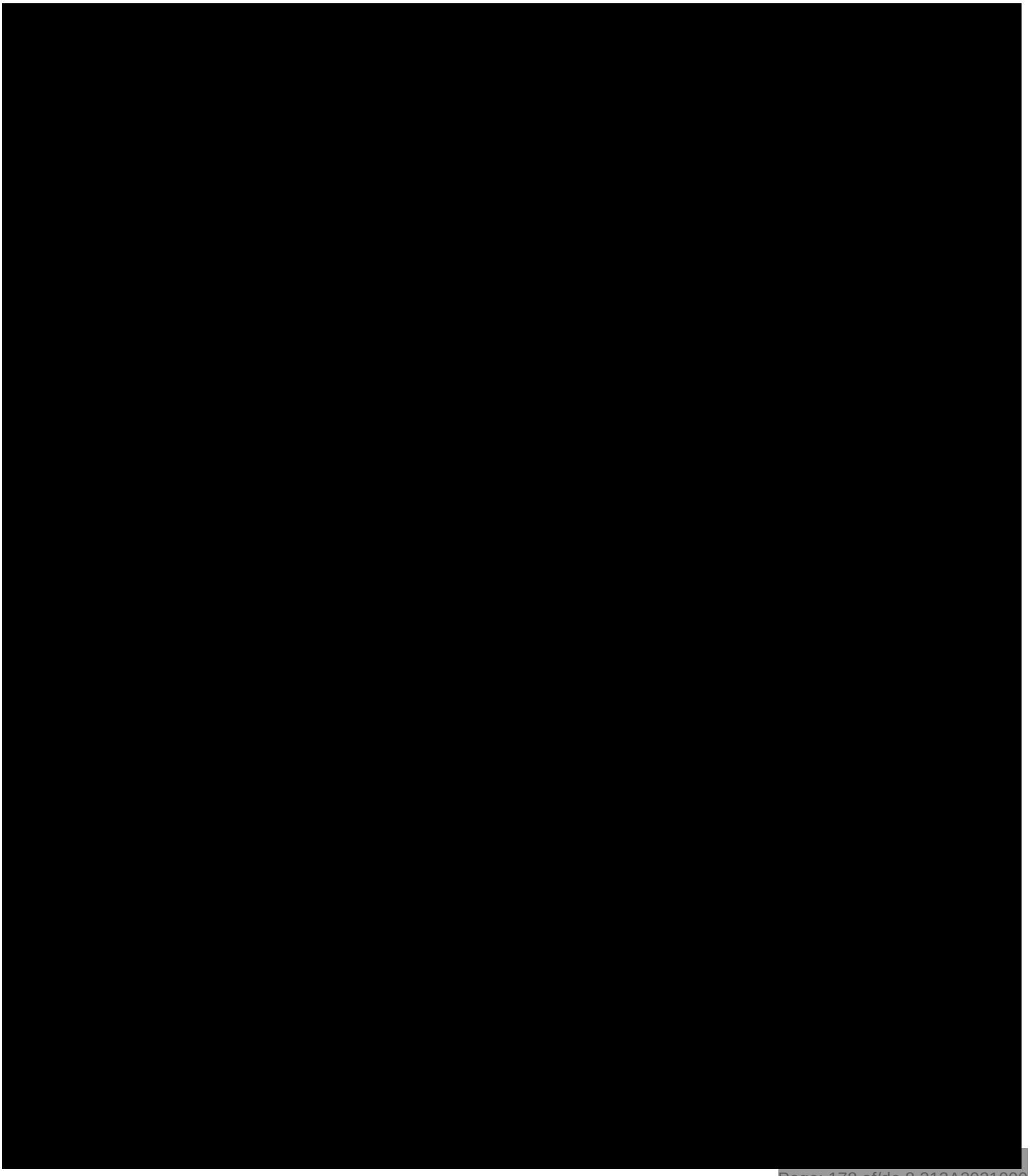

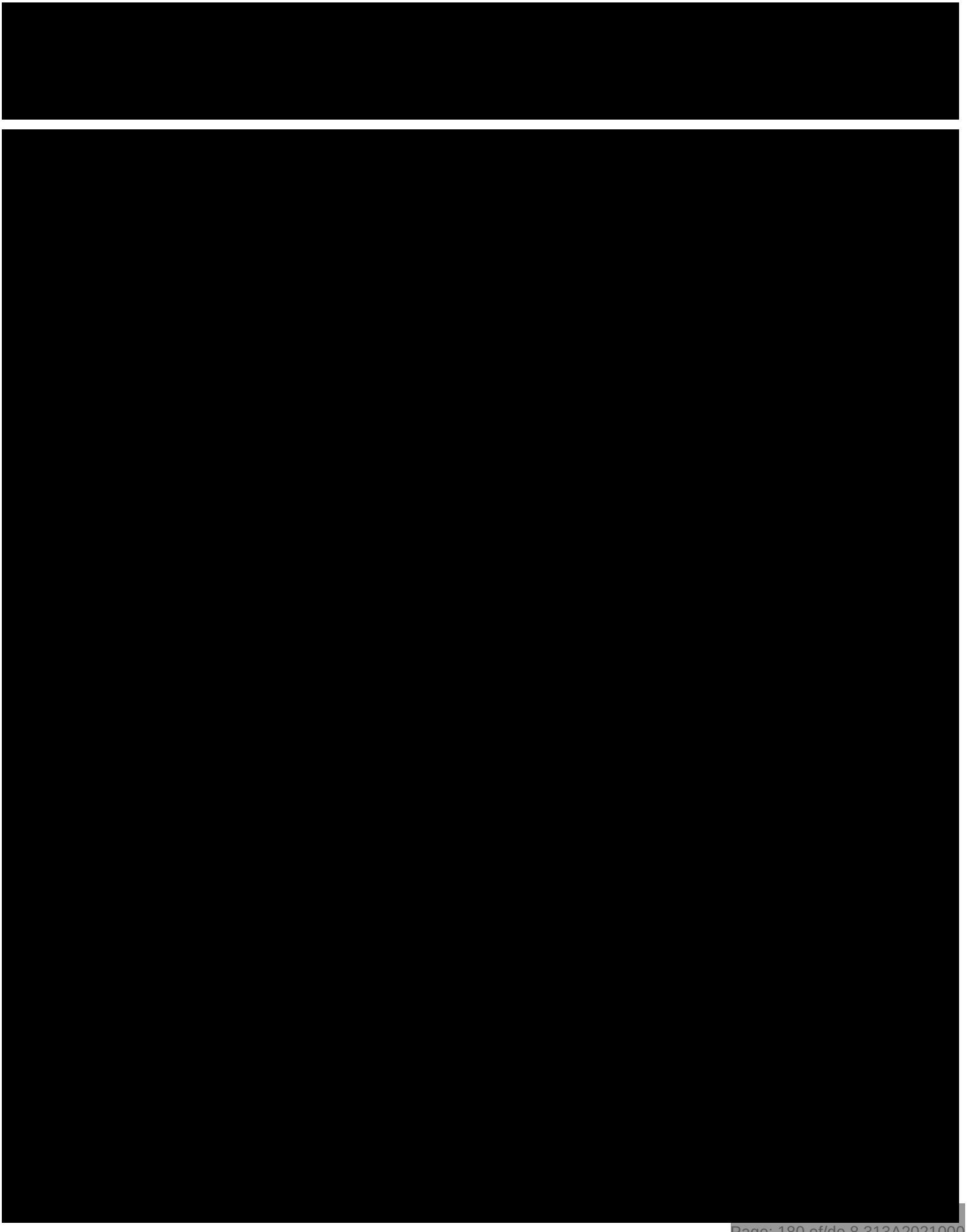

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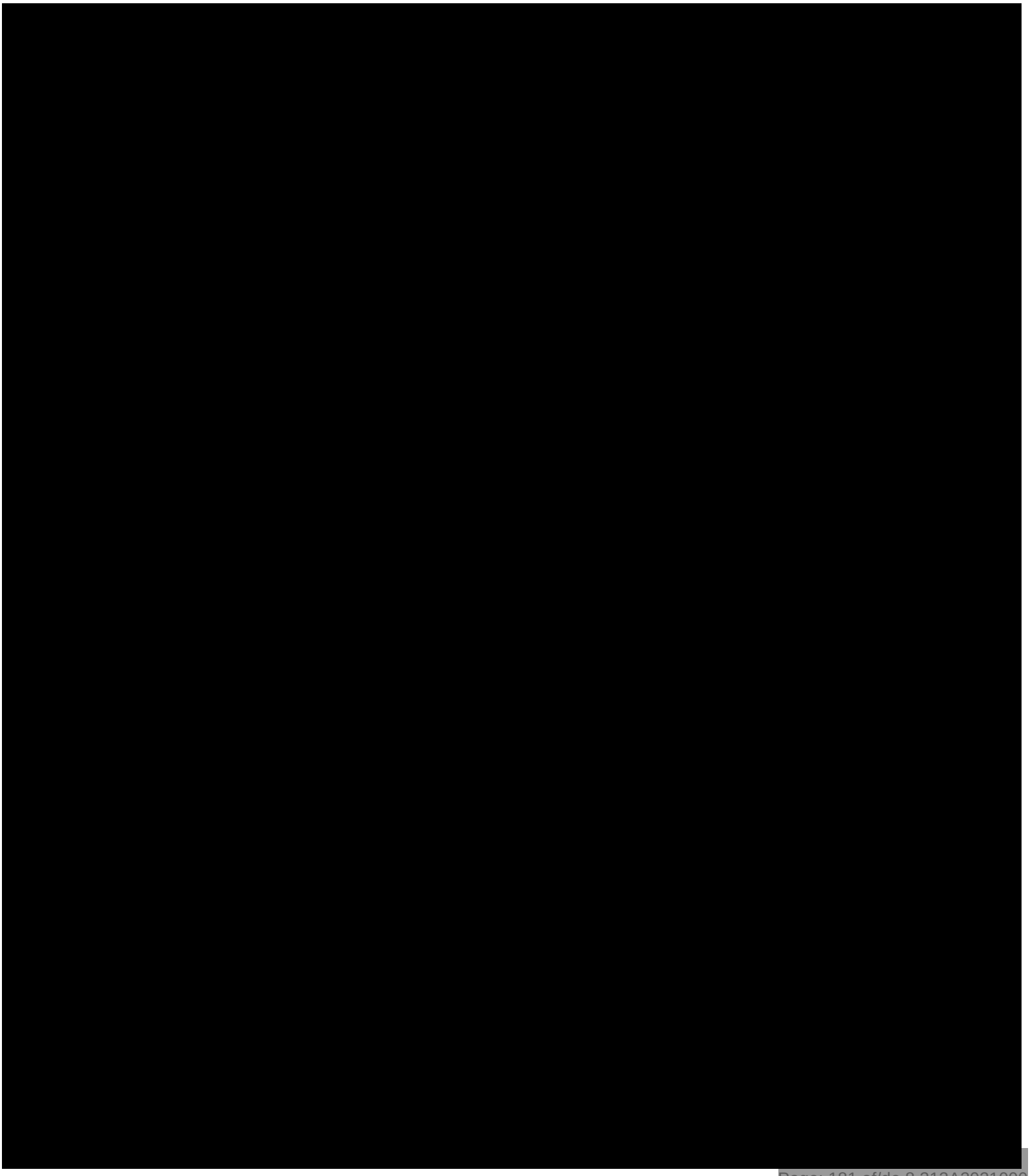

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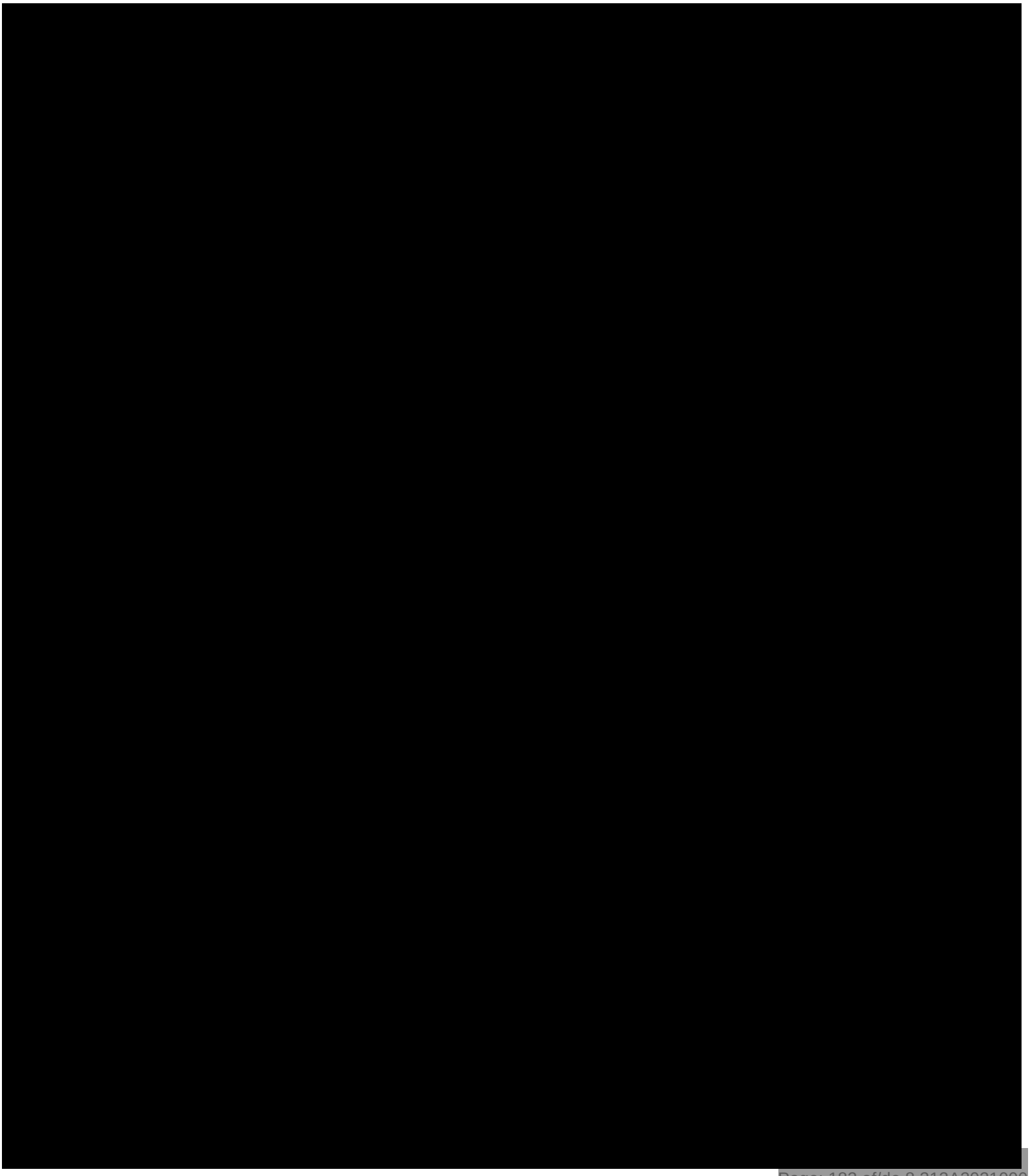

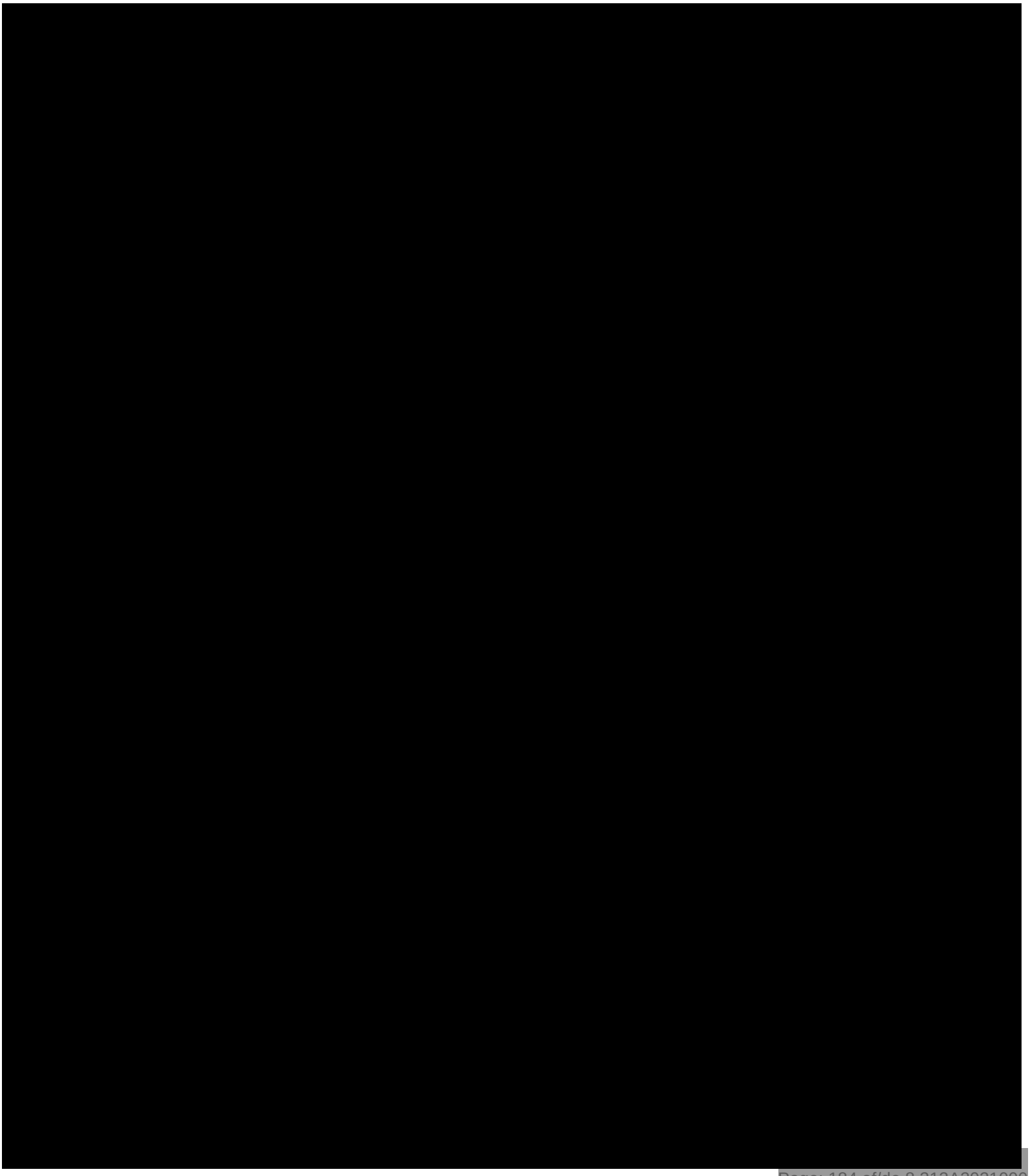

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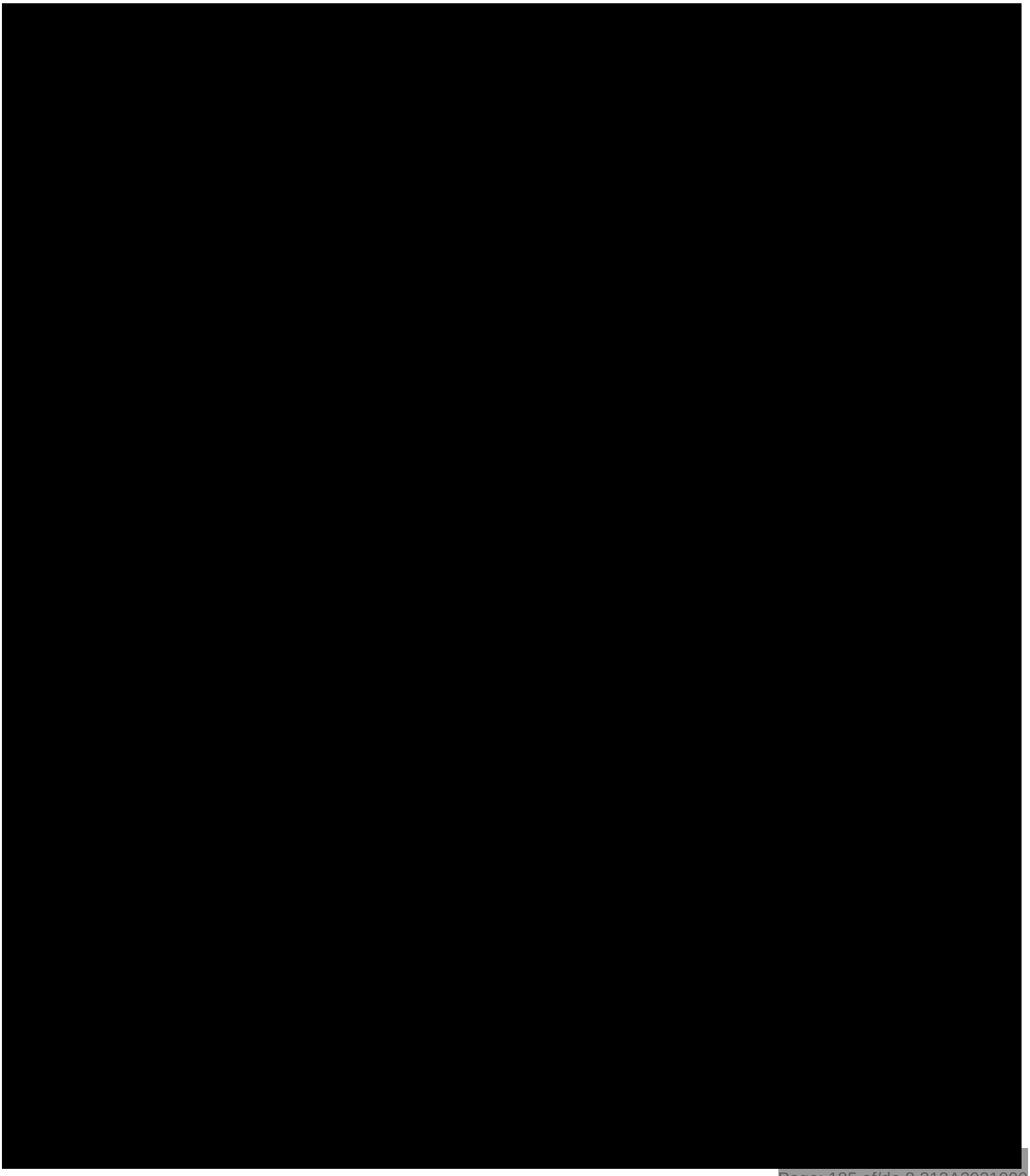

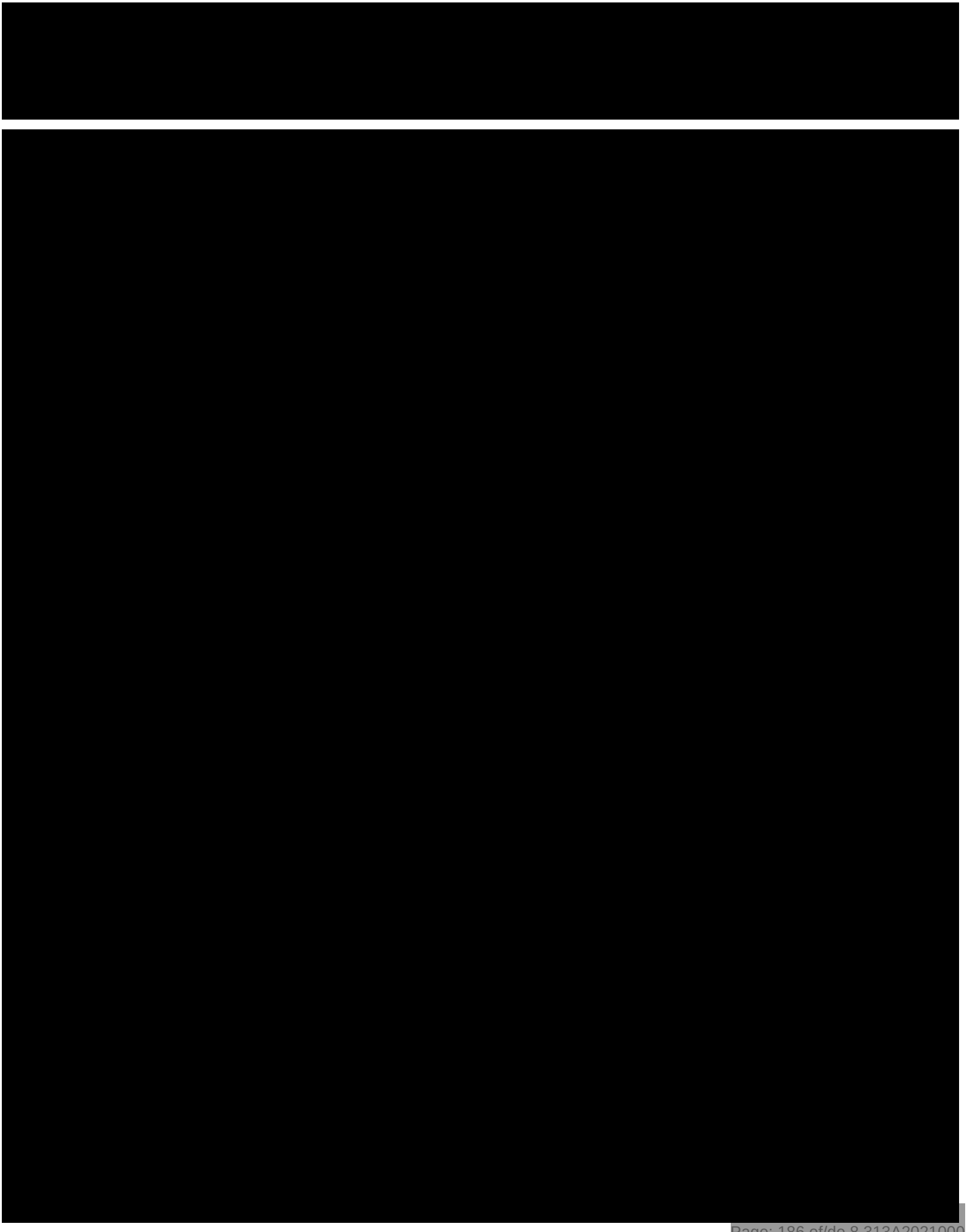

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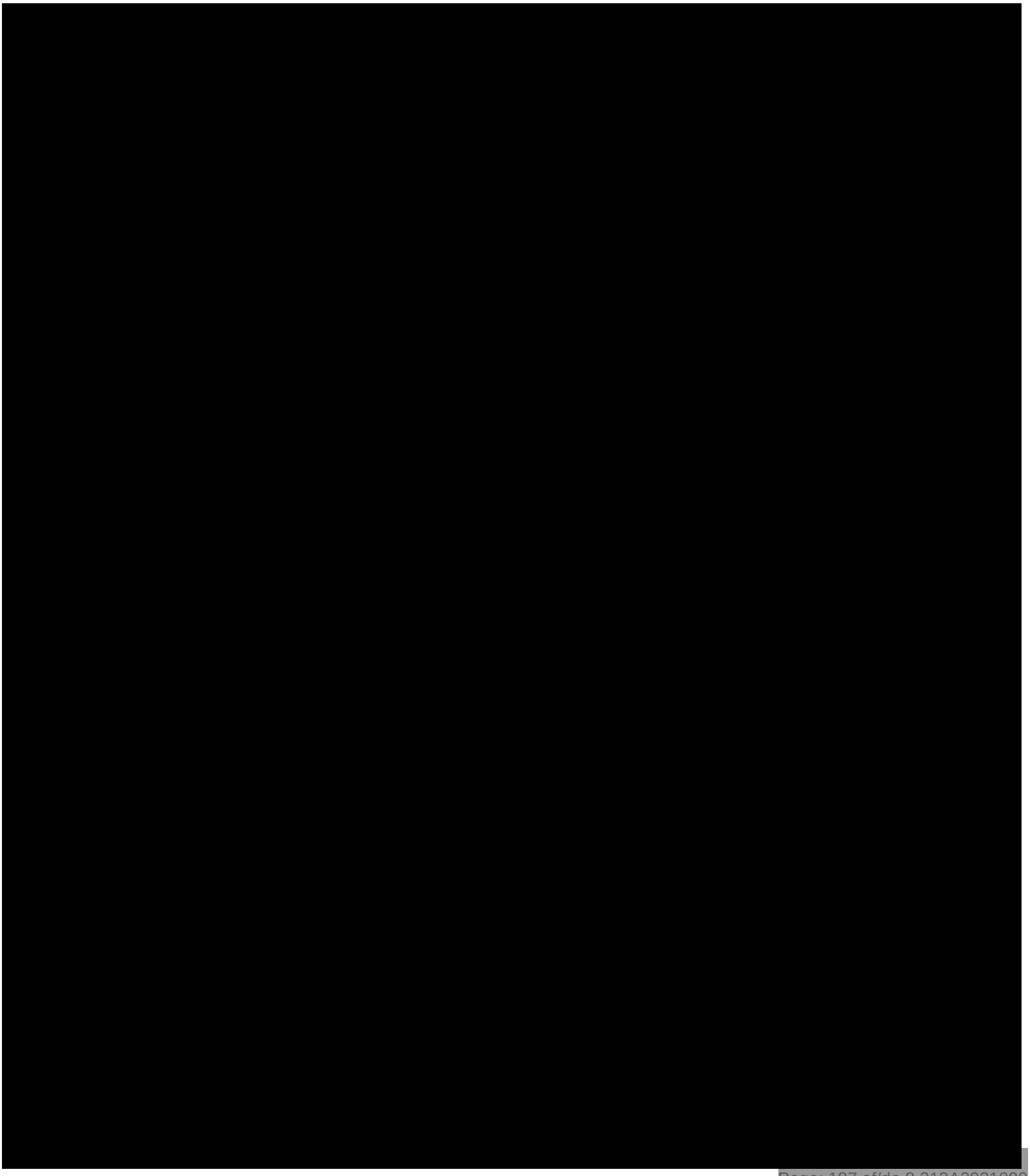

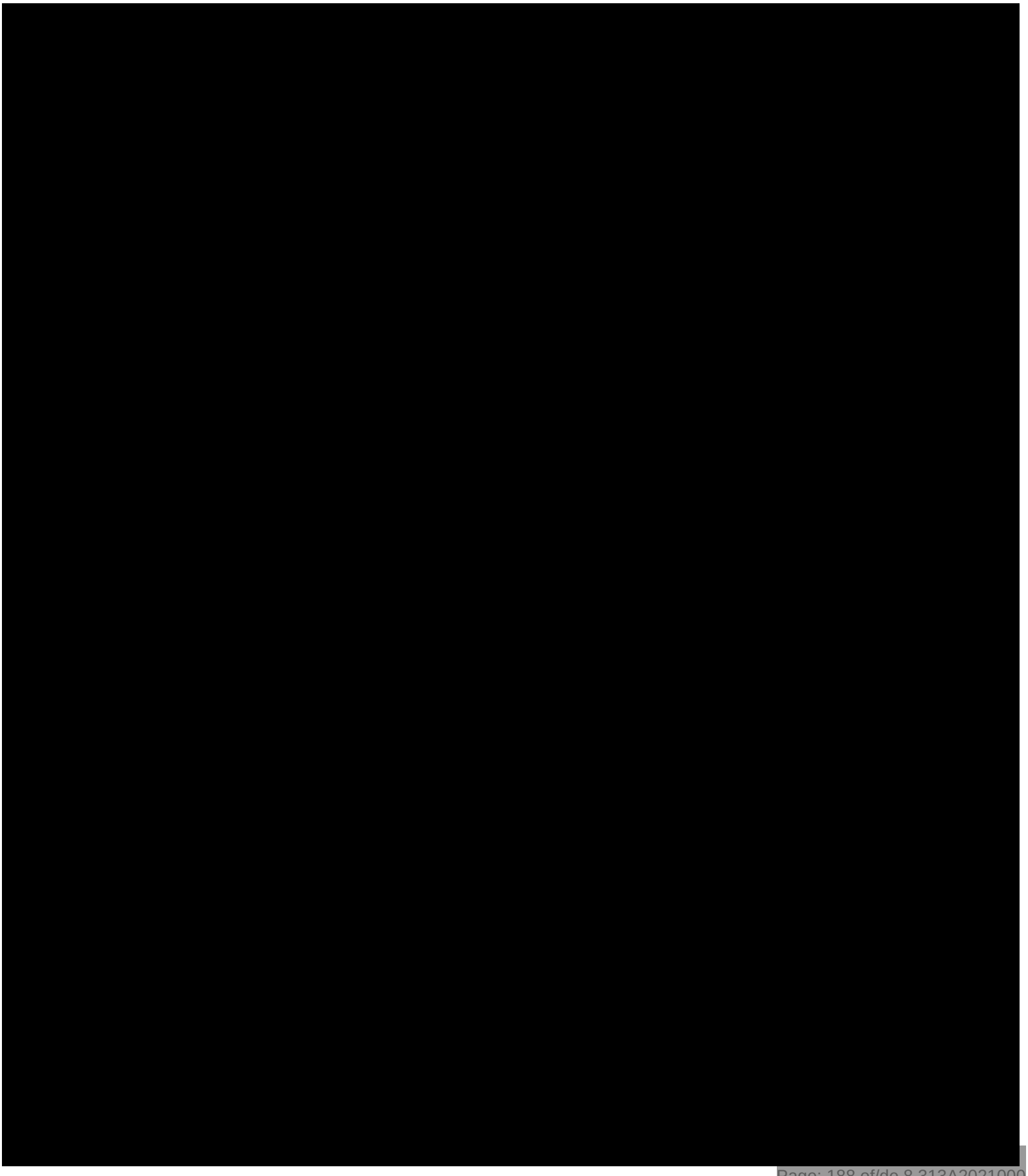

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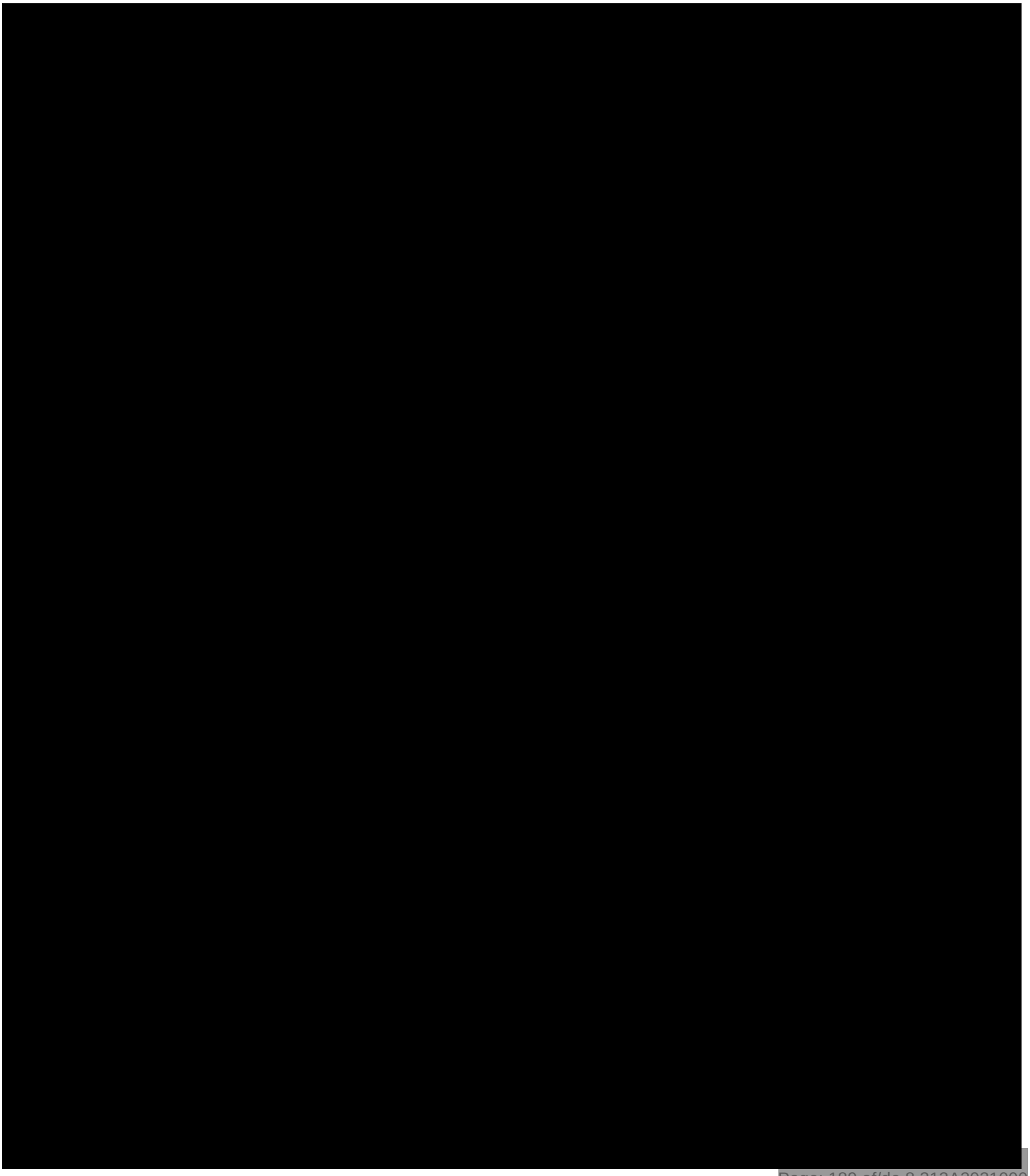

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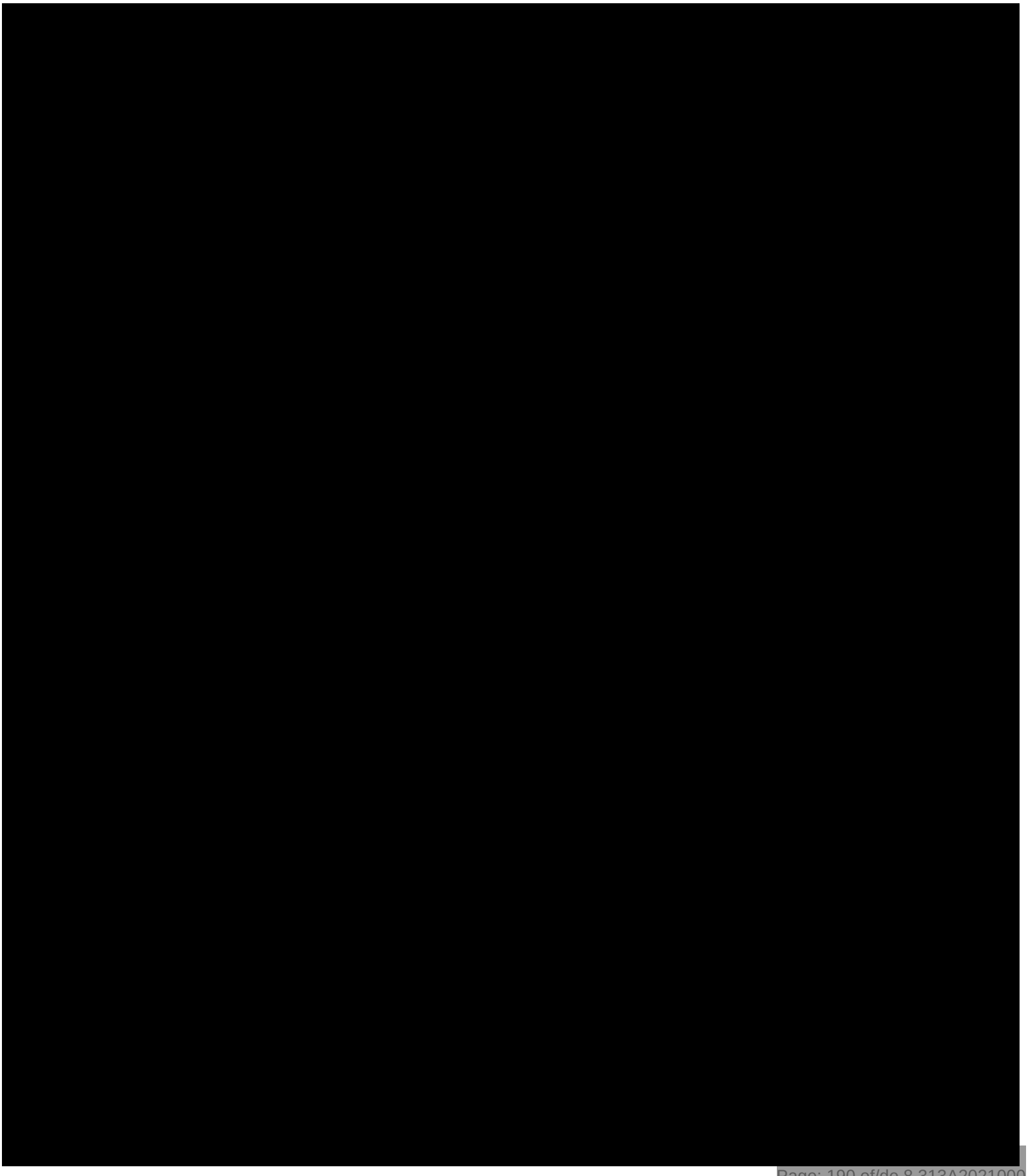

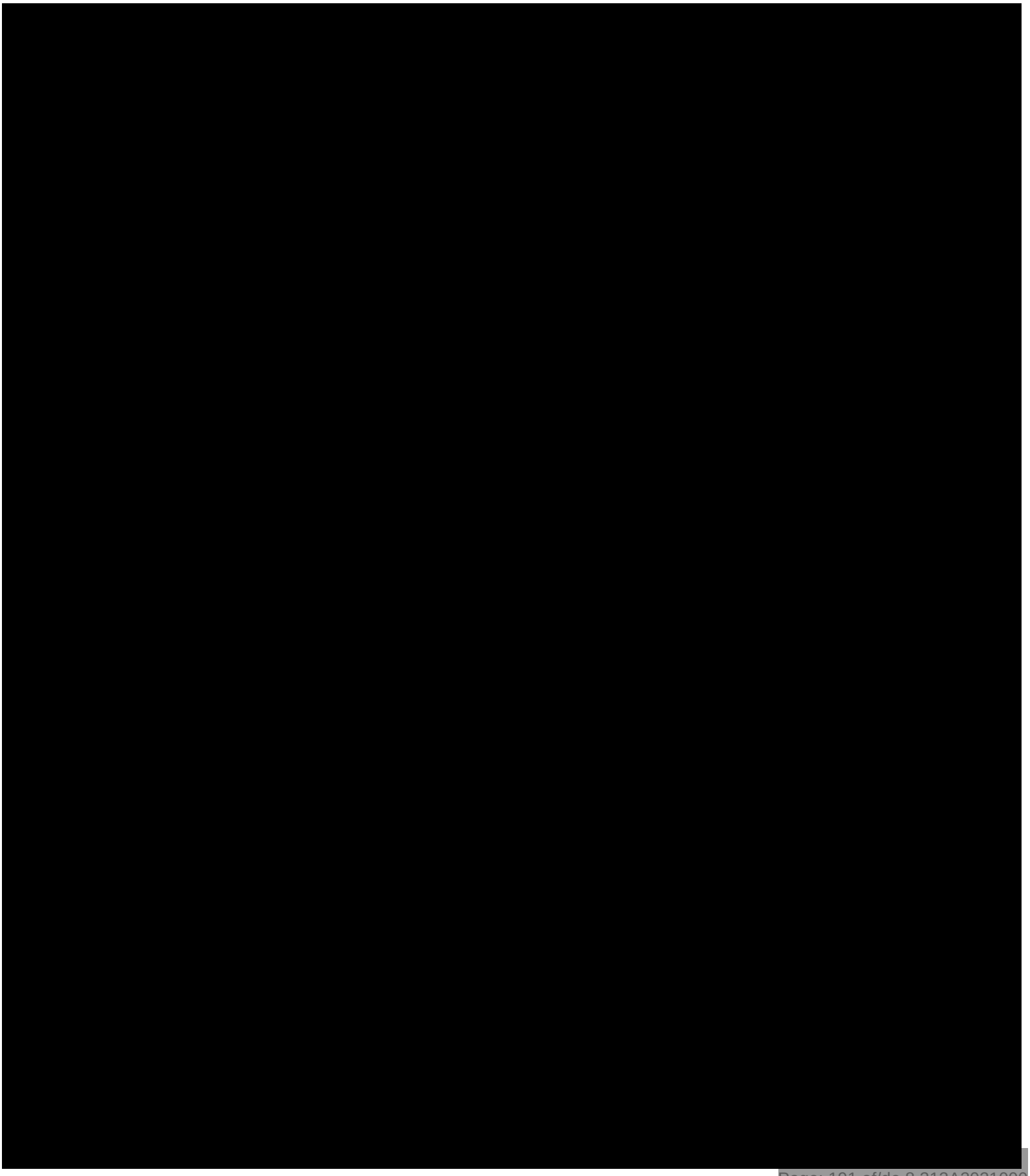

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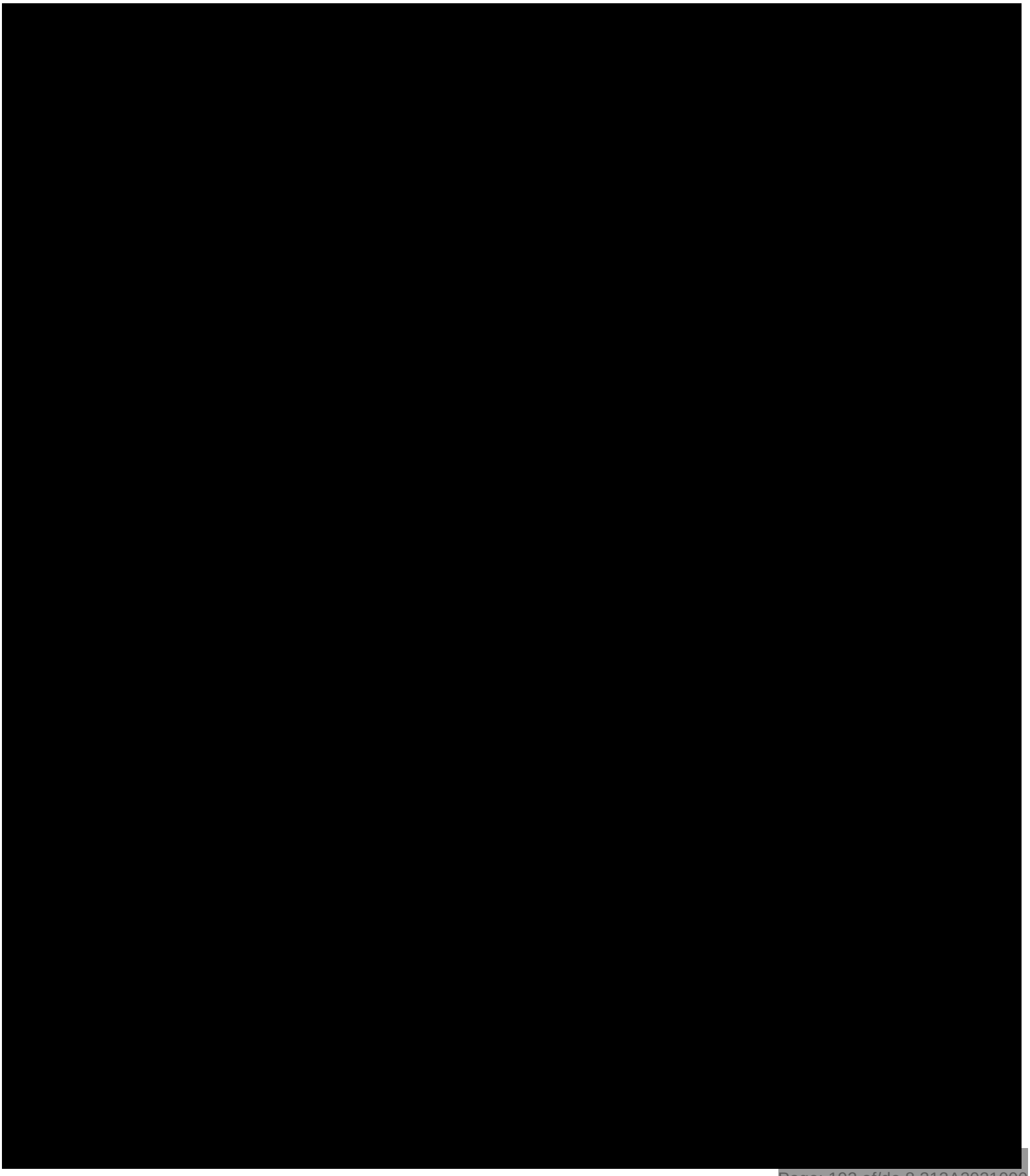

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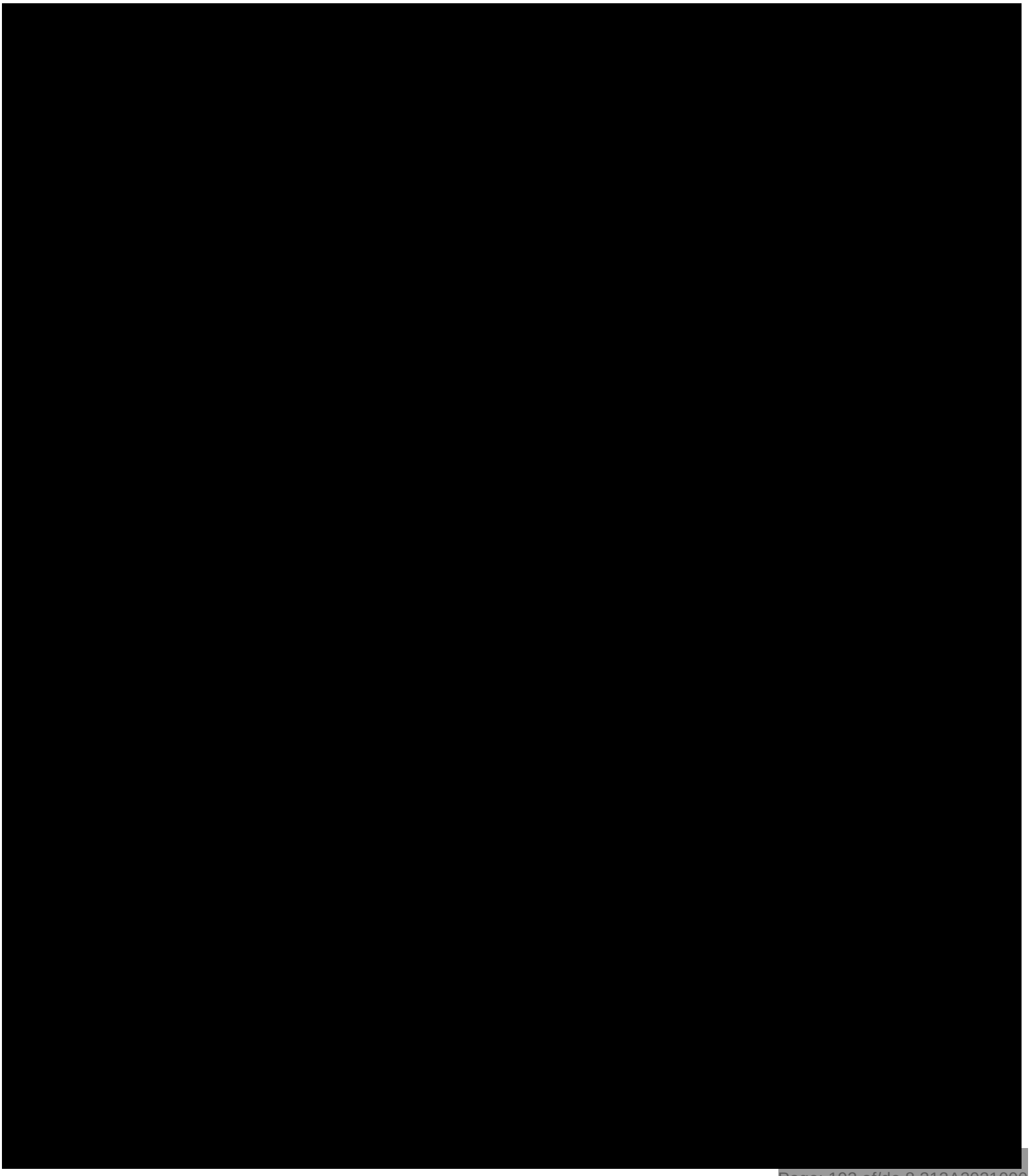

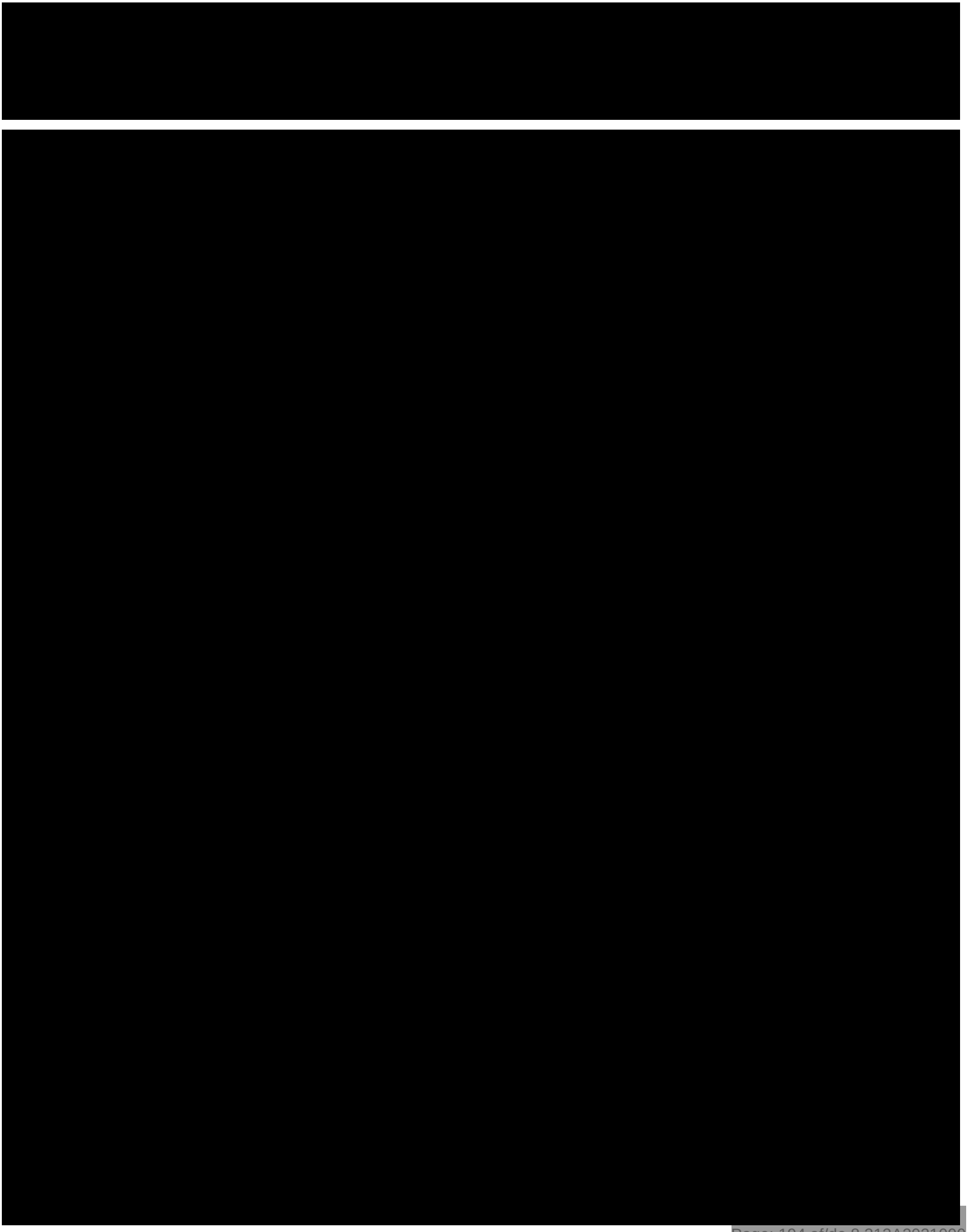

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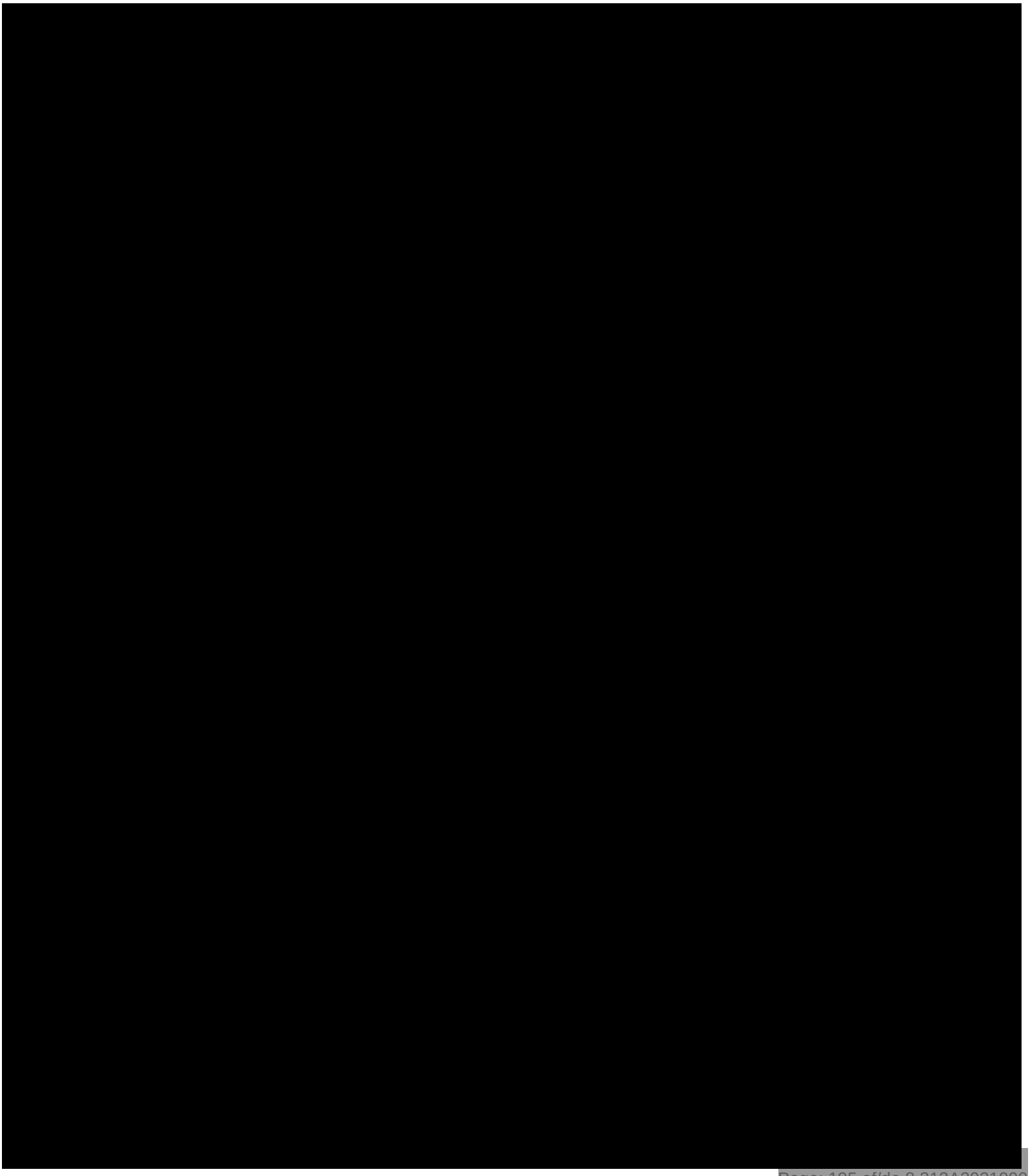

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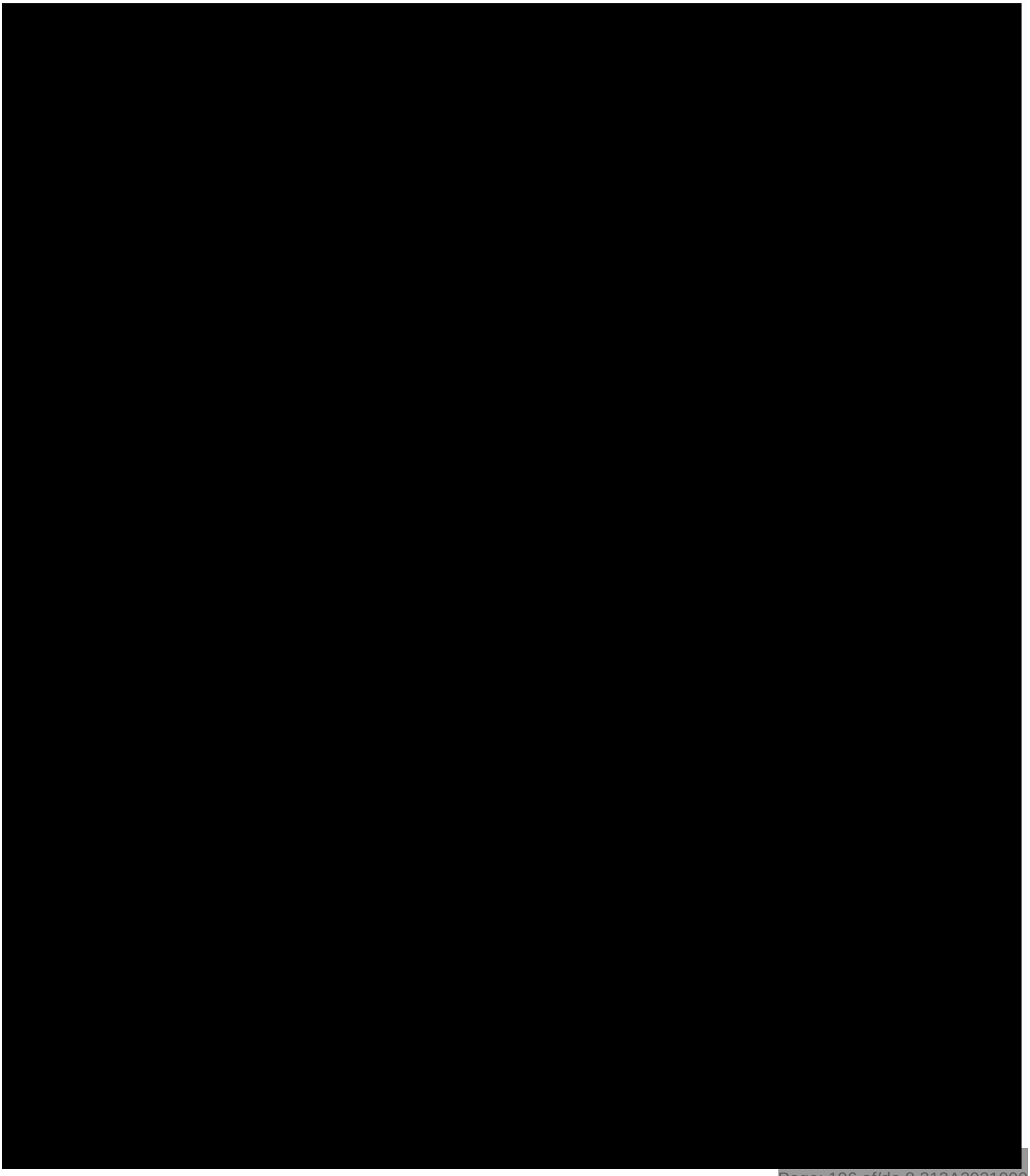

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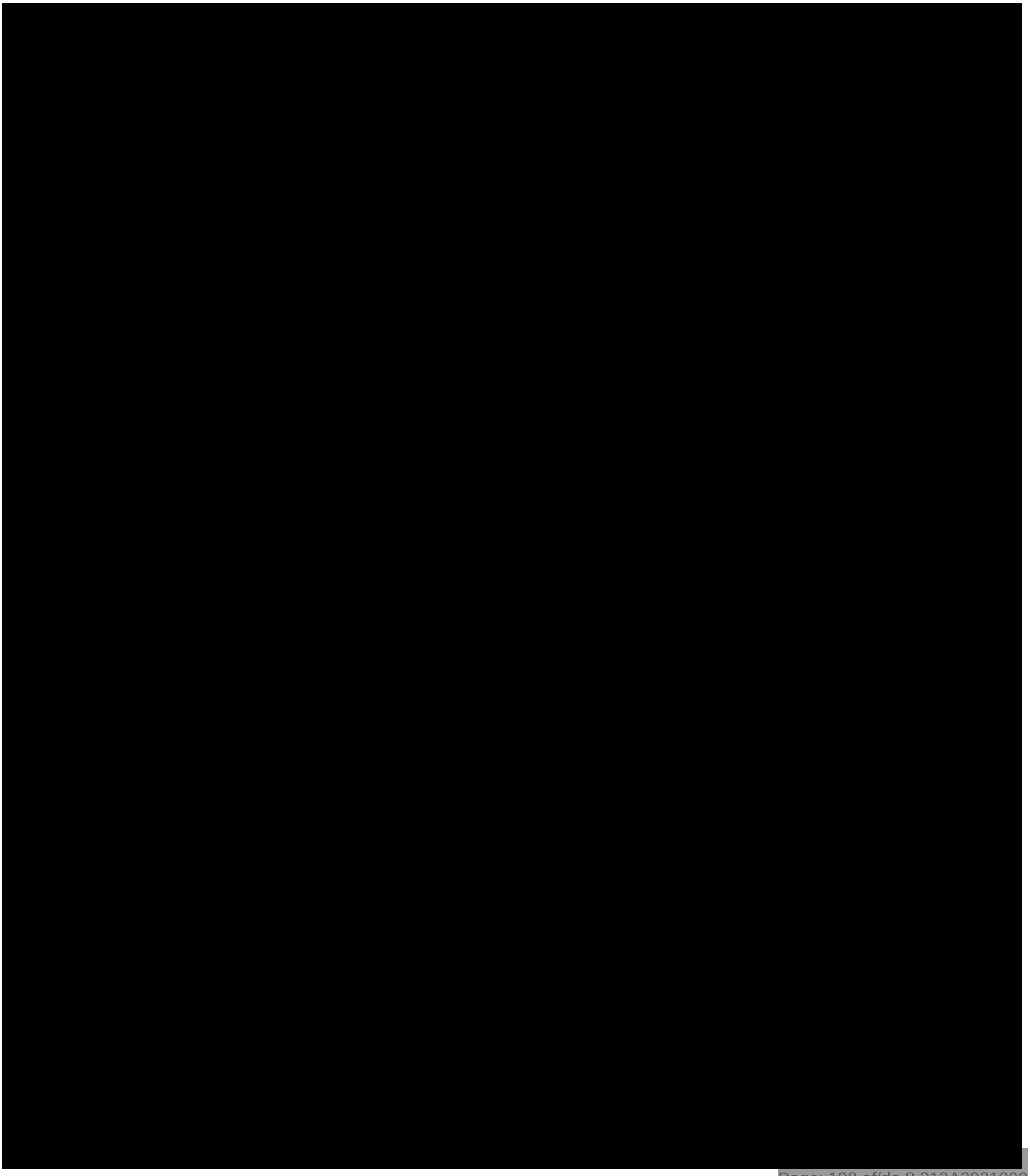

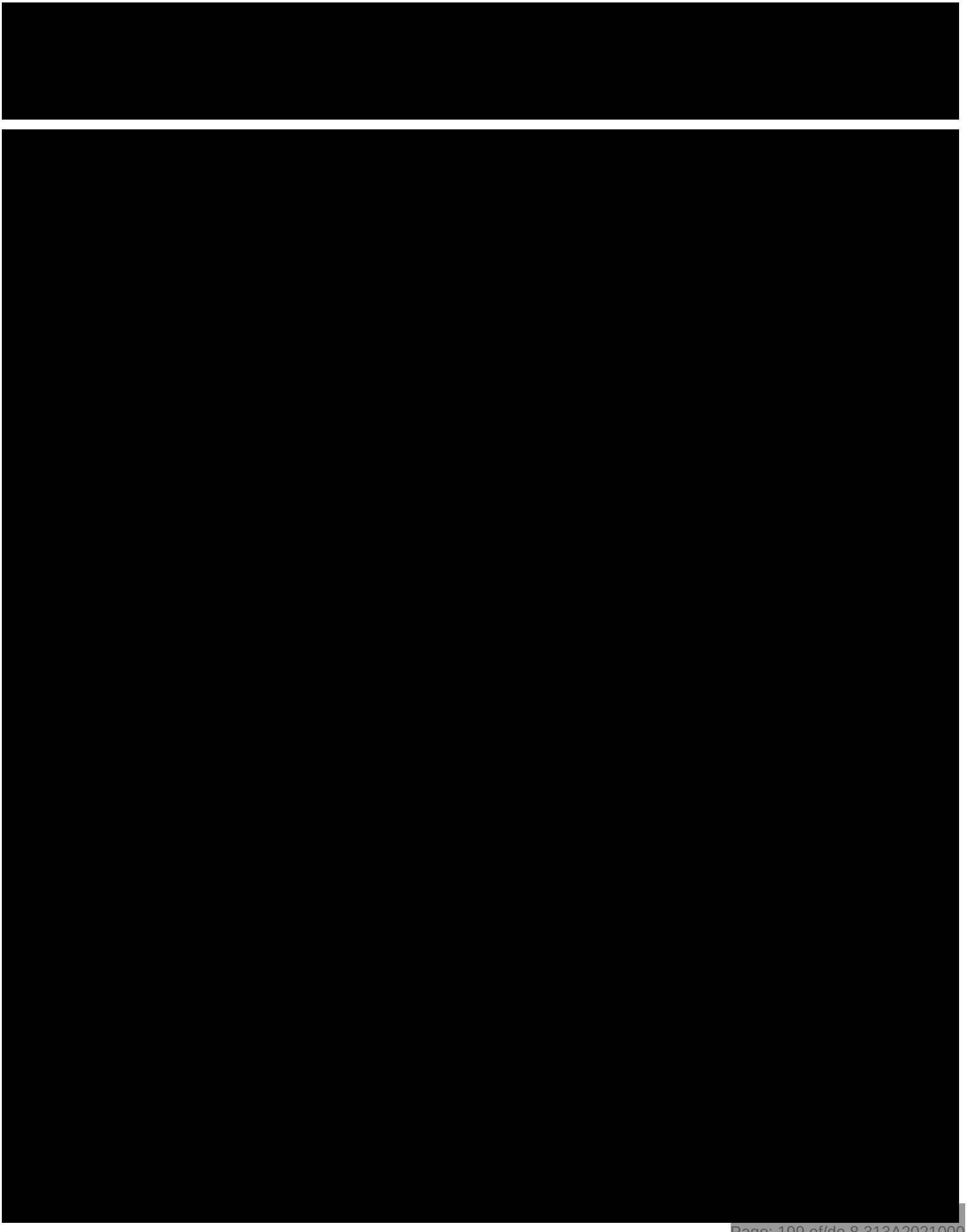

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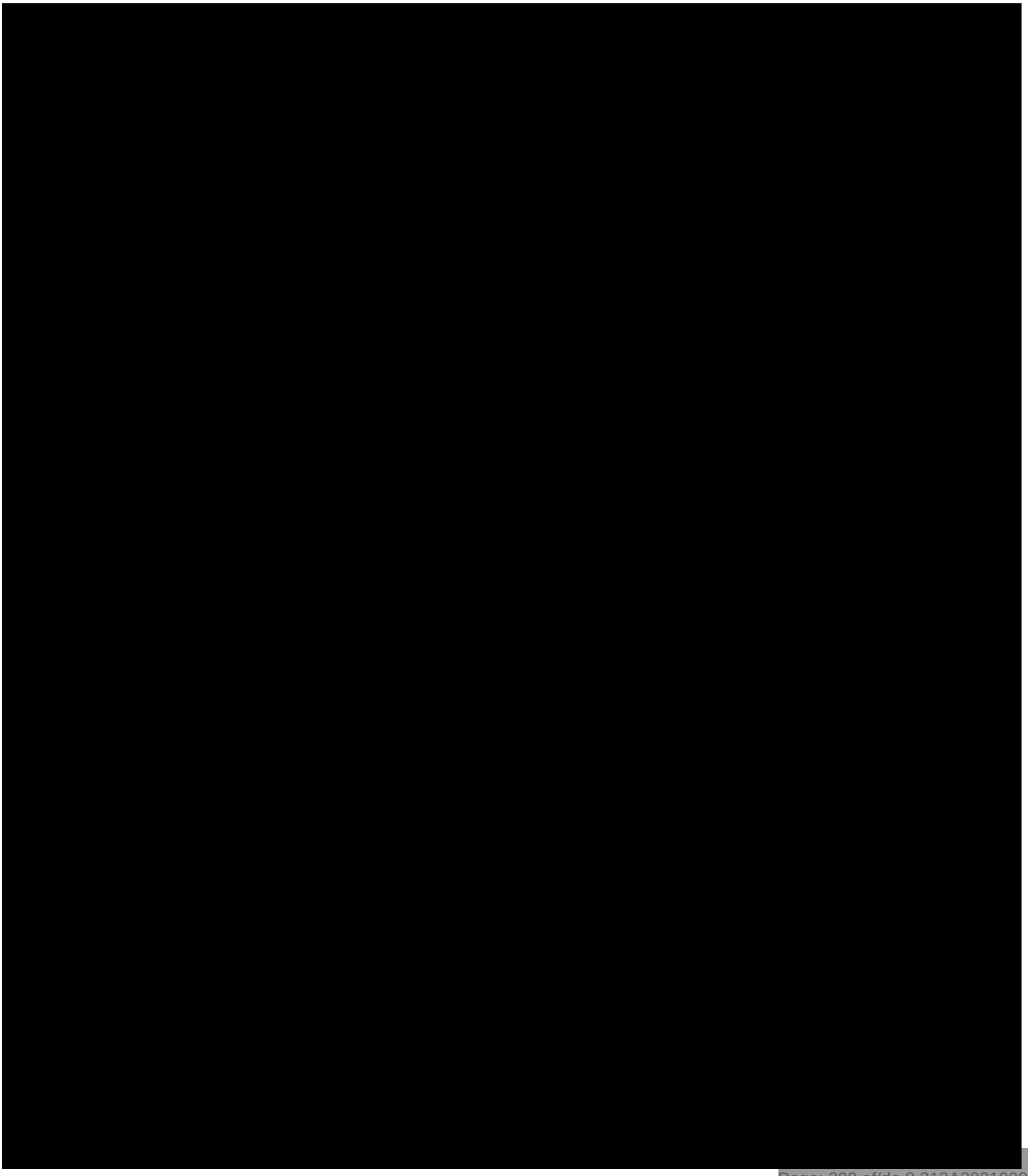

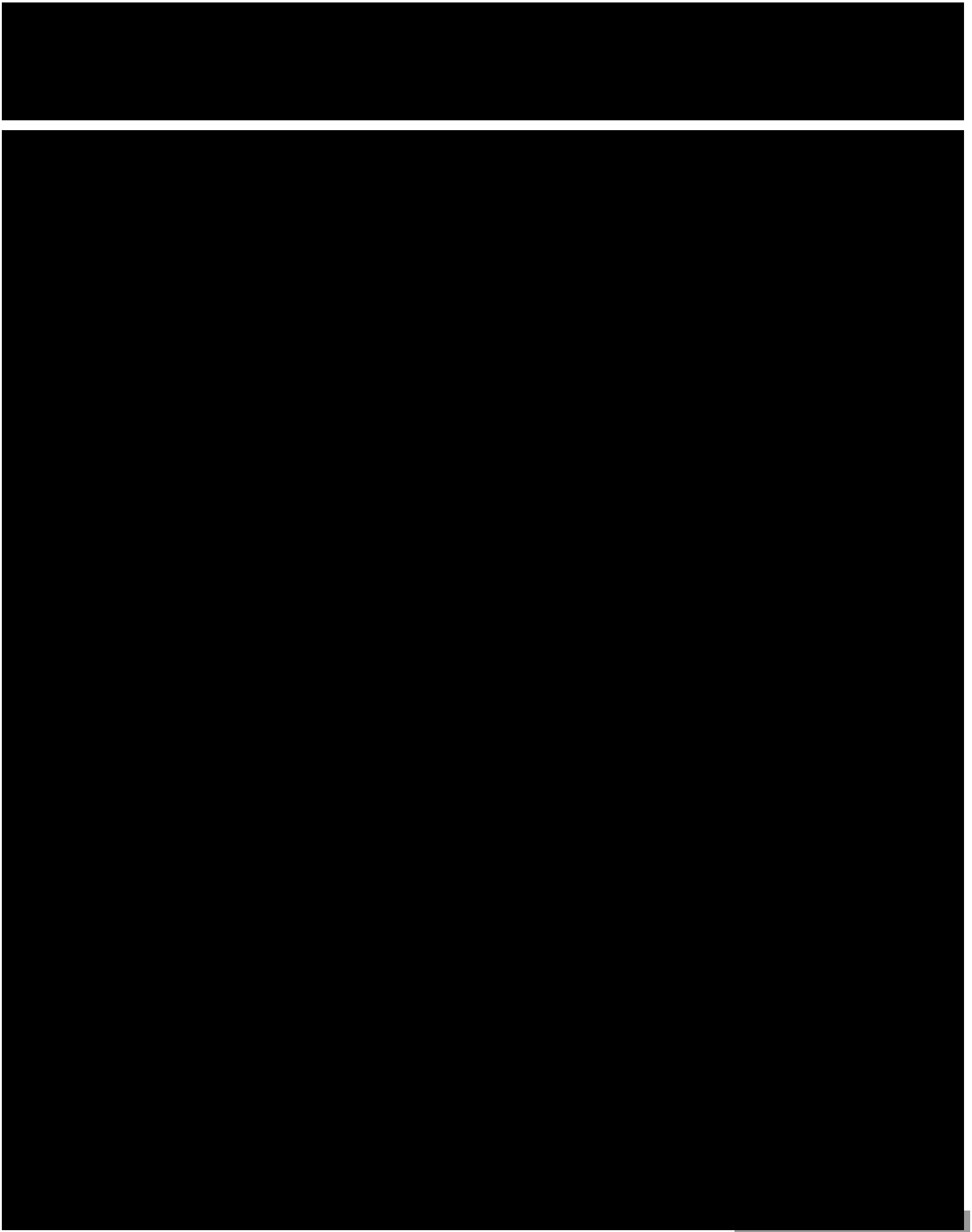

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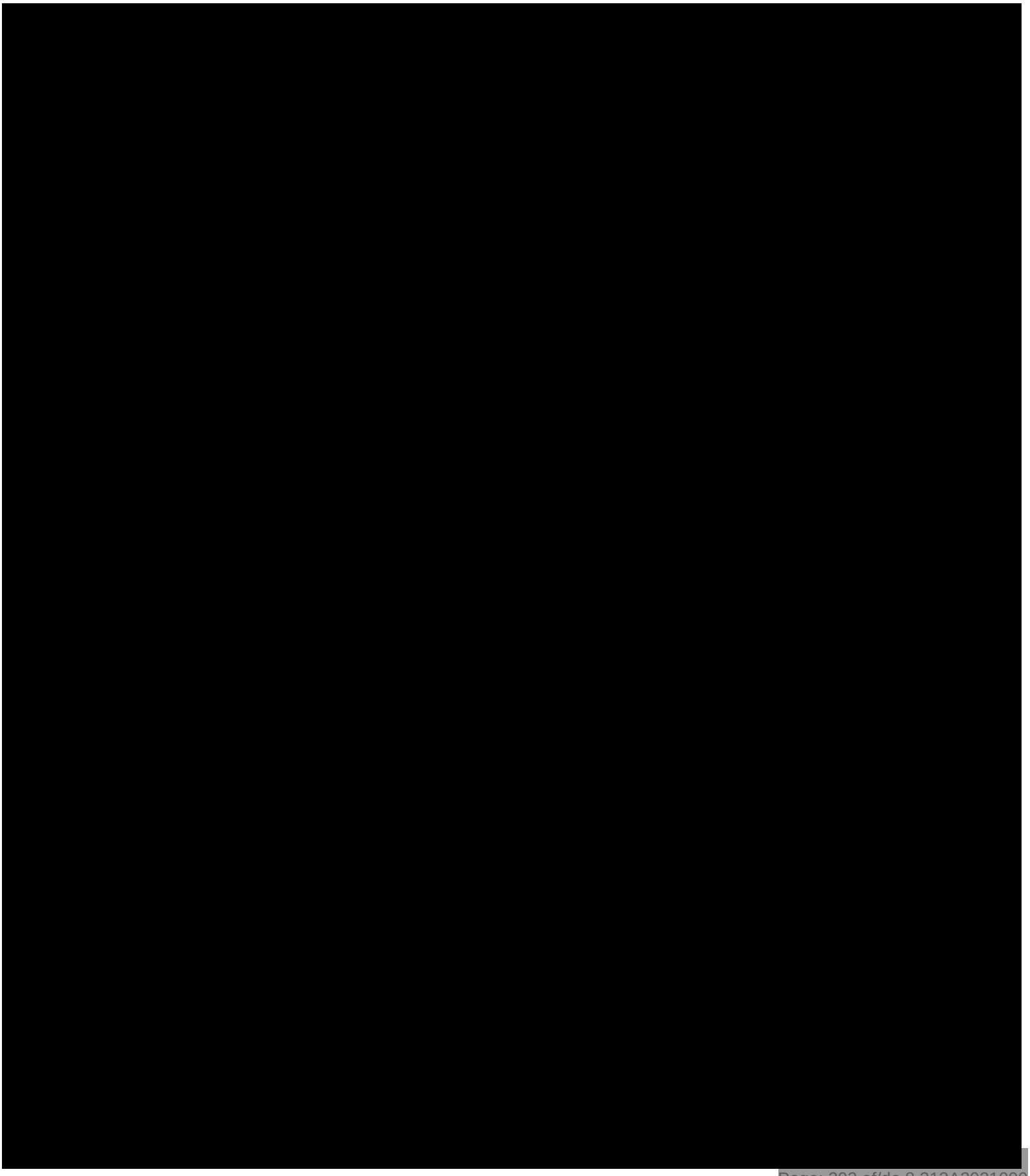

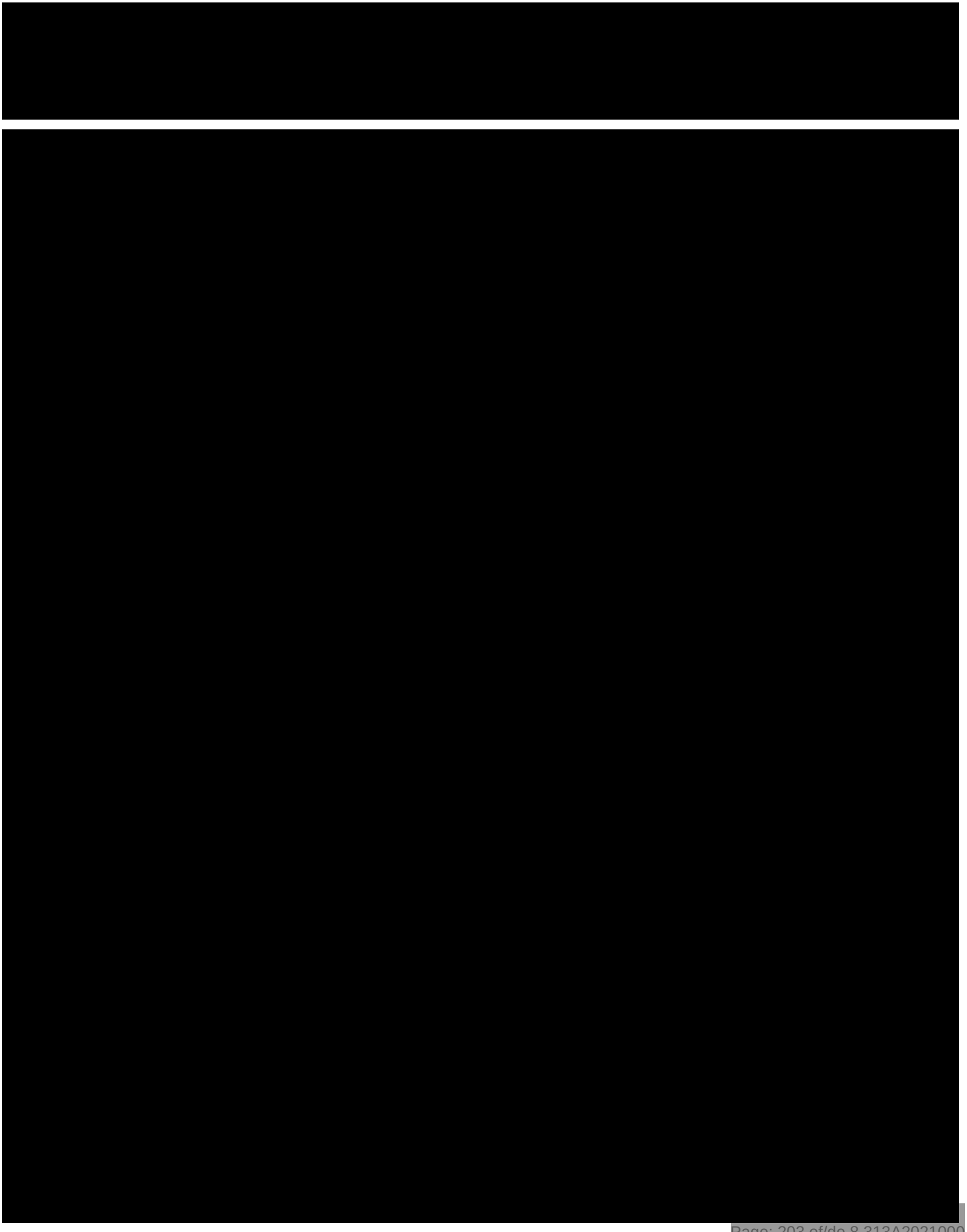

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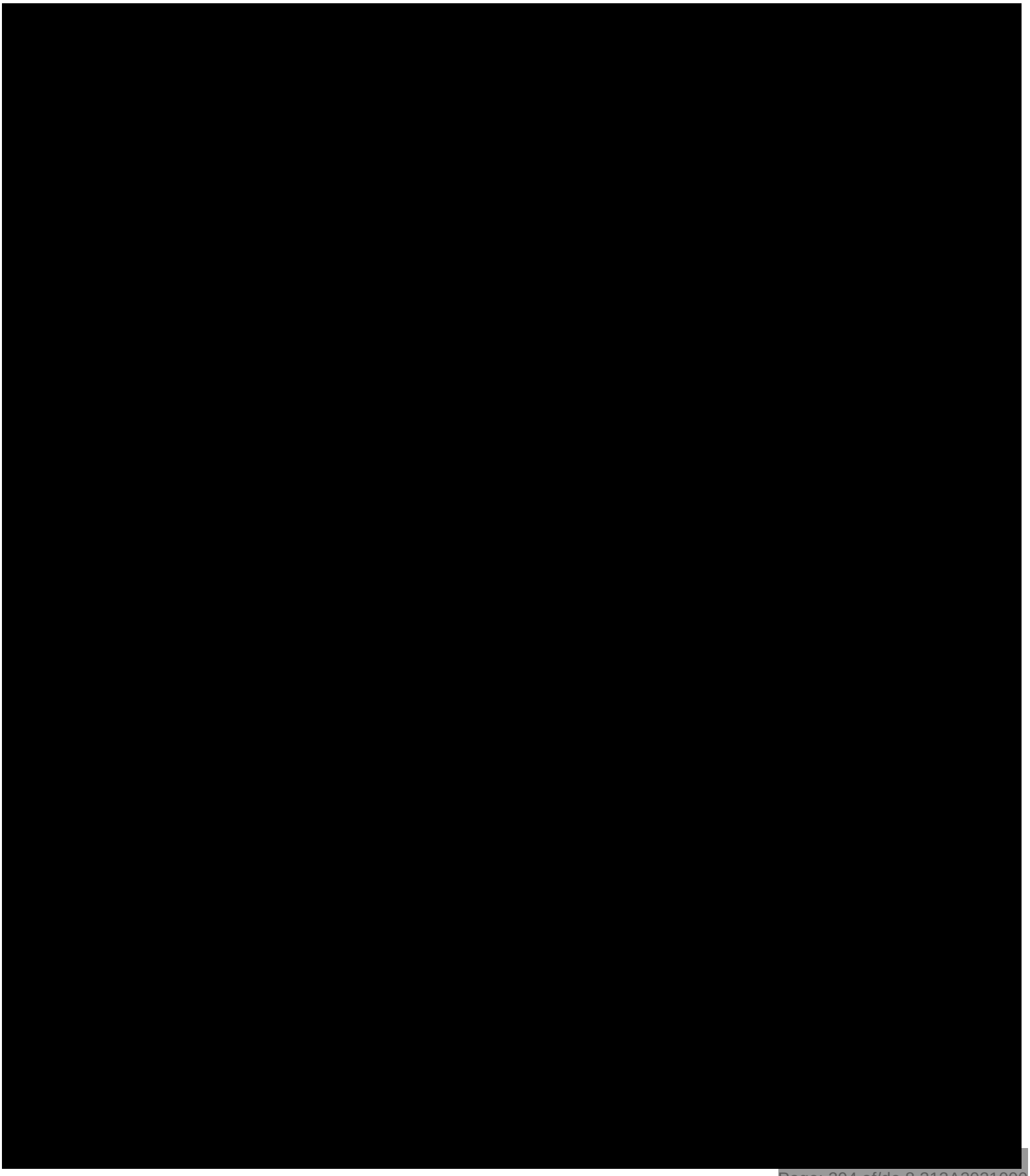

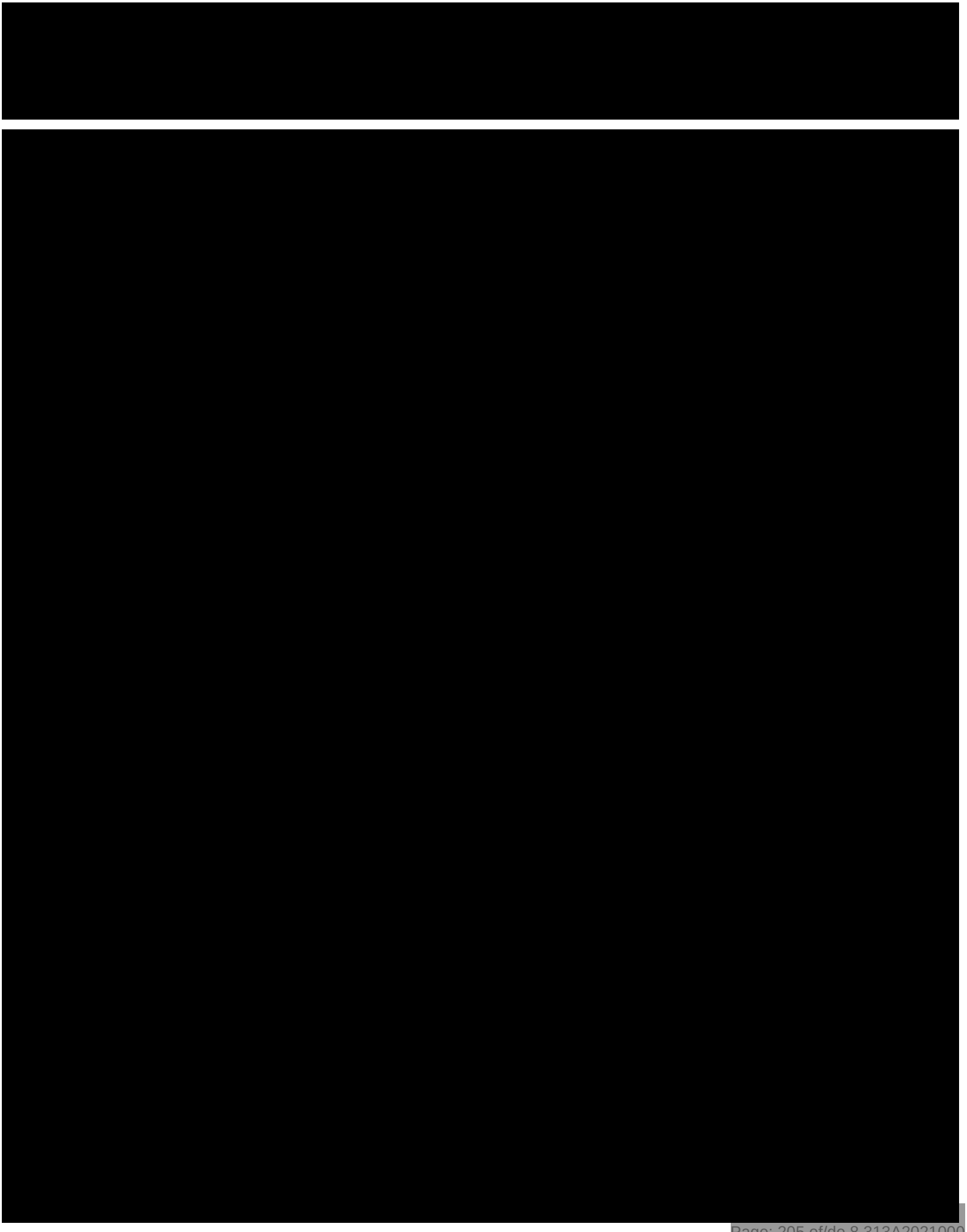

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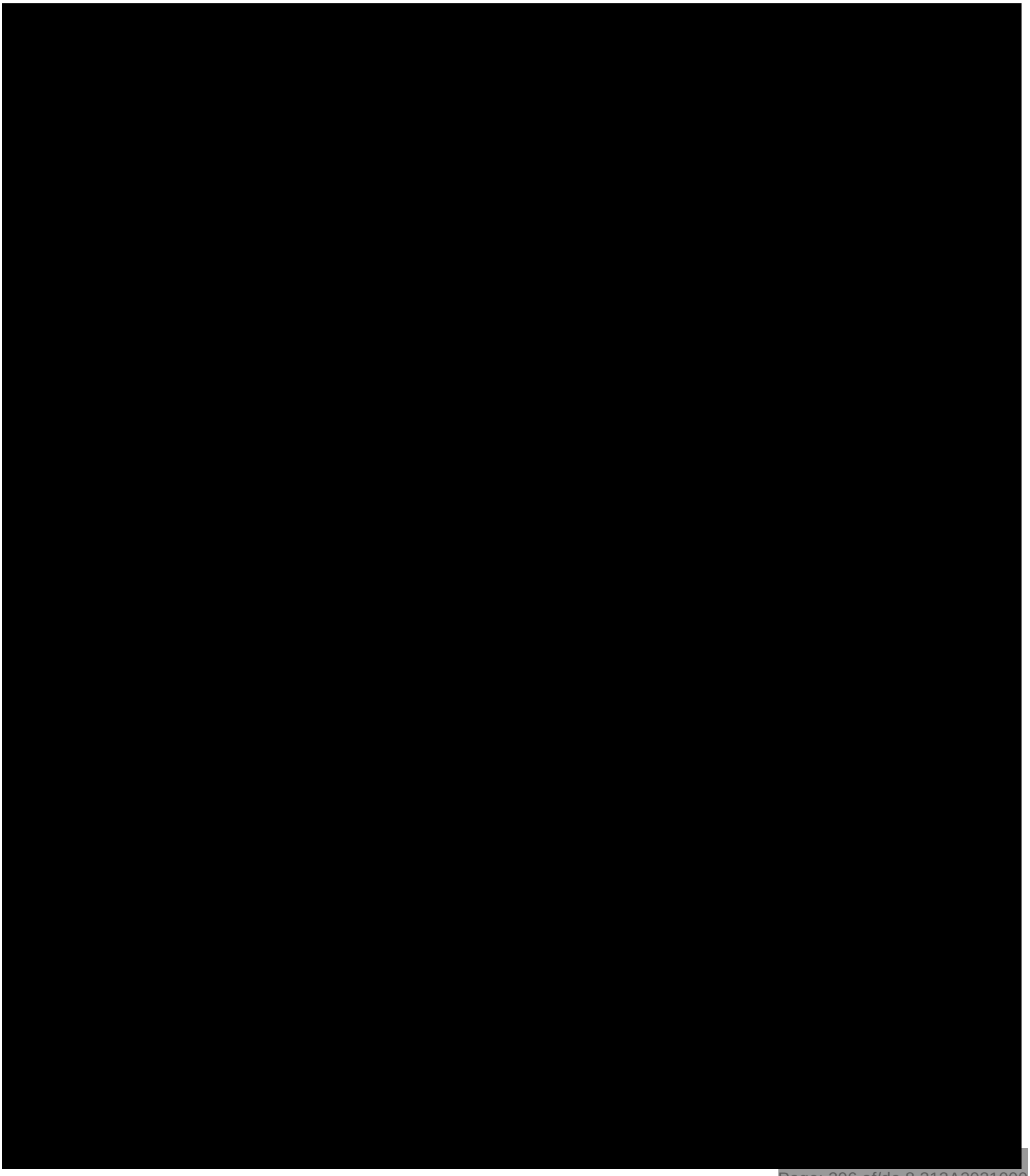

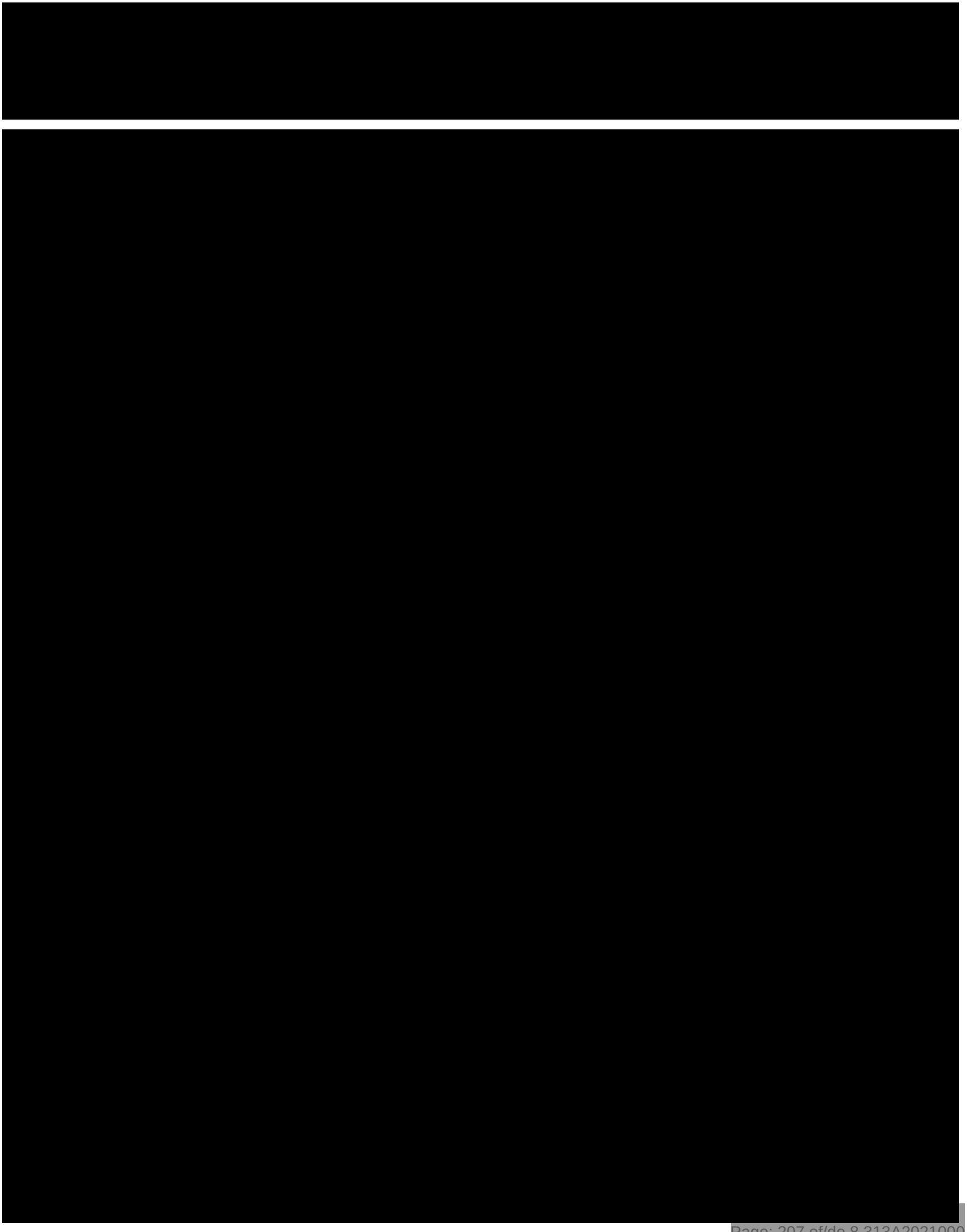

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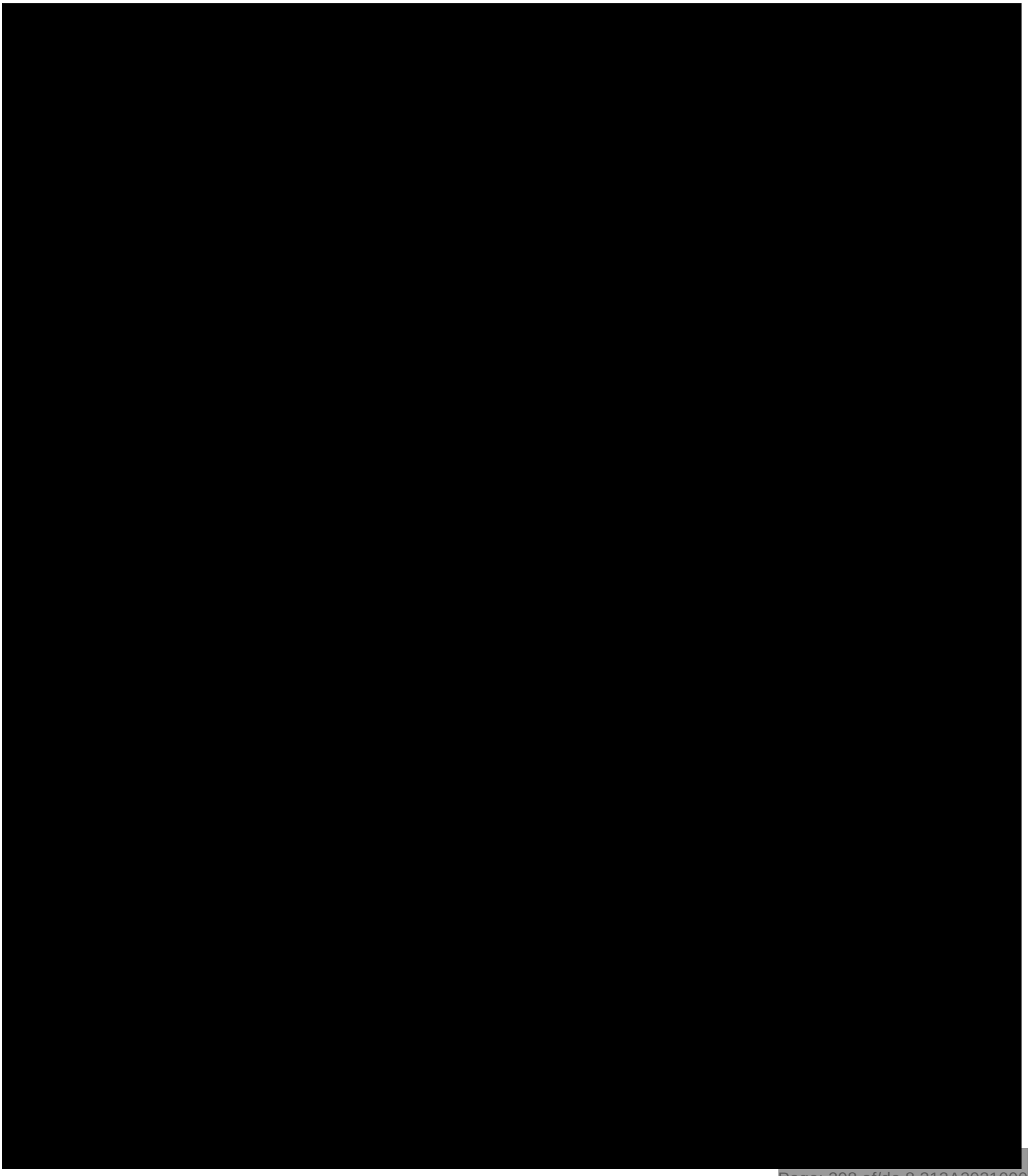

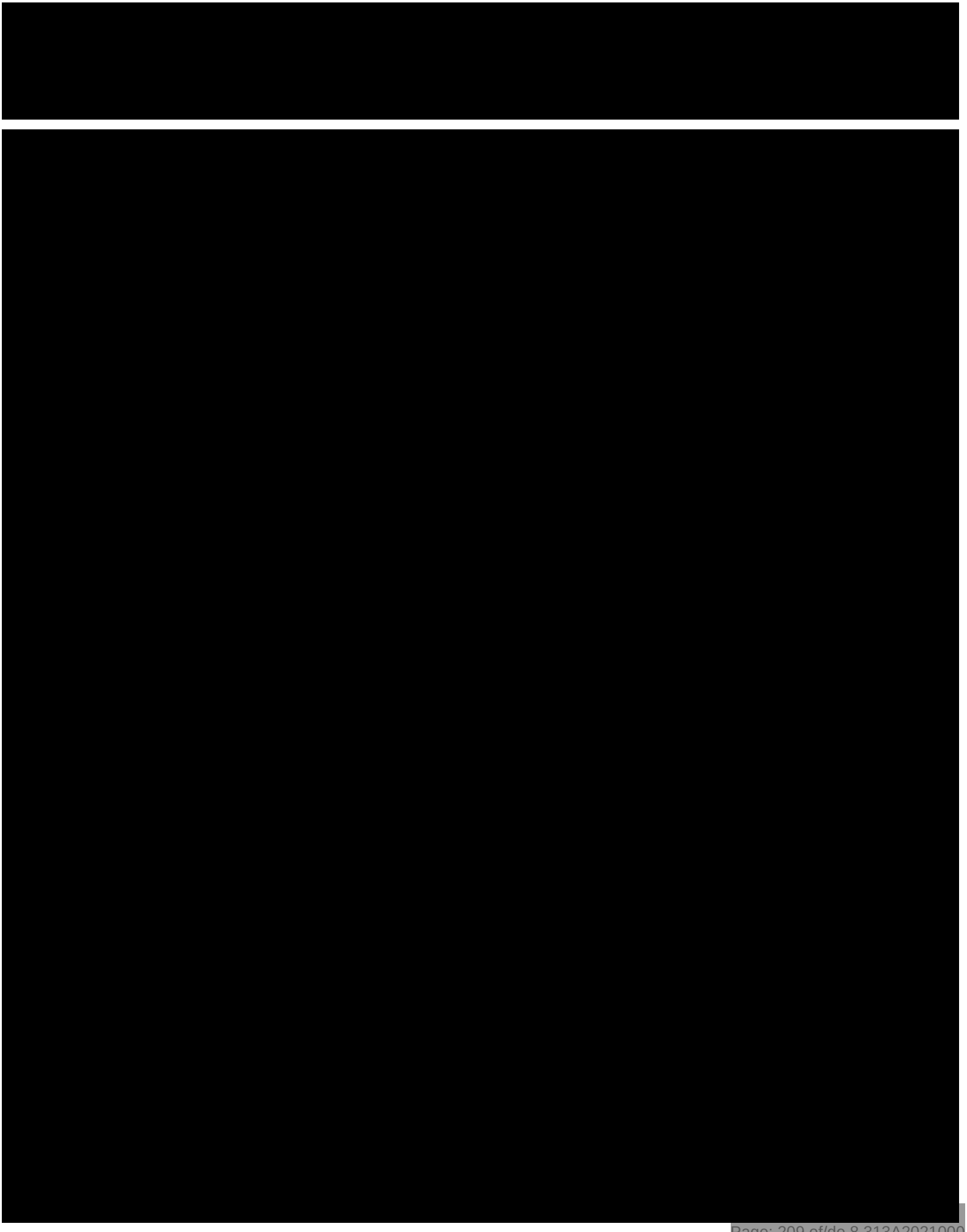

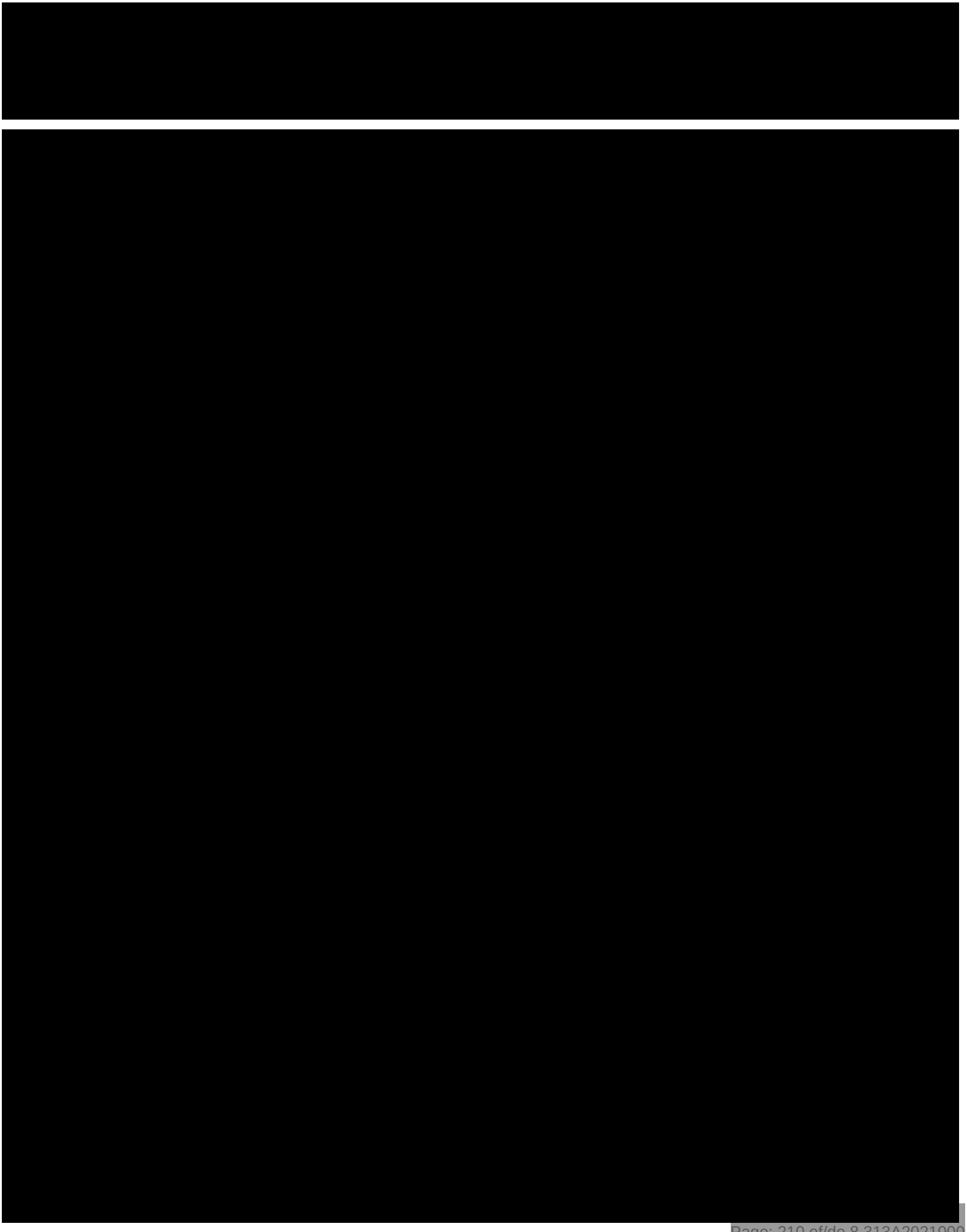

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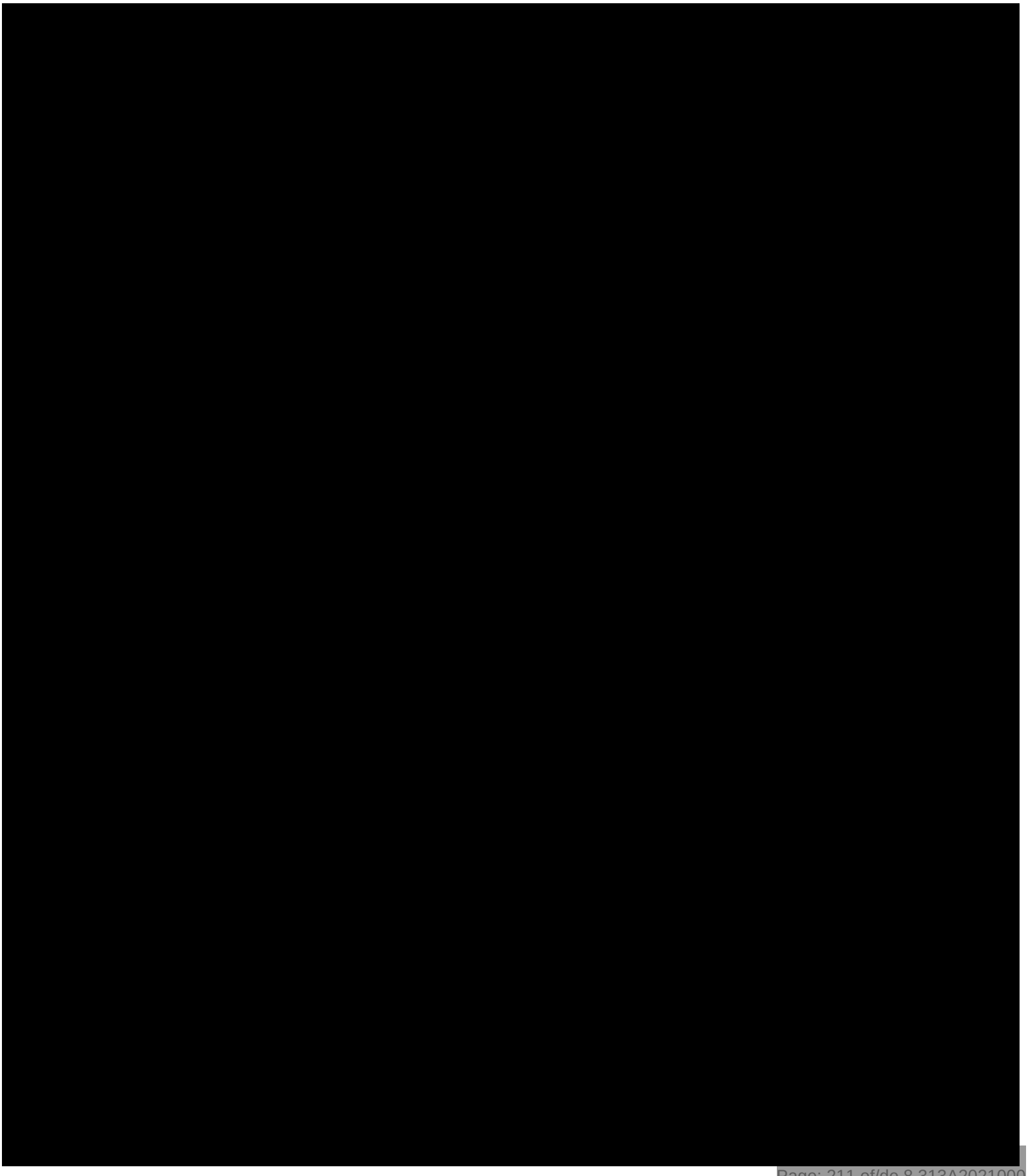

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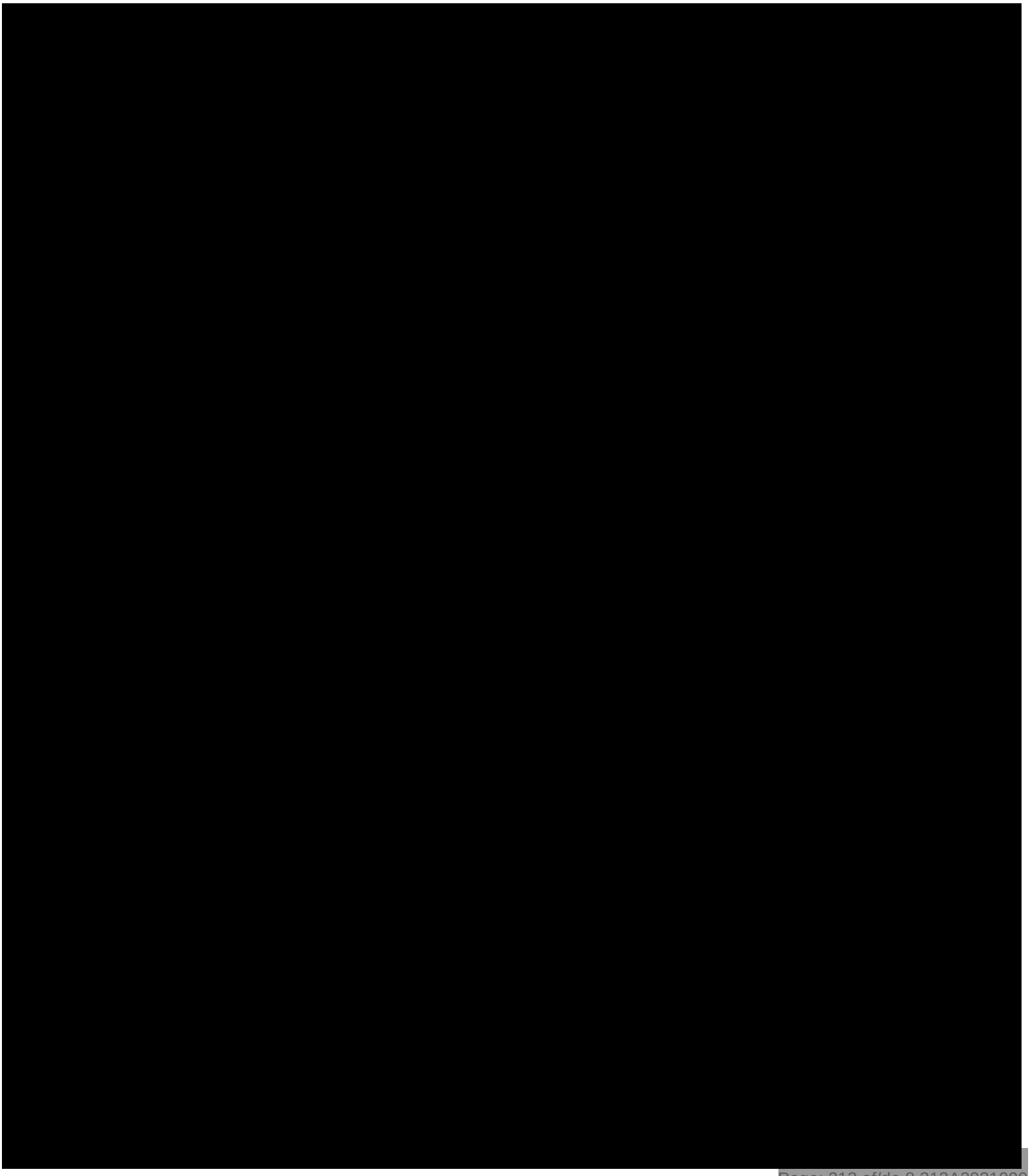

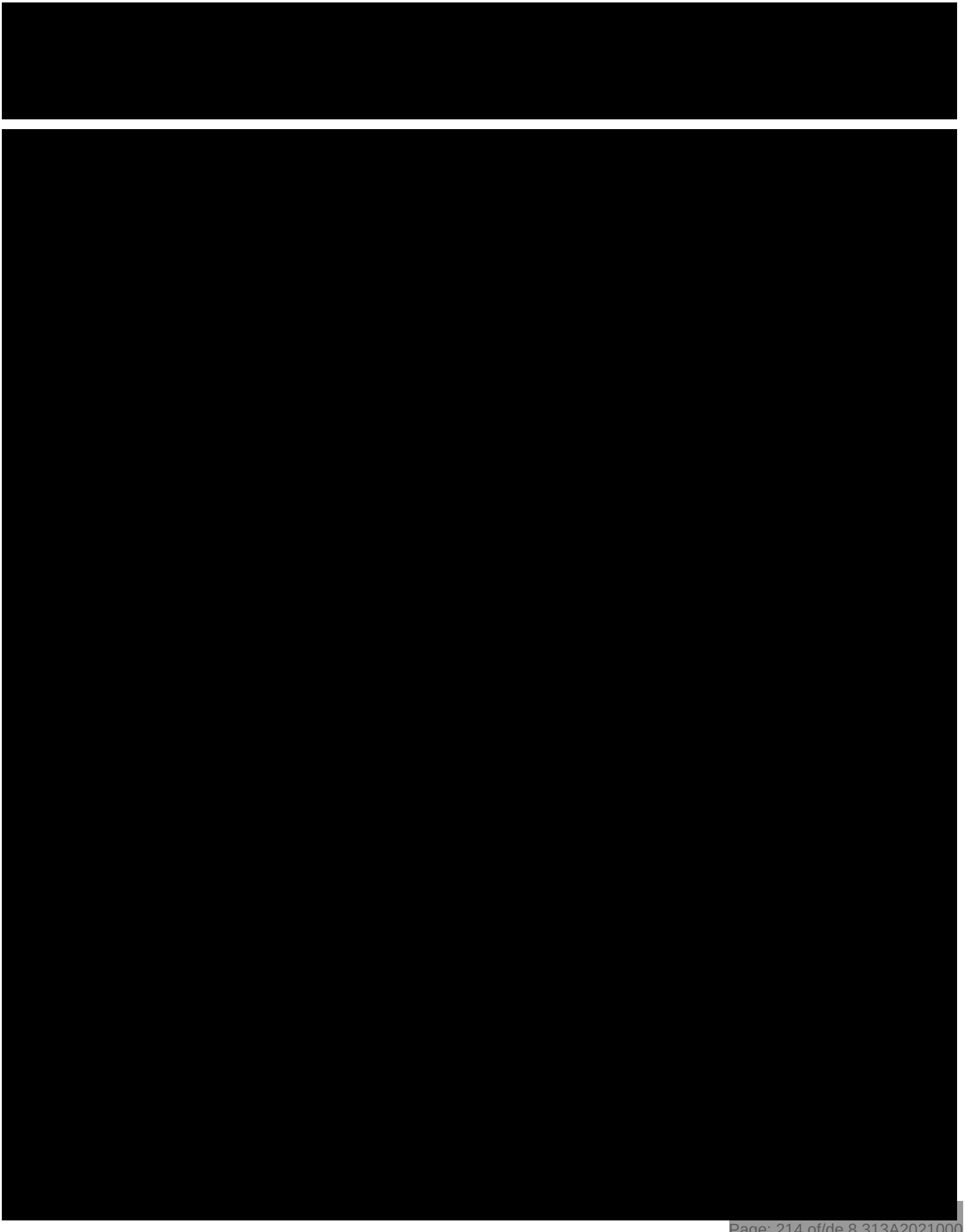

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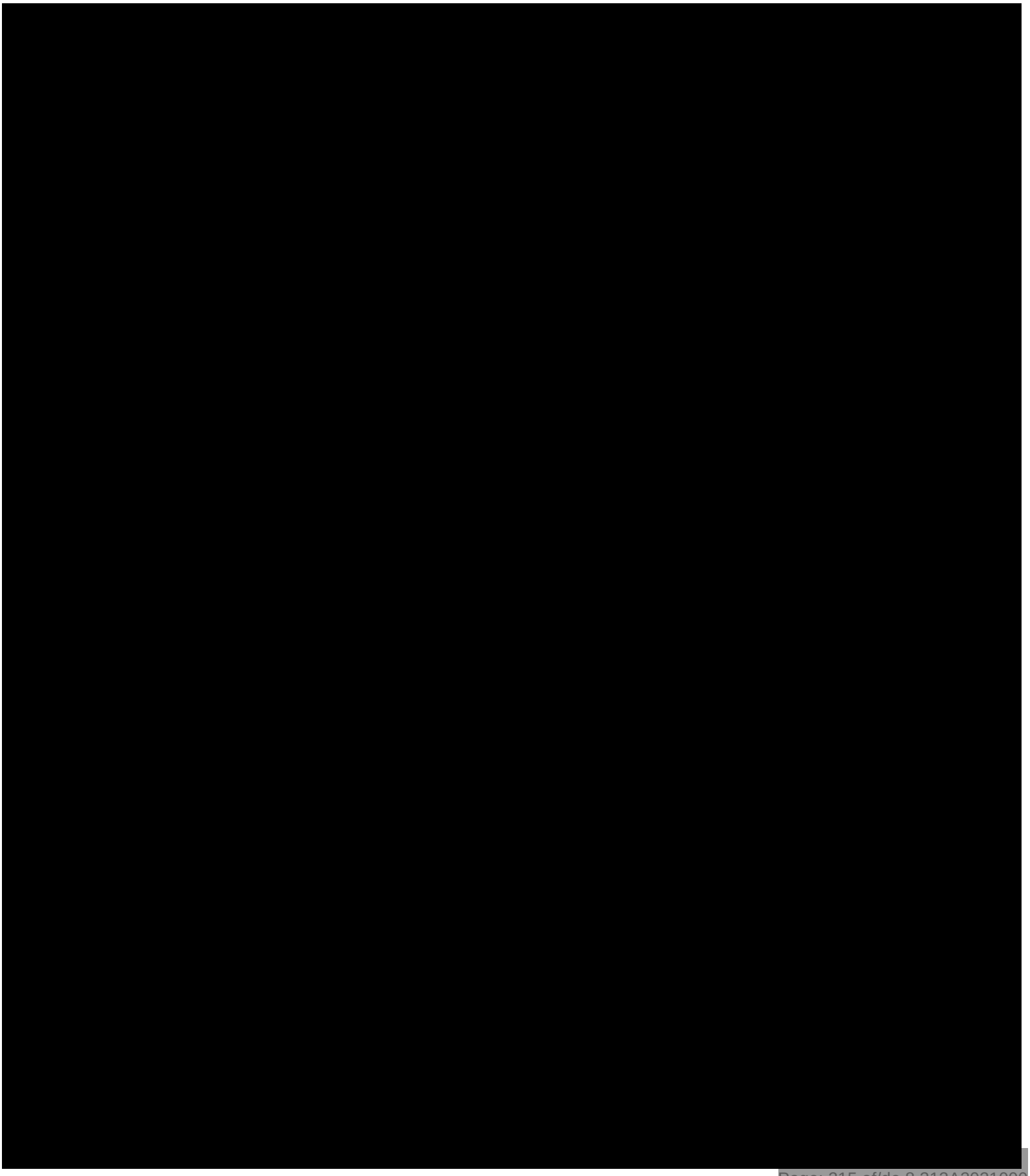

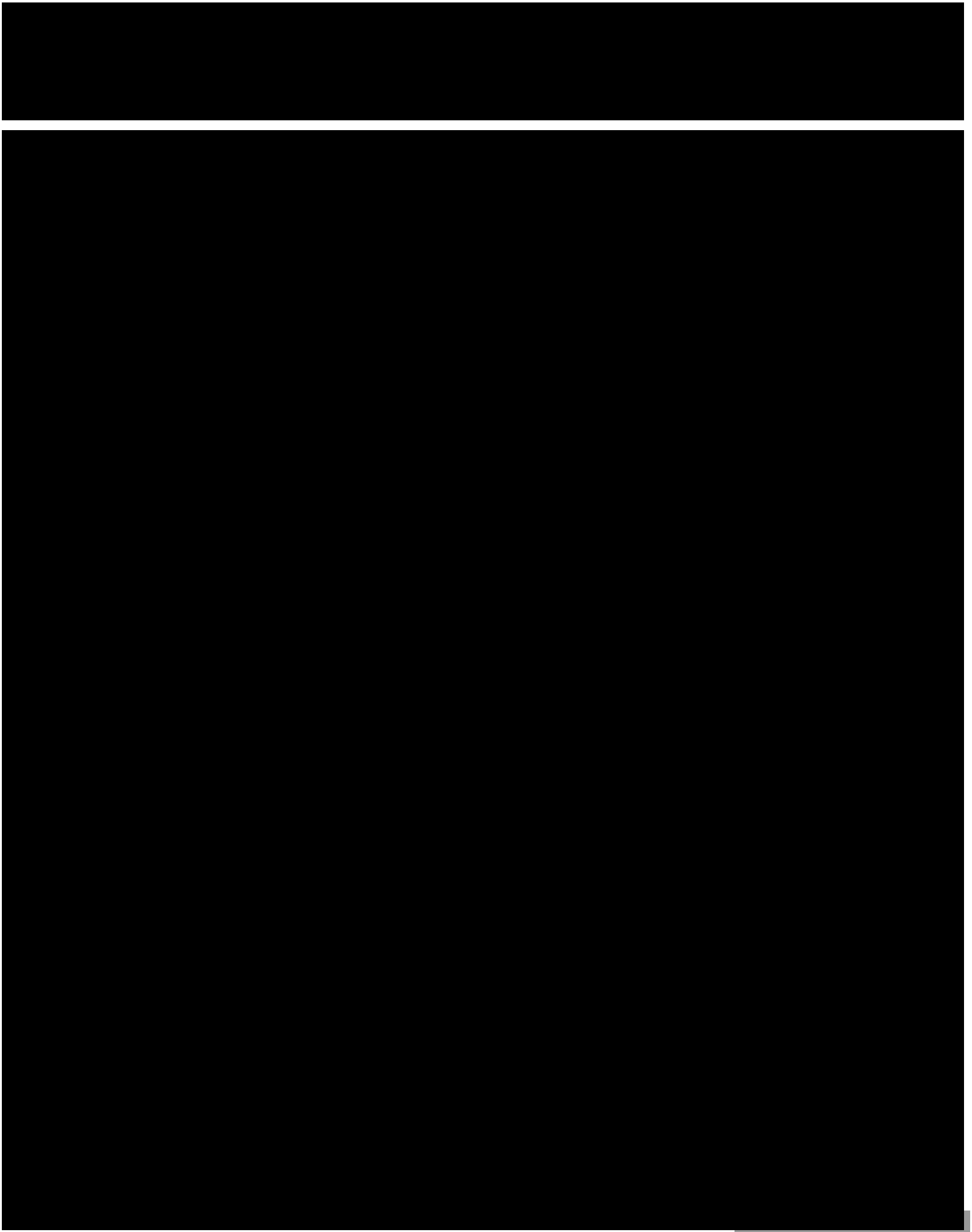

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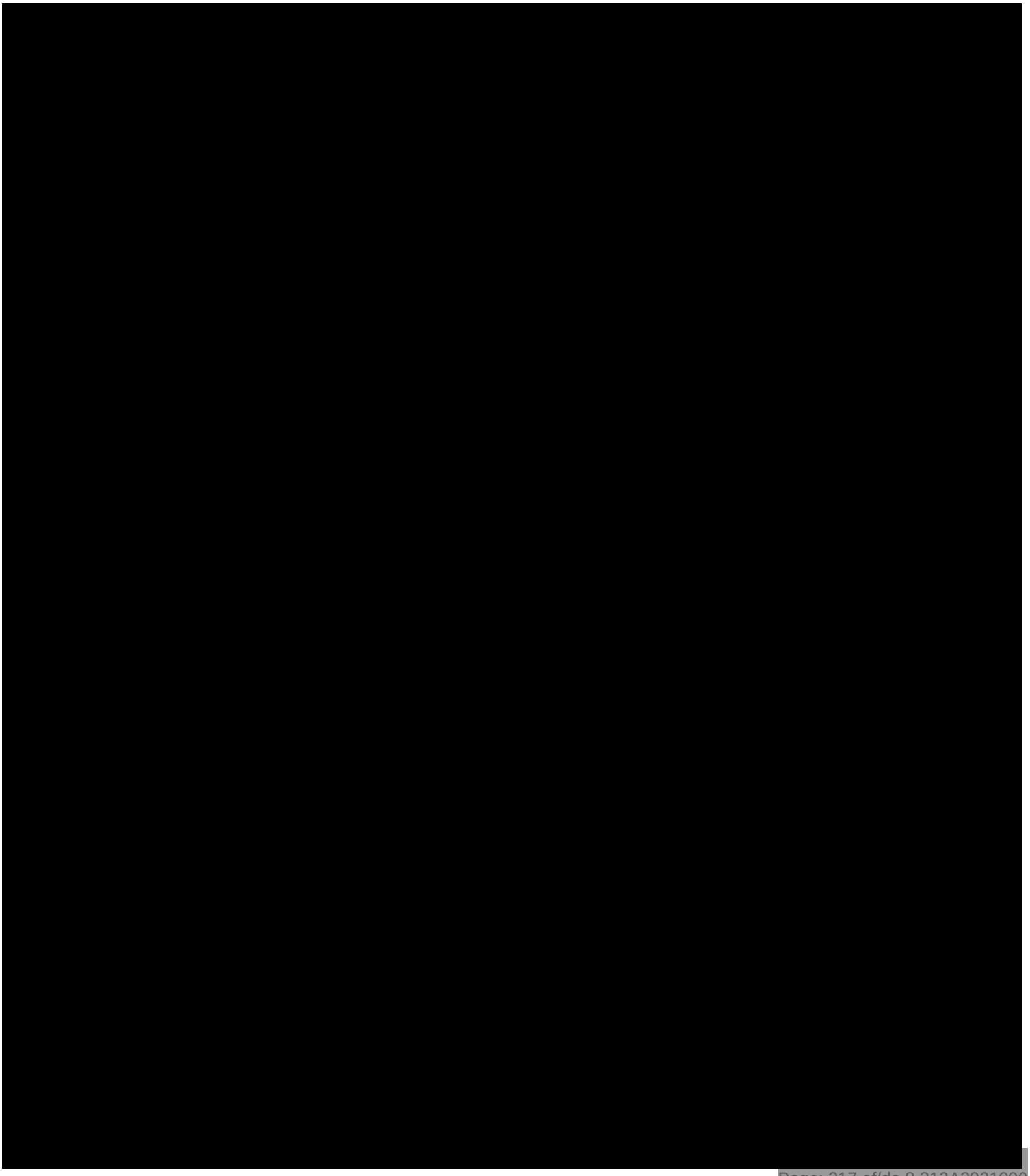

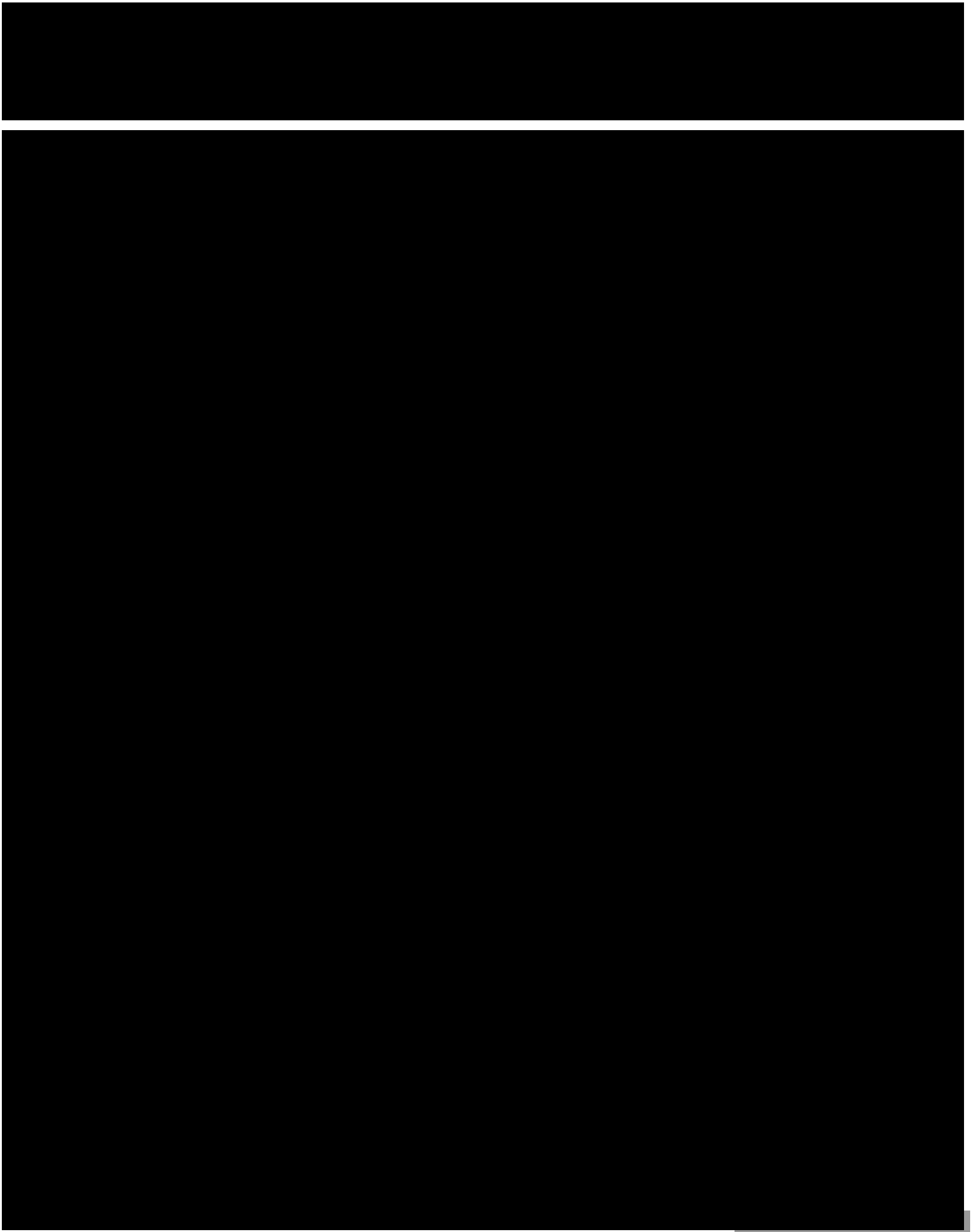

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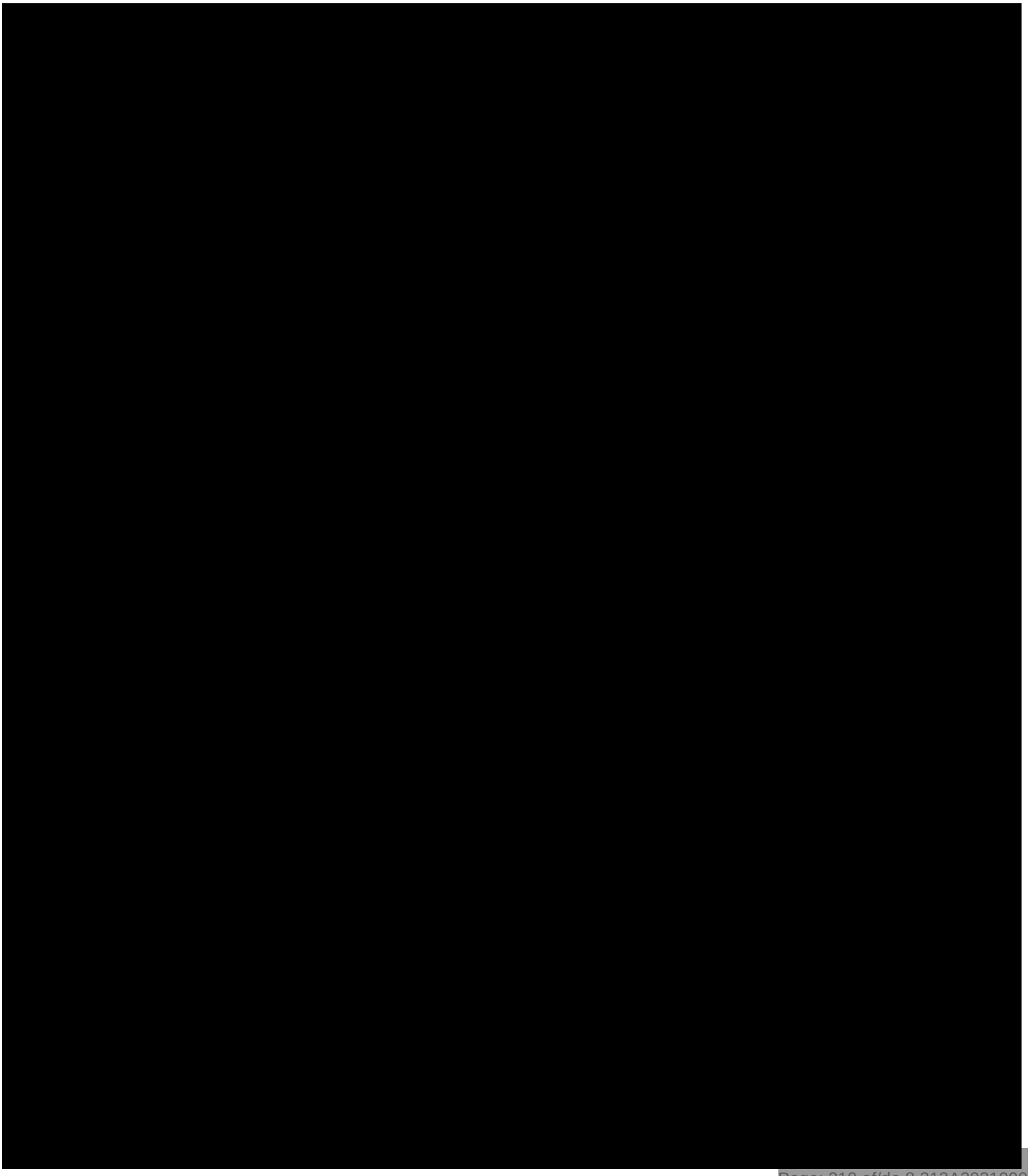

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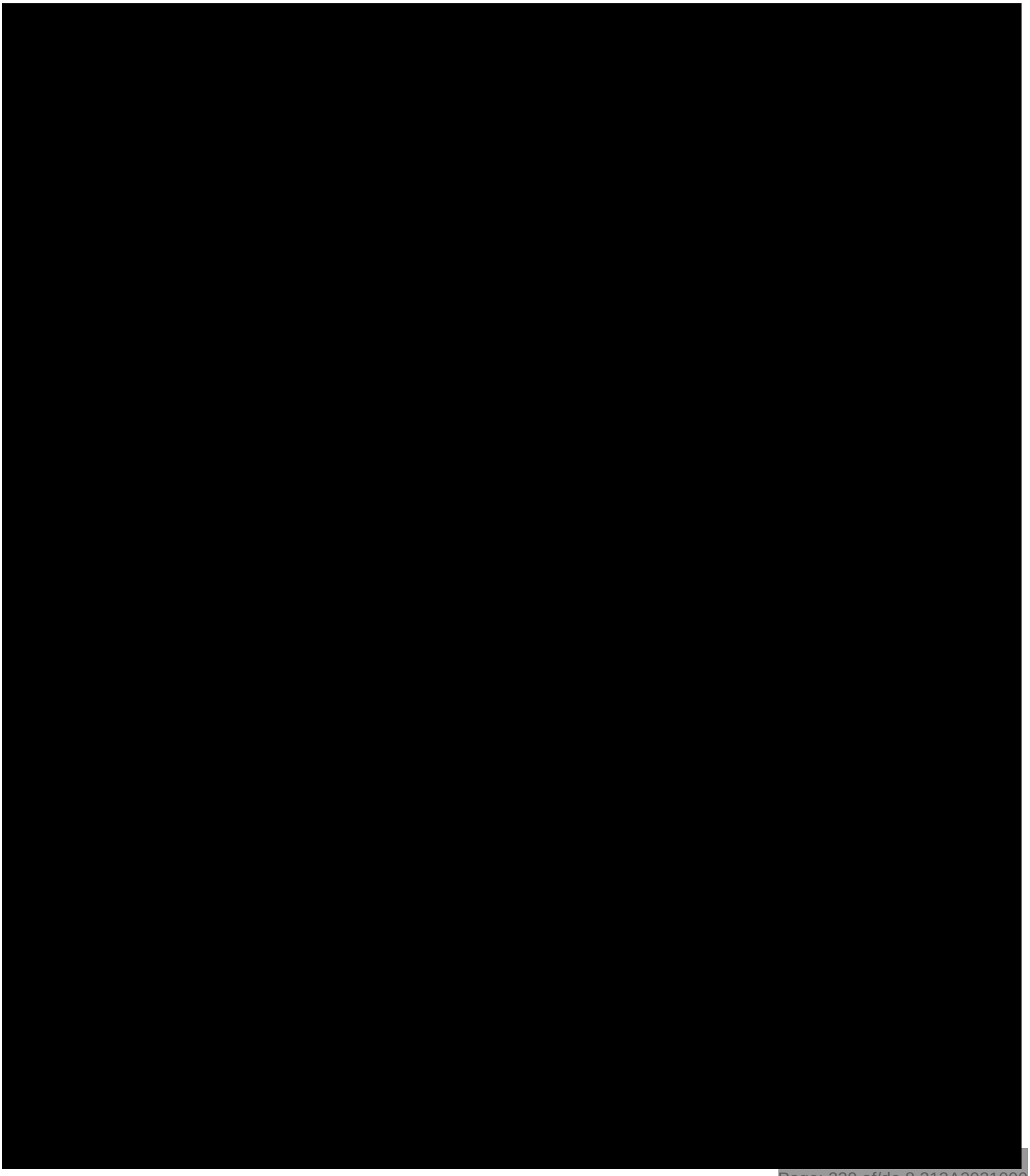

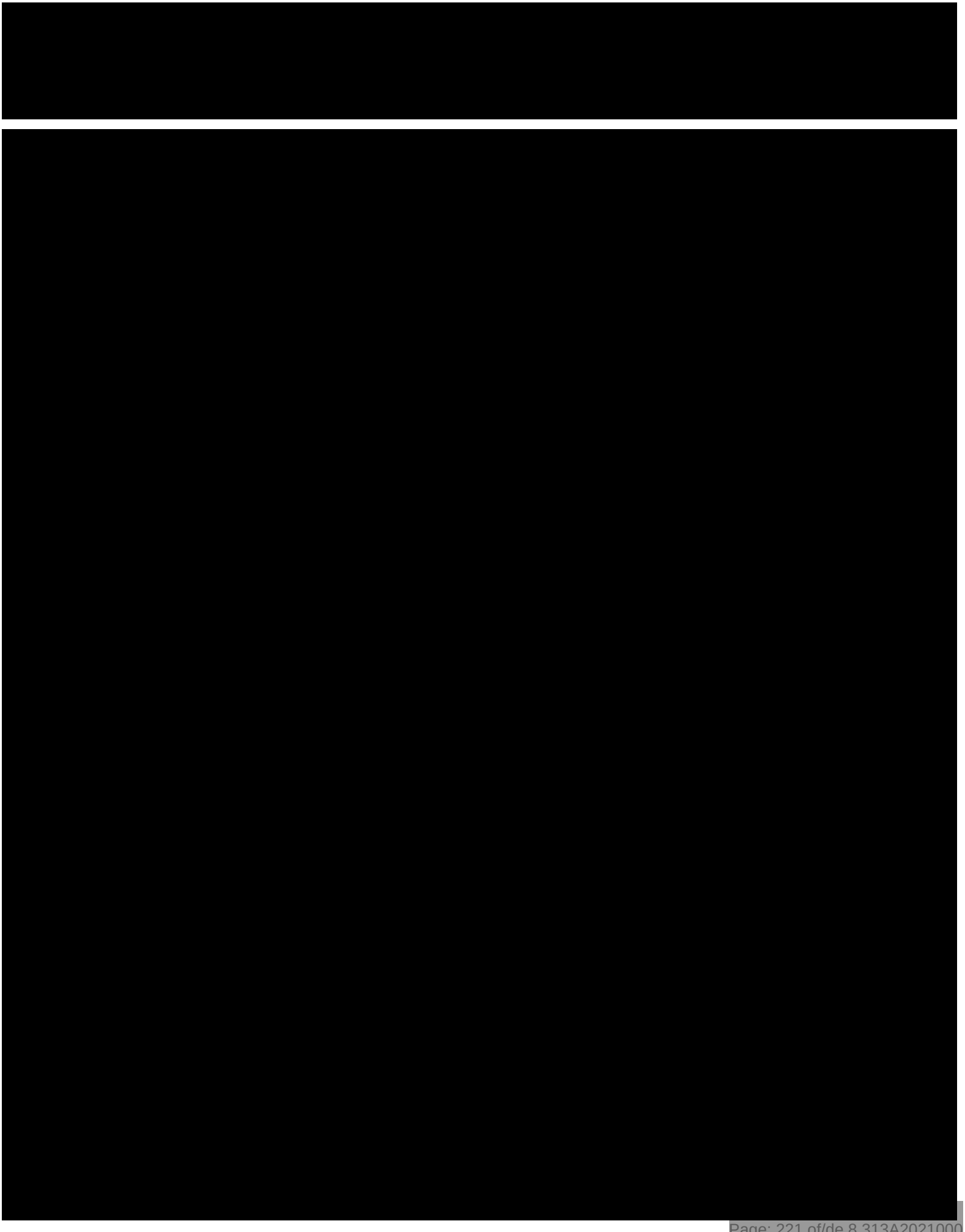

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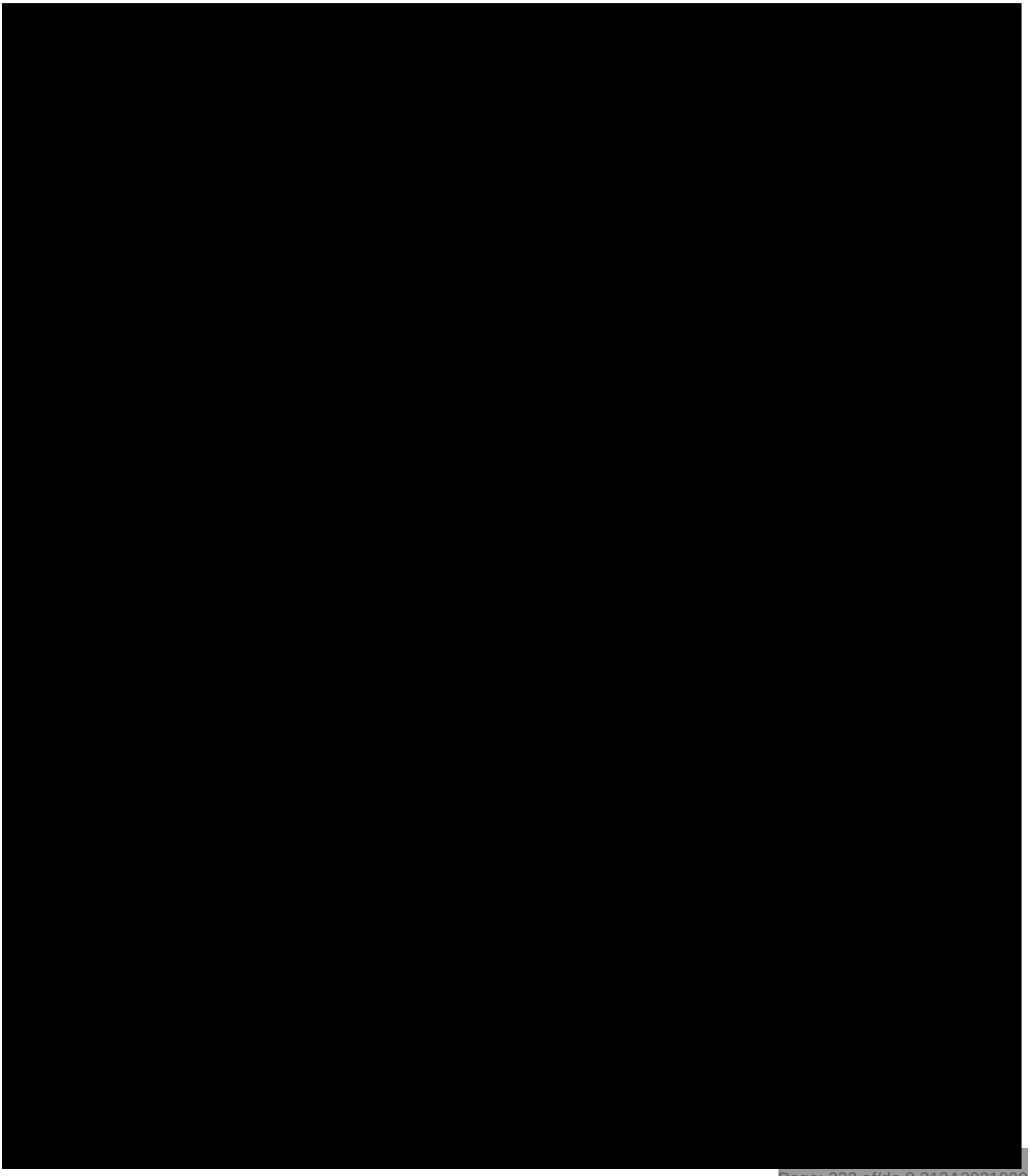

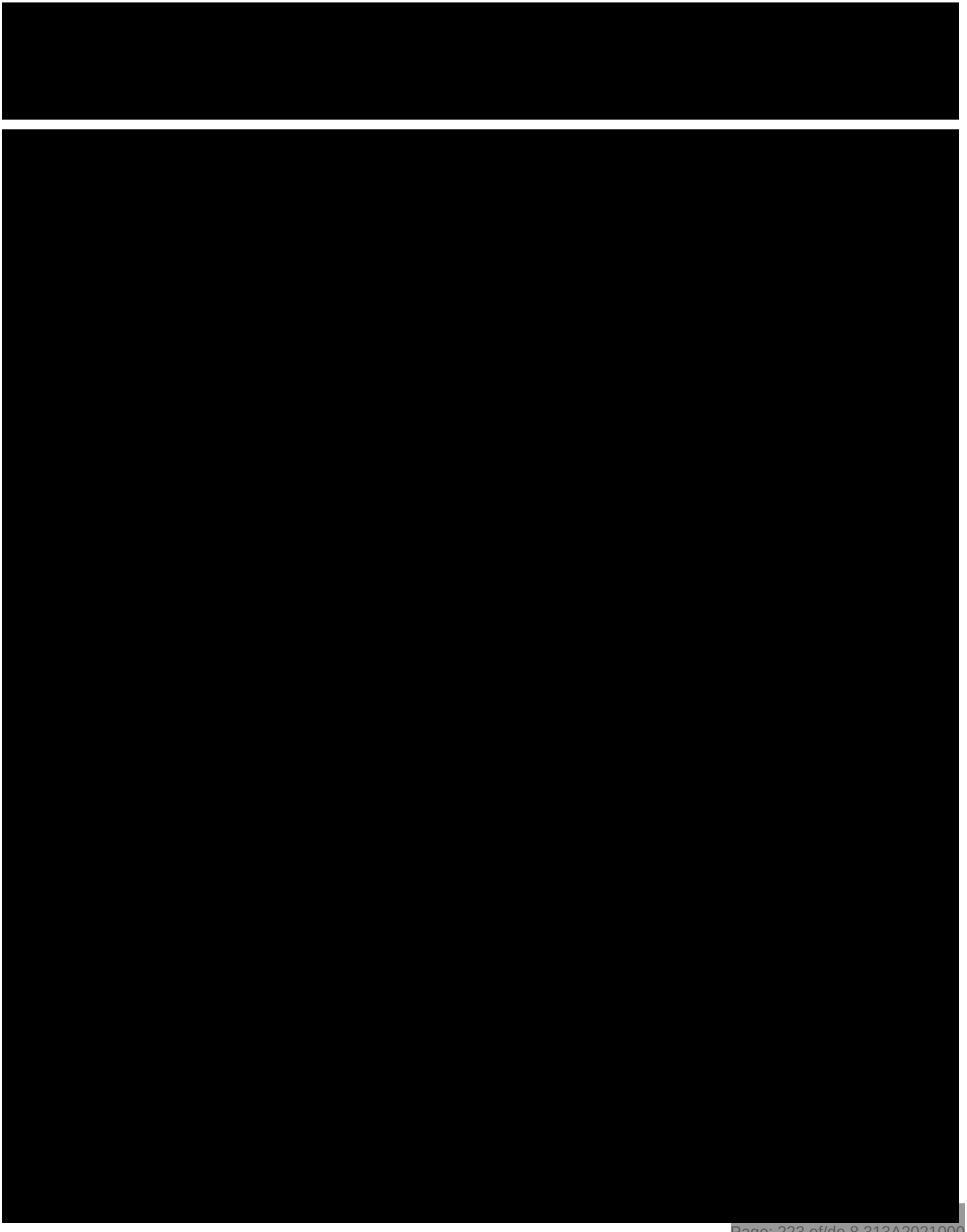

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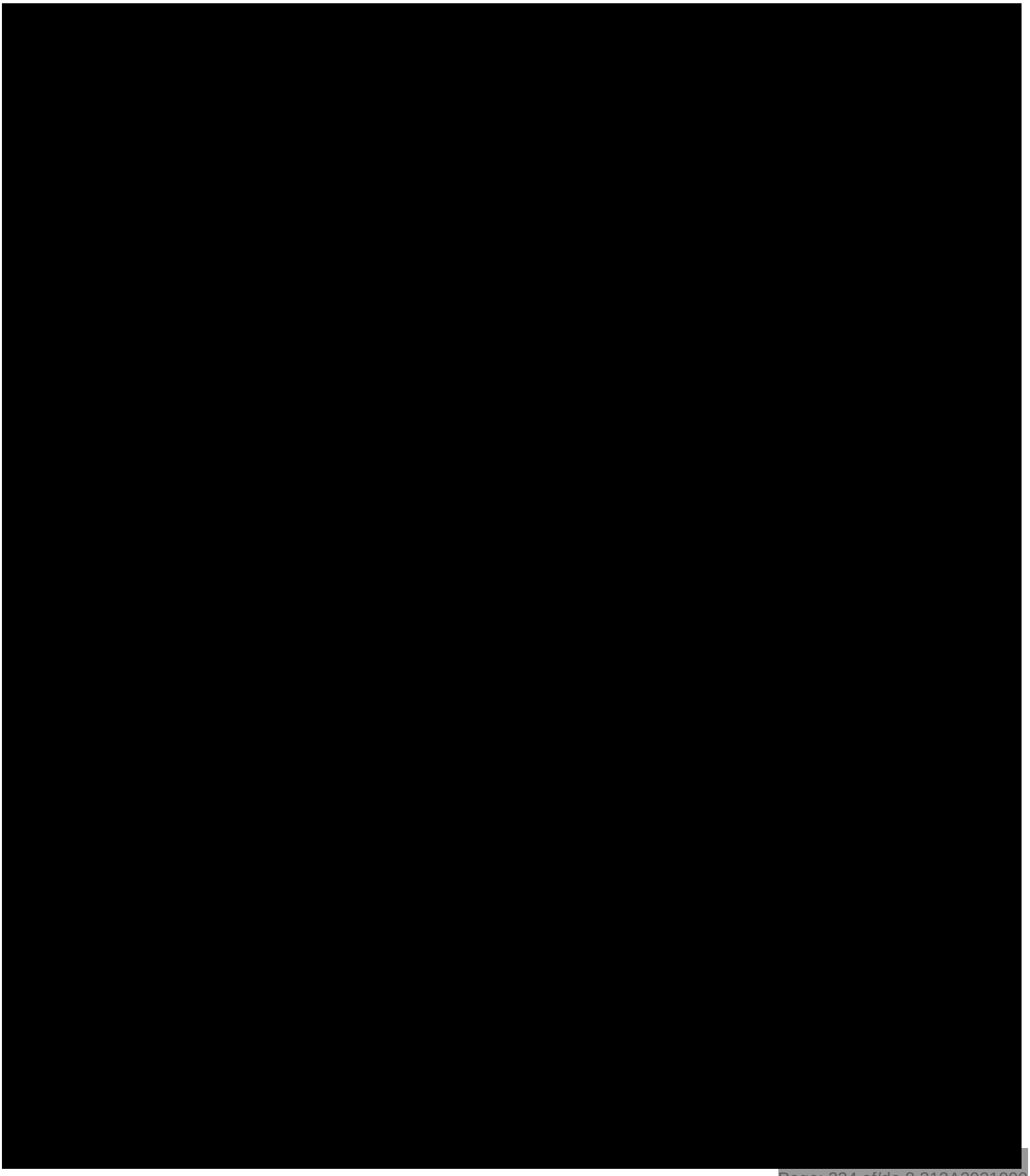

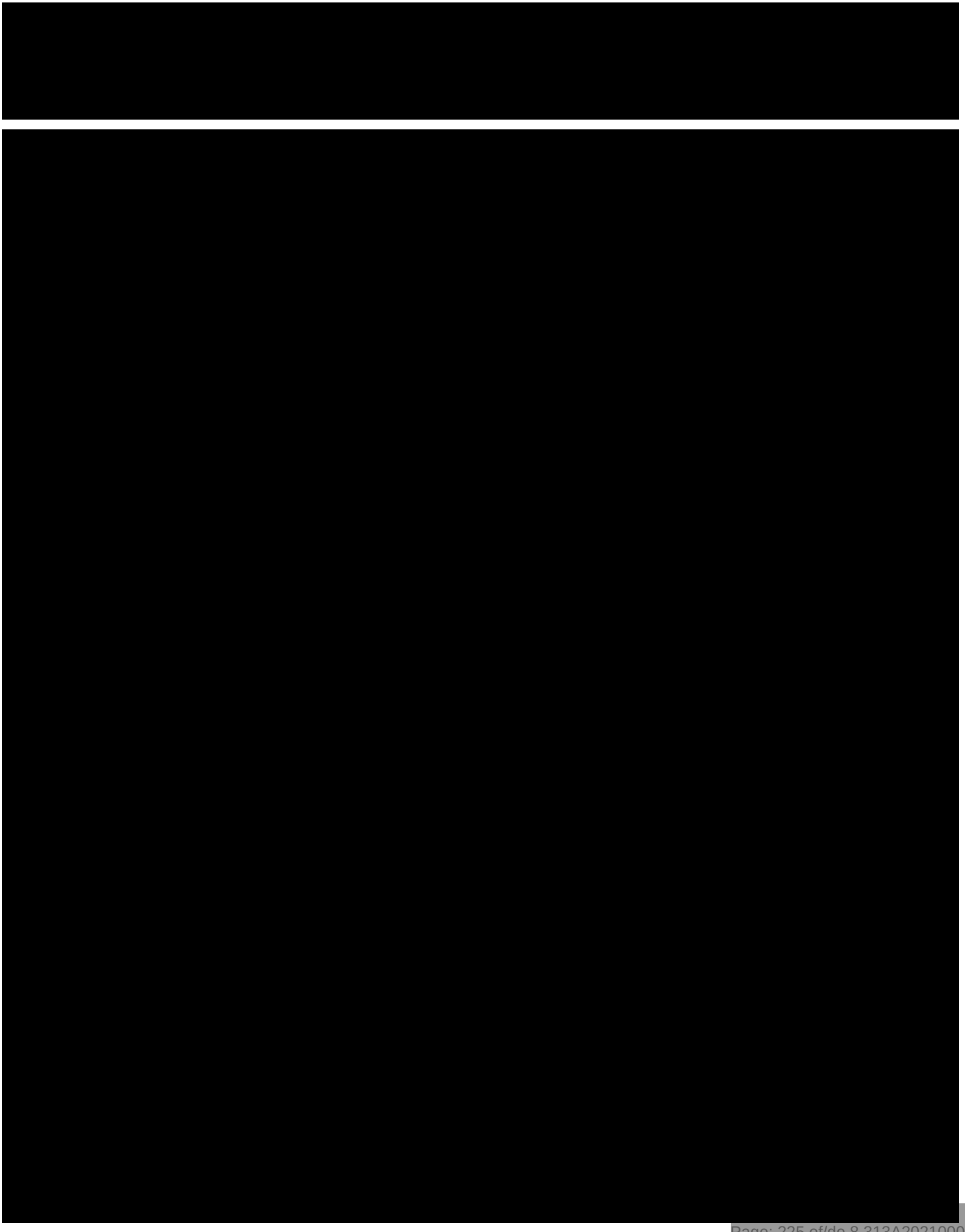

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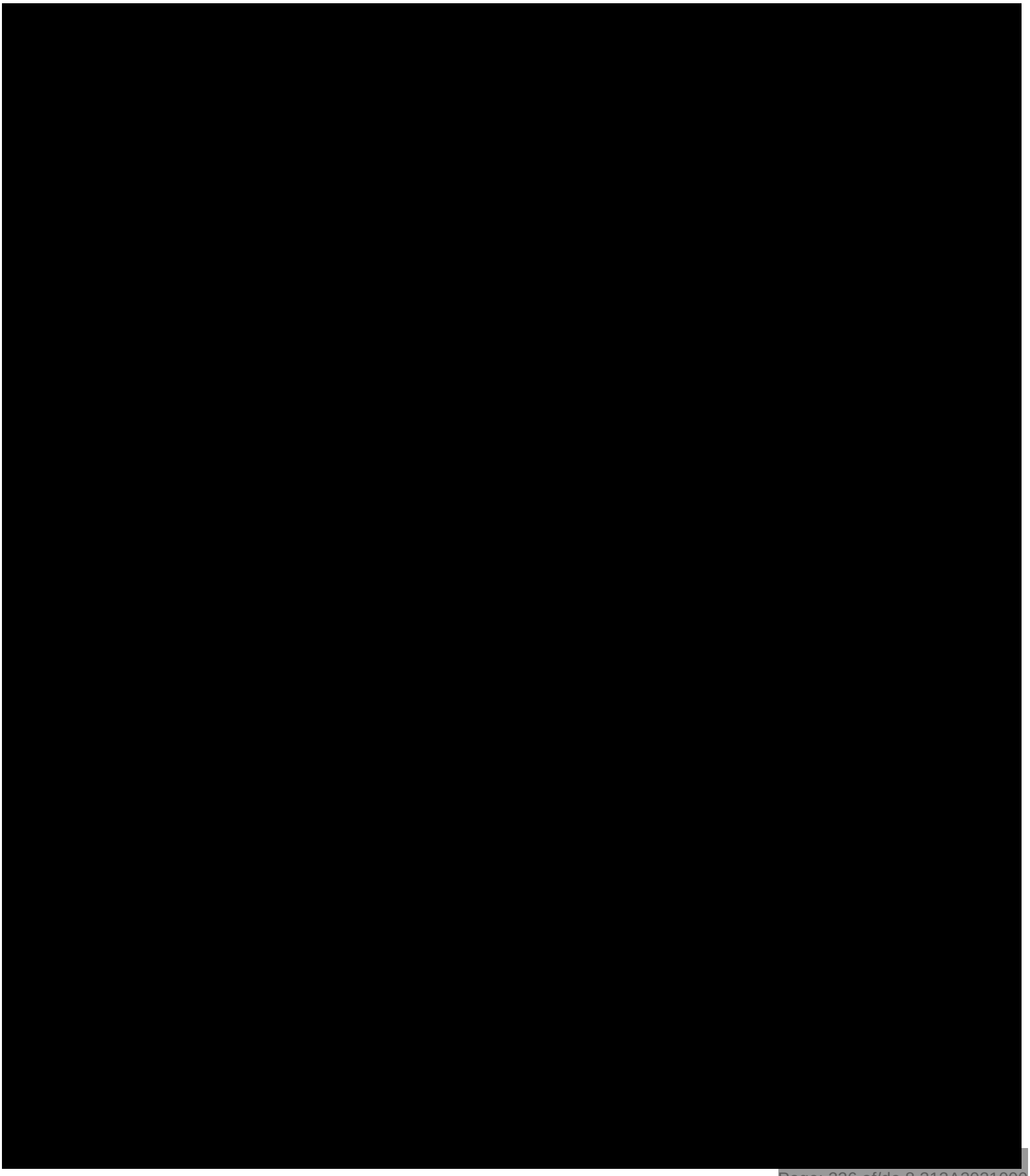

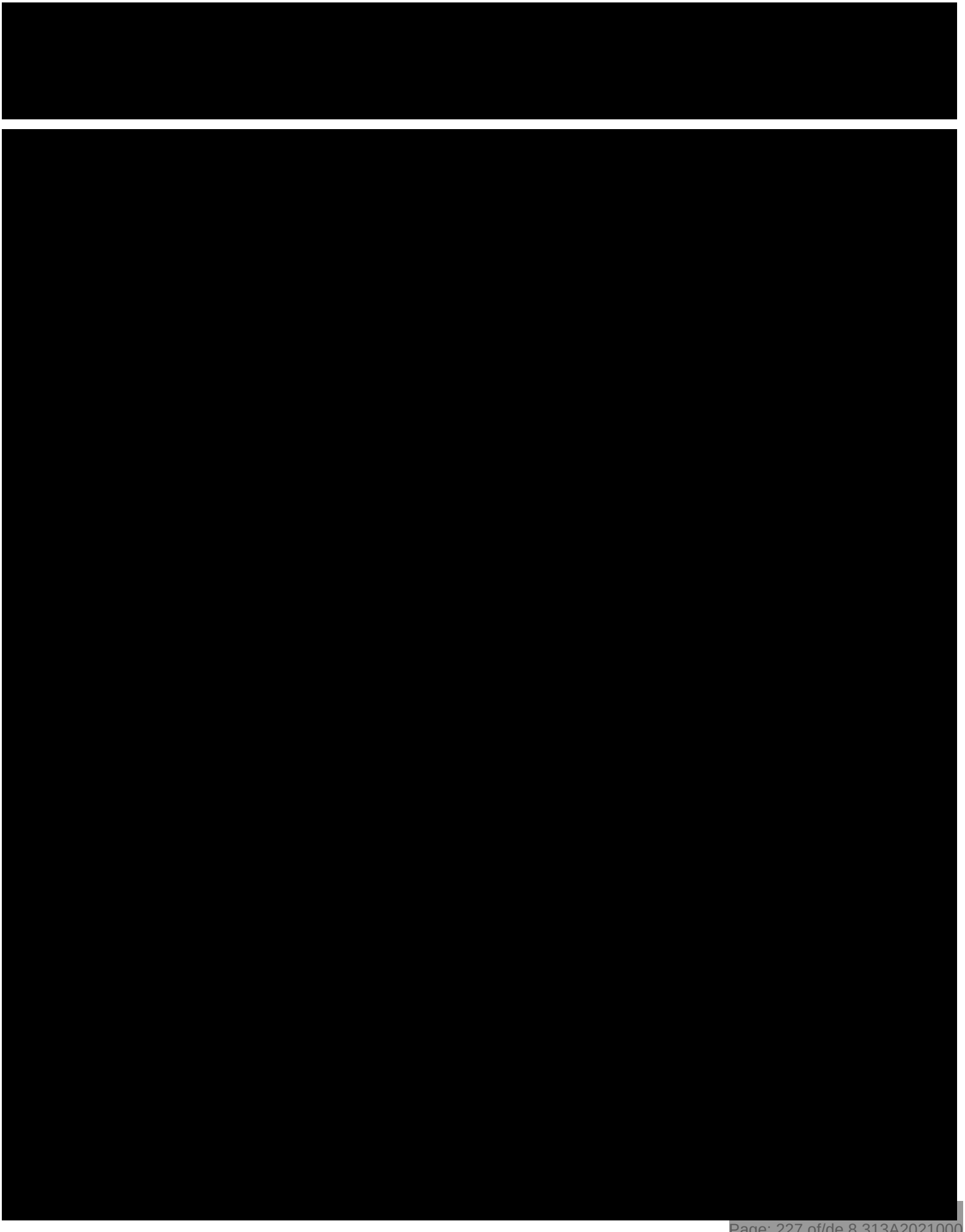

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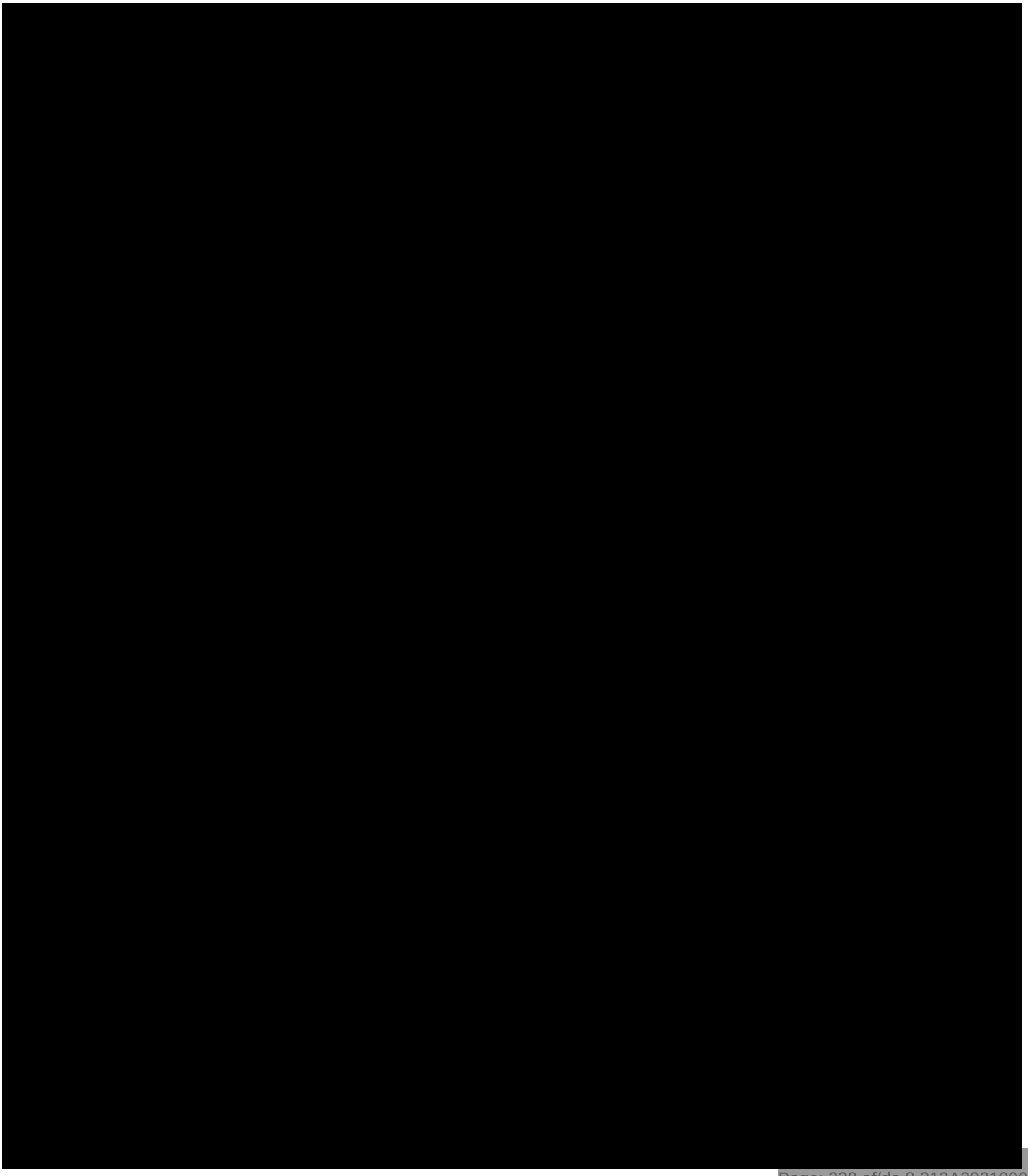

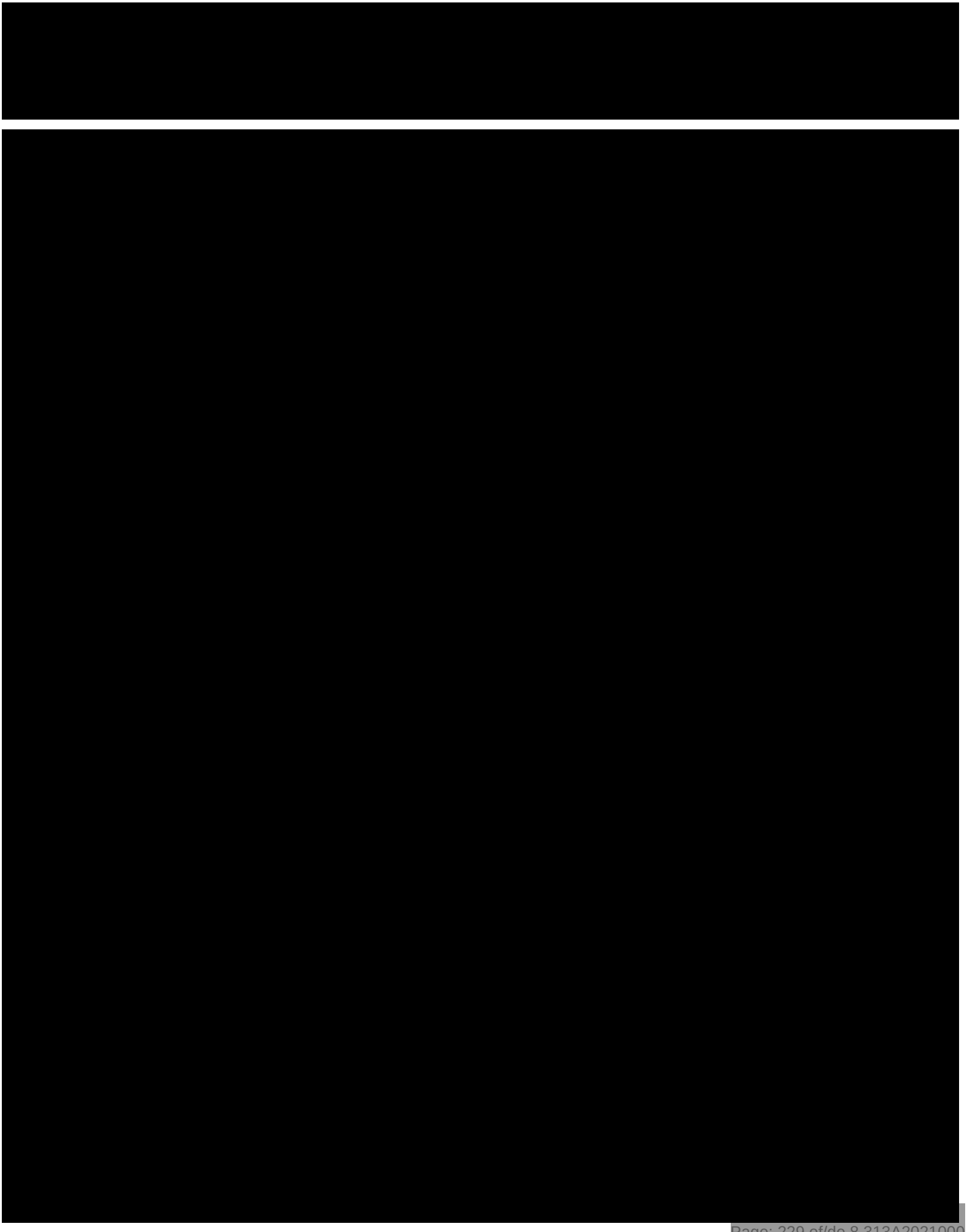

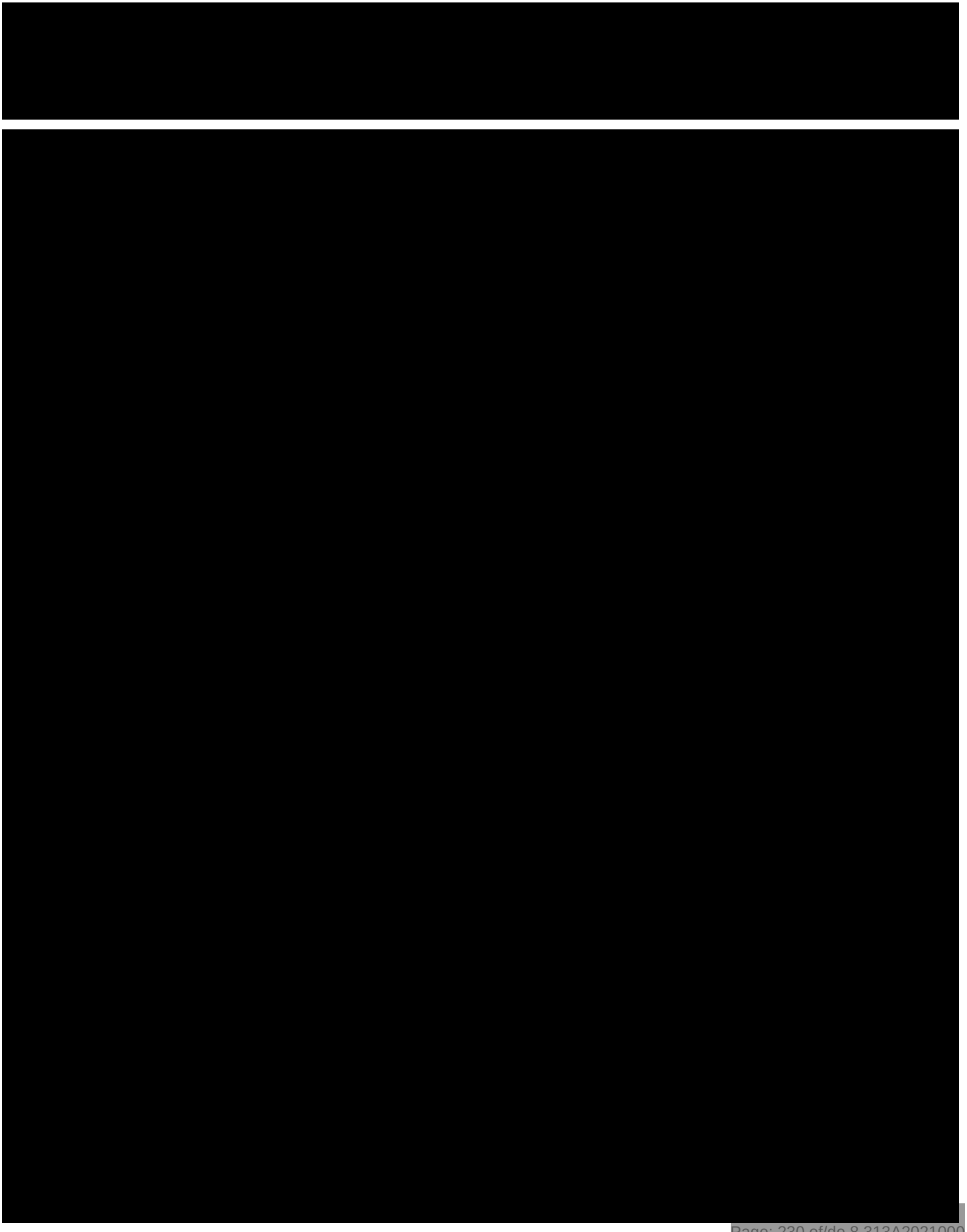

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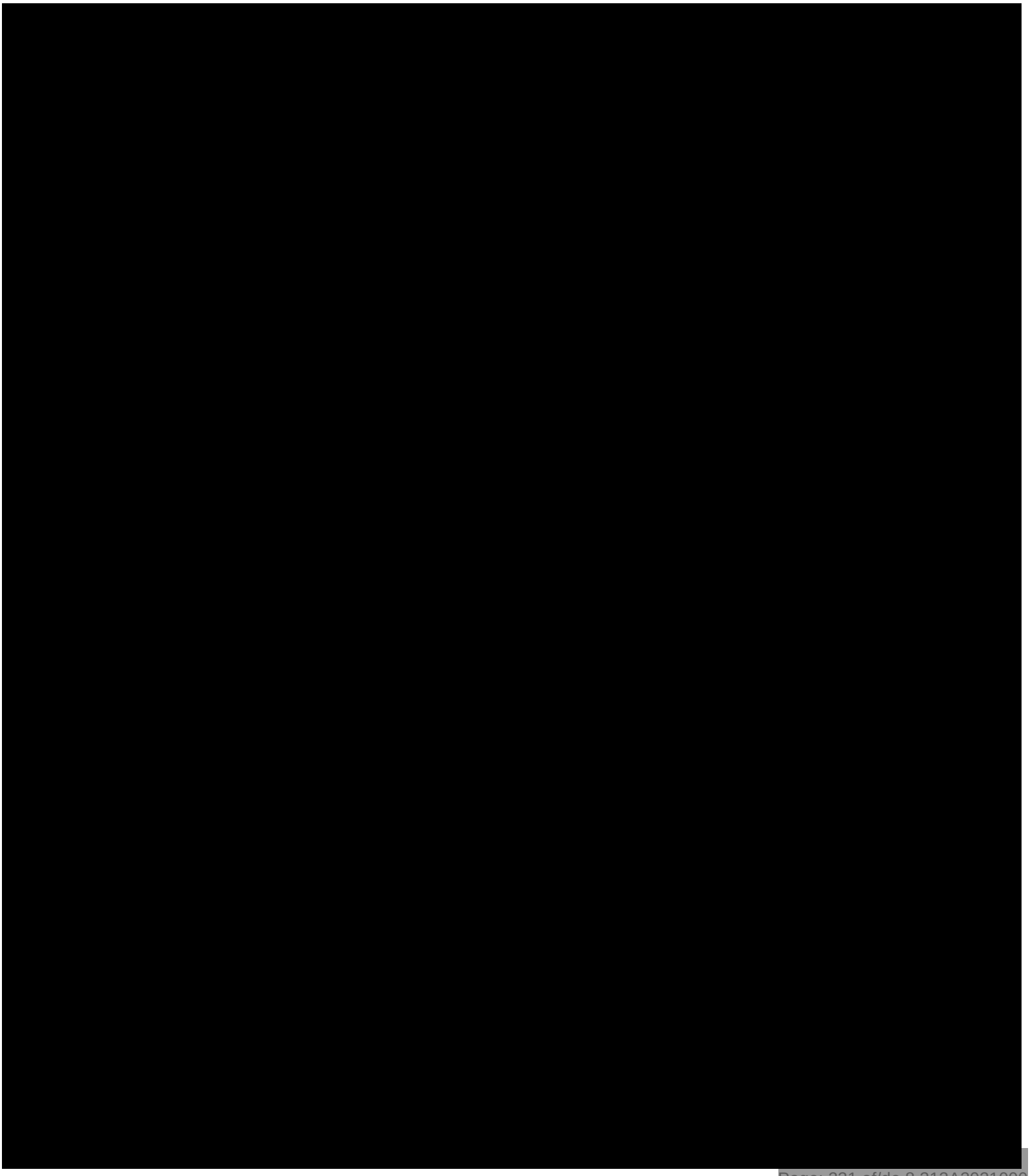

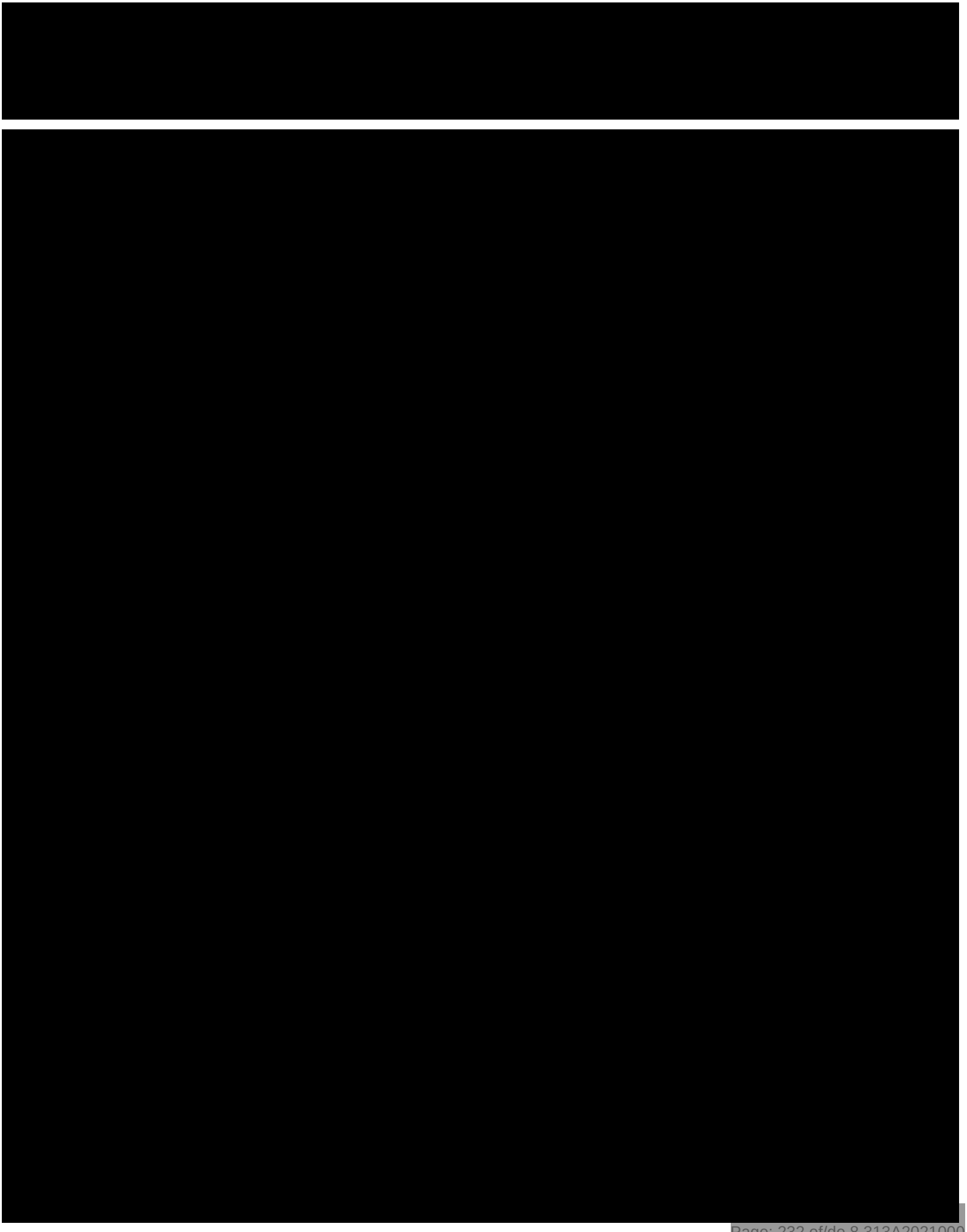

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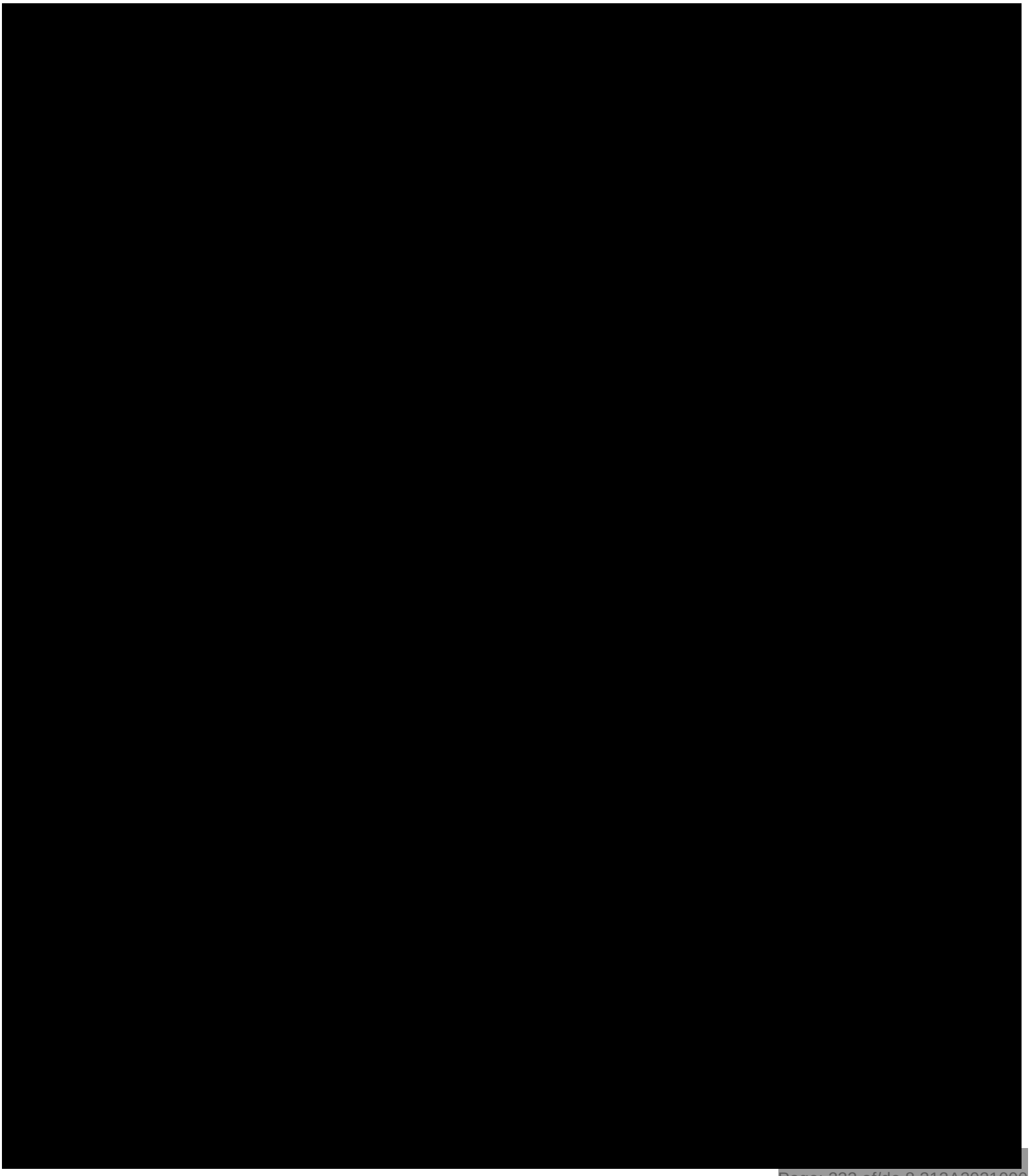

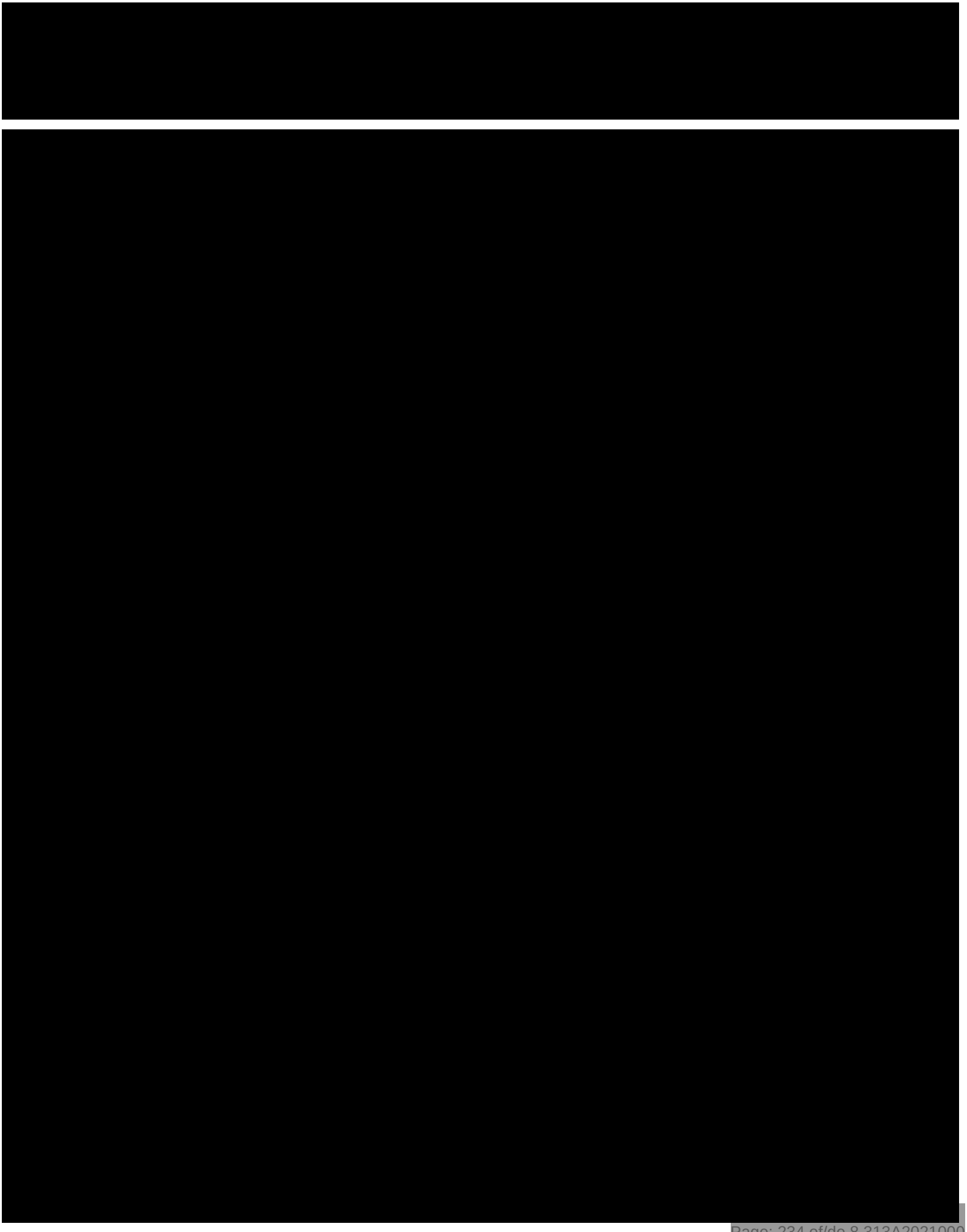

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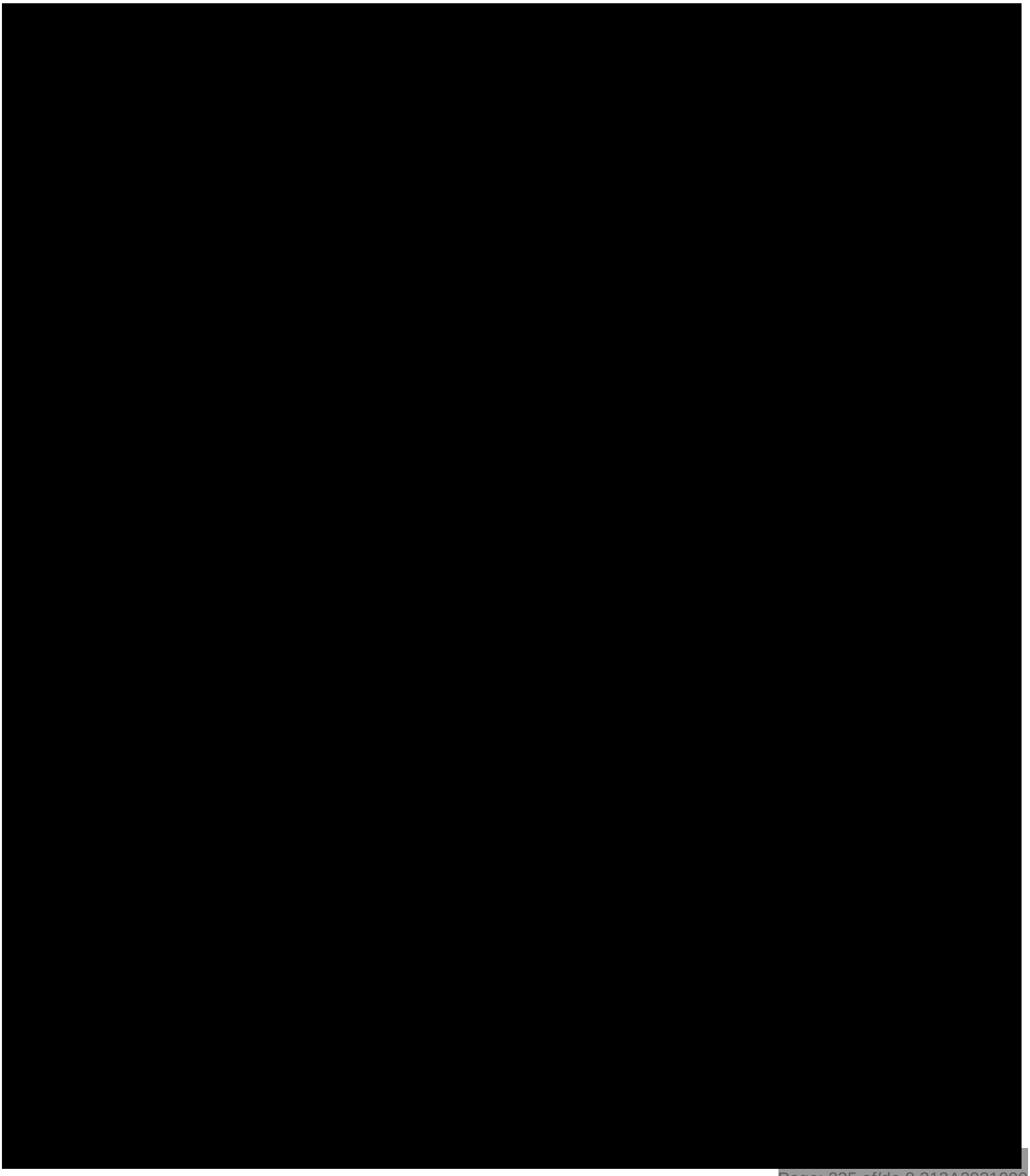

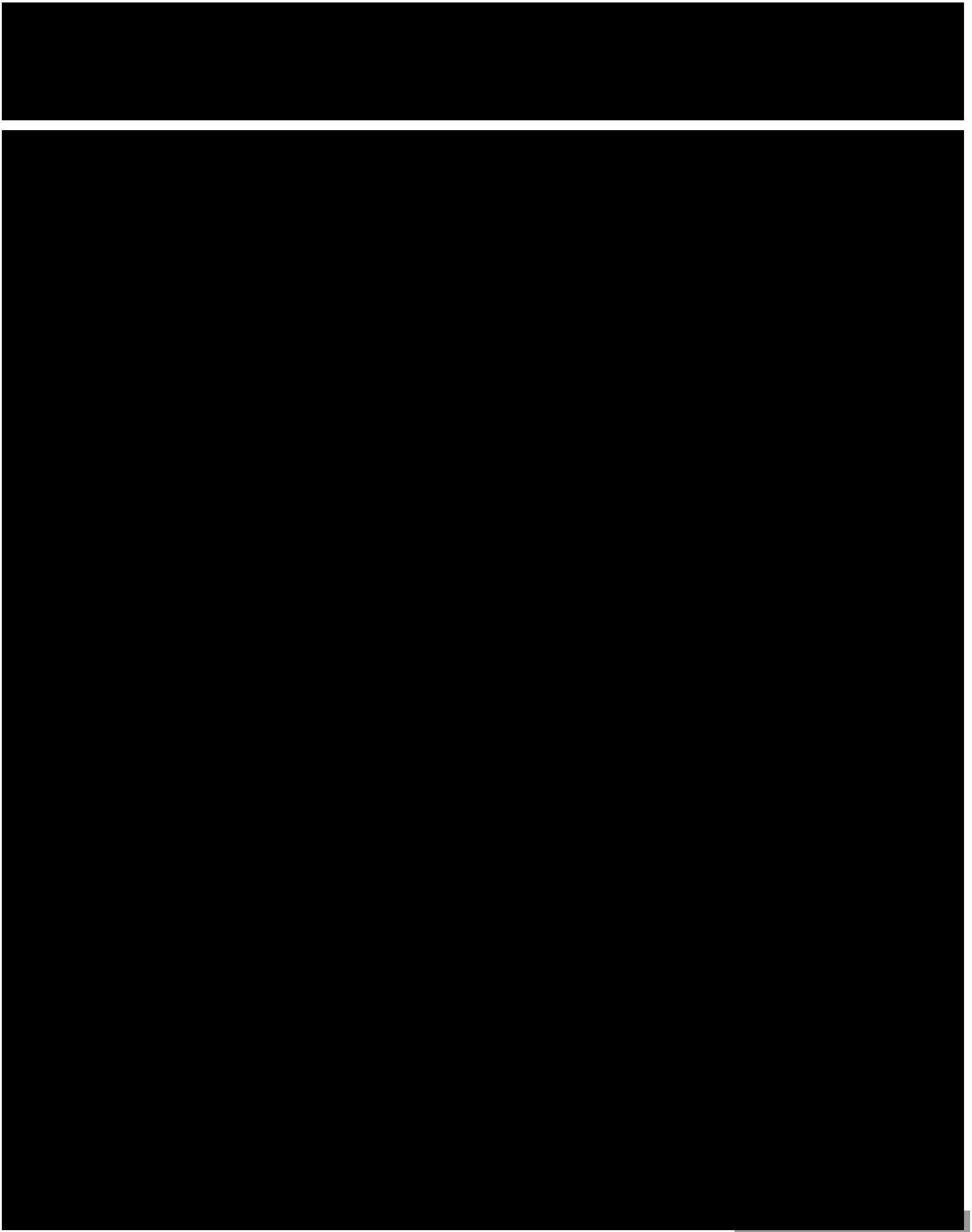

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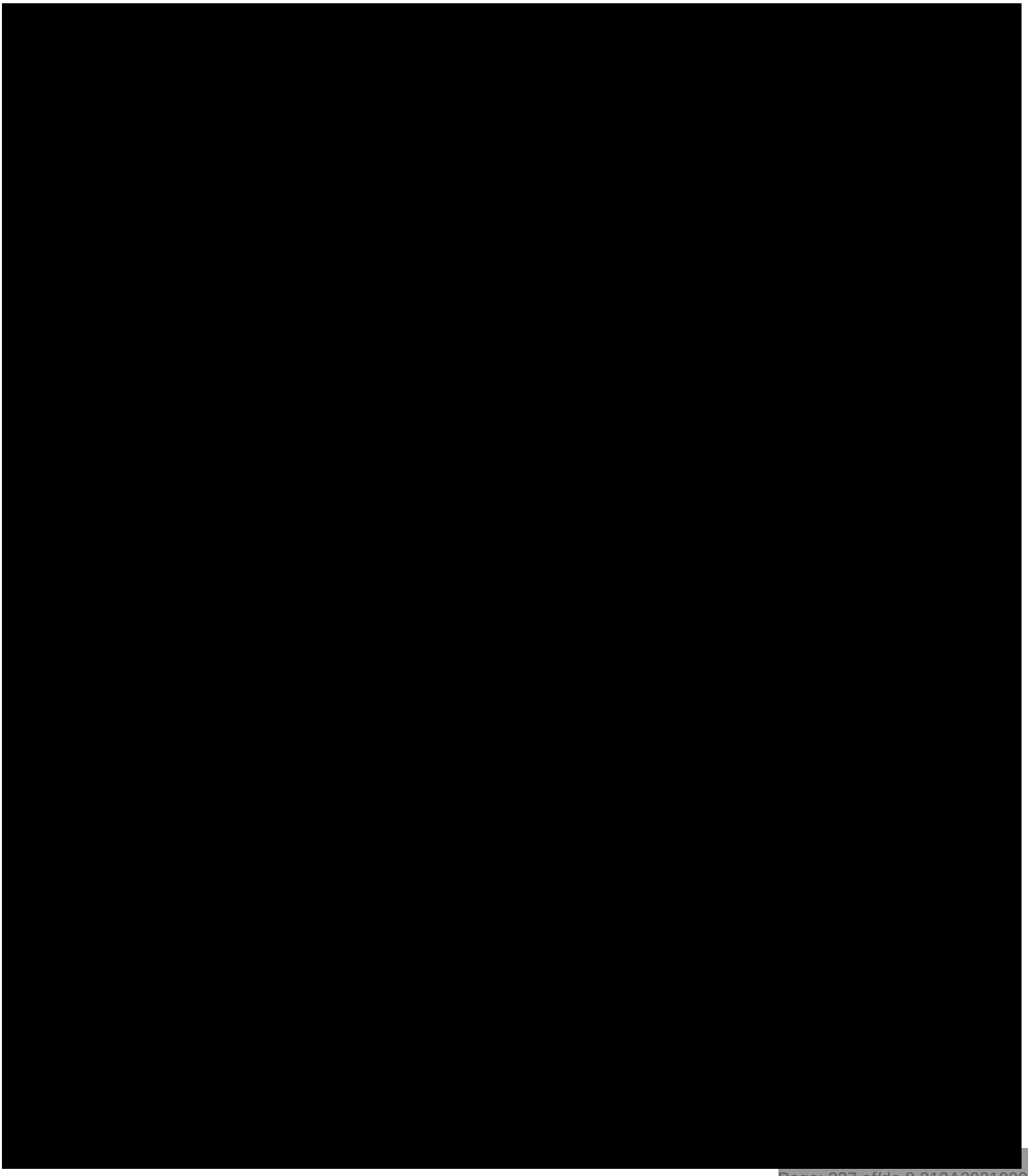

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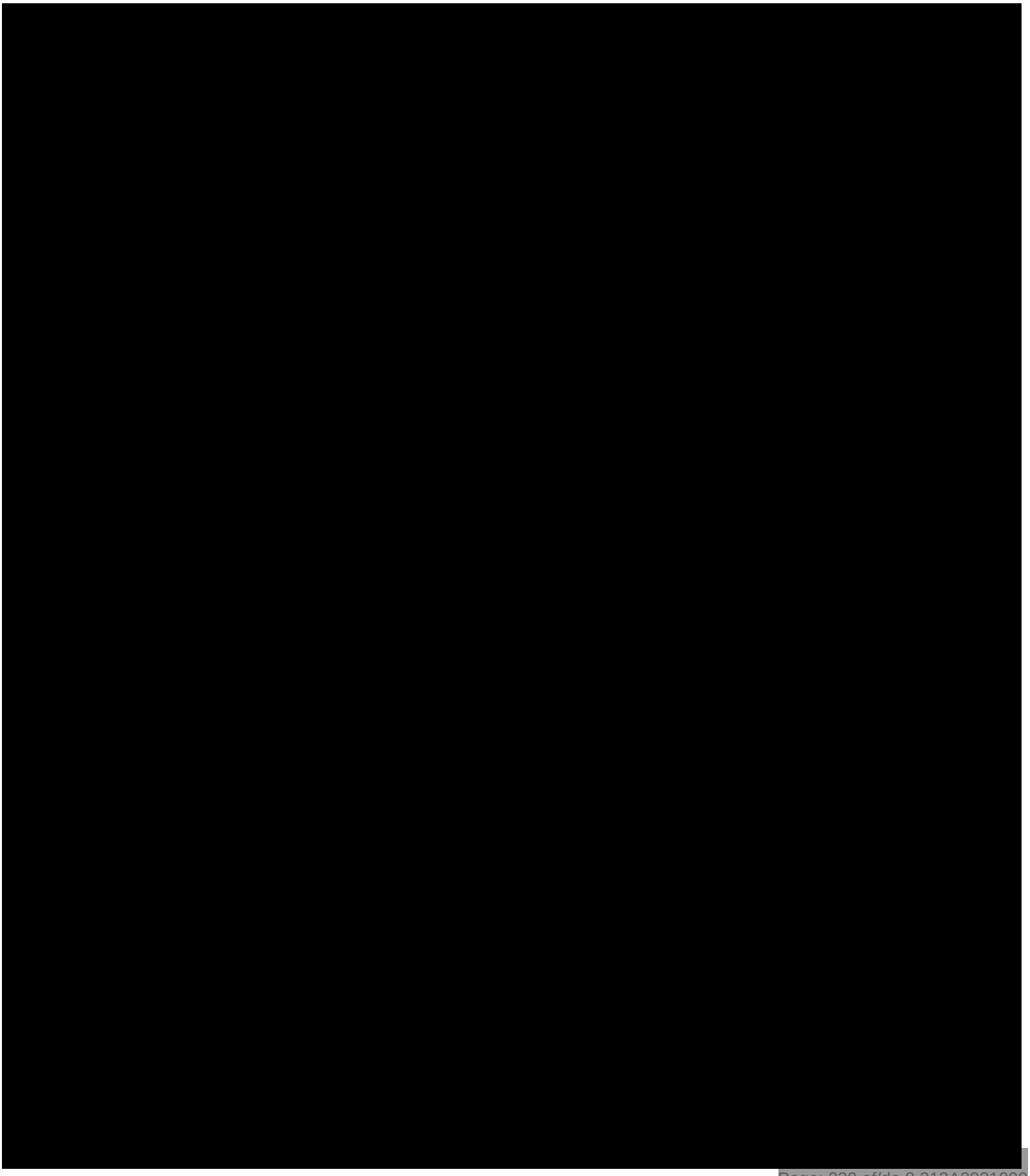

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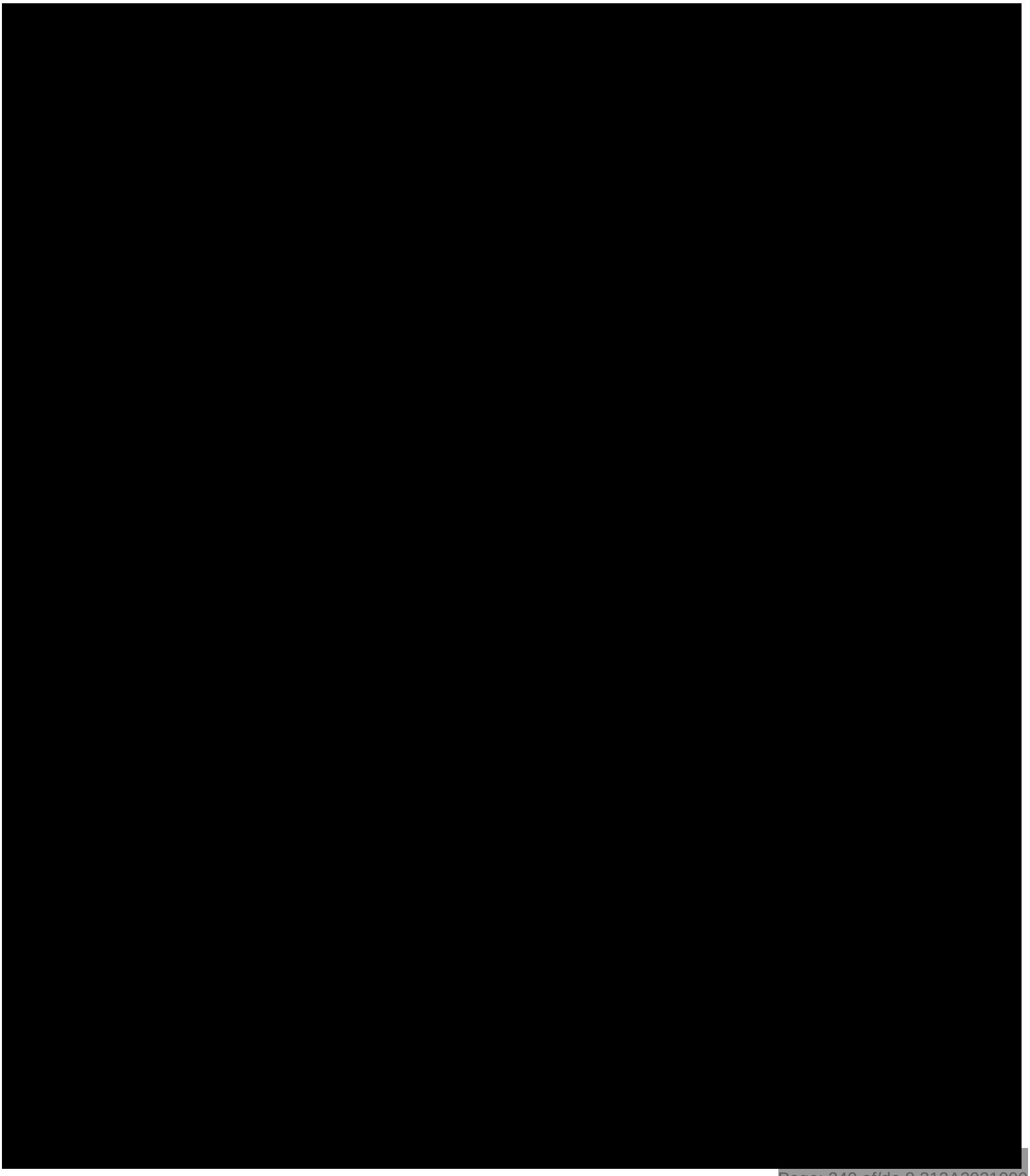

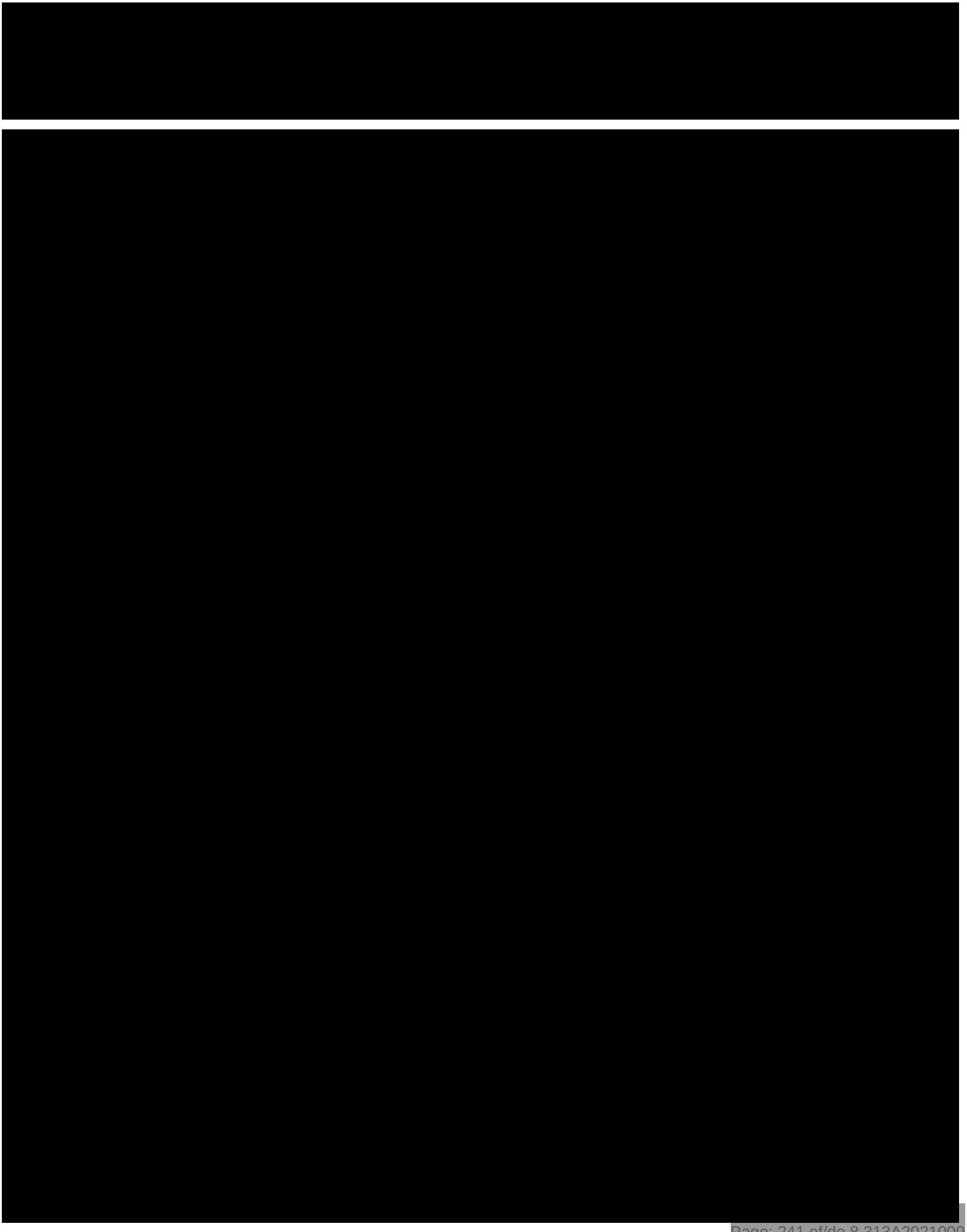

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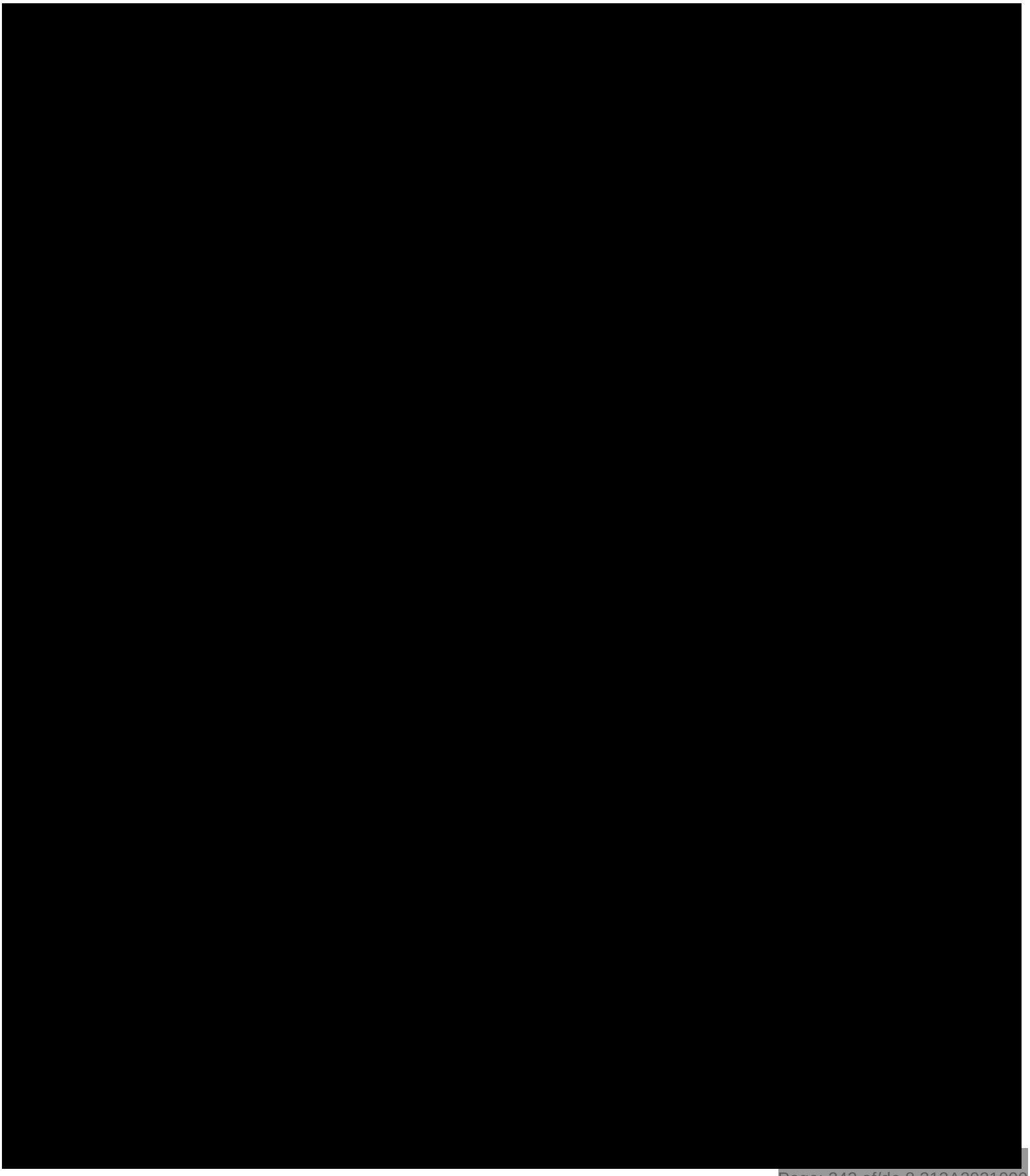

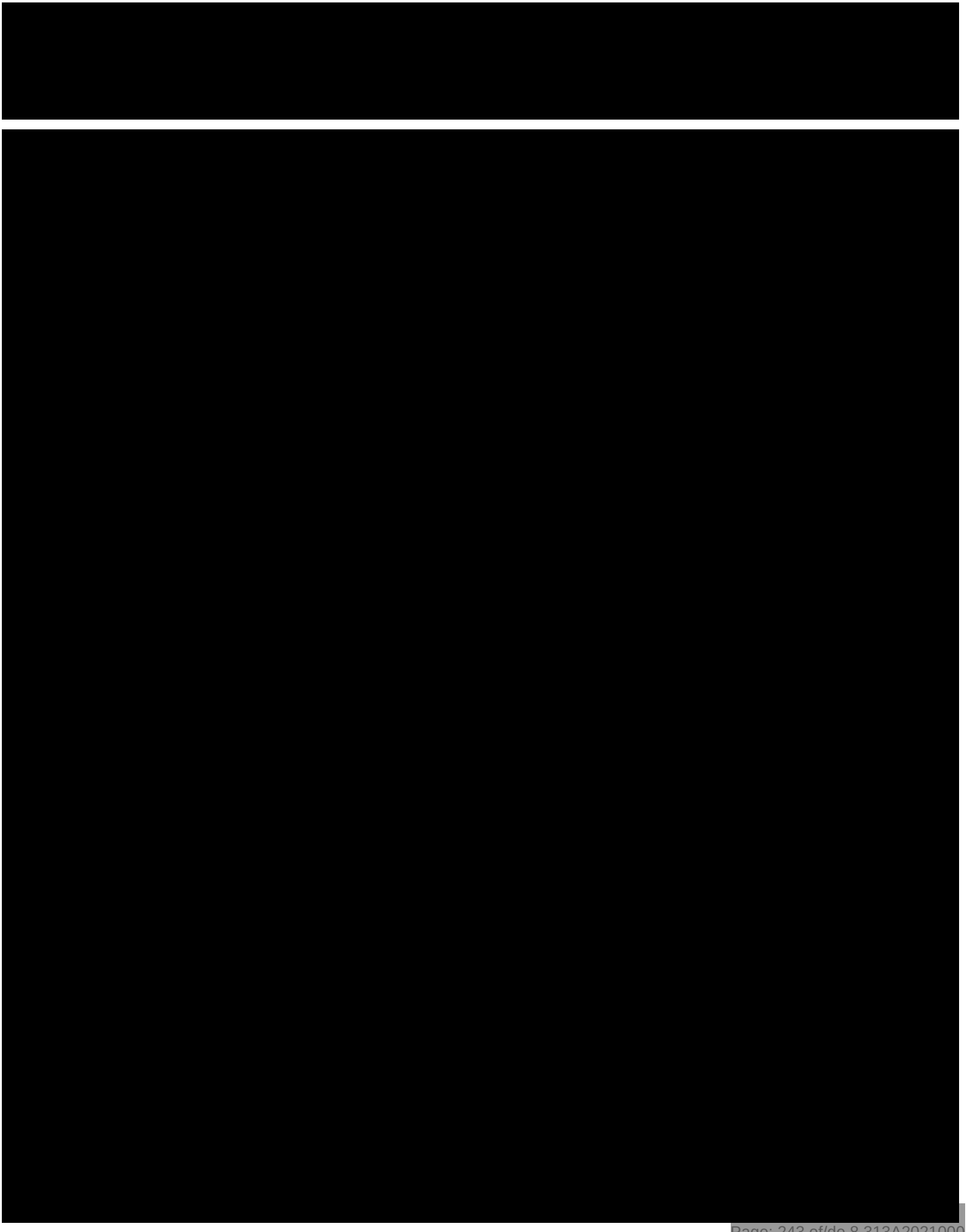

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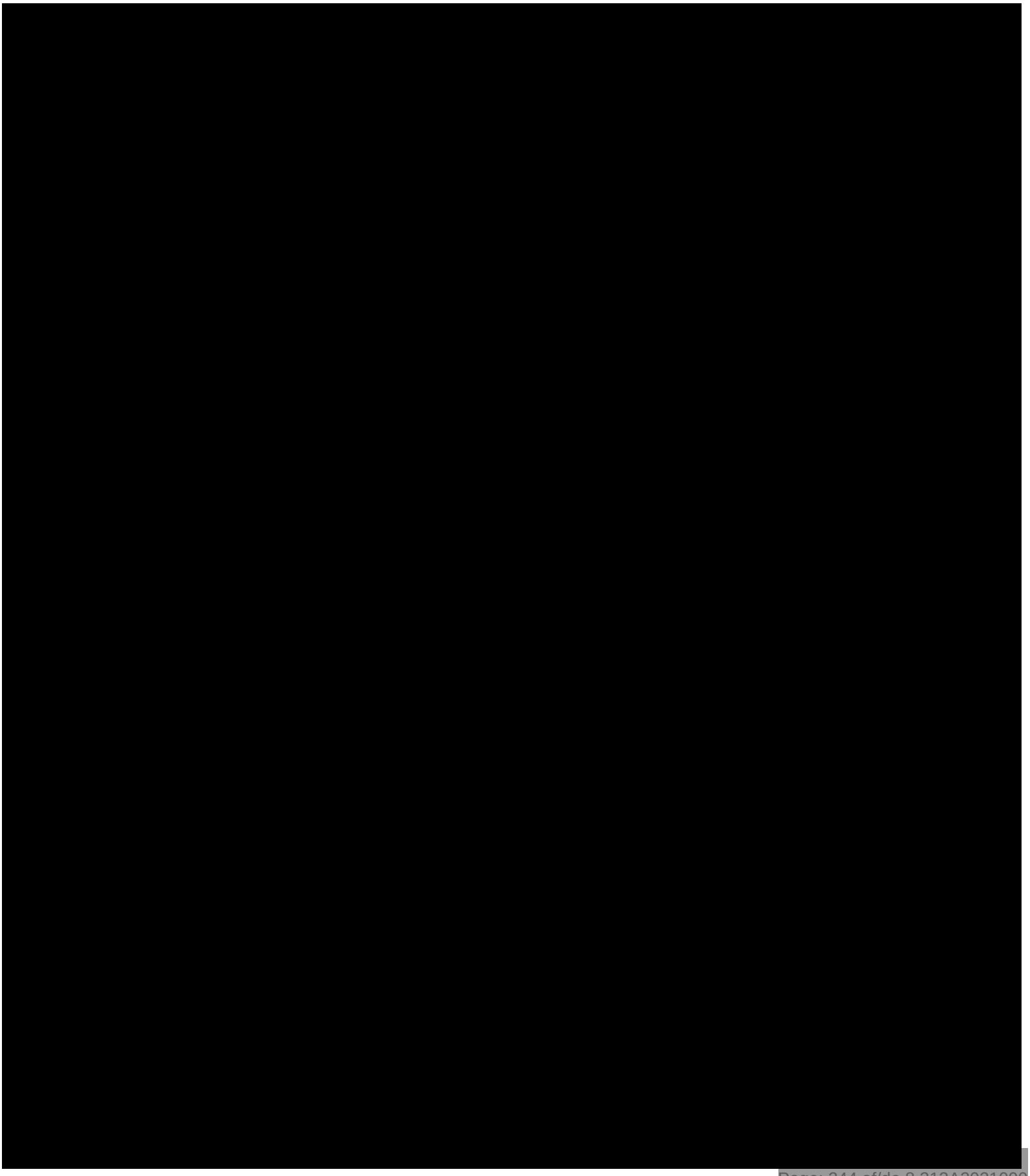

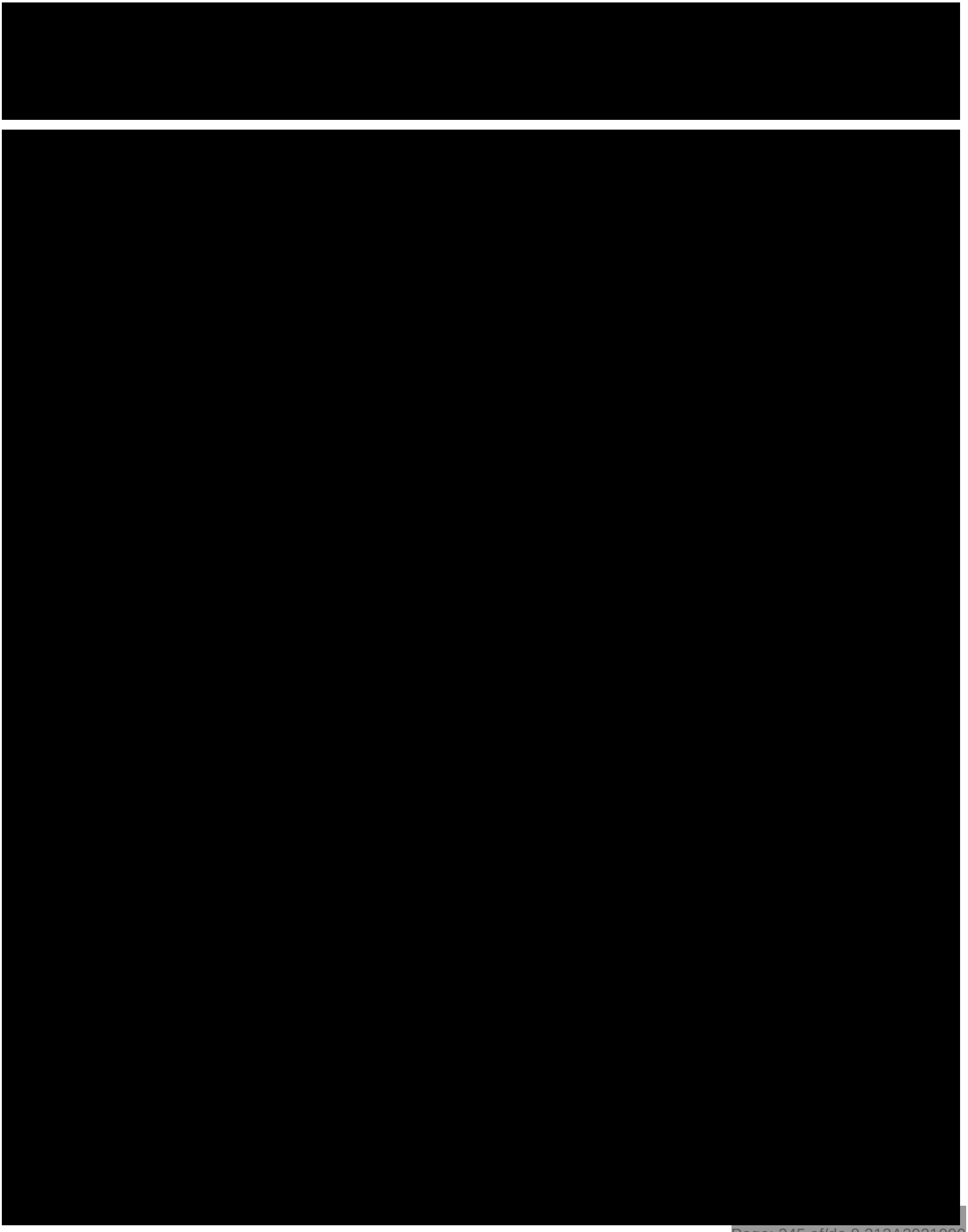

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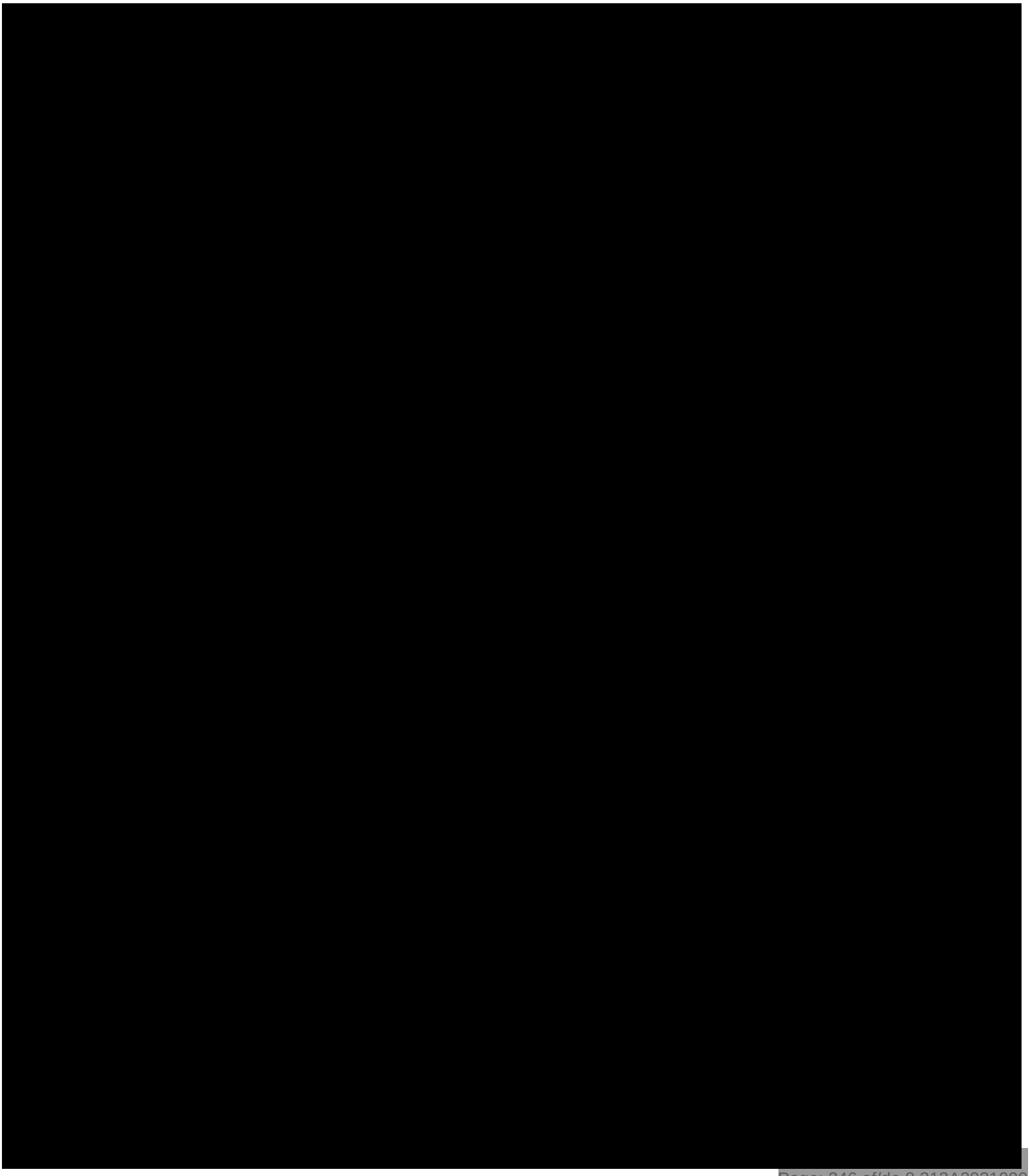

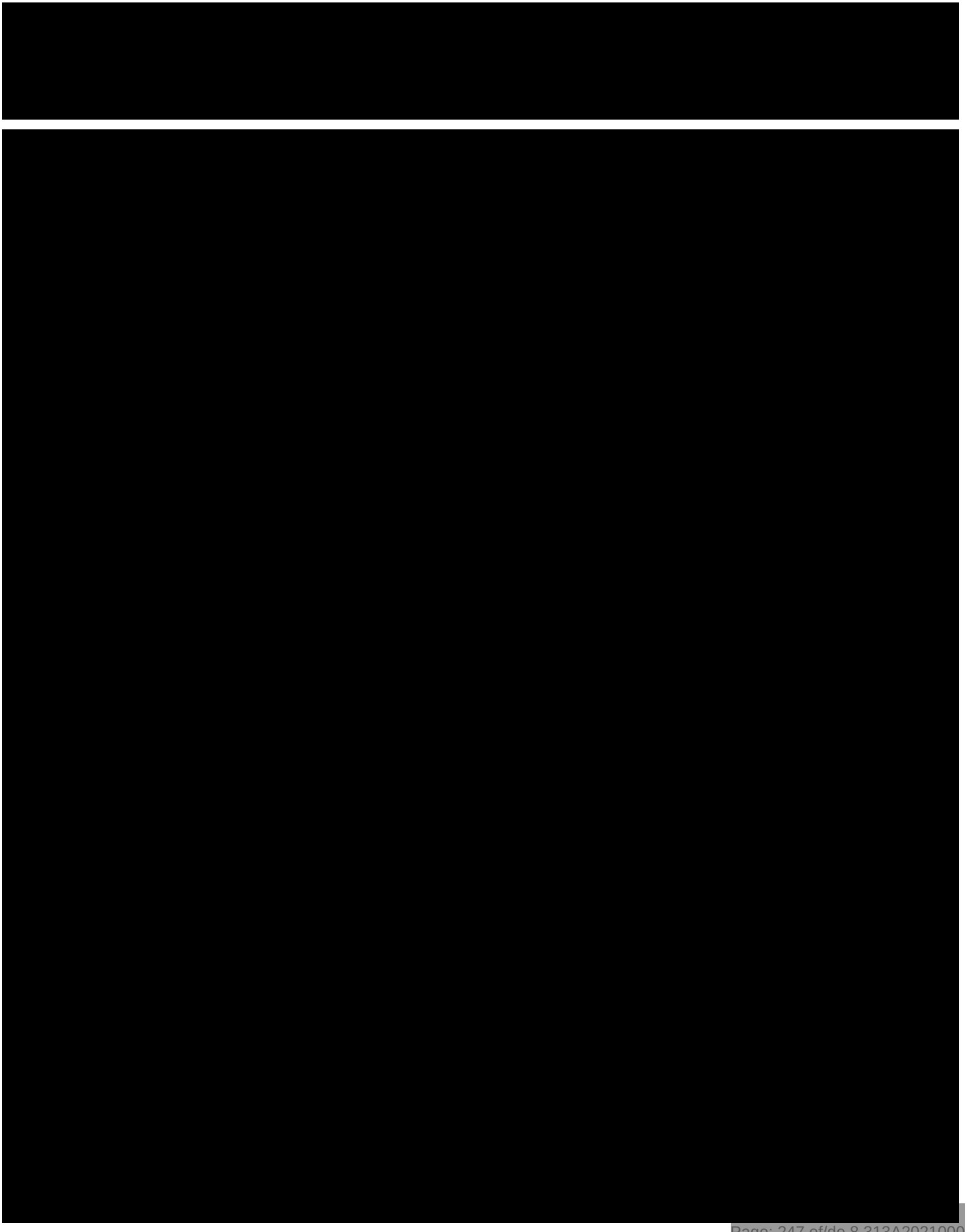

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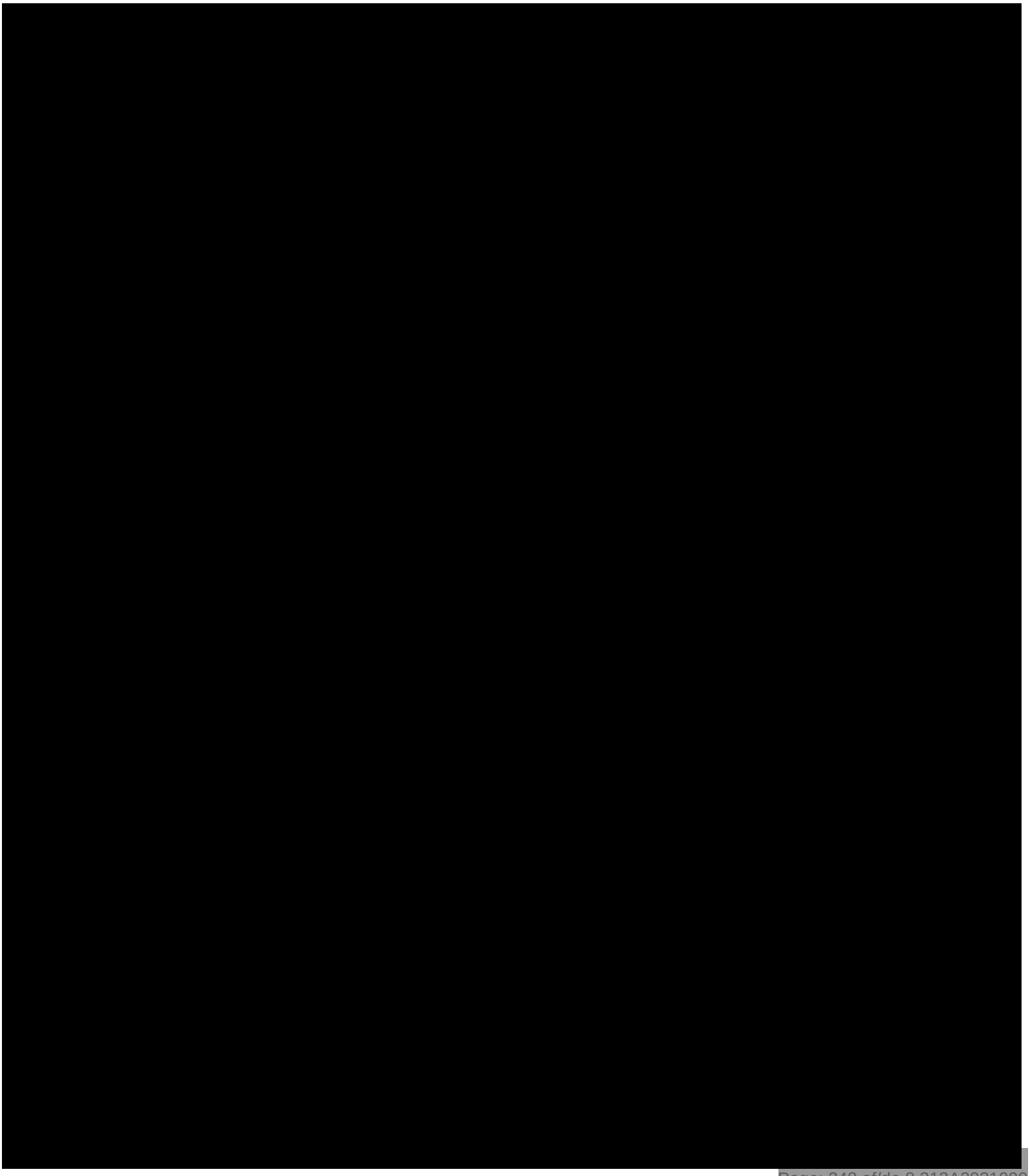

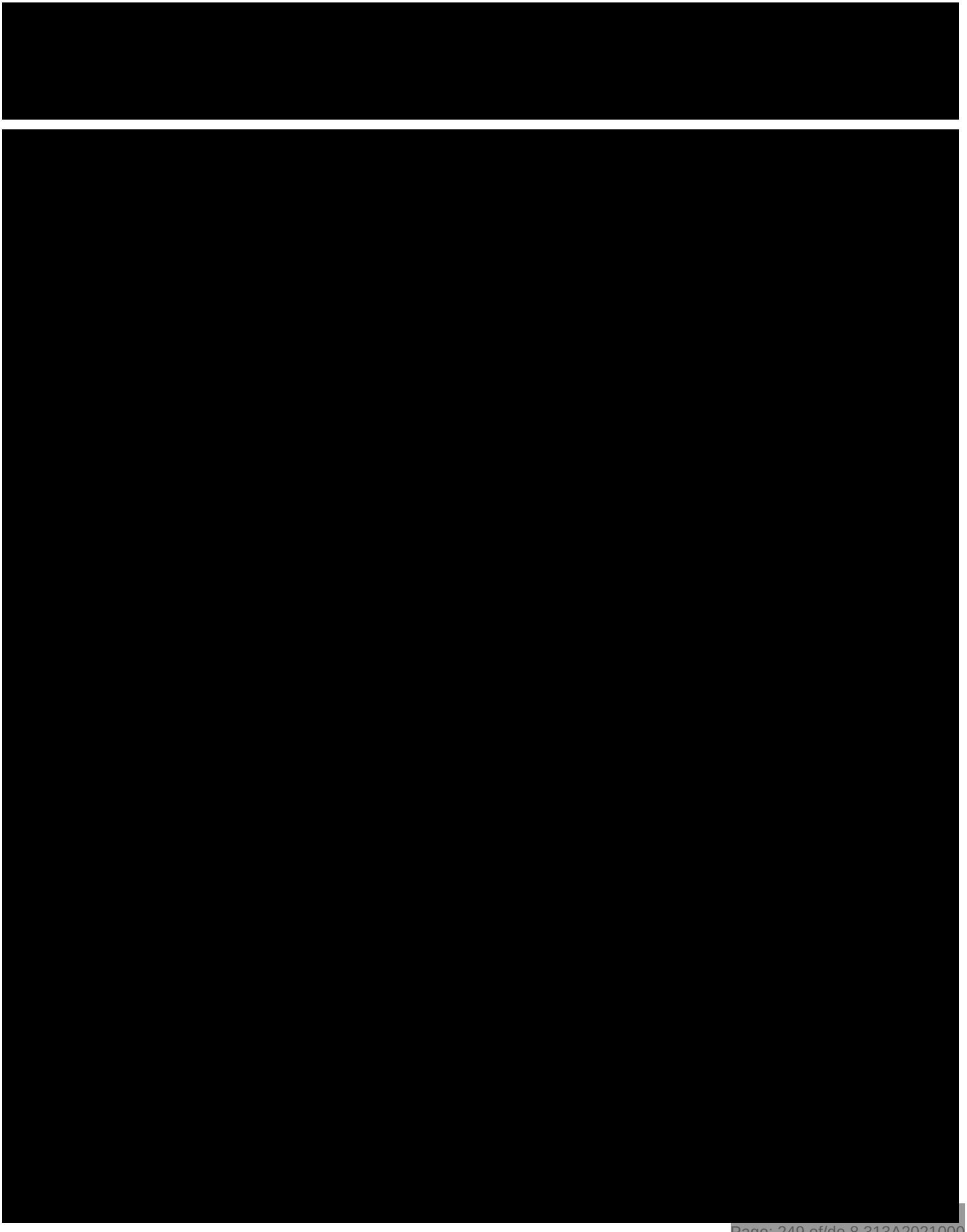

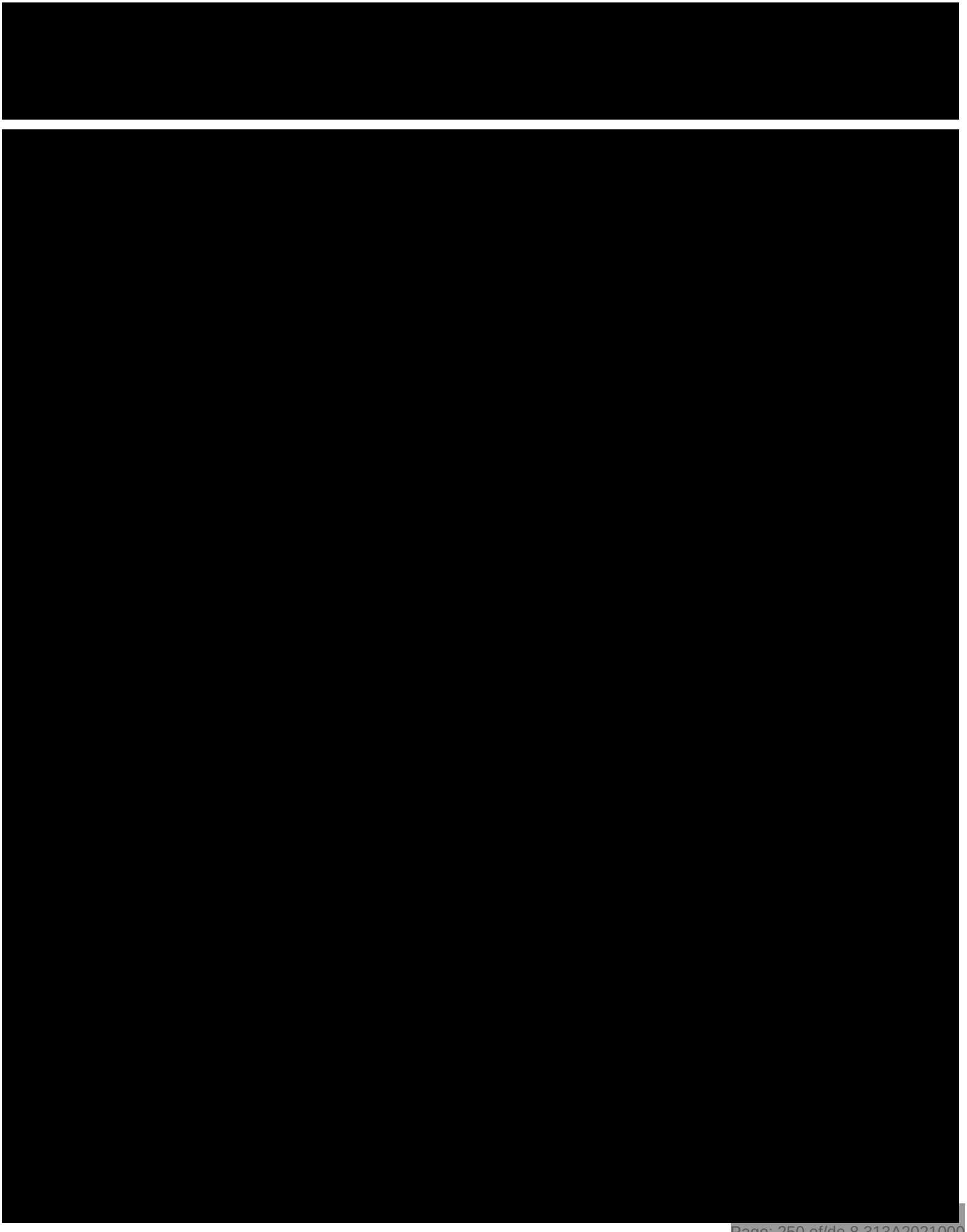

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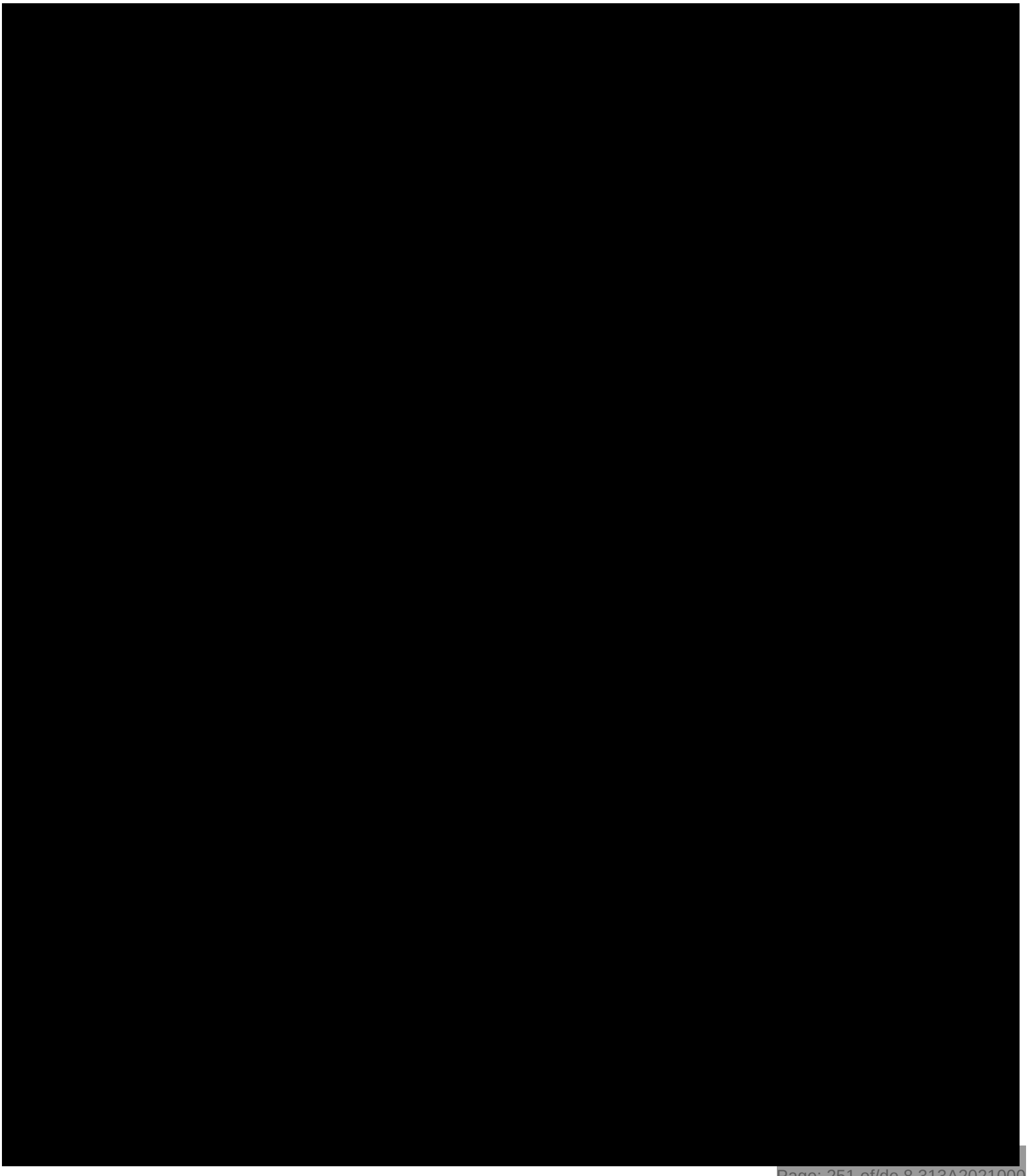

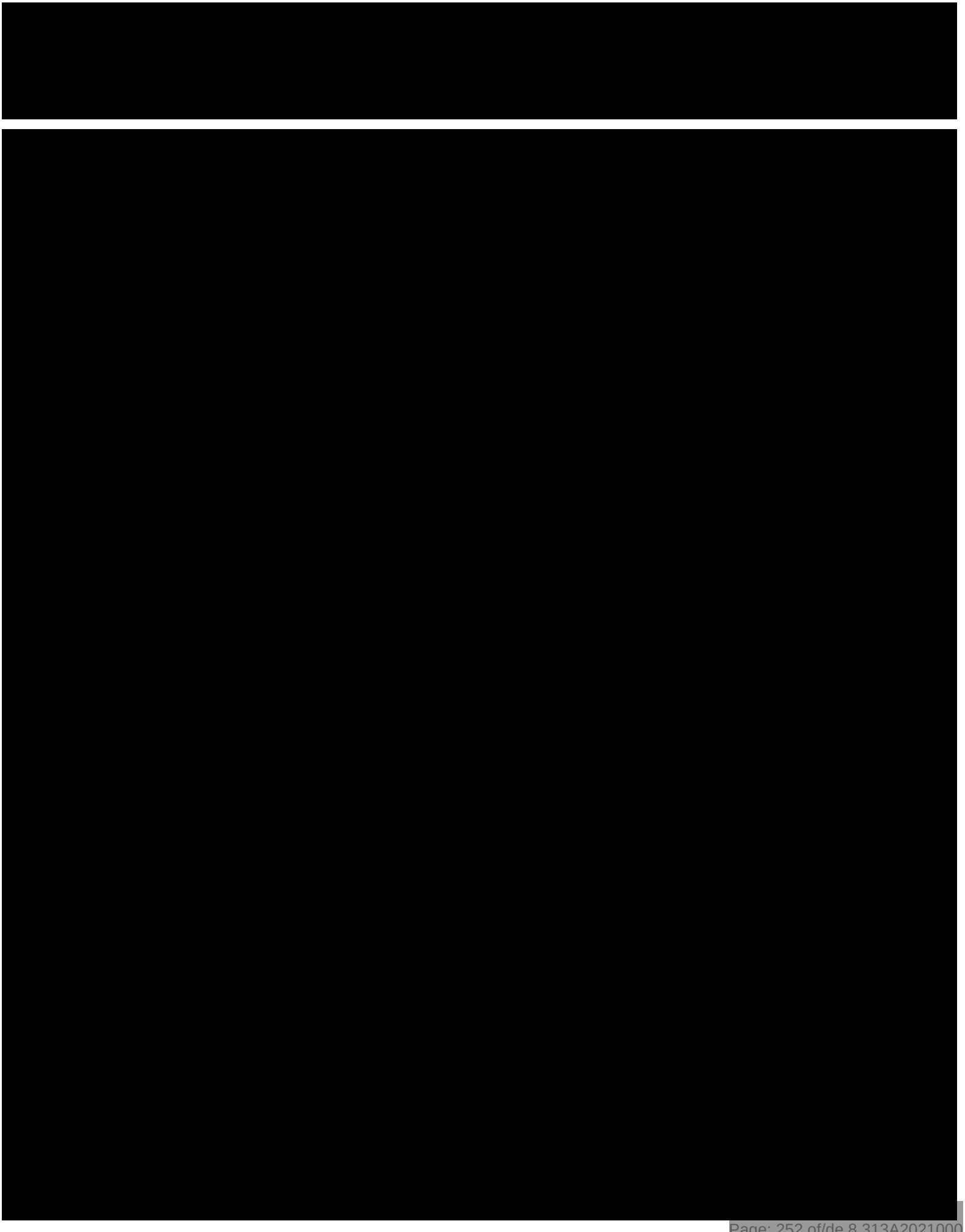

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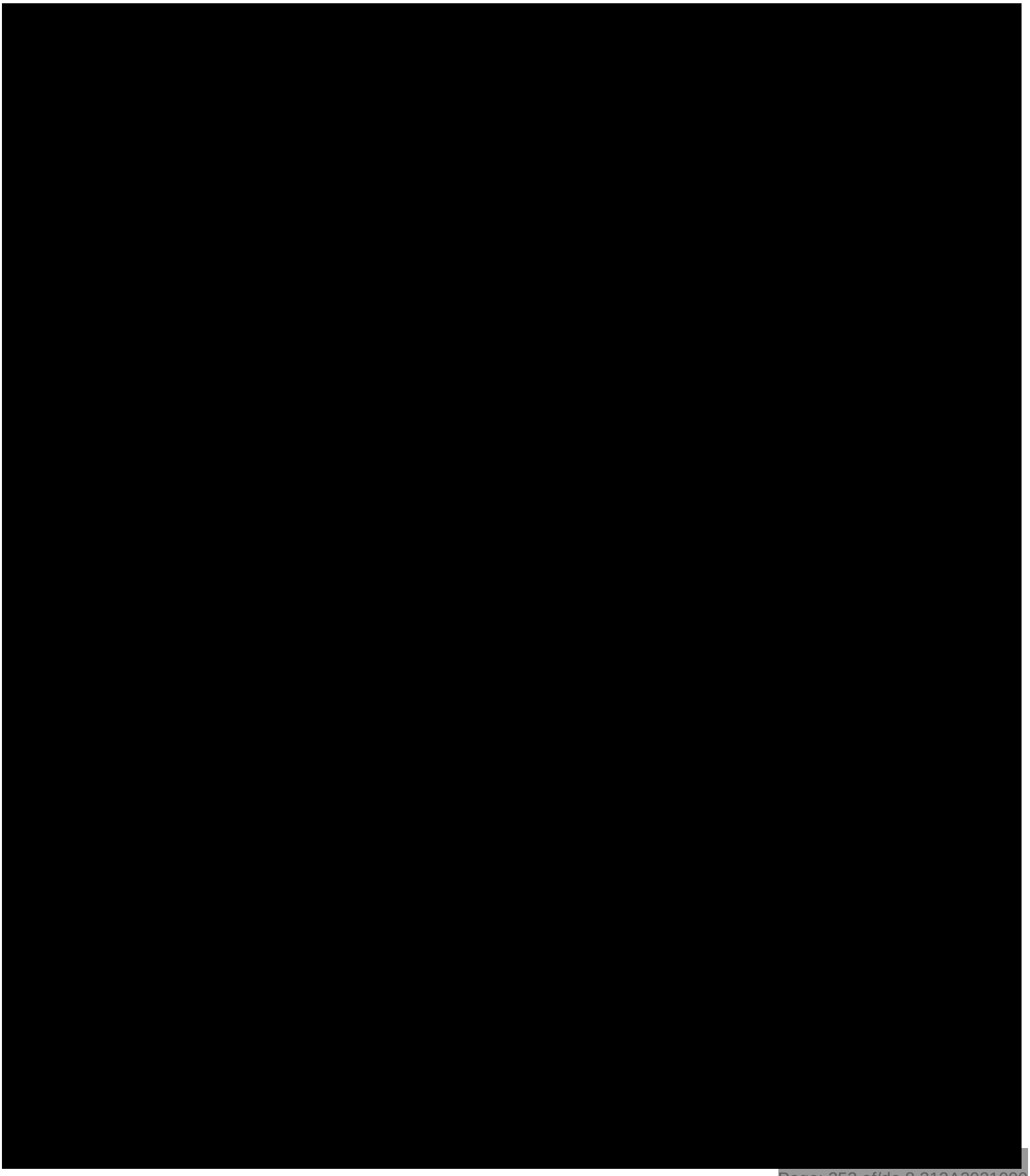

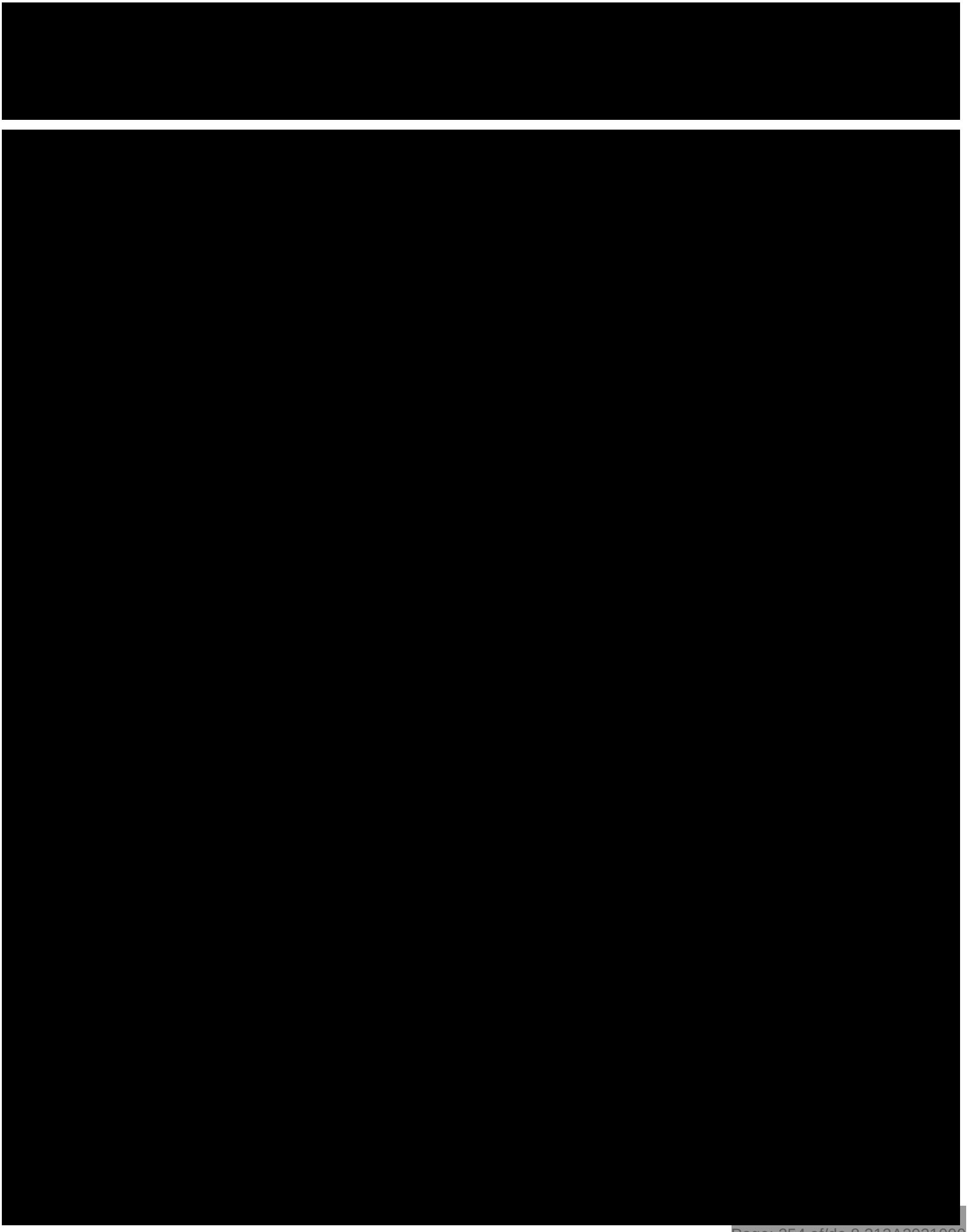

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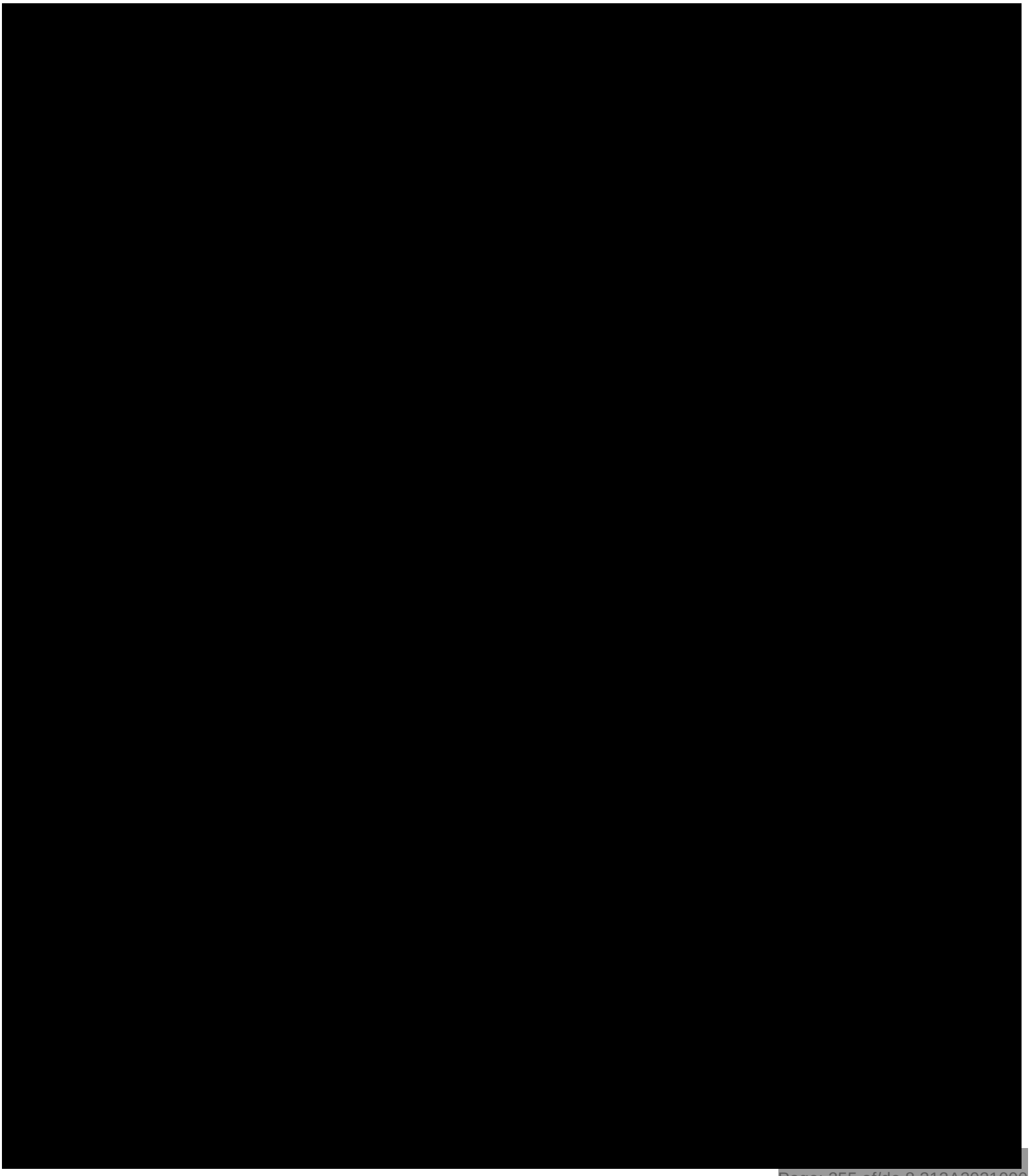

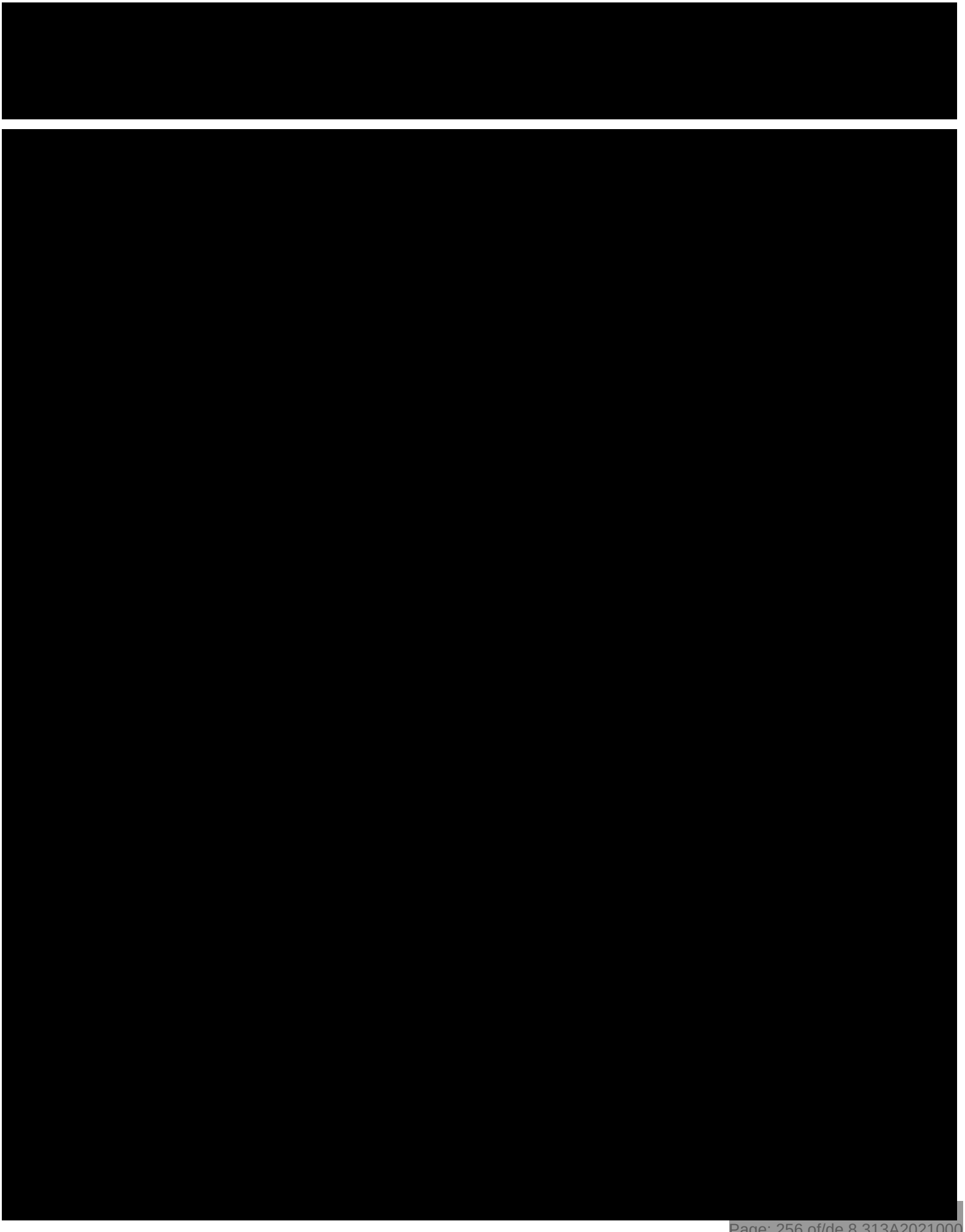

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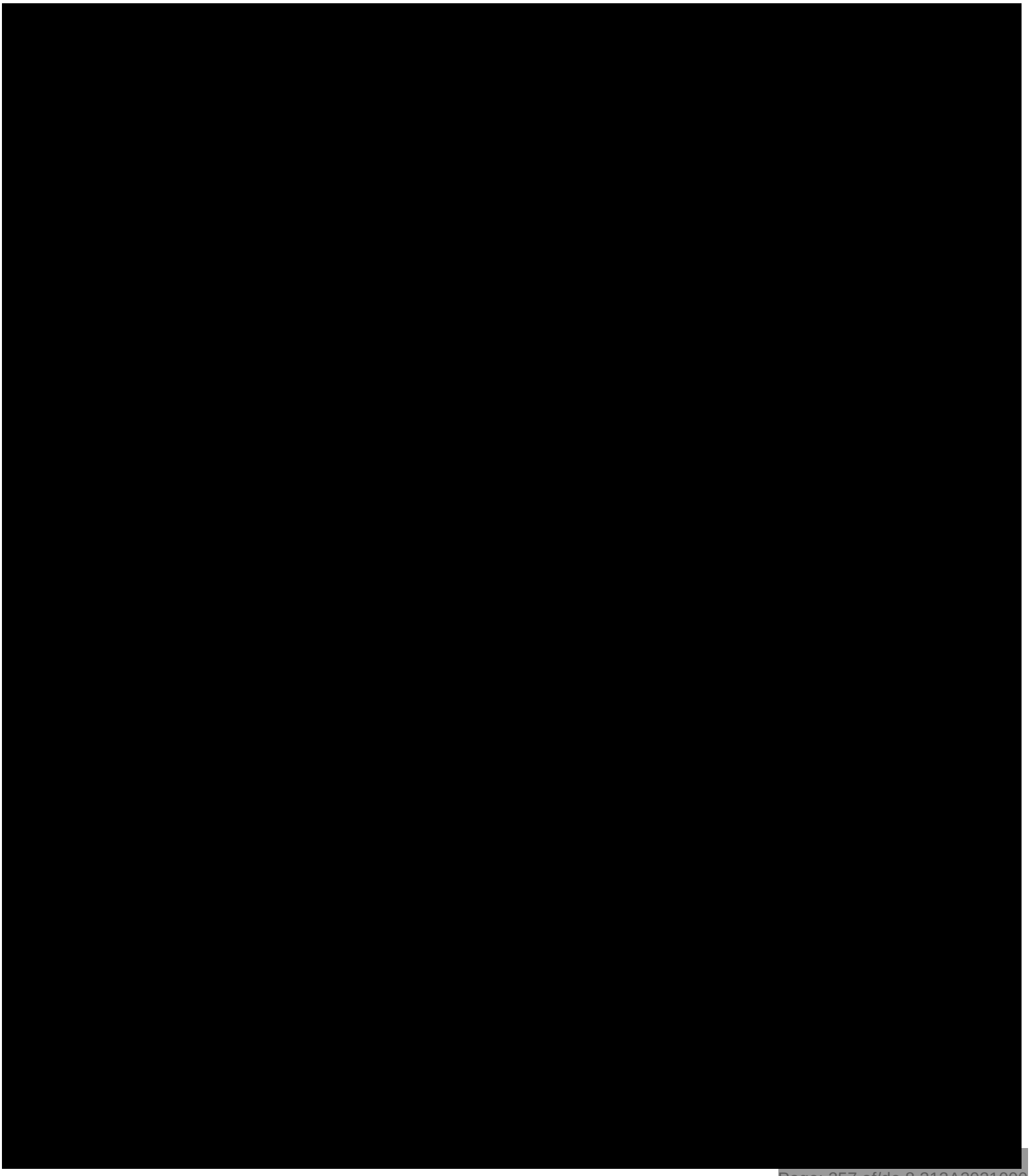

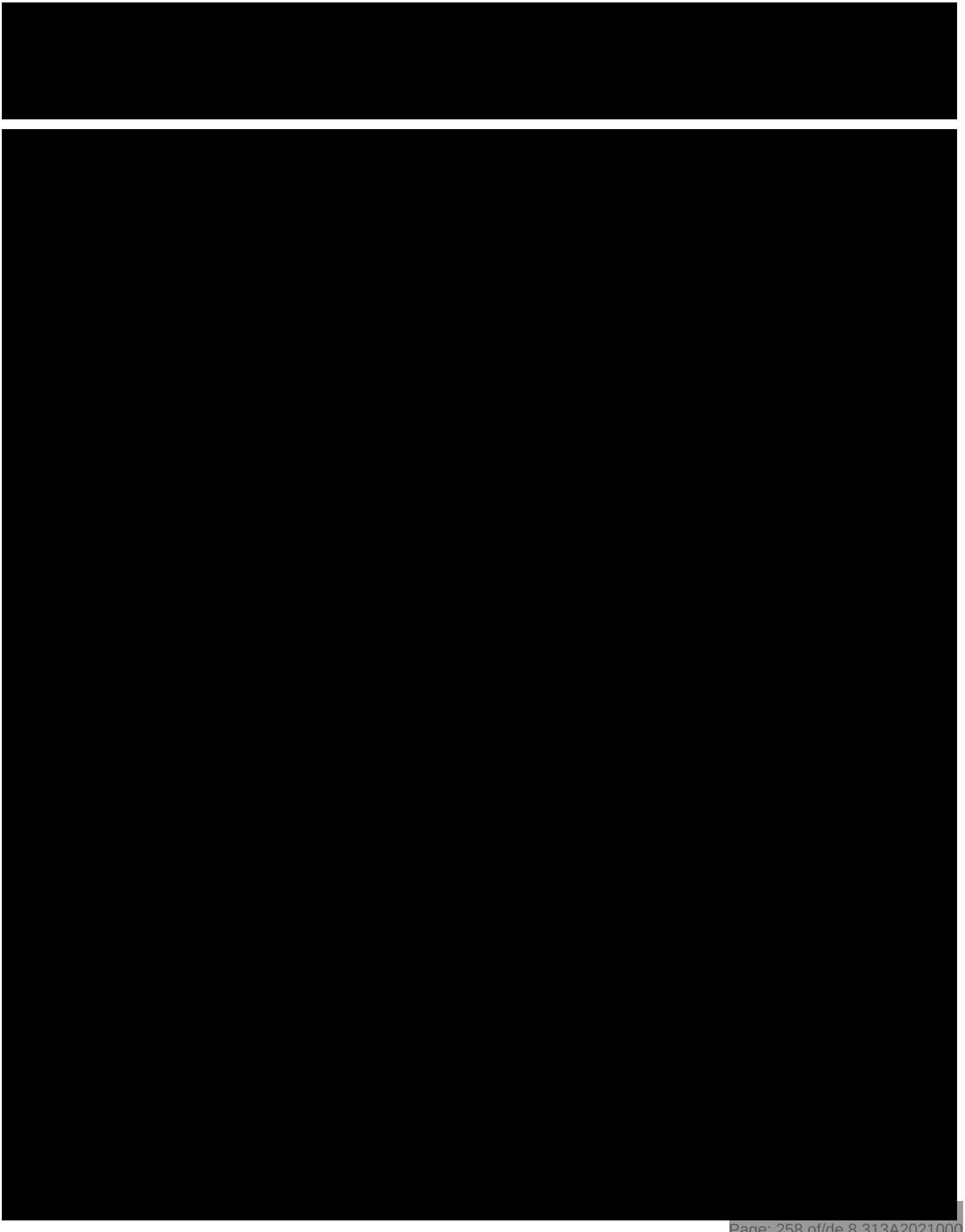

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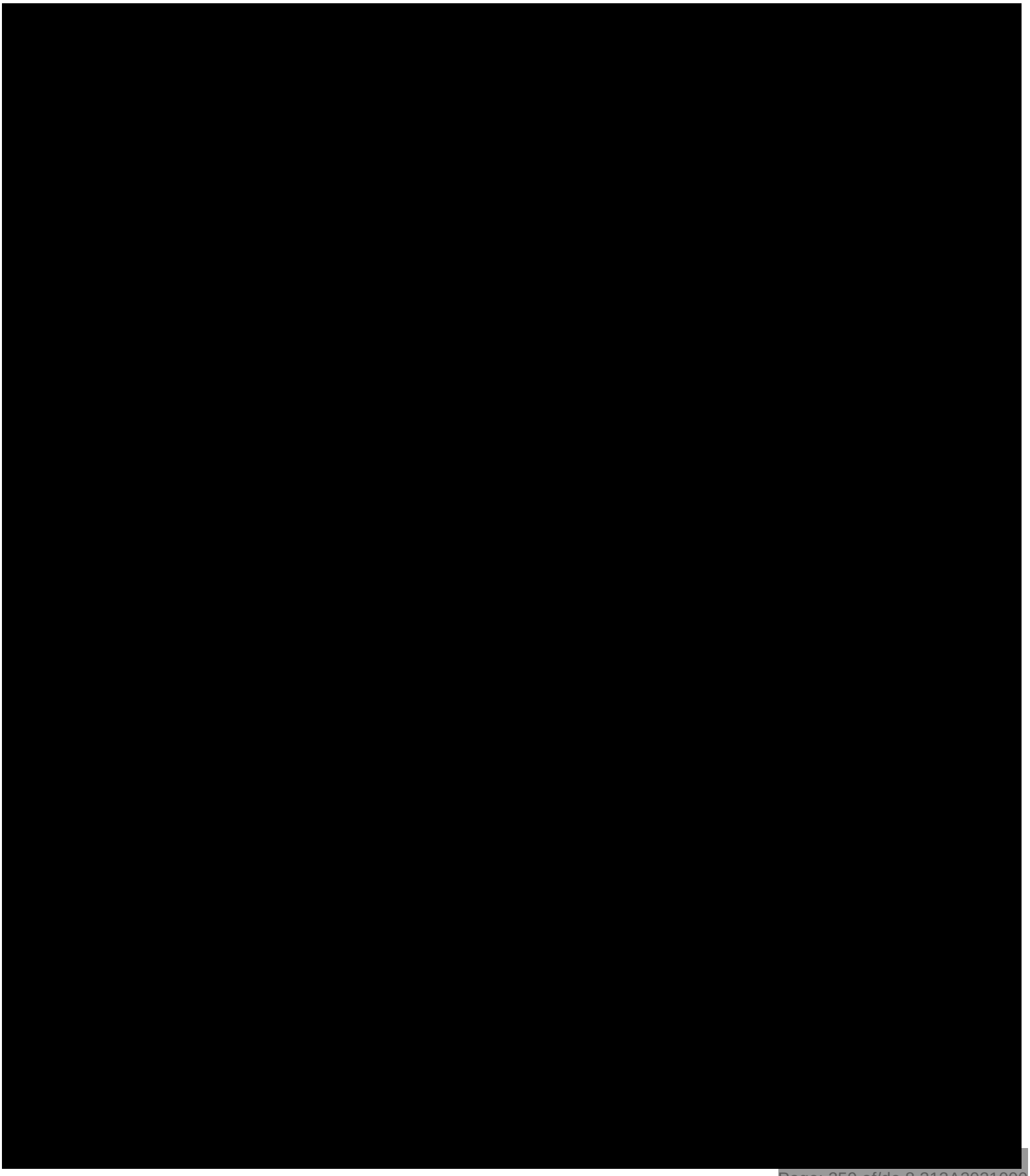

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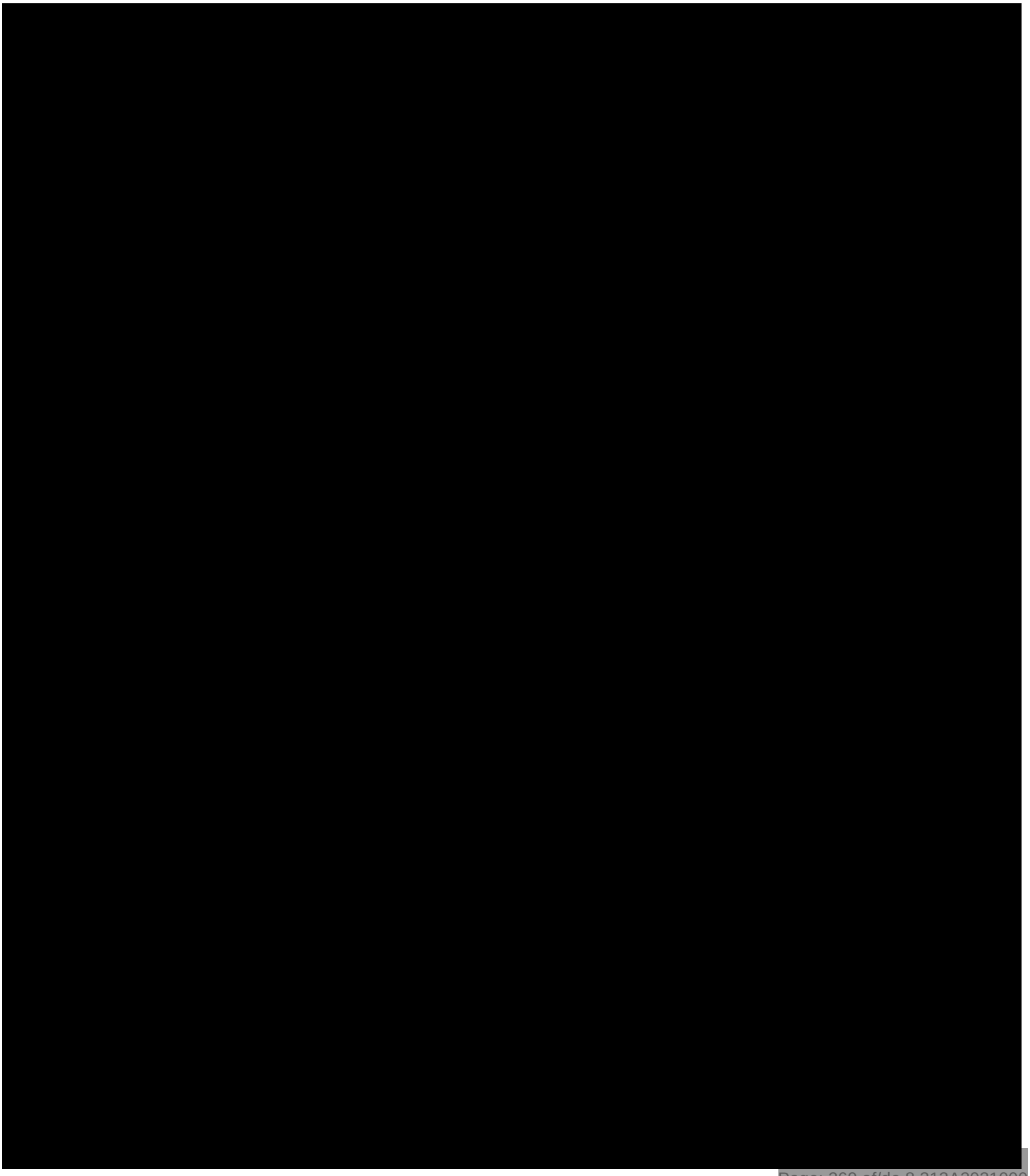

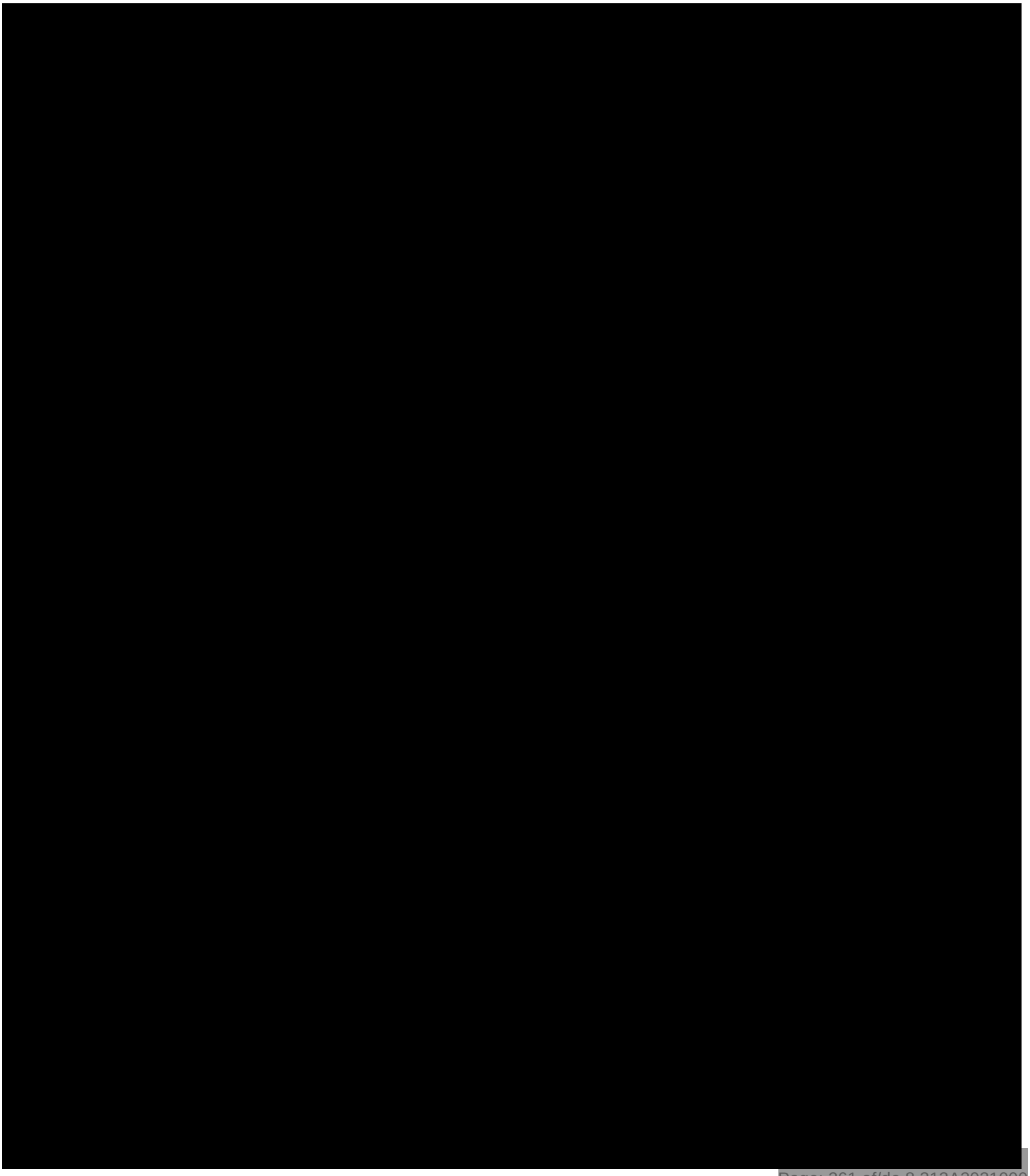

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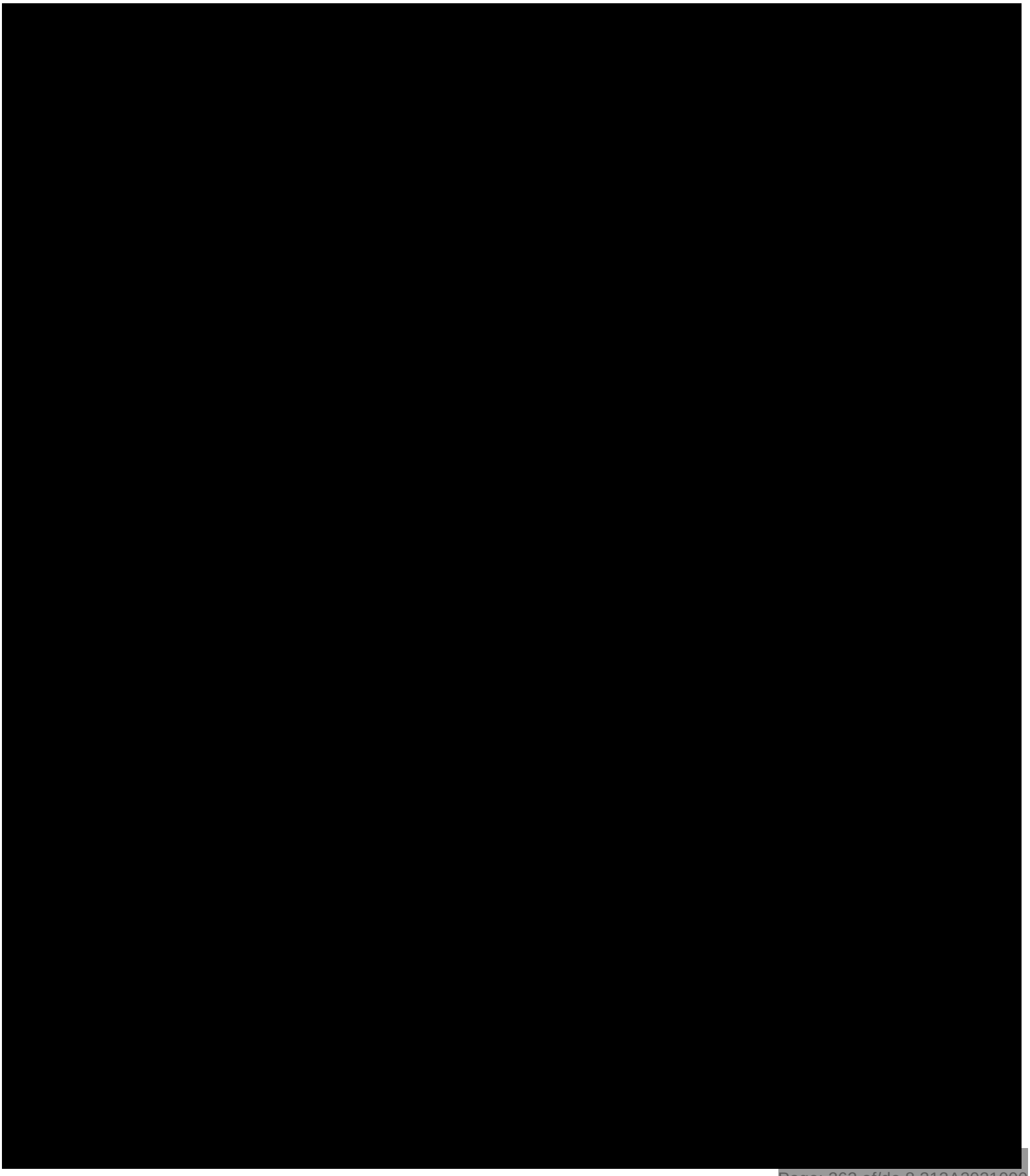

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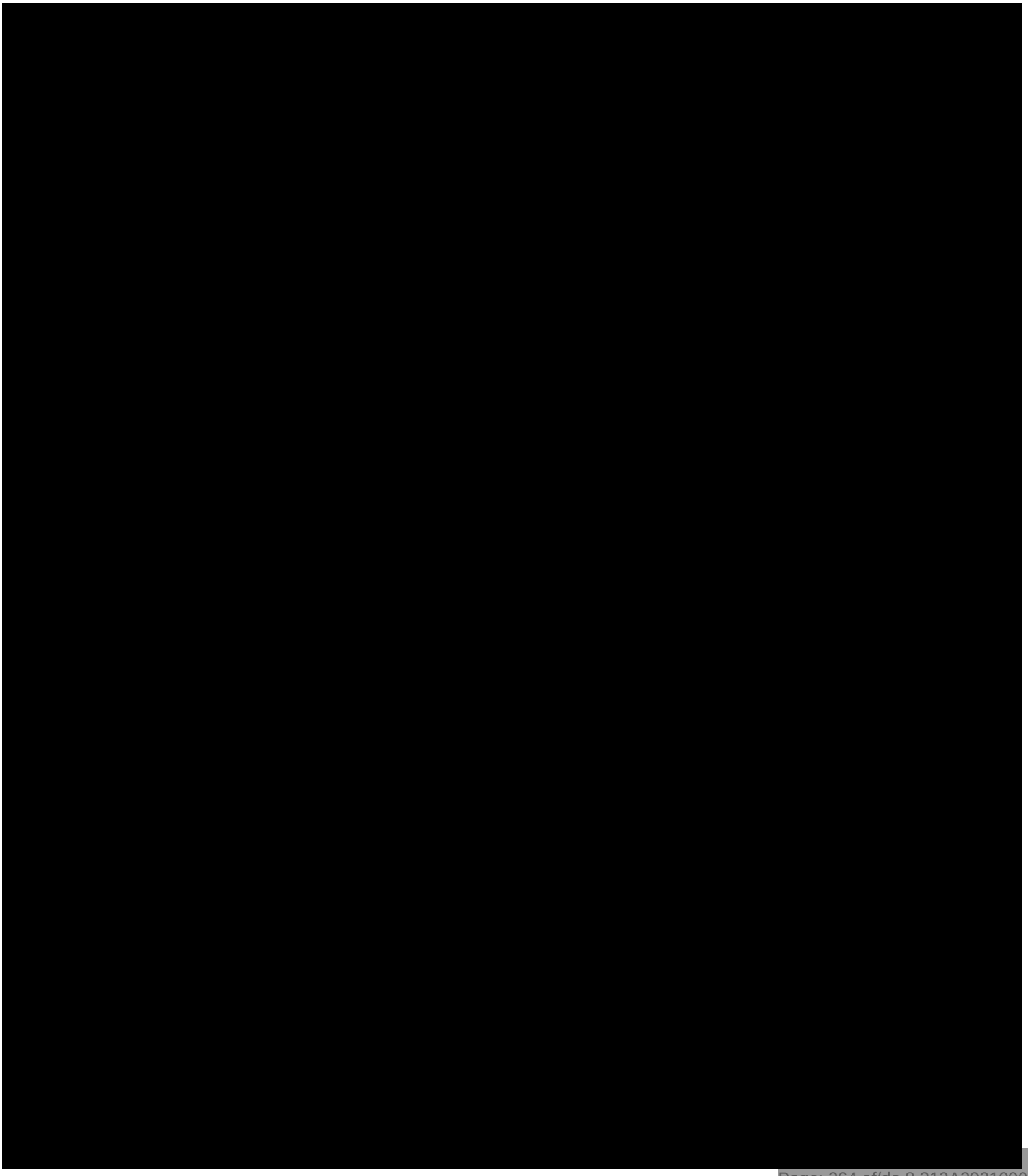

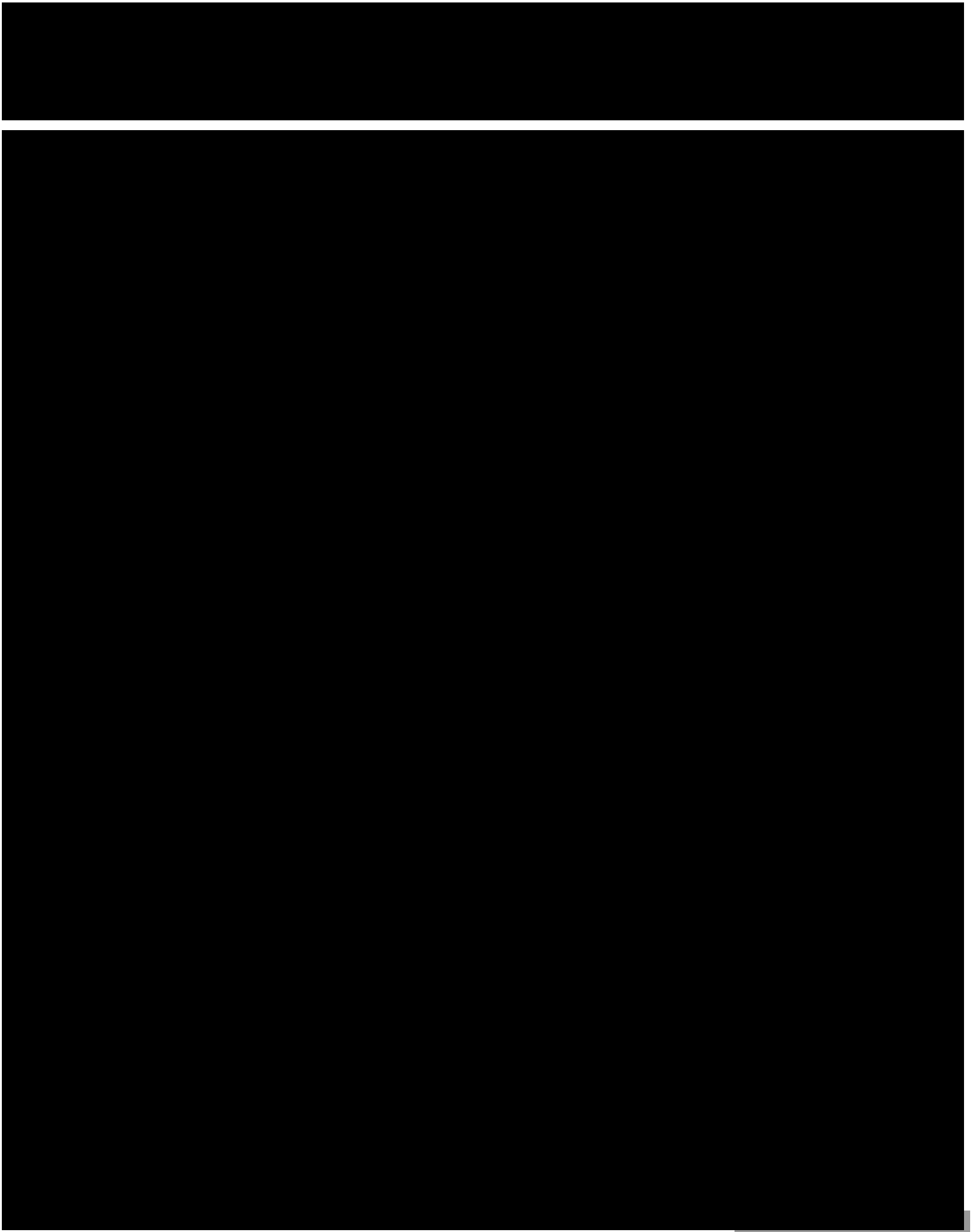

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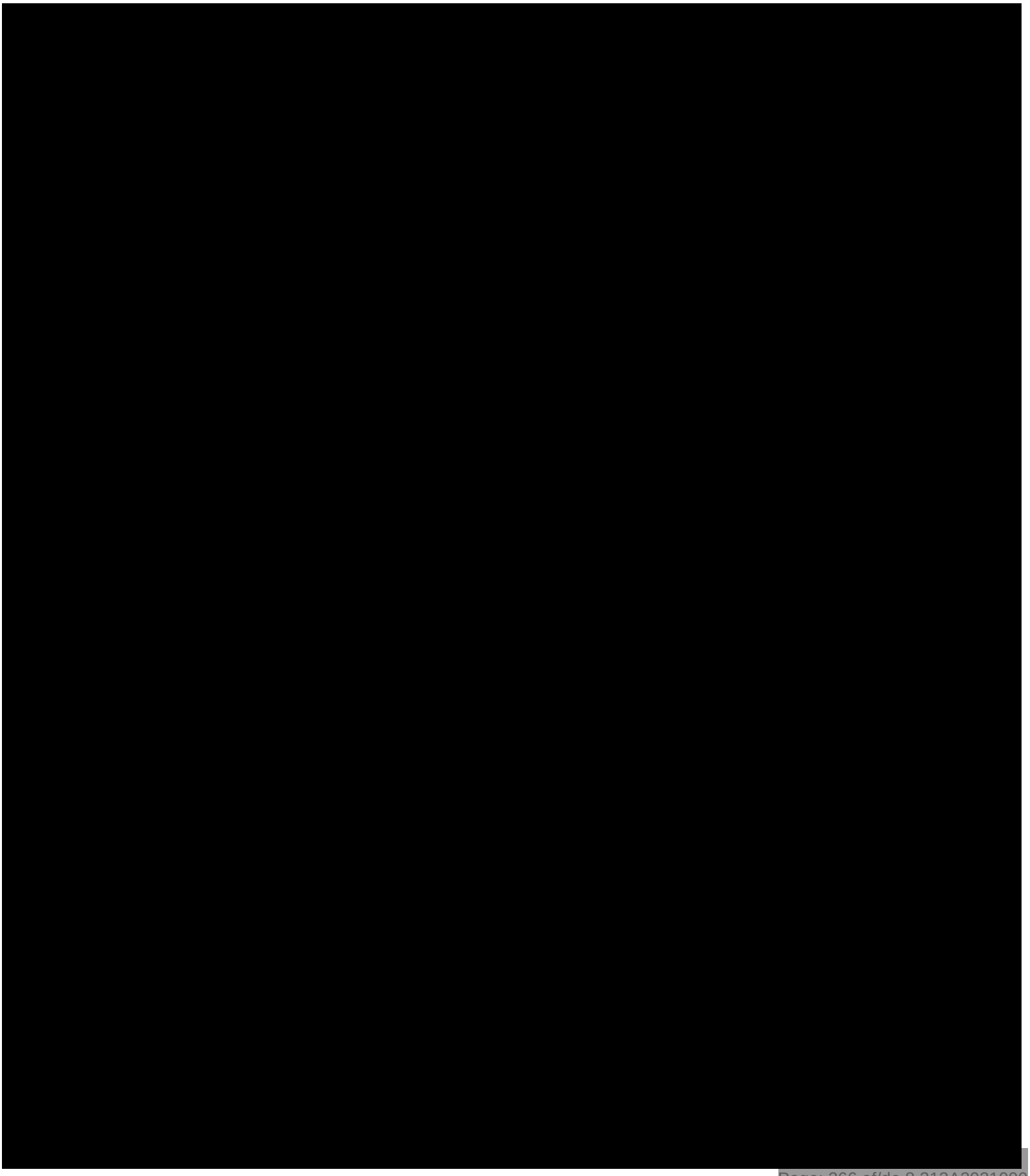

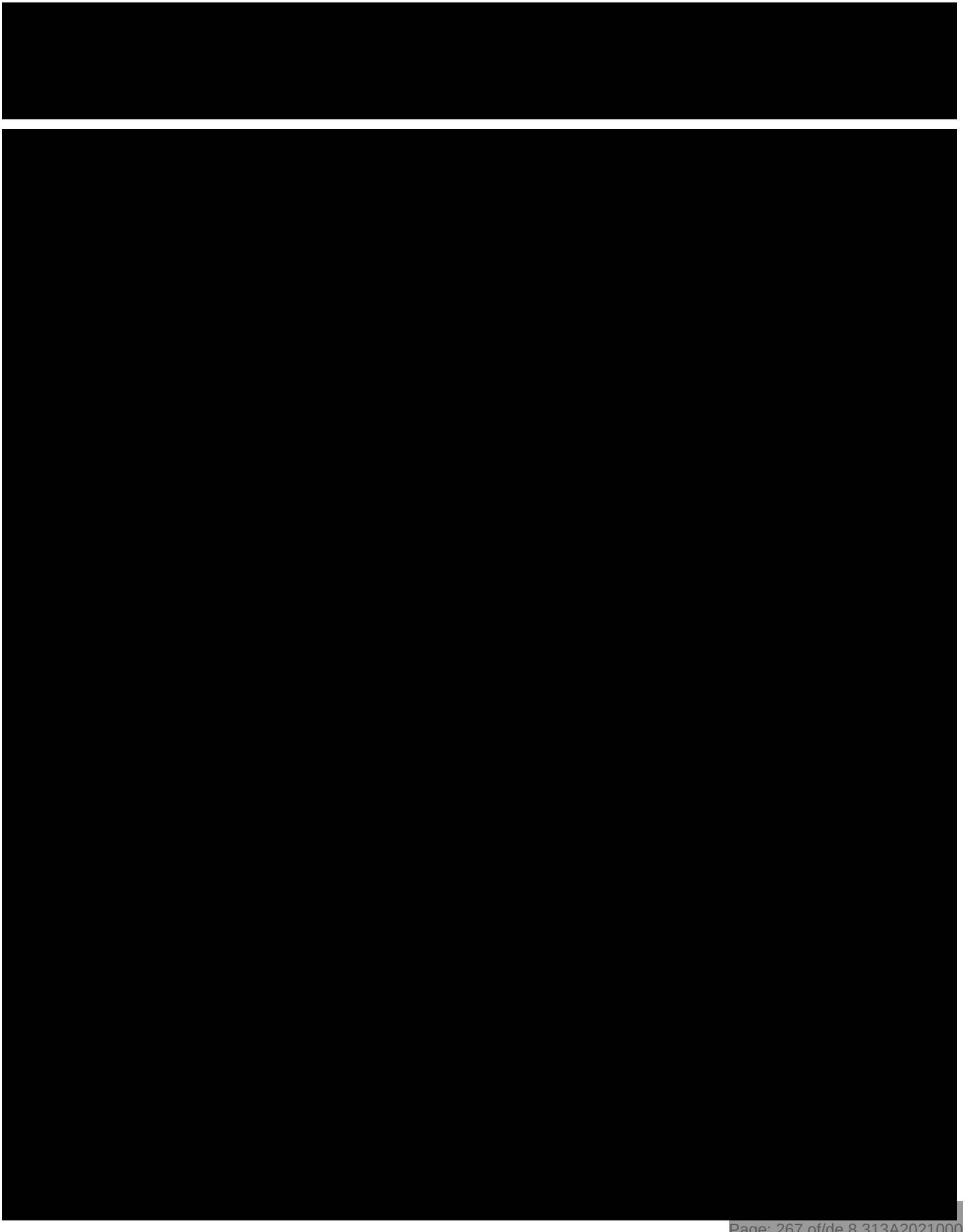

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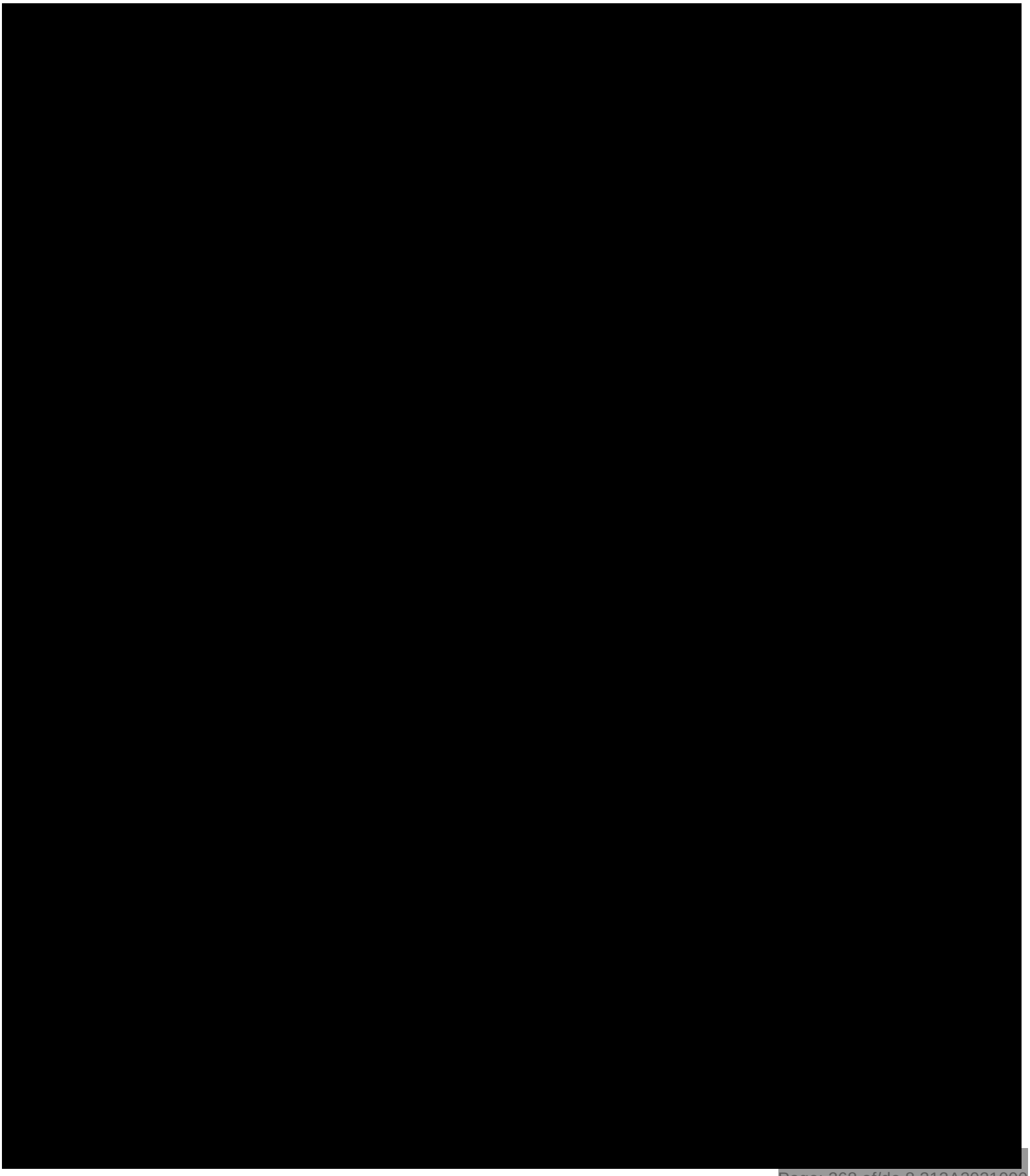

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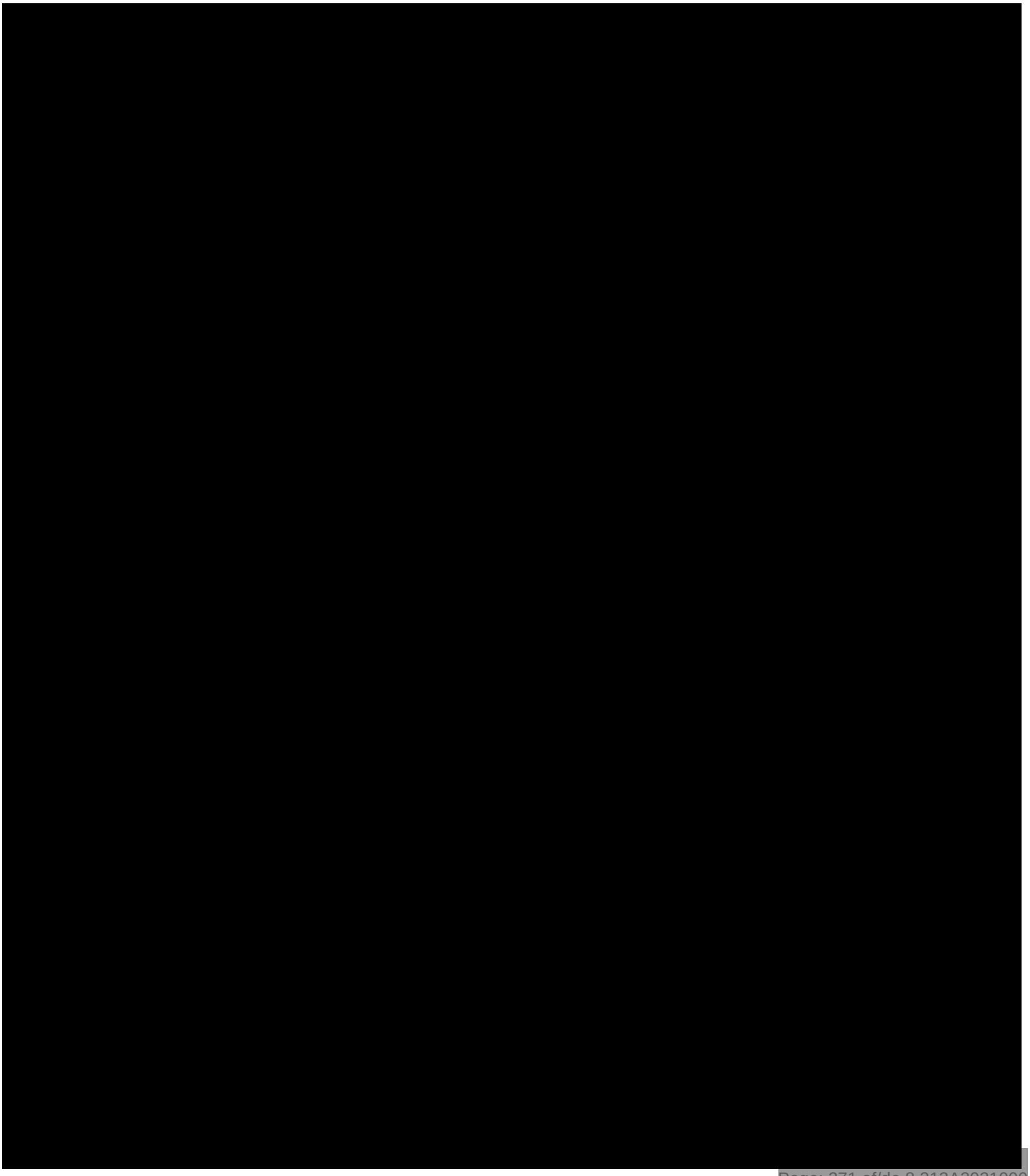

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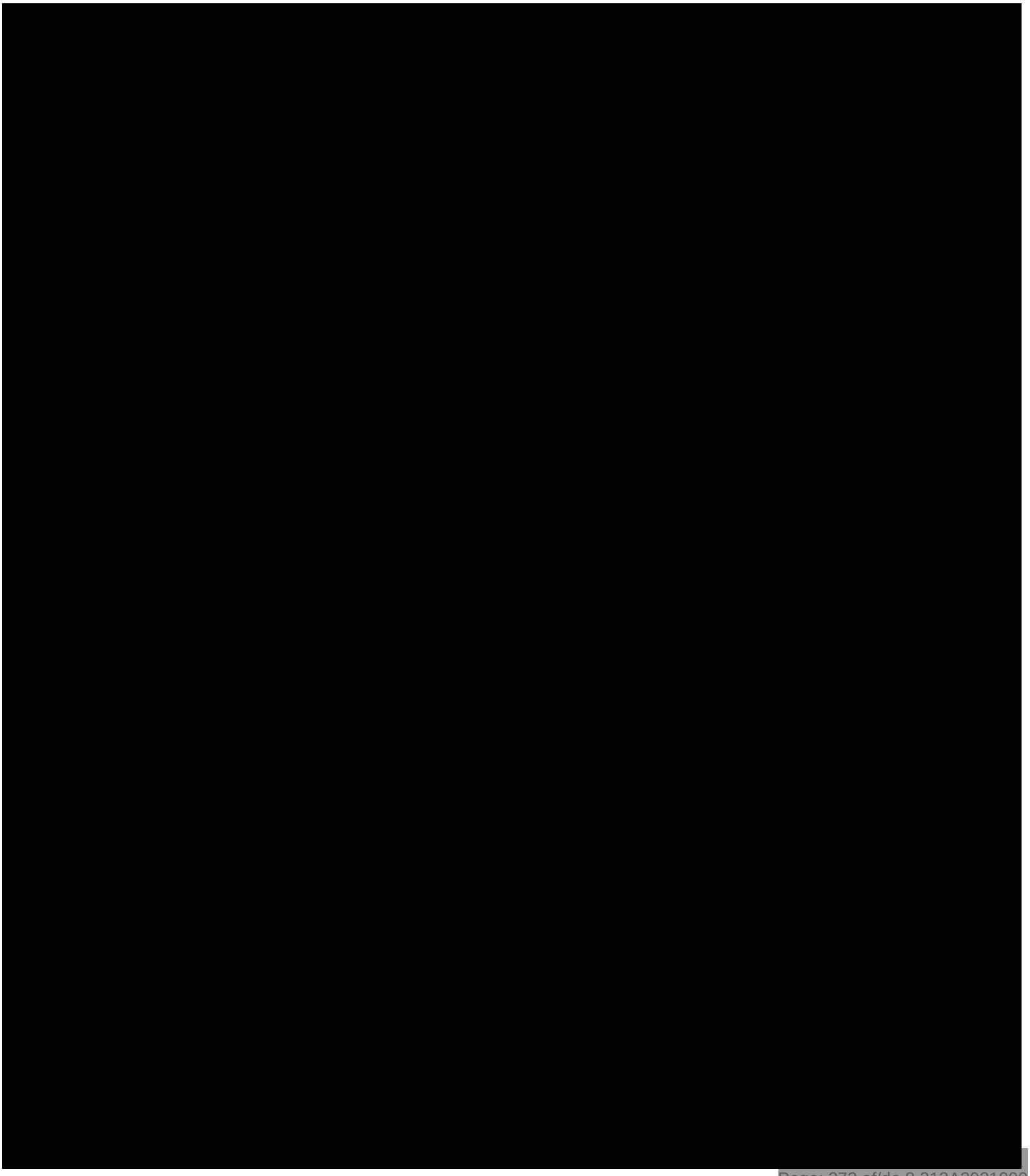

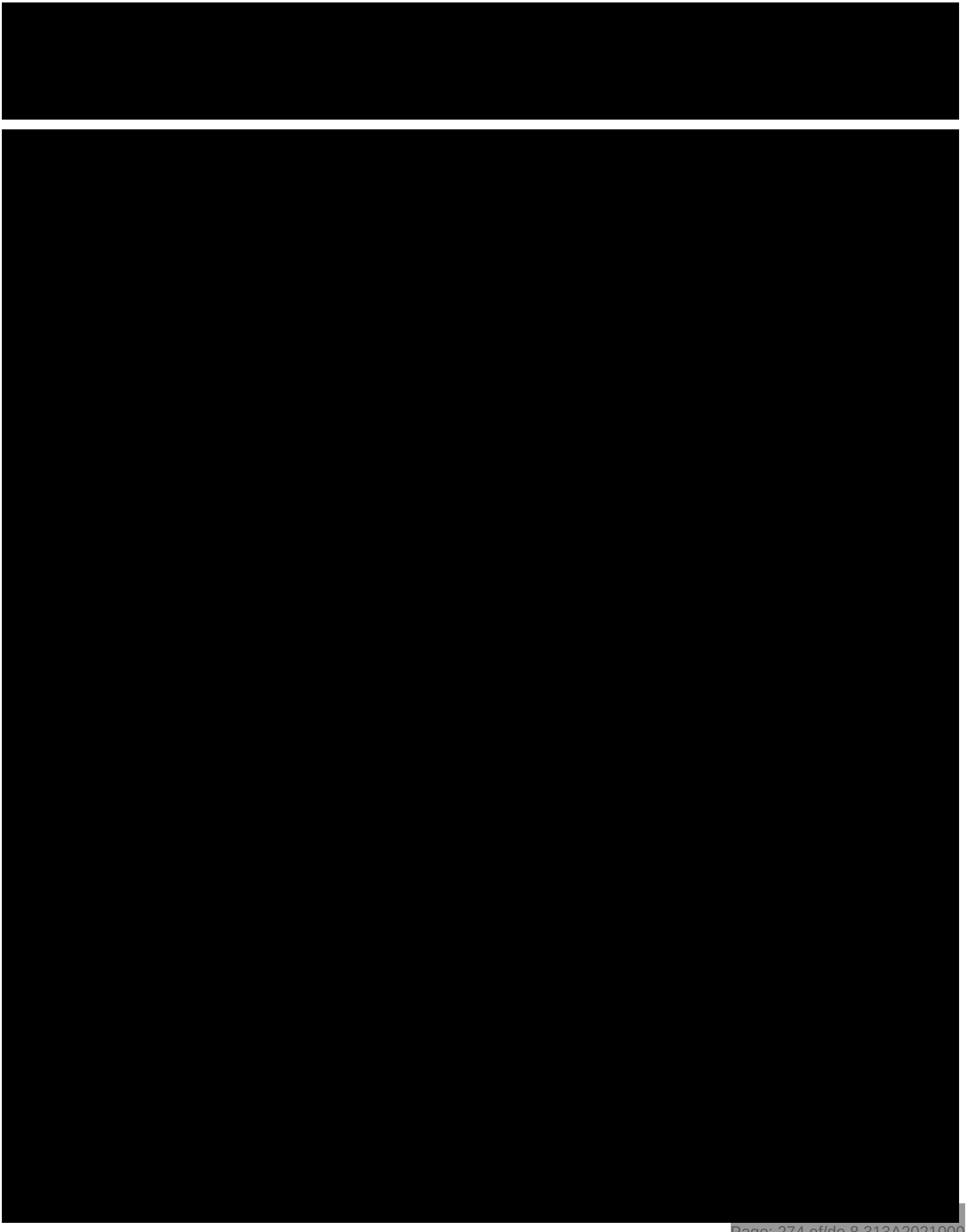

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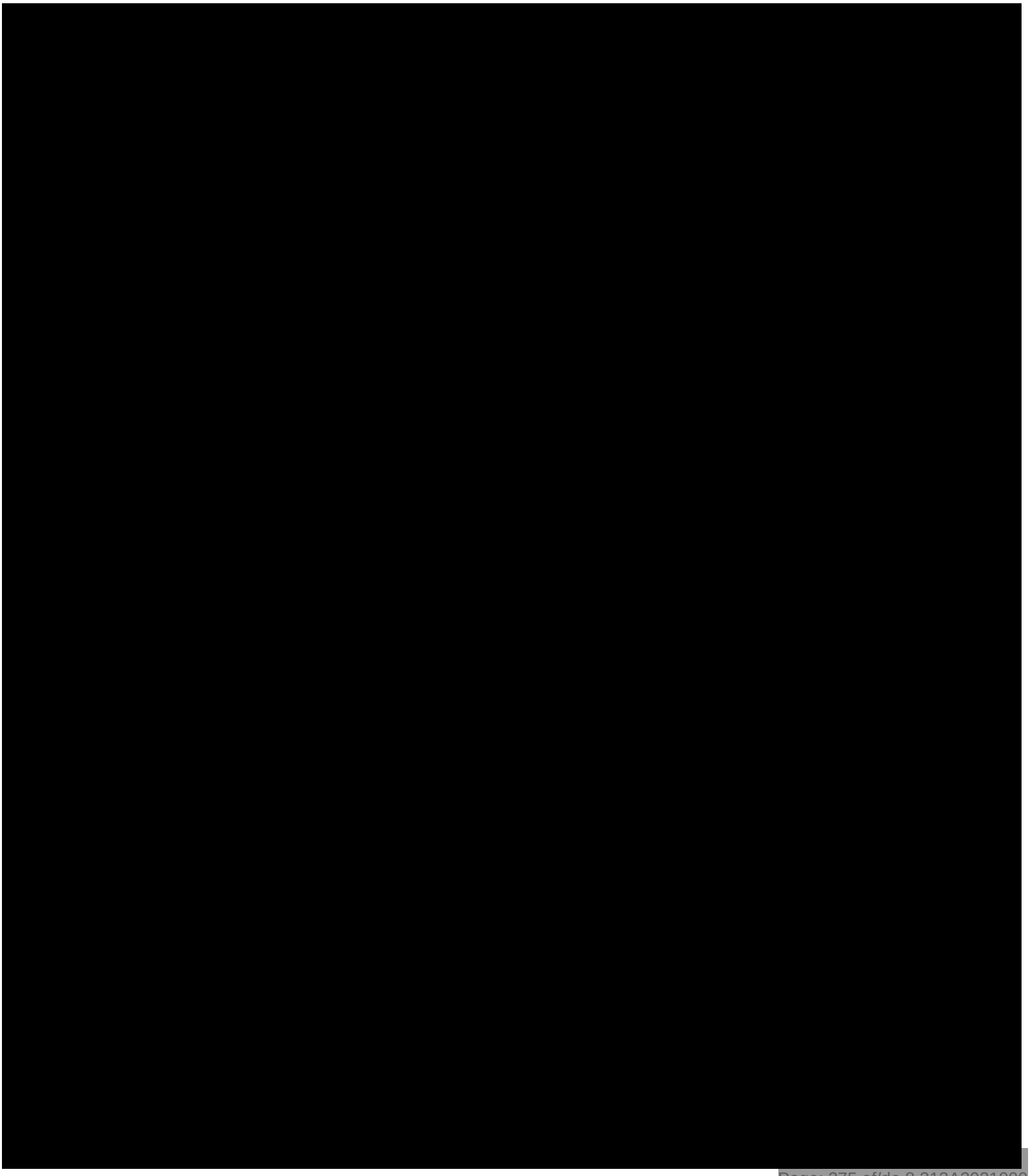

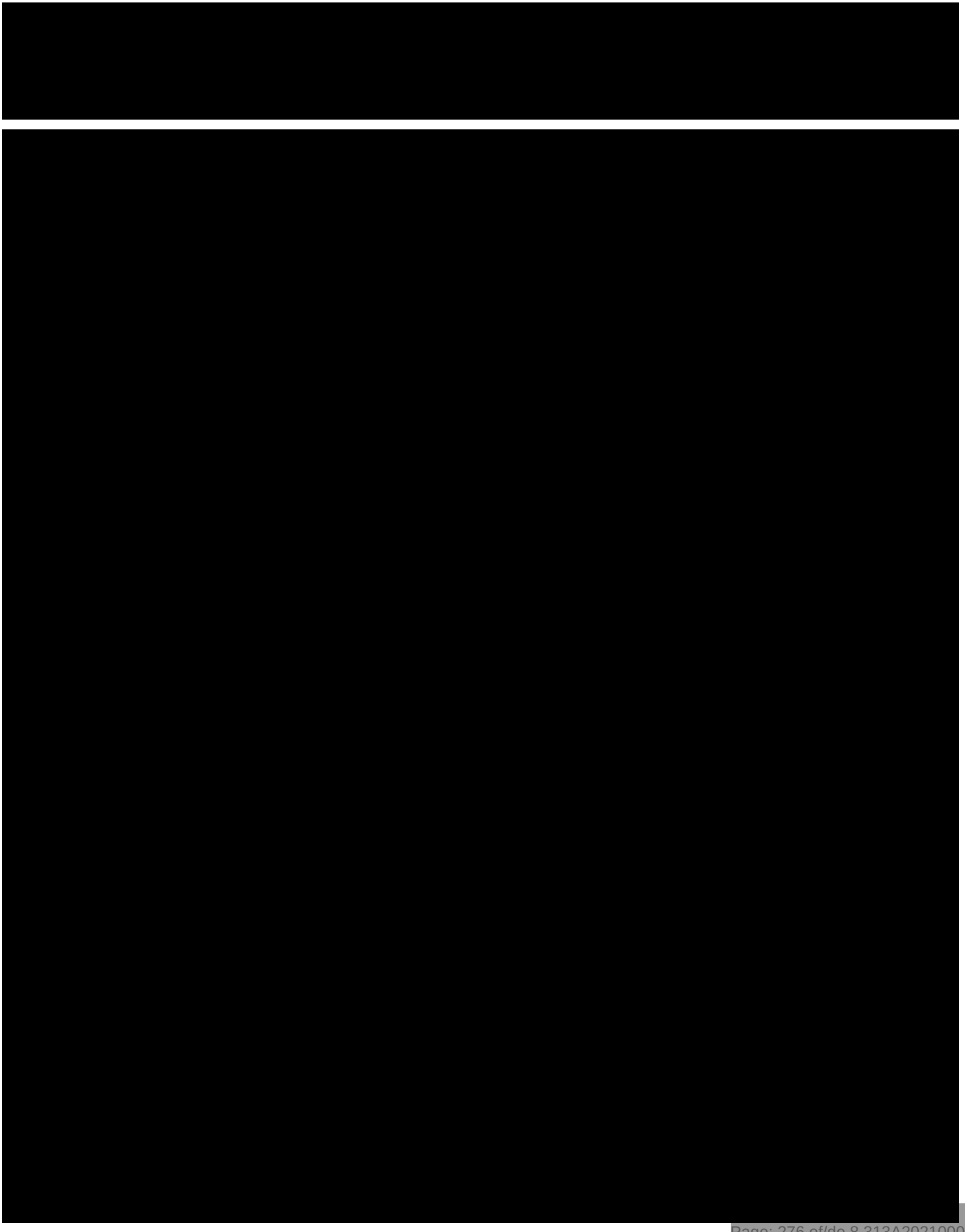

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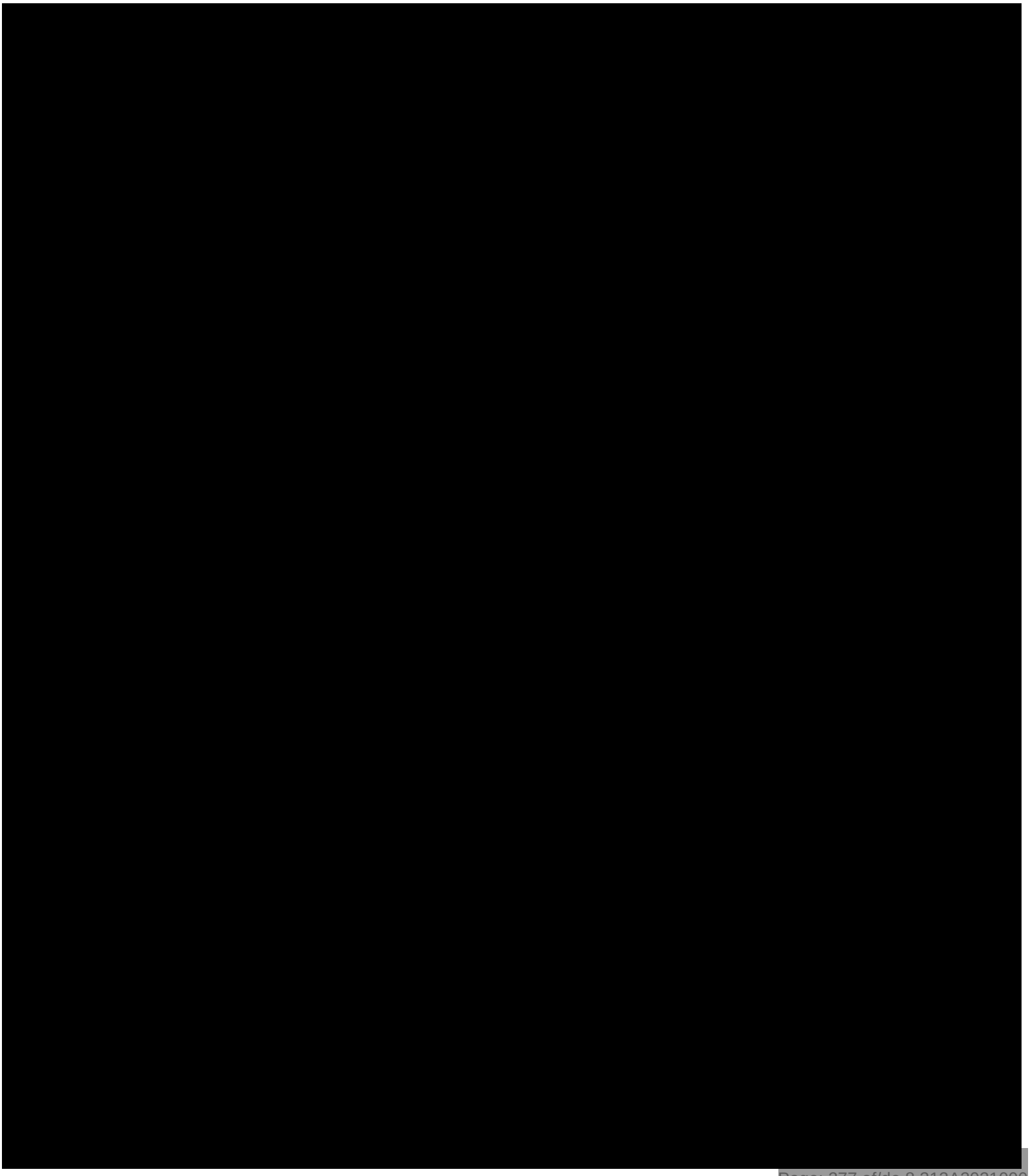

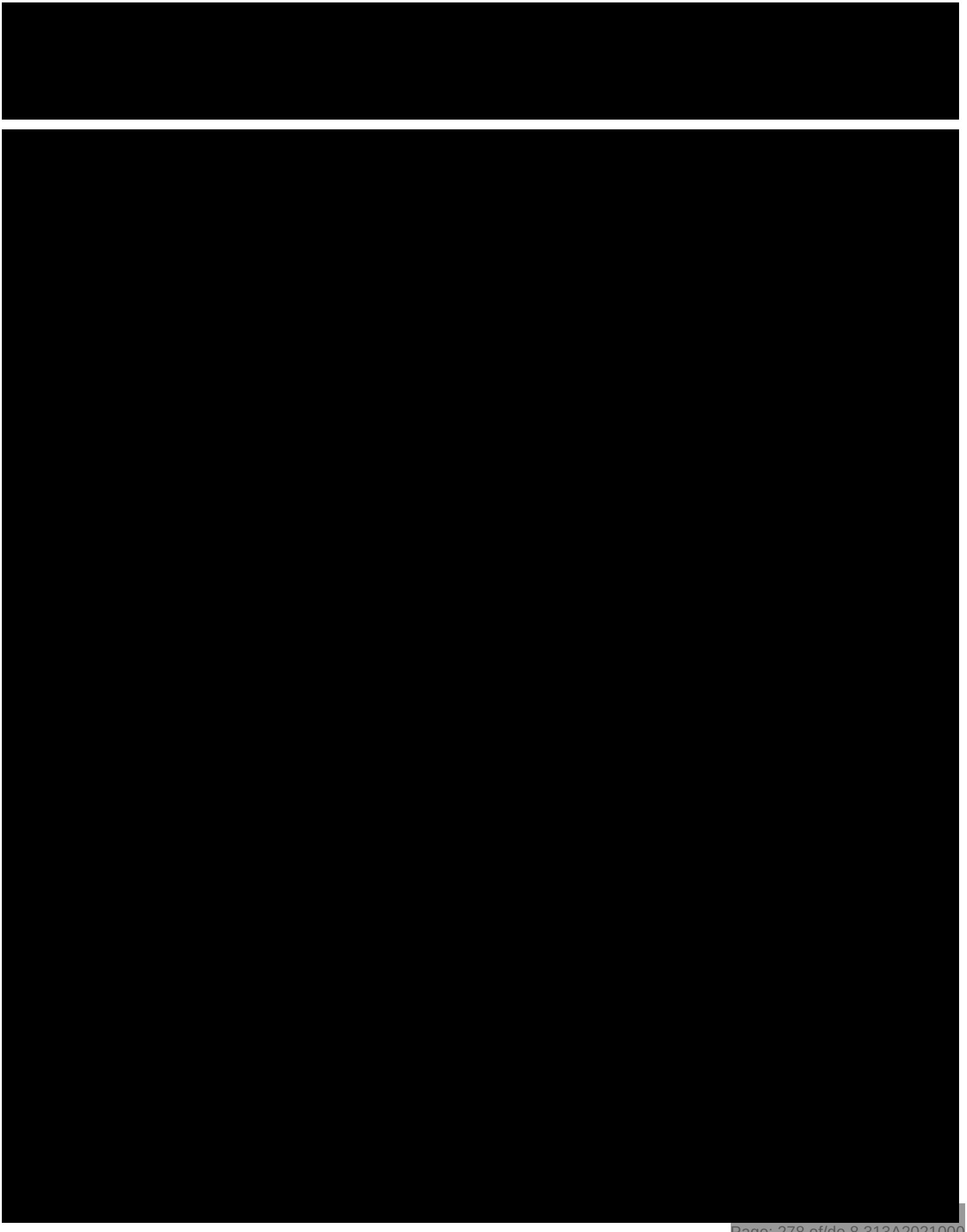

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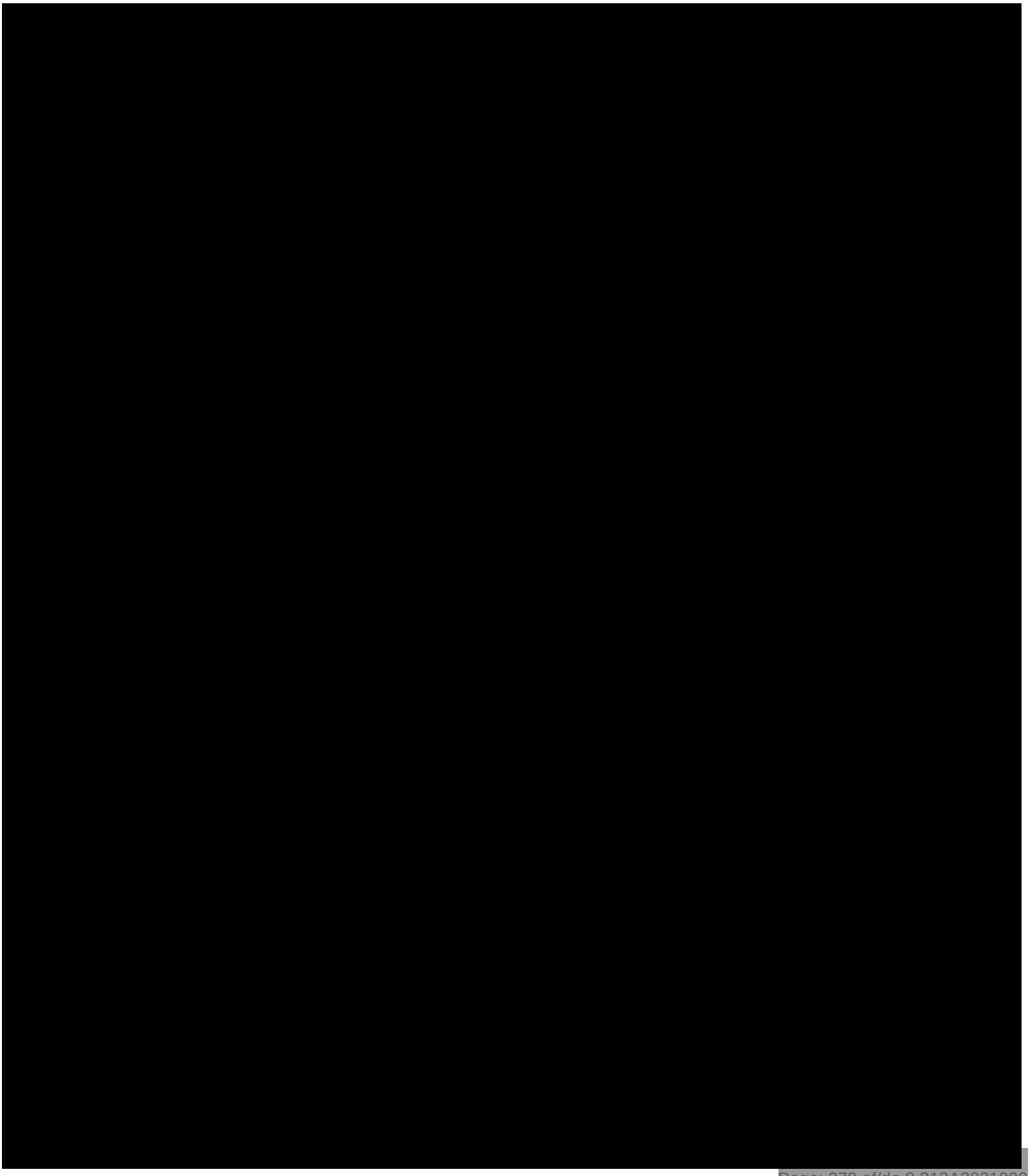

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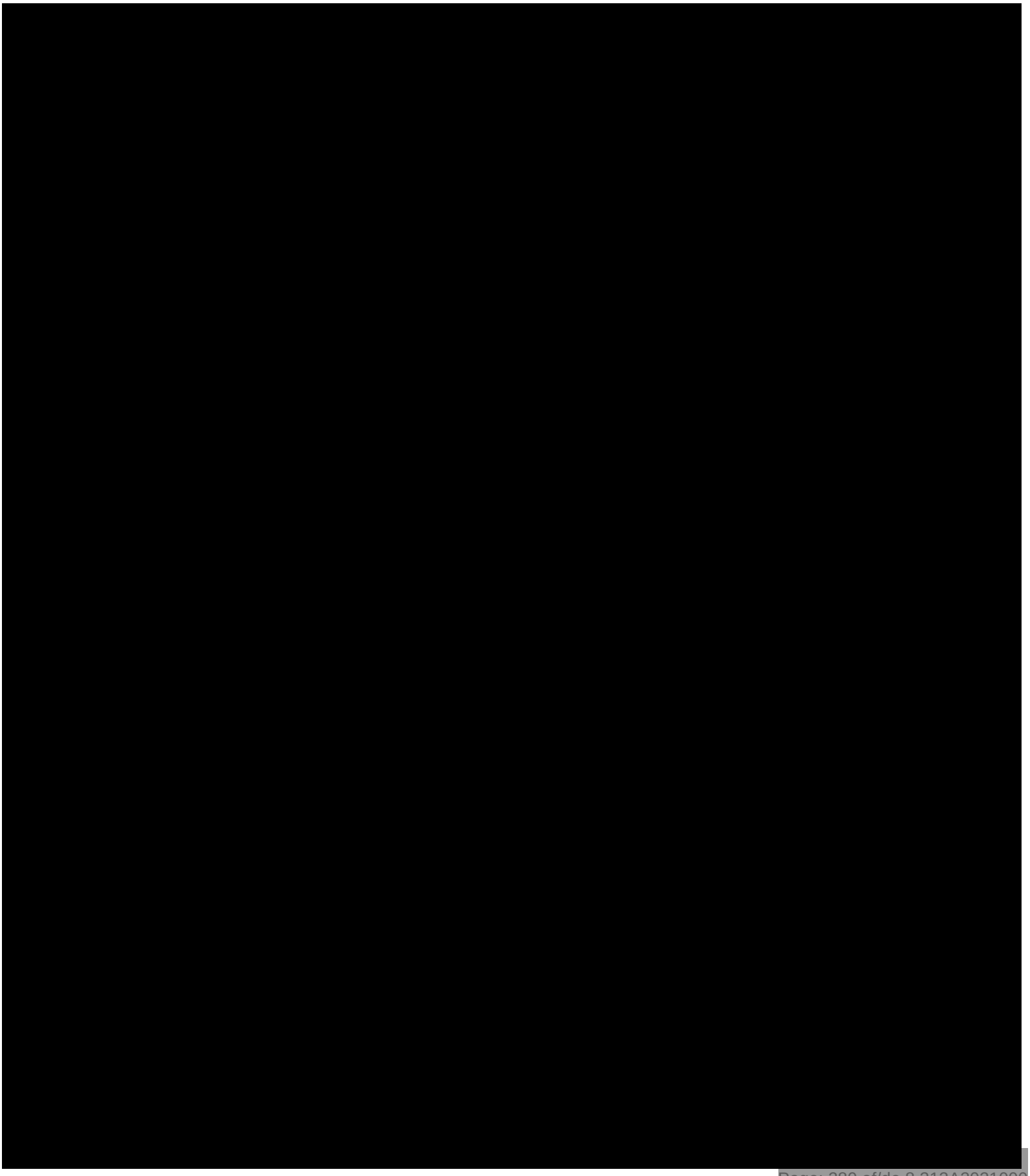

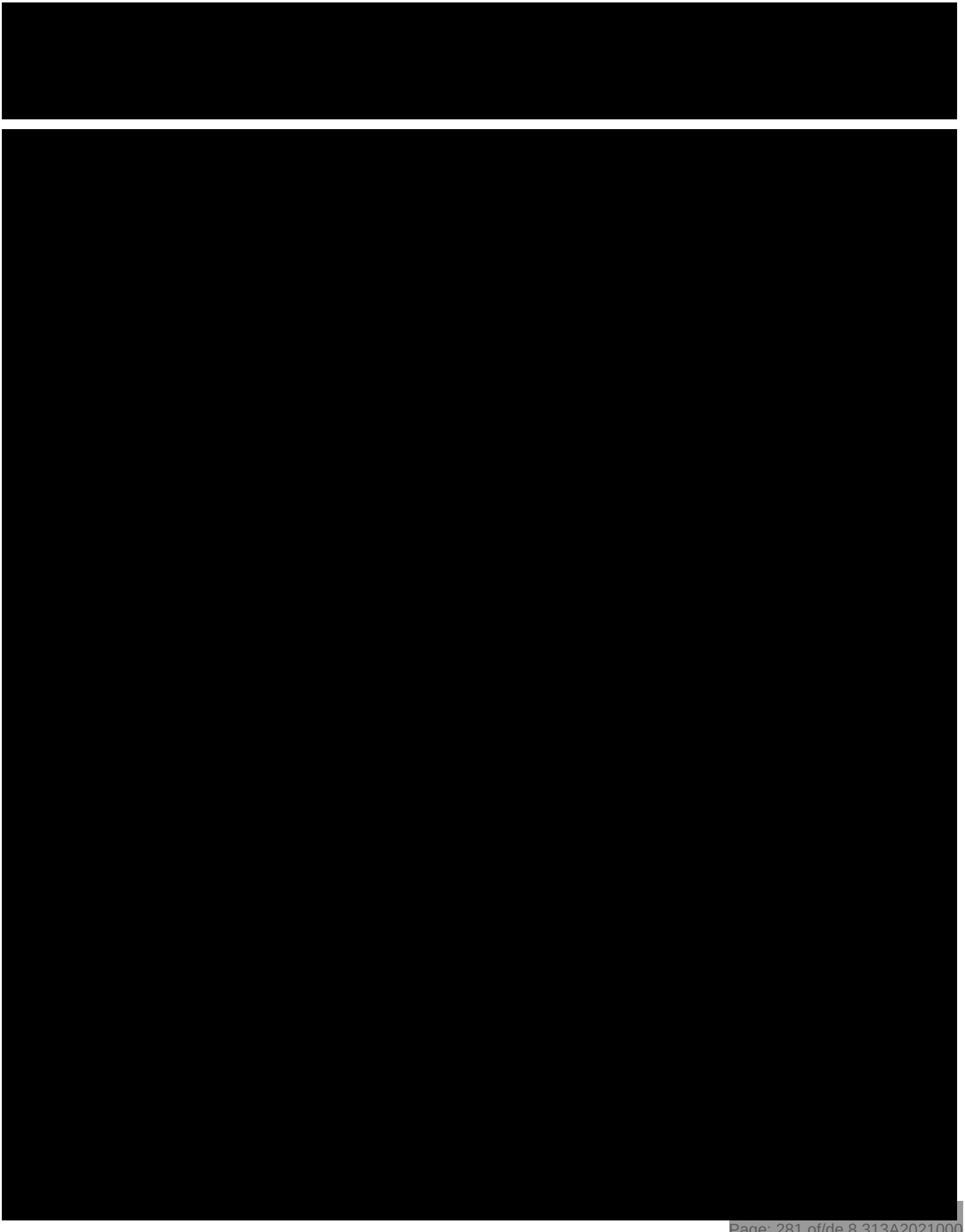

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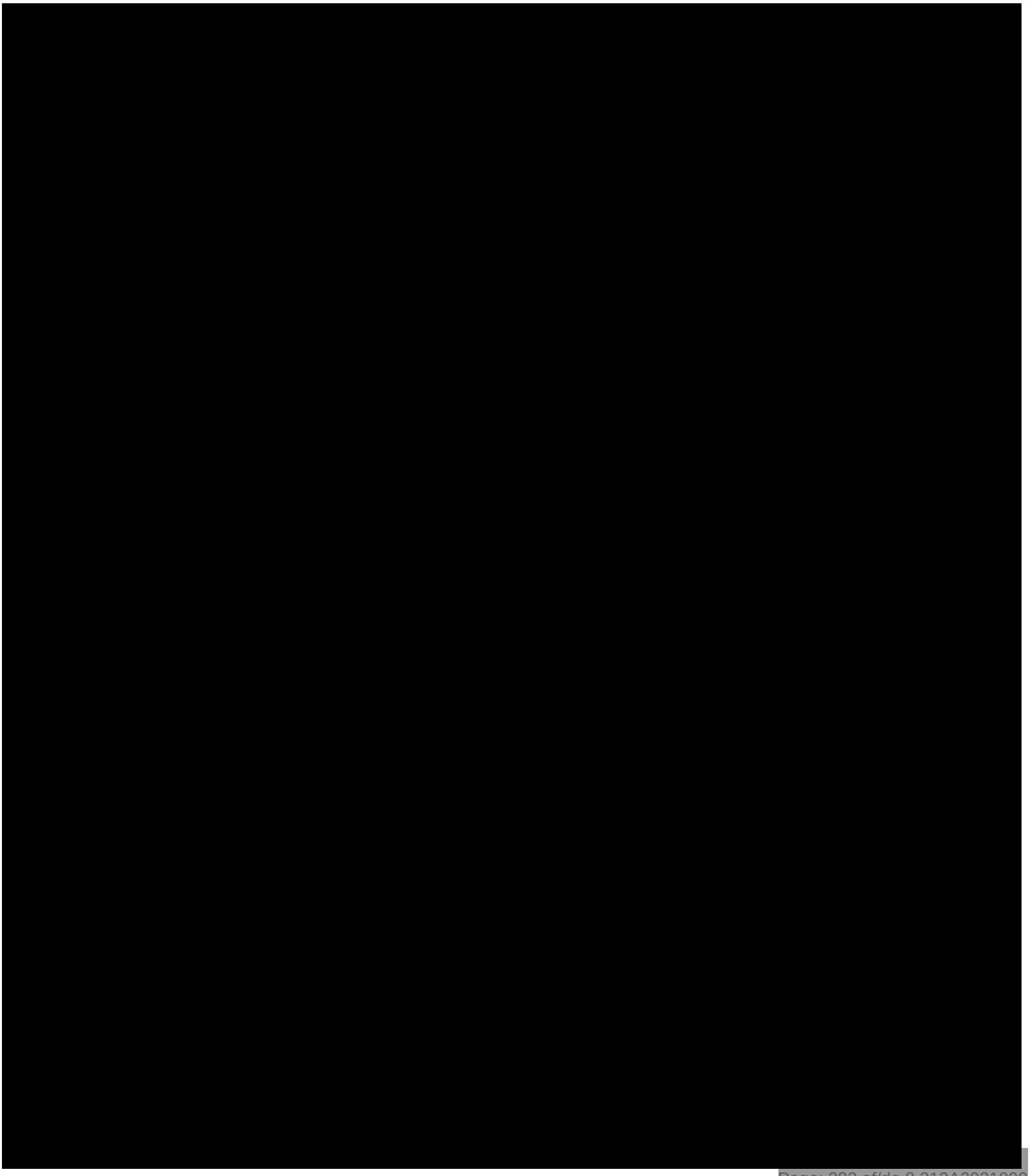

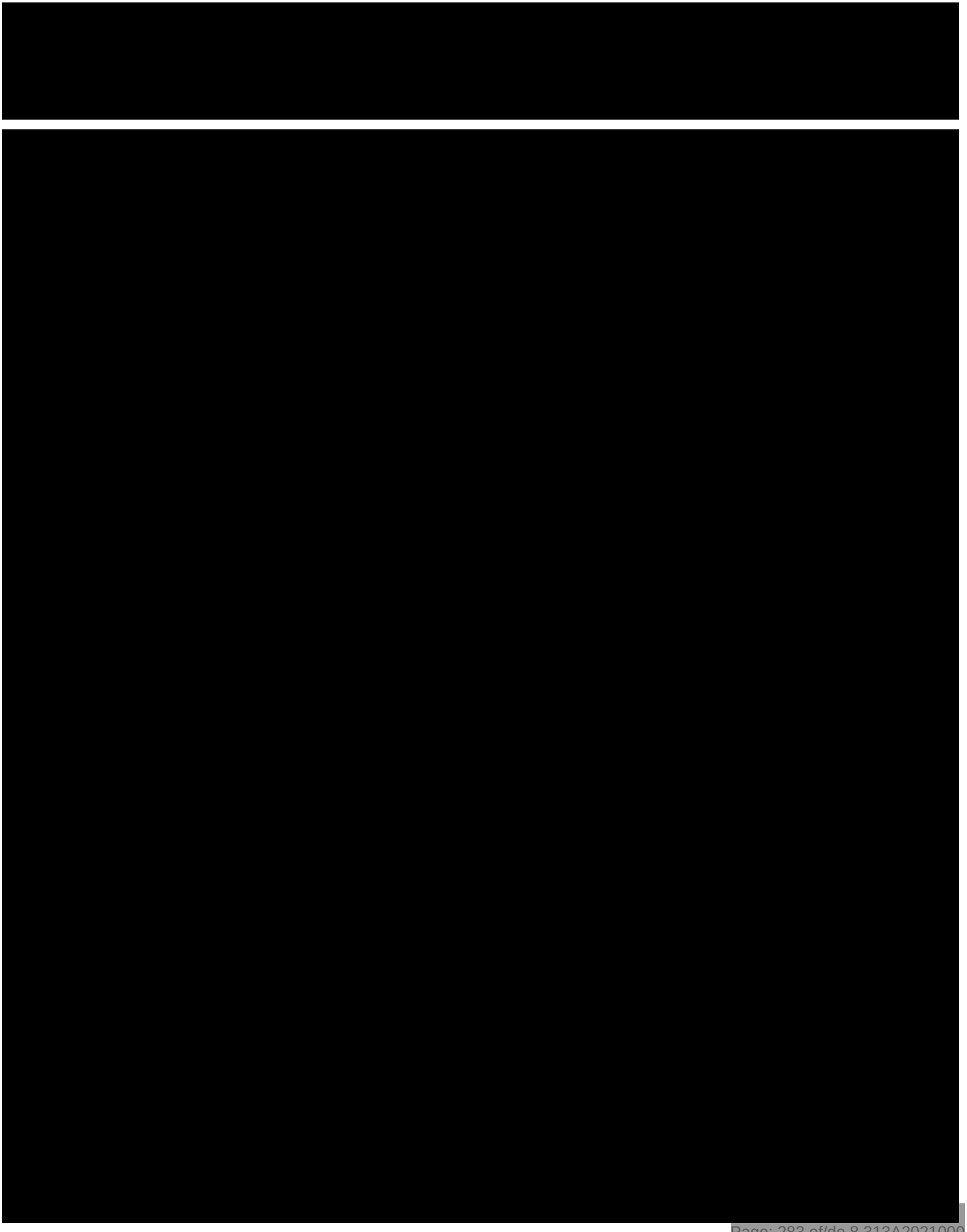

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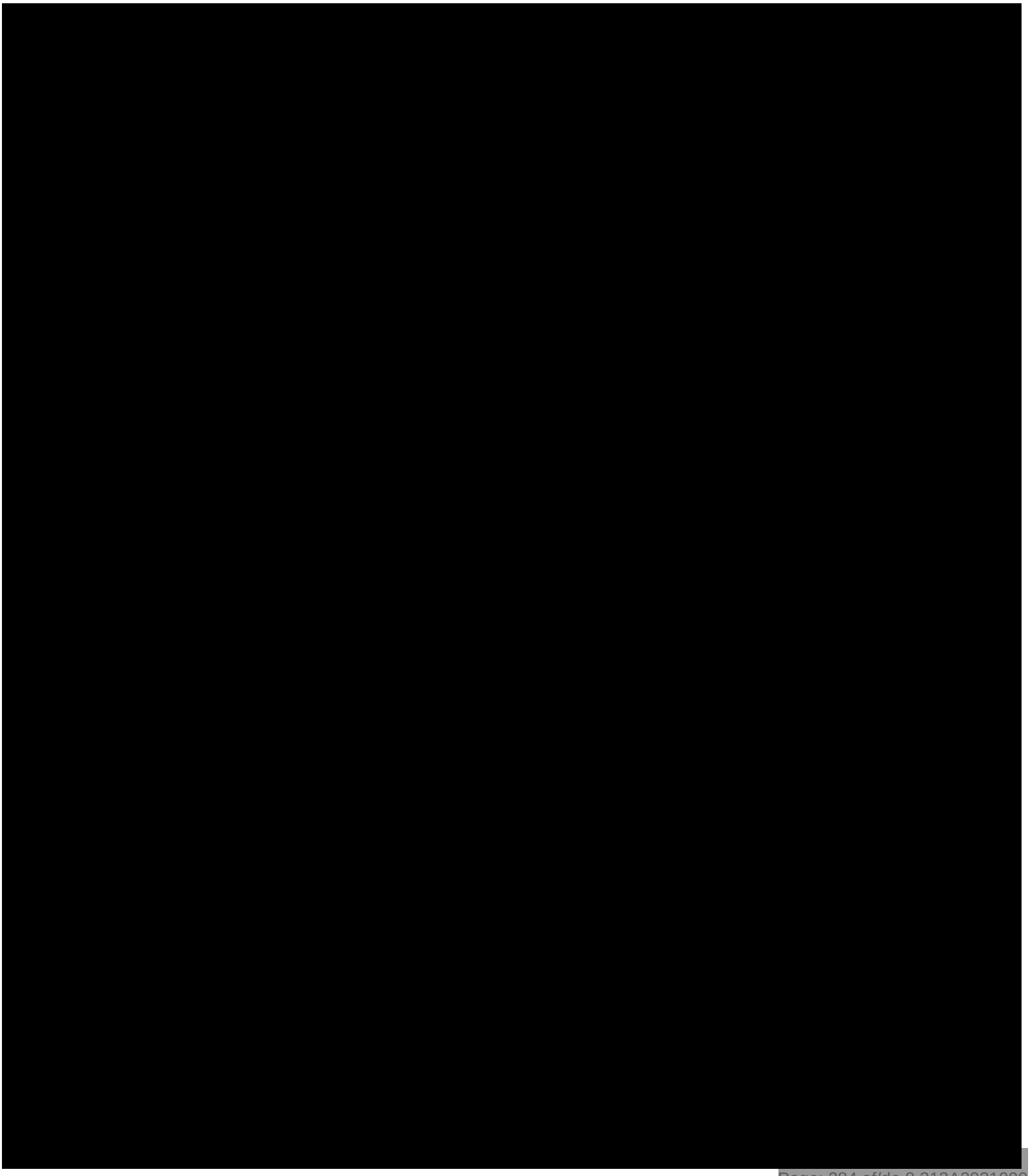

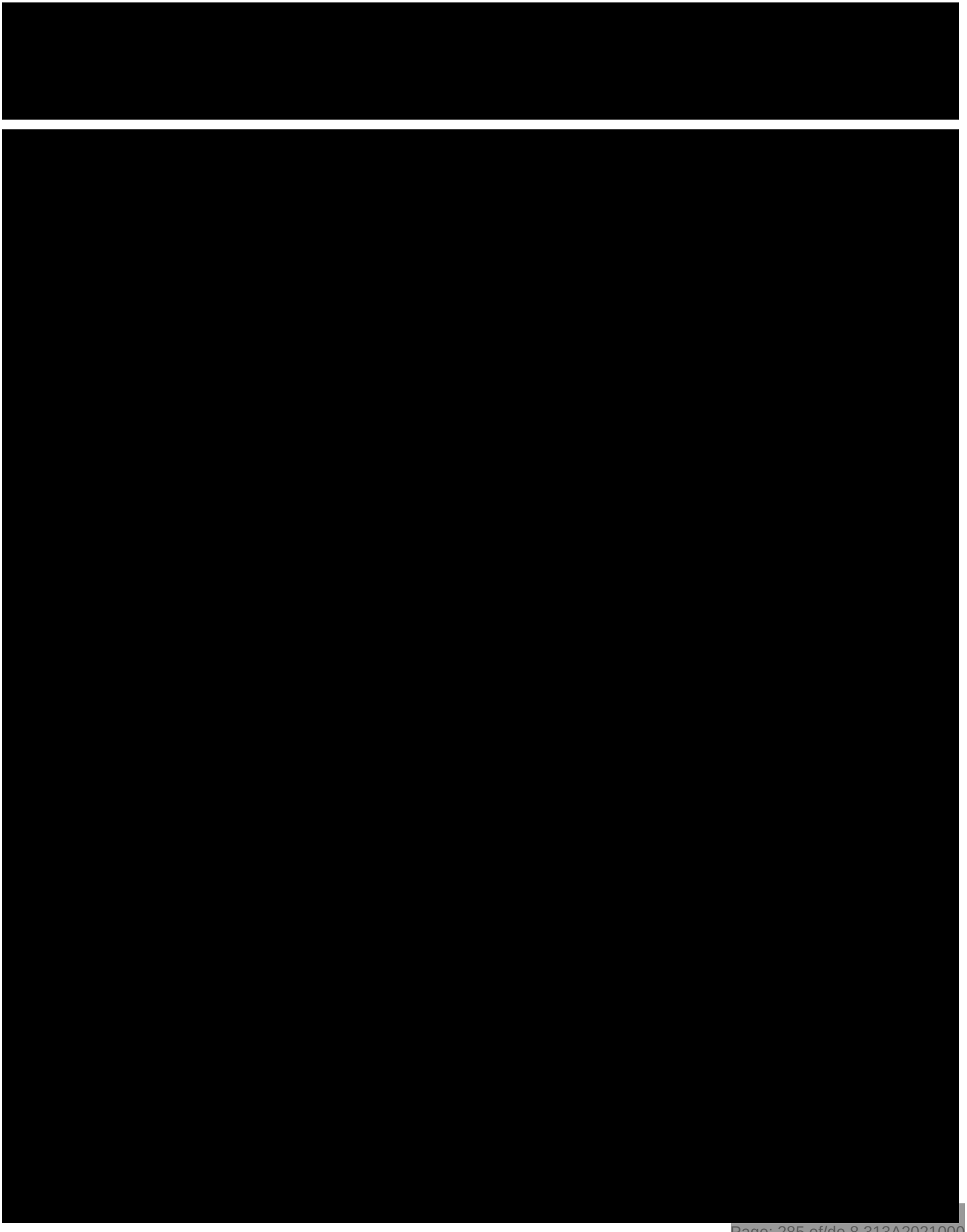

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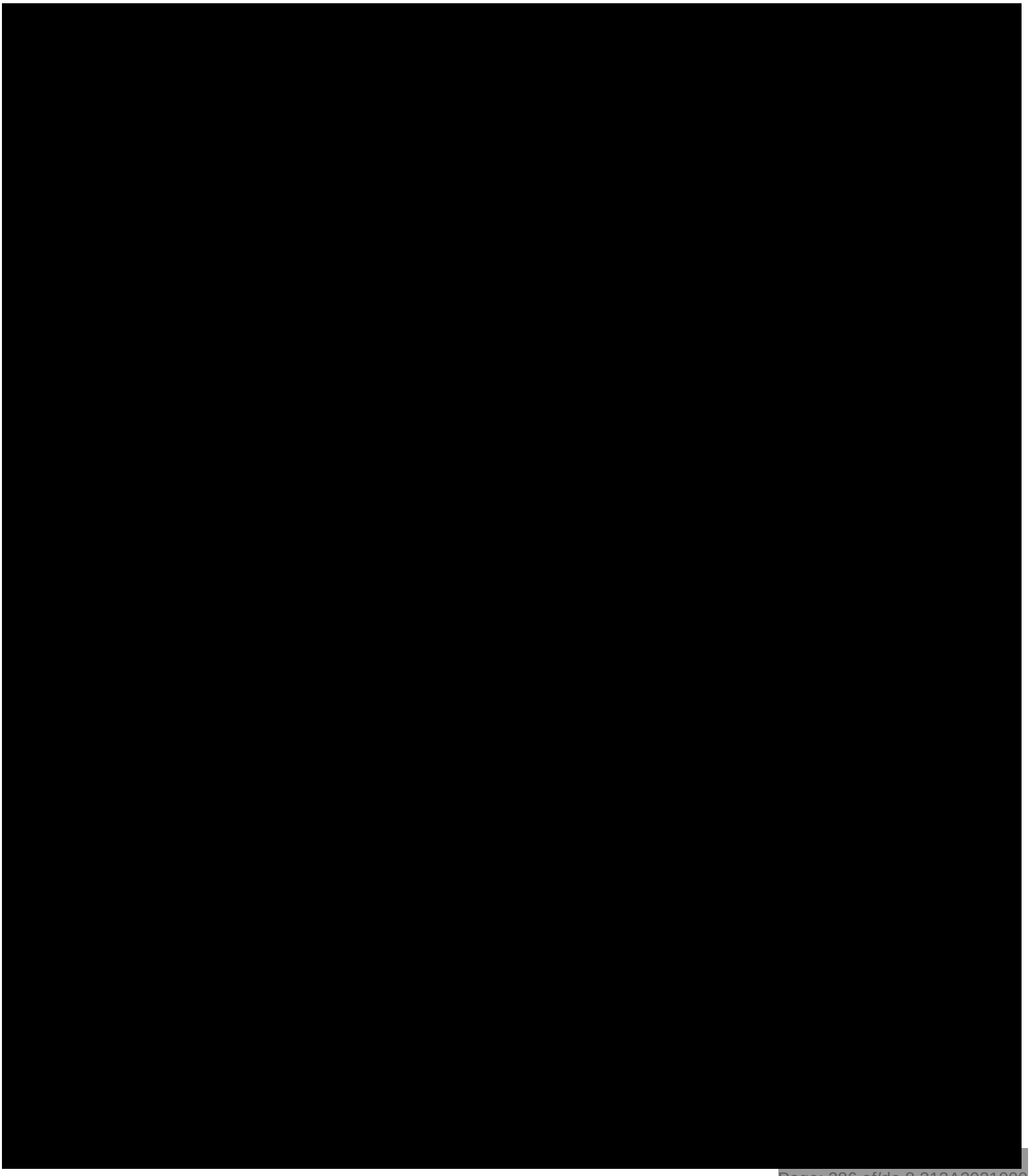

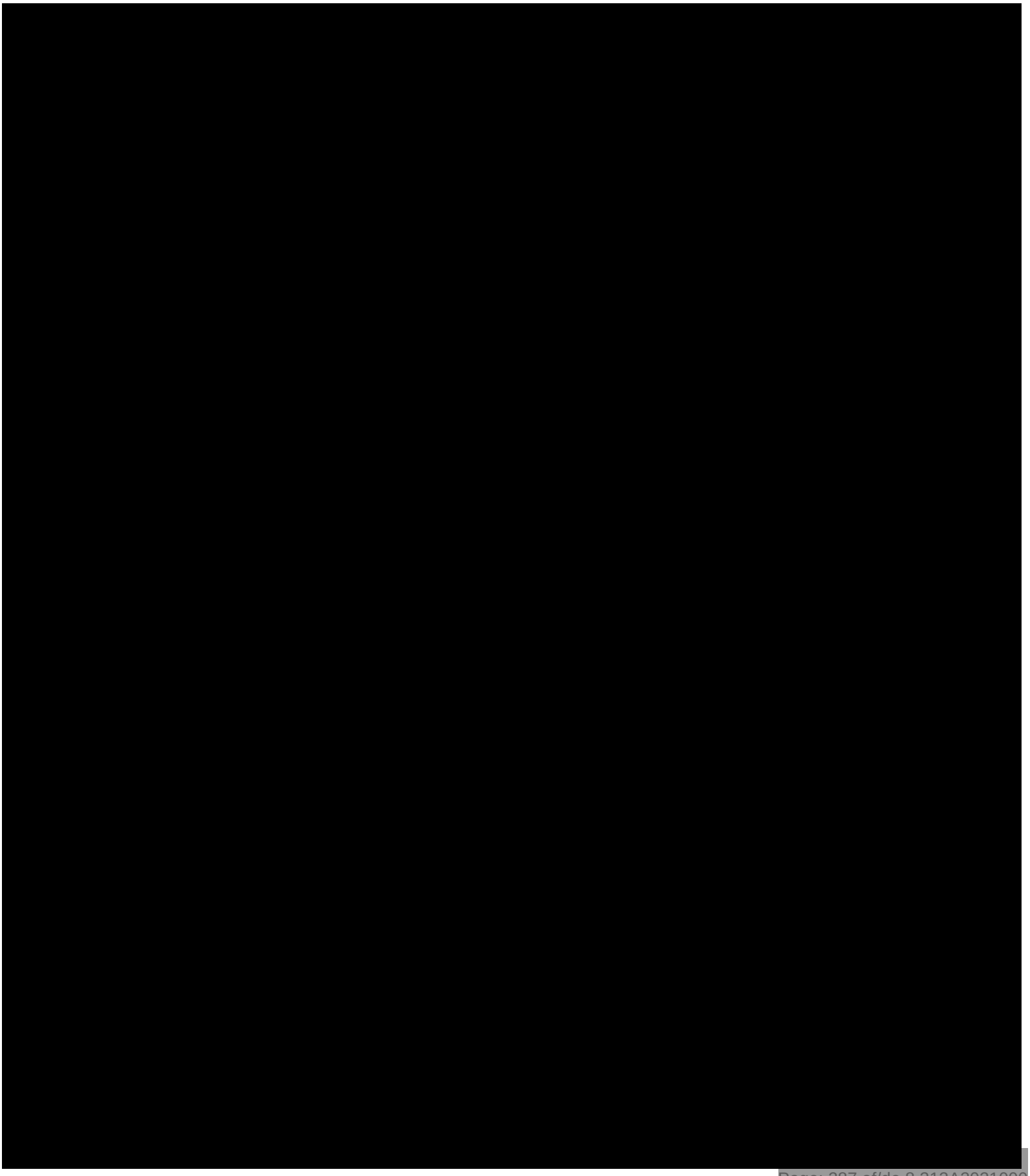

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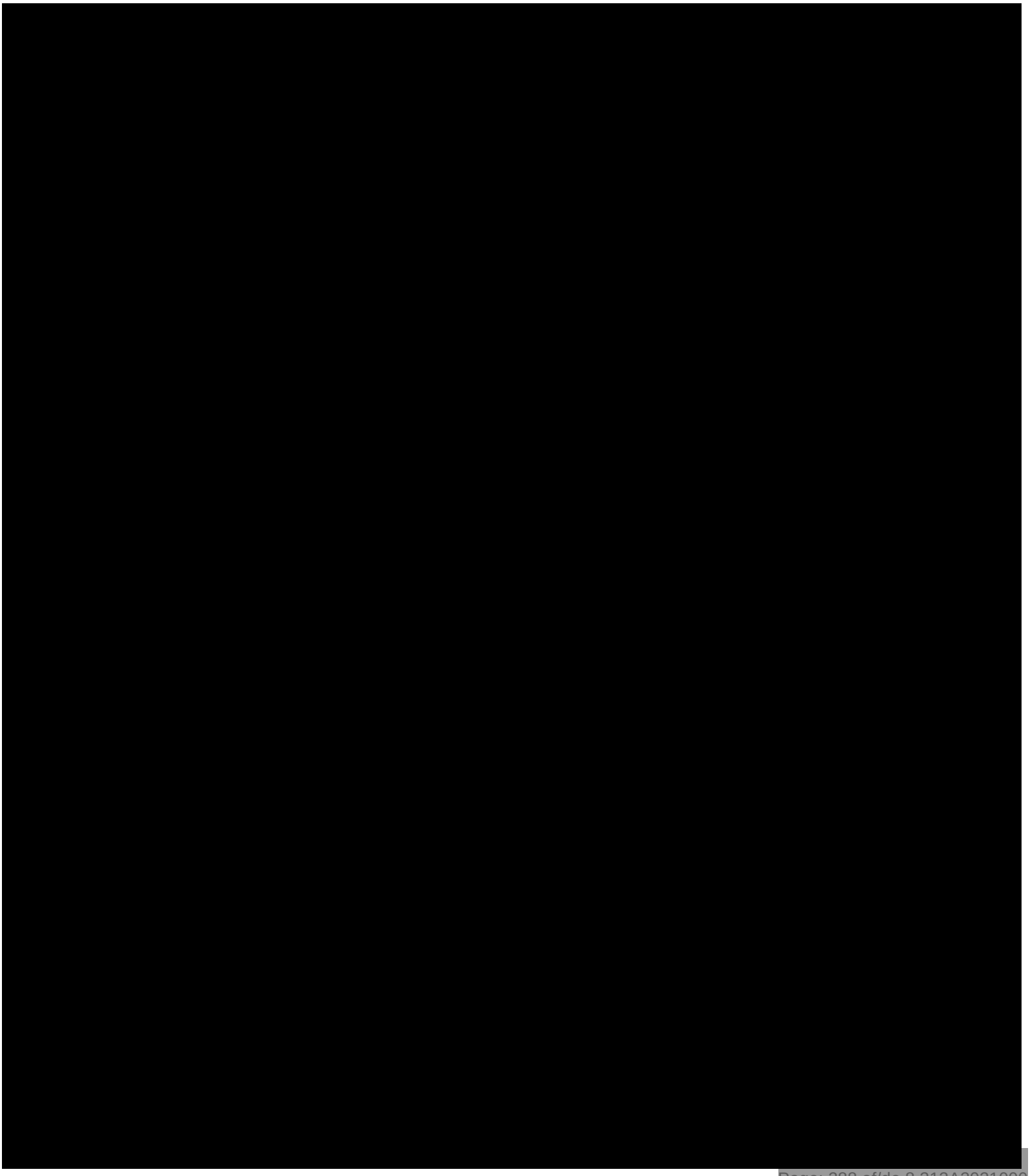

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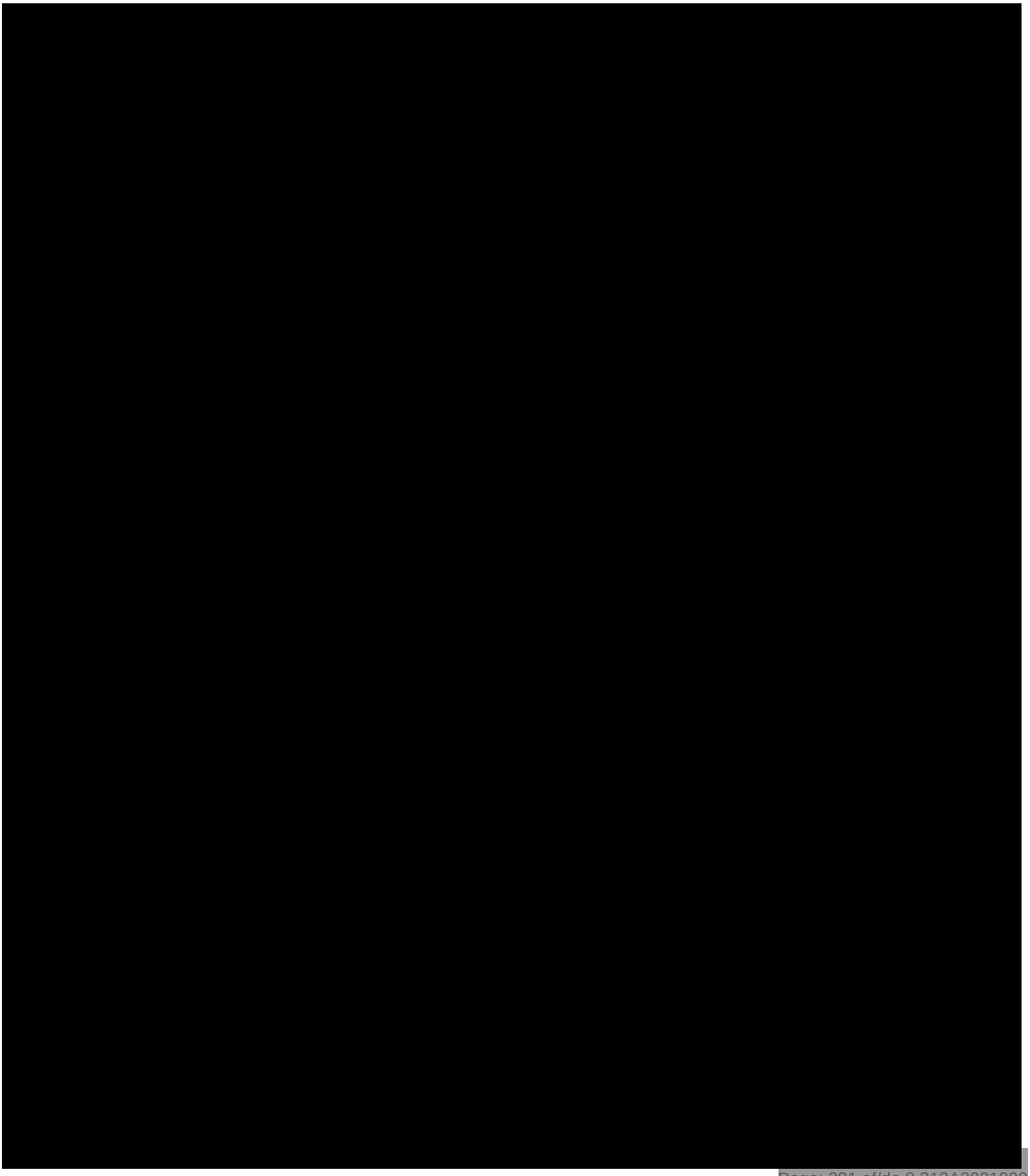

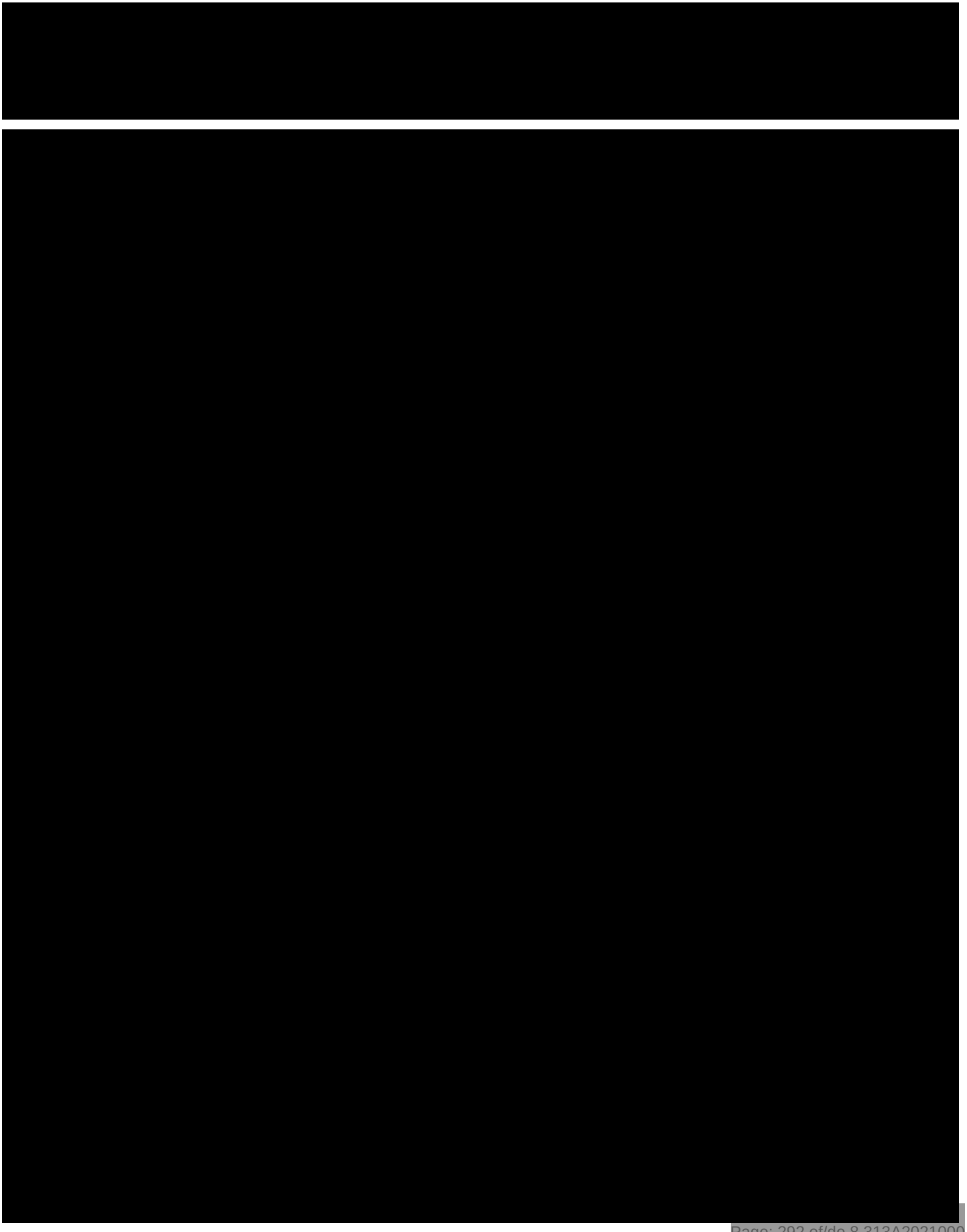

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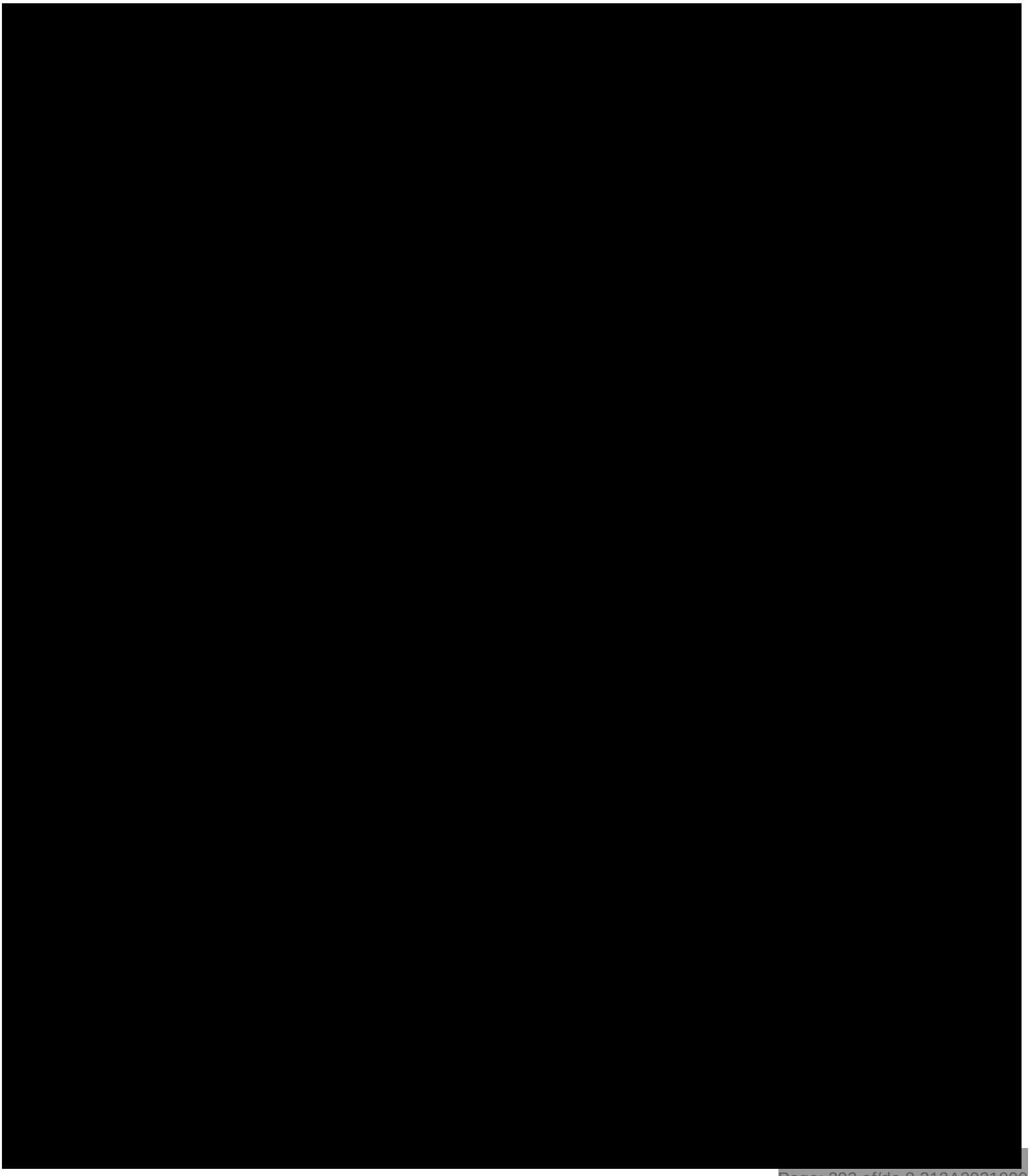

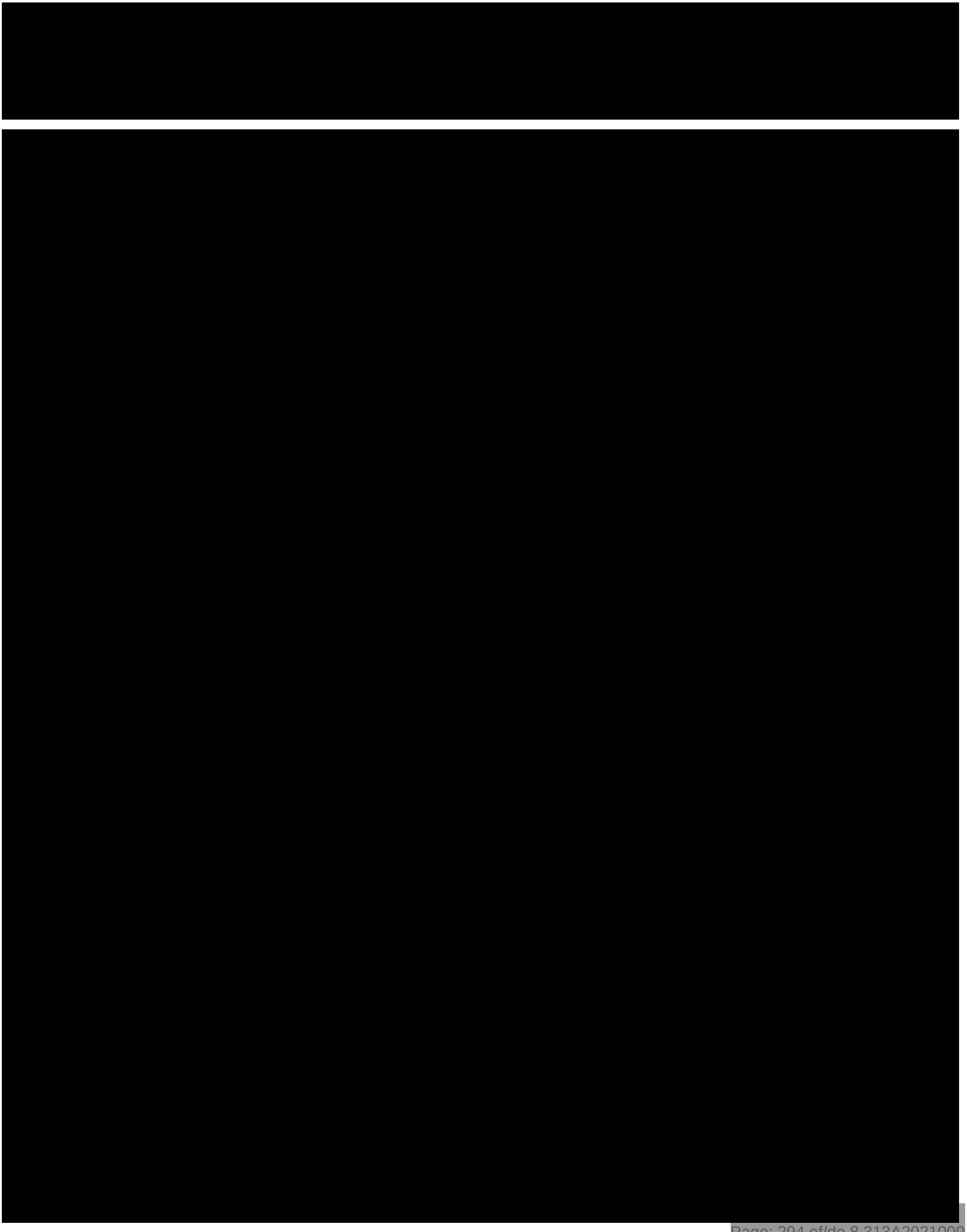

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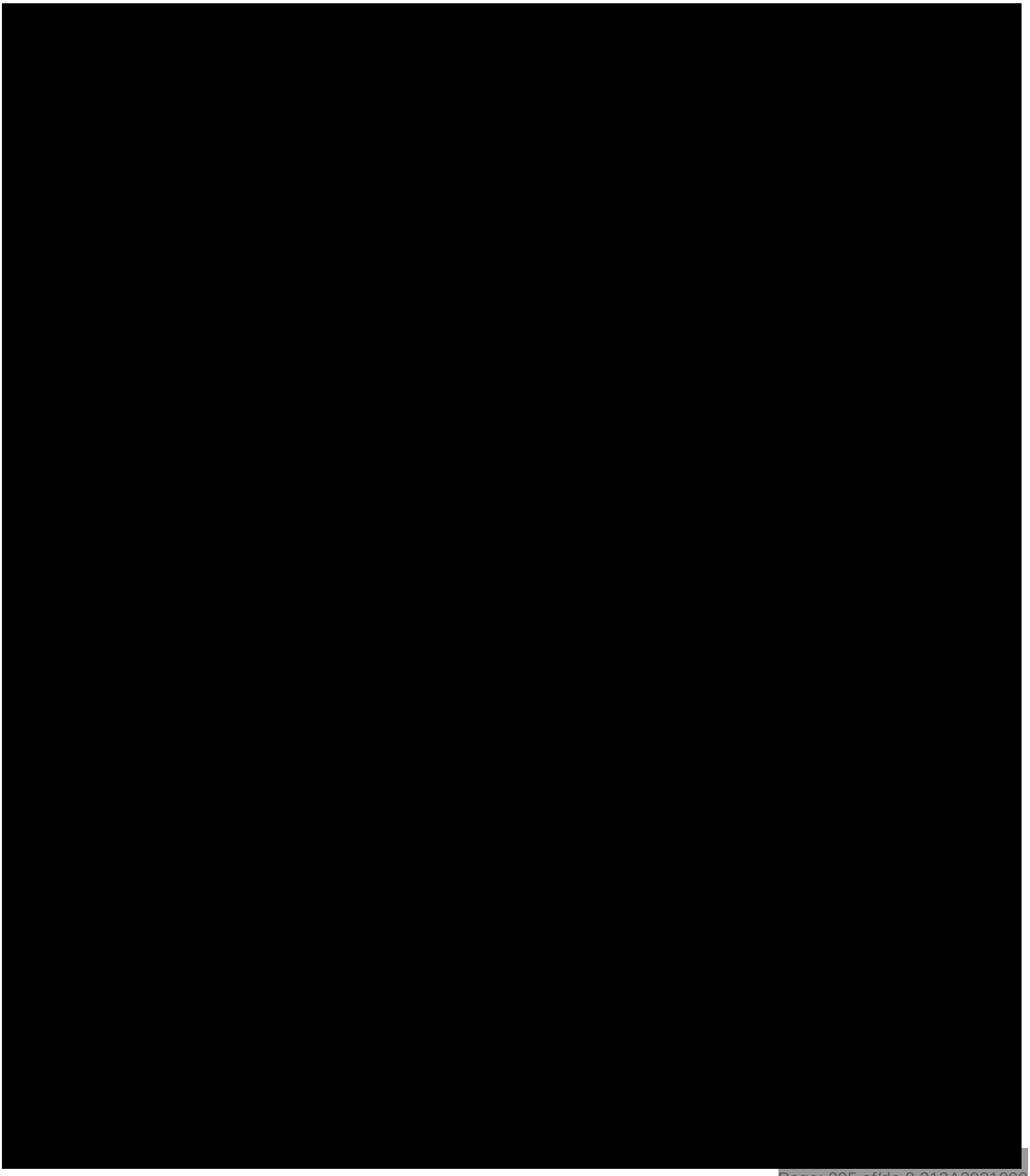

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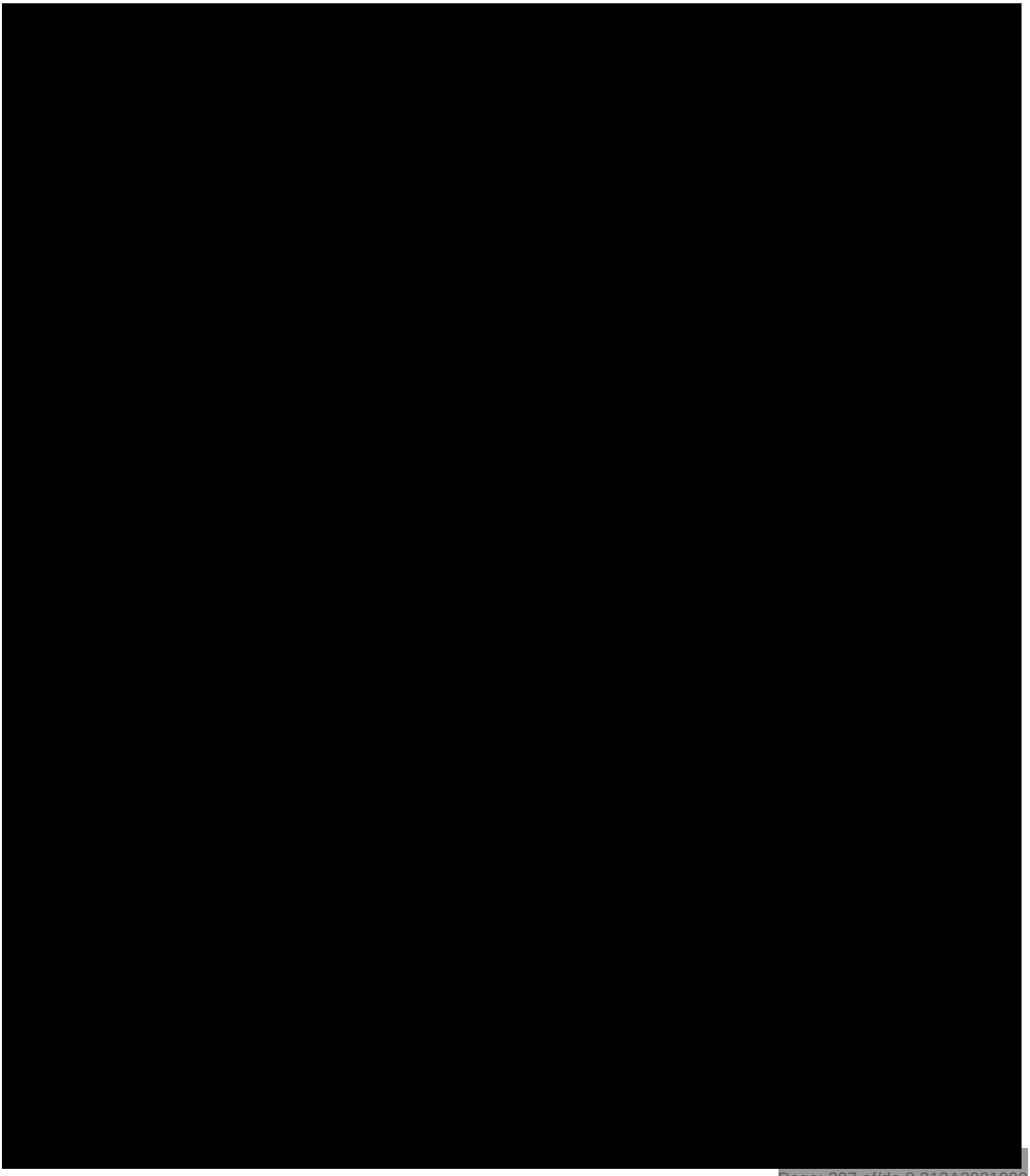

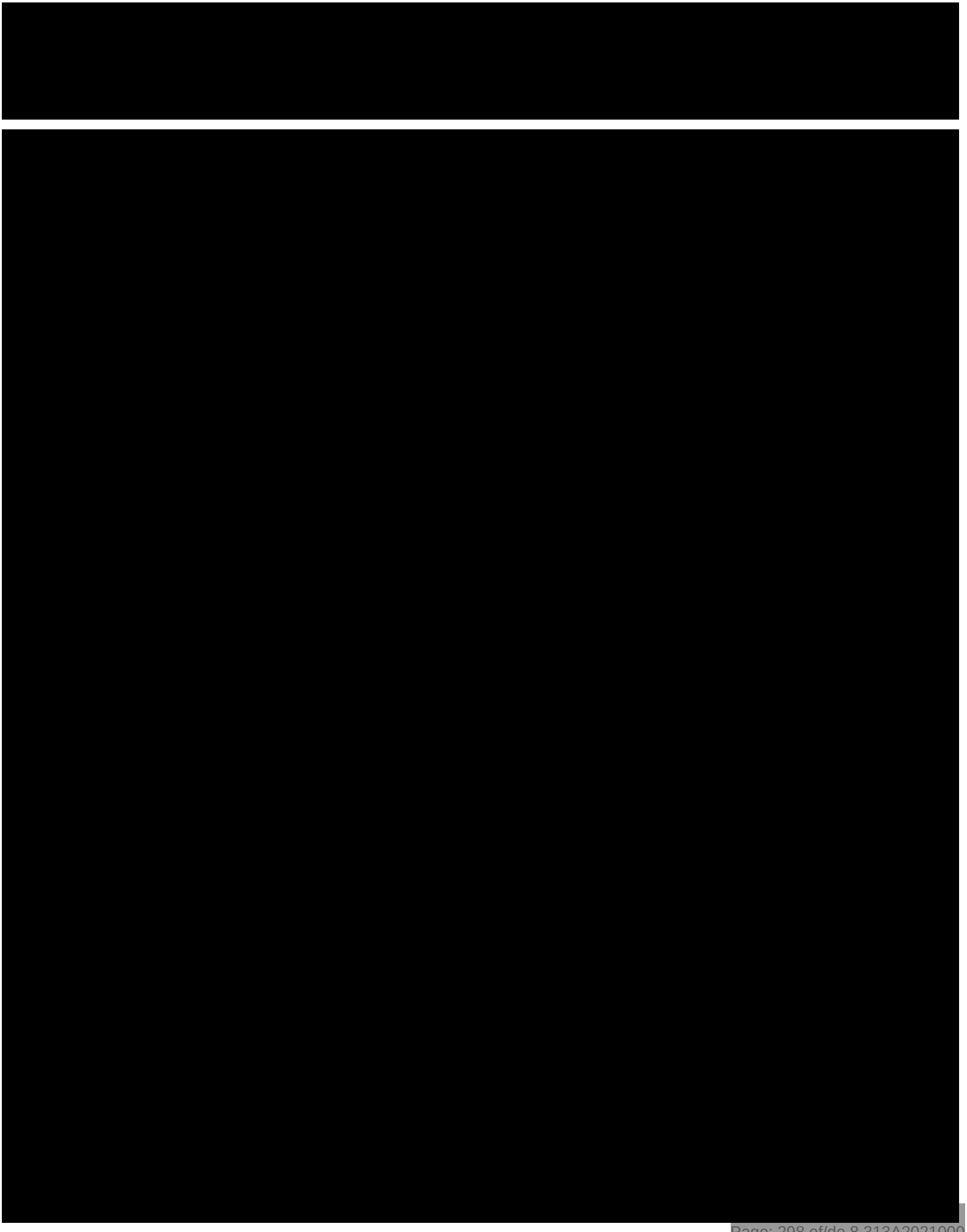

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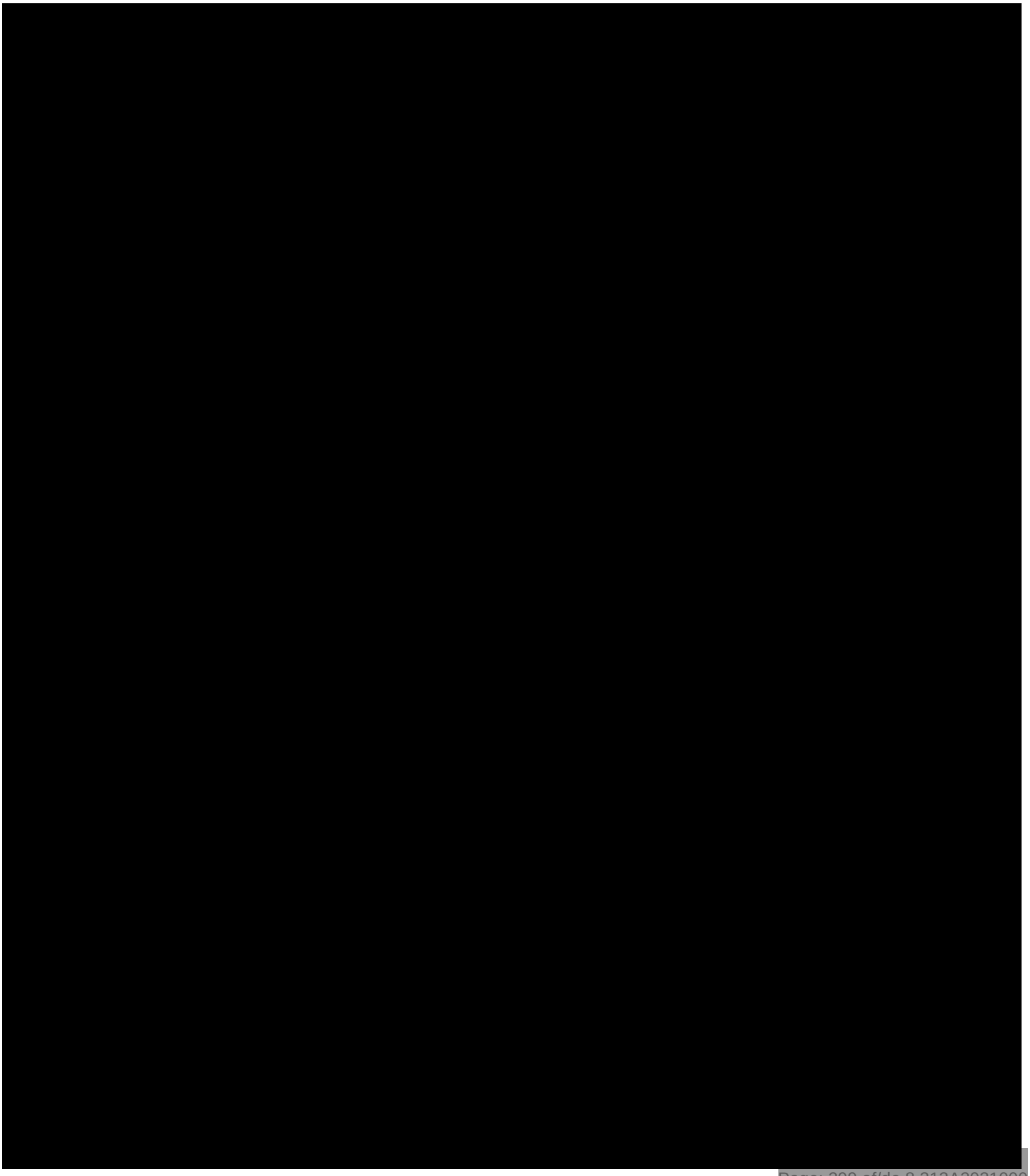

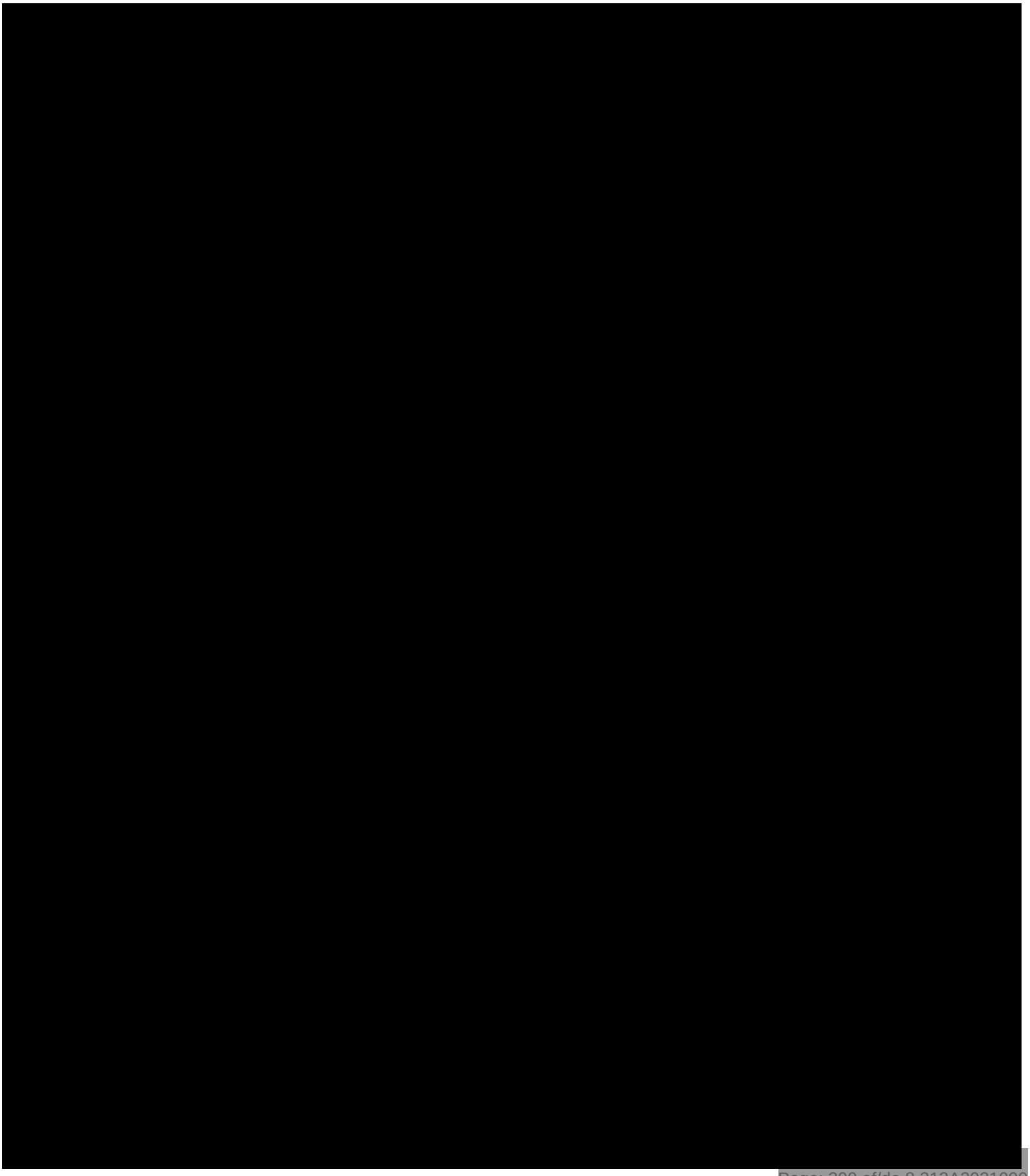

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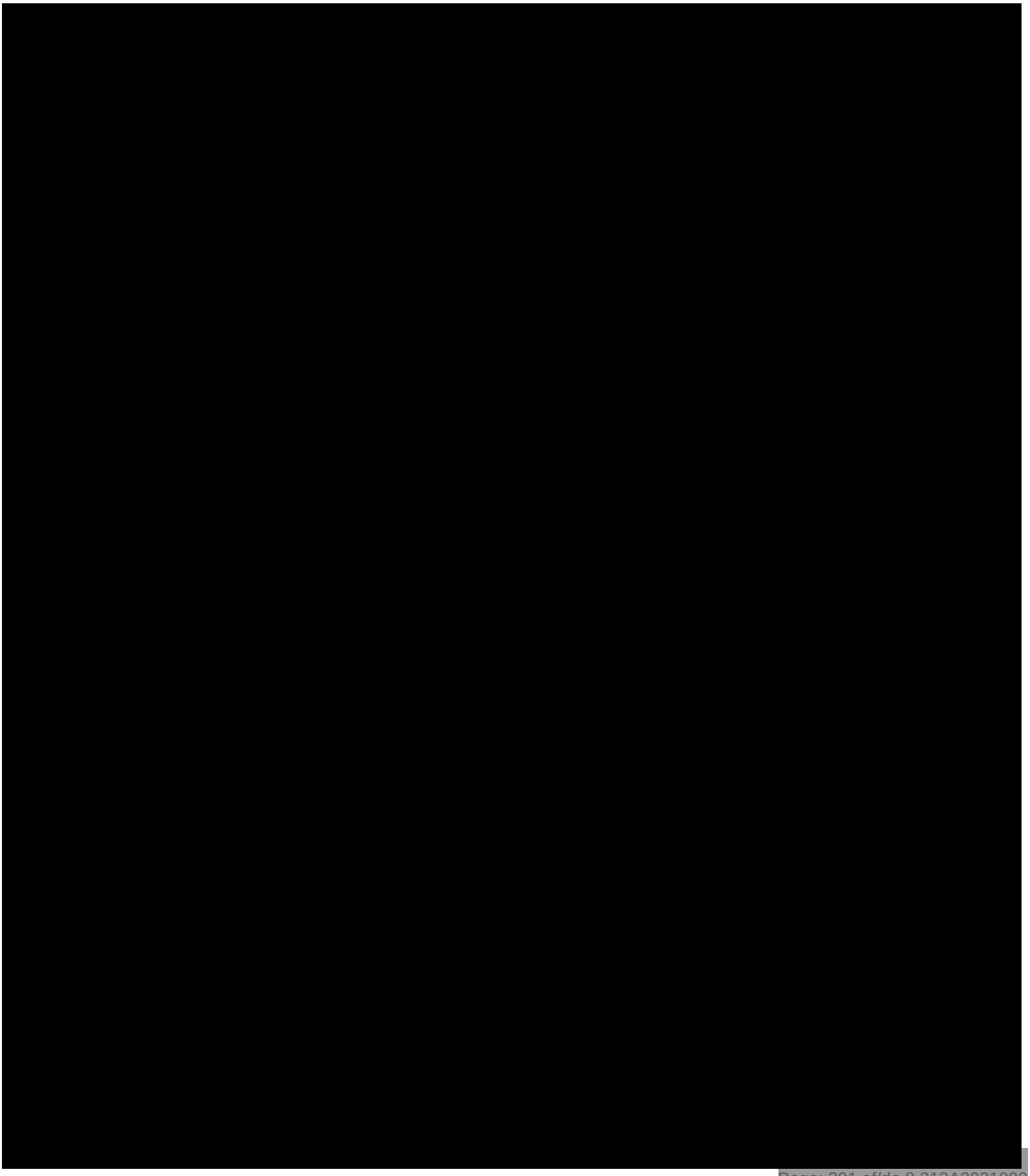

Miller, Kaitlin (PHAC/ASPC)

From: Thom, Alan (PHAC/ASPC)
Sent: 2021-01-28 6:38 PM
To: VRAT Contract Support / GTDV Soutient En Contrat (PHAC/ASPC)
Cc: Chalhoub, Isabelle (PHAC/ASPC)
Subject: RE: Novavax Advance Payment Invoice - Canada

Sorry for the delay. The invoice is in accordance with the provisions of the contract and can go for Section 34.

Alan Thom
Manager, Vaccine Supply & Assurance
Immunization Programs and Pandemic Preparedness Division / Division des programmes d'immunisation et de la préparation en cas de pandémie
Centre for Immunization & Respiratory Infectious Diseases (CIRID)
PUBLIC HEALTH AGENCY OF CANADA | AGENCE DE LA SANTÉ PUBLIQUE DU CANADA
130 Colonnade Road, Room/pièce 159A-01, Ottawa, ON K1A 0K9
Phone | Téléphone: **613 222-4614**

alan.thom@canada.ca

From: Miller, Kaitlin (PHAC/ASPC) <kaitlin.miller@canada.ca> **On Behalf Of** VRAT Contract Support / GTDV Soutient En Contrat (PHAC/ASPC)
Sent: 2021-01-28 9:38 AM
To: Thom, Alan (PHAC/ASPC) <alan.thom@canada.ca>
Cc: Chalhoub, Isabelle (PHAC/ASPC) <isabelle.chalhoub@canada.ca>
Subject: RE: Novavax Advance Payment Invoice - Canada
Importance: High

Hello,

Could you please confirm invoice for advanced payment?

The vendor code has been updated and Accounting has the invoice in the system. Once I have invoice confirmation I can verify for Roman to approve for Section 34.

Thanks,
Kaitlin

From: Miller, Kaitlin (PHAC/ASPC) **On Behalf Of** VRAT Contract Support / GTDV Soutient En Contrat (PHAC/ASPC)
Sent: 2021-01-28 8:24 AM
To: Thom, Alan (PHAC/ASPC) <alan.thom@canada.ca>
Subject: RE: Novavax Advance Payment Invoice - Canada

Hi Alan,

[redacted]

In the mean time, could you please confirm invoice for advanced payment?

Thank you,
Kaitlin

From: Thom, Alan (PHAC/ASPC) <alan.thom@canada.ca>
Sent: 2021-01-27 11:11 PM
To: VRAT Contract Support / GTDV Soutient En Contrat (PHAC/ASPC) <phac.VRAT.Contract.aspc@canada.ca>
Subject: FW: Novavax Advance Payment Invoice - Canada

[redacted]

Alan Thom
Manager, Vaccine Supply & Assurance
Immunization Programs and Pandemic Preparedness Division / Division des programmes d'immunisation et de la préparation en cas de pandémie
Centre for Immunization & Respiratory Infectious Diseases (CIRID)
PUBLIC HEALTH AGENCY OF CANADA | AGENCE DE LA SANTÉ PUBLIQUE DU CANADA
130 Colonnade Road, Room/pièce 159A-01, Ottawa, ON K1A 0K9
Phone | Téléphone: **613 222-4614**

alan.thom@canada.ca

From: [redacted]
Sent: 2021-01-27 3:38 PM
To: 'Kurt.Young@tpsgc-pwgsc.gc.ca' <Kurt.Young@tpsgc-pwgsc.gc.ca>; Thom, Alan (PHAC/ASPC) <alan.thom@canada.ca>; P2P East Invoices / Factures est (HC/SC) <hc.p2p.east.invoices-factures.est.sc@canada.ca>

Cc: [redacted]

Subject: Novavax Advance Payment Invoice - Canada

Hello Kurt and Alan,

[redacted] We ask that you please reply confirming your receipt of this invoice.

A physical copy of the attached invoice will also be mailed to the Public Health Agency of Canada address indicated on the invoice. Please contact us should any questions arise.

Thank you,

[redacted]

NOVAVAX

Creating Tomorrow's Vaccines Today

21 Firstfield Rd.
Gaithersburg, MD 20878
www.novavax.com

NOVAVAX
Creating Tomorrow's Vaccines Today

INVOICE

21 Firstfield Road
Gaithersburg, MD 20878
T 240-268-2000
[redacted]

Invoice Number: CANADA 00001

Bill To: Public Health Agency of Canada
P2P Invoices
200 Eglantine Driveway
Jeanne Mance Building
18th Floor, RM 1855C
Ottawa, Ontario
K1A OK9

Invoice Date: January 27, 2021

Customer ID: CANAD001

Contract Number: H1020-203683/001/PH
Client Reference Number: In Progress
Procurement Business Number [redacted]
Financial Code: 1480-234000-57502-2269118-TF01

Item	Description	Quantity	Amount	VAT Amount	Total
	NVX-CoV2373 Advance Payment	1	[redacted]		
Total					

Payment Terms: Net 30 days

0% Dutch VAT – export supply (Article 146 EU VAT Directive)

Wiring Instructions:

Remittance email: [redacted]
Email: [redacted]

[redacted]

For Novavax, Inc.

Investment Advisor Services
425 Walnut Street
Cincinnati, OH 45202

usbank.com

Please accept the funding instructions to send money to the account for NOVAVAX INC. custodied at US Bank, N.A..

[redacted]

Please let me know if you have questions. Thank you!

ibrahima kane

[redacted]

From: Lourenco, Celia (HC/SC)
To: [redacted]
Cc: [redacted] Hardy, Stephanie (HC/SC)
Subject: RE: Novavax COVID-19 US Phase 3 Data - Confidential
Date: 2021-06-14 10:54:00 AM

Dear [redacted]
Thank you very much for this update, with seemingly very positive results. We look forward to receiving the data package to review in detail, and will certainly be in touch with any questions.
With best regards,
Celia
Celia Lourenco, PhD
Director General / Directrice générale
Biologic and Radiopharmaceutical Drugs Directorate / Direction des médicaments biologiques et radiopharmaceutiques
Health Products and Food Branch / Direction générale des produits de santé et des aliments
Santé Canada / Health Canada
celia.lourenco@canada.ca
613-297-2532

From: [redacted]
Sent: 2021-06-13 11:50 PM
To: Lourenco, Celia (HC/SC)
Cc: [redacted]
Subject: Novavax COVID-19 US Phase 3 Data - Confidential
Dear Celia –
Novavax recently unblinded the US COVID-19 Phase 3 Clinical Study results, demonstrating 90% overall efficacy and 100% protection against moderate and severe disease. These results support the previously reported findings from the UK Phase 3 Study. The topline data will be announced early Monday morning (US time) [redacted] We would be pleased to set up a call to review the data in more detail following our announcement.
We appreciate your continued support of our program. Please let me know if you have any questions.
[redacted]
Novavax, Inc.
[redacted]

Bettle, Megan (HC/SC)

From: Bettle, Megan (HC/SC)
Sent: 2021-01-15 1:27 PM
To: [redacted]
Subject: RE: Health Canada - Introductions and Regulatory Strategy - agenda items

Hi [redacted]
I will be pulling some information together for Pierre Sabourin for this introductory conversation – please let me know if there are specific agenda items that you would like to include.
Thanks! megan
Megan Bettle, PhD
Director General, COVID-19 Regulatory Response Team
Health Products and Food Branch
Health Canada / Government of Canada
megan.bettle@canada.ca
Mobile: 613-793-6156

Megan Bettle, PhD
Directrice générale, Équipe d'intervention réglementaire de la COVID-19
Direction générale des produits de santé et des aliments
Santé Canada / Gouvernement du Canada
megan.bettle@canada.ca
Mobile: 613-793-6156

-----Original Appointment-----
From: Frank Czworka
Sent: 2021-01-14 1:29 PM
To: [redacted] Pierre (HC/SC); Lourenco, Celia (HC/SC); Bettle, Megan (HC/SC)
Subject: Health Canada - Introductions and Regulatory Strategy
When: 2021-01-19 12:30 PM-1:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: Microsoft Teams Meeting

Microsoft Teams meeting

Join on your computer or mobile app
Click here to join the meeting

Join with a video conferencing device
251959971@t.plcm.vc
Video Conference ID: [redacted]
Alternate VTC dialing instructions

Or call in (audio only)
+1 301-960-3919,,57212812# United States, Silver Spring
Phone Conference ID: [redacted]

Find a local number | Reset PIN

Learn More | Meeting options

From: Lourenco, Celia (HC/SC)
To: [redacted]
Subject: RE: Check in with Novavax
Date: 2021-01-27 5:03:00 PM
Attachments: image001.jpg

Sounds good, I didn't actually receive yours…

From: [redacted]
Sent: 2021-01-27 5:02 PM
To: Lourenco, Celia (HC/SC)
Subject: RE: Check in with Novavax

I will cancel mine then

From: Lourenco, Celia (HC/SC) <celia.lourenco@canada.ca>
Sent: Wednesday, January 27, 2021 4:59 PM
To: [redacted]
Subject: RE: Check in with Novavax

I will adjust for 30 min, starting at 8am. Celia

From: [redacted]
Sent: 2021-01-27 4:47 PM
To: Lourenco, Celia (HC/SC) <celia.lourenco@canada.ca>; [redacted] Hardy, Stephanie (HC/SC) <stephanie.hardy@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Rosu-Myles, Michael (HC/SC) <michael.rosu-myles@canada.ca>
Subject: RE: Check in with Novavax

Hi Celia – I sent out a meeting invitation from Novavax for 30 minutes.
Filip – Do you agree 30 minutes is sufficient time for this discussion?
Thanks,
[redacted]

-----Original Appointment-----
From: Lourenco, Celia (HC/SC) <celia.lourenco@canada.ca>
Sent: Wednesday, January 27, 2021 4:13 PM
To: [redacted] Hardy, Stephanie (HC/SC); Bouthillier, Leo (HC/SC); Rosu-Myles, Michael (HC/SC)
Subject: Check in with Novavax
When: Thursday, January 28, 2021 7:30 AM-8:30 AM (UTC-05:00) Eastern Time (US & Canada).
Where: Microsoft Teams Meeting

Microsoft Teams meeting

Join on your computer or mobile app
Click here to join the meeting

Or call in (audio only)
+1 647-557-1930,,872560129# Canada, Toronto
Phone Conference ID: [redacted]
Find a local number | Reset PIN

Learn More | Meeting options

Bettle, Megan (HC/SC)

From: [redacted]
Sent: 2021-01-30 10:06 AM
To: Bettle, Megan (HC/SC)
Cc: [redacted]
Subject: Re: Listing of submission

Thank you for the notice Megan. Have a great weekend.
[redacted]

Get Outlook for iOS

From: Bettle, Megan (HC/SC)
Sent: Saturday, January 30, 2021 9:44:34 AM
To: [redacted]
Subject: Listing of submission

[SENDER IS EXTERNAL TO NOVAVAX]

[redacted] I wanted to let you know that HC is posting receipt of the Novavax submission on our list of Covid submissions received, as we have done with all submissions.

There will be no social media or additional communications from the regulatory side on this.

Please let me know if there are any questions.

Thx, Megan

Sent from my iPhone

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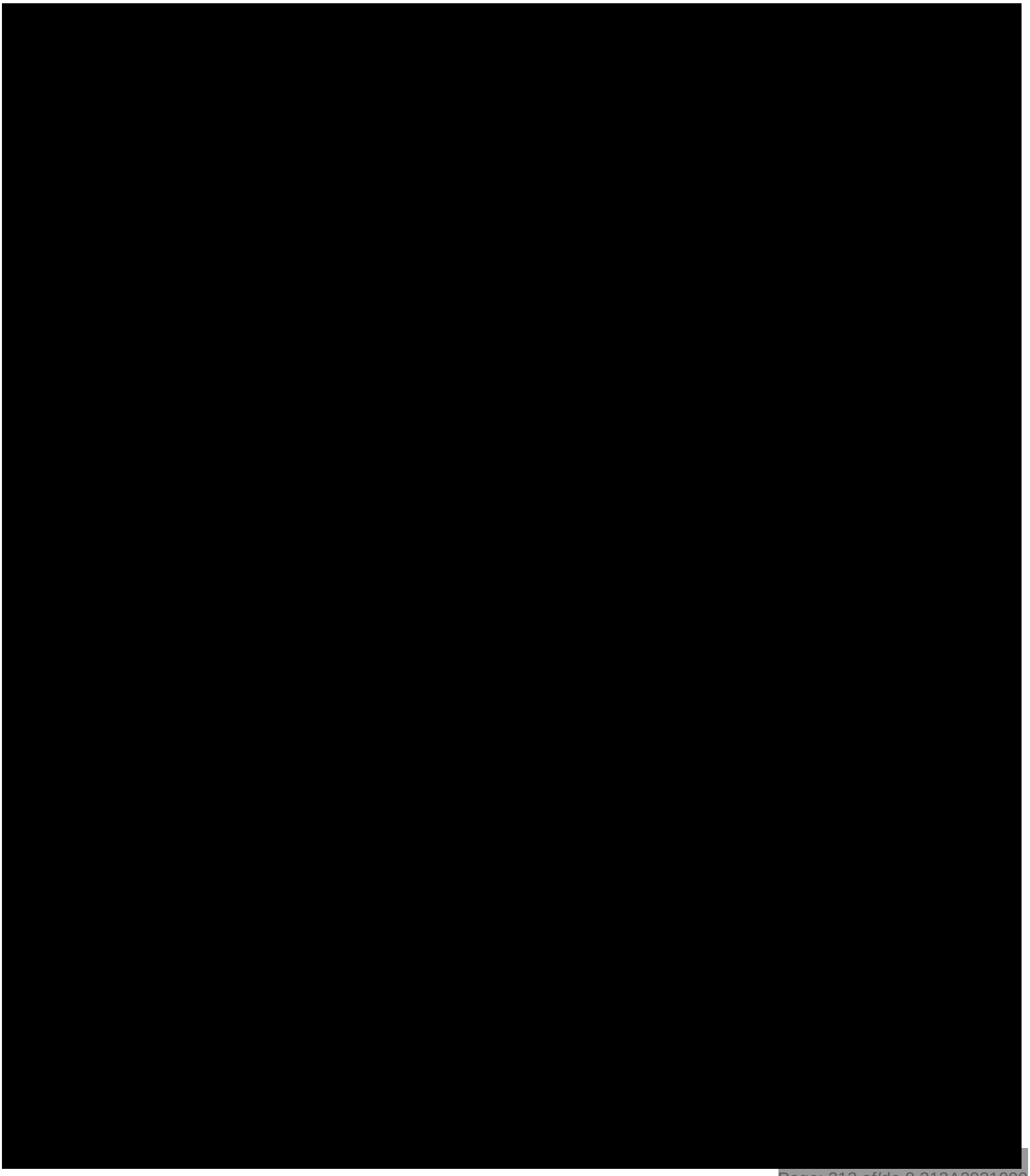

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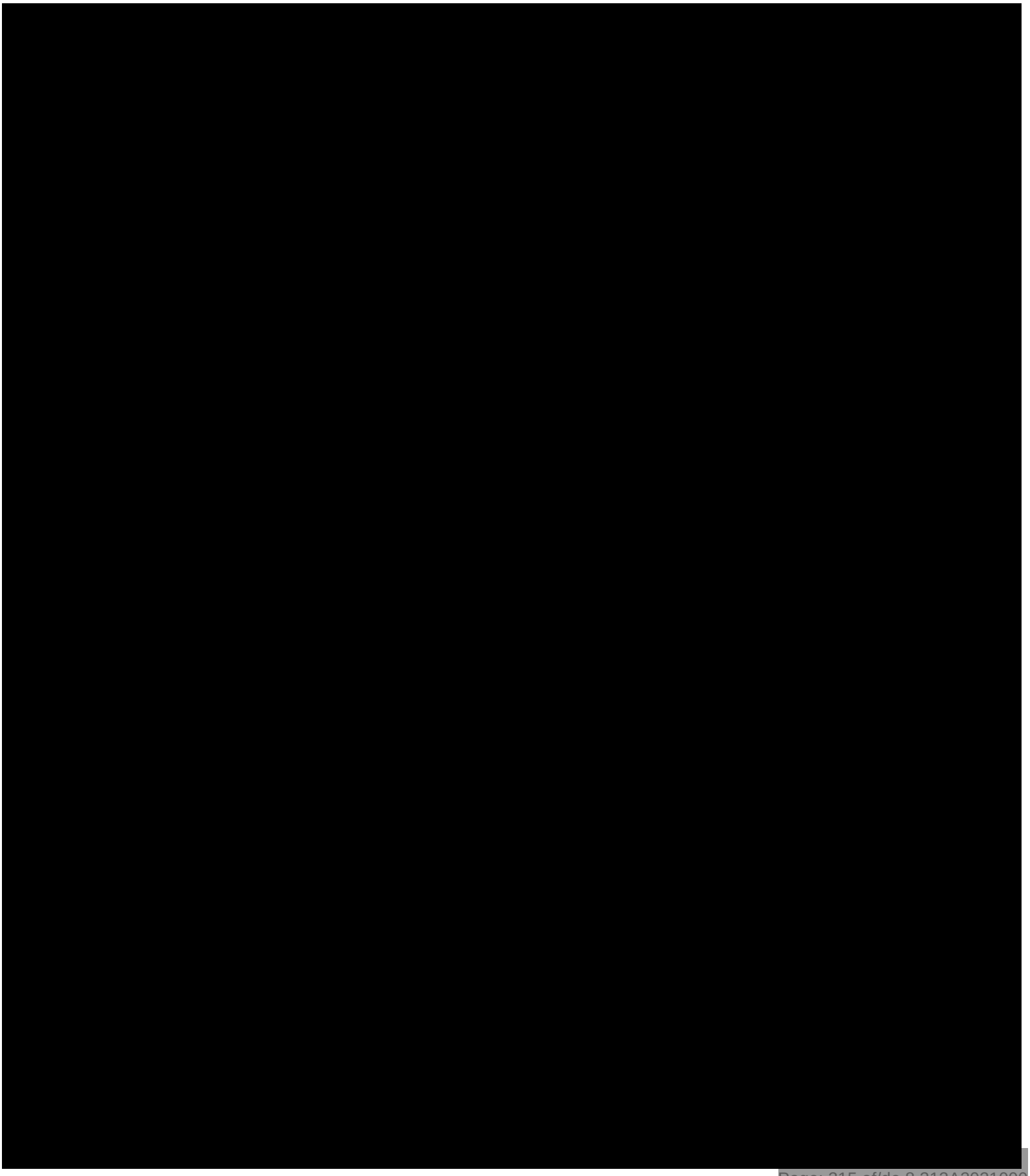

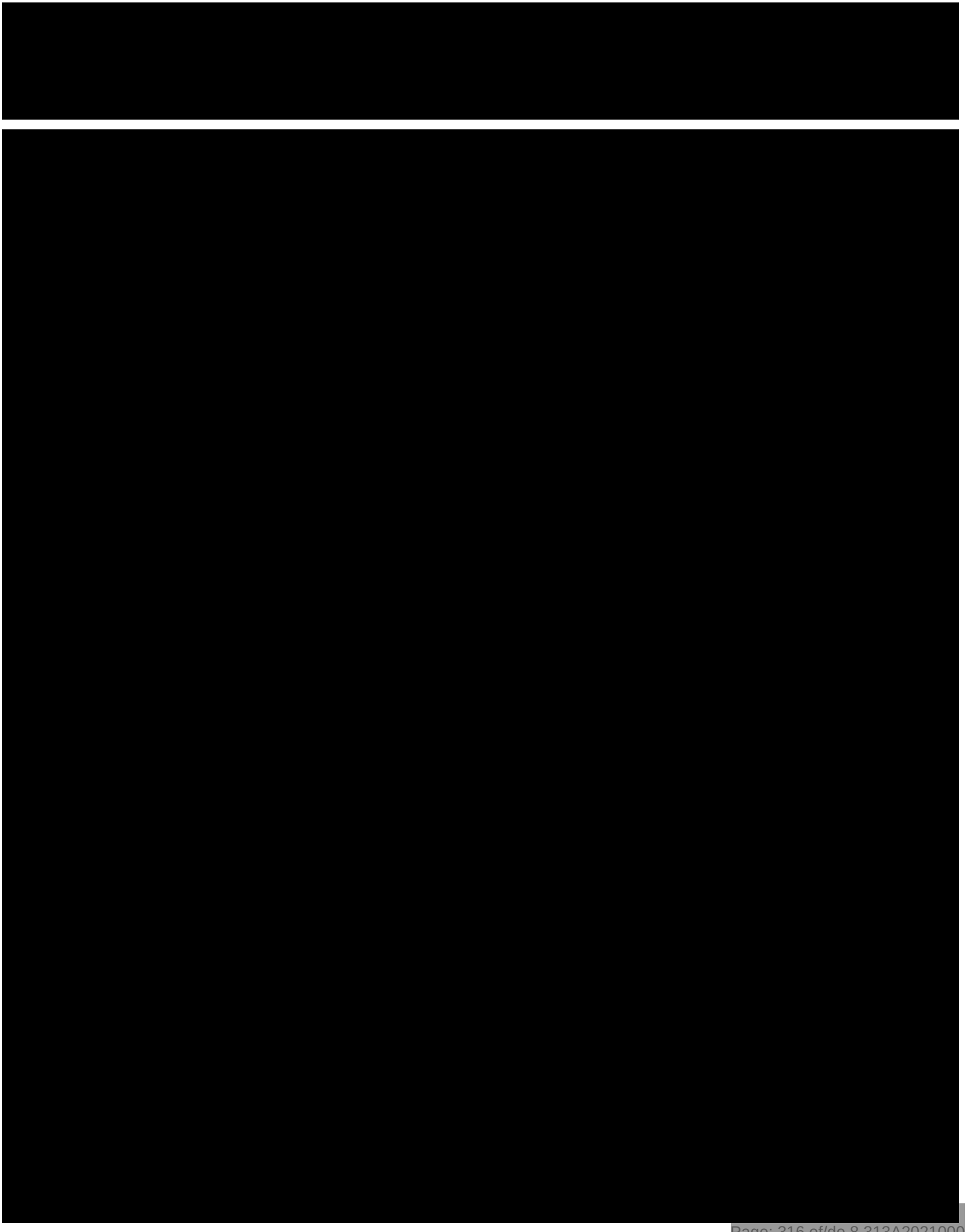

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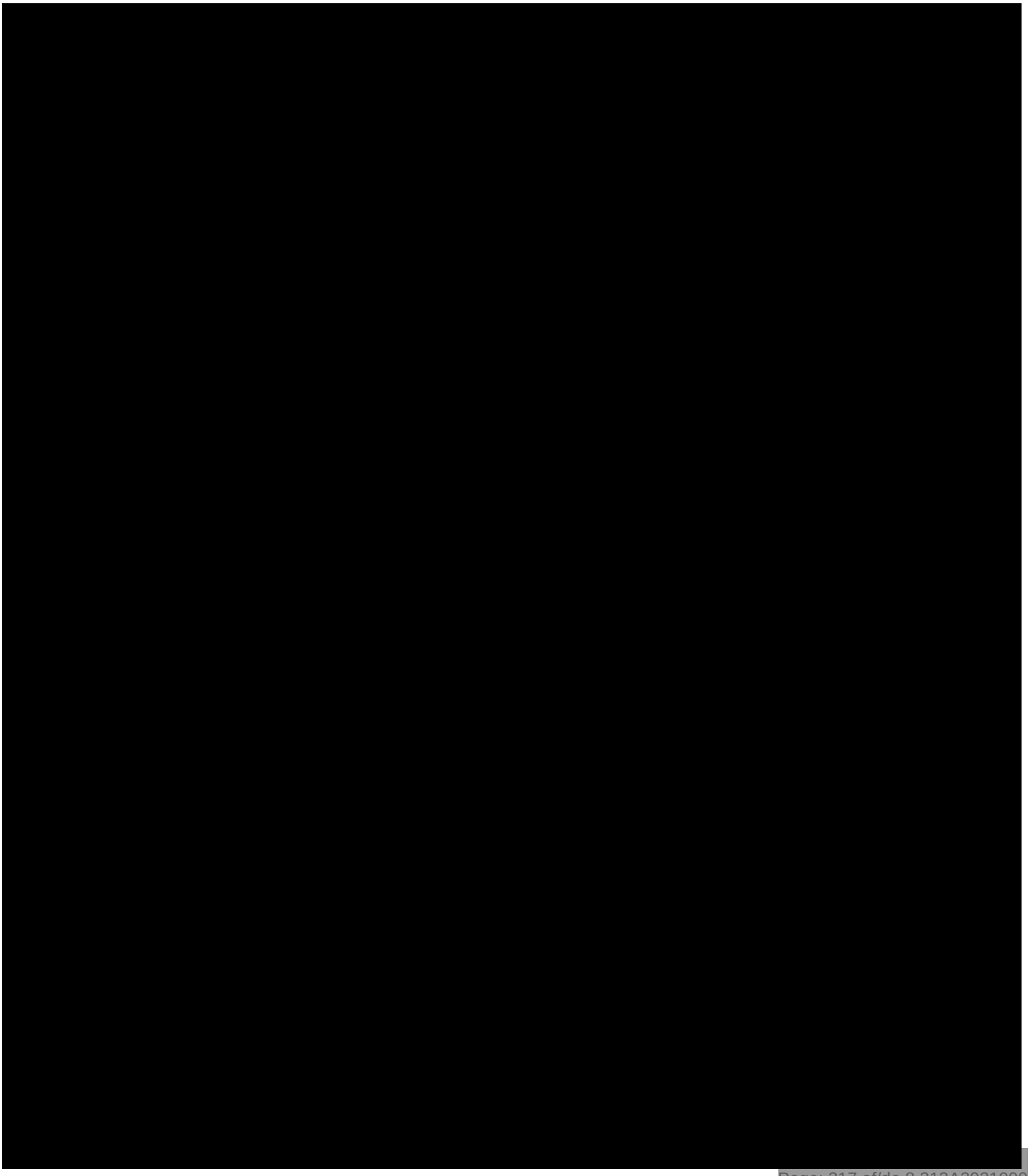

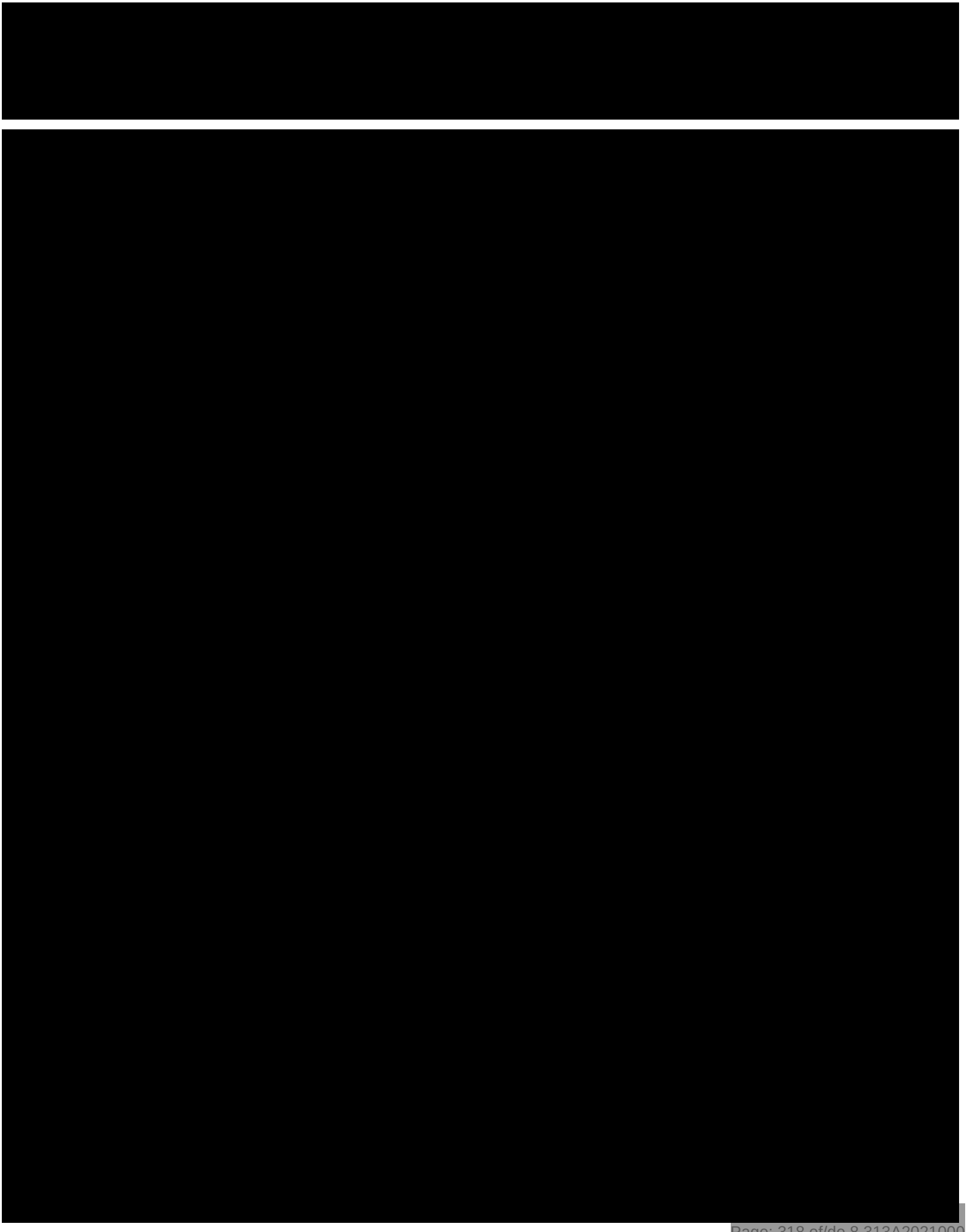

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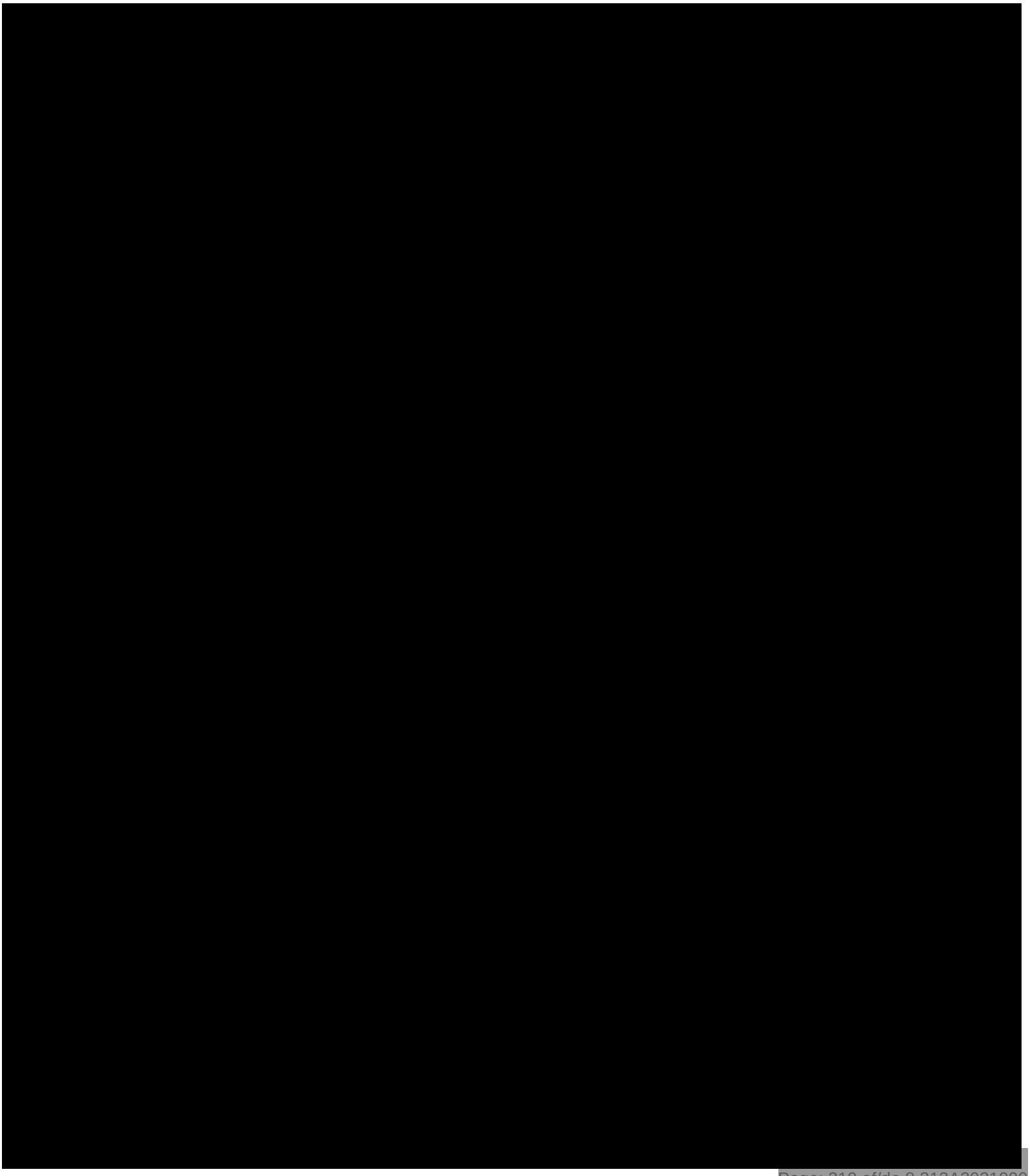

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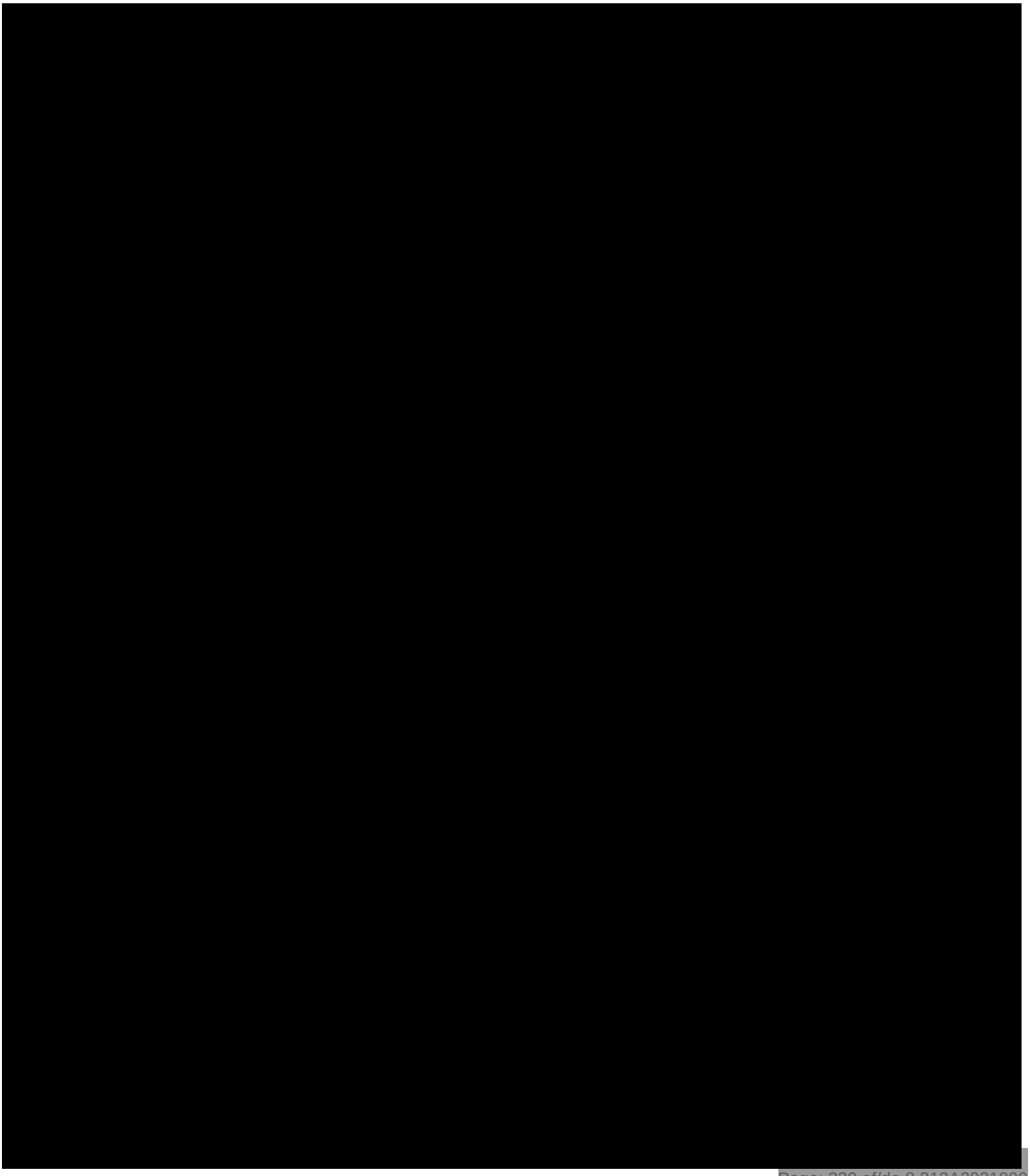

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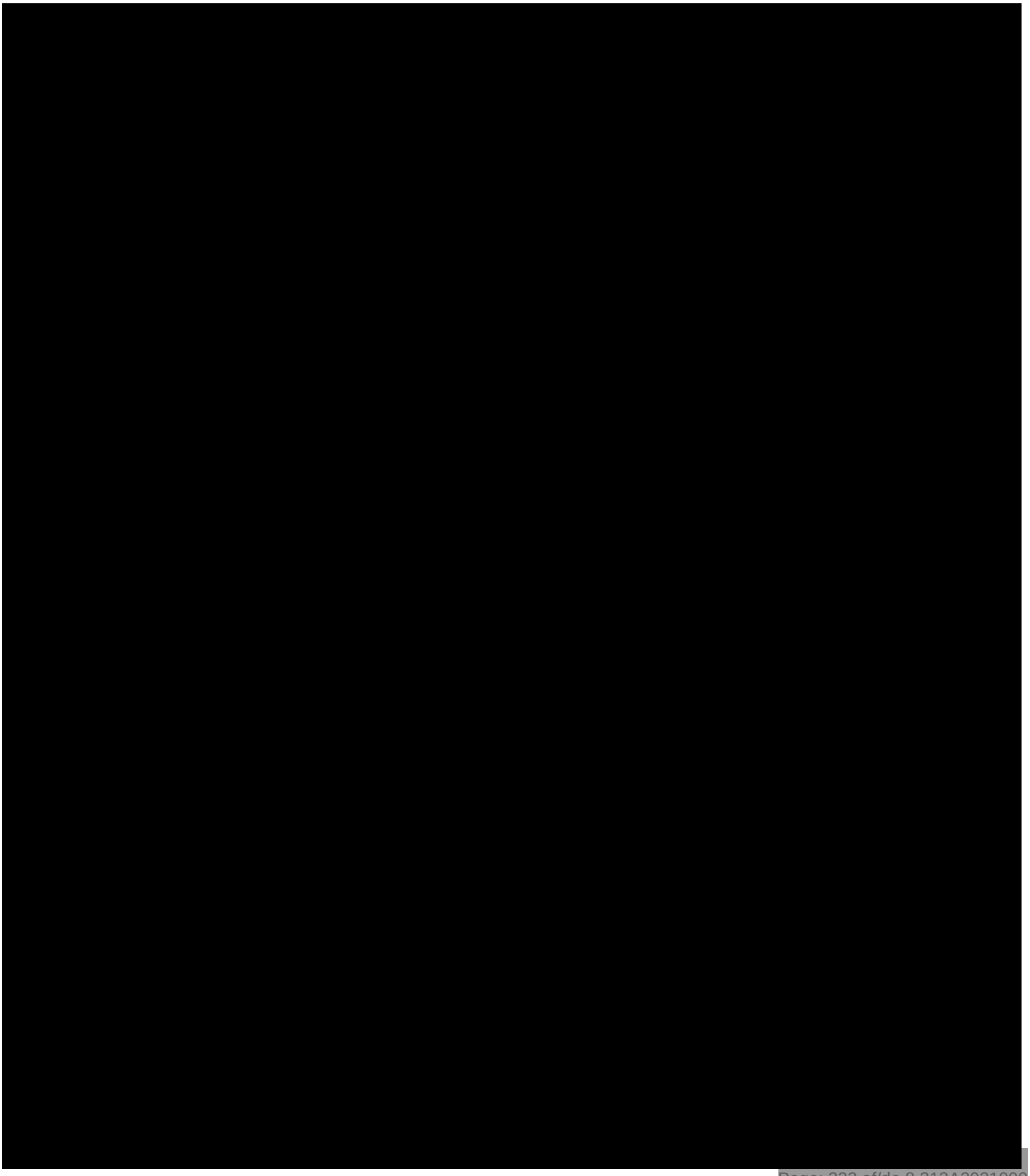

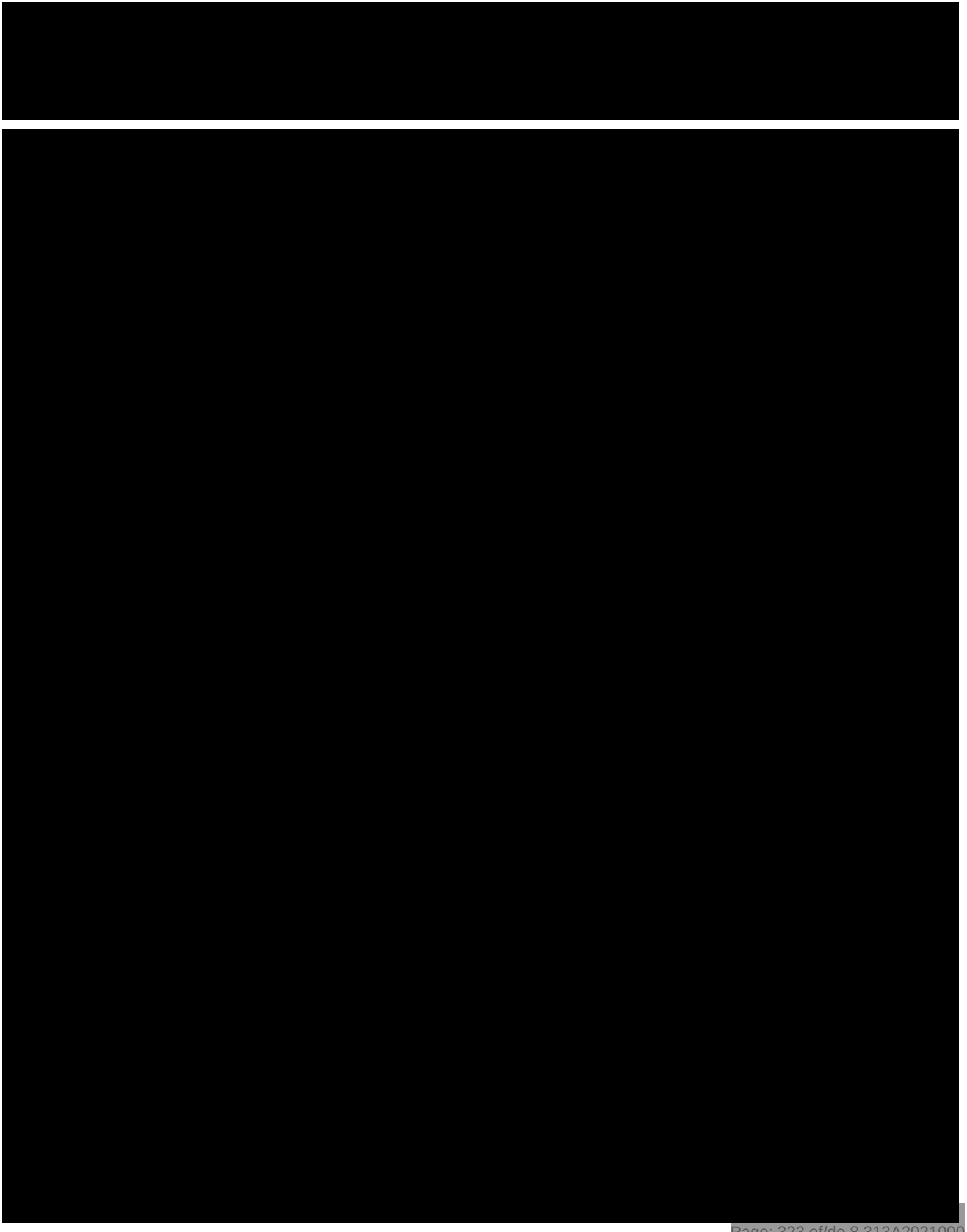

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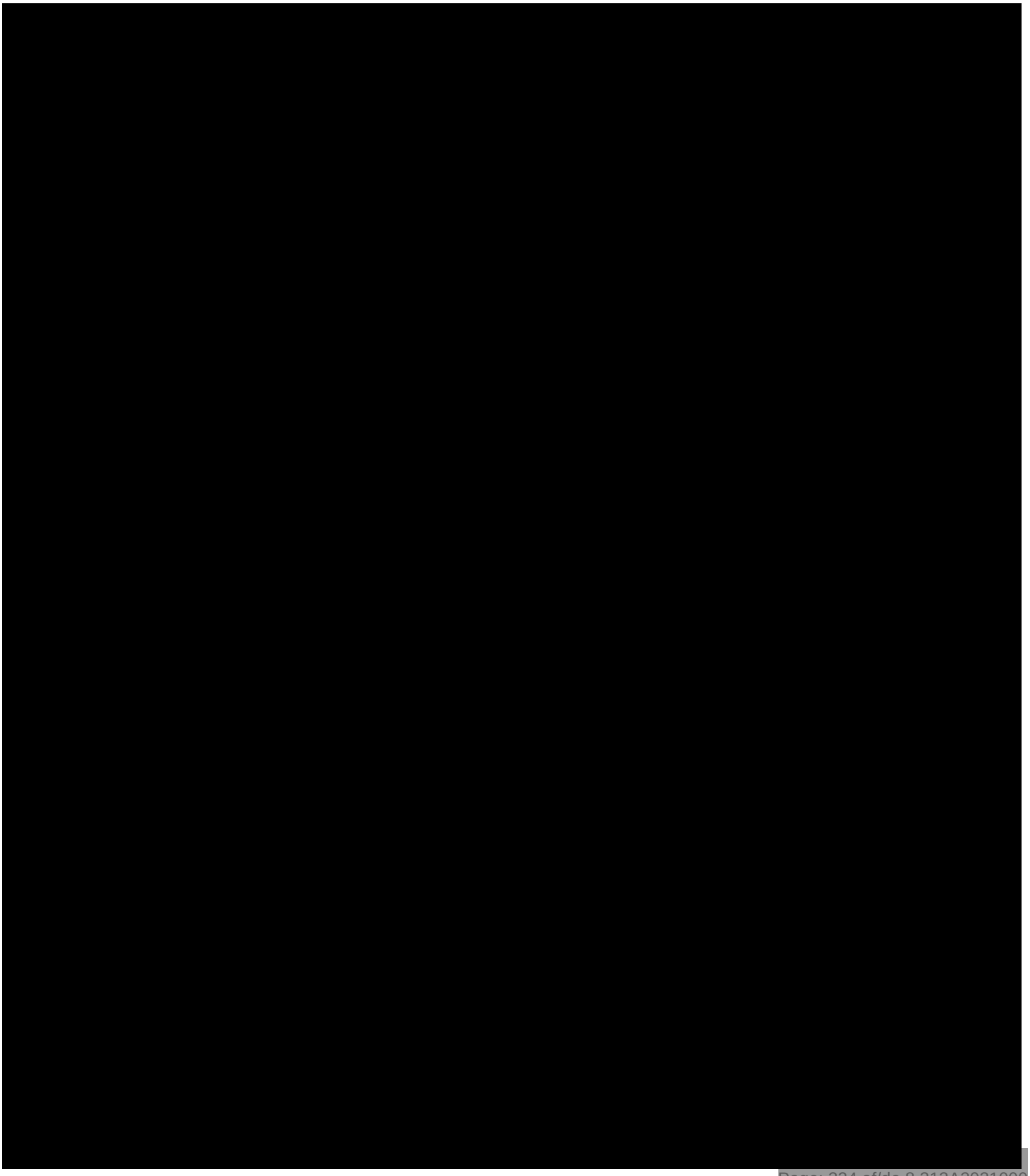

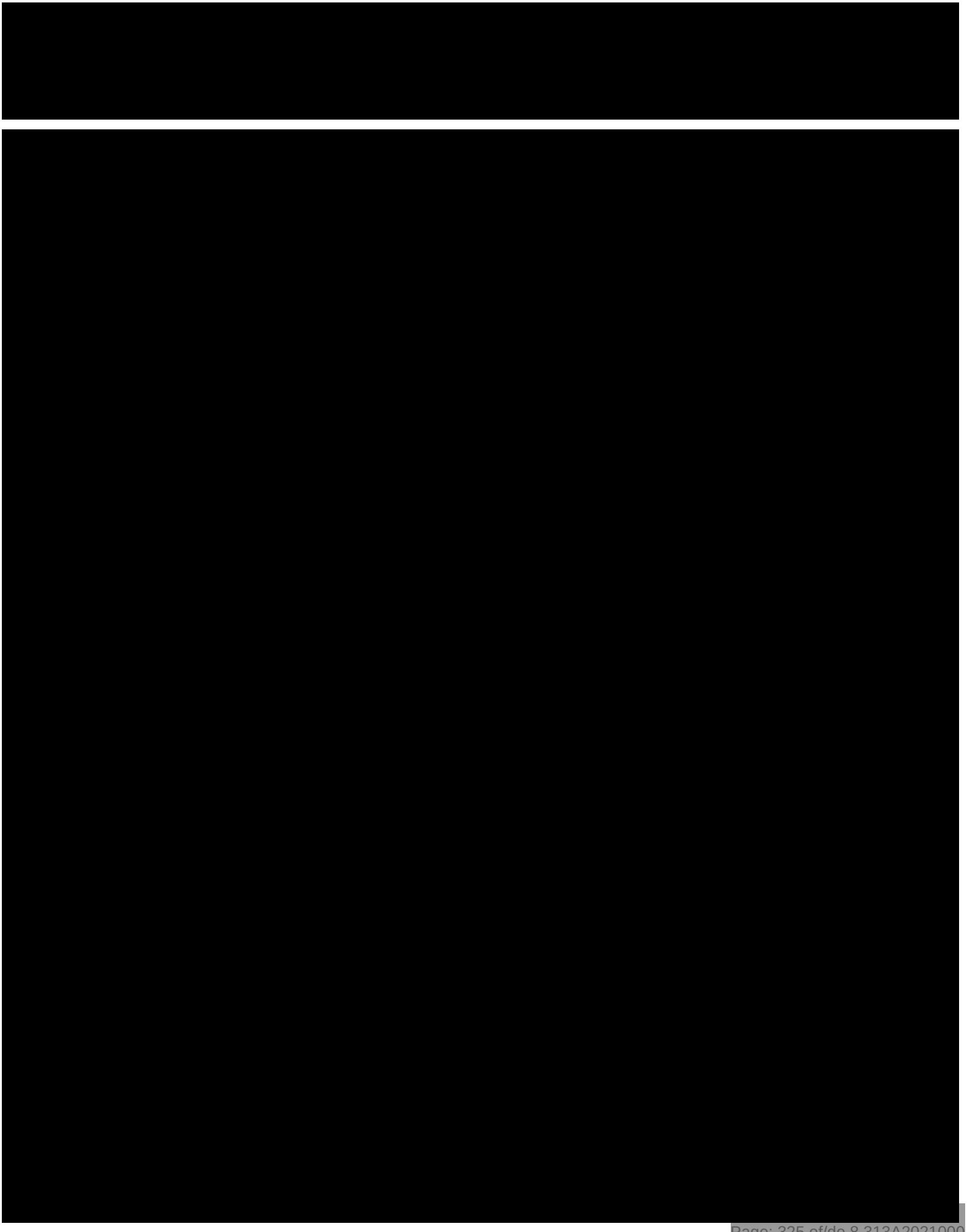

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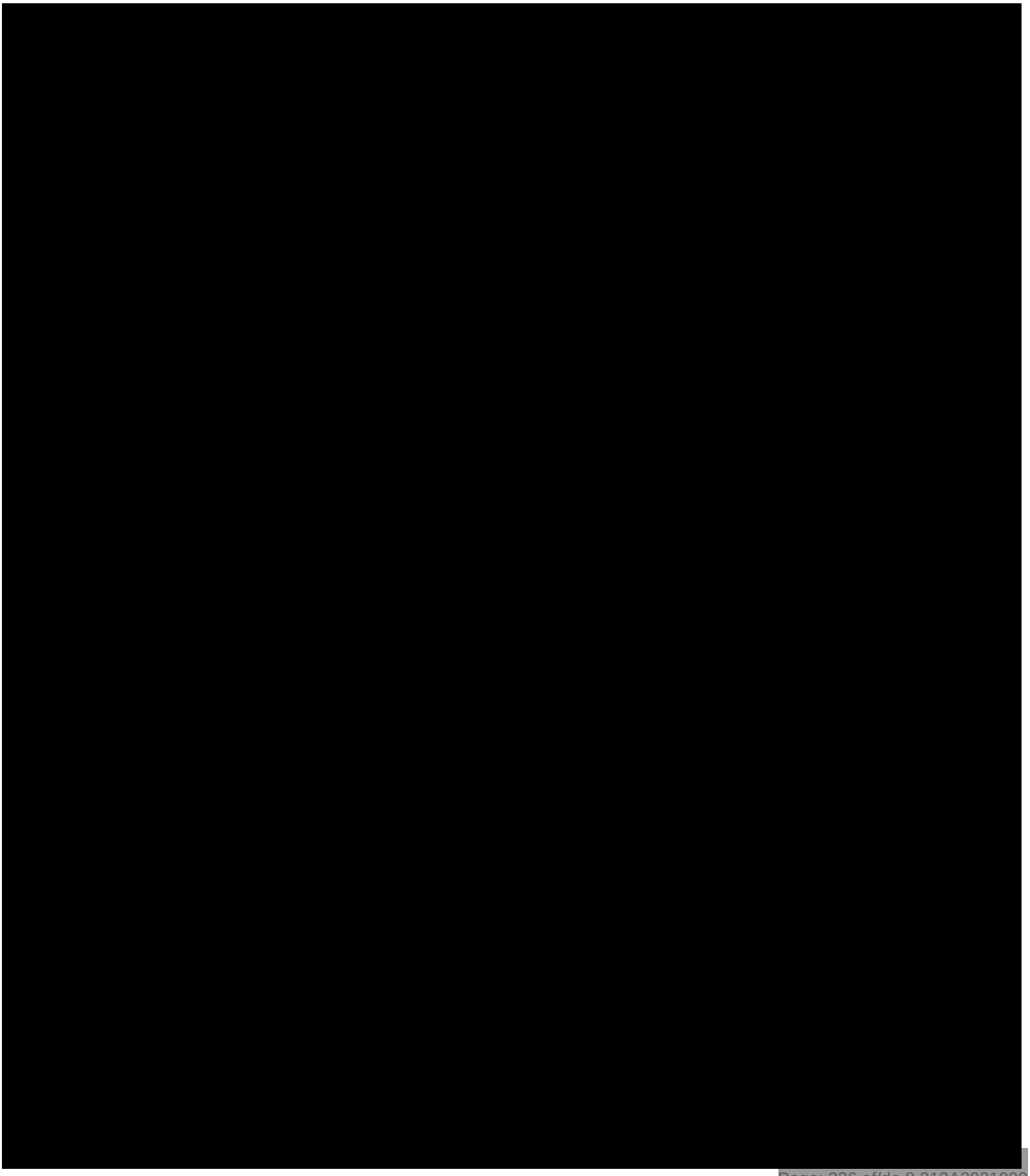

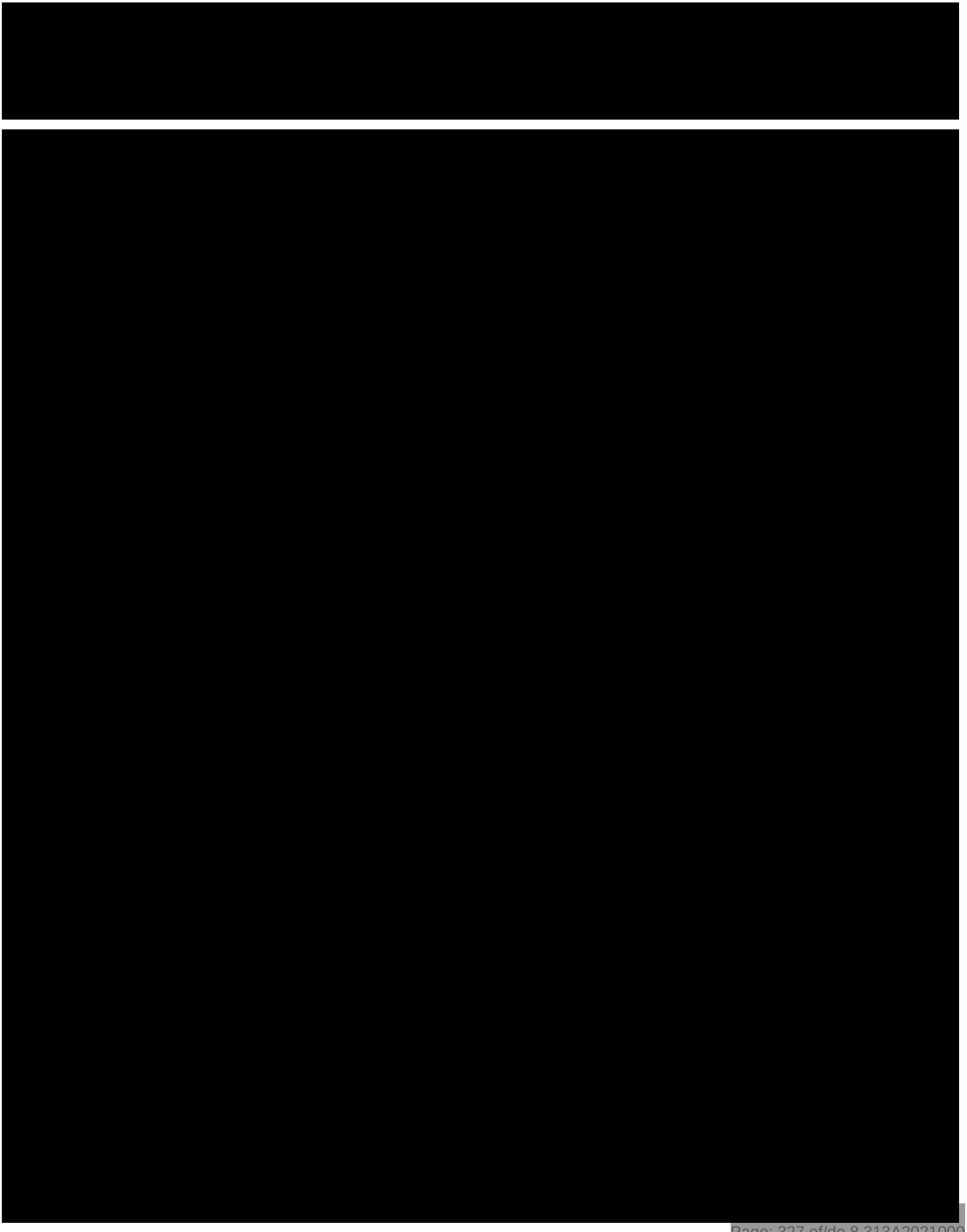

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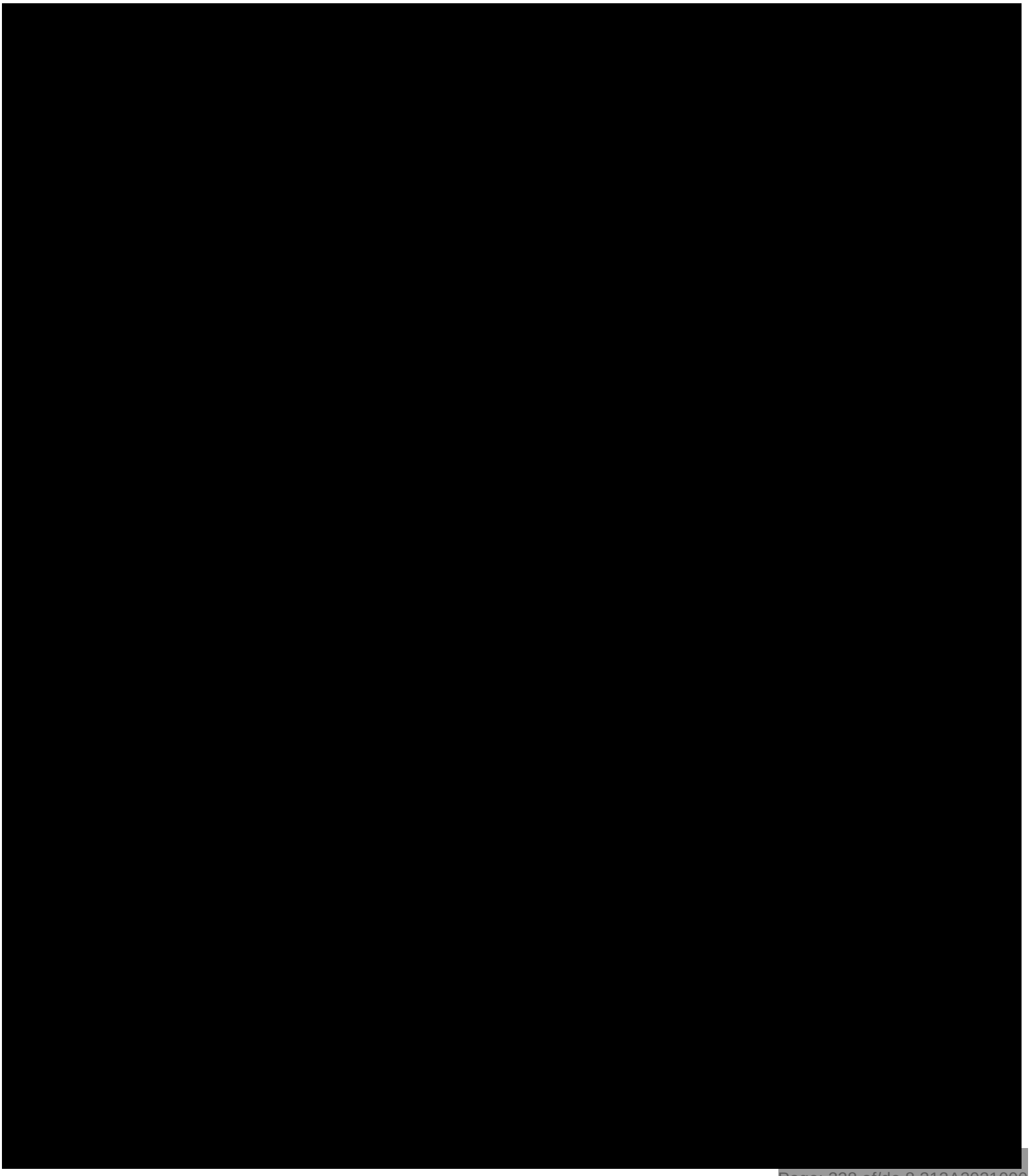

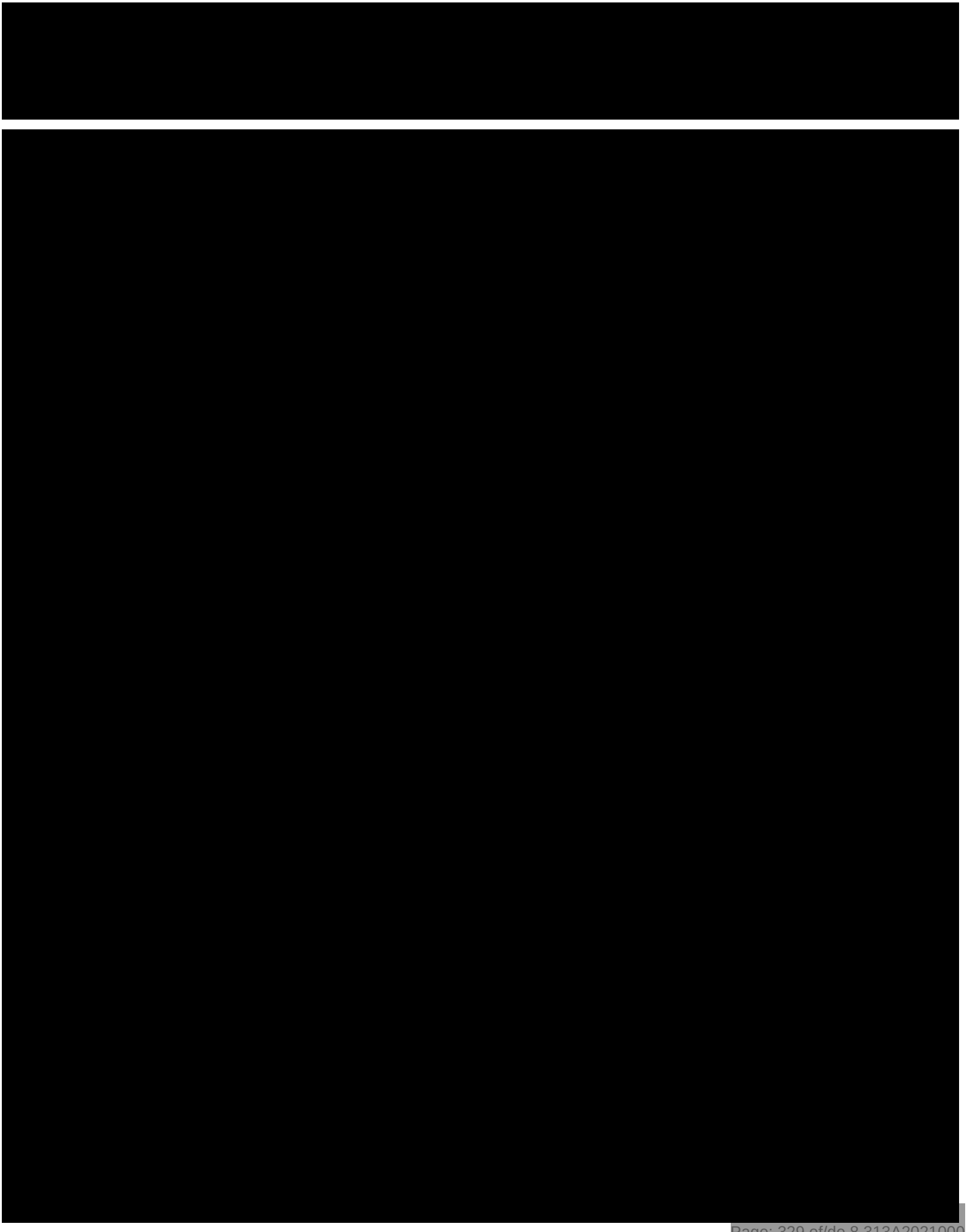

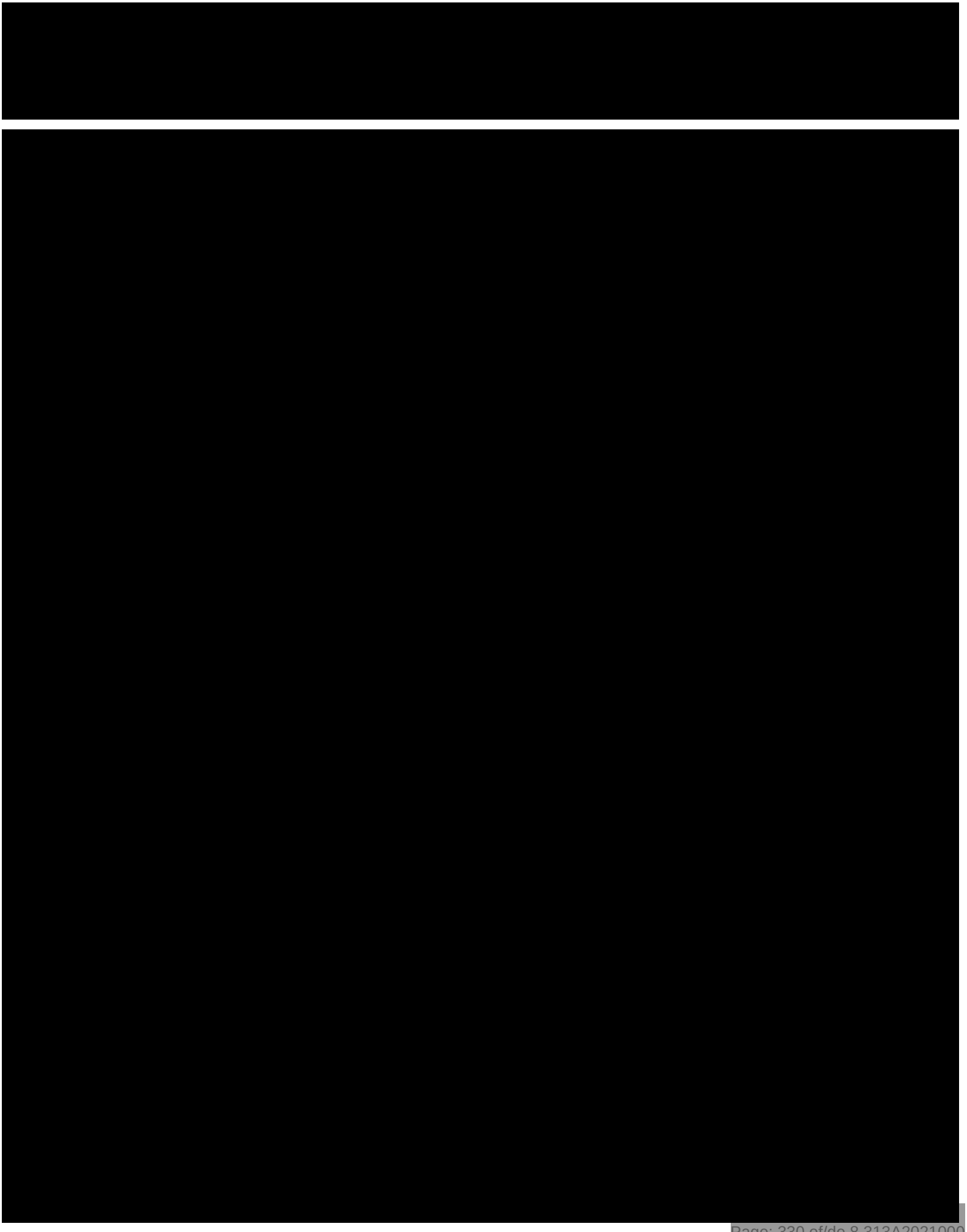

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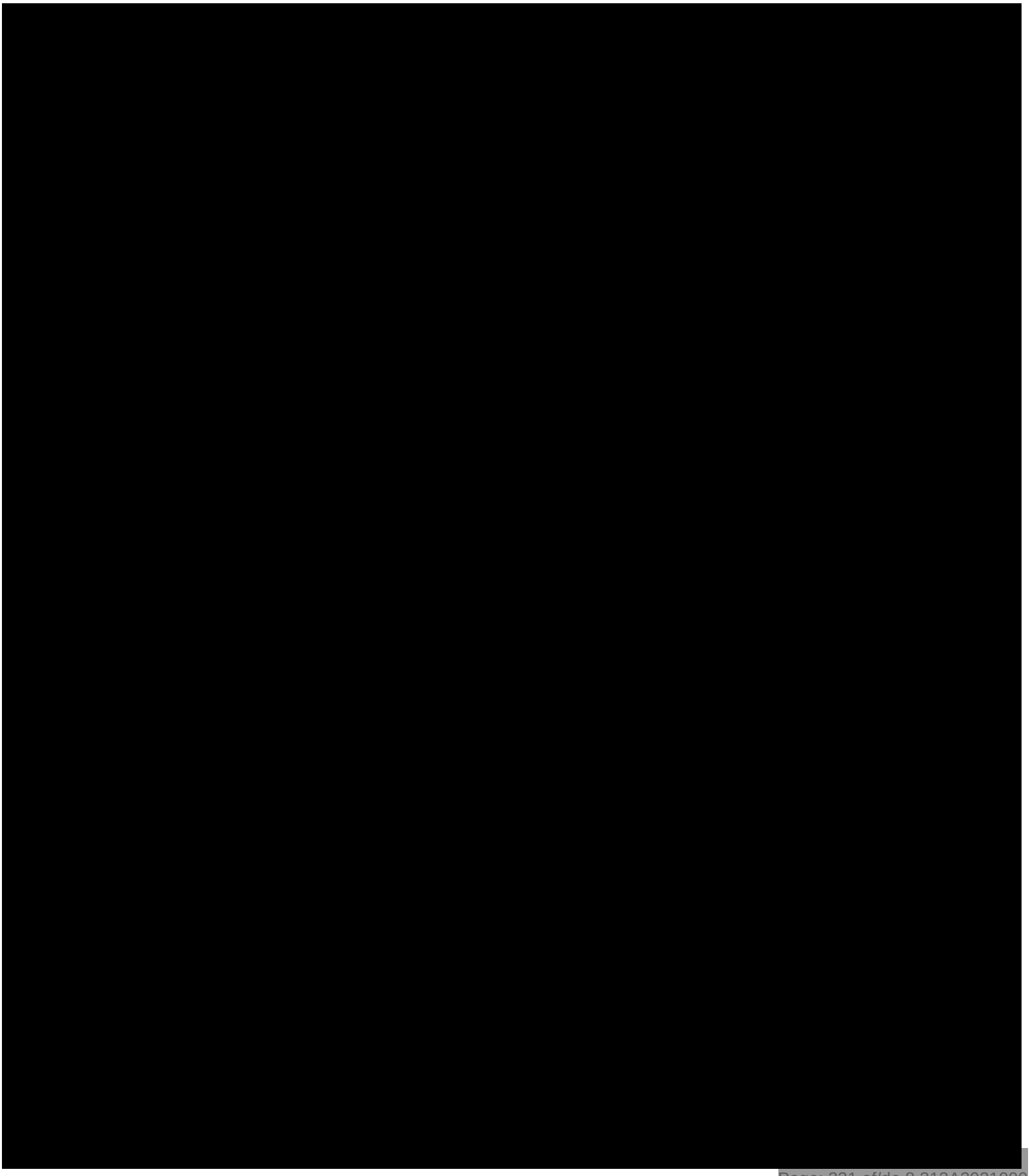

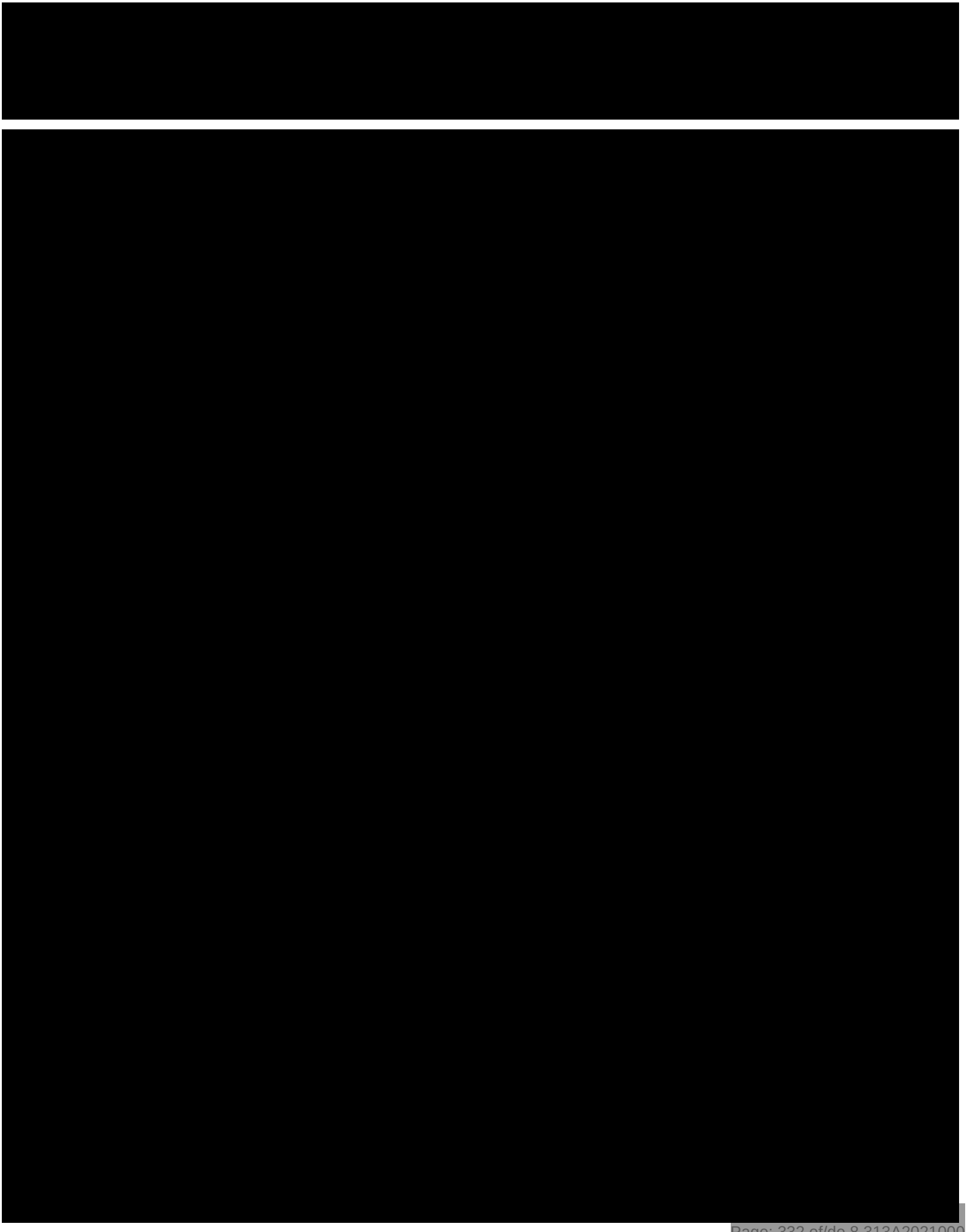

From: Lourenco, Celia (HC/SC)
To: [redacted]
Cc: Panetta, Vincent (HC/SC); Pham, Co (HC/SC); Tang, Marianne (HC/SC); Hardy, Stephanie (HC/SC); [redacted]
Subject: Regulatory Project Manager for Novavax submission
Date: 2021-01-21 7:12:00 PM

Hello [redacted]

It was a pleasure speaking with you yesterday. I would just like to follow up with you to inform you that the Regulatory Project Manager for your submission will be Vincent Panetta, copied. Please feel free to reach out to Vincent to get your submission going, and to answer any questions you have about the filing process.

We look forward to working with you.

Best regards,

Celia
Celia Lourenco, PhD
Director General / Directrice générale
Biologic and Radiopharmaceutical Drugs Directorate / Direction des médicaments biologiques et radiopharmaceutiques
Health Products and Food Branch / Direction générale des produits de santé et des aliments
Health Canada / Santé Canada
celia.lourenco@canada.ca
613-297-2532

Bettle, Megan (HC/SC)

From: Bettle, Megan (HC/SC)
Sent: 2020-12-17 4:05 PM
To: [redacted]
Subject: RE: Connecting Novavax & regulator

Sure, that sounds like a good plan.

Thx, megan

Megan Bettle, PhD
Director General, COVID-19 Regulatory Response Team
Health Products and Food Branch
Health Canada / Government of Canada
megan.bettle@canada.ca
Mobile: 613-793-6156

Megan Bettle, PhD
Directrice générale, Équipe d'intervention réglementaire de la COVID-19
Direction générale des produits de santé et des aliments
Santé Canada / Gouvernement du Canada
megan.bettle@canada.ca
Mobile: 613-793-6156

From: [redacted]
Sent: 2020-12-17 3:58 PM
To: Bettle, Megan (HC/SC)
Subject: RE: Connecting Novavax & regulator

Dear Megan,
Thank you so much for the outreach – I sincerely appreciate your willingness to chat. To that end, I've learned that our CEO and Regulatory lead will be on a call with the MoH tomorrow (at the request of the ministry). I am unsure of the agenda but I was told that our regulatory colleague will review our plan for engaging with Health Canada. I was also told a representative from Health Canada was going to be on that call so possibly, questions can be answered there.

To that end, lets see how that call goes and if there are additional questions I will reach out directly.

Sound OK?
Thank you,
[redacted]

From: Bettle, Megan (HC/SC) <megan.bettle@canada.ca>
Sent: Wednesday, December 16, 2020 3:19 PM
To: [redacted]
Subject: RE: Connecting Novavax & regulator

[SENDER IS EXTERNAL TO NOVAVAX]

Hi [redacted]

Just following up on this email from Arianne. I had understood that Novavax was already in contact with the Biologic and Radiopharmaceutical Drugs Directorate about making a submission under the Interim Order, but please let me know what the specific questions are or how I can help facilitate any further discussions.

Thanks, megan

Megan Bettle, PhD
Director General, COVID-19 Regulatory Response Team
Health Products and Food Branch
Health Canada / Government of Canada
megan.bettle@canada.ca
Mobile: 613-793-6156

Megan Bettle, PhD
Directrice générale, Équipe d'intervention réglementaire de la COVID-19
Direction générale des produits de santé et des aliments
Santé Canada / Gouvernement du Canada
megan.bettle@canada.ca
Mobile: 613-793-6156

-----Original Message-----
From: Arianne Reza <Arianne.Reza@tpsgc-pwgsc.gc.ca>
Sent: 2020-12-15 7:12 PM
To: Bettle, Megan (HC/SC) <megan.bettle@canada.ca>; [redacted]
Cc: Sabourin, Pierre (HC/SC) <pierre.sabourin@canada.ca>
Subject: Connecting Novavax & regulator

Hi [redacted]

Thank you for the excellent conversation today. As indicated, we are looking to ensure that there are accelerated discussions between you and HC regulator. Megan will be the point of contact for Health Canada.

Kind regards,
Arianne

Sent from my iPhone

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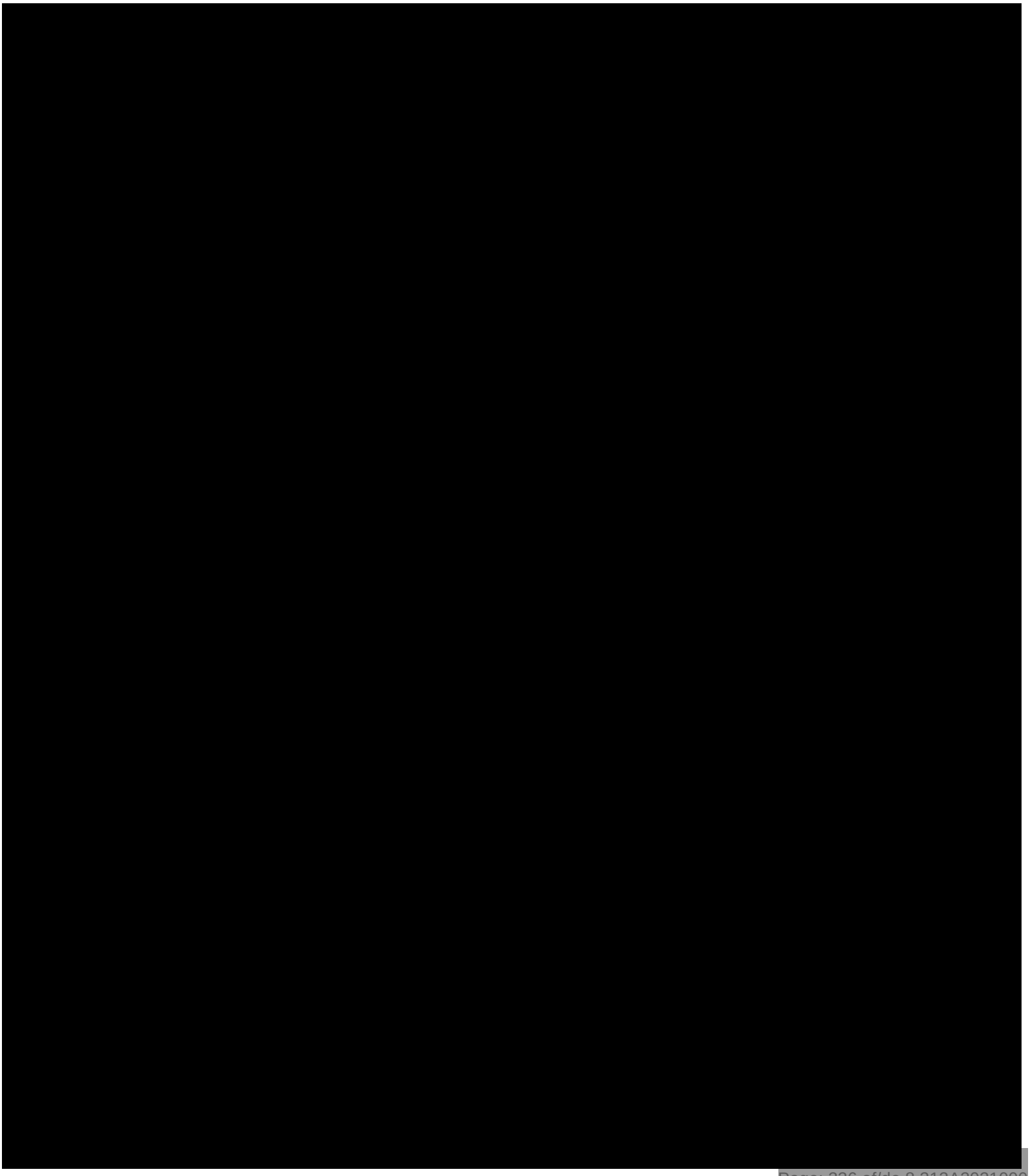

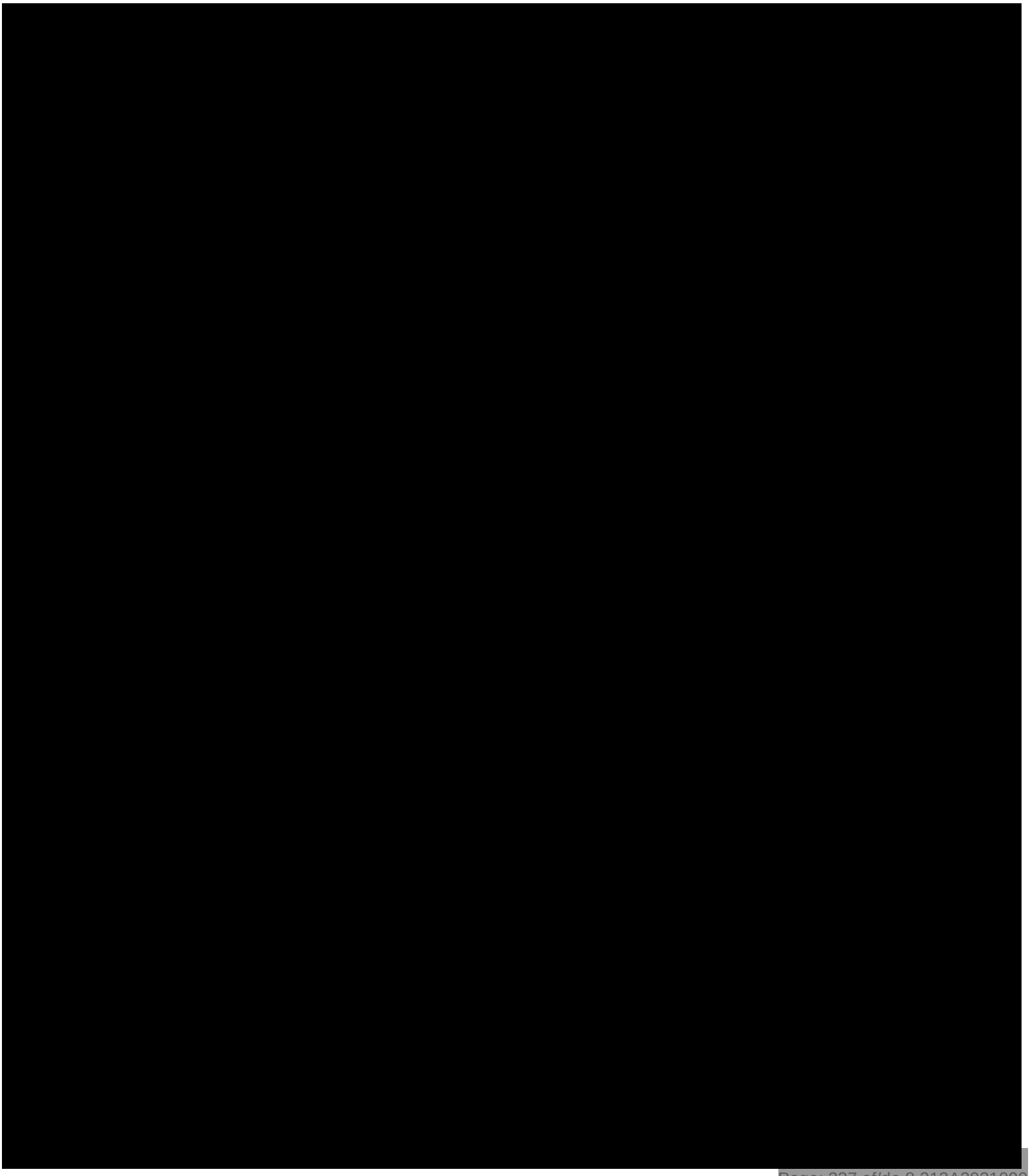

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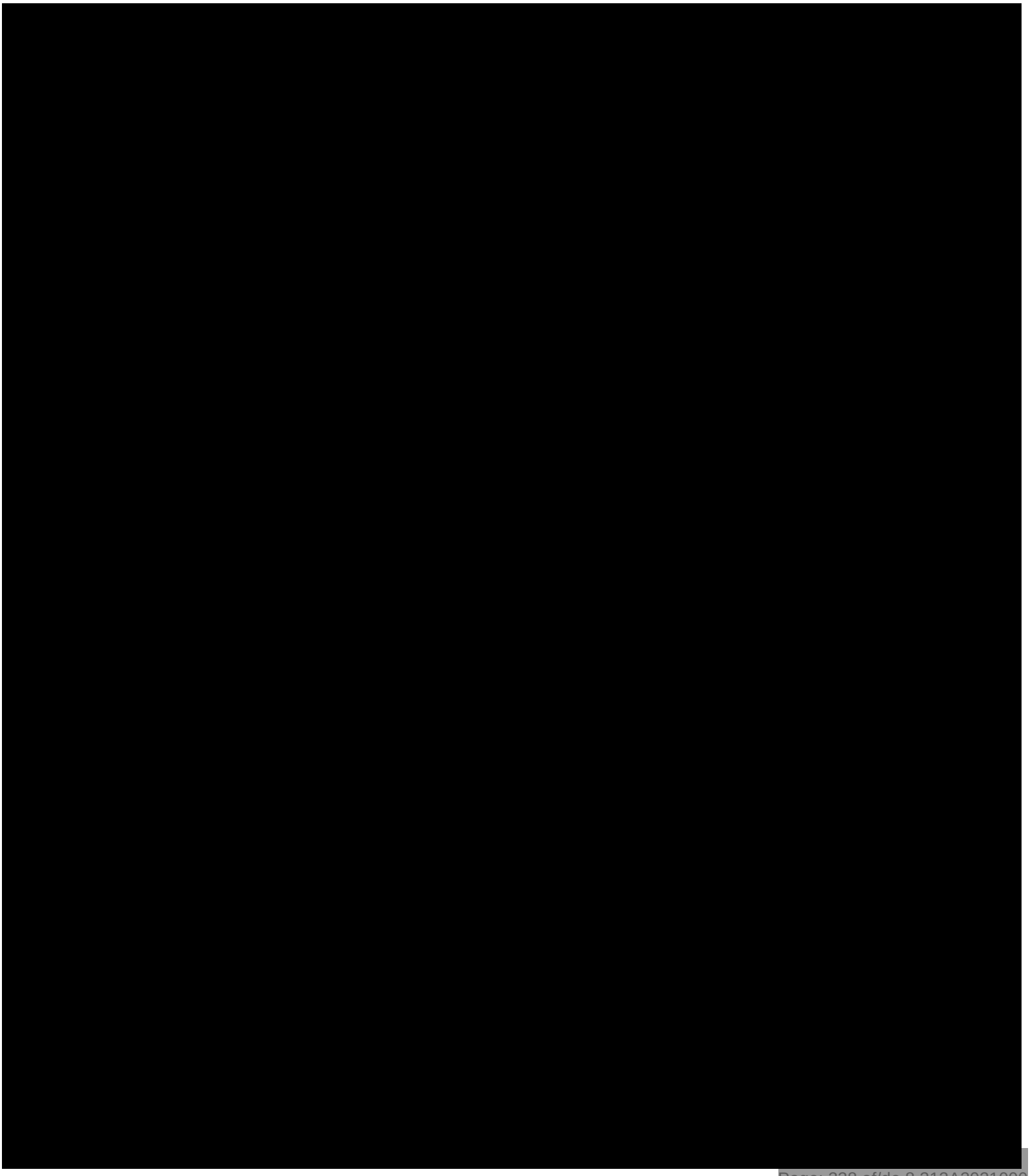

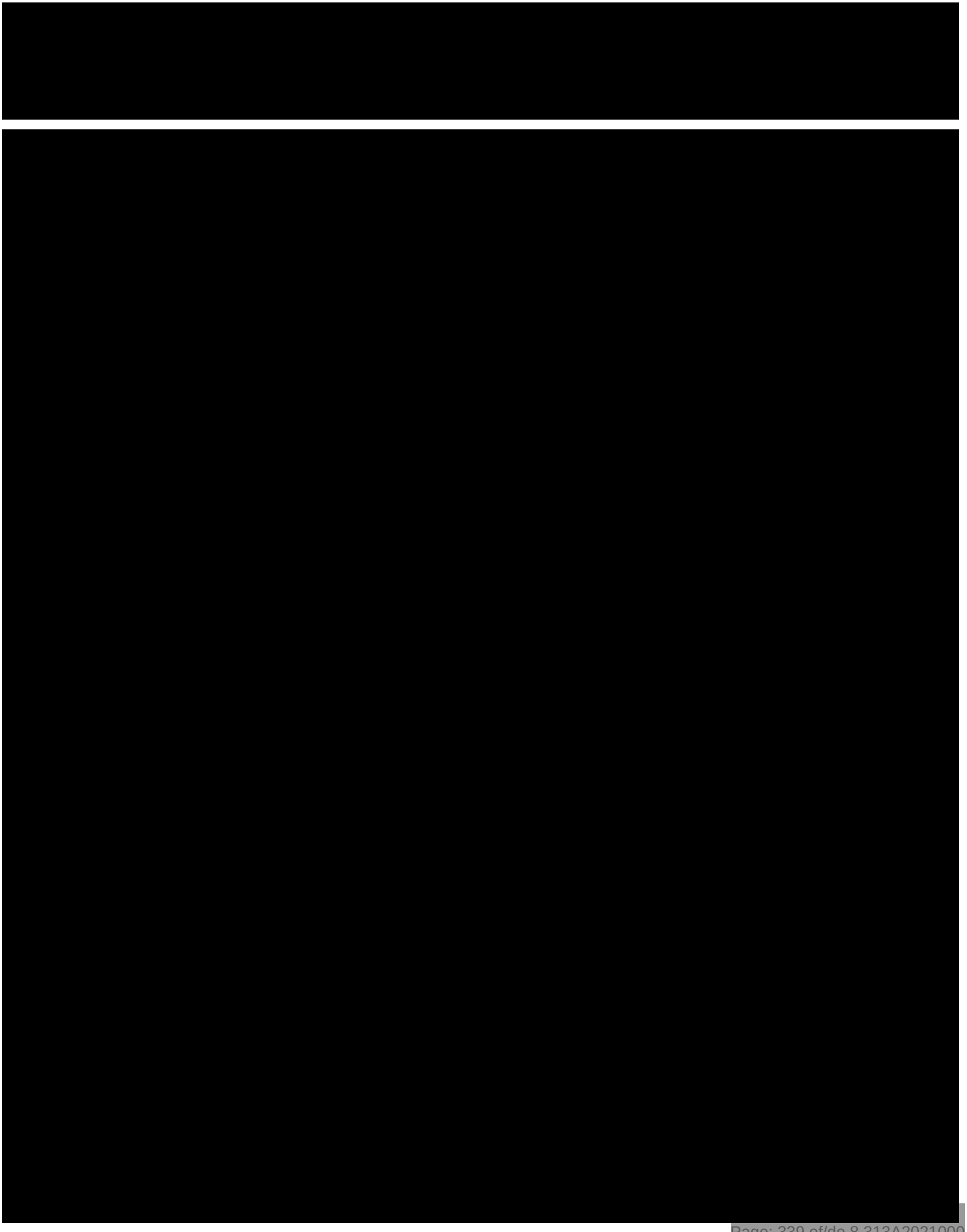

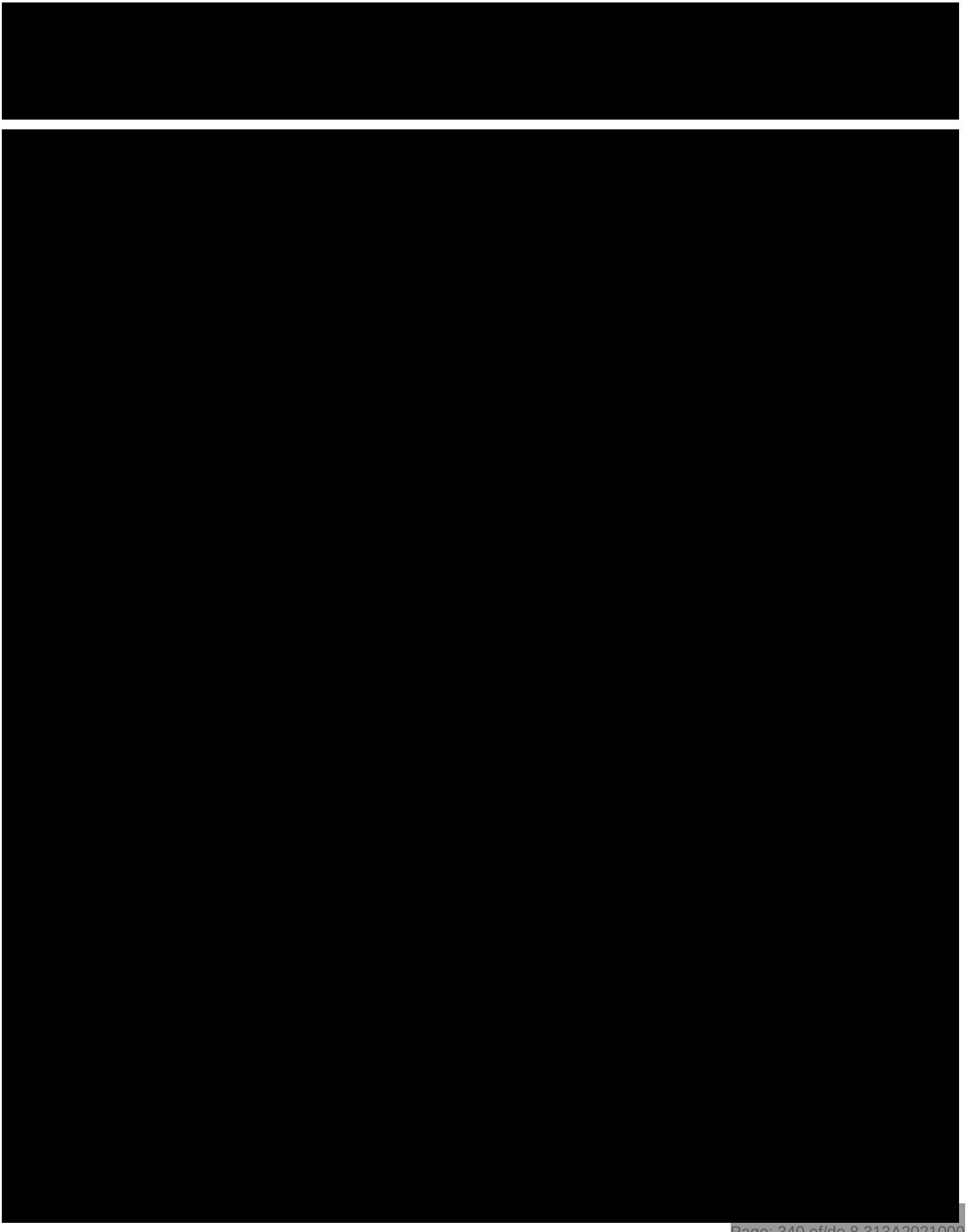

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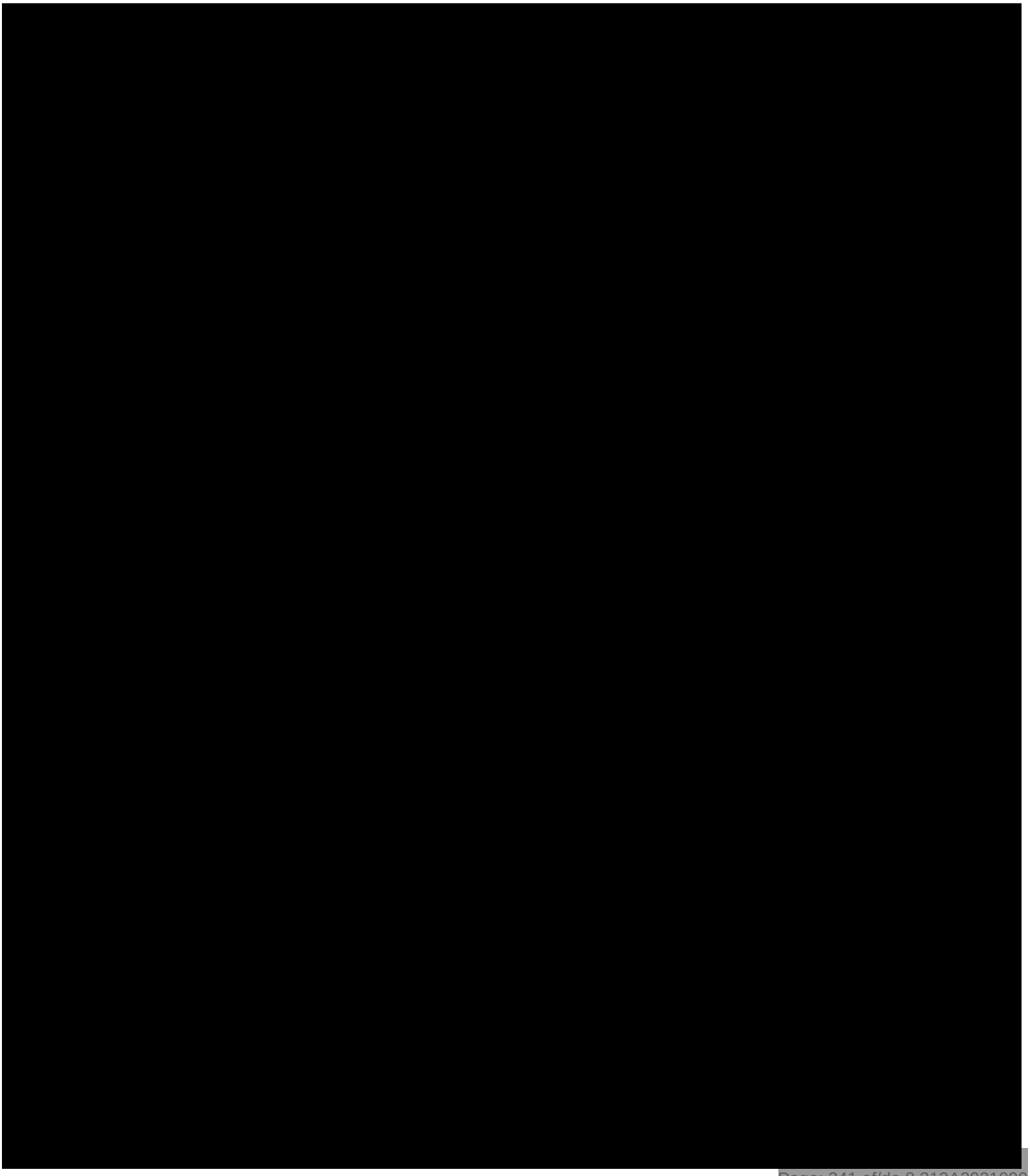

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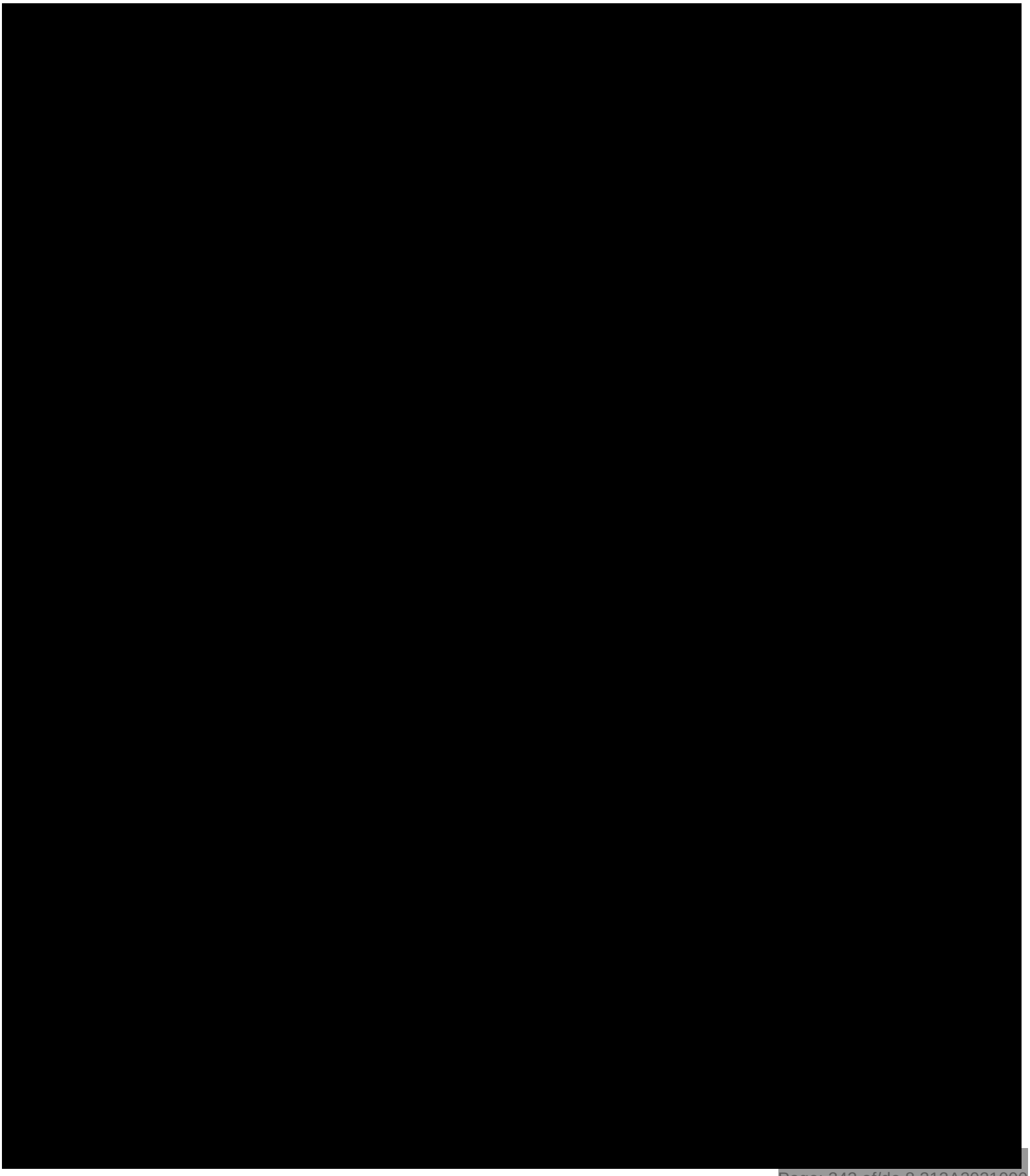

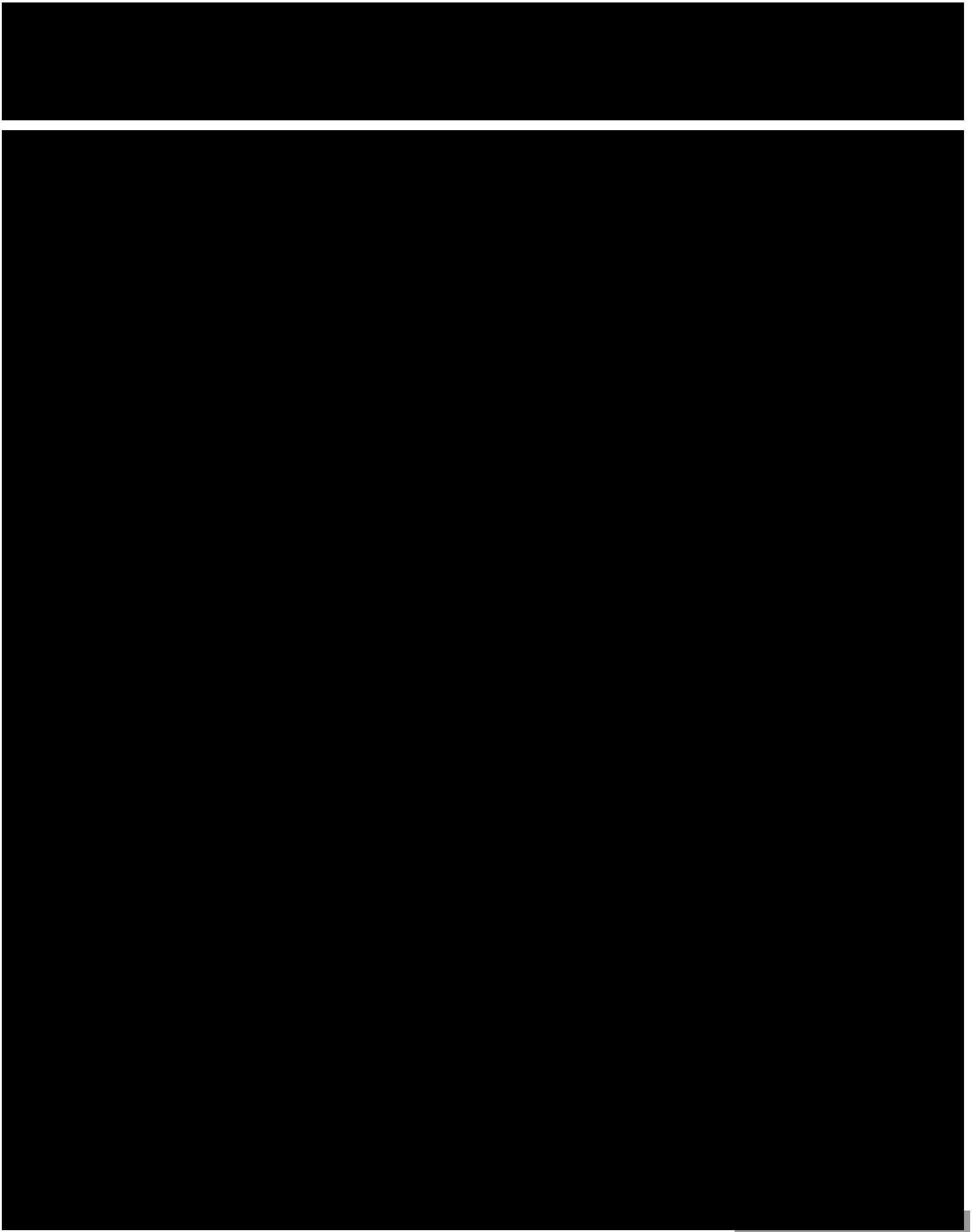

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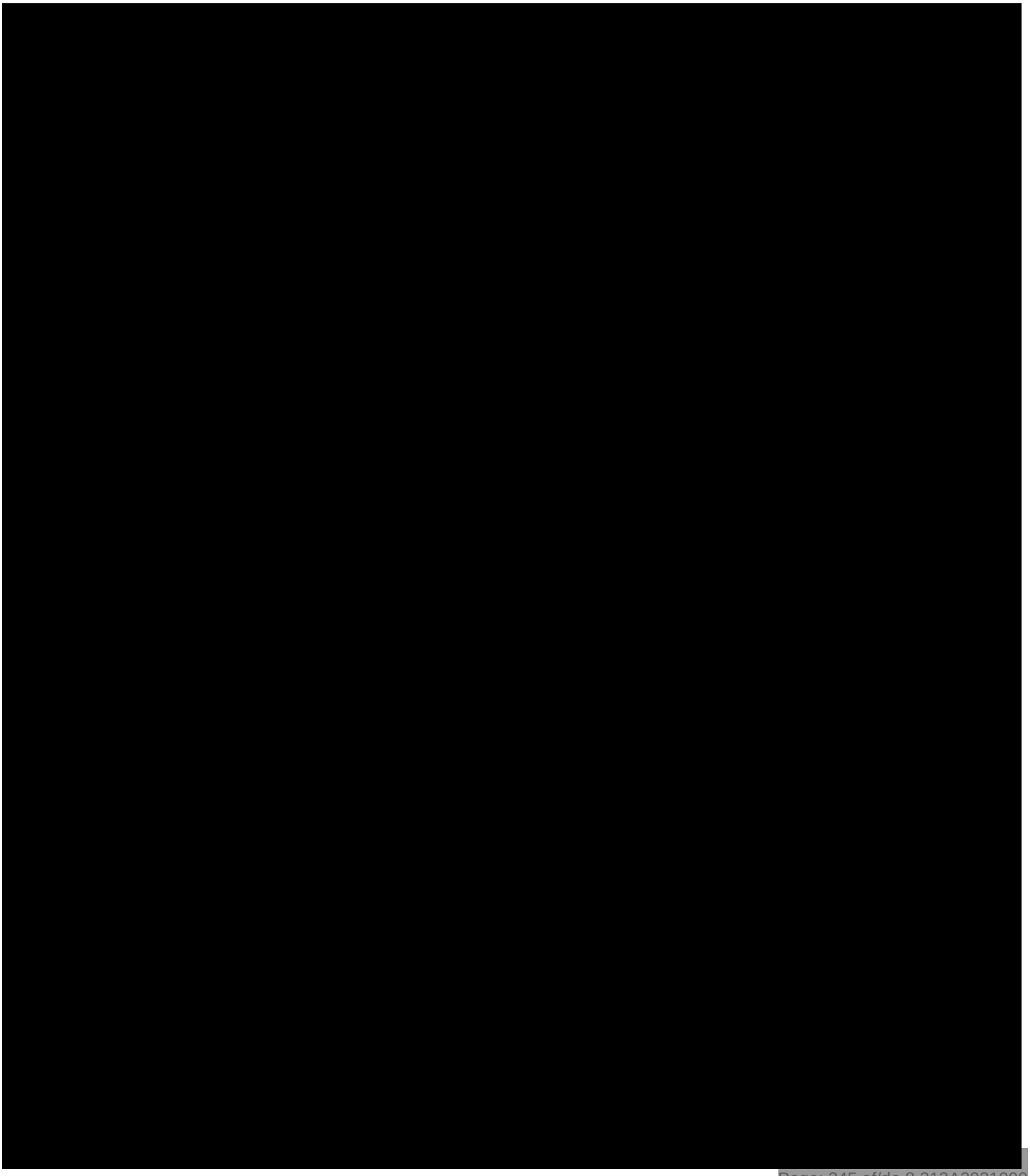

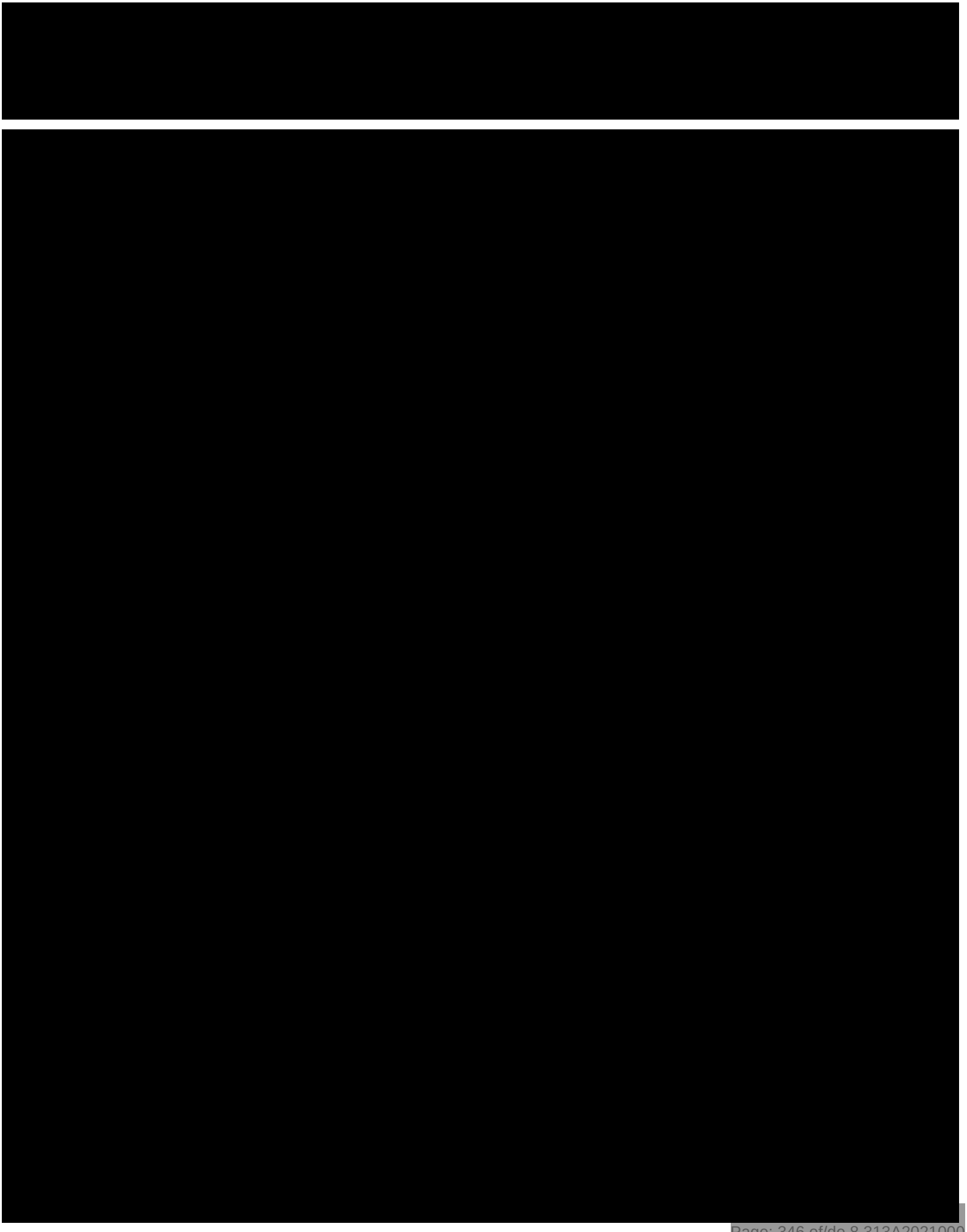

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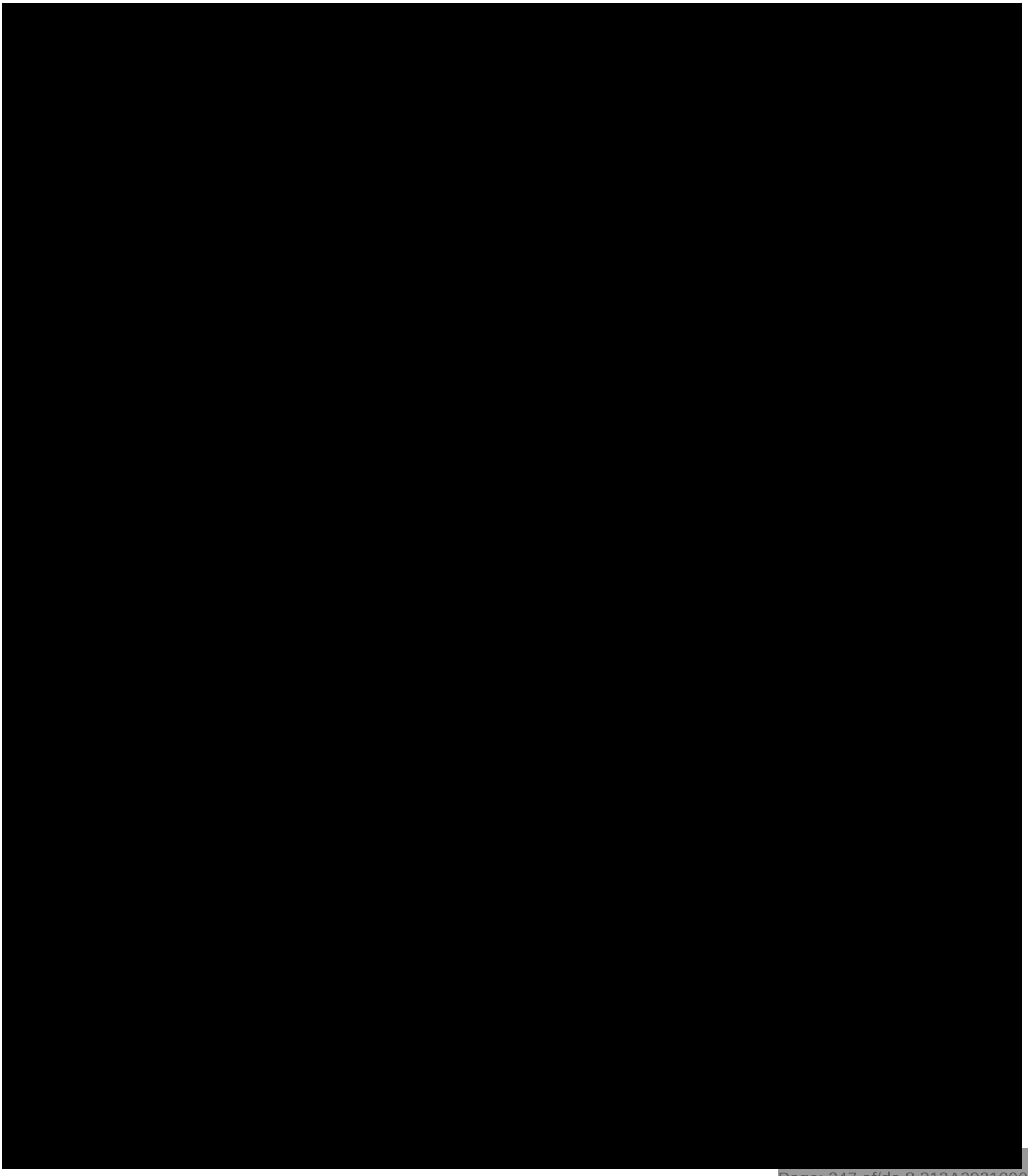

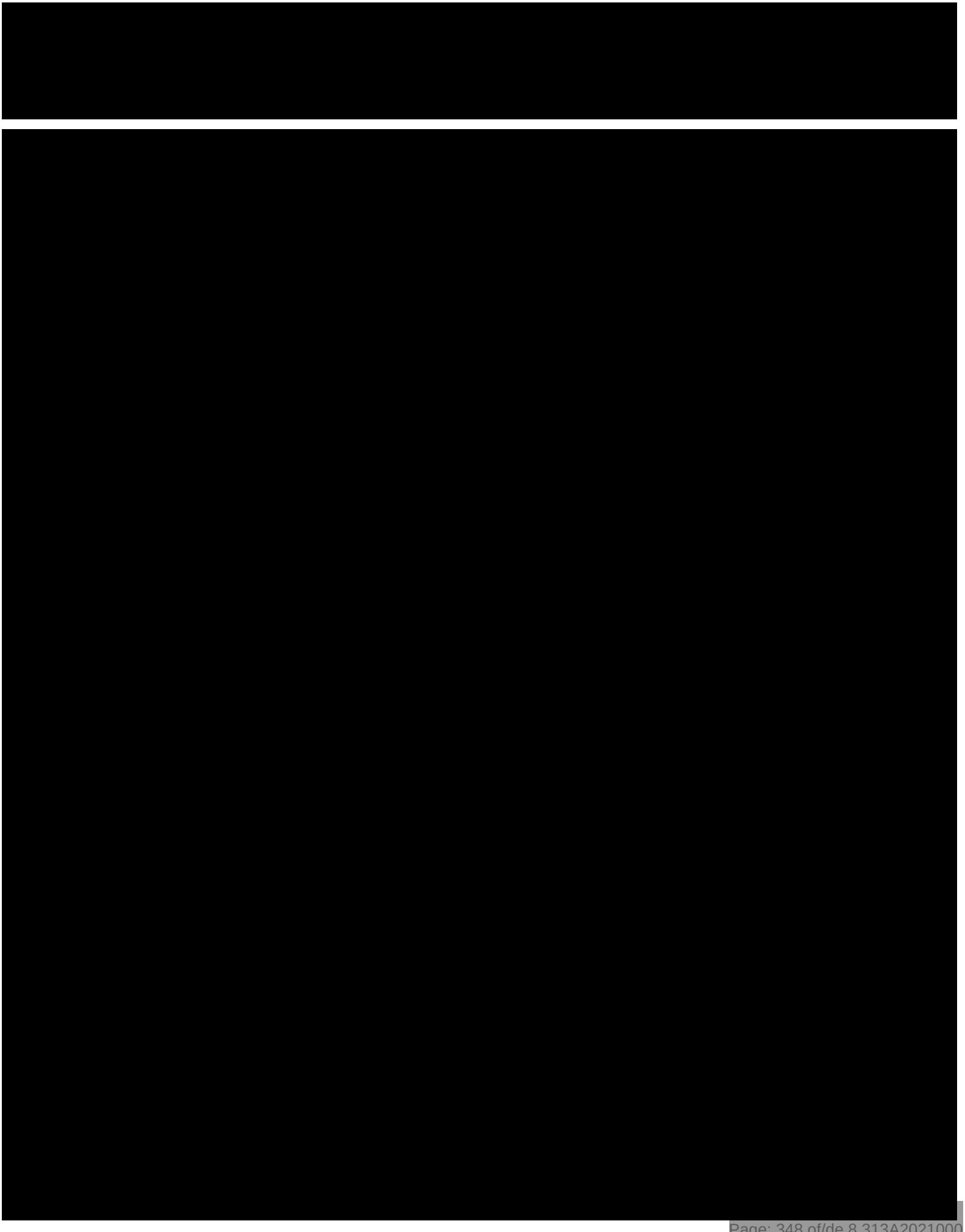

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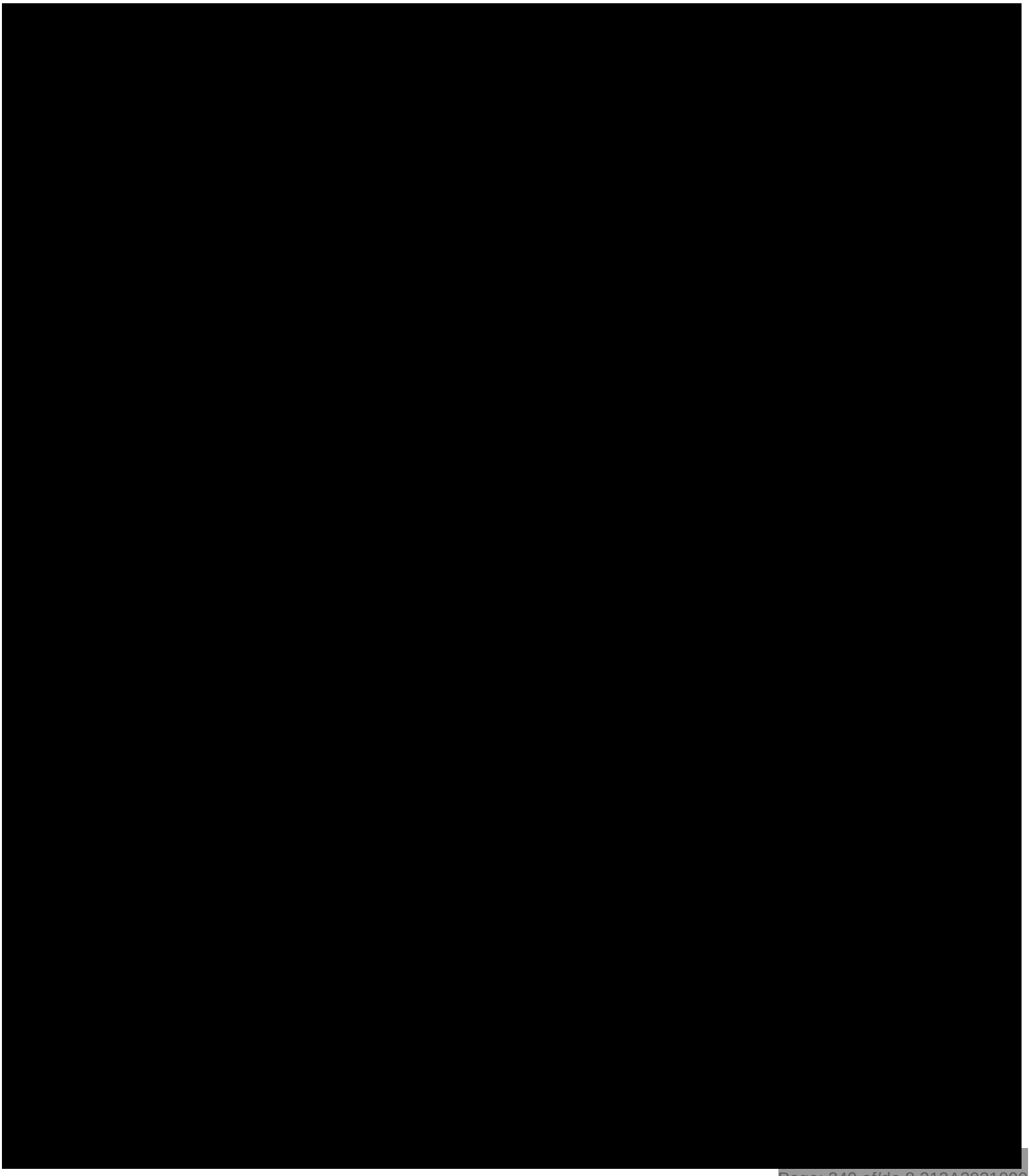

From: Patel, Shalu (HC/SC)
To: [redacted]
Cc: [redacted] Panetta, Vincent (HC/SC)
Subject: RE: Novavax COVID-19 Vaccine- Brand Name - COVID-19 Interim Order Drug Application Amendment Control [redacted]
Date: Wednesday, May 12, 2021 5:48:15 PM
Attachments: image001.png
image002.png
image003.png
image004.png
image005.png

Dear [redacted]

[redacted]

[redacted]

Please do not hesitate to contact us should you have any further questions.

Kind regards,
Shalu

From: Patel, Shalu (HC/SC)
Sent: 2021-05-04 1:28 PM
To: [redacted]
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Novavax COVID-19 Vaccine- Brand Name - COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear [redacted]

Thank you for your response. I will take this back to my team and reach out to you if we need any additional information.

Kind regards,
Shalu

From: [redacted]
Sent: 2021-05-04 12:44 PM
To: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Novavax COVID-19 Vaccine- Brand Name - COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear Shalu

Thanks for your question

[redacted]

Regards

[redacted] **MSc., RAC**
[redacted] REGULATORY AFFAIRS
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Wilmington, NC 28401-3331
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From: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Sent: Tuesday, May 4, 2021 9:35 AM
To: [redacted]
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Novavax COVID-19 Vaccine- Brand Name - COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear [redacted]

[redacted]

Kind regards,
Shalu

From: [redacted]
Sent: 2021-05-04 3:08 AM
To: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Novavax COVID-19 Vaccine- Brand Name - COVID-19 Interim Order Drug Application Amendment Control # [redacted]

Dear Shalu

[redacted]

[redacted]

Thanks a lot for your efforts.

Regards

[redacted] **MSc., RAC**
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From: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Sent: Thursday, April 22, 2021 5:30 PM
To: [redacted]
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Novavax COVID-19 Vaccine- Brand Name - COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear [redacted]

Please note our responses to your inquiry below in red font.

[redacted]

Should you have any further questions or clarifications, please do not hesitate to contact us.

Kind regards,
Shalu

From: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Sent: Wednesday, April 21, 2021 6:29 PM
To: [redacted]

Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Novavax COVID-19 Vaccine- Brand Name - COVID-19 Interim Order Drug Application Amendment Control # [redacted]

Dear [redacted]

Thank your for your inquiry. We are currently consulting internally and hoping to get back to you as soon as possible.

Kind regards,
Shalu

From: [redacted]
Sent: 2021-04-20 5:06 PM
To: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE:Novavax COVID-19 Vaccine- Brand Name - COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear Shalu

Hope you are doing great.

[redacted]

Thanks a lot for your time.
Regards

[redacted] **MSc., RAC**
[redacted] REGULATORY AFFAIRS
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From: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Sent: Friday, April 16, 2021 9:16 AM
To: [redacted]
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Revised Rolling Submission- COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear [redacted]

Thank you for the update! We will notify our internal review teams.

[redacted]

Kind regards,
Shalu

From: [redacted]
Sent: 2021-04-15 6:45 PM
To: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Revised Rolling Submission- COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear Shalu

Hope you are doing great.

[redacted]

Regards

[redacted] **MSc., RAC**
[redacted] REGULATORY AFFAIRS
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From: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Sent: Thursday, April 8, 2021 7:52 PM
To: [redacted]
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Revised Rolling Submission- COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear [redacted]

Thank you, please continue to keep us posted.

Kind regards,
Shalu

From: [redacted]
Sent: 2021-04-08 5:19 PM
To: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>

Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Revised Rolling Submission- COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear Shalu

[redacted]

Please do not hesitate to contact me if you have any questions.

Thanks and best regards
[redacted] **MSc., RAC**
[redacted] REGULATORY AFFAIRS
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From: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Sent: Thursday, April 8, 2021 11:28 AM
To: [redacted]
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Revised Rolling Submission- COVID-19 Interim Order Drug Application Amendment Control # [redacted]

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Dear [redacted]

Hope all is well.

We would like to follow-up on the timelines for the quality submission as well as Clinical Roll 2. Please let us know if there are any updates to the application plan.

Kind regards,
Shalu

From: Patel, Shalu (HC/SC)
Sent: 2021-03-03 8:23 PM
To: [redacted]
Cc: [redacted] Antonio, Christopher (HC/SC) <christopher.antonio@canada.ca>; Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>; Akel, Sereen H (HC/SC) <sereenh.akel@canada.ca>; Eassa, Samar (HC/SC) <samar.eassa@canada.ca>
Subject: RE: Revised Rolling Submission- COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear [redacted]

[redacted]

Should you have any questions, please let us know.

Kind regards,
Shalu

From: [redacted]
Sent: 2021-03-03 3:37 PM
To: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Cc: [redacted] Antonio, Christopher (HC/SC) <christopher.antonio@canada.ca>; Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>; Akel, Sereen H (HC/SC) <sereenh.akel@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Eassa, Samar (HC/SC) <samar.eassa@canada.ca>
Subject: RE: Revised Rolling Submission- COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear Shalu,

[redacted]

[redacted]

Should you have any questions, please do not hesitate to contact me.

Regards

[redacted] **MSc., RAC**
[redacted] REGULATORY AFFAIRS
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From: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Sent: Wednesday, February 24, 2021 5:21 PM
To: [redacted]
Cc: [redacted] Antonio, Christopher (HC/SC) <christopher.antonio@canada.ca>; Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>; Akel, Sereen H (HC/SC) <sereenh.akel@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Eassa, Samar (HC/SC) <samar.eassa@canada.ca>
Subject: RE: Nonclinical Roll#2 - COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear [redacted]

Thank you so much for the update.

Please also copy my colleagues, Chris, Vincent, Saj, Samar, and Sereen in all correspondence moving forward.

Kind regards,

Shalu

From: [redacted]
Sent: 2021-02-24 5:03 PM
To: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Cc: [redacted]
Subject: RE: Nonclinical Roll#2 - COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear Shalu

Hope you are doing great.

[redacted]

Thanks

Regards
[redacted] **MSc., RAC**
[redacted]REGULATORY AFFAIRS
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Ridgen, Patrick (HC/SC)

From: Patel, Shalu (HC/SC)
Sent: 2021-05-12 5:48 PM
To: [redacted]
Cc: [redacted] Panetta, Vincent (HC/SC)
Subject: RE: Novavax COVID-19 Vaccine- Brand Name - COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear [redacted]

[redacted]

Please do not hesitate to contact us should you have any further questions.

Kind regards,
Shalu

From: Patel, Shalu (HC/SC)
Sent: 2021-05-04 1:28 PM
To: [redacted]
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Novavax COVID-19 Vaccine- Brand Name - COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear [redacted]

[redacted]

Kind regards,
Shalu

From: [redacted]
Sent: 2021-05-04 12:44 PM
To: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Novavax COVID-19 Vaccine- Brand Name - COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear Shalu

Thanks for your question

[redacted]

Regards

[redacted] **MSc., RAC**
[redacted] REGULATORY AFFAIRS
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From: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Sent: Tuesday, May 4, 2021 9:35 AM
To: [redacted]
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Novavax COVID-19 Vaccine- Brand Name - COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear [redacted]

[redacted]

Kind regards,
Shalu

From: [redacted]
Sent: 2021-05-04 3:08 AM
To: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Novavax COVID-19 Vaccine- Brand Name - COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear Shalu

[redacted]

[redacted]

Thanks a lot for your efforts.

Regards

[redacted] **MSc., RAC**
[redacted] REGULATORY AFFAIRS
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From: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Sent: Thursday, April 22, 2021 5:30 PM
To: [redacted]
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Novavax COVID-19 Vaccine- Brand Name - COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear [redacted]

Please note our responses to your inquiry below in red font.

[redacted]

Should you have any further questions or clarifications, please do not hesitate to contact us.

Kind regards,
Shalu

From: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Sent: Wednesday, April 21, 2021 6:29 PM
To: [redacted]
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Novavax COVID-19 Vaccine- Brand Name - COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear [redacted]

[redacted]

Kind regards,
Shalu

From: [redacted]
Sent: 2021-04-20 5:06 PM
To: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE:Novavax COVID-19 Vaccine- Brand Name - COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear Shalu

Hope you are doing great.

[redacted]

Thanks a lot for your time.
Regards

[redacted] **MSc., RAC**
[redacted] REGULATORY AFFAIRS
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From: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Sent: Friday, April 16, 2021 9:16 AM
To: [redacted]
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Revised Rolling Submission- COVID-19 Interim Order Drug Application Amendment Control [redacted]

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Dear [redacted]

Thank you for the update! We will notify our internal review teams.

[redacted]

Kind regards,
Shalu

From: [redacted]
Sent: 2021-04-15 6:45 PM
To: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Revised Rolling Submission- COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear Shalu

Hope you are doing great.

[redacted]

Regards

[redacted] **MSc., RAC**
[redacted] REGULATORY AFFAIRS
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From: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Sent: Thursday, April 8, 2021 7:52 PM
To: [redacted]
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Revised Rolling Submission- COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear [redacted]

Thank you, please continue to keep us posted.

Kind regards,
Shalu

From: [redacted]
Sent: 2021-04-08 5:19 PM
To: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Revised Rolling Submission- COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear Shalu

[redacted]

Please do not hesitate to contact me if you have any questions.

Thanks and best regards
[redacted] **MSc., RAC**
[redacted] REGULATORY AFFAIRS
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From: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Sent: Thursday, April 8, 2021 11:28 AM
To: [redacted]
Cc: [redacted] Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: RE: Revised Rolling Submission- COVID-19 Interim Order Drug Application Amendment Control [redacted]

CAUTION: External Email. THINK BEFORE YOU CLICK. This could be a phishing email. Do not click on links or open any attachments unless you were expecting this message, recognize the sender, and have checked for valid links.

Dear [redacted]

Hope all is well.

[redacted]

Kind regards,
Shalu

From: Patel, Shalu (HC/SC)
Sent: 2021-03-03 8:23 PM
To: [redacted]
Cc: [redacted] Antonio, Christopher (HC/SC) <christopher.antonio@canada.ca>; Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>; Akel, Sereen H (HC/SC) <sereenh.akel@canada.ca>; Eassa, Samar (HC/SC) <samar.eassa@canada.ca>
Subject: RE: Revised Rolling Submission- COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear [redacted]

[redacted]

Should you have any questions, please let us know.

Kind regards,
Shalu

From: [redacted]
Sent: 2021-03-03 3:37 PM
To: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Cc: [redacted] Antonio, Christopher (HC/SC) <christopher.antonio@canada.ca>; Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>; Akel, Sereen H (HC/SC) <sereenh.akel@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Eassa, Samar (HC/SC) <samar.eassa@canada.ca>
Subject: RE: Revised Rolling Submission- COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear Shalu,

[redacted]

[redacted]

Should you have any questions, please do not hesitate to contact me.

Regards

[redacted] **MSc., RAC**
[redacted] REGULATORY AFFAIRS
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From: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Sent: Wednesday, February 24, 2021 5:21 PM
To: [redacted]
Cc: [redacted] Antonio, Christopher (HC/SC) <christopher.antonio@canada.ca>; Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>; Akel, Sereen H (HC/SC) <sereenh.akel@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Eassa, Samar (HC/SC) <samar.eassa@canada.ca>
Subject: RE: Nonclinical Roll#2 - COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear [redacted]

Thank you so much for the update.

Please also copy my colleagues, Chris, Vincent, Saj, Samar, and Sereen in all correspondence moving forward.

Kind regards,
Shalu

From: [redacted]
Sent: 2021-02-24 5:03 PM
To: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Cc: [redacted]
Subject: RE: Nonclinical Roll#2 - COVID-19 Interim Order Drug Application Amendment Control [redacted]

Dear Shalu

Hope you are doing great.

[redacted]

Thanks

Regards

[redacted] **MSc., RAC**
[redacted]REGULATORY AFFAIRS
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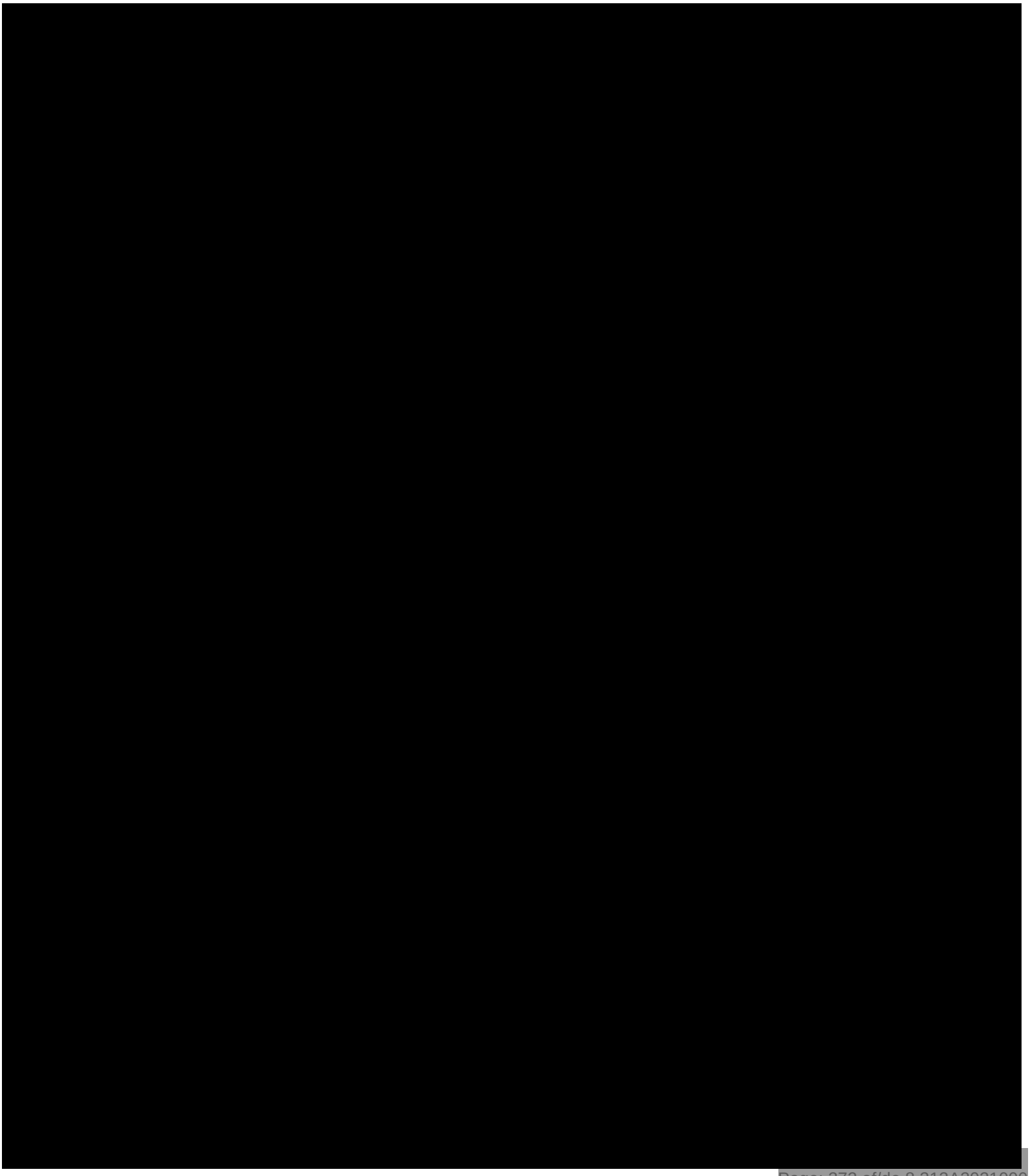

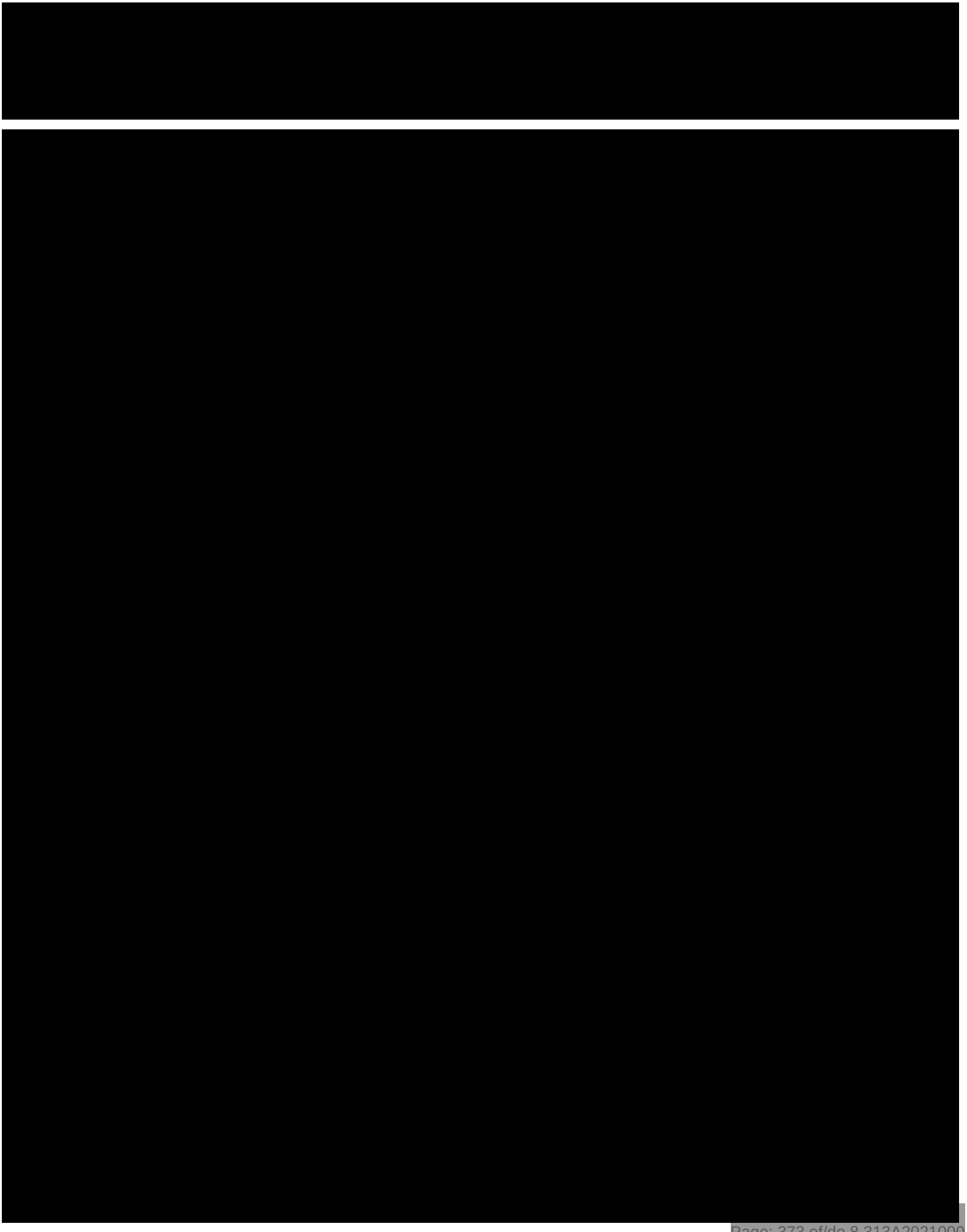

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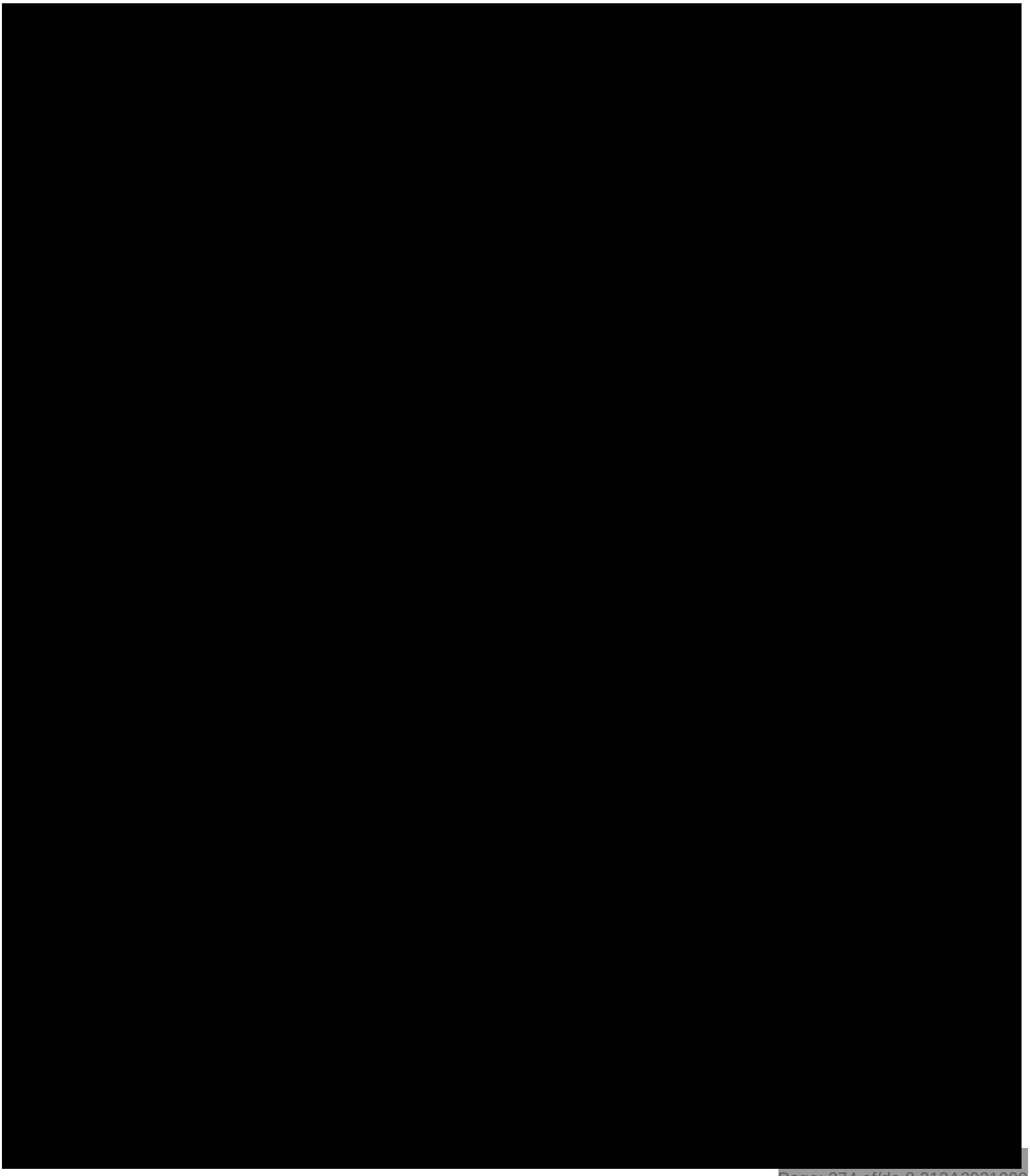

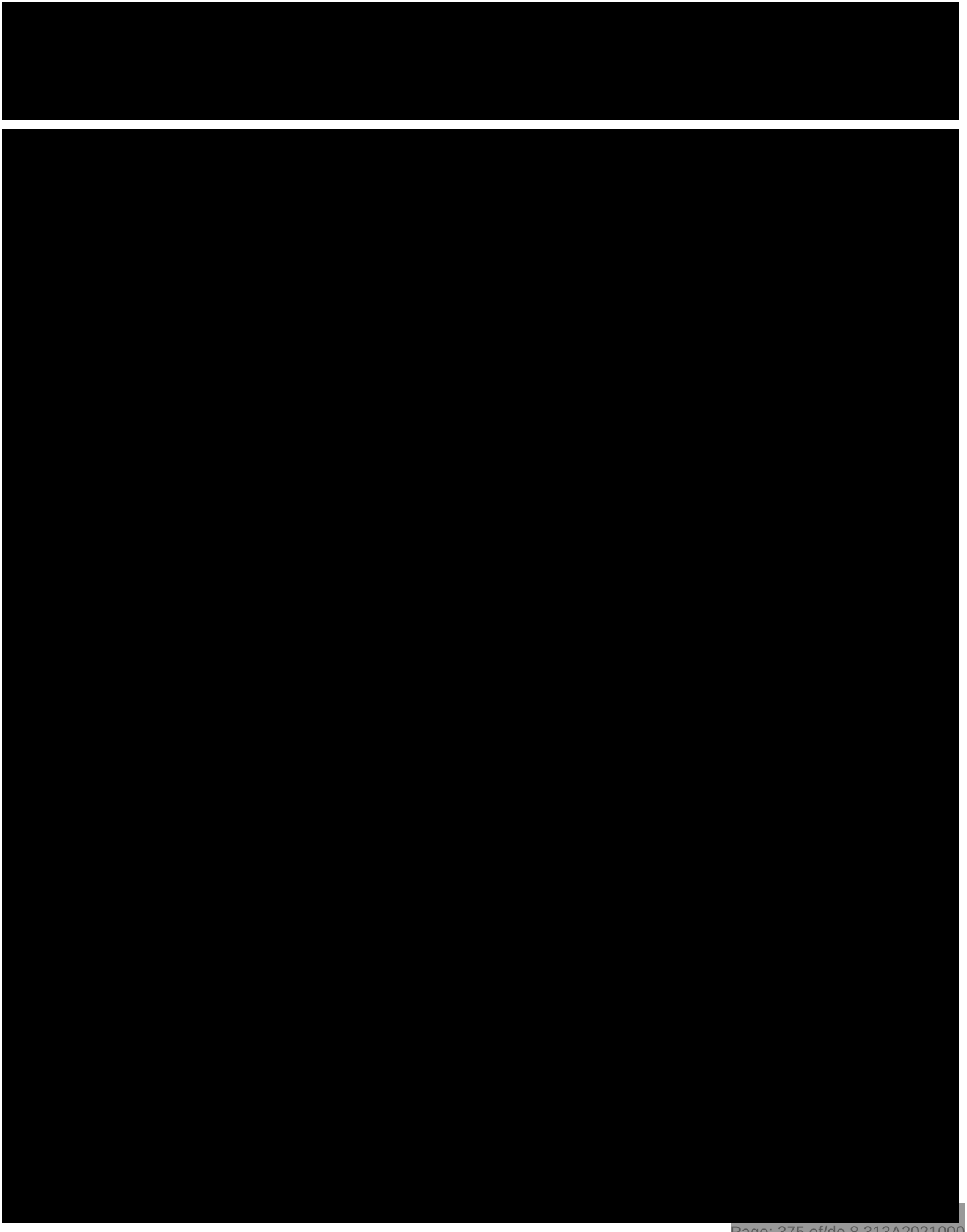

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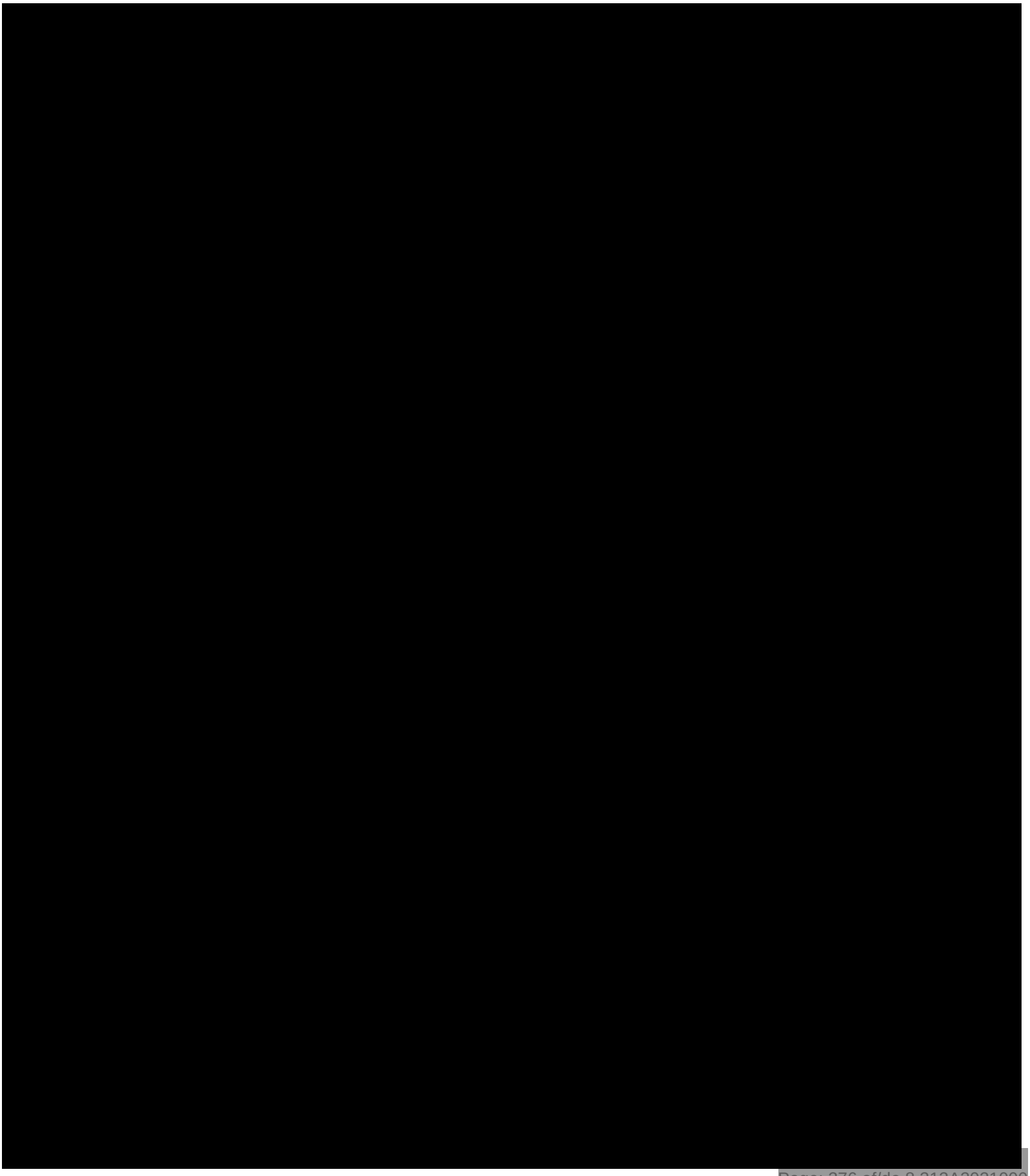

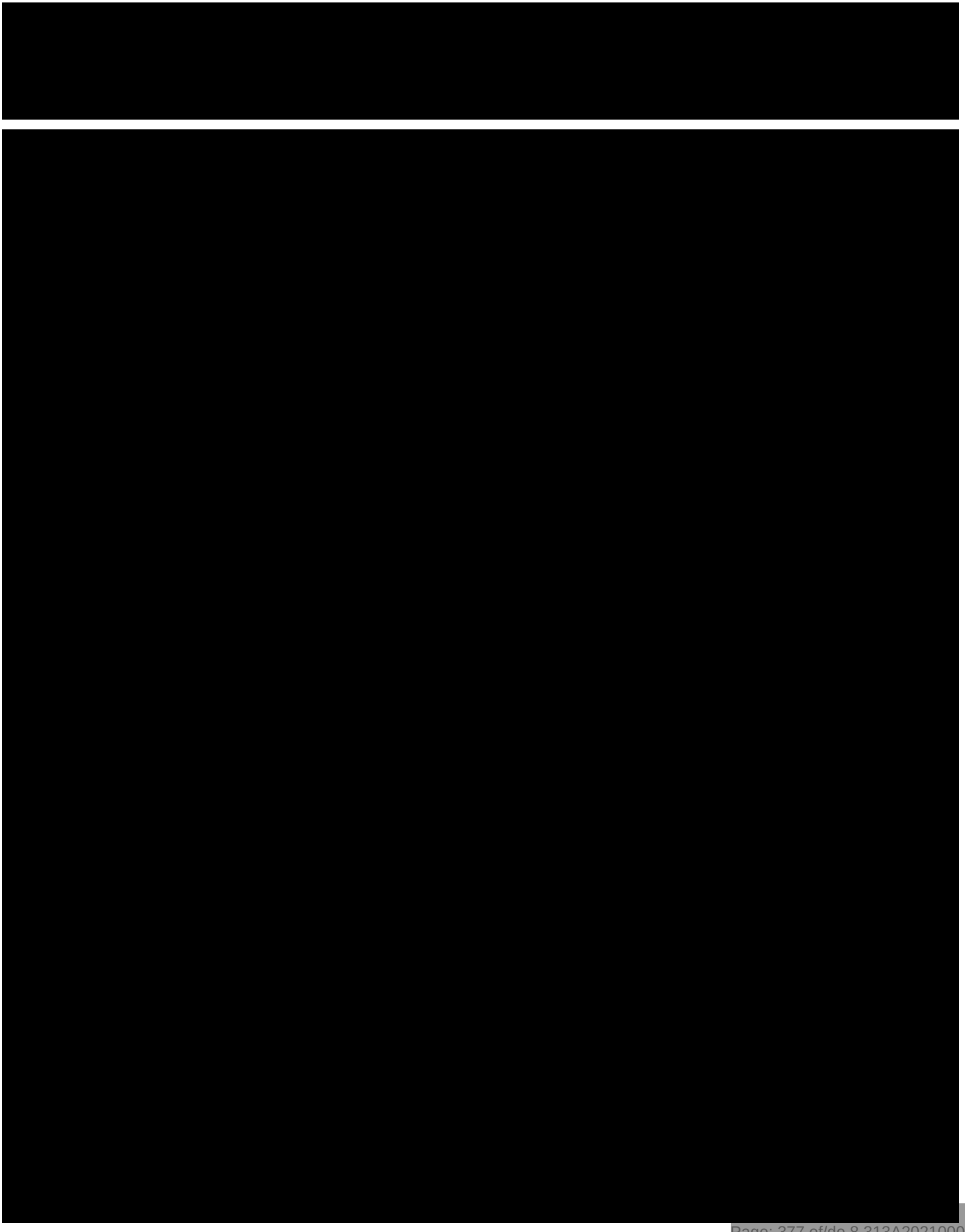

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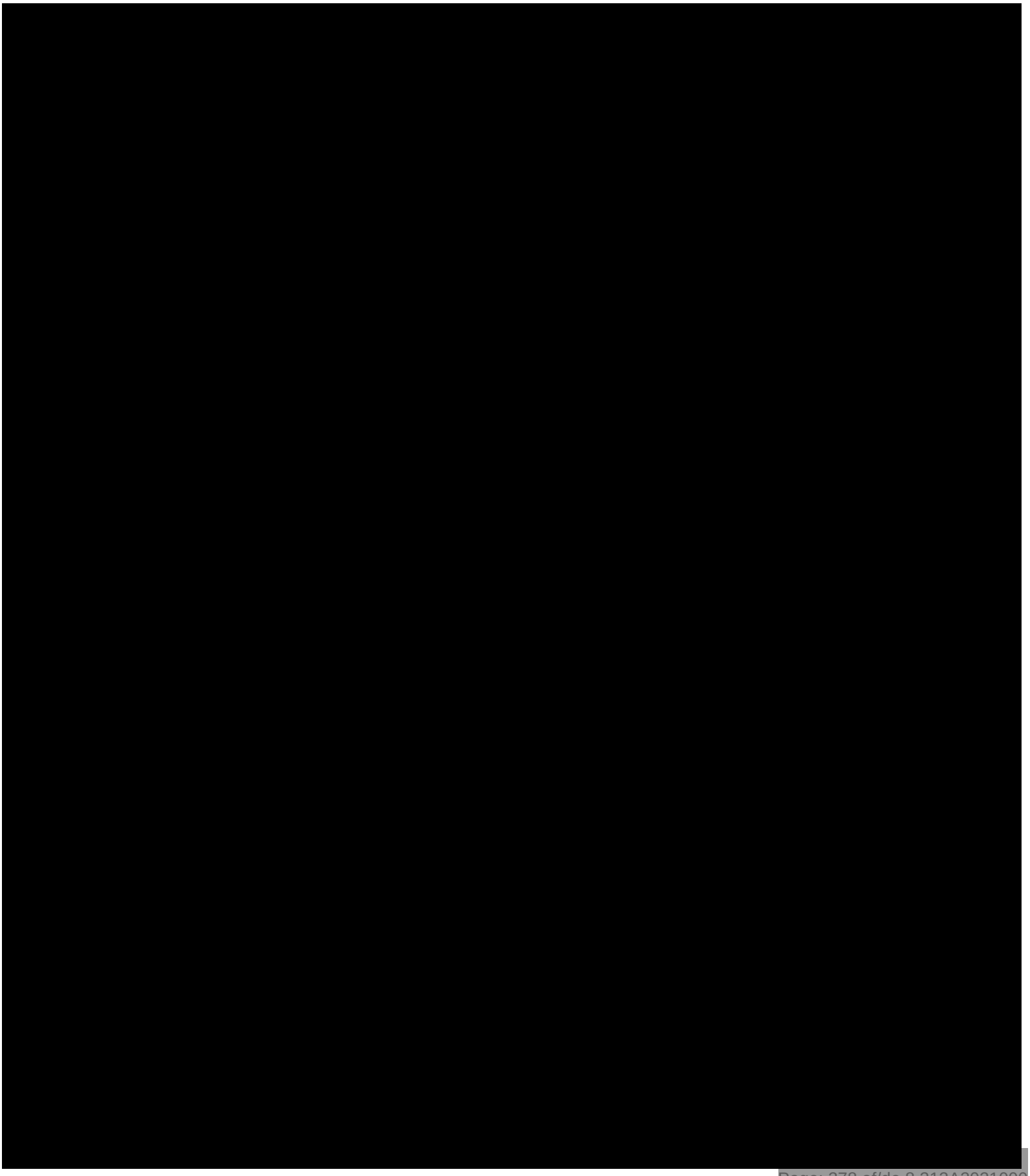

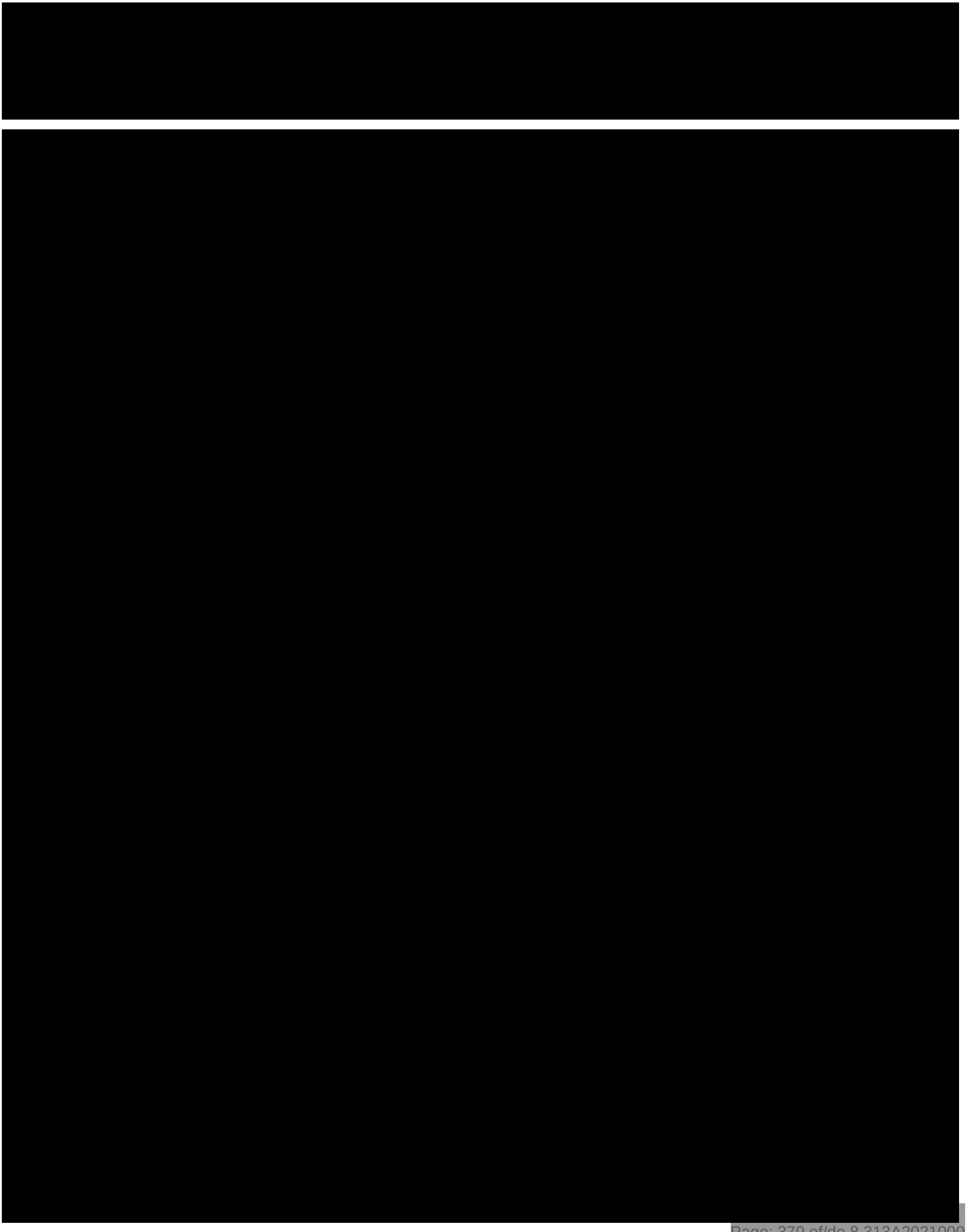

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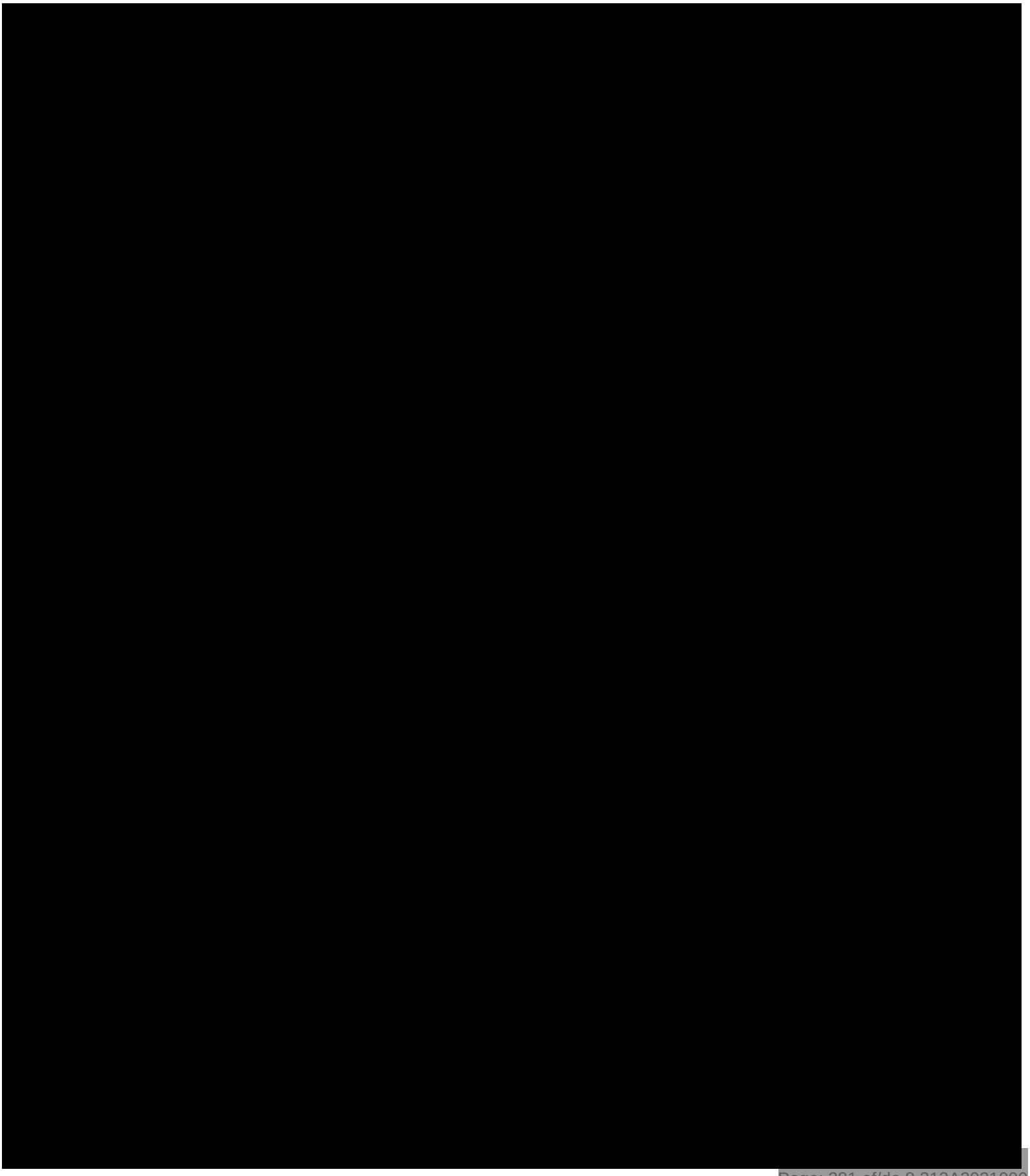

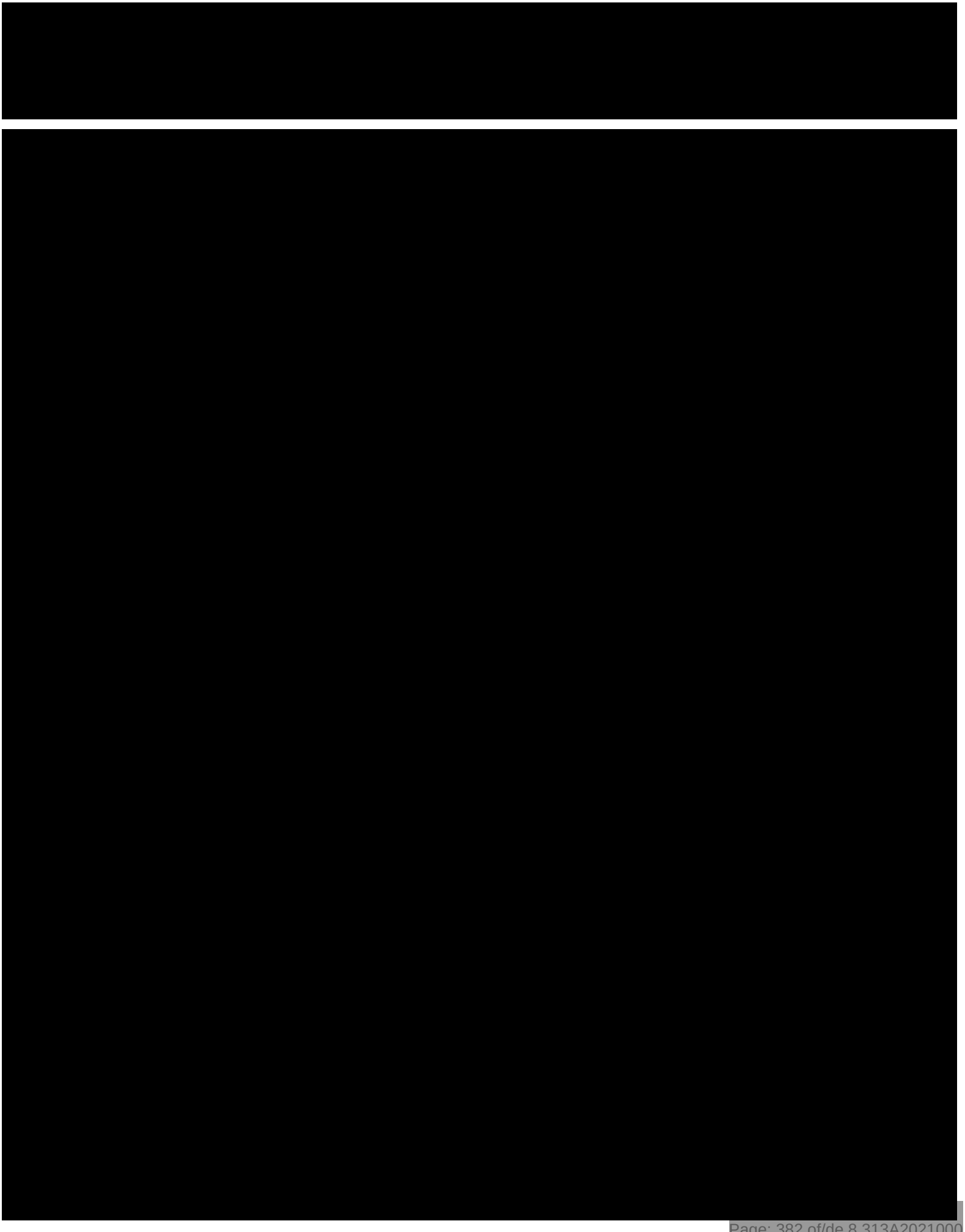

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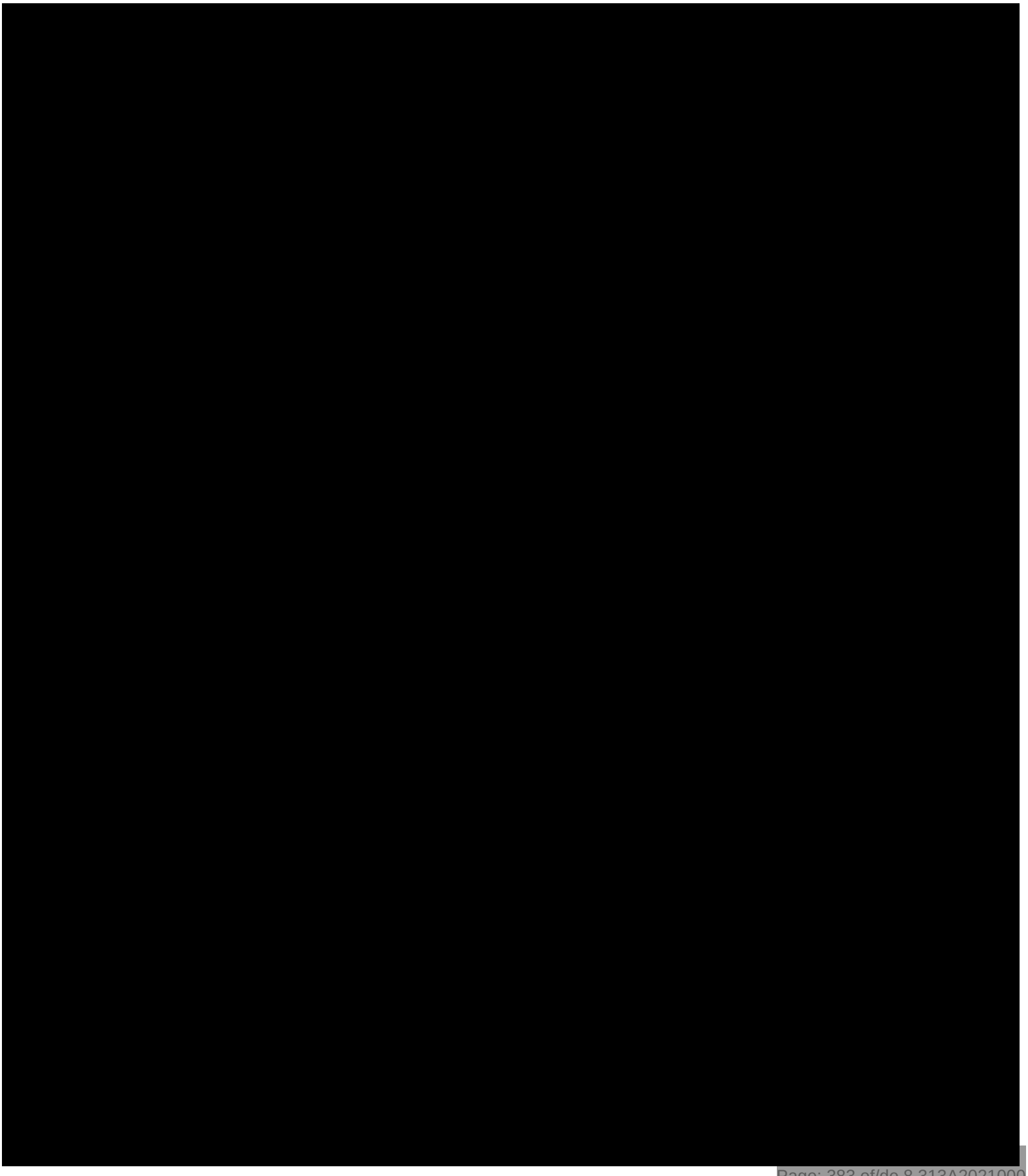

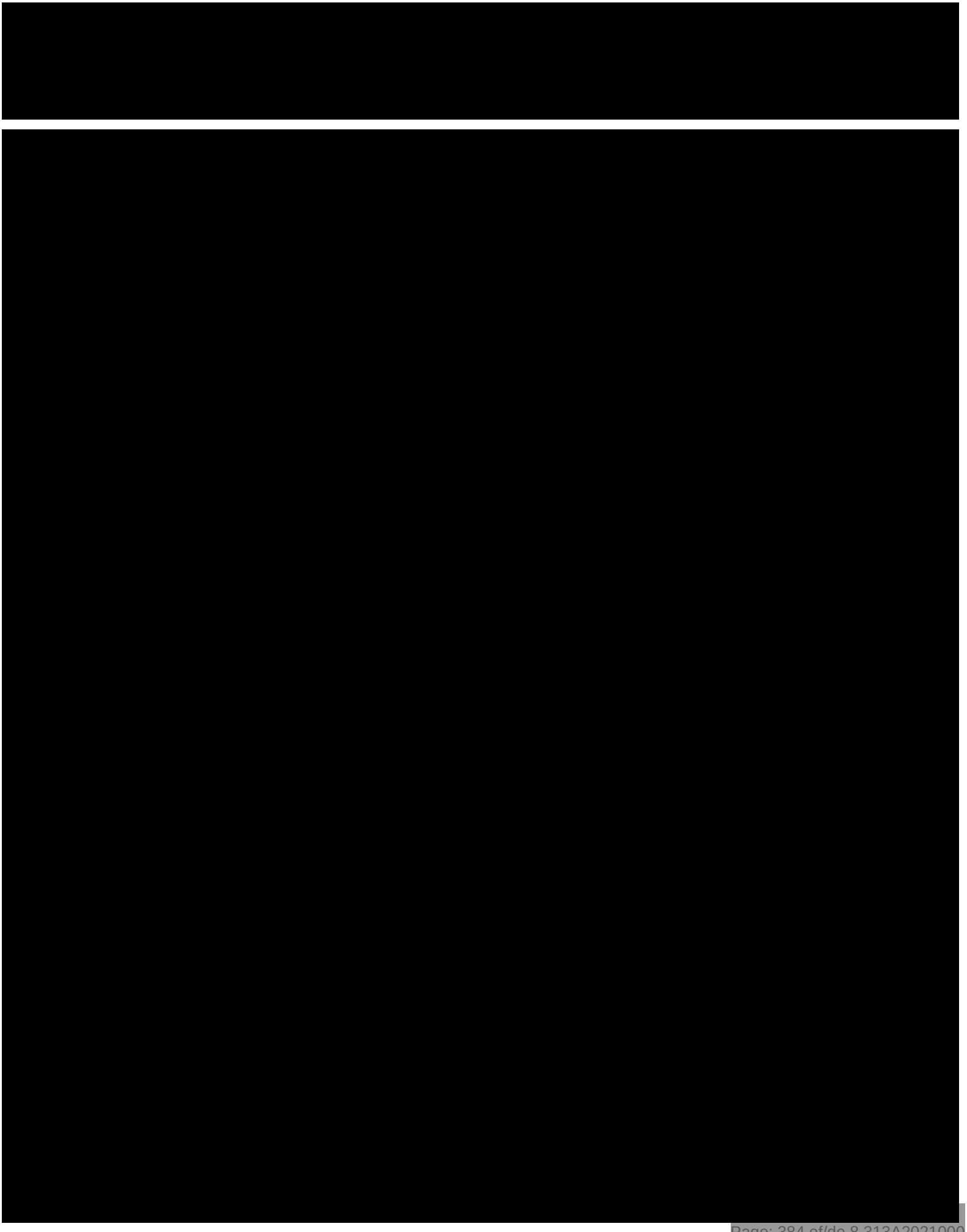

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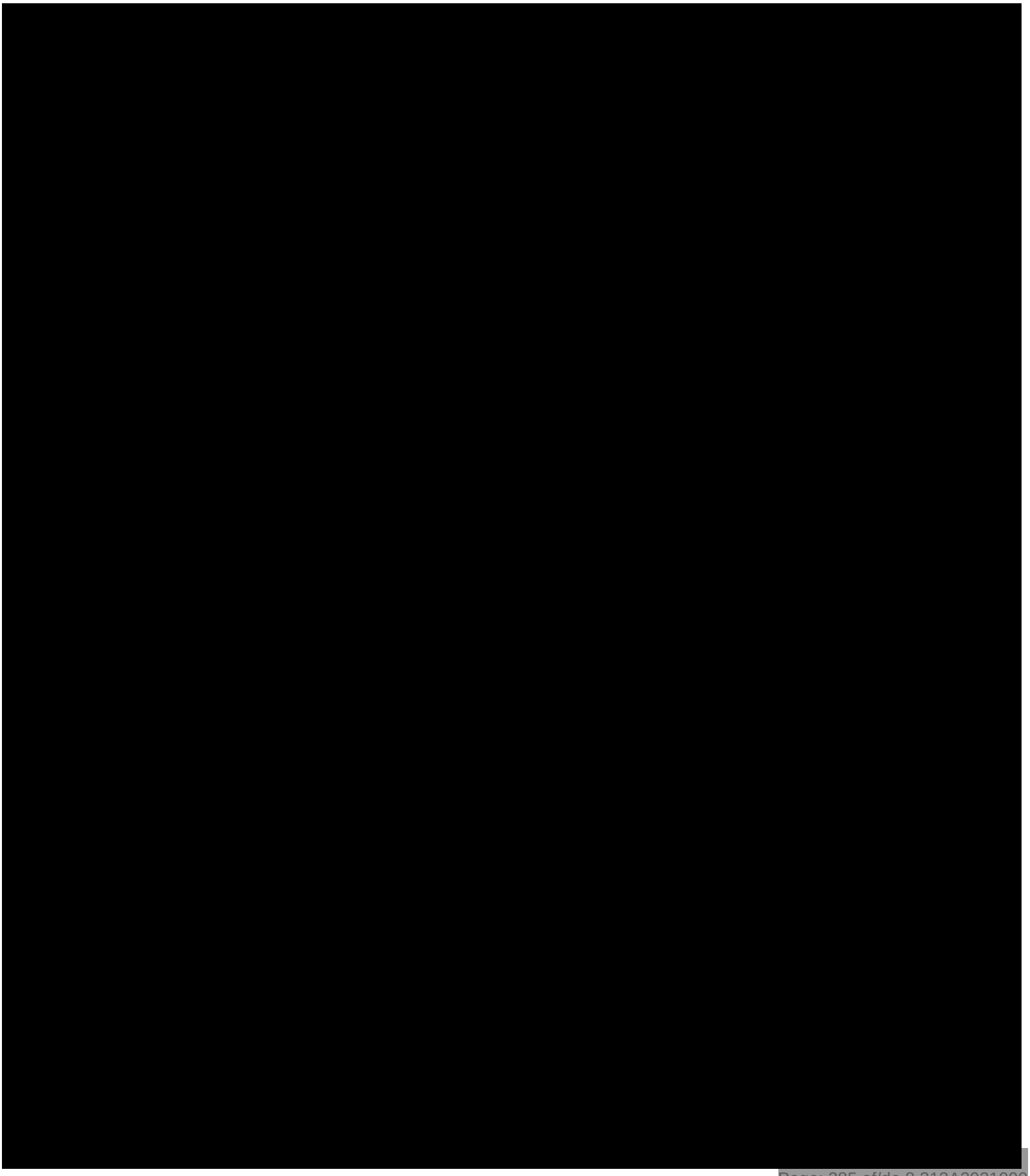

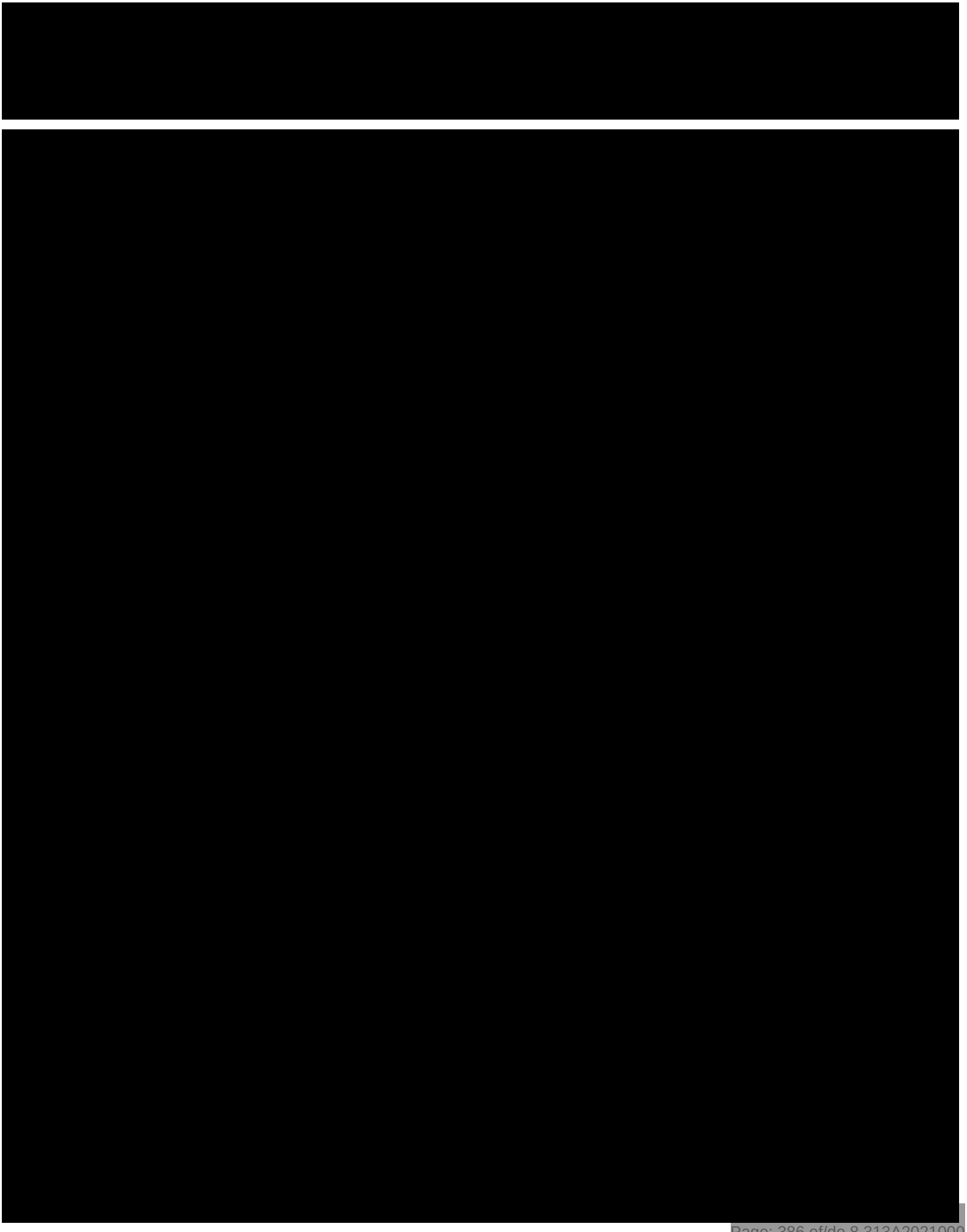

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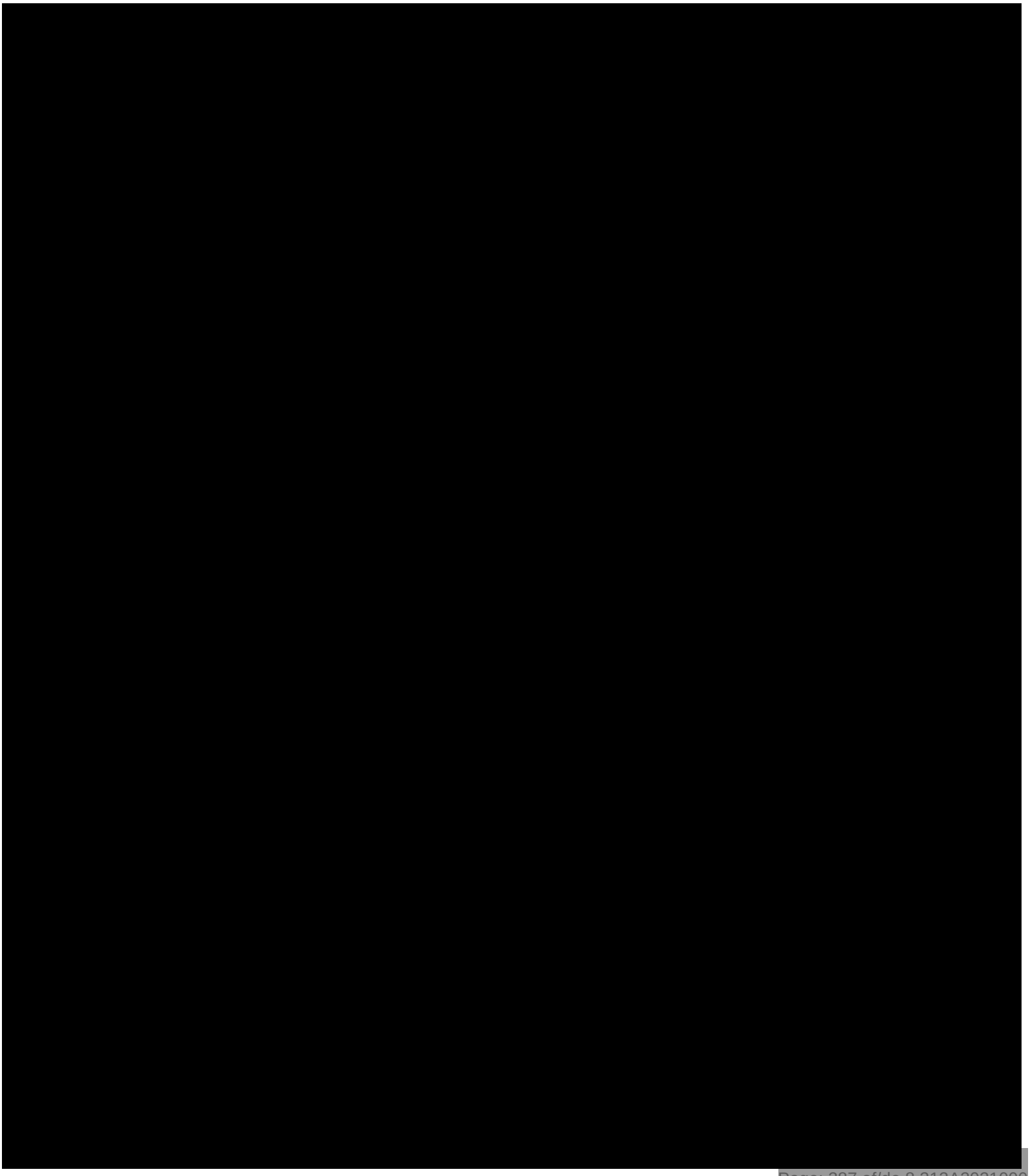

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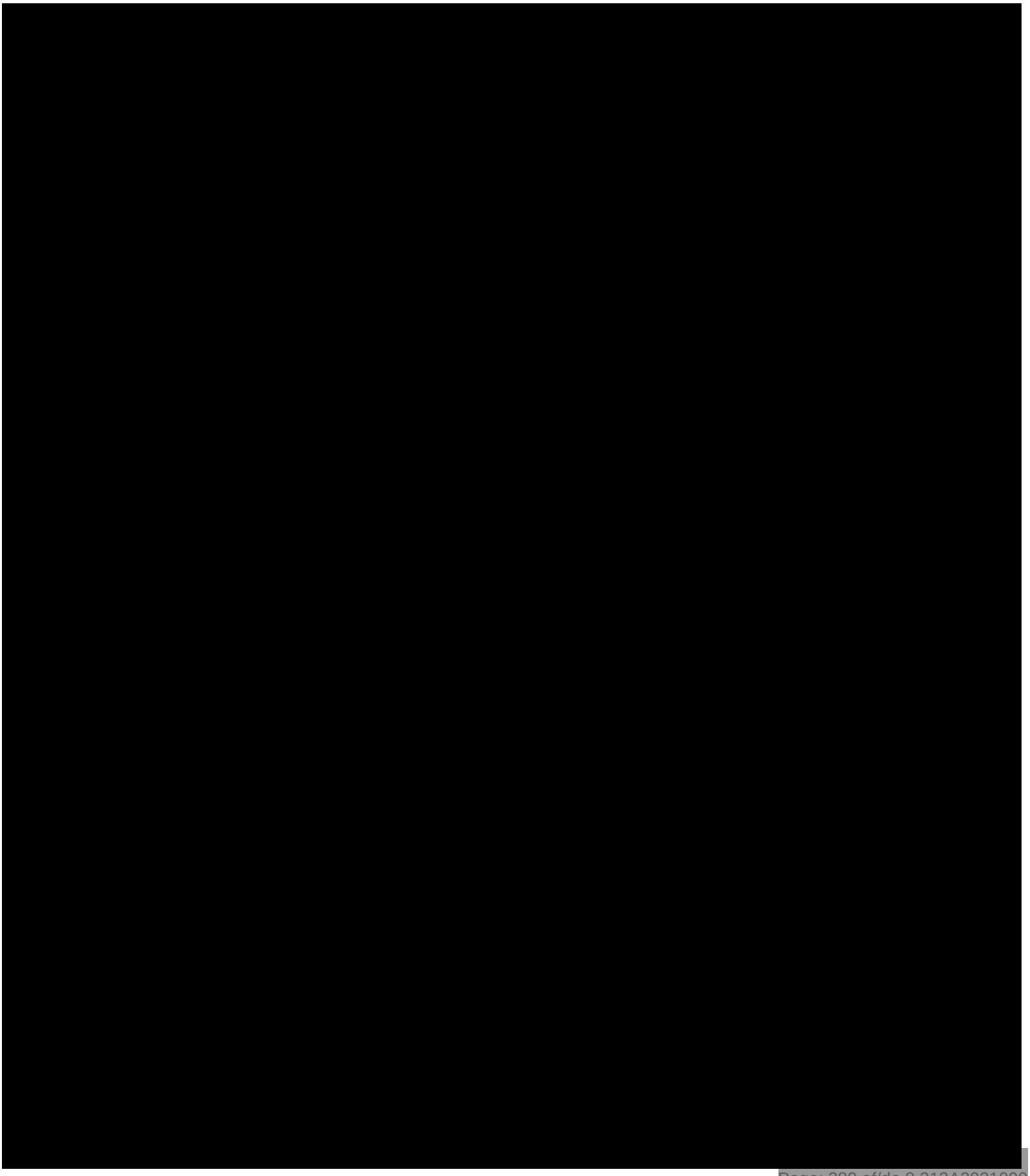

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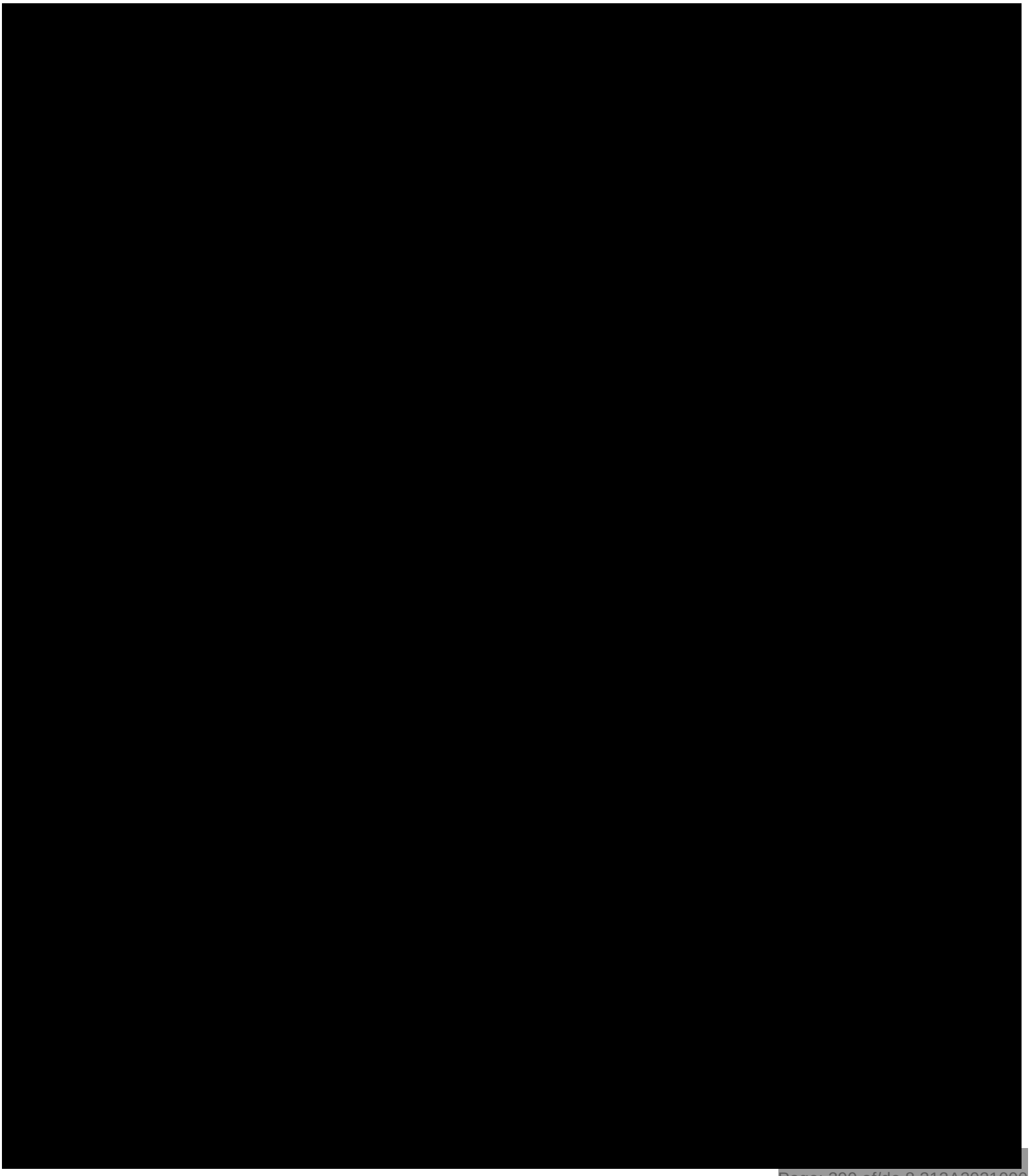

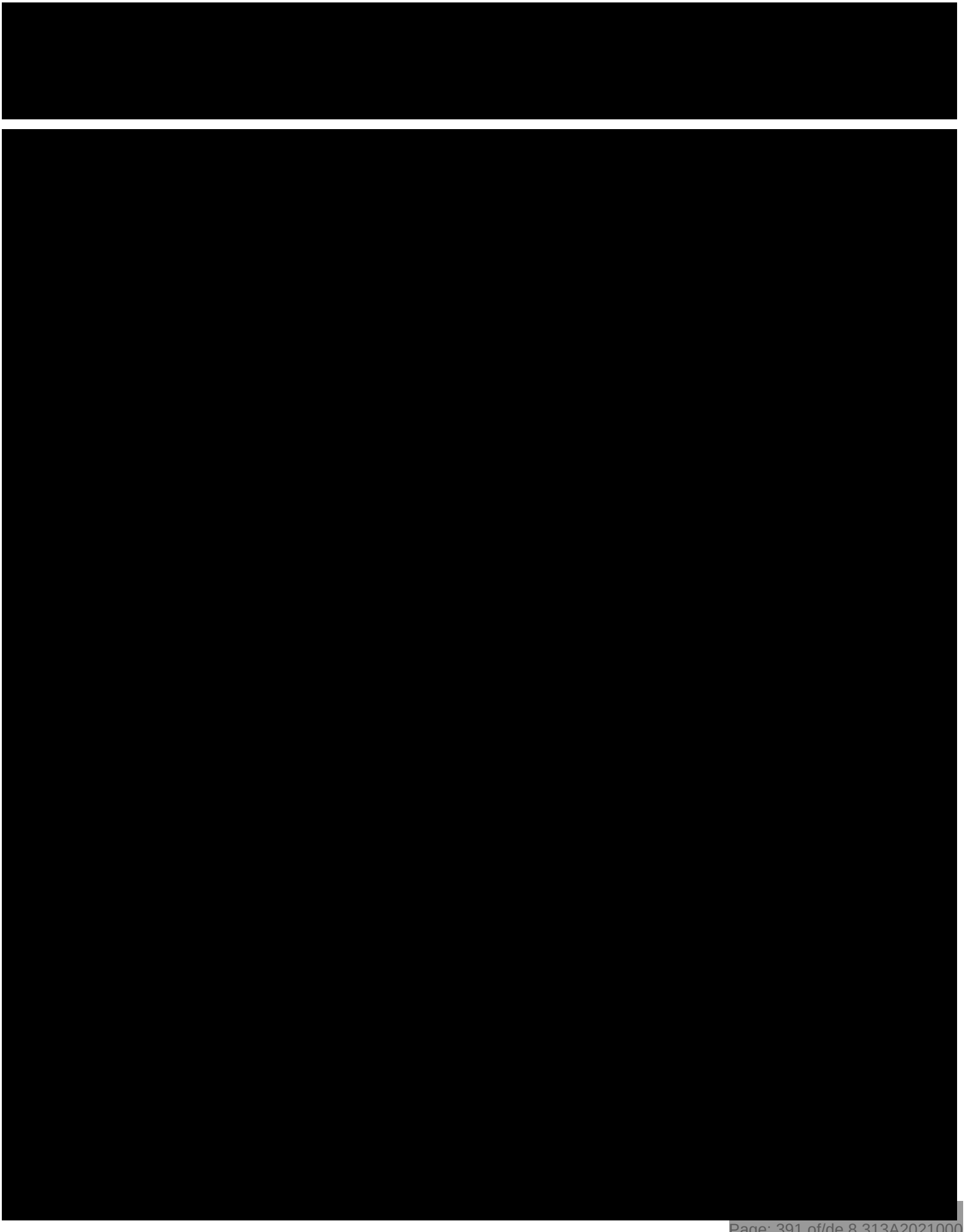

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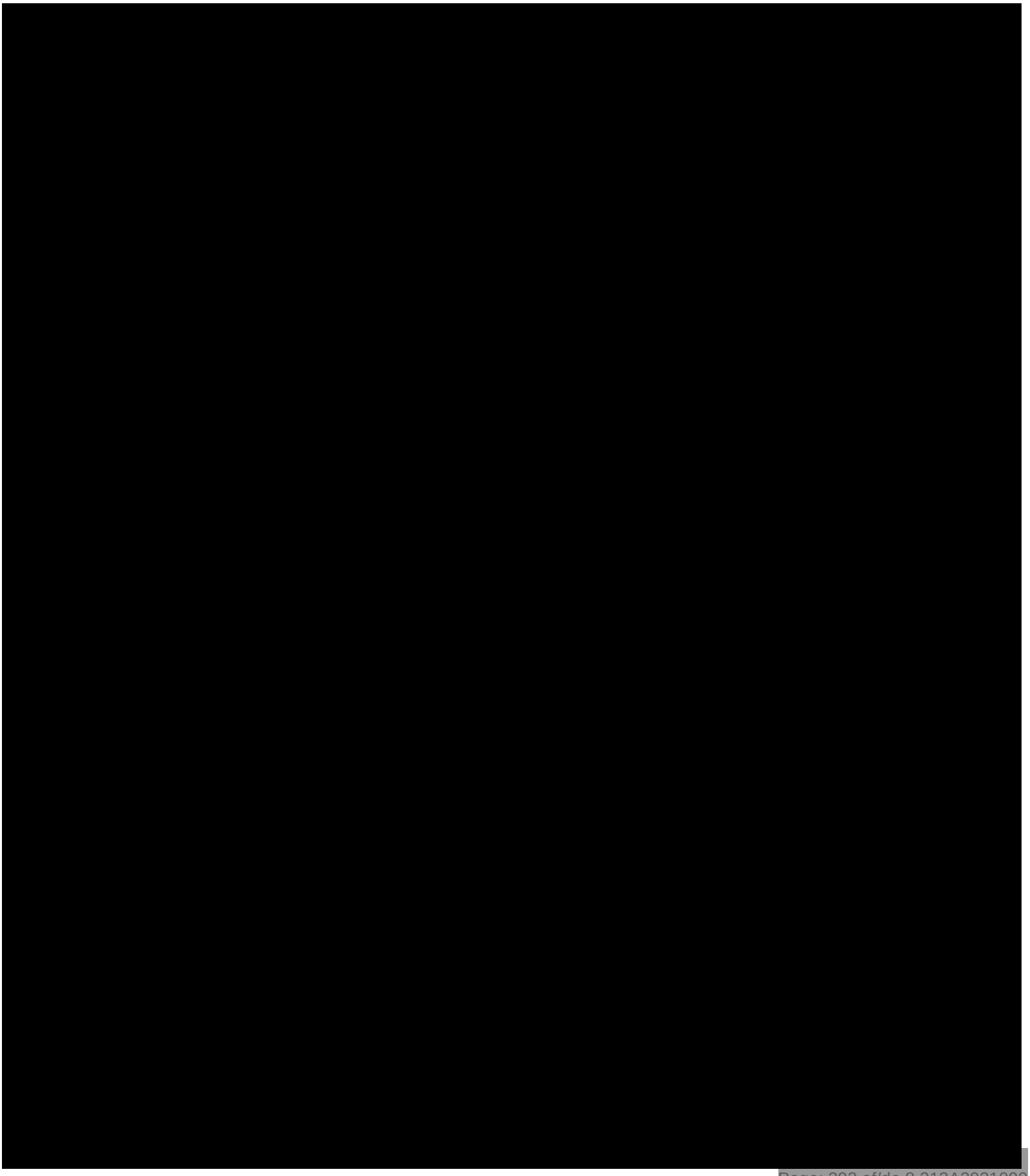

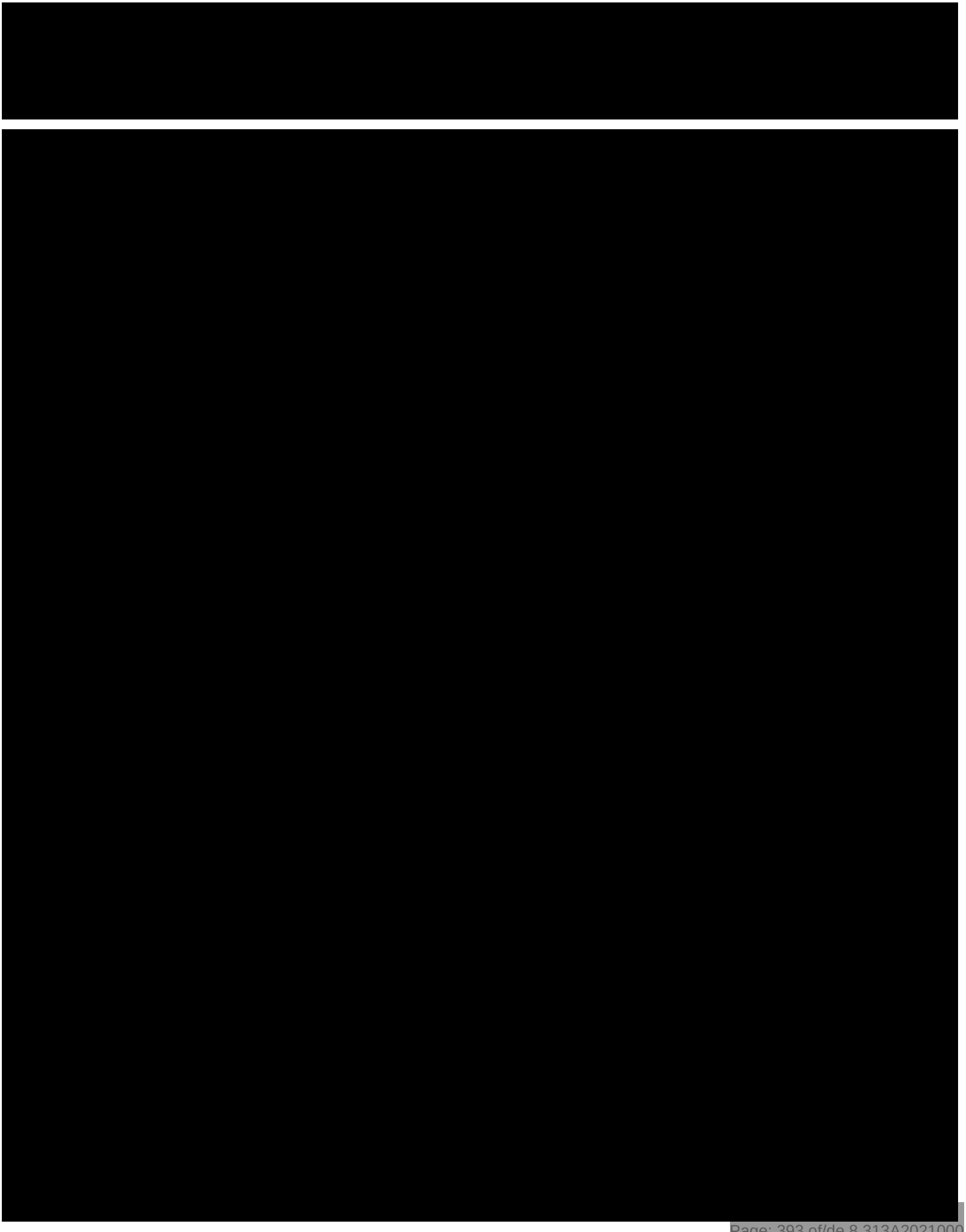

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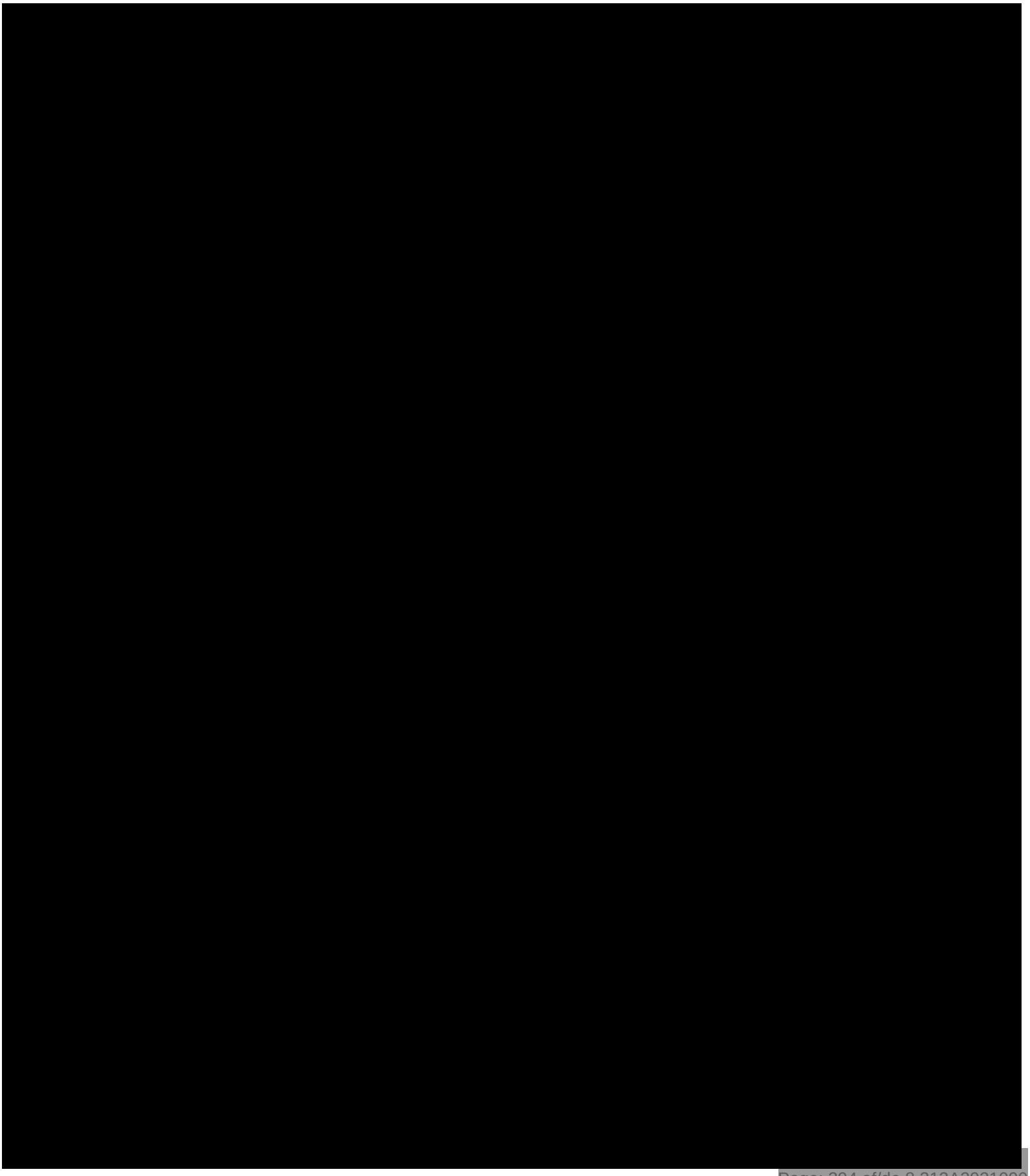

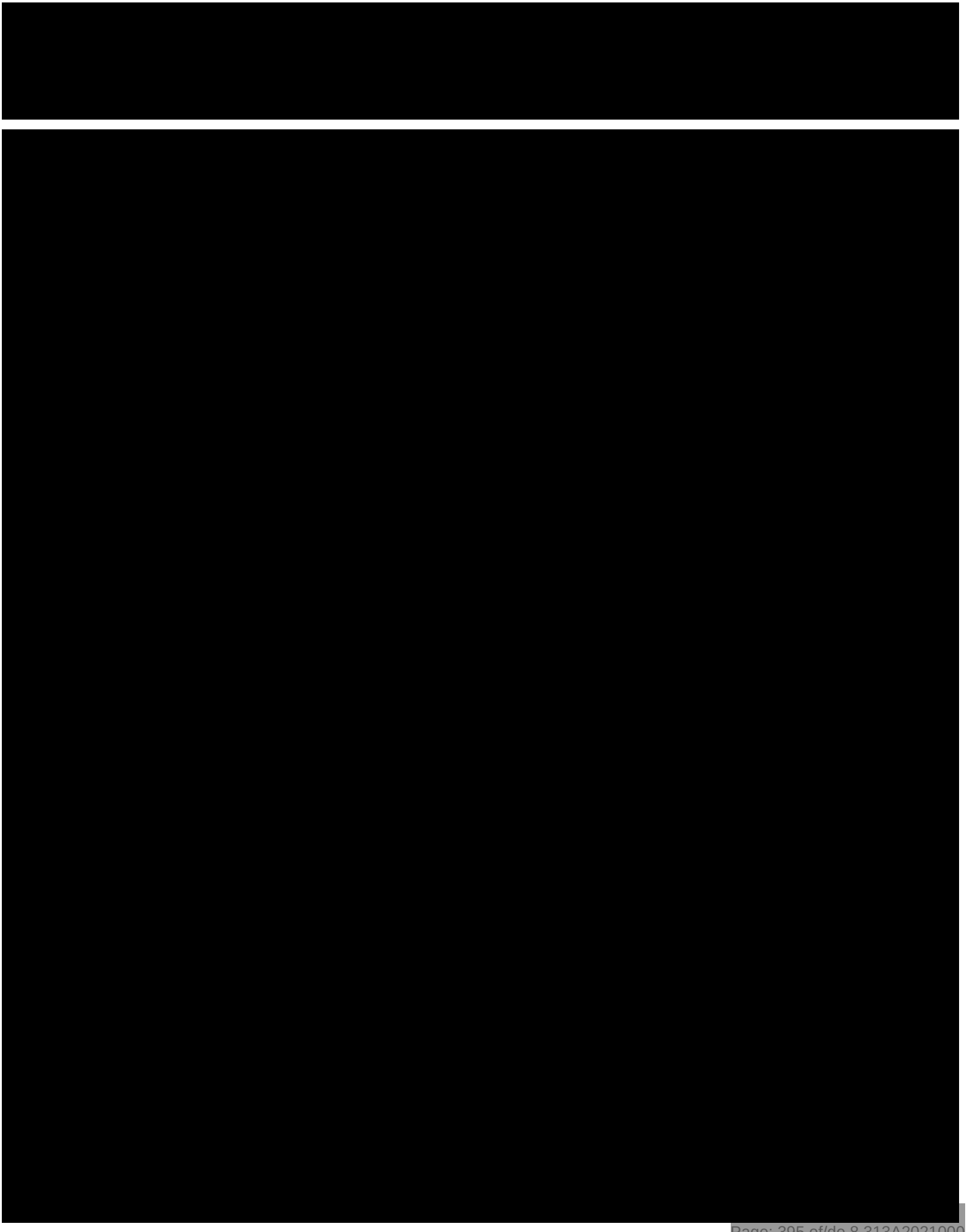

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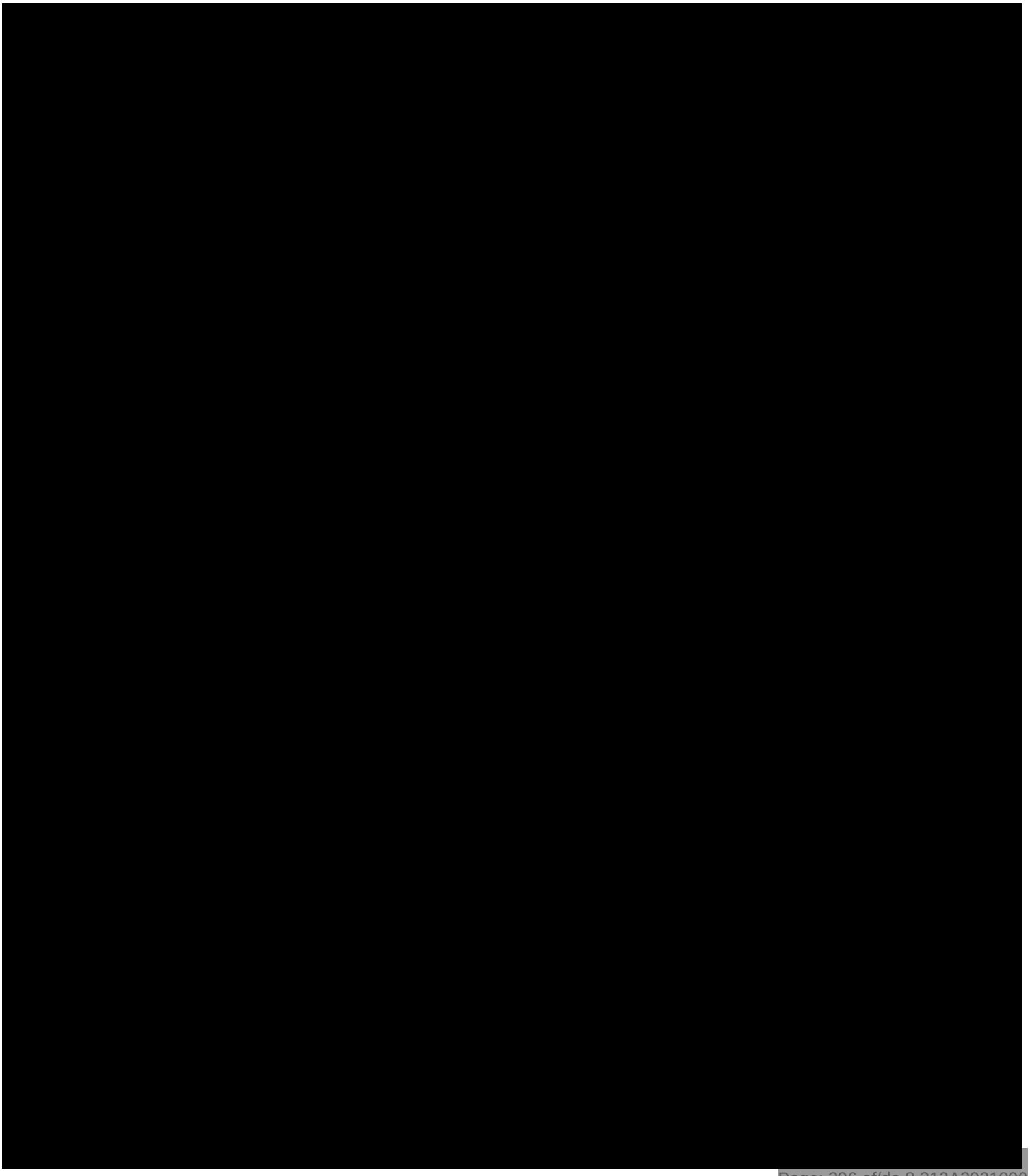

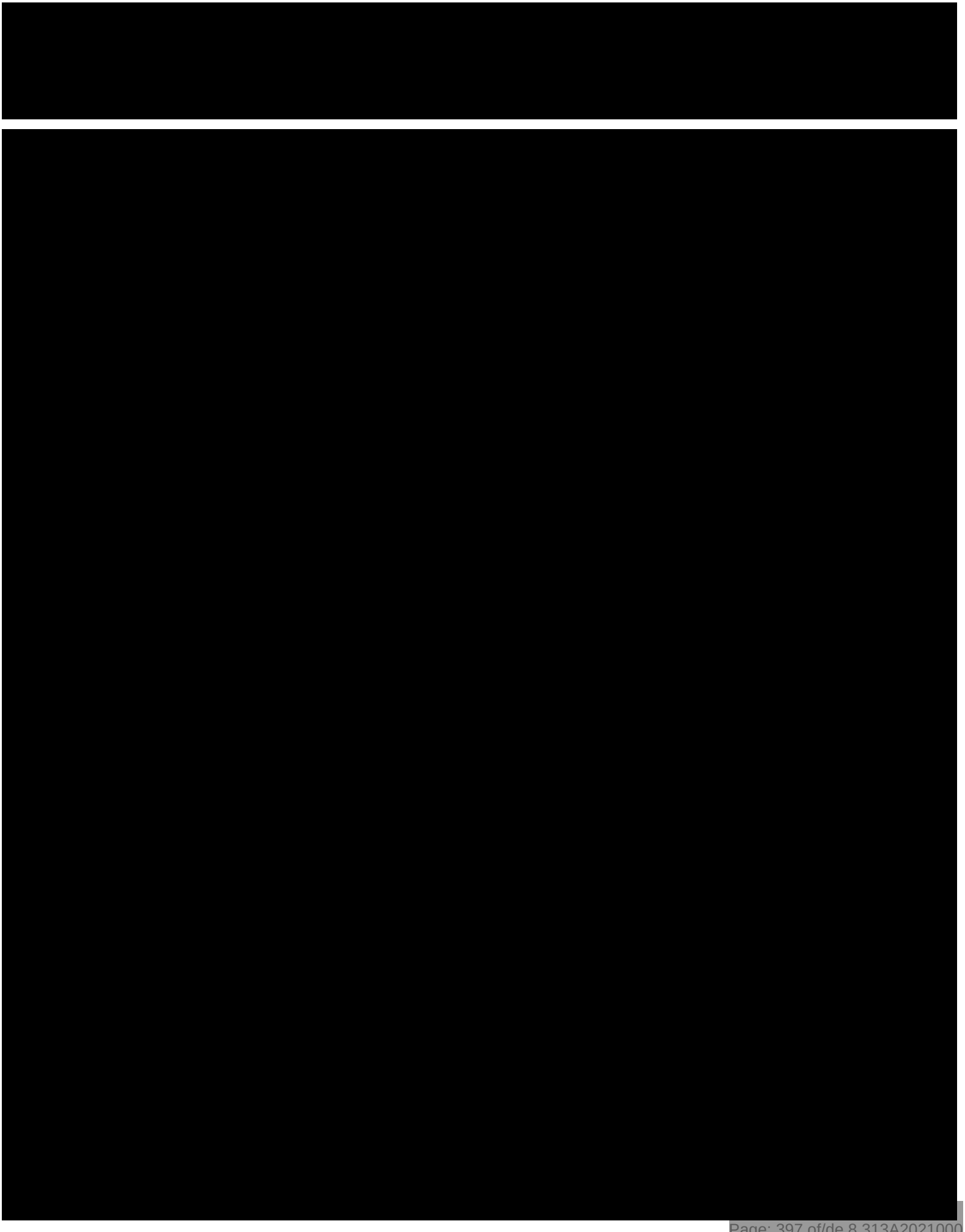

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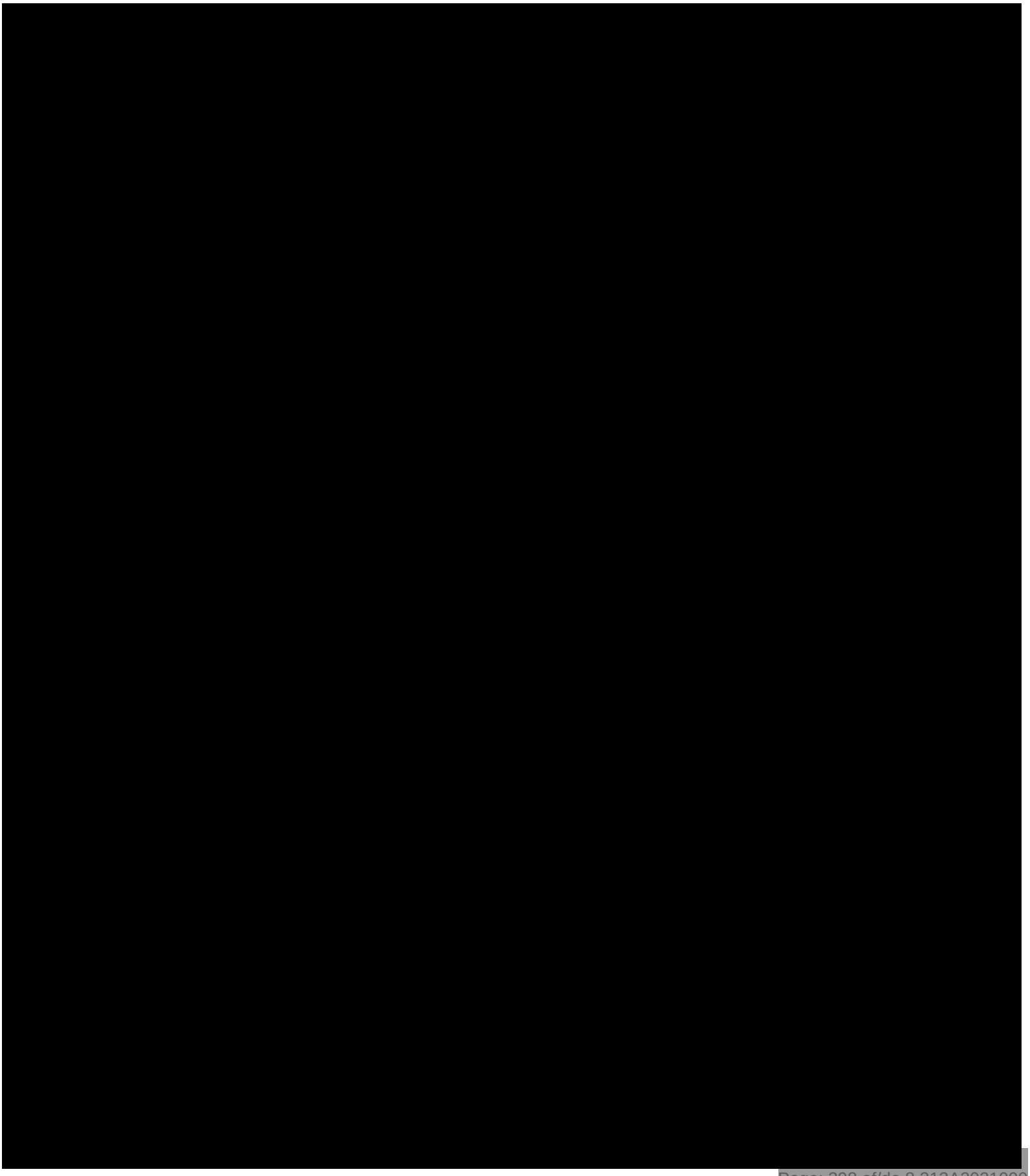

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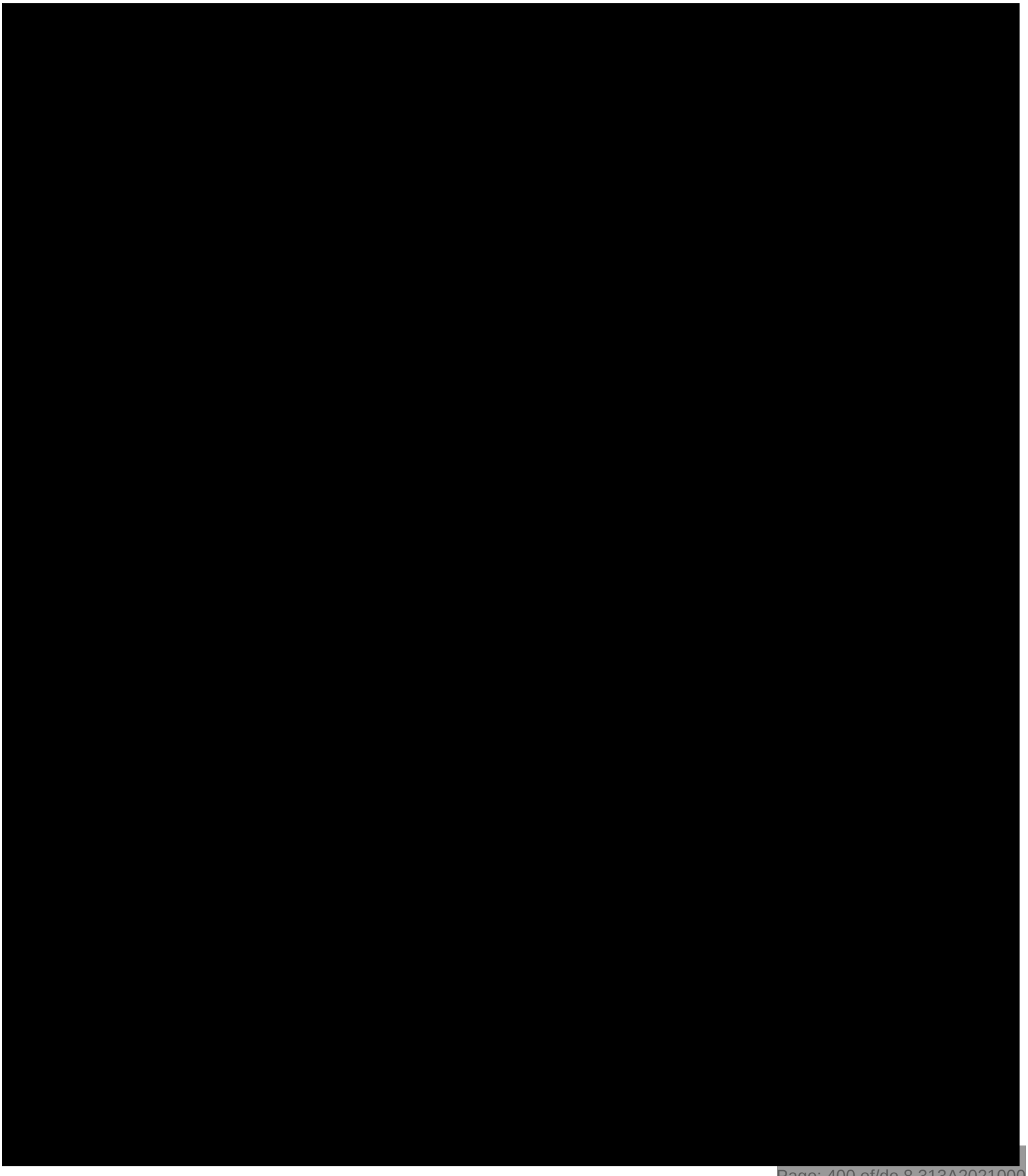

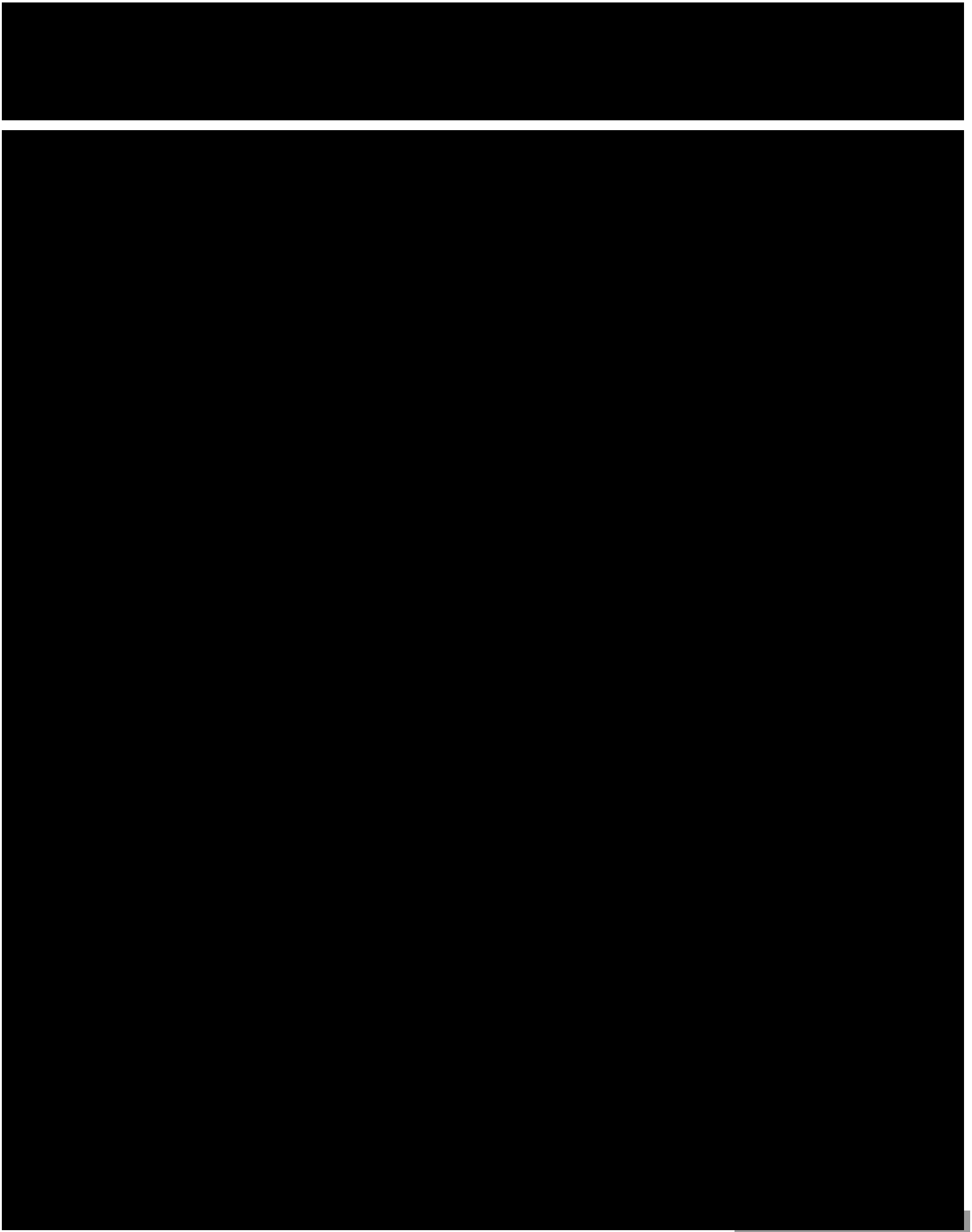

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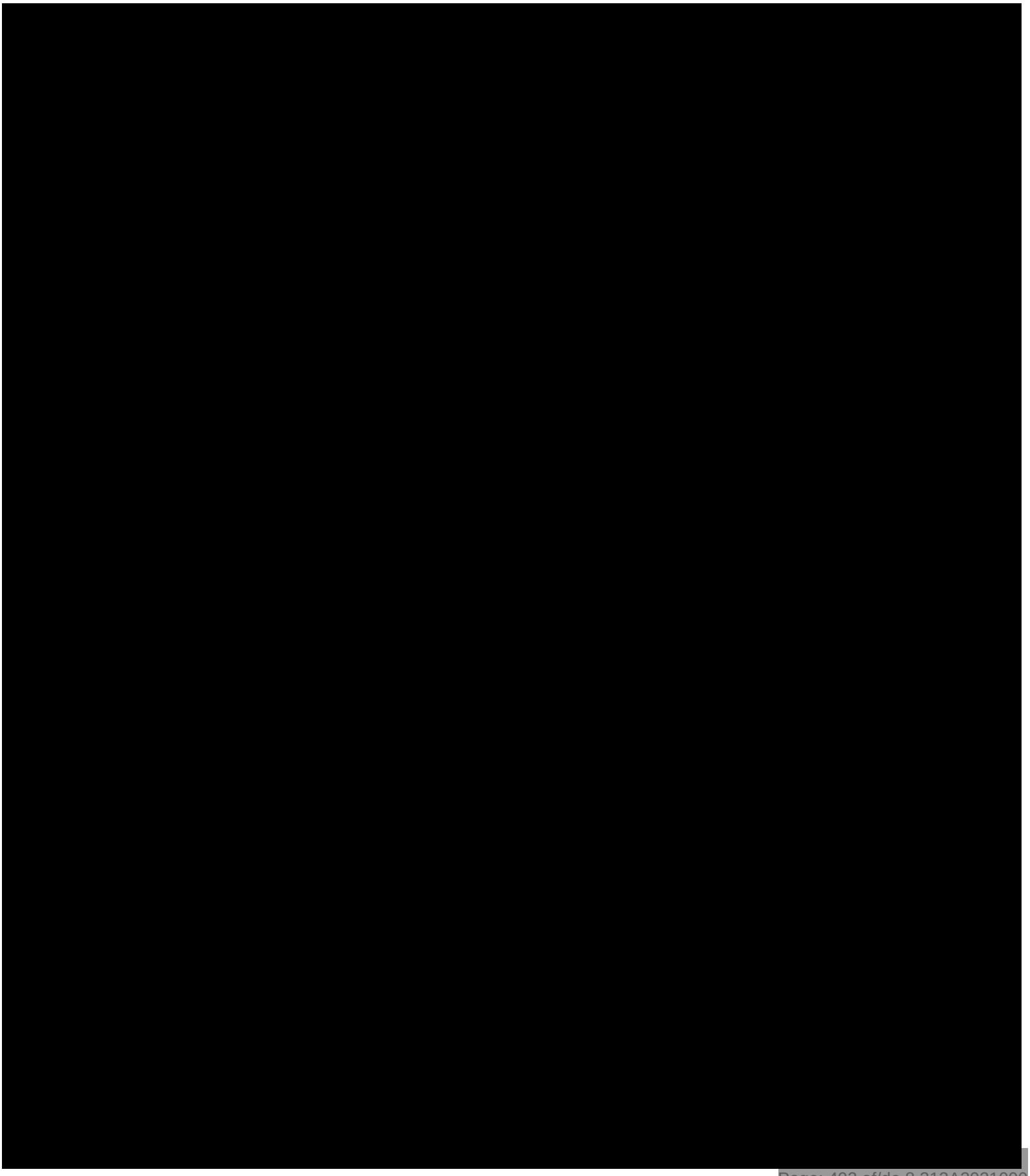

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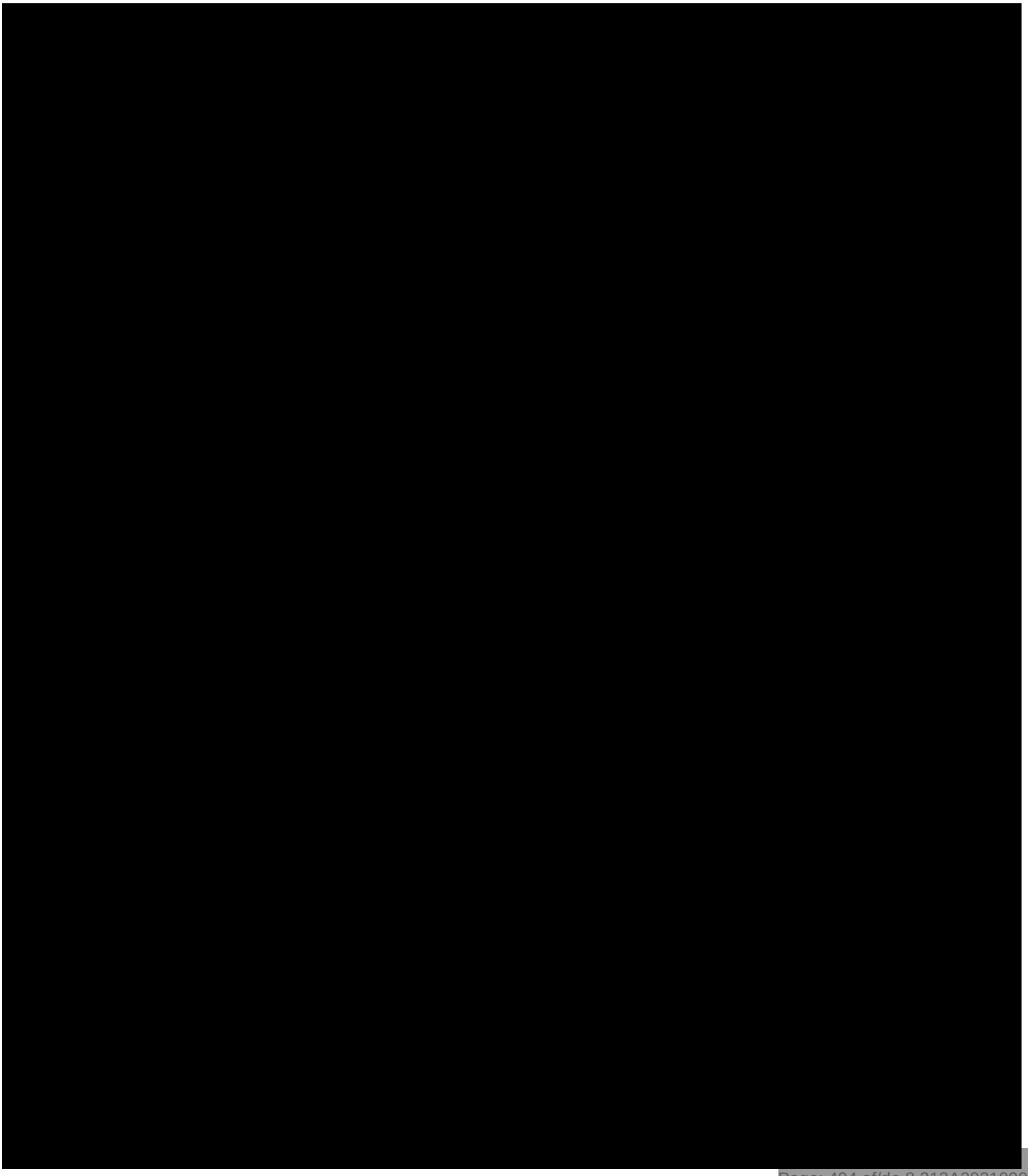

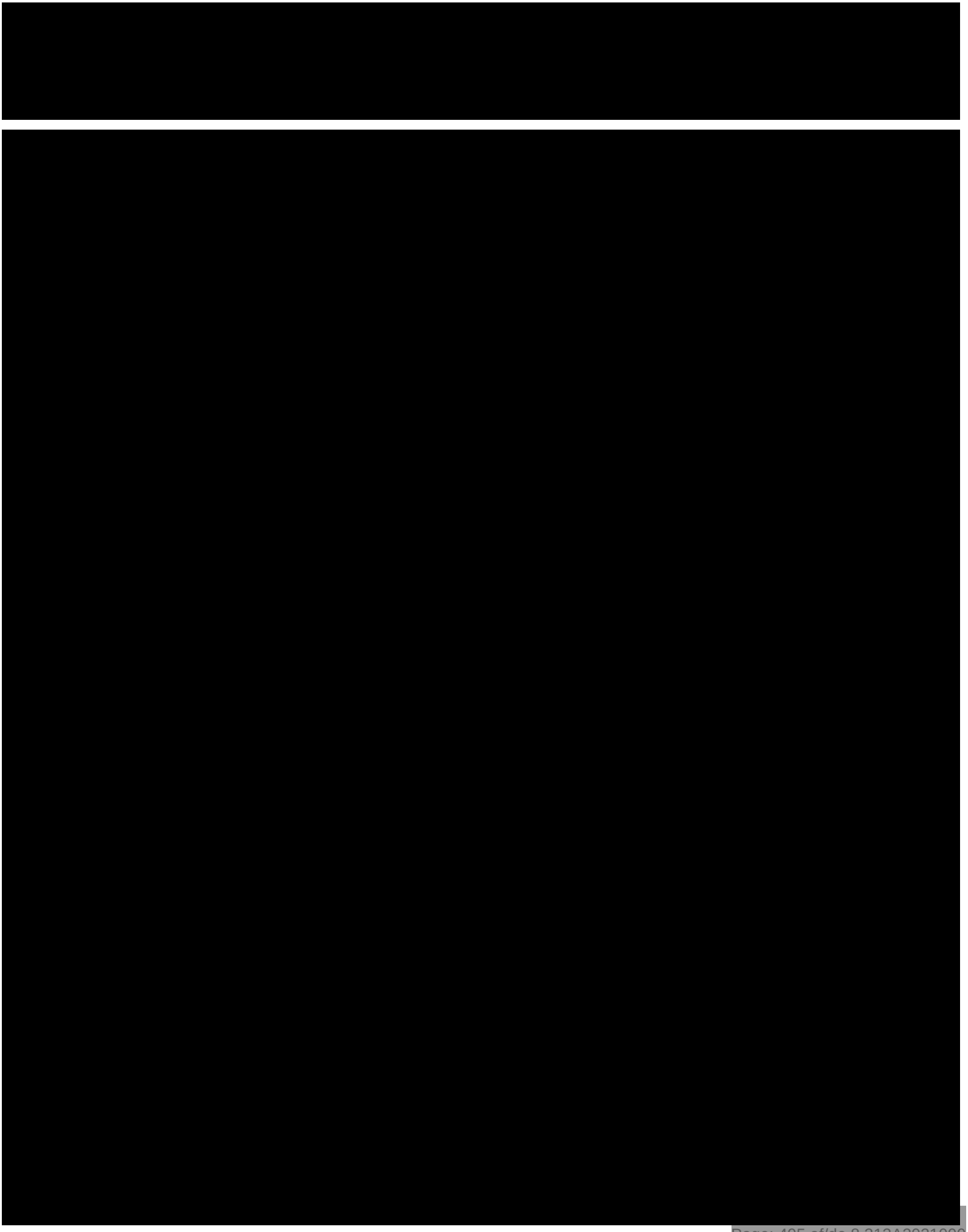

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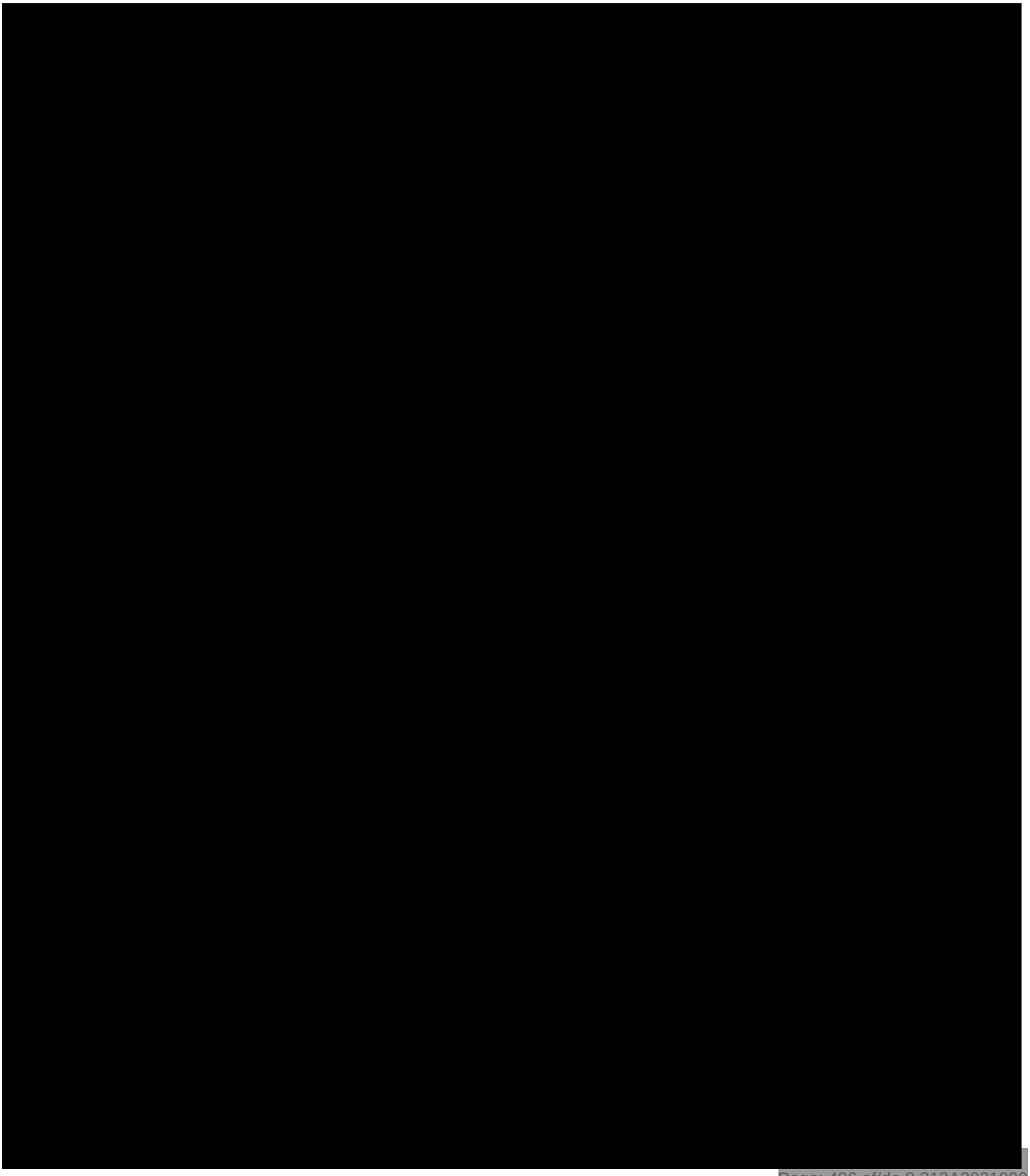

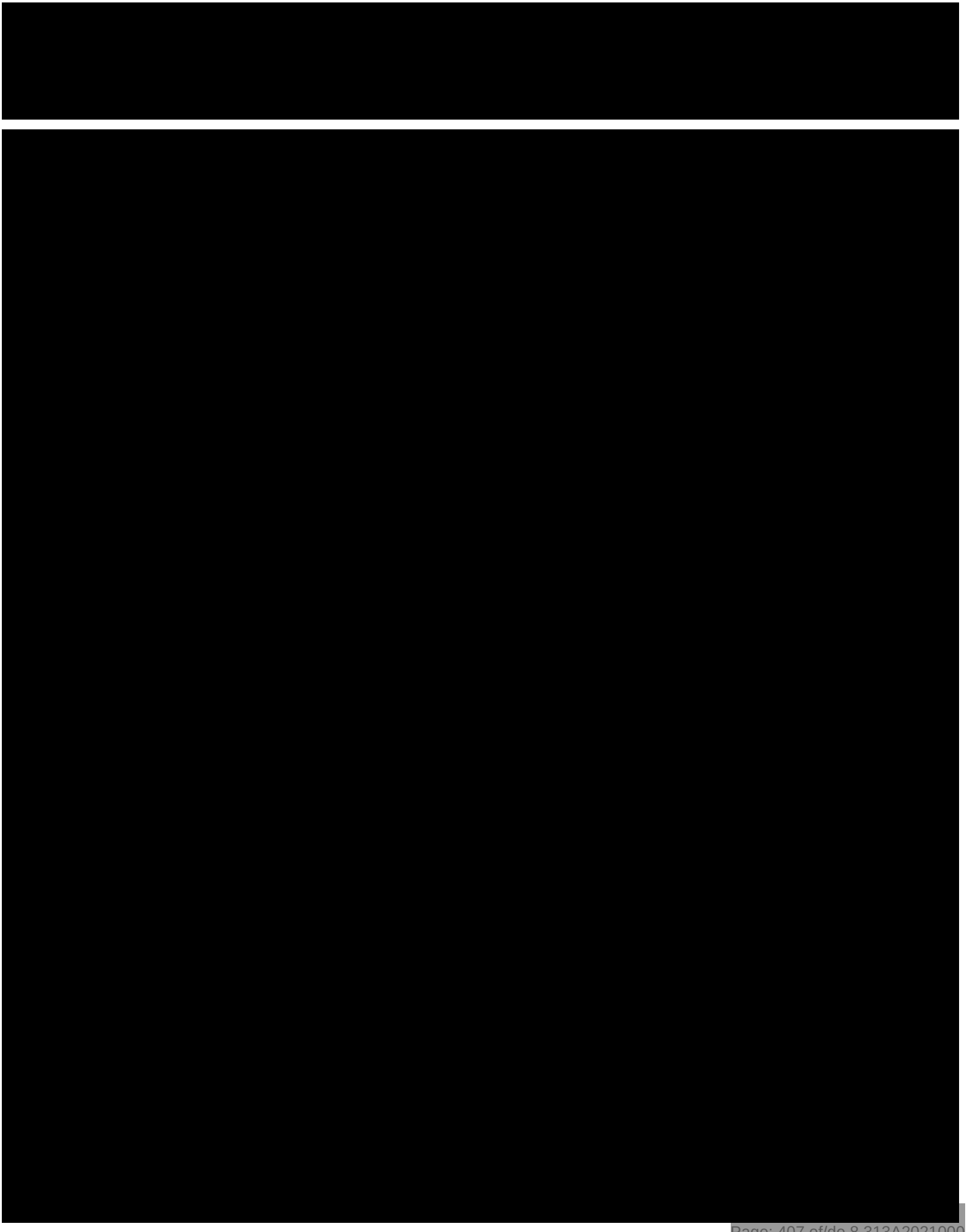

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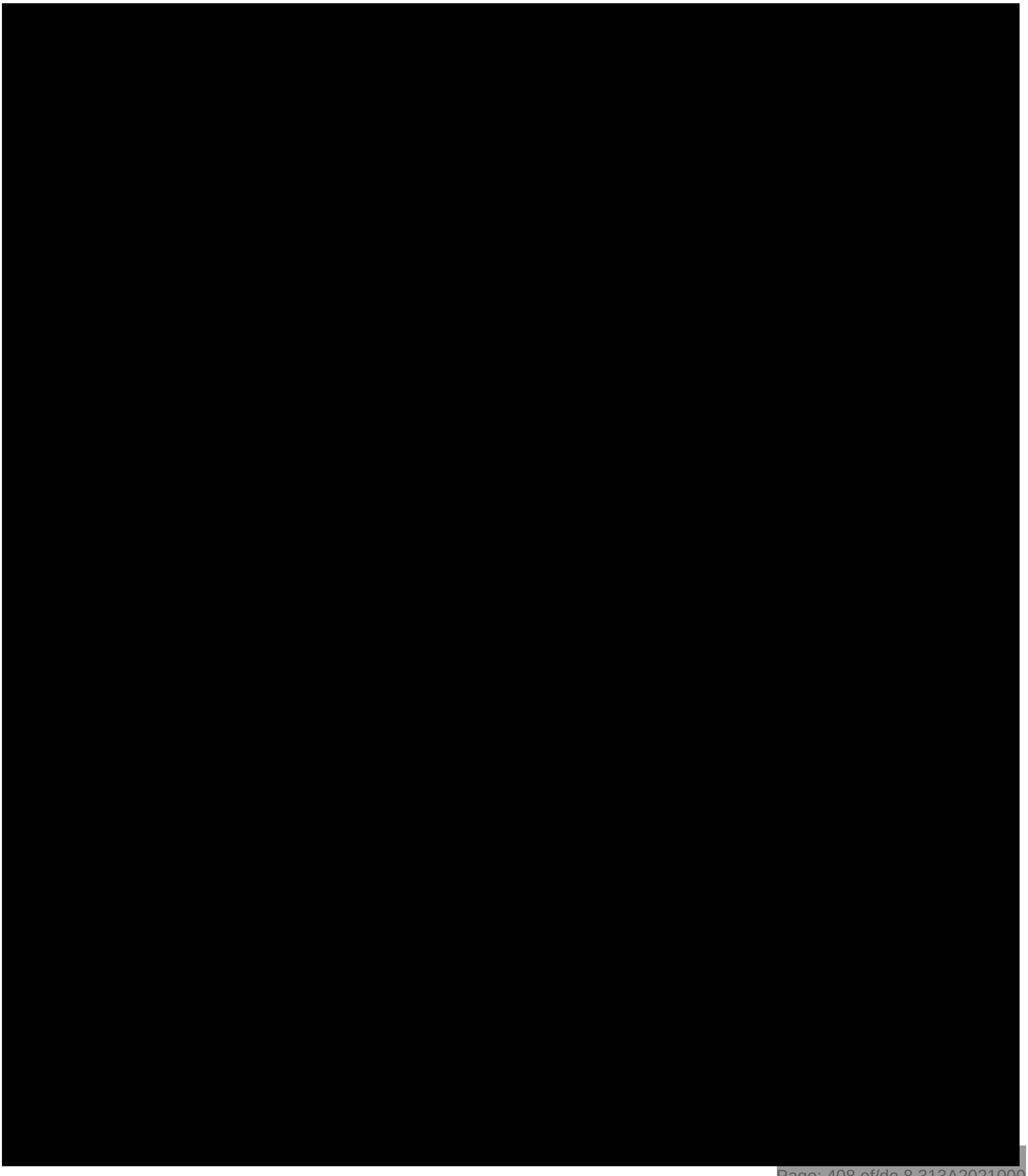

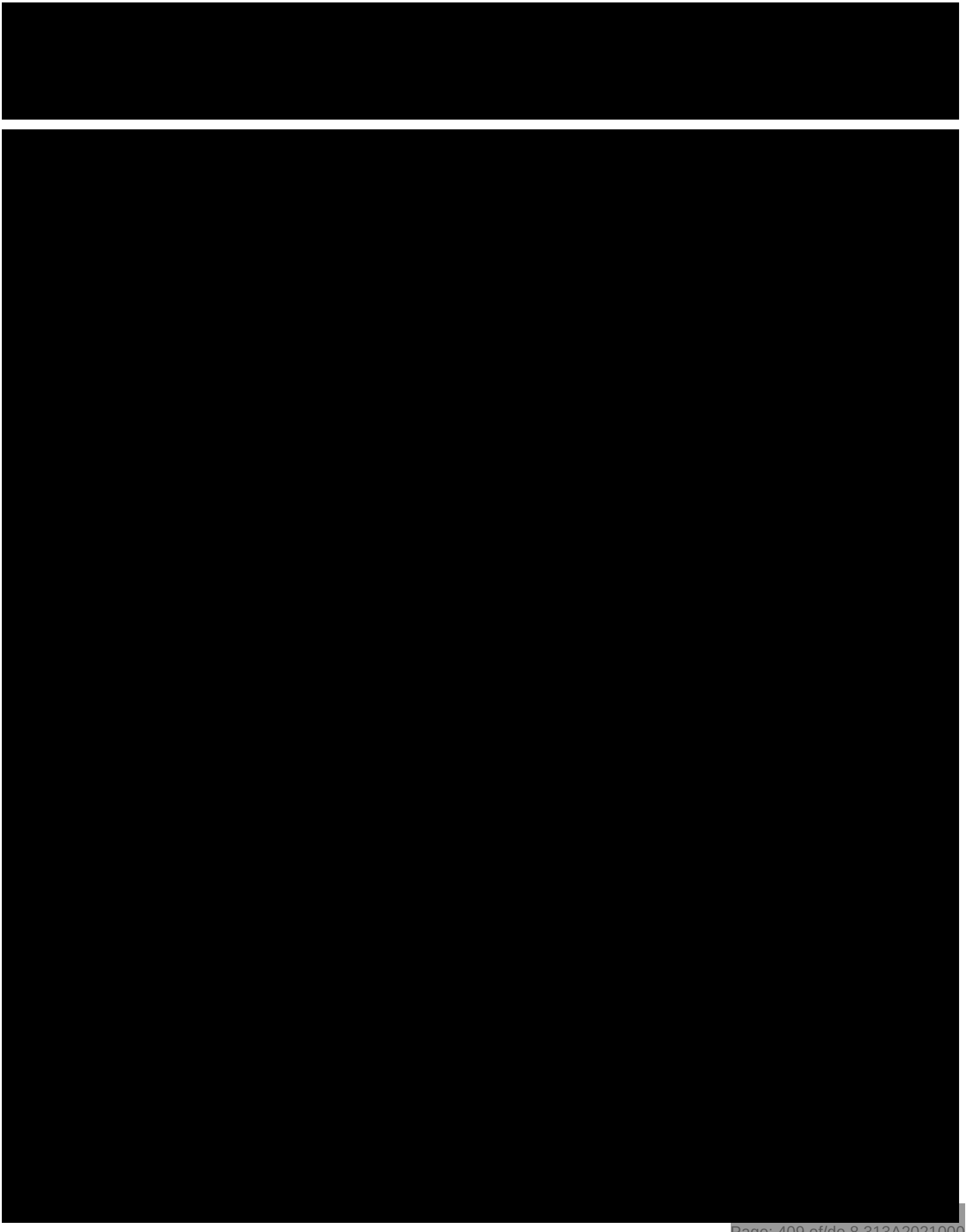

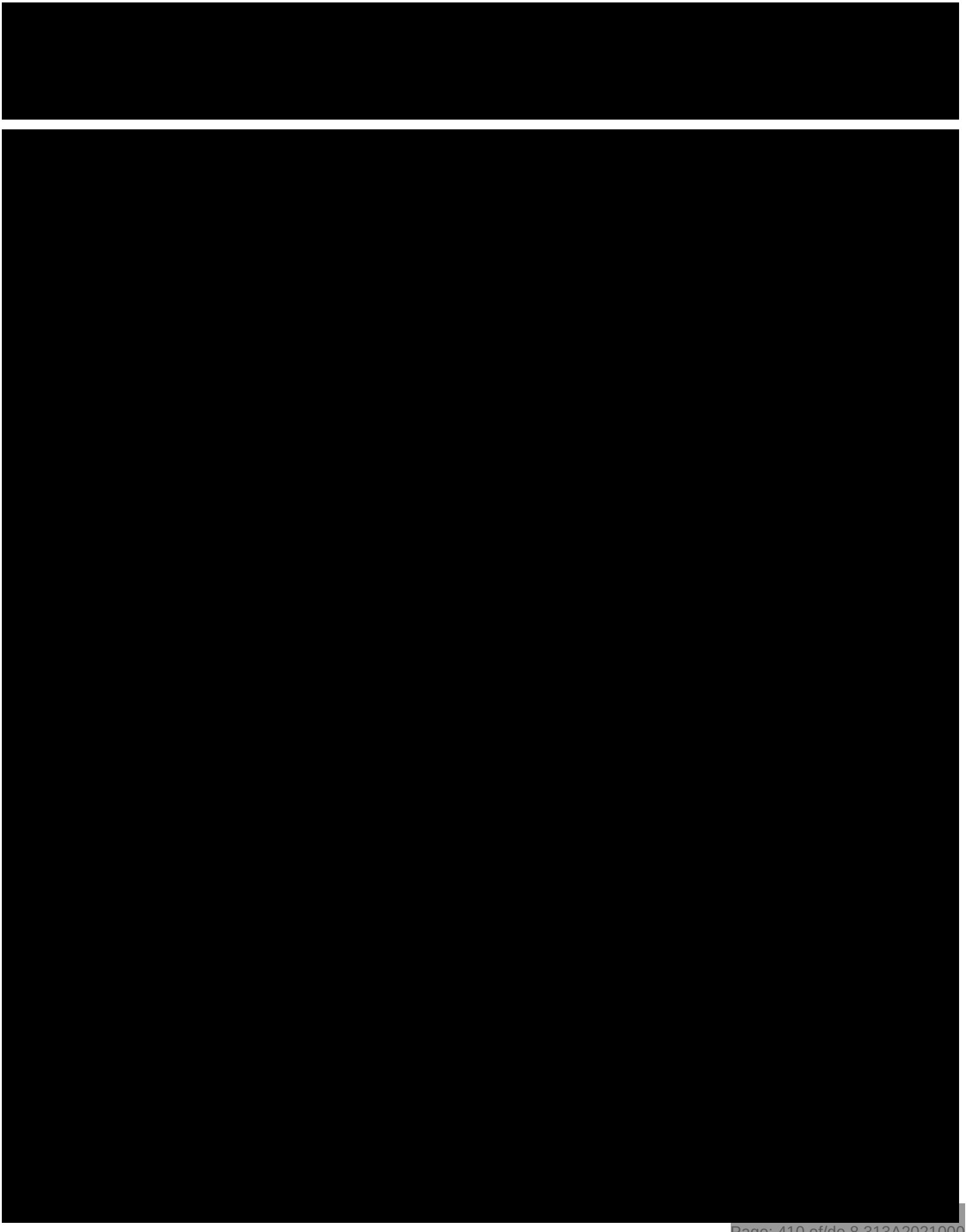

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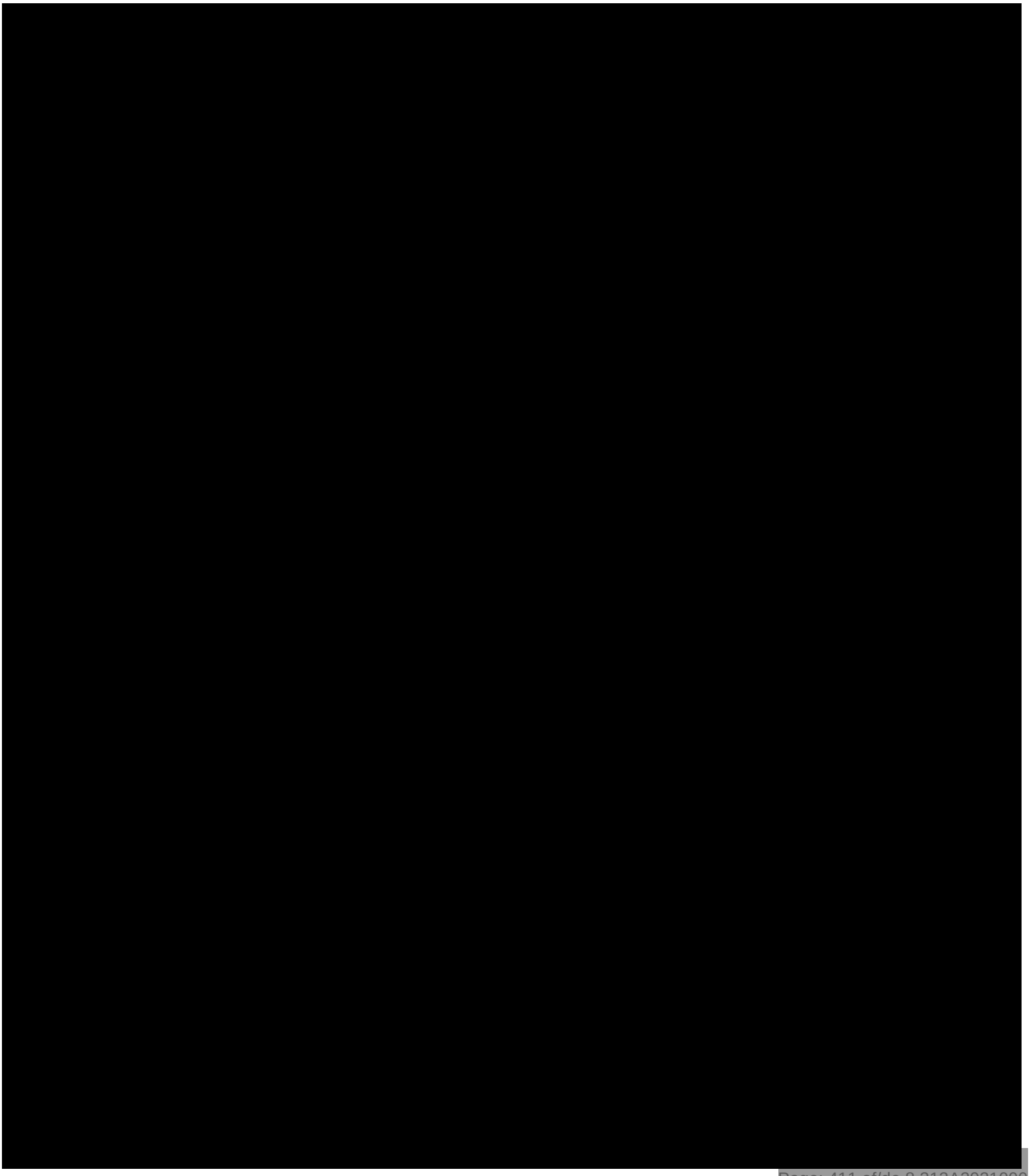

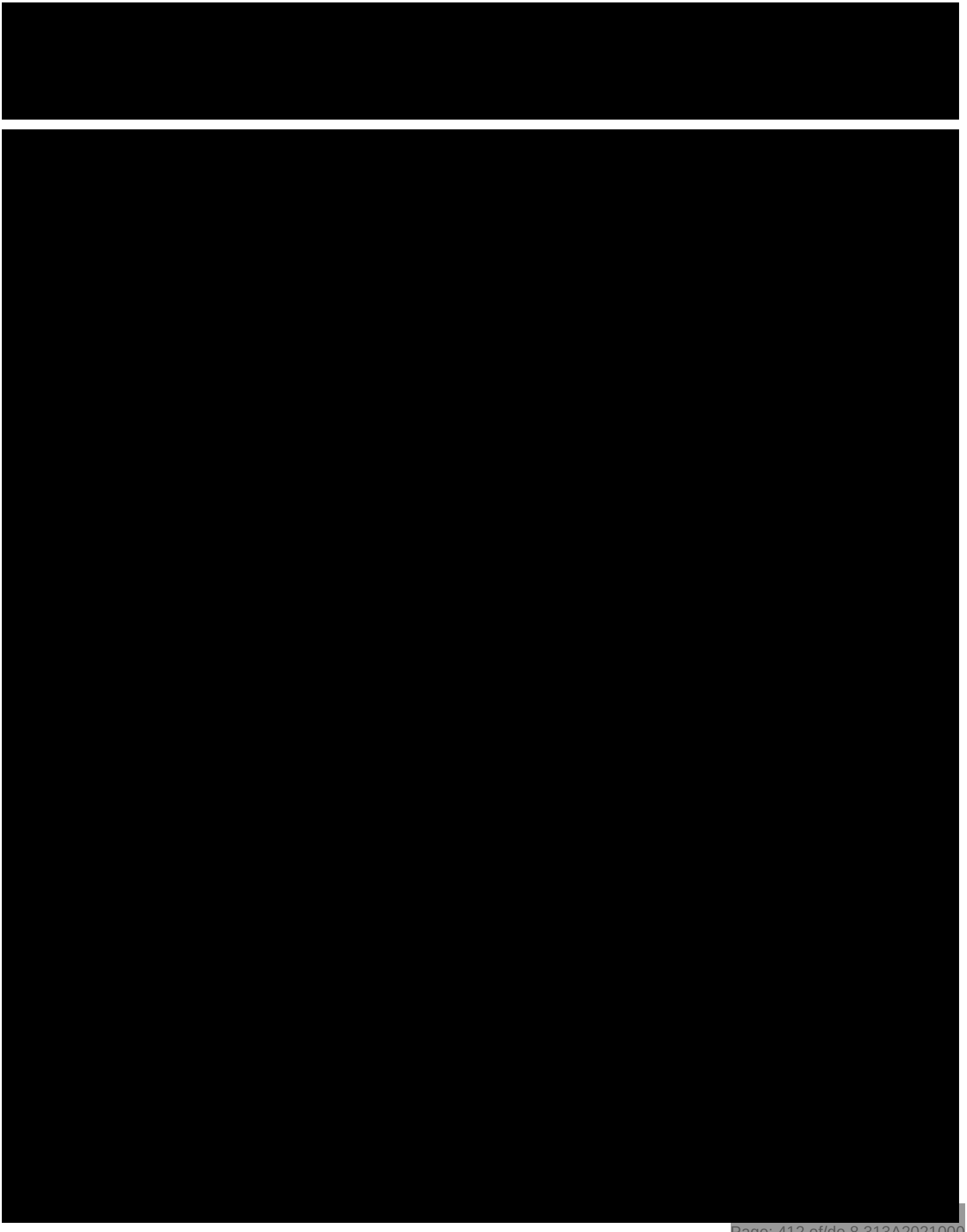

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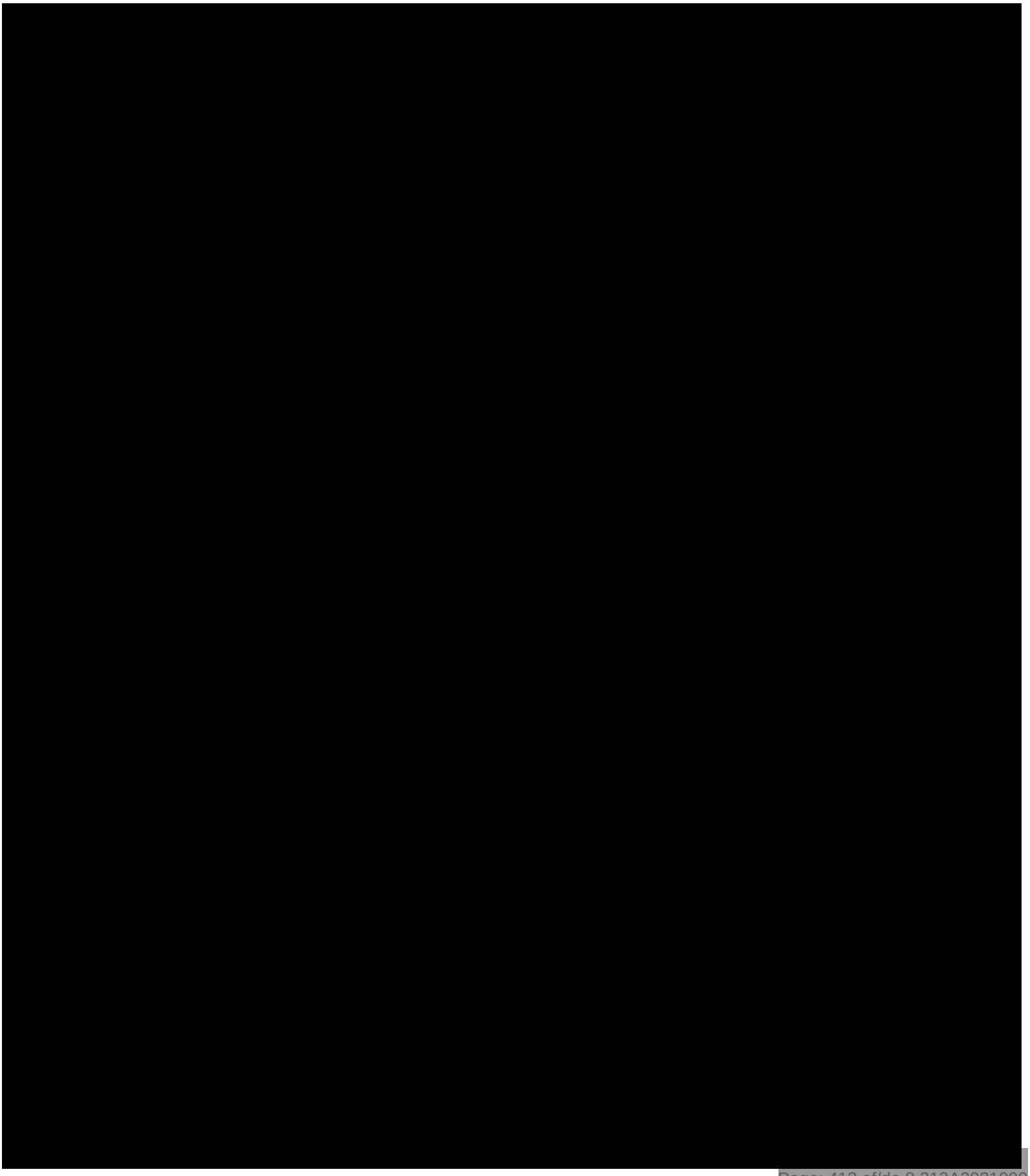

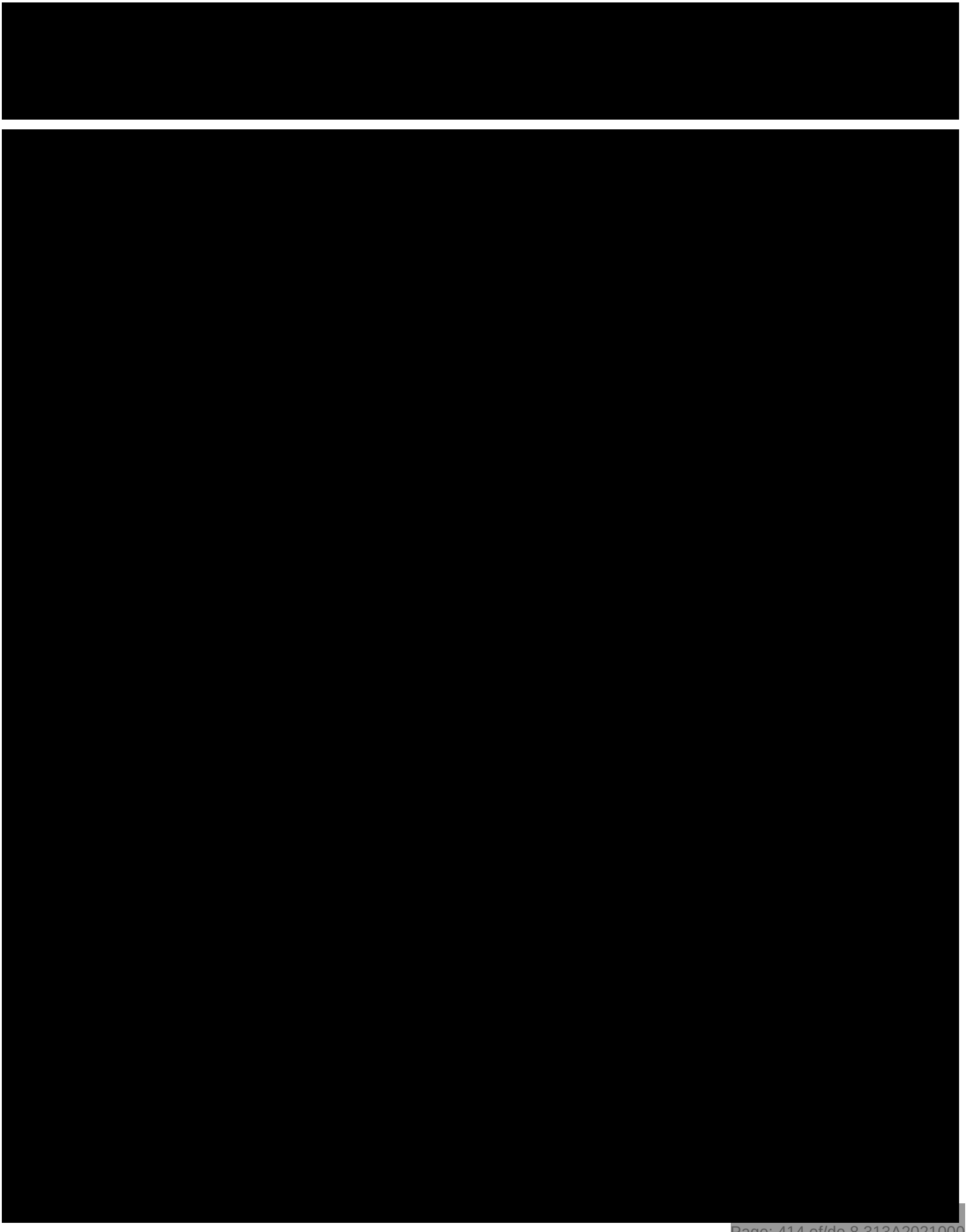

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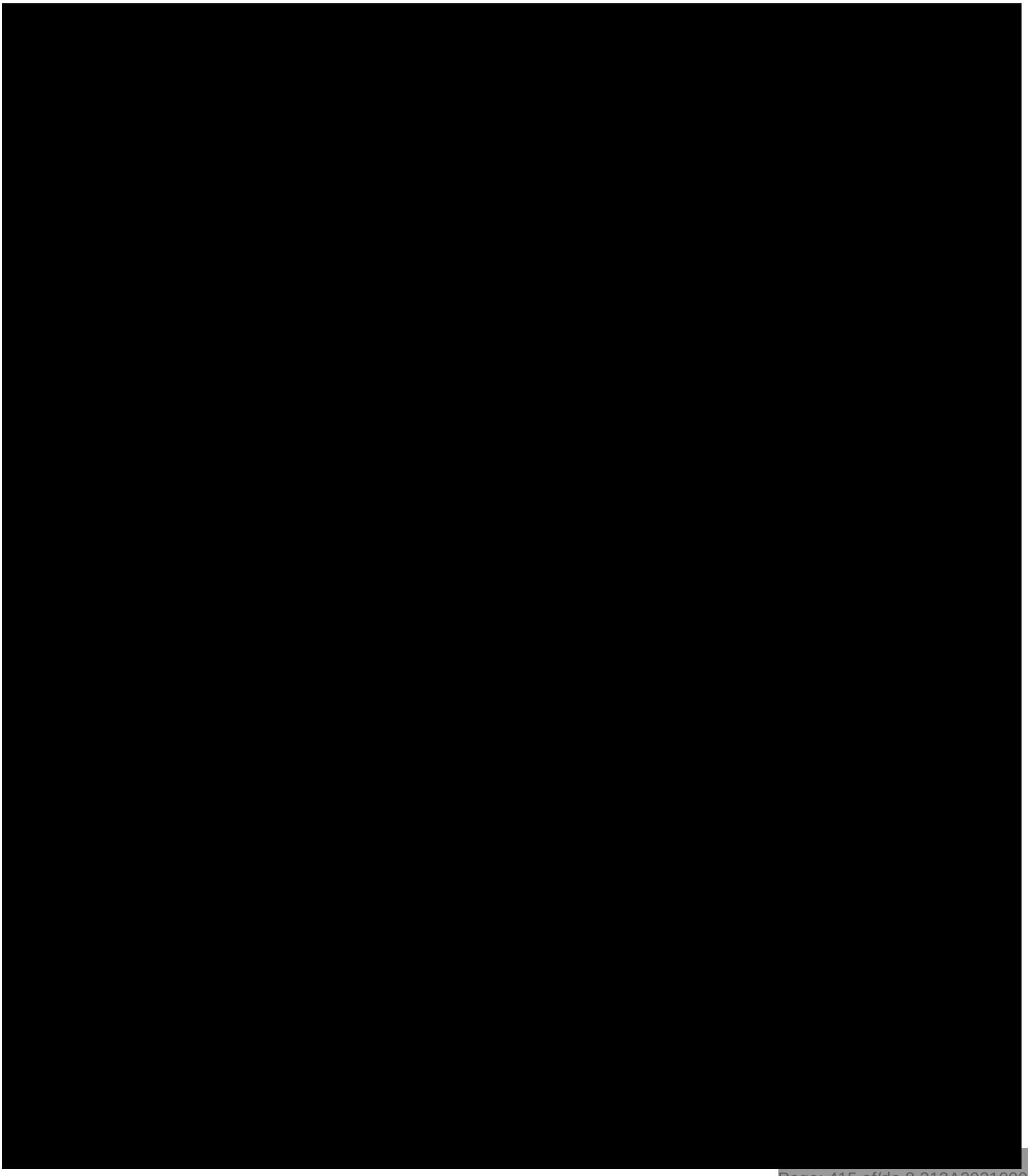

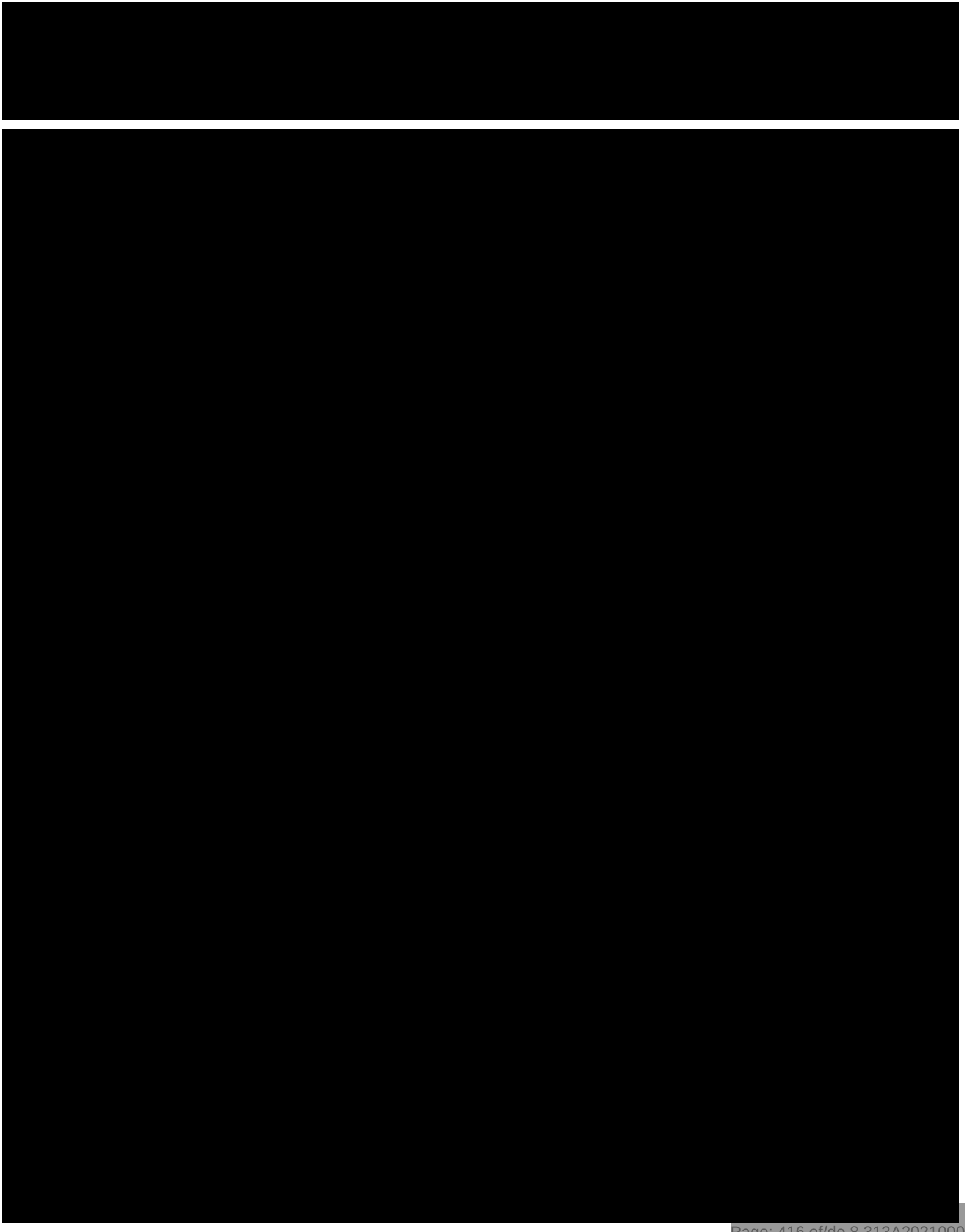

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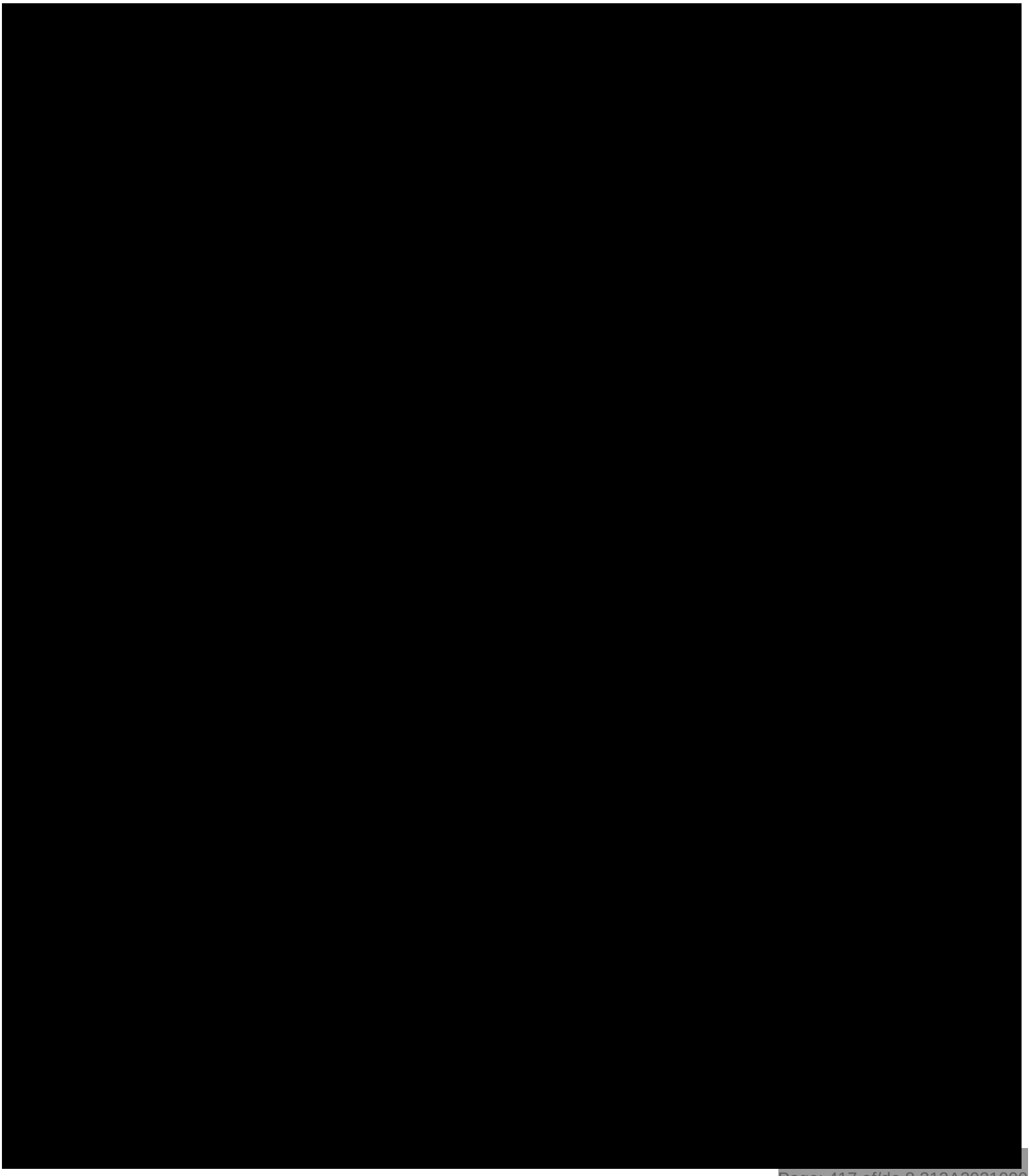

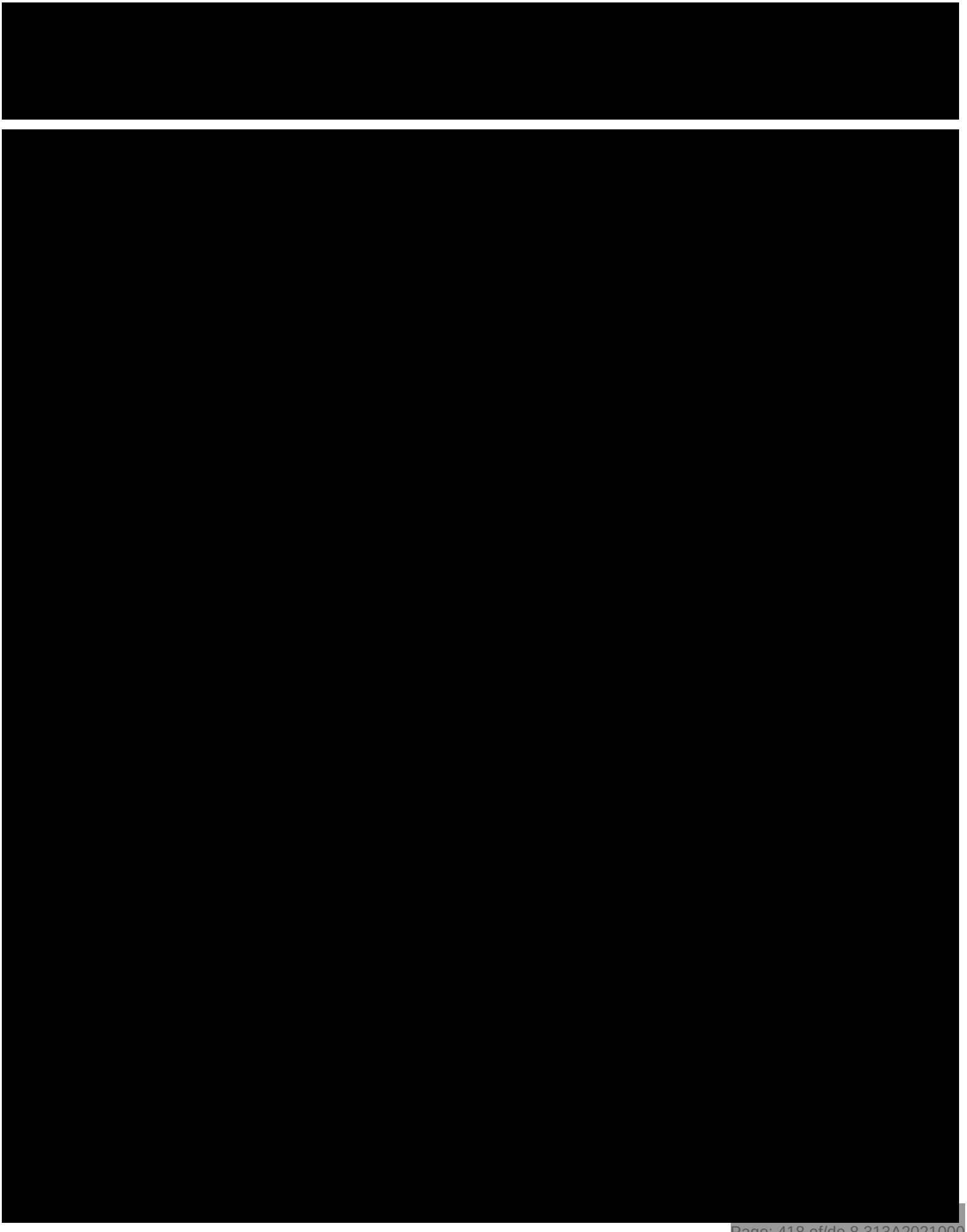

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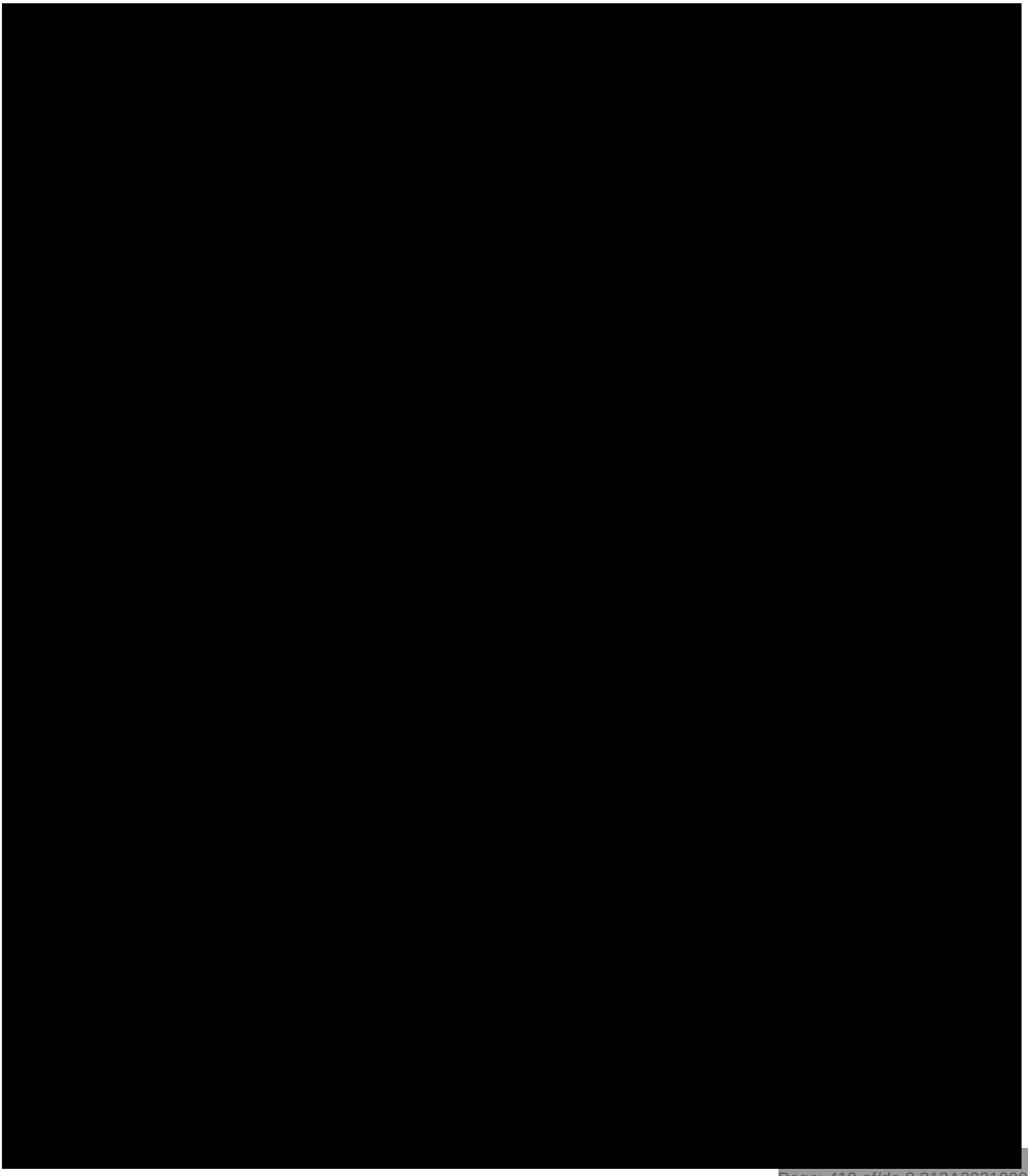

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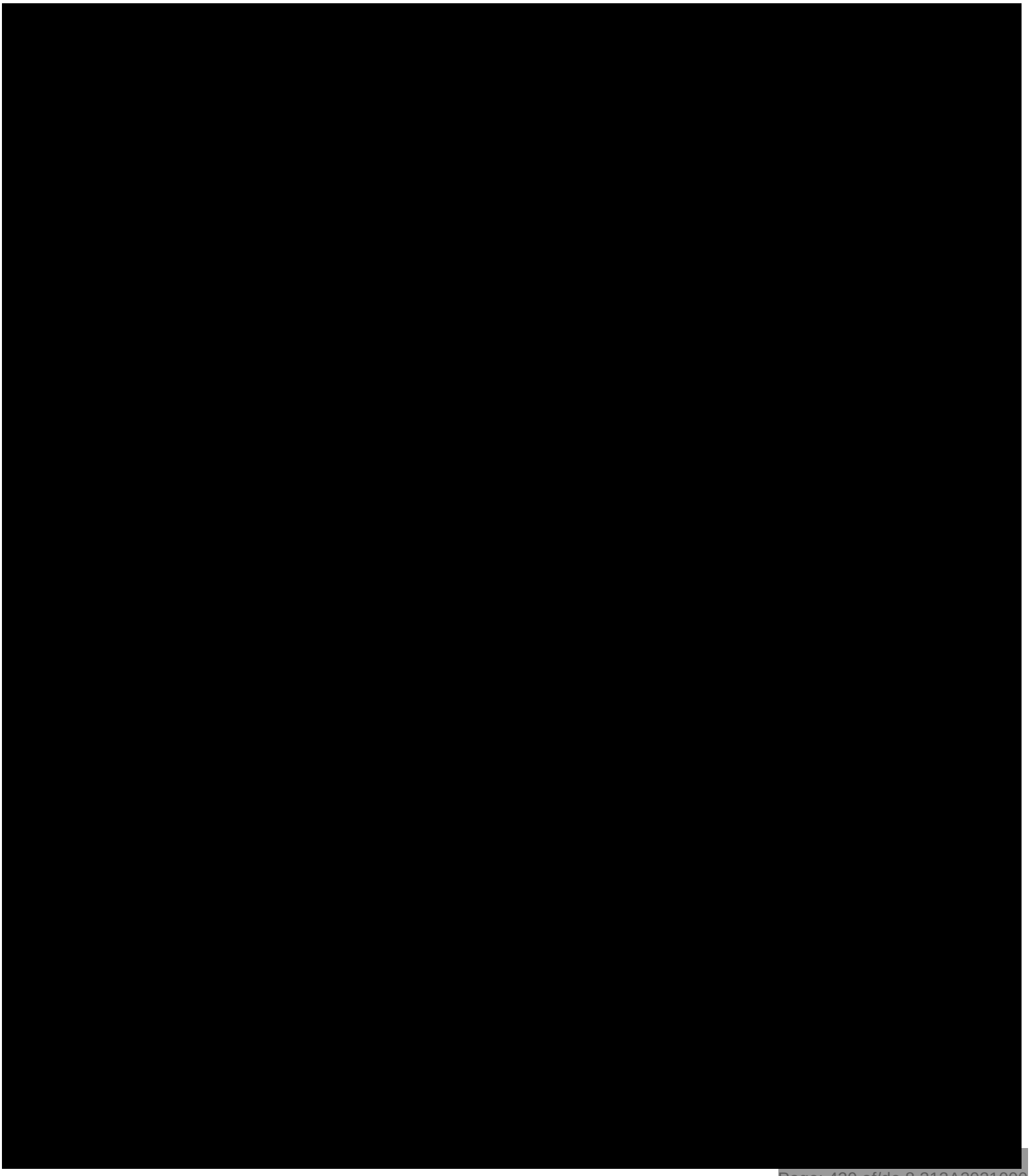

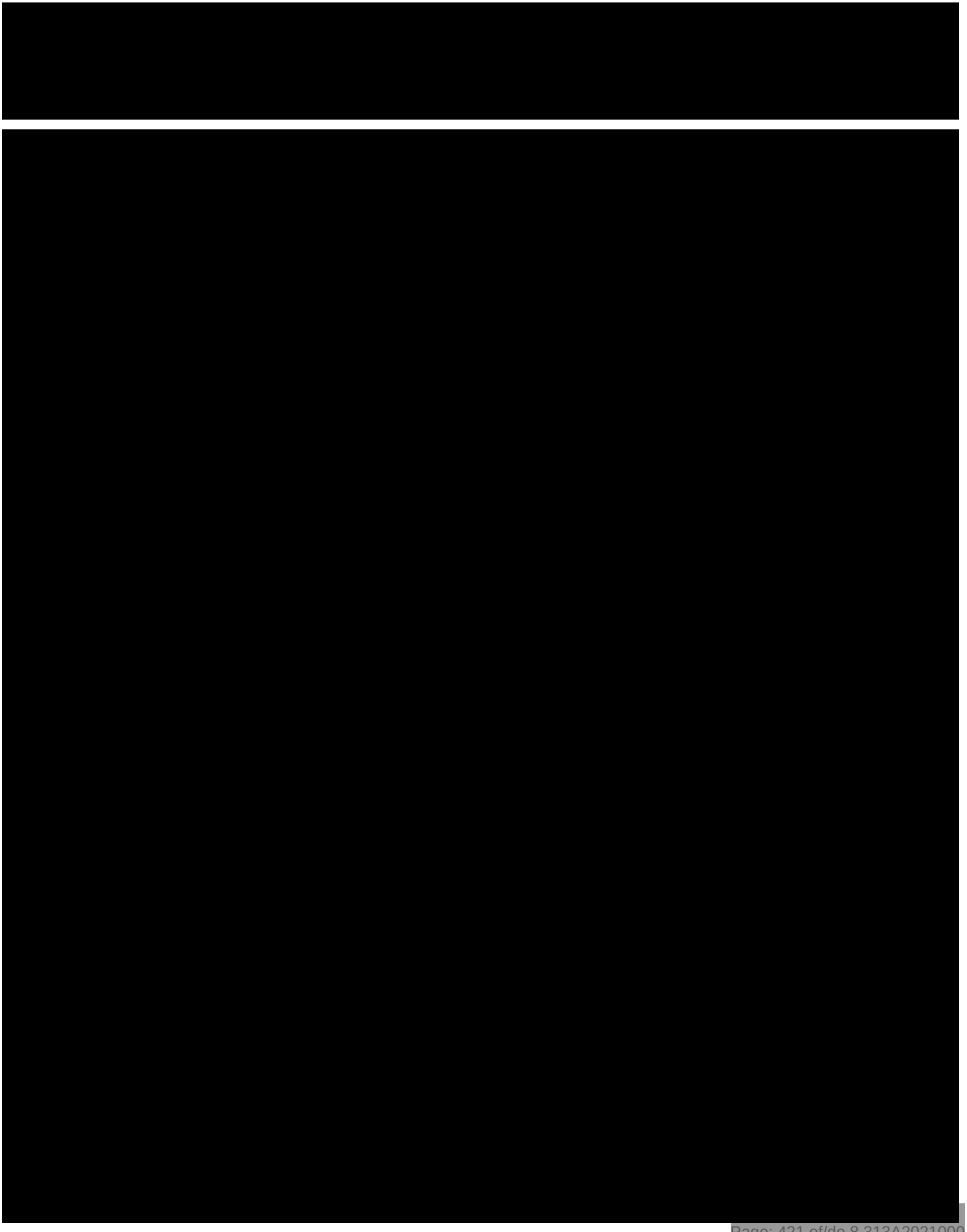

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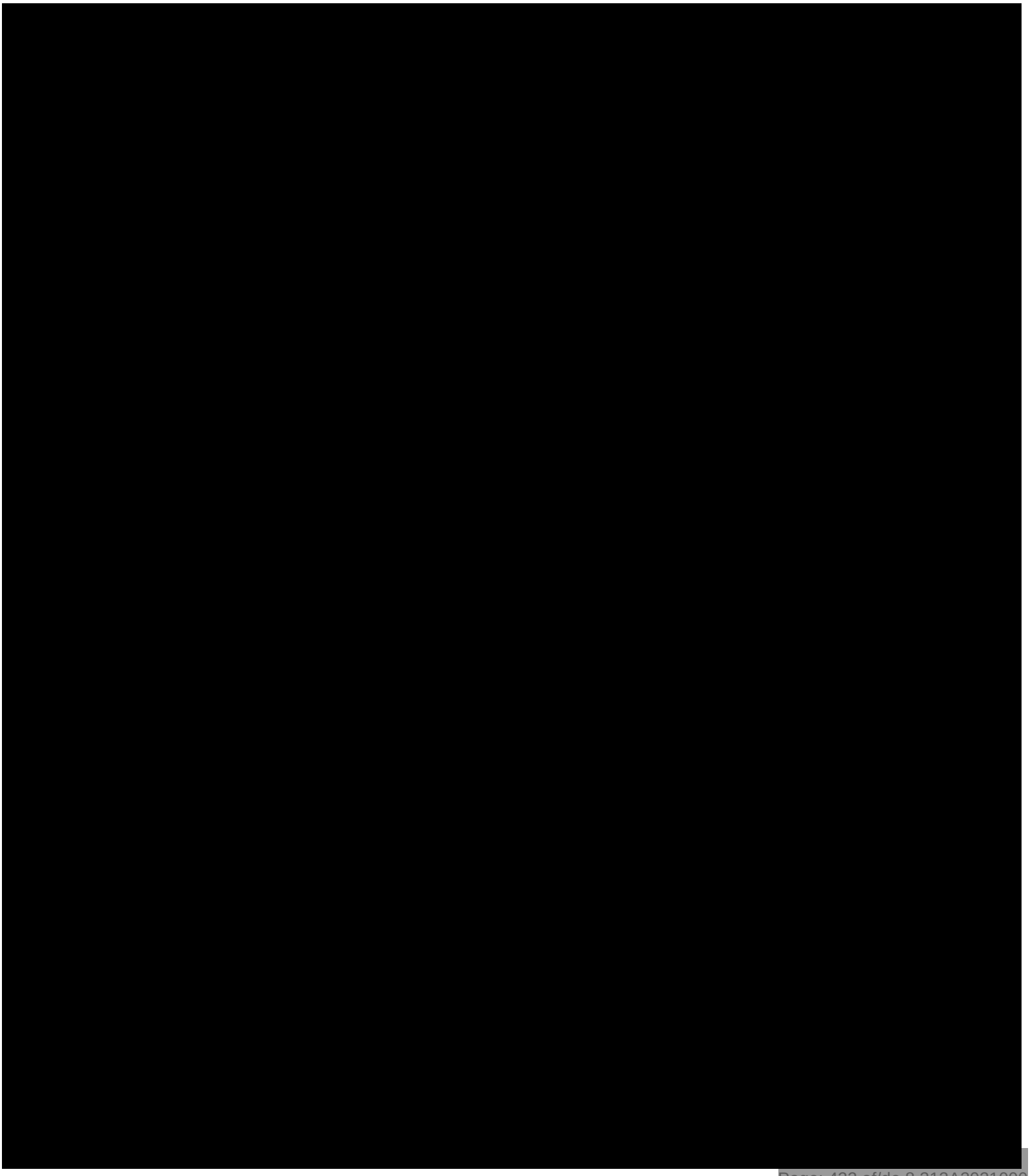

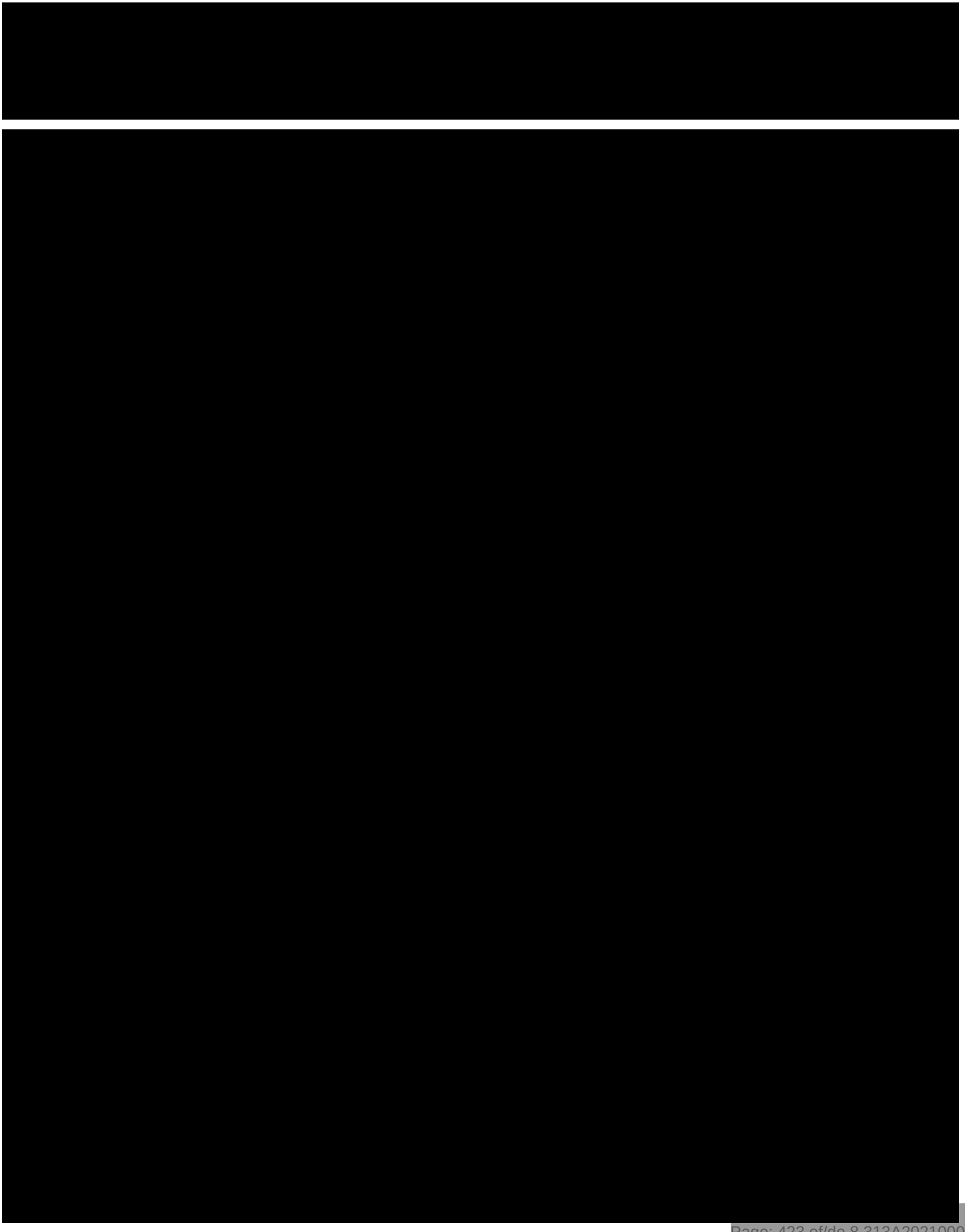

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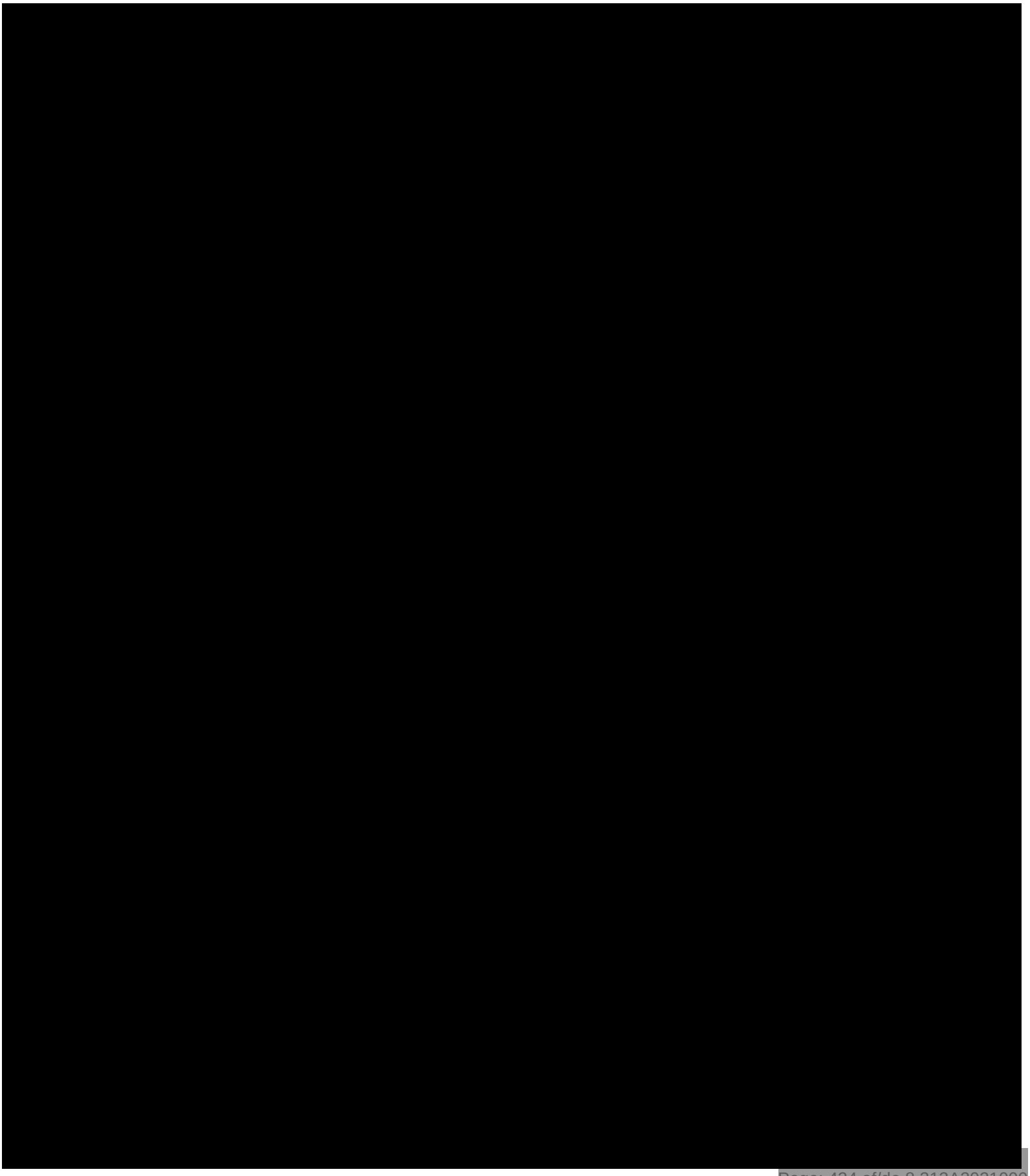

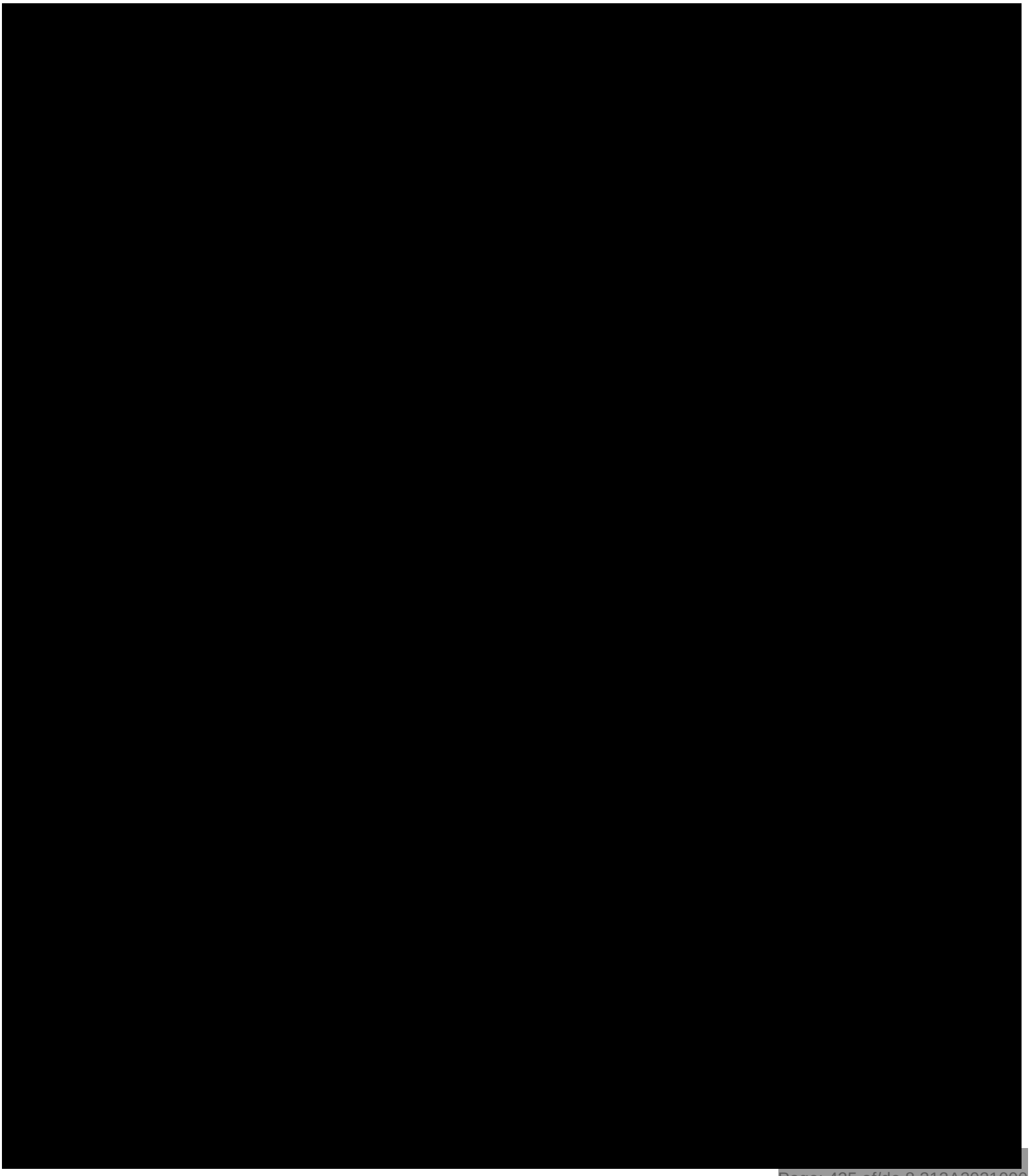

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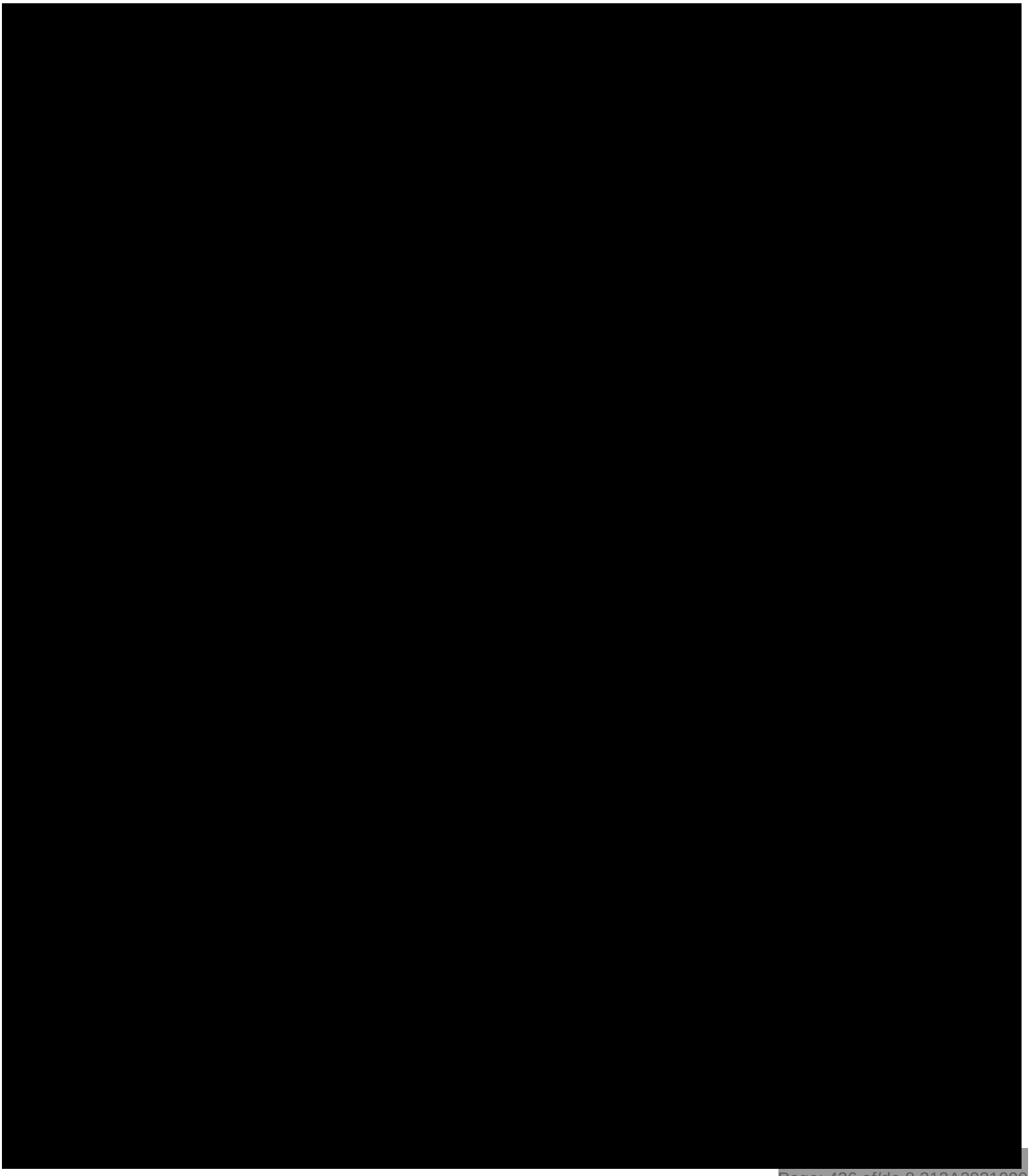

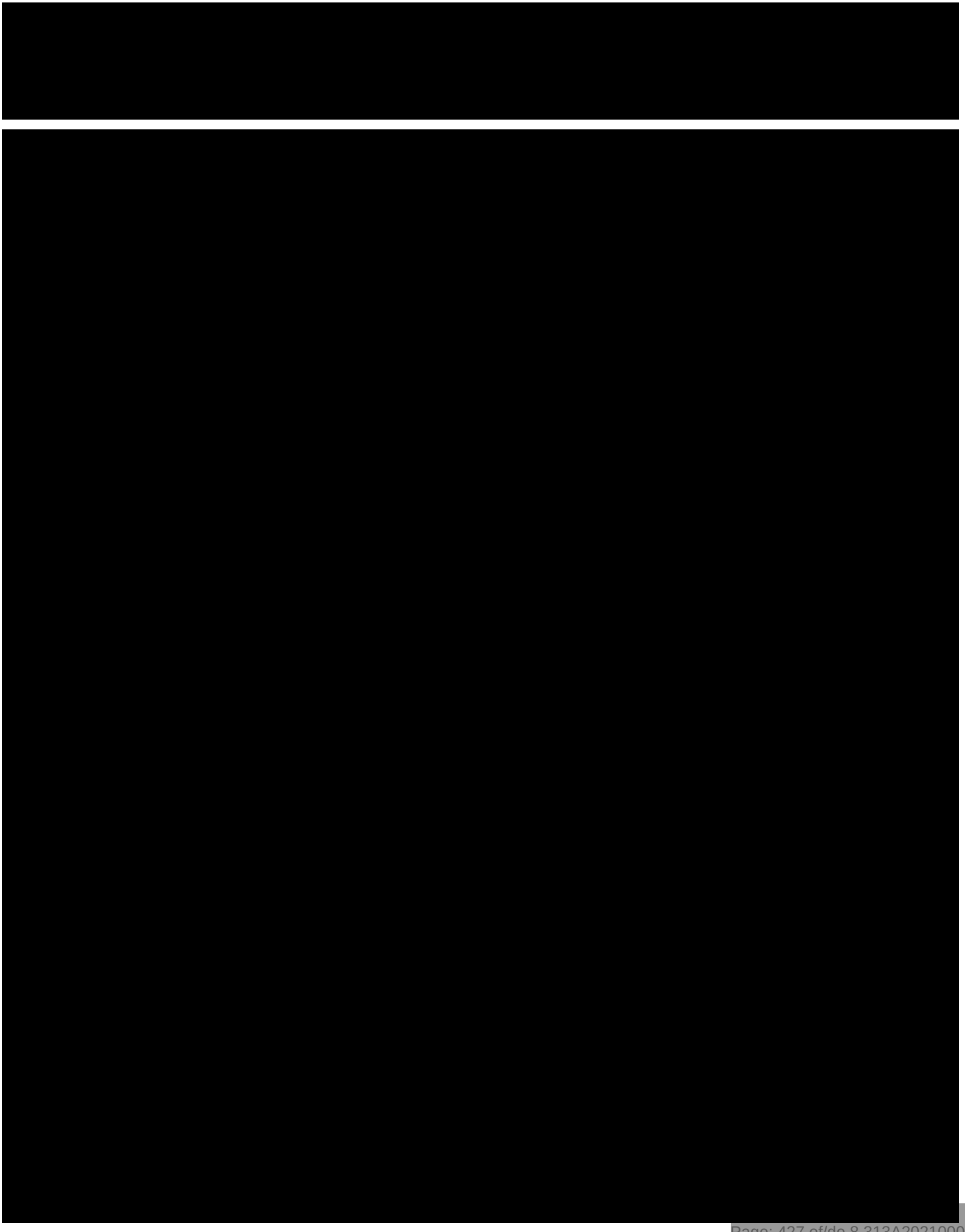

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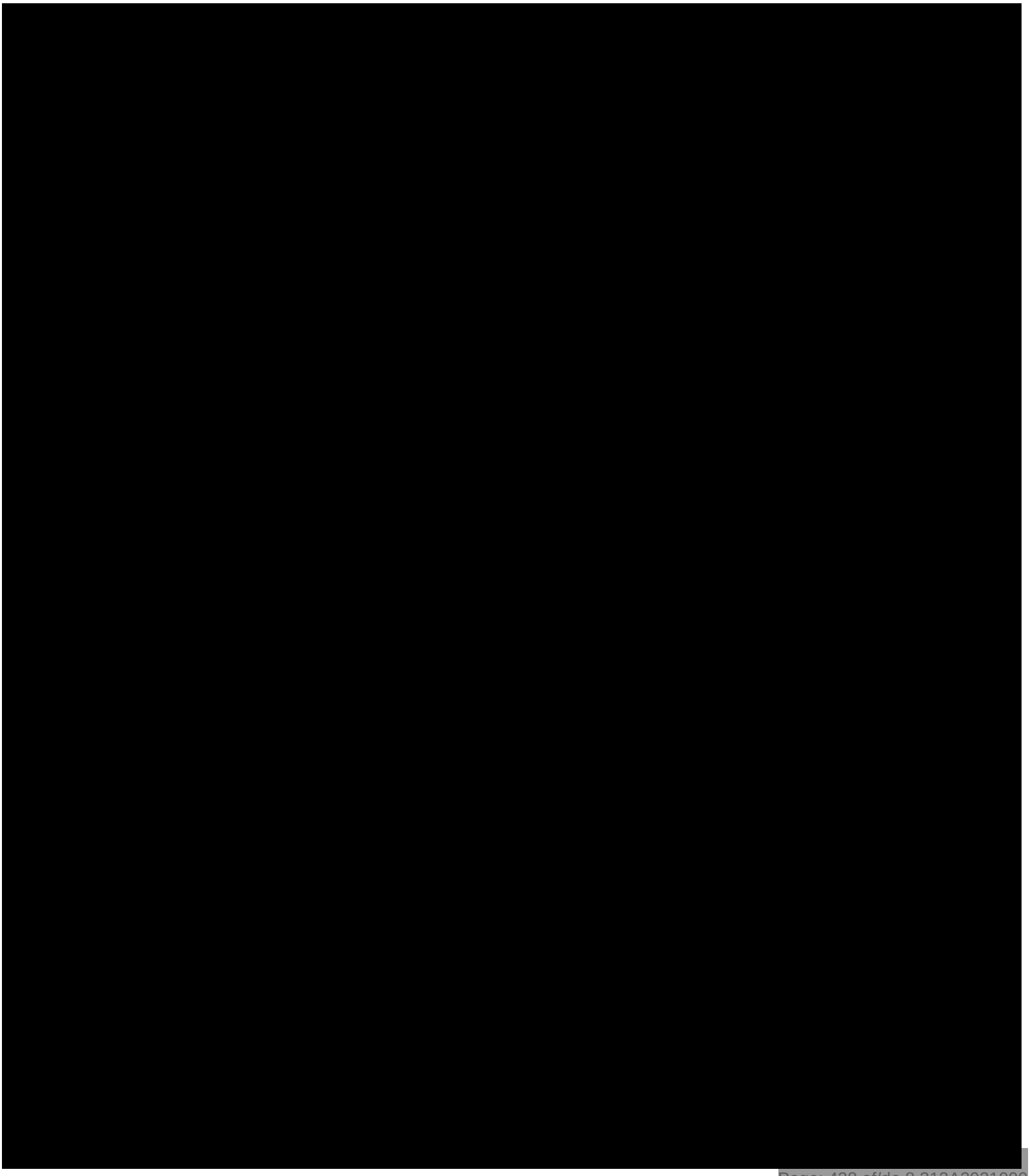

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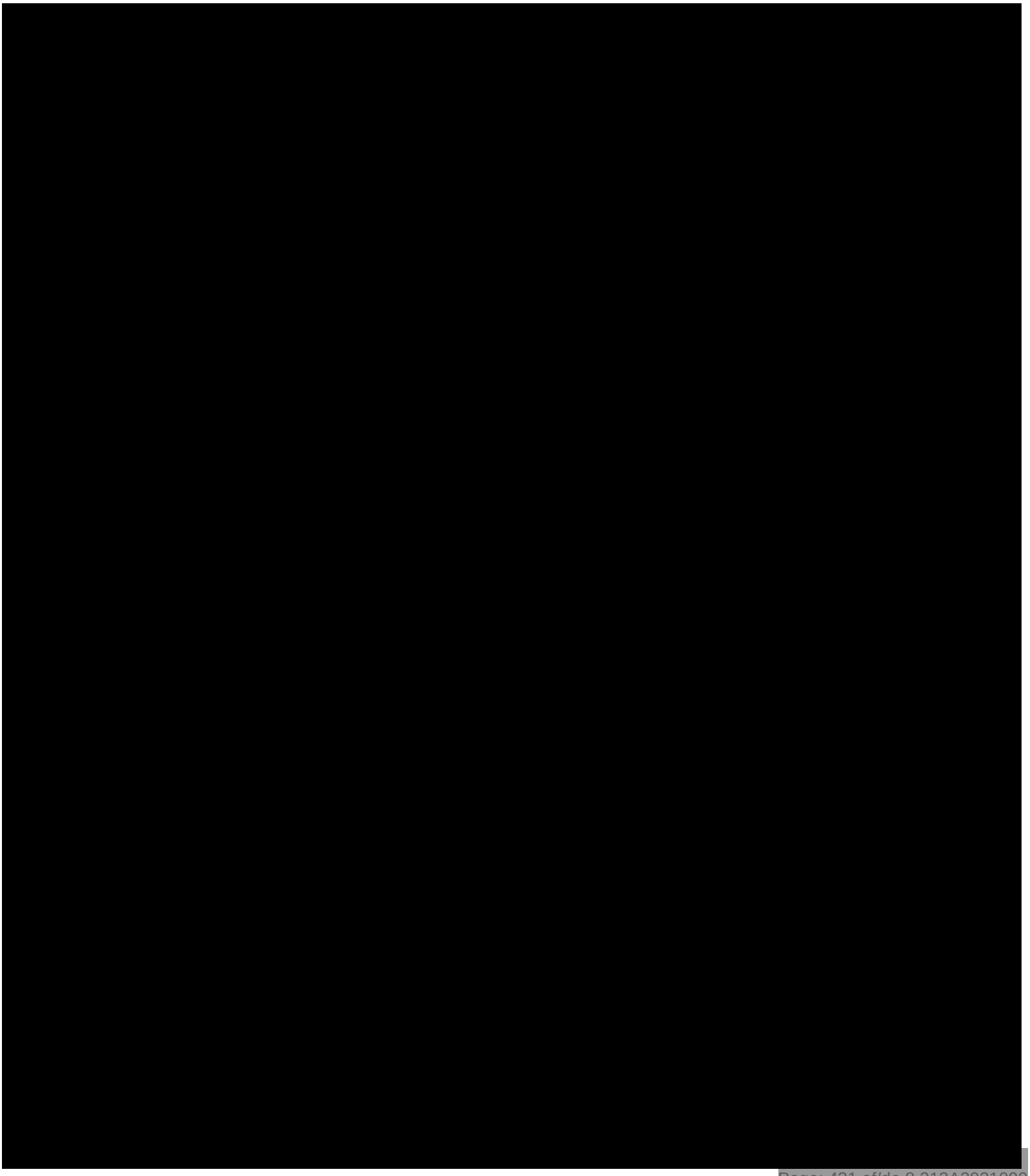

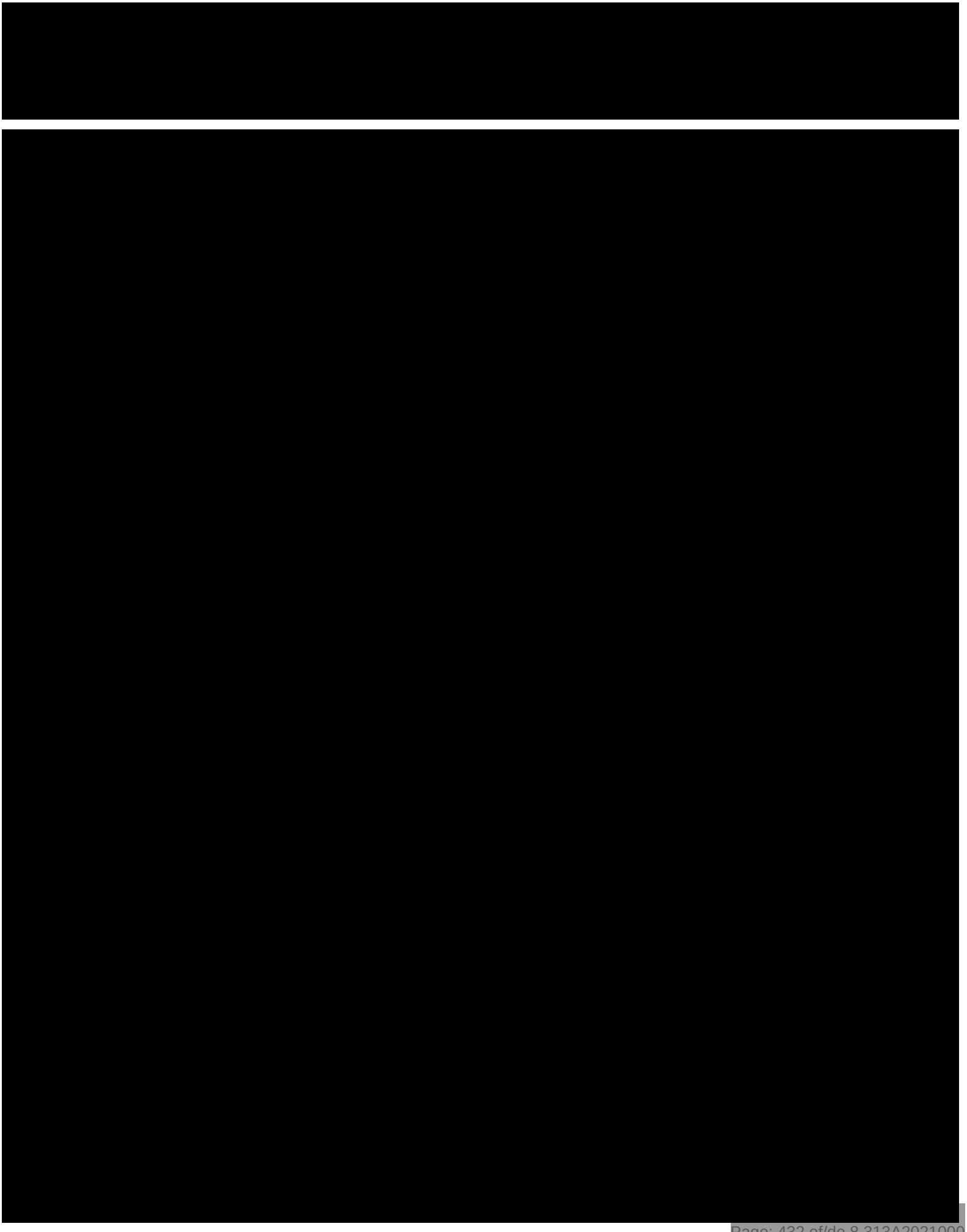

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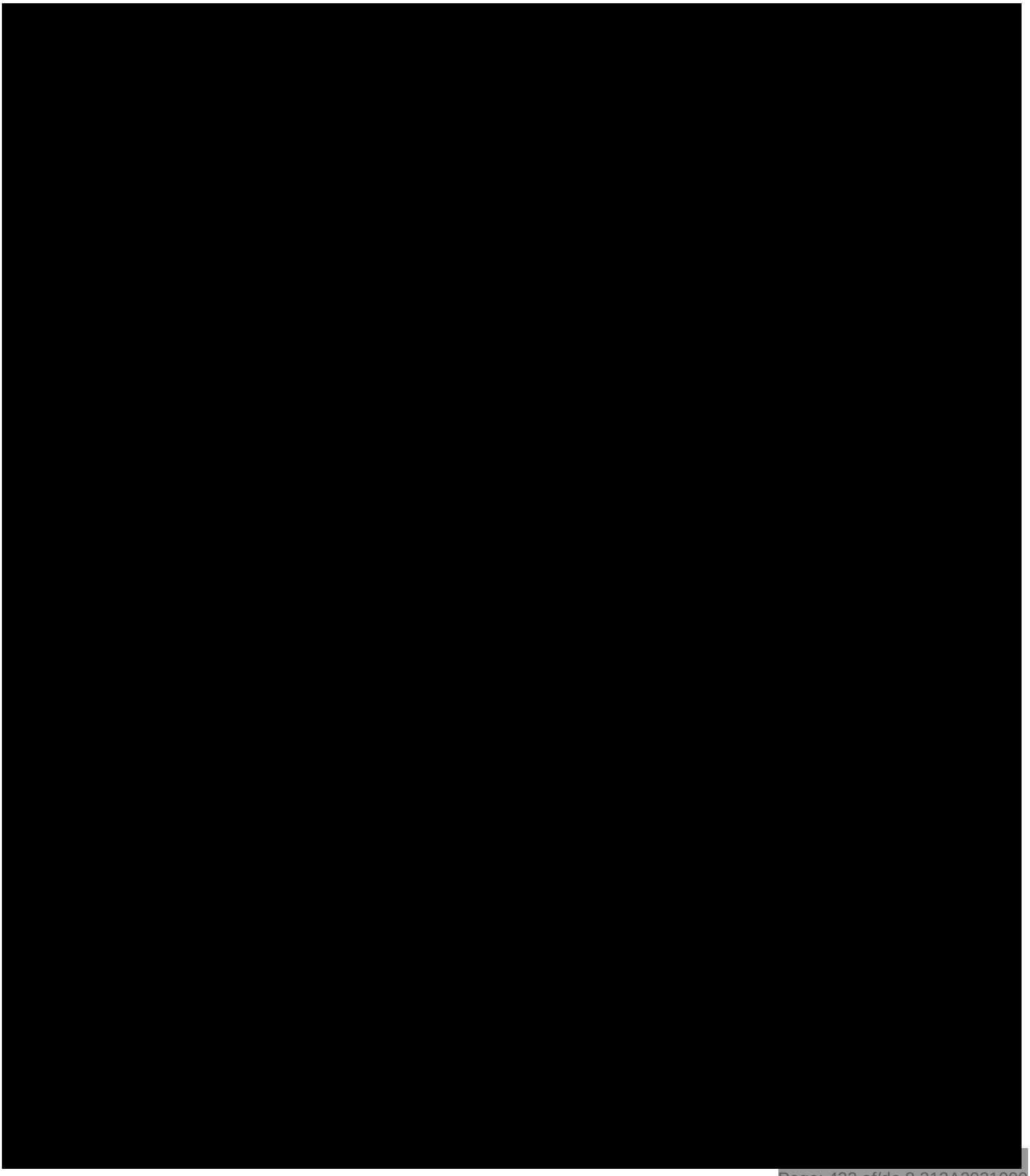

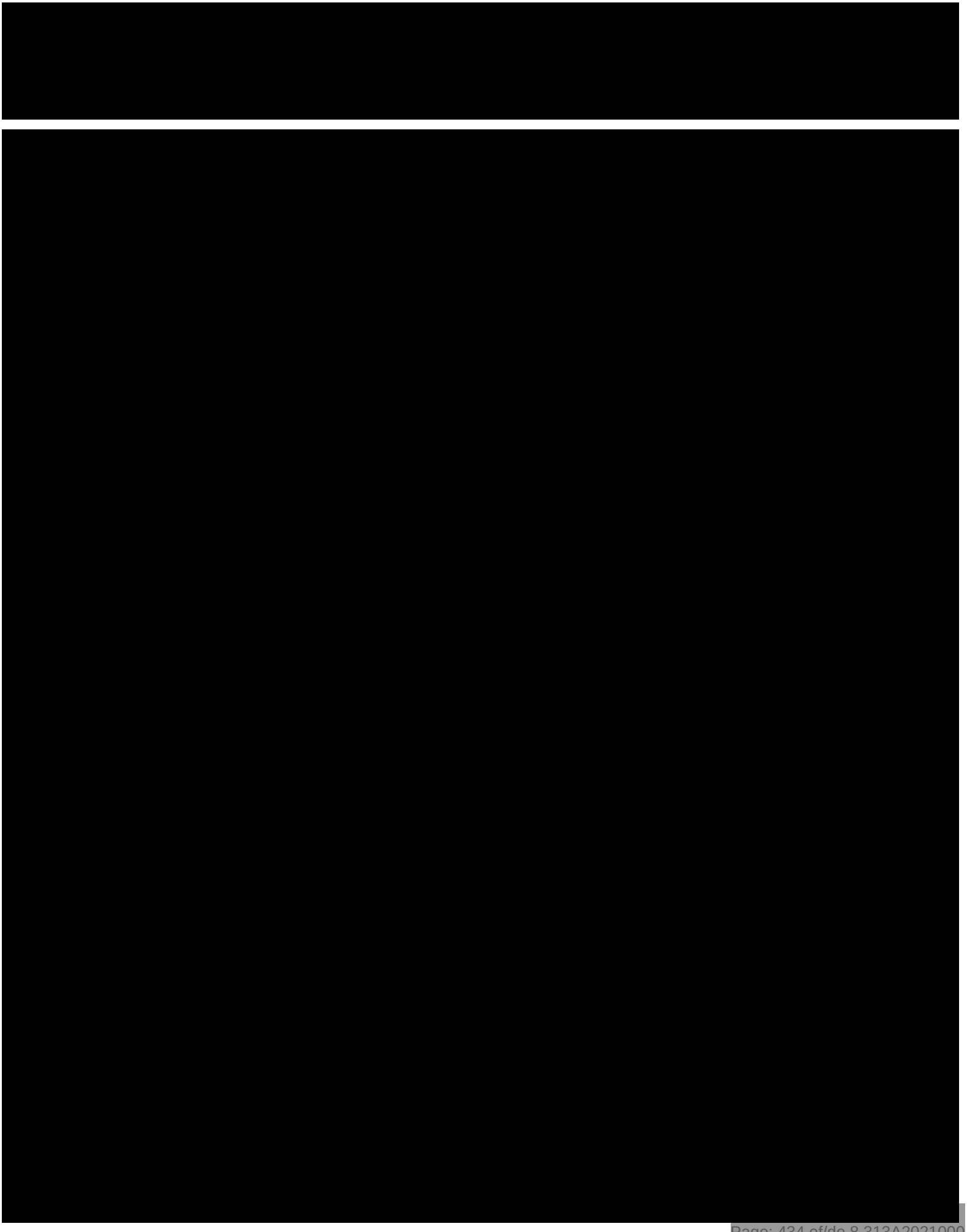

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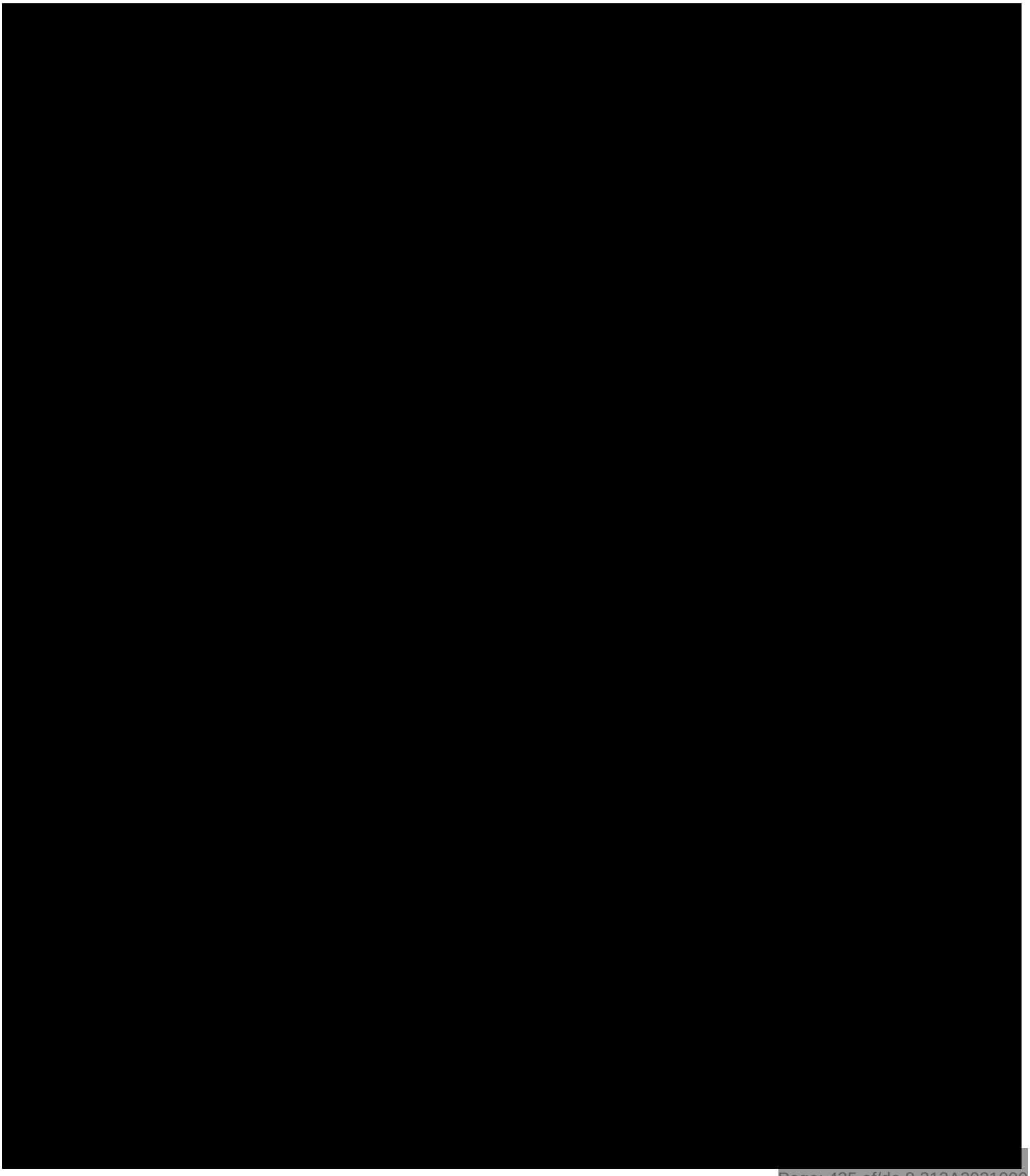

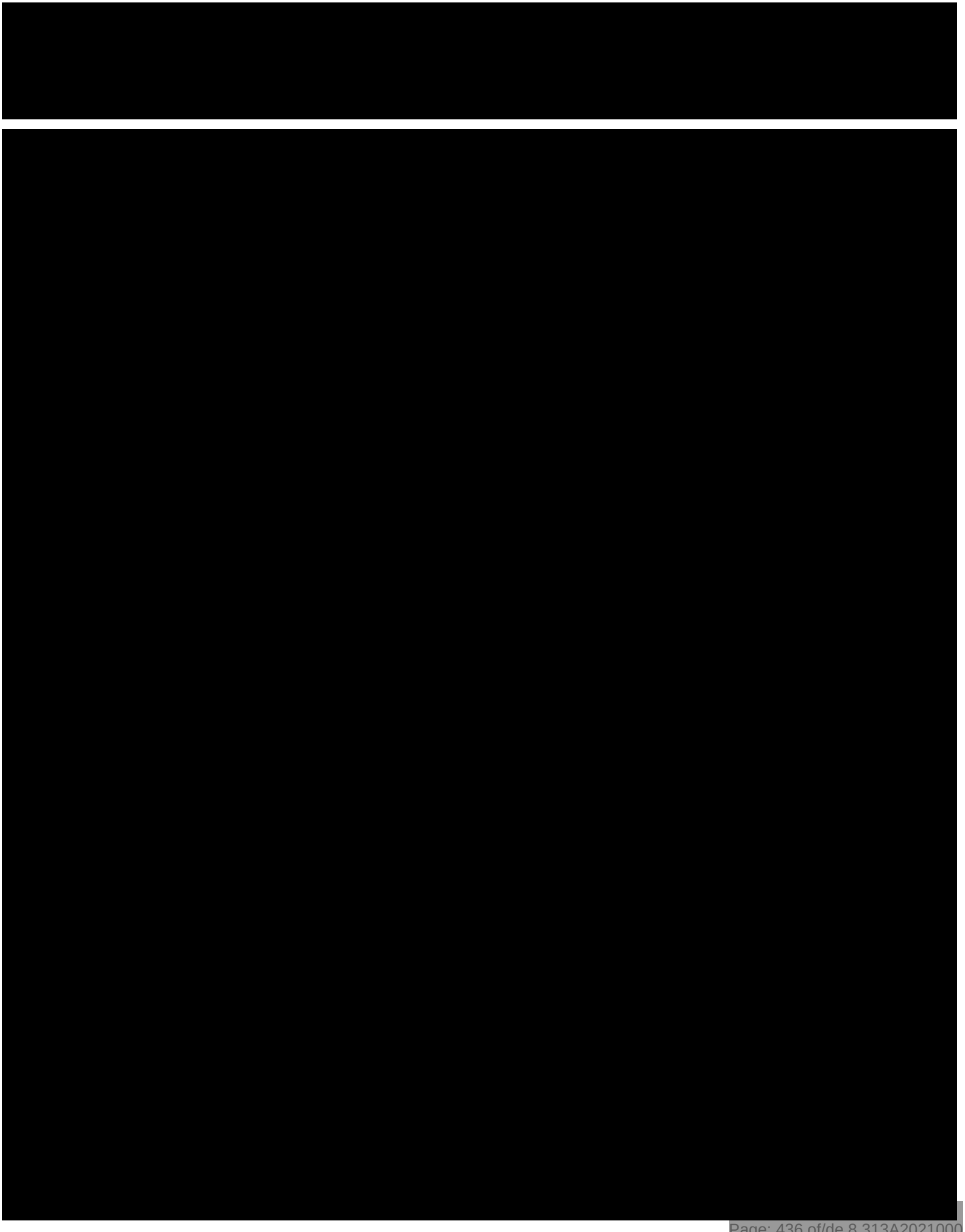

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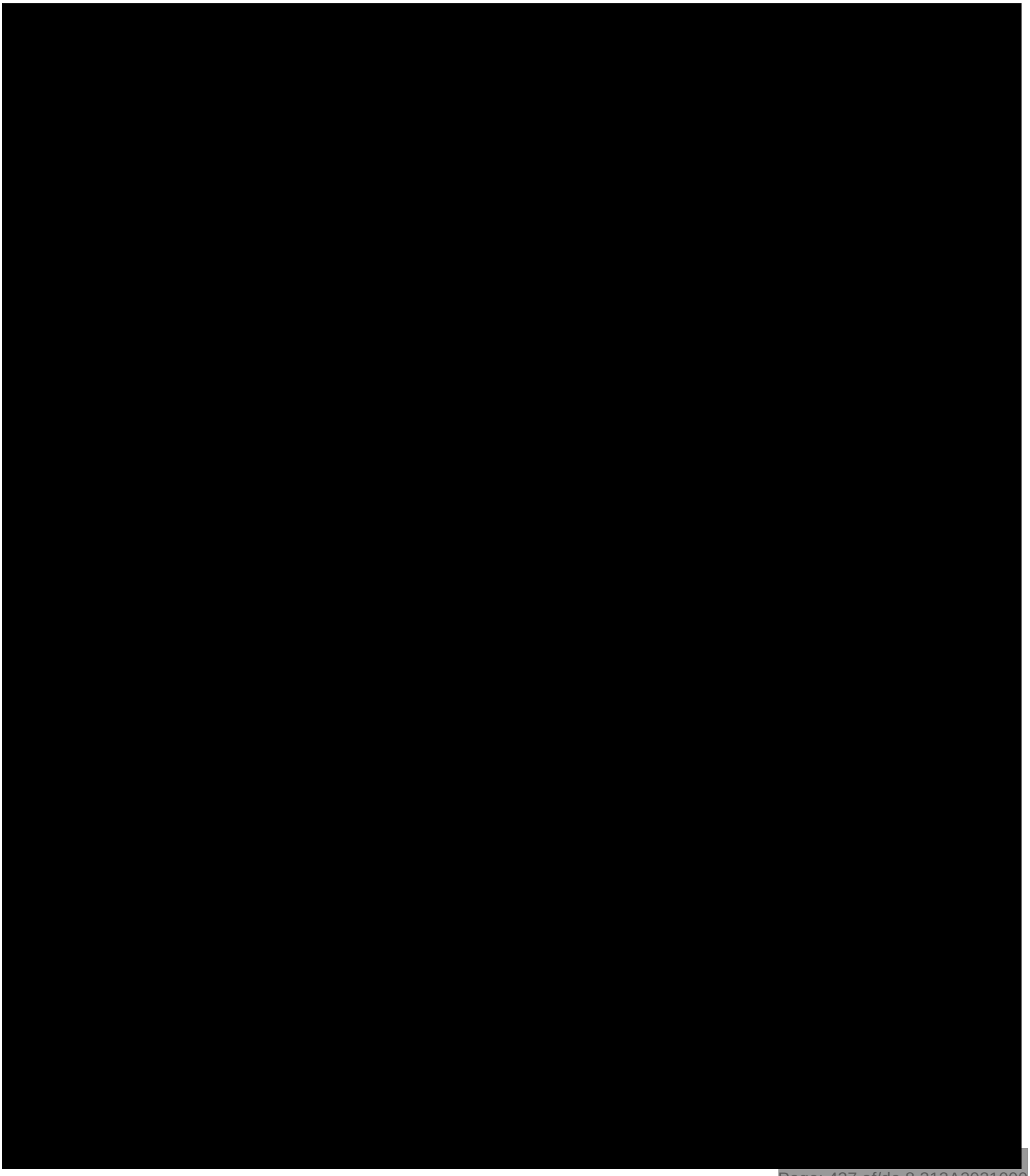

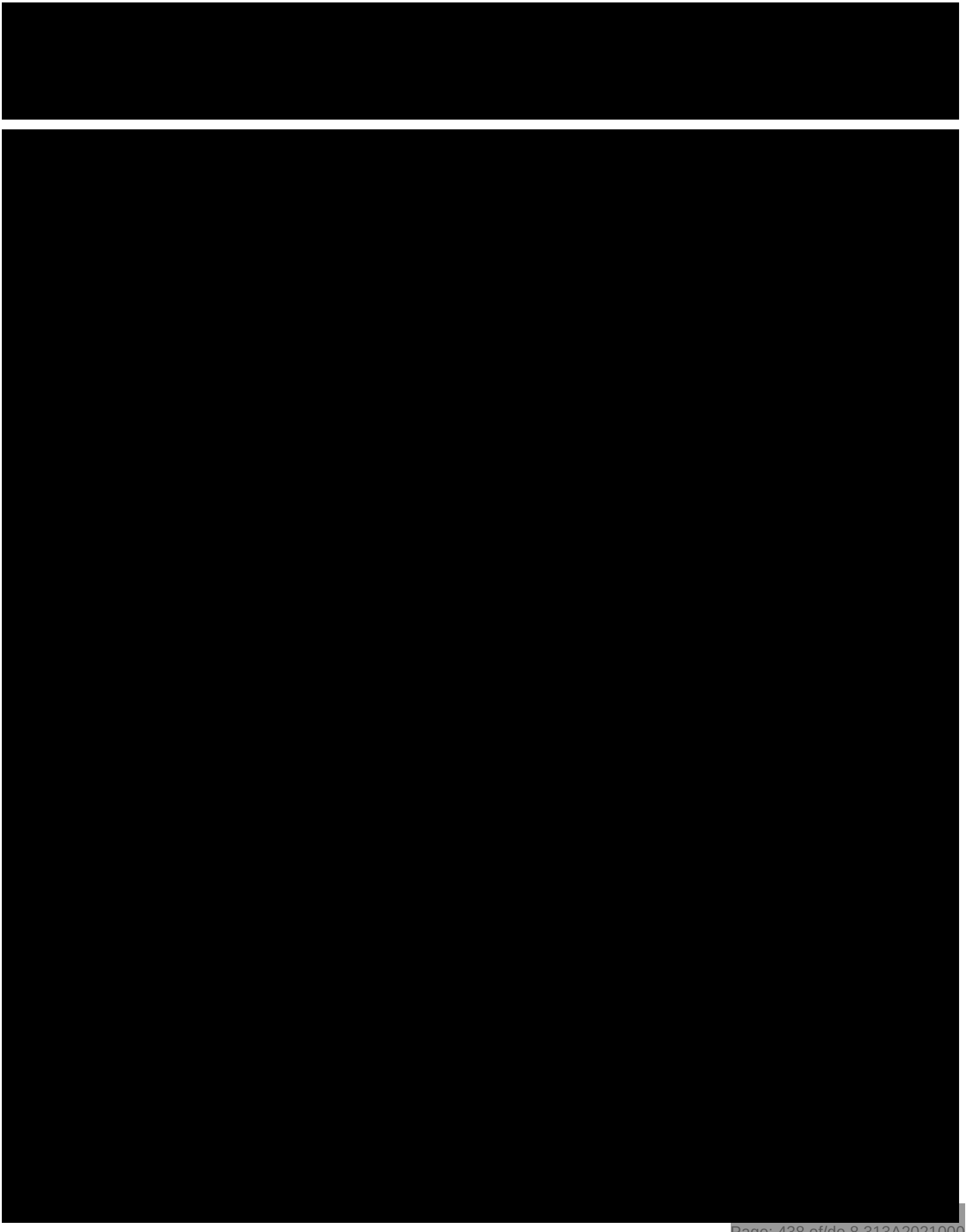

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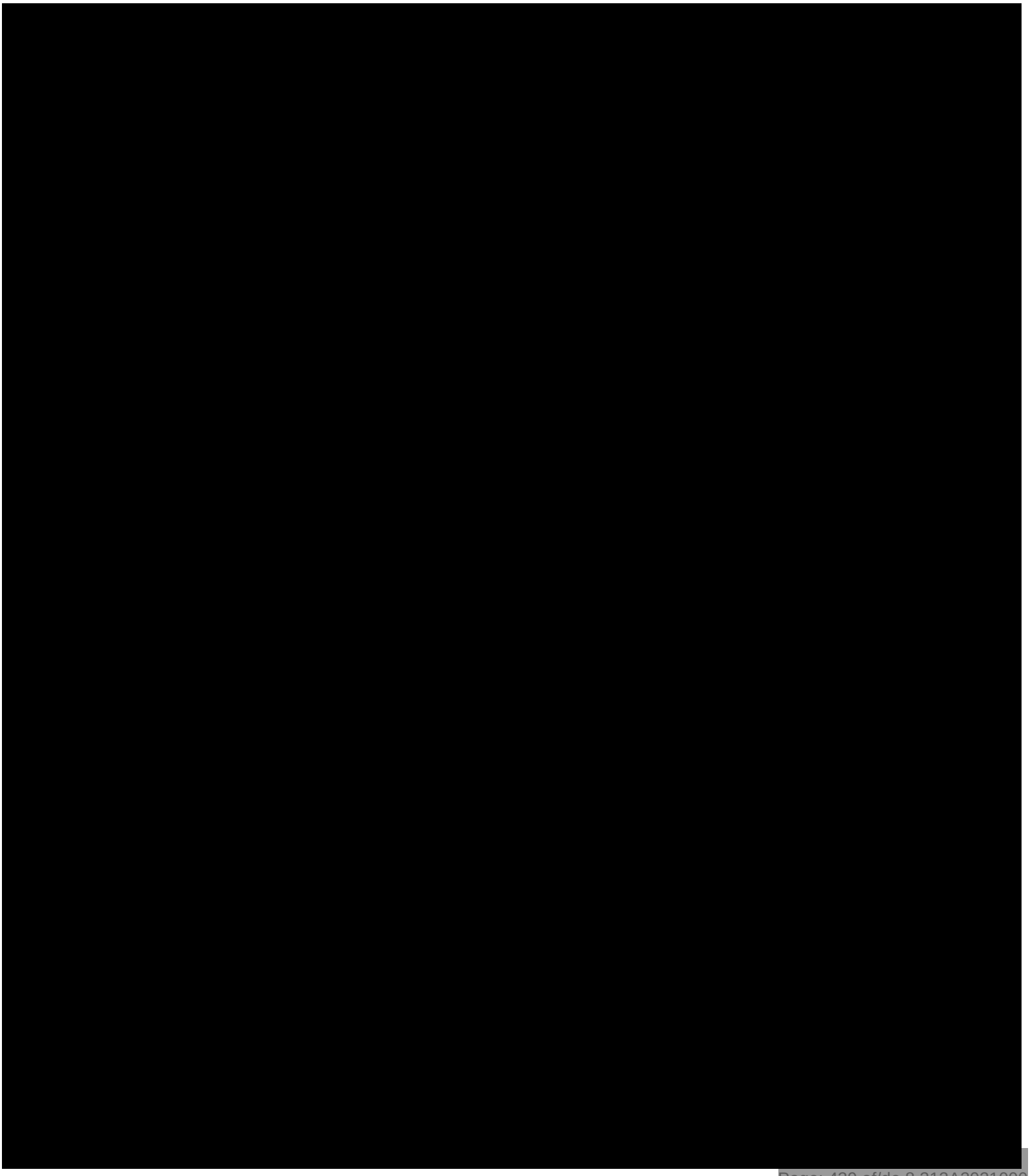

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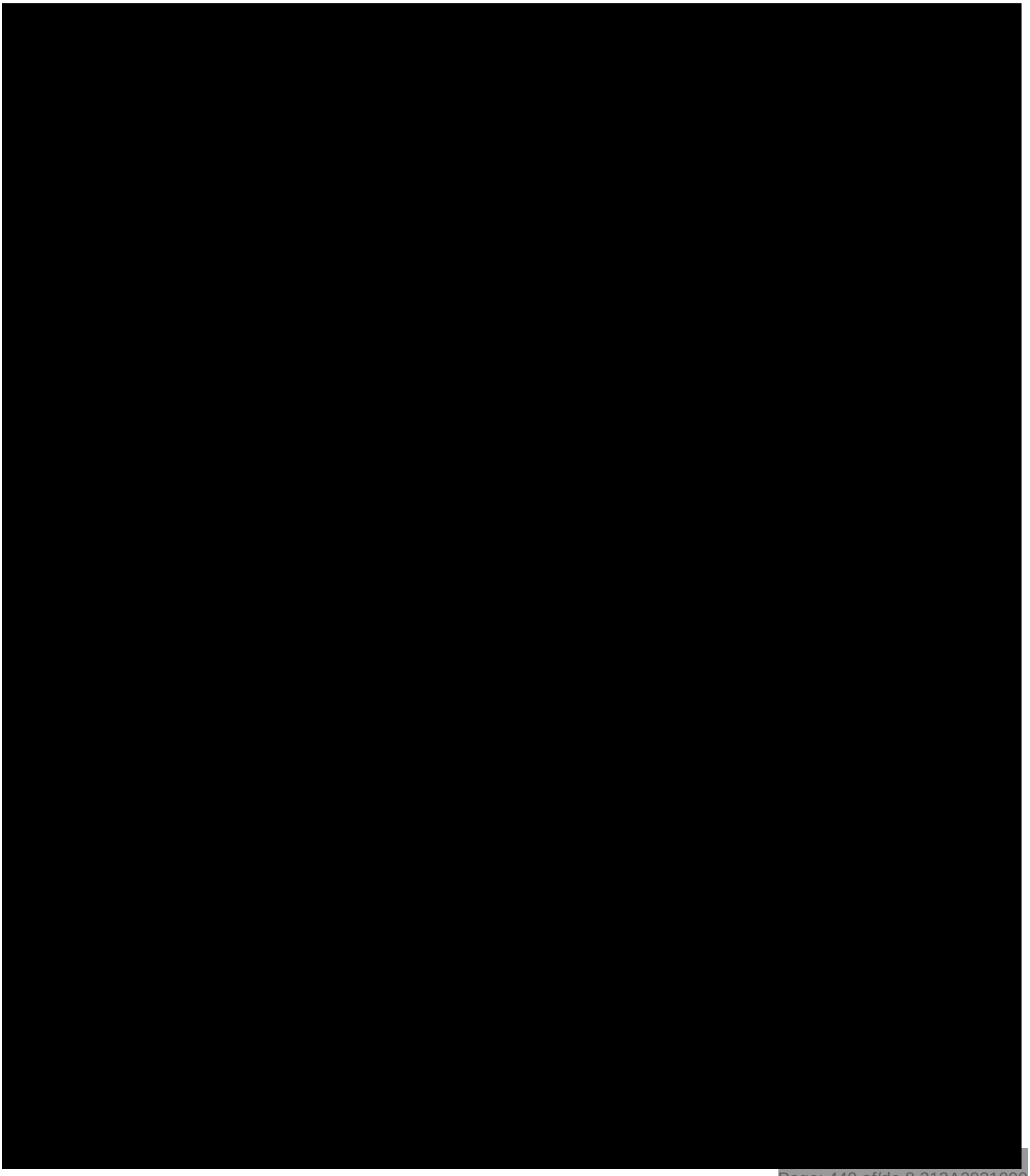

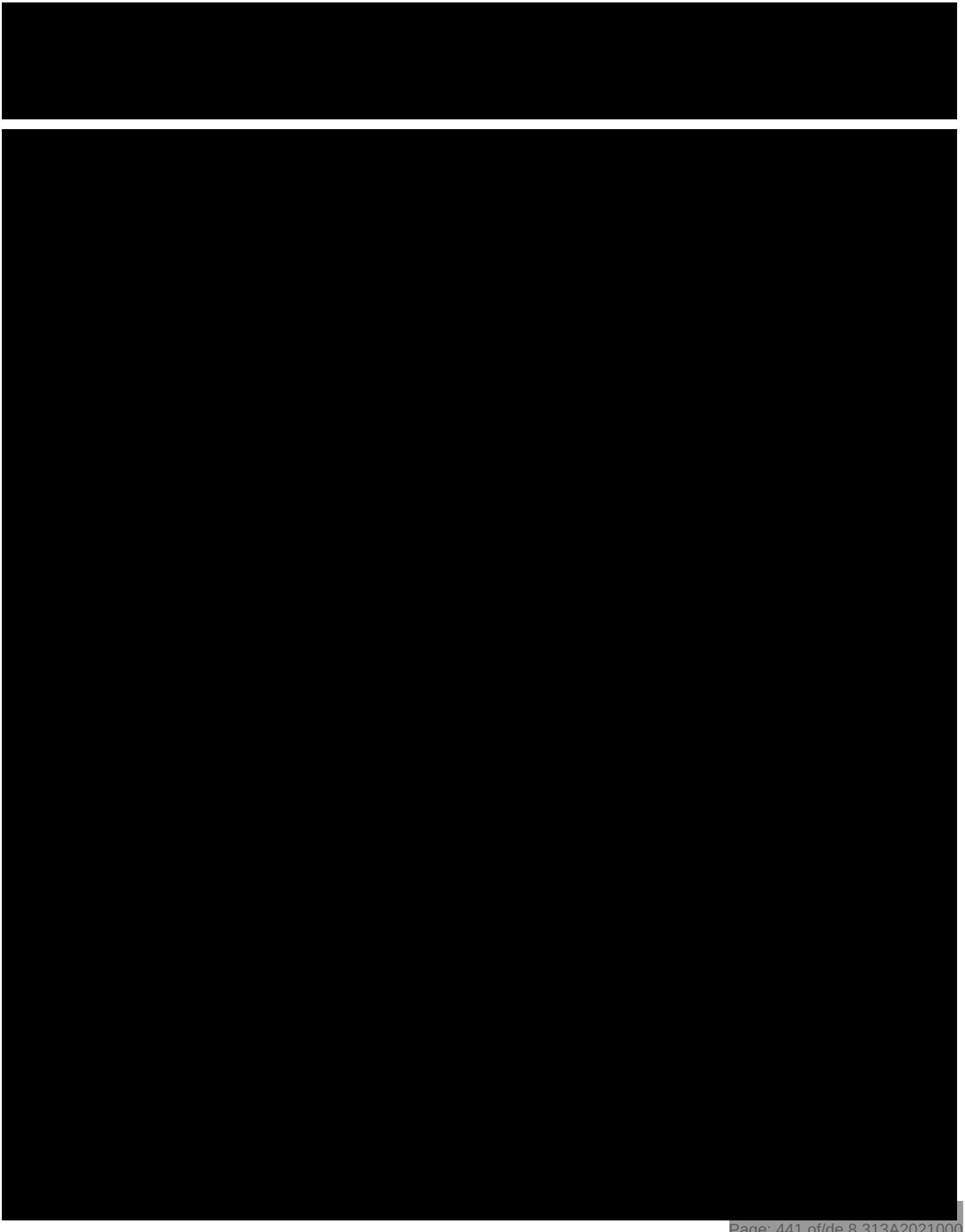

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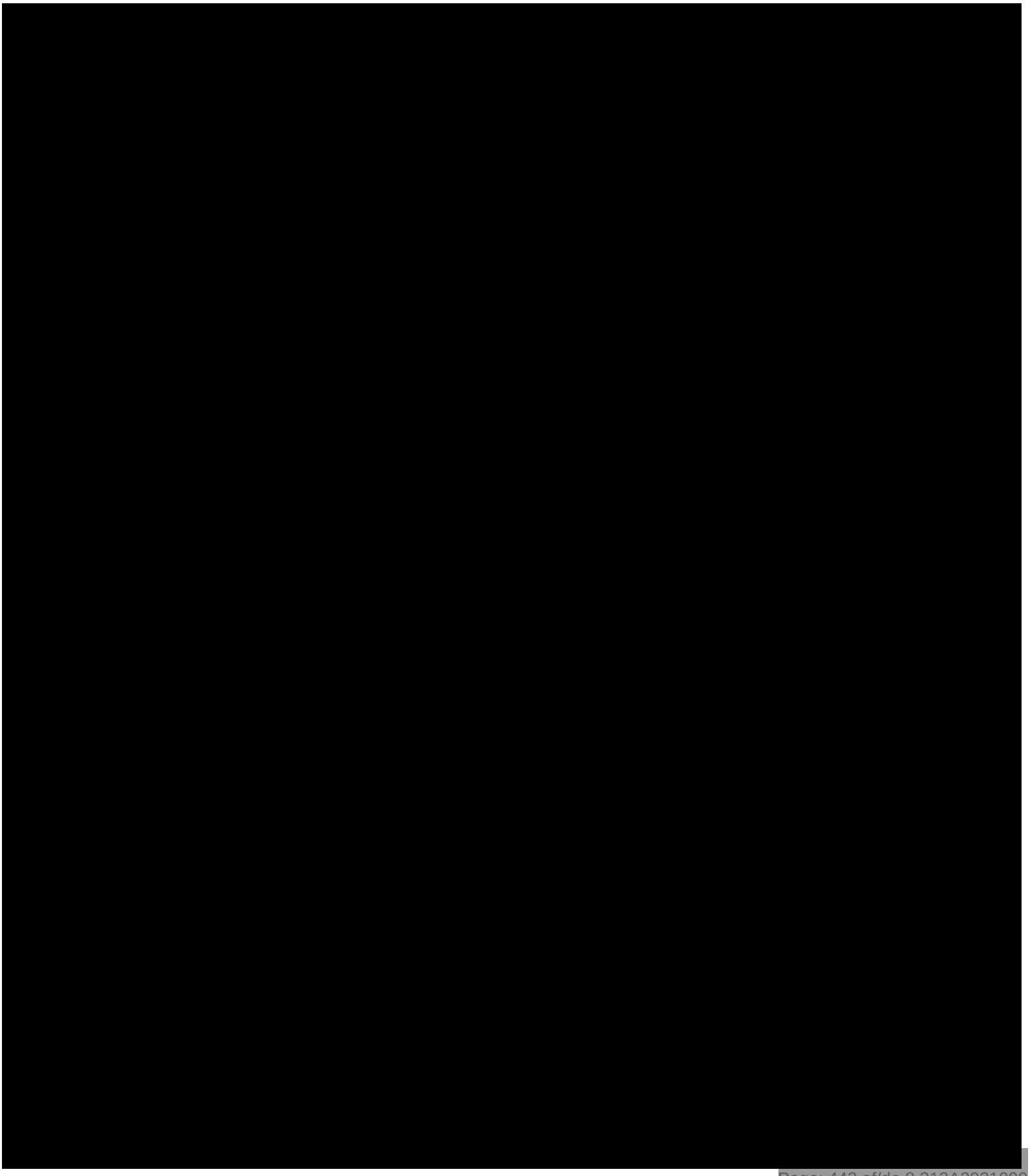

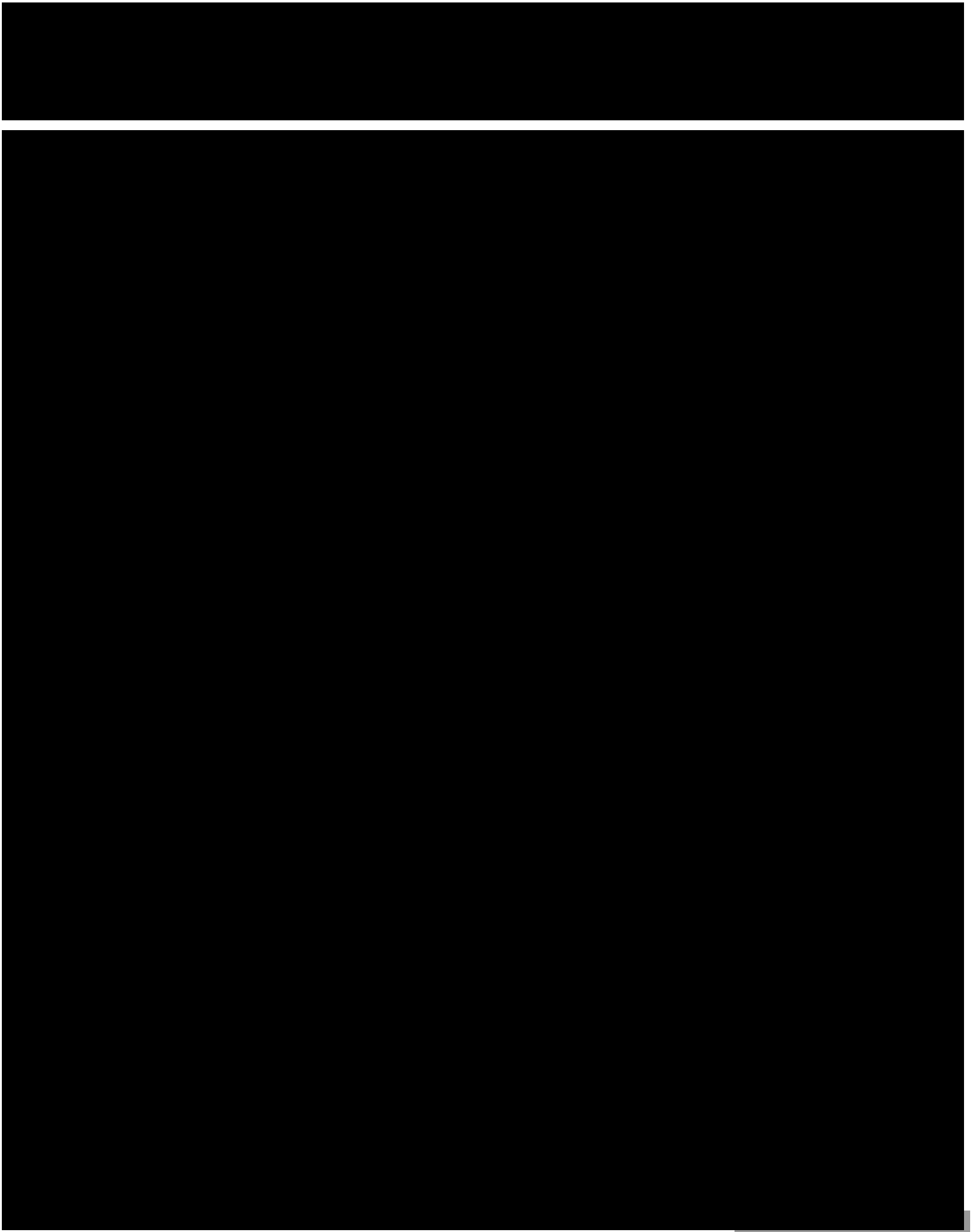

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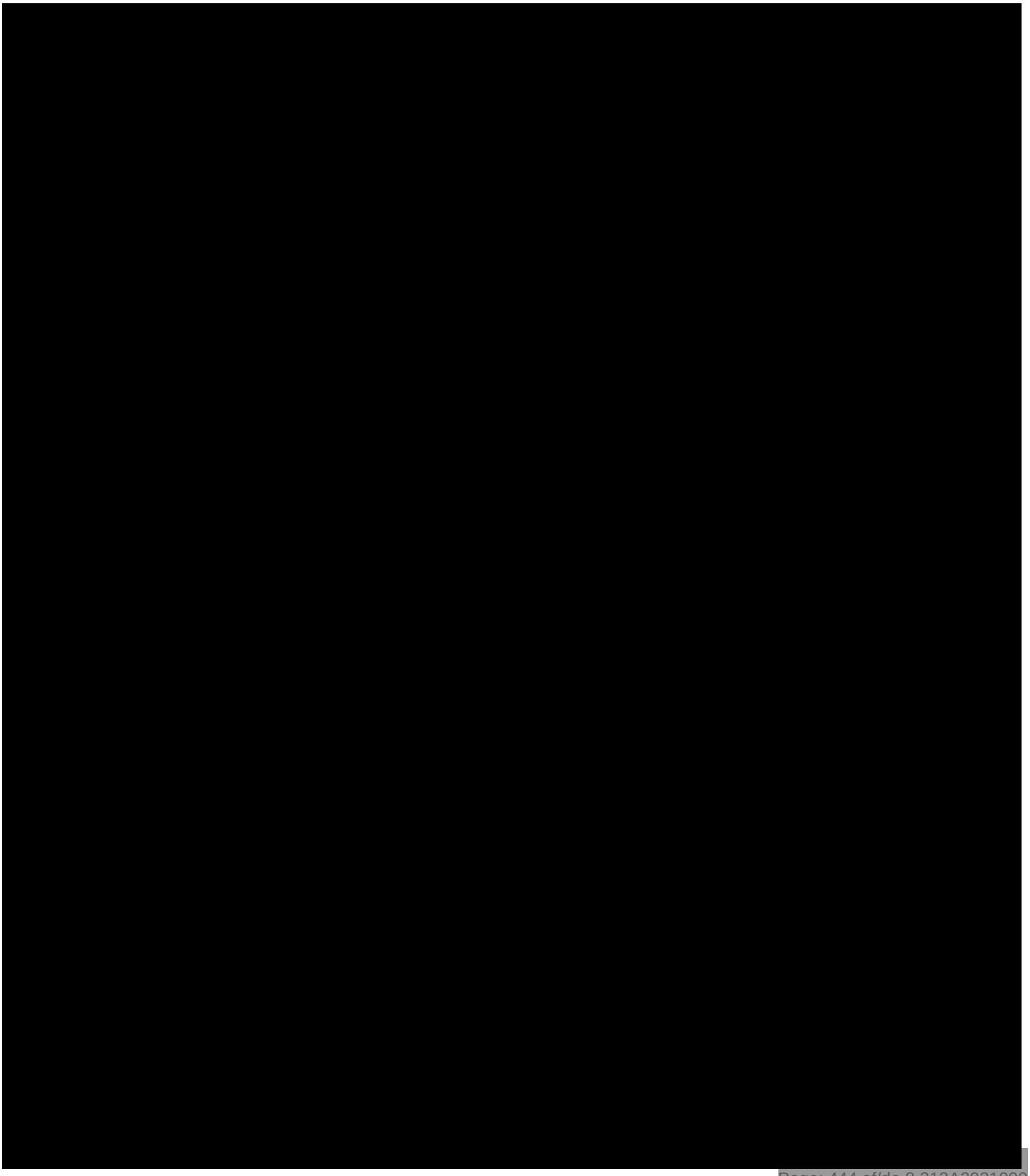

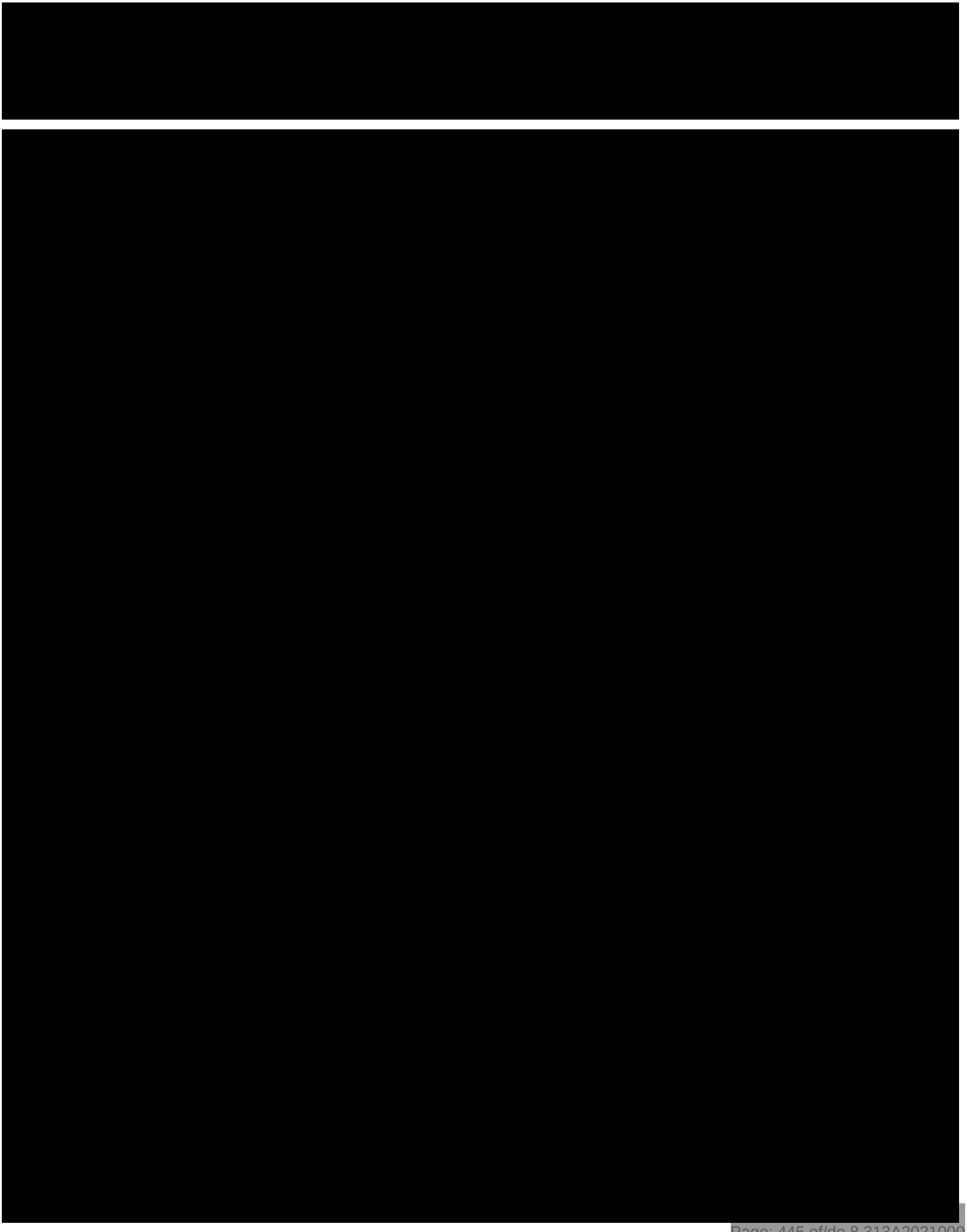

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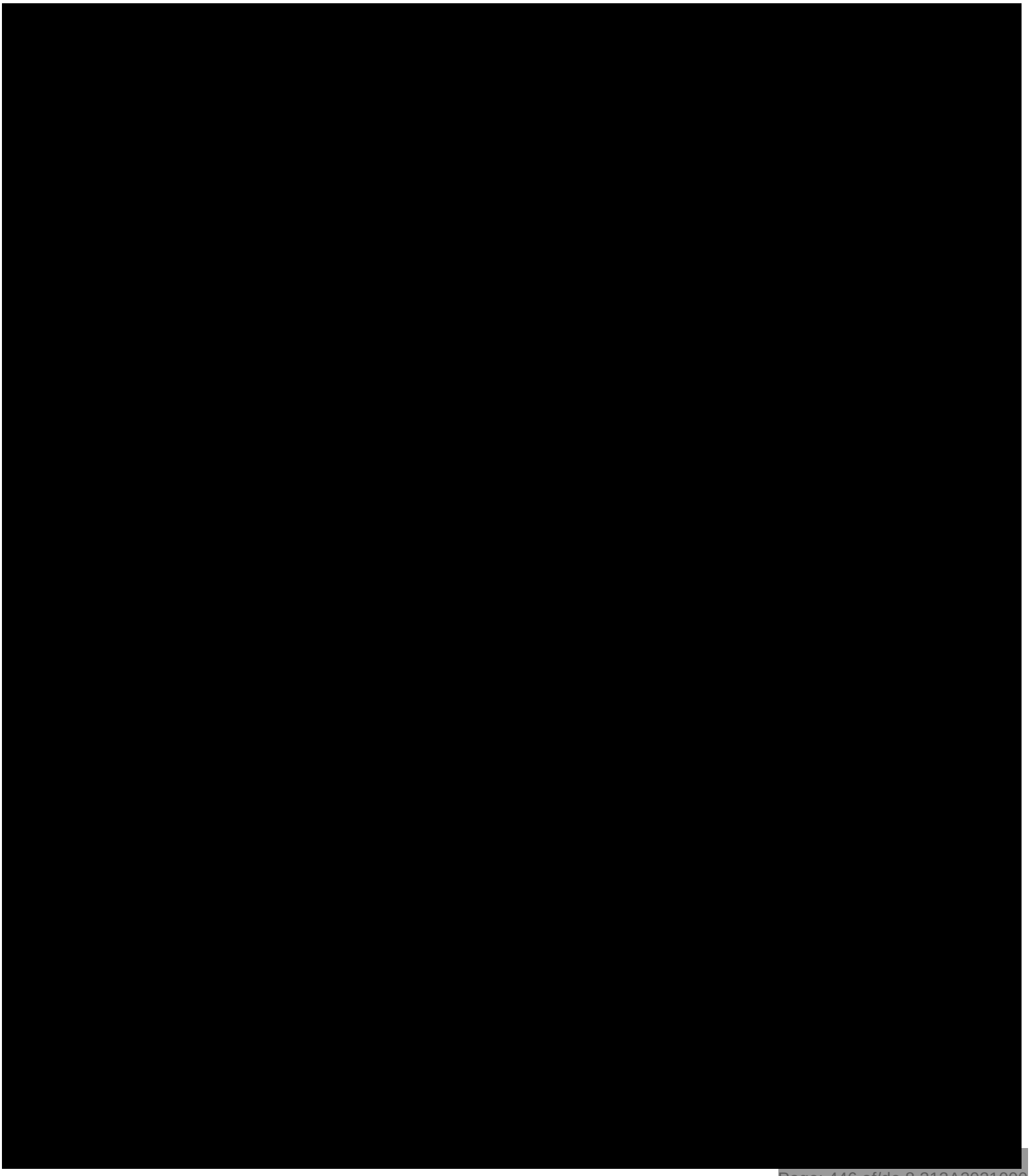

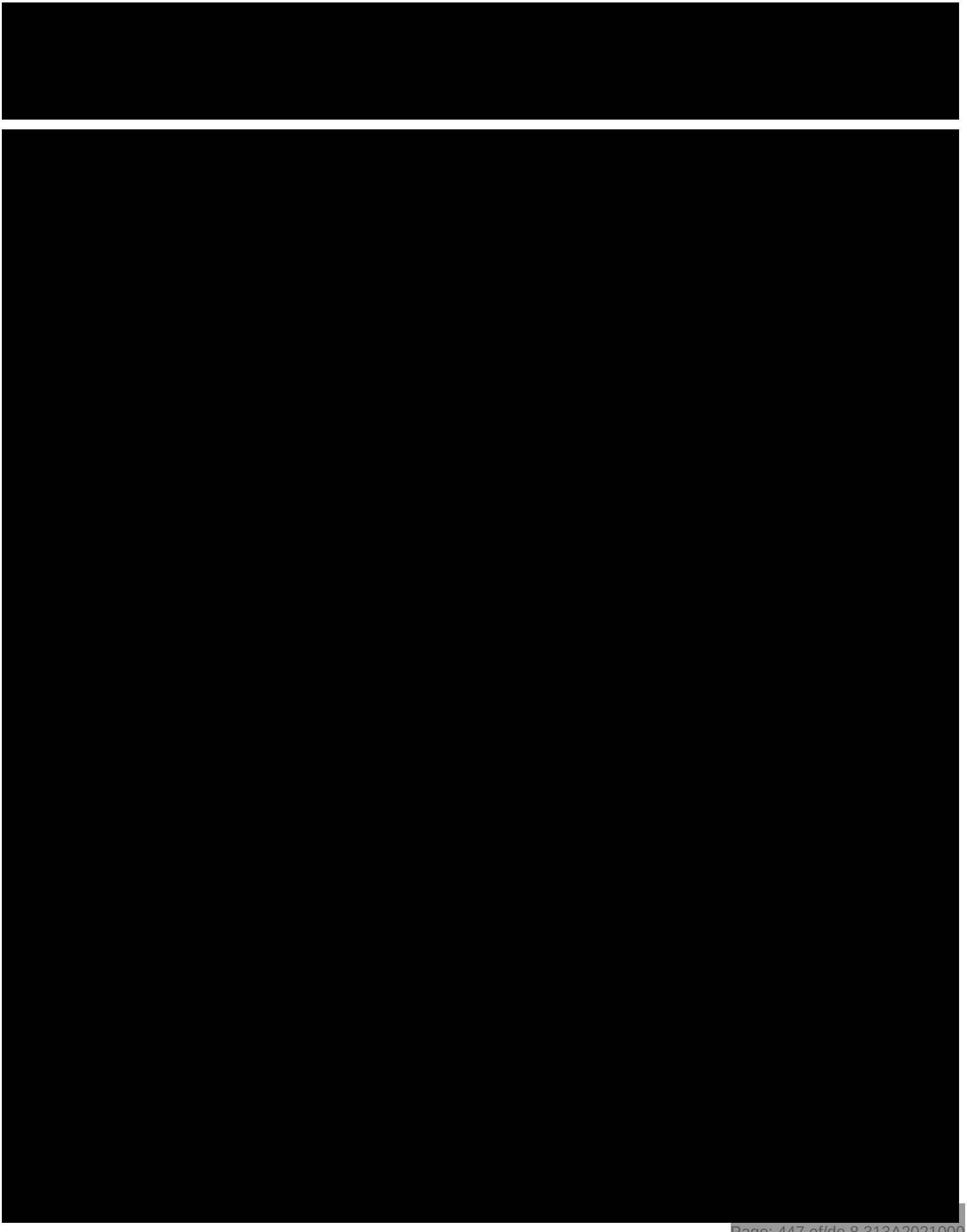

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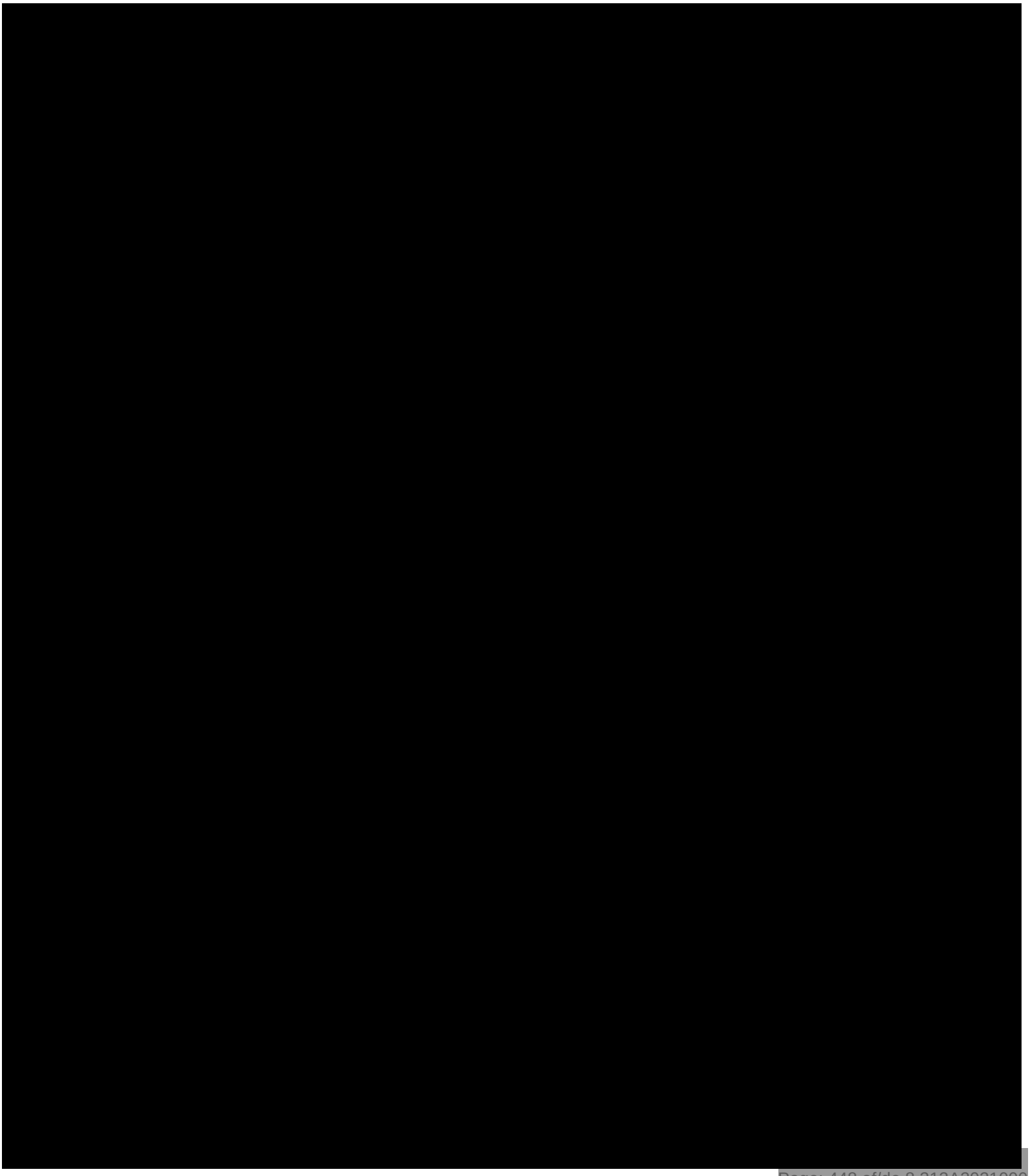

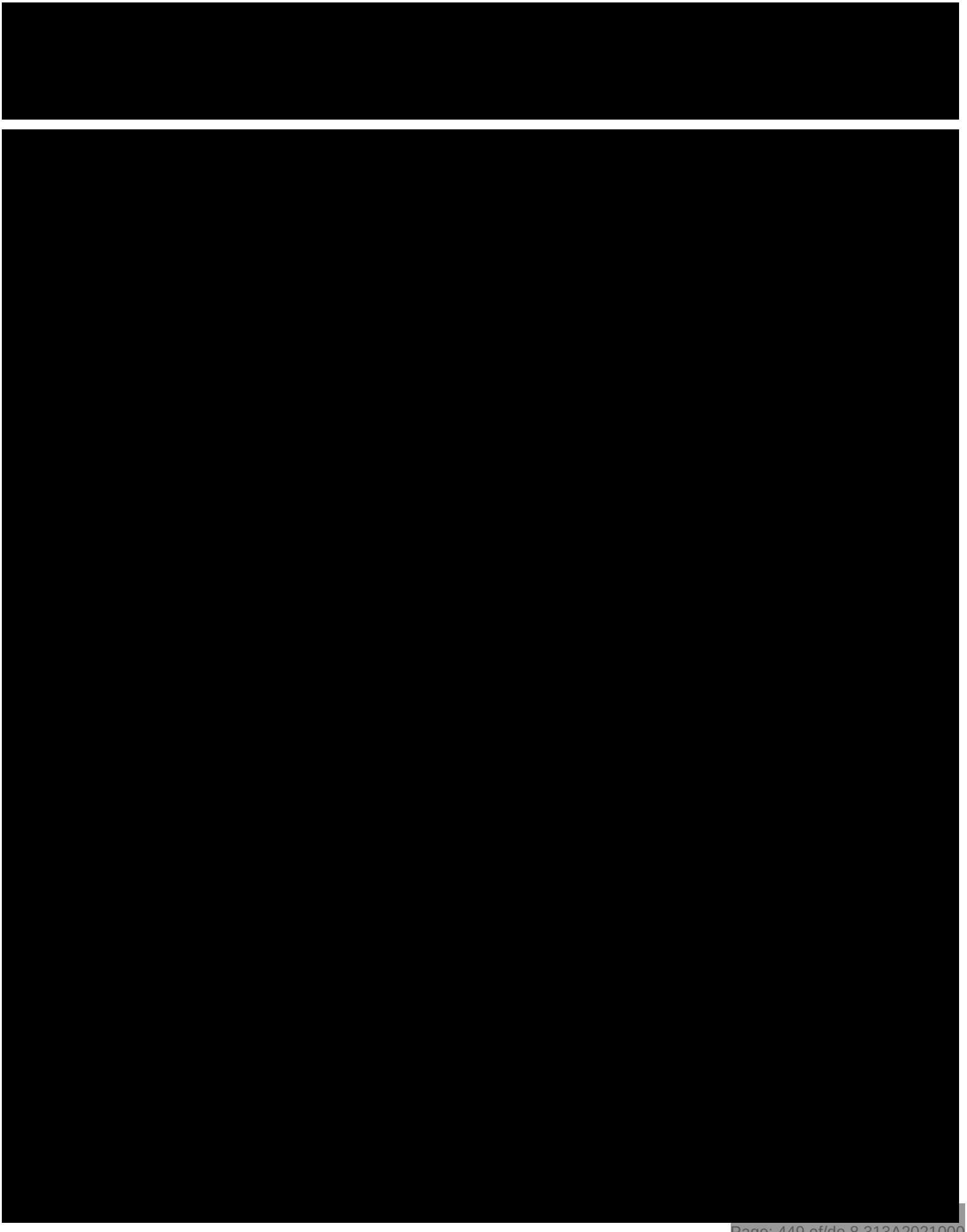

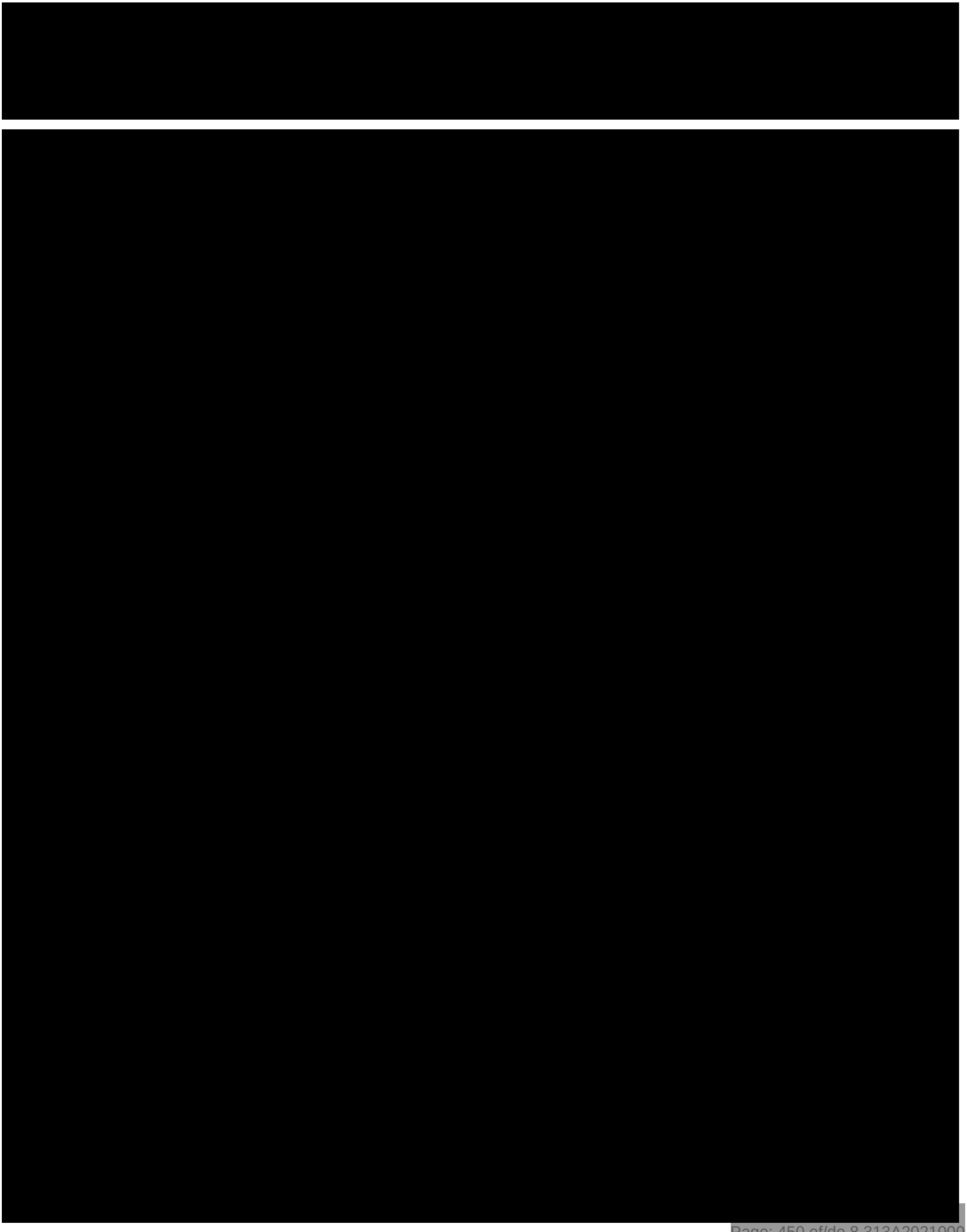

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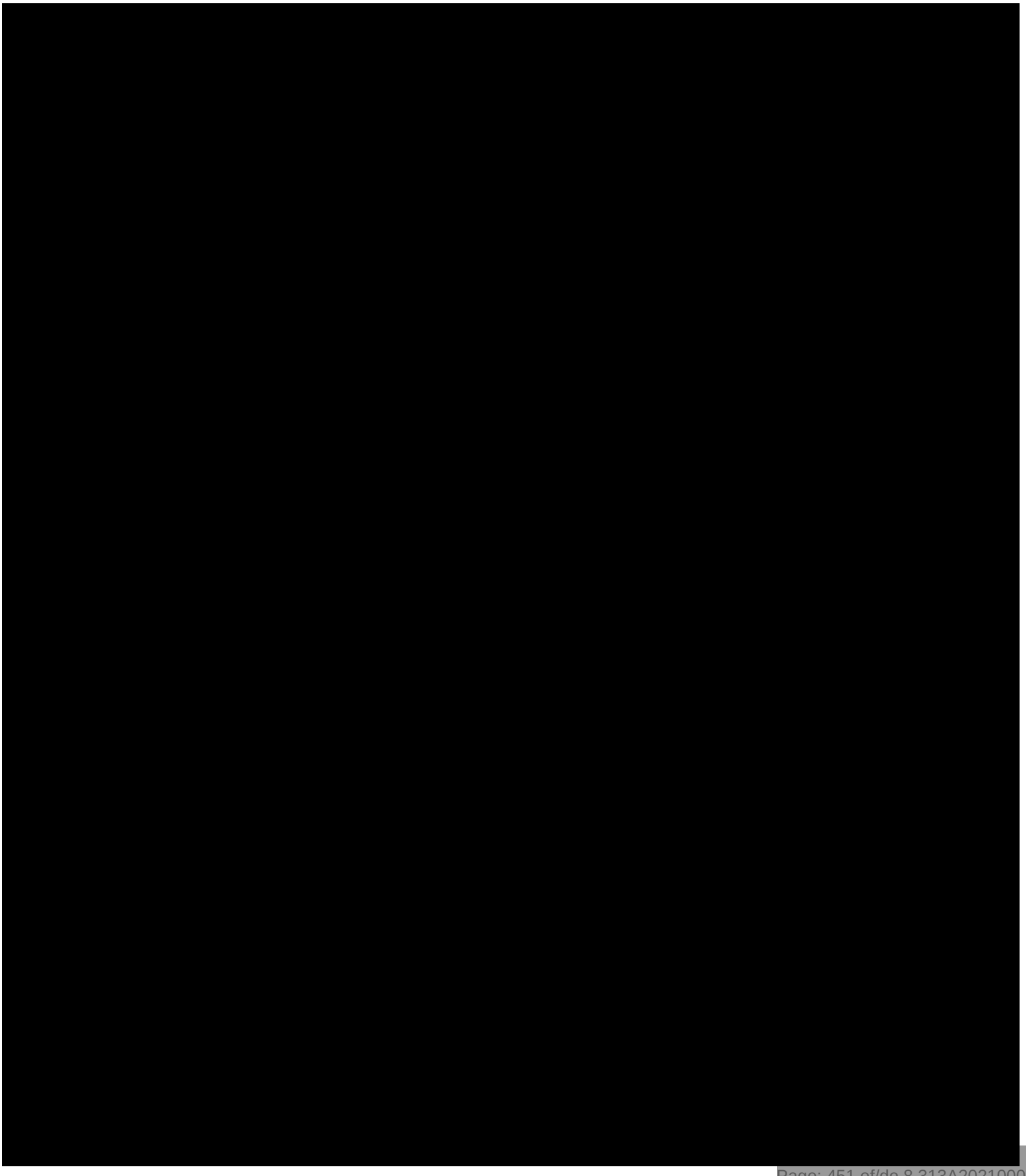

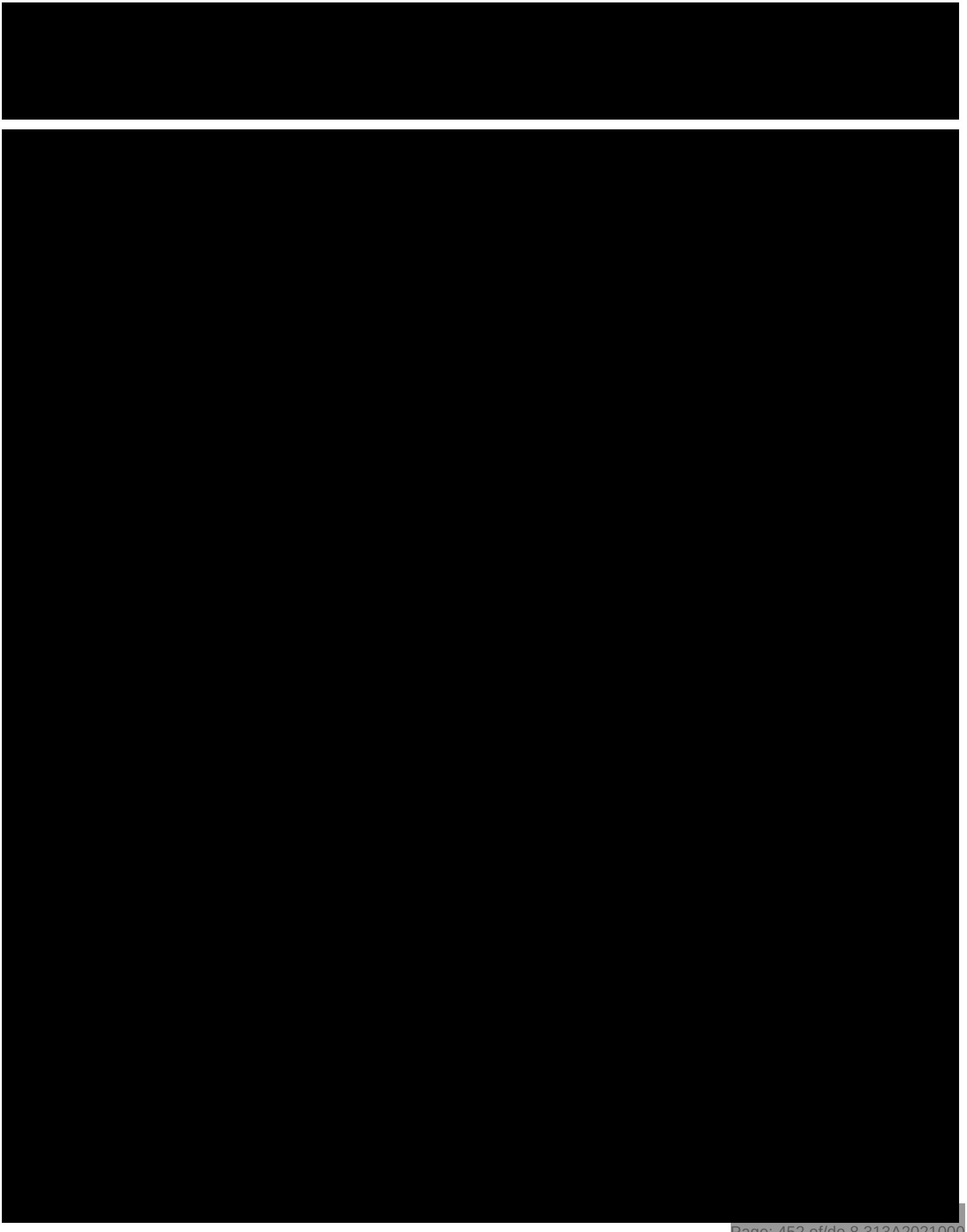

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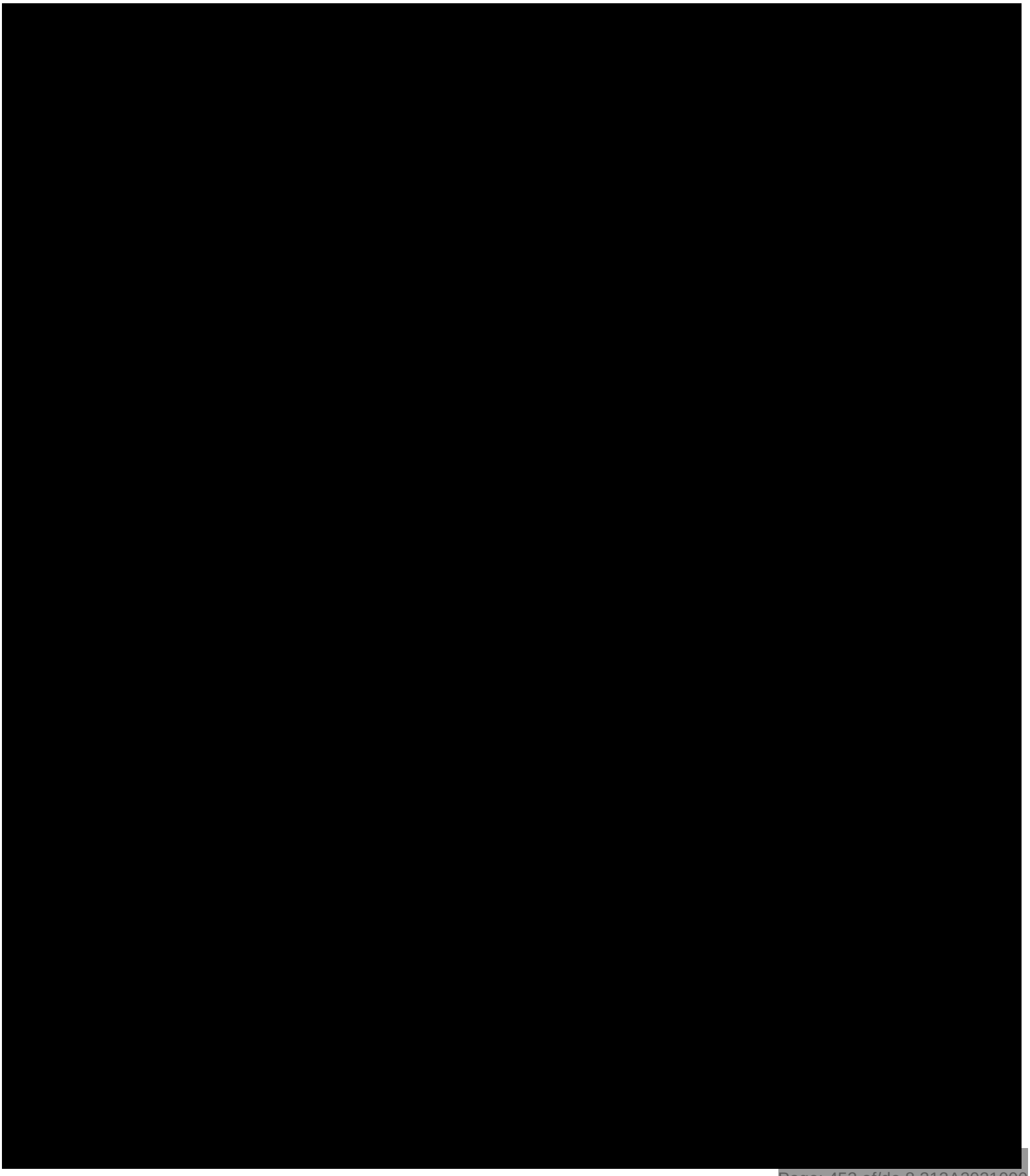

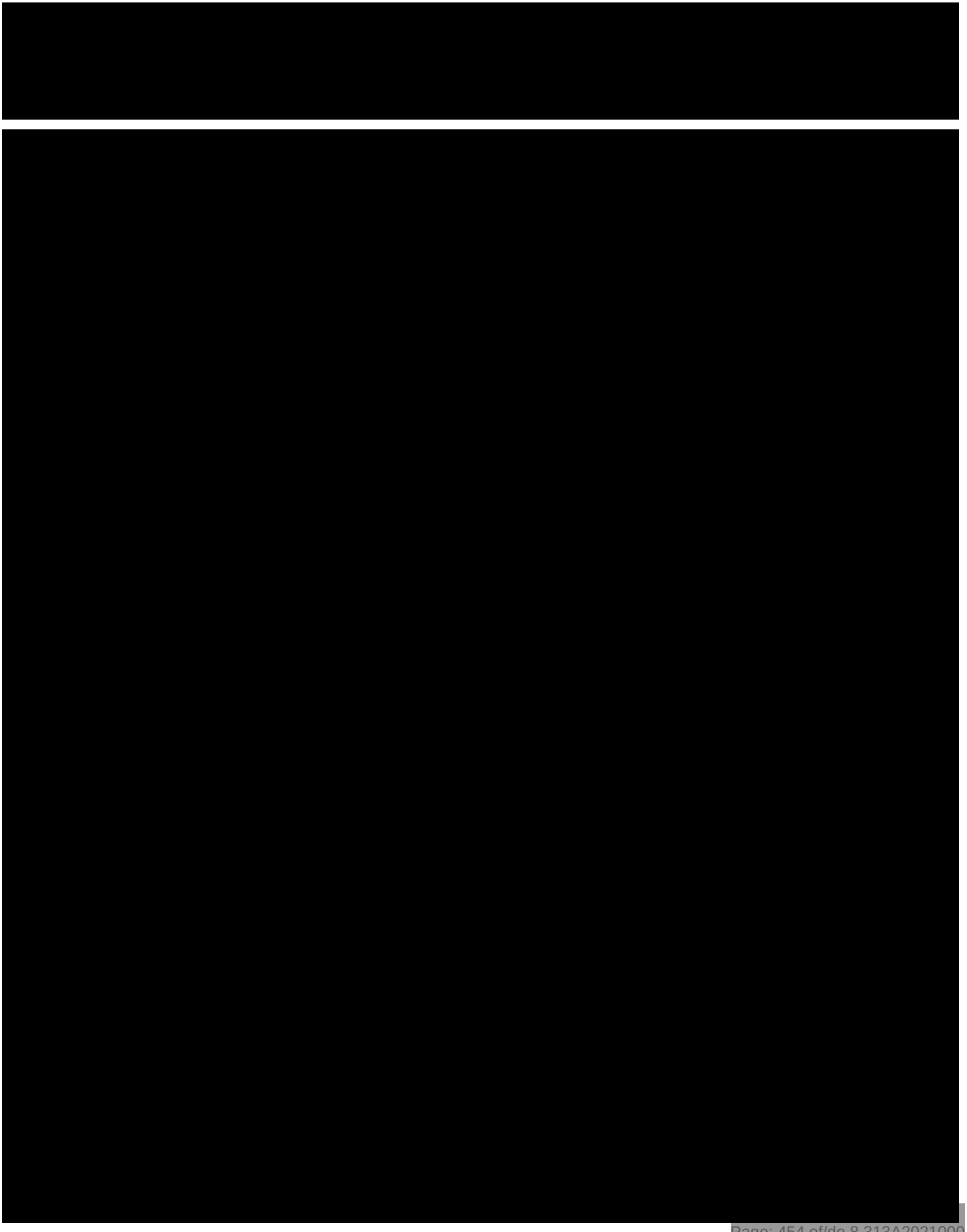

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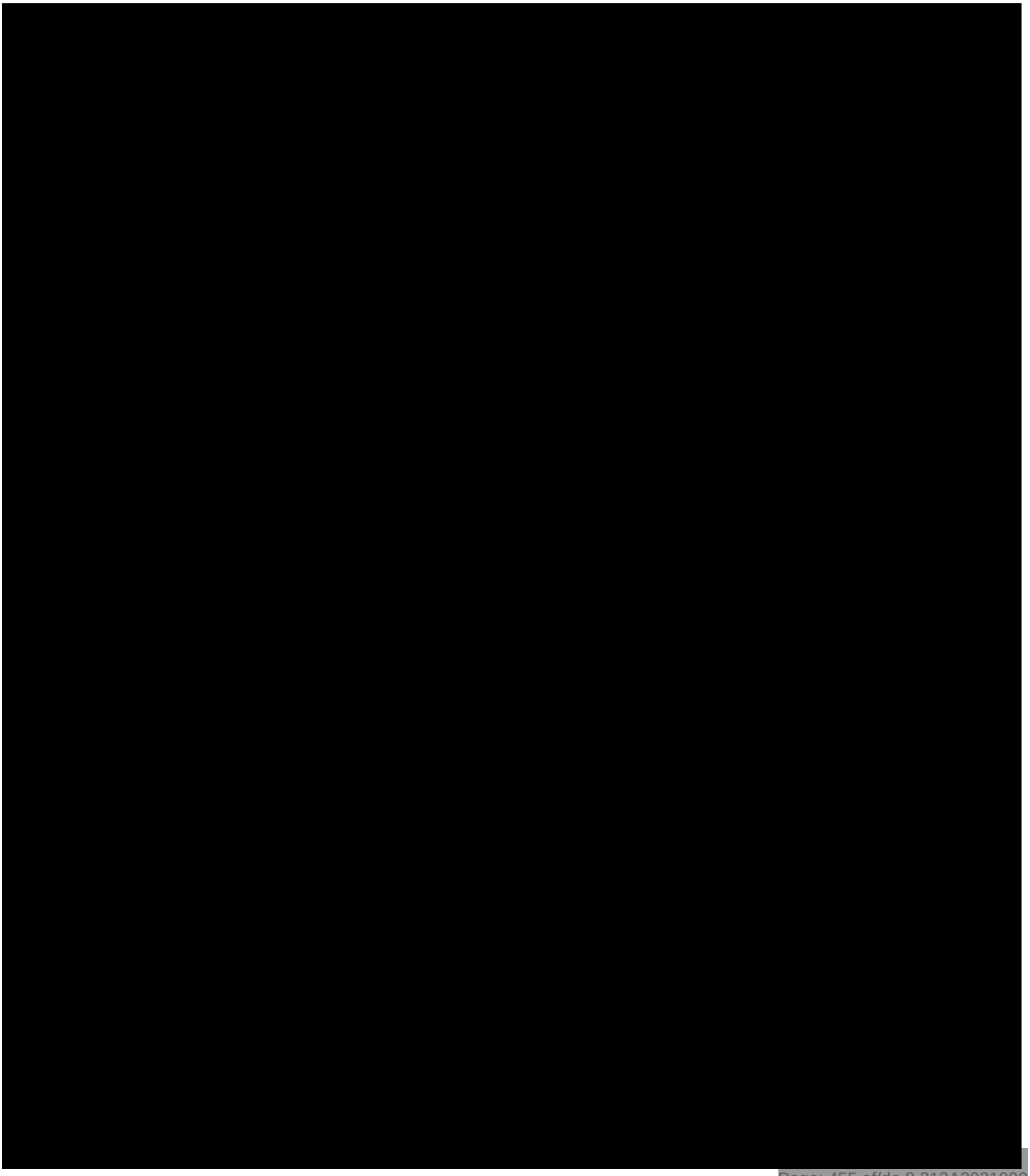

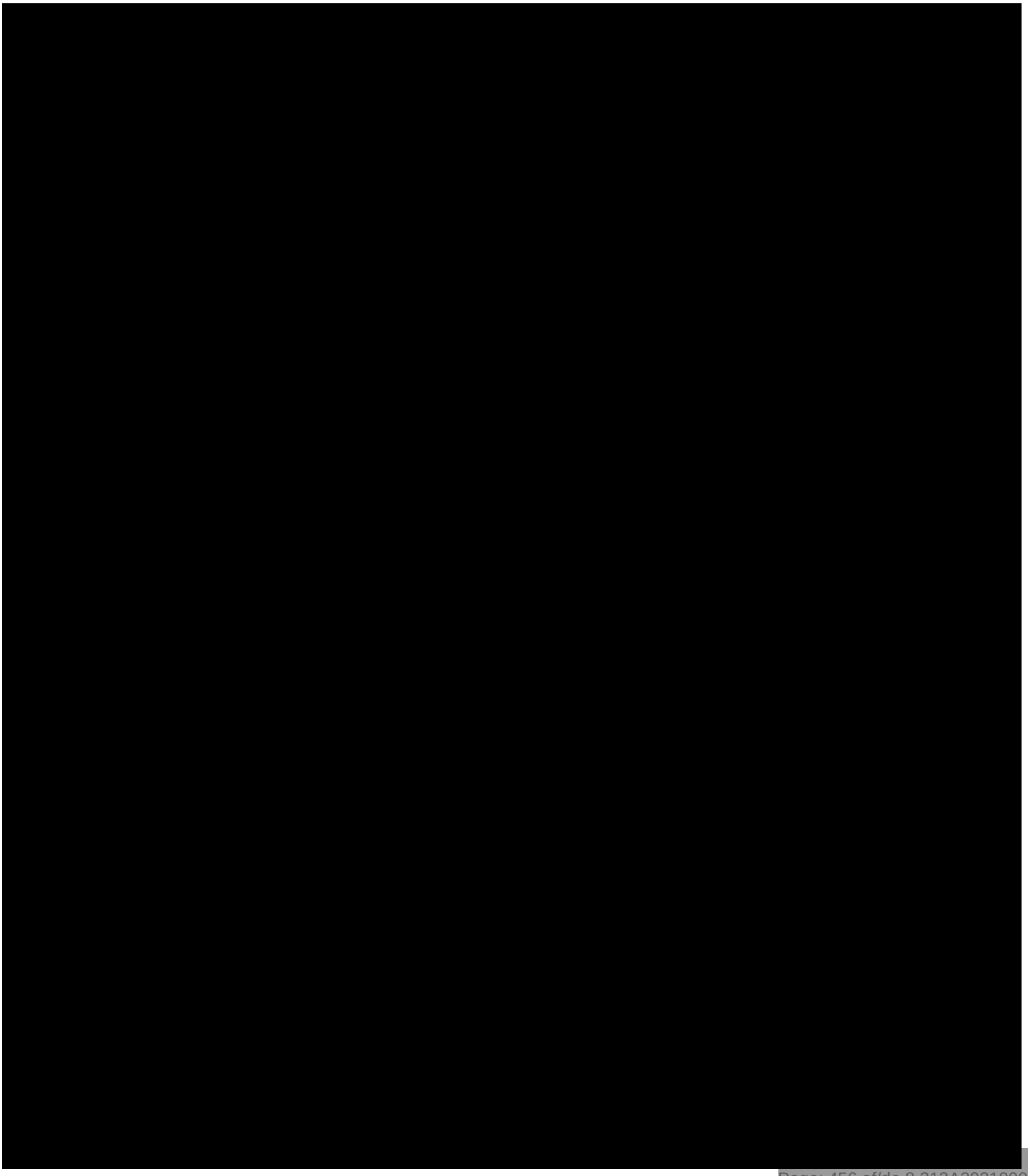

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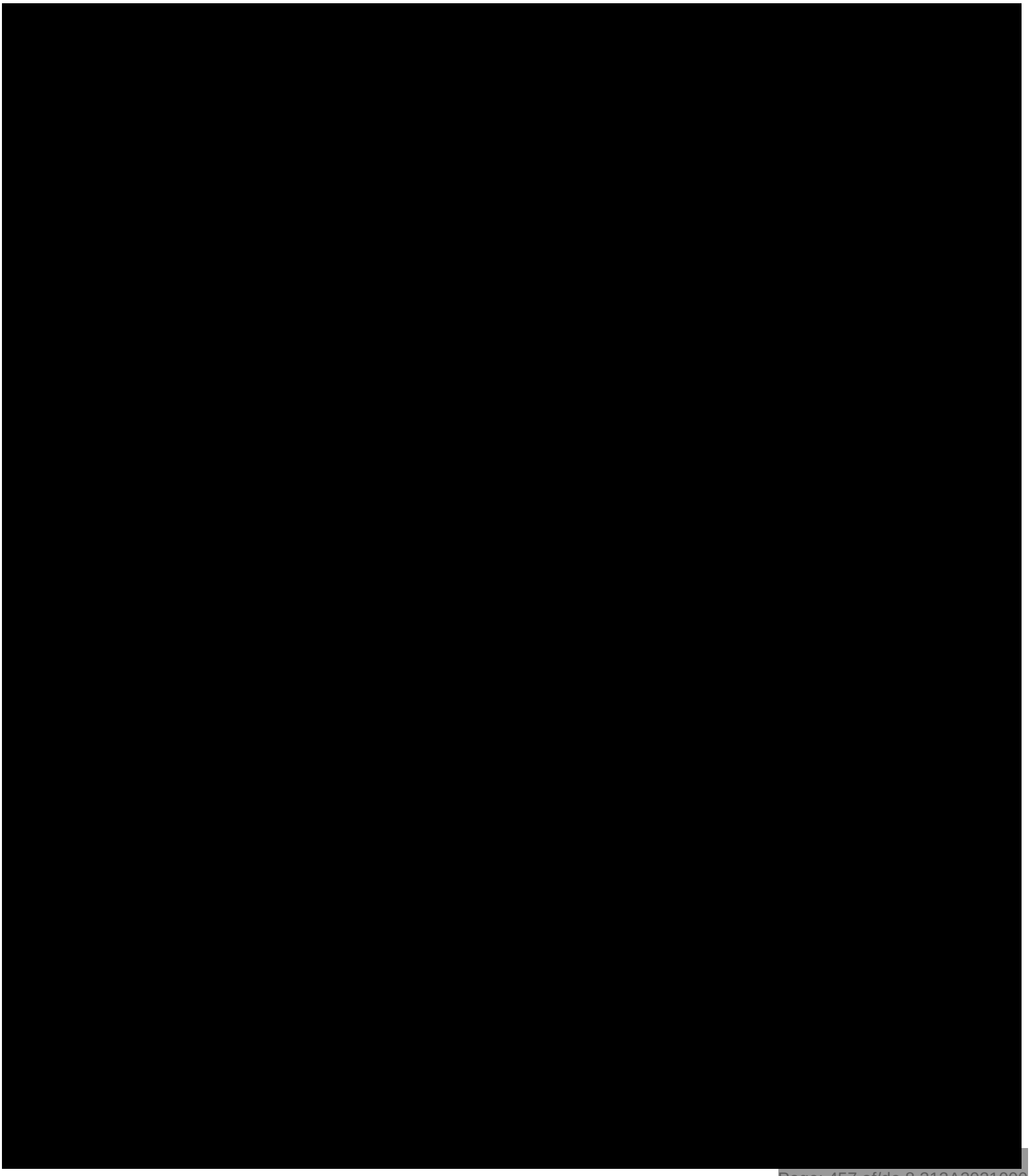

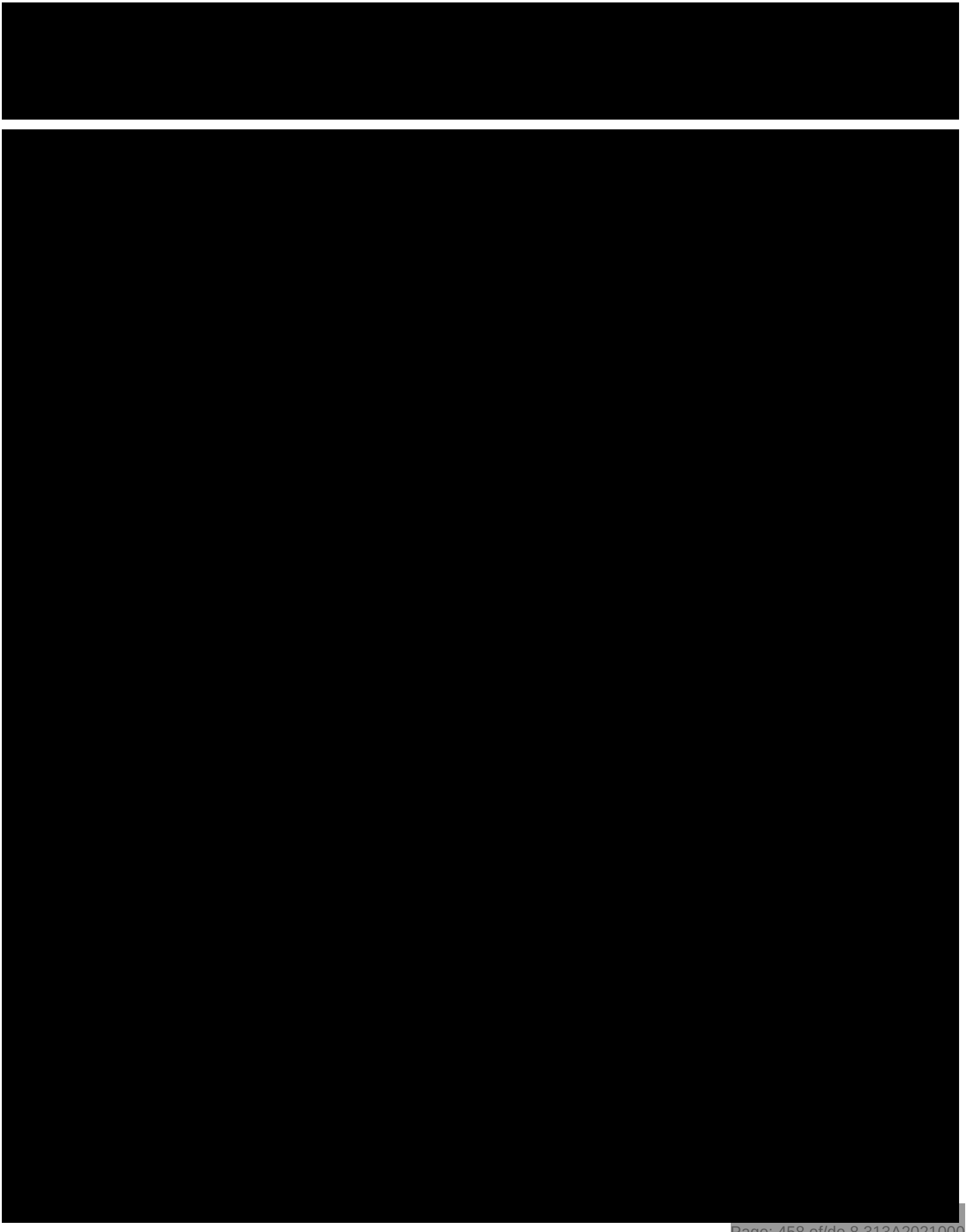

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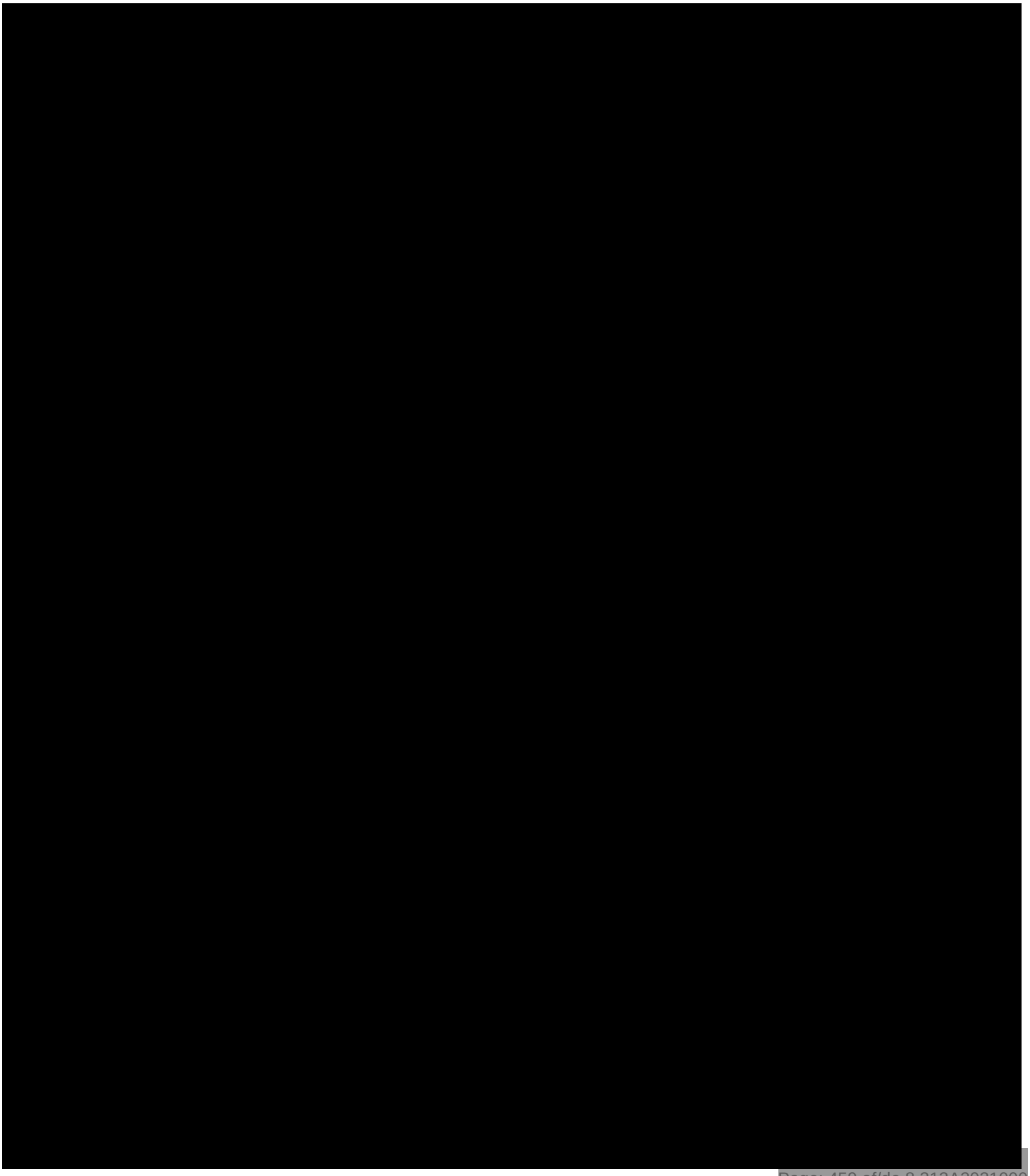

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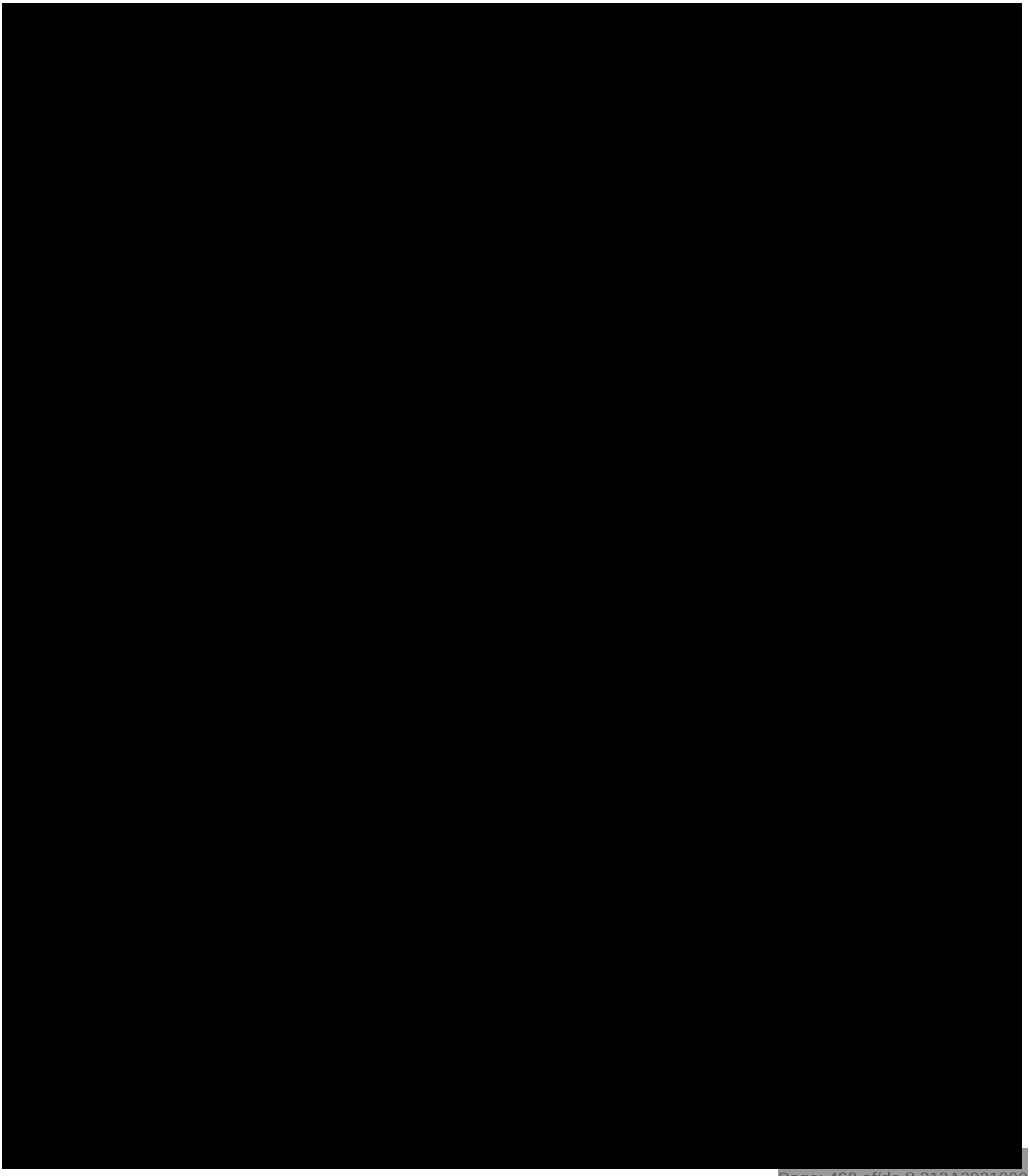

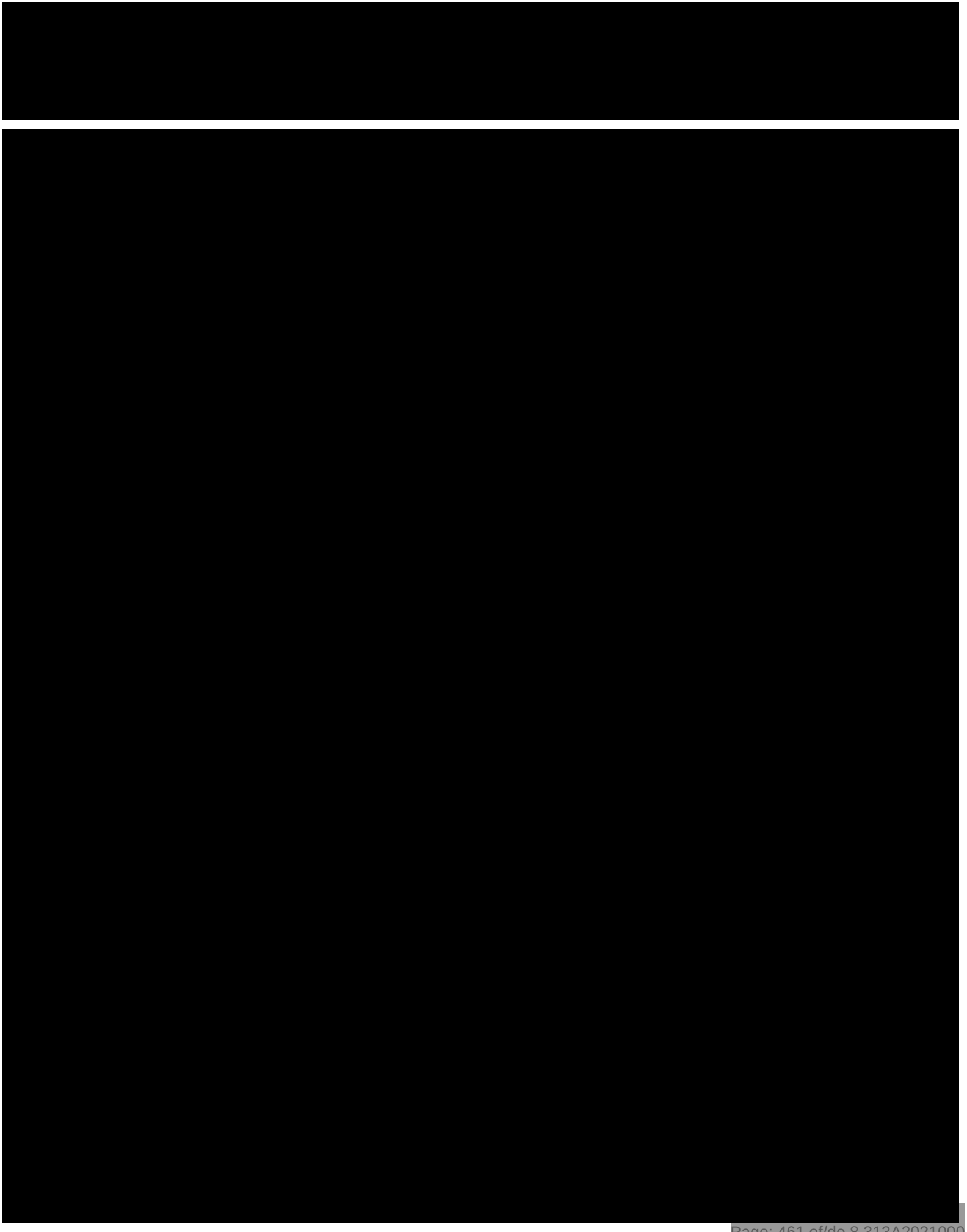

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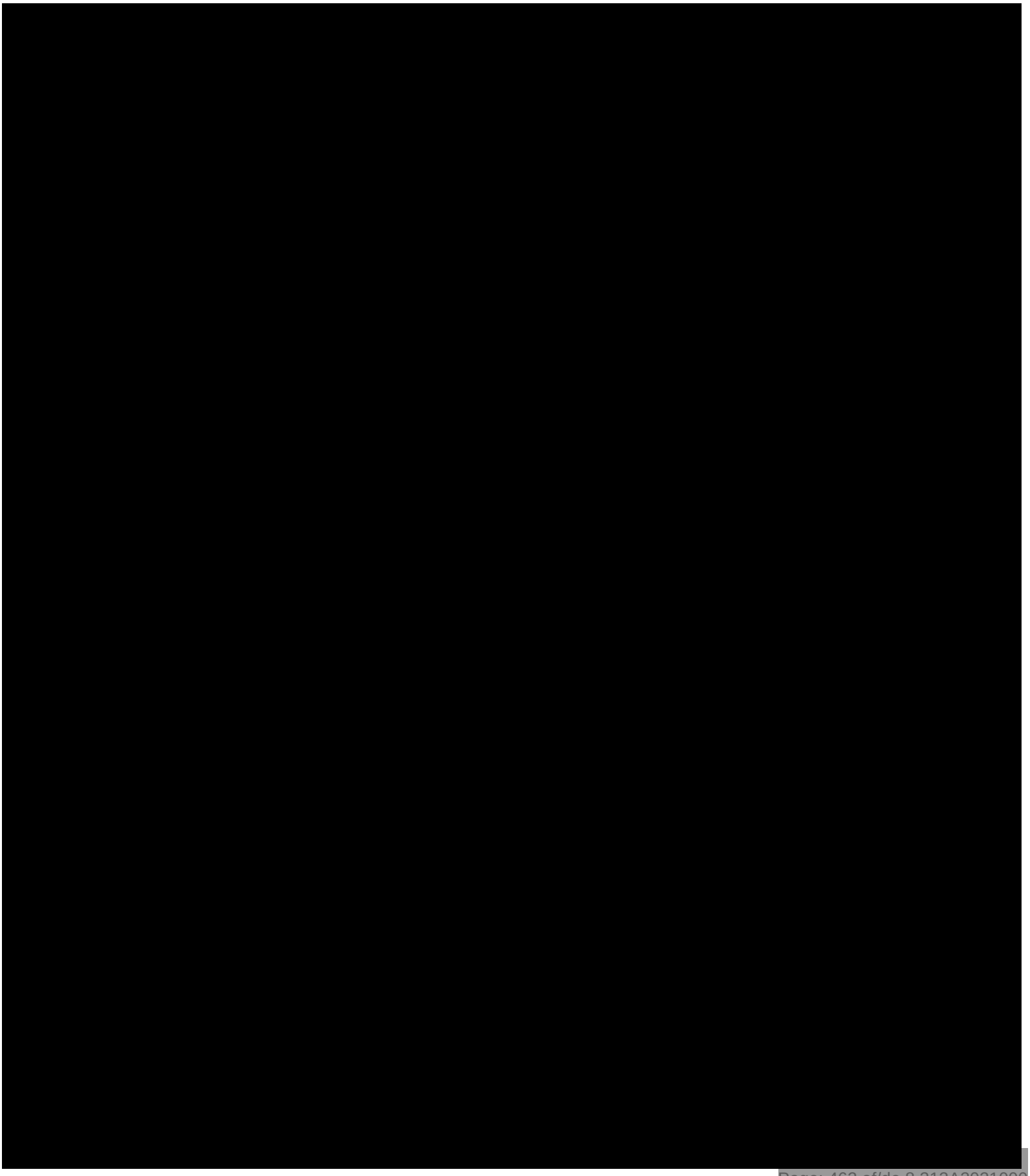

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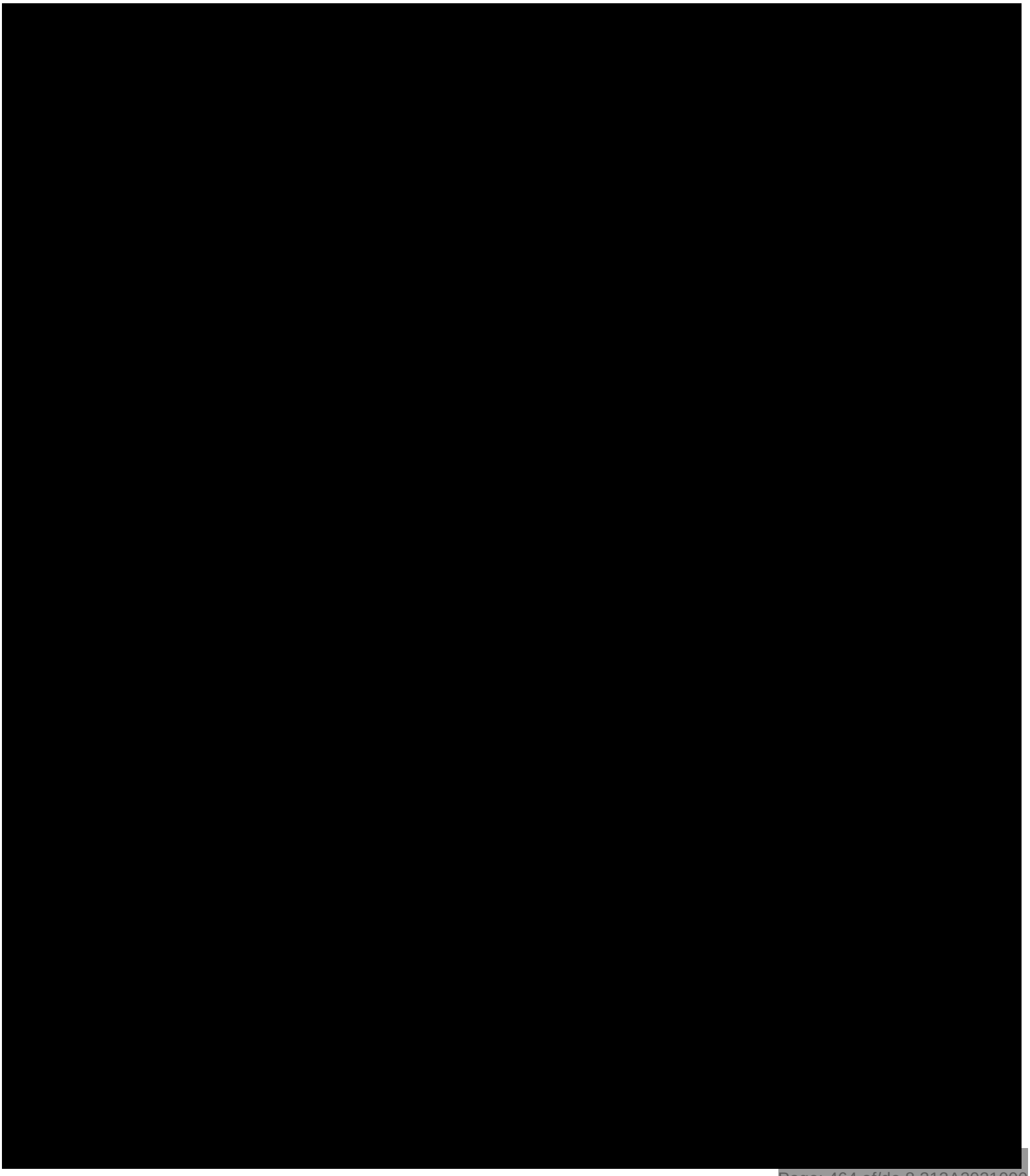

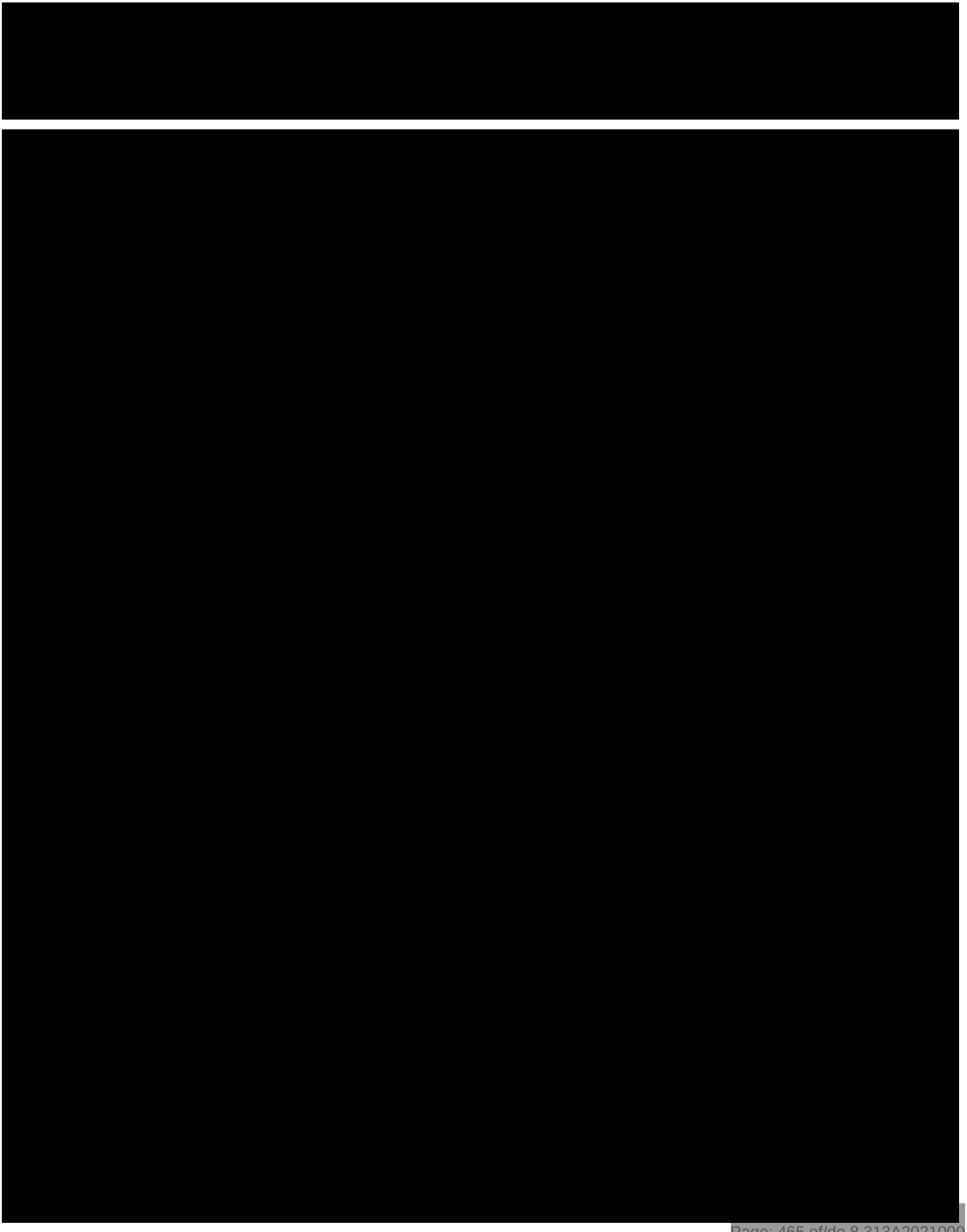

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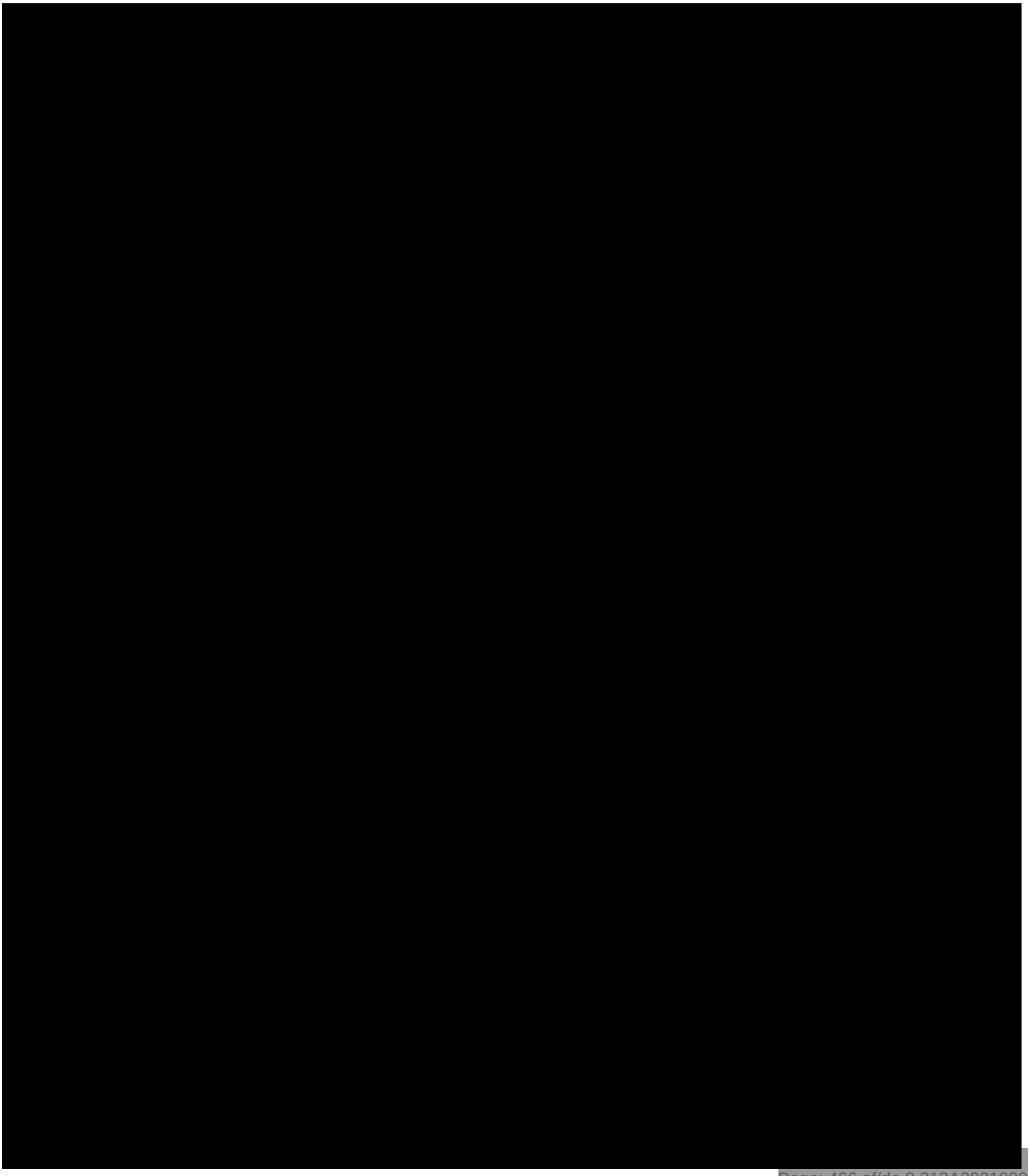

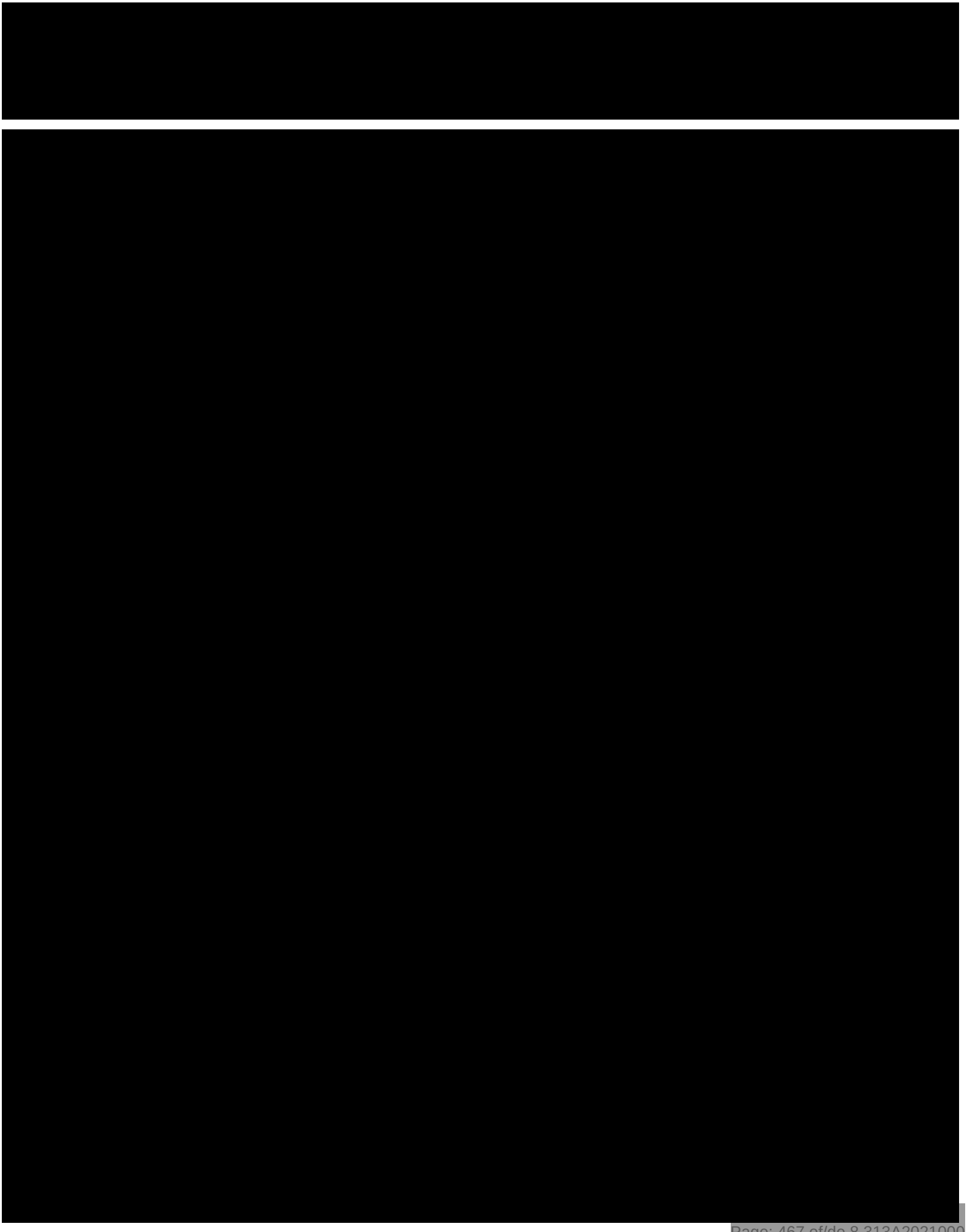

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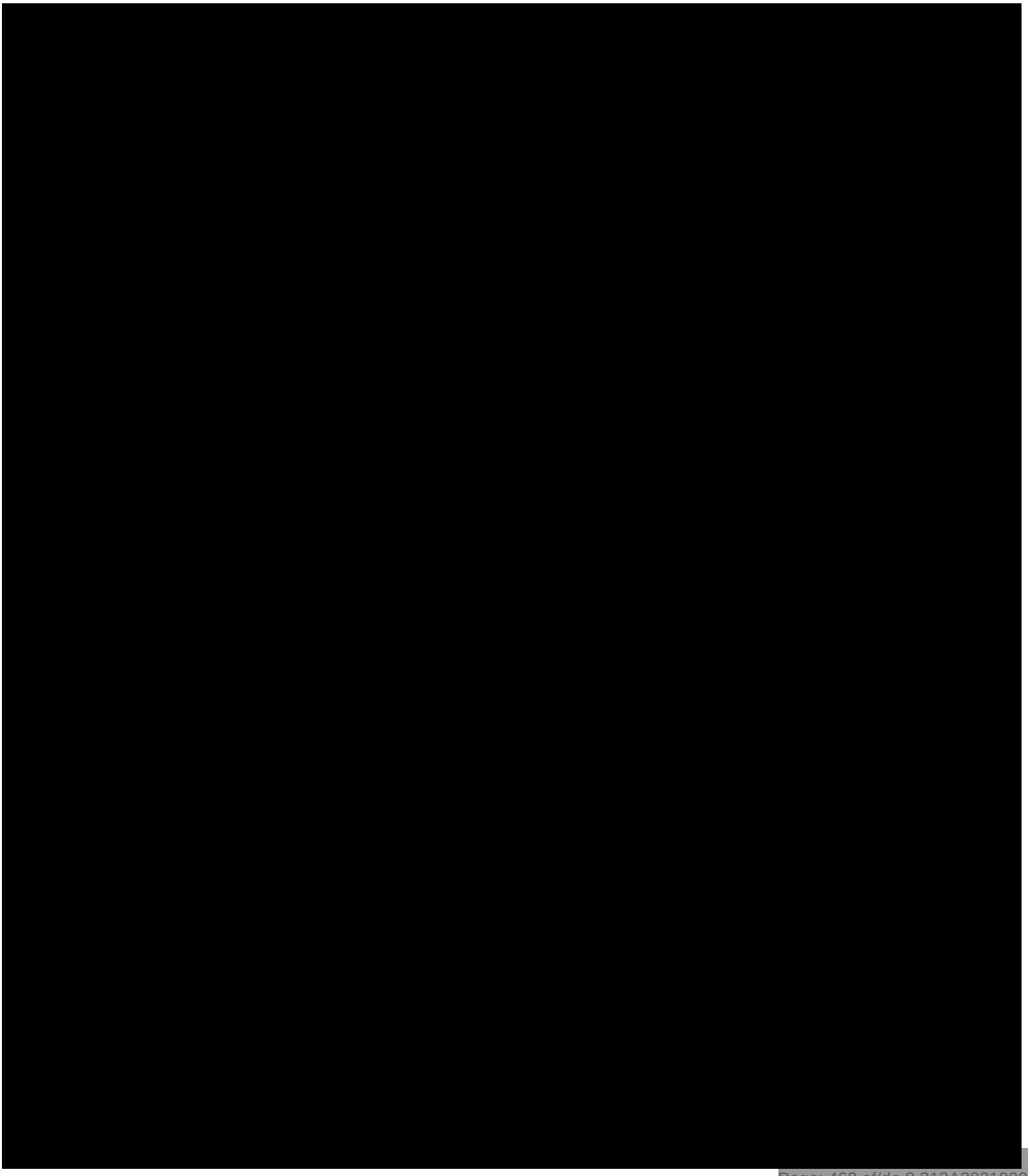

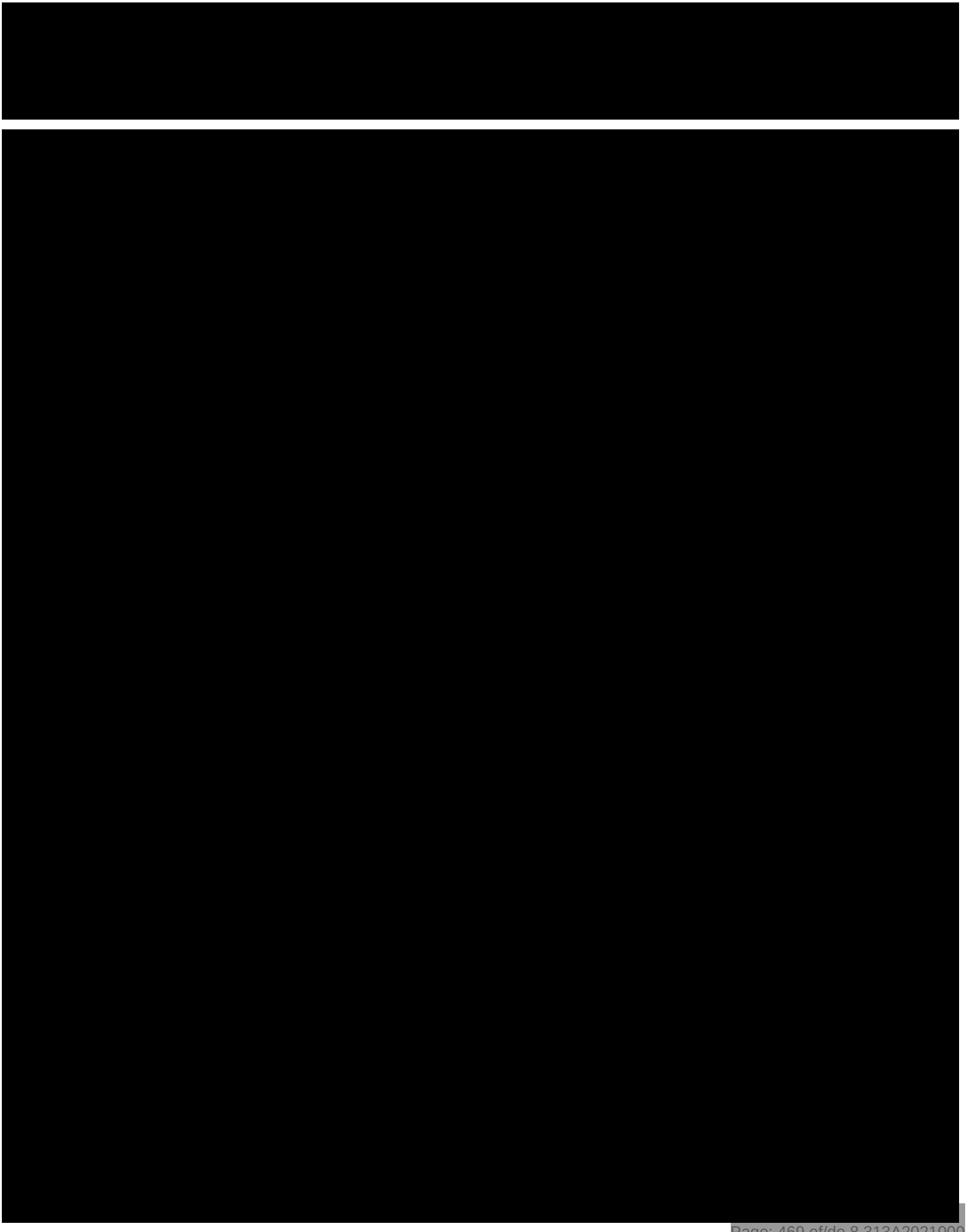

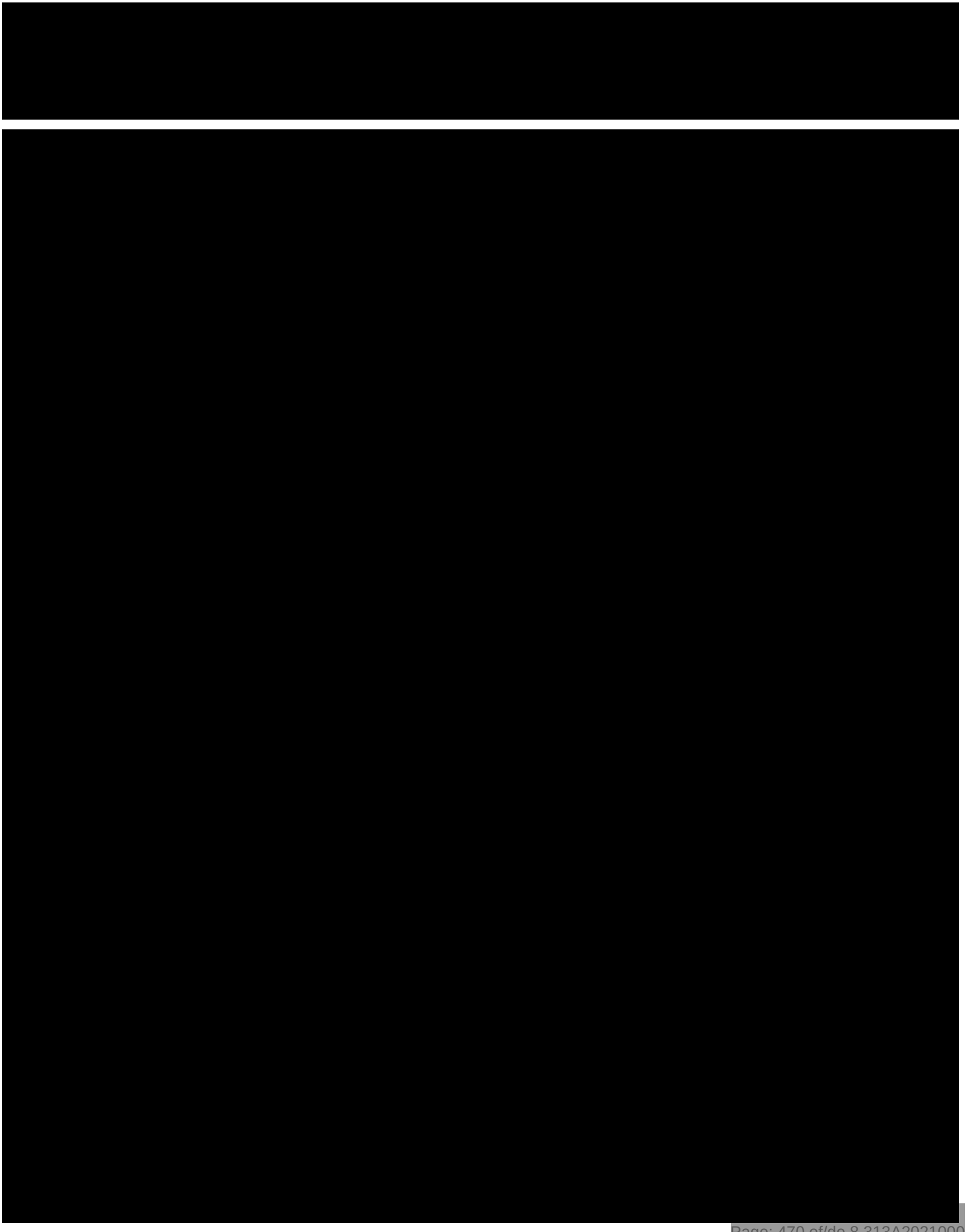

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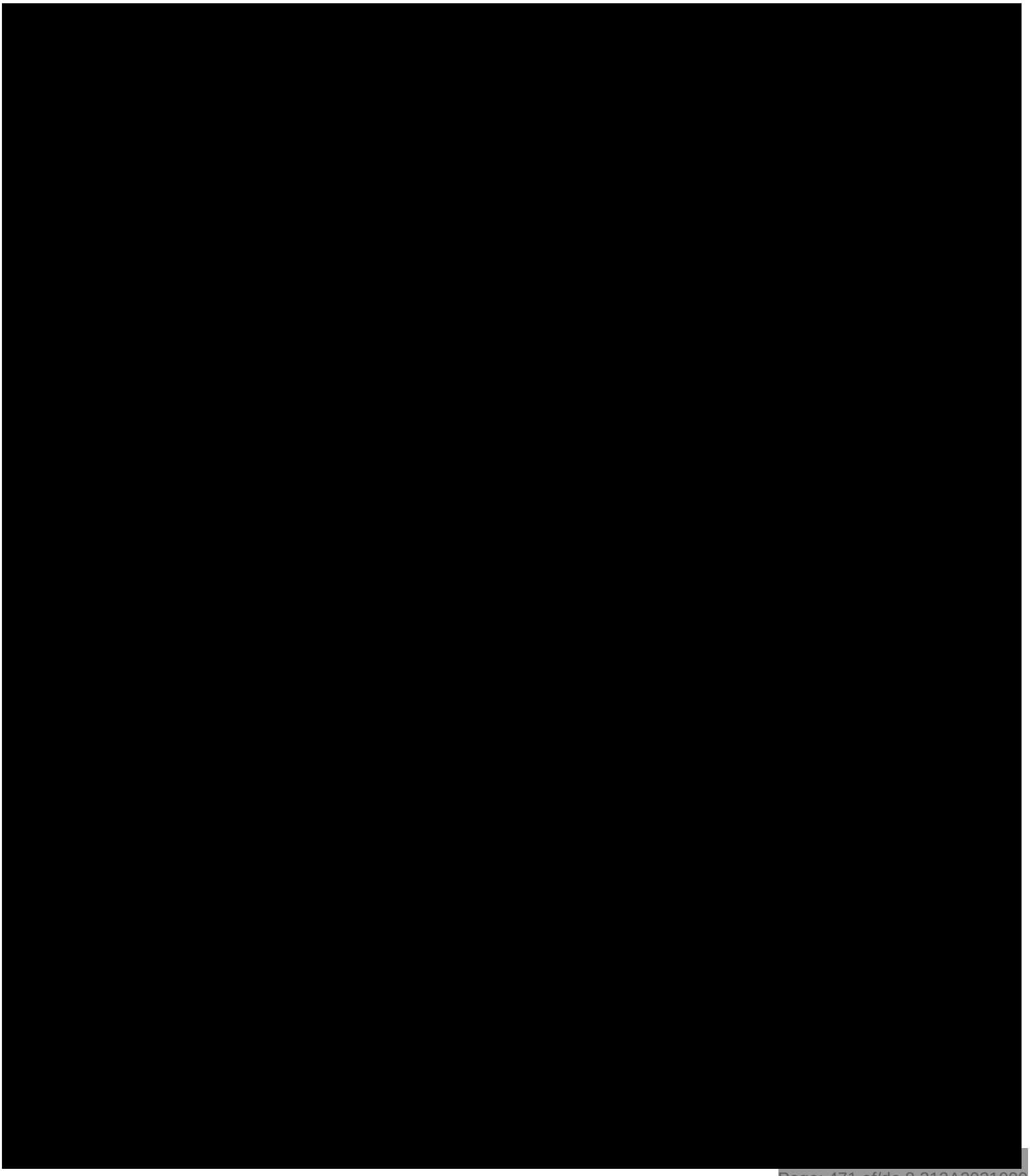

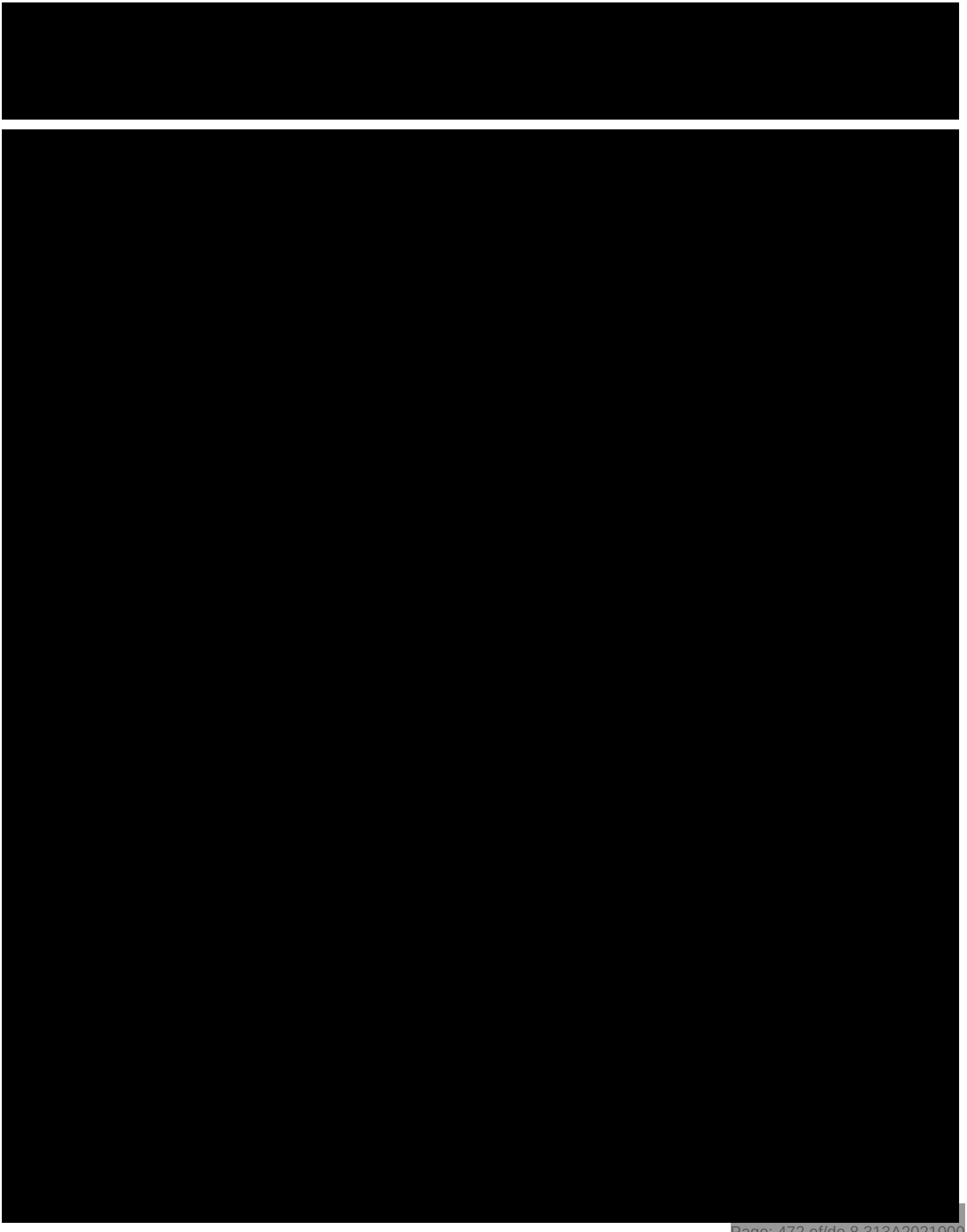

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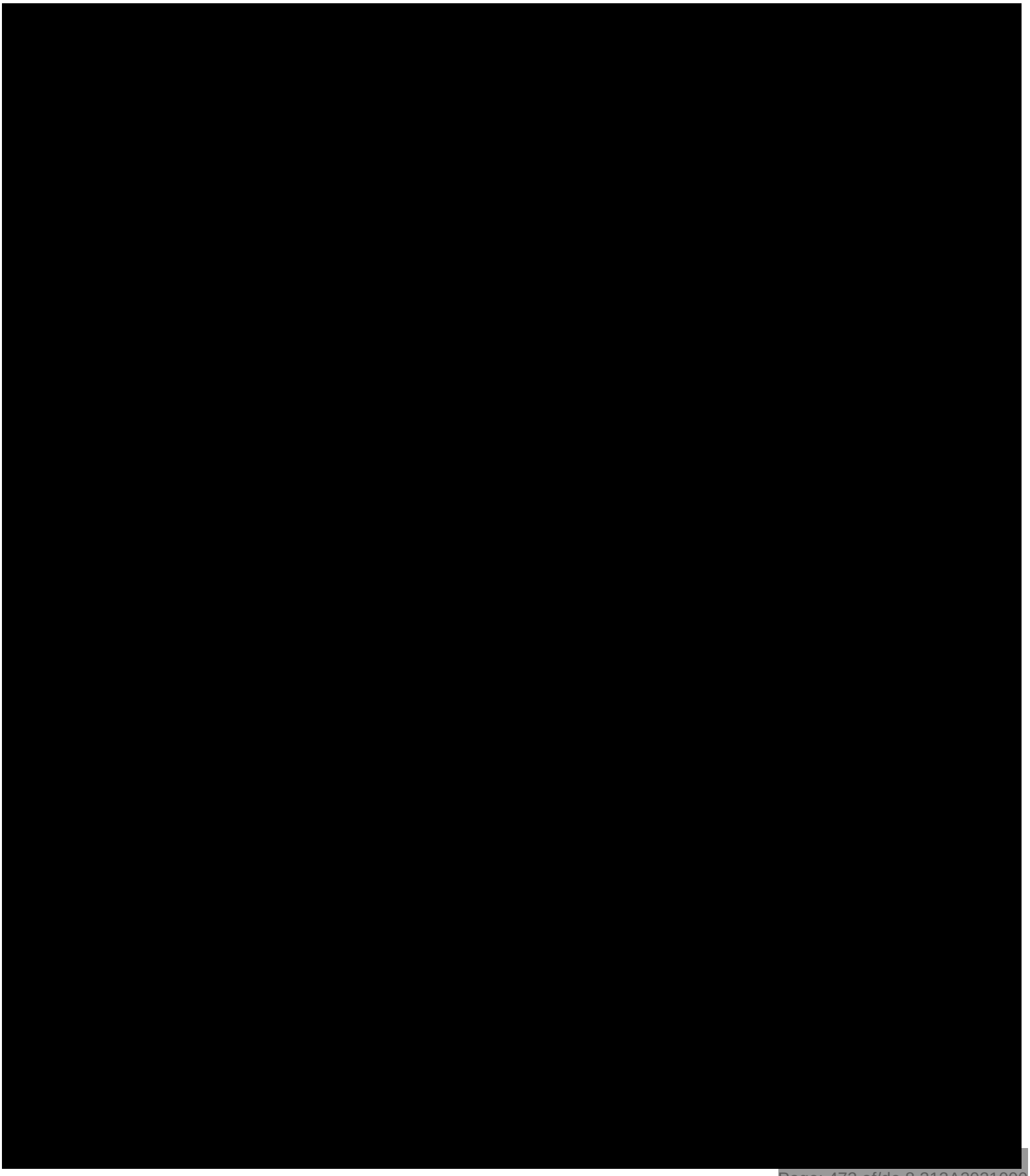

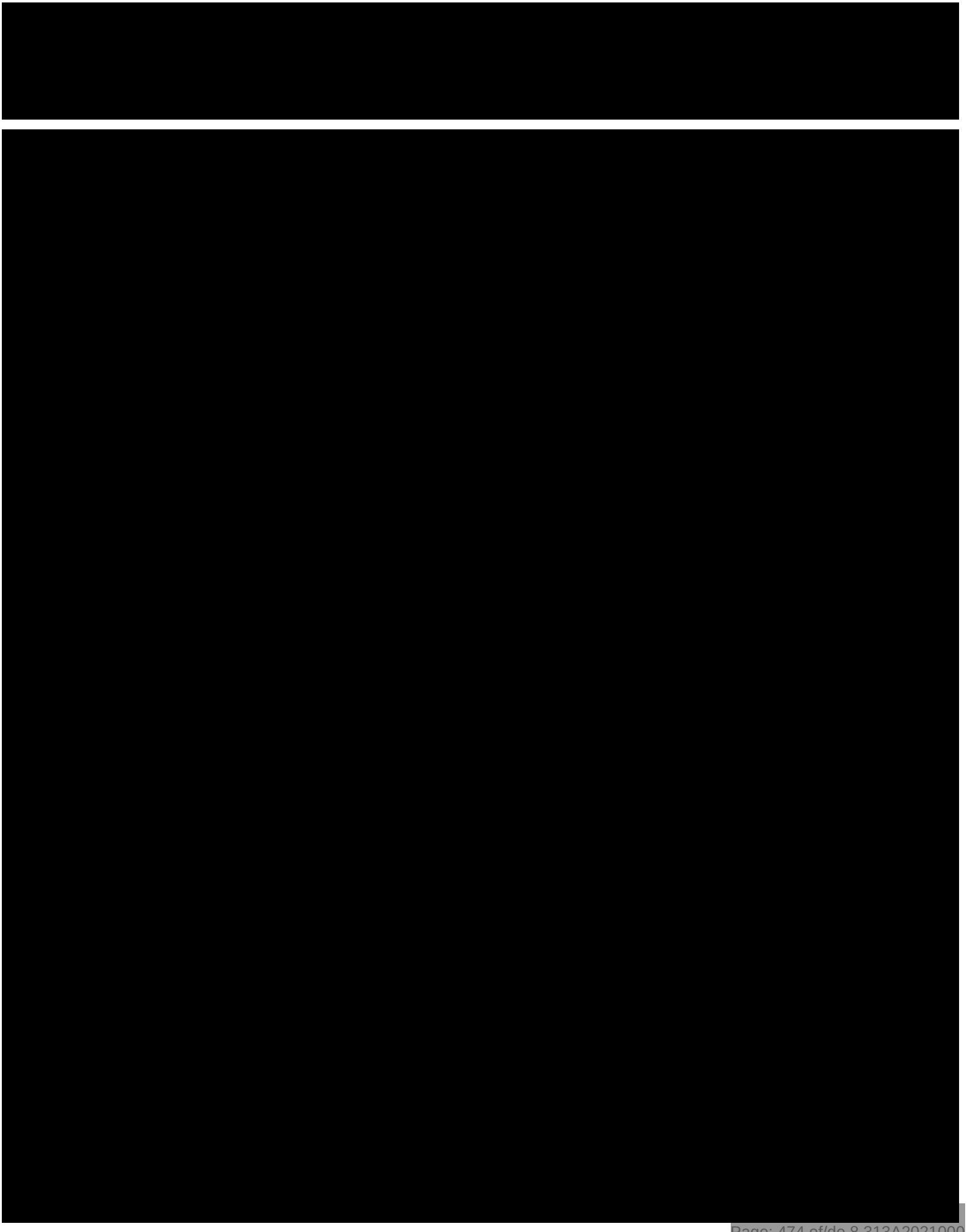

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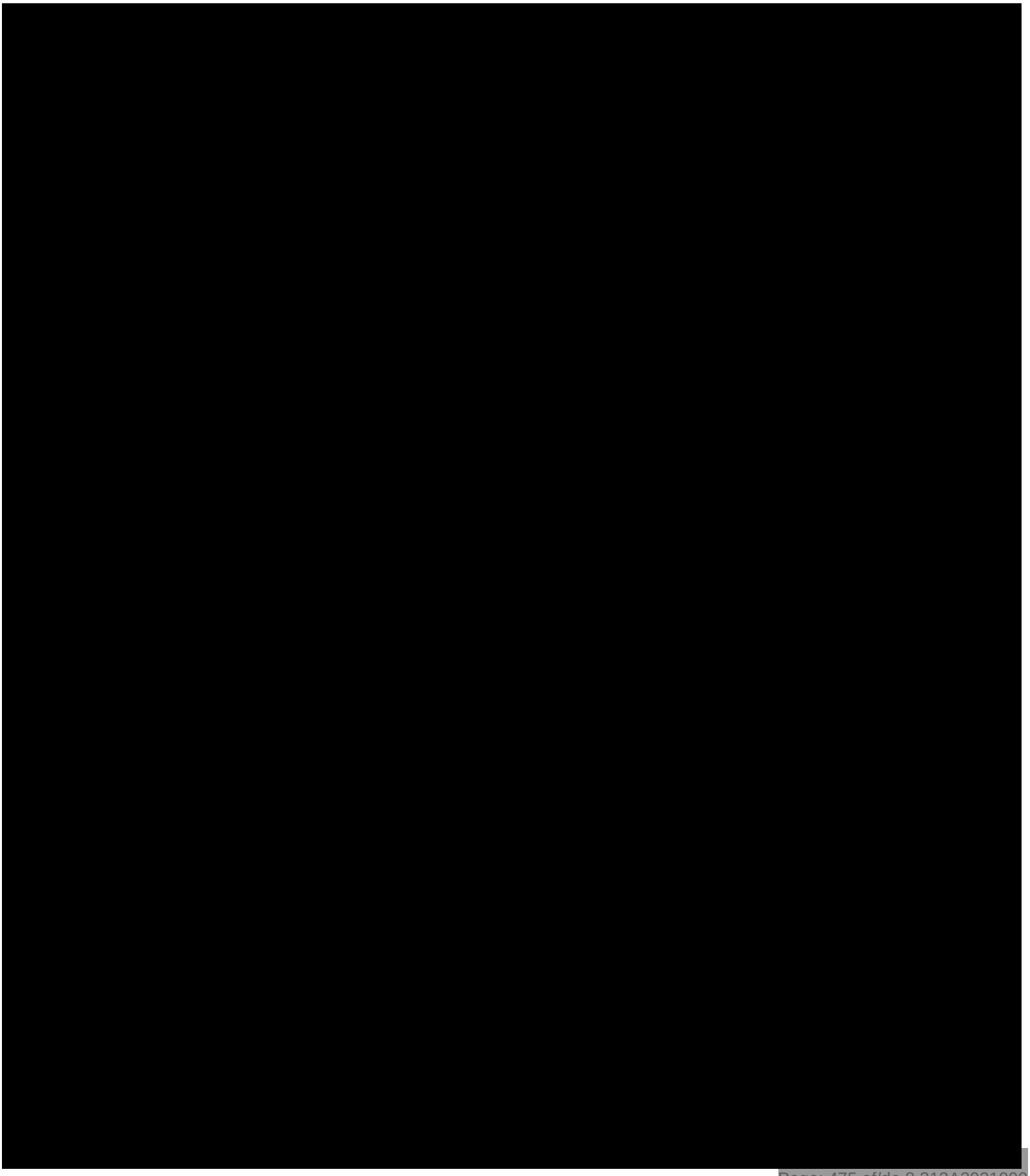

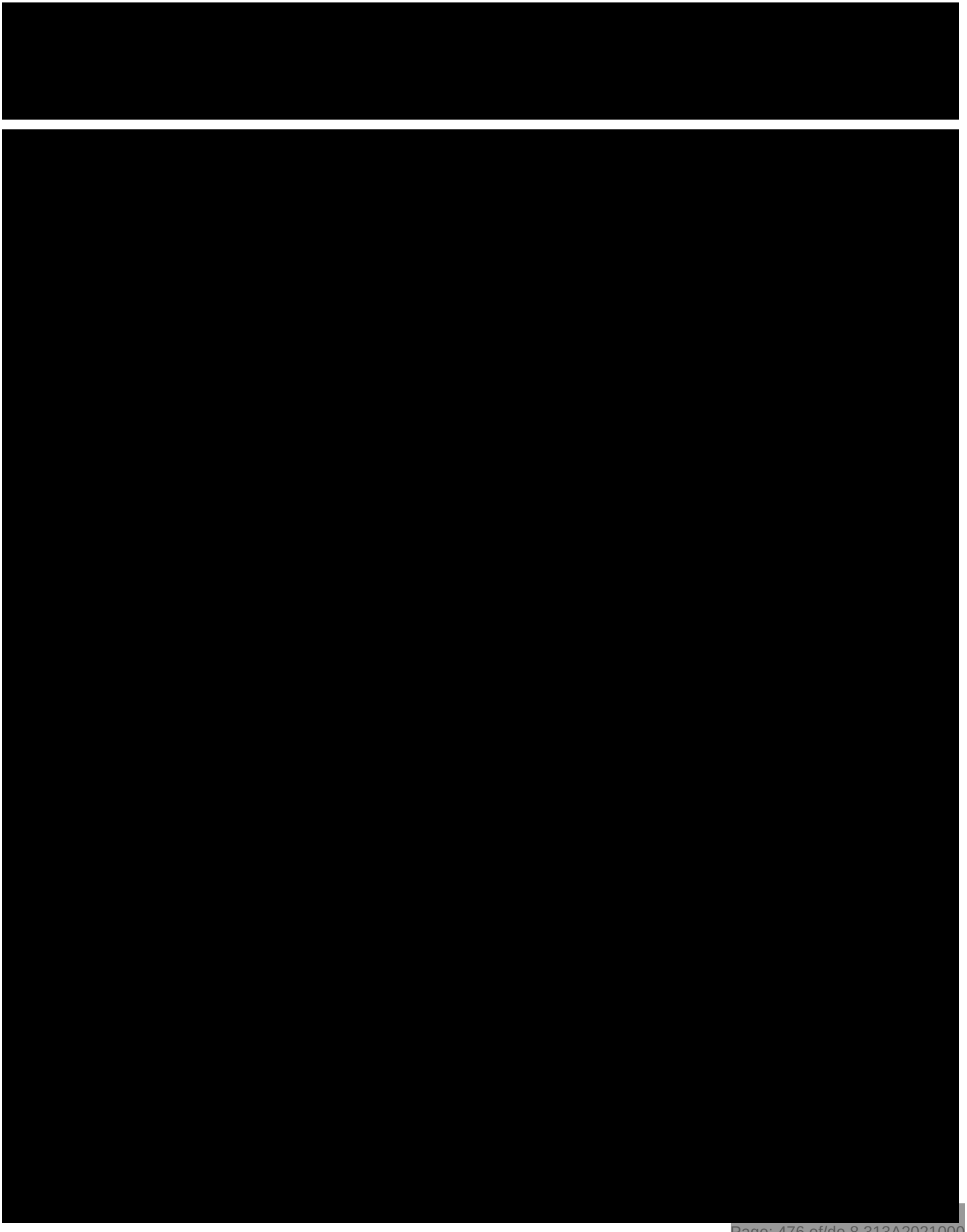

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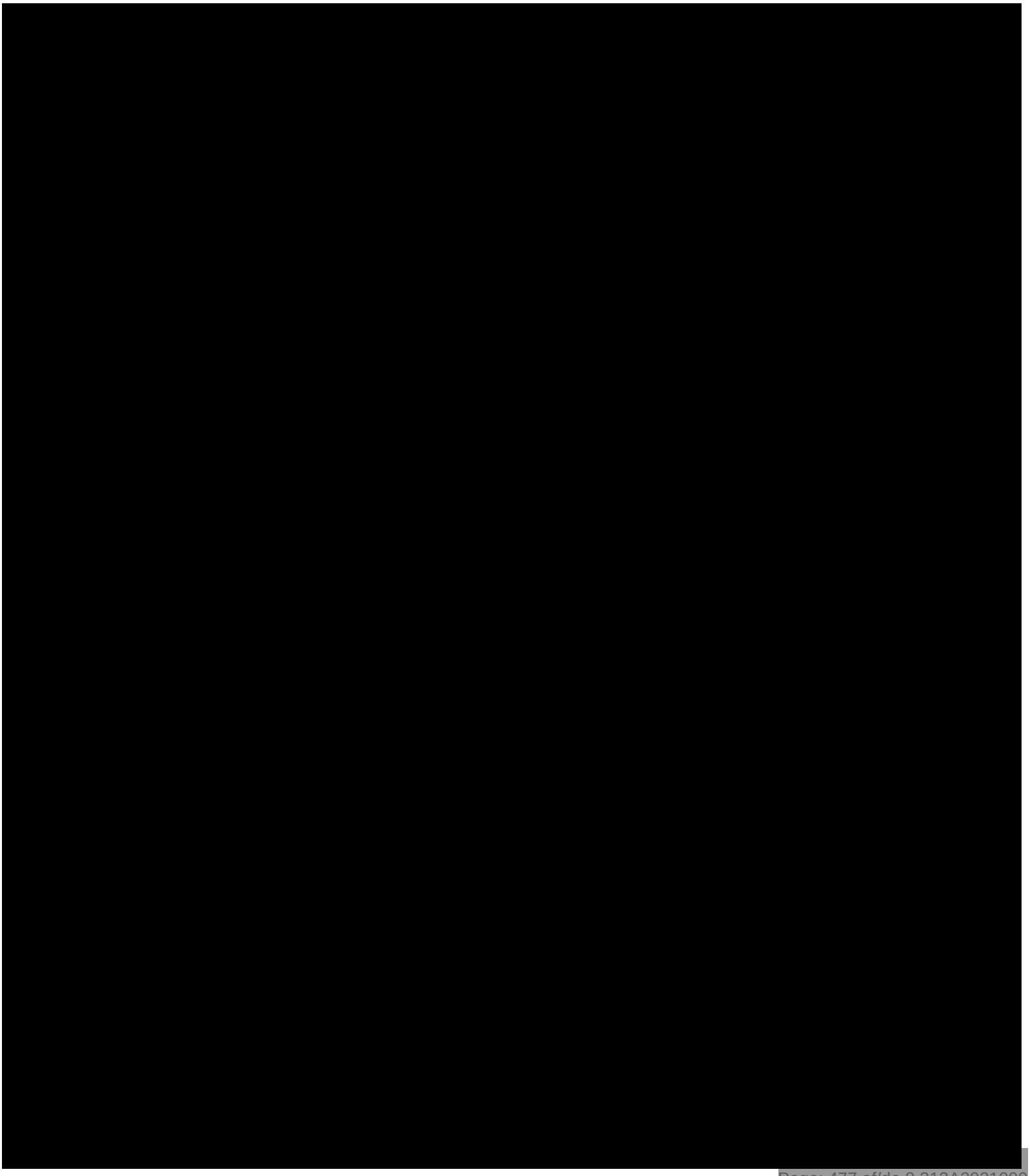

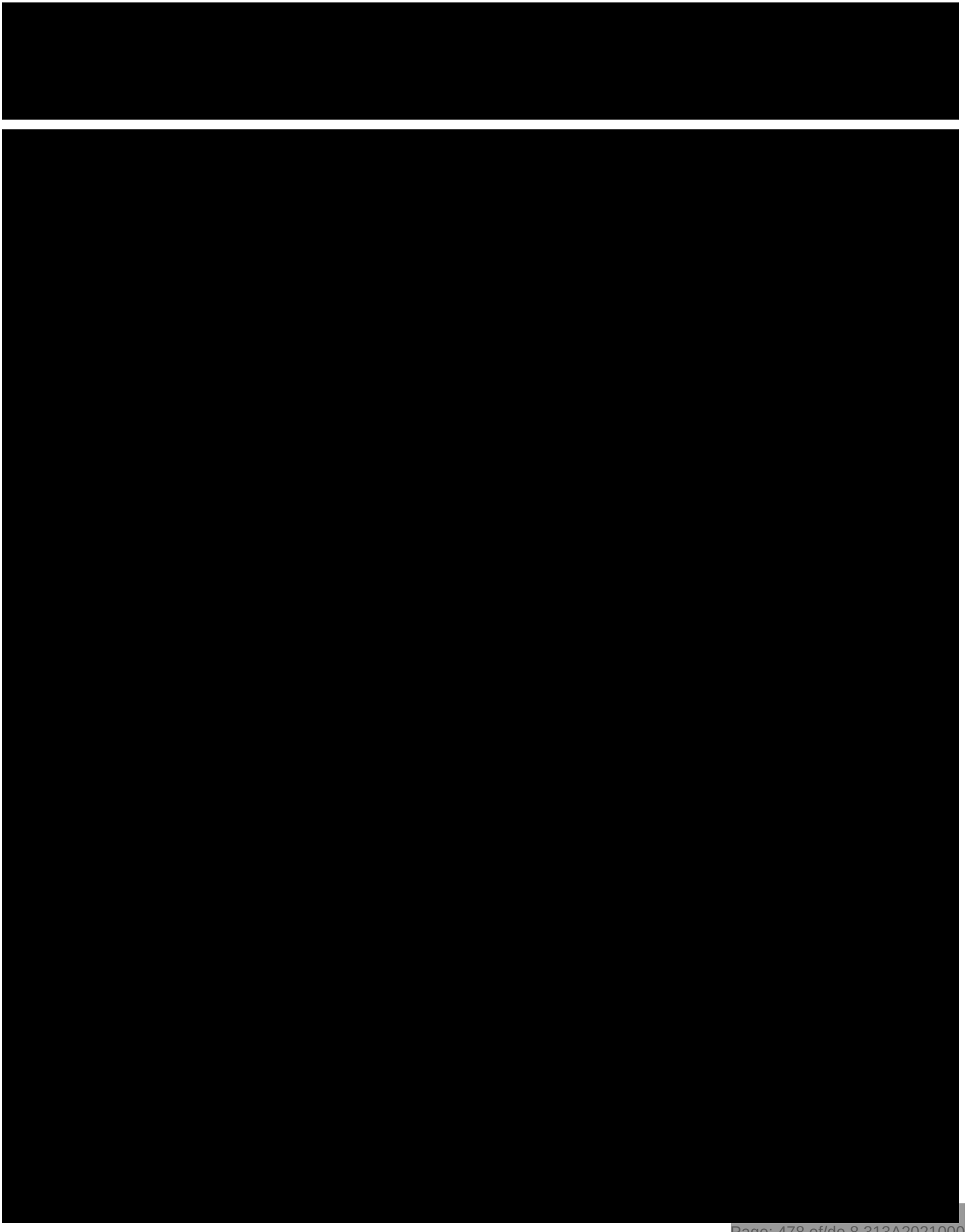

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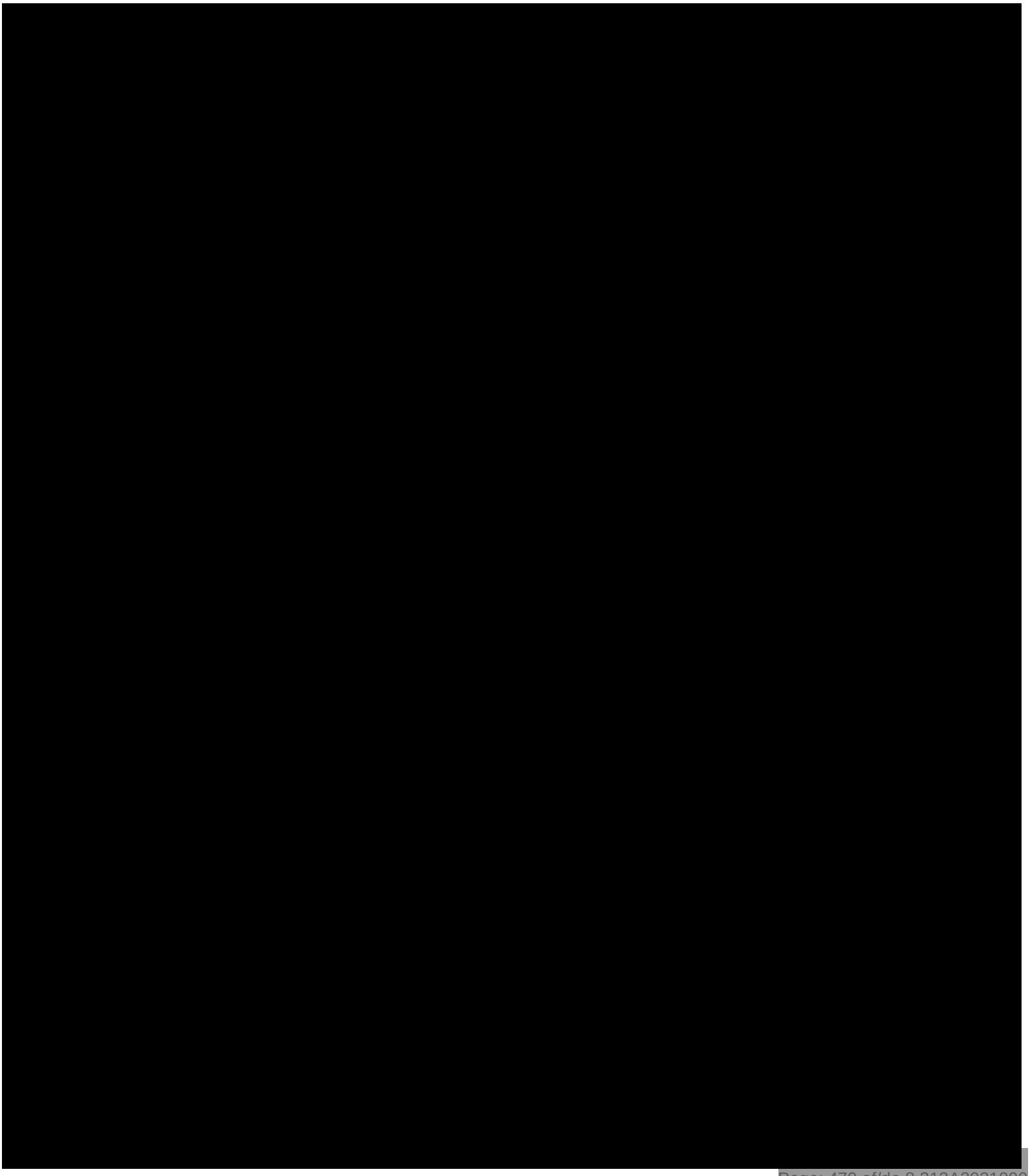

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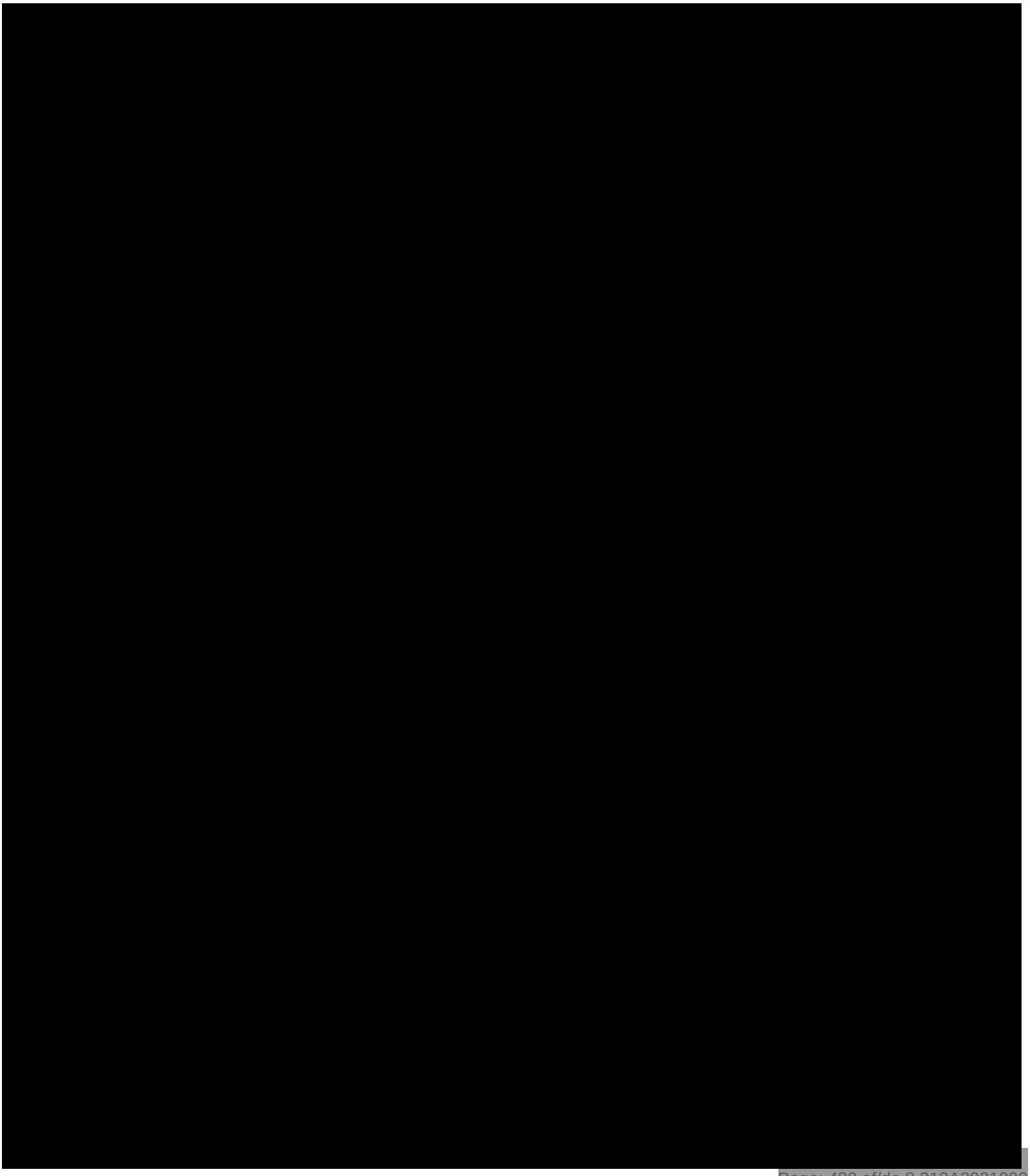

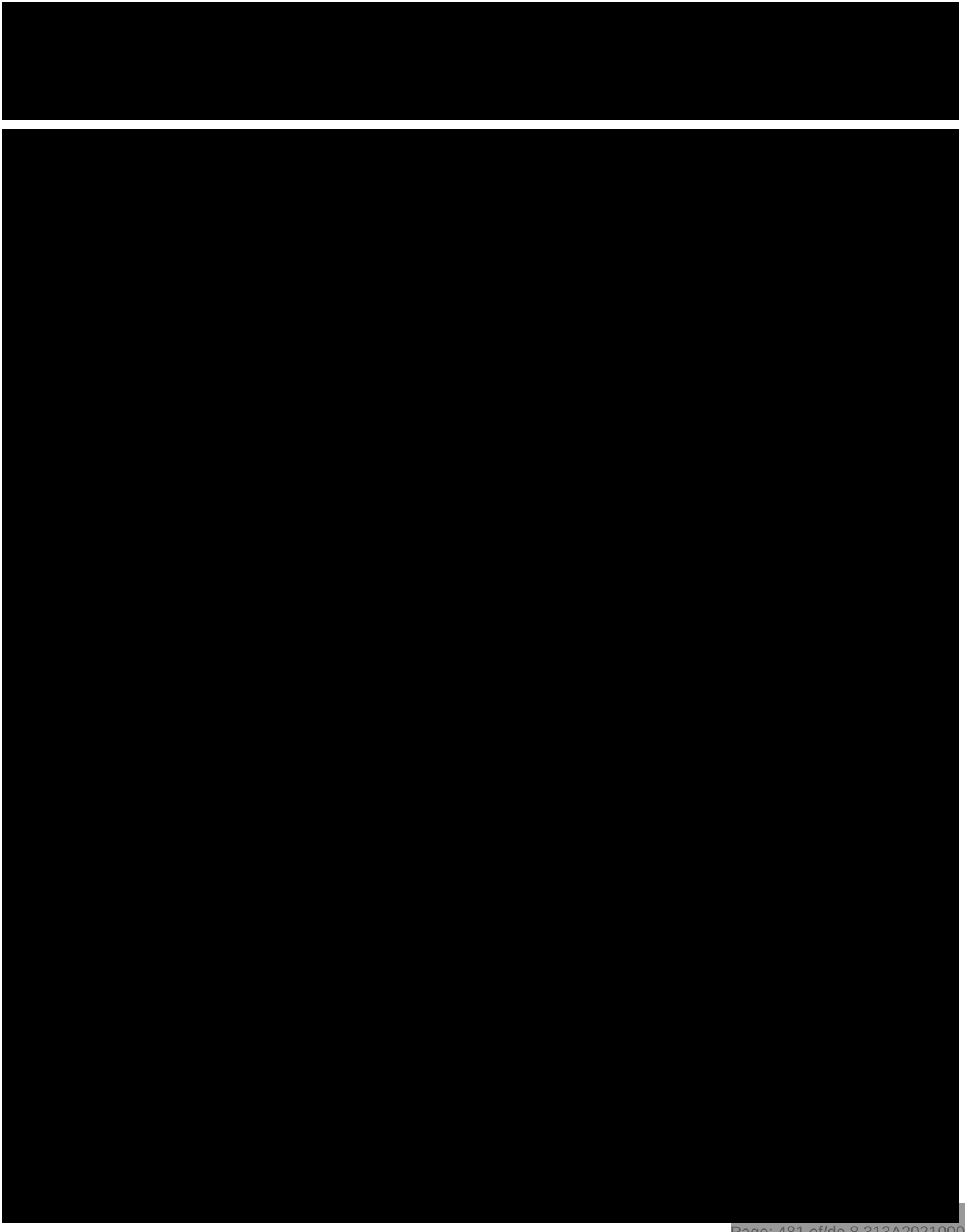

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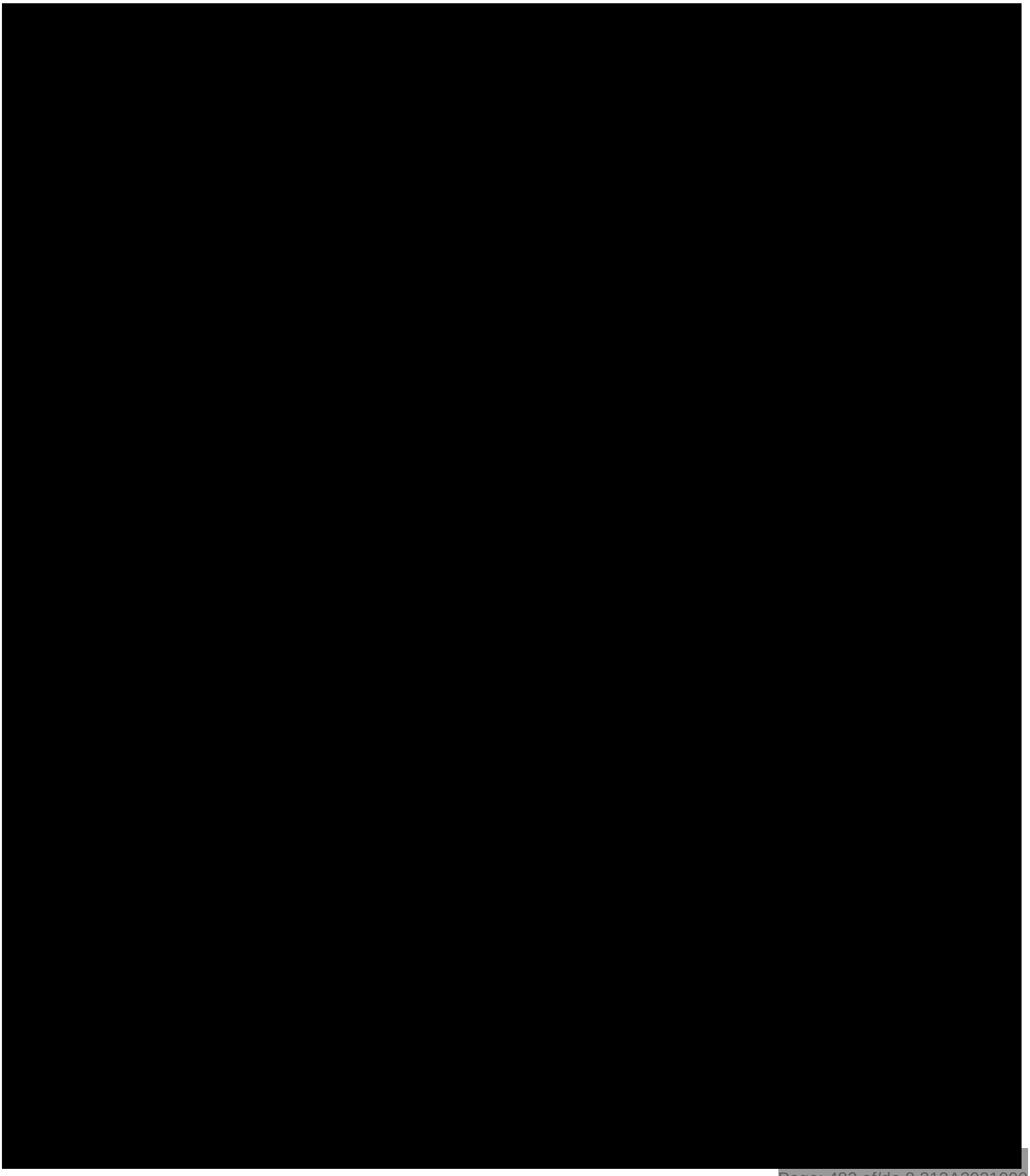

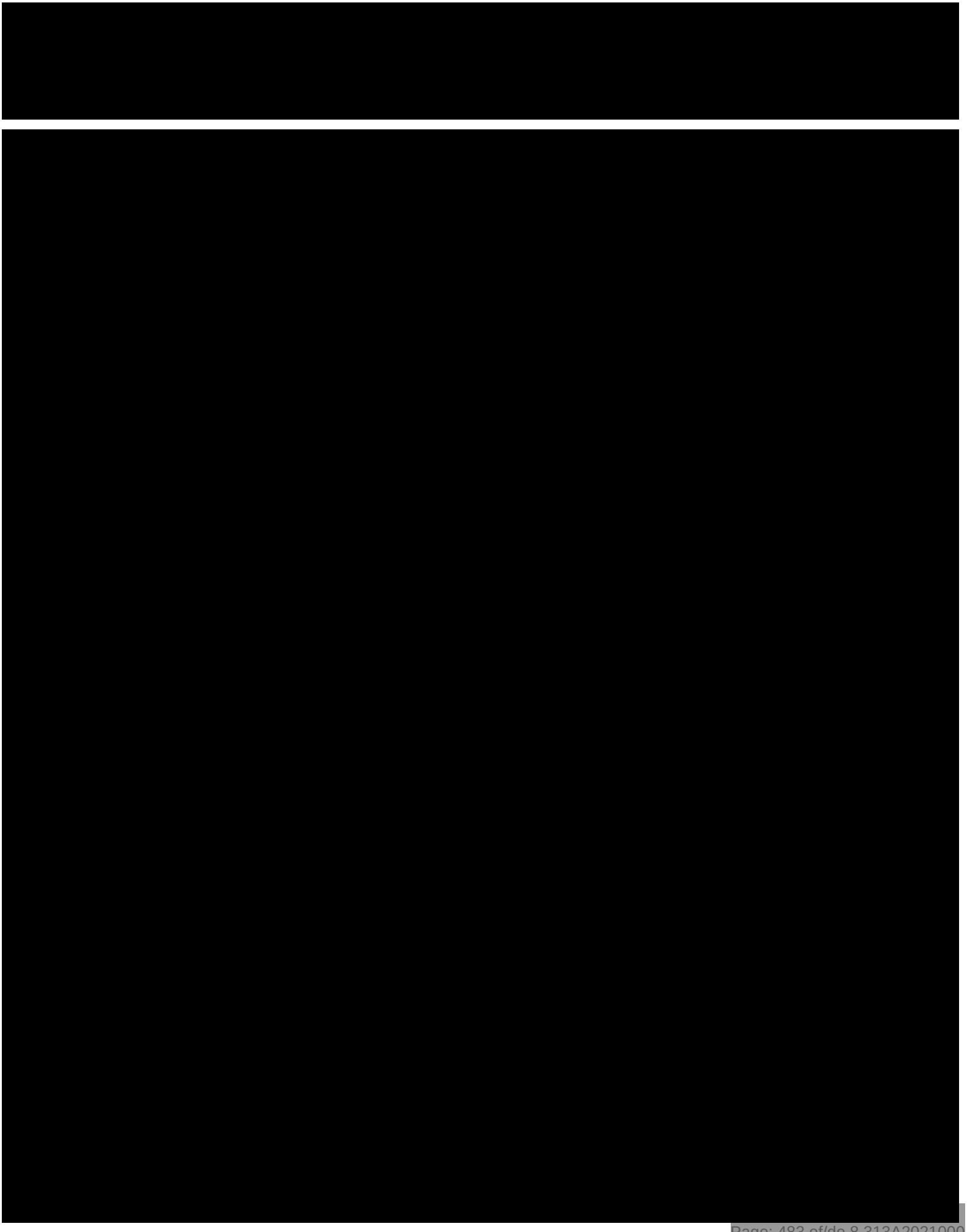

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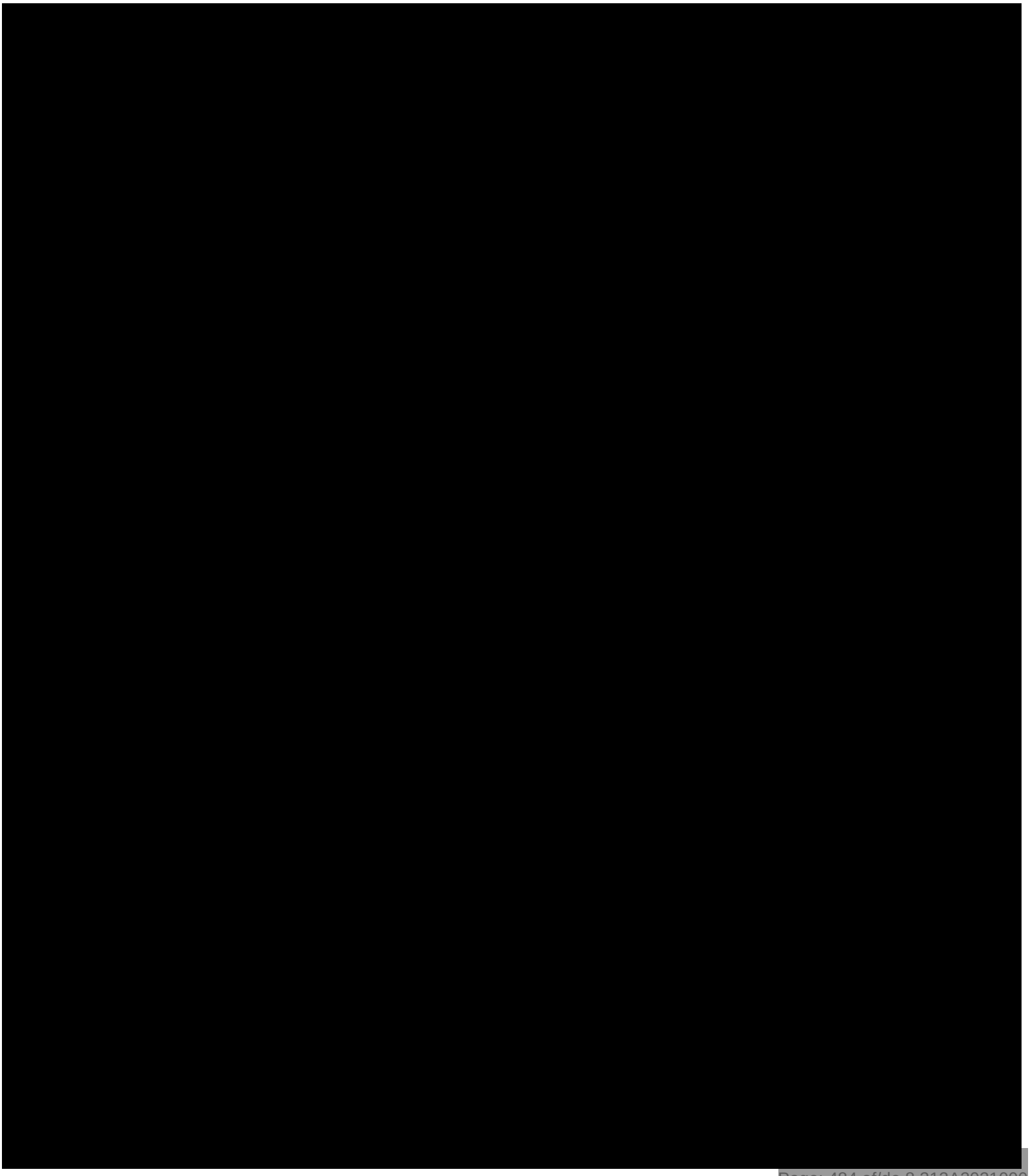

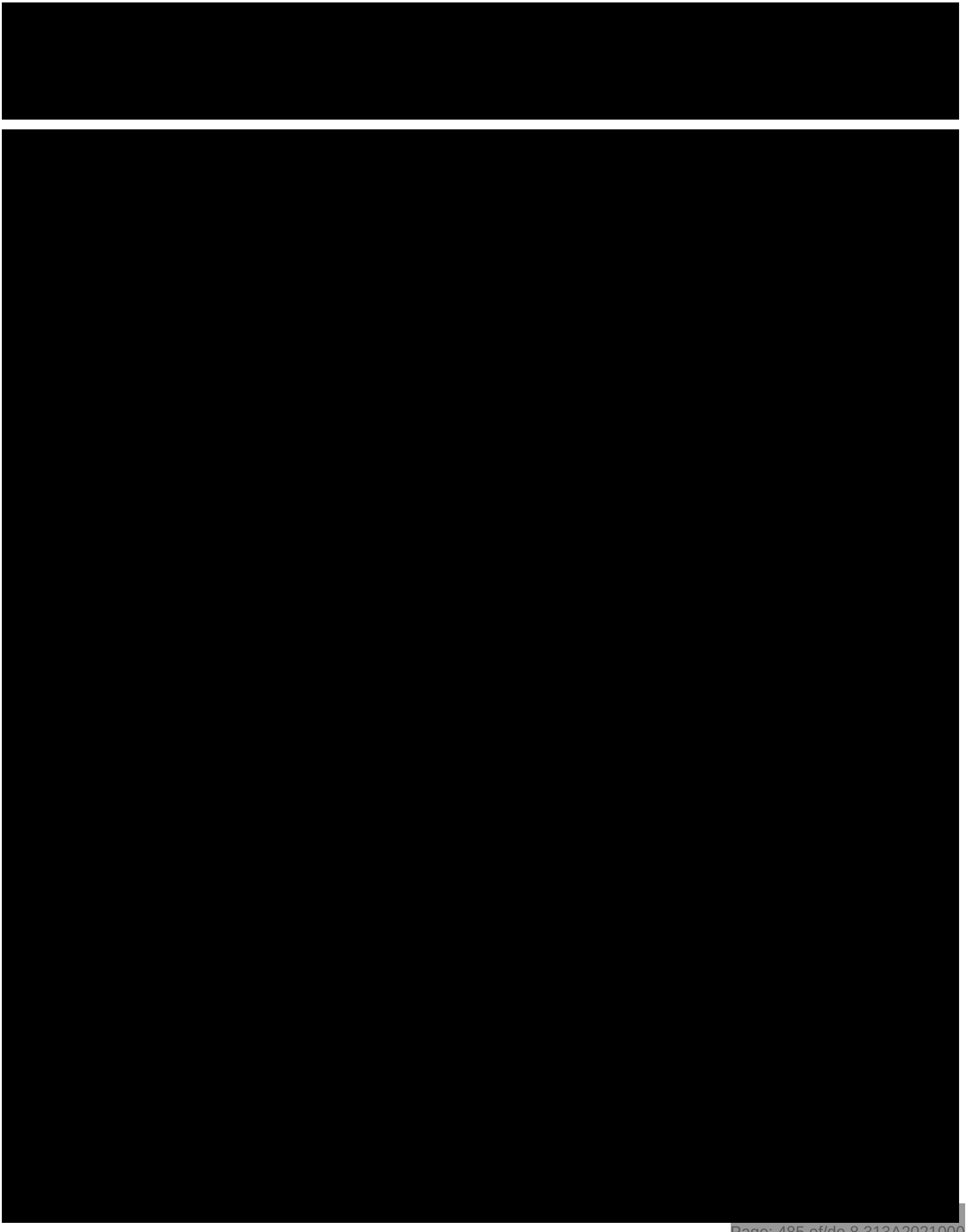

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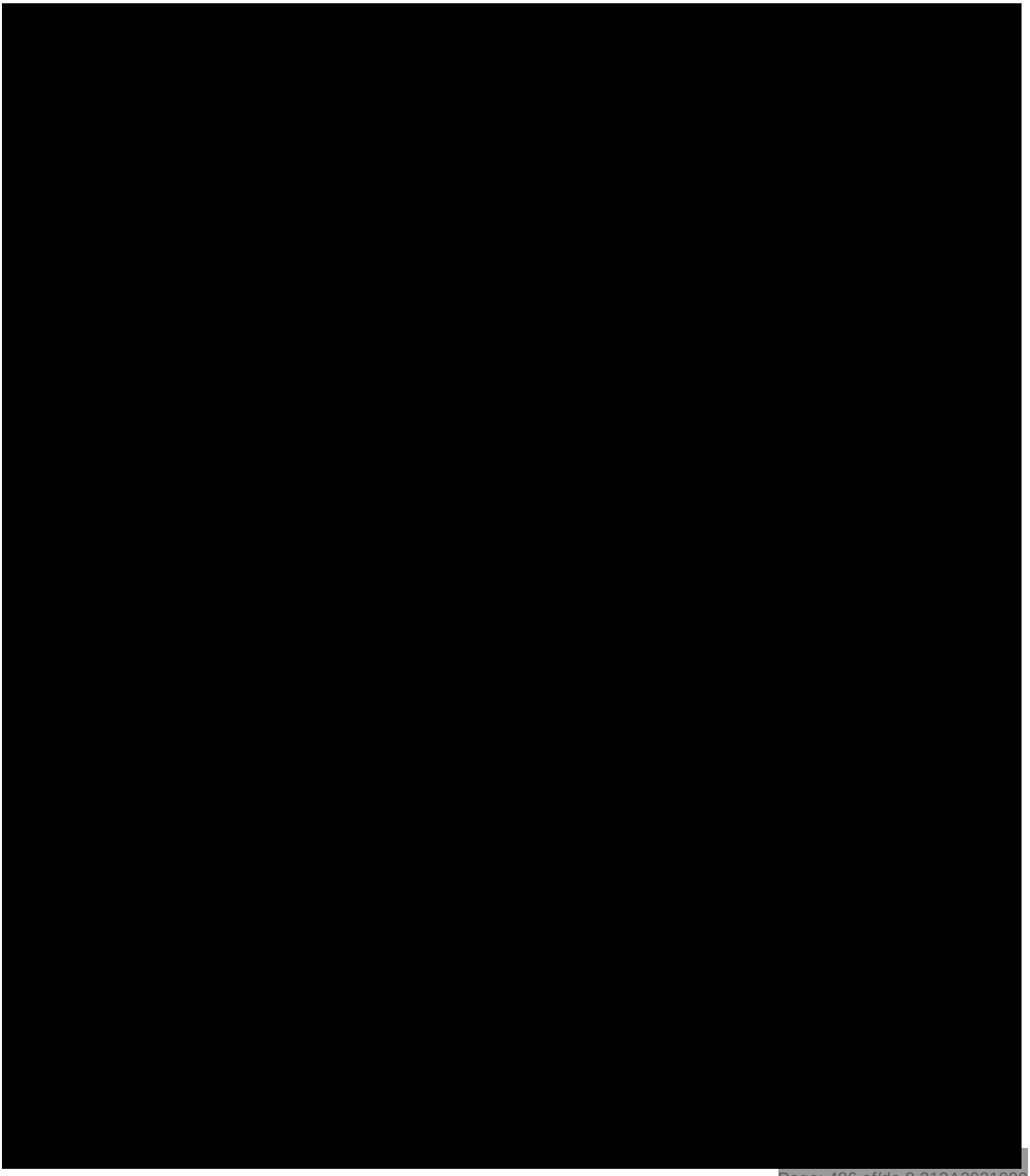

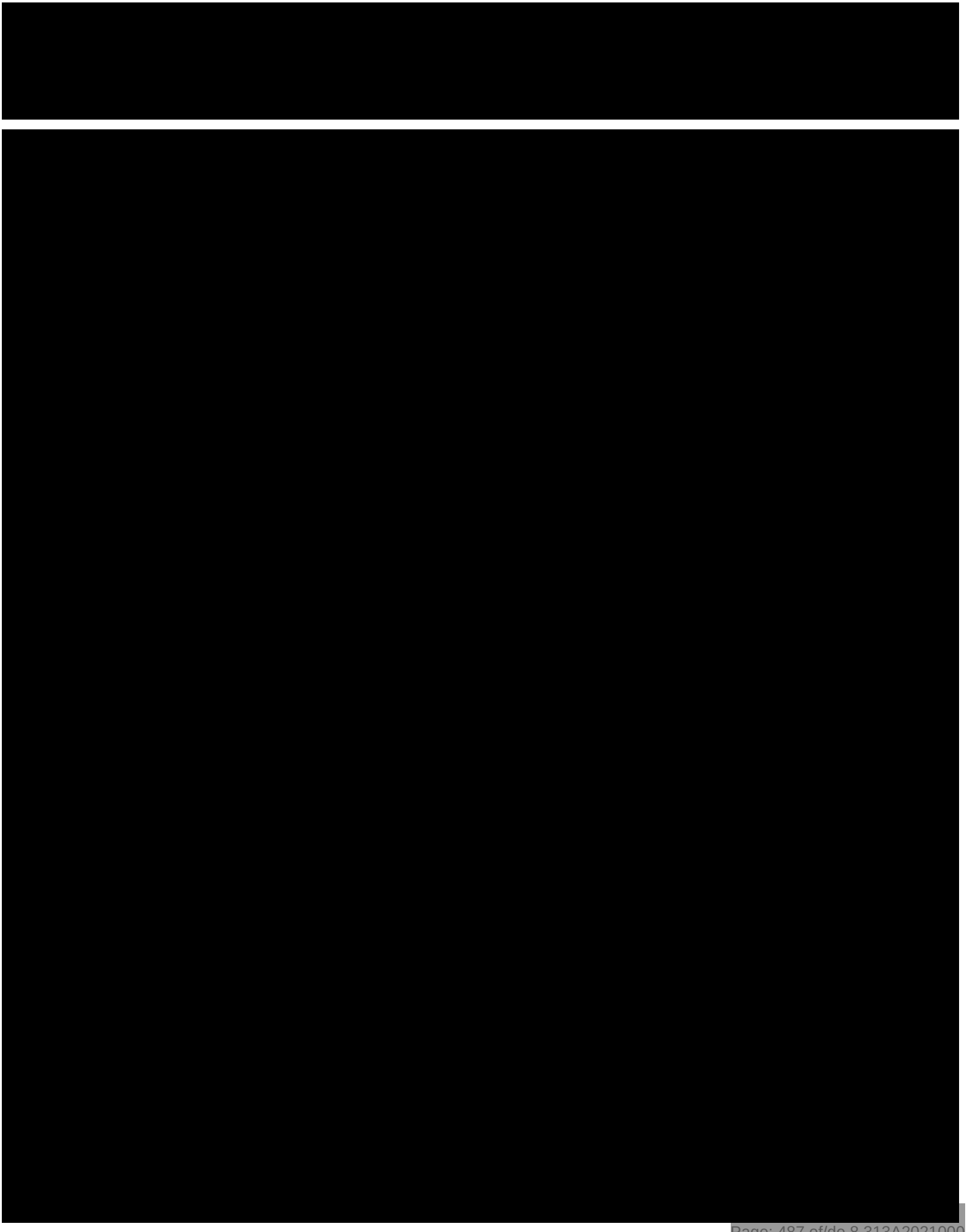

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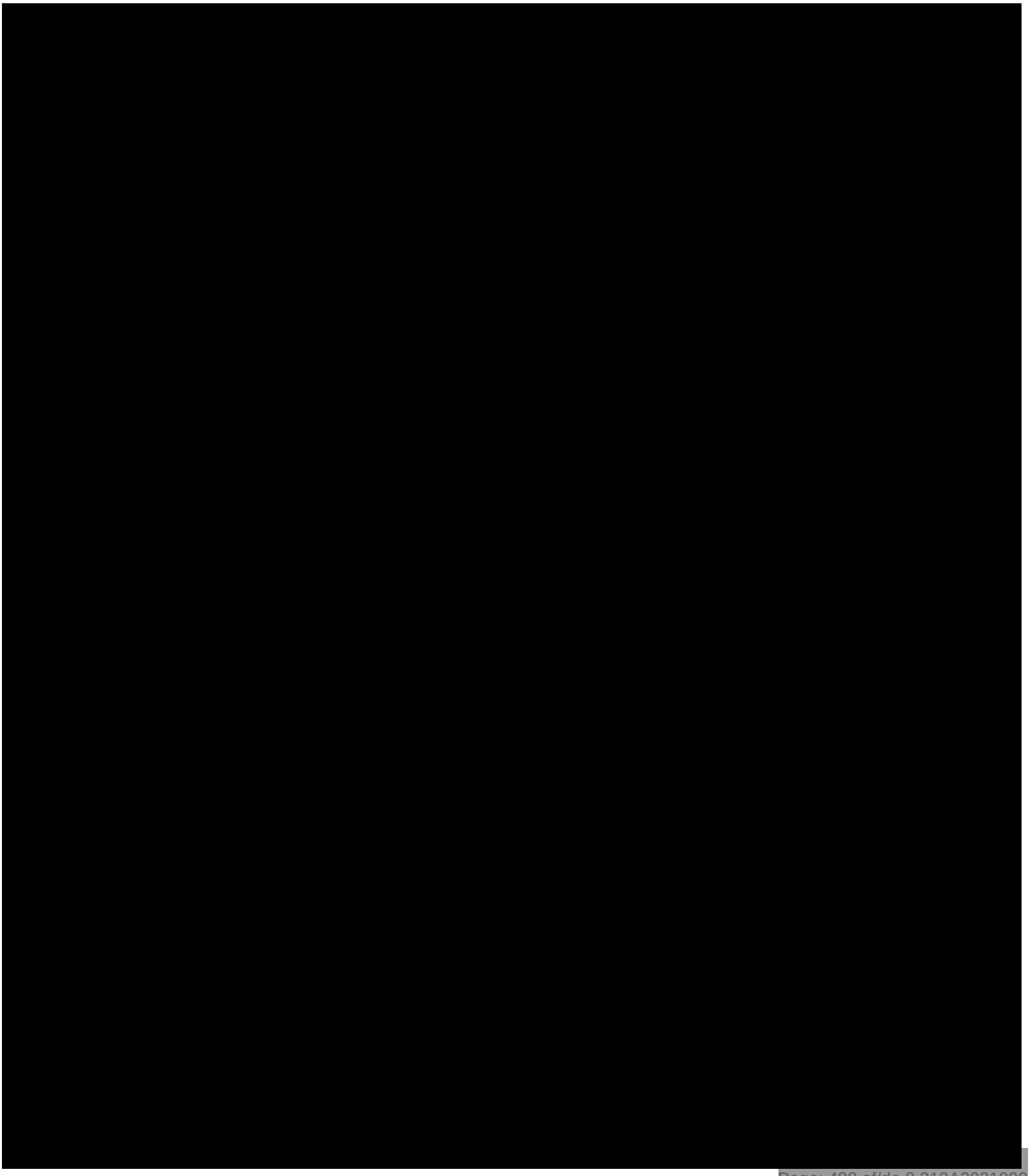

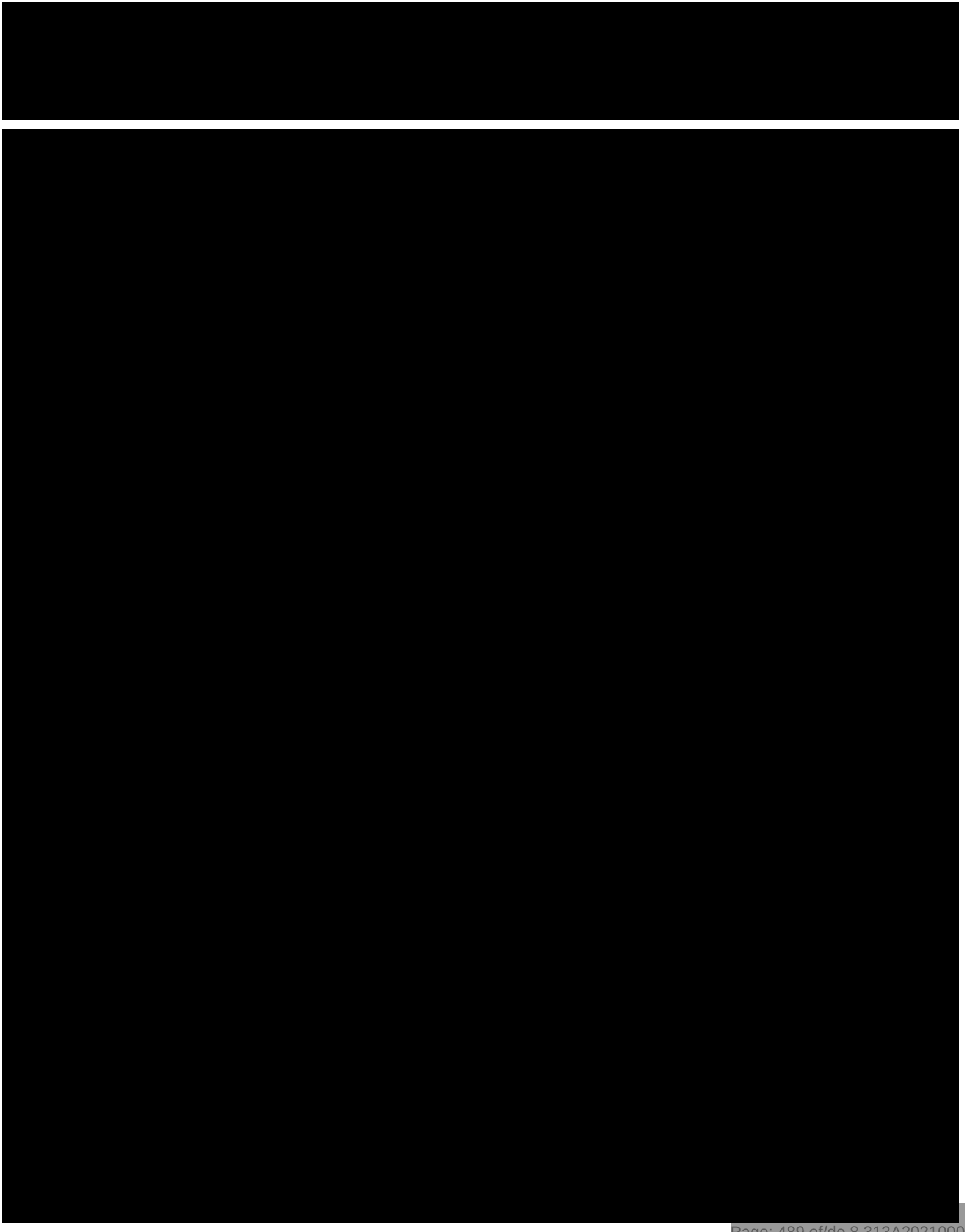

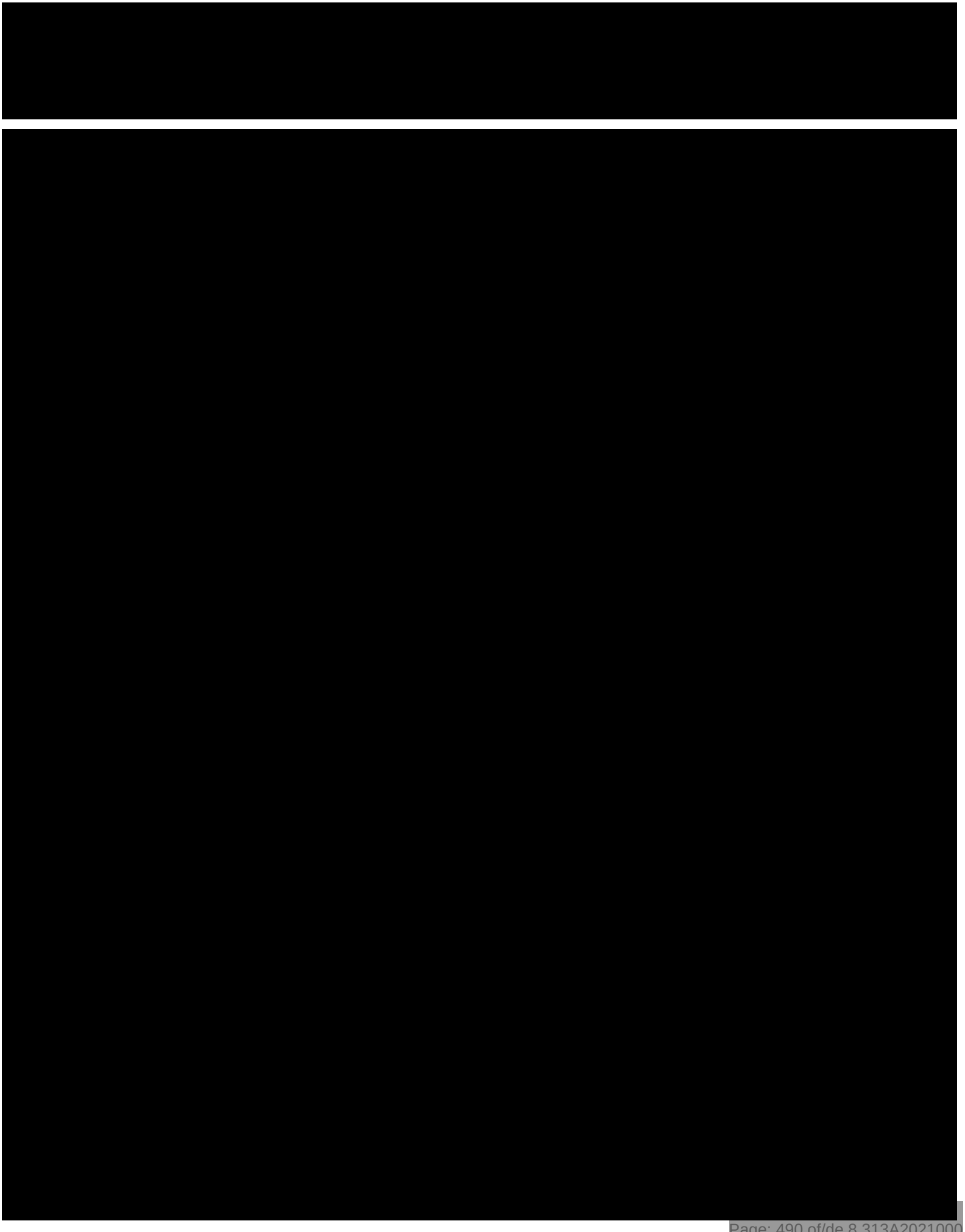

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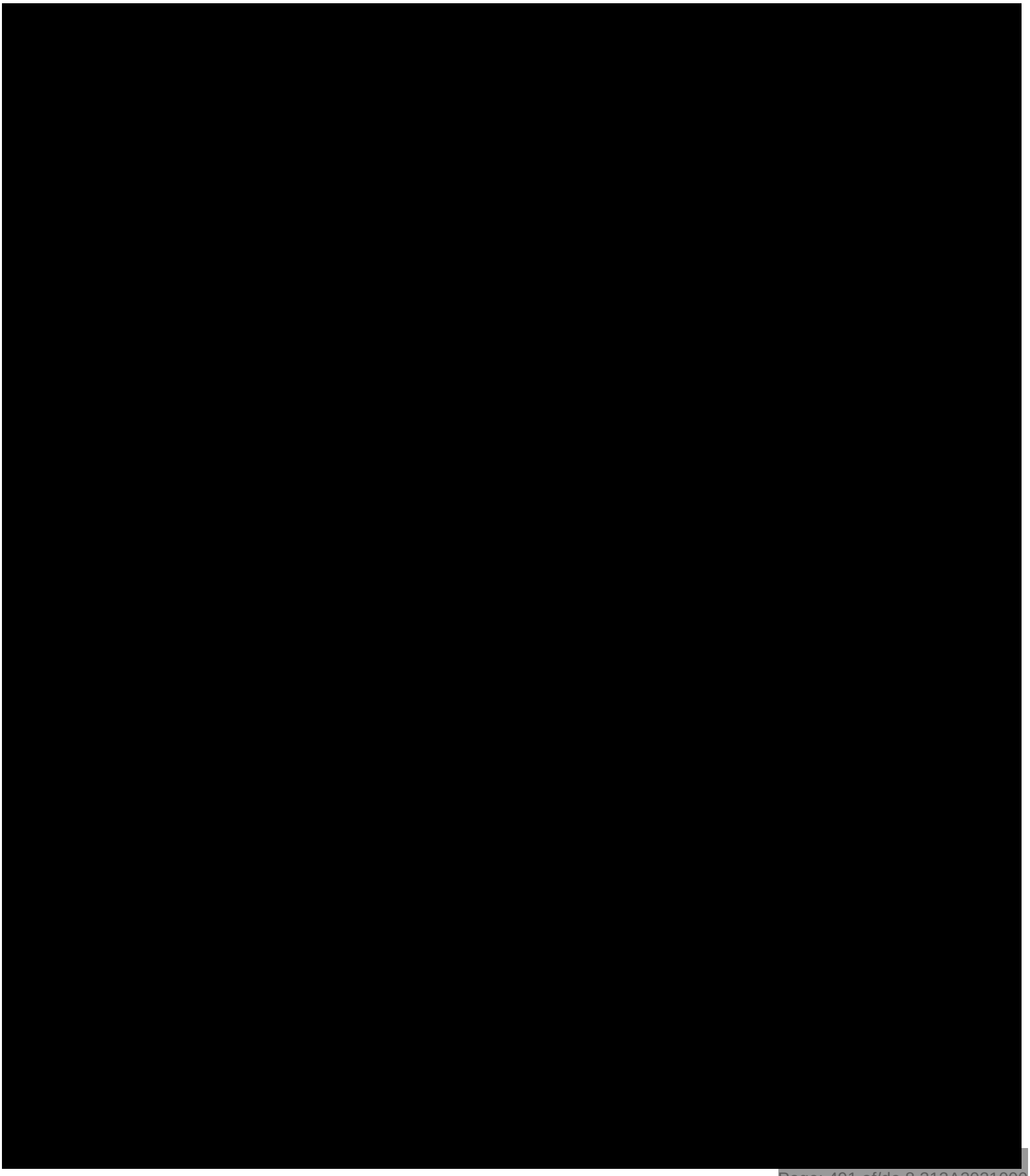

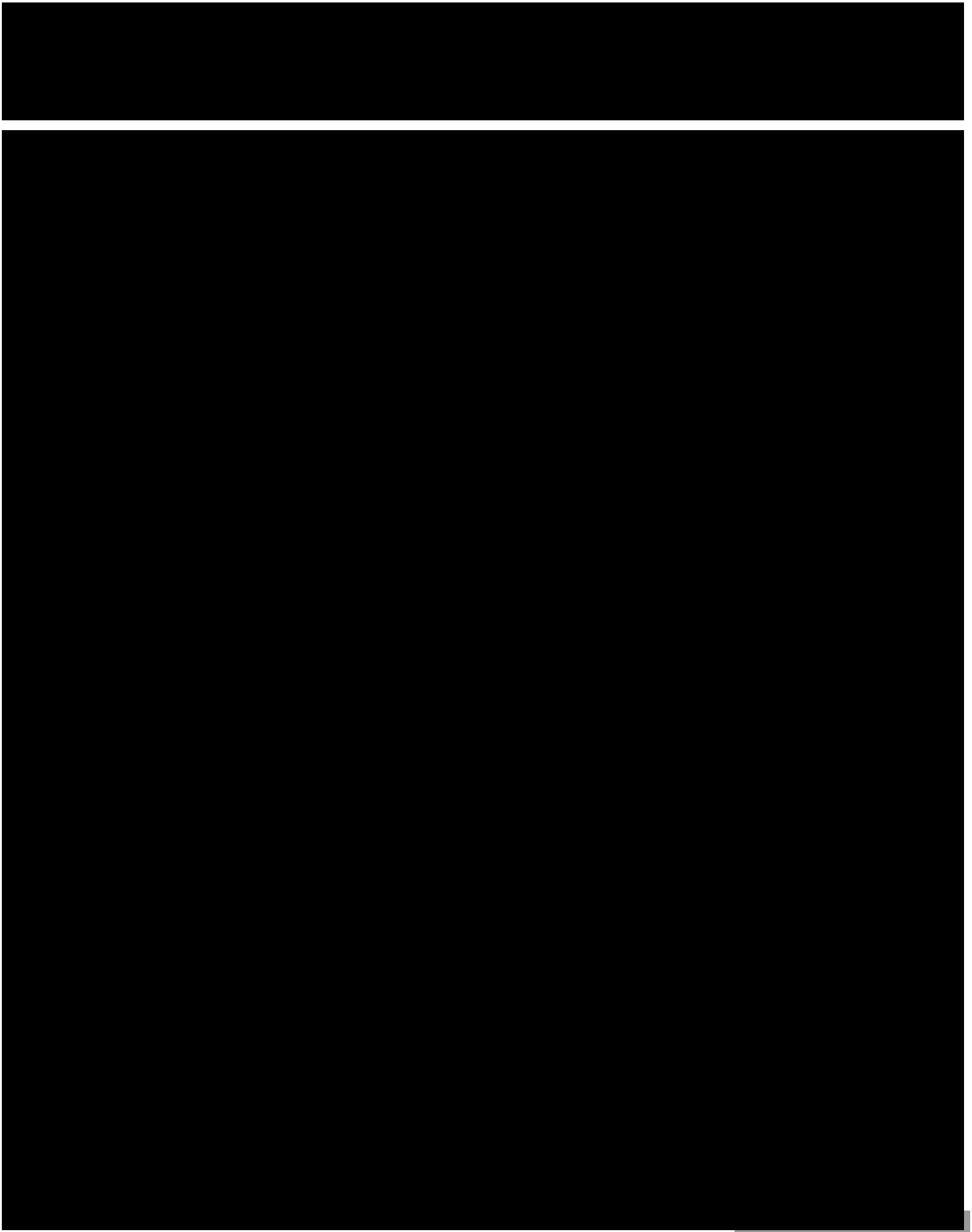

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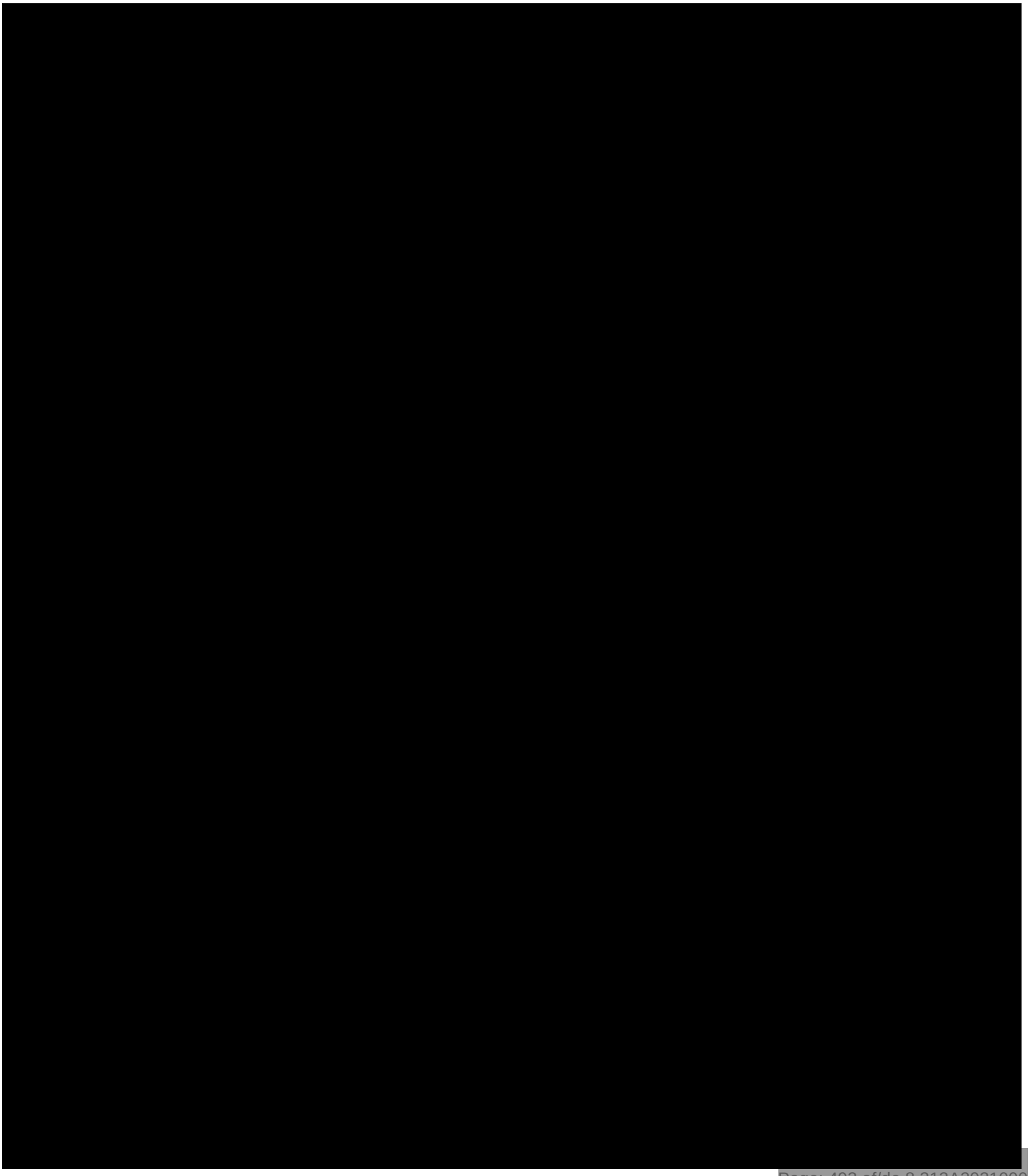

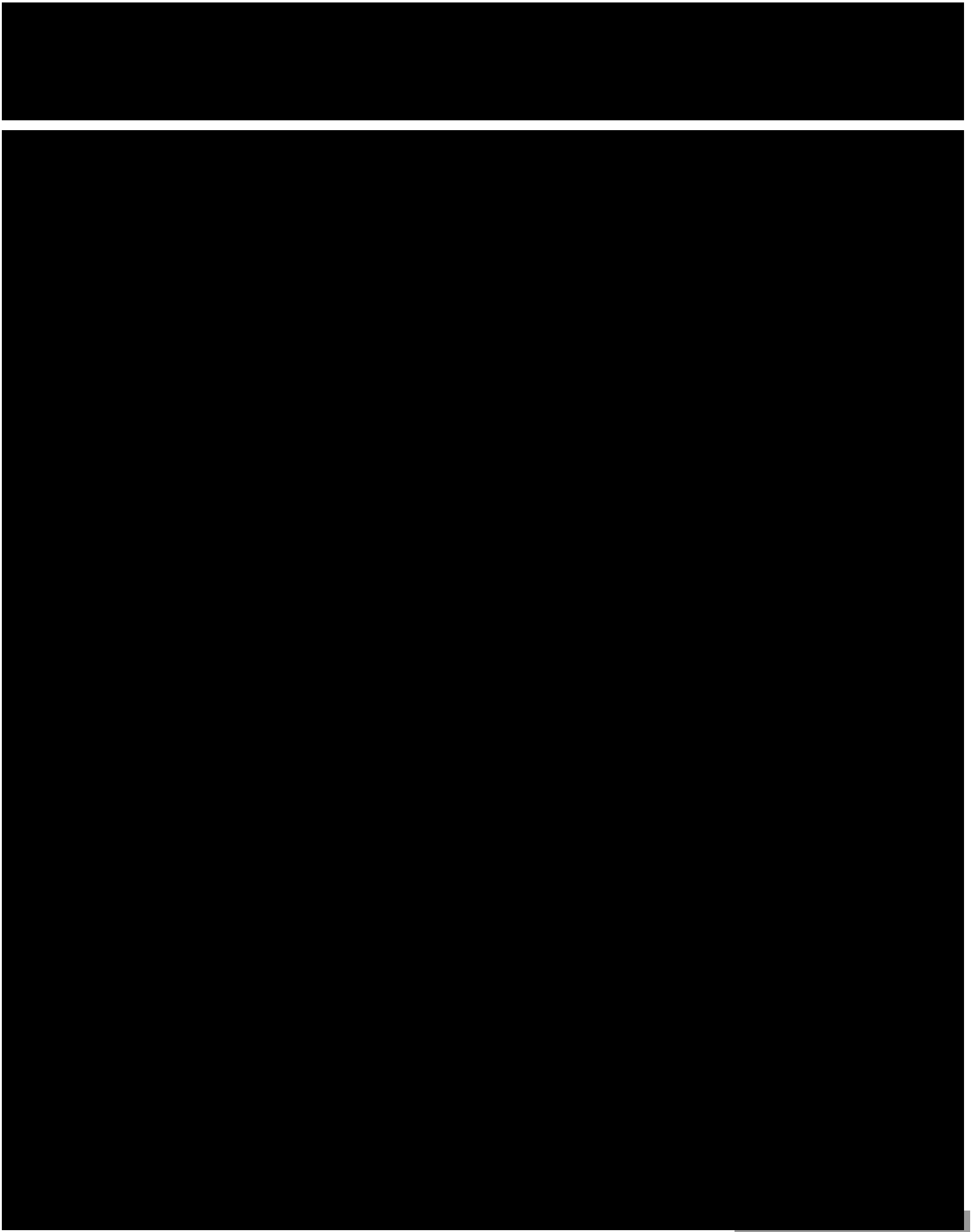

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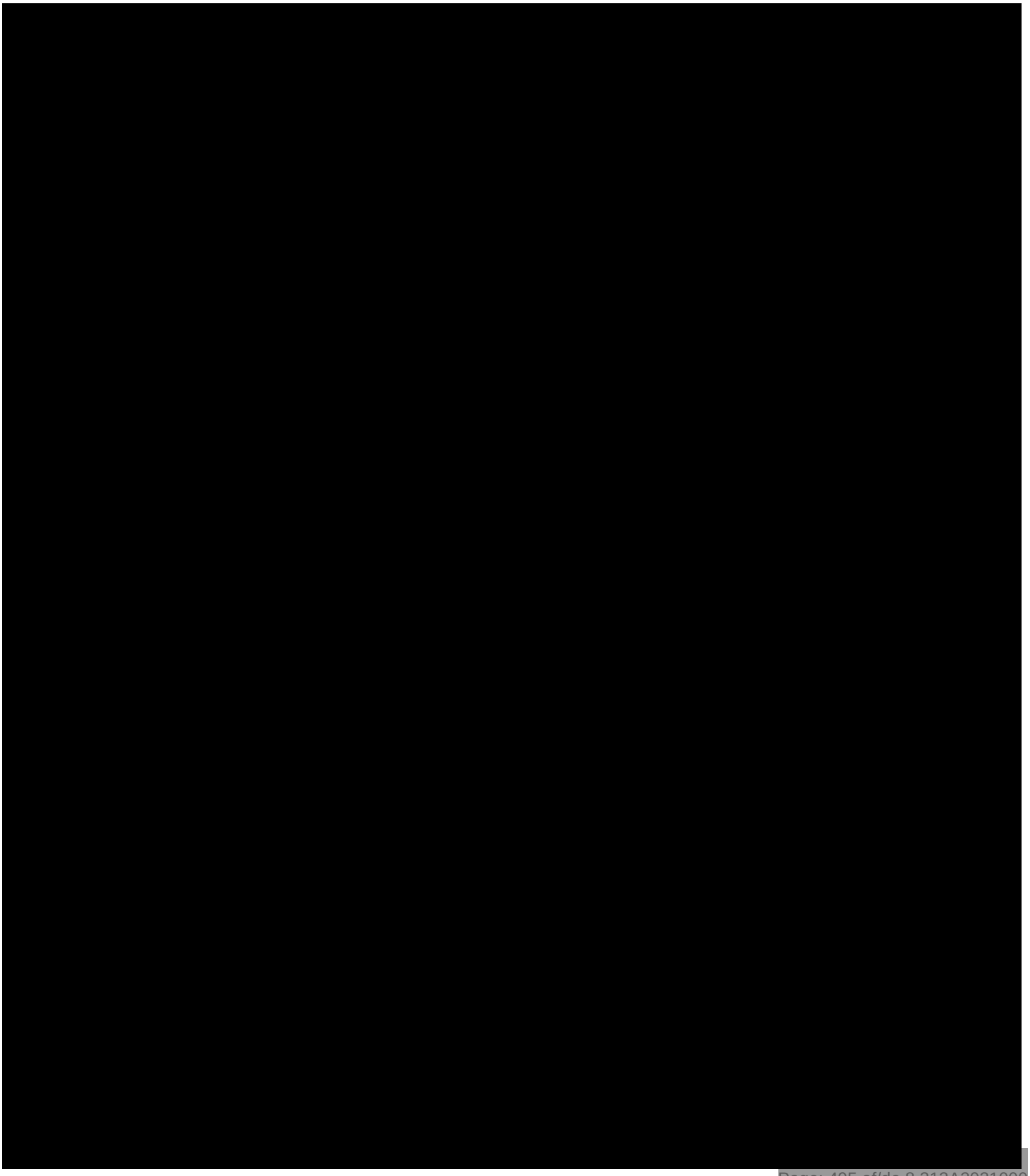

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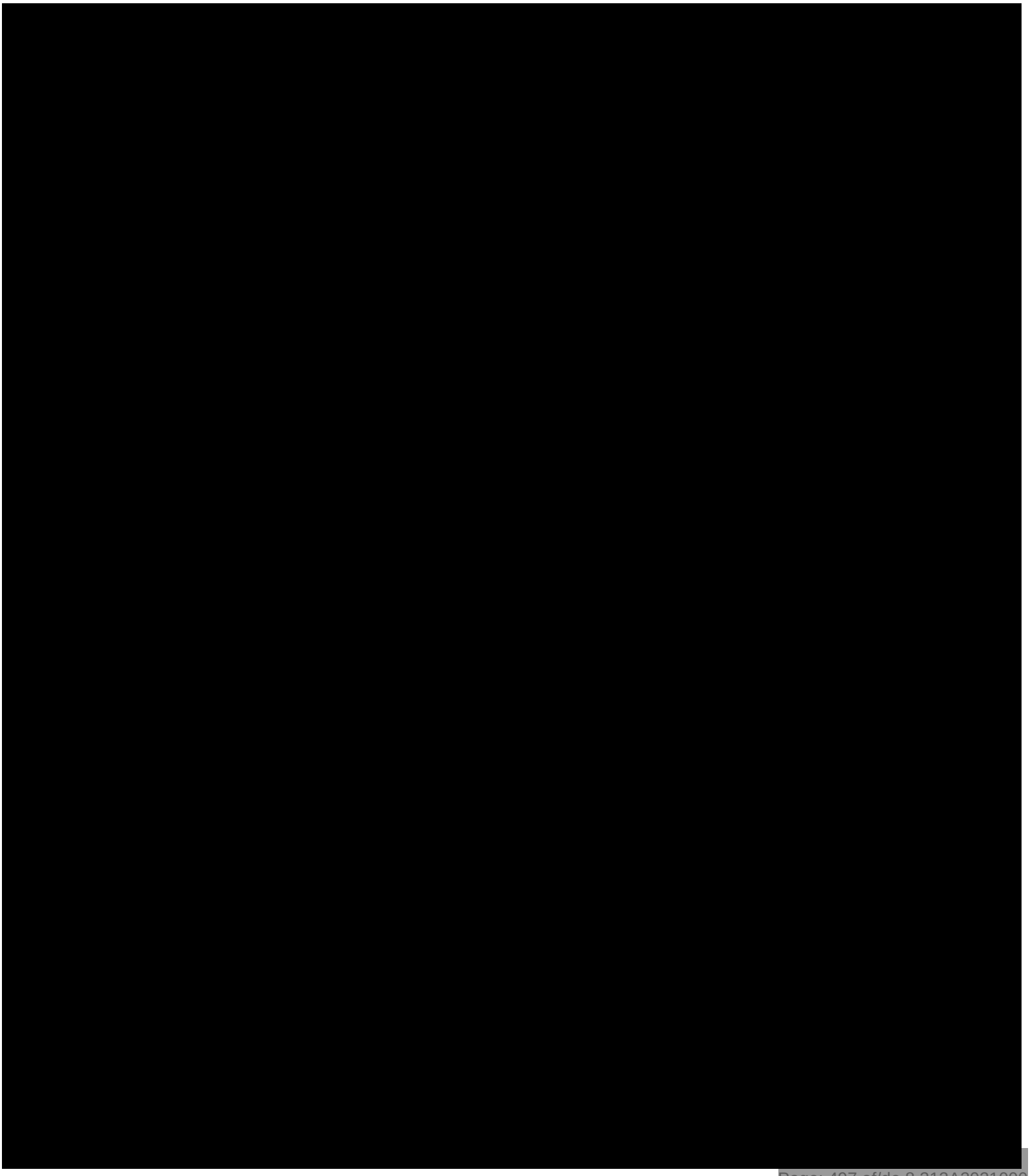

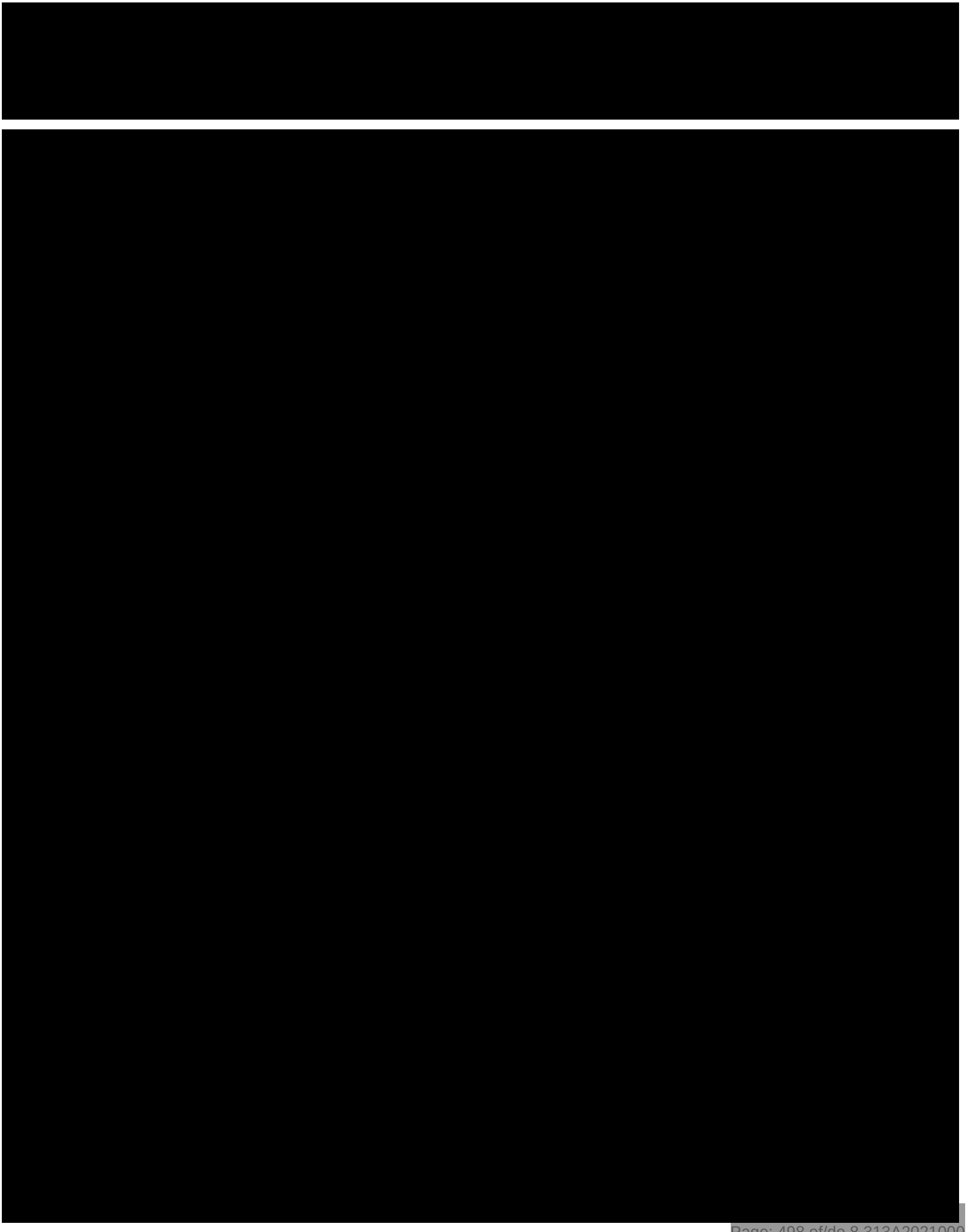

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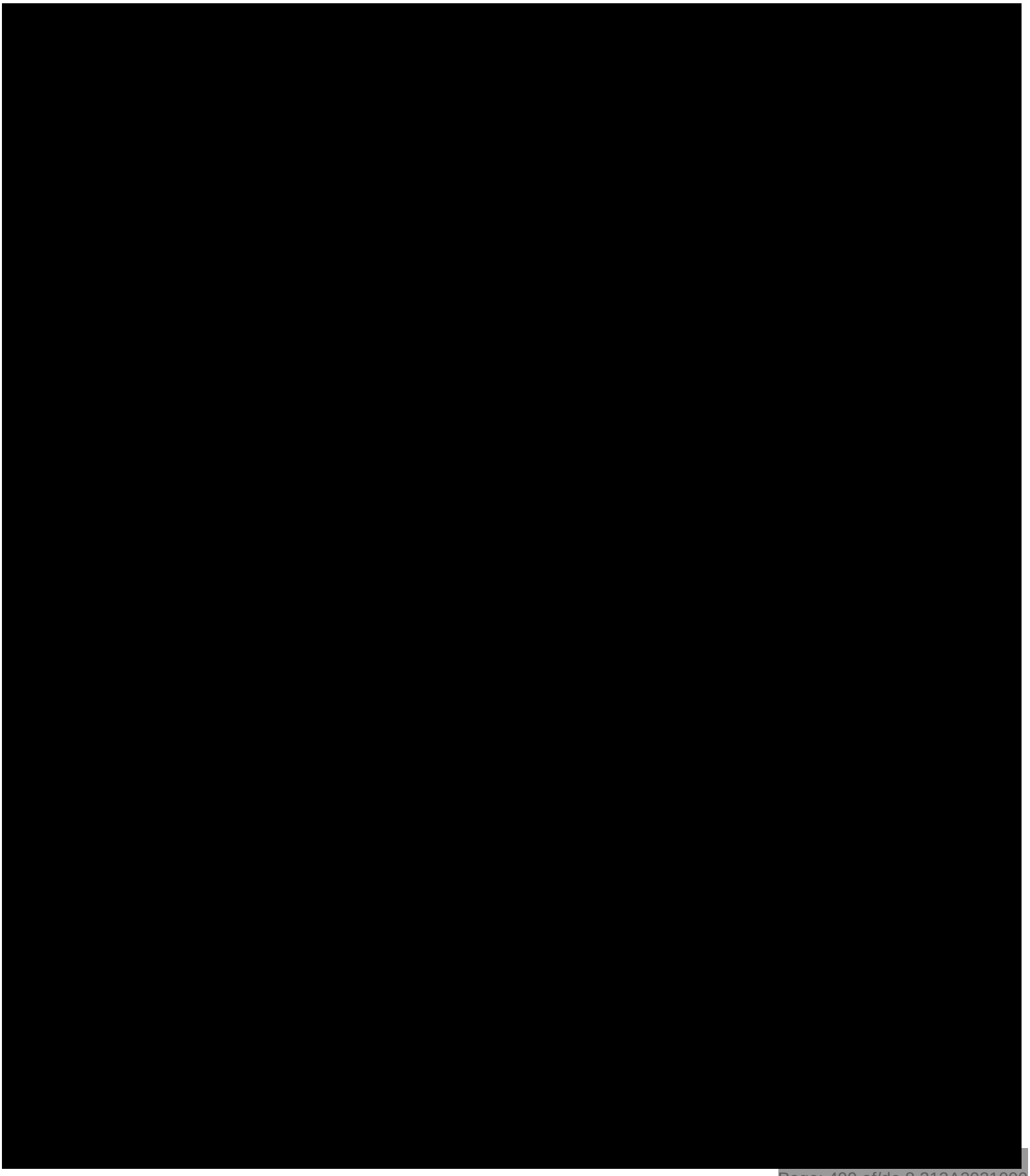

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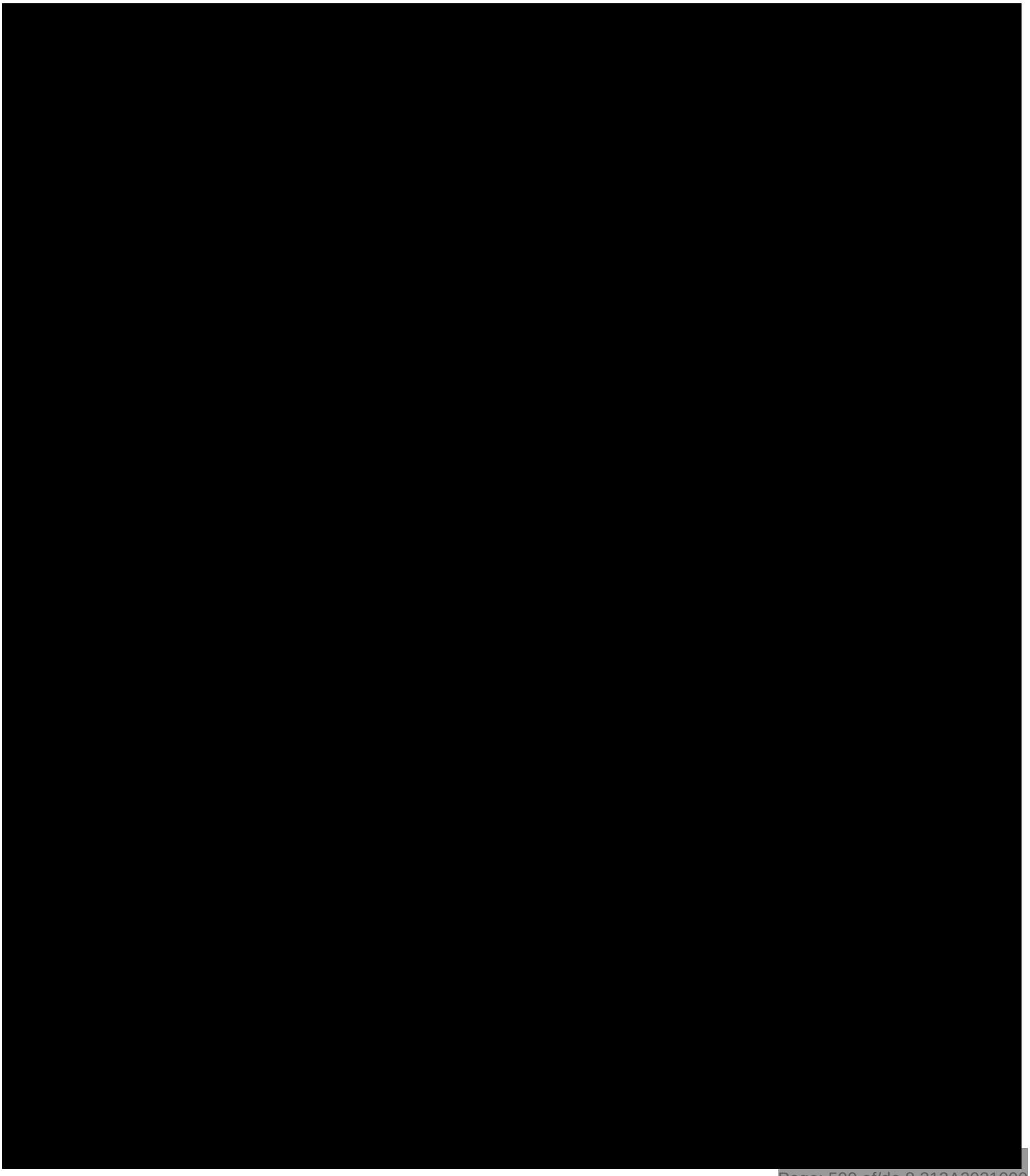

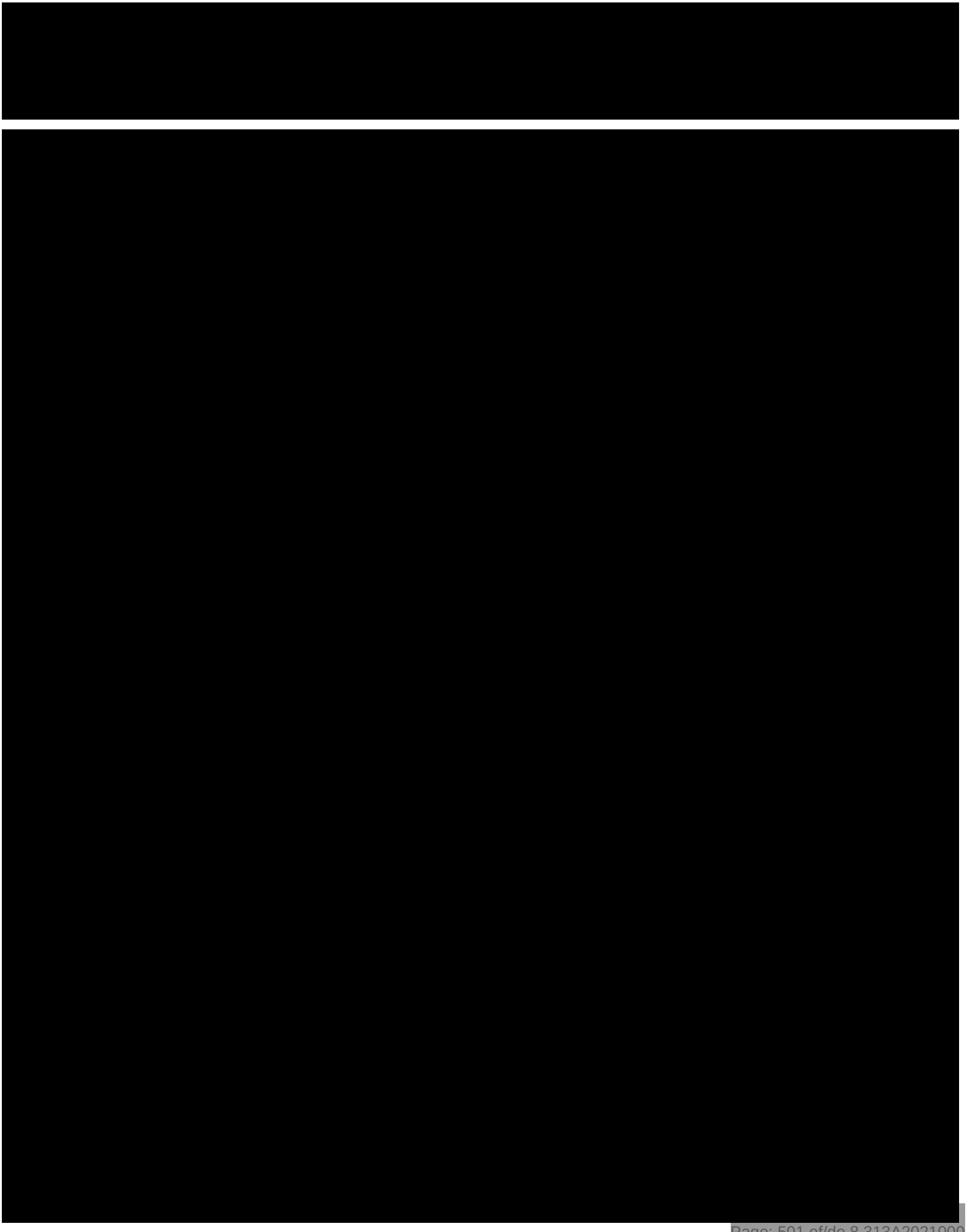

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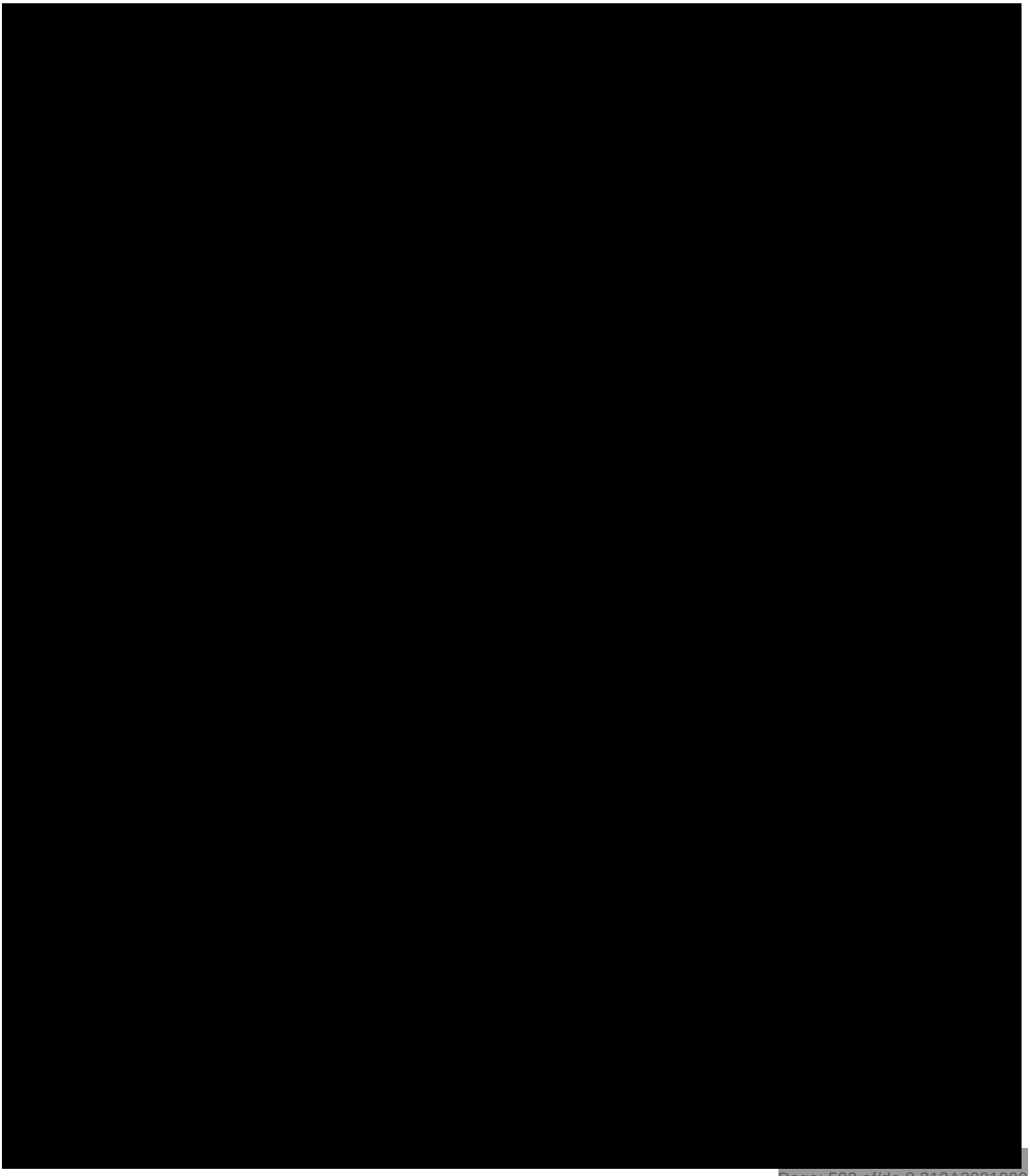

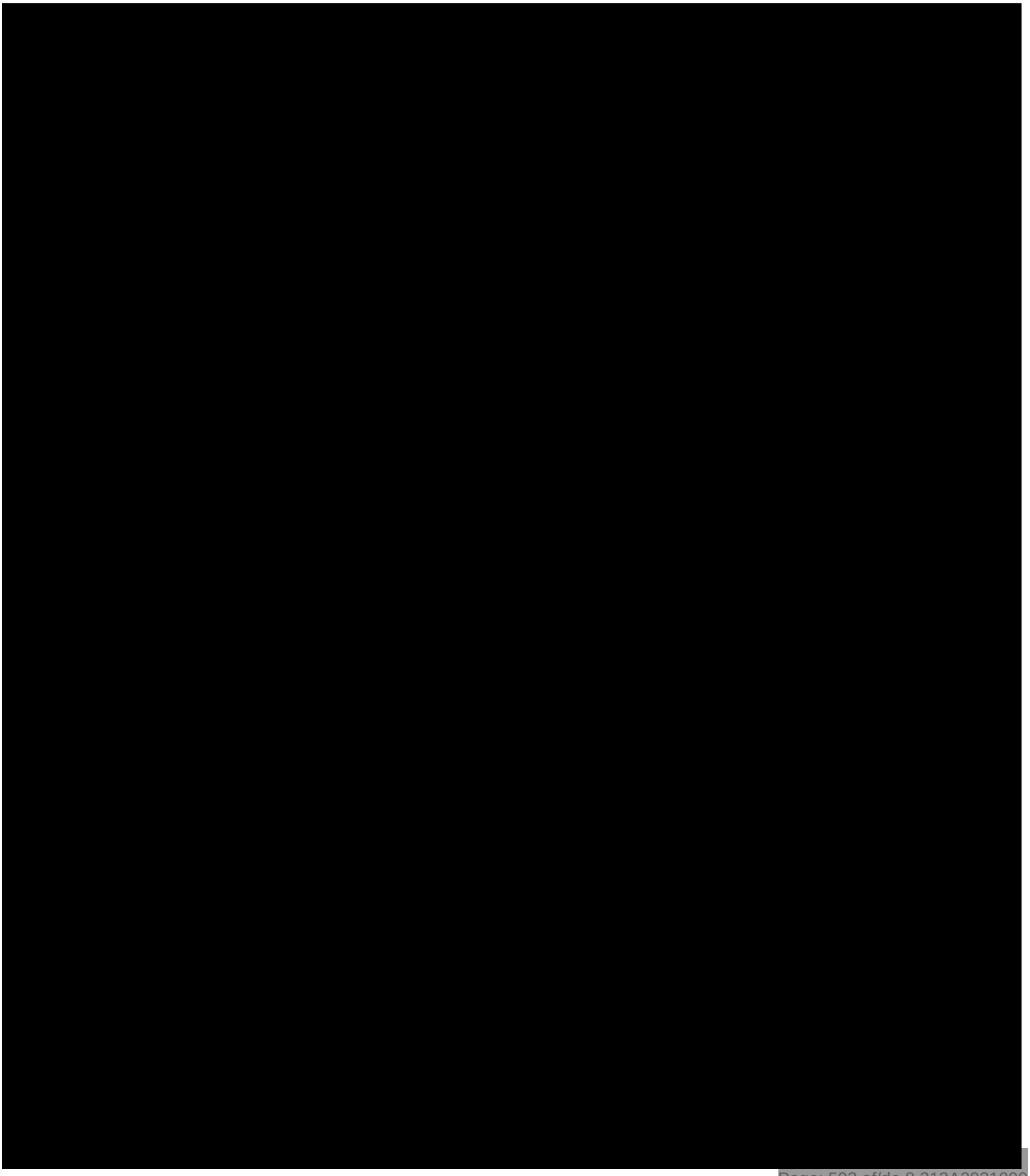

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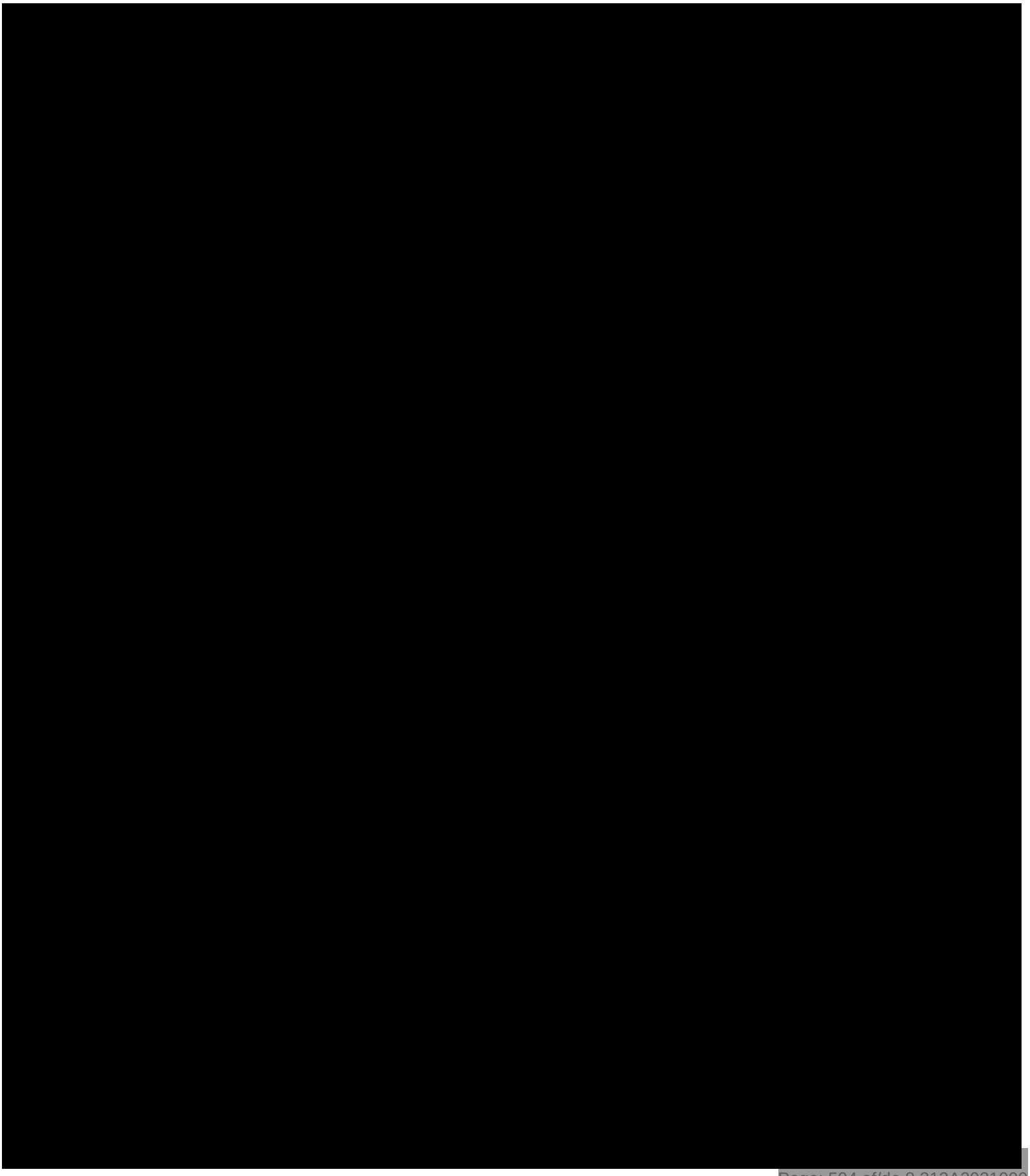

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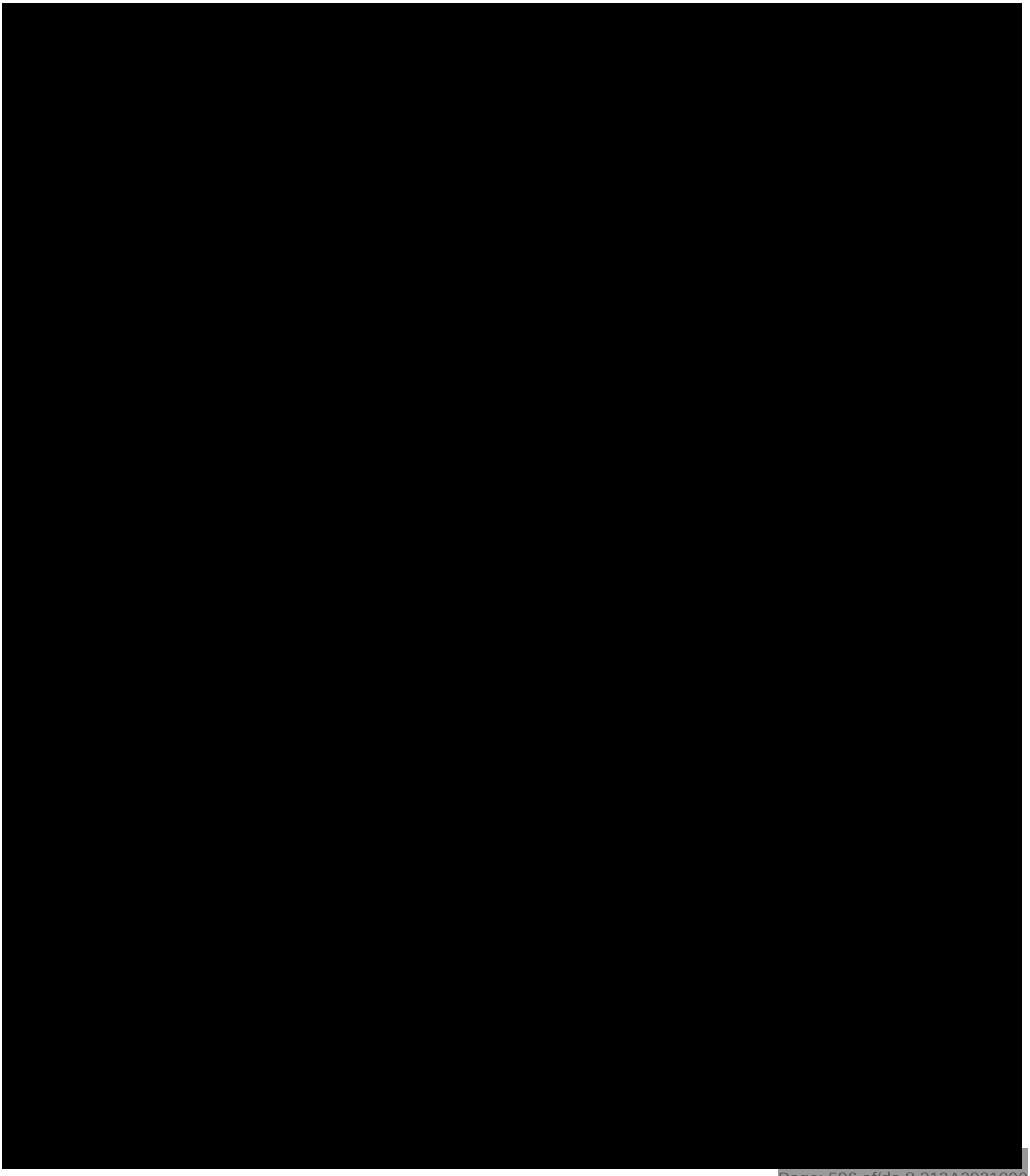

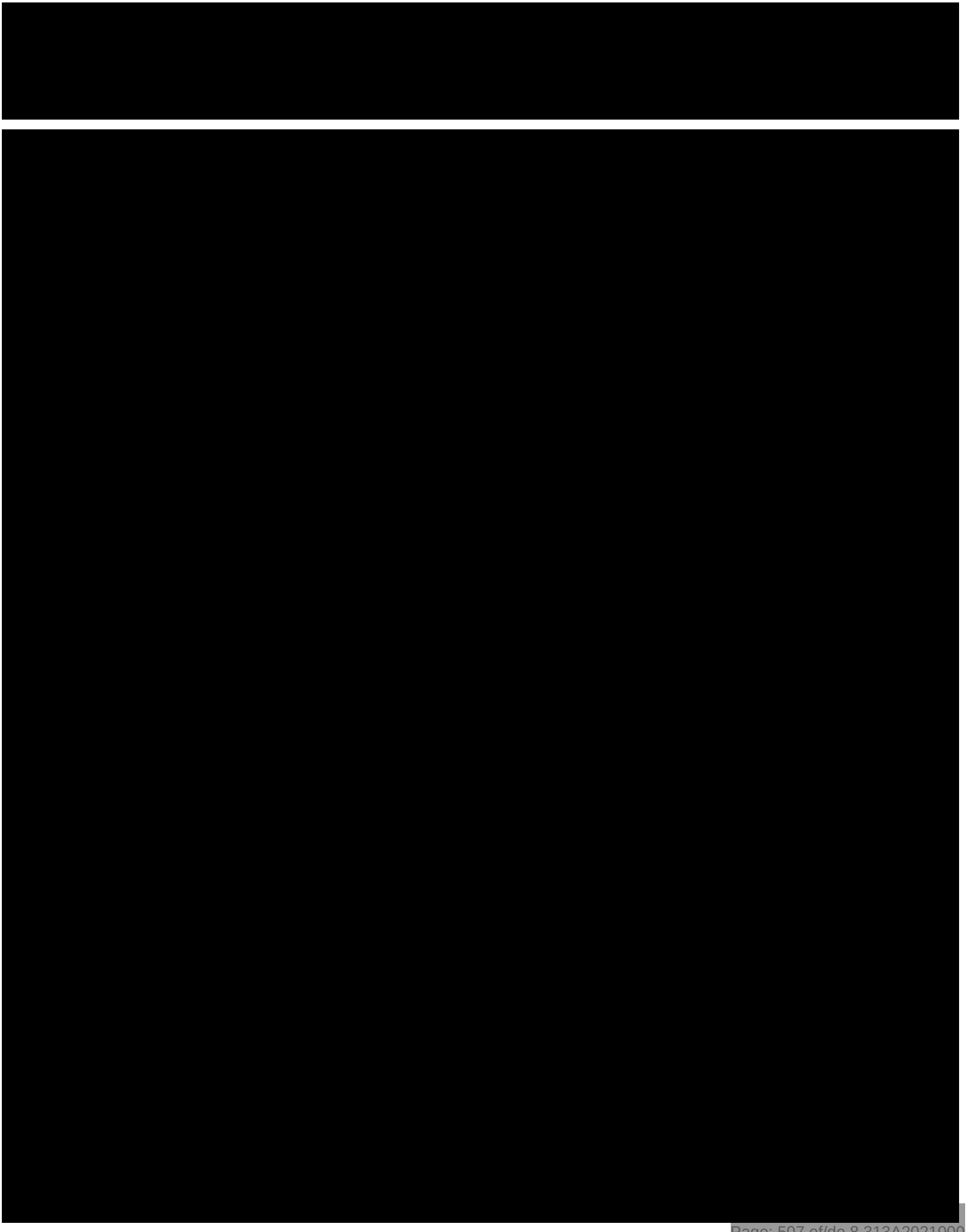

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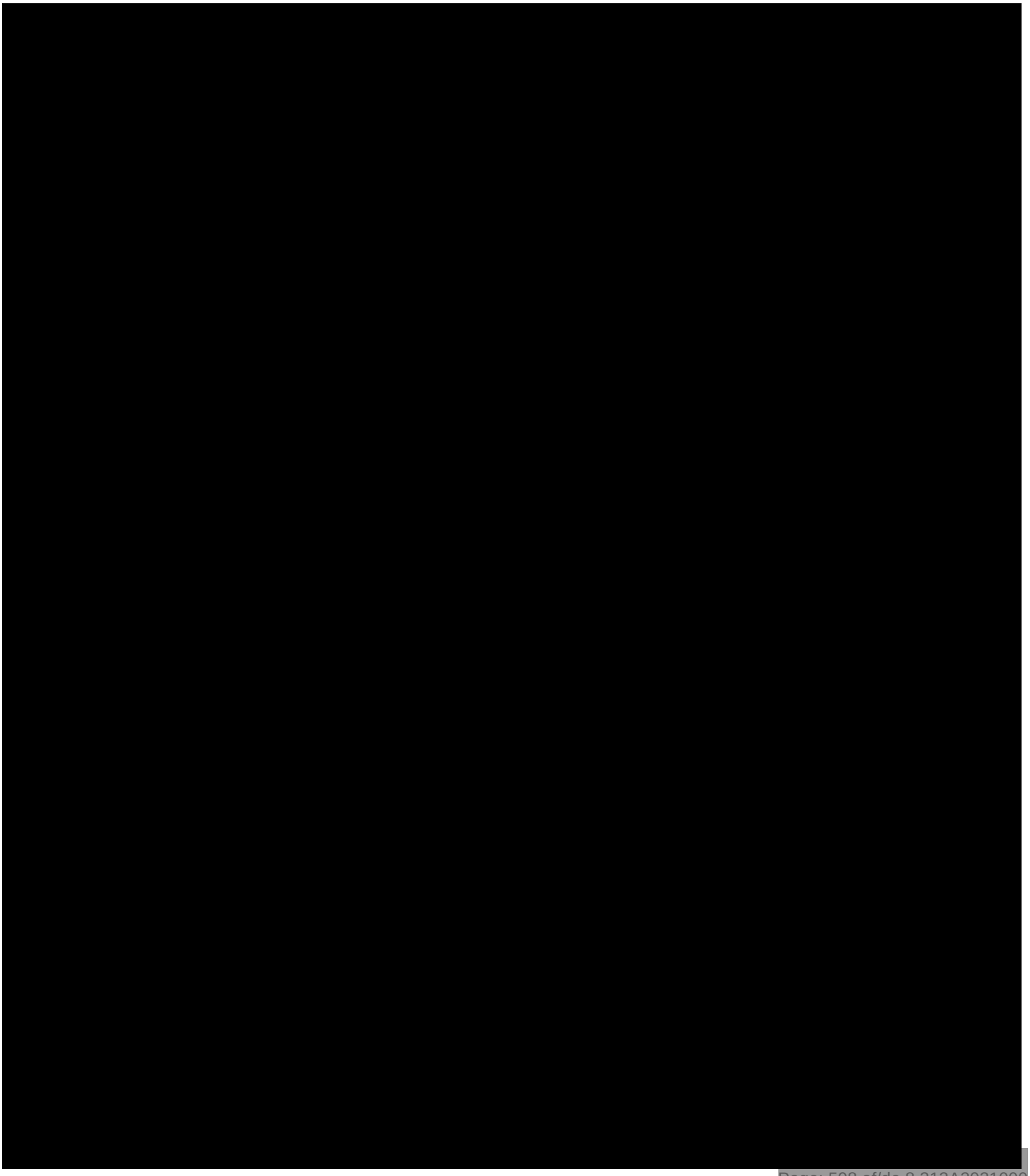

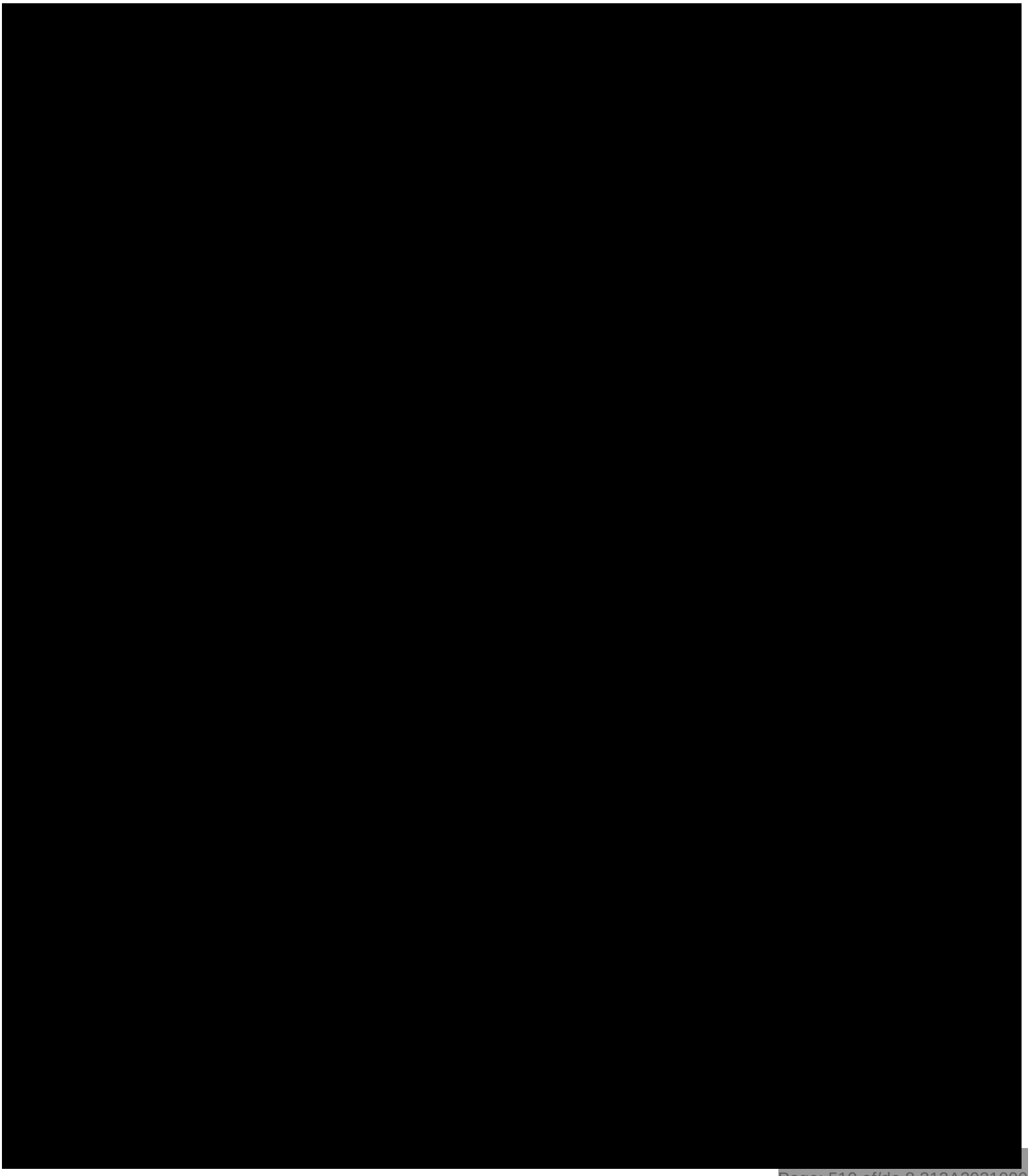

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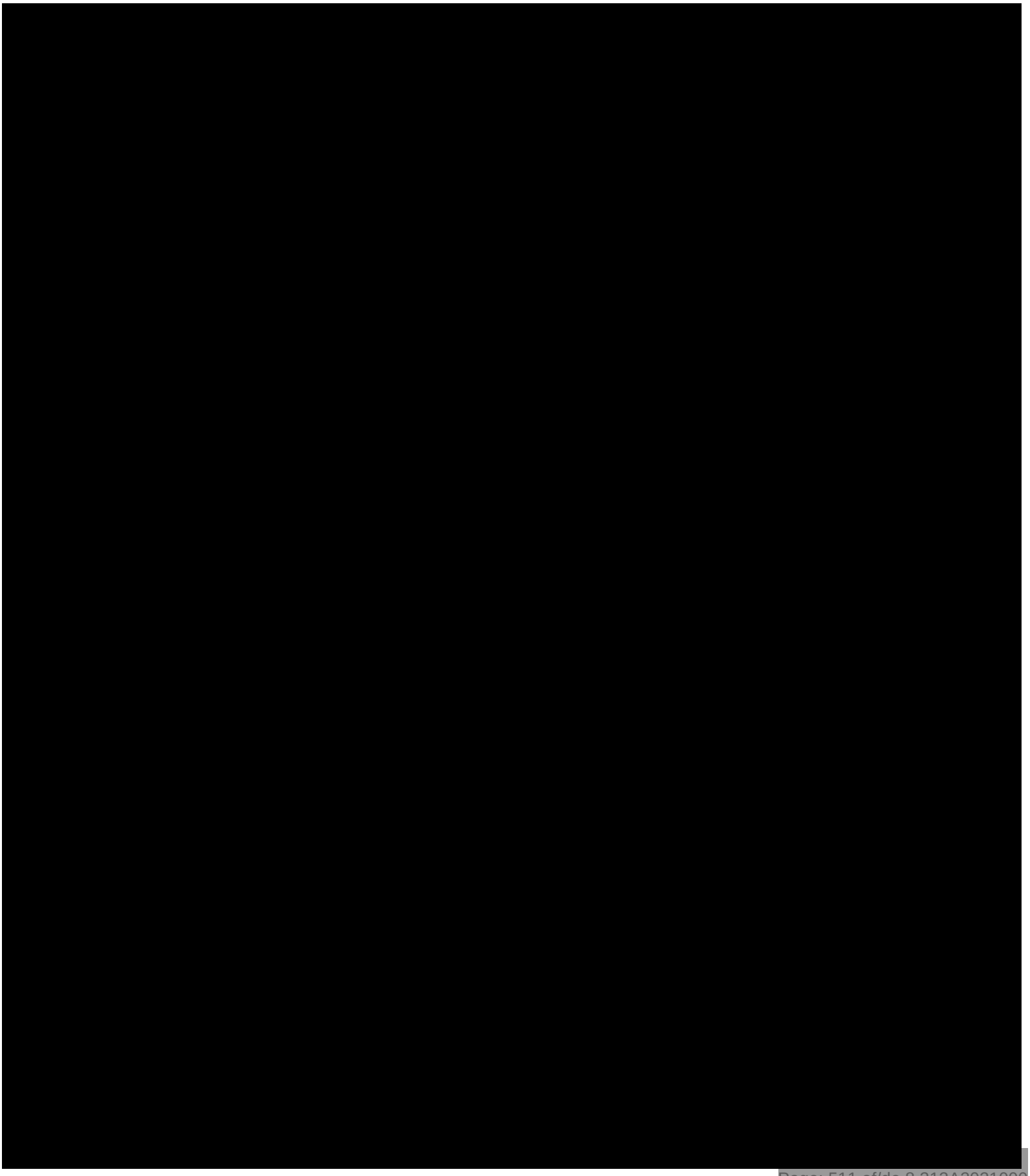

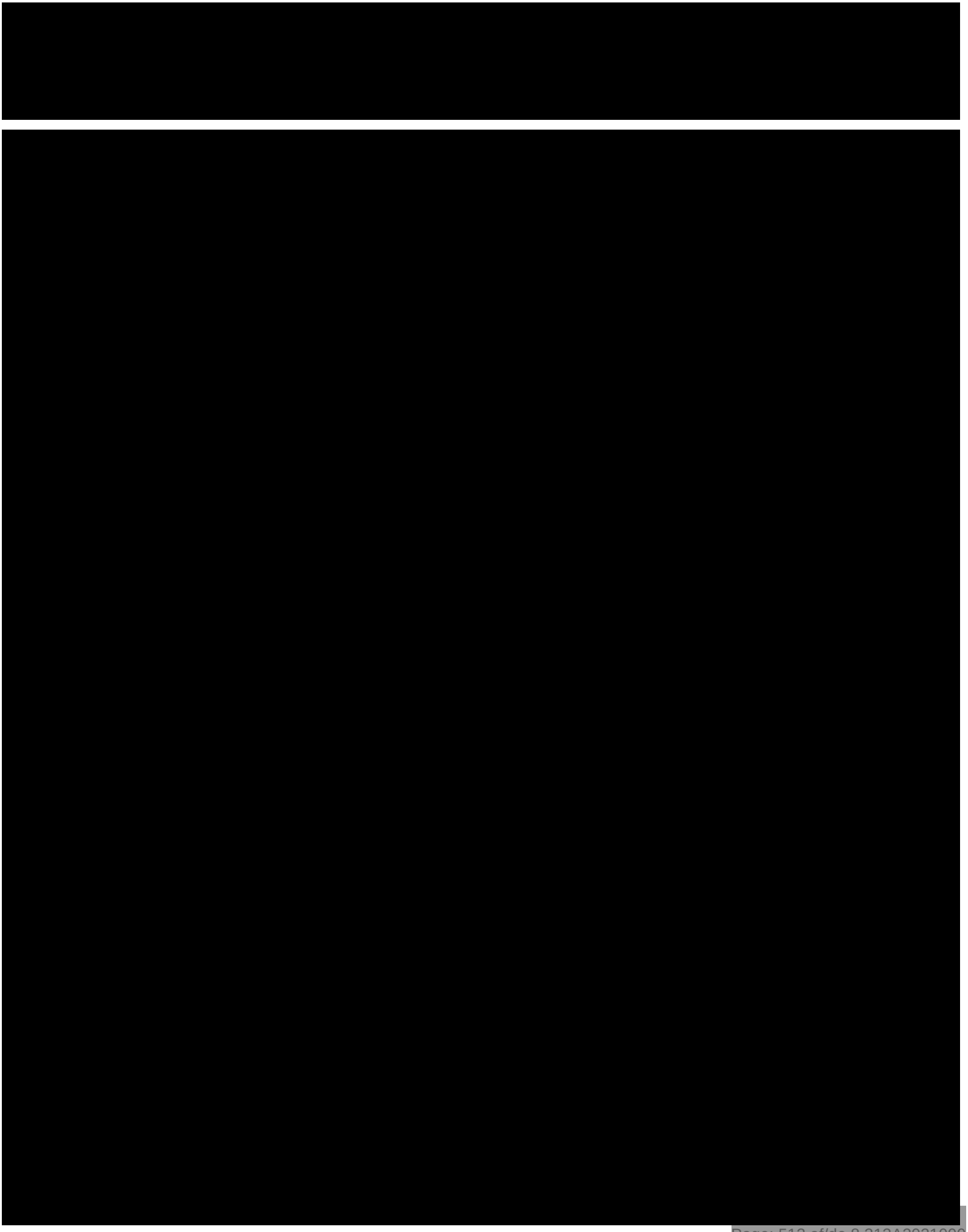

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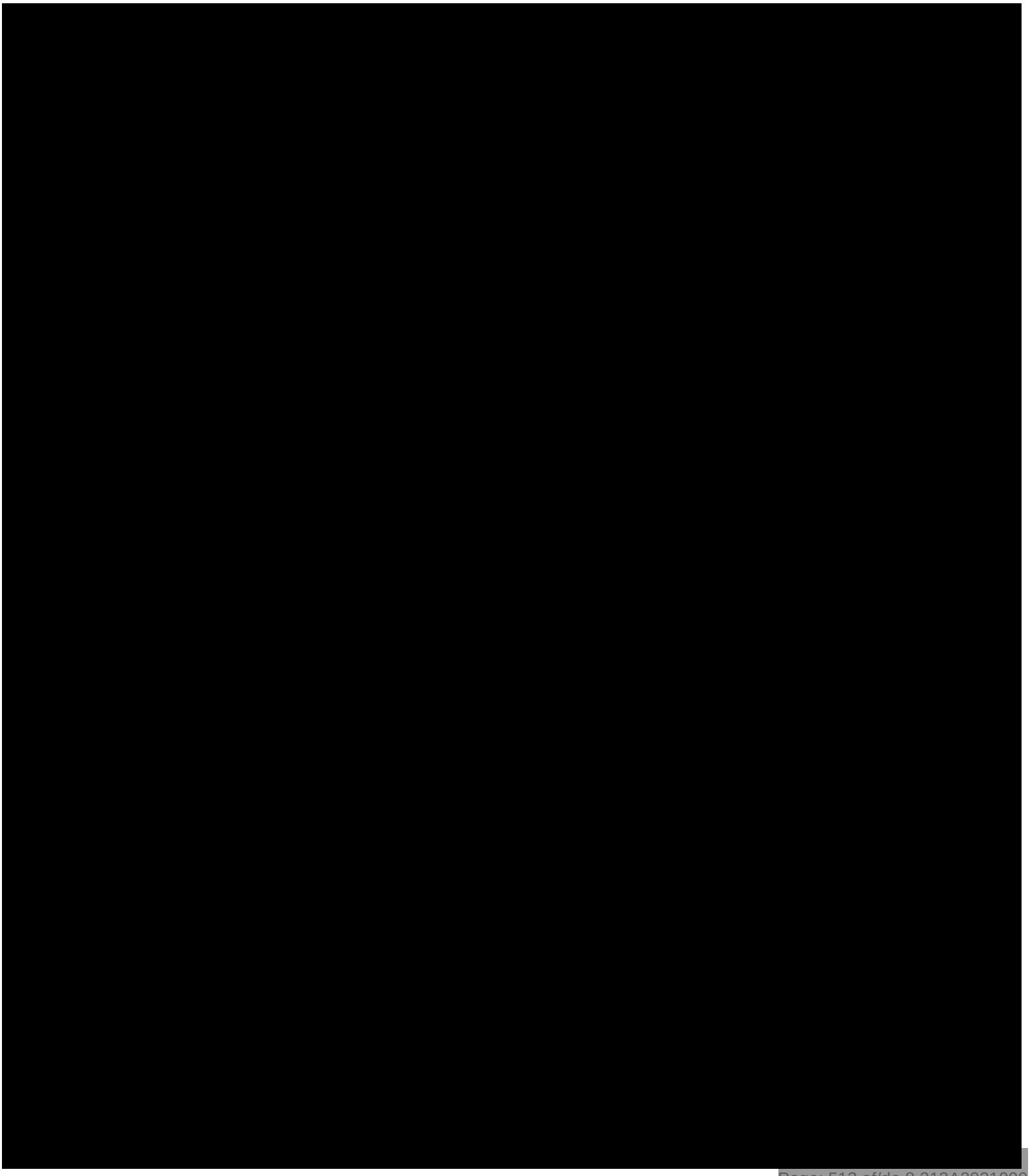

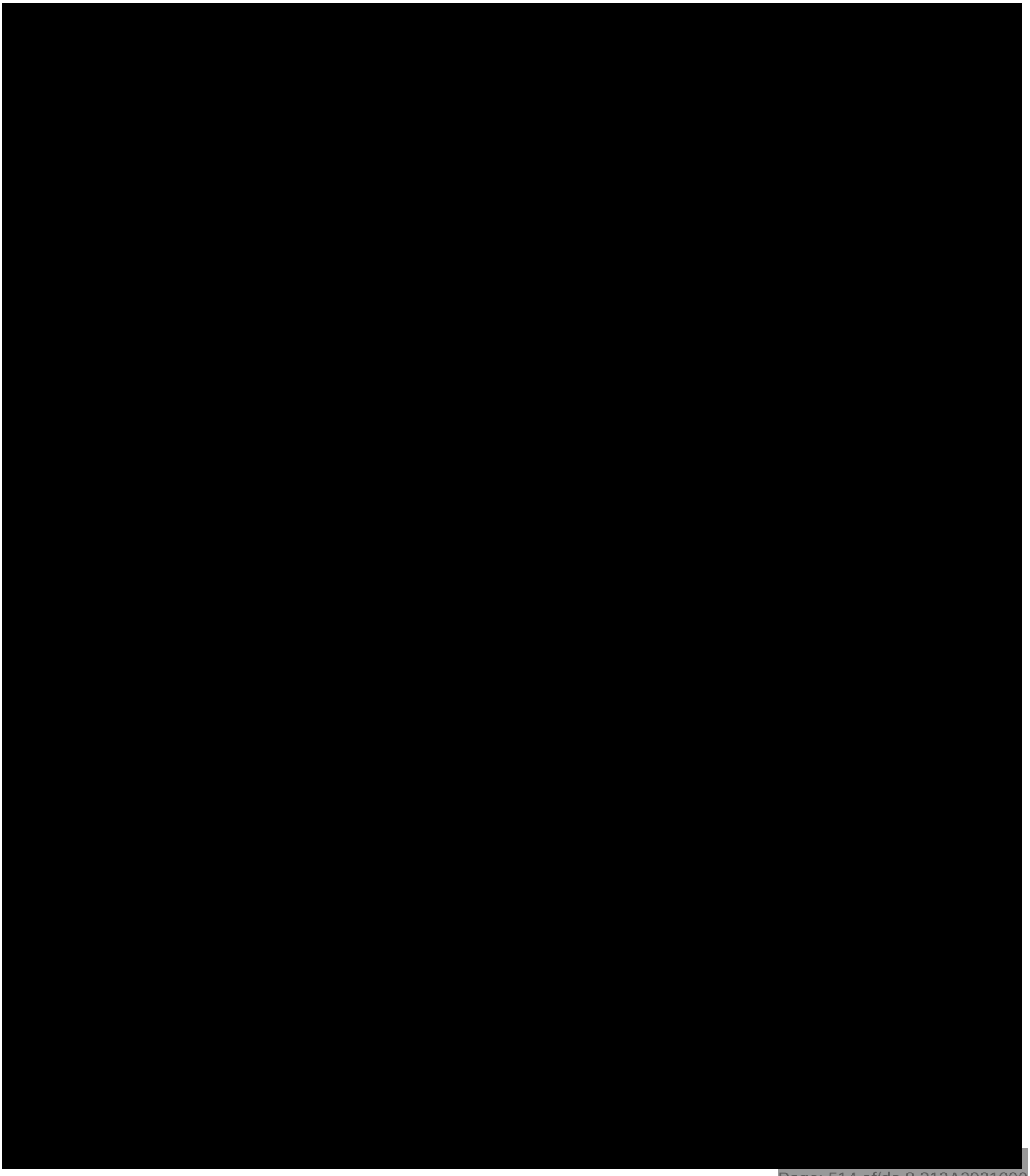

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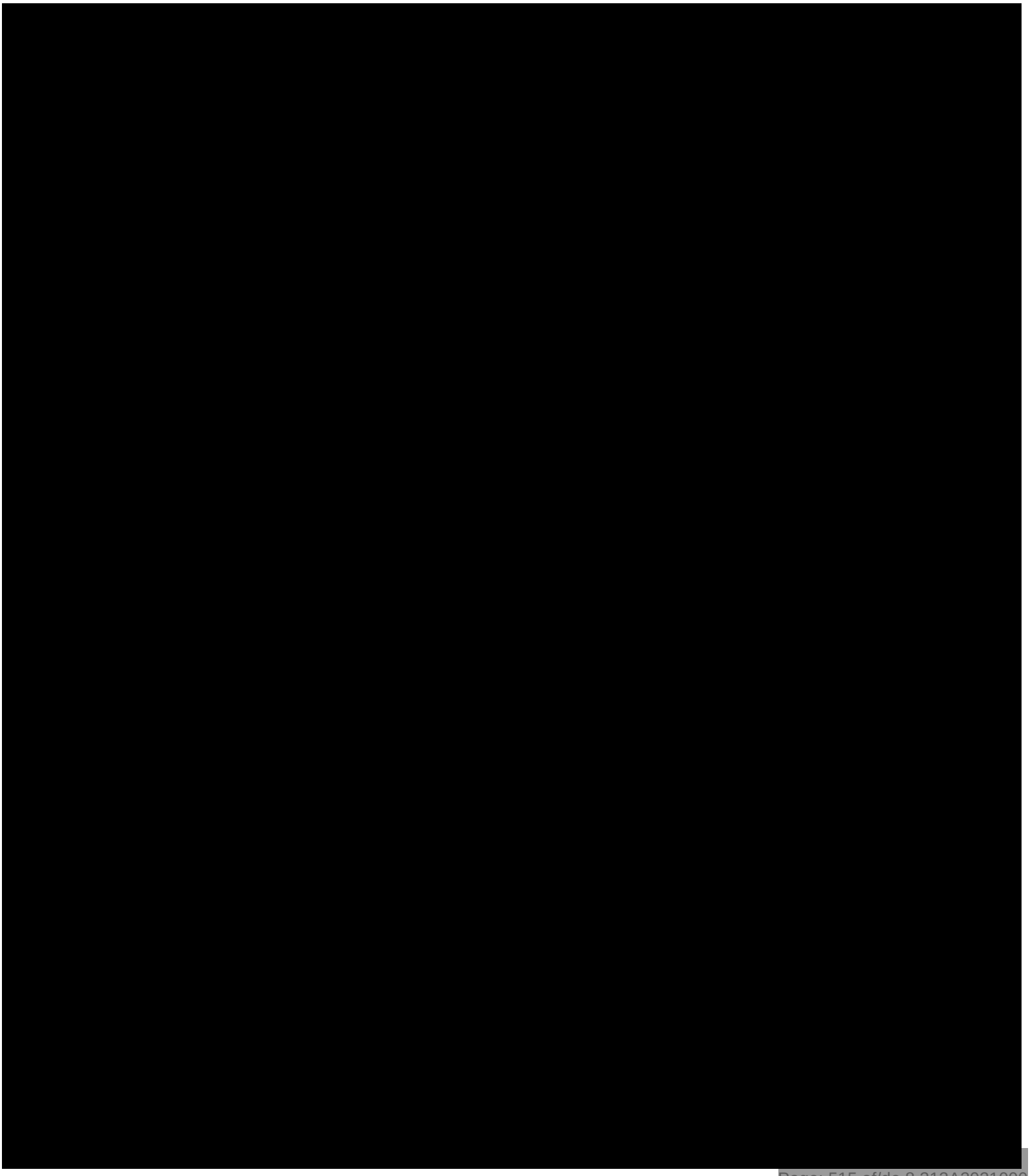

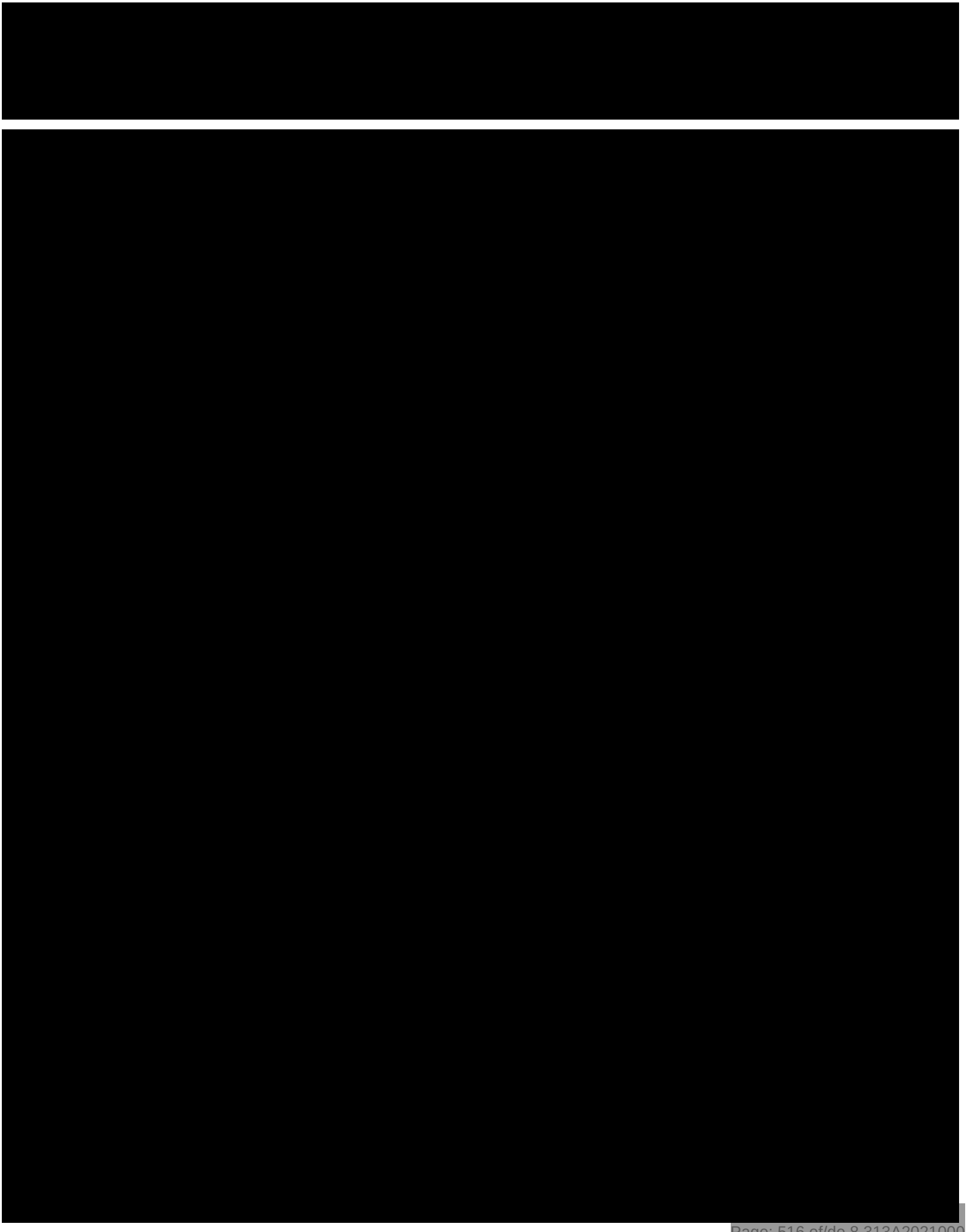

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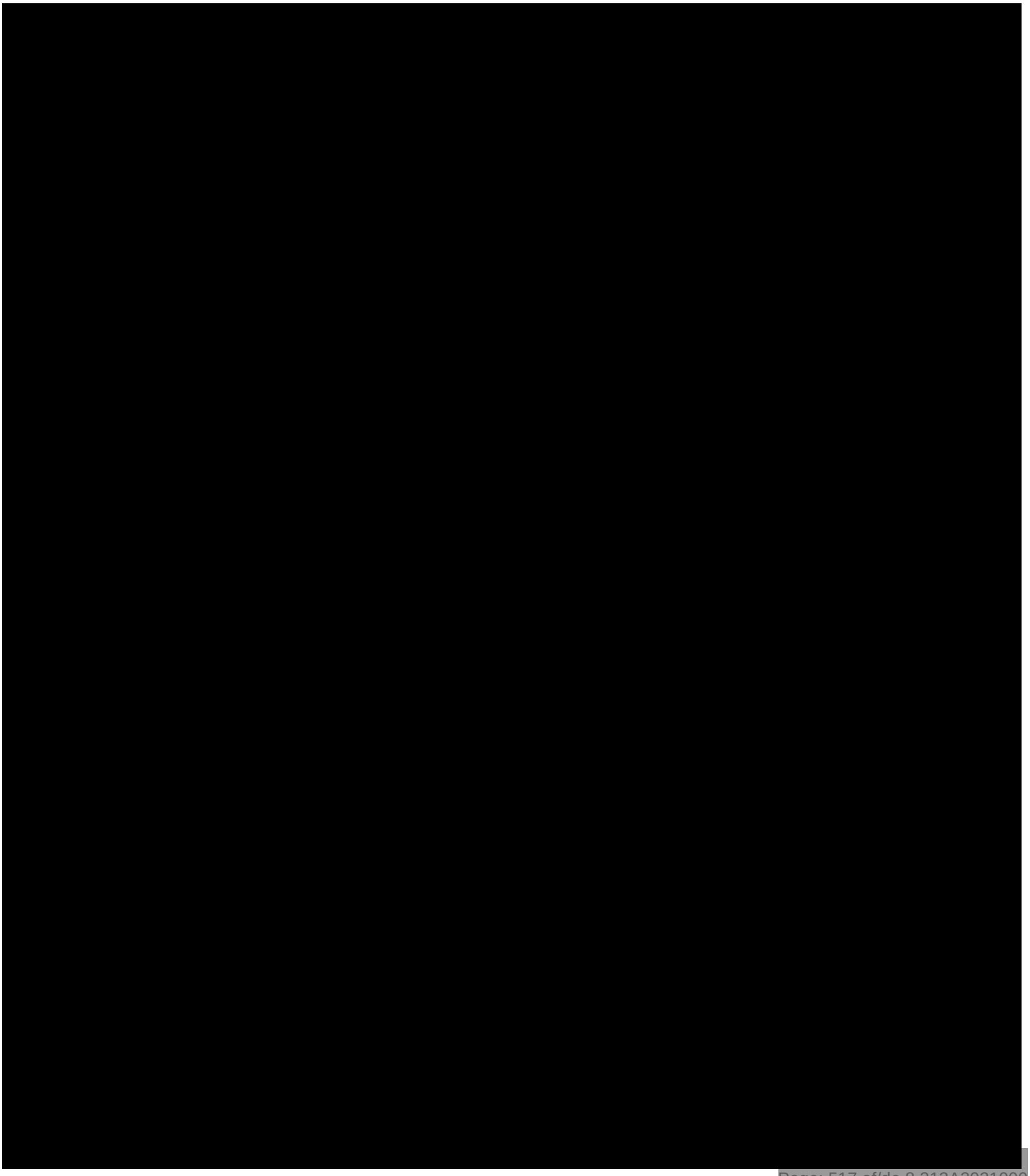

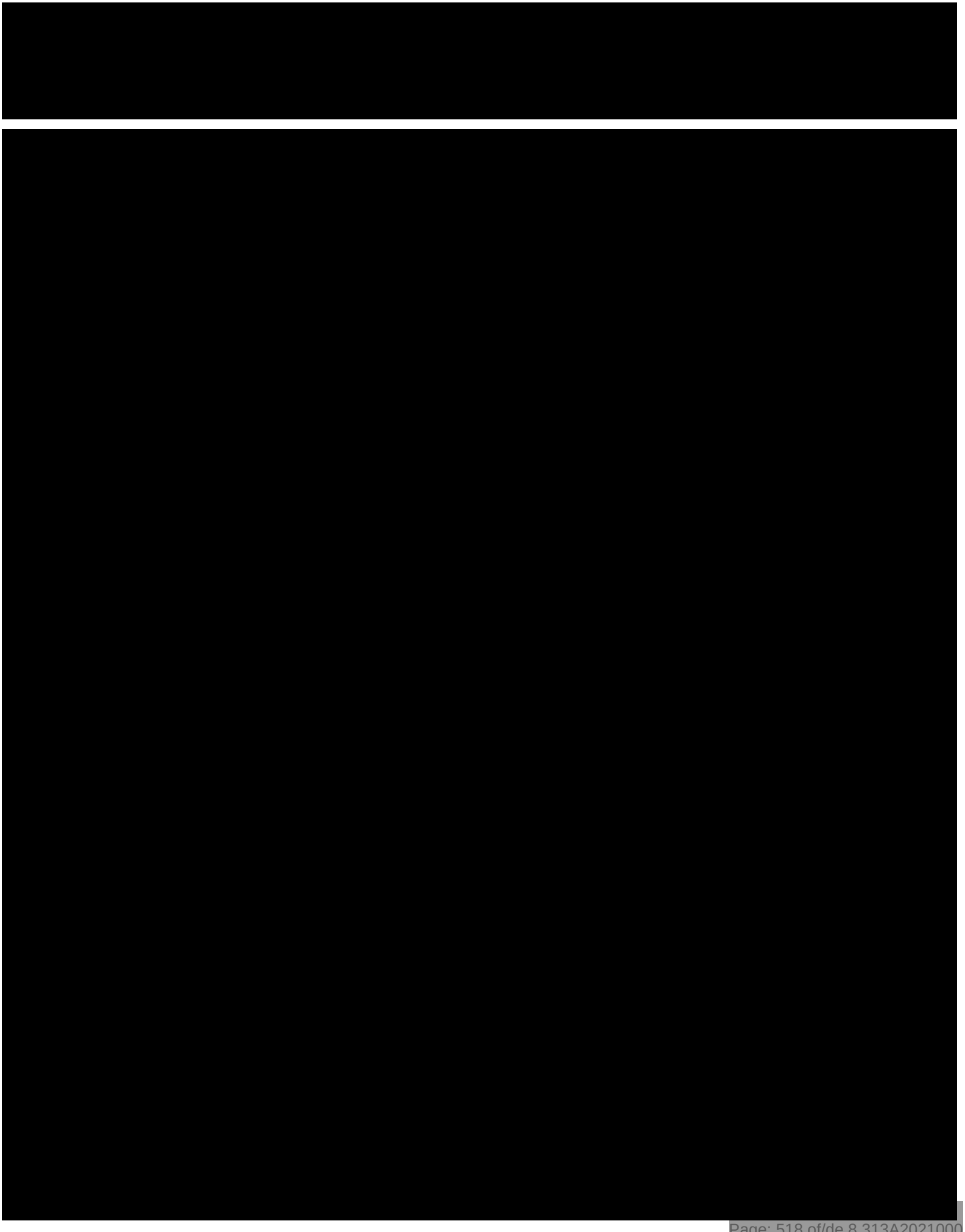

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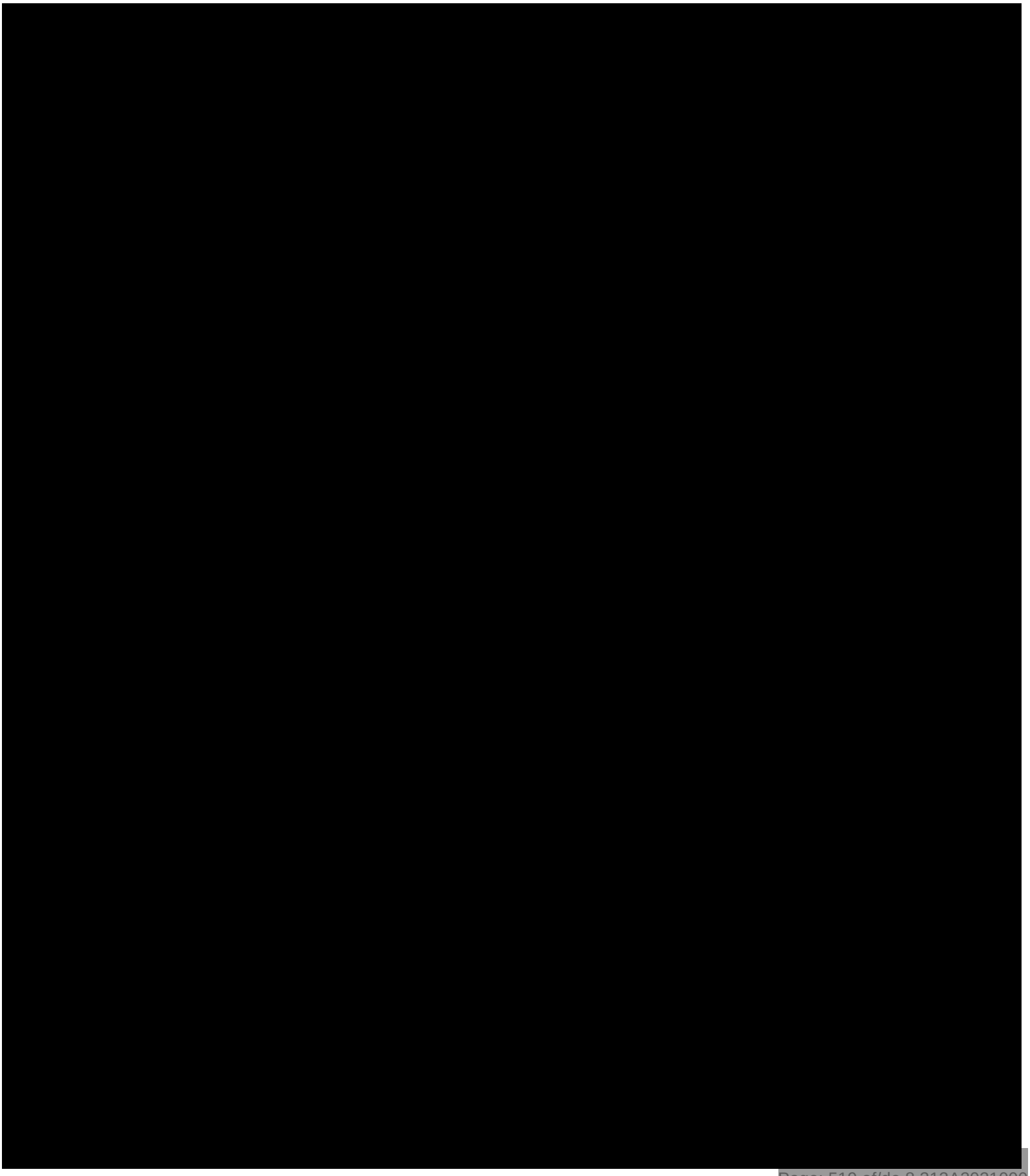

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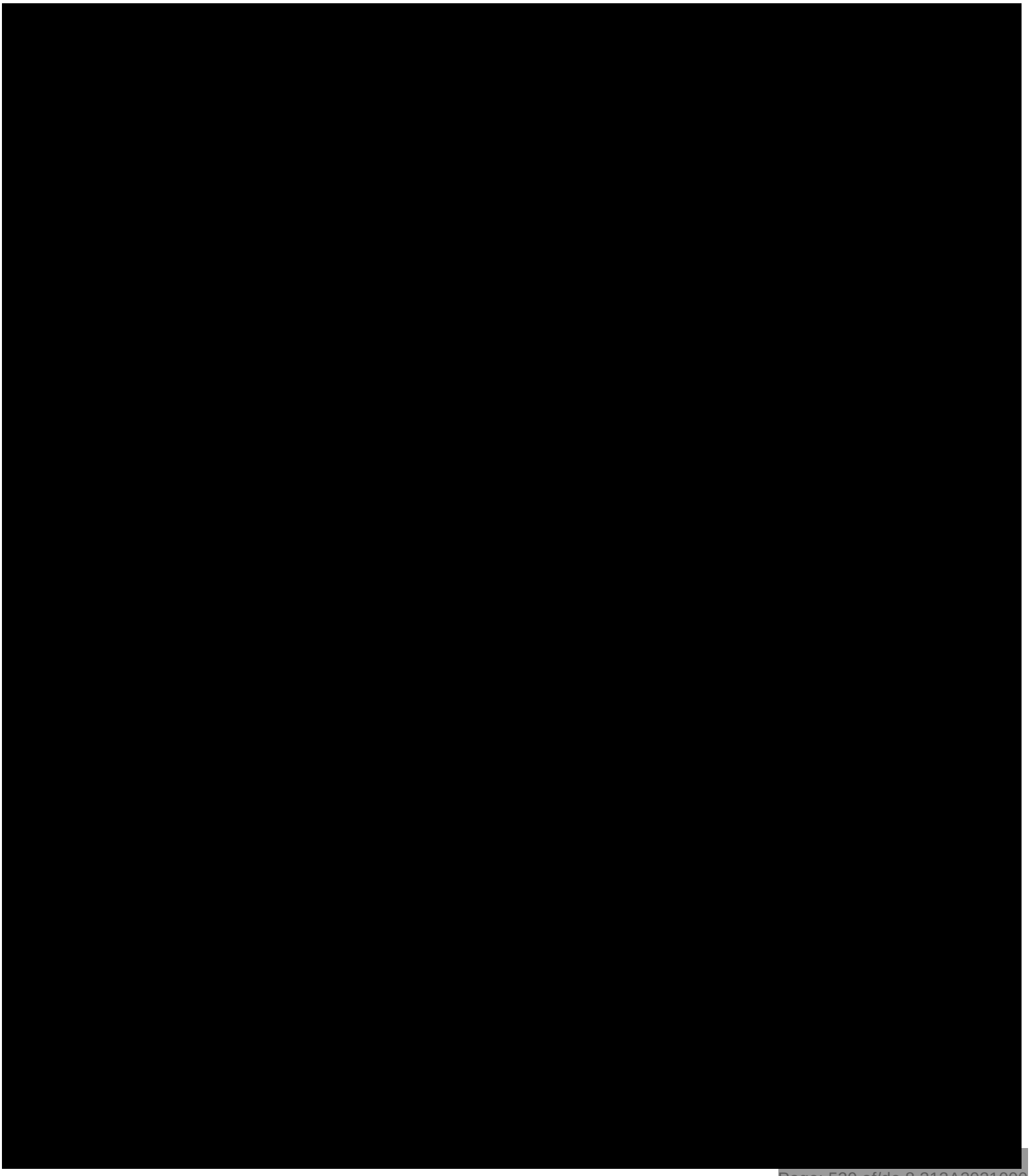

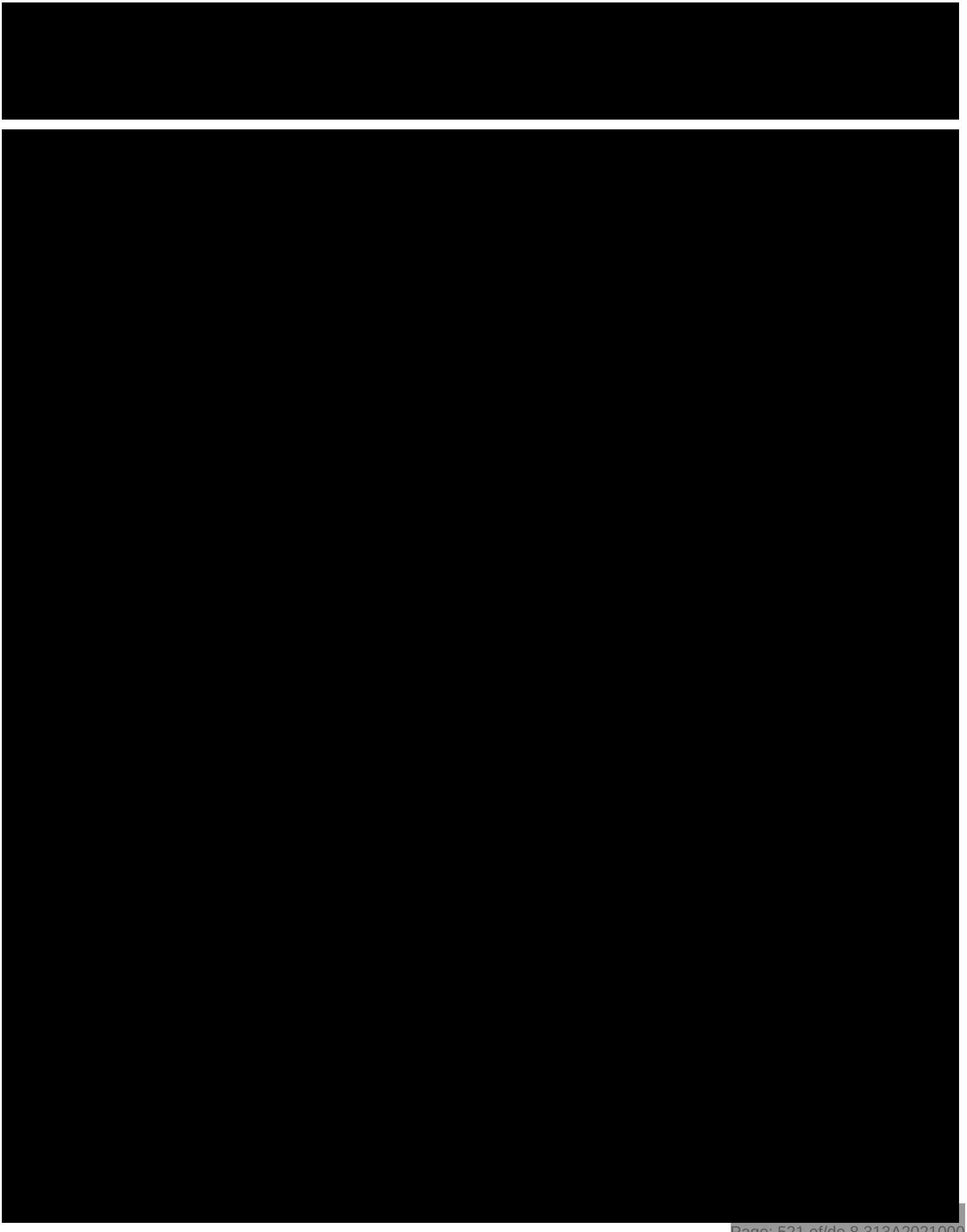

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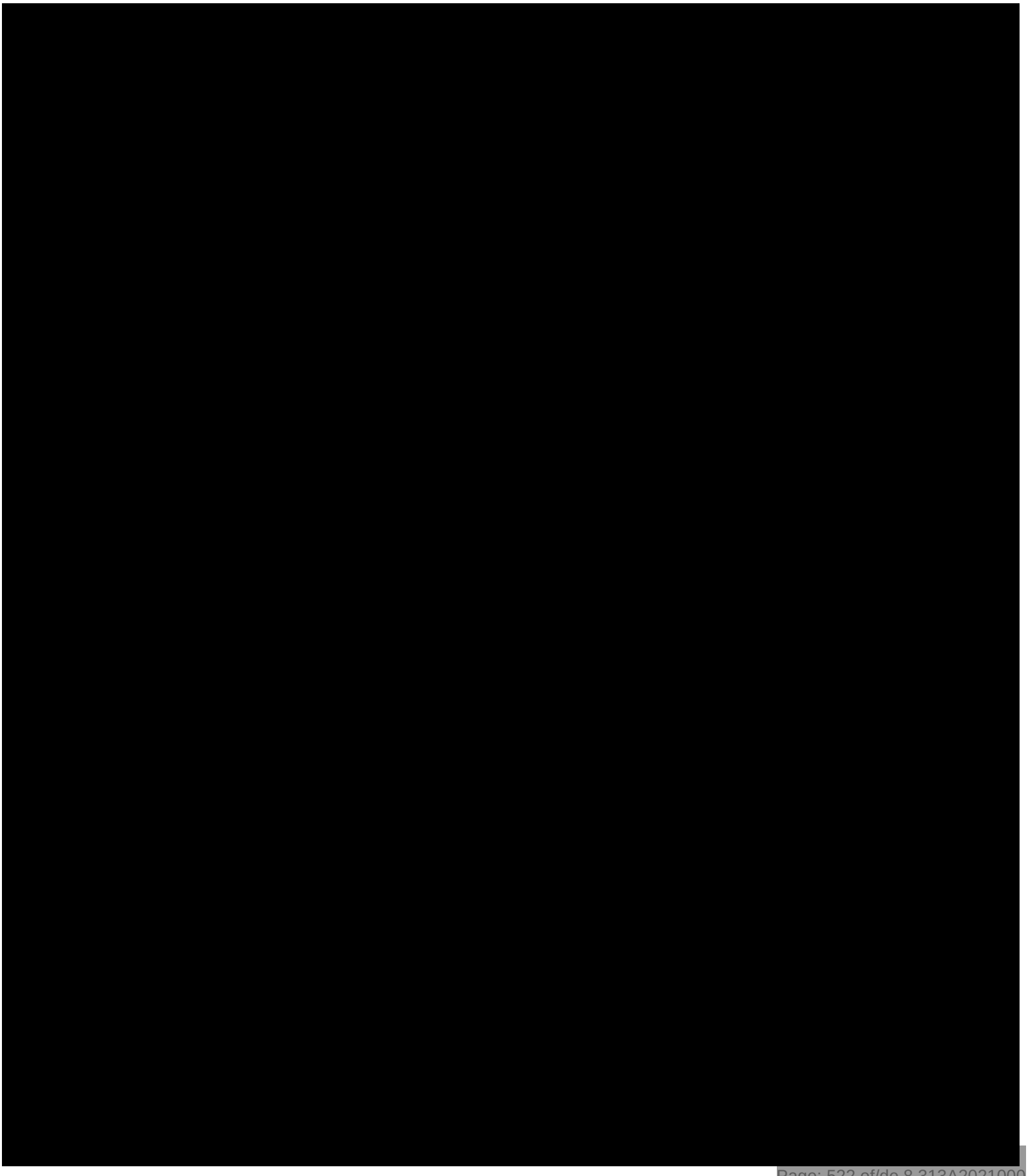

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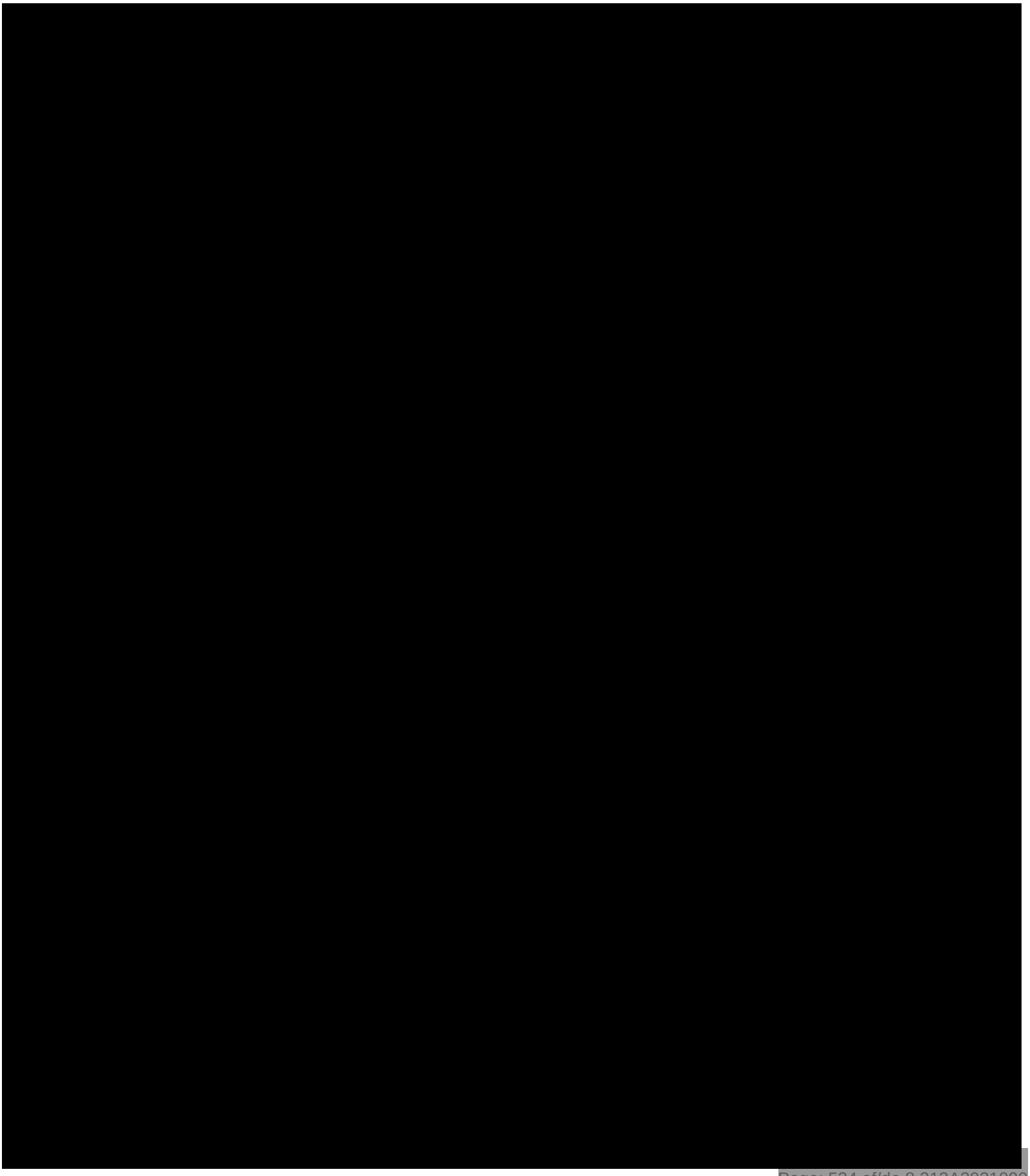

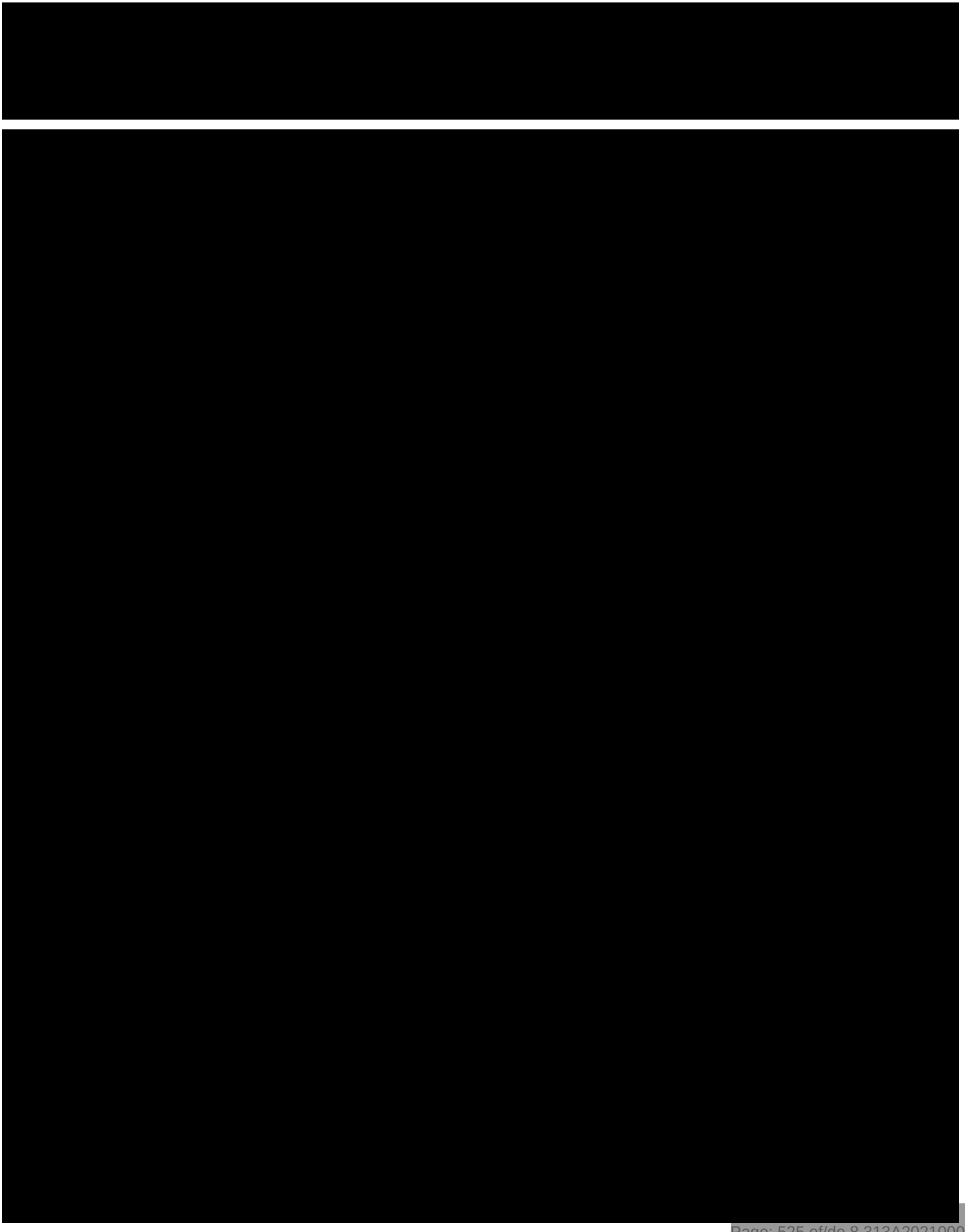

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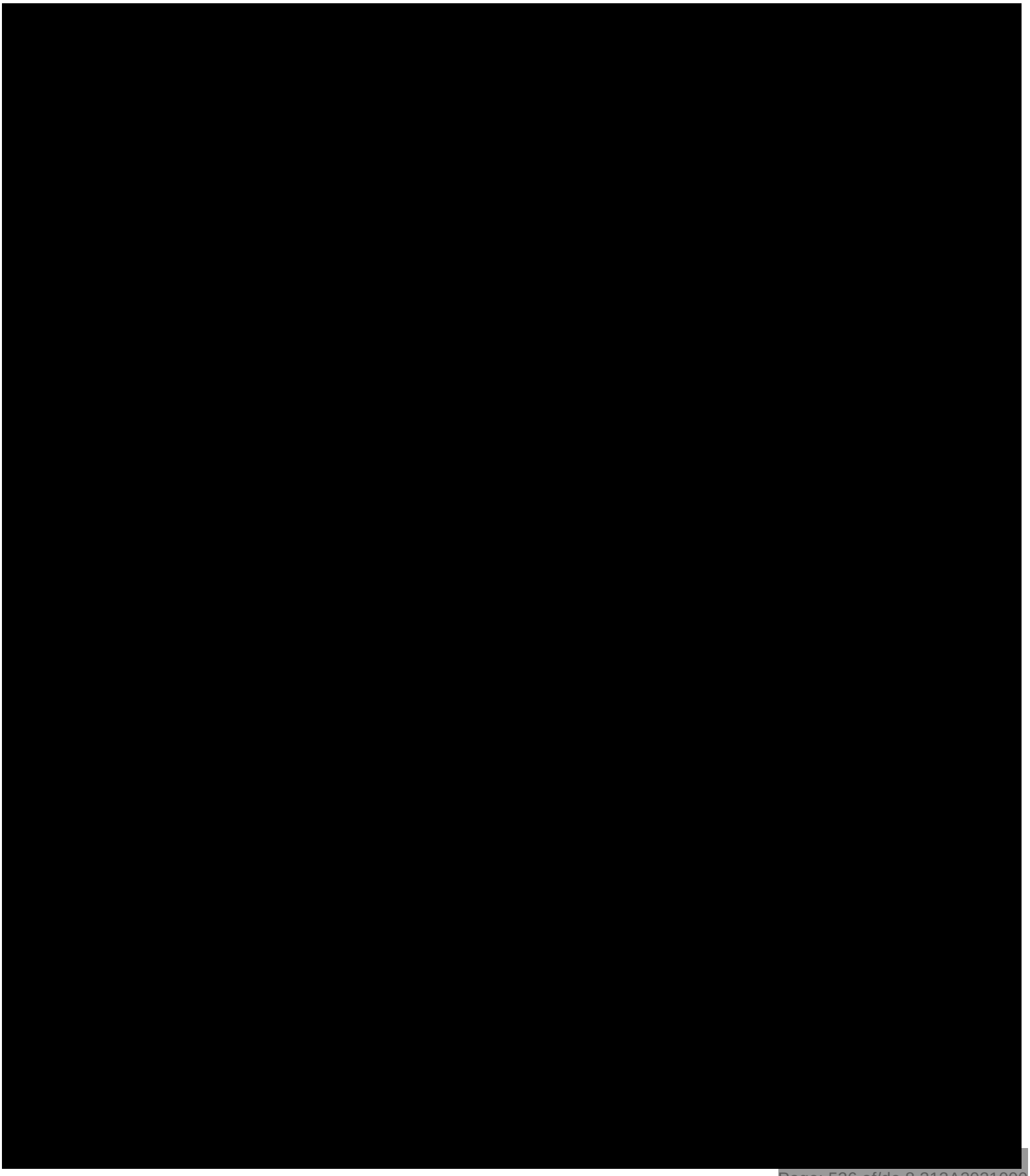

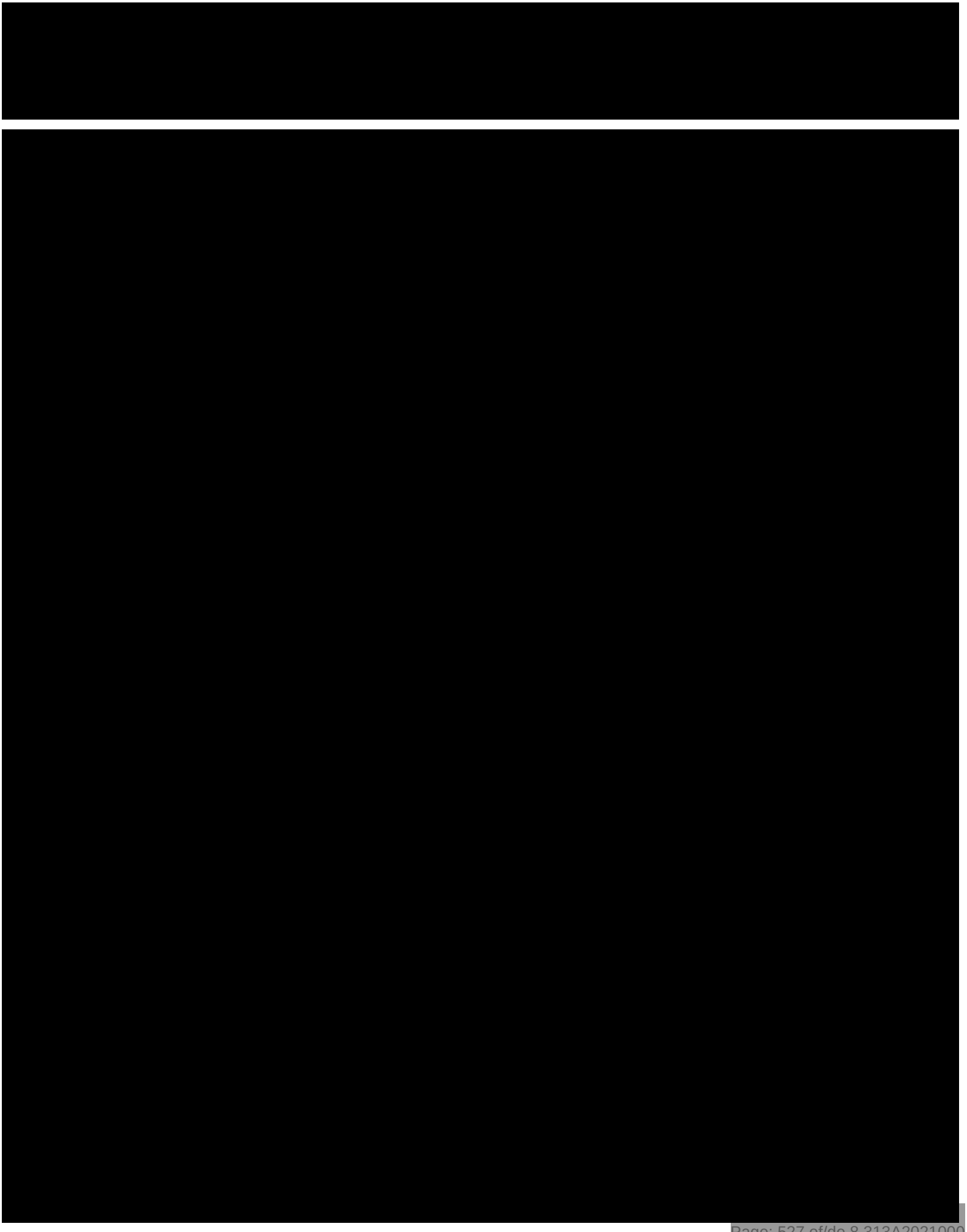

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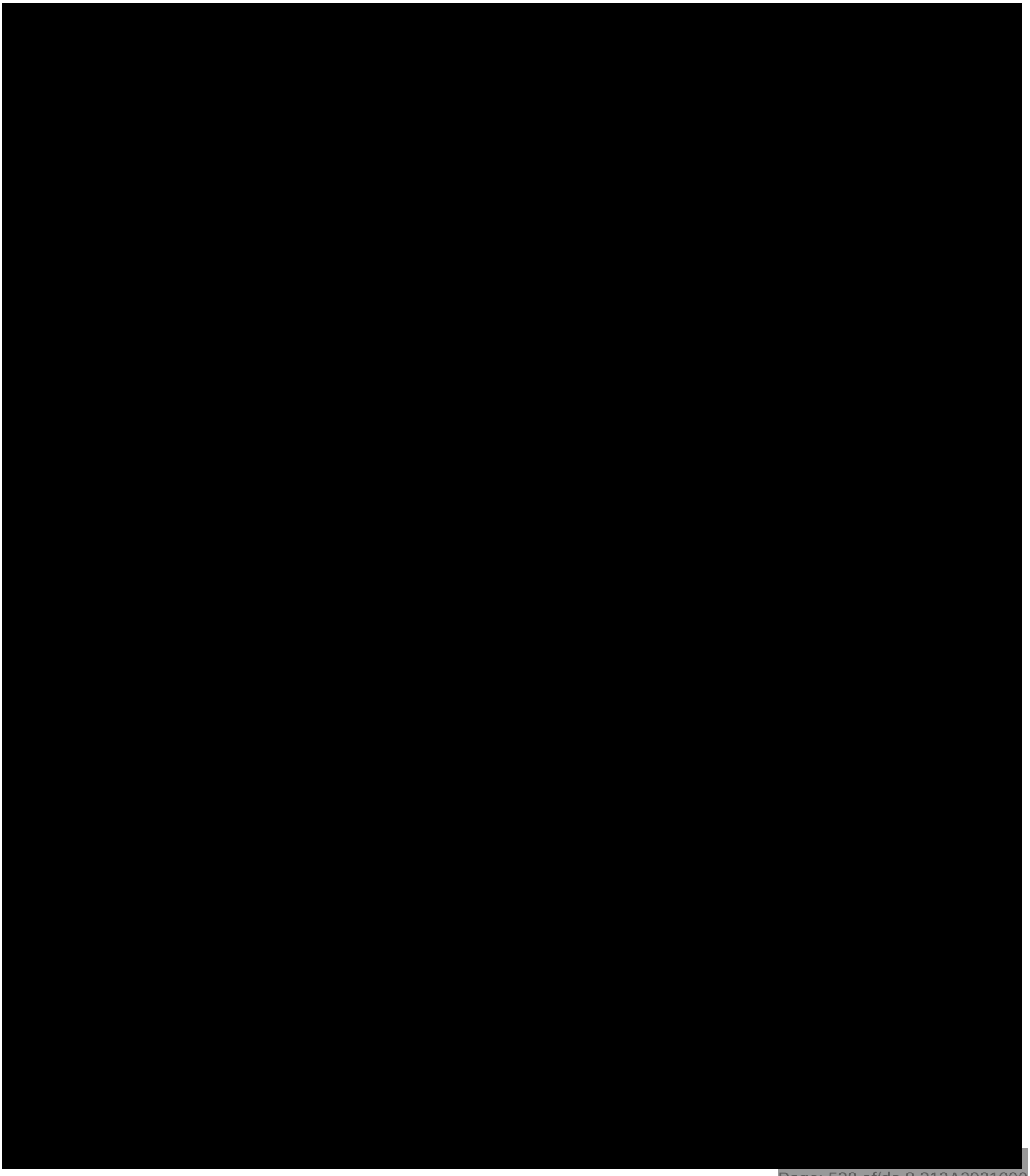

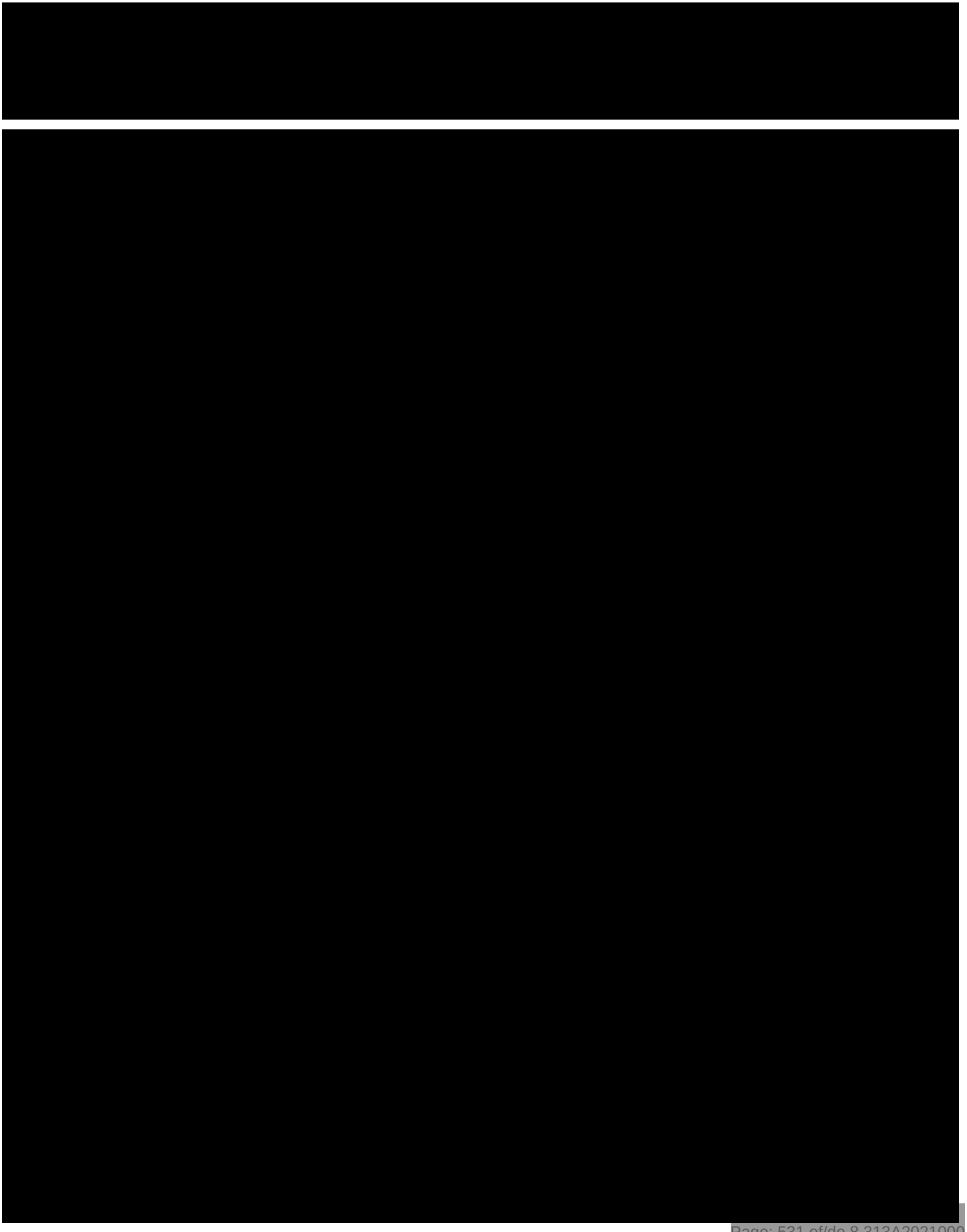

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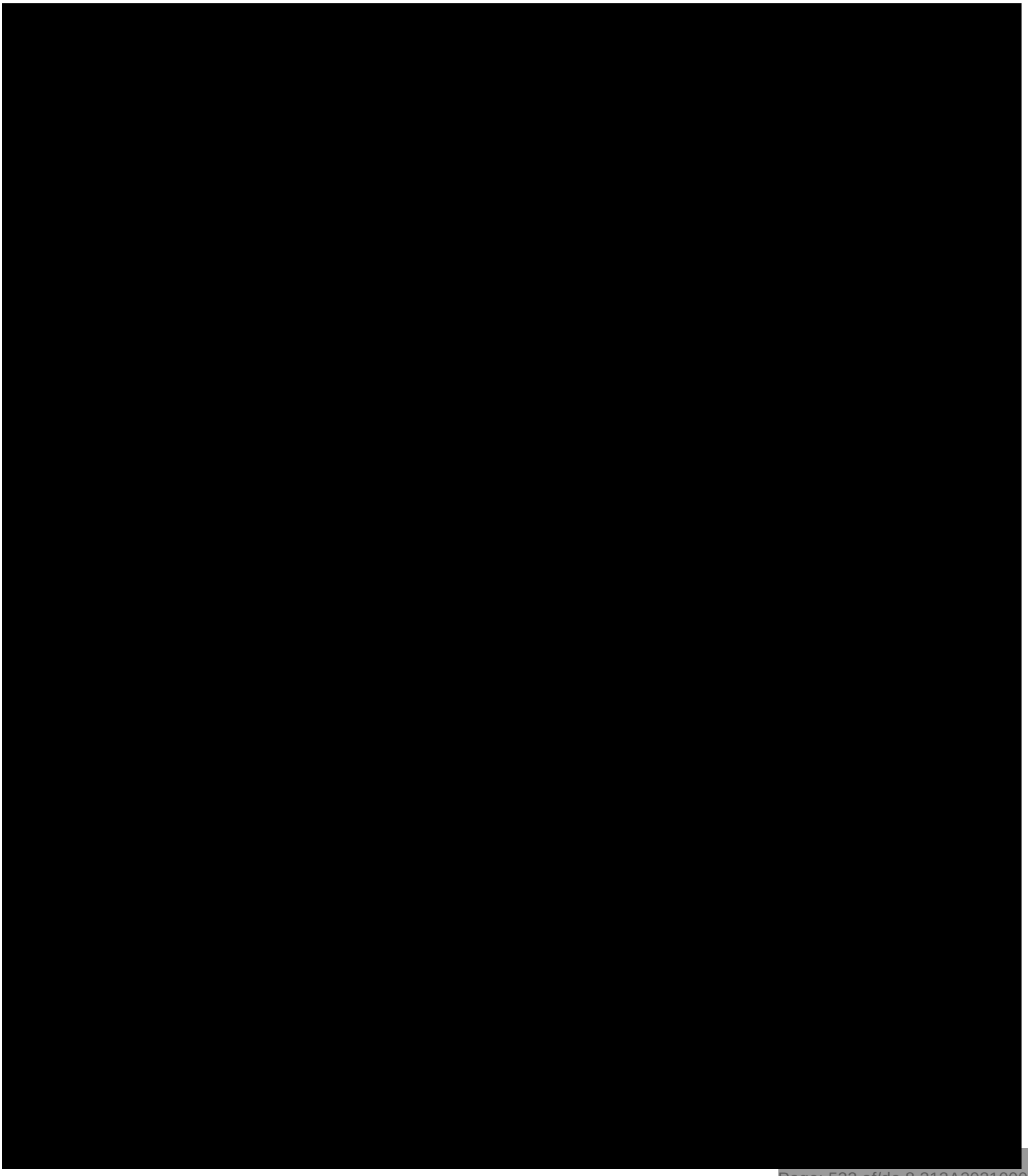

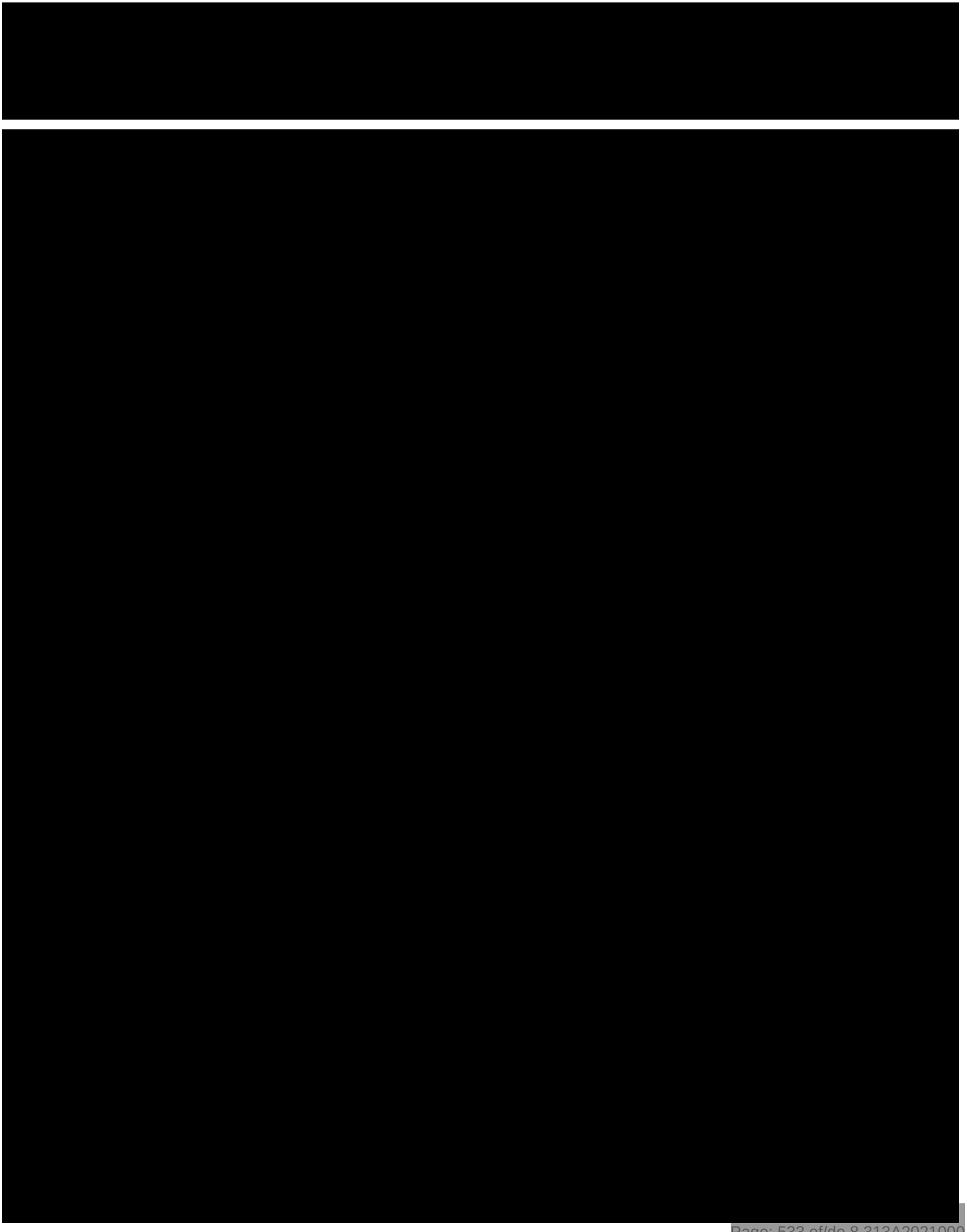

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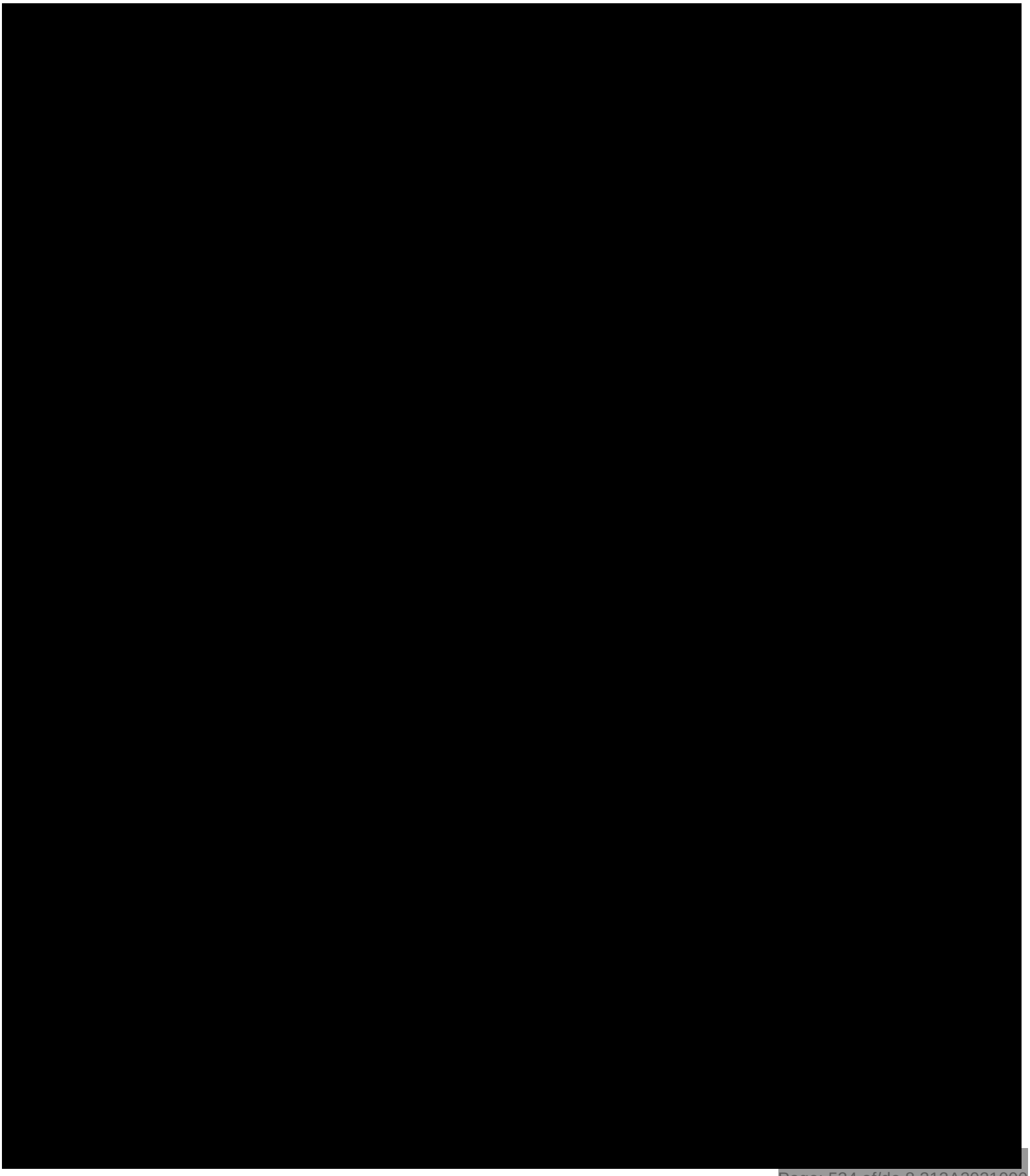

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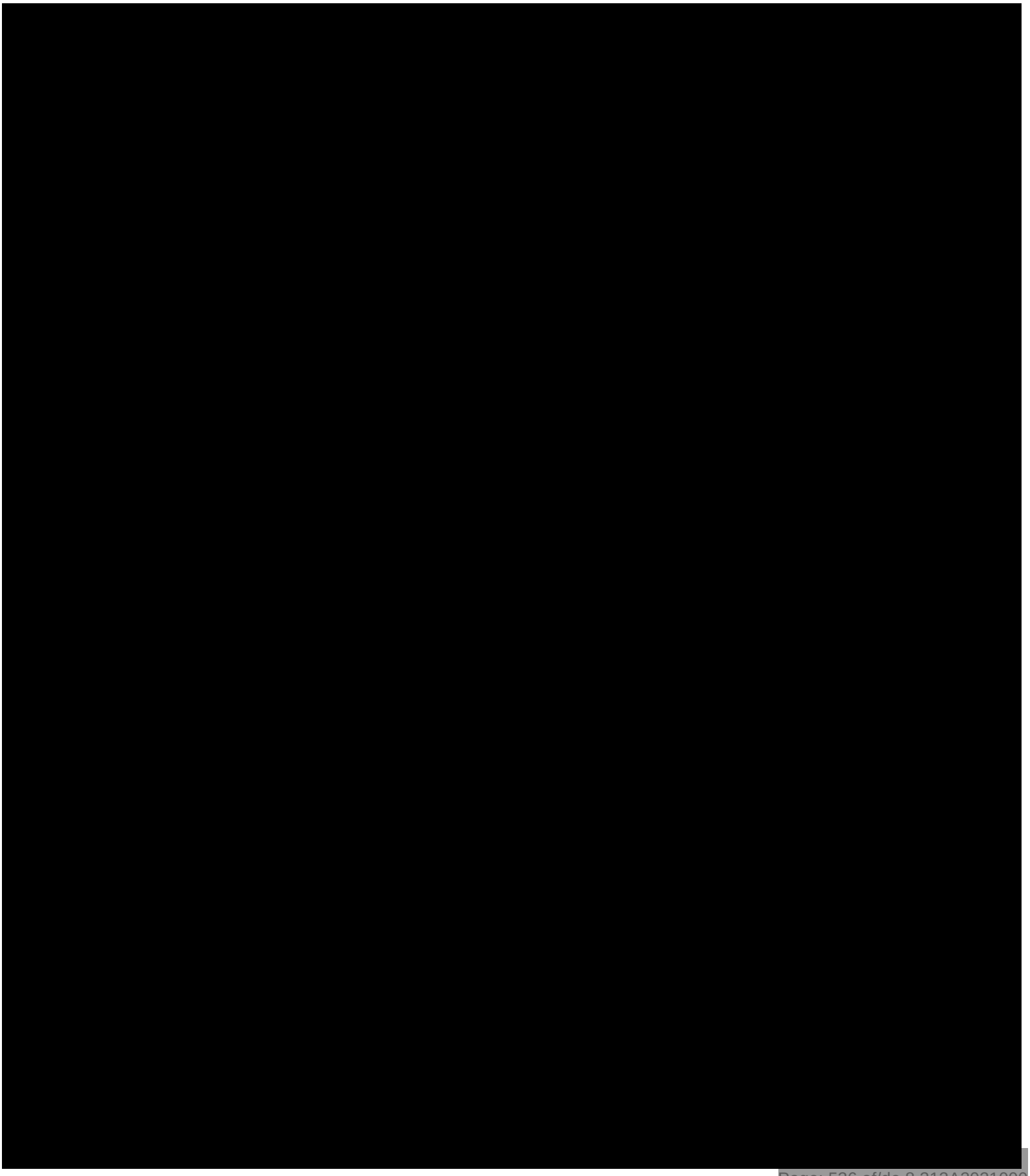

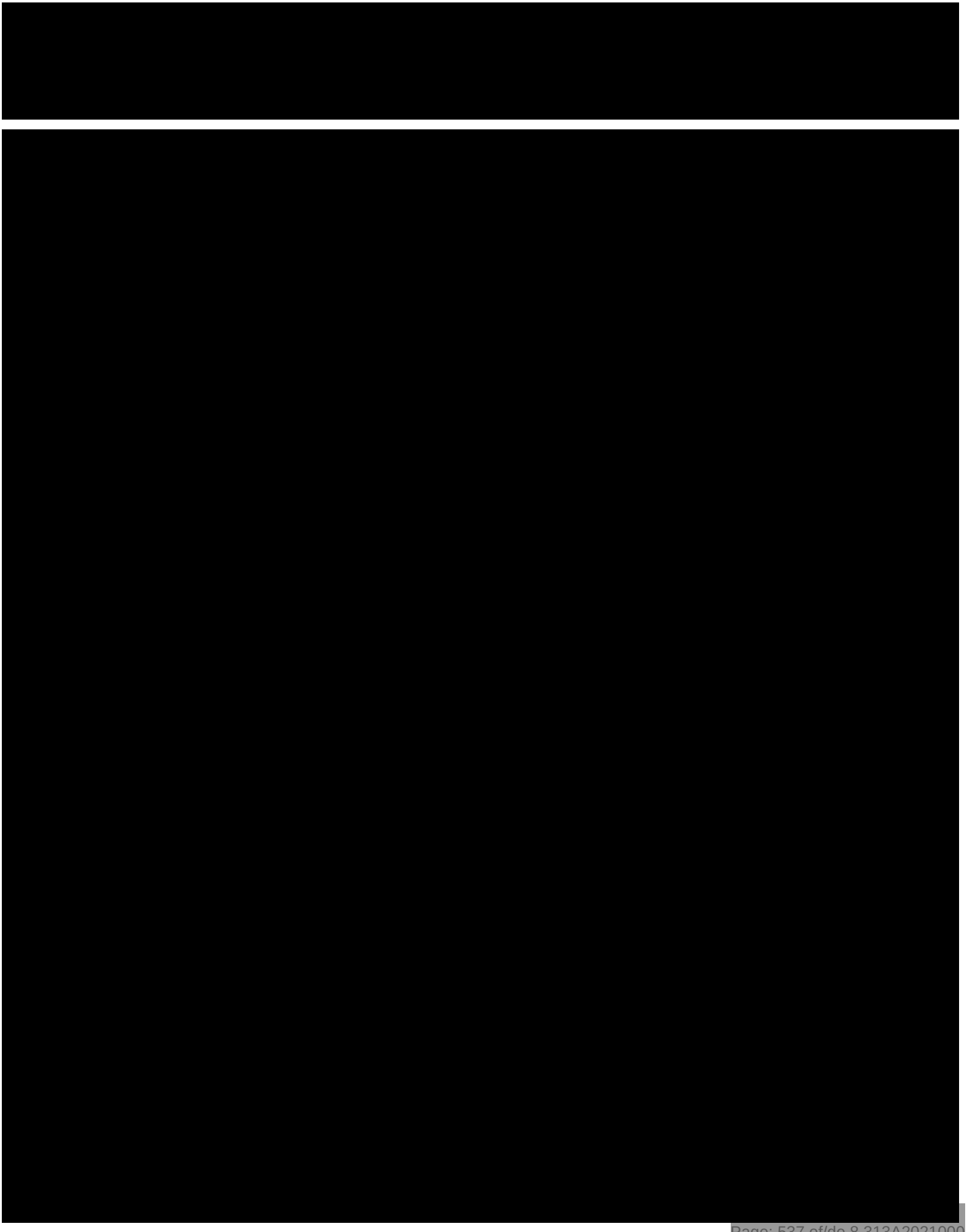

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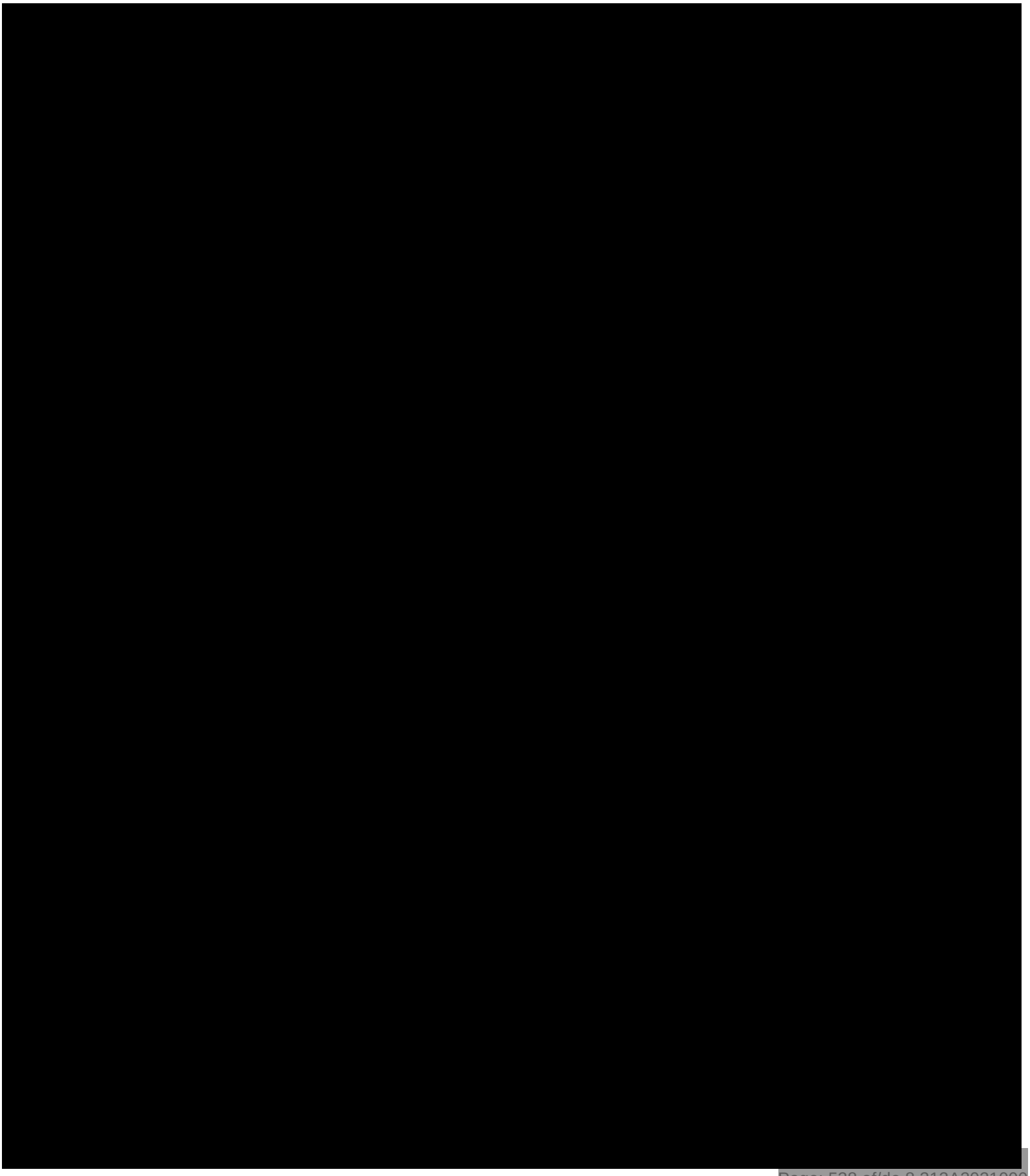

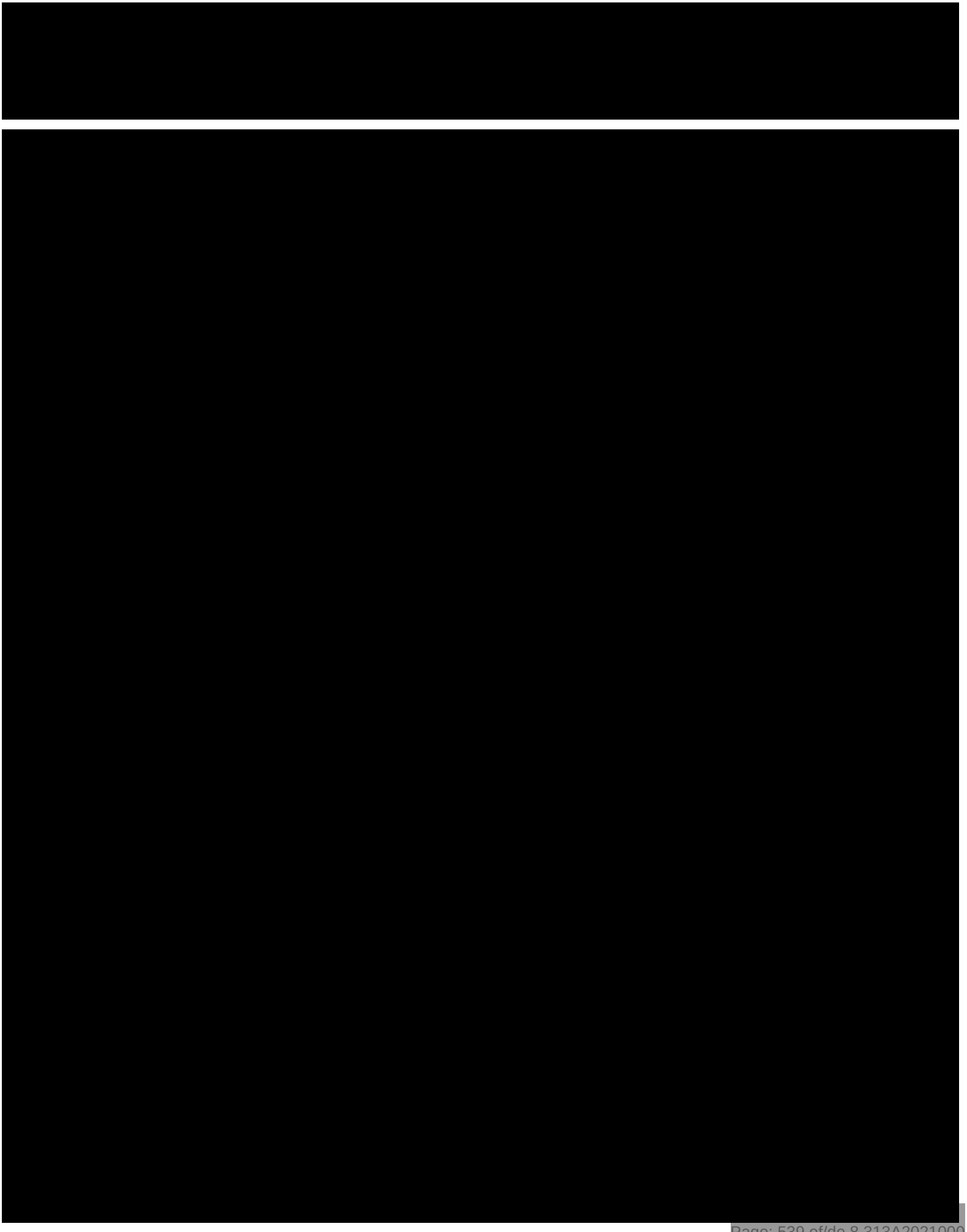

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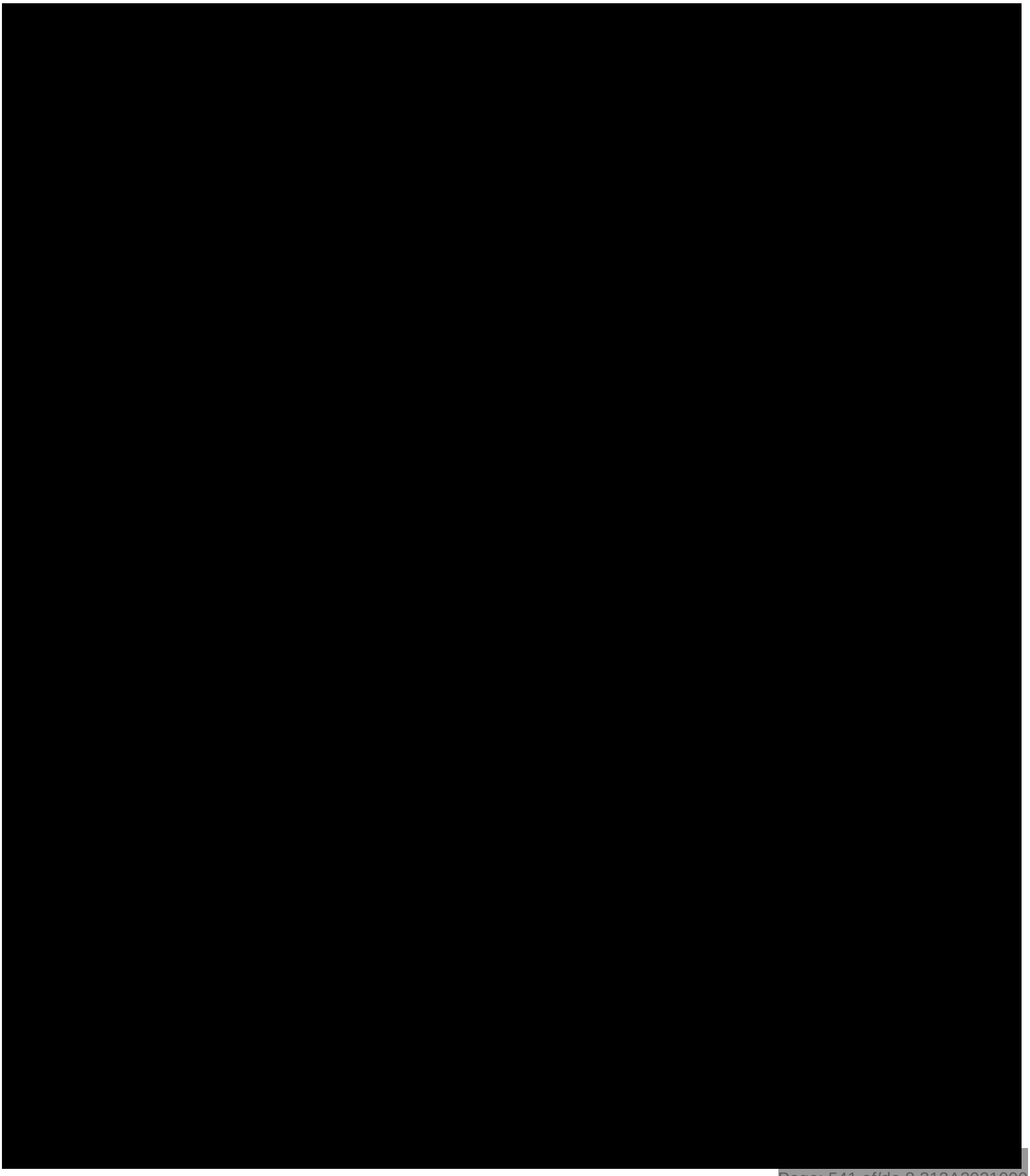

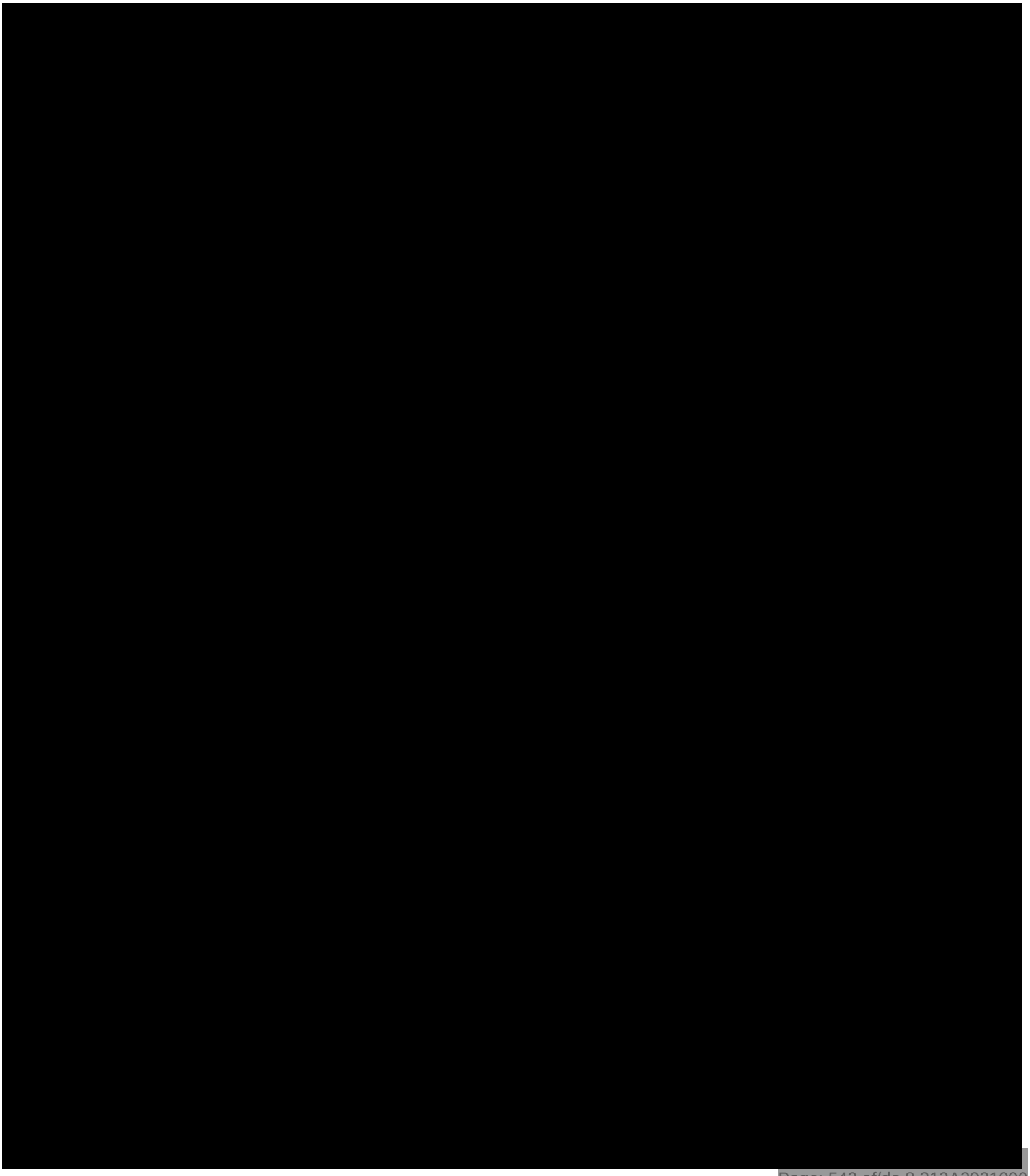

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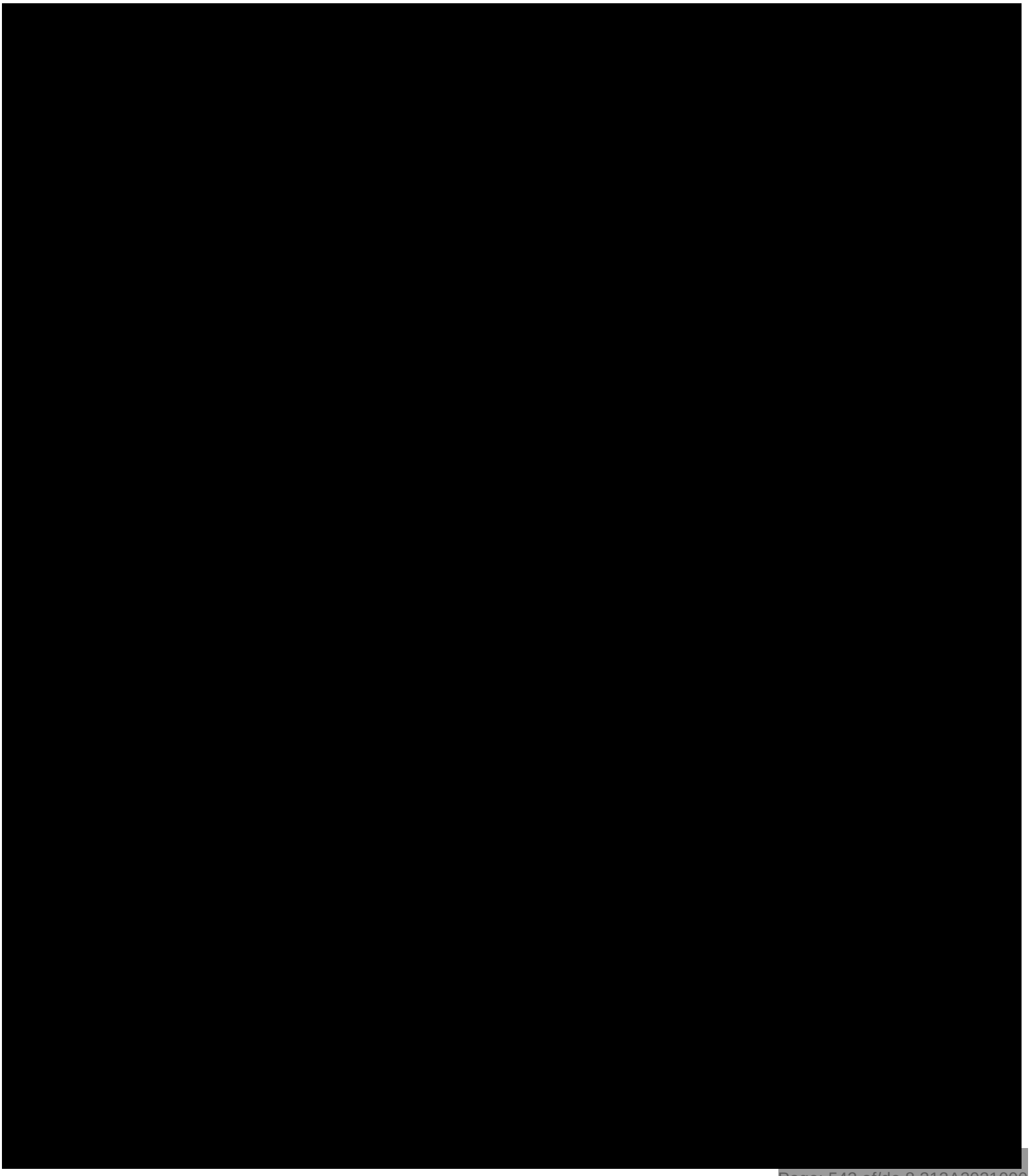

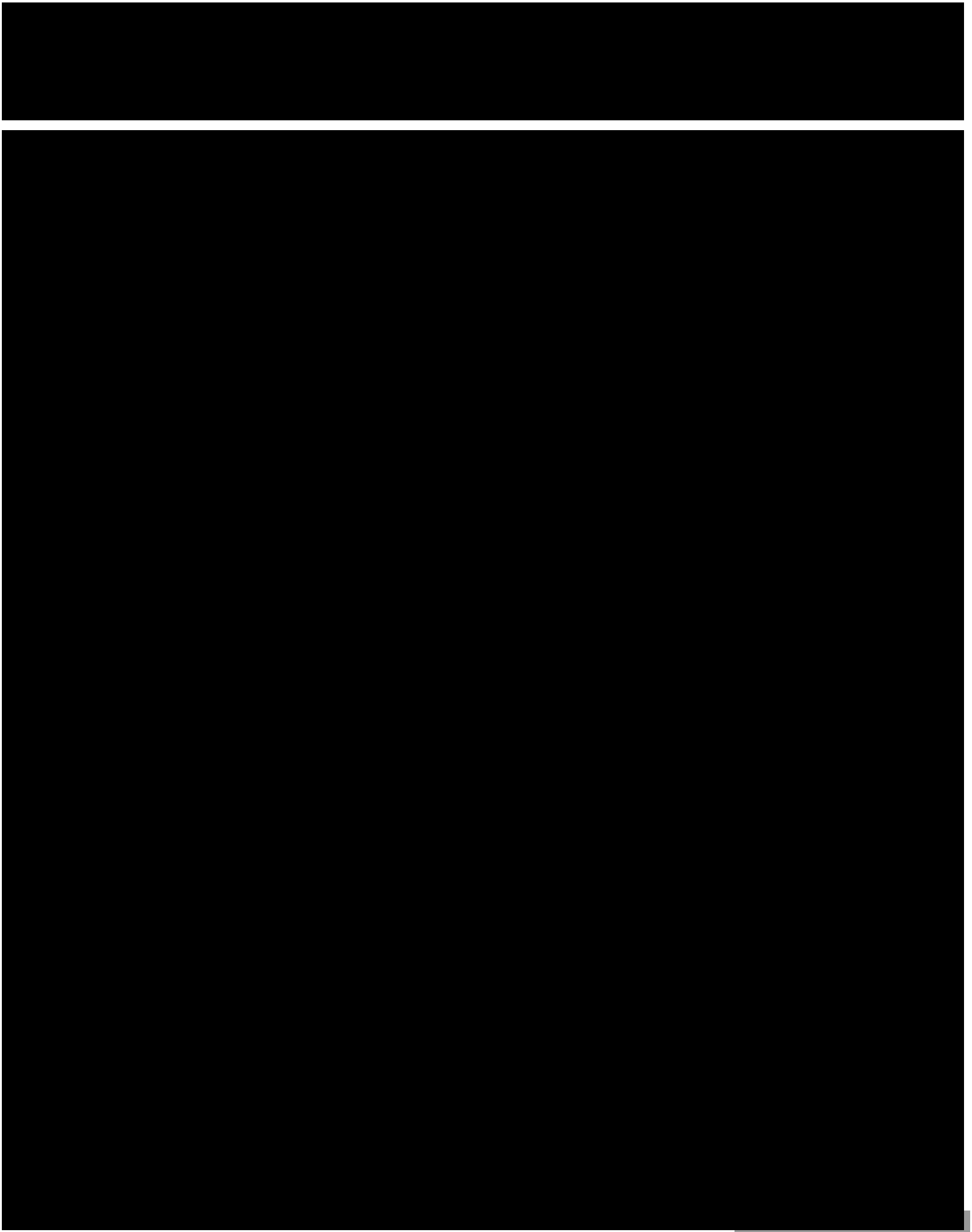

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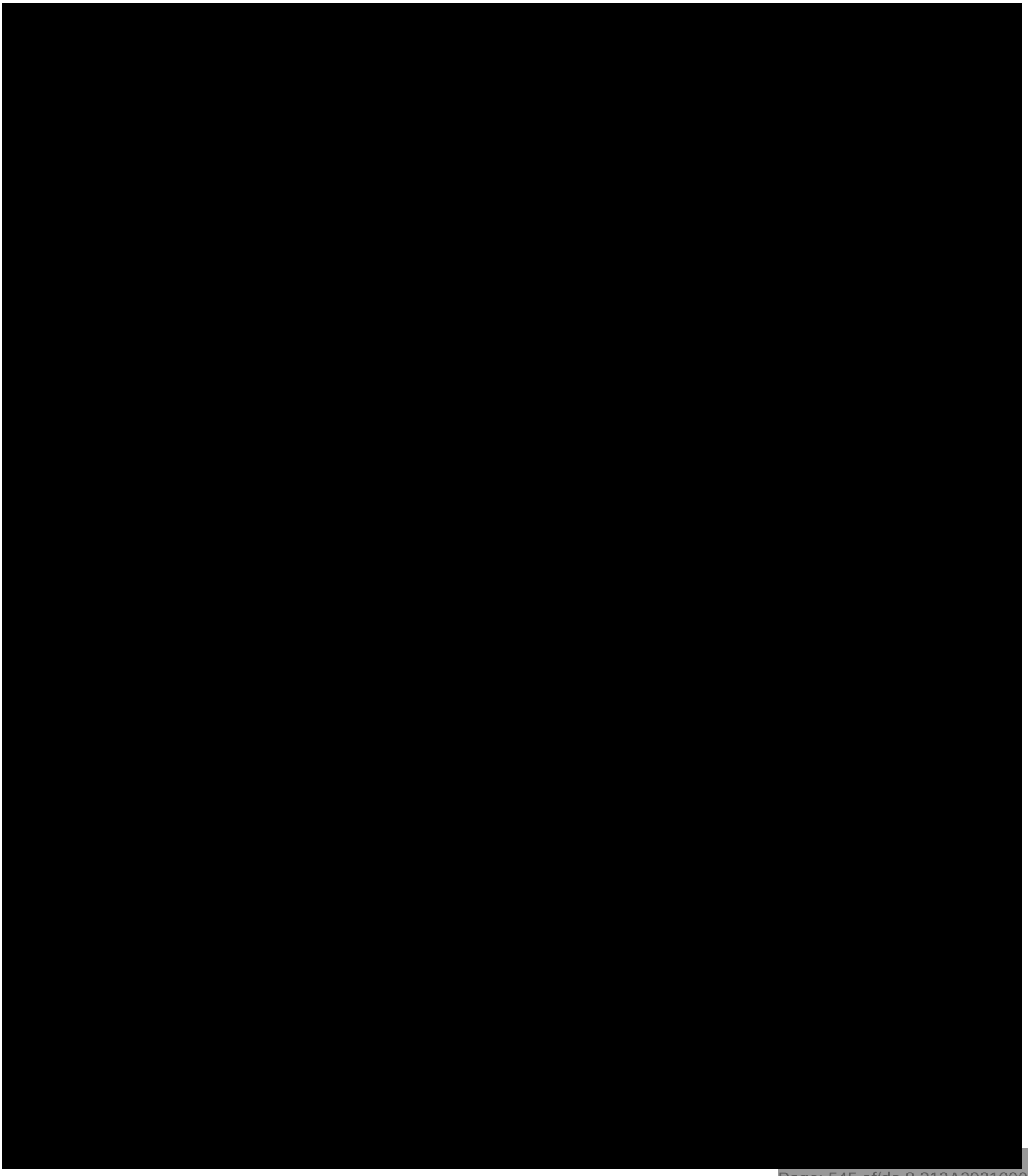

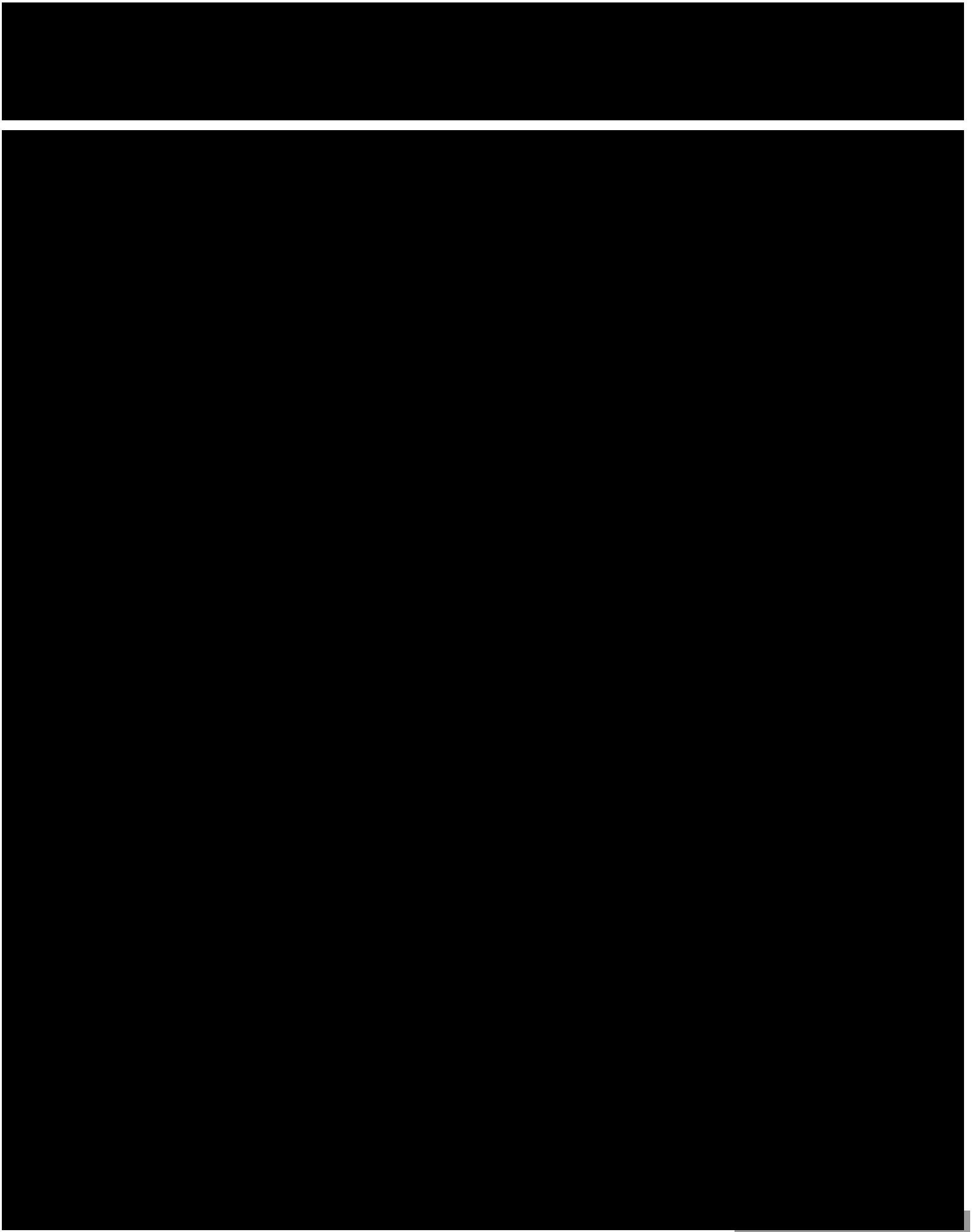

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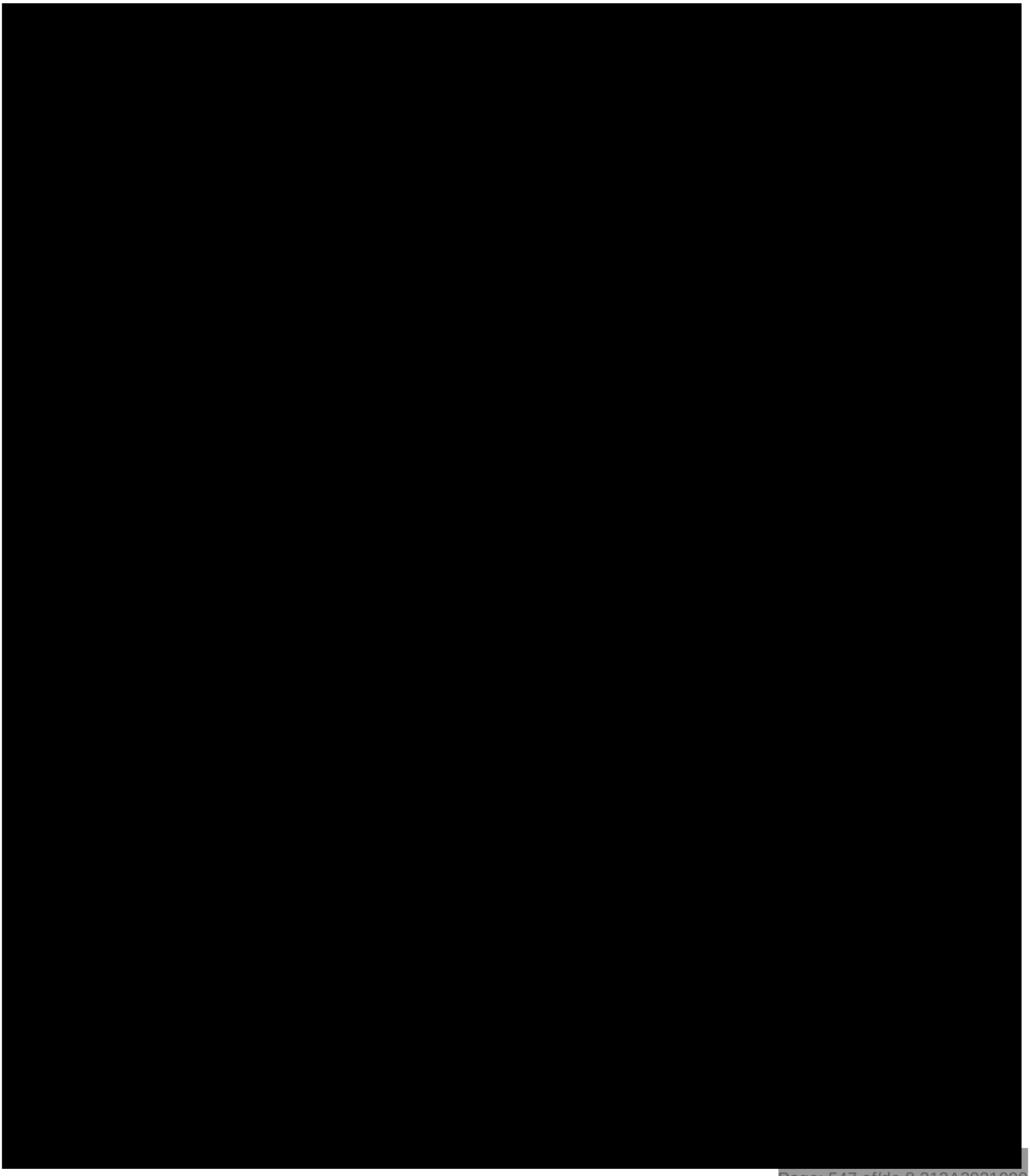

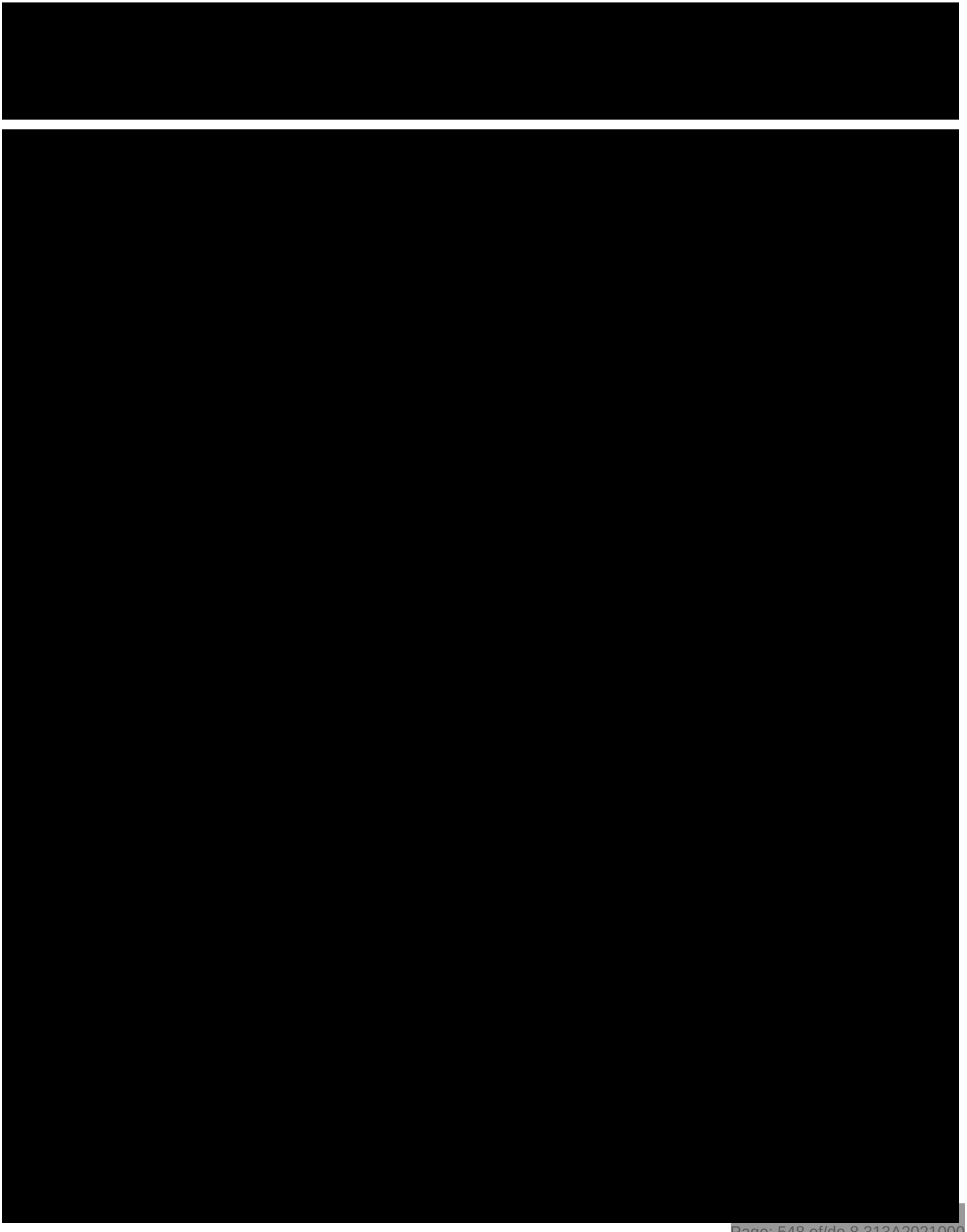

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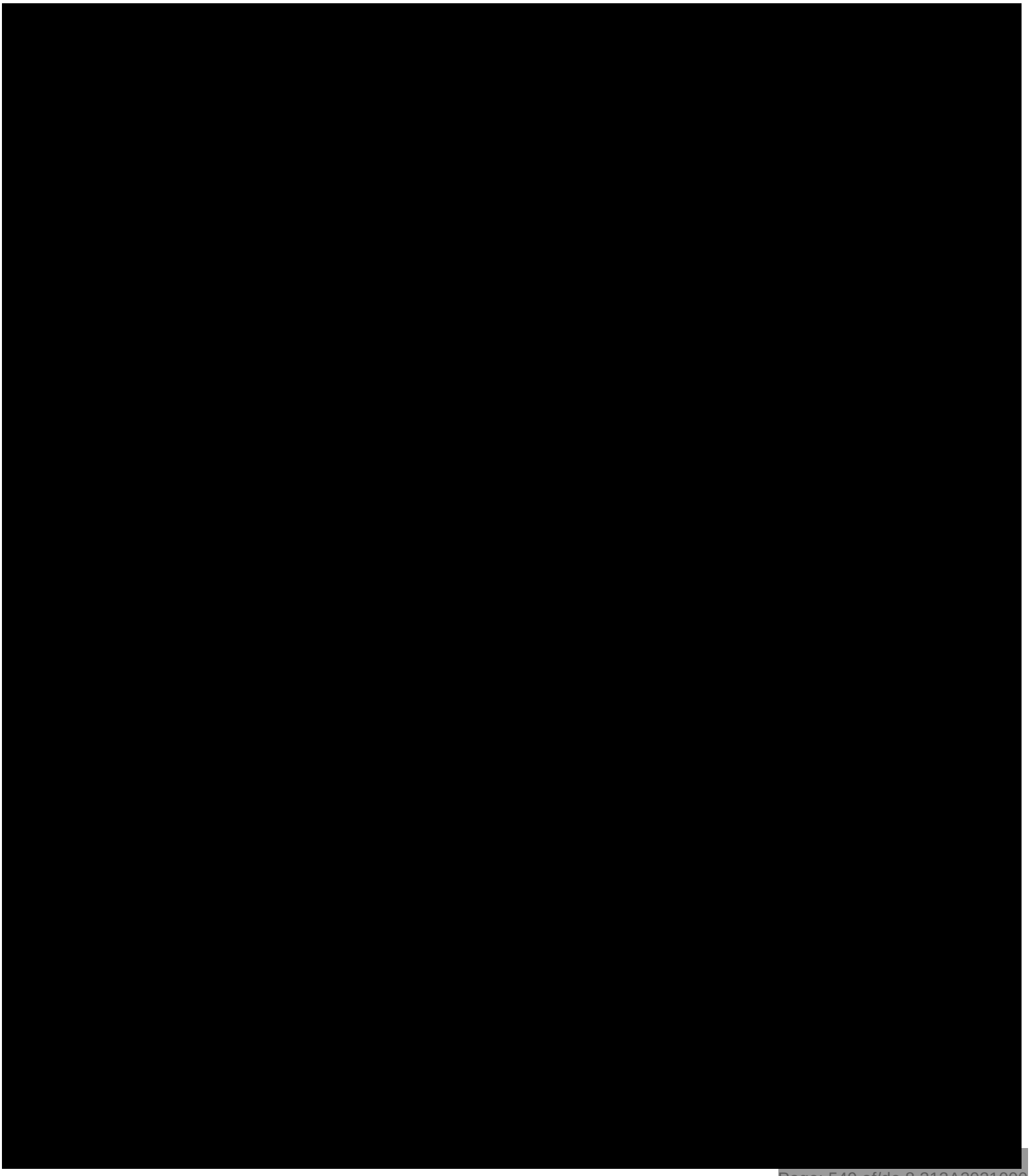

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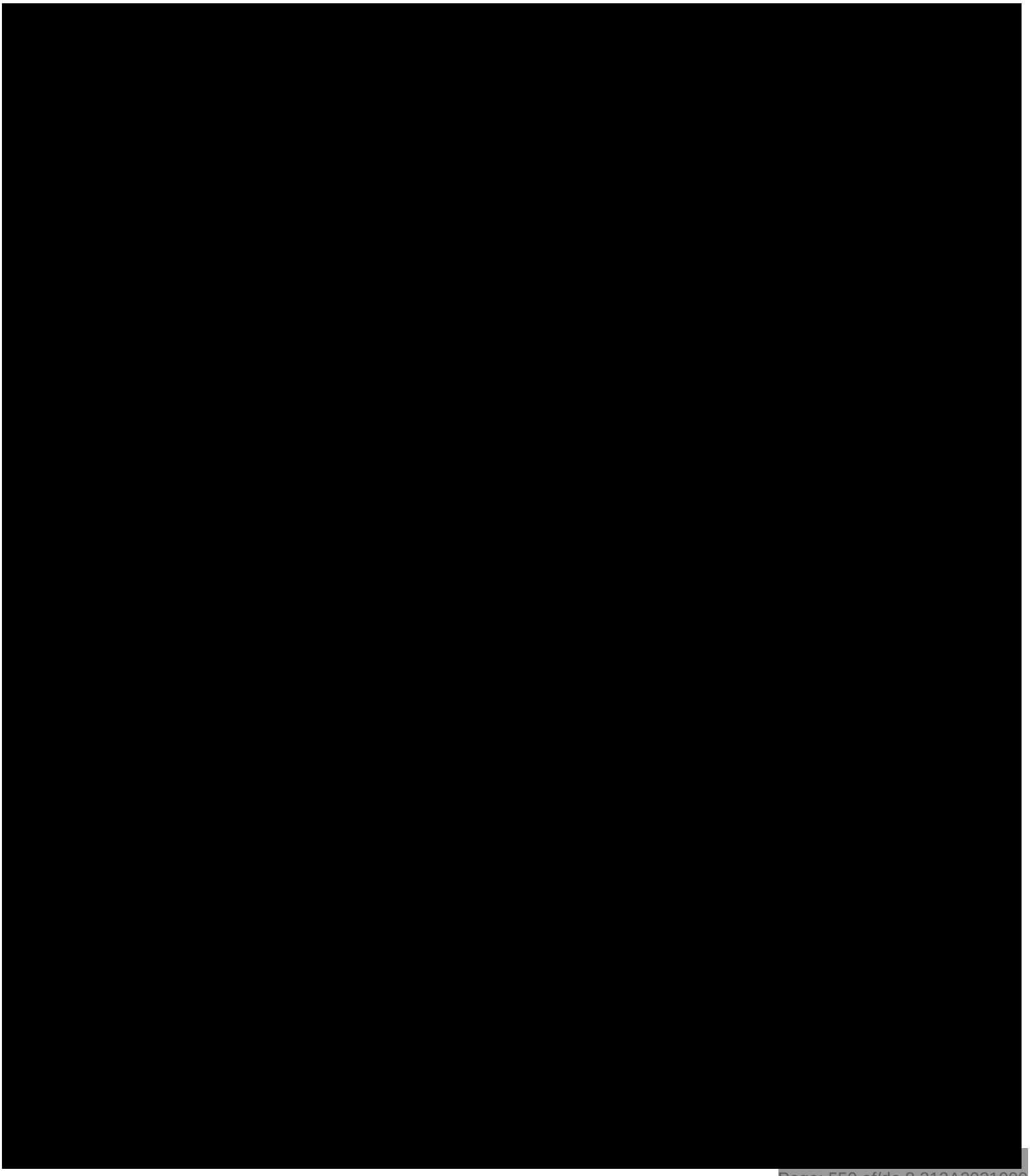

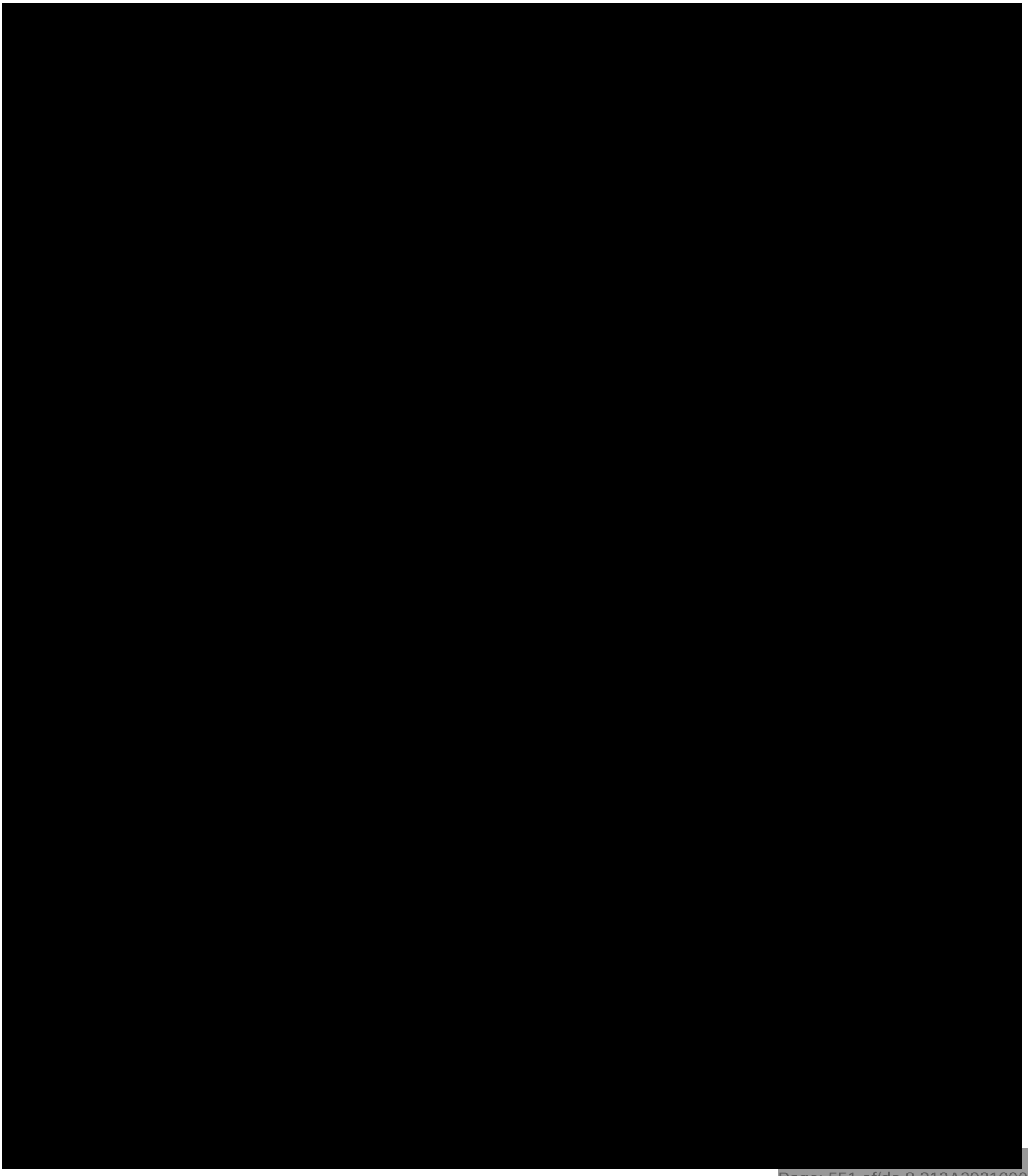

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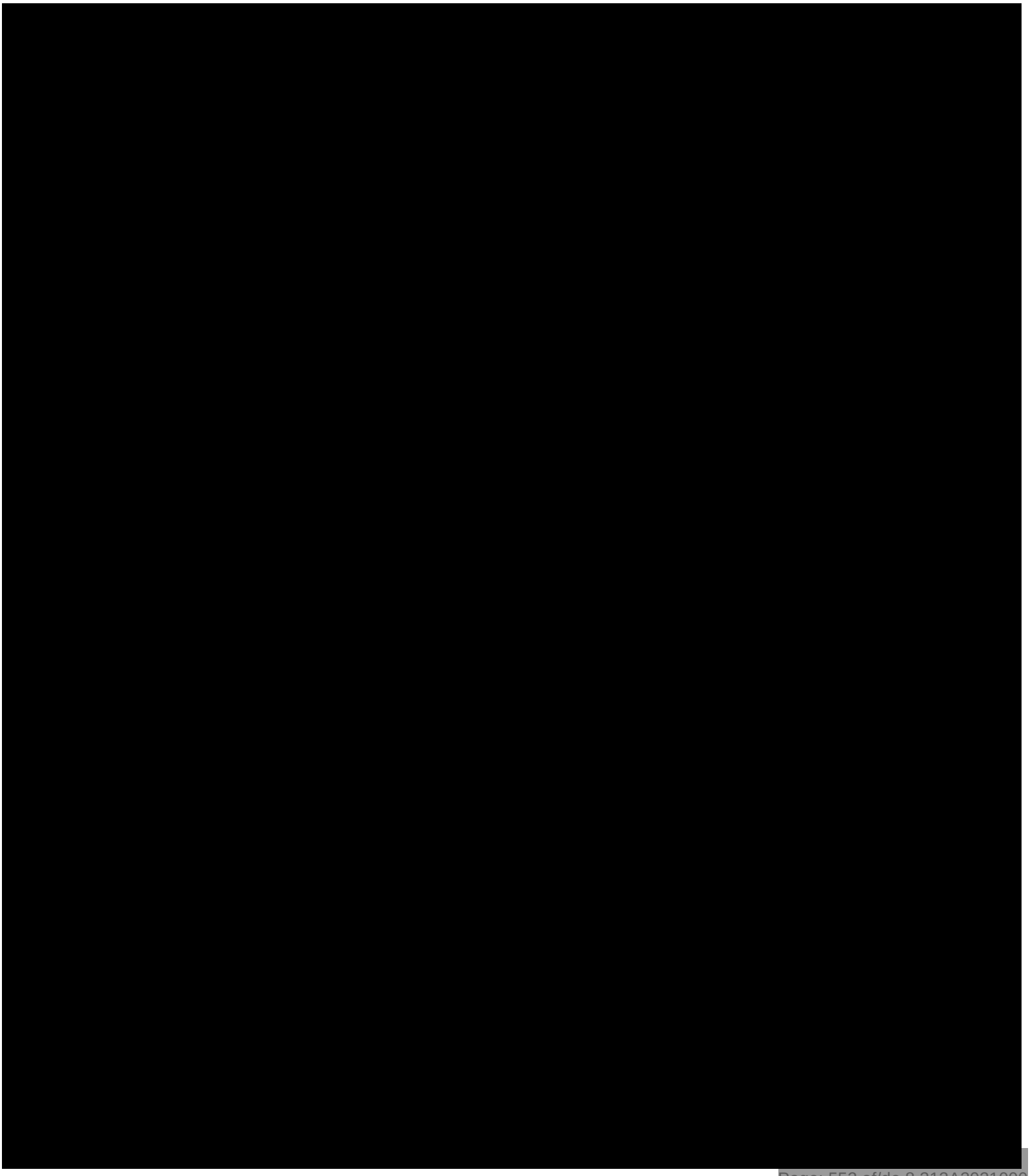

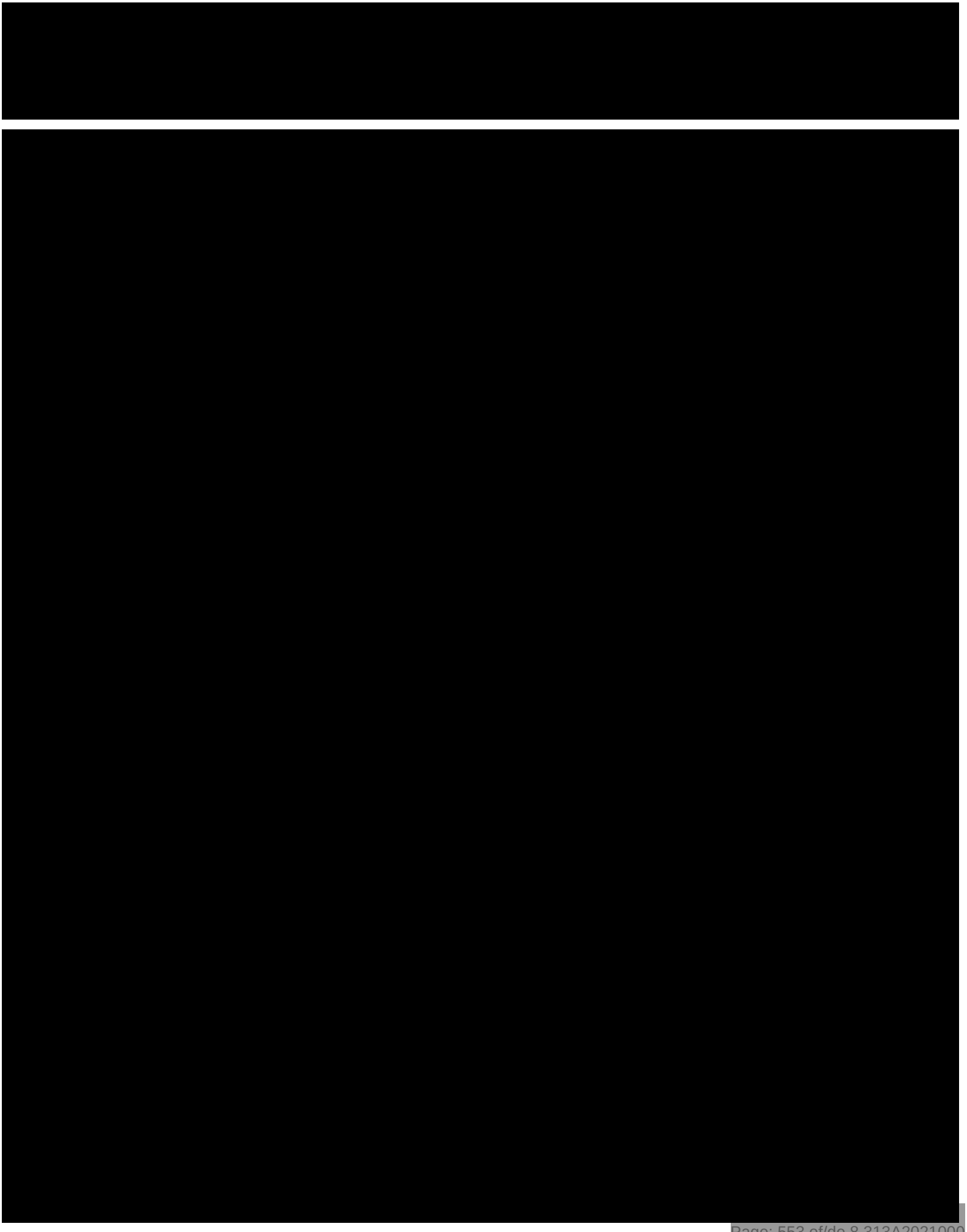

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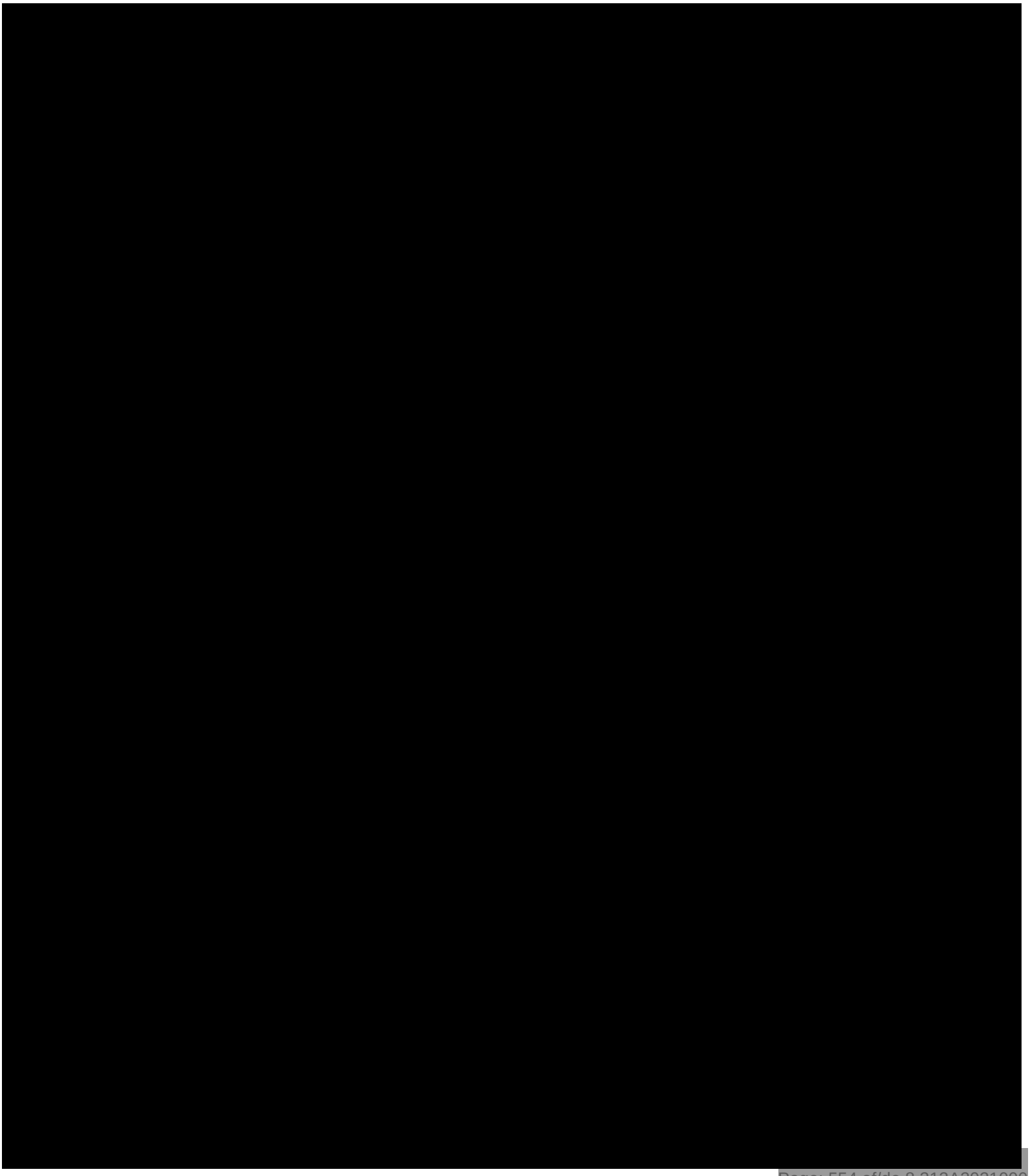

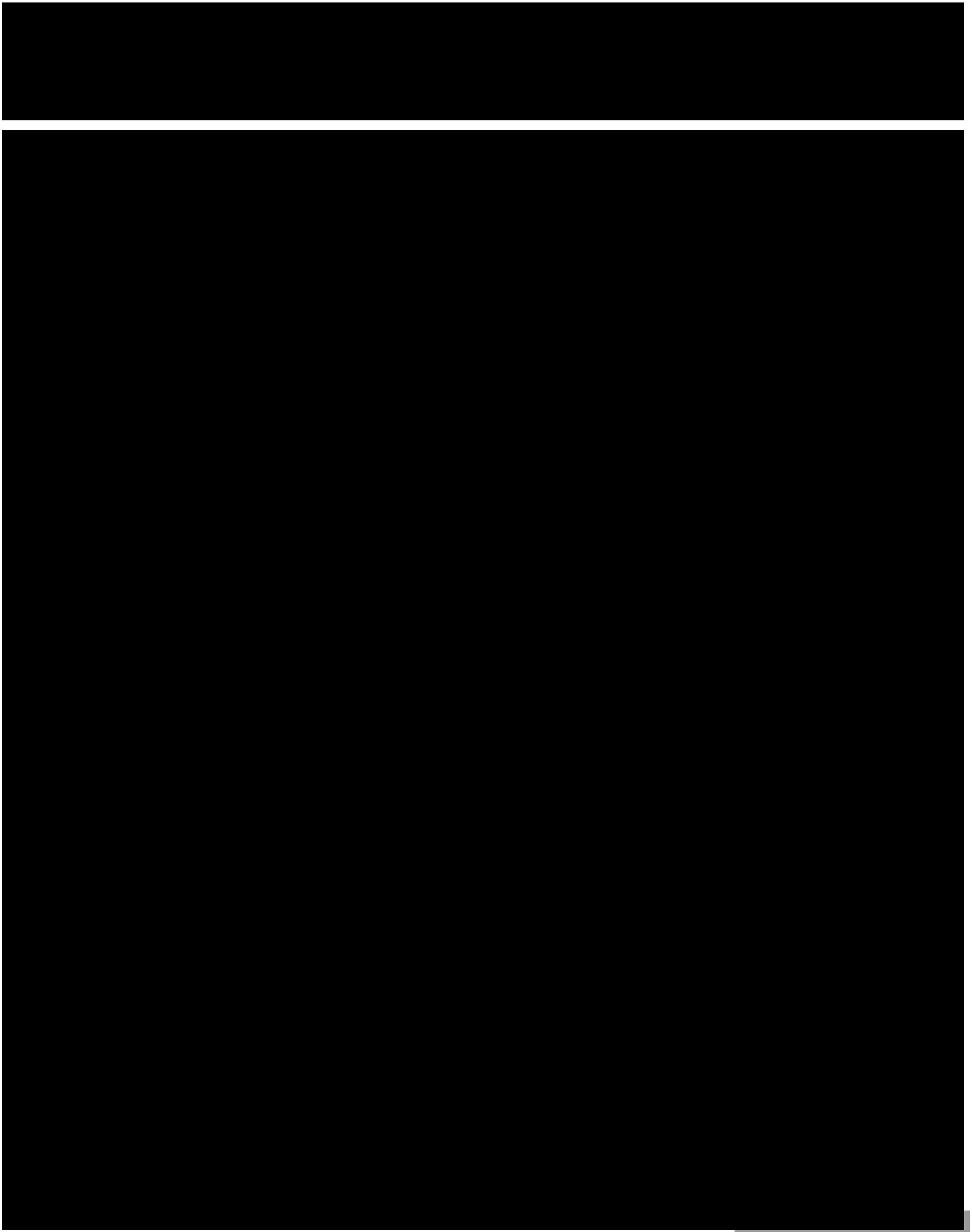

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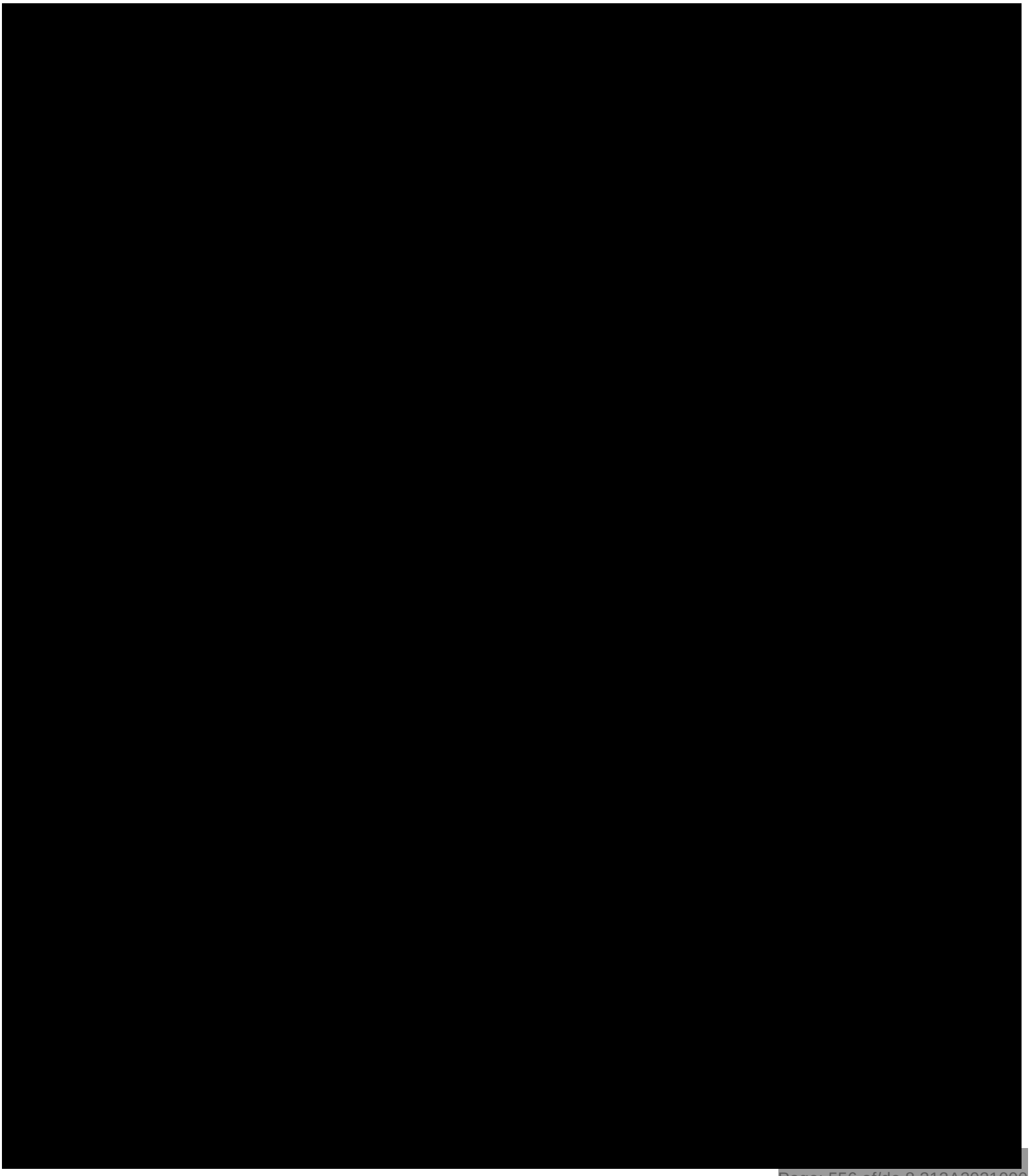

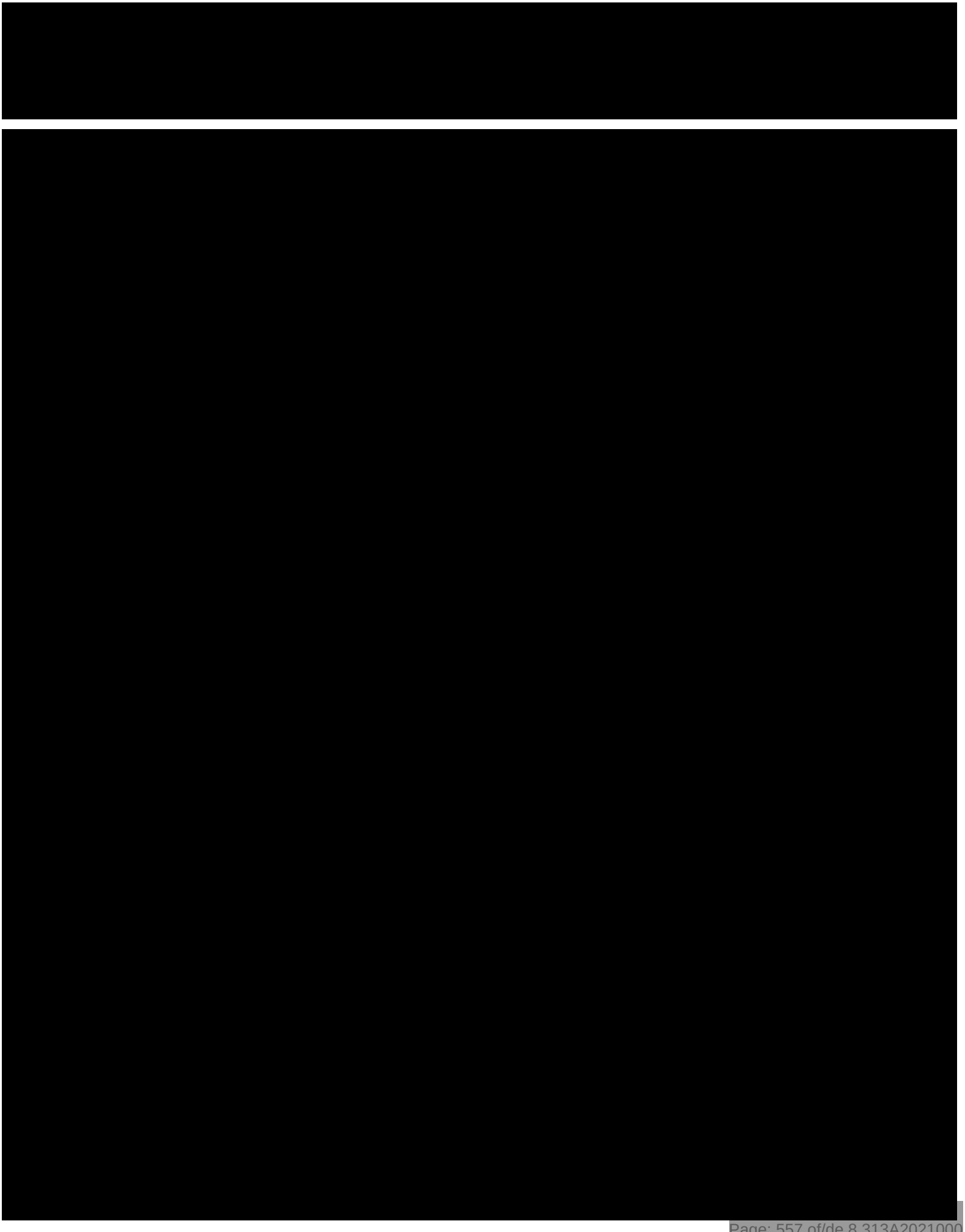

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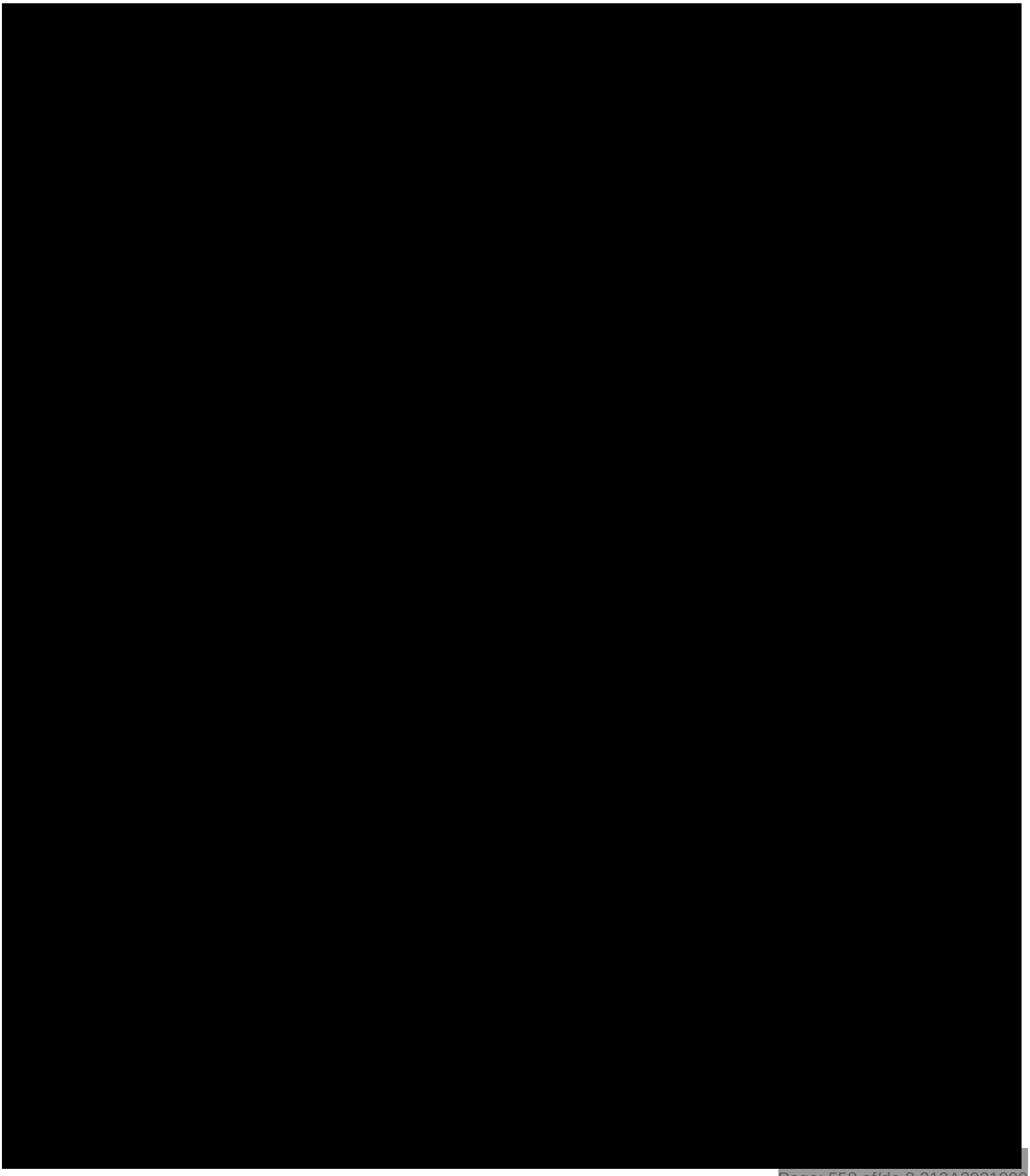

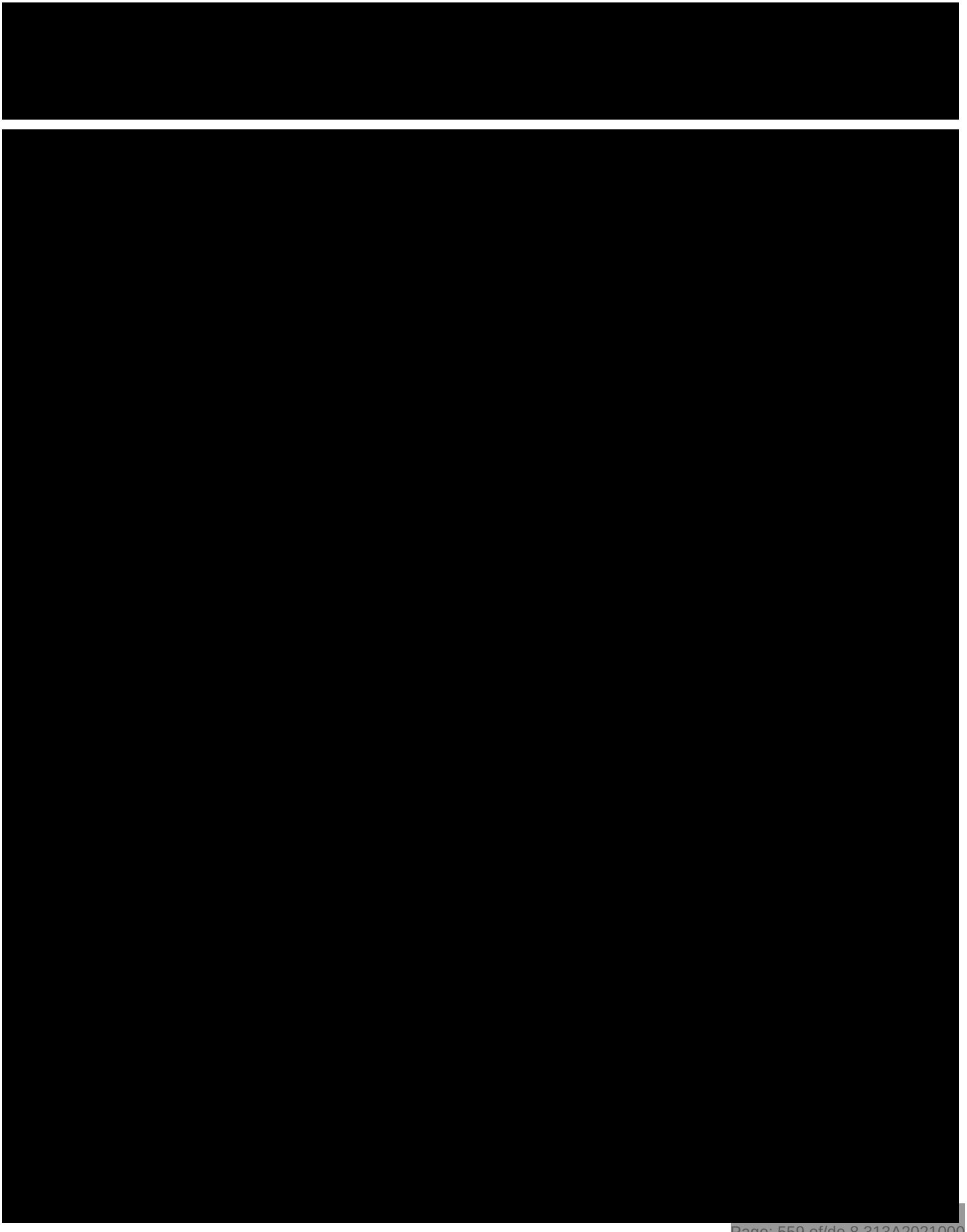

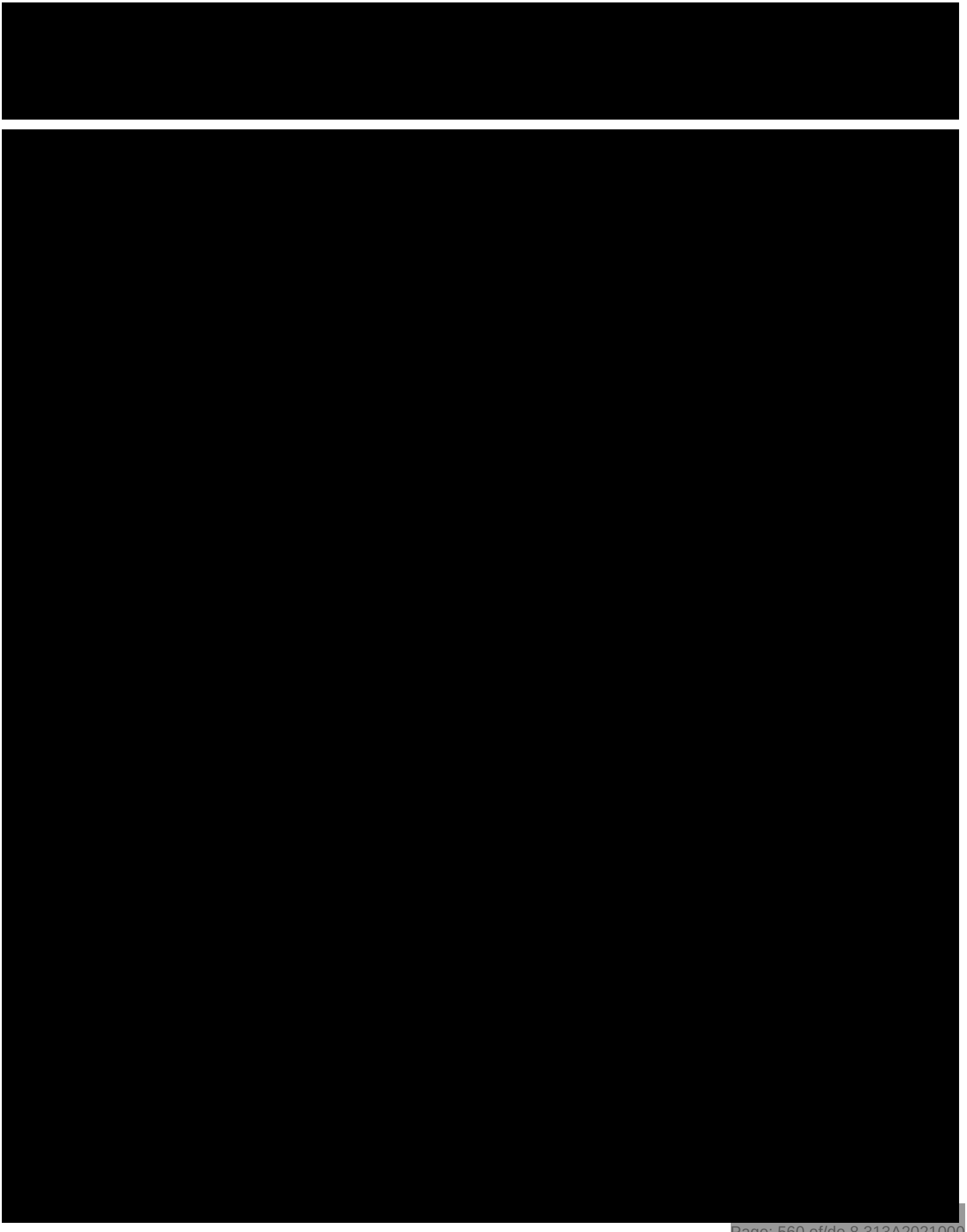

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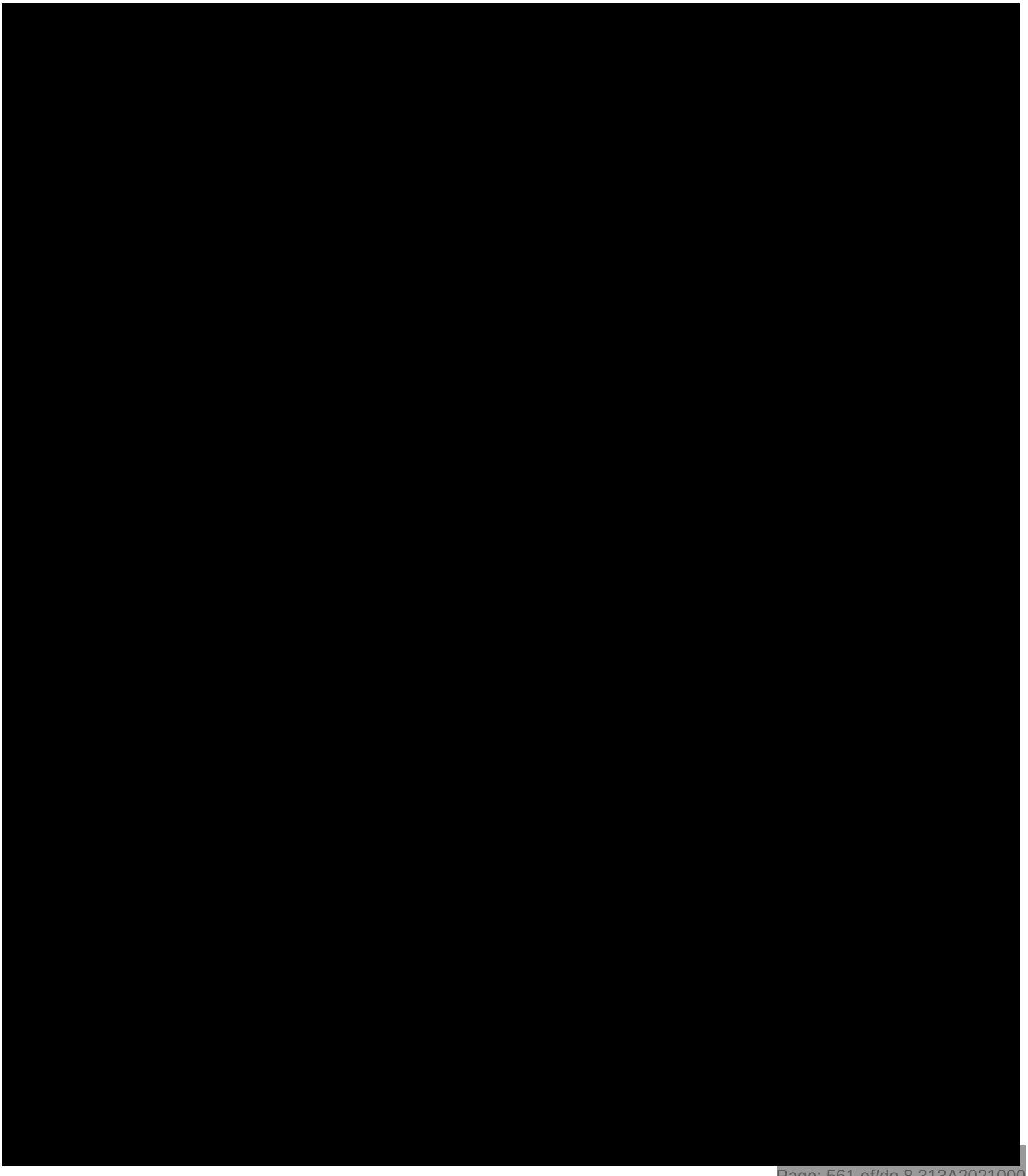

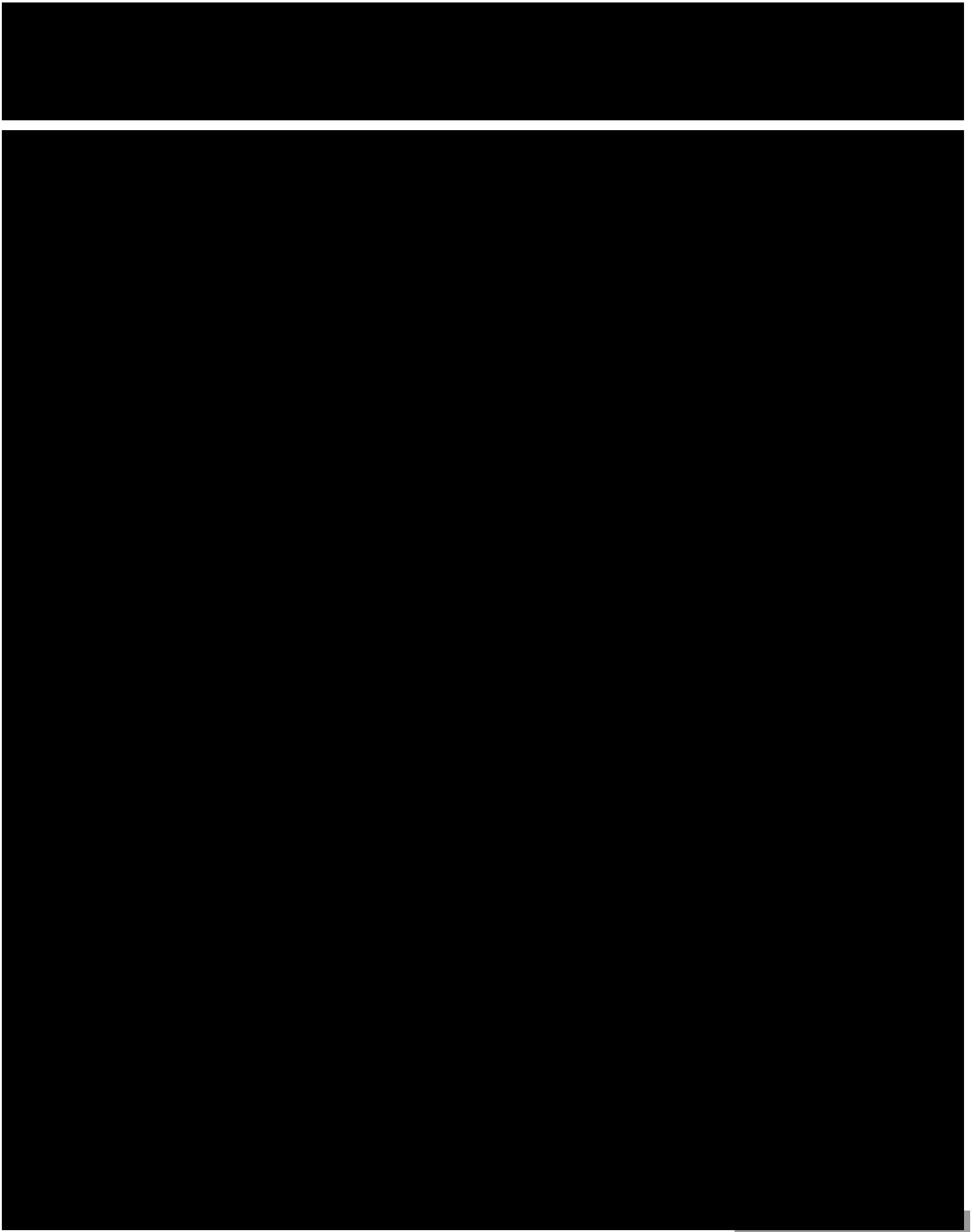

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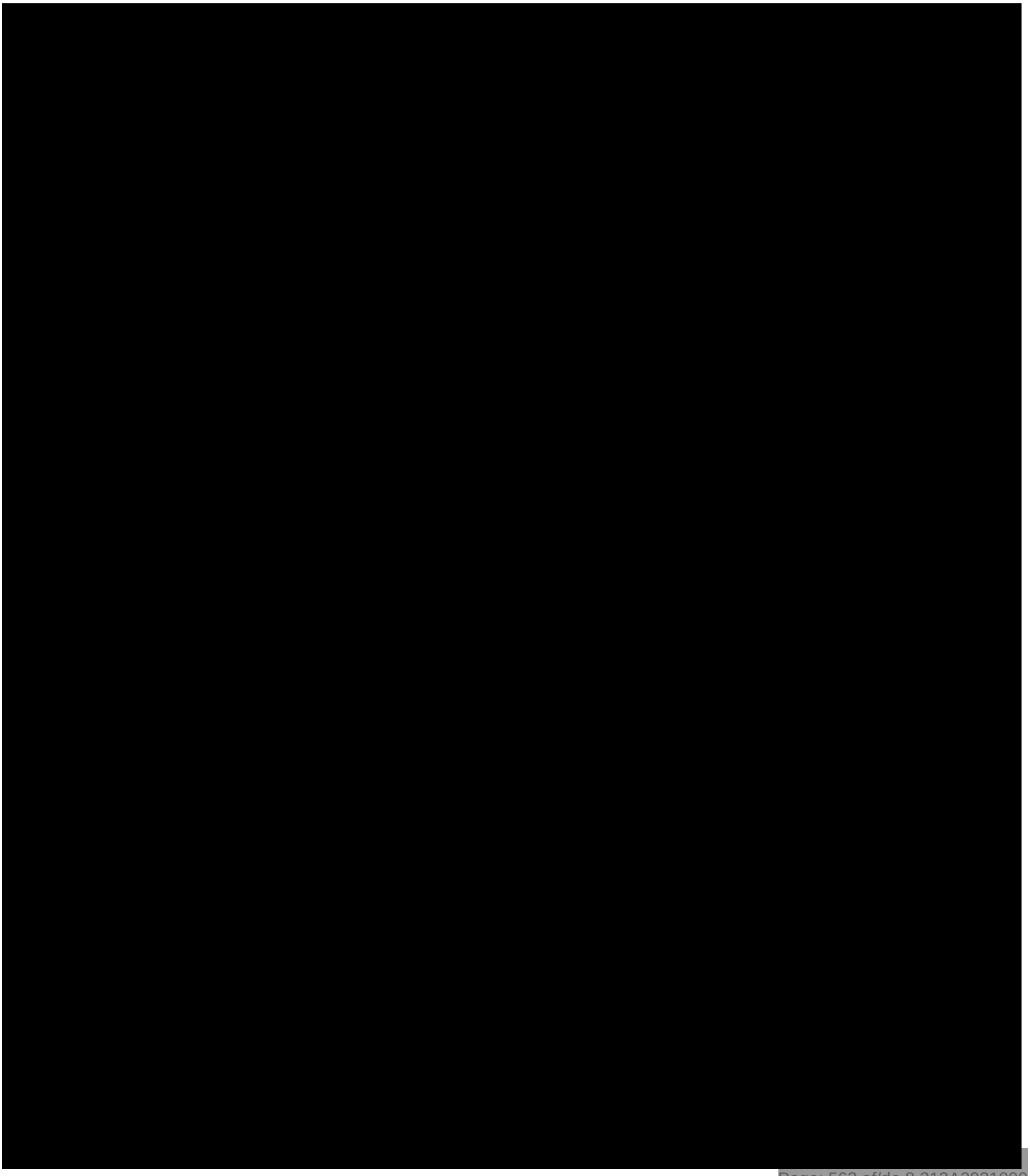

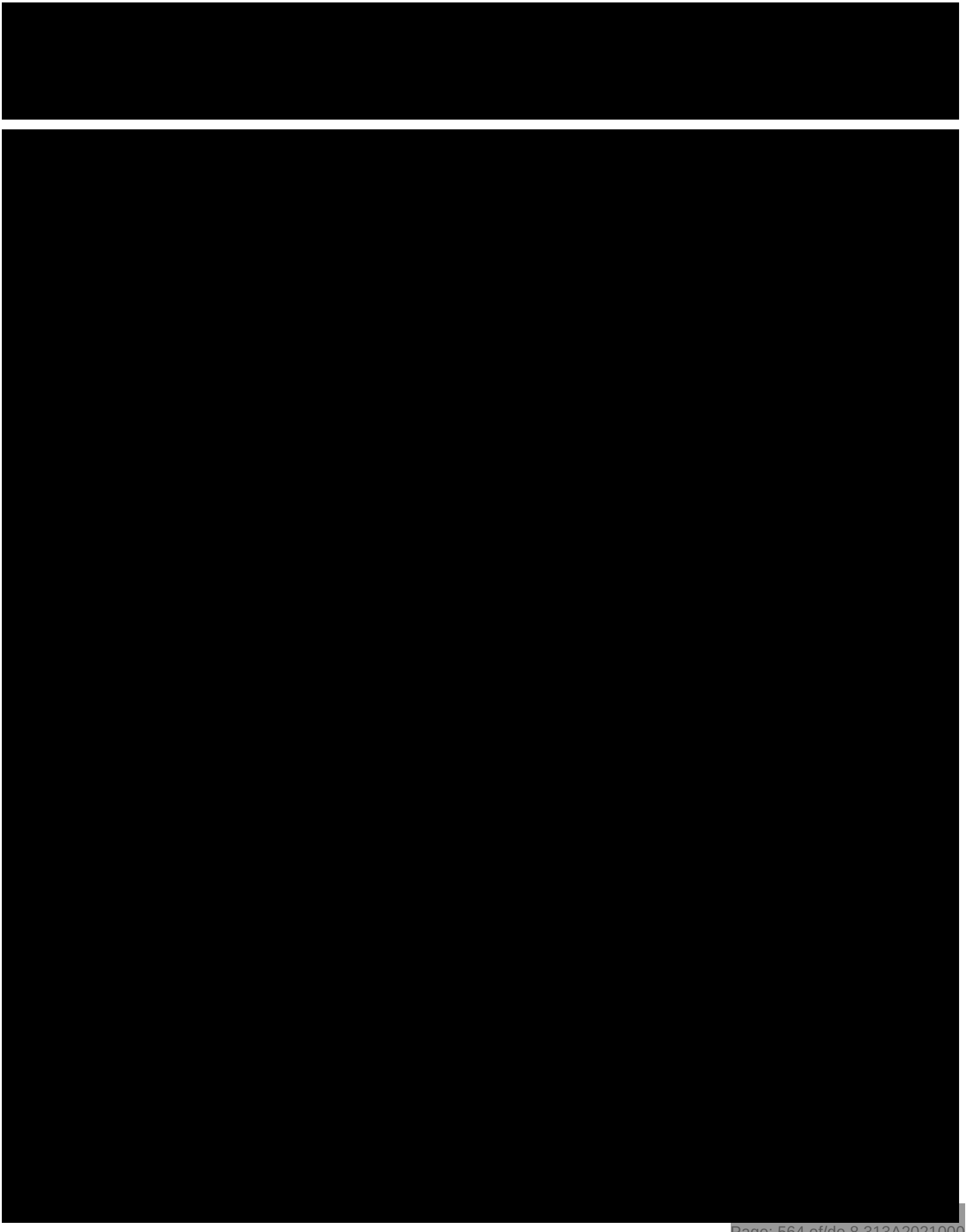

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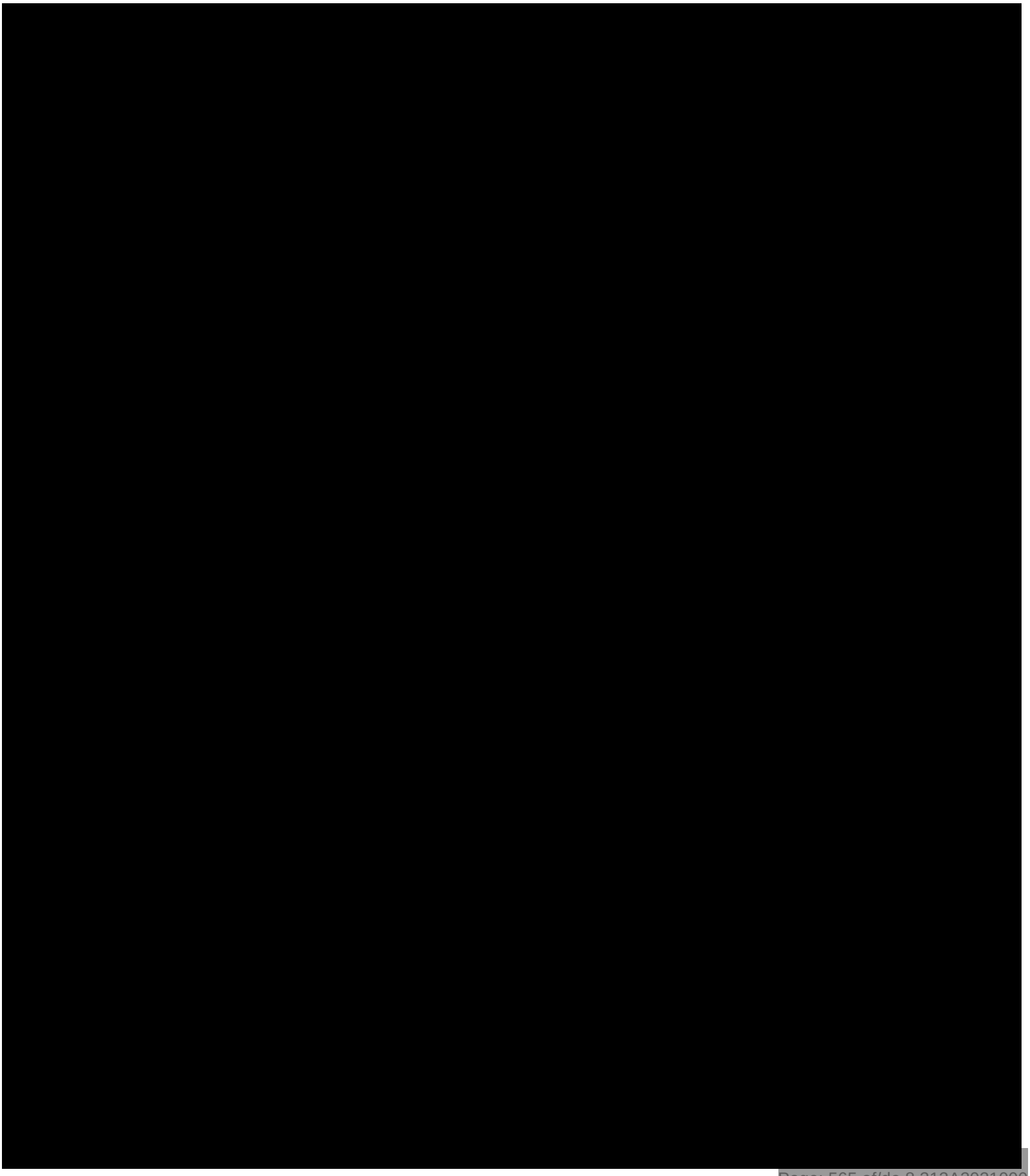

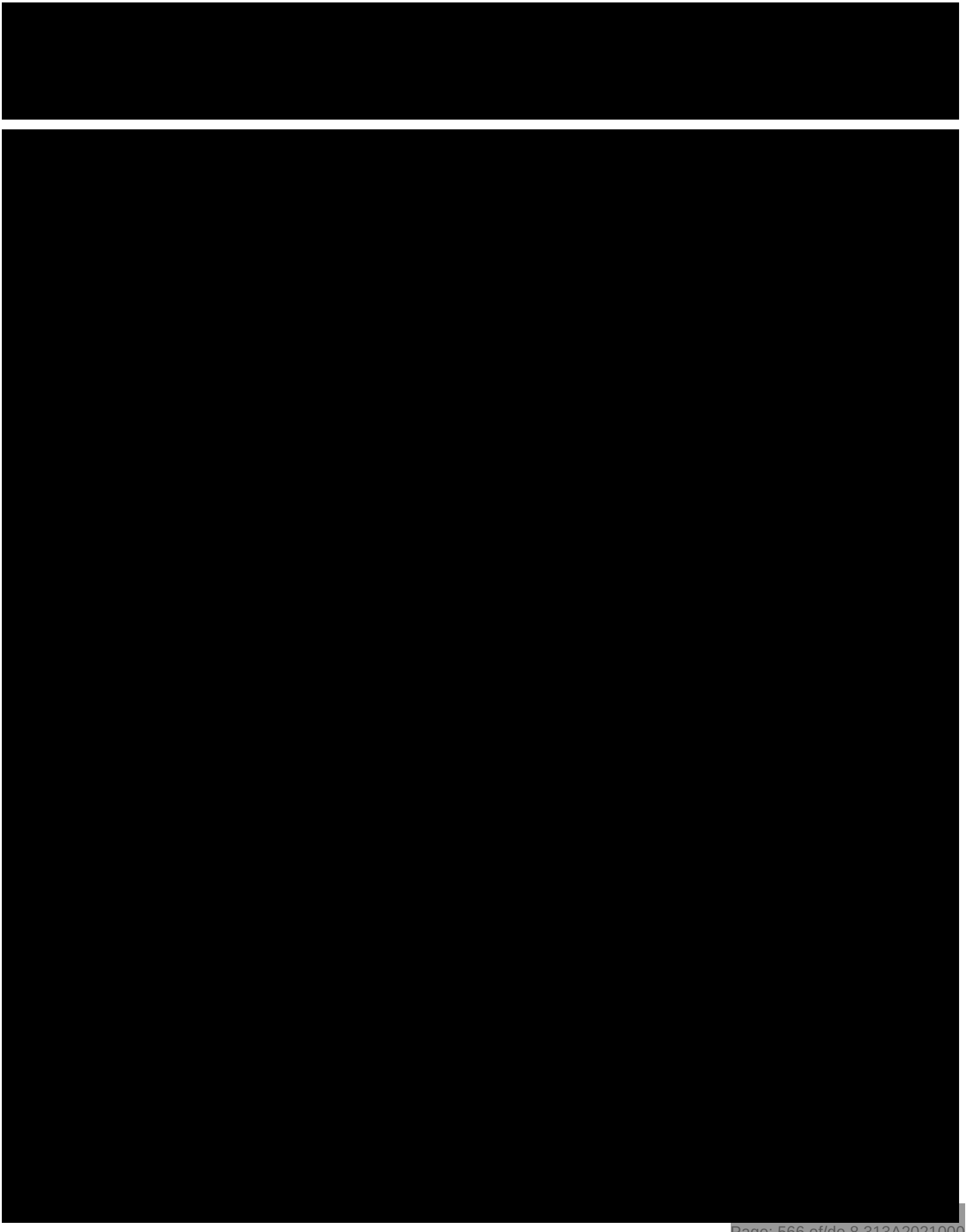

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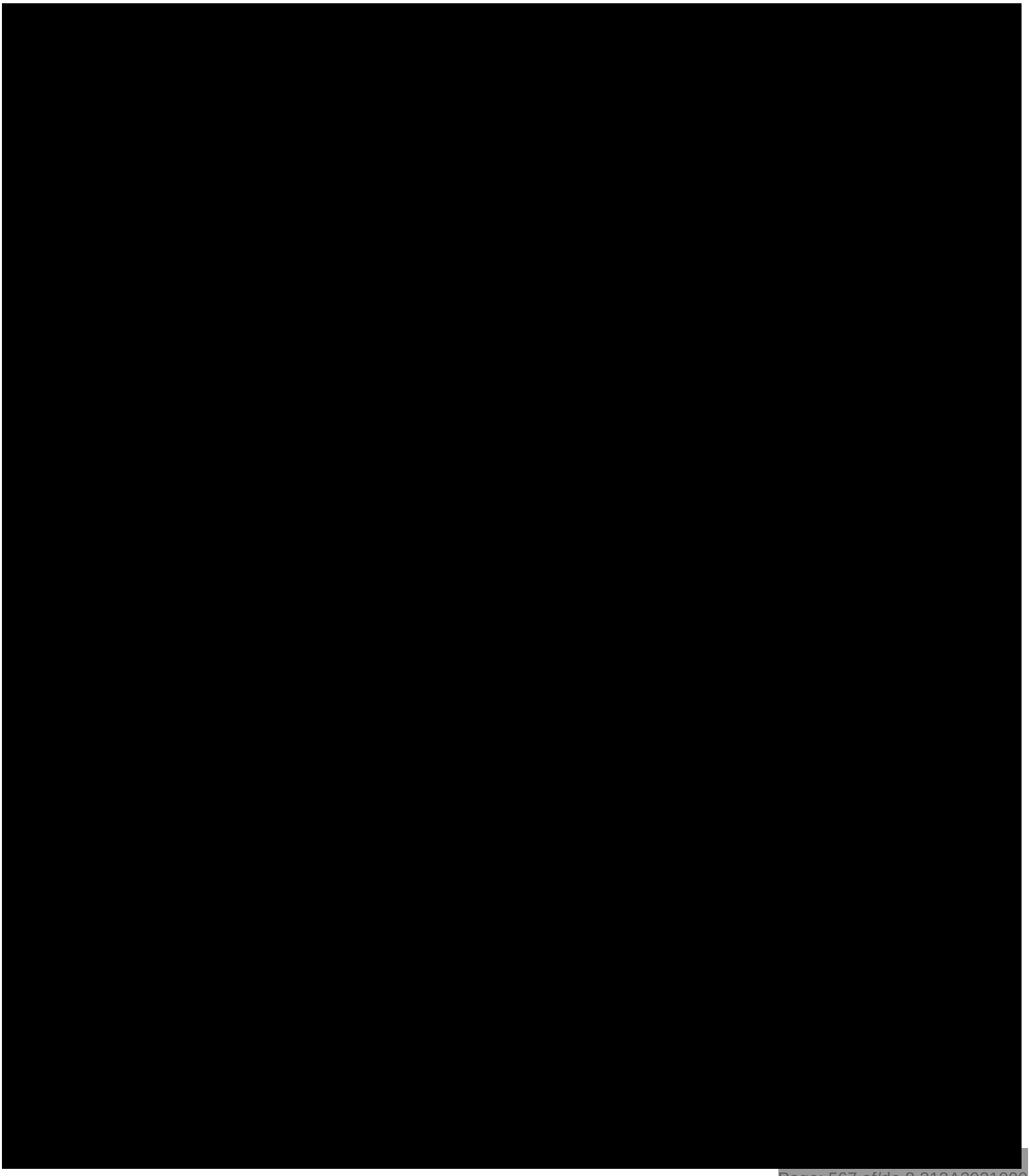

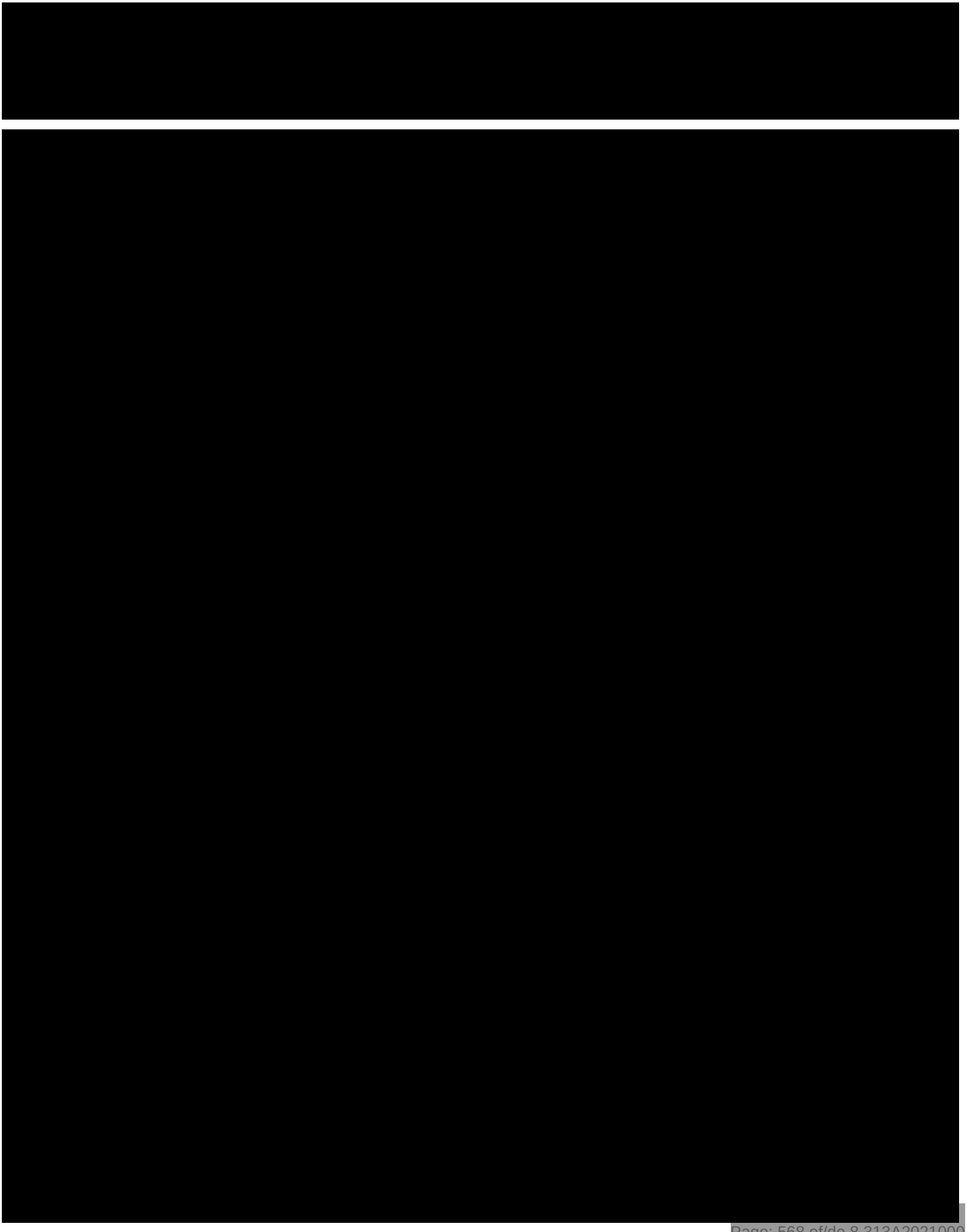

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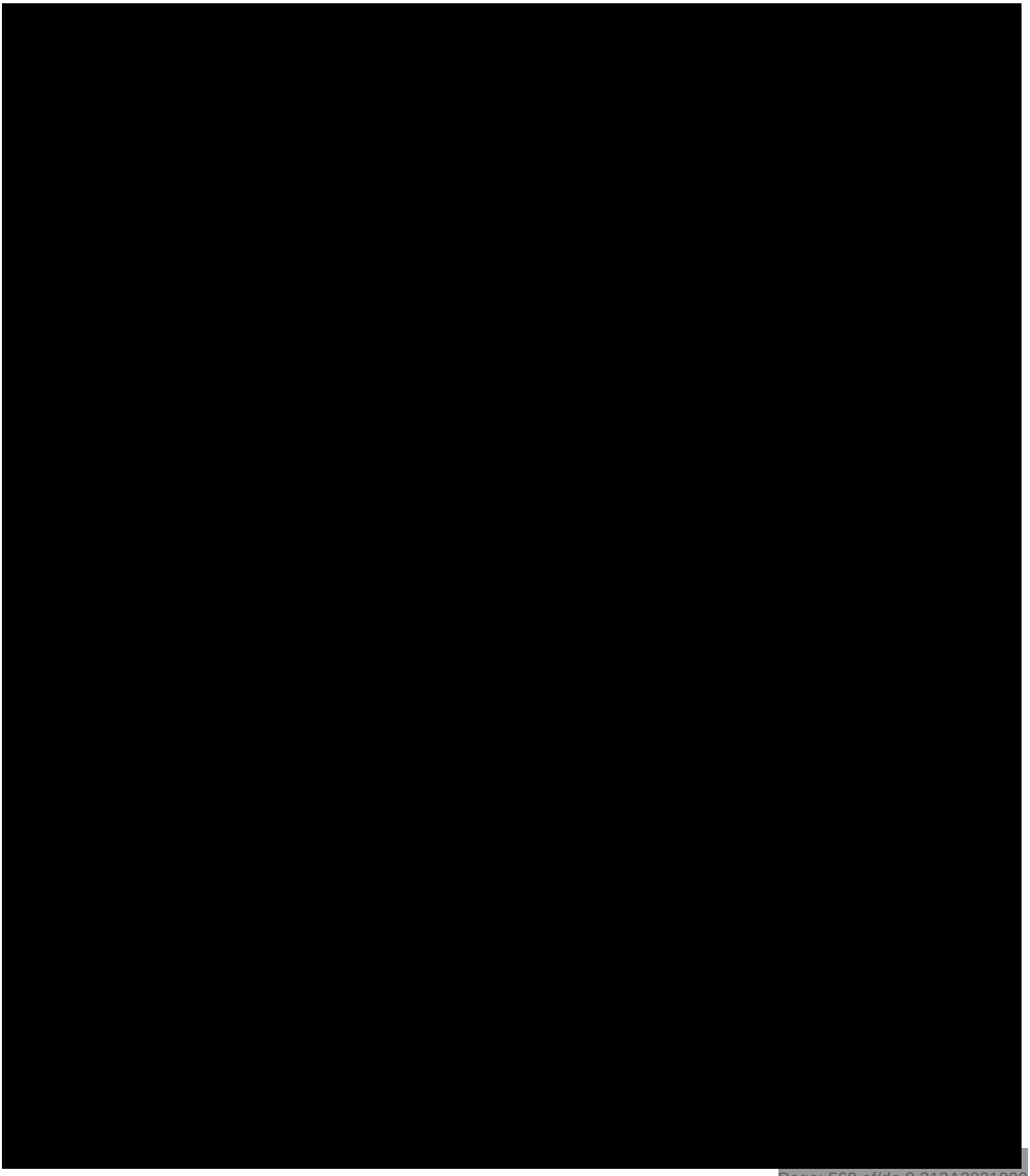

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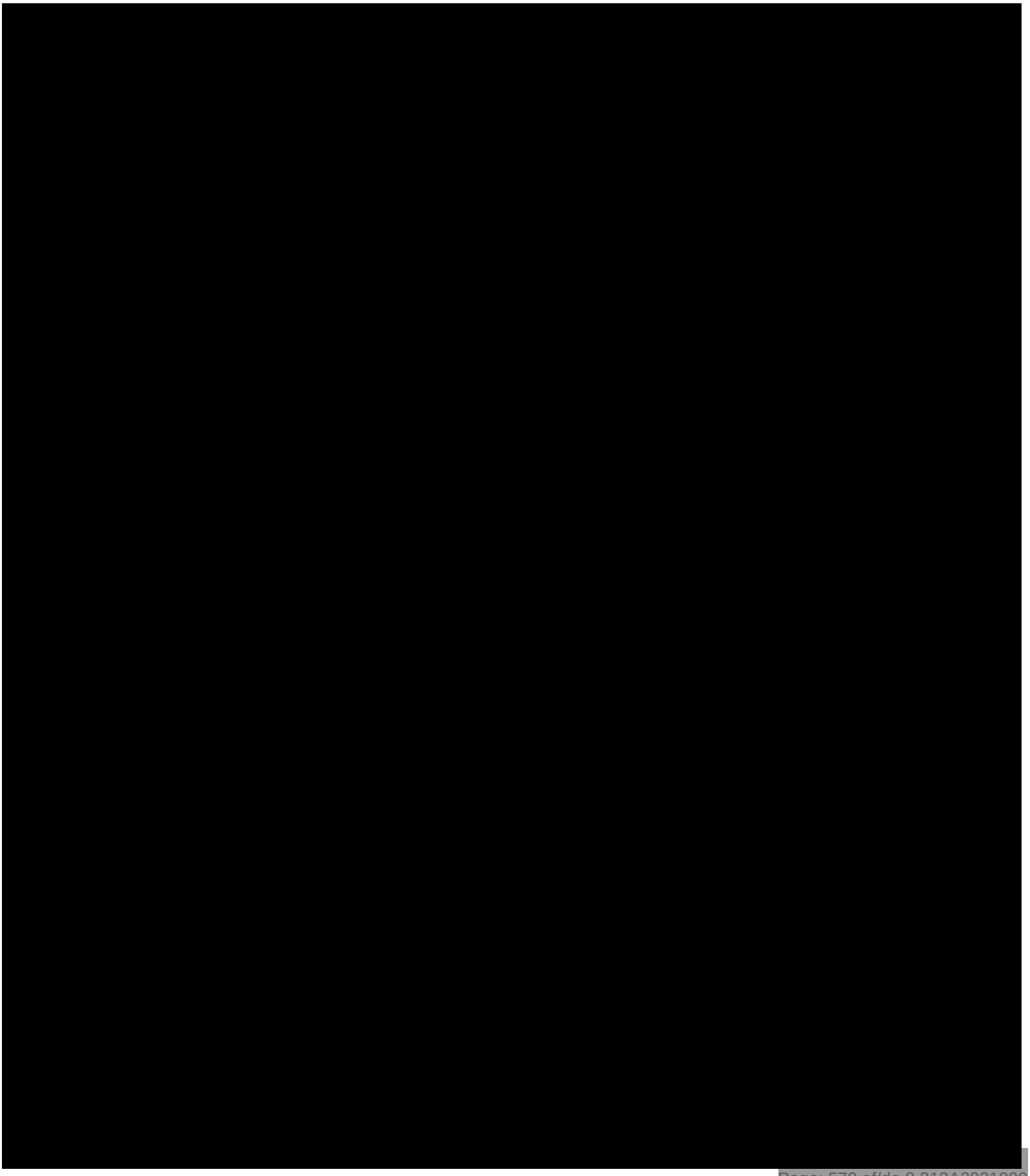

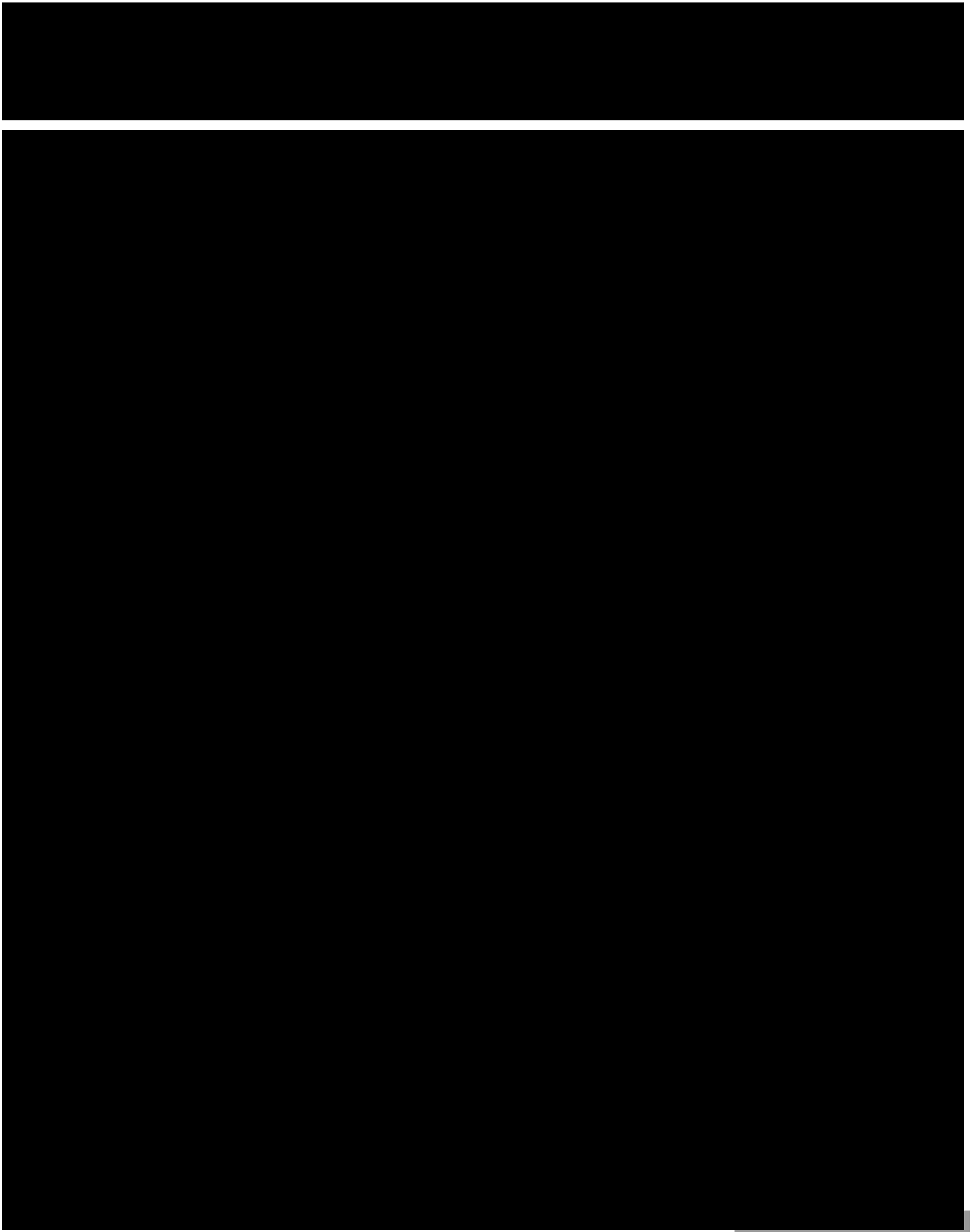

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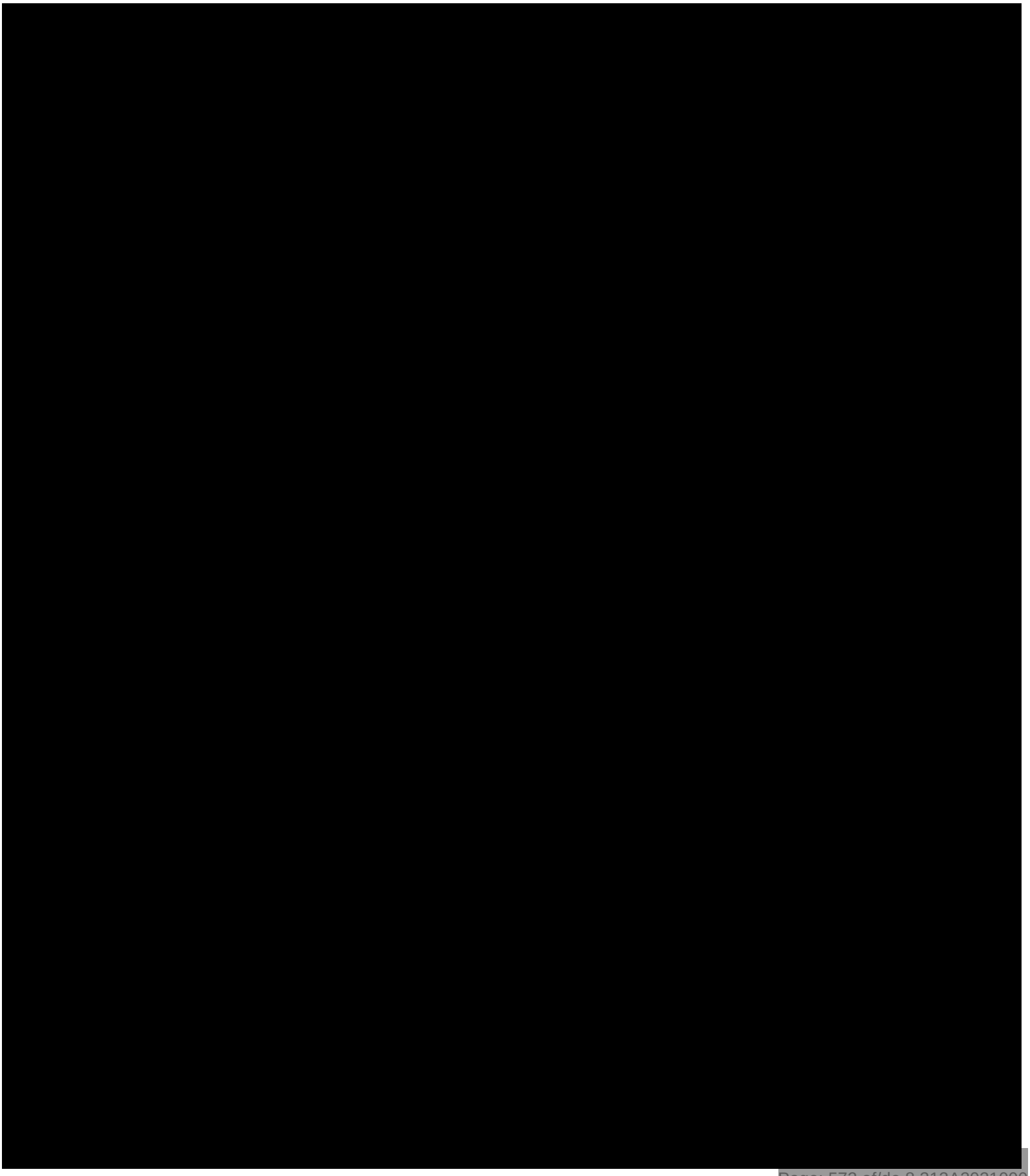

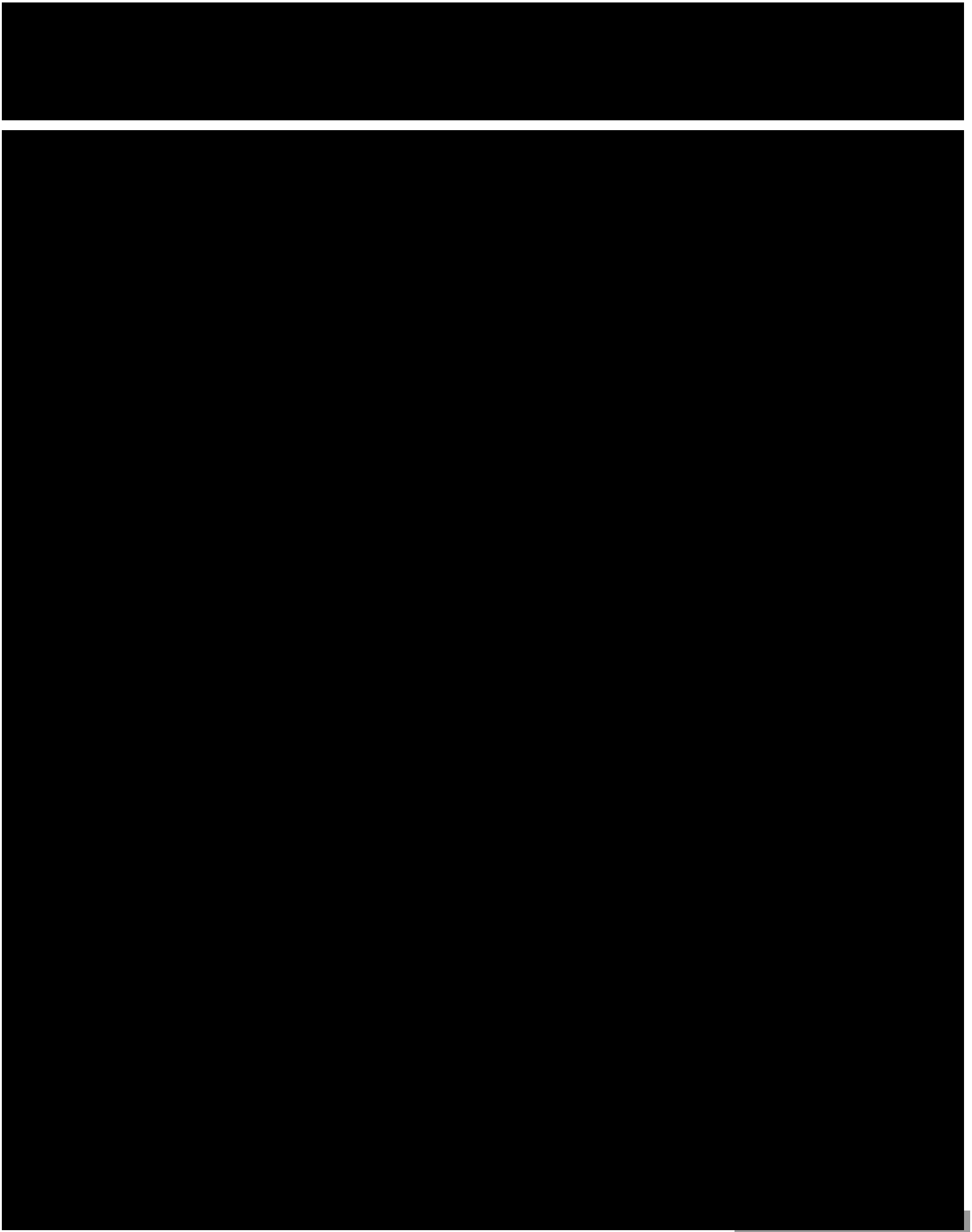

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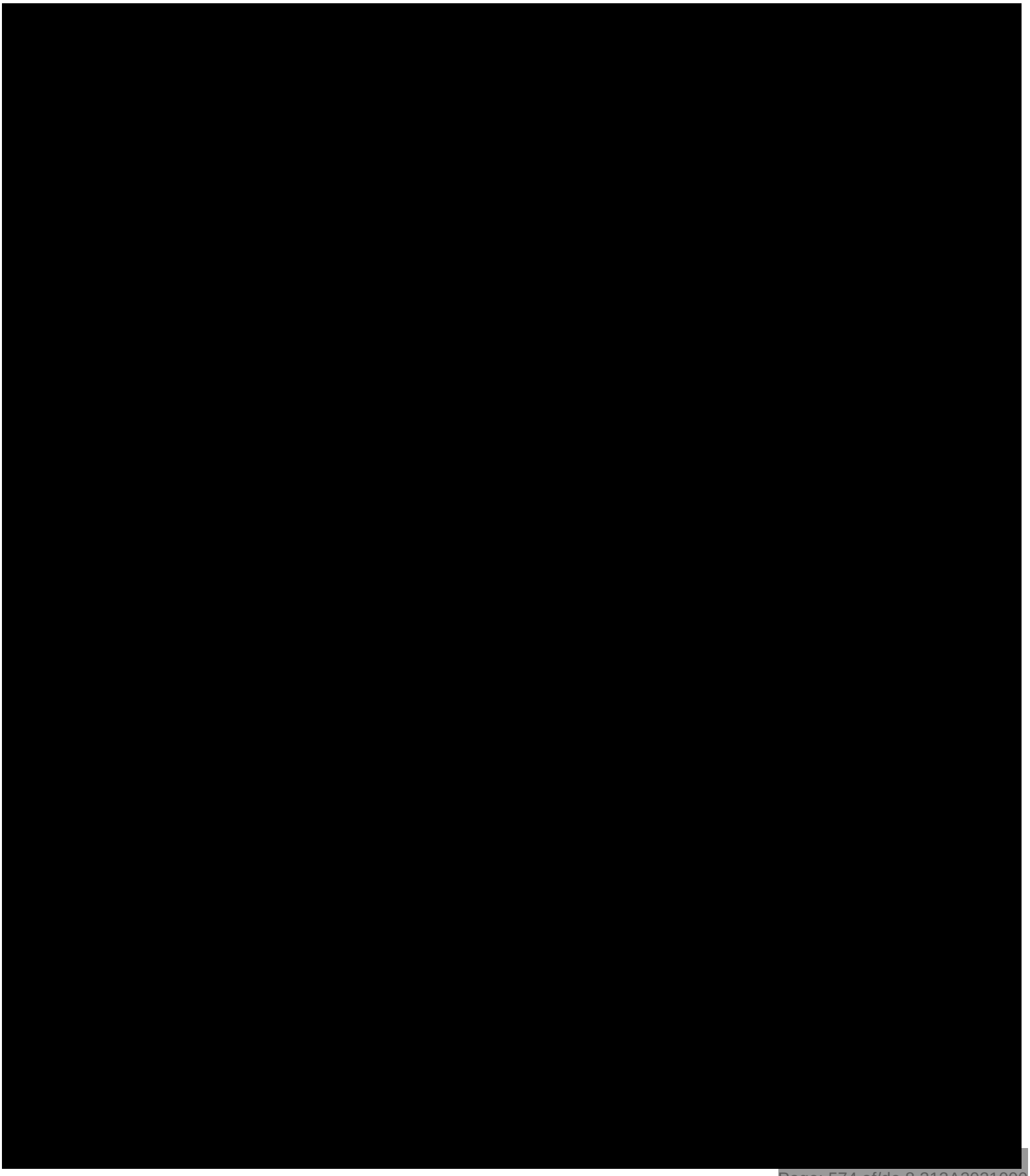

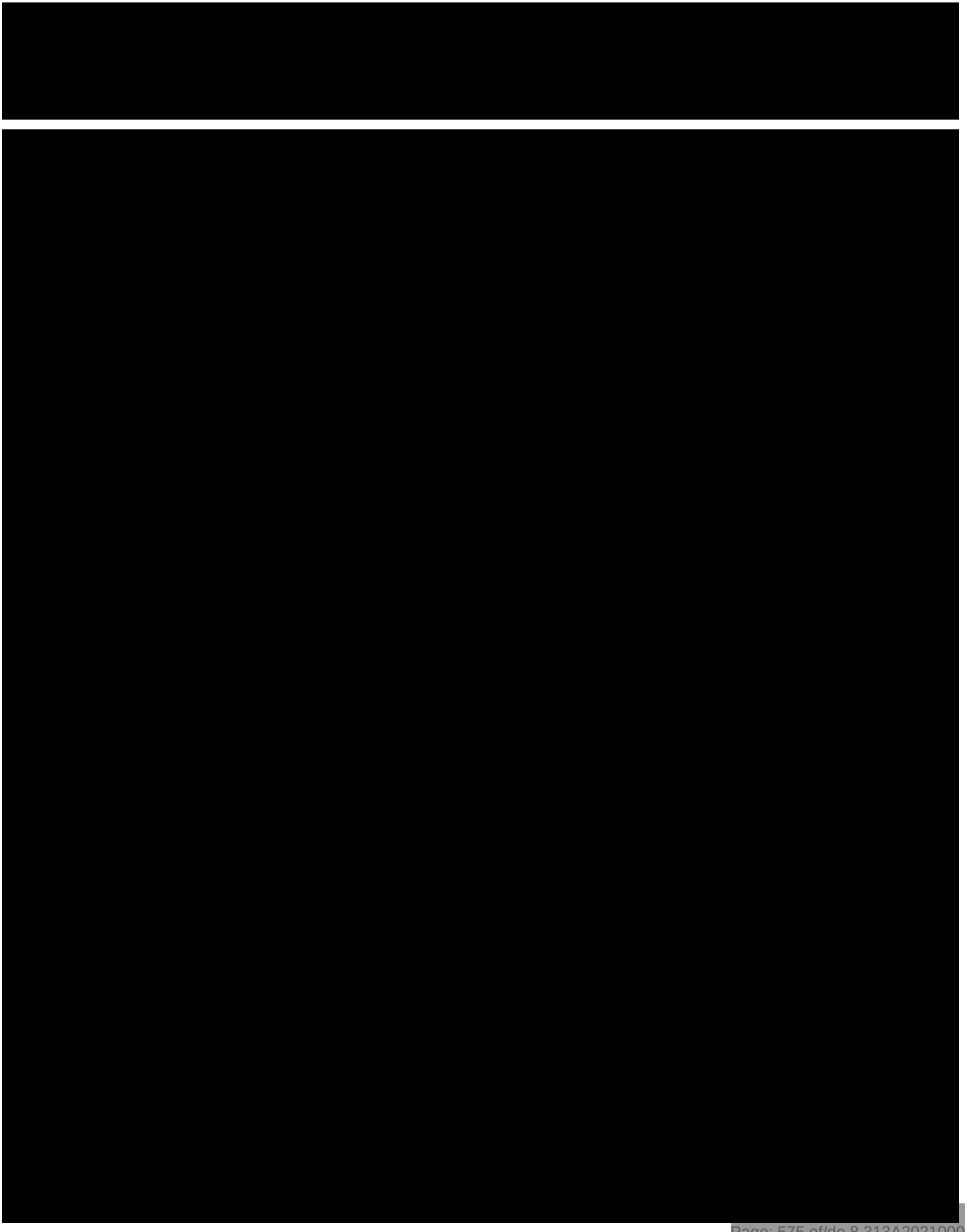

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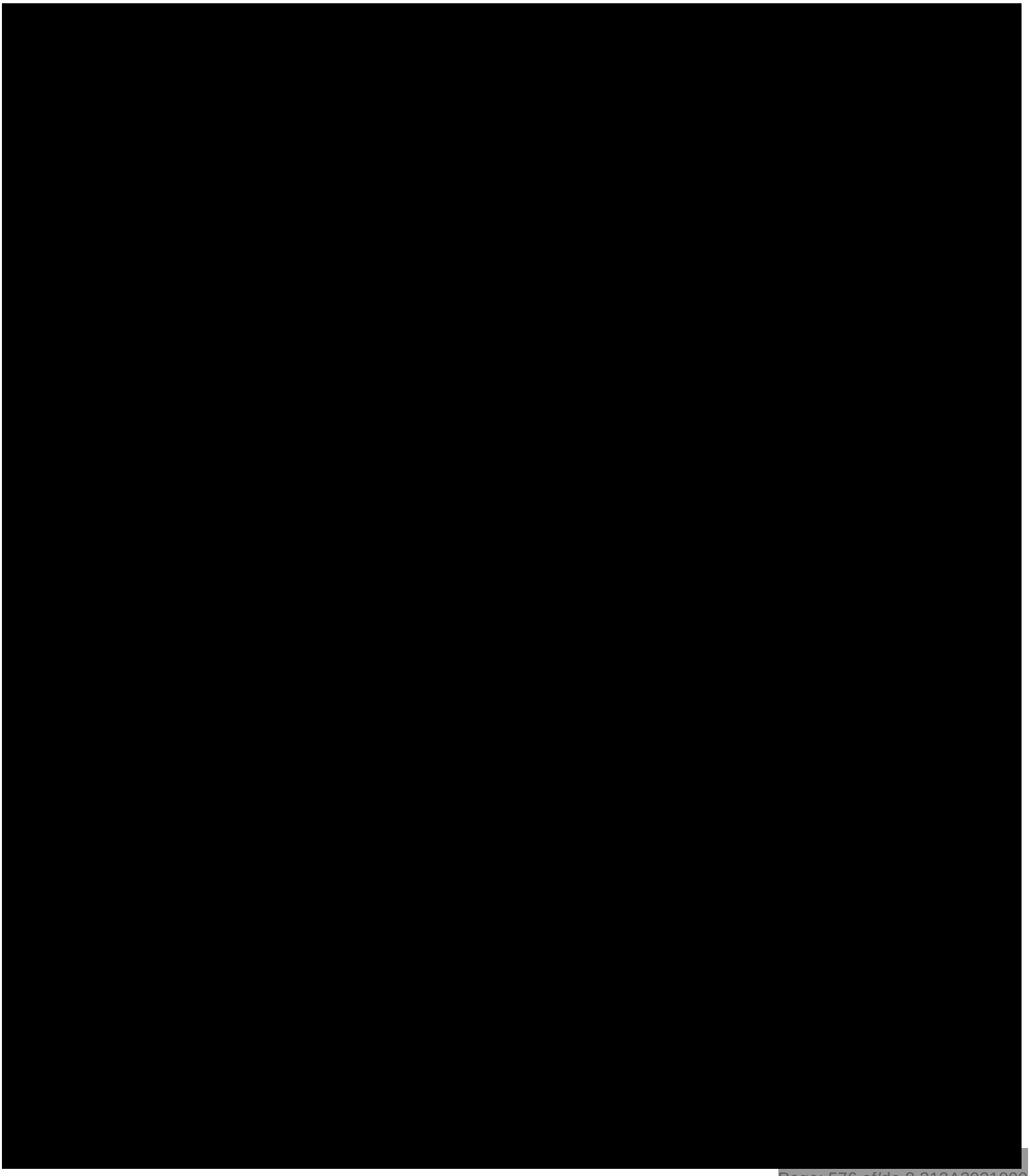

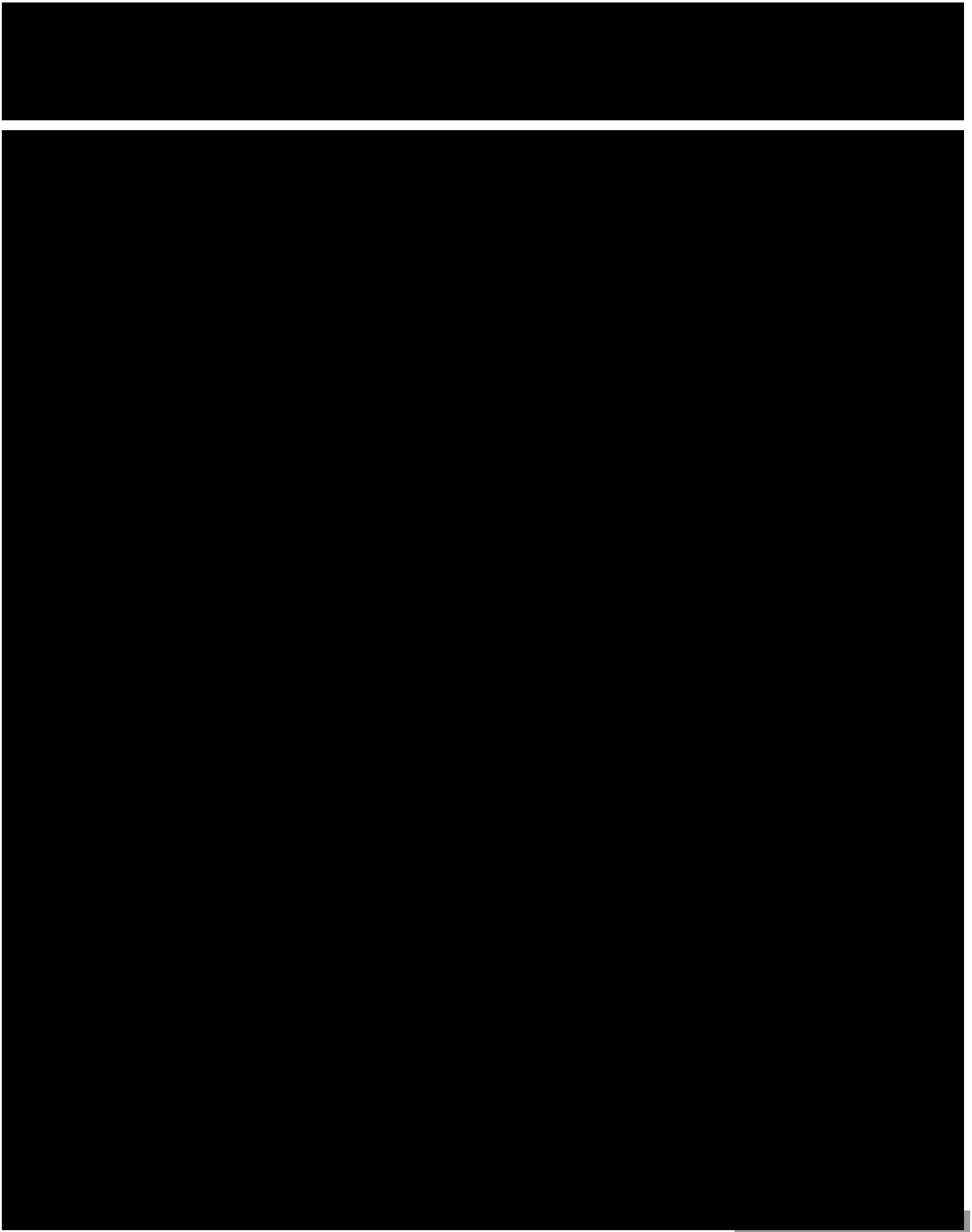

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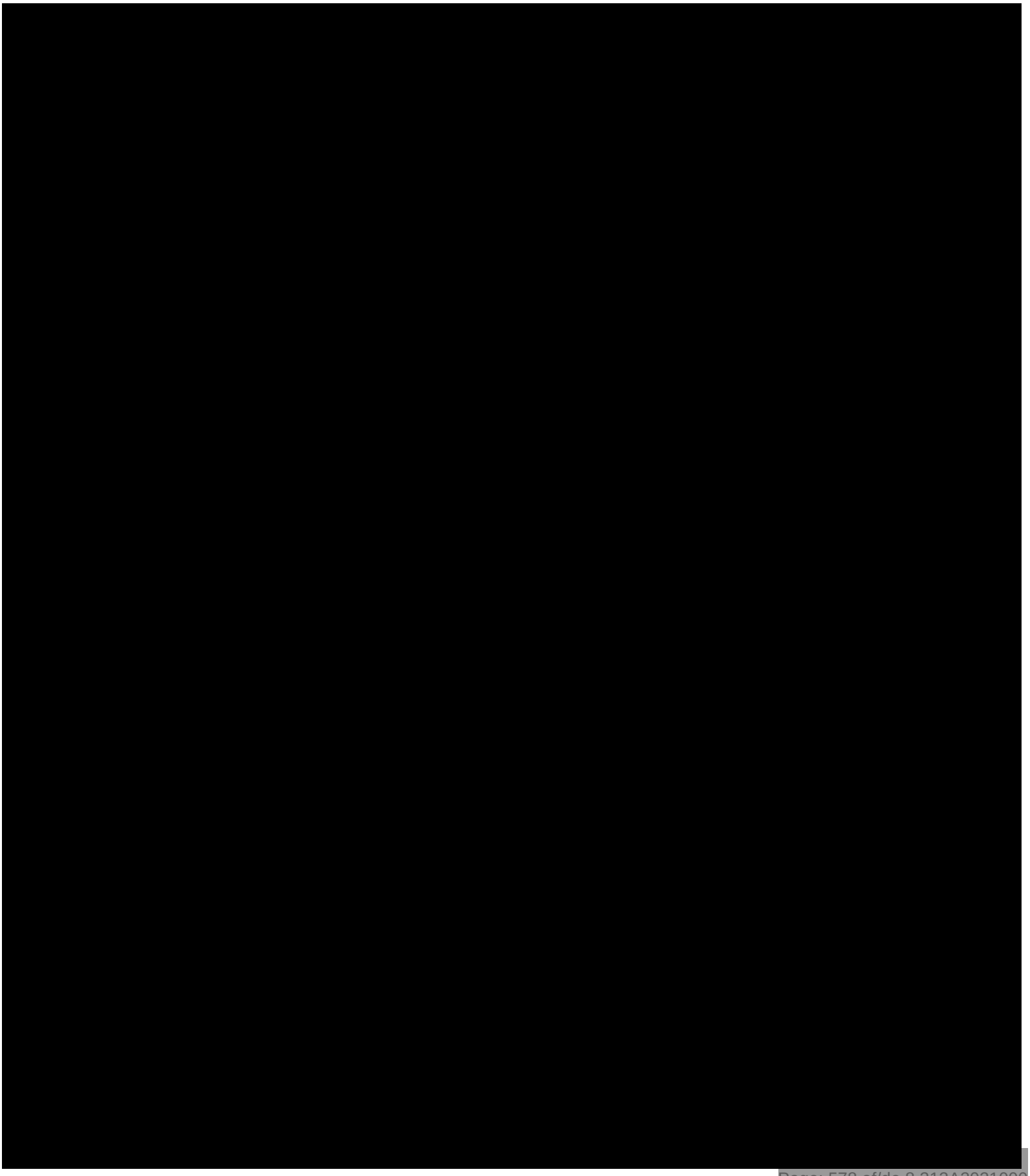

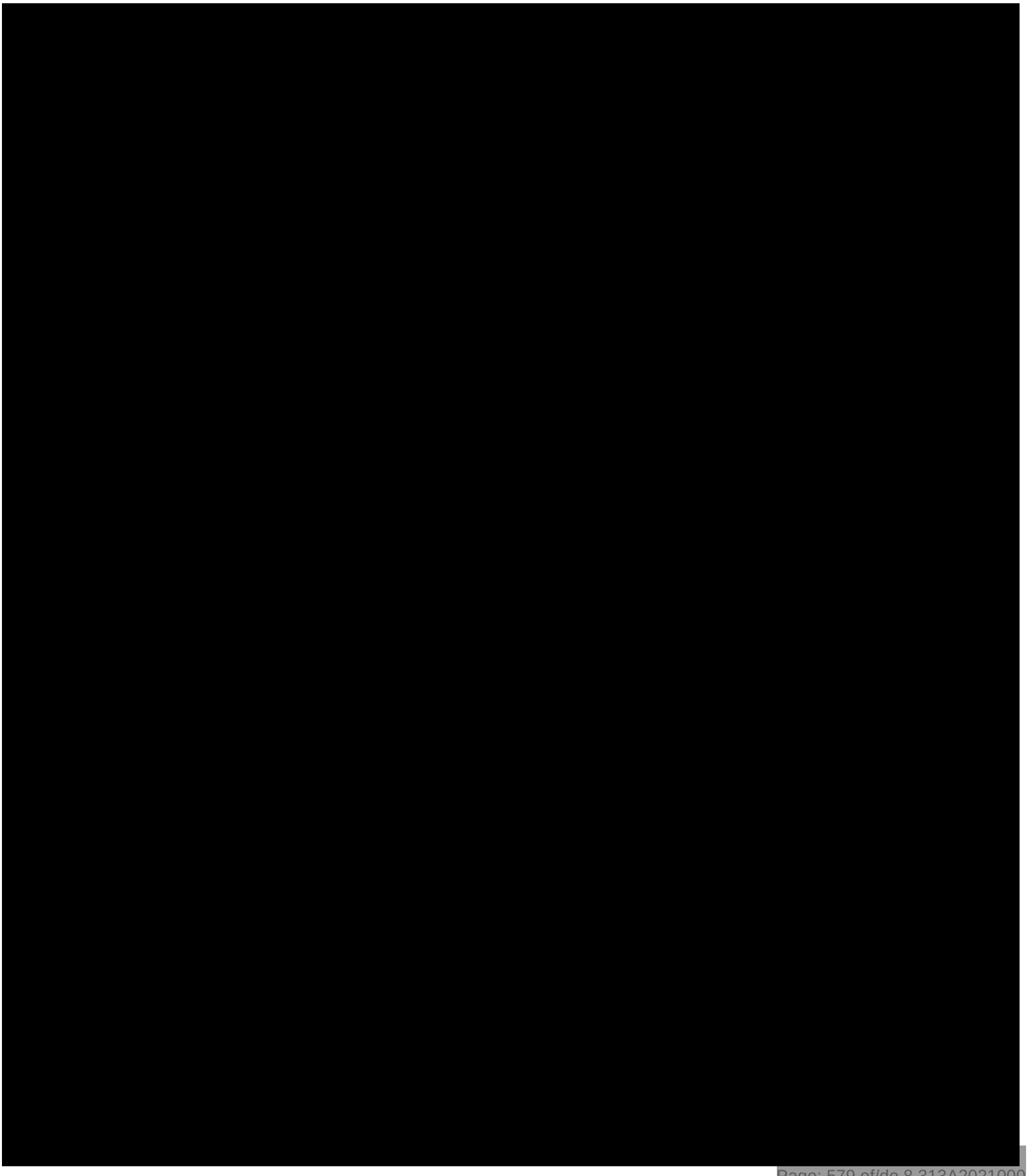

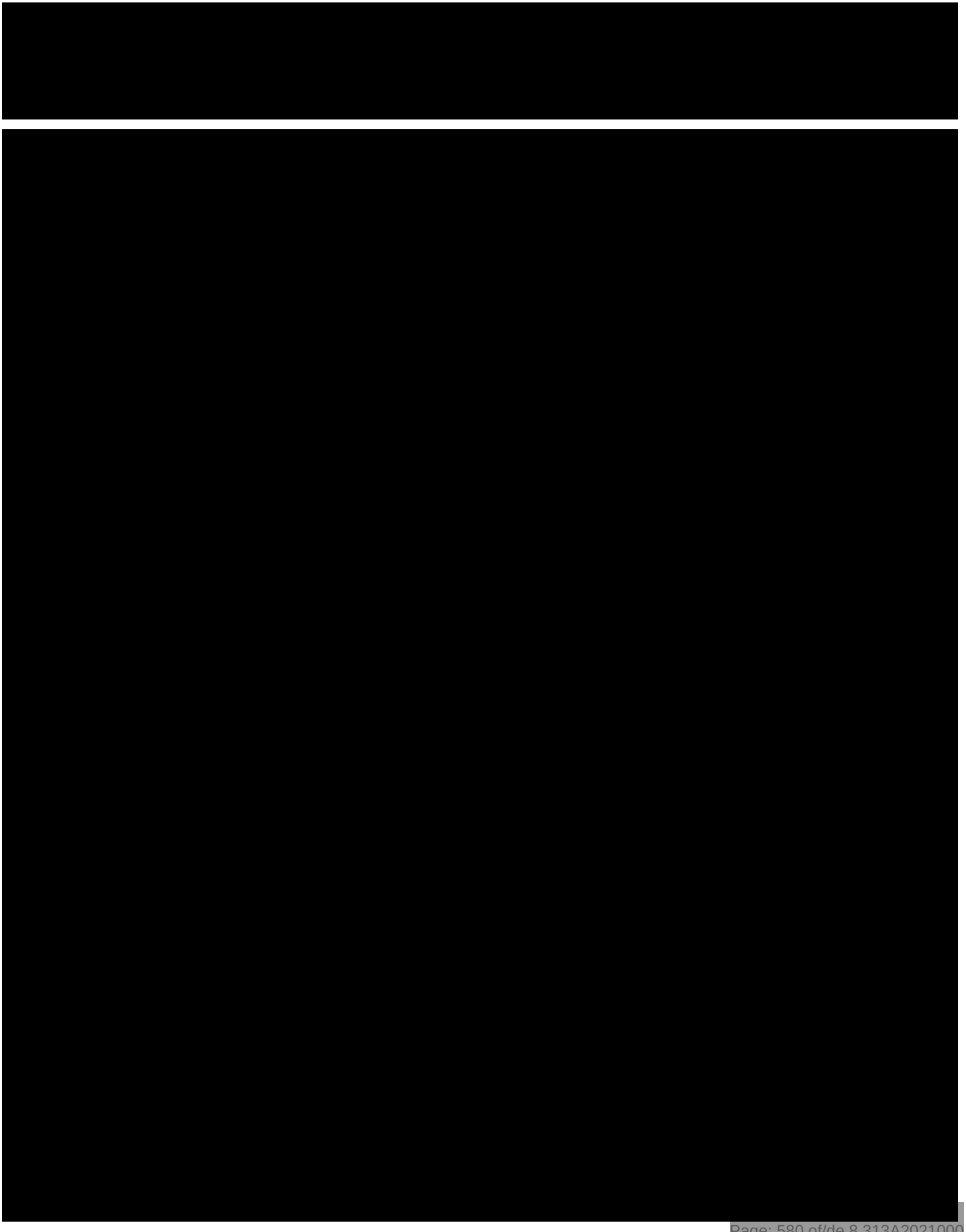

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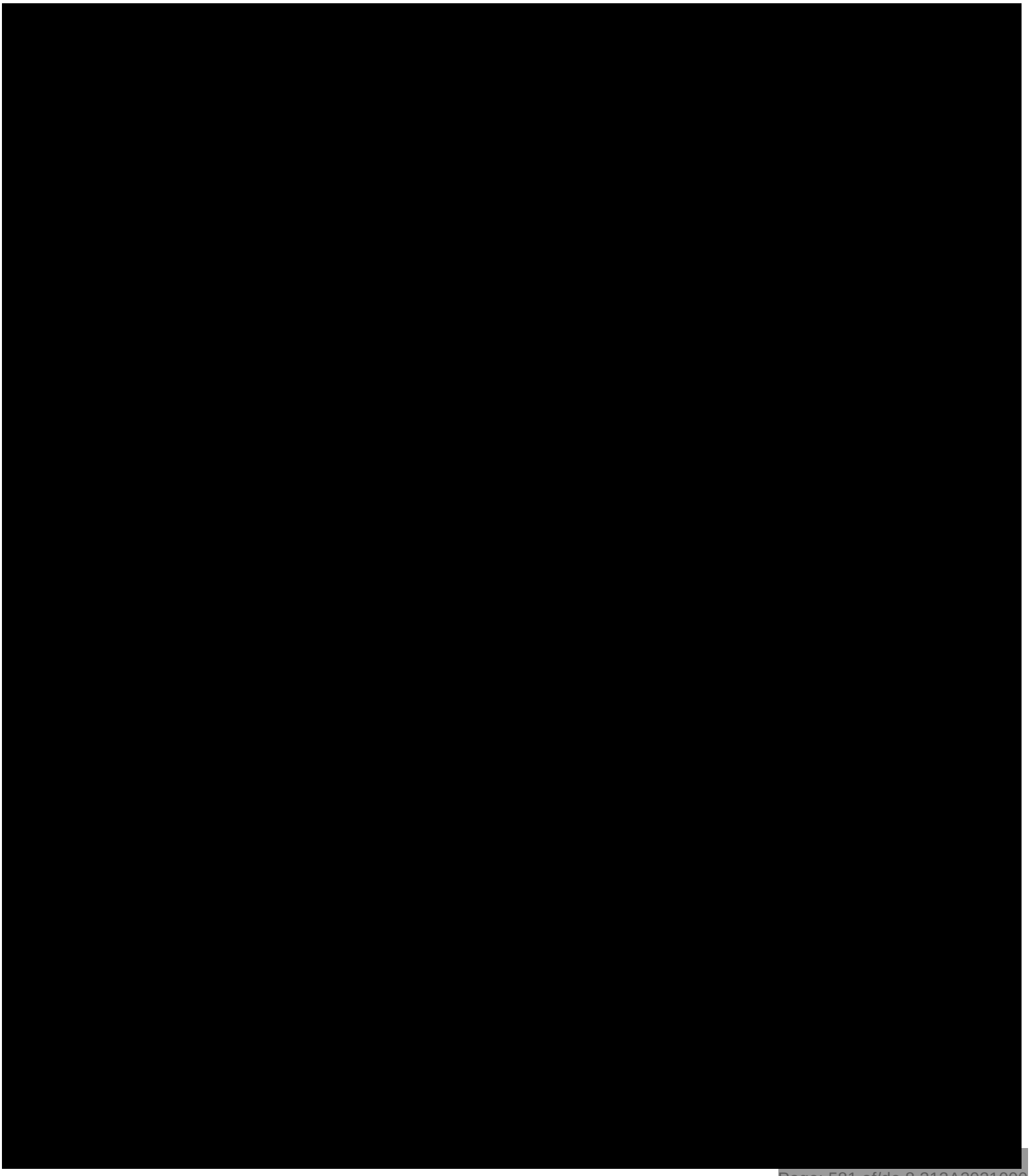

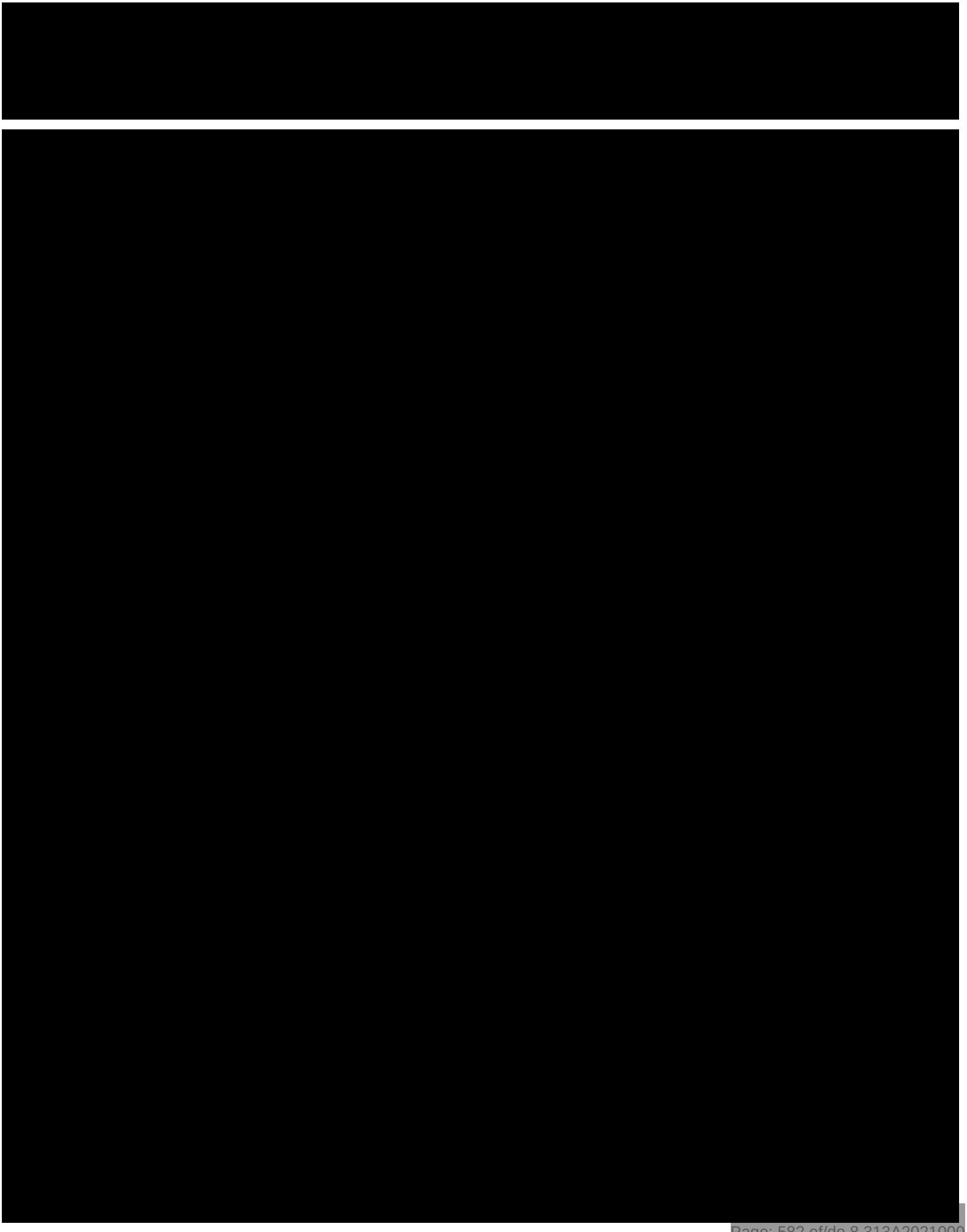

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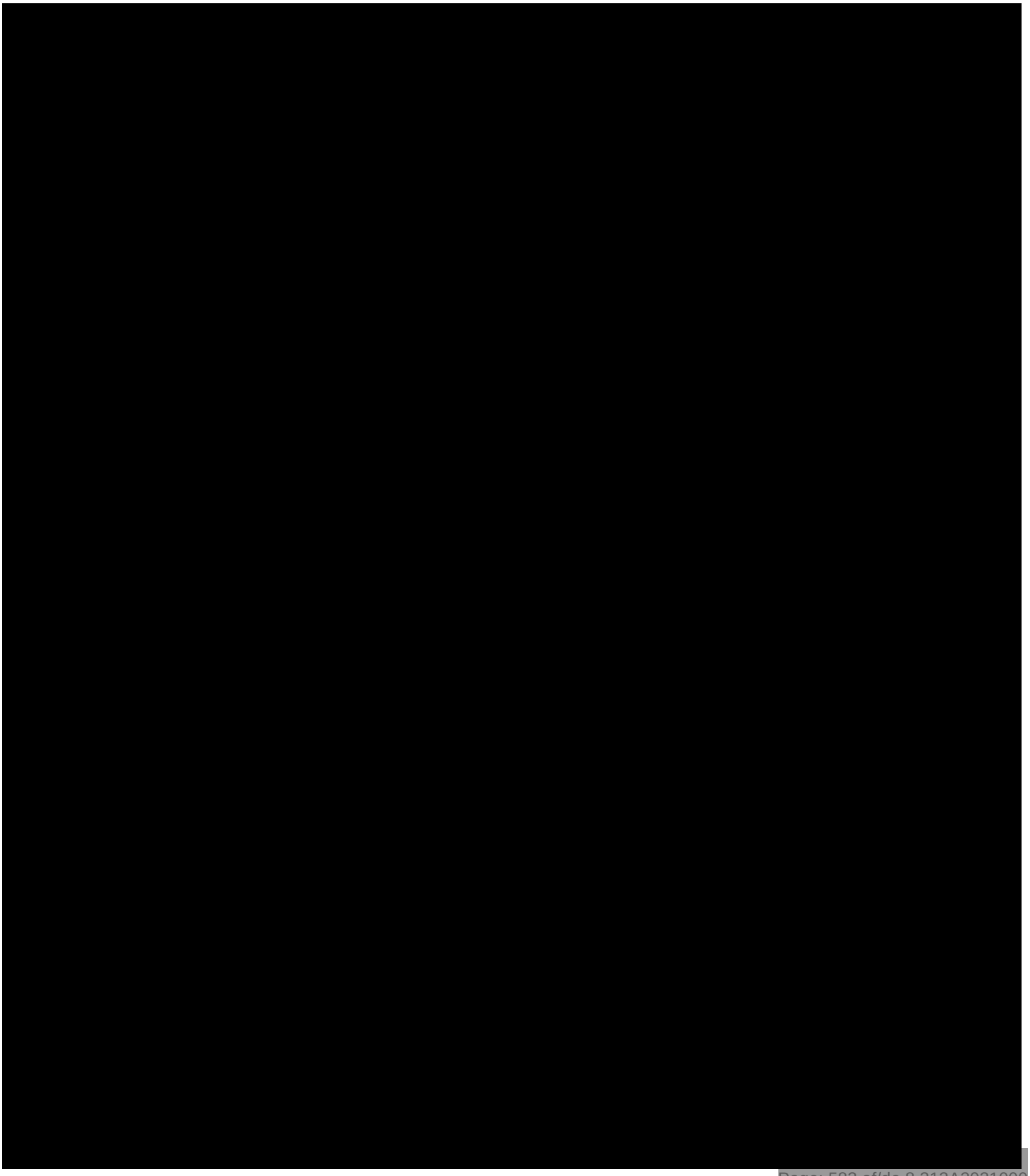

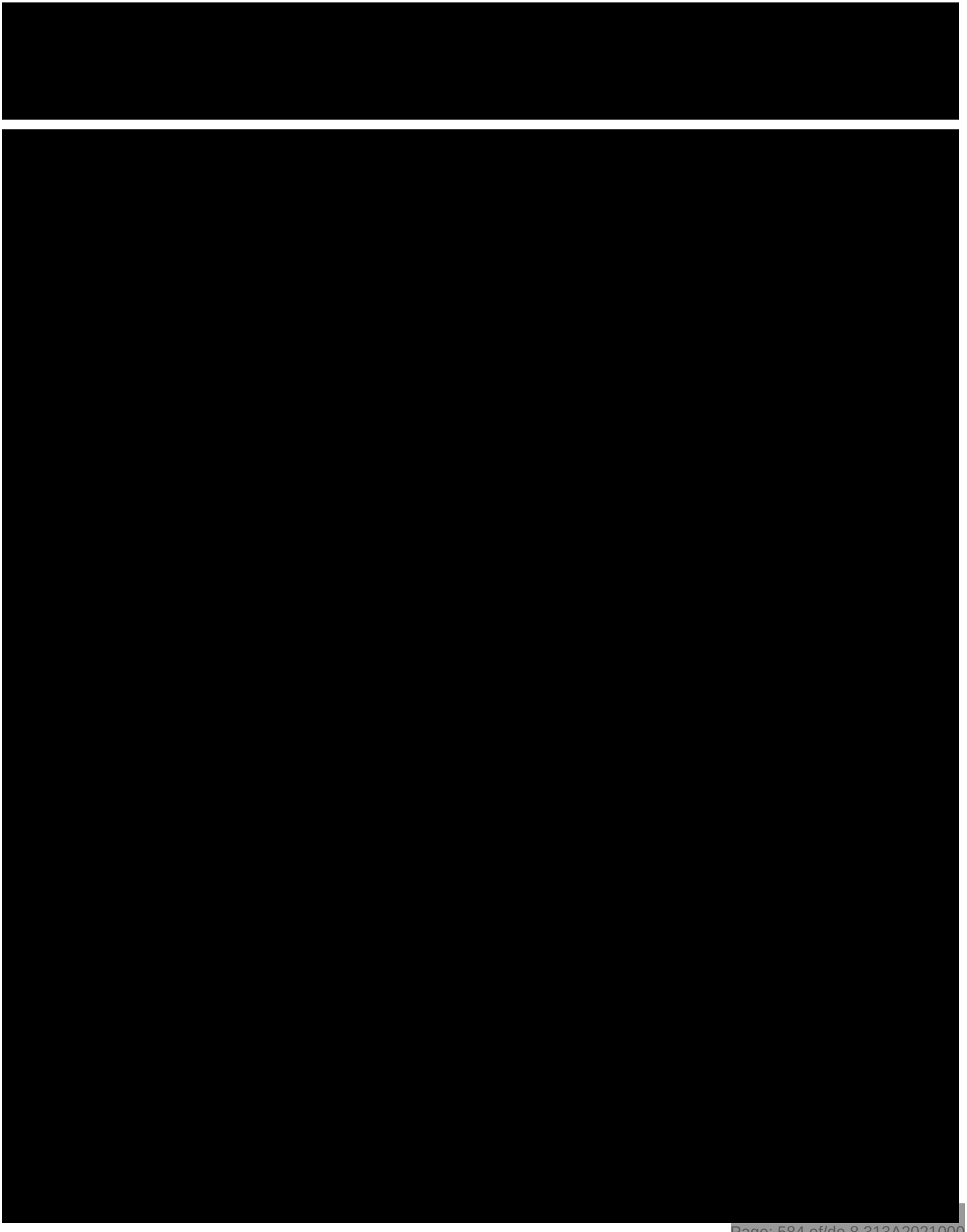

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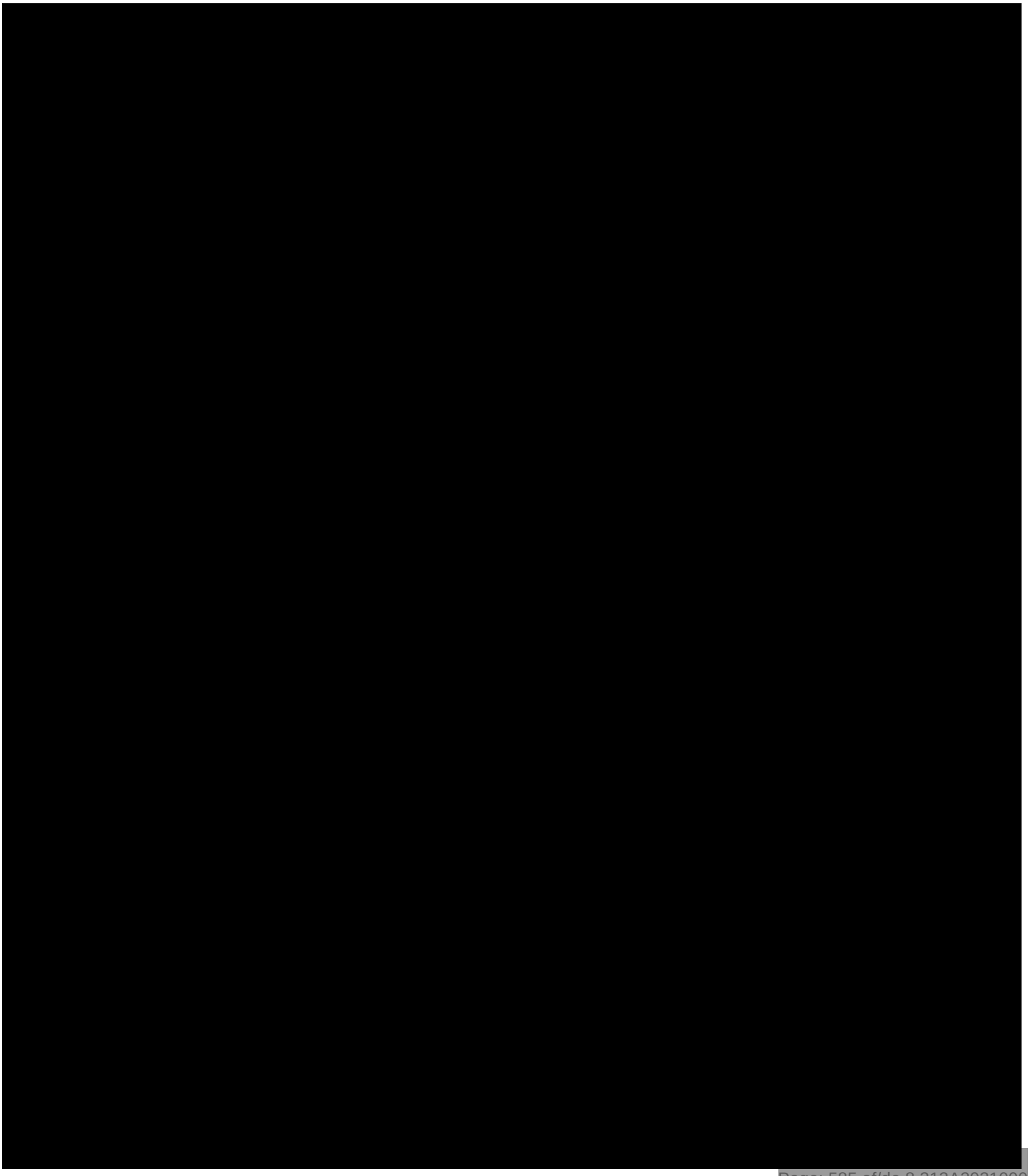

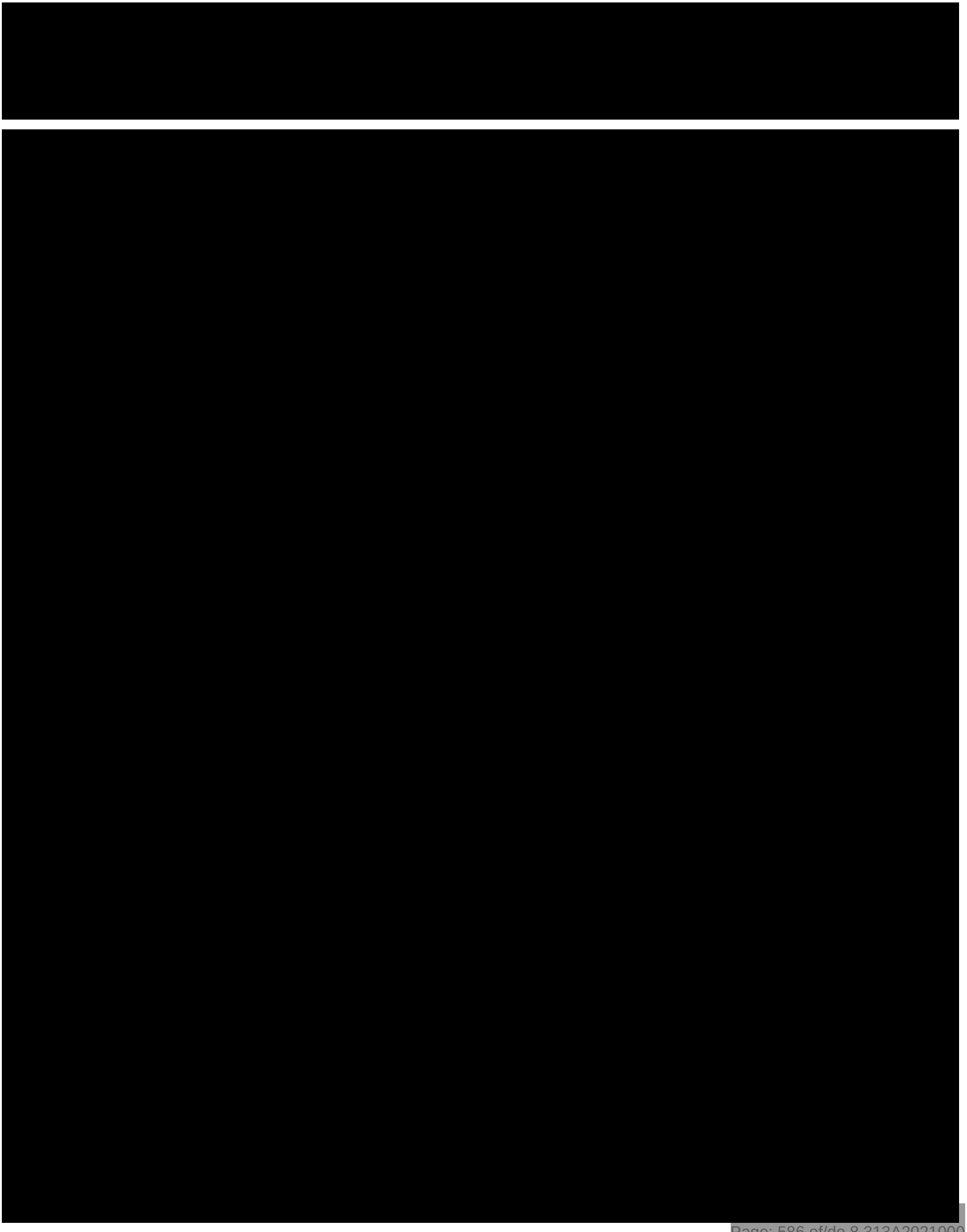

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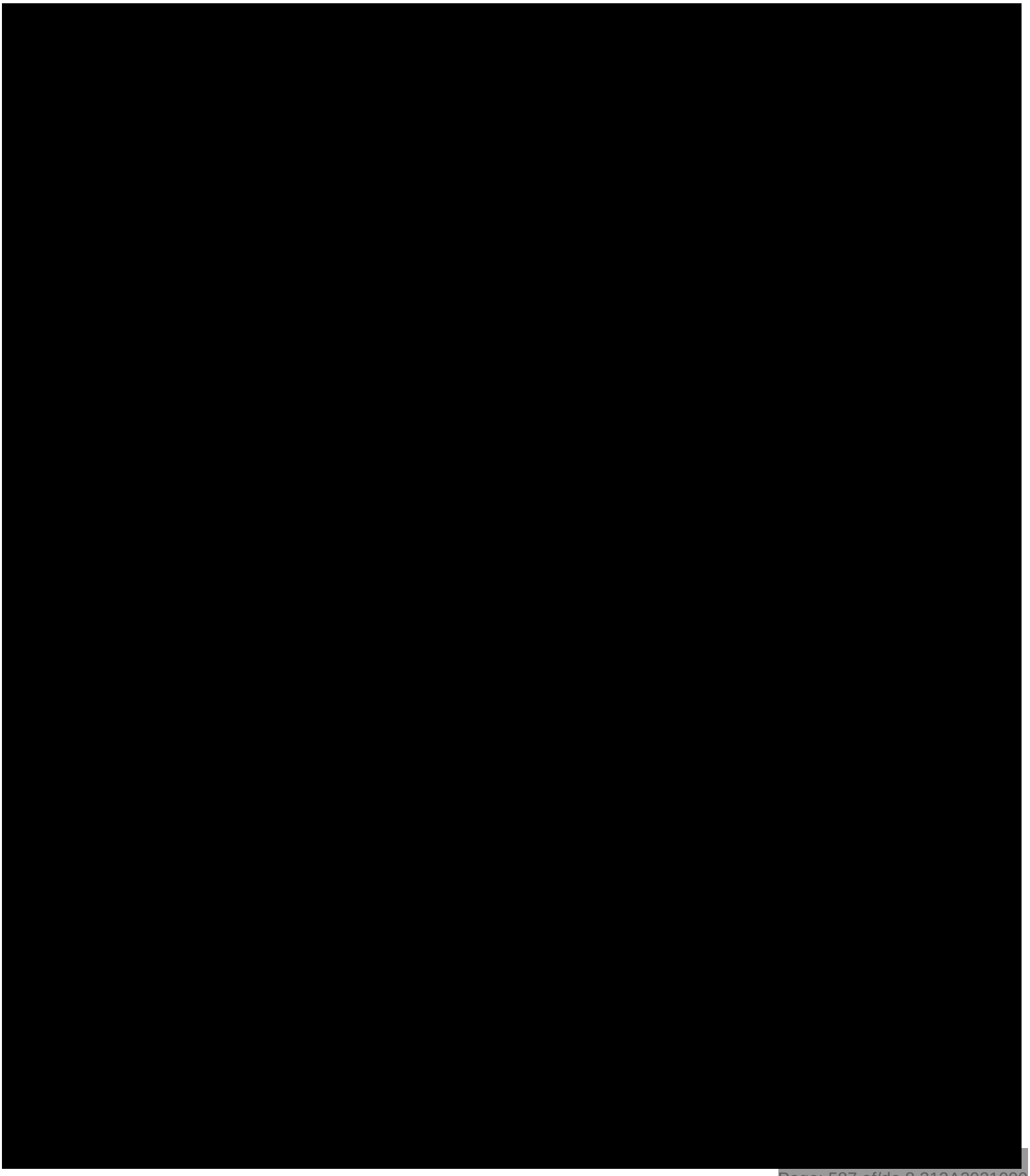

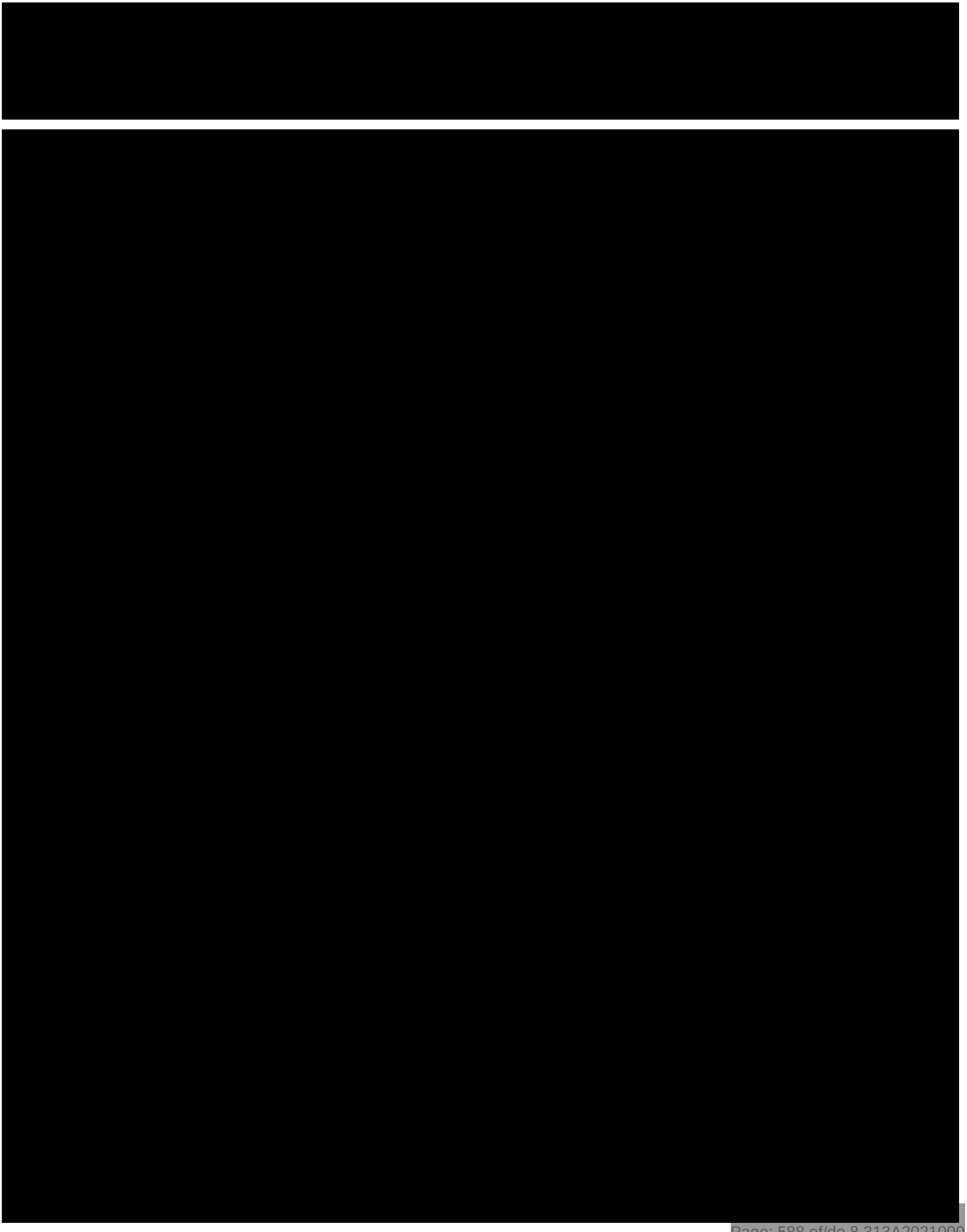

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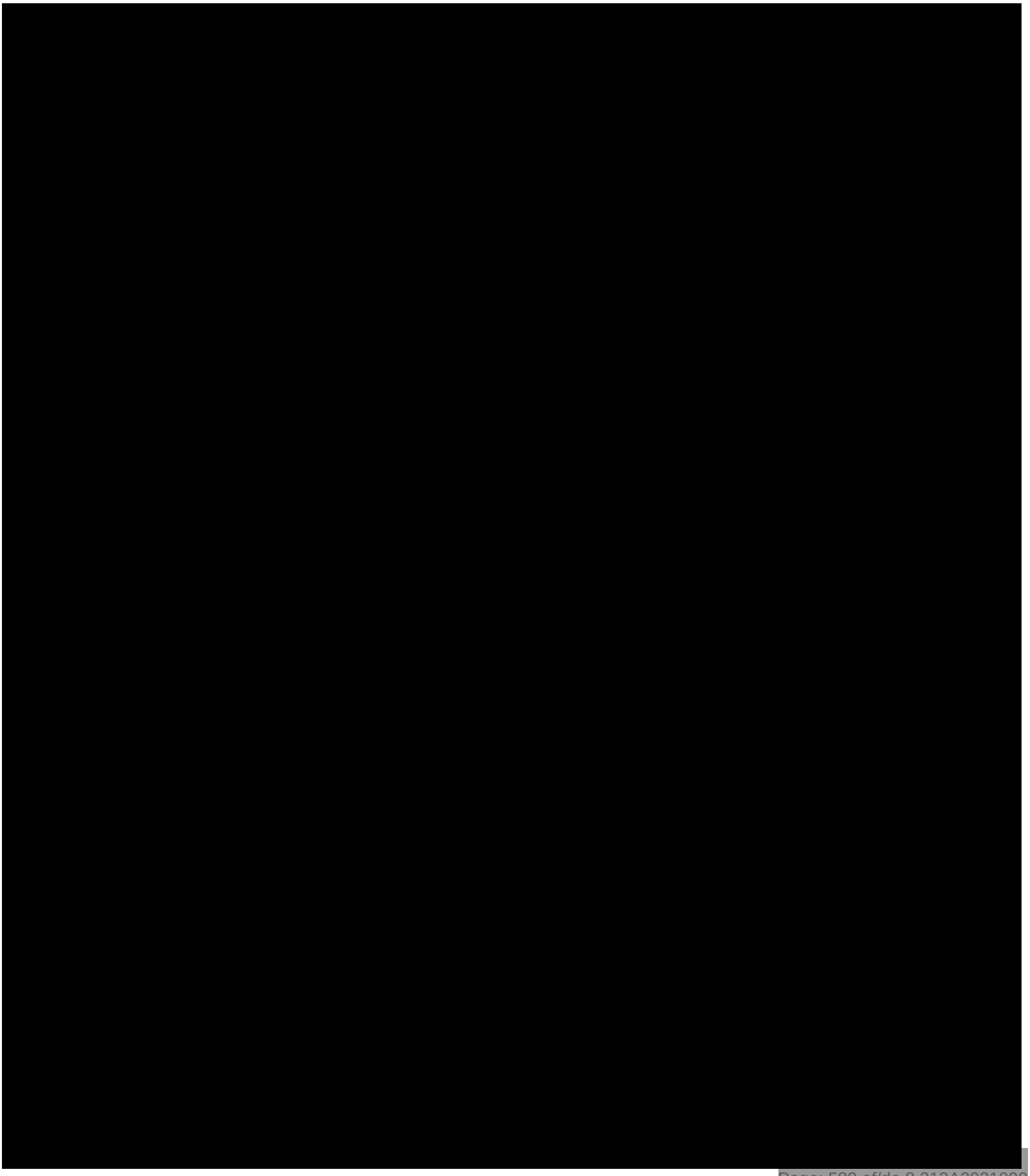

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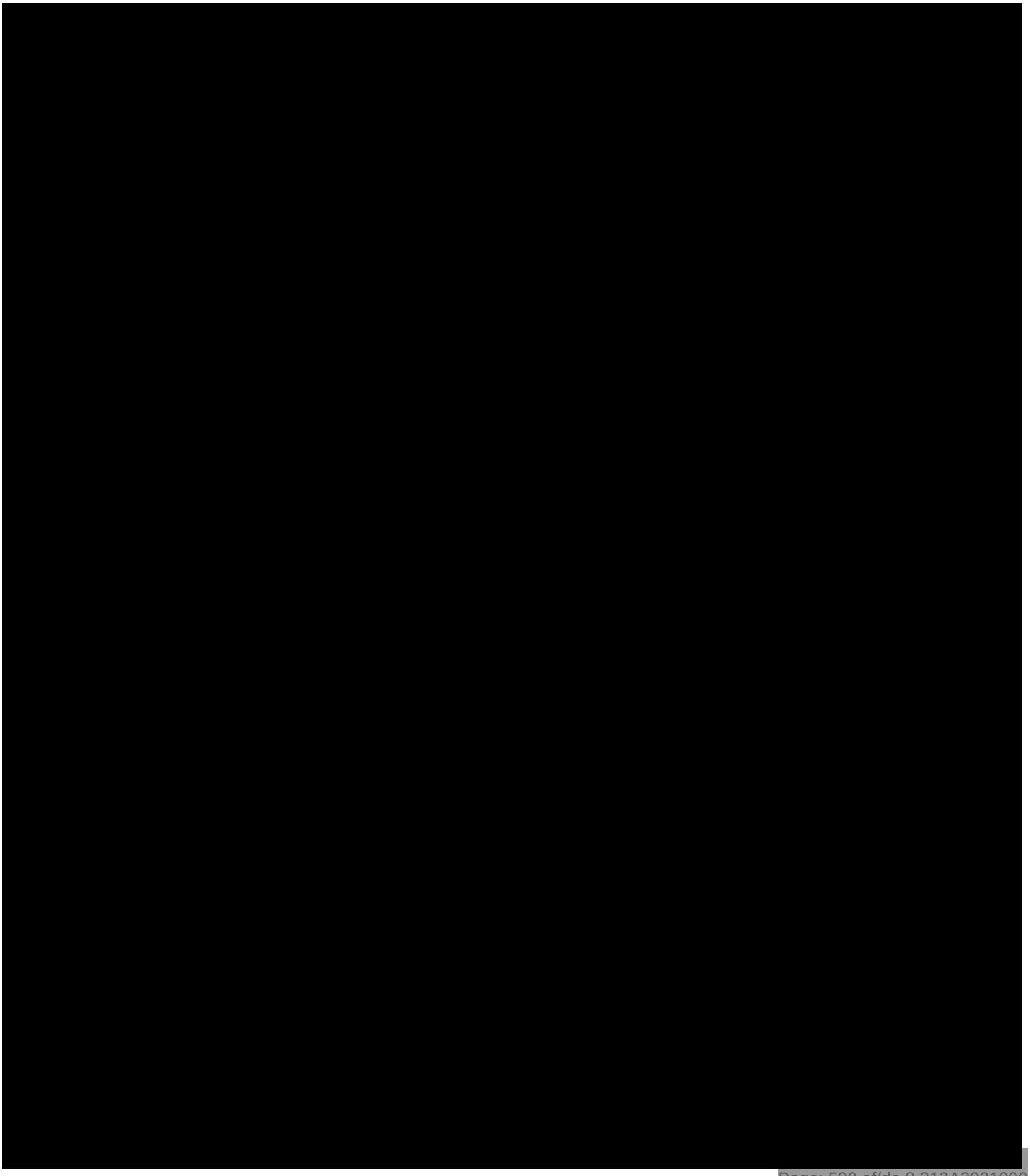

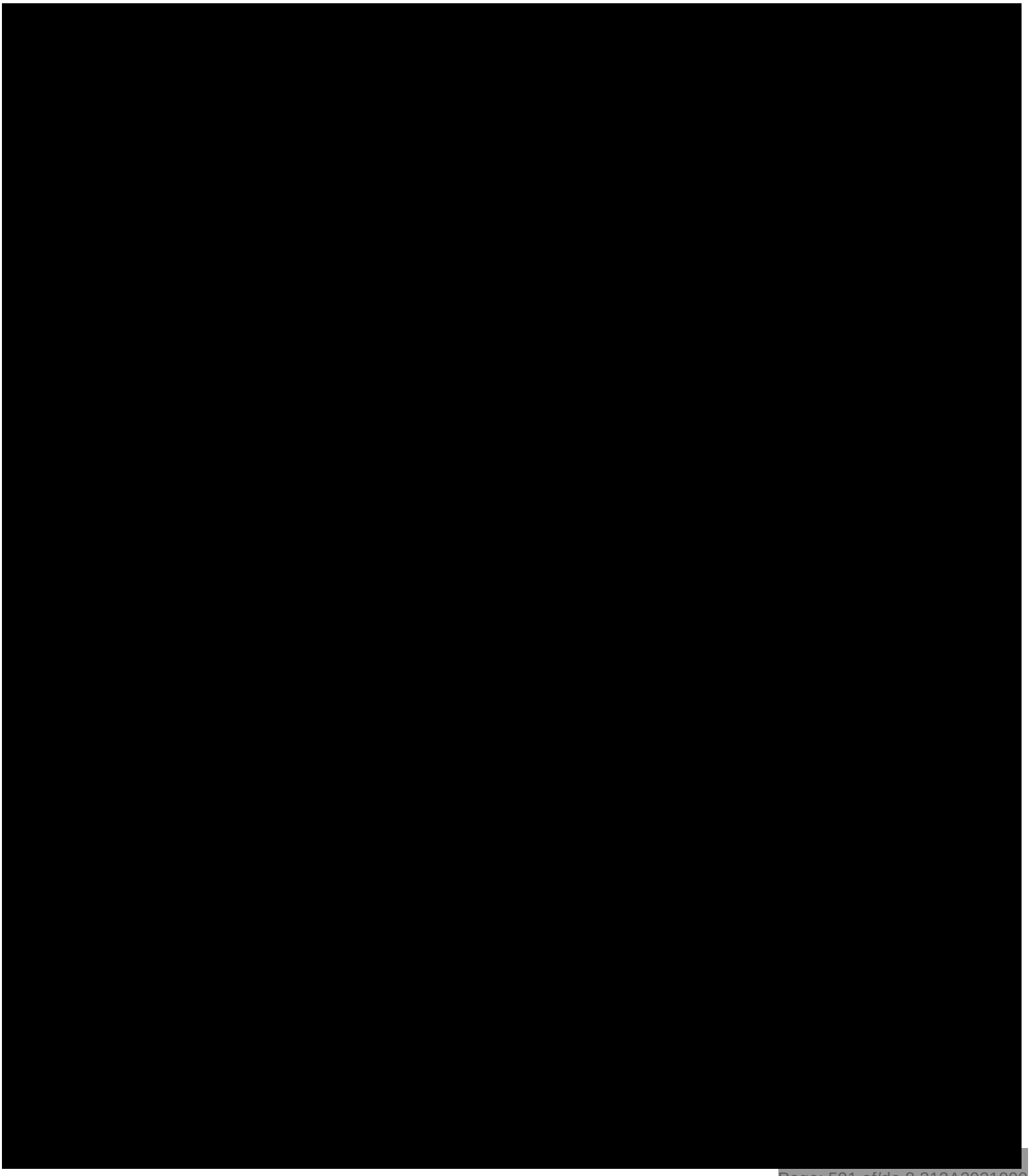

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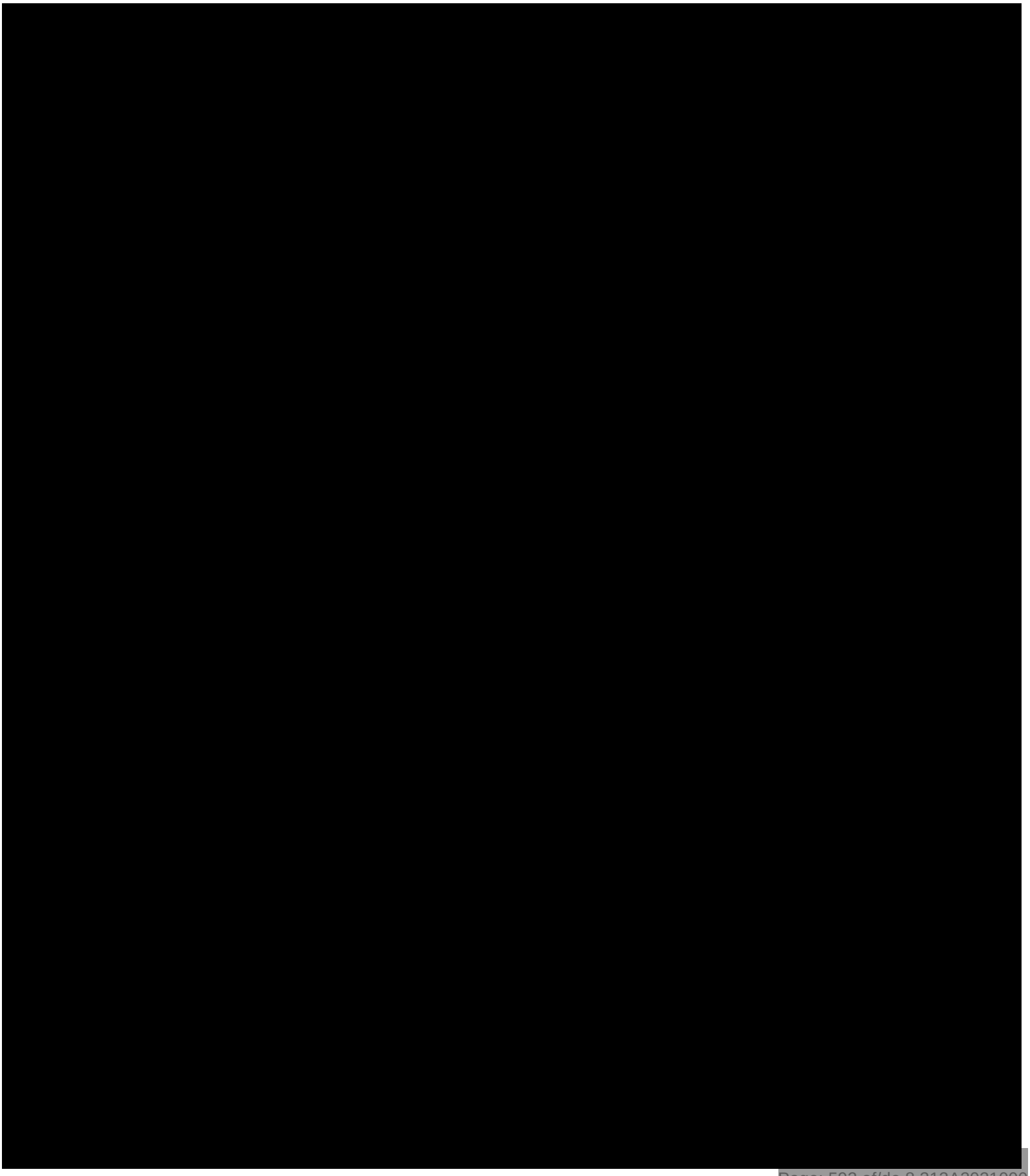

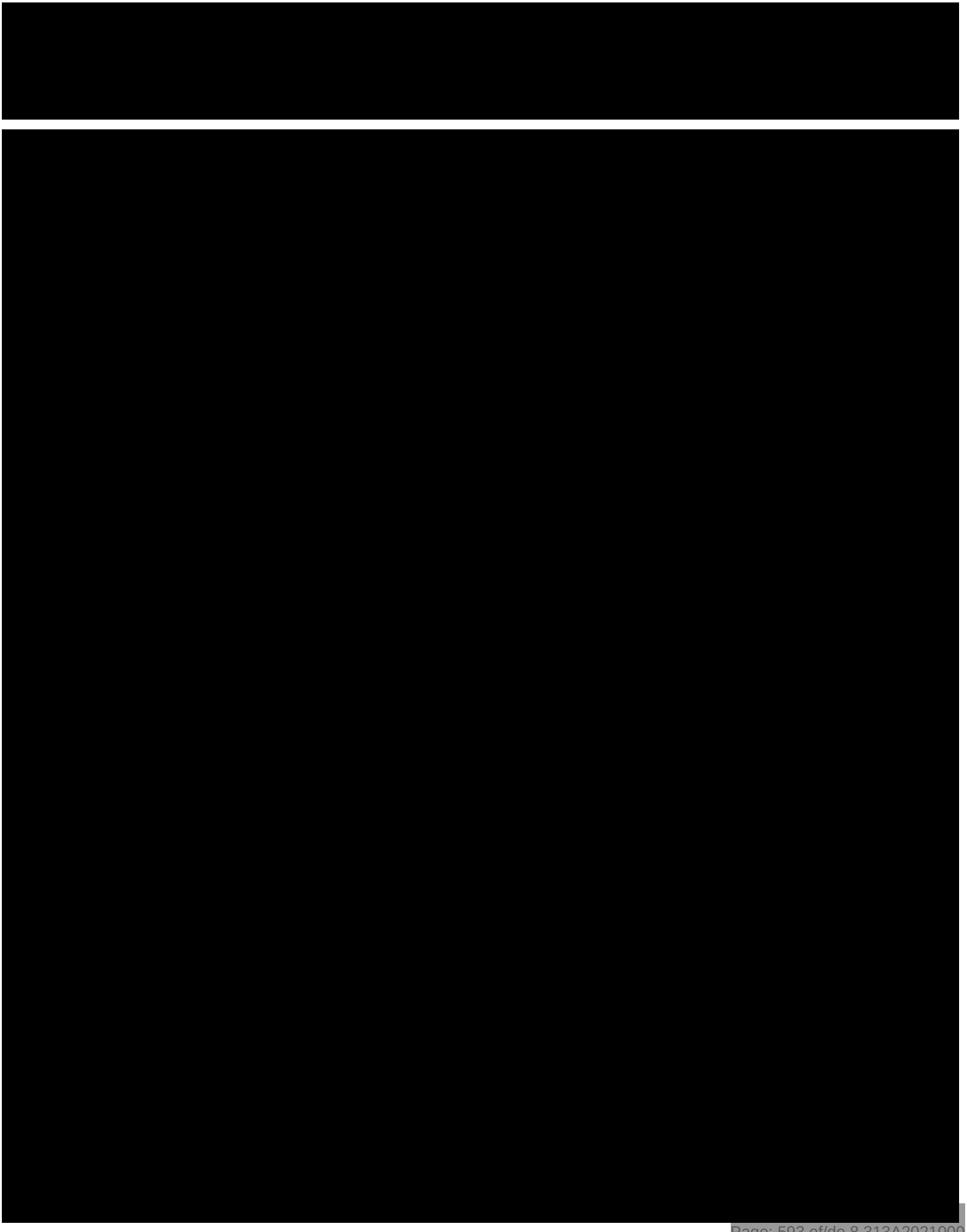

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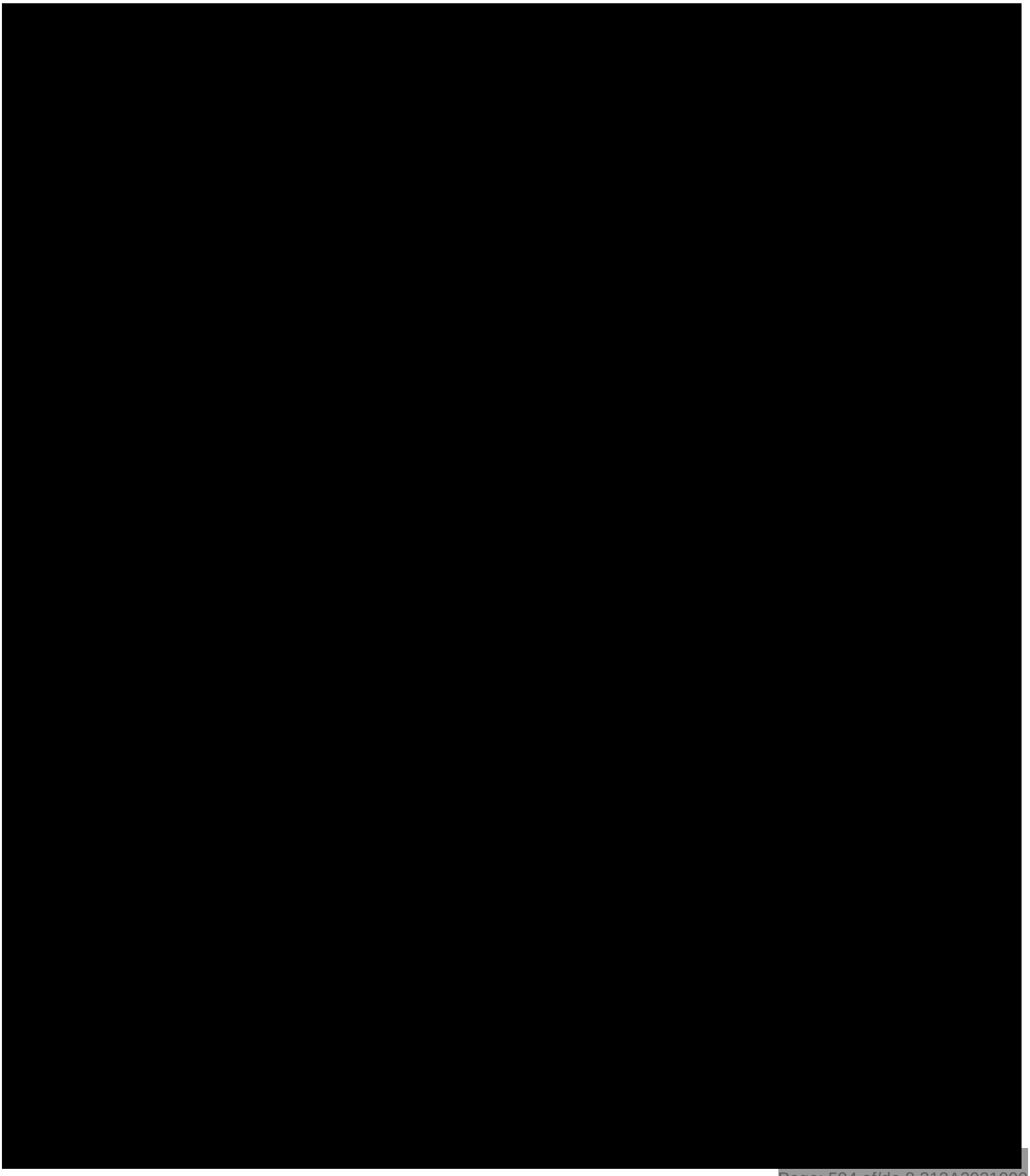

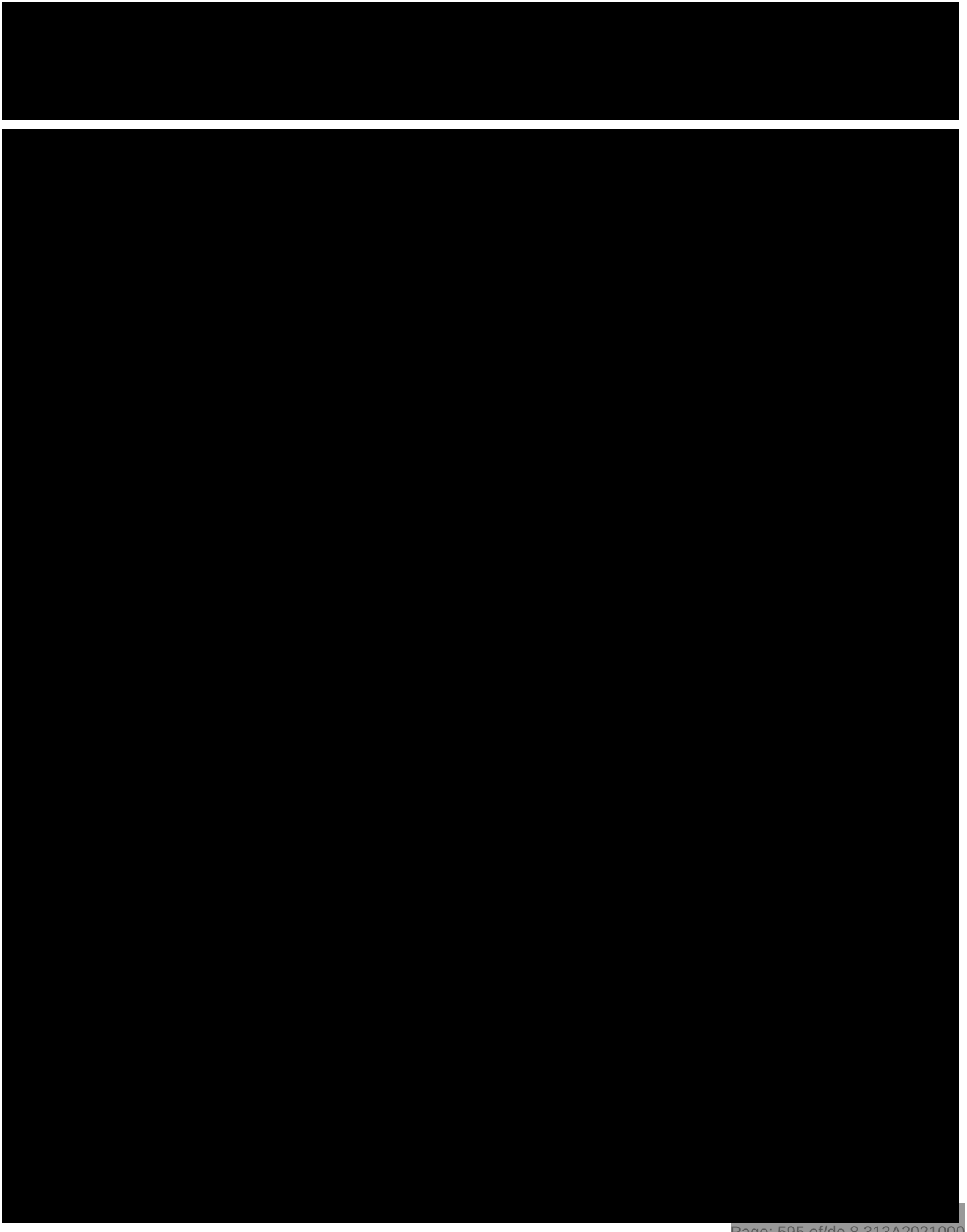

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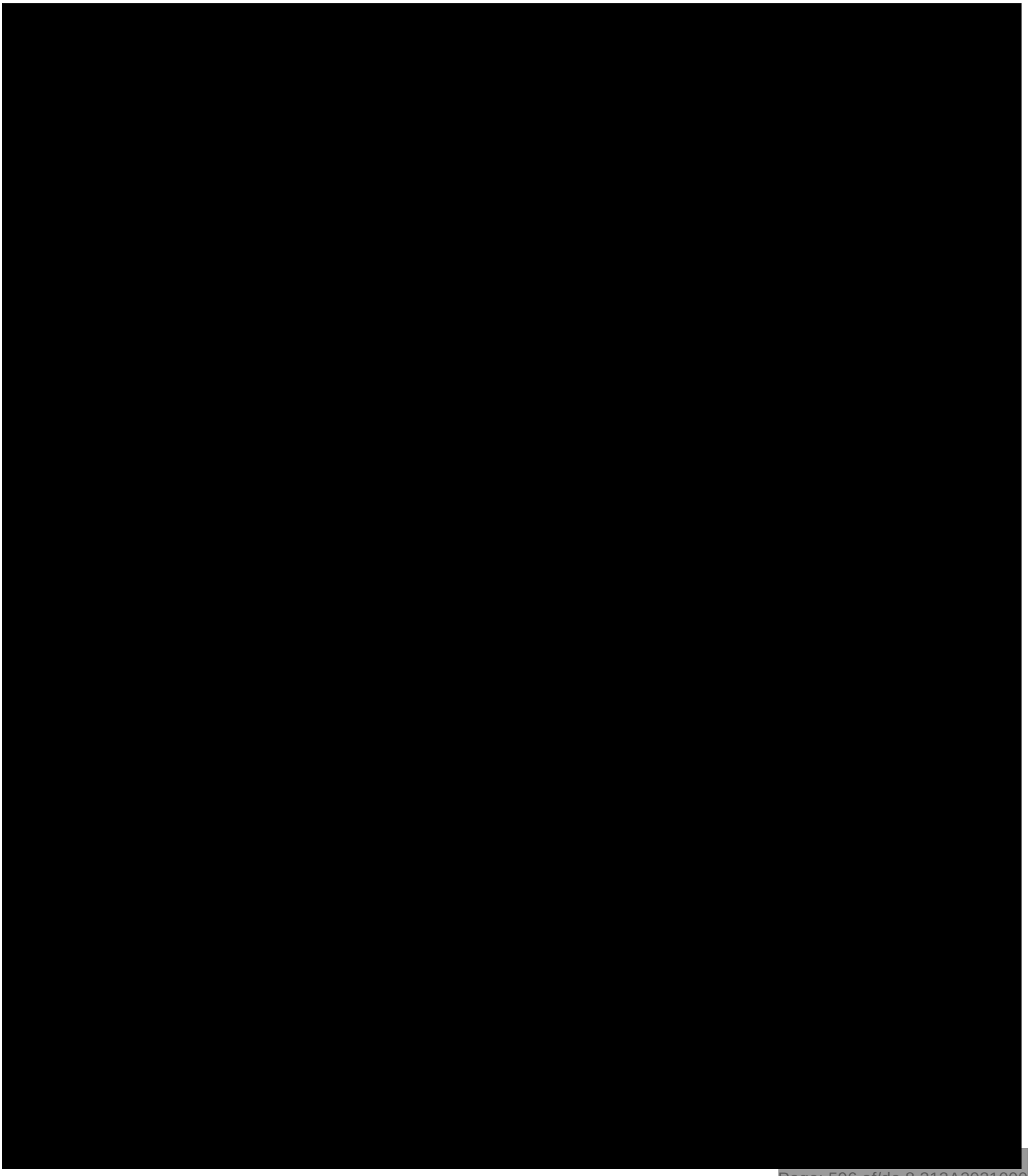

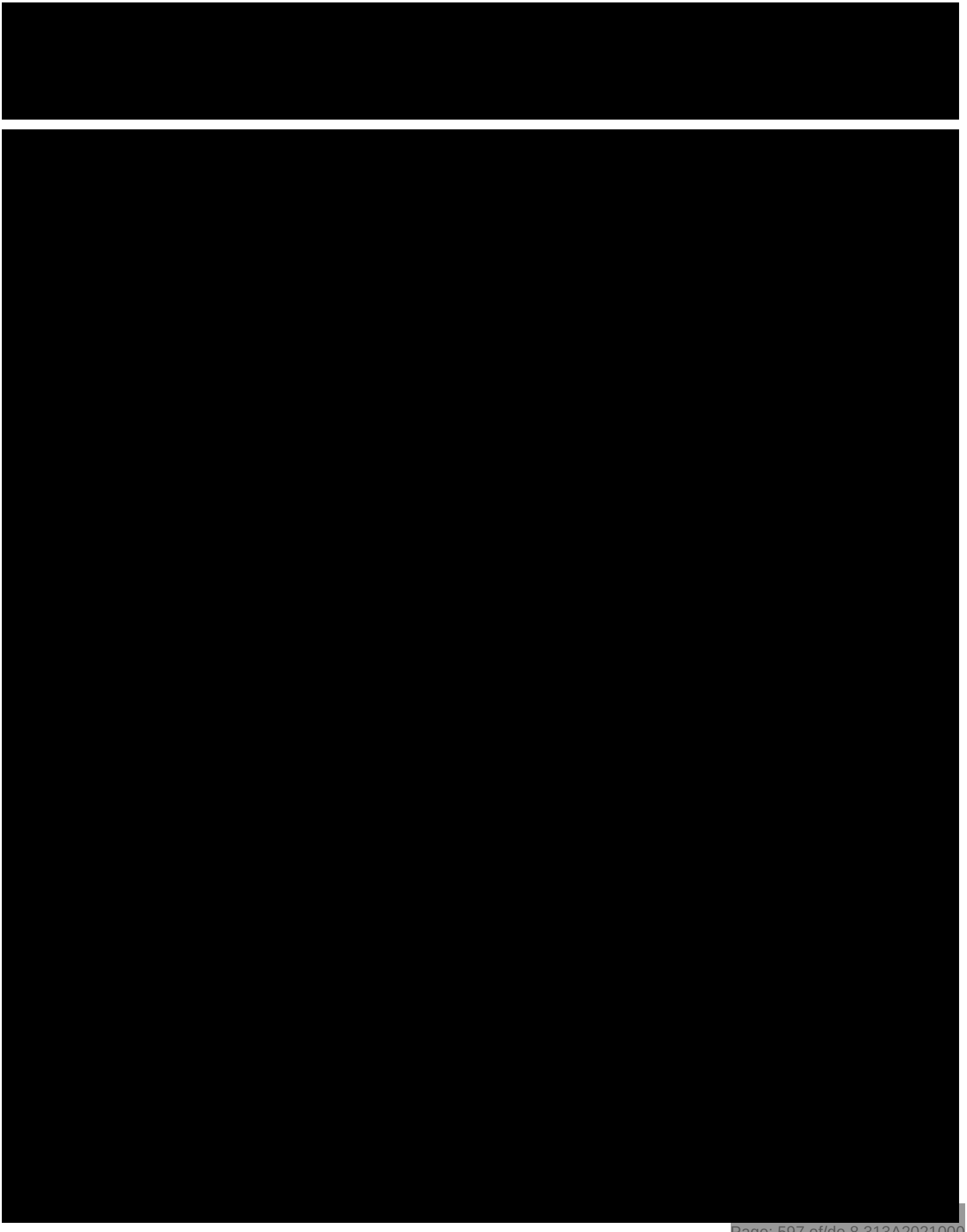

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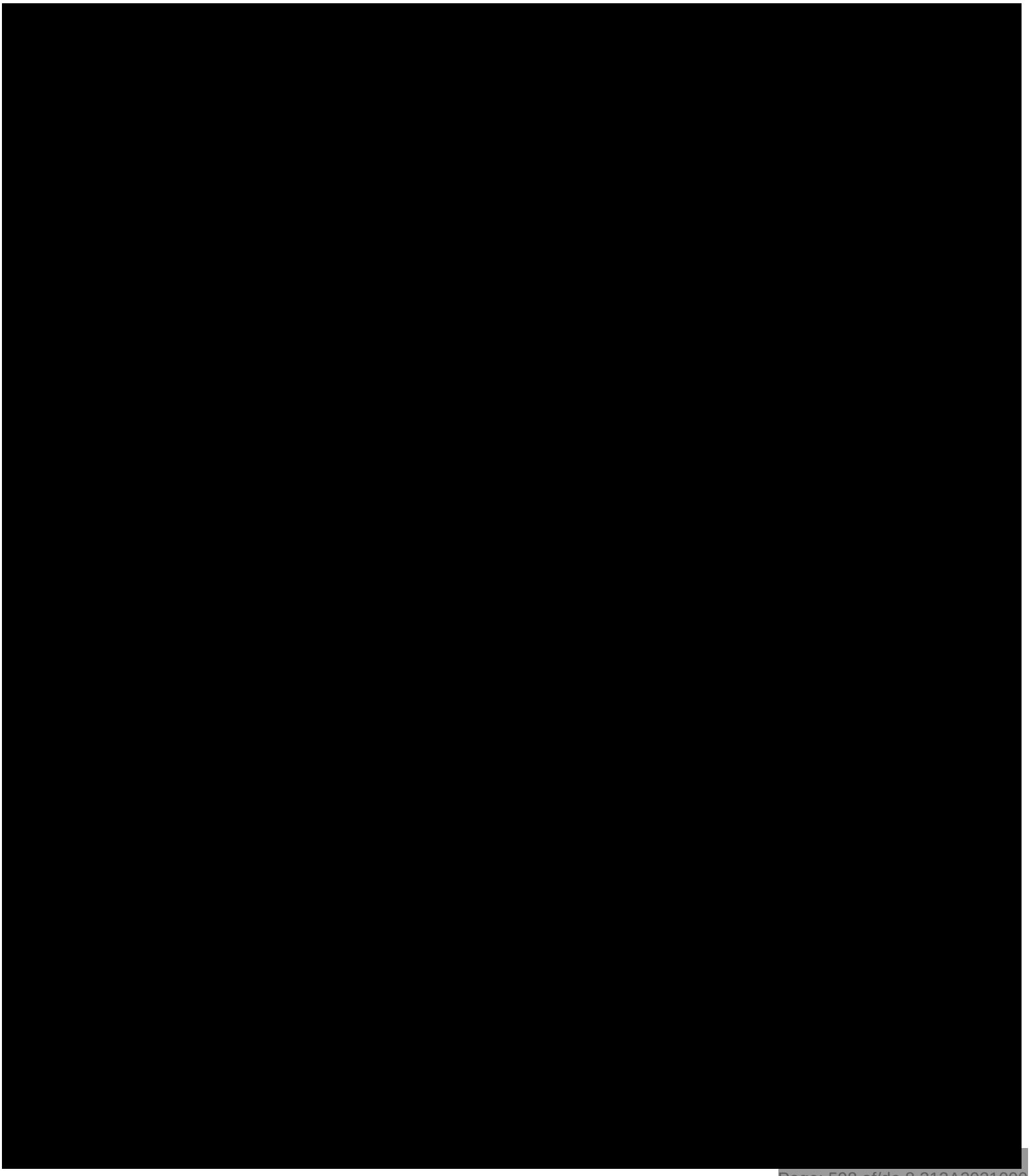

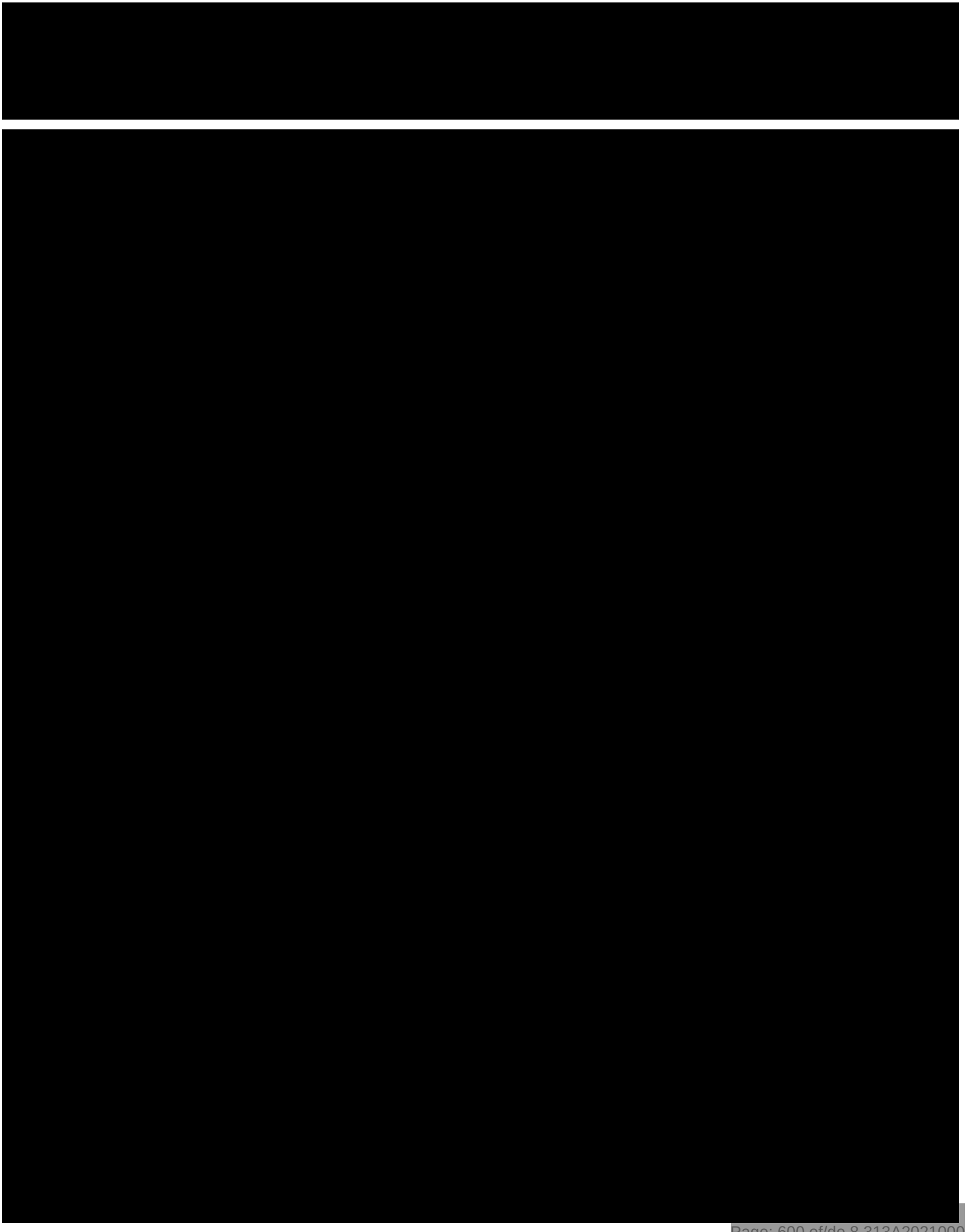

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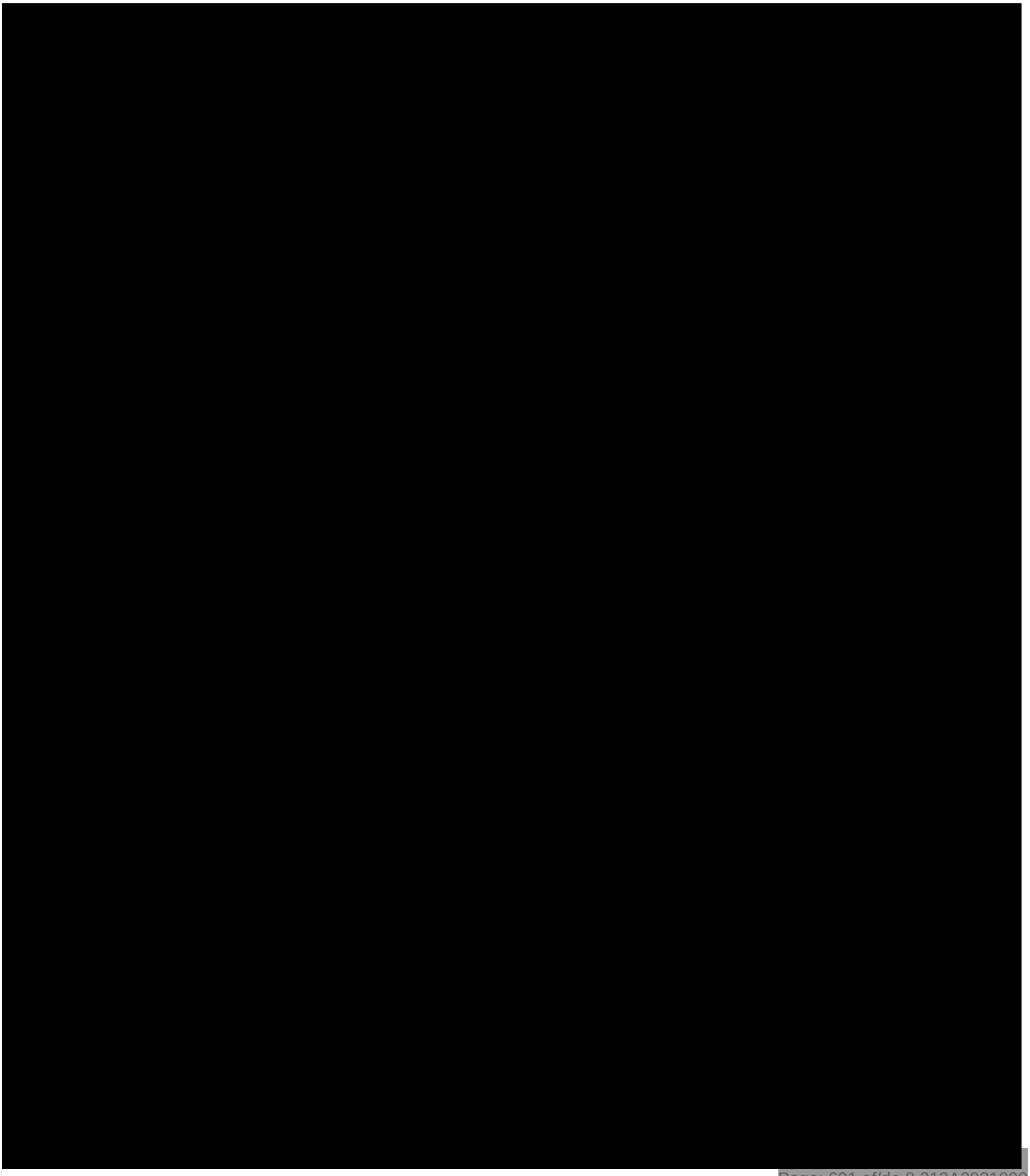

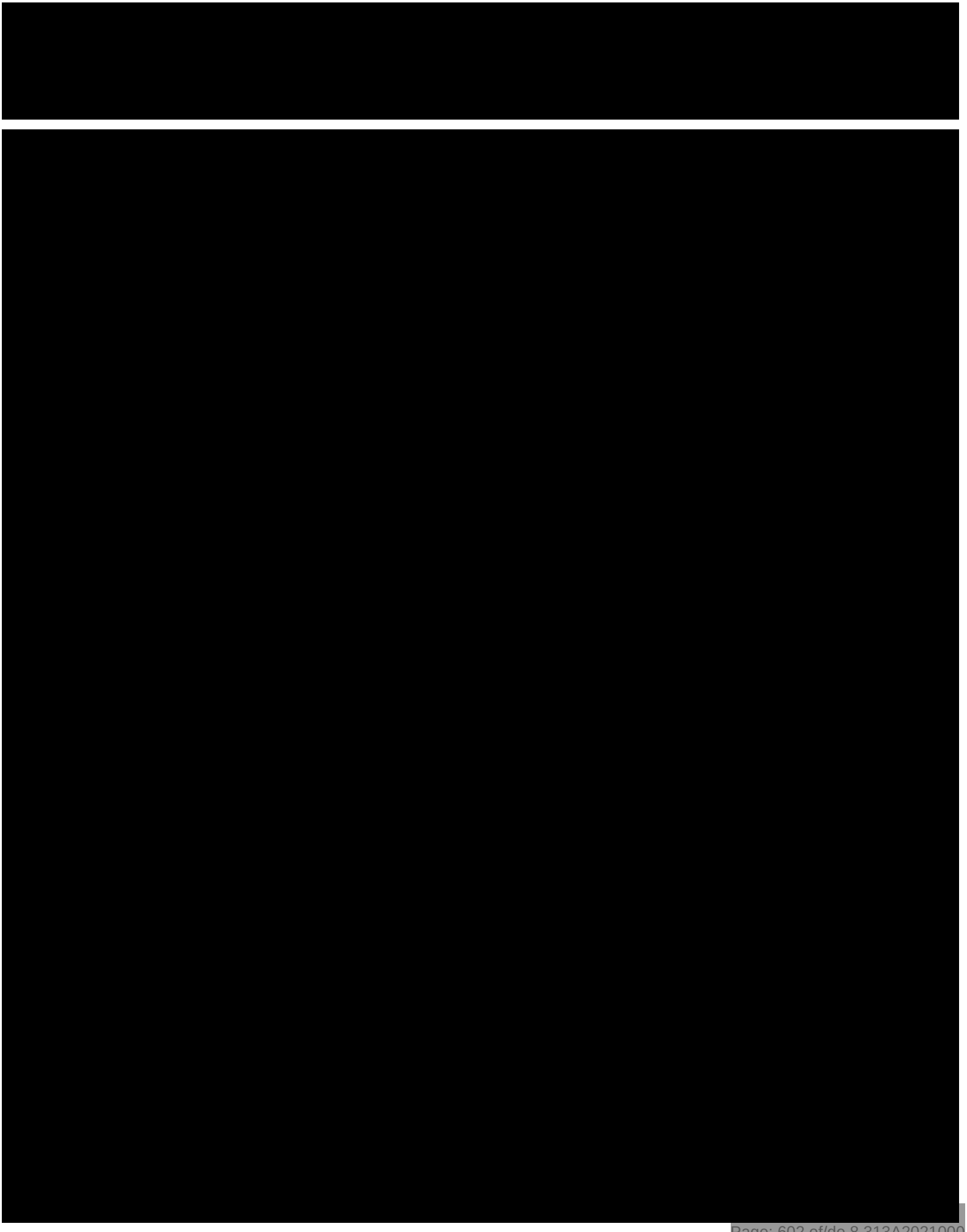

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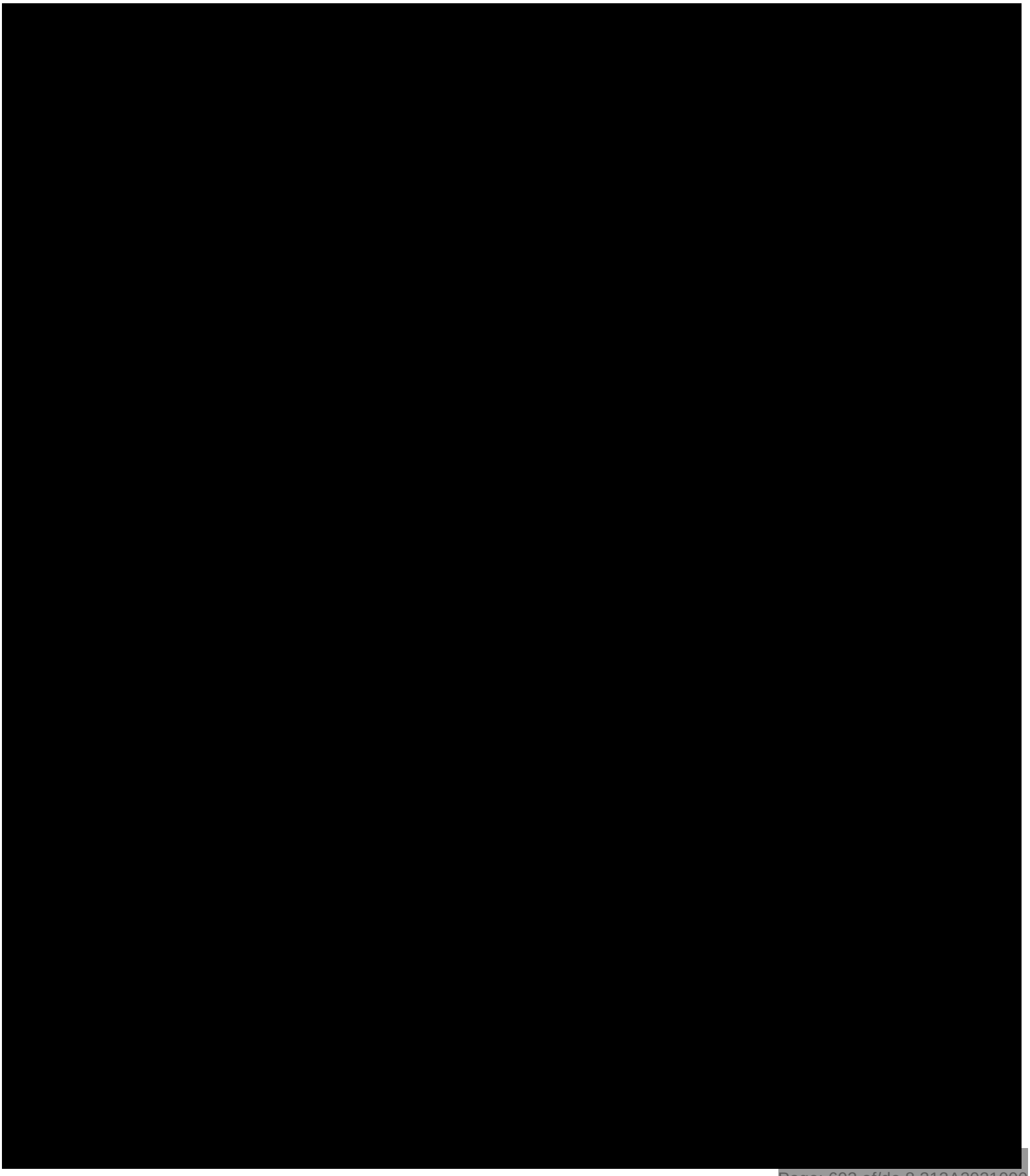

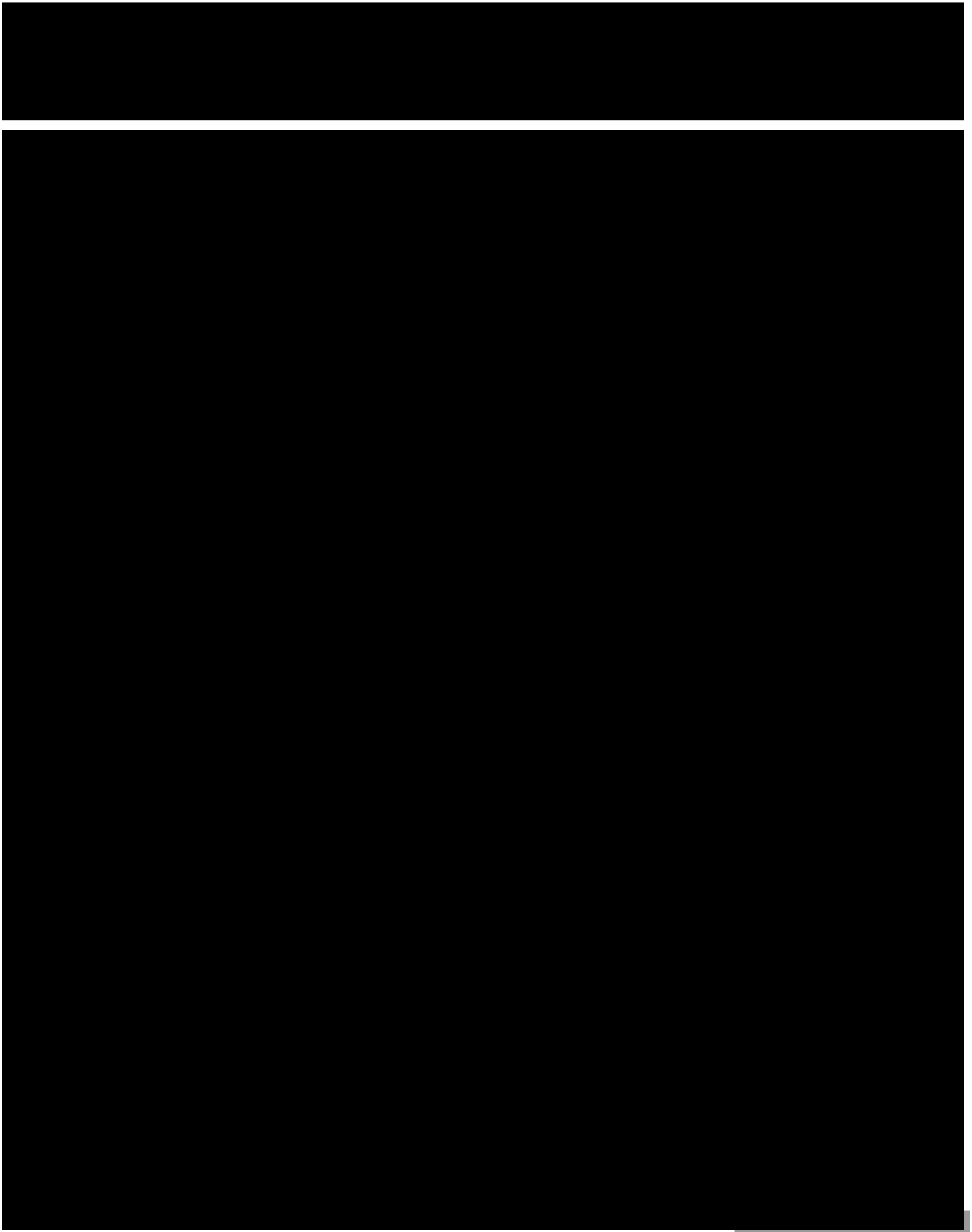

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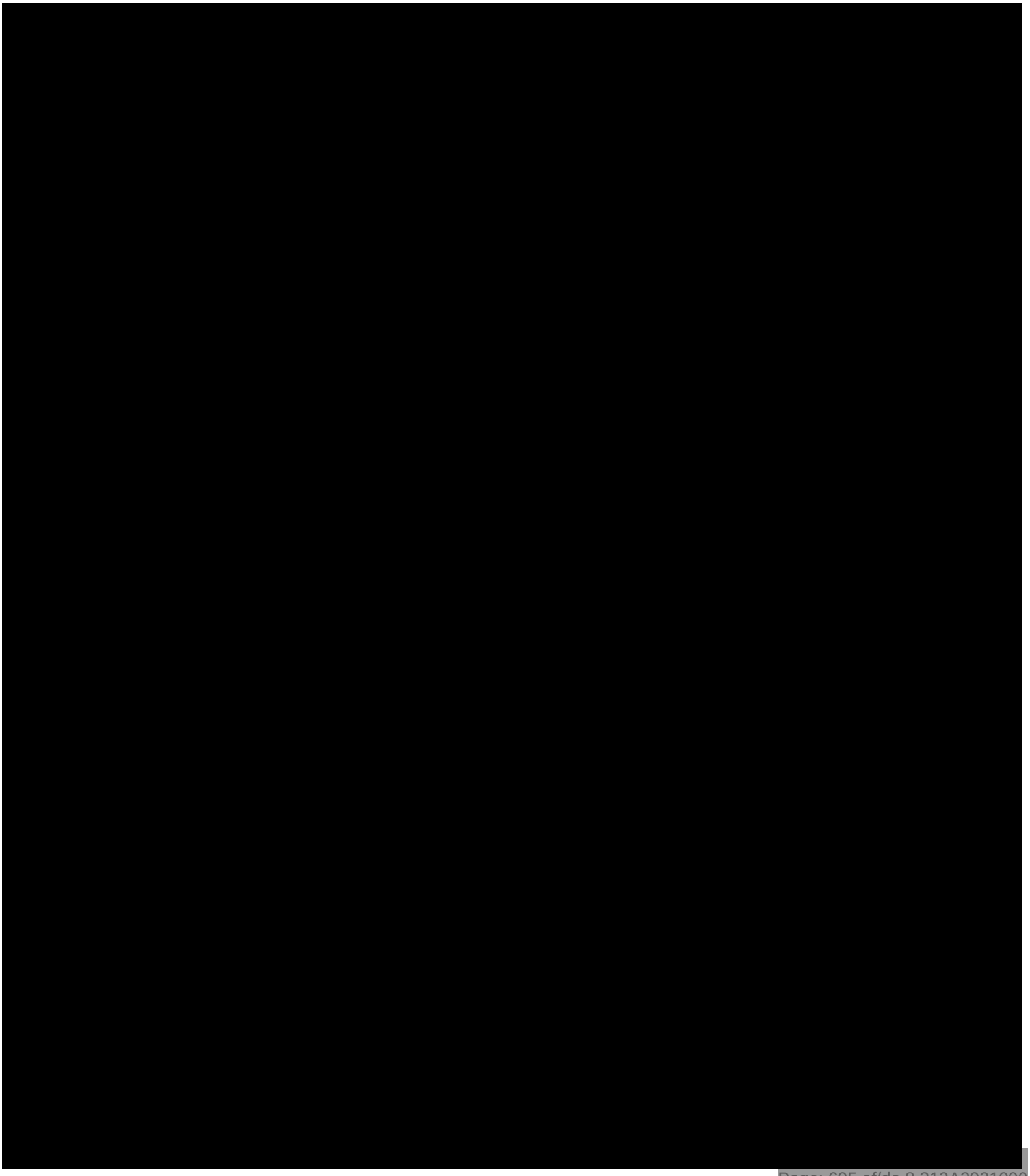

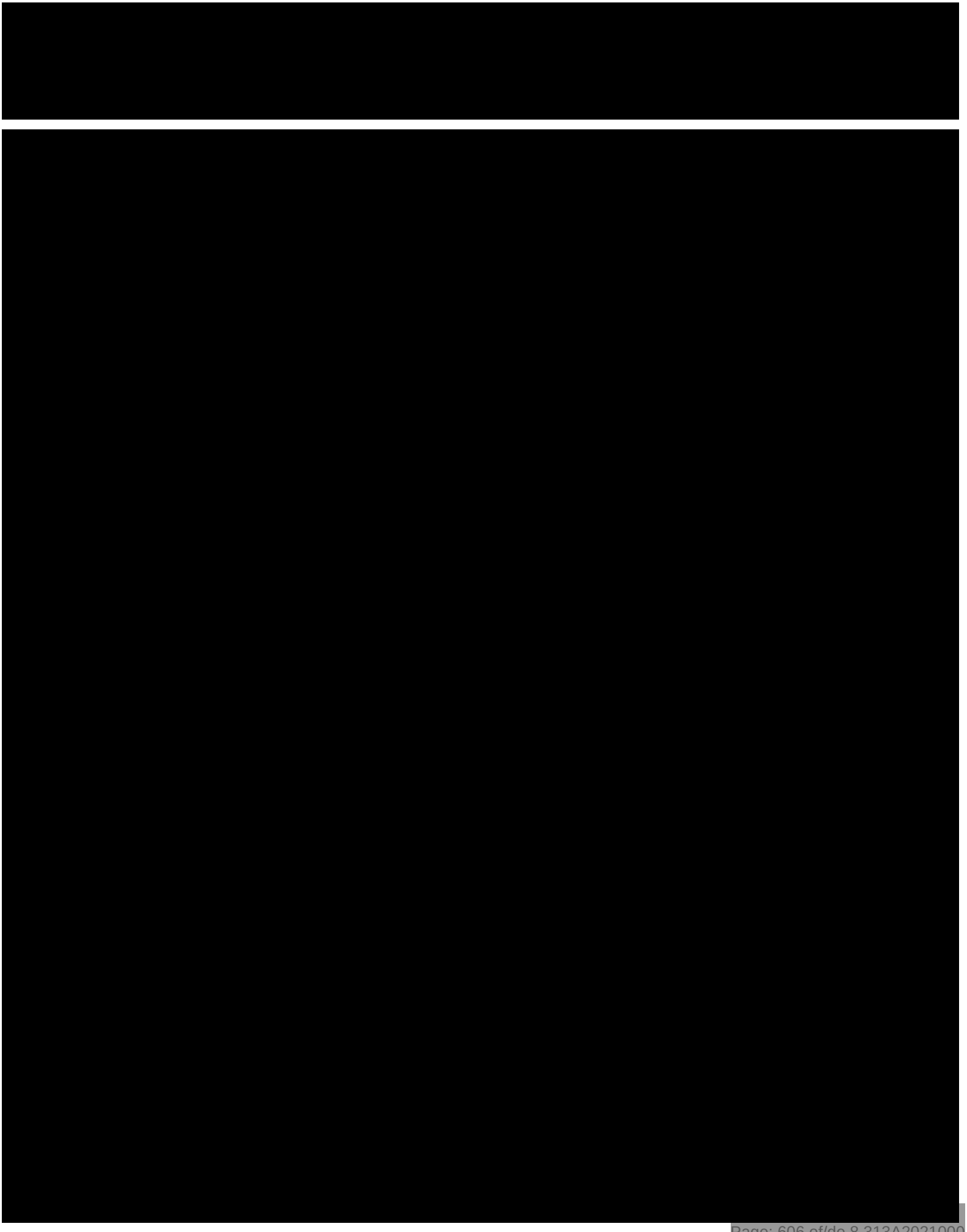

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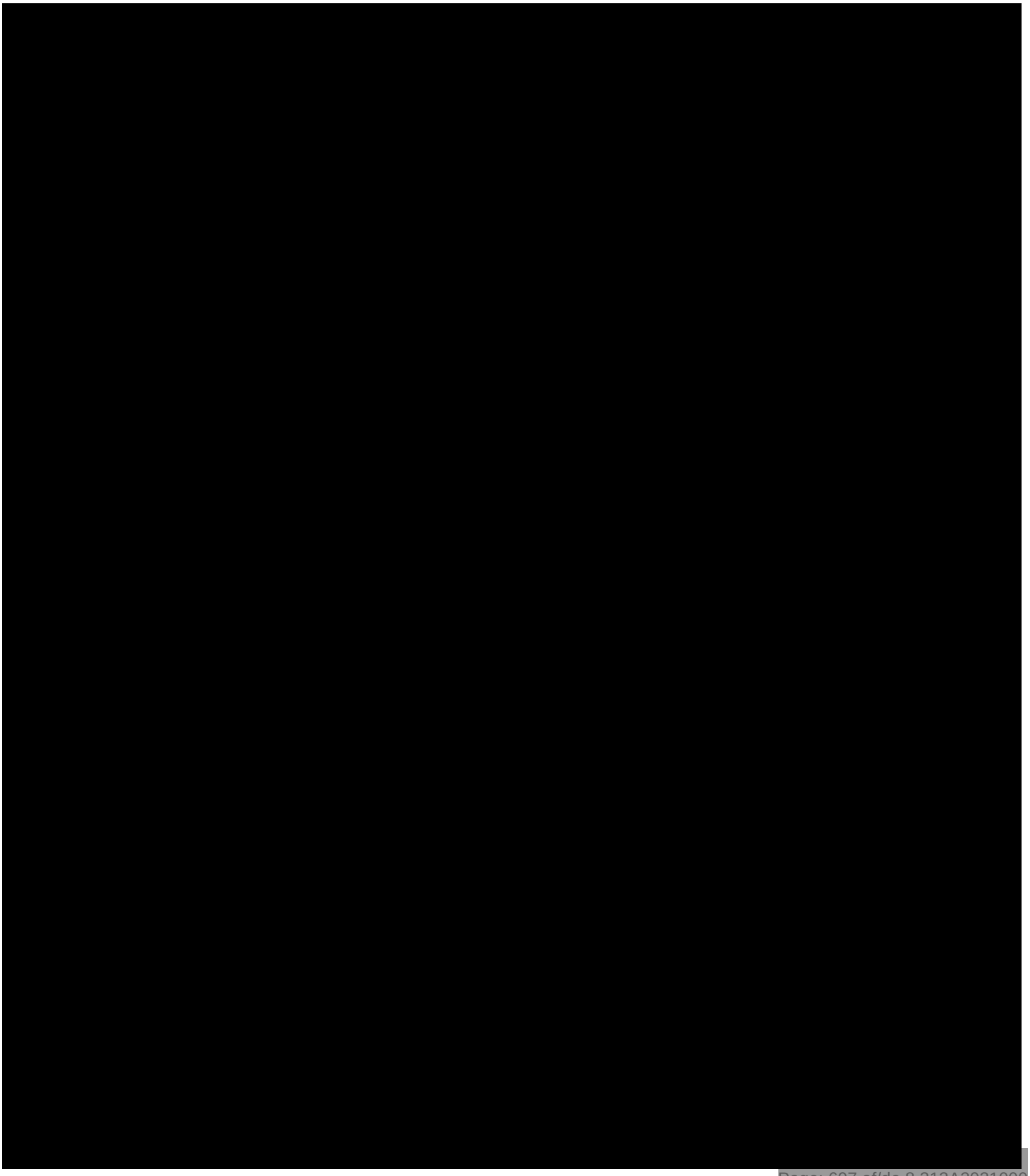

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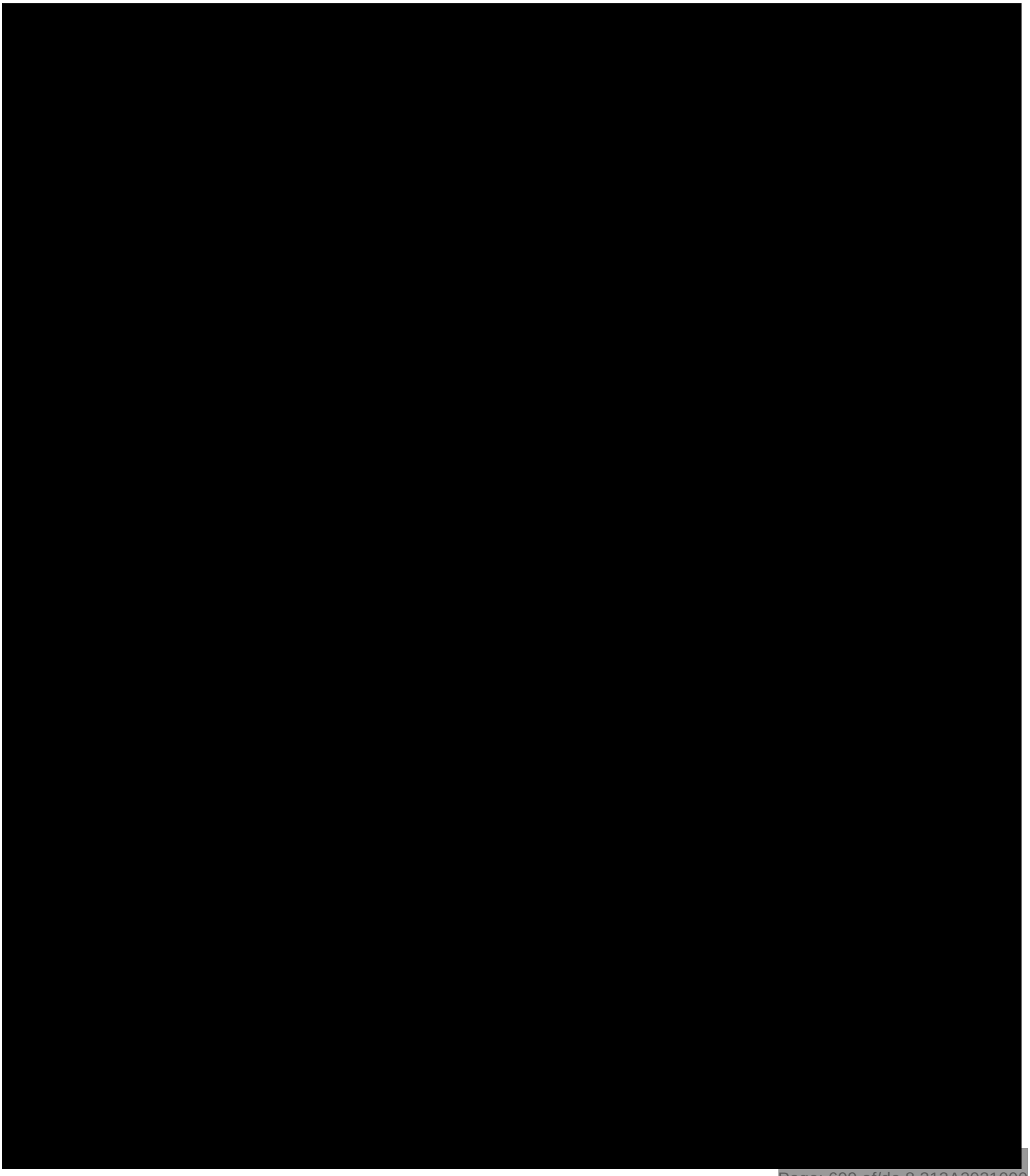

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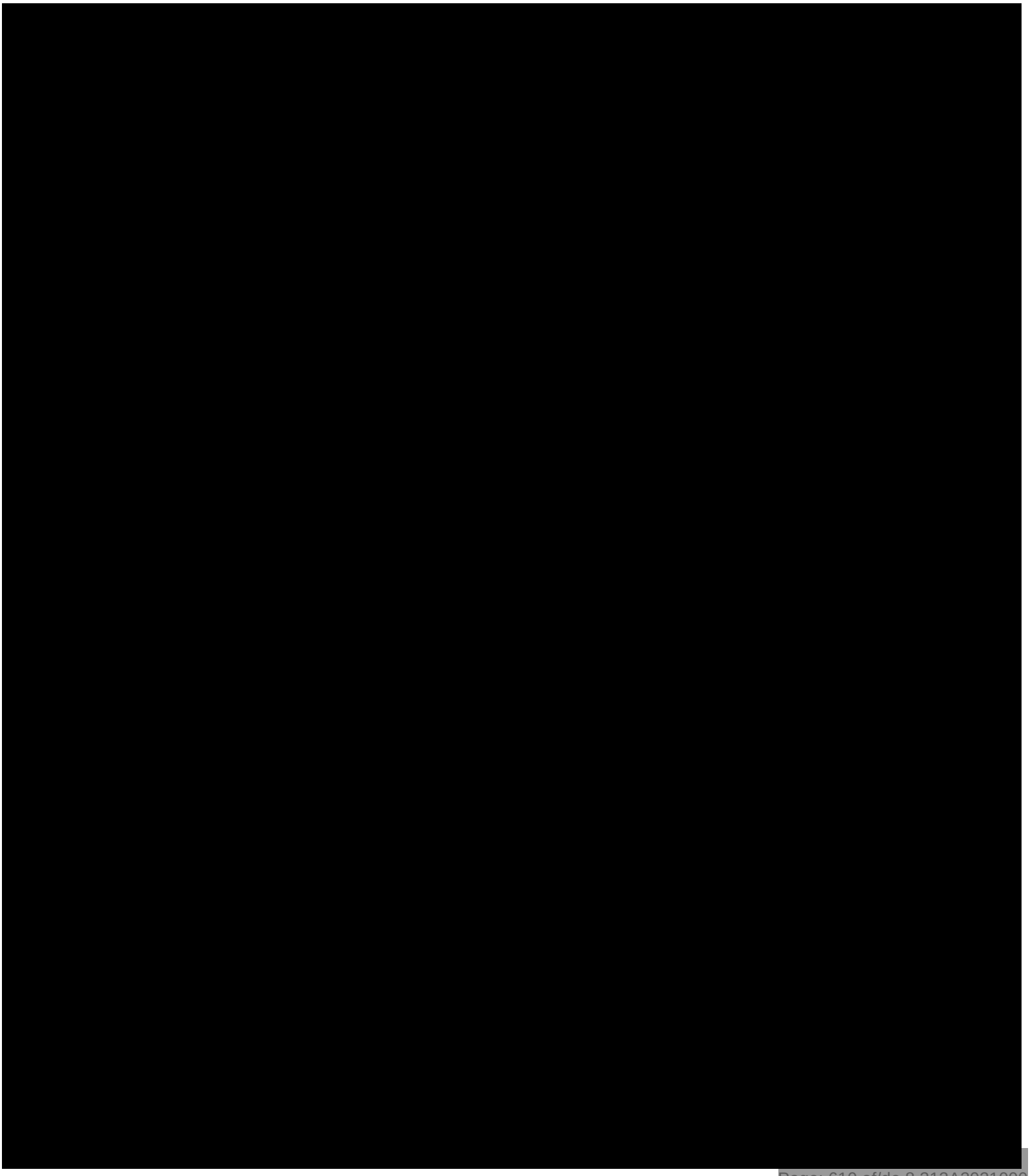

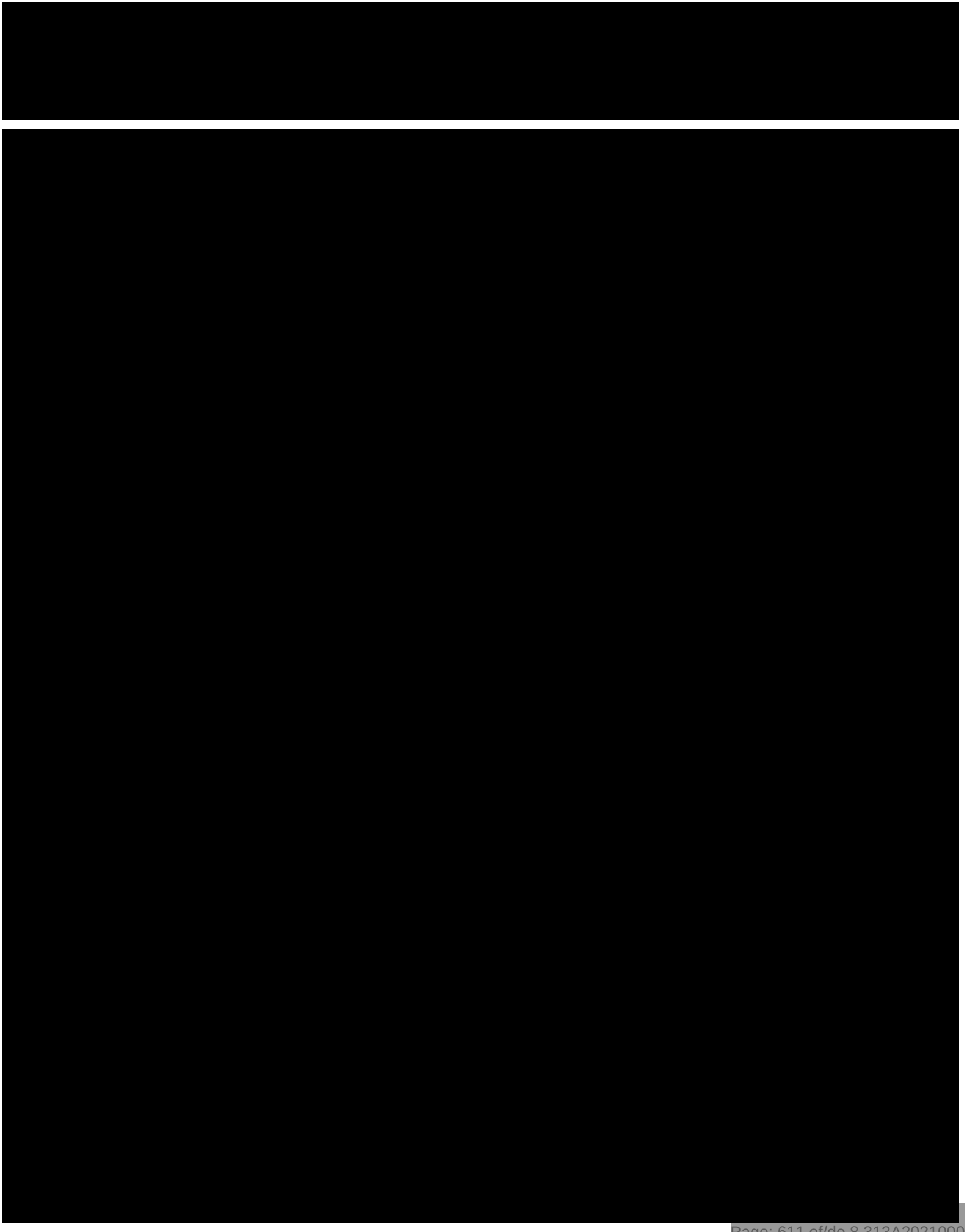

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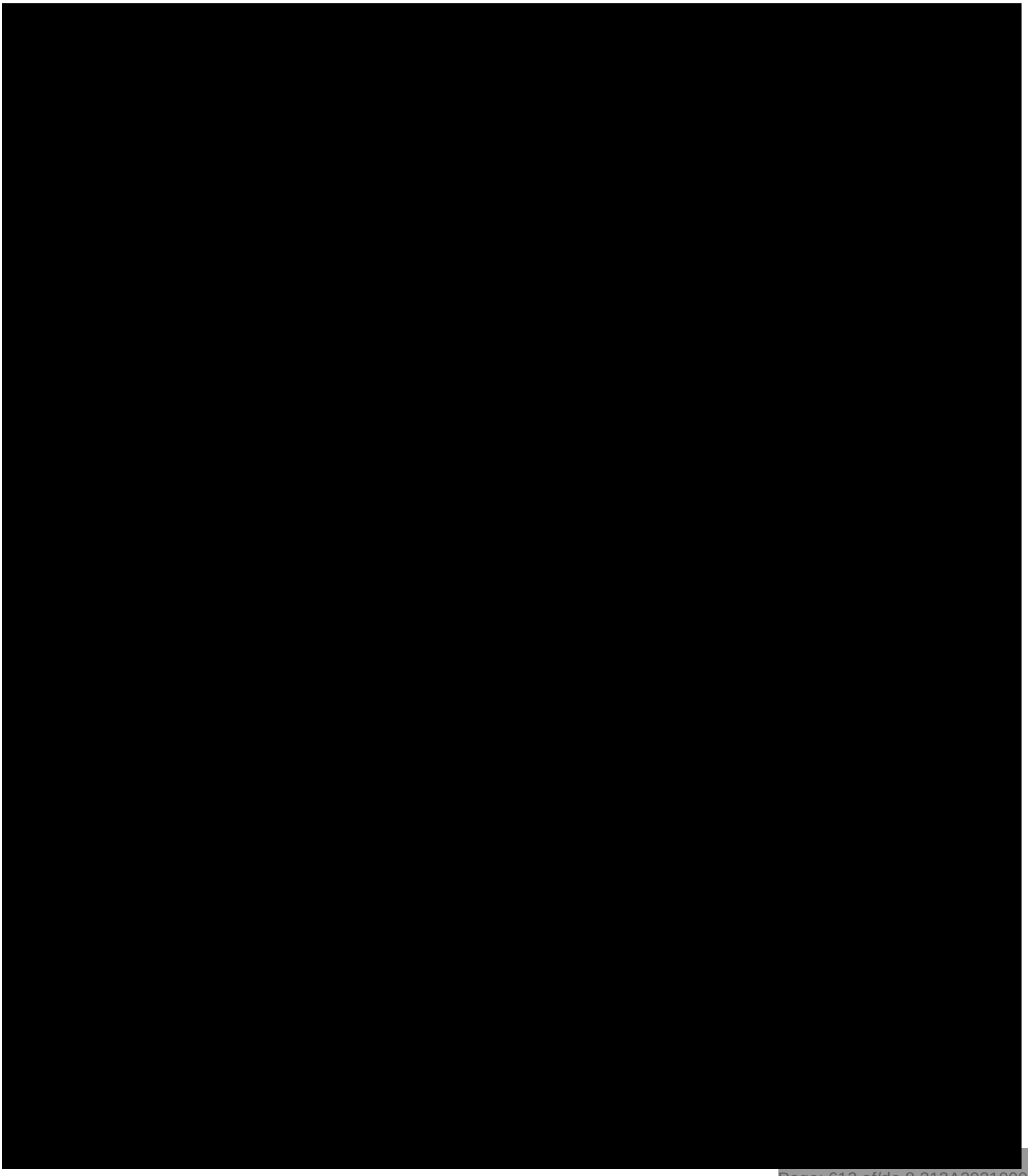

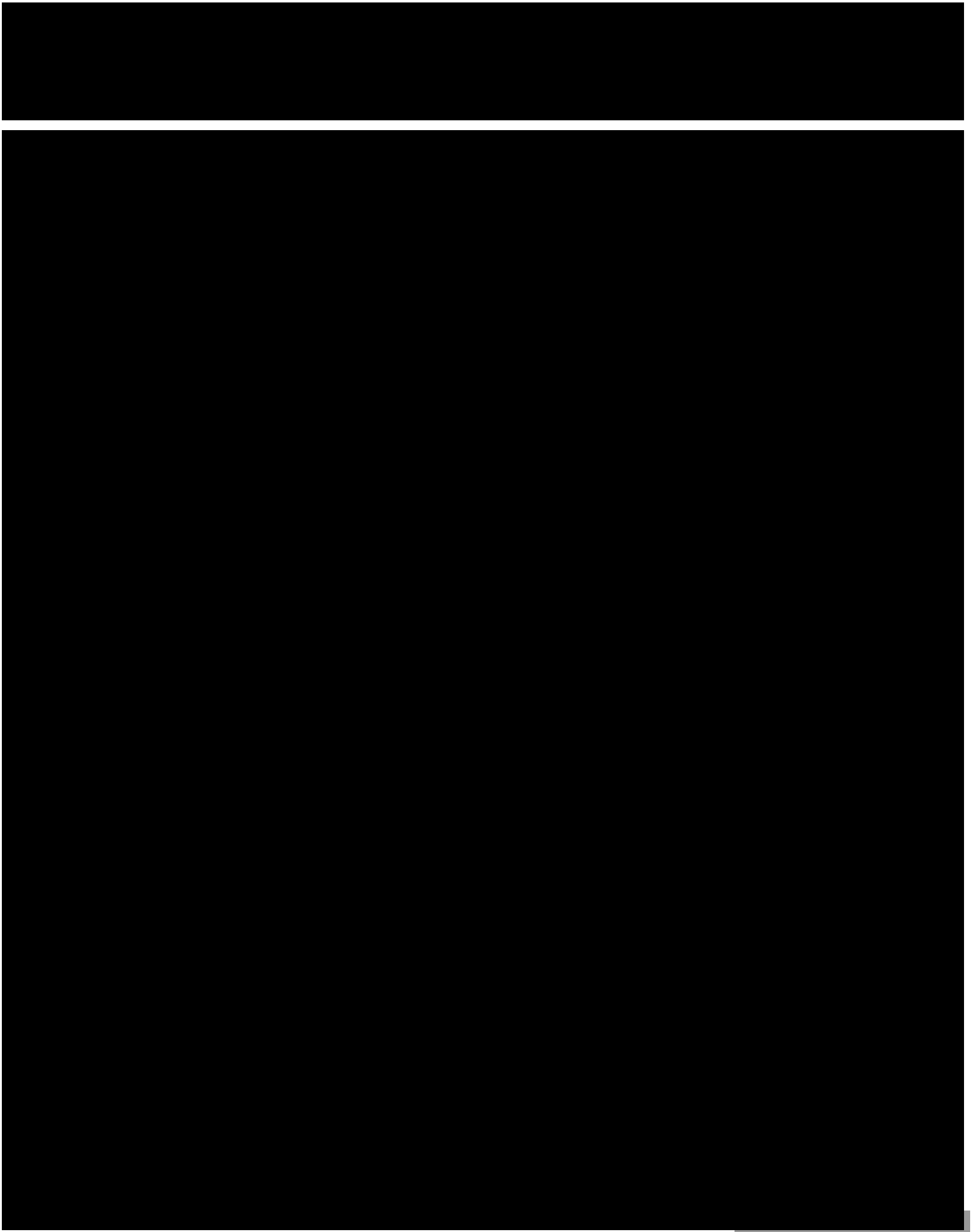

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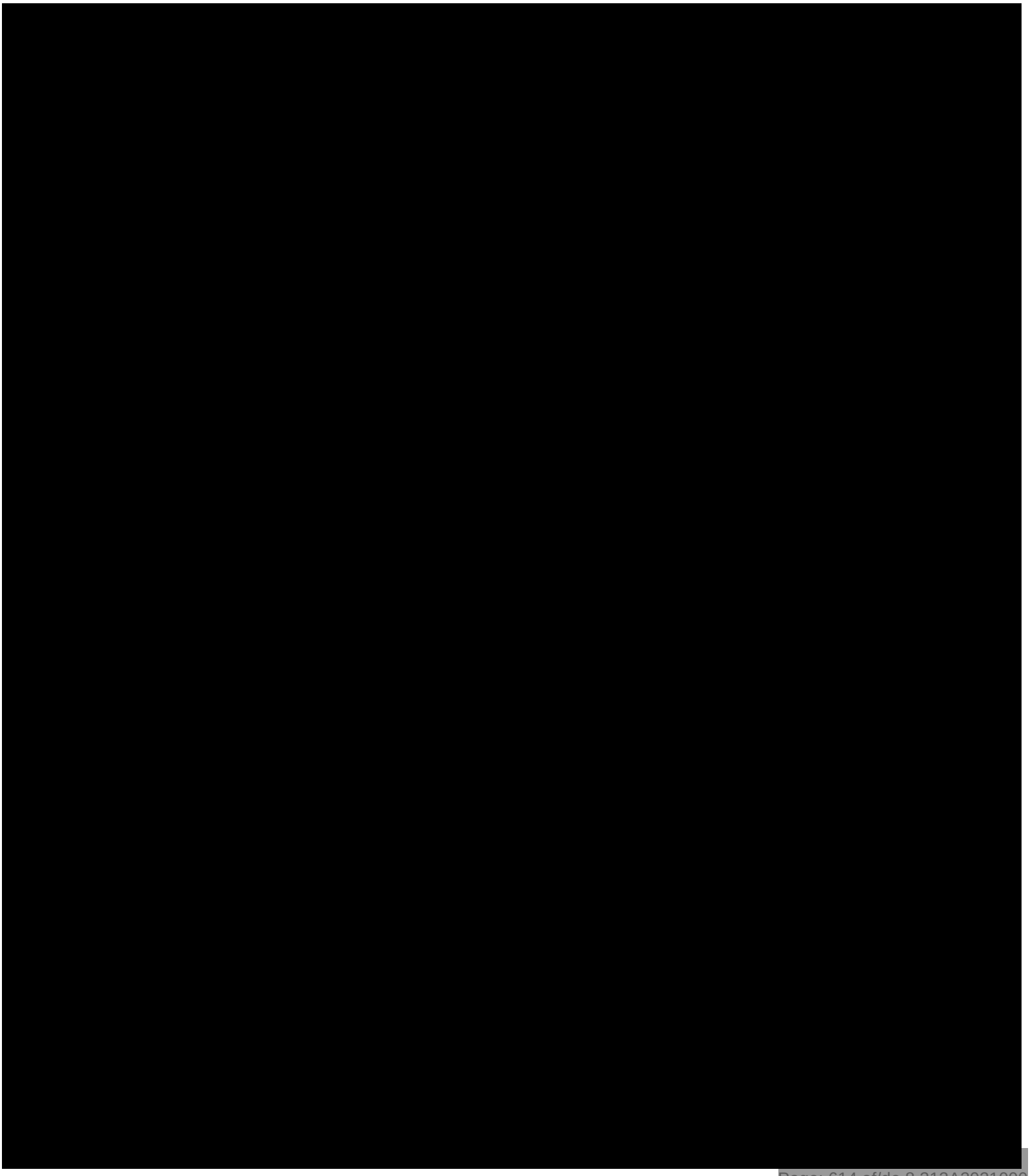

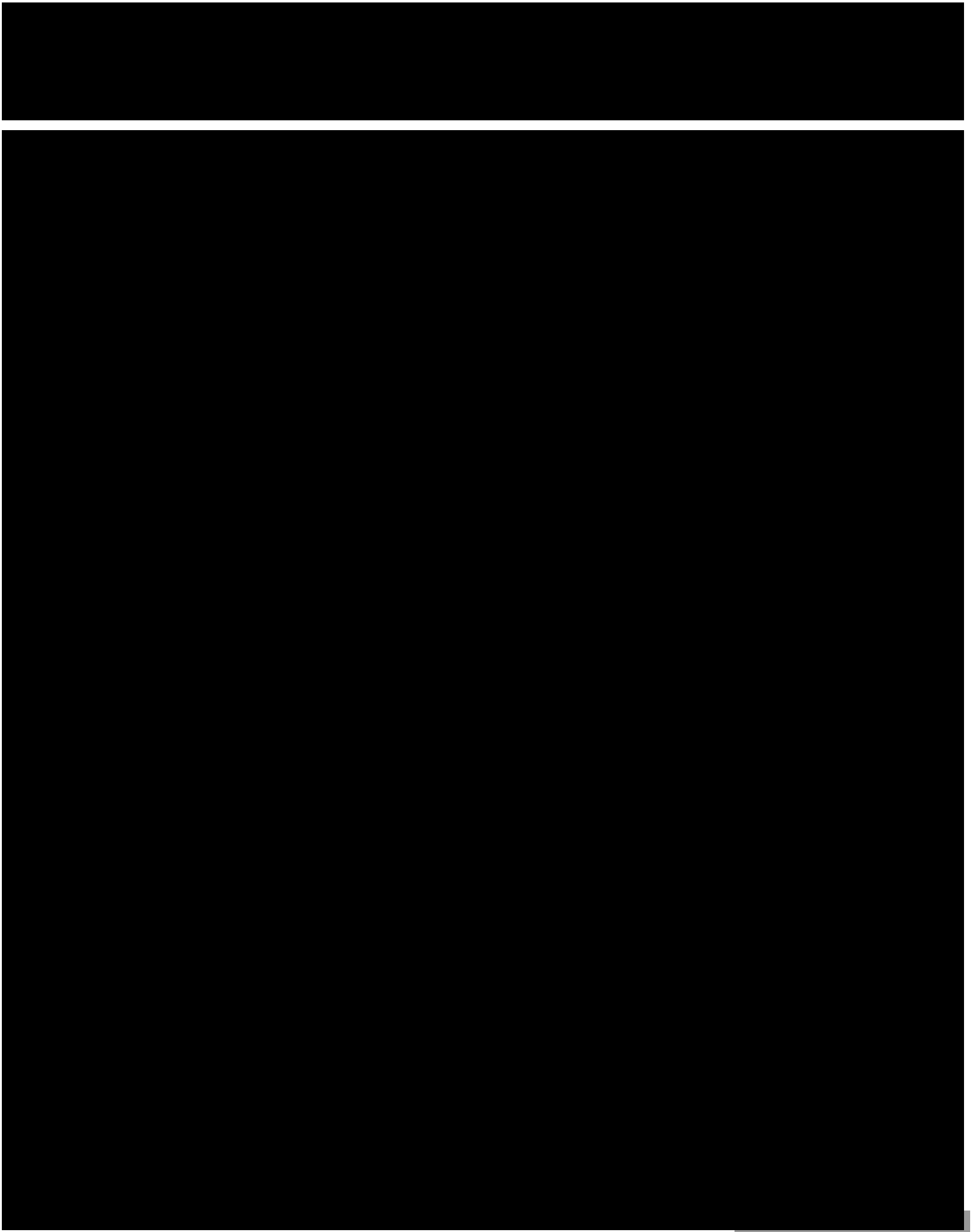

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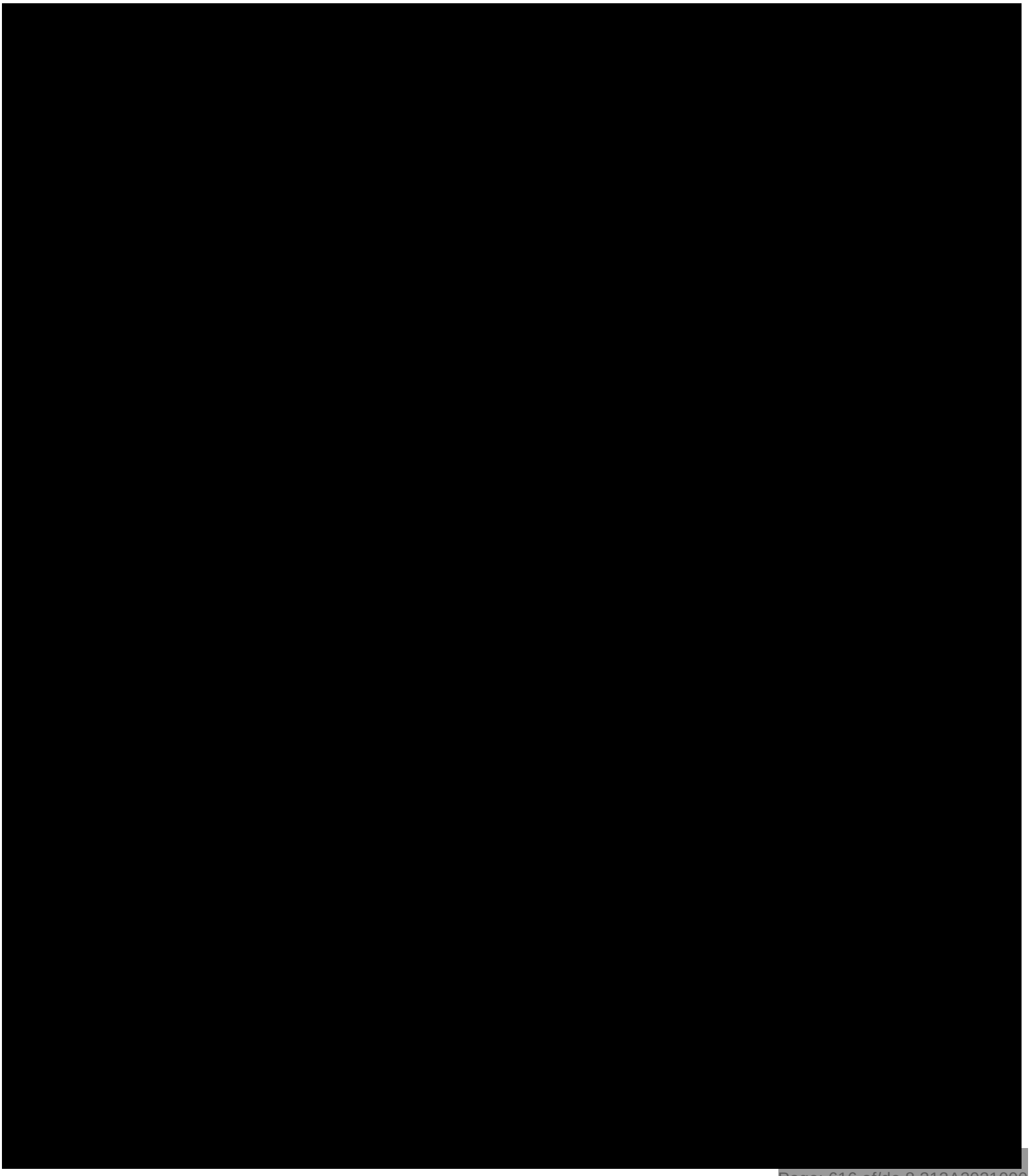

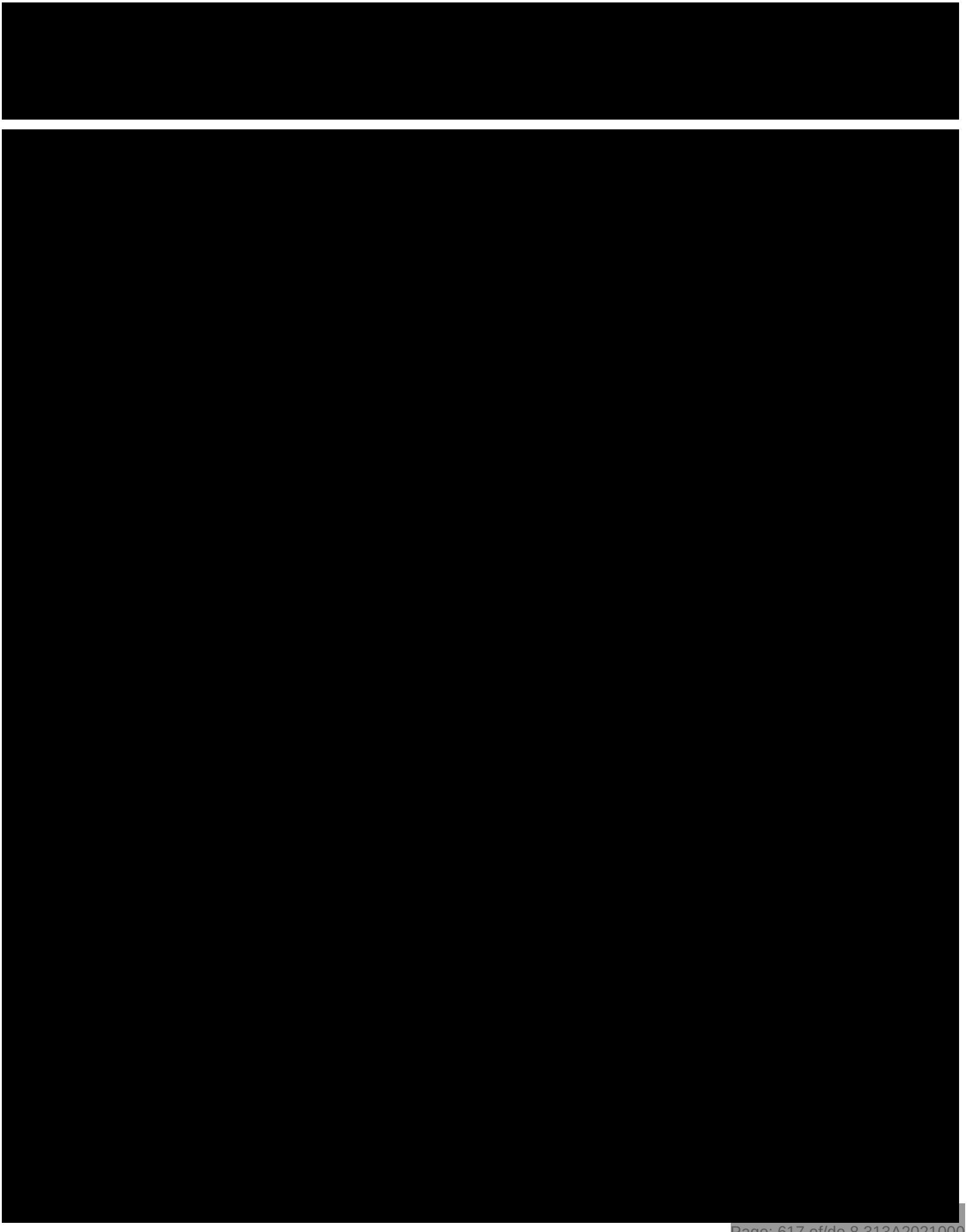

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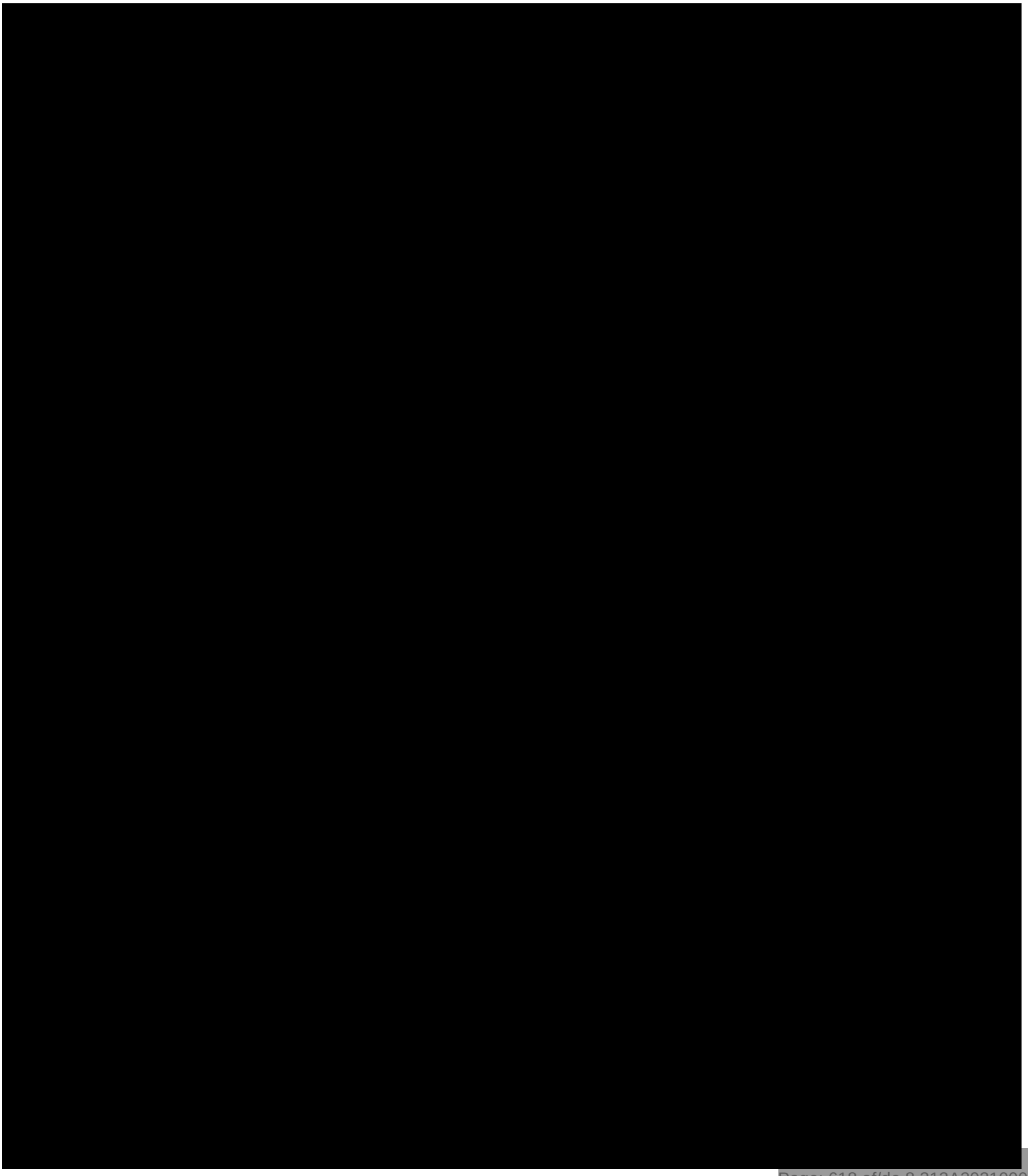

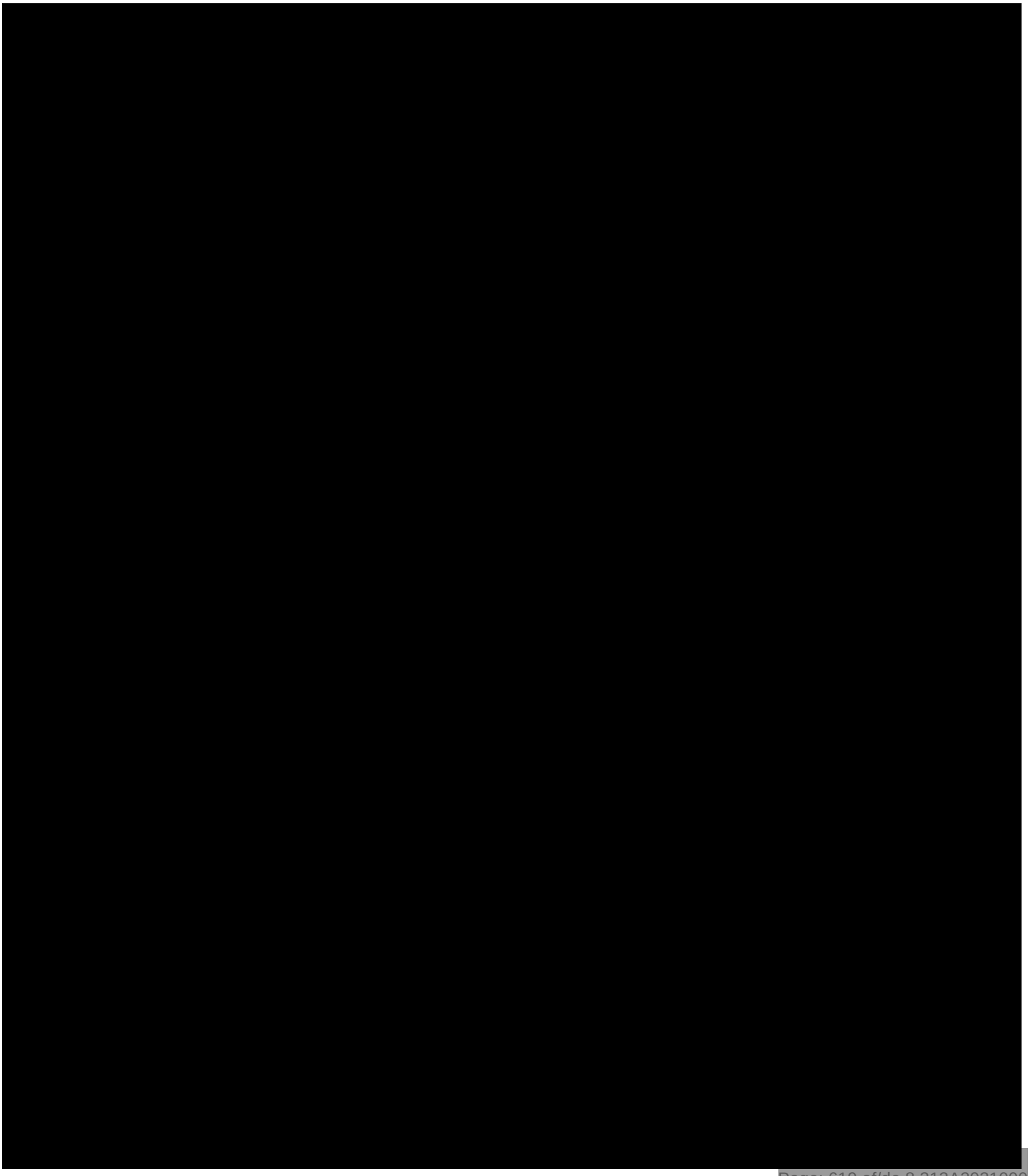

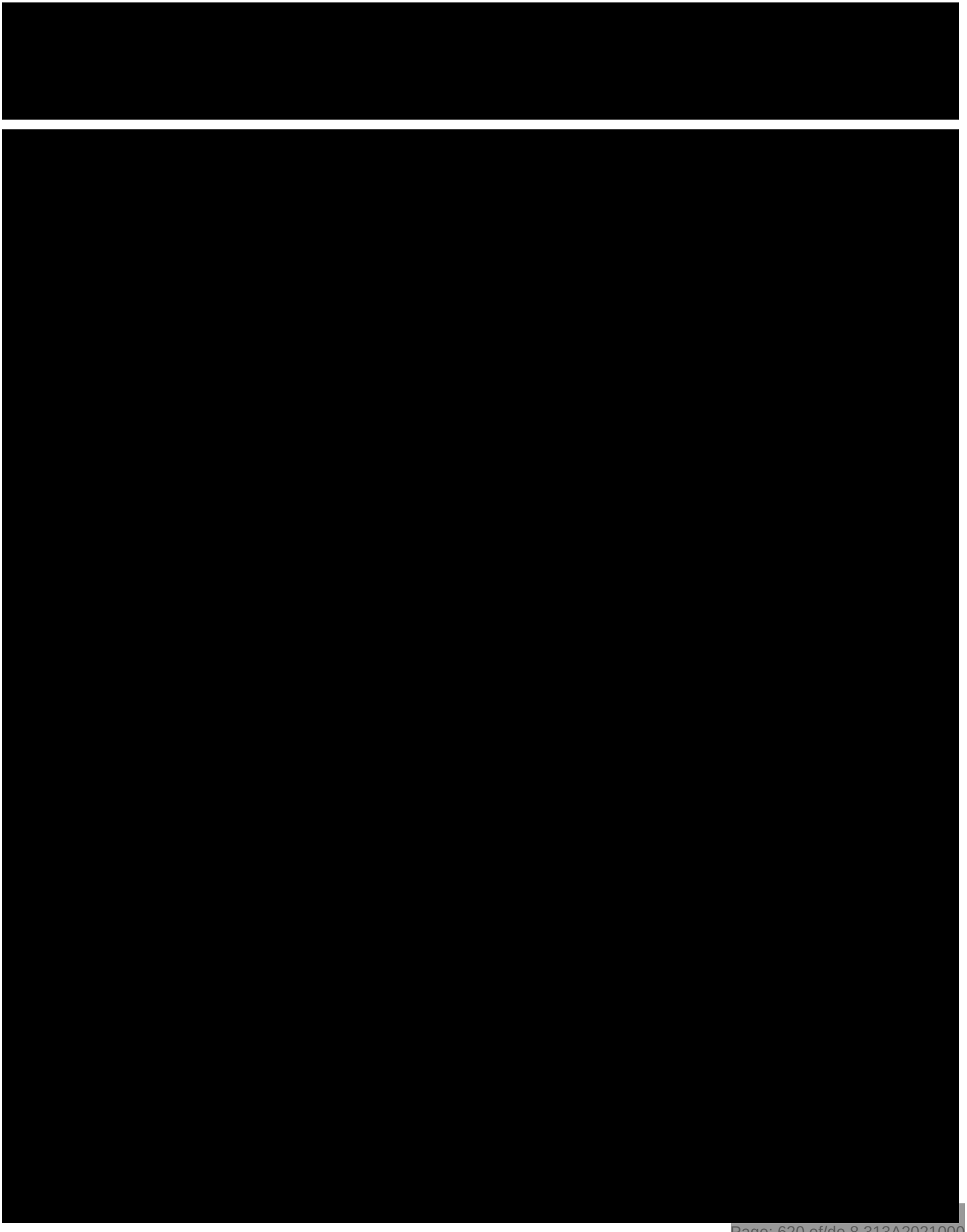

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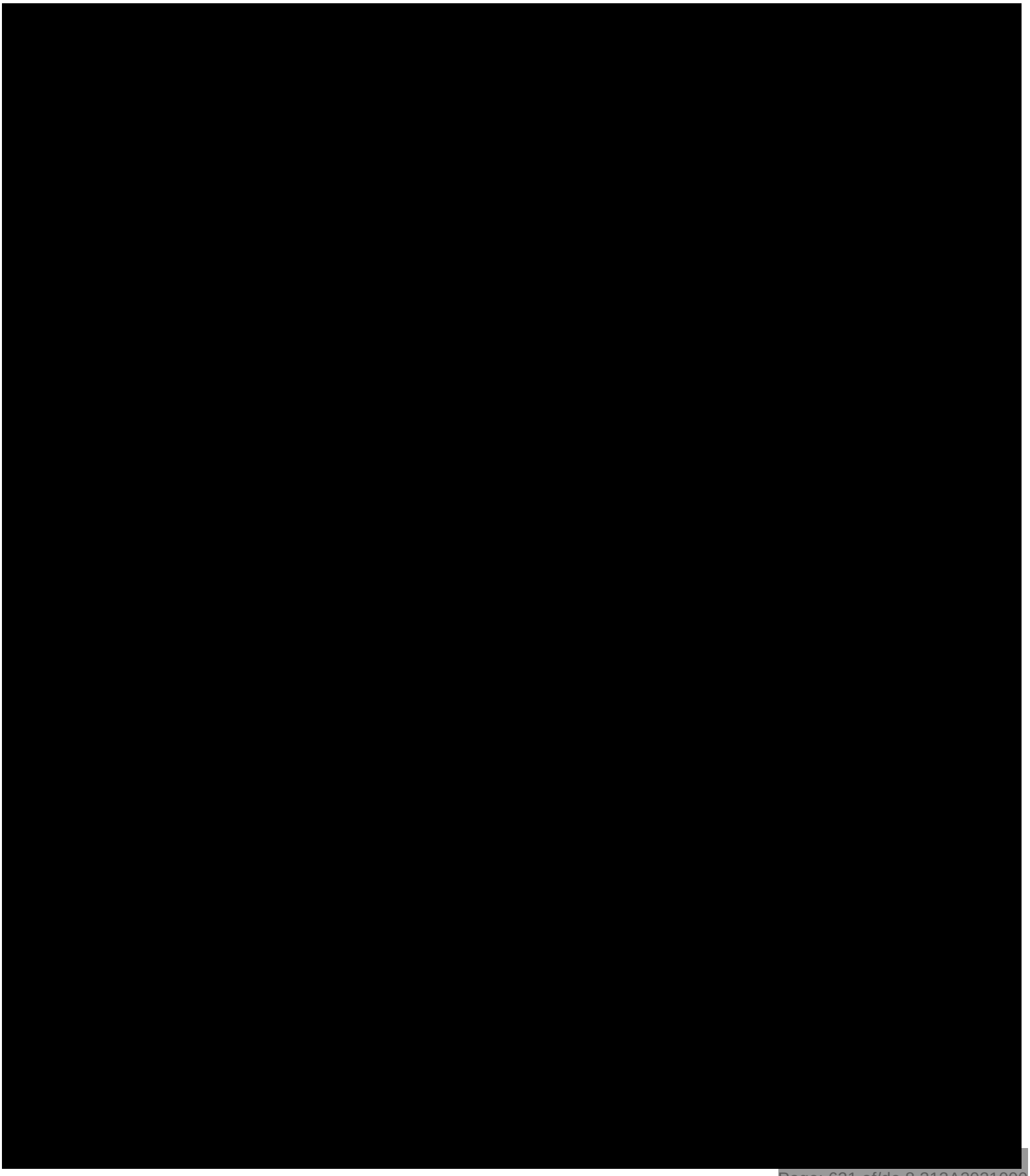

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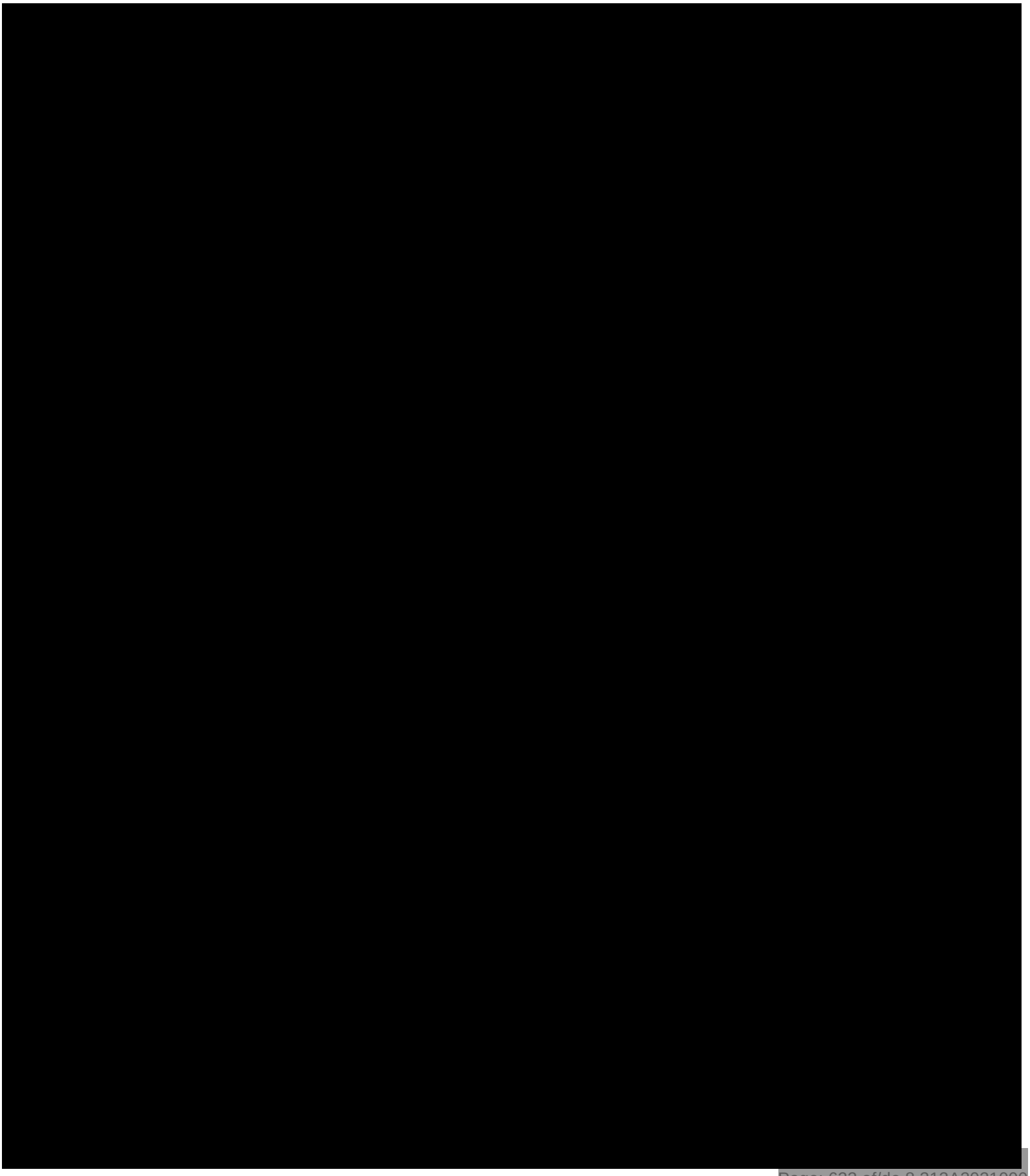

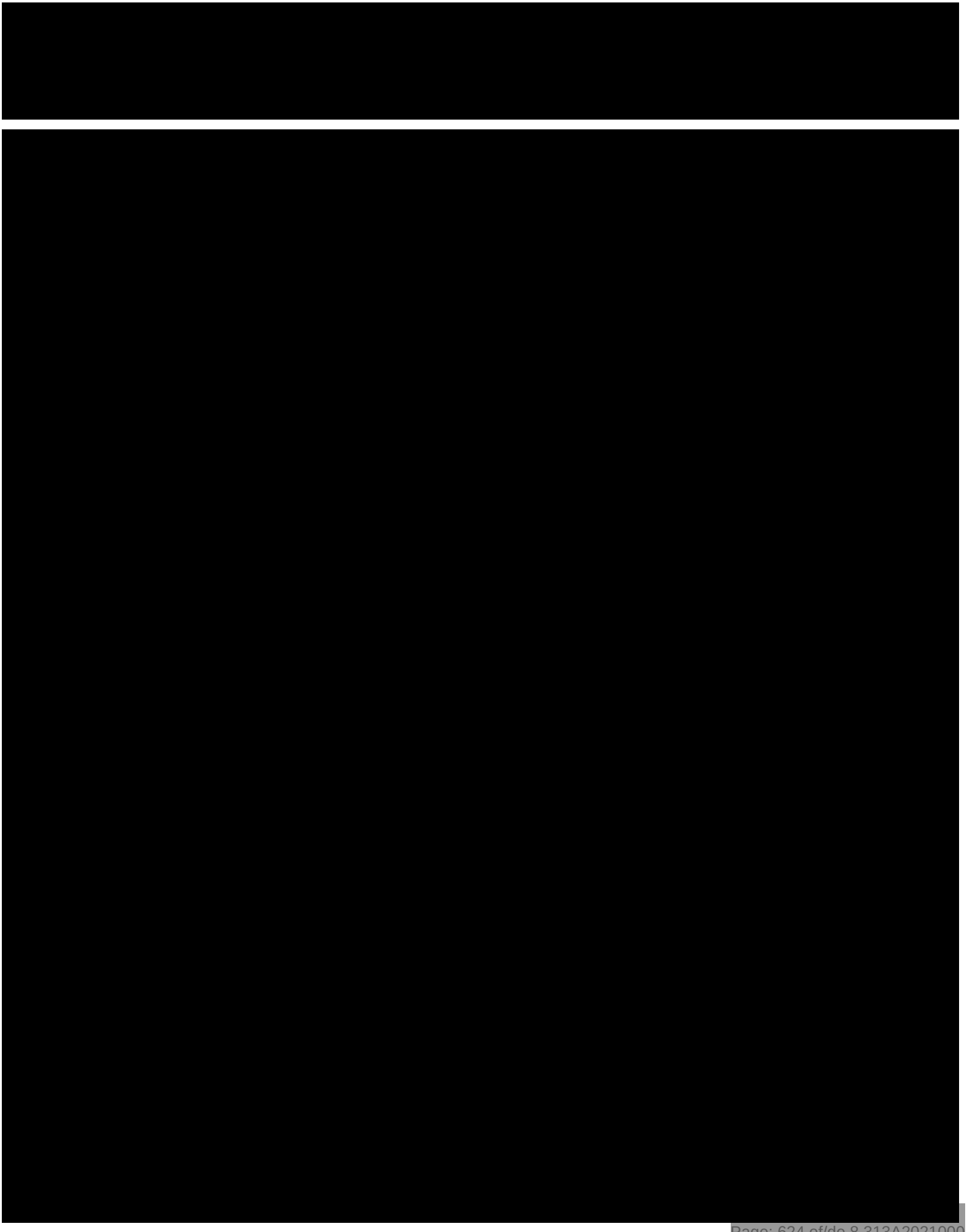

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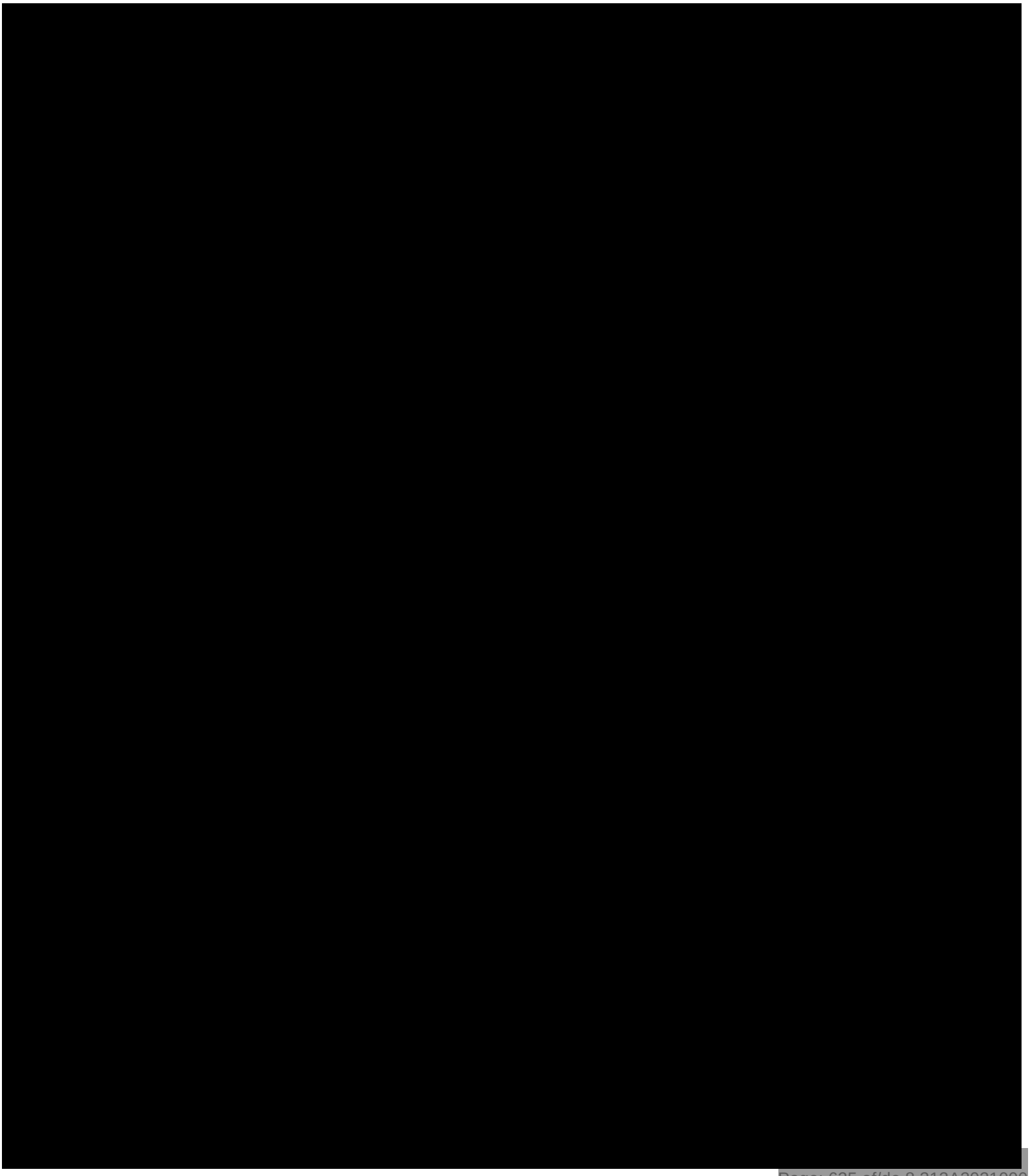

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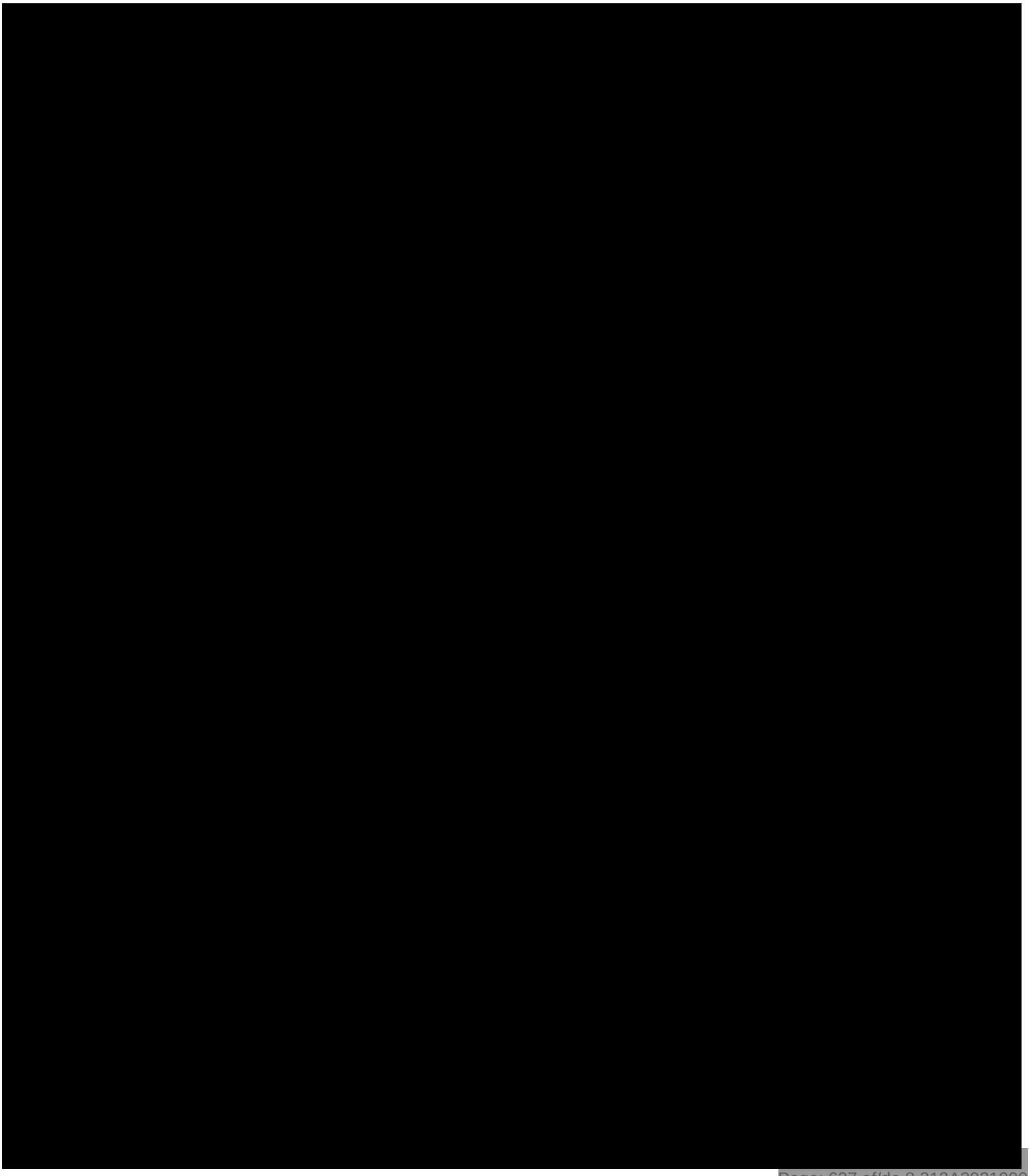

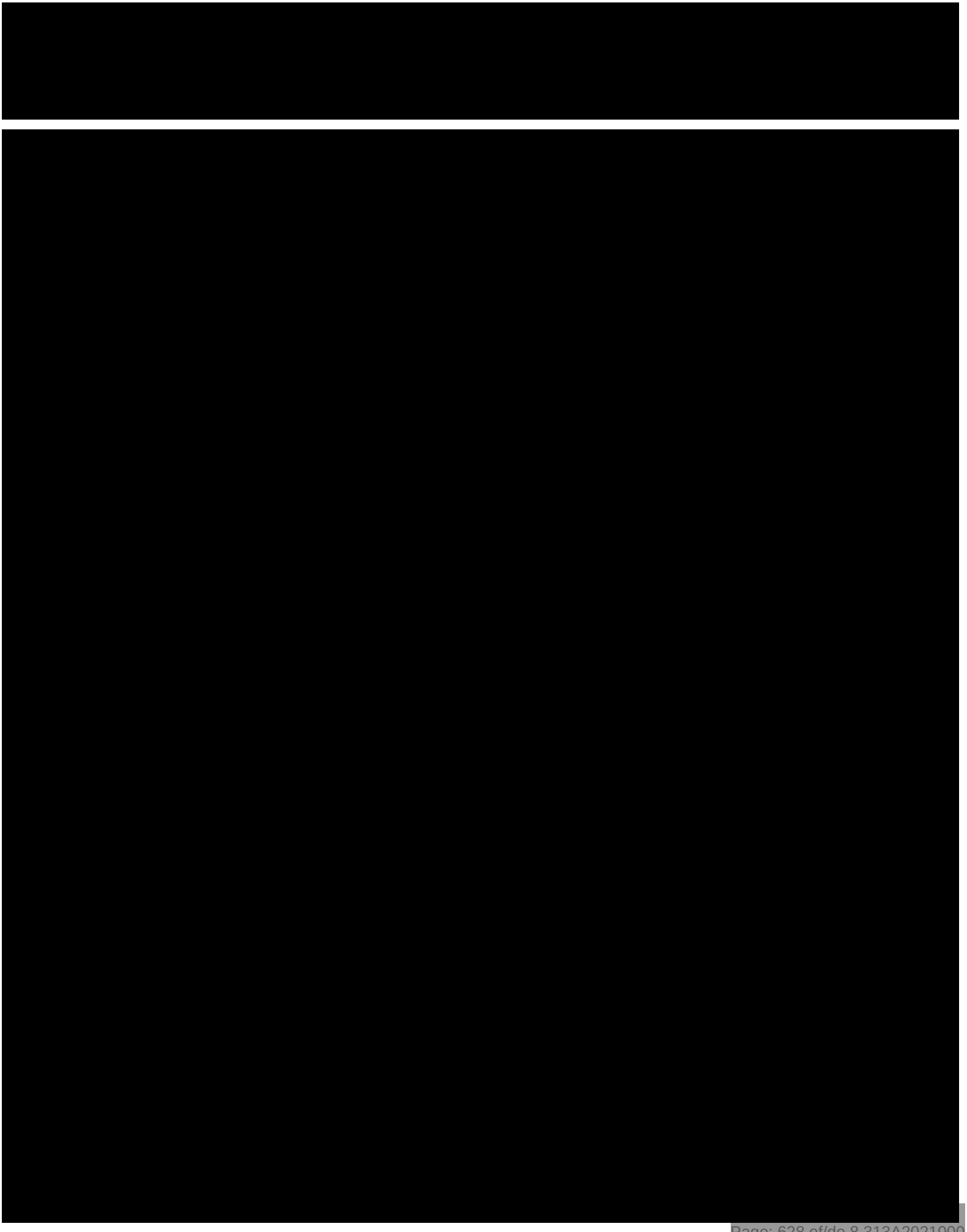

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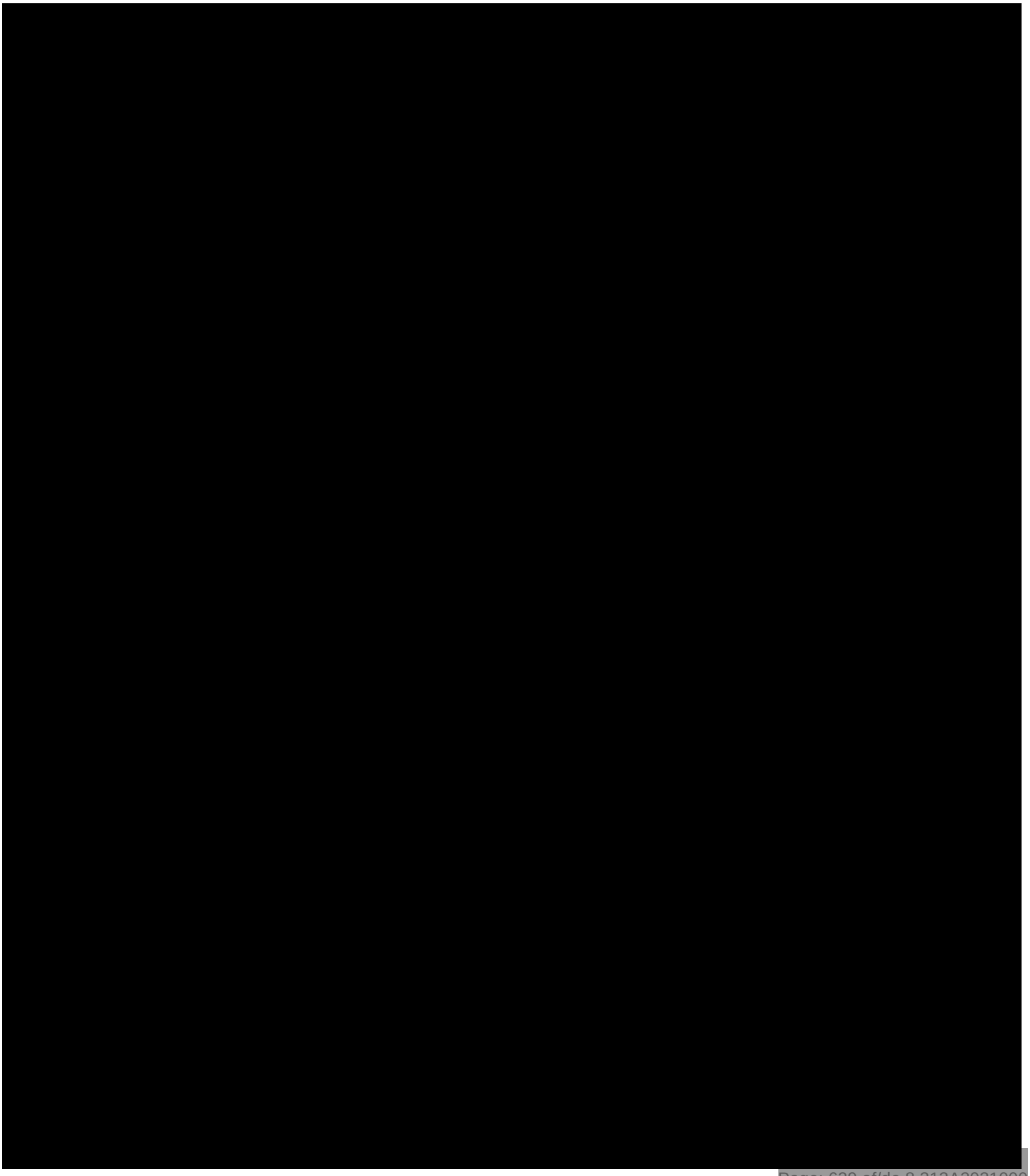

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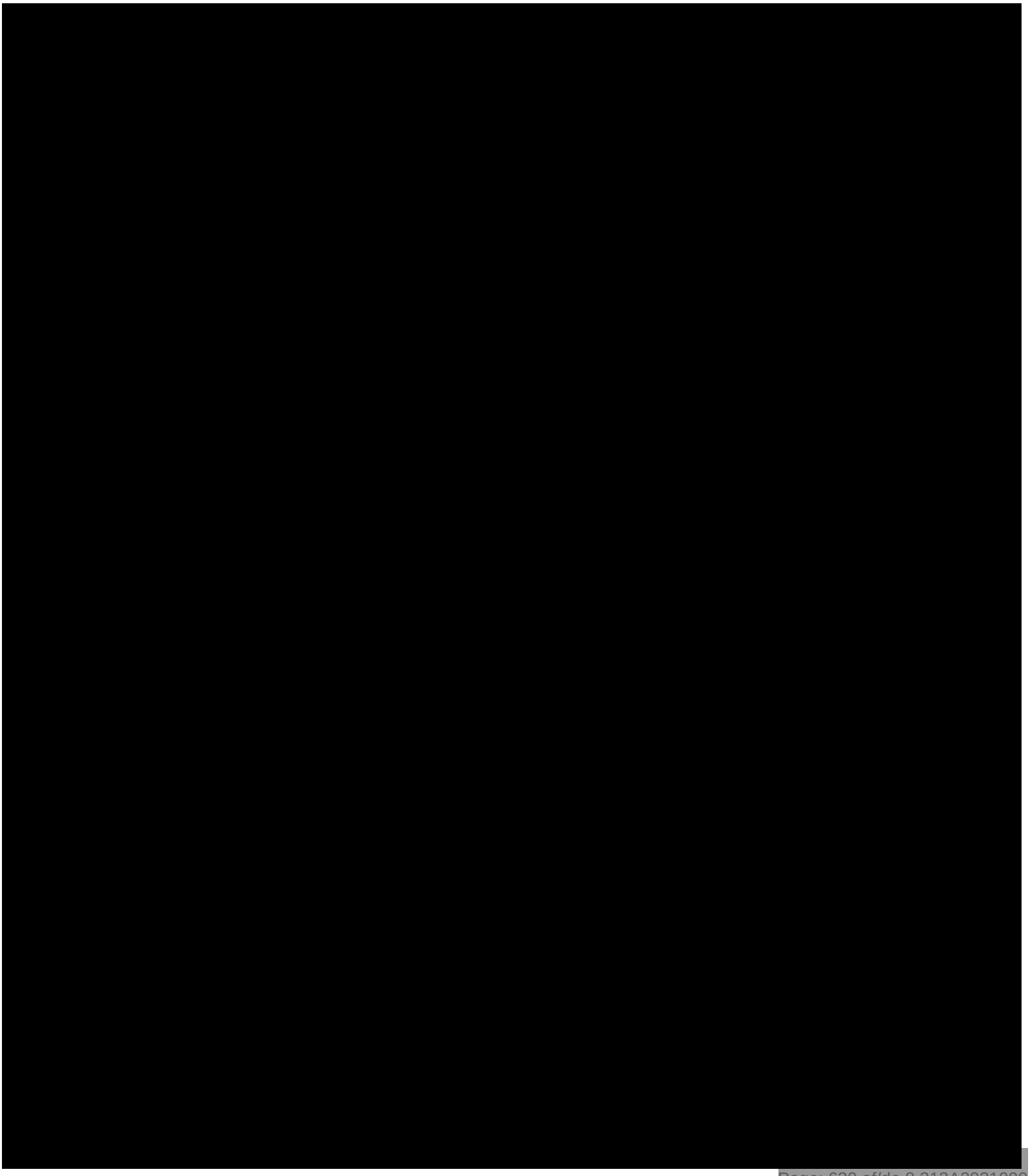

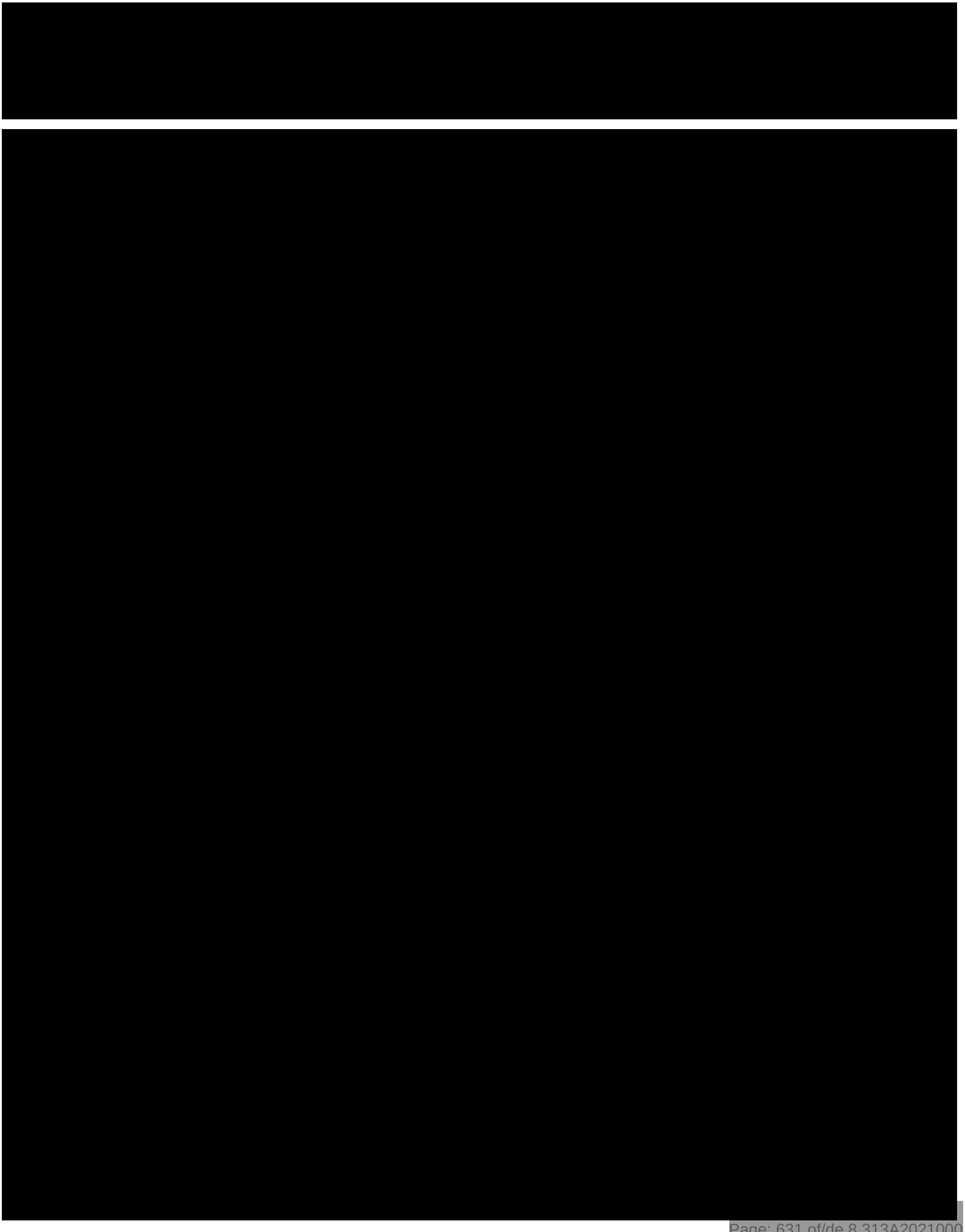

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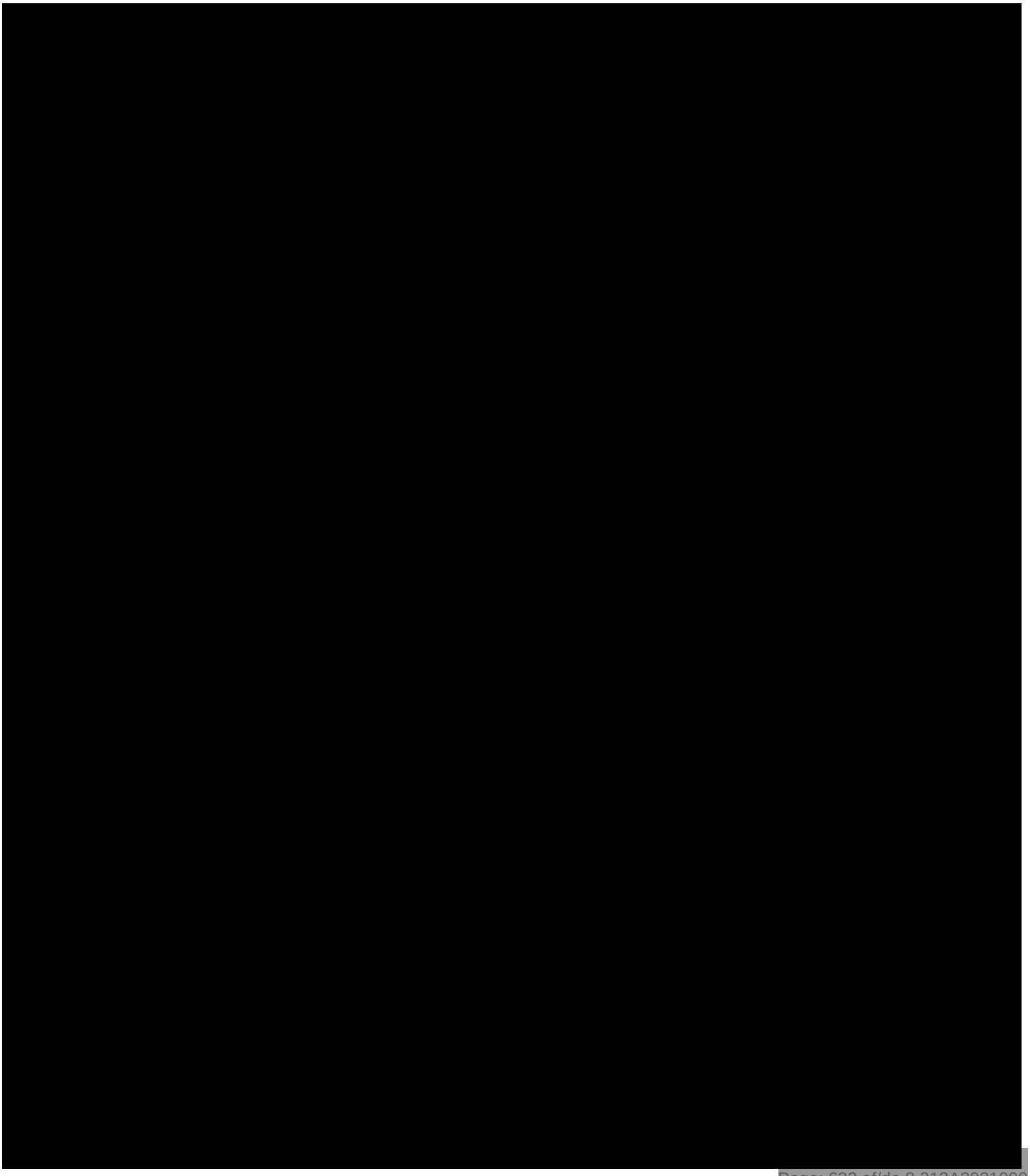

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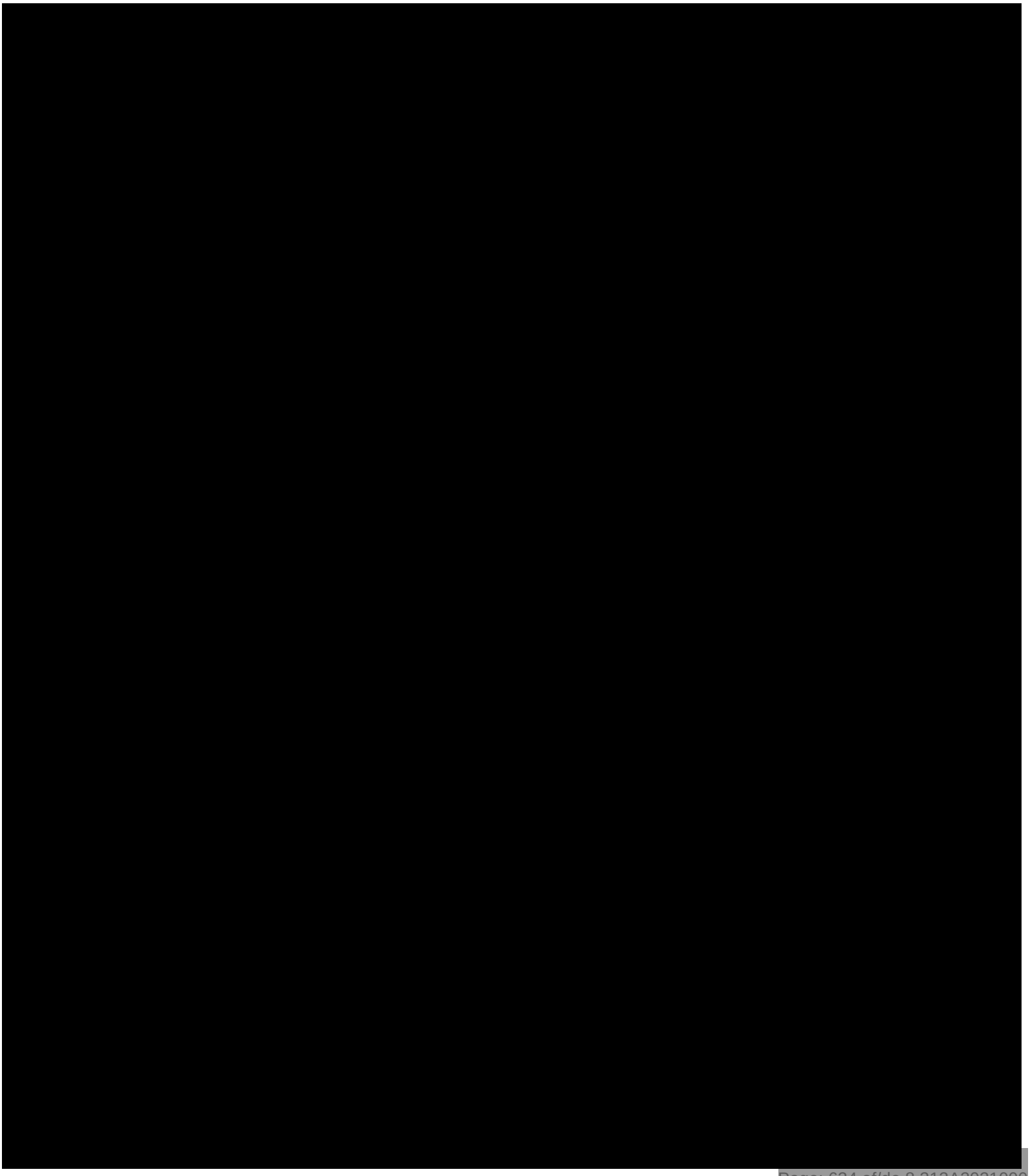

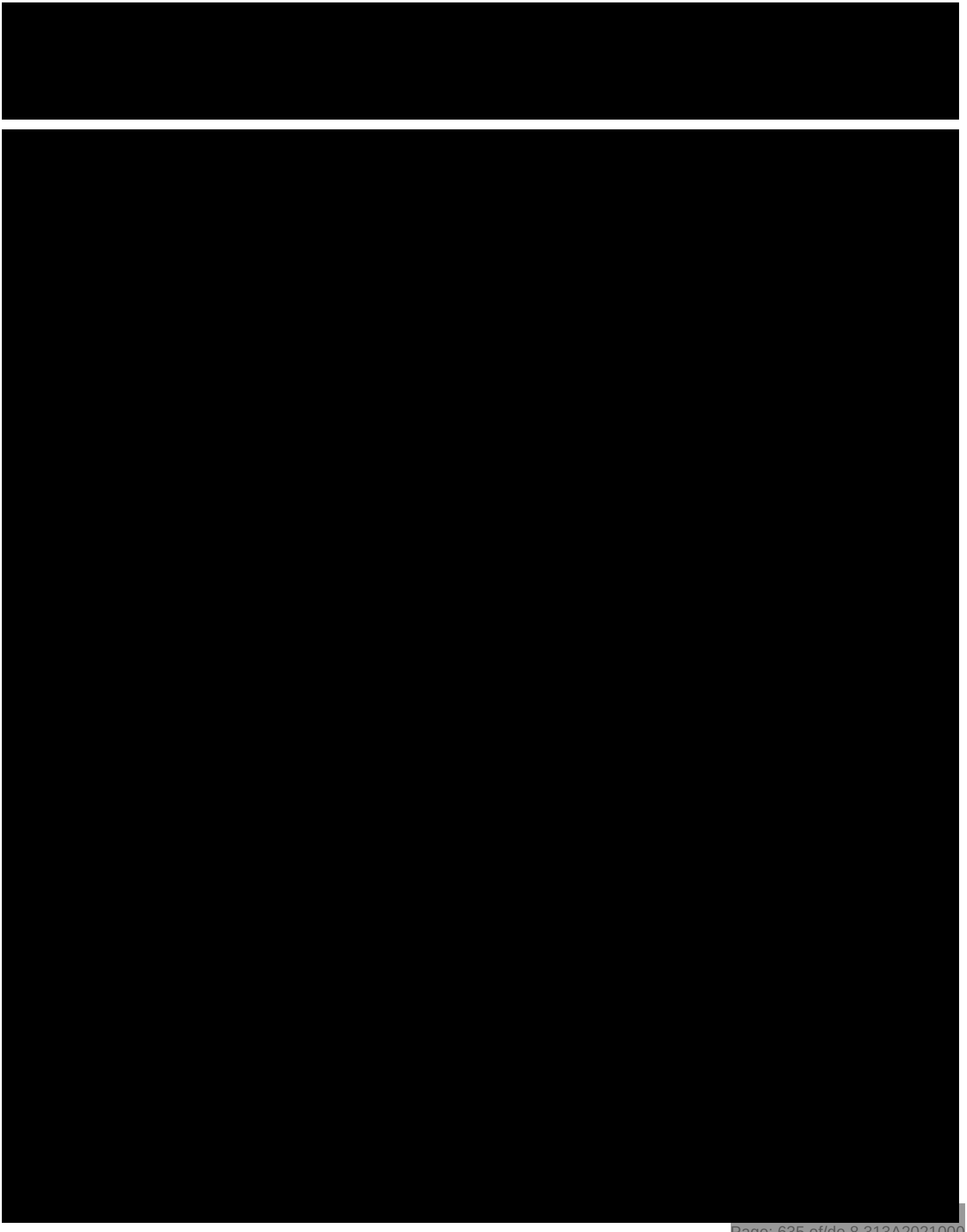

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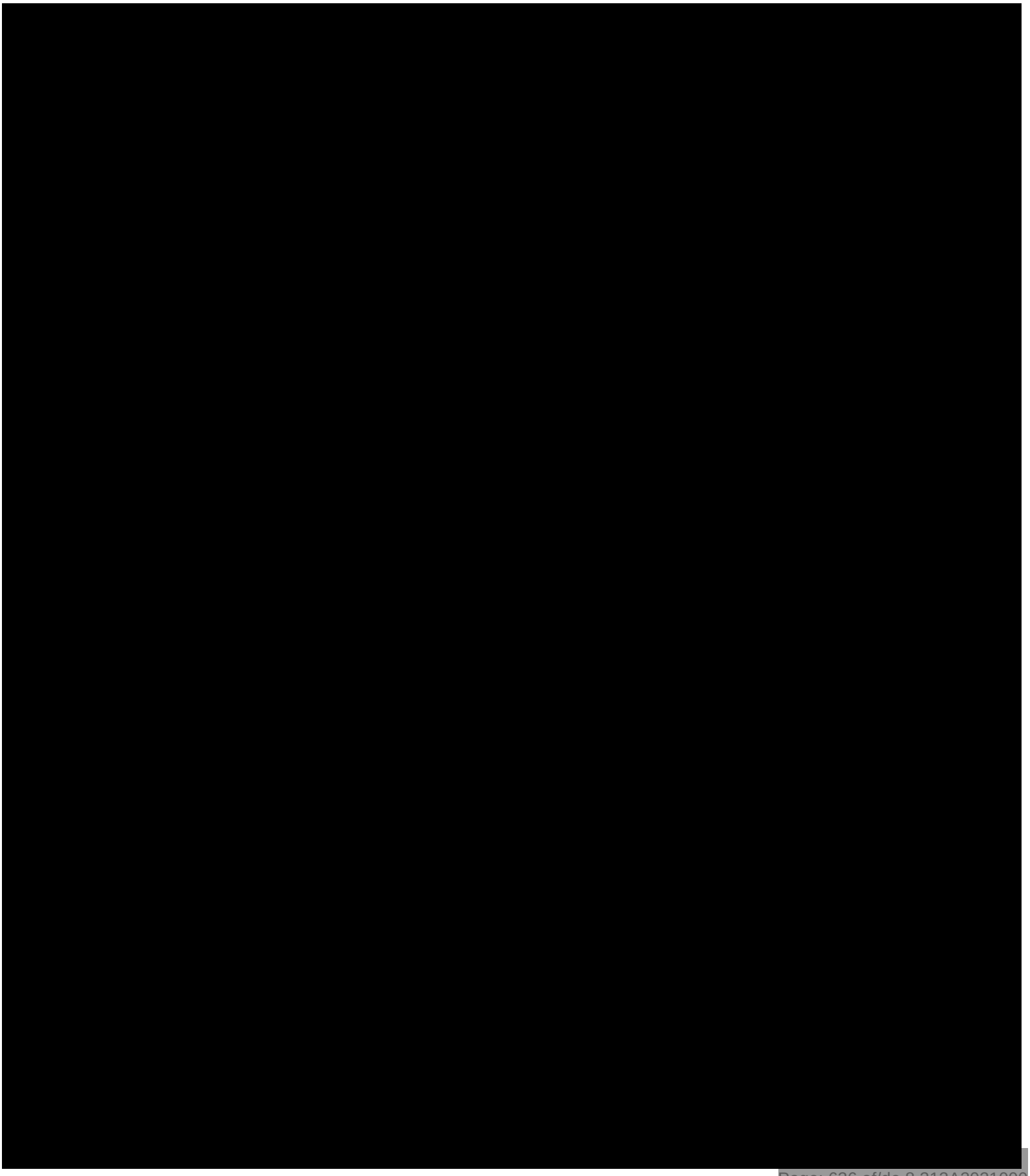

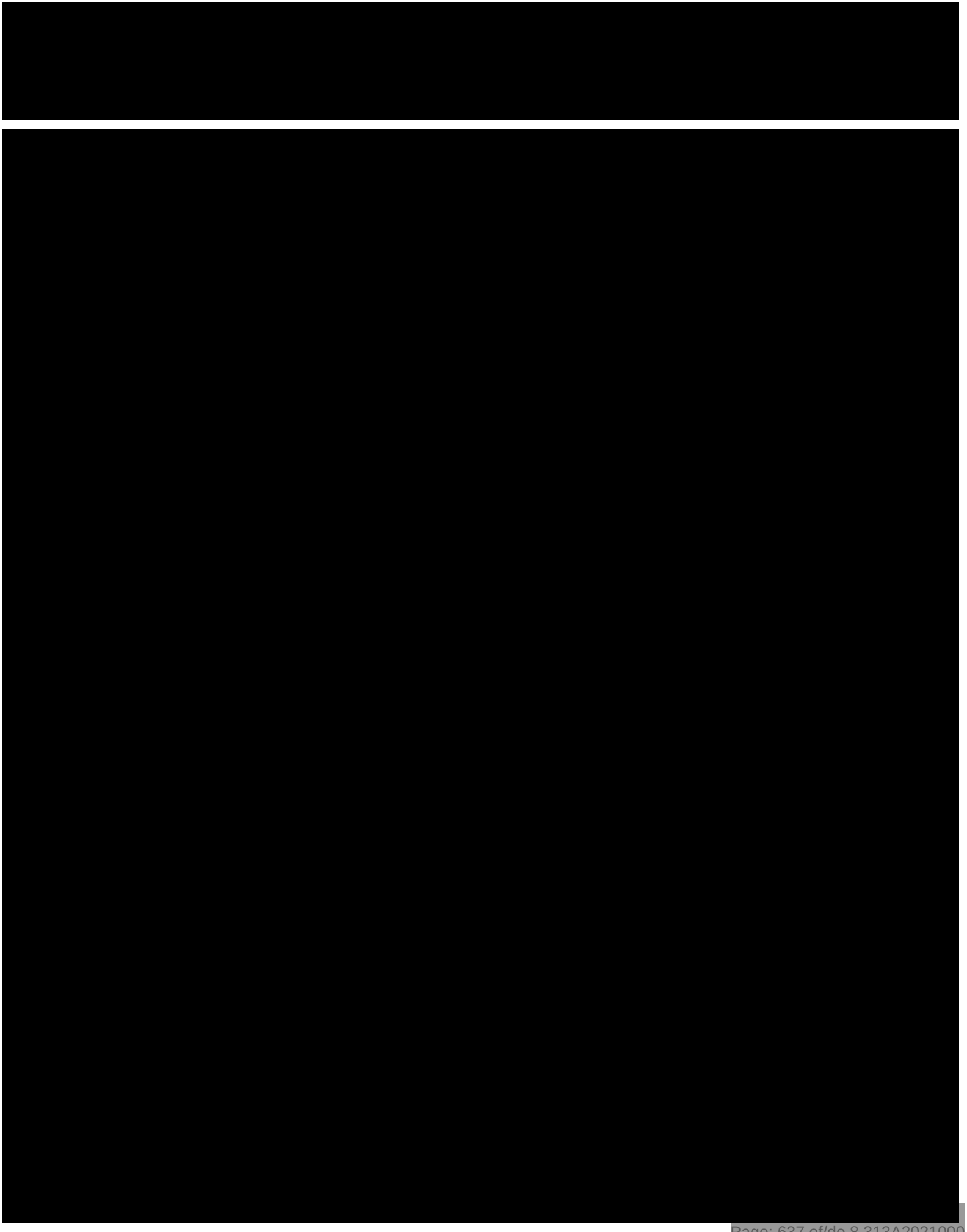

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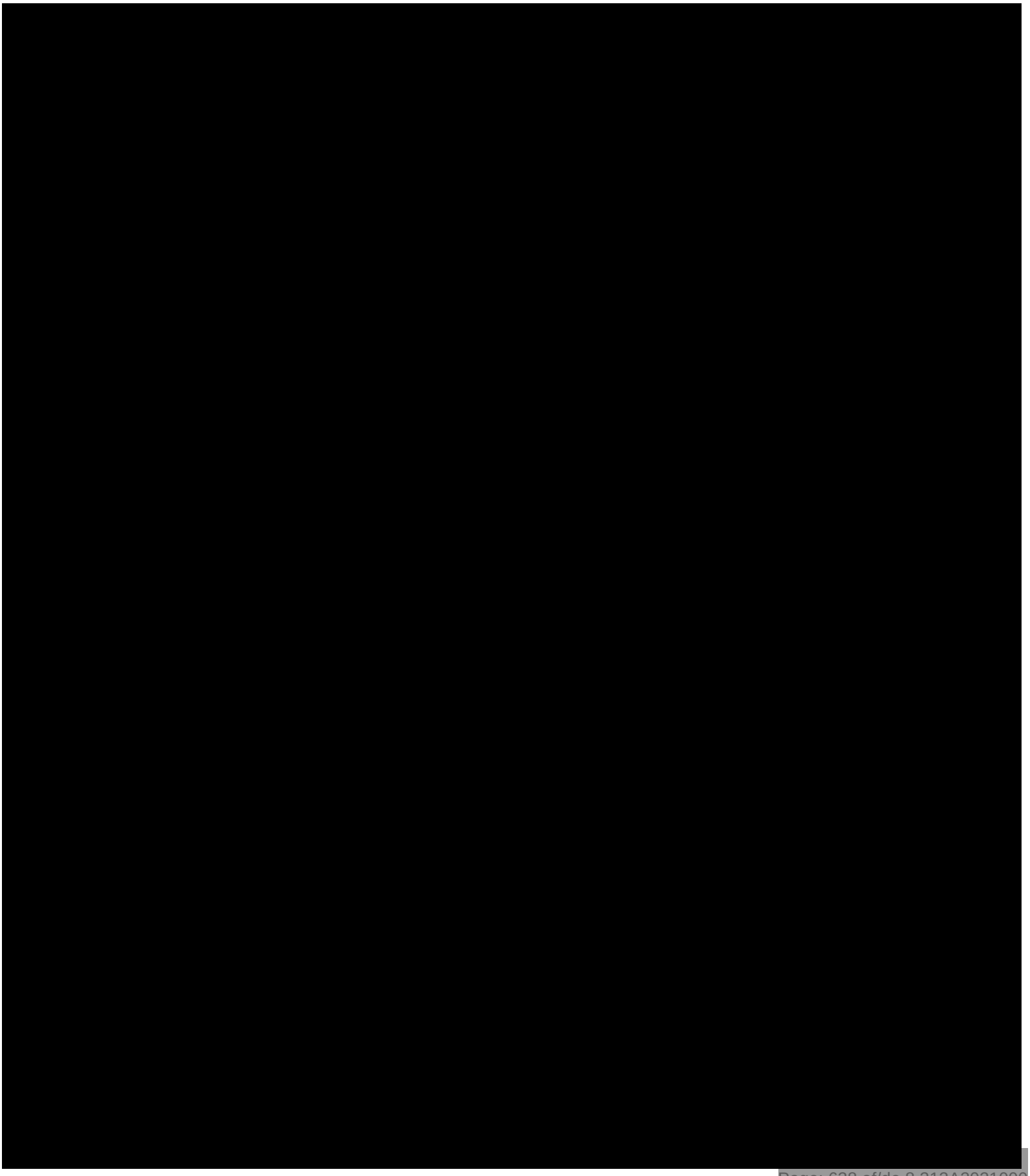

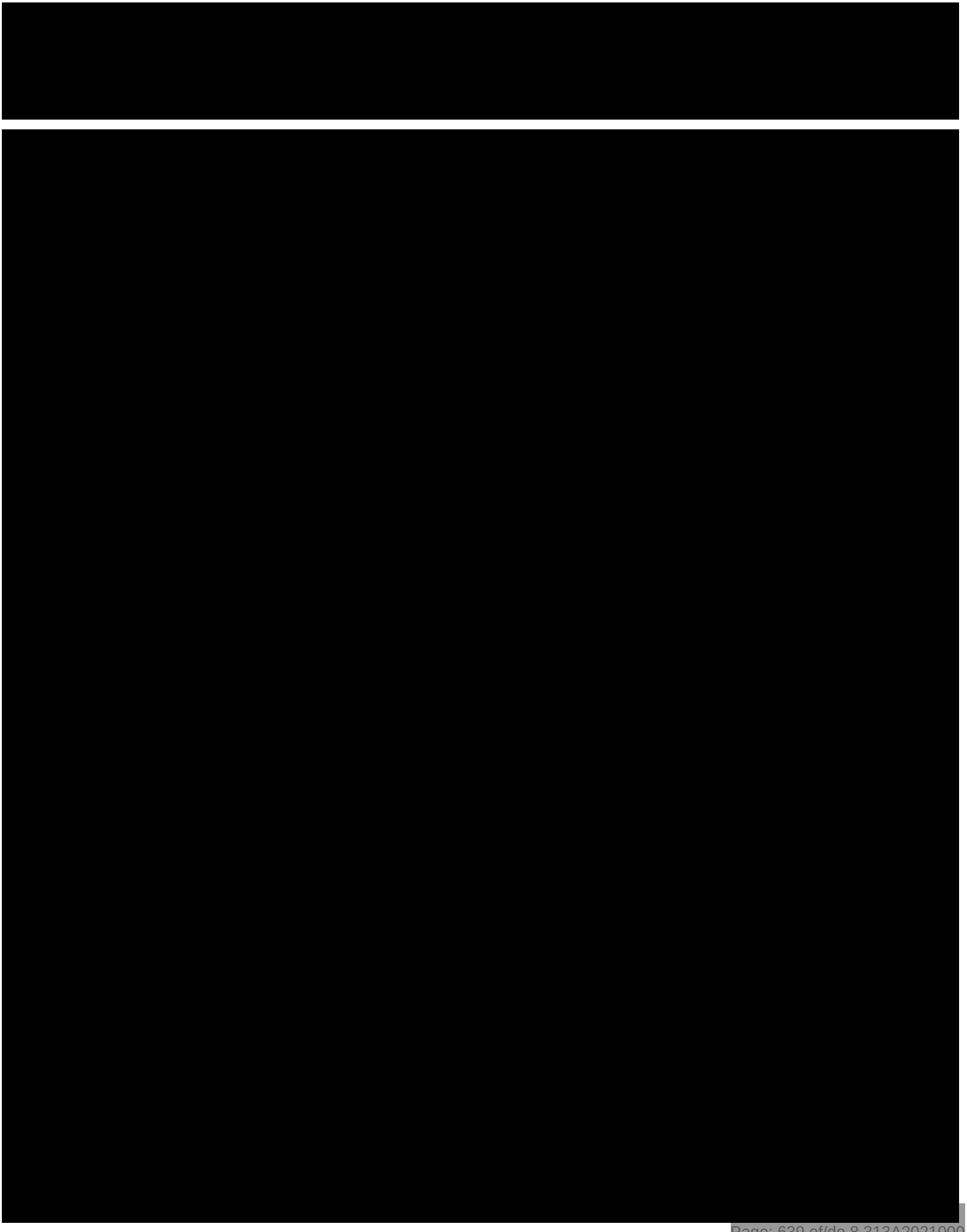

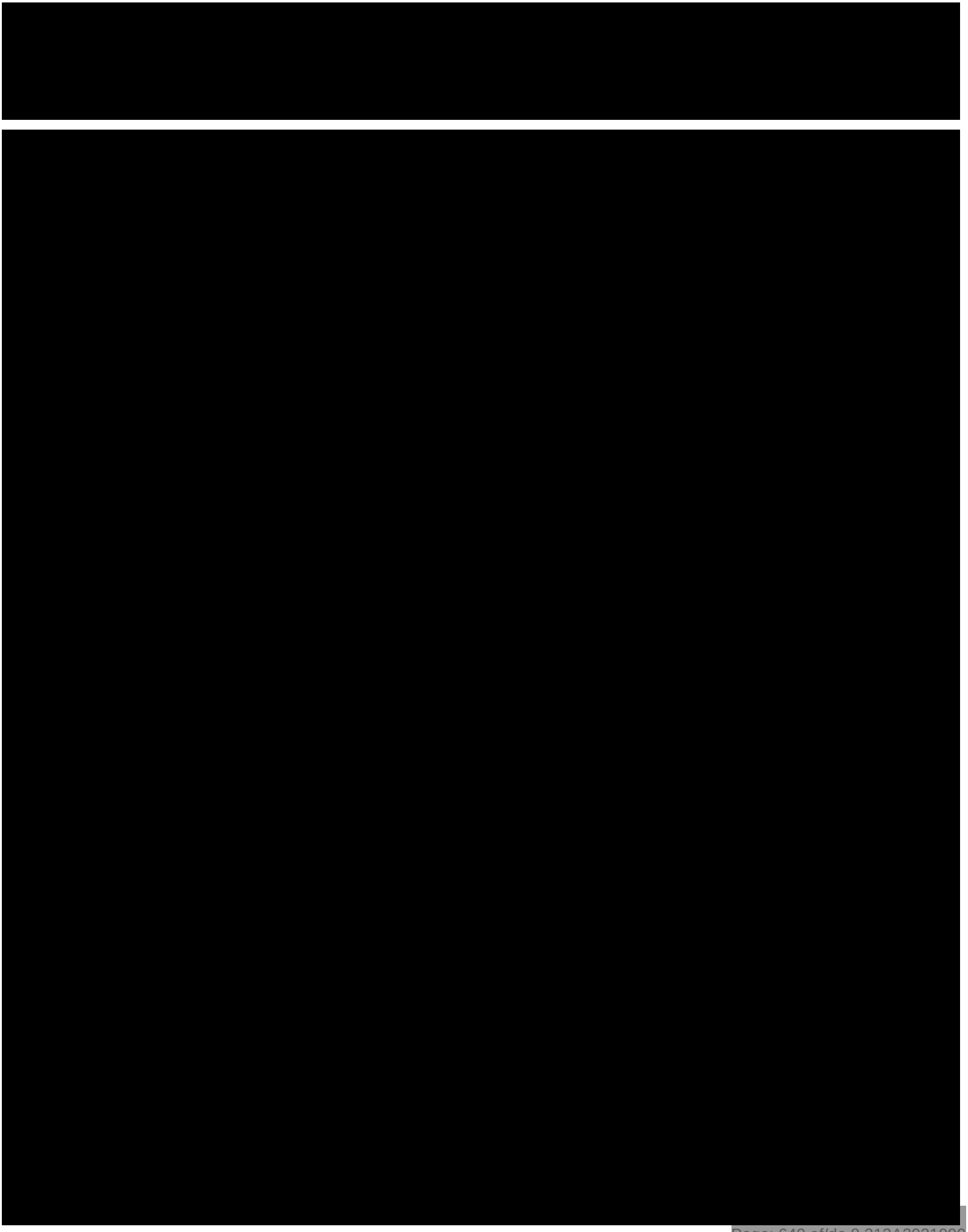

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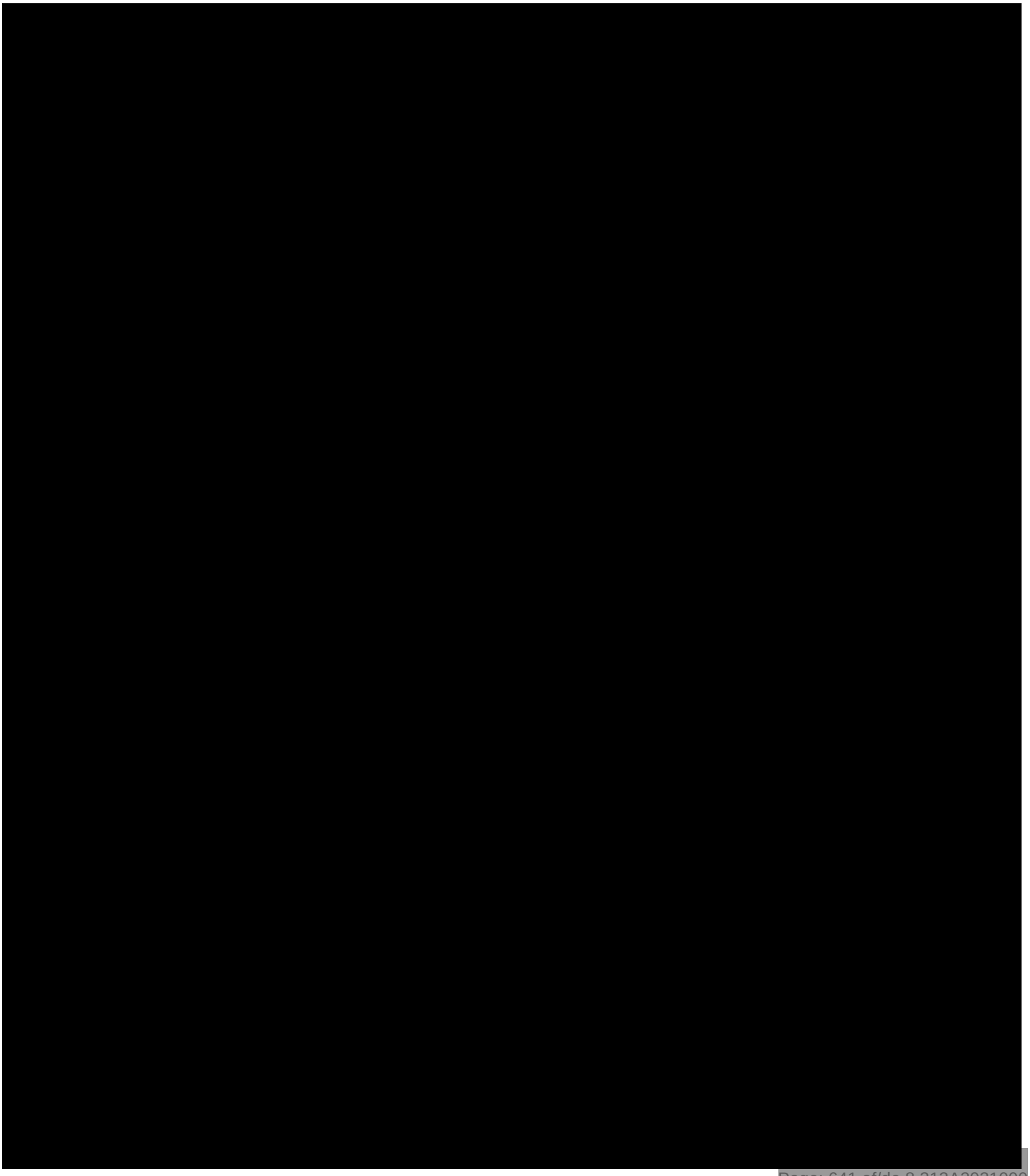

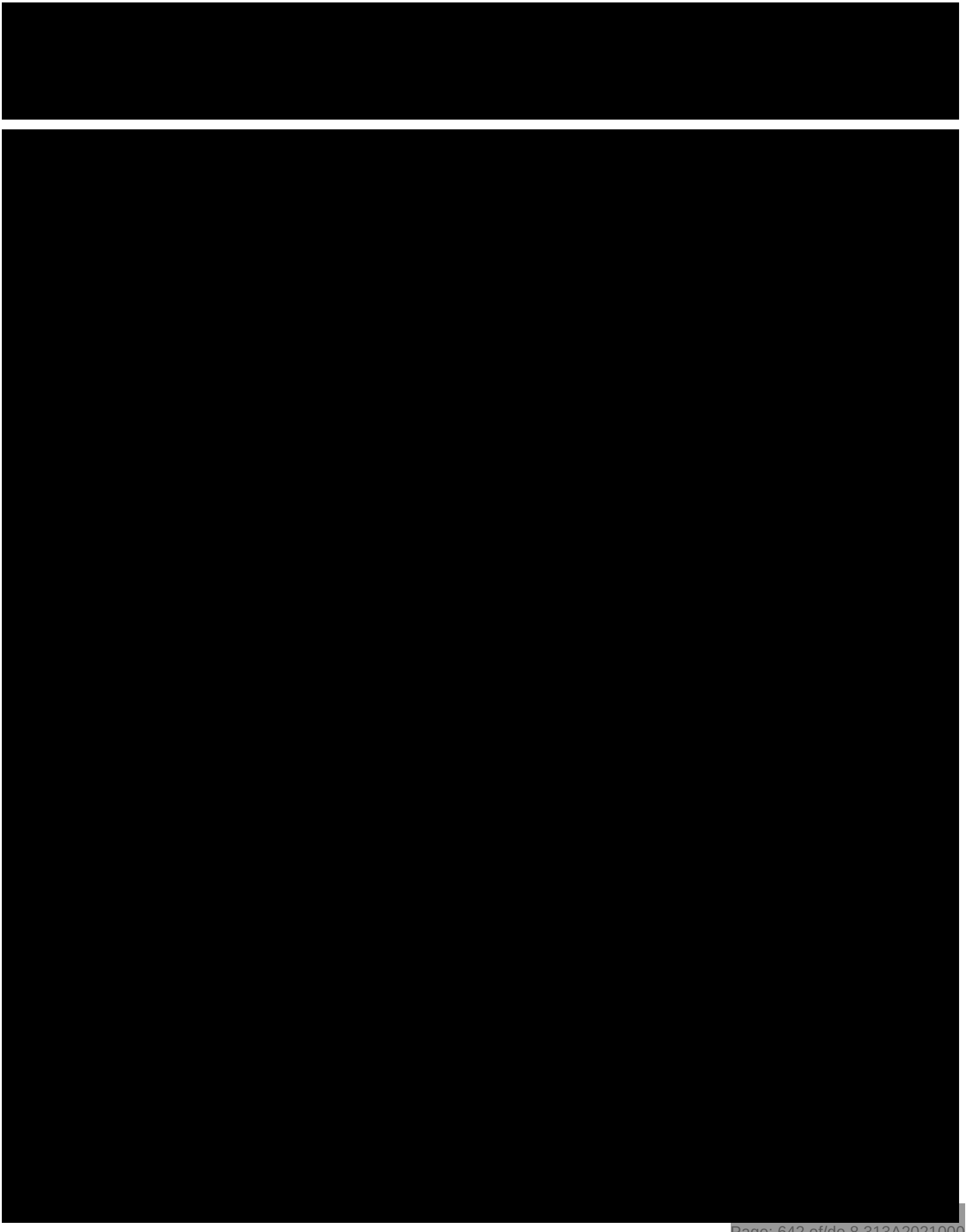

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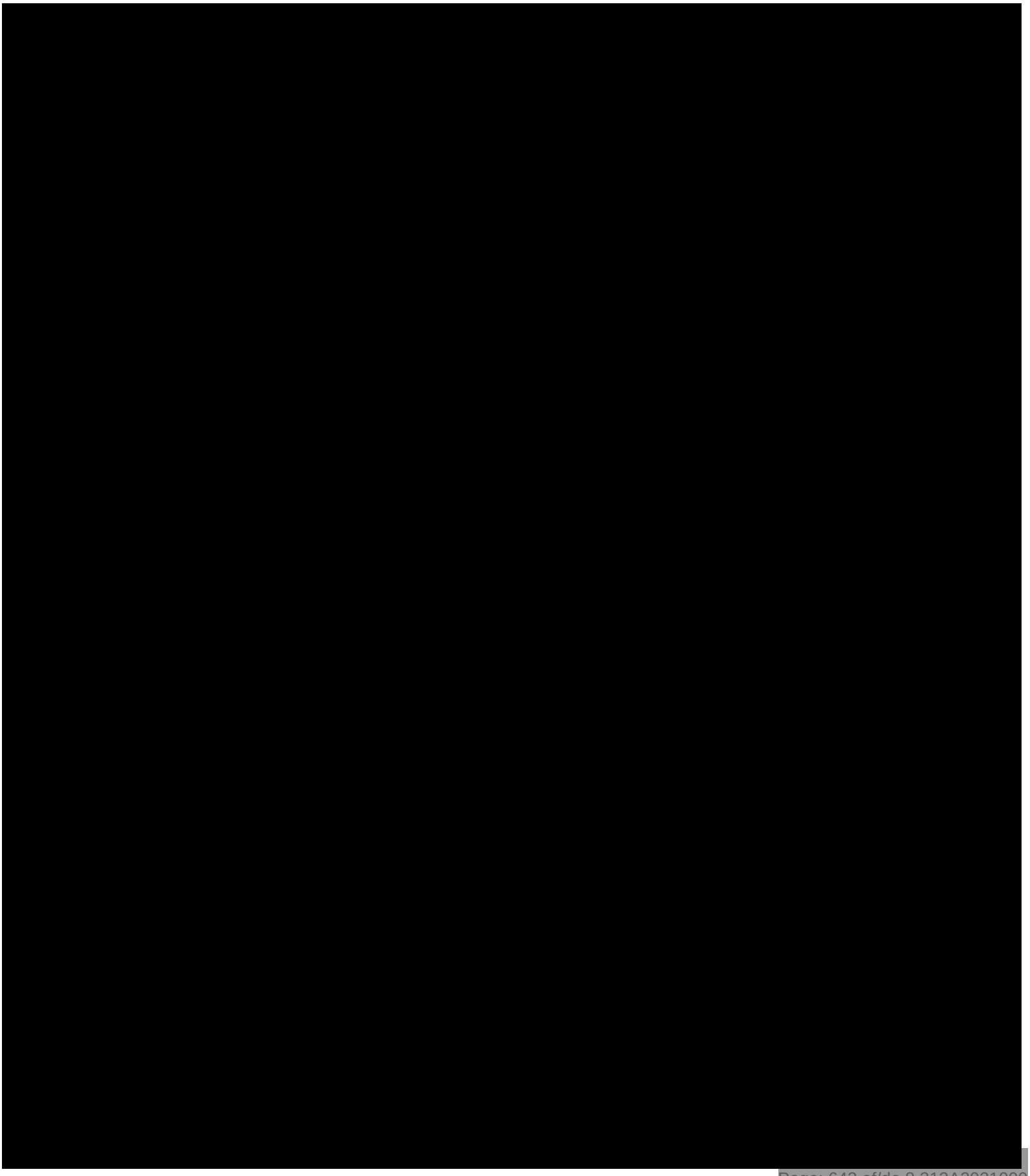

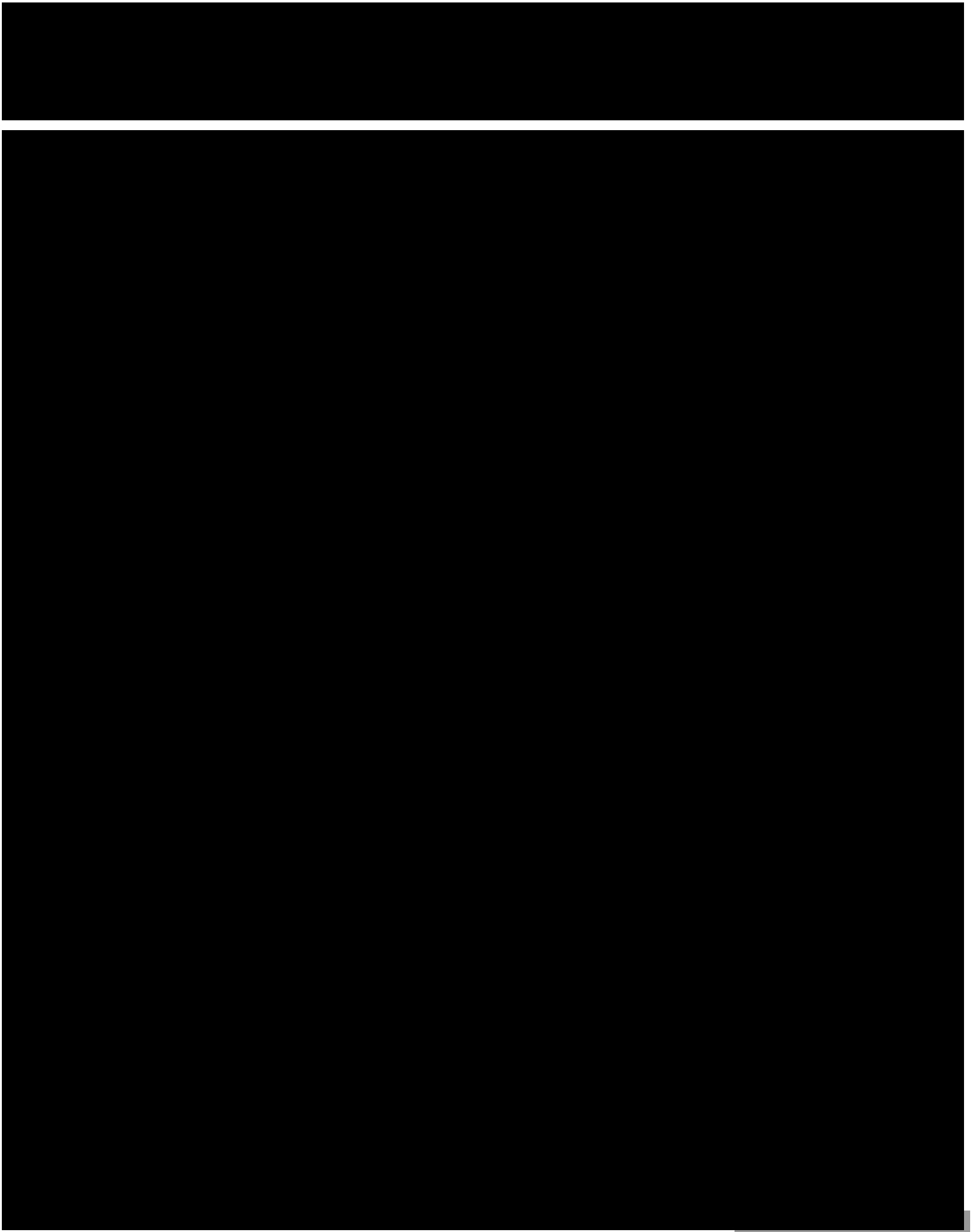

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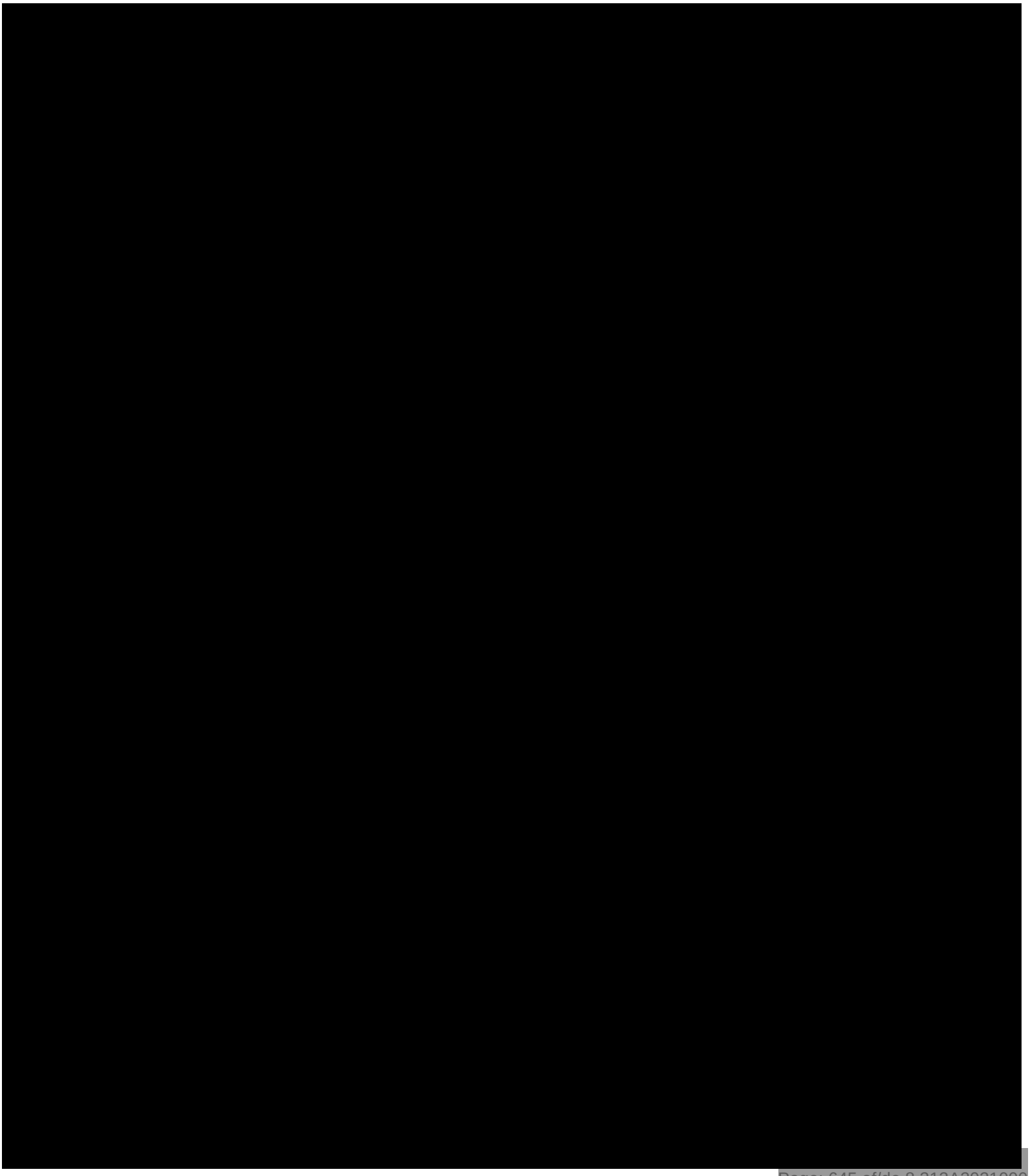

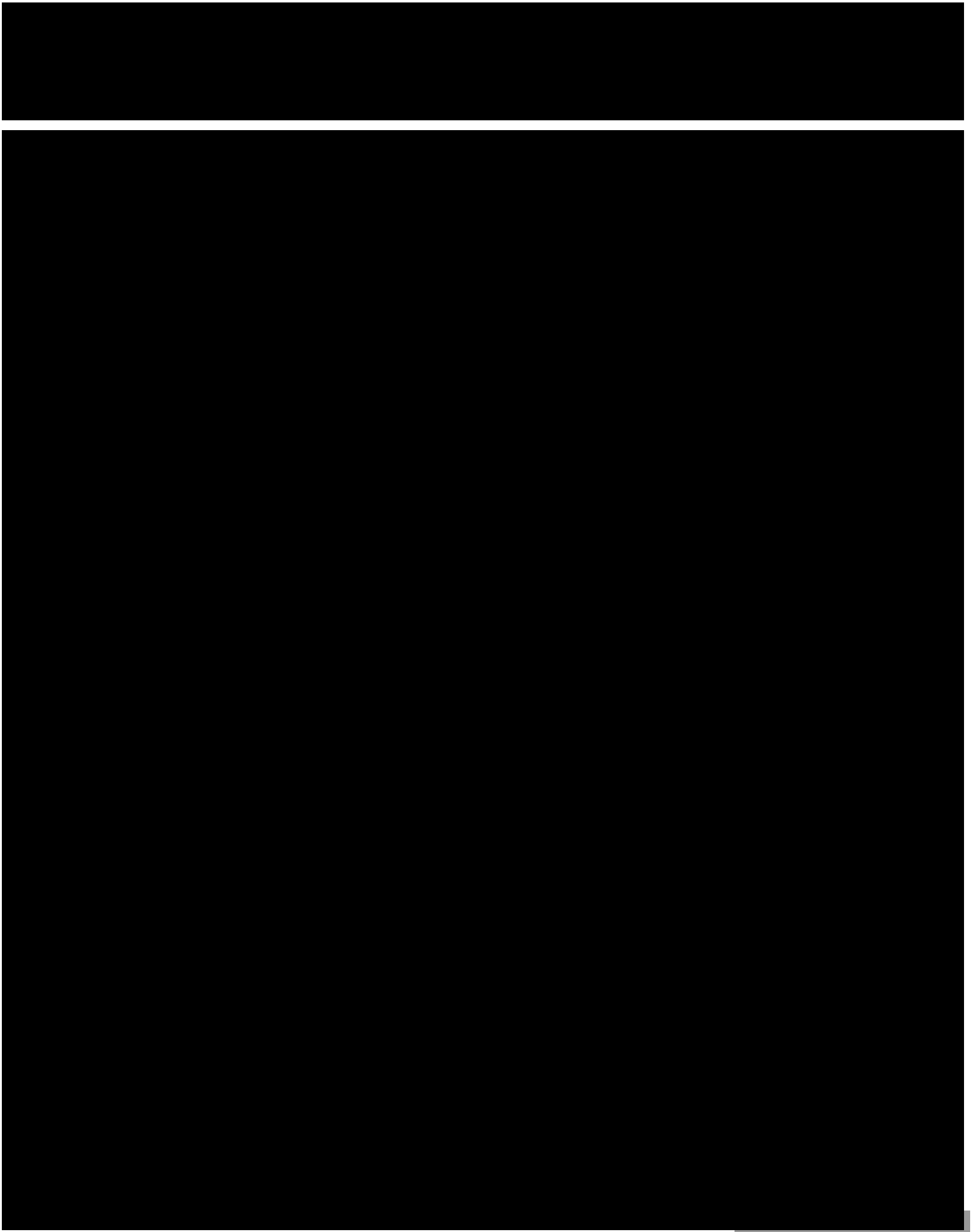

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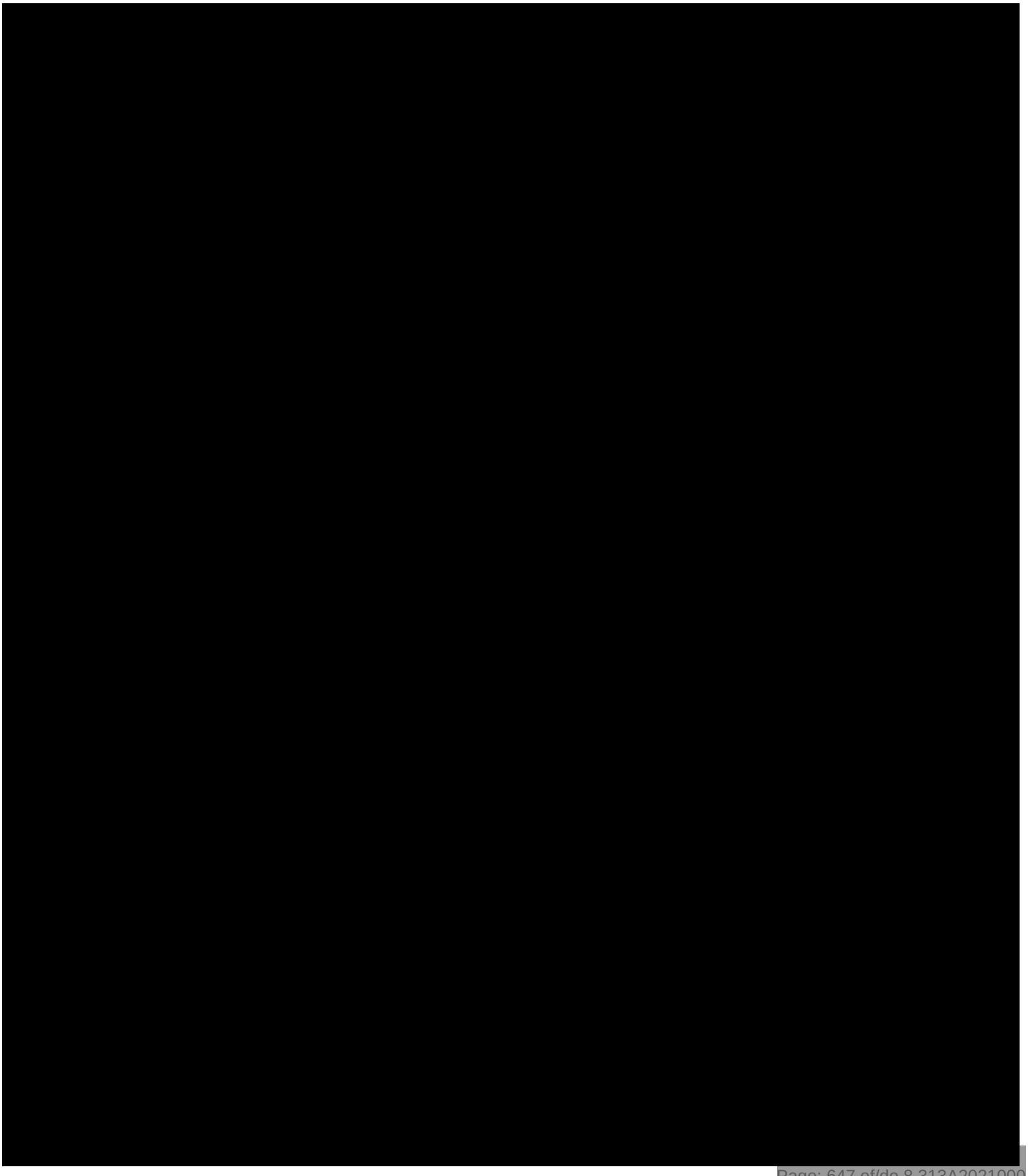

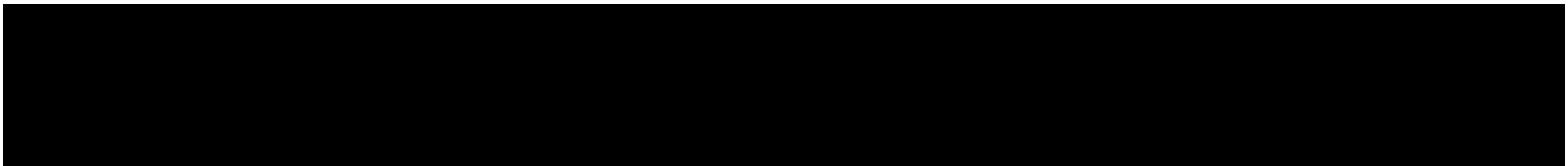

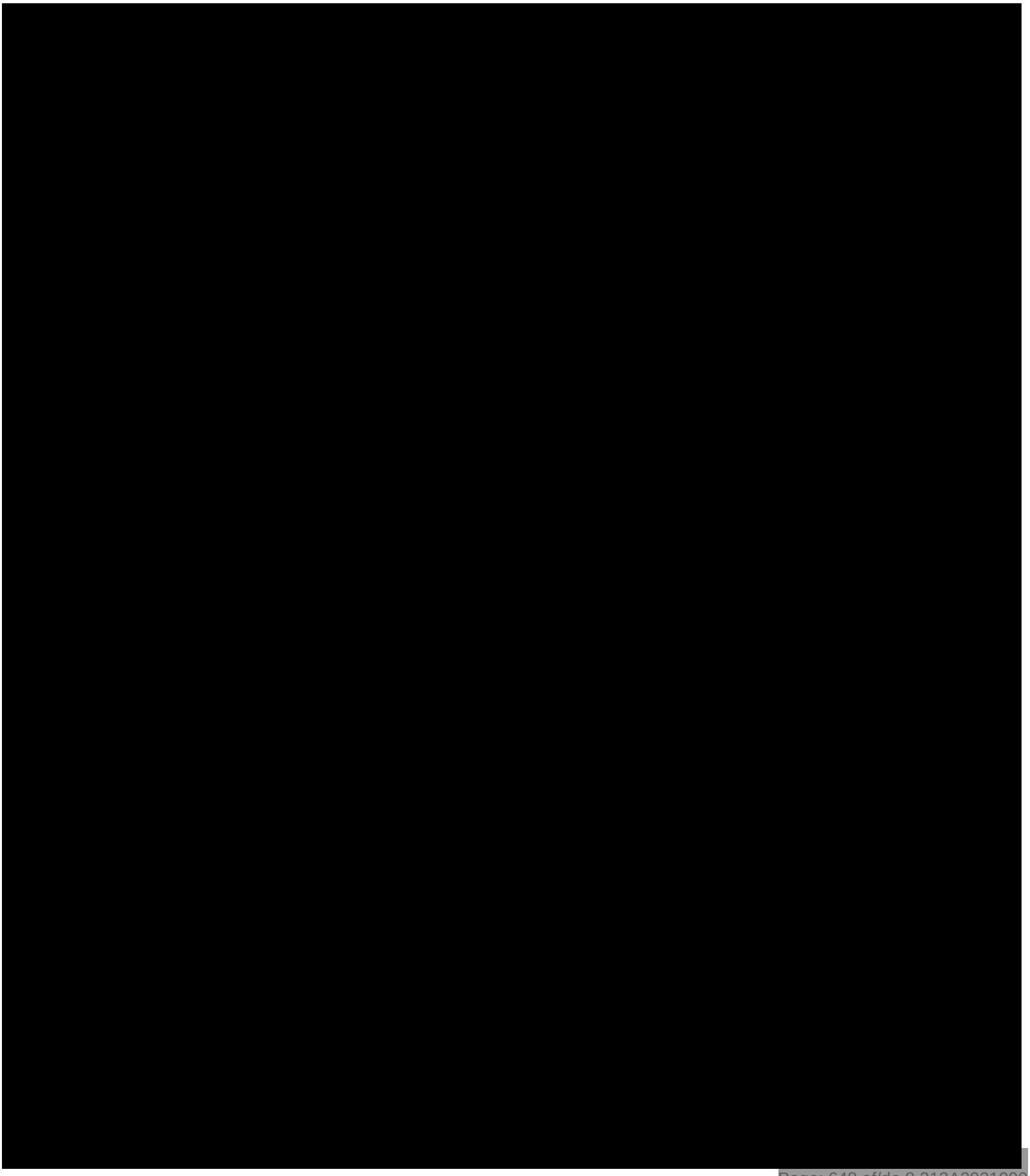

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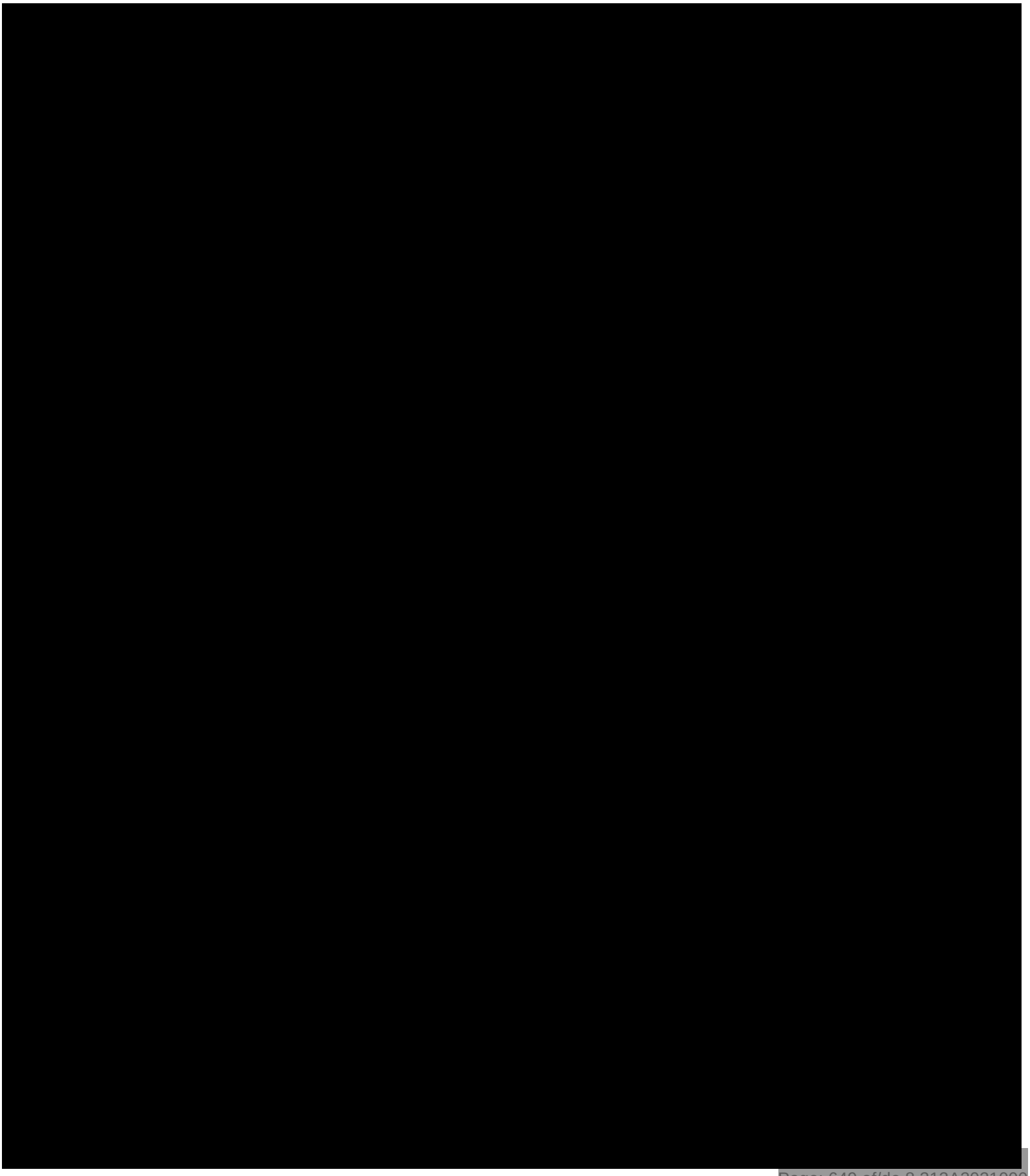

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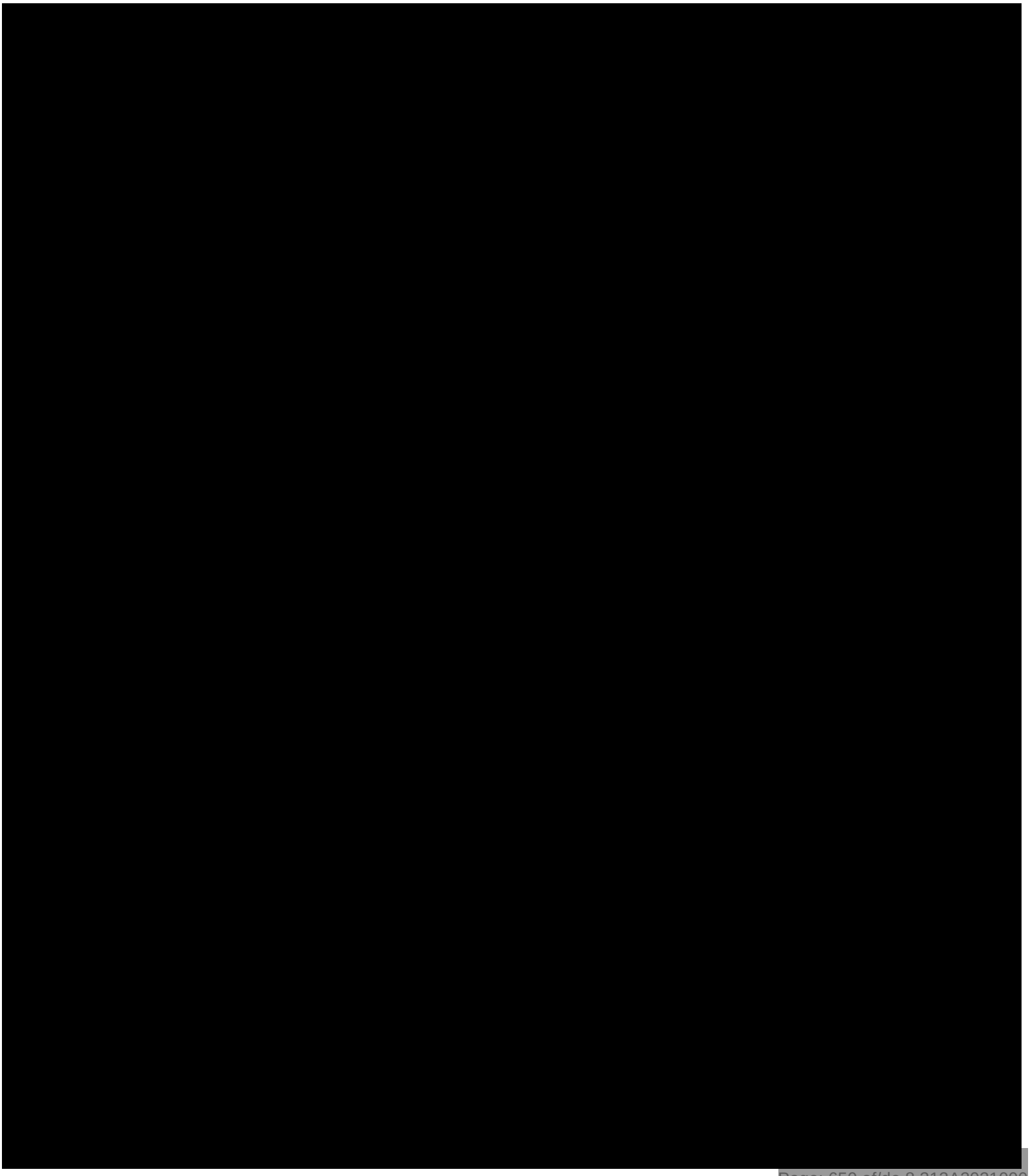

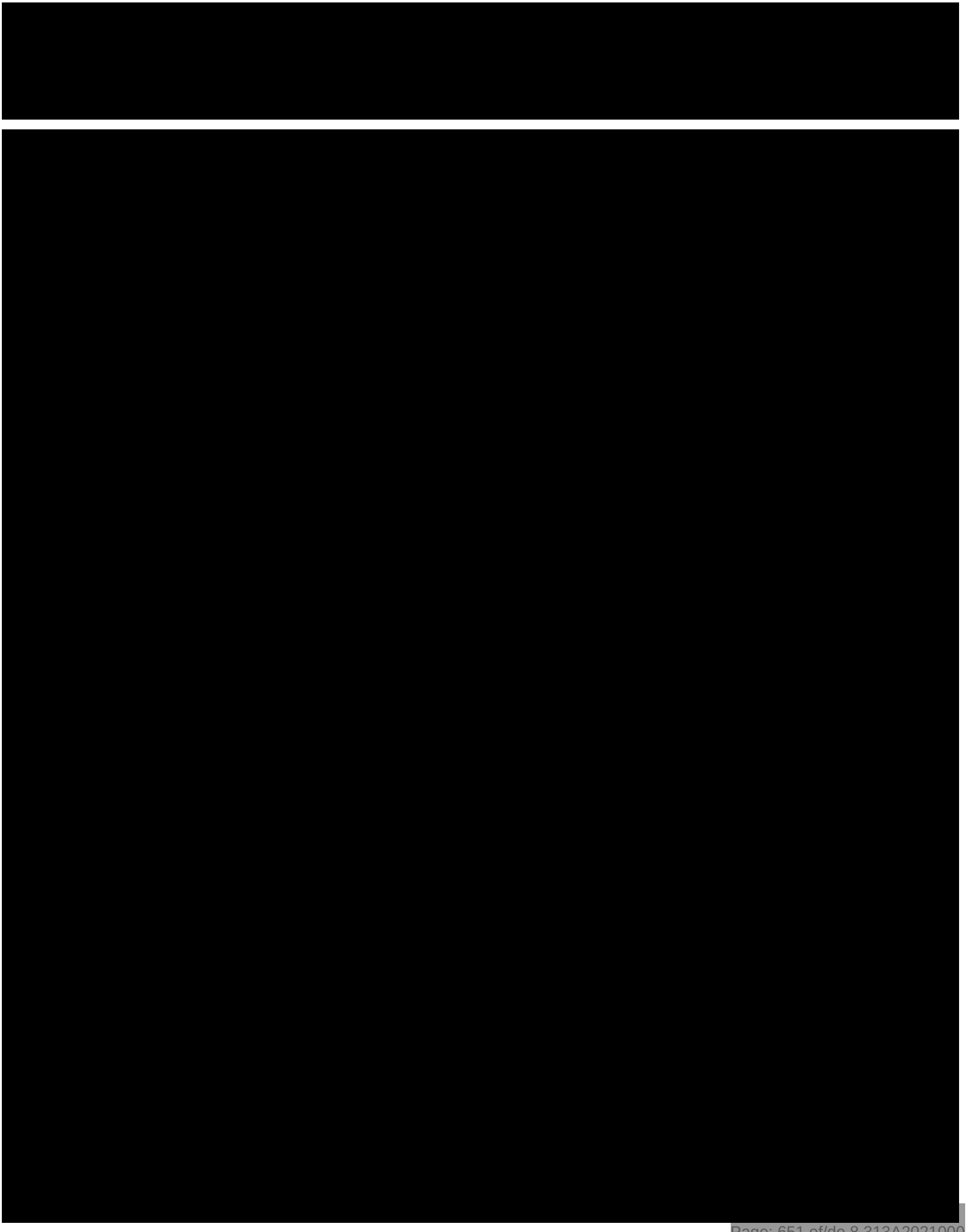

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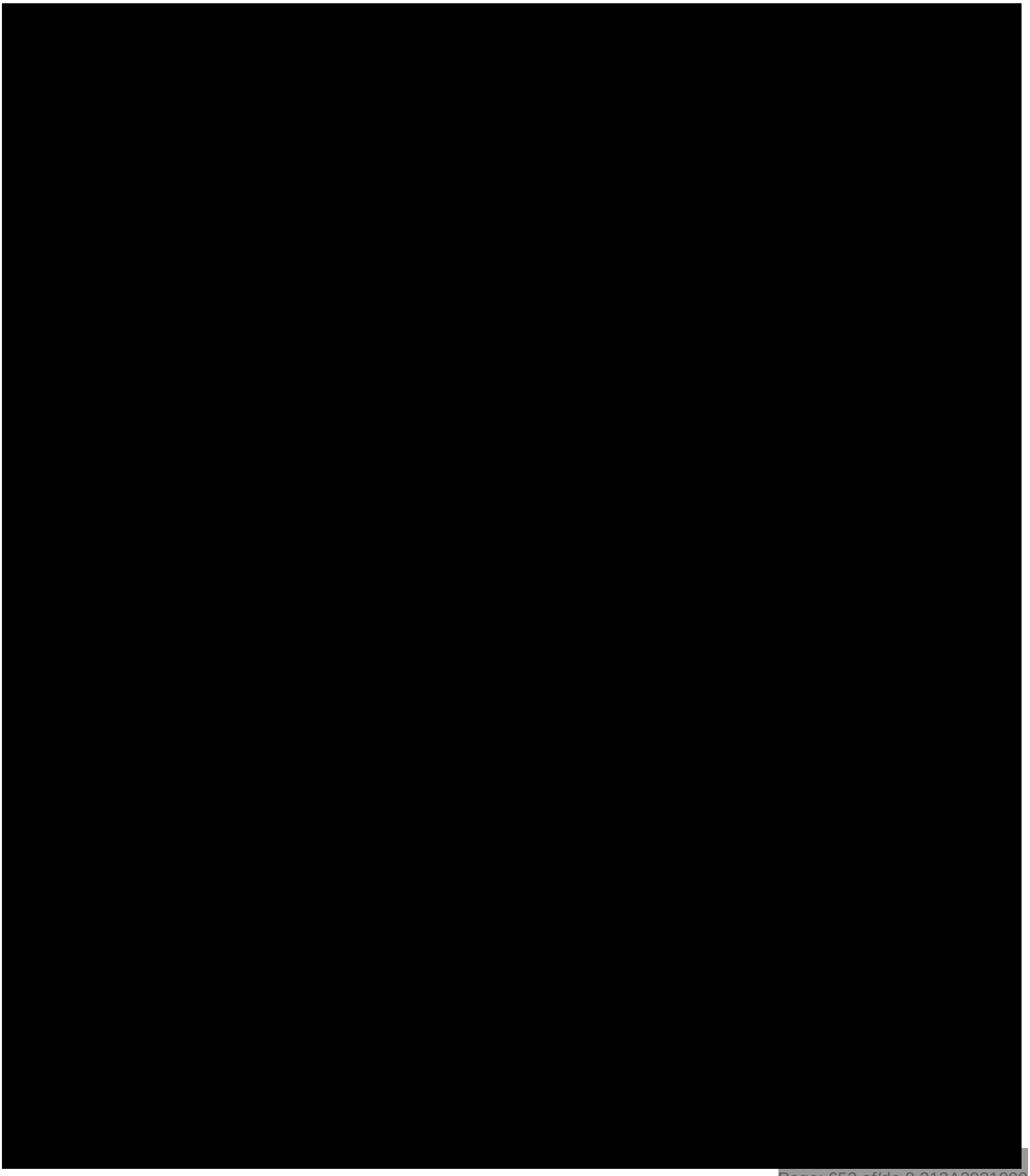

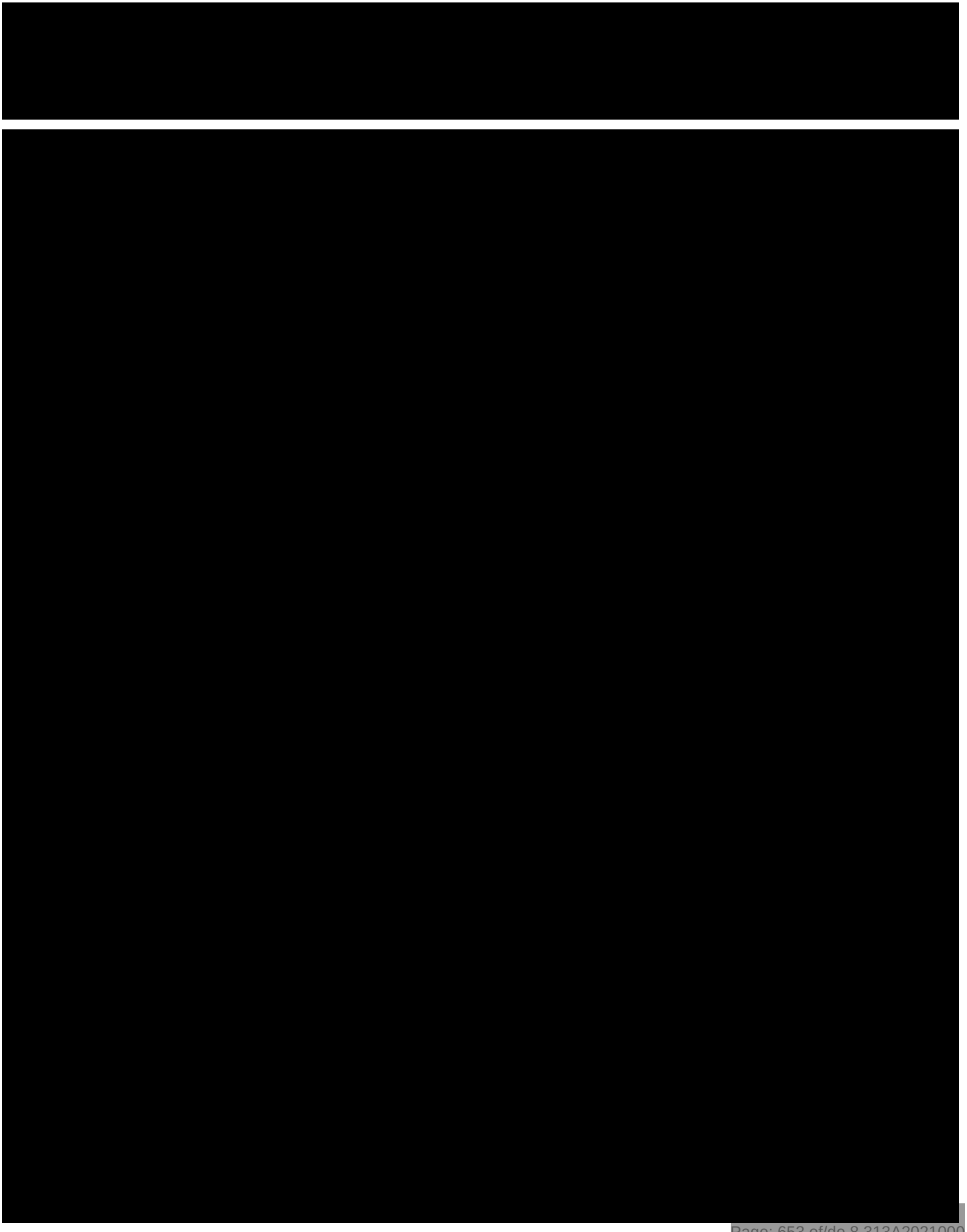

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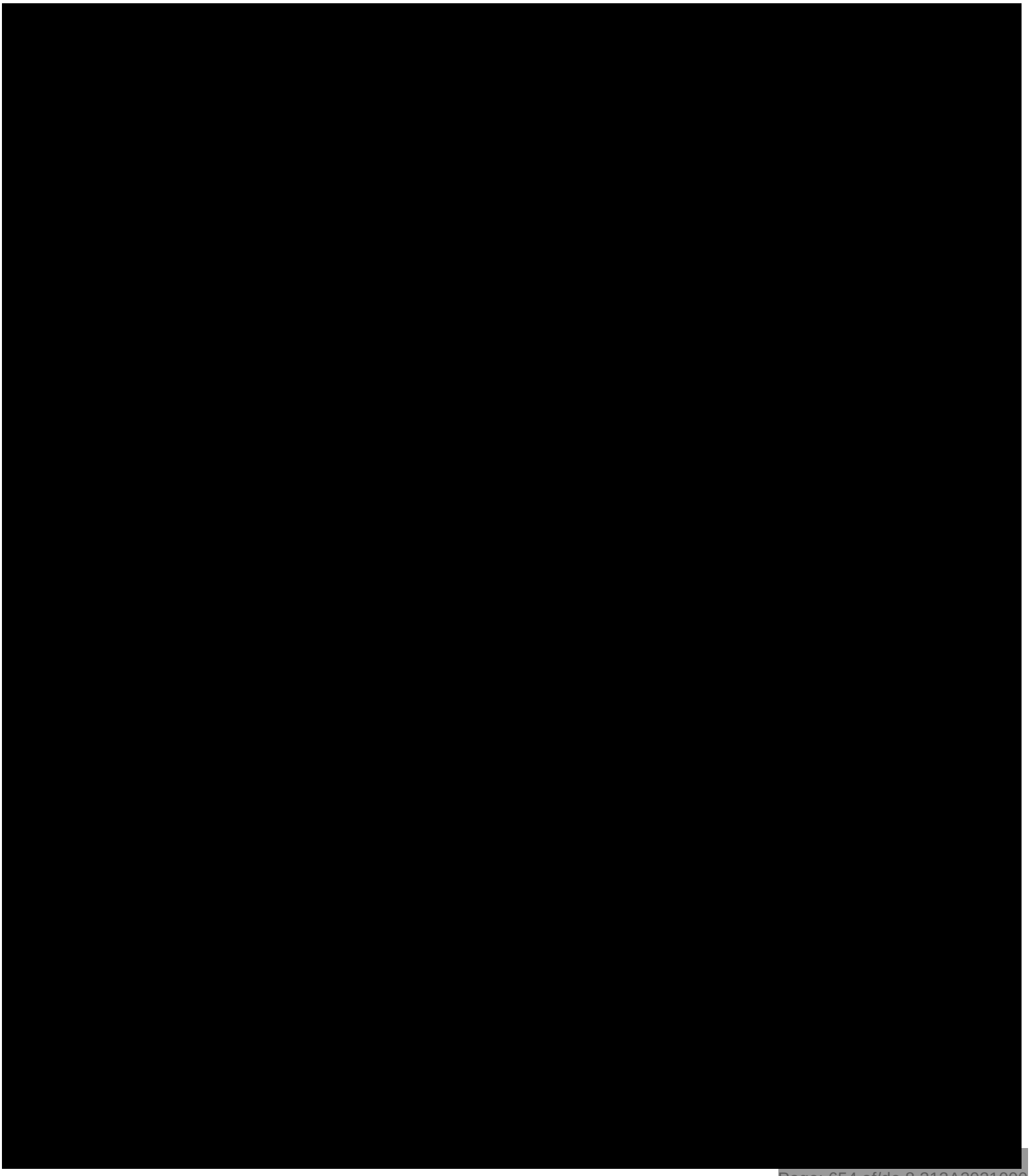

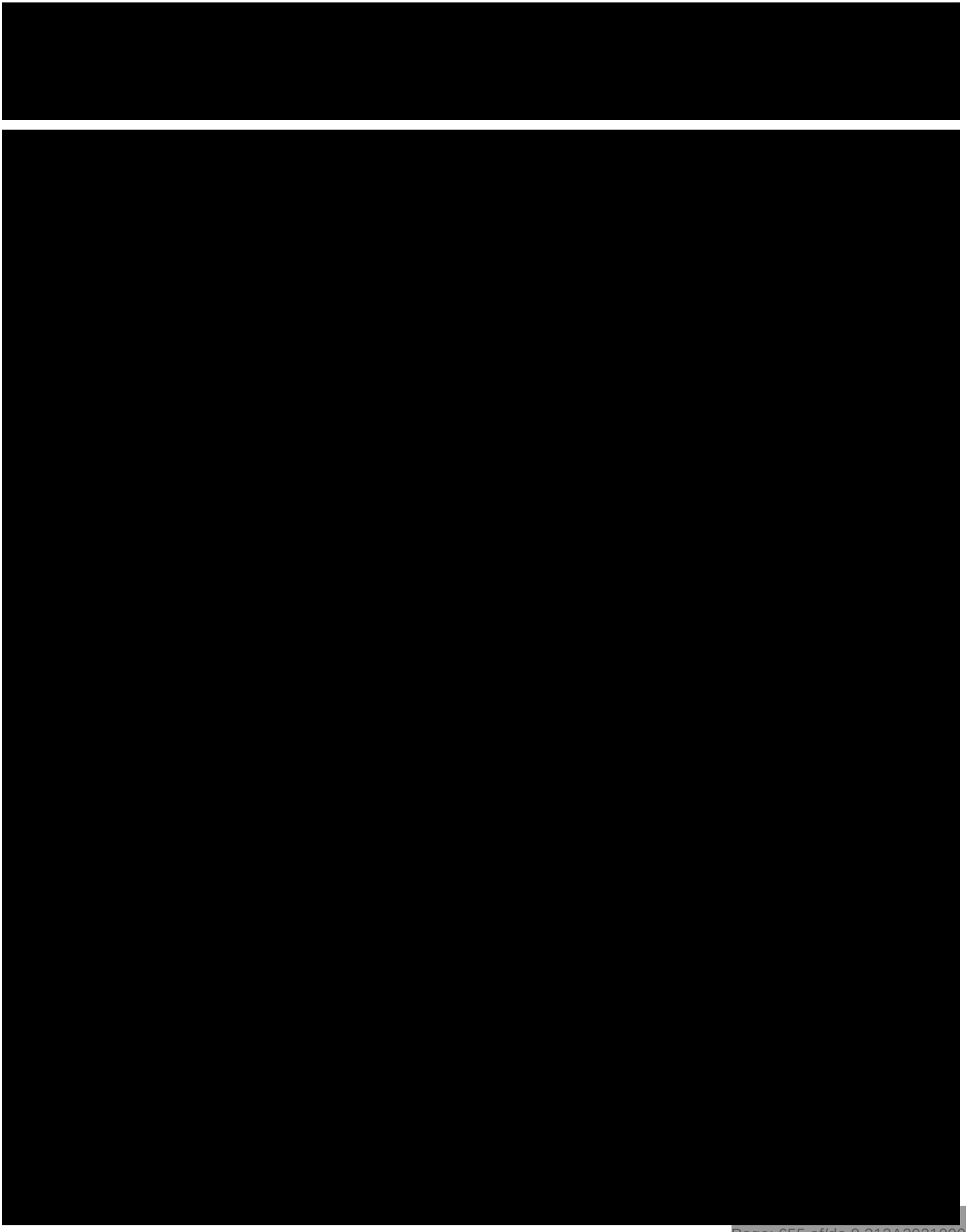

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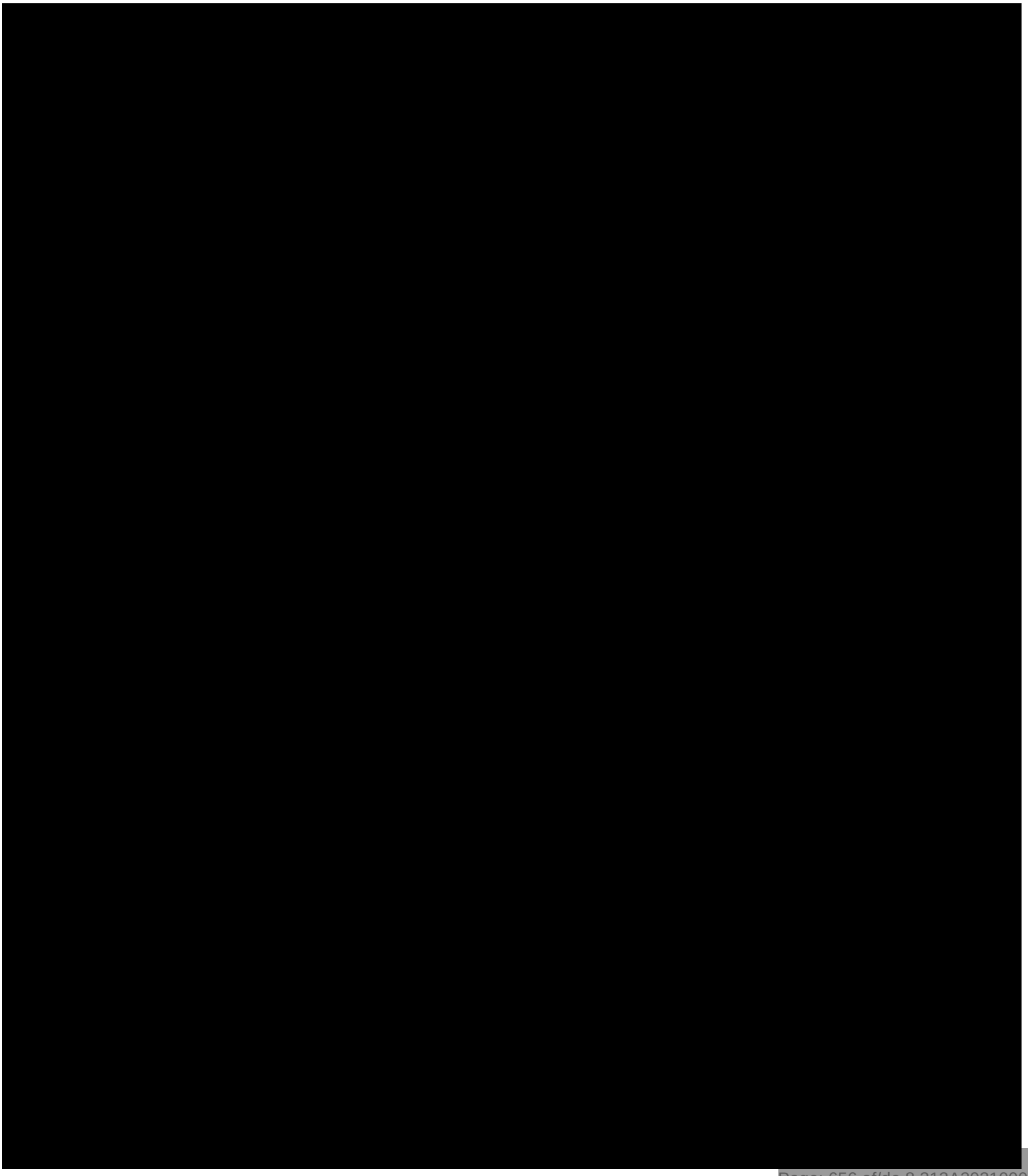

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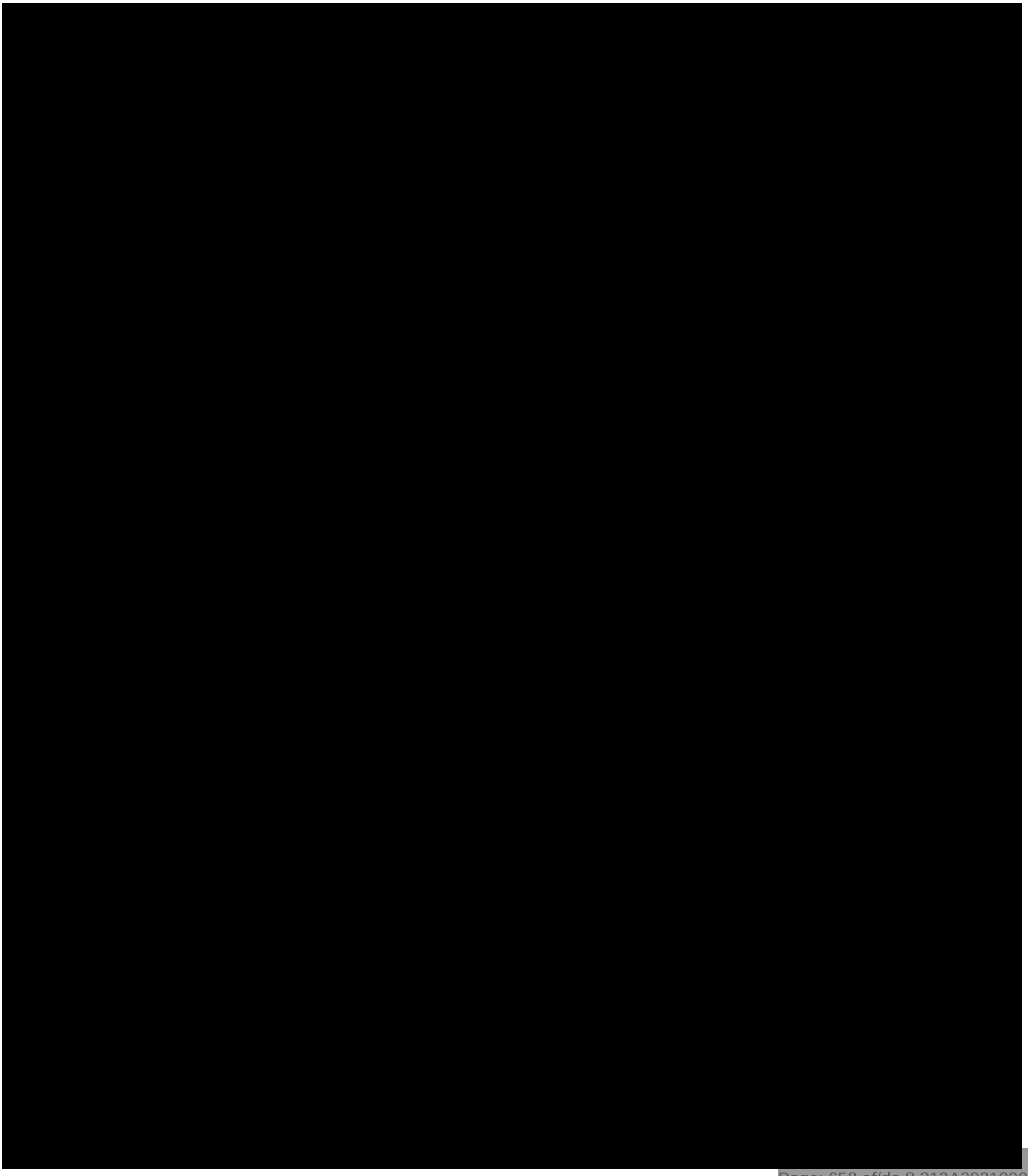

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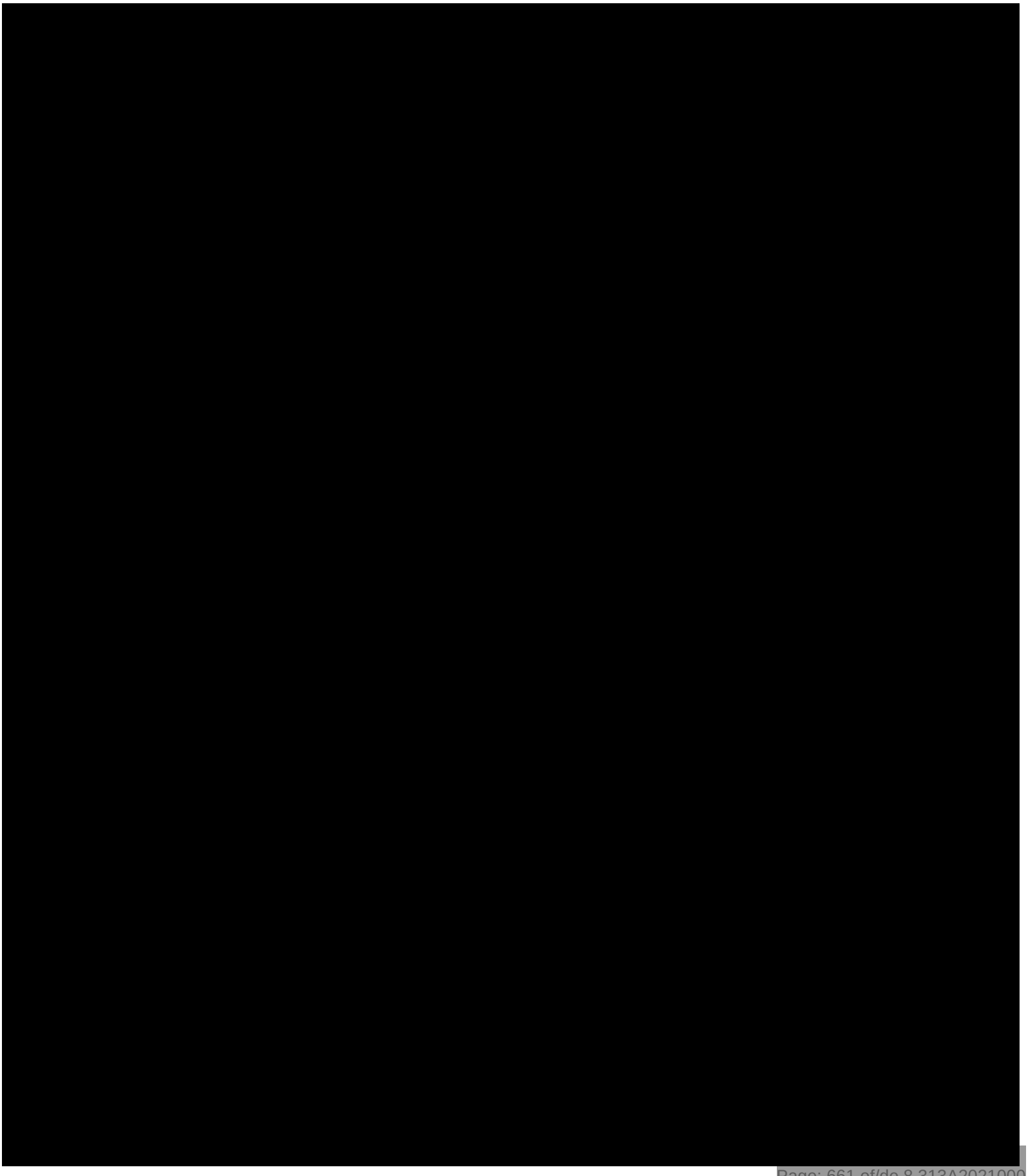

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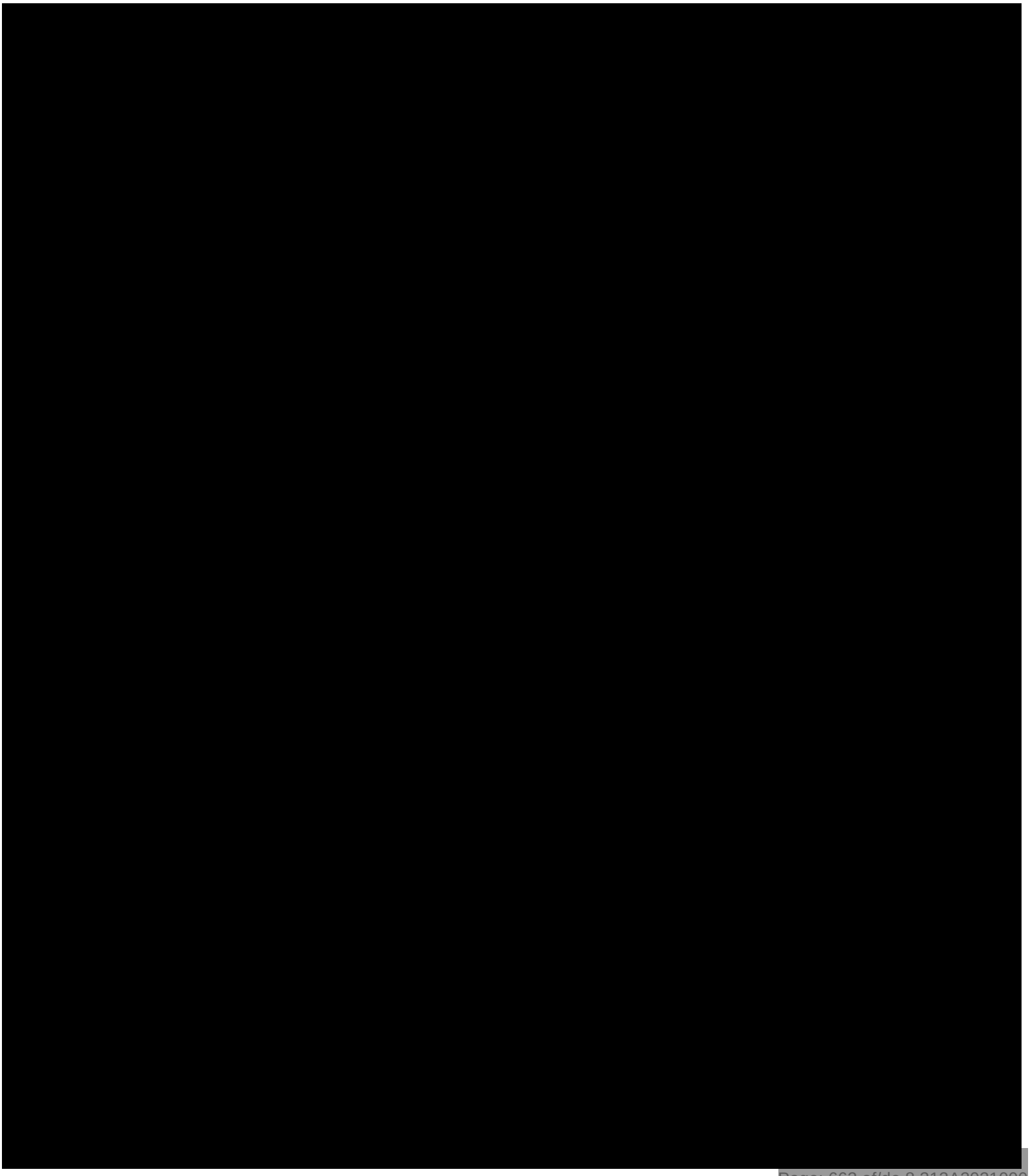

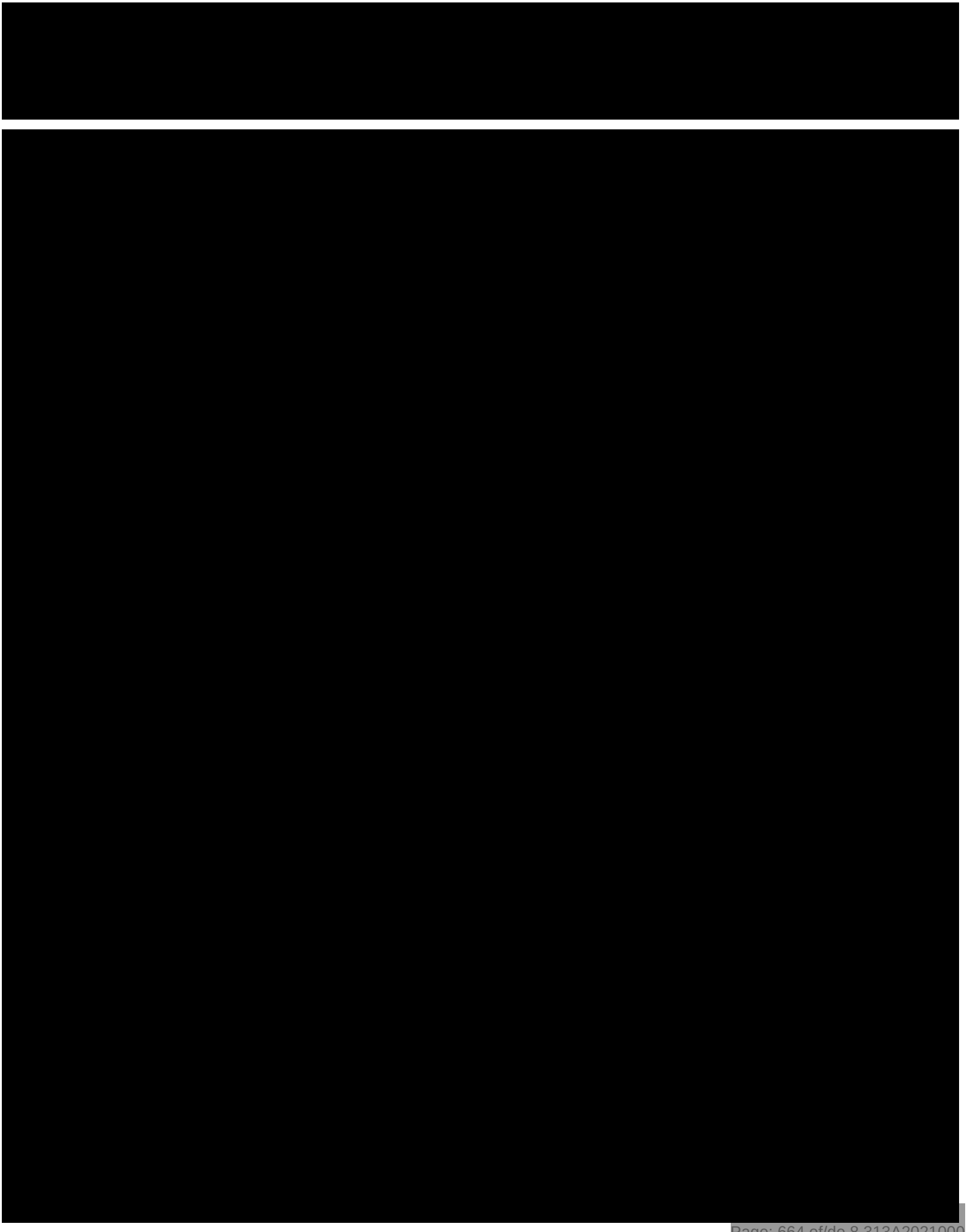

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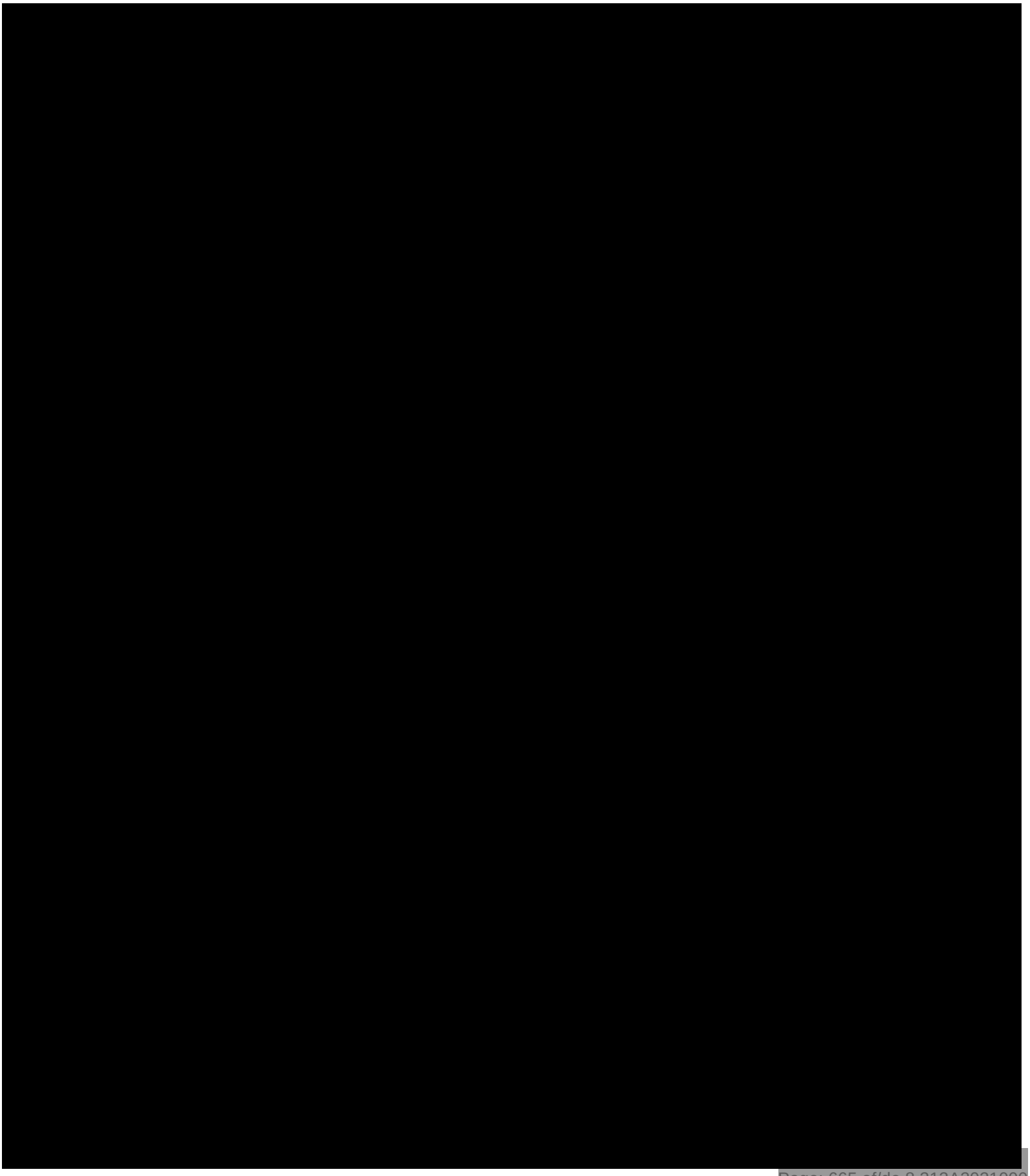

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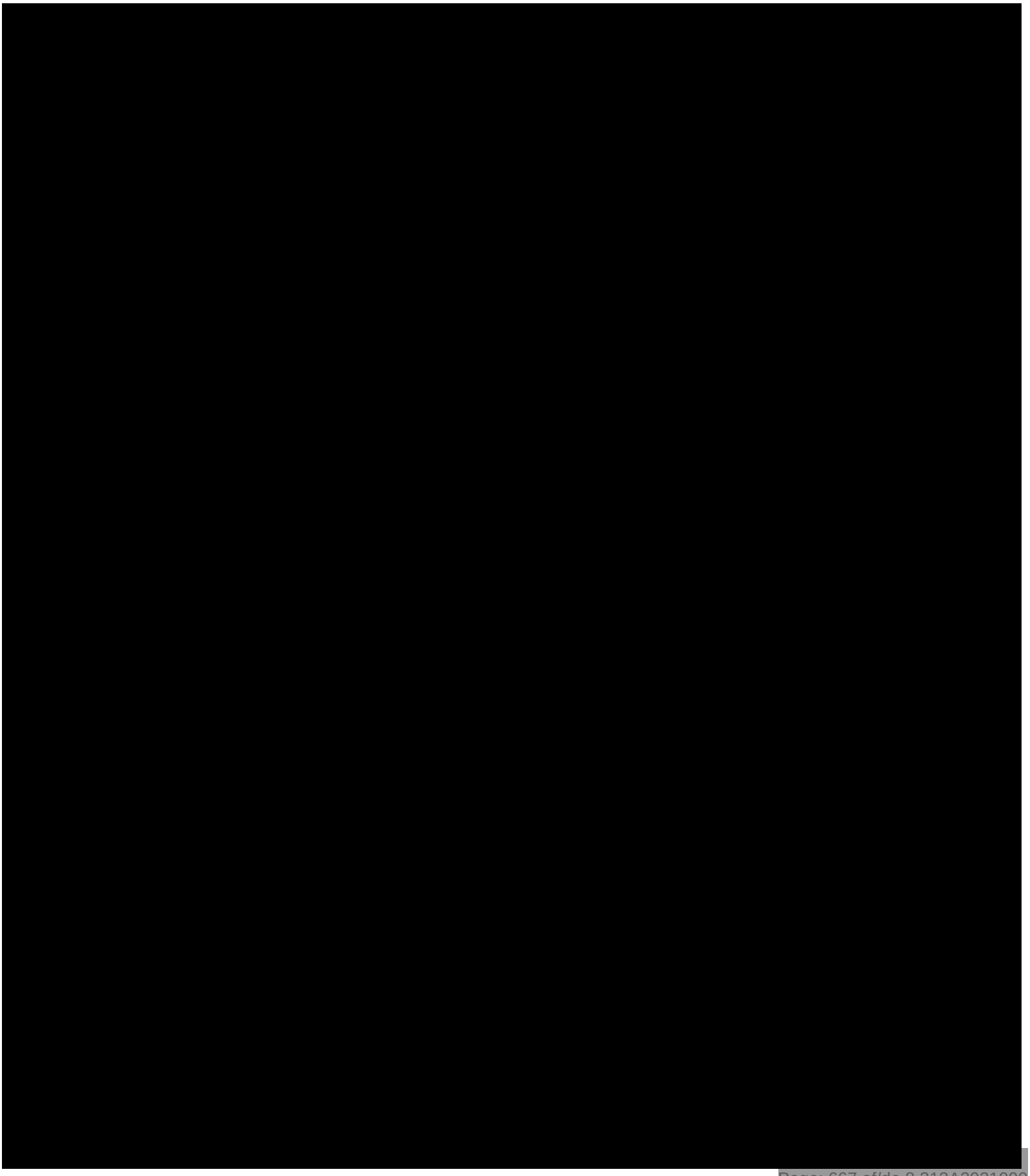

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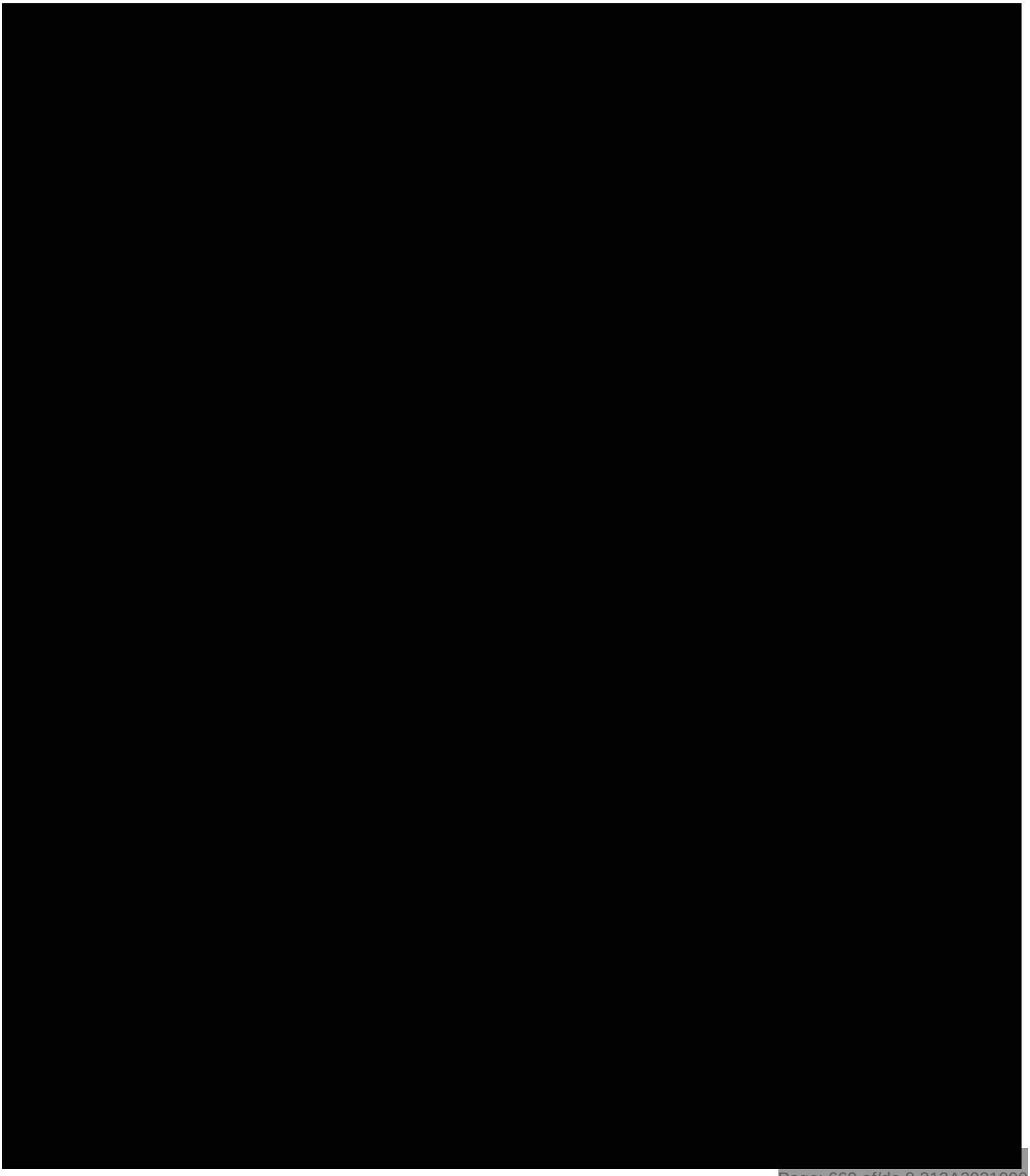

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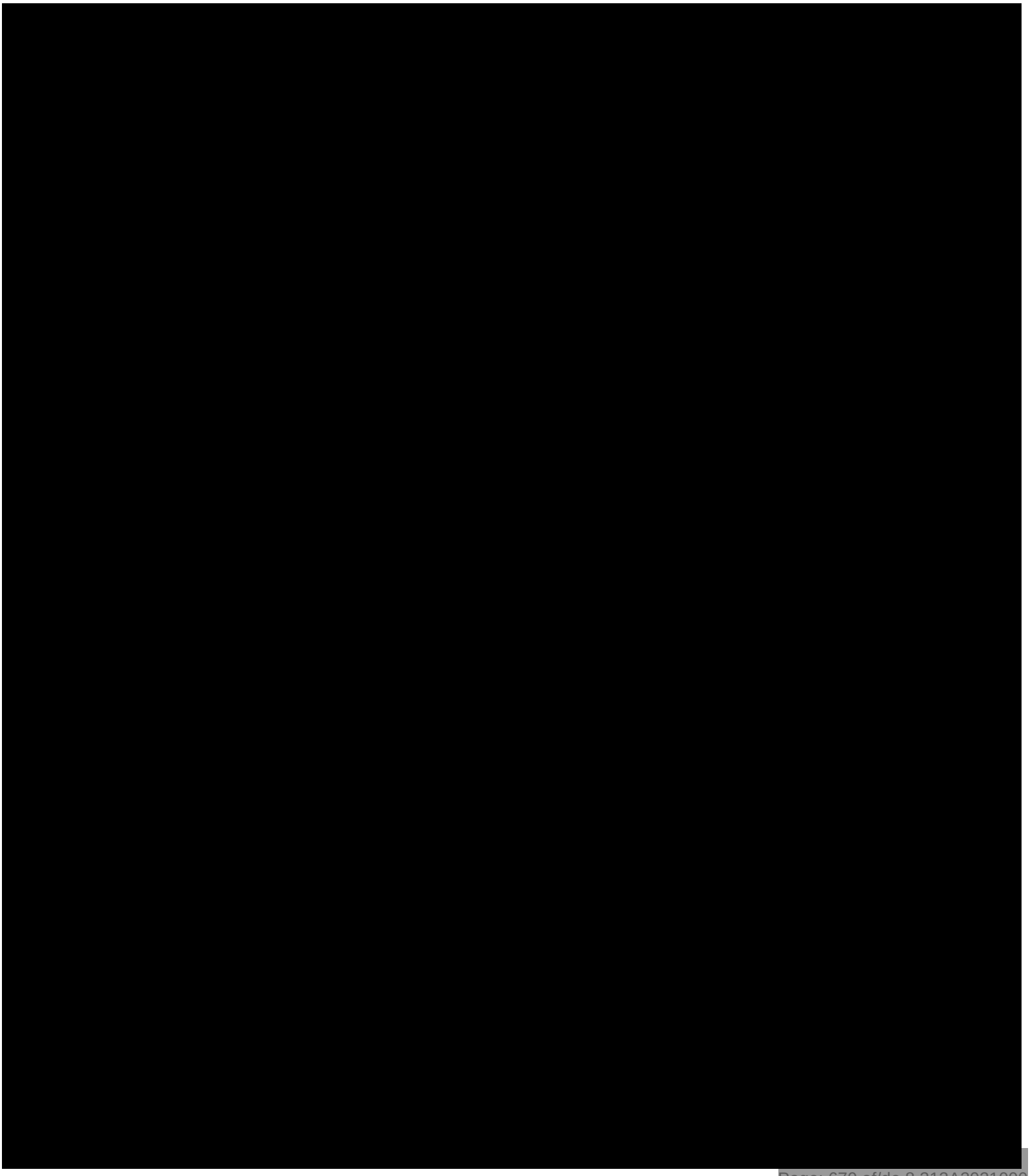

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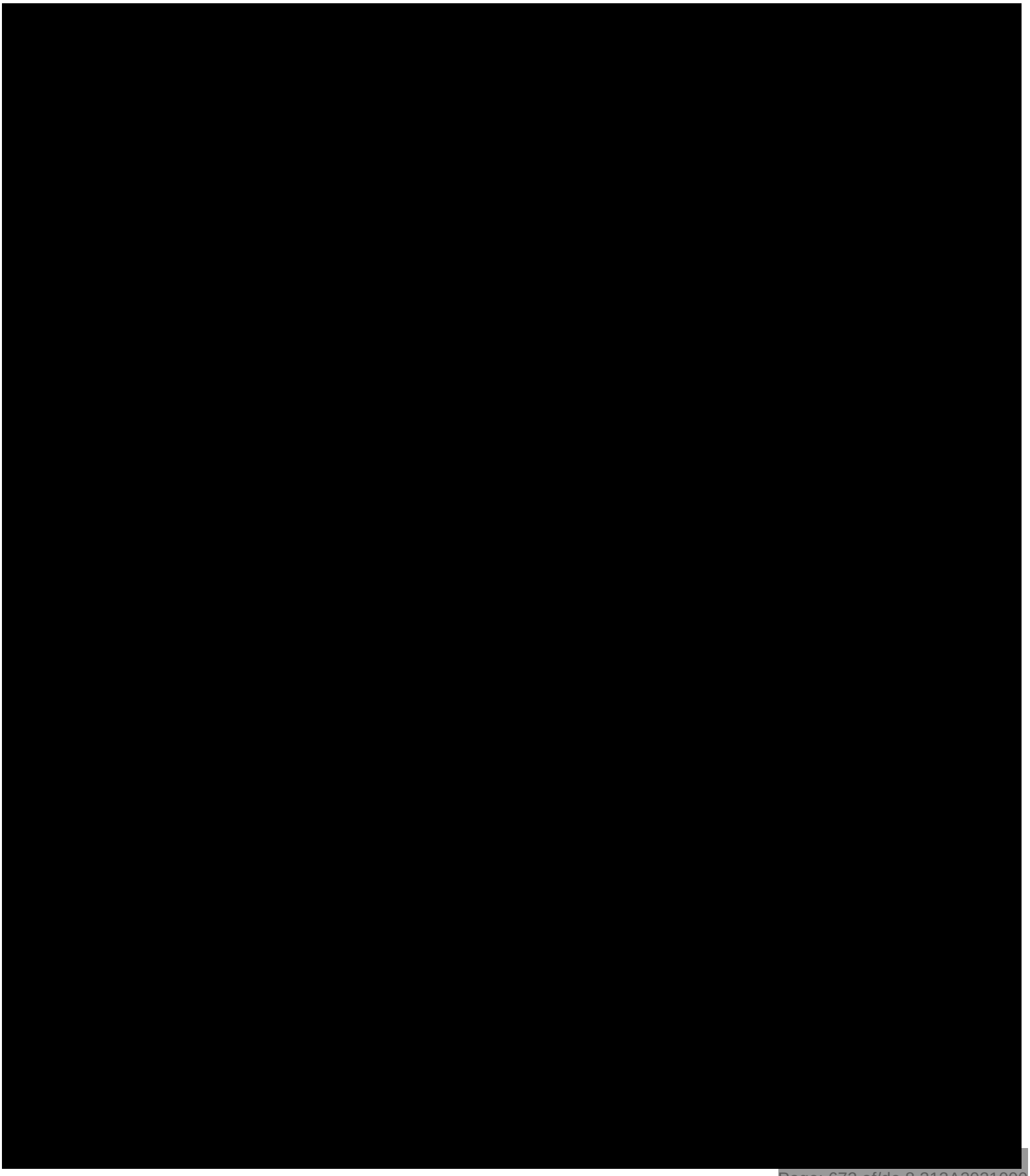

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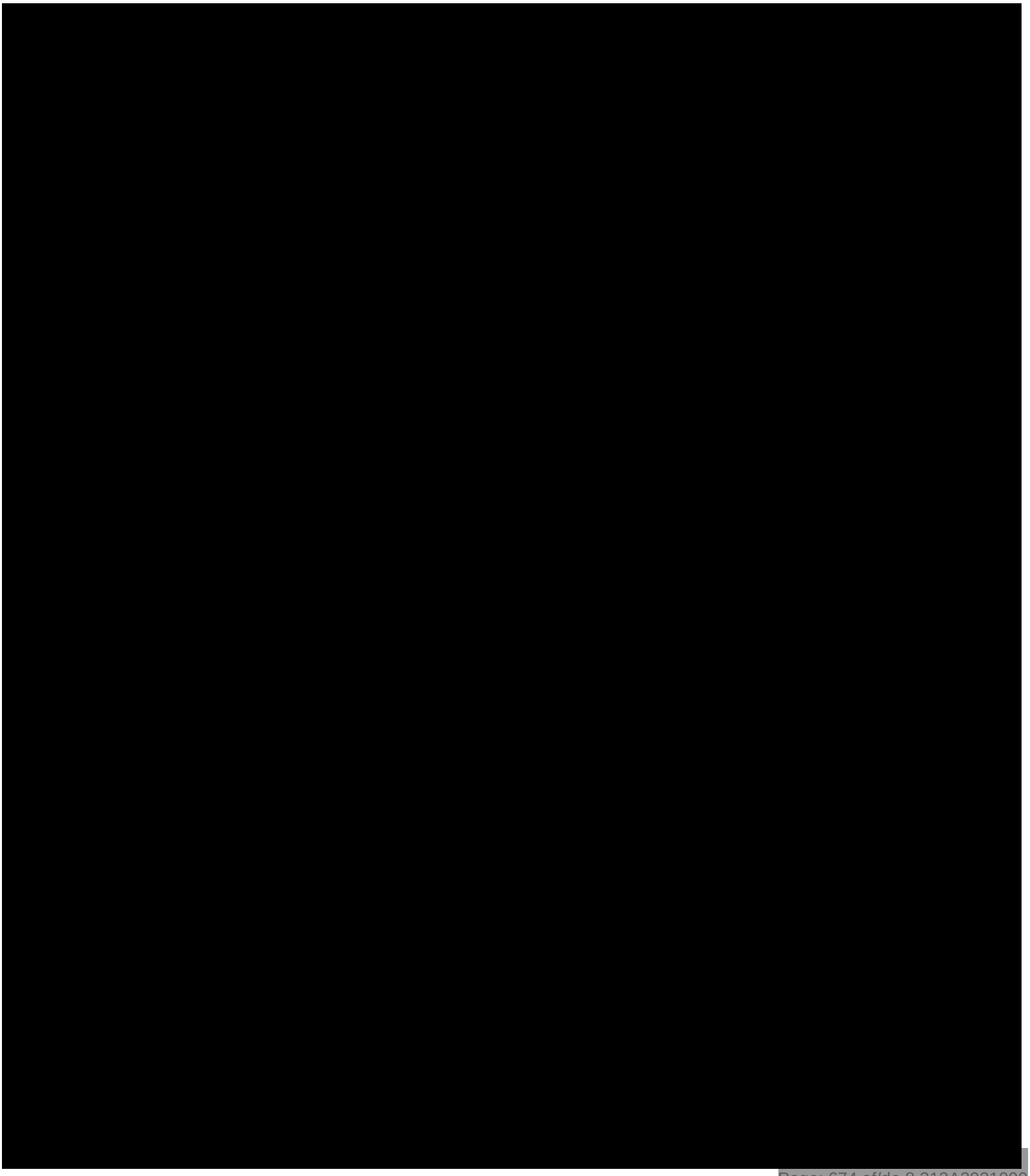

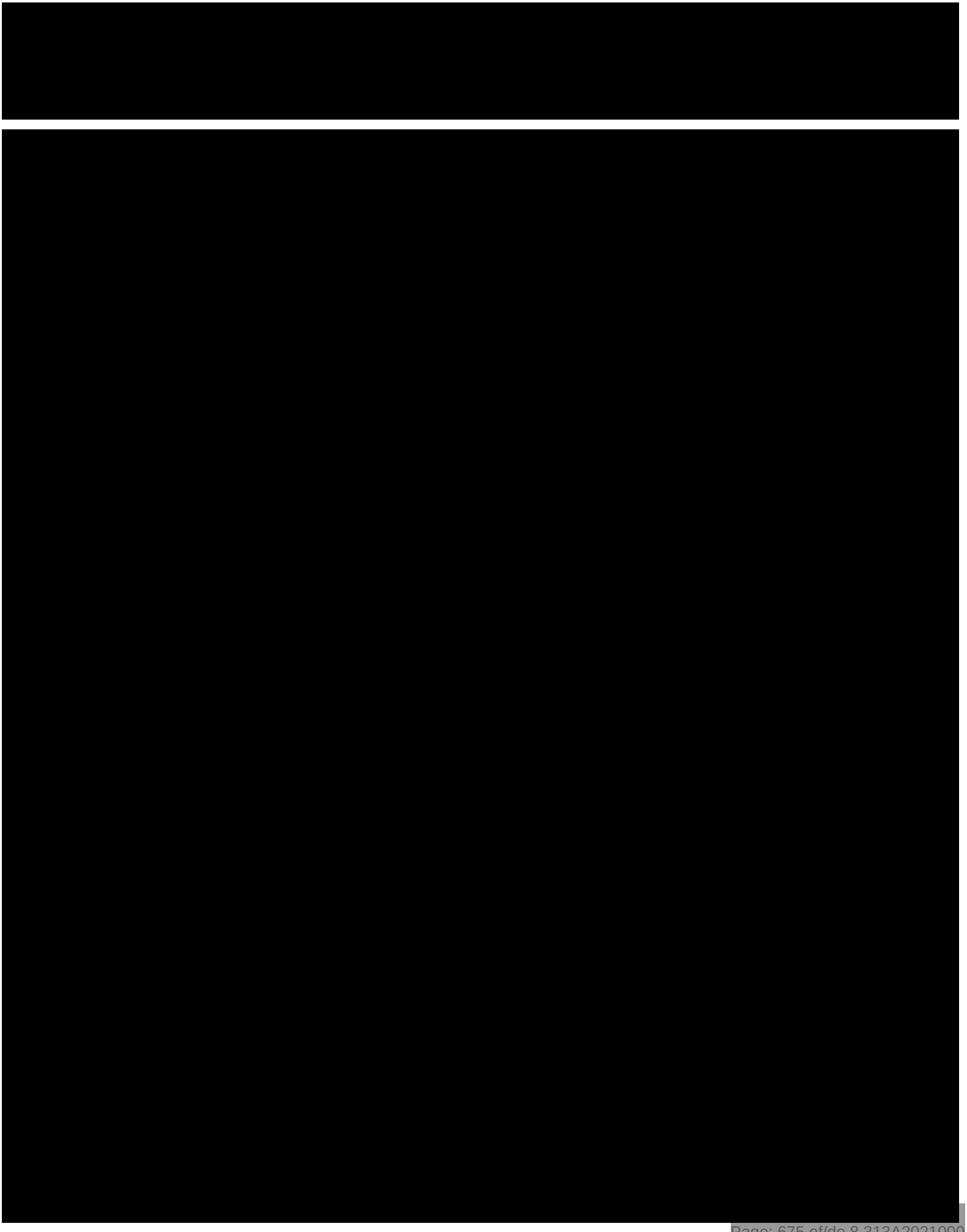

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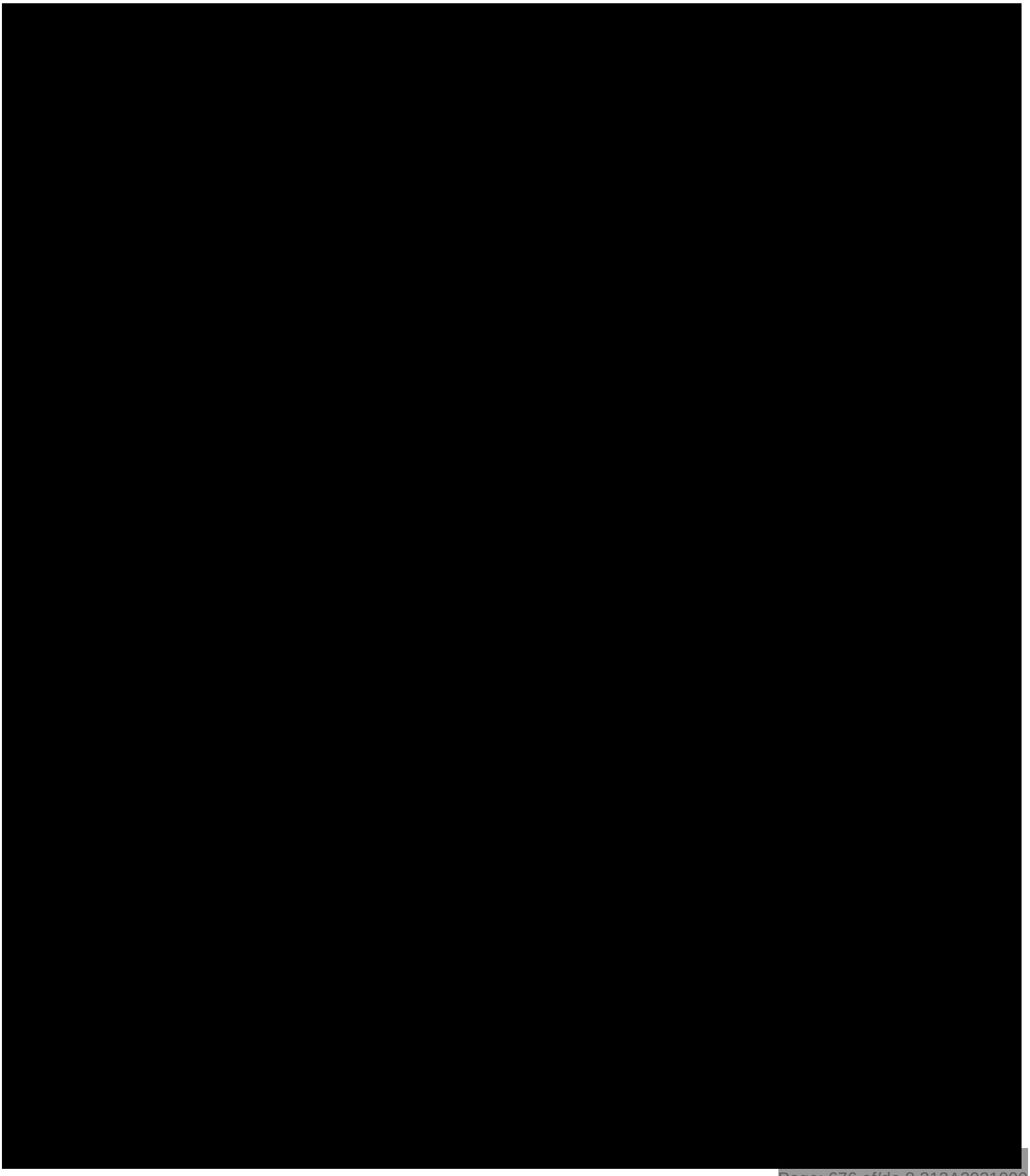

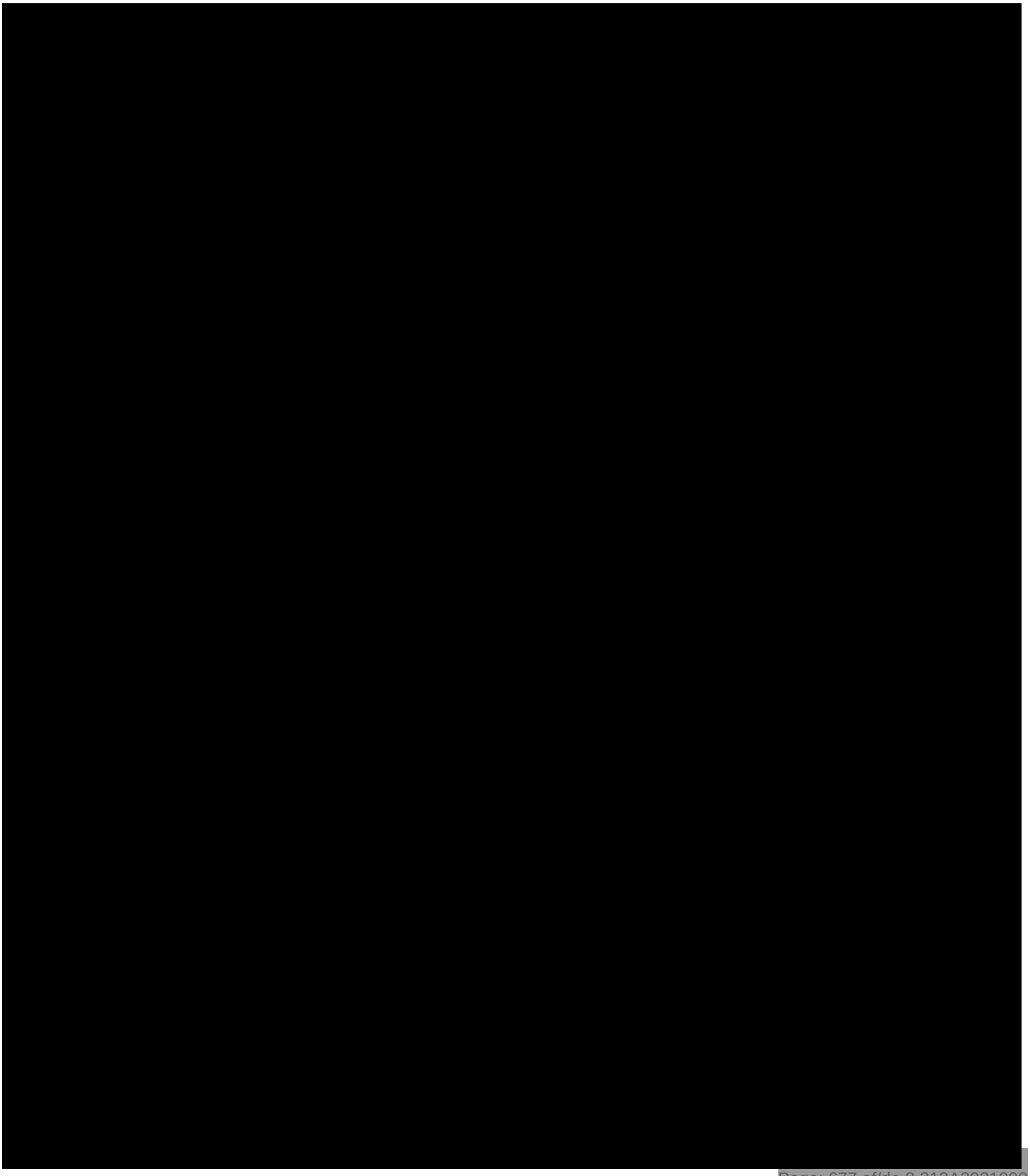

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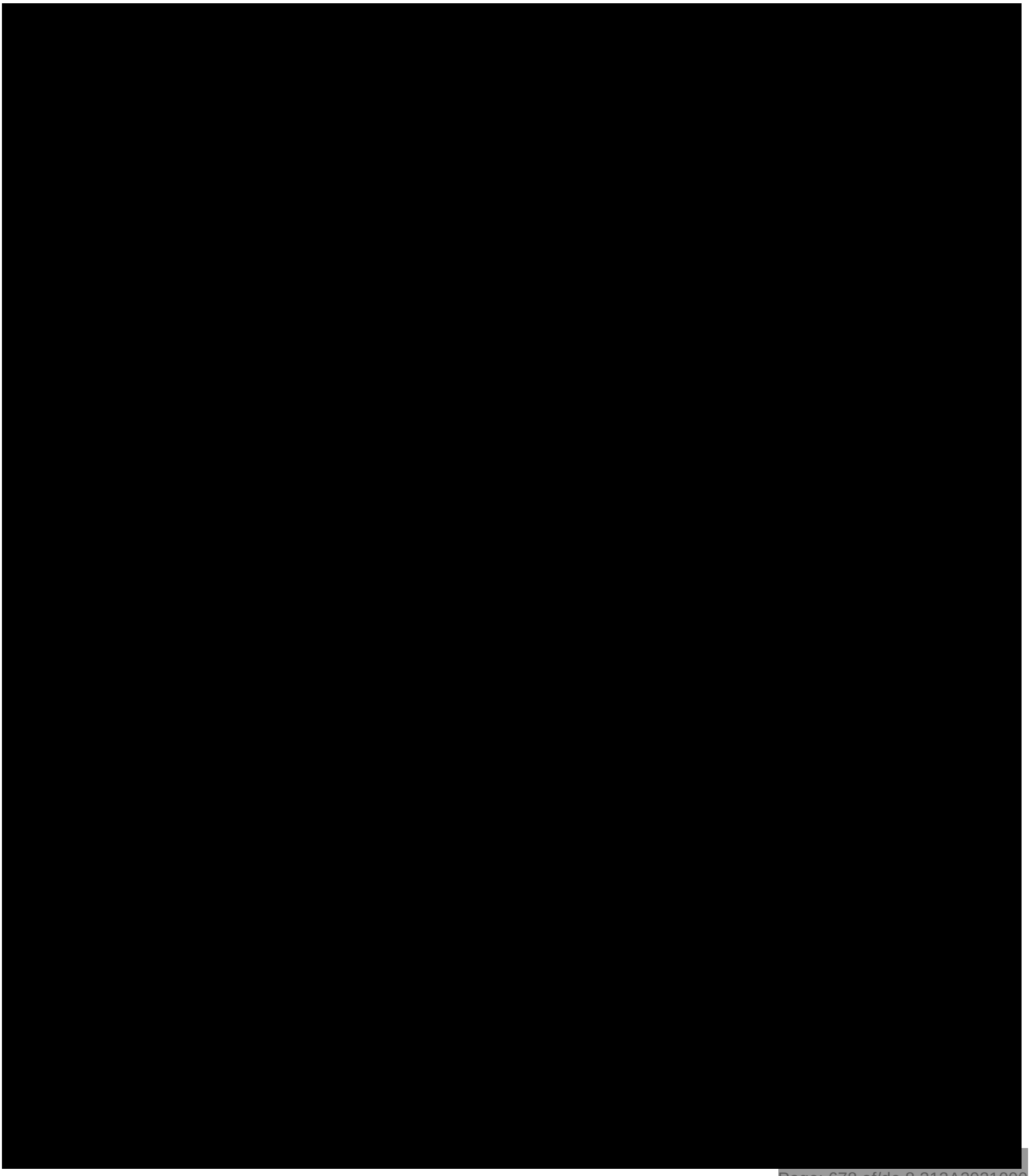

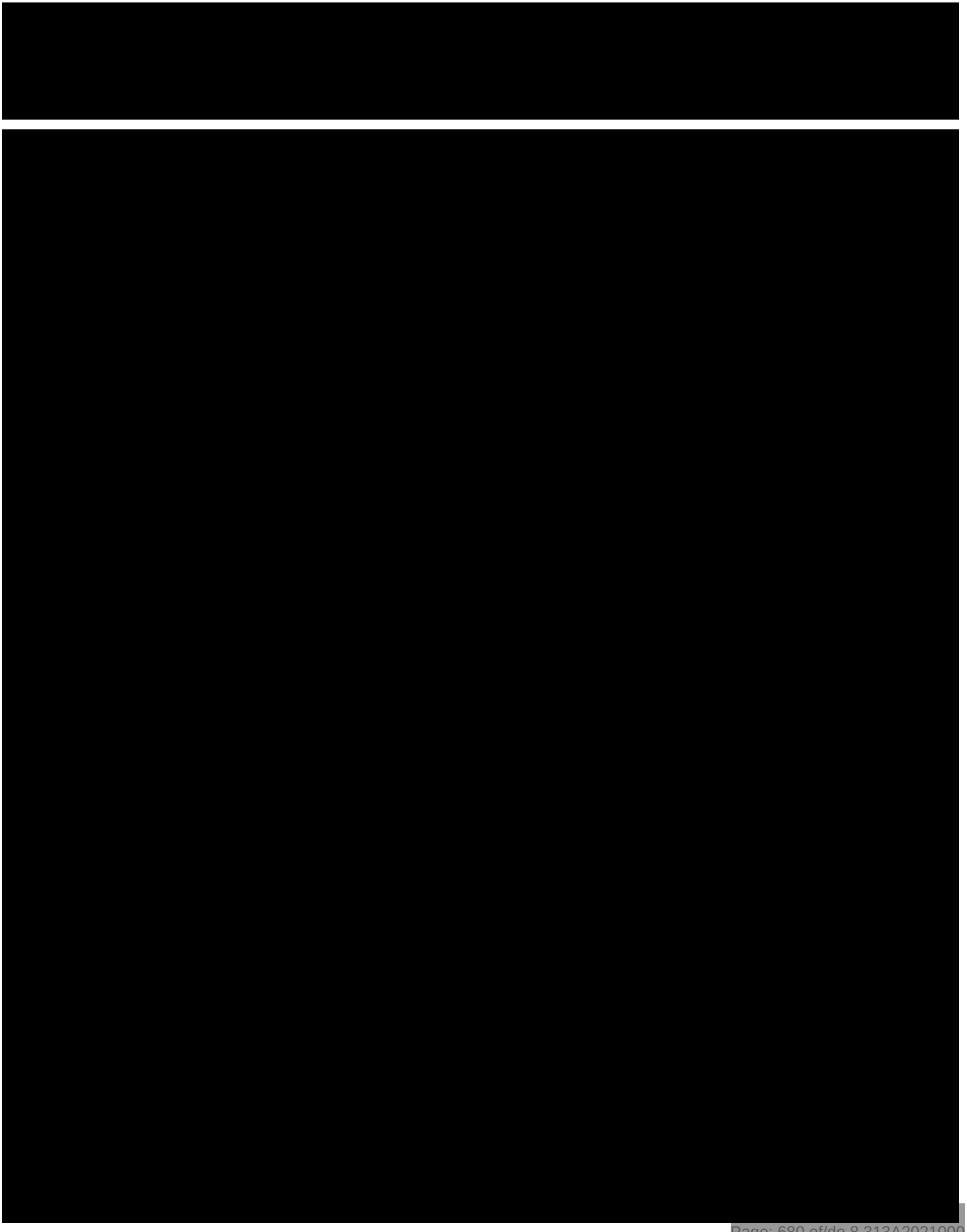

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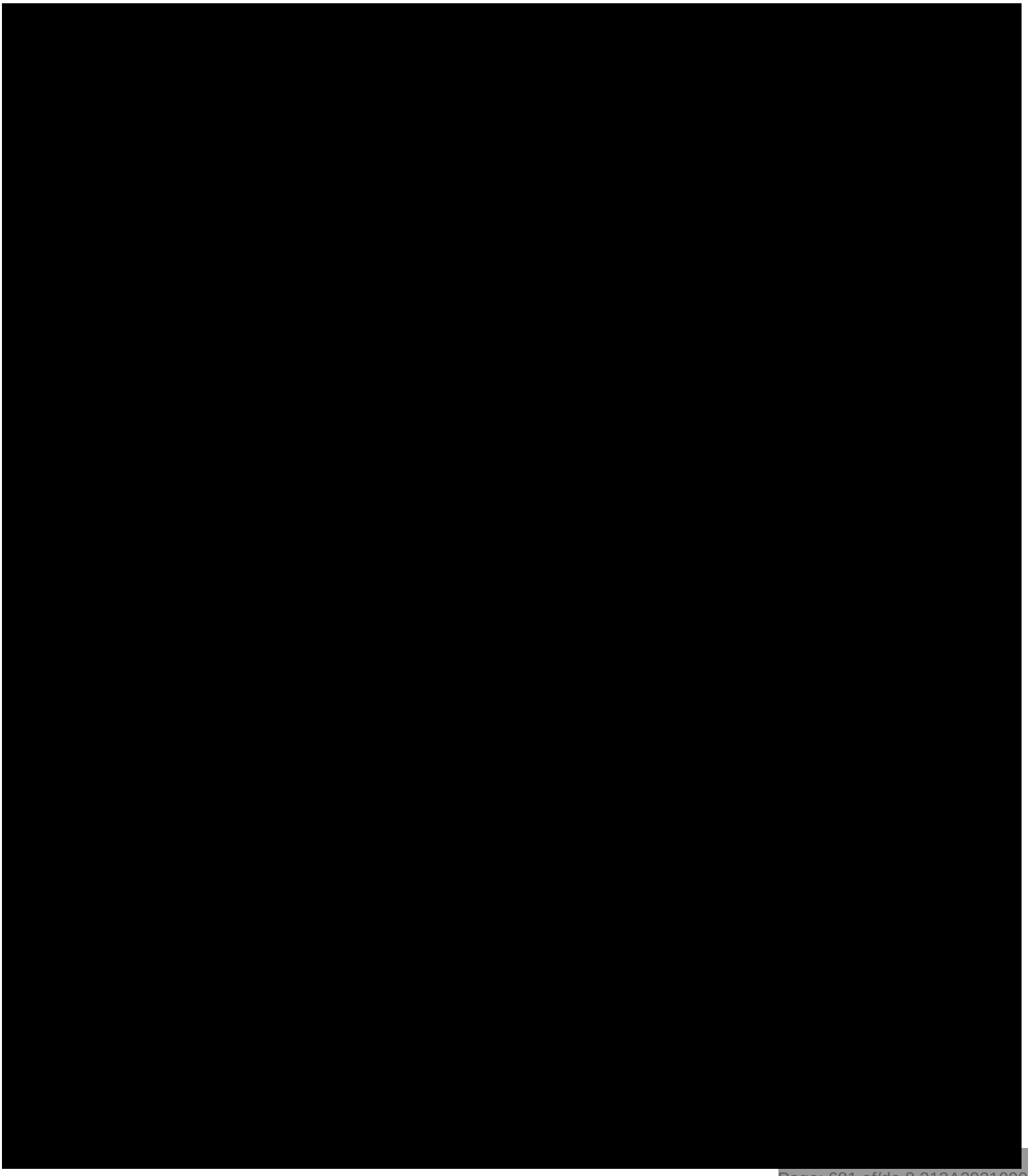

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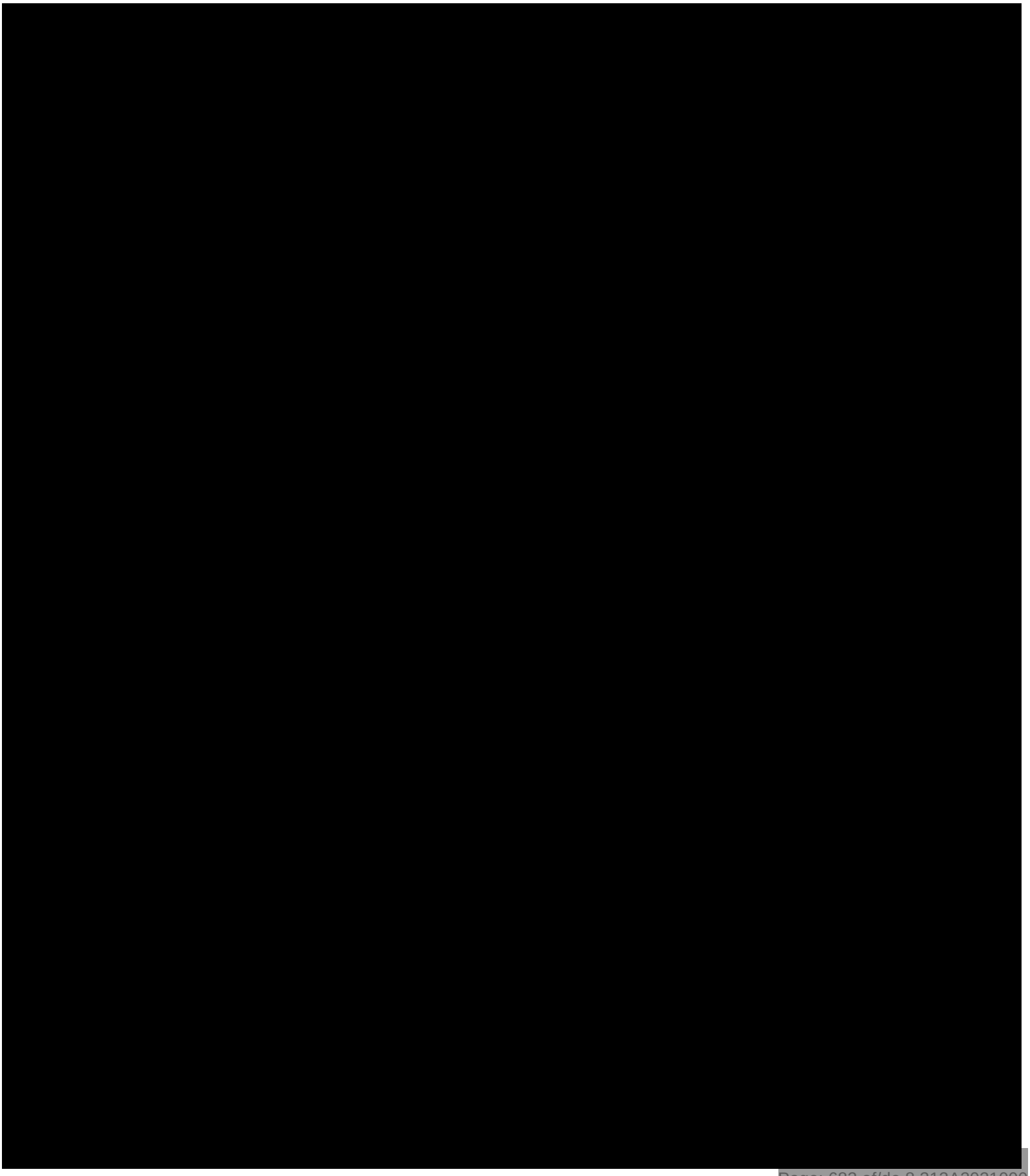

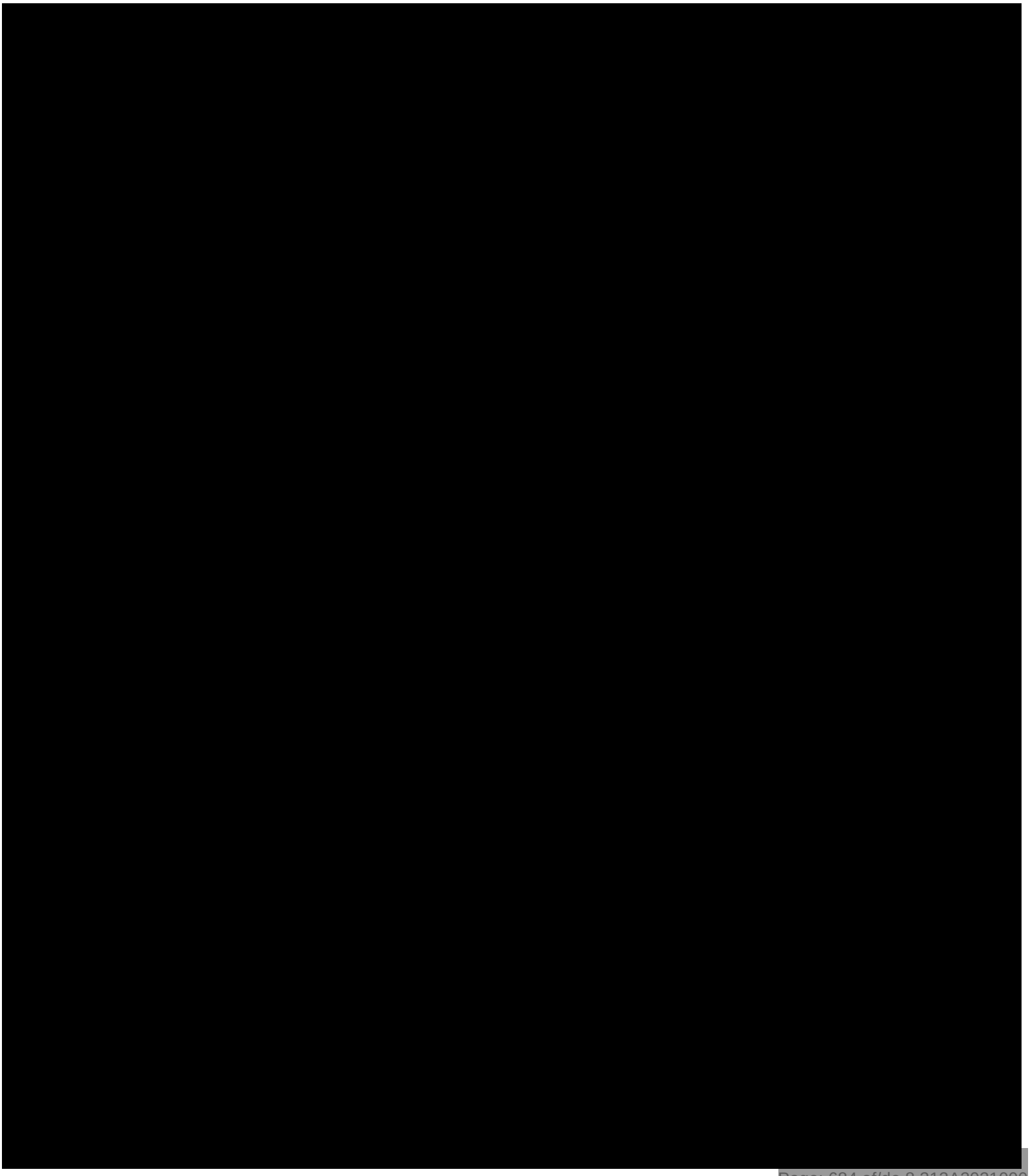

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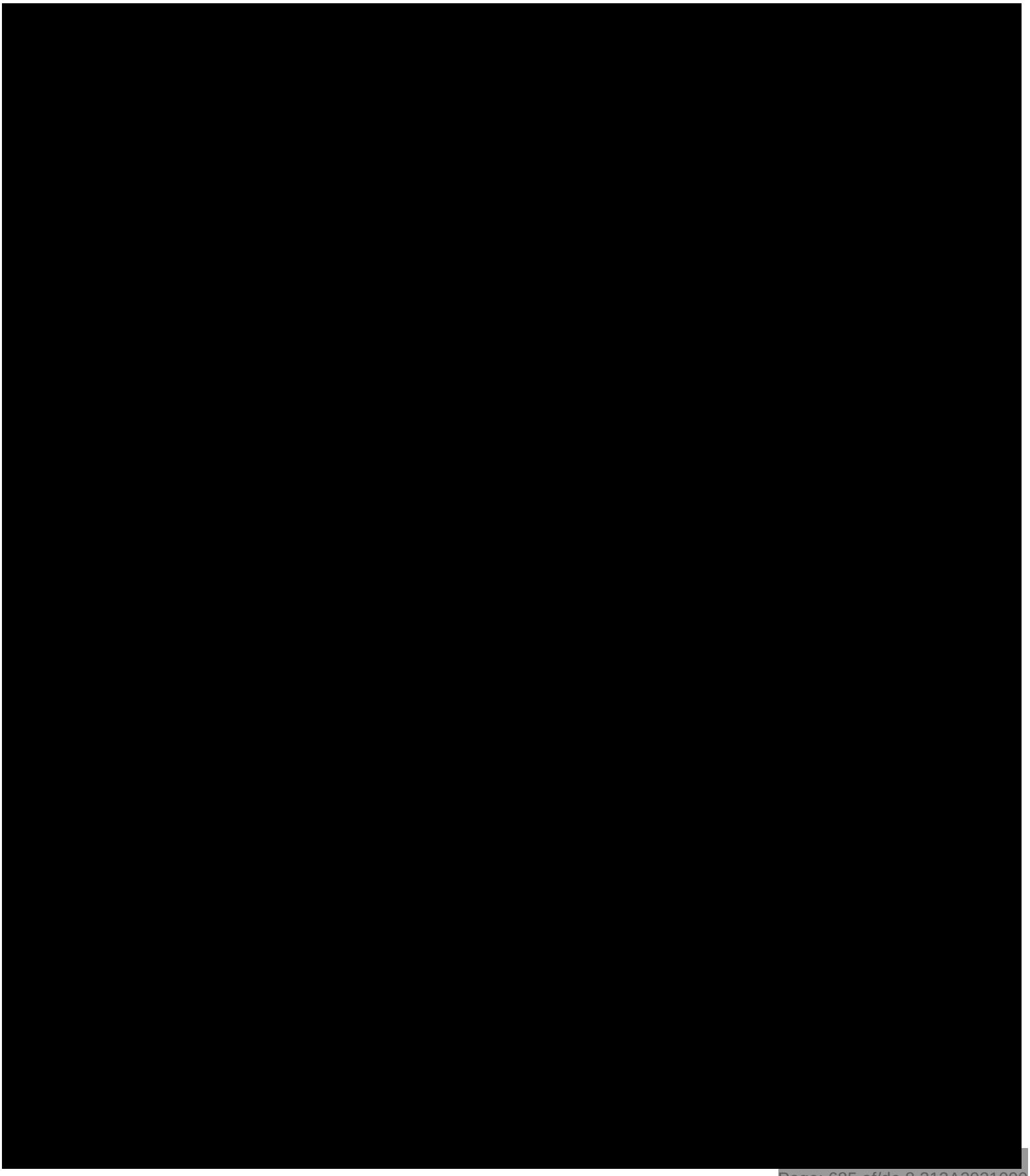

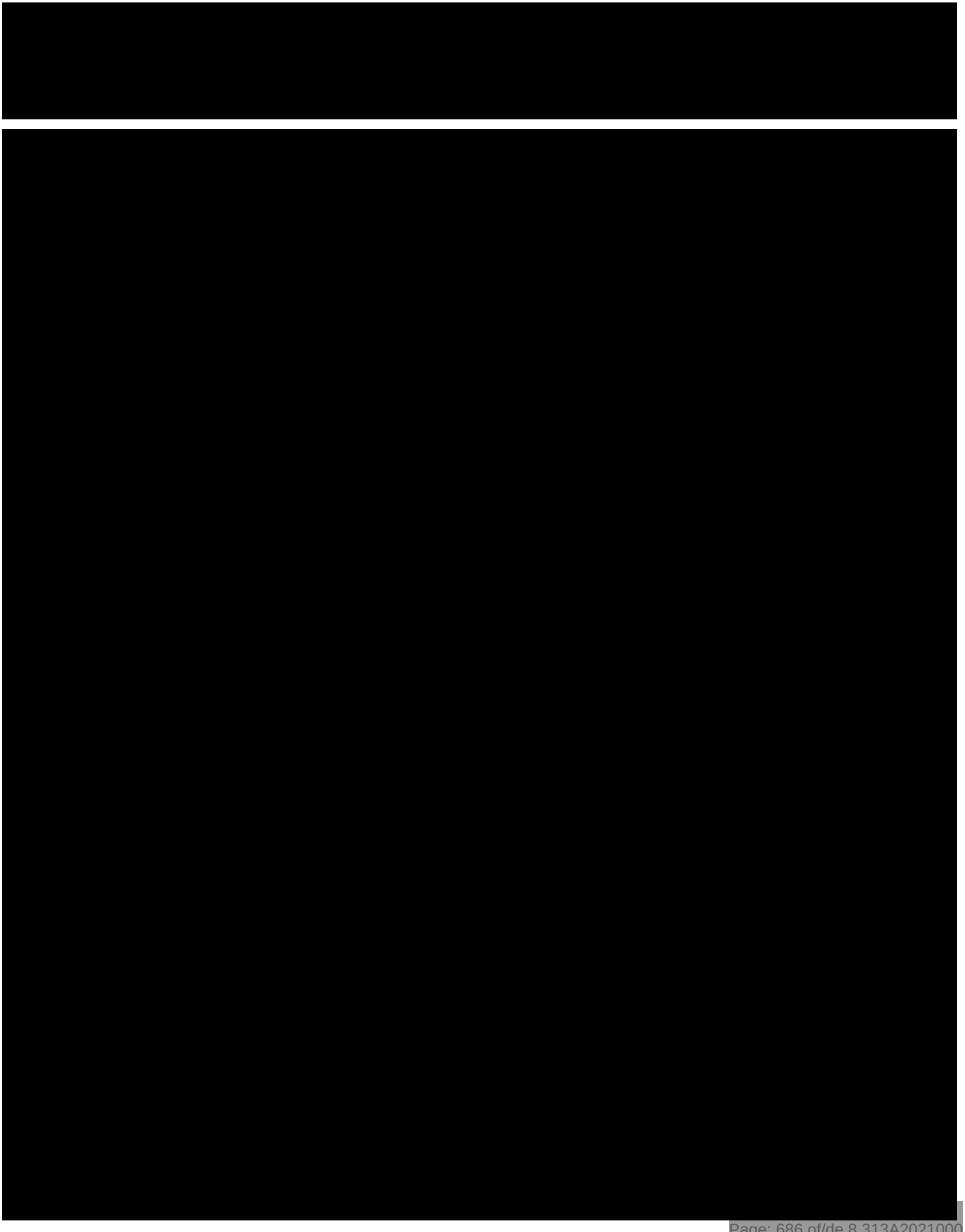

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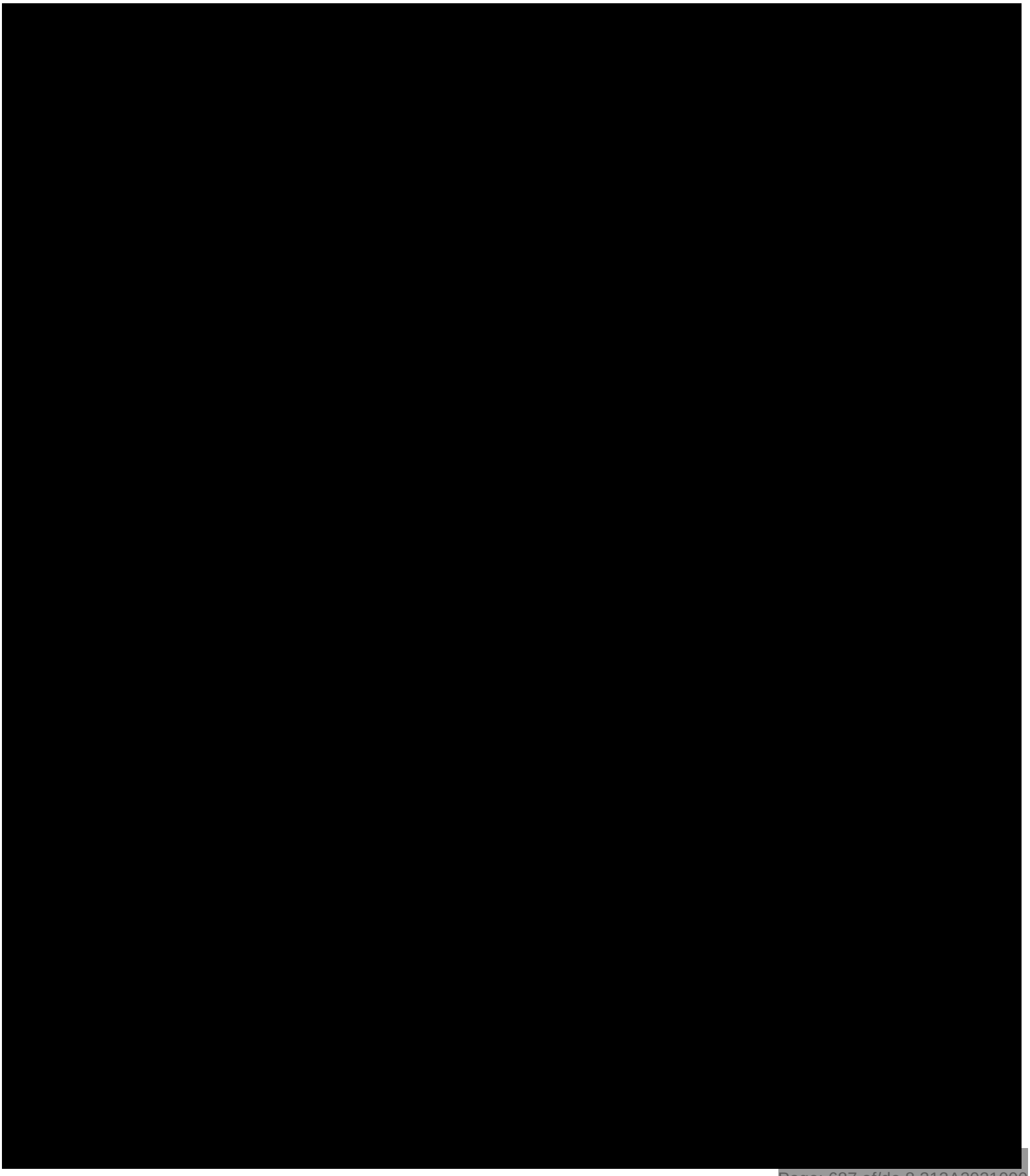

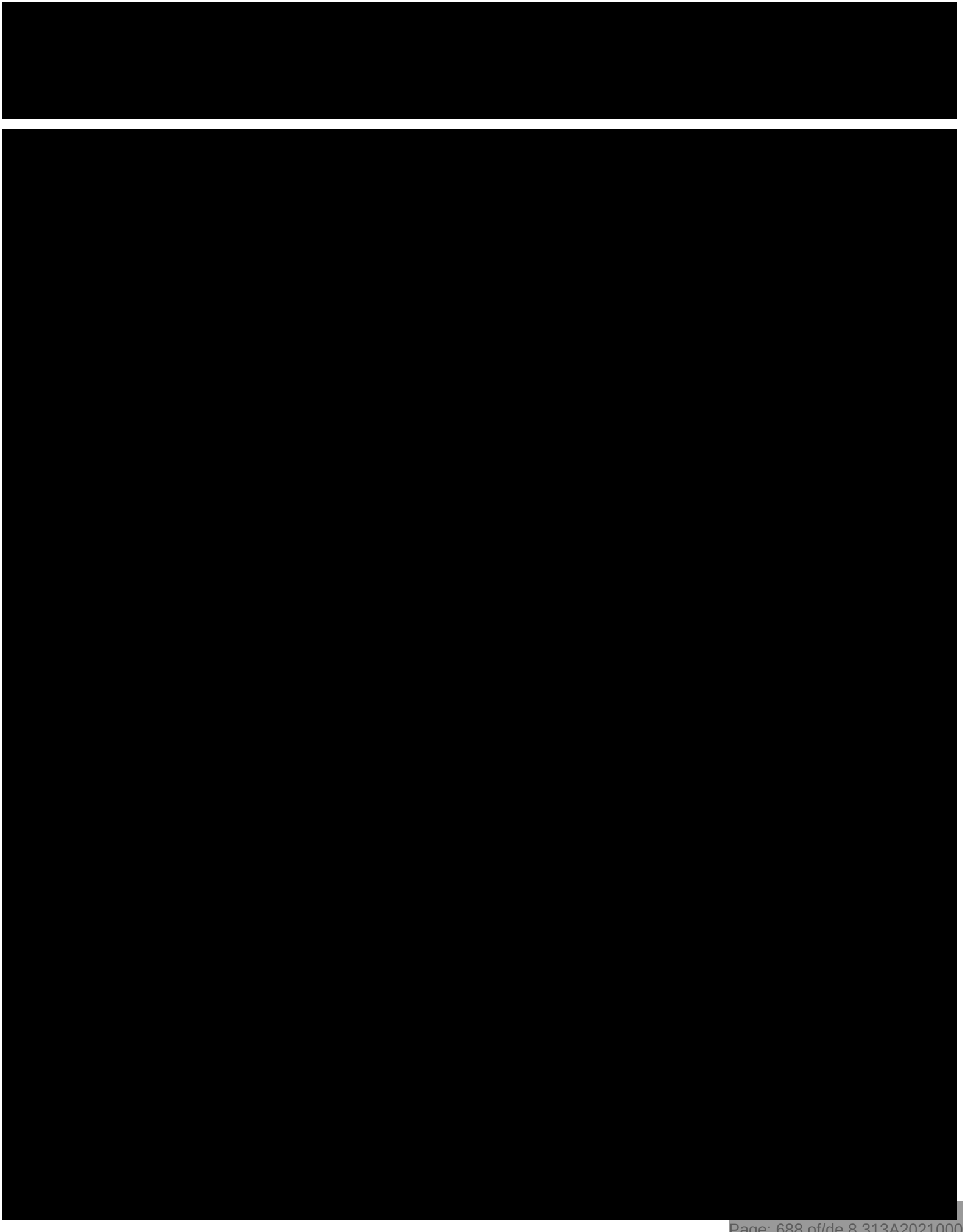

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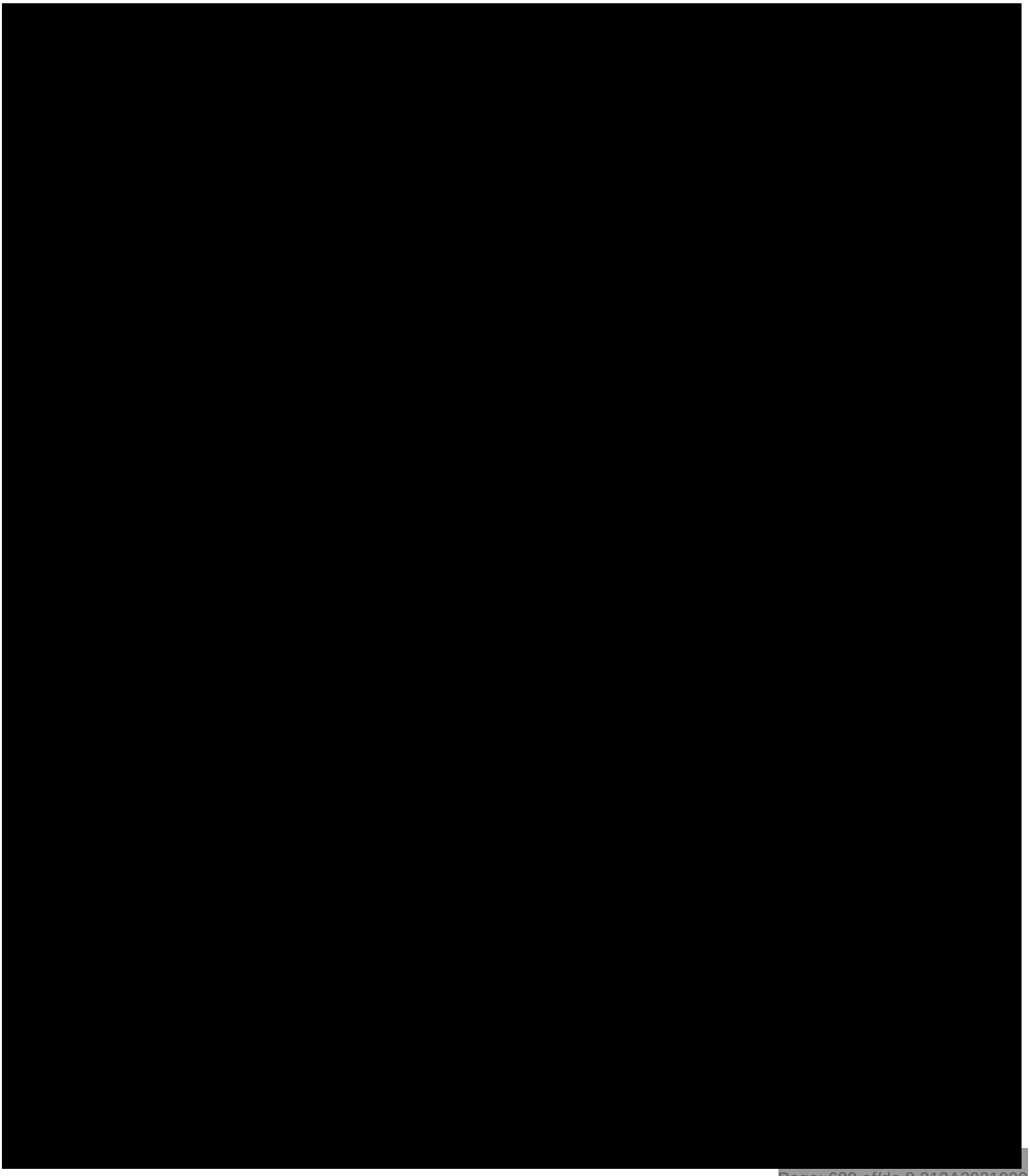

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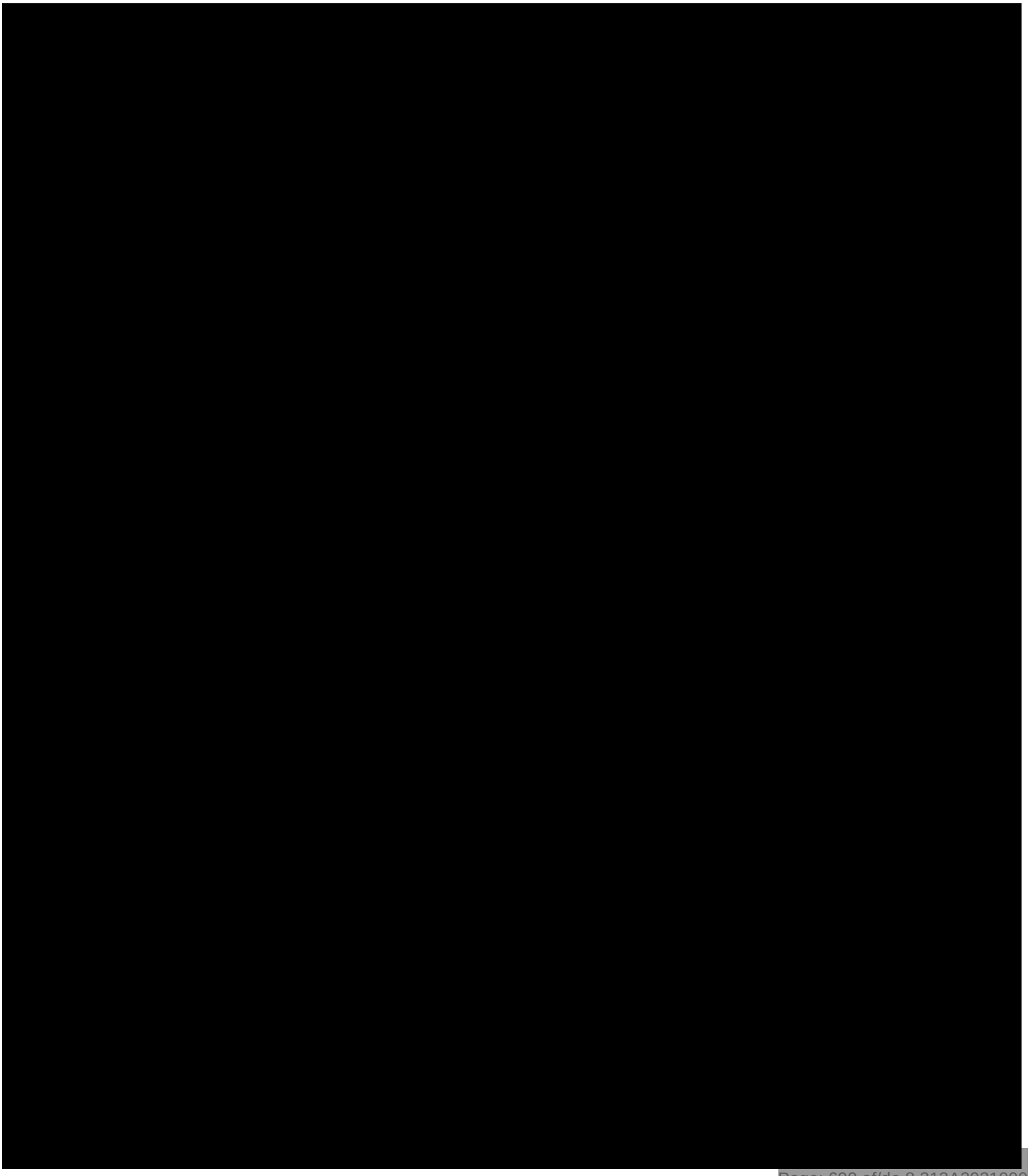

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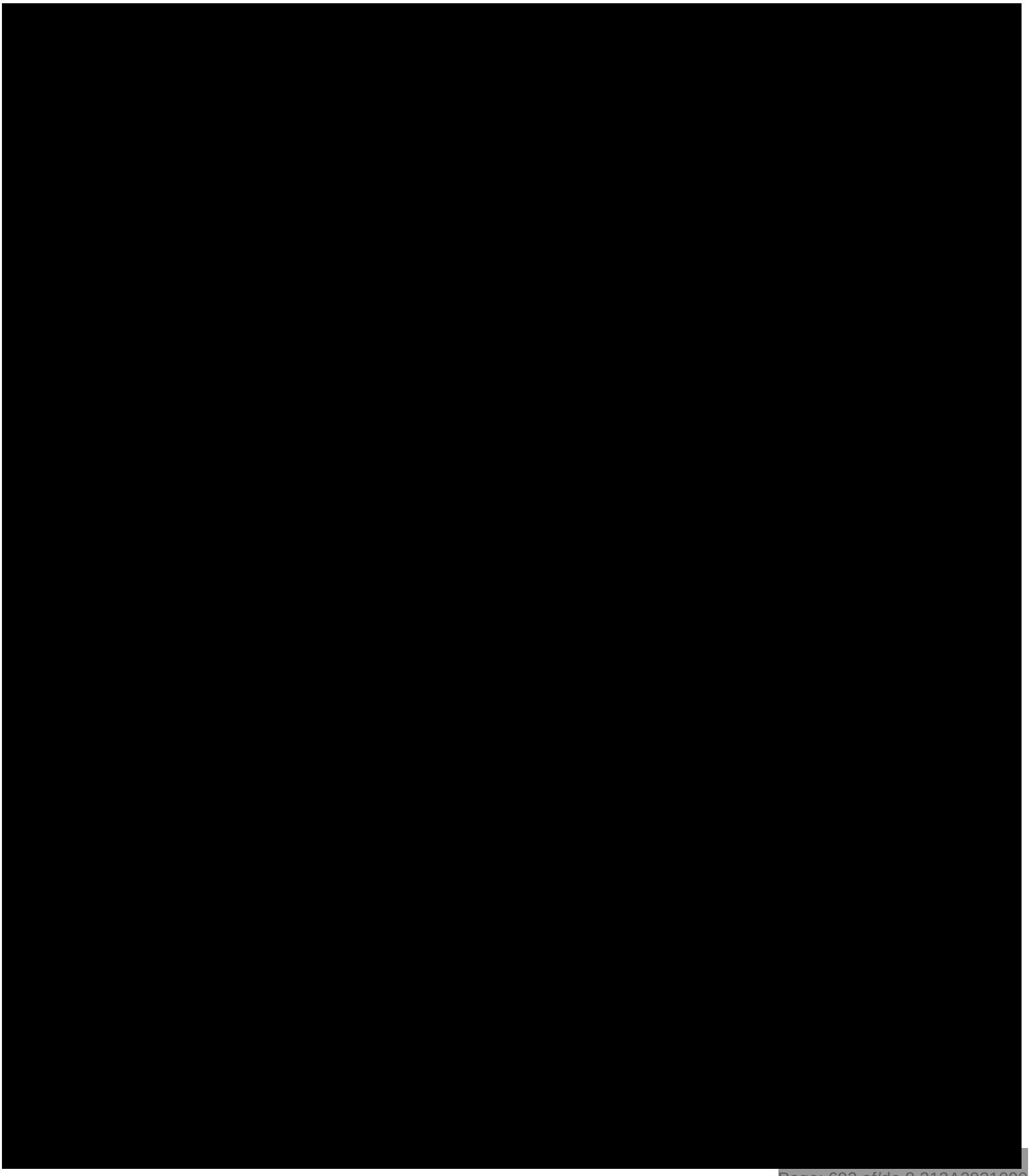

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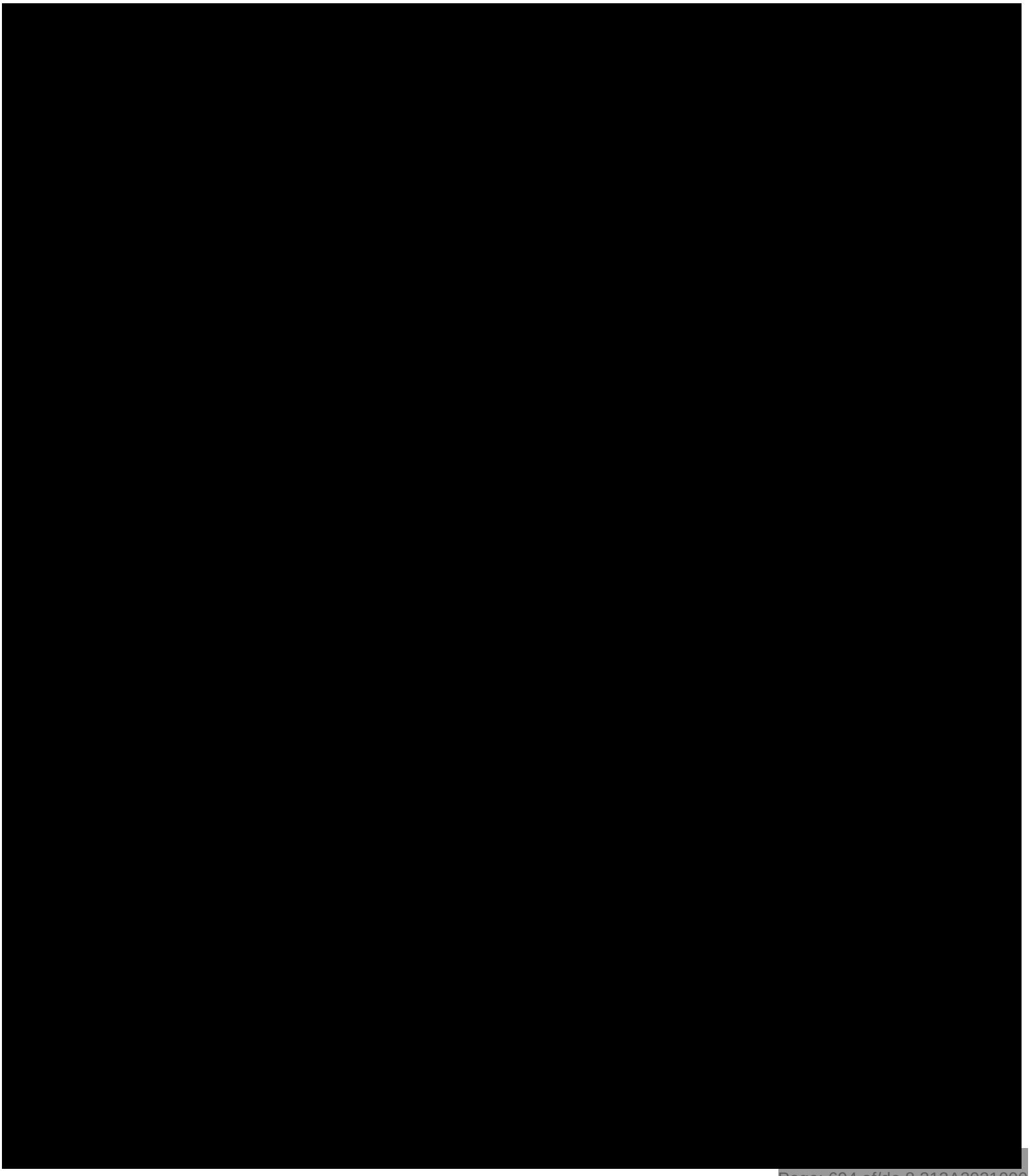

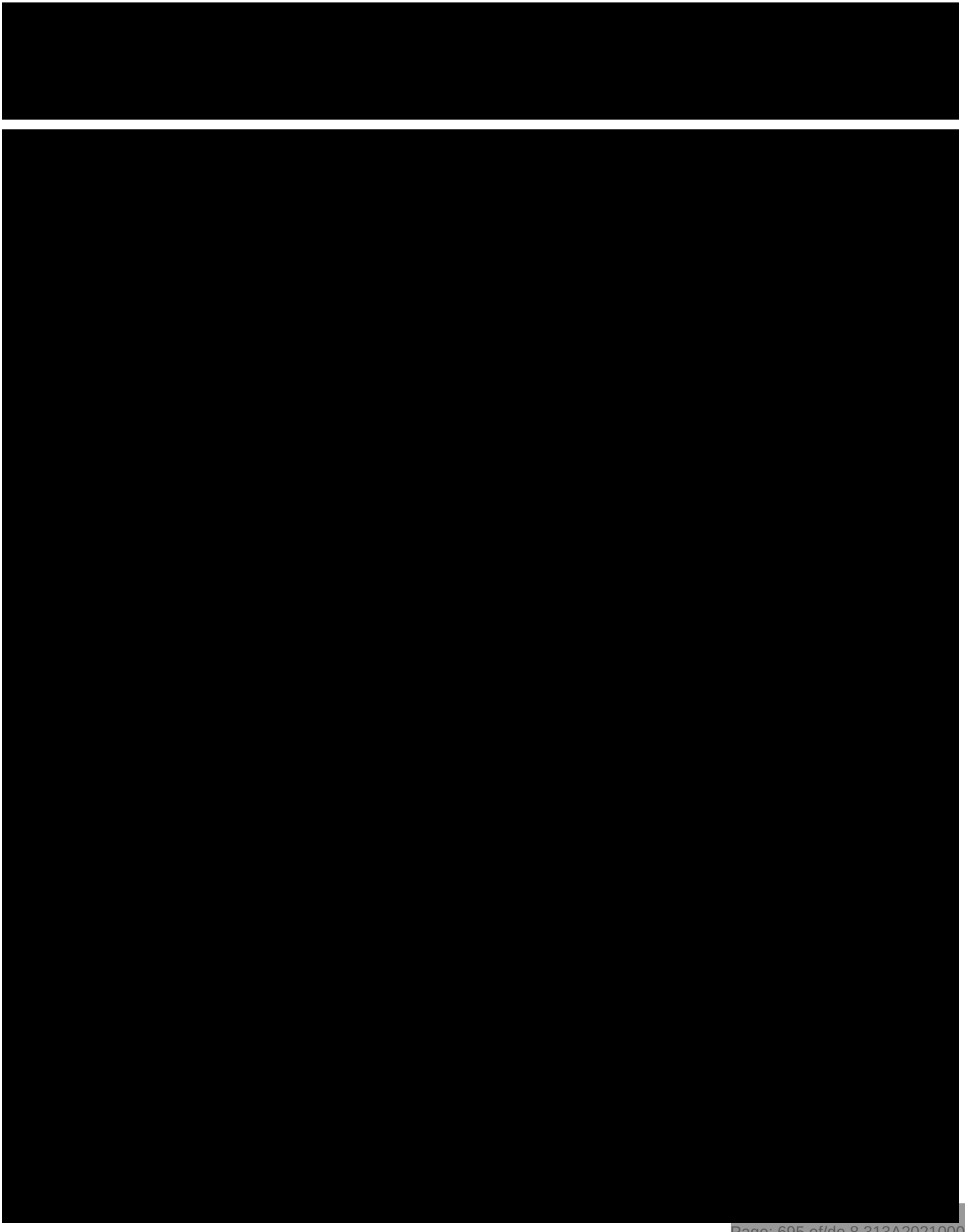

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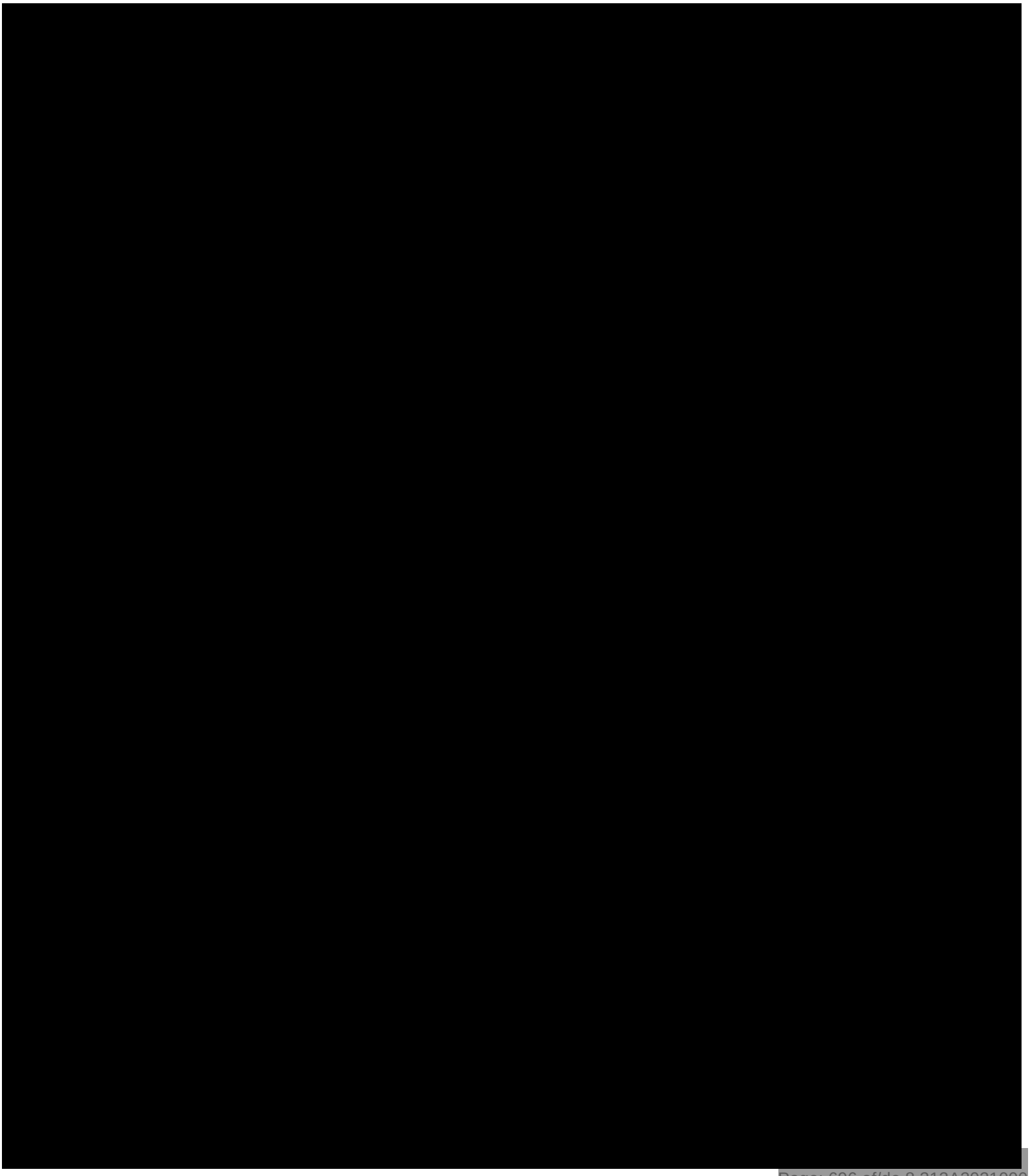

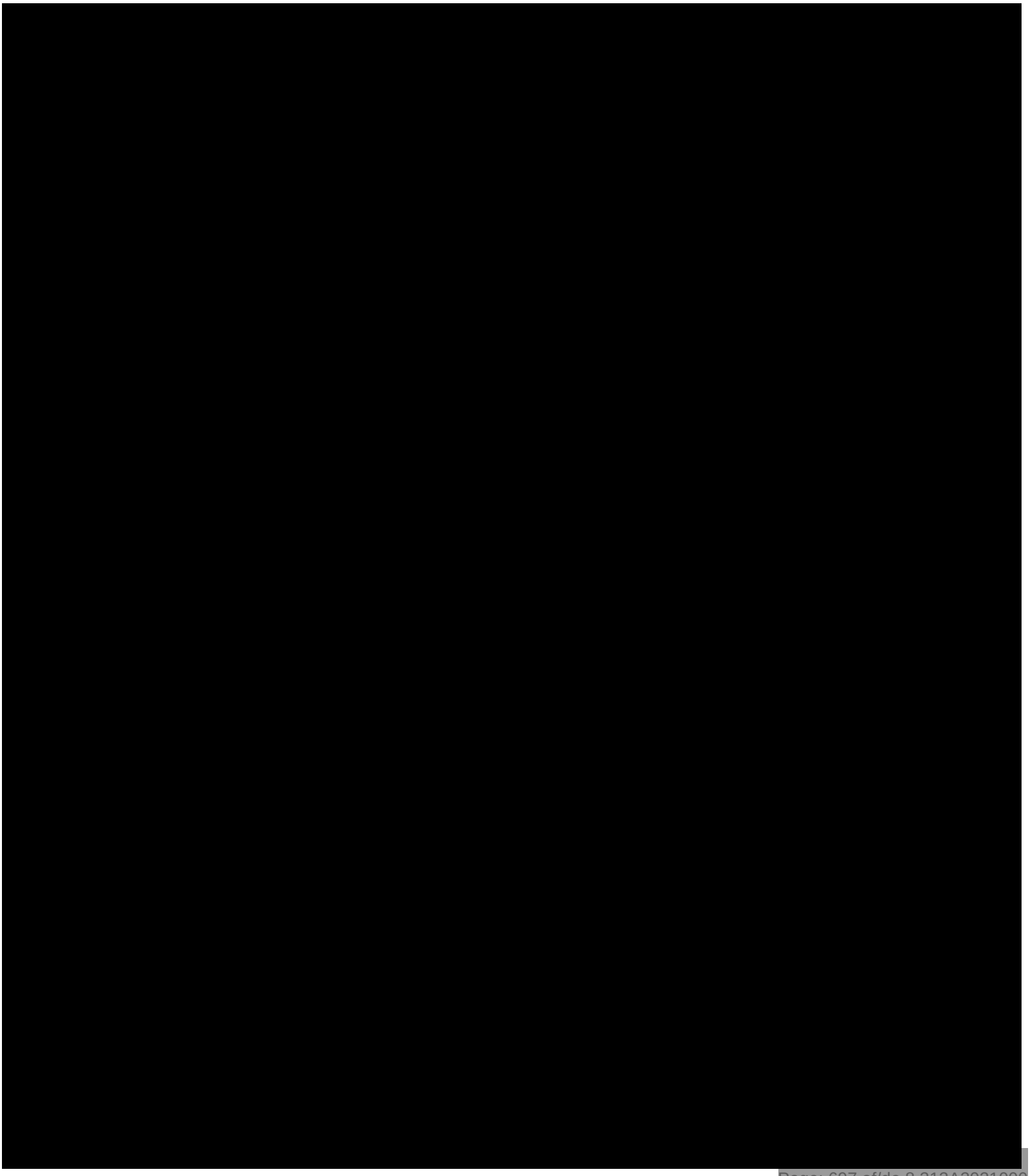

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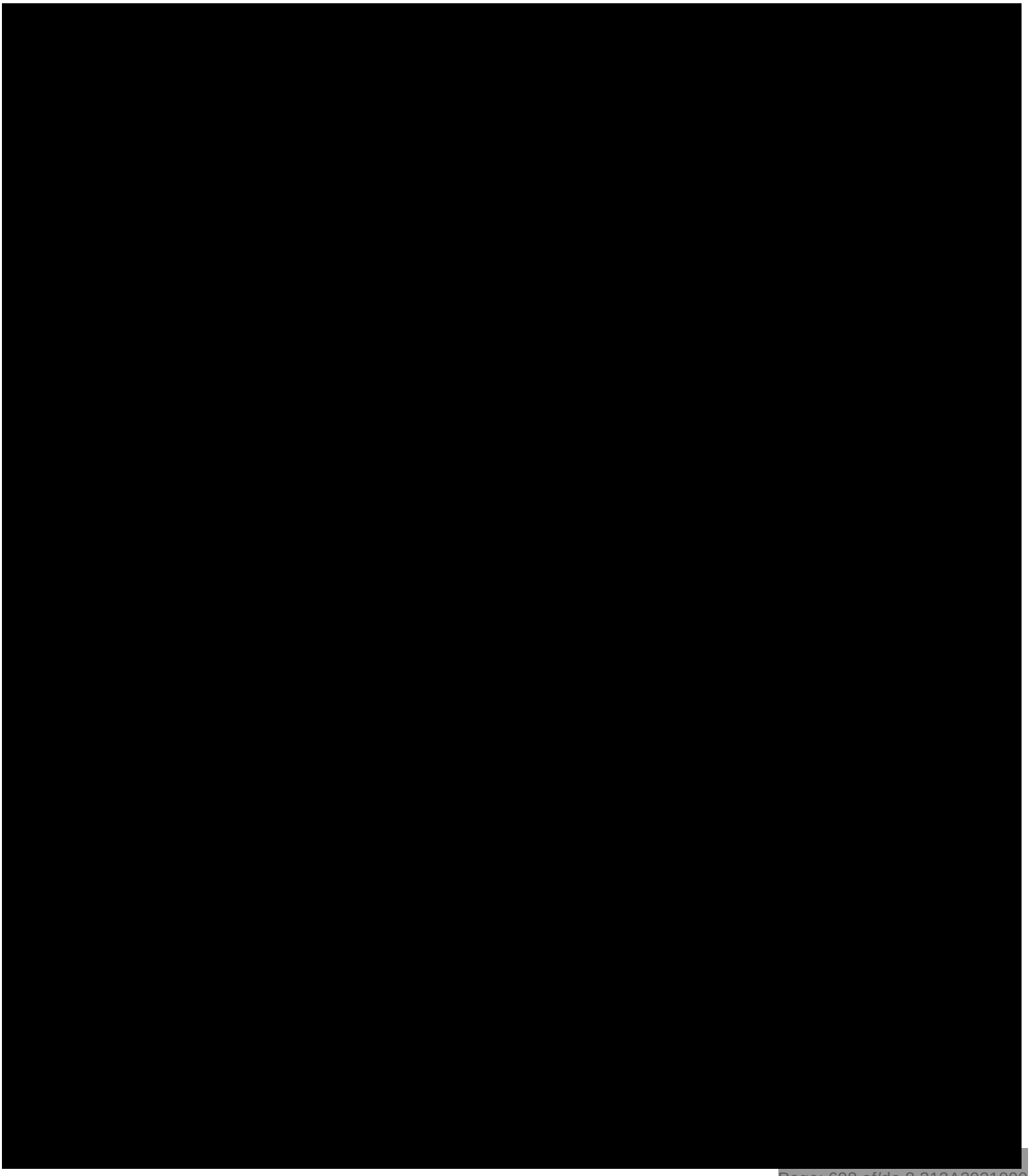

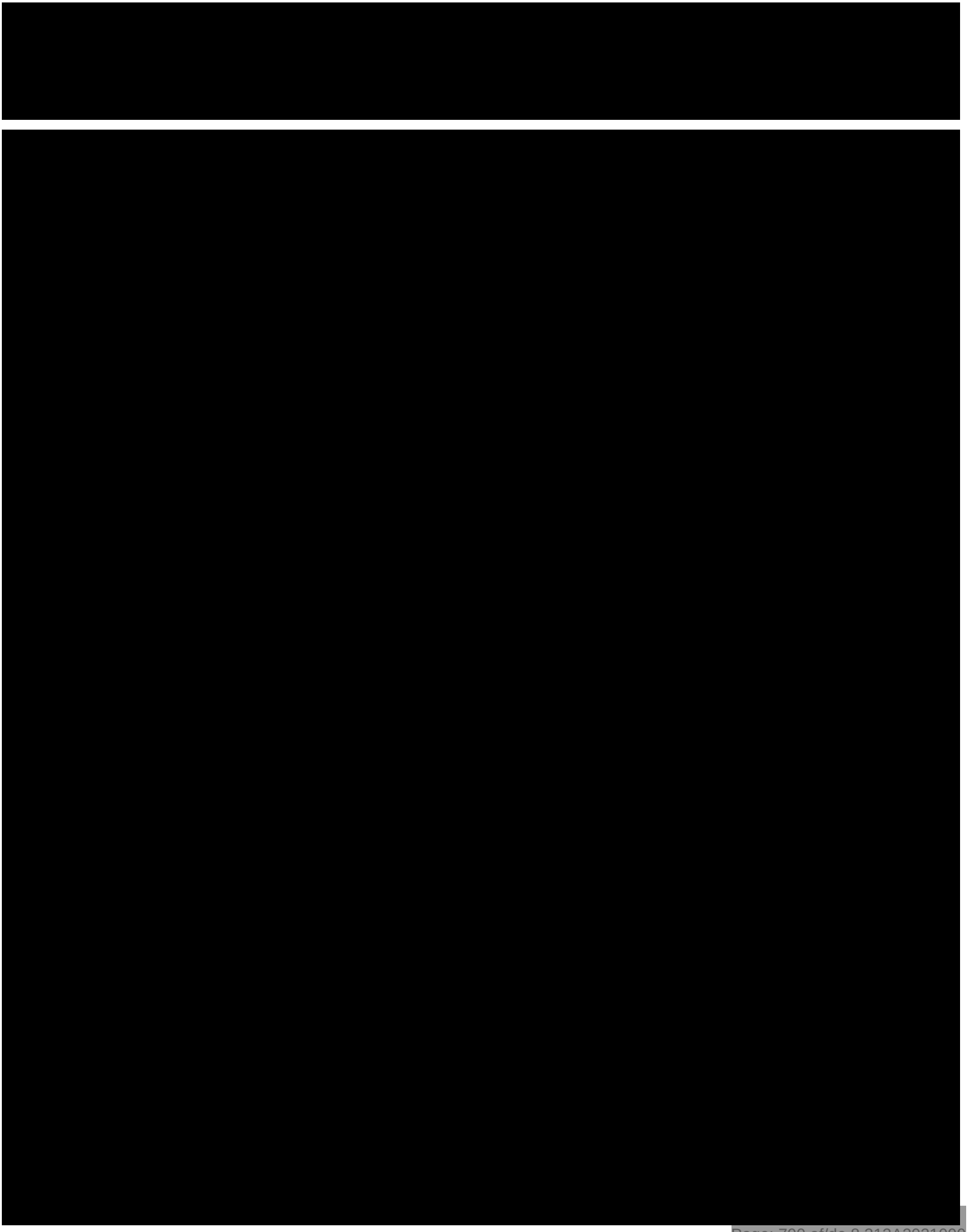

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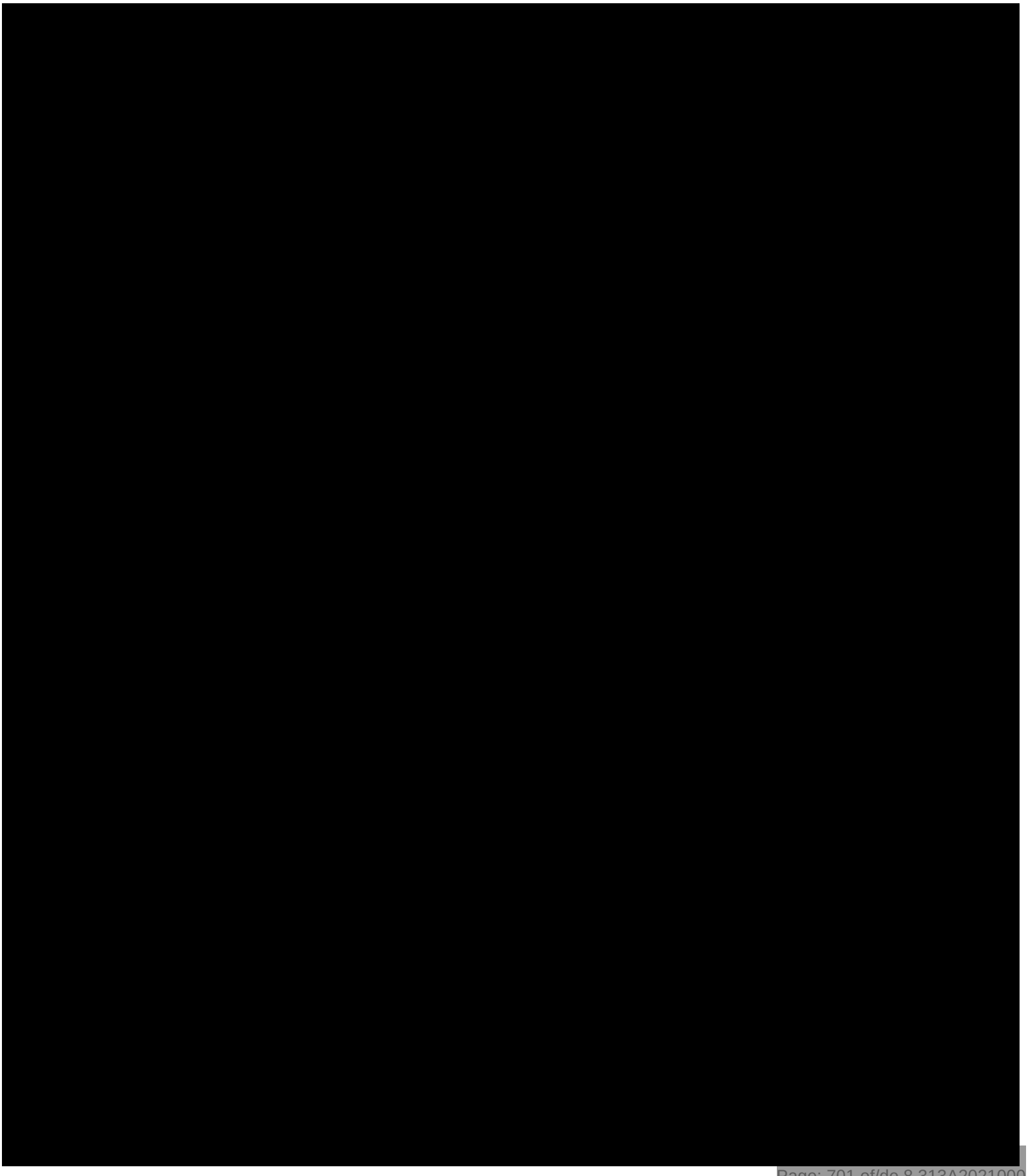

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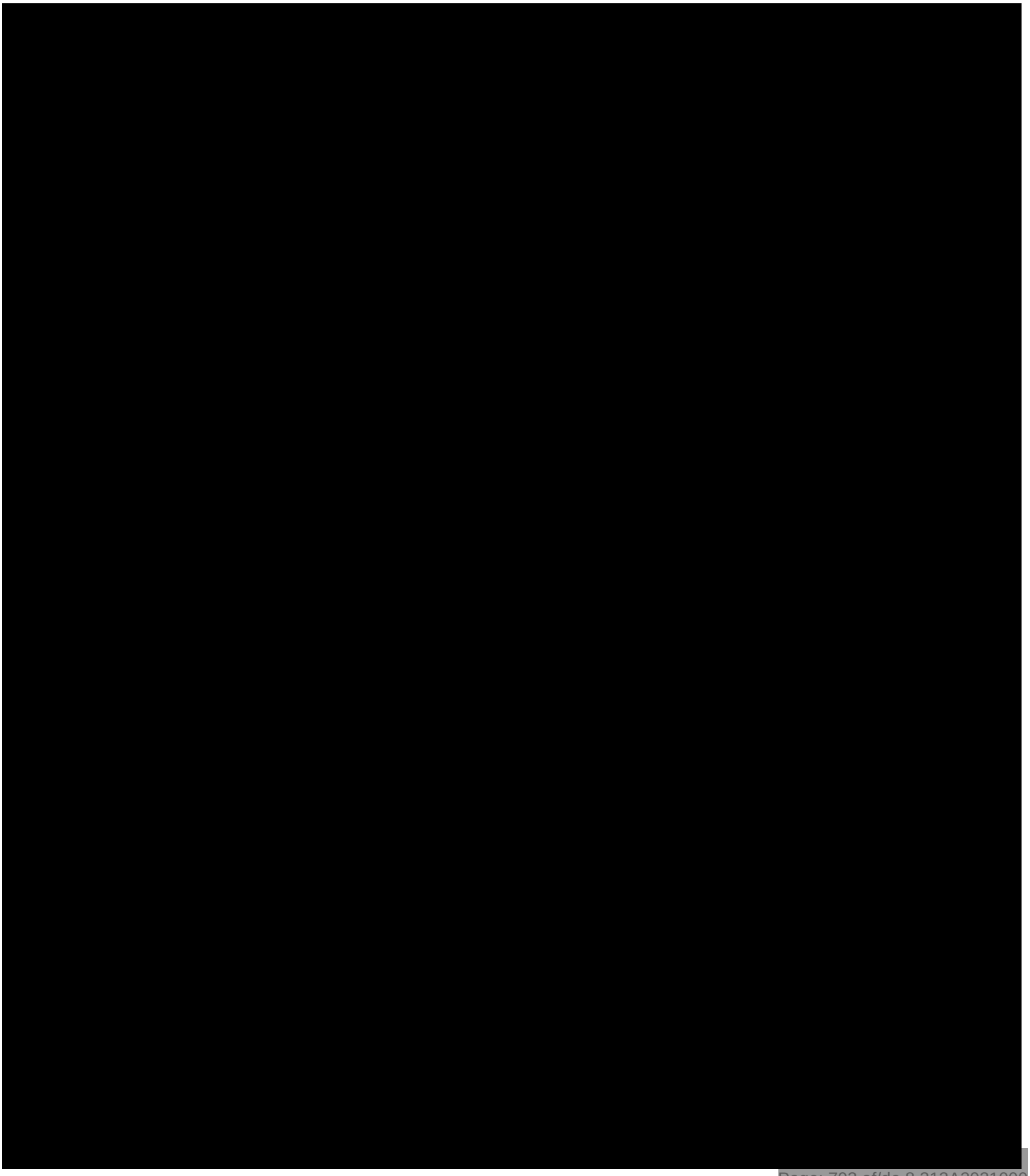

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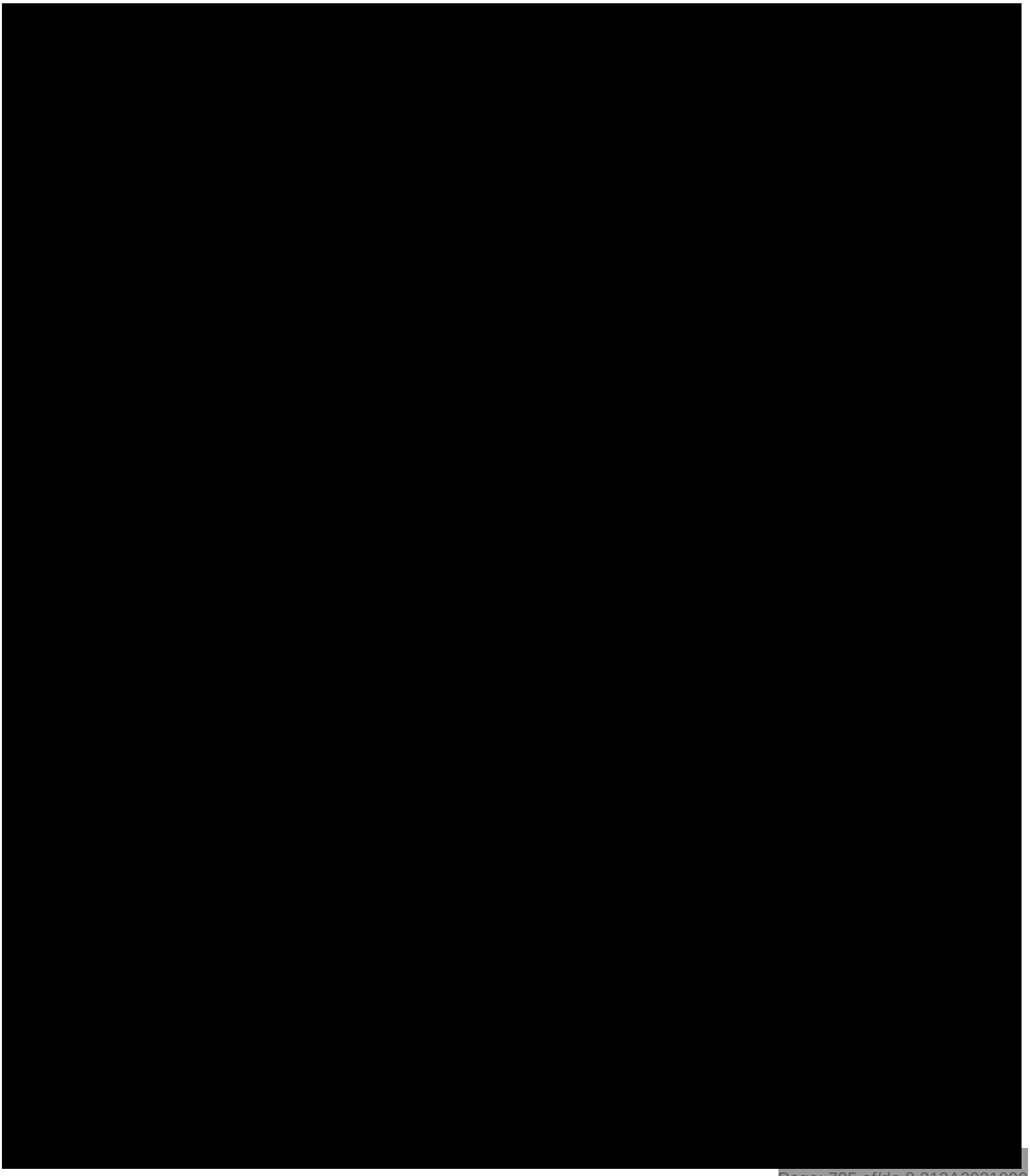

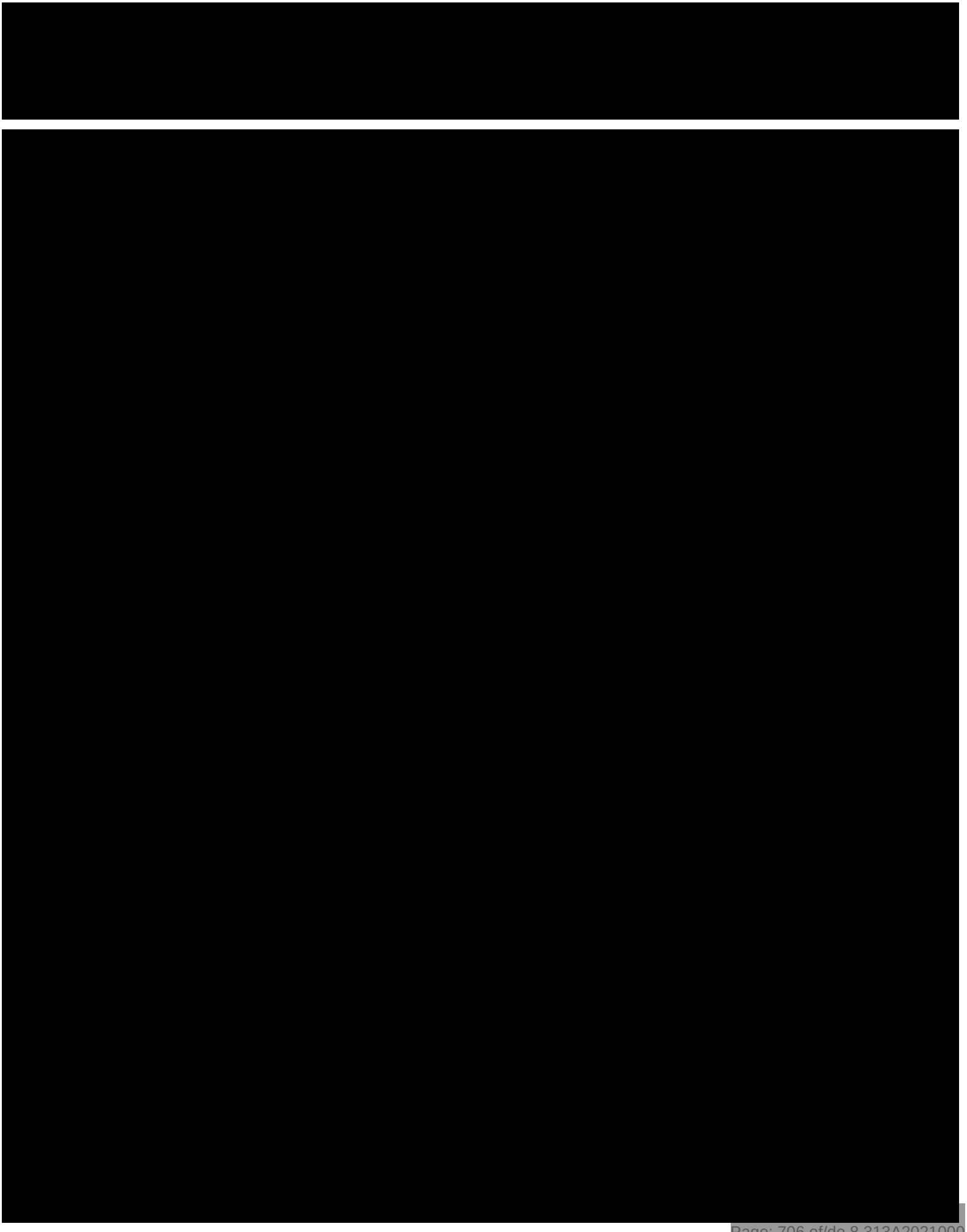

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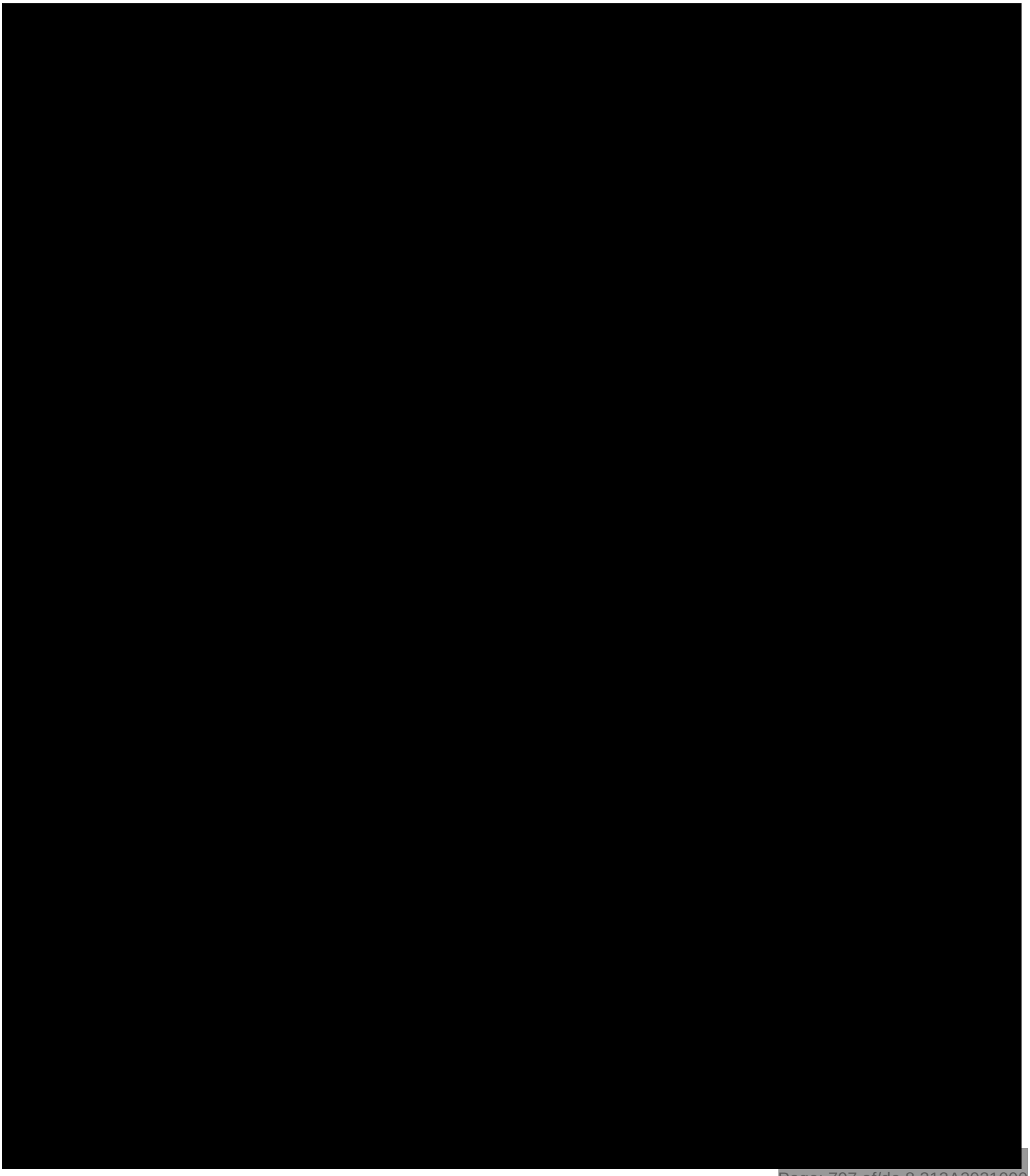

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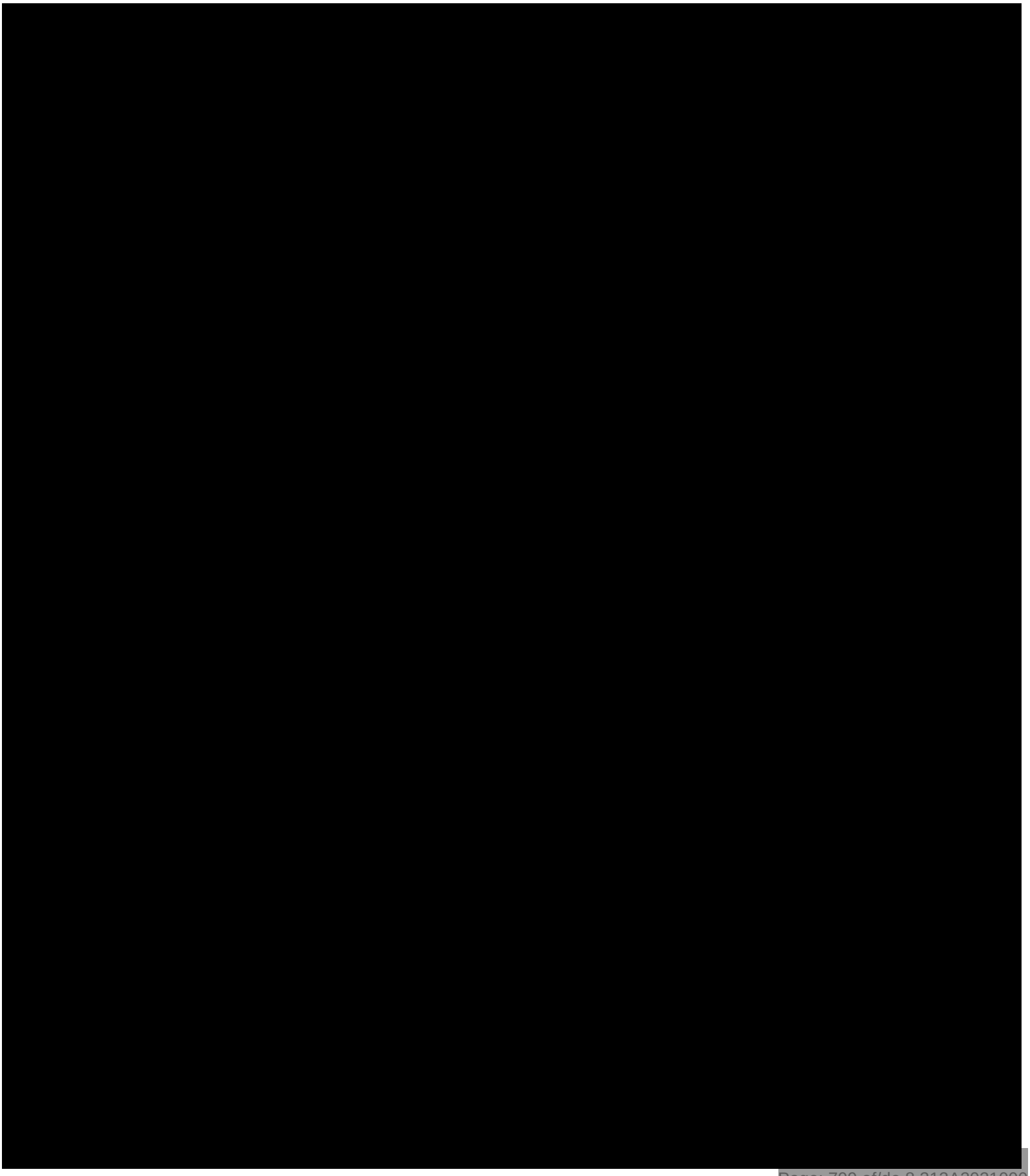

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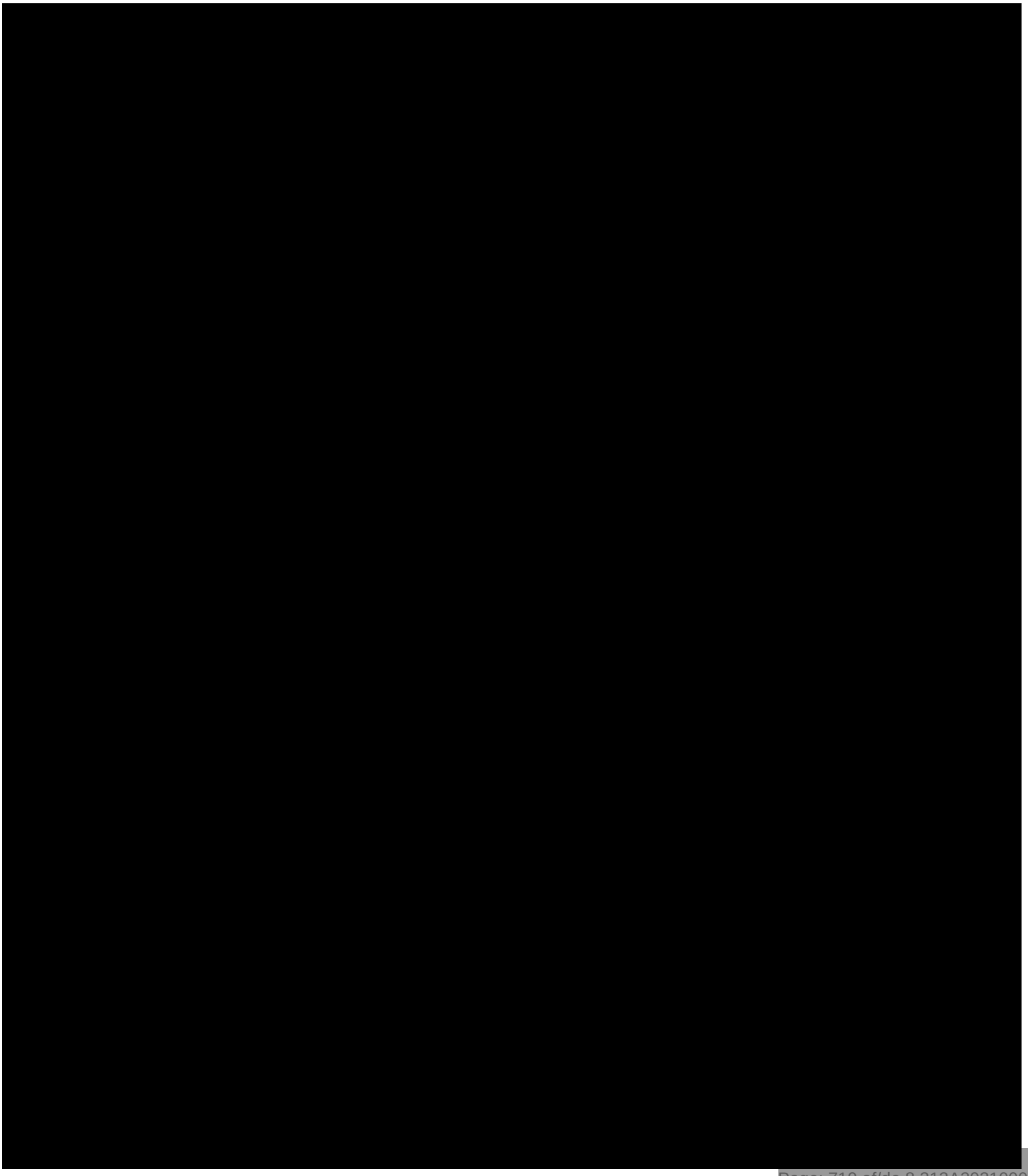

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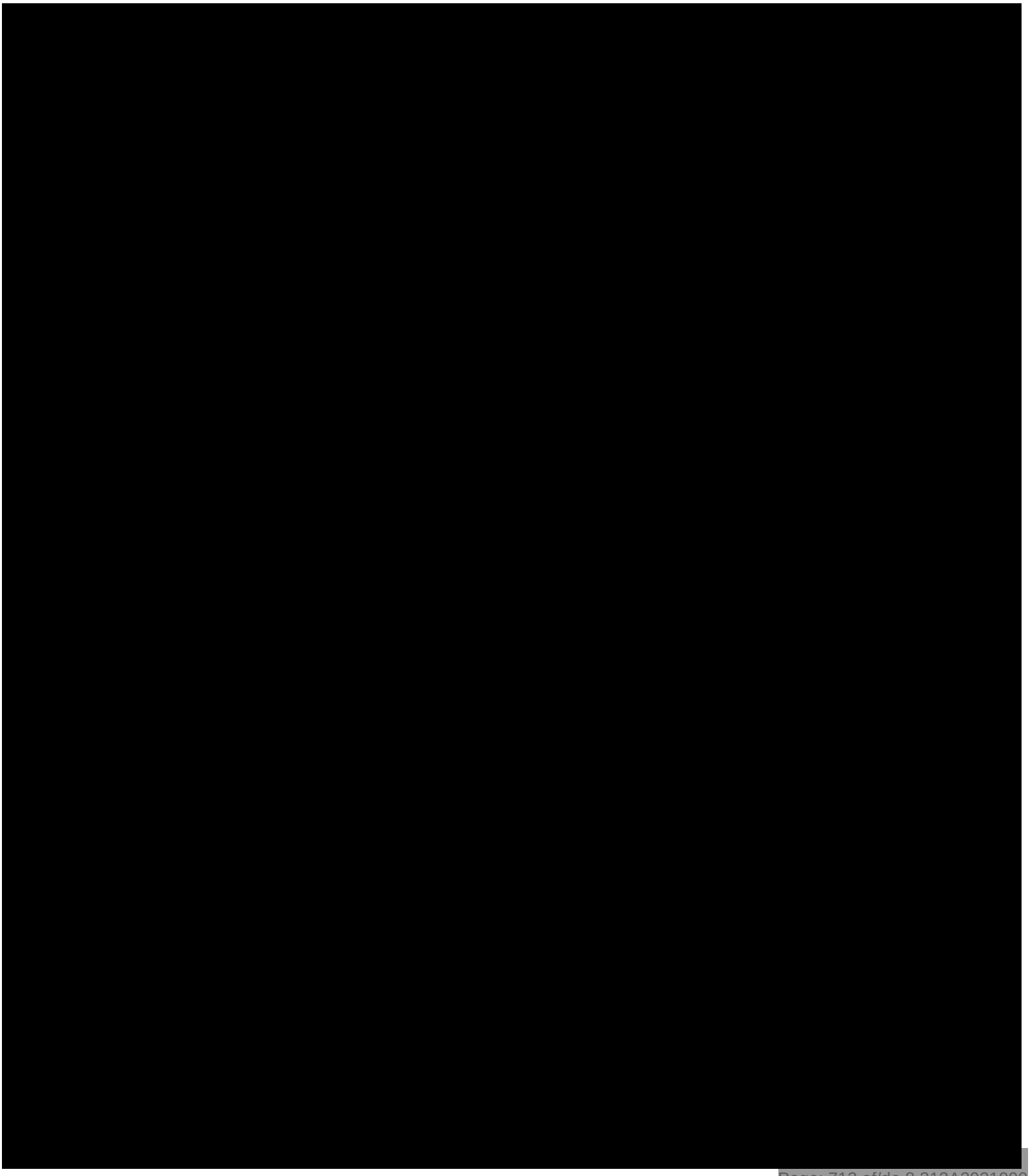

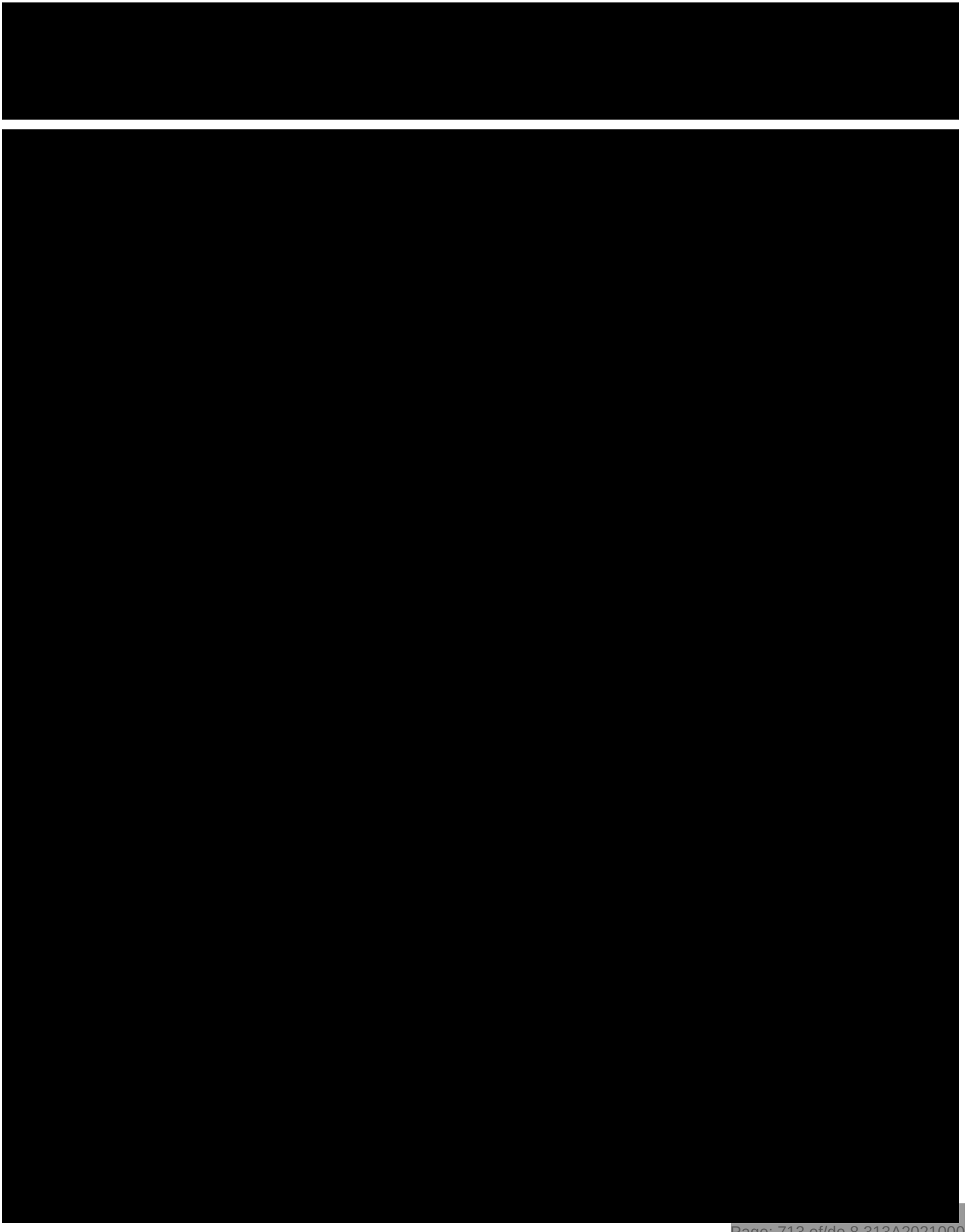

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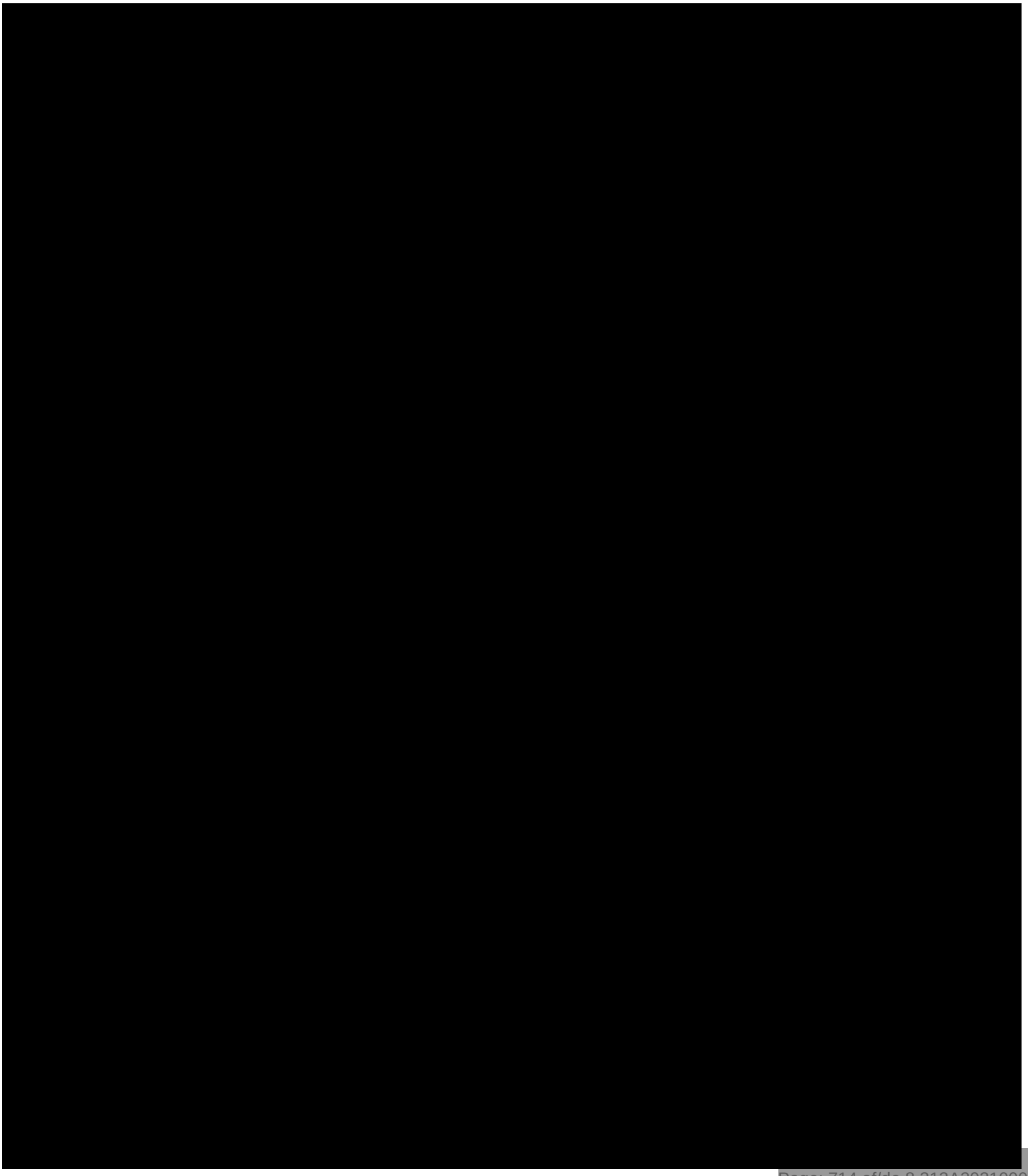

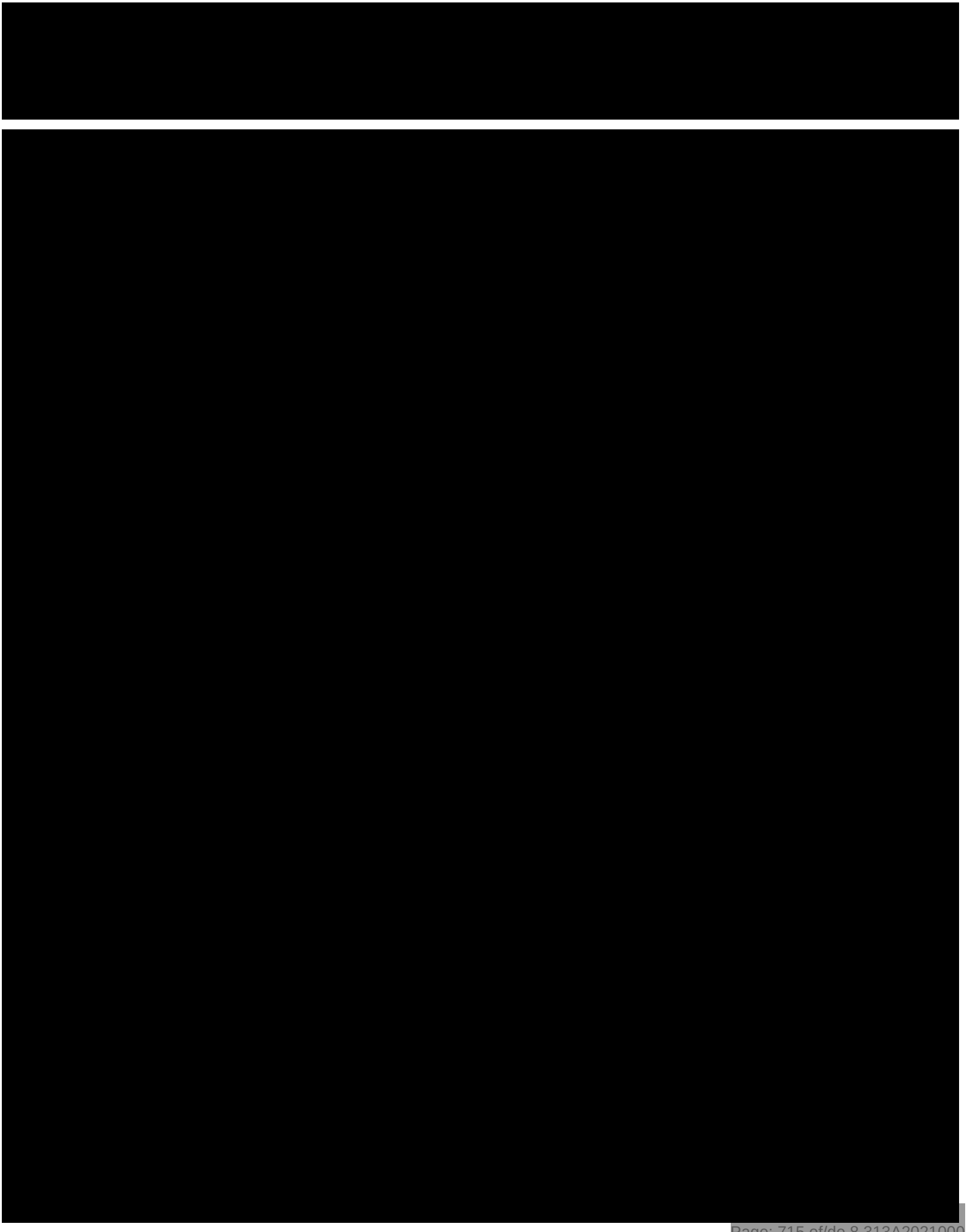

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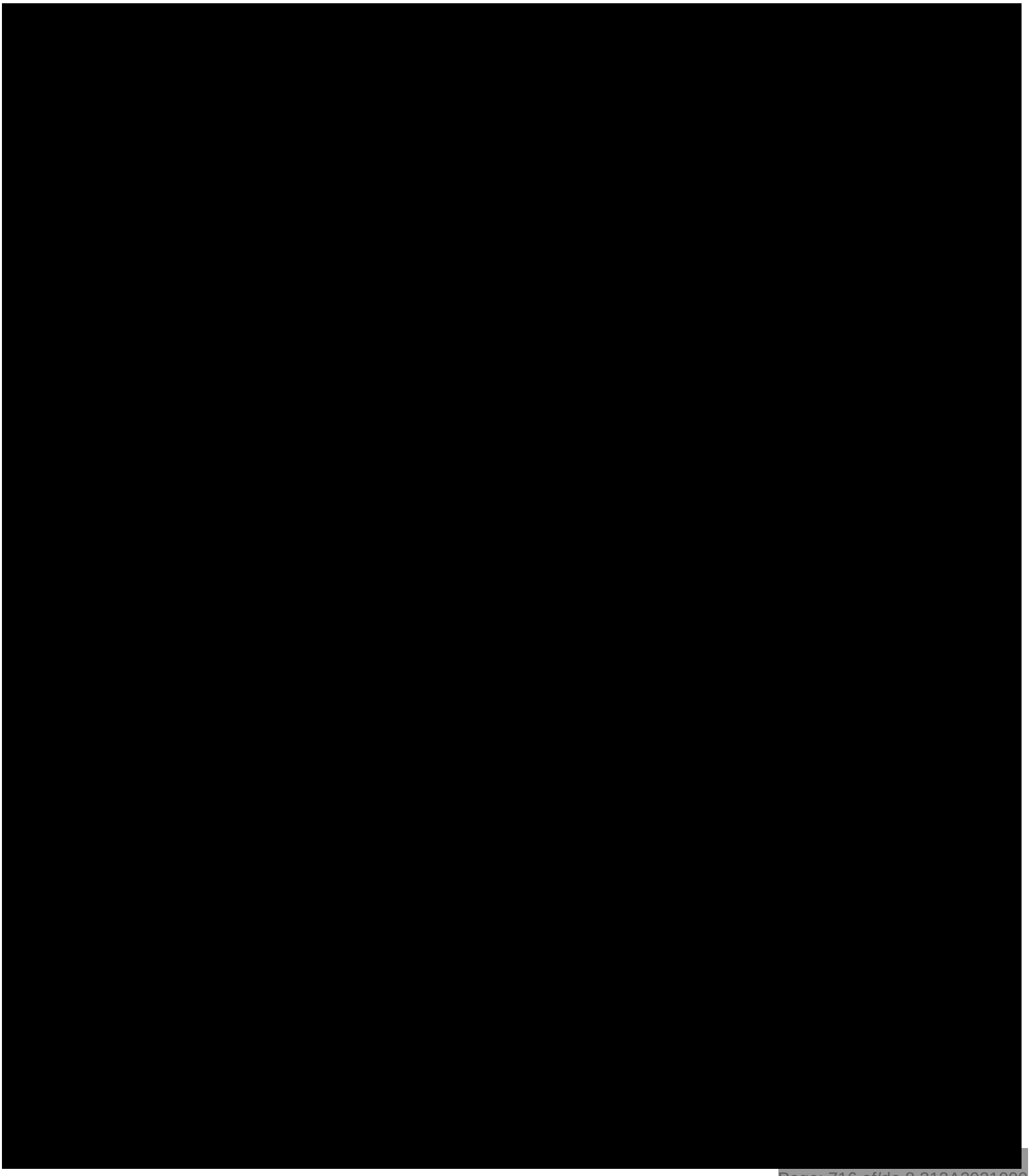

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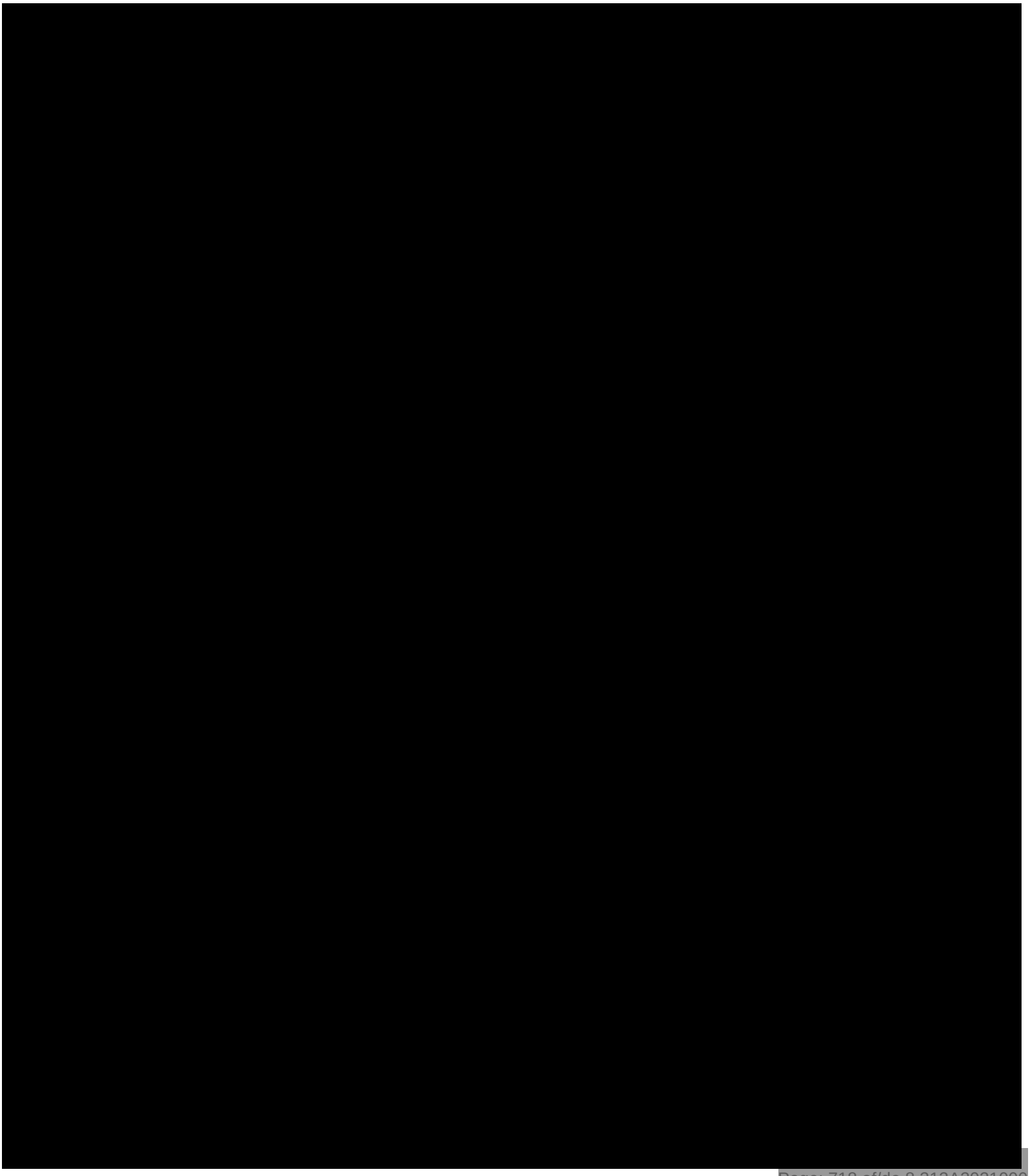

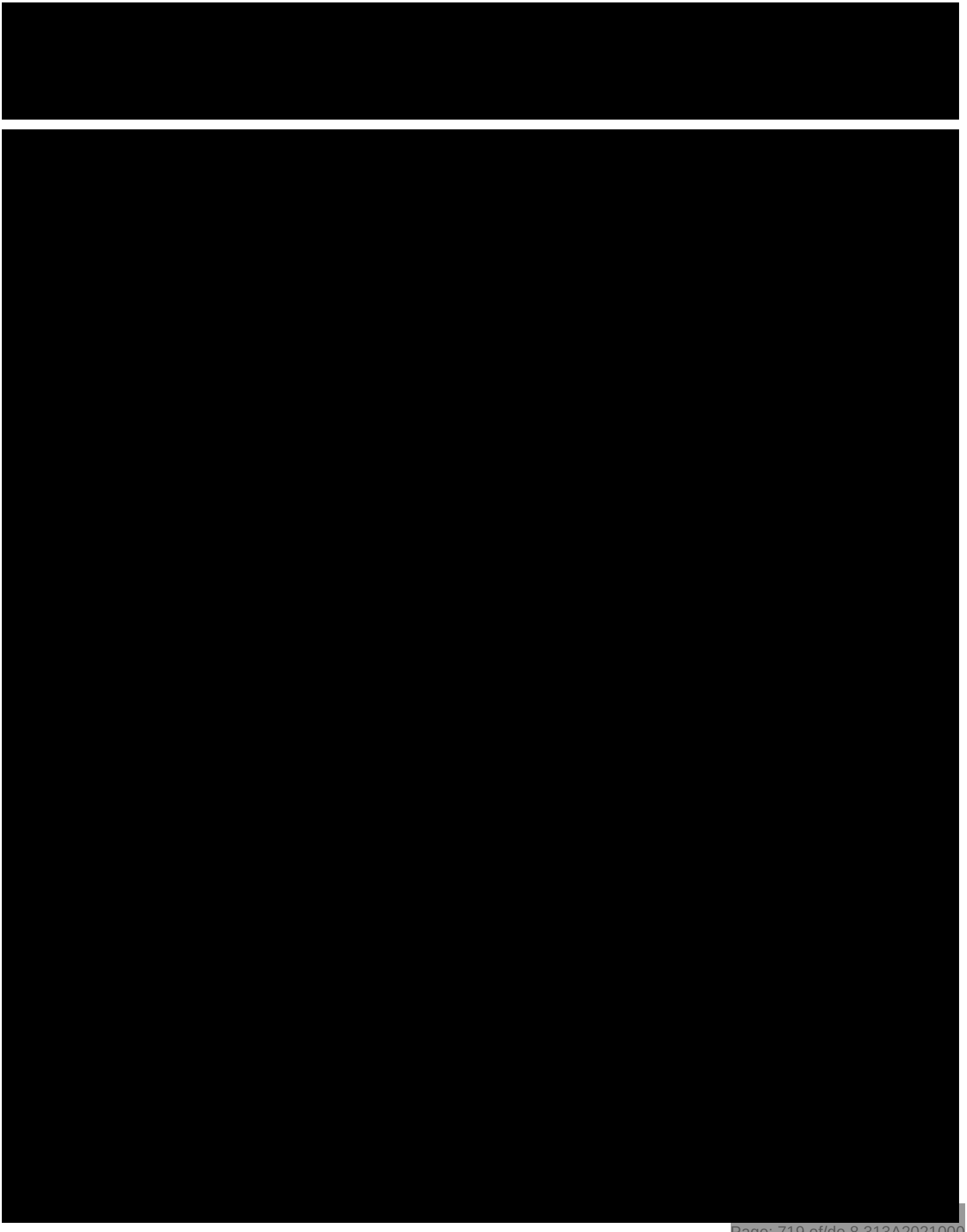

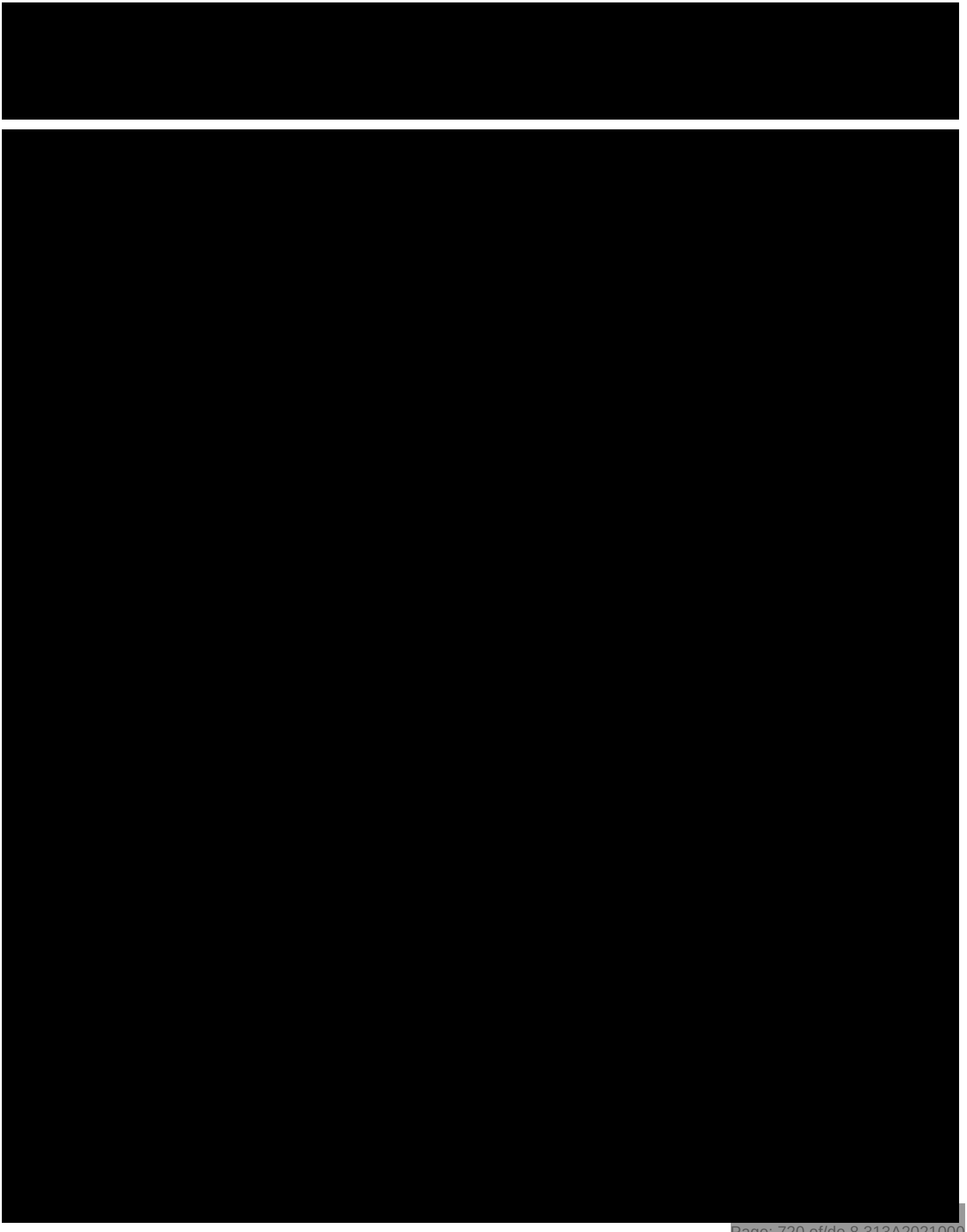

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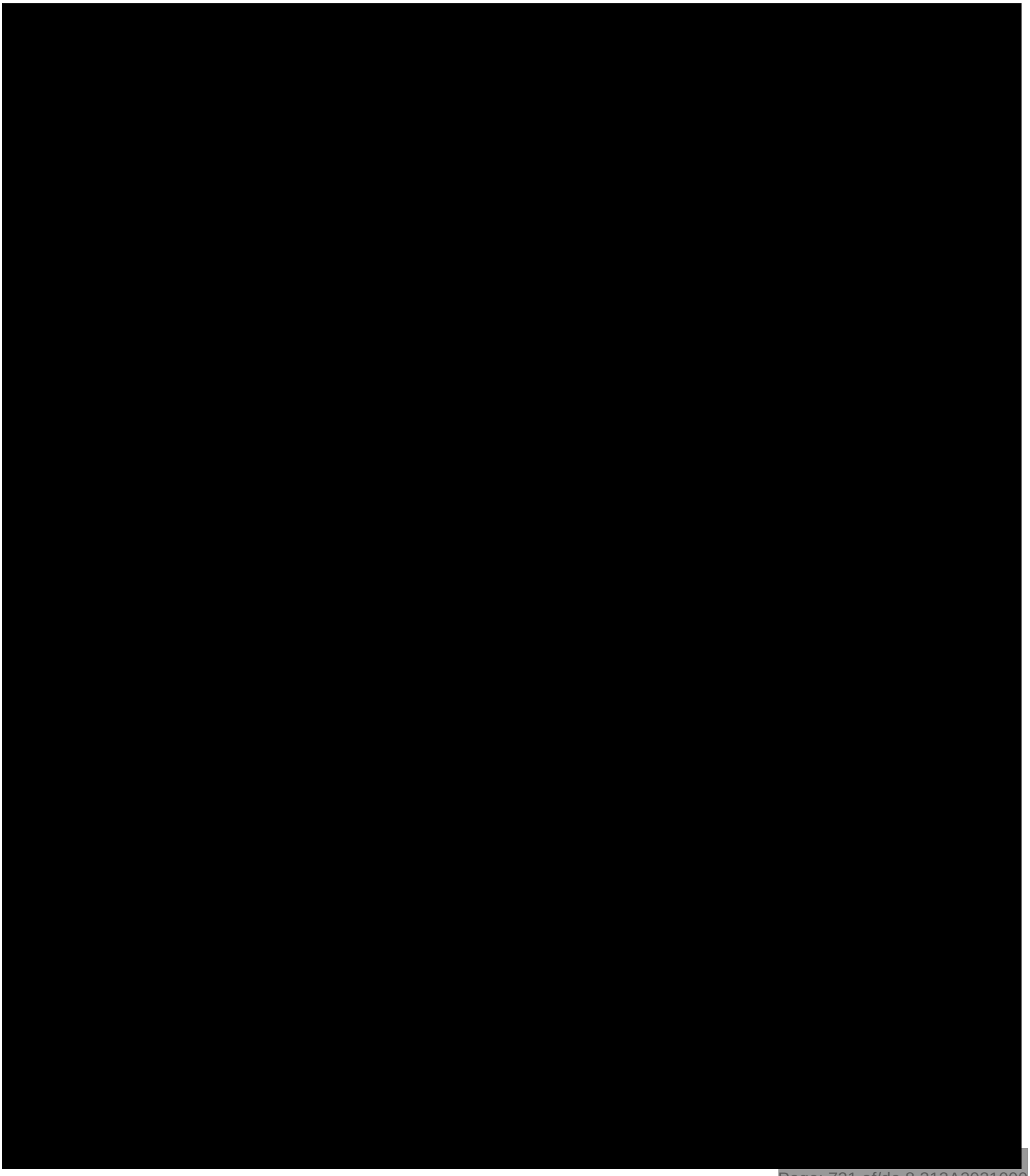

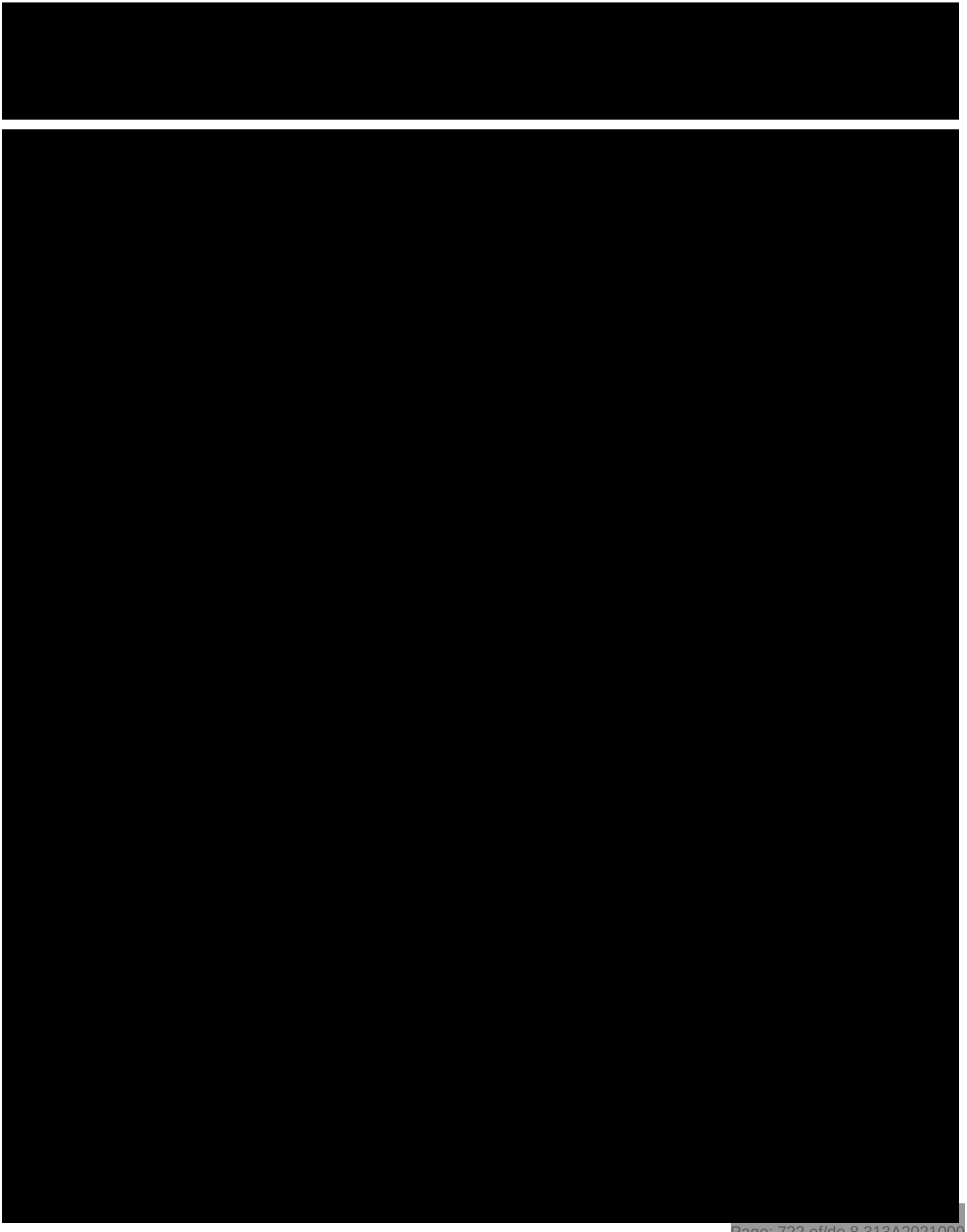

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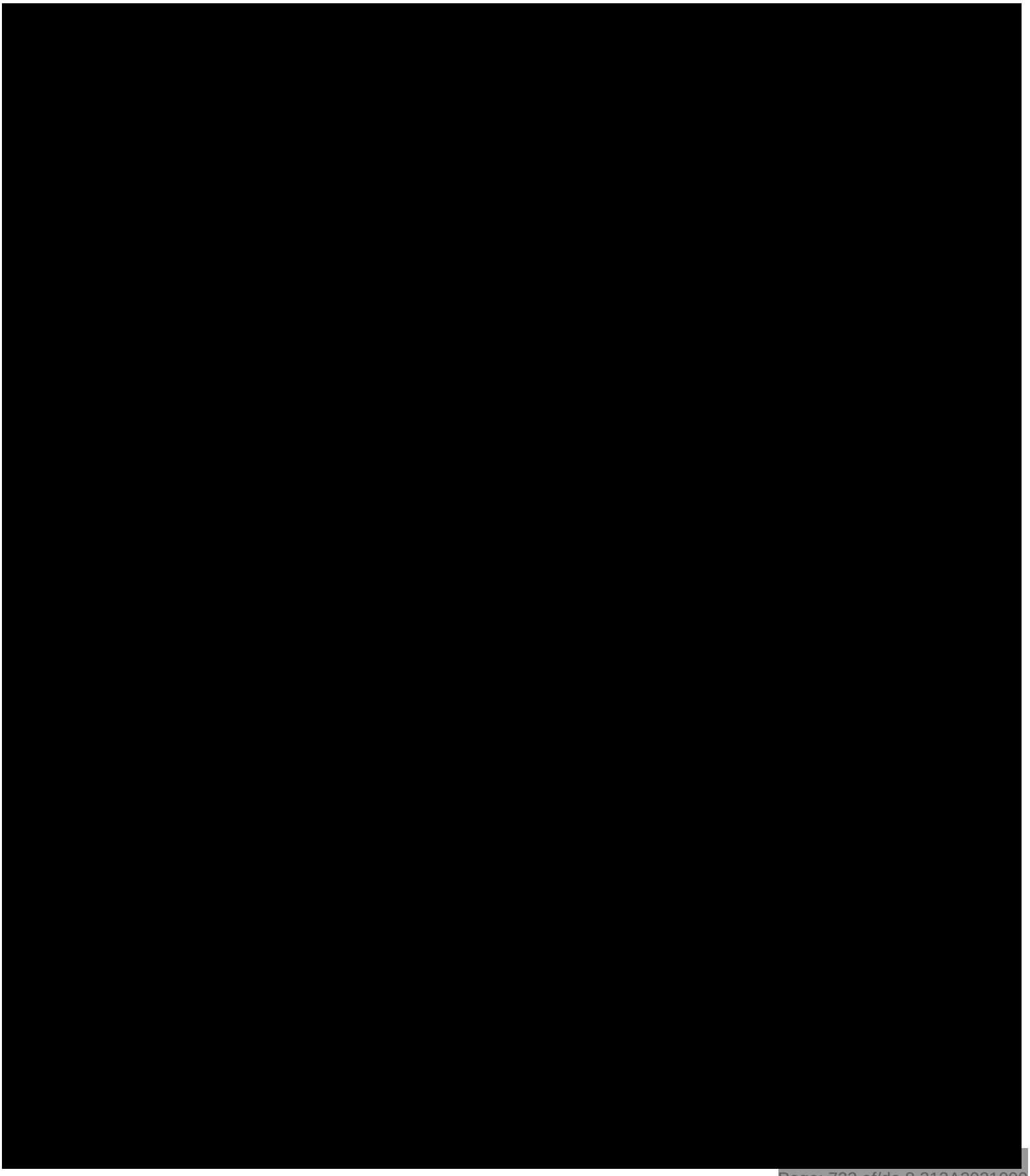

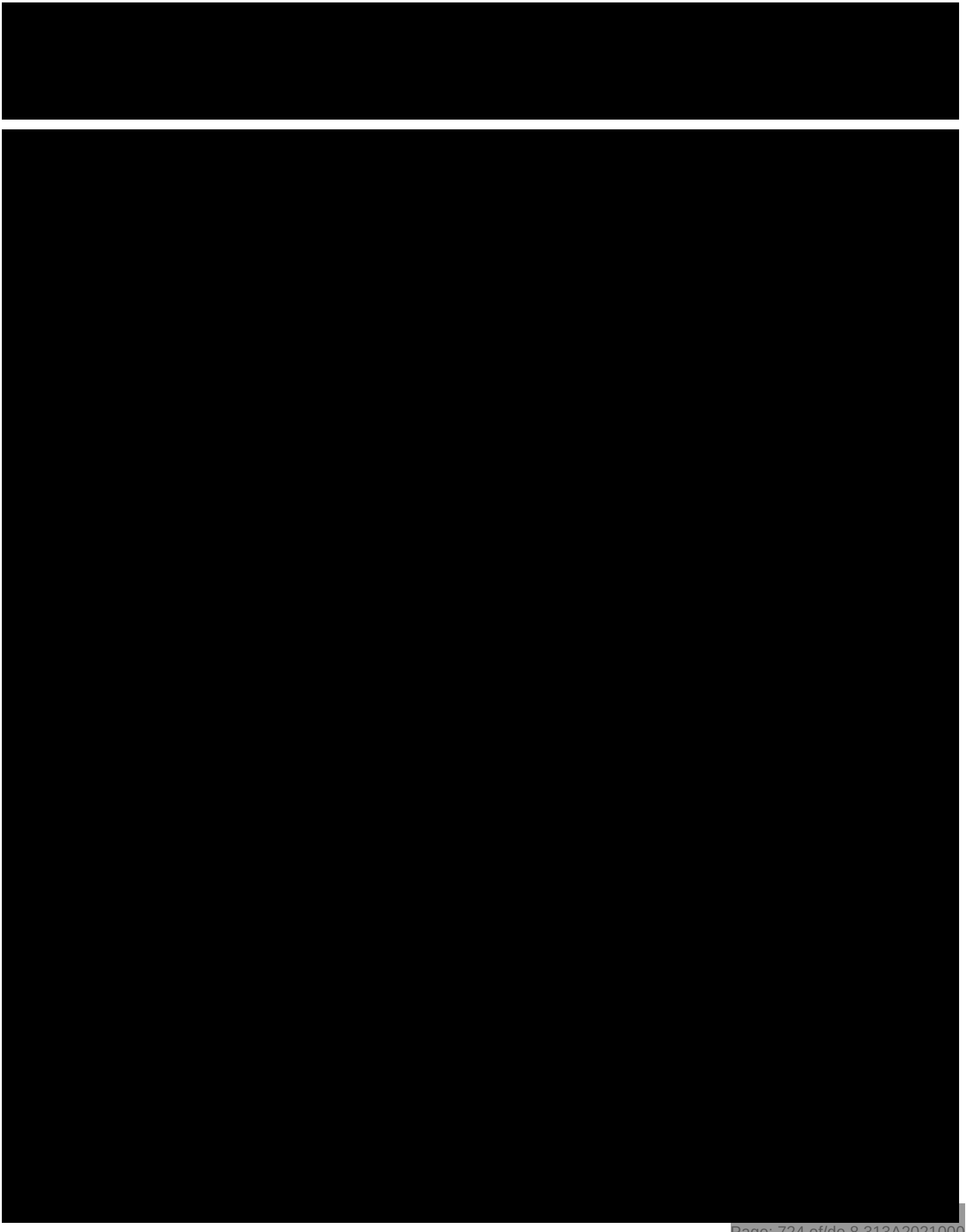

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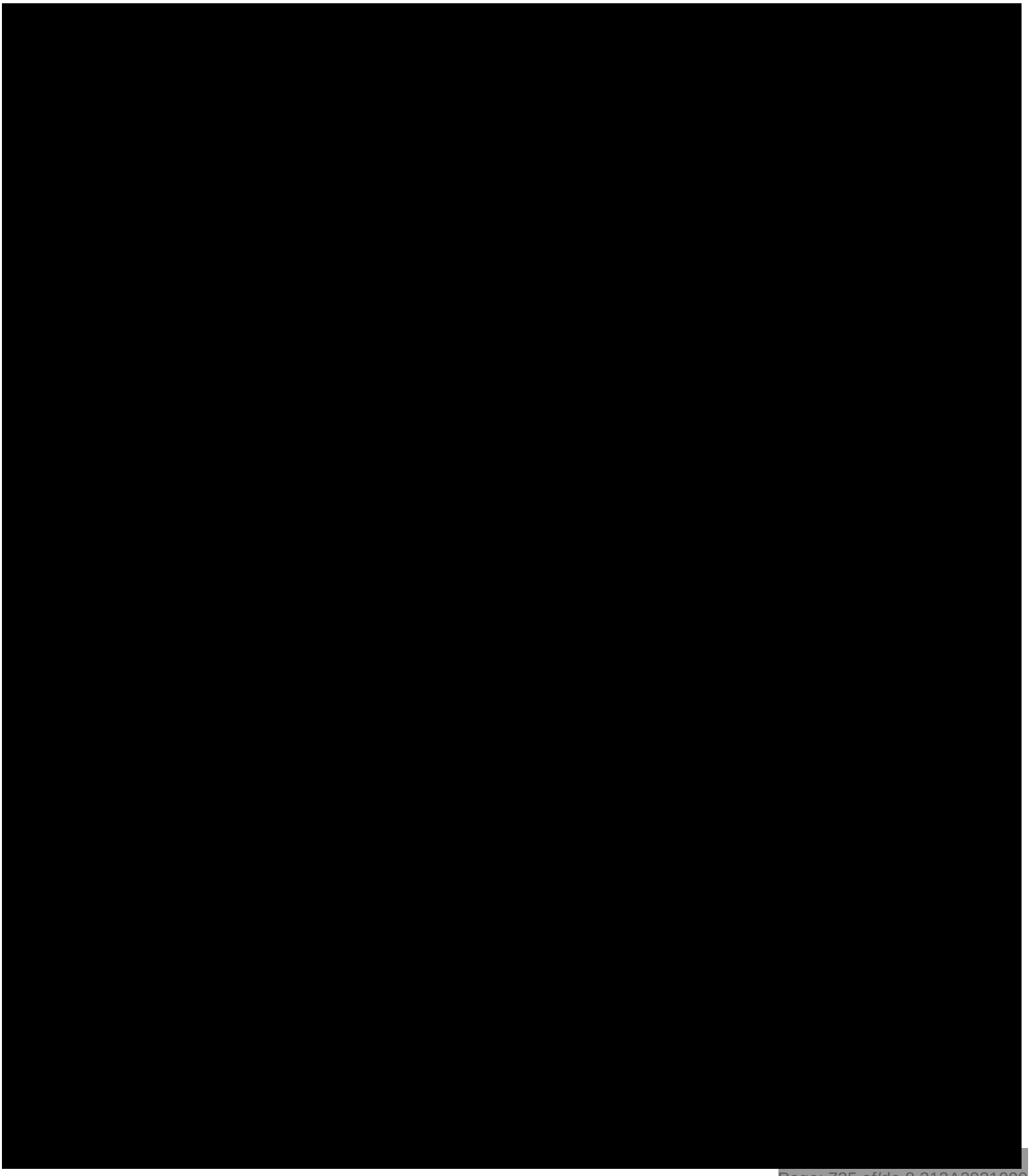

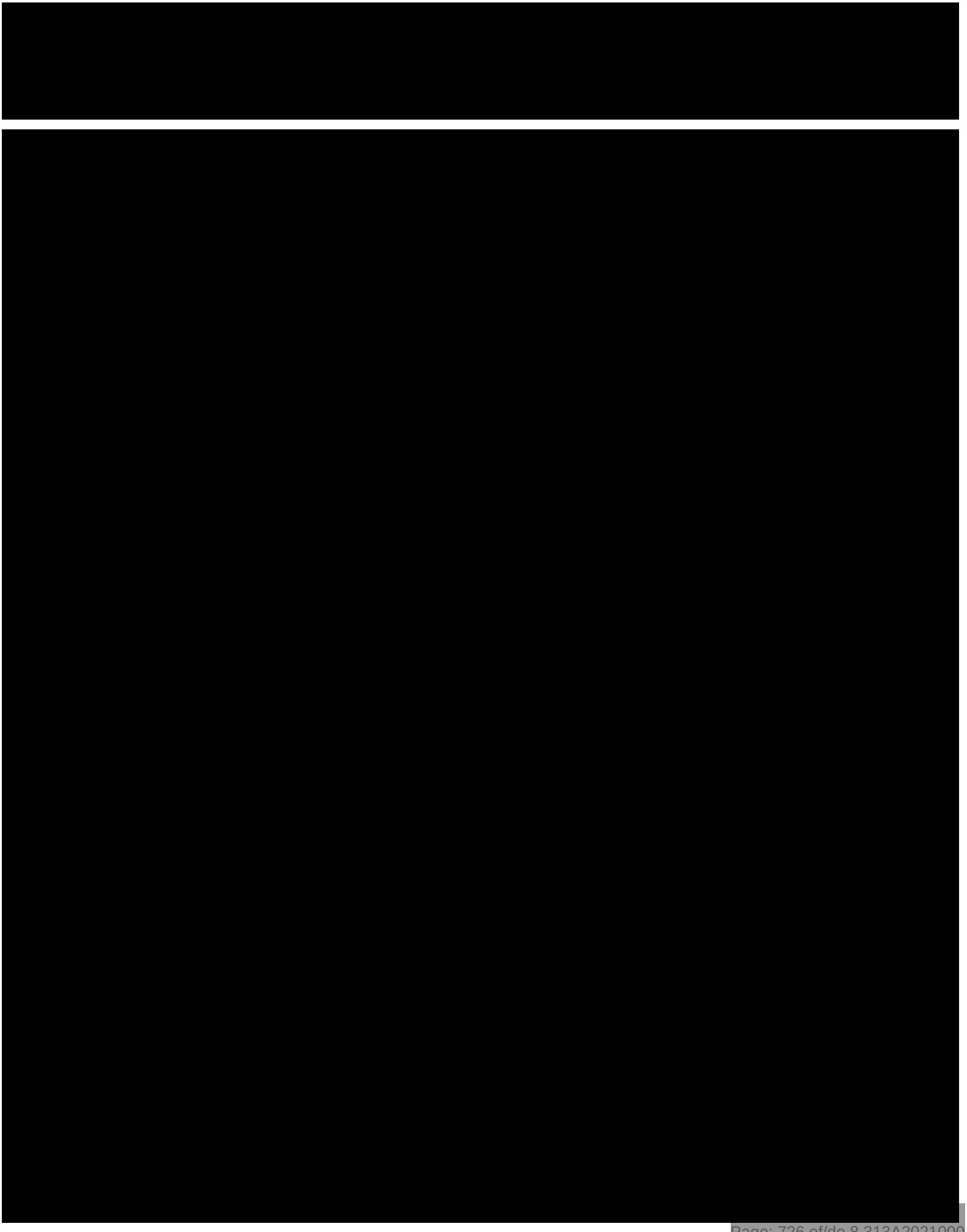

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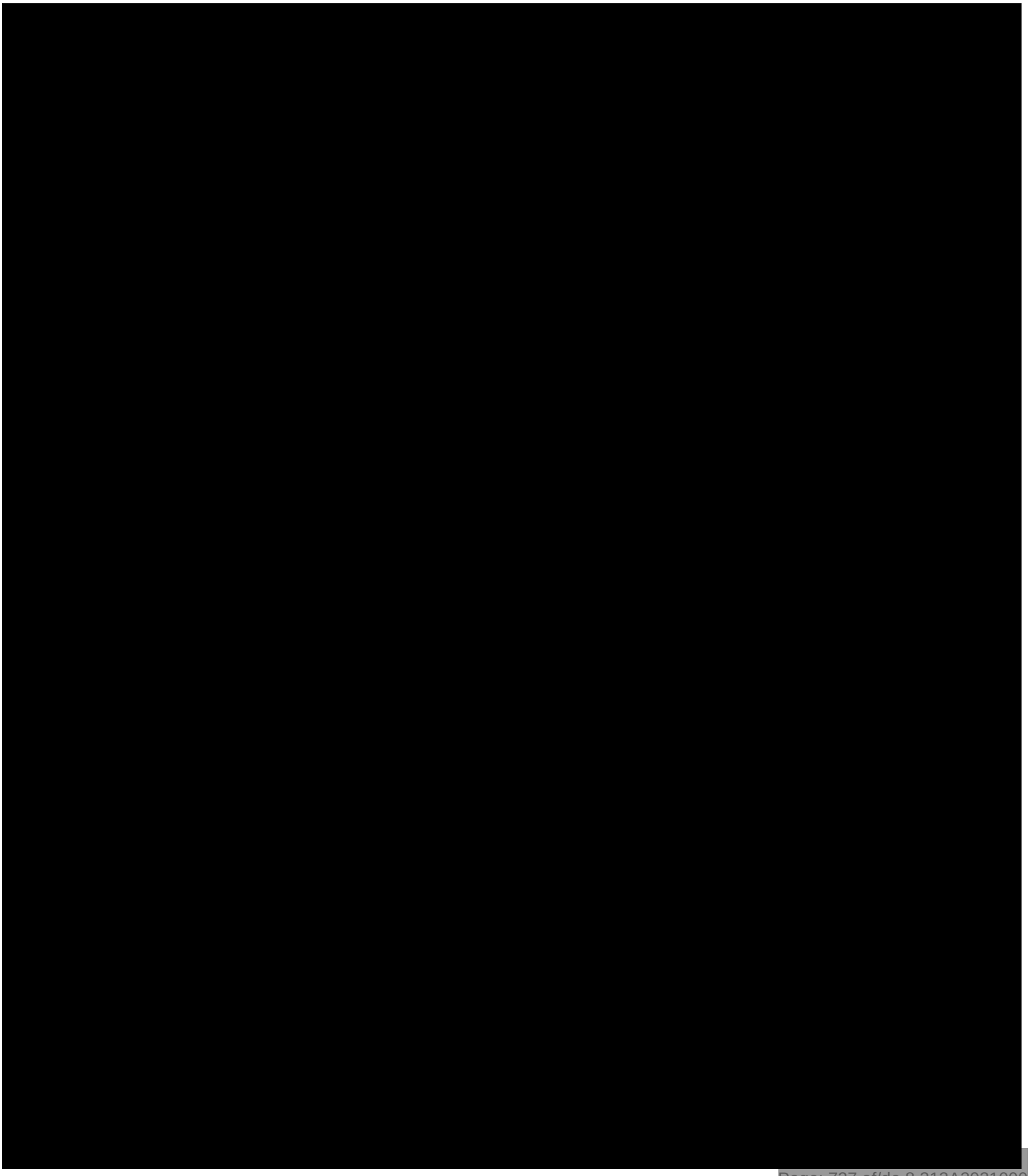

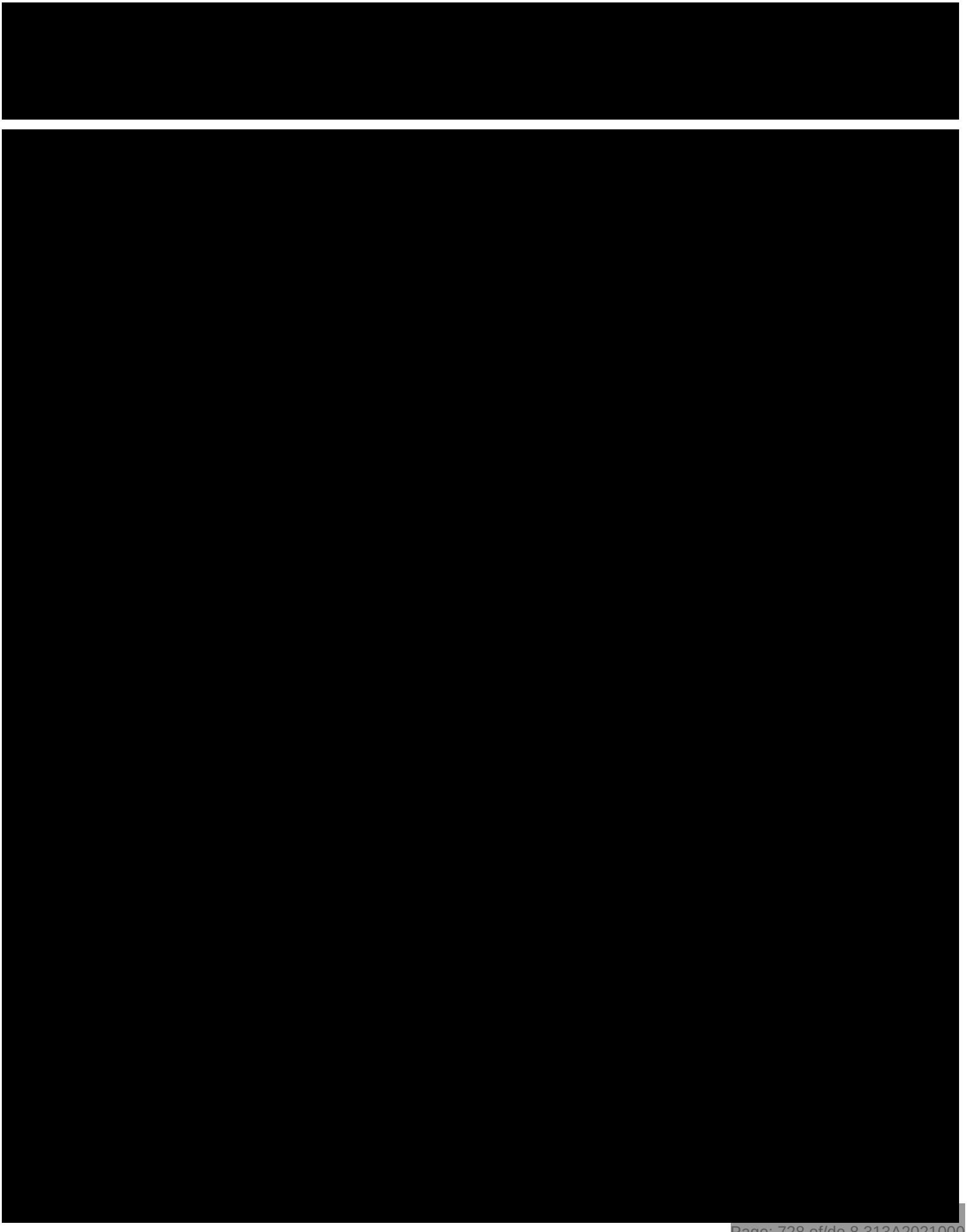

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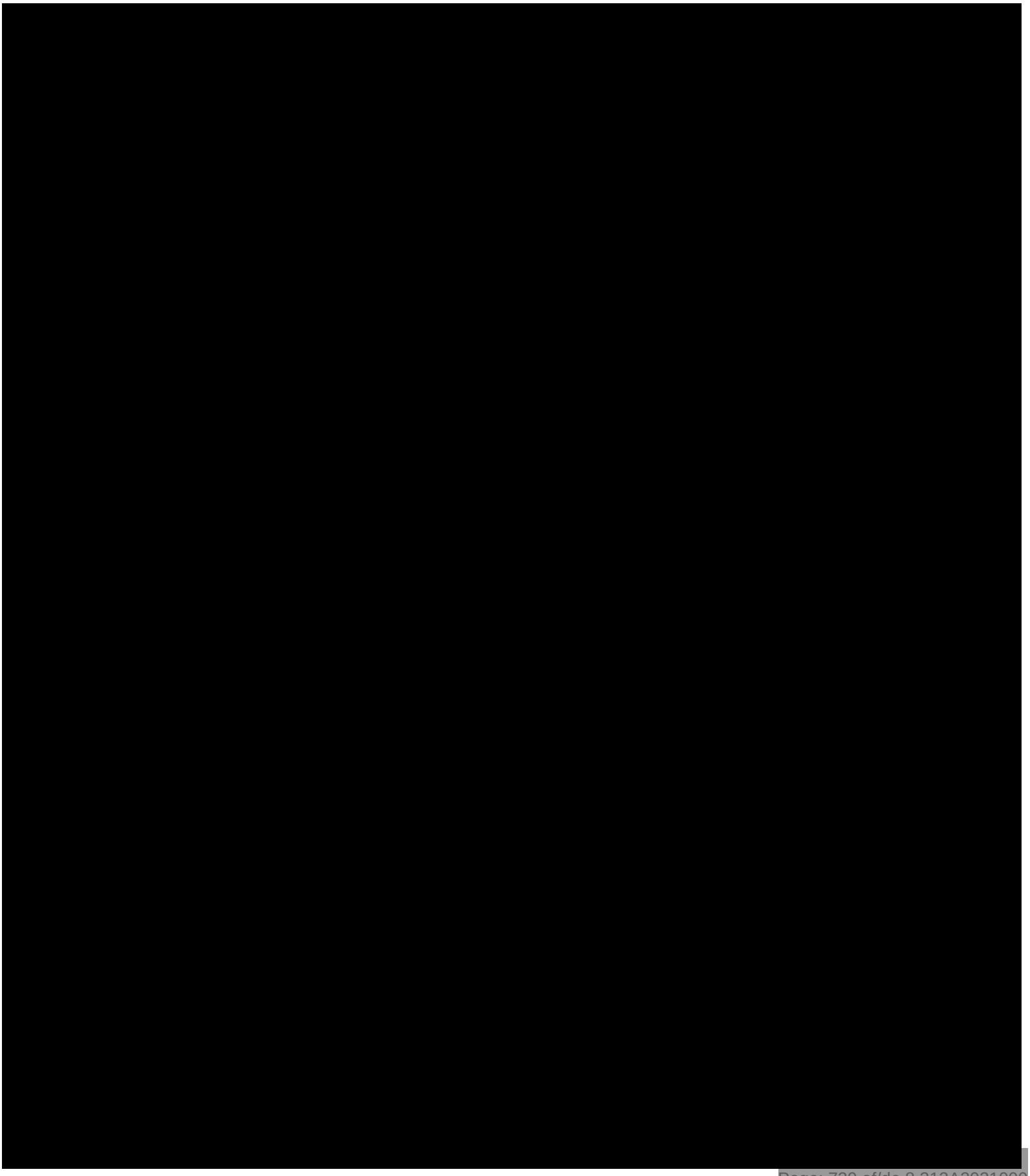

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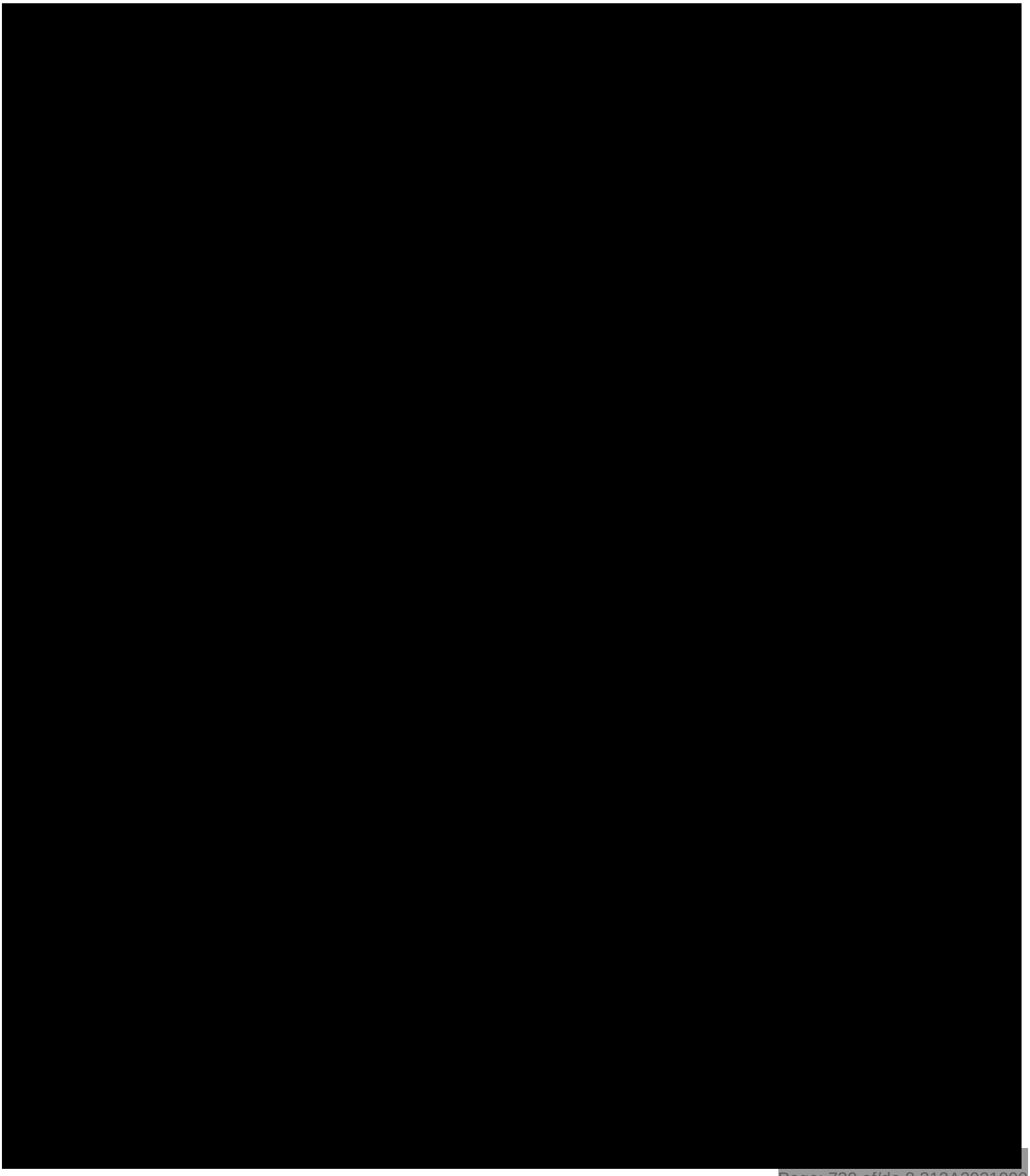

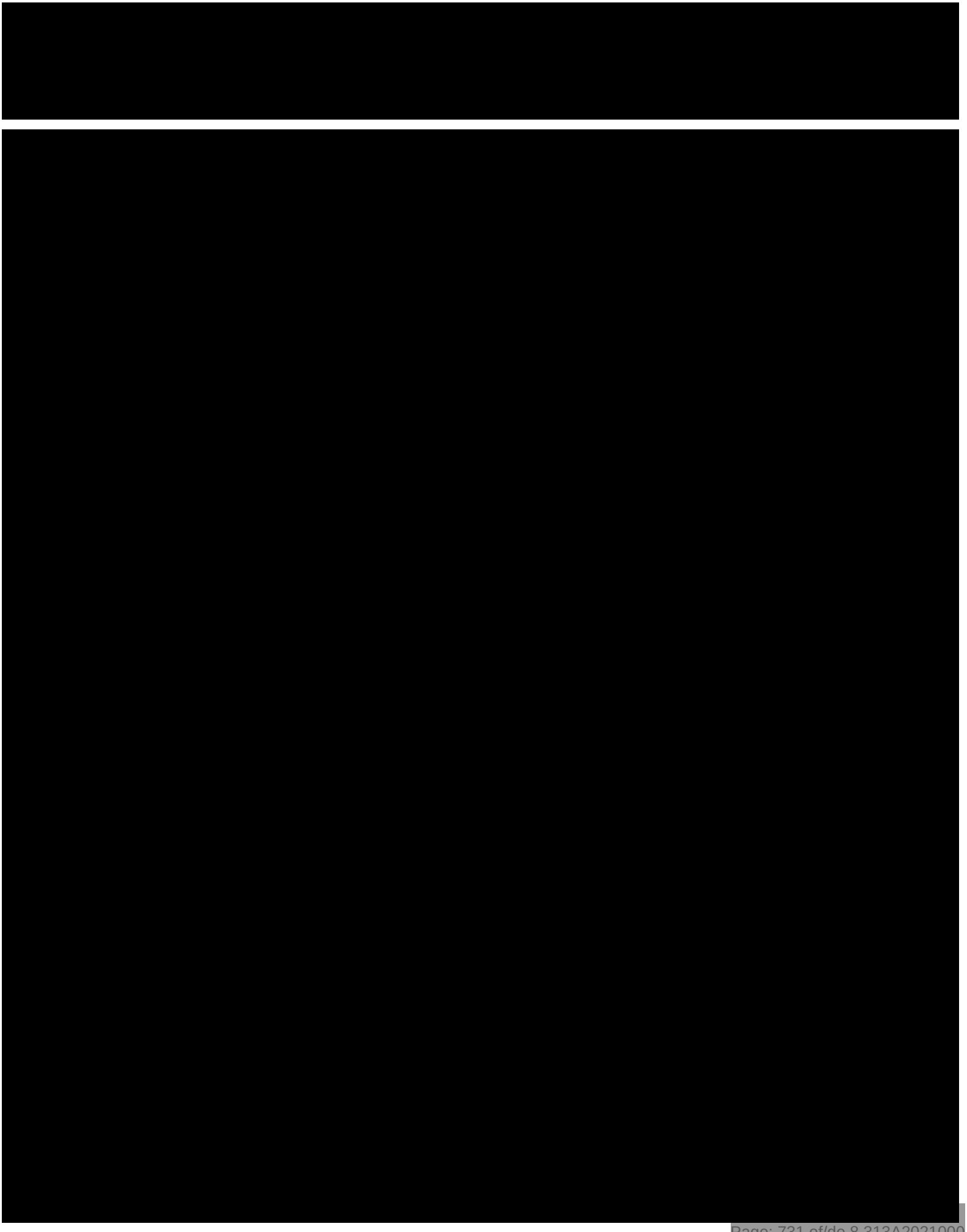

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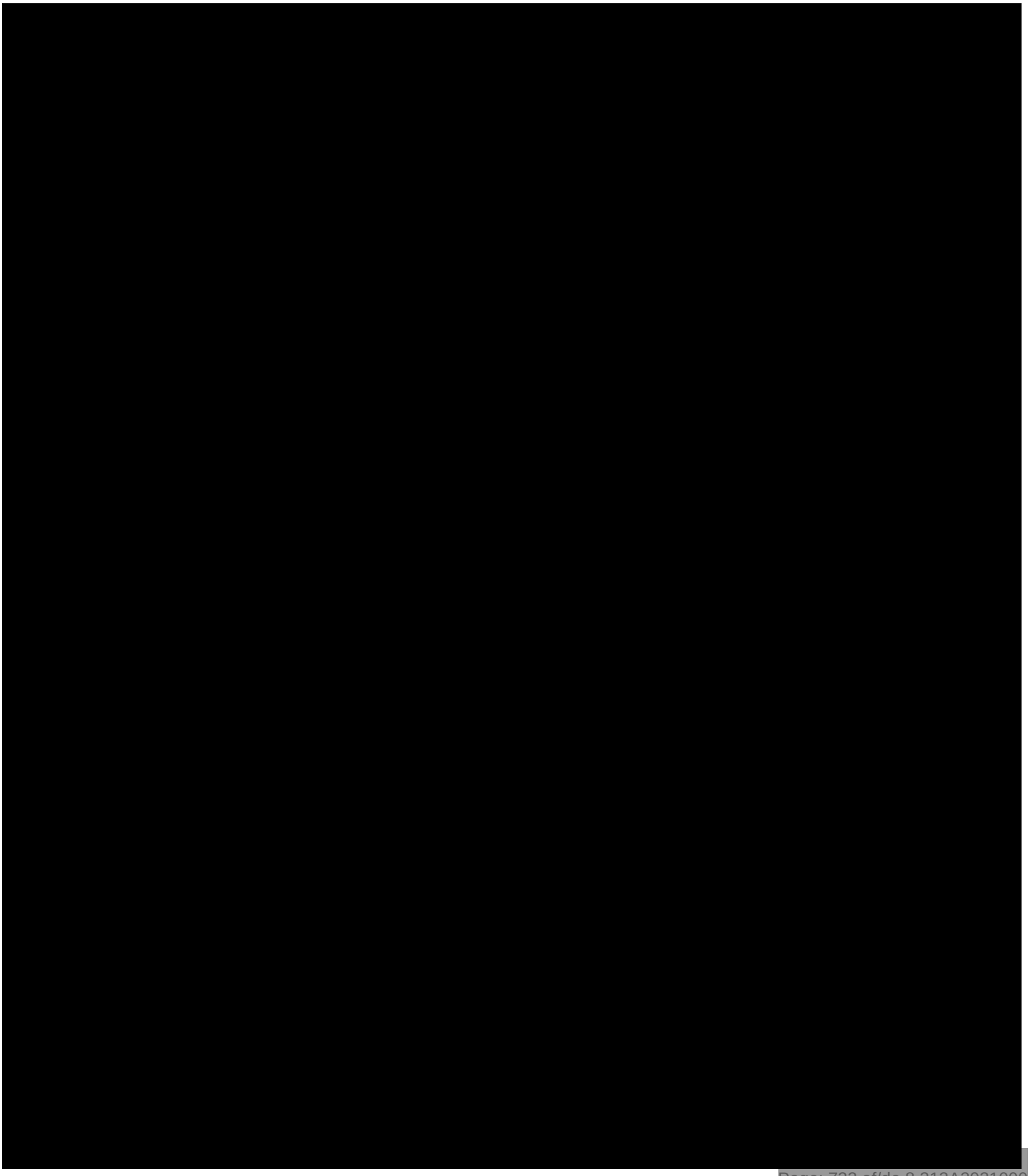

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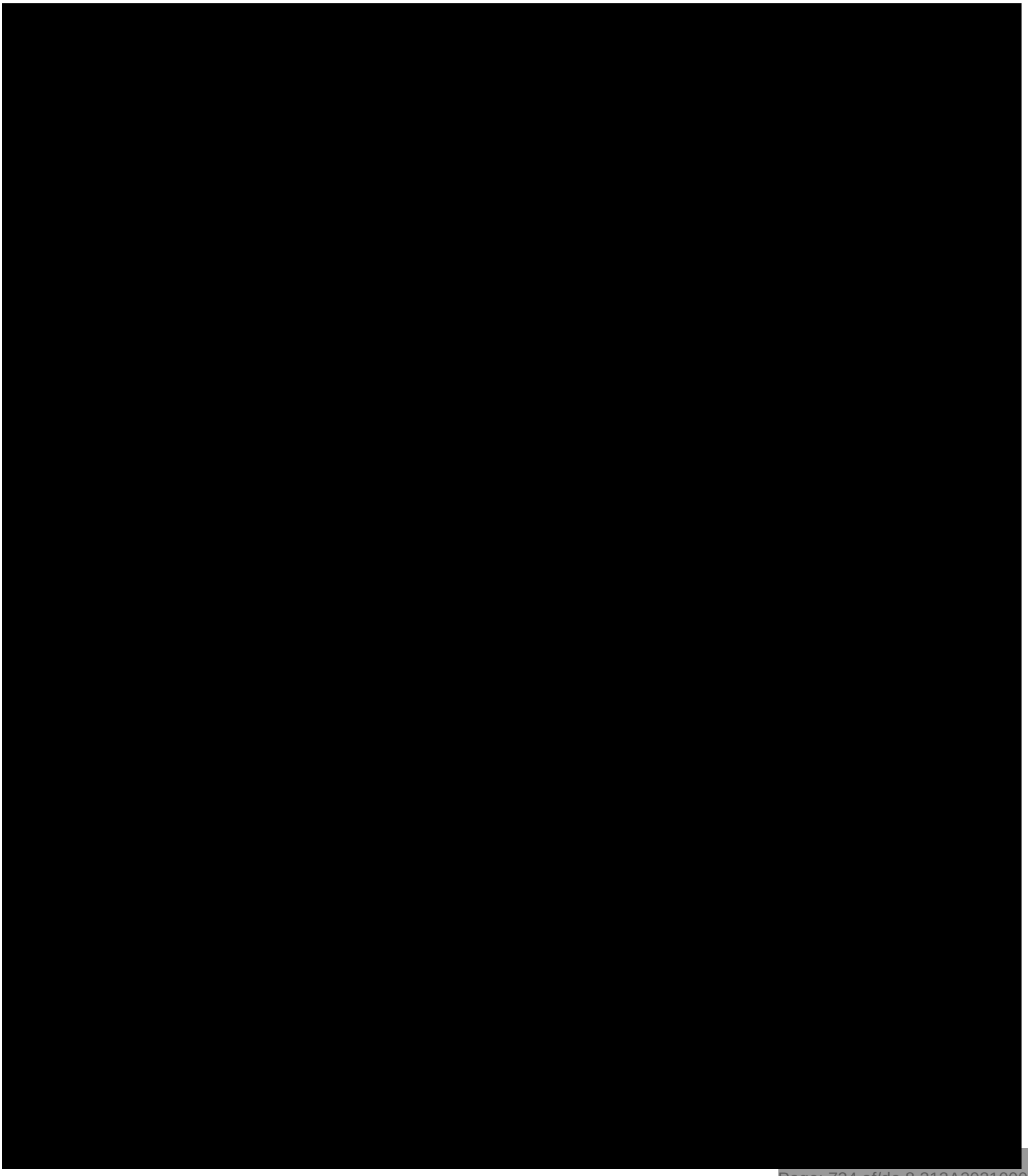

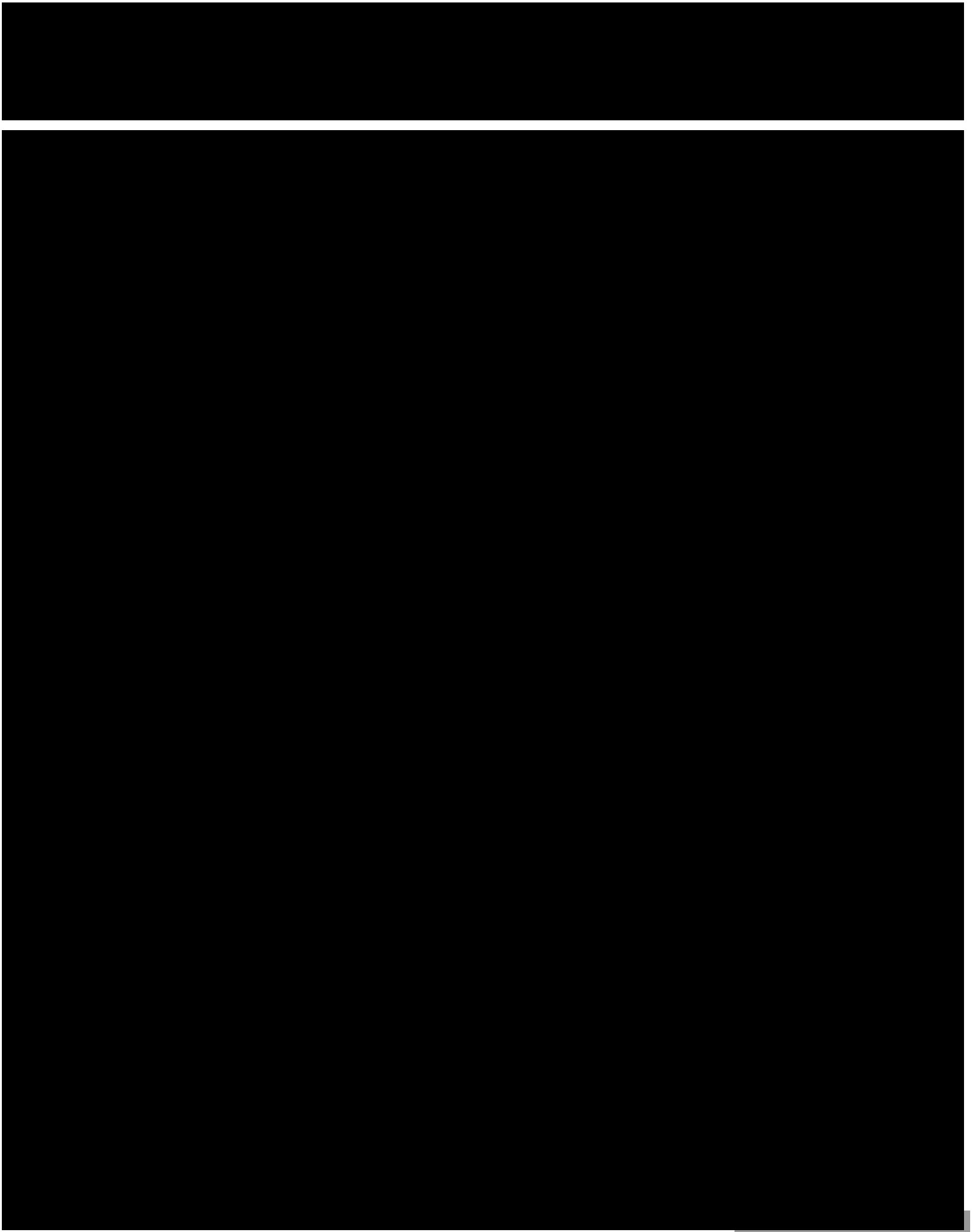

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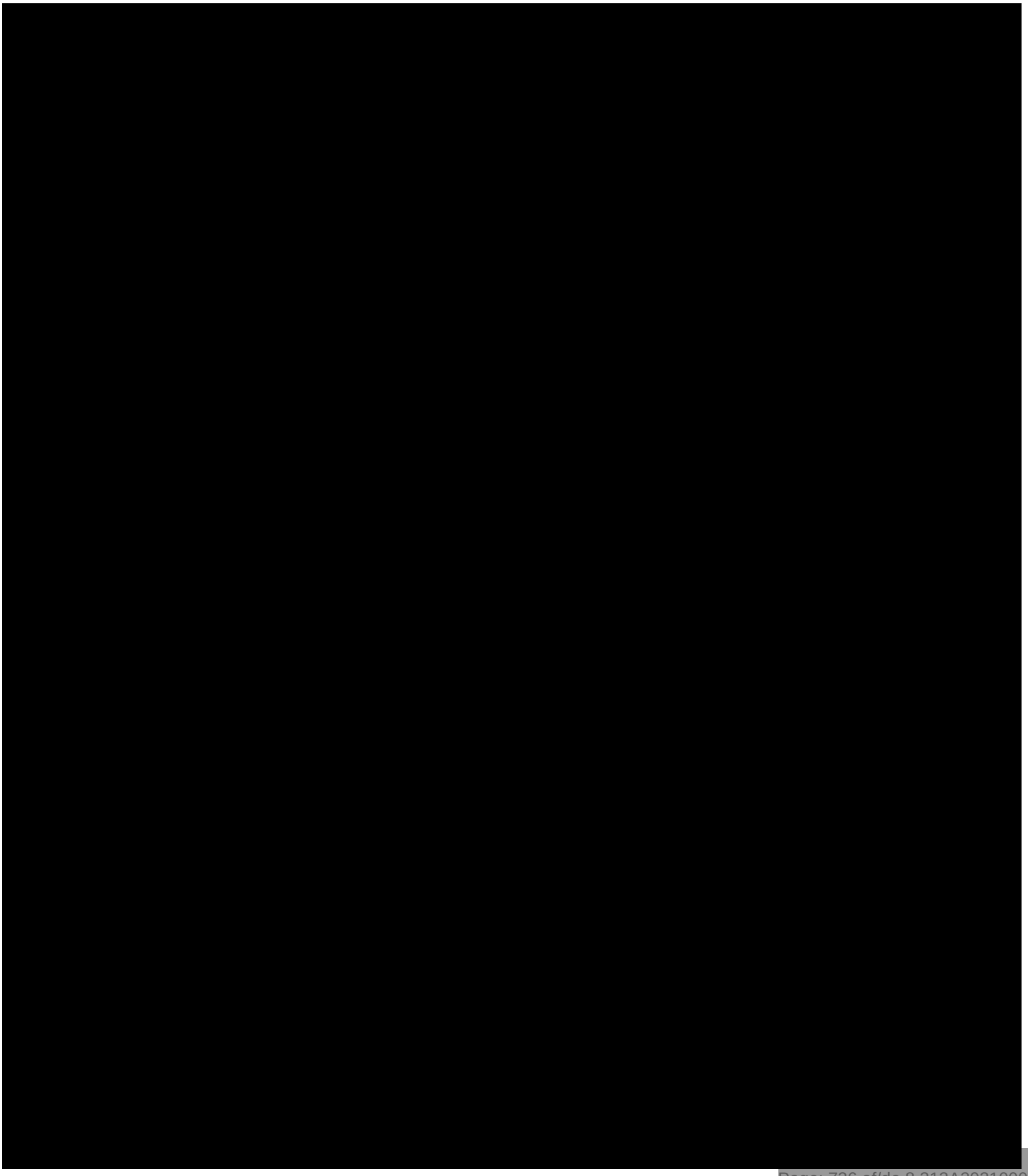

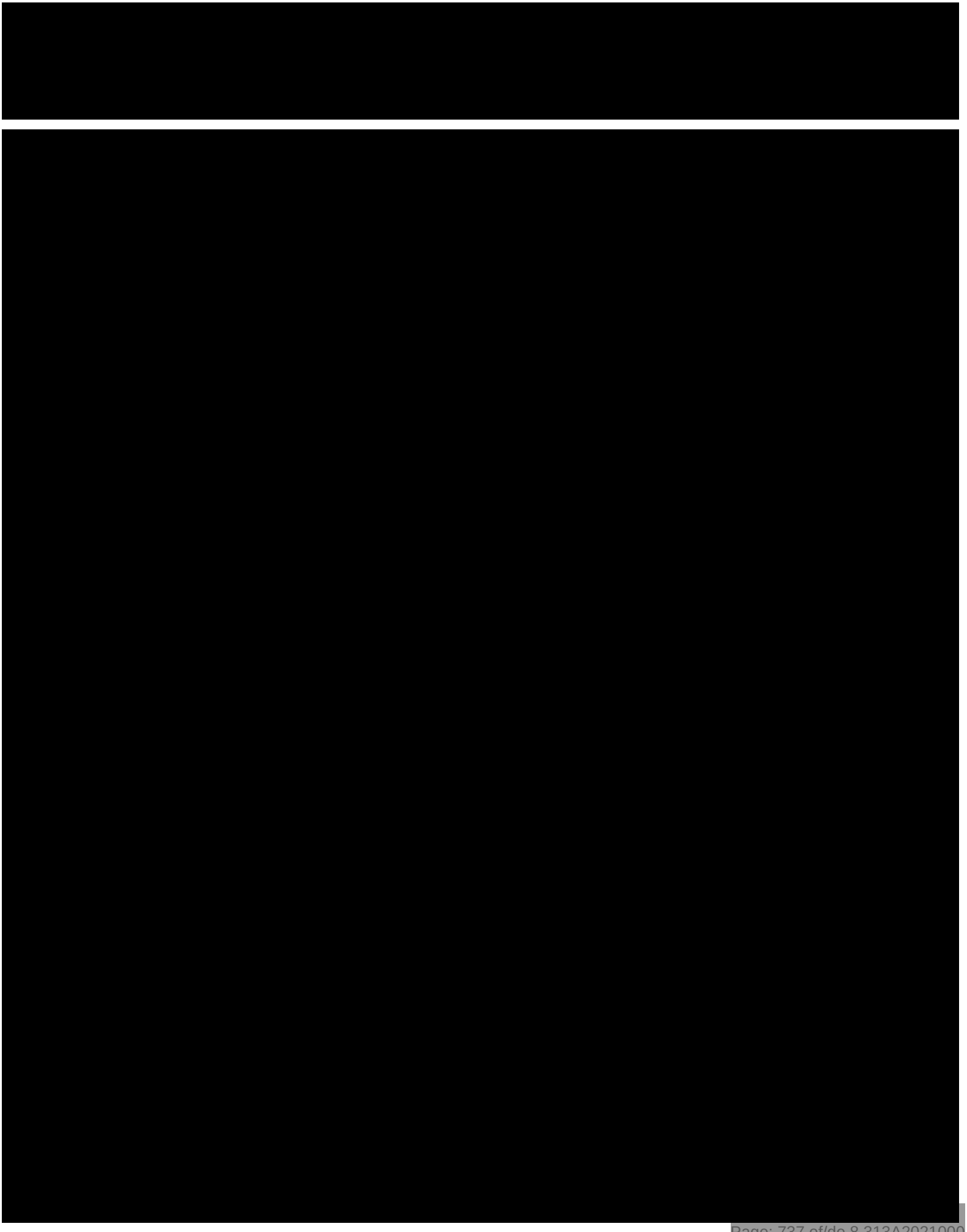

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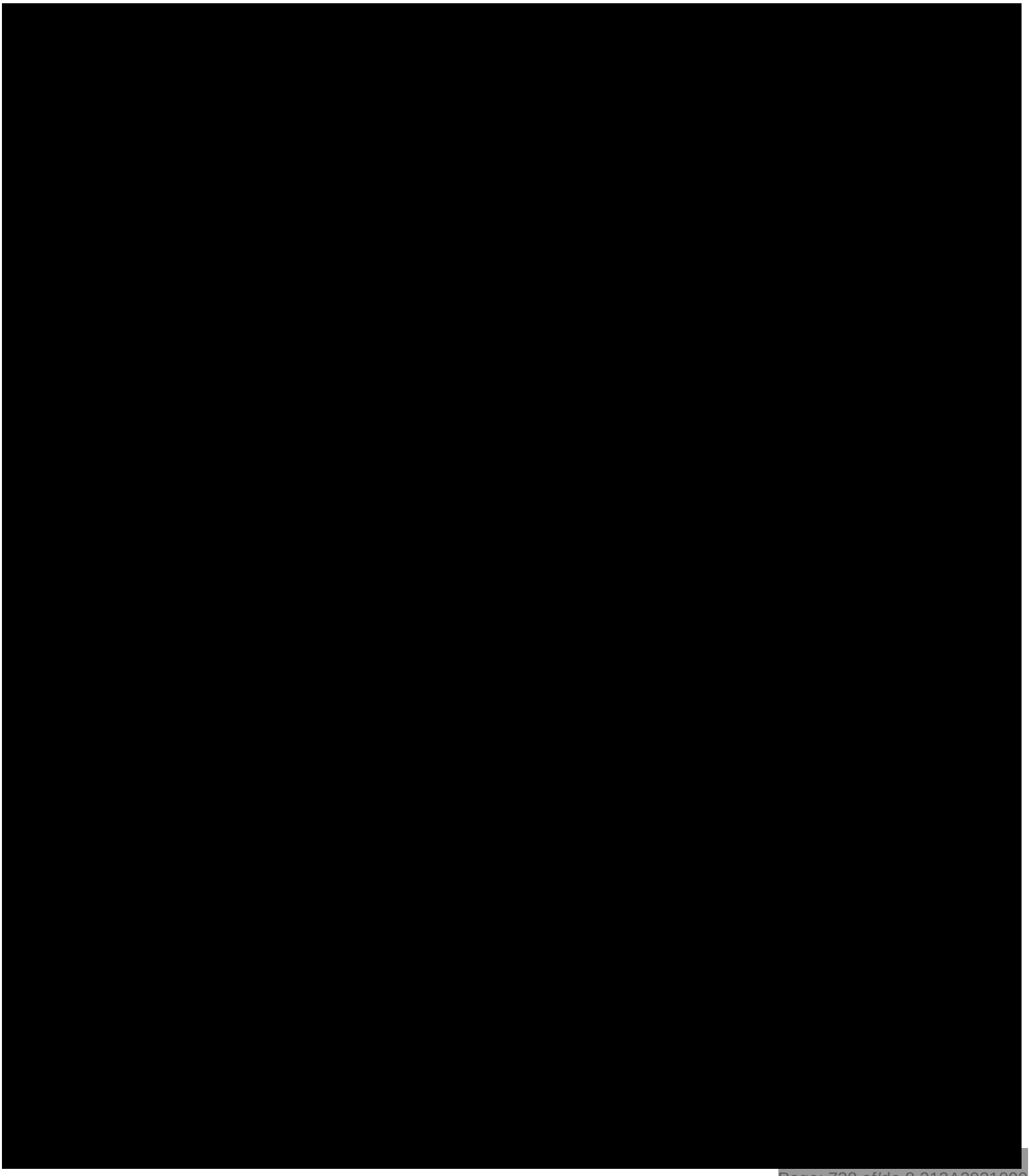

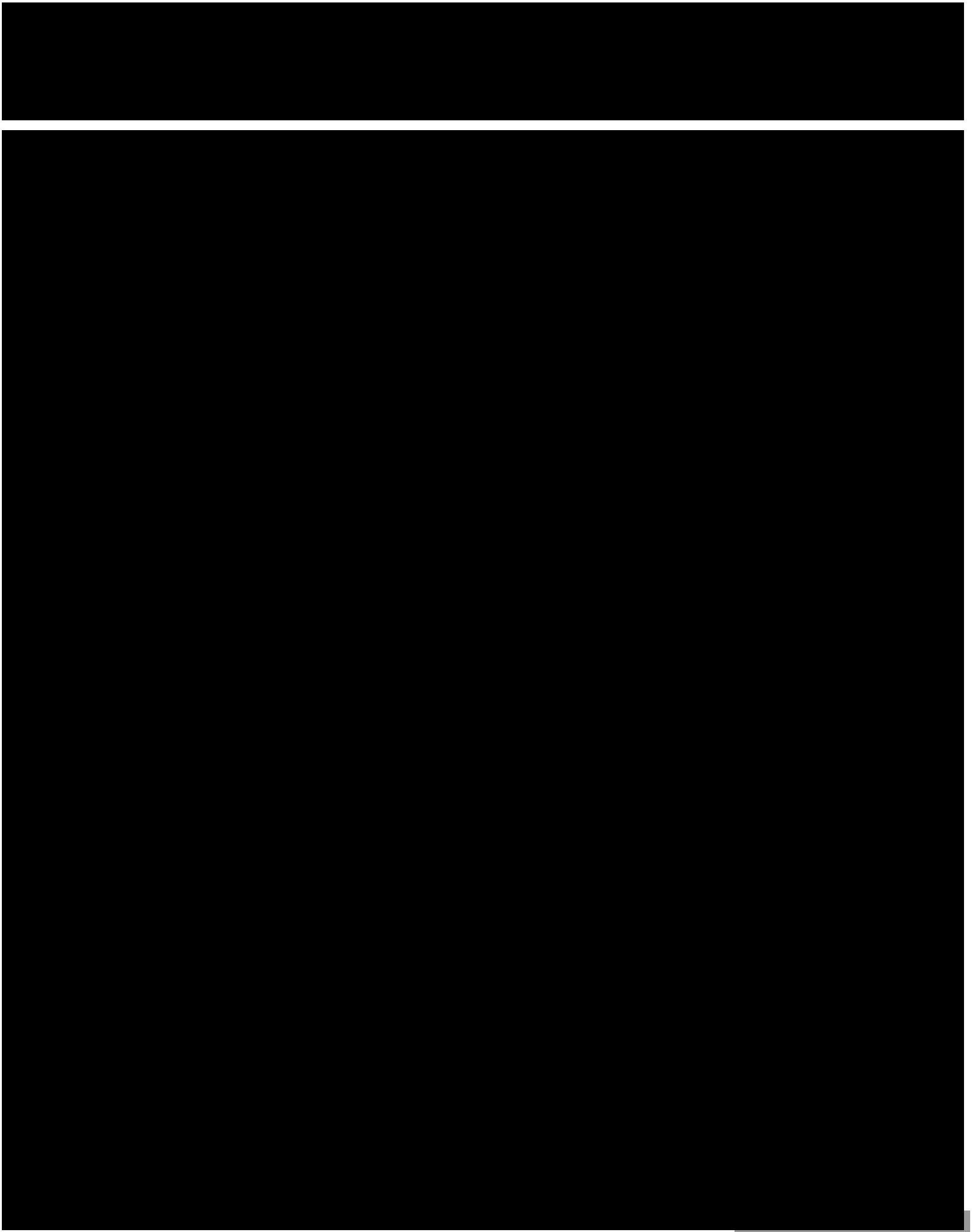

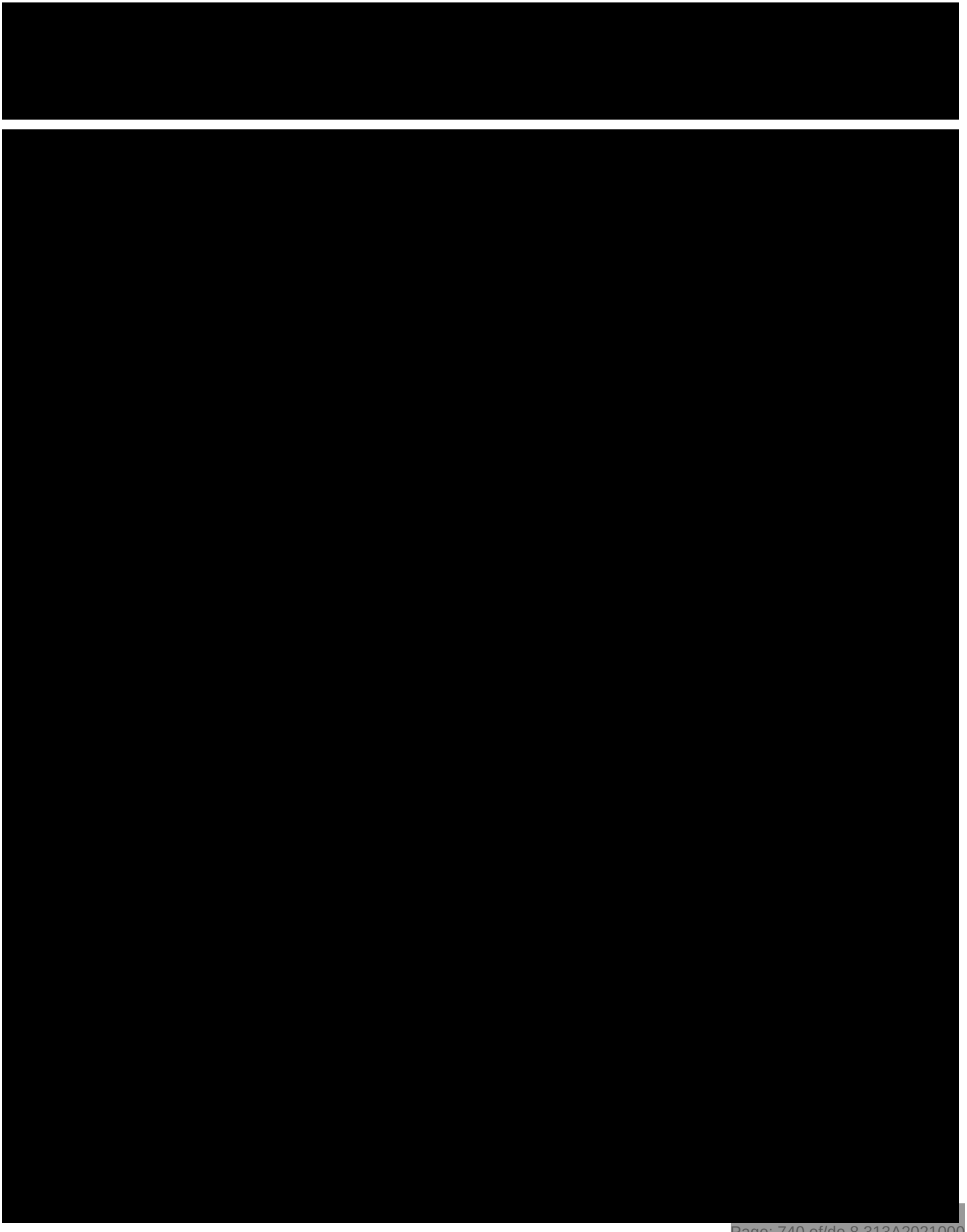

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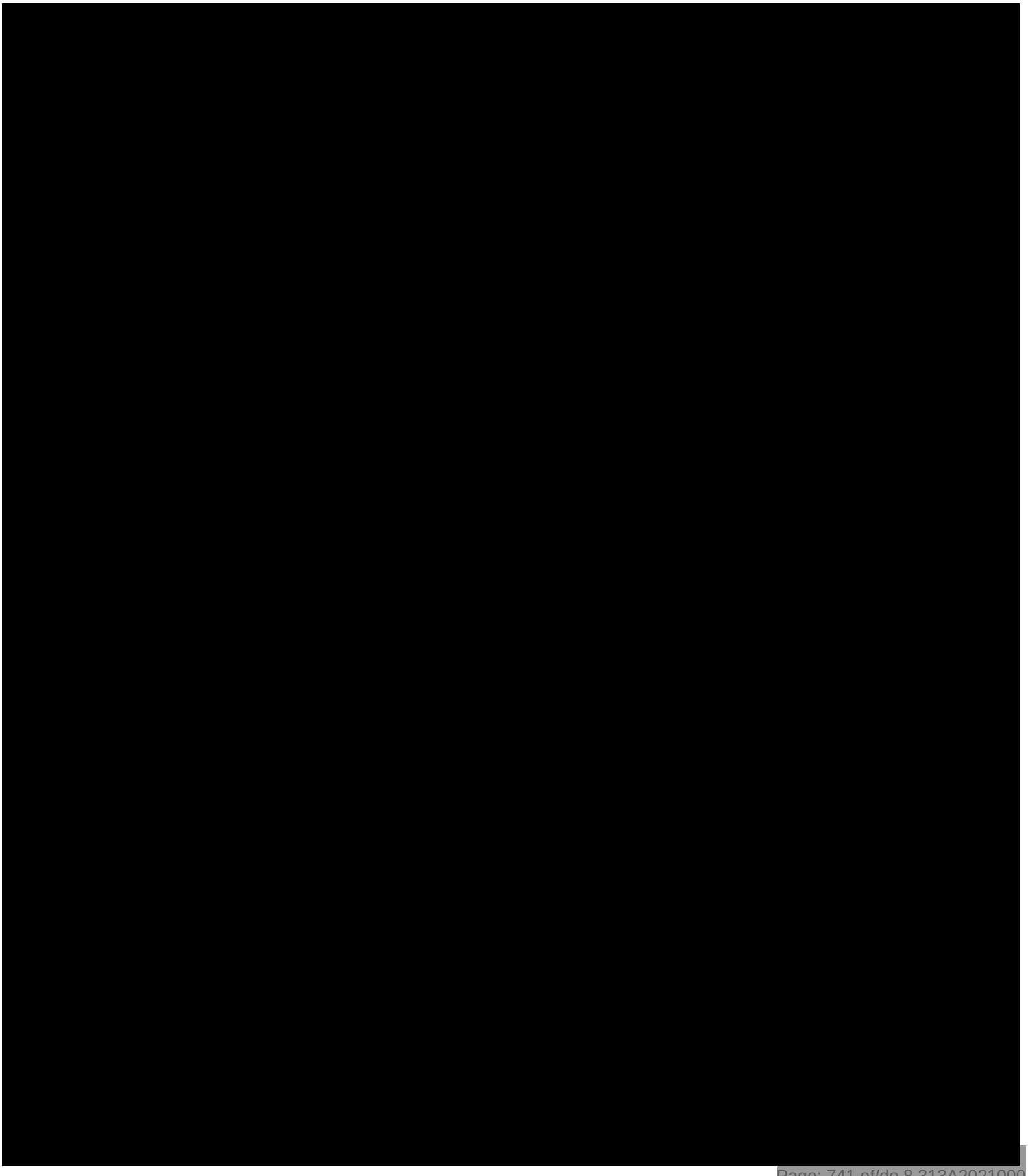

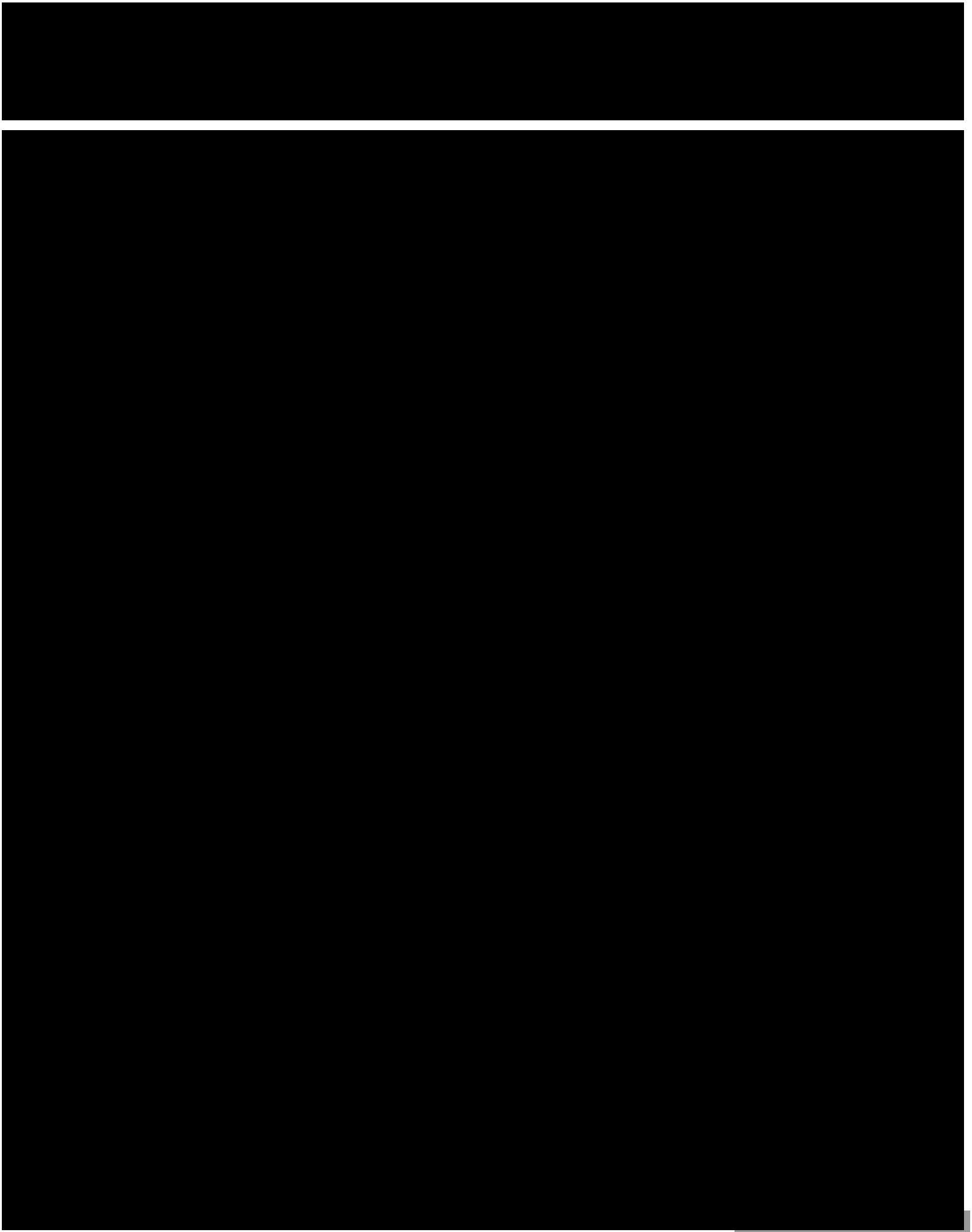

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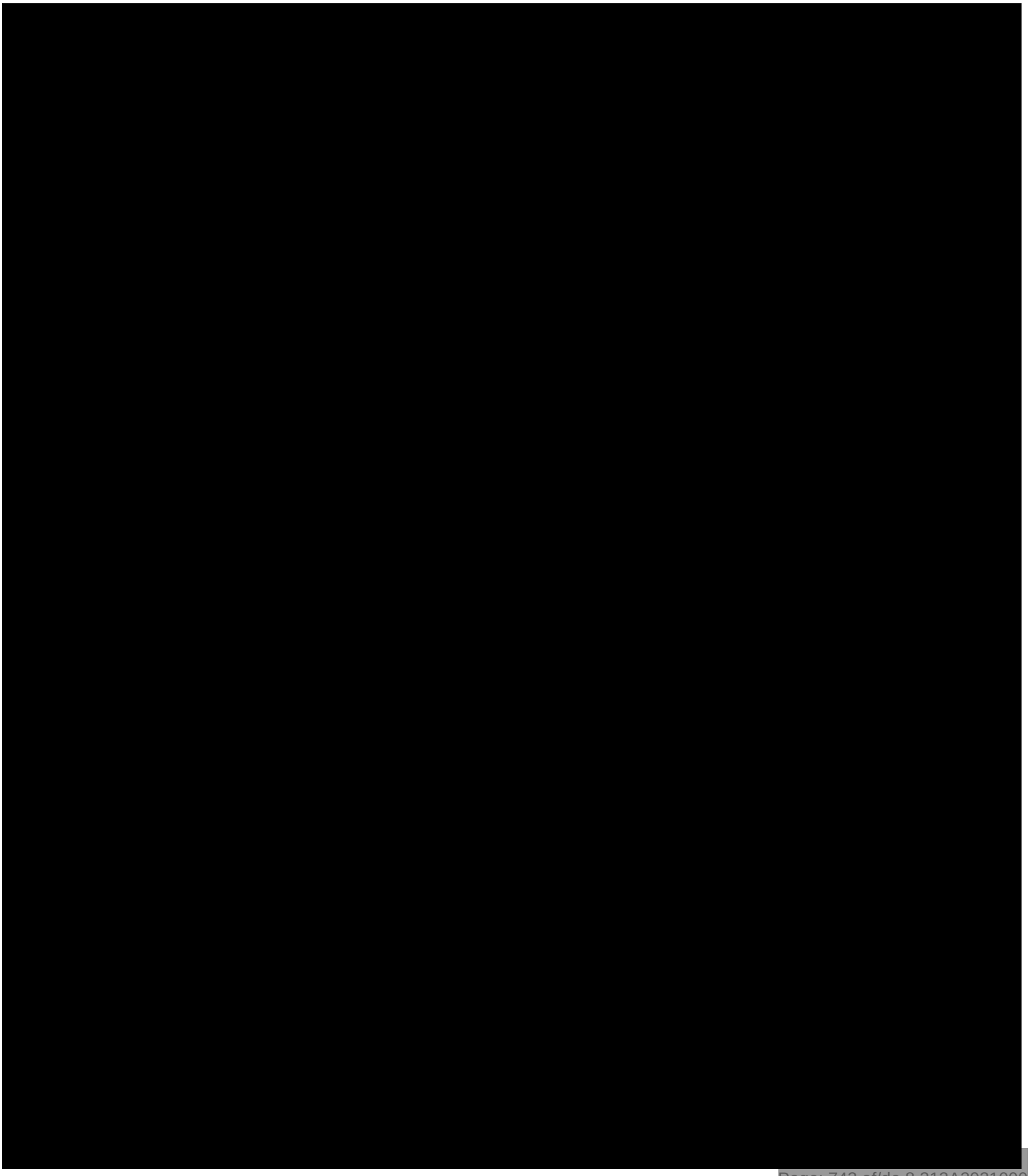

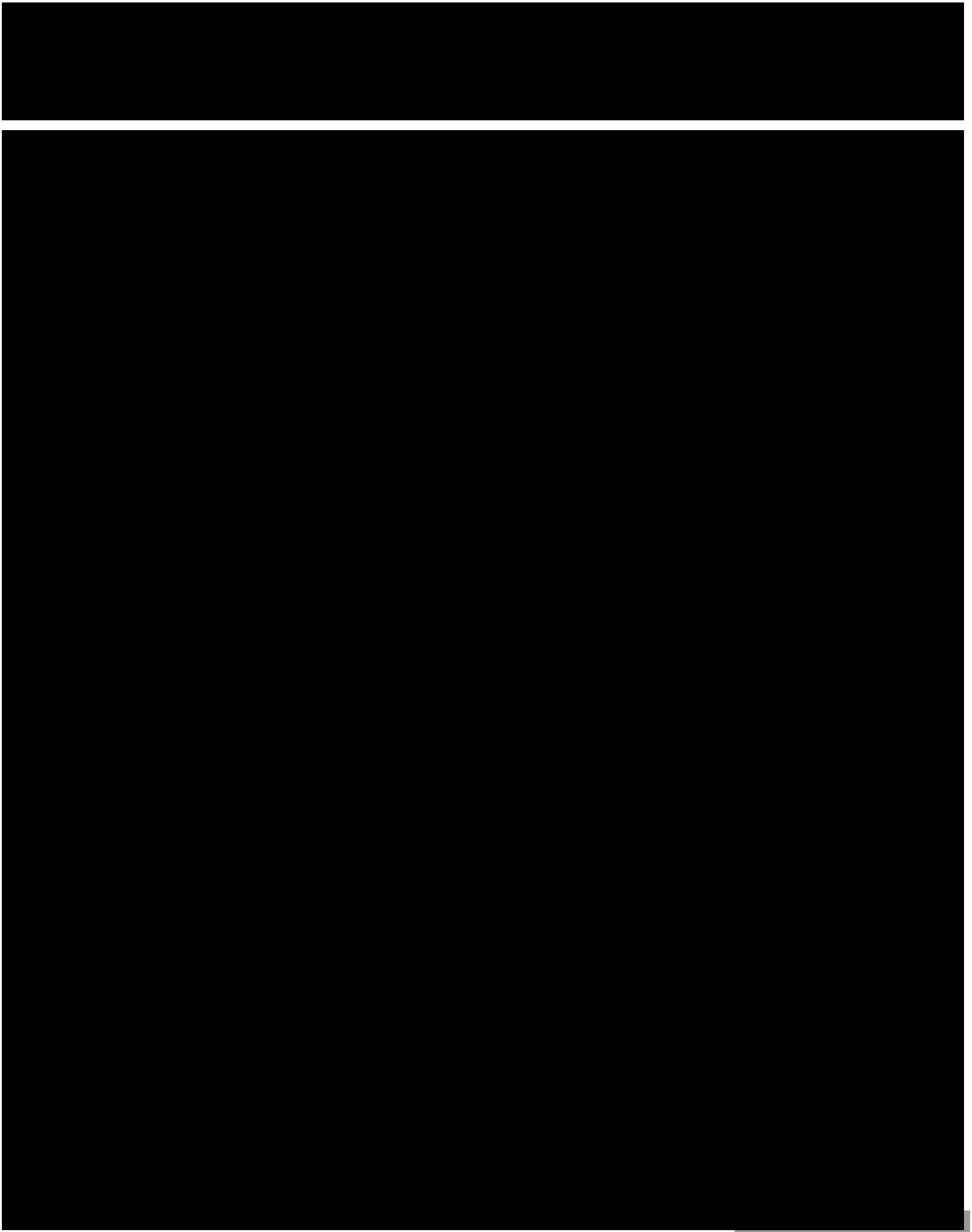

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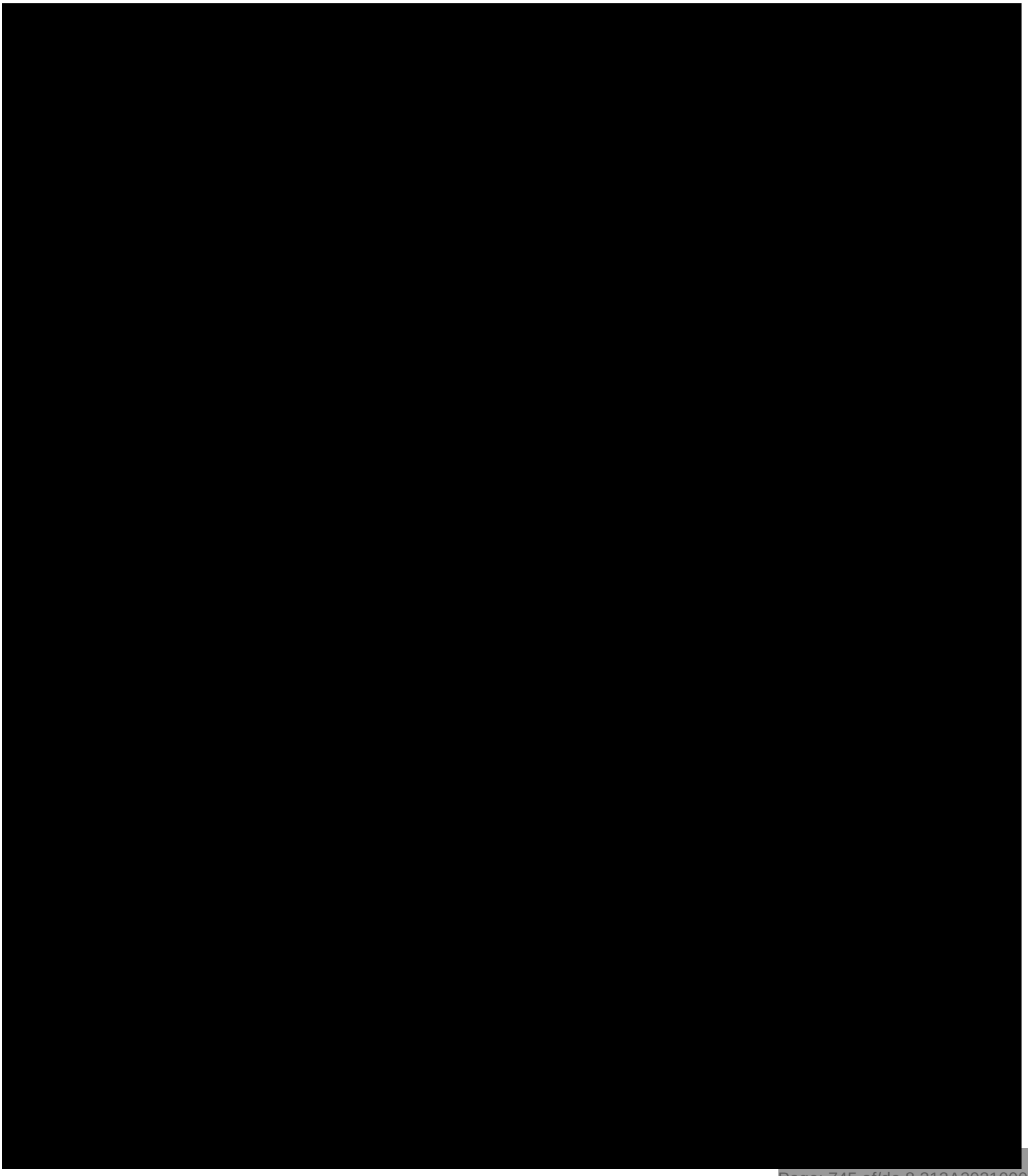

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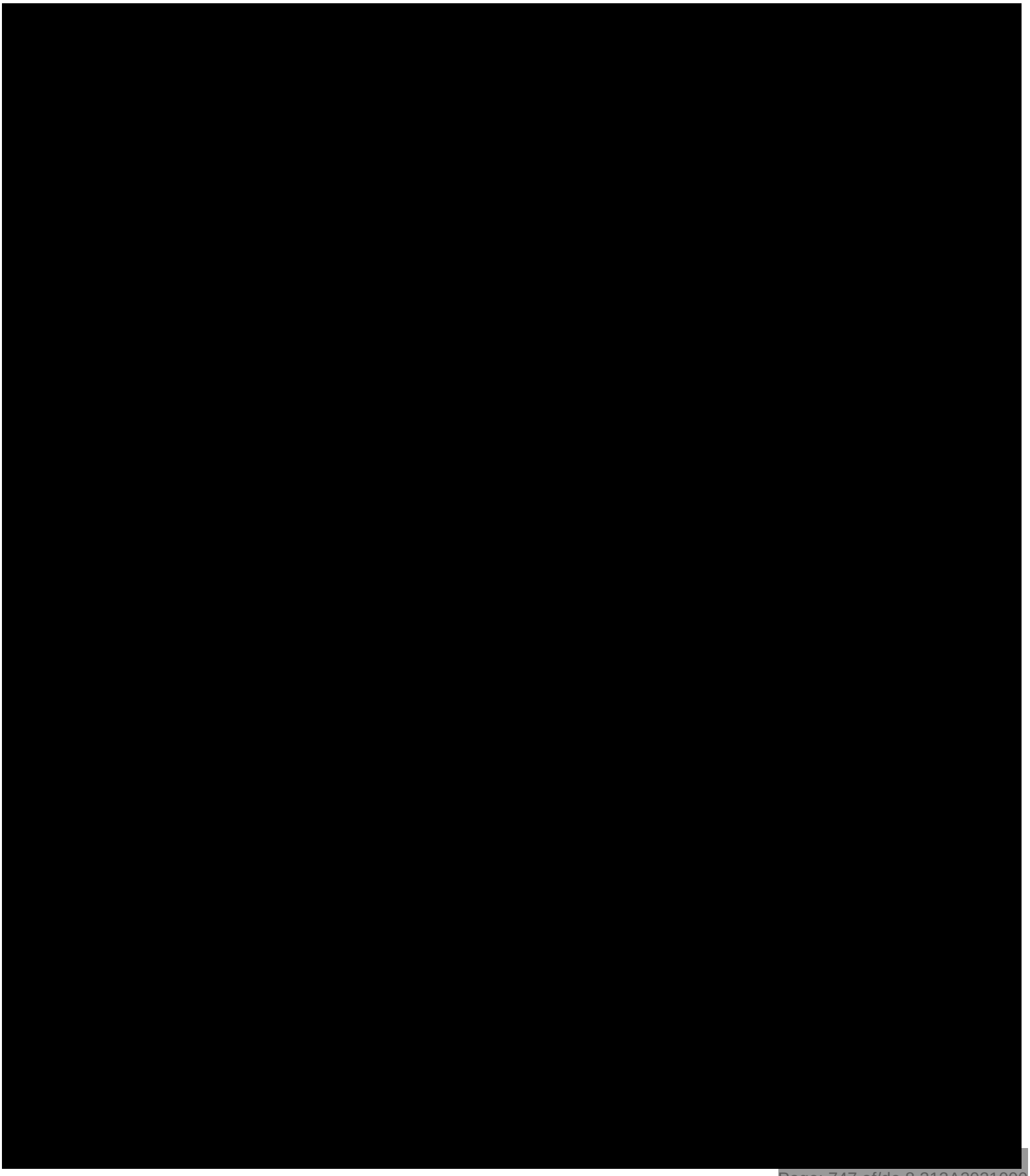

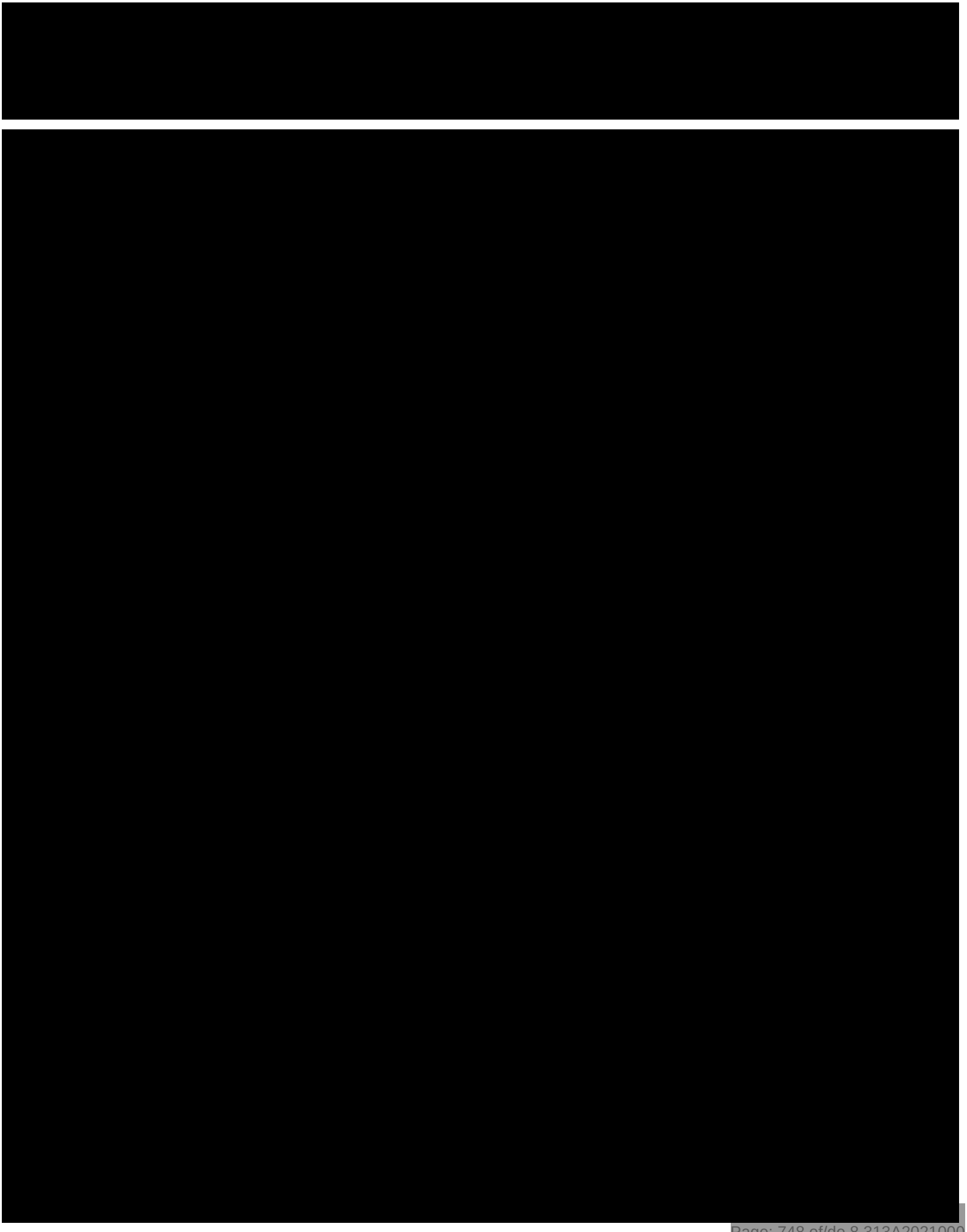

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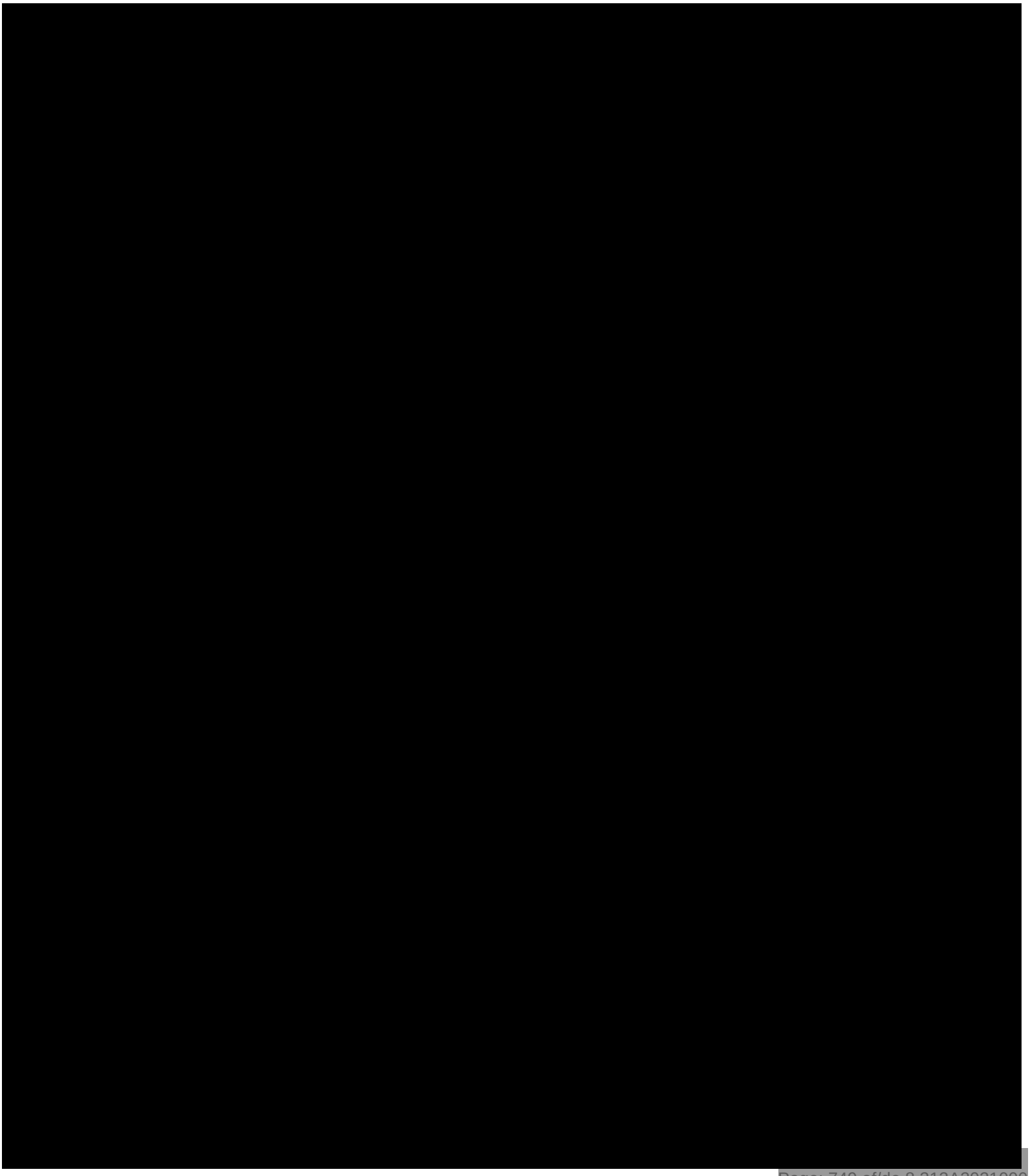

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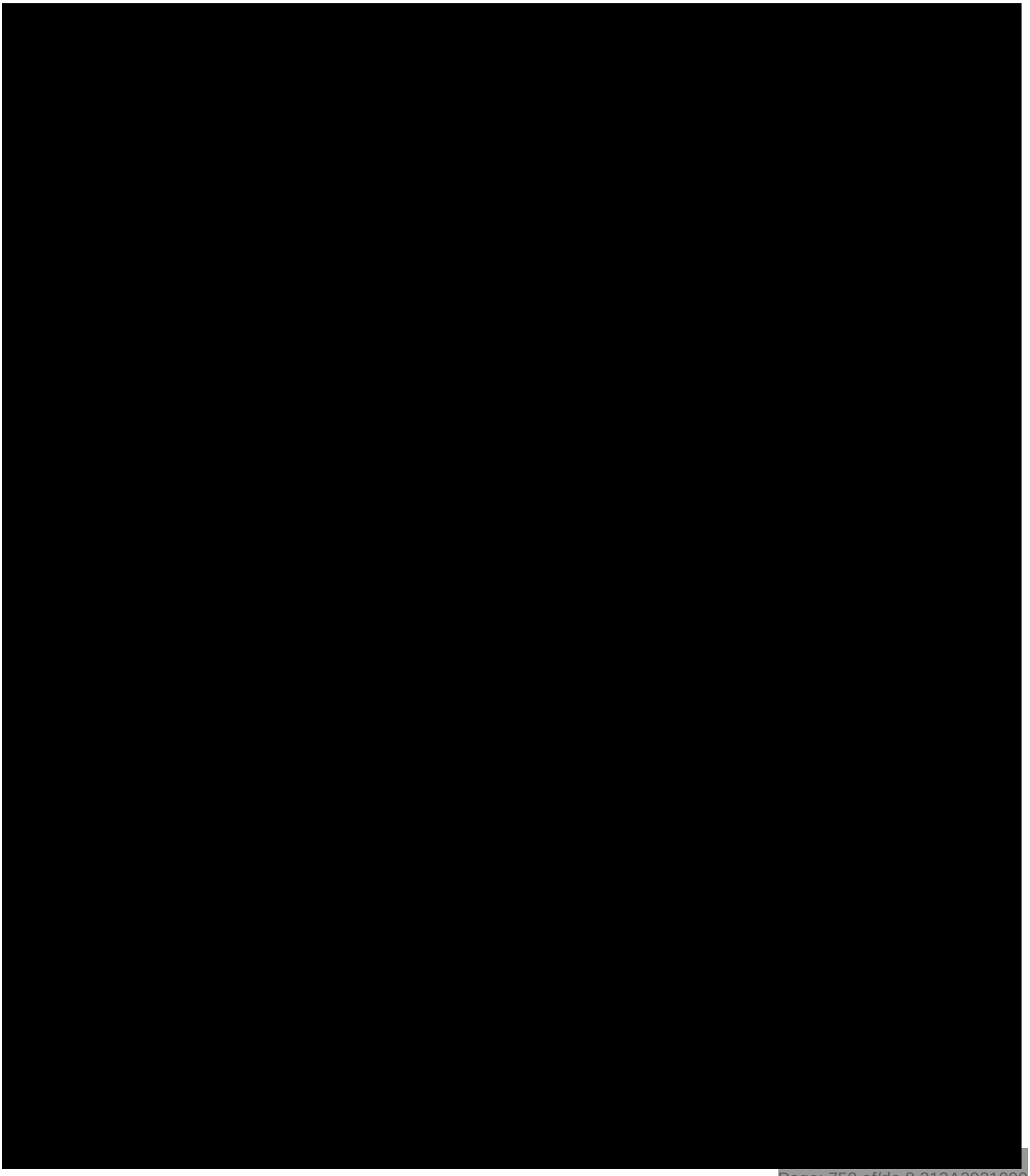

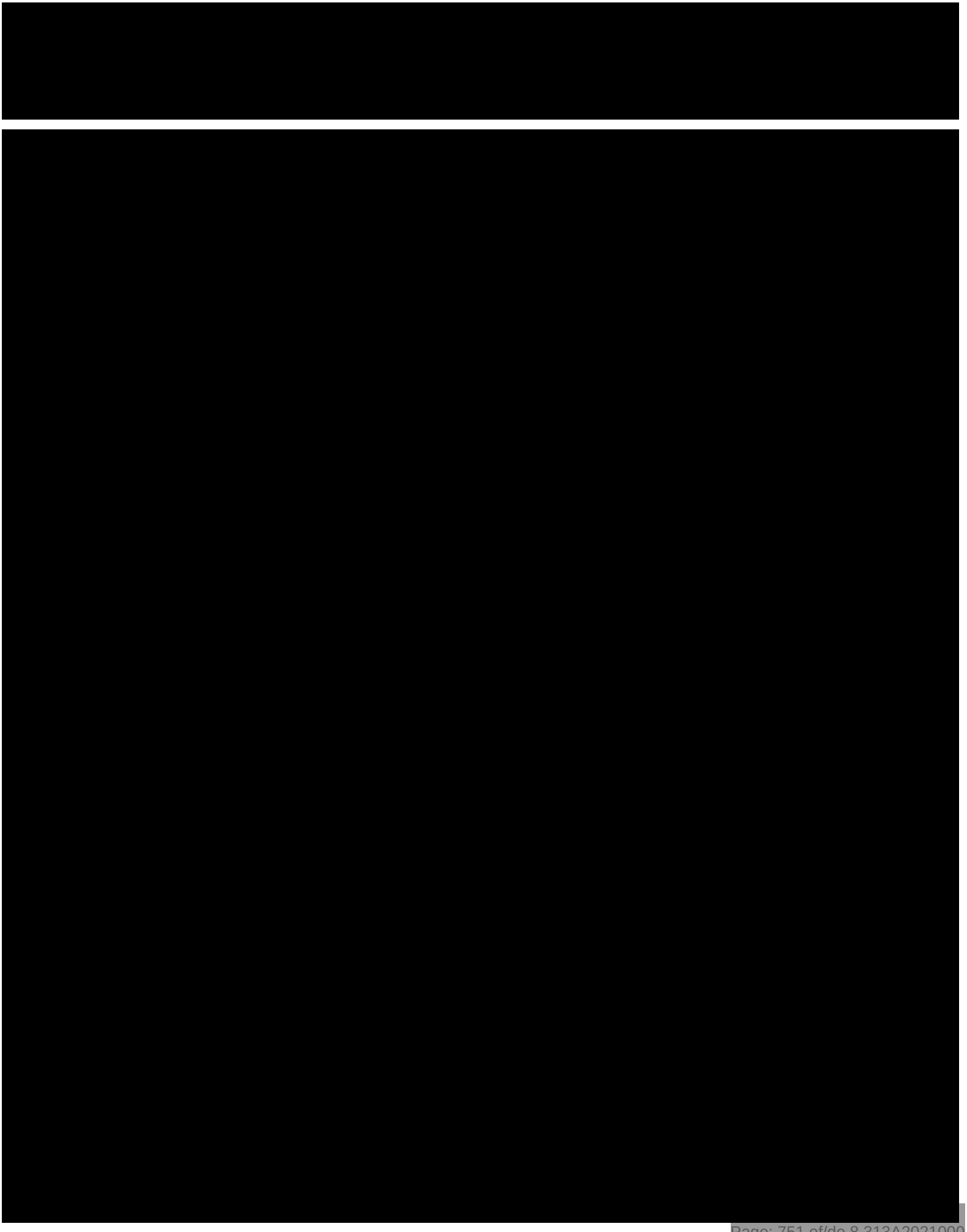

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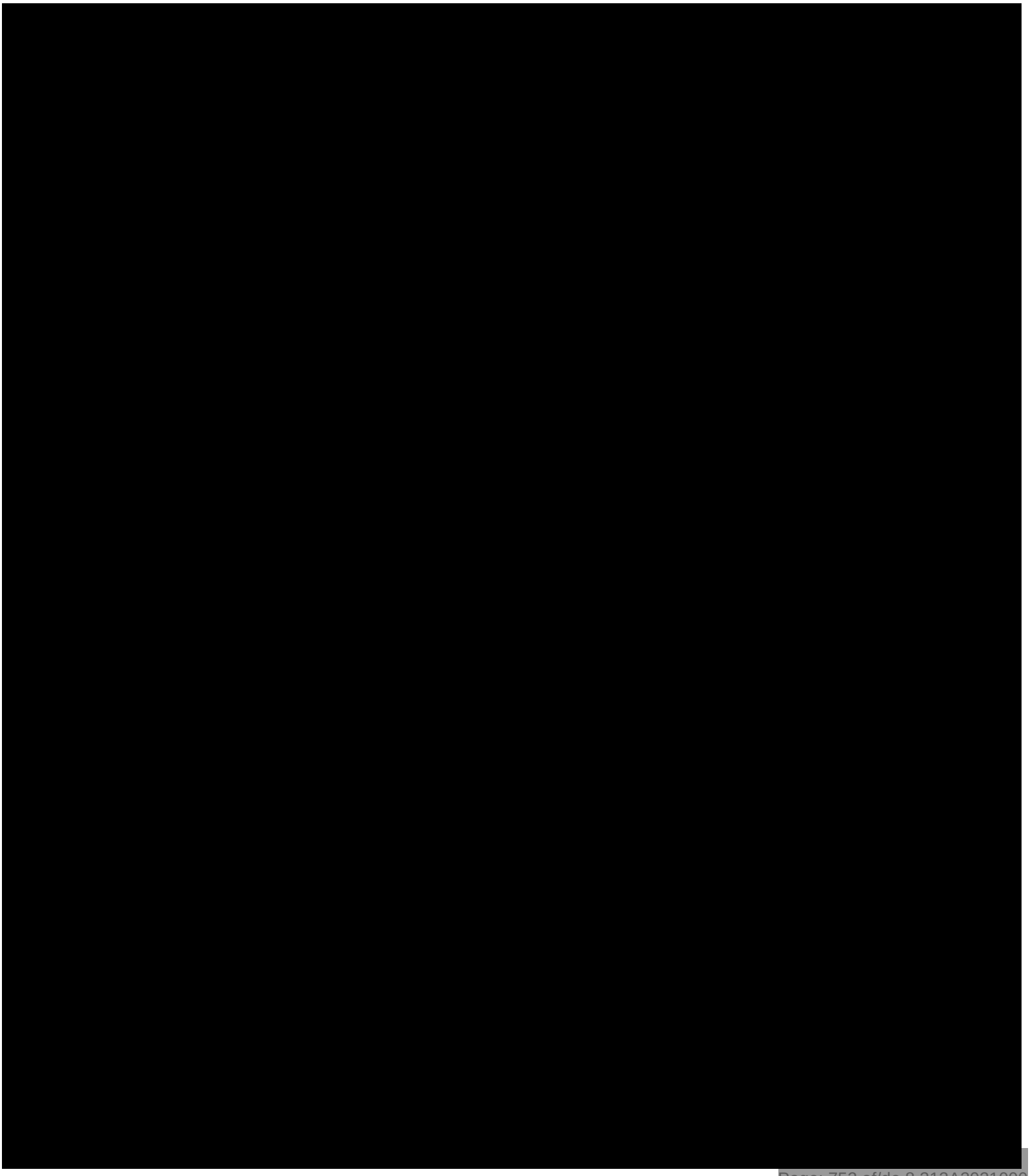

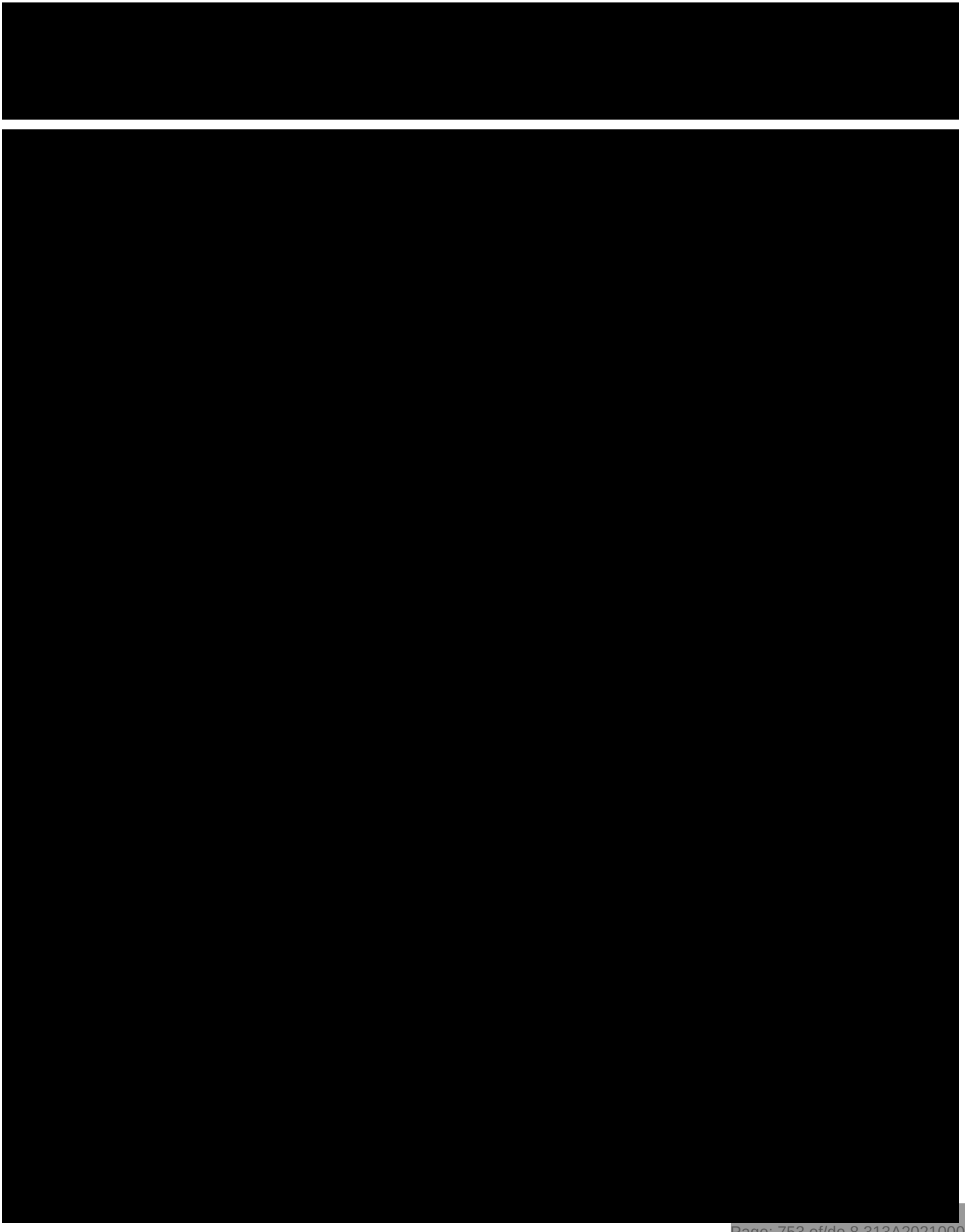

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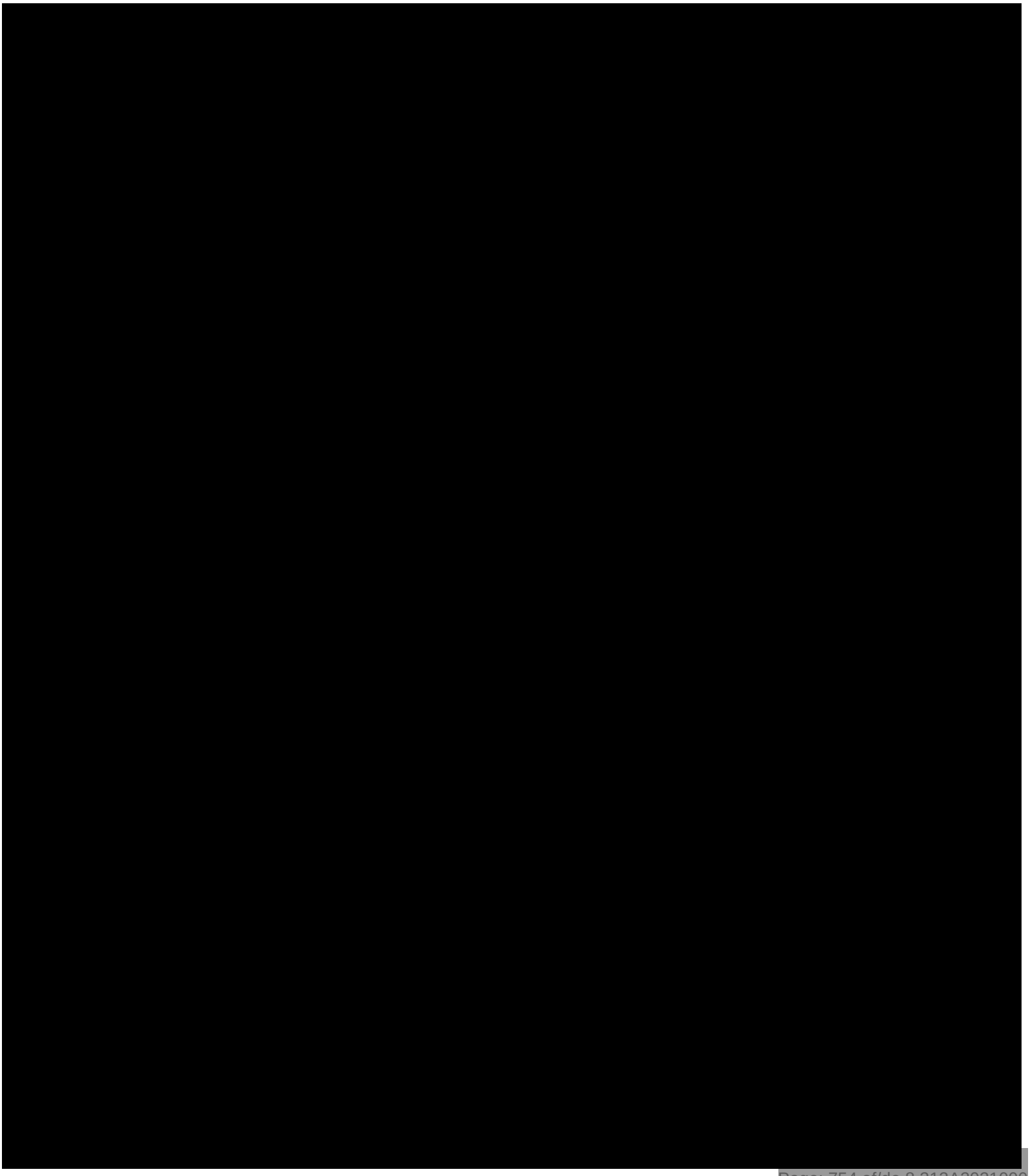

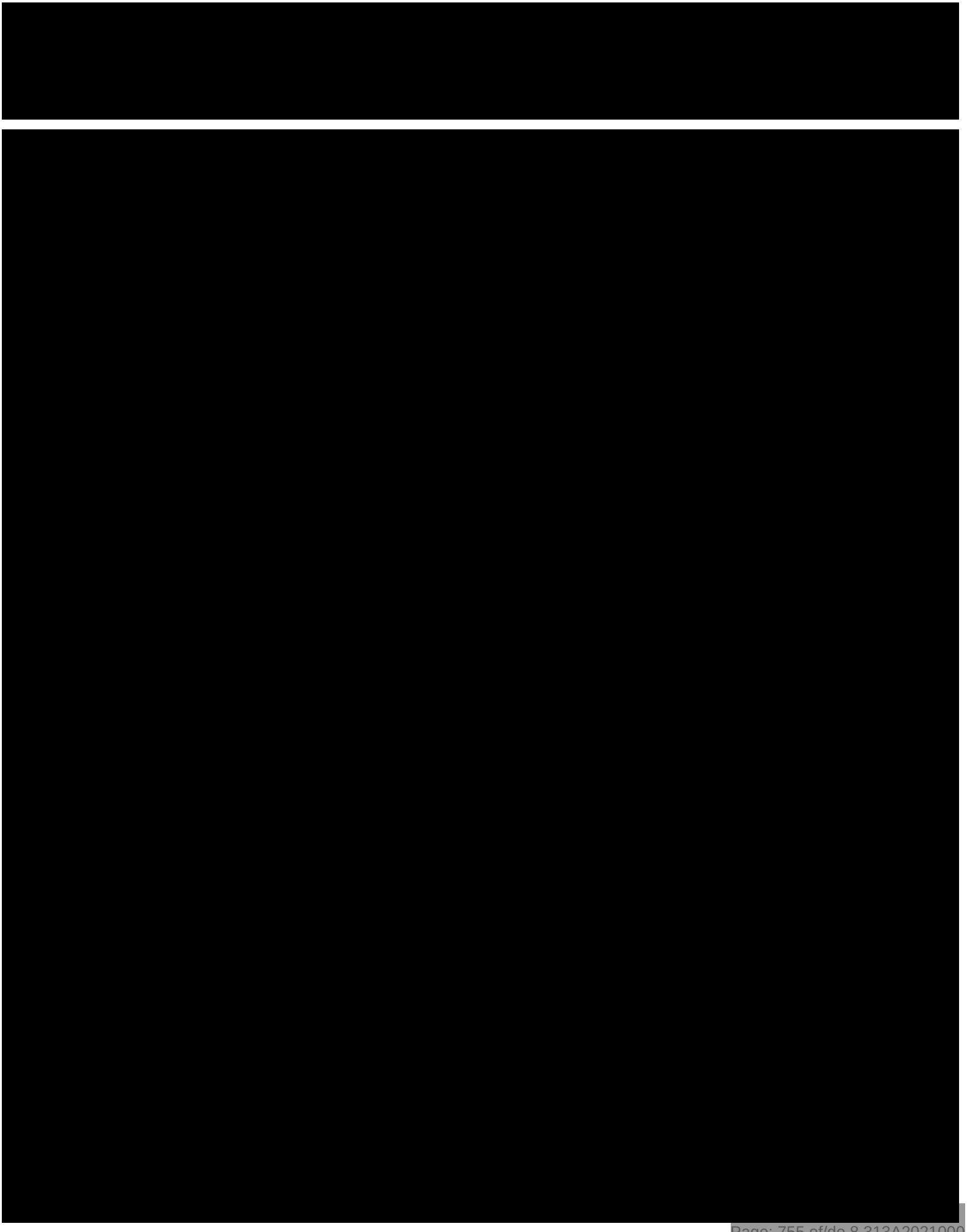

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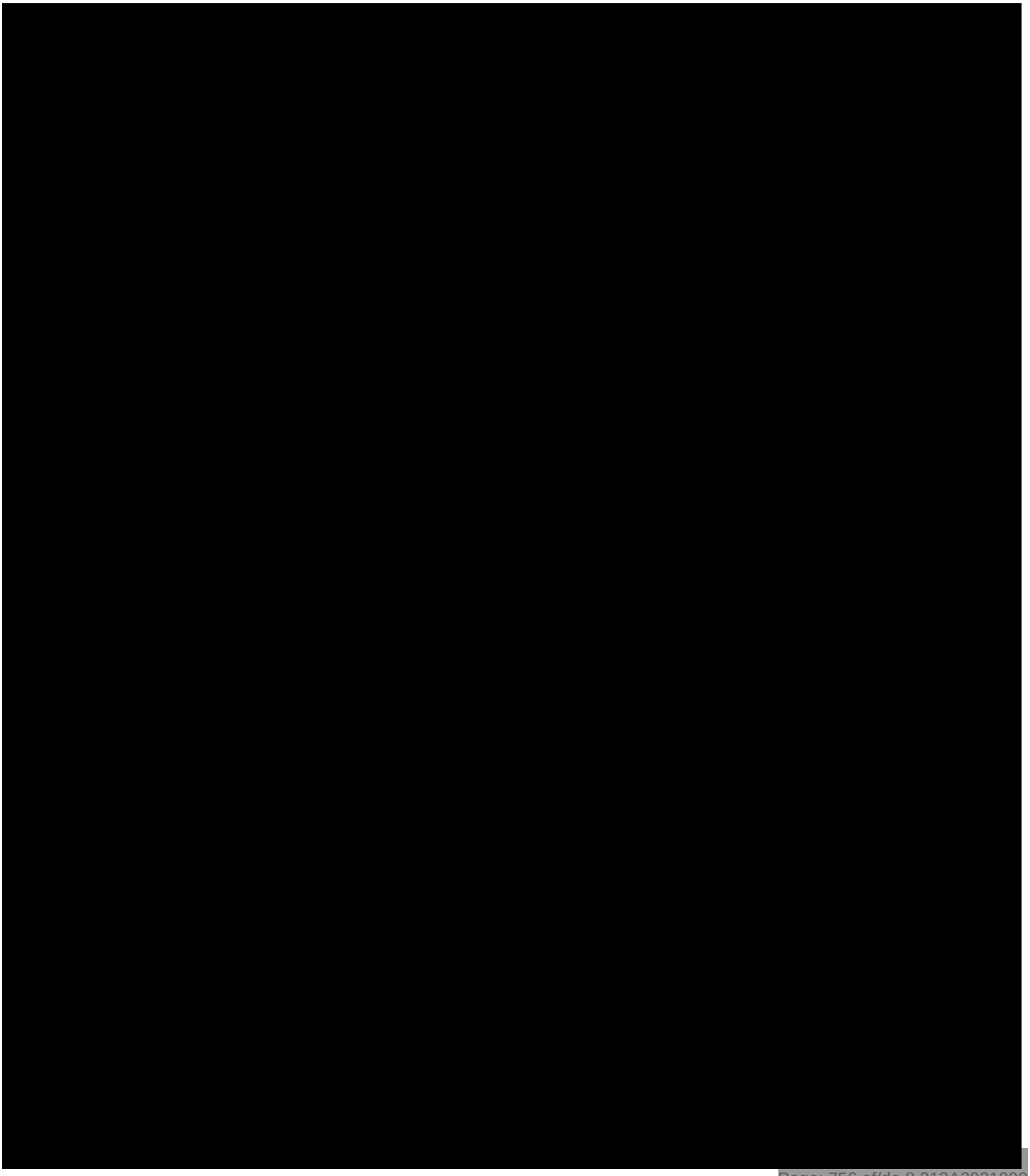

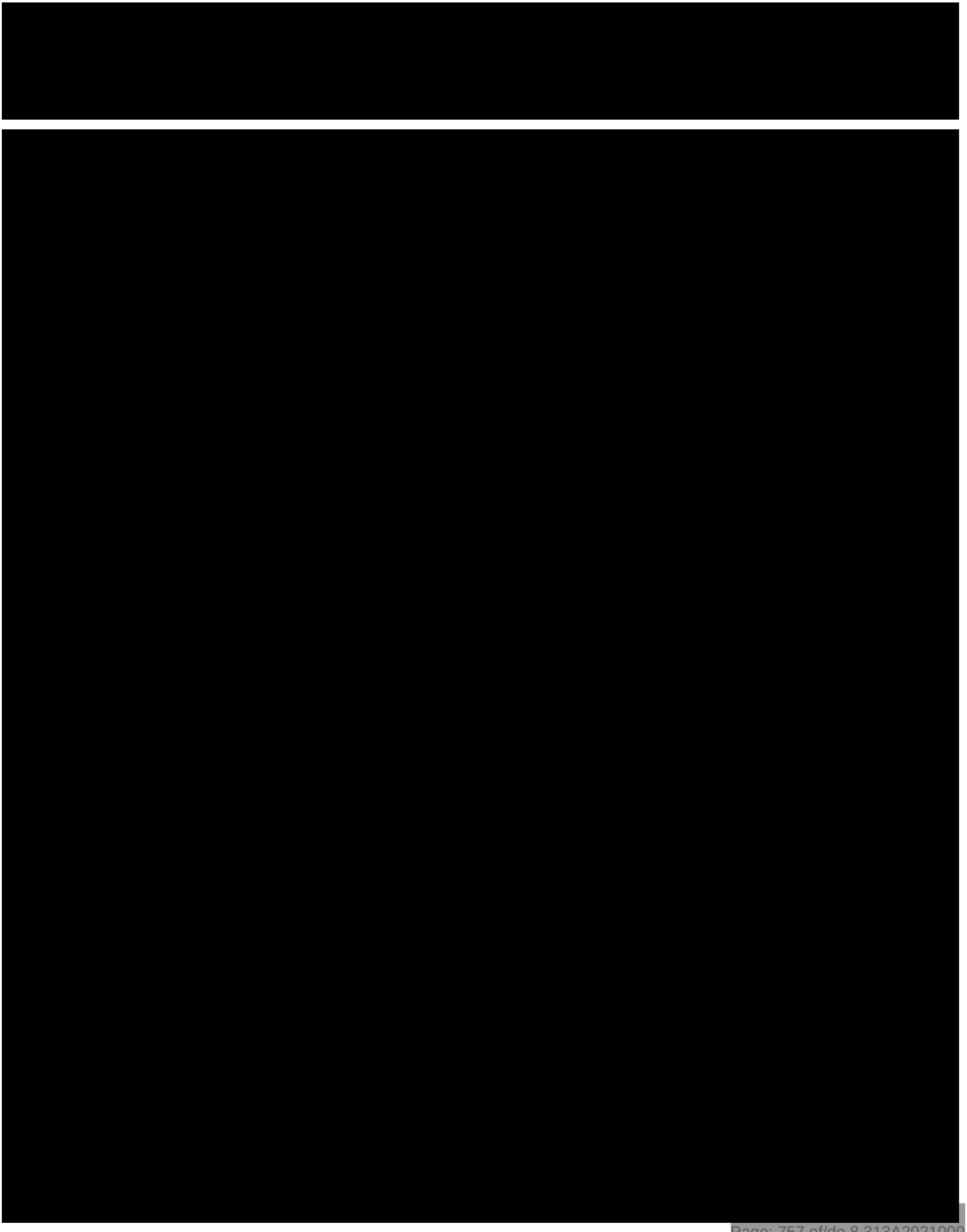

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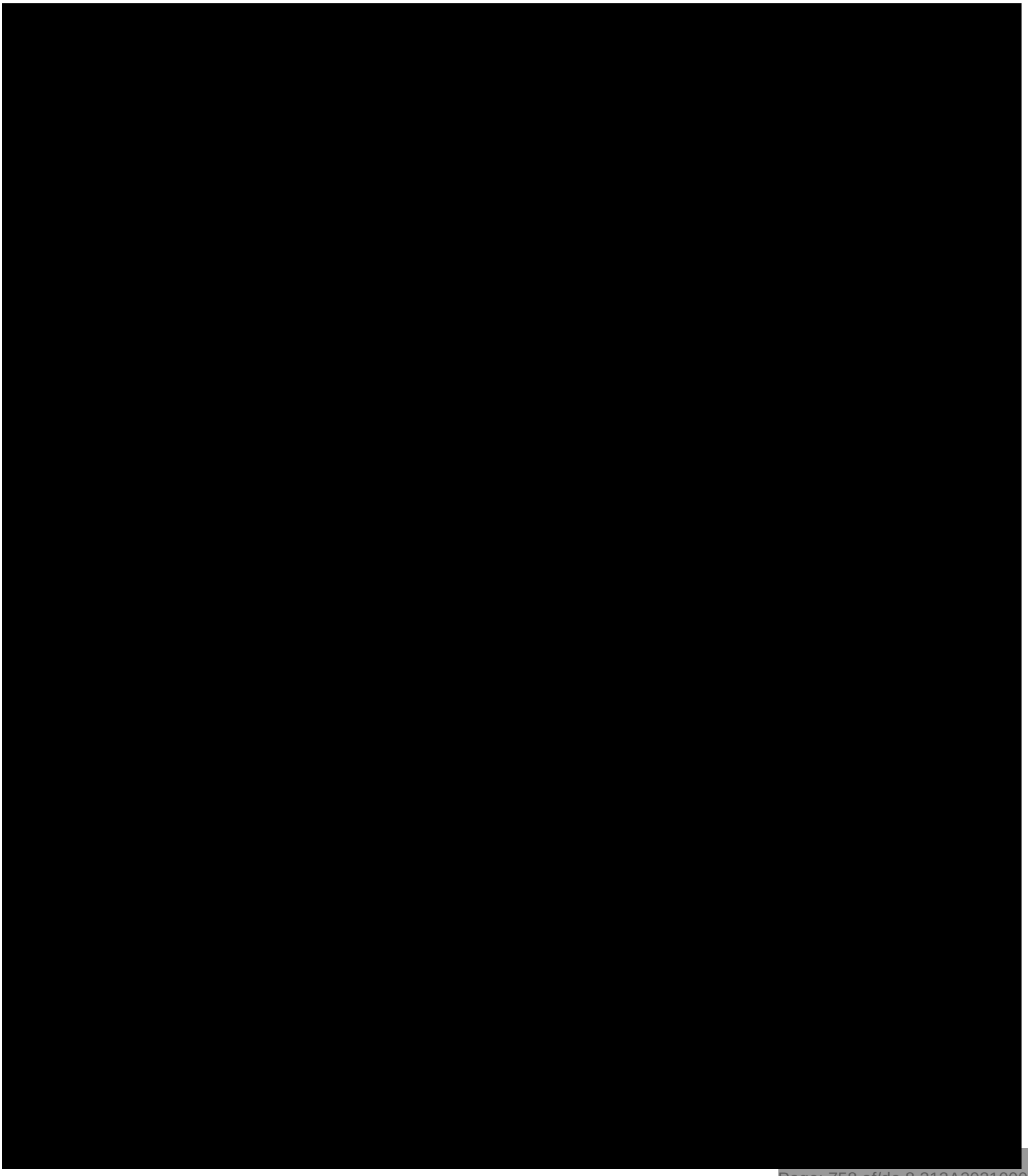

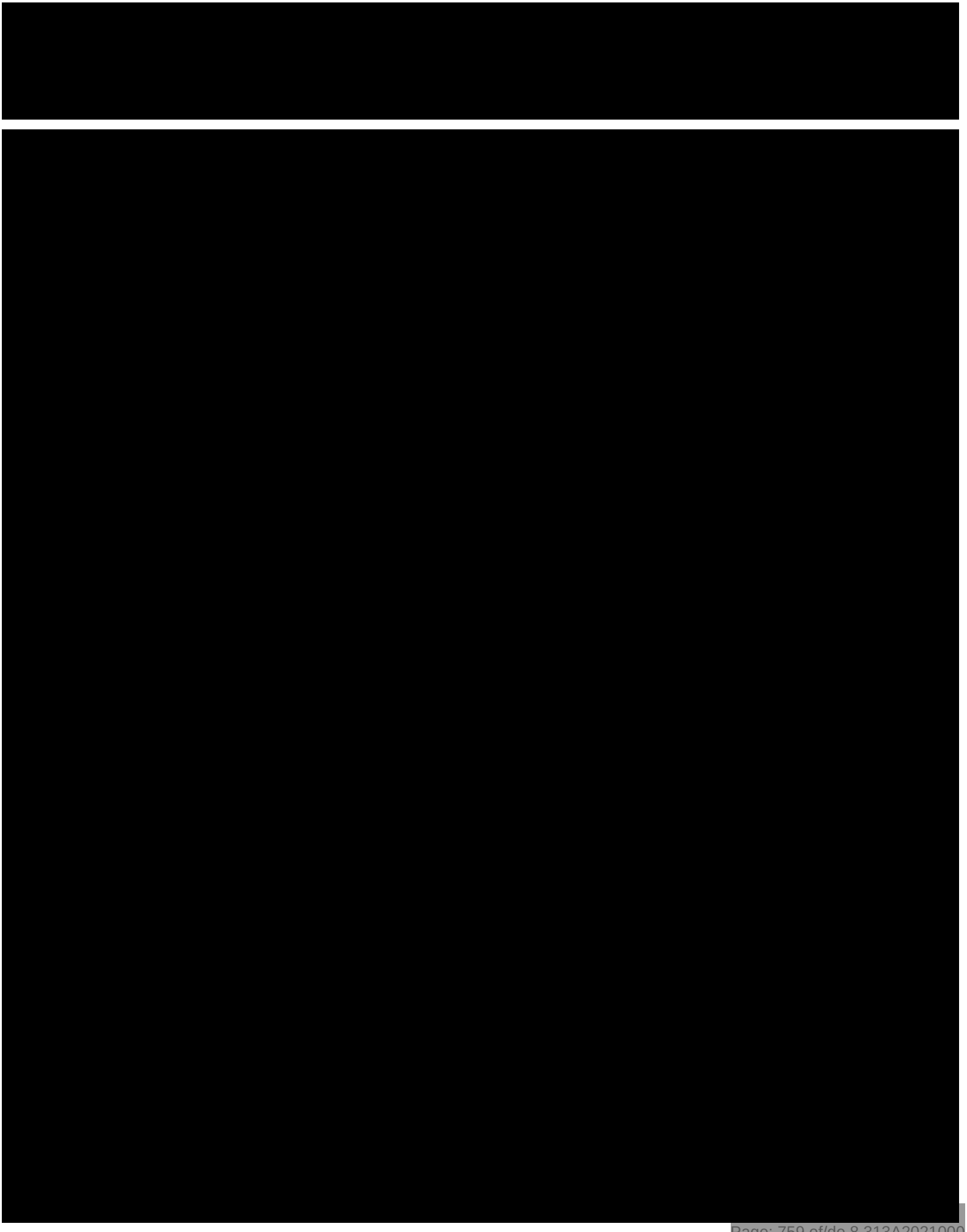

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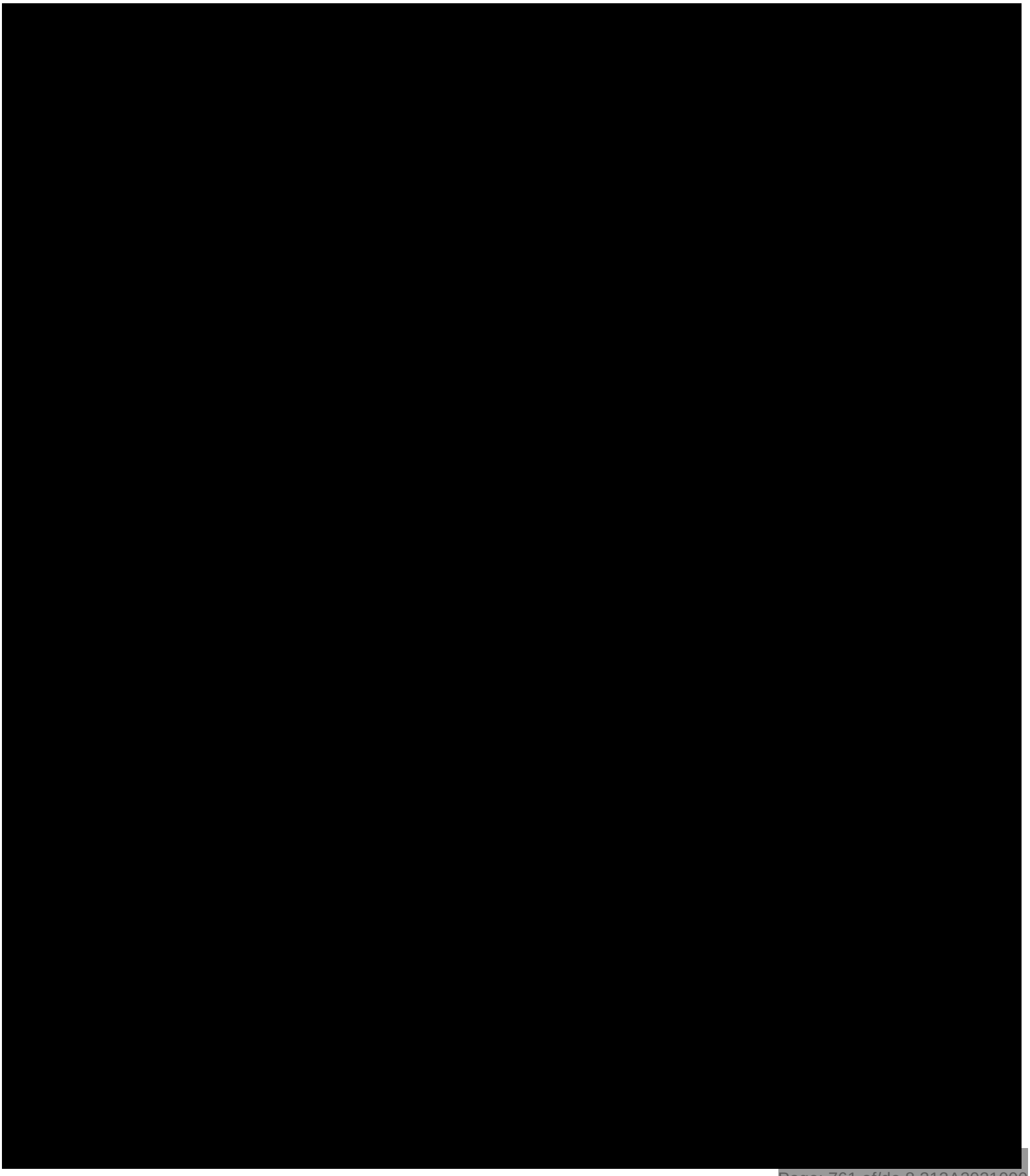

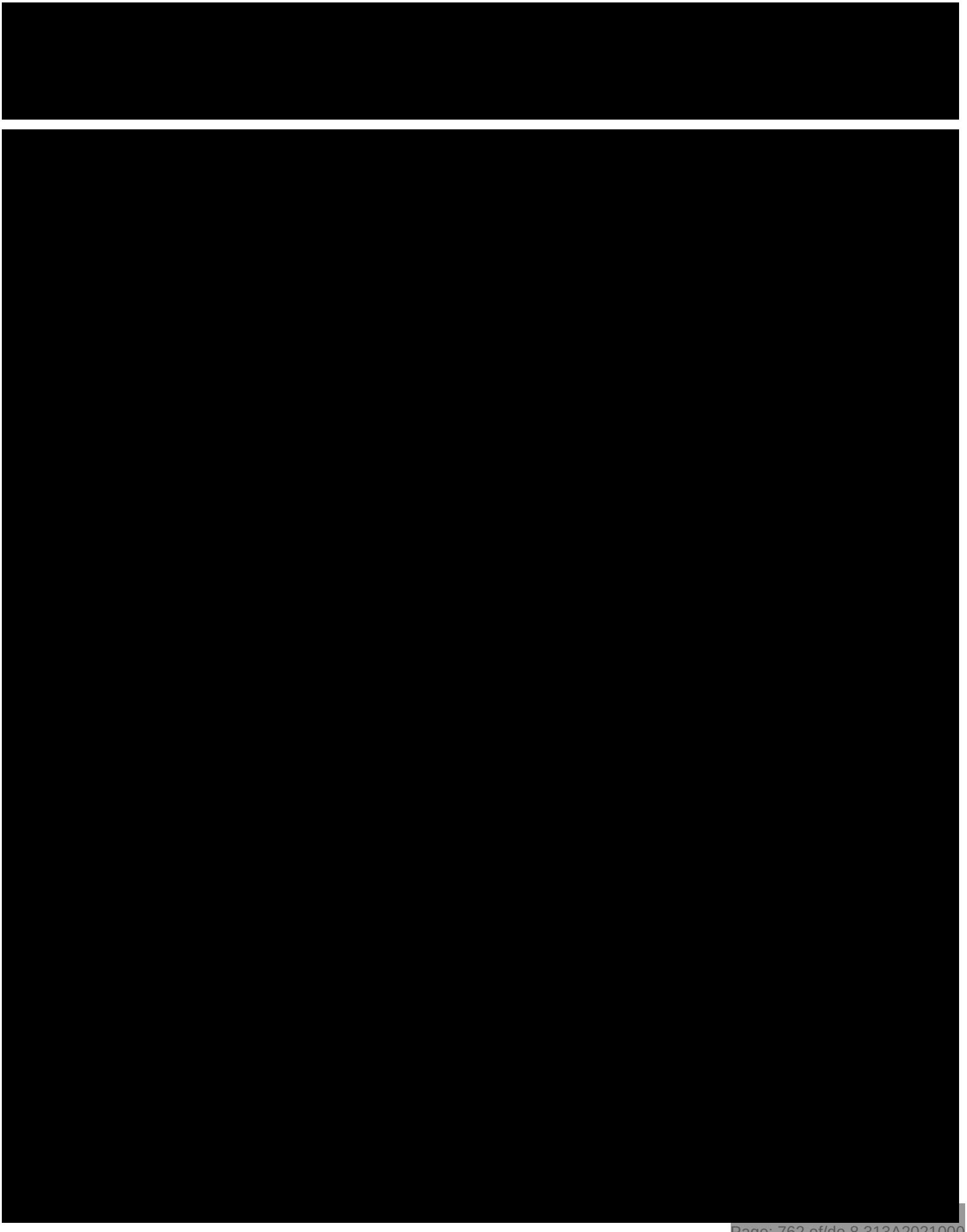

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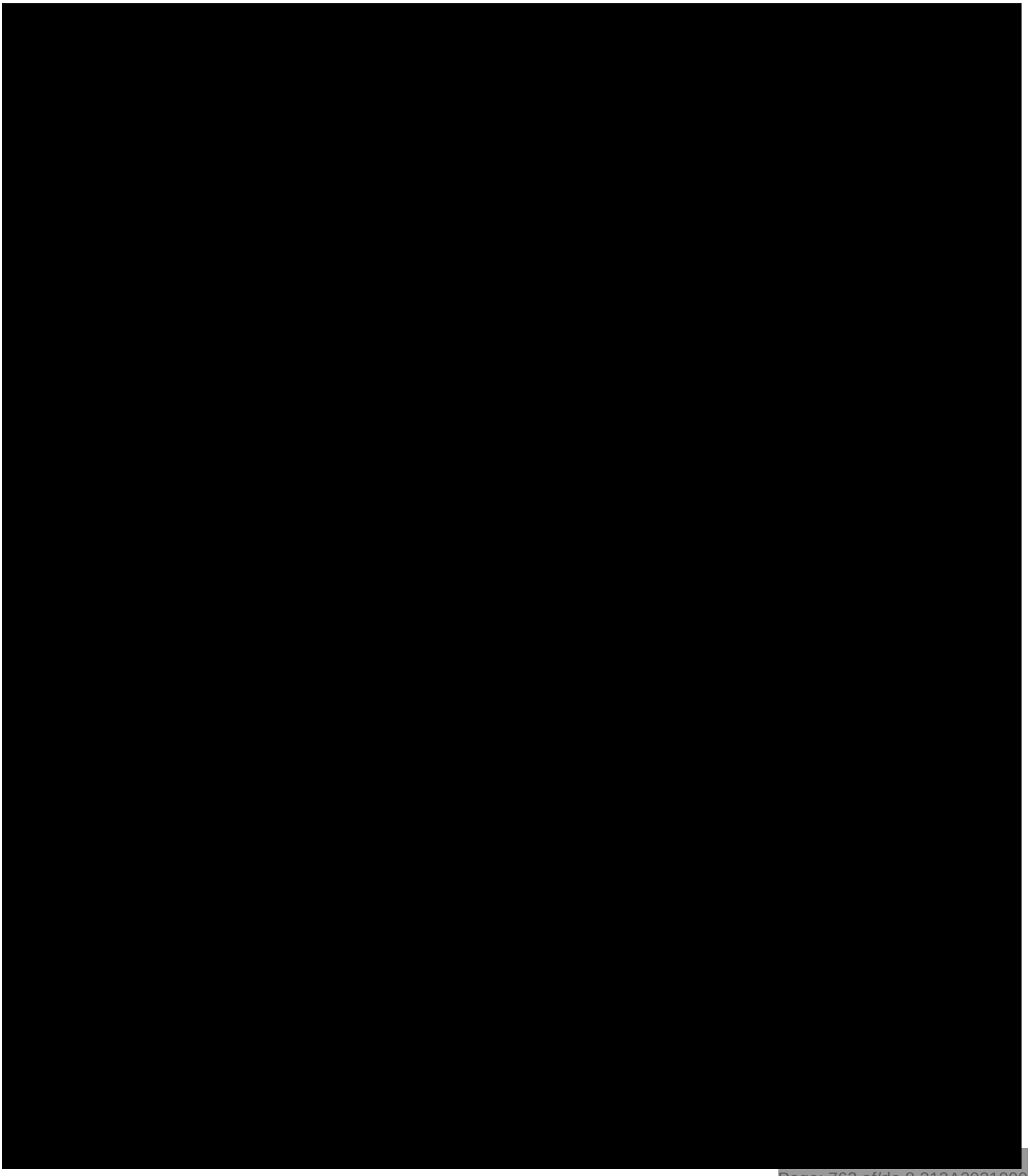

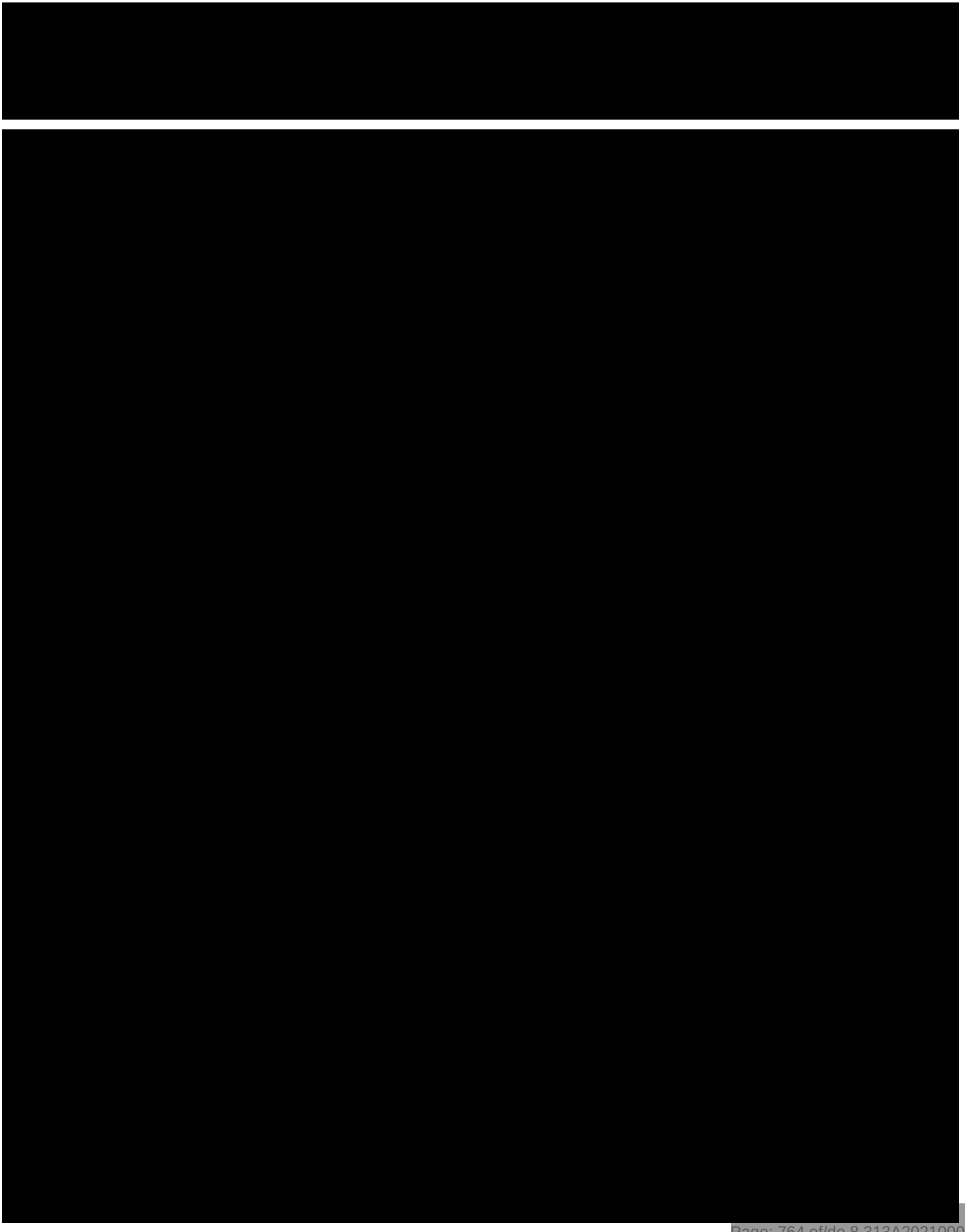

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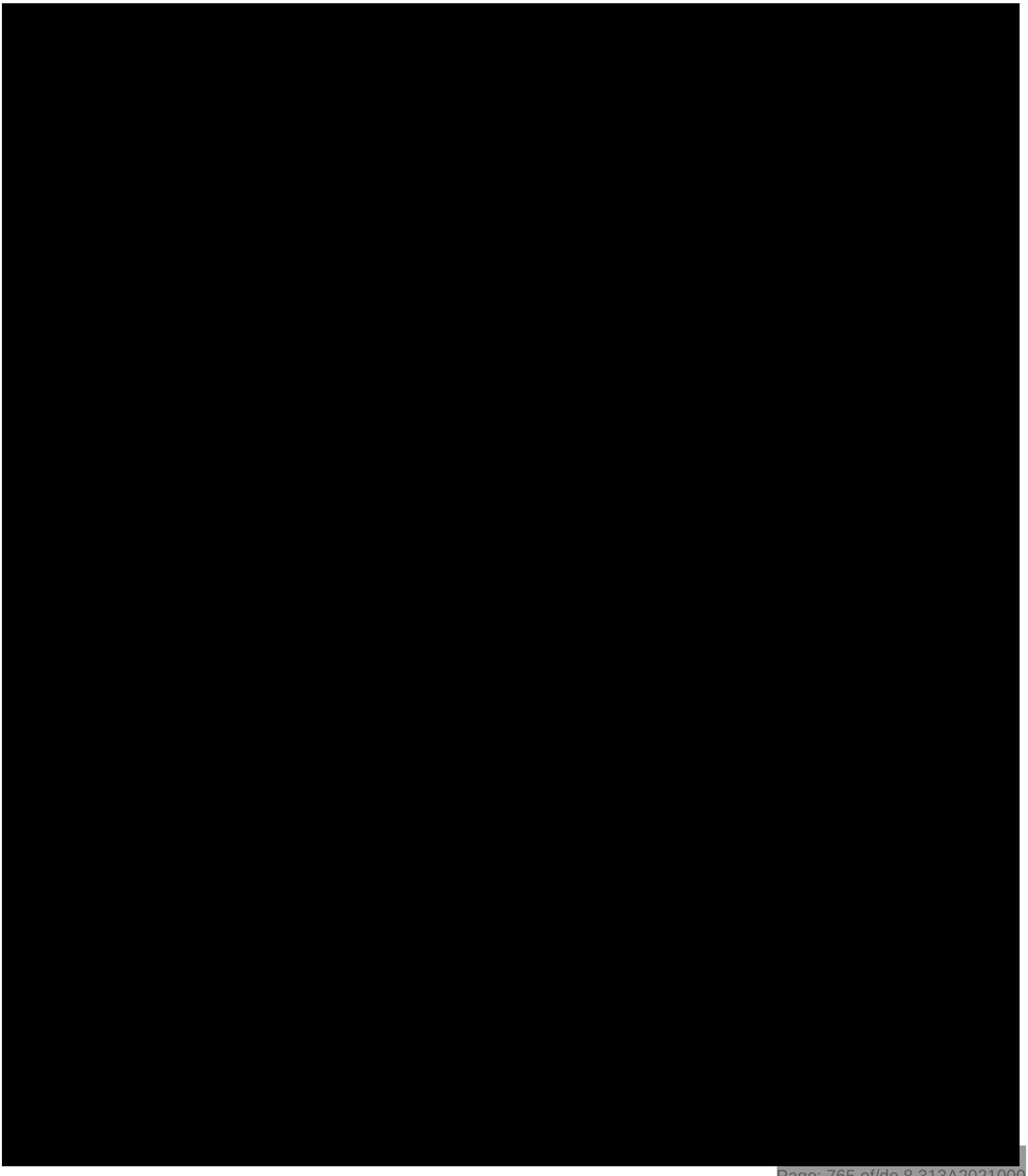

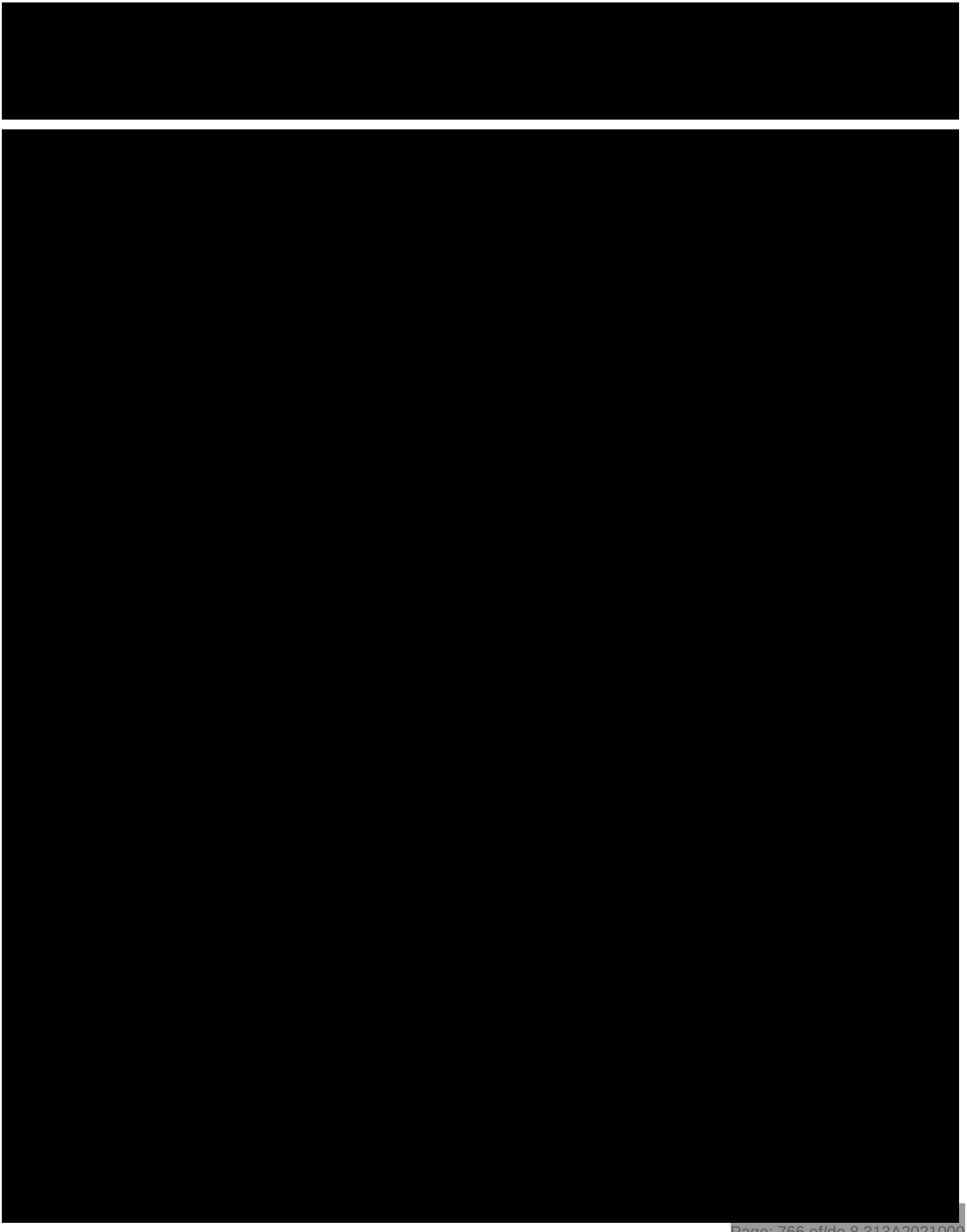

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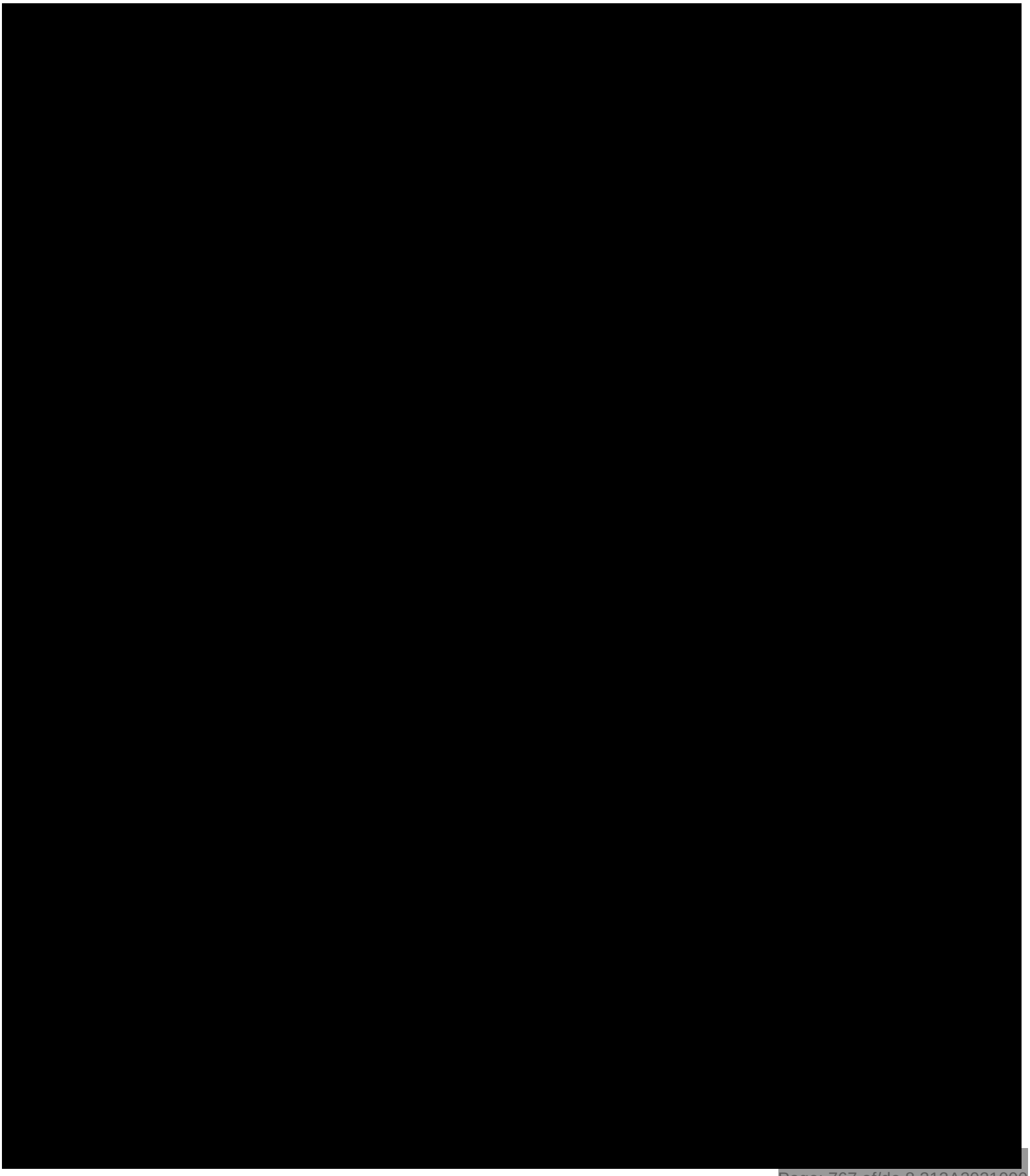

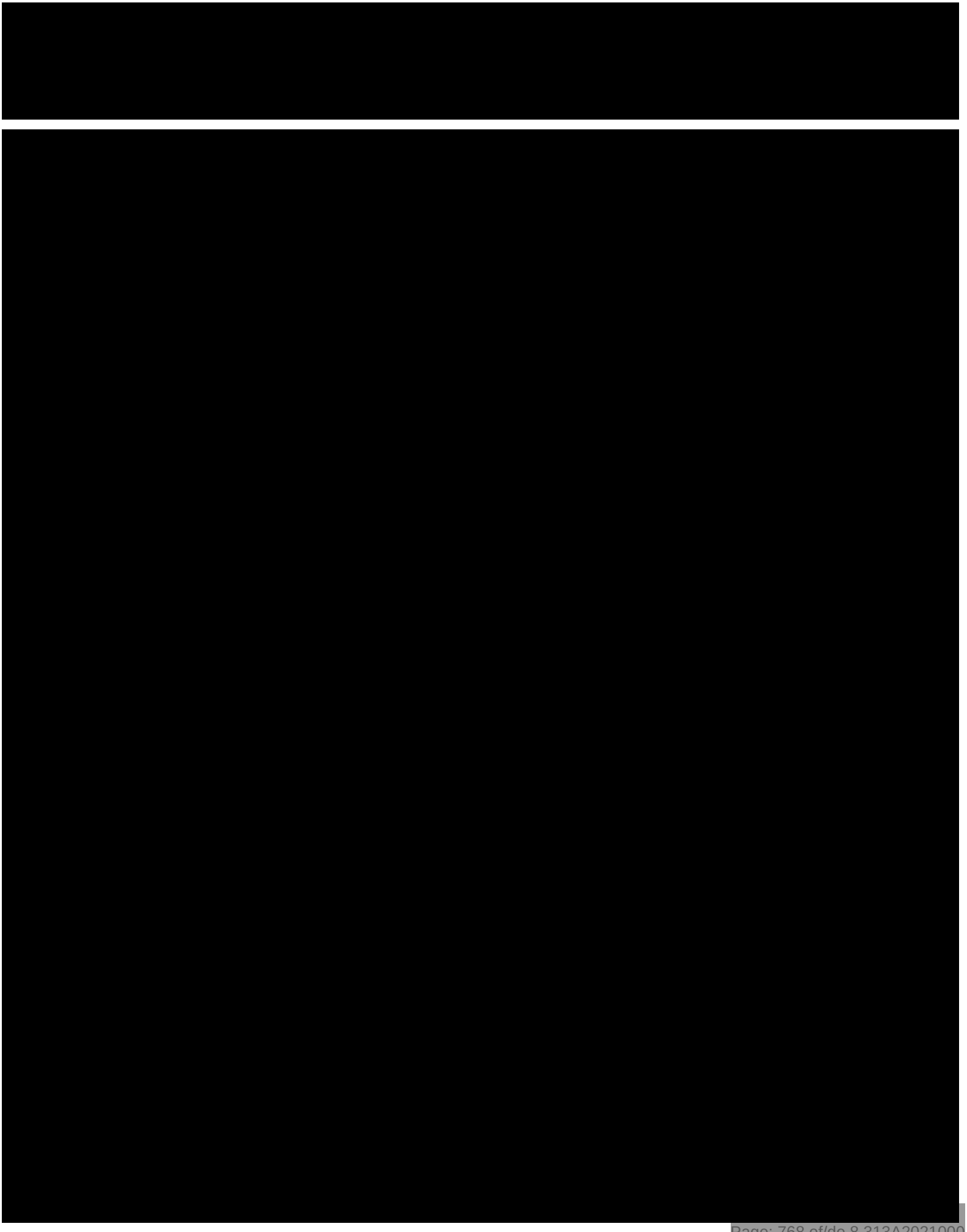

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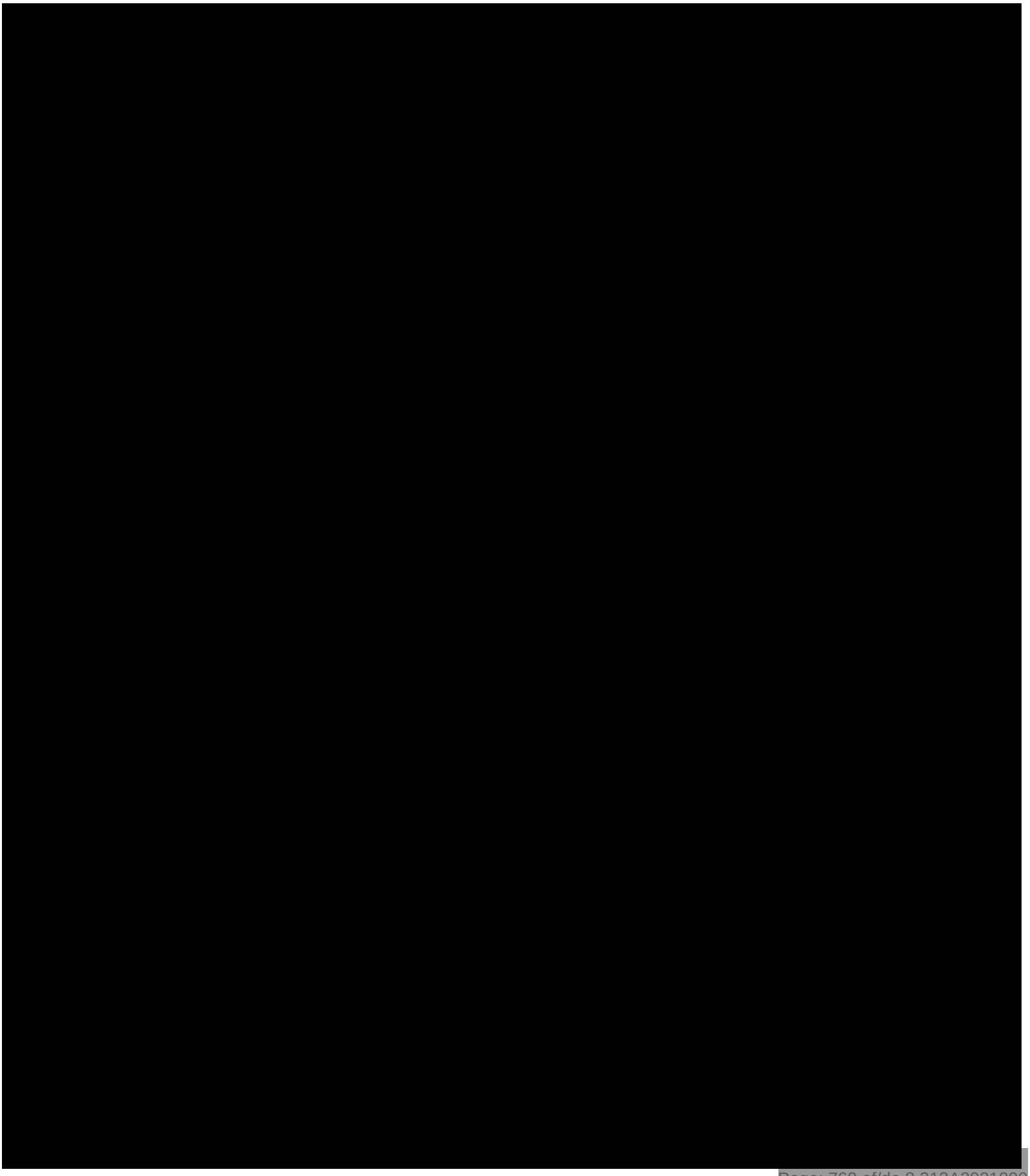

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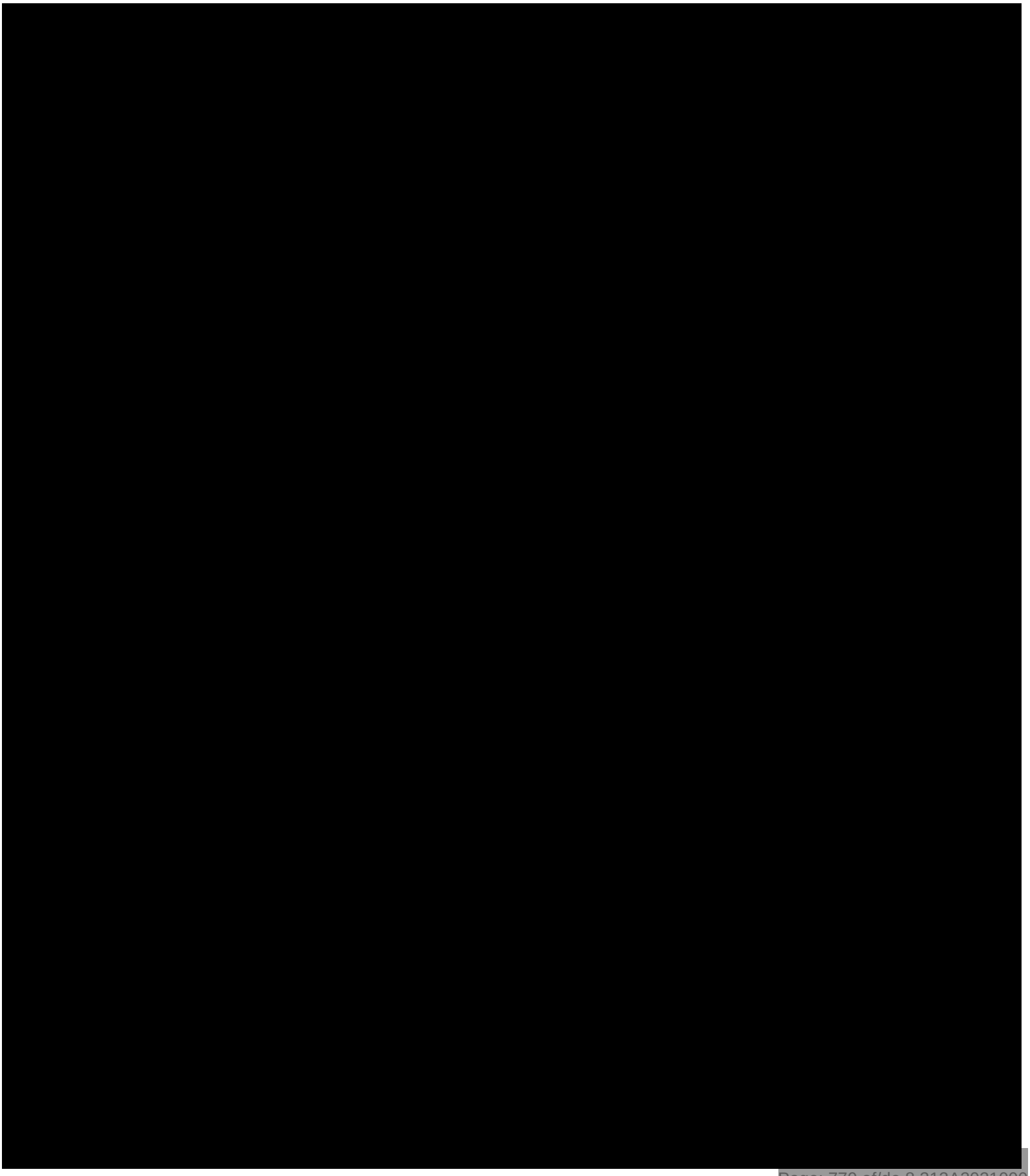

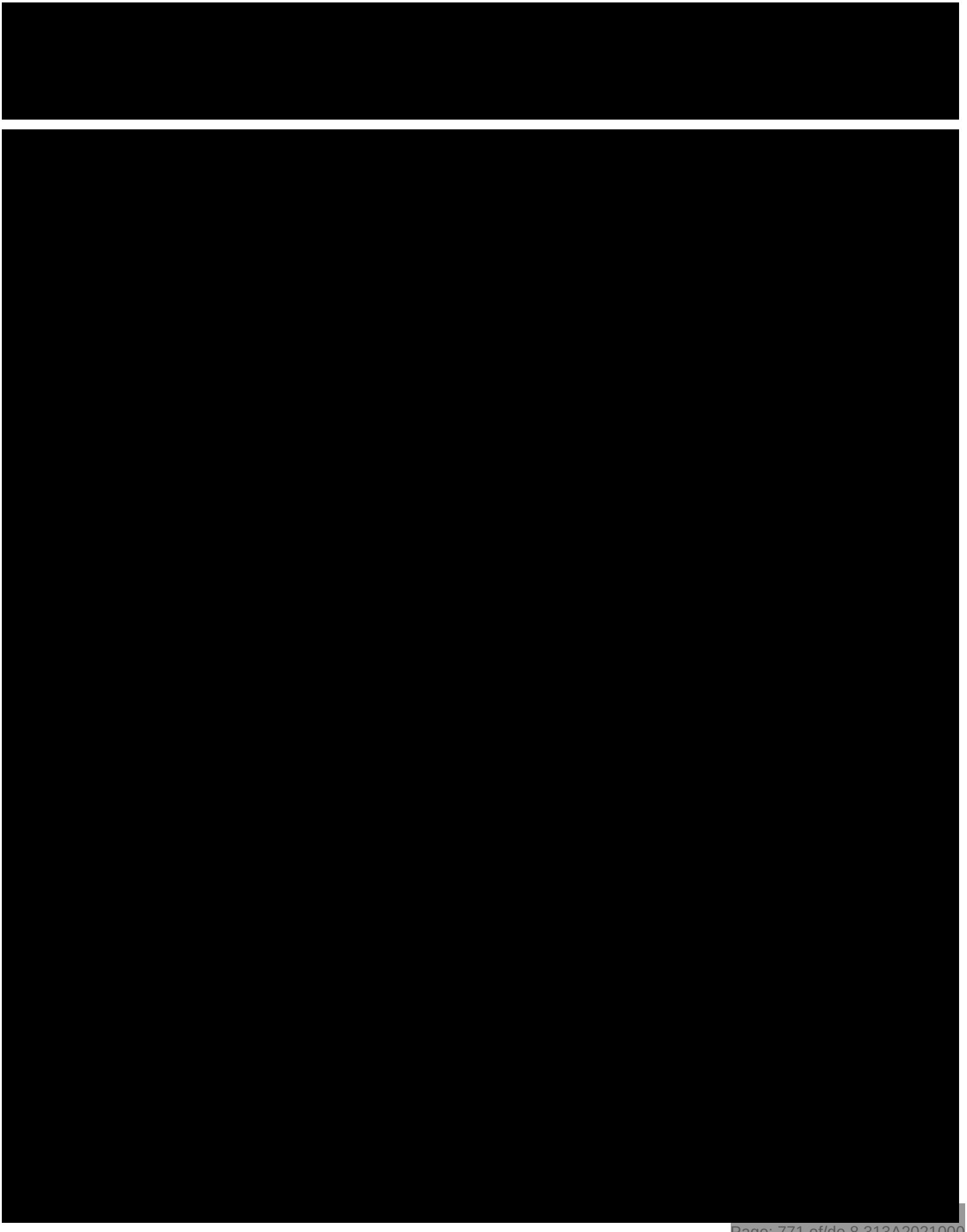

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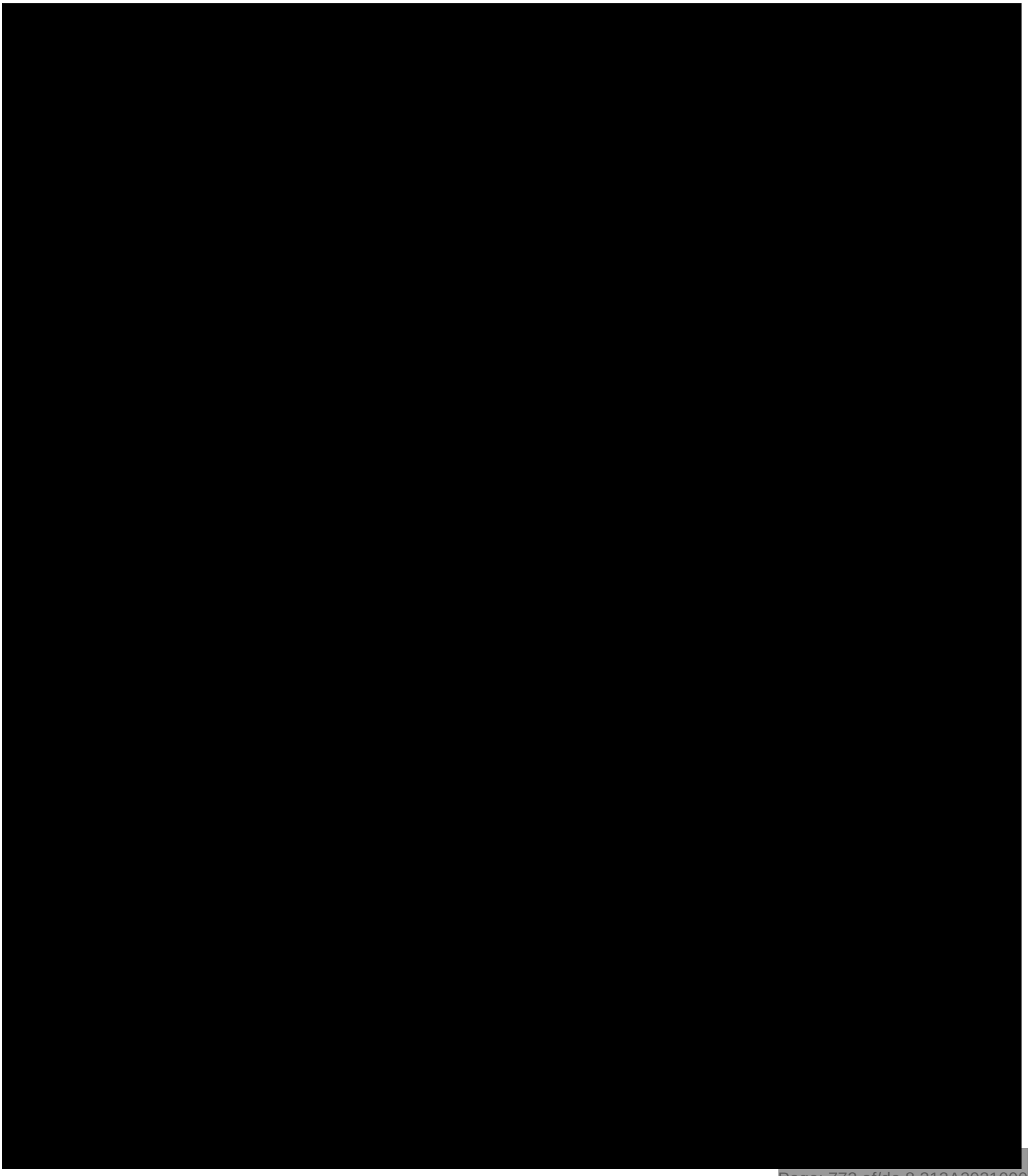

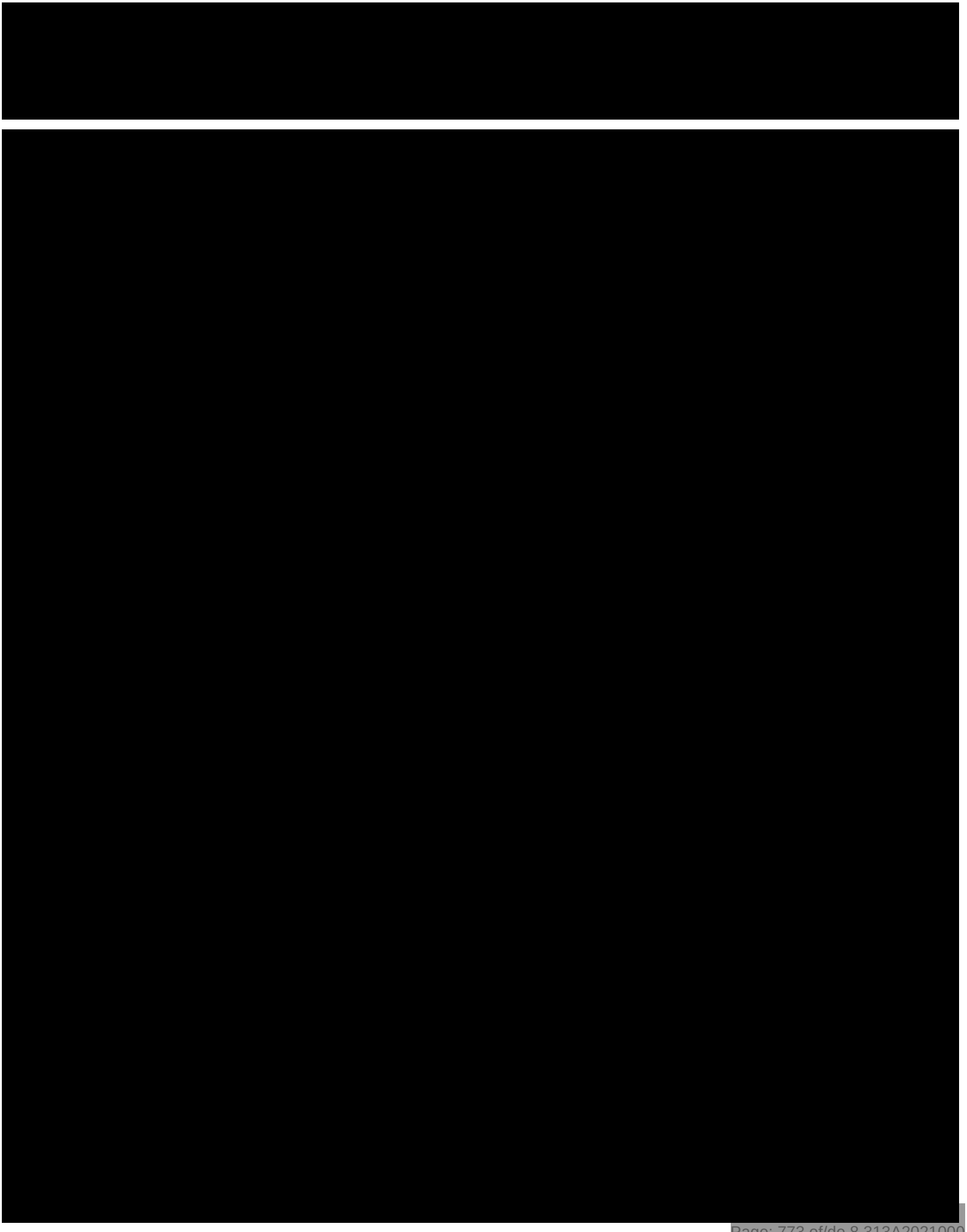

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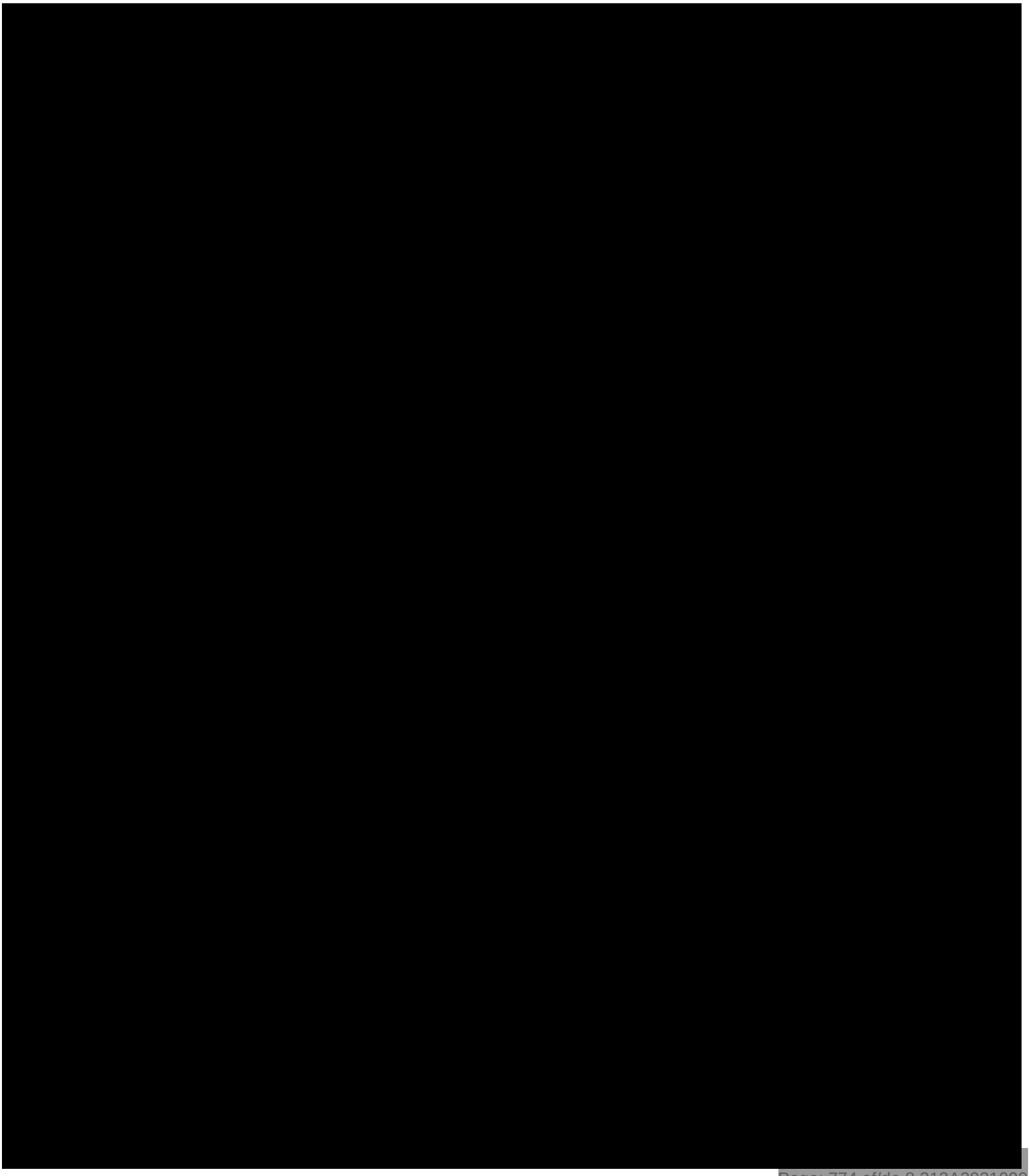

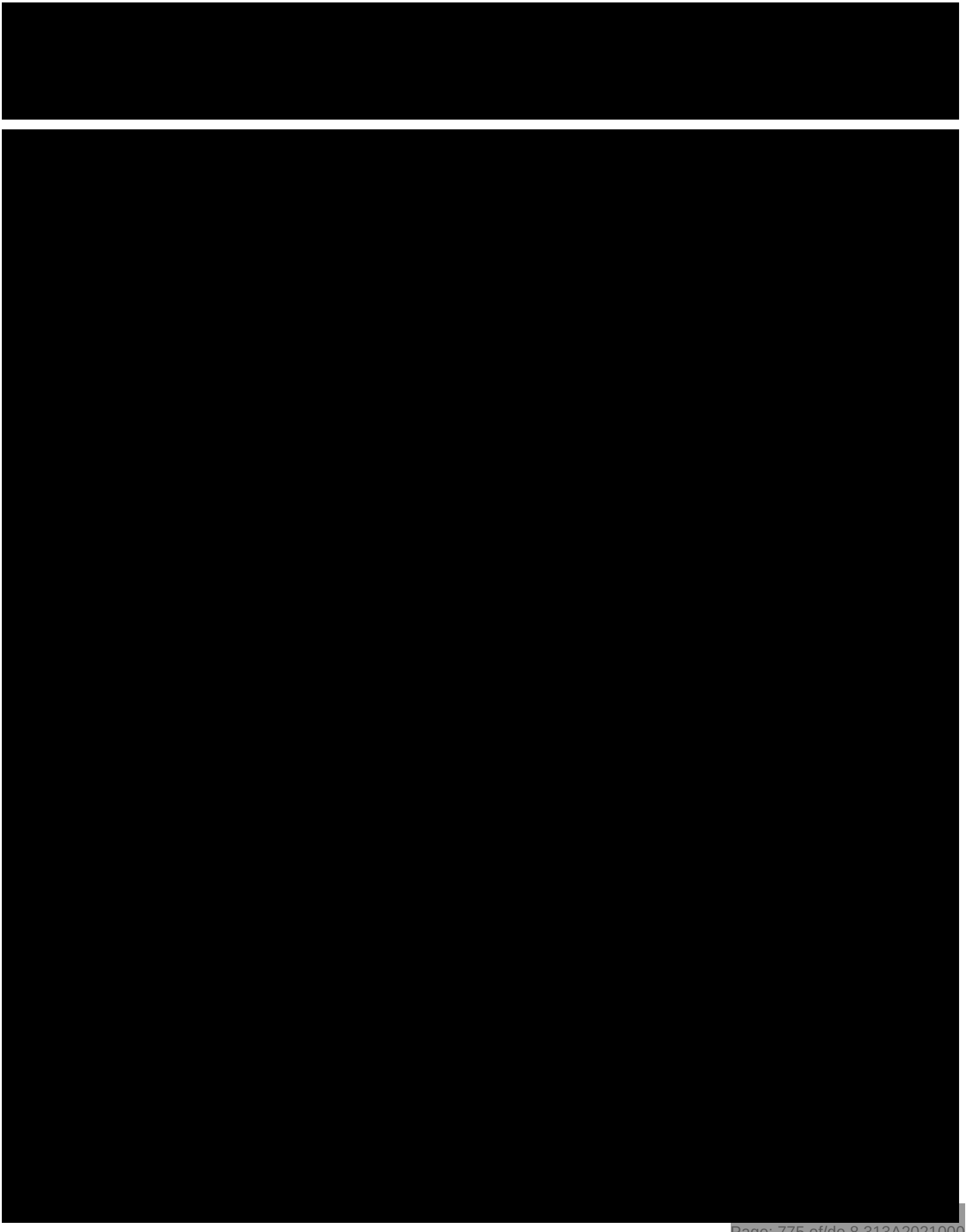

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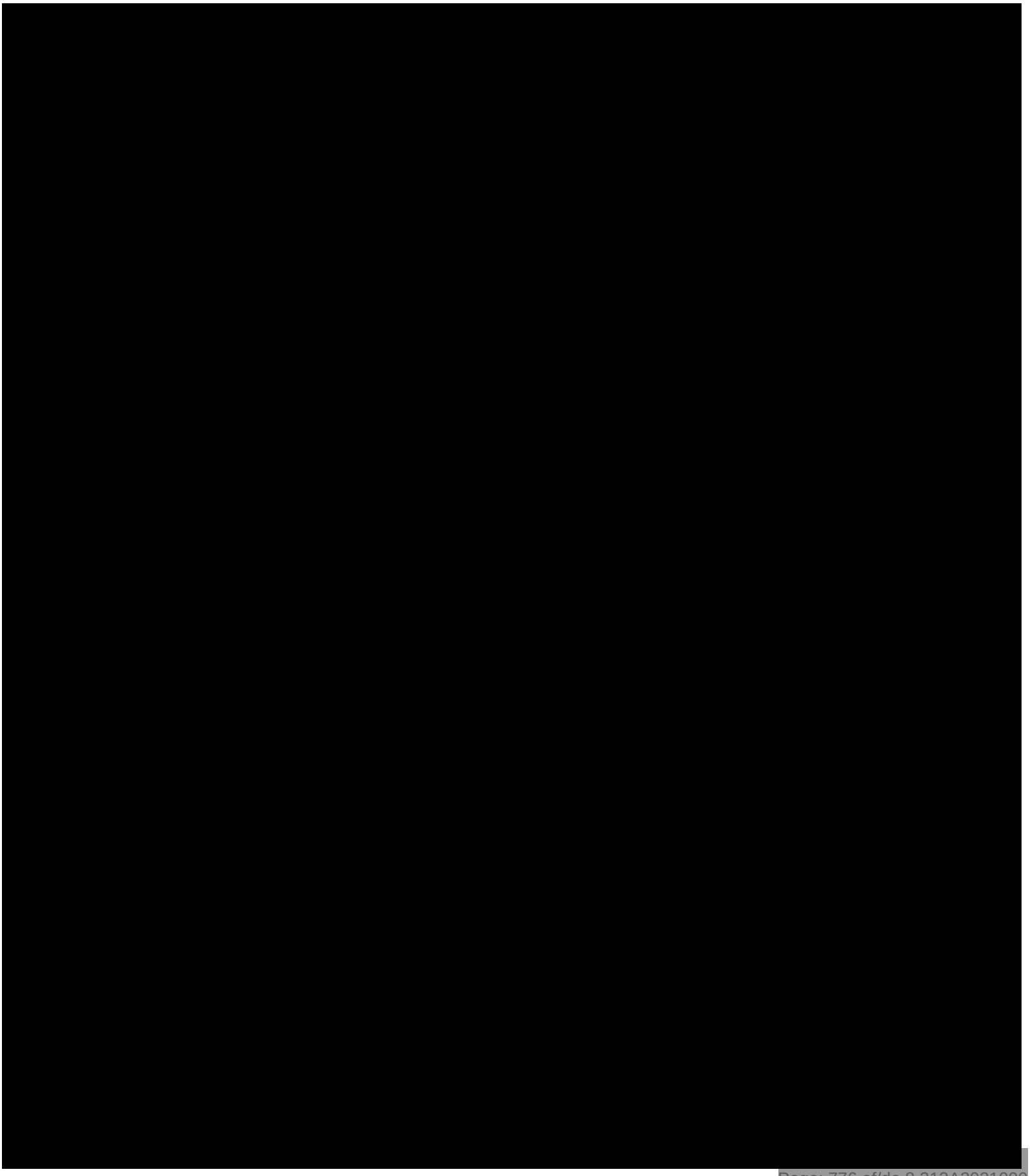

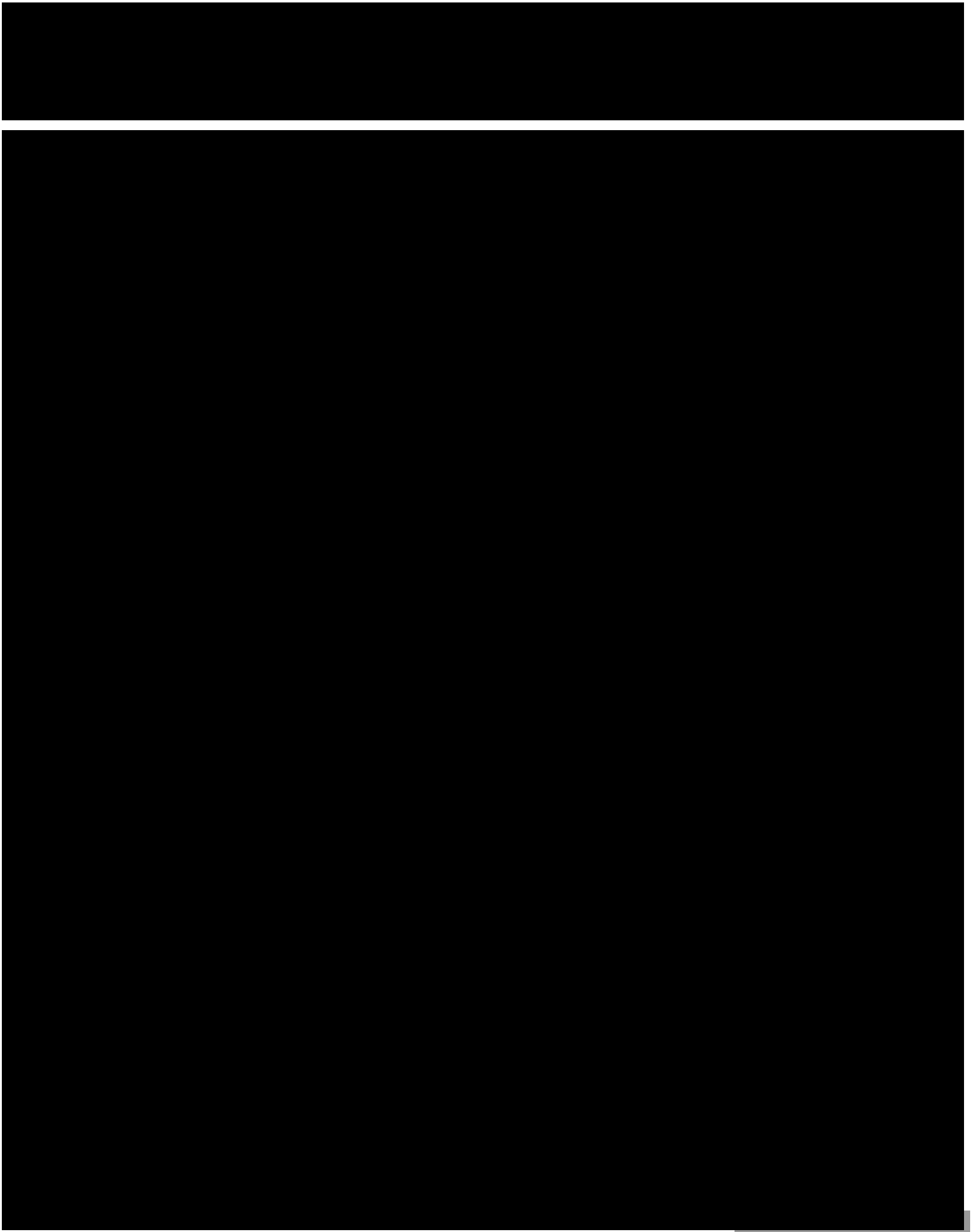

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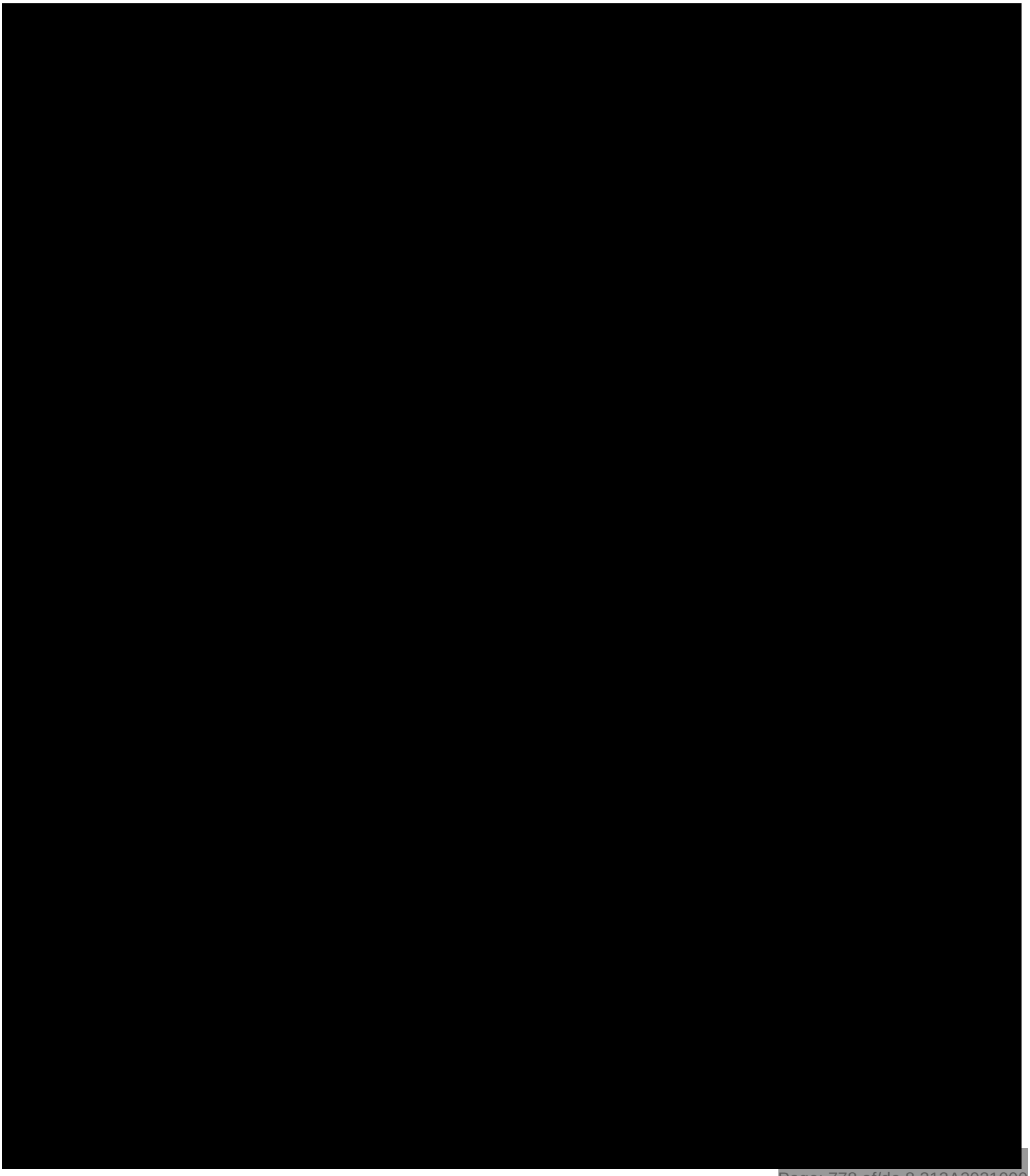

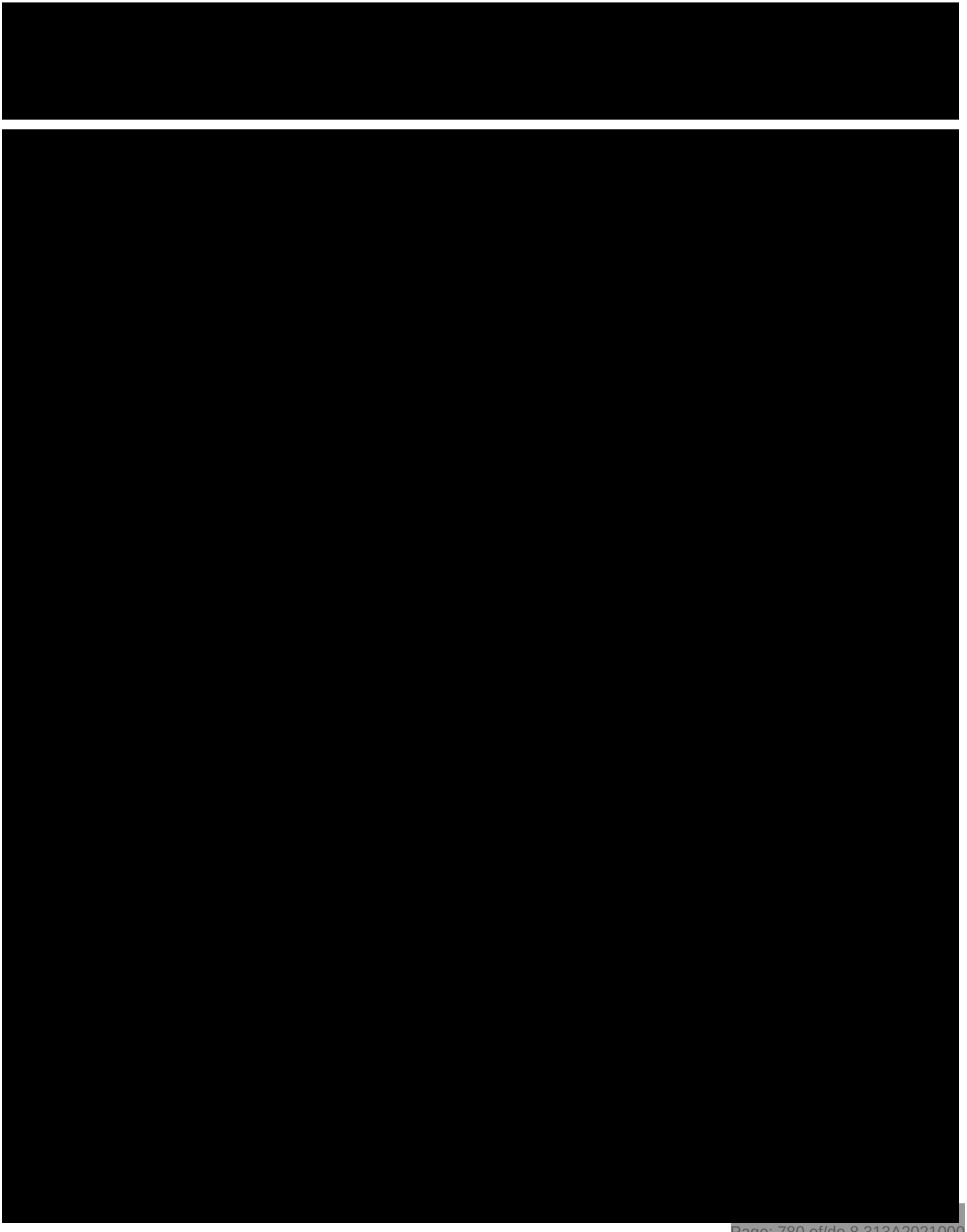

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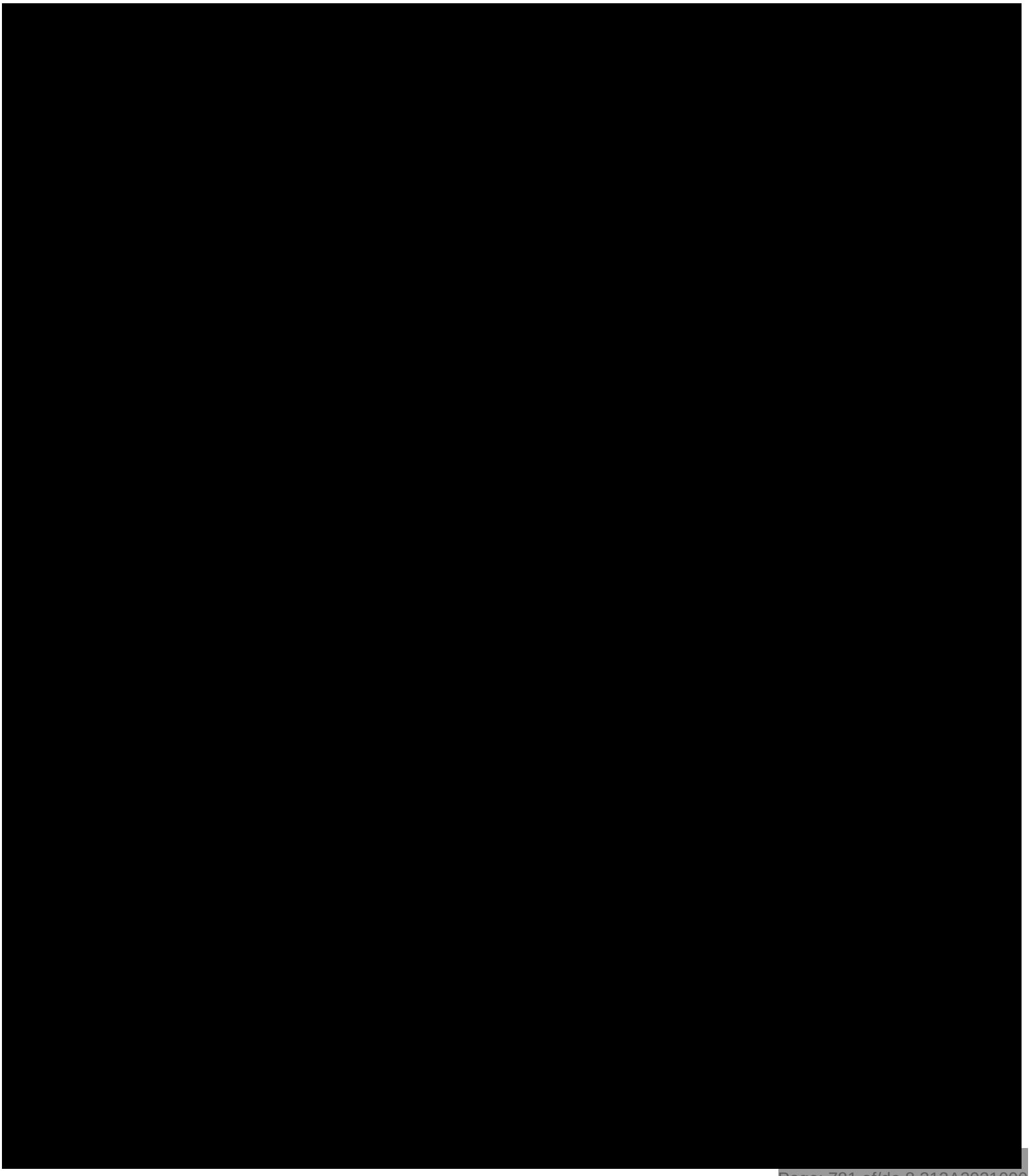

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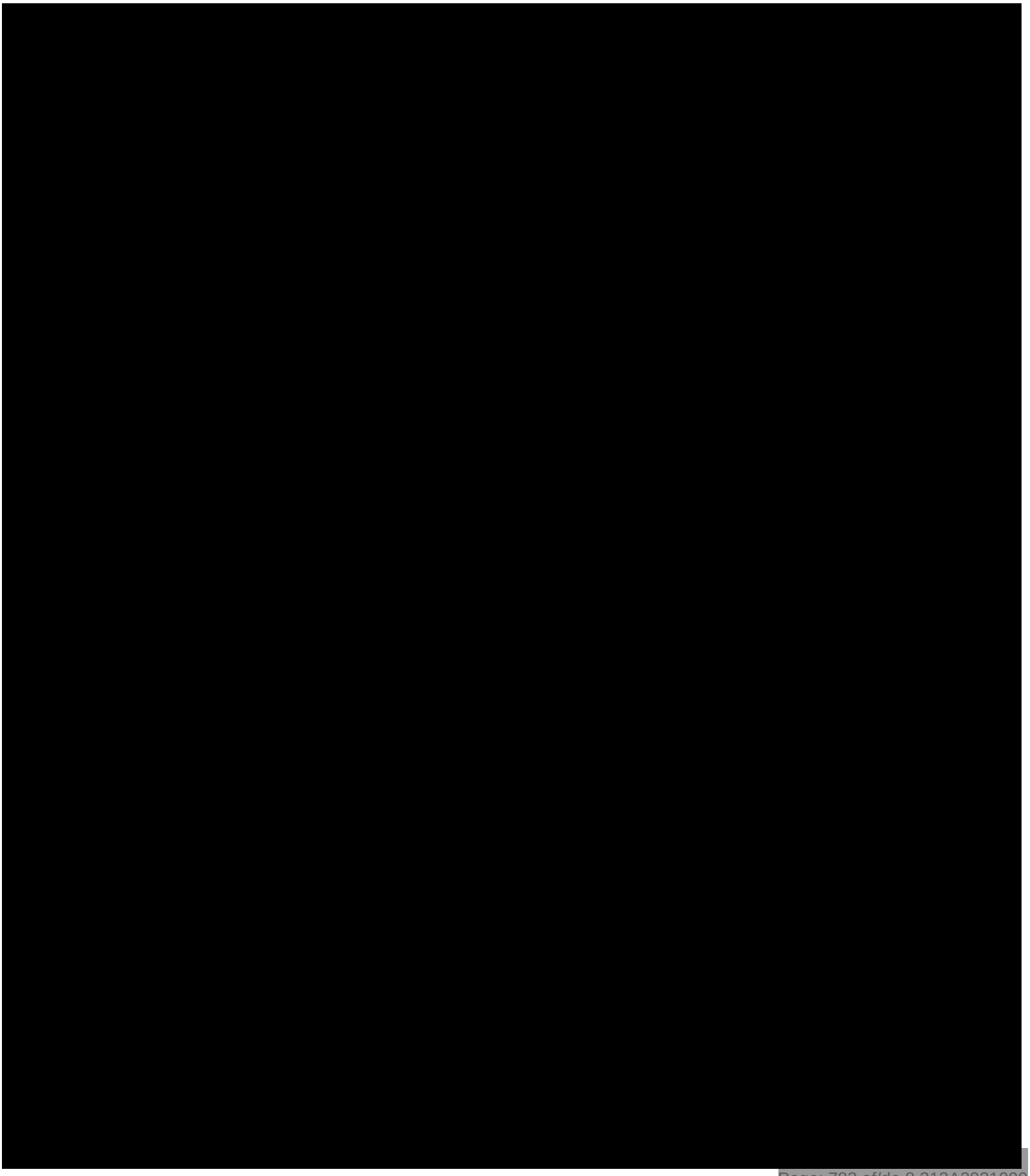

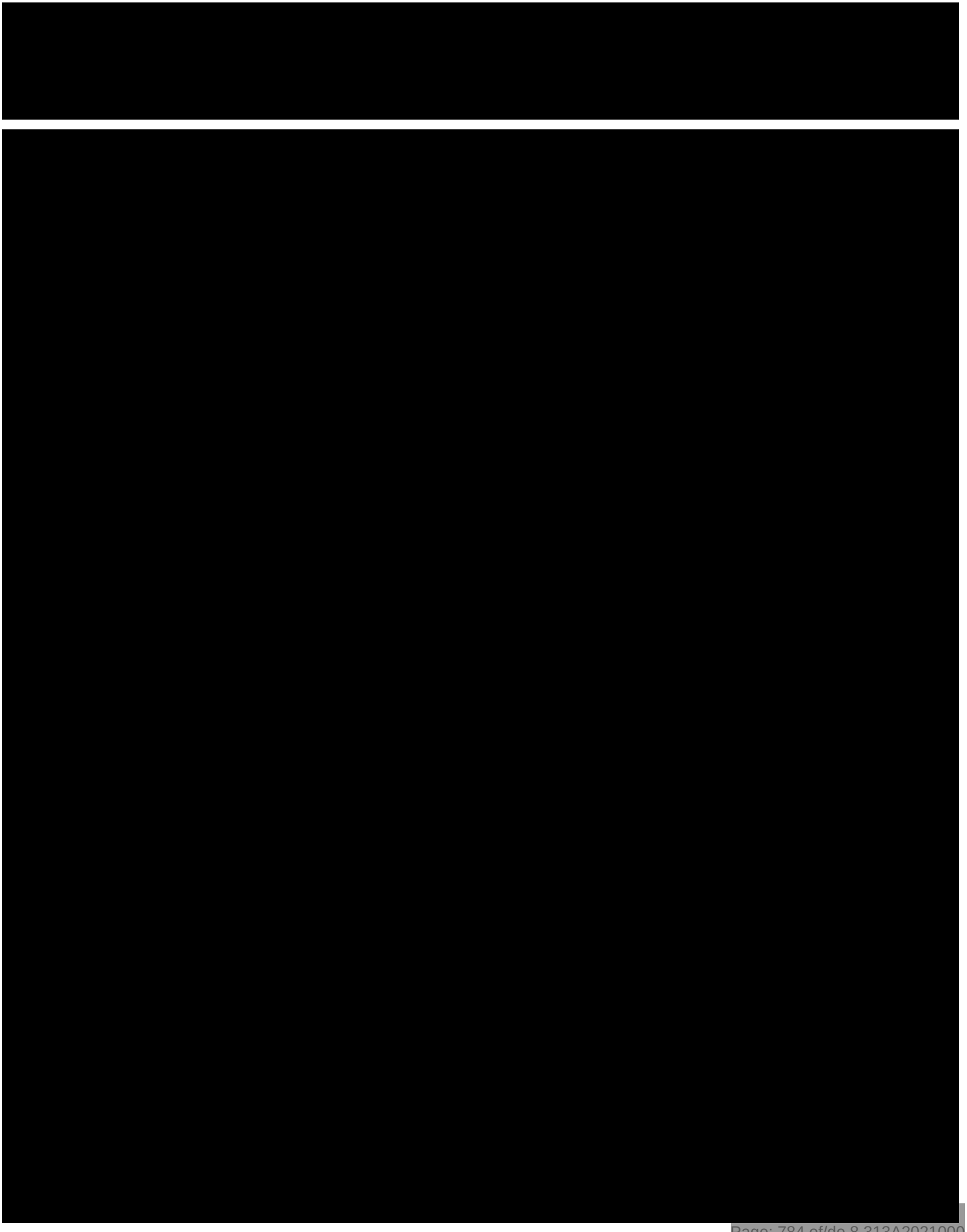

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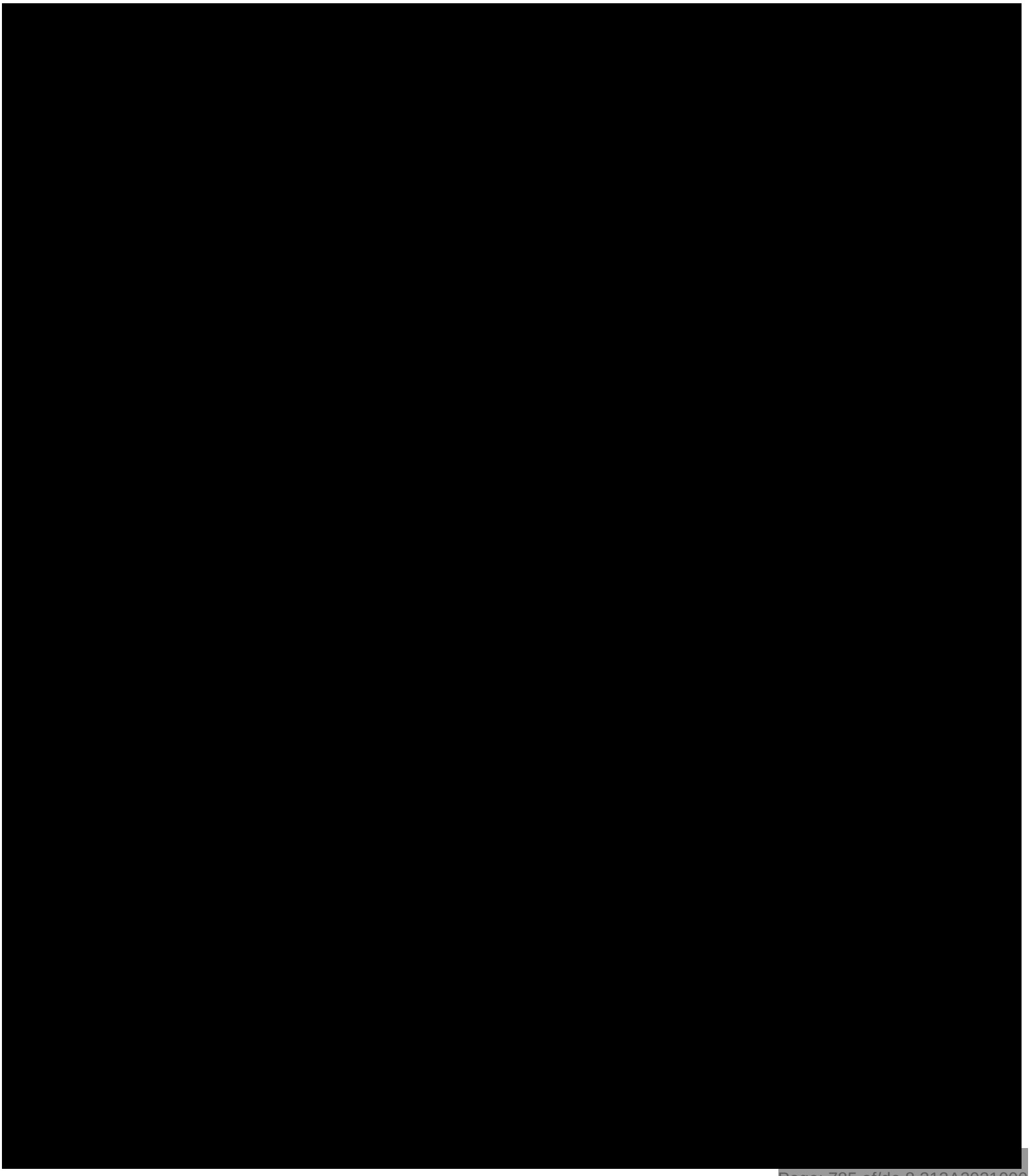

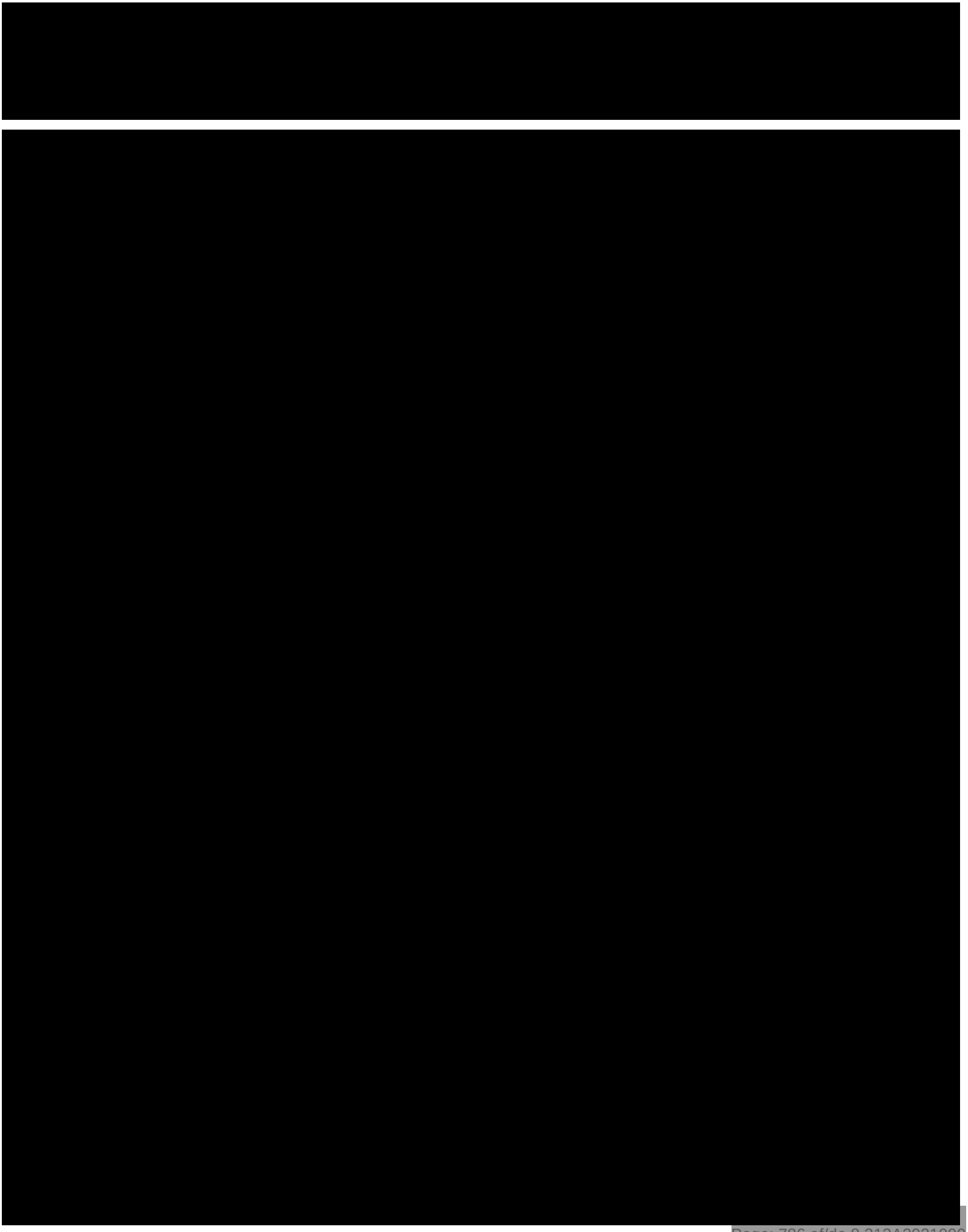

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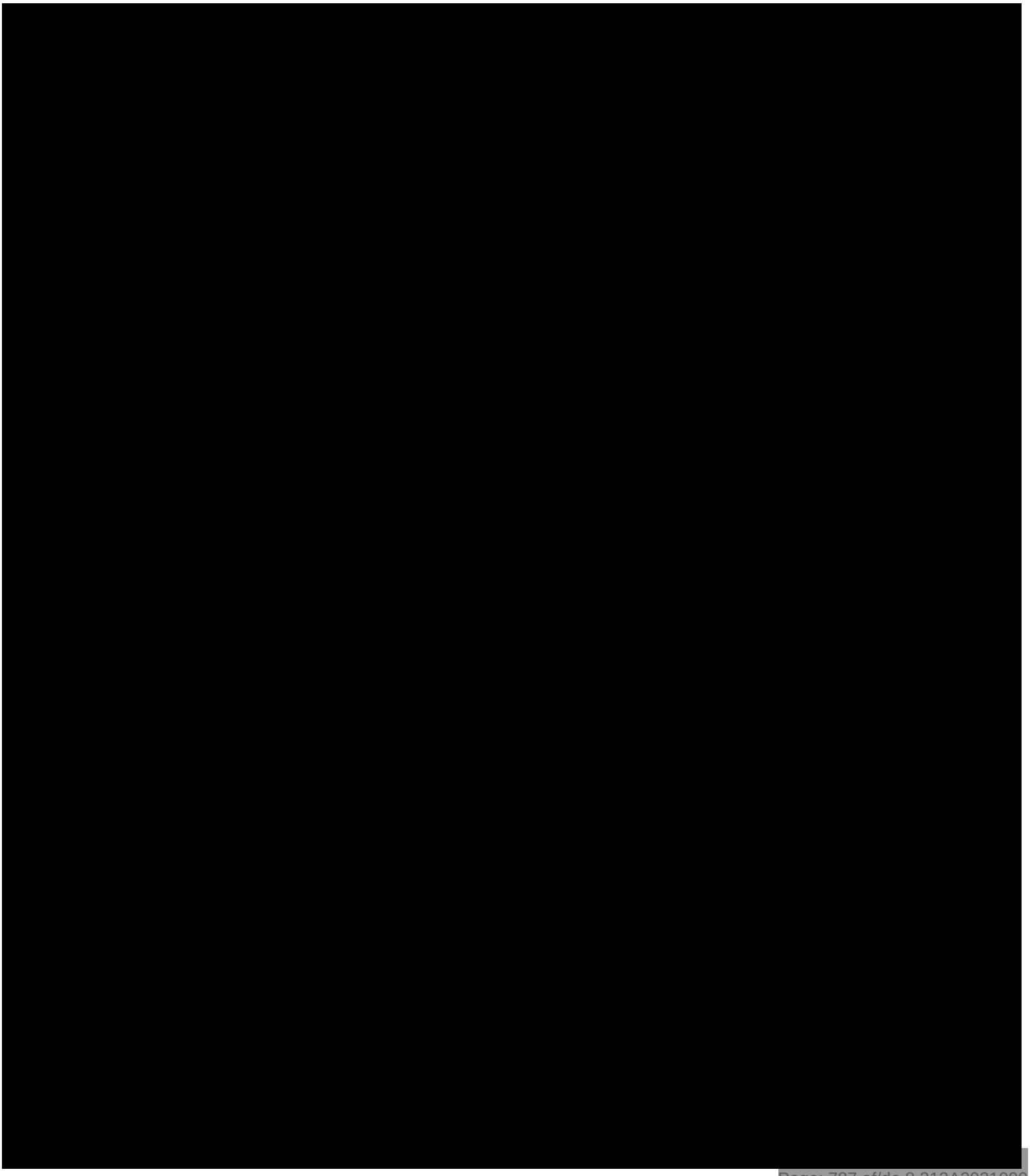

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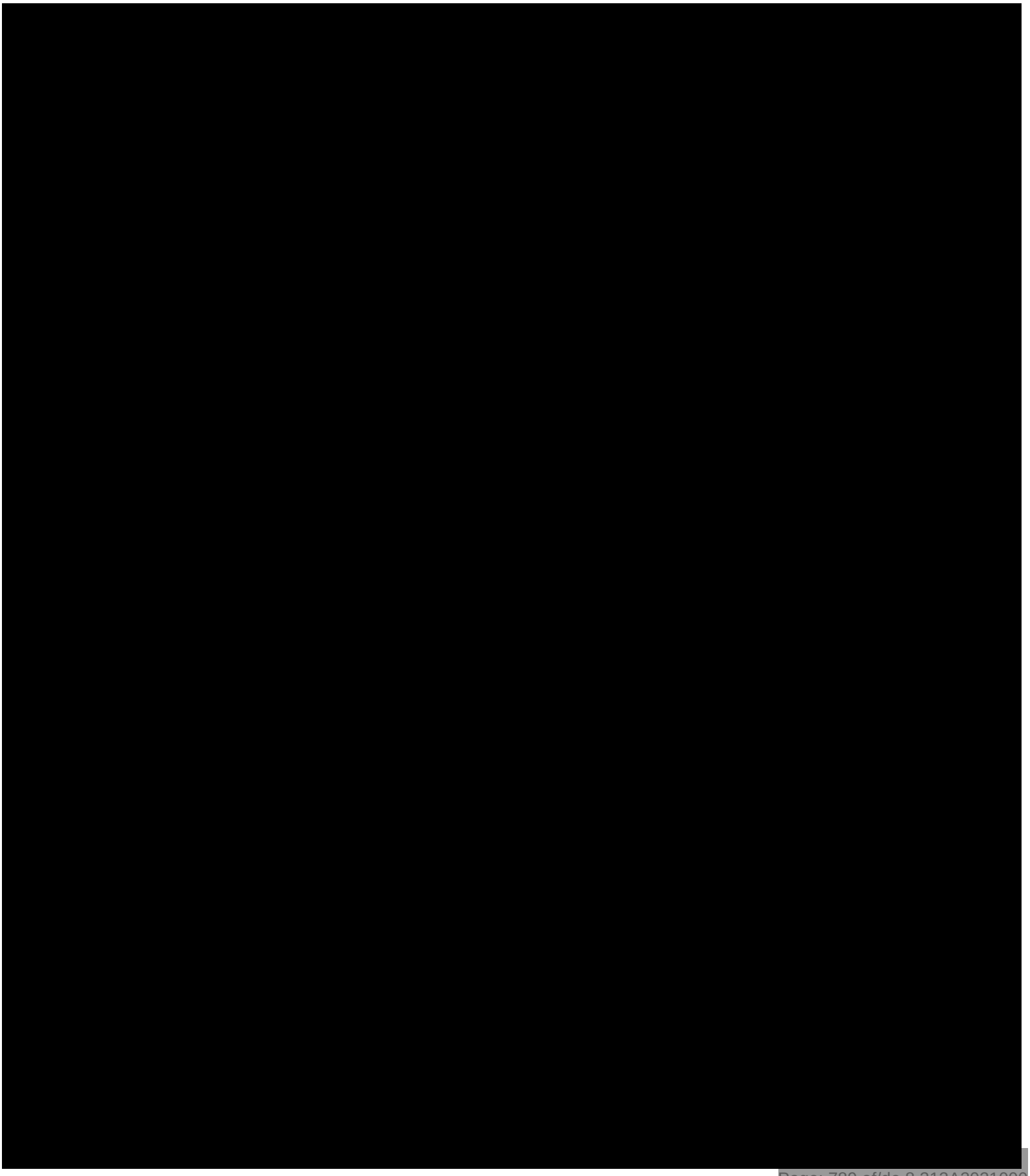

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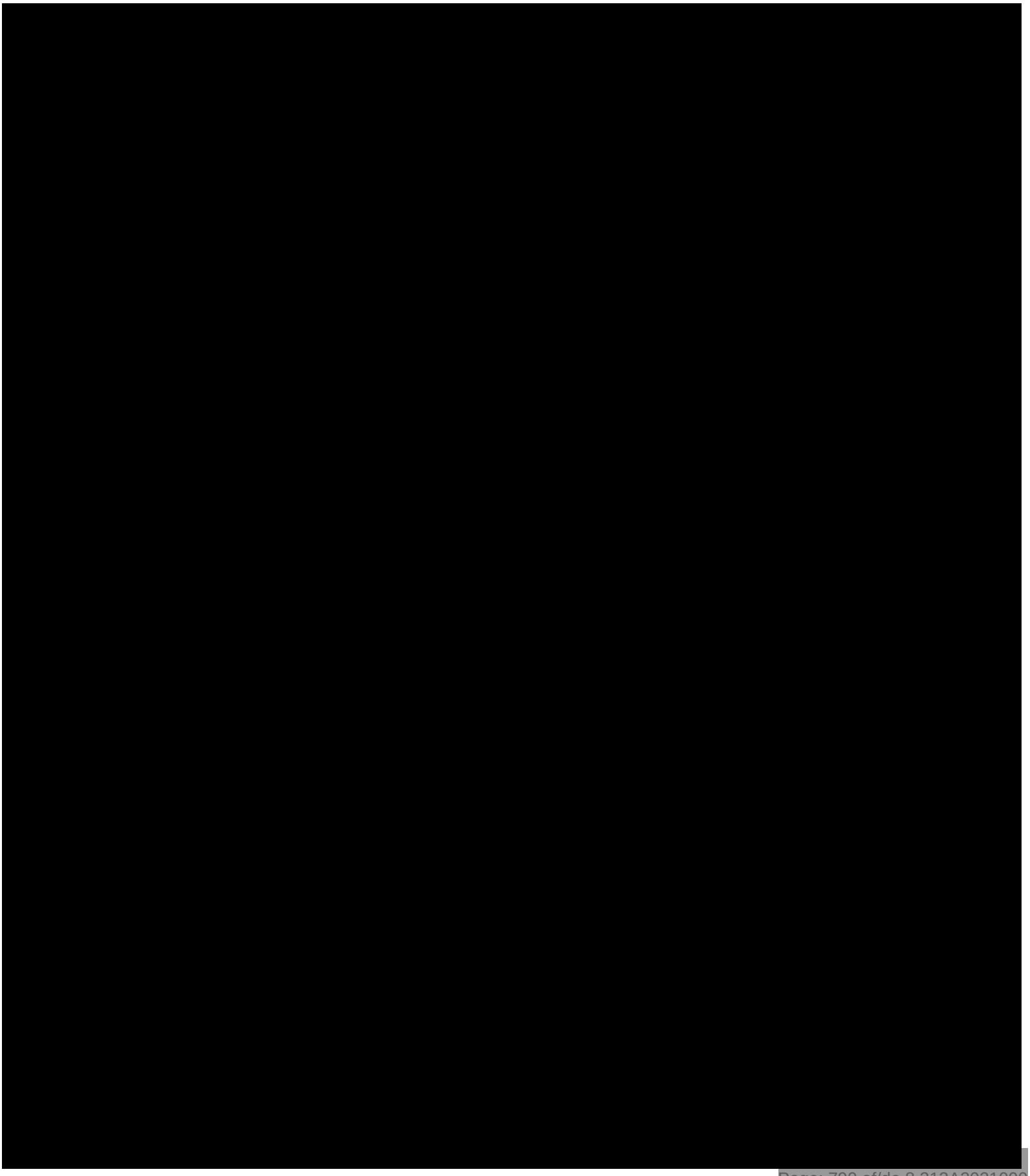

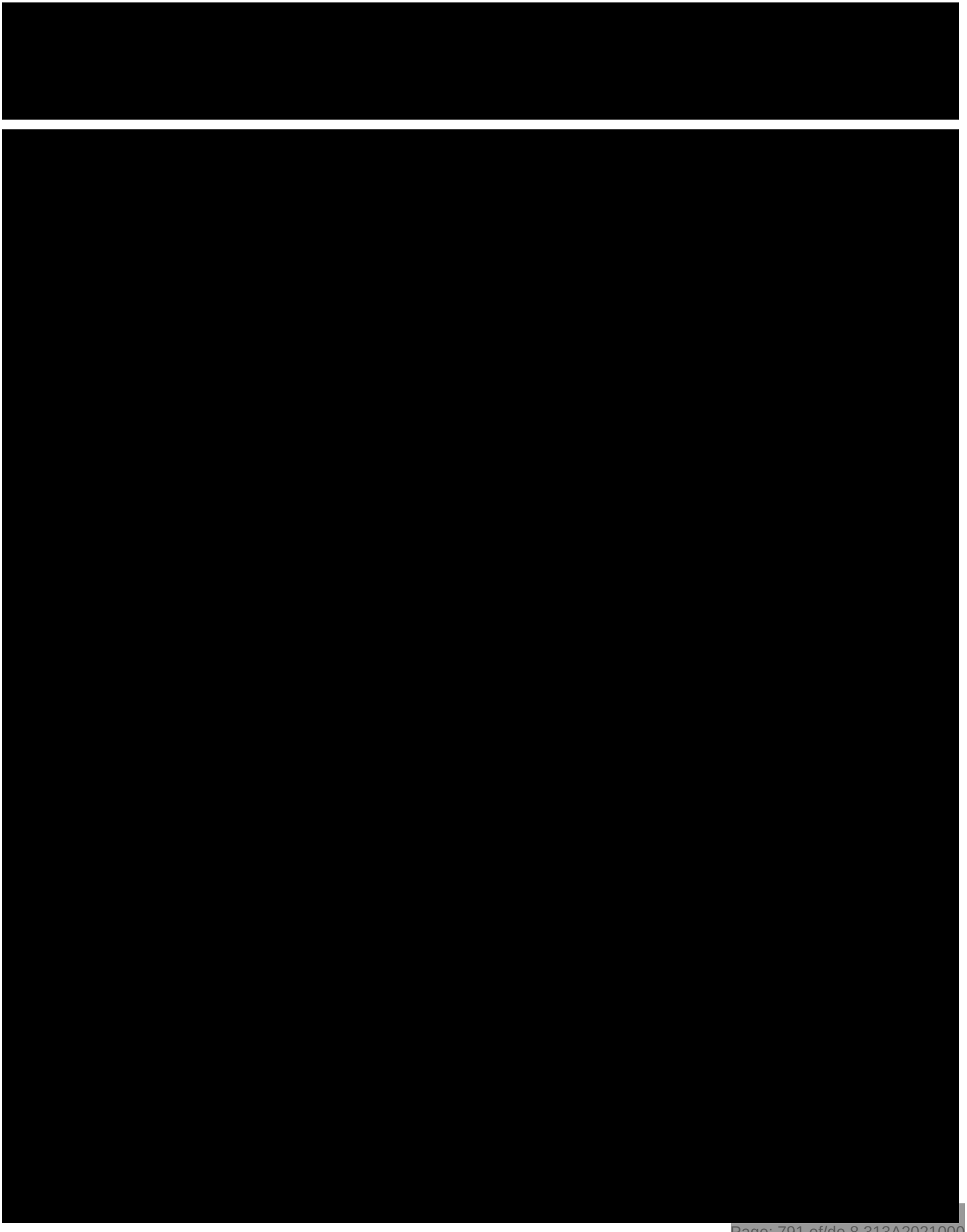

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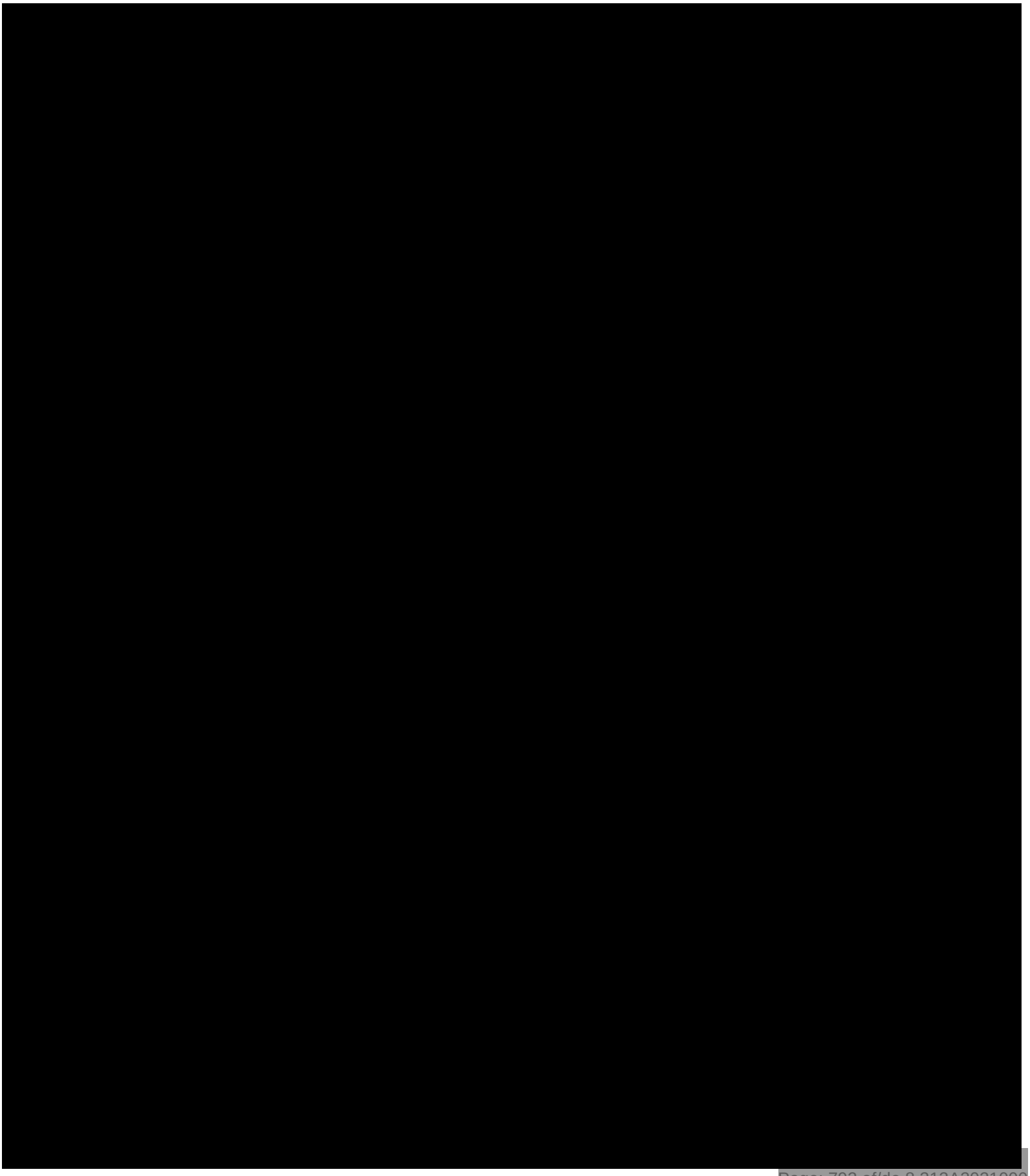

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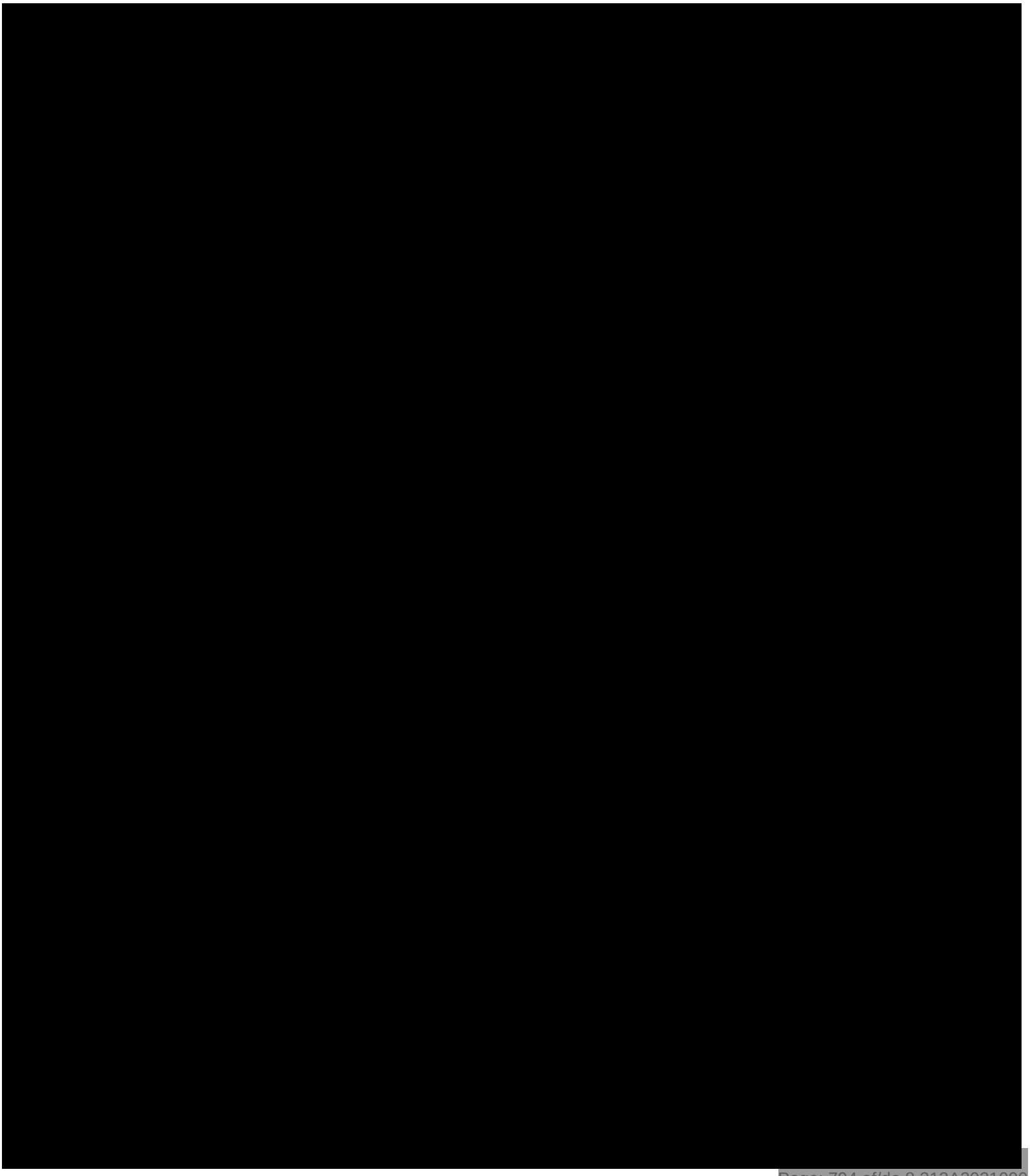

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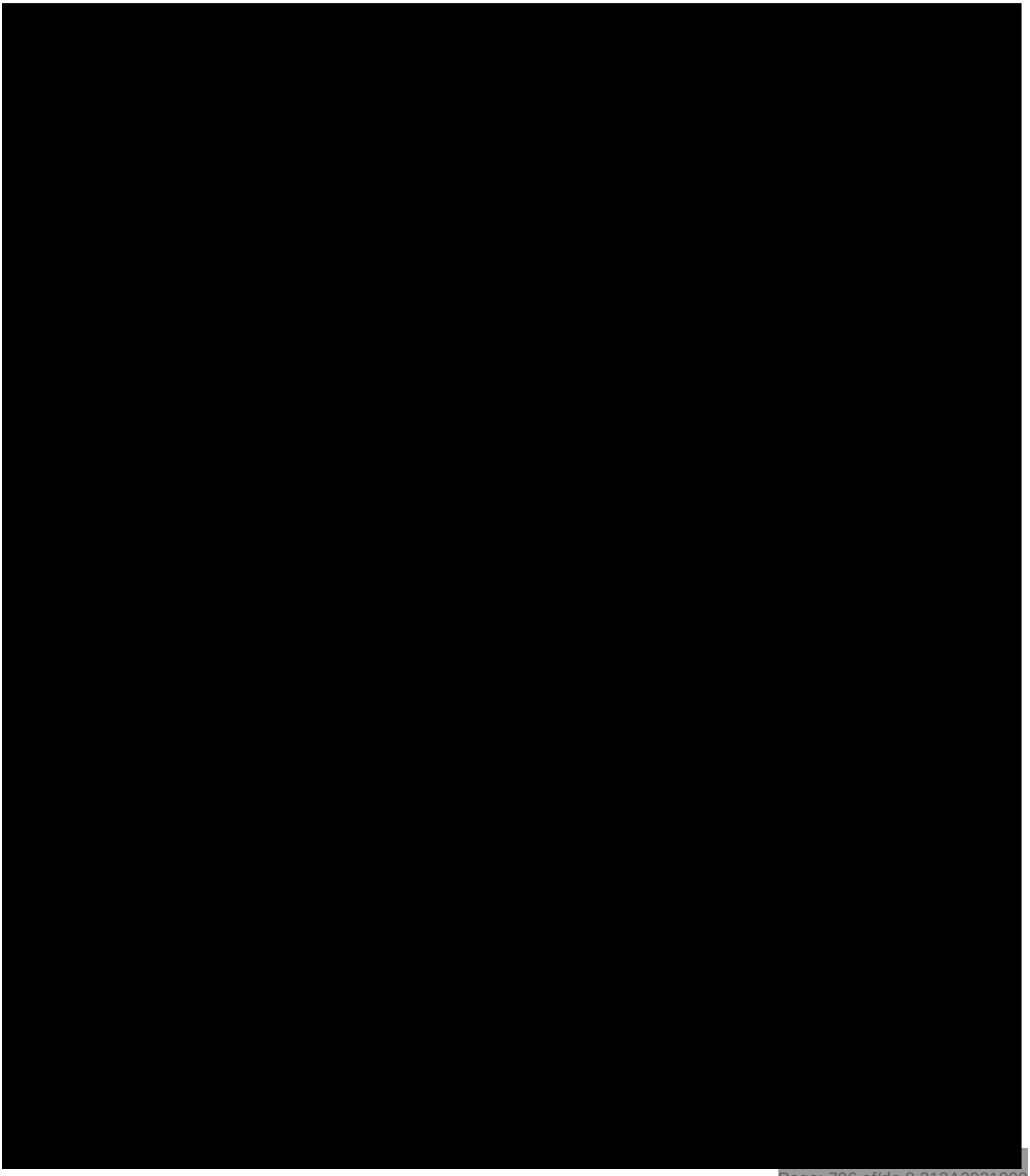

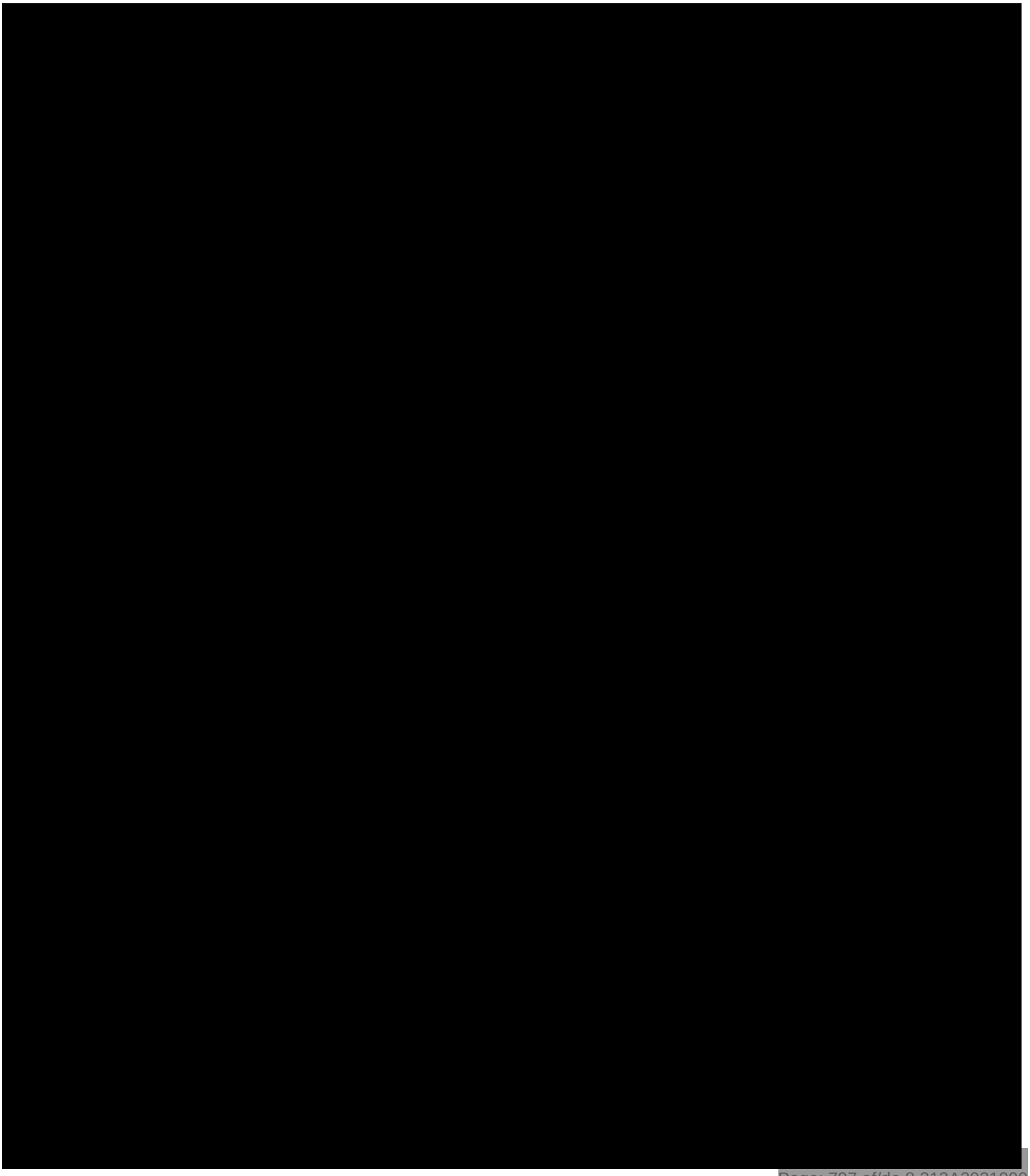

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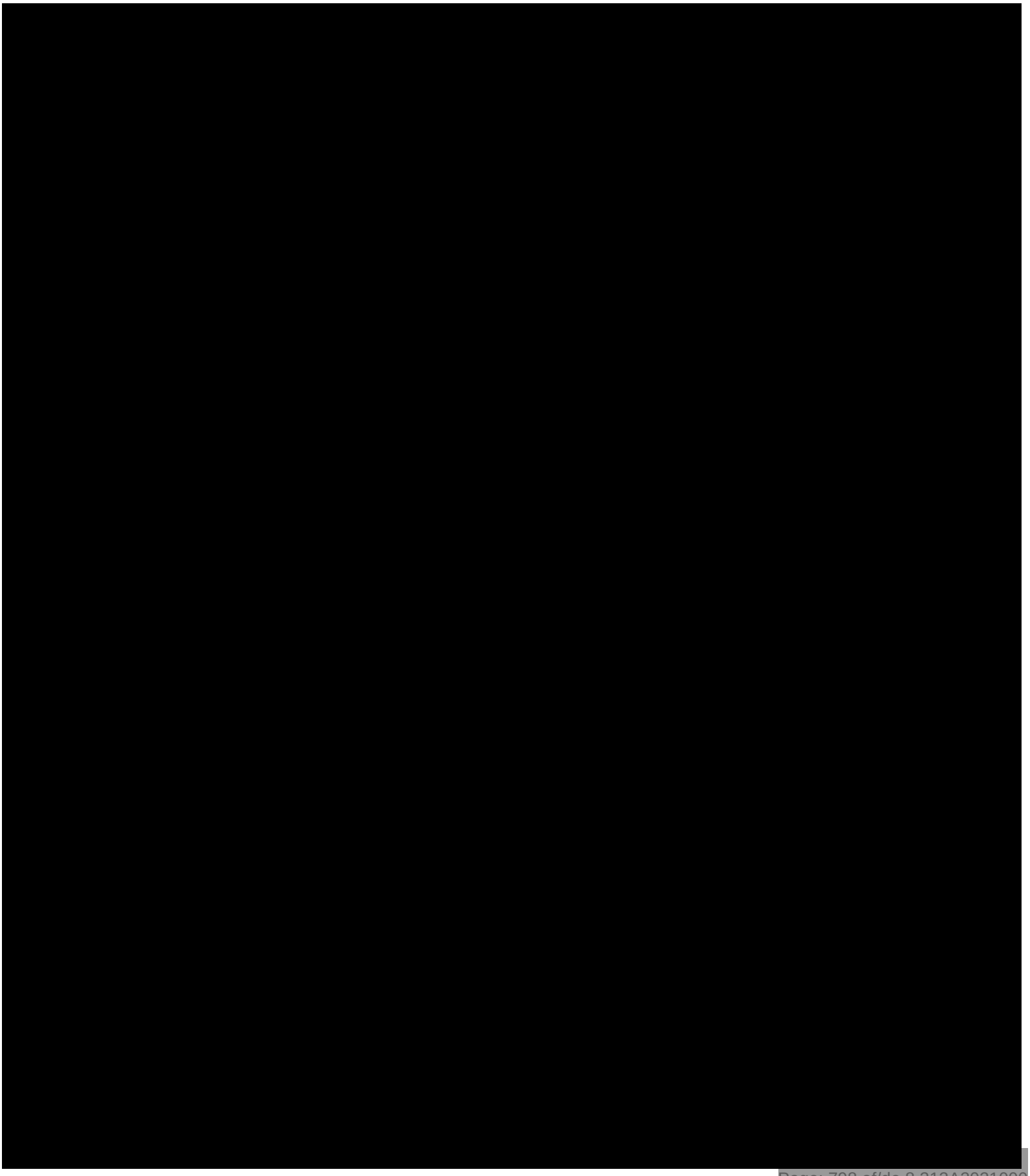

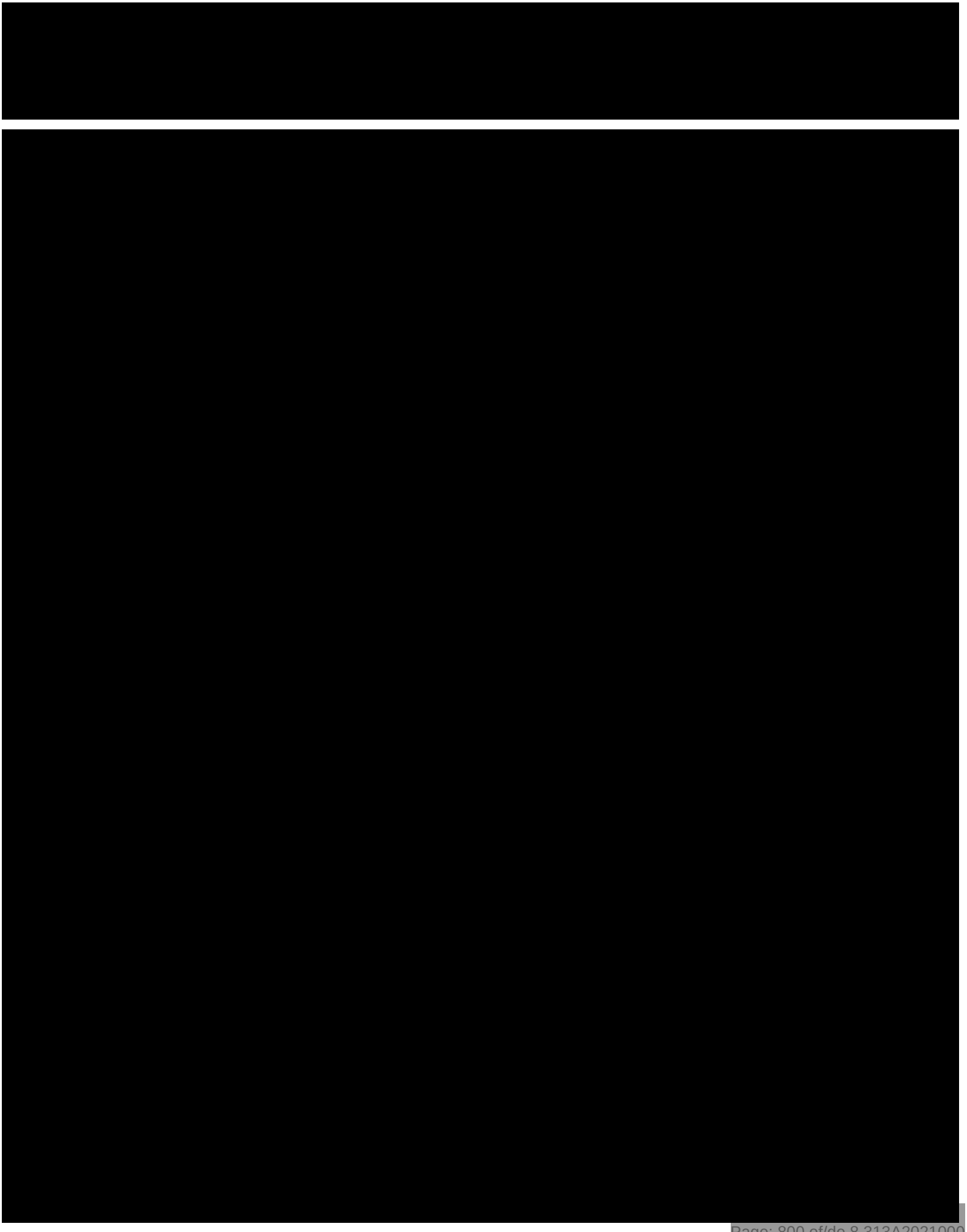

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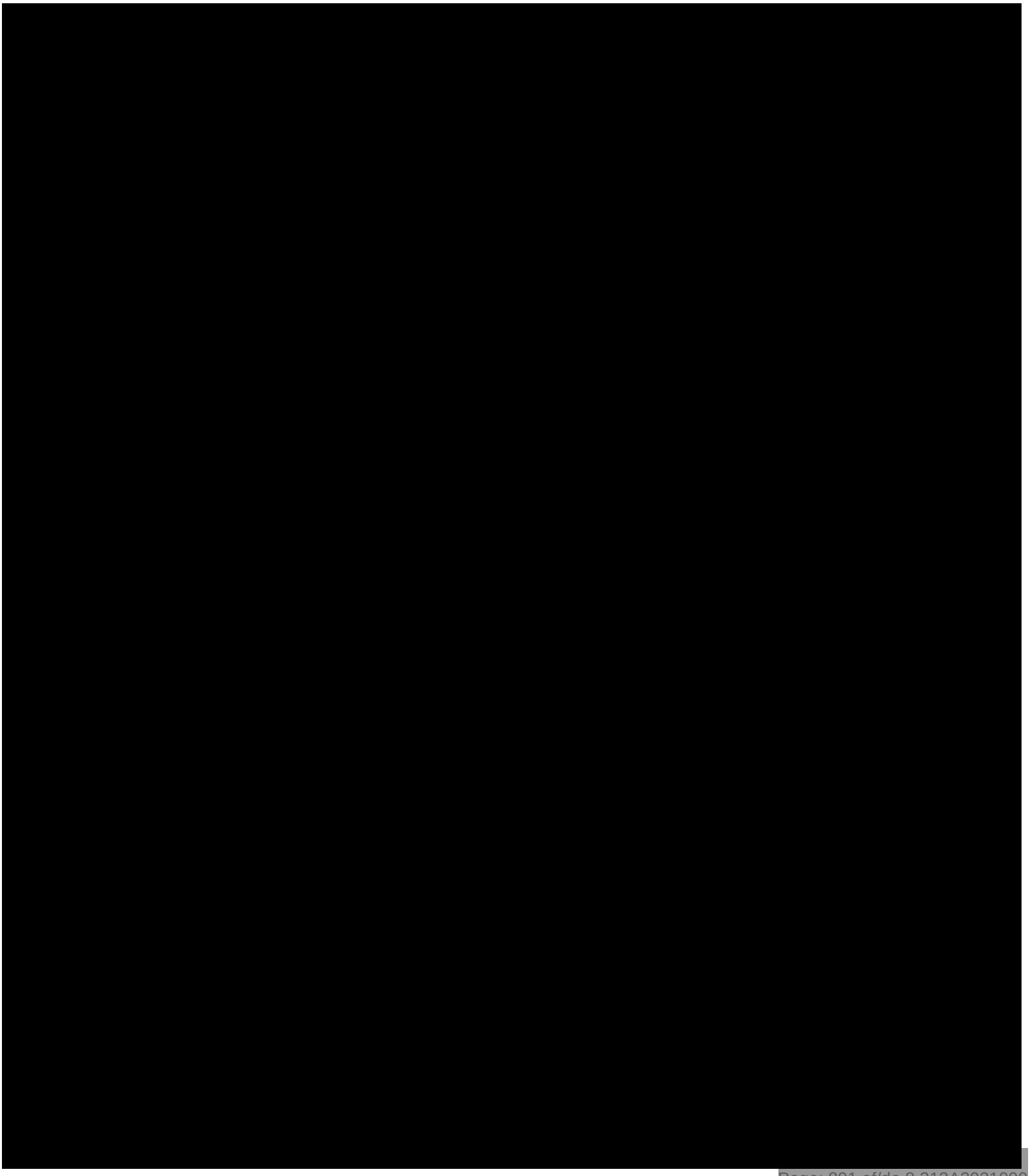

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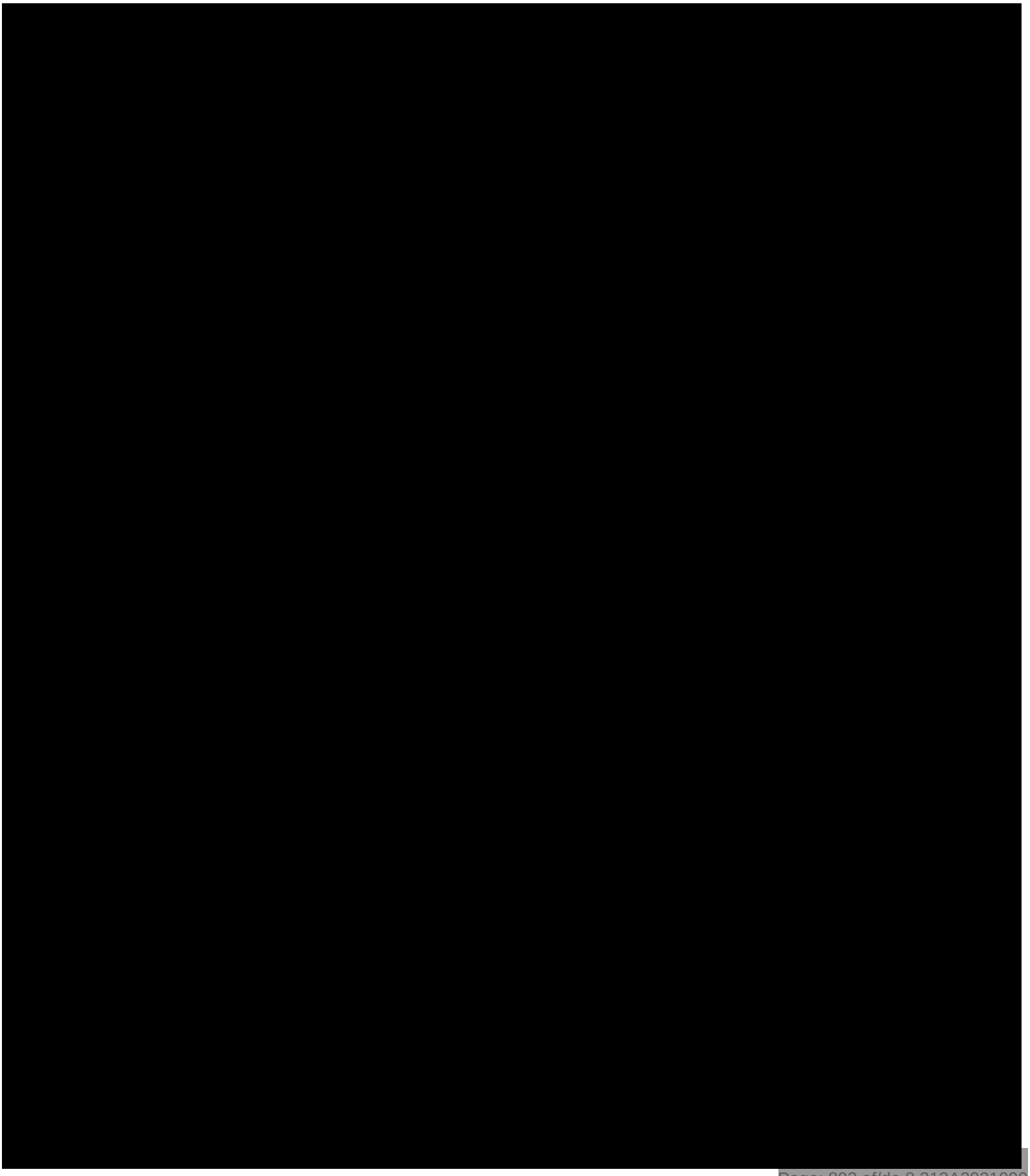

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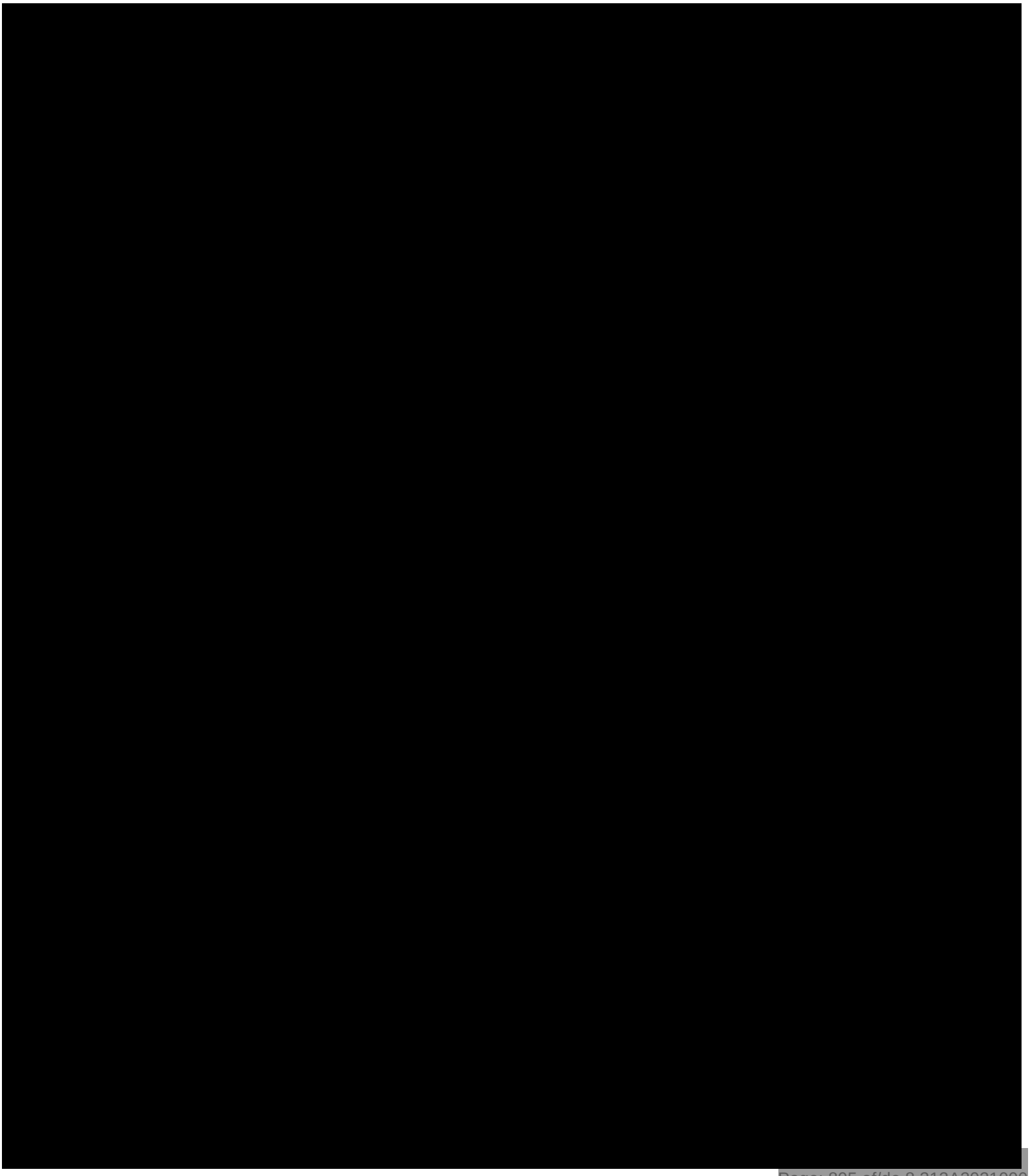

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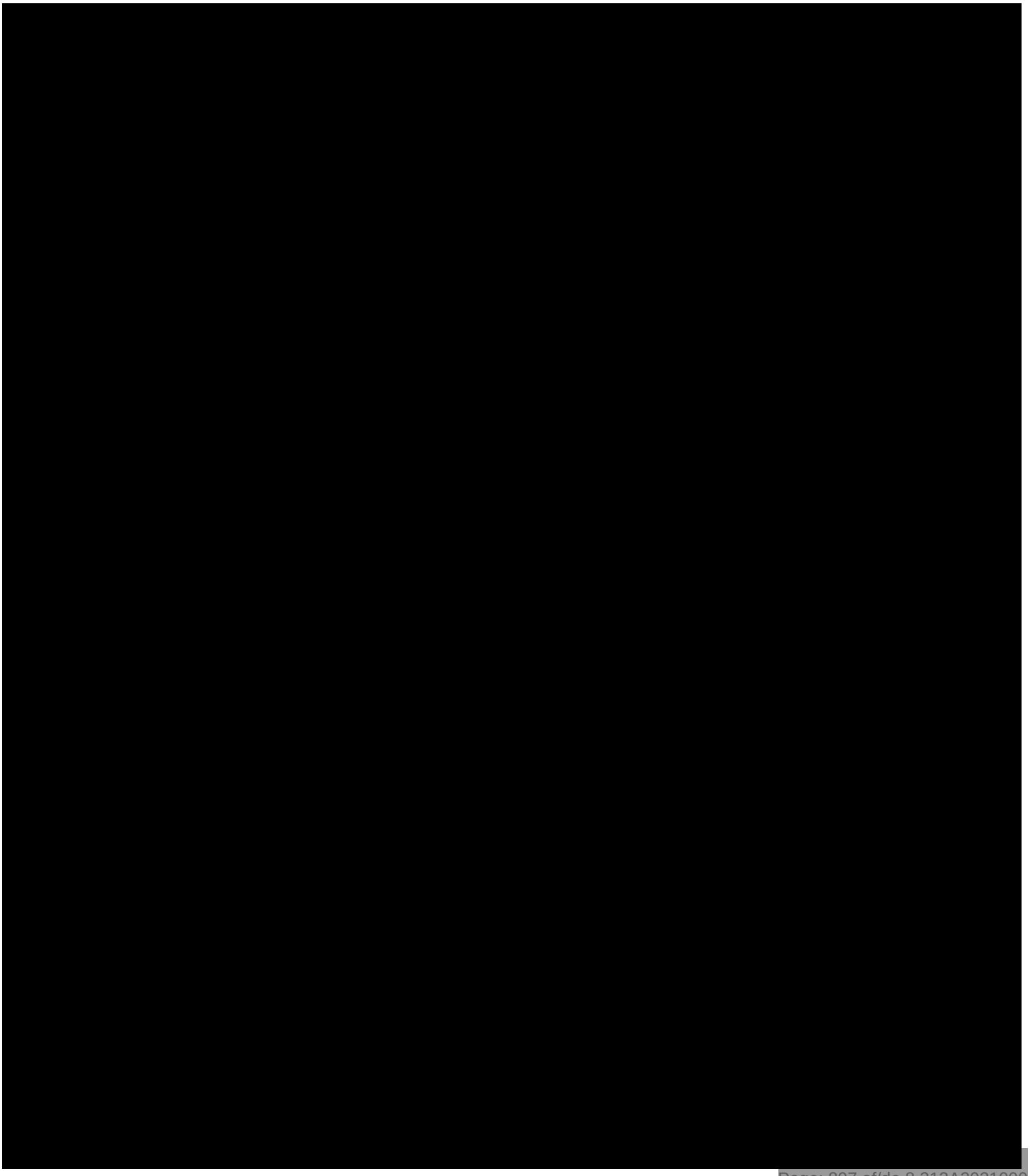

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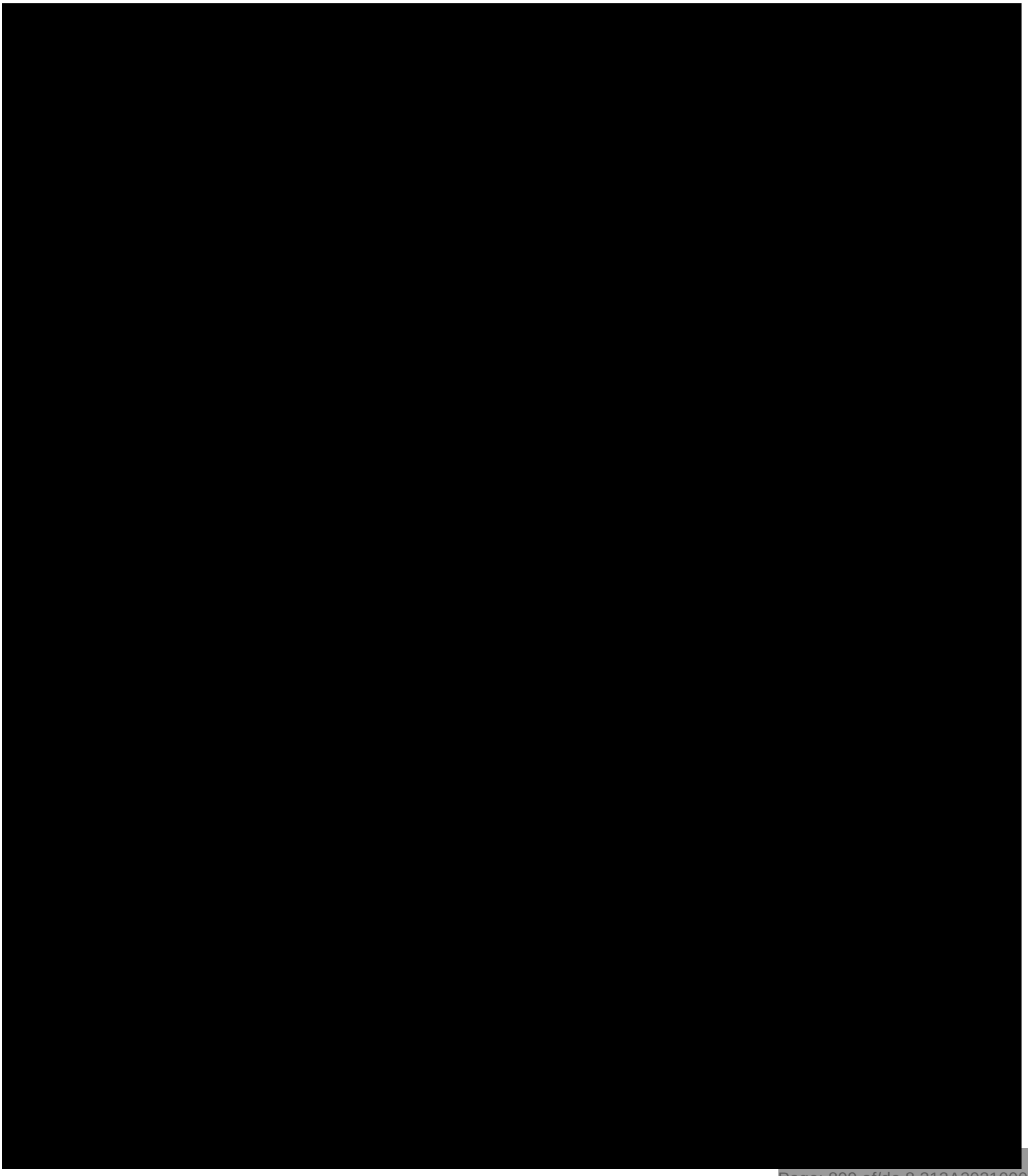

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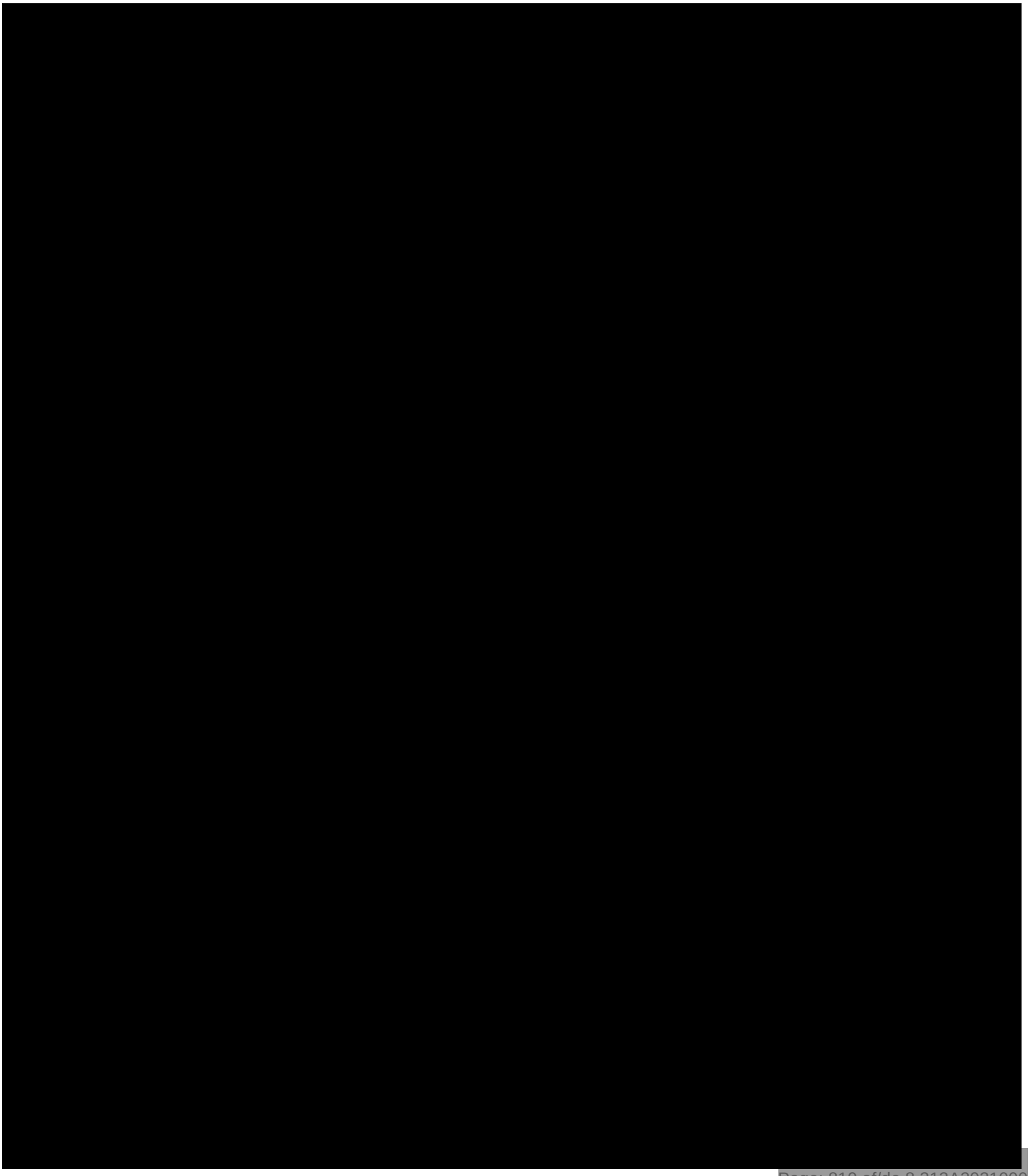

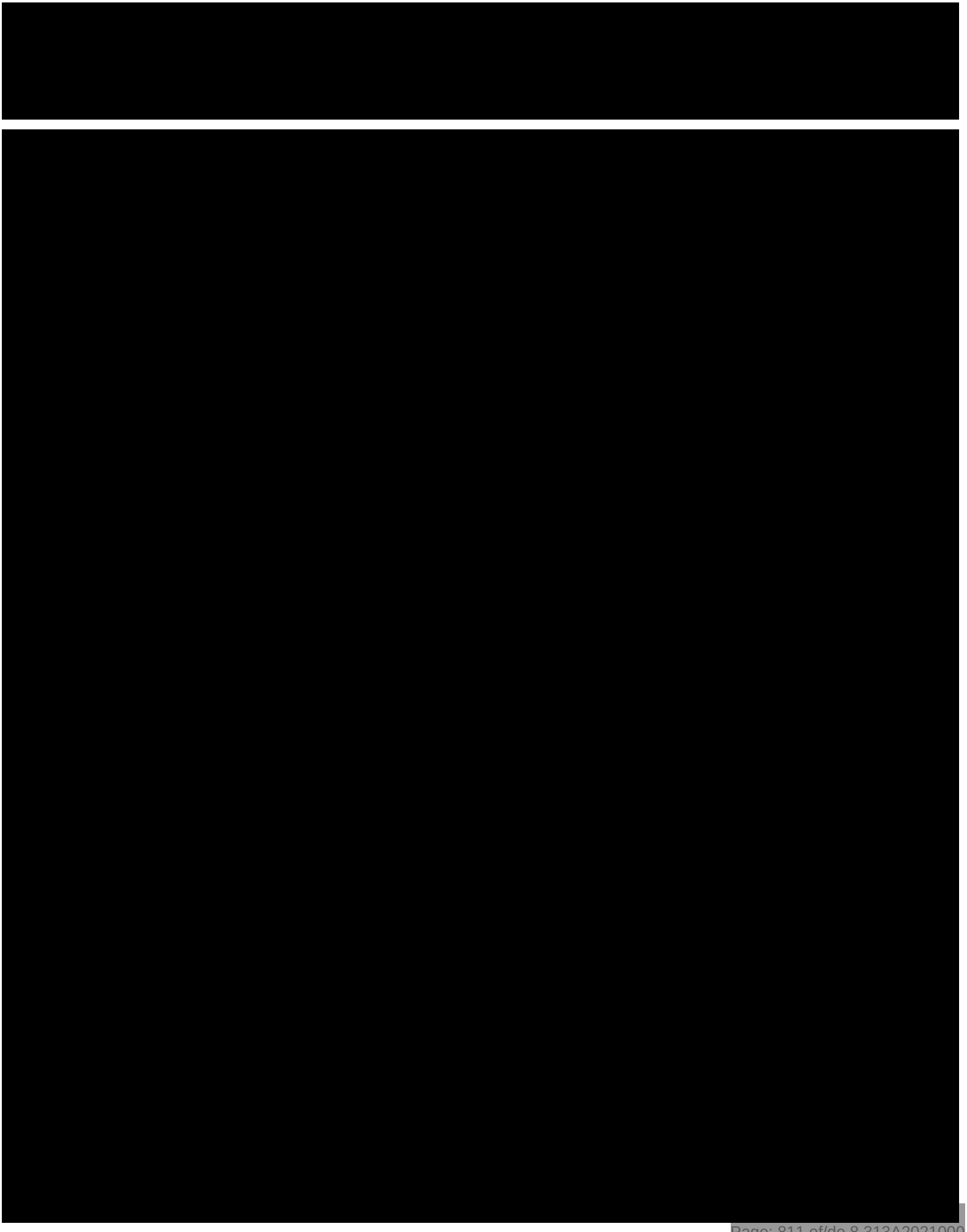

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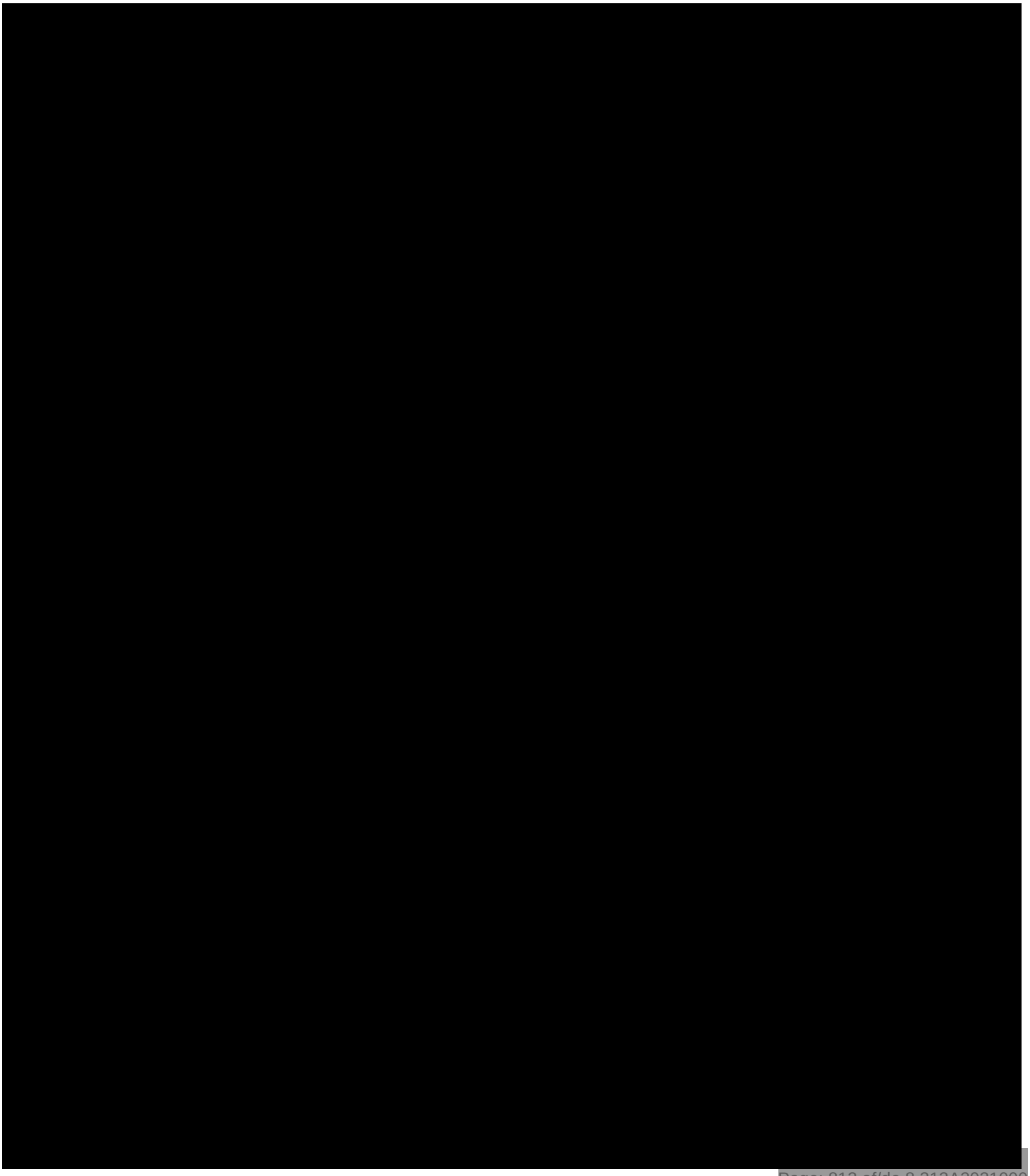

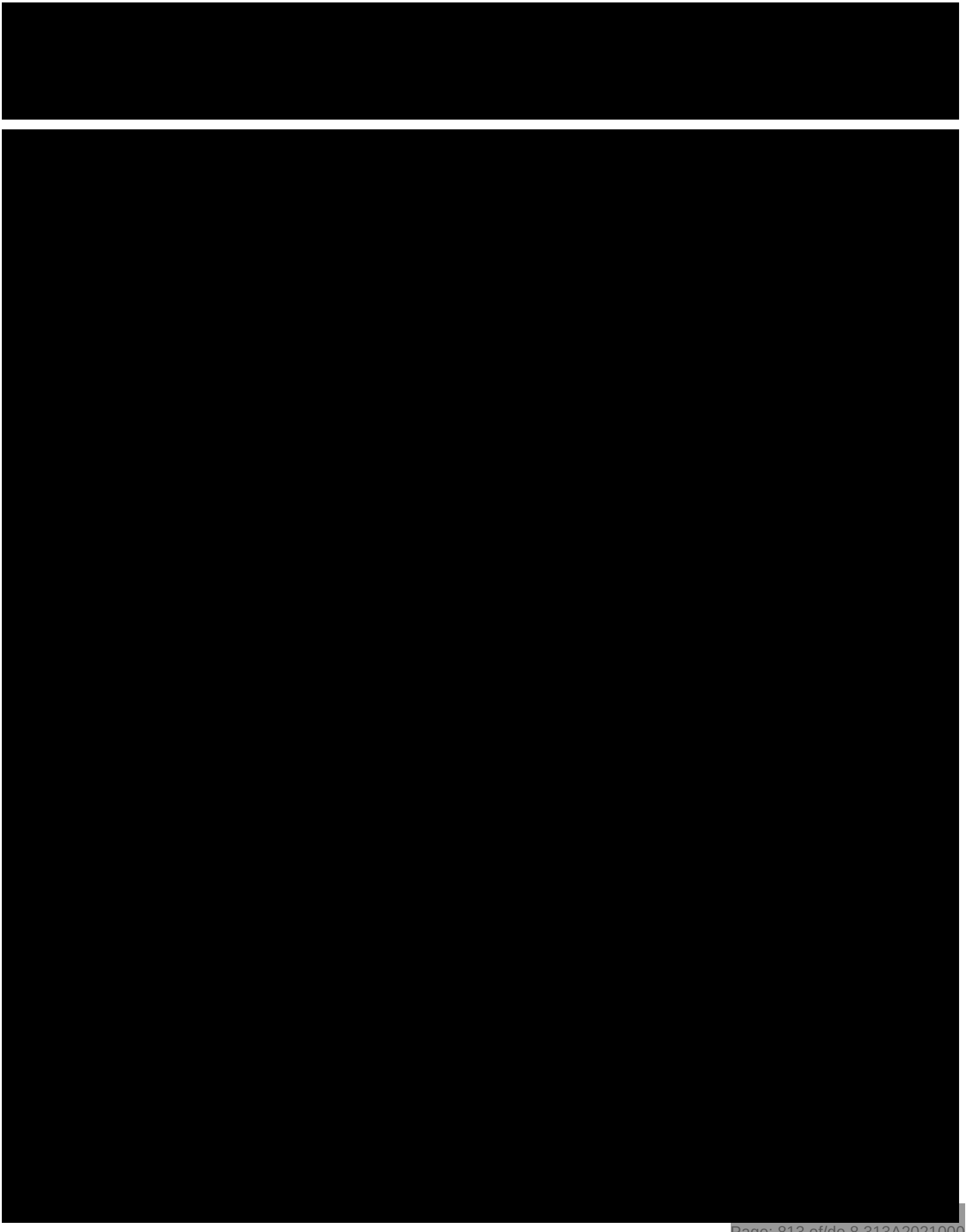

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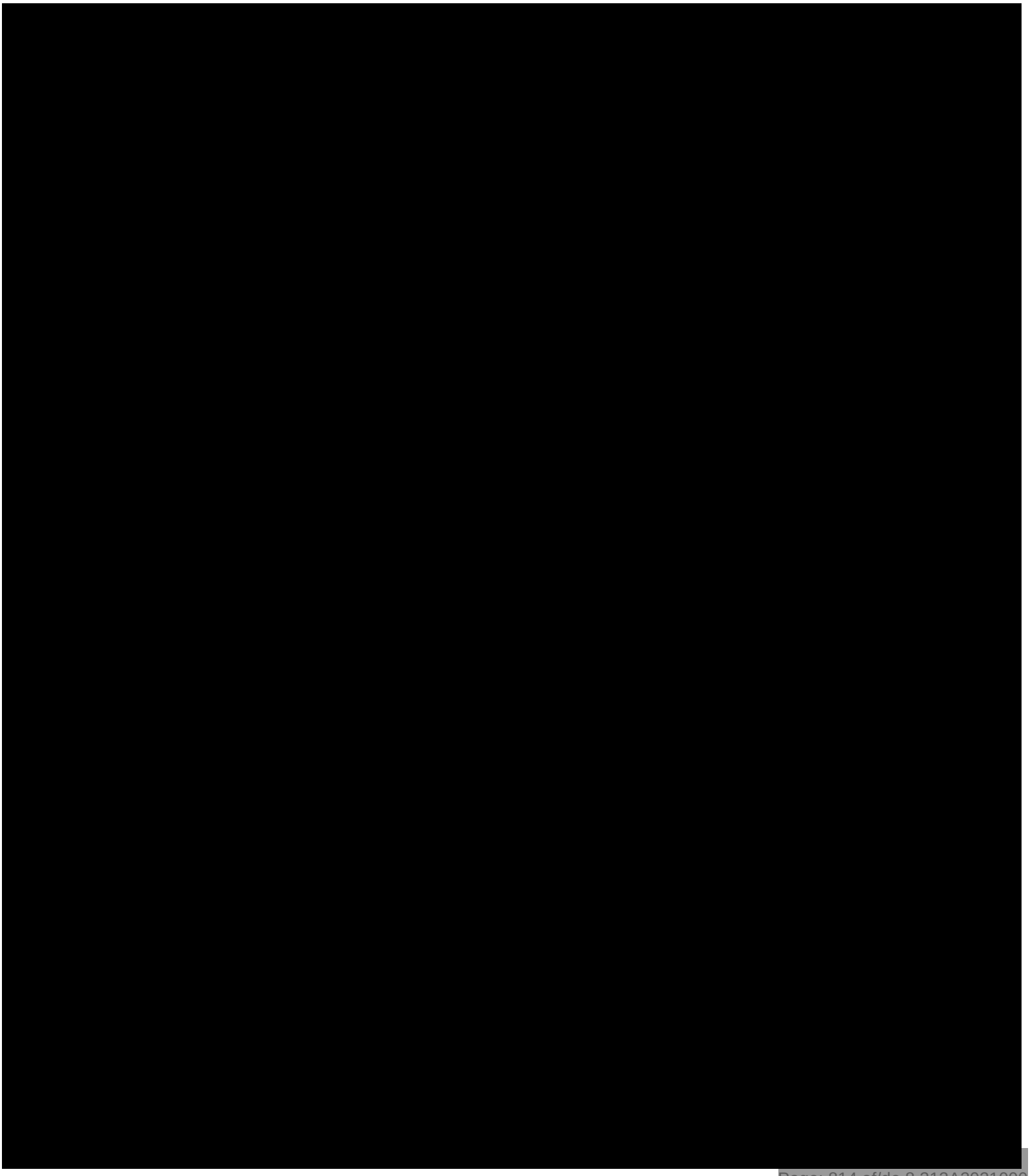

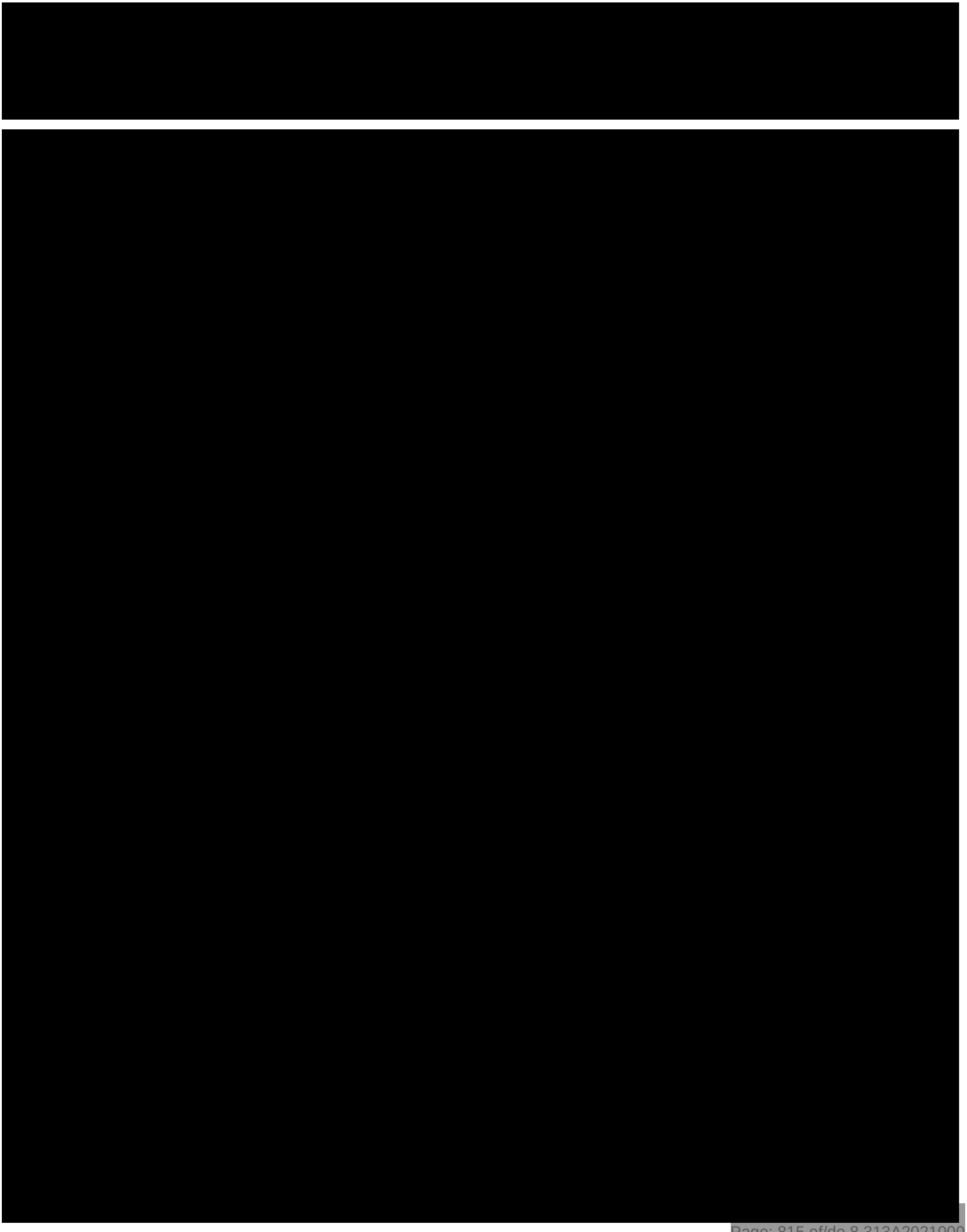

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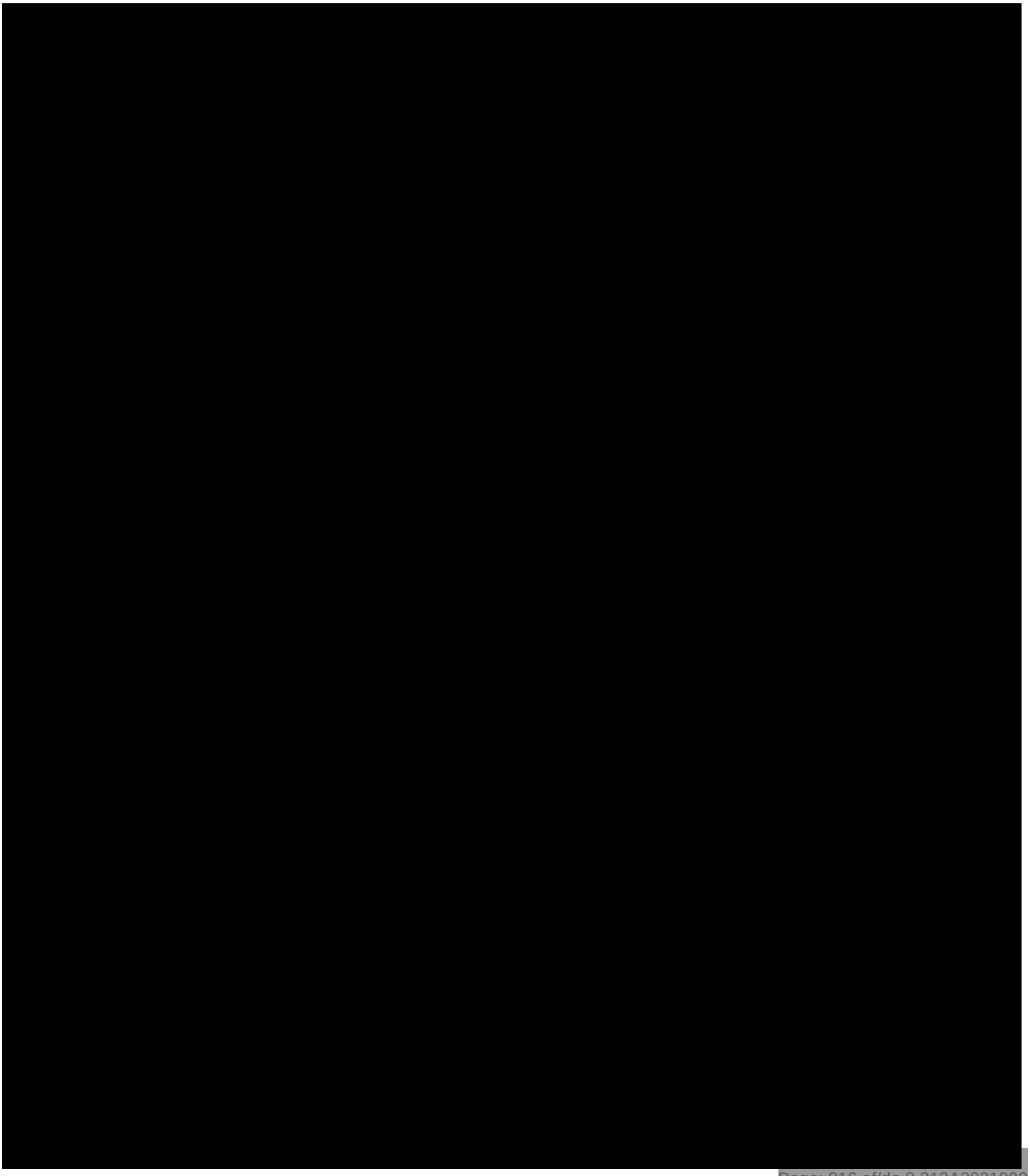

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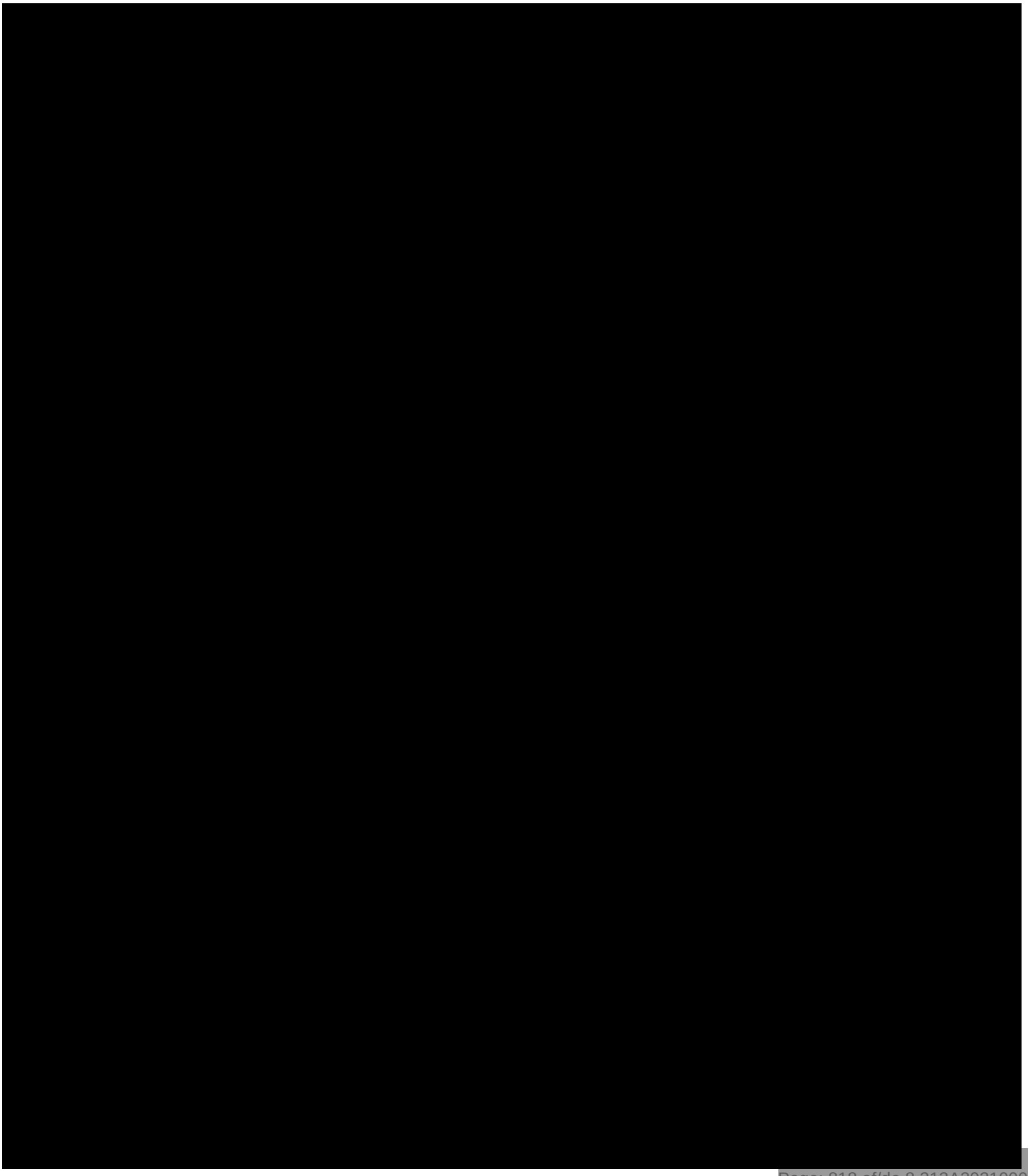

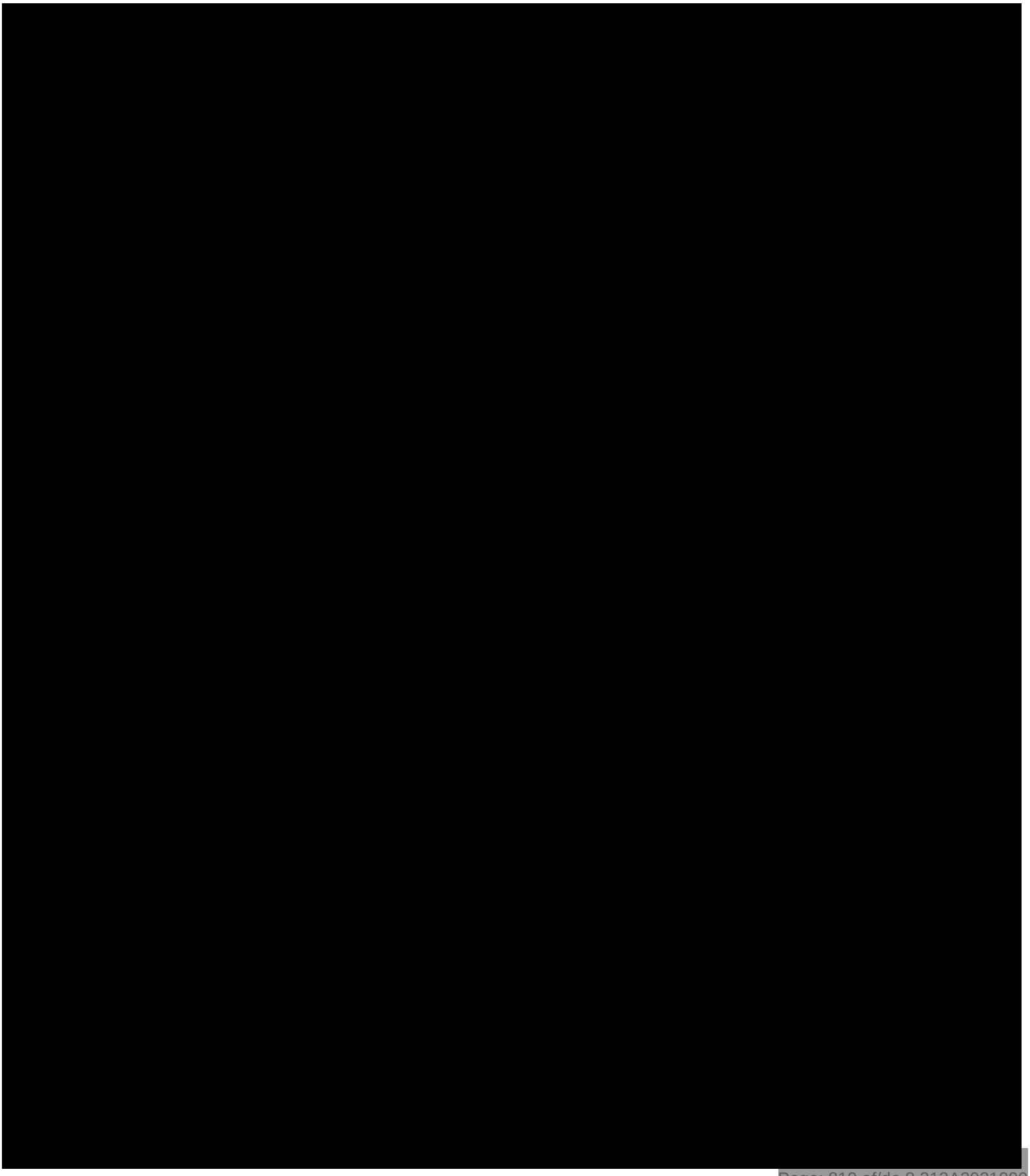

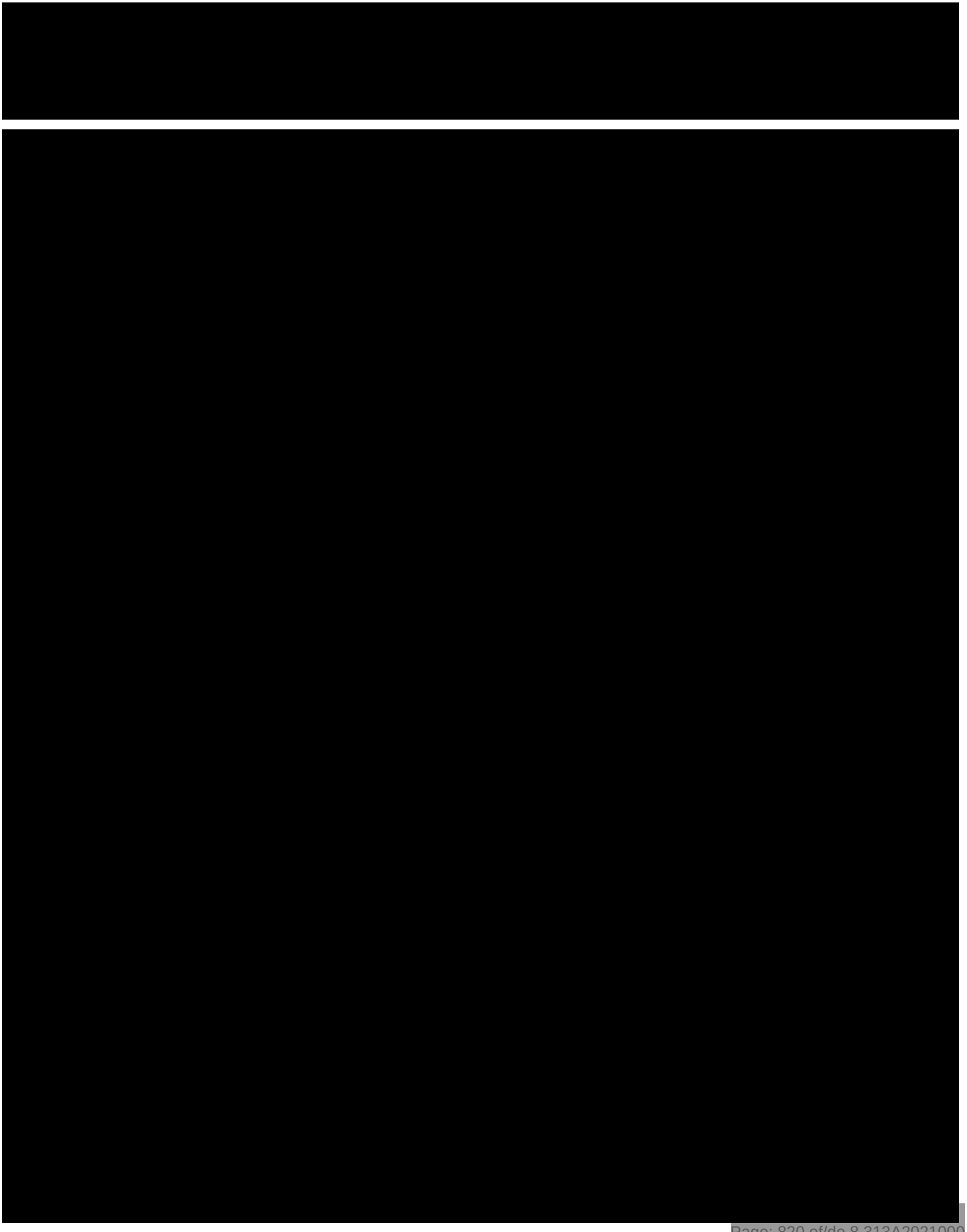

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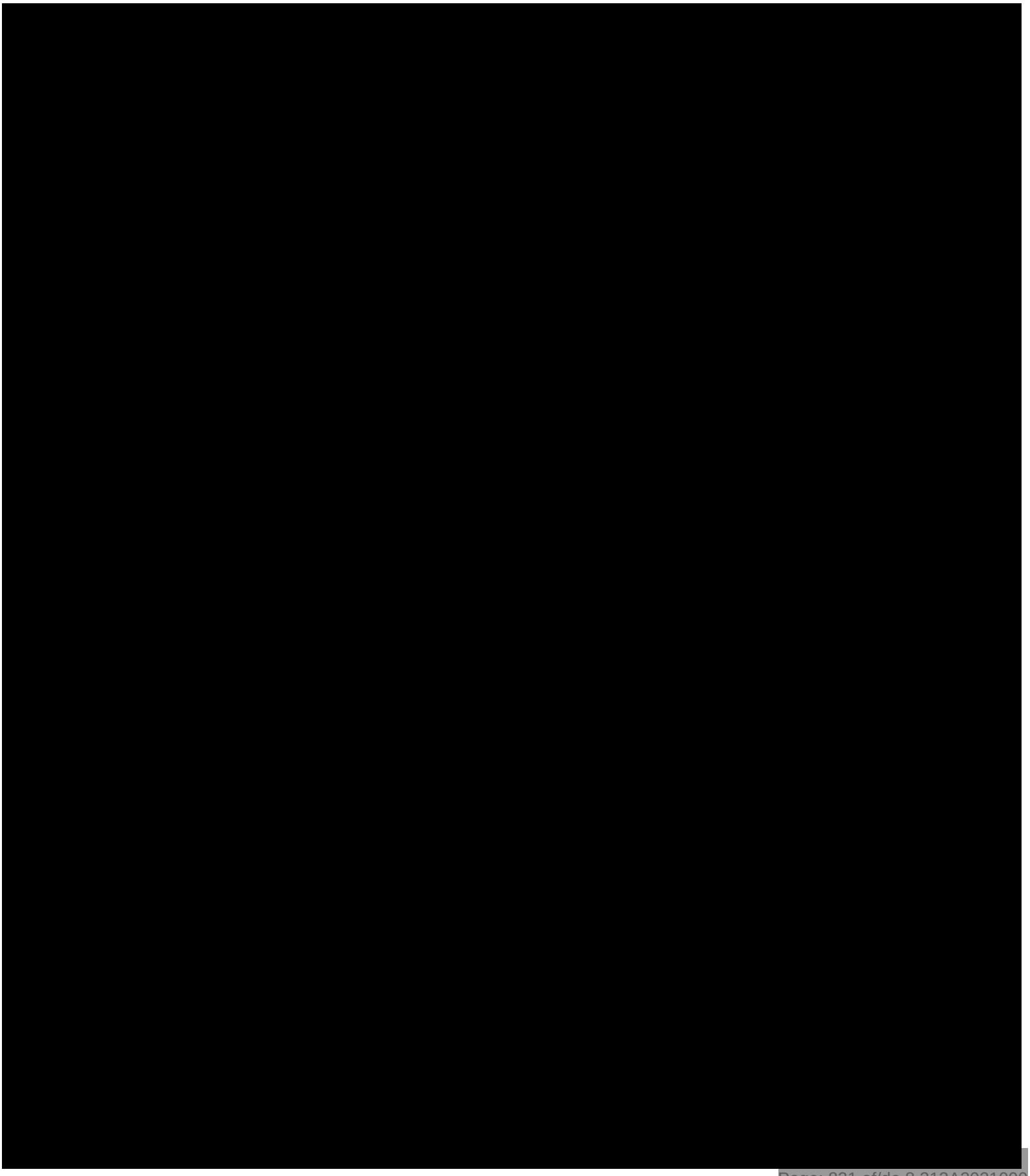

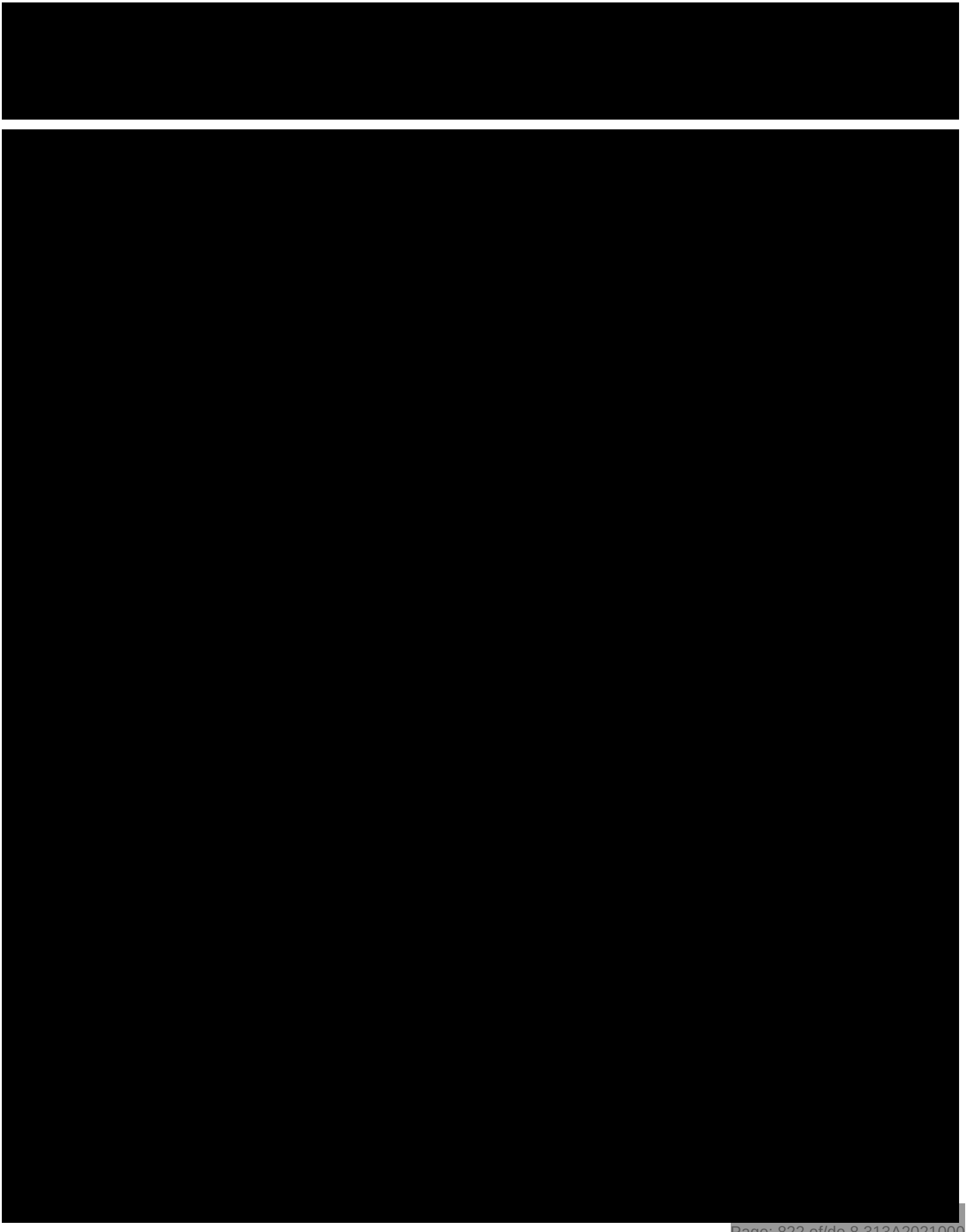

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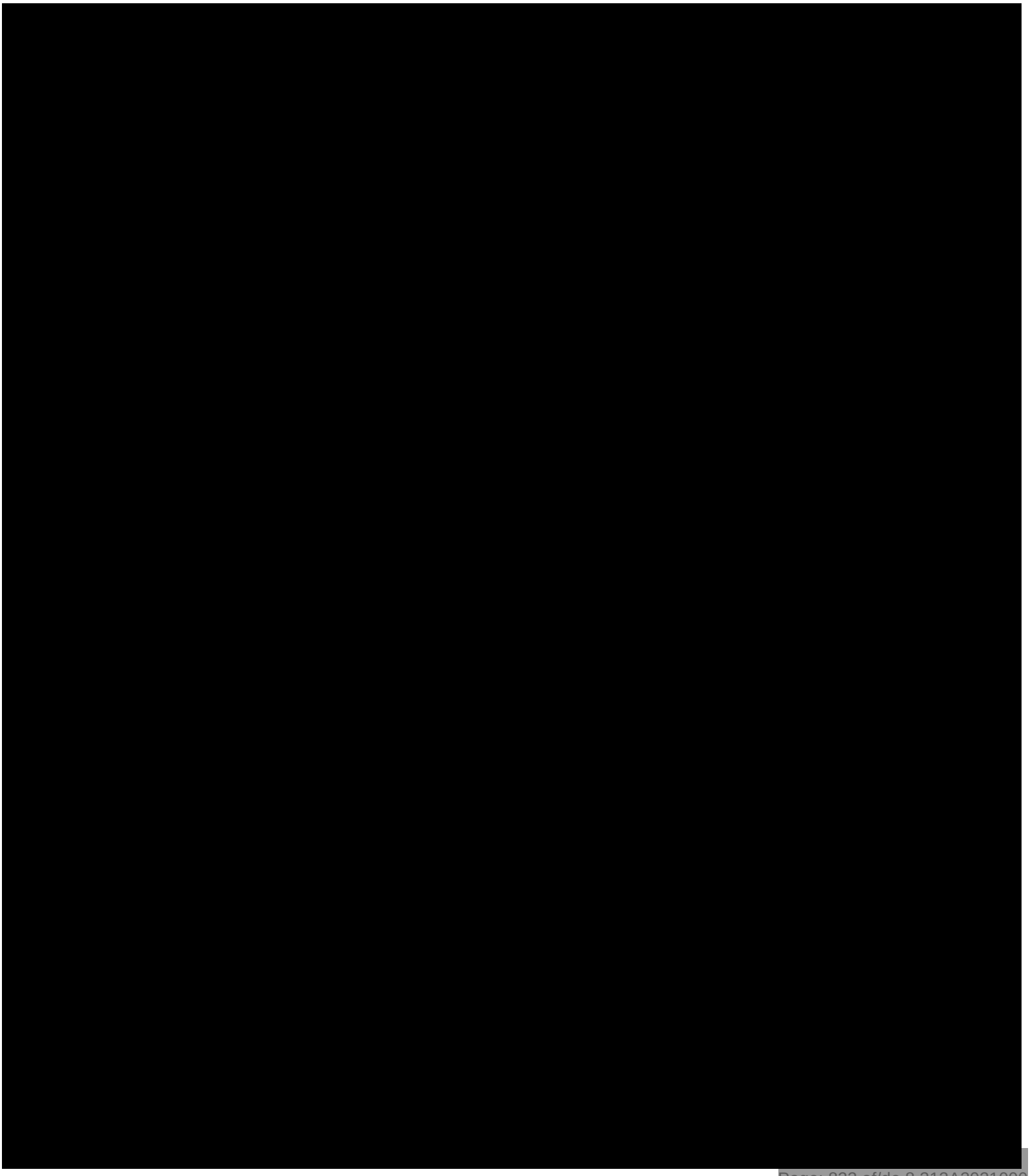

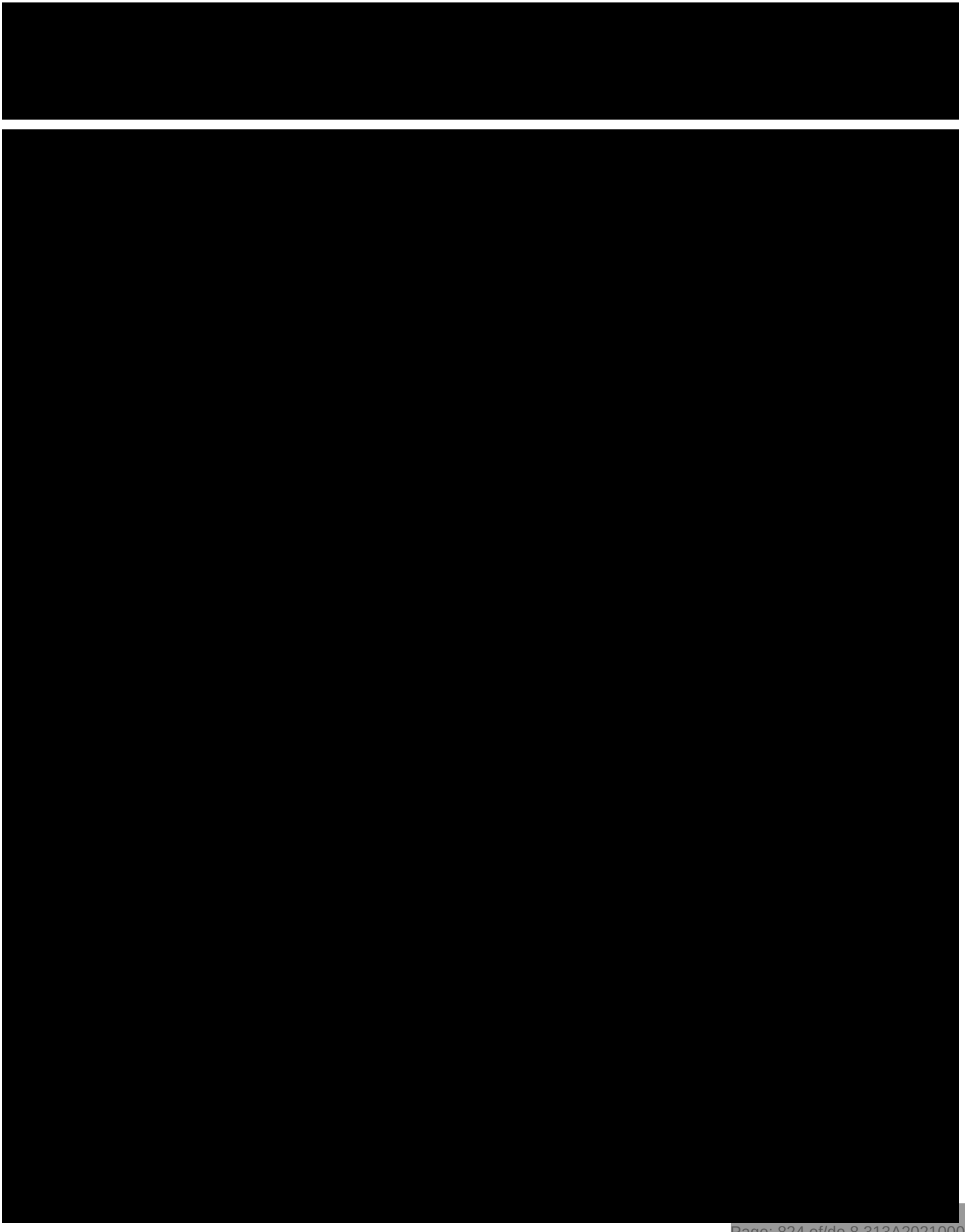

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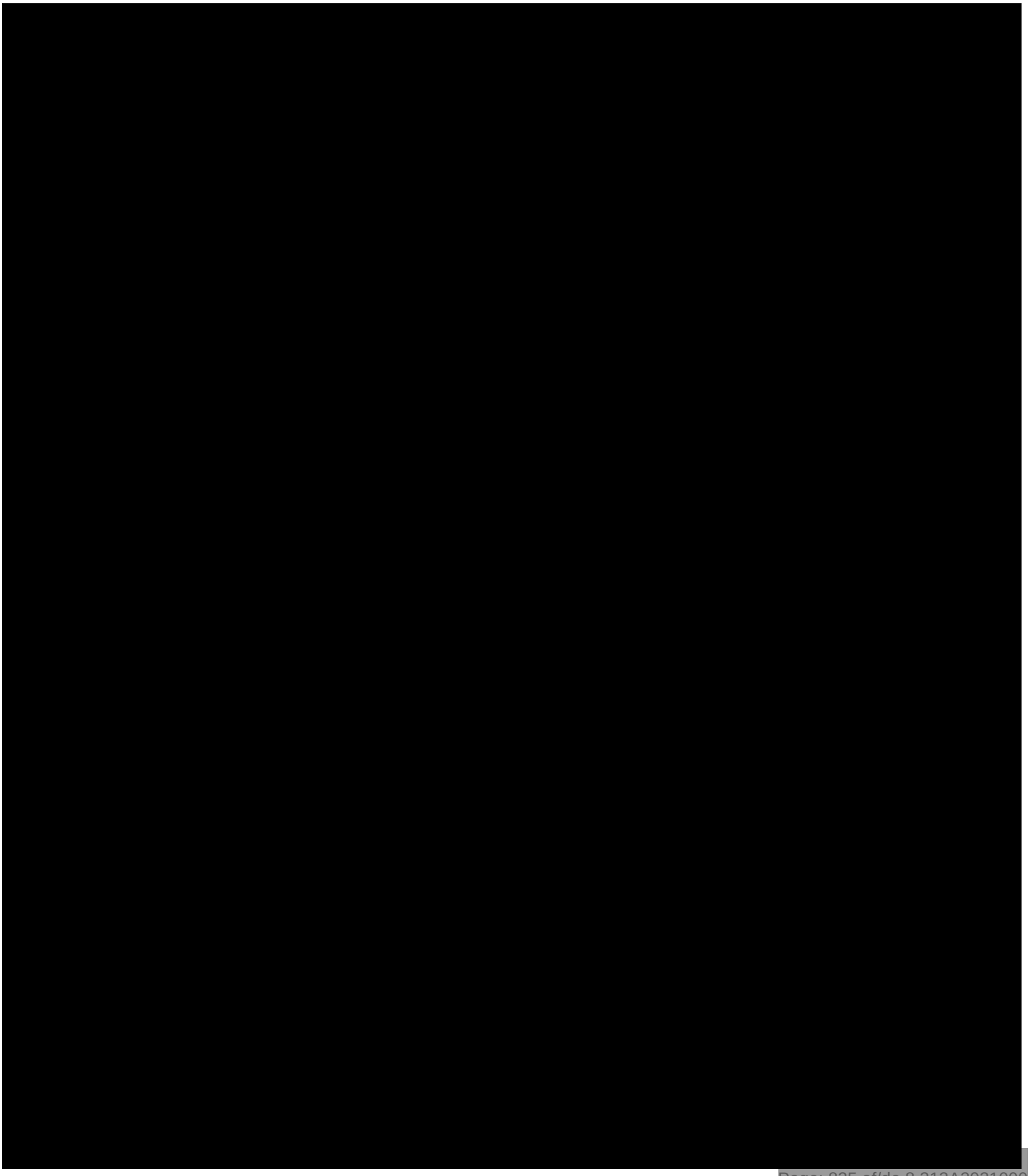

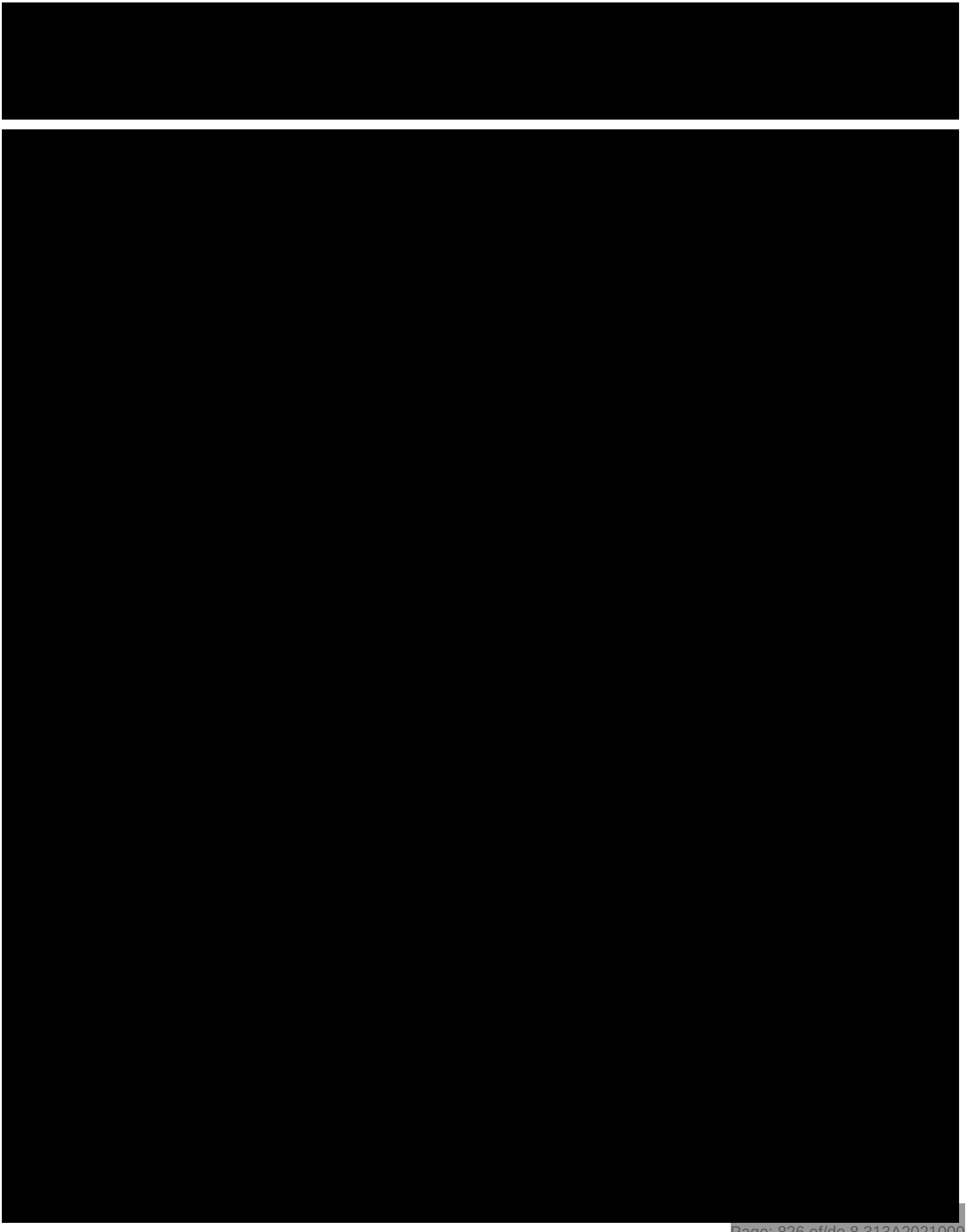

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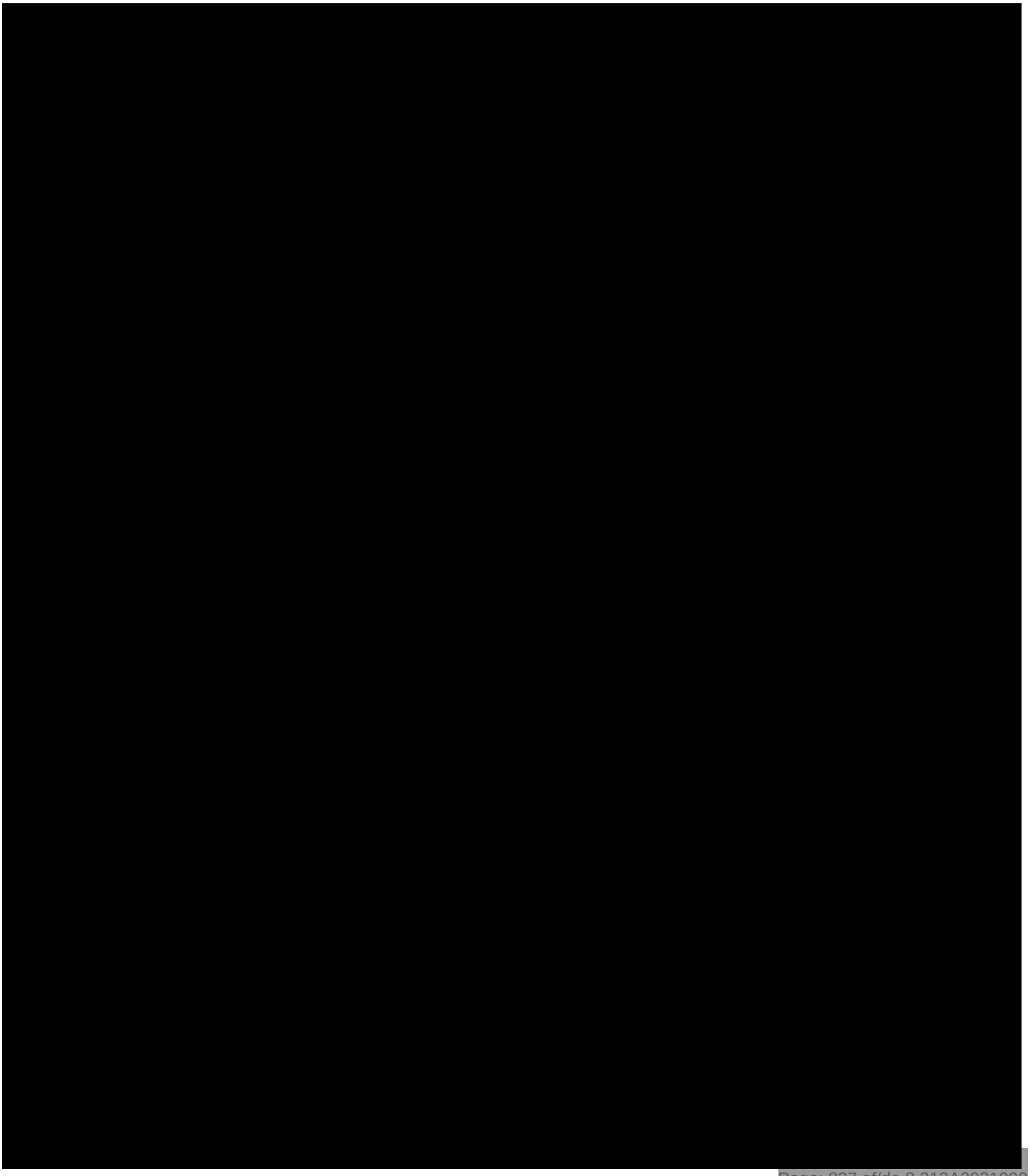

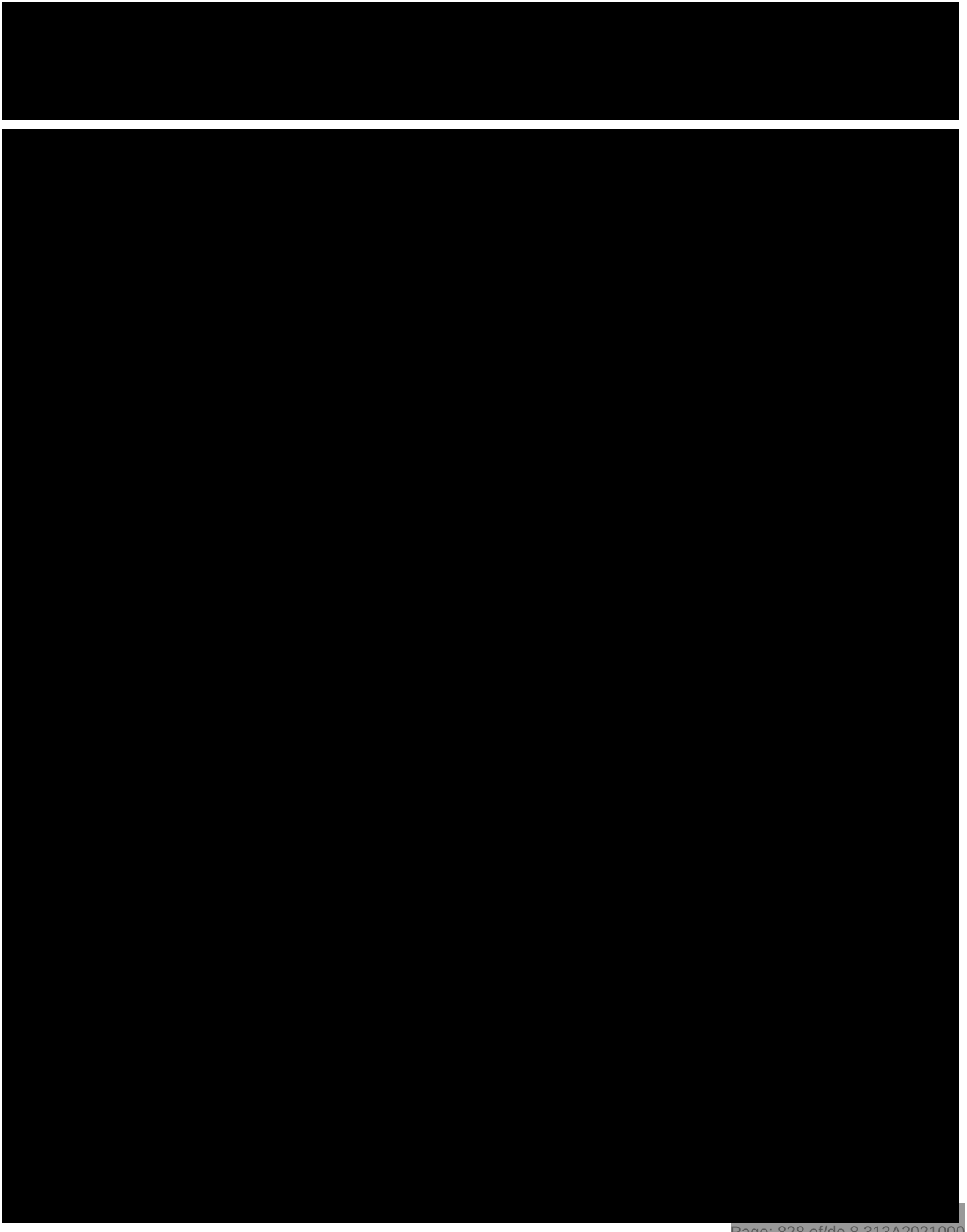

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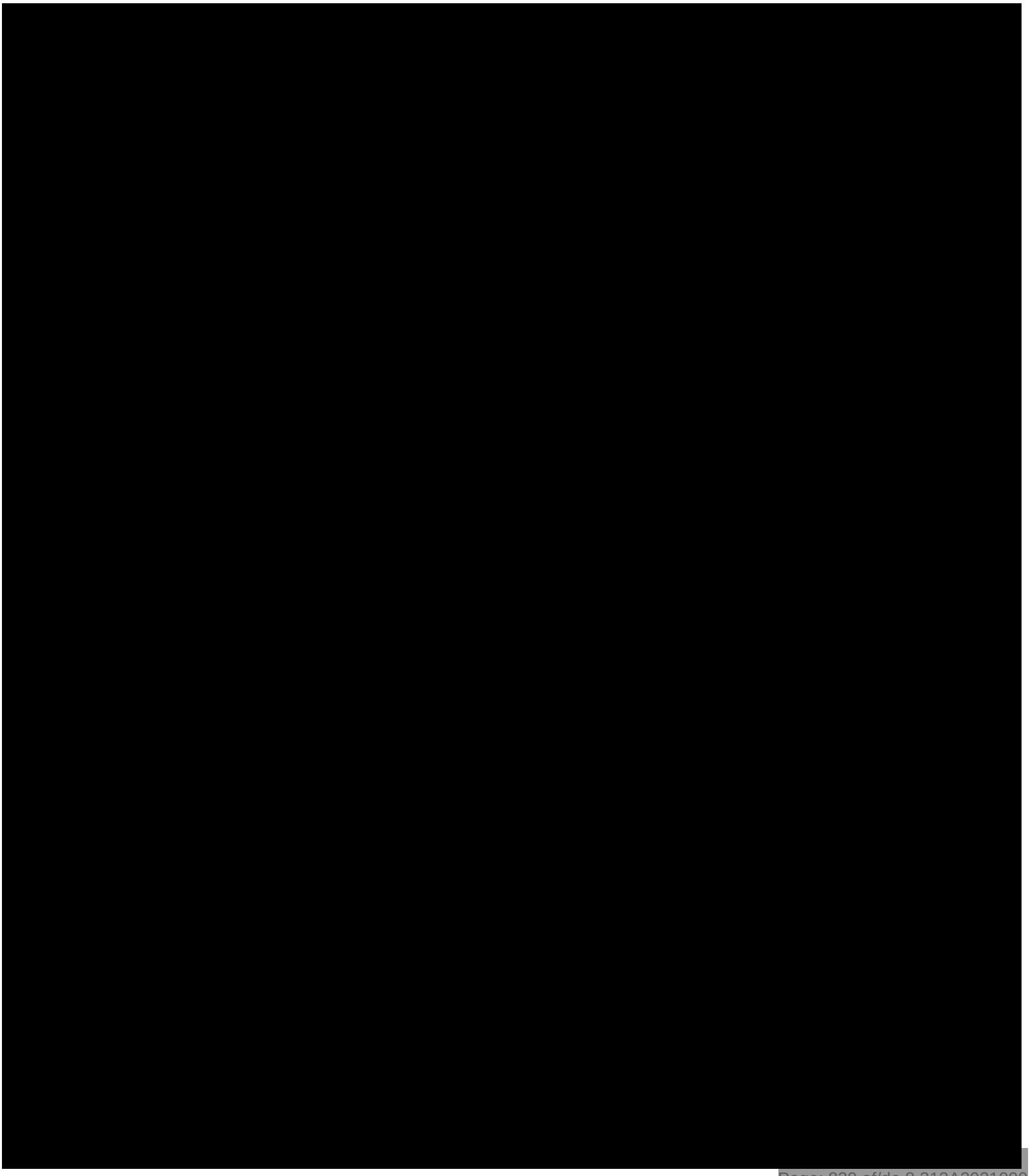

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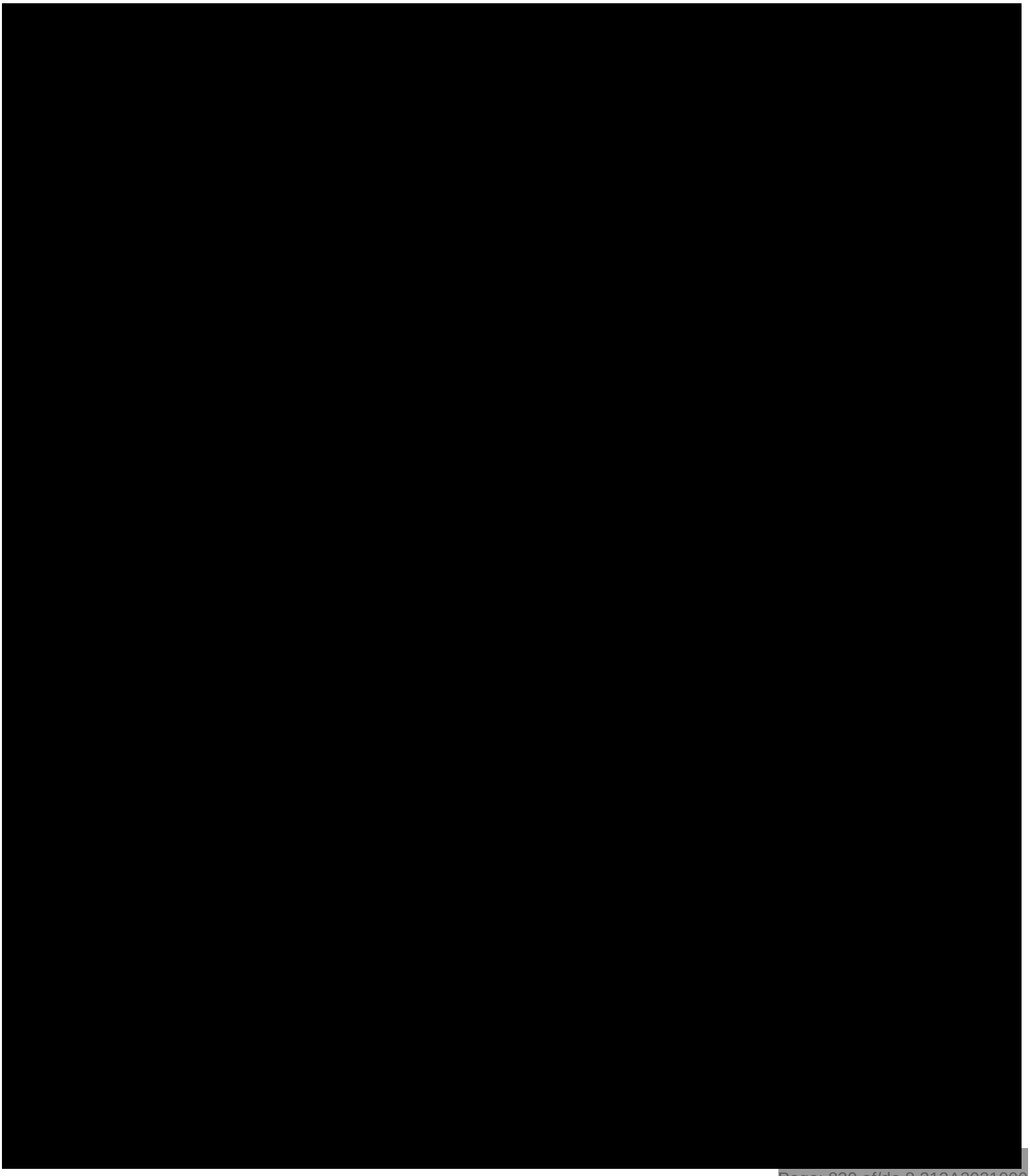

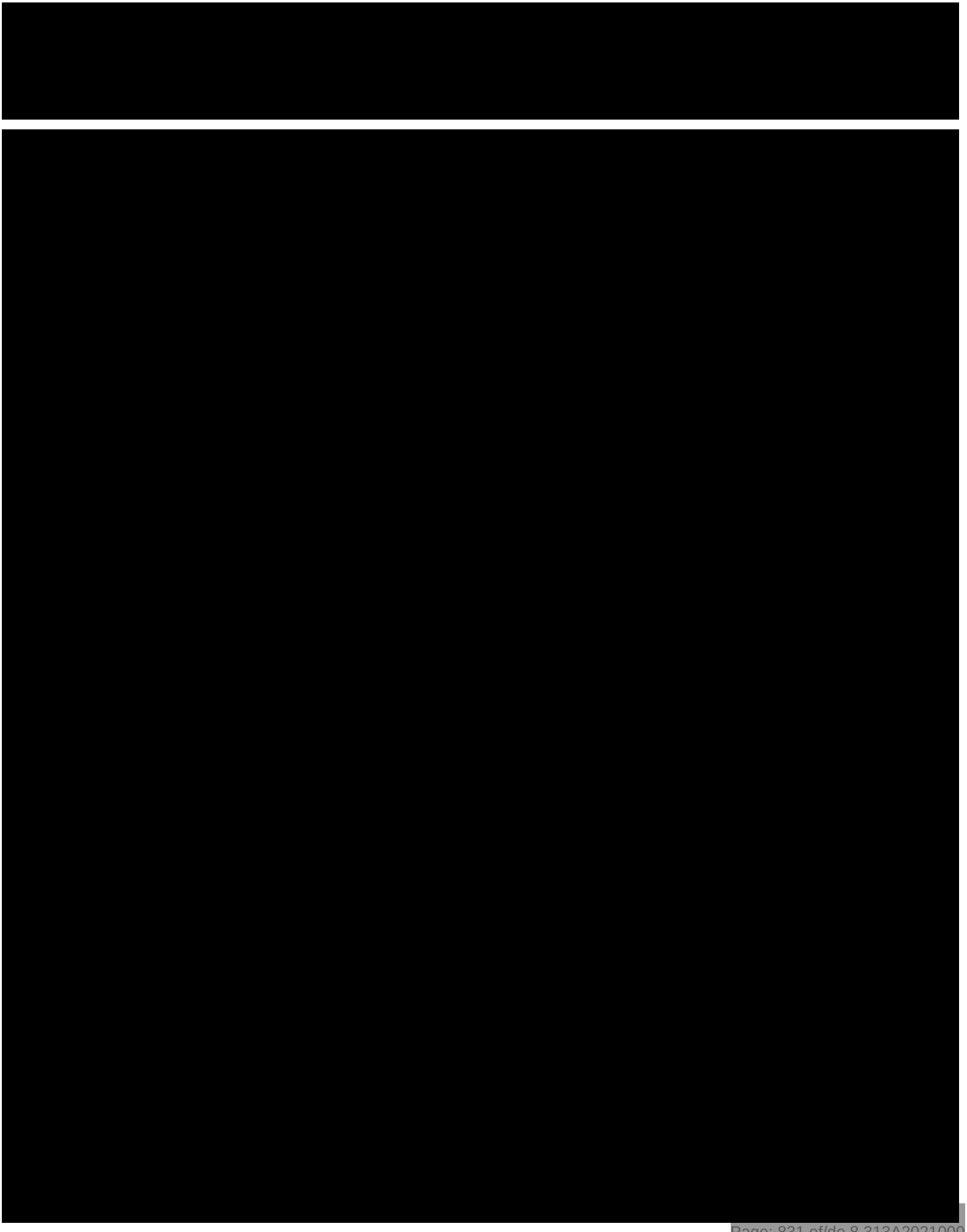

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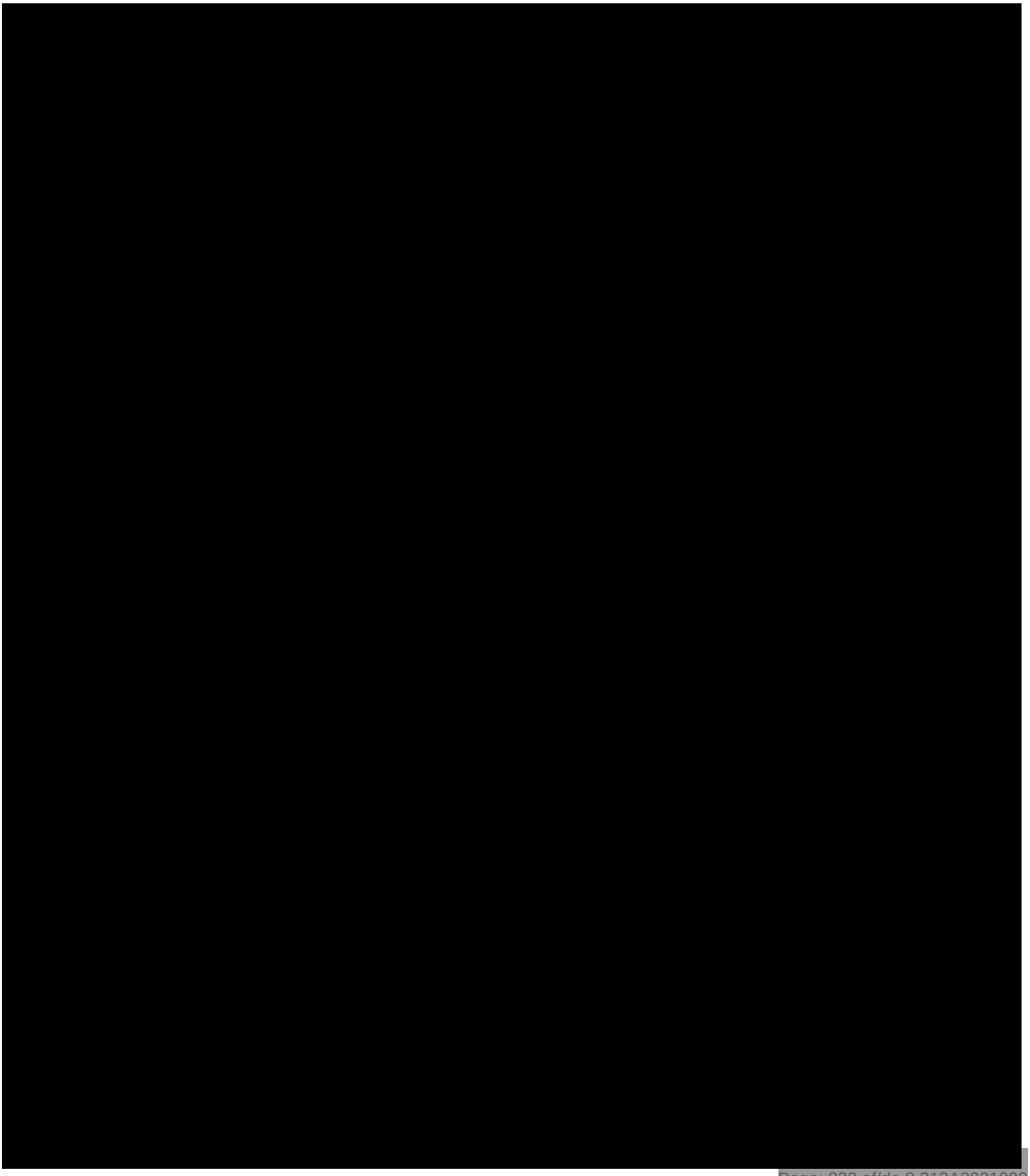

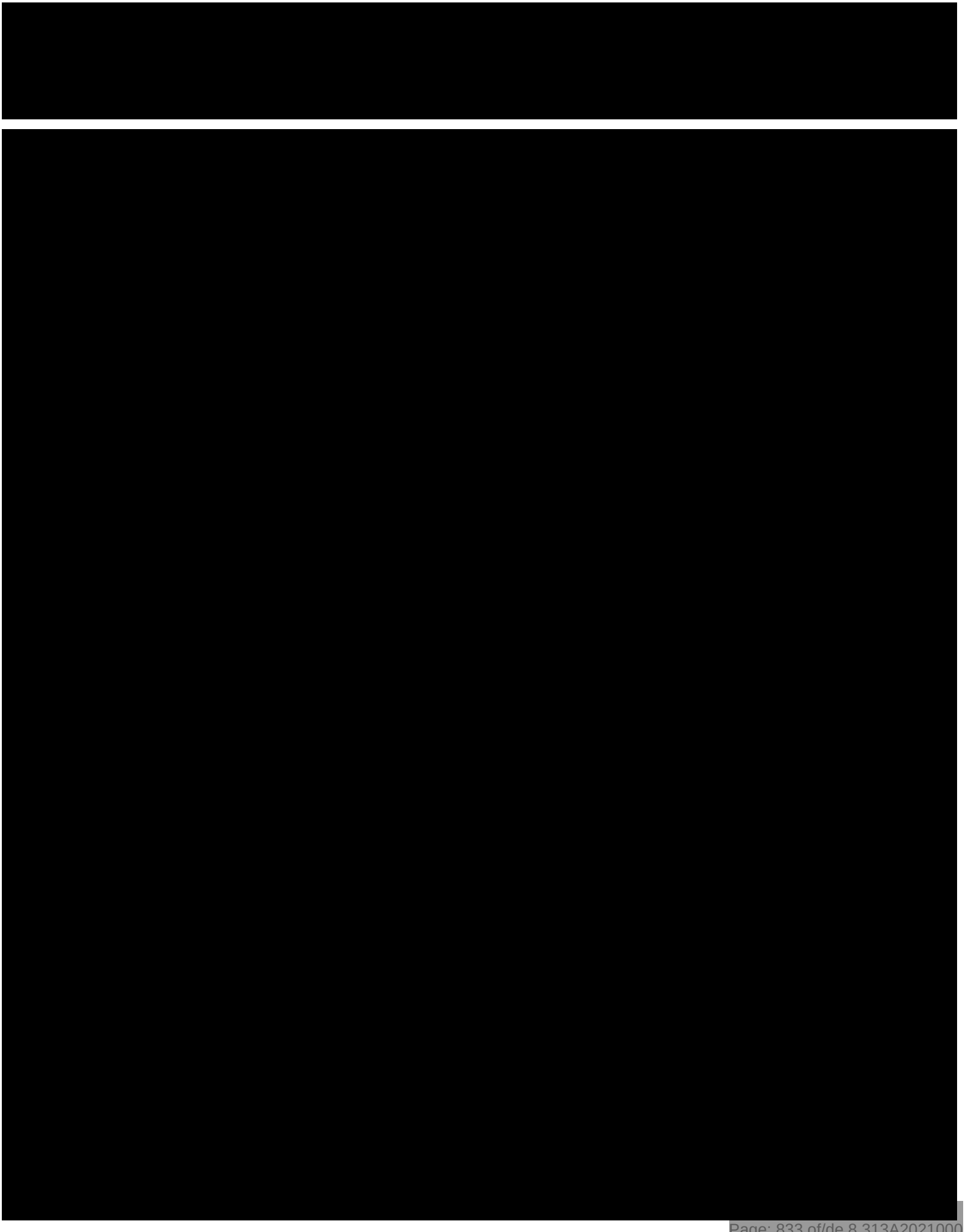

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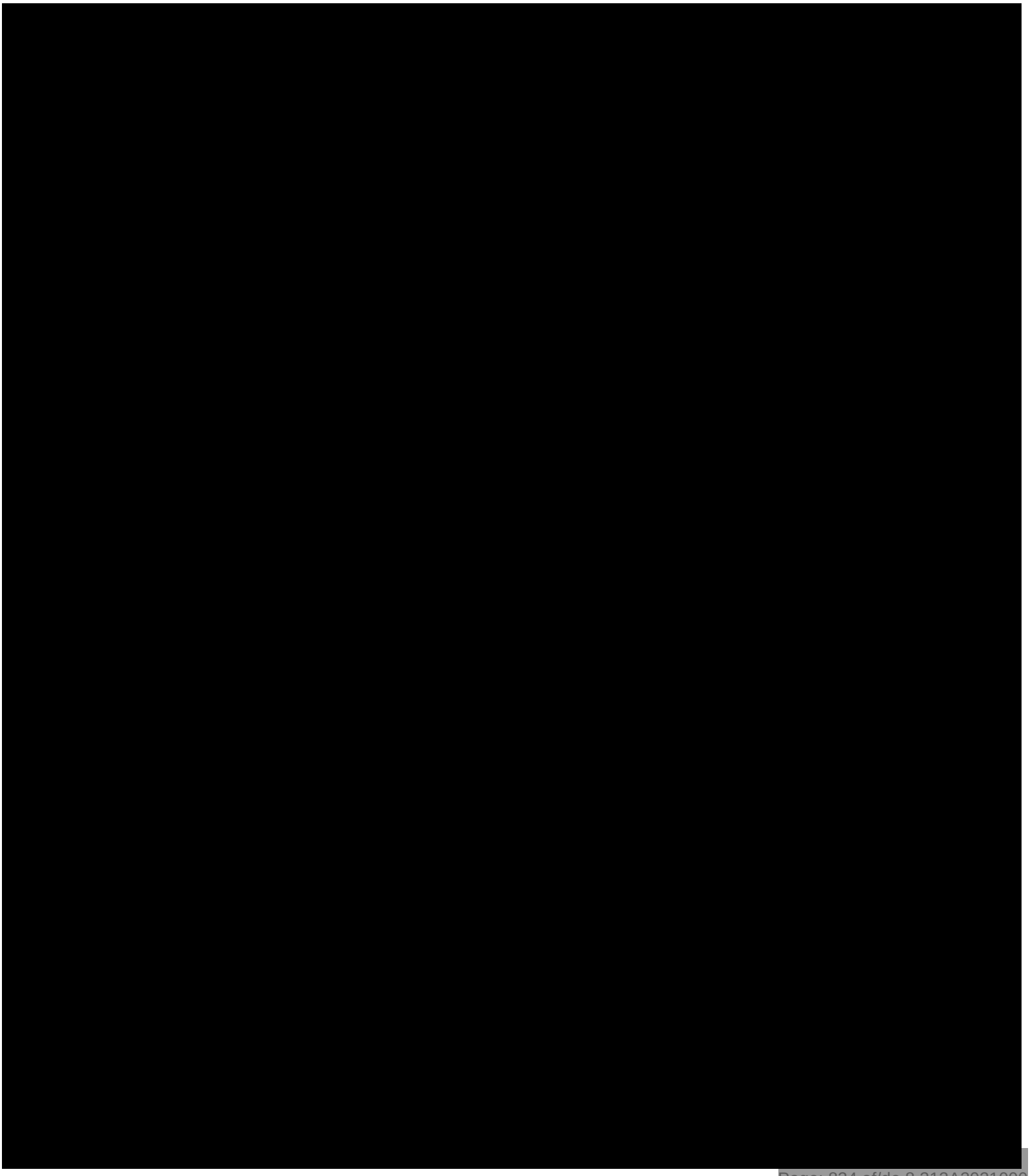

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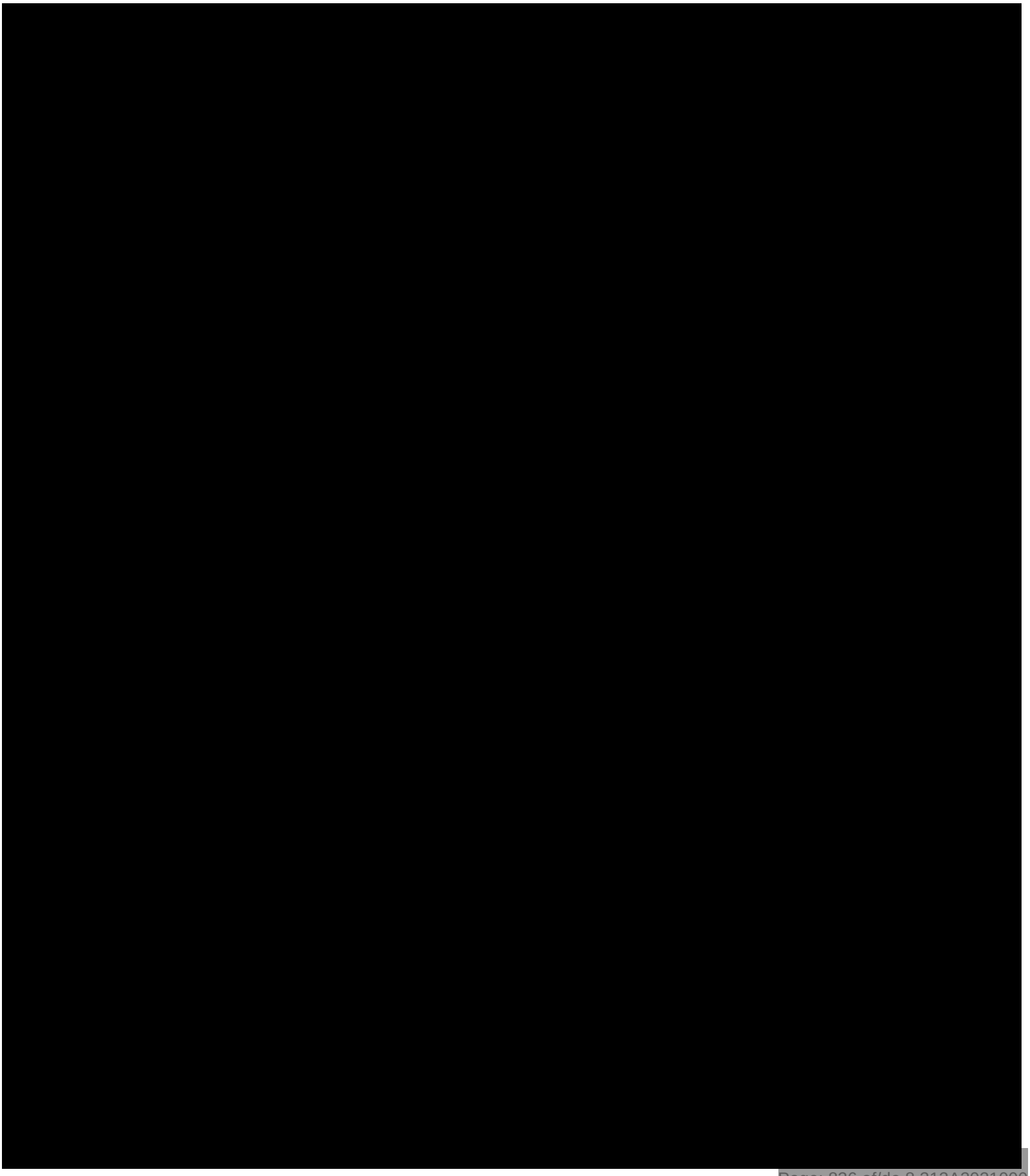

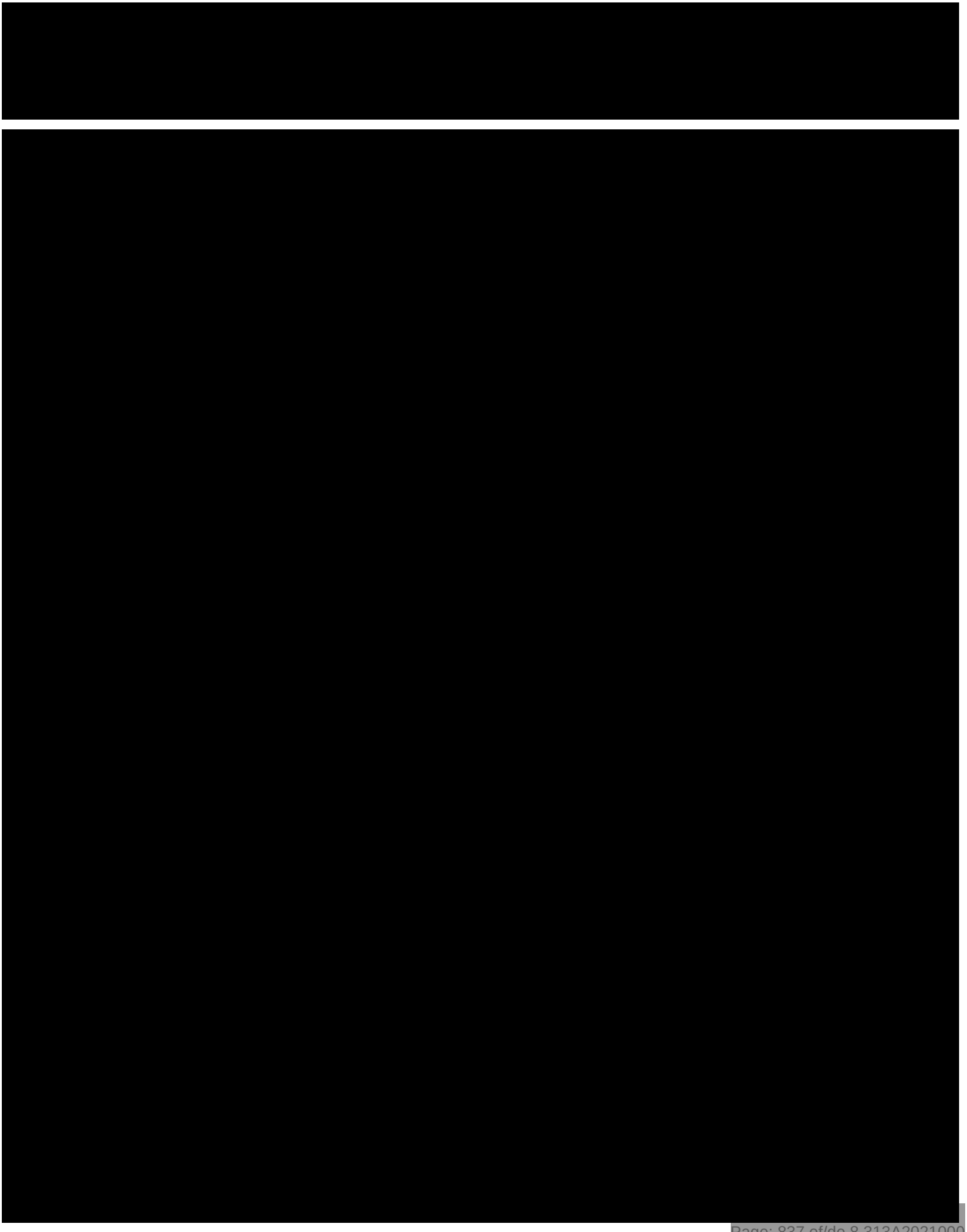

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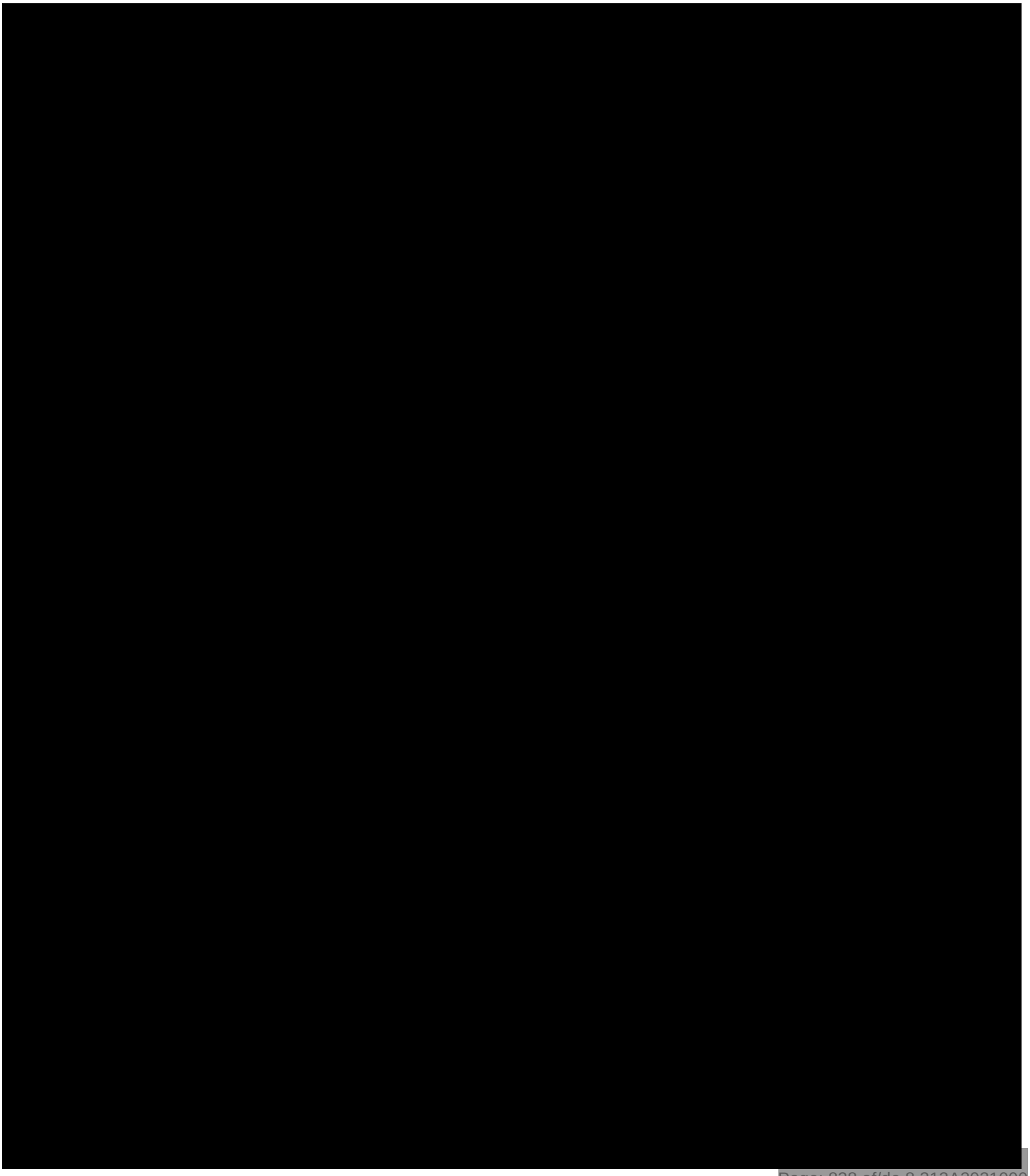

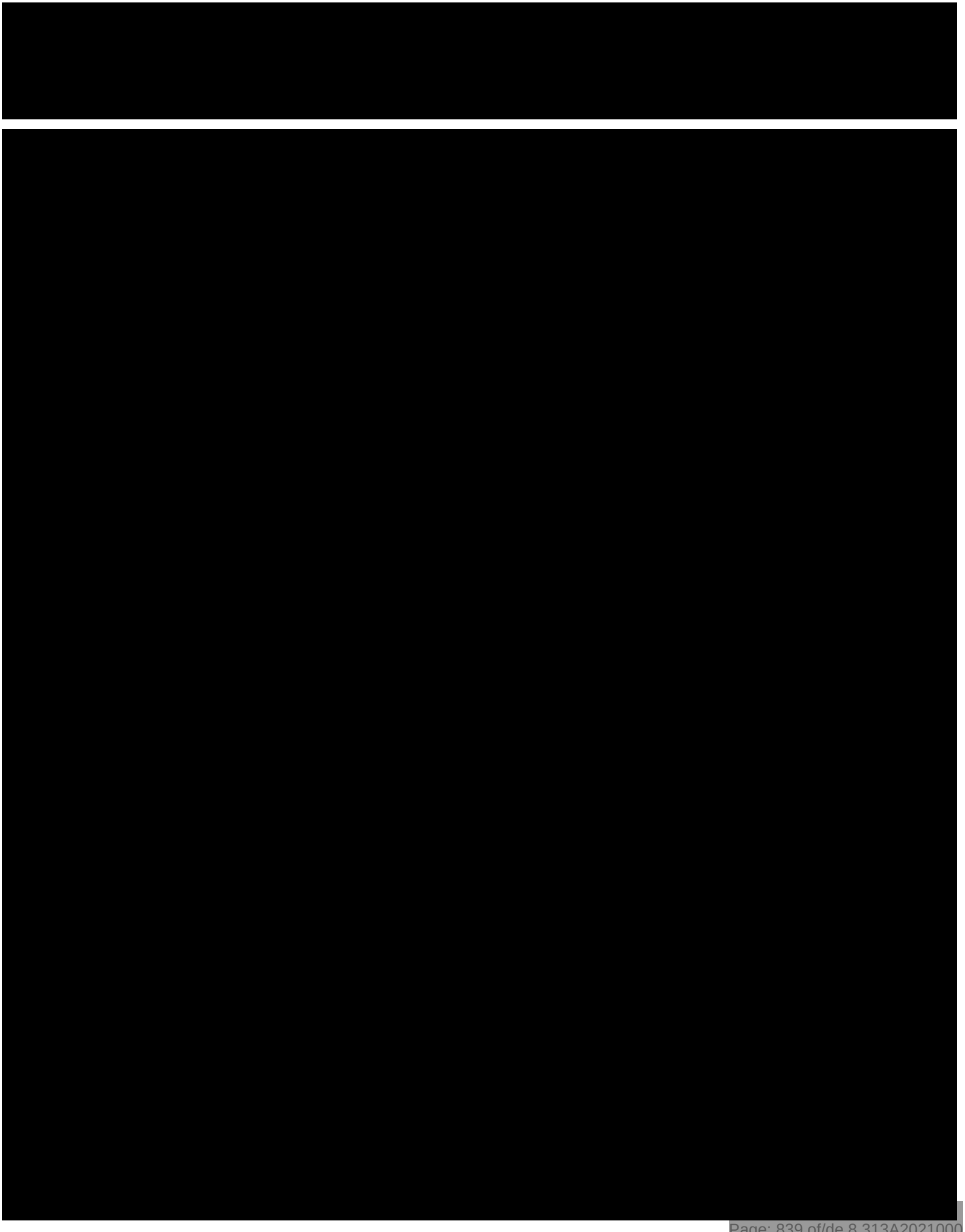

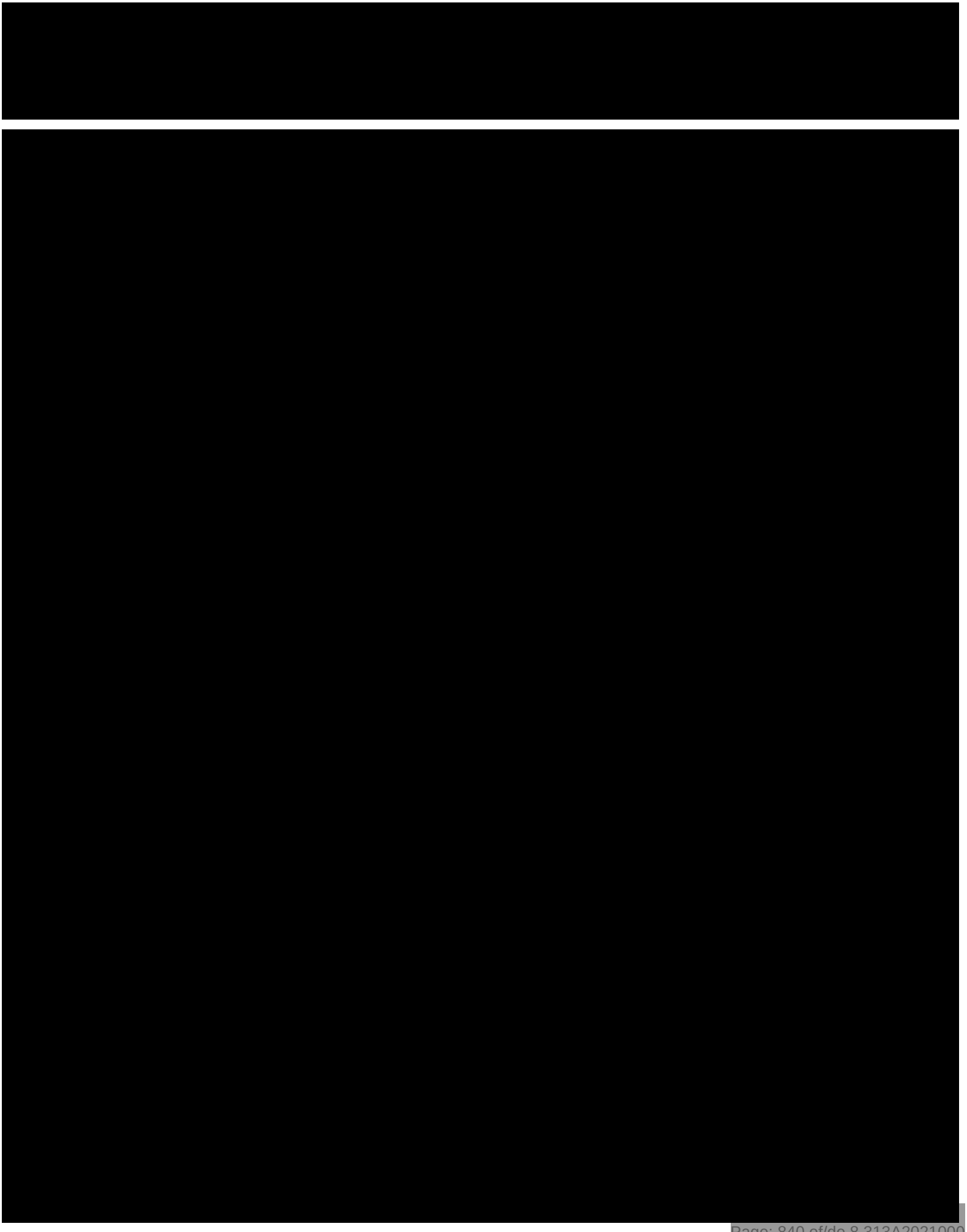

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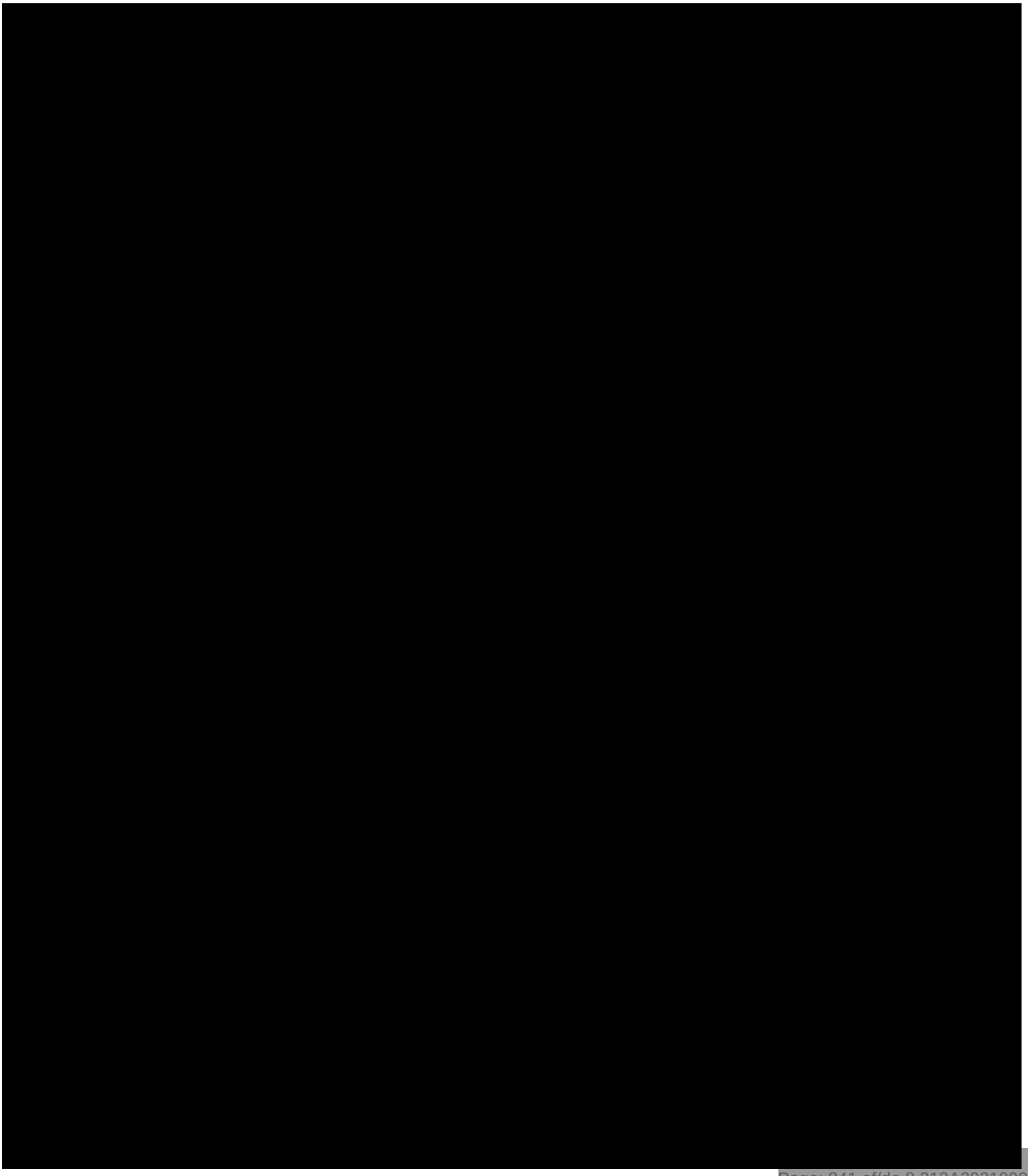

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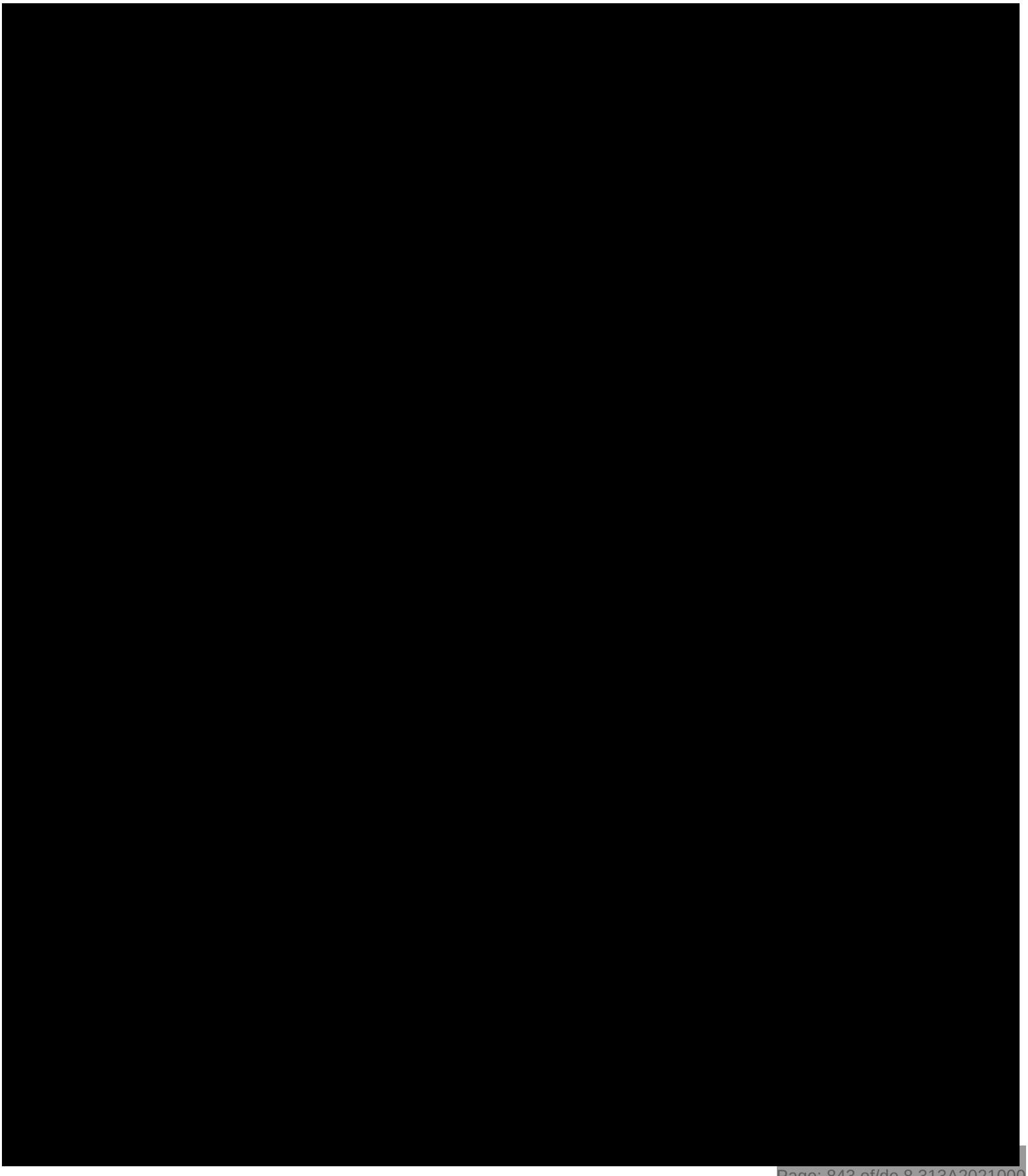

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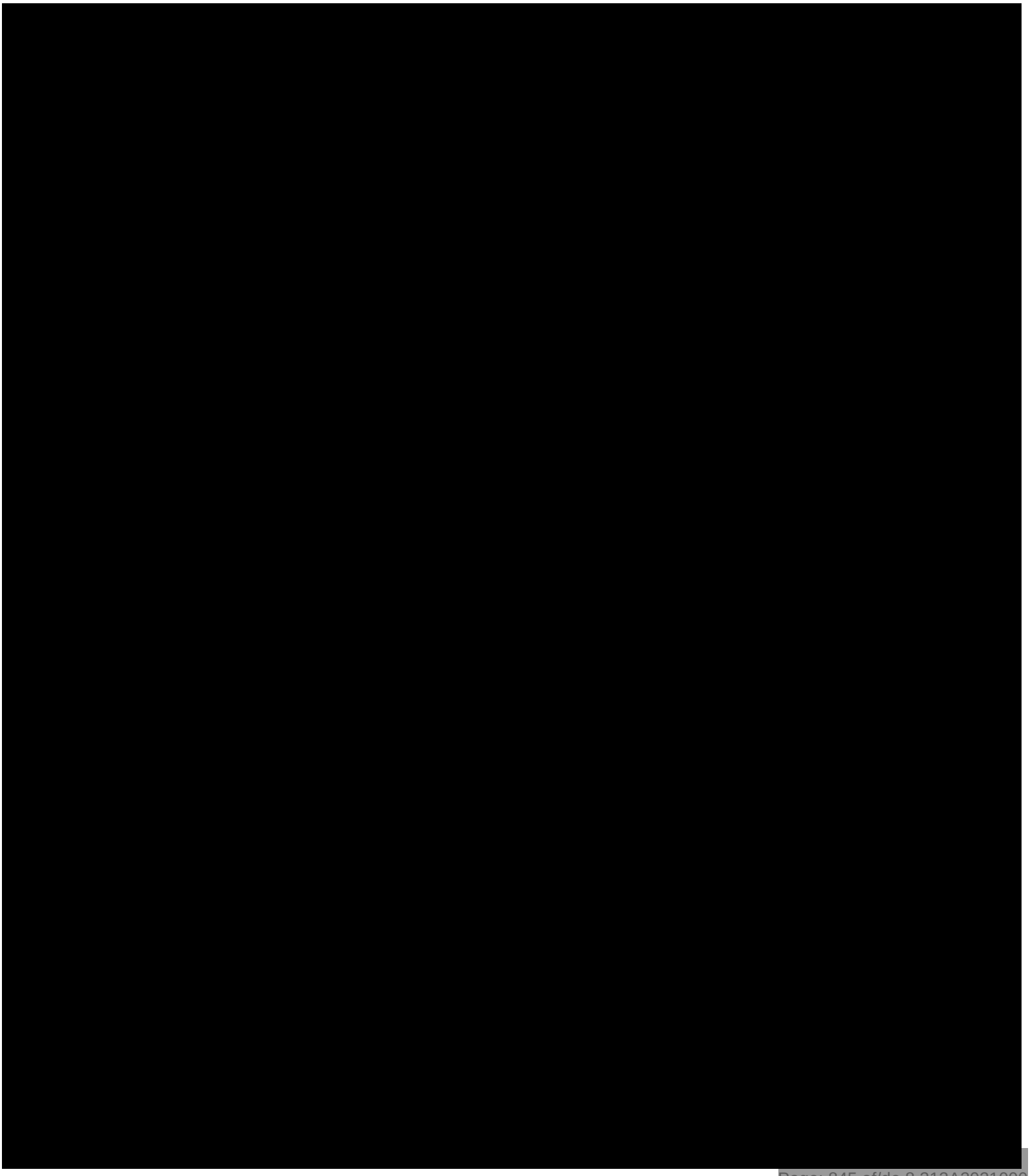

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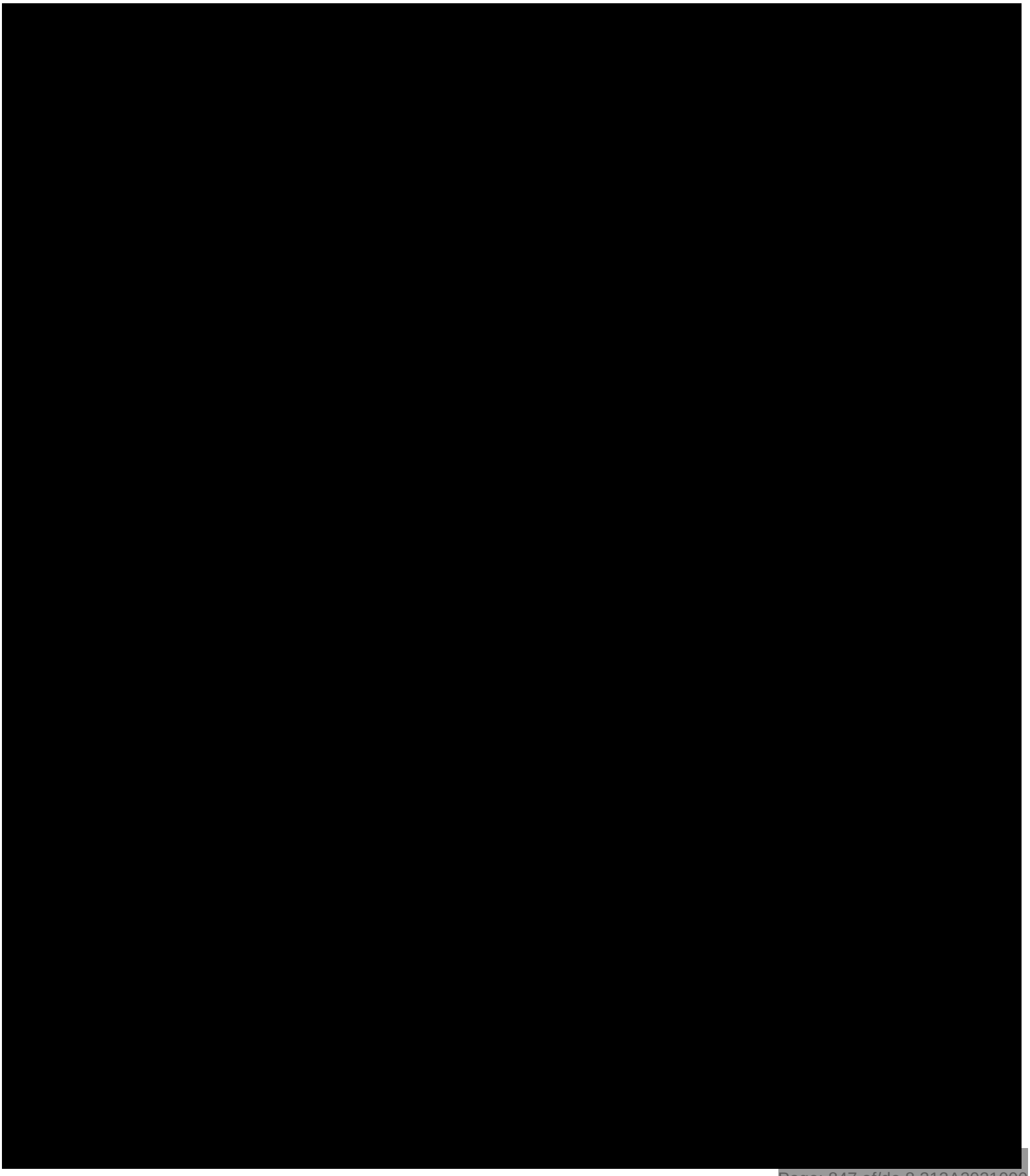

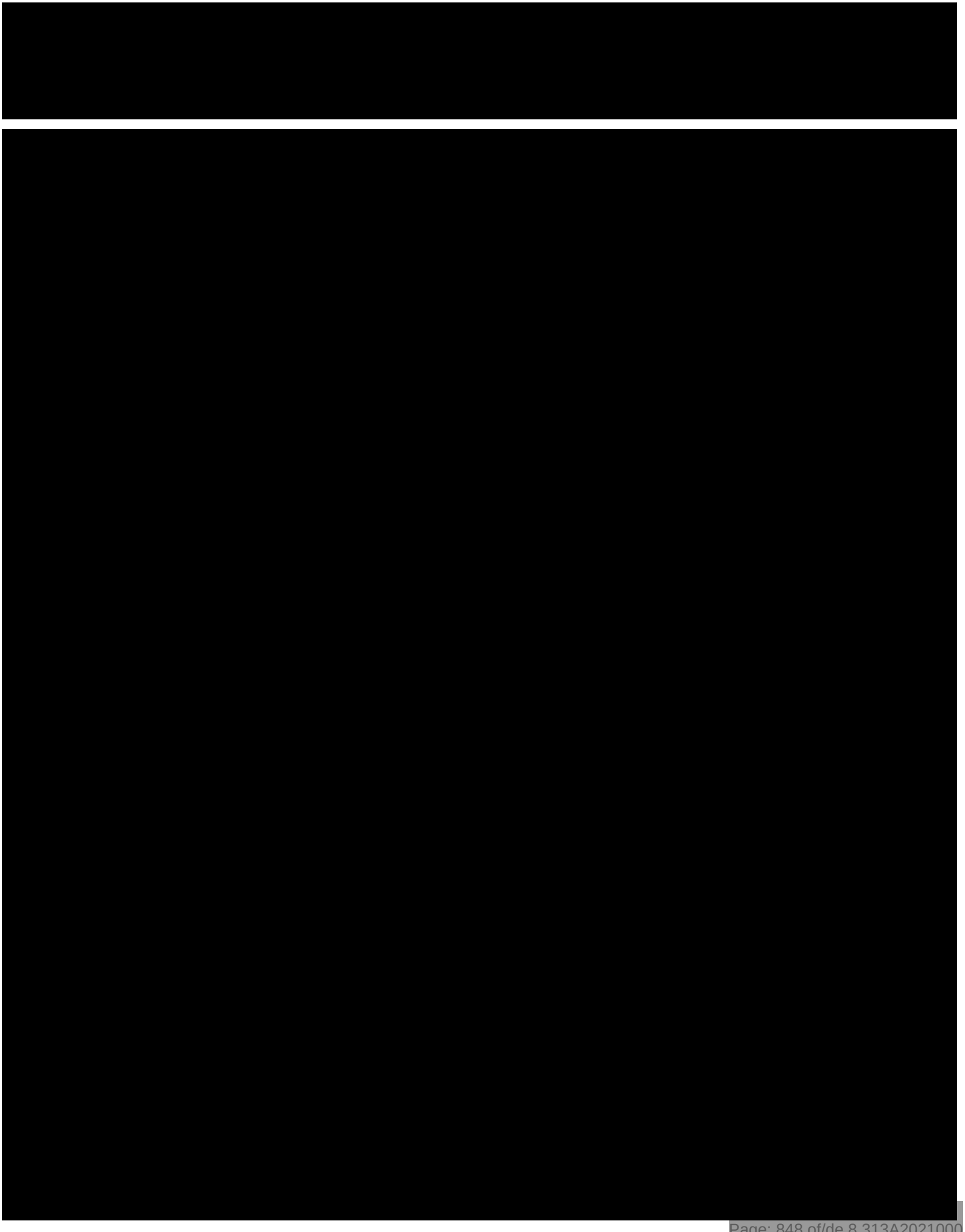

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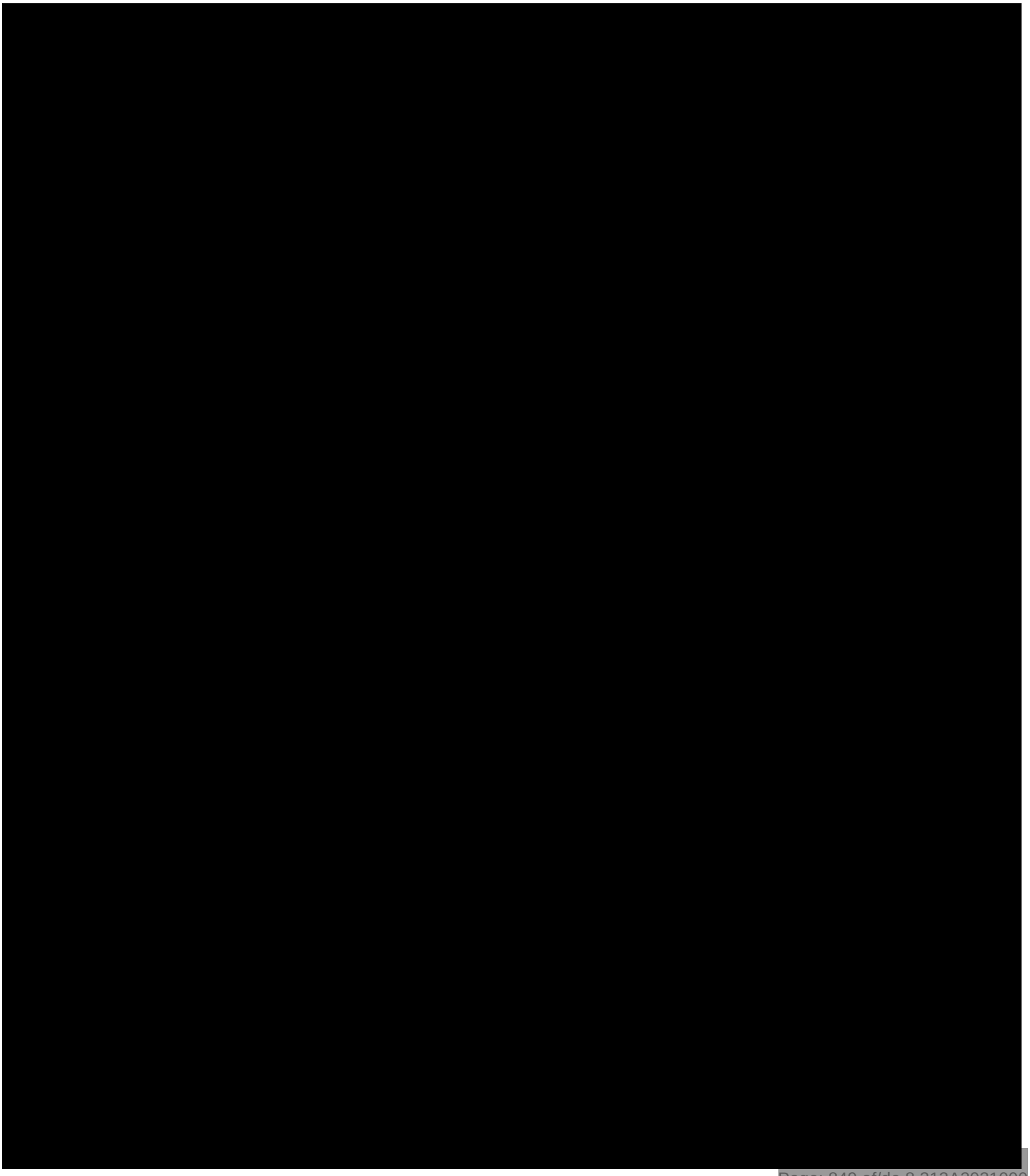

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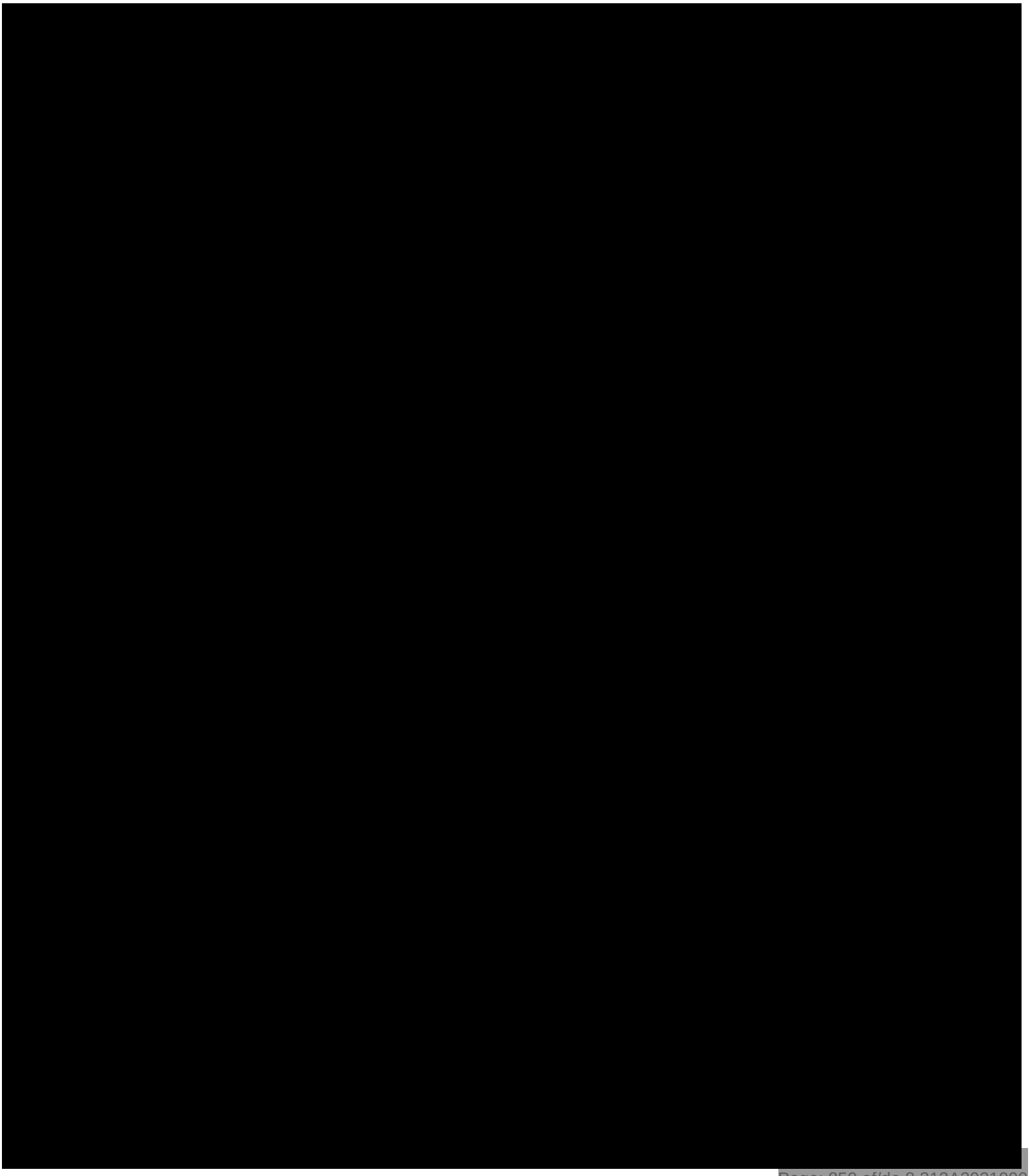

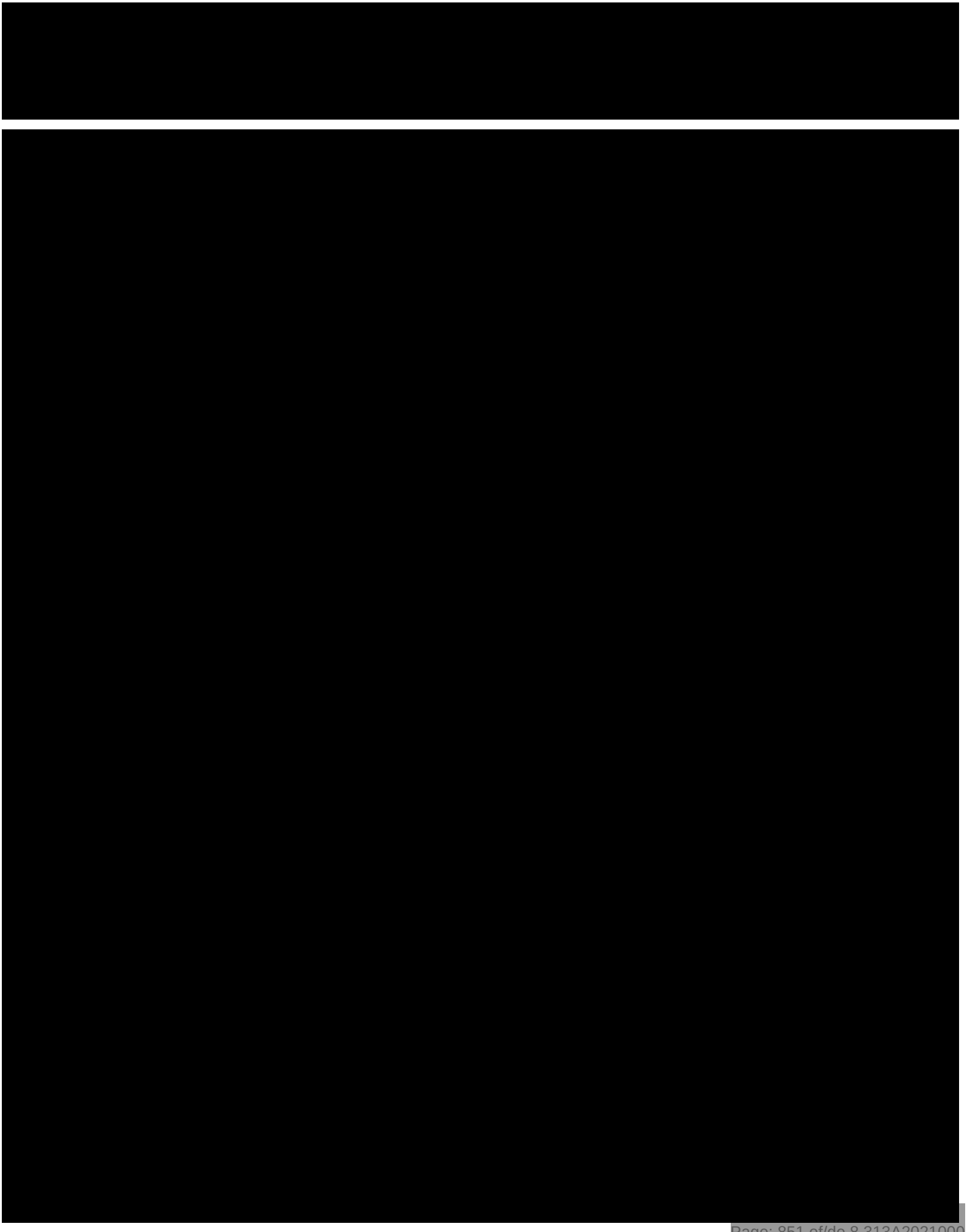

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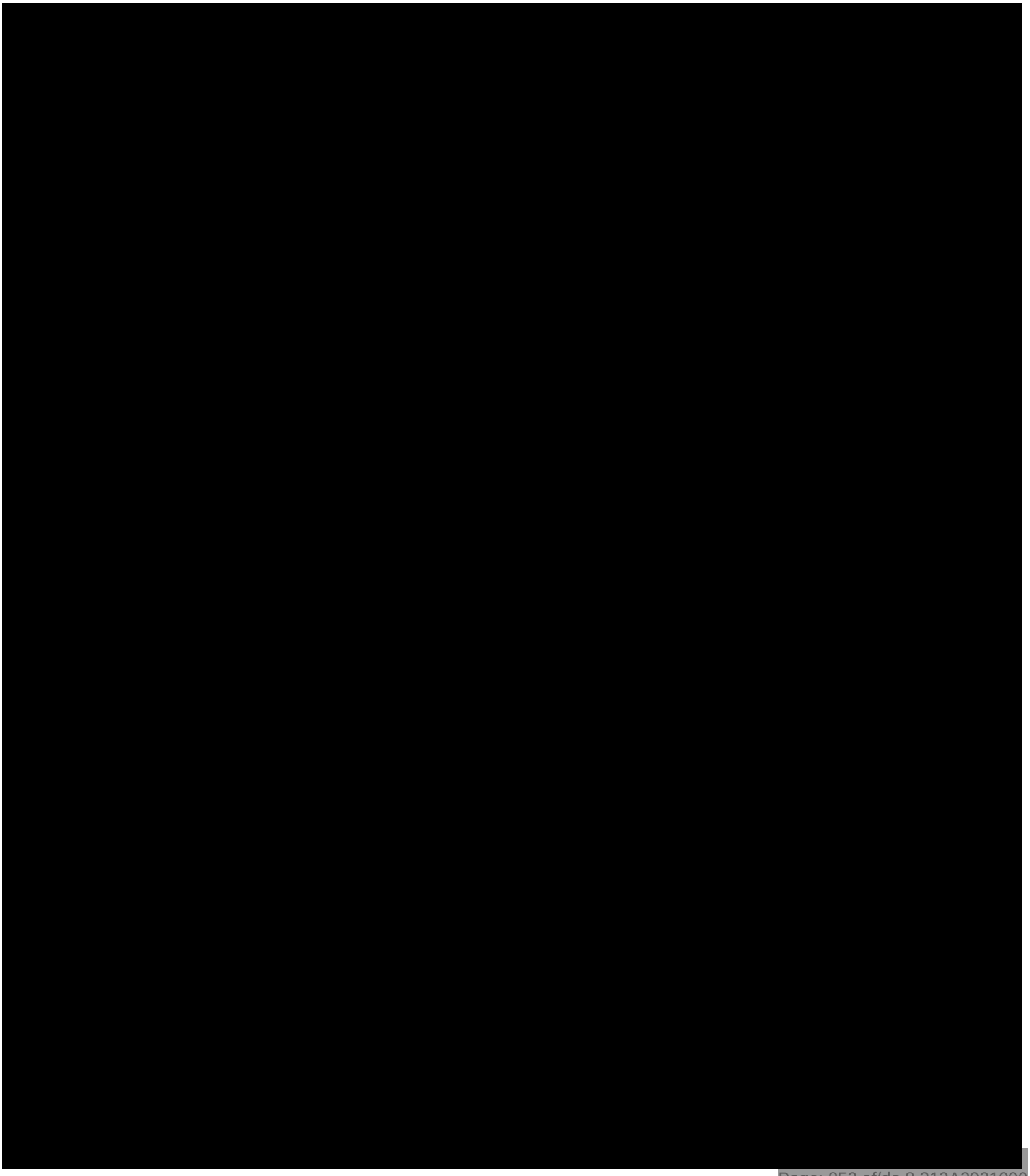

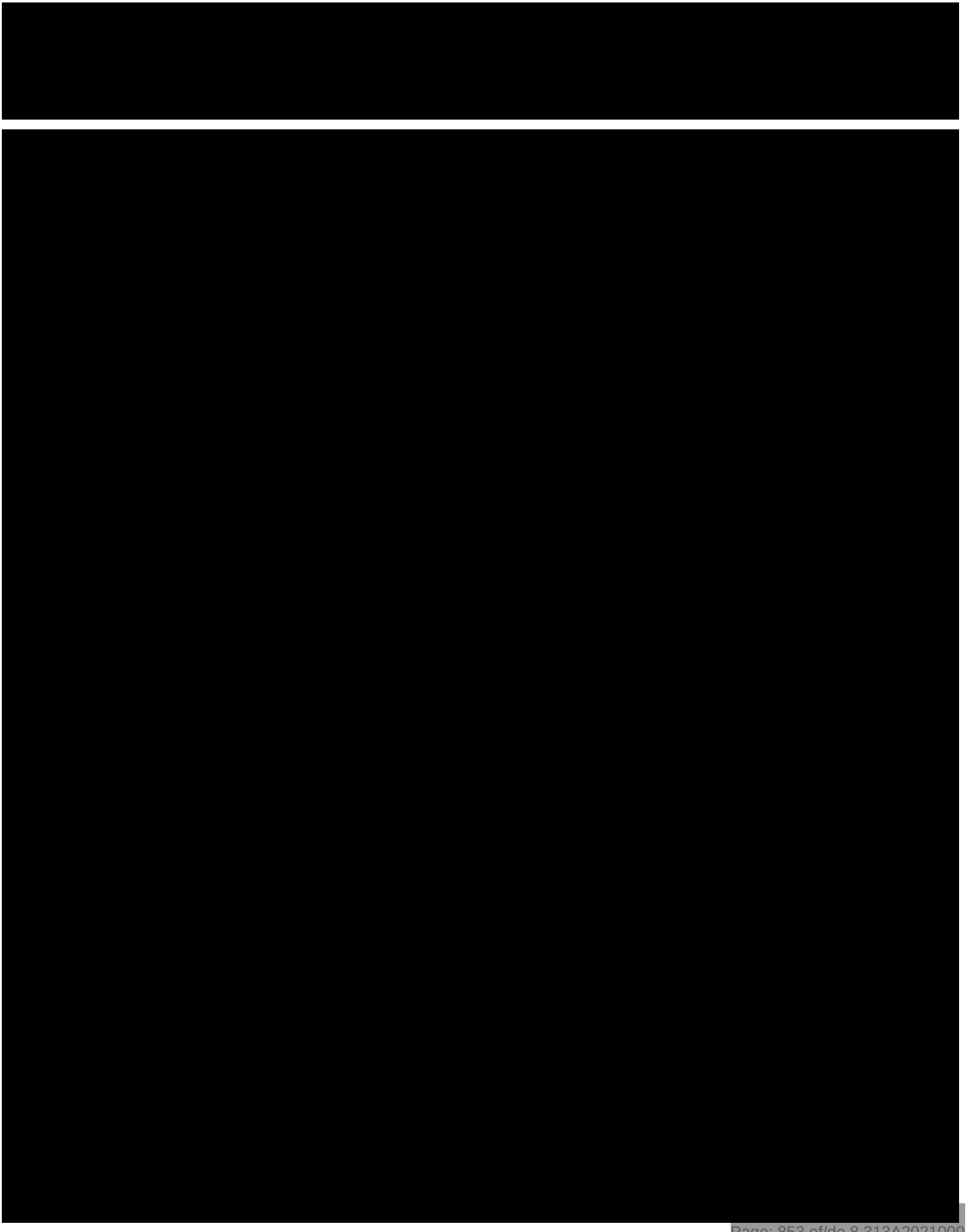

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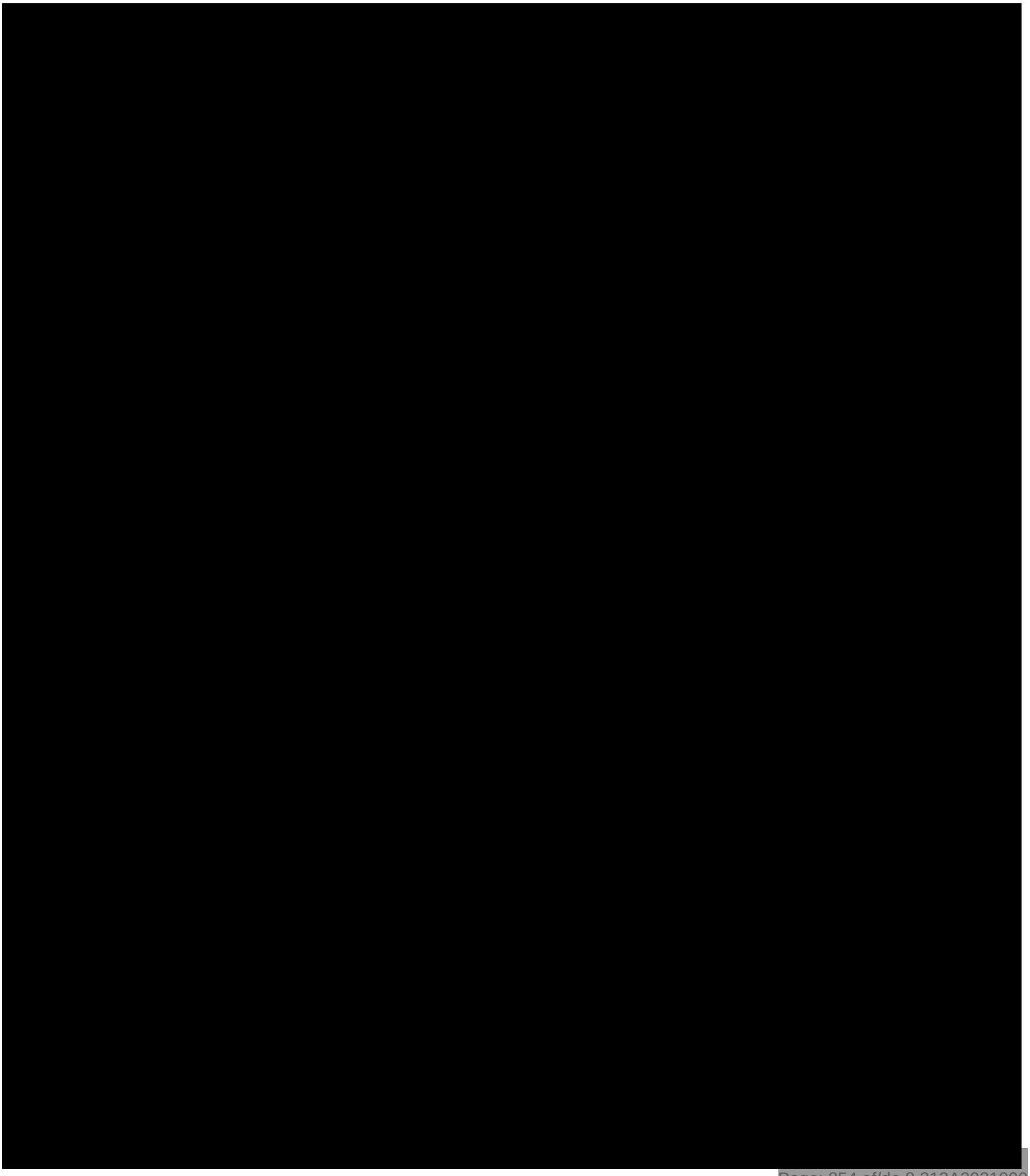

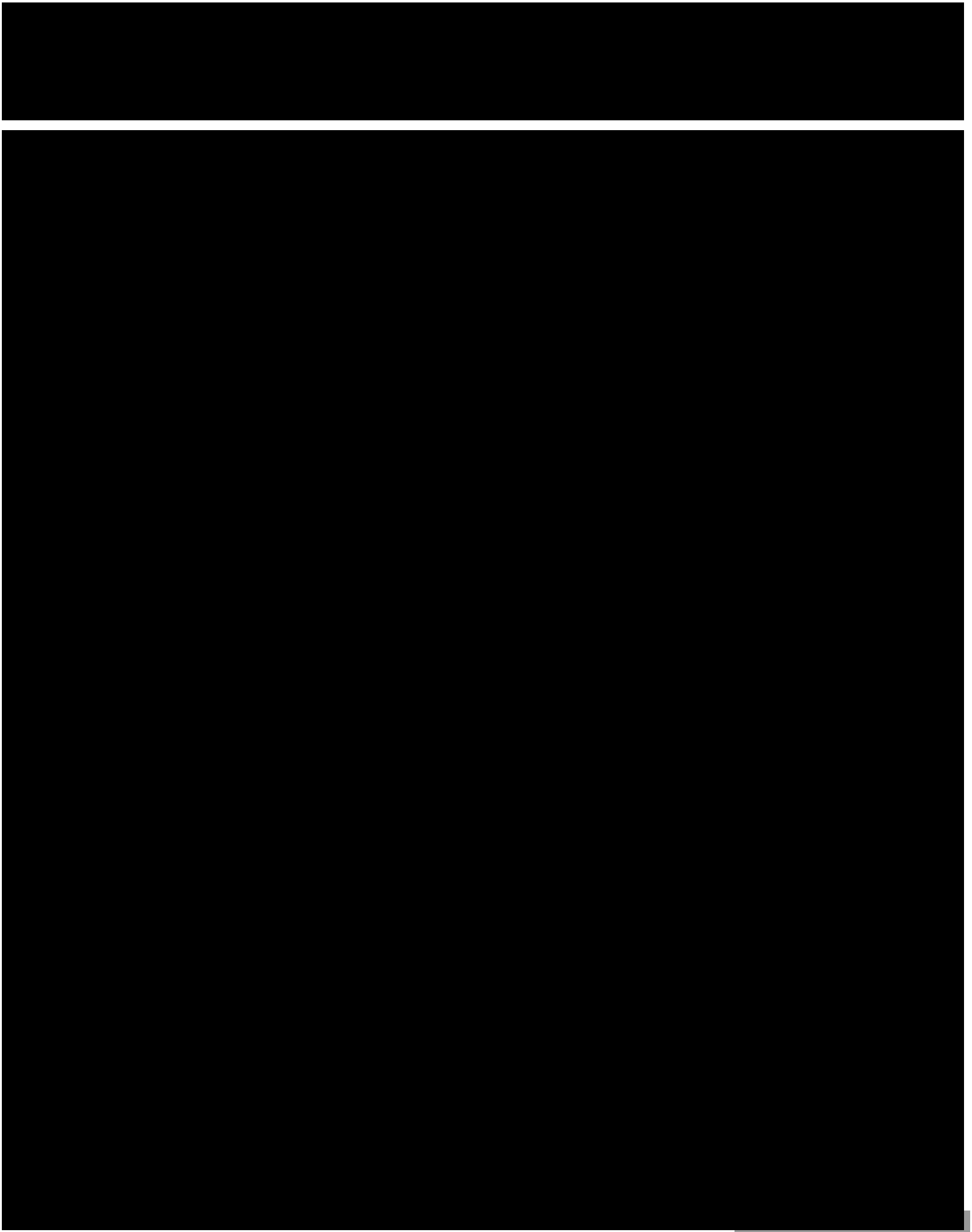

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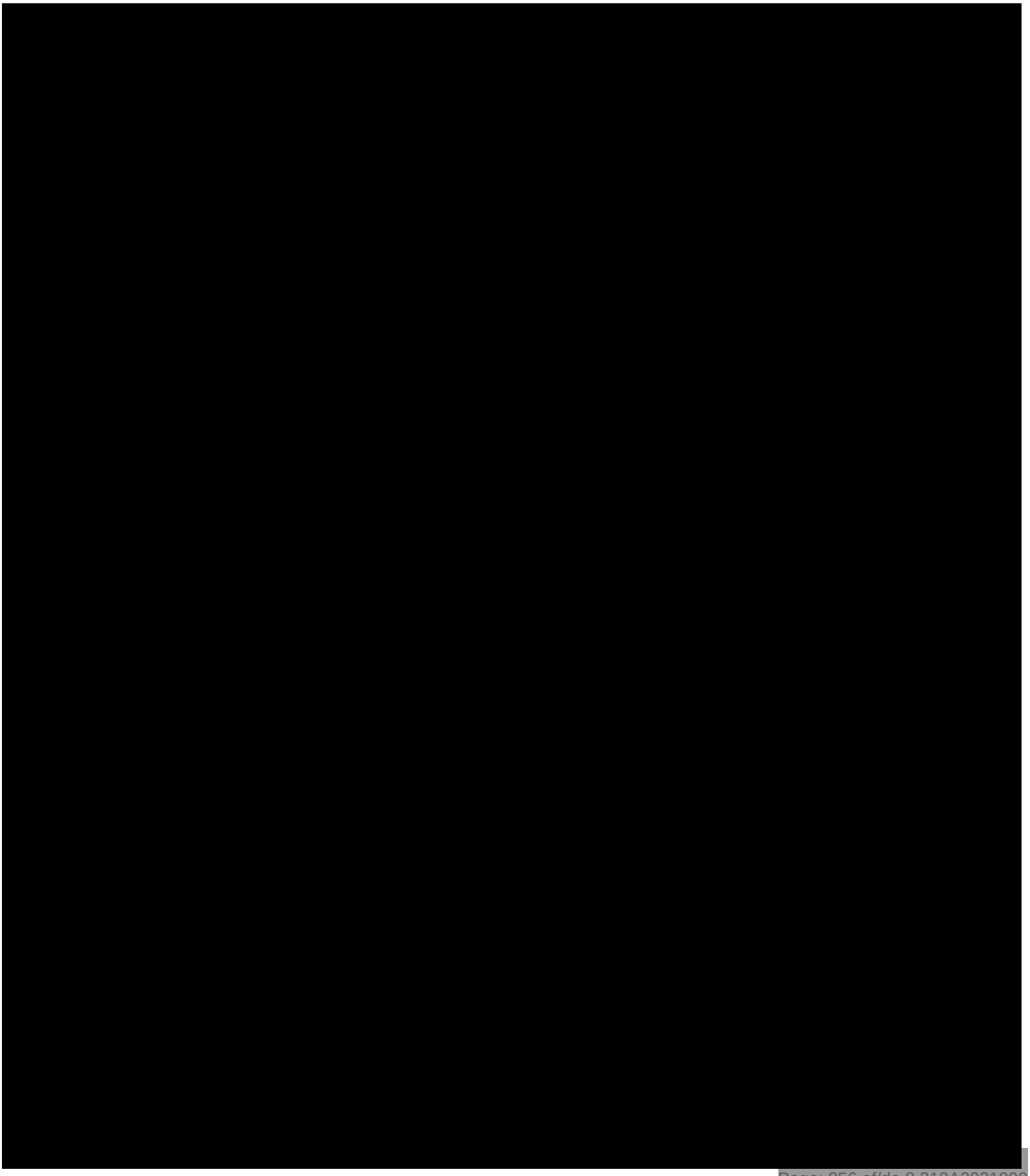

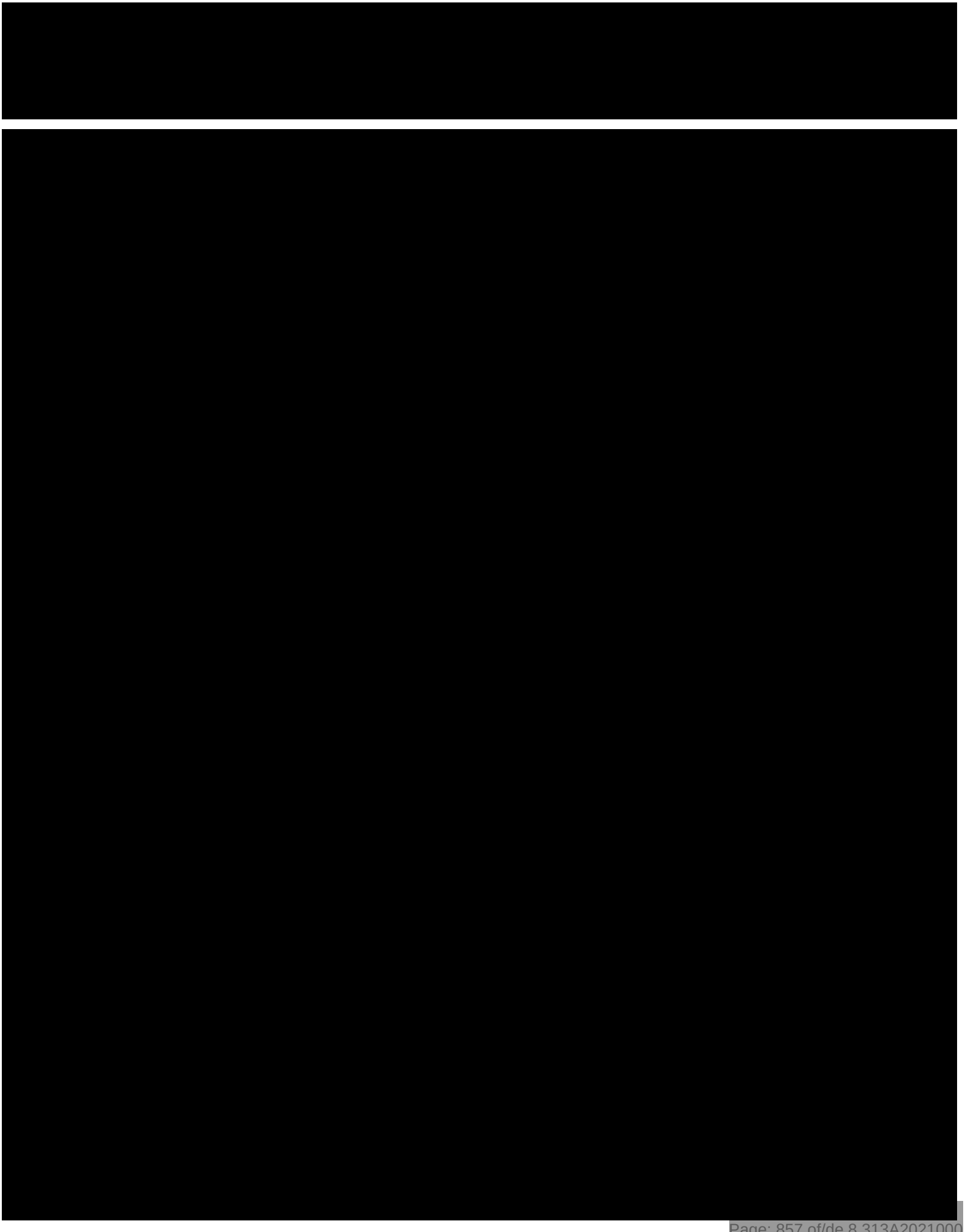

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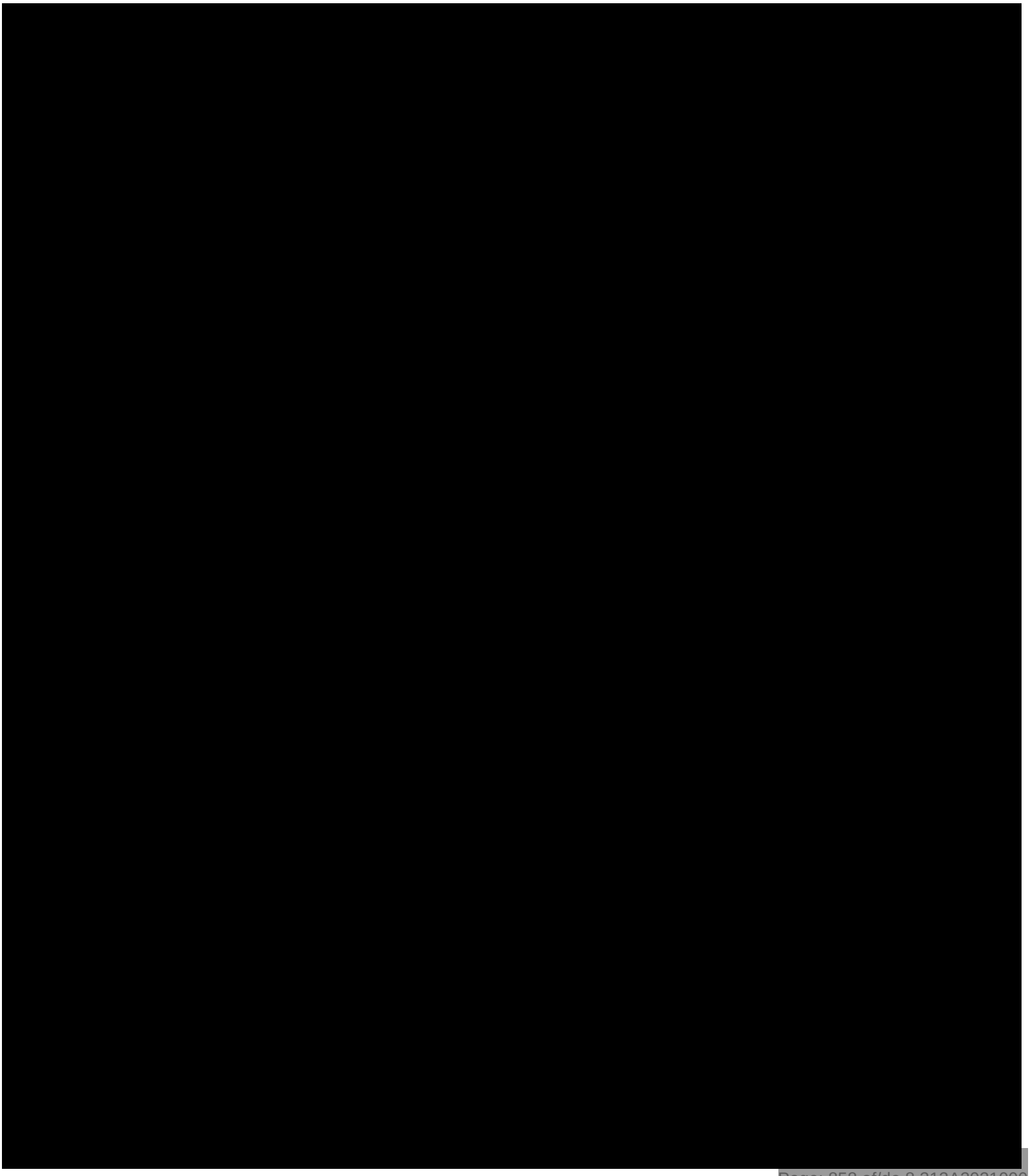

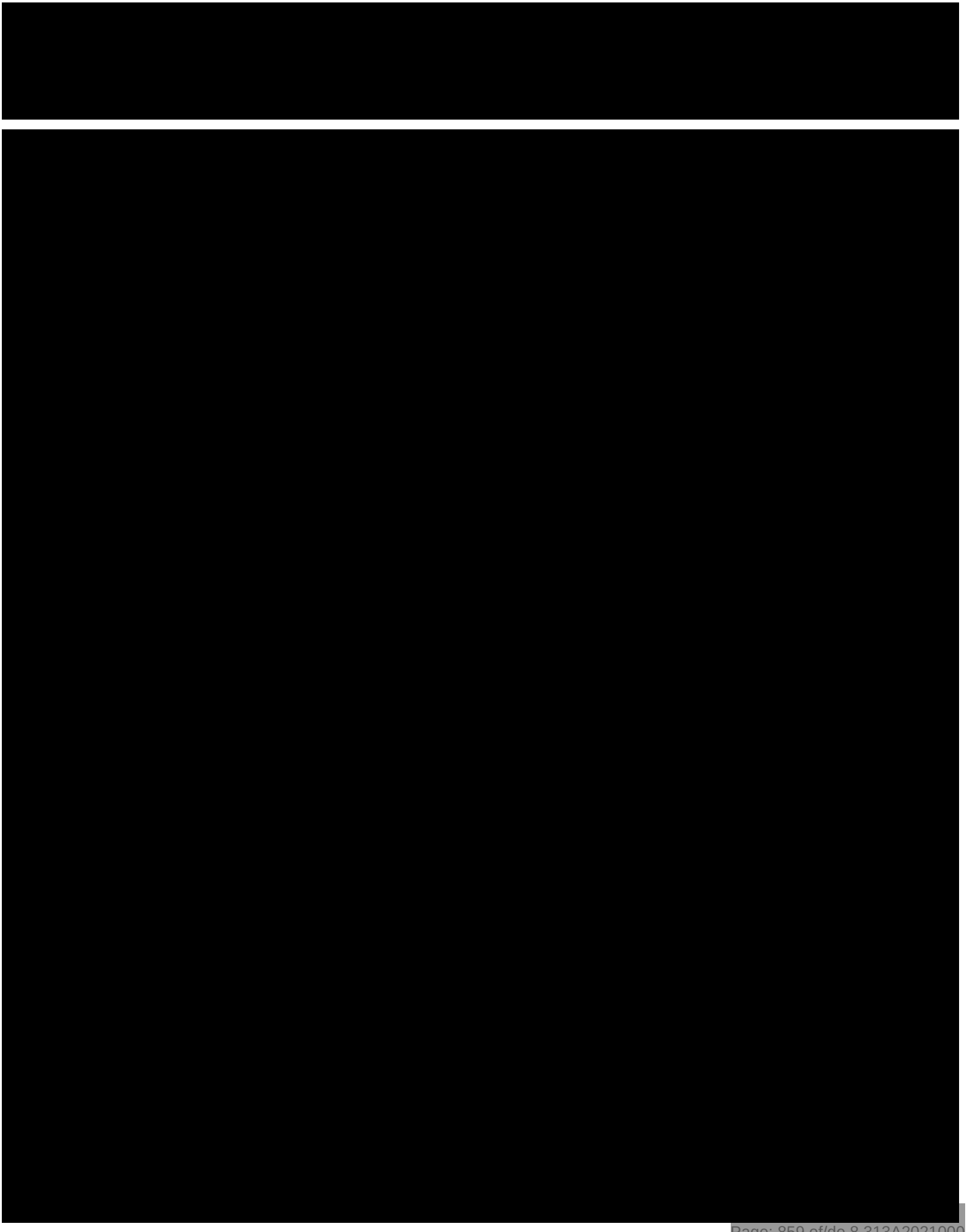

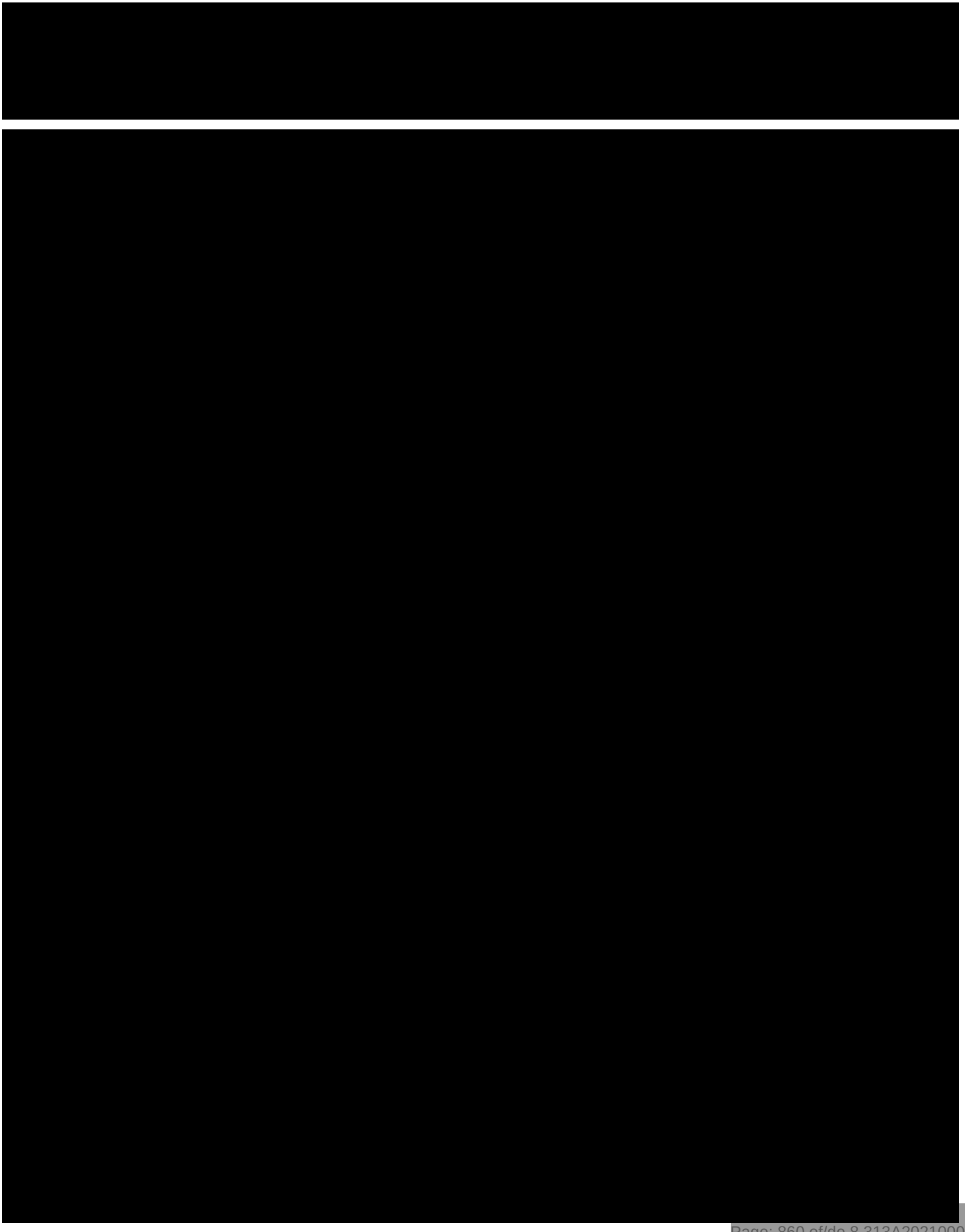

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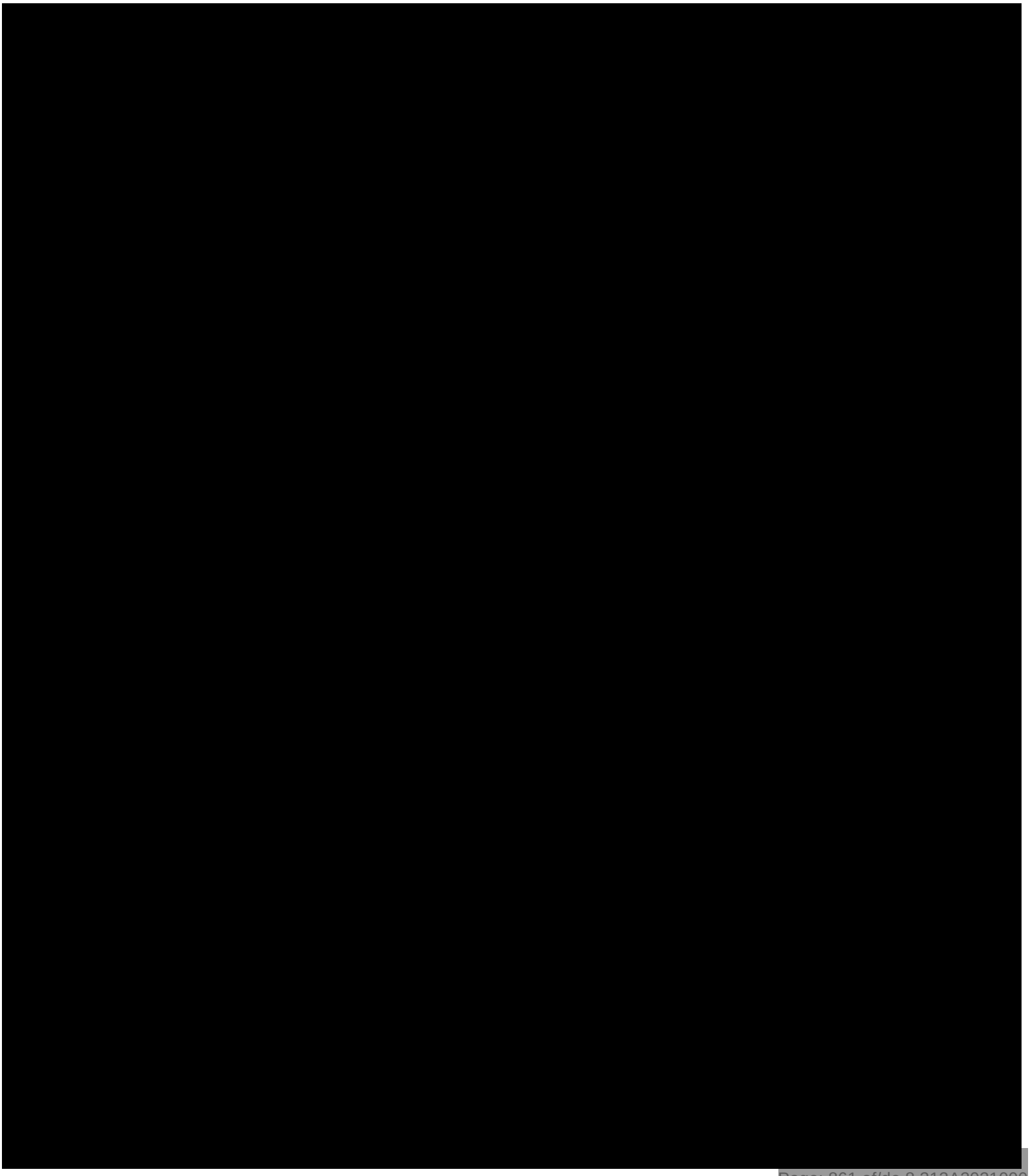

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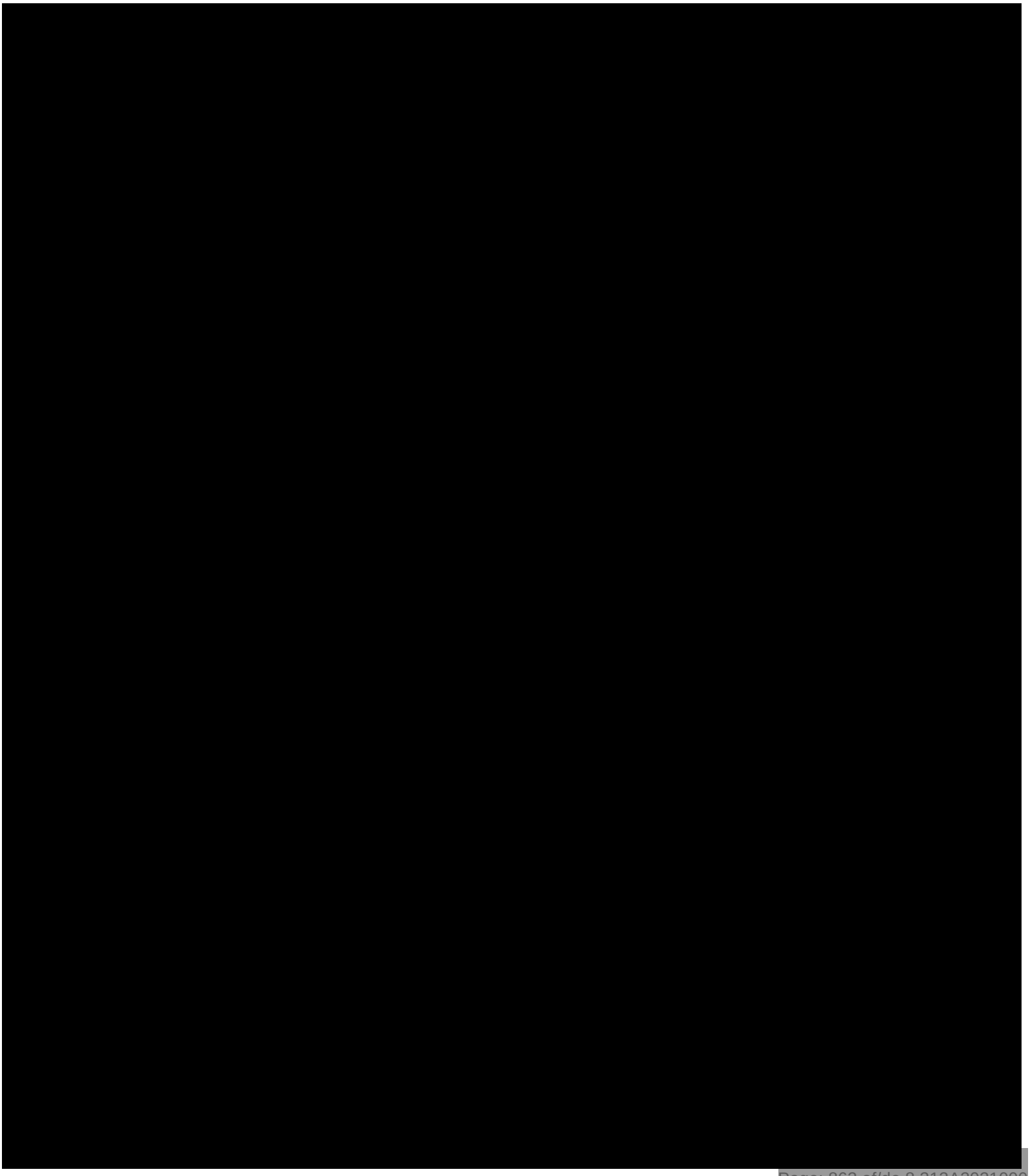

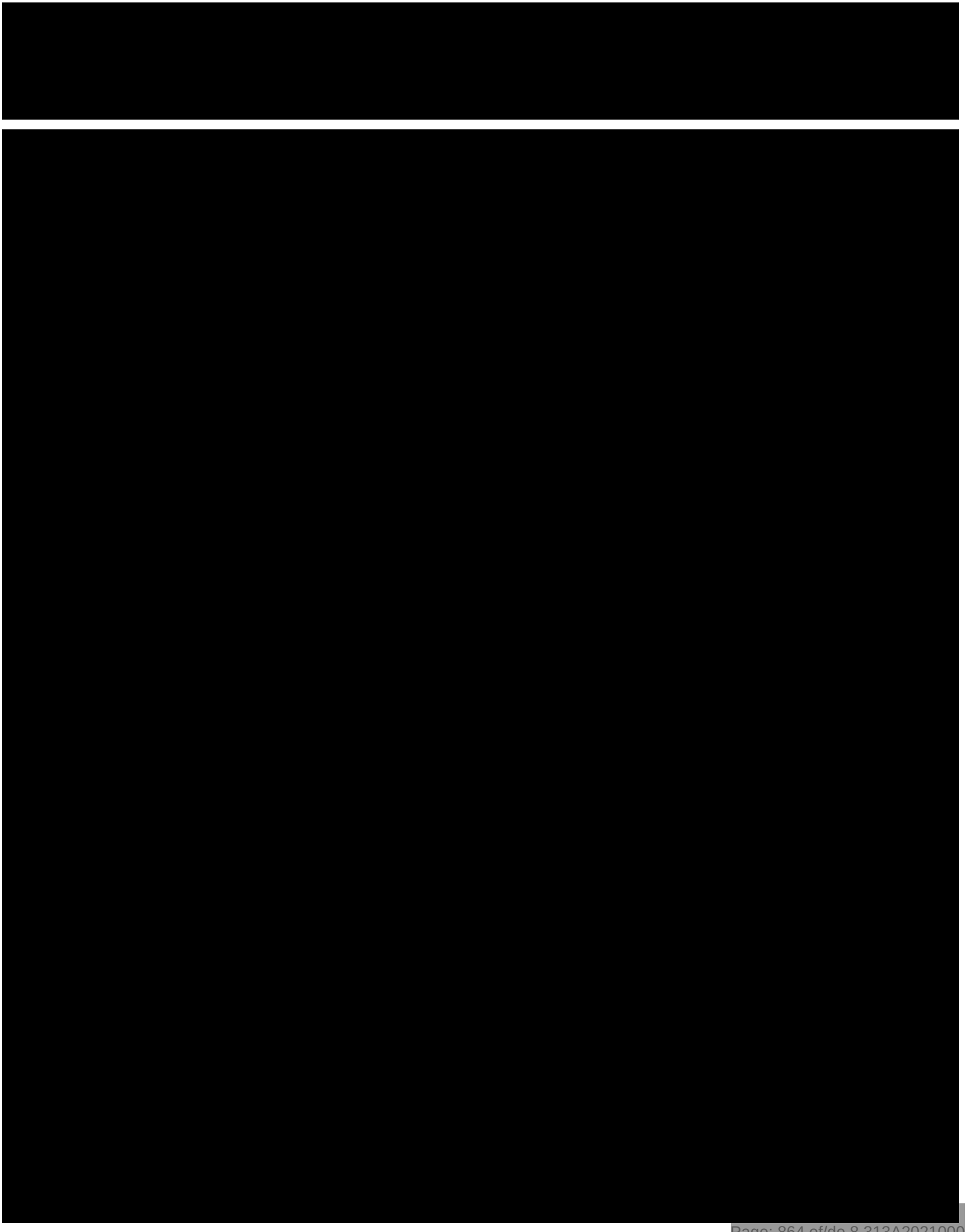

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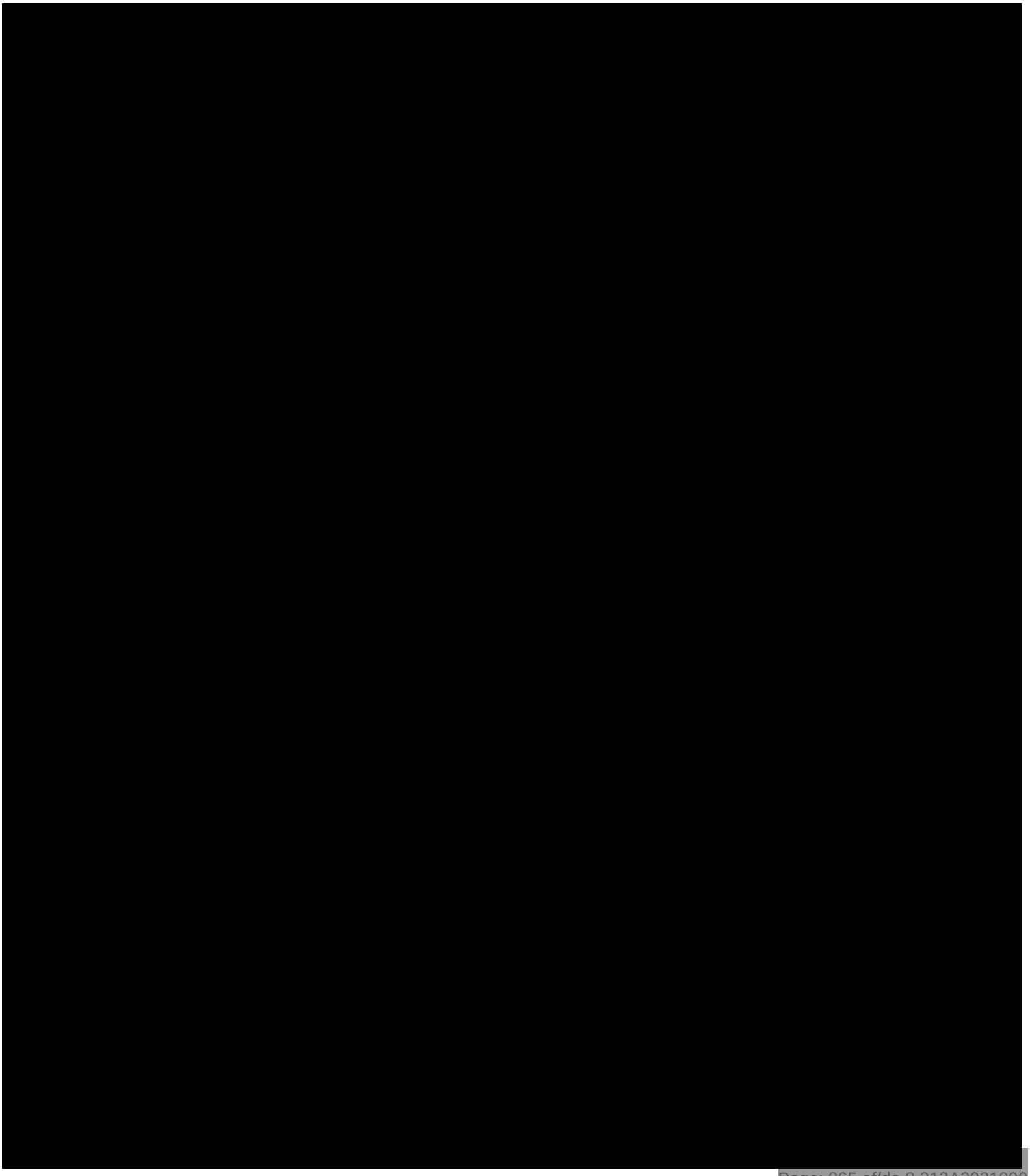

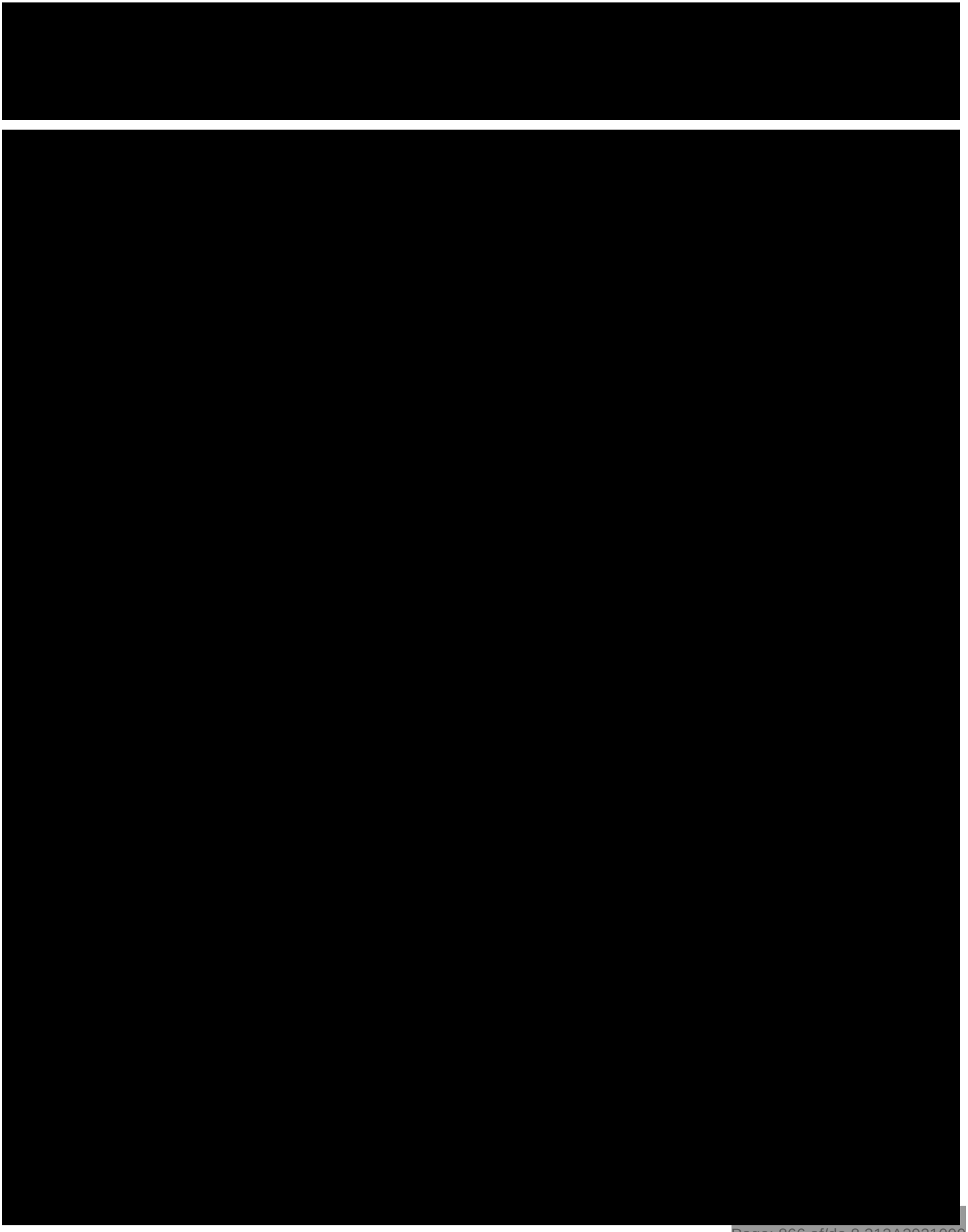

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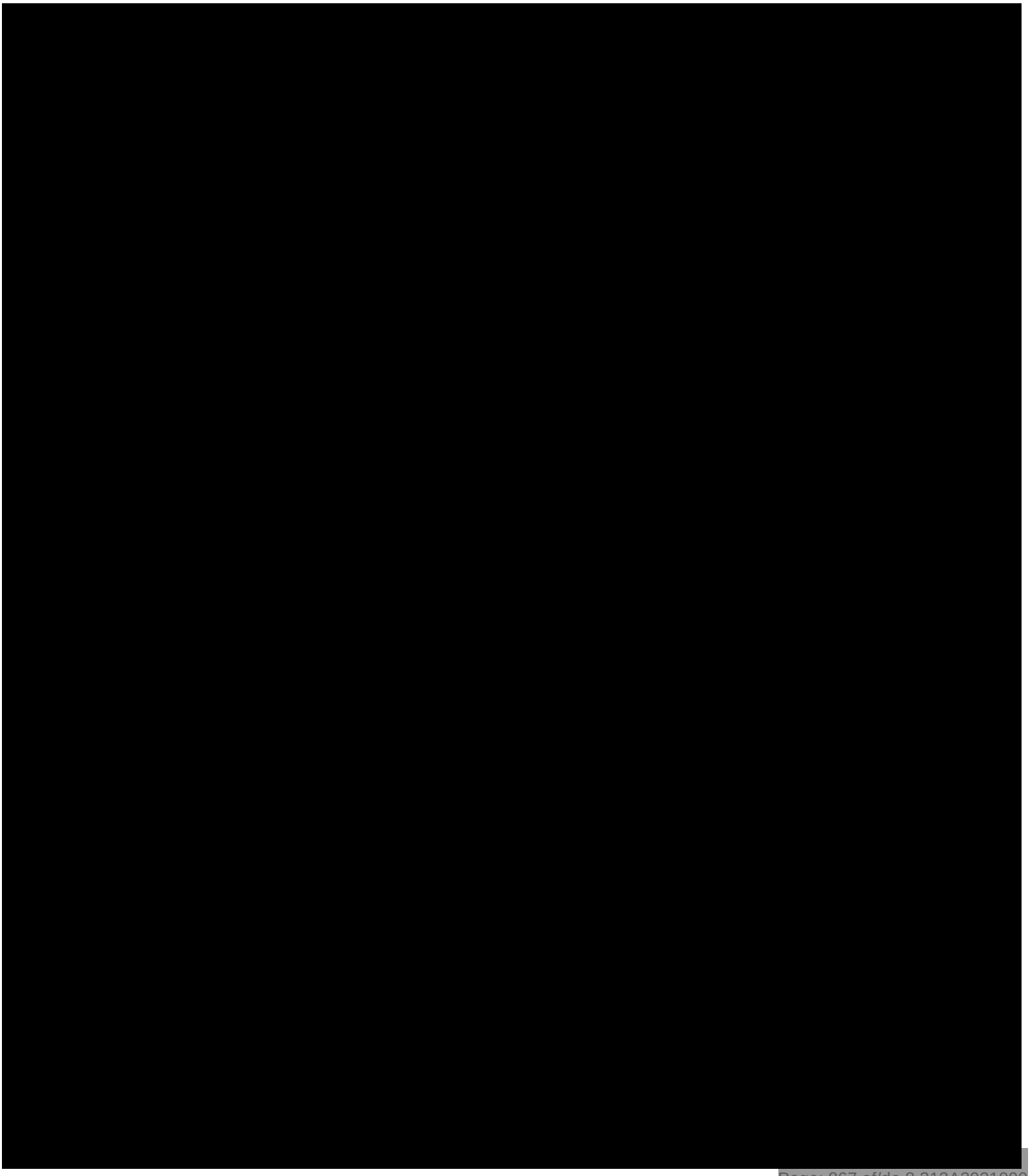

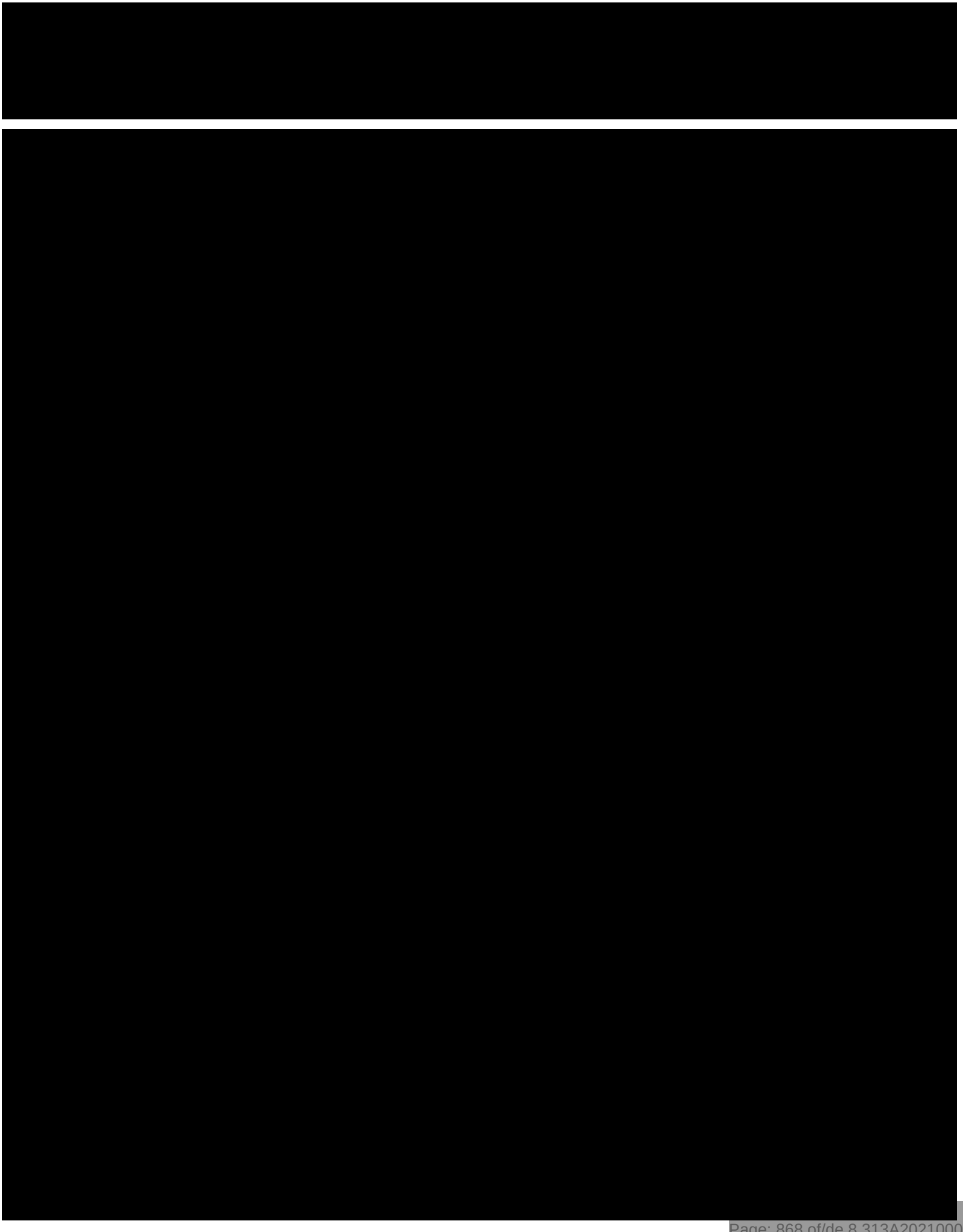

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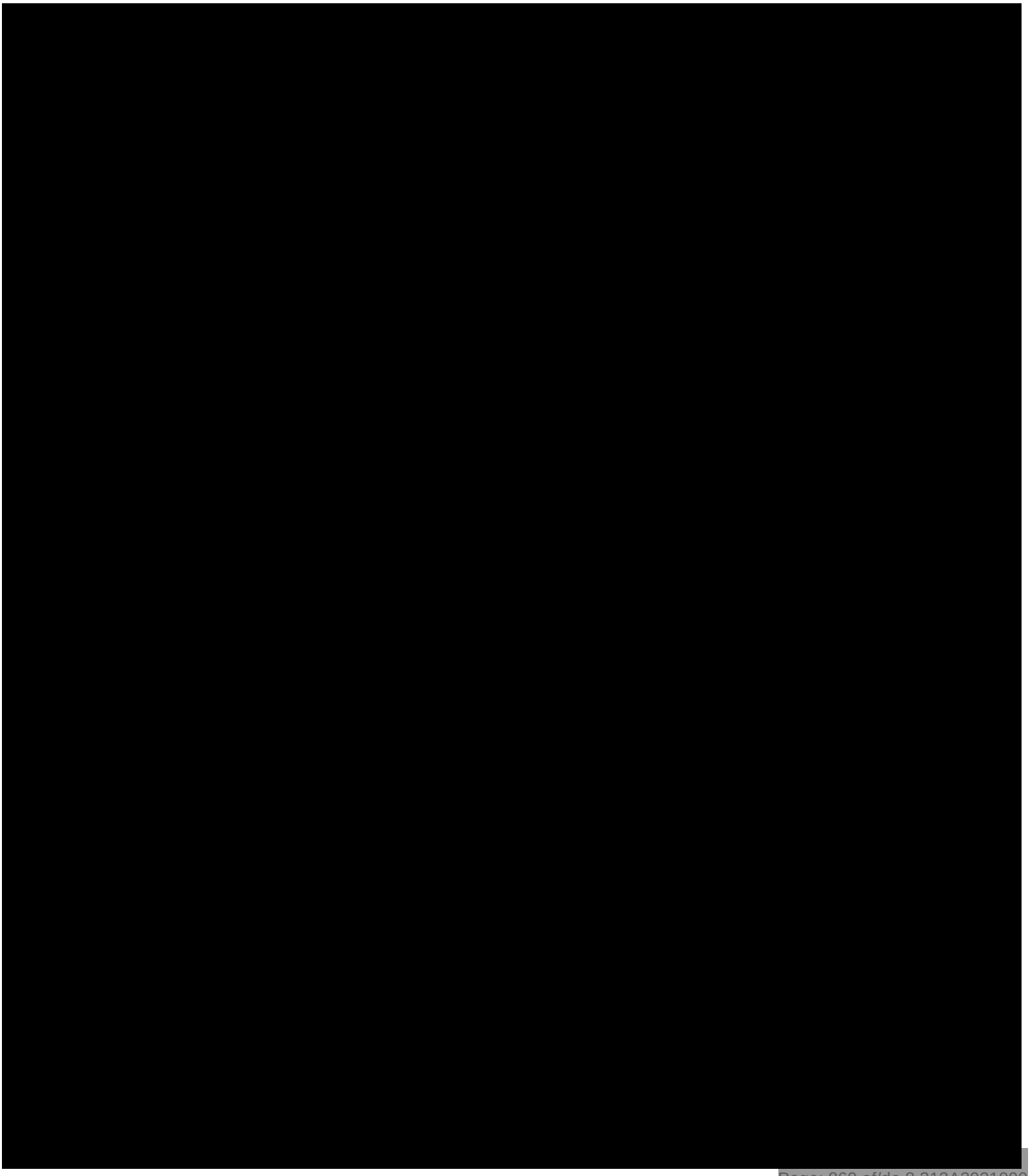

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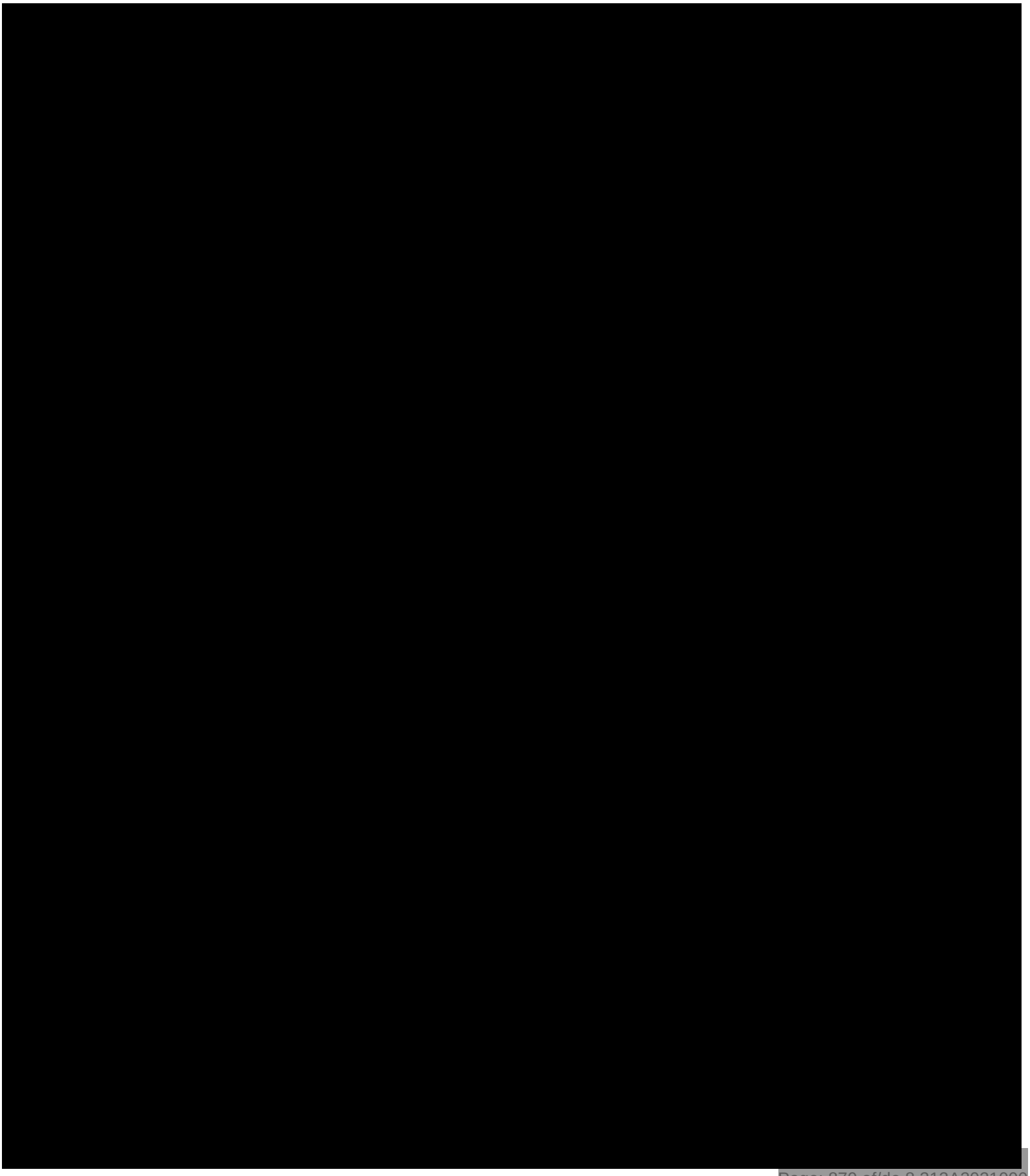

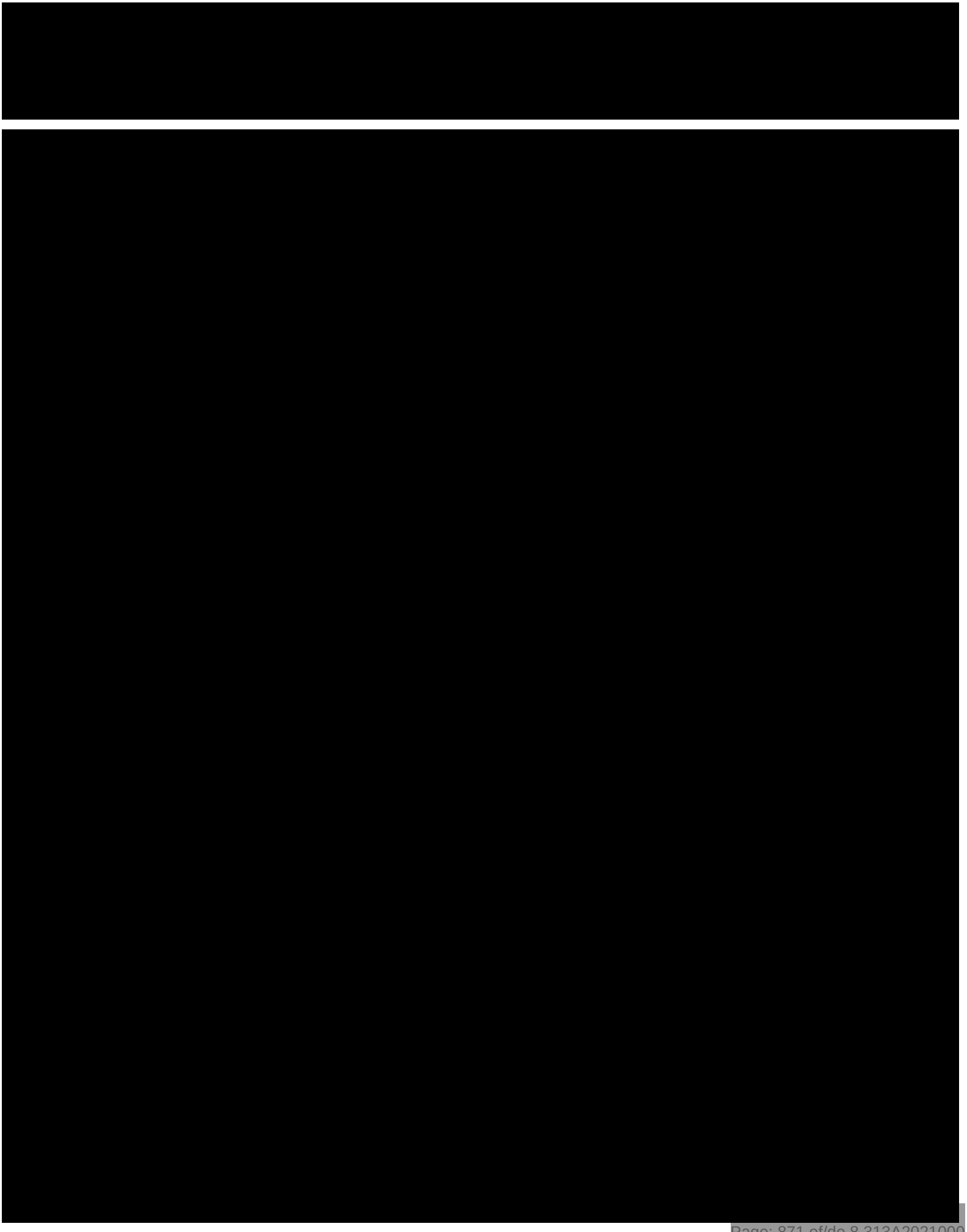

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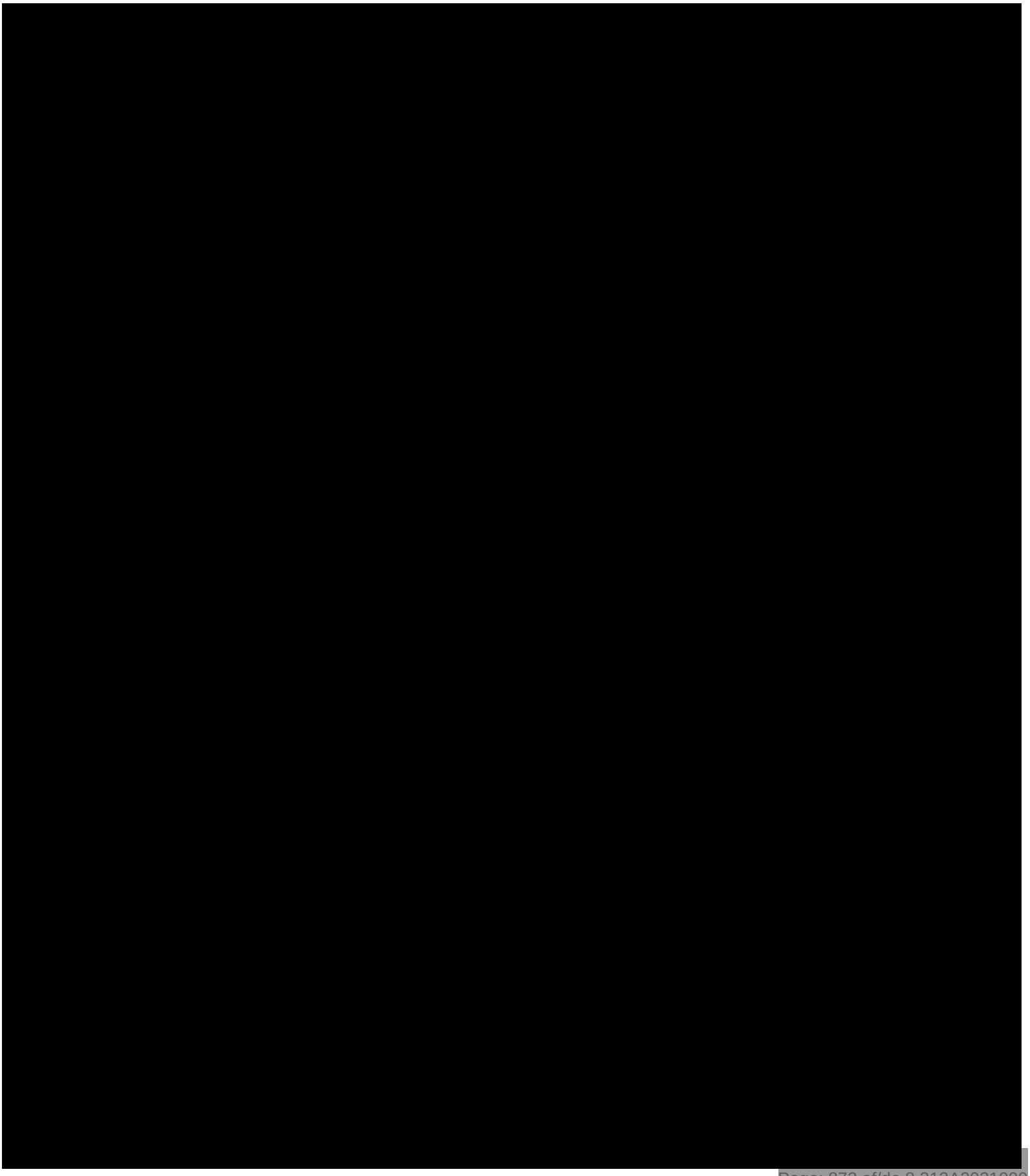

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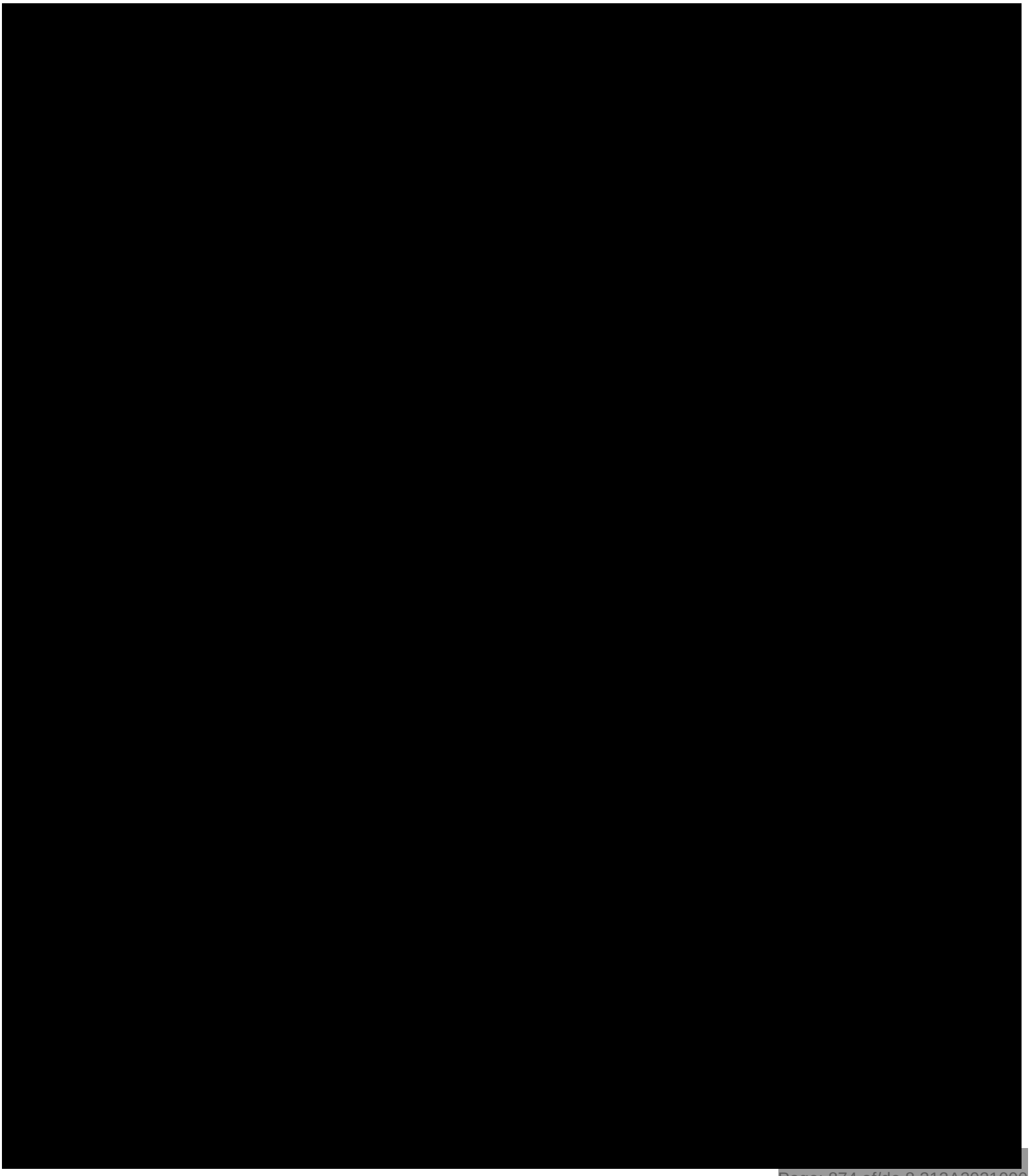

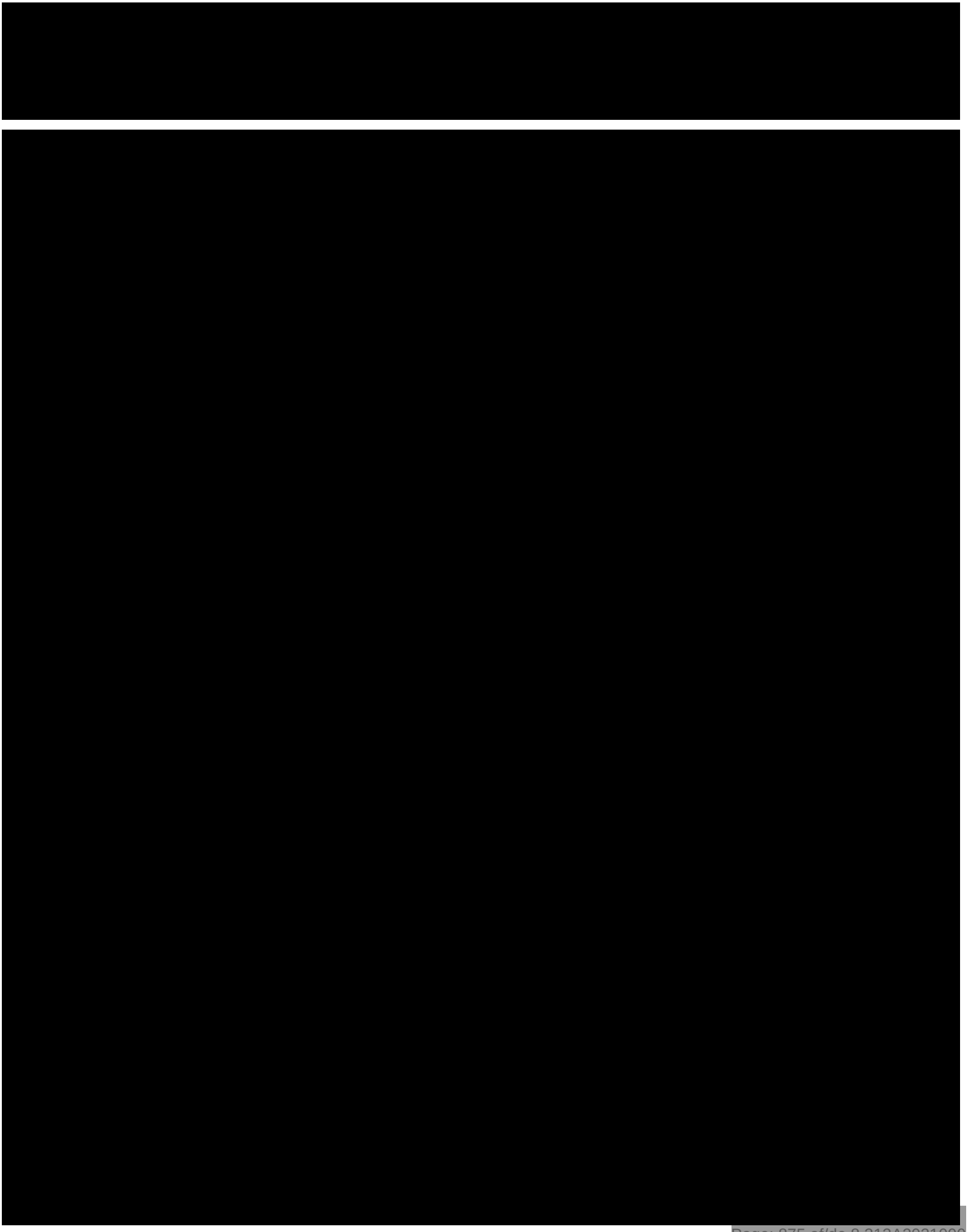

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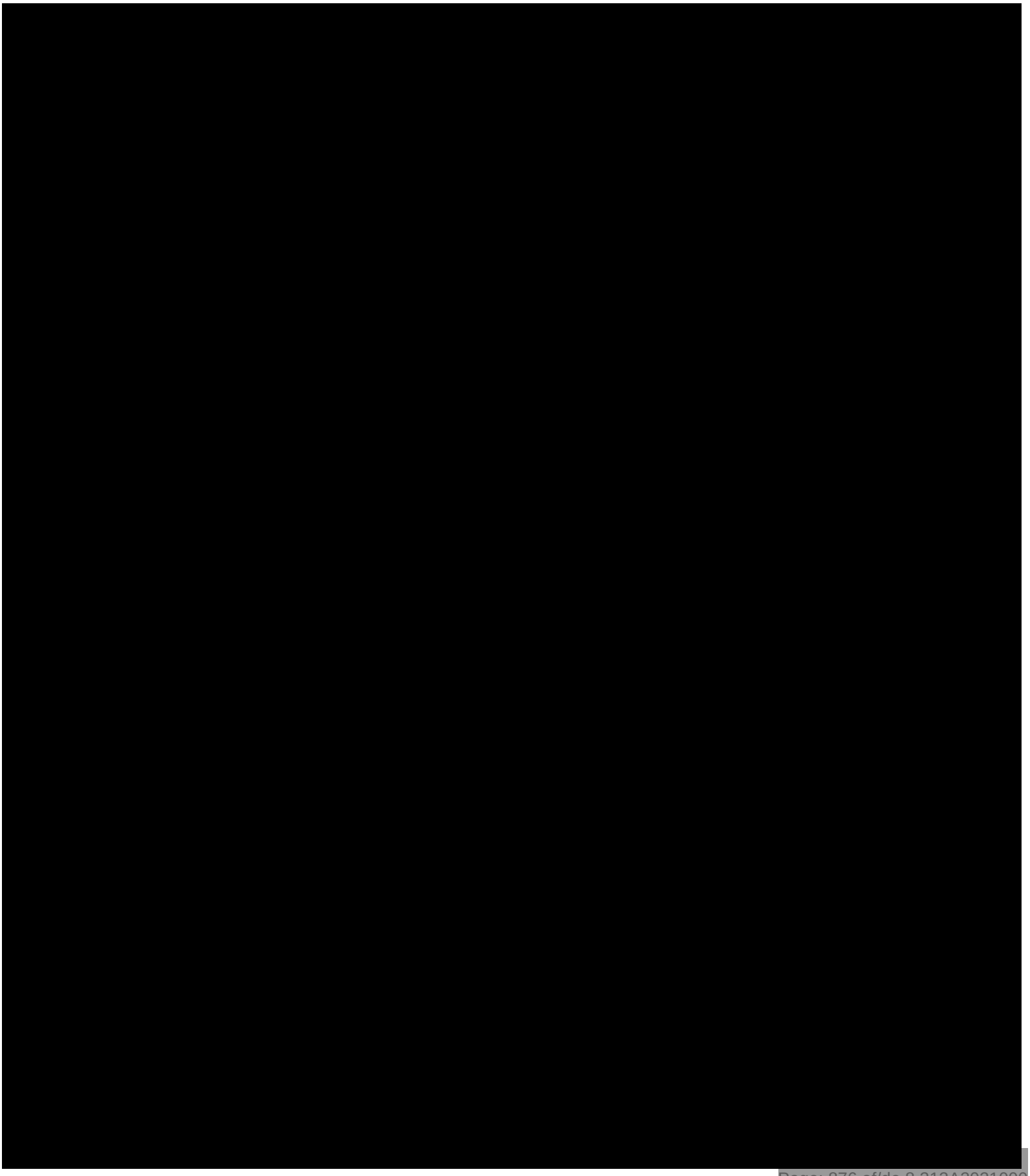

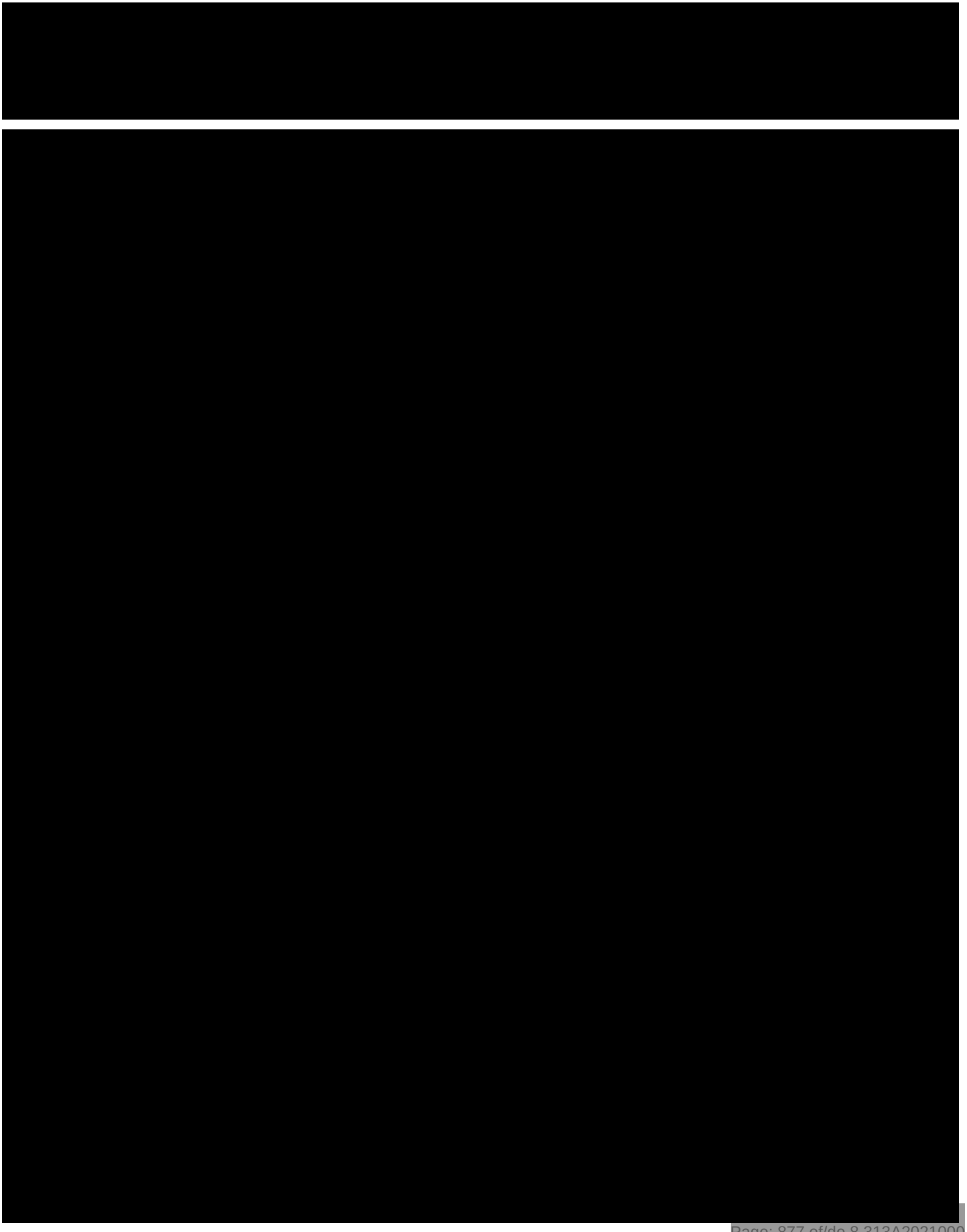

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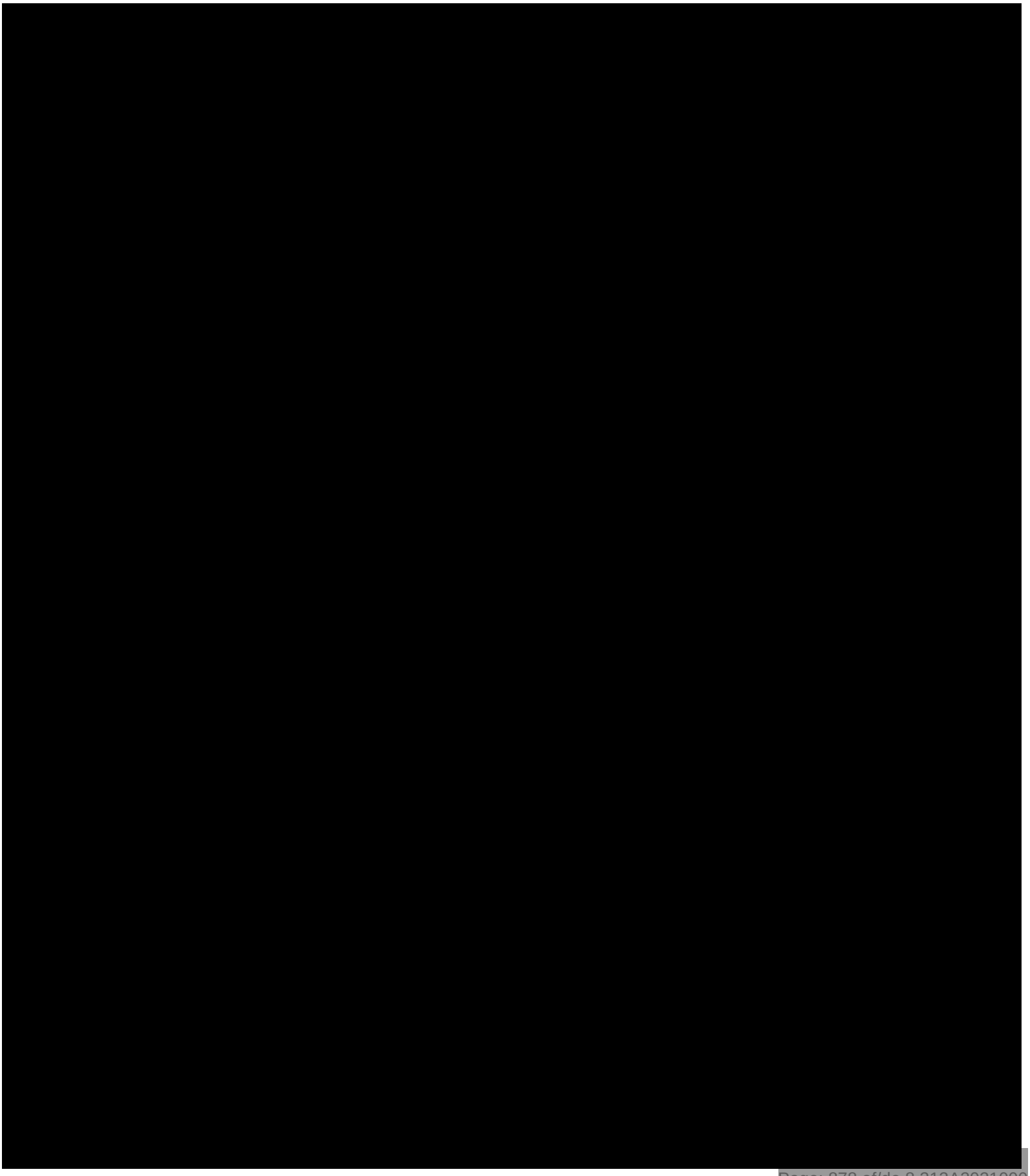

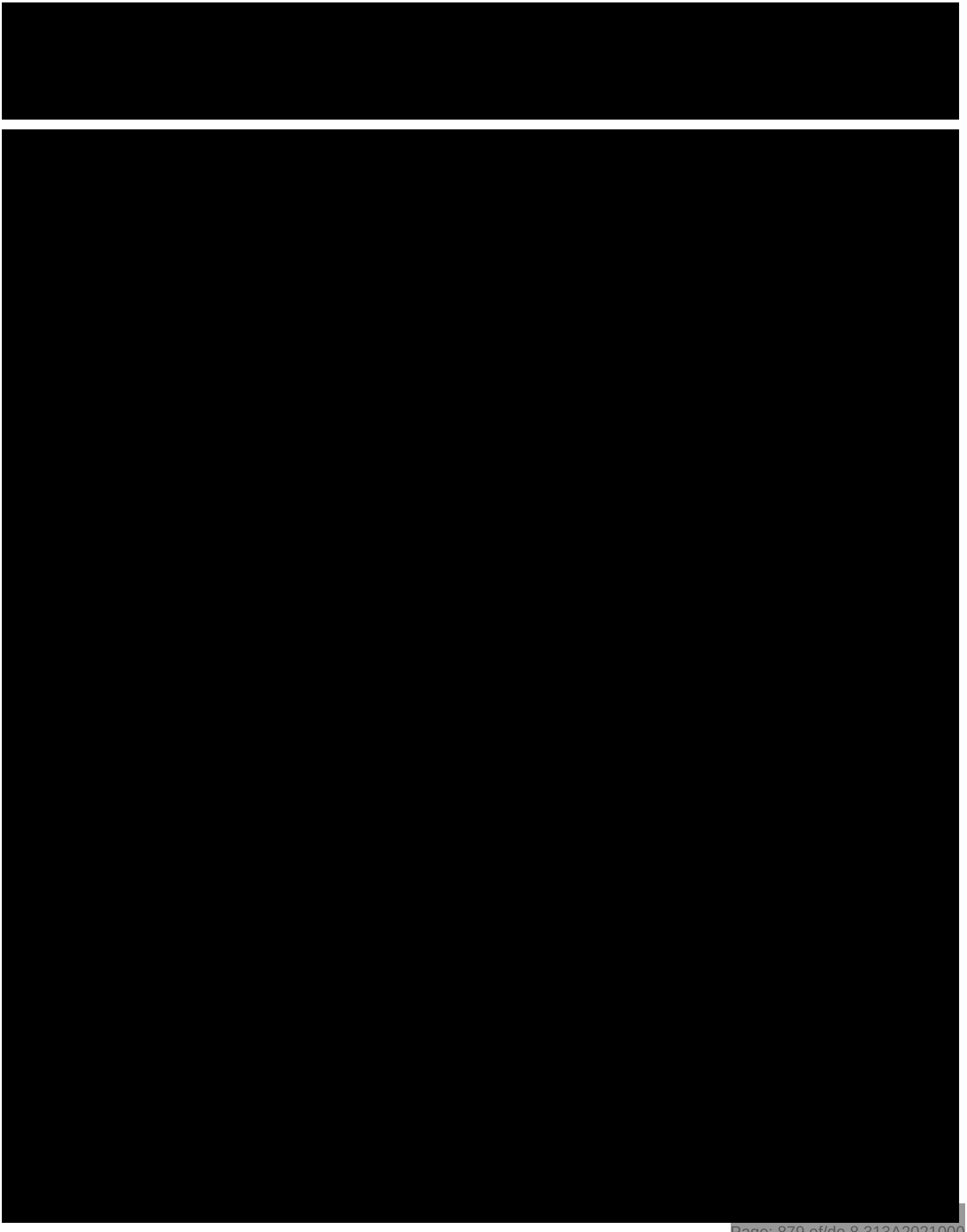

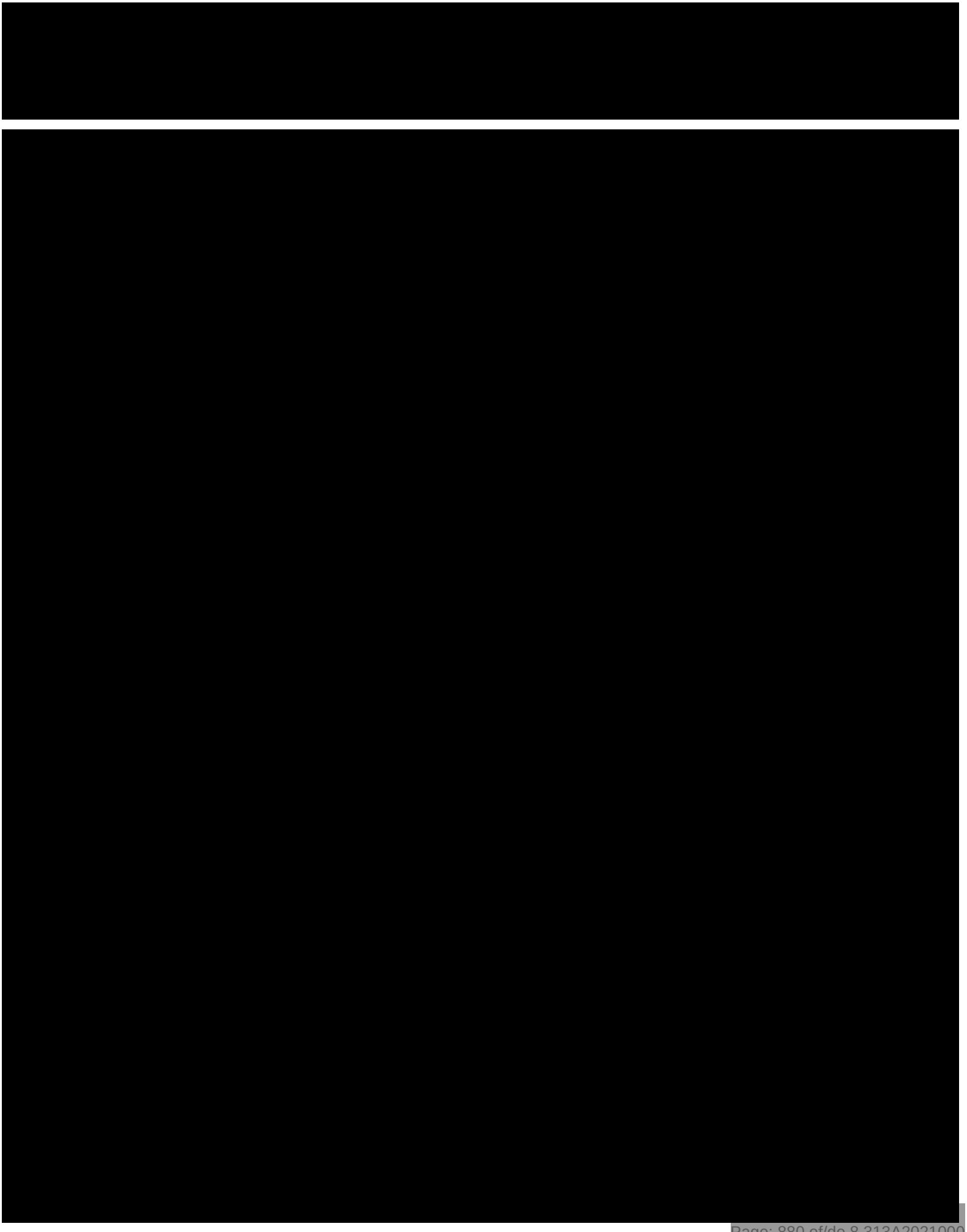

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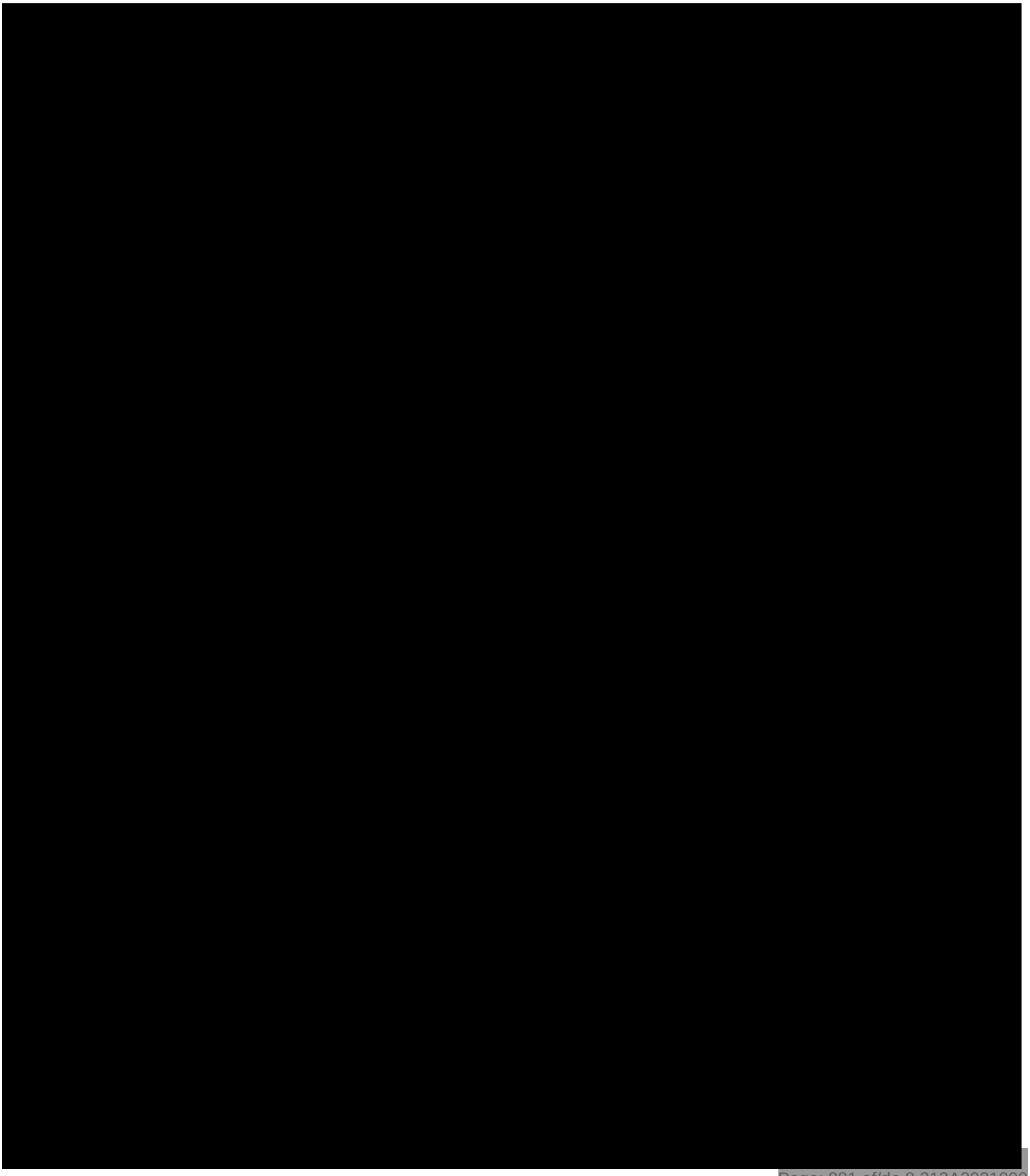

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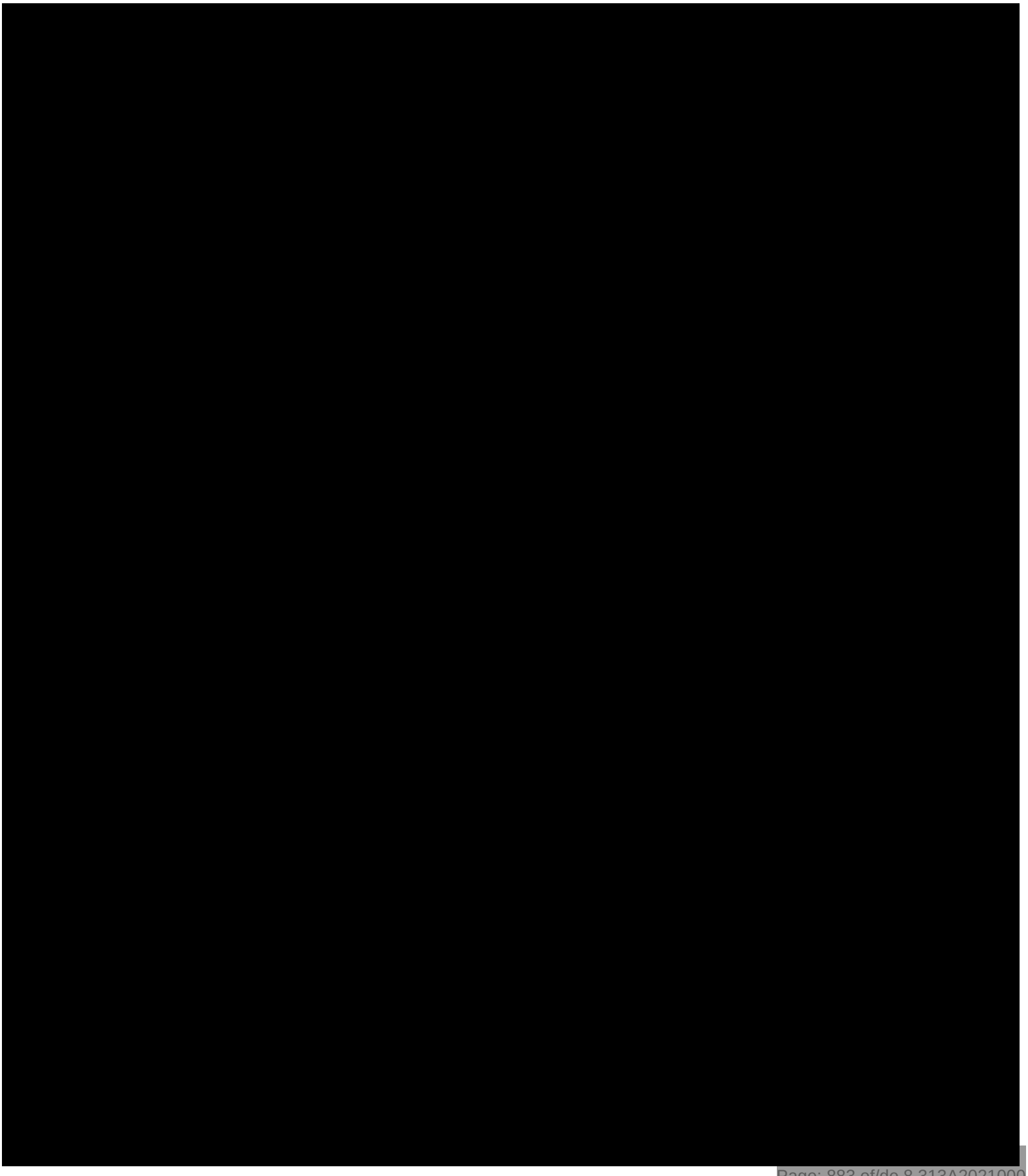

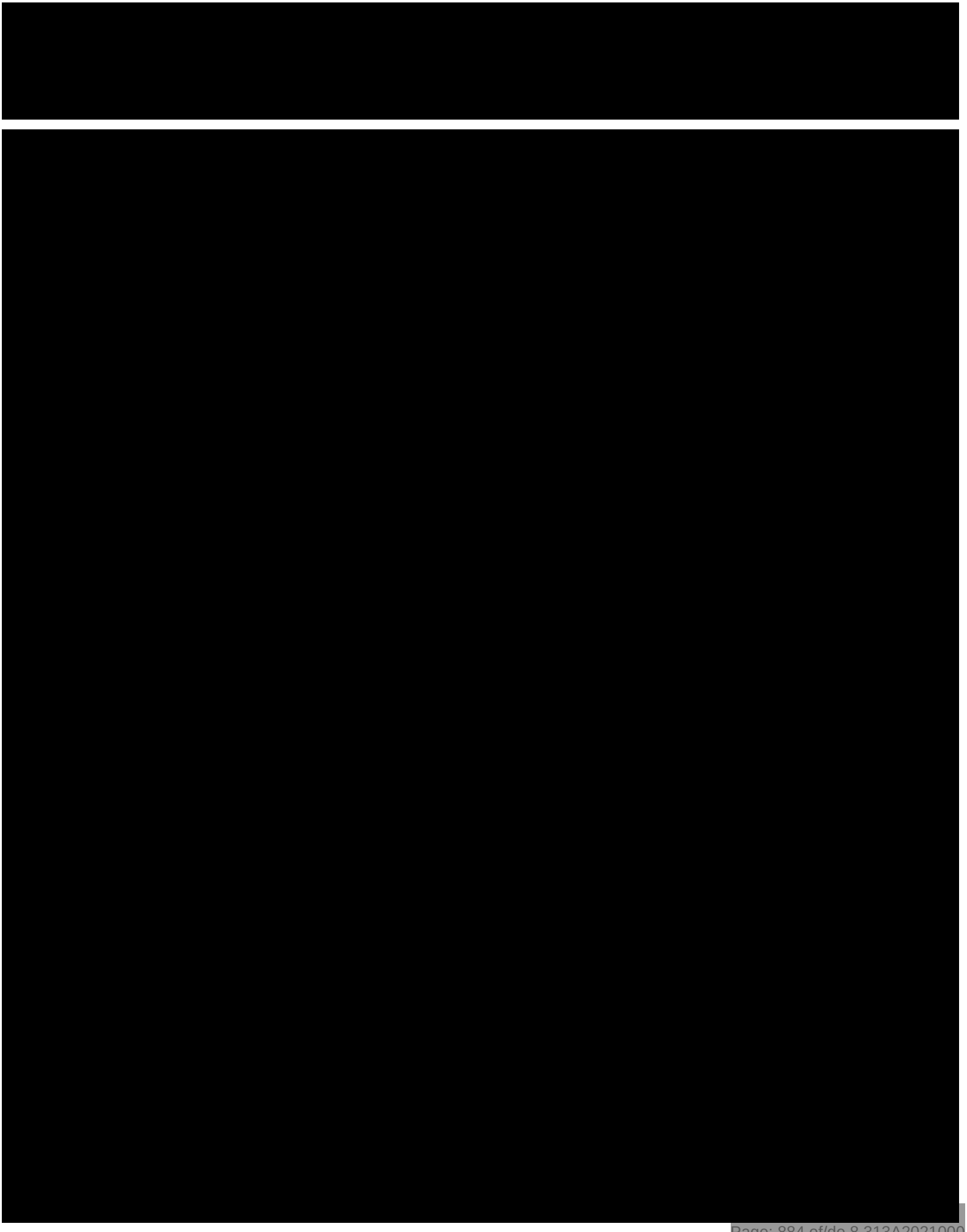

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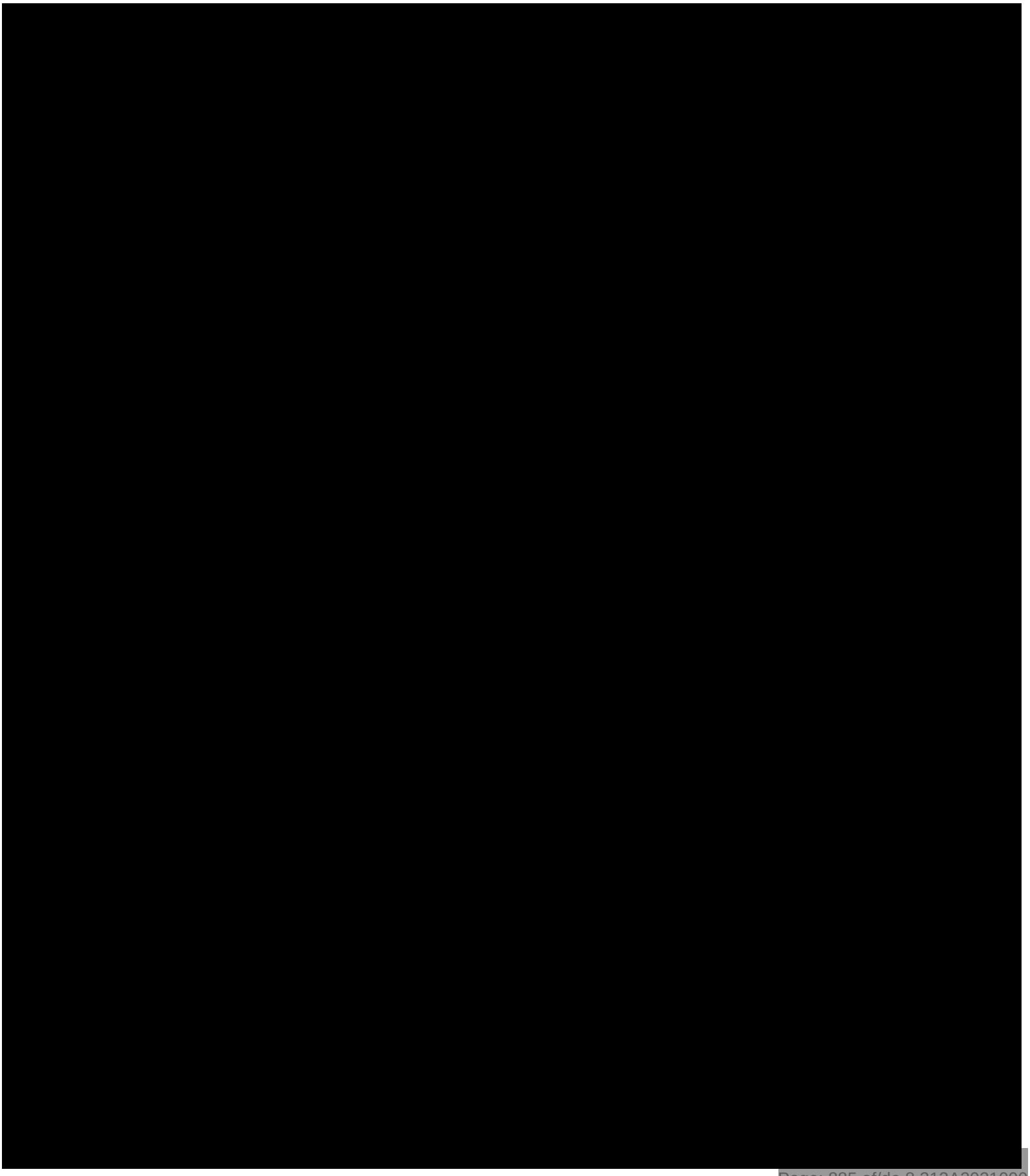

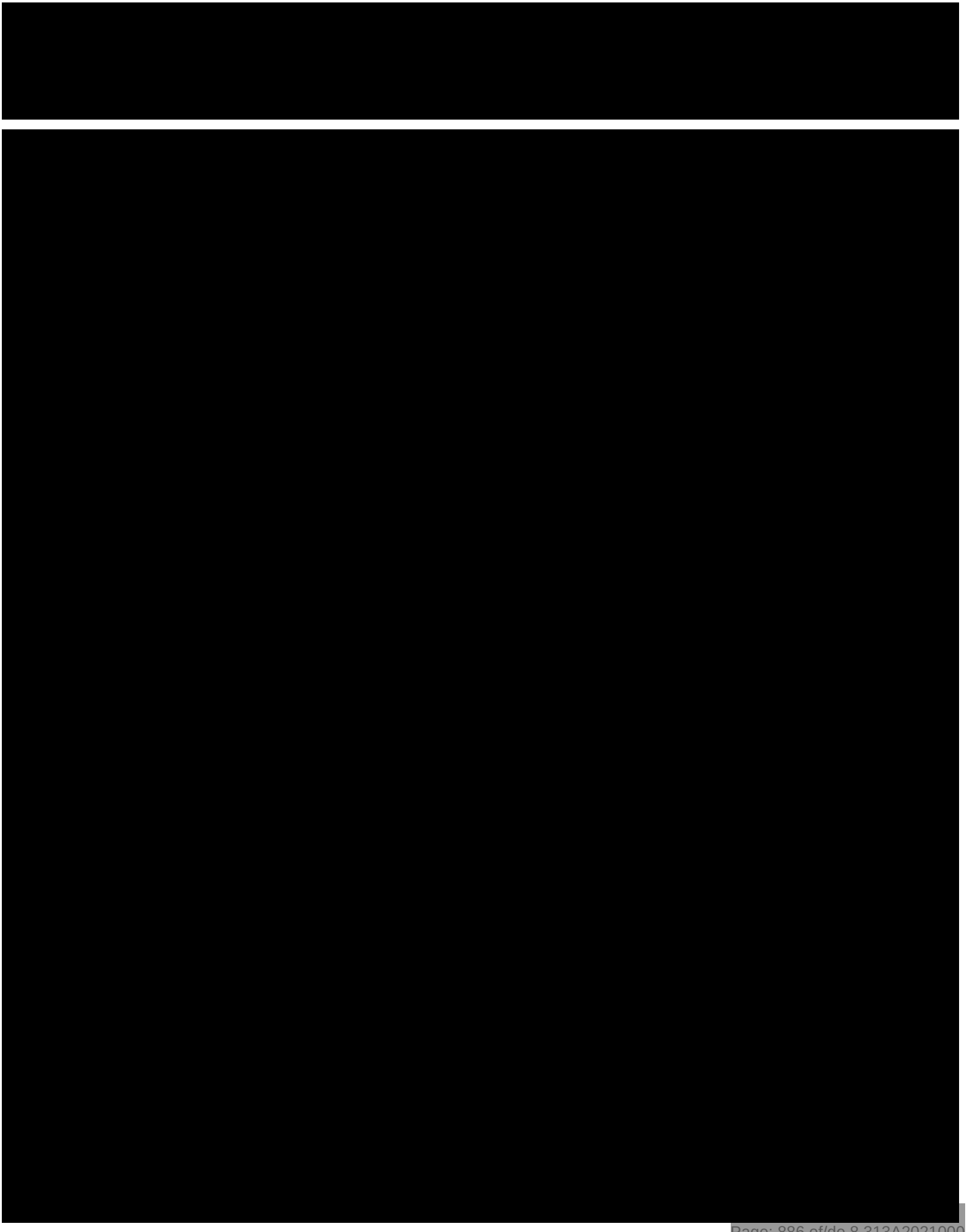

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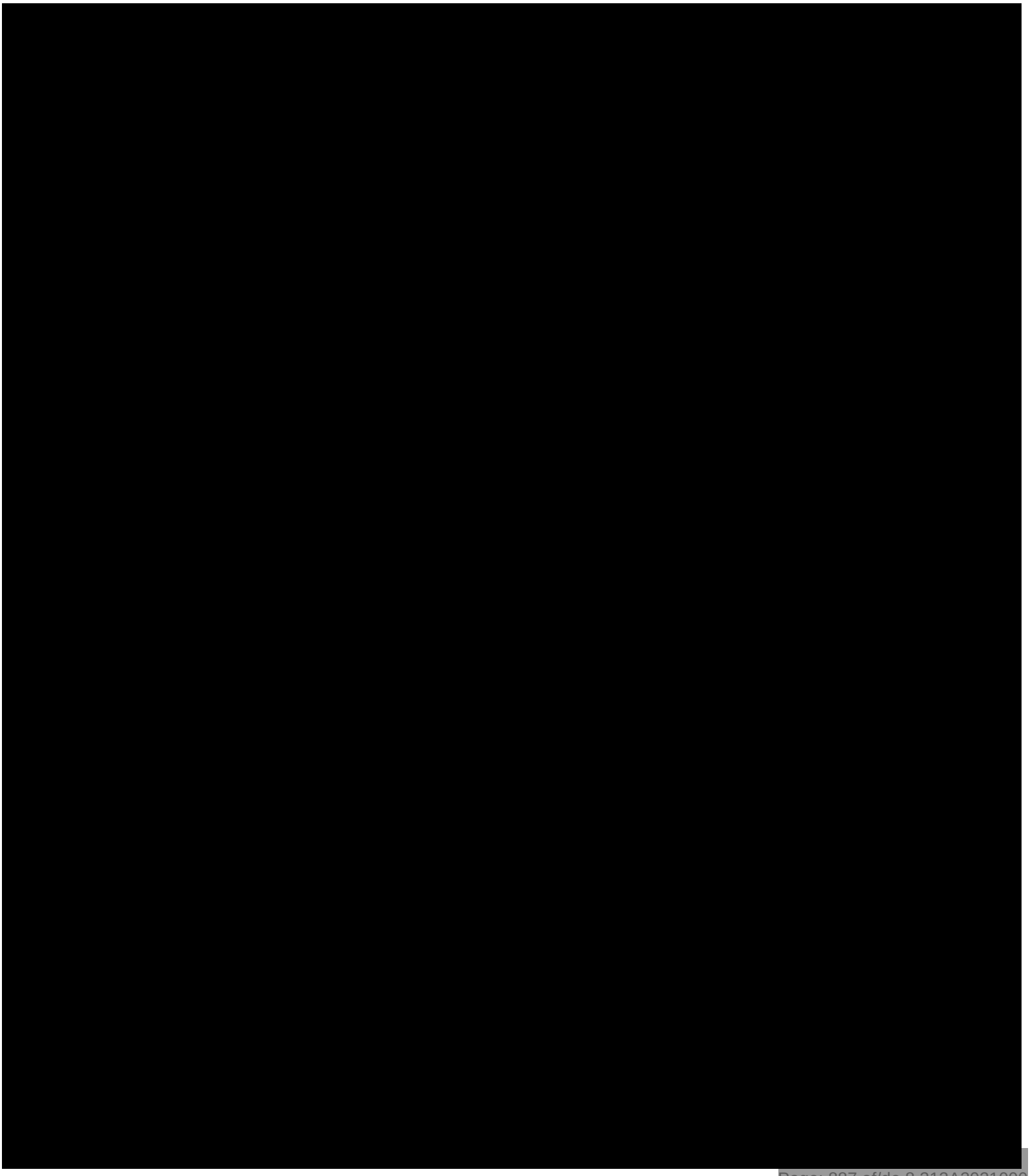

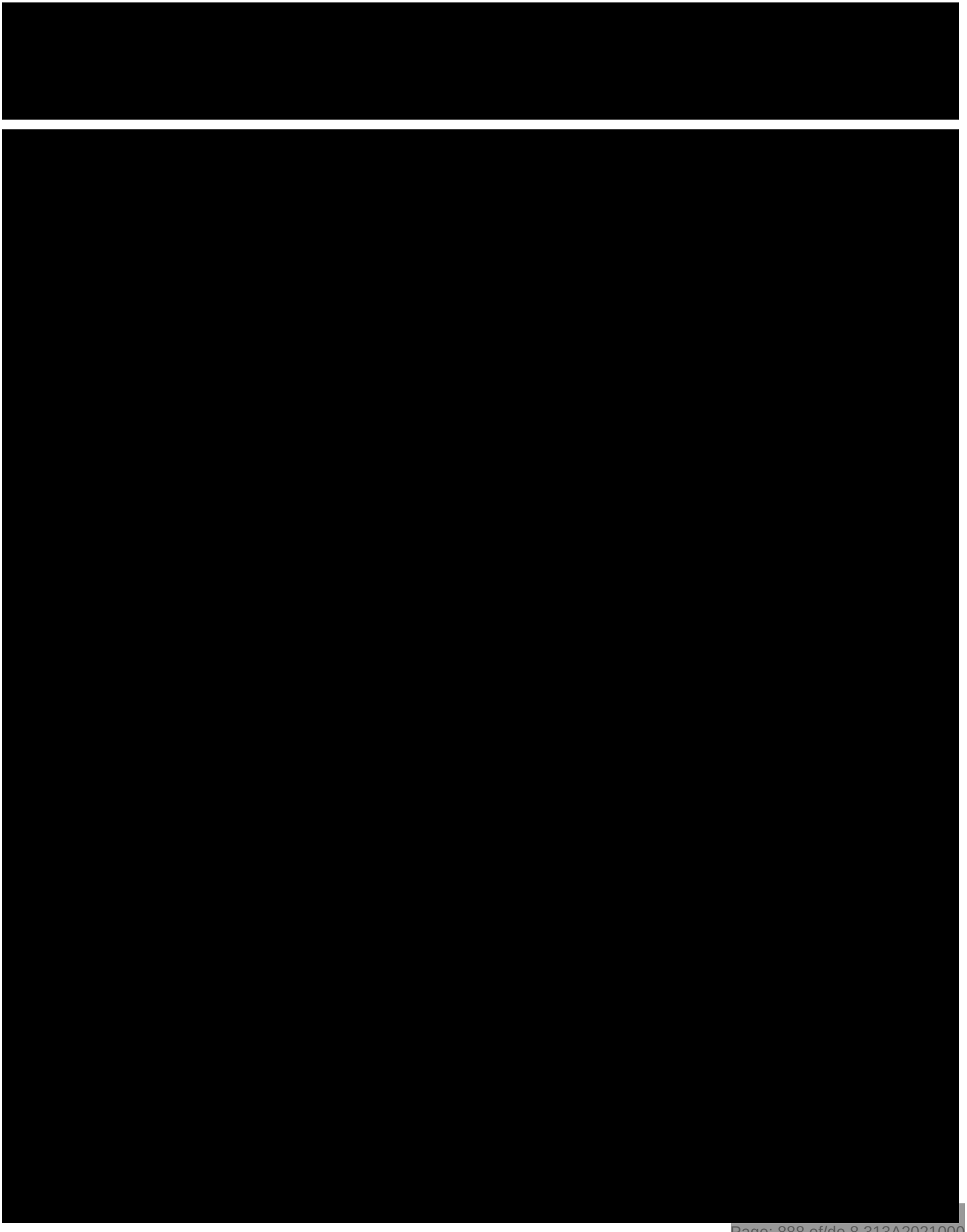

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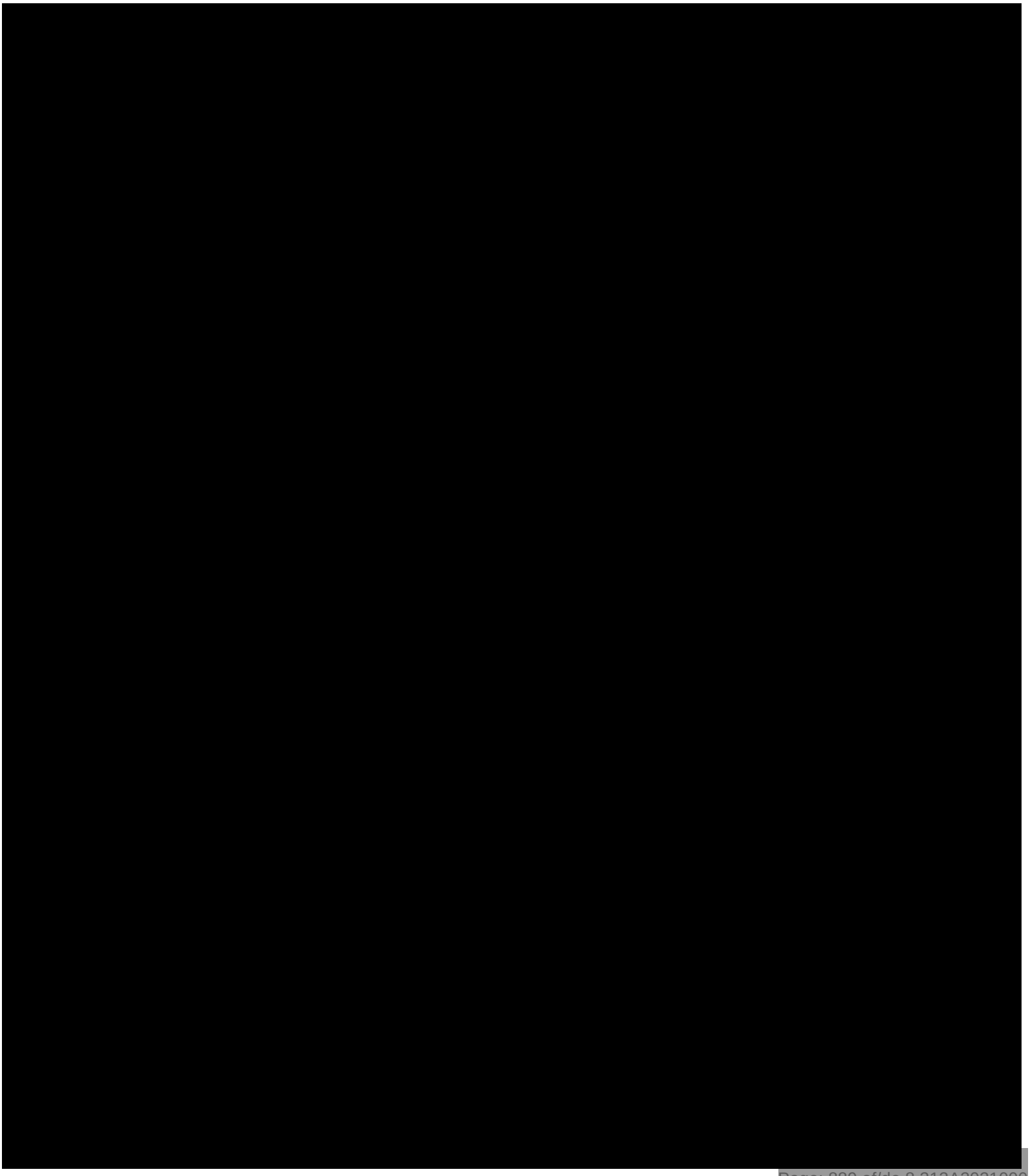

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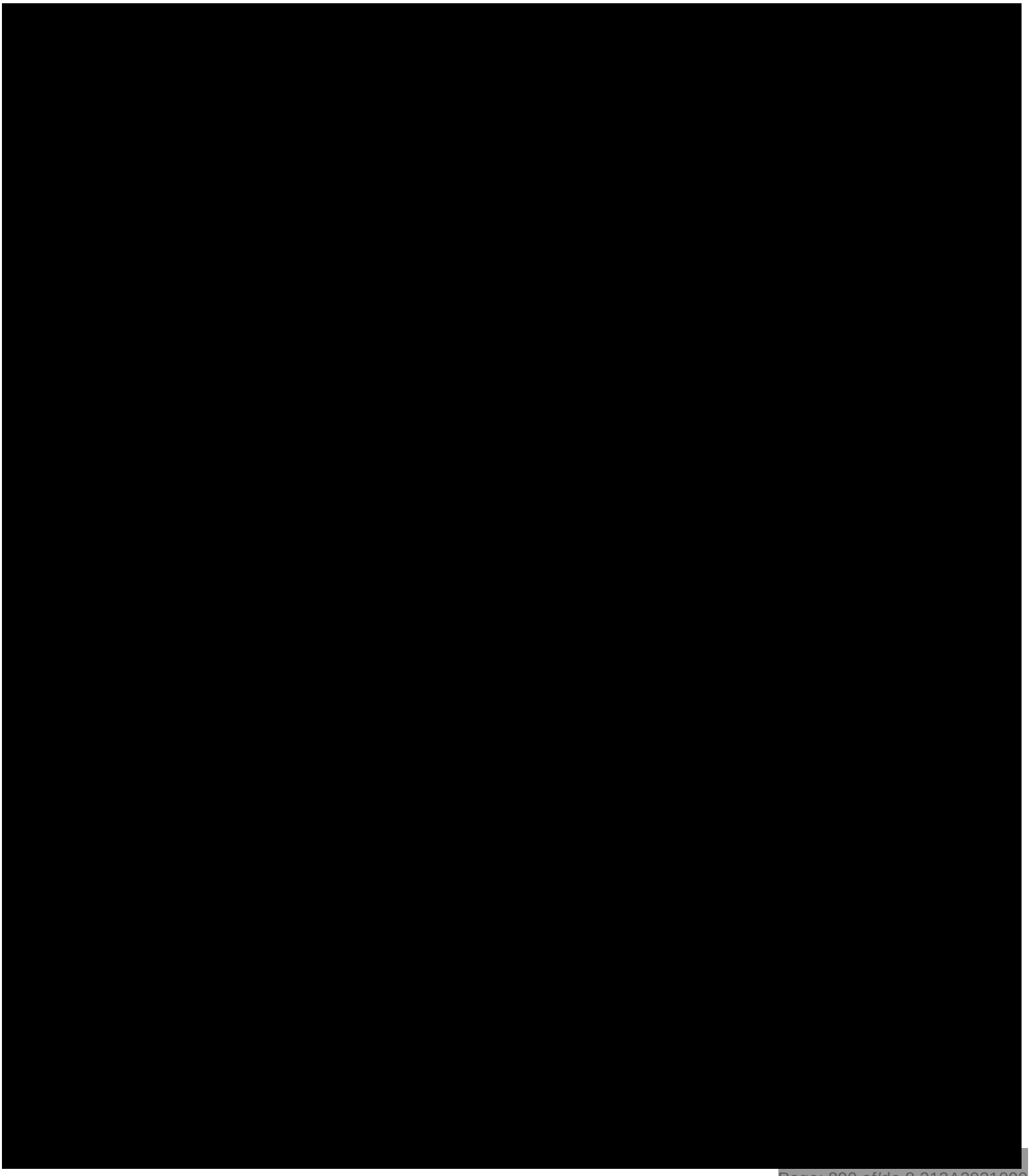

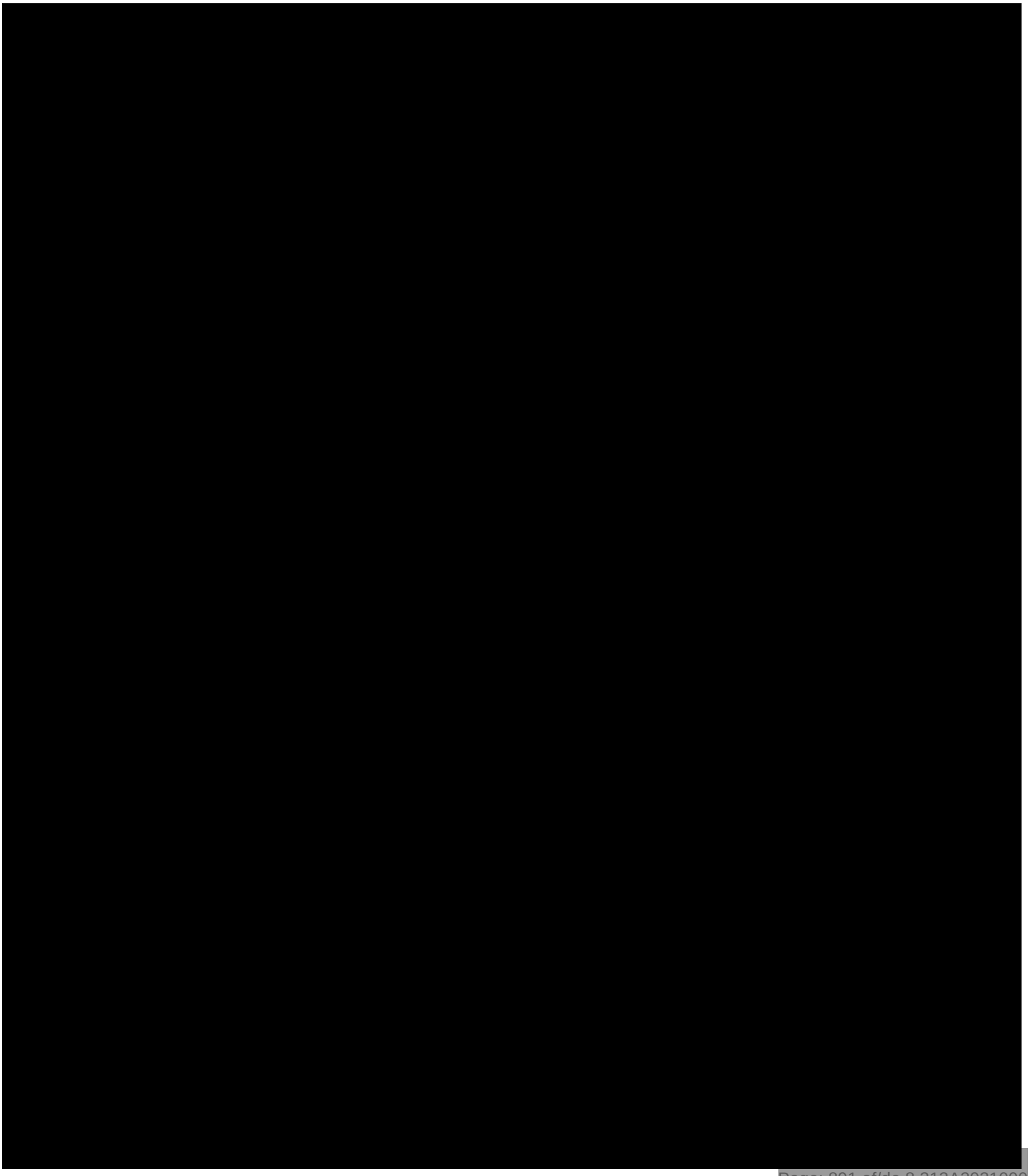

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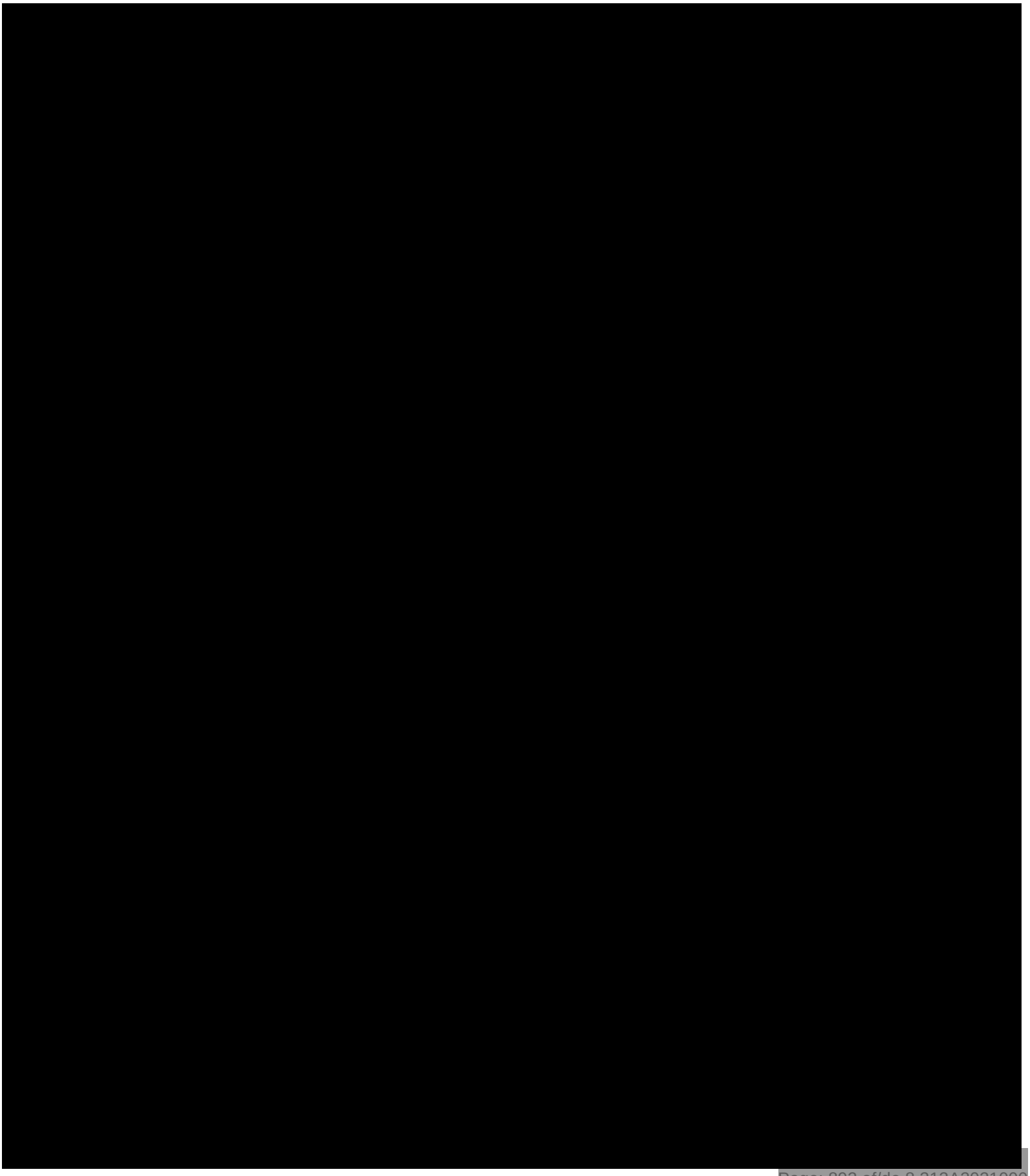

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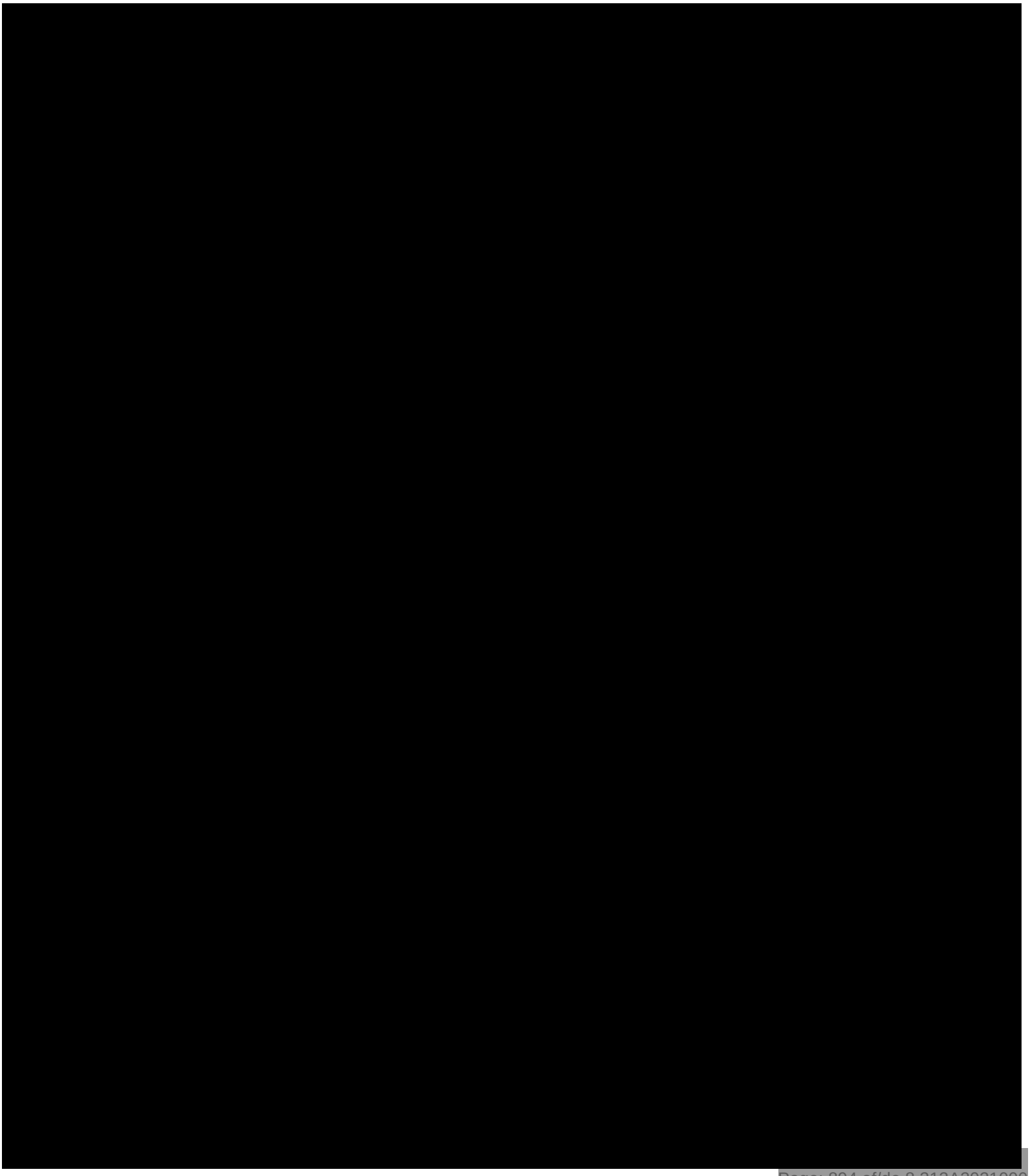

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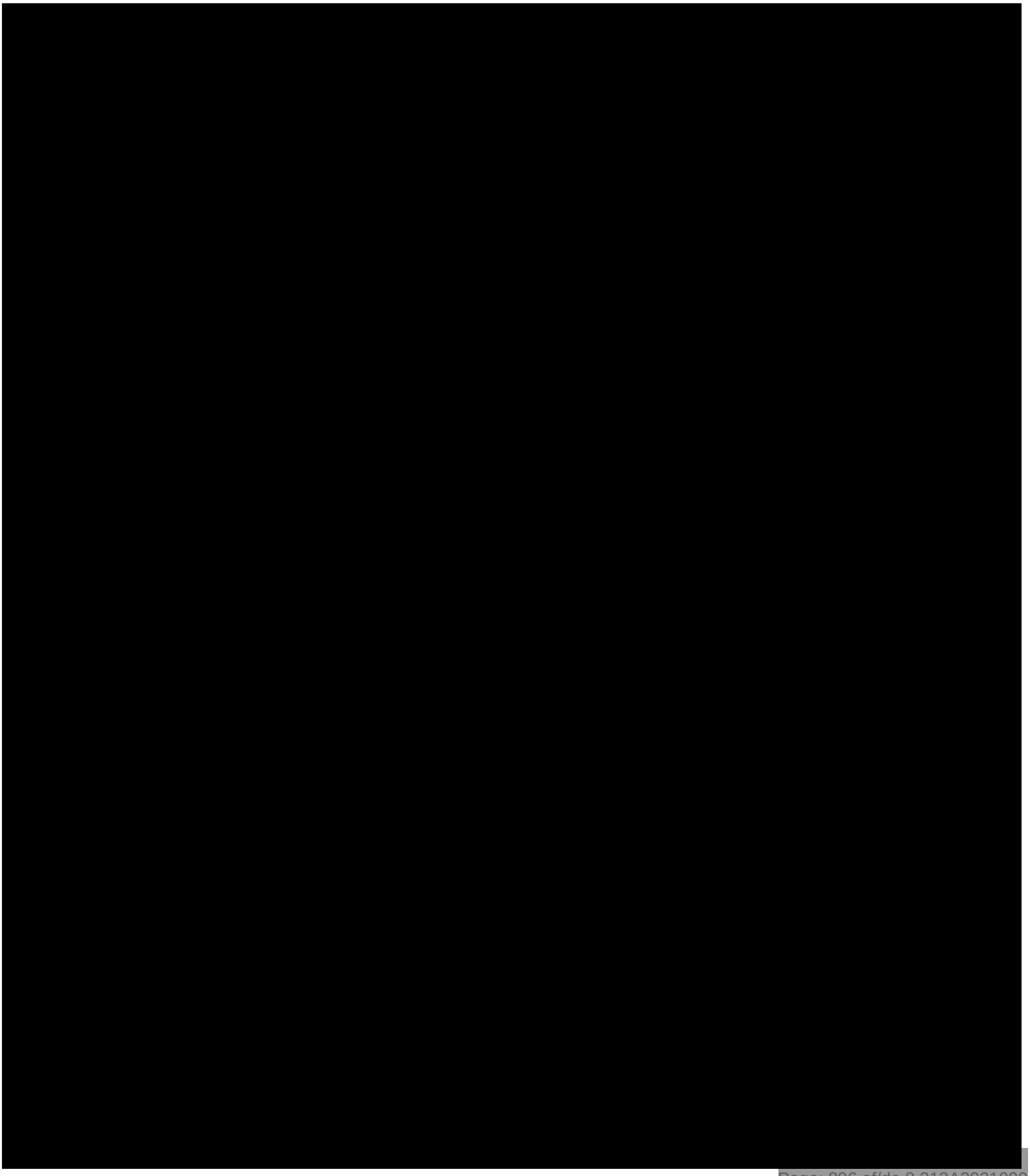

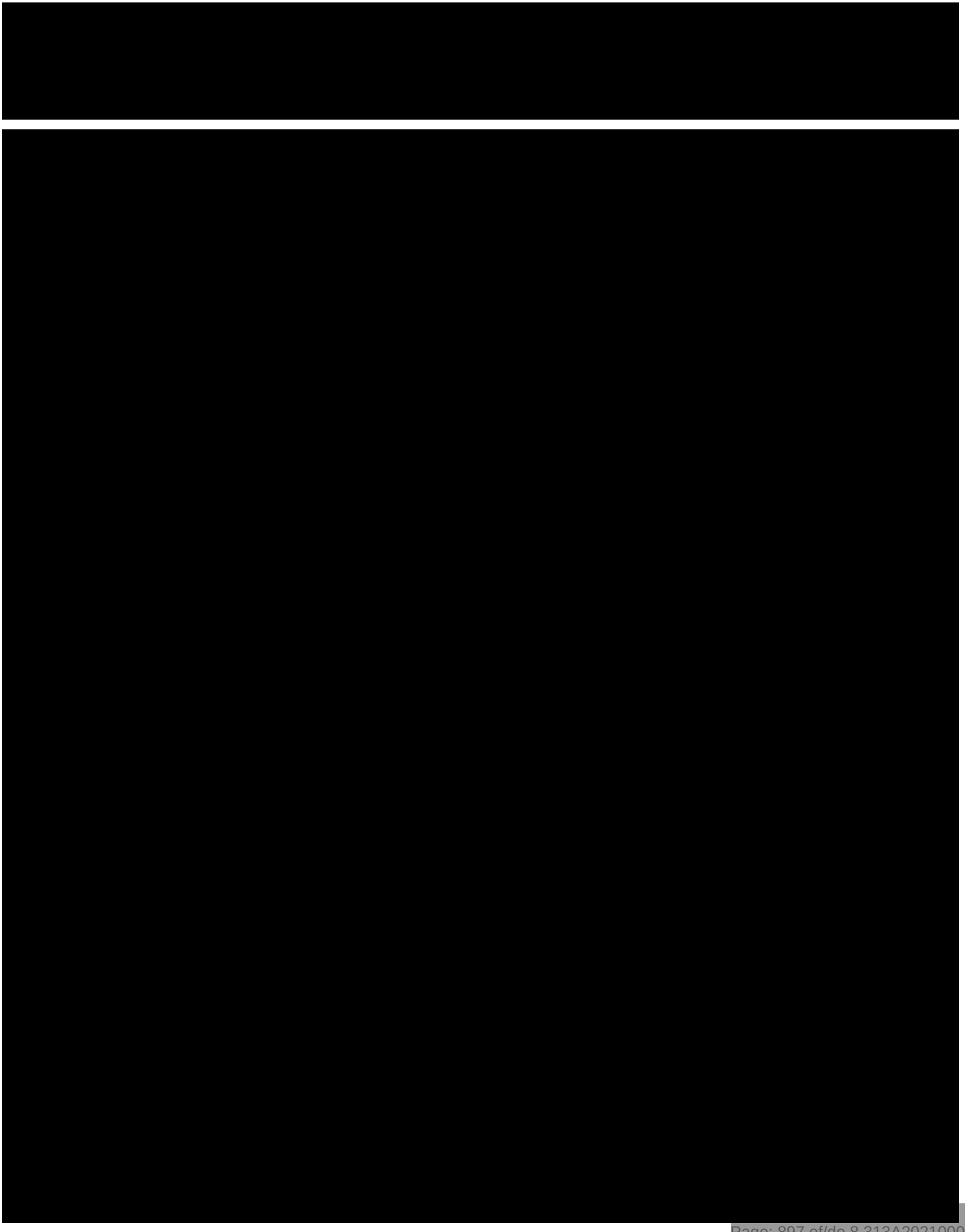

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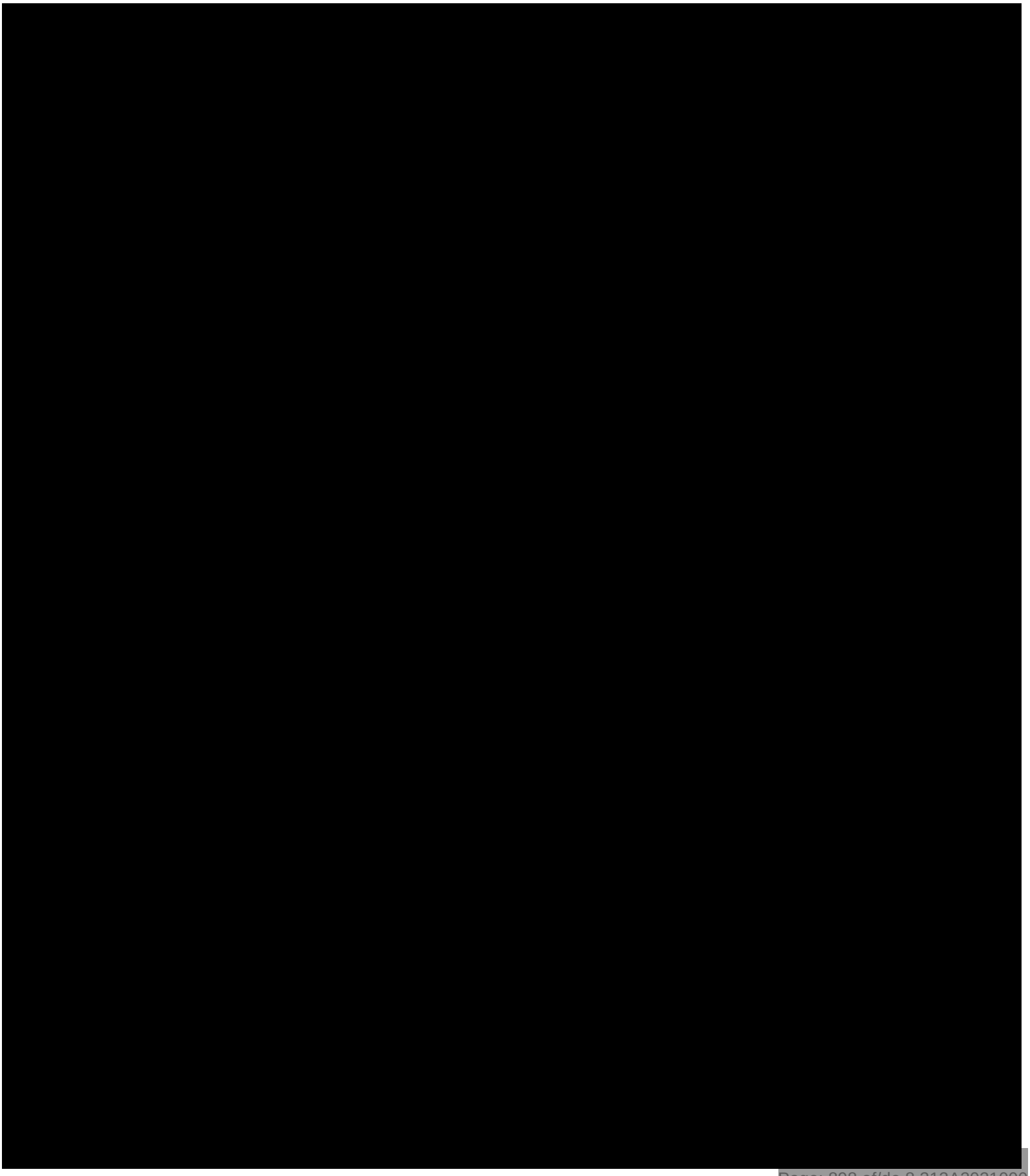

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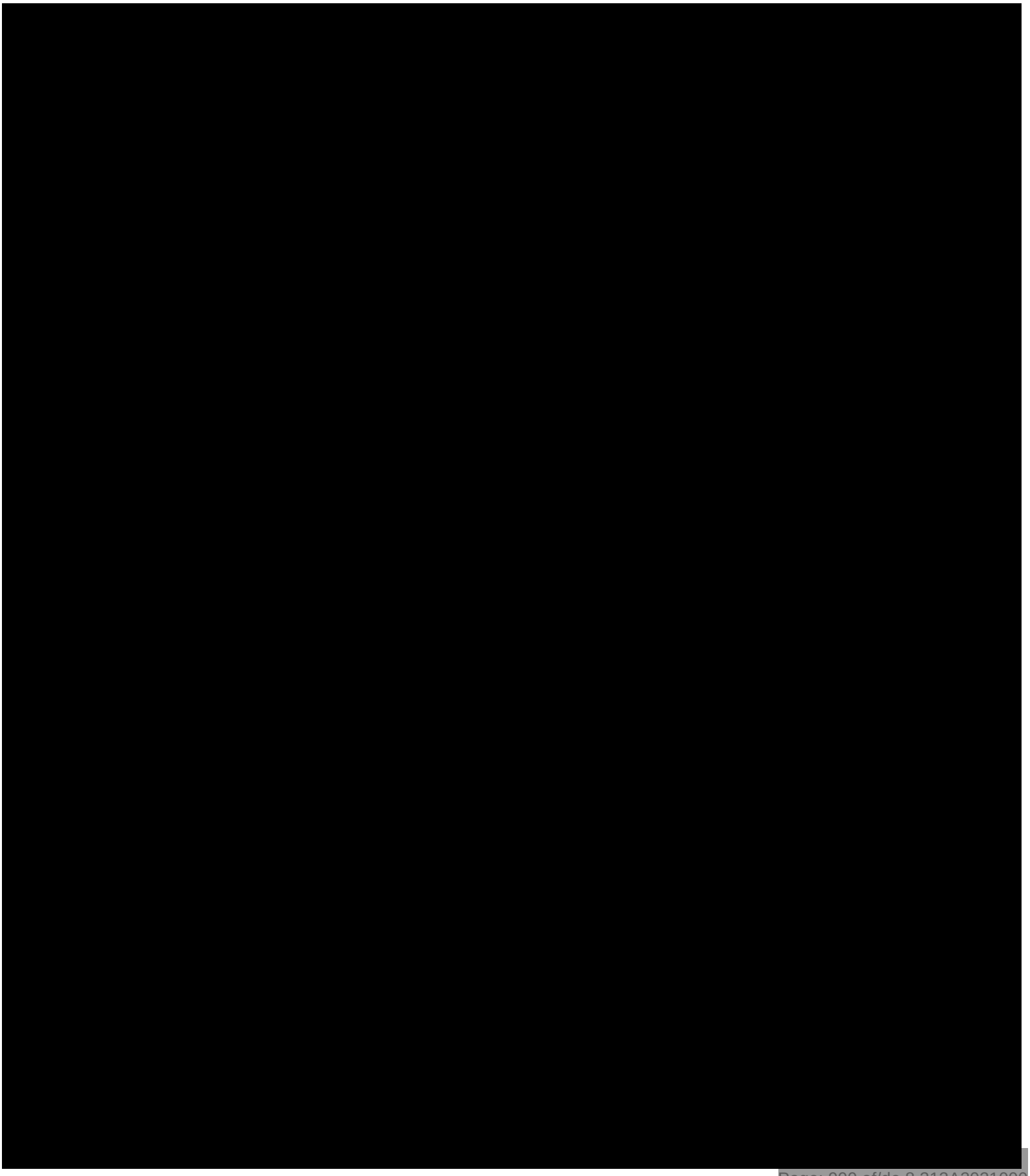

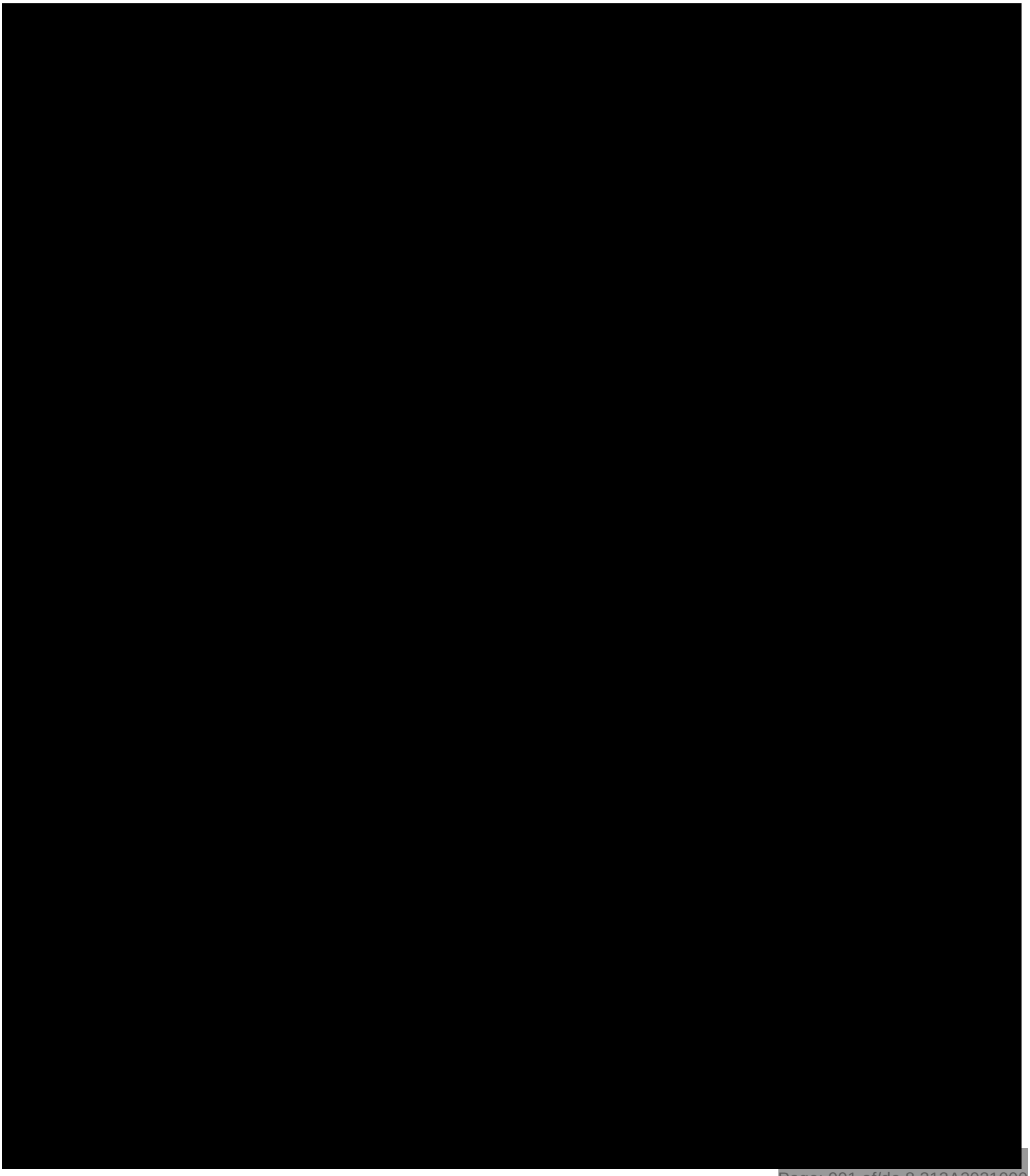

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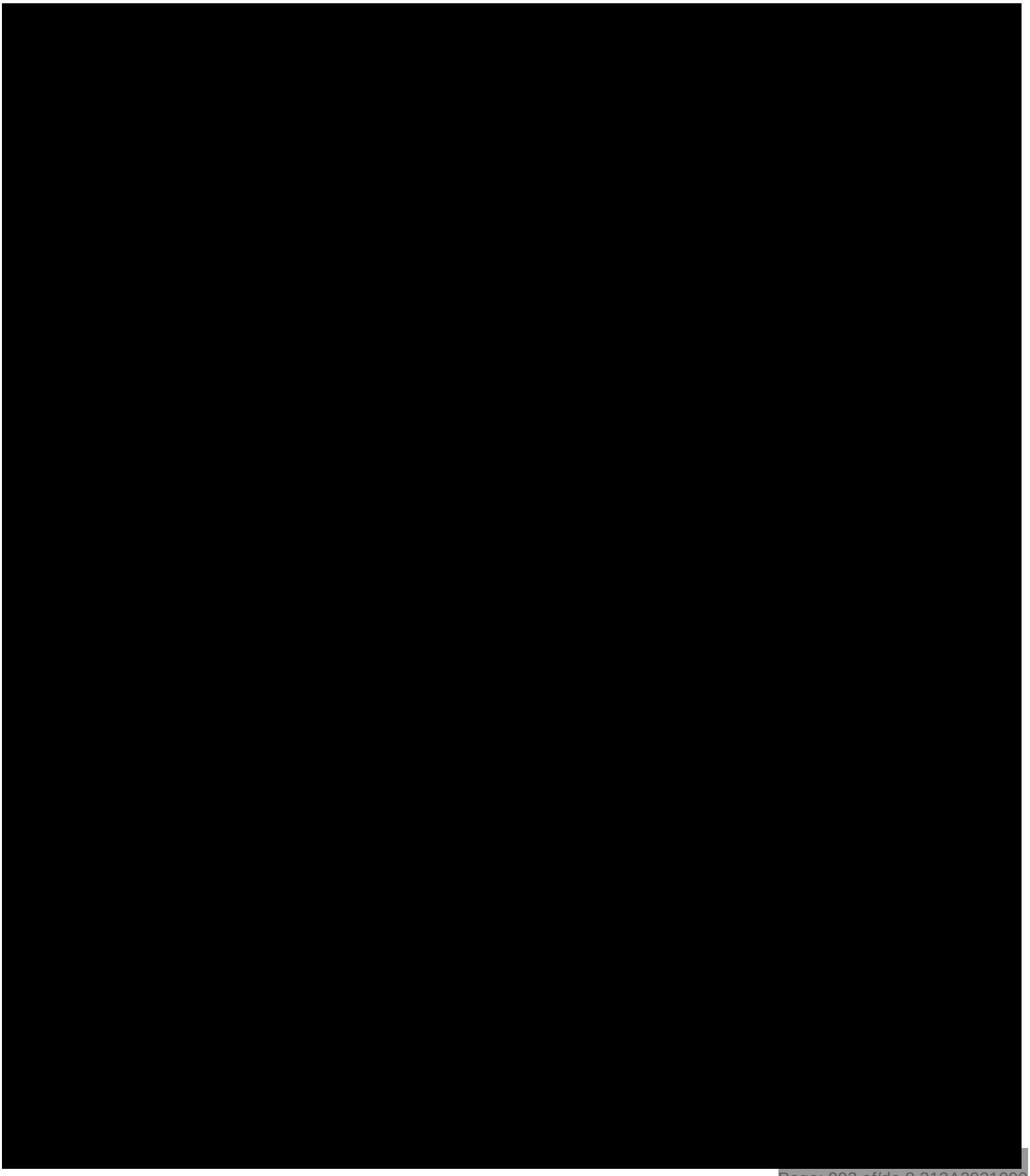

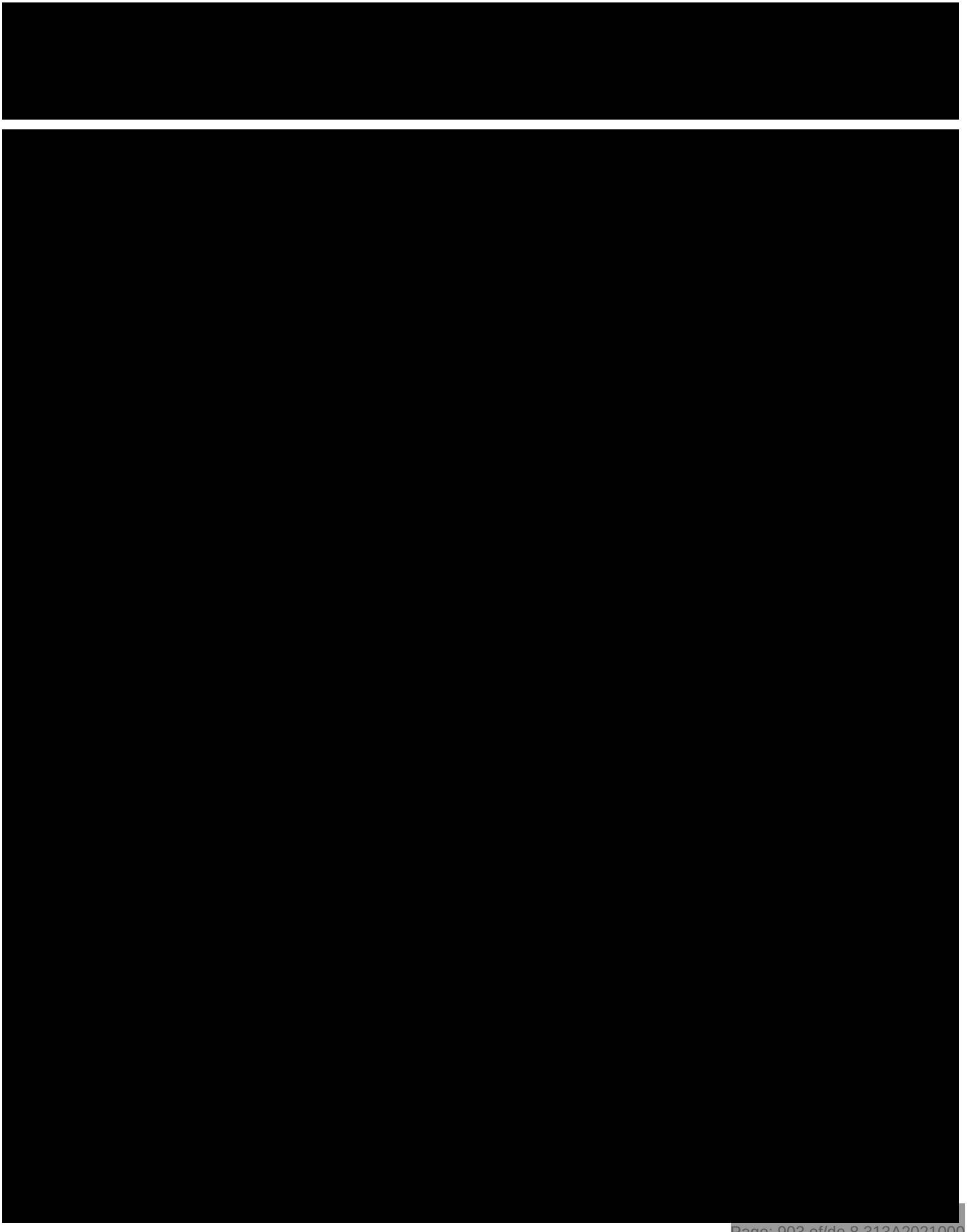

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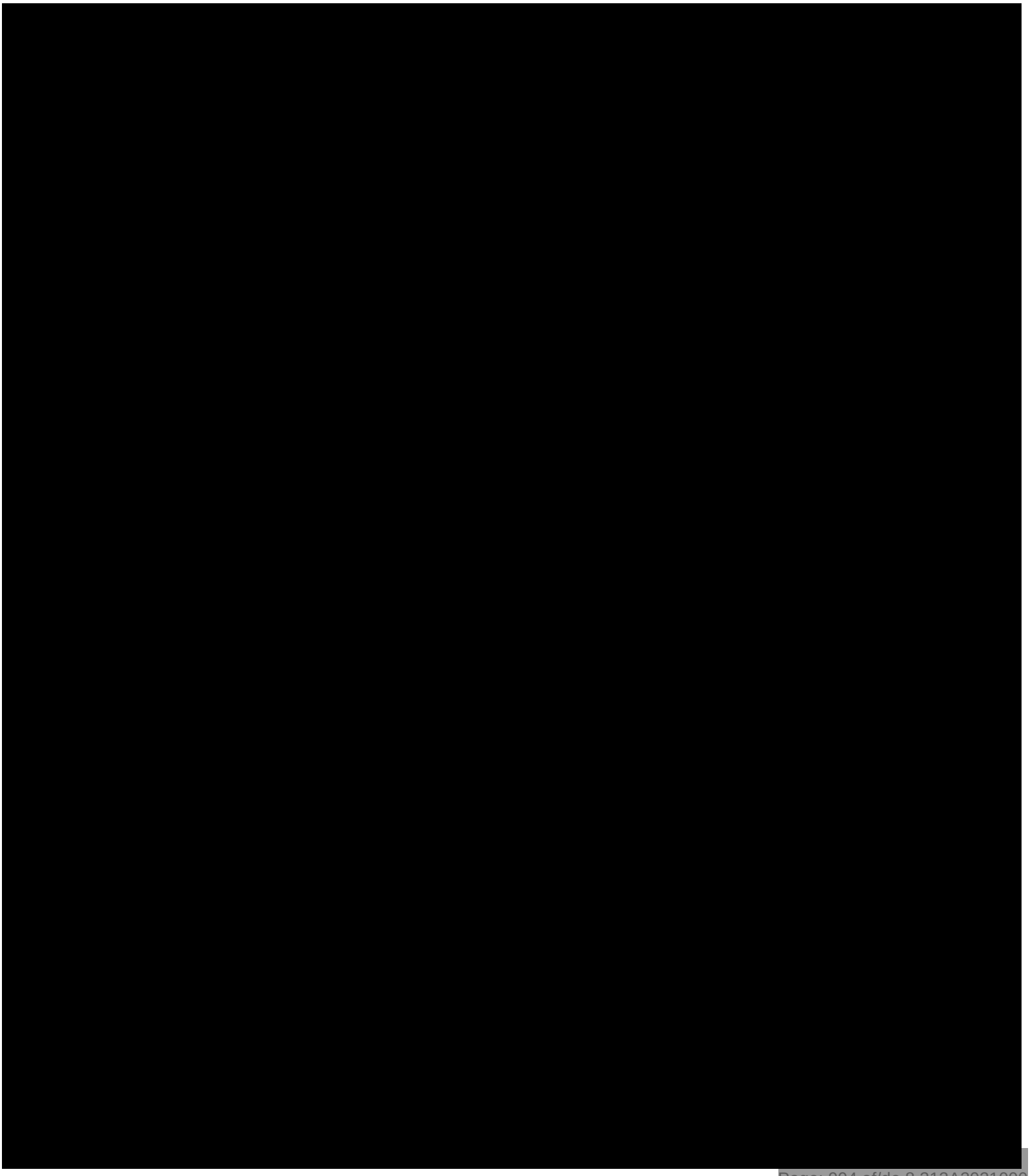

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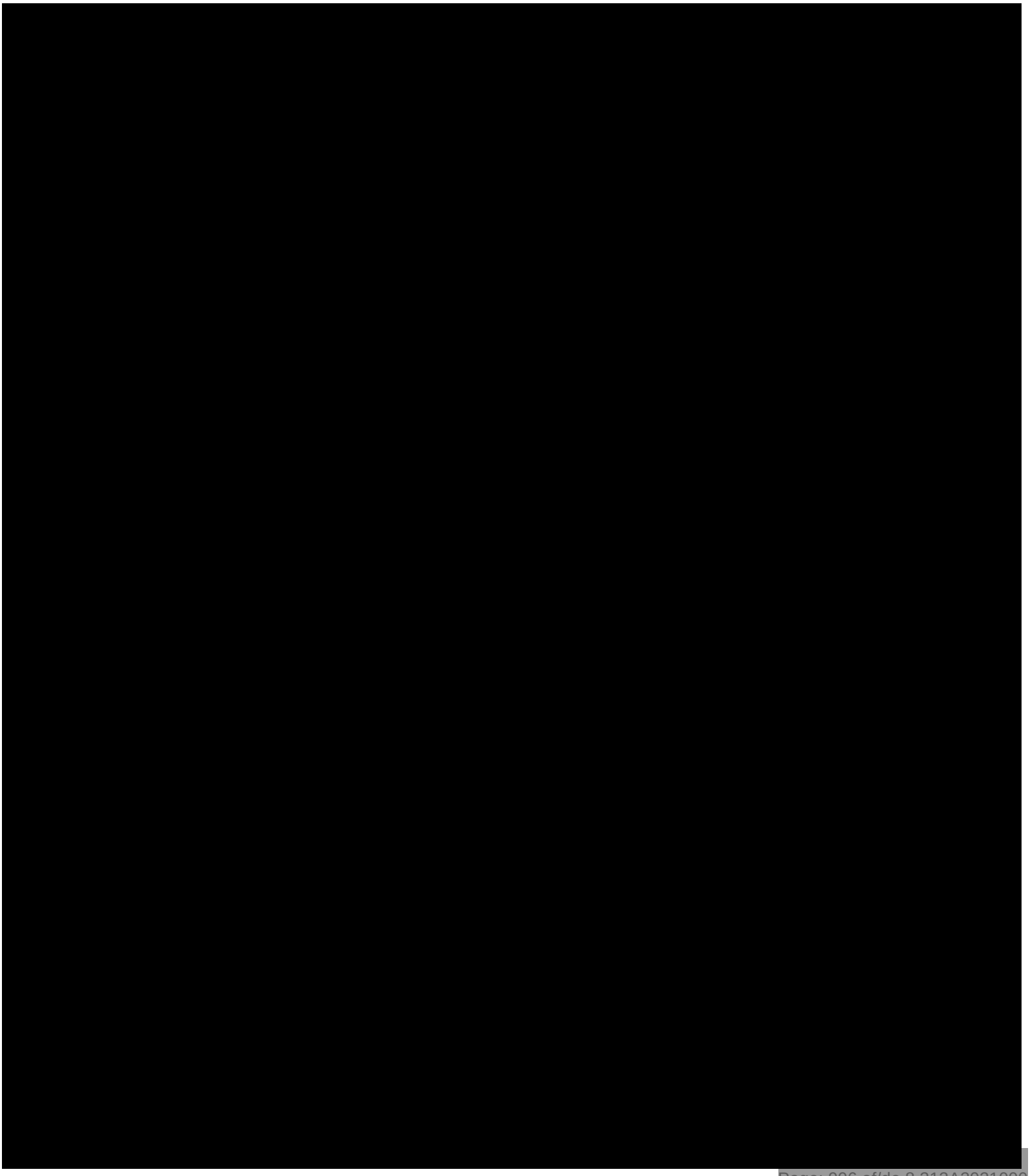

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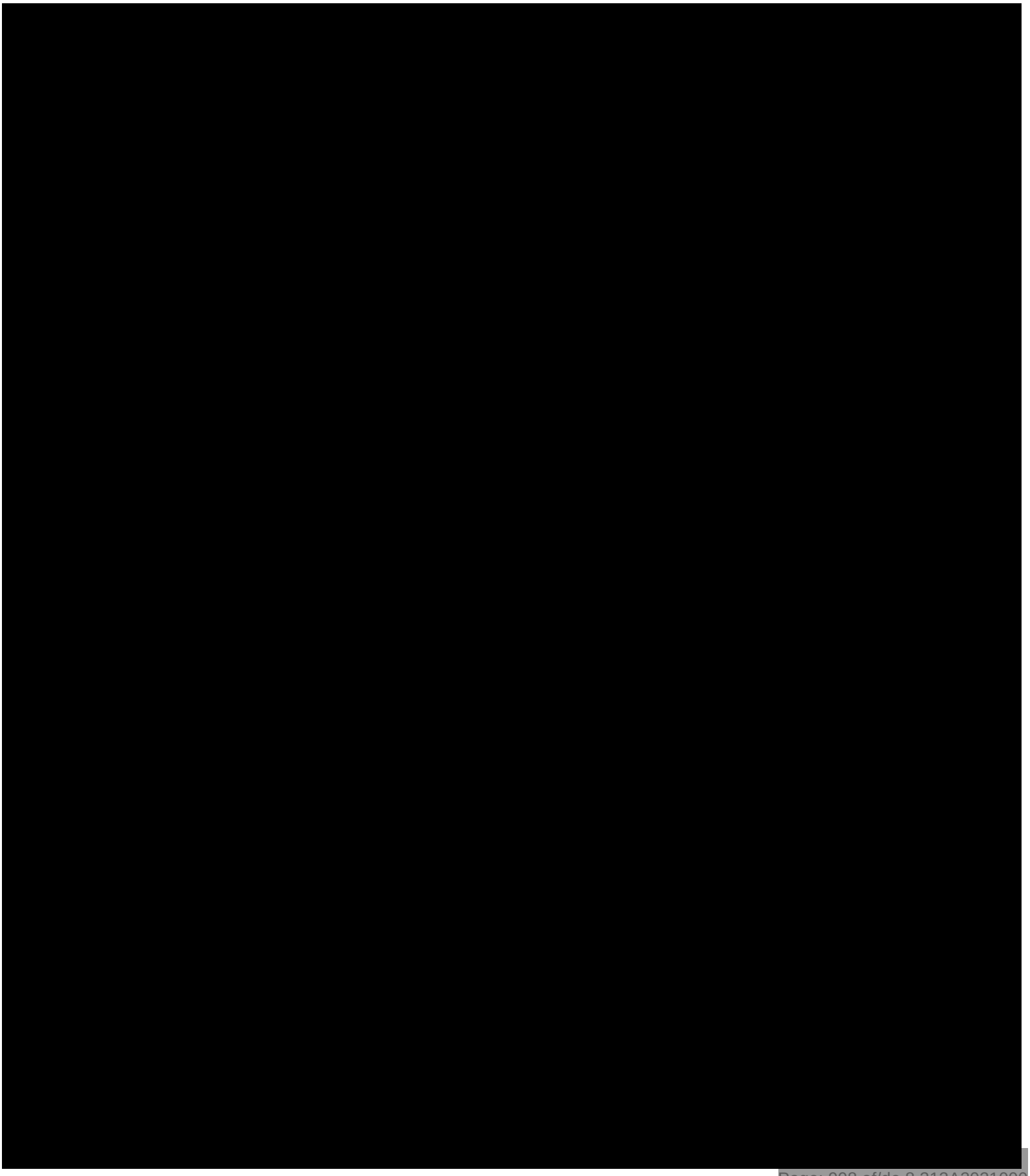

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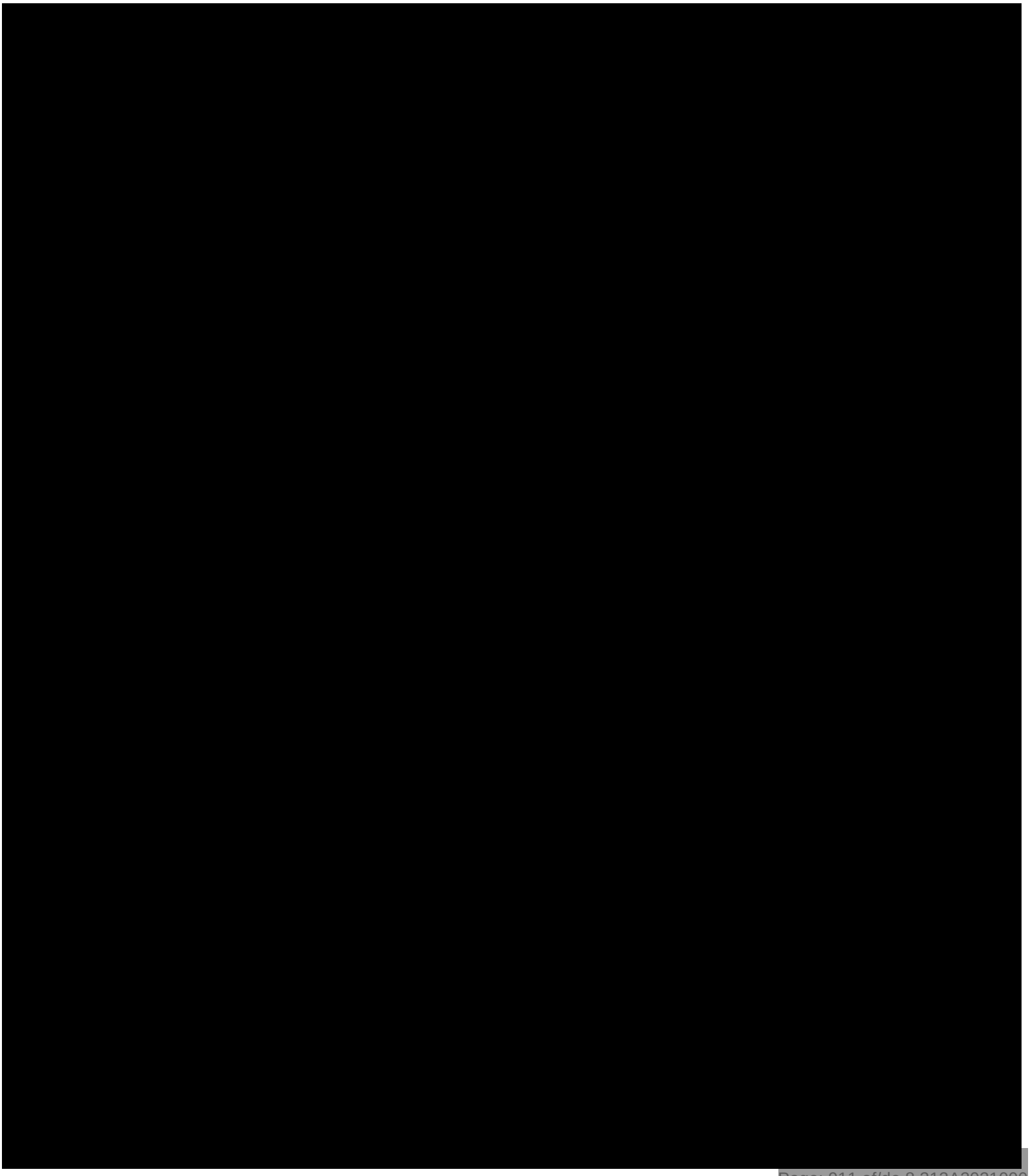

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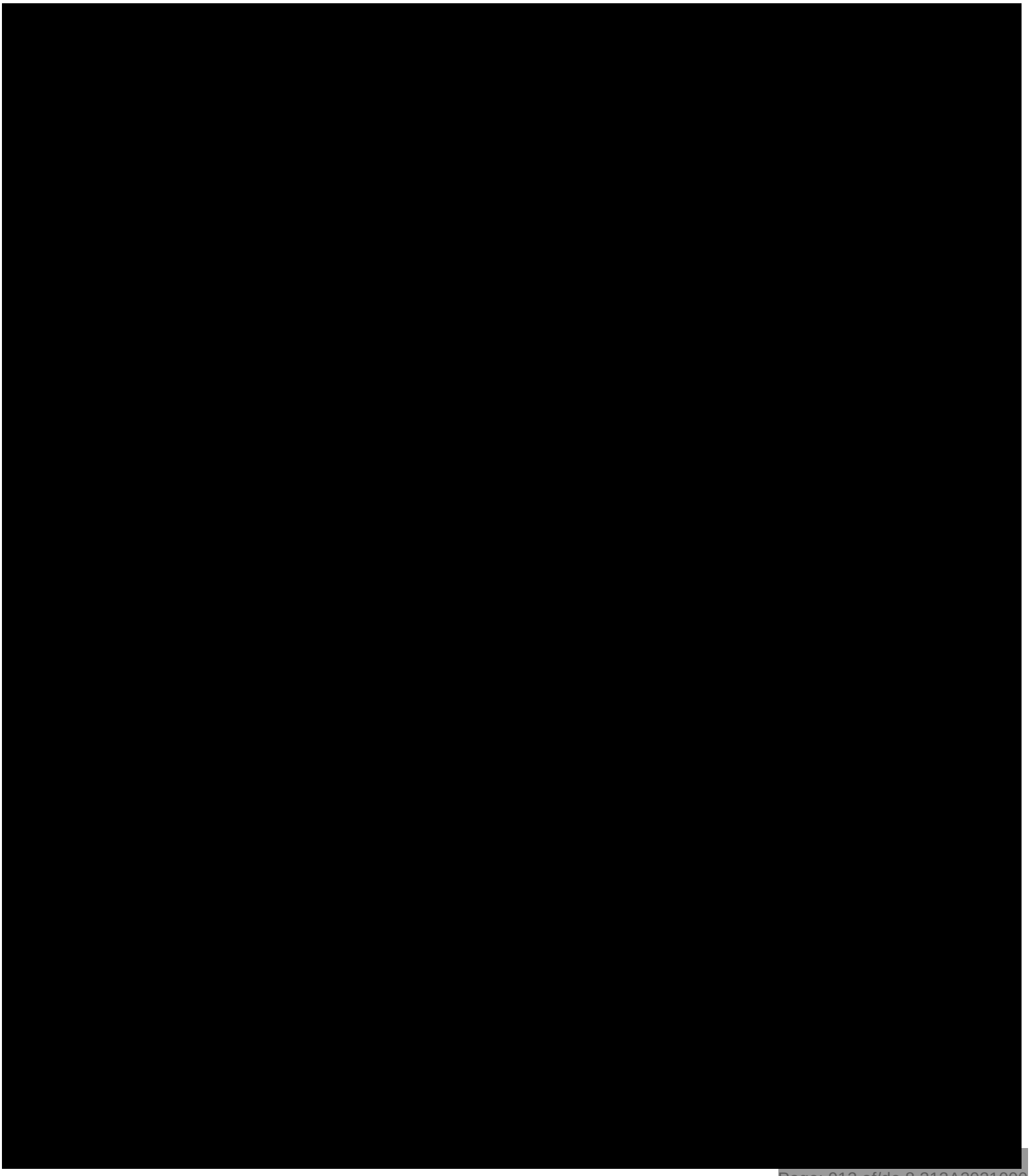

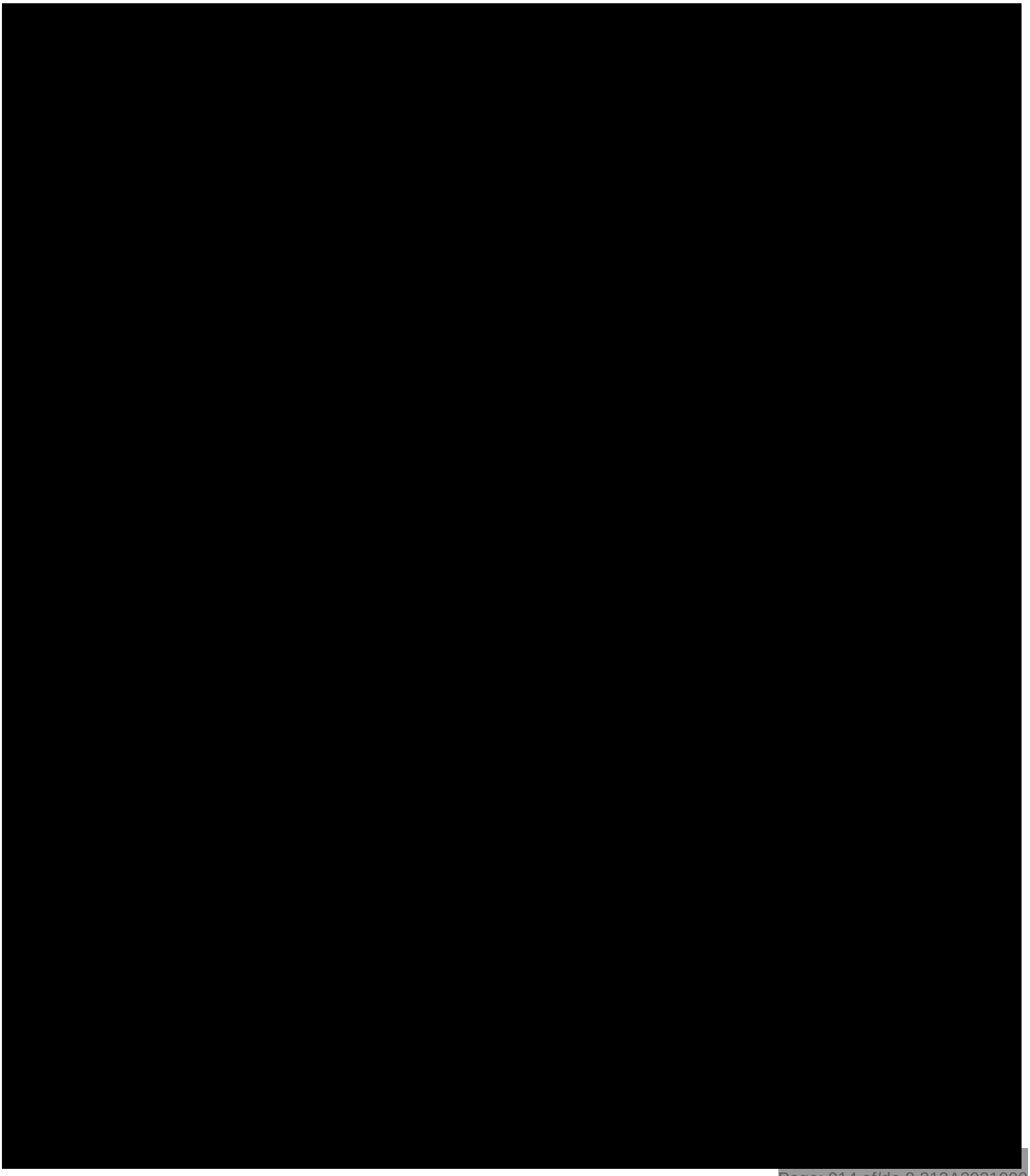

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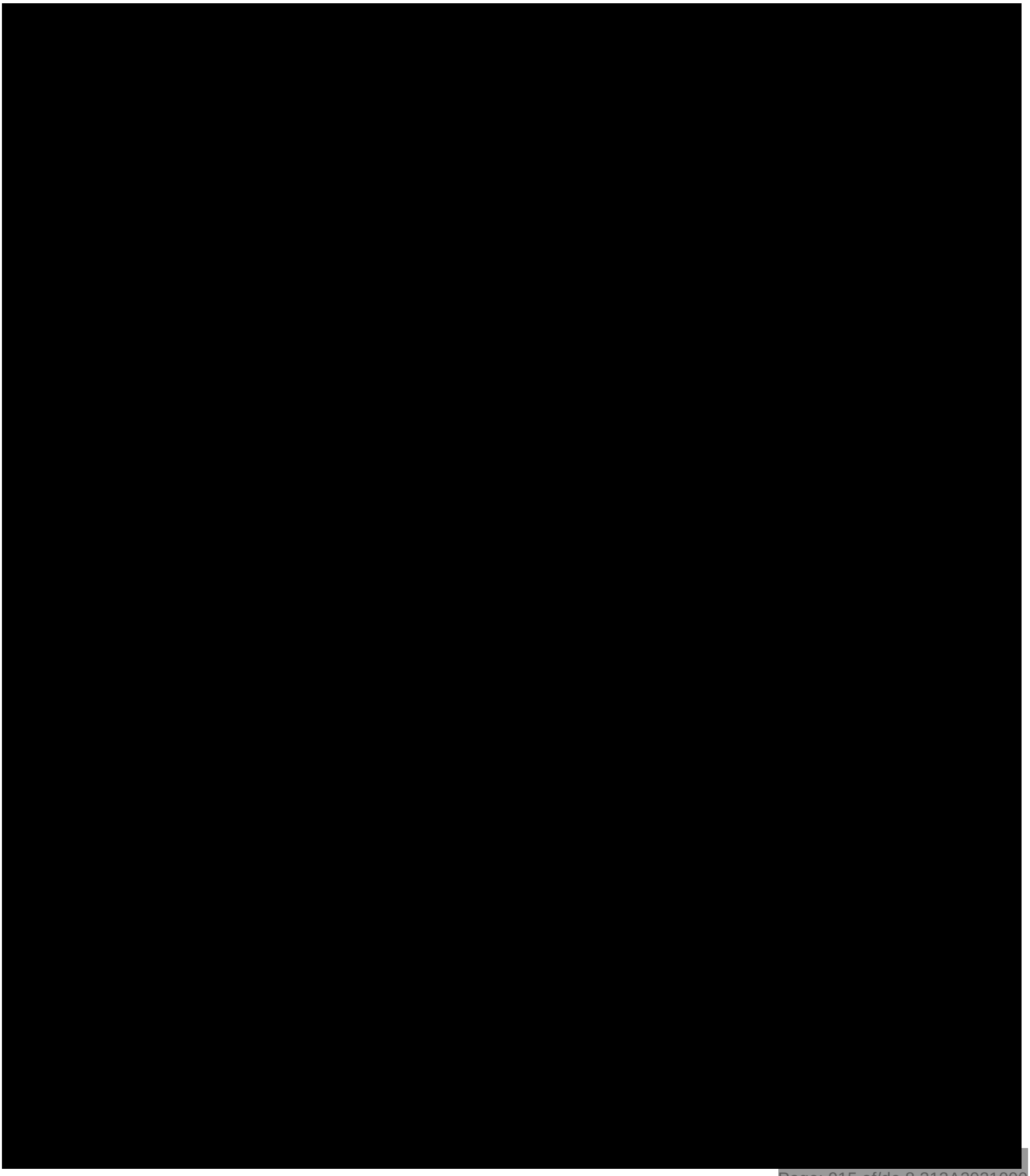

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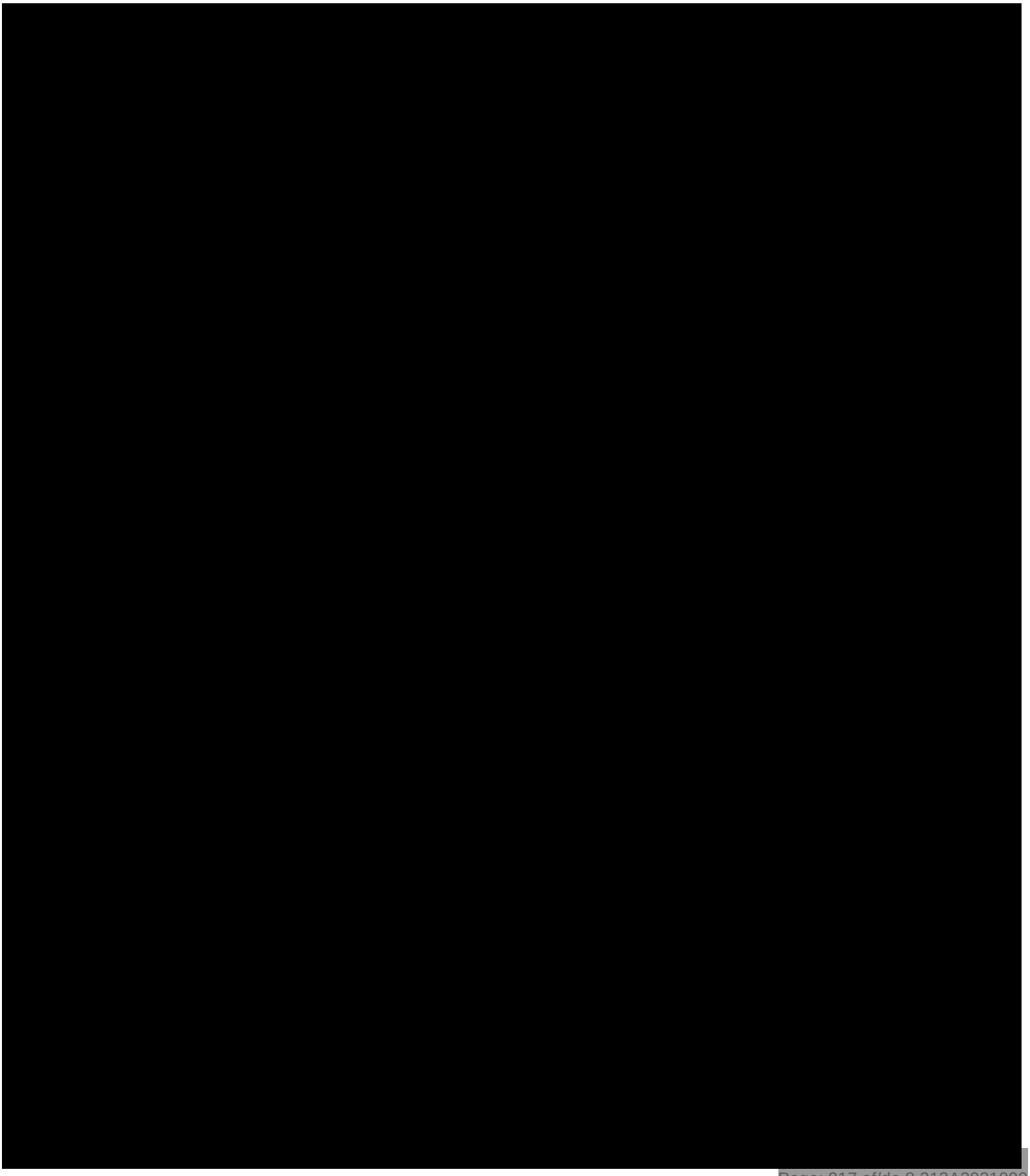

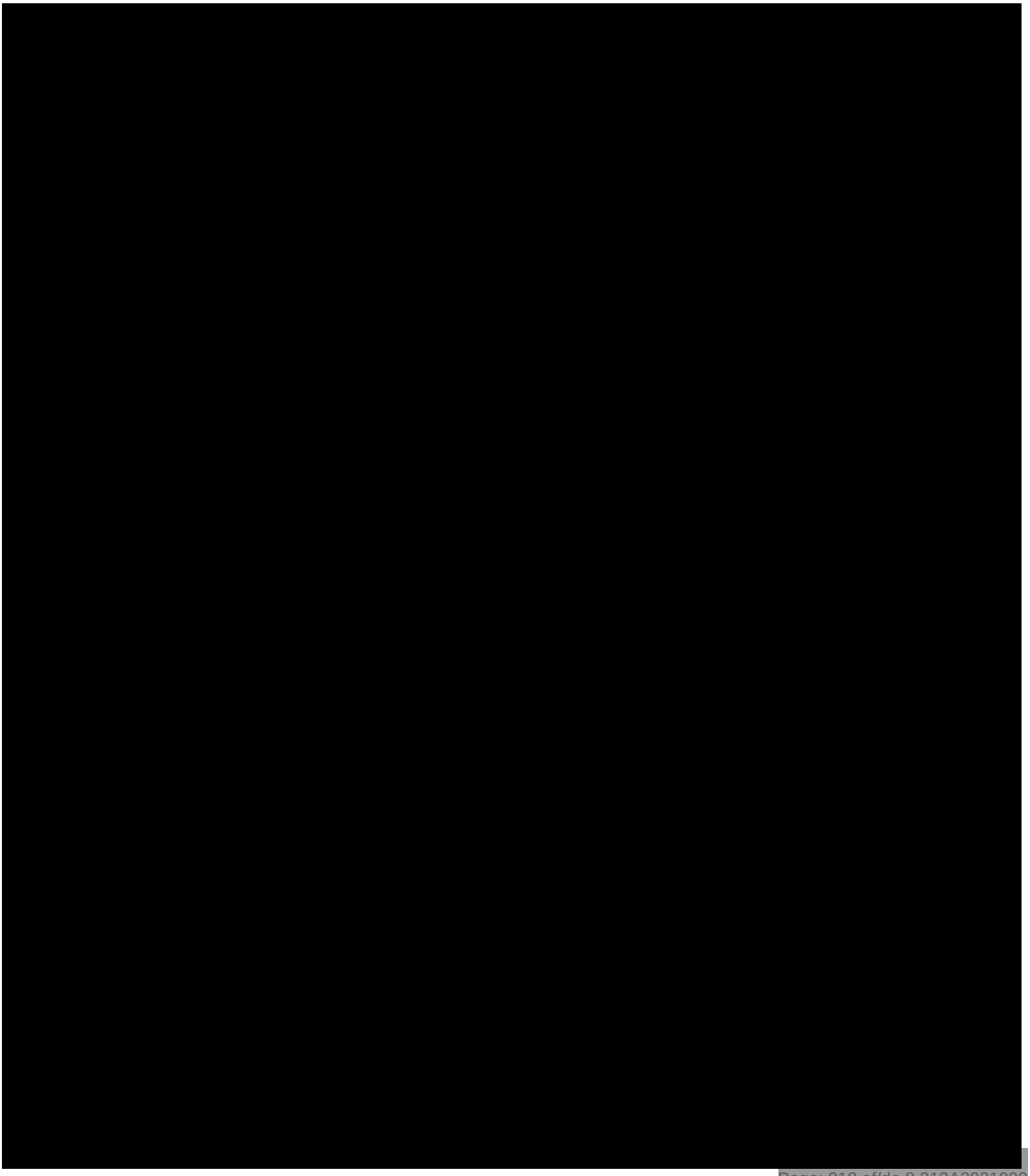

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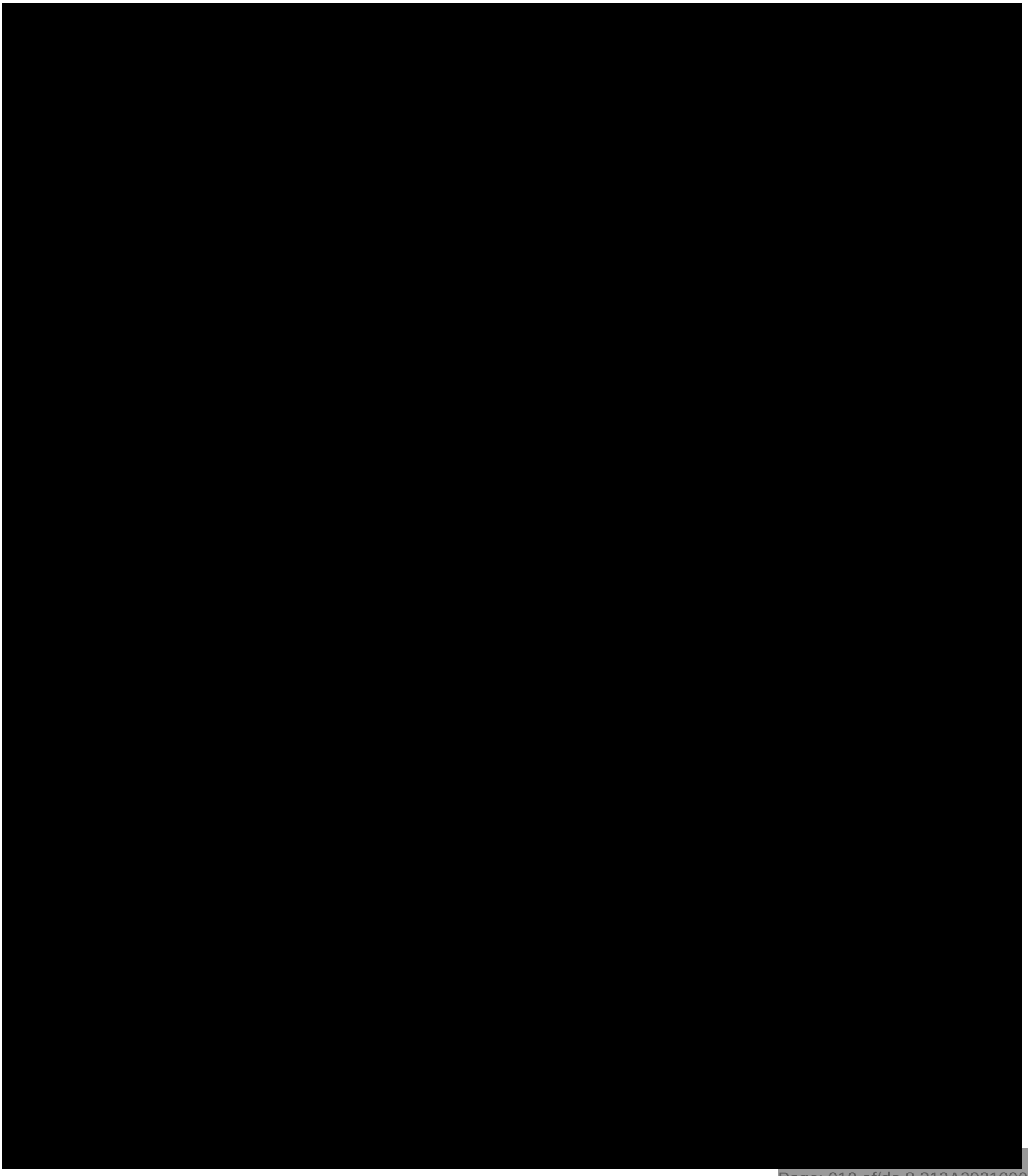

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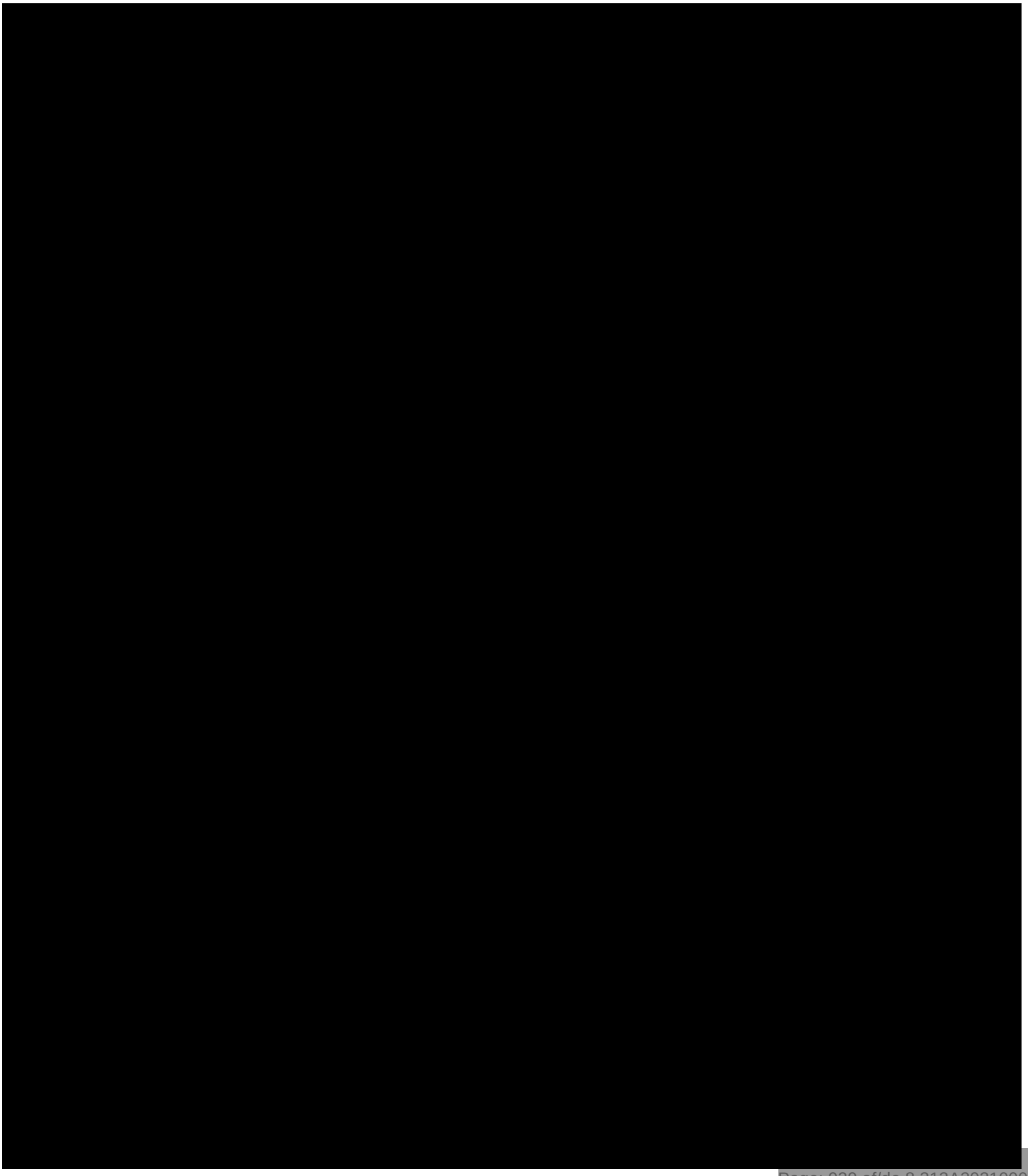

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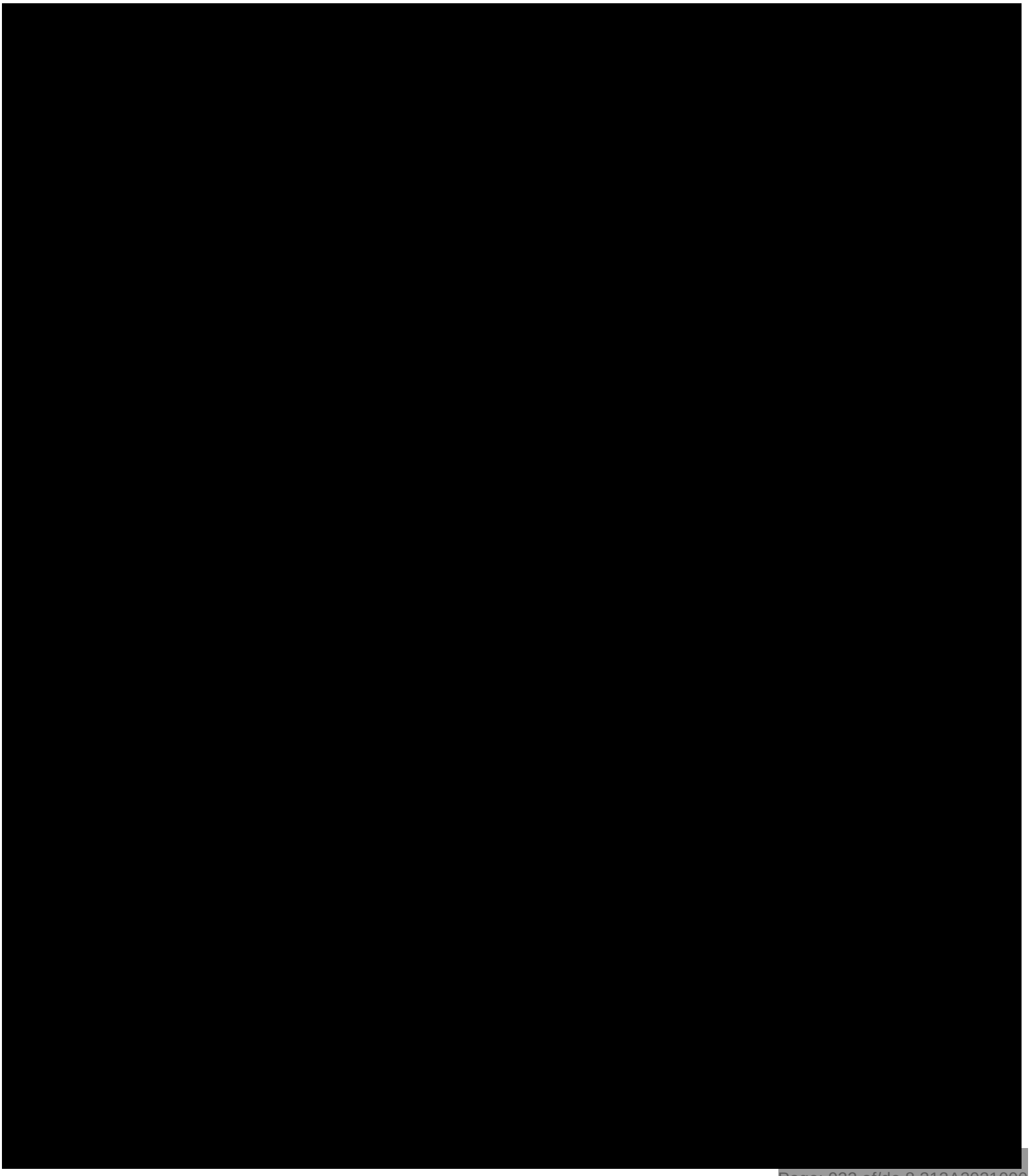

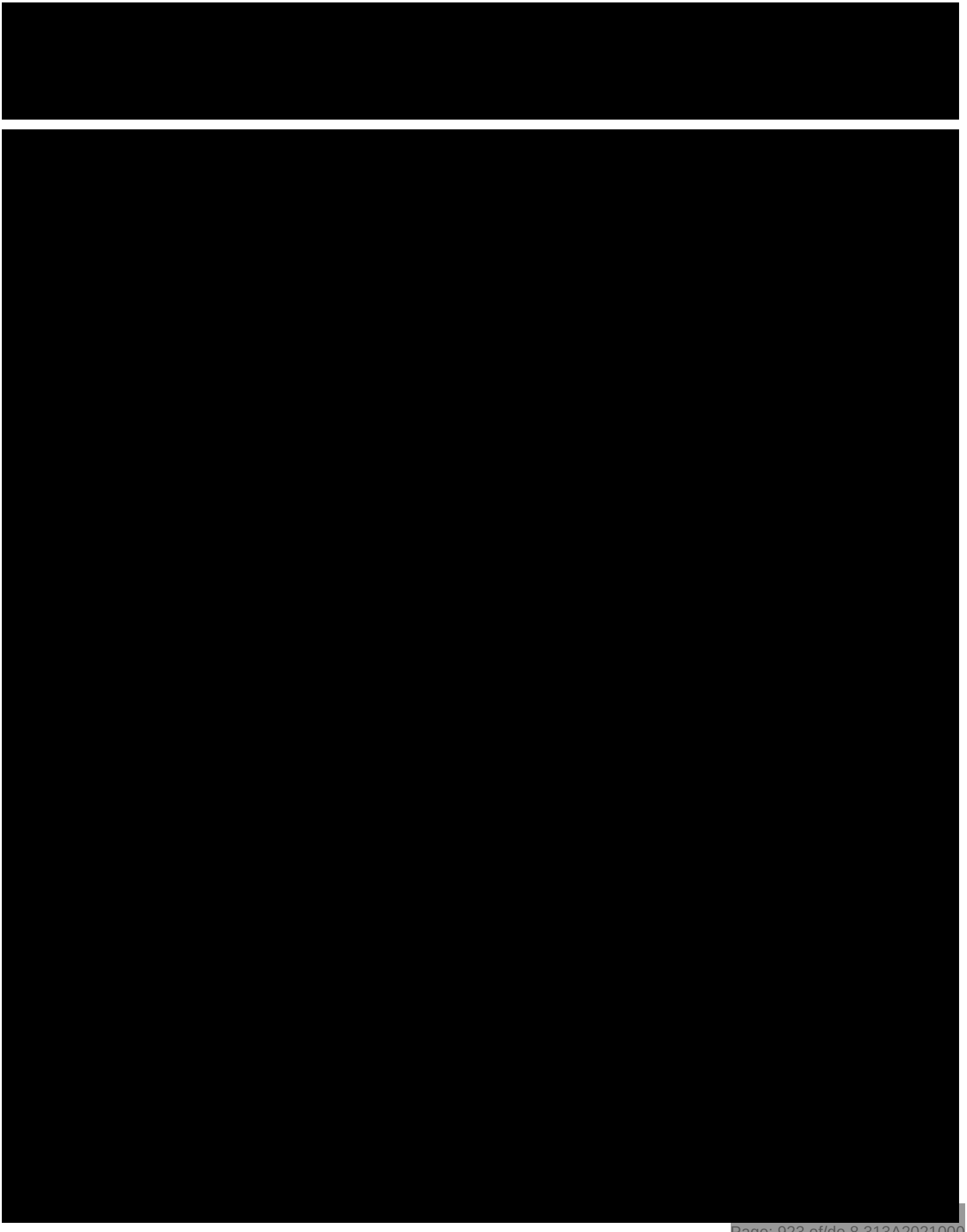

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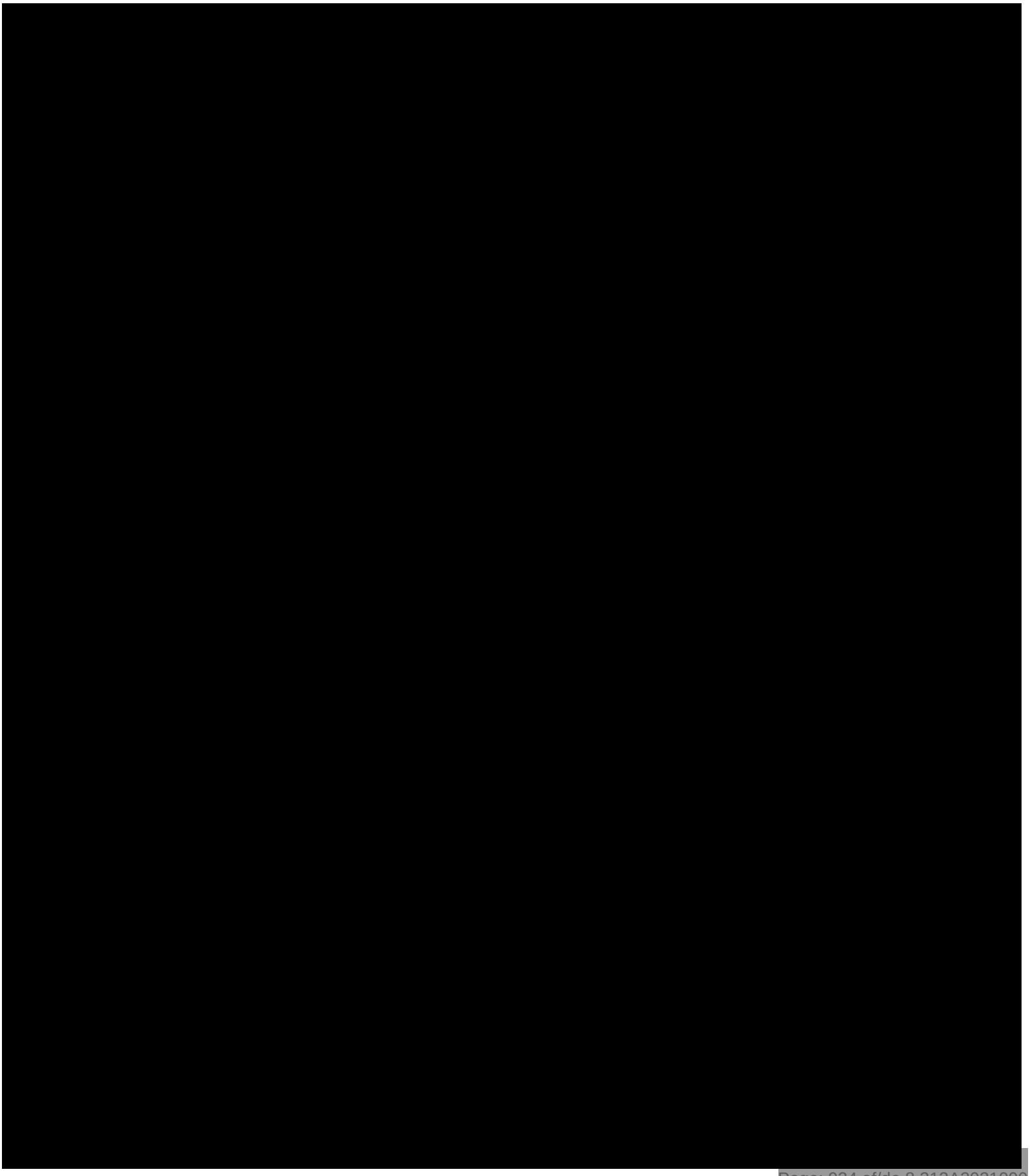

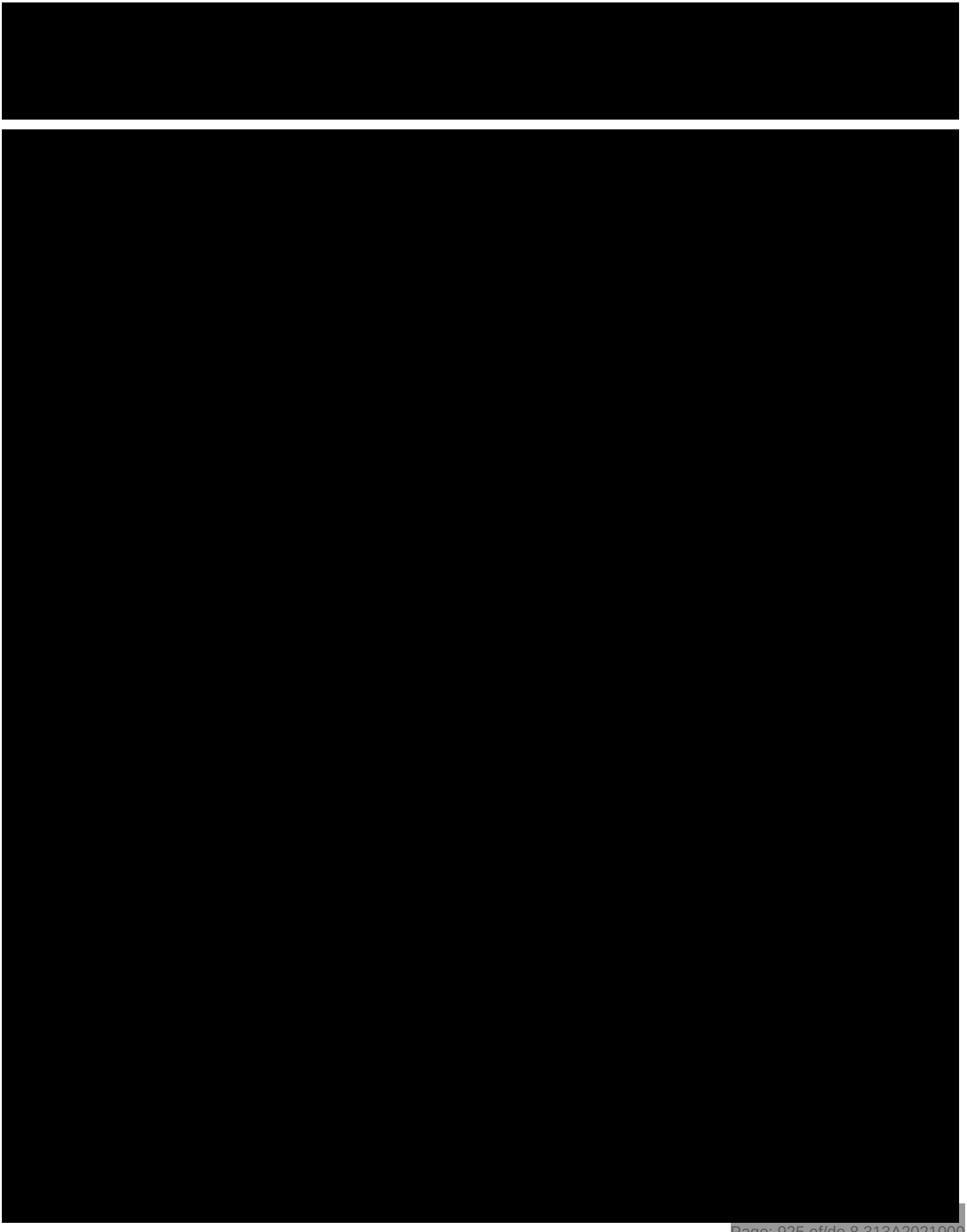

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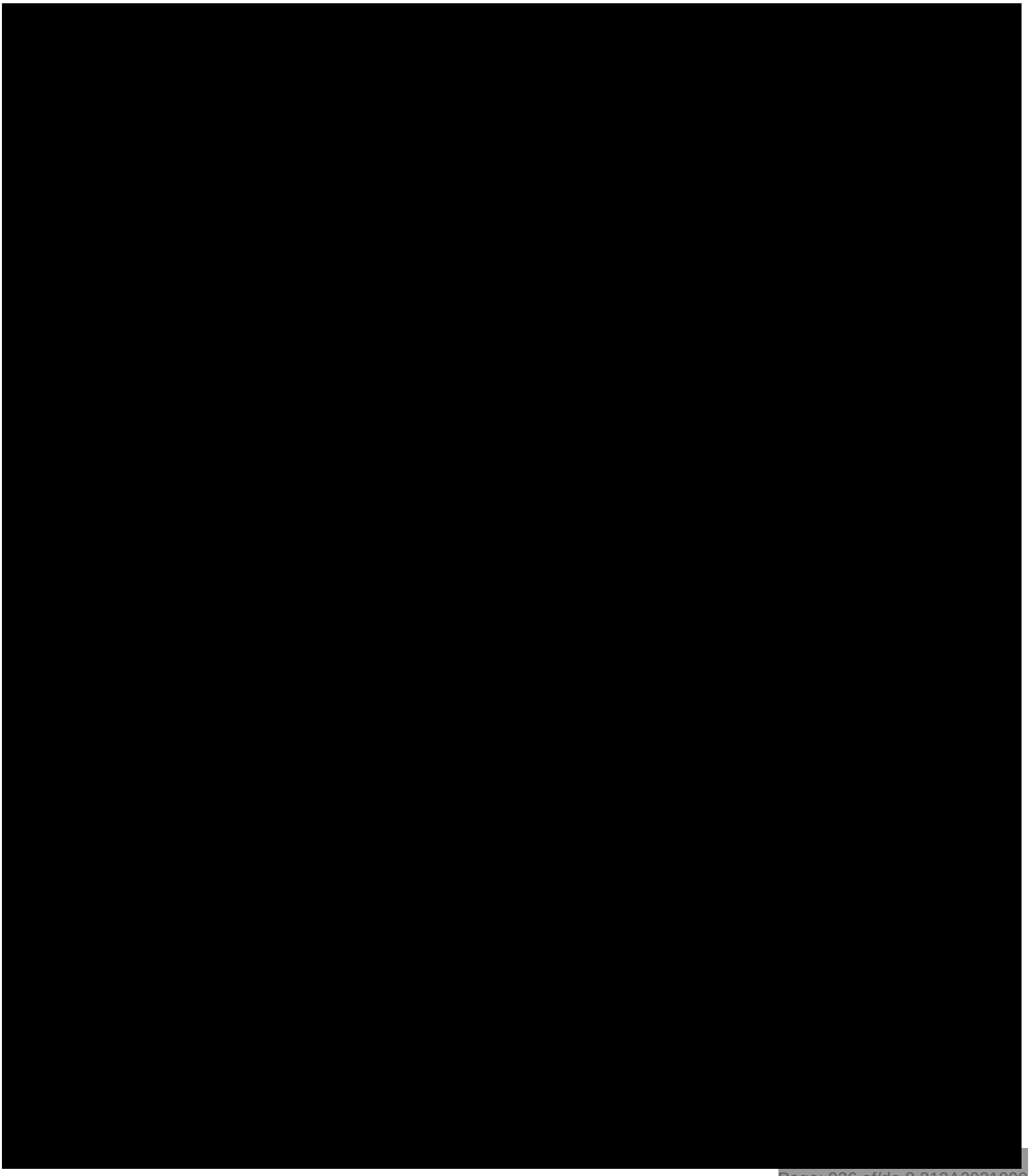

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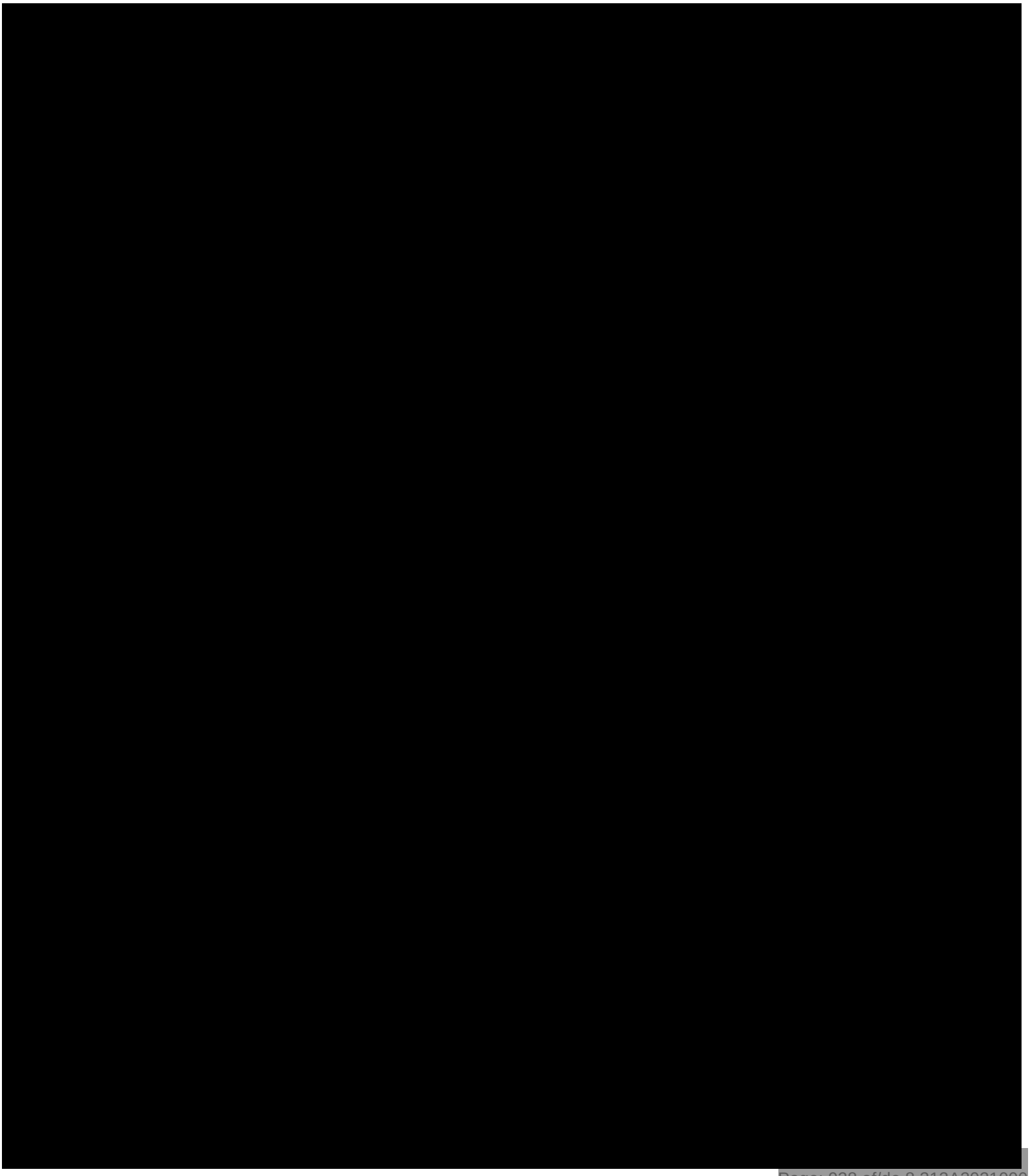

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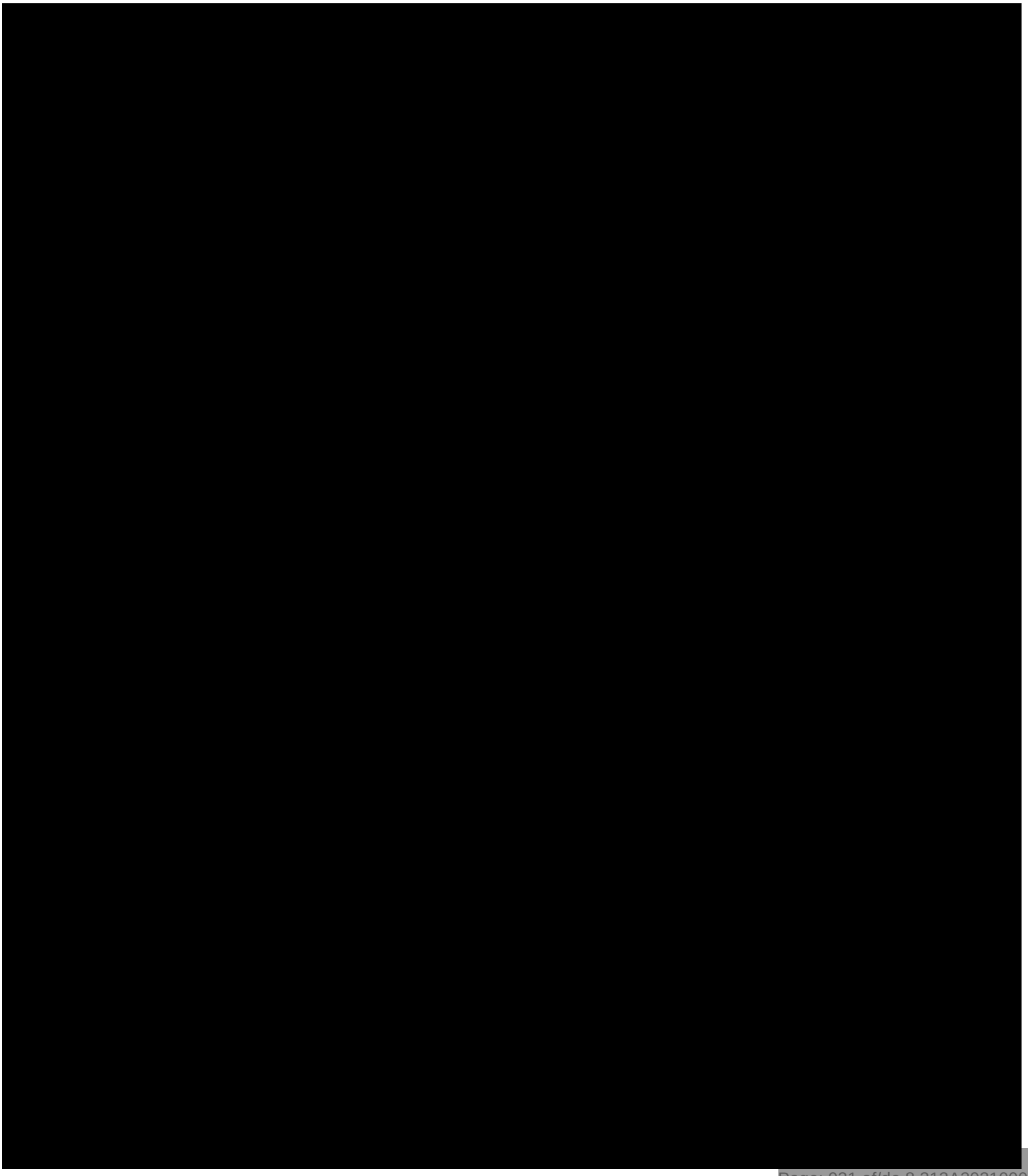

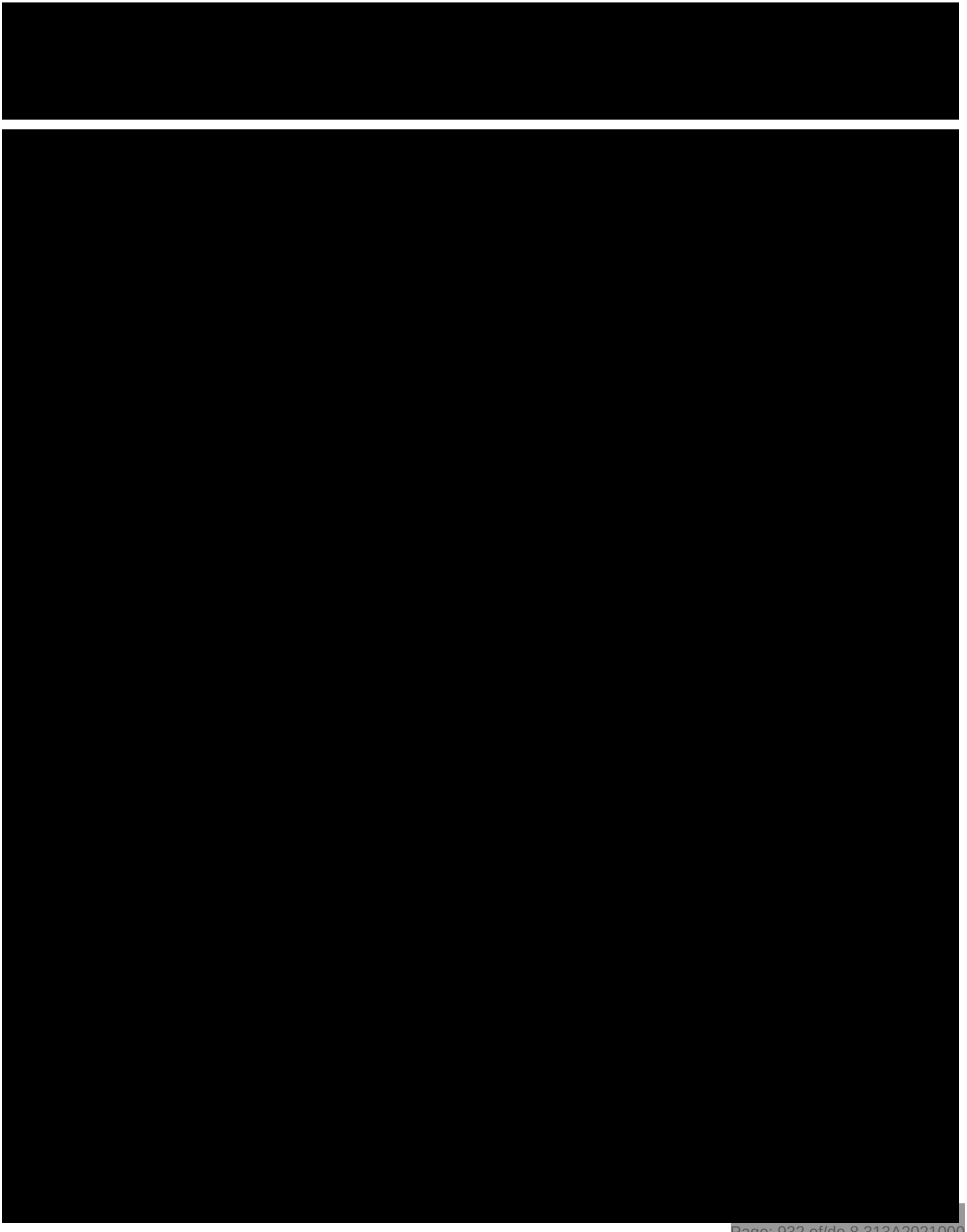

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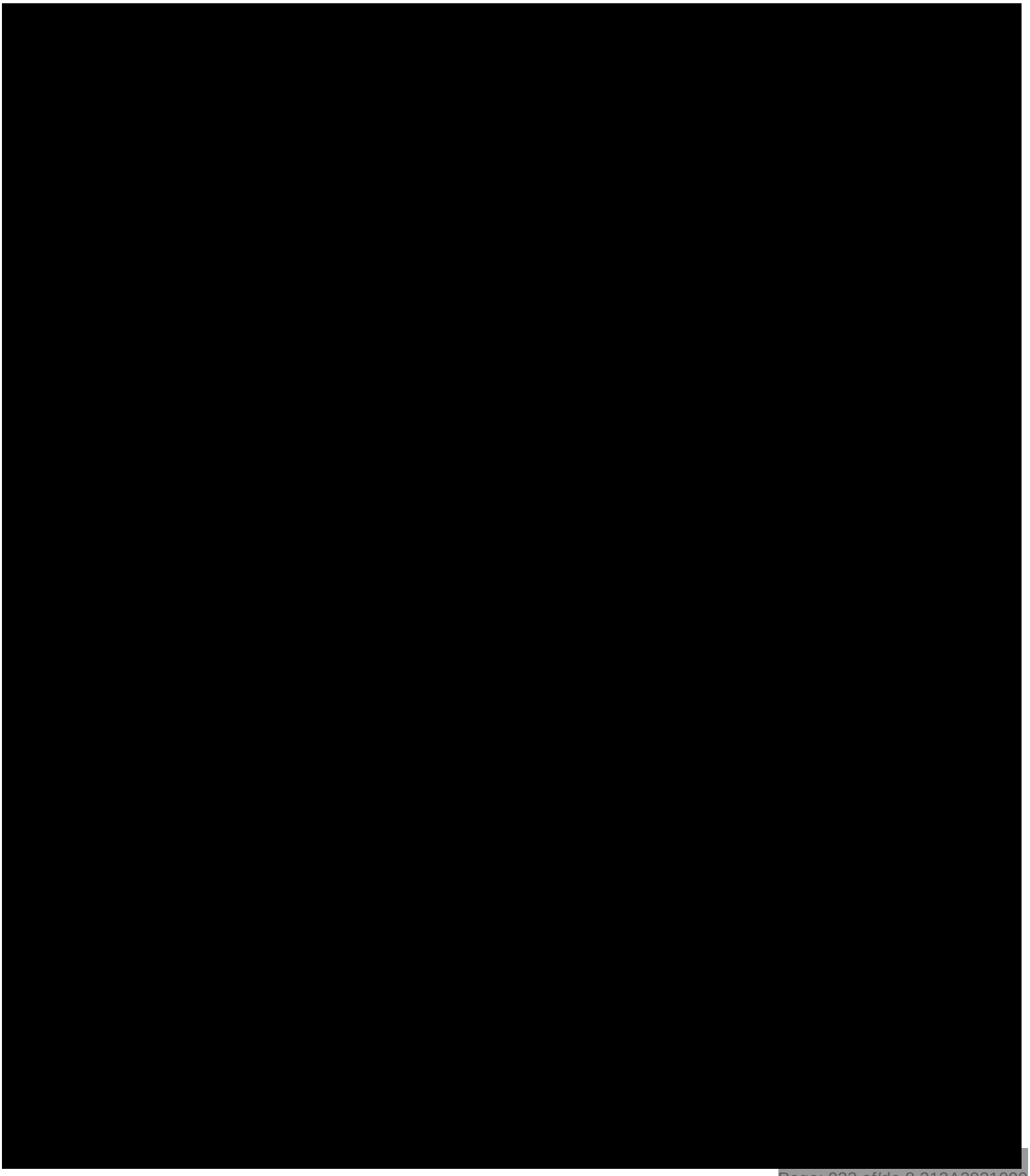

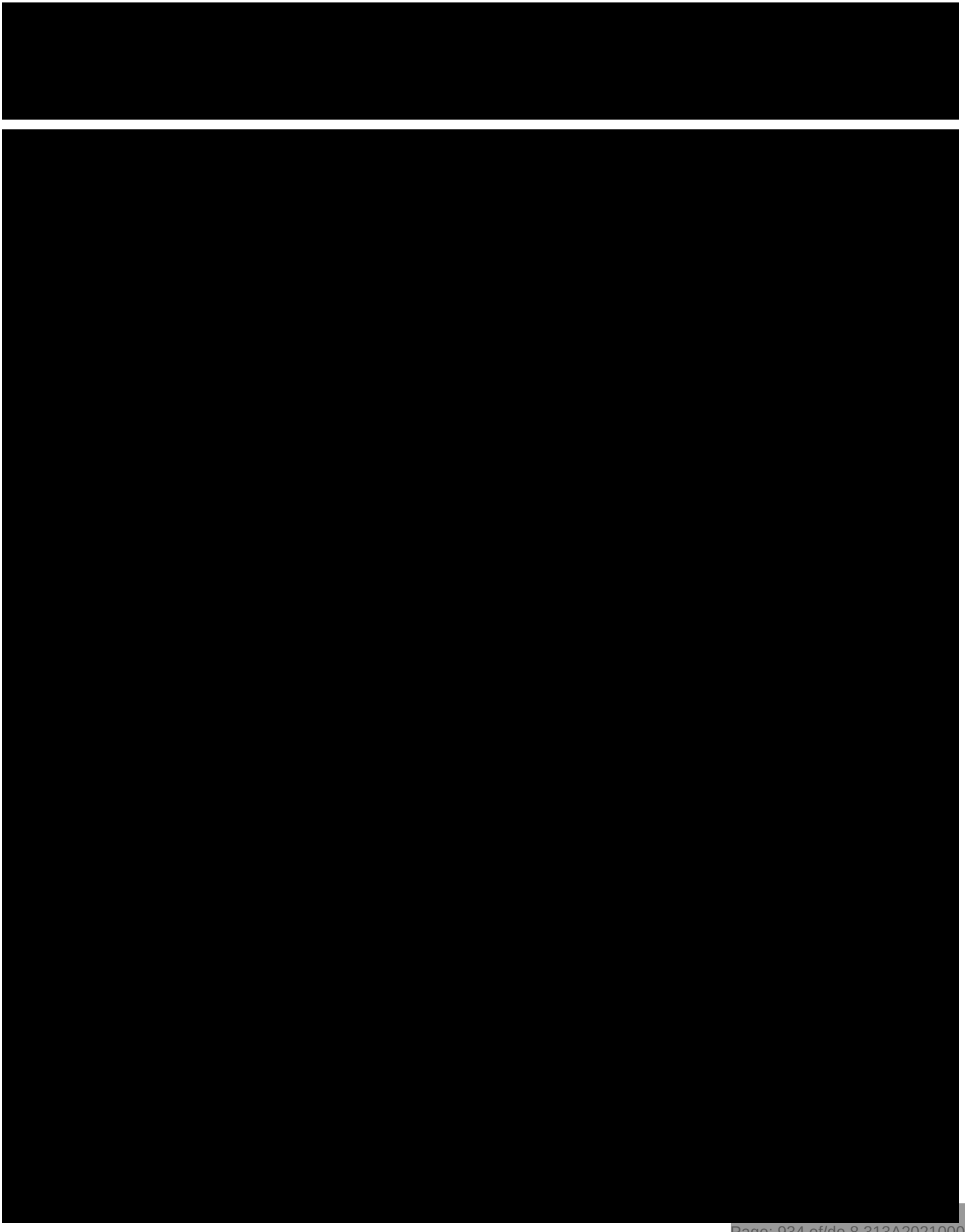

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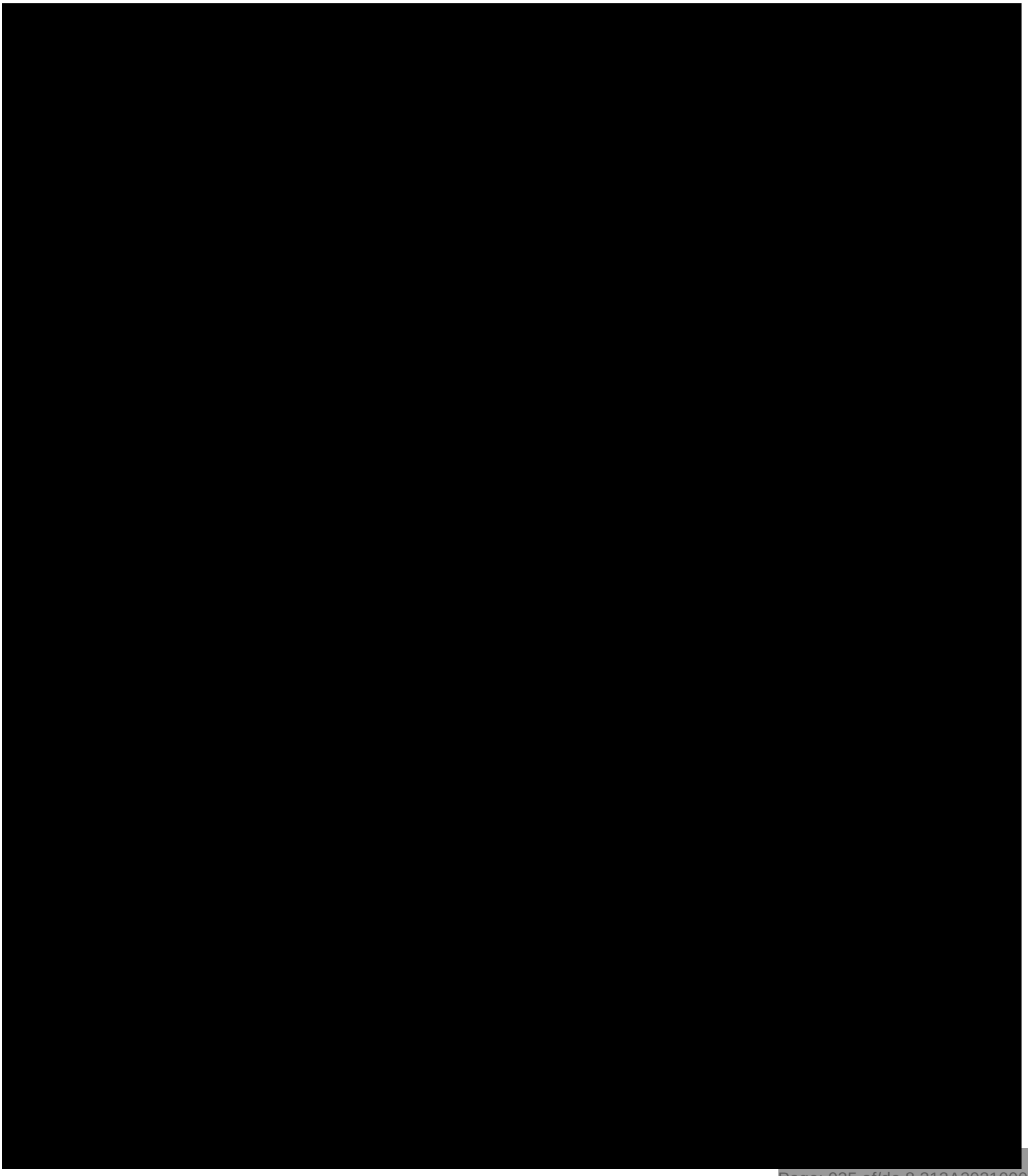

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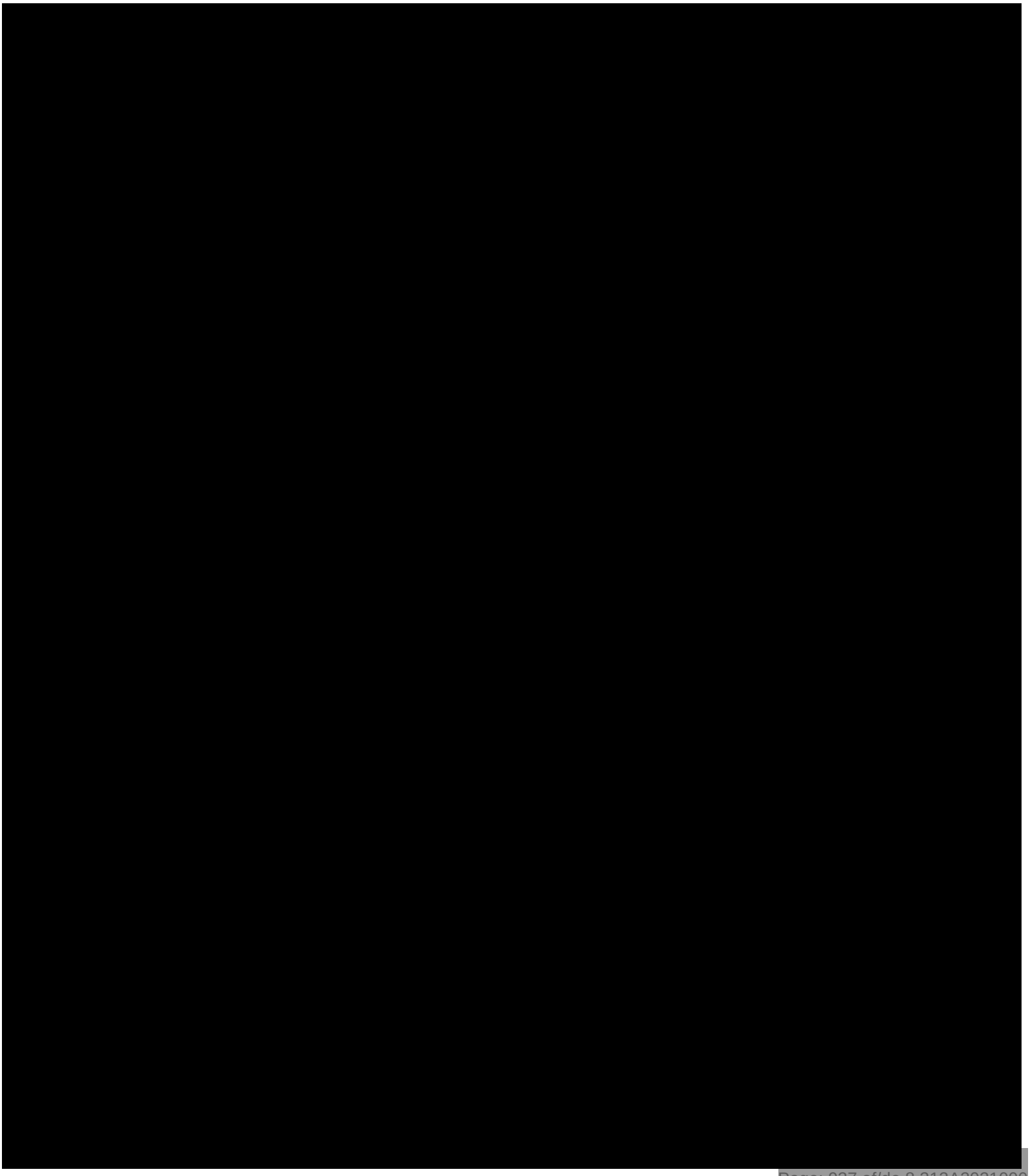

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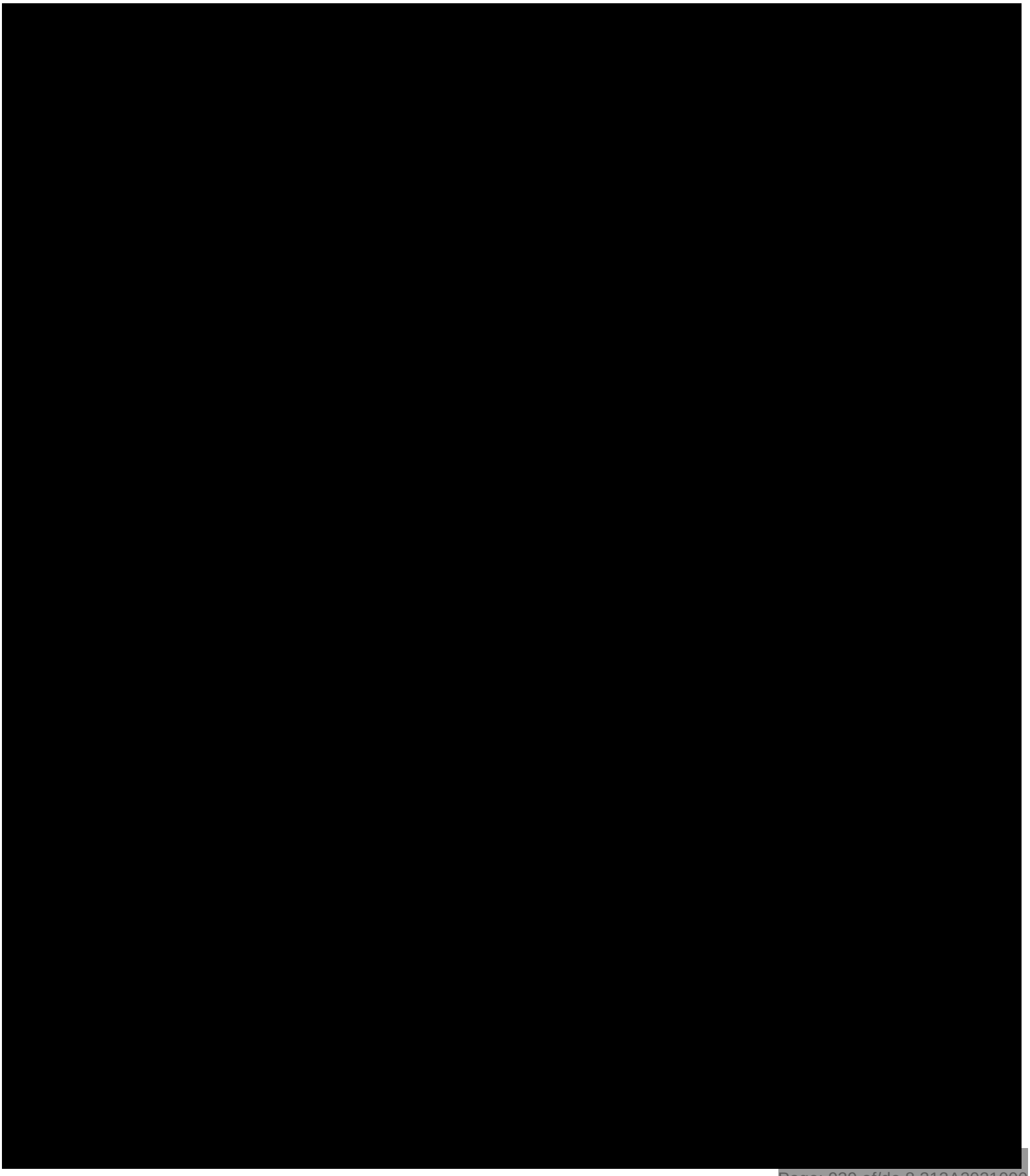

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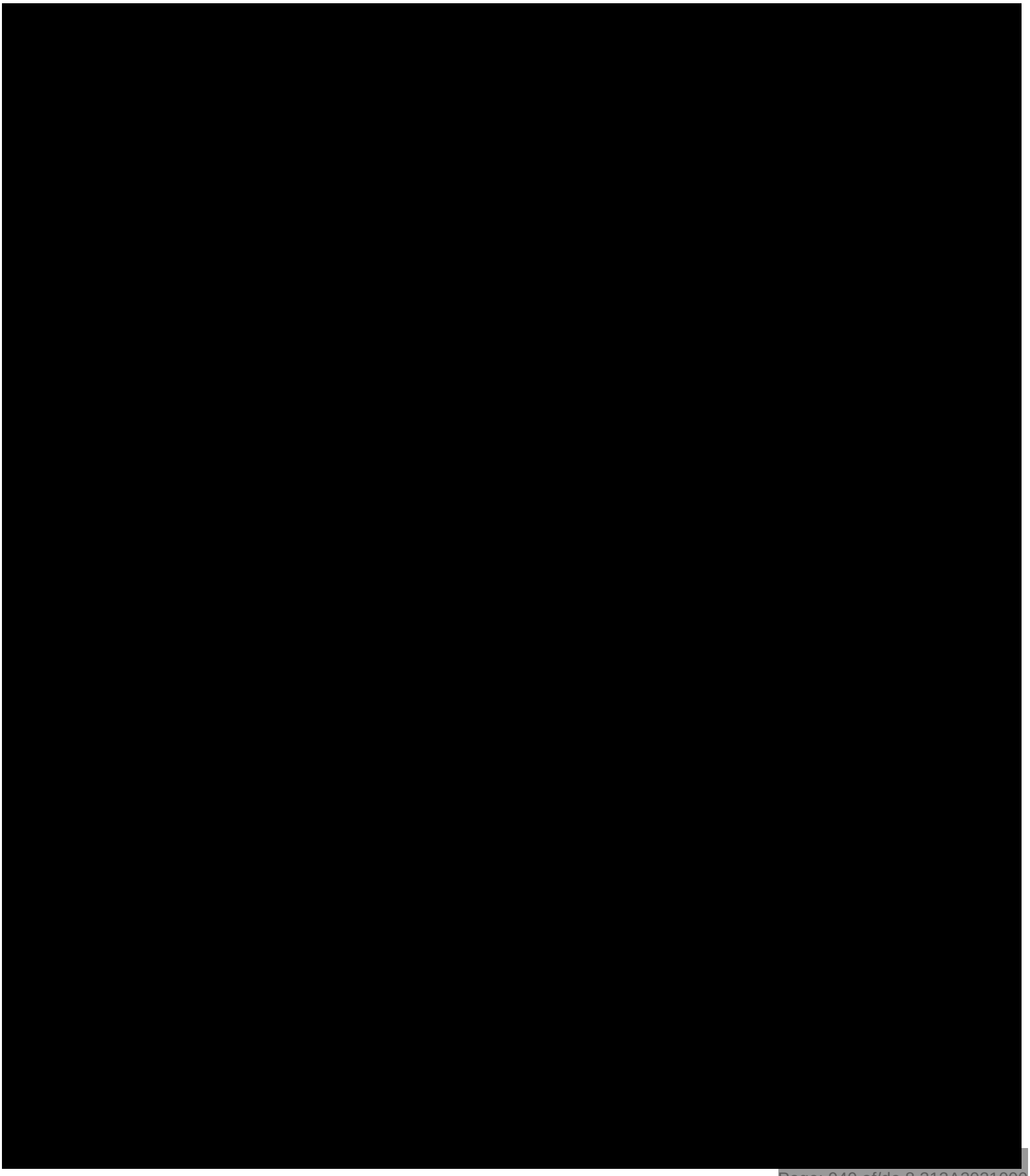

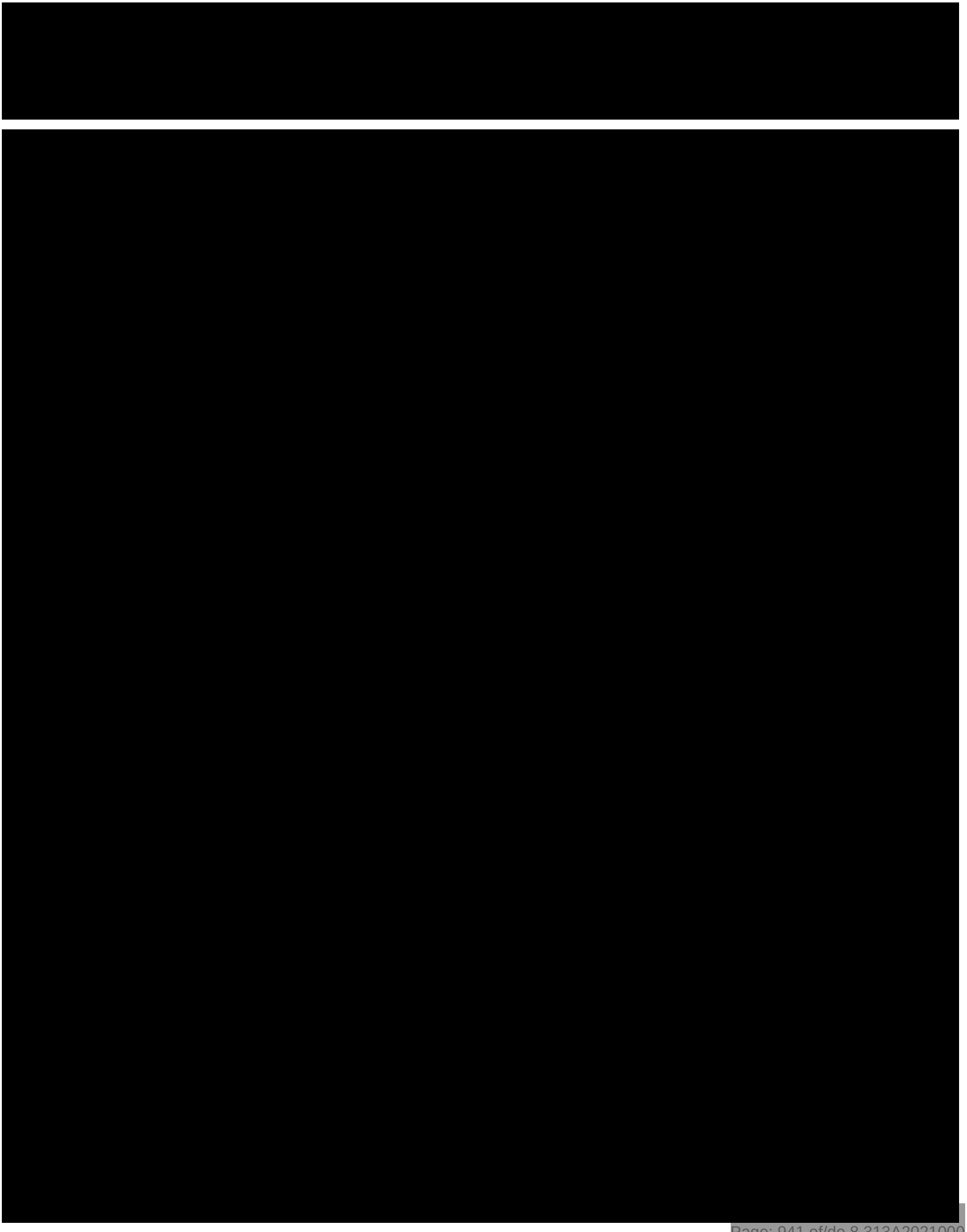

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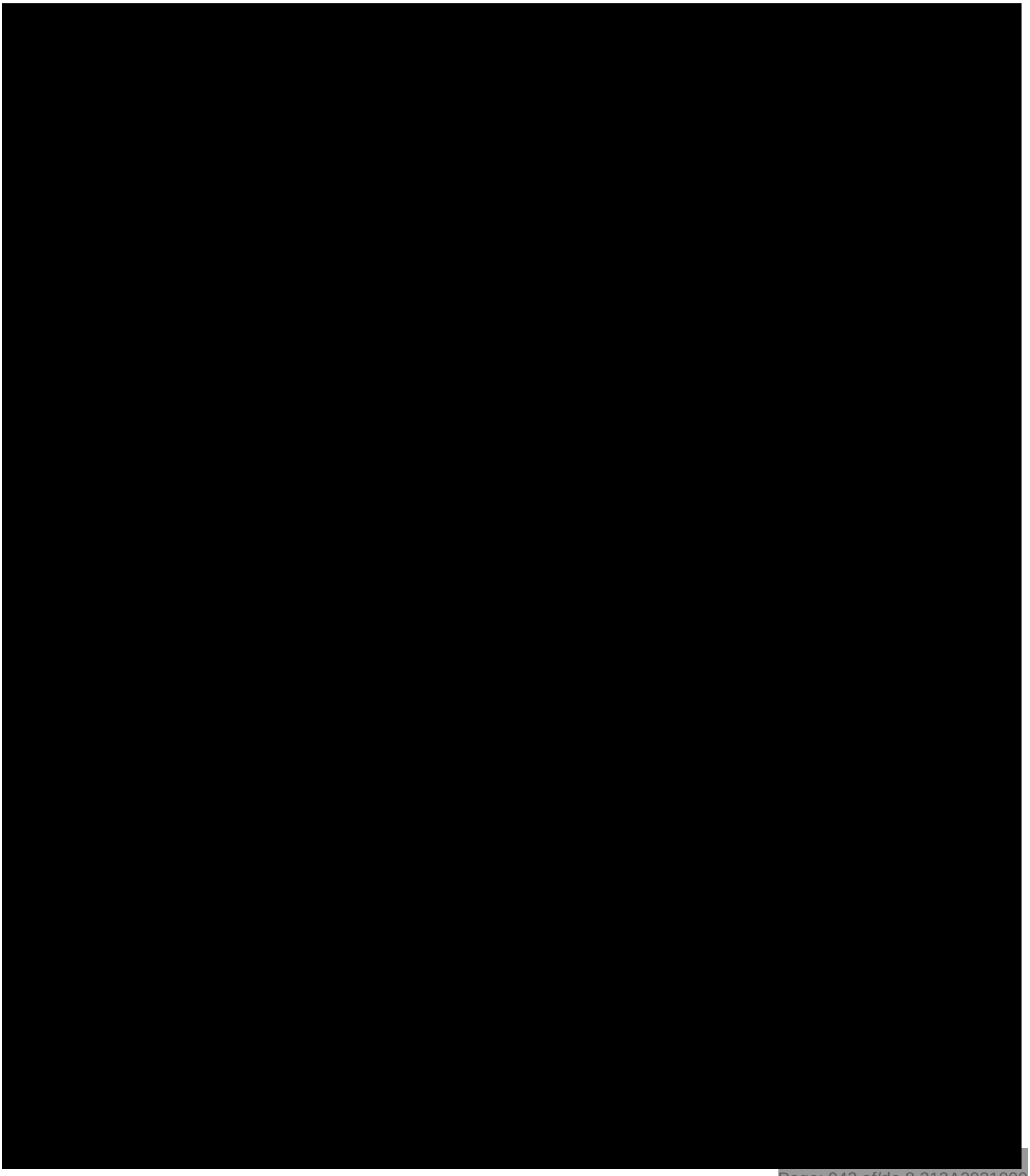

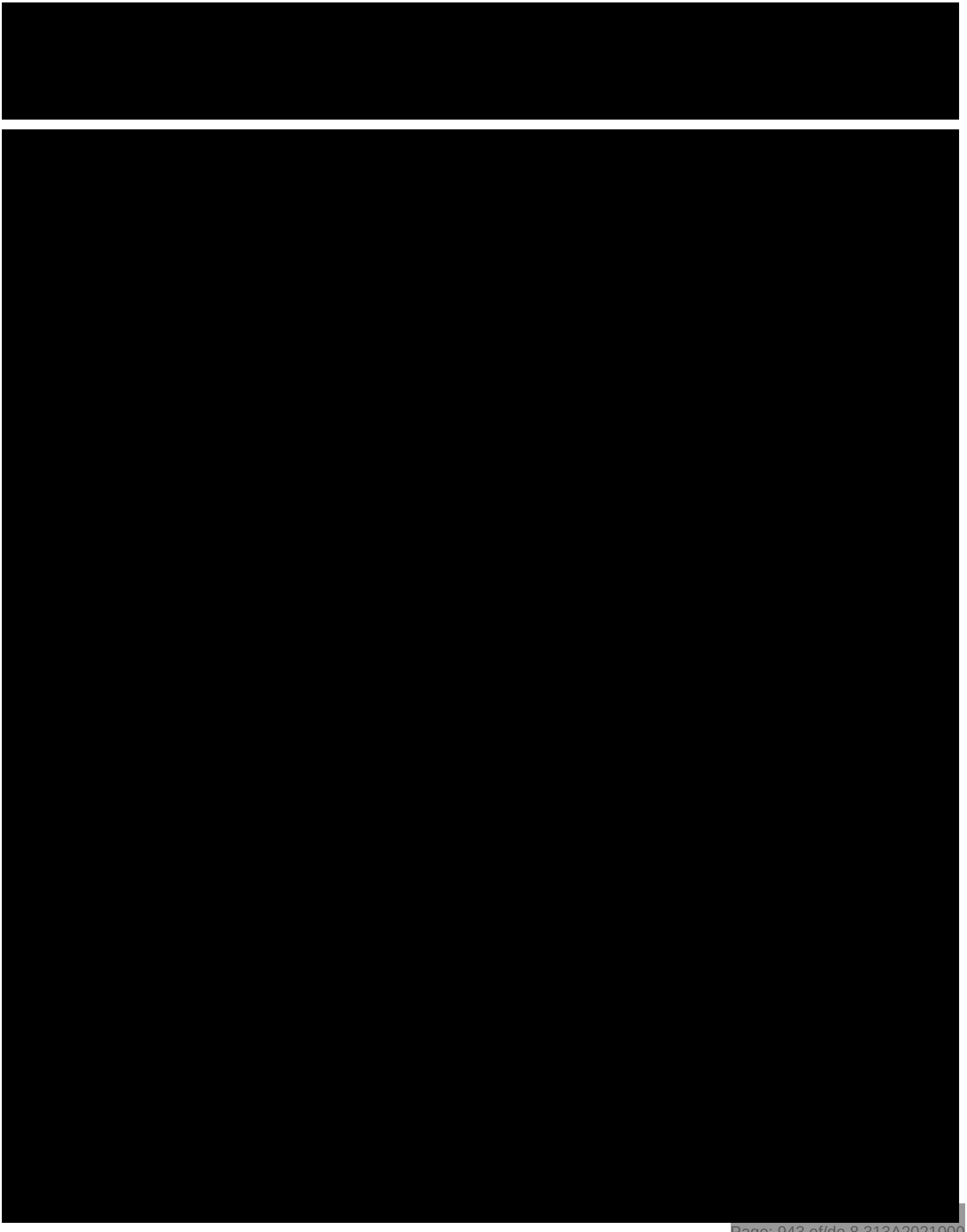

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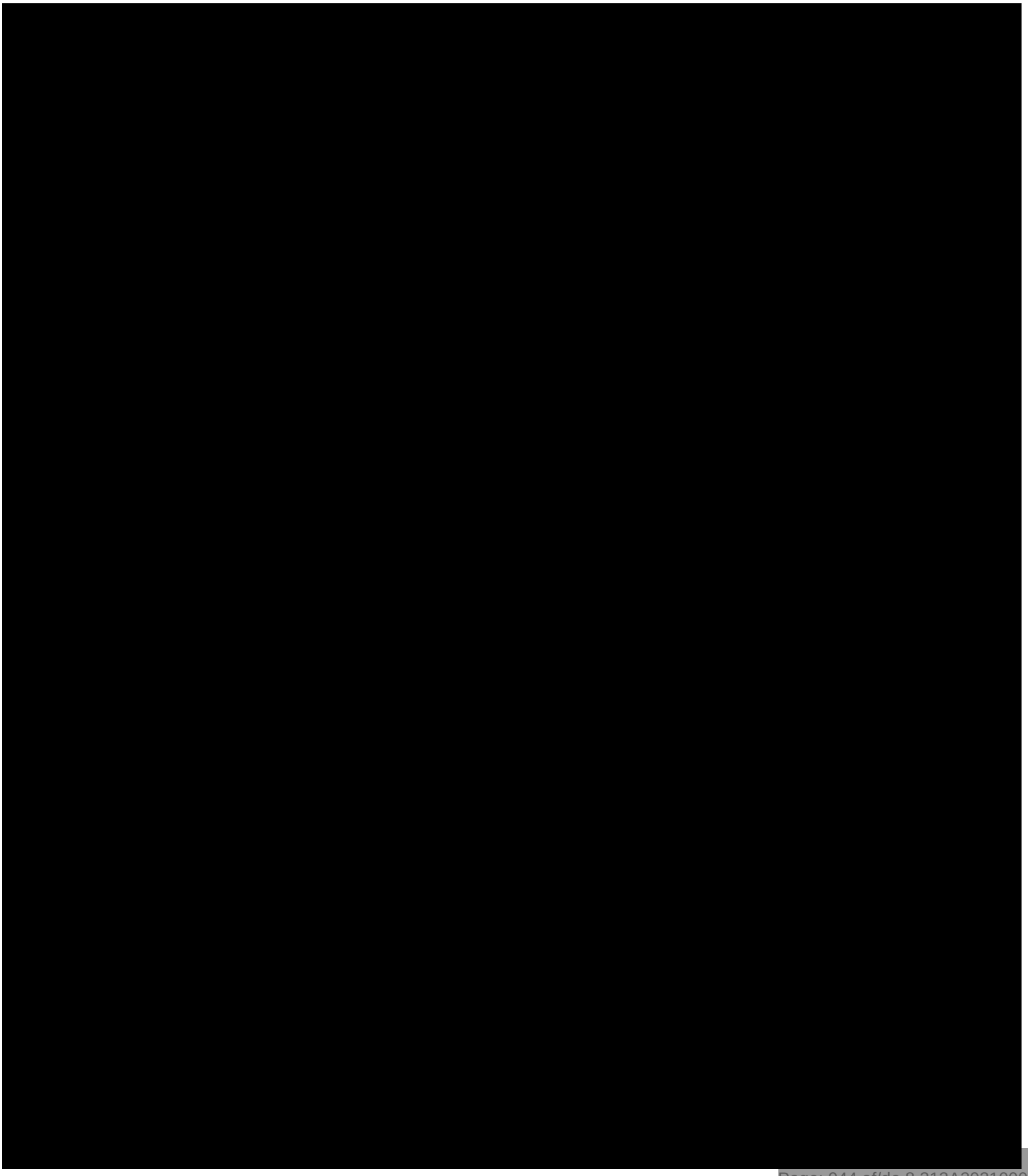

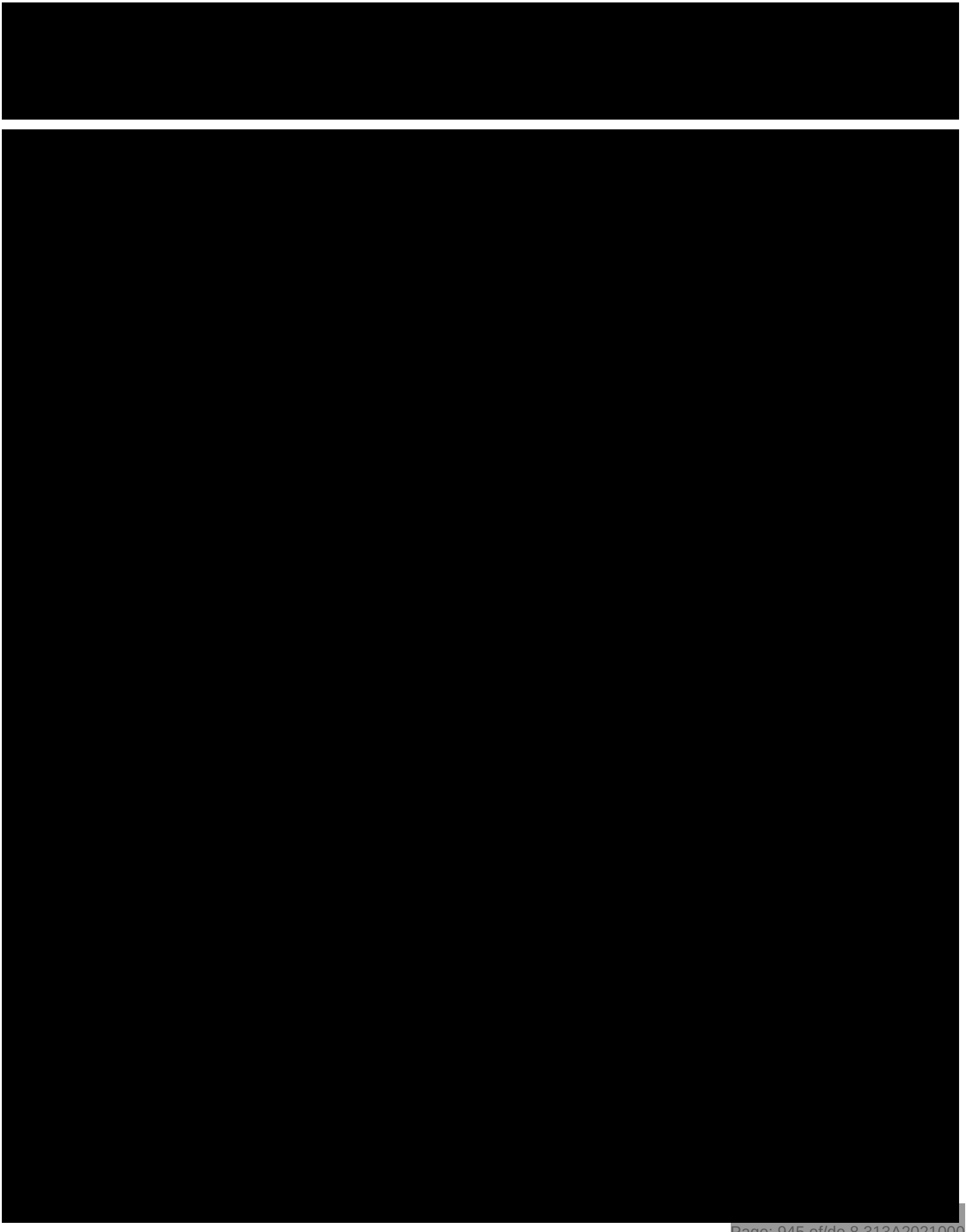

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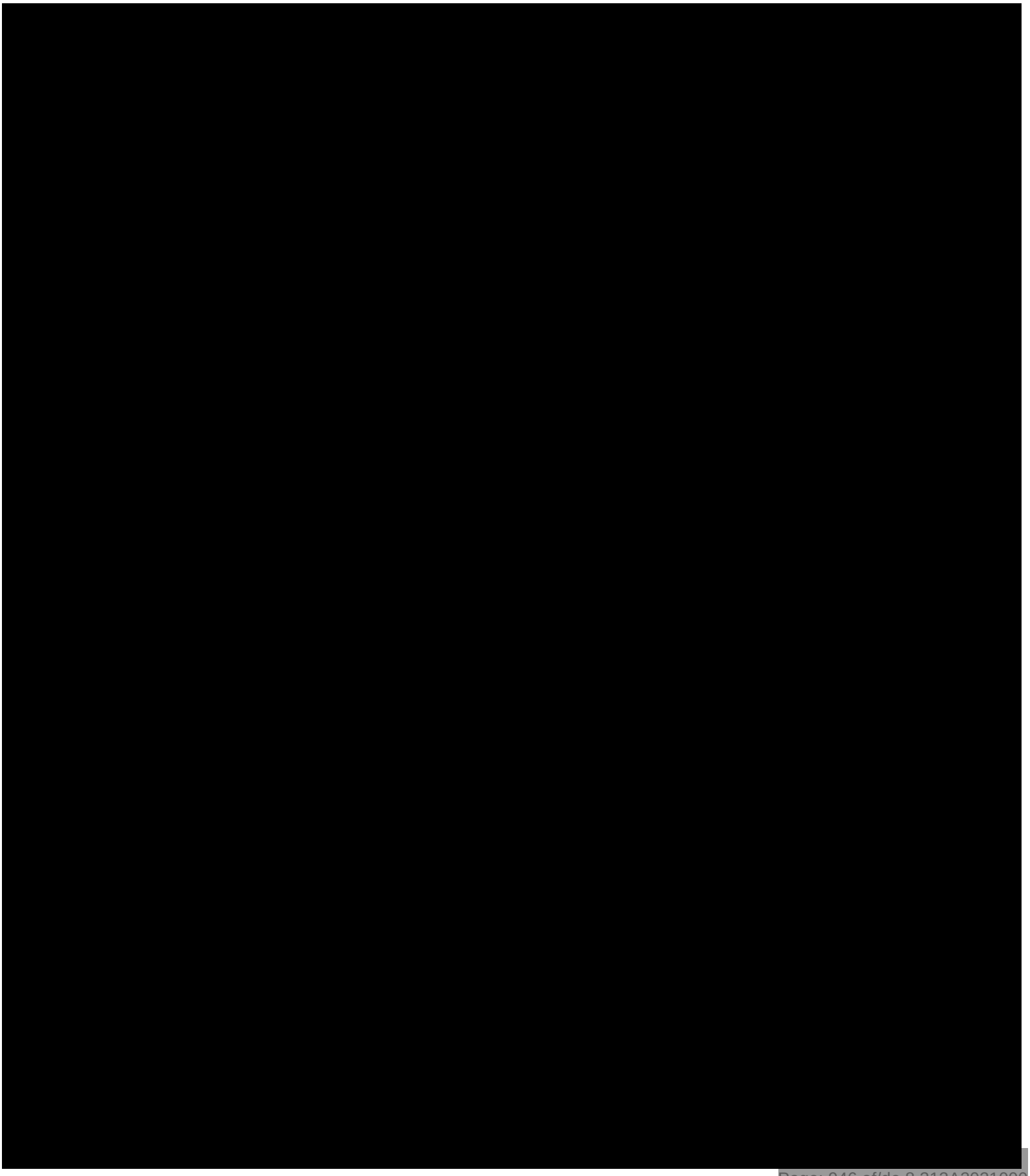

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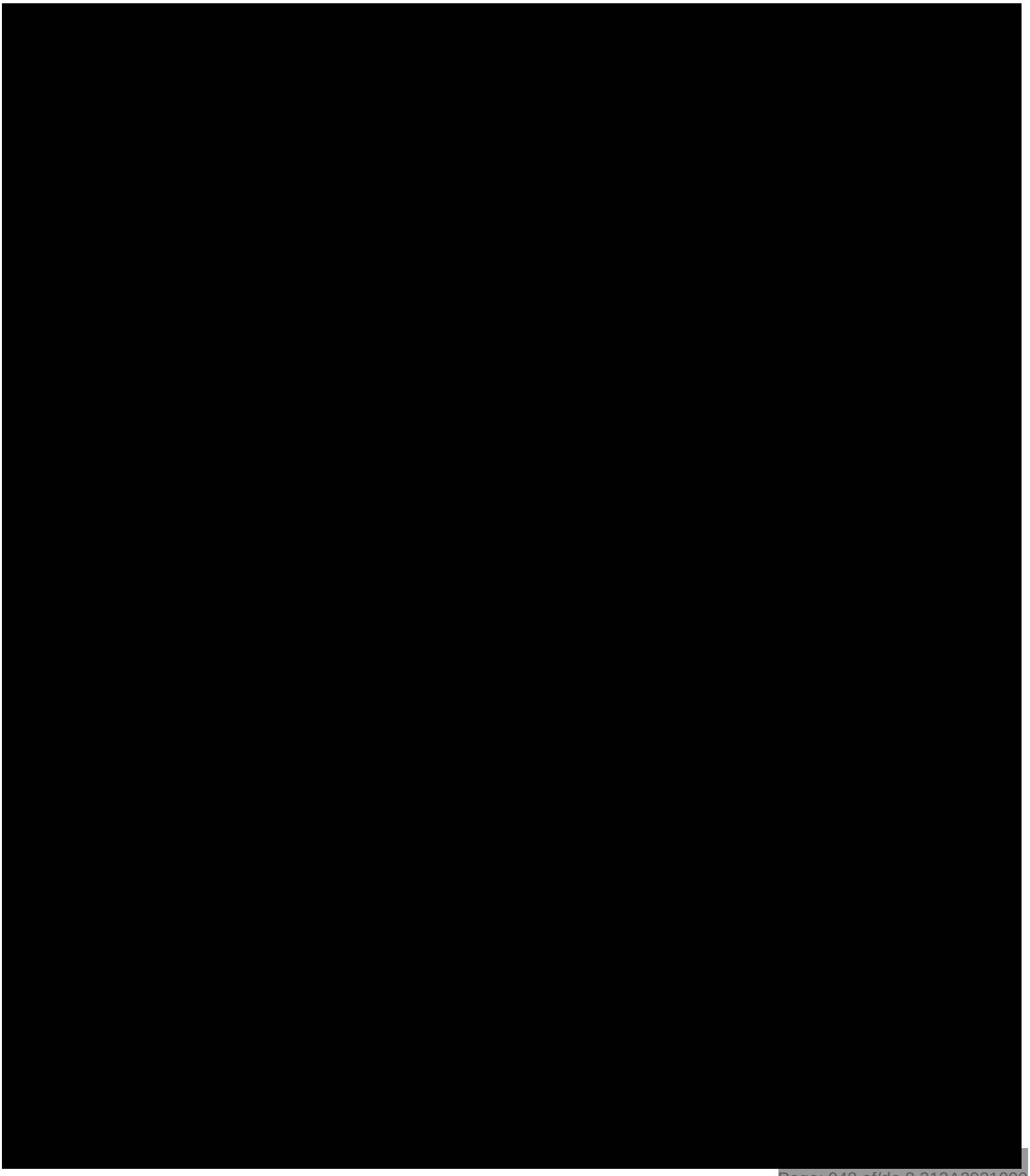

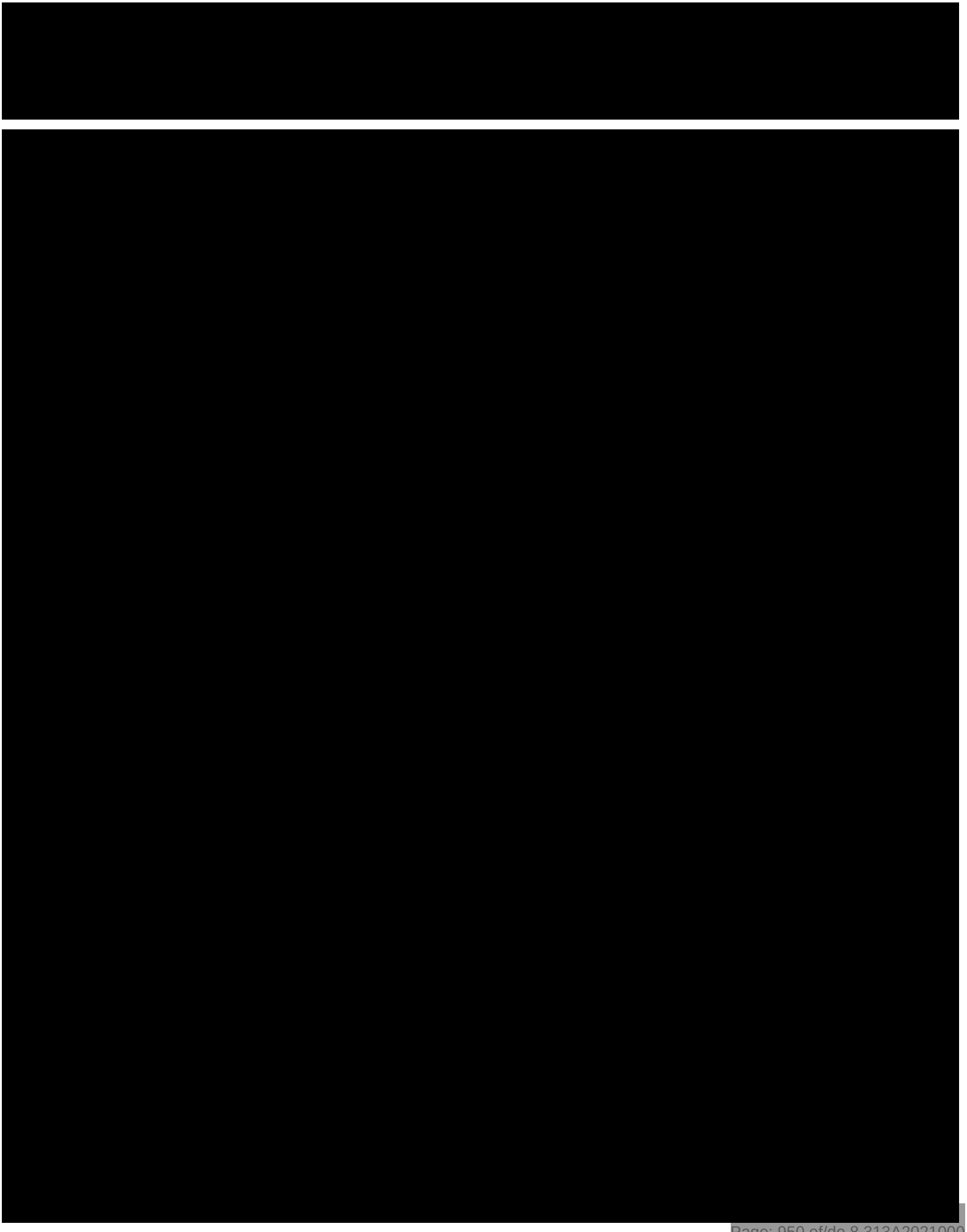

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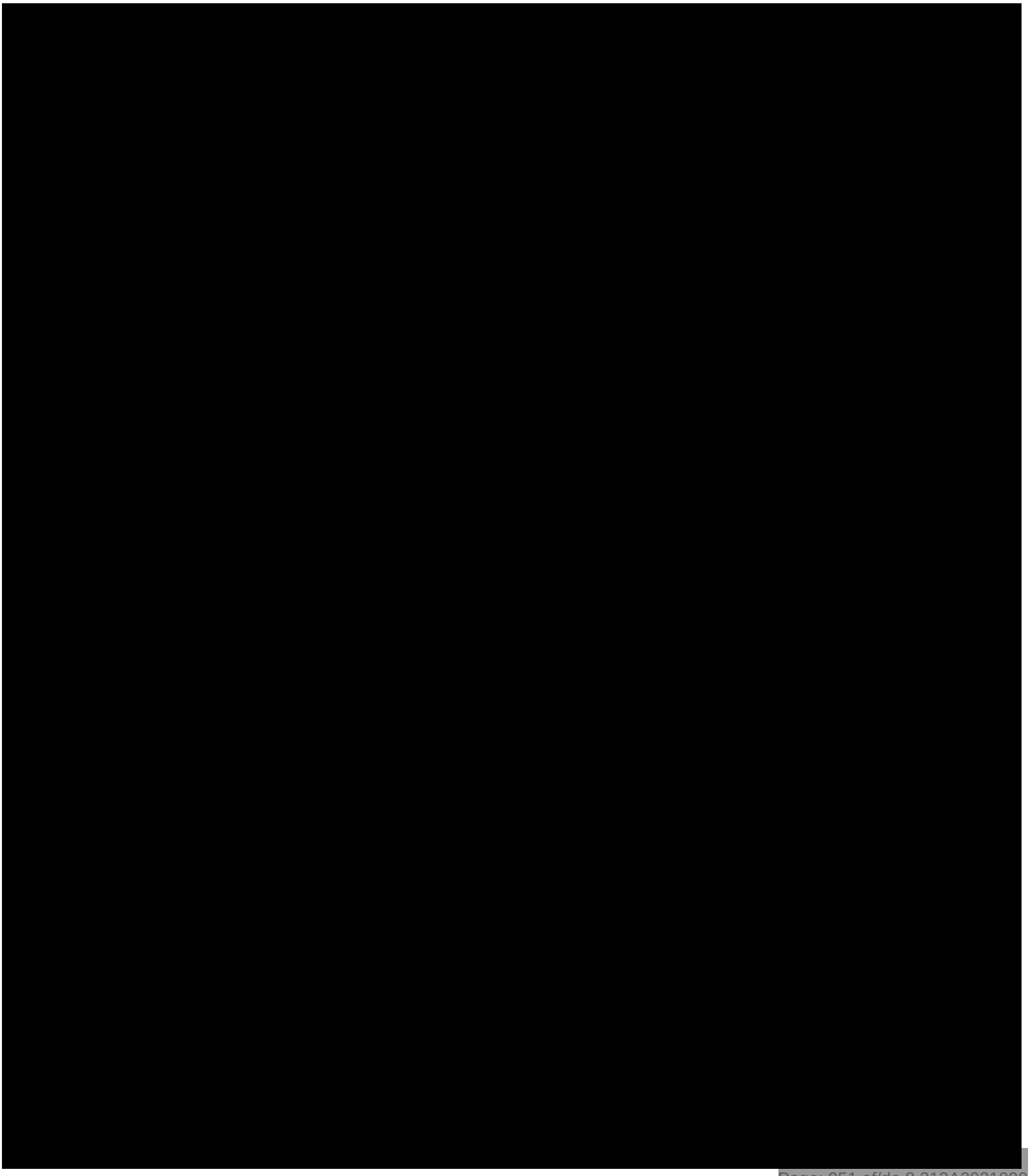

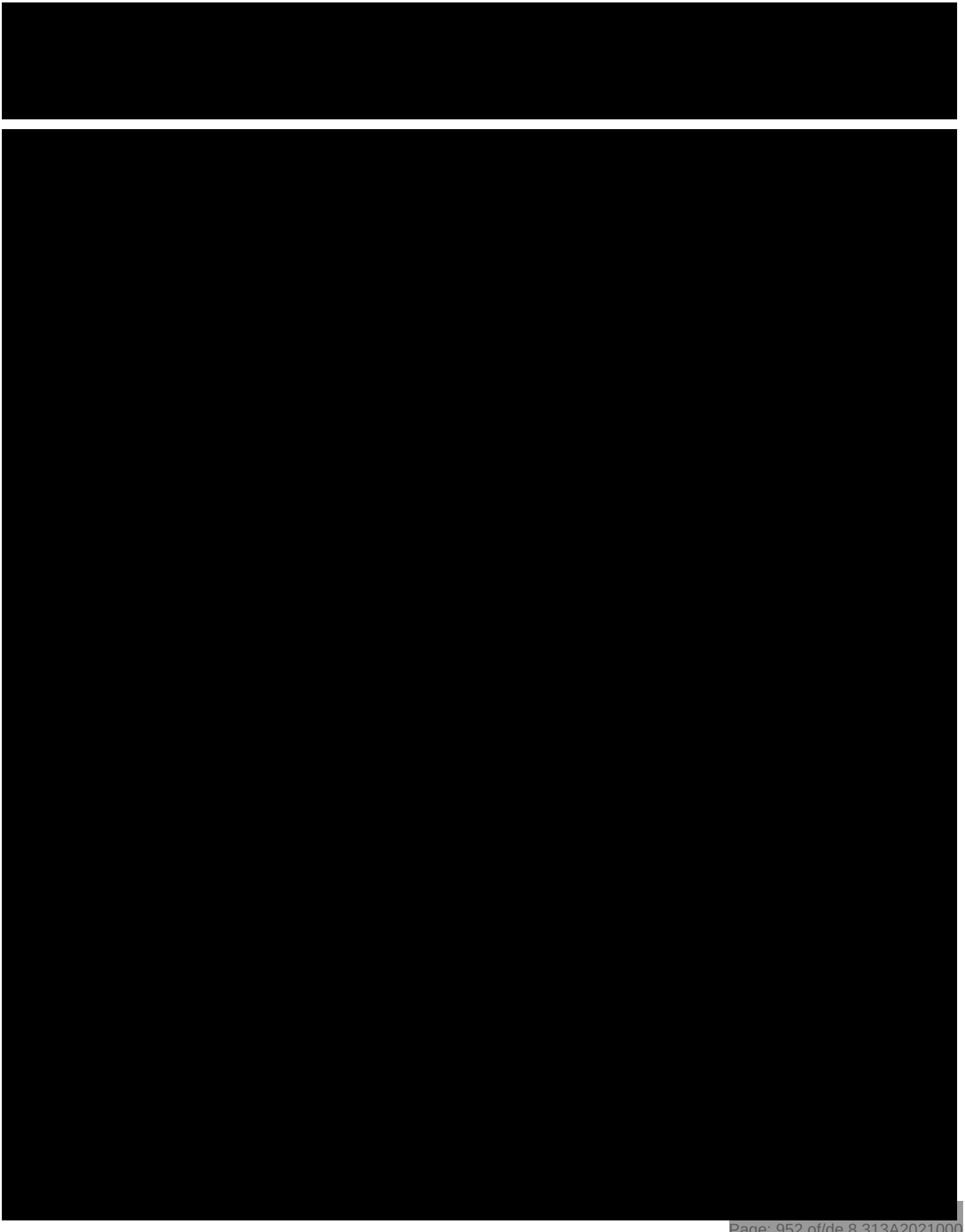

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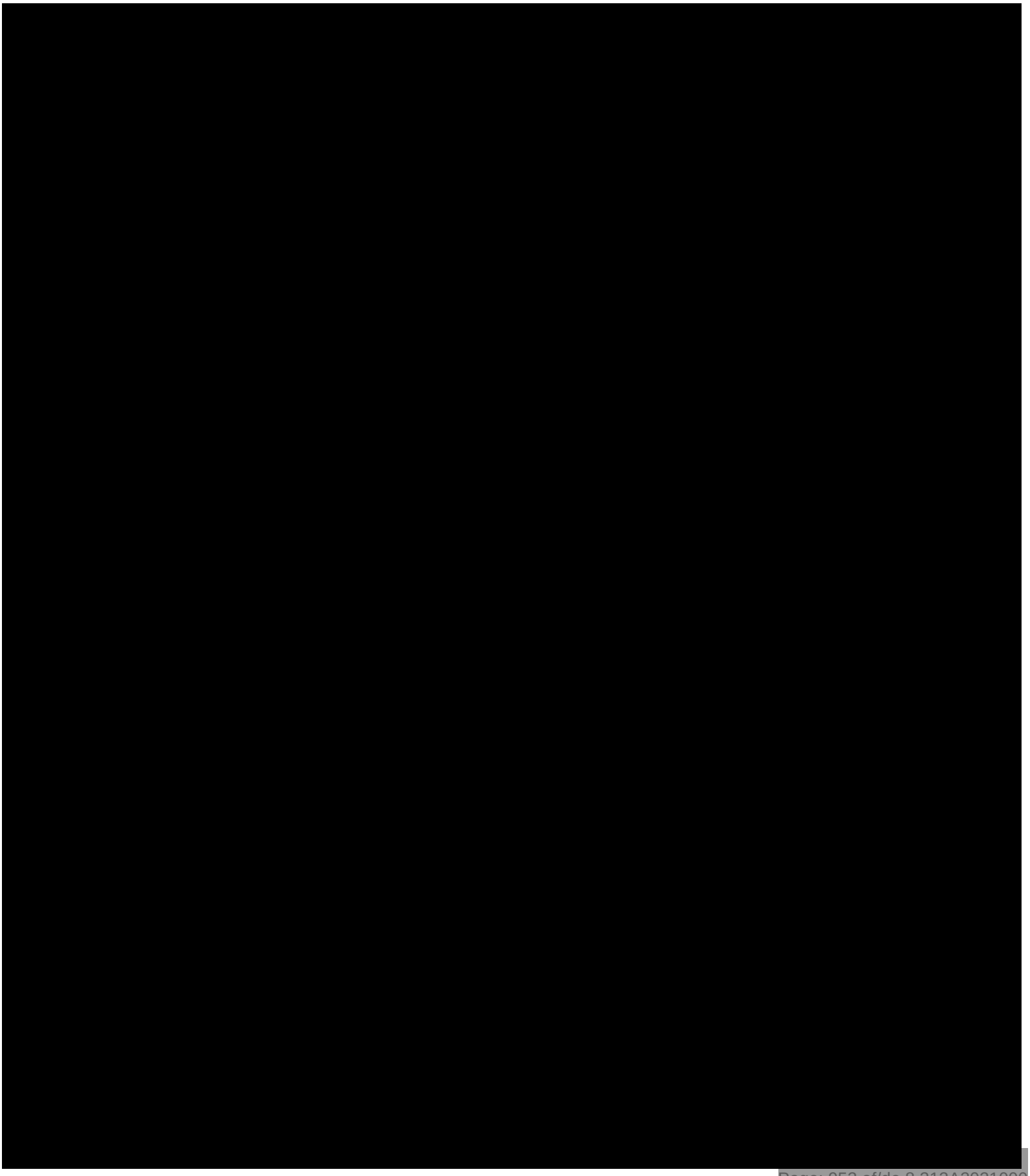

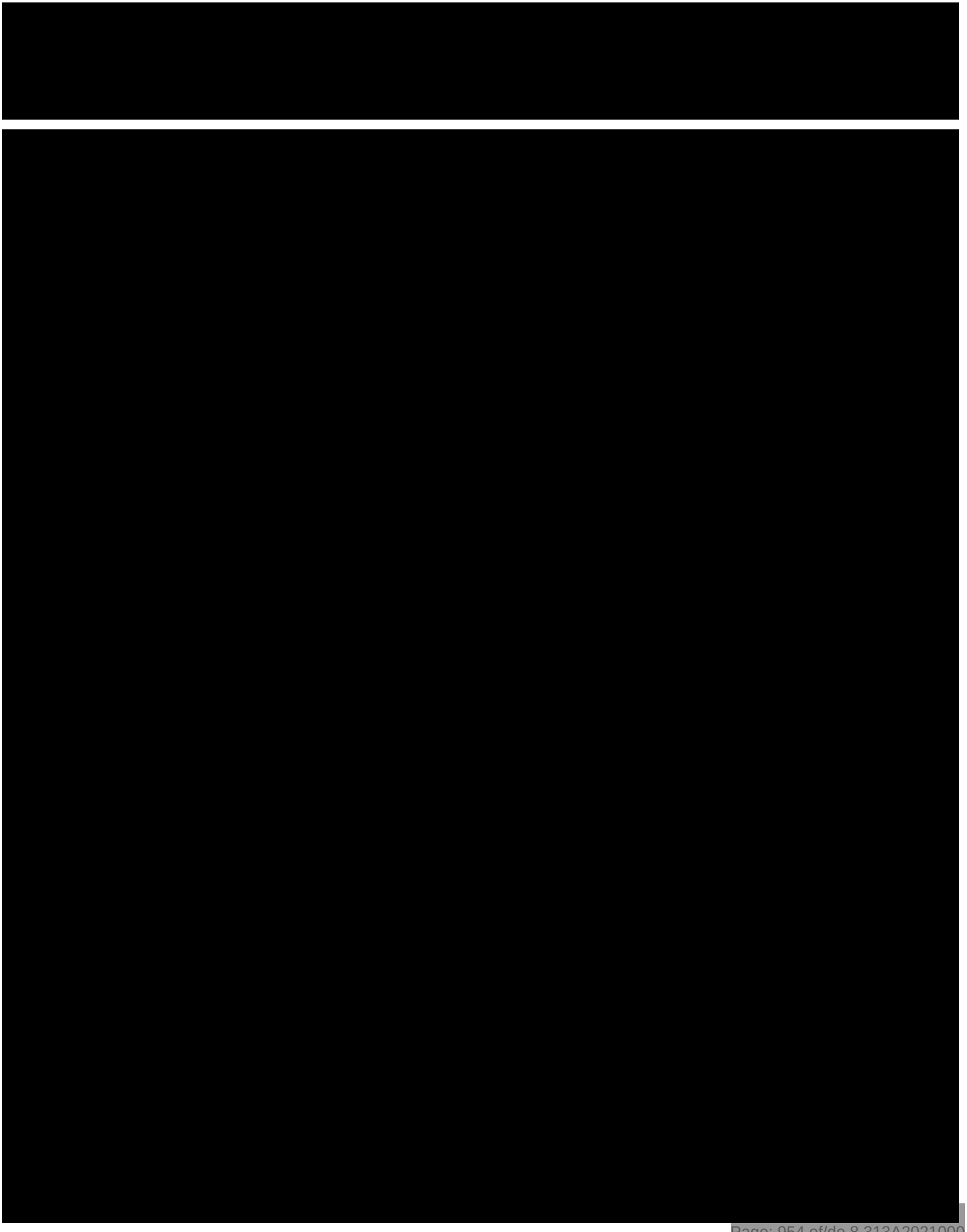

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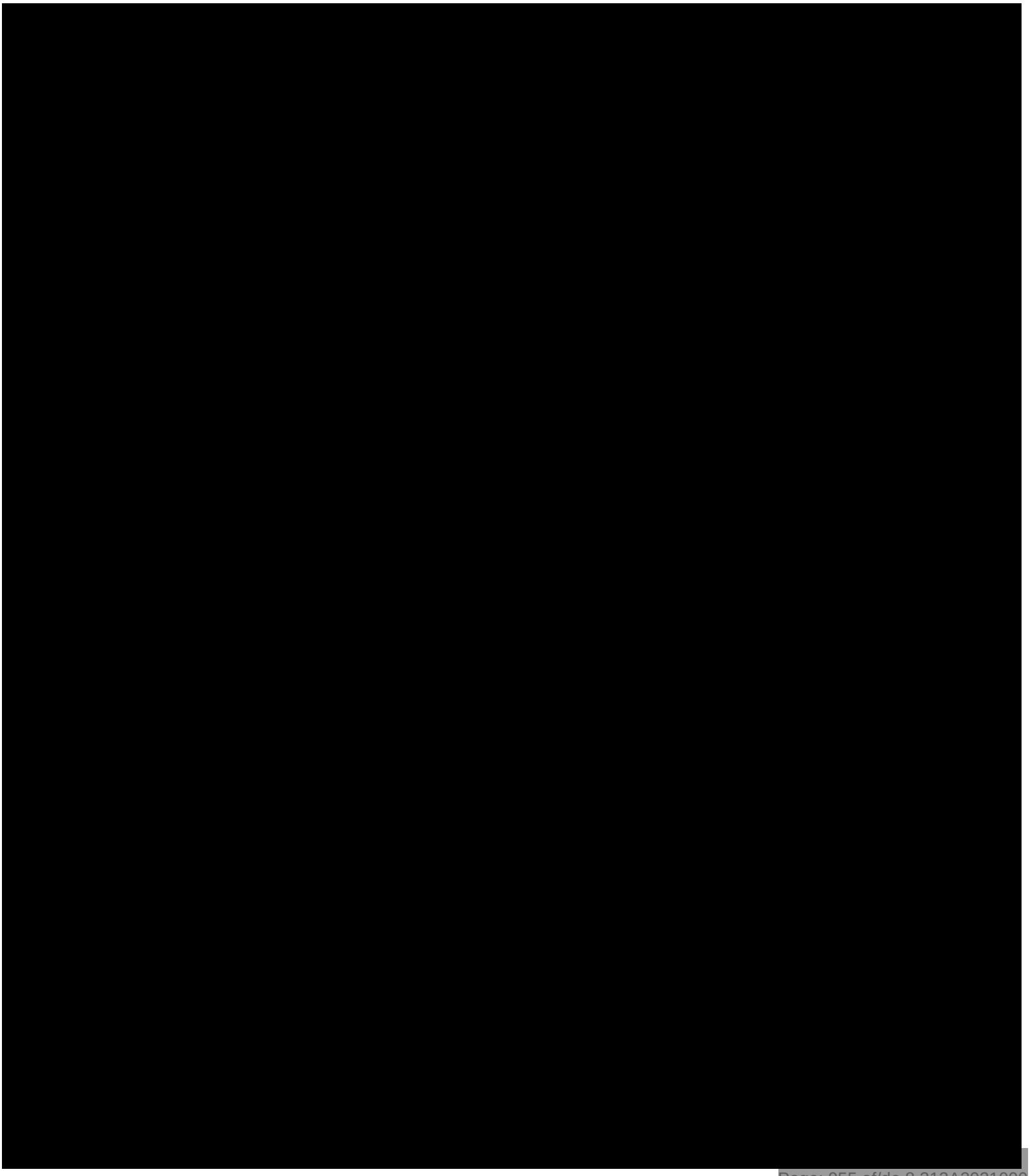

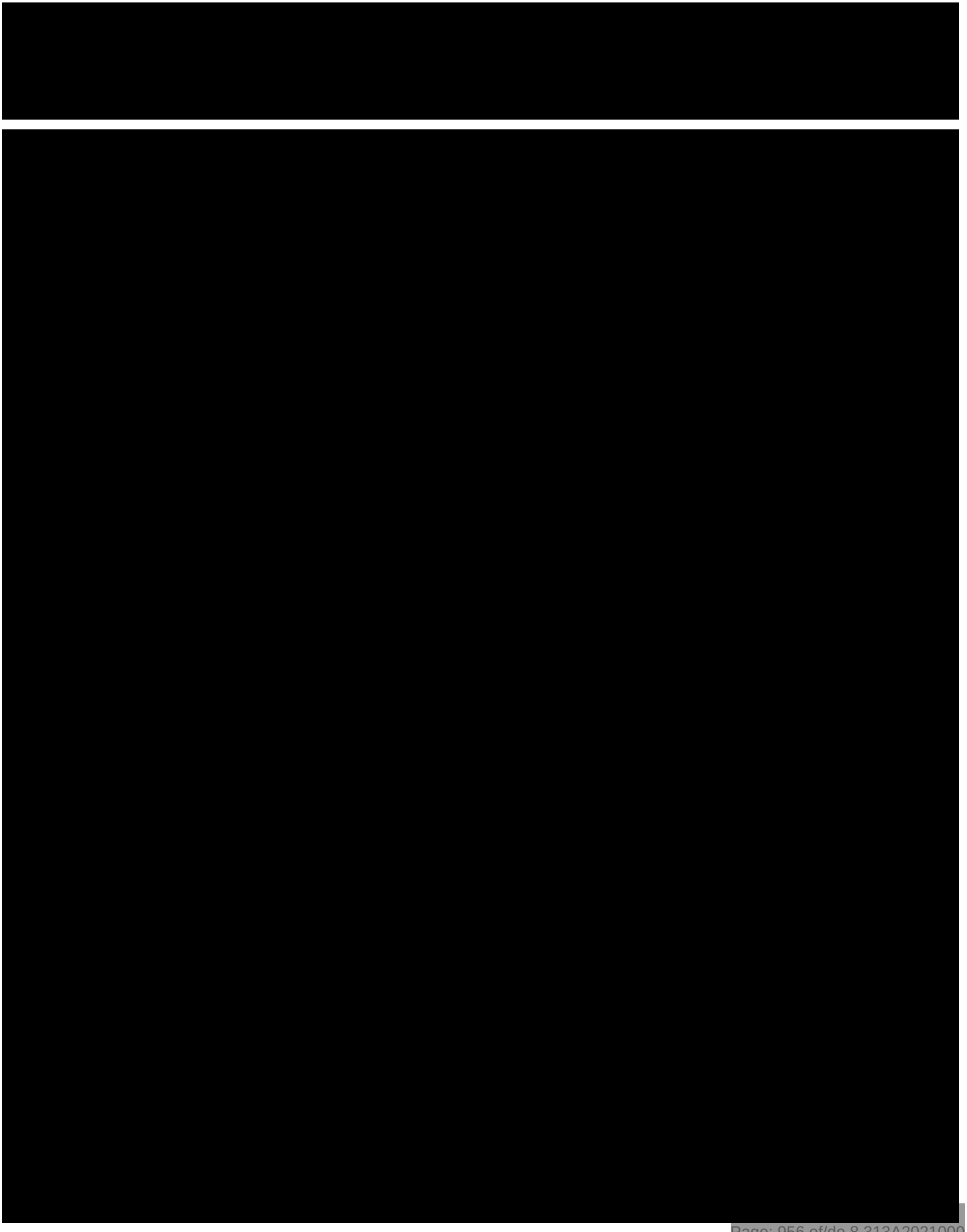

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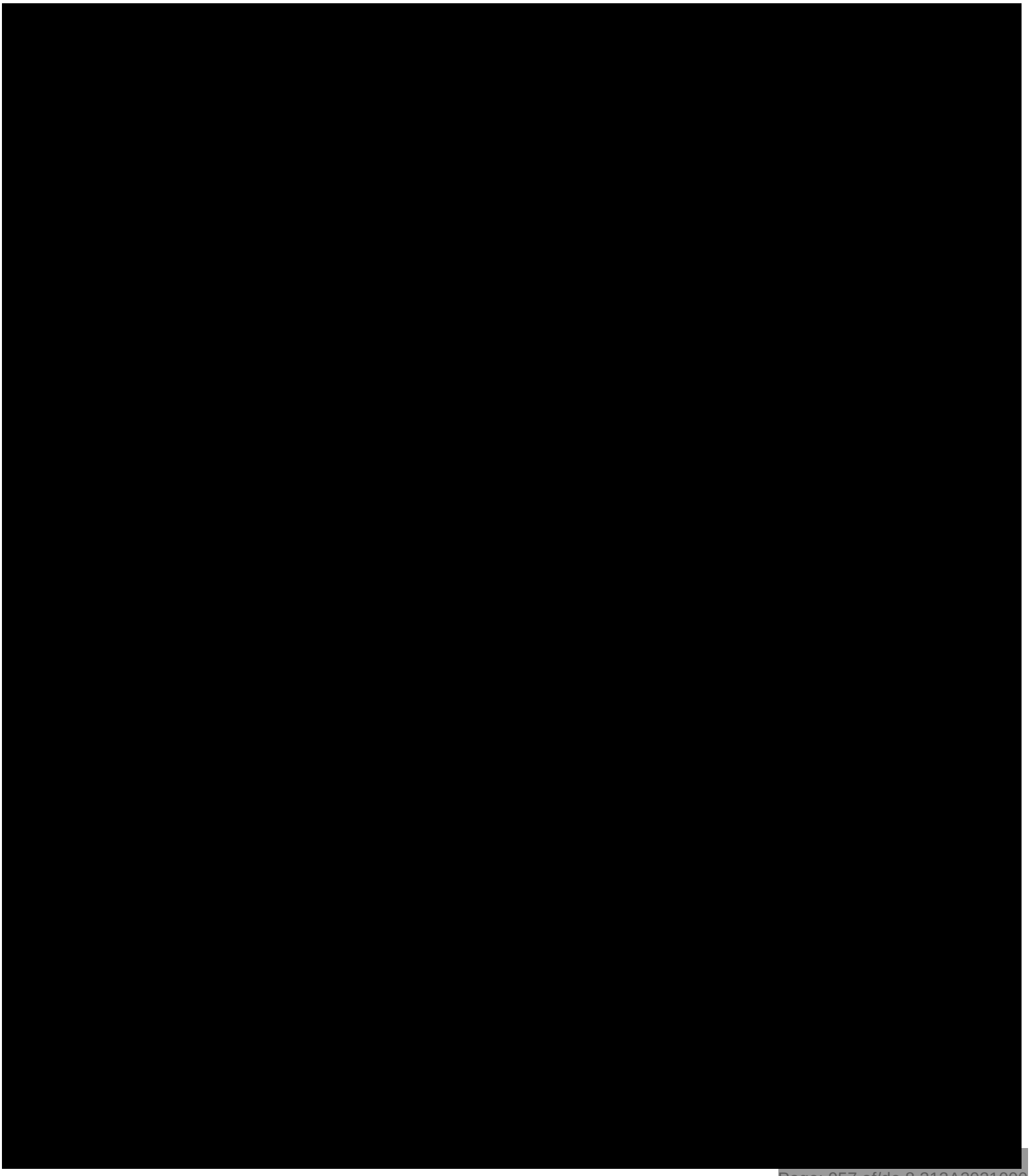

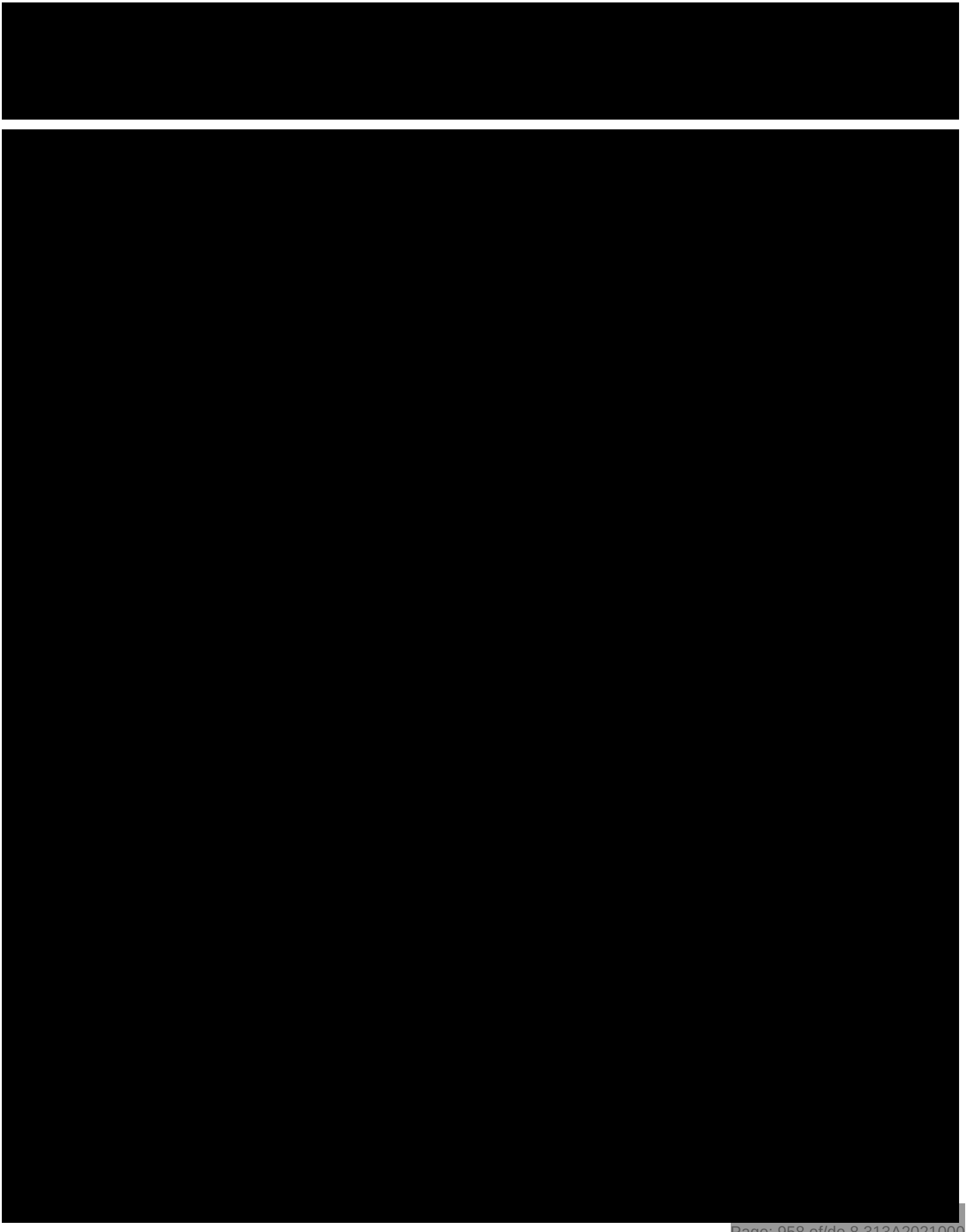

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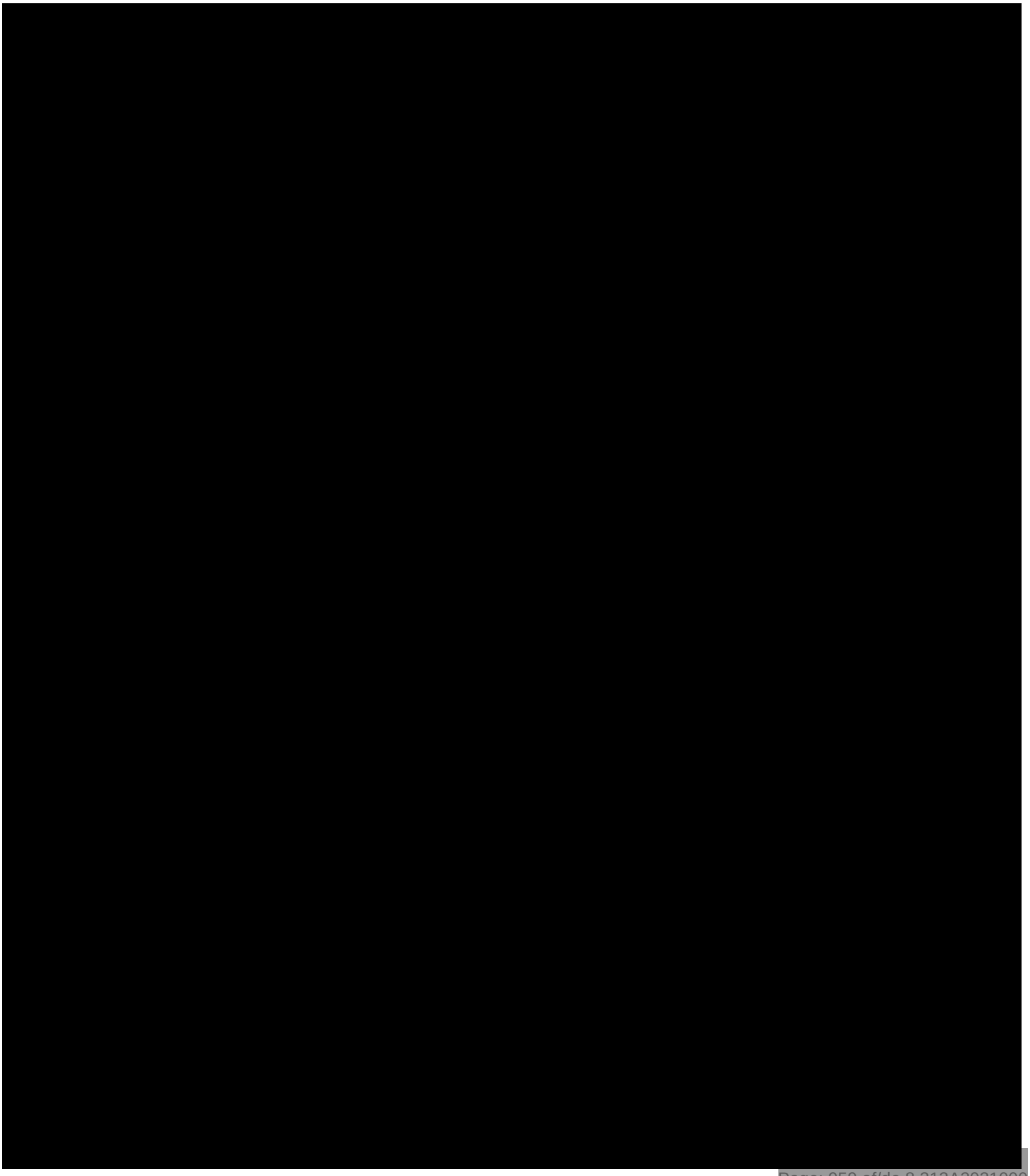

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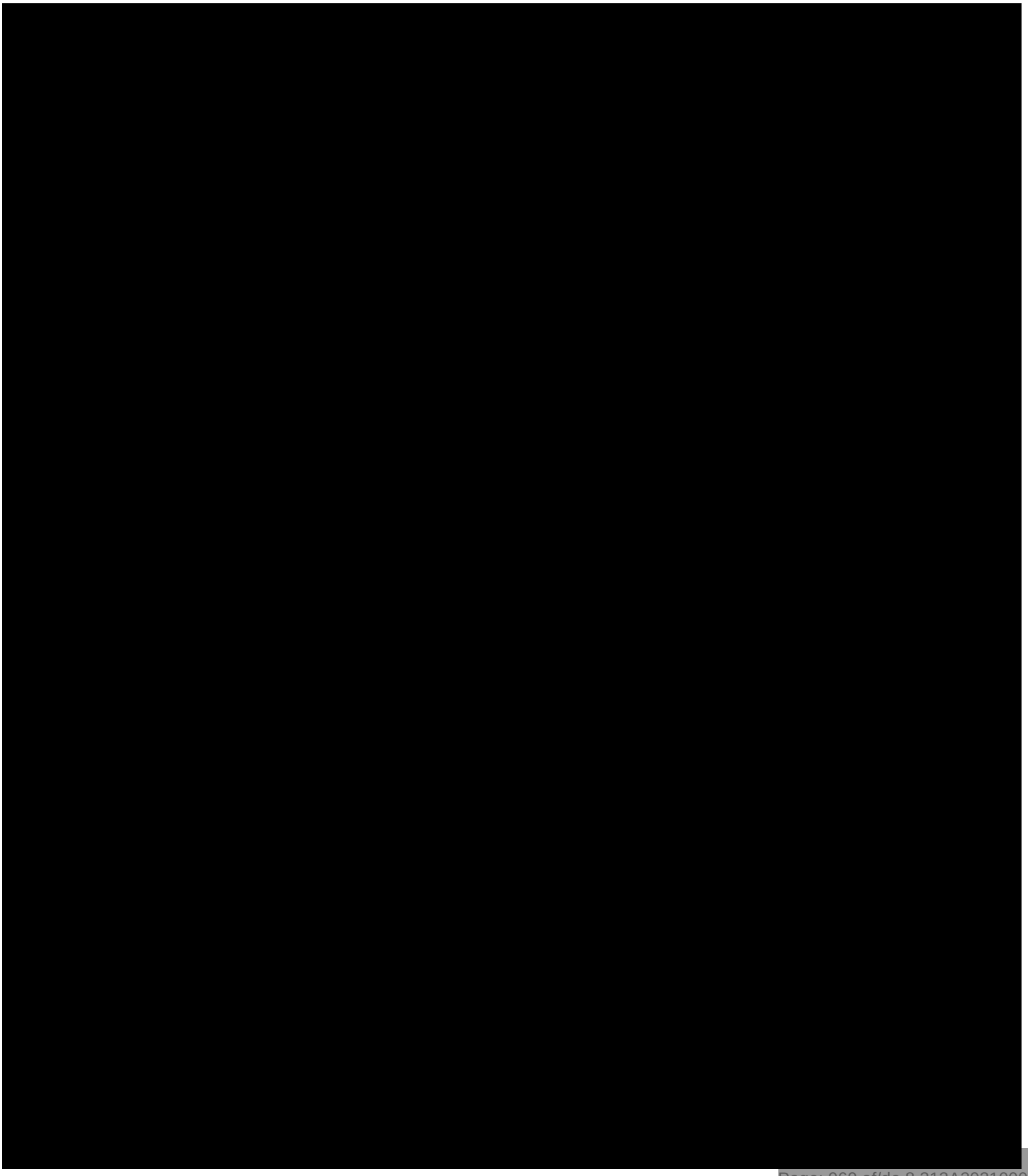

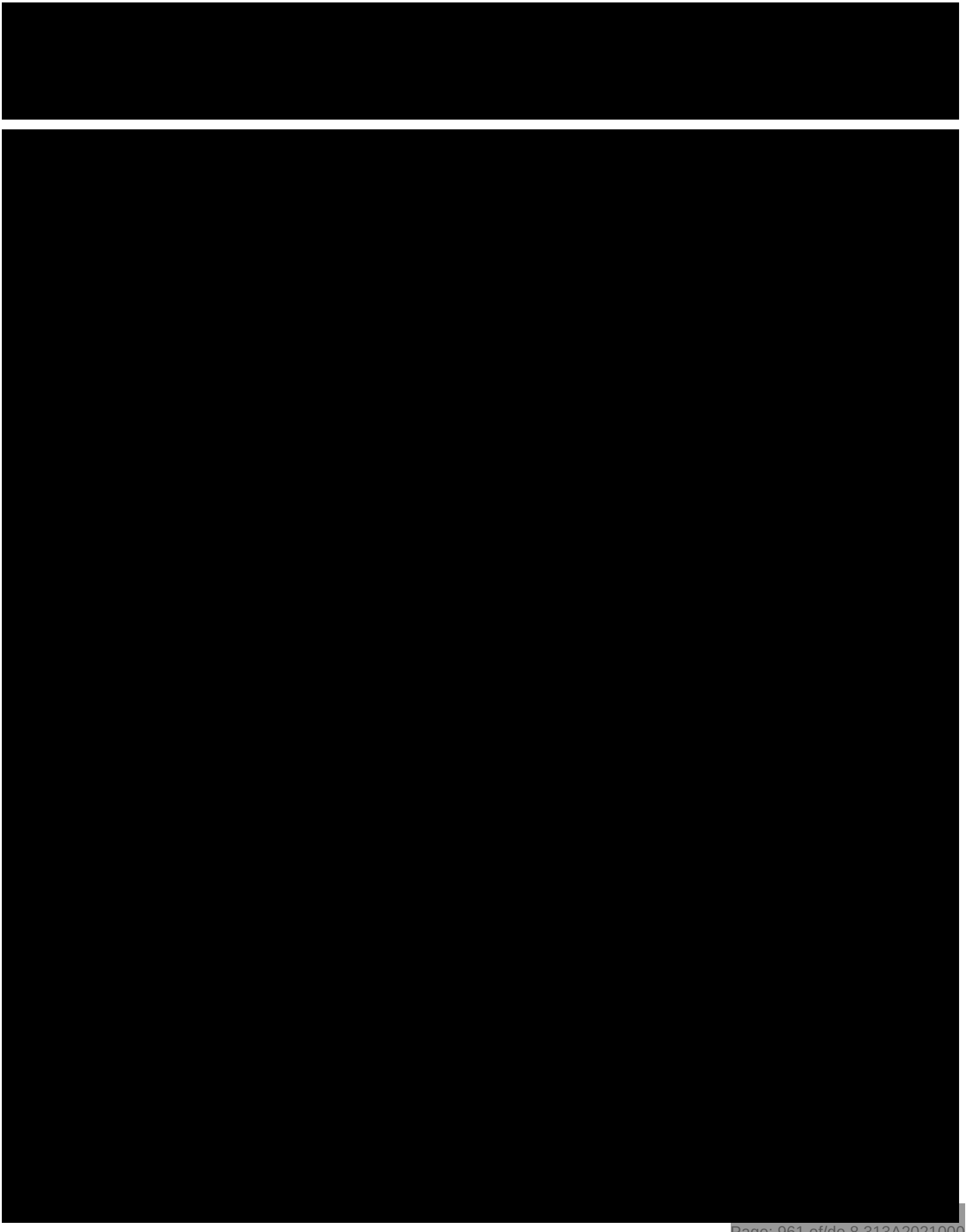

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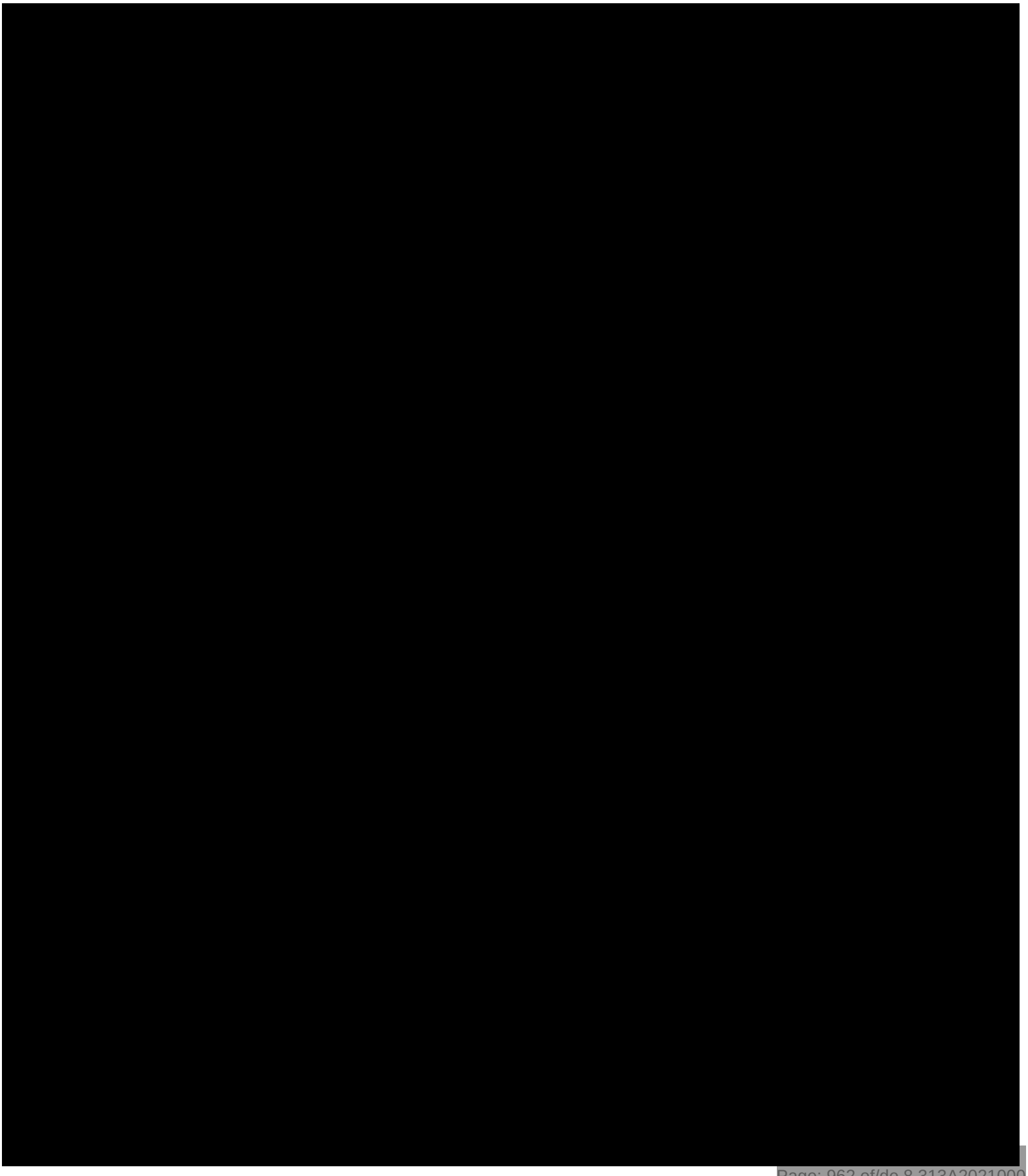

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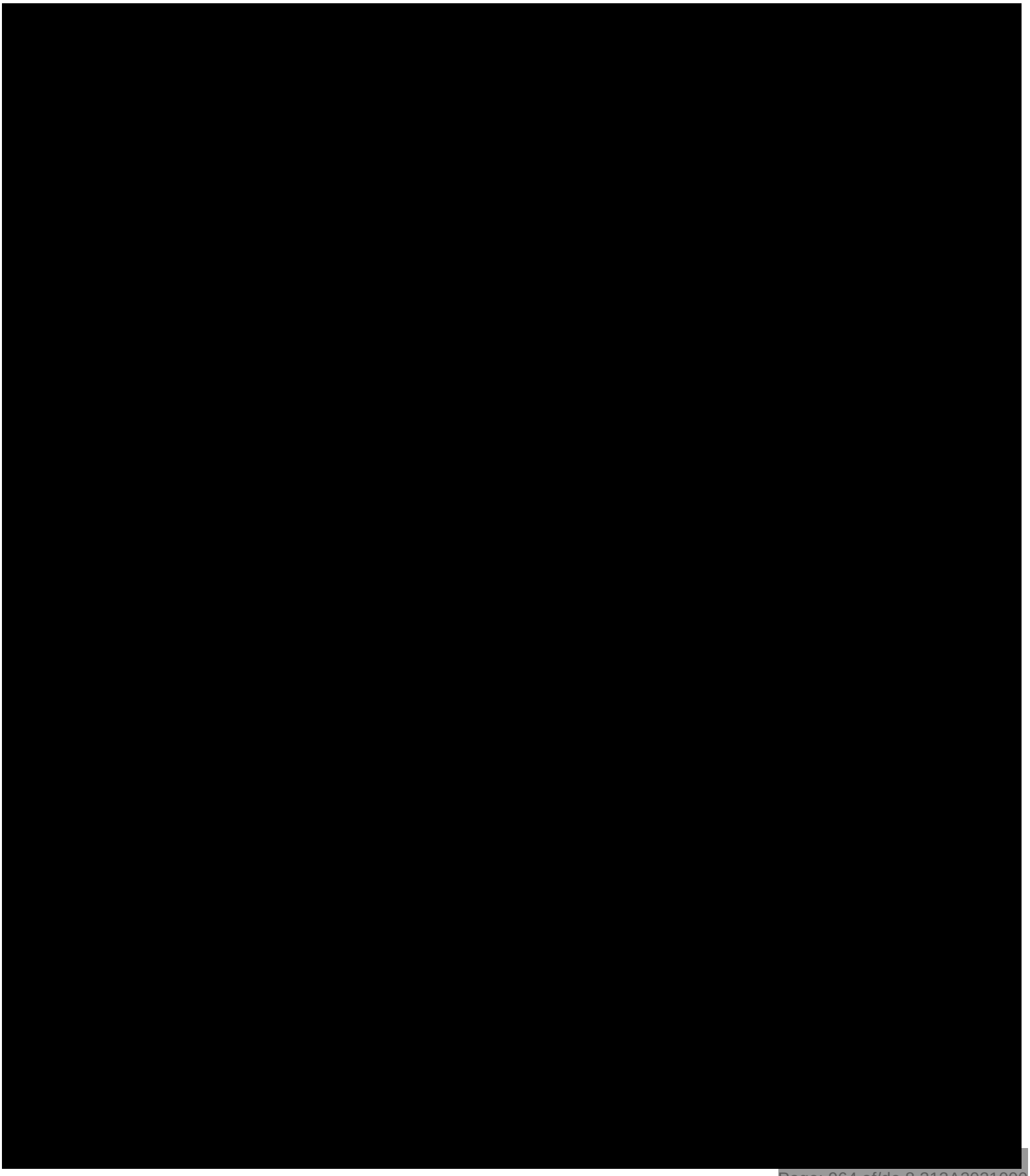

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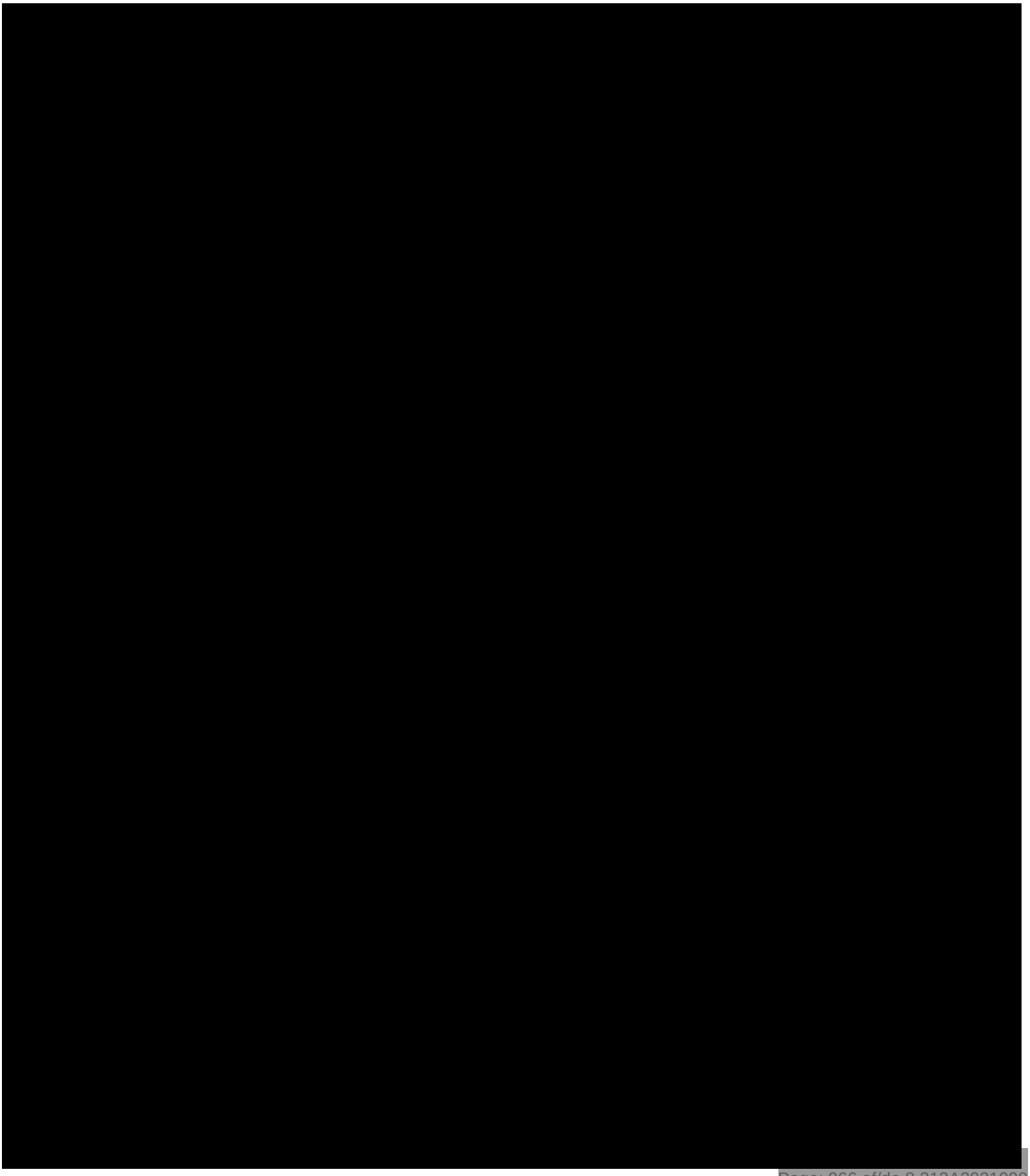

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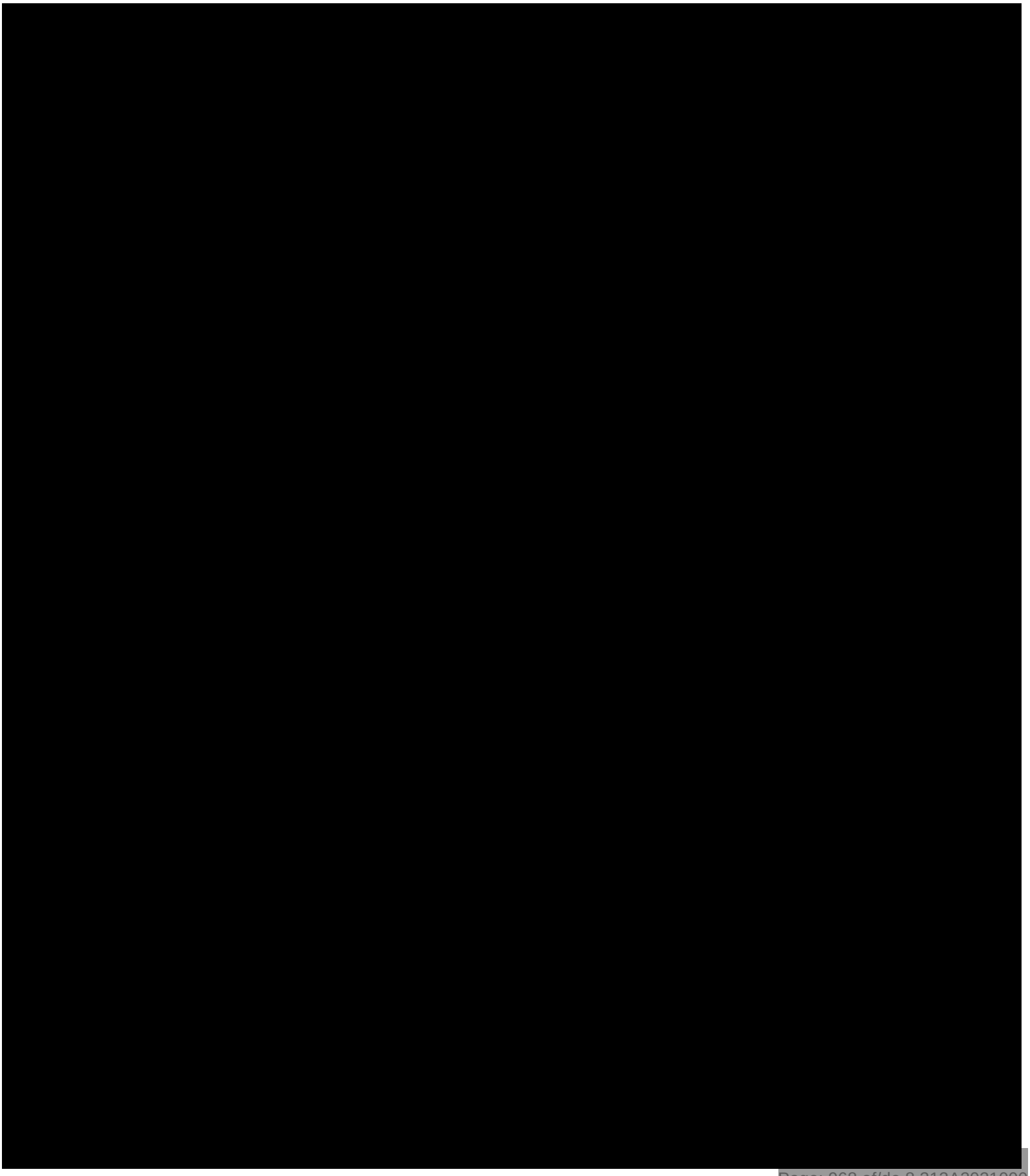

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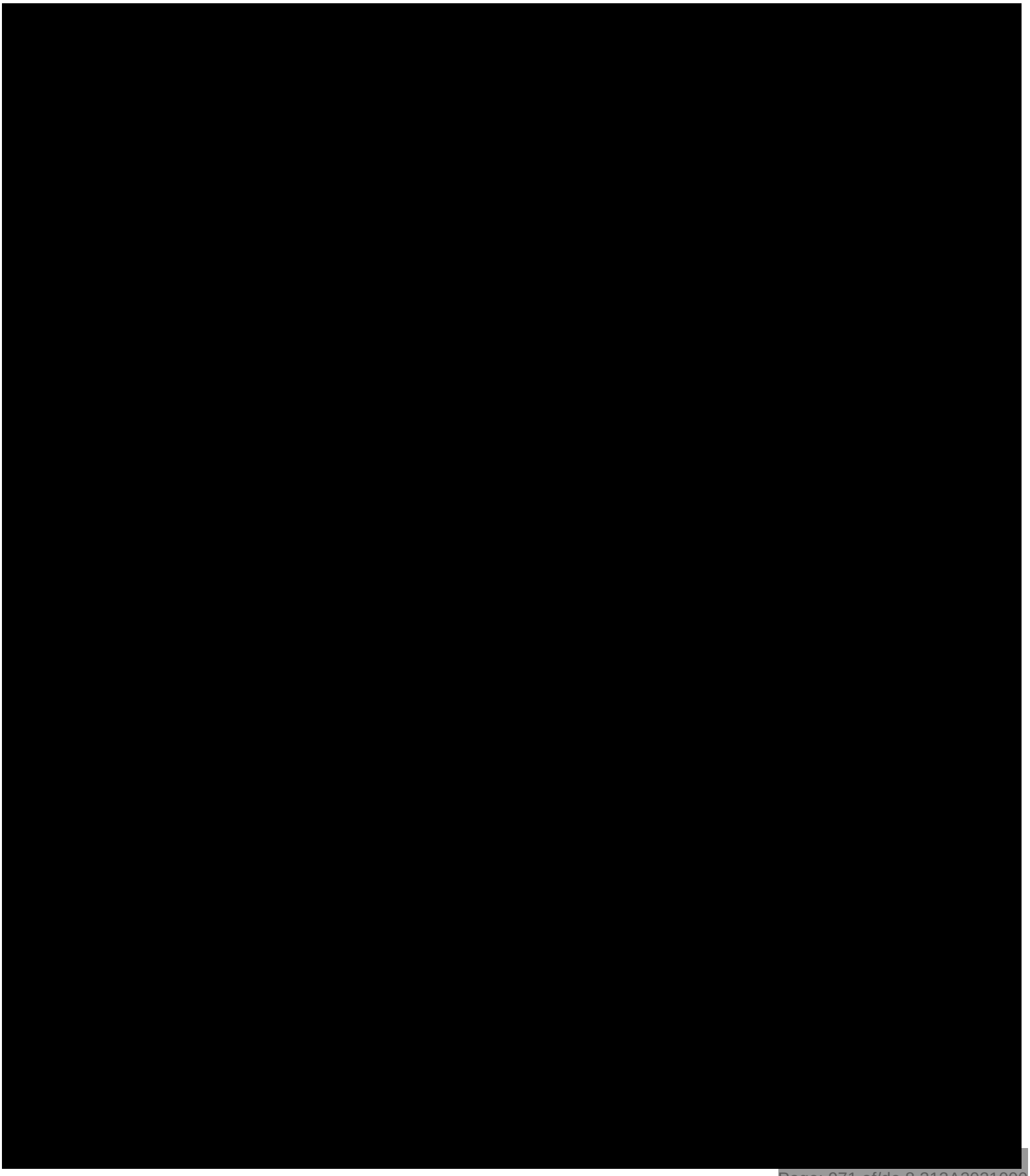

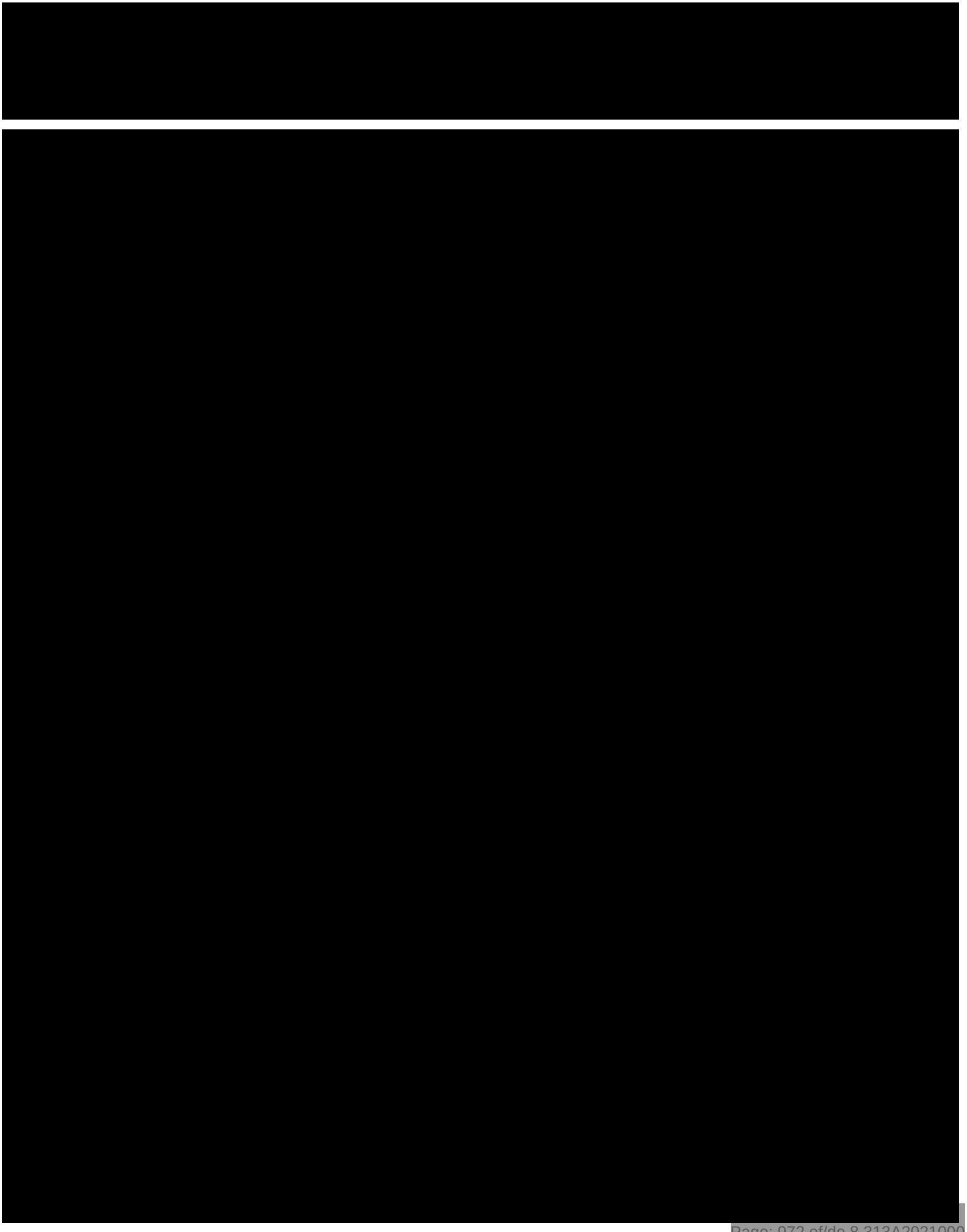

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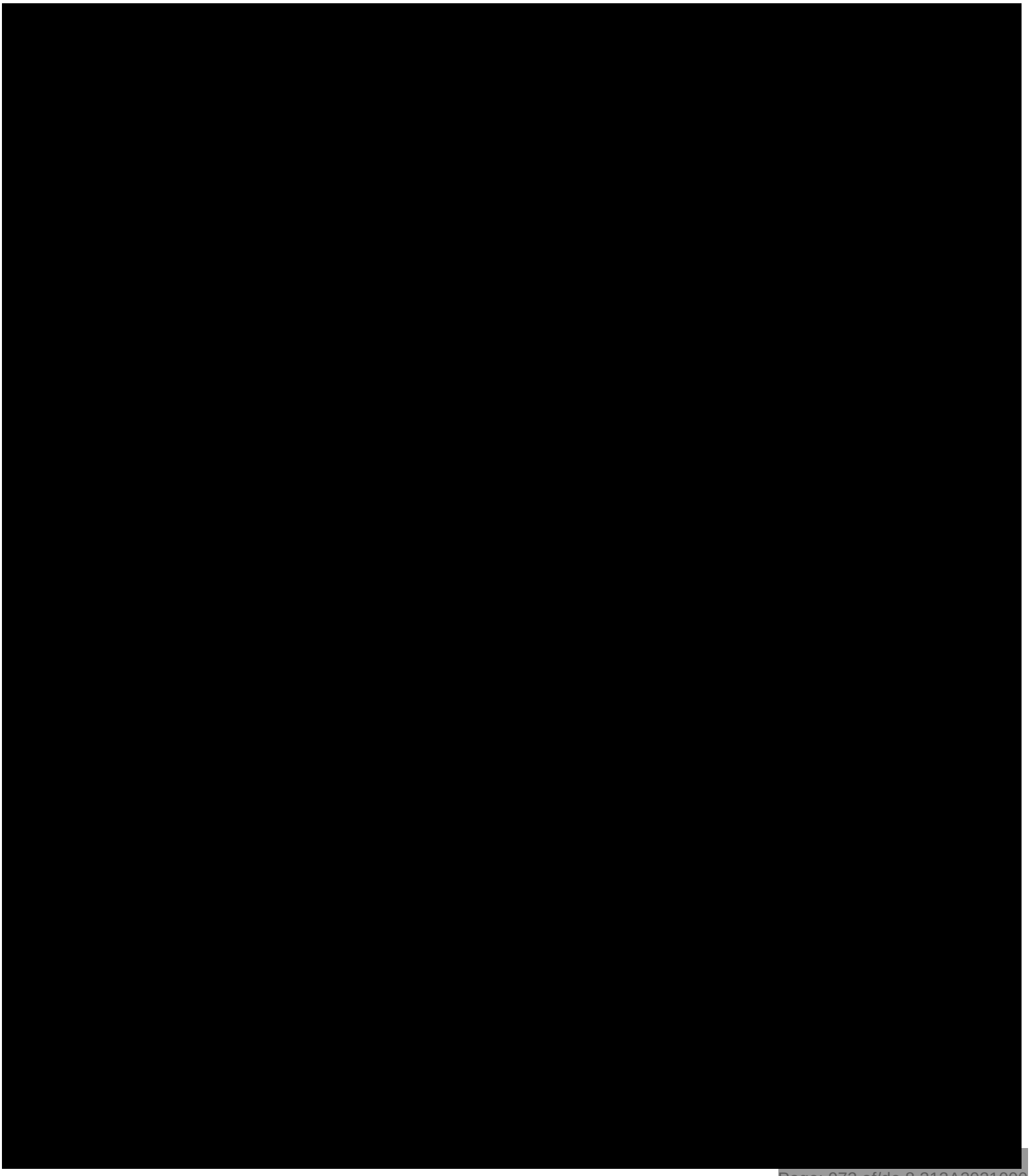

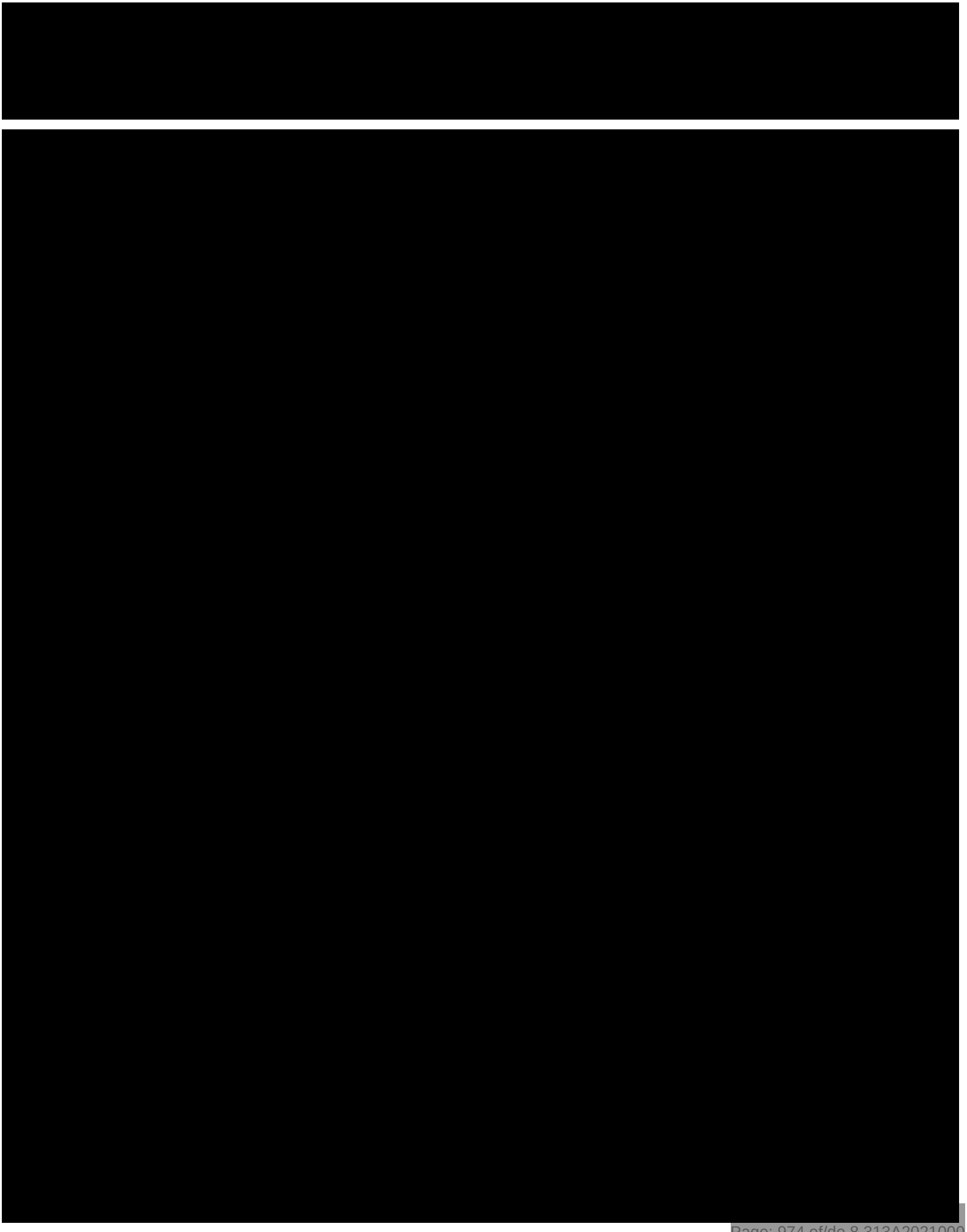

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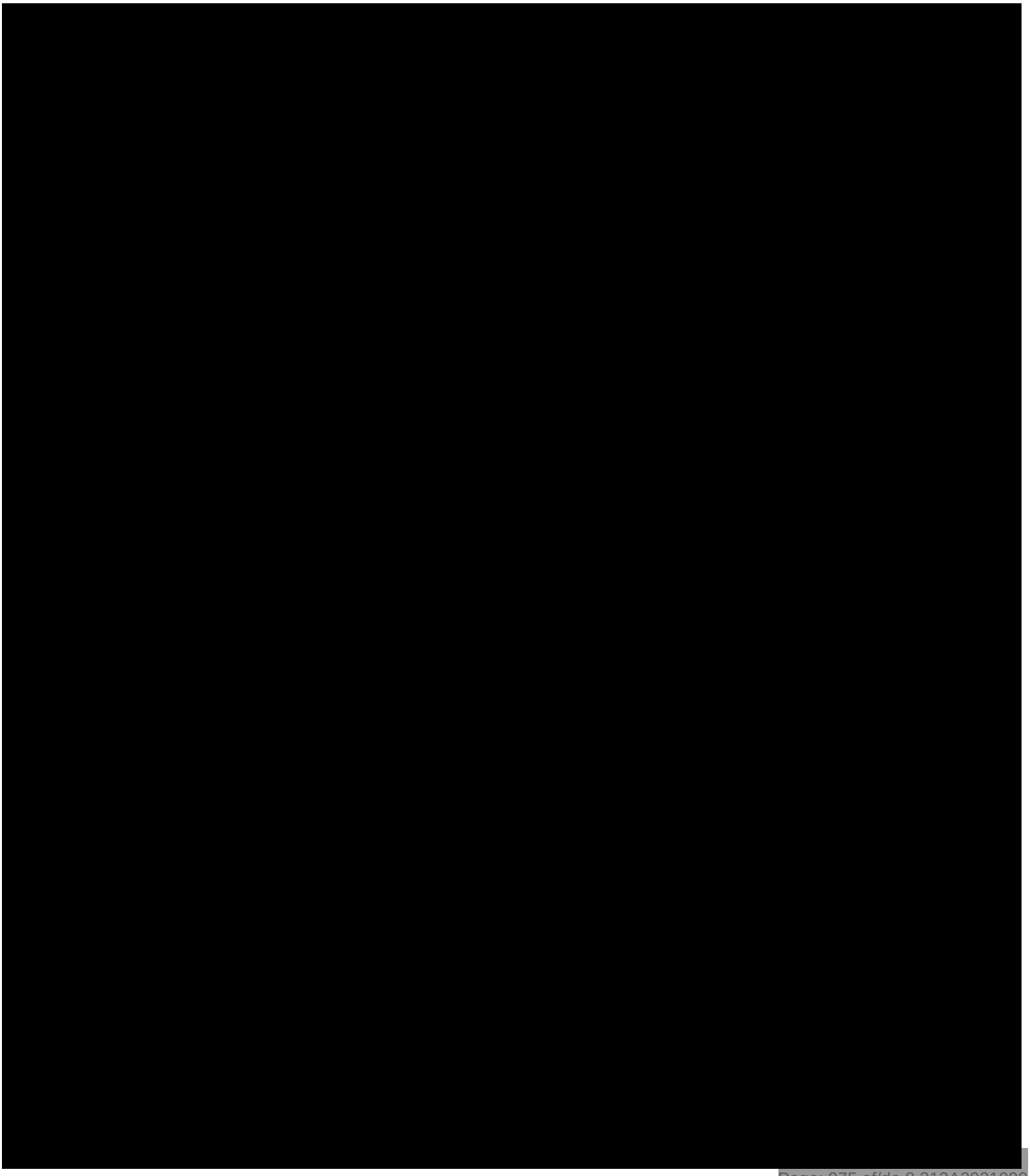

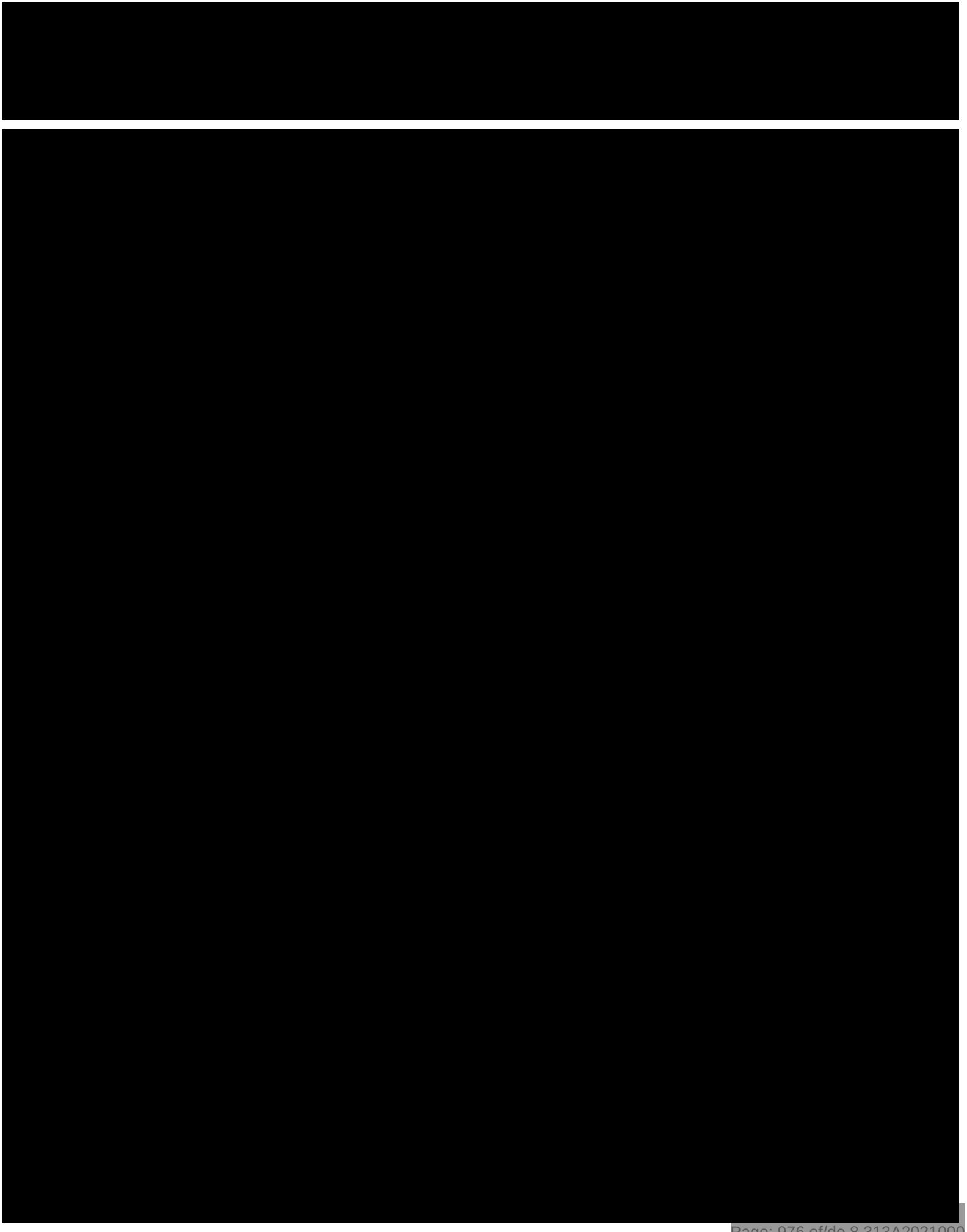

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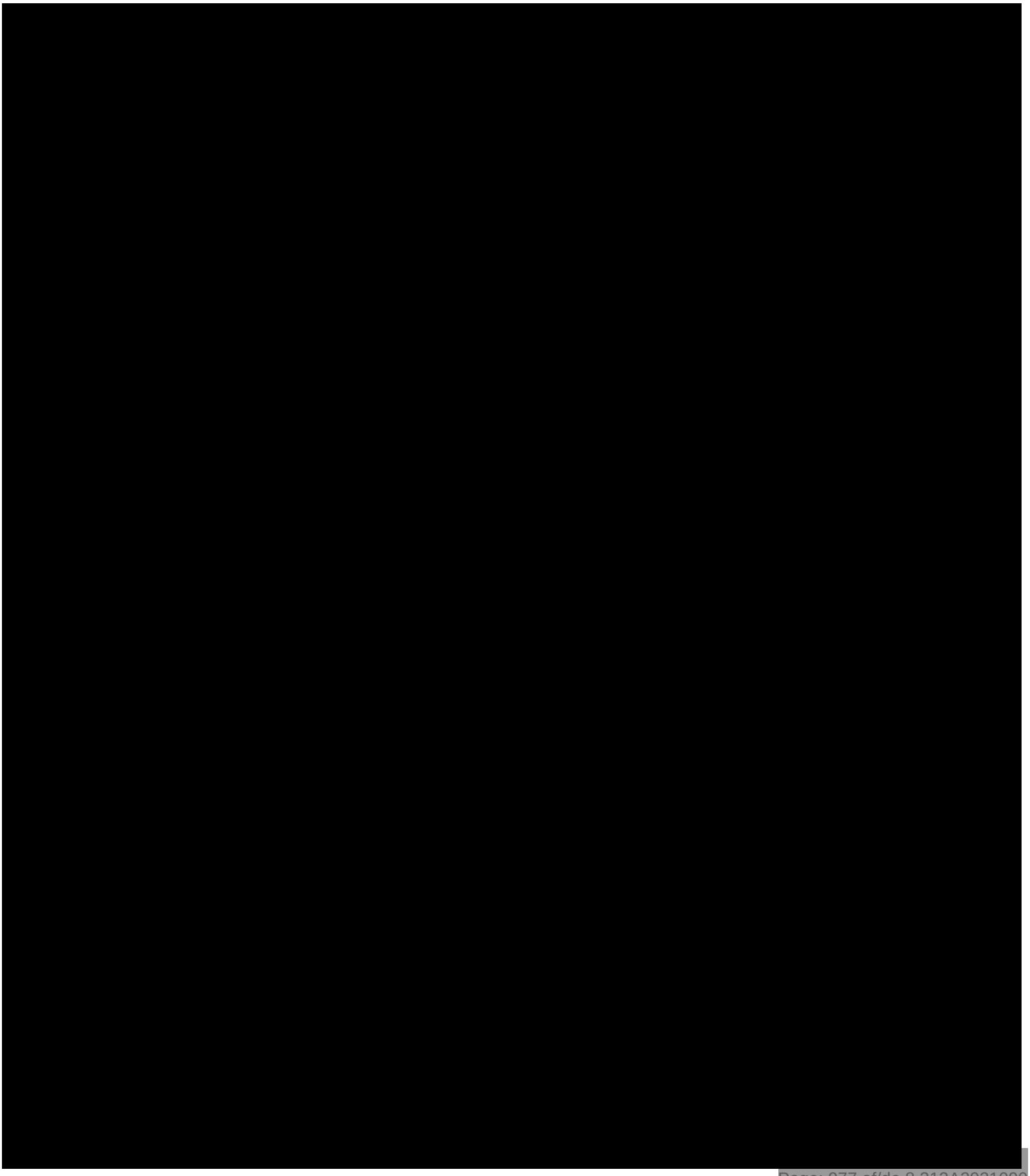

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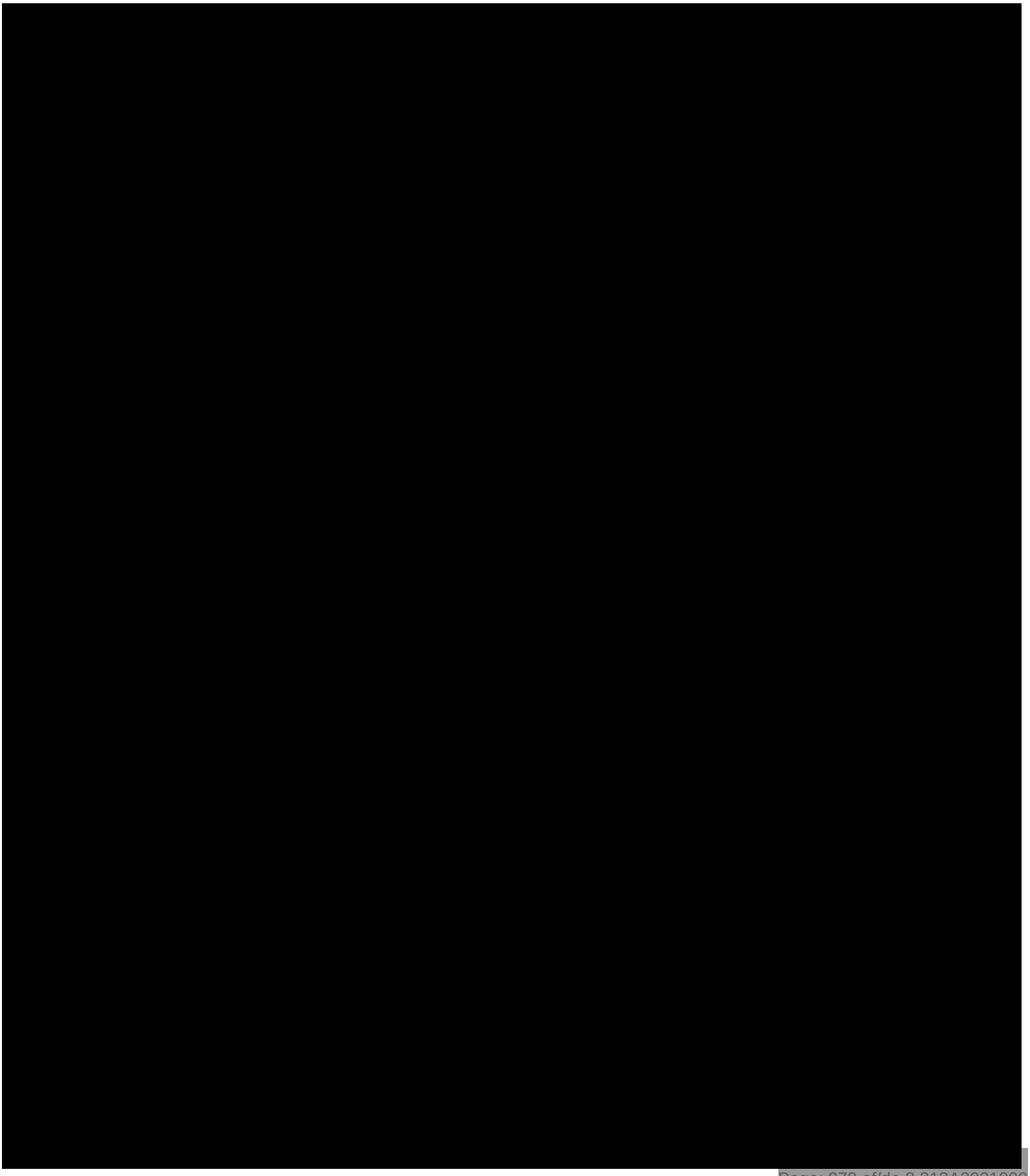

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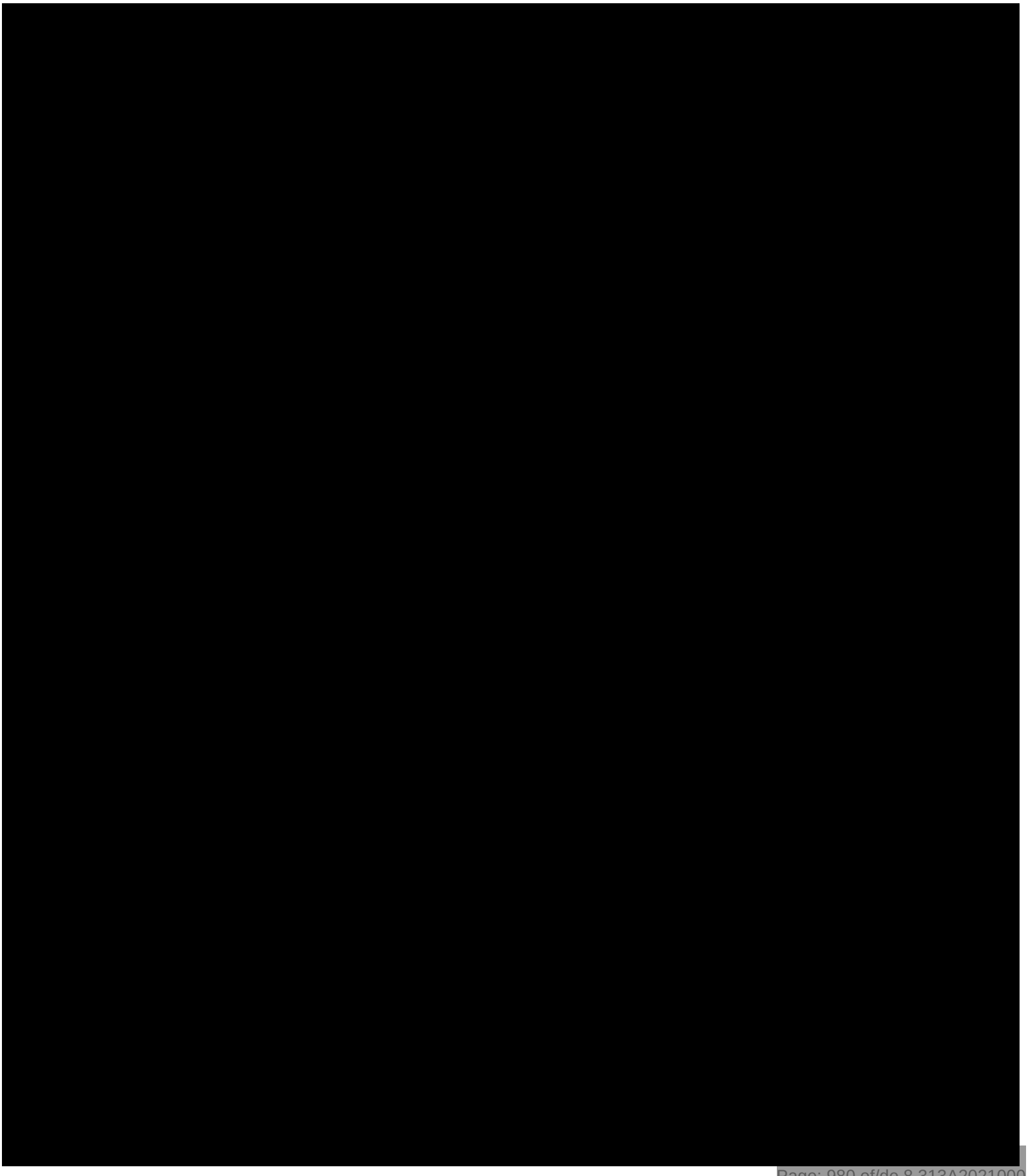

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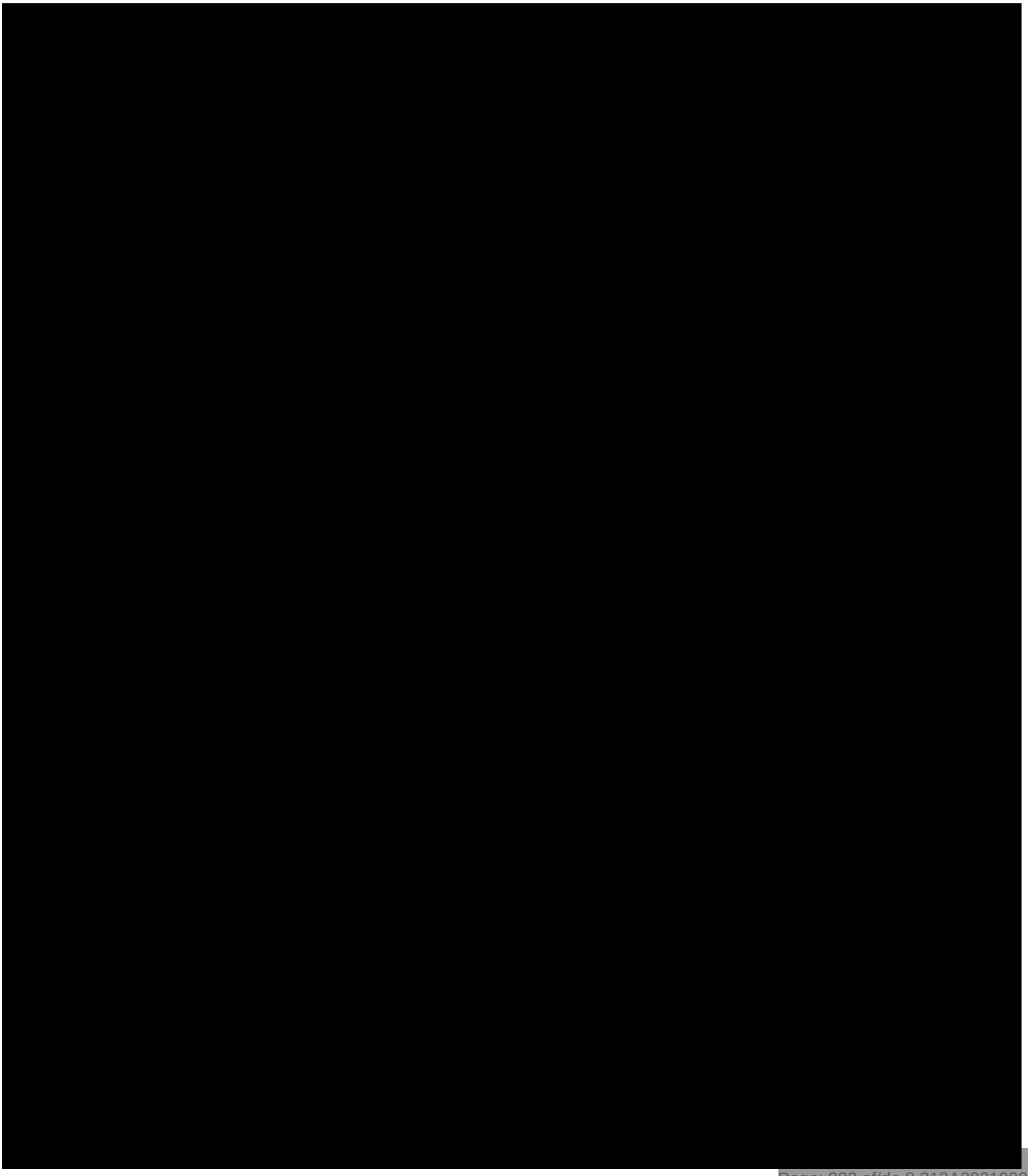

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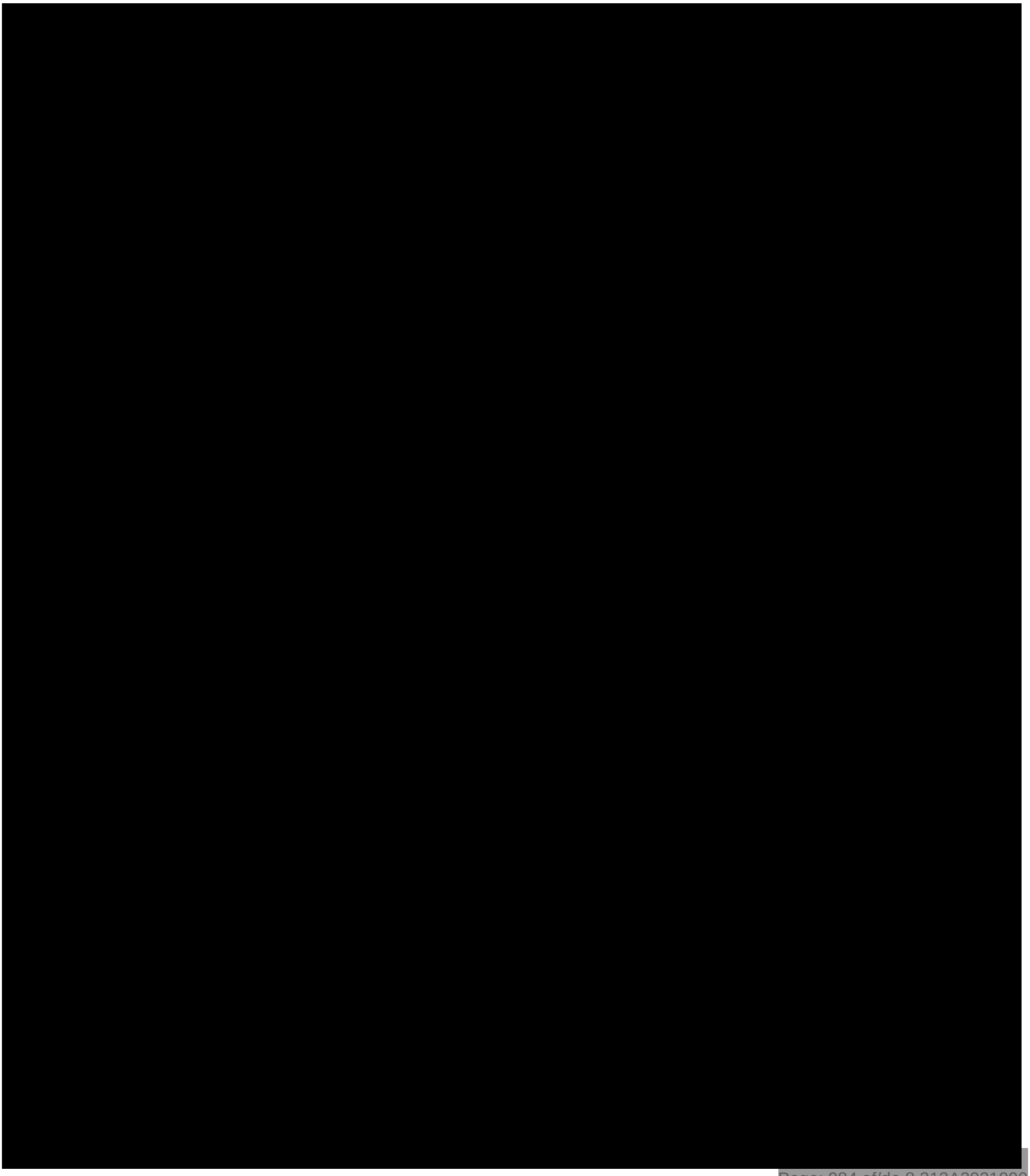

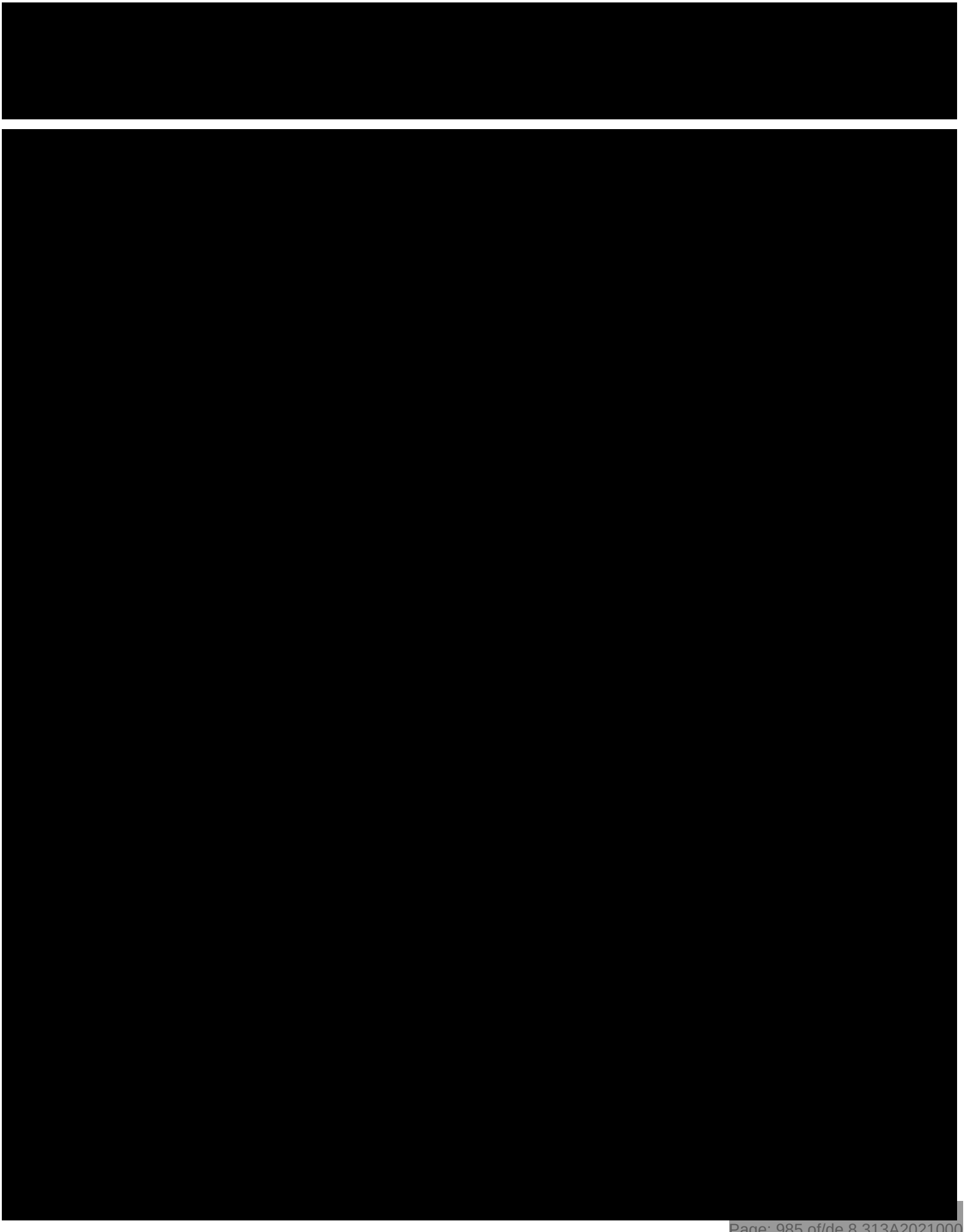

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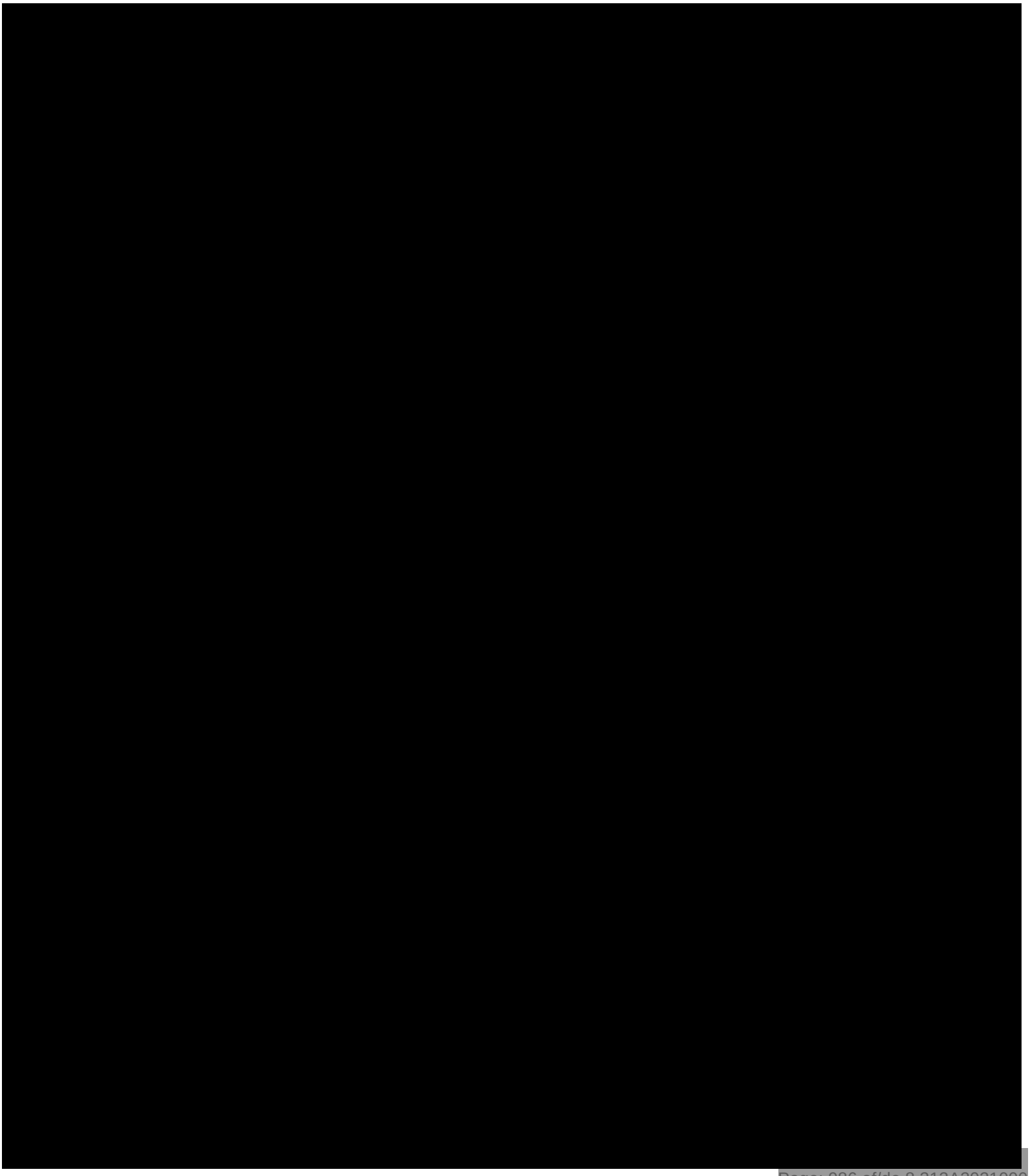

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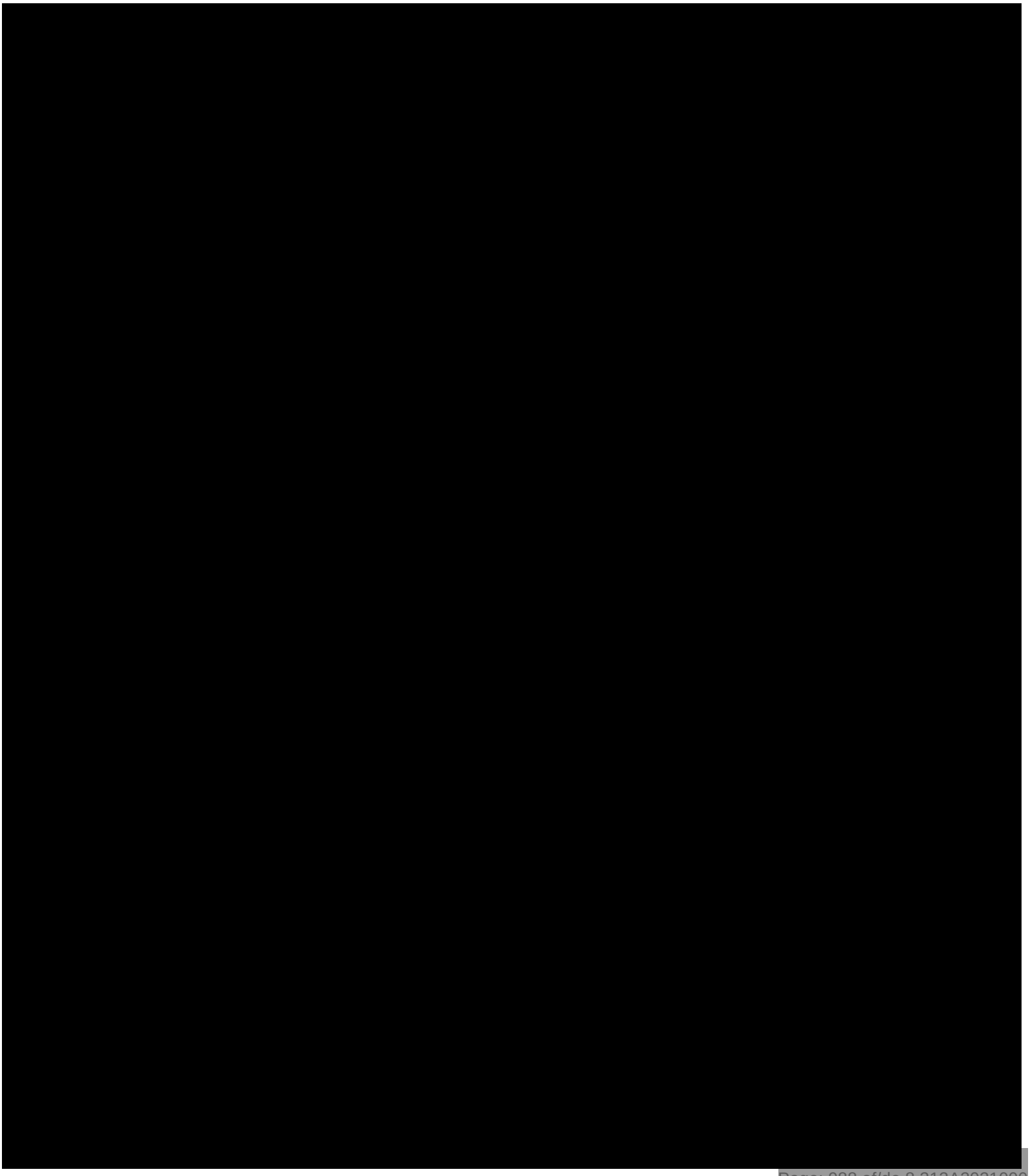

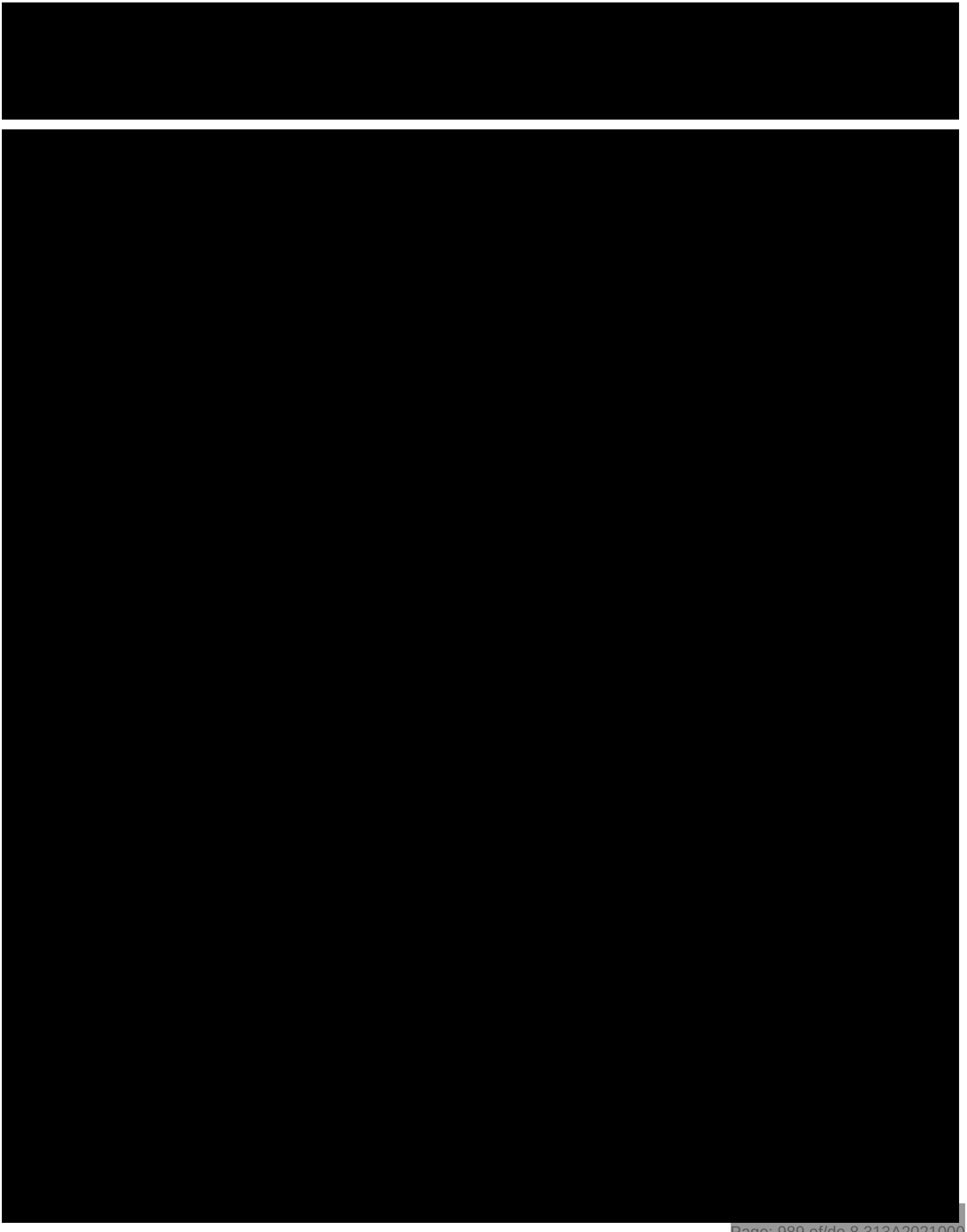

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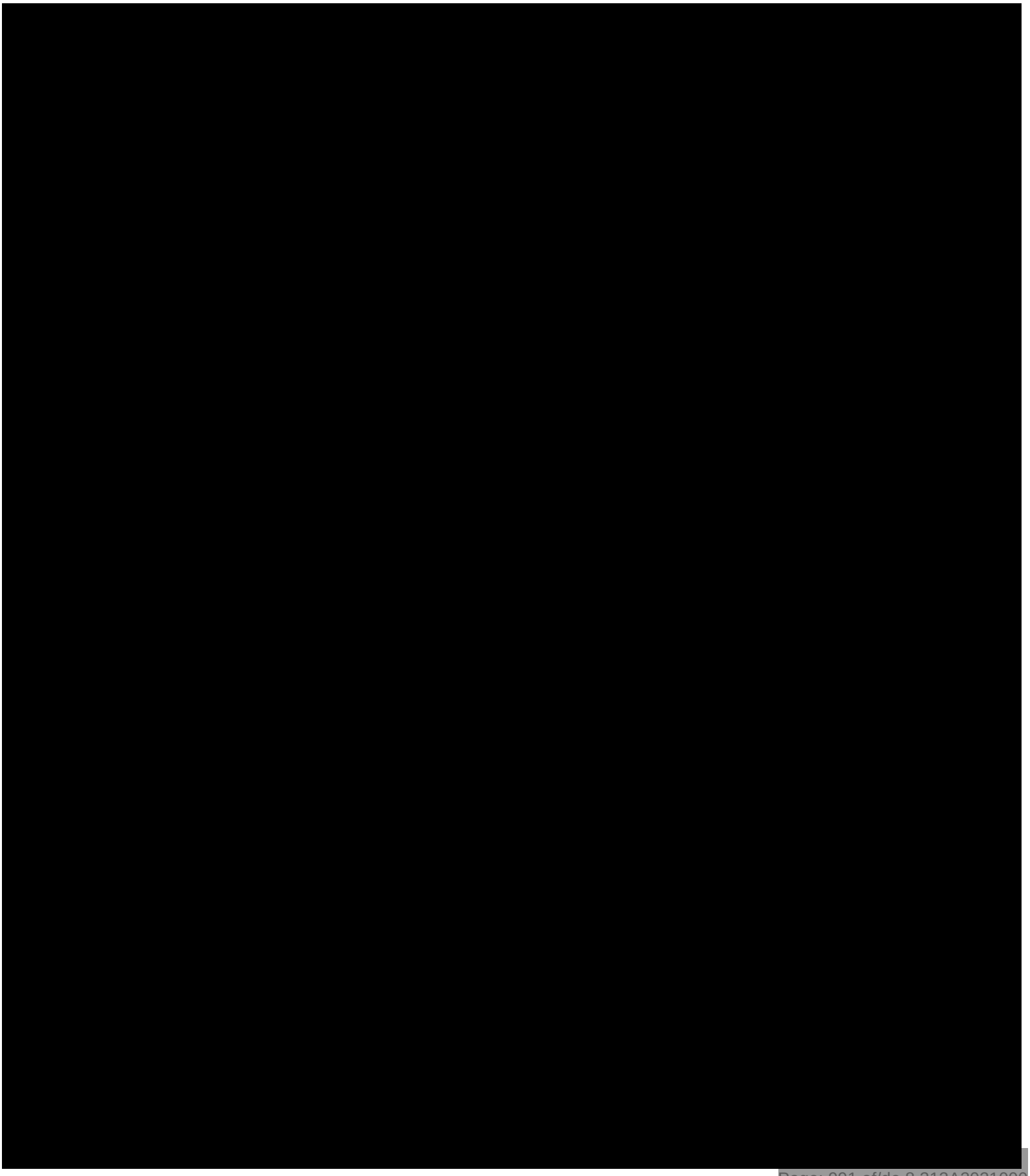

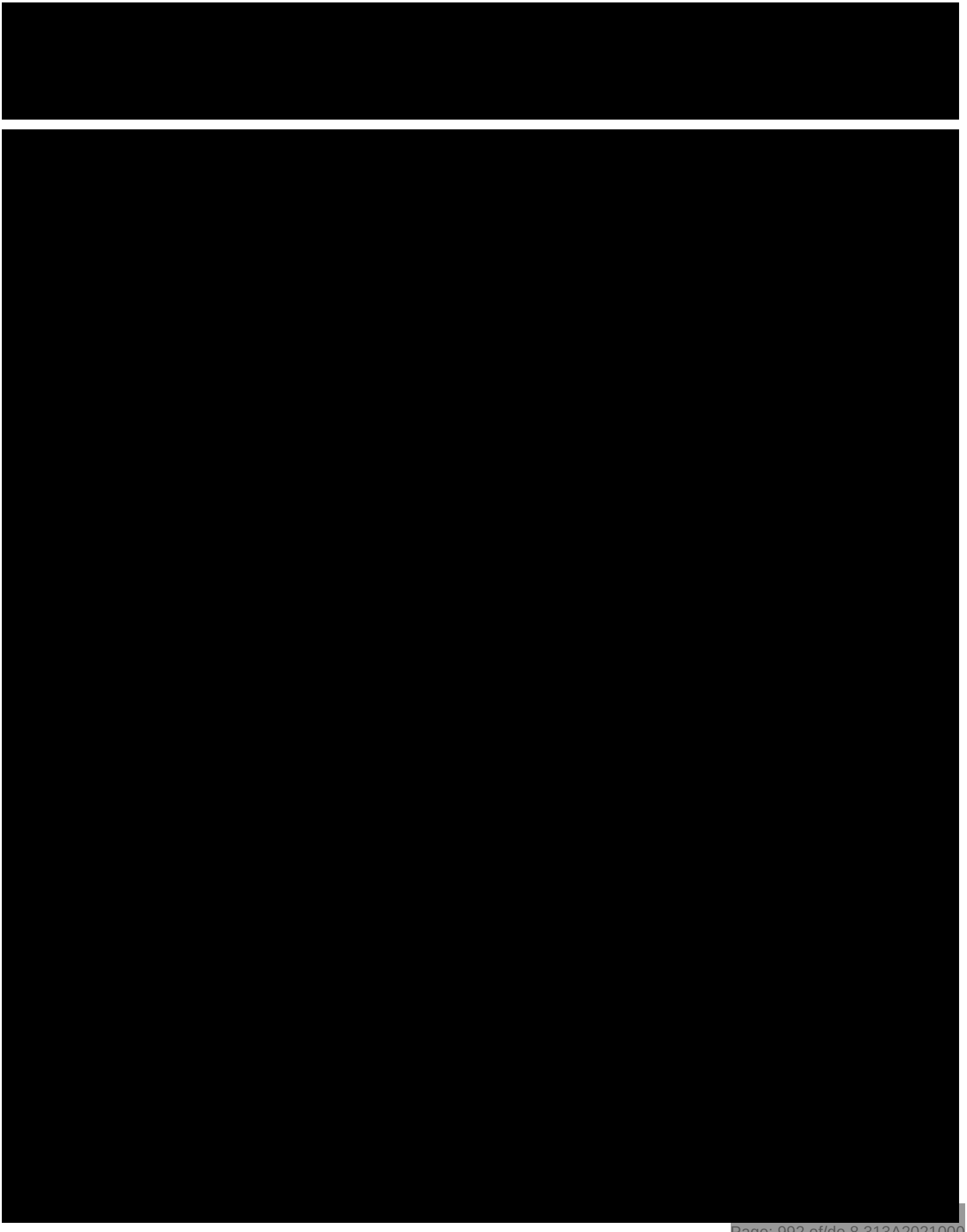

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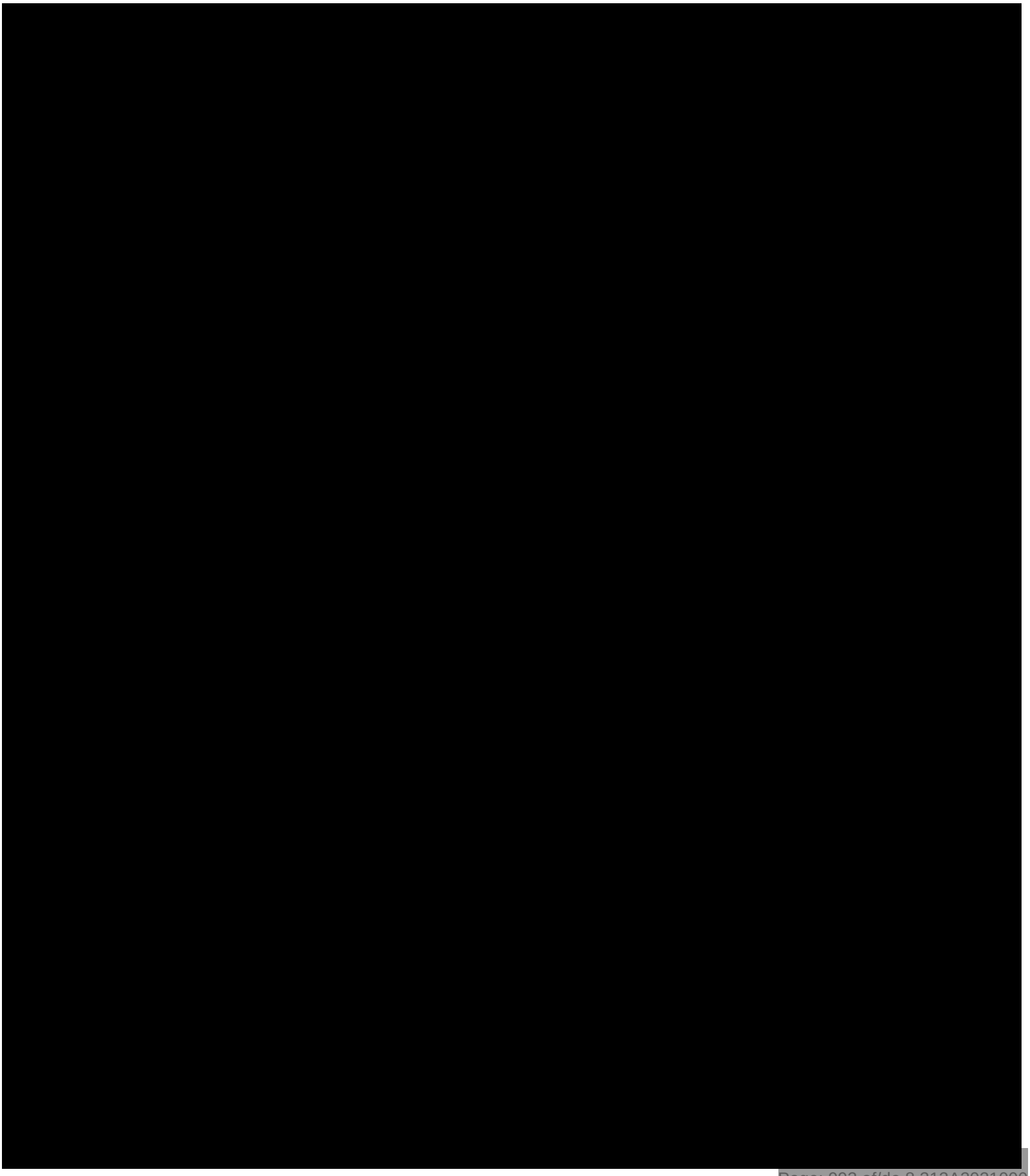

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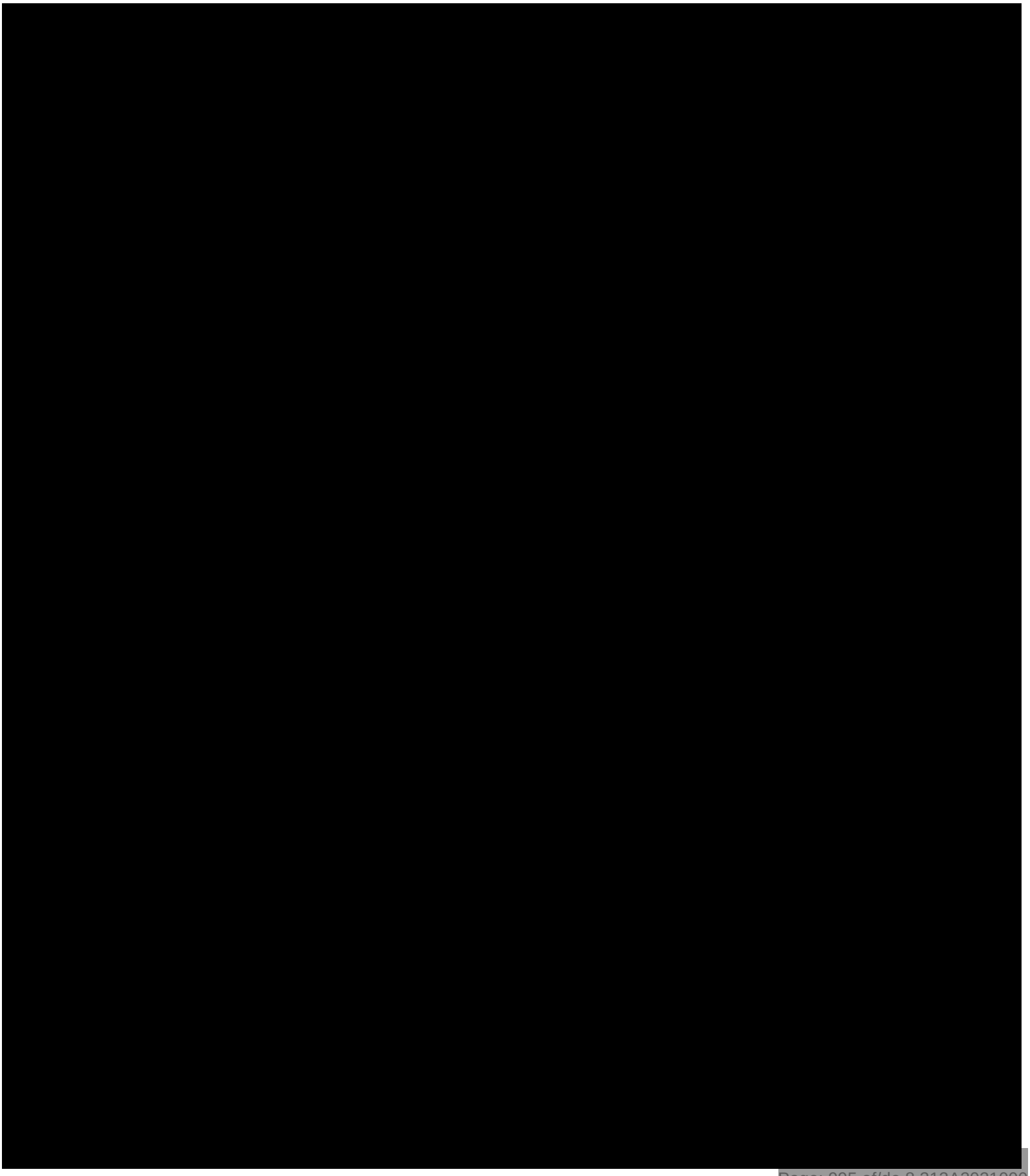

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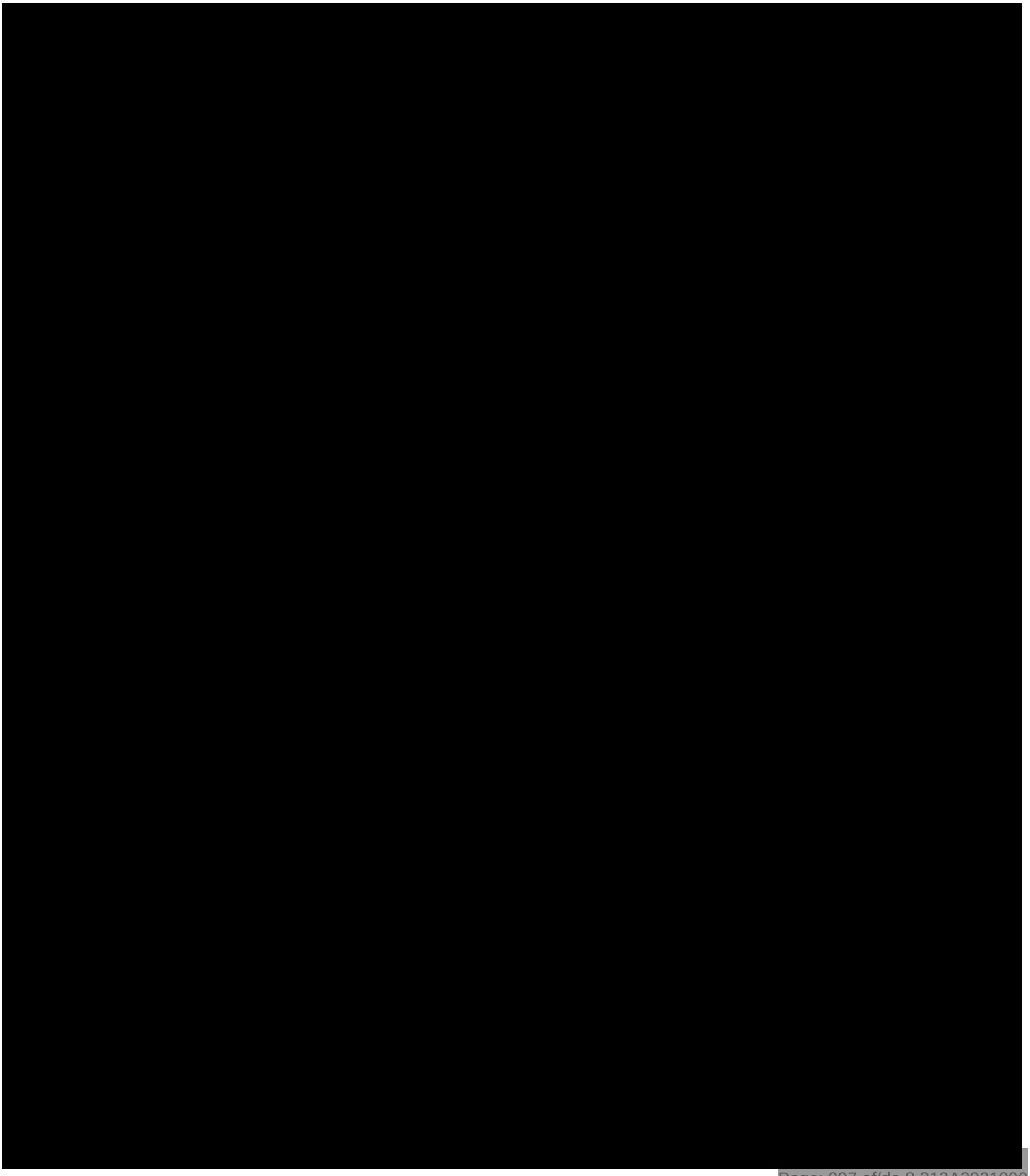

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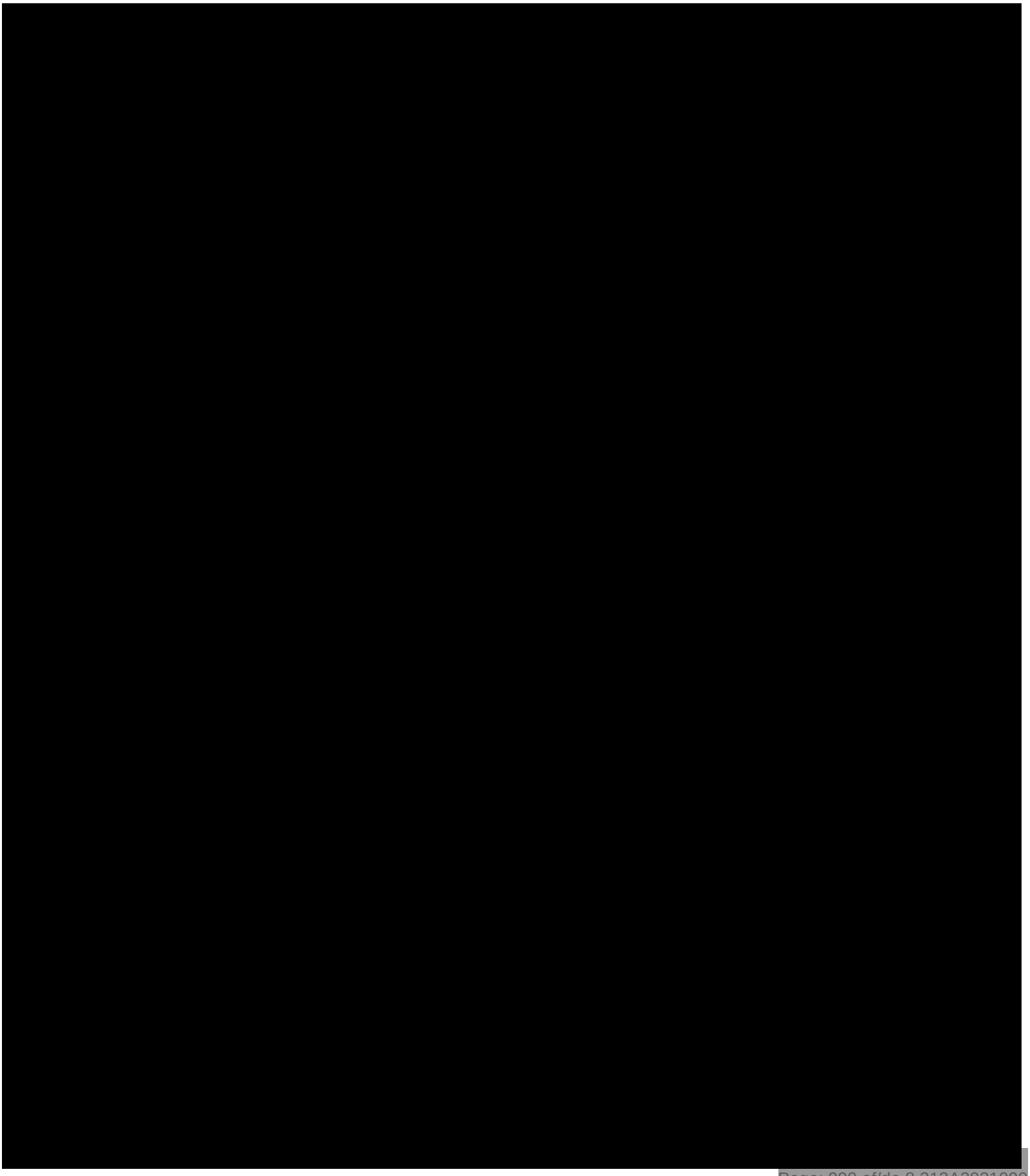

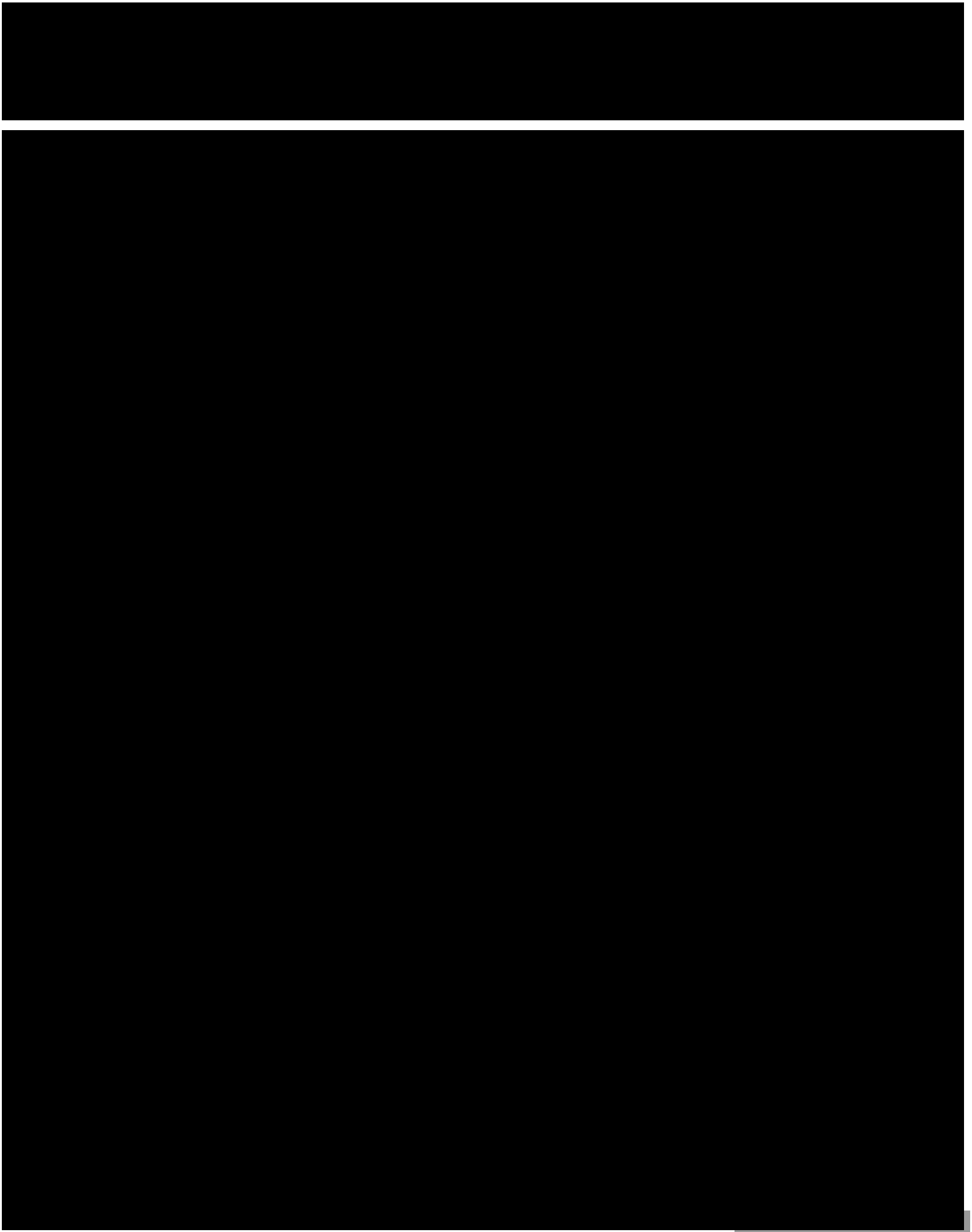

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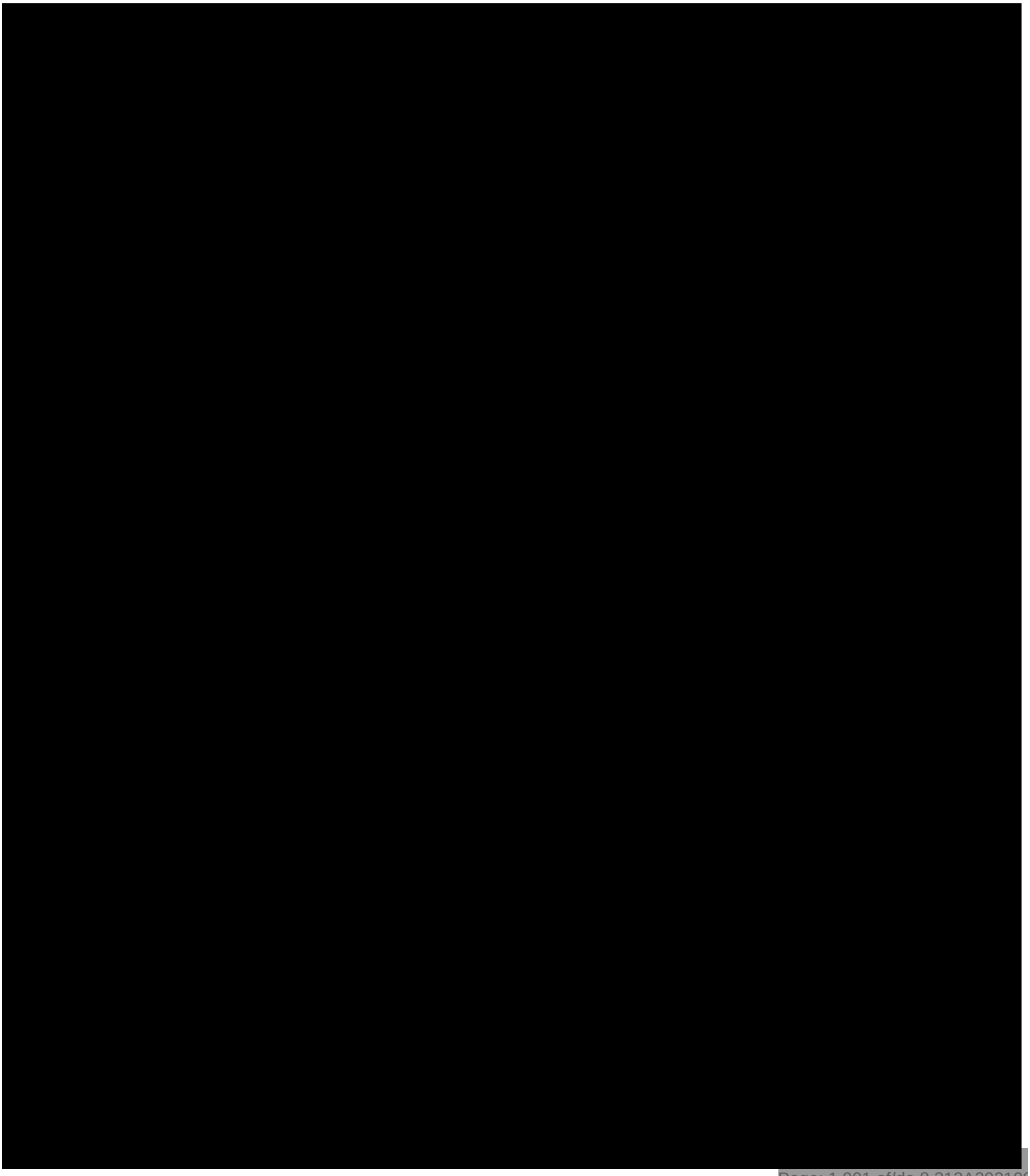

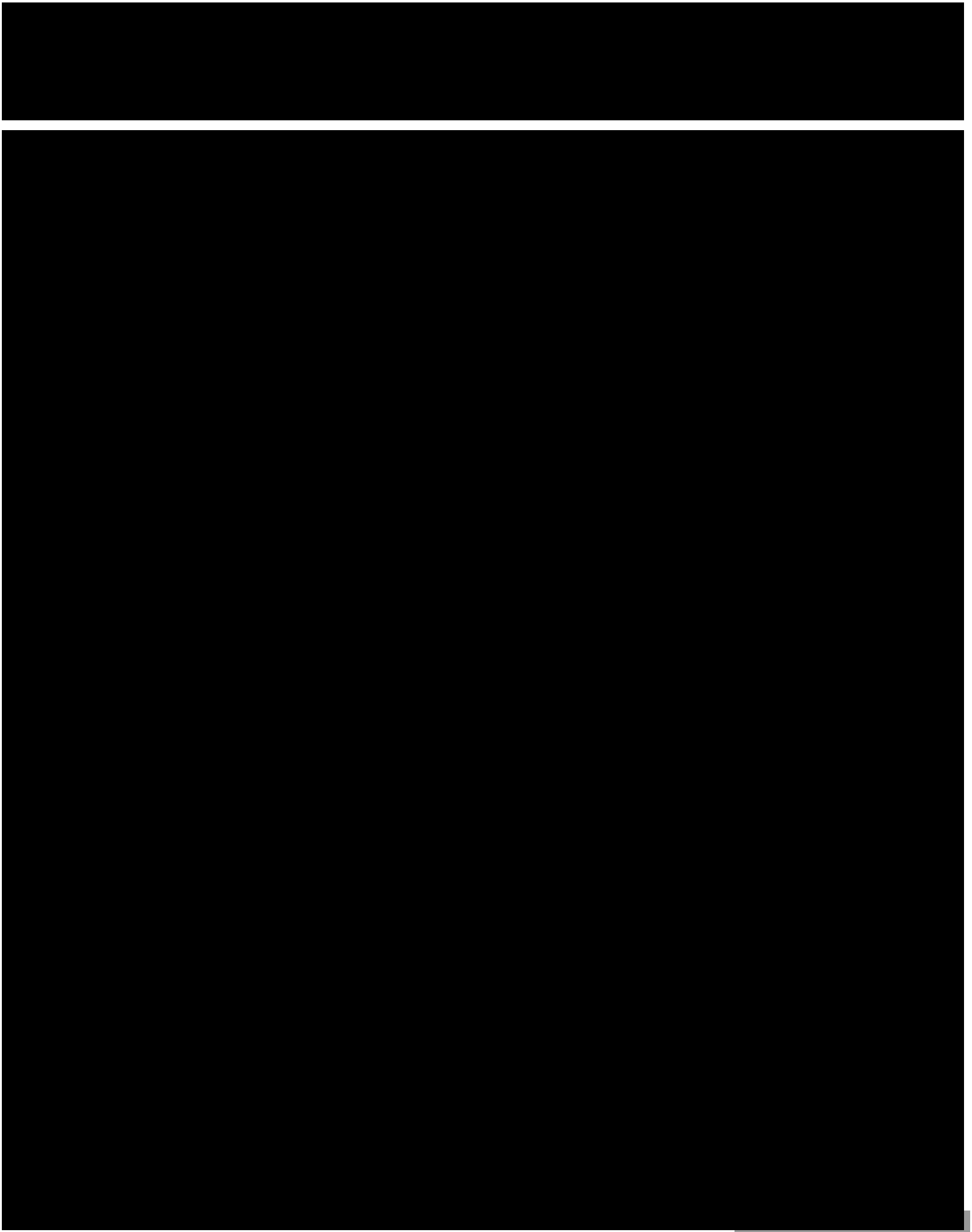

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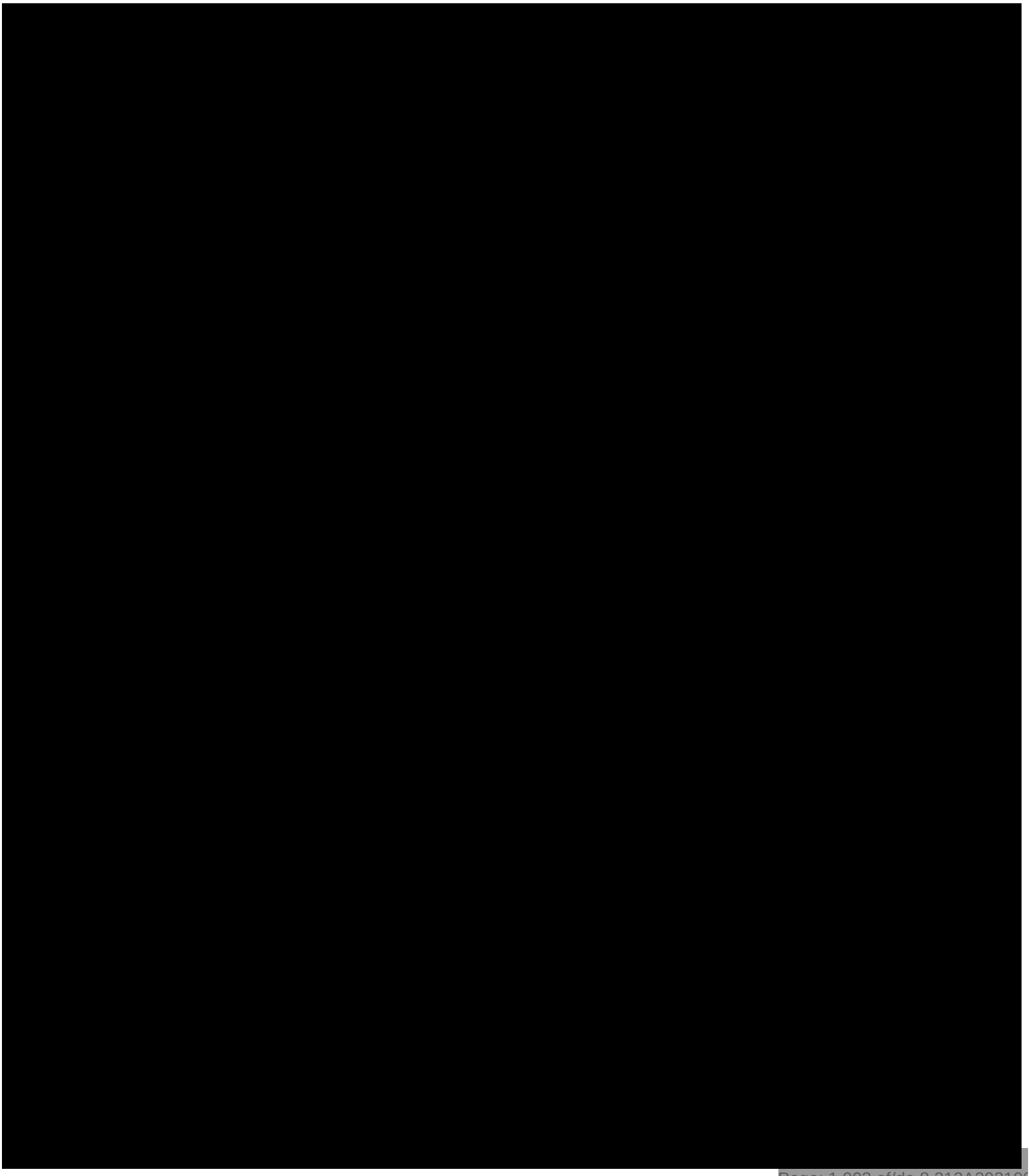

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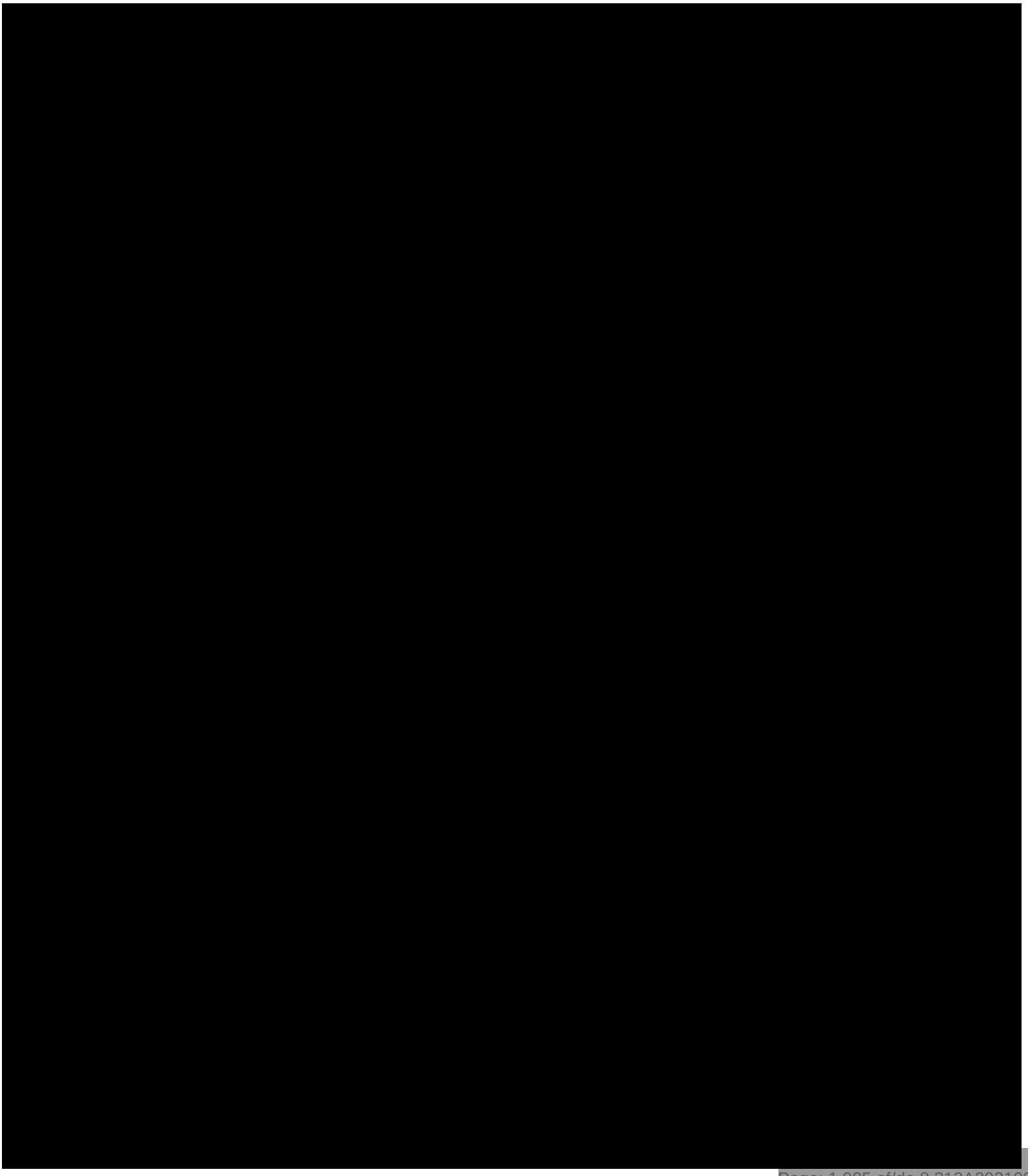

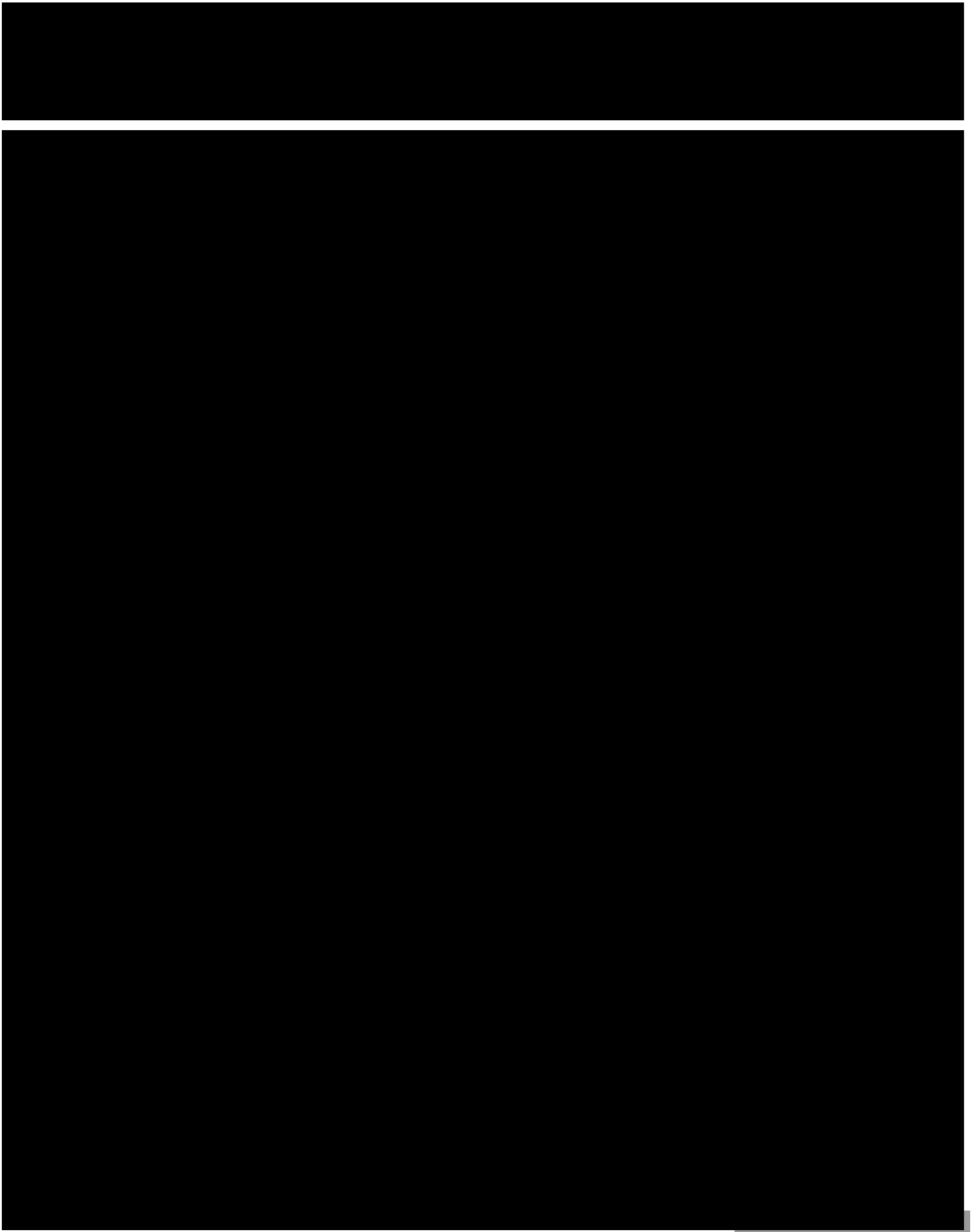

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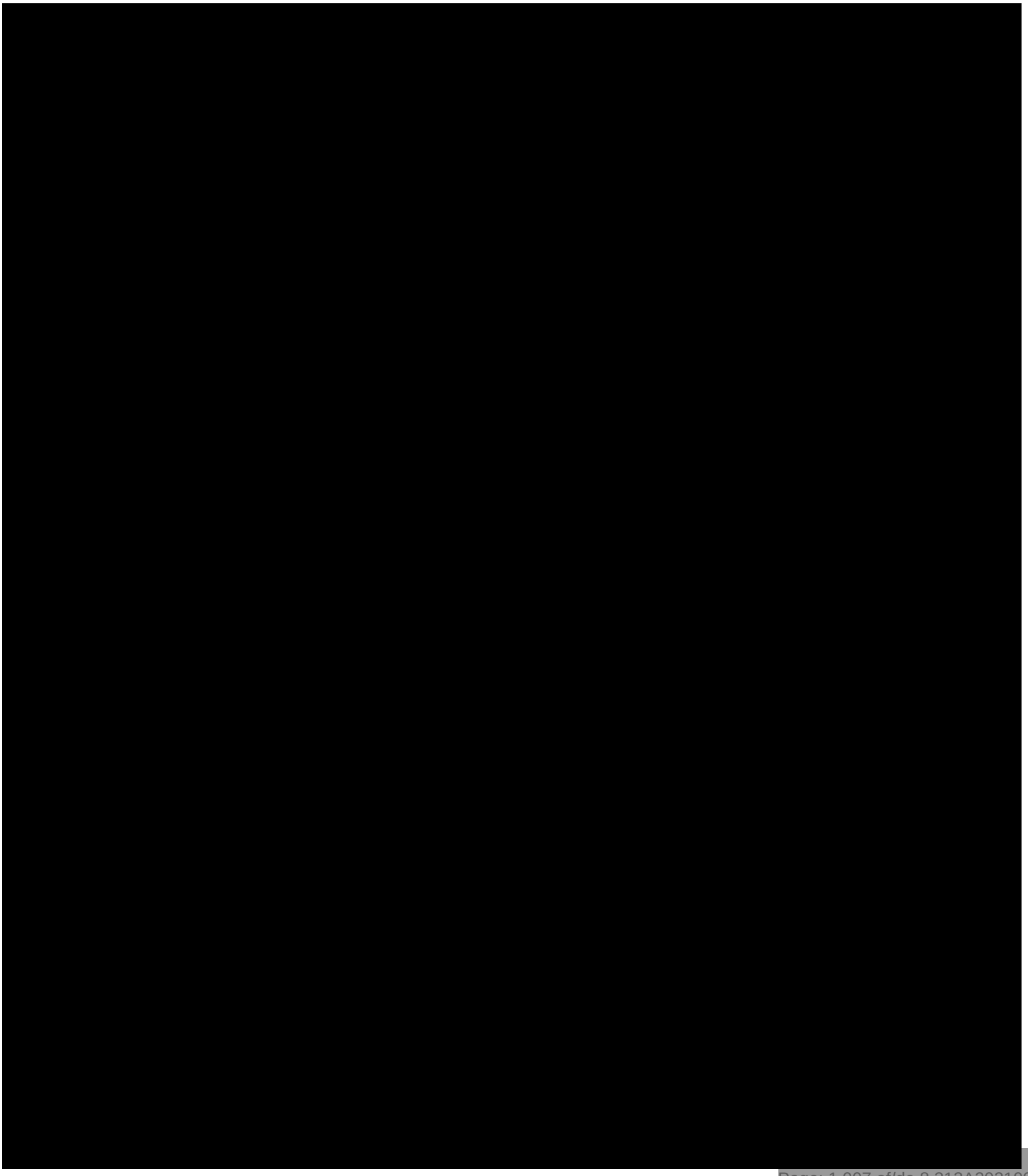

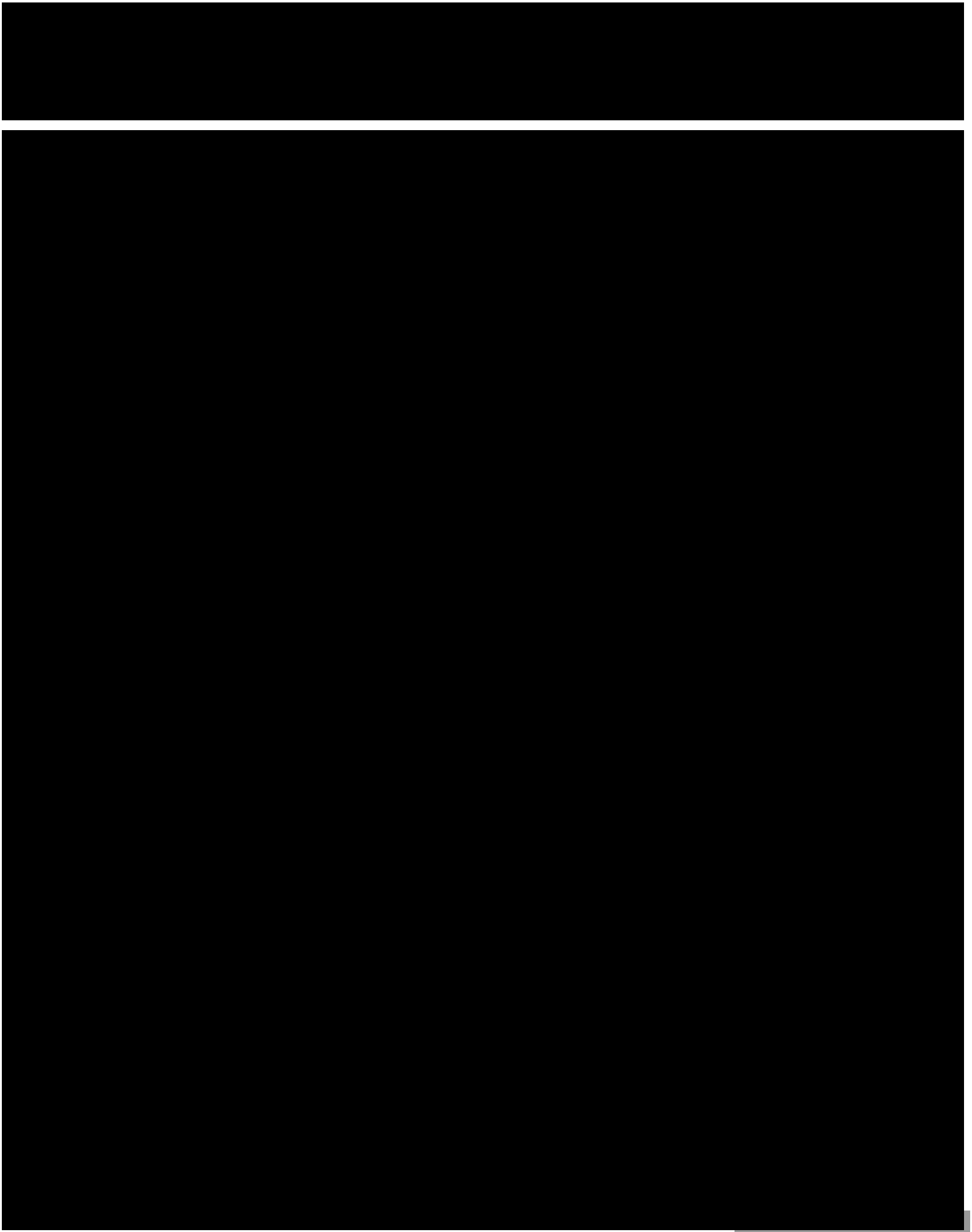

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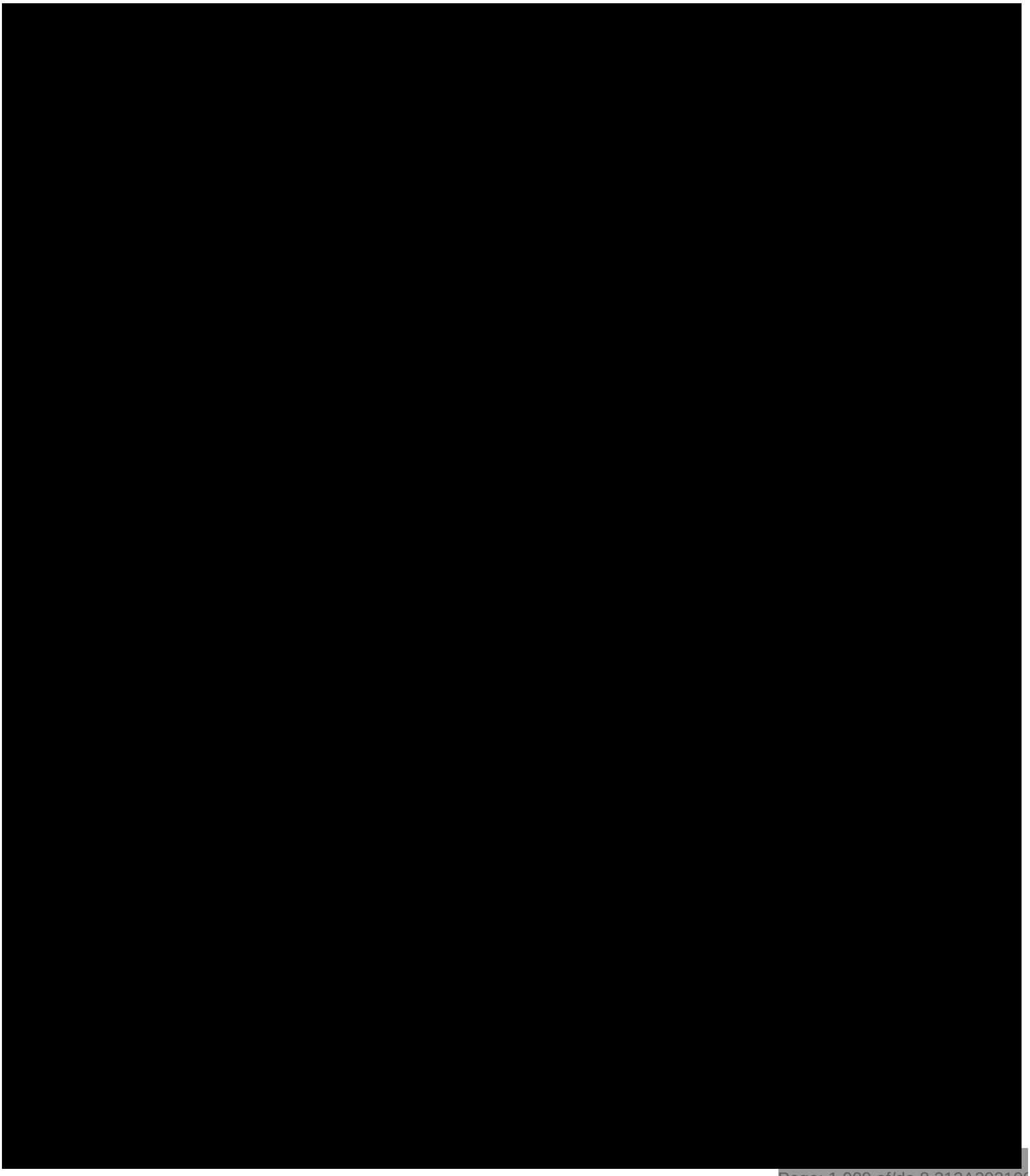

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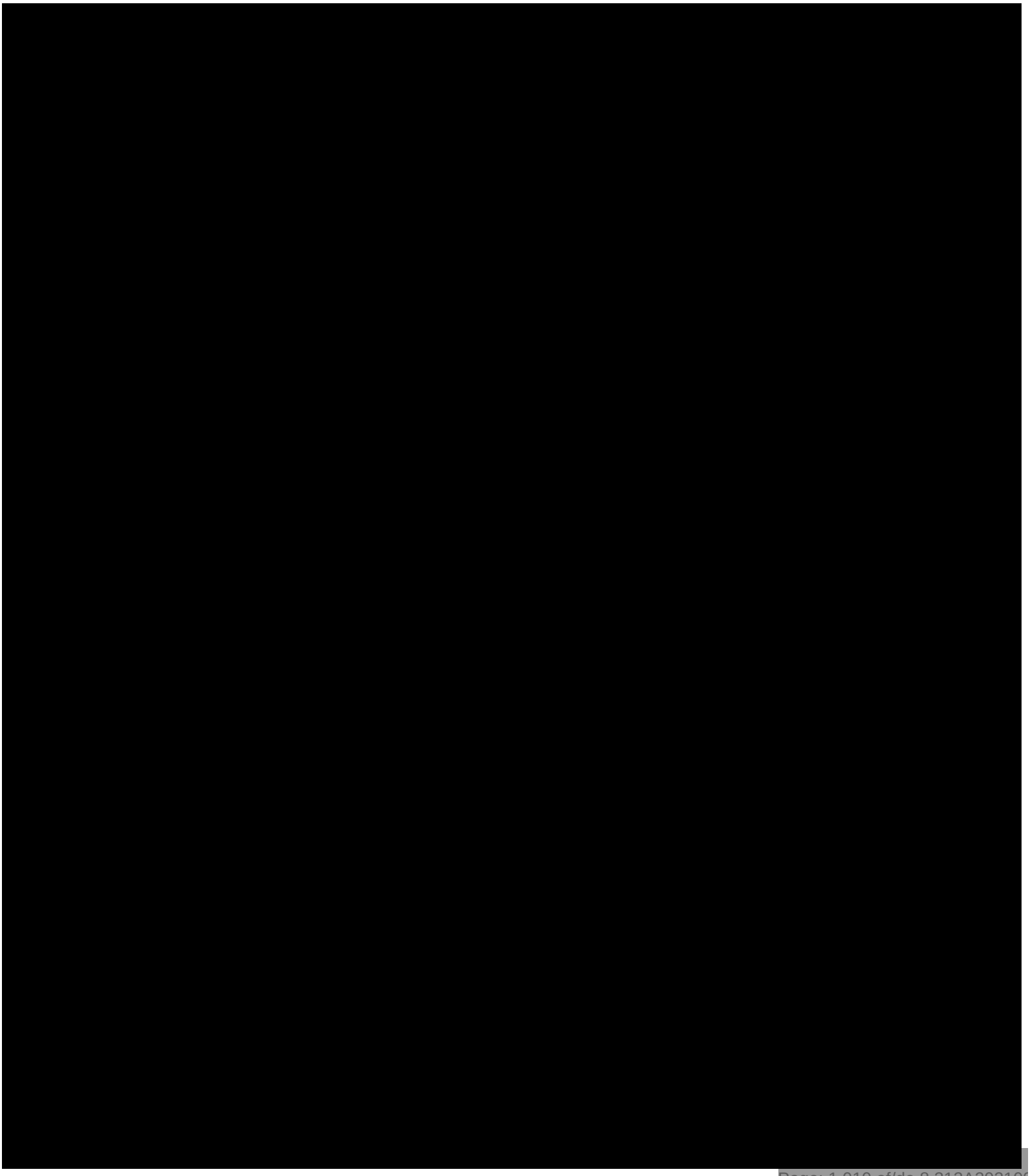

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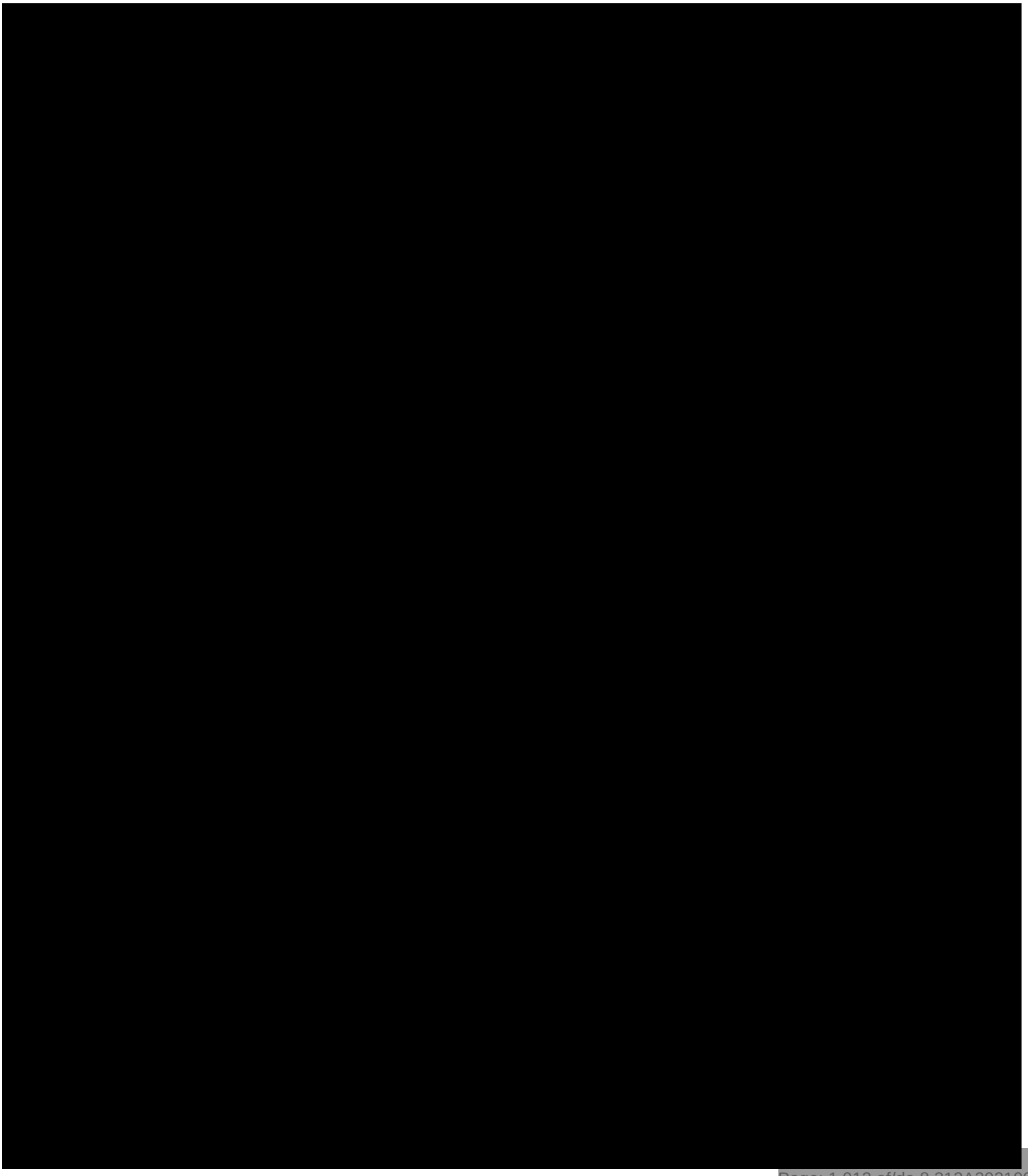

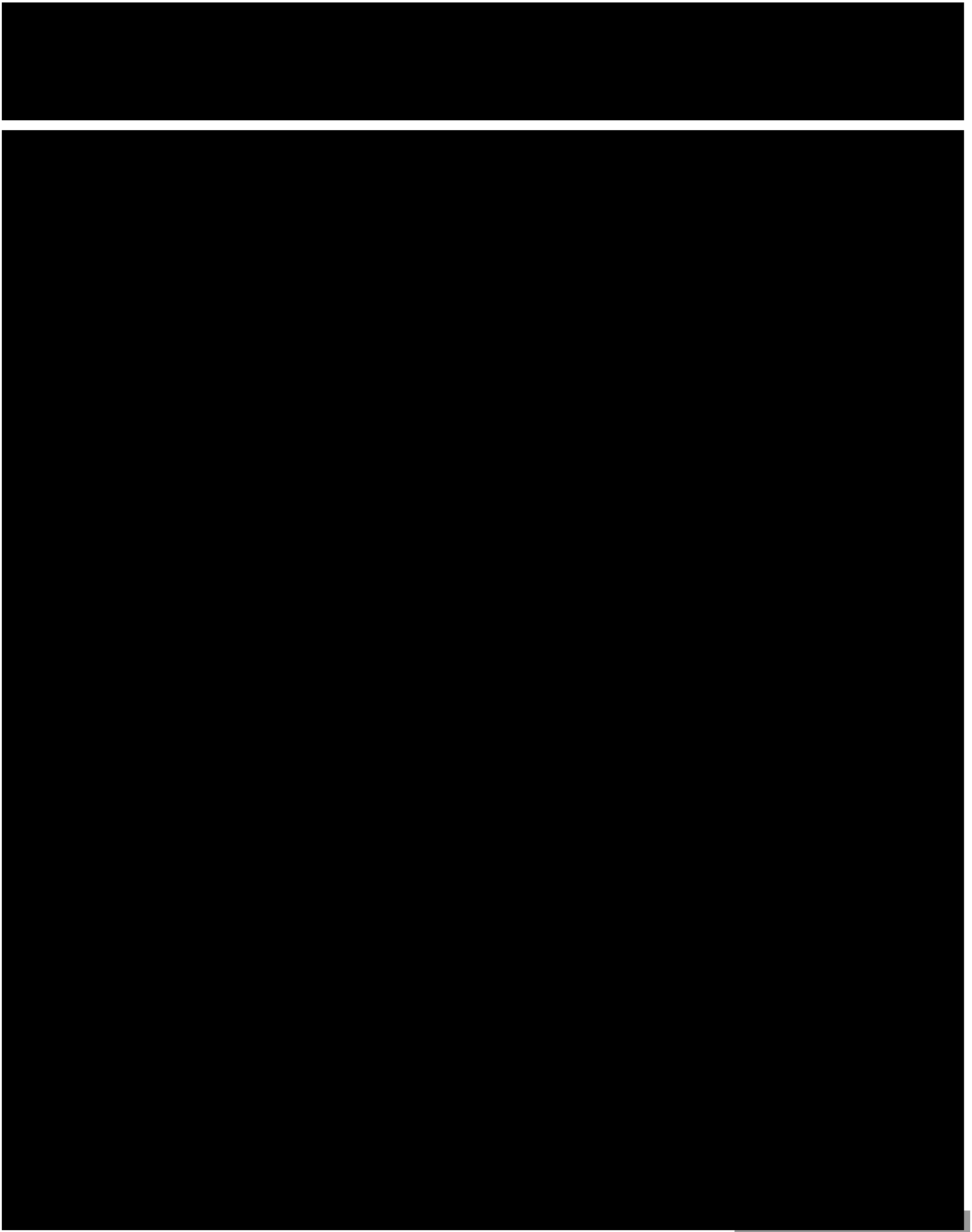

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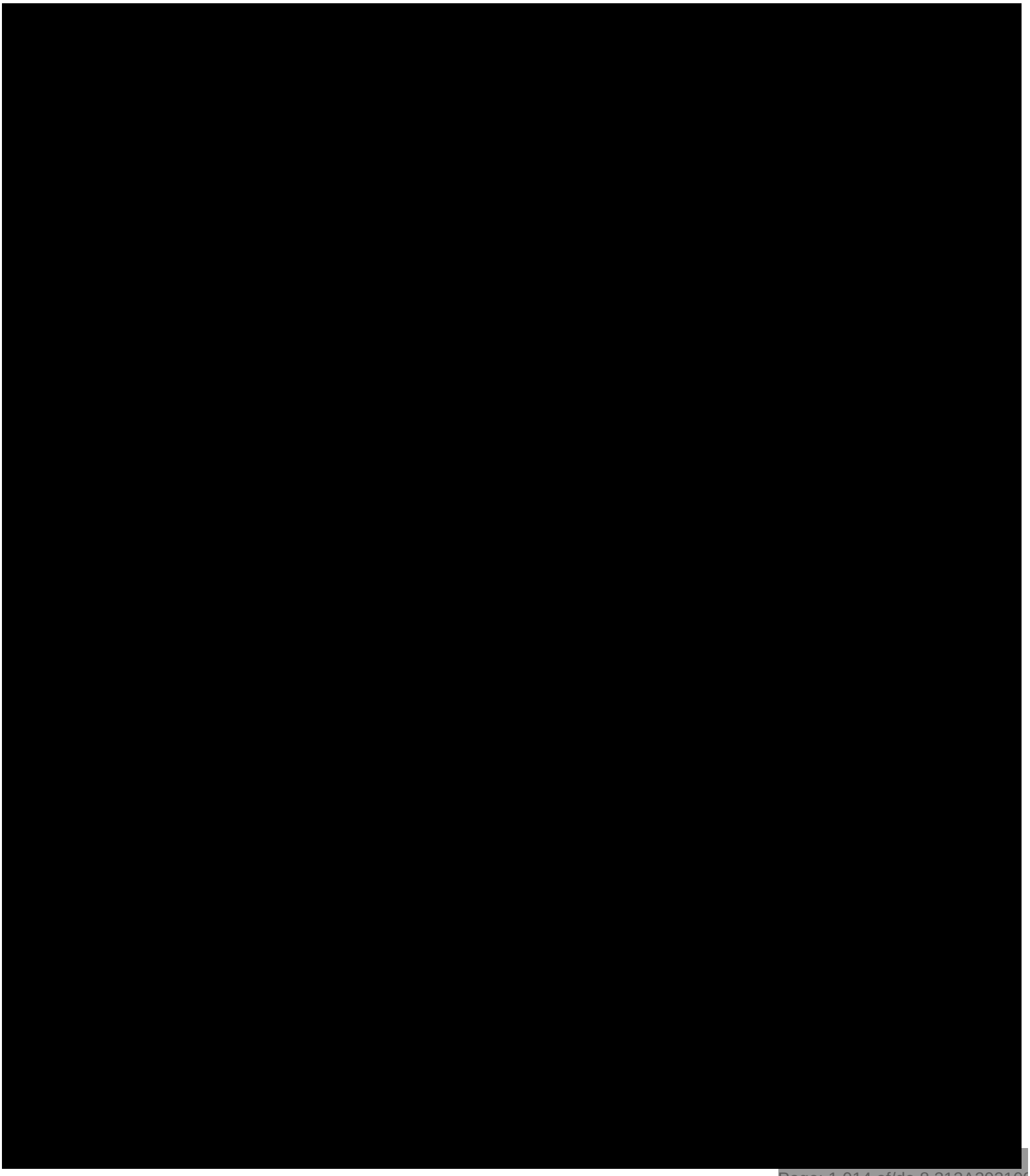

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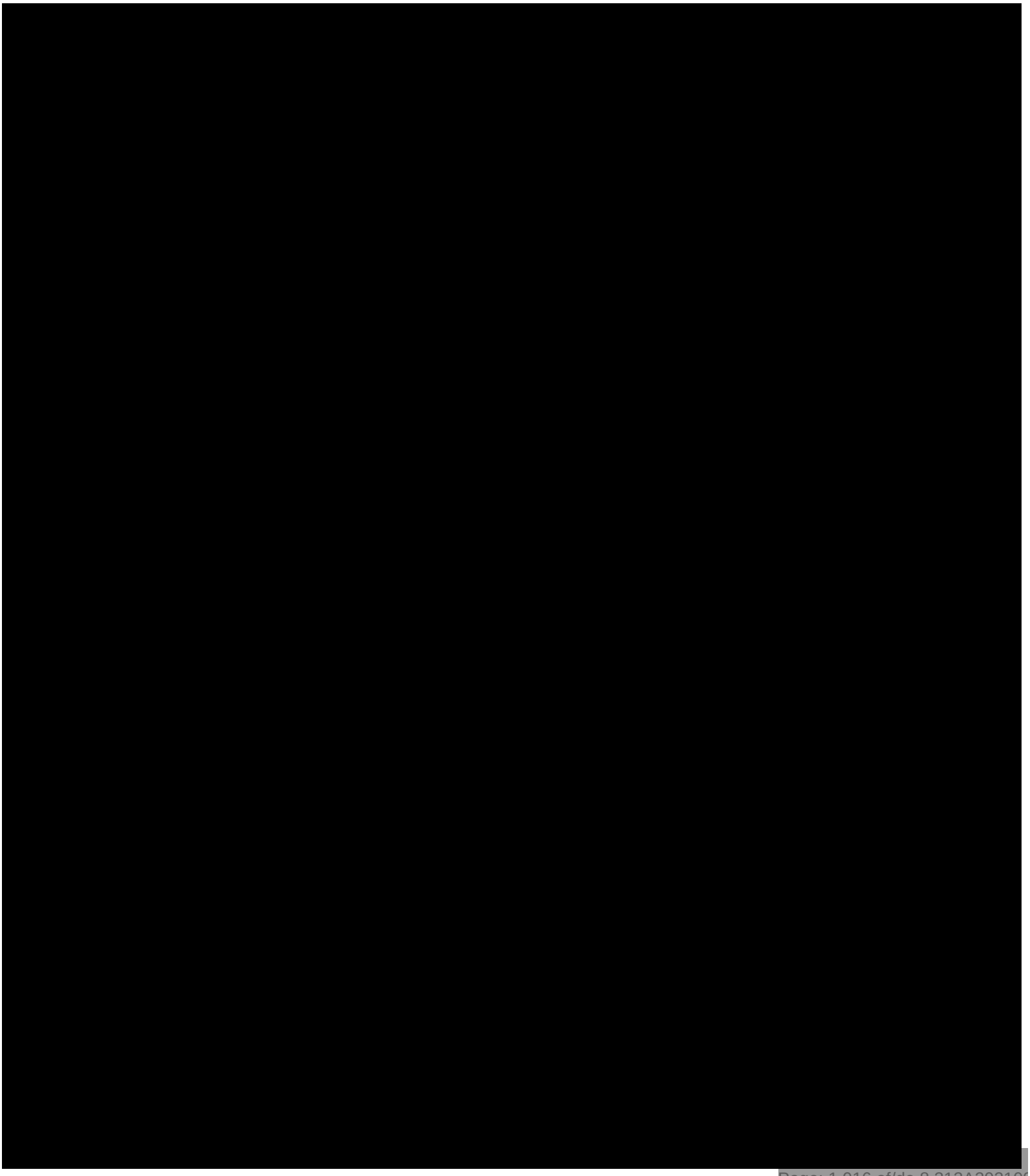

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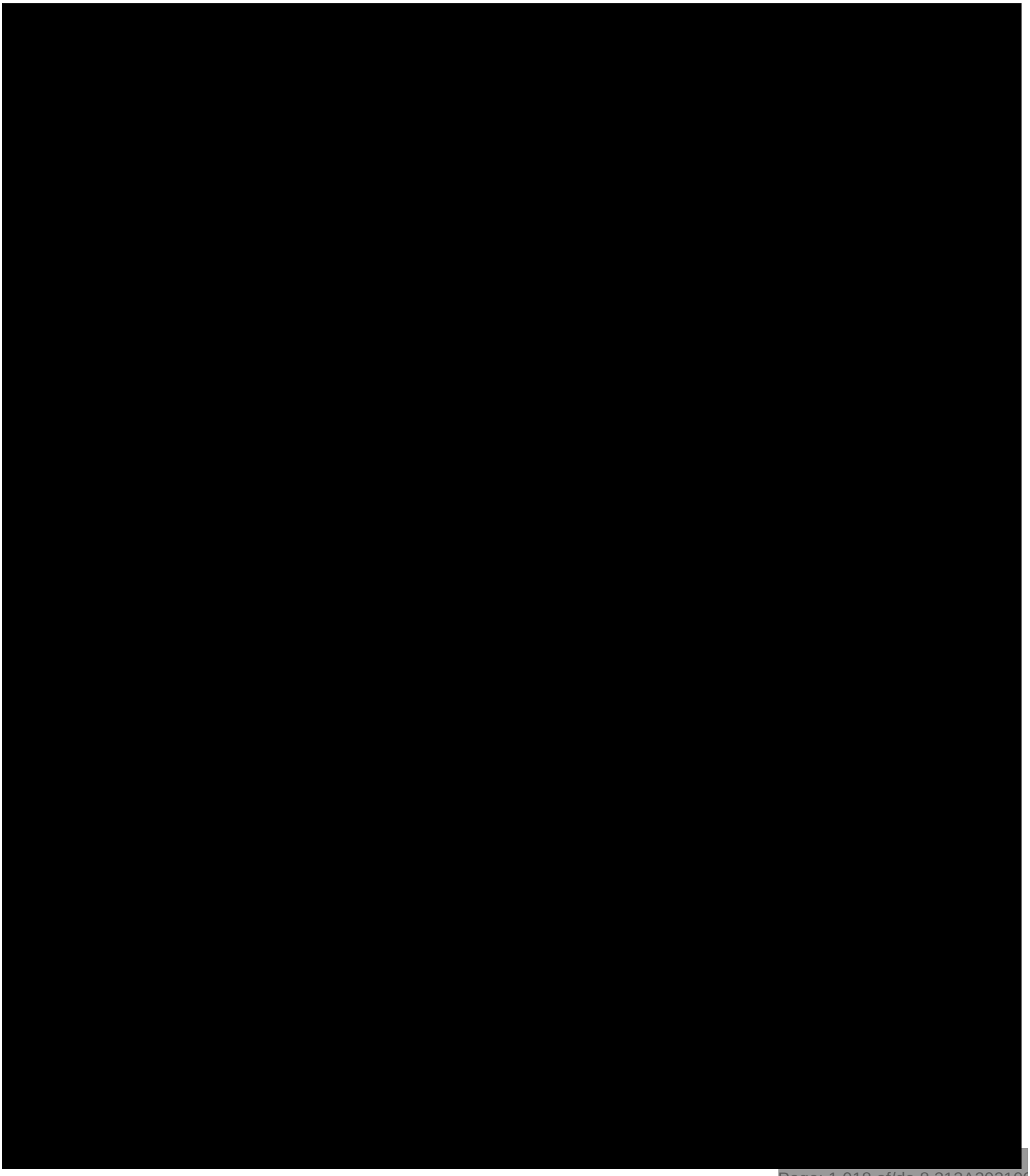

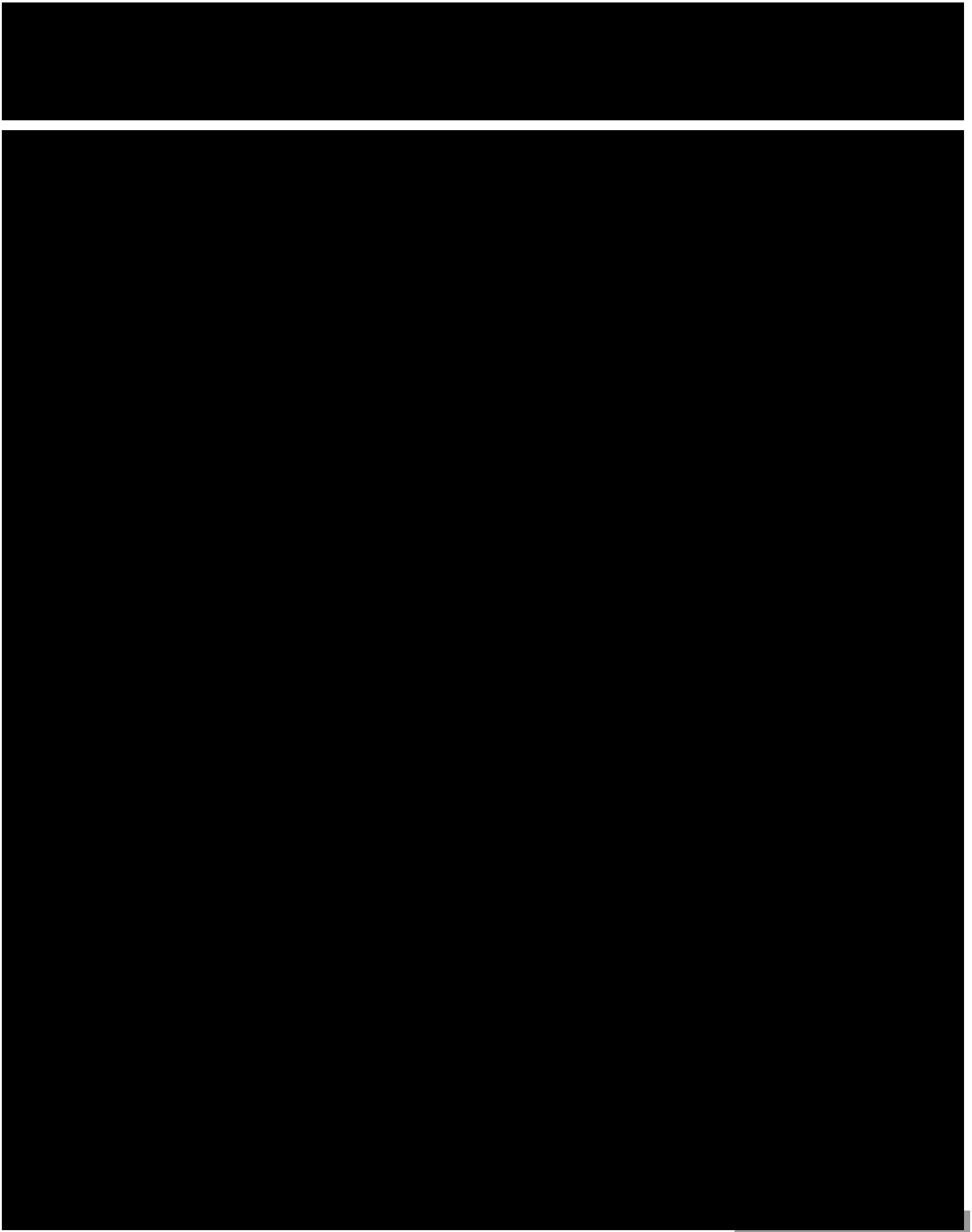

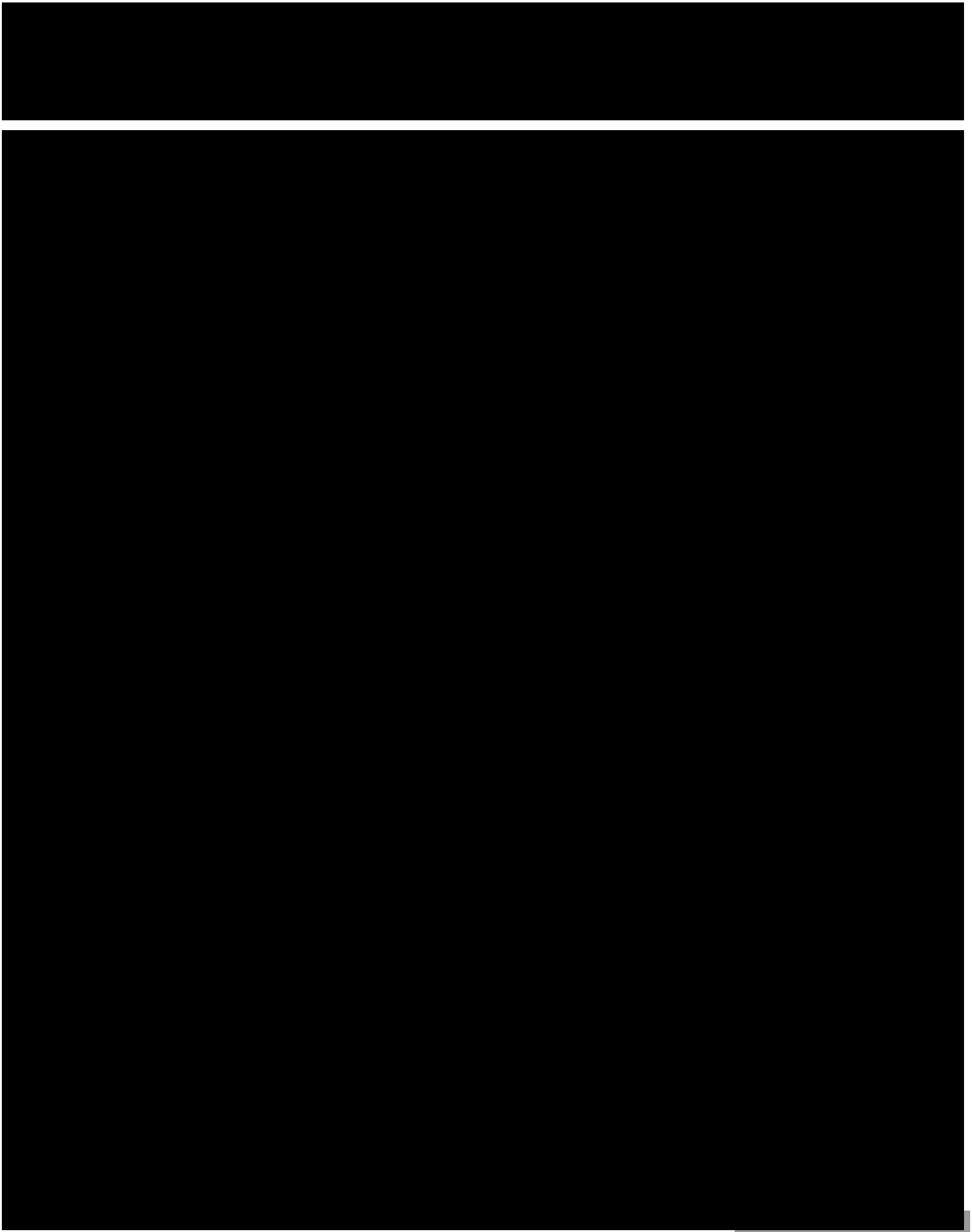

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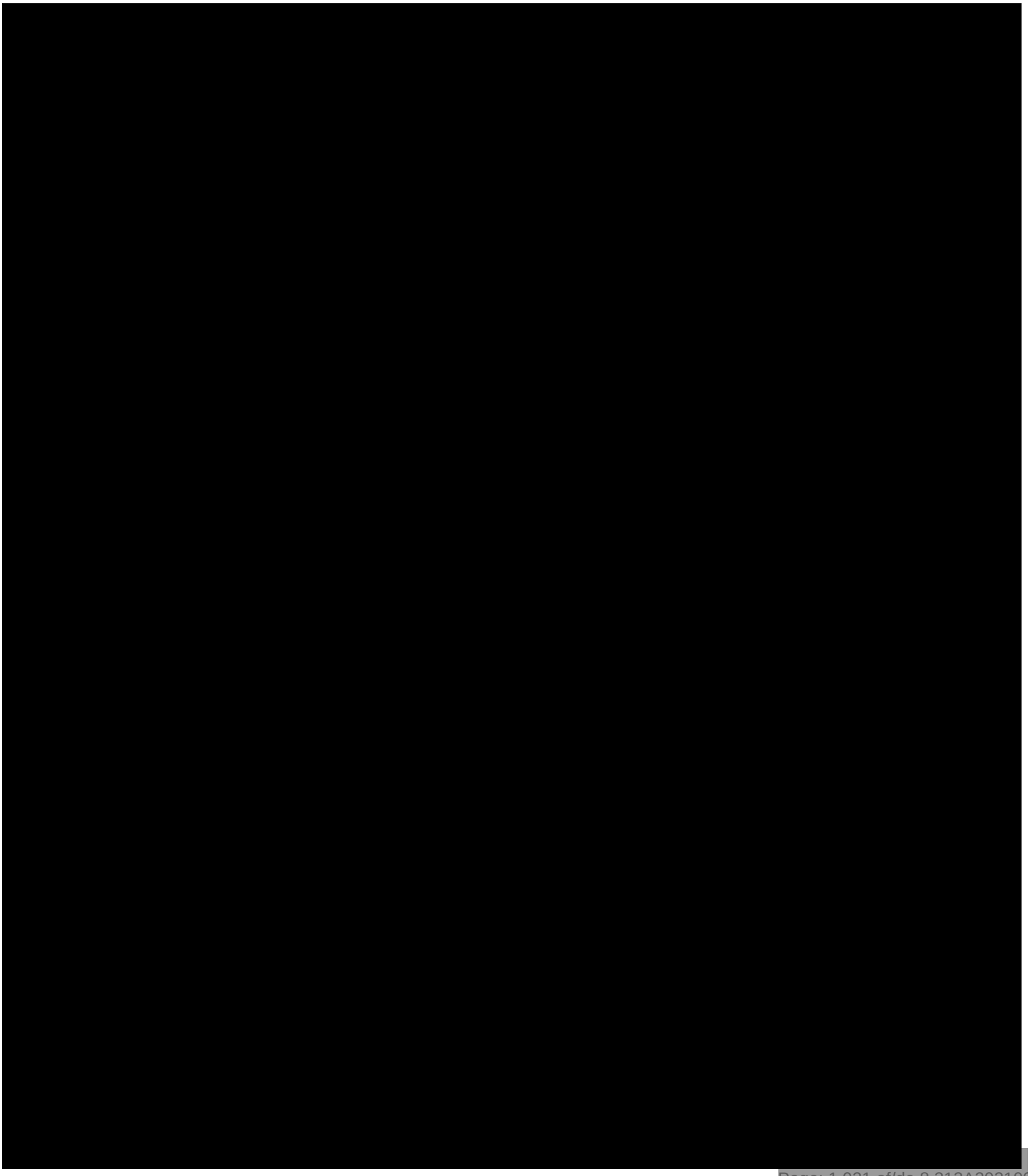

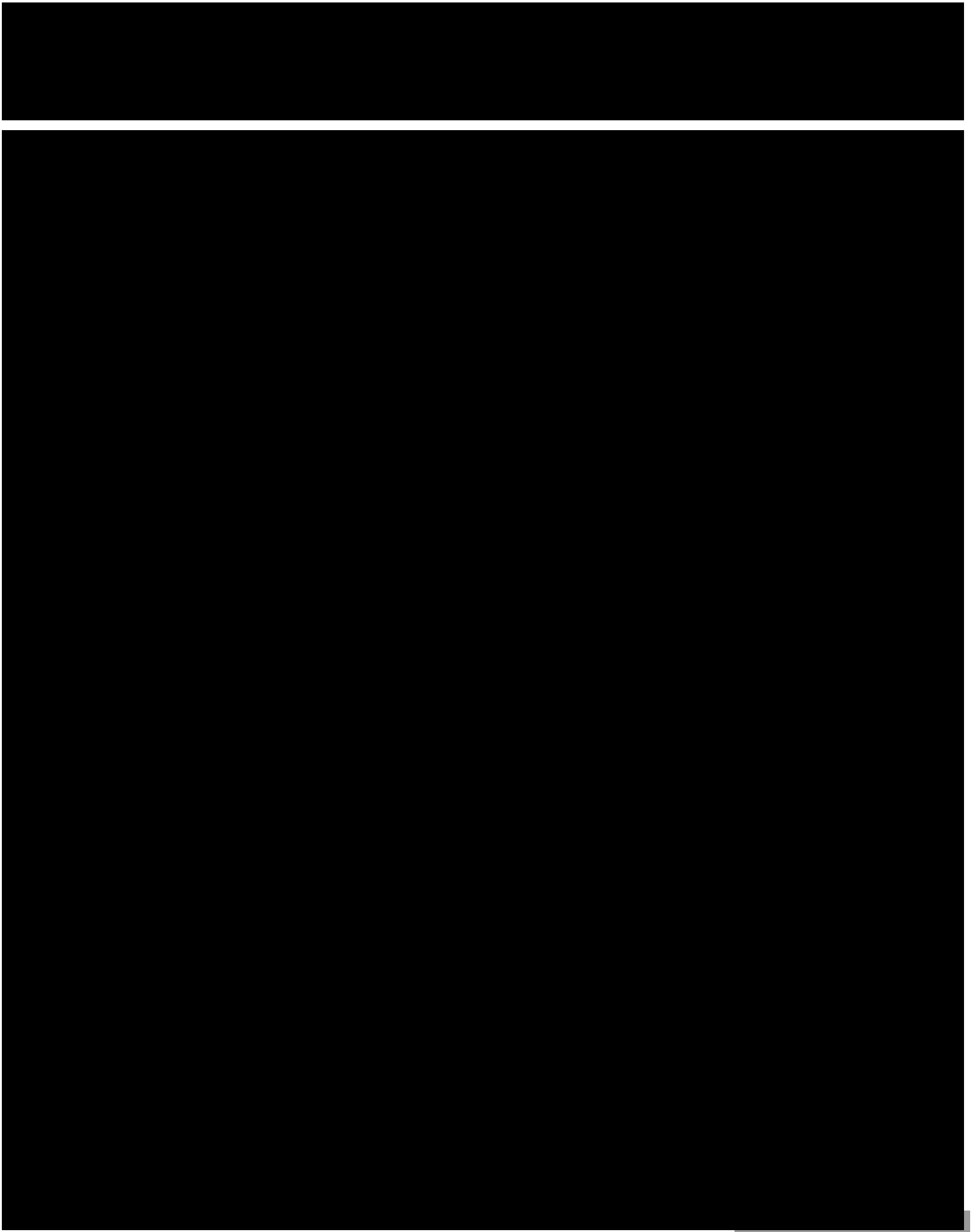

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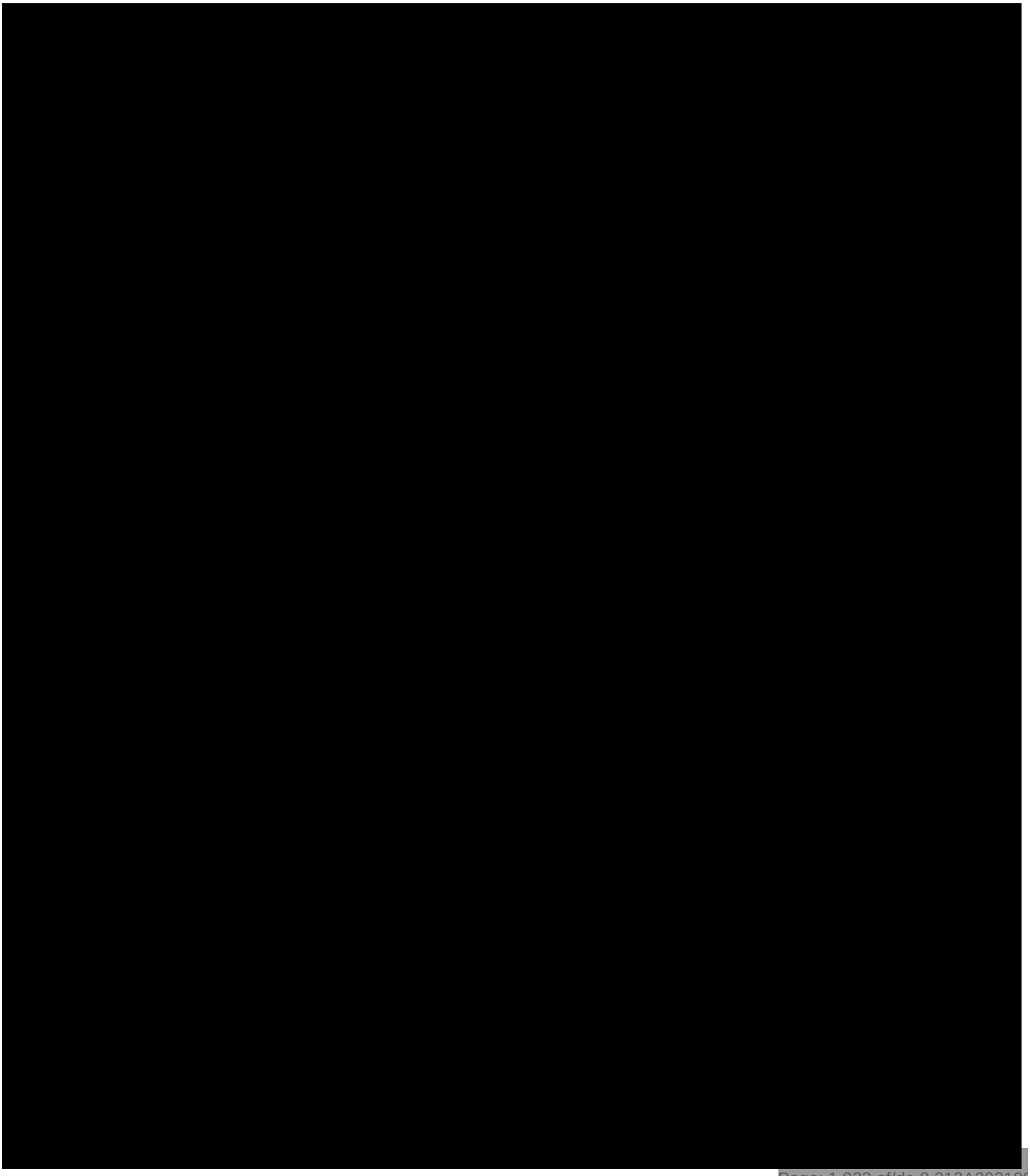

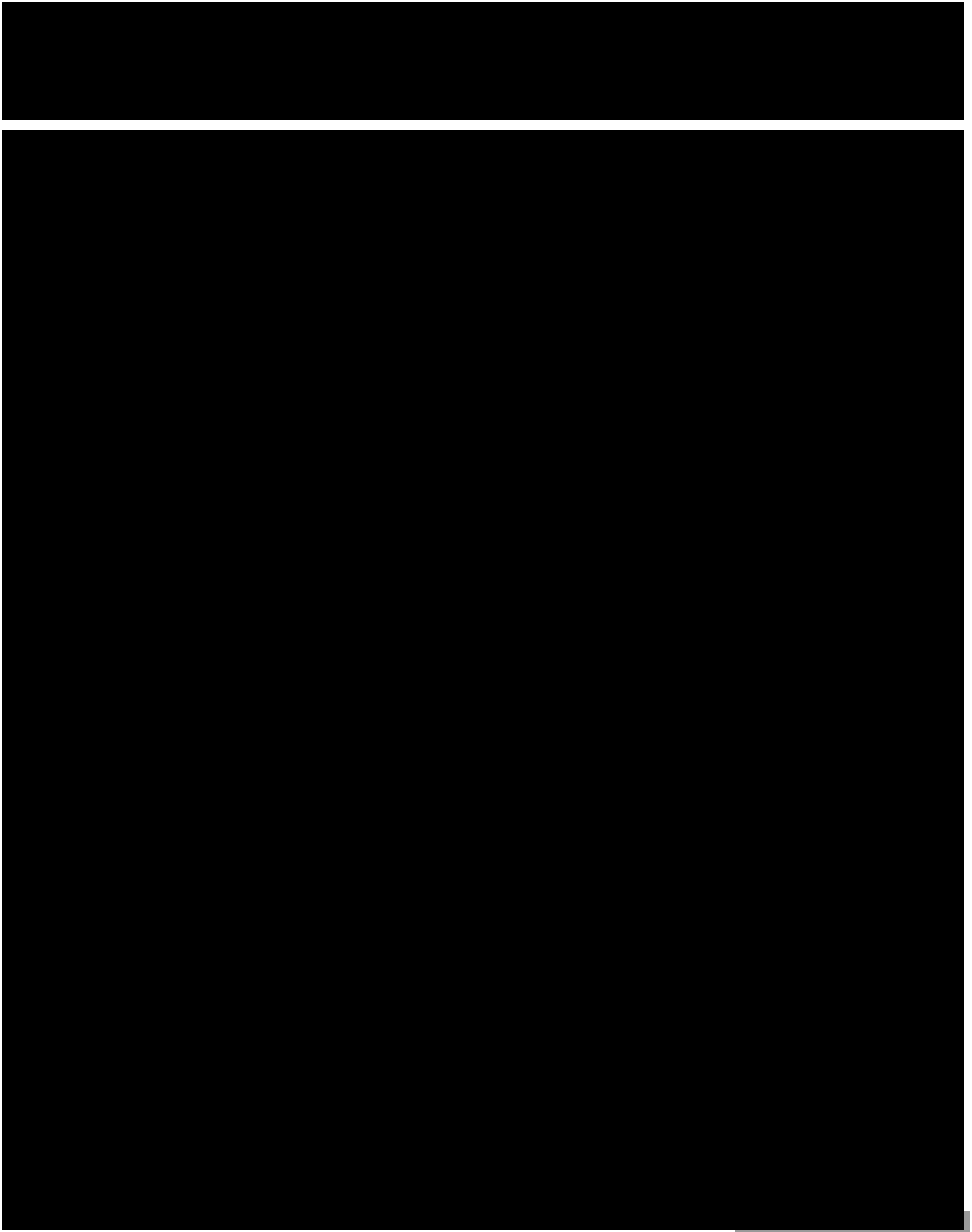

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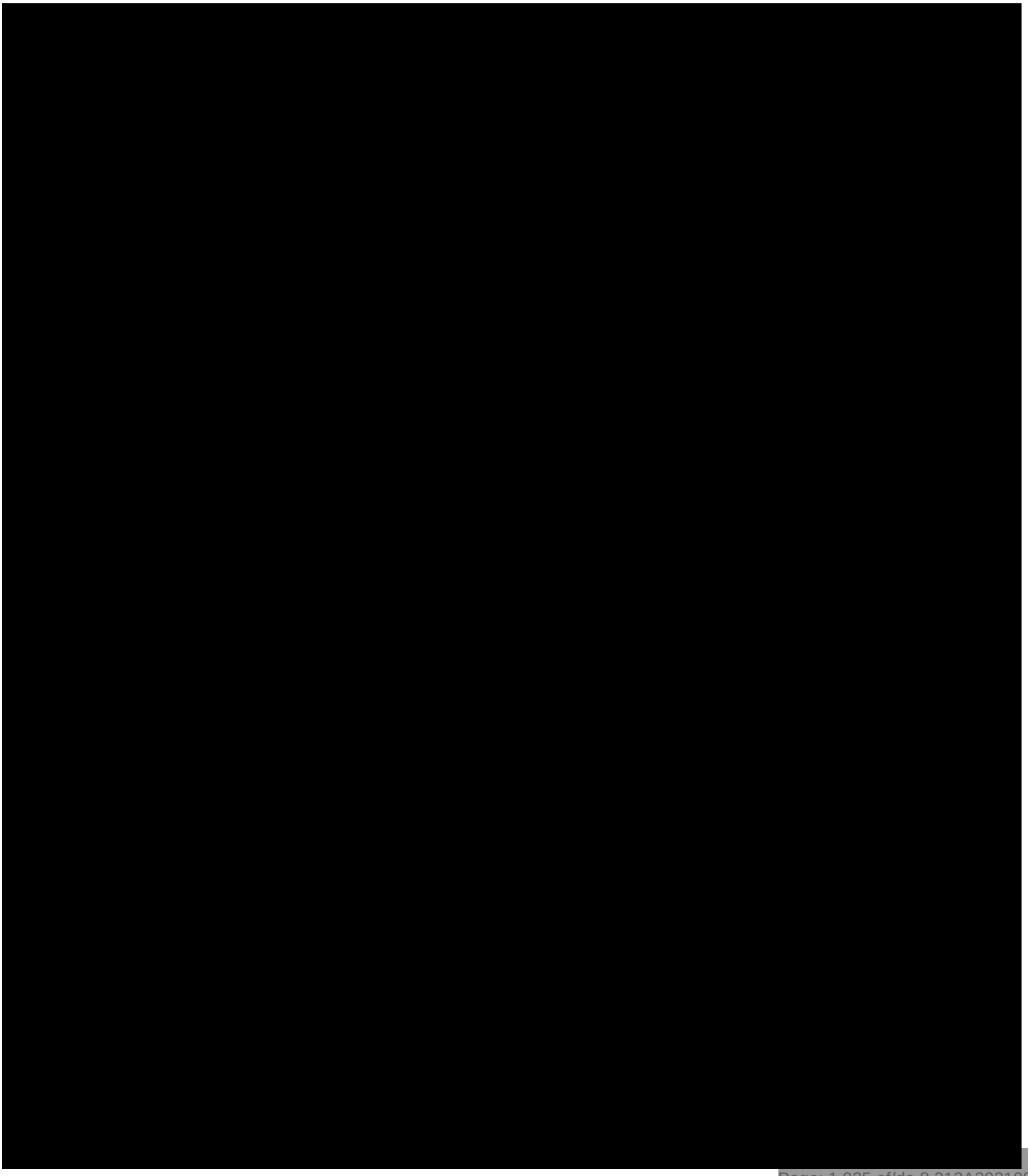

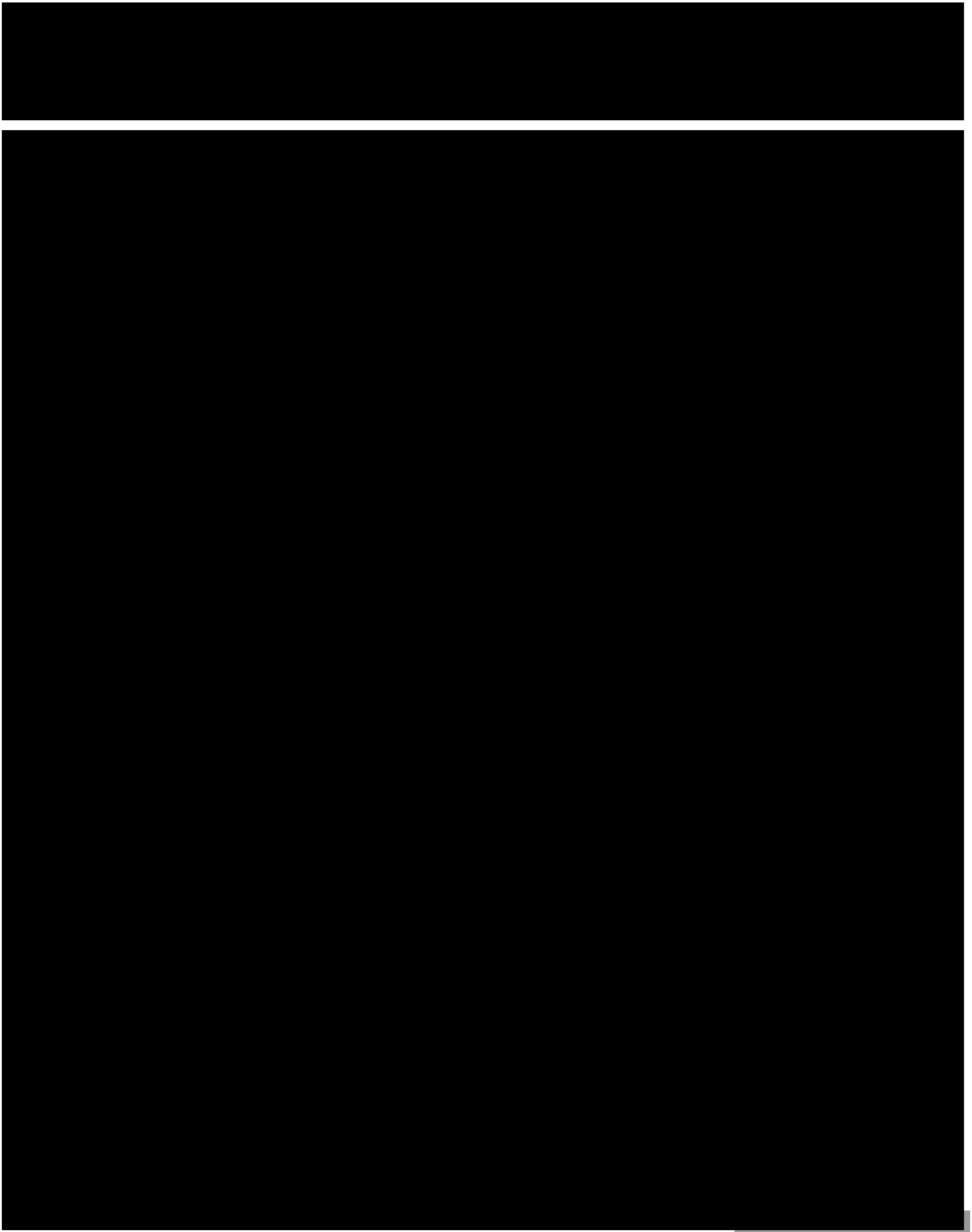

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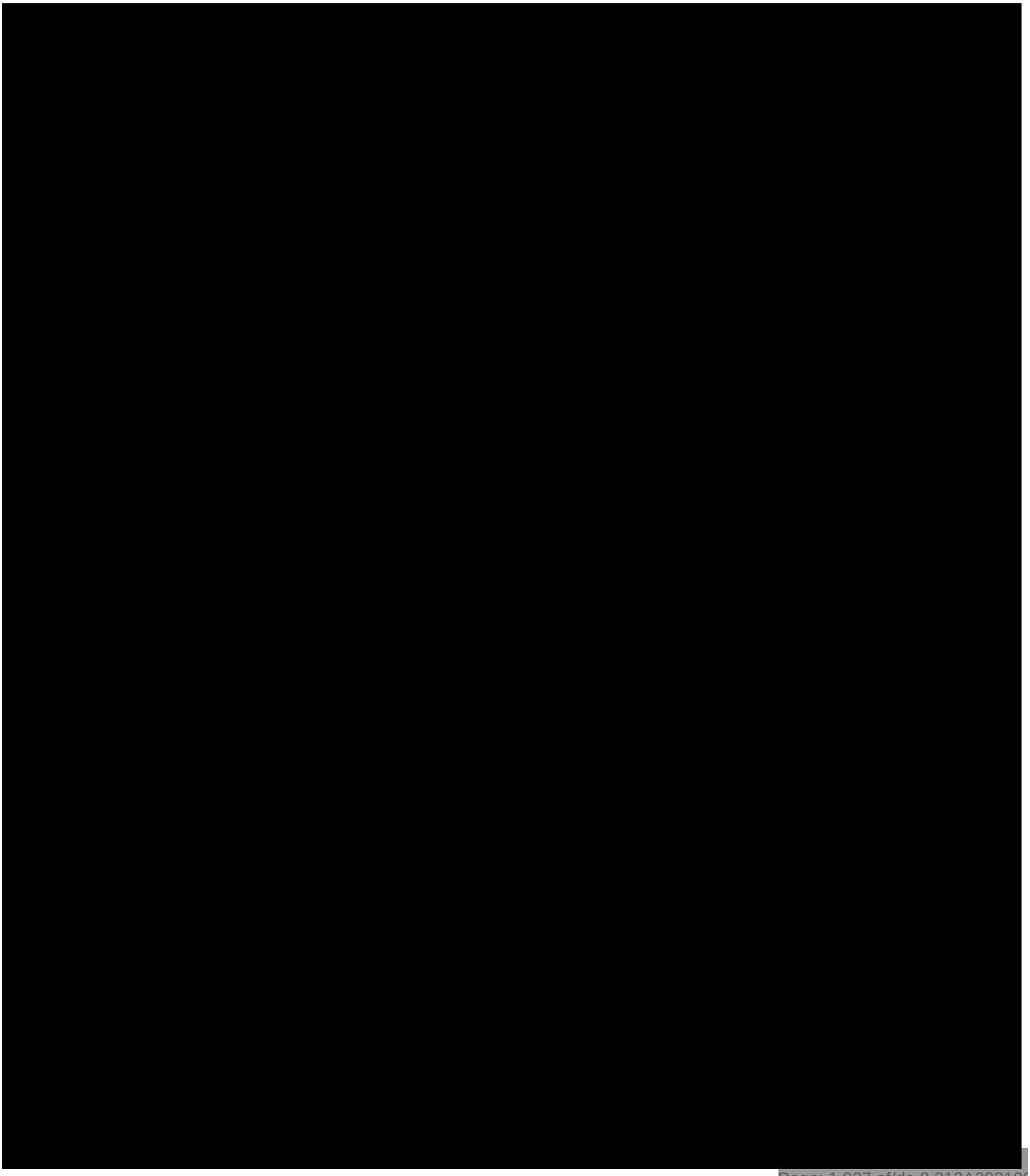

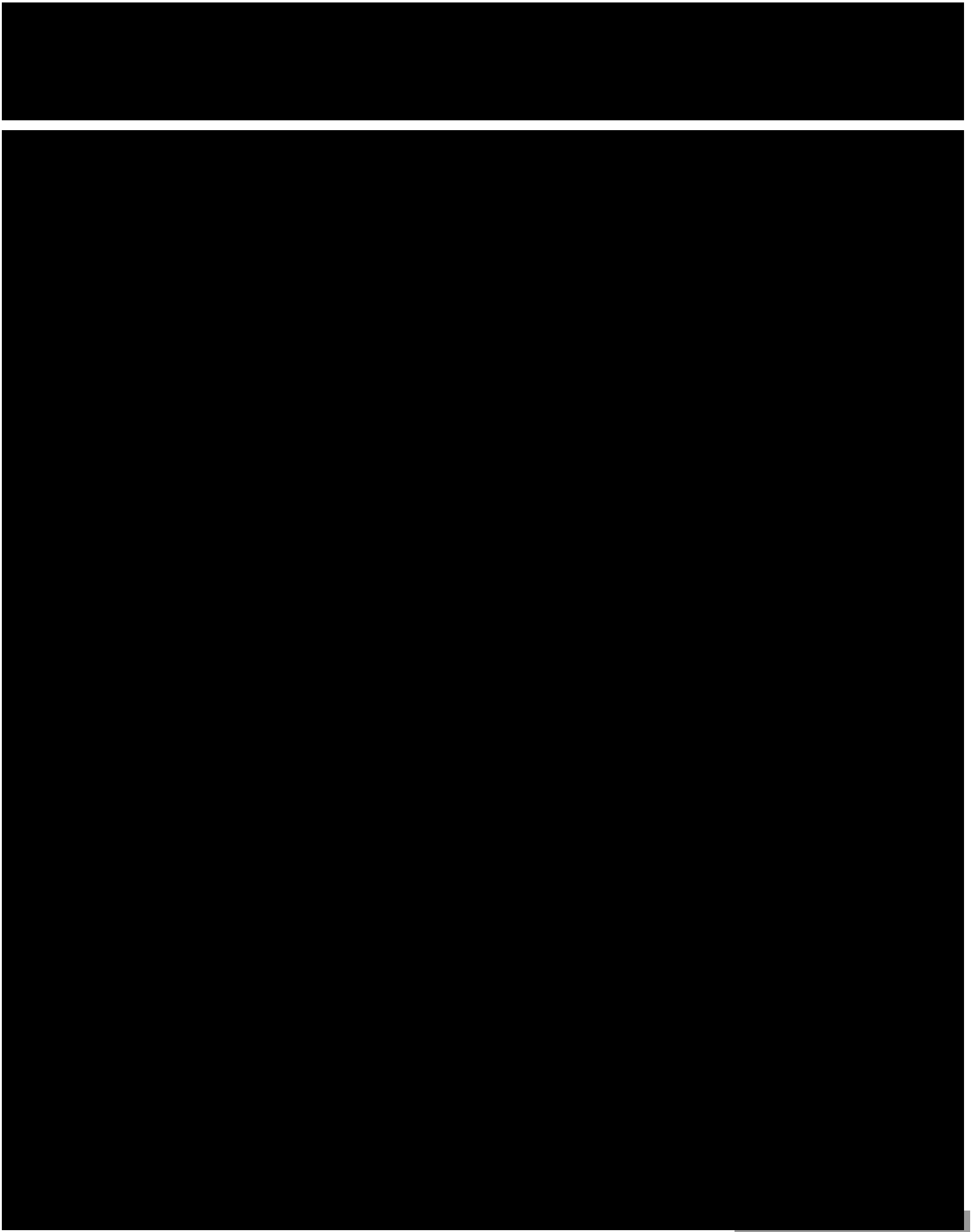

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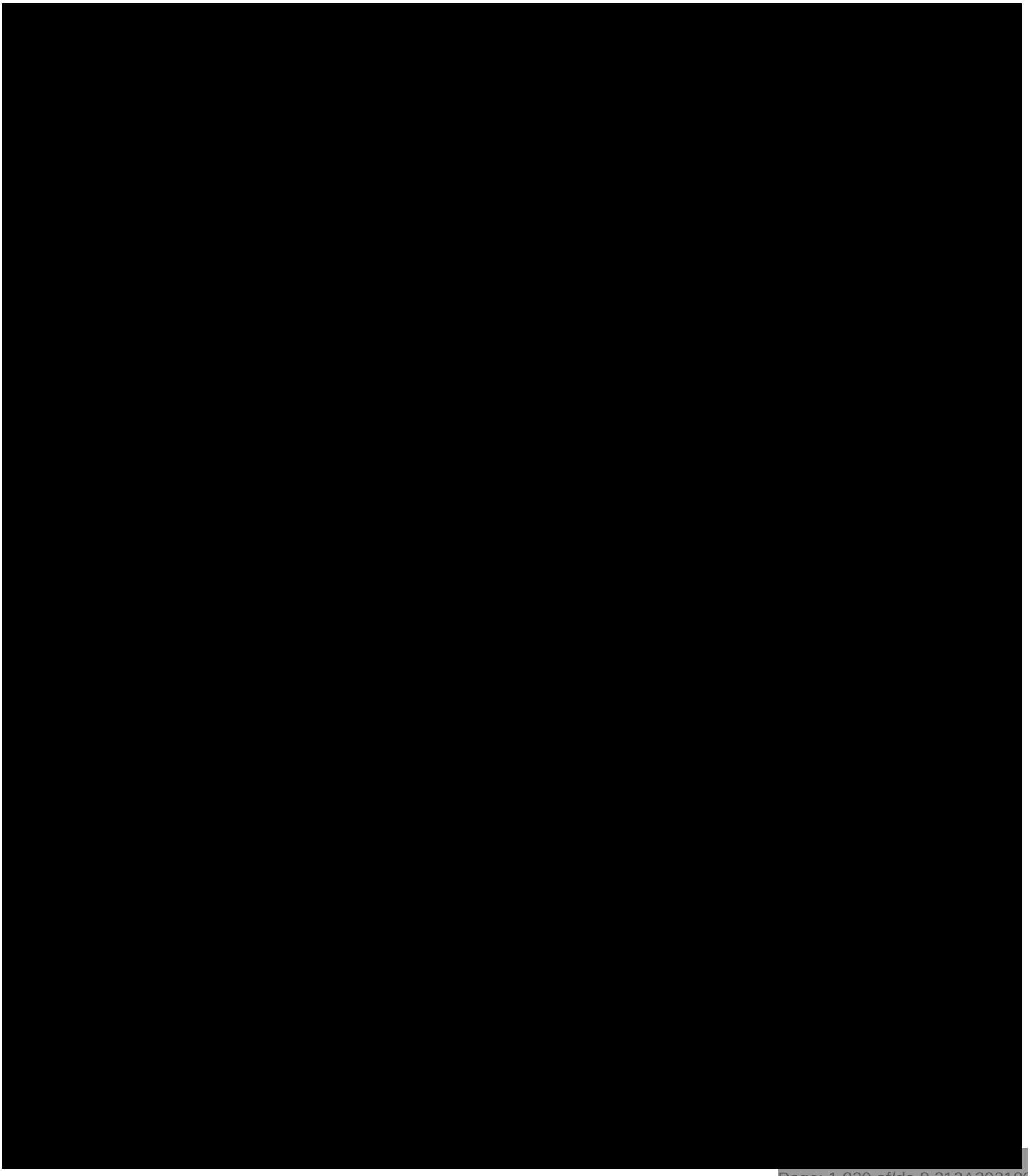

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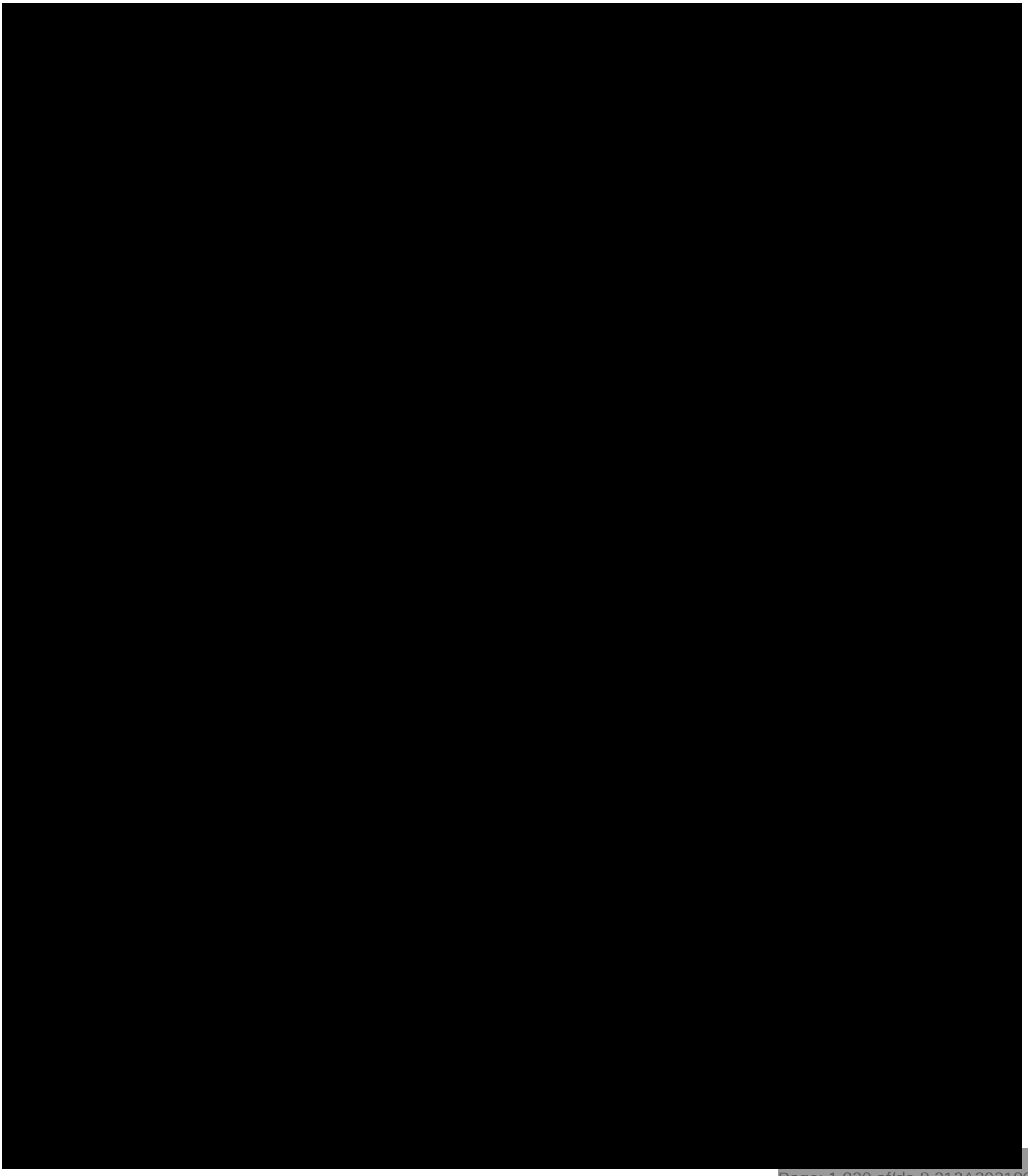

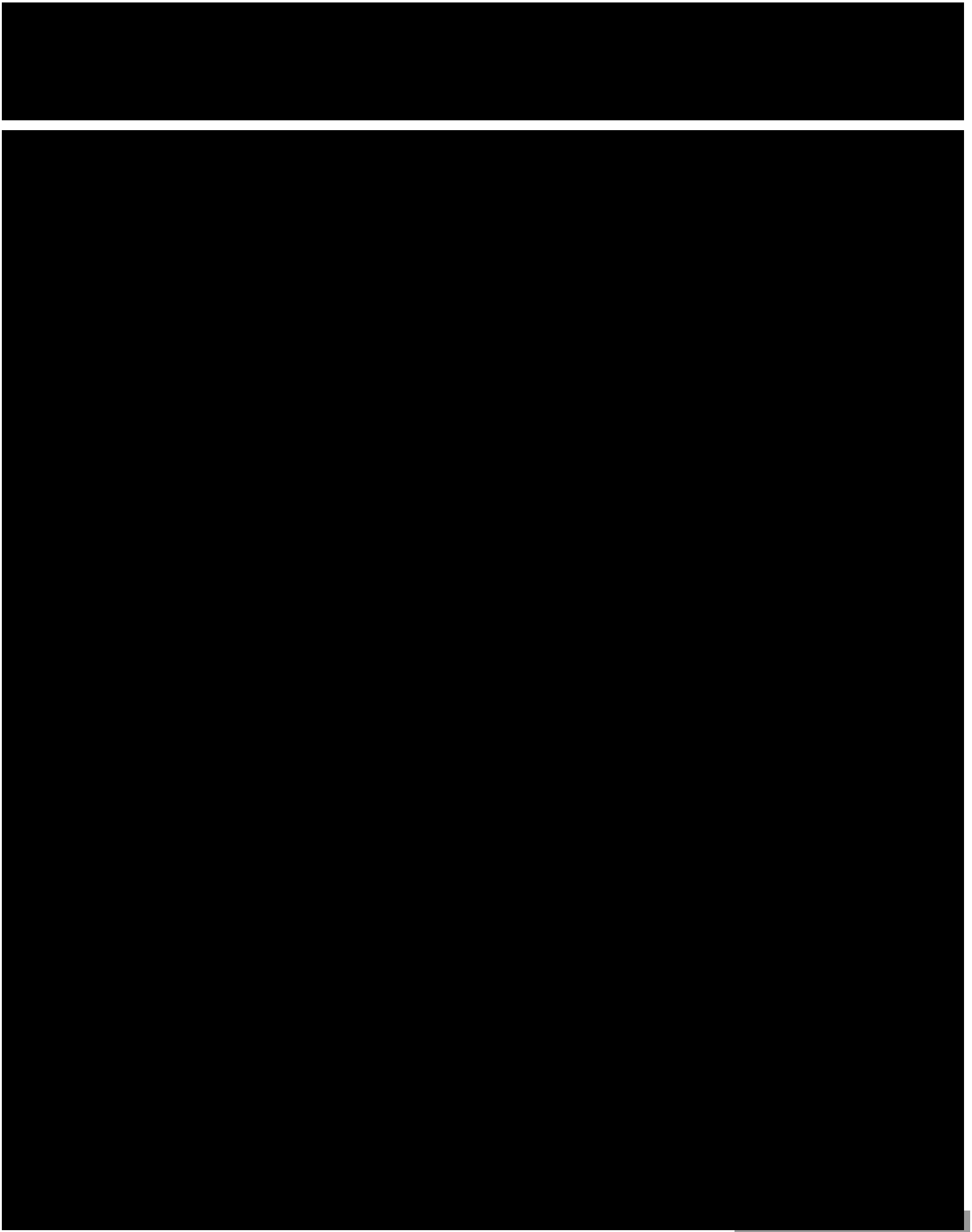

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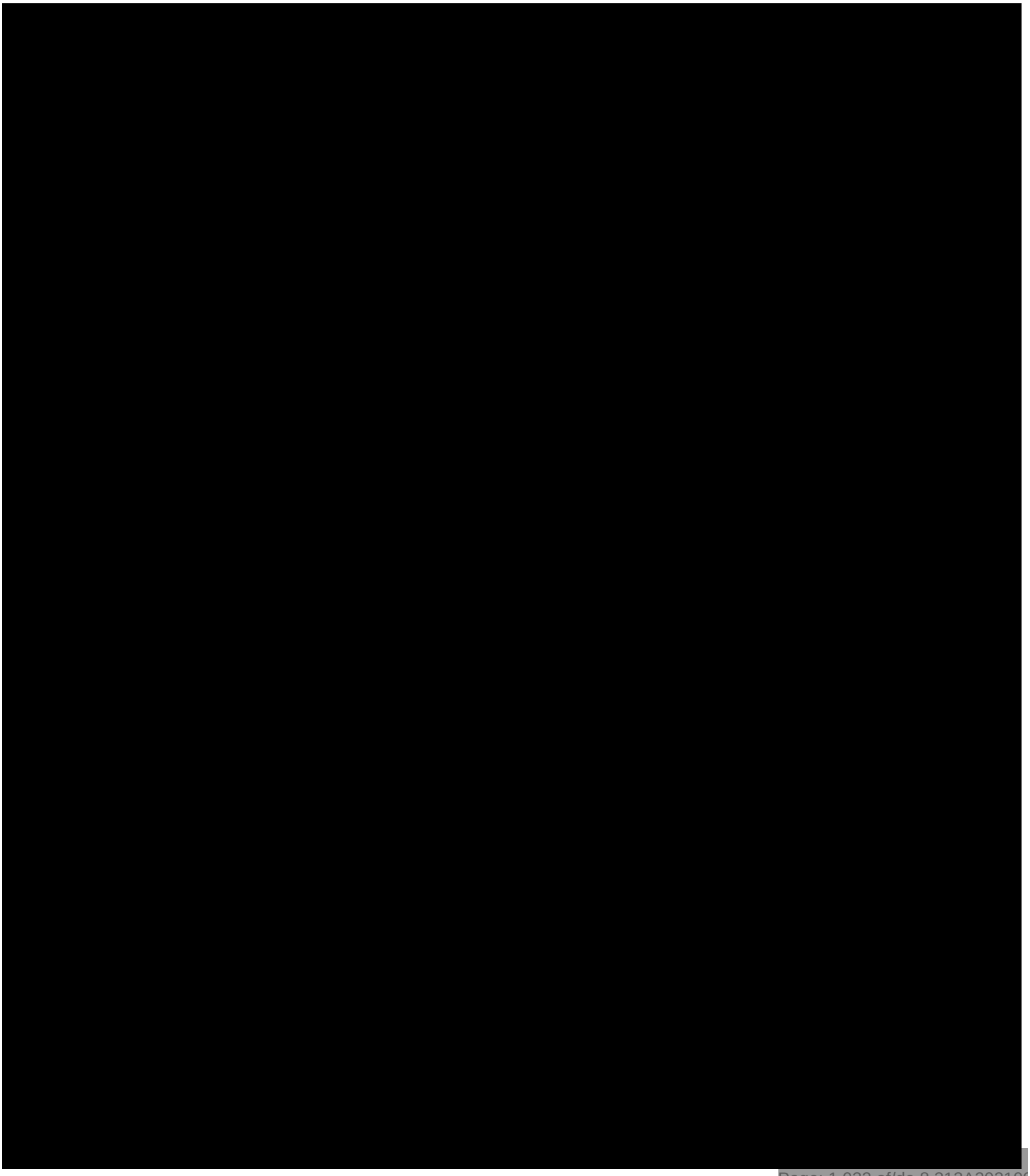

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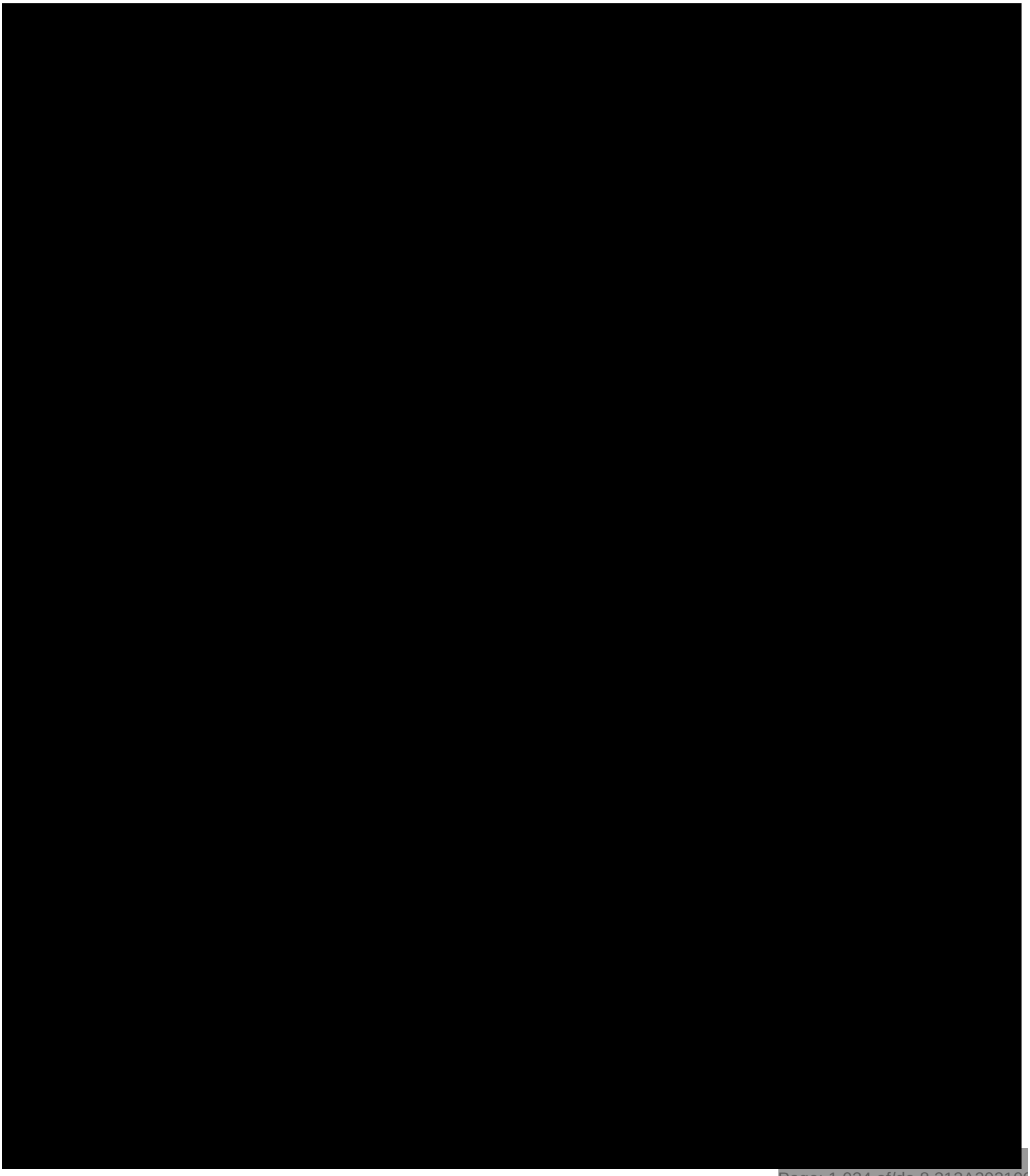

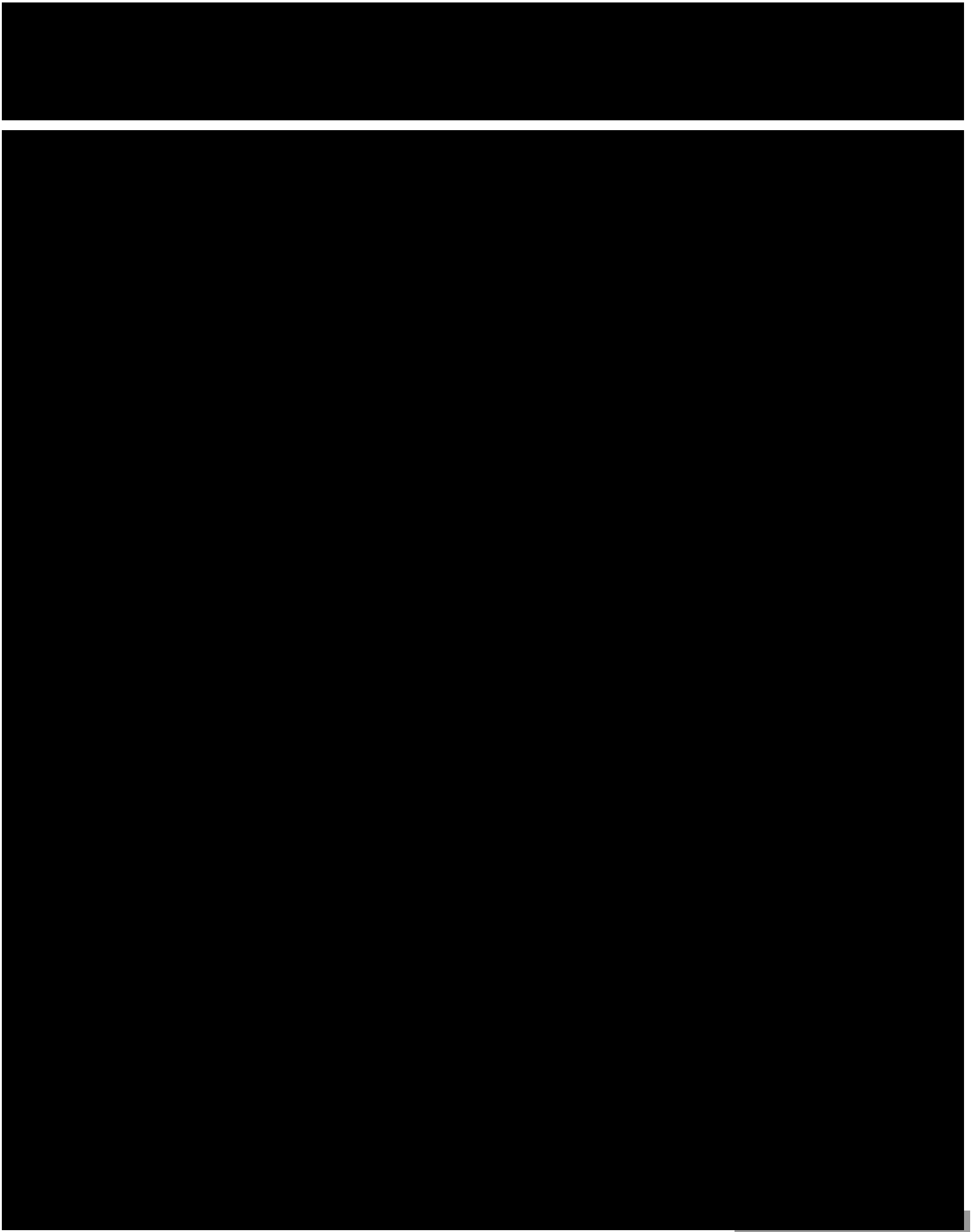

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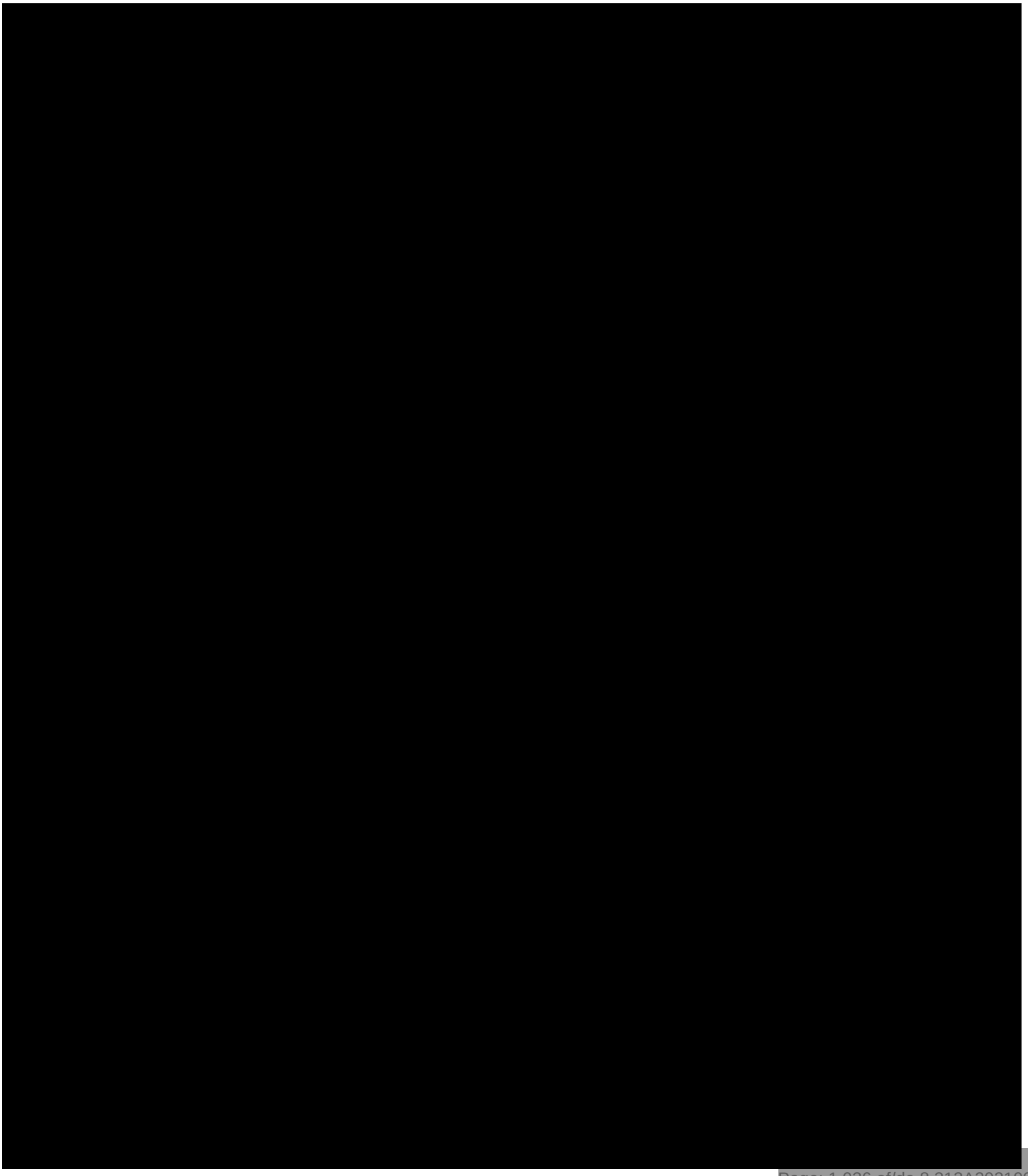

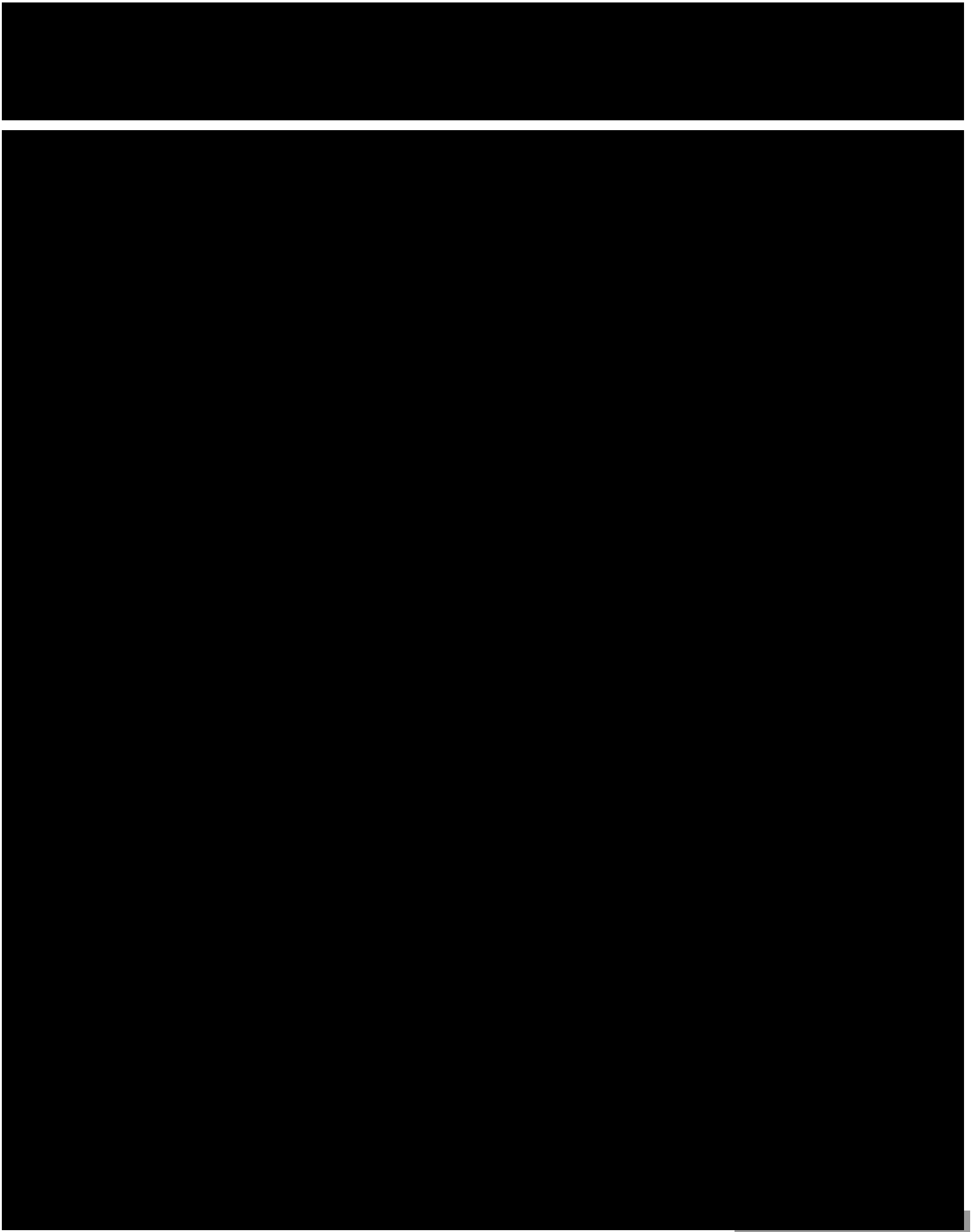

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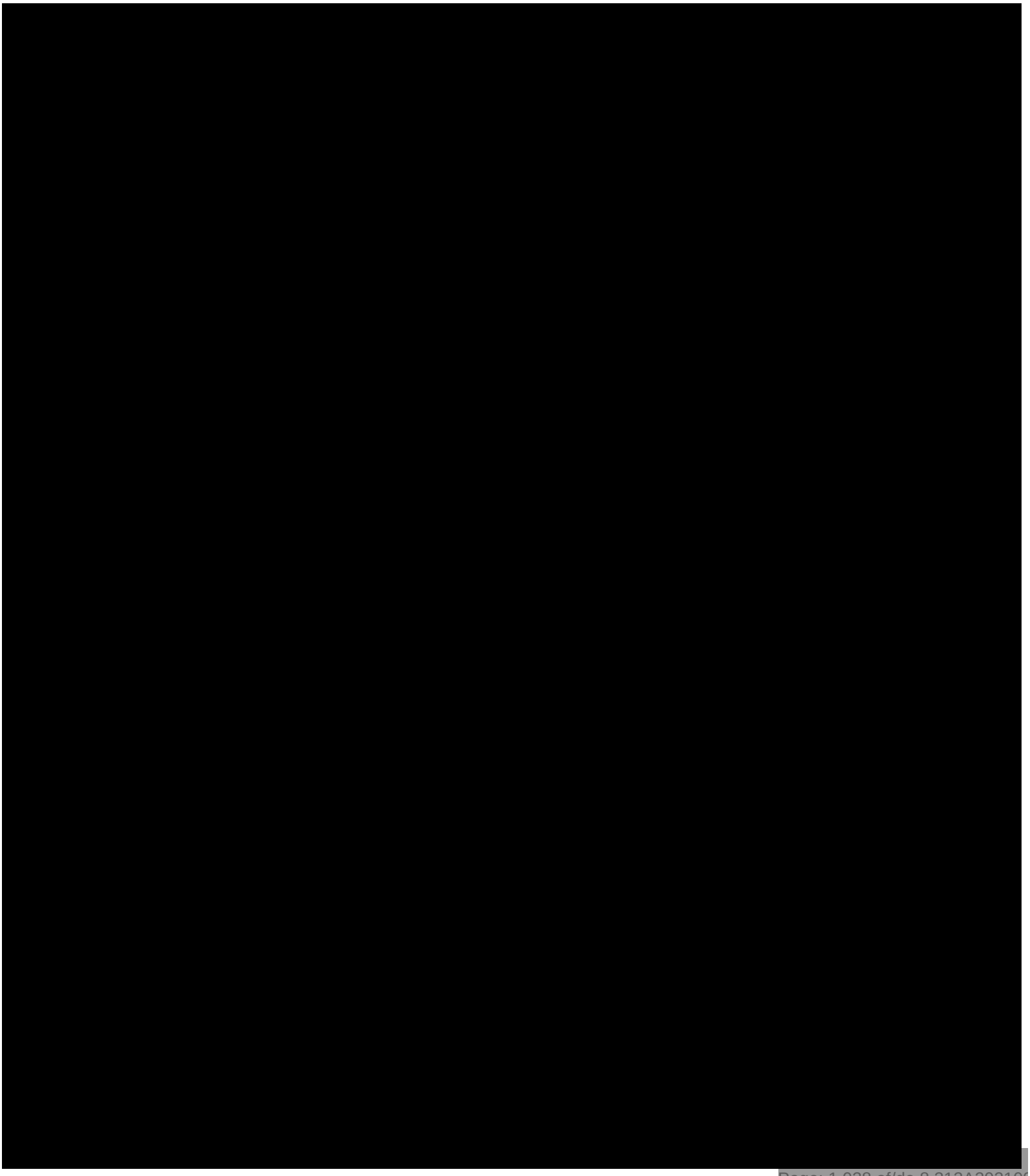

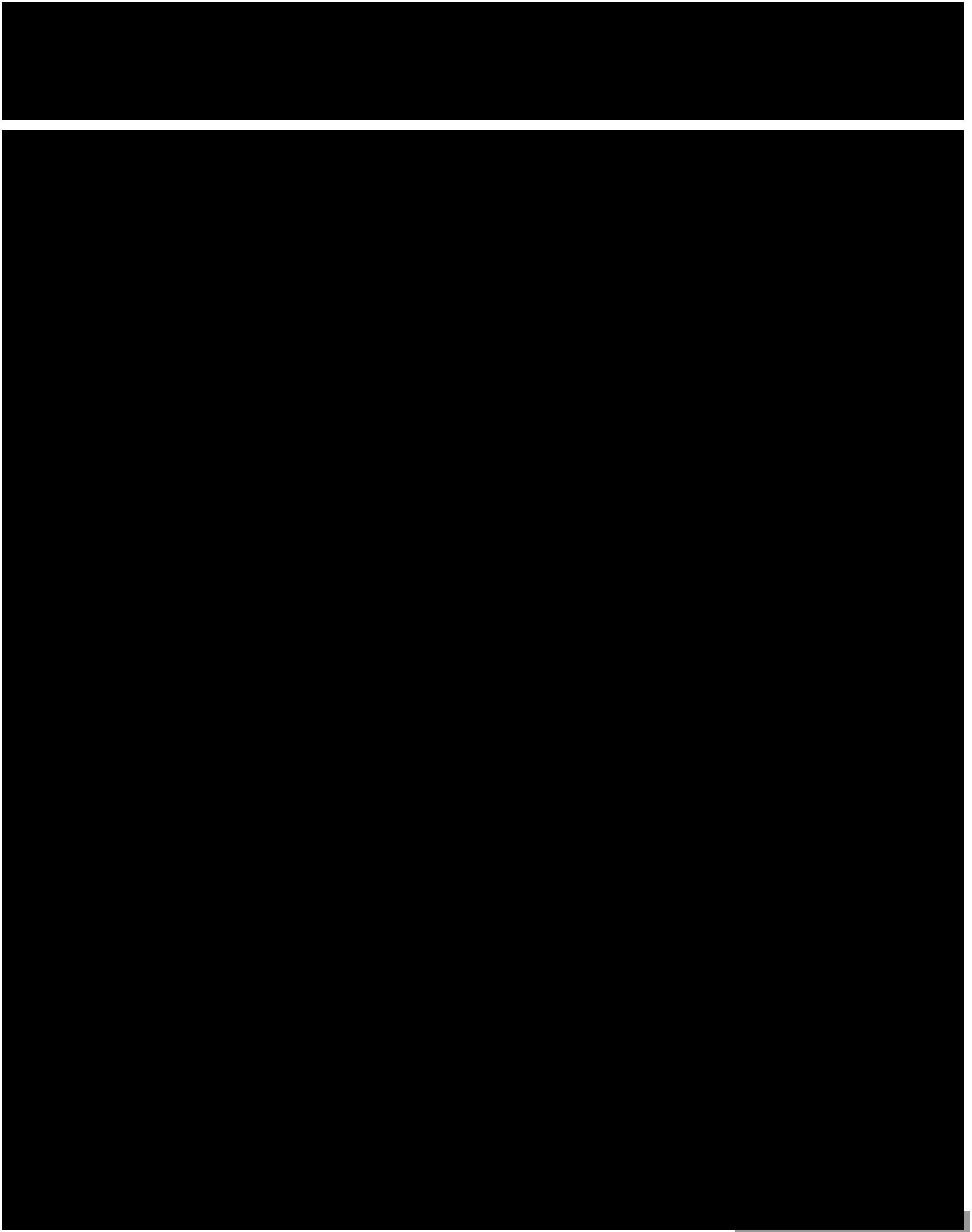

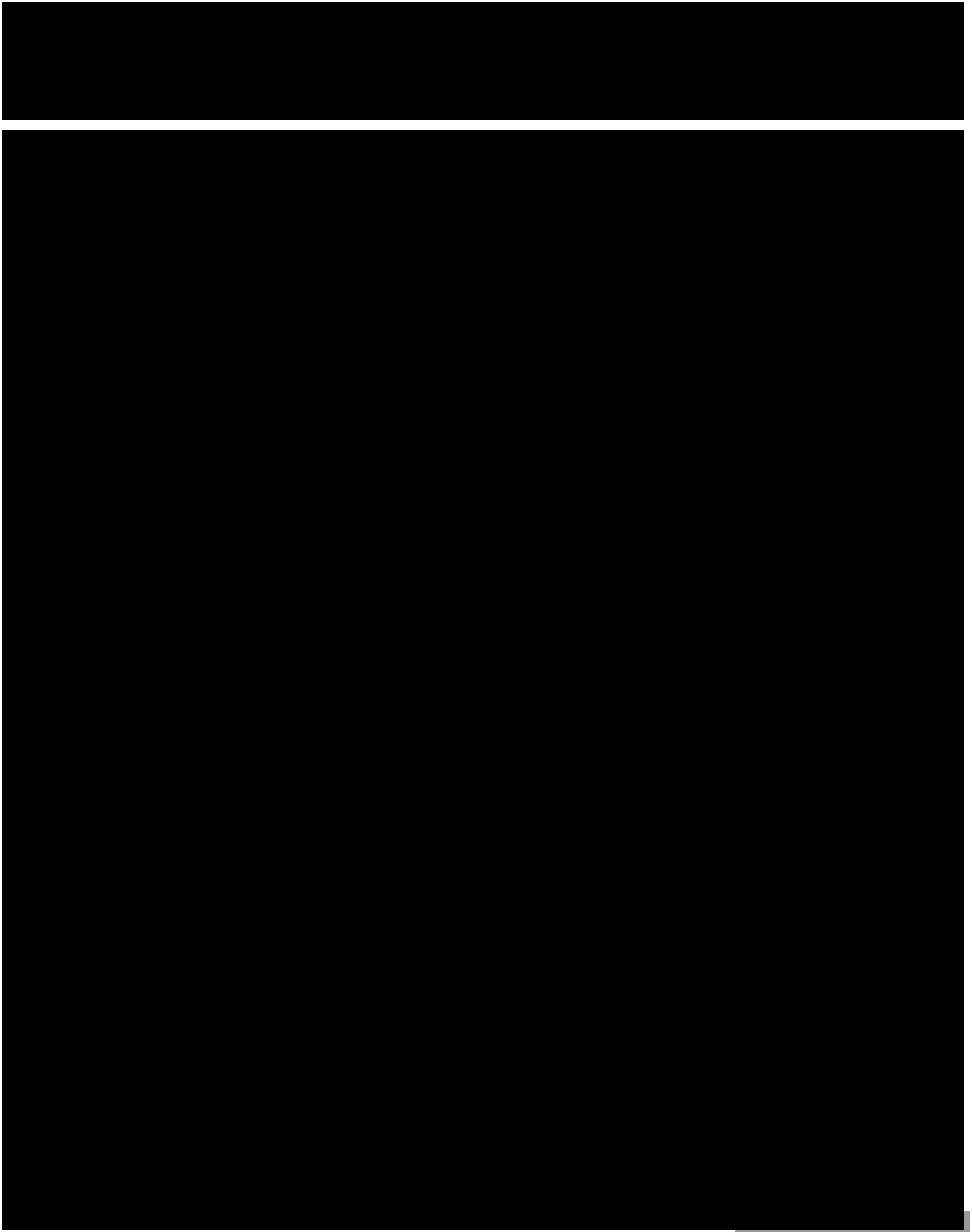

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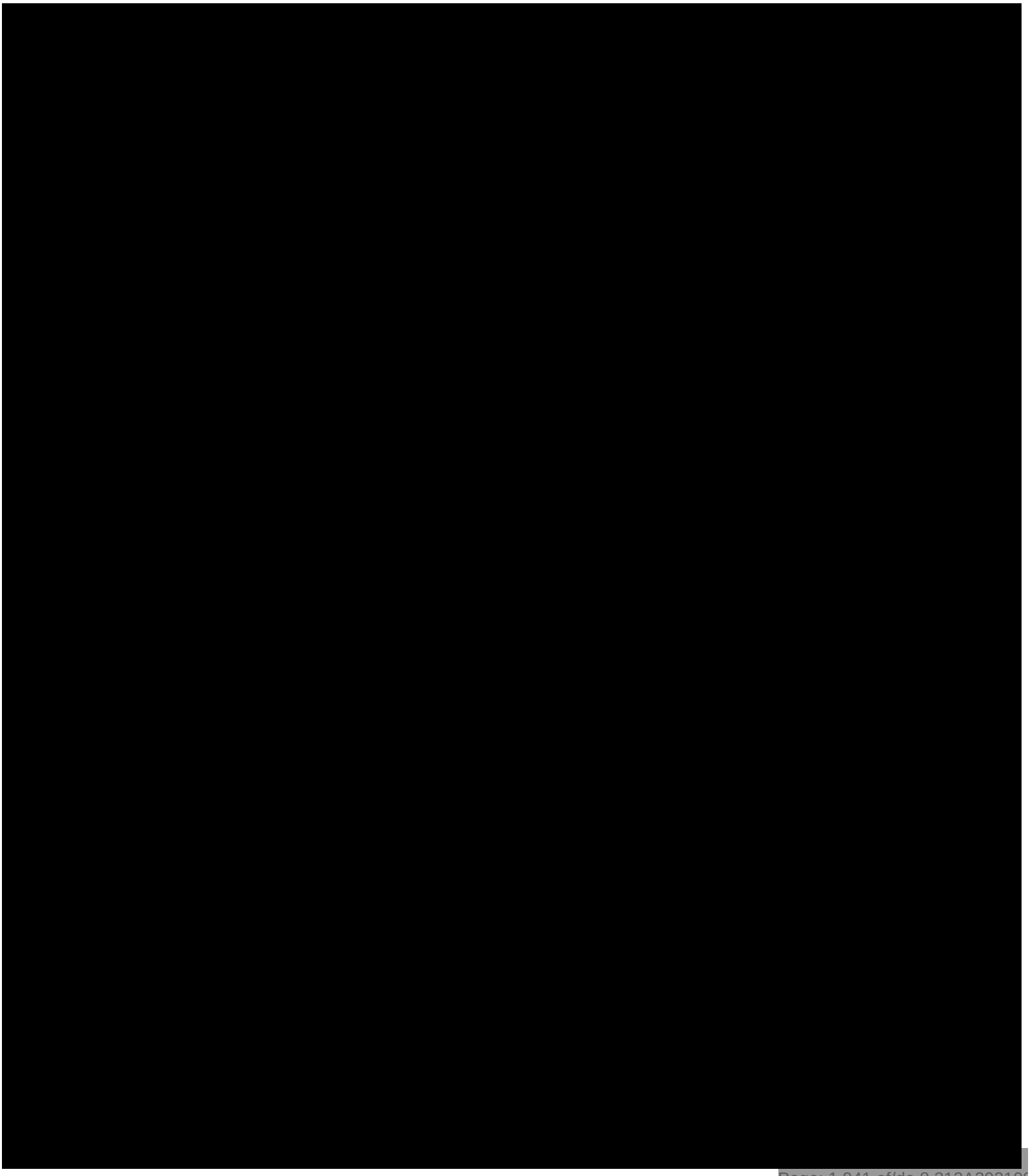

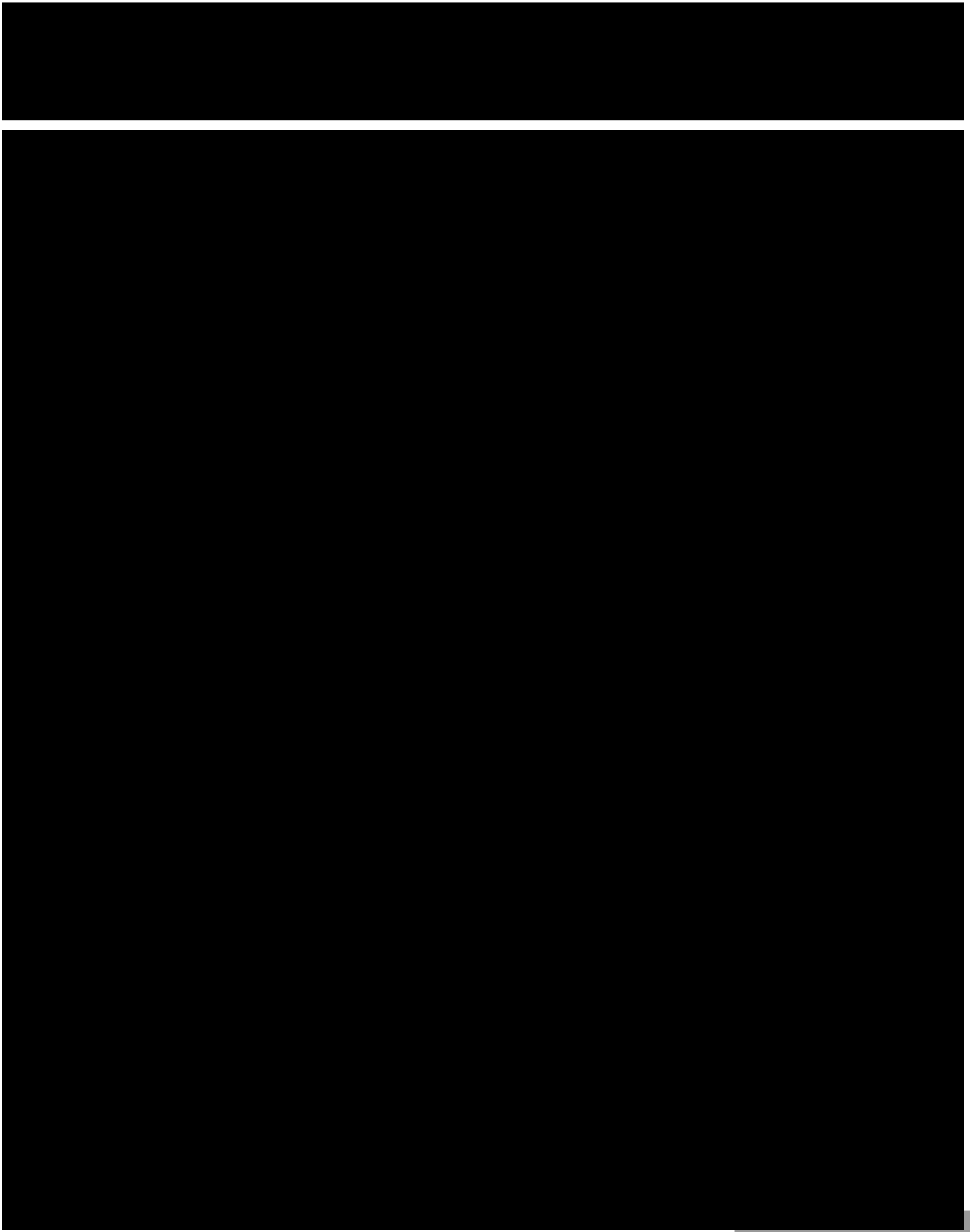

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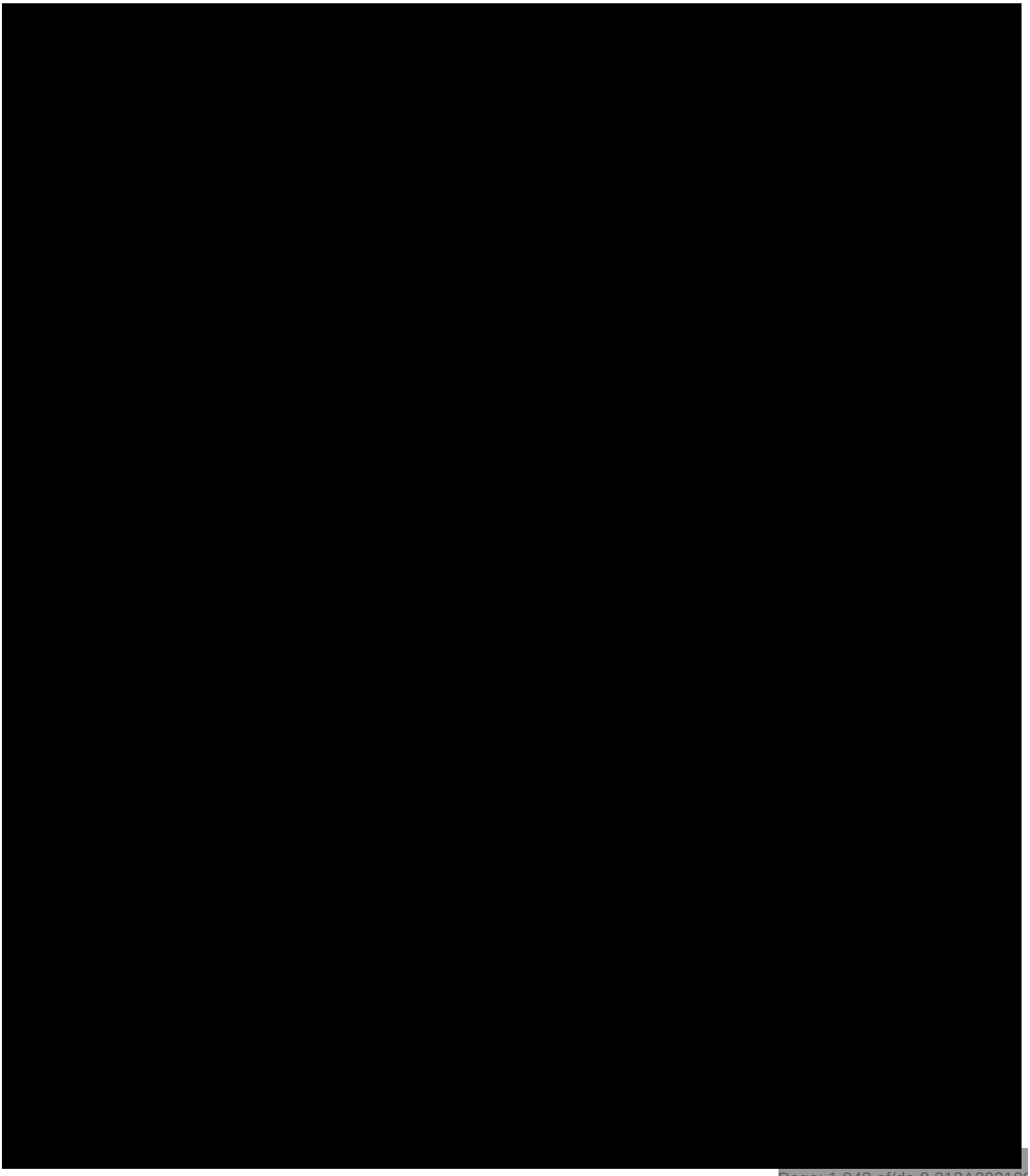

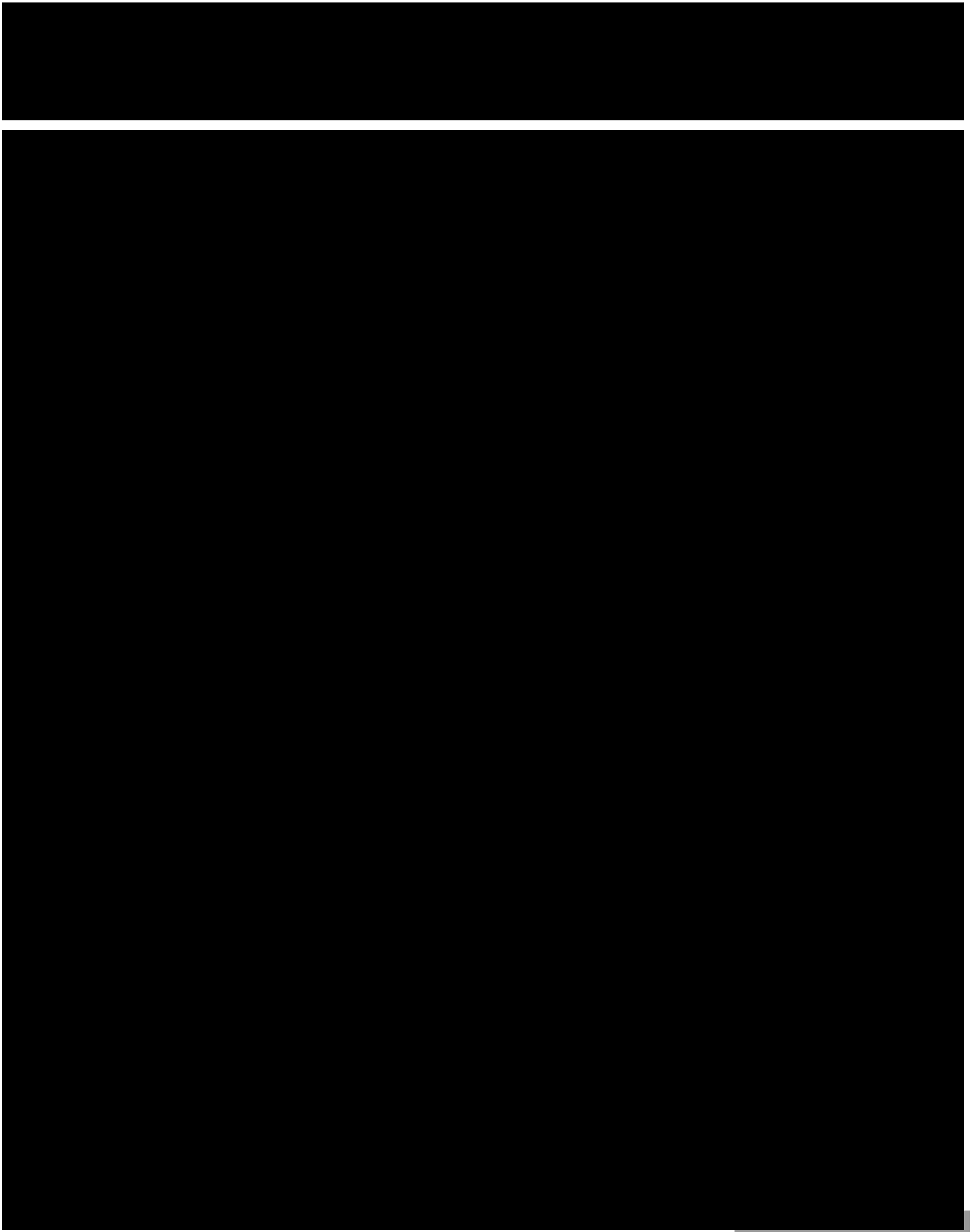

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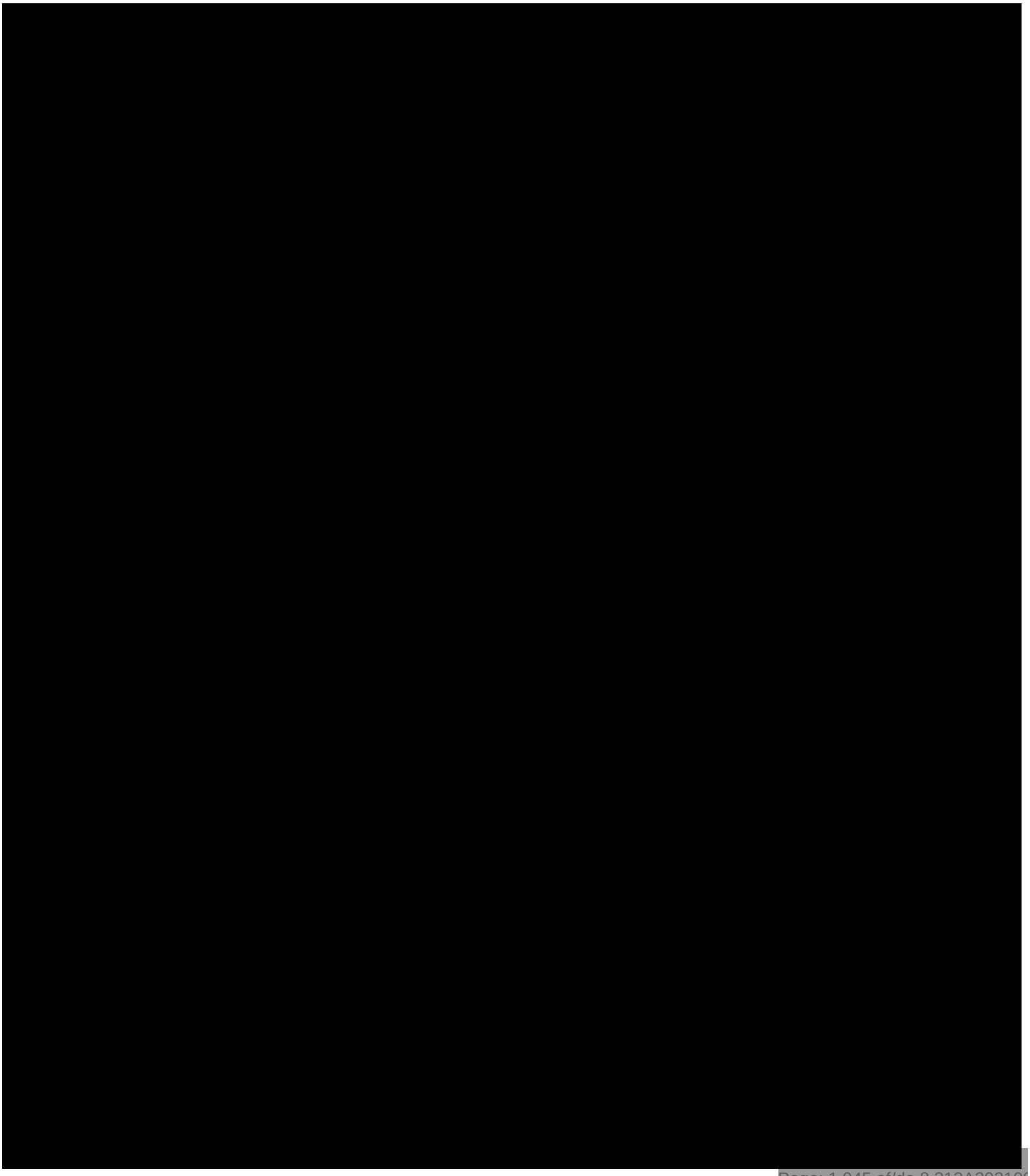

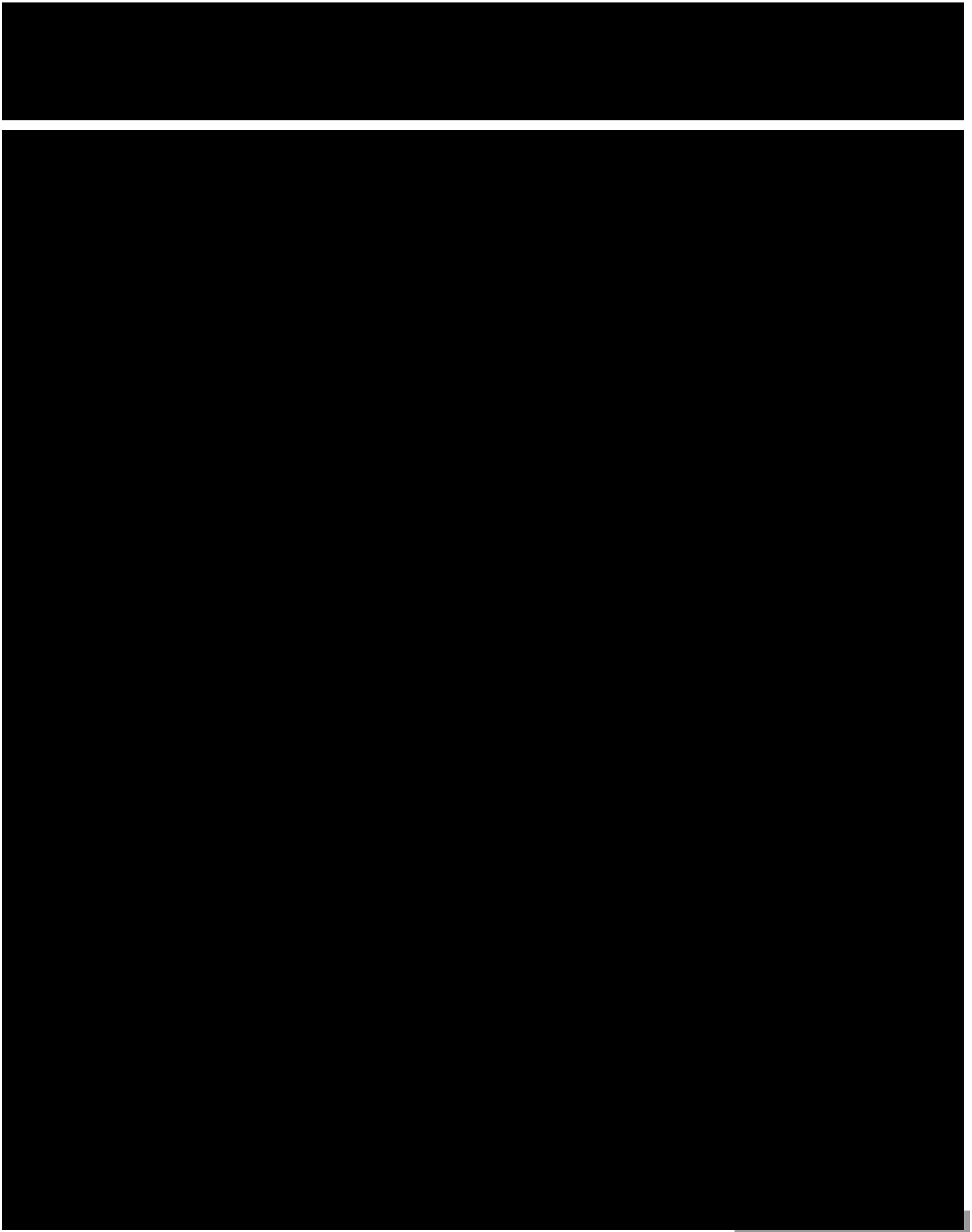

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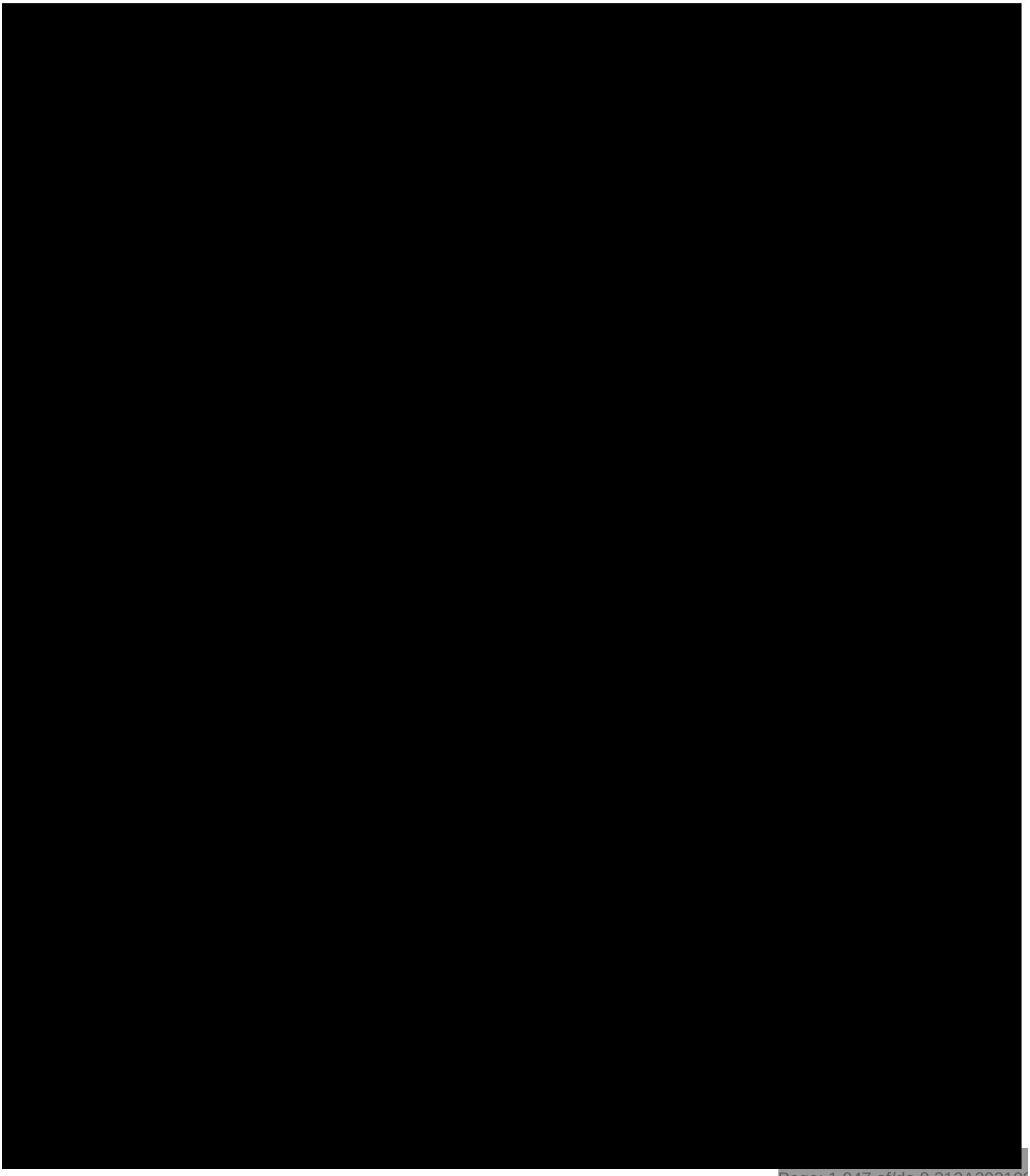

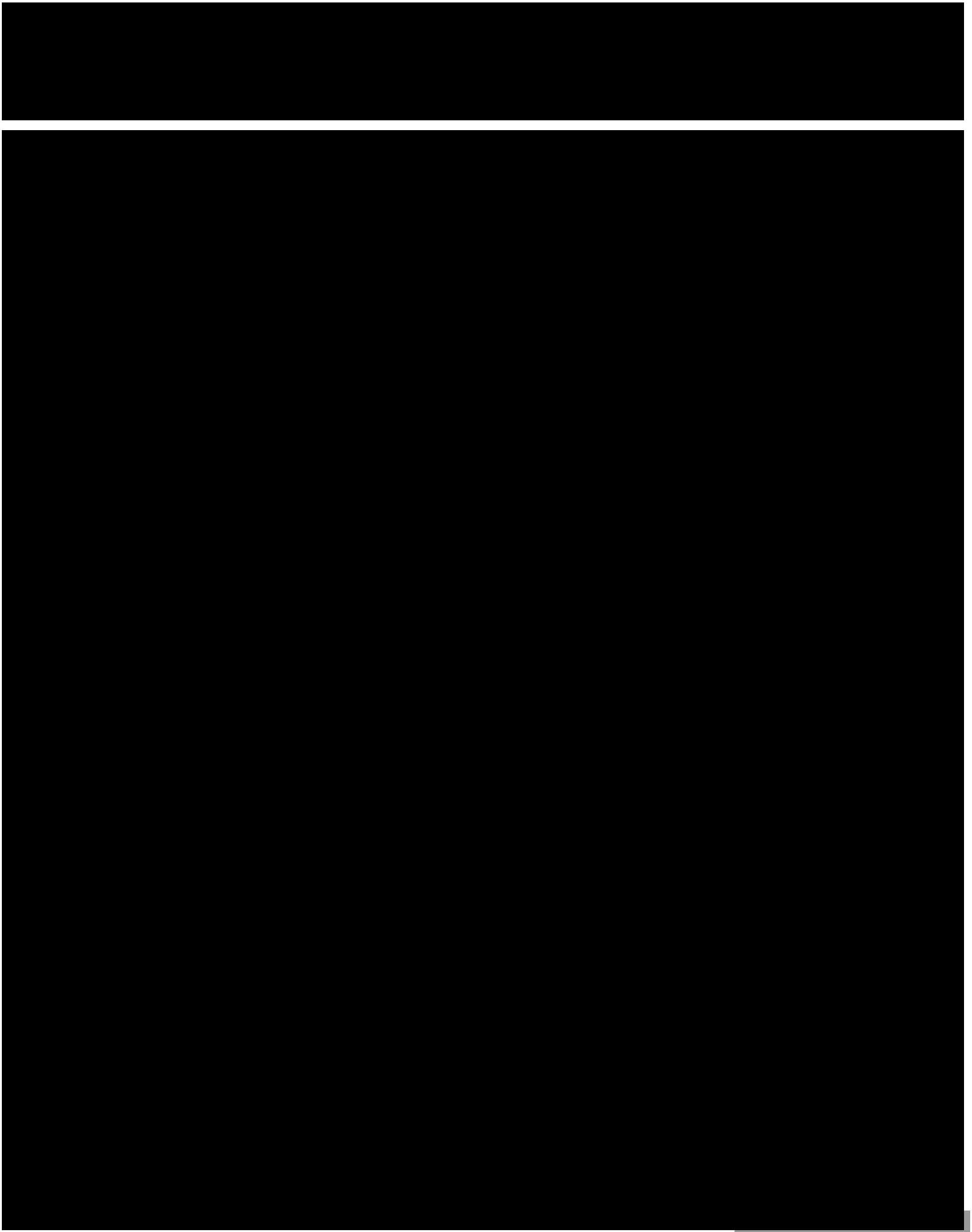

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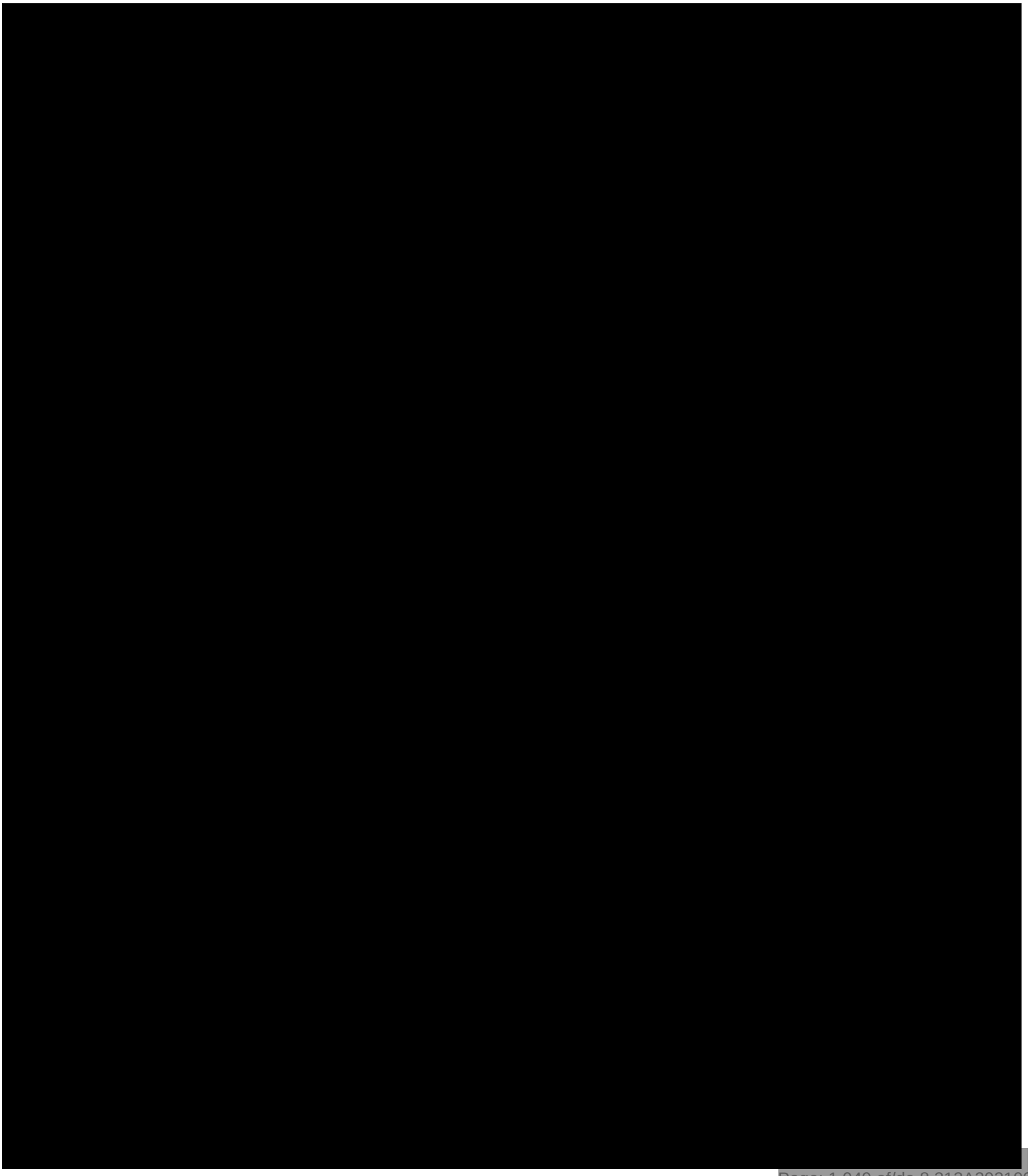

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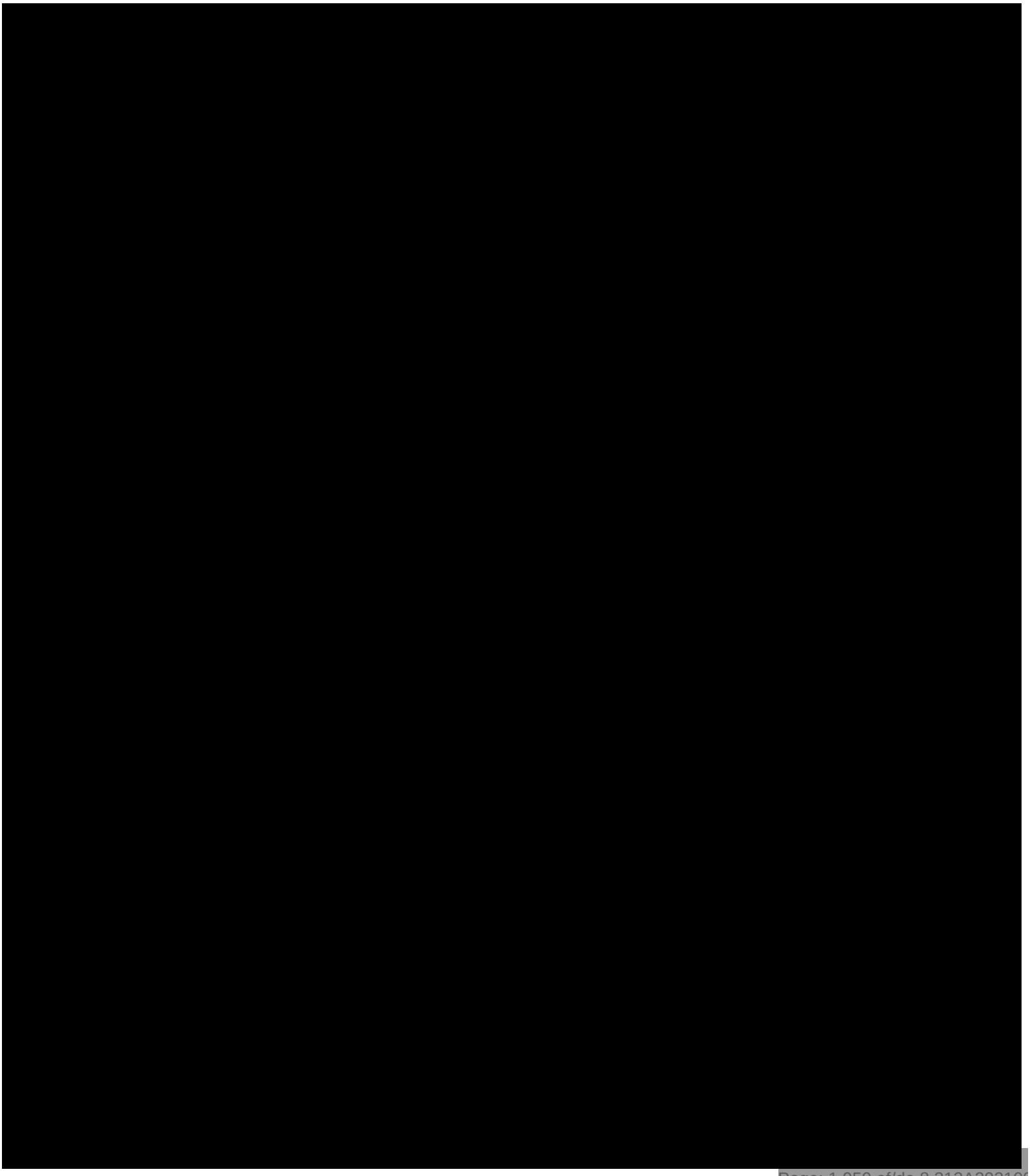

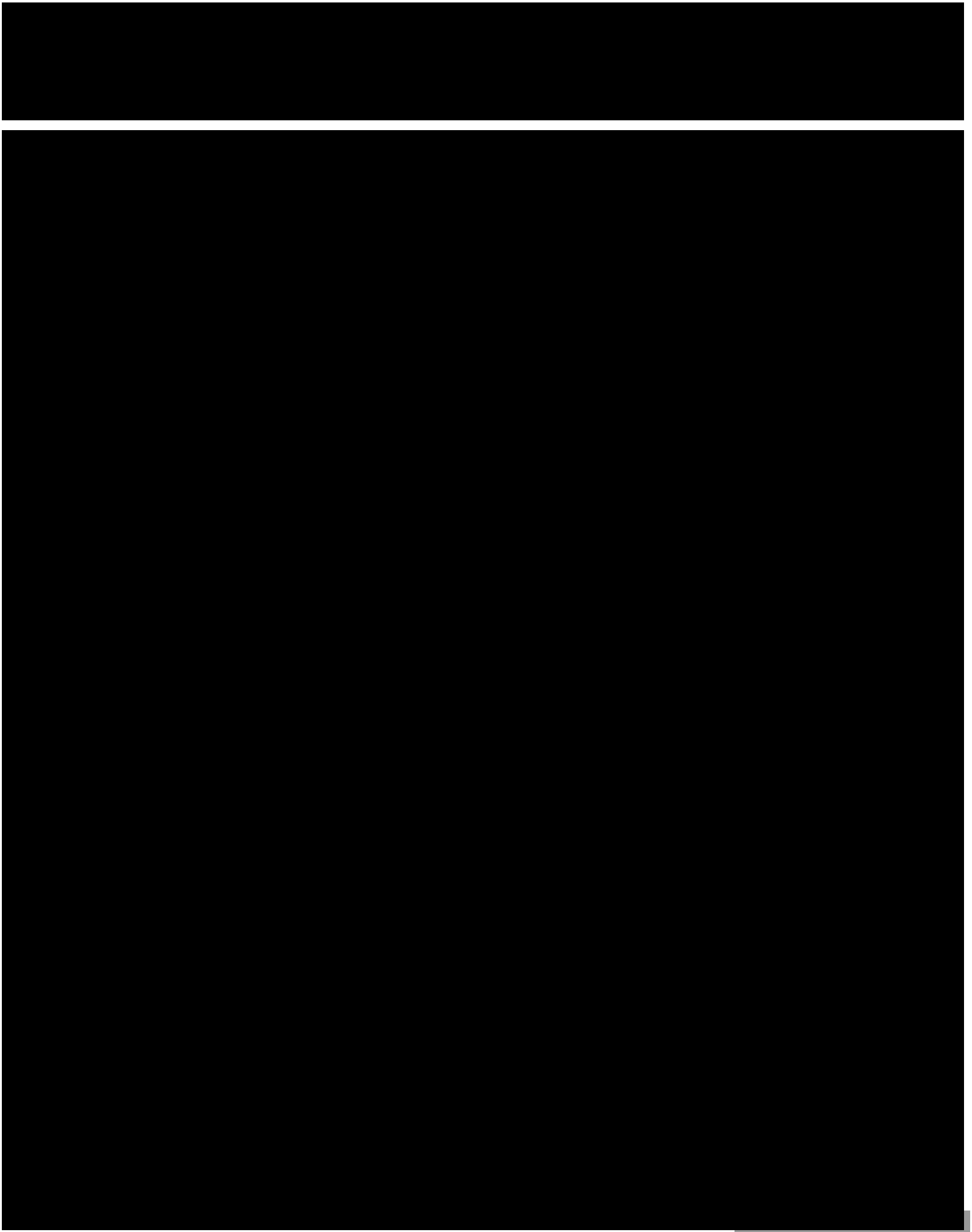

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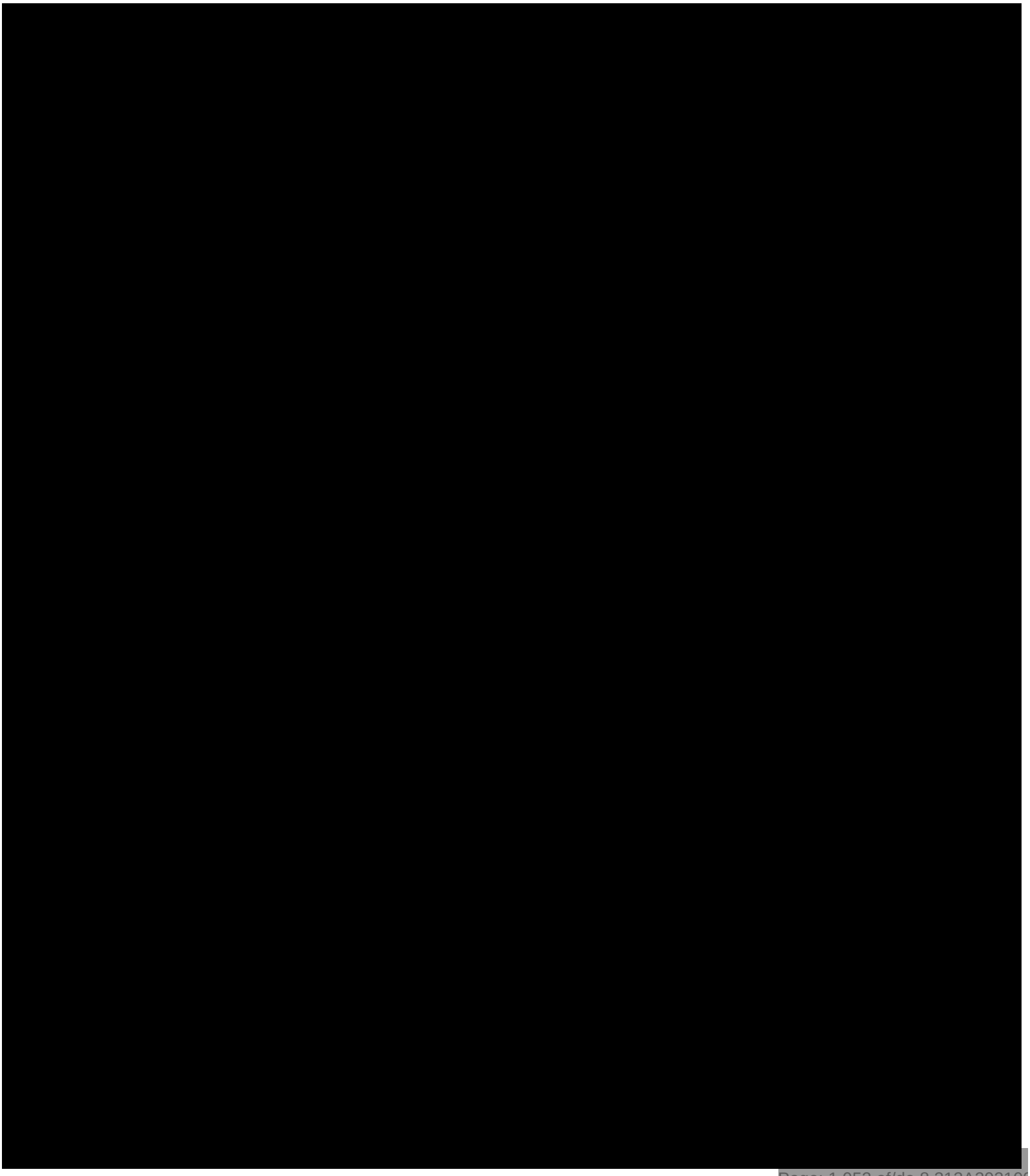

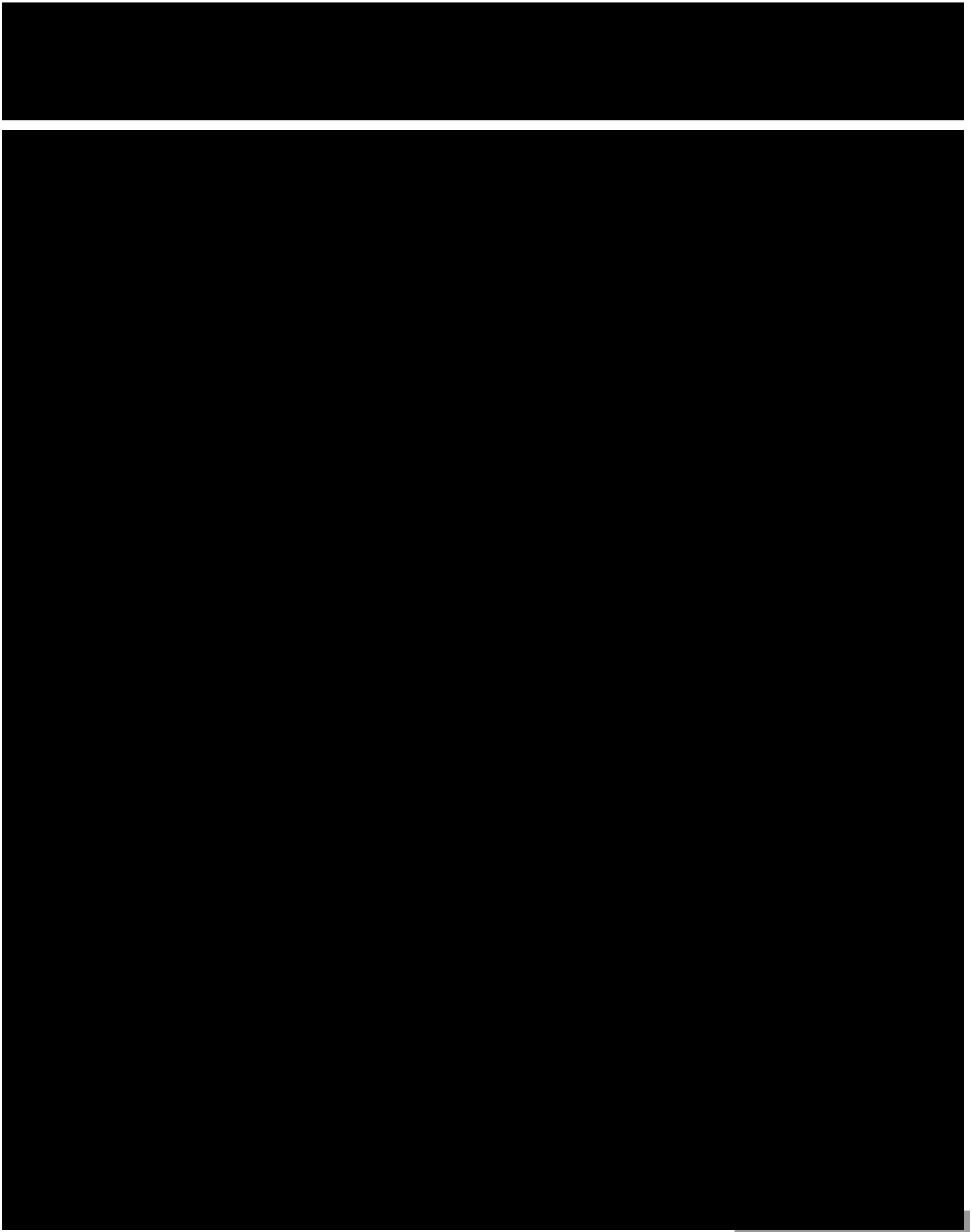

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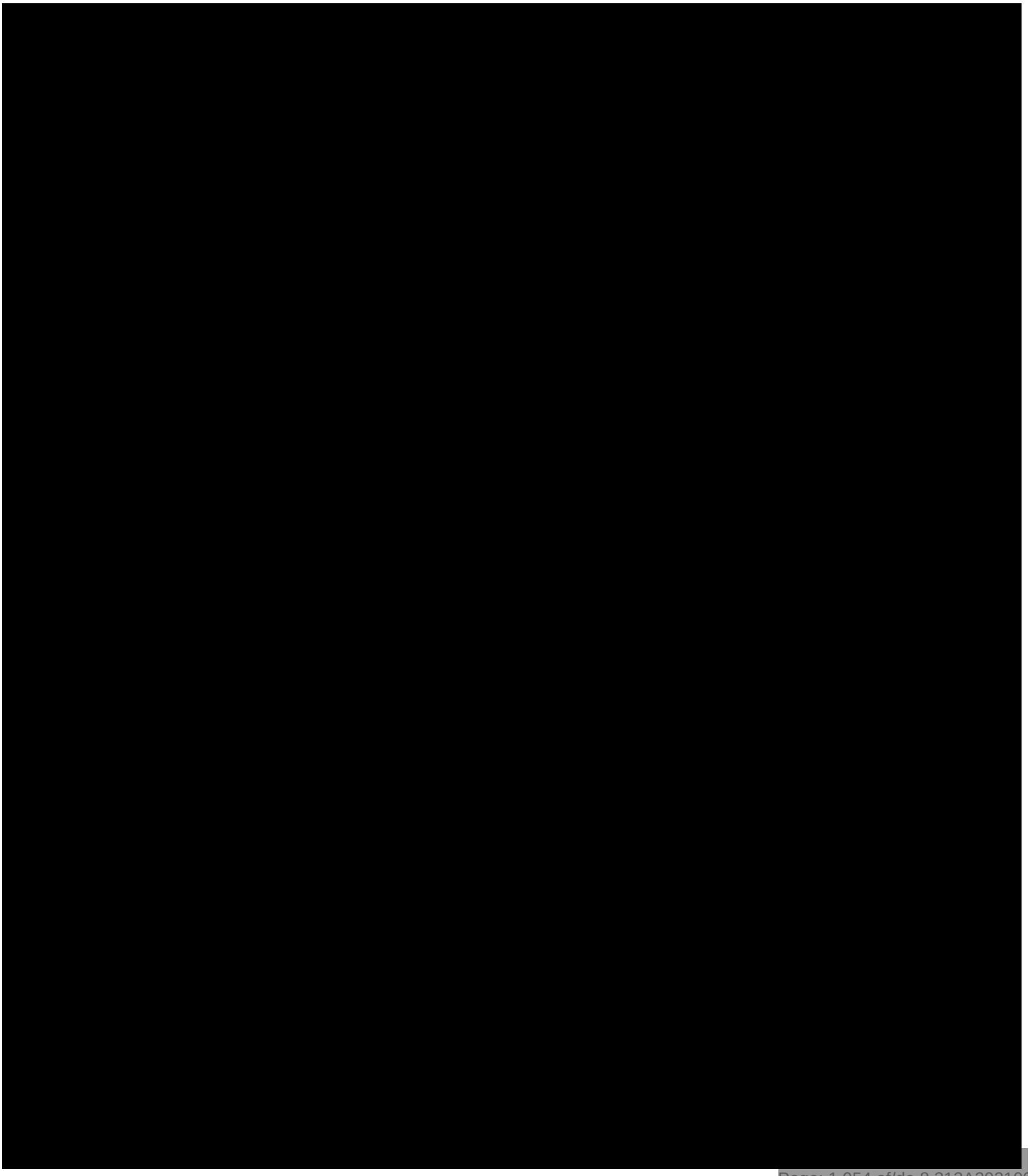

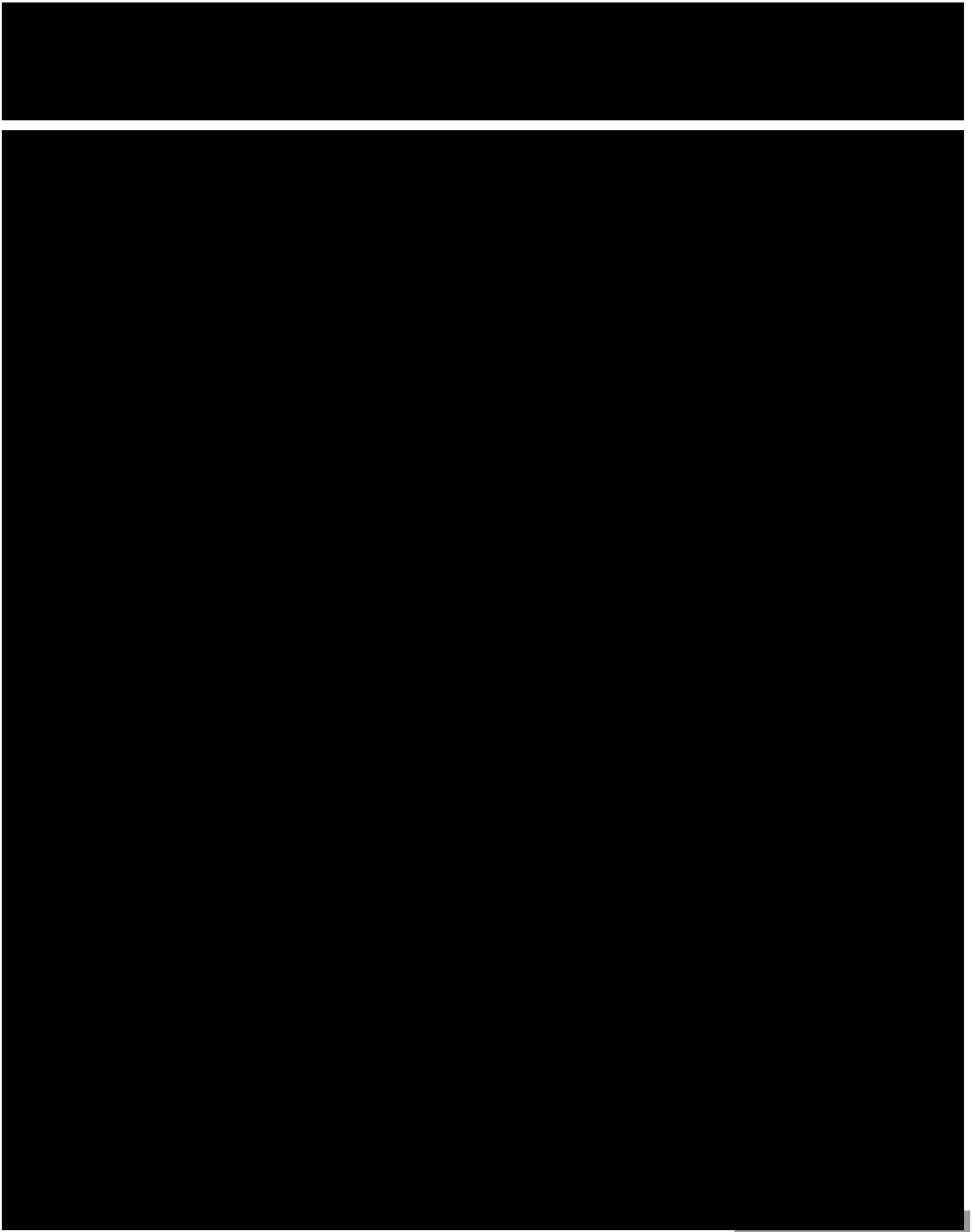

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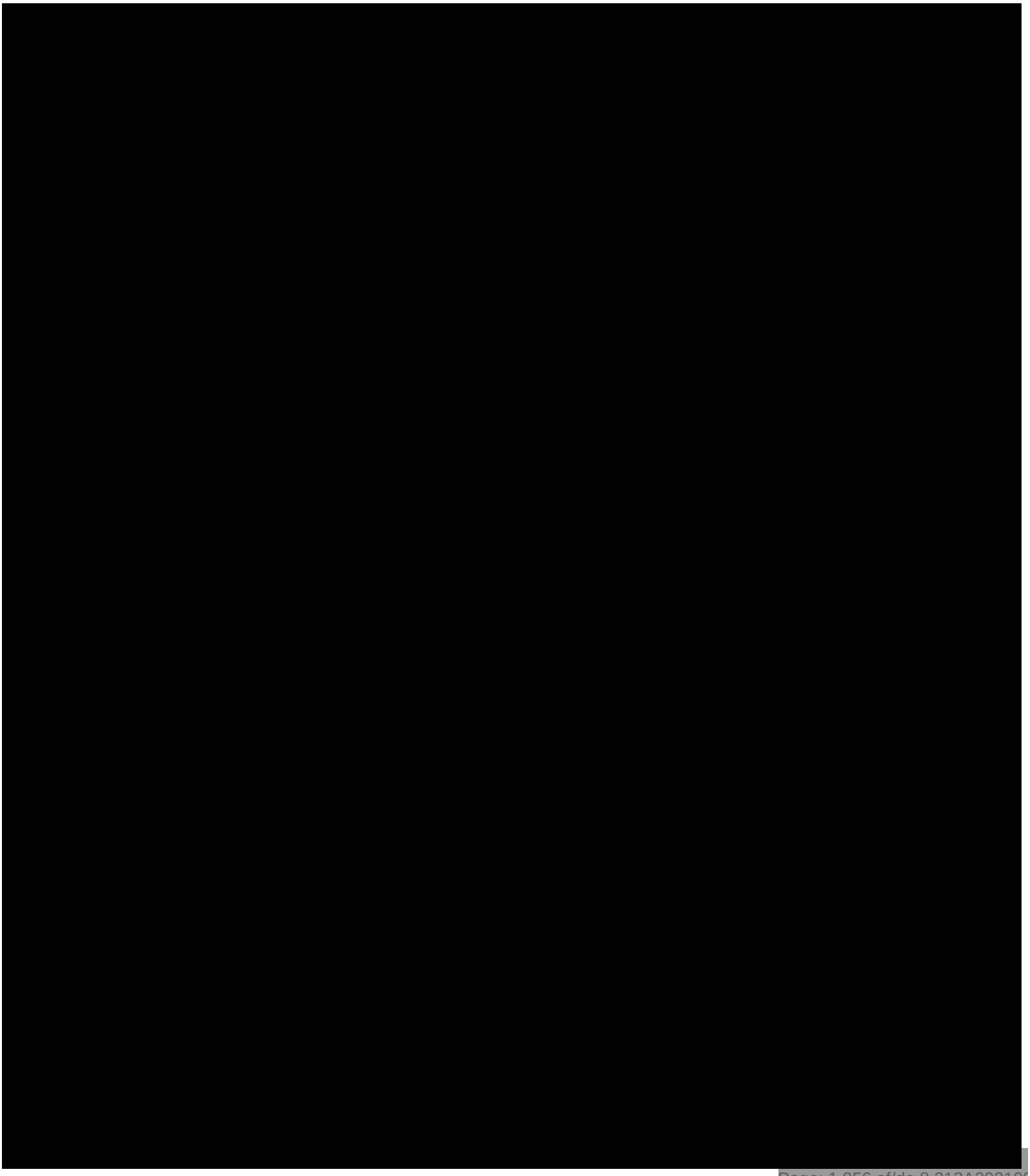

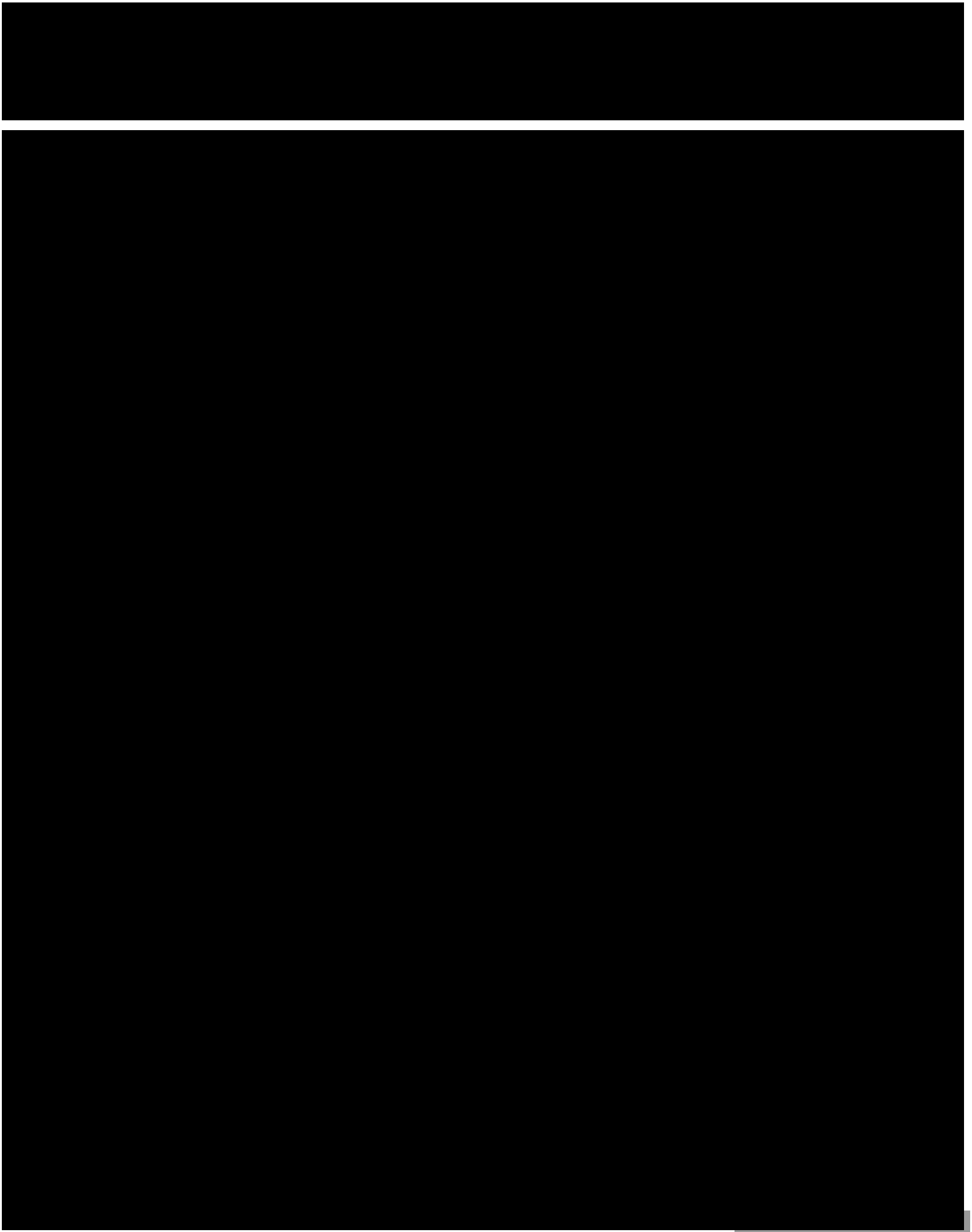

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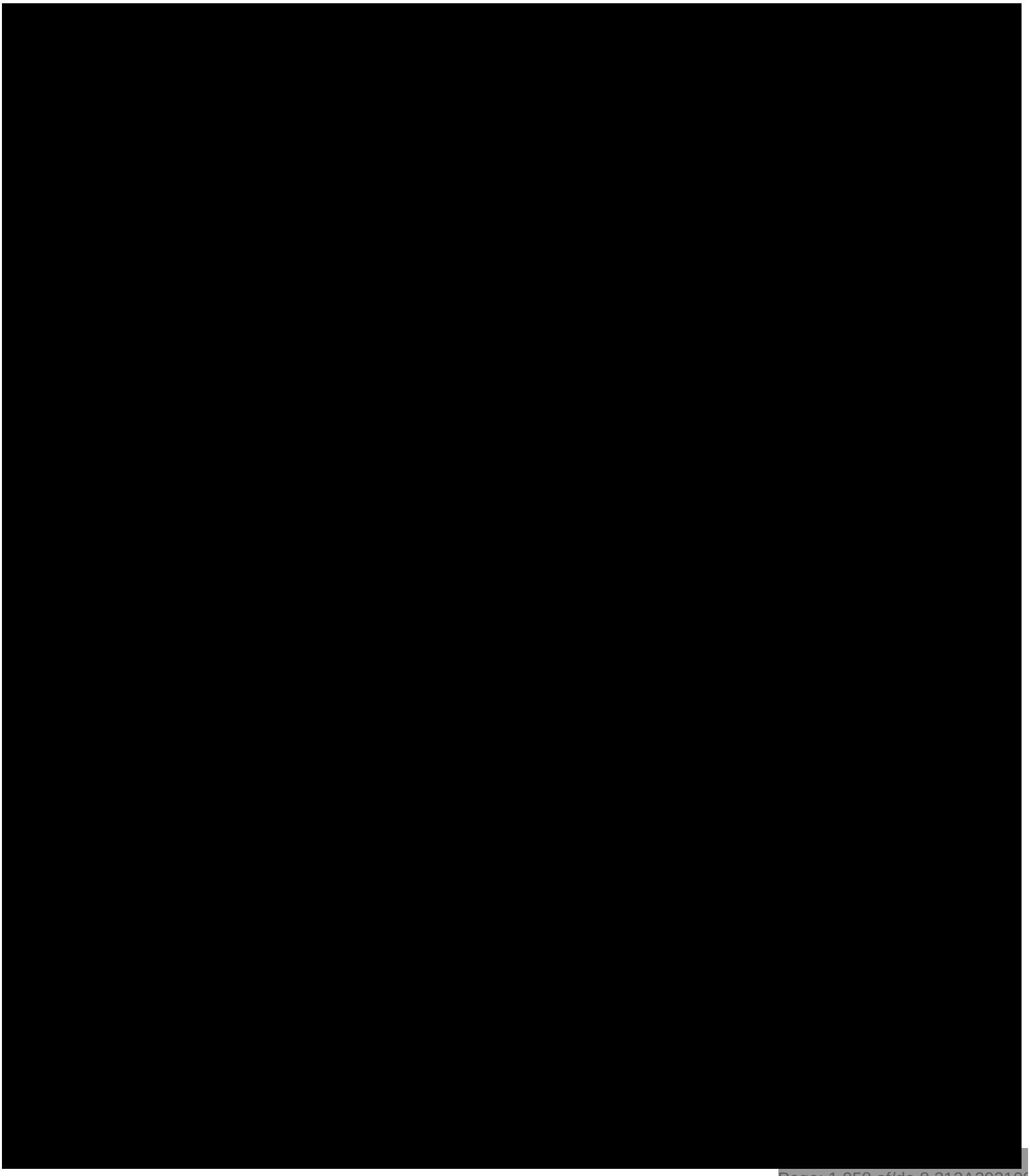

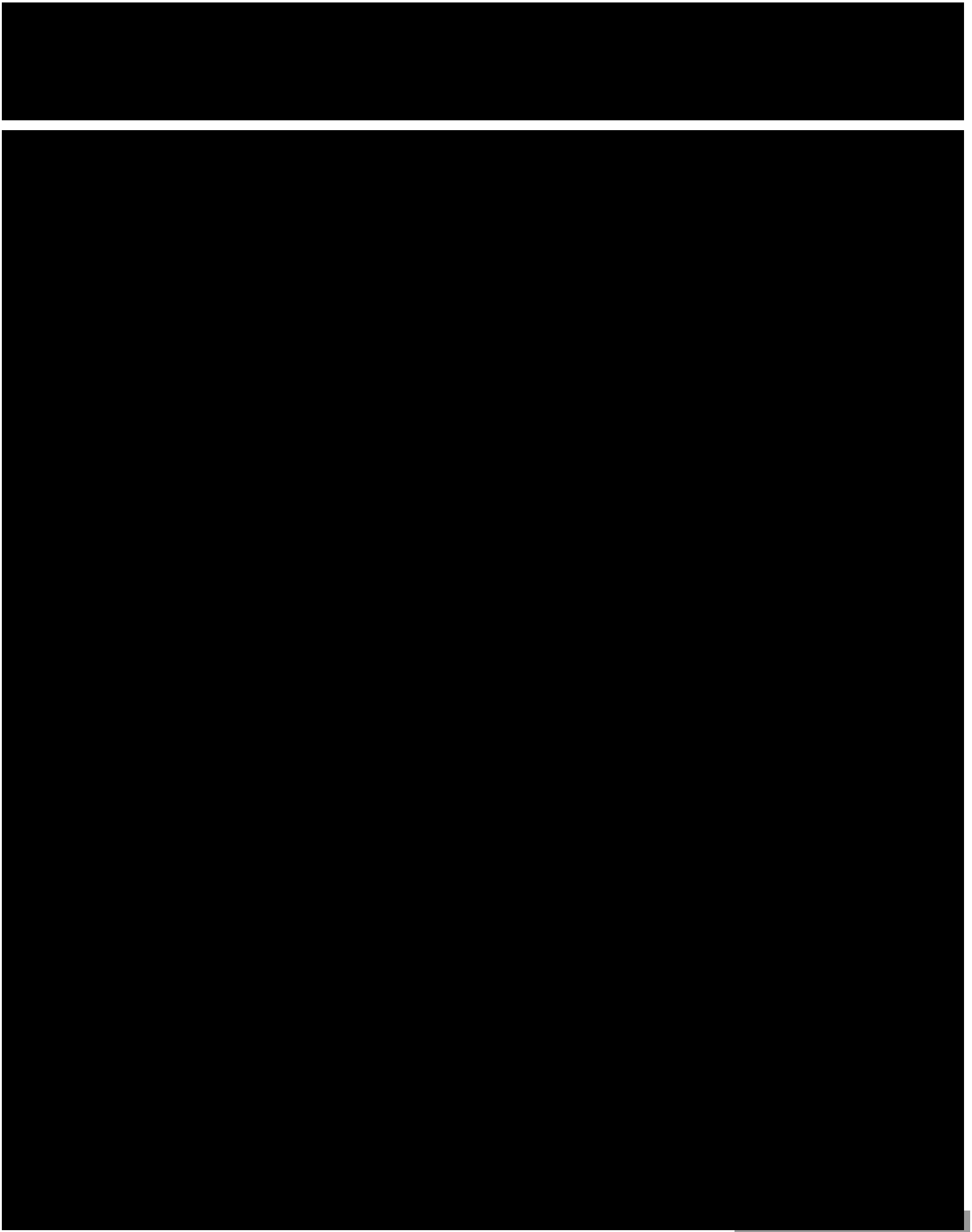

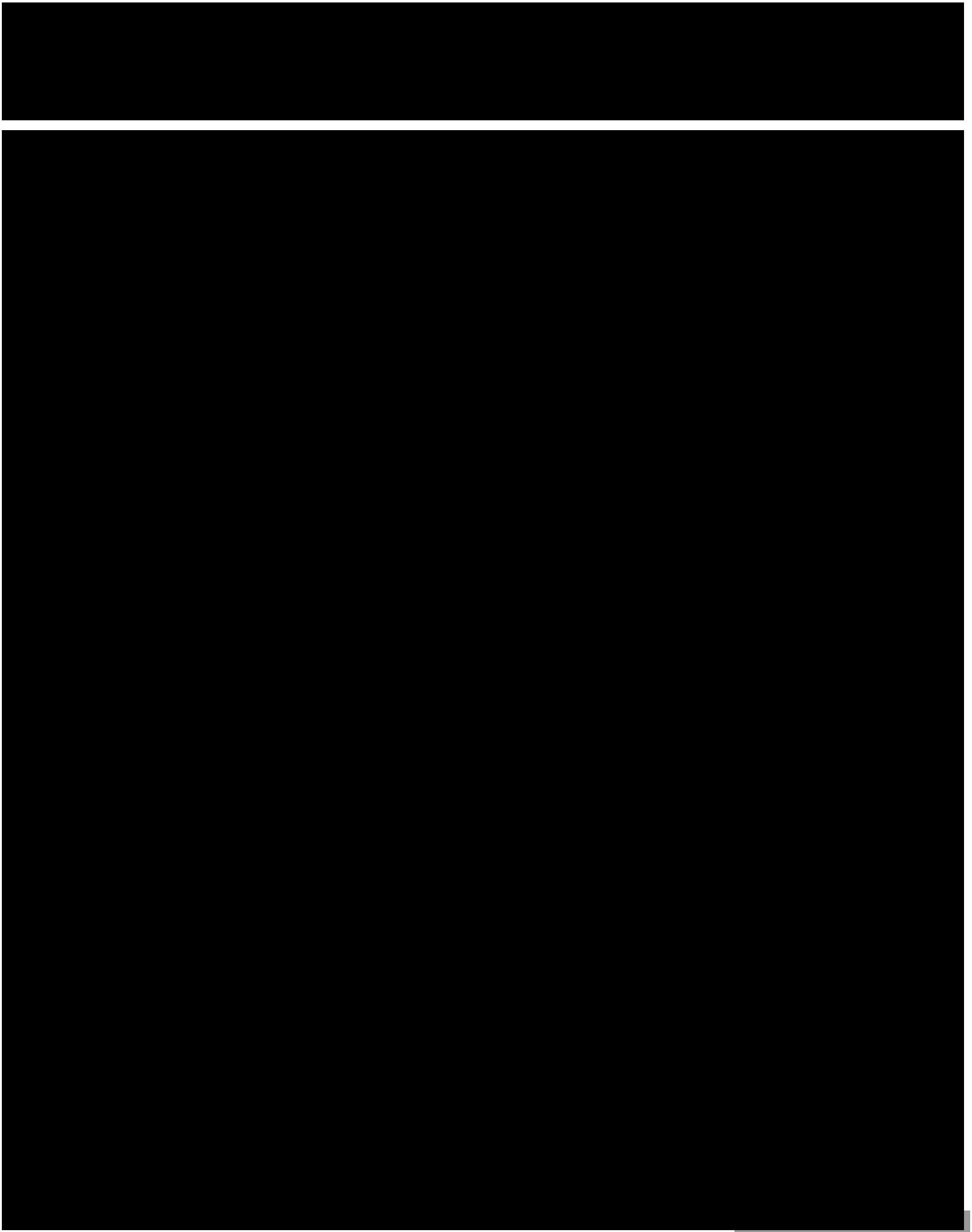

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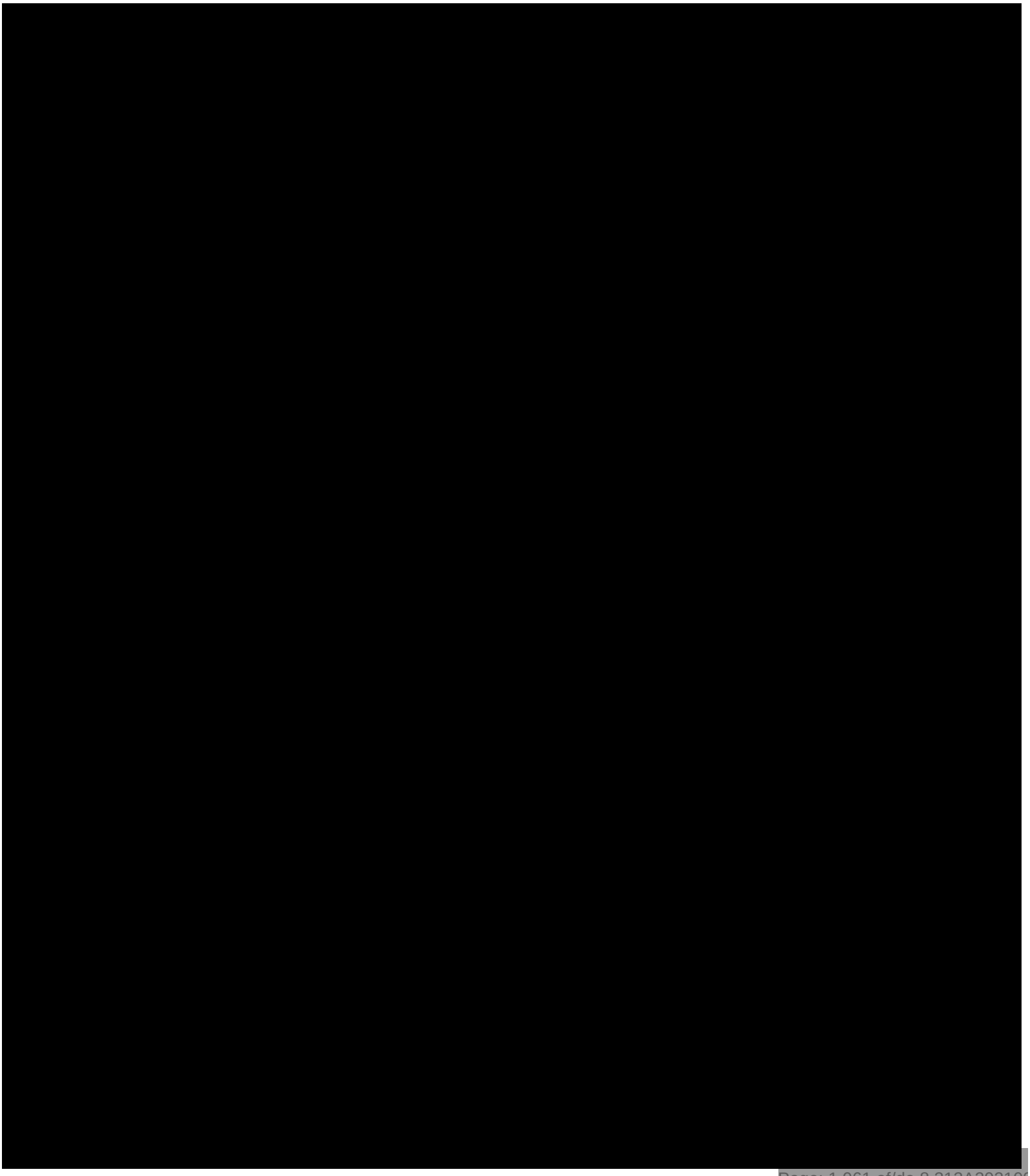

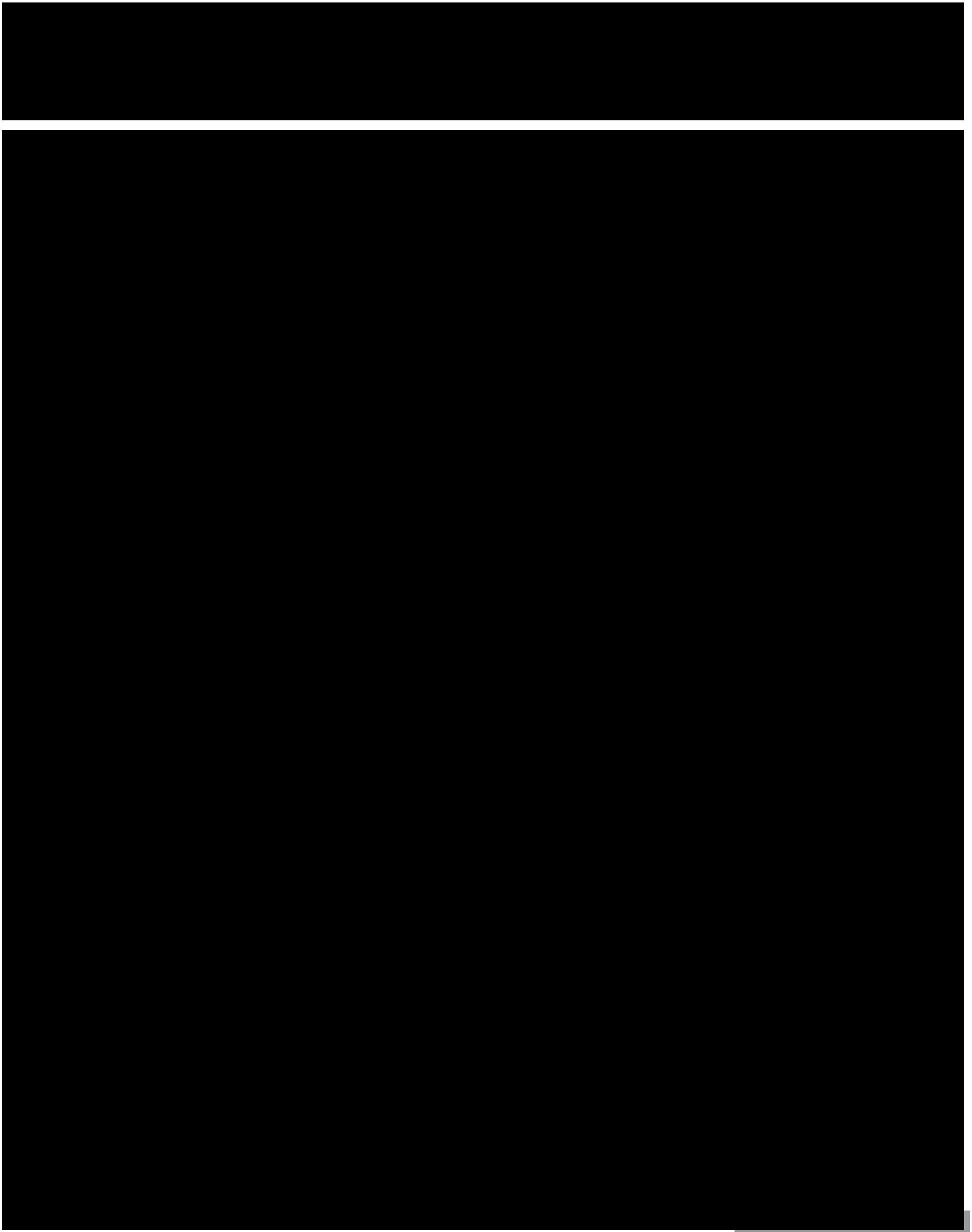

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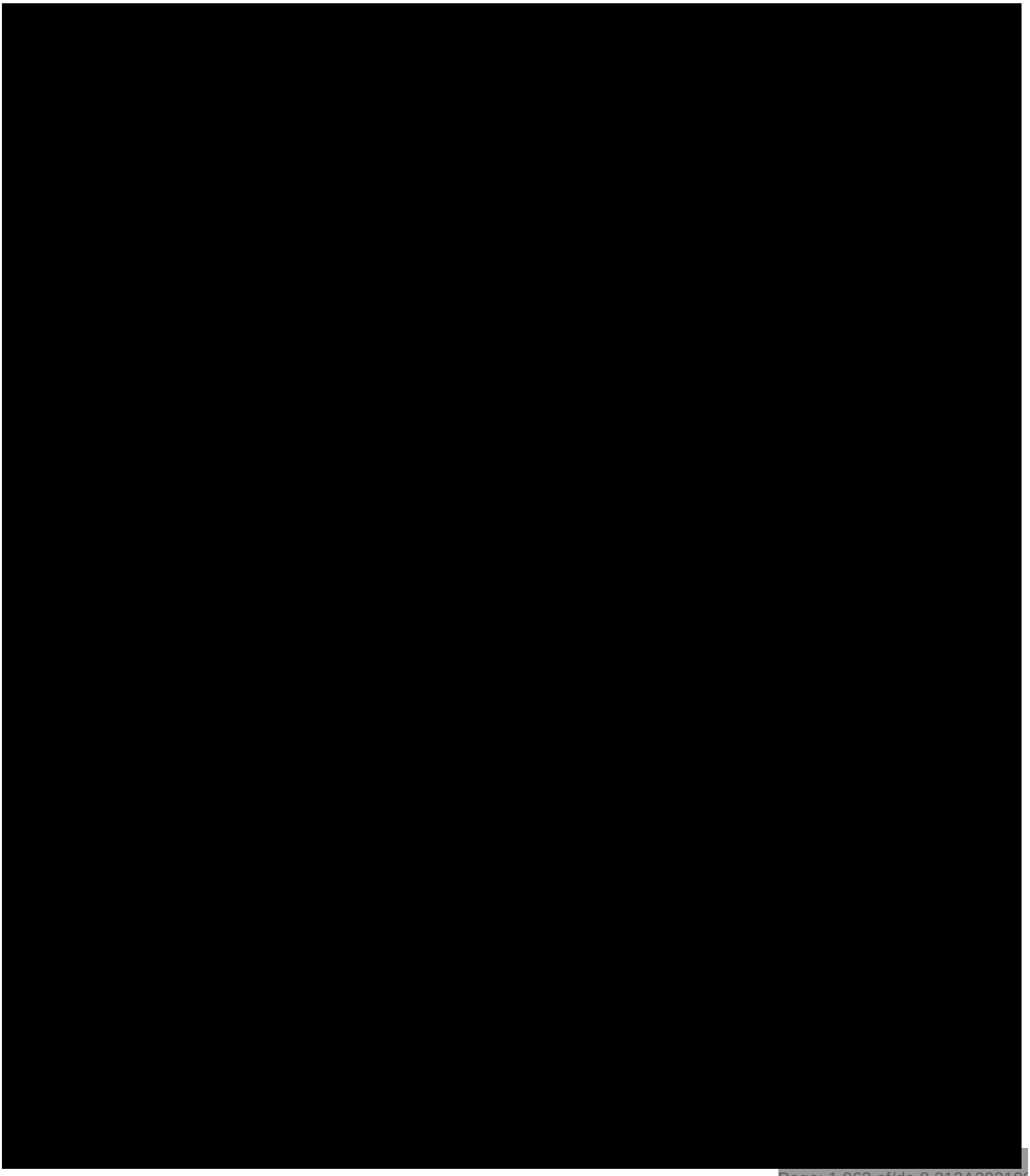

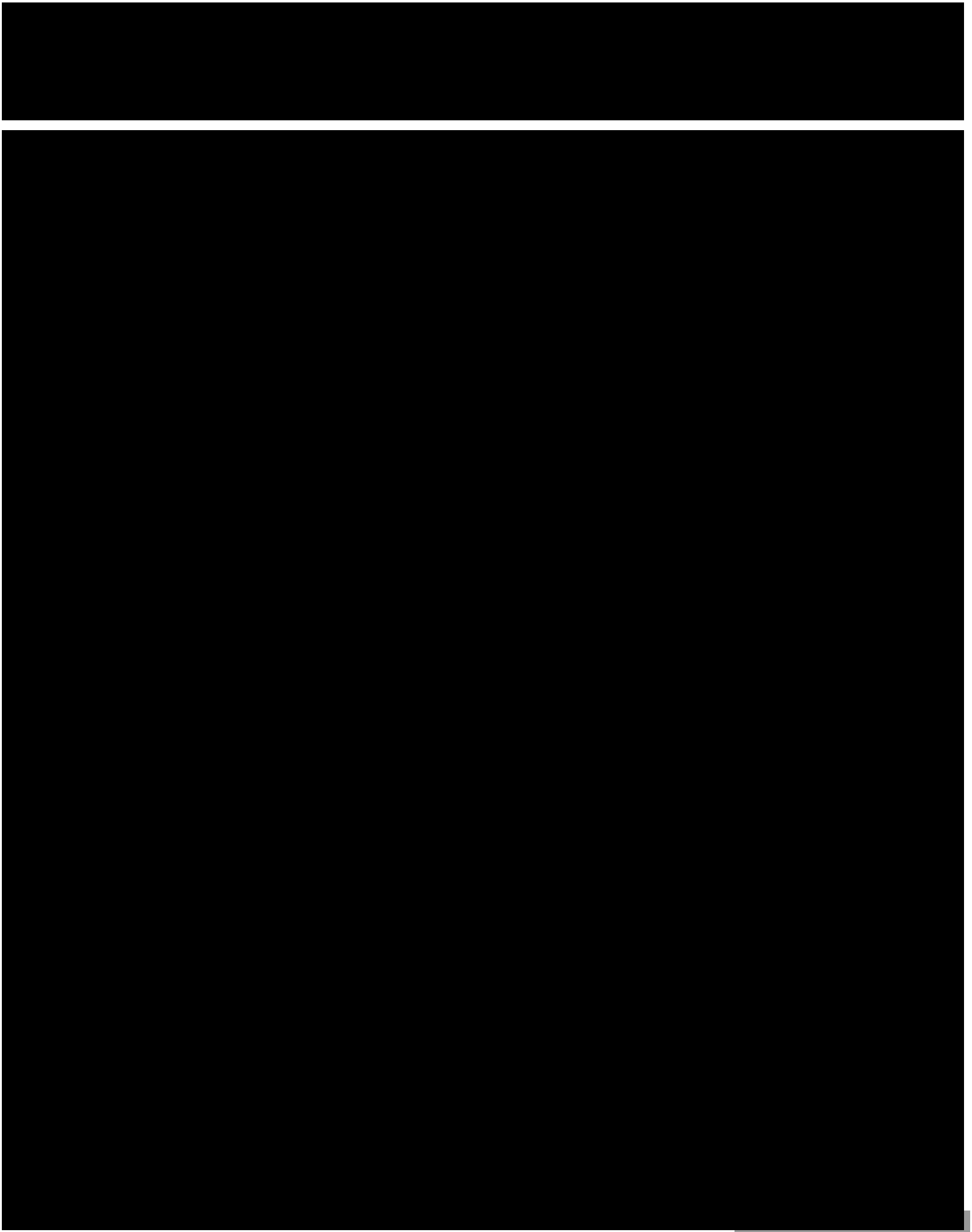

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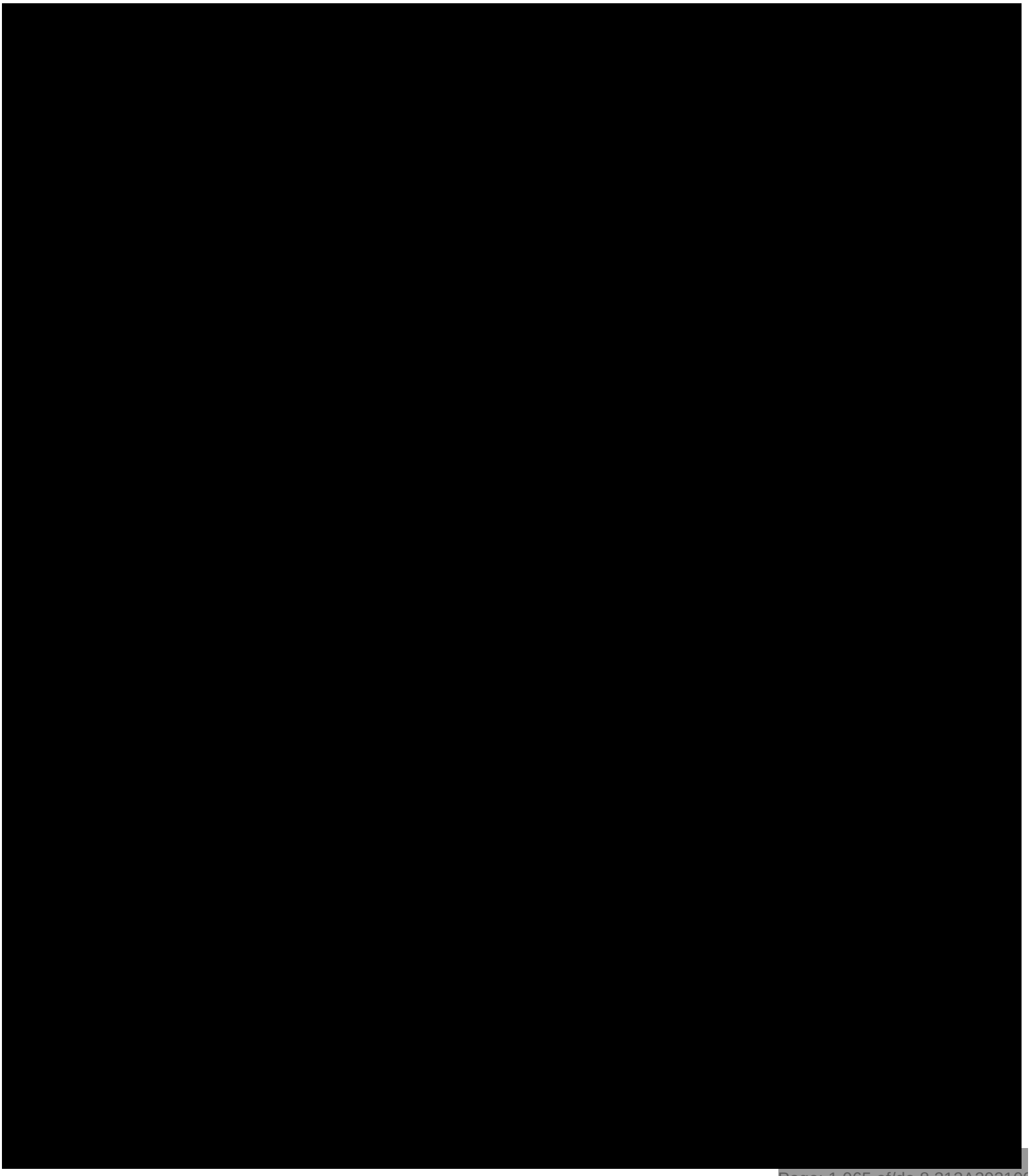

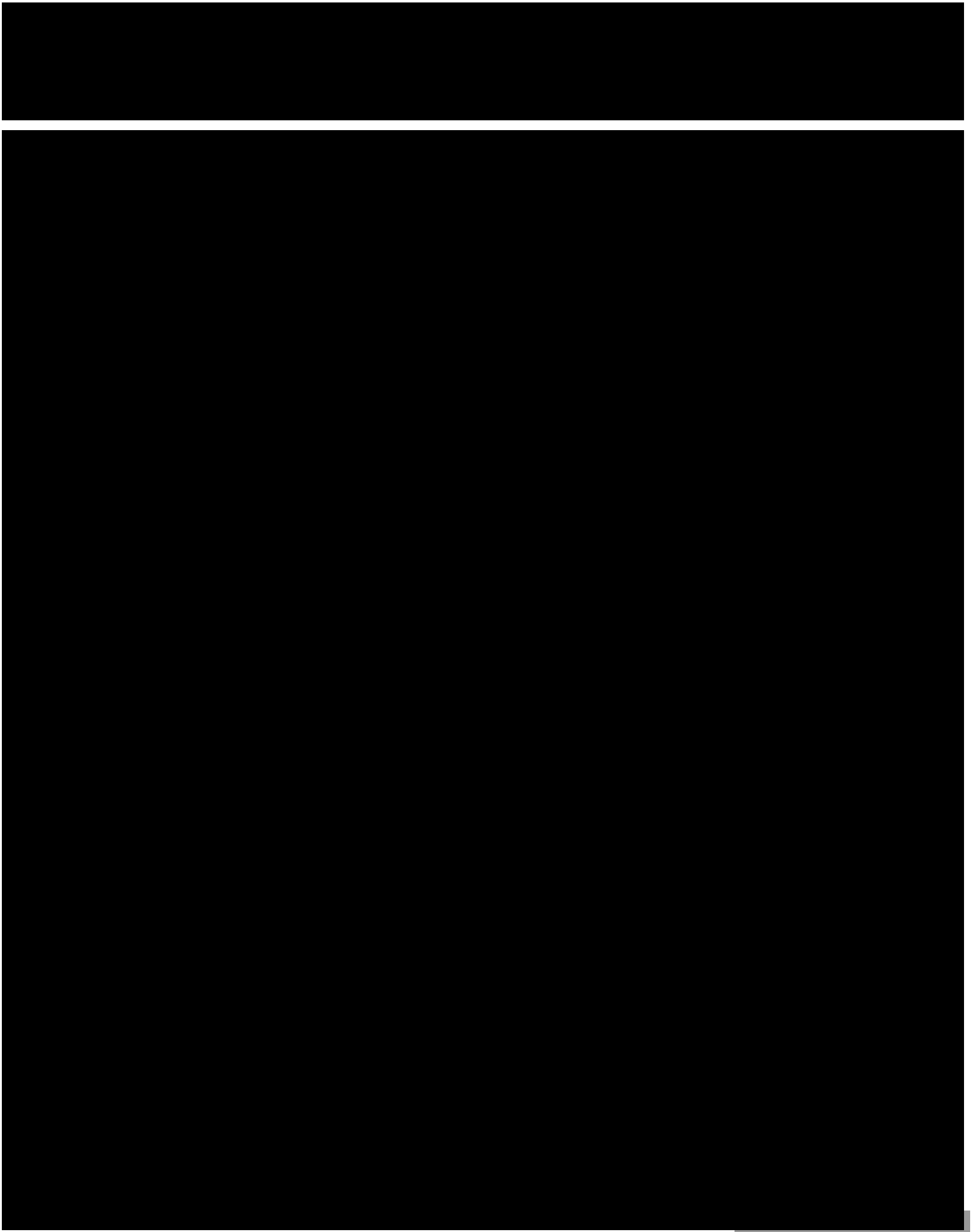

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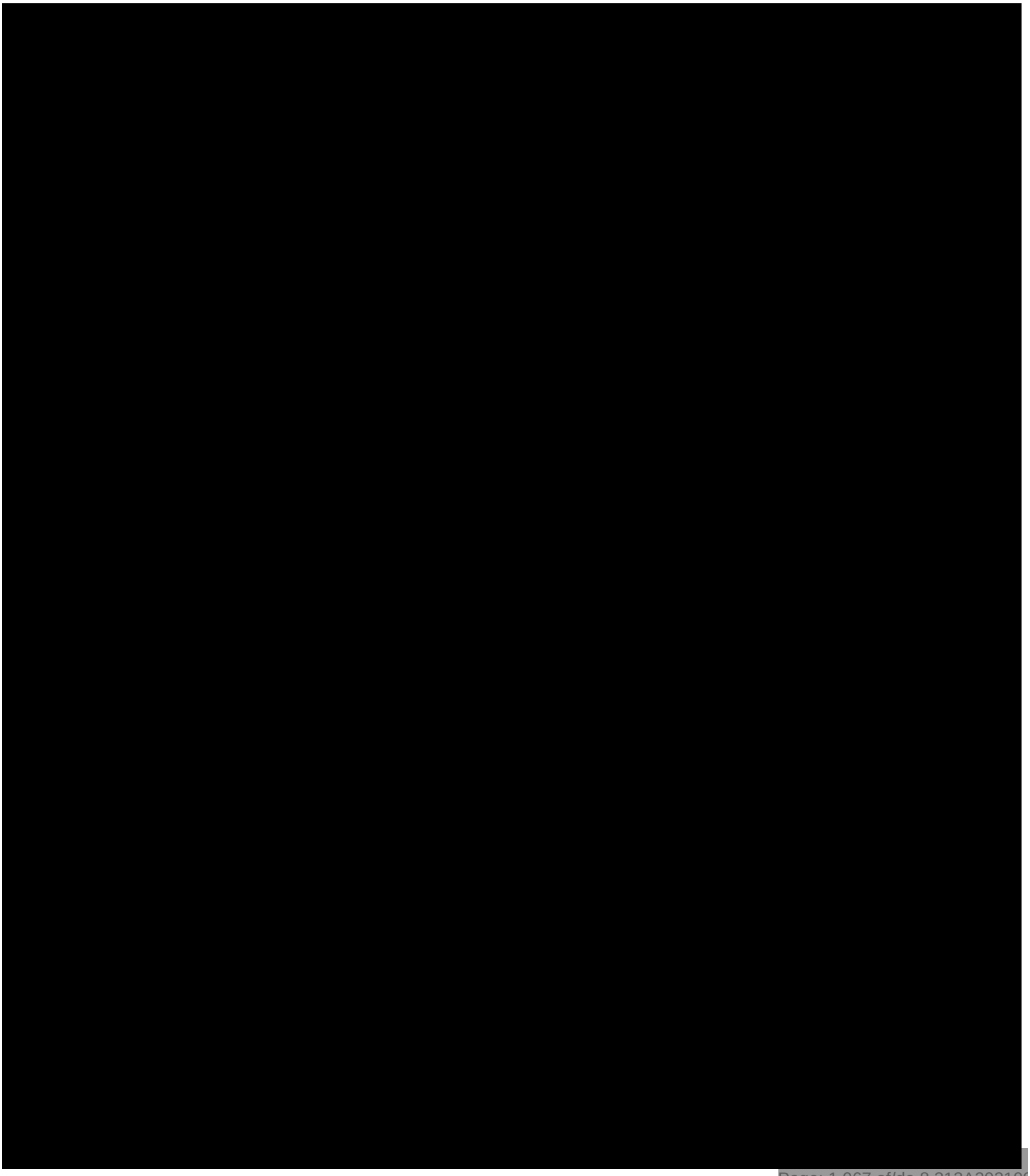

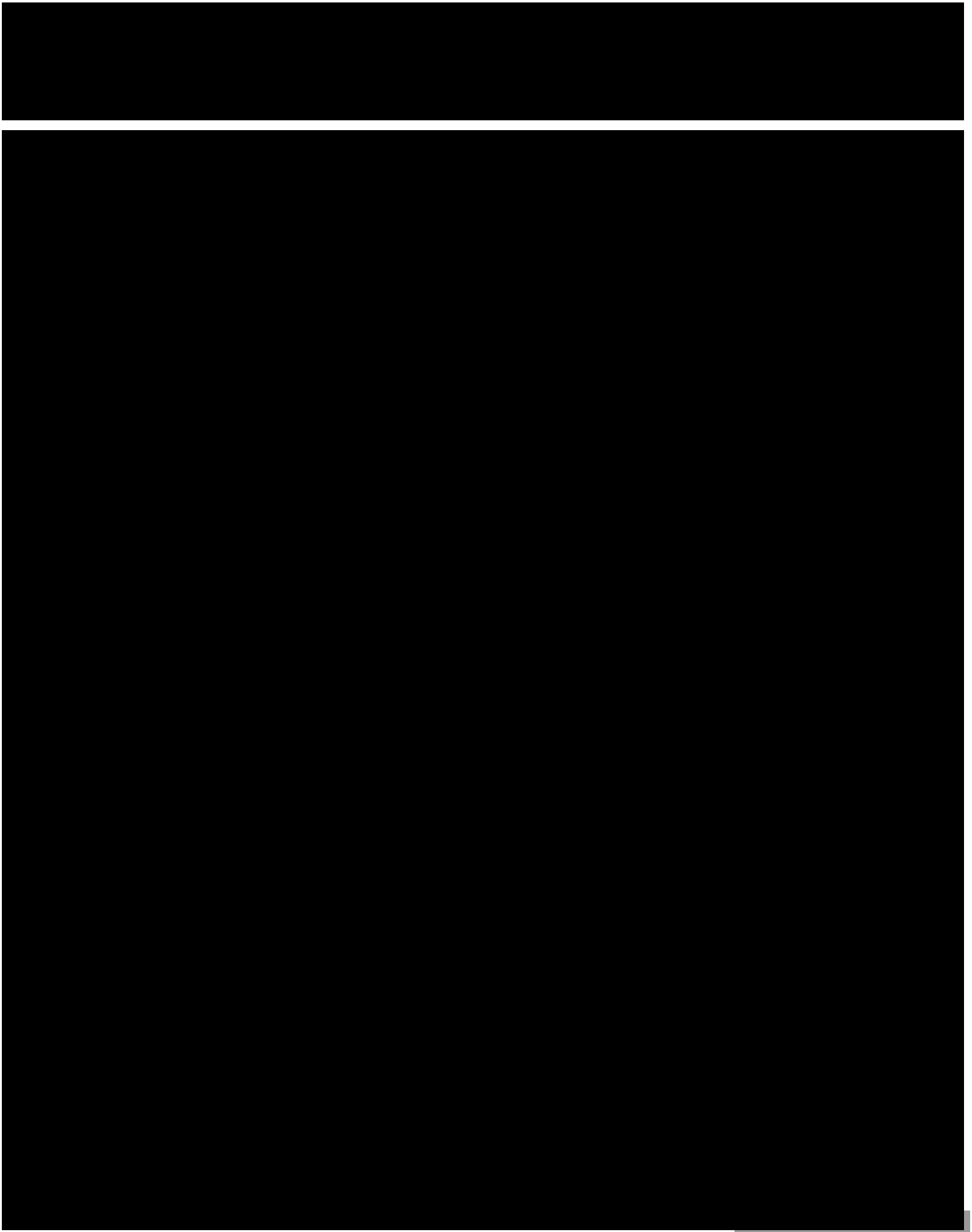

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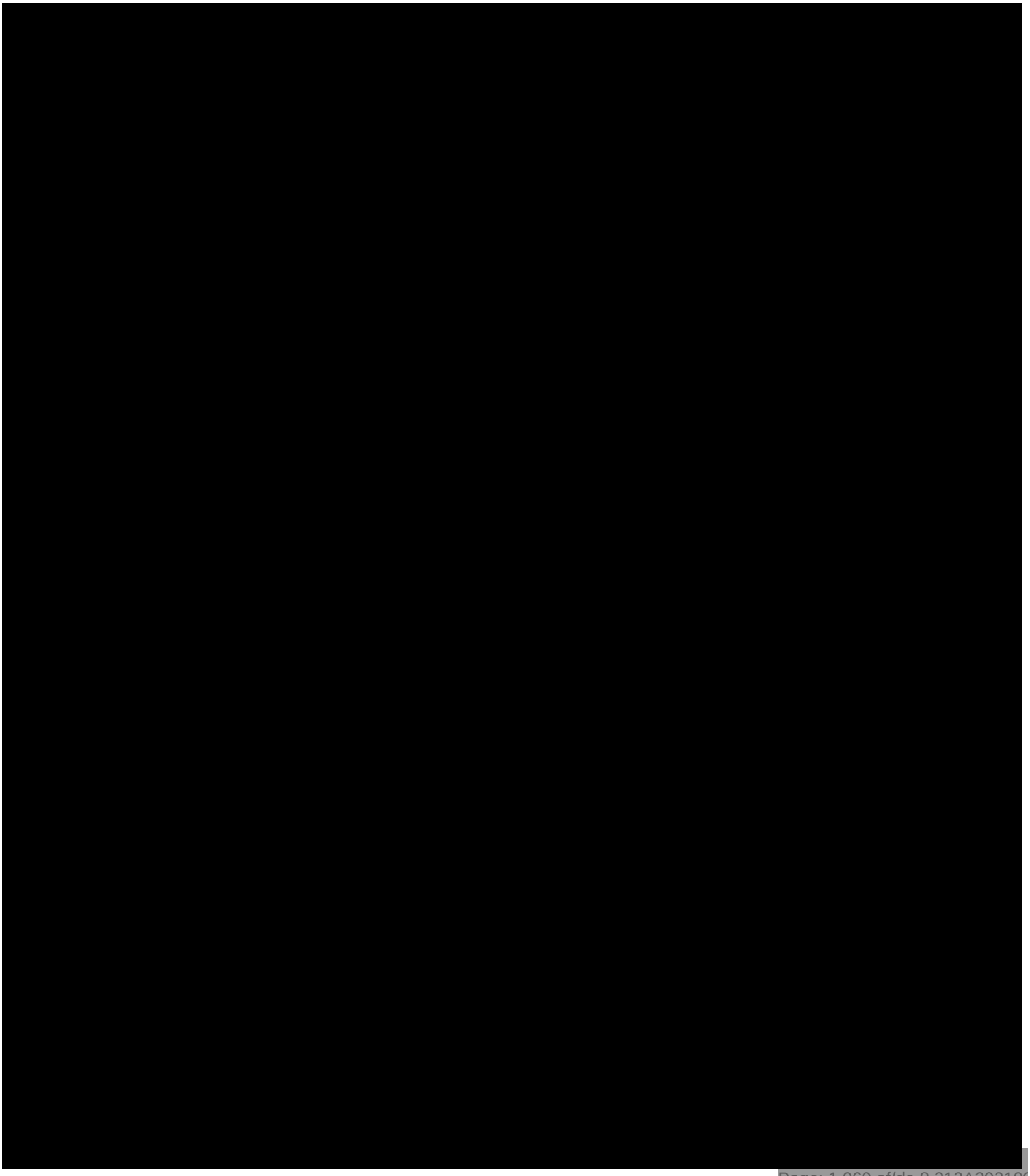

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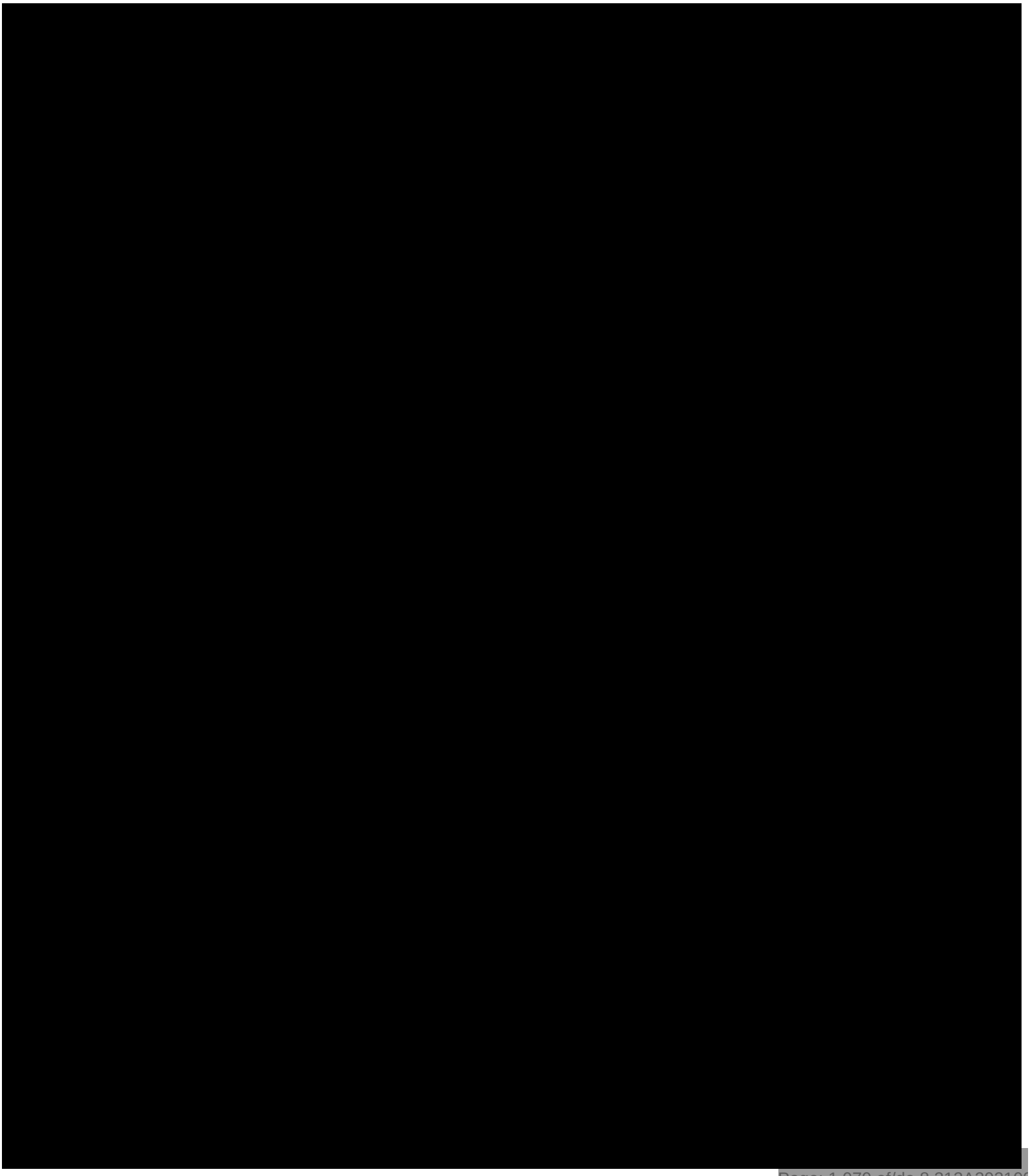

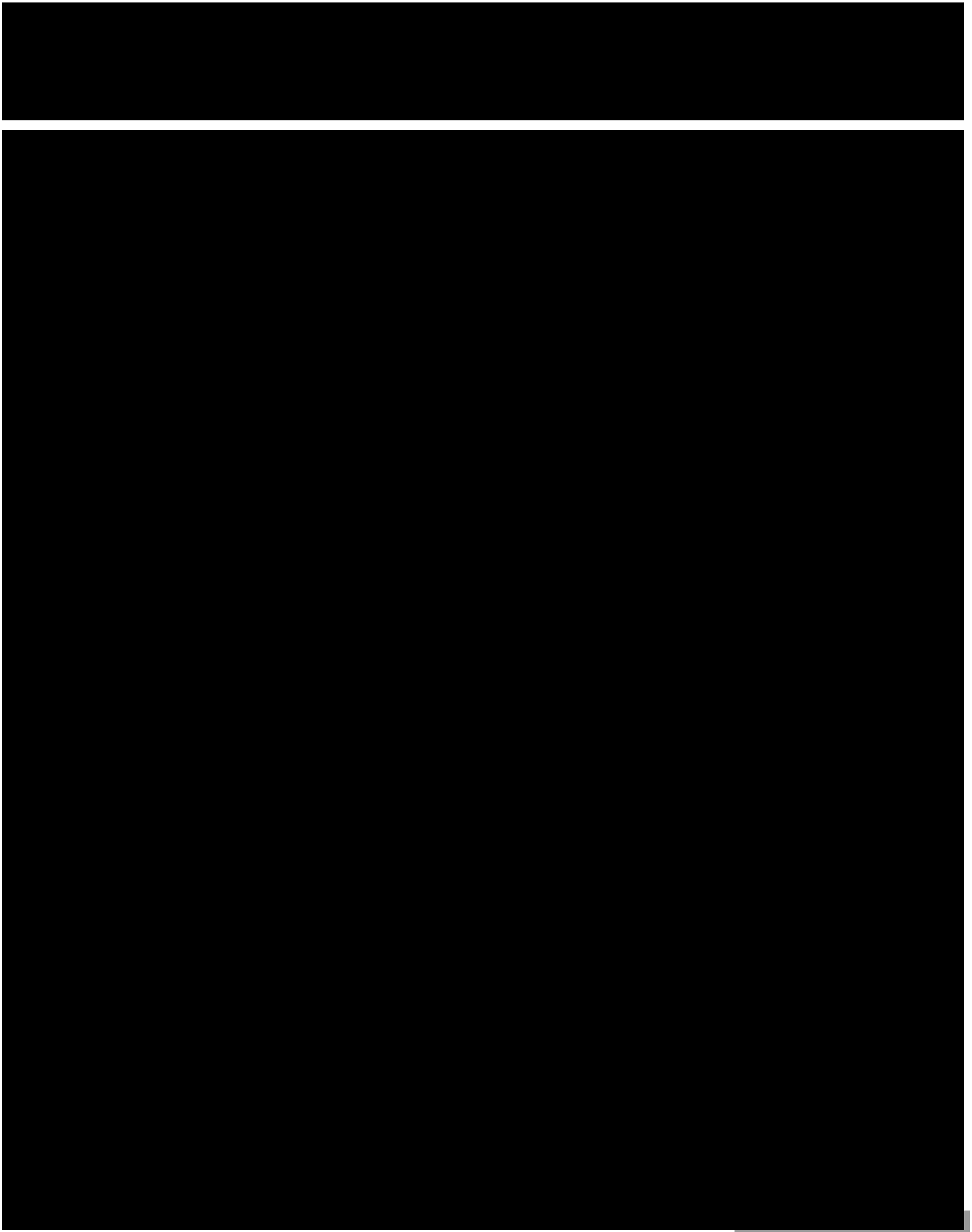

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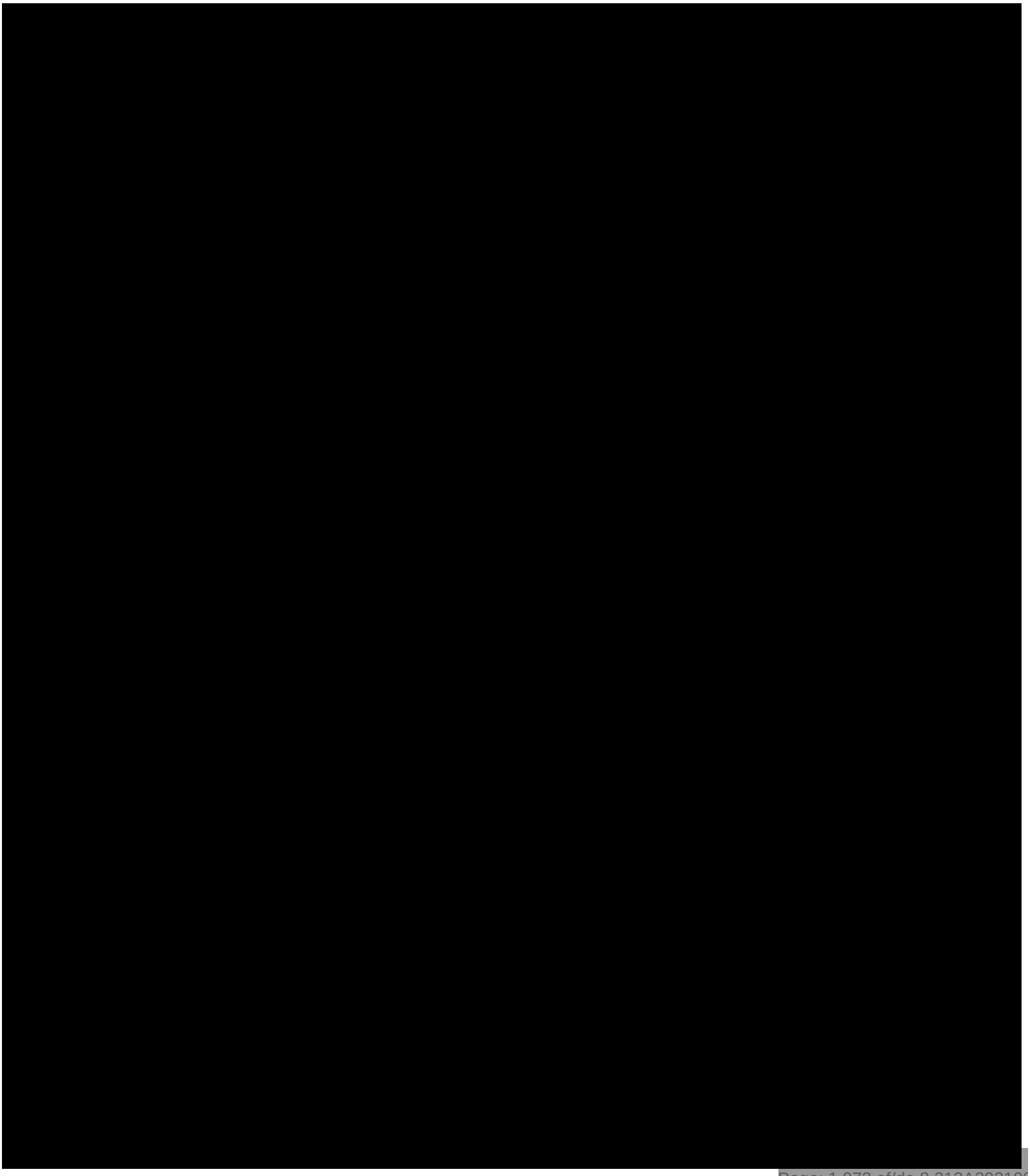

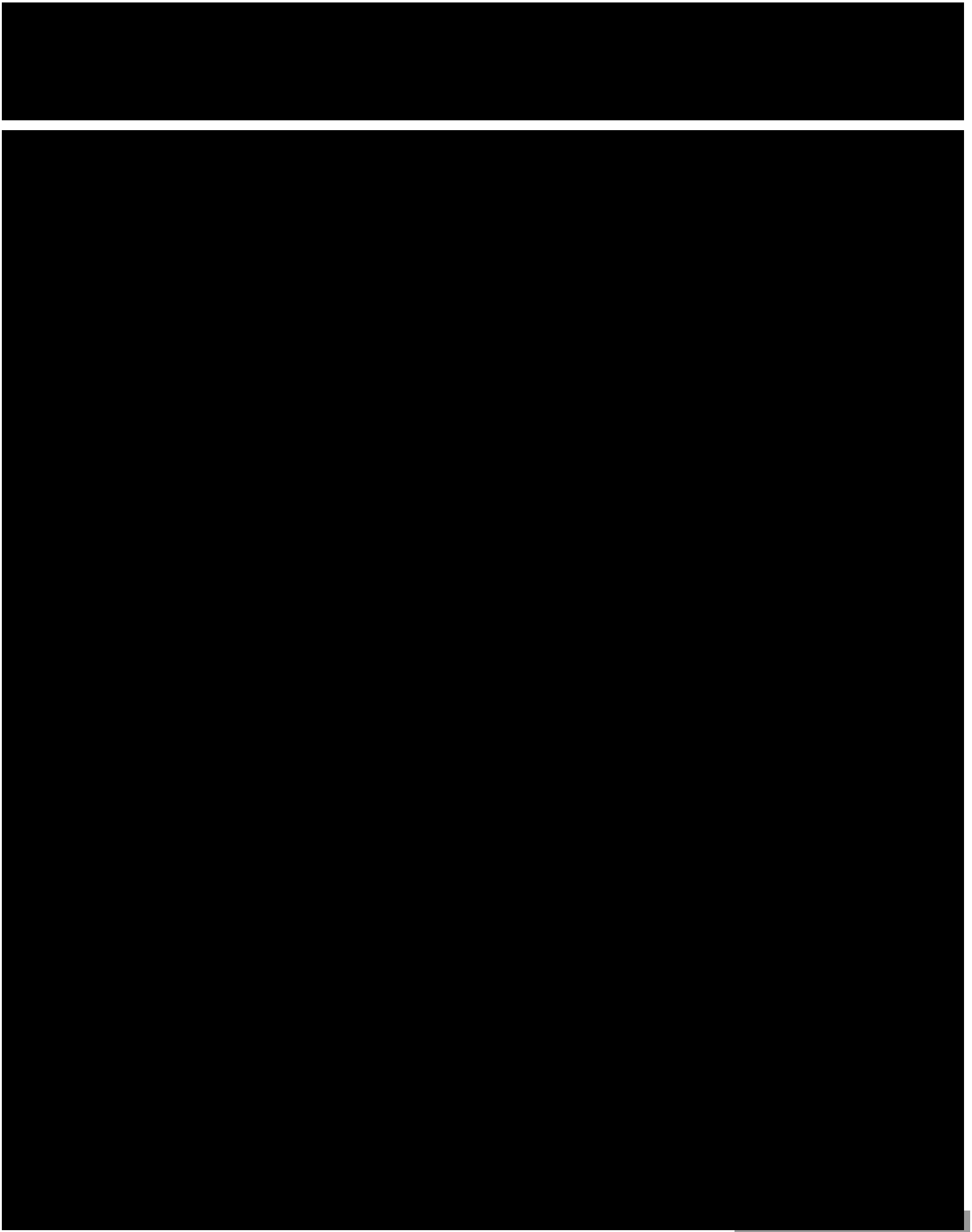

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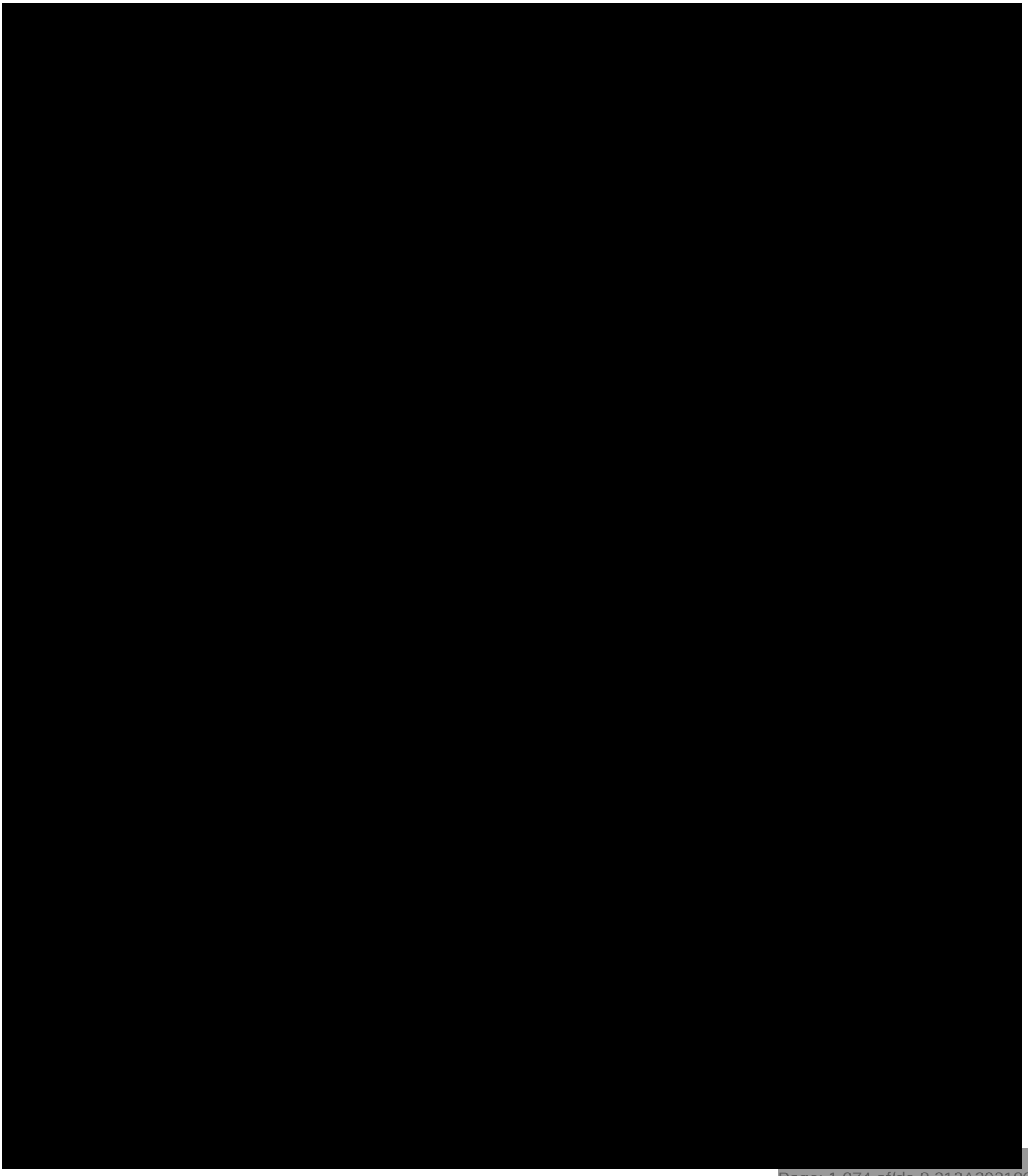

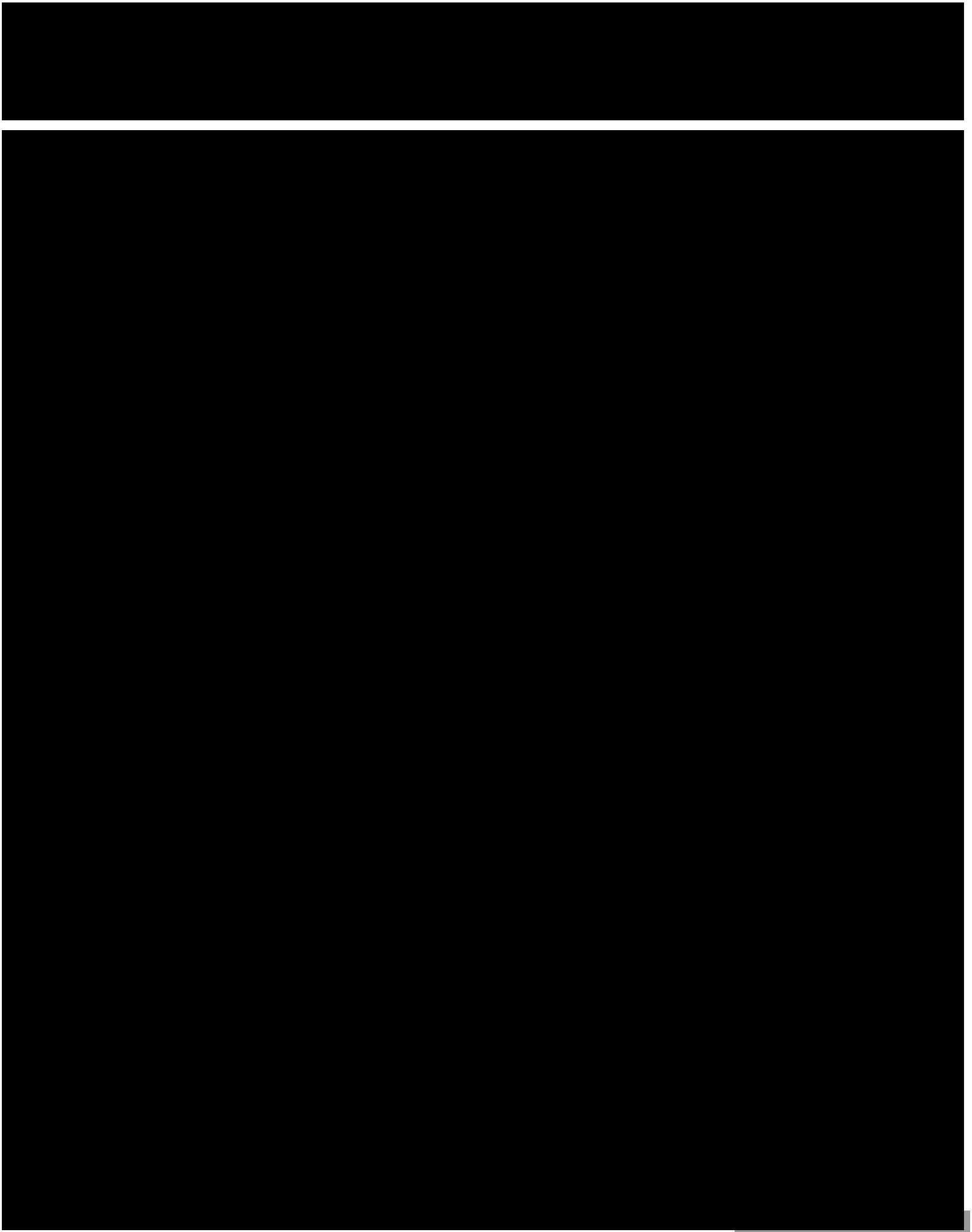

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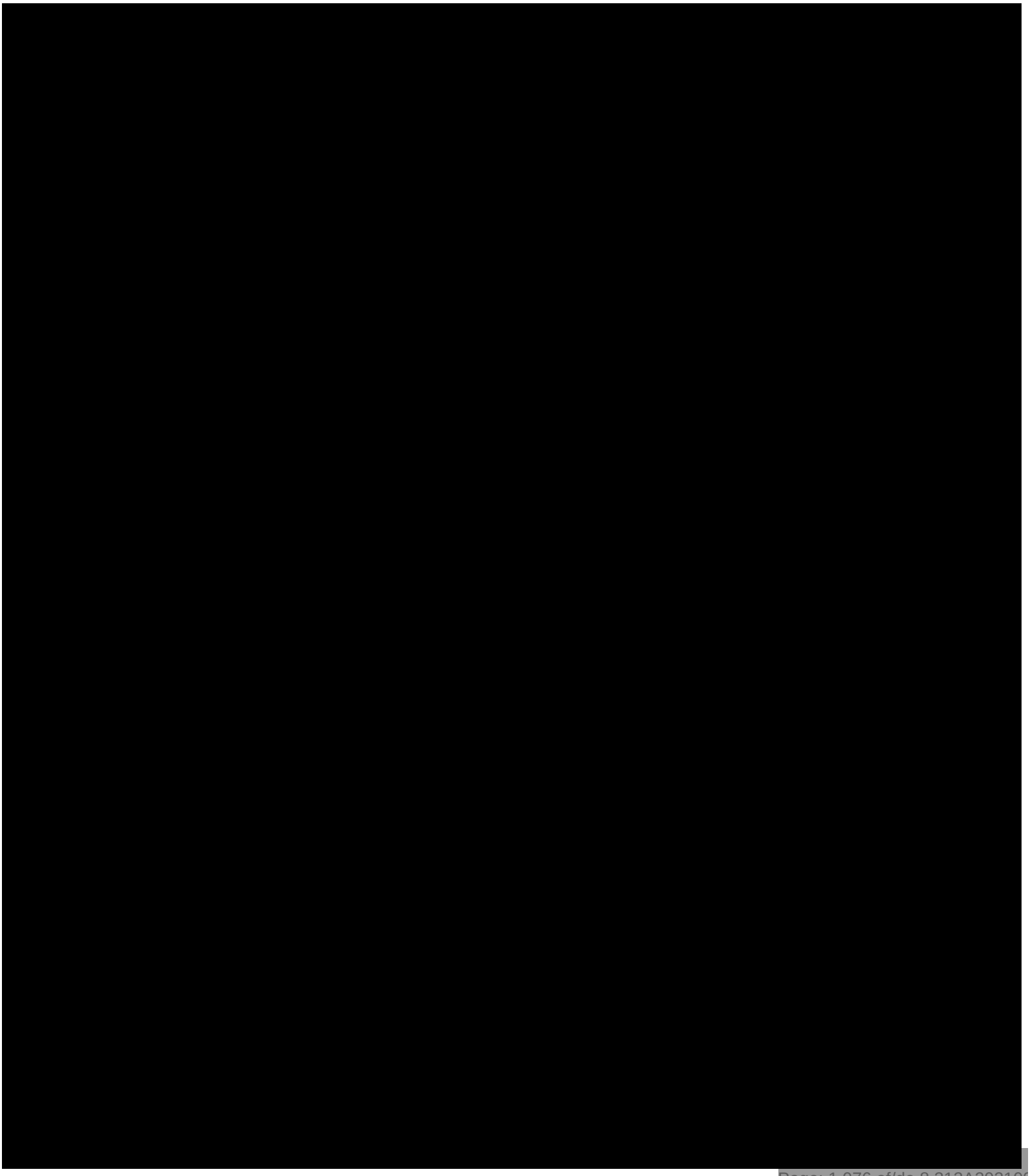

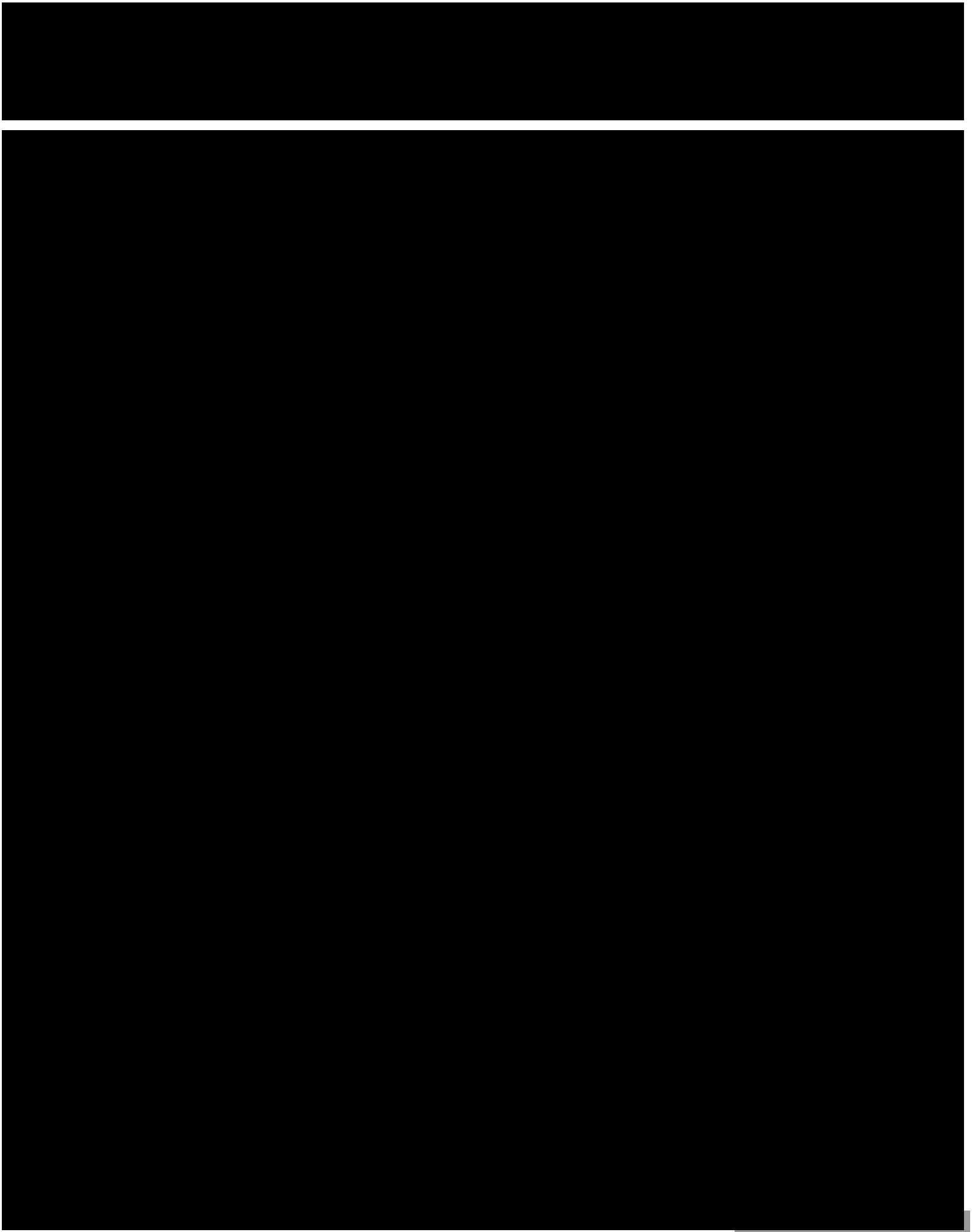

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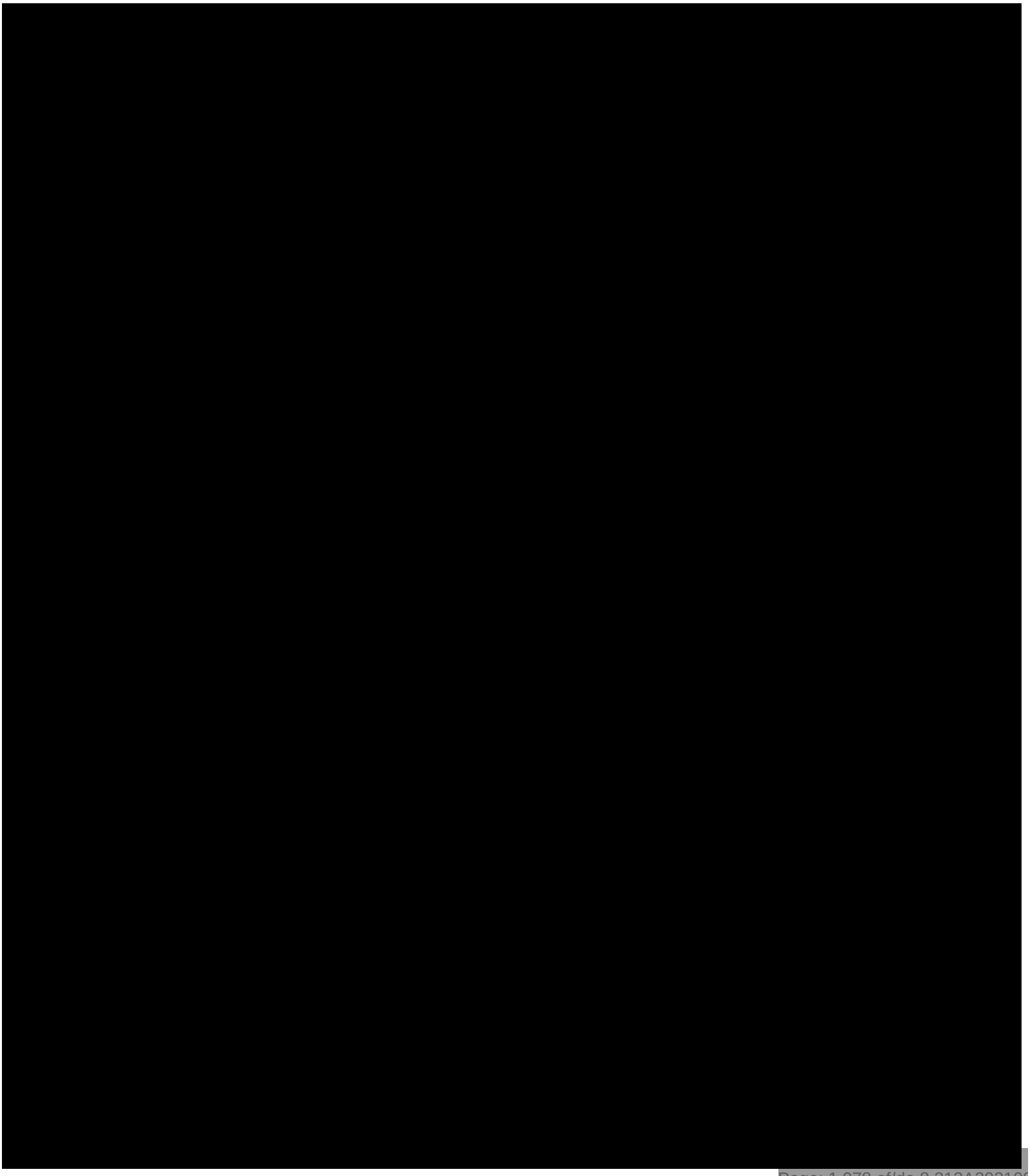

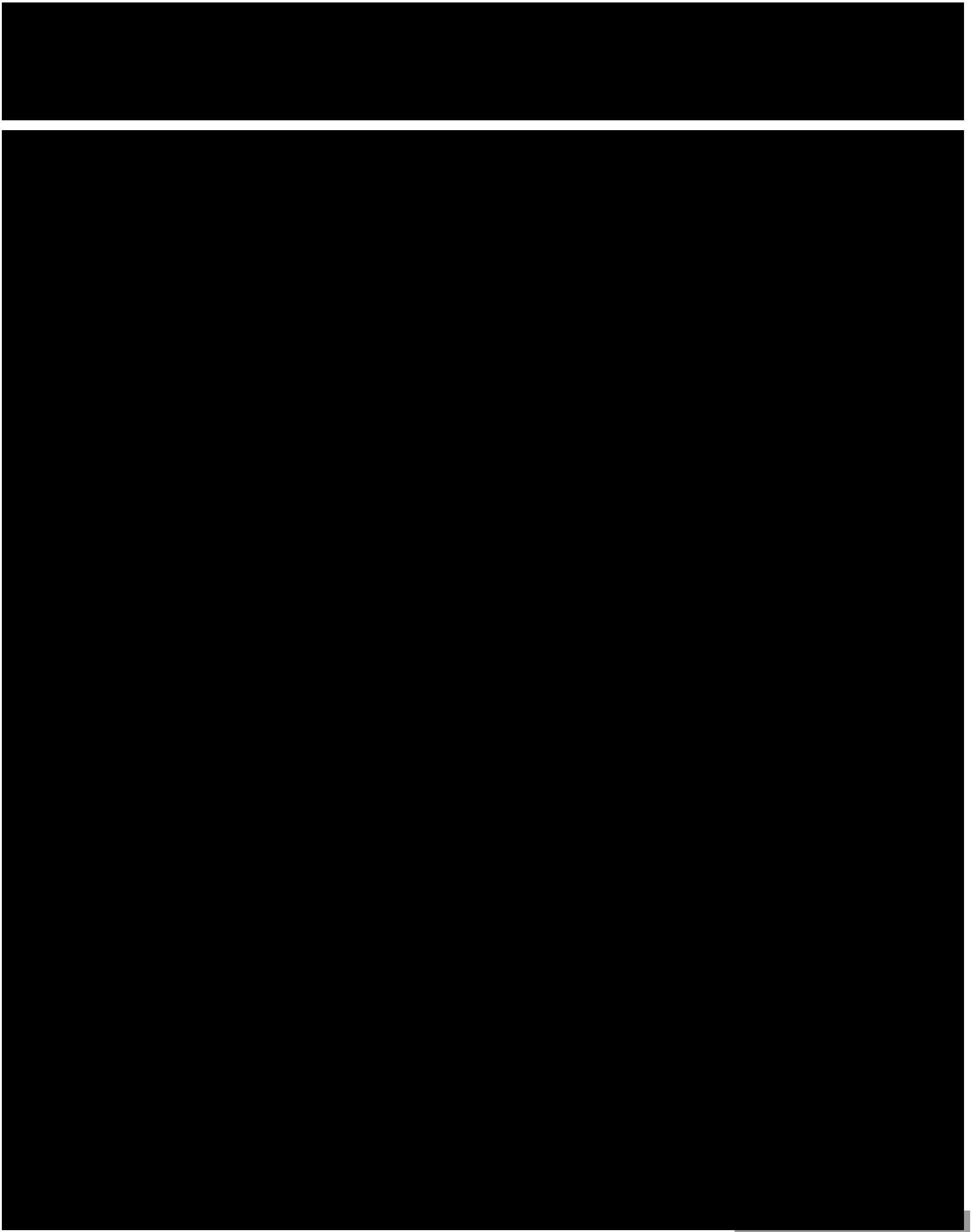

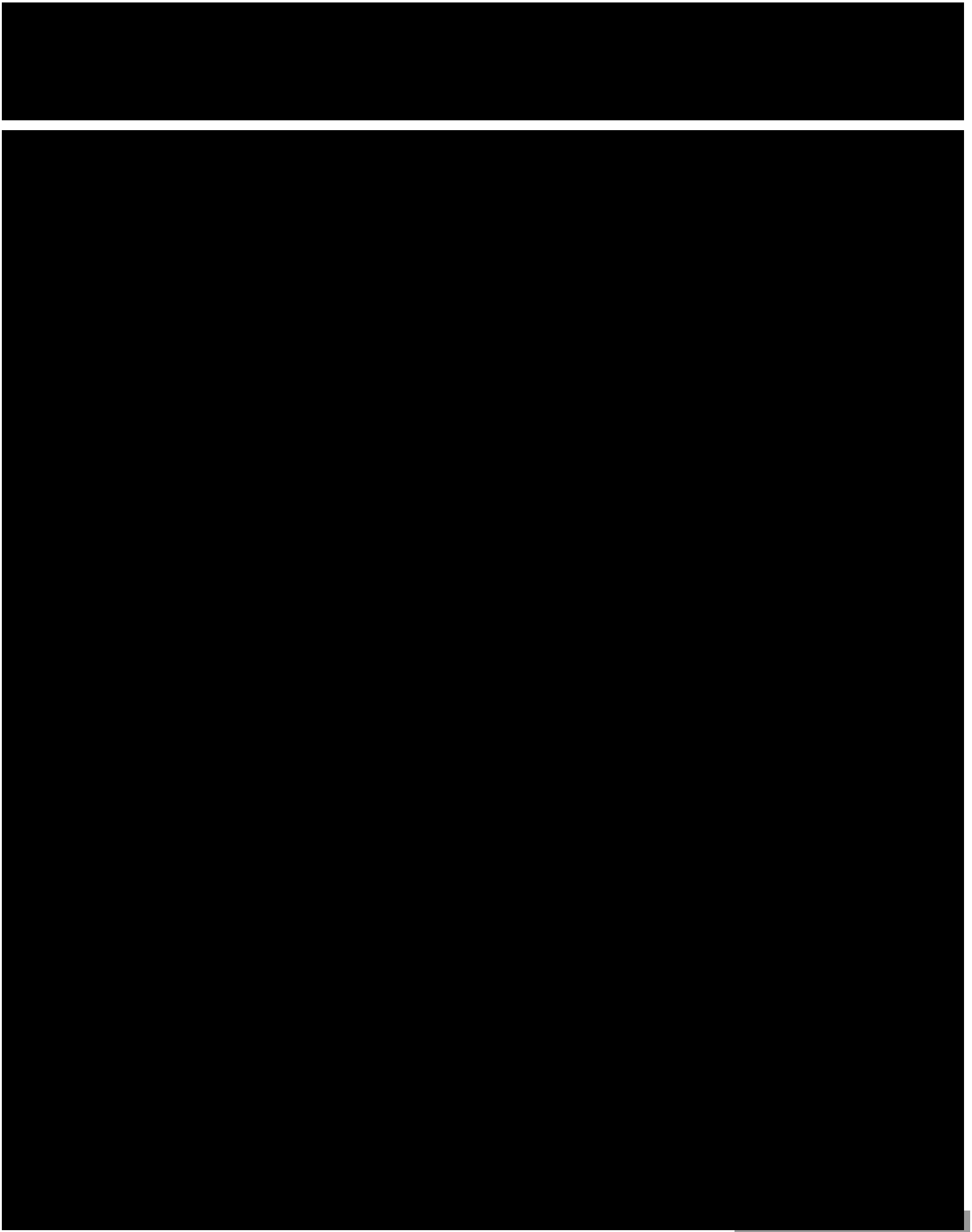

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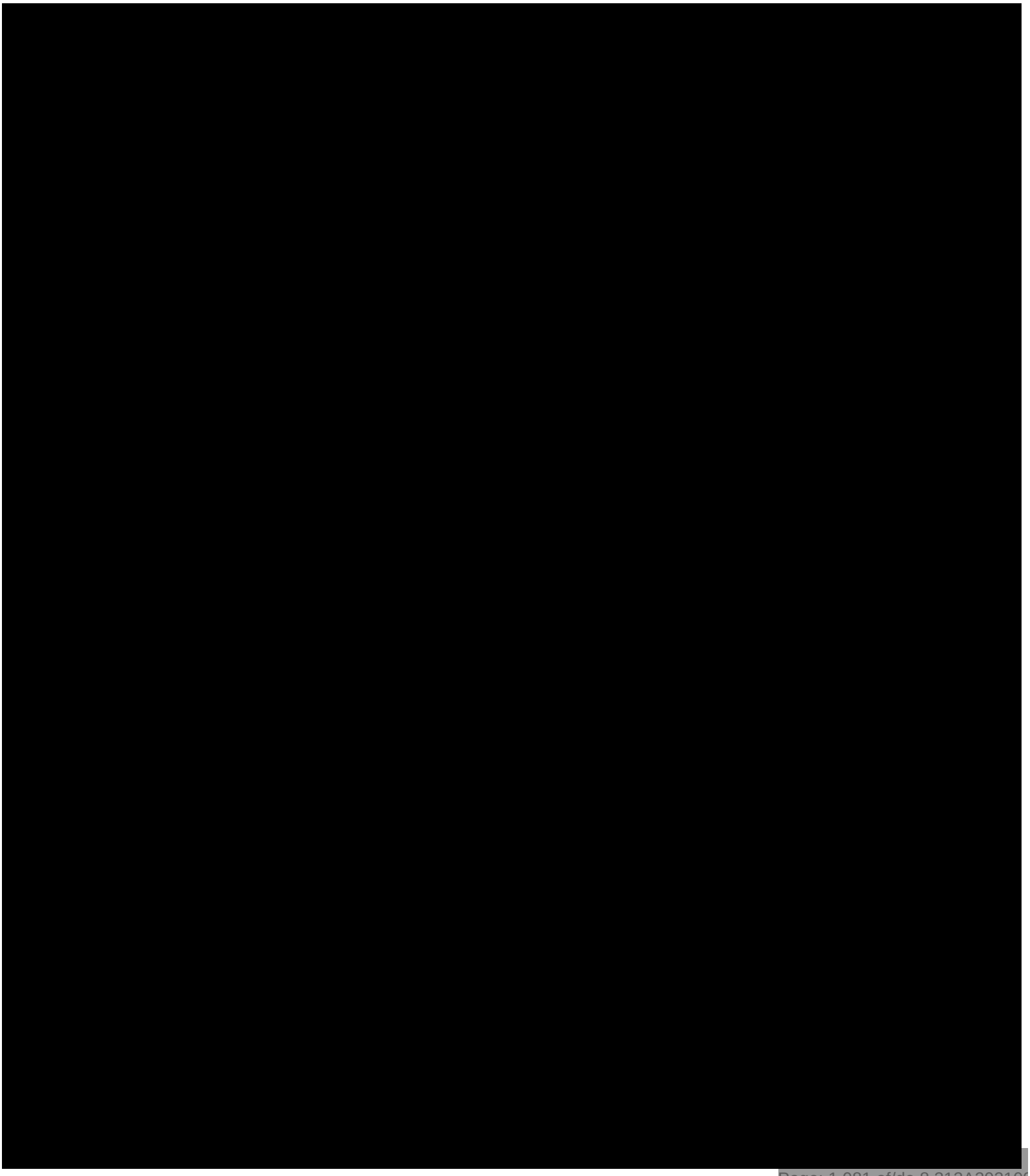

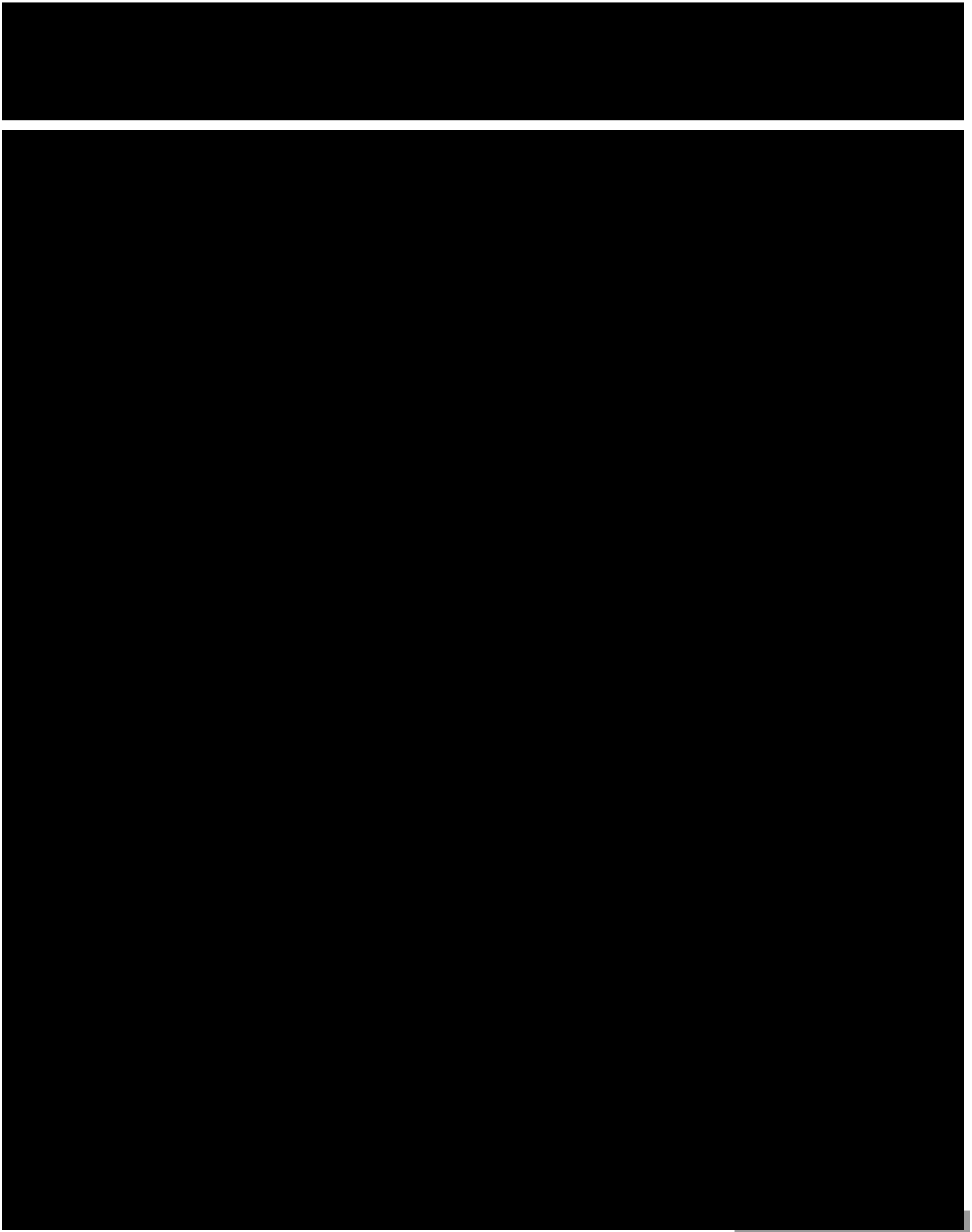

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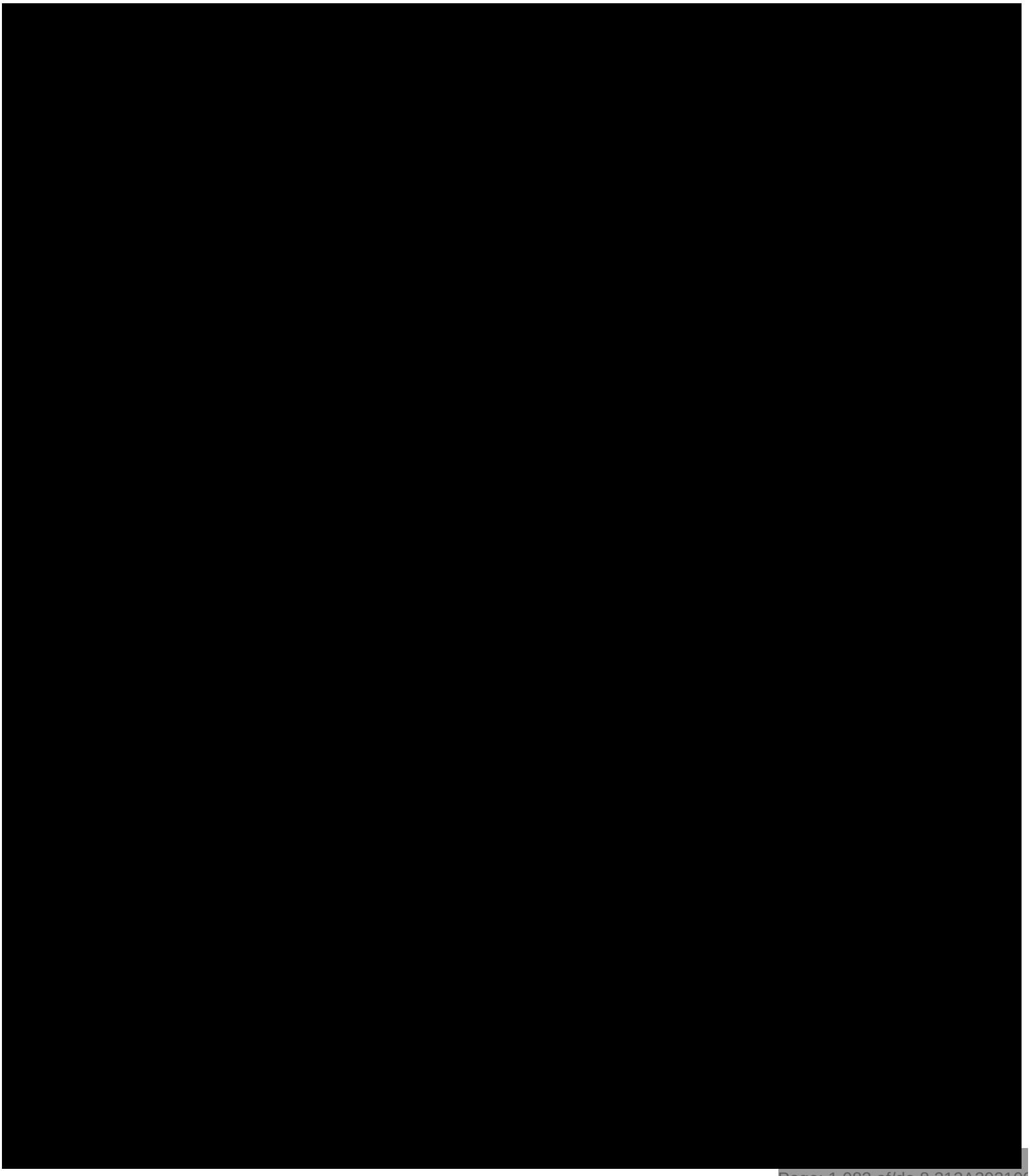

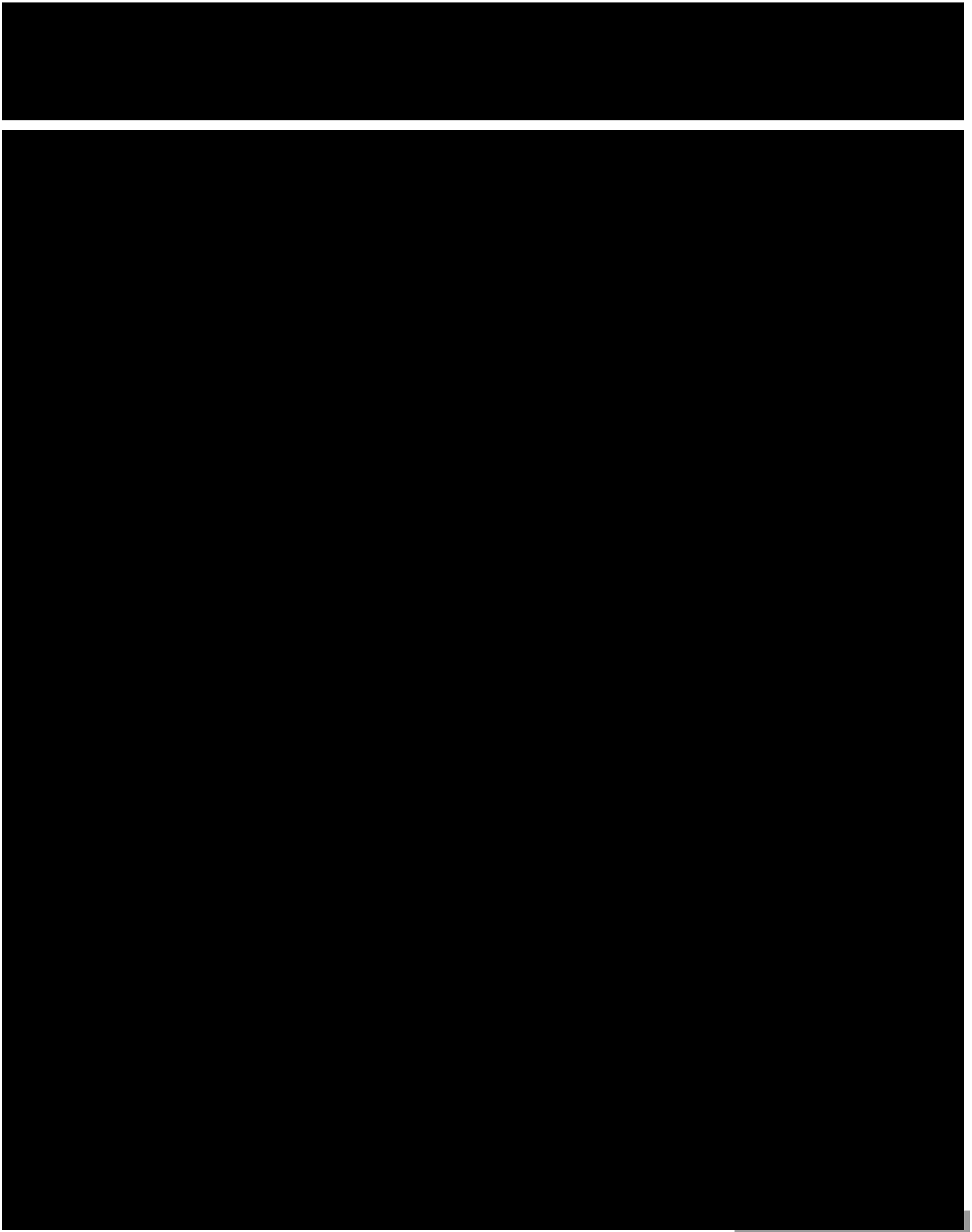

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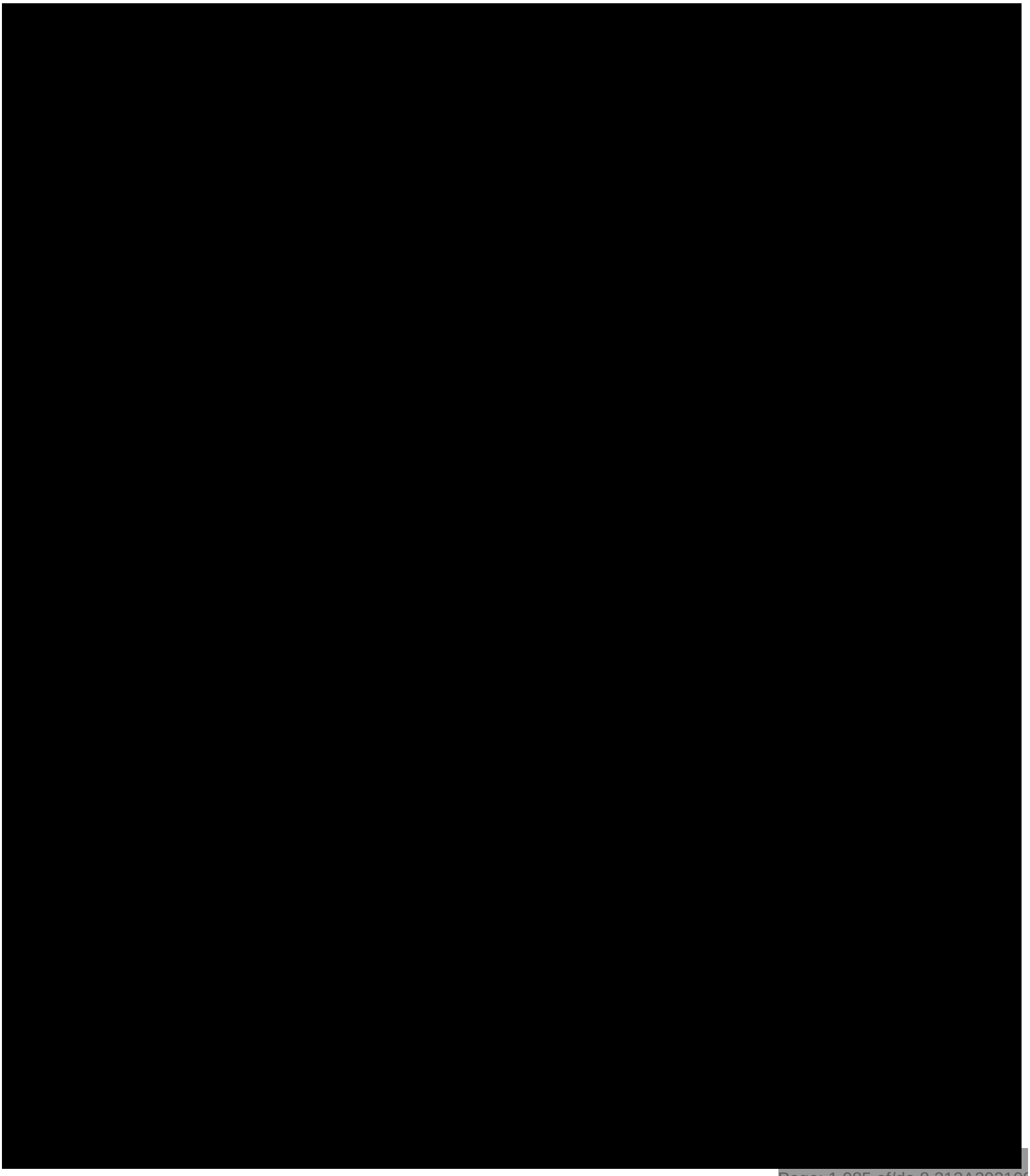

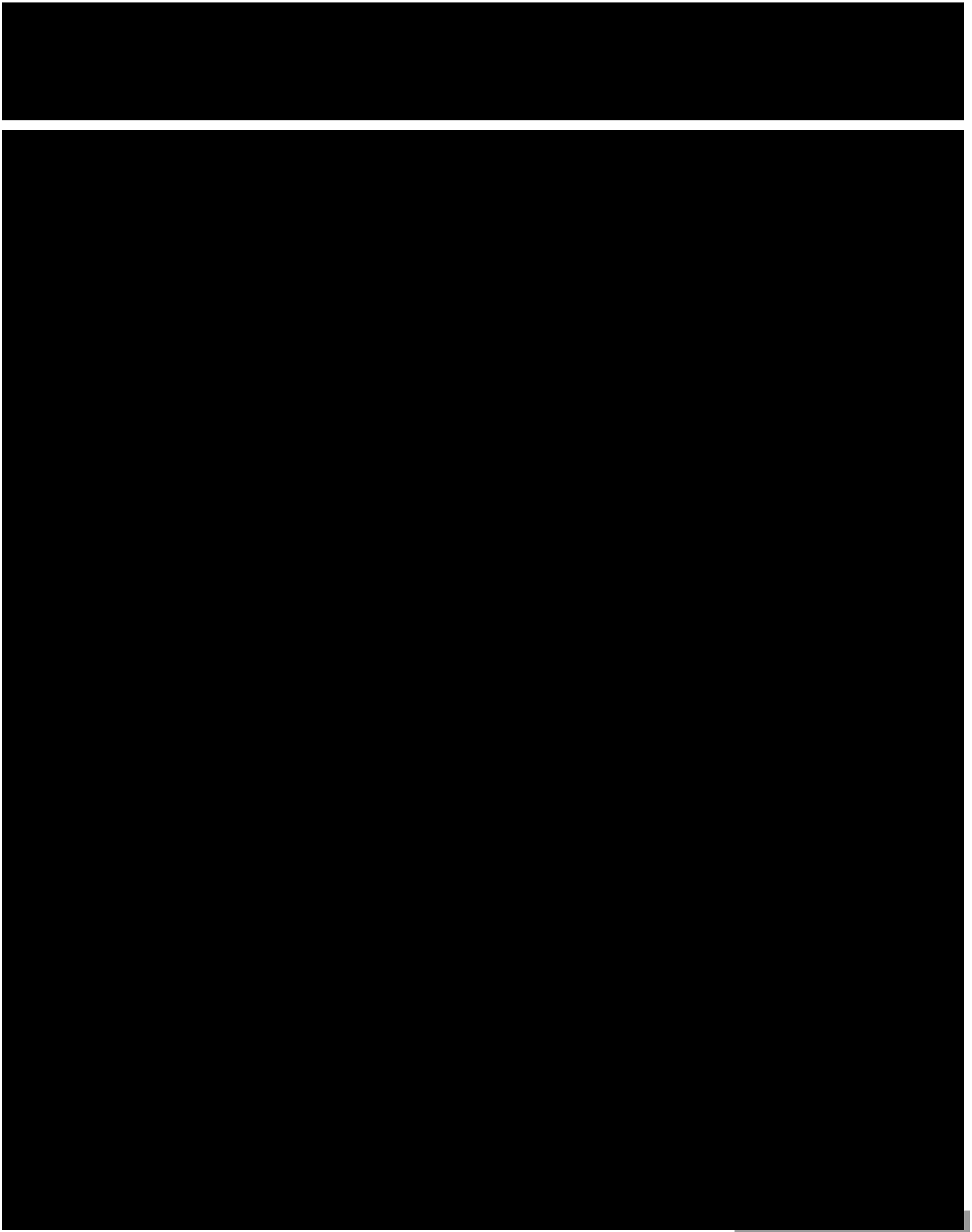

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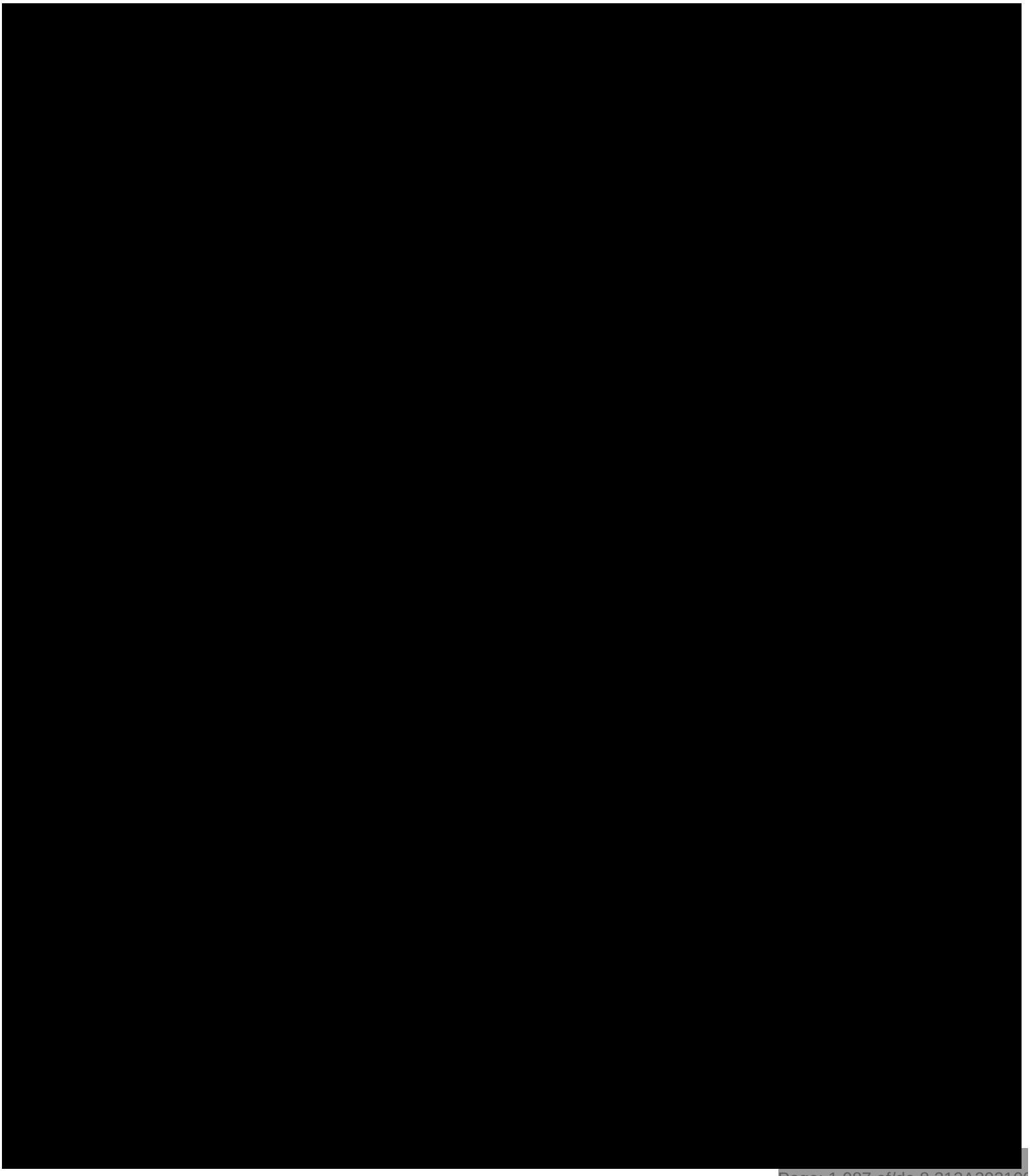

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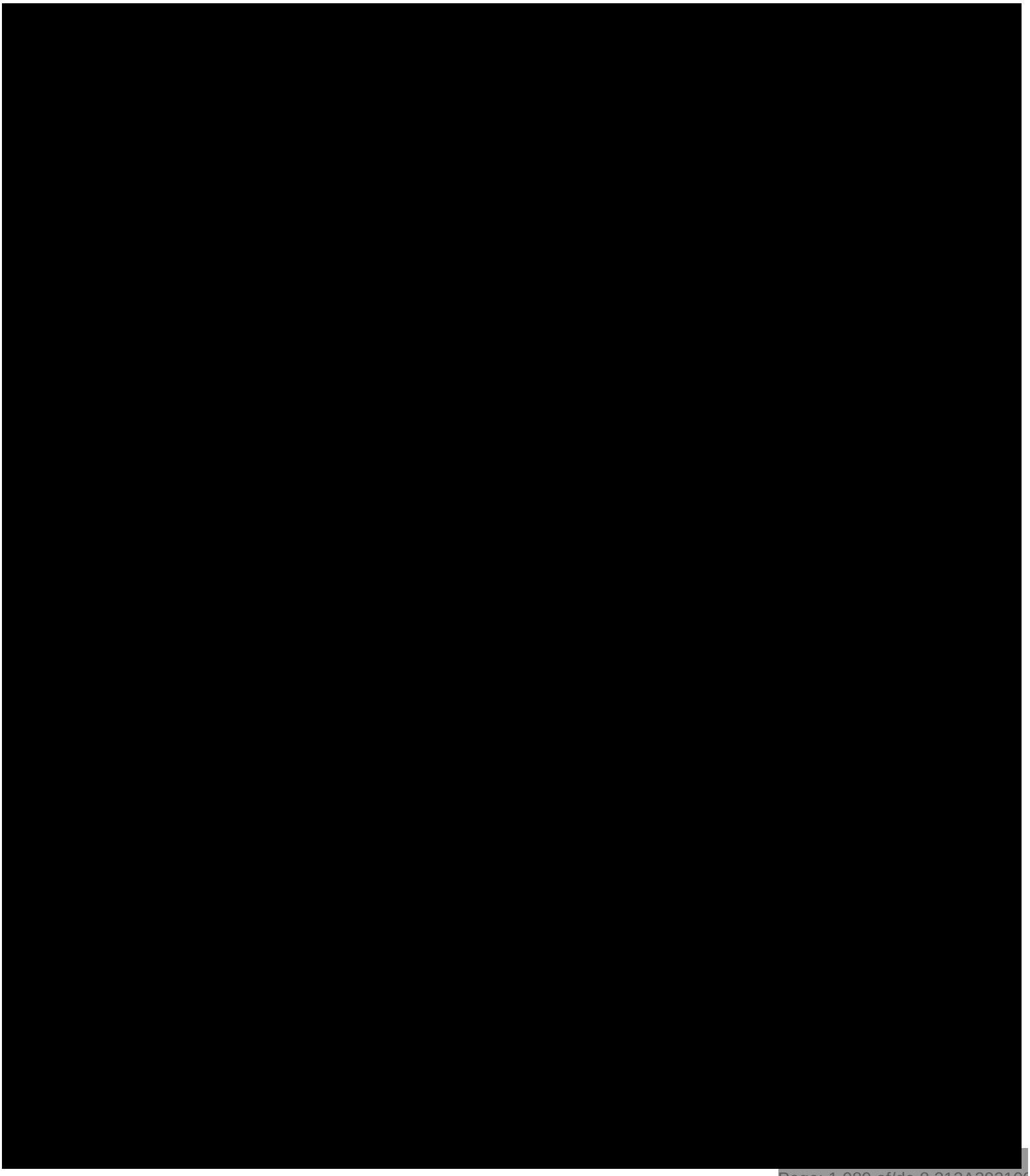

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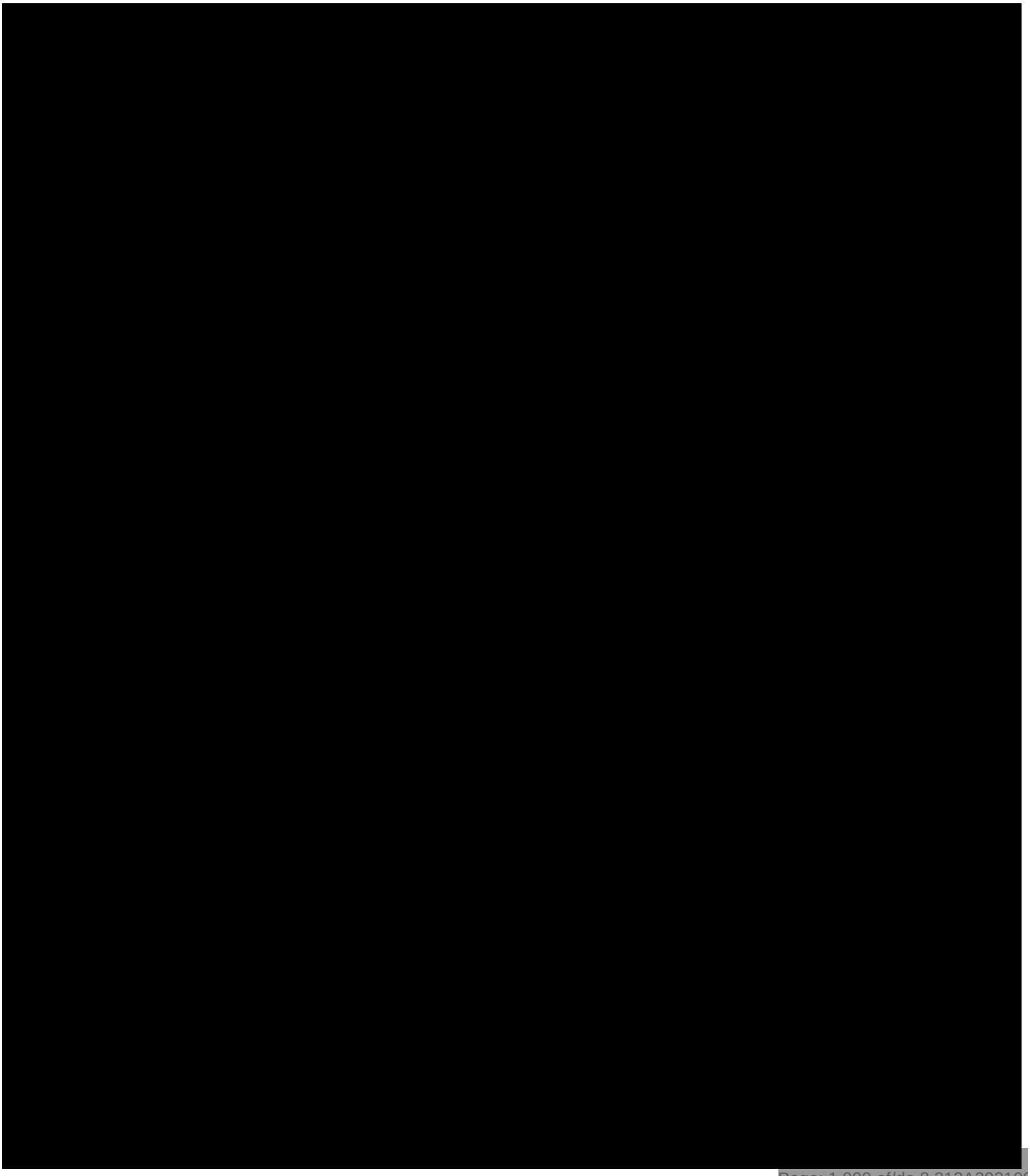

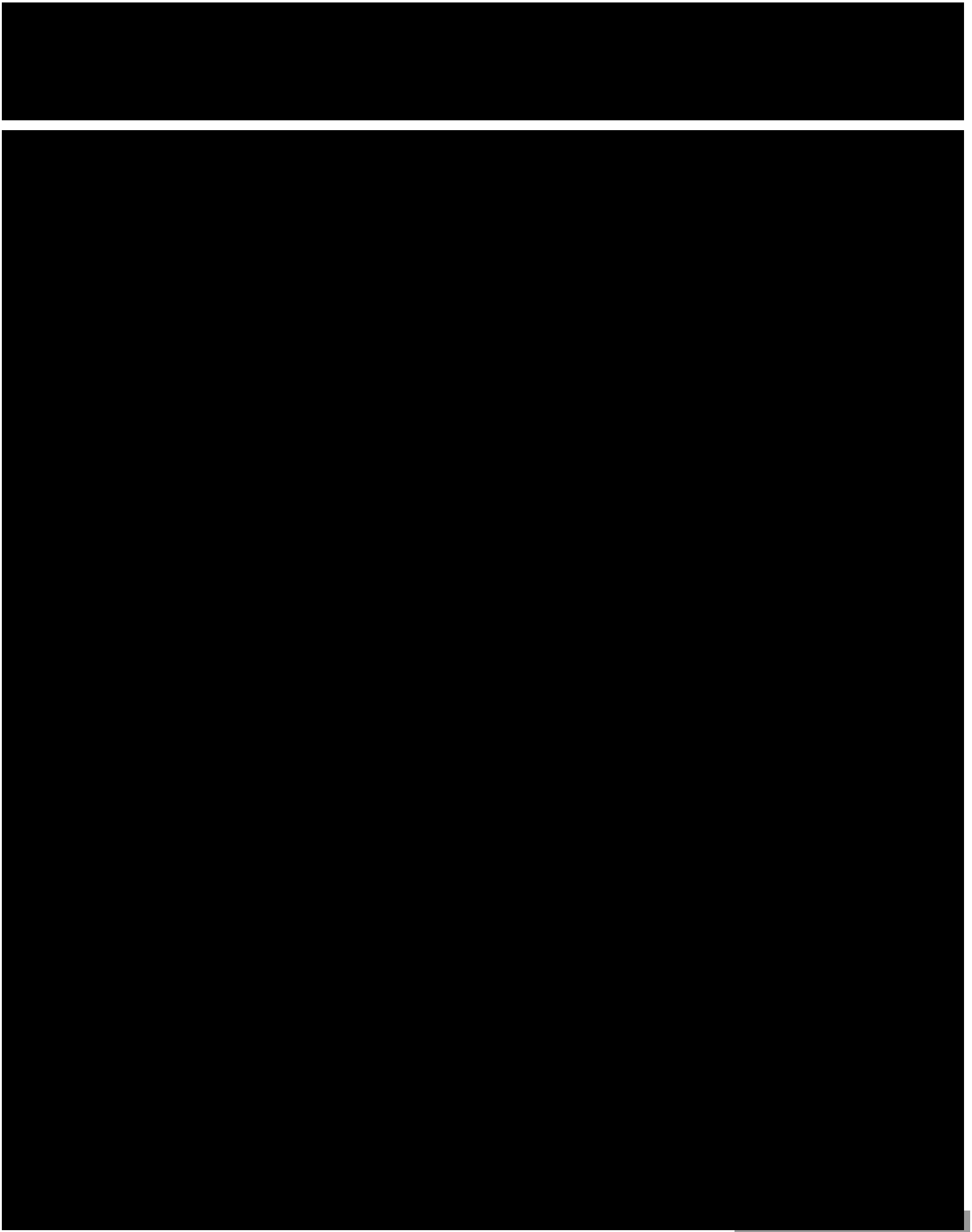

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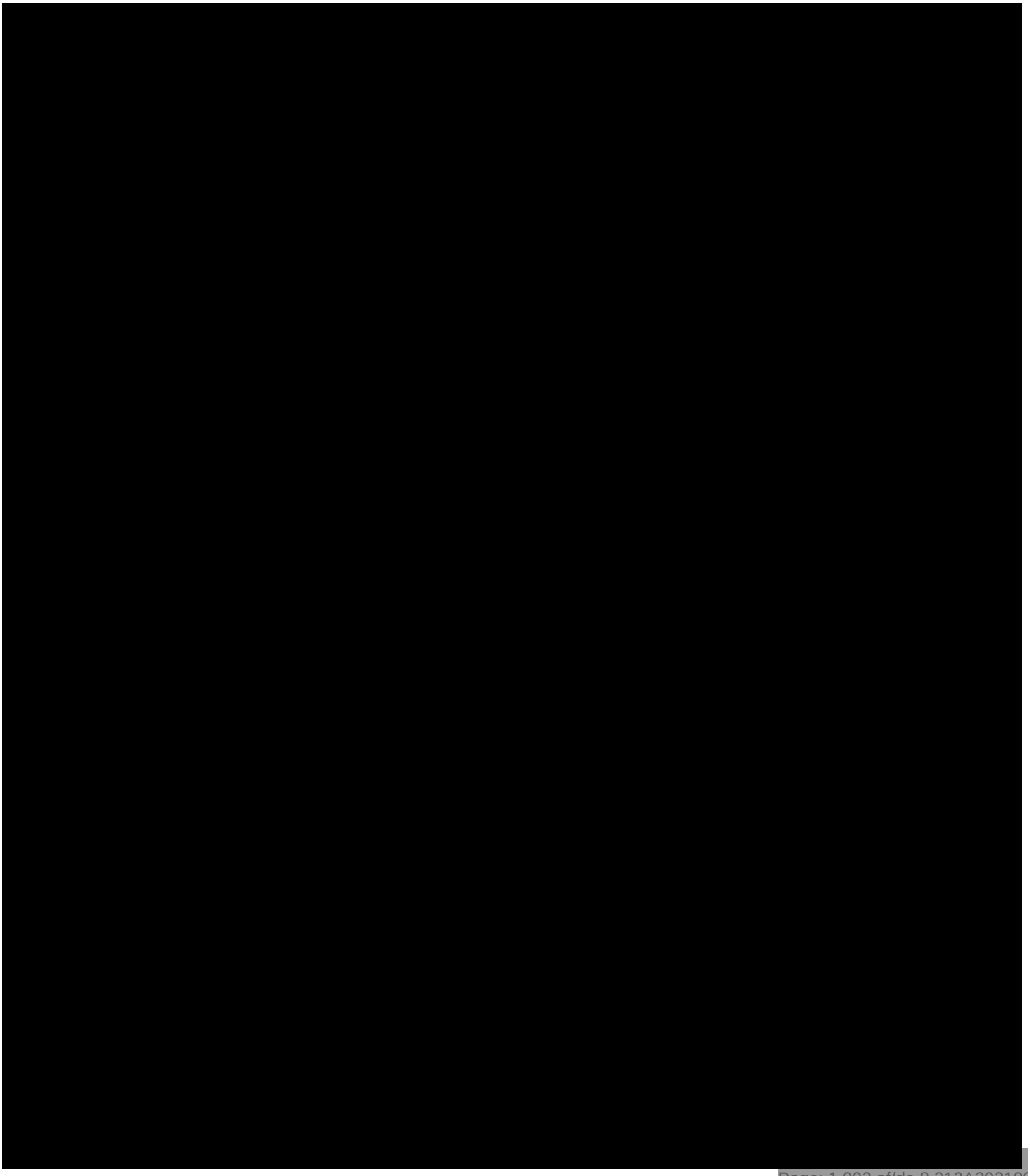

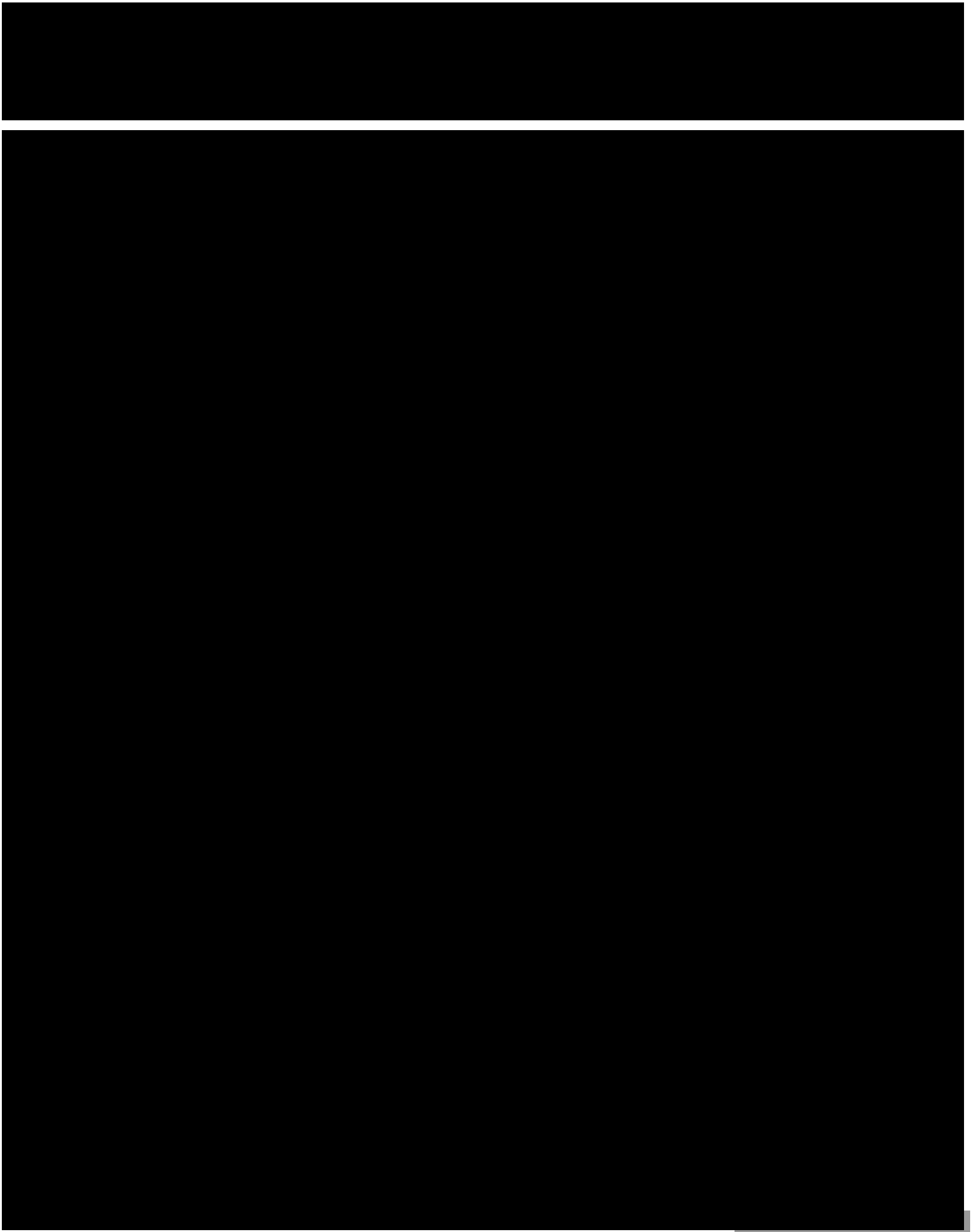

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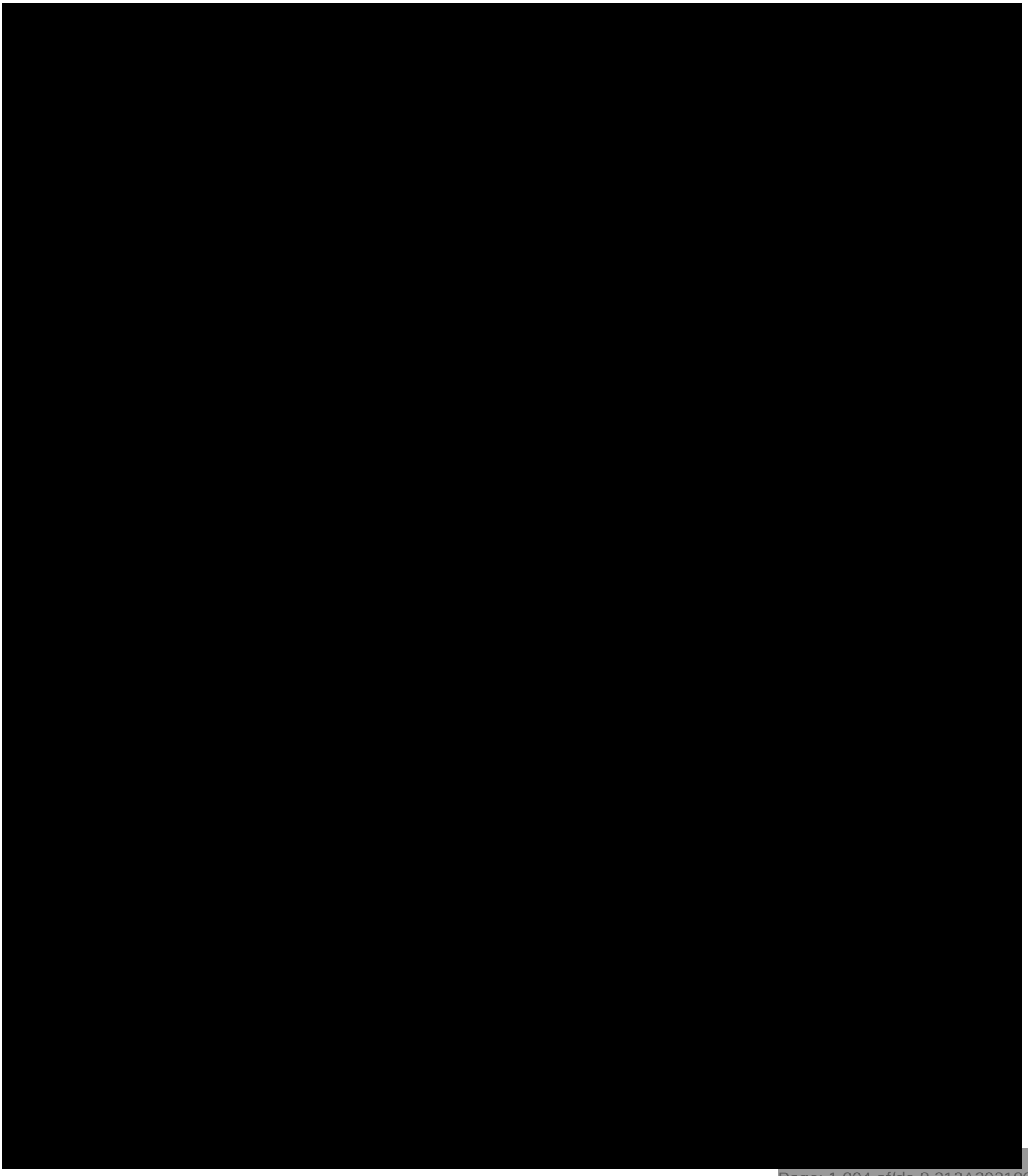

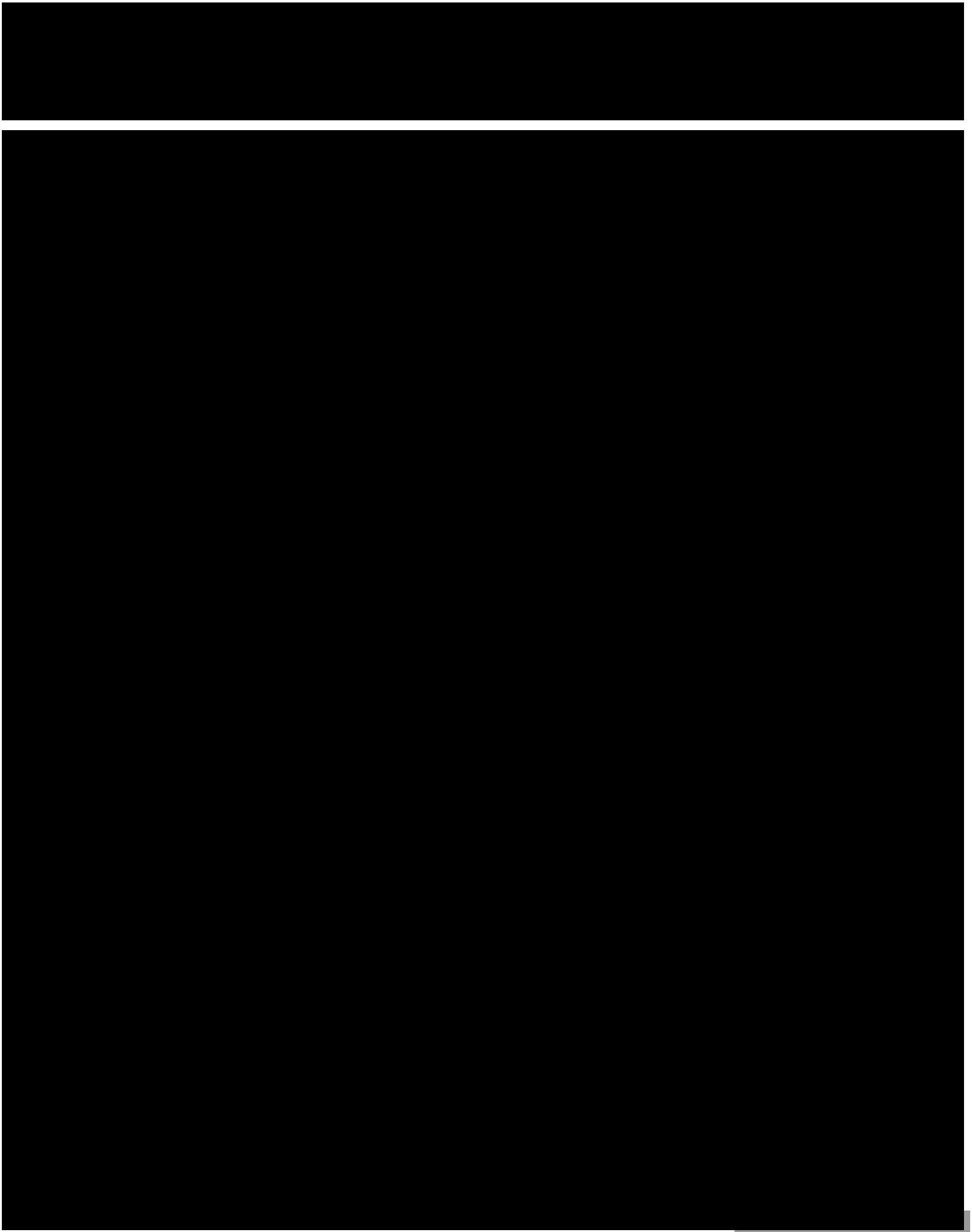

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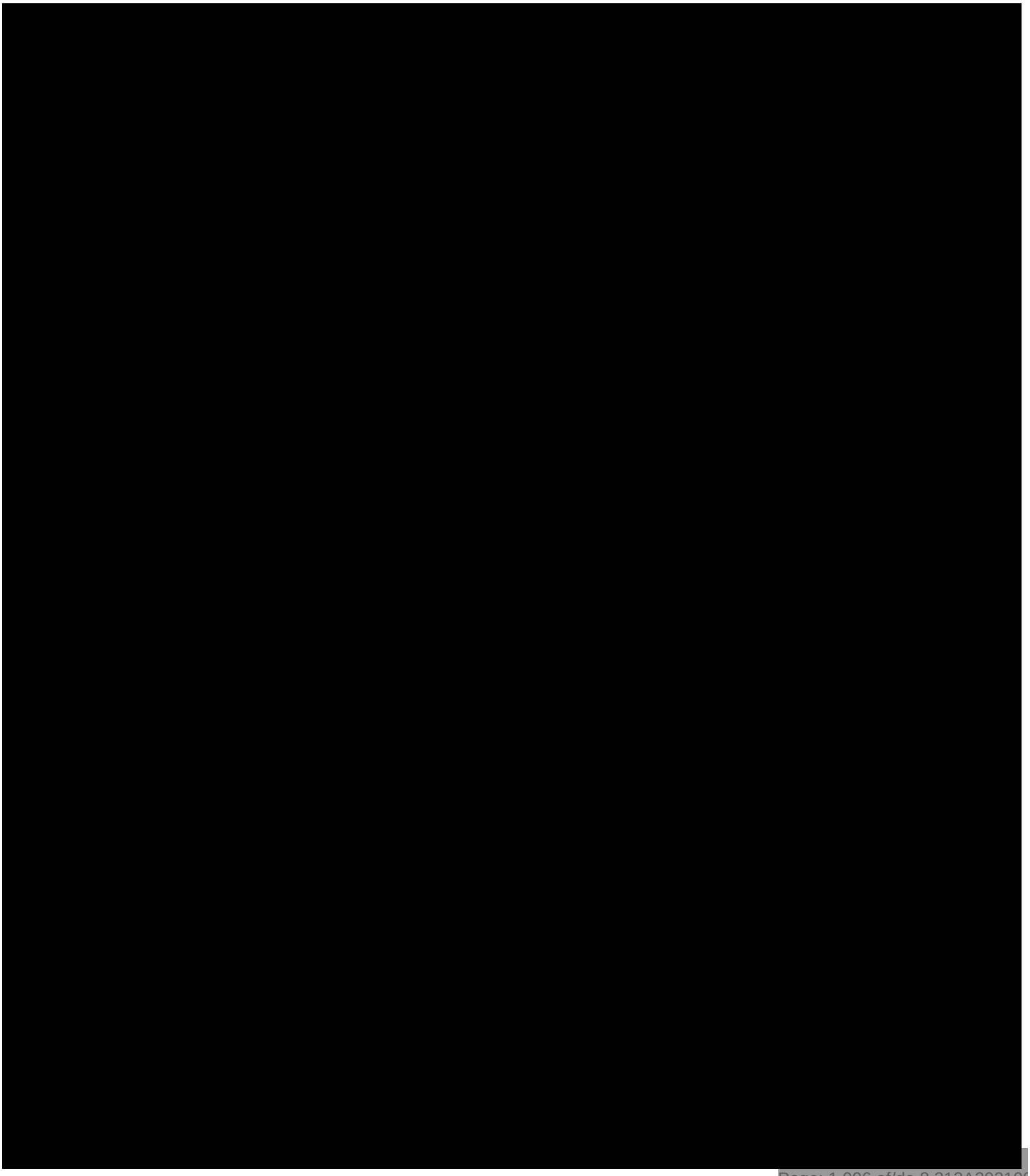

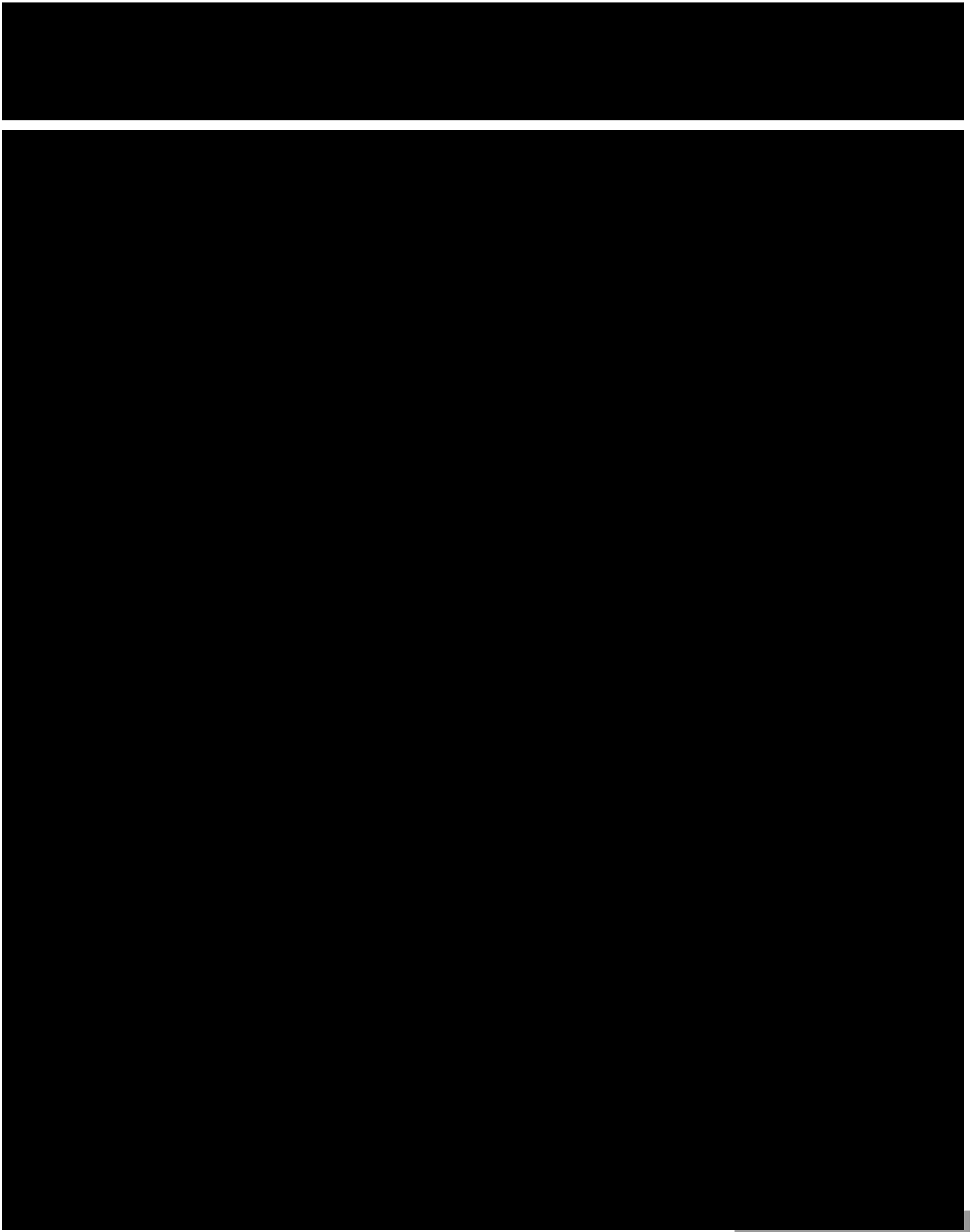

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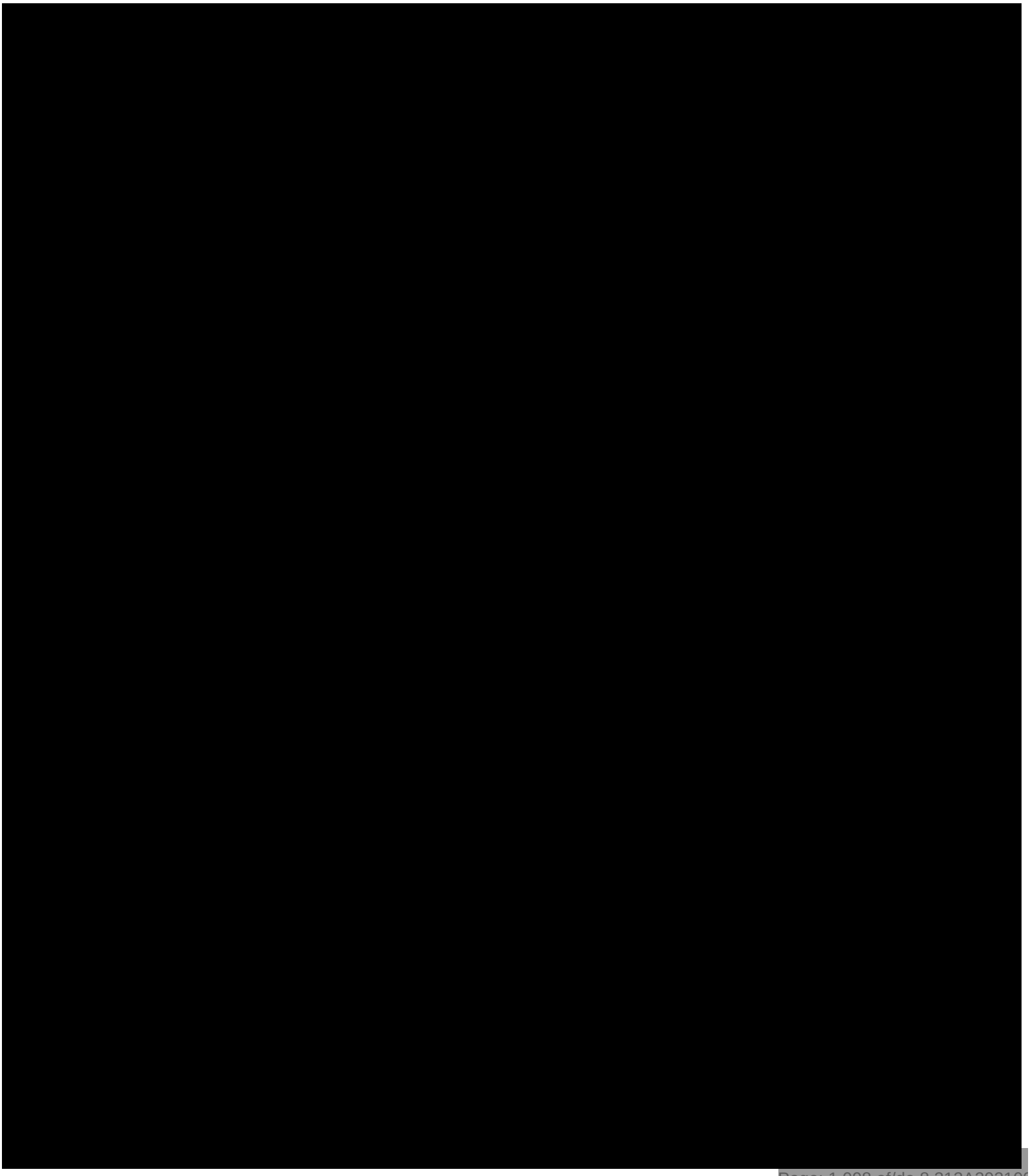

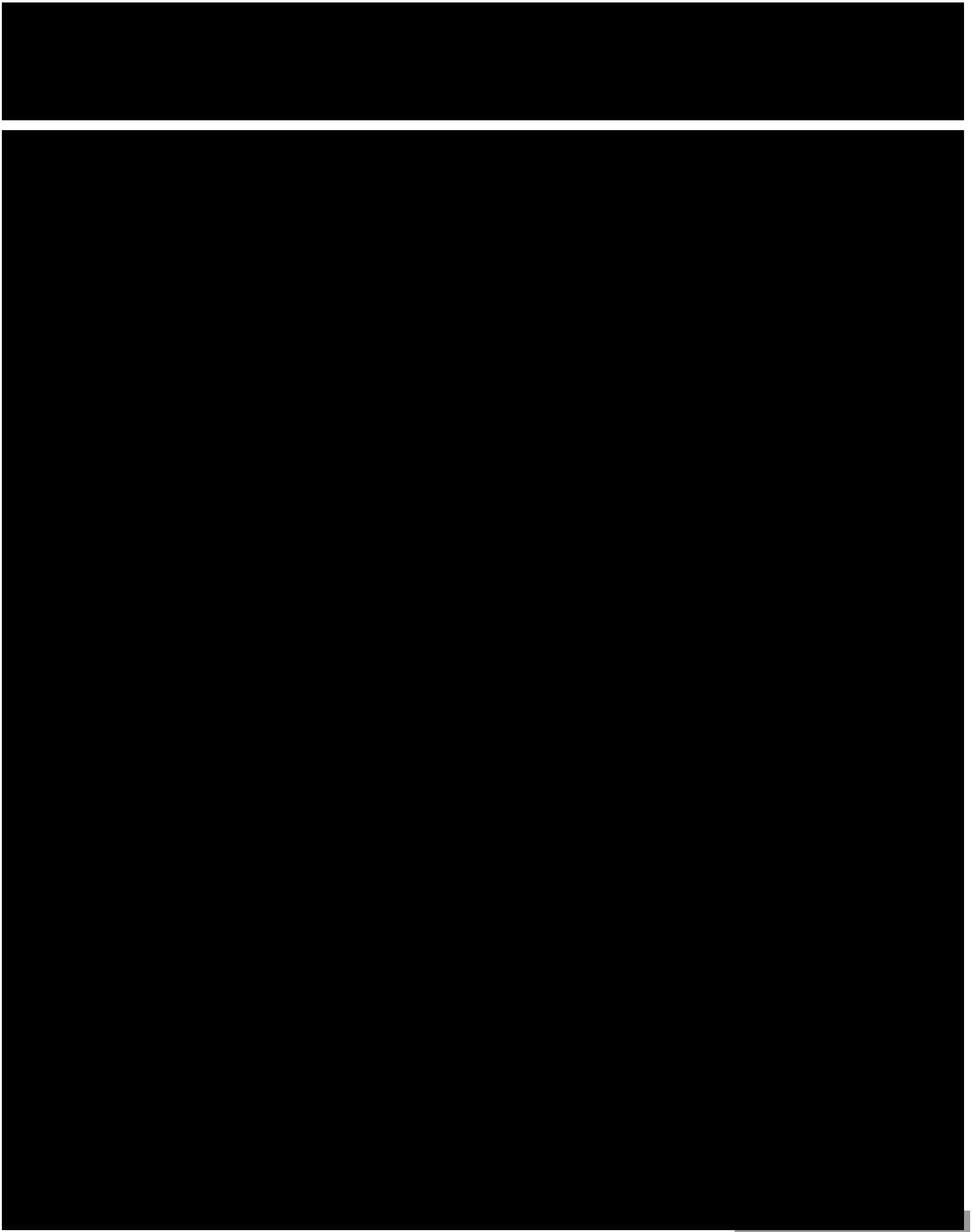

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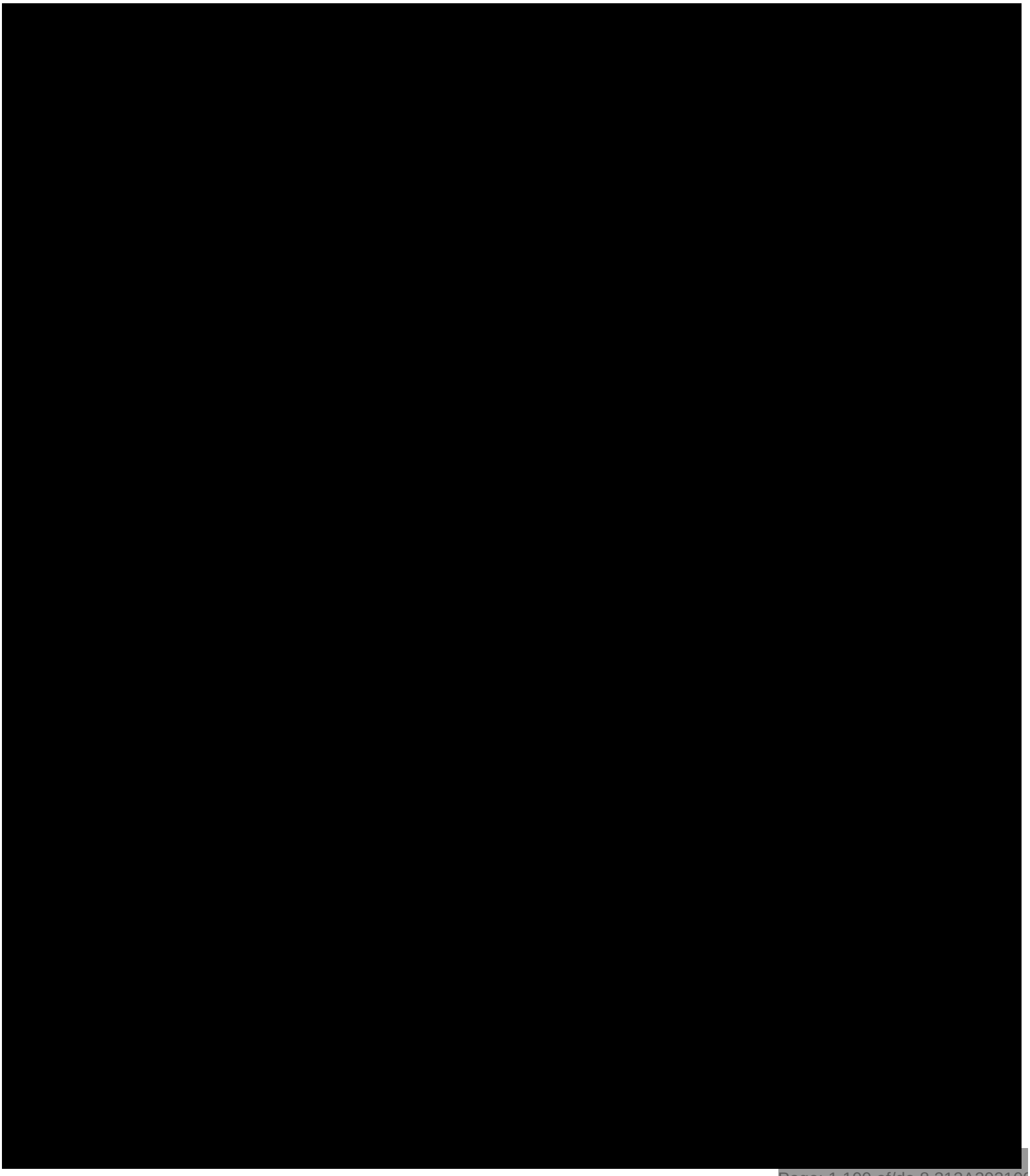

Guidance on amendments to the Food and Drug Regulations for drugs for use in relation to COVID-19: Overview

- Overview
- Preparing a submission
- Drug establishment licences and good manufacturing practices
- Intellectual property
- Post-market requirements
- Pre-positioning of COVID-19 drugs
- Submission scenarios, reference documents and key contacts

This guidance applies to sponsors of new COVID-19 drug submissions as well as sponsors seeking a Notice of Compliance (NOC) for COVID-19 drugs that received temporary authorization under the Interim order respecting the importation, sale and advertising of drugs for use in relation to COVID-19 (ISAD IO). It also applies to new COVID-19 drug establishment licences under the *Food and Drug Regulations*.

This document will help manufacturers prepare a submission for a Notice of Compliance for a COVID-19 drug under the *Regulations.* It also outlines the process for meeting the post-market regulatory requirements.

On this page

- Background
- Scope and application
- Policy objectives
- Policy statements
- Explanation of key terms
- Note about guidance documents in general

Background

The COVID-19 pandemic posed an immediate and significant risk to the health and safety of Canadians. To address the associated public health need in Canada, the Minister of Health made a number of interim orders to expedite and facilitate access

to drugs, medical devices and foods for a special dietary purpose. The Minister used the power granted under section 30.1 of the *Food and Drugs Act* to make these interim orders.

The ISAD IO came into effect on September 16, 2020 and provided:

- an optional, expedited authorization pathway for the importation, sale and advertising of drugs to be used in relation to COVID-19
- modified requirements for drug establishment licence (DEL) applications for those drugs
- the introduction of a mechanism for the placement of COVID 19 drugs in Canadian facilities prior to the authorization to sell in Canada (pre-positioning)

The ISAD IO ends 1 year after it came into effect. After this time, drugs authorized through the ISAD IO would no longer have been legally permitted to be sold in Canada, unless transition measures were implemented.

The ISAD IO provided a temporary emergency authorization for COVID-19 drugs to address the pandemic. The authorization was not a Notice of Compliance. In order for drugs to receive an NOC, a submission needs to be made under Division 8 of the *Food and Drug Regulations*.

The *Food and Drug Regulations* have been amended to allow for modified requirements that facilitate the regulatory process for new COVID-19 drugs to receive an NOC through a new drug submission (NDS). The amendments maintain some of the mechanisms introduced through the ISAD IO, thus continuing to provide Canadians with quick access to safe and effective COVID-19 drugs. This guidance document explains the modified requirements provided in these amendments to the *Regulations*.

For more information on these measures and the ISAD IO, refer to the following items:

- Explanatory note
- Interim order respecting the importation, sale and advertising of drugs for use in relation to COVID-19
- Information and application requirements for drugs authorized under the interim order: Guidance document
- Canada Gazette II of amendments to the *Food and Drug Regulations*

Scope and application

COVID-19 means the coronavirus disease 2019. This guidance document applies to:

- drug products authorized under the interim order
- manufacturers planning to file a submission for a Notice of Compliance (NOC) for a designated COVID-19 drug as defined in C.08.001.2
- establishments seeking a DEL related to COVID-19 drugs

- pre-positioning mechanism introduced under the ISAD IO

A "designated COVID-19 drug" is a new drug for which the purpose and conditions of use recommended by the manufacturer relate to COVID-19. For the purpose of this document, COVID-19 drugs also include designated COVID-19 drugs.

For guidance on obtaining product authorization for disinfectants, hand sanitizers and veterinary health products, manufacturers should refer to the following guidance documents:

- Management of drug submissions and applications
- Management of disinfectant drug applications
- Human-use antiseptic drugs
- Veterinary health products: About the VHP notification program

The amendments introduced in Part C, Divisions 1, 1A, 2 and 8 of the *Regulations* are described in this guidance document. The amendments introduce similar provisions found in the ISAD IO with regards to requirements for drug product authorizations, DEL applications and pre-positioning of products prior to authorization. The integration of these measures in the *Regulations* aims to give Canadians continued and timely access to safe and effective COVID-19 drugs.

Policy objectives

The objective of the amended *Regulations* is to allow for a mechanism for continued and timely access to safe and effective COVID-19 drugs. The review, authorization and oversight of these drugs will be conducted under the *Regulations*.

The amendments to the *Regulations* offer the following benefits:

- continues to support access to safe, effective, and high quality COVID-19 drugs
- enables the sale and advertising of COVID-19 drugs that were authorized under the ISAD IO to continue after the IO expires
- enables manufacturers of new COVID-19 drugs for which an authorization was not sought under the ISAD IO to seek authorization under the *Regulations* with similar requirements as those provided under the ISAD IO
- continues the post-market regulatory obligations placed on authorization holders, manufacturers and importers after the ISAD IO expires
- continues to allow the early importation and placement in Canadian facilities (pre-positioning) of a promising COVID-19 drug for which a federal government contract for its procurement is in place, before that drug receives market authorization in Canada
- continues an agile approach for DELs that authorizes regulated activities for COVID-19 drugs

Under the amended *Regulations*:

1) Health Canada only grants an NOC for a COVID-19 drug under the *Regulations* if it's determined that the benefits and risks of the product are supported by evidence of the drug's safety, efficacy and consistent quality.
2) Any uncertainties or risk mitigation measures related to the drug in the context of the public health need due to COVID-19 are managed through the use of terms and conditions.
3) As with all drugs, Health Canada assesses and monitors the safety and effectiveness of all COVID-19 drugs for which an NOC was issued. If required, Health Canada takes immediate action, including compliance and enforcement measures and the suspension or cancellation of an NOC to protect the health and safety of Canadians.

Policy statements

Manufacturers of COVID-19 drugs may be able to obtain an NOC under the *Regulations* by leveraging certain options and modified requirements carried over from the ISAD IO.

These amendments to the *Regulations* allow for a submission for drugs to treat or prevent COVID-19 to be filed earlier through a "rolling submission" process. Manufacturers are responsible for completing the required documentation and providing the necessary evidence to Health Canada. COVID-19 drug submissions will be prioritized based on public health needs.

Licensing decisions are based on the materials submitted in the application. Health Canada will consider the necessity of the drug in addressing urgent COVID-19-related public health needs.

Manufacturers who have a valid authorization issued under the ISAD IO can file a new drug submission (NDS) under the *Regulations*. Sale of the drug may continue while the submission is in review, as long as it was filed within the 90-day period. (See section on "Timelines within which to file a submission under the *Regulations* to obtain a Notice of Compliance.") Where an expanded indication for COVID-19 was authorized under the ISAD IO for a marketed drug, the manufacturer is able to submit an SNDS to add the new COVID-19 indication. Modified requirements, including the ability to file a rolling submission, are not available to these SNDSs.

With this approach, manufacturers who initially obtained an authorization under the ISAD IO may submit an NDS with the same data as was included in their interim order application, along with any necessary updates. Where applicable, newly available data should be included in the NDS. To facilitate an expedited review, the sponsor should provide a summary of the submission package highlighting any changes. COVID-19 drugs are reviewed on an expedited timeline above the usual performance standards. As such, the Priority Review Policy does not apply.

Manufacturers who had their ISAD IO authorization revoked or who have never applied can also file an NDS submission leveraging the modified requirements for COVID-19 drugs in the *Regulations*.

Explanation of key terms

Designated COVID-19 drug: As defined in C.08.001.2, is a "new drug" under C.08.001. As such, it is subject to the requirements in Part C, Division 8 of the *Food and Drug Regulations*, including the:

- existing NDS and supplemental NDS (SNDS) provisions that require an NOC (see C.08.002(1) and C.08.003(1)) to allow a new drug to be sold
- submission outcomes under C.08.004
- suspension provisions under C.08.006

For this document, designated COVID-19 drugs will be collectively referred to as COVID-19 drugs.

Drug: According to the *Food and Drugs Act*, includes any substance or mixture of substances manufactured, sold or represented for use in:

- the diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical state or its symptoms in human beings or animals
- restoring, correcting or modifying organic functions in human beings or animals
- disinfection in premises where food is manufactured, prepared or kept

Note about guidance documents in general

Guidance documents provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. They also provide guidance to Health Canada staff on how mandates and objectives should be met fairly, consistently and effectively.

Guidance documents are administrative, not legal, instruments. This means that flexibility can be applied by industry. However, to be acceptable, alternate approaches to the principles and practices described in this document must be supported by adequate justification. They should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As always, Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, to help us adequately assess the safety, efficacy or quality of a therapeutic product. We must make sure that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

Guidance on amendments to the Food and Drug Regulations for drugs for use in relation to COVID-19: Preparing a submission or supplement

- Overview
- Preparing a submission
- Drug establishment licences and good manufacturing practices
- Intellectual property
- Post-market requirements
- Pre-positioning of COVID-19 drugs
- Submission scenarios, reference documents and key contacts

On this page

- Submission scenarios
- Modified requirements
- Format and structure for filing
- Content and requirements for filing
- Risk management plan
- Labelling
- Notice of compliance (NOC) for a COVID-19 drug
- Drug identification number (DIN)
- Market notification
- Transparency
- Performance standards
- Fees

Submission scenarios

The Governor in Council introduced amendments to the *Regulations* to provide a mechanism for COVID-19 drugs to be authorized through the issuance of an NOC, based on modified requirements that have been transferred from the ISAD IO.

Table 1 provides an overview of the modified requirements for COVID-19 drugs in the *Regulations*.

The "NDS CV" submission type has been created for NDSs that seek approval on the basis of any of the requirements in subsections C.08.002(2.1), C.08.002(2.2) or C.08.002(2.3) of the *Regulations*. To make use of any of the alternative requirements, the manufacturer must make the statements required by paragraphs C.08.002(2.4)(a) and meet the requirement in C.08.002(2.4)(b). To meet the requirements in subsection C.08.002(2.1), the manufacturer must also make the statement required by paragraph C.08.002(2.1)(a) and meet the requirement in C.08.002(2.1)(b). Manufacturers should ensure that all statements required are made in module 1.2.3, "Certification and Attestation Forms.

For more details, please refer to Submission scenarios. NDS CV submission type means NDS [COVID].

Table 1: Overview of modified requirements for COVID-19 drug submissions

	Submission type	**Available modified requirements**	**Terms and conditions**
New drug with same data as filed under IO (and possible additional data)	NDS	C.08.002(2.1): supportive evidence C.08.002(2.2): draft label C.08.002(2.3): rolling submission	Yes, only if C.08.002(2.1) is used
New COVID-19 drug (not previously filed under the ISAD IO)	NDS	C.08.002(2.1): supportive evidence C.08.002(2.2): draft label C.08.002(2.3): rolling submission	Yes, only if C.08.002(2.1) is used
Marketed drug adding additional indication for COVID-19	SNDS	None	No
Supplemental new drug submissions following authorization of the NDS	SNDS	None	Yes, if carried forward from NDS C.08.002 (2.1) and may include additional (C.01.014.21(1)(b))

Timelines within which to file a submission under the *Regulations* to obtain a Notice of Compliance

The amendments to the *Regulations* provide that an ISAD IO authorization will be revoked unless a submission is filed within:

- 90 days following the coming into force of the amendments, if the drug was authorized under the ISAD IO before the amendments came into force or
- 90 days following the issuance of an authorization under the ISAD IO, if the drug was authorized after the amendments came into force

Where a submission has been filed within these timelines, the COVID-19 drug may continue to be sold under the ISAD IO authorization until the submission has been approved, rejected or withdrawn. This is the case even after the ISAD IO ceases to have effect.

If a manufacturer fails to file a submission under the *Regulations* within the prescribed timelines, the manufacturer will have to wait until the product is authorized under the *Regulations* to resume sale.

Modified requirements

Manufacturers of COVID-19 drugs will have the option to follow similar requirements under the *Regulations* to those under the ISAD IO, as set out in paragraphs C.08.002(2.1) to (2.3). To make use of these alternate requirements, manufacturers must include a statement identifying that the purpose and conditions of use specified in the NDS relate only to COVID-19.

Manufacturers should ensure that all statements required are made in module 1.2.3, "Certification and Attestation Forms." Manufacturers are also encouraged to identify in a cover letter the modified requirements they intend to follow.

Modified requirements include:

- ability to file a rolling submission(C.08.002(2.3))
- exemption from submitting detailed reports of tests made to establish the safety and clinical effectiveness of the new drug under C.08.002(2)(g) and (h)
    - however, the manufacturer must provide sufficient evidence that the benefits of the drug outweigh the risks, taking into account uncertainties as well as the public health need due to COVID-19 (C.08.002(2.1)(b))
- exemption from being required under C.08.002(2)(j.1) to provide a mock-up label if the manufacturer provides a draft of the label
    - submission must also include any package insert and document provided upon request that sets out supplementary information on use of the drug (C.08.002(2.2))
- exemption from being required under C.08.002(2)(o) to conduct an assessment as to whether there is a likelihood the new drug will be mistaken for another drug due to a resemblance between the brand names
    - commonly referred to as a brand name assessment

The options available in subsections C.08.002(2.1), C.08.002(2.2) and C.08.002(2.3) only apply if the manufacturer has met the requirements outlined in subsection C.08.002(2.4).

Health Canada intends to assess the requirements of subsections C.08.002(2.1), C.08.002(2.2), C.08.002(2.3) and C.08.002(2.4) in screening.

In accordance with C.08.002(2.5), the amended regulations do not apply if the manufacturer is seeking a notice of compliance for a COVID-19 drug on the basis of a direct or indirect comparison between the COVID-19 drug and another COVID-19

drug (for example, a generic or biosimilar submission). Submissions will be assessed under C.08.002(2.5) before a submission receives a filing date.

Safety and efficacy: C.08.002(2.1) as an alternative to C.08.002(2)(g) and C.08.002(2)(h)

The *Regulations* were amended to allow manufacturers who seek approval for a COVID-19 drug to file a submission with an alternative data package where justified based on the urgent public health needs resulting from COVID-19. As more products emerge to address the public health needs brought upon by COVID-19, manufacturers should discuss data requirements with Health Canada prior to filing. A data package based on C.08.002(2.1) may only be appropriate in some circumstances.

Following discussion with Health Canada, a manufacturer may file an NDS for a COVID-19 drug without complying with the requirements set out in paragraphs C.08.002(2)(g) and C.08.002(2)(h). To do so:

- the manufacturer must state that the NDS is for a COVID-19 drug (C.08.002(2)(2.1)(a))
- the NDS must contain sufficient safety, efficacy and quality evidence such that the benefits of the new drug outweigh the risks (C.08.002(2)(2.1)(b))

Manufacturers should make the required statement in module 1.2.3, "Certification and Attestation Forms." Manufacturers are encouraged to specify in a cover letter that the NDS relies on subsection C.08.002(2.1) of the *Regulations* to facilitate processing.

A manufacturer who relies on C.08.002(2.1) to provide evidence of safety and efficacy will be subject to any terms and conditions that might be imposed on an NOC issued for the COVID-19 drug. (See paragraph C.01.014.21(1)(b).) In the context of the public health need related to COVID-19, the manufacturer is required to include in the NDS sufficient safety, efficacy and quality evidence showing that the drug's benefits outweigh the risks. Health Canada reviews the NDS and will apply terms and conditions on the authorization to require the manufacturer to address risks and uncertainties after authorization.

If the manufacturer has a full data package to support the NDS, then they may choose not to rely on C.08.002(2.1).

For more information, see the following guidance documents on:

- Evidence requirements for COVID-19 vaccines
- Evidence requirements for COVID-19 drugs

Product labels

C.08.002(2.2) provides for exemption from the requirement in C.08.002(2)(j.1) to provide a mock-up of labels of the drug.

However, the submission must contain a draft of every label to be used with the new drug. This includes any package insert and any document that sets out supplementary information on the use of the new drug.

Manufacturers are encouraged to specify in a cover letter that the NDS relies on subsection C.08.002(2.2) of the *Regulations* to facilitate processing.

Rolling submissions

C.08.002(2.3) carries over a manufacturer's ability to file a rolling submission, as permitted in the ISAD IO. It is recognized that submissions may not be complete at the time of initial filing. Health Canada will begin its review using the information submitted by the manufacturer and accept new evidence as it becomes available until the submission is deemed complete. A manufacturer may file an NDS for a new COVID-19 drug without including some of the data otherwise required under:

- paragraphs C.08.002(2)(e) to C.08.002(2)(k), C.08.002(2)(m) and C.08.002(2)(n)
- paragraph C.08.002(2.1)(b) or
- subsection C.08.002(2.2)

This rolling review process can reduce the time it takes to authorize these critical new drugs while maintaining appropriate standards of safety, efficacy and quality.

To file a rolling submission, the manufacturer must include all applicable forms and other administrative components. The NDS must also include a plan identifying the missing parts of the submission. This plan must specify how and when the missing information or material will be provided to the Minister during the review period. (See C.08.002(2.3).)

Manufacturers are encouraged to specify in a cover letter that the NDS relies on subsection C.08.002(2.3) of the *Regulations* to facilitate processing. As with other NDSs under Division 8, the filing date refers to the date that:

- the NDS is deemed administratively complete by Health Canada
- all the elements and forms required for processing are completed and submitted to Health Canada

The filing date may differ from the date of original receipt if the submission is considered to be administratively incomplete at that time. Data or information that is subsequently provided in a rolling submission will be considered solicited information under the NDS and will not change the filing date of the submission.

Sufficient information must be submitted within a reasonable timeframe. The Minister reviews the NDS based on the requirements and makes a decision, as per section C.08.004 of the *Regulations*.

The plan should contain:

- a list of the non-clinical, clinical and quality data to be provided (planned and in progress)
- a timeframe for when this clinical and quality data will be available
- a timeframe for when this clinical and quality data will be filed for review

If the missing information outlined in the plan will be submitted as multiple packages, the plan must clearly specify what information will be contained in each data package. For example:

- data package A will be submitted on DD/MM/YYYY and contains results from studies XX, YY and ZZ
- data package B will be submitted on DD/MM/YYYY and contains results from studies MM, NN and OO

Pre-submission meetings provide an opportunity to discuss the plan in detail. These meetings should be used to:

- establish submission content and timelines
- determine the data that will be submitted when the submission is filed
- determine the data that will be provided at a later date

The cover letter should refer to the plan. If changes are required to labelling to reflect the new information, annotated and clean copies of the drug labels should be included.

Health Canada will:

- review the submission to ensure it includes the detailed plan
- assess the information submitted by the manufacturer
- accept new evidence as it becomes available until the review has been completed

Any subsequent data or information sent later is considered solicited information under the NDS if the data or information is provided according to the plan or in response to Health Canada's request. Information or data provided otherwise may be considered unsolicited information.

Health Canada will not issue an NOC until the Minister is satisfied that the NDS complies with the requirements of C.08.002.

Regulatory activity and transaction details for designated COVID-19 drugs

As noted above, modified requirements introduced through amendments to the *Regulations* are only available for an NDS. The "NDS CV" submission type has been created for NDSs that use any of the provisions in subsections C.08.002(2.1), C.08.002(2.2) or C.08.002(2.3) of the *Regulations*. The manufacturer must select the "NDS CV" submission type in the appropriate Regulatory Enrolment Process (REP) regulatory transaction template when submitting their NDS. "NDS CV"

submission types are described as "Drug Submission with modified requirements for Designated COVID-19 drugs."

To file an NDS that does not benefit from any of the modified requirements mentioned in the 3 subsections above, a manufacturer must select the regular NDS submission type when submitting its NDS.

Pre-submission meetings

Manufacturers are encouraged to have regular communications with Health Canada. Early and ongoing consultation(s) with Health Canada help ensure that regulatory requirements are met.

Before filing an NDS, manufacturers are encouraged to request a pre-submission meeting to discuss all aspects of their submission. At this meeting, Health Canada will expect you to describe your submission plan and indicate how and when you will provide the Minister with the missing information or material, if applicable (subsection C.08.002(2.3)).

To request a pre-submission meeting with the appropriate directorate, consult the guidance documents on the:

- Management of drug submissions and applications
- Management of regulatory submissions for veterinary drugs

For relevant contact information, please see key contacts.

Format and structure for filing

For general procedures on how to file applications, please also refer to the guidance documents on the:

- Management of drug submissions and applications or
- Management of regulatory submissions for veterinary drugs

Submissions for human drugs should be formatted, structured and filed as outlined in the:

- Guidance document on the preparation of regulatory activities in the eCTD format
- Organisation and document placement for Canadian module 1
- Guidance document on the regulatory enrolment process (REP)

Manufacturers who cannot comply with the formatting requirements may contact the Office of Submissions and Intellectual Property for further options and guidance. Please send an email to hc.ereview.sc@canada.ca.

Submissions for veterinary drugs should be formatted, structured and filed as outlined in the following guidance documents on the:

- Preparation of regulatory activities in the non-eCTD format
- Regulatory enrolment process (REP)

Manufacturers who cannot comply with the formatting requirements may contact the Veterinary Drugs Directorate by email at hc.vdd.skmd.so-dgps.dmv.cp.sc@canada.ca.

Submissions made under the *Regulations* must be independent from any ISAD IO application. At a minimum, they must contain the same data that was included in the ISAD IO application, along with any required updates. The sponsor must include all the data they rely on to support their submission in the NDS.

Submissions filed under the *Regulations* for which an application was previously filed under the ISAD IO will receive the same dossier ID as the ISAD IO application. Manufacturers are expected to identify this dossier ID in relevant correspondence.

Content and requirements for filing

For both the non-clinical and clinical information package, you may not need to include as much information as you do for a data package in a typical drug submission. This is balanced by additional information, which is to be provided as part of the rolling submissions as well as the terms and conditions of authorization.

Non-clinical information and requirements

Key non-clinical information may be required to:

- demonstrate the potential for clinical effectiveness under the proposed conditions of use
- support the safety of the COVID-19 drug

All key studies should be conducted in accordance with good laboratory practices.

For more information, consult the following guidance document:

- Non-clinical laboratory study data supporting drug product applications and submissions: Adherence to good laboratory practice

Clinical information and requirements

A manufacturer may submit an NDS relying on the modified requirements in C.08.002(2.1) to (2.3). All known information should be provided to support the safety and efficacy of the COVID-19 drug. This includes all available clinical trial data and the safety and efficacy summary documents.

For more information, consult the following guidance documents on:

- Evidence requirements for COVID-19 vaccines

- Evidence requirements for COVID-19 drugs

Quality (chemistry and manufacturing) information and requirements

For further guidance on meeting application and information requirements, consult the list of guidance documents. Under section C.08.002(2.3) in the *Regulations,* the manufacturer may provide the information and material normally required under paragraphs (2)(e), (f) and (m) on a rolling basis. The manufacturer must specify in their plan how and when they will provide the missing information to Health Canada.

For more information, consult the following guidance documents on:

- Evidence requirements for COVID-19 vaccines
- Evidence requirements for COVID-19 drugs

Comparative submissions for subsequent entry drugs

Under the Abbreviated New Drug Submissions (ANDS) and NDS pathways of the *Food and Drug Regulations*, manufacturers of subsequent entry drugs (generics and biosimilars) can seek an NOC on the basis of a comparison to a drug that has already received an NOC.

Manufacturers must demonstrate similarity to an authorized reference drug (for example, in the case of generics, a Canadian reference product as defined in section C.08.001.1). This is done by filing a comparative submission that relies, in part, on the previously authorized evidence of safety and effectiveness for the reference drug. The manufacturer may then submit a reduced data package in the submission.

The amendments do not extend the modified requirements provided under new subsections C.08.002(2.1), (2.2) and (2.3) to cases where manufacturers seek an NOC for a COVID-19 drug on the basis of a direct or indirect comparison between that drug and another COVID-19 drug.

The *Regulations* do not allow comparative submissions to be filed while benefitting from any of the modified requirements, even where consent from the reference product manufacturer is provided. Therefore, comparative submissions are expected to be filed as an ANDS or a comparative NDS.

Health Canada will apply subsection C.08.002(2.5) of the *Regulations* in processing and comparative submissions that seek approval on the basis of any of the new subsections C.08.002(2.1), (2.2) and (2.3) will not receive a filing date. When it appears that the filing of a submission is prevented, the manufacturer will be provided with a written preliminary decision and an opportunity to make representations in response. If, following consideration of the representations, Health Canada remains of the view that the submission cannot be filed, the manufacturer will be notified and the submission will not be processed further.

Manufacturers of subsequent entry products are prohibited from filing a submission on the basis of a direct or indirect comparison to a COVID-19 drug for which an authorization was issued under the ISAD IO (C.08.003.01(2)). Note that subsection C.08.003.01(2) is not intended to prevent the filing of a submission that contains new data from clinical trials comparing the efficacy of the new drug to an existing one. Also note that C.08.003.01 does not prevent the filing of a submission or supplement on the basis of a comparison to a COVID-19 drug that has received an NOC (C.08.003.01(3)).

Manufacturers who intend to file a submission seeking an NOC for a COVID-19 drug on the basis of a comparison with another COVID-19 drug are encouraged to contact Health Canada for a pre-submission meeting.

Information and requirements for veterinary drugs

A COVID-19 drug submission should contain all available information to help Health Canada assess the drug's safety, efficacy and quality. Information should include evidence of its efficacy in the target species, animal safety, human safety and quality.

For drugs used in a food-producing animal, information should be provided on the safety of drug residues in meat and other food products from the treated animal intended for human consumption.

Risk management plan

Manufacturers should submit a Risk Management Plan (RMP) for a COVID-19 drug. If an RMP has been filed as part of the ISAD IO application, an updated RMP with the most recent post marketing data, risk minimization measures and pharmacovigilance activities should be submitted.

The RMP should focus on the product's updated safety risks in the context of COVID-19 use to ensure that:

- the benefit-risk profile of the product is managed optimally during its life-cycle
- knowledge gaps at the time of authorization are described and risks are further quantified and characterized over time

It should:

- outline the product's safety risks related to COVID-19 use
- outline the pharmacovigilance activities and risk minimization activities used to identify, characterize, prevent or minimize risks
- contain an evaluation of the effectiveness of such risk minimization measures

For information on the scope of RMPs, please refer to the following guidance document:

- Submission of risk management plans and follow-up commitments

For COVID-19 drugs submitted for authorization, the RMP should include the following:

- safety specification section on the identified risks, potential risks and missing information for the product (for example, special populations where there is limited information or who were excluded from clinical trials), with a focus on risks in COVID-19 patients, where appropriate
- pharmacovigilance plan on the specific activities to be taken to identify and report safety issues, including expedited adverse reaction reporting, periodic reporting and ongoing/planned studies to quantify and characterize those risks (for example, registries, prospective cohort studies)
- risk minimization plan to manage the safety risks including routine risk minimization measures (for example, labelling) and additional measures beyond those considered routine (such as educational materials for health care professionals or patients, or a restricted access or distribution program), if needed
- plan to measure the effectiveness of additional risk minimization activities

An RMP that has been reviewed and accepted as part of the submission for a COVID-19 drug is expected to be implemented. If the manufacturer filed under the requirement in subsection C.08.002(2.1), any elements of an RMP that are essential for the safe and effective use of the product could be identified as terms or conditions and must be implemented.

A Canadian addendum that demonstrates that the RMP meets Canadian regulatory requirements must accompany the core RMP. Information on these requirements are provided in the following guidance documents and recent notice:

- Evidence requirements for COVID-19 vaccines
- Evidence requirements for COVID-19 drugs
- Notice of clarification to drug manufacturers and sponsors on Canadian-specific considerations in risk management plans

If you have a question about the type of quality, safety and effectiveness information required, please contact the appropriate directorate within Health Canada. Please refer to the key contacts for relevant contact information.

Labelling

Manufacturers of a COVID-19 drug must comply with all applicable labelling requirements in the *Food and Drugs Act* and parts A and C of the *Regulations:*

- A.01.014
- A.01.015
- A.01.60.1 to A.01.068
- A.01.065

- C.01.004 to C.01.011
- C.01.401
- C.03.202
- C.03.203
- C.03.206 to C.03.209
- C.04.019 and C.04.020

Existing regulatory provisions on the labelling of veterinary drugs also apply.

Manufacturers that file an NDS for a COVID-19 drug using the modified requirements may be asked to include a warning statement on the inner and outer labels. This statement may be displayed on any panel. The data submitted to support the NDS and any associated terms and conditions that the Minister places on the DIN will dictate this.

The plain language labelling requirements for mock-up labels and a brand name assessment package do not apply (C.08.002(2)(j.1) and C.08.002(2)(o)).

While exempt from these requirements, manufacturers are strongly encouraged to complete and submit a brand name assessment package and to provide mock-up labels:

- at the time of NDS filing (if available) or
- at the earliest time after the NDS is filed

Manufacturers may also file these materials after the NOC is granted.

Health Canada may apply labelling terms and conditions as necessary. We will request that the sponsor submit a brand name assessment and final mock-up package labels at an agreed-upon time if the sponsor chooses to use the labelling modified requirements provided by the *Regulations*.

Manufacturers that are unable to provide a complete brand name assessment package at the time of filing or at the earliest time after the NDS is filed, may provide a package where simulation exercises are omitted.

Plain language labelling and Look-alike Sound-alike components are not needed with respect to the labelling of veterinary drugs.

Consult the list of guidance documents for further guidance on labelling.

Filing a supplement to an NDS for a COVID-19 drug

A manufacturer of a COVID-19 drug that holds an authorization for a new drug under the ISAD IO may file an NDS under section C.08.002 of the *Regulations*. Once the manufacturer receives an NOC for the COVID-19 drug, they may file a supplement to that new drug submission (SNDS) for any changes post-NOC. Where applicable, the manufacturer may also be able to incorporate the change as part of its NDS.

Consult the following guidance documents on post-NOC:

- Framework document for pharmaceutical, biologic and radiopharmaceutical drugs for human use only
- Safety and efficacy document for pharmaceutical, biologic and radiopharmaceutical drugs for human use only
- Post-notice of compliance (NOC) changes: Quality document

Notice of compliance (NOC) for a COVID-19 drug

For Health Canada to issue an NOC (C.08.004) for the sale of a COVID-19 drug, the NDS must meet the requirements of section C.08.002. For drugs relying on the modified requirements in C.08.002 (2.1), the NDS must contain enough evidence to support the conclusion that the drug's benefits outweigh the risks when used as indicated. The evidence takes into consideration the uncertainties around the drug in the context of the public health need related to COVID-19.

Drug identification number (DIN)

When the manufacturer of a COVID-19 drug that was previously authorized under the ISAD IO submits an NDS to obtain an NOC, the DIN that was assigned under the ISAD IO remains active until the NDS has been approved, rejected or withdrawn. This ensures that all regulatory obligations associated with the DIN continue.

Once an NOC is issued for a COVID-19 drug, Health Canada may assign the same digits for the DIN under C.01.014.2 as were issued under section 7 of the ISAD IO.

If the submission that was submitted under the *Regulations* is rejected or withdrawn, the DIN will be revoked at that time.

Manufacturers should refer to the Guidance document on the regulatory requirements for drug identification numbers (DINs) for more information on DINs.

Terms and conditions on a DIN pertaining to a COVID-19 drug relying on modified requirements in C.08.002(2.1)

Health Canada may at any time impose or amend terms and conditions on a DIN (C.01.014.21(1)(b)) of a COVID-19 drug where the manufacturer relied on C.08.002(2.1) to obtain an NOC. If the manufacturer only used other provisions, then the terms and conditions power does not apply.

This authority allows Health Canada to issue an NOC for a COVID-19 drug while attaching additional conditions that the DIN holder must comply with. These terms or conditions are used to ensure appropriate oversight, manage uncertainties or mitigate risks. However, the terms and conditions on a DIN for a COVID-19 drug using the submission flexibility in C.08.002(2.1) will be based on what's needed

when a submission is not able to meet the usual data requirements. Examples of anticipated terms and conditions include:

- specific pharmacovigilance and risk mitigation and management measures
- additional quality information
- confirmation of effectiveness
- drug shortage measures introduced to prevent or alleviate a shortage

The terms and conditions are on the DIN and remain on the DIN regardless of subsequent SNDSs (supplement to a new drug submission). The exception is if the Minister removes the terms and conditions as part of the (SNDS) process.

The terms and conditions may also apply to drugs authorized on the basis of a comparison to a COVID-19 drug, where the NOC of the comparator product had relied on these submission flexibilities (C.01.014.21(1.1)(b)). This ensures that any post-market commitments for a reference product may also be imposed on NOCs issued on the basis of a comparison.

Terms and conditions can be imposed or amended at any time on a DIN for a COVID-19 drug (C.01.014.21(1.1)(a)) that was filed as:

- an NDS under section C.08.002 relying on the data flexibility referred to in C.08.002(2.1)
- a supplement to an NDS for that new drug

They can also be imposed or amended at any time on a DIN for a COVID-19 drug (C.01.014.21(1.1)(b)) authorized on the basis of a direct or indirect comparison to another COVID-19 drug (see C.01.014.21(1.1)(a)) and filed as:

- an NDS filed under C.08.002
- an abbreviated new drug submission (ANDS) filed under C.08.002.1
- a supplement to a new drug submission or an abbreviated new drug submission that is filed under section C.08.003

Health Canada will discuss the terms and conditions with the sponsor prior to imposing them. All terms and conditions are enforceable under section 21.7 of the Act.

Terms and conditions do not apply to any drugs, including COVID-19 drugs, authorized through the existing NDS and SNDS pathway if the manufacturer:

- is able to satisfy the full data requirements (C.08.002(2)(g) and (h))
- has not relied on C.08.002(2.1)

Submitting information to fulfill terms and conditions

Information on the fulfilment of terms and conditions should be submitted as solicited information with an accompanying cover letter. The subject should state "Solicited information, fulfilling Terms and Conditions for COVID-19 drug." Supporting documentation is to be provided.

Health Canada will review the documentation to determine if the conditions have been met. Once we are satisfied that the manufacturer has complied with all the terms and conditions, we will indicate this in a letter and reference the original file/control number.

Market notification

A market notification for a drug authorized under the ISAD IO does not constitute market notification of a drug under the *Regulations*. This is the case even if the same digits have been issued to the drug as the DIN under both the ISAD IO and the *Regulations*.

The manufacturer of a COVID-19 drug authorized under the *Regulations* must notify Health Canada when they first sell the COVID-19 drug under an NOC. The manufacturer must complete, sign, date and return the Health Canada-issued drug notification form (DNF) within 30 days of the date of the first sale. All pages of the DNF must be returned to Health Canada.

The DIN assigned under the ISAD IO will be revoked once the same DIN is assigned to the drug under the *Regulations*. Our drug product database will indicate the DIN as "approved" until the manufacturer submits a completed DNF, at which point the DIN will be "marketed."

If the manufacturer did not file mock-up labels during review, the manufacturer should submit final mock-ups or final printed labels when the COVID-19 drug is marketed or launched.

For more information on market notifications or notifications for the 'interruption of sale,' consult the:

- Guidance document on the regulatory requirements for drug identification numbers (DINs)

Changes in product ownership, mergers and buyouts or licensing agreements

Submissions proposing administrative changes should be filed within Administrative (Abbreviated) New Drug Submissions ((A)NDS).

If sponsors are proposing labelling changes along with the proposed administrative changes, they must file these changes within an (A)NDS 'labelling only' to obtain Health Canada authorization. They must do so before making any changes to labelling materials on the market.

Refer to the following guidance document for more information:

- Administrative processing of submissions and applications involving human or disinfectant drugs

Notification of discontinuation of sale

The manufacturer of a COVID-19 drug must submit the notification of discontinuation of sale to Health Canada within 30 days after the COVID-19 drug is permanently discontinued in Canada. The date of discontinuance is when the manufacturer last sells its drug, not when it is last sold at retail.

For information and general procedures on notification of discontinuance, authorization holders should consult the:

- Guidance document on the regulatory requirements for drug identification numbers (DINs)

For more information on additional requirements on how to report a discontinuance of sale, see the section on shortages or discontinuation of sale.

Transparency

Health Canada will continue to communicate up-to-date information about COVID-19 drugs under the amended *Food and Drug Regulations*.

You can find the following information online:

- COVID-19 vaccines and treatments portal
- submissions for COVID-19 drugs that have been accepted for review in the lists for drug and health product submissions under review
- regulatory decision summaries (RDS) and summary basis of decisions documents (SBDs) for COVID-19 drugs in the drug and health product register
- clinical information used to seek approval of COVID-19 drugs can be viewed on Health Canada's clinical information portal or the drug and health product register
- drug inspection outcomes and measures in the drug and health product inspections database

In addition, Health Canada will continue to provide the most up-to-date approved Risk Management Plans for COVID vaccines in their entirety to external stakeholders upon request.

Please also consult the following guidance documents:

- Public release of clinical information

Performance standards

Health Canada aims to prioritize submissions for COVID-19 drugs. Drug submissions will be prioritized and reviewed to reflect the public health need.

The time required to review a submission will depend on the submission itself, the volume of data to be assessed and the ability of the manufacturer to submit the data as per the plan, where applicable. Published performance standards will apply to submissions related to COVID-19 drugs, other than rolling submissions, made under the *Regulations*.

Rolling submissions will not be subject to performance standards (in other words, credits to manufacturers due to missed performance standards). This is explained in the Fees section below.

For more information, refer to the following guidance documents on the:

- Management of drug submissions and applications
- Management of regulatory submissions for veterinary drugs

Fees

Submission fees

Pre-market evaluation fees will be remitted for submissions filed under the *Food and Drug Regulations* seeking approval for a COVID-19 drug, provided that:

- an application was previously filed under the ISAD IO for the same drug and
- no submission was previously filed under the *Food and Drug Regulations* for that drug

Once a drug has received an NOC under the *Regulations*, the existing Drug Right To Sell (DRTS) fee will apply.

Where an application had not been filed under the ISAD IO, the following fees will apply to COVID-19 drug submissions filed under the *Regulations*:

- existing evaluation fees will be charged for submissions
- existing small business mitigation measures are available for COVID-19 drug submissions, and include
    - full waiver of evaluation fee for the company's first drug submission with Health Canada
    - a 50% reduction in all other evaluation fees as well as a 25% reduction in DIN and DEL fees

Please consult the guidance document on:

- Fees for the review of human and disinfectant drug submissions and applications

Submissions with fees have associated performance standards. Penalties may apply:

- Published performance standards will apply, but it's expected that most COVID-19 drug submissions will be managed and reviewed efficiently.
- Rolling submissions will not be subject to performance standards (in other words, the 25% remittance to manufacturers due to missed performance standards will not apply).

Guidance on amendments to the Food and Drug Regulations for drugs for use in relation to COVID-19: Drug establishment licences and good manufacturing practices

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- Drug establishment licences for COVID-19 drugs
- Applying for a new or amended DEL for a COVID-19 drug
- DEL terms and conditions
- DEL suspension and cancellation
- DEL performance standards
- DEL establishment licence fees
- Transitioning of DELs issued or amended under the ISAD IO
- Good manufacturing practices

Drug establishment licences for COVID-19 drugs

Division 1A of Part C of the *Regulations* applies to COVID-19 drugs. A person must hold a drug establishment licence (DEL) authorizing any activities conducted with respect to COVID-19 drugs.

You can find the following information online:

- how to interpret the *Regulations* for DEL requirements in the Guidance on drug establishment licences (GUI-0002)

- your responsibilities related to the DEL application process and how Health Canada manages DEL applications in the document on the Management of applications and performance for drug establishment licences (GUI-0127)

For more information about drug establishment licences and COVID-19, see our page on drug establishment licences and COVID-19.

If you have questions about the DEL requirements or DEL applications for COVID-19 drugs, please email us at hc.del.questions-leppp.sc@canada.ca. Include the term "COVID-19" in your email subject line for a faster response.

Applying for a new or amended DEL for a COVID-19 drug

New drug establishment licence (DEL) applications (C.01A.005(1)) or amendment applications (C.01A.006(1) (1.1)) for a COVID-19 drug can be submitted under the *Regulations*. Follow the standard process and use the most current version of the application form (FRM-0033).

When applying for a new or amended DEL for a COVID-19 drug, be sure to include the following information:

- the subject line "COVID-19 drug" in the application email, which signals that this is a high-priority application
- a statement in the body of the application email or cover letter that the DEL application is for a COVID-19 drug submitted under C.01A.005(2) or C.01A.006(1.1) of the *Regulations*
- the name of the drug

Submit your completed application form by email to hc.el.applications-le.sc@canada.ca.

For more information on DEL requirements, please consult the following guidance documents on:

- Drug establishment licences (GUI-0002)
- How to demonstrate foreign building compliance with drug good manufacturing practices (GUI-0080)
- Management of applications and performance for drug establishment licences (GUI-0127)

Issuance of a DEL for a COVID-19 drug

Health Canada issues or amends DELs in accordance with Part C, Division 1A of the *Regulations*.

COVID-19-related DEL applications submitted under the *Regulations* are processed in an expedited manner. Timelines for the expedited review are determined on a case-by-case basis. The materials submitted in the application and the volume of information to be assessed are factors in how quickly we can review the application.

For more information on the issuance of a DEL or DEL amendments, please consult the:

- Guidance on drug establishment licences (GUI-0002)

DEL terms and conditions

At any time, Health Canada may impose or amend terms and conditions on DELs for a COVID-19 drug submitted under the *Regulations*. Decisions to impose or amend terms and conditions are based on the need to mitigate or manage additional oversight for risk-based reasons. These reasons include matters related to available evidence, medical necessity and activities conducted.

The ability to impose or amend terms and conditions gives Health Canada the agility to facilitate rapid access to COVID-19 drugs while mitigating risks.

Terms and conditions previously imposed on a DEL issued under the ISAD IO for a COVID-19 drug will continue to apply under the *Regulations* as necessary.

Every person who holds a DEL must conduct the licensable activities in accordance with the licence, and any terms and conditions imposed on it.

DEL holders that do not comply with the terms and conditions imposed on their licence will be subject to compliance and enforcement action for the contravention of s. 21.7 of the Food and Drugs Act. Such actions will align with the legislative framework and the principles outlined in our compliance and enforcement policy for health products (POL-0001).

DEL suspension and cancellation

Health Canada can suspend or cancel a DEL in full or in part for any of the reasons set out in sections C.01A.016 to C.01A.017.1 in order to prevent a risk to the health and safety of the consumer in relation to a COVID-19 drug. When a DEL is suspended or cancelled, the DEL holder must cease all suspended/cancelled activities.

For more information on DEL suspension and cancellation, consult the:

- Guidance on drug establishment licences (GUI-0002)

DEL performance standards

DEL applications related to COVID-19 drugs will be prioritized and reviewed based on the:

- public health need
- materials submitted in the application
- volume of information to be assessed

For more information on the performance standard, consult the guidance document on the:

- Management of applications and performance for drug establishment licences (GUI-0127)

Drug establishment licence fees

DEL fees will be remitted for applications submitted under the ISAD IO until September 16, 2021. After that time, drug establishment licence fees will apply to the review of DEL applications submitted for a COVID-19 drug.

Please consult the guidance document on:

- Fees for the review of human and veterinary drug establishment licence applications

Fees apply for the review of the following types of DEL applications:

- an application for a new or reinstated DEL
- an application for an amendment to add a domestic building to a DEL
- an application for the annual licence review of a DEL

The DEL fee is calculated using the following components:

- Domestic component: the fee charged for each building listed on the licence or application based on the most upstream activity at that building
- Foreign building component: the fee charged for each unique foreign building (or building outside Canada) on the licence or application

Fees can be requested to be waived or reduced for applications filed by:

- a small business
- a publicly funded health care institution
- any branch or agency of the Government of Canada or of a province or territory

Transitioning of DELs issued or amended under the ISAD IO

Applications that have been submitted under section 20 of the ISAD IO before it expires but have not been issued will continue to be reviewed as though they were submitted under subsections C.01A.005(2) or C.01A.006(1.1) of the *Food and Drug Regulations*. For such applications, DEL fees do not apply.

Notification

DEL holders who wish to maintain their licence, or part of their licence, for a COVID-19 drug under the *Regulations* must notify Health Canada before the ISAD IO expires. We recommend doing so at least 30 days before the ISAD IO expires.

To maintain a DEL issued under section 20 of the ISAD IO, please submit the following information to Health Canada:

- include "Maintain COVID-19 drug IO DEL" in the subject line of the notification email
- include details indicating the notification is being submitted to maintain a DEL or part of a DEL issued for an application submitted under section 20 of the ISAD IO
- include the application number assigned by the Drug Establishment Licensing Unit

Health Canada will review your notification to maintain and will inform you if additional information is required.

Failure to notify us will result in the DEL being cancelled, in whole or in part by operation of the transitional rule of the *Regulations*.

Good manufacturing practices

For information on the requirements around good manufacturing practices (GMP), consult the:

- Good manufacturing practices guide for drug products (GUI-0001)

Evidence requirements to support GMP compliance of foreign buildings is included in the following guidance:

- How to demonstrate foreign building compliance with drug good manufacturing practices (GUI-0080)

If you're unable to obtain documents outlined in GUI-0080 due to the pandemic, please email us at hc.foreign.site-etranger.sc@canada.ca. You should contact us before you send in your DEL application. Be sure to include "COVID-19" in your subject line.

If you're unable to host a GMP drug inspection at your facility due to the pandemic, please email us at hc.drug.gmp.questions-bpf.medicaments.sc@canada.ca. We may consider operational relief and flexibilities to inspection timelines as set under the current fee regime on a case-by-case basis. To monitor compliance, GMP inspections will be conducted using a risk-based approach for licensable activities.

Extension of certain flexible measures for DEL and GMP compliance, as communicated in DEL bulletins, will continue until further notice.

For more information about good manufacturing practices and COVID-19, see our page on good manufacturing practices and COVID-19.

Finished product testing

DEL holders must meet all product release requirements as outlined in the *Food and Drug Regulations*.

Finished product testing requirements in C.02.019 of the Regulations no longer apply to a distributor or importer of a schedule D (biologic) COVID-19 drug if it's subject to a written request under the lot release program (C.04.015).

Licence holders must comply with testing requirements set out in Division 2 of the *Regulations*. If you are unable to meet these requirements due to the pandemic, contact us at hc.drug.gmp.questions-bpf.medicaments.sc@canada.ca.

For more information on the lot release program requirements, refer to the:

- Guidance for sponsors on the lot release program for schedule D (biologic) drugs
- Good manufacturing practices guide for drug products (GUI-0001)

Guidance on amendments to the Food and Drug Regulations for drugs for use in relation to COVID-19: Intellectual property

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- Data protection
- Patented Medicines (Notice of Compliance) Regulations
- Certificate of supplementary protection

Intellectual property

As a consequence of the review, authorization and oversight of COVID-19 drugs under the *Regulations*, manufacturers may benefit from intellectual property protections that are available in respect of a submission that results in an NOC. These protections include:

- data protection under section C.08.004.1 of the *Food and Drug Regulations*
- protection under the *Patented Medicines (Notice of Compliance) Regulations (PM (NOC) Regulations)*
- protection under the *Certificate of Supplementary Protection* regime

Data protection

The amendments contain one interpretive provision clarifying the impact of an authorization under the ISAD IO on data protection eligibility, but do not alter these protections.

Subsection C.08.004.1(1) of the *Food and Drug Regulations* provides that an "innovative drug" is one that contains a medicinal ingredient not previously approved in a drug by the Minister and that is not a variation of a previously approved medicinal ingredient. The amendments introduce language to explain that, for the purpose of the definition of "innovative drug" in subsection C.08.004.1(1) of the *Regulations*, a medicinal ingredient is not considered to be approved in a drug by reason of an authorization under the ISAD IO. This provision is not intended to change the scope or current interpretation of "approved" under the existing definition. Rather, it explains the intended application of that definition where a medicinal ingredient was used in a drug authorized under the ISAD IO.

The interpretation of "innovative drug" ensures that an authorization granted under the ISAD IO does not preclude data protection eligibility under the *Regulations*.

Data protection will be assessed in accordance with the existing process, as described in the Guidance document on data protection under C.08.004.1 of the *Food and Drug Regulations*.

Patented Medicine (Notice of Compliance) Regulations

The amendments to the *Food and Drug Regulations* do not disturb the operation of the *Patent Act* or the *Patented Medicine (NOC) Regulations*. Patent lists may be added to the Patent Register at the time the submission or supplement is approved under the *Regulations,* provided the requirements of the *PM(NOC) Regulations* are met.

For a rolling submission, data or information provided after the filing date will not change the filing date of the submission. As with other submissions, patent lists provided after the filing date of the submission must meet the timing requirements of subsection 4(6) of the *PM(NOC) Regulations* to be considered for inclusion on the Patent Register.

The *PM(NOC) Regulations* will continue to be administered in accordance with existing processes. These are described in the guidance document on Patented Medicines (Notice of Compliance) Regulations.

Certificate of supplementary protection

The amendments to the *Food and Drug Regulations* do not disturb the operation of the *Patent Act* or the *Certificate of Supplementary Protection Regulations (CSP Regulations)*. Therefore, a certificate of supplementary protection may be issued in respect of a patent to a drug approved under the *Regulations*, provided the requirements of the *CSP Regulations* and *Patent Act* have been met.

Though not introduced for this purpose, the provisions contained in these amendments allow an earlier filing of an NDS, making it easier for manufacturers to file their NDS within the time period specified in paragraph 106(1)(f) under the

Patent Act and 6(1)(b) established under the *CSP Regulations* to be eligible to obtain a certificate of supplementary protection.

The certificate of supplementary protection scheme will continue to be administered in accordance with existing laws and the process described in the Guidance document on certificates of supplementary protection. Stakeholders are encouraged to consult section 2.2.2 of this document to review Health Canada's continued interpretation respecting an "application for a marketing approval equivalent to an authorization for sale" for the purpose of paragraph 106(1)(f) of the *Patent Act* and paragraph 6(1)(b) of the *CSP Regulations*.

Guidance on amendments to the Food and Drug Regulations for drugs for use in relation to COVID-19: Post-market requirements

- Overview
- Preparing a submission
- Drug establishment licences and good manufacturing practices
- Transparency, intellectual property and data protection
- Post-market requirements
- Pre-positioning of COVID-19 drugs
- Submission scenarios, reference documents and key contacts

The only amendment related to post-market regulation is the Minister's new (continued) authority to impose terms and conditions for a designated COVID-19 drug (C.01.014.21).

To ensure the safe and effective use of a product, additional post-market requirements may be imposed as a term or condition on the authorization. An example of a post-market term or condition on the authorization is the submission and implementation of a risk management plan ((RMP) and/or elements thereof). Otherwise, existing post-market regulations remain the same.

For more information on the scope of RMPs, consult the:

- Guidance document on the submission of risk management plans and follow-up commitments

On this page

- Pharmacovigilance reporting requirements
- Annual summary reporting
- Issue-related summary reports
- Other post-market requirements

Pharmacovigilance reporting requirements

Adverse reaction reporting

Adverse reactions must be reported to the Canada Vigilance Program.

The market authorization holder (MAH) must report within 15 days of receiving the following information (C.01.017):

- domestic serious expected and unexpected adverse drug reactions
- foreign serious unexpected adverse reactions
- unusual failures in efficacy for new drugs (C.08.007, C.08.008)

However, adverse reactions associated with COVID-19 drugs are a priority. MAHs are strongly encouraged to submit reports related to this priority area to Health Canada without delay. MAHs should identify in the report that the drug is a COVID-19 drug.

For information and general procedures on how to report serious adverse drug reactions, consult the guidance document on:

- reporting adverse reactions to marketed health products

You can also obtain more information on submitting reports electronically.

For details on how to report adverse reactions associated with veterinary drugs, MAHs of veterinary drugs are encouraged to contact the Veterinary Drugs Directorate by email at hc.pv-vet.sc@canada.ca.

Annual summary reporting

Once a year and when requested by the Minister of Health, MAHs must conduct a concise, critical analysis of the adverse reactions and serious adverse reactions to a drug. They must also prepare a summary report relating to the reports received during the previous 12 months (C.01.018).

For information on preparing and submitting an annual summary report, consult the guidance document on:

- Preparing and submitting summary reports for marketed drugs and natural health products

Issue-related summary reports

Health Canada may request an issue-related summary report (C.01.019) any time. This report is a concise, critical analysis of a specific safety or effectiveness issue.

For information on preparing and submitting an issue-related summary report, consult the guidance document on:

- Preparing and submitting summary reports for marketed drugs and natural health products

Additional good pharmacovigilance practices

For additional information on good pharmacovigilance requirements, consult the:

- Good pharmacovigilance practices (GVP) guidelines (GUI-0102)

Foreign actions reporting

Under section C.01.050 of the *Regulations*, authorization holders must notify Health Canada of foreign regulatory actions. These include serious risk related to recalls, suspension or revocation of manufacturing or market authorizations within one of the specified foreign regulatory jurisdictions.

For information on this reporting requirement, consult the guidance document on:

- Notifying Health Canada of foreign actions

Other post-market requirements

Record keeping

Under sections C.01.020(1) of the *Regulations*, manufacturers of a COVID-19 drug must maintain records and case reports as they relate to sections C.01.017 to C.01.019.

Under section C.02.020, DEL holders must maintain records for each COVID-19 drug that they fabricate, package/label, distribute or import.

For more information, consult the:

- Good manufacturing practices guide for drug products (GUI-0001)

Shortages or discontinuation of sale

For drugs for human use, authorization holders should consult sections C.01.014.9 and C.01.014.10 and the guide to reporting drug shortages and discontinuations. The guide contains additional information and general procedures on how to report drug shortages and discontinuations of sale.

For details on shortages, see the Interim order respecting the prevention and alleviation of shortages of drugs in relation to COVID-19.

For more information on reporting shortages, authorization holders of veterinary drugs should contact the Veterinary Drugs Directorate by email at hc.vdd.vetdrugs-medsvet.dmv.sc@canada.ca.

Compliance and enforcement

Health Canada monitors compliance, undertakes enforcement activities and works to prevent non-compliance. When taking compliance and enforcement action, Health Canada considers a number of factors while adhering to the legislative framework and principles of our compliance and enforcement policy for health products (POL-0001).

For further guidance, see the list of guidance documents.

Guidance on amendments to the Food and Drug Regulations for drugs for use in relation to COVID-19: Pre-positioning of COVID-19 drugs

- Overview
- Preparing a submission
- Drug establishment licences and good manufacturing practices
- Intellectual property
- Post-market requirements
- Pre-positioning of COVID-19 drugs
- Submission scenarios, reference documents and key contacts

A promising COVID-19 drug may be imported into Canada before it receives a Canadian market authorization. This early importation and placement in Canadian facilities is referred to as "pre-positioning." It facilitates the immediate distribution of the drug upon authorization, making it available to Canadians as early as possible.

This mechanism may be used to import a promising COVID-19 drug into Canada if the Chief Public Health Officer (CPHO) of the Public Health Agency of Canada has notified the Minister identifying the COVID-19 drug that is to be pre-positioned.

To be eligible to import a COVID-19 drug for pre-positioning, several conditions are required:

- The Government of Canada has entered into a contract for its procurement.
- An authorization for the drug has not been issued.
- The manufacturer has filed a submission for the drug's authorization.
- The importer of the drug to be pre-positioned has a valid Canadian drug establishment licence.
- The CPHO has provided the Minister with information required under C.08.009.03.
- The DEL holding importer has provided the Minister with information required under C.08.009.03(2), including

- Evidence demonstrating the foreign building(s) for which the COVID-19 drug is fabricated, packaged, labelled or tested meets the applicable requirements of the provisions of Divisions 2 to 4 of Part C of the *Regulations*.

Importation and distribution of a pre-positioned drug

Following the review of the information provided by the CPHO and importer, the Minister of Health issues a letter to the CPHO indicating whether the requirements of pre-positioning have been met. To facilitate importation of the pre-positioned drug into Canada, a copy of this letter should accompany the product across the border.

The person importing a COVID-19 drug for pre-positioning must have a drug establishment licence (DEL), but does not require the activity of importation to be licensed on the DEL. However, the DEL holder responsible for importing the pre-positioned COVID-19 drug will be subject to certain sections in Part C, Divisions 2 to 4 of the *Regulations* concerning storage, distribution, quality control and rapid recall.

A pre-positioned COVID-19 drug cannot be distributed for use until it is authorized in Canada. It can, however, be moved to an alternate storage facility, as long as the Minister has been notified by the CPHO of the civic address of that facility.

Once the drug receives market authorization in Canada, all DEL requirements apply to subsequent importation and distribution.

Pre-positioned COVID-19 drugs that do not receive market authorization under the *Regulations* must be destroyed or returned to the manufacturer.

For guidance on meeting the regulatory requirements for record keeping, storage and distribution of pre-positioned COVID-19 drugs, consult the:

- Good manufacturing practices guide for drug products (GUI-0001)

Evidence requirements to support the GMP compliance is included in the following guidance document:

- How to demonstrate foreign building compliance with drug good manufacturing practices (GUI-0080)

For more information about good manufacturing practices and COVID-19, visit Good manufacturing practices and COVID-19.

Transition of pre-positioned drugs from the ISAD IO to the *Regulations*

COVID-19 drugs that met the requirements under sections 27 to 30 of the ISAD IO are deemed to have been pre-positioned under the *Regulations*.

Any information provided under sections 27 to 30 of the ISAD IO before it expires but has not been deemed to have met all requirements to pre-position will continue to be reviewed under the *Regulations.*

Guidance on amendments to the Food and Drug Regulations for drugs for use in relation to COVID-19: Submission scenarios, reference documents and key contacts

- Overview
- Preparing a submission
- Drug establishment licences and good manufacturing practices
- Intellectual property
- Post-market requirements
- Pre-positioning of COVID-19 drugs
- Submission scenarios, reference documents and key contacts

On this page

- Submission scenarios
- Reference documents
- Key contacts

Submission scenarios

Please refer to Table 1 in this guidance document for a summary of submission scenarios.

Scenario 1

COVID-19 drug is authorized under the ISAD IO (authorization was not suspended or revoked) and a submission is subsequently filed under the *Food and Drug Regulations* for that drug

Manufacturers would file an NDS under Division 8 of the *Regulations*. The submission must include the same data as was included in the ISAD IO application, along with any necessary updates. This can include new evidence that was not available when the application was filed under the ISAD IO. Manufacturers would outline in a summary the changes to the application compared to the ISAD IO filing.

To maintain the ability to sell the COVID-19 drug authorized under the ISAD IO, the NDS must be filed:

- within 90 days following coming into force of the amendments, if the drug was authorized under the ISAD IO before the amendments came into force or
- 90 days following issuance of an authorization under the ISAD IO, if the drug was authorized after the amendments came into force

Manufacturers can continue selling the COVID-19 drug under the ISAD IO authorization until the NDS is approved, rejected or withdrawn. This is the case even after the ISAD IO expires.

Many of the regulatory provisions found in the ISAD IO are available when filing a submission under the *Regulations*. These are further described in:

- Rolling submissions
- Clinical information and requirements
- Non-clinical information and requirements
- Quality (chemistry and manufacturing) information and requirements
- Product labels
- Labelling

An NDS filed under the amended *Regulations* would support the issuance of the notice of compliance (NOC), along with any applicable terms and conditions. Further details are provided in the:

- Issuance of a notice of compliance for a COVID-19 drug
- Terms and conditions on a drug identification number relying on modified requirements in C.08.002(2.1)

While the NDS is under review, the DIN that was assigned under the ISAD IO remains assigned to the drug authorized under the ISAD IO. This continues to ensure the operation of all regulatory obligations associated with the drug. Sponsors are invited to discuss with Health Canada their plans for packaging and labelling and reuse of a DIN.

Scenario 2

An NDS is filed for a COVID-19 drug for which an application was never filed under the ISAD IO

Manufacturers of new COVID-19 drugs who did not file an application under the ISAD IO may file an NDS seeking approval of the drug on the basis of the modified requirments under the amended NDS pathway in the *Regulations*.

Many of the regulatory provisions found in the ISAD IO are available when filing a submission under the *Regulations*. These are further described in:

- Rolling submissions

- Clinical information and requirements
- Non-clinical information and requirements
- Quality (chemistry and manufacturing) information and requirements
- Product labels
- Labelling

An NDS filed under the amended *Regulations* would support the issuance of the NOC, along with any applicable terms and conditions. Further details are provided in the:

- Issuance of a notice of compliance for a COVID-19 drug
- Terms and conditions on a drug identification number relying on modified requirements in C.08.002(2.1)

The manufacturer will have to wait to receive an NOC before marketing its drug.

Scenario 3

An SNDS for a marketed drug is filed where an expanded indication for COVID-19 was authorized under the ISAD IO

Where an expanded indication for COVID-19 was authorized under the ISAD IO for a marketed drug, the manufacturer is able to submit an SNDS to add the new COVID-19 indication. The amended *Regulations*, including the ability to file an incomplete submission (rolling submission), are not available in this scenario.

To maintain the ability to sell the drug for use in relation to COVID-19, the SNDS must be filed:

- within 90 days following coming into force of the amendments, if the drug was authorized before the amendments came into force or
- 90 days following issuance of an authorization under the ISAD IO, if the drug was authorized after the amendments came into force

Manufacturers can continue selling the COVID-19 drug under the ISAD IO authorization until the SNDS is approved, rejected or withdrawn (even after the ISAD IO expires). Manufacturers are encouraged to file the SNDS before the ISAD IO authorization ceases to have effect.

The manufacturer must include all available known information on the use of the approved drug for COVID-19.

Scenario 4

A submission seeking approval for a subsequent entry drug on the basis of a direct or indirect comparison to a COVID-19 drug (i.e. a comparative submission)

Subsequent entry submissions seeking approval for a COVID-19 drug on the basis of a direct or indirect comparison to another COVID-19 drug are not eligible to

benefit from the amended *Regulations*. These submissions will be filed as an ANDS or a comparative NDS.

Reference documents

Authorization application guidance documents and webpages:

- Management of drug submissions and applications
- Guidance document: Preparation of regulatory activites in the eCTD format
- Guidance document: Preparation of regulatory activities in the "Non-eCTD electronic-only" format
- Regulatory enrolment process
- Common electronic submissions gateway
- Management of regulatory submissions for veterinary drugs
- Filing submissions electronically

General guidance documents:

- Information and submission requirements for biosimilar biologic drugs
- Drug submissions relying on third-party data (literature and market experience)
- The use of foreign reviews by Health Canada
- Determining prescription status for human and veterinary drugs
- Questions and answers: Prescription drug list
- Regulatory requirements for drug identification numbers (DINs)
- Drug establishment licences and COVID-19
- Good manufacturing practices and COVID-19
- Compliance and enforcement policy for health products (POL-0001)
- Drug and medical device databases
- Regulatory roadmap for biologic (Schedule D) drugs in Canada

Safety and efficacy guidance documents:

- Non-clinical laboratory study data supporting drug product applications and submissions: Adherence to good laboratory practice
- Preparation of comparative bioavailability information for drug submissions in the CTD format
- *Cochrane Handbook for Systematic Reviews of Interventions*
- Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement

Quality guidance documents:

- Preparation of quality information for drug submissions in the CTD format: Biotechnological/biological (biotech) products
- Preparation of quality information for drug submissions in the CTD format: Conventional biotherapeutic products
- Quality (chemistry and manufacturing) guidance: New drug submissions (NDSs) and abbreviated new drug submissions (ANDSs)

Labelling guidance documents:

- Review of drug brand names: Guidance document for industry
- Frequently asked questions review of drug brand names
- Good label and package practices guide for prescription drugs (GLPPG)
- Questions and answers: Plain language labelling regulations for prescription drugs
- Labelling of special containers policy
- Labelling of pharmaceutical drugs for human use
- Product monograph guidance documents and notices

Establishment licensing guidance documents:

- Guidance on drug establishment licences and drug establishment licensing fees (GUI-0002)
- Management of applications and performance for drug establishment licences (GUI-0127)

Good manufacturing practices (GMP) guidance documents:

- Good manufacturing practices guide for drug products (GUI-0001)
- Annex 2 to the current edition of the good manufacturing practices guidelines schedule D drugs (biological drugs) (GUI-0027)
- How to demonstrate foreign building compliance with drug good manufacturing practices (GUI-0080)
- Good manufacturing practices (GMP) for Active Pharmaceutical Ingredients (APIs) (GUI-0104)

Good laboratory practices (GLP) guidance document:

- Good laboratory practices (GLP) guidelines (Dir-9801)

Post-market vigilance guidance documents :

- Reporting adverse reactions to marketed health products (overview)
- Report an adverse reaction to a drug: industry
- Preparing and submitting summary reports for marketed drugs and natural health products
- Good pharmacovigilance practices (GVP) guidelines (GUI-0102)
- Notifying Health Canada of foreign actions: Guidance document for industry
- Amendments to the *Food and Drugs Act*: Guide to new authorities (power to require and disclose information, power to order a label change and power to order a recall)
- Format and content for post-market drug benefit-risk assessment in Canada
- Submission of risk management plans and follow-up commitments
- Guide to reporting drug shortages and discontinuations
- Recall policy for health products (POL-0016)
- Drug and natural health products recall guide (GUI-0039)

Post-notice of compliance (NOC) changes guidance documents:

- Framework document (pharmaceutical, biologic and radiopharmaceutical drugs for human use only)
- Quality document
- Safety and efficacy document (for pharmaceutical, biologic and radiopharmaceutical drugs for human use only)

Advertising guidance documents:

- Marketing of drugs and medical devices

Disinfectants guidance documents and monograph :

- Management of disinfectant drug applications
- Safety and efficacy requirements for surface disinfectant drugs
- Disinfectant drugs
- Applying for a drug identification number (DIN) for a disinfectant drug during the COVID-19 pandemic
- Hard-surface disinfectants monograph

Non-prescription pharmaceuticals and hand sanitizer (antiseptic skin cleansers) guidance documents and monographs:

- Human-use antiseptic drugs
- Management of drug submissions and applications
- Compendium of monographs

Key contacts

To help ensure that we prioritize your inquiry, please include "COVID-19 drug" in the subject line of your email.

Biologic and Radiopharmaceutical Drugs Directorate
Office of Regulatory Affairs
Email: hc.brdd.ora.sc@canada.ca

Therapeutic Products Directorate
Regulatory Project Management Division
Email: hc.rpmd-dgpr.sc@canada.ca

Veterinary Drugs Directorate
Submission and Knowledge Management Division
Email: hc.vdd.skmd.so-dgps.dmv.cp.sc@canada.ca

Natural and Non-prescription Health Products Directorate
General Enquiries
Email: hc.nnhpd-dpsnso.sc@canada.ca

For intellectual property-related inquiries:

Office of Patented Medicines and Liaison
Email: hc.opml-bmbl.sc@canada.ca

For application format-related inquiries:

Office of Submissions and Intellectual Property
Email: hc.ereview.sc@canada.ca

For adverse reaction reporting-related inquiries:

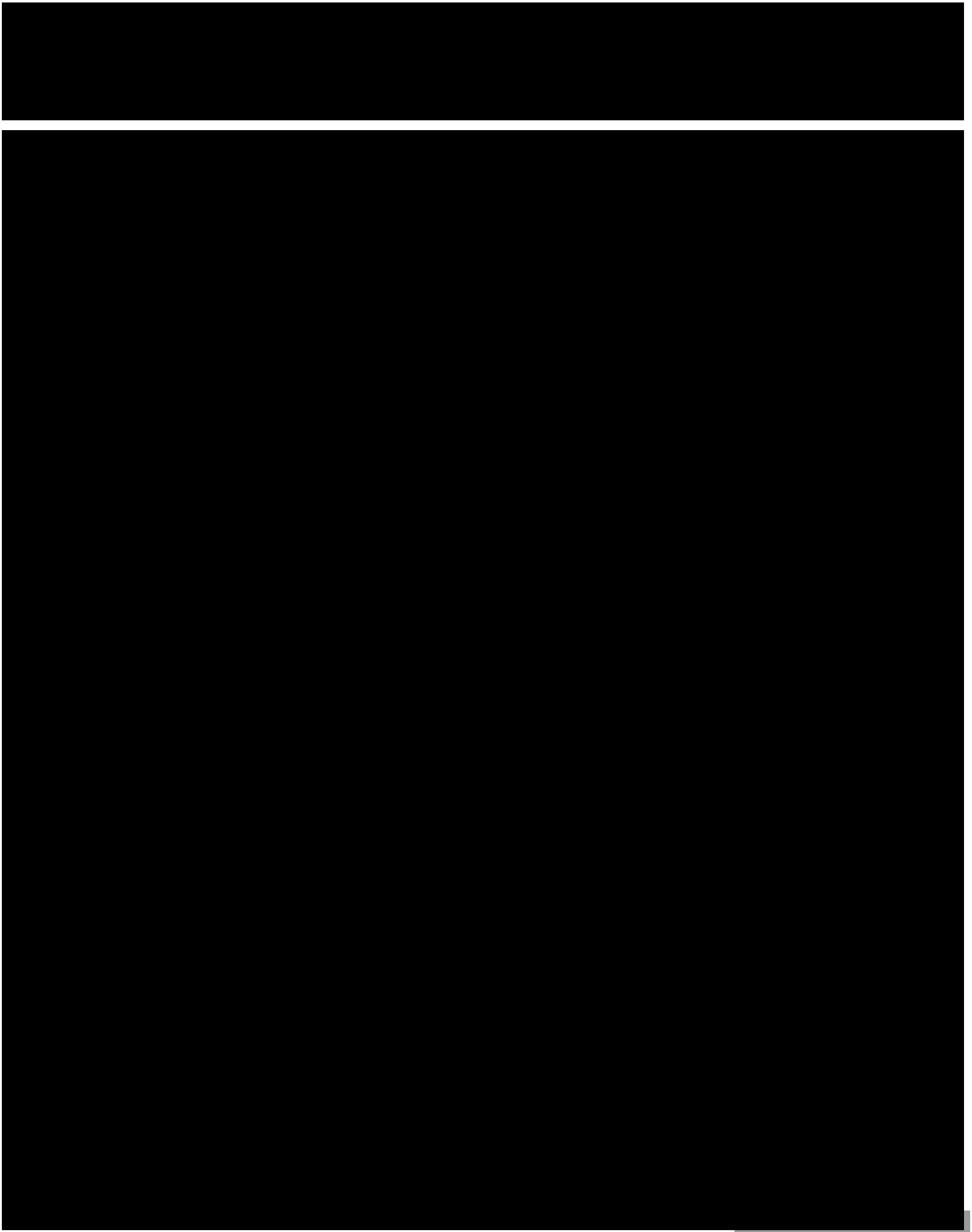
Canada Vigilance Program (CVP)

For inquiries about good manufacturing practices (GMP) compliance requirements:

Email: GMP_Questions_BPF@hc-sc.gc.ca

For drug establishment licensing (DEL)-related inquiries:

Email: hc.del.questions-leppp.sc@canada.ca



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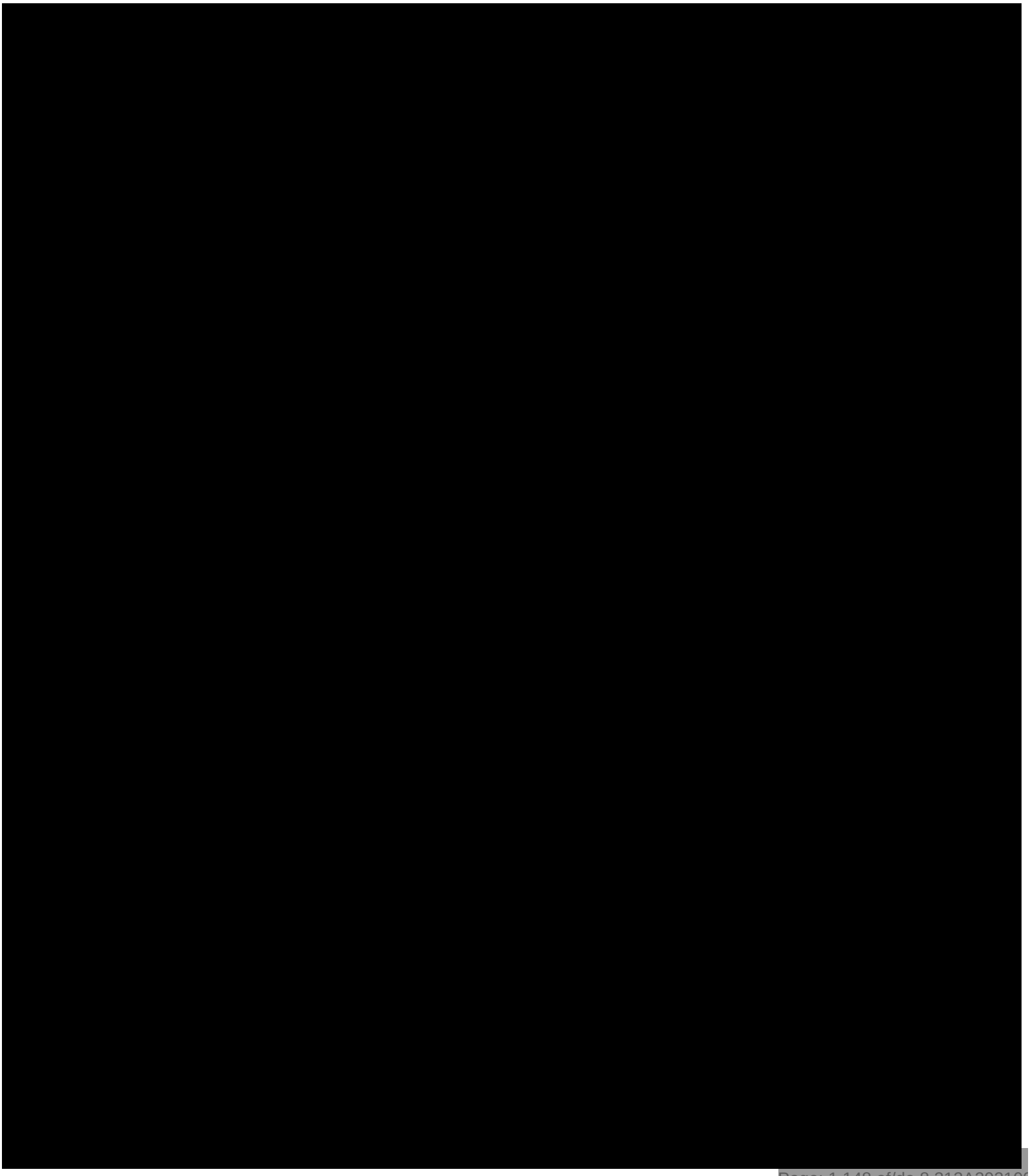

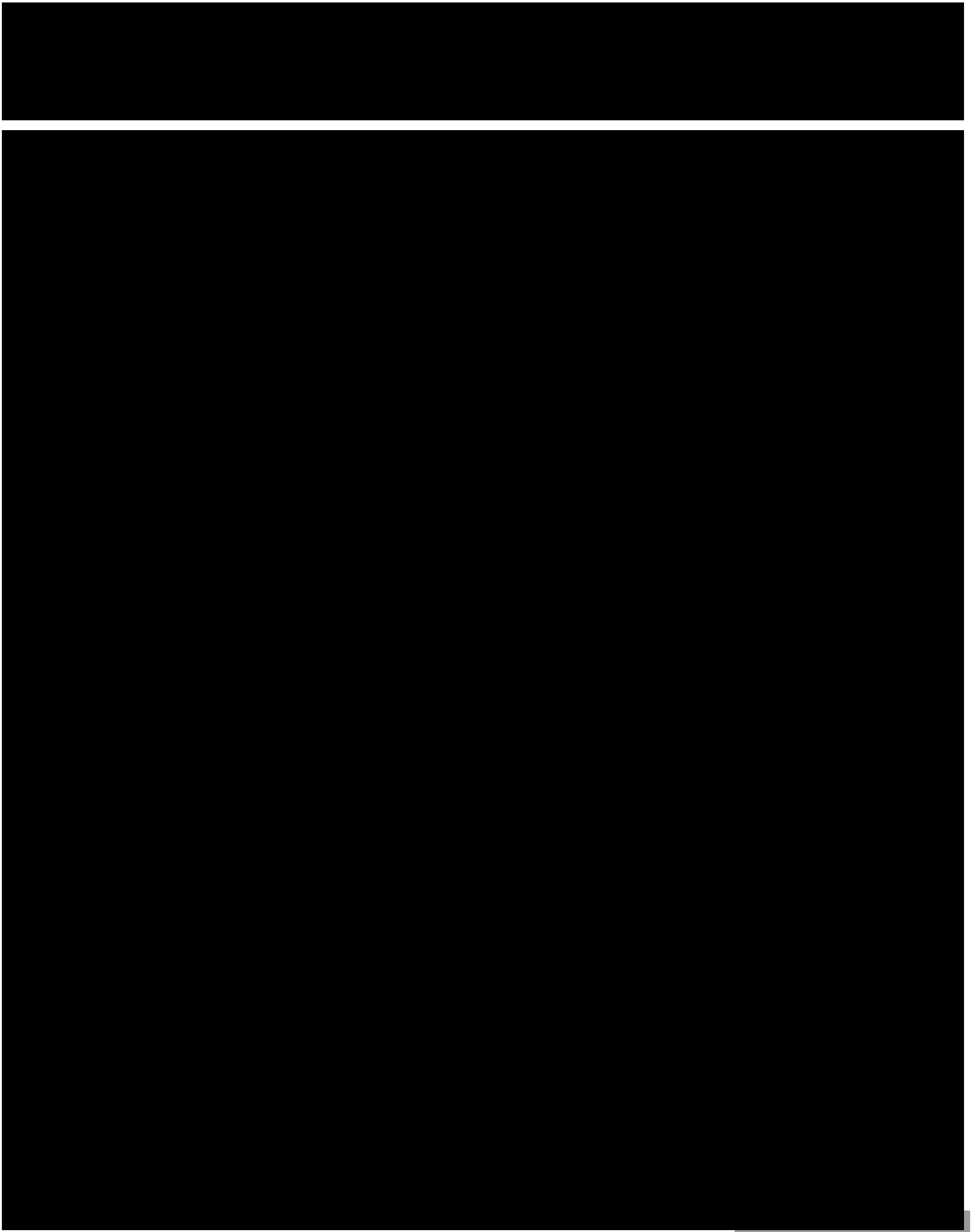

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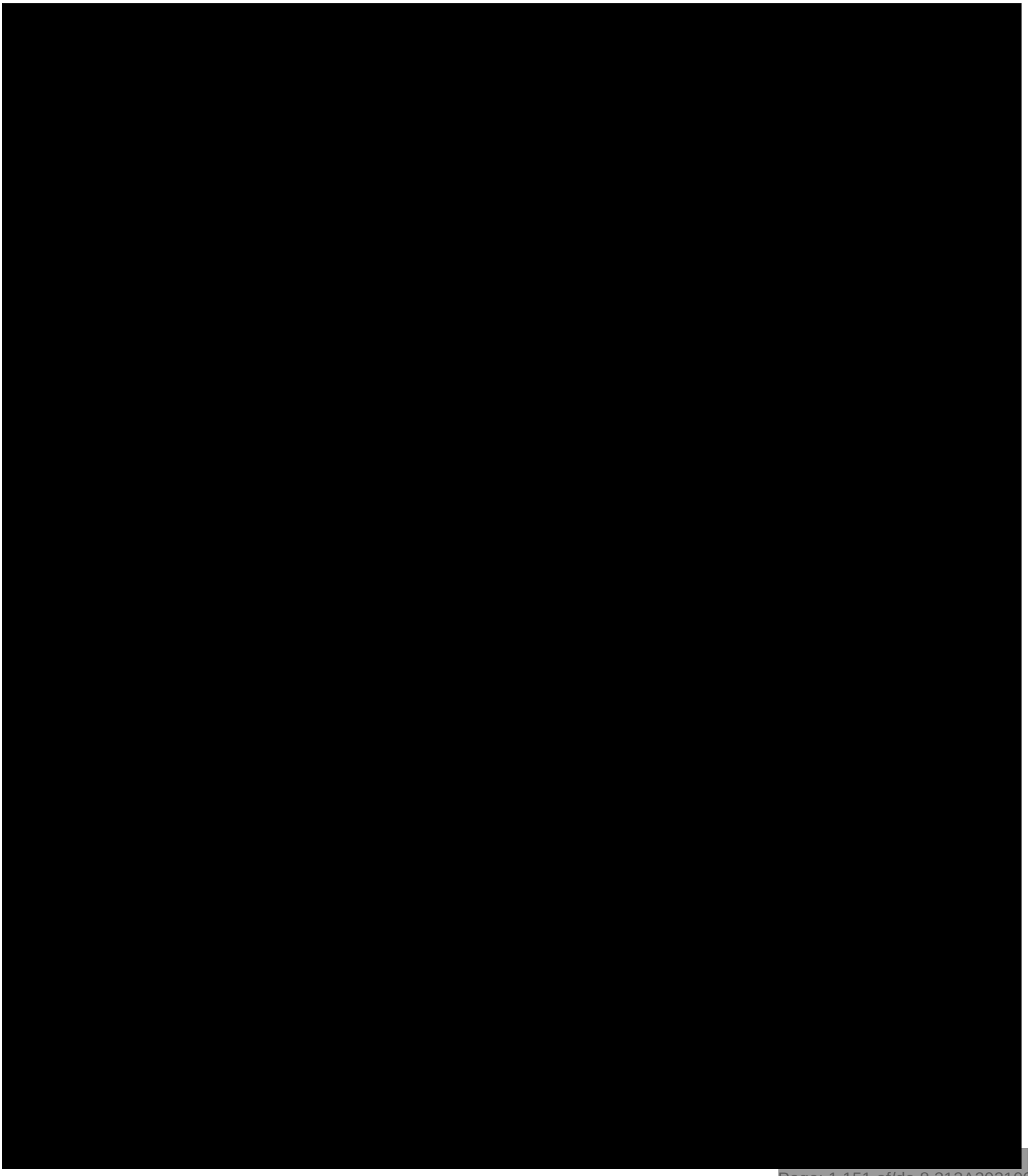

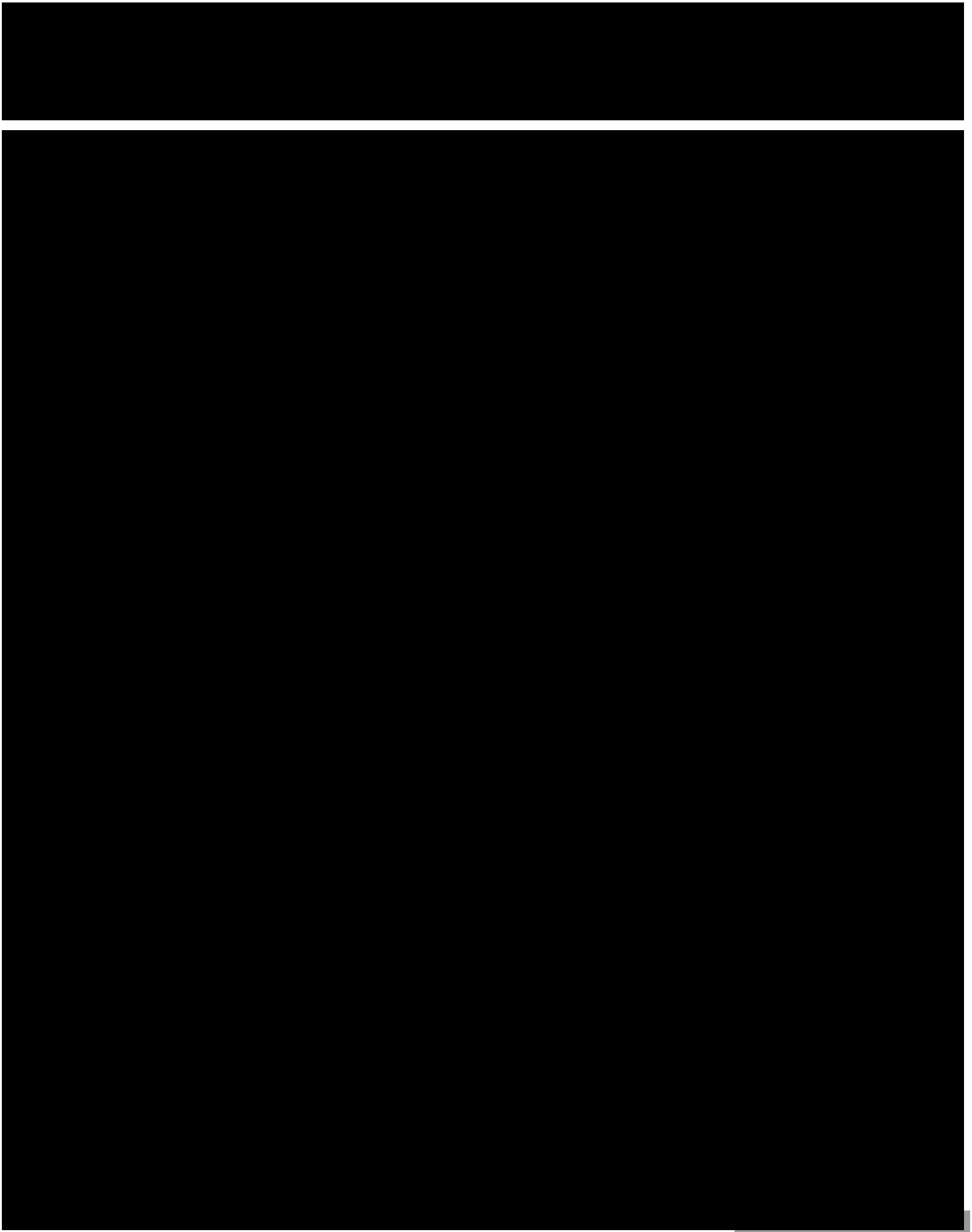

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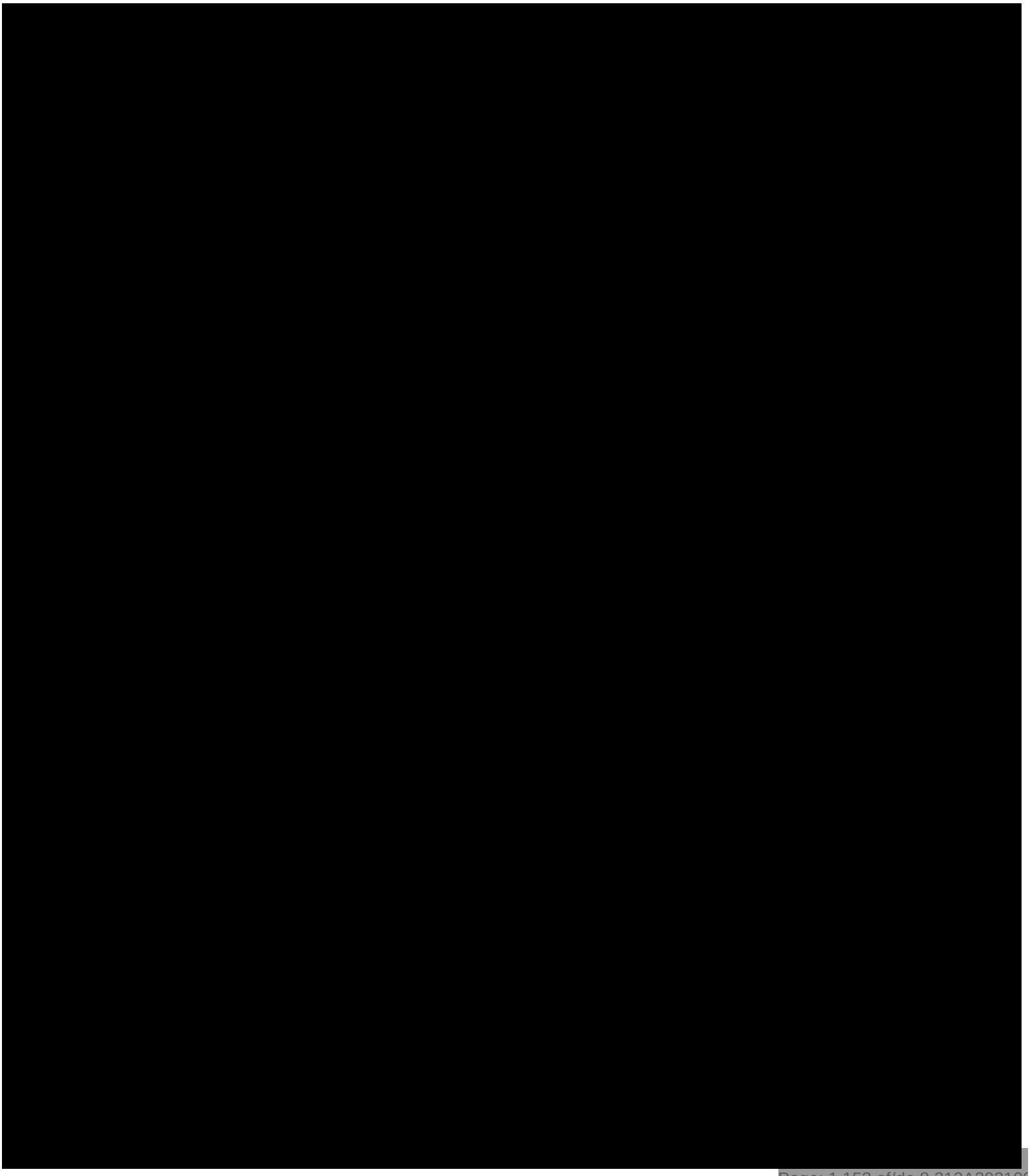

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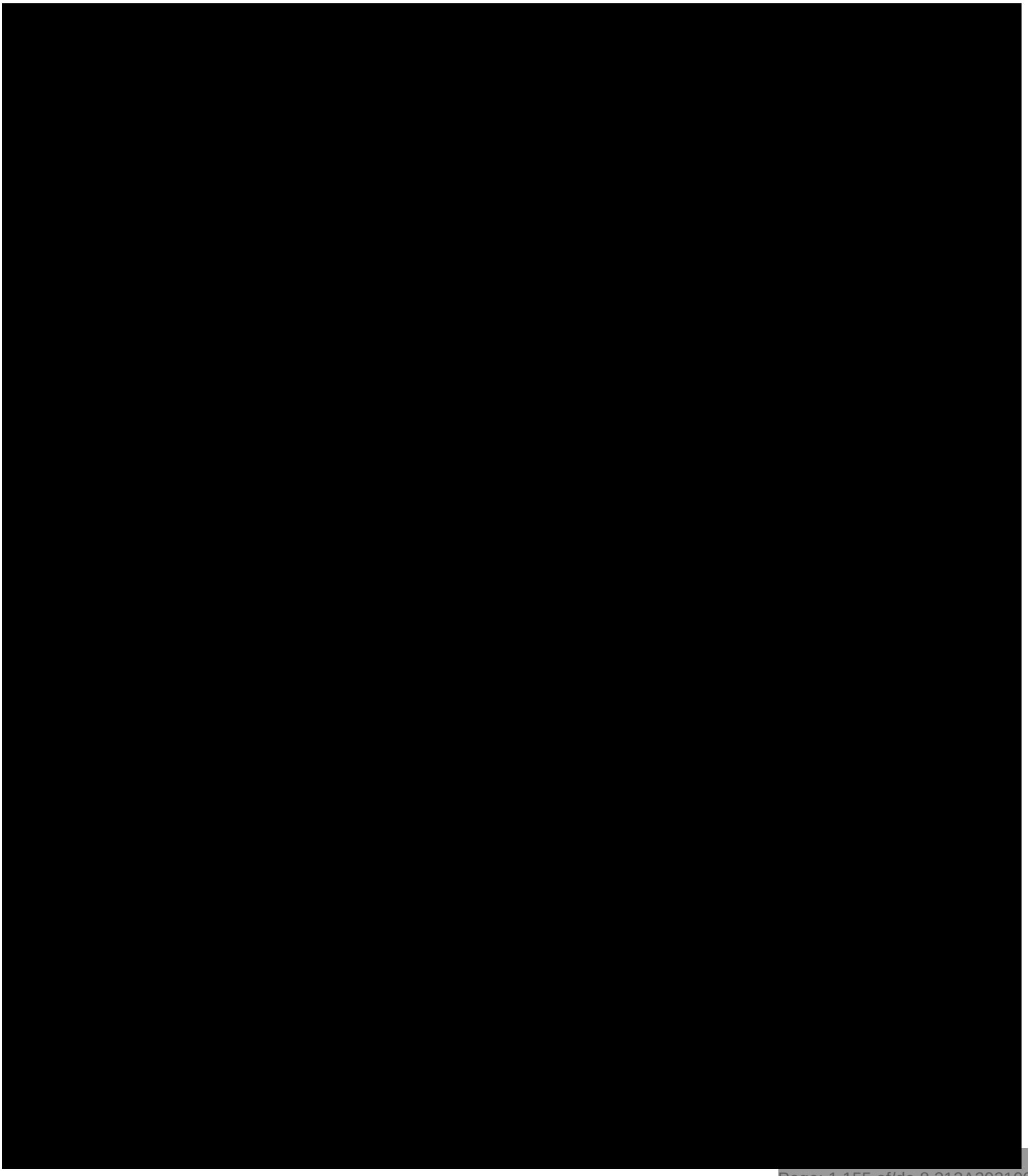

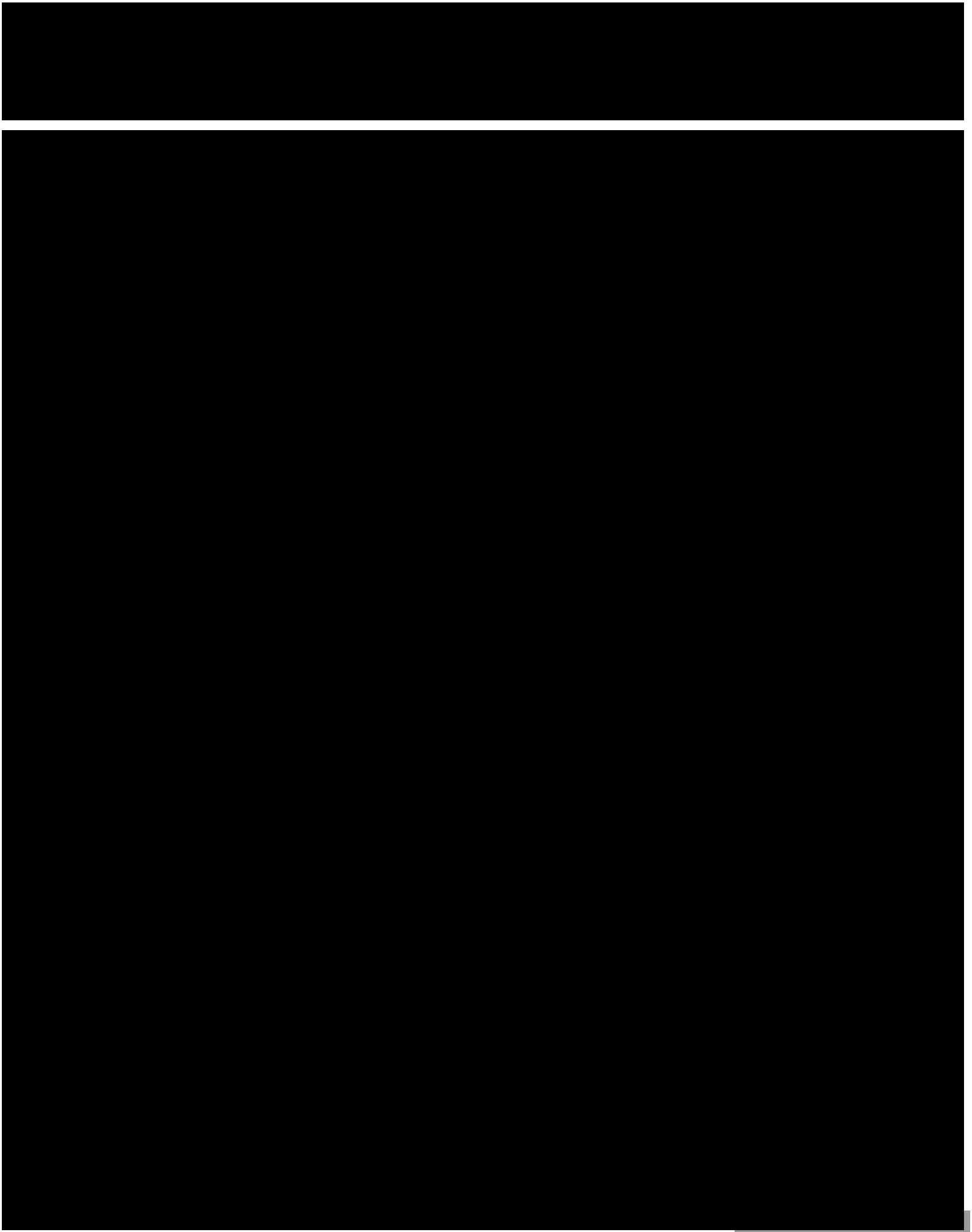

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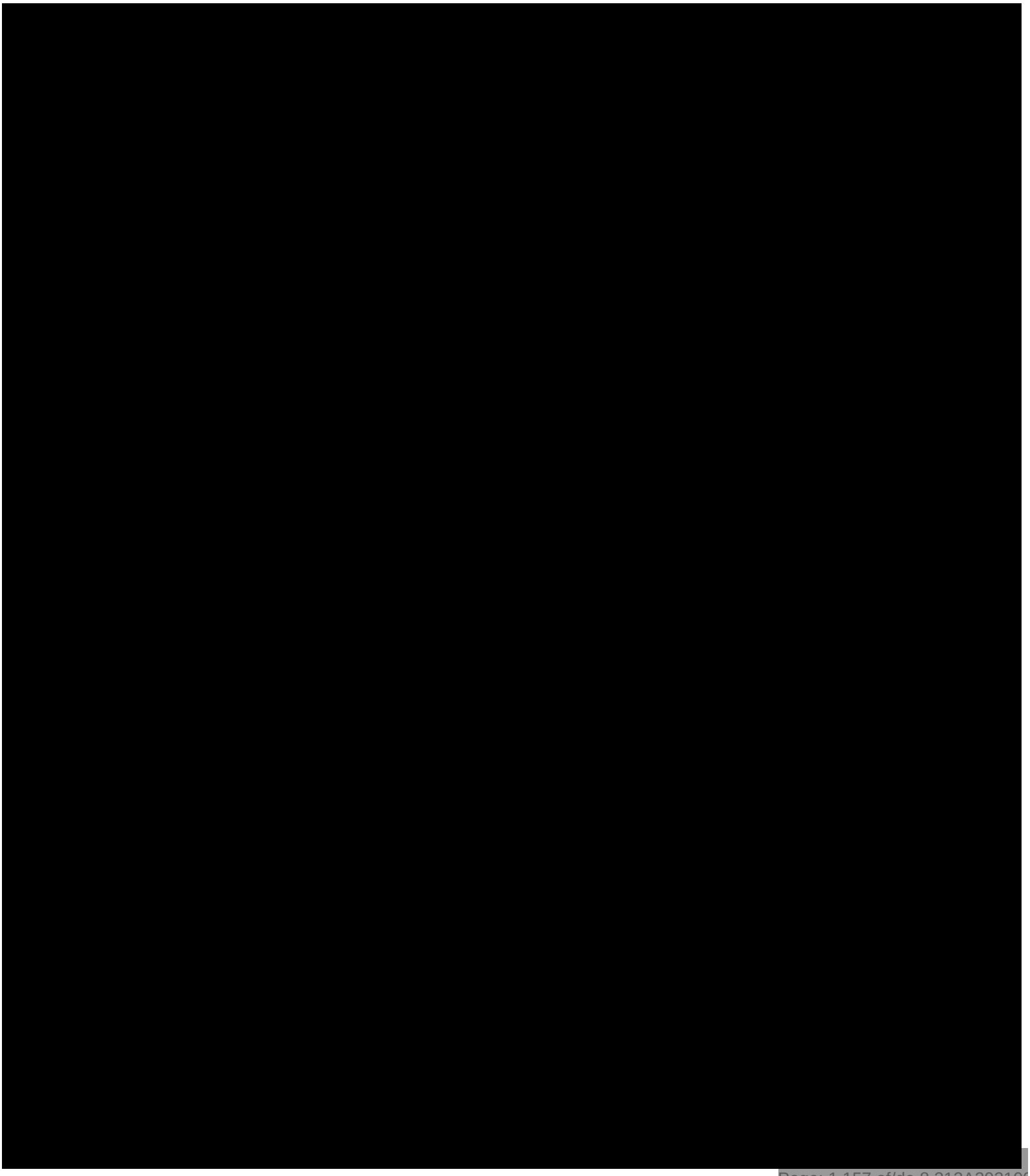

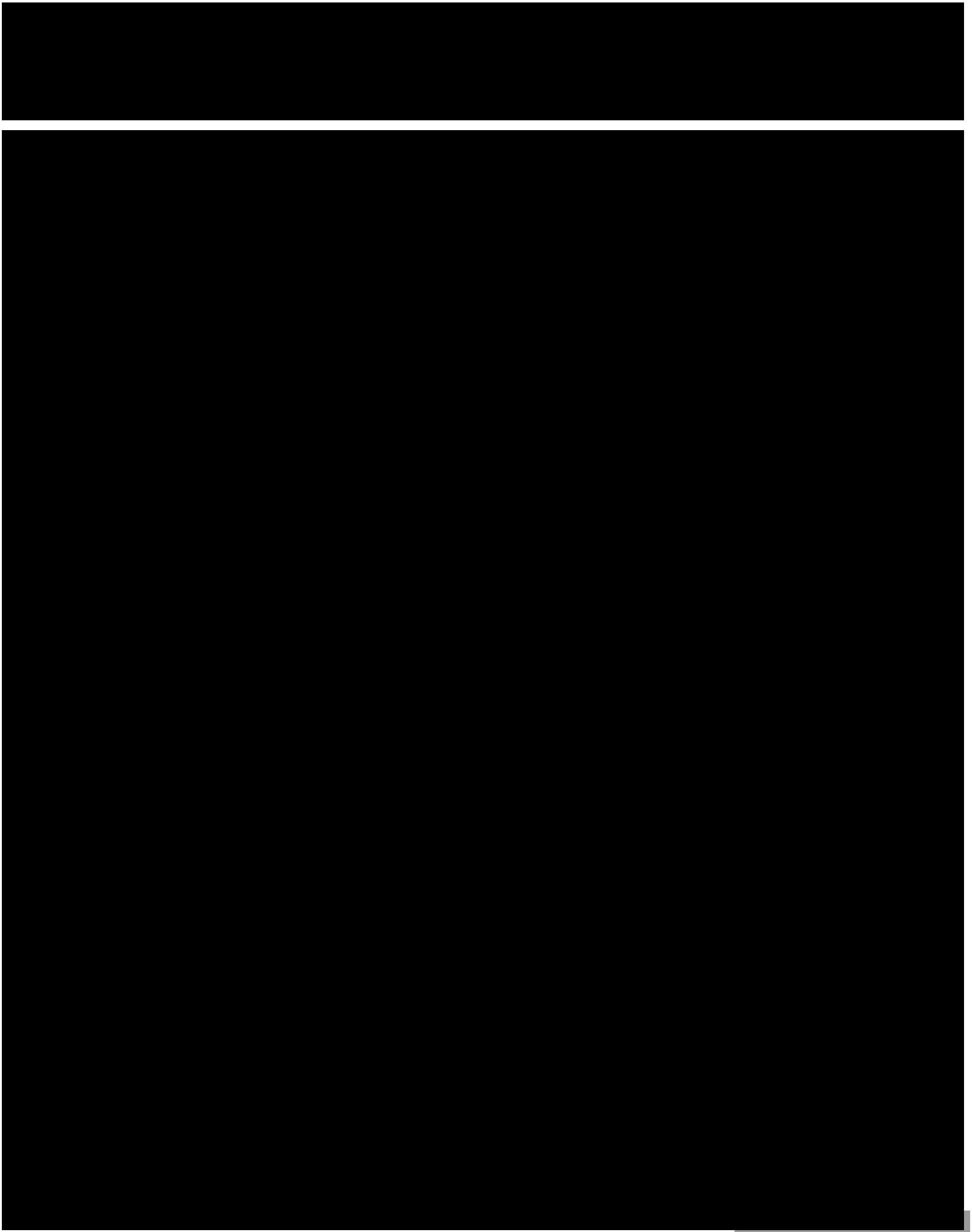

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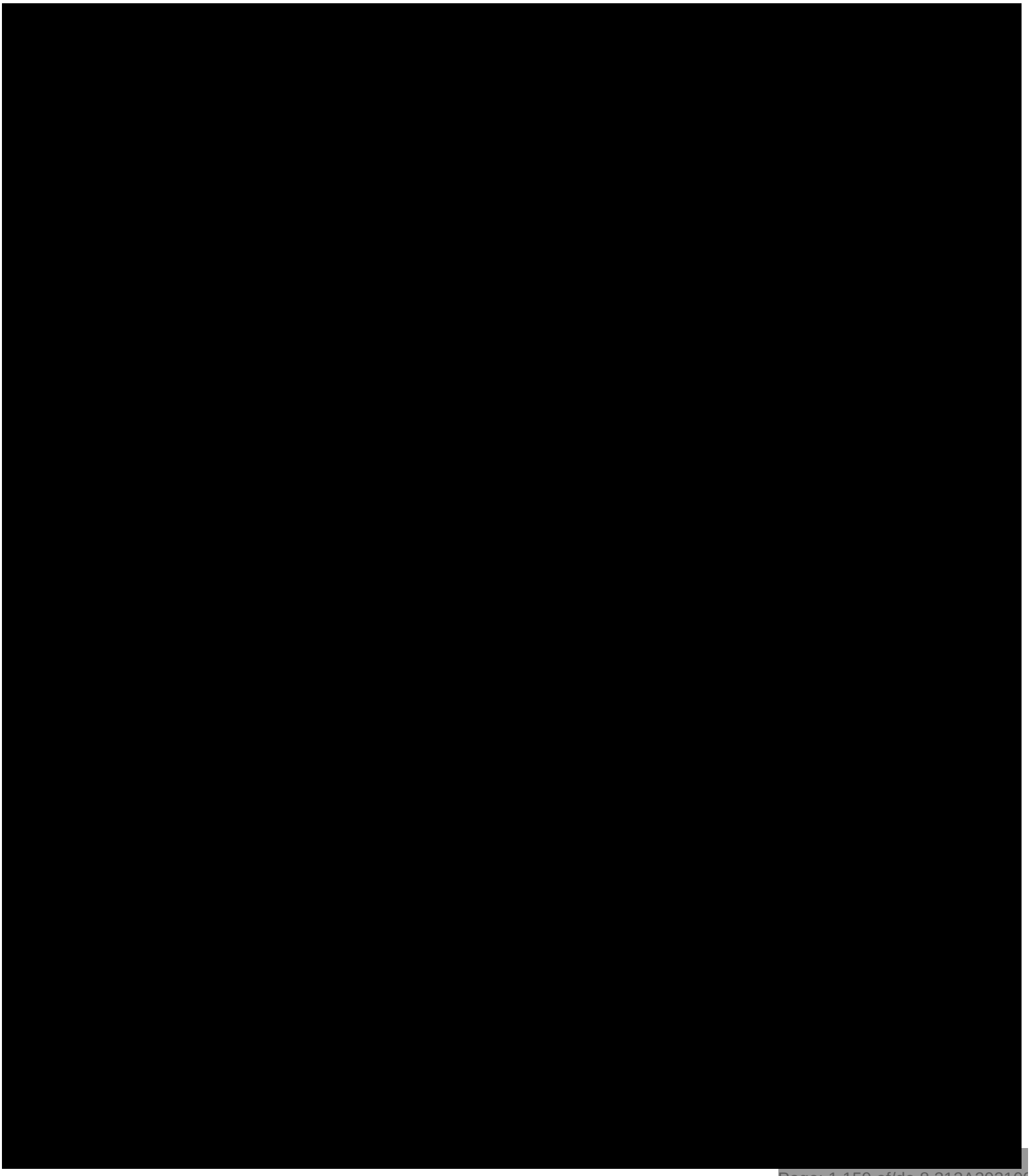

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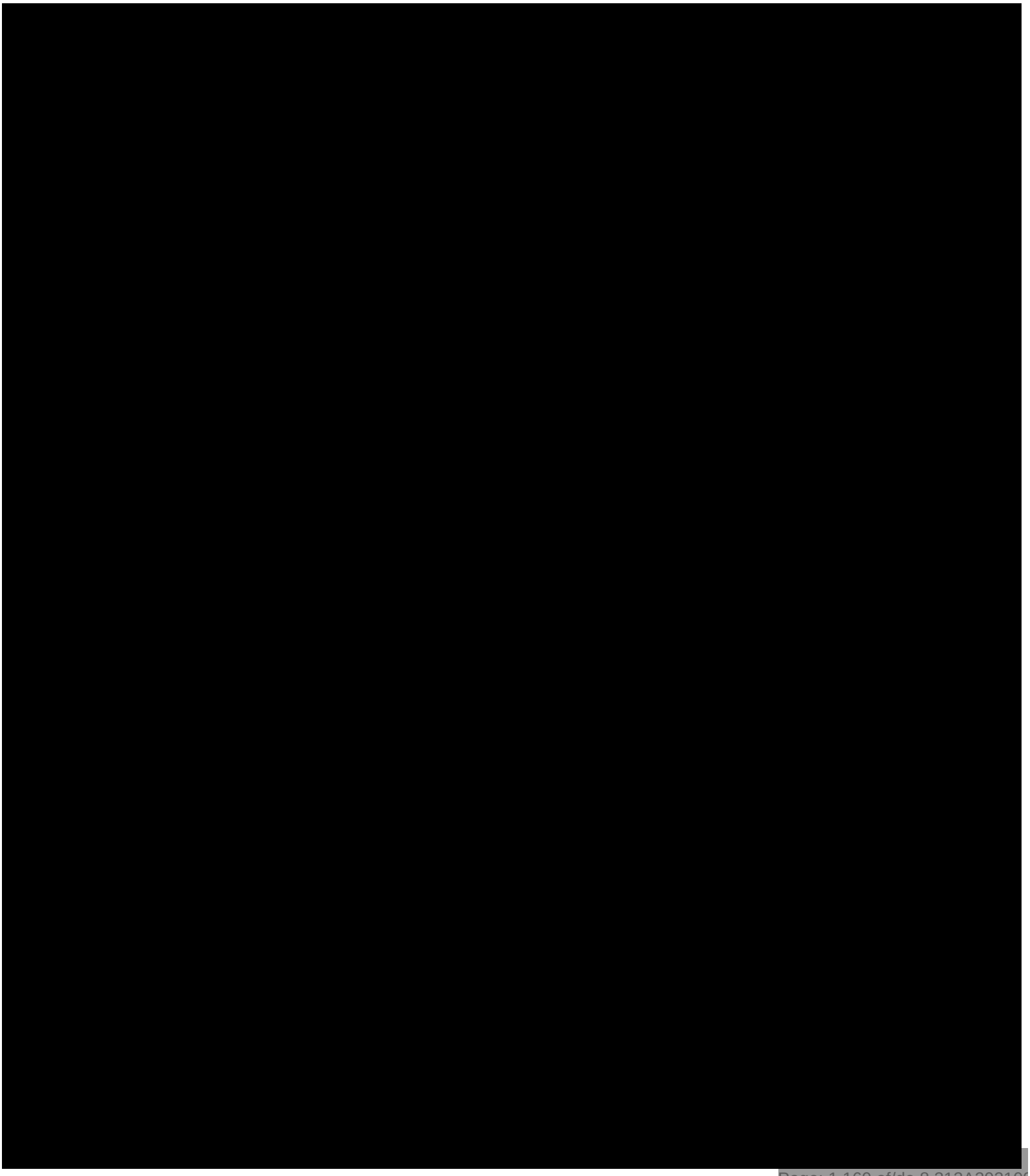

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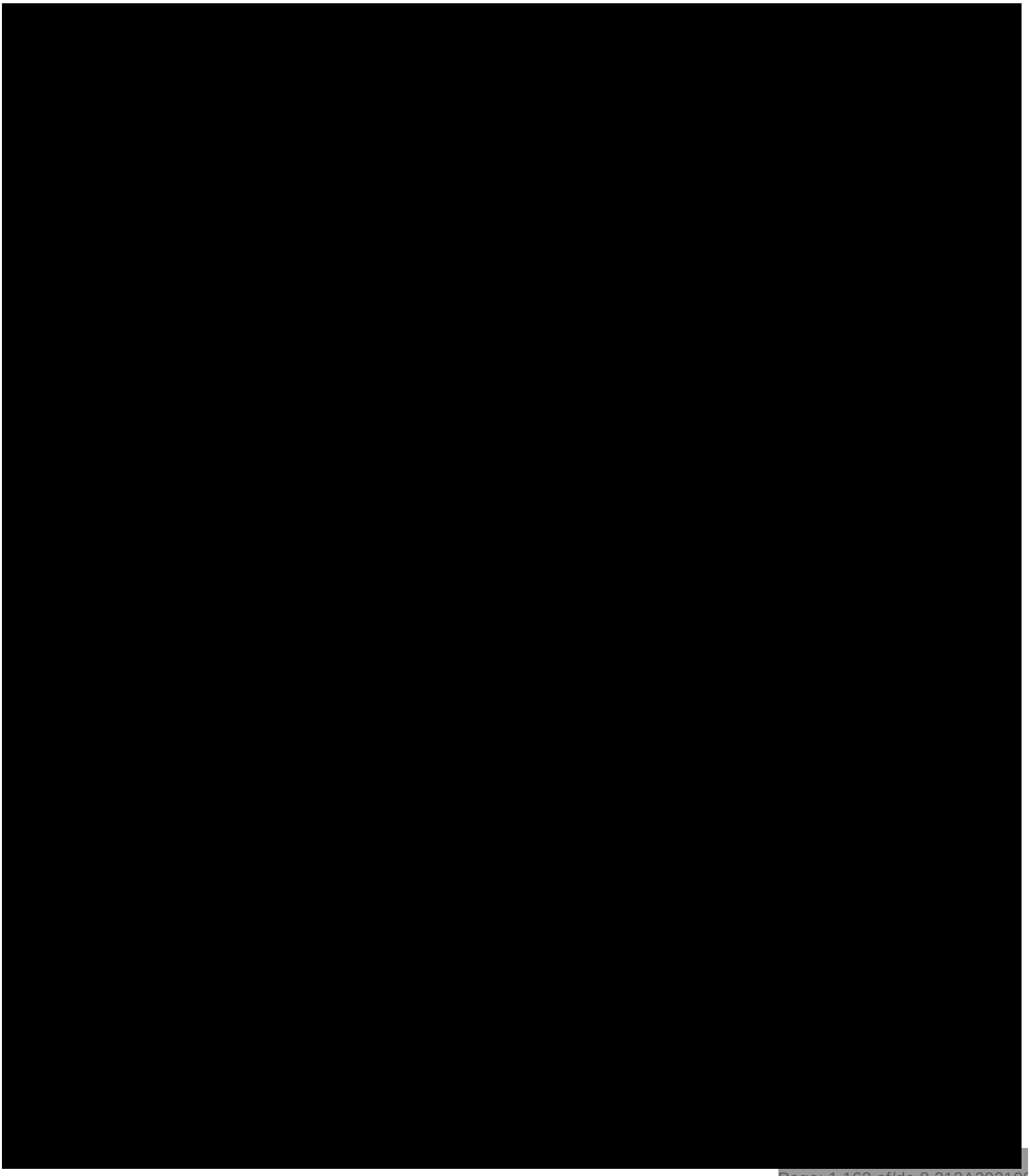

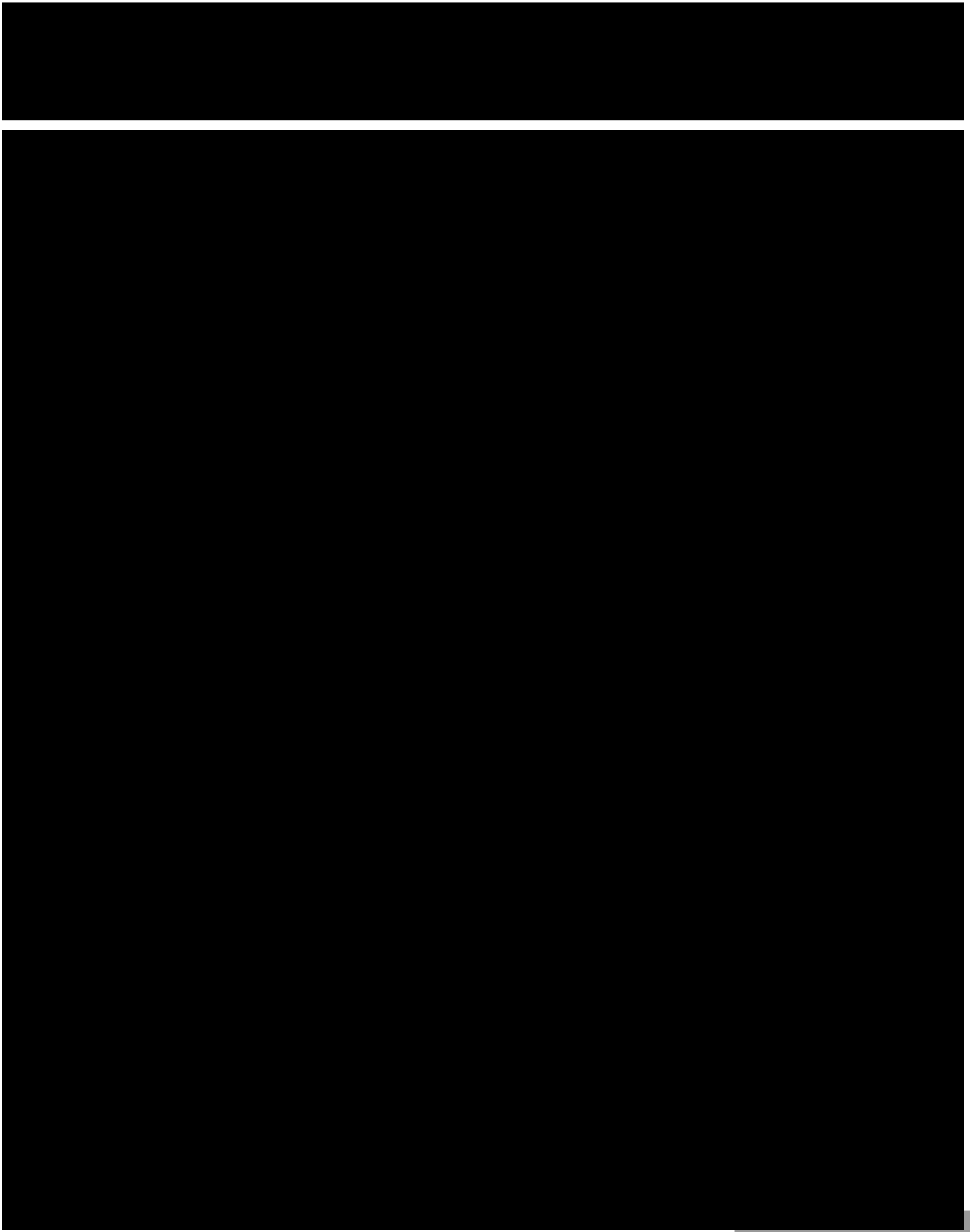

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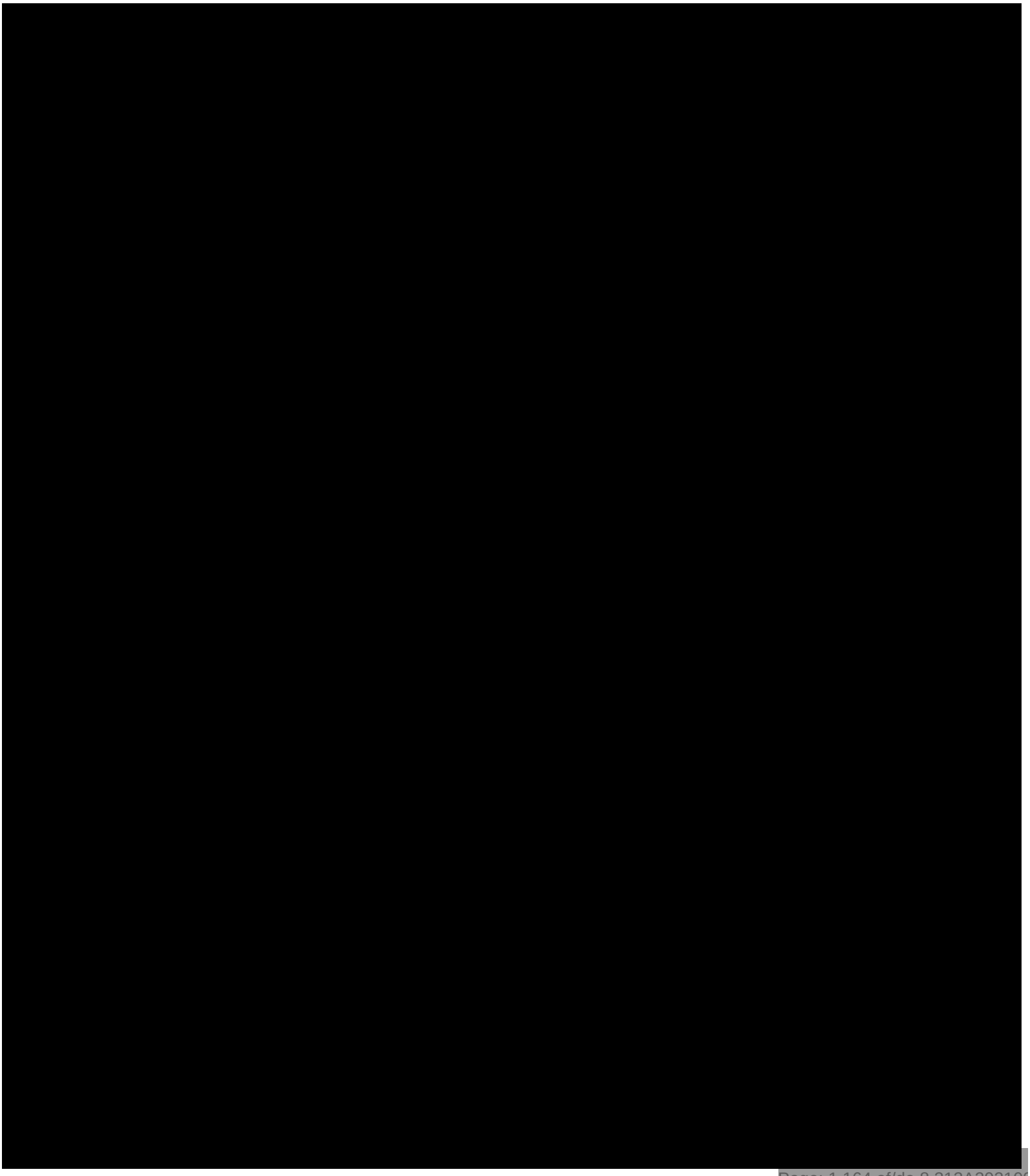

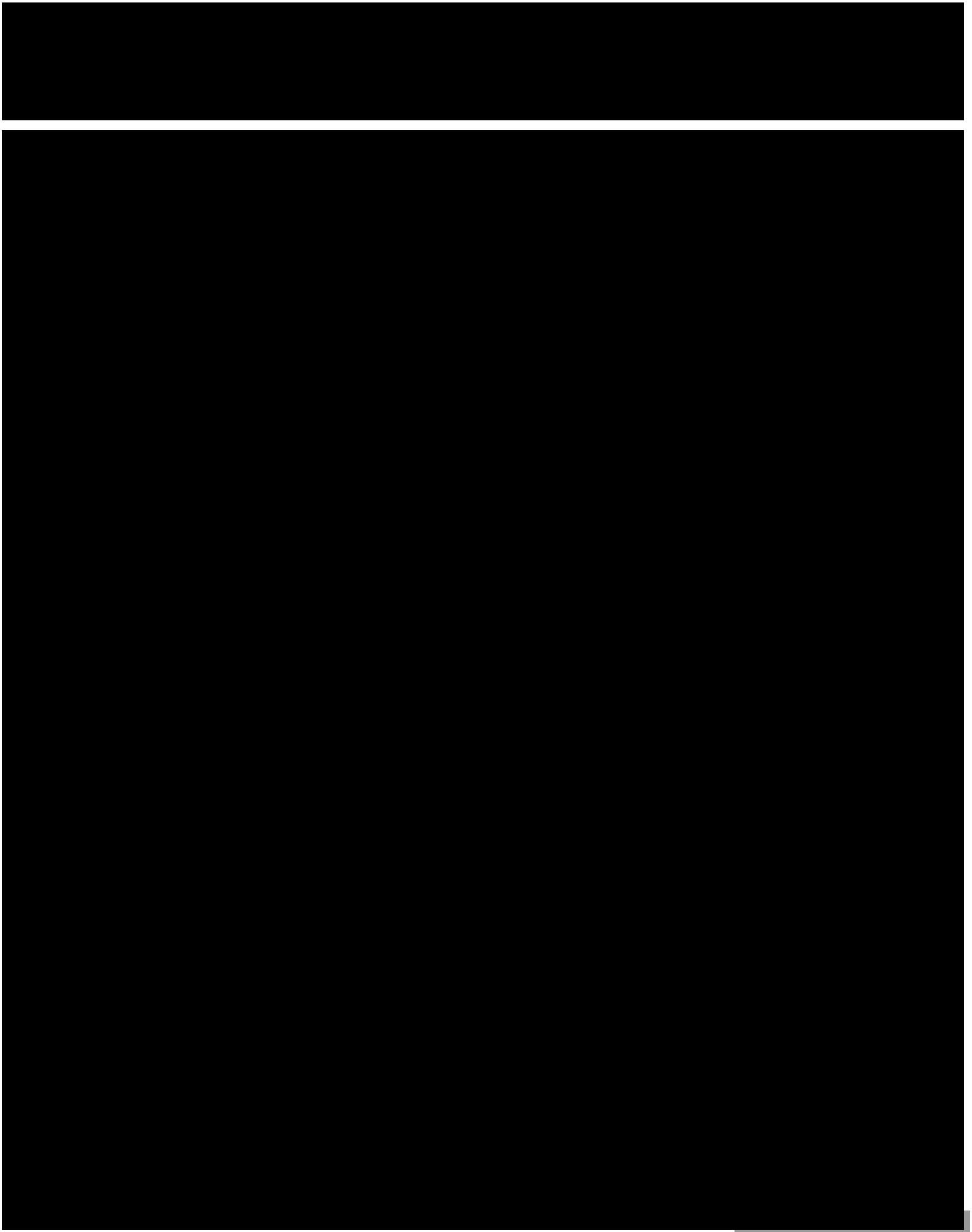

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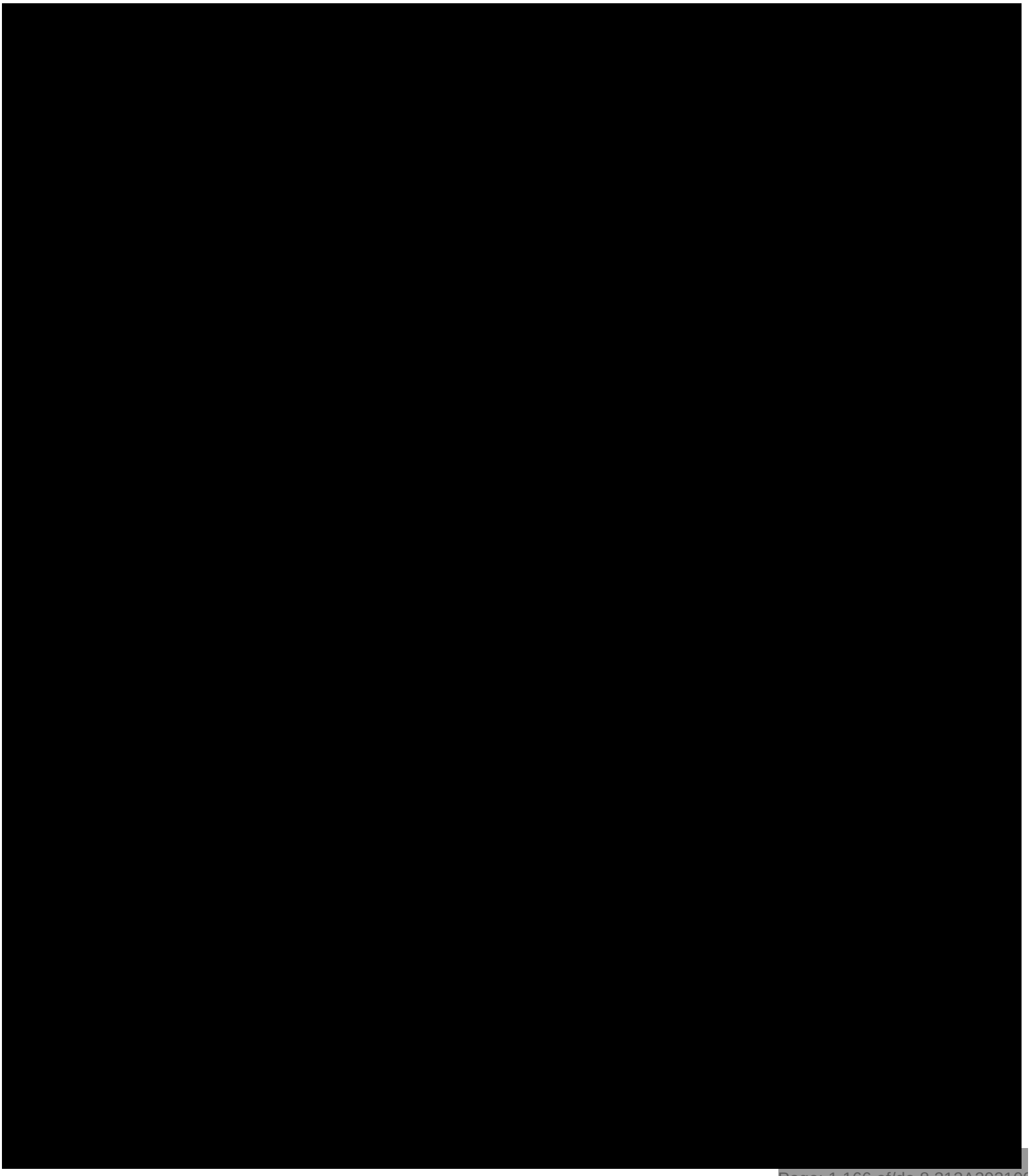

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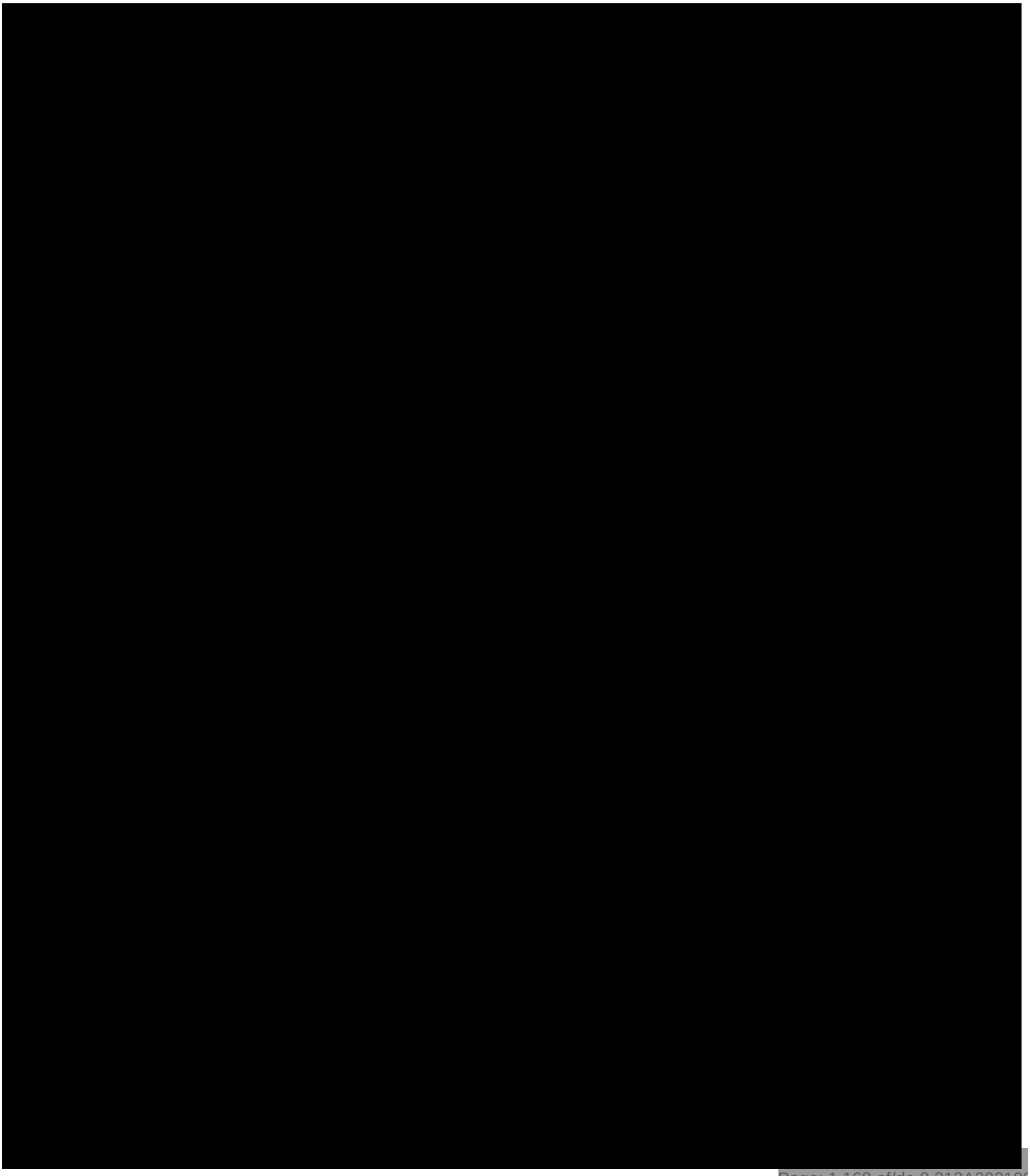

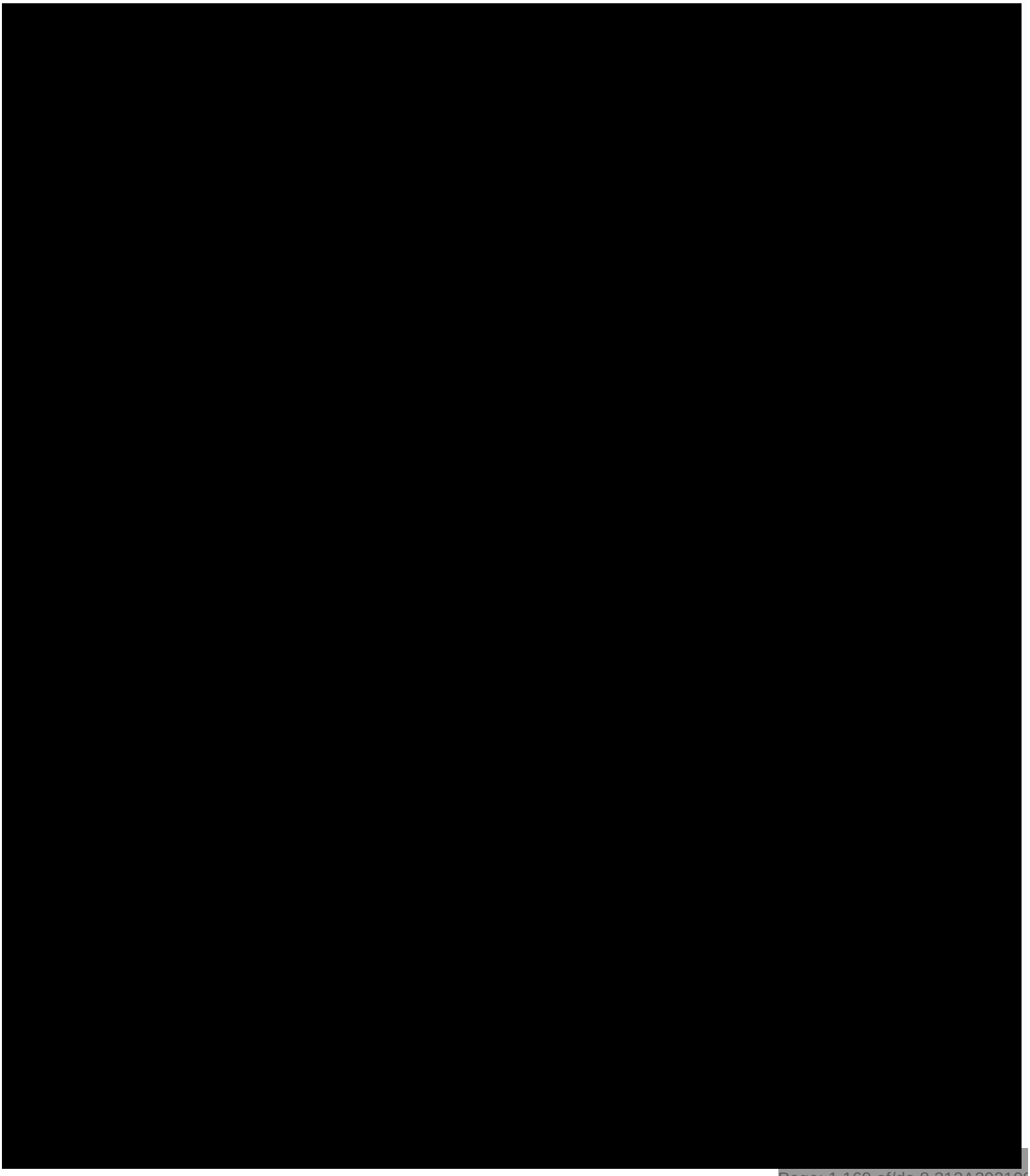

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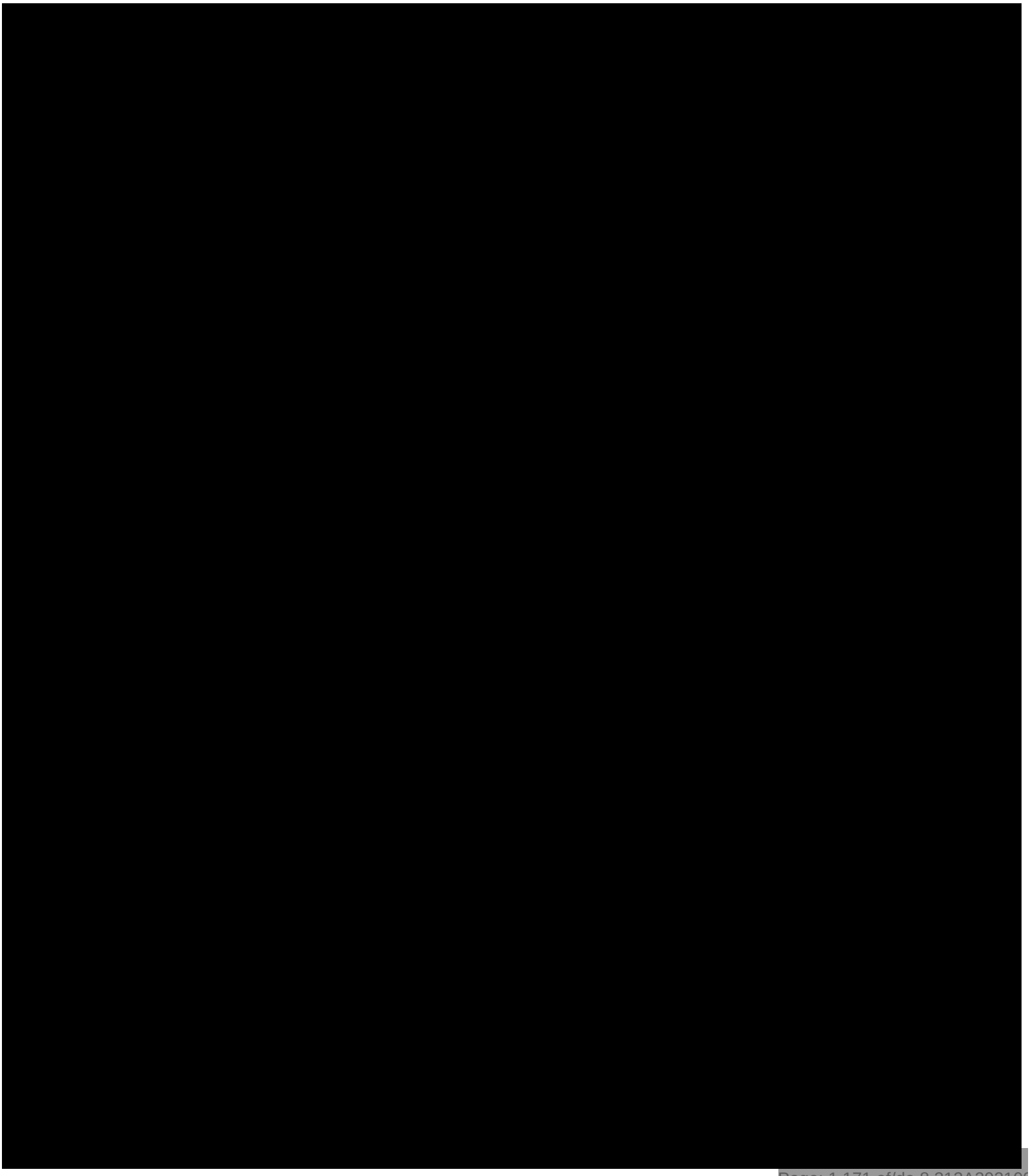

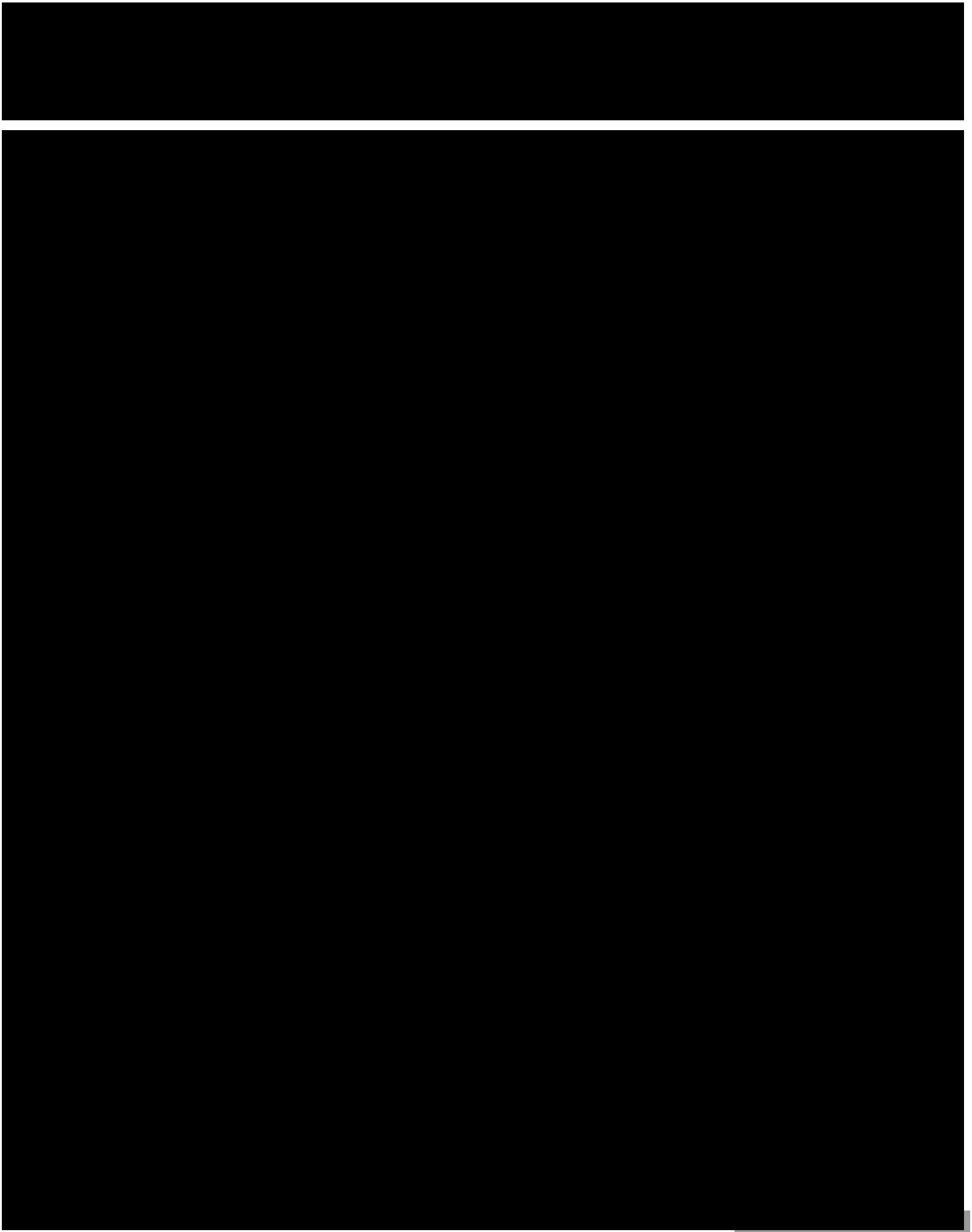

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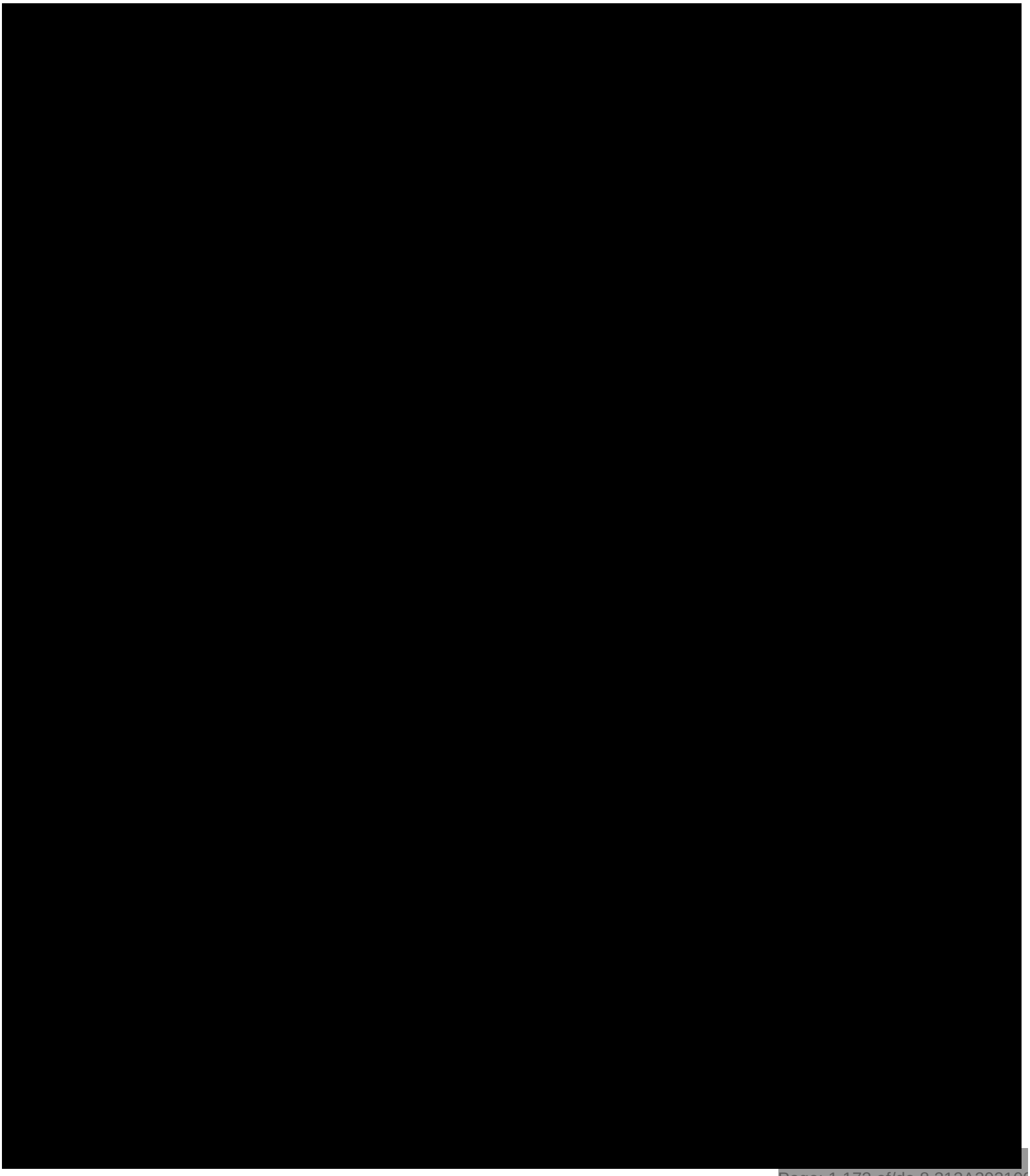

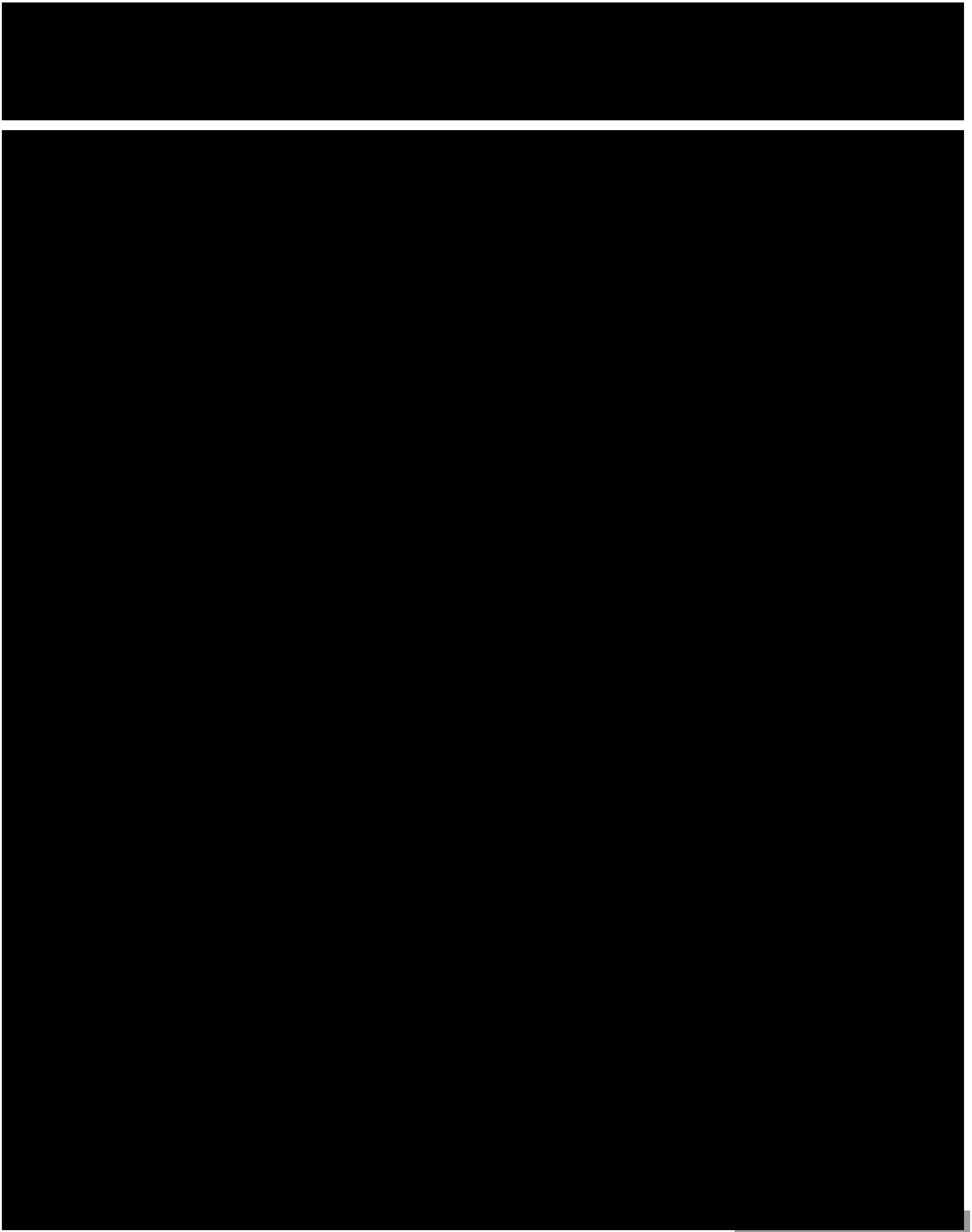

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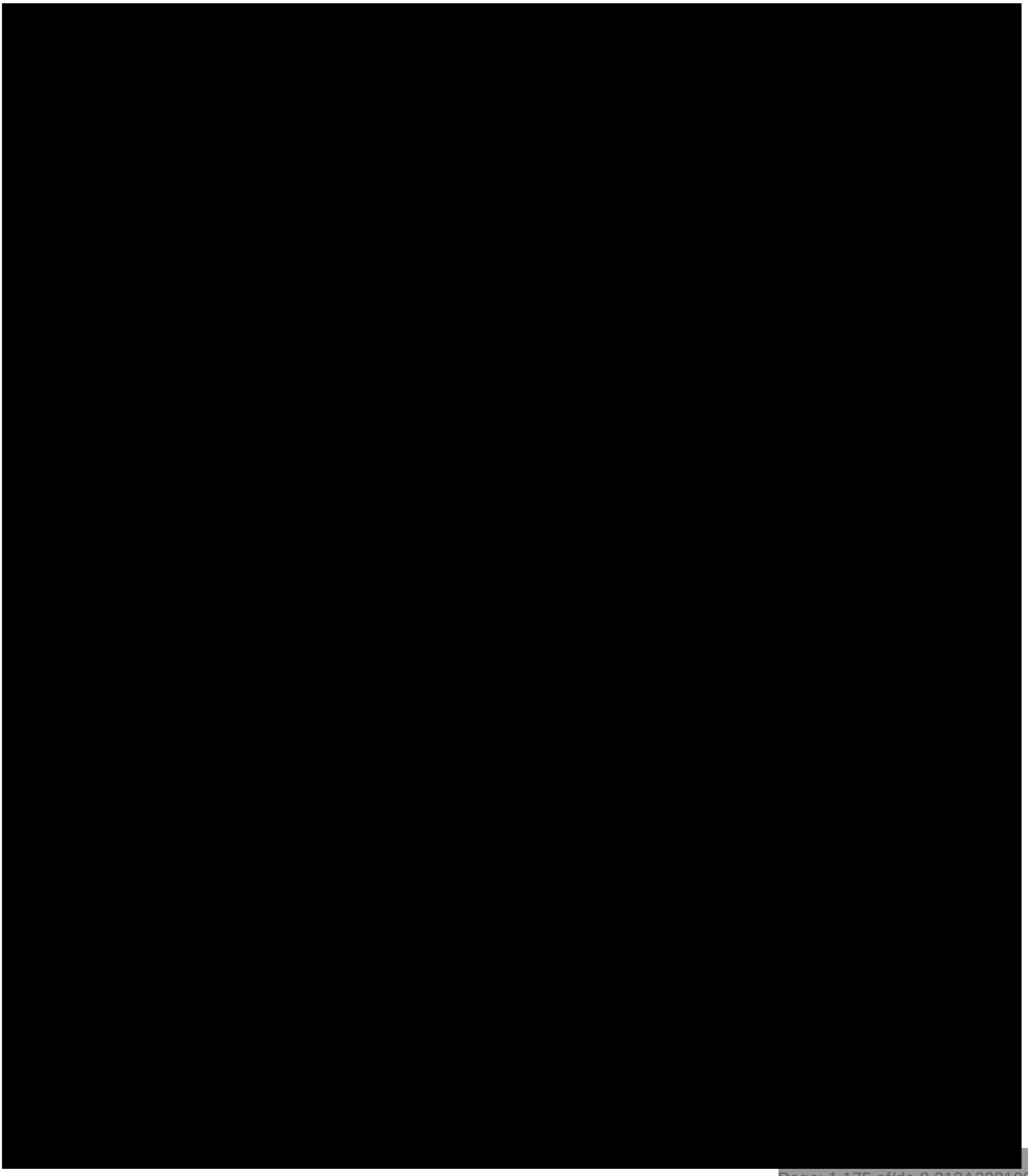

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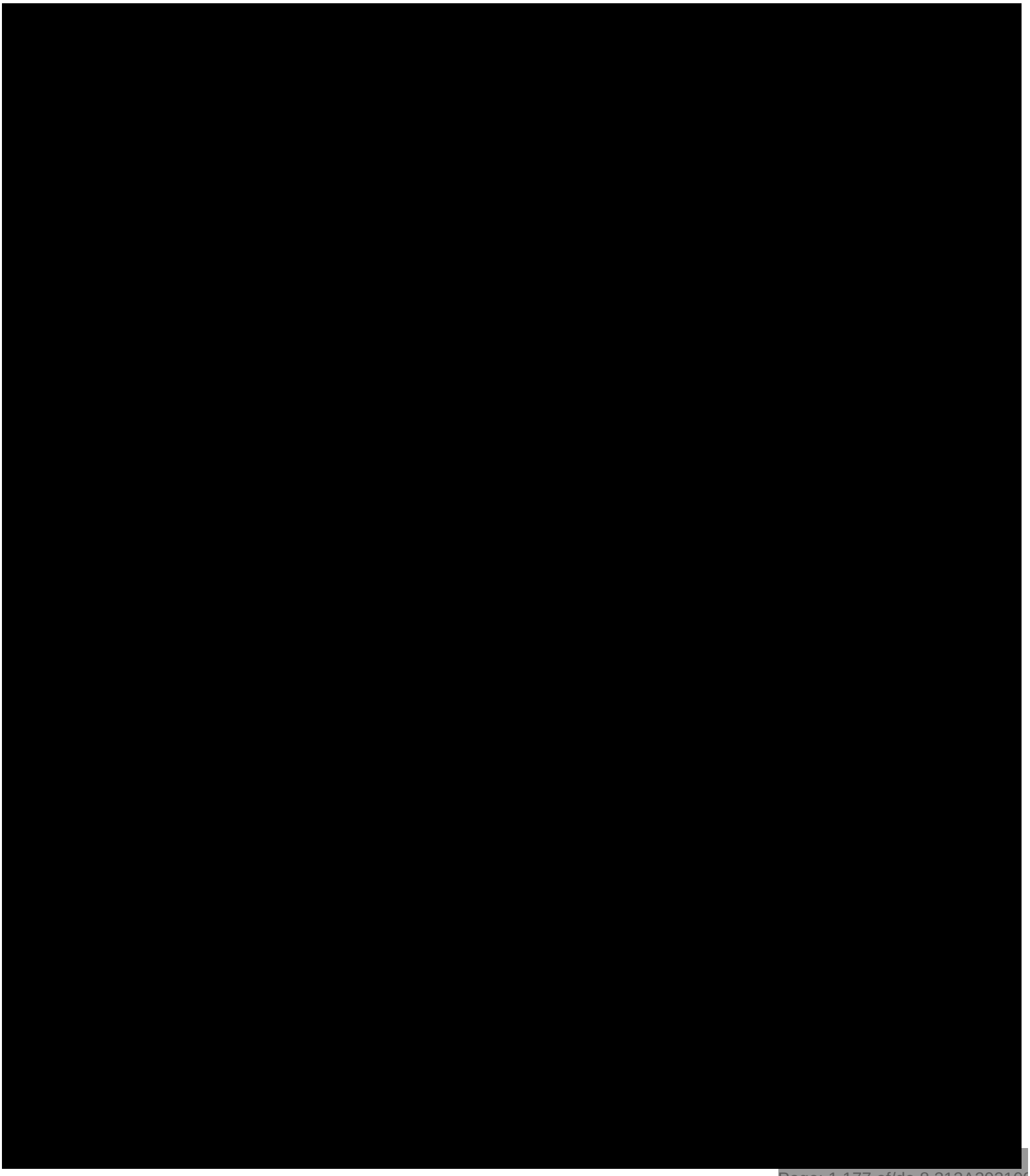

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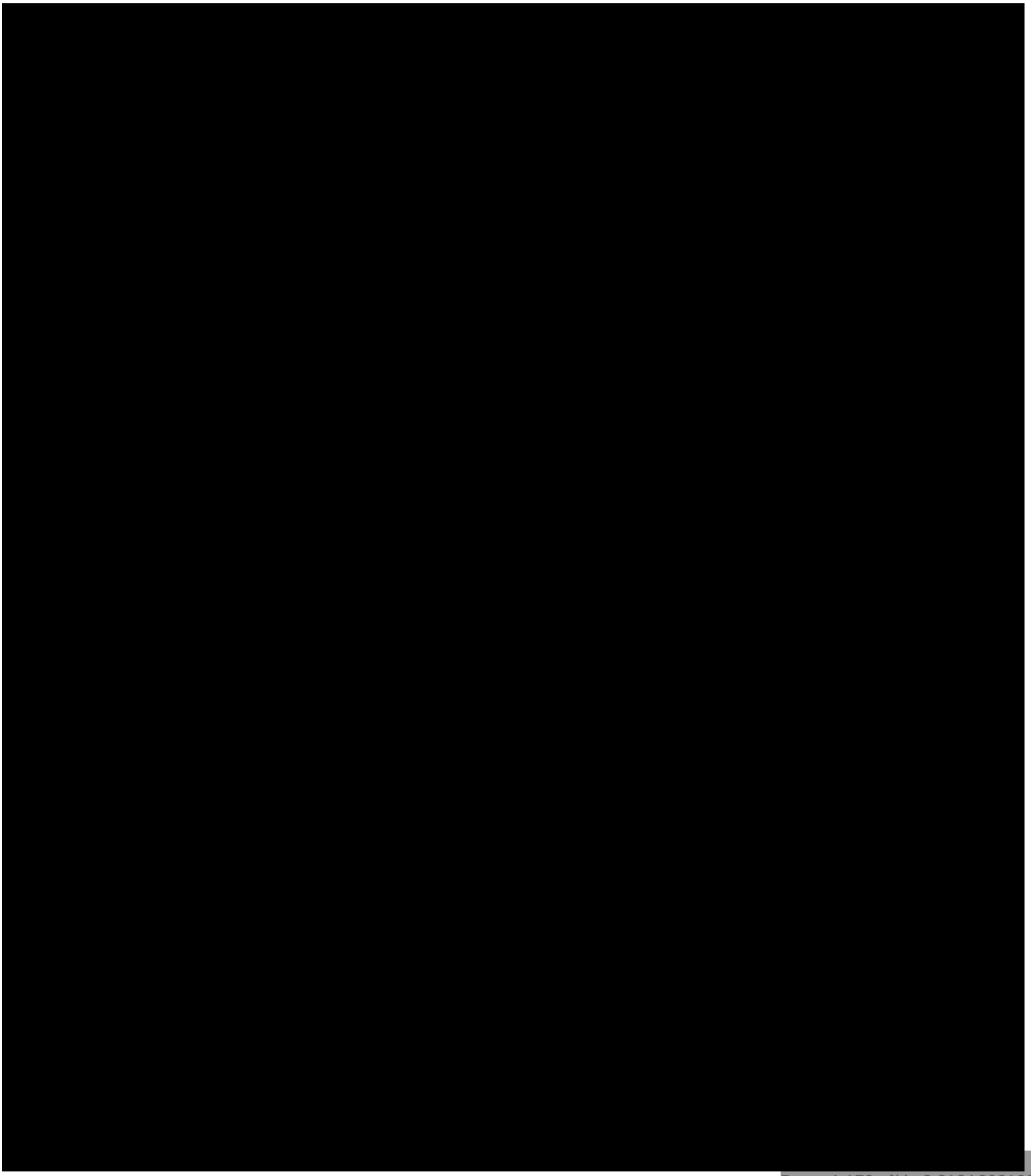

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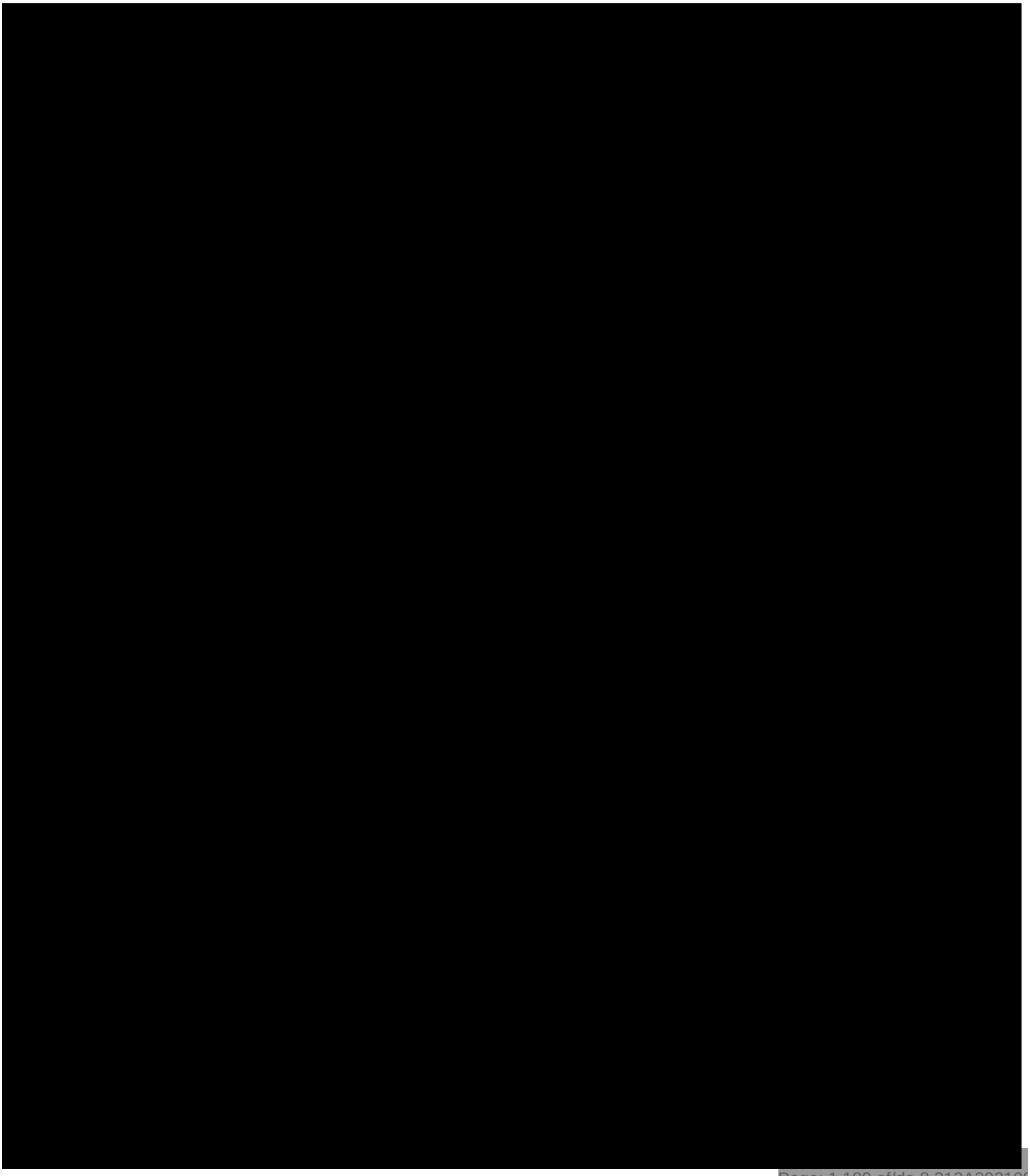

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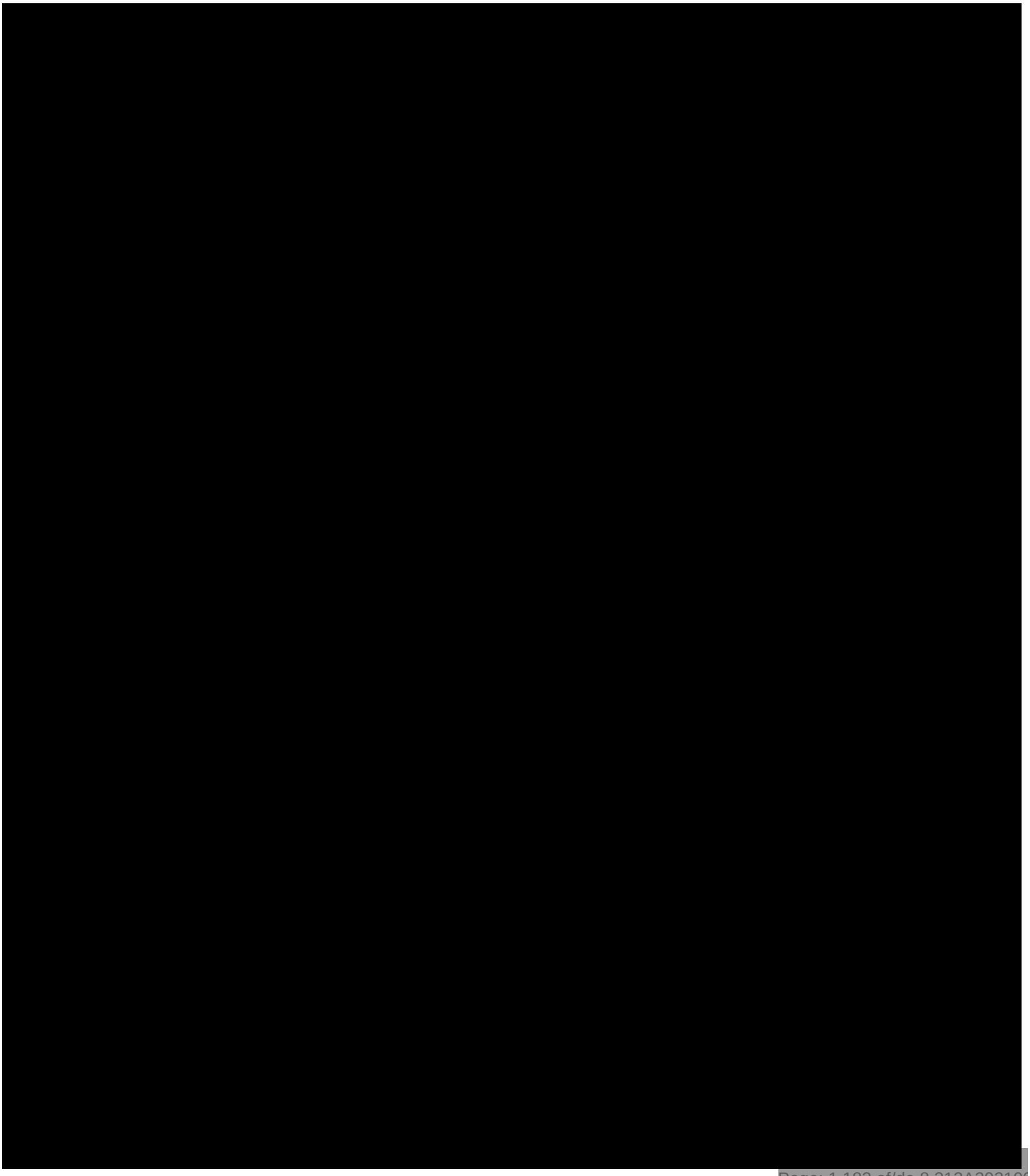

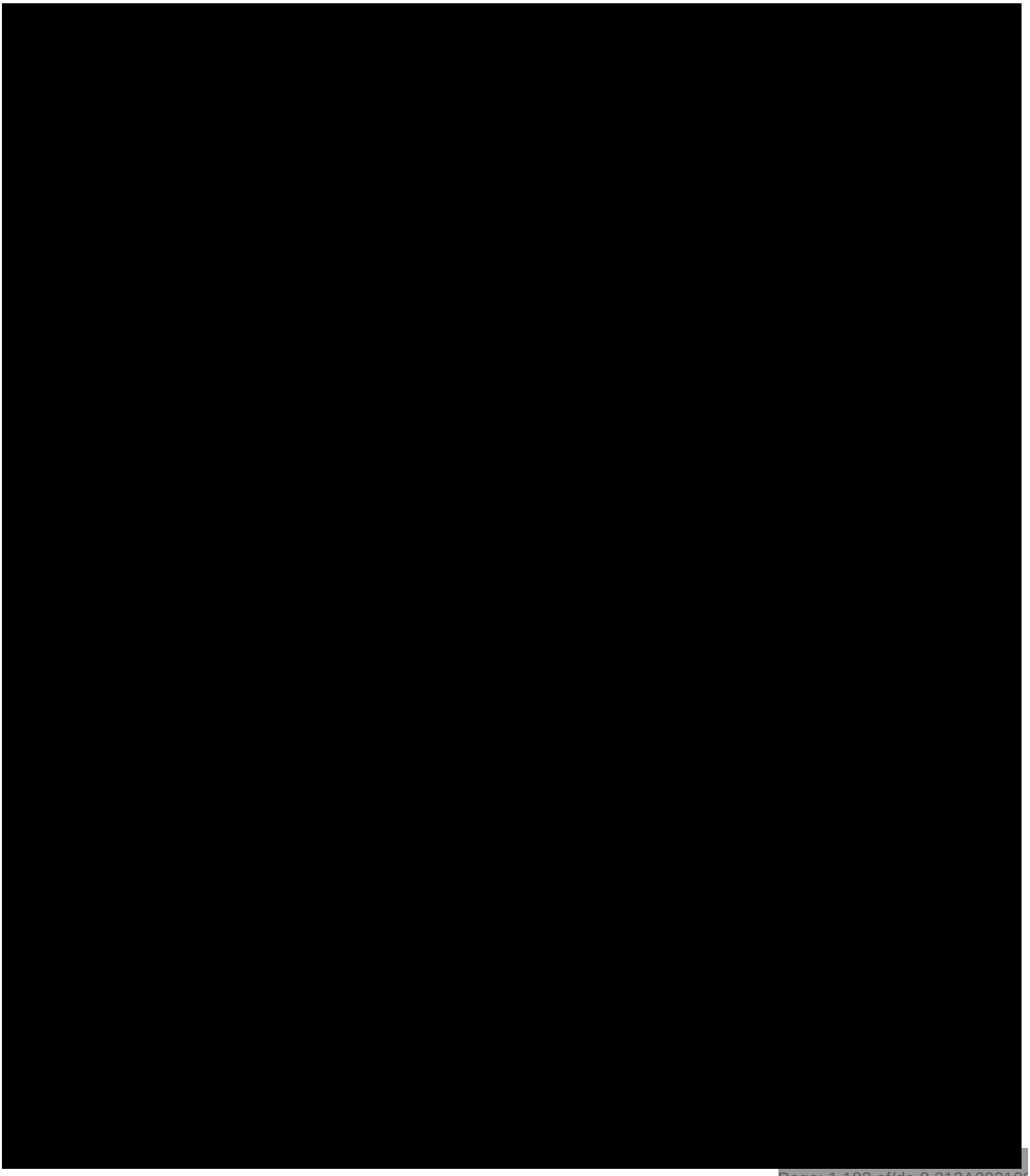

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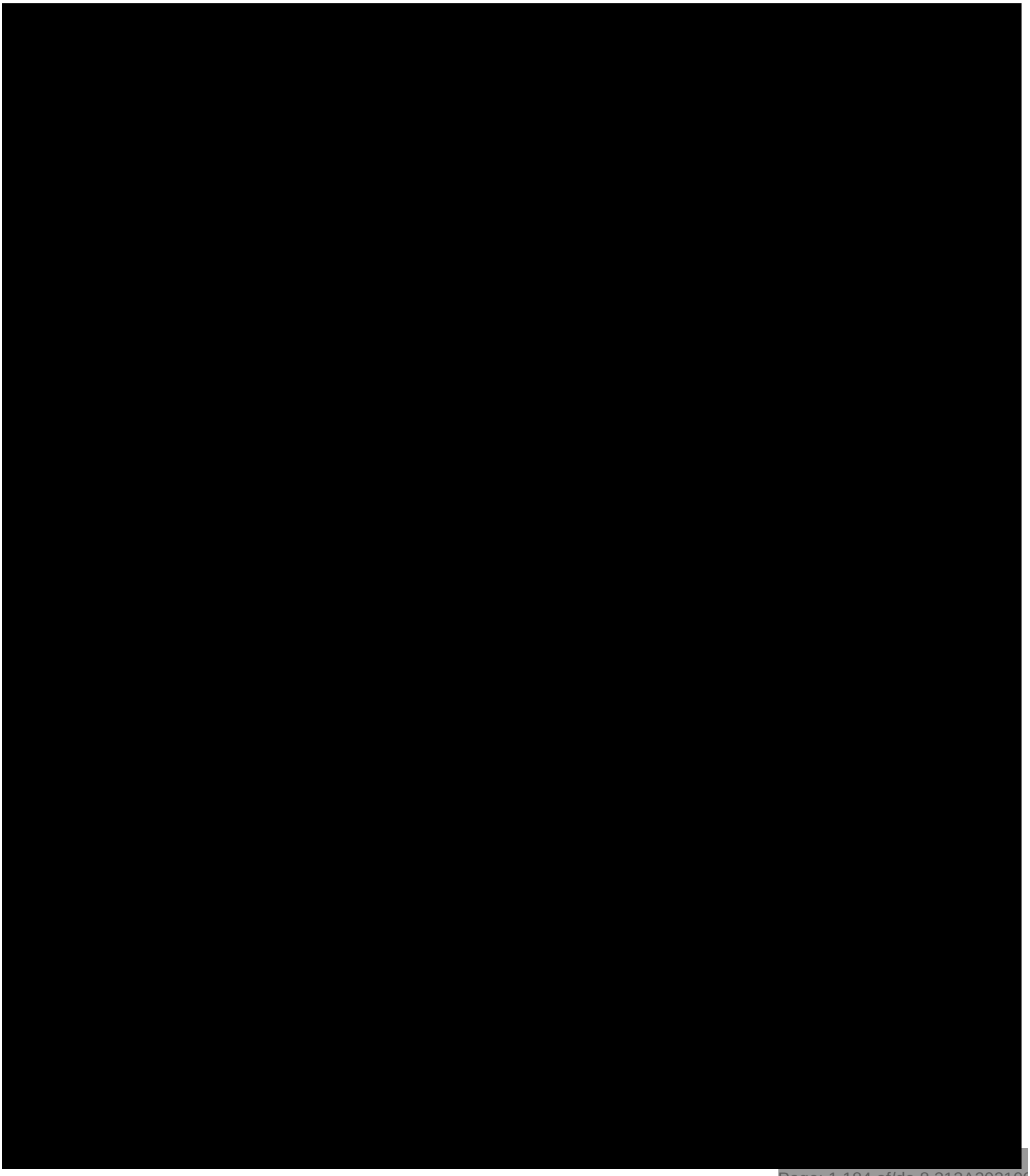

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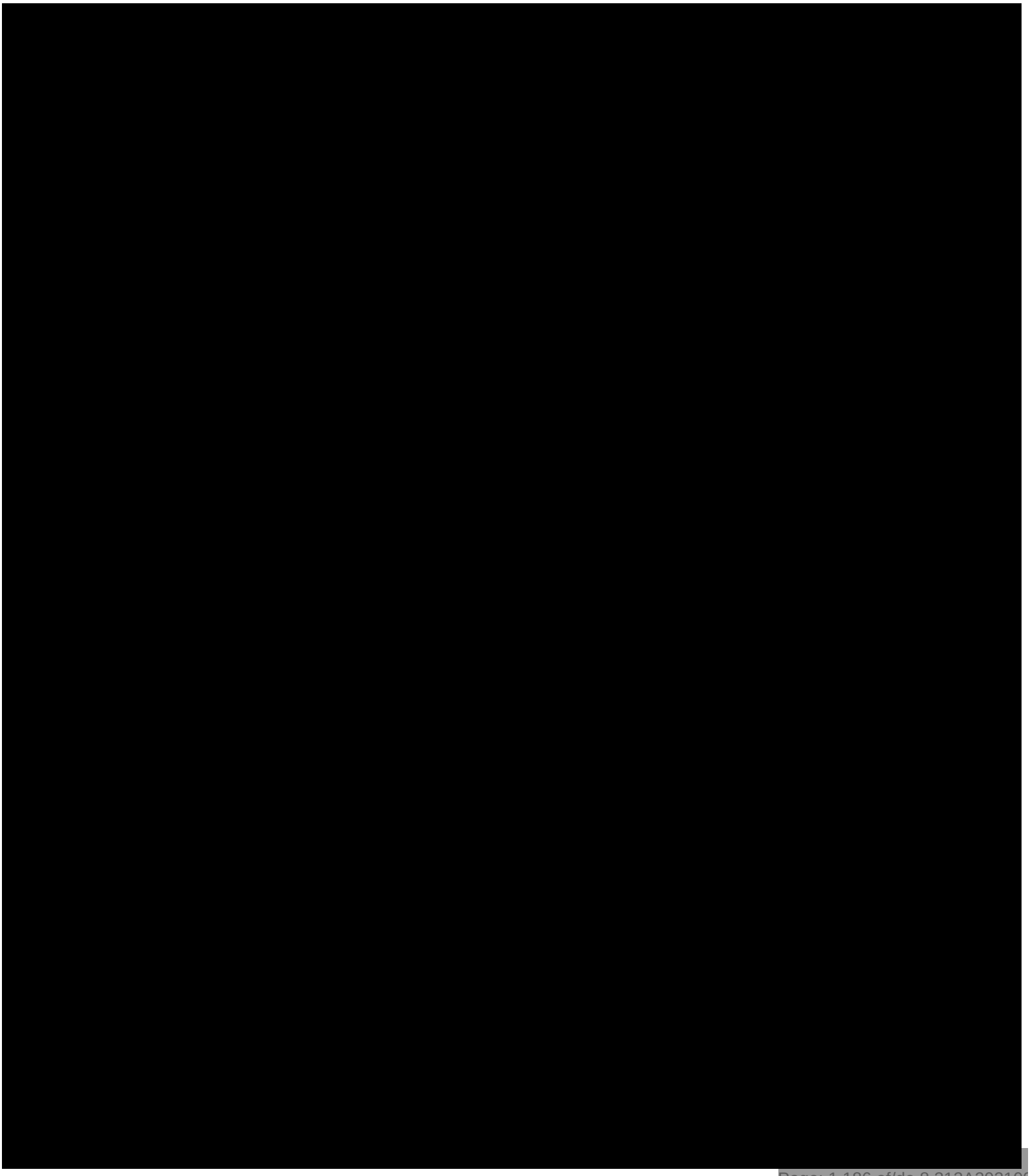

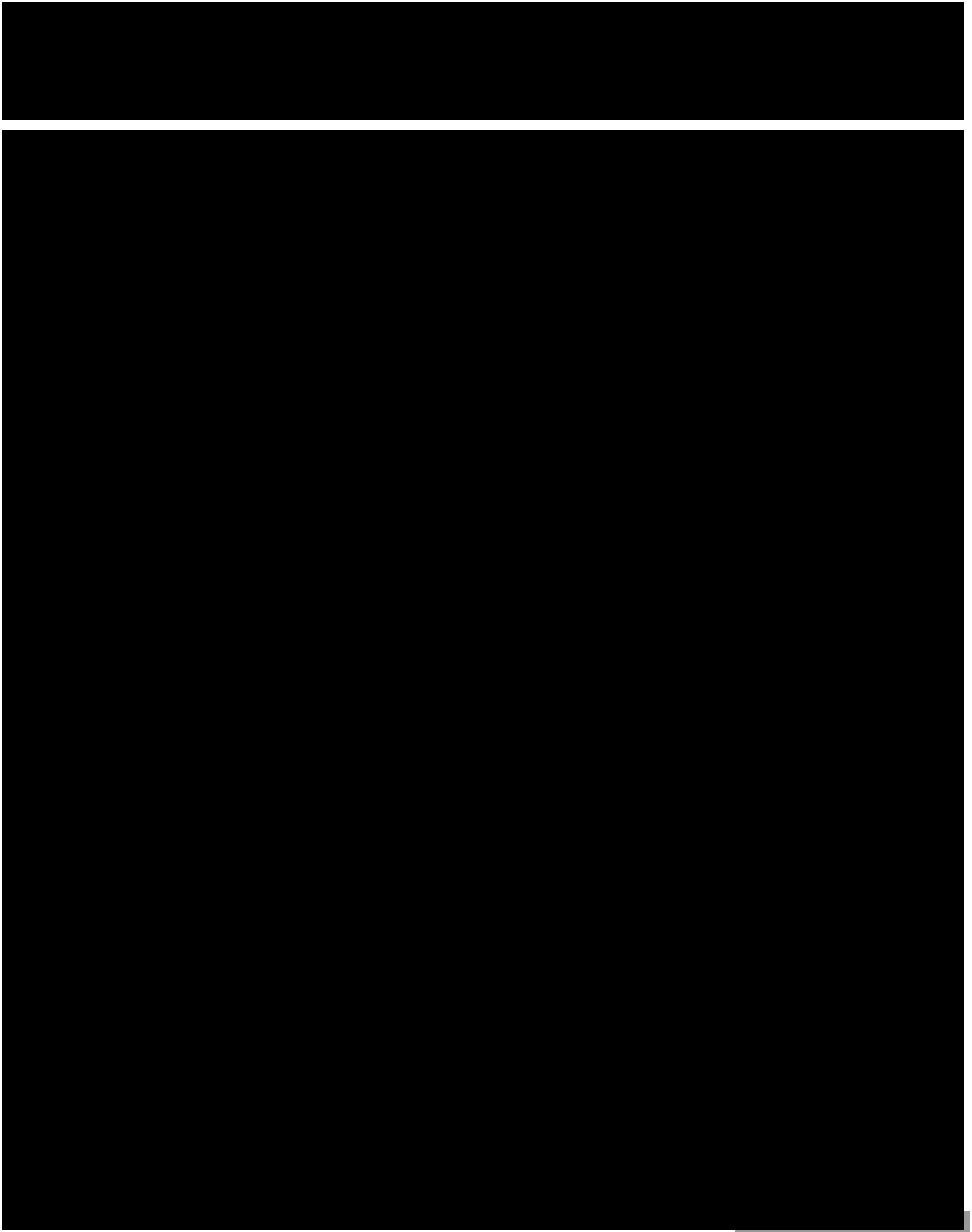

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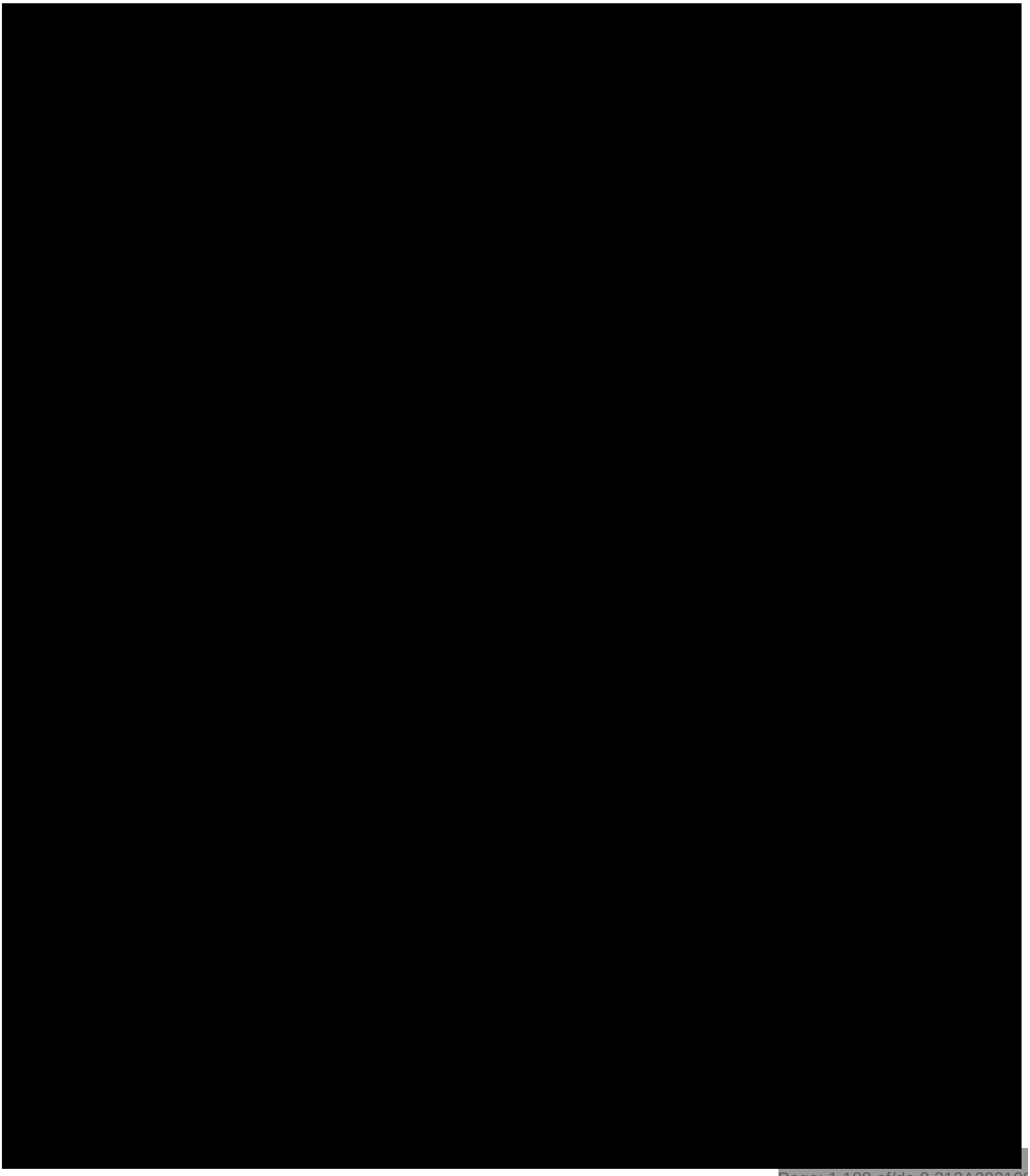

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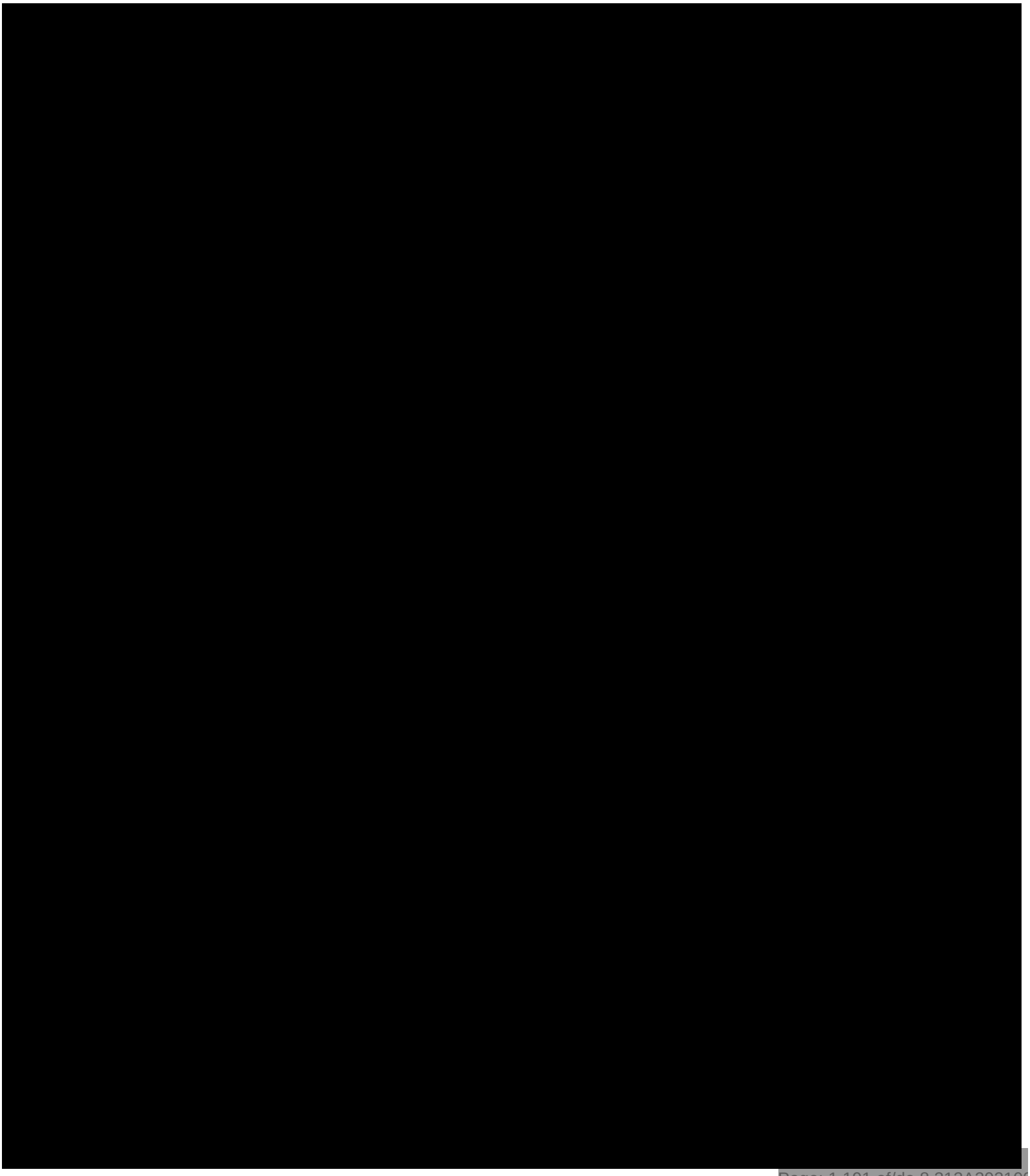

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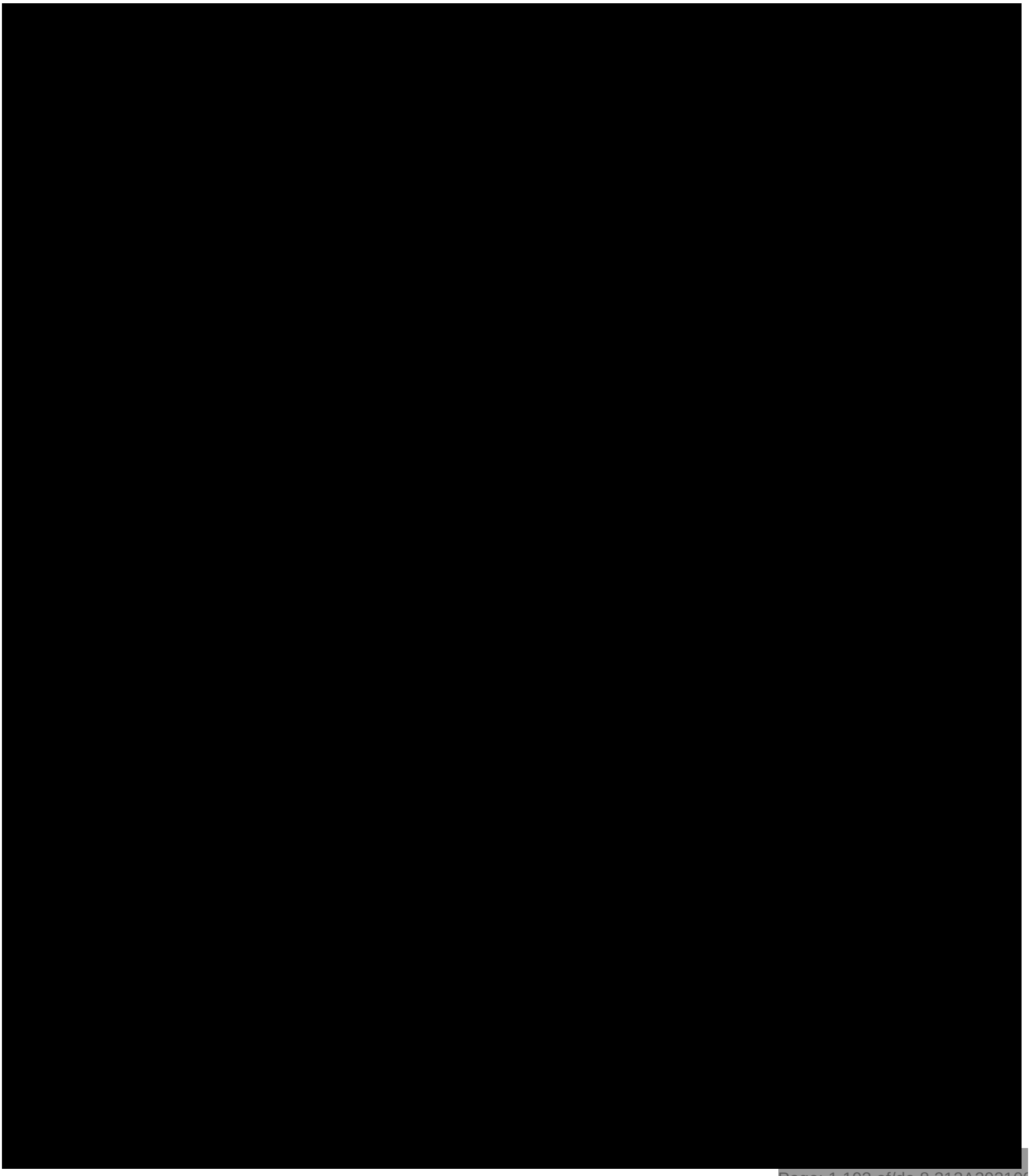

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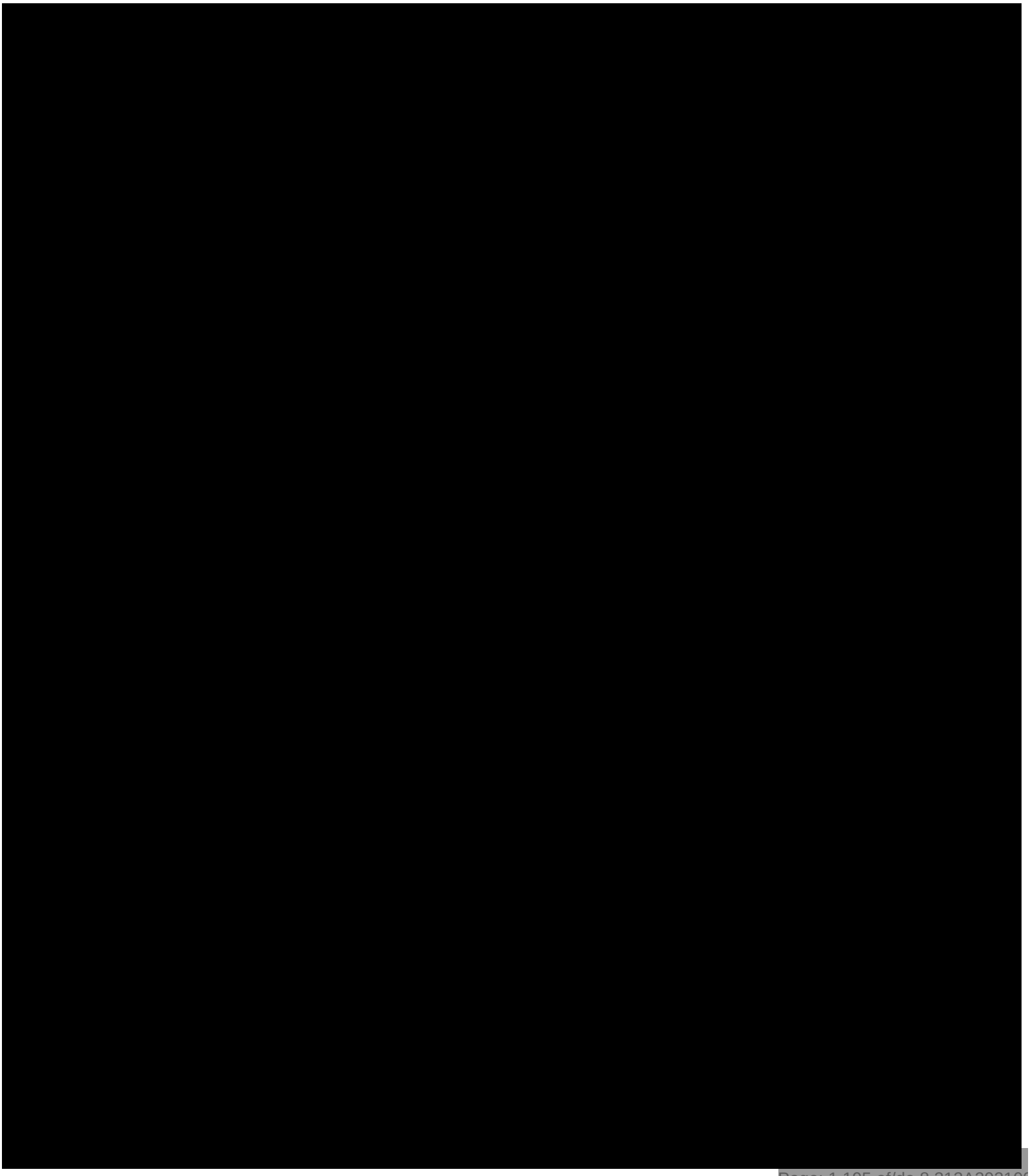

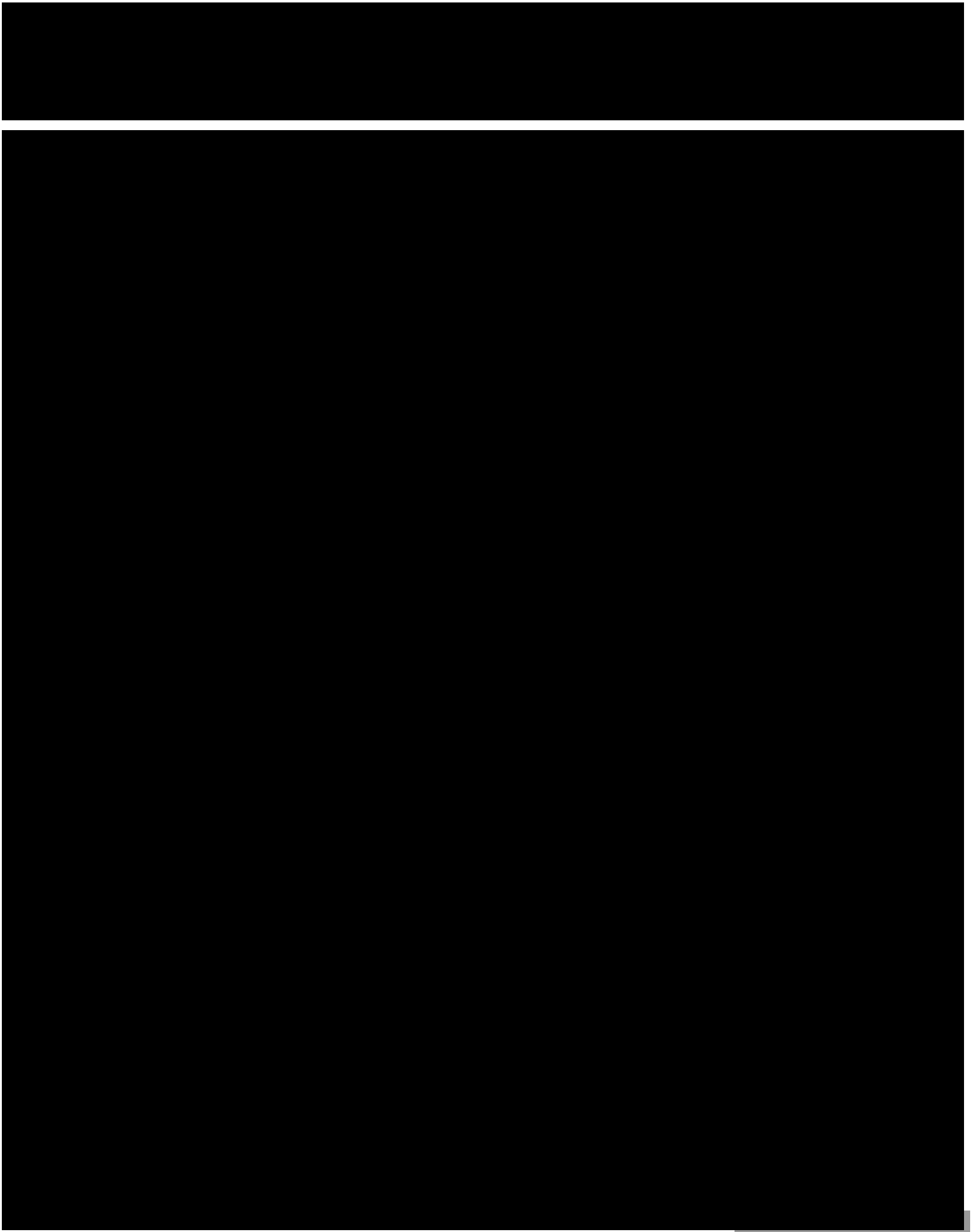

Contains Nonbinding Recommendations

Development and Licensure of Vaccines to Prevent COVID-19

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
June 2020

Preface

Public Comment

This guidance is being issued to address the coronavirus disease 2019 (COVID-19) public health emergency. This guidance is being implemented without prior public comment because the Food and Drug Administration (FDA or Agency) has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket FDA-2020-D-1137 and complete title of the guidance in the request.

Additional Copies

Additional copies are available from the FDA webpage titled "COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders," *available at* https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders, the FDA webpage titled "Search for FDA Guidance Documents," *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents, and the FDA webpage titled "Biologics Guidances," *available at* https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances. You may also send an email request to ocod@fda.hhs.gov to receive an additional copy of the guidance. Please include the docket number FDA-2020-D-1137 and complete title of the guidance in the request.

Questions

For questions about this document, contact the Office of Communication, Outreach, and Development (OCOD) by email at ocod@fda.hhs.gov or at 800-835-4709 or 240-402-8010.

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Development and Licensure of Vaccines to Prevent COVID-19

Guidance for Industry

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

FDA plays a critical role in protecting the United States from threats such as emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic which has been caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). FDA is committed to providing timely guidance to support response efforts to this pandemic.

FDA is issuing this guidance to assist sponsors in the clinical development and licensure of vaccines for the prevention of COVID-19.

This guidance is intended to remain in effect for the duration of the public health emergency related to COVID-19 declared by the Secretary of Health and Human Services (HHS) on January 31, 2020, effective January 27, 2020, including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the Public Health Service Act (PHS Act) (42 U.S.C. 247d(a)(2)). The recommendations described in the guidance are expected to assist the Agency and sponsors in the clinical development and licensure of vaccines for the prevention of COVID-19 and reflect the Agency's current thinking on this issue.

Given this public health emergency, and as discussed in the Notice in the *Federal Register* of March 25, 2020, titled "Process for Making Available Guidance Documents Related to Coronavirus Disease 2019" (85 FR 16949), *available at* https://www.govinfo.gov/content/pkg/FR-2020-03-25/pdf/2020-06222.pdf, this guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), (21 U.S.C. 371(h)(1)(C)), and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices. However, FDA expects that the recommendations set forth in this revised guidance will continue to apply outside the context of the current public health emergency.

Therefore, within 60 days following the termination of the public health emergency, FDA intends to revise and replace this guidance with an updated guidance that incorporates any appropriate changes based on comments received on this guidance and the Agency's experience with implementation.

In general, FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named "SARS-CoV-2" and the disease it causes has been named "COVID-19." On January 31, 2020, the Secretary of HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.[1] In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.[2]

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health. There are currently no FDA-licensed vaccines to prevent COVID-19. Commercial vaccine manufacturers and other entities are developing COVID-19 vaccine candidates using different technologies including RNA, DNA, protein, and viral vectored vaccines.

This guidance describes FDA's current recommendations regarding the data needed to facilitate clinical development and licensure of vaccines to prevent COVID-19. There are currently no accepted surrogate endpoints that are reasonably likely to predict clinical benefit of a COVID-19 vaccine. Thus, at this time, the goal of development programs should be to pursue traditional approval via direct evidence of vaccine safety and efficacy in protecting humans from SARS-CoV-2 infection and/or clinical disease.

This guidance provides an overview of key considerations to satisfy regulatory requirements set forth in the investigational new drug application (IND) regulations in 21 CFR Part 312 and licensing regulations in 21 CFR Part 601 for chemistry, manufacturing, and controls (CMC), and nonclinical and clinical data through development and licensure, and for post-licensure safety evaluation of COVID-19 preventive vaccines.[3] FDA is committed to supporting all scientifically sound approaches to attenuating the clinical impact of COVID-19. Sponsors engaged in the development of vaccines to prevent COVID-19 should also see the guidance for industry and investigators, *COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products* (Ref. 1).

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[1] Secretary of Health and Human Services Alex M. Azar, Determination that a Public Health Emergency Exists. (Jan. 31, 2020, renewed April 21, 2020), *available at* https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx. [2] Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak (Mar. 13, 2020), *available at* https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/.

[3] Novel devices used to administer COVID-19 vaccines raise additional issues which are not addressed in this guidance.

There are many COVID-19 vaccines currently in development and FDA recognizes that the considerations presented here do not represent all the considerations necessary to satisfy statutory and regulatory requirements applicable to the licensure of vaccines intended to prevent COVID-19. The nature of a particular vaccine and its intended use may impact specific data needs. We encourage sponsors to contact the Center for Biologics Evaluation and Research (CBER) Office of Vaccines Research and Review (OVRR) with specific questions.

III. CHEMISTRY, MANUFACTURING, AND CONTROLS – KEY CONSIDERATIONS

A. General Considerations

- COVID-19 vaccines licensed in the United States must meet the statutory and regulatory requirements for vaccine development and approval, including for quality, development, manufacture, and control (section 351(a) of the Public Health Service Act (PHS Act), (42 U.S.C. 262)). The vaccine product must be adequately characterized and its manufacture in compliance with applicable standards including current good manufacturing practice (cGMP) (section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) and 21 CFR Parts 210, 211, and 610). It is critical that vaccine production processes for each vaccine are well defined and appropriately controlled to ensure consistency in manufacturing.

- COVID-19 vaccine development may be accelerated based on knowledge gained from similar products manufactured with the same well-characterized platform technology, to the extent legally and scientifically permissible. Similarly, with appropriate justification, some aspects of manufacture and control may be based on the vaccine platform, and in some instances, reduce the need for product-specific data. FDA recommends that vaccine manufacturers engage in early communications with OVRR to discuss the type and extent of chemistry, manufacturing, and control information needed for development and licensure of their COVID-19 vaccine.

B. Manufacture of Drug Substance and Drug Product

- Data should be provided to show that all source material used in manufacturing is adequately controlled, including, for example, history and qualification of cell banks, history and qualification of virus banks, and identification of all animal derived materials used for cell culture and virus growth.

- Complete details of the manufacturing process must be provided in a Biologics License Application (BLA) to support licensure of a COVID-19 vaccine (21 CFR 601.2). Accordingly, sponsors should submit data and information identifying critical process parameters, critical quality attributes, batch records, defined hold times, and the in-process testing scheme. Specifications should be established for

each critical parameter. Validation data from the manufacture of platform-related products may provide useful supportive information, particularly in the identification of critical parameters.

- In-process control tests must be established that allow quality to be monitored for each lot for all stages of production (section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) and, as applicable, 21 CFR 211.110(a)).

- Data to support the consistency of the manufacturing process should be provided, including process validation protocols and study reports, data from engineering lots, and drug substance process performance qualification.

- The manufacturing process must be adequately validated (section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) and, as applicable, 21 CFR 211.100(a) and 211.110). Validation would typically include a sufficient number of commercial-scale batches that can be manufactured routinely, meeting predetermined in-process controls, critical process parameters, and lot release specifications. Typically, data on the manufacture of at least three commercial-scale batches are sufficient to support the validation of the manufacturing process (Ref. 2).

- A quality control system should be in place for all stages of manufacturing, including a well-defined testing program to ensure in process/intermediate product quality and product quality throughout the formulation and filling process. This system should also include a well-defined testing program to ensure drug substance quality profile and drug product quality for release. Data on the qualification/validation for all quality indicating assays should be submitted to the BLA to support licensure.

- All quality-control release tests, including key tests for vaccine purity, identity and potency, should be validated and shown to be suitable for the intended purpose. Release specifications are product specific and will be discussed with the sponsor as part of the review of a BLA.

- If adequately justified, final validation of formulation and filling operations may be completed after product approval if the impact on product quality is not compromised. It is important that any data that will be submitted after product approval be agreed upon prior to licensure and be submitted as a postmarketing commitment using the appropriate submission category.

- For vaccine licensure, the stability and expiry date of the vaccine in its final container, when maintained at the recommended storage temperature, should be demonstrated using final containers from at least three final lots made from different vaccine bulks.

- Storage conditions, including container closure integrity, must be fully validated (21 CFR 211.166).

- The vaccine must have been shown to maintain its potency for a period equal to that from the date of release to the expiry date (21 CFR 601.2 and 610.10). Post marketing commitments to provide full shelf life data may be acceptable with appropriate justification.

- A product specific stability program should be established to verify that licensed product maintains quality over the defined shelf life.

C. Facilities and Inspections

- Facilities must be of suitable size and construction to facilitate operations and should be adequately designed to prevent contamination, cross-contamination and mix-ups (section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) and, as applicable,21 CFR 211.42(a)). All utilities (including plumbing and sanitation) must be validated, and HVAC systems must provide adequate control over air pressure, micro-organisms, dust, humidity, and temperature, and sufficient protection or containment as needed (section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) and, as applicable, 21 CFR 211.46(c)) (Ref. 3). Facility and equipment cleaning and maintenance processes must be developed and validated (section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) and, as applicable, 21 CFR 211.56(c) and 211.67(b)).

- Manufacturing equipment should be qualified and sterile filtration and sterilization processes validated. Aseptic processes should be adequately validated using media simulations and personnel should be trained and qualified for their intended duties.

- A quality control unit must be established and must have the responsibility for oversight of manufacturing, and review and release of components, containers and closures, labeling, in-process material, and final products (section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) and, as applicable, 21 CFR 211.22). The quality control unit must have the responsibility for approving validation protocols, reports, investigate deviations, and institute corrective and preventive actions.

- FDA recommends that vaccine manufacturers engage in early communication with CBER's Office of Compliance and Biologics Quality, Division of Manufacturing and Product Quality to discuss facility preparation and inspection timing.

- Pre-license inspections of manufacturing sites are considered part of the review of a BLA and are generally conducted following the acceptance of a BLA filing (21 CFR 601.20). During the COVID-19 public health emergency, FDA is utilizing all available tools and sources of information to support regulatory decisions on applications that include sites impacted by FDA's ability to inspect due to COVID-19. During this interim period, we are using additional tools, where available, to determine the need for an on-site inspection and to support the

application assessment, such as reviewing a firm's previous compliance history, and requesting records in advance of or in lieu of on-site inspections or voluntarily from facilities and sites.

IV. NONCLINICAL DATA – KEY CONSIDERATIONS

A. General Considerations

- The purpose of nonclinical studies of a COVID-19 vaccine candidate is to define its immunogenicity and safety characteristics through *in vitro* and *in vivo* testing. Nonclinical studies in animal models[4] help identify potential vaccine related safety risks and guide the selection of dose, dosing regimen, and route of administration to be used in clinical studies. The extent of nonclinical data required to support proceeding to first in human (FIH) clinical trials depends on the vaccine construct, the supportive data available for the construct and data from closely related vaccines.

- Data from studies in animal models administered certain vaccine constructs against other coronaviruses (SARS-CoV and MERS-CoV) have raised concerns of a theoretical risk for COVID-19 vaccine-associated enhanced respiratory disease (ERD). In these studies, animal models were administered vaccine constructs against other coronaviruses and subsequently challenged with the respective wild-type virus. These studies have shown evidence of immunopathologic lung reactions characteristic of a Th-2 type hypersensitivity similar to ERD described in infants and animals that were administered formalin-inactivated respiratory syncytial virus (RSV) vaccine and that were subsequently challenged with RSV virus due to natural exposure or in the laboratory, respectively (Refs. 4-9). Vaccine candidates should be assessed in light of these studies as described in section D, below.

- FDA recommends that vaccine manufacturers engage in early communications with FDA to discuss the type and extent of nonclinical testing required for the particular COVID-19 vaccine candidate to support proceeding to FIH clinical trials and further clinical development.

B. Toxicity Studies (Refs. 10-14)

- For a COVID-19 vaccine candidate consisting of a novel product type and for which no prior nonclinical and clinical data are available, nonclinical safety studies will be required prior to proceeding to FIH clinical trials 21 CFR 312.23(a)(8).

[4] The preclinical program for any investigational product should be individualized with respect to scope, complexity, and overall design. We support the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. Proposals, with justification for any potential alternative approaches (e.g., in vitro or in silico testing), should be submitted during early communication meetings with FDA (see section VI of this document). We will consider if such an alternative method could be used in place of an animal test method.

- In some cases, it may not be necessary to perform nonclinical safety studies prior to FIH clinical trials because adequate information to characterize product safety may be available from other sources. For example, if the COVID-19 vaccine candidate is made using a platform technology utilized to manufacture a licensed vaccine or other previously studied investigational vaccines and is sufficiently characterized, it may be possible to use toxicology data (e.g., data from repeat dose toxicity studies, biodistribution studies) and clinical data accrued with other products using the same platform to support FIH clinical trials for that COVID-19 vaccine candidate. Vaccine manufacturers should summarize the findings and provide a rationale if considering using these data in lieu of performing nonclinical safety studies.

- When needed to support proceeding to FIH clinical trials, nonclinical safety assessments including toxicity and local tolerance studies must be conducted under conditions consistent with regulations prescribing good laboratory practices for conducting nonclincial laboratory studies (GLP) (21 CFR Part 58). Such studies should be completed and analysed prior to initiation of FIH clinical trials. When toxicology studies do not adequately characterize risk, additional safety testing should be conducted as appropriate.

- Data from toxicity studies may be submitted as unaudited final draft toxicicologic reports to accelerate proceeding to FIH clincial trials with COVID-19 vaccine candidates. The final, fully quality-assured reports should be available to FDA within 120 days of the start of the FIH clinical trial.

- Use of COVID-19 preventive vaccines in pregnancy and in women of childbearing potential will be an important consideration for vaccination programs. Therefore, FDA recommends that prior to enrolling pregnant women and women of childbearing potential who are not actively avoiding pregnancy in clinical trials, sponsors conduct developmental and reproductive toxicity (DART) studies with their respective COVID-19 vaccine candidate. Alternatively, sponsors may submit available data from DART studies with a similar product using comparable platform technology if, after consultation with the agency, the agency agrees those data are scientifically sufficient.

- Biodistribution studies in an animal species should be considered if the vaccine construct is novel in nature and there are no existing biodistribution data from the platform technology. These studies should be conducted if there is a likelihood of altered infectivity and tissue tropism or if a novel route of administration and formulation is to be used.

C. Characterization of the Immune Response in Animal Models

- Immunogenicity studies in animal models responsive to the selected COVID-19 vaccine antigen should be conducted to evaluate the immunologic properties of the COVID-19 vaccine candidate and to support FIH clinical trials. The aspects of

immunogenicity to be measured should be appropriate for the vaccine construct and its intended mechanism of action.

- Studies should include an evaluation of humoral, cellular, and functional immune responses, as appropriate to each of the included COVID-19 antigens. Use of antigen-specific enyzme linked immunosorbent assays (ELISA) should be considered to characterize the humoral response. Evaluation of cellular reponses should include the examination of CD8+ and CD4+ T cell responses using sensitive and specific assays. The functional activity of immune responses should be evaluated *in vitro* in neutralization assays using either wild-type virus or pseudovirion virus. The assays used for immunogencity evaluation should be demonstrated to be suitable for their intended purpose.

D. Studies to Address the Potential for Vaccine-associated Enhanced Respiratory Disease

- Current knowledge and understanding of the potential risk of COVID-19 vaccine associated ERD is limited, as is understanding of the value of available animal models in predicting the likelihood of such occurrence in humans. Nevertheless, studies in animal models (e.g., rodents and non-human primates) are considered important to address the potential for vaccine-associated ERD.

- Post-vaccination animal challenge studies and the characterization of the type of the nonclinical and clinical immune response induced by the particular COVID-19 vaccine candidate can be used to evaluate the likelihood of the vaccine to induce vaccine-associated ERD in humans.

- To support proceeding to FIH clinical trials, sponsors should conduct studies characterizing the vaccine-induced immune response in animal models evaluating immune markers of potential ERD outcomes. These should include assessments of functional immune responses (e.g., neutralizing antibody) versus total antibody responses and Th1/Th2 balance in animals vaccinated with clinically relevant doses of the COVID-19 vaccine candidate.

- COVID-19 vaccine candidates with immunogenicity data demonstrating high neutralizing antibody titers and Th1-type T cell polarization may be allowed to proceed to FIH trials without first completing postvaccination challenge studies in appropriate animal models, provided adequate risk mitigation strategies are put in place in the FIH trials. In these situations, postvaccination challenge studies are expected to be conducted in parallel with FIH trials to ensure the potential for vaccine-associated ERD is addressed prior to enrolling large numbers of human subjects into Phase 2 and 3 clinical trials. For COVID-19 vaccine candidates for which other data raise increased concerns about ERD, postvaccination animal challenge data and/or animal immunopathology studies are critical to assess protection and/or ERD *prior* to advancing to FIH clinical trials.

- The totality of data for a specific COVID-19 vaccine candidate, including data from postvaccination challenge studies in small animal models and from FIH clinical trials characterizing the type of immune responses induced by the vaccine will be considered in determining whether Phase 3 studies can proceed in the absence of postvaccination challenge data to address risk of ERD.

V. CLINICAL TRIALS – KEY CONSIDERATIONS

A. General Considerations

- Understanding of SARS-CoV-2 immunology, and specifically vaccine immune responses that might predict protection against COVID-19, is currently limited and evolving. Thus, while evaluation of immunogenicity is an important component of COVID-19 vaccine development, at this time, the goal of development programs should be to pursue traditional approval via direct evidence of vaccine efficacy in protecting humans from SARS-CoV-2 infection and/or disease.

- Clinical development programs for COVID-19 vaccines might be expedited by adaptive and/or seamless clinical trial designs (described below) that allow for selection between vaccine candidates and dosing regimens and for more rapid progression through the usual phases of clinical development.

- Regardless of whether clinical development programs proceed in discrete phases with separate studies or via a more seamless approach, an adequate body of data, including data to inform the risk of vaccine-associated ERD, will be needed as clinical development progresses to support the safety of vaccinating the proposed study populations and number of participants and, for later stage development, to ensure that the study design is adequate to meet its objectives.

- FDA can provide early advice, and potentially concurrence in principle, on plans for expedited/seamless clinical development. However, sponsors should plan to submit summaries of data available at each development milestone for FDA review and concurrence prior to advancing to the next phase of development.

- Conducting clinical trials in the setting of a public health emergency presents operational challenges. FDA has issued guidance to provide general considerations to assist sponsors in assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity for the duration of the COVID-19 public health emergency. It should be noted that not all of the recommendations in that guidance may be applicable to vaccine development, given some of the different considerations for these products (Ref. 15).

B. Trial Populations

- Once acceptable pre-clinical data are available, FIH and other early phase studies (which typically expose 10–100 participants to each vaccine candidate being evaluated) should first enroll healthy adult participants who are at low risk of severe COVID-19. Exclusion of participants at higher risk of severe COVID-19 from early phase studies is necessary to mitigate potential risk of vaccine-associated ERD until additional data to inform that potential risk becomes available through ongoing product development.

    - As the understanding of COVID-19 pathogenesis continues to evolve, exclusion criteria should reflect the current understanding of risk factors for more severe COVID-19, such as those described by the Centers for Disease Control and Prevention (Ref. 16).

    - Older adult participants (e.g., over 55 years of age) may be enrolled in FIH and other early phase studies so long as they do not have medical comorbidities associated with an increased risk of severe COVID-19. Some preliminary safety data in younger adults (e.g., 7 days after a single vaccination) should be available prior to enrolling older adult participants, especially for vaccine platforms without prior clinical experience.

    - If possible, early clinical studies should also exclude participants at high risk of SARS-CoV-2 exposure (e.g., healthcare workers).

- Sponsors should collect and evaluate at least preliminary clinical safety and immunogenicity data for each dose level and age group (e.g., younger versus older adults) to support progression of clinical development to include larger numbers (e.g., hundreds) of participants and participants at higher risk of severe COVID-19.

    - Preliminary immunogenicity data from early phase development should include assessments of neutralizing vs. total antibody responses and Th1 vs. Th2 polarization.

    - Additional data to further inform potential risk of vaccine-associated ERD and to support progression of clinical development, if available, may include preliminary evaluation of COVID-19 disease outcomes from earlier clinical development and results of non-clinical studies evaluating protection and/or histopathological markers of vaccine-associated ERD following SARS-CoV-2 challenge.

- To generate sufficient data to meet the BLA approval standard, late phase clinical trials to demonstrate vaccine efficacy with formal hypothesis testing will likely need to enroll many thousands of participants, including many with medical comorbidities for trials seeking to assess protection against severe COVID-19.

    - Initiation of late phase trials should be preceded by adequate characterization of safety and immunogenicity (e.g., in a few hundred participants for each

vaccine candidate, dose level, and age group to be evaluated) to support general safety, potential for vaccine efficacy, and low risk of vaccine-associated ERD.

- Results of non-clinical studies evaluating protection and/or histopathological markers of vaccine-associated ERD following SARS-CoV-2 challenge and COVID-19 disease outcomes from earlier clinical development are other potentially important sources of information to support clinical trials with thousands of participants.

- Although establishing vaccine safety and efficacy in SARS-CoV-2 naïve individuals is critical, vaccine safety and COVID-19 outcomes in individuals with prior SARS-CoV-2 infection, which might have been asymptomatic, is also important to examine because pre-vaccination screening for prior infection is unlikely to occur in practice with the deployment of licensed COVID-19 vaccines. Therefore, COVID-19 vaccine trials need not screen for or exclude participants with history or laboratory evidence of prior SARS-CoV-2 infection. However, individuals with acute COVID-19 (or other acute infectious illness) should be excluded from COVID-19 vaccine trials.

- FDA encourages the inclusion of diverse populations in all phases of vaccine clinical development. This inclusion helps to ensure that vaccines are safe and effective for everyone in the indicated populations.

  - FDA strongly encourages the enrollment of populations most affected by COVID-19, specifically racial and ethnic minorities.

  - Evaluation of vaccine safety and efficacy in late phase clinical development in adults should include adequate representation of elderly individuals and individuals with medical comorbidities.

  - FDA encourages vaccine developers to consider early in their development programs data that might support inclusion of pregnant women and women of childbearing potential who are not actively avoiding pregnancy in pre-licensure clinical trials (Ref. 17).

  - It is important for developers of COVID-19 vaccines to plan for pediatric assessments of safety and effectiveness, given the nature of the COVID-19 public health emergency, and to help ensure compliance with the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act (21 U.S.C. 355c)) (Ref. 18). The epidemiology and pathogenesis of COVID-19, and the safety and effectiveness of COVID-19 vaccines, may be different in children compared with adults. In order to ensure compliance with 21 CFR Part 50 Subpart D (Additional safeguards for children in clinical investigations), considerations on the prospect of direct benefit and acceptable risk to support initiation of pediatric studies, and the appropriate design and endpoints for pediatric studies, should be discussed in the context of specific vaccine development programs.

C. Trial Design

- Early phase trials often aim to down-select among multiple vaccine candidates and/or dosing regimens via randomization of participants to different treatment groups. While including a placebo control and blinding are not required for early phase studies, doing so may assist in interpretation of preliminary safety data.

- Later phase trials, including efficacy trials, should be randomized, double-blinded, and placebo controlled.

    - An individually randomized controlled trial with 1:1 randomization between vaccine and placebo groups is usually the most efficient study design for demonstrating vaccine efficacy. Other types of randomization, such as cluster randomization, may be acceptable but require careful consideration of potential biases that are usually avoided with individual randomization.

    - An efficacy trial that evaluates multiple vaccine candidates against a single placebo group may be an acceptable approach to further increase efficiency, provided that the trial is adequately designed with appropriate statistical methods to evaluate efficacy.

    - If the availability of a COVID-19 vaccine proven to be safe and effective precludes ethical inclusion of a placebo control group, that vaccine could serve as the control treatment in a study designed to evaluate efficacy with non-inferiority hypothesis testing.

- Protocols for adaptive trials should include pre-specified criteria for adding or removing vaccine candidates or dosing regimens, and protocols for seamless trials should include pre-specified criteria (e.g., safety and immunogenicity data) for advancing from one phase of the study to the next.

- Follow-up of study participants for COVID-19 outcomes (in particular, for severe COVID-19 disease manifestations) should continue as long as feasible, ideally at least one to two years, to assess duration of protection and potential for vaccine-associated ERD as immune responses to the vaccine wane.

- Efficacy trials should include contingency plans for continued follow up and analysis of safety and effectiveness outcomes in the event that a safe and effective vaccine becomes available (e.g., as demonstrated in a planned interim analysis or as demonstrated in another clinical trial). In that case, discussion with the agency may be necessary to address ethical arguments to break the blind and offer vaccine to placebo recipients.

- In cases where statistical equivalency testing of vaccine immune responses in humans is required to support manufacturing consistency (clinical lot-to-lot consistency trial), this testing can be incorporated into the design of an efficacy trial and does not need to be conducted in a separate study.

D. Efficacy Considerations

- Either laboratory-confirmed COVID-19 or laboratory-confirmed SARS-CoV-2 infection is an acceptable primary endpoint for a COVID-19 vaccine efficacy trial.

  - Acute cases of COVID-19 should be virologically confirmed (e.g., by RT-PCR).

  - SARS-CoV-2 infection, including asymptomatic infection, can be monitored for and confirmed either by virologic methods or by serologic methods evaluating antibodies to SARS-CoV-2 antigens not included in the vaccine.

- Standardization of efficacy endpoints across clinical trials may facilitate comparative evaluation of vaccines for deployment programs, provided that such comparisons are not confounded by differences in trial design or study populations. To this end, FDA recommends that either the primary endpoint or a secondary endpoint (with or without formal hypothesis testing) be defined as virologically confirmed SARS-CoV-2 infection with one or more of the following symptoms:

  - Fever or chills
  - Cough
  - Shortness of breath or difficulty breathing
  - Fatigue
  - Muscle or body aches
  - Headache
  - New loss of taste or smell
  - Sore throat
  - Congestion or runny nose
  - Nausea or vomiting
  - Diarrhea

- As it is possible that a COVID-19 vaccine might be much more effective in preventing severe versus mild COVID-19, sponsors should consider powering efficacy trials for formal hypothesis testing on a severe COVID-19 endpoint. Regardless, severe COVID-19 should be evaluated as a secondary endpoint (with or without formal hypothesis testing) if not evaluated as a primary endpoint. FDA recommends that severe COVID-19 be defined as virologically confirmed SARS-CoV-2 infection with any of the following:

  - Clinical signs at rest indicative of severe systemic illness (respiratory rate $\geq$ 30 per minute, heart rate $\geq$ 125 per minute, SpO2 $\leq$ 93% on room air at sea level or PaO2/FiO2 < 300 mm Hg)
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO)
  - Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors)
  - Significant acute renal, hepatic, or neurologic dysfunction

- Admission to an ICU
- Death

- SARS-CoV-2 infection (whether or not symptomatic) should be evaluated as a secondary or exploratory endpoint, if not evaluated as a primary endpoint.

- The above diagnostic criteria may need to be modified in certain populations; for example, in pediatric patients and those with respiratory comorbidities. Sponsors should discuss their proposed case definitions with the Agency prior to initiating enrollment.

E. Statistical Considerations

- To ensure that a widely deployed COVID-19 vaccine is effective, the primary efficacy endpoint point estimate for a placebo-controlled efficacy trial should be at least 50%, and the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate is >30%.

  - The same statistical success criterion should be used for any interim analysis designed for early detection of efficacy.

  - A lower bound ≤30% but >0% may be acceptable as a statistical success criterion for a secondary efficacy endpoint, provided that secondary endpoint hypothesis testing is dependent on success on the primary endpoint.

- For non-inferiority comparison to a COVID-19 vaccine already proven to be effective, the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary relative efficacy point estimate is >-10%.

- For each vaccine candidate, appropriate statistical methods should be used to control type 1 error for hypothesis testing on multiple endpoints and/or interim efficacy analyses.

- Late phase studies should include interim analyses to assess risk of vaccine-associated ERD (see section F) and futility.

- Study sample sizes and timing of interim analyses should be based on the statistical success criteria for primary and secondary (if applicable) efficacy analyses and realistic, data-driven estimates of vaccine efficacy and incidence of COVID-19 (or SARS-CoV-2 infection) for the populations and locales in which the trial will be conducted.

F. Safety Considerations

- The general safety evaluation of COVID-19 vaccines, including the size of the safety database to support vaccine licensure, should be no different than for other preventive vaccines for infectious diseases. Safety assessments throughout clinical development should include:

  - Solicited local and systemic adverse events for at least 7 days after each study vaccination in an adequate number of study participants to characterize reactogenicity (including at least a subset of participants in late phase efficacy trials).

  - Unsolicited adverse events in all study participants for at least 21–28 days after each study vaccination.

  - Serious and other medically attended adverse events in all study participants for at least 6 months after completion of all study vaccinations. Longer safety monitoring may be warranted for certain vaccine platforms (e.g., those that include novel adjuvants).

  - All pregnancies in study participants for which the date of conception is prior to vaccination or within 30 days after vaccination should be followed for pregnancy outcomes, including pregnancy loss, stillbirth, and congenital anomalies.

- The pre-licensure safety database for preventive vaccines for infectious diseases typically consists of at least 3,000 study participants vaccinated with the dosing regimen intended for licensure. FDA anticipates that adequately powered efficacy trials for COVID-19 vaccines will be of sufficient size to provide an acceptable safety database for each of younger adult and elderly populations, provided that no significant safety concerns arise during clinical development that would warrant further pre-licensure evaluation.

- COVID-19 vaccine trials should periodically monitor for unfavorable imbalances between vaccine and control groups in COVID-19 disease outcomes, in particular for cases of severe COVID-19 that may be a signal for vaccine-associated ERD.

  - Studies should include pre-specified criteria for halting based on signals of potential vaccine-associated ERD.

  - FDA recommends use of an independent data safety monitoring board (DSMB) (Ref. 18) for vaccine-associated ERD and other safety signal monitoring, especially during later stage development.

VI. POST-LICENSURE SAFETY EVALUATION – KEY CONSIDERATIONS

A. General Considerations

- As with all licensed vaccines, there can be limitations in the safety database accrued from the pre-licensure clinical studies of a COVID-19 vaccine. For example:
    - The number of subjects receiving a COVID-19 vaccine in pre-licensure clinical studies may not be adequate to detect some adverse reactions that may occur infrequently.
    - Pre-licensure safety data in some subpopulations likely to receive a COVID-19 vaccine (e.g., pregnant individuals, or individuals with medical comorbidities) may be limited at the time of licensure.
    - For some COVID-19 vaccines, the safety follow-up period to monitor for possible vaccine-associated ERD and other adverse reactions may not have been completed for all subjects enrolled in pre-licensure clinical studies before the vaccine is licensed.

- For COVID-19 vaccines, it is likely that during the early postmarketing period, a large population might be vaccinated in a relatively short timeframe. Thus, FDA recommends early planning of pharmacovigilance activities before licensure.

- To facilitate accurate recording and identification of vaccines in health records, manufacturers should consider establishment of individual Current Procedural Terminology (CPT) codes and the use of bar codes to label the immediate container.

B. Pharmacovigilance Activities for COVID-19 Vaccines

- Routine pharmacovigilance for licensed biological products includes expedited reporting of serious and unexpected adverse events as well as periodic safety reports in accordance with 21 CFR 600.80 (Postmarketing reporting of adverse experiences).

- FDA recommends that at the time of a BLA submission for a COVID-19 vaccine, applicants submit a Pharmacovigilance Plan (PVP) as described in the FDA Guidance for Industry; E2E Pharmacovigilance Planning (Ref. 20). The contents of a PVP for a COVID-19 vaccine will depend on its safety profile and will be based on data, which includes the pre-licensure clinical safety database, preclinical data, and available safety information for related vaccines, among other considerations.

- The PVP should include actions designed to address all important identified risks, important potential risks or important missing information. Pharmacoepidemiologic studies or other actions to evaluate notable potential risks, such as vaccine-associated ERD, should be considered. FDA may recommend one or more of the following as components of a PVP for a COVID-19 vaccine:

- Submission of reports of specific adverse events of interest in an expedited manner beyond routine required reporting;
- Submission of adverse event report summaries at more frequent intervals than specified for routine required reporting;
- Ongoing and/or extended safety follow-up (under an IND) for vaccine-associated ERD of subjects enrolled in pre-licensure clinical studies;
- A pharmacoepidemiologic study to further evaluate (an) important identified or potential risk(s) from the clinical development program, such as vaccine-associated ERD or other uncommon or delayed-onset adverse events of special interest;
- A pregnancy exposure registry that actively collects information on vaccination during pregnancy and associated pregnancy and infant outcomes (Ref. 21).

C. Required Postmarketing Safety Studies

- Section 505(o)(3) of the FD&C Act (21 U.S.C. 355(o)(3)) authorizes FDA to require certain postmarketing studies or clinical trials for prescription drugs approved under section 505(b) of the FD&C Act (21 U.S.C. 355(b)) and biological products approved under section 351 of the PHS Act (42 U.S.C. 262) (Ref. 22). Under section 505(o)(3), FDA can require such studies or trials at the time of approval to assess a known serious risk related to the use of the drug, to assess signals of serious risk related to the use of the drug, or to identify an unexpected serious risk when available data indicate the potential for a serious risk. Under section 505(o)(3), FDA can also require such studies or trials after approval if FDA becomes aware of new safety information, which is defined at section 505-1(b)(3) of the FD&C Act (21 U.S.C. 355-1(b)(3)).

- For COVID-19 vaccines, FDA may require postmarketing studies or trials to assess known or potential serious risks when such studies or trials are warranted.

VII. DIAGNOSTIC AND SEROLOGICAL ASSAYS – KEY CONSIDERATIONS

- Diagnostic assays used to support the pivotal efficacy analysis (e.g., RT-PCR) should be sensitive and accurate for the purpose of confirming infection and should be validated before use.

- Assays used for immunogenicity evaluation should be suitable for their intended purpose of assessing relevant immune responses to vaccination and be validated before use in pivotal clinical trials.

VIII. ADDITIONAL CONSIDERATIONS

A. Additional Considerations in Demonstrating Vaccine Effectiveness

- Given the current state of knowledge about COVID-19, the most direct approach to demonstrate effectiveness for a COVID-19 vaccine candidate is based on clinical endpoint efficacy trials showing protection against disease (see section V. D. above).

- Once additional understanding of SARS-CoV-2 immunology, and specifically vaccine immune responses that might be reasonably likely to predict protection against COVID-19, is acquired, accelerated approval of a COVID-19 vaccine pursuant to section 506 of the FD&C Act (21 U.S.C. 356) and 21 CFR 601.40 may be considered if an applicant provides sufficient data and information to meet the applicable legal requirements. For a COVID-19 vaccine, it may be possible to approve a product under these provisions based on adequate and well-controlled clinical trials establishing an effect of the product on a surrogate endpoint (e.g., immune response) that is reasonably likely to predict clinical benefit.

- A potential surrogate endpoint likely would depend on the characteristics of the vaccine, such as antigen structure, mode of delivery, and antigen processing and presentation in the individual vaccinated. For example, an immune marker established for an adenovirus-based vaccine cannot be presumed applicable to a VSV-based vaccine, given that the two vaccines present antigen in different ways and engender different types of protective immune responses.

- Since SARS-CoV-2 represents a novel pathogen, a surrogate endpoint reasonably likely to predict protection from COVID-19 should ideally be derived from human efficacy studies examining clinical disease endpoints. If the surrogate endpoint is derived from other data sources, sponsors should consult the FDA to reach agreement on the use of the surrogate endpoint.

- An adequate dataset evaluating the safety of the vaccine in humans would need to be provided for consideration of licensure.

- For drugs granted accelerated approval, postmarketing confirmatory trials have been required to verify and describe the predicted effect on clinical benefit. These studies should usually be underway at the time of the accelerated approval, 21 CFR Part 601, Subpart E, and must be completed with due diligence (section 506(c)(3)(A) of the FD&C Act (21 U.S.C. 356(c)(3)(A)) and 21 CFR 601.41).

- If it is no longer possible to demonstrate vaccine effectiveness by way of conducting clinical disease endpoint efficacy studies, the use of a controlled human infection model to obtain evidence to support vaccine efficacy may be considered. However, many issues, including logistical, human subject protection, ethical, and scientific issues, would need to be satisfactorily addressed. At this

time no controlled human infection models for SARS-CoV-2 have been established or characterized.

B. Emergency Use Authorization

- An Emergency Use Authorization (EUA) may be issued only after several statutory requirements are met (section 564 of the FD&C Act (21 U.S.C. 360bbb-2)) (Ref. 23). Among these requirements is a determination by FDA that the known and potential benefits of a product, when used to diagnose, prevent, or treat serious or life-threatening diseases, outweigh the known and potential risks of the product.

- Issuance of an EUA (Ref. 23) may be appropriate for a COVID-19 vaccine provided the standard for issuing an EUA is met. Issuance of an EUA for a COVID-19 vaccine prior to the completion of large randomized clinical efficacy trials could reduce the ability to demonstrate effectiveness of the investigational vaccine in a clinical disease endpoint efficacy trial to support licensure, and such clinical disease endpoint efficacy trials may be needed to investigate the potential for vaccine-associated ERD. Thus, for a vaccine for which there is adequate manufacturing information, issuance of an EUA may be appropriate once studies have demonstrated the safety and effectiveness of the vaccine but before the manufacturer has submitted and/or FDA has completed its formal review of the biologics license application.

- In the case of investigational vaccines being developed for the prevention of COVID-19, any assessment regarding an EUA would be made on a case by case basis considering the target population, the characteristics of the product, the preclinical and human clinical study data on the product, and the totality of the available scientific evidence relevant to the product.

IX. REFERENCES

1. COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products; Guidance for Industry, May 2020, https://www.fda.gov/media/137927/download.

2. Guidance for Industry: Process Validation: General Principles and Practices, January 2011, https://www.fda.gov/media/71021/download.

3. Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product, January 1999, https://www.fda.gov/media/73614/download.

4. Perlman S and Dandekar AA, 2005, Immunopathogenesis of Coronavirus Infections: Implications for SARS, Nat Rev Immunol 5: 917-927, https://doi.org/10.1038/nri1732.

5. Haagmans BL, Boudet F, Kuiken T, deLang A, et al., 2005, Protective immunity induced by the inactivated SARS coronavirus vaccine, Abstract S 12-1 Presented at the X International Nidovirus Symposium, Colorado, Springs, CO.

6. Tseng C-T, Sbrana E, Iwata-Yoshikawa N, Newman P, et al., 2012, Immunization with SARS Coronavirus Vaccines Leads to Pulmonary Immunopathology on Challenge with the SARS Virus, PloS One, 7(4): e35421, https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0035421.

7. Yasui F, Kai C, Kitabatake M, Inoue S, et al., 2008, Prior Immunization With Severe Acute Respiratory Syndrome (SARS) – associated Coronavirus (SARS-CoV) Nucleocapsid Protein Causes Severe Pneumonia in Mice Infected with SARS-CoV, J Immunol, 181(9): 6337-6348, https://www.jimmunol.org/content/181/9/6337.long.

8. Bolles M, Deming D, Long K, Agnihothram S, et al., 2011, A Double-Inactivated Severe Acute Respiratory Syndrome Coronavirus Vaccine Provides Incomplete Protection In Mice And Induces Increased Eosinophilic Proinflammatory Pulmonary Response Upon Challenge, J Virol 85(23) 12201-12215, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3209347/.

9. Agrawal AS, Tao X, Algaissi A, Garron T, et al., 2016, Immunization With Inactivated Middle East Respiratory Syndrome Coronavirus Vaccine Leads To Lung Immunopathology On Challenge With Live Virus, Hum Vaccin Immunother, 12(9): 2351-2356, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5027702/.

10. Guidance for Industry: Considerations For Plasmid DNA Vaccines For Infectious Disease Indications, November 2007, https://www.fda.gov/media/73667/download.

11. [Intentionally left blank.]

12. Guidance for Industry: Considerations For Developmental Toxicity Studies For Preventive And Therapeutic Vaccines For Infectious Disease Indications, February 2006, https://www.fda.gov/media/73986/download.

13. World Health Organization, WHO Guidelines On Nonclinical Evaluation Of Vaccines, Annex 1, WHO Technical Report Series, 2005; 927:31-63, https://www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/ANNEX%201Nonclinical.P31-63.pdf?ua=1.

14. World Health Organization, Guidelines On The Nonclinical Evaluation Of Vaccine Adjuvants And Adjuvanted Vaccines, Annex 2, WHO Technical Report Series, TRS 987:59-100, https://www.who.int/biologicals/areas/vaccines/TRS_987_Annex2.pdf?ua=1.

15. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency; Guidance for Industry, Investigators, and Institutional Review Boards, March 2020 and updated June 2020, https://www.fda.gov/media/136238/download.

16. Centers for Disease Control and Prevention, Coronavirus Disease 2019 (COVID-19) At Risk for Severe Illness, last reviewed May 14, 2020, https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html.

17. Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials; Draft Guidance for Industry, April 2018, https://www.fda.gov/media/112195/download.*

18. Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act, September 2005, https://www.fda.gov/media/72274/download.*

19. Guidance for Industry: Establishment and Operation of Clinical Trial Data Monitoring Committees, March 2006, https://www.fda.gov/media/75398/download.

20. Guidance for Industry: E2E Pharmacovigilance Planning, April 2005, https://www.fda.gov/media/71238/download.

21. Postapproval Pregnancy Safety Studies; Draft Guidance for Industry, May 2019, https://www.fda.gov/media/124746/download.*

22. Guidance for Industry: Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act, April 2011, https://www.fda.gov/media/131980/download.

23. Emergency Use Authorization of Medical Products and Related Authorities; Guidance for Industry and Other Stakeholders, January 2017, https://www.fda.gov/media/97321/download.

* When finalized, this guidance will represent FDA's current thinking on this topic.

Guidance for Industry

Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448 or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact CBER Division of Vaccines and Related Products Applications at (301) 827-3070.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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Guidance for Industry[1]

Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to provide you, sponsors, with recommendations for the conduct of developmental toxicity[2] studies for investigational preventive and therapeutic vaccines for infectious disease indications. The recommendations set forth in this document pertain to the assessment of the developmental toxicity potential of preventive and therapeutic vaccines for infectious diseases indicated for females of childbearing potential and pregnant individuals.[3] This guidance applies prospectively to investigational vaccines, i.e., vaccines under investigational new drug applications (IND) and vaccines the subject of a new biologics license application (BLA). These recommendations do not apply retrospectively to already licensed vaccines except those the subject of additional INDs. This guidance document finalizes the draft guidance entitled "Guidance for Industry: Considerations for Reproductive Toxicity Studies for Preventive Vaccines for Infectious Disease Indications" dated August 2000 (65 FR 54534; September 8, 2000).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or

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[1] The Maternal Immunization Working Group in the Center for Biologics Evaluation and Research at the Food and Drug Administration prepared this guidance. The document was revised based on public comments submitted to the Division of Dockets Management on the draft guidance dated August 2000, and on recommendations made by an expert panel convened at a Workshop entitled "Non-clinical Safety Evaluation of Preventive Vaccines: Recent Advances and Regulatory Considerations" held December 2 & 3, 2002, Arlington, VA, discussing approaches for developmental toxicity assessments for vaccines.

[2] Developmental toxicity is any adverse effect induced prior to attainment of adult life. This includes effects induced or manifested in the embryonic or fetal period and those induced or manifested postnatally (Ref. 1).

[3] This document does not address concerns regarding male reproductive toxicity and male and female fertility studies.

recommended, but not required.

II. BACKGROUND

The Center for Biologics Evaluation and Research (CBER) reviews a broad spectrum of applications for investigational vaccines intended for the prevention and treatment of infectious diseases and indicated for immunization of adolescents and adults. Thus, the target population for vaccines often includes females of childbearing potential who may become pregnant during the vaccination period. A number of vaccines are in clinical development specifically for maternal immunization indications with the goal of preventing infectious disease in the pregnant mother and/or neonate through passive antibody transfer from mother to fetus. Unless the vaccine is specifically indicated for maternal immunization, no studies are conducted prior to product licensure to determine the vaccine's safety in pregnant women. During clinical development of most vaccines not specifically intended for use during pregnancy, pregnant women are ineligible to participate in clinical trials. If pregnancy occurs during a study, treatment is usually discontinued and the woman does not receive additional immunizations. Consequently, there are few clinical data to address developmental toxicity of the vaccine in pregnant women or females of childbearing potential at the time of product licensure.

As more women of childbearing potential participate in clinical trials and as more preventive and therapeutic vaccines are developed for adolescents and adults, there is increasing concern about the unintentional exposure of an embryo/fetus before information is available about the risk versus benefit of the vaccine. Also, following approval, vaccines not indicated for use during pregnancy may be recommended by health policy makers for use in pregnant women (Ref. 2). In addition, use of licensed vaccines in females of childbearing potential will likely result in inadvertent exposure of the pregnant woman and her fetus to the vaccine. Considering that more than half of pregnancies in the U.S. are unintended, it is unlikely that vaccine exposure would be avoided in these pregnancies prior to their clinical recognition (Ref. 3). In these situations, in the absence of clinical data, it is difficult for the practitioner to make an informed risk assessment, even in situations where immunization of pregnant women may be appropriate.

Until recently, few licensed vaccines have been tested for developmental toxicity in animals prior to their use in humans. However, for the reasons listed above, we, FDA, recommend that you address during the IND studies the risks versus the benefits of immunization programs for pregnant women and/or females of childbearing potential by performing developmental toxicity studies in animal models. Potential risks involved in prenatal immunization programs include developmental adverse effects caused by the inherent biological activity of the vaccine antigen and constituents of the vaccine product (e.g., adjuvants, preservatives, and stabilizers). In addition, potential adverse effects on the pregnancy status and or the developing embryo/fetus may be the result of maternal immune modulation (Refs. 4 and 5).

Because pregnant women are usually excluded from clinical trials, data from developmental toxicity studies in animal models offer one approach to screen for potential developmental hazards. Studies in animal models may frequently present the only information available to draw conclusions regarding developmental risk to be included in the product labeling required under

section 201.57(f)(6) in Title 21 Code of Federal Regulations (§ 201.57(f)(6)). As there is virtually no scientific literature on animal developmental toxicity testing for vaccine products, this guidance will outline general and specific recommendations that should be taken into account in the assessment of developmental toxicity for preventive and therapeutic vaccines for infectious disease indications.

III. VACCINE TARGET POPULATION AND TIMING OF PRE-CLINICAL DEVELOPMENTAL TOXICITY STUDIES

For the purpose of this document, vaccines are a heterogeneous class of preventive, in some cases therapeutic, medicinal products, the administration of which is intended to elicit an immune response(s) that can prevent and/or lessen the severity of one or more infectious diseases. A vaccine may be a live attenuated preparation of bacteria, viruses, or parasites, inactivated (killed) whole organisms, living irradiated cells, crude fractions or purified immunogens, including those derived from recombinant deoxyribonucleic acid (DNA) in a host cell, conjugates formed by covalent linkage of components, synthetic antigens, polynucleotides (such as plasmid DNA vaccines), living vectored cells expressing specific heterologous immunogens, or cells pulsed with immunogen. It may also be a combination of vaccines listed above. Antigens may be presented plain or delivered in combination with other antigens, adjuvants, additives and other excipients. Therapeutic vaccines for non-infectious diseases and monoclonal antibodies used as immunogens are not considered in this guidance (Ref. 6).

Developmental toxicity studies are usually not necessary for vaccines indicated for immunization during childhood. However, for vaccines indicated for adolescents and adults and for vaccines that are indicated or may have the potential to be indicated for immunization of pregnant women, we recommend that you consider developmental toxicity studies.

There are currently differences in the timing of these developmental toxicity studies, as follows, to support inclusion of either pregnant individuals or females of childbearing potential in clinical trials.

Maternal immunization: For products indicated specifically for immunization of pregnant women, we recommend that you have the data from non-clinical developmental toxicity studies available prior to the initiation of any clinical trial enrolling pregnant women.

Females of childbearing potential: For vaccines indicated for females of childbearing potential, you may include subjects in clinical trials without non-clinical developmental toxicity studies, provided that appropriate precautions are taken by subjects enrolled in these trials to avoid vaccination during pregnancy, such as pregnancy testing and use of birth control. For these products, we recommend that you include data from developmental toxicity studies with the initial BLA submission (§ 601.2), regardless of whether such studies have been submitted earlier to the IND.

Males: Currently, males may be included in Phase I, II, and III clinical trials in the absence of nonclinical male fertility studies, although such studies may be recommended for certain

products in the future.

IV. DESIGN OF DEVELOPMENTAL TOXICITY STUDIES

A. General Considerations and Recommendations

The decision whether a developmental toxicity study needs to be performed should be made on a case-by-case basis taking into consideration historical use, product features, intended target population and intended clinical use. We recommend the developmental toxicity study be designed to detect potential developmental adverse effects induced by components present in the vaccine formulation. However, despite efforts to maximize the predictive value of developmental toxicity studies, there may always be limitations in evaluating or screening for potential risks and thus, limitations in reducing the uncertainties of risk. Also, lack of adverse effects on embryo/fetal development in an animal study does not necessarily imply absence of risk for humans. Factors that may limit risk prediction include, but are not limited to, species-specific differences in the immune response, different developmental time lines, and differences in placentation. Nevertheless, developmental toxicity studies in animal models are the best currently available non-clinical tools to screen for adverse developmental effects of the product in humans. Information about developmental risk from animal data is frequently the only information available at the time of product licensure. The good laboratory practice regulations in 21 CFR Part 58 apply to nonclinical laboratory studies that support or are intended to support applications.

1. Previous clinical experience

All available clinical experience in pregnant women should be considered in any potential application with respect to the design of developmental toxicity studies in animals. Clinical experience derived from immunization of pregnant women may be helpful in the evaluation of the potential for any adverse outcome on the viability and development of offspring. Such information may also aid in the design/monitoring of appropriate non-clinical studies, and for product labeling. However, clinical data that may have been obtained from small numbers of pregnant women enrolled in non-IND studies, e.g., immunized with the vaccine or a related product, will generally not replace the need for animal developmental toxicity studies.

2. Previous non-clinical experience

We recommend that you review all data generated from prior acute or repeat dose non-clinical toxicity studies for their possible contribution to the interpretation of any adverse developmental effects that appear in the developmental toxicology studies. In addition, data from prior non-clinical studies do frequently form the basis for the choice of the animal model and vaccine dose used in the developmental toxicity study.

3. Vaccine formulation

We recommend that you perform the non-clinical developmental toxicity study on the same lot as proposed for the clinical trial. If this is not feasible, we recommend that non-clinical lots be comparable to clinical lots with respect to physico-chemical data, stability, and formulation and be manufactured in accordance with applicable cGMPstandards.
In addition, even though pivotal clinical studies are frequently conducted with an intended final formulation, optimizations of formulations are frequently made prior to product marketing. In these cases, we will assess, on a case-by-case basis, the applicability of non-clinical studies conducted with earlier clinical formulations of the vaccine to the commercial formulation of the vaccine. For a product specifically intended for maternal immunization, we recommend that you perform non-clinical developmental toxicity studies in advance of clinical studies that enroll pregnant women. In these cases, to avoid performing multiple developmental toxicology studies during development, you may find it advantageous to conduct Phase I and Phase II studies in non-pregnant subjects. Results from these studies can be used as the basis for advancing the most promising product formulation(s) to studies that enroll pregnant women.

4. Vaccine product class

There are a number of vaccines in clinical development that may be similar to or of the same product class as either investigational or already licensed products, for which developmental toxicity studies may have been performed. In these cases, we will examine the need for additional development toxicity studies for the product under investigation on a case-by case basis. Regarding combination vaccines in clinical development, for which the individual components are licensed and on which developmental toxicity assessments have been performed, we may not recommend further developmental toxicity assessments. However, if the combination vaccine is formulated with new adjuvant, new preservative or if significant changes to the individual products or their manufacture were made and/or concerns exist that combining the individual licensed products may increase their toxic potential, we recommend additional developmental toxicity studies. Similarly, if no developmental toxicity studies have been conducted for the individual licensed or unlicensed components, we recommend that you conduct developmental toxicity studies. In some instances, documentation on clinical and epidemiological data, e.g., exposure to the infectious agent or use of related, licensed vaccines during pregnancy, may be sufficient to evaluate the risk of the investigational product and may be provided by you and considered by FDA in determining the need for developmental toxicity studies in animal models. In these cases, we recommend that you contact FDA to reach agreement regarding the need for additional developmental toxicity studies for that particular product.

5. Application of ICH guidance document S5A

The ICH S5A guidance document entitled "Detection of Toxicity to Reproduction for Medicinal Products," addresses the design of animal studies primarily for detection of toxicity on reproduction, dividing the reproductive cycle into different segments, defined as stages A – F (see Ref. 1). The ICH S5A guidance suggests that different studies can be conducted to address the various segments of the reproduction cycle. For preventive and therapeutic vaccines for infectious diseases, the primary concern is potential untoward effects of the test article on development and growth of the embryo and fetus. Thus, the primary focus is on developmental toxicity studies to detect adverse effects on the pregnant/lactating female and development of the embryo/fetus and the offspring following exposure of the female to the vaccine from implantation through the end of pregnancy, with follow-up of the offspring through weaning. These stages are defined as stages C, D, and E in the ICH S5A document. Depending on the product and on a case-by-case basis, we might require additional studies to address additional segments of the reproductive cycle.

We recommend use of the ICH S5A guidance as a general point of reference to assist you in the general design of developmental toxicity studies and evaluation of endpoints. However, we want to emphasize distinguishable factors relevant to vaccines. The most important feature distinguishing vaccines from other pharmaceutical products is the intended vaccine-induced immune response. Also, vaccines are usually administered in limited, episodic dosages with months or even years between doses. Vaccines include a broad range of product categories such as live attenuated, inactivated, recombinant, polynucleotide, polysaccharide, protein antigens, vectored vaccines, and conjugate vaccines. These may be adjuvanted or consist of a combination of different vaccine antigens. Thus, given the complexity of these issues, the non-clinical testing strategies outlined in the ICH S5A document may not be directly applicable to vaccines, and study designs outlined in the ICH S5A document may need to be tailored to the vaccine product under consideration. Outlined below are specific considerations that we recommend you take into account when designing developmental toxicity studies for vaccines. We also recommend that prior to the conduct of the study, you establish an early dialogue with CBER to reach agreement on a specific protocol including study endpoints.

B. Specific Considerations

1. Animal model

We recommend that you provide in your IND submission a justification for the choice of the animal model to be used in the developmental toxicity study. This should include a demonstration that the species is able to develop an immune response to the vaccine antigen, even though there may be quantitative and qualitative differences in immune responses between species. The laboratory

species most often used for developmental toxicity studies, on the basis of availability of background data and historical experience, are rats, rabbits and mice. Most human vaccines are immunogenic in rodents or rabbits. In some cases, only non-human primates may show an adequate immune response. However, because of the technical and logistic difficulties involved in using non-human primates for developmental toxicity studies, we recommend you only consider these animals if no alternative models are available.

In addition to demonstrating an immune response in the pregnant female, we recommend that you verify the exposure of the fetus to maternal antibodies. Thus, since there are differences between primates, non-rodents, and rodent animal species in terms of timing of maternal antibody transfer to the offspring, we recommend that you evaluate the pre- and postnatal exposure of the offspring to maternal antibody as a criterion for selecting the most appropriate experimental model. In addition, the species selected should be amenable to fetal and postnatal examinations.

In cases where lack of an appropriate animal model hinders the assessment of an immune response, developmental toxicity studies may still provide important information regarding potential embryo/fetal toxic effects of the vaccine components/formulation and safety of the product in the pregnant animal. In most cases, it is sufficient to conduct developmental toxicity studies using only one species; thus, there is no requirement for the routine use of two species, i.e., one rodent and one non-rodent.

The number of animals per group should be sufficient to allow meaningful interpretation of the data. For example, for a developmental toxicity study using rats or rabbits, we recommend that you assign an adequate number of animals to each group to allow an evaluation of at least 40 animals per group. These animals can be further allocated to the Caesarean and littering subgroup using 20 animals each.

2. Pharmacodynamics

We recommend that you obtain information about the onset and duration of the antibody response in pilot studies because these data may help in selecting the proper species, study design, and dosing schedules. Initial information can be derived from non-pregnant animals. However, it may also be necessary to perform these pilot studies in a small group of pregnant animals to evaluate antibody formation in relation to test article exposure and placental antibody transfer to the fetus if there is evidence that antibody formation may differ in pregnant versus non-pregnant animals.

We recognize that antibody induction presents only one aspect of the overall immune response induced by the vaccine and that other immunological parameters, such as cytokines and induction of cytotoxic T cells, may be as

important. However, given the relative lack of validated assays to assess the induction of these other parameters, antibody assessments are currently used as a marker for vaccine induced effects in these studies. This does not exclude the evaluation of additional immunologic parameters on a case-by-case basis. For example, if data are available which indicate that a vaccine antigen induces a particular cytokine response, respective cytokine measurements may be included, especially if the cytokine is one that may affect pregnancy.

3. Experimental procedure

In order to detect adverse effects on the pregnant/lactating female animal and development and growth of the embryo/fetus and the offspring, we recommend that the female be exposed to the vaccine during the interval from implantation through closure of the hard palate and also at later stages of pregnancy. The offspring should be followed to weaning and observed for normal growth and development. We recommend that you submit one subgroup of pregnant females to Caesarean examination at the end of pregnancy for routine uterine and fetal examinations, and allow another subgroup to litter and rear their offspring to weaning in order to monitor the post-natal development of the offspring up to weaning.

4. Dosage

We recommend that you assess a single dose level that is capable of inducing an immune response in the animal model. Where possible, we recommend that you administer animals the maximum human dose (e.g., 1 human dose = 1 rabbit dose) regardless of body weight. If it is not feasible to administer the maximum human dose (e.g., limitation in total volume that can be administered; dosing induced local toxicity affecting pregnancy), we recommend that you administer a dose that exceeds the human dose on a mg/kg bases while still capable of inducing an immune response in the animal.

5. Frequency and route of administration

We recommend that the vaccination regimen optimize maternal antibody titers throughout the embryonic, fetal, and early post-natal periods. Timing and number of doses will depend on the onset and duration of the immune response of the particular product. Because of concerns that a daily dosing regimen may lead to overexposure to the vaccine antigen that could potentially result in immune tolerance, we recommend episodic dosing of pregnant animals rather than daily dosing. In addition, episodic dosing appears to be more relevant, as it better mimics the clinically proposed immunization schedule for most preventive and therapeutic vaccines for infectious disease indications. Considering the short gestational period of animal species most frequently used, it may be necessary to administer priming doses to the animals several days or weeks prior to mating in

order to elicit a peak antibody production during the critical phases of pregnancy, i.e., the period of organogenesis.

When dosing prior to implantation, stress reactions may be observed in the animal that may affect the pregnancy status. Therefore, with treatment of animals prior to mating/insemination, it may be necessary to add more animals to the study to ensure that sufficient animals become pregnant for evaluation.

We recommend that you administer one or several additional doses during organogenesis (i.e., implantation to closure of the hard palate) to evaluate potential direct embryotoxic effects of the components of the vaccine formulation and to maintain a high level of antibody throughout the remainder of gestation. In certain cases, subgroups of animals that are dosed at certain time points may be included to evaluate if the vaccine acts as a selective toxicant, bearing in mind that it may be difficult to adjust vaccine administration with gestational timelines. We recommend that the route of administration mimic the clinical intended route of administration.

6. Control groups

We recommend that you dose control animals with placebo at the same time and frequency as test group animals. Since the potential toxicity of each of the components presented in the vaccine formulation will need to be evaluated, we recommend that you consider additional groups if components other than the vaccine antigen contained in the vaccine formulation (e.g. excipients, preservatives) cause effects or affect the activity of the test substance. In addition, if the vaccine is formulated with adjuvant, we recommend that you consider the inclusion of an adjuvant-only control arm, particularly if the adjuvant is novel.

7. Endpoints

In general, the study endpoints should include those recommended for studies for effects on prenatal and postnatal development including maternal functions as stated in the ICH S5A document (see Ref. 1). When deciding on the endpoints to be evaluated, we recommend that you take into consideration the nature of the vaccine and particular concerns associated with that product. The following parameters listed are intended to provide a basic panel of endpoints to be evaluated that are not meant to be all-inclusive.

a. Premating/preinsemination period

Clinical observations including data on general appearance and body weights should be obtained weekly and on days of test article administration.

b. Gestational period

We recommend that you observe maternal animals during the study for signs of morbidity and mortality, and record clinical observations regarding general appearance and behavior. We recommend that the evaluations include body weight and body weight change, potential signs of local toxicity, food consumption, duration of pregnancy, abortions, premature deliveries, and parturition (for maternal animals not subjected to Caesarian sectioning).

c. Caesarean sectioning group

i. Maternal Observations

At terminal examination of groups subjected to Caesarean sectioning, we recommend that you conduct a necropsy (macroscopic examination) and preserve maternal tissue with macroscopic findings for histological evaluations as deemed necessary by the gross findings. For example, histological evaluations may be indicated if you observe effects on organ to body weight ratios. We recommend that you record the number and distribution of corpora lutea, implantation sites, viable and nonviable fetuses, and early and late resorptions and that you perform a gross evaluation of the placenta.

ii. Fetal examinations

We recommend that you obtain individual body weights of live fetuses and examine each viable fetus for gross external, visceral, and skeletal alterations. Late resorptions and dead fetuses should also be examined for gross external alterations to the extent possible. All fetuses should be examined internally to determine sex.

d. Natural delivery group

i. Maternal observations

In addition to the parameters outlined in section IV.B.7.b (Gestational period), we recommend that you determine the duration of gestation and parameters such as the fertility index, gestation index, and live birth index. Animals that deliver a litter should be sacrificed at the end of the pre-weaning period. We recommend that you perform a gross necropsy of the thoracic, abdominal and pelvic viscera, and record the number and distribution of implantation sites as well as any observed abnormalities. Animals that die or are sacrificed because of moribund condition, abortion or premature delivery should be examined for the cause of death and pregnancy status recorded. We recommend that you also examine aborted fetuses and/or delivered pups to the extent possible.

ii. F1 generation

We recommend postnatal follow-up from birth to weaning to assess normal growth, body weight gain, and nursing activity as indicators for normal development. We also recommend that you include into the study design tests to screen for normal neuro-development, for example, auditory and visual function tests. Viability and lactation indices should be determined and individual sexes should be recorded. At terminal sacrifice, we recommend that you perform a necropsy, record any abnormalities and retain gross lesions for possible histological examinations. We recommend that you evaluate pups that die before examination for vital status at birth and examine pups found dead for gross lesions and cause of death.

8. Immunological endpoints

In addition to evaluating potential developmental adverse effects and adverse effects on the pregnant animal, we recommend that you include an assessment of the vaccine induced antibody response to verify exposure of the embryo/fetus to maternal antibody. Serum specimen from maternal animals prior to and at additional time points following dosing should be collected to assess the development of antibodies. Sampling is usually conducted prior to test article administration and at day of Caesarean sectioning (where applicable) and at the end of the weaning period.

In addition, we recommend that you obtain cord blood samples to assess placental transfer of maternal antibodies from animals in the Caesarean subgroup. We recommend that you also assess antibody levels from a representative number of pups/litters at the end of the weaning period to verify exposure of the neonates to maternal antibody induced. Antibody evaluations in developmental toxicity studies serve the purpose of verifying an effect of the vaccine in the test species as opposed to evaluating potential immunotoxic effects. You may evaluate additional immune parameters on a case-by-case basis. For example, if evidence exists that the vaccine antigen or other vaccine components can trigger the release of a particular cytokine potentially affecting pregnancy, you may include respective assessments.

9. Additional assessments

In cases where non-clinical developmental toxicity studies reveal vaccine-induced adverse effects on either the pregnant/lactating animal, embryo/fetal development, or development of the offspring, we recommend you conduct further animal studies to evaluate the cause of the effect. Such studies may include broader immunological evaluations, e.g., histochemical analysis for antibody depositions, as well as neurological assessments.

V. REFERENCES

1. International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Industry (ICH-S5A) Detection of Toxicity to Reproduction for Medicinal Products, (59 FR 48746, September 22, 1994), http://www.fda.gov/cder/guidance/s5a.pdf.

2. Recommended adult immunization schedule-United States, 2002-2003, MMWR October 11, 2002, Vol. 51 (40); 904-908.

3. Colley, Gilbert B., Brantley, M.D., Larson, M.K., *Family Planning Practices and Pregnancy Intention, 1997.* Atlanta, GA: Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 2000, http://www.cdc.gov/reproductivehealth/prams/pdf/97/PRAMS_sr_97.pdf.

4. Barrow, P.C., *Reproductive toxicology studies and immunotherapeutics*. Toxicology 185 (2003), 205-212.

5. Thellin, O., Heinen, E., *Pregnancy and the immune system: between tolerance and rejection*. Toxicology 185 (2003), 179-184.

6. Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product (January 1999), http://www.fda.gov/cber/gdlns/cmcvacc.pdf.

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PRECLINICAL SAFETY EVALUATION OF BIOTECHNOLOGY-DERIVED PHARMACEUTICALS
S6(R1)

Parent Guideline dated 16 July 1997

Current *Step 4* version

Addendum dated 12 June 2011 incorporated at the end of June 2011

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

S6(R1)
Document History

First Codification	History	Date	New Codification **November 2005**

Parent Guideline: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

S6	Approval by the Steering Committee under *Step 2* and release for public consultation.	6 November 1996	S6
S6	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	16 July 1997	S6

Addendum to the Parent Guideline

S6(R1)	Approval by the Steering Committee under *Step 2* and release for public consultation.	29 October 2009	S6(R1)

Current *Step 4* version

S6(R1)	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies. The Addendum has been incorporated into the parent Guideline which is now renamed S6(R1).	12 June 2011	S6(R1)

PRECLINICAL SAFETY EVALUATION OF BIOTECHNOLOGY-DERIVED PHARMACEUTICALS

ICH Harmonised Tripartite Guideline

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PART I:

PRECLINICAL SAFETY EVALUATION OF BIOTECHNOLOGY-DERIVED PHARMACEUTICALS

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 16 July 1997, this Guideline is recommended for adoption to the three regulatory parties to ICH

1. INTRODUCTION

1.1 Background

Biotechnology-derived pharmaceuticals (biopharmaceuticals) were initially developed in the early 1980s. The first marketing authorisations were granted later in the decade. Several guidelines and points-to-consider documents have been issued by various regulatory agencies regarding safety assessment of these products. Review of such documents, which are available from regulatory authorities, may provide useful background in developing new biopharmaceuticals.

Considerable experience has now been gathered with submission of applications for biopharmaceuticals. Critical review of this experience has been the basis for development of this guidance that is intended to provide general principles for designing scientifically acceptable preclinical safety evaluation programs.

1.2 Objectives

Regulatory standards for biotechnology-derived pharmaceuticals have generally been comparable among the European Union, Japan and United States. All regions have adopted a flexible, case-by-case, science-based approach to preclinical safety evaluation needed to support clinical development and marketing authorisation. In this rapidly evolving scientific area, there is a need for common understanding and continuing dialogue among the regions.

The primary goals of preclinical safety evaluation are: 1) to identify an initial safe dose and subsequent dose escalation schemes in humans; 2) to identify potential target organs for toxicity and for the study of whether such toxicity is reversible; and 3) to identify safety parameters for clinical monitoring. Adherence to the principles presented in this document is intended to improve the quality and consistency of the preclinical safety data supporting the development of biopharmaceuticals.

1.3 Scope

This guidance is intended primarily to recommend a basic framework for the preclinical safety evaluation of biotechnology-derived pharmaceuticals. It applies to products derived from characterised cells through the use of a variety of expression systems including bacteria, yeast, insect, plant, and mammalian cells. The intended indications may include *in vivo* diagnostic, therapeutic, or prophylactic uses. The active substances include proteins and peptides, their derivatives and products of which they are components; they could be derived from cell cultures or produced using recombinant DNA technology including production by transgenic plants and animals. Examples include but are not limited to: cytokines, plasminogen activators,

recombinant plasma factors, growth factors, fusion proteins, enzymes, receptors, hormones, and monoclonal antibodies.

The principles outlined in this guidance may also be applicable to recombinant DNA protein vaccines, chemically synthesised peptides, plasma derived products, endogenous proteins extracted from human tissue, and oligonucleotide drugs.

This document does not cover antibiotics, allergenic extracts, heparin, vitamins, cellular blood components, conventional bacterial or viral vaccines, DNA vaccines, or cellular and gene therapies.

2. SPECIFICATION OF THE TEST MATERIAL

Safety concerns may arise from the presence of impurities or contaminants. It is preferable to rely on purification processes to remove impurities and contaminants rather than to establish a preclinical testing program for their qualification. In all cases, the product should be sufficiently characterised to allow an appropriate design of preclinical safety studies.

There are potential risks associated with host cell contaminants derived from bacteria, yeast, insect, plants, and mammalian cells. The presence of cellular host contaminants can result in allergic reactions and other immunopathological effects. The adverse effects associated with nucleic acid contaminants are theoretical but include potential integration into the host genome. For products derived from insect, plant and mammalian cells, or transgenic plants and animals there may be an additional risk of viral infections.

In general, the product that is used in the definitive pharmacology and toxicology studies should be comparable to the product proposed for the initial clinical studies. However, it is appreciated that during the course of development programs, changes normally occur in the manufacturing process in order to improve product quality and yields. The potential impact of such changes for extrapolation of the animal findings to humans should be considered.

The comparability of the test material during a development program should be demonstrated when a new or modified manufacturing process or other significant changes in the product or formulation are made in an ongoing development program. Comparability can be evaluated on the basis of biochemical and biological characterisation (i.e., identity, purity, stability, and potency). In some cases additional studies may be needed (i.e., pharmacokinetics, pharmacodynamics and/or safety). The scientific rationale for the approach taken should be provided.

3. PRECLINICAL SAFETY TESTING

3.1 General Principles

The objectives of the preclinical safety studies are to define pharmacological and toxicological effects not only prior to initiation of human studies but throughout clinical development. Both *in vitro* and *in vivo* studies can contribute to this characterisation. Biopharmaceuticals that are structurally and pharmacologically comparable to a product for which there is wide experience in clinical practice may need less extensive toxicity testing.

Preclinical safety testing should consider:

1) selection of the relevant animal species;

2) age;

3) physiological state;

4) the manner of delivery, including dose, route of administration, and treatment regimen; and

5) stability of the test material under the conditions of use.

Toxicity studies are expected to be performed in compliance with Good Laboratory Practice (GLP); however, it is recognised that some studies employing specialised test systems which are often needed for biopharmaceuticals, may not be able to comply fully with GLP. Areas of non-compliance should be identified and their significance evaluated relative to the overall safety assessment. In some cases, lack of full GLP compliance does not necessarily mean that the data from these studies cannot be used to support clinical trials and marketing authorisations.

Conventional approaches to toxicity testing of pharmaceuticals may not be appropriate for biopharmaceuticals due to the unique and diverse structural and biological properties of the latter that may include species specificity, immunogenicity, and unpredicted pleiotropic activities.

3.2 Biological Activity/Pharmacodynamics

Biological activity may be evaluated using *in vitro* assays to determine which effects of the product may be related to clinical activity. The use of cell lines and/or primary cell cultures can be useful to examine the direct effects on cellular phenotype and proliferation. Due to the species specificity of many biotechnology-derived pharmaceuticals, it is important to select relevant animal species for toxicity testing. *In vitro* cell lines derived from mammalian cells can be used to predict specific aspects of *in vivo* activity and to assess quantitatively the relative sensitivity of various species (including human) to the biopharmaceutical. Such studies may be designed to determine, for example, receptor occupancy, receptor affinity, and/or pharmacological effects, and to assist in the selection of an appropriate animal species for further *in vivo* pharmacology and toxicology studies. The combined results from *in vitro* and *in vivo* studies assist in the extrapolation of the findings to humans. *In vivo* studies to assess pharmacological activity, including defining mechanism(s) of action, are often used to support the rationale of the proposed use of the product in clinical studies.

For monoclonal antibodies, the immunological properties of the antibody should be described in detail, including its antigenic specificity, complement binding, and any unintentional reactivity and/or cytotoxicity towards human tissues distinct from the intended target. Such cross-reactivity studies should be carried out by appropriate immunohistochemical procedures using a range of human tissues.

3.3 Animal Species/Model Selection

The biological activity together with species and/or tissue specificity of many biotechnology-derived pharmaceuticals often preclude standard toxicity testing designs in commonly used species (e.g., rats and dogs). Safety evaluation programs should include the use of relevant species. A relevant species is one in which the test material is pharmacologically active due to the expression of the receptor or an epitope (in the case of monoclonal antibodies). A variety of techniques (e.g., immunochemical or functional tests) can be used to identify a relevant species. Knowledge of receptor/epitope distribution can provide greater understanding of potential *in vivo* toxicity.

Relevant animal species for testing of monoclonal antibodies are those that express the desired epitope and demonstrate a similar tissue cross-reactivity profile as for human tissues. This would optimise the ability to evaluate toxicity arising from the binding to the epitope and any unintentional tissue cross-reactivity. An animal species which does not express the desired epitope may still be of some relevance for assessing toxicity if comparable unintentional tissue cross-reactivity to humans is demonstrated.

Safety evaluation programs should normally include two relevant species. However, in certain justified cases one relevant species may suffice (e.g., when only one relevant species can be identified or where the biological activity of the biopharmaceutical is well understood). In addition even where two species may be necessary to characterise toxicity in short term studies, it may be possible to justify the use of only one species for subsequent long term toxicity studies (e.g., if the toxicity profile in the two species is comparable in the short term).

Toxicity studies in non-relevant species may be misleading and are discouraged. When no relevant species exists, the use of relevant transgenic animals expressing the human receptor or the use of homologous proteins should be considered. The information gained from use of a transgenic animal model expressing the human receptor is optimised when the interaction of the product and the humanised receptor has similar physiological consequences to those expected in humans. While useful information may also be gained from the use of homologous proteins, it should be noted that the production process, range of impurities/contaminants, pharmacokinetics, and exact pharmacological mechanism(s) may differ between the homologous form and the product intended for clinical use. Where it is not possible to use transgenic animal models or homologous proteins, it may still be prudent to assess some aspects of potential toxicity in a limited toxicity evaluation in a single species, e.g., a repeated dose toxicity study of $\leq$ 14 days duration that includes an evaluation of important functional endpoints (e.g., cardiovascular and respiratory).

In recent years, there has been much progress in the development of animal models that are thought to be similar to the human disease. These animal models include induced and spontaneous models of disease, gene knockout(s), and transgenic animals. These models may provide further insight, not only in determining the pharmacological action of the product, pharmacokinetics, and dosimetry, but may also be useful in the determination of safety (e.g., evaluation of undesirable promotion of disease progression). In certain cases, studies performed in animal models of disease may be used as an acceptable alternative to toxicity studies in normal animals (*Note 1*). The scientific justification for the use of these animal models of disease to support safety should be provided.

3.4 Number/Gender of Animals

The number of animals used per dose has a direct bearing on the ability to detect toxicity. A small sample size may lead to failure to observe toxic events due to observed frequency alone regardless of severity. The limitations that are imposed by sample size, as often is the case for non-human primate studies, may be in part compensated by increasing the frequency and duration of monitoring. Both genders should generally be used or justification given for specific omissions.

3.5 Administration/Dose Selection

The route and frequency of administration should be as close as possible to that proposed for clinical use. Consideration should be given to pharmacokinetics and bioavailability of the product in the species being used, and the volume which can be

safely and humanely administered to the test animals. For example, the frequency of administration in laboratory animals may be increased compared to the proposed schedule for the human clinical studies in order to compensate for faster clearance rates or low solubility of the active ingredient. In these cases, the level of exposure of the test animal relative to the clinical exposure should be defined. Consideration should also be given to the effects of volume, concentration, formulation, and site of administration. The use of routes of administration other than those used clinically may be acceptable if the route must be modified due to limited bioavailability, limitations due to the route of administration, or to size/physiology of the animal species.

Dosage levels should be selected to provide information on a dose-response relationship, including a toxic dose and a no observed adverse effect level (NOAEL). For some classes of products with little to no toxicity it may not be possible to define a specific maximum dose. In these cases, a scientific justification of the rationale for the dose selection and projected multiples of human exposure should be provided. To justify high dose selection, consideration should be given to the expected pharmacological/physiological effects, availability of suitable test material, and the intended clinical use. Where a product has a lower affinity to or potency in the cells of the selected species than in human cells, testing of higher doses may be important. The multiples of the human dose that are needed to determine adequate safety margins may vary with each class of biotechnology-derived pharmaceutical and its clinical indication(s).

3.6 Immunogenicity

Many biotechnology-derived pharmaceuticals intended for human are immunogenic in animals. Therefore, measurement of antibodies associated with administration of these types of products should be performed when conducting repeated dose toxicity studies in order to aid in the interpretation of these studies. Antibody responses should be characterised (e.g., titer, number of responding animals, neutralising or non-neutralising), and their appearance should be correlated with any pharmacological and/or toxicological changes. Specifically, the effects of antibody formation on pharmacokinetic/pharmacodynamic parameters, incidence and/or severity of adverse effects, complement activation, or the emergence of new toxic effects should be considered when interpreting the data. Attention should also be paid to the evaluation of possible pathological changes related to immune complex formation and deposition.

The detection of antibodies should not be the sole criterion for the early termination of a preclinical safety study or modification in the duration of the study design unless the immune response neutralises the pharmacological and/or toxicological effects of the biopharmaceutical in a large proportion of the animals. In most cases, the immune response to biopharmaceuticals is variable, like that observed in humans. If the interpretation of the data from the safety study is not compromised by these issues, then no special significance should be ascribed to the antibody response.

The induction of antibody formation in animals is not predictive of a potential for antibody formation in humans. Humans may develop serum antibodies against humanised proteins, and frequently the therapeutic response persists in their presence. The occurrence of severe anaphylactic responses to recombinant proteins is rare in humans. In this regard, the results of guinea pig anaphylaxis tests, which are generally positive for protein products, are not predictive for reactions in humans; therefore, such studies are considered of little value for the routine evaluation of these types of products.

4. SPECIFIC CONSIDERATIONS

4.1 Safety Pharmacology

It is important to investigate the potential for undesirable pharmacological activity in appropriate animal models and, where necessary, to incorporate particular monitoring for these activities in the toxicity studies and/or clinical studies. Safety pharmacology studies measure functional indices of potential toxicity. These functional indices may be investigated in separate studies or incorporated in the design of toxicity studies. The aim of the safety pharmacology studies should be to reveal any functional effects on the major physiological systems (e.g., cardiovascular, respiratory, renal, and central nervous systems). Investigations may also include the use of isolated organs or other test systems not involving intact animals. All of these studies may allow for a mechanistically-based explanation of specific organ toxicities, which should be considered carefully with respect to human use and indication(s).

4.2 Exposure Assessment

4.2.1 Pharmacokinetics and Toxicokinetics

It is difficult to establish uniform guidelines for pharmacokinetic studies for biotechnology-derived pharmaceuticals. Single and multiple dose pharmacokinetics, toxicokinetics, and tissue distribution studies in relevant species are useful; however, routine studies that attempt to assess mass balance are not useful. Differences in pharmacokinetics among animal species may have a significant impact on the predictiveness of animal studies or on the assessment of dose response relationships in toxicity studies. Alterations in the pharmacokinetic profile due to immune-mediated clearance mechanisms may affect the kinetic profiles and the interpretation of the toxicity data. For some products there may also be inherent, significant delays in the expression of pharmacodynamic effects relative to the pharmacokinetic profile (e.g., cytokines) or there may be prolonged expression of pharmacodynamic effects relative to plasma levels.

Pharmacokinetic studies should, whenever possible, utilise preparations that are representative of that intended for toxicity testing and clinical use, and employ a route of administration that is relevant to the anticipated clinical studies. Patterns of absorption may be influenced by formulation, concentration, site, and/or volume. Whenever possible, systemic exposure should be monitored during the toxicity studies.

When using radiolabeled proteins, it is important to show that the radiolabeled test material maintains activity and biological properties equivalent to that of the unlabeled material. Tissue concentrations of radioactivity and/or autoradiography data using radiolabeled proteins may be difficult to interpret due to rapid *in vivo* metabolism or unstable radiolabeled linkage. Care should be taken in the interpretation of studies using radioactive tracers incorporated into specific amino acids because of recycling of amino acids into non-drug related proteins/peptides.

Some information on absorption, disposition and clearance in relevant animal models should be available prior to clinical studies in order to predict margins of safety based upon exposure and dose.

4.2.2 Assays

The use of one or more assay methods should be addressed on a case-by-case basis and the scientific rationale should be provided. One validated method is usually considered sufficient. For example, quantitation of TCA-precipitable radioactivity

following administration of a radiolabeled protein may provide adequate information, but a specific assay for the analyte is preferred. Ideally the assay methods should be the same for animals and humans. The possible influence of plasma binding proteins and/or antibodies in plasma/serum on the assay performance should be determined.

4.2.3 Metabolism

The expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids. Therefore, the metabolic pathways are generally understood. Classical biotransformation studies as performed for pharmaceuticals are not needed.

Understanding the behaviour of the biopharmaceutical in the biologic matrix, (e.g., plasma, serum, cerebral spinal fluid) and the possible influence of binding proteins is important for understanding the pharmacodynamic effect.

4.3 Single Dose Toxicity Studies

Single dose studies may generate useful data to describe the relationship of dose to systemic and/or local toxicity. These data can be used to select doses for repeated dose toxicity studies. Information on dose- response relationships may be gathered through the conduct of a single dose toxicity study, as a component of pharmacology or animal model efficacy studies. The incorporation of safety pharmacology parameters in the design of these studies should be considered.

4.4 Repeated Dose Toxicity Studies

For consideration of the selection of animal species for repeated dose studies see Section 3.3. The route and dosing regimen (e.g., daily versus intermittent dosing) should reflect the intended clinical use or exposure. When feasible, these studies should include toxicokinetics.

A recovery period should generally be included in study designs to determine the reversal or potential worsening of pharmacological/toxicological effects, and/or potential delayed toxic effects. For biopharmaceuticals that induce prolonged pharmacological/toxicological effects, recovery group animals should be monitored until reversibility is demonstrated. The duration of repeated dose studies should be based on the intended duration of clinical exposure and disease indication. This duration of animal dosing has generally been 1-3 months for most biotechnology-derived pharmaceuticals. For biopharmaceuticals intended for short-term use (e.g., ≤ to 7 days) and for acute life-threatening diseases, repeated dose studies up to two weeks duration have been considered adequate to support clinical studies as well as marketing authorisation. For those biopharmaceuticals intended for chronic indications, studies of 6 months duration have generally been appropriate although in some cases shorter or longer durations have supported marketing authorisations. For biopharmaceuticals intended for chronic use, the duration of long term toxicity studies should be scientifically justified.

4.5 Immunotoxicity Studies

One aspect of immunotoxicological evaluation includes assessment of potential immunogenicity (see Section 3.6). Many biotechnology-derived pharmaceuticals are intended to stimulate or suppress the immune system and therefore may affect not only humoral but also cell-mediated immunity. Inflammatory reactions at the injection site may be indicative of a stimulatory response. It is important, however, to recognise that simple injection trauma and/or specific toxic effects caused by the formulation vehicle may also result in toxic changes at the injection site. In addition,

the expression of surface antigens on target cells may be altered, which has implications for autoimmune potential. Immunotoxicological testing strategies may require screening studies followed by mechanistic studies to clarify such issues. Routine tiered testing approaches or standard testing batteries, however, are not recommended for biotechnology-derived pharmaceuticals.

4.6 Reproductive Performance and Developmental Toxicity Studies

The need for reproductive/developmental toxicity studies is dependent upon the product, clinical indication and intended patient population (*Note 2*). The specific study design and dosing schedule may be modified based on issues related to species specificity, immunogenicity, biological activity and/or a long elimination half-life. For example, concerns regarding potential developmental immunotoxicity, which may apply particularly to certain monoclonal antibodies with prolonged immunological effects, could be addressed in a study design modified to assess immune function of the neonate.

4.7 Genotoxicity Studies

The range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed. Moreover, the administration of large quantities of peptides/proteins may yield uninterpretable results. It is not expected that these substances would interact directly with DNA or other chromosomal material (*Note 3*).

Studies in available and relevant systems, including newly developed systems, should be performed in those cases where there is cause for concern about the product (e.g., because of the presence of an organic linker molecule in a conjugated protein product). The use of standard genotoxicity studies for assessing the genotoxic potential of process contaminants is not considered appropriate. If performed for this purpose, however, the rationale should be provided.

4.8 Carcinogenicity Studies

Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals. However, product-specific assessment of carcinogenic potential may still be needed depending upon duration of clinical dosing, patient population and/or biological activity of the product (e.g., growth factors, immunosuppressive agents, etc.) When there is a concern about carcinogenic potential a variety of approaches may be considered to evaluate risk.

Products that may have the potential to support or induce proliferation of transformed cells and clonal expansion possibly leading to neoplasia should be evaluated with respect to receptor expression in various malignant and normal human cells that are potentially relevant to the patient population under study. The ability of the product to stimulate growth of normal or malignant cells expressing the receptor should be determined. When *in vitro* data give cause for concern about carcinogenic potential, further studies in relevant animal models may be needed. Incorporation of sensitive indices of cellular proliferation in long term repeated dose toxicity studies may provide useful information.

In those cases where the product is biologically active and non-immunogenic in rodents and other studies have not provided sufficient information to allow an assessment of carcinogenic potential then the utility of a single rodent species should be considered. Careful consideration should be given to the selection of doses. The use of a combination of pharmacokinetic and pharmacodynamic endpoints with consideration of comparative receptor characteristics and intended human exposures

represents the most scientifically based approach for defining the appropriate doses. The rationale for the selection of doses should be provided.

4.9 Local Tolerance Studies

Local tolerance should be evaluated. The formulation intended for marketing should be tested; however, in certain justified cases, the testing of representative formulations may be acceptable. In some cases, the potential adverse effects of the product can be evaluated in single or repeated dose toxicity studies thus obviating the need for separate local tolerance studies.

NOTES

Note 1 Animal models of disease may be useful in defining toxicity endpoints, selection of clinical indications, and determination of appropriate formulations, route of administration, and treatment regimen. It should be noted that with these models of disease there is often a paucity of historical data for use as a reference when evaluating study results. Therefore, the collection of concurrent control and baseline data is critical to optimise study design.

Note 2 There may be extensive public information available regarding potential reproductive and/or developmental effects of a particular class of compounds (e.g., interferons) where the only relevant species is the non-human primate. In such cases, mechanistic studies indicating that similar effects are likely to be caused by a new but related molecule, may obviate the need for formal reproductive/developmental toxicity studies. In each case, the scientific basis for assessing the potential for possible effects on reproduction/development should be provided.

Note 3 With some biopharmaceuticals there is a potential concern about accumulation of spontaneously mutated cells (e.g., via facilitating a selective advantage of proliferation) leading to carcinogenicity. The standard battery of genotoxicity tests is not designed to detect these conditions. Alternative *in vitro* or *in vivo* models to address such concerns may have to be developed and evaluated.

PART II:

ADDENDUM TO S6

PRECLINICAL SAFETY EVALUATION OF BIOTECHNOLOGY-DERIVED PHARMACEUTICALS

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process on 12 June 2011 and been incorporated in the parent Guideline at the end of June 2011, this Guideline is recommended for adoption to the three regulatory parties to ICH

Preamble:

This addendum should be read in close conjunction with the original ICH S6 Guideline. In general the addendum is complementary to the guideline, and where the addendum differs from the original guideline, the guidance in the addendum prevails.

1. INTRODUCTION

1.1 Purpose of the Addendum

The purpose of the addendum is to complement and provide clarification on and update the following topics discussed in the original ICH S6 Guideline: species selection, study design, immunogenicity, reproductive and developmental toxicity and assessment of carcinogenic potential. Scientific advances and experience gained since publication of the original ICH S6 Guideline call for this addendum. This harmonised addendum will help to define the current recommendations and reduce the likelihood that substantial differences will exist among regions.

This guidance should facilitate the timely conduct of clinical trials, reduce the use of animals in accordance with the 3Rs (reduce/refine/replace) principles and reduce the use of other drug development resources. Although not discussed in this guidance, consideration should be given to the use of appropriate *in vitro* alternative methods for safety evaluation. These methods, if accepted by all ICH regulatory authorities, can be used to replace current standard methods.

This guidance promotes safe and ethical development and availability of new pharmaceuticals.

1.2 Background

The recommendations of this addendum further harmonise the nonclinical safety studies to support the various stages of clinical development among the regions of European Union (EU), Japan, and the United States. The present addendum represents the consensus that exists regarding the safety evaluation of biotechnology-derived pharmaceuticals.

1.3 Scope of the Guideline

This addendum does not alter the scope of the original ICH S6 Guideline. For biotechnology-derived products intended to be used in oncology the Guidance on *Nonclinical Evaluation for Anticancer Pharmaceuticals* (ICH S9 Guideline) should be consulted.

2. SPECIES SELECTION

2.1 General Principles

A number of factors should be taken into account when determining species relevancy. Comparisons of target sequence homology between species can be an appropriate starting point, followed by *in vitro* assays to make qualitative and quantitative cross-species comparisons of relative target binding affinities and receptor/ligand occupancy and kinetics.

Assessments of functional activity are also recommended. Functional activity can be demonstrated in species-specific cell-based systems and/or *in vivo* pharmacology or toxicology studies. Modulation of a known biologic response or of a pharmacodynamic (PD) marker can provide evidence for functional activity to support species relevance.

Consideration of species differences in target binding and functional activity in the context of the intended dosing regime should provide confidence that a model is capable of demonstrating potentially adverse consequences of target modulation. When the target is expressed at very low levels in typical healthy preclinical species (e.g., inflammatory cytokines or tumour antigens), binding affinity and activity in cell-based systems can be sufficient to guide species selection.

Assessment of tissue cross reactivity in animal tissues is of limited value for species selection (see *Note 1*). However, in specific cases (i.e., where the approaches described above cannot be used to demonstrate a pharmacologically relevant species) tissue cross-reactivity (TCR) studies can be used to guide selection of toxicology species by comparison of tissue binding profiles in human and those animal tissues where target binding is expected.

As described in ICH S6 Guideline, when no relevant species can be identified because the biopharmaceutical does not interact with the orthologous target in any species, use of homologous molecules or transgenic models can be considered.

For monoclonal antibodies and other related antibody products directed at foreign targets (i.e., bacterial, viral targets etc.), a short-term safety study (see ICH S6 Guideline) in one species (choice of species to be justified by the sponsor) can be considered; no additional toxicity studies, including reproductive toxicity studies, are appropriate. Alternatively, when animal models of disease are used to evaluate proof of principle, a safety assessment can be included to provide information on potential target-associated safety aspects. Where this is not feasible, appropriate risk mitigation strategies should be adopted for clinical trials.

Species selection for an antibody-drug/toxin conjugate (ADC) incorporating a novel toxin/toxicant should follow the same general principles as an unconjugated antibody (see above and see *Note 2*).

2.2 One or Two Species

If there are two pharmacologically relevant species for the clinical candidate (one rodent and one non-rodent), then both species should be used for short-term (up to 1 month duration) general toxicology studies. If the toxicological findings from these studies are similar or the findings are understood from the mechanism of action of the product, then longer-term general toxicity studies in one species are usually considered sufficient. The rodent species should be considered unless there is a scientific rationale for using non-rodents. Studies in two non-rodent species are not appropriate.

The use of one species for all general toxicity studies is justified when the clinical candidate is pharmacologically active in only one species. Studies in a second species with a homologous product are not considered to add further value for risk assessment and are not recommended.

2.3 Use of Homologous Proteins

Use of homologous proteins is one of the alternative approaches described under ICH S6 Guideline Section 3.3. Studies with homologous proteins can be used for hazard detection and understanding the potential for adverse effects due to exaggerated pharmacology, but are generally not useful for quantitative risk assessment. Therefore, for the purposes of hazard identification it can be possible to conduct safety evaluation studies using a control group and one treatment group provided there is a scientific justification for the study design and dose selected (e.g., maximum pharmacological dose).

3. STUDY DESIGN

3.1 Dose Selection and Application of PK/PD Principles

The toxicity of most biopharmaceuticals is related to their targeted mechanism of action; therefore, relatively high doses can elicit adverse effects which are apparent as exaggerated pharmacology.

A rationale should be provided for dose selection taking into account the characteristics of the dose-response relationship. Pharmacokinetic-pharmacodynamic (PK-PD) approaches (e.g., simple exposure-response relationships or more complex modeling and simulation approaches) can assist in high dose selection by identifying 1) a dose which provides the maximum intended pharmacological effect in the preclinical species; and 2) a dose which provides an approximately 10-fold exposure multiple over the maximum exposure to be achieved in the clinic. The higher of these two doses should be chosen for the high dose group in preclinical toxicity studies unless there is a justification for using a lower dose (e.g., maximum feasible dose).

Where *in vivo*/*ex vivo* PD endpoints are not available, the high dose selection can be based on PK data and available *in vitro* binding and/or pharmacology data. Corrections for differences in target binding and *in vitro* pharmacological activity between the nonclinical species and humans should be taken into account to adjust the exposure margin over the highest anticipated clinical exposure. For example, a large relative difference in binding affinity and/or *in vitro* potency might suggest that testing higher doses in the nonclinical studies is appropriate. In the event that toxicity cannot be demonstrated at the doses selected using this approach, then additional toxicity studies at higher multiples of human dosing are unlikely to provide additional useful information.

3.2 Duration of Studies

For chronic use products, repeat dose toxicity studies of 6 months duration in rodents or non-rodents are considered sufficient, providing the high dose is selected in accordance with the principles above in Section 3.1. Studies of longer duration have not generally provided useful information that changed the clinical course of development.

For chronic use of biopharmaceutical products developed for patients with advanced cancer, the principles for duration of toxicology studies are outlined in ICH S9 Guideline.

3.3 Recovery

Recovery from pharmacological and toxicological effects with potential adverse clinical impact should be understood when they occur at clinically relevant exposures. This information can be obtained by an understanding that the particular effect observed is generally reversible/non-reversible or by including a non-dosing period in at least one study, at at least one dose level, to be justified by the sponsor. The purpose of the non-dosing period is to examine reversibility of these effects, not to assess delayed toxicity. The demonstration of complete recovery is not considered essential. The addition of a recovery period just to assess potential for immunogenicity is not required.

3.4 Exploratory Clinical Trials

The flexible approaches to support exploratory clinical trials as outlined in ICH M3(R2) Guideline can be applicable to biopharmaceuticals. It is recommended that these approaches be discussed and agreed upon with the appropriate regulatory authority.

4. IMMUNOGENICITY

Immunogenicity assessments are conducted to assist in the interpretation of the study results and design of subsequent studies. Such analyses in nonclinical animal studies are not relevant in terms of predicting potential immunogenicity of human or humanized proteins in humans.

Measurement of anti-drug antibodies (ADA) in nonclinical studies should be evaluated when there is 1) evidence of altered PD activity; 2) unexpected changes in exposure in the absence of a PD marker; or 3) evidence of immune-mediated reactions (immune complex disease, vasculitis, anaphylaxis, etc.). Since, it is difficult to predict whether such analysis will be called for prior to completion of the in-life phase of the study, it is often useful to obtain appropriate samples during the course of the study, which can subsequently be analyzed when warranted to aid in interpretation of the study results. When ADAs are detected, their impact on the interpretation of the study results should be assessed (see also Part I, Section 3.6, Paragraph 2 for further guidance on the impact of immunogenicity).

Characterization of neutralizing potential is warranted when ADAs are detected and there is no PD marker to demonstrate sustained activity in the *in vivo* toxicology studies. Neutralizing antibody activity can be assessed indirectly with *ex vivo* bioactivity assay or an appropriate combination of assay formats for PK-PD, or directly in a specific neutralizing antibody assay.

5. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

5.1 General Comments

Reproductive toxicity studies should be conducted in accordance with the principles outlined in ICH S5(R2) Guideline; however, the specific study design and dosing schedule can be modified based on an understanding of species specificity, the nature of the product and mechanism of action, immunogenicity and/or pharmacokinetic behaviour and embryo-fetal exposure.

An assessment of reproductive toxicity with the clinical candidate in a relevant species is generally preferred. The evaluation of toxicity to reproduction should be conducted only in pharmacologically relevant species. When the clinical candidate is pharmacologically active in rodents and rabbits, both species should be used for

embryo-fetal development (EFD) studies, unless embryo-fetal lethality or teratogenicity has been identified in one species.

Developmental toxicity studies should only be conducted in non-human primates (NHPs) when they are the only relevant species.

When the clinical candidate is pharmacologically active only in NHPs, there is still a preference to test the clinical candidate. However an alternative model can be used in place of NHPs if appropriate scientific justification is provided

When no relevant animal species exists for testing the clinical candidate, the use of transgenic mice expressing the human target or homologous protein in a species expressing an ortholog of the human target can be considered, assuming that sufficient background knowledge exists for the model (e.g., historical background data) (see Part I, *Note 1*). For products that are directed at a foreign target such as bacteria and viruses, in general no reproductive toxicity studies would be expected (see Section 2.1).

When the weight of evidence (e.g., mechanism of action, phenotypic data from genetically modified animals, class effects) suggests that there will be an adverse effect on fertility or pregnancy outcome, these data can provide adequate information to communicate risk to reproduction, and under appropriate circumstances additional nonclinical studies might not be warranted.

5.2 Fertility

For products where mice and rats are pharmacologically relevant species, an assessment of fertility can be made in one of these rodent species (see ICH S5 Guideline). ICH S5 Guideline study designs can be adapted for other species provided they are pharmacologically relevant; in addition, the design of the study should be amended as appropriate, for example to address the nature of the product and potential for immunogenicity.

It is recognized that mating studies are not practical for NHPs. However, when the NHP is the only relevant species, the potential for effects on male and female fertility can be assessed by evaluation of the reproductive tract (organ weights and histopathological evaluation) in repeat dose toxicity studies of at least 3 months duration using sexually mature NHPs. If there is a specific cause for concern based on pharmacological activity or previous findings, specialized assessments such as menstrual cyclicity, sperm count, sperm morphology/motility, and male or female reproductive hormone levels can be evaluated in a repeat dose toxicity study.

If there is a specific concern from the pharmacological activity about potential effects on conception/implantation and the NHP is the only relevant species, the concern should be addressed experimentally. A homologous product or transgenic model could be the only practical means to assess potential effects on conception or implantation when those are of specific concern. However, it is not recommended to produce a homologous product or transgenic model solely to conduct mating studies in rodents. In absence of nonclinical information, the risk to patients should be mitigated through clinical trial management procedures, informed consent and appropriate product labeling.

5.3 Embryo-Fetal Development (EFD) and Pre/Post-Natal Development (PPND)

Potential differences in placental transfer of biopharmaceuticals should be considered in the design and interpretation of developmental toxicity studies (see *Note 3*).

For products pharmacologically active only in NHPs, several study designs can be considered based on intended clinical use and expected pharmacology. Separate EFD and/or PPND studies, or other study designs (justified by the sponsor) can be appropriate, particularly when there is some concern that the mechanism of action might lead to an adverse effect on embryo-fetal development or pregnancy loss. However, one well-designed study in NHPs which includes dosing from day 20 of gestation to birth (enhanced PPND, ePPND) can be considered, rather than separate EFD and/or PPND studies.

For the single ePPND study design described above, no Caesarian section group is warranted, but assessment of pregnancy outcome at natural delivery should be performed. This study should also evaluate offspring viability, external malformations, skeletal effects (e.g., by X-ray) and, ultimately, visceral morphology at necropsy. Ultrasound is useful to track maintenance of pregnancy but is not appropriate for detecting malformations. These latter data are derived from post-partum observations. Because of confounding effects on maternal care of offspring, dosing of the mother post-partum is generally not recommended. Other endpoints in the offspring can also be evaluated if relevant for the pharmacological activity. The duration of the post-natal phase will be dependent on which additional endpoints are considered relevant based on mechanism of action (see *Note 4*).

Developmental toxicity studies in NHPs can only provide hazard identification. The number of animals per group should be sufficient to allow meaningful interpretation of the data (see *Note 5*).

The sponsor should justify the study design if other NHP species are used. The developmental toxicity studies in NHPs as outlined above are just hazard identification studies; therefore it might be possible to conduct these studies using a control group and one dose group, provided there is a scientific justification for the dose level selected. An example of an appropriate scientific justification would be a monoclonal antibody which binds a soluble target with a clinical dosing regimen intended to saturate target binding. If such a saturation of target binding can be demonstrated in the animal species selected and there is an up to 10-fold exposure multiple over therapeutic drug levels, a single dose level and control group would provide adequate evidence of hazard to embryo-fetal development.

5.4 Timing of Studies

If women of child-bearing potential are included in clinical trials prior to acquiring information on effects on embryo-fetal development, appropriate clinical risk management is appropriate, such as use of highly effective methods of contraception (see ICH M3(R2) Guideline).

For biopharmaceuticals pharmacologically active only in NHPs, where there are sufficient precautions to prevent pregnancy (see ICH M3(R2) Guideline, Section 11.3, Paragraph 2), an EFD or ePPND study can be conducted during Phase III, and the report submitted at the time of marketing application. When a sponsor cannot take sufficient precaution to prevent pregnancy in clinical trials, either a complete report of an EFD study or an interim report of an ePPND study should be submitted before initiation of Phase III (see *Note 6*). Where the product is pharmacologically active only in NHPs and its mechanism of action raises serious concern for embryo-fetal development, the label should reflect the concern without warranting a developmental toxicity study in NHPs and therefore administration to women of child-bearing potential should be avoided.

If the rodent or rabbit is a relevant species, see ICH M3(R2) Guideline for timing of reproductive toxicity studies. ICH M3(R2) Guideline should also be followed for the timing of data on fertility for products where rodents are relevant species.

For oncology products which fall within the scope of ICH S9 Guideline, see that guidance for aspects relating to timing of study conduct.

6. CARCINOGENICITY

The need for a product-specific assessment of the carcinogenic potential for biopharmaceutical should be determined with regard to the intended clinical population and treatment duration (see ICH S1A Guideline). When an assessment is warranted, the sponsor should design a strategy to address the potential hazard.

This strategy could be based on a weight of evidence approach, including a review of relevant data from a variety of sources. The data sources can include published data (e.g., information from transgenic, knock-out or animal disease models, human genetic diseases), information on class effects, detailed information on target biology and mechanism of action, *in vitro* data, data from chronic toxicity studies and clinical data. In some cases, the available information can be sufficient to address carcinogenic potential and inform clinical risk without additional nonclinical studies.

The mechanism of action of some biopharmaceuticals might raise concern regarding potential for carcinogenicity (e.g., immunosuppressives and growth factors). If the weight of evidence (see above) supports the concern regarding carcinogenic potential, rodent bioassays are not warranted. In this case potential hazard can be best addressed by product labeling and risk management practices. However, when the weight of evidence is unclear, the sponsor can propose additional studies that could mitigate the mechanism-based concern (see Part I, Section 4.8).

For products where there is insufficient knowledge about specific product characteristics and mode of action in relation to carcinogenic potential, a more extensive assessment might be appropriate (e.g., understanding of target biology related to potential carcinogenic concern, inclusion of additional endpoints in toxicity studies).

If the weight of evidence from this more extensive assessment does not suggest carcinogenic potential, no additional nonclinical testing is recommended. Alternatively, if the weight of evidence suggests a concern about carcinogenic potential, then the sponsor can propose additional nonclinical studies that could mitigate the concern, or the label should reflect the concern.

The product-specific assessment of carcinogenic potential is used to communicate risk and provide input to the risk management plan along with labeling proposals, clinical monitoring, post-marketing surveillance, or a combination of these approaches.

Rodent bioassays (or short-term carcinogenicity studies) with homologous products are generally of limited value to assess carcinogenic potential of the clinical candidate.

Alternative approaches can be considered as new strategies/assays are developed.

NOTES

Note 1 Tissue cross-reactivity (TCR) studies are *in vitro* tissue-binding assays employing immunohistochemical (IHC) techniques conducted to characterize binding of monoclonal antibodies and related antibody-like products to antigenic determinants in tissues. Other technologies can be employed in place of IHC techniques to demonstrate target/binding site distribution.

A TCR study with a panel of human tissues is a recommended component of the safety assessment package supporting initial clinical dosing of these products. However, in some cases the clinical candidate is not a good IHC reagent and a TCR study might not be technically feasible.

TCR studies can provide useful information to supplement knowledge of target distribution and can provide information on potential unexpected binding. Tissue binding *per se* does not indicate biological activity *in vivo*. In addition, binding to areas not typically accessible to the antibody *in vivo* (i.e., cytoplasm) is generally not relevant. Findings should be evaluated and interpreted in the context of the overall pharmacology and safety assessment data package.

When there is unexpected binding in human tissues an evaluation of selected animal tissues can provide supplemental information regarding potential correlations or lack thereof with preclinical toxicity. TCR using a full panel of animal tissues is not recommended.

Since a bi-specific antibody product will be evaluated in a TCR study using a panel of human tissues, there is no need to study the individual binding components.

Evaluating the tissue binding of homologous products does not provide additional value when TCR studies have been conducted with the clinical candidate in a human tissue panel, and is not recommended.

TCR studies cannot detect subtle changes in critical quality attributes. Therefore TCR studies are not recommended for assessing comparability of the test article as a result of process changes over the course of a development program.

Note 2 If two species have been used to assess the safety of the ADC, an additional short-term study or arm in a short-term study should be conducted in at least one species with the unconjugated toxin. In these cases a rodent is preferred unless the toxin is not active in the rodent. If only one pharmacologically relevant species is available, then the ADC should be tested in this species. A novel toxicant calls for an approach to species selection similar to that used for a new chemical entity on a case-by case approach (e.g., for anticancer products in accordance with ICH S9 Guideline). For toxins or toxicants which are not novel and for which there is a sufficient body of scientific information available, separate evaluation of the unconjugated toxin is not warranted. Data should be provided to compare the metabolic stability of the ADC in animals with human.

Note 3 The species-specific profile of embryo-fetal exposure during gestation should be considered in interpreting studies. High molecular weight proteins (>5,000 D) do not cross the placenta by simple diffusion. For monoclonal antibodies with molecular weight as high as 150,000 D, there exists a specific transport mechanism, the neonatal Fc receptor (FcRn) which determines fetal exposure and varies across species.

In the NHPs and humans, IgG placental transfer is low in the period of organogenesis and begins to increase in early second trimester, reaching highest levels late in the third trimester. (5) Therefore, standard embryo-fetal studies in NHPs, which are dosed from early pregnancy up to Gestation Day 50, might not be of value to assess direct embryo-fetal effects in the period of organogenesis, although effects on embryo-fetal development as an indirect result of maternal effects can be evaluated. Furthermore, maternal

dosing in NHPs after delivery is generally without relevance as IgG is only excreted in the milk initially (i.e., in the colostrum), and not later during the lactation and nursing phase.

Rodents differ from the NHPs and humans, as IgG crosses the yolk sac in rodents by FcRn transport mechanisms and exposure can occur relatively earlier in gestation than with NHPs and humans. In addition, delivery of rodents occurs at a stage of development when the pups are not as mature as the NHP or the human neonate. Therefore, rat/mouse dams should be dosed during lactation in order to expose pups via the milk up to at least day 9 of lactation when the offspring are at an equivalent stage of development as human neonates.

Note 4 The minimum duration of post-natal follow-up should be one month to cover early functional testing (e.g., growth and behaviour).

In general, if there is evidence for adverse effects on the immune system (or immune function) in the general toxicology studies, immune function testing in the offspring during the post-partum phase of the enhanced Pre/Post-Natal Development (ePPND) study is warranted. When appropriate, immunophenotyping can be obtained as early as post-natal day 28. The duration of post-natal follow-up for assessment of immune function can be 3-6 months depending on the functional test used.

Neurobehavioural assessment can be limited to clinical behavioural observations. Instrumental learning calls for a training period, which would result in a post-natal duration of at least 9 months and is not recommended.

Note 5 A detailed discussion of the approach to determine group sizes in cynomolgus monkey ePPND studies can be found in Jarvis *et al*, 2010 (6). Group sizes in ePPND studies should yield a sufficient number of infants (6-8 per group at post-natal day 7) in order to assess post-natal development and provide the opportunity for specialist evaluation if necessary (e.g., immune system).

Most ePPND studies accrue pregnant animals over weeks and months. Consideration should be given to terminating further accrual of pregnant animals into the study, and adapting the study design (e.g., by Caesarian section) when pre-natal losses in a test item group indicate a treatment-related effect.

Reuse of vehicle-control treated maternal animals is encouraged.

If there is some cause for concern that the mechanism of action might lead to an effect on EFD or pregnancy loss, studies can be conducted in a limited number of animals in order to confirm the hazard.

Note 6 Endpoints to be included in an interim report of an ePPND study in NHPs:

- Dam data: survival, clinical observations, bodyweight, gestational exposure data (if available), any specific PD endpoints;
- Pregnancy data: number of pregnant animals started on study, pregnancy status at both the end of organogenesis (gestation day (GD) 50) and at GD100, occurrence of abortions and timing of abortions. There is no need for ultrasound determinations of fetal size in the interim report; these are not considered essential since actual birth weight will be available;
- Pregnancy outcome data: number of live births/still births, infant birth weight, infant survival and bodyweight at day 7 post-partum, qualitative external morphological assessment (i.e., confirming appearance is within normal limits), infant exposure data (if available), any specific PD endpoints in the infant if appropriate.

REFERENCES

1. ICH S5(R2) Guideline: Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility; June 1993.
2. ICH S1A Guideline: Guideline on the Need for Carcinogenicity Studies for Pharmaceuticals; November 1995.
3. ICH M3(R2) Guideline: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals; June 2009.
4. ICH S9 Guideline: Nonclinical Evaluation for Anticancer Pharmaceuticals; November 2008.
5. Pentsuk N, Van der Laan JW. An interspecies comparison of placental antibody transfer: new insights into developmental toxicity testing of monoclonal antibodies. Birth defects research (Part B) 2009; 86: 328-344.
6. Jarvis P, Srivastav S, Vogelwedde E, Stewart J, Mitchard T, Weinbauer G. The Cynomolgous Monkey as a model for Developmental Toxicity Studies: Variability of Pregnancy losses, Statistical power estimates, and Group Size considerations. Birth Defects Research (Part B) 2010, 89: 175-187.

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ICH S5 (R3) guideline on reproductive toxicology: Detection of Toxicity to Reproduction for Human Pharmaceuticals

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ICH S5 (R3) guideline on reproductive toxicology: detection of toxicity to reproduction for medicinal products including toxicity to male fertility

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List of abbreviations

AUC: Area Under the Curve

C_{max}: Maximum plasma concentration

C_{min}: Minimum plasma concentration

DART: Developmental and Reproductive Toxicity

DRF: Dose Range Finding

EFD: Embryo-Fetal Development

ePPND: Enhanced Pre- and Postnatal Developmental

FEED: Fertility and Early Embryonic Developmental

GD: Gestation Day

GI: Gastrointestinal

GLP: Good Laboratory Practices

ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IV: Intravenous

LOAEL: Lowest Observed Adverse Effect Level

LLO: Late Life Onset

MOA: Mechanism of Action

MEFL: Malformation or Embryo-Fetal Lethality

MFD: Maximum Feasible Dose

MRHD: Maximum Recommended Human Dose

NHP: Non-Human Primate

NOAEL: No Observed Adverse Effect Level

PD: Pharmacodynamic

pEFD: Preliminary Embryo-Fetal Development

PK: Pharmacokinetic

PND: Postnatal Day

PPND: Pre- and Postnatal Developmental

SDLT: Severely Debilitating or Life-Threatening

TK: Toxicokinetic

WOCBP: Women of Child Bearing Potential

1. Introduction & general principles

The purpose of this document is to recommend international standards for, and promote harmonization of, the assessment of nonclinical developmental and reproductive toxicity (DART) testing required to support human clinical trials and marketing authorization for pharmaceuticals. The guideline describes potential strategies and study designs to supplement available data to identify, assess, and convey risk. General concepts and recommendations are also provided that should be considered when interpreting study data.

This is a revision of the ICH guideline "S5 Detection of Toxicity to Reproduction for Medicinal Products" that was originally published in 1993. This revision brings the guideline into alignment with other ICH guidelines, elaborates on the use of exposure margins in dose level selection, incorporates a section on risk assessment, and expands the scope to include vaccines and biopharmaceuticals. It also describes qualification of alternative assays, potential scenarios of use, and provides options for deferral of developmental toxicity studies.

To assess a human pharmaceutical's effect on reproduction and development, there should generally be information available that addresses the potential impact of exposure to a pharmaceutical and, when appropriate, its metabolites (ICH M3 (1), ICH S6 (2)) on all stages of reproduction and development. No guideline can provide sufficient information to cover all possible cases, and flexibility in testing strategy is warranted.

1.1. Aim of studies

The aim of DART studies is to reveal any effect of the pharmaceutical on mammalian reproduction relevant for human risk assessment. As appropriate, the set of studies conducted should encompass observations through one complete life cycle (i.e., from conception in one generation through conception in the following generation), and permit detection of immediate and latent adverse effects. The following stages of reproduction are generally assessed:

A. Premating to conception (adult male and female reproductive functions, development and maturation of gametes, mating behavior, fertilization).

B. Conception to implantation (adult female reproductive functions, preimplantation development, implantation).

C. Implantation to closure of the hard palate (adult female reproductive functions, embryonic development, major organ formation).

D. Closure of the hard palate to the end of pregnancy (adult female reproductive functions, fetal development and growth, organ development and growth).

E. Birth to weaning (parturition and lactation, neonate adaptation to extrauterine life, pre-weaning development and growth).

F. Weaning to sexual maturity (post-weaning development and growth, adaptation to independent life, onset of puberty and attainment of full sexual function, and effects on second generation).

The risks to all stages should be assessed, unless the stage is not relevant to the intended population. The stages covered in individual studies are left to the discretion of the Sponsor, although the timing of studies within the pharmaceutical development process is dependent on study populations and phase of pharmaceutical development (see ICH M3, ICH S6 and ICH S9 (3)).

2. Scope of the guideline

This guideline applies to all pharmaceuticals, including biopharmaceuticals, vaccines (and their novel constitutive ingredients) for infectious diseases, and novel excipients that are part of the final pharmaceutical product. For the purposes of this guideline, the term "pharmaceutical" is used to encompass all of these treatment modalities. This guideline does not apply to cellular therapies, gene therapies and tissue-engineered products. The methodological principles (e.g., study design, dose selection and species selection, etc.) outlined in this guideline apply to all compounds for which the conduct of reproductive and/or developmental toxicity studies is appropriate. This guideline should be read in conjunction with ICH M3, ICH S6, and ICH S9 regarding whether and when nonclinical DART studies are warranted.

3. General considerations on reproductive toxicity assessment

The majority of pharmaceuticals being developed should be assessed for all stages of the reproductive cycle identified above, although there can be some exceptions which should be justified, as indicated below. To support clinical development, these stages have typically been evaluated using three *in vivo* study types: 1) a fertility and early embryonic development study (FEED - stages A and B), 2) embryo-fetal development studies in two species (EFD - stages C and D), and 3) a pre- and a postnatal development study (PPND – stages C through F). For each compound, the stages that are to be evaluated should be determined and the most appropriate studies to conduct should be identified. Key factors to consider when developing an overall integrated testing strategy to evaluate effects on reproduction and development include:

- The targeted patient population and conditions of use (especially in relation to reproductive potential and severity of disease);
- The formulation of the pharmaceutical and route(s) of administration intended for humans;
- Relevant data on toxicity (which can also include data from *in vitro*, *ex vivo* and non-mammalian studies, and structure-activity relationships), pharmacodynamics, pharmacokinetics, and pharmacological similarity to other pharmaceuticals;
- Aspects of the general biology of the pharmaceutical target, or known roles of the target in reproduction or development.

These concepts are discussed in more detail throughout the guideline.

To the extent that it does not diminish the overall risk assessment, the experimental strategy should minimize the use of animals. Approaches towards this goal can include the conduct of studies that combine typical study types (see Section 7), as well as appropriately qualified alternative assays for risk assessment (see Annex 2). Since many clinical development programs are terminated prior to Phase 3, animal use can also be reduced by appropriately timing studies to support ongoing clinical development (e.g., embryo-fetal developmental toxicity data to support enrollment of women of childbearing potential) as per ICH M3.

DART studies should, in general, be conducted according to Good Laboratory Practice (GLP) regulations, as they will contribute to the risk assessment. However, if a relevant DART risk is identified in a non-GLP study, repetition of the study to confirm the finding(s) under GLP conditions is not necessarily warranted. A relevant risk is one that occurs at or near intended clinical exposures and is of a nature that is reasonably likely to translate to humans (see Section 9). It is recognized that GLP compliance is not expected for some study types, or aspects of some studies, employing specialized

test systems or methods. However, high quality scientific standards should be applied with data collection records readily available. Areas of non-compliance should be identified within the study report and their impact on study results/data interpretation should be considered relative to the overall safety assessment.

3.1. Target patient population/ therapeutic indication considerations

The intended patient population or therapeutic indication can influence the extent of DART testing. Studies evaluating all stages of reproduction and development are not warranted if the disease indicates that DART will have minimal impact on the risk of the pharmaceutical in the target population. For example, studies covering all stages are not necessarily appropriate for an exclusively post-menopausal female patient population, for use in the pediatric or juvenile pre-pubescent population, or for patient populations in hospitalized settings where pregnancy can be excluded.

3.2. Pharmacology considerations

Before designing a testing strategy, it should be determined if the intended pharmacologic effects of a pharmaceutical are known to be incompatible with fertility, normal EFD, or assessment of particular endpoints (e.g., a general anesthetic and assessment of mating behavior). This assessment can be based on data with other pharmaceuticals with similar pharmacology, known effects of target engagement, or on knowledge of effects in humans with related genetic diseases. For example, it would be appropriate to modify the design of a PPND study for a pharmaceutical developed to prevent pre-term labor. If the intended pharmacologic effects are incompatible with the study endpoints, testing for a particular reproductive endpoint is not warranted, with justification.

3.3. Toxicity considerations

Repeated–dose toxicity studies with sexually mature animals can provide important information on toxicity to reproductive organs that can affect the design of a DART study. The existing toxicology data for the compound should always be considered, taking into account the dose levels, toxicokinetic profile, and dosing duration. For example, the standard fertility study design can be modified to alter the duration of dosing, or the start of cohabitation, for a compound that affects testicular tissue.

3.4. Timing considerations

General guidance on the timing for conduct of studies assessing reproductive and developmental endpoints is described in ICH M3, ICH S6, and ICH S9. The timing for when to conduct specific DART assessments should take into consideration the need for these data to support the safe use of the pharmaceutical in clinical trials or the intended patient population. Consequently, it can be appropriate to consider altering the timing of the assessment of specific reproductive stages. Additional options are discussed in Section 4.2.2 and 4.2.3.

3.5. Toxicokinetics (TK)

Exposure data can be generated in either reproductive (dose range finding (DRF) or pivotal) or repeated-dose toxicity studies. However, given the potential for meaningful changes in TK parameters induced by pregnancy, it is recommended to determine if pregnancy alters exposure. If dose selection is based on exposure ratio (see section 6.1.3), GLP-compliant TK data in pregnant animals is expected. Sampling day(s) should be justified.

When warranted, determination of the pharmaceutical's concentration in the embryo or fetus can facilitate interpretation of discordant or equivocal evidence of developmental hazard. This information can be collected in a separate study to determine the actual exposure. However, a direct comparison to the potential levels in the human conceptus is not appropriate.

Evidence of lactational excretion can be obtained, when warranted, by sampling milk or by demonstrating exposure in offspring during the pre-weaning period.

General concepts regarding TK data collection are discussed in ICH S3A (4).

4. Design and evaluation of in vivo mammalian studies

The strategy to evaluate the potential reproductive and developmental risk of a pharmaceutical generally includes one or more *in vivo* studies. The key factor is that, in total, they leave no gaps between stages and allow for evaluation of all stages of the reproductive process, although in some species (e.g., the non-human primate (NHP)) it is not possible to evaluate all stages. For most pharmaceuticals, the 3-study design will usually be appropriate, although various combinations of these study designs can be conducted to address specific product needs and to reduce animal use. Study details for the FEED, EFD, and PPND studies, and combinations thereof, can be found in Annex 1. The stages covered in individual studies are left to the discretion of the sponsor. All available pharmacological, toxicokinetic, and toxicological data for the pharmaceutical should be considered in determining which study design(s) should be used.

4.1. Strategy to address fertility and early embryonic development (FEED)

The aim of the FEED study is to test for adverse effects resulting from treatment initiated prior to mating of males and/or females and continued through mating and implantation. This comprises evaluation of Stages A and B of the reproductive process. Results from repeated-dose toxicity studies of at least two weeks duration can often be used to design the fertility study without conducting further dose ranging studies, although studies of such short duration can be insufficient to reveal all adverse effects.

A mating phase is expected in most cases when a FEED study is warranted to support exposure of the target population. Such studies are typically performed in rodents. If no adverse effects on fertility are anticipated, both sexes can be treated and cohabited together in the same study. If effects on fertility are identified in the study, the affected sex should then be determined. In contrast, if adverse effects are anticipated based on mode of action or on the results of repeated-dose studies, each treated sex can be cohabited with untreated animals of the opposite sex. This can be achieved using separate treatment arms within a single study or by the conduct of two separate FEED studies. Reversibility of adverse effects on fertility and early embryonic development can have an important impact on risk assessment.

The FEED study design in female rodents (see Annex 1) allows for the detection of effects on the estrous cycle, tubal transport, implantation, and development of preimplantation stages of the embryo. When estrous/menstrual cycles are evaluated, it is important to obtain baseline cycle data (over 2 or 3 cycles minimum) to distinguish between treatment-related effects and inter/intra animal variability. The monitoring of estrous cyclicity should continue through the time of confirmation of mating.

The FEED study design for male rodents that includes 2 to 4 weeks of treatment prior to cohabitation allows for the detection of effects on spermatogenesis and epididymal transport. When data from repeated-dose studies suggest toxicity to the testis, it can be appropriate to extend the duration of pre-cohabitation treatment to 10 weeks; this permits assessment of effects on the full spermatogenic

cycle as well as epididymal transport. The FEED study additionally permits detection of functional effects (e.g., on libido, epididymal sperm maturation, ejaculation) that cannot be detected by histological examinations of the male reproductive organs.

When there is cause for concern based on mode of action or data from previous studies, additional examinations can be included in repeated-dose toxicity and/or fertility studies (e.g., sperm collection for counts and morphology/motility assessments, measuring hormone levels, or monitoring of the estrous/menstrual cycle) to further characterize potential effects on fertility.

4.1.1. Considerations for biopharmaceuticals

If the biopharmaceutical is pharmacologically active in rodents or rabbits, a FEED study in one of these species is recommended. Mating evaluations are not generally feasible in non-rodents such as dogs and NHPs. For example, if NHPs are the only pharmacologically relevant species (as for many monoclonal antibodies, see ICH S6), histopathological examinations of the reproductive tissues from the repeated-dose toxicity studies of at least three months duration can serve as a substitute for the fertility assessments. Such an approach should include a comprehensive histopathological examination of the reproductive organs from both male and female animals (Note 1). Unless the biopharmaceutical is intended to treat advanced cancer, in which case FEED studies are not warranted, animals should be sexually mature at study initiation in order for an adequate evaluation of the reproductive tissues to be made. These data would only provide information on the structure of the reproductive tissues, as no functional assessment of fertility can be made and predicting effects on fertility and early embryonic development is not always possible based solely on the results of histopathology assessments.

4.2. Strategies to address embryo-fetal development (EFD)

The aim of the EFD studies is to detect adverse effects on the pregnant female and development of the embryo and fetus following treatment (Stage C) of the pregnant female during organogenesis. EFD studies include evaluation of fetal development and survival (Stages C through D).

For most small molecules, effects on EFD are typically evaluated in two species (i.e., rodent and non-rodent (typically rabbit)). At least one of the test species should exhibit the desired pharmacodynamic response. If the pharmaceutical is not pharmacodynamically active in any routinely used species (Section 5.1) then non-routine species (Section 5.2), genetically modified animals, or use of a species-specific surrogate molecule (Section 5.3) (e.g., in the case of oligonucleotides) can be considered, provided there is sufficient characterization of the model to ensure pharmacologic relevance. Genetically modified animals and surrogate molecules are generally most useful for hazard identification, but have limitations when used for risk assessment. Even when there are no relevant models (e.g., the pharmacological target only exists in humans, either normally or in the diseased state), EFD studies should be conducted in two species to detect the adversity of off-target effects or secondary pharmacology.

Clearly positive results for the induction of malformations or embryo-fetal lethality (MEFL), in a single species, at exposures similar to that at the projected clinical exposure at the maximum recommended human dose (MRHD) can be sufficient for risk assessment.

Under limited circumstances, other approaches can be used in place of definitive EFD studies (see Annex 2). Alternatively, there can be adequate information to communicate risk without conducting EFD studies. Evidence suggesting an adverse effect of the intended pharmacological mechanism on EFD (e.g., mechanism of action, phenotypic data from genetically modified animals) can be sufficient to communicate risk.

4.2.1. Considerations for Biopharmaceuticals

The effect of biopharmaceuticals on EFD should typically be assessed in two species (one rodent and one non-rodent) if both are pharmacologically relevant. However, the rodent is often not pharmacologically relevant, in which case EFD assessment in a single pharmacologically relevant non-rodent species can be conducted. In cases where the NHP is the only relevant species, an enhanced pre-and postnatal development (ePPND) study can be conducted instead of an EFD study. Biopharmaceuticals intended for the treatment of advanced cancer typically need only be assessed in a single pharmacologically relevant species (ICH S9).

When no relevant species can be identified because the biopharmaceutical does not interact with the orthologous target in any species relevant to reproductive toxicity testing, use of surrogate molecules or transgenic models can be considered, as described in ICH S6. Calculating safety margins relative to human exposures with surrogate molecules is not appropriate. If there are no relevant species, genetically modified animals or surrogates available, *in vivo* reproductive toxicity testing is not meaningful. In this case, the approach used for risk assessment, or rationale for not conducting studies, should be justified.

4.2.2. Alternative approaches for addressing EFD Risk

4.2.2.1. Use of alternative assays

A number of alternative *in vitro*, *ex vivo*, and non-mammalian *in vivo* assays (alternative assays) have been developed to detect potential hazards to embryo-fetal development. They have been used as drug discovery screens for adverse effects on EFD and have assisted in the understanding of the mechanism of toxicity, which can be useful for translating nonclinical data to human risk (especially for human-specific targets).

The continued use of alternative assays for these purposes is encouraged.

If properly qualified, alternative assays have the potential to defer or replace (in certain circumstances) conventional *in vivo* studies. This has the added benefit of potentially reducing animal use. Concepts to consider when qualifying these assays, and examples when the use of such assays could be appropriate, appear in Annex 2. Approaches that incorporate alternative assays should provide a level of confidence for human safety assurance at least equivalent to that provided by the current testing paradigms described above. Based on the direction of scientific development as of the writing of this document, it is expected that for regulatory purposes multiple alternative assays will be used within a tiered or battery approach. These testing strategies will be qualified within a certain context of use, which is defined by the chemical applicability domain of the assay, and by characterization of the biological mechanisms covered by the assay.

4.2.3. Potential approaches to defer definitive in vivo testing as part of an integrated testing strategy

The design of an appropriate testing strategy relies on a cumulative weight-of-evidence approach. ICH M3 allows preliminary embryo-fetal developmental (pEFD) toxicity data from two species to support the limited inclusion of women of childbearing potential (WOCBP) (up to 150 WOCBP for up to 3 months) before conducting definitive EFD studies. Based on these considerations, this guideline expands on ICH M3 by allowing two additional options to support inclusion of WOCBP prior to Phase 3 clinical trials:

1) Qualified alternative assays which predict the outcome in one species (see Annex 2), can be combined with a pEFD from a second species to enable the limited inclusion of WOCBP (up to 150 WOCBP for up to 3 months). The alternative assay and the second species should generally cover both a rodent and a non-rodent species.

2) Additional endpoints incorporated into at least one GLP pEFD study (specifically increasing the group size of evaluable litters with inclusion of skeletal examinations) performed in a pharmacologically relevant species, if available, combined with a pEFD in a 2nd species allows all regions to include an unlimited number of WOCBP in clinical trials through Phase 2.

4.3. Strategy to address effects on pre- and postnatal development (PPND)

The aim of the PPND study is to detect adverse effects following exposure of the maternal animal from implantation through weaning to evaluate effects on the pregnant or lactating female and development of the offspring. Since manifestations of effects induced during this period can be delayed, development of the offspring is monitored through sexual maturity (i.e., Stages C to F). The rodent is usually used to assess PPND; however, other species can be used as appropriate (See Annex 1).

In most cases, a preliminary (dose range finding) PPND study is not warranted, because the appropriate information is generally available from prior studies. However, a preliminary PPND study with termination of the pups before or at weaning can be used to select dose levels or inform study design and/or to provide pup exposure data.

If a modified PPND/ePPND study design is being considered to support pediatric development, see ICH S11 (5).

4.3.1. Considerations for biopharmaceuticals For pharmaceuticals that can only be tested in the NHP, the ePPND study can provide a limited assessment of postnatal effects, but it is not generally feasible to follow the offspring through maturity (See Annex 1 and ICH S6).

5. Test system selection

5.1. Routine test species

Mammalian species should be used to detect DART. The use of the same species and strain as in already completed toxicity studies can eliminate the need to use additional animals or conduct additional studies to characterize pharmacokinetics and metabolism, and/or for dose range finding. The species used should be well-characterized and relevant for detecting effects on the endpoints in a particular study (e.g., with respect to health, fertility, fecundity, background rates of malformation and embryo-fetal death, etc.).

5.1.1. Selection of species for DART testing

The rat is generally appropriate for DART testing and is the most often used rodent species for reasons of practicality, general knowledge of pharmacology in this species, the extensive toxicology data usually available for interpretation of nonclinical observations and the large amount of historical background data. The mouse is also often used as the rodent species for many of the same reasons.

For assessment of EFD only, a second mammalian non-rodent species is typically evaluated, although there are exceptions (e.g., vaccines and biopharmaceuticals, see Sections 5.1.2 and 5.2, respectively). The rabbit has proven to be useful in identifying human teratogens that have not been detected in

rodents and is routinely used as the non-rodent species based on the extensive historical background data, availability of animals, and practicality.

5.1.2. Species selection for preventative and therapeutic vaccines

The animal species selected for testing of vaccines (with or without adjuvants) should demonstrate an immune response to the vaccine. The type of developmental toxicity study conducted, and the choice of the animal model, should be justified based on the immune response observed and the ability to administer an appropriate dose. Typically, rabbits, rats, or mice are used in developmental toxicity studies for vaccines. Even though quantitative and qualitative differences can exist in the responses (e.g., in humoral and cellular endpoints) between species, it is usually sufficient to conduct developmental toxicity studies in a single species. Although the degree and time course of transfer of maternal antibodies across the placenta varies between species, a developmental toxicity study in rabbits, rats, or mice can still provide important information regarding potential embryo-fetal toxicity of the vaccine components/formulation and safety of the product during pregnancy. NHP should be used only if no other relevant animal species demonstrates an immune response.

When there is a lack of an appropriate animal model (including NHP), an EFD toxicity study in rabbits, rats, or mice can still provide important information regarding potential embryo-fetal toxicity of the vaccine components/formulation and safety of the product during pregnancy.

5.2. Non-routine test species

Species other than the rat, mouse or rabbit can be used to evaluate the effects of pharmaceuticals on various reproductive stages. When considering the use of other species, their advantages and disadvantages (summarized in Table 1 of Annex 1) should be considered in relation to the pharmaceutical being tested, the study design and selected endpoints, and the ability to extrapolate results to the human situation.

NHPs should be considered a non-routine test species. They are most typically used for evaluating effects on embryo-fetal development and early postnatal development for biopharmaceuticals that are only pharmacologically active in primates, as described in ICH S6. However, there are additional considerations that limit the utility of studies in NHPs for assessing some endpoints for DART risk assessment (see Annex 1 and ICH S6).

5.3. Use of disease models, genetically modified models, and surrogate molecules

Animal models of disease, genetically modified models, and surrogate molecules can be valuable for investigating the effect of the intended pharmacology on development and reproduction. Studies in disease models can be of value in cases where the data obtained from healthy animals could be misleading or otherwise not apply to the disease conditions in the clinical setting. The model should be pharmacologically relevant and appropriate for the development and reproductive endpoints being assessed. The pathophysiology of the disease course in the model should be characterized. Some differences from the human pathophysiology would not preclude its use if these are unlikely to confound data interpretation. Animal-to-animal variability should be characterized and appropriate within the context of the study. If historical control information is limited, reference data for the study endpoints should be available or should be generated during the study to aid data interpretation.

Genetically modified models can be used to provide information about on-target effects of a pharmaceutical on DART parameters through permanent or conditional alterations in target activity.

Such models can inform on whether the biology of the target is closely linked to adverse effects on reproduction and development in routine test species.

When the pharmaceutical does not have adequate activity against the target in the routine test species, surrogate molecules can be used to assess potential adverse effects on reproduction and development.

6. Dose level selection, route of administration and schedule

The choice of dose levels, schedule and route of administration are important study design considerations and should be based on all available information (e.g., pharmacology, repeated-dose toxicity, pharmacokinetics, and dose range finding studies). Guidance on the principles of dose selection for small molecules and biopharmaceuticals is given in ICH M3 and ICH S6, respectively. When sufficient information on tolerability in the test system is not available, dose range finding studies are advisable.

6.1. Dose selection There are a number of dose selection endpoints that can be used for DART studies. All endpoints discussed in this section are considered equally appropriate in terms of study design. The high dose in the definitive studies should be one that is predicted to comply with one or more of the concepts set forth in sections 6.1.1 to 6.1.5 below. The selected doses should take into account observations made in previous studies (e.g., repeated-dose, TK, DRF, etc.). There can be instances where fewer than three dose levels are sufficient to provide the necessary information for risk assessment.

Justification for high dose selection using endpoints other than those discussed below can be made on a case-by-case basis.

6.1.1. Toxicity–based endpoint

This endpoint is based on inducing a minimal level of toxicity in the parental animals at the high dose. Factors limiting the high dose determined from previously conducted studies could include, but are not limited to:

- Alterations in body weight (gain or absolute; either reductions or increases). Minor, transient changes in body weight gain or body weight are not appropriate for dose selection. When assessing weight change effects, the entire dosing duration of the study should be considered.
- Exaggerated pharmacological responses (e.g., excessive sedation or hypoglycemia)
- Toxicological responses (e.g., convulsions, excessive embryo-fetal lethality, clinical pathology perturbations). Specific target organ toxicity that would interfere with the study endpoints within the duration of the planned DART study.

6.1.2. Saturation of systemic exposure endpoint

High dose selection based on saturation of systemic exposure measured by systemic availability of pharmaceutical-related substances can be appropriate. There is little value in increasing the administered dose if it does not result in increased plasma concentration of parent or metabolites.

6.1.3. Exposure margin based endpoint

It can be appropriate to select doses based on predicted exposure margins relative to the exposure at the MRHD. For small molecules, a systemic exposure representing a large multiple of the human AUC or C_{max} at the MRHD can be an appropriate endpoint for high dose selection. Doses providing an exposure in pregnant animals > 25-fold the exposure at the MRHD are generally considered appropriate as the maximum dose for DART studies (Note 2). The 25-fold exposure margin should be established in a GLP-compliant dose range finding/pEFD or definitive study. Usually this multiple should be determined based on parent drug levels; however, consideration should also be given to ensuring an adequate exposure margin to major human metabolites (see ICH M3 and ICH M3 Q&A). In the case of prodrugs, it can be more appropriate to establish the exposure multiple on the basis of the active metabolite, particularly if the test species has a lower ratio of active metabolite to prodrug, compared to humans. The basis for the moiety used for comparison (parent drug or metabolite) should be justified.

For pharmaceuticals that have demonstrated pharmacodynamic activity in the test species only at exposures > 25-fold that projected at the MRHD, higher doses can be warranted to assess adverse effects of exaggerated pharmacology. However, irrelevant off-target effects are more likely to be observed.

When exposure-based endpoints are used as the basis for selection of the dose levels for EFD studies, TK data from pregnant animals in a GLP-compliant study is expected. The choice for the use of total vs. fraction unbound pharmaceutical exposures should be justified and consistent with the entire nonclinical development program as outlined in ICH S3A.

6.1.3.1. Exposure-based approach for biopharmaceuticals

Exposure-based margins can be appropriate to select doses for biopharmaceuticals as per ICH S6. Generally, the dose should provide the maximum intended pharmacological effect in the preclinical species or provide an approximately 10-fold exposure multiple over the maximum exposure to be achieved in the clinic, whichever is higher. ICH S6 should be consulted with regard to dose adjustment for differences in target binding affinity and other relevant factors.

6.1.4. Maximum feasible dose (MFD) endpoint

The MFD can be used for high dose selection when the physico-chemical properties of the pharmaceutical (or formulation) associated with the route/frequency of administration and the anatomical/physiological attributes of the test species limit the amount of the pharmaceutical that can be administered. Use of the MFD should maximize exposure in the test species, rather than maximize the administered dose, as per ICH M3 Q&A (1). Note that changes to the frequency of dose administration can be considered to increase the total feasible daily exposure (see Section 6.3).

6.1.5. Limit dose endpoint

A limit dose of 1 g/kg/day can generally be applied when other dose selection factors have not been attained with lower dose levels (see also ICH M3 for other considerations).

6.1.6. Selection of lower dose levels

It is generally desirable to establish a no observed adverse effect level (NOAEL) for DART. The selection of lower dose levels should take into account exposure, pharmacology, and toxicity, such that the dose-response of findings can be established when appropriate. The low dose should generally

provide a low multiple (e.g., 1 to 5-fold) of the human exposure at the MRHD. Dose levels that yield exposures that are sub-therapeutic in humans should be justified.

6.2. Route

In general, the route of administration should be the clinical route. If, however, sufficient exposure cannot be achieved using the clinical route or the clinical route is not feasible, a different route should be considered. When multiple routes of administration are being evaluated in humans, a single route in the test species can be adequate provided that sufficient systemic exposure is achieved compared to that of all clinical routes and that there is adequate coverage for the metabolites.

6.3. Schedule

Dosing schedules used in the toxicity studies determine the exposure profile, which can be important in the risk assessment. Although mimicking the clinical schedule is often sufficient, a more or a less frequent schedule can be appropriate. For example, twice daily dosing can be warranted with compounds that are quickly metabolized in the test species, although pragmatic factors (e.g., study logistics, stress on animals) should be considered when a more frequent schedule is contemplated. It can also be important to alter the dosing schedule to ensure that adequate exposure is obtained at all critical stages of reproduction and/or development being evaluated in a given study.

6.4. Dose selection and study designs for vaccines

This guideline covers vaccines (adjuvanted or not) used in both preventative and therapeutic indications against infectious diseases. While not within the scope of this guideline, the principles outlined can be applicable to the nonclinical testing of vaccines for other indications as well (e.g., cancer).

The types of reproductive and/or developmental toxicity studies used for preventative and therapeutic vaccines depend on the target population for the vaccine and the relevant reproductive risk. Generally, DART studies are not warranted for vaccinees being developed for neonates, pre-pubertal children, or geriatric populations.

For reproductive toxicity studies of vaccines, it is typically sufficient to assess a single dose level capable of eliciting an immune response in the animal model (Section 5.1.2), using the clinical route of administration. This single dose level should be the maximum human dose without correcting for body weight (i.e., 1 human dose = 1 animal dose). If it is not feasible to administer the maximum human dose to the animal because of a limitation in total volume that can be administered, or because of dose-limiting toxicity, whether local or systemic, a dose that exceeds the human dose on a mg/kg basis can be used. To use a reduced dose, justification as to why a full human dose cannot be used in an animal model should be provided.

The vaccination regimen should maximize maternal antibody titers and/or immune response throughout the embryonic, fetal, and early postnatal periods. Timing and number of doses will depend on the onset and duration of the immune response of the particular vaccine. When developing vaccines to be given during pregnancy, a justification should be provided for the specific study design, based upon its intended use (e.g., protecting the mother during pregnancy or protecting the child early postnatally).

Daily dosing regimens can lead to overexposure to the vaccine constituents. Episodic dosing of pregnant animals rather than daily dosing is recommended. Also, episodic dosing better approximates the proposed clinical immunization schedule for most preventive and therapeutic vaccines. Considering

the short gestational period of routine animal species, it is generally recommended to administer a priming dose(s) to the animals several days or weeks prior to mating in order to elicit peak immune response during the critical phases of pregnancy (i.e., the period of organogenesis). The dosing regimen can be modified according to the intended vaccination schedule in humans.

At least one dose should be administered during early organogenesis to evaluate potential direct embryotoxic effects of the components of the vaccine formulation and to maintain a high antibody response throughout the remainder of gestation. If embryo-fetal toxicity is observed, this can be further assessed using subgroups of animals that are dosed at certain time points.

In cases where a vaccine includes a novel active constitutive ingredient (including novel adjuvants), consideration of additional testing strategies similar to those for non-vaccine products can be appropriate.

7. Possible combination study designs in rodents

Although three separate study designs, i.e., FEED (stages A and B), EFD (stages C through D) and PPND (stages C through F) have been employed to develop the majority of pharmaceuticals, various combinations of these study designs can be conducted to reduce animal use. The main advantage of combination designs is that all relevant stages of the reproductive process can be assessed using fewer animals. Combination studies can also better mimic the exposure duration in the clinic, especially for drugs with long half-lives. A common combination study design is a combined Fertility and EFD study (stages A through D) with a separate PPND study (stages C through F).

Designs and study details for FEED, EFD, and PPND studies, and combinations thereof, can be found in Annex 1.

In cases where no effects on male or female fertility are anticipated, or where extending the dosing period is appropriate due to observation of reproductive organ toxicity in a repeated-dose toxicity study, a combination design of repeated-dose and fertility studies can be considered. After a defined dosing period within the repeated-dose toxicity study, males can be paired with sexually mature females (whether untreated, or dosed for at least two weeks prior to mating). This combination study can reduce the number of animals used, but the number of mating pairs per group should be at least 16. Further, if treated, dosing of females can be extended until the end of organogenesis, thereby allowing evaluation of EFD endpoints (Annex 1).

8. Data reporting and statistics

8.1. Data reporting Individual values should be tabulated in a clear concise manner to account for all animals in the study. The data tables should allow ready tracking of individual animals and their conceptuses, from study initiation through study conclusion.

Fetal morphologic abnormalities should be described using industry-harmonized terminology. All findings for each litter should be clearly listed by conceptus. Summary listings should be prepared by type of abnormality. The inclusion or exclusion of data from non-pregnant animals in summary tables should be clearly indicated.

Interpretation of study data relies primarily on comparison with the concurrent control group. Historical control/reference data can be used to assist data interpretation. Recent historical control data from the performing laboratory is preferable. Contemporary data typically from a five-year period is desirable and permits identification of genetic drift.

8.2. Statistics

Statistical testing to assess the significance of differences between the treated and control groups is expected in definitive studies. Many of the datasets from DART studies do not follow a normal distribution, necessitating the use of non-parametric statistical methods. Cesarean, fetal and postnatal data summary statistics should be calculated using the litter as the unit of analysis. Statistical significance need not convey a positive signal, nor lack of statistical significance impute absence of effect. Determination of biological plausibility, based on all available pharmacologic and toxicologic data, is often useful.

9. Principles of risk assessment

As described in the preceding sections of this guideline, all available data garnered from the pharmaceutical, related compounds, human genetics, and knowledge of the role of target biology in human reproduction should be used to address potential reproductive risks in humans under the conditions of use, both during clinical trials and after marketing authorization. Any limitations (e.g., test system relevance, achieved exposure), uncertainties and data gaps in the available nonclinical DART data package should be addressed and their impact assessed. Generally, the results from definitive *in vivo* studies in an appropriate species with adequate exposures carry more weight than those from alternative assays or preliminary studies. Risk assessment is a continuous process through product development as more information becomes available.

Not all findings reported in DART studies are adverse. When a finding is deemed adverse, several factors should be considered in a weight-of-evidence evaluation for risk assessment. These can include exposure margins, biological plausibility, evidence of a dose-response relationship, potential for reversibility, the potential for confounding parental toxicity, and evidence for cross-species concordance. For rare malformations, the absence of increased frequency with dose does not always alleviate concern.

Comparison of pharmaceutical exposure at the NOAEL in the test species to the exposure at the MRHD is an important component of the risk assessment. This comparison should be based on the most relevant metric (e.g., AUC, C_{max}, $C_{min,}$ body surface area-adjusted dose). In general, there is increased concern when the NOAEL occurs at exposures less than 10-fold the human exposure at the MRHD; above this threshold, concern is reduced. Effects that are limited to occurrence at more than 25-fold the human exposure at the MRHD are usually of minor concern for the clinical use of the pharmaceutical. The most relevant margin is generally the exposure metric in the most sensitive species, unless appropriately justified otherwise. Biological plausibility is assessed by comparison of pharmacologic mechanism of action with the known role of the target in reproduction or development. A finding that can be interpreted as a consequence of pharmacology suggests that it will be of concern for humans. This relationship is further strengthened by evidence that the finding is dose-related, whether characterized as increasing incidence or severity. Absence of biological plausibility does not preclude off-target toxicity, particularly if this is characterized by a dose-response relationship.

Understanding the potential for reversibility will alter the risk assessment. Effects on male and female fertility that are reversible after cessation of treatment are of less concern. Conversely, critical irreversible developmental endpoints, such as death or malformation, are of increased concern. Other forms of developmental toxicity (e.g., growth retardation, functional deficits), may or may not be reversible. Generally, transient findings (e.g., skeletal variations, such as wavy ribs in rodents) are of less concern when they occur in isolation. Similarly, variations that are indicative of growth retardation in the presence of reduced fetal weight are of less concern. However, an overall increase in the

incidence of variations (qualitatively similar or not) can suggest increased concern for dysmorphogenesis in the presence of an equivocal increase in malformations.

The role of parental toxicity should be considered in determination of the relevance of findings. Embryo-fetal toxicity observed in the presence of maternal toxicity should be considered carefully to determine the likelihood that the finding is relevant for humans. Specifically, evaluation of the concordance between individual litter findings and the severity of maternal toxicity in the dam could be helpful in this assessment. It should not be assumed that developmental toxicity is secondary to maternal toxicity, unless such a relationship is demonstrated de novo, or relevant published literature can be cited.

Also, consistency of findings reported among studies, or between species can strengthen the concern for an adverse effect. Increased fetal lethality seen in a rodent EFD study that is consistent with decreased live litter sizes in the PPND study is an example of cross-study concordance. Observations of increased post implantation loss in rats and rabbits is an example of cross-species concordance. Further knowledge of the mechanism of reproductive or developmental effects identified in animal studies can help to explain differences in responses between species and provide information on the human relevance of the effect (e.g., corticosteroid-induced cleft palate in mice).

A specific risk assessment conducted for breastfeeding would be predicated on hazards identified by the *in vivo* littering study (PPND or ePPND). These hazards can include adverse effects on offspring growth and development that are attributed to excretion of the pharmaceutical in the milk. Systemic exposure data in the pups from the littering study, if available, can also be compared with projected lactational exposures in the human infant. While interspecies differences in milk composition preclude a direct quantitative correlation of animal milk levels to human milk levels of a pharmaceutical, the presence of pharmaceutical in animal milk generally indicates the presence of pharmaceutical in human milk.

Lastly, available human data can influence the overall assessment of human reproductive risk.

10. Endnotes

Note 1: In particular, the testes and epididymides should be sampled and processed using methods which preserve the tissue architecture of the seminiferous epithelium. A detailed qualitative microscopic evaluation with awareness of the spermatogenic cycle is a sensitive means to detect effects on spermatogenesis. While generally not warranted, additional experimental endpoints (e.g., immunohistochemistry, homogenization resistant spermatid counts, flow cytometry, quantitative analysis of staging) can be incorporated into the study design to further characterize any identified effects. In females, a detailed qualitative microscopic examination of the ovary (including follicles, corpora lutea, stroma, interstitium, and vasculature), uterus and vagina should be conducted with awareness of the reproductive cycle and the presence of primordial and primary follicles.

Note 2: An analysis of 22 known human or presumed human teratogens showed that if MEFL was observed, exposure at the lowest observed adverse effect level (LOAEL) in at least one species was < 6-fold the exposure at the MRHD (Andrews et al. (6)). This indicates that using a > 25-fold exposure ratio for high-dose selection in the EFD toxicity studies would have been sufficient to detect the teratogenic hazard for all these pharmaceuticals. The analysis also showed that for human teratogens that were detected in animal species, the exposure at the NOAEL in at least one species was < 4-fold the exposure at the MRHD.

In addition, a survey was conducted on EFD toxicity studies by the IQ DruSafe Leadership Group (Andrews et al. (7)). This survey identified 153 and 128 definitive rat and rabbit EFD studies,

respectively, that achieved ≥ 15-fold animal to human parent drug exposure ratios (using human exposure at the intended therapeutic dose) in the absence of confounding (i.e., dose-limiting) maternal toxicity. These data show that dosing animals to achieve exposures ≥ 25-fold human exposures when there is no maternal toxicity (that would otherwise limit the high dose), only infrequently detects MEFL. In all these cases, MEFL findings were not observed until exposures exceeded 50-fold and findings at such high exposures are not believed to be relevant to human risk assessment. In the absence of confounding maternal toxicity, the selection of a high dose for EFD and PPND studies that represents a > 25-fold exposure ratio to human plasma exposure of total parent compound at the intended maximal therapeutic dose is therefore considered pragmatic and reasonably sufficient for detecting outcomes relevant for human risk assessment.

11. Glossary

Disclaimer: The definitions in this glossary are specific for their use within this guideline.

Alternative assay(s): *In vitro, ex vivo* or non-mammalian *in vivo* assay(s) intended to predict malformations or embryo-fetal lethality; see MEFL.

Applicability domain: refers to the definition of the physicochemical properties of the substances that can be reliably tested in the assay and the biological mechanisms of action covered by the assay.

Assay qualification (for regulatory use): Confirmation of the predictivity of an alternative assay(s) to identify MEFL, as observed *in vivo*.

Constitutive ingredients: Chemicals or biologic substances used as excipients, diluents, or adjuvants in a vaccine, including any diluent provided as an aid in the administration of the product and supplied separately.

Developmental toxicity: Any adverse effect induced prior to attainment of adult life. It includes effects induced or manifested from conception to postnatal life.

GD 0: The day on which positive evidence of mating is detected (e.g., sperm is found in the vaginal smear / vaginal plug in rodents, or observed mating in rabbits).

Malformation: Permanent structural deviation that generally is incompatible with or severely detrimental to normal development or survival.

Preliminary EFD (pEFD) toxicity study: An embryo-fetal developmental toxicity study that includes exposure over the period of organogenesis, has adequate dose levels, uses a minimum of 6 pregnant animals per group, and includes assessments of fetal survival, fetal weight, and external and soft tissue alterations (see ICH M3).

Surrogate molecule: A molecule showing similar pharmacologic activity in the test species as that shown by the human pharmaceutical in the human.

Vaccine: For the purpose of this guideline, this term refers to preventative or therapeutic vaccines for infectious diseases. Vaccine (inclusive of the term vaccine product) is defined as the complete formulation and includes antigen(s) (or immunogen(s)) and any additives such as adjuvants, excipients or preservatives. The vaccine is intended to stimulate the immune system and result in an immune response to the vaccine antigen(s). The primary pharmacological effect of the vaccine is the prevention and/or treatment of an infection or infectious disease.

Variation: Structural change that does not impact viability, development, or function (e.g., delays in ossification) which can be reversible, and are found in the normal population under investigation.

12. References

1) International Council on Harmonisation M3(R2): Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (2009) together with ICH M3(R2) Questions & Answers (2012).

2) International Council on Harmonisation S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (2011).

3) International Council on Harmonisation S9: Nonclinical Evaluation for Anticancer Pharmaceuticals (2009).

4) International Council on Harmonisation S3A: Note for Guidance on Toxicokinetics: The Assessment of Systemic Toxicity in Toxicity Studies (1994) together with ICH S3A Questions and Answers (2017).

5) International Council on Harmonisation S11: Nonclinical Safety Testing in Support of Development of Pediatric Medicines (2019, step 2).

6) Andrews PA, Blanset D, Lemos Costa P, Green M, Green ML, Jacobs A, et al. Analysis of exposure margins in developmental toxicity studies for detection of human teratogens. Regul Toxicol Pharmacol. 2019a;105:62-8.

7) Andrews PA, McNerney ME, DeGeorge JJ. Reproductive and developmental toxicity testing: An IQ-DruSafe industry survey on current practices. Regul Toxicol Pharmacol. 2019b;107:104413.

Annex 1 *In Vivo* study designs

Outlined below are advantages and disadvantages to the use of various species utilized in DART studies.

Table 1: Principle Advantages and Disadvantages of Various Species for Developmental and Reproductive Toxicity Testing

Routine Species		
Species	**Advantages**	**Disadvantages**
Rat	• Well-understood biology • Widely used for pharmacodynamics and drug discovery • Robust reproductive capacity with short gestation • Large group sizes and litter size • Data available from repeated-dose toxicity study • Suitable for all stages of testing • Widespread laboratory experience and availability • Extensive historical data	• Different placentation to human (e.g., timing, inverted yolk sac) • Dependence on prolactin as the primary hormone for establishment and maintenance of early pregnancy, which makes them sensitive to some pharmaceuticals (e.g., dopamine agonists) • Highly sensitive to pharmaceuticals that disrupt parturition (e.g., nonsteroidal anti-inflammatory drugs in late pregnancy) • Less sensitive than humans to fertility perturbations • Limited application for foreign proteins – Limited or no pharmacologic activity – Potential impact of immunogenicity

Rabbit	• Similar advantages to rats • Non-rodent model • Suitable for serial semen sampling and mating studies • Placental transfer of antibodies more closely approximates primates than rodents, an advantage for DART testing of vaccines	• Limitations similar to rat for foreign proteins • Limited historical data for fertility and pre-/postnatal studies • Sensitive to gastrointestinal disturbances; (e.g., some antibiotics) • Prone to spontaneous abortion • General physical condition difficult to monitor using clinical signs • Should generate PD, toxicity, and TK data as not generally used for toxicology programs (except for vaccines)
Mouse	• Similar advantages to rats • Genetically modified models available or can be generated • Surrogate molecules are often available • Uses small amounts of test material	• Similar limitations to rats • Small fetus size and tissue volumes • Stress sensitivity • Malformation clusters are known to occur

Non-routine Species		
Species	**Advantages**	**Disadvantages**
Cynomolgus Monkey (NHP)	• Generally more phylogenetically and physiologically similar to humans than other species • More likely than rodents to show similar pharmacology to humans • Placentation similar to human • Data available from repeated-dose toxicity study • Transfer of antibodies across the placenta similar to humans	• Small group size, hence low statistical power and wide variability across groups • Low fecundity – Single offspring • High background pregnancy lossLimited availability of breeding animals • Long menstrual cycle (30 days) and gestation (165 days) • Impractical for fertility (mating) studies • F1 reproduction function not practical to evaluate due to late sexual maturity (around 3 to 6 years of age) • Sexual maturity cannot be determined by age and body weight • Ethical considerations • Less historical control data and laboratory experience/capability • Highly variable age, weight and pregnancy history at the start
Mini-pig	• Alternate non-rodent for general toxicity testing • Short period of organogenesis (GD 11-35) • Defined genetic background and specific-pathogen-free animals • Sexual maturity by 7 months • Larger litter size compared to NHP • Suitable for serial semen sampling and mating studies	• Limited number of experienced laboratories • Long gestation (114 days) • Uses a large amount of test material • Minimal to no prenatal transfer of antibodies

	• Sufficient historical background data on reproductive endpoints	
Limited Use Species (primarily used for investigative purposes)		
Species	**Advantages**	**Disadvantages**
Hamster	• Alternate rodent model that can be pharmacologically relevant	• High postnatal loss due to cannibalization • Limited historical control data and laboratory experience • Limited availability of postnatal behavioral and functional tests • IV route difficult • Aggressive • Sensitive to GI disturbances • Should generate PD, toxicity, and TK data as not generally used for toxicology programs • Blood sampling is difficult
Dog	• Usually have repeated-dose toxicity data • Readily amenable to semen collection	• Long gestation (63 days) • Limited historical control data and laboratory experience • Limited availability of postnatal behavioral and functional tests • Uses a large amount of test material

Other mammalian species not listed here can also be used to evaluate the effects of pharmaceuticals on DART endpoints.

1.1 In Vivo *study design considerations*

Generally, within and between reproductive studies animals should be of comparable age, weight and parity at the start. The easiest way to fulfil these factors is to use animals that are young, sexually mature adults at the time of the start of dosing. The number of animals per group specified in individual studies is a balance based on scientific judgment from many years of experience with these study designs, and ethical considerations on the appropriate use of animals. Smaller group sizes can be sufficient to demonstrate anticipated adverse effects on reproduction or development at clinically relevant exposures of the pharmaceutical.

Evaluation of 16 to 20 litters for rodents and rabbits provides a degree of consistency among studies. Below 16 litters inter-study results become inconsistent, and above 20 to 24 litters per group, consistency and precision is not greatly enhanced. These numbers refer to litters available for

evaluation. If groups are subdivided for different evaluations the number of animals starting the study should be adjusted accordingly.

The suggested study designs below can be modified, particularly with respect to parameters, timings, and assessments and still meet the study objectives. Expert judgment should be used for adapting these framework designs for individual laboratories and purposes.

1.1.1 Fertility and Early Embryonic Development (FEED) Study

The FEED study is designed to assess the maturation of gametes, mating behavior, fertility, preimplantation development of the embryo, and implantation. For females, this includes effects on the estrous cycle and tubal transport. For males, it includes detection of functional effects (e.g., epididymal sperm maturation) that cannot be detected by histological examinations of the male reproductive organs.

A combined male/female FEED study, in which both sexes are administered test article, is commonly used (See Table 2). However separate male only or female only studies can be conducted by substituting the appropriate number of untreated females or males in the study designs.

Table 2: FEED Study Design: Rodents, combined male and female study

Parameter	
Group size	at least 16 of each sex
Number of dose groups	4 (including 1 control)
Administration period[a]	M: ≥ 2 weeks prior to cohabitation through at least confirmation of mating F: ≥ 2 weeks prior to cohabitation through implantation (GD6)
Mating ratio	1 male:1 female
Mating period[b]	≥ 2 weeks
Estrous cycle evaluation	Daily, commencing 2 weeks before cohabitation and until confirmation of mating
Clinical observations/mortality	At least once daily
Body weight	At least twice weekly
Food consumption	At least once weekly (except during mating)
Male necropsy[c]	Preserve testes and epididymides for possible histological examination; and evaluate on a case by case basis. Perform macroscopic examination and preserve organs with findings for possible histological evaluation; keep corresponding organs of sufficient controls for comparison.
Sperm analysis[d]	Optional
Female necropsy[e]	On a case by case basis, preserve ovaries and uteri for possible histological examination and evaluation. Perform macroscopic examination and preserve organs with findings for possible histological evaluation; keep corresponding organs of sufficient controls for comparison.
Scheduled cesarean section Uterine implantation data	Cesarean sections typically performed mid-gestation; corpora lutea counts, number of implantation sites, live and dead embryos

a. Available data from repeated-dose toxicity studies and genotoxicity studies should be used to justify dosing duration, especially for detecting effects on spermatogenesis. A premating treatment

interval of 2 weeks for females and 2 weeks for males can be used provided no effects have been found in repeated-dose toxicity studies of at least 2 weeks duration that preclude this. Treatment of males should continue throughout confirmation of mating, although termination following confirmation of female fertility can be valuable. Treatment of females should continue through at least implantation. This will permit evaluation of functional effects on fertility that cannot be detected by histopathological examination in repeated-dose toxicity studies and effects on mating behavior.

b. Most rats or mice will mate within the first 5 days of cohabitation (i.e., at the first available estrus), but in some cases females can become pseudopregnant. Leaving the female with the male for longer than 2 weeks can allow these females to restart estrous cycles and become pregnant.

c. It can be of value to delay euthanasia of the males until the outcome of mating is known. In the event of an effect on fertility, males could be mated with untreated females to ascertain any potential male-mediation of the effect. A more complete evaluation of toxicity to the male reproductive system can be achieved if dosing is continued beyond mating and euthanasia delayed so that the males are exposed for the total duration of a spermatogenic cycle (e.g., 10 weeks).

d. Sperm analysis (e.g., sperm counts, motility, and/or morphology) sometimes can be useful if issues arise to support risk assessment.

e. Termination of females around days 13-15 of pregnancy in general is adequate to assess effects on fertility and reproductive function (e.g., to differentiate between live implantations and resorption sites). There is an option to terminate females near the end of gestation.

1.1.2 Embryo-Fetal Developmental (EFD) toxicity study

The EFD toxicity study is designed to assess maternal toxicity relative to that in non-pregnant females, and to evaluate potential effects on embryo-fetal survival, intrauterine growth, and morphological development.

Suggested study designs for rodents, rabbits and cynomolgus monkeys are described below.

1.1.2.1 Dose range finding Embryo-Fetal Developmental (EFD) toxicity study

Dose range finding studies in mated females are most often used to select appropriate dose levels, or dose schedules, for the definitive rodent and rabbit EFD studies. Tolerability and TK data from existing repeated-dose toxicity studies can, however, be sufficient for this purpose.

1.1.2.2 Preliminary Embryo-Fetal Developmental (pEFD) toxicity study

The pEFD toxicity study (Table 3) is similar in design to the definitive EFD toxicity study. A typical pEFD toxicity study design includes dosing over the period of organogenesis, has adequate dose levels, evaluates a minimum of 6 pregnant females per group, and includes assessments of fetal survival, fetal weight, external fetal abnormalities and soft tissue abnormalities (see ICH M3).

1.1.2.3 Definitive Embryo-Fetal Developmental (EFD) toxicity study

The females are submitted to cesarean section near term. Assessments of fetal survival, fetal weight, external fetal abnormalities, soft tissue abnormalities and skeletal examinations are performed (Table 3). The timing given in Table 3 is for rodent, rabbit and cynomolgus monkeys; for other species appropriate timing should be used.

Table 3: EFD Toxicity Study Designs for Rodent, Rabbit and NHP

	pEFD	EFD		
Parameter	**Rodent/Rabbit**	**Rat (Mouse)**	**Rabbit**	**NHP[a]**
GLP Status	Optional[c]	Yes	Yes	Yes
Minimum number of pregnant females	6	16	16	16[b]
Number of dose groups	4 (including 1 control)	4 (including 1 control)	4 (including 1 control)	At least 2 (including 1 control)
Administration period[d]	Species appropriate	GD6/7-17 (6/7-15)	GD6/7-19	Approximately GD 20 - to at least GD 50
Antemortem endpoints				
Clinical observations/mortality	At least once daily	At least once daily	At least once daily	At least once daily
Body weight	At least twice weekly	At least twice weekly[e]	At least twice weekly[e]	At least once weekly
Food consumption	At least once weekly	At least once weekly	At least once weekly	Optional
Toxicokinetics	Optional[c]	Yes	Yes	Yes
Postmortem endpoints				
Cesarean section [f]	Species appropriate	GD20/21 (17/18)	GD28/29	GD100
Macroscopic examination	Yes	Yes	Yes	Optional
Gravid uterine weight	Optional	Optional	Optional	NA
Corpora lutea	Yes	Yes	Yes	NA
Implant sites	Yes	Yes	Yes	NA
Live and dead conceptuses	Yes	Yes	Yes	Yes

Early and late resorptions	Yes	Yes	Yes	NA
Gross evaluation of placenta	Yes	Yes	Yes	Yes
Weight of placenta	Optional	Optional	Optional	Optional
Fetal body weight	Yes	Yes	Yes	Yes
Fetal sex	Yes	Yes	Yes	Yes
Fetal external evaluations[g]	Yes	Yes	Yes	Yes
Fetal soft tissue evaluations[g]	Yes	Yes[g]	Yes	Yes
Fetal skeletal evaluations[h]	Optional[c]	Yes[g]	Yes	Yes

a. If a NHP other than the Cynomolgus monkey is used, the study design should be adapted.

b. Group sizes in EFD studies should yield a sufficient number of fetuses in order to assess potential adverse effects on morphological development.

c. If the pEFD is used to defer a definitive EFD study, then the pEFD should be done in accordance with GLP regulations, TK data in pregnant animals should be collected, and skeletal evaluations should be performed.

d. For rodents and rabbits, females are dosed with the test substance from implantation to closure of the hard palate (i.e., stage C of the reproductive process, see Section 1.1). For NHP, females are dosed from confirmation of pregnancy (approximately GD 20) to at least Day 50 (end of major organogenesis)

e. Daily weighing of pregnant females during treatment can provide useful information.

f. For rodents and rabbits, cesarean sections should be conducted approximately one day prior to expected parturition. Preserve organs with macroscopic findings for possible histological evaluation; keep corresponding organs of sufficient controls for comparison. For NHP, cesarean sections should be conducted on approximately GD 100.

g. All fetuses should be examined for viability and abnormalities. To permit subsequent assessment of the relationship between observations made by different techniques fetuses should be individually identified.

h. Although it is preferable to examine all rodent fetuses for both soft tissue and skeletal alterations (if methods allow), it is acceptable to submit 50% of fetuses in each litter to separate examinations.

1.1.3 Pre- and Postnatal Developmental (PPND) toxicity study

The PPND toxicity study is designed to assess enhanced toxicity relative to that in non-pregnant females, pre- and postnatal viability of offspring, altered growth and development, and functional deficits in offspring, including sexual maturation, reproductive capacity at maturity, sensory functions, motor activity, and learning and memory.

The females are permitted to deliver and rear their offspring to weaning at which time at least one male and one female offspring per litter are selected for rearing to adulthood and mating to assess reproductive competence (see Table 4).

Table 4: PPND Toxicity Study Design: Rats

Parameter	
Group size	At least 16 litters
Number of dose groups	4 (including 1 control)
Administration period	From implantation (GD 6/7) through weaning (postnatal day (PND) 20)
F0 Females	
Clinical observations/mortality	At least once daily
Body weight	At least twice weekly
Food consumption	At least once weekly until mid-lactation
Parturition observations	GD 21 until complete
Necropsy	PND 21 At necropsy, preserve and retain tissues with macroscopic findings and corresponding control tissues for possible histological evaluation, count uterine implantation sites
F1 Pre-weaning	
Clinical observations/mortality	Daily from PND 0
Pre-and postweaning survival	Daily from PND 0
Body weight and sex	PND 0/1 and then at least twice per week
Optional Standardization of litter size	≥ PND 4, to 4 or 5 pups per sex
Physical development[a]	Preweaning landmarks of development and reflex ontogeny (e.g. eye opening, pinna unfolding, surface righting, auditory startle, air righting, and response to light)
F1 Post-weaning	
Selection for post-weaning evaluation and group size[b]	PND 21, at least 1 male and 1 female/litter where possible to achieve 16 animals per group/sex
Clinical observations/mortality	Daily
Body weight	Weekly
Optional Food consumption	Weekly

Sexual maturation[c]	Females: vaginal opening
	Males: preputial separation
Other functional tests[d]	Assess sensory functions, motor activity, and learning and memory.
Reproductive performance	At least 10 weeks old, paired for mating (1M:1F) within the same group (not siblings)

a. The best indicator of physical development is bodyweight, however, measurement of bodyweight alone is not an acceptable substitute for the evaluation of other developmental parameters.

b. At least one animal per sex per litter should be retained to conduct behavioral and other functional tests, and to assess reproductive function. There can be circumstances where more animals per litter can be retained for independent functional assessments.

c. Body weight should be recorded at the time of attainment to determine whether any differences from control are specific or related to general growth.

d. Learning and memory should be evaluated in a complex learning task. Assessments of locomotor activity and startle reflex with prepulse inhibition (if conducted) should be evaluated over a sufficient period of time to demonstrate habituation.

1.1.3.1 Enhanced Pre- and Postnatal Developmental (ePPND) Toxicity Study in Non-Human Primate (NHP)

The ePPND toxicity study (Table 5) is a study in NHP that combines the endpoints from both the EFD and PPND studies. In this study dosing is extended throughout the gestation period to parturition (e.g., GD20 to parturition). See ICH S6 for information on timing and additional parameters to be evaluated.

Table 5: ePPND Toxicity Study Design: for Cynomolgus Monkey[a]

Parameter	
Group size[b]	Approximately 16 pregnant females
Number of dose groups	At least 2 (including 1 control)
Administration period	From confirmation of pregnancy (approximately GD 20) to parturition
F0 Females	
Clinical observations/mortality	At least once daily
Body weight	At least weekly
Parturition observations	Document day of completion
Placenta	Collect and preserve if possible
Necropsy and tissue evaluation	Only as warranted
Exposure Assessment	TK profiles and/or systemic drug levels should be measured, as appropriate
F1	

Clinical observations/mortality	Daily from PND 0
Body weights	Weekly
Morphometry/Physical and/or functionalassessment	At regular intervals, as appropriate
Neurobehavioural test battery .	At least 1 interval during the first 2 weeks postpartum
Grip strength	PND 28
Mother-infant interaction	Minimally in early postnatal period to confirm nursing; as appropriate thereafter
Exposure assessment	Systemic drug levels should be measured, as appropriate
External evaluation	At regular intervals
Skeletal evaluation	Approximately PND 28 or later
Visceral evaluation	At necropsy
Necropsy	At minimum 1 month, depends on aim of the evaluations
	Preserve and retain tissues for possible histological evaluation

a. If an NHP other than the Cynomolgus monkey is used, the study design should be adapted.

b. Group sizes in ePPND studies should yield a sufficient number of infants in order to assess potential adverse effects on pregnancy outcome, as well as dysmorphology and postnatal development, providing the opportunity for specialist evaluation if warranted (e.g., immune system). Most ePPND studies accrue pregnant animals over several months.

1.1.4 Combination studies

The possibility also exists to combine study types to meet the goals of the development program. This is accomplished by incorporating appropriate endpoints measured in the separate studies summarized above into a single study. Concepts for various combination studies are provided below.

1.1.4.1 FEED and EFD

The aim of the combined FEED/EFD study is to test for toxic effects resulting from treatment from before mating (males/females) through mating, implantation and until the end of organogenesis. This comprises evaluation of stages A through D of the reproductive process (see Section 1.1). This study design is most often used with rodents, although it could be used with non-rodents.

A combined male/female FEED/EFD can be used, but a separate female only option is possible where male fertility is assessed in a separate study such as a repeated dose study of suitable duration. The study would then use untreated males for mating purposes only. For specific study design and observational parameters see Sections 1.1.1. and 1.1.2 of this Annex.

1.1.4.2 Male fertility and repeated-dose toxicology study

It is also possible to evaluate male fertility during a rodent repeated-dose toxicity study. In this combination study, males that have been dosed for a defined number of weeks are paired with untreated females. Following cohabitation, the males continue to be dosed until the scheduled termination of the repeated-dose toxicity study. The untreated females are subjected to cesarean section approximately two weeks after evidence of mating. The study endpoints collected are identical to those outlined in Section 1.1.1 of this Annex. To adequately assess effects, at least 16 males per group should be included in the study. Female fertility and other FEED endpoints will need to be evaluated in a separate study.

Annex 2 Alternative assays

Data generated from qualified alternative assays (see glossary) conducted alone or in conjunction with one or more *in vivo* studies can be utilized to support hazard identification and risk assessment under limited circumstances.

Potential uses can include:

- circumstances where there is evidence suggesting an adverse effect on EFD (e.g., a mechanism of action affecting fundamental pathways in developmental biology, phenotypic data from genetically modified animals, class effects) (see Section 1.2.2 and Figure 1 of this Annex)
- toxicity in animal species precludes attaining systemic exposures relevant to the human exposures under conditions of use
- as support for a weight of evidence assessment when there are equivocal findings in animal studies
- as partial support for clinical trials including up to 150 WOCBP for up to 3 months duration (see Section 4.2.3 of Guidance)
- pharmaceuticals being developed for certain severely debilitating or life-threatening diseases or late-life onset diseases (see Sections 1.2.3, 1.2.4 and Figure 2 of this Annex).

When alternative assays are used to support risk assessment, incorporation of these assays into an integrated testing strategy should be justified. Assay(s) used for risk assessment should be conducted in accordance with GLP and qualified for context of use (i.e. applicability domain and regulatory conditions under which assay results are reliable). Strategies incorporating alternative assays should also assess the effects of drug metabolites when warranted (ICH M3). This annex does not recommend specific assays; instead, basic scientific principles are included to assist in assay qualification for regulatory use. Alternative assays used to explore mechanism of action, or otherwise not intended to substitute for *in vivo*-derived EFD endpoints, are not expected to be qualified in this rigorous manner.

1.1 Qualification of alternative assays for prediction of MEFL

Test methods must be appropriate in order for test results to be of value. Accordingly, the endpoints measured should be scientifically justified with respect to assay objectives and predictions. The relationships among the assay's predictions, endpoint(s) assessed, and the applicability domain, should be supported empirically. To qualify[1] an alternative assay or a combination of assays for use in risk assessment for regulatory purposes, a comprehensive description of the methodology and findings should be provided, including the following:

- A thorough description and justification of the predictive model, including which species (e.g., rat, rabbit and/or human) and endpoint(s) it is predicting. The currently available *in vitro* alternative assays used for evaluating potential hazards to development are designed to detect MEFL.
- An evaluation of the biological plausibility of the model including a description of the mechanisms of embryo-fetal development (e.g., cell migration, differentiation, vasculogenesis, neurulation, gastrulation) and subsequent developmental adverse effects studied with the model. In addition, any limitations of each of the individual assays should be discussed. The description should include

[1] qualified alternative assays within the context of this guideline have not been subject to formal validation as those can only be applied under certain specific circumstances.

a discussion and supporting data to show that the duration and timing of exposure supports the prediction of MEFL *in vivo*.

- An assessment of the accuracy and ability for the alternative assay to detect MEFL. The performance of the assay is compared to the data generated from *in vivo* studies with compounds that induce MEFL in the absence of confounding maternal toxicity. If the compound is not a marketed pharmaceutical, then *in vivo* data should be provided.
- A discussion determining whether an effect is negative or positive in the assay.
- Definition and justification of the threshold for molecular and metabolic markers predicting MEFL.
- The details of the algorithm employed for determining positive and negative outcomes *in vivo*. The predictive model should correlate concentrations tested in the alternative assay(s) to the *in vivo* exposure, preferably in pregnant animals, that results in an adverse outcome in the species being predicted.
- The list of compounds in each of the training sets (data used to discover potentially predictive relationships) and test sets (data used to assess the strength and utility of a predictive relationship) for qualification of the assay and the basis for selection of these compounds.
- Data sources (e.g., literature, study reports, regulatory reviews) for all *in vivo* exposure and MEFL data used for compounds in the qualification data set, if not obtained from the Reference Compound List (Section 1.3 of Annex 2).
- Data demonstrating the test method's performance covering an appropriate range of biological and chemical domains that are justified for the intended use of the alternative assay (context of use).
- Data demonstrating the sensitivity, specificity, positive and negative predictive values, and reproducibility of an assay or battery of assays to predict *in vivo* developmental outcomes. The performance of the training and test sets can be evaluated separately and/or together, provided the selected approach is justified.
- In cases when more than one assay is conducted, a separate description of the performance of each assay, in addition to the integrated assessment used for the predictive model. A clear description of how the results of individual assays are integrated into the final prediction.
- Historical data for assay development and use (e.g., viability, numbers and types of malformations), including positive controls.

The sponsor should state to which health authorities (if any) the assay qualification has been previously been submitted. Note that acceptance of an assay by one regulatory authority does not bind other health authorities to accept the assay. Last, evaluation of human teratogens not detected *in vivo* by rat and/or rabbit is encouraged since some alternative assay(s) might predict MEFL that are not detectable by *in vivo* studies.

1.2 Examples of EFD testing strategies utilizing alternative assays

This section provides illustrative examples of integrated testing strategies into which alternative assays are incorporated to test for adverse effects on EFD.

1.2.1 Potential approach to defer in vivo testing as part of an integrated testing strategy

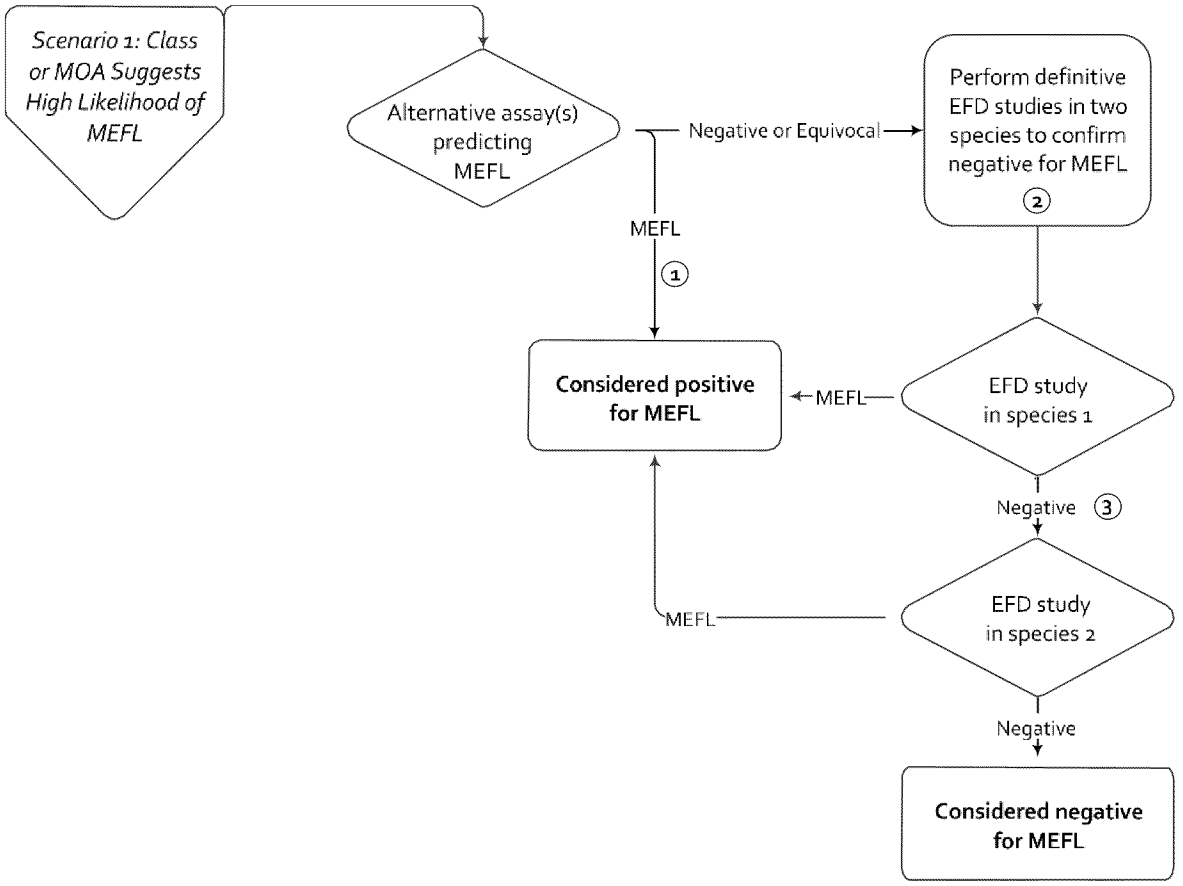
See Section 4.2.3 of the Guidance.

1.2.2 Pharmaceuticals expected to be embryo-fetal toxicants

For pharmaceuticals that are expected to adversely affect embryo-fetal development based on mechanism of action, pharmacologic class or target biology, it can be appropriate to confirm this activity in a qualified alternative assay(s) (see Figure 1 of this Annex).

When a qualified alternative assay clearly predicts MEFL at clinically relevant extrapolated exposures, this can be sufficient to identify the compound as an EFD risk, and further testing would generally not be warranted. If the alternative assay does not predict MEFL, this should be confirmed in definitive *in vivo* EFD studies in two species. Conducting the studies in series, as shown in Annex 2 Figure 1, can allow for reduction in animal use, as the second *in vivo* assay would not be warranted if the first one is positive. Under this scenario, since the pharmaceutical is expected to adversely affect embryo-fetal development, there is no merit in using *in vivo* EFD studies to attempt to negate a positive alternative assay response.

Figure 1: Use of Alternative Assays for Pharmaceuticals Expected to be EFD Toxicants



1) No additional assessment is warranted if unequivocal MEFL signal is observed at clinically relevant extrapolated exposures.

2) Alternatively, pEFD studies can be used; however, negative results should be confirmed by a definitive study in the relevant species

3) Conducting *in vivo* EFD studies in series, as shown, can permit reduction in animal use, as 2nd *in vivo* assay is not warranted if the first study is positive.

1.2.3 Pharmaceuticals intended to treat severely debilitating or life-threatening diseases

Considering the risk/benefit for pharmaceuticals intended to treat severely debilitating or life-threatening conditions (compared to less severe chronic diseases) where the likelihood of pregnancy is low, the use of qualified alternative assay(s) can be considered an appropriate component of the EFD risk assessment (see Annex 2 Figure 2).

When a qualified alternative assay clearly predicts MEFL in the first species (e.g., rat) at clinically relevant extrapolated exposures, this can be considered, on a case-by-case basis, to sufficiently characterize the EFD risk. However, if the results are equivocal or thought to represent a false positive, definitive *in vivo* studies in one or two species should be conducted to assist human risk assessment. If no EFD signal is observed in the two definitive *in vivo* studies at appropriate exposure margins the

results of the alternative assay could be considered of minimal concern for human risk. However, for alternative assays that have been qualified to predict human MEFL (i.e., not predicting only animal MEFL), additional data (e.g., mechanistic or genetic) should be provided to support a conclusion that the alternative assay results represent a false positive finding. If one or both of the *in vivo* studies are positive for EFD toxicity, the compound is considered to be positive for EFD risk. Conducting the studies in series, as shown in Annex 2 Figure 2, can allow for reduction in animal use, as the second *in vivo* assay would not be warranted if the first one is positive.

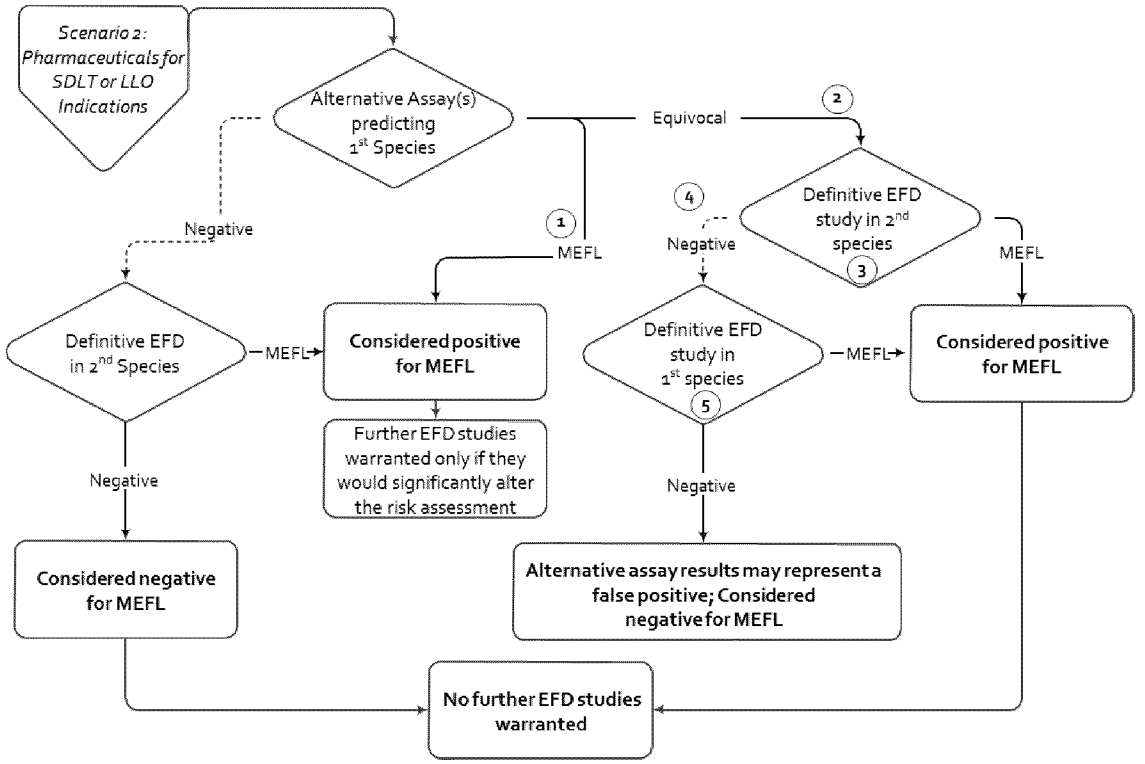
If the alternative assay for the first species predicts a negative outcome (i.e., no MEFL), a definitive *in vivo* EFD study in the second species should be conducted to confirm the assessment. If positive, the compound is considered positive for EFD risk. If negative, the compound is considered negative for EFD risk, and no further testing is generally warranted, unless it is judged that additional studies would significantly alter the risk assessment.

1.2.4 Pharmaceuticals intended to treat late-life onset diseases

Some diseases are typically only diagnosed at a later age, but may nonetheless be diagnosed in reproductively capable women at a low incidence (e.g., bullous pemphigoid, which is typically diagnosed after age 60). Given the generally low rate of fertility in the female population with such late-life onset diseases, there is a diminished likelihood that a pharmaceutical used exclusively in this population will lead to an increase in the incidence of birth defects. Whether an EFD assessment is warranted under this scenario should be determined on a case-by-case basis. This scenario is not intended for situations where the treatment population is presumptively infertile (e.g., post-menopausal osteoporosis), for which no EFD assessment would typically be warranted.

The testing strategy under this scenario is similar to that depicted for severely debilitating or life-threatening diseases, with the exception that the first *in vivo* assessment in the second species can be conducted as a pEFD study.

Figure 2: Use of Alternative Assays for Severely Debilitating or Life-threatening or Late Life Onset Diseases



1) A clearly positive MEFL signal at clinically relevant extrapolated exposures can be sufficient to consider a pharmaceutical positive for EFD toxicity, without further assessment, on a case-by-case basis.

2) While pEFD studies can be used, negative results from definitive *in vivo* EFD studies in two species are warranted to establish that alternative assay results represent a false positive.

3) For late-life onset diseases, given low likelihood of pregnancy in this patient population a pEFD study in the 2nd species can generally be sufficient.

4) Conducting *in vivo* EFD studies in series, as shown, can permit reduction in animal use, as 2nd *in vivo* assay is not to be conducted if the first is positive.

5) Same species as the alternative assay is intended to predict.

1.3 Reference compound list

The Reference Compound List contains 29 compounds that have been shown to induce MEFL in nonclinical studies (in the absence of overt maternal toxicity) and/or humans (Table 1 of this Annex).

Only findings of MEFL were recognized for NOAEL and LOAEL determinations. Doses associated with the induction of reversible or minor manifestations of developmental toxicity (e.g., changes in fetal weight, growth suppression, and skeletal variations) were not used for this assessment. (see Section 9, of the Guidance).

The general robustness of the studies (e.g., compliance with GLP regulations, the number of animals in the study, number of dose levels) was considered when determining which NOAEL and LOAEL values to use. When multiple sources were available, the data from a study designed in a manner consistent

with the design recommended in the ICH S5(R2) guideline was accepted as the definitive data. When there were multiple robust sources of data that did not closely align, the highest NOAEL (to avoid bias towards claiming a low margin) and lowest LOAEL (as is routinely done in regulatory assessments) were generally used, even if the data were from different studies.

The compounds in this list as well as others can be used to support qualification of an alternative assay or battery of assays.

Compounds not causing MEFL (negative compounds) should also be used to assess assay specificity. Such compounds would lack MEFL regardless of additional effects on embryo/fetus such as fetal body weight changes, structural variations or delayed/reduced ossification. These compounds can be negative at all *in vivo* doses tested, or can be positive (MEFL observed) at higher doses/exposures provided the alternative assay within its context of use predicts the transition from negative to positive. That is, the alternative assay should predict a negative result at some extrapolated level under the conditions for which the *in vivo* study yielded a negative result (no MEFL). In the Reference Compound List, three compounds are provided as an example for negative controls (Cetirizine, Saxagliptin, Vildagliptin). These compounds did not induce MEFL in rat and rabbit at an exposure multiple (AUC and Cmax) of >25 fold at the MRHD.

Table 1: Reference Compound Positive Control Examples for Qualifying Alternative Assays

Positive Controls	**Human Teratogen**	**Rat MEFL**	**Rabbit MEFL**
Acitretin	X	X	X
Aspirin	X	X	
Bosentan		X	
Busulfan	X	X	X
Carbamazepine	X	X	X
Cisplatin		X	
Cyclophosphamide	X	X	X
Cytarabine	X	X	
Dabrafenib		X	
Dasatinib		X	
Fluconazole	X	X	X
5-Fluorouracil	X	X	X
Hydroxyurea	X	X	X
Ibrutinib		X	X
Ibuprofen	X	X	
Imatinib		X	
Isotretinoin (13-*cis*-retinoic acid)	X	X	X

Positive Controls	**Human Teratogen**	**Rat MEFL**	**Rabbit MEFL**
Methotrexate	X	X	X
Pazopanib		X	X
Phenytoin (Diphenylhydantoin)	X	X	X
Pomalidomide	presumed	X	X
Ribavirin		X	X
Tacrolimus		X	X
Thalidomide	X	X	X
Topiramate	X	X	X
Tretinoin (all-*trans*-retinoic acid)	X	X	X
Trimethadione	X	X	
Valproic acid	X	X	X
Vismodegib	presumed	X	

1.3.1 positive control reference compounds

Acitretin (etretin)

CAS No.: 55079-83-9

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
7.5 mg/kg oral GD7-16 (Kistler) C_{max} = 1.5 µg/mL[a] AUC = 6.6 µg·h/mL[a]	15 mg/kg oral GD7-16 (Kistler) C_{max} = 3.0 µg/mL[a] AUC = 13.2 µg·h/mL[a]	15 mg/kg: malformed humeri, dilated renal pelvis 30 mg/kg: cleft palate; malformed humeri, radii and ulnae	0.2 mg/kg oral GD7-19 (Kistler) no PK data available	0.6 mg/kg oral GD7-19 (Kistler) no PK data available	0.6 mg/kg: cleft palate, open eyelid, skeletal 2 mg/kg: cleft palate, skull and tail malformations, ectrodactyly of the fore- and hindfeet and malformations of the long bones	50 mg (0.83 mg/kg, 29.4 mg/m^2) Exposure values at steady state: C_{max} = 0.79 µg/mL[b] $AUC_{(0-24h)}$: 3.6 µg·h/mL[b]	NOAEL: rat C_{max} = 1.9 (1.5/0.79) AUC = 1.8 (6.6/3.6) rabbit[c] C_{max} = 0.2 (0.2/0.83) AUC = 0.08 (2.4/29.4) LOAEL: rat	Acitretin is the major metabolite (free acid) of etretinate (ethyl ester)

Rat NOAEL Dose C_{max} AUC	Rat LOAEL Dose C_{max} AUC	Rat Findings	Rabbit NOAEL Dose C_{max} AUC	Rabbit LOAEL Dose C_{max} AUC	Rabbit Findings	Human Dose C_{max} AUC	Margins NOAEL/Human LOAEL/Human	Notes
							C_{max} = 3.8 (3.0/0.79) AUC = 3.7 (13.2/3.6) rabbit[c] C_{max} = 0.7 (0.6/0.83) AUC = 0.2 (7.2/29.4)	

a. Extrapolated from reported values at 5 mg/kg (Brouwer): C_{max} = ~1.0 µg/mL from visual inspection of graph, AUC = 4.4 µg·h/mL.

b. Steady state values after 21 daily doses administered with food (FDA, United States): C_{max} = 0.786 µg/mL, $AUC_{(0\text{-}24h)}$ = 3.569 µg·h/mL.

c. In the absence of rabbit PK data, C_{max} ratio was based on mg/kg dose ratio and AUC was based on mg/m^2 dose ratio.

References

Brouwer KR, McNamara PJ. Influence of pregnancy on the pharmacokinetic disposition of two aromatic retinoids (etretinate and acitretin) in the rat. II. Single and multiple oral dosing studies. Drug Metab Dispos. 1989;17:652-5.

FDA, United States. Approval package review of NDA 019821, part 01 (28 Oct 1996), page 86.

Kistler A, Hummler H. Teratogenesis and reproductive safety evaluation of the retinoid etretin (Ro 10-1670). Arch Toxicol. 1985;58:50-6.

Additional References Evaluated

FDA, United States. Pharm/tox review of NDA 019821 (08 Jun 1988), page 13. [There were no details provided for study findings, study appears to be the same as reported by Kistler and Hummer.]

Acetylsalicylic acid (aspirin)

CAS No.: 50-78-2

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
125 mg/kg oral GD6-17 (n=20 Sprague Dawley) [Gupta][a] aspirin C_{max} = ~25 µg/mL[b] AUC = 6.6 – 25.3 µg·h/mL[b] salicylate	200 mg/kg oral GD7-17 (n=20 Sprague Dawley) [Nakatsuka][e] aspirin C_{max} = ~40 µg/mL[b] AUC = 10.5 – 40.5 µg·h/mL[b] salicylate	Nakatsuka (200 mg/kg): malformations including craniorachischisis, abdominal hernia, exencephaly, club foot, open eyelid, severe defects of vertebral and costal bones; increased resorptions Gupta (250 mg/kg):	350 mg/kg oral GD7-19 (n=20 NZW) [Cappon][f] aspirin: aspirin PK data in rabbits is not available salicylate C_{max} = 490 µg/mL[g]	Not Applicable: no MEFL findings in rabbits up to a maternally toxic dose	None	650 mg (10.8 mg/kg) q4h 3900 mg daily oral (2294 mg/m^2 daily) aspirin C_{max}= 7.08 µg/mL[h] $AUC_{(0-24h)}$ = 48.3 µg·h/mL[h] salicylic acid C_{max} = 45.2 µg/mL[i]	**Aspirin** NOAEL: rat C_{max} = 3.5 (25/7.08) AUC = 0.1 – 0.5 (6.6/48.3 to 25.3/48.3) rabbit[j] C_{max} = 32.4 (350/10.8) AUC = 1.8 (4200/2294)	The aspirin metabolite, salicylate (salicylic acid) has much higher concentrations in comparison to the parent and is pharmacologically active. Since aspirin concentrations were often BLQ, salicylate exposure data are also reported.

C_{max} = 132 µg/mL[c] AUC = 8333 µg·h/mL[d]	C_{max} = 211 µg/mL[c] AUC = 13,333 µg·h/mL[d]	ablepharia, cranio-rachischisis, exencephaly, various low occurrence head malformations, bent fore and hind paw, kinked tail, protruding tongue, gastroschisis, ectopic adrenal, various low occurrence cardio-vascular malformations, VSD, DH, hypoplastic kidney, hypoplastic testes; decreased implantations, increased resorptions and post implantation loss	AUC = 4865 µg·h/mL[g]			AUC = 1448 µg·h/mL[i]	LOAEL: rat C_{max} = 5.6 (40/7.08) AUC = 0.2 – 0.8 (10.5/48.3 to 40.5/48.3) rabbit LOAEL not identified **Salicylate** NOAEL: rat C_{max}: 2.9 (132/45.2) AUC: 5.8 (8333/1448) rabbit C_{max}: 10.8 (490/45.2) AUC: 3.4 (4865/1448) LOAEL: rat C_{max}: 4.7 (211/45.2)	salicylic acid MW = 138.12 g/mol aspirin MW = 180.16 g/mol

							AUC: 9.2 (13,333/1448) rabbit LOAEL not identified	

a. Nakatsuka and Fujii reported a NOAEL of 100 mg/kg in Sprague Dawley rats; the highest NOAEL of the 2 studies is reported here.

b. Extrapolated or actual reported value at 200 mg/kg oral dose in Sprague Dawley rats (Wientjes): C_{max} = 40 µg/mL (visual inspection of Figure 1); AUC = 629 – 2430 µg·min/mL (recalculated as 10.5 – 40.5 µg·h/mL). C_{max} data for aspirin is also available in Wistar rats administered 200 mg/kg (Higgs).

c. Extrapolated from reported value at 200 mg/kg oral dose in Sprague Dawley rats (Wientjes): C_{max} = 211 µg/mL (Table 5); no AUC values were reported for salicylate. C_{max} data for salicylate is also available in Wistar rats administered 200 mg/kg (Higgs) and in Fischer rats administered 90 mg/kg (Kapetanovica).

d. Extrapolated from reported value at oral 90 mg/kg/day on D15 in Fischer rats (Kapetanovica): AUC = 6000 µg·h/mL. Note the AUC in Table 2 is reported as 6.0 µg·h/mL, but this is incompatible with the plot in Figure 1a. An AUC estimated from concentrations visually estimated from Figure 1a was 5319 µg·h/mL (personal calculation); thus it is assumed that the reported value should actually be 6000 µg·h/mL.

e. Gupta reported a LOAEL of 250 mg/kg in Sprague Dawley rats; the lowest LOAEL of the 2 studies is reported here.

f. Data from Cappon is reported since the study design complied with ICH S5 standards. Data are also available in which 200 mg/kg was reported as the NOAEL (McColl, Schardein), but these studies were pre-ICH S5. McColl reported small auricles in hearts (18% v 4.5% in controls) and increased presence of 13th rib (93% vs 56% in controls) at 200 mg/kg aspirin, but these are considered variations. Schardein reported marked reduction in litter size at 200 mg/kg/day, but this dose was maternally toxic.

g. Extrapolated from reported values on D3 after 50 mg/kg/day oral dose in NZW rabbits (Marangos): C_{max} = 70 µg/mL and AUC = 695 µg·h/mL. Note that the extrapolation is 7-fold and that there are no data available on the linearity of the pharmacokinetics in rabbits.

h. Extrapolated to 6 daily doses every 4 hours from reported values after a single 1000 mg dose (Schurer): C_{max} = 10.89 µg/mL, AUC = 12.38 µg·h/mL. The C_{max} after a single dose likely represents the C_{max} at steady state since the half life is short (approximately 0.5 hours) and no accumulation is expected using the equation: accumulation = $1/(1 - e^{-k \cdot tau})$, where k = 0.693/t½ with t½ = 0.5 hours and tau = 4 hours. For $AUC_{(0\text{-}24h)}$, the single dose AUC at 1000 mg was extrapolated to 650 mg and multiplied by 6 (the maximum recommended doses in 24 hours). Data are also available following administration of 500 mg (Nagelschmitz).

i. Extrapolated to 6 daily doses every 4 hours from reported values after a single 1000 mg dose (Schurer): C_{max} = 53.5 µg/mL, AUC = 371.32 µg·h/mL. For C_{max}, an accumulation factor of 1.3 was applied that was estimated from the equation: accumulation = $1/(1 - e^{-k \cdot tau})$, where k = 0.693/t½ with t½ = 2.0 hours and tau = 4 hours (i.e., $1/(1 - e^{-1.386}) = 1/(1 - 0.25) = 1/0.75 = 1.3$). For $AUC_{(0\text{-}24h)}$, the single dose AUC at 1000 mg was extrapolated to 650 mg and multiplied by 6 (the maximum recommended doses in 24 hours). Data are also available following administration of 500 mg (Nagelschmitz).

j. In the absence of PK data, C_{max} ratio was based on mg/kg dose ratio and AUC was based on mg/m^2 dose ratio.

References

Cappon GD, Gupta U, Cook JC, Tassinari MS, Hurtt ME. Comparison of the developmental toxicity of aspirin in rabbits when administered throughout organogenesis or during sensitive windows of development. Birth Defects Res B Dev Reprod Toxicol. 2003;68:38-46.

Gupta U, Cook JC, Tassinari MS, Hurtt ME. Comparison of developmental toxicology of aspirin (acetylsalicylic acid) in rats using selected dosing paradigms. Birth Defects Res B Dev Reprod Toxicol. 2003;68:27-37.

Kapetanovic IM, Bauer KS, Tessier DM, Lindeblad MO, Zakharov AD, Lubet R, et al. Comparison of pharmacokinetic and pharmacodynamic profiles of aspirin following oral gavage and diet dosing in rats. Chem Biol Interact. 2009;179:233-9.

Marangos MN, Onyeji CO, Nicolau DP, Nightingale CH. Disposition kinetics of aspirin in female New Zealand white rabbits. Lab Anim Sci. 1995;45:67-9.

Nakatsuka T, Fujii T. Comparative teratogenicity study of diflunisal (MK-647) and aspirin in the rat. Oyo Yakuri. 1979;17:551-7.

Schurer M, Bias-Imhoff U, Schulz HU, Schwantes U, Riechers AM. Lack of influence of glycine on the single dose pharmacokinetics of acetylsalicylic acid in man. Int J Clin Pharmacol Ther. 1996;34:282-7.

Wientjes MG, Levy G. Nonlinear pharmacokinetics of aspirin in rats. J Pharmacol Exp Ther. 1988;245:809-15.

Additional References Evaluated

Higgs GA, Salmon JA, Hendersonn B, Vane JR. Pharmacokinetics of aspirin and salicylate in relation to inhibition of arachidonate cyclooxygenase and antiinflammatory activity. Proc Natl Acad Sci. USA. 1986;84:1417-20.

McColl JD, Robinson S, Globus M. Effect of some therapeutic agents on the rabbit fetus. Toxicol Appl Pharmacol. 1967;10:244-252.

Nagelschmitz J, Blunck M, Kraetzschmar J, Ludwig M, Wensing G, Hohlfeld T. Pharmacokinetics and pharmacodynamics of acetylsalicylic acid after intravenous and oral administration to healthy volunteers. Clin Pharmacol. 2014;6:51-9.

Schardein JL, Blatz AT, Woosley ET, Kaump DH. Reproduction studies on sodium meclofenamate in comparison to aspirin and phenylbutazone. Toxicol Appl Pharmacol. 1969;15:46-55.

all-*Trans*-retinoic acid (ATRA), tretinoin

CAS No.: 302-79-4

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins[a]** **NOAEL/Human** **LOAEL/Human**	**Notes**
5 mg/kg oral GD6-15 (Wistar) [Seegmiller] C_{max} = 0.15 µg/mL[b] $AUC_{(0-8h)}$ = 0.25 µg·h/mL[b]	10 mg/kg oral GD6-15 (Wistar) [Seegmiller] C_{max} = 0.30 µg/mL[b] $AUC_{(0-8h)}$ = 0.50 µg·h/mL[b]	cleft palate, sporadic gross external and soft tissue malformations, skeletal alterations	2 mg/kg oral GD6-18 [Tzimas, 1994] C_{max} = 0.10 µg/mL[c] $AUC_{(0-24h)}$ = 0.207 µg·h/mL[c]	6 mg/kg oral GD6-18 [Tzimas, 1994] C_{max} = 0.30 µg/mL[c] $AUC_{(0-8h)}$ = 0.622 µg·h/mL[c]	fetal resorptions and a decrease in live fetuses; visceral ectopia, skin erosions, acaudia, torsion of hindlimbs, and omphalocele	45 mg/m^2/day in two divided doses C_{max} = 0.394 µg/mL[d] AUC = 0.537 µg·h/mL[d]	NOAEL: rat C_{max} = 0.4 (0.15/0.394) AUC = 0.5 (0.25/0.537) rabbit C_{max} = 0.3 (0.100/0.394) AUC = 0.4 (0.207/0.537) LOAEL: rat	tretinoin induces its own metabolism, so PK margins are highly dependent on day of assessment

							C_{max} = 0.8 (0.30/0.394) AUC = 0.9 (0.50/0.537) <u>rabbit</u> C_{max} = 0.8 (0.300/0.394) AUC = 1.2 (0.622/0.537)	

a. Since tretinoin induces its own metabolism, which causes a significant decrease in plasma exposures with repeated dosing, single dose PK data in animals and humans were used for calculating exposure margins.

b. Extrapolated or actual value after single 5 mg/kg oral dose on GD9 in Wistar rats (Tzimas 1997): C_{max} = 0.15 µg/mL, $AUC_{(0\text{-}8h)}$ = 0.25 µg·h/mL. Pharmacokinetic data are also available after a single dose of 6 mg/kg on GD12 (Collins, 1995): C_{max} = 0.320 µg/mL from visual inspection of graph, $AUC_{(0\text{-}8h)}$ = 0.820 µg·h/mL; as well as after 6 daily doses (Collins 1994, 1995): C_{max} = 0.046 or 0.052 µg/mL, and $AUC_{(0\text{-}24h)}$ = 0.098 µg·h/mL or $AUC_{(0\text{-}10h)}$ = 0.090 µg·h/mL, respectively.

c. Extrapolated or actual value after single 6 mg/kg oral dose on GD12 in Swiss hare rabbits (Collins 1995): C_{max} = 0.300 µg/mL from visual inspection of graph, $AUC_{(0\text{-}8h)}$ = 0.622 µg·h/mL. Pharmacokinetic data are also available following 6 daily doses in Swiss hare rabbits (Collins 1995): C_{max} = 0.110 µg/mL, $AUC_{(0\text{-}10h)}$ = 0.281 µg·h/mL; and from (Tzimas 1994): C_{max} = 0.105 µg/mL, $AUC_{(0\text{-}24h)}$ = 0.321 µg·h/mL.

d. PK data after first dose (US label).

References

Collins MD, Tzimas G, Bürgin H, Hummler H, Nau H. Single versus multiple dose administration of all-trans-retinoic acid during organogenesis: differential metabolism and transplacental kinetics in rat and rabbit. Toxicol Appl Pharmacol. 1995;130:9-18.

Seegmiller RE, Ford WH, Carter MW, Mitala JJ, Powers WJ Jr. A developmental toxicity study of tretinoin administered topically and orally to pregnant Wistar rats. J Am Acad Dermatol. 1997;36(3 Pt 2):S60-6

Tzimas G, Bürgin H, Collins MD, Hummler H, Nau H. The high sensitivity of the rabbit to the teratogenic effects of 13-cis-retinoic acid (isotretinoin) is a consequence of prolonged exposure of the embryo to 13-cis-retinoic acid and 13-cis-4-oxo-retinoic acid, and not of isomerization to all-trans-retinoic acid. Arch Toxicol. 1994;68:119-28.

Tzimas G, Thiel R, Chahoud I, Nau H. The area under the concentration-time curve of all-trans-retinoic acid is the most suitable pharmacokinetic correlate to the embryotoxicity of this retinoid in the rat. Toxicol Appl Pharmacol. 1997;143:436-44.

US label tretinoin.

Additional References Evaluated

Collins MD, Tzimas G, Hummler H, Bürgin H, Nau H. Comparative teratology and transplacental pharmacokinetics of all-trans-retinoic acid, 13-cis-retinoic acid,and retinyl palmitate following daily administrations in rats. Toxicol Appl Pharmacol. 1994;127:132-44. [PK data after 6 daily doses]

Kochhar DM, Christian MS. Tretinoin: a review of the nonclinical developmental toxicology experience. J Am Acad Dermatol. 1997;36(3 Pt 2):S47-59. [review article of other papers already cited]

Tembe EA, Honeywell R, Buss NE, Renwick AG. All-trans-retinoic acid in maternal plasma and teratogenicity in rats and rabbits. Toxicol Appl Pharmacol. 1996;141:456-72. [single dose teratology and PK at ≥20 mg/kg]

FDA, United States. Pharmtox review of NDA 021108/S000 (31 Aug 2000), page 16,26. [p. 16: same study as Seegmiller; p. 26: review mentions "only a modest increase in intrauterine death" at 2.5 mg/kg in an oral rat developmental toxicity study, but there are no study details to allow confirmation].

US label tretinoin. [fetal resorptions and a decrease in live fetuses were stated as findings in all species studied, but the dose at which these occurred was not mentioned]

Bosentan

CAS No.: 147536-97-8

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Notes**
60 mg/kg oral GD6-15 (FDA, United States, p. 39, 155) C_{max} = 4.5 µg/mL[a] AUC = 13.2 µg·h/mL[a]	300 mg/kg oral GD6-15 (FDA, United States, p. 39, 155) C_{max} = 16.25 µg/mL[b] AUC = 53.5 µg·h/mL[b]	<u>Cesarean sections</u> 300 mg/kg: agenesis of soft palate (1 litter) 1500 mg/kg: agenesis of soft palate (14 litters), shortened tongues, abnormal origin of the right subclavian artery (1 litter); abnormalities of the skull (shortened and misshapen mandibles, abnormally shaped palatine, abnormally shaped tympanic annulus and hyoid bone, fusion of the pterygoid process with the tympanic annulus, bent internal pterygoid process) <u>Spontaneous delivery fetuses (PPND groups) that died on study</u>:[c]	1500 mg/kg/day oral (750 mg/kg BID) GD7-18 (FDA, United States, p. 66) C_{max} = 1.435 µg/mL[d] AUC = 27.7 µg·h/mL[d]	LOAEL not identified	none	

		300 mg/kg: agenesis of the soft palate, anophthalmia, and microphthalmia				

a. Extrapolated from reported values in plasma after 10 doses of 200 mg/kg oral bosentan in pregnant rats (FDA, United States, p. 78): C_{max} = 15 µg/mL, AUC = 44 µg·h/mL.

b. Interpolated from reported values in plasma after 10 doses of 200 and 600 mg/kg oral bosentan in pregnant rats (FDA, United States, p. 78): at 200 mg/kg, C_{max} = 15 µg/mL, AUC = 44 µg·h/mL; at 600 mg/kg, C_{max} = 20 µg/mL, AUC = 82 µg·h/mL.

c. In a separate PPND study with higher levels of impurities and pup sacrifice on PND4, agenesis of the soft palate was also observed in 3 litters at 120 mg/kg (FDA, United States, p. 58)

d. Actual values in plasma after 12 doses of 1500 mg/kg/day oral bosentan administered as 2 divided doses (750 mg/kg each) 5 to 6 hours apart in pregnant Himalayan rabbits (FDA, United States, p. 78): C_{max} = 1.435 µg/mL, AUC = 27.70 µg·h/mL.

References

FDA, United States. Pharmacology Review NDA 021290 (30 Aug 2001).

Busulfan

CAS No.: 55-98-1

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose[a]** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
NOAEL not identified	3 mg/kg oral single dose GD12 (18 mg/m^2) [Dodo] C_{max} = 0.84 µg/mL[b] AUC = 2.70 µg·h/mL[b]	3 mg/kg: fused carpal bones 10 mg/kg: low incidence of limb and rib malformations 30 mg/kg: high incidence of limb and rib malformations	1.3 mg/kg oral GD7–14 (15.6 mg/m^2) [Somers] no rabbit PK data found	3.6 mg/kg oral GD7-14 (43.2 mg/m^2) [Somers] no rabbit PK data found	increased resorptions and decreased live young, abnormalities in liver and gall bladder	4 – 8 mg daily oral (0.06 – 0.13 mg/kg, 2.4 – 4.7 mg/m^2) for 8 mg dose C_{max} = 0.128 µg/mL[c] AUC = 0.529 µg·h/mL[c]	NOAEL: rat NOAEL not identified rabbit[d] C_{max} = 10 (1.3/0.13) AUC = 3.3 (15.6/4.7) LOAEL: rat C_{max} = 6.6 (0.84/0.128)	human dose is daily but MEFL NOAEL was single dose, margins likely even lower if rats dosed through organogenesis

							AUC = 5.1 (2.7/0.529) rabbit[d] C_{max} = 27.7 (3.6/0.13) AUC = 9.2 (43.2/4.7)	

a. Note that Busulfex is a concentrated busulfan intravenous formulation with dimethylformamide indicated for bone marrow ablation. Myleran is the original busulfan oral drug product indicated for treatment of chronic myelogenous leukemia. The doses used below are for remission induction in chronic myelogenous leukemia.

b. Extrapolated from reported values after 1 mg/kg busulfan oral dose to fasted rats (strain not specified) (FDA, United States): C_{max} = 0.28 µg/mL, AUC = 0.9 µg·h/mL.

c. Extrapolated from the average of dose-normalized (to 2 mg) values across the range 2 to 6 mg (C_{max} = 0.03 µg/mL, AUC = 0.130 µg·h/mL) and dose-normalized values (to 4 mg) from 4 and 8 mg in a separate study (C_{max} = 0.068 µg/mL, AUC = 0.269 µg·h/mL) (US label, Ehrsson).

d. In the absence of rabbit PK data, C_{max} ratio was based on mg/kg dose ratio and AUC was based on mg/m^2 dose ratio.

References

Dodo T, Uchida K, Hirose T, Fukuta T, Kojima C, Shiraishi I, et al. Increases in discontinuous rib cartilage and fused carpal bone in rat fetuses exposed to the teratogens, busulfan, acetazolamide, vitamin A, and ketoconazole. Hum Exp Toxicol. 2010;29:439-50.

Ehrsson H, Hassan M, Ehrnebo M, Beran M. Busulfan kinetics. Clin Pharmacol Ther. 1983;34:86-9.

FDA, United States. Pharmtox review NDA 020954 (04Feb1999), page 11.

Somers GF. The evaluation of drugs for foetal toxicity and teratogenicity in the rabbit. Excerpta Medica International Congress. 1969;181:227-34. [Proc Eur Soc Study Drug Toxic. 1969;10:227-34].

Additional References Evaluated

Bishop and Wassom. Toxicological review of busulfan (Myleran). Mutat Res. 1986;168:15-45.

Carbamazepine

CAS No.: 298-46-4

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
200 mg/kg oral GD7-18 [Vorhees][a] C_{max} = 33 µg/mL[b] $AUC_{(0-24\ h)}$ = 547 µg·h/mL[b]	400 mg/kg oral GD4-14 [FDA, United States 1967, Vorhees] C_{max} = 65 µg/mL[b] $AUC_{(0-24h)}$ = 1094 µg·h/mL[b]	400 mg/kg GD4-14 [FDA, United States 1967] abortions 600 mg/kg GD7-18 SD rats [Vorhees] increased resorptions, increased kinked tails 650 mg/kg [US label] offspring showed low incidence of cleft	NOAEL was not identified [FDA, United States 1967]	225 mg/kg GD5-12 [FDA, United States 1967] C_{max} = 29 µg/mL[c] $AUC_{(0-24h)}$ = 267 µg·h/mL[c]	No malformations up to 450 mg/kg GD5-12 Decreased numbers of fetuses, increased resorptions at 225 – 450 mg/kg	Up to 800 mg twice daily (1600 mg/day) C_{max} = 11.7 µg/mL[d] $AUC_{(0-24h)}$ = 232 µg·h/mL[d]	NOAEL: Rat C_{max} = 2.8 (33/11.7) AUC = 2.4 (547/232) Rabbit No NOAEL identified LOAEL: Rat C_{max} = 5.6 (65/11.7)	Human exposure is invariant, independent of dose.

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
		palate, talipes, or anophthalmos					AUC = 4.7 (1094/232) Rabbit C_{max} = 2.5 (29/11.7) AUC = 1.2 (267/232)	

a. Data from Vorhees was used for establishing the NOAEL because the data were much more detailed than provided in the FDA, United States review, which suggested a NOAEL of 300 mg/kg.

b. Extrapolated or actual data after 200 mg/kg oral single dose in Sprague Dawley male rats (Shi): C_{max} = 32.7 µg/mL, $AUC_{(0\text{-}24h)}$ = 32.8 mg·min/mL (547 µg·h/mL).

c. Extrapolated from reported value after 80 mg/kg oral single dose in Angora grey rabbits (Kourmaravelou): C_{max} = 10.4 µg/mL, $AUC_{(0\text{-}24h)}$ = 94.8 µg·h/mL. Data are also available from Abushammala at a dose of ~20.6 mg/kg. The data from Kourmaravelou were used because the dose was closer to the LOAEL, which provided a smaller extrapolation range (<3-fold).

d. From actual data for 1600 mg dose of conventional tablet carbamazepine (FDA, United States 1996). C_{max} = 11.66 µg/mL, AUC = 232.27 µg·h/mL.

References

FDA, United States. Pharmtox review of Tegretol NDA 016608 Part 02 (19 December 1967), page 5.

FDA, United States. Approval package of Carbatrol NDA 020712 Part 02 (23 December 1996), page 33.

Koumaravelou K, Adithan C, Shashindran CH, Asad M, Abraham BK. Effect of honey on carbamazepine kinetics in rabbits. Indian J Exp Biol. 2002;40:560-3.

Shi L, Dang XL, Liu XY, Wei HM, Yang MM, Zhang Y. Effect of *Sophora flavescens* on the pharmacokinetics of carbamazepine in rats. Arch Pharm Res. 2014;37:1617-23.

US Label Tegretol.

Vorhees CV, Acuff KD, Weisenburger WP, Minck DR. Teratogenicity of carbamazepine in rats. Teratology. 1990;41:311-17.

Additional References Evaluated

Abushammala I. The effect of pioglitazone on pharmacokinetics of carbamazepine in healthy rabbits. Saudi Pharm J. 2015;23:177-81.

El-Sayed MG, Aly AE, Kadri M, Moustafa AM. Comparative study on the teratogenicity of some antiepileptics in the rat. East Afr Med J. 1983;60:407-15.

Tolbert D, Cloyd J, Biton V, Bekersky I, Walzer M, Wesche D, et al. Bioequivalence of oral and intravenous carbamazepine formulations in adult patients with epilepsy. Epilepsia. 2015;56:915-23. (PK data for oral carbamazepine was similar to cited data, AUC is invariant across dose levels.)

Cisplatin

CAS No.: 15663-27-1

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Notes**
0.3 mg/kg IP on GD6,8,11, or 14 in Wistar rats (Keller) C_{max} = 0.32 µg/mL[a] AUC = 0.25 µg·h/mL[a]	1 mg/kg IP on GD8 or 11 in Wistar rats (Keller) C_{max} = 1.08 µg/mL[a] AUC = 0.85 µg·h/mL[a]	increased fetal mortality, decreased live fetuses per dam	NOAEL not identified	LOAEL not identified	No data found	

a. Extrapolated from values in plasma (unbound) after an intraperitoneal 5 mg/kg cisplatin single dose in male Donryu rats (Tamura): C_{max} = 5.4 µg/mL, $AUC_{(0\text{-inf})}$ = 254 µg·min/mL (4.23 µg·h/mL).

References

Keller KA, Aggarwal SK. Embryotoxicity of cisplatin in rats and mice. Toxicol Appl Pharmacol. 1983;69:245-56.

Tamura T, Imai J, Matsukawa Y, Horikiri Y, Suzuki T, Yoshino H, et al. Pharmacokinetic behaviour of cisplatin in peritoneal fluid after intraperitoneal administration of cisplatin-loaded microspheres. J Pharm Pharmacol. 2001;53:1331-9.

Additional References Evaluated

Chen Y, Brott D, Luo W, Gangl E, Kamendi H, Barthlow H, et al. Assessment of cisplatin-induced kidney injury using an integrated rodent platform. Toxicol Appl Pharmacol. 2013;268:352-61.

Darwish MA, Abo-Youssef AM, Khalaf MM, Abo-Saif AA, Saleh IG, Abdelghany TM. Resveratrol influences platinum pharmacokinetics: A novel mechanism in protection against cisplatin-induced nephrotoxicity. Toxicol Lett. 2018;290:73-82.

Okada A, Fukushima K, Fujita M, Nakanishi M, Hamori M, Nishimura A, et al. Alterations in cisplatin pharmacokinetics and its acute/sub-chronic kidney injury over multiple cycles of cisplatin treatment in rats. Biol Pharm Bull. 2017;40:1948-55.

Sekiya S, Iwasawa H, Takamizawa H. Comparison of the intraperitoneal and intravenous routes of cisplatin administration in an advanced ovarian cancer model of the rat. Am J Obstet Gynecol. 1985;153:106-11. [No C_{max} or AUC values were reported. Substantial differences in PK were noted between the intravenous and intraperitoneal routes]

Toro-Cordova A, Flores-Cruz M, Santoyo-Salazar J, Carrillo-Nava E, Jurado R, Figueroa-Rodriguez PA, et al. Liposomes loaded with cisplatin and magnetic nanoparticles: physicochemical characterization, pharmacokinetics, and *in vitro* efficacy. Molecules. 2018;23(9). pii: E2272. doi: 10.3390/molecules23092272. [PK following 6 mg/kg intravenous cisplatin: C_{max} = 21.3 µg/mL, $AUC_{(0-t)}$ = 7.49 µg·h/mL·kg, which is 2.25 µg·h/mL in 300 g rats.]

Summary of Cisplatin PK data evaluated

Note: There was no obvious choice for the best PK data to use. Chen required a 15-fold extrapolation, Darwish was unclear whether the data were total Pt or unbound drug, and Tamura used a different strain of rat (Donryu) than used for the EFD toxicity study (Wistar). There are substantial differences in PK between the intravenous and intraperitoneal routes (Sekiya, et al., 1985), so intravenous data were not used.

Reference	**Route**	**Dose (mg/kg)**	**C_{max} (µg/mL)**		**AUC (µg·h/mL)**		**Notes**
			Reported	**Normalized to 1.0 mg/kg**	**Reported**	**Normalized to 1.0 mg/kg**	
Chen	IP	15	10.36	0.69	81.74 (0-inf)	5.45	unbound drug (DDTC-derivatized)
Darwish	IP	6	5.66	0.94	9.77	1.63	unclear whether unbound or total drug
Tamura[a]	IP	5	5.4	1.08	4.23	0.85	unbound drug (ultrafilterable)
Okada	IV	5	7.3	1.5	3.0 (0-2h)	0.6	unbound drug (DDTC-derivatized)
Toro-Cordova	IV	6	21.3	3.55	2.25[b] (0-t)	0.375	unbound (ultrafilterable, DDTC-derivatized)

All studies used male Wistar rats except for Tamura et al., which used male Donryu rats.

a. PK parameters were derived from Figure 4 using scanning software (CurveUnscan).

b. Reported as $AUC_{(0\text{-}t)}$ = 7.49 µg·h/mL·kg, which is 2.25 µg·h/mL in 300 g rats.

Cyclophosphamide

CAS No.: 50-18-0

Rat NOAEL Dose **C_{max}** **AUC**	**Rat LOAEL Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL Dose** **C_{max}** **AUC**	**Rabbit LOAEL Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human Dose** **C_{max}** **AUC**	**Margins NOAEL/Huma** **LOAEL/Human**	**Notes**
NOAEL not identified (<2.5 mg/kg) [Chaube]	2.5 mg/kg IP GD9 [Chaube] Cytoxan C_{max} = 4.1 µg/mL[a] AUC = 3.65 µg·h/mL[a] PM C_{max} = 0.55 µg/mL[b] $AUC_{(0-24h)}$ = 2.13 µg·h/mL[b]	2.5 mg/kg GD9 [Chaube] embryolethal 5 mg/kg GD11 [von Kreybig, Mirkes] encephalocele, exencephaly, microcephaly, limb defects (ie, syndactyly and ectrodactyly), defective facial development (cleft palate)	NOAEL not identified (<30 mg/kg)	30 mg/kg IV single doses on GD6-14 [Mirkes, Fritz] Cytoxan C_{max} = 151 µg/mL[c] $AUC_{(0-8h)}$ = 24.1 µg·h/mL[d] PM C_{max} = 0.07 µg/mL[e] $AUC_{(0-8h)}$ = 0.297 µg·h/mL[e]	embryo-fetal resportions, omphalocele, cleft lip/ palate, forelimb skeletal defects	1600 mg/m^2 (40 mg/kg) IV (highest dose, q 3 – 4 weeks)[f] Cytoxan C_{max} = 106 µg/mL[g] AUC = 798 µg·h/mL[g] PM C_{max} = 14.4 µg/mL[h] AUC = 352 µg·h/mL[h]	NOAEL: rat: NOAEL not identified, but LOAEL margins were <0.1 rabbit NOAEL not identified, but LOAEL margins were <1.5 LOAEL: rat C_{max}: 0.04 (4.1/106) AUC: 0.005 (3.65/798)	• MW CP = 261.086 • MW PM = 221.018 • Cytoxan is a prodrug, MEFL has been attributed to both phosphoramide mustard (PM) and acrolein metabolites

							rabbit C_{max} = 1.4 (151/106) AUC = 0.03 (24.1/798) PM margins rat C_{max} = 0.04 (0.55/14.4) AUC = 0.006 (2.13/352) rabbit C_{max} = 0.005 (0.07/14.4) AUC = 0.0008 (0.297/352)	

a. Extrapolated from reported value after 20 mg/kg intravenous single dose in Sprague Dawley rats (Hong): C_0 = 125.3 µM (32.7 µg/mL), AUC/D = 265.3 min/L (in rats with mean BW = 0.330 kg the administered dose = 6.6 mg/rat; thus AUC = 265.3 min/L x 6.6 mg = 1751 mg·min/L = 29.2 µg·h/mL).

b. Extrapolated from reported value after 20 mg/kg intravenous single dose in Sprague Dawley rats (Hong): C_{max} = 20 µM (4.4 µg/mL) from visual inspection of graph, $AUC_{(0\text{-}24h)}$ = 76.9 µM·h (17.0 µg·h/mL) from calculation based on concentration values estimated by visual inspection of graph.

c. Extrapolated from reported value after 45 mg/kg cytoxan intravenous single dose in 2 New Zealand White rabbits (Holm): C_{max} = 227 µg/mL from visual inspection of graphs (mean of 2 rabbits). Values for the *R* and *S* isomers were added together; parent cytoxan is a racemic mixture. Data are also available after a 20 mg/kg intravenous single dose in New Zealand White rabbits (Anthony), but the reported C_{max} value (2.2 µM [0.574 µg/mL] from visual inspection of graph) is inconsistent with the reported AUC and thus was not used.

d. Extrapolated from reported value after 20 mg/kg cytoxan intravenous single dose in New Zealand White rabbits (Anthony): $AUC_{(0\text{-}8h)}$ = 3683 µmol·min/L (16.0 µg·h/mL). Data are also available after a 45 mg/kg intravenous single dose in 2 New Zealand White rabbits (Holm), but the reported AUC values for total racemate (3189 and 1259 µg·min/mL [53.15 and 20.98 µg·h/mL]) in 2 rabbits differed by 2.5-fold and t_{last} was ≤90 minutes so these values were not used.

e. Extrapolated from reported value after 20 mg/kg cytoxan intravenous single dose in NZW rabbits (Anthony): C_{max} = 0.22 µM (0.049 µg/mL) from visual inspection of graph, $AUC_{(0\text{-}8h)}$ = 53.7 µmol·min/L (0.198 µg·h/mL).

f. From SmPC.

g. Extrapolated from reported value after 1000 mg/m^2 intravenous single dose cytoxan (Chan): C_0 = 254.4 µM (66.4 µg/mL), $AUC_{(0\text{-}inf)}$ = 1910 µM·h (499 µg·h/mL).

h. Extrapolated from reported value after 1000 mg/m^2 intravenous single dose cytoxan (Chan): C_0 = 40.5 µM (9.0 µg/mL), $AUC_{(0\text{-}inf)}$ = 996.3 µM·h (220 µg·h/mL).

References

Anthony LB, Long QC, Struck RF, Hande KR. The effect of cimetidine on cyclophosphamide metabolism in rabbits. Cancer Chemother Pharmacol. 1990;27:125-30.

Chan KK, Hong PS, Tutsch K, Trump DL. Clinical pharmacokinetics of cyclophosphamide and metabolites with and without SR-2508. Cancer Res. 1994;54:6421-9.

Chaube S, Kury G, Murphy ML: Teratogenic effects of cyclophosphamide (NSC-26271) in the rat. Cancer Chemother Rep 1967;51:363-76.

Fritz H, Hess R. Effects of cyclophosphamide on embryonic development in the rabbit. Agents Actions. 1971;2:83-6.

Holm KA, Kindberg CG, Stobaugh JF, Slavik M, Riley CM. Stereoselective pharmacokinetics and metabolism of the enantiomers of cyclophosphamide. Preliminary results in humans and rabbits. Biochem Pharmacol. 1990;39:1375-84.

Hong PS, Srigritsanapol A, Chan KK. Pharmacokinetics of 4-hydroxycyclophosphamide and metabolites in the rat. Drug Metab Dispos. 1991;19:1-7.

Mirkes PE. Cyclophosphamide teratogenesis: a review. Teratog Carcinog Mutagen. 1985;5:75-88.

von Kreybig T. Die teratogene wirkung cyclophosphamid wahrend der embryonalen entwicklungsphase bei der ratte. Naunyn-Schniedeb Arch Exp Pathol Pharmakol. 1965;252:173-95.

Additional References Evaluated

Claussen U, Hettwer H, Voelcker G, Krengel HG, Servos G. The embryotoxicity of cyclophosphamide in rabbits during the histiotrophic phase of nutrition. Teratog Carcinog Mutagen. 1985;5:89-100.

US label cyclophosphamide.

Cytarabine

CAS No.: 147-94-4

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
10 mg/kg IP single dose GD10,11, or 12 [Chaube] C_{max} = ~5.8 µg/mL[a] $AUC_{(0\text{-}inf)}$ = ~15.9 µg·h/mL[a]	20 mg/kg IP single dose GD11 or 12 [Chaube] C_{max} = ~11.6 µg/mL[a] $AUC_{(0\text{-}inf)}$ = ~31.7 µg·h/mL[a]	≥20 mg/kg cleft palate, micrognathia, deformed rear appendages, paws and tail; skeletal defects including distortion and fusion of the bones of the skull and appendages, embryofetal mortality	no rabbit data found[b]	no rabbit data found[b]	no rabbit data found	100 mg/m^2 IV every 12 hours (days 1 to 7) many regimens are used including CIV C_{max} = ~2.8 µg/mL[c] AUC = 6.6 µg·h/mL[c]	NOAEL: rat C_{max}: 2.1 (5.8/2.8) AUC: 2.4 (15.9/6.6) LOAEL: rat C_{max}: 4.1 (11.6/2.8) AUC: 4.8 (31.7/6.6)	• half-life is short, rapidly deaminated to inactive uridine arabinoside by cytidine deaminase • active moiety is Ara-CTP which inhibits DNA polymerase • MW = 243.217

a. Extrapolated or reported value after 20 mg/kg intraperitoneal [^{14}C]cytarabine single dose in male Sprague Dawley rats (Parker): C_{max} = ~11.6 µg/mL from visual inspection of graph, $AUC_{(0\text{-}inf)}$ = ~31.7 µg·h/mL from calculation based on concentration values estimated by visual inspection of graph. Note that the reported plasma concentrations represent total radioactivity and that at 4 hours only 71% of the total plasma radioactivity was attributed to intact cytarabine (Parker). The AUC value used, and the calculated margins, thus represents an upper bound and the true AUC for intact cytarabine would certainly be lower. Also note that teratology was performed in Wistar rats. PK data are also available in male Sprague Dawley rats administered 5 mg/kg intravenous cytarabine single dose (Zhang), in male Sprague Dawley rats administered 2.64 µg/kg intravenous [^{3}H]cytarabine (Simard), and in Wistar rats administered 5.4 mg/kg intramuscular cytarabine in solution with chitosan-beta-glycerophosphate (Mulik).

b. Rabbit PK data are available in male New Zealand white rabbits administered single doses 50 mg/kg intravenous cytarabine (Zimmerman): C_{max} = 400 µM (97 µg/mL) from visual inspection of graph, AUC estimated from CL = 8.16 mL/(min·kg) and dose = 50 mg/kg, AUC = dose/CL = (50/8.16)(1 h/60 min) = 102 µg·h/mL.

c. Extrapolated to 100 mg/m^2 BID dose from reported value after single 100 mg intravenous dose (1.67 mg/kg, 60 mg/m^2) (Wan): C_{max} = ~7.0 µmol/L (1.7 µg/mL) from visual inspection of graph, AUC = dose/CL = 100 mg/845 mL/min = 1.97 µg·h/mL (which gives AUC = 3.29 µg·h/mL at 100 mg/m^2 and 6.6 µg·h/mL for 100 mg/m^2 BID).

Mouse NOAEL **Dose** **C_{max}** **AUC**	**Mouse LOAEL** **Dose** **C_{max}** **AUC**	**Mouse Findings**	**Margins** **NOAEL/Human** **LOAEL Human**	**Notes**
0.5 mg/kg IP GD6-15 Swiss mice [Ortega] C_{max} = ~0.50 µg/mL[d] AUC = ~0.46 µg·h/mL[d]	2 mg/kg IP GD6-15 Swiss mice [Ortega] C_{max} = ~2 µg/mL[d] AUC= ~1.83 µg·h/mL[d]	cleft palate, renoureteral alterations, polydactyly, oligodactyly	NOAEL: mice C_{max}: 0.16 (0.46/2.8)[f] AUC: 0.06 (0.39/6.6)[f] LOAEL: mice	this table is included because: a) it shows that with the mouse teratology data, which was included in the US label, exposure margins at the NOAEL were <1, b) rat exposure margins at the NOAEL were much higher, c) rabbit data are not available, so it provides data in a 2nd species

C_{max} = ~0.41 µg/mL[e] AUC = 0.315 µg·h/mL[e]	C_{max} = ~1.62 µg/mL[e] AUC = 1.26 µg·h/mL[e]		C_{max}: 0.65 (1.81/2.8)[f] AUC: 0.23 (1.55/6.6)[f]	

d. Extrapolated from reported value after administration of a 30 mg/kg intraperitoneal single dose cytarabine to Swiss mice (Dedrick): C_{max} = ~30 µg/mL from visual inspection of graph, $AUC_{(0\text{-}24h)}$ = ~27.5 µg·h/mL from calculation based on concentration values estimated by visual inspection of graph. Note large extrapolation range.

e. Extrapolated from reported value after administration of a 2.466 mmol/kg (600 mg/kg) intravenous single dose cytarabine to mice (Bayne): C_{max} = 2 µmol/mL (486 µg/mL) from visual inspection of graph, AUC = 1.553 µmol·h/mL (378 µg·h/mL). Note large extrapolation range.

f. Mouse values were taken as the average of the 2 sources, which gave similar values despite the 20-fold difference in administered dose, suggesting PK was linear.

References

Bayne WF, Mayer LD, Swenson CE. Pharmacokinetics of CPX-351 (cytarabine/daunorubicin HCl) liposome injection in the mouse. J Pharm Sci. 2009;98:2540-8.

Chaube S, Kreis W, Uchida K, Murphy ML. The teratogenic effect of 1-beta-D-arabinofuranosylcytosine in the rat. Protection by deoxycytidine. Biochem Pharmacol. 1968;17:1213-6.

Dedrick RL, Forrester DD, Cannon JN, el-Dareer SM, Mellett LB. Pharmacokinetics of 1-beta-D-arabinofuranosylcytosine (ARA-C) deamination in several species. Biochem Pharmacol. 1973;22:2405-17.

Mulik R, Kulkarni V, Murthy RS. Chitosan-based thermosensitive hydrogel containing liposomes for sustained delivery of cytarabine. Drug Dev Ind Pharm. 2009;35(1):49-56.

Parker RJ, Priester ER, Sieber SM. Comparison of lymphatic uptake, metabolism, excretion, and biodistribution of free and liposome-entrapped [14C]cytosine-beta-D-arabinofuranoside following intraperitoneal administration to rats. Drug Metab Dispos. 1982;10:40-6.

Ortega A, Puig M, Domingo JL. Maternal and developmental toxicity of low doses of cytosine arabinoside in mice. Teratology. 1991;44:379-84.

Simard P, Hoarau D, Khalid MN, Roux E, Leroux JC. Preparation and *in vivo* evaluation of PEGylated spherulite formulations. Biochim Biophys Acta. 2005;1715(1):37-48.

Wan SH, Huffman DH, Azarnoff DL, Hoogstraten B, Larsen WE. Pharmacokinetics of 1-beta-D-arabinofuranosylcytosine in humans. Cancer Res. 1974;34:392-7.

Zhang B, Lu Y, Chen J, Wu W. Effects of interior gelation on pharmacokinetics and biodistribution of liposomes encapsulating an anti-cancer drug cytarabine. J Biomed Nanotechnol. 2010;6:704-9.

Zimmerman CL. The disposition of cytosine arabinoside and its metabolite after single doses to rabbits. Biopharm Drug Dispos. 1990;11:121-9.

Additional References Evaluated

Goto T, Endo A. Dose- and stage-related sex difference in the incidence of cytosine arabinoside induced digit anomalies in the mouse fetus. Teratology. 1987;35:35-40. [Single dose data only.]

Kochhar DM, Penner JD, McDay JA. Limb development in mouse embryos. II. Reduction defects, cytotoxicity and inhibition of DNA synthesis produced by cytosine arabinoside. Teratology. 1978;18:71-92. [Single dose data only.]

Percy DH. Teratogenic effects of the pyrimidine analogues 5-iododeoxyuridine and cytosine arabinoside in late fetal mice and rats. Teratology. 1975;11:103-17. [Rats were dosed subcutaneously on GD18-21 and offspring sacrificed on PND10 and 20. NOAEL was 12.5 mg/kg and LOAEL was 25 mg/kg.]

Scott WJ, Ritter EJ, Wilson JG. Studies on induction of polydactyly in rats with cytosine arabinoside. Dev Biol. 1975;45:103-11. [100 mg/kg was the only dose level.]

Dabrafenib

CAS No.: 1195765-45-7

Rat NOAEL **Dose**	**Rat LOAEL** **Dose**	**Rat Findings**	**Rabbit NOAEL** **Dose**	**Rabbit LOAEL** **Dose**	**Rabbit Findings**	**Notes**

C_{max} **AUC**	**C_{max}** **AUC**		**C_{max}** **AUC**	**C_{max}** **AUC**		
20 mg/kg oral pcD1-17[a] (FDA, United States, p. 115) C_{max} = 1.17 µg/mL[b] $AUC_{(0-t)}$ = 4.10 µg·h/mL[b]	300 mg/kg oral pcD1-17[a] (FDA, United States, p. 115) C_{max} = 2.17 µg/mL[c] $AUC_{(0-t)}$ = 22.6 µg·h/mL[c]	cardiac interventricular septal defects; decrease in the number of corpora lutea, number of implants, and the number of live fetuses	No rabbit data found	No rabbit data found	None	

a. From a combined female fertility and embryofetal development toxicity study in which females were dosed from 2 weeks prior to mating to post-coitum D17. Cesarean sections were performed on post-coitum D21.

b. Actual values in plasma after 20 mg/kg oral dabrefenib for 24 days in rats (FDA, United States, p. 119): C_{max} = 1.17 µg/mL, $AUC_{(0-t)}$ = 4.10 µg·h/mL.

c. Actual values in plasma after 300 mg/kg oral dabrefenib for 24 days in rats (FDA, United States, p. 119: C_{max} = 2.17 µg/mL, $AUC_{(0-t)}$ = 22.6 µg·h/mL.

References

FDA, United States. Pharmacology Review NDA 202806 (25 Apr 2013).

Dasatinib

CAS No.: 302962-49-8

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Notes**
NOAEL not identified	2.5 mg/kg oral GD6-15 (FDA, United States, p. 225) C_{max} = 0.021 µg/mL[a] $AUC_{(0\text{-}8h)}$ = 0.105 µg·h/mL[a]	increased post-implantation loss and resorptions, decreased litter size; bent scapula or humerus	6 mg/kg oral GD7-19 (FDA, United States, p. 236) C_{max} = 0.227 µg/mL $AUC_{(0\text{-}inf)}$ = 0.834 µg·h/mL	LOAEL for MEFL not identified	None: findings in the definitive study were limited to an increase in skeletal variations (delays in ossifications); embryolethality observed in the DRF at 10 mg/kg was associated with severe maternal toxicity	

a. Actual values in plasma after 10 days (GD15) of 2.5 mg/kg oral dasatinib in pregnant Sprague Dawley rats (FDA, United States, p. 227): C_{max} = 0.021 µg/mL, $AUC_{(0\text{-}8h)}$ = 0.105 µg·h/mL.

b. Actual values in plasma after 13 days (GD19) of 6 mg/kg oral dasatinib in pregnant NZW rabbits (FDA, United States, p. 238): C_{max} = 0.227 µg/mL, AUC = 0.834 µg·h/mL.

References

FDA, United States. Pharmacology Review NDA 21986/22072 (28 Jun 2006).

Additional References Evaluated

Kassem MG, Ezzeldin E, Korashy HM, Mostafa GA. High-performance liquid chromatographic method for the determination of dasatinib in rabbit plasma using fluorescence detection and its application to a pharmacokinetic study. J Chromatogr B Analyt Technol Biomed Life Sci. 2013;939:73-9. [PK at 2.5 mg/kg was substantially different than reported in FDA, United States review: C_{max} = 0.459 µg/mL, AUC = 3.289 µg·h/mL]

Fluconazole

CAS No.: 86386-73-4

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
50 mg/kg oral [US label] C_{max} = 33.8 µg/mL[a] $AUC_{(0\text{-}inf)}$ = 380 µg·h/mL[b]	80 mg/kg oral [US label] C_{max} = 54 µg/mL[a] $AUC_{(0\text{-}inf)}$ = 608 µg·h/mL[b]	at ≥80 mg/kg: embryolethality, cleft palate, abnormal craniofacial ossification adactylia, brachygnathia [US Label, FDA, United States 1990a].	25 mg/kg oral [US Label, FDA, United States 1990a] C_{max} = 27 µg/mL[c] AUC = 521 µg·h/mL[d]	75 mg/kg oral [US Label, FDA, United States1990a] C_{max} = 81 µg/mL[c] AUC = 1563 µg·h/mL[d]	abortions (at maternally toxic dose)	400 mg C_{max} = 9.07 µg/mL[e] $AUC_{(0\text{-}24h)}$= 134.8 µg·h/mL[e]	NOAEL: rat C_{max} = 3.7 (33.8/9.07) AUC = 2.8 (380/134.8) rabbit C_{max} = 3.0 (27/9.07) AUC = 3.9 (521/134.8) LOAEL: rat	

							C_{max} = 6.0 (54/9.07) AUC = 4.5 (608/134.8) <u>rabbit</u> C_{max} = 8.9 (81/9.07) AUC = 11.6 (1563/134.8)	

a. Extrapolated from reported value after 20 mg/kg fluconazole oral single dose in rats (FDA, United States 1990a, p. 7): C_{max} = 13.5 µg/mL.

b. Extrapolated from reported value after 20 mg/kg fluconazole oral single dose in rats (Humphrey): $AUC_{(0\text{-}inf)}$ = 152 µg·h/mL.

c. Extrapolated from reported value after 10 mg/kg fluconazole oral single dose in rabbits (FDA, United States 1990a, p. 7): C_{max} = 10.8 µg/mL.

d. Calculated using plasma clearance value for rabbits (0.8 mL/min·kg, FDA, United States 1990a, p 8): AUC = Dose/Cl = (25 mg/kg)/(0.8 mL/min·kg)(1 h/60 min) = 521 µg·h/mL.

e. Actual value after 400 mg/day fluconazole oral single dose (FDA, United States 1990b, p. 7, 50-52): C_{max} = 9.07 µg/mL, $AUC_{(0\text{-}24h)}$ = 134.8 µg·h/mL. Data are also available after 14 days of repeated administration, which shows significant drug accumulation. C_{max} = 18.89 µg/mL, $AUC_{(0\text{-}24h)}$ = 349.9 µg·h/mL. Since PK was not available for repeated administration in animals, the single-dose human PK data were used for margin calculations.

References

Humphrey MJ, Jevons S, Tarbit MH. Pharmacokinetic evaluation of UK-49,858, a metabolically stable triazole antifungal drug, in animals and humans. Antimicrob Agents Chemother. 1985;28:648-53.

FDA, United States. Pharmacology Review NDA 019949 (26 Jan 1990a), p. 7, 13.

FDA, United States. Clinical Pharmacology Review NDA 019949 (17 Apr 1990b), p. 7, 50 – 52.

US label Diflucan.

Additional References Evaluated

Brammer KW, Farrow PR, Faulkner JK. Pharmacokinetics and tissue penetration of fluconazole in humans. Rev Infect Dis. 1990;12 Suppl 3:S318-26 .

Pittrow L, Penk A. Plasma and tissue concentrations of fluconazole and their correlation to breakpoints. Mycoses. 1997;40:25-32.

5-Fluorouracil

CAS No.: 51-21-8

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Huma** **LOAEL/Human**	**Notes**
10 mg/kg single dose IP GD9 [Wilson] C_{max} = 2.6 µg/mL[a] AUC = 3.89 µg·h/mL[a]	15 mg/kg single dose IP GD9 [Wilson] C_{max} = 3.87 µg/mL[a] AUC = 5.83 µg·h/mL[a]	Wilson: 15 mg/kg: malformations, embryofetal lethality Kuwagata: ≥17 mg/kg: micro-/anophthalmos, craniofacial defect, hydrocephaly, brain hernia	NOAEL not identified [DeSesso]	40 mg/kg SC GD12 [DeSesso] C_{max} = 111 µg/mL[b] AUC = 11 µg·h/mL[b]	limb anomalies 85% of term fetuses	500 mg/m^2 (400 – 600 mg/m^2) in a variety of dosing regimens, including doses up to 3000 mg/m^2 CIV for 46 hours[c] C_{max} = 29 µg/mL[d] AUC = 11.5 µg·h/mL[d]	NOAEL: rat C_{max} = 0.09 (2.6/29) AUC = 0.3 (3.89/11.5) rabbit no NOAEL identified LOAEL: rat C_{max} = 0.1 (3.87/29) AUC = 0.5 (5.83/11.5) rabbit C_{max} = 3.8 (111/29)	• note: half-life is very short (most patients have undetectable 5-FU levels in plasma 90 min after IV) and PK is nonlinear • 5FU is a pro-drug: thymidylate synthetase inhibitor is 5FdUMP

							AUC = 1.0 (11/11.5)	• MW = 130.077

a. Extrapolated from reported value after 30 mg/kg 5FU intraperitoneal single dose in Sprague Dawley rats (Zhang): C_{max} = 7.74 µg/mL, AUC = 11.66 µg·h/mL.

b. Extrapolated from reported value after 20 mg/kg 5FU intravenous single dose in rabbits (Kar): C_{max} = 0.427 µmol/mL (55.5 µg/mL), AUC = 2.535 µmol·min/mL (5.5 µg·h/mL).

c. The dose of 500 mg/m^2 IV bolus was used for comparison although higher doses (e.g., ~1500 mg/m^2/day CIV) are used. Very low margins were calculated and using higher human doses would make them even lower.

d. Extrapolated from reported value after 14.7 mg/kg (544 mg/m^2) 5FU oral single dose (Schaaf): C_{max} = 32 µg/mL from visual inspection of graph, AUC = 12.55 µg·h/mL. Data are also available after a 370 mg/m^2 dose (Bocci): C_{max} = 48.41 µg/mL, AUC = 13.61 µg·h/mL.

References

DeSesso JM, Scialli AR, Goeringer GC. Teratology. 1995;51:172 (abstract)

Kar R, Cohen RA, Terem TM, Nahabedian MY, Wile AG. Pharmacokinetics of 5-fluorouracil in rabbits in experimental regional chemotherapy. Cancer Res. 1986;46:4491-5.

Kuwagata M, Takashima H, Nagao T. A comparison of the *in vivo* and *in vitro* response of rat embryos to 5-fluorouracil. J Vet Med Sci. 1998;60:93-9.

Schaaf LJ, Dobbs BR, Edwards IR, Perrier DG. Nonlinear pharmacokinetic characteristics of 5-fluorouracil (5-FU) in colorectal cancer patients. Eur J Clin Pharmacol. 1987;32:411-8.

Wilson JG. Teratogenic interaction of chemical agents in the rat. J Pharmacol Exp Therapeut. 1964;144:429-36.

Zhang C, Li G, Wang Y, Cui F, Zhang J, Huang Q. Preparation and characterization of 5-fluorouracil-loaded PLLA-PEG/PEG nanoparticles by a novel supercritical CO_2 technique. Int J Pharm. 2012;436:272-81.

Additional References Evaluated

Bocci G, Danesi R, Di Paolo AD, Innocenti F, Allegrini G, Falcone A, et al. Comparative pharmacokinetic analysis of 5-fluorouracil and its major metabolite 5-fluoro-5,6-dihydrouracil after conventional and reduced test dose in cancer patients. Clin Cancer Res. 2000;6:3032-7

Chaube S, Murphy ML. The teratogenic effects of the recent drugs active in cancer chemotherapy. In: Woolham, DHM, editor. Advances in Teratology, Volume 3. New York: Academic Press. 1968. pp. 180-237. [no incidence were provided, but confirms malformations in rats as detailed by Kuwagata]

Huang Y, Wei Y, Yang H, Pi C, Liu H, Ye Y, Zhao L. A 5-fluorouracil-loaded floating gastroretentive hollow microsphere: development, pharmacokinetic in rabbits, and biodistribution in tumor-bearing mice. Drug Des Devel Ther. 2016;10:997-1008. [no systemic PK, only oral after 50 mg/kg dose; C_{max} = 2.55µg/mL, AUC = 5.82 µg·h/mL]

Shuey DL, Lau C, Logsdon TR, Zucker RM, Elstein KH, Narotsky MG, et al. Biologically based dose-response modeling in developmental toxicology: biochemical and cellular sequelae of 5-fluorouracil exposure in the developing rat. Toxicol Appl Pharmacol. 1994a;126:129-44. [malformations were seen at 35 and 40 mg/kg administered SC on GD14; MEFL effects were seen at lower doses in other studies]

Shuey DL, Buckalew AR, Wilke TS, Rogers JM, Abbott BD. Early events following maternal exposure to 5-fluorouracil lead to dysmorphology in cultured embryonic tissues. Teratology. 1994b;50:379-86. [10 – 40 mg/kg SC on GD14, all malformations studied in explants]

US Adrucil label. [confirms malformations in rats as detailed by Kuwagata]

Zhao B, Zhao XL. [Pharmacokinetic studies on 5-fluorouracil and its metabolite in rabbits by high pressure liquid chromatography]. Zhongguo Yao Li Xue Bao (Acta Pharmacol Sin). 1988;9:275-8. Chinese. [PK after 170 mg/kg IV dose, which would require greater extrapolation than data from Kar]

Hydroxyurea

CAS No.: 127-07-1

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings[a]**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
100 mg/kg IP GD9-12 [Wilson] C_{max} = 47.3 µg/mL[b] AUC not available	137 mg/kg IP GD9-12 [Wilson] C_{max} = 80.6 µg/mL[b] AUC not available	embryofetal lethality, ocular and cerebral malformations	NOAEL not identified PK not available	30 mg/kg [US label] PK not available	650 mg/kg SC GD12 [DeSesso 1990]: cleft lip, cleft palate, reduction deformities of limbs and tail 750 mg/kg SC GD12 [DeSesso 1977]: skull and facial anomalies as well as severe reduction	<u>oral for oncology indications:</u> 80 mg/kg Q3D, 20 – 30 mg/kg/day <u>oral for sickle cell anemia</u> 15 – 35 mg/kg/day (555 – 1295 mg/m^2) C_{max} = 52 µg/mL[c] $AUC_{(0\text{-}inf)}$ = 184 µg·h/mL[c]	NOAEL: <u>rat</u> C_{max} = 0.9 (47.3/52) C_{max} dose = 2.9 (100/35)[d] AUC = 0.5 (600/1295)[e] <u>rabbit</u> NOAEL not identified LOAEL: <u>rat</u> C_{max} = 1.6 (80.6/52)	• PK is nonlinear with short half-life (15 min in rats, 2 – 4 h • in humans) • MW = 76.05g/mol • PK after IP and IV is similar (Wilson) • bioavailability is 70 – 80% in rats and humans,

					deformities of all limbs		C_{max} dose = 3.9 (137/35)[d] AUC = 0.6 (822/1295)[e] <u>rabbit</u>[f] C_{max} = 0.9 (30/35) AUC = 0.3 (360/1295)	respectively (Beckloff) • no robust data for adverse human pregnancy outcomes

a. US label states that "Hydroxyurea is embryotoxic and causes fetal malformations (partially ossified cranial bones, absence of eye sockets, hydrocephaly, bipartite sternebrae, missing lumbar vertebrae) at 180 mg/kg/day in rats and 30 mg/kg/day in rabbits", but it is not clear which effects are in which species. Thus, 30 mg/kg is accepted as the LOAEL, but the findings are listed from publications with rabbits with SC doses of 650 and 750 mg/kg.

b. Actual values after 100 and 137 mg/kg hydroxyurea IP doses in pregnant Wistar rats (Wilson): C_{max} = 47.3 at 100 mg/kg and 80.6 µg/mL at 137 mg/kg.

c. Extrapolated from reported value after 1000 mg (16.7 mg/kg) hydroxyurea oral single dose (MHRA): C_{max} = 24.6 µg/mL, $AUC_{(0\text{-inf})}$ = 87.79 µg·h/mL. The dose for margin calculations was chosen to be 35 mg/kg/day. Although higher intermittent doses are used for oncology indications, the dose for sickle cell anemia is believed to be more relevant for assessing risk of developmental toxicity. As summarized in the table below, other human PK data are also available.

d. Although rat C_{max} data are available, this was after IP administration whereas the human data is after oral administration. Thus, in the absence of more direct PK comparisons, the estimated ratio based on mg/kg dose is also provided.

e. In the absence of rat AUC data, AUC ratio was based on mg/m^2 dose ratio.

f. In the absence of rabbit PK data, C_{max} ratio was based on mg/kg dose ratio and AUC was based on mg/m^2 dose ratio.

References

DeSesso JM, Jordan RL. Drug-induced limb dysplasias in fetal rabbits. Teratology. 1977;15:199-211.

DeSesso JM, Goeringer GC. Ethoxyquin and nordihydroguaiaretic acid reduce hydroxyurea developmental toxicity. Reprod Toxicol. 1990;4:267-75.

MHRA Public Assessment Report PL 10880/128-9, page 48.

US label Hydrea and Droxea.

Wilson JG, Scott WJ, Ritter EJ, Fradkin R. Comparative distribution and embryotoxicity of hydroxyurea in pregnant rats and rhesus monkeys. Teratology. 1975;11:169-78.

Additional References Evaluated

Beckloff GL, Lerner HJ, Frost D, Russo-Alesi FM, Gitomer S. Hydroxyurea (NSC-32065) in biologic fluids: dose-concentration relationship. Cancer Chemother Rep. 1965;48:57-8. [PK data in cancer subjects, no AUC]

Charache S, Dover GJ, Moore RD, Eckert S, Ballas SK, Koshy M, et al. Hydroxyurea: effects on hemoglobin F production in patients with sickle cell anemia. Blood. 1992;79:2555-65. [PK data in sickle cell anemia subjects]

Chaube S, Murphy ML. The effects of hydroxyurea and related compounds on the rat fetus. Cancer Res. 1966;26:1448-57. [effects of single and repeated IP doses ≥125 mg/kg]

Gwilt PR, Tracewell WG. Pharmacokinetics and pharmacodynamics of hydroxyurea. Clin Pharmacokinet. 1998;34:347-58. [review article of PK publications]

Millicovsky G, DeSesso JM. Cardiovascular alterations in rabbit embryos *in situ* after a teratogenic dose of hydroxyurea: an *in vivo* microscopic study. Teratology. 1980;22:115-24. [effects on *ex vivo* embryos after 500 and 750 mg/kg to does on GD12]

Philips FS, Sternberg SS, Schwartz HS, Cronin AP, Sodergren JE, Vidal PM. Hydroxyurea. I. Acute cell death in proliferating tissues in rats. Cancer Res. 1967;27:61-75. [C_{max} after 46, 184, and 1840 mg/kg IV dose, nonlinear PK]

Tracewell WG, Vaughan WP, Gwilt PR. Nonlinear disposition of hydroxyurea. J Pharm Sci. 1994;83:1060-1. [formal PK analysis of Philips data]

Villani P, Maserati R, Regazzi MB, Giacchino R, Lori F. Pharmacokinetics of hydroxyurea in patients infected with human immunodeficiency virus type I. J Clin Pharmacol. 1996;36:117-21. [PK in HIV subjects]

Human Pharmacokinetic Data

Reference	Population	Dose	Route	C_{max} (µg/mL)	AUC (µg·h/ml)	Notes

Charache	sickle cell anemia	25 mg/kg	oral	19	$AUC_{(0\text{-}6)}$ = 1216	AUC units were published as "µg mL/min", value seems wrong since (C_{max} ☐ 6 h = 114 µg·h/mL)
Villani	HIV	mean 7.6 mg/kg BID	oral	0.135 nmol/L = 0.135 µmol/mL = 10.3 µg/mL	$AUC_{(0\text{-}12h)}$ = 540 µmol·h/L = 41.1 µg·h/mL; $AUC_{(0\text{-}24h)}$ = 82.1 µg·h/mL	
MHRA review	not stated – BE study	1000 mg (16.6 mg/kg)	oral	24.6	$AUC_{(0\text{-}inf)}$ = 87.79 µg·h/mL	use these values
Beckloff	cancer	20 mg/kg	oral	20.7	—	
		80 mg/kg	oral	128.1	—	

Ibrutinib

CAS No.: 936563-96-1

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL[a]** **Dose** **C_{max}** **AUC**	**Rabbit Findings[b]**	**Notes**
40 mg/kg oral GD6-17 (FDA, United States, p. 126) C_{max} = 1.31 µg/mL[c]	80 mg/kg oral GD6-17 (FDA, United States, p. 126) C_{max} = 2.627 µg/mL[d]	malformations including dextrocardia, retroesophageal aortic arch, persistent truncus arteriosus, right-sided aortic arch, and interrupted aortic arch;	30 mg/kg oral GD7-19 (FDA, United States, p. 135)	100 mg/kg oral GD7-19 (FDA, United States, p. 135)[c] C_{max} = 1.83 µg/mL[f]	increased pre- and post-implantation loss (increased early resorptions), decreased viable fetuses, abortions	

$AUC_{(0\text{-}24h)}$ = 5.348 µg·h/mL[c]	$AUC_{(0\text{-}24h)}$ = 13.729 µg·h/mL[d]	increased post-implantation loss (increased early resorptions), decreased viable fetuses	C_{max} = 0.311 µg/mL[e] AUC = 1.31 µg·h/mL[e]	AUC = 21.00 µg·h/mL[f]		

a. The LOAEL for MEFL was a maternally toxic dose as indicated by increased mortality and abortions, clinical signs, and reductions in body weight and food consumption.

b. This was a dose range finding study with limited numbers of animals (n=6) and fetal evaluations limited to external morphology. It is thus unknown if there were visceral or skeletal alterations.

c. Actual values in plasma after 11 doses of 40 mg/kg oral ibrutinib in pregnant rats (FDA, United States, p. 130): C_{max} = 1.31 µg/mL, $AUC_{(0\text{-}24h)}$ = 5.348 µg·h/mL.

d. Actual values in plasma after 11 doses of 100 mg/kg oral ibrutinib in pregnant rats (FDA, United States, p. 130): C_{max} = 2.627 µg/mL, $AUC_{(0\text{-}24h)}$ = 13.729 µg·h/mL.

e. Actual values in plasma after 13 doses of 30 mg/kg oral ibrutinib in pregnant rabbits (FDA, United States, p. 136): C_{max} = 0.311 µg/mL, AUC = 1.31 µg·h/mL.

f. Actual values in plasma after 13 doses of 100 mg/kg oral ibrutinib in pregnant rabbits (FDA, United States, p. 136): C_{max} = 1.83 µg/mL, AUC = 21.00 µg·h/mL.

References

FDA, United States. Pharmacology Review NDA 020552 (21 Aug 2013).

Ibuprofen

CAS No.: 15687-27-1

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL[c]** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
180 mg/kg oral GD1-20 [Adams] C_{max} = 205 µg/mL[a] AUC = 597 µg·h/mL[a]	oral GD1-20: No LOAEL idenitifed [Adams] oral GD9-10: 300 mg/kg [Cappon 2003][b] <u>at 300 mg/kg</u> C_{max} = 341 µg/mL[a] AUC = 995 µg·h/mL[a]	GD1-20: None GD9-10: ventricular septal defects	60 mg/kg oral GD1-29 [Adams] C_{max} = 26.6 µg/mL[d] $AUC_{(0\text{-}inf)}$ = 80.5 µg·h/mL[d] 500 mg/kg oral GD9-11 [Cappon 2003][b] C_{max} = 222 µg/mL[d] $AUC_{(0\text{-}inf)}$ = 671 µg·h/mL[d]	No LOAEL identified	None	Maximum dose is 800 mg QID, 3200 mg/day (13.3 mg/kg/dose, 53 mg/kg/day) [US label] C_{max} = 59 µg/mL[e] AUC = 839 µg·h/mL[e]	NOAEL: <u>rat</u> C_{max} = 3.4 (205/59.7) AUC = 0.7 (597/839) <u>rabbit[c]</u> <u>60 mg/kg NOAEL</u> C_{max} = 0.5 (26.6/59) AUC = 0.1 (80.5/839) <u>500 mg/kg NOAEL</u> C_{max} = 3.8 (222/59)	

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL[c]** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
							AUC = 0.8 (671/839) LOAEL: rat C_{max} = 5.8 (341/59) AUC = 1.2 (995/839) rabbit no LOAEL	

a. Extrapolated from reported value after 25 mg/kg ibuprofen (suspension) single oral dose in Sprague Dawley rats (You): C_{max} = 28.4 µg/mL, $AUC_{(0-inf)}$= 4971.3 µg·min/mL (82.9 µg·h/mL). Note that different data (5- to 7-fold lower values) are available from the same laboratory at 25 mg/kg where the only difference appears to be that ibuprofen was administered in hard gelatin capsules versus a suspension (Newa): C_{max} = 5.32 µg/mL, AUC = 12.41 µg·h/mL.

b. To enhance detection of VSD and midline defects (seen in humans and with other NSAIDS), exposure was limited to the sensitive period of cardiovascular development and midline closure (i.e., GD9-10 in rats and GD9-11 in rabbits). By limiting the exposure period, maternal GI toxicity was reduced, allowing for the administration of higher doses.

c. Two values are included for the rabbit NOAEL since neither study design was ideal for assessing the risk of developmental toxicity according to current conventions. The study by Adams dosed rabbits on GD1-29 instead of the conventional GD7-19, whereas the study by Cappon dosed rabbits only on GD9-11 to enhance detection of VSD and midline defects.

d. Extrapolated from reported value after 56 mg/kg ibuprofen single oral dose in male New Zealand White rabbits (Kondal): C_{max} = 24.85 µg/mL, $AUC_{(0\text{-}inf)}$ = 75.14 µg·h/mL.

e. Extrapolated from reported value after 14.8 mg/kg (mean) ibuprofen single oral dose (Konstan): C_{max} = 65.5 µg/mL, $AUC_{(0\text{-}inf)}$ = 14.0 mg·min/mL (233 µg·h/mL). Note the C_{max} was multiplied by 0.9 (13.3/14.8) to give the extrapolated C_{max}. The C_{max} after a single dose likely represents the C_{max} at steady state since the half life is short (approximately 1.8 to 2 hours [US label]) and little accumulation is expected using the equation: accumulation = $1/(1 - e^{-k \cdot tau})$, where k = 0.693/t½ with t½ = 2 hours and tau = 6 hours (yielding an accumulation fatcor of 1.1). The AUC was multiplied by 4 to get the daily AUC for QID dosing (at 59.2 mg/kg/day), and then by 0.9 to give the extrapolated AUC for 53 mg/kg/day.

References

Adams SS, Bough RG, Cliffe EE, et al. Absorption, distribution and toxicity of ibuprofen. Toxicol Appl Pharmacol. 1969;15:310-30.

Cappon GD, Cook JC, Hurtt ME. Relationship between cyclooxygenase 1 and 2 selective inhibitors and fetal development when administered to rats and rabbits during the sensitive periods for heart development and midline closure. Birth Defects Res B Dev Reprod Toxicol. 2003;68:47-56.

Kondal A1, Garg SK. Influence of acidic beverage (Coca-Cola) on pharmacokinetics of ibuprofen in healthy rabbits. Indian J Exp Biol. 2003;41:1322-4.

Konstan MW, Krenicky JE, Finney MR, Kirchner HL, Hilliard KA, Hilliard JB, et al. Effect of ibuprofen on neutrophil migration *in vivo* in cystic fibrosis and healthy subjects J Pharmacol Exp Ther. 2003;306:1086-91.

Newa M, Bhandari KH, Kim JO, Im JS, Kim JA, Yoo BK, et al.. Enhancement of solubility, dissolution and bioavailability of ibuprofen in solid dispersion systems. Chem Pharm Bull (Tokyo). 2008;56:569-74.

US Motrin label.

You X, Xing Q, Tuo J, Song W, Zeng Y, Hu H. Optimizing surfactant content to improve oral bioavailability of ibuprofen in microemulsions: just enough or more than enough? Int J Pharm. 2014;471:276-84.

Additonal References Evaluated

Cappon GD, Fleeman TL, Cook JC, Hurtt ME. Combined treatment potentiates the developmental toxicity of ibuprofen and acetazolamide in rats. Drug Chem Toxicol. 2005;28:409-21. [confirmed VSD findings in Cappon 2003]

Cook JC, Jacobson CF, Gao F, Tassinari MS, Hurtt ME, DeSesso JM. Analysis of the nonsteroidal anti-inflammatory drug literature for potential developmental toxicity in rats and rabbits. Birth Defects Res B Dev Reprod Toxicol. 2003;68:5-26. [review article: captured data from Adams]

Malm H, Borisch C. Analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, and antigout medications. In: Schaefer C, Peters P, Miller RK, editors. Drugs during pregnancy and lactation: treatment options and risk assessment (Third Edition). Boston: Academic Press; 2015. p. 27-58. [mainly human data]

Imatinib

CAS No.: 152459-95-5 (220127-57-1 as mesilate)

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Notes**
30 mg/kg oral GD6-15 (FDA, United States, p. 69) C_{max} = 3.57 µg/mL[a] AUC = 39.28 µg·h/mL[a]	100 mg/kg oral GD6-15 (FDA, United States, p. 69) C_{max} = 12.14 µg/mL[b] AUC = 142.55 µg·h/mL[b]	exencephaly and/or protruding tongue, encephalocele, absent frontal or parietal bones; increased post-implantation loss, decreased live fetuses	60 mg/kg oral GD7-19 (FDA, United States, p. 72) C_{max} = 53.06 µg/mL[c] AUC = 699.8 µg·h/mL[c]	LOAEL not identified	None	

a. Interpolated from reported values in plasma after 15 and 50 mg/kg imatinib oral single dose in female rats (FDA, United States, p. 24): at 15 mg/kg, C_{max} = 1.69 µg/mL, $AUC_{(0\text{-}24h)}$ = 15.40 µg·h/mL; at 50 mg/kg, C_{max} = 6.07 µg/mL, $AUC_{(0\text{-}24h)}$ = 71.276 µg·h/mL.

b. Extrapolated from reported value in plasma after 50 mg/kg imatinib oral single dose in female rats (FDA, United States, p. 24): C_{max} = 6.07 µg/mL, $AUC_{(0\text{-}24h)}$ = 71.276 µg·h/mL.

c. Reported value after 60 mg/kg oral imatinib single dose in rabbits species (FDA, United States, p. 26): C_{max} = 53.06 µg/mL, $AUC_{(0\text{-}24h)}$ = 699.8 µg·h/mL.

References

FDA, United States. Pharmacology Review NDA 021335 (04 May 2001).

Isotretinoin (13-*cis*-retinoic acid)

CAS No.: 4759-48-2

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
50 mg/kg oral dose on GD10 [Tembe] C_{max} = 0.9 µg/mL[a] $AUC_{(0\text{-}10h)}$ = 4.8 µg·h/mL[a]	100 mg/kg oral dose on GD10 [Tembe] C_{max} = 1.8 µg/mL[a] $AUC_{(0\text{-}10h)}$ = 9.6 µg·h/mL[a]	LOAEL: microtia and talipes. Higher doses: microcephaly, anotia, exopthalmos, protruding tongue, cleft lip, mandibular hypoplasia, cleft palate, overdeveloped papillae, analatresia, spina bifide,deformed tail, and acaudate; increased resorptions	3 mg/kg oral GD8-11 [Eckhoff] C_{max} = 0.95 µg/mL[b] AUC = 12.2 µg·h/mL[b]	15 mg/kg oral GD8-11 [Eckhoff] C_{max} = 3.1 µg/mL[c] AUC = 49.1 µg·h/mL[c]	increased resorptions, malformations including eye defects, tail defects, cardiomegaly, skin tag on face	0.5 mg/kg BID (1 mg/kg/day) C_{max} = 0.32 µg/mL[d] AUC = 7.52 µg·h/mL[d]	NOAEL: <u>rat</u> C_{max} = 2.8 (0.9/0.32) AUC = 0.6 (4.8/7.52) <u>rabbit</u> C_{max} = 3.0 (0.95/0.32) AUC = 1.6 (12.2/7.52) LOAEL: <u>rat</u> C_{max} = 5.6 (1.8/0.32)	

Rat NOAEL Dose C_{max} AUC	Rat LOAEL Dose C_{max} AUC	Rat Findings	Rabbit NOAEL Dose C_{max} AUC	Rabbit LOAEL Dose C_{max} AUC	Rabbit Findings	Human Dose C_{max} AUC	Margins NOAEL/Human LOAEL/Human	Notes
							AUC = 1.3 (9.6/7.52) <u>rabbit</u> C_{max} = 9.7 (3.1/0.32) AUC = 6.5 (49.1/7.52)	

a. Extrapolated from reported value after 500 mg/kg isotretinoin oral single dose in Wistar rats (Tembe): C_{max} = 9.07 µg/mL, $AUC_{(0\text{-}10h)}$ = 47.9 µg·h/mL.

b. Actual values after 3 mg/kg isotretinoin oral single dose in New Zealand White rabbits (Eckhoff): C_{max} = 0.952 µg/mL, AUC = 12.2 µg·h/mL.

c. Actual values after 15 mg/kg isotretinoin oral single dose in New Zealand White rabbits (Eckhoff): C_{max} = 3.099 µg/mL, $AUC_{(0\text{-}10h)}$ = 49.1 µg·h/mL.

d. Extrapolated from reported value after 80 mg (1.33 mg/kg) isotretinoin oral single dose with food (US label): C_{max} = 0.86 µg/mL, $AUC_{(0\text{-}10h)}$ = 10.0 µg·h/mL. The C_{max} extrapolation was based on a 0.5 mg/kg dose, whereas the AUC extrapolation was based on the daily dose of 1 mg/kg/day. PK data are also available while fasting, but the higher values from the fed state were used for margin calculations: C_{max} = 0.3 µg/mL, AUC = 3.7 µg·h/mL.

References

Eckhoff C, Chari S, Kromka M, Staudner H, Juhasz L, Rudiger H, et al. Teratogenicity and transplacental pharmacokinetics of 13-cis-retinoic acid in rabbits. Toxicol Appl Pharmacol. 1994;125:34-41.

Tembe EA, Honeywell R, Buss NE, Renwick AG. All-trans-retinoic acid in maternal plasma and teratogenicity in rats and rabbits. Toxicol Appl Pharmacol. 1996;141:456-72.

US label isotretinoin.

Methotrexate

CAS No.: 59-05-2

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL (Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose[c]** **C_{max}** **AUC**	**NOAEL** **Margins**	**Notes**
NOAEL not identified	0.1 mg/kg IP GD9 [Jordan, Woo] C_{max} = 0.21 µg/mL[a] AUC = 0.067 µg·h/mL[a]	resorbed litters, malformations	NOAEL not identified	0.3 mg/kg IV GD10 [Jordan] C_{max} = 1.58 µg/mL[b] AUC = 0.61 µg·h/mL[b]	hydrocephalus, microphthalmia, cleft lip and palate, micrognathia, dysplastic sacral and caudal vertebrate, phocomelia, hemimelia, syndactyly, and ectrodactyly; embryolethality, resorptions	psoriasis: 10 – 25 mg Q7D (5.9 – 14.7 mg/m^2) oral or IV[c] ALL: induction – 3.3 mg/m^2 daily; maintenance – 15 mg/m^2 oral twice/week choriocarcinoma: 15 – 30 mg oral QD□□ 5 (8.8 – 17.6 mg/m^2) lymphoma: 10 – 25 mg QD□□ 4-8 oral (5.9 – 14.7 mg/m^2); 0.625 – 2.5	NOAEL: rat NOAEL not identified rabbit NOAEL not identified LOAEL: rat C_{max} = 0.1 (0.21/2.14)	Note: animal MEFL data is after single dose, so margins would likely be eve n lower if dosed throughout organogenesis

						mg/kg (23 – 92.5 mg/m^2) mycosis fungoides: 5 – 50 mg Q7D oral (2.9 – 29 mg/m^2) RA: 7.5 mg Q7D oral (4.4 mg/m^2) C_{max} = 2.14 µg/mL[d] AUC = 3.28 µg·h/mL[d]	AUC = 0.02 (0.067/3.28) rabbit C_{max} = 0.7 (1.58/2.14) AUC = 0.2 (0.61/3.28)	

a. Extrapolated from reported value after 0.31 mg/kg methotrexate intravenous single dose in Wistar rats (Scheufler 1982): C_0 = 0.64 µg/mL, $AUC_{(0.1\text{-}4h)}$ = 0.207 µg·h/mL. Other PK data are also available as shown in the table below. The data from Scheufler 1982 were chosen for margin calculations because it required the least degree of extrapolation in the same strain as the teratology study.

b. Extrapolated from reported value after 1.33 mg/kg methotrexate intravenous single dose in male rabbits (Iven): C_{max} = 7 µg/mL, AUC = 2.72 µg·h/mL. Data are also available after a 10 mg/kg methotrexate intravenous single dose in female New Zealand White rabbits (Stagni): C_{max} = 74 µg/mL, AUC = 31.4 µg·h/mL. The data from Iven were chosen for margin calculations because it required the least degree of extrapolation to the dose in the teratology study.

c. As noted there is a wide variety of doses, schedules, and routes used in a variety of indications (US label). An intravenous dose of 25 mg (14.7 mg/m^2) in psoriasis was chosen for PK margin comparisons since this was the highest dose in a non-oncology indication and would also provide a higher exposure than a 50 mg (29 mg/m^2) oral dose (mycosis fungoides) since oral bioavailability is only ~40%.

d. Extrapolated to 14.7 mg/m^2 f rom reported value after 30 mg/m^2 methotrexate intravenous single dose (Campbell): C_{max} = 4.37 µg/mL from visual inspection of graph, $AUC_{(0\text{-}inf)}$ = 6.69 µg·h/mL. Oral data are also available (Campbell): C_{max} = 0.50 µg /mL from visual inspection of graph, $AUC_{(0\text{-}inf)}$ = 2.34µg·h/mL.

References

Campbell MA, Perrier DG, Dorr RT, Alberts DS, Finley PR. Methotrexate: bioavailability and pharmacokinetics. Cancer Treat Rep. 1985;69:833-8.

Iven H, Brasch H, Engster J. Pharmacokinetics of methotrexate and 7-hydroxy-methotrexate in rabbits. Cancer Chemother Pharmacol. 1985;15:115-20.

Jordan RL, Wilson JG, Schumacher HJ. Embryotoxicity of the folate antagonist methotrexate in rats and rabbits. Teratology. 1977;15:73-9.

Scheufler E. Evidence of nonlinear pharmacokinetics of methotrexate in the rat. Pharmacology. 1982;25:51-6.

US label methotrexate.

Woo DC, McClain RM, Hoar RM. Potentiation of methotrexate embryolethality by aspirin in rats. Teratology. 1978;17:37-41.

Additional References Evaluated

Berry CL. Transient inhibition of DNA synthesis by methotrexate, in the rat embryo and foetus. J Embryol Exp Morphol. 1971;26:469-74. [increased resoprtions at ≥1 mg/kg]

Hyoun SC, Običan SG, Scialli AR. Teratogen update: methotrexate. Birth Defects Res A Clin Mol Teratol. 2012;94:187-207. [review article]

Kim MM, Lee SH, Lee MG, Hwang SJ, Kim CK. Pharmacokinetics of methotrexate after intravenous and intramuscular injection of methotrexate-bearing positively charged liposomes to rats. Biopharm Drug Dispos. 1995;16:279-93. [PK in Sprague Dawley rats at 4 mg/kg dose]

Scheufler E, Zetler G, Iven H. Pharmacokinetics and organ distribution of methotrexate in the rat. Pharmacology. 1981;23:75-81. [PK only at 31 mg/kg dose]

Stagni G, Shukla C. Pharmacokinetics of methotrexate in rabbit skin and plasma after iv-bolus and iontophoretic administrations. J Control Release. 2003;93:283-92. [PK only at 10 mg/kg dose]

Wilson JG, Scott WJ, Ritter EJ, Fradkin R. Comparative distribution and embryotoxicity of methotrexate in pregnant rats and rhesus monkeys. Teratology. 1979;19:71-9. [no AUC data, only concentrations at 0.25 hours]

Rat Pharmacokinetic Data

Reference	Dose (mg/kg)	Route	Strain	C_{max} (µg/mL)	AUC (µg·h/mL)	Notes
Wilson	0.3	IV	Wistar	0.40	—	C_0 was estimated from graph since 1st timepoint was 0.25 hours
Scheufler 1981	31	IV	Wistar	177	$AUC_{(0\text{-inf})}$ = 38.4	C_{max} is C_0
Scheufler 1982	0.31	IV	Wistar	0.64	$AUC_{(0.1\text{-}4h)}$ = 0.207	
Kim	4.0	IV	Sprague Dawley	40	$AUC_{(0\text{-inf})}$ = 2.88	C_{max} was from visual inspection of graph, AUC was 173 µg·min/mL

Pazopanib

CAS No.: 444731-52-6

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Notes**
1 mg/kg oral GD6-17 (FDA, United States, p. 218) C_{max} = 3.47 µg/mL[a] AUC = 0.028 µg·h/mL[a]	3 mg/kg oral GD6-17 (FDA, United States, p.218) C_{max} = 10.4 µg/mL[a] AUC = 0.083 µg·h/mL[a]	malformations in the great vessels, missing innominate artery	3 mg/kg oral GD7-19 (FDA, United States, p. 225) C_{max} = 0.130 µg/mL[b] $AUC_{(0-t)}$ = 0.517 µg·h/mL[c]	10 mg/kg oral GD7-19 (FDA, United States, p. 225) C_{max} = 1.063 µg/mL[d] $AUC_{(0-t)}$ = 1.723 µg·h/mL[d]	increased post-implantation loss	

a. Extrapolated or actual reported value in plasma after 3 mg/kg oral pazopanib for 28 days to Sprague Dawley rats (FDA, United States, p. 249): C_{max} = 10.4 µg/mL, AUC = 83 µg·h/L (0.083 µg·h/mL).

b. Actual values in plasma after 3 mg/kg pazopanib in rabbits (FDA, United States, p. 227): C_{max} = 0.130 µg/mL.

c. Extrapolated from reported value after 10 mg/kg pazopanib to rabbits (FDA, United States, p. 227): $AUC_{(0-t)}$ = 1.723 µg·h/mL.

d. Actual values in plasma after 10 mg/kg pazopanib in rabbits (FDA, United States, p. 227): C_{max} = 1.063 µg/mL, $AUC_{(0-t)}$ = 1.723 µg·h/mL.

References

FDA, United States. Pharmacology Review NDA 022456 (18 Sep 2009).

Additional References Evaluated

US Label Votrient.

Phenytoin

CAS No.: 57-41-0

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
150 mg/kg oral GD6-15 [Kim] C_{max} = 13.4 µg/mL[a] AUC = 205 µg·h/mL[a]	300 mg/kg oral GD6-15 [Kim] C_{max} = 26.8 µg/mL[a] AUC = 410 µg·h/mL[a]	external findings (protruding tongue, meningoencepha-locele, domed head, anasarca, and limb hyperflexion), skeletal malformation (short rib)	50 mg/kg oral GD7-18 [McClain] C_{max} = 27 µg/mL[b] $AUC_{(0-24h)}$ = 193 µg·h/mL[c]	75 mg/kg oral GD7-18 [McClain] C_{max} = 34 µg/mL[d] $AUC_{(0-24h)}$ = 290 µg·h/mL[c]	open eyes, cleft palate, and limb abnormalities that included shortened and curved long bones, pes caves, syndactyly	up to 625 mg/day oral solution[e] C_{max} = 14.5 µg/mL[f] AUC = 291 µg·h/mL[g]	NOAEL: rat C_{max} = 0.9 (13.4/14.5) AUC = 0.7 (205/291) rabbit C_{max} = 1.9 (27/14.5) AUC = 0.7 (193/291) LOAEL: rat	

							C_{max} = 1.8 (26.8/14.5) AUC = 1.4 (410/291) <u>rabbit</u> C_{max} = 2.3 (34/14.5) AUC = 1.0 (290/291)	

a. Actual or extrapolated from reported value after 150 mg/kg phenytoin oral dose on GD8 in Sprague Dawley rats (Rowland): C_{max} = 13.4 µg/mL, $AUC_{(0\text{-inf})}$ = 205 µg·h/mL. PK data are also available on GD17: C_{max} = 30.2 µg/mL, $AUC_{(0\text{-inf})}$ = 906 µg·h/mL.

b. Actual value after 50 mg/kg phenytoin oral single dose in female New Zealand White rabbits (McClain): C_{max} = 27 µg/mL. PK data are also available after 30 mg/kg phenytoin oral dose in male New Zealand White rabbits (Medhi): C_{max} = 12.8 µg/mL. The value from McClain was used because it was from females, required no extrapolation, and was generated in conjunction with the developmental toxicity study.

c. Extrapolated from reported value after 30 mg/kg phenytoin oral dose in male New Zealand White rabbits (Medhi): AUC = 116 µg·h/mL, from calculation based on concentration values estimated by visual inspection of graph since published value was inconsistent with other data in the paper.

d. Interpolated from actual values after 50 or 100 mg/kg phenytoin oral single dose in female New Zealand White rabbits (McClain): C_{max} = 27 µg/mL and 41 µg/mL at 50 and 100 mg/kg, respectively.

e. Phenytoin is available as an oral solution with an MRHD of 625 mg/day (dosing interval not clear) and as extended release capsules with an MRHD up to 600 mg/day (in 3 divided doses). For exposure comparisons, a dose of 250 mg (10 mL) as a single dose was used for C_{max} and a dose of 625 mg/day oral solution was used for AUC since exposure was higher for the solution than for extended release capsules (FDA, United States 1986).

f. Extrapolated to a 250 mg dose from reported value after 125 mg phenytoin oral solution single dose (FDA, United States 2002): C_{max} = 2.268 µg/mL, $AUC_{(0\text{-inf})}$ = 58.2 µg·h/mL. PK data are also available for a 100 mg oral solution dose and for extended release capsules (FDA, United States 1986). For C_{max}, an accumulation factor of 3.2 was applied that was estimated from the equation: accumulation = $1/(1 - e^{-k \cdot tau})$, where k = 0.693/t½ with t½ = 14.924 hours and tau = 8 hours (i.e., $1/(1 - e^{-0.372}) = 1/(1 - 0.690) = 1/0.31 = 3.2$).

g. Extrapolated to 625 mg/day from reported value after 125 mg phenytoin oral solution single dose (FDA, United States 2002): $AUC_{(0\text{-inf})}$ = 58.2 µg·h/mL.

References

ANDA #40-420 Bioequivalence Review, Phenytoin FDA, United States Approval package, Clinical Pharmacology and Biopharmaceutics Review 040420/S-000

FDA, United States Approval Package (Bioequivalence Review) for ANDA 088771 (22 Oct 1986), p. 32.

FDA, United States Approval Package (Bioequivalence Review) for ANDA 040420 (19 Apr 2002), p. 40.

Kim SH, Lee IC, Baek HS, Lim JH, Moon C, Shin DH, Kim SH, Park SC, Kim JC. Dose-response effects of diphenylhydantoin on pregnant dams and embryo-fetal development in rats. Birth Defects Res B Dev Reprod Toxicol. 2012;95:337-45.

McClain RM, Langhoff L. Teratogenicity of diphenylhydantoin in the New Zealand white rabbit. Teratology. 1980;21:371-9.

Medhi B, Prakash A, Joshi R, Byrav DS. Effect of esomeprazole on pharmacokinetics of phenytoin in rabbits. Indian J Physiol Pharmacol. 2012;56:382-7.

Rowland JR, Binkerd PE, Hendrickx AG. Developmental toxicity and pharmacokinetics of oral and intravenous phenytoin in the rat. Reprod Toxicol. 1990;4:191-202.

US label Dilantin oral solution.

US label Dilantin extended release capsules.

Pomalidomide

CAS No.: 19171-19-8

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**

NOAEL not identified	25 mg/kg oral GD6-17 [FDA, United States 2013a] C_{max} = 2.7 µg/mL[a] $AUC_{(0-24)}$ = 34.3 µg·h/mL[a]	absence of urinary bladder and thyroid gland, fusion and misalignment of lumbar and thoracic vertebral elements (vertebral, central and/or neural arches) resorptions; increased post-implantation loss, decreased viable fetuses	NOAEL not identified	10 mg/kg GD7-19 [FDA, United States 2013a] C_{max} = 0.072 µg/mL[b] AUC_T = 0.418 µg·h/mL[b]	interventricular septal defects; misaligned, fused or small caudal vertebrae	4 mg per day ☐ 21 (2.4 mg/m^2/day) C_{max} = 0.079 µg/mL[c] $AUC_{(0-24h)}$ = 0.402 µg·h/mL[d]	NOAEL: rat NOAEL not identified rabbit NOAEL not identified LOAEL: rat C_{max} = 34 (2.7/0.079) AUC = 85 (34.3/0.402) rabbit C_{max} = 0.9 (0.072/0.079) AUC = 1.0 (0.418/0.402)	

a. Actual value on GD17 after 25 mg/kg pomalidomide oral dose in pregnant Sprague Dawley rats (FDA, United States 2013a, p. 152): C_{max} = 2.729 µg/mL, $AUC_{(0-24h)}$ = 34.34 µg·h/mL.

b. Actual value on GD17 after 10 mg/kg pomalidomide oral dose in pregnant New Zealand White rabbits (FDA, United States 2013a, p. 163): C_{max} = 0.072 µg/mL, AUC_T = 0.418 µg·h/mL.

c. Actual value after 4 mg pomalidomide oral dose for 8 days in multiple myeloma subjects (FDA, United States 2013b, p. 24): C_{max} = 0.079 µg/mL.

d. Actual value after 4 mg/kg mg pomalidomide oral dose for 4 weeks (FDA, United States 2013a, p. 180): $AUC_{(0-24h)}$ = 0.402 µg·h/mL.

References

FDA, United States Pharmtox Review for Pomalyst NDA 204026 (08 Feb 2013a), pp. 149-156, 158-170, 178-180.

FDA, United States ClinPharm Review for Pomalyst NDA 204026 (08 Feb 2013b), p. 25.

Additional References Evaluated

Gay F, Mina R, Troia R, Bringhen S. Pharmacokinetic evaluation of pomalidomide for the treatment of myeloma. Expert Opin Drug Metab Toxicol. 2013;9:1517-27. [review article, data from Hoffman]

Hoffmann M, Kasserra C, Reyes J, Schafer P, Kosek J, Capone L, et al. Absorption, metabolism and excretion of [14C]pomalidomide in humans following oral administration. Cancer Chemother Pharmacol. 2013;71:489-501. [PK in healthy volunteers, used data for patients from FDA, United States reviews]

Ribavirin

CAS No.: 36791-04-5

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Notes**
0.3 mg/kg oral GD6-15 (FDA, United States, p. 64) C_{max} = 3.8 ng/mL[a] AUC = 8.28 ng·h/mL[a]	1.0 mg/kg oral GD6-15 (FDA, United States, p. 64) C_{max} = 12.7 ng/mL[a] AUC = 27.6 ng·h/mL[a]	hydrocephaly, retinal folds, diaphragmic hernia, displaced adrenal, displaced oesophagus, vascular defects; extra vertabra, scoliosis, fused ribs and vertebrae, split sternum, ectrodactyly, malrotated hind limbs; increased post-implantation loss	0.3 mg/kg oral GD6-18 (FDA, United States, p. 68) No rabbit PK data found	1.0 mg/kg oral GD6-18 (FDA, United States, p. 68) No rabbit PK data found	anomalous cervicothoracic arteries	Ribavirin undergoes significant 1st pass metabolism. As a prodrug, it is rapidly anabolized to ribavirin monophosphate and ribavirin triphosphate, which play a role in its antiviral activity (Dixit). It is also deribosylated to triazole carboxamide (Lin). The contribution of each of these metabolites to the developmental effects in rats is unknown.

a. Extrapolated from reported value in plasma after 10 mg/kg ribavirin oral single dose in female Sprague Dawley rats (FDA, United States, p. 76): C_{max} = 0.127 µg/mL, AUC = 0.276 µg·h/mL. Note ≥10-fold extrapolation.

References

FDA, United States. Pharmacology Review NDA 020903 (18 May 1998).

Additional References Evaluated

Dixit NM, Perelson AS. The metabolism, pharmacokinetics and mechanisms of antiviral activity of ribavirin against hepatitis C virus. Cell Mol Life Sci. 2006;63:832-42

Liao S, Jin X, Li J, Zhang T, Zhang W, Shi W, et al. Effects of silymarin, glycyrrhizin, and oxymatrine on the pharmacokinetics of ribavirin and its major metabolite in rats. Phytother Res. 2016;30:618-26. [at 30 mg/kg in fasted male Sprague Dawley rats: C_{max} = 1.36 µg/mL, $AUC_{(0\text{-}inf)}$ = 14.7 µg·h/mL]

Lin CC, Yeh LT, Luu T, Lourenco D, Lau JY. Pharmacokinetics and metabolism of [^{14}C]ribavirin in rats and cynomolgus monkeys. Antimicrob Agents Chemother. 2003;47:1395-8. [at 30 mg/kg in fasted male Sprague Dawley rats: C_{max} = 0.433 µg/mL, $AUC_{(0\text{-}inf)}$ = 3.04 µg·h/mL]

Tacrolimus

CAS No.: 104987-11-3

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Notes**
1.0 mg/kg oral GD7-17 (FDA, United States, p. 18) C_{max} = 2.9 ng/mL[a] $AUC_{(0\text{-}inf)}$ = 10.9 ng·h/mL[a]	3.2 mg/kg oral GD7-17 (FDA, United States, p. 18) C_{max} = 20 ng/mL[b] $AUC_{(0\text{-}inf)}$ = 68.9 ng·h/mL[b]	slight increase in post implantation loss (late resorptions)	0.32 mg/kg oral GD6-18 (FDA, United States, p. 19) C_{max} = 0.93 ng/mL[c] AUC = 17.6 µg·h/mL[c]	1.0 mg/kg oral GD6-18 (FDA, United States, p. 19) C_{max} = 2.9 ng/mL[c] AUC = 55 ng·h/mL[c]	ventricular hypoplasia, interventricular septal defect, bulbous aortic arch and stenosis of arch and ductus arteriosus, omphalocele, gallbladder agenesis, skeletal malformations; increased post-implantation loss, decreased litter size	• Maternal toxicity seen in both rats and rabbits at LOAEL • Ratio of blood:plasma is 4:1 • Metabolites are 3-fold parent

						• 99% protein bound

a. Actual values in plasma after 1.0 mg/kg tacrolimus oral single dose in male rats (FDA, United States, p. 25): C_{max} = 2.9 ng/mL, $AUC_{(0\text{-inf})}$ = 10.9 ng·h/mL.

b. Actual values in plasma after 3.2 mg/kg tacrolimus oral single dose in male rats (FDA, United States, p. 25): C_{max} = 20 ng/mL, $AUC_{(0\text{-inf})}$ = 68.9 ng·h/mL.

c. Extrapolated from reported value after 2 mg/kg tacrolimus oral single dose in NZW rabbits (Piekoszewski): C_{max} = 5.79 ng/mL, AUC = 110 ng·h/mL.

References

FDA, United States. Pharmacology Review NDA 50-708/50-709 (08 Apr 1994).

Piekoszewski W, Chow FS, Jusko WJ. Disposition of tacrolimus (FK 506) in rabbits. Role of red blood cell binding in hepatic clearance. Drug Metab Dispos. 1993;21:690-8.

Additional References Evaluated

Iwasaki K, Shiraga T, Nagase K, Hirano K, Nozaki K, Noda K. Pharmacokinetic study of FK 506 in the rat. Transplant Proc. 1991;23:2757-9.

Thalidomide

CAS No.: 50-35-1

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**[a]	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
10 mg/kg[b] [Janer] C_{max} = 0.97µg/mL[c] $AUC_{(0-24h)}$ = 10.75 µg·h/mL[c]	50 mg/kg[b] [Newman, Schardein] C_{max} = 4.87µg/mL[c] $AUC_{(0-24h)}$ = 53.75 µg·h/mL[c]	decreased implanta-tion sites	20 mg/kg oral GD7-19 [Christian] <u>at GD19</u> C_{max} = 0.82 µg/mL[d] $AUC_{(0-24h)}$ = 4.18 µg·h/mL[d]	60 mg/kg oral GD7-19 [Christian] <u>at GD19</u> C_{max} = 2.16 µg/mL[e] $AUC_{(0-24h)}$ = 14.4 µg.h/mL[e]	• resorptions • rotated or flexed limbs (4/38 fetuses at 60 mg/kg and 15/25 fetuses at 180 mg/kg) • hydrocephaly (n=2/38) • increased postimplantation loss, including dead fetuses, and numerous external and visceral malformations at 180 mg/kg	50 mg oral[f] C_{max} = 0.62 µg/mL[g] $AUC_{(0-inf)}$ = 4.9 µg·h/mL[g]	NOAEL: <u>rat</u> C_{max} = 1.6 (0.97/0.62) AUC = 2.2 (10.75/4.9) <u>rabbit</u> C_{max} = 1.3 (0.82/0.62) AUC = 0.9 (4.18/4.9) LOAEL: <u>rat</u> C_{max} = 7.9 (4.87/0.62)	

							AUC = 11.0 (53.75/4.9) <u>rabbit</u> C_{max} = 3.5 (2.16/0.62) AUC = 2.9 (14.4/4.9)	

a. Numerous developmental toxicity studies in rats have been reported in the literature with a variety of divergent results in different strains (Newman, Neubert, Janer, Schardein). Many of these older studies do not meet today's standards for design. Although malformations cannot be reproducibly induced, embryolethality appears to be a common effect at doses ≥100 mg/kg (Newman).

b. Based on literature reviews by Newman and Schardein, a dose of 50 mg/kg was chosen as the LOAEL. Based on review by Janer, 10 mg/kg appeared to be the highest dose with no evidence of developmental toxicity.

c. Extrapolated or actual value after 50 mg/kg thalidomide oral dose for 8 days in female Fischer rats (FDA, United States p. 86): C_{max} = 4.87 µg/mL, $AUC_{(0\text{-}24h)}$ = 53.75 µg·h/mL. PK data are also available after 30 mg/k oral single dose in female Fischer rats (FDA, United States, p. 22, 91): C_{max} = 10.4 µg/mL, $AUC_{(0\text{-}18h)}$ = 63.99 µg·h/mL; and after a 100 mg/kg oral single dose in male Sprague Dawley rats (FDA, United States, p. 73): C_{max} = 21.60 µg/mL, $AUC_{(0\text{-}48h)}$ = 348.5 µg·h/mL.

d. Actual value after 20 mg/kg thalidomide oral doses in pregnant New Zealand White rabbits (Christian). GD7: C_{max} = 1.77 µg/mL, $AUC_{(0\text{-}24h)}$ = 13.4 µg·h/mL; GD19: C_{max} = 0.824 µg/mL, $AUC_{(0\text{-}24h)}$ = 4.18 µg·h/mL.

e. Actual value after 60 mg/kg thalidomide oral doses in pregnant New Zealand White rabbits (Christian). GD7: C_{max} = 6.39 µg/mL, $AUC_{(0\text{-}24h)}$ = 78.7 µg·h/mL; GD19: C_{max} = 2.16 µg/mL, $AUC_{(0\text{-}24h)}$ = 14.4 µg·h/mL.

f. Currently approved doses range from 100 to 400 mg/day. A dose of 50 mg was used for PK comparisons because that was the lowest dose used to treat insomnia when thalidomide was first developed. Also, one 50 mg tablet of thalidomide during the time-sensitive window is sufficient to cause birth defects in 50% of pregnancies (Vargesson).

g. Actual value after 50 mg single dose to healthy volunteers (Teo, US label): C_{max} = 0.62 µg/mL, AUC = 4.90 µg·h/mL.

References

Christian MS, Laskin OL, Sharper V, Hoberman A, Stirling DI, Latriano L. Evaluation of the developmental toxicity of lenalidomide in rabbits. Birth Defects Res B Dev Reprod Toxicol. 2007;80:188-207.

FDA, United States. Pharmtox review NDA 020785 (11 May 1998).

Janer G, Slob W, Hakkert BC, Vermeire T, Piersma AH. A retrospective analysis of developmental toxicity studies in rat and rabbit: what is the added value of the rabbit as an additional test species? Regul Toxicol Pharmacol. 2008;50:206-17.

Neubert R, Neubert D. Peculiarities and possible mode of actions of thalidomide. In: Kavlock RJ, Daston GP, editors. Handbook of experimental pharmacology 124: Drug toxicity in embryonic development II. New York: Springer-Verlag; 1997. p.41-119.

Newman LM, Johnson EM, Staples RE. Assessment of the effectiveness of animal developmental toxicity testing for human safety. Reprod Toxicol. 1993;7:359-90.

Schardein JL, Macina OT. Human developmental toxicants: aspects of toxicology and chemistry. Boca Raton: CRC Press; 2007. p. 127-141.

Teo SK, Colburn WA, Tracewell WG, Kook KA, Stirling DI, Jaworsky MS, Scheffler MA, Thomas SD, Laskin OL. Clinical pharmacokinetics of thalidomide. Clin Pharmacokinet. 2004;43:311-27.

Vargesson N. Thalidomide embryopathy: an enigmatic challenge. ISRN Development Biol. 2013;2013:Article ID 241016. http://dx.doi.org/10.1155/2013/241016

US label Thalomid.

Additional References Evaluated

Brock N, [Experimental contribution to the testing of teratogenic drug effects in the laboratory rat]. Naunyn-Schmiedebergs Archiv fur experimentelle Pathologie und Pharmakologie. 1964;249:117-145 [500 mg/kg only dose tested]

EMA Assessment Report for Thalidomide Pharmion. EMEA/176582/2008, p. 13. [same PK values as FDA, United States review, $AUC_{(0\text{-}inf)}$ = 55.25 µg·h/mL at 50 mg/kg on D8]

Eriksson T, Riesbeck K, Ostraat O, Ekberg H, Björkman S. Drug exposure and flow cytometry analyses in a thalidomide treatment schedule that prolongs rat cardiac graft survival. Transplant Proc. 1992;24:2560-1. [no PK parameters published]

FDA, United States. Pharmtox review NDA 021430 (23 Nov 2005). [review for multiple myeloma, no new PK or teratology data from NDA 020785]

FDA, United States. Pharmtox review NDA 204026 (08 Feb 2013). [thalidomide was used as a positive control in the rabbit developmental toxicity study ata dose of 180 mg/kg]

Topiramate

CAS No.: 97240-79-4

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
100 mg/kg oral GD6-15 [US label, FDA, United States 1996a] C_{max} = 49 µg/mL[a] AUC = 893 µg·h/mL[b]	400 mg/kg oral GD6-15 [US label, FDA, United States 1996a] C_{max} = 168.6 µg/mL[c] AUC = 3573 µg·h/mL[b]	ectrodactyly, hydronephrosis	20 mg/kg oral GD6-18 [US label, FDA, United States 1996a] C_{max} = 13 µg/mL[d] AUC = 67 µg·h/mL[d]	35 mg/kg oral GD6-18 [US label, FDA, United States 1996a] C_{max} = 23 µg/mL[d] AUC = 117 µg·h/mL[d]	embryofetal mortality at ≥35 mg/kg	400 mg/day in two divided doses C_{max} = 13.5 µg/mL[e] AUC = 229 µg·h/mL[e]	NOAEL: rat C_{max} = 3.6 (49/13.5) AUC = 3.9 (893/229) rabbit C_{max} = 1.0 (13/13.5) AUC = 0.3 (67/229) LOAEL: rat	• In rats: Although reduced fetal BW and increased incidence of structural variations were observed at 20 mg/kg, the NOAEL for MEFL is assumed to

							C_{max} = 12.5 (169/13.5) AUC = 15.6 (3573/229) <u>rabbit</u> C_{max} = 1.7 (23/13.5) AUC = 0.5 (117/229)	be 100 mg/kg • In rats: Clinical signs of maternal toxicity were seen at ≥400 mg/kg and maternal BW gain was reduced at ≥100 mg/kg • In rabbits: maternal toxicity (decreased BW gain, clinical signs, and/or mortality) was seen at ≥35 mg/kg

a. Extrapolated from reported value after 200 mg/kg topiramate for GD12-15 (4 days) in pregnant female Sprague Dawley rats (FDA, United States, p. 48): $C_{1.5h}$ = 97.3 µg/mL.

b. Extrapolated from reported value after 30 mg/kg topiramate for 8 days in female Sprague Dawley rats (FDA, United States, p. 12): C_{max} = 22.2 µg/mL, AUC = 268.2 µg·h/mL.

c. Actual value after 400 mg/kg topiramate for GD12-15 (4 days) in pregnant female Sprague Dawley rats (FDA, United States, p. 48): $C_{1.5h}$ = 168.6 µg/mL.

d. Extrapolated from reported value after 60 mg/kg topiramate for 14 days in female New Zealand White rabbits (FDA, United States, p. 13): C_{max} =39.1 µg/mL, AUC = 201 µg·h/mL.

e. Extrapolated from reported value after 100 mg/kg topiramate BID oral for 14 days (FDA, United States 1996b): C_{max} = 6.76 µg/mL, $AUC_{(0\text{-}24h)}$ = 57.2 µg·h/mL. PK data at a number of other doses and schedules and in combination with other drugs are also available (FDA, United States 1995b, Bialer).

References

Bialer M, Doose DR, Murthy B, Curtin C, Wang SS, Twyman RE, et al. Pharmacokinetic interactions of topiramate. Clin Pharmacokinet. 2004;43:763-80.

FDA, United States. Pharmtox Review NDA 020505 (24 Dec 1996a).

FDA, United States. Clinical Pharmacology Review NDA 020505 (24 Dec 1996b), p. 39.

Trimethadione

CAS No.: 127-48-0

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
60 mg/kg oral GD6-15 [Buttar 1976] Trimethadione C_{max} = 58.9 µg/mL[a] $AUC_{(0\text{-}inf)}$ = 203 µg·h/mL[a] Dimethadione C_{max} = 97.7µg/mL[b] $AUC_{(0\text{-}inf)}$ = 4872 µg·h/mL[b]	240 mg/kg oral GD6-18 [Buttar 1976] Trimethadione C_{max} = 235 µg/mL[a] $AUC_{(0\text{-}inf)}$ = 814 µg·h/mL[a] Dimethadione C_{max} = 391 µg/mL[b]	240 mg/kg GD6-15 [Buttar]: "adverse fetal effects on survival and litter size" 250 mg/kg GD7-18 [Vorhees]: embryolethality, malformations (primarily cardiac, with a lower incidence of esophageal and kidney defects)	No rabbit data found Trimethadione AUC = 10.78 µg·h/mL[c]	No rabbit data found	No rabbit data found	600 mg QID (10 mg/kg ☐ 4) [highest dose, US label] Trimethadione C_{max} = 42.75 µg/mL[d] $AUC_{(0\text{-}inf)}$ = 1000 µg·h/mL[d] Dimethadione C_{max} = 1251 µg/mL[e]	Trimethadione NOAEL: rat C_{max} = 1.4 (58.9/42.75) AUC = 0.2 (203/1000) rabbit NOAEL not identified LOAEL: rat C_{max} = 5.5 (235/42.75) AUC = 0.8 (814/1000) rabbit	Dimethadione is the only metabolite, has much higher exposures than trimethadione, and is a confirmed teratogen (Buttar 1978). Thus, margins for dimethadione are also listed.

	$AUC_{(0\text{-inf})}$ = 19,488 µg·h/mL[b]					$AUC_{(0\text{-inf})}$ = 36,670 µg·h/mL[e]	LOAEL not identified <u>Dimethadione</u> NOAEL: <u>rat</u> C_{max} = 0.1 (97.7/1251) AUC = 0.1 (4872/36670) LOAEL: <u>rat</u> C_{max} = 0.3 (391/1251) AUC = 0.5 (19488/36670)	

a. Extrapolated from reported value after 100 mg/kg trimethadione oral single dose in male Wistar rats (Tanaka 1981): C_{max} = 98.1 µg/mL, $AUC_{(0\text{-inf})}$ = 339 µg·h/mL.

b. Extrapolated from reported value after 100 mg/kg trimethadione oral single dose in male Wistar rats (Tanaka 1981): dimethadione C_{max} = 162.8 µg/mL, $AUC_{(0\text{-inf})}$ = 8120 µg·h/mL.

c. Actual value after 4 mg/kg trimethadione intravenous single dose in Japanese White rabbits (Tanaka 1999): $AUC_{(0\text{-inf})}$ = 10.78 µg·h/mL calculated from Cl = 0.371 L/(kg·h).

d. Extrapolated from reported value after 4 mg/kg trimethadione oral single dose (Kobayashi): C_{max} = 6.0 µg/mL, $AUC_{(0\text{-inf})}$ = 100.1 µg·h/mL. For C_{max}, an accumulation factor of 2.85 was applied that was estimated from the equation: accumulation = $1/(1 - e^{-k \cdot tau})$, where k = 0.693/t½ with t½ = 9.6 hours and tau = 6 hours (i.e., $1/(1 - e^{-0433}) = 1/(1 - 0.649) = 1/0.351 = 2.85$).

e. Extrapolated from reported value after 4 mg/kg trimethadione oral single dose (Kobayashi): dimethadione C_{max} = 12.83 µg/mL, $AUC_{(0\text{-}inf)}$ = 3667 µg·h/mL. For C_{max}, an accumulation factor of 39 was applied that was estimated from the equation: accumulation = $1/(1 - e^{-k \cdot tau})$, where k = 0.693/t½ with t½ = 160 hours and tau = 6 hours (i.e., $1/(1 - e^{-0.026}) = 1/(1 - 0.974) = 1/0.026 = 39$).

References

Buttar HS, Dupui I, Khera KS. Fetotoxicity of trimethadione and paramethadione in rats. Toxicol Appl Pharmacol. 1976;37:126 [abstract]

Buttar HS, Dupuis I, Khera KS. Dimethadione-induced fetotoxicity in rats. Toxicology. 1978;9:155-64.

Tanaka E, Kinoshita H, Yamamoto T, Kuroiwa Y, Takabatake E. Pharmacokinetic studies of trimethadione and its metabolite in rats with chemical-induced liver injury. J Pharmacobiodyn. 1981;4:576-83.

Tanaka E, Ishikawa A, Horie T. *In vivo* and *in vitro* trimethadione oxidation activity of the liver from various animal species including mouse, hamster, rat, rabbit, dog, monkey and human. Hum Exp Toxicol. 1999;18:12-16.

Vorhees CV. Fetal anticonvulsant syndrome in rats: dose- and period-response relationships of prenatal diphenylhydantoin, trimethadione and phenobarbital exposure on the structural and functional development of the offspring. J Pharmacol Exp Ther. 1983;227:274-87.

US label trimethadione.

Additional References Evaluated

Midha KK. Metabolism and disposition of trimethadione in pregnant rats. Epilepsia. 1979;20:417-23. [only useful data are concentrations at 6 hours after last dose following dosing 60 and 240 mg/kg GD6-15: at 60 mg/kg , C_{6h} = 11.3 µg/mL]

Schardein JL, Schwetz BA, Kenel MF. Species sensitivities and prediction of teratogenic potential. Environ Health Perspect. 1985;61:55-67. [claimed rats are an insensitive species for detecting trimethadione teratogenesis]

Tanaka E, Yoshida T, Kuroiwa Y. Dose-independent pharmacokinetics of trimethadione and its metabolite in rats. J Pharm Sci. 1985;74:340-1. [PK values after 4 mg/kg trimethadione oral single dose in male Wistar rats: trimethadione C_{max} = 3.0 µg/mL, $AUC_{(0\text{-}inf)}$ = 8.21 µg·h/mL, and dimethadione C_{max} = 10.2 µg/mL, $AUC_{(0\text{-}inf)}$ = 465.8 µg·h/mL. The values after 100 mg/kg (Tanaka 1981) were used instead].

Taylor JD, Bertcher EL. The determination and distribution of trimethadione (tridione) in animal tissues. J Pharmacol Exp Ther. 1952;106:277-85. [levels in rabbit brain after 1000 mg/kg IP]

Valproic Acid

CAS No.: 99-66-1 (sodium valproate: 1069-66-5)

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
65 mg/kg oral GD6-15, SD rats [FDA, United States, 1995] C_{max} = 73.8 µg/mL[a] AUC = 230 µg·h/mL[a]	200 mg/kg oral, SD rats, GD7-18 [Voorhees], GD8-17 [Binkerd]; [US Depacon label] C_{max} = 227 µg/mL[a] AUC = 707 µg·h/mL[a]	hydronephrosis, cardiovascular defects	150 mg/kg oral GD6-18 [FDA, United States, 1977] C_{max} = 410 µg/mL[b] AUC = 690 µg·h/mL[b]	350 mg/kg oral GD6-18 [FDA, United States, 1977] C_{max} = 957 µg/mL[b] AUC = 1610 µg·h/mL[b]	resorptions; external abnormalities (cleft palate, umbilical hernia, bilateral talipes, exencephaly, hypoplastic ears, gastrochisis, bilateral talipes); visceral malformations (intraventricular septal defects, misshapen ventricle, renal agenesis); skeletal malformations (supernumerary ribs, fused ribs)	60 mg/kg/day oral in 2 divided doses (30 mg/kg/dose) [highest approved dose, US Depakote and Depakene labels] C_{max} = 205 µg/mL[c] $AUC_{(0\text{-}inf)}$ = 4180 µg·h/mL[d]	NOAEL: rat C_{max} = 0.4 (73.8/205) AUC = 0.06 (230/4180) rabbit C_{max} = 2.0 (410/205) AUC = 0.2 (690/4180) LOAEL: rat	

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
							C_{max} = 1.1 (227/205) AUC = 0.2 (707/4180) rabbit C_{max} = 4.7 (957/205) AUC = 0.4 (1610/4180)	

a. Extrapolated or actual value after 200 mg/kg valproic acid oral dose on GD17 in pregnant Sprague Dawley rats (Binkerd): C_{max} = 227 µg/mL, AUC = 707 µg·h/mL. PK data are also available on GD8: C_{max} = 341µg/mL, AUC = 1019 µg·h/mL

b. Extrapolated from reported value after 70 mg/kg valproic acid oral single dose in male New Zealand White rabbits (Bourin): C_{max} = 191.3 µg/mL, $AUC_{(0\text{-inf})}$ = 322 µg·h/mL. Rabbit PK data are also available after 50 mg/kg oral (FDA, United States), 20 mg/kg oral (van Jaarsveld), 43 mg/kg intravenous (Nakashima), and 75 mg/kg intravenous (Yokogawa).

c. Extrapolated from reported value after 1000 mg valproic acid oral BID for 5 days (Nitsche): C_{max} = 114 µg/mL.

d. Extrapolated from reported value after 1000 mg valproic acid oral single dose (Nitsche): $AUC_{(0\text{-inf})}$ = 1161 µg·h/mL.

References

Binkerd PE, Rowland JM, Nau H, Hendrickx AG. Evaluation of valproic acid (VPA) developmental toxicity and pharmacokinetics in Sprague-Dawley rats. Fundam Appl Toxicol. 1988;11:485-93.

Bourin M, Guenzet J, Thomare P, Kergueris MF, Ortega A, Larousse C. Effects of administration route on valproate pharmacokinetics in the rabbit. Fundam Clin Pharmacol. 1991;5:331-9.

FDA, United States Approval Package, NDA 018081 (S-001, S-025) and 018082 (S-008) (1995), Part 2. p. 7-8,10,12,28.

FDA, United States Pharmtox reviews IND 011152 (March 1977), p. 31-32, 34.

Nitsche V, Mascher H. The pharmacokinetics of valproic acid after oral and parenteral administration in healthy volunteers. Epilepsia. 1982;23:153-62

Ong LL, Schardein JL, Petrere JA, Sakowski R, Jordan H, Humphrey RR, et al. Teratogenesis of calcium valproate in rats. Fundam Appl Toxicol. 198;3:121-6.

Vorhees CV. Teratogenicity and developmental toxicity of valproic acid in rats. Teratology. 1987;35(2):195-202.

US Depacon (valproate injection) label.

US Depakene (valproate capsule) label.

US Depakote (valproex tablets) label.

Additional References Evaluated

FDA, United States Pharmtox reviews IND 011152 (1977), p. 48. [after 50 mg/kg [^{14}C]valproic acid oral single dose in rabbits (FDA, United States): C_{max} = 86 µg/mL].

Katayama H, Mizukami K, Yasuda M, Hatae T. Effects of carnitine on valproic acid pharmacokinetics in rats. J Pharm Sci. 2016;105:3199-3204. [PK data in male Wistar rats after 32 mg/kg oral: C_{max} = 40.7 µg/mL, $AUC_{(0\text{-}inf)}$ = 3458 µg·min/mL (57.6 µg·h/mL)]

Nakashima M, Takeuchi N, Hamada M, Matsuyama K, Ichikawa M, Goto S. *In vivo* microdialysis for pharmacokinetic investigations: a plasma protein binding study of valproate in rabbits. Biol Pharm Bull. 1994;17:1630-4. [PK after 43 mg/kg intravenous valproic acid in anesthetized male Japanese Albino rabbits: C_0 = 157 µg/mL, $AUC_{(0\text{-}inf)}$ = 308 µg·h/mL]

Rha JH, Jang IJ, Lee KH, Chong WS, Shin SG, Lee N, Myung HJ. Pharmacokinetic comparison of two valproic acid formulations--a plain and a controlled release enteric-coated tablets. J Korean Med Sci. 1993 Aug;8(4):251-6.

van Jaarsveld MF, Walubo A, du Plessis JB. Interaction between valproic acid and acyclovir after intravenous and oral administration in a rabbit model. Basic Clin Pharmacol Toxicol. 2007;101:434-40. [PK after 20 mg/kg valproic acid oral single dose in New Zealand White rabbts: C_{max} = 64.2 µg/mL, $AUC_{(0\text{-}inf)}$ = 227 µg·h/mL].

Yokogawa K, Iwashita S, Kubota A, Sasaki Y, Ishizaki J, Kawahara M, Matsushita R, Kimura K, Ichimura F, Miyamoto K. Effect of meropenem on disposition kinetics of valproate and its metabolites in rabbits. Pharm Res. 2001;18:1320-6. [PK after 75 mg/kg intravenous dose in male albino rabbits: C_{max} = 238 µg/mL, $AUC_{(0\text{-}6h)}$ = 17.5 mg·min/L (292 µg·h/mL)]

Zaccara G, Messori A, Moroni F. Clinical pharmacokinetics of valproic acid--1988. Clin Pharmacokinet. 1988;15:367-89.

Vismodegib

CAS No.: 879085-55-9

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** **C_{max}** **AUC**	**Rabbit LOAEL** **Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
NOAEL not identified	10 mg/kg GD6-17 oral [FDA, United States, 2011] C_{max} = 7.22 µg/mL[a] $AUC_{(0-24h)}$ = 50.5 µg·h/mL[a]	malformations included absent and/or fused digits on the hind limb, open perineum, multiple craniofacial anomalies	no rabbit data found	no rabbit data found	no rabbit data found	150 mg oral C_{max} = 13.0 µg/mL[b] $AUC_{(0-24h)}$ = 306 µg·h/mL[b]	NOAEL: rat: NOAEL not identified rabbit: no data found LOAEL: rat C_{max} = 0.6 (7.22/13) AUC = 0.2 (50.5/306) rabbit	MW = 421.3

							no data found	

a. Reported value after 10 daily oral doses of 10 mg/kg vismodegib in female pregnant Wistar rats (FDA, United States, 2011): C_{max} = 7.22 µg/mL, $AUC_{(0\text{-}24h)}$ = 50.5 µg·h/mL

b. Reported value after 14 daily oral doses of 150 mg vismodegib (FDA, United States, 2012): C_{max} = 30.9 µM (13.0 µg/mL), $AUC_{(0\text{-}24h)}$ = 727 µmol·h/L (306 µg·h/mL).

References

FDA, United States. Pharmacology Review NDA 203388 (08 Sep 2011), p. 66-9.

FDA, United States. Clinical Pharmacology Review NDA 203388 (13 Jan 2012), p. 48.

1.3.2 Negative control reference compounds

CETIRIZINE

CAS No.: 83881-51-0

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL Dose** **C_{max}** **AUC**	**Rabbit LOAEL Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
NOAEL (MEFL) 75 mg/kg oral GD6-15 (FDA, United States 1989)	225 mg/kg oral GD6-15 (FDA, United States 1989)	225 mg/kg: pre- and post-implantation loss in presence of	NOAEL (MEFL) 135 mg/kg oral GD6-18	Not established	No MEFL observed	10 mg MRHD Exposure values after single dose: C_{max} = 0.33 µg/mL[d]	NOAEL: rat (75 mg/kg/day) C_{max}: 136 (45/0.33) AUC: 111 (334/3.02)	None

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL Dose** **C_{max}** **AUC**	**Rabbit LOAEL Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
C_{max} = 45 µg/mL[a] AUC = 301 µg•h/mL[b] <u>Exposure data at lower doses</u> 8 mg/kg oral GD6-15 (FDA, United States 1989) C_{max} = 4.6 µg/mL[a] AUC = 32 µg•h/mL[b] 25 mg/kg oral	C_{max} = 128 µg/mL[a] AUC = 1010 µg•h/mL[b]	maternal toxicity (death, clinical signs)	(FDA, United States 1989) C_{max} = 137 µg/mL[c] AUC = 642 µg•h/mL[c] <u>Exposure data at lower doses</u> 15 mg/kg oral GD6-18 (FDA, United States 1989) C_{max} = 15 µg/mL[c] AUC = 71 µg•h/mL[c]			$AUC_{(0-24h)}$: 3.0 µg•hr/mL[d]	<u>Rabbit (135 mg/kg/day)</u> C_{max}: 415 (137/0.33) AUC: 213 (642/3.02) LOAEL: <u>Rat (225 mg/kg/day)</u> C_{max}: 388 (128/0.33) AUC: 334 (1010/3.02) <u>rabbit</u> Not applicable	

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL Dose** **C_{max}** **AUC**	**Rabbit LOAEL Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
GD6-15 (FDA, United States 1989) C_{max} = 12 µg/mL[a] AUC = 41 µg•h/mL[b]			45 mg/kg oral GD6-18 (FDA, United States 1989) C_{max} = 51 µg/mL[c] AUC = 116 µg•h/mL[c]					

a. From reported Cmax values in a 4-week repeated-dose toxicity study in rats at steady state (day 23) at doses of 25, 75 and 225 mg/kg/day. Cmax for 8 mg/kg/day was linearly extrapolated from these data. (FDA, United States 1993, page 4).

b. From reported AUC values in a 4-week repeated-dose toxicity study in rats at steady state (day 23) at doses of 25 mg/kg/day and 225 mg/kg/day. AUC for 8 and 75 mg/kg/day were linearly extrapolated from these data (FDA, United States 1993, page 4).

c. From reported Cmax and AUC values in pregnant rabbits exposed from GD6-18 at steady state (GD18) at doses of 25, 45 and 90 mg/kg/day. Cmax and AUC for 15 and 135 mg/kg/day were linearly extrapolated from these data. (FDA, United States 1993, page 5).

d. Single administration of 10 mg cetirizine with water (FDA, United States, 2003).

References

FDA, United States. Pharmacology review of NDA 019835 (11 Apr 1989) part 01, pages 10-11 (rat and rabbit EFD overview).

FDA, United States. Pharmacology review of NDA 019835 (11 Apr 1989) part 02, pages 10-30 (rat and rabbit EFD summary).

FDA, United States. Pharmacology review of NDA 019835 (18 Oct 1993), pages 4 (rat PK data) and 5 (rabbit PK data).

FDA, United States. Clinical Pharmacology and Biopharmaceutics Review 021621/S-000 (31 Oct 2003) (Clinical AUC, single dose pg 11)

US Label Zyrtec.

EU SmPC Zyrtec.

Saxagliptin

CAS No.: 361442-04-8

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL Dose** **C_{max}** **AUC**	**Rabbit LOAEL Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
NOAEL (MEFL) 900 mg/kg oral GD6-15 (FDA, United States 2009) *Saxagliptin* C_{max} = 249 µg/mL[a] AUC_{0-24} = 647 µg•h/mL[a] *BMS-510849* C_{max} = 21.1 µg/mL[b]	Not established	No MEFL observed	NOAEL (MEFL) 200 mg/kg oral GD7-19 (FDA, United States 2009) *Saxagliptin* C_{max} = 43 µg/mL[c] AUC_{0-24} = 111 µg•h/mL[a] *BMS-510849* C_{max} = 125 µg/mL[c]	Not established	No MEFL observed	5 mg MRHD Exposure values after single dose: *Saxagliptin* C_{max} = 0.024 µg/mL[d] $AUC_{(0-24h)}$: 0.078 µg•hr/mL[d] *BMS-510849* C_{max} = 0.047 µg/mL[d] $AUC_{(0-24h)}$: 0.214 µg•hr/mL[d]	NOAEL: rat (900 mg/kg/day) *Saxagliptin* C_{max}: 10,375 (249/0.024) AUC: 8,294 (647/0.078) *BMS-510849* C_{max}: 449 (21.1/0.047) AUC: 673 (144/0.214)	BMS-510849 is a major active metabolite of saxagliptin. (US Label and EU EPAR Onglyza)

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL Dose** **C_{max}** **AUC**	**Rabbit LOAEL Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
AUC_{0-24} = 144 µg•h/mL[a] Exposure data at lower doses 64 mg/kg oral GD6-15 *Saxagliptin* C_{max} = 17.7 µg/mL[a] AUC_{0-24} = 23.6 µg•h/mL[a] *BMS-510849* C_{max} = 1.5 µg/mL[b]			AUC_{0-24} = 434 µg•h/mL[a] Exposure data at lower doses 8 mg/kg oral GD7-19 *Saxagliptin* C_{max} = 2 µg/mL[c] AUC_{0-24} = 2.5 µg•h/mL[a] *BMS-510849* C_{max} = 5 µg/mL[c]				Rabbit (200 mg/kg/day) *Saxagliptin* C_{max}: 1,792 (43/0.024) AUC: 1,423 (111/0.078) *BMS-510849* C_{max}: 2,659 (125/0.047) AUC: 2,028 (434/0.214) LOAEL: rat Not applicable rabbit	

Rat NOAEL **Dose** **C_{max}** **AUC**	**Rat LOAEL** **Dose** **C_{max}** **AUC**	**Rat Findings**	**Rabbit NOAEL Dose** **C_{max}** **AUC**	**Rabbit LOAEL Dose** **C_{max}** **AUC**	**Rabbit Findings**	**Human** **Dose** **C_{max}** **AUC**	**Margins** **NOAEL/Human** **LOAEL/Human**	**Notes**
AUC_{0-24} = 6.3 µg•h/mL[a] 240 mg/kg oral GD6-15 *Saxagliptin* C_{max} = 66.3 µg/mL[a] AUC_{0-24} = 121 µg•h/mL[a] *BMS-510849* C_{max} = 5.6 µg/mL[b] AUC_{0-24} = 28.9 µg•h/mL[a]			AUC_{0-24} = 7.4 µg•h/mL[a] 40 mg/kg oral GD7-19 *Saxagliptin* C_{max} = 9 µg/mL[c] AUC_{0-24} = 12.3 µg•h/mL[a] *BMS-510849* C_{max} = 25 µg/mL[c] AUC_{0-24} = 47.9 µg•h/mL[a]				Not applicable	

a. From reported AUC values in pregnant rats (GD15) and pregnant rabbits (GD19) at steady state at doses of 64, 240 and 900 mg/kg/day saxagliptin for rat and 8, 40 and 200 mg/kg/day saxagliptin for rabbit (FDA, United States, 2009, part 02, page 84)

b. From reported Cmax values in a 4-week repeated-dose toxicity study in female rats at steady state (day 28) at doses of 150, 300 and 225 mg/kg/day, corresponding to 50, 78 and 139 ug/mL for saxagliptin and 4.6, 7.9 and 11 ug/mL for the active metabolite.. Saxagliptin Cmax values were linearly extrapolated from these data. (FDA, United States, 2009, part 04, page 56)

c. From reported Cmax values in a rabbit EFD study at steady state (GD19) at 40 mg/kg/day saxagliptin (Cmax 8.5 µg/mL). Saxagliptin Cmax values were linearly extrapolated from these data.

d. Single administration of 5 mg saxagliptin (US Label Onglyza, page 12).

References

FDA, United States. Pharmacology Review 022350/S-000 (3 March 2009) Part 02, page 84 (rat and rabbit AUC data Saxagliptin and active metabolite)

FDA, United States. Pharmacology Review 022350/S-000 (3 March 2009) Part 03, pages 57-59 (rat and rabbit EFD studies).

FDA, United States. Pharmacology Review 022350/S-000 (3 March 2009) Part 04, page 56 (rat Cmax data Saxagliptin and active metabolite)

FDA, United States. Pharmacology Review 200678Orig1s000 (10 January 2010) for Saxagliptin + metformin, page 44 table 30 (rabbit Cmax data Saxagliptin and active metabolite)

US Label Onglyza.

EU EPAR Onglyza.

Vildagliptin

CAS No.: 274901-16-5

Rat NOAEL Dose C_{max} AUC	Rat LOAEL Dose C_{max} AUC	Rat Findings	Rabbit NOAEL Dose C_{max} AUC	Rabbit LOAEL Dose C_{max} AUC	Rabbit Findings	Human Dose C_{max} AUC	Margins NOAEL/Human LOAEL/Human	Notes
NOAEL (MEFL) 750 mg/kg oral GD6-17 (TGA, Australia 2010) AUC_{0-24} = 241 µg•h/mL[a] Exposure data at lower doses 75 mg/kg oral	Not established	No MEFL observed	NOAEL (MEFL) 150 mg/kg oral GD7-20 (TGA, Australia 2010) AUC_{0-24} = 80 µg•h/mL[a] Exposure data at lower doses	Not established	No MEFL observed	50 mg b.i.d. MRHD (100 mg/day) Exposure values after 50 mg b.i.d.: $AUC_{(0-24h)}$: 2.06 µg•hr/mL[b]	NOAEL: rat (750 mg/kg/day) AUC: 117 (241/2.06) Rabbit (150 mg/kg/day) AUC: 39 (80/2.06) LOAEL:	

Rat NOAEL Dose C_{max} AUC	Rat LOAEL Dose C_{max} AUC	Rat Findings	Rabbit NOAEL Dose C_{max} AUC	Rabbit LOAEL Dose C_{max} AUC	Rabbit Findings	Human Dose C_{max} AUC	Margins NOAEL/Human LOAEL/Human	Notes
GD6-17 **AUC_{0-24} = 23 µg•h/mL[a]** **225 mg/kg oral** **GD6-17** **AUC_{0-24} = 68 µg•h/mL[a]**			**15 mg/kg oral** **GD7-20** **AUC_{0-24} = 6 µg•h/mL[a]** **50 mg/kg oral** **GD7-20** **AUC_{0-24} = 19 µg•h/mL[a]**				**Not applicable**	

a. Calculated from exposure ratios compared to human exposure at MRHD (2.06 µg•hr/mL at 50 mg BID) of AUC data provided within the rat and rabbit EFD studies (TGA, Australia, 2010, page 19)

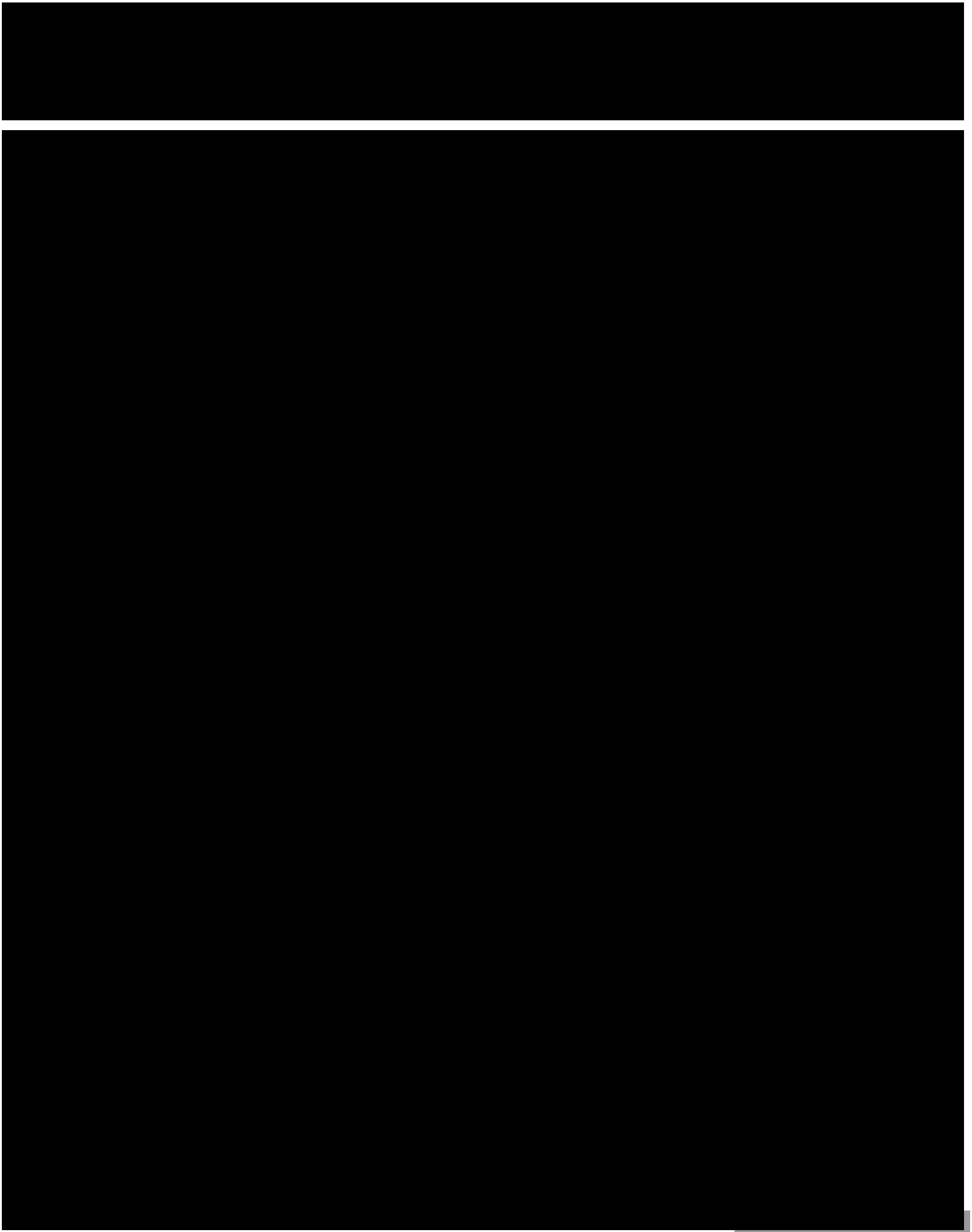
b. Human exposure data at 50 mg BID (TGA, Australia, 2010, page 14)

References

TGA, Australia. Australian Public Assessment Report for Vildagliptin (April 2010) pages 19 (EFD studies), 14, 24 (exposure data) and 72 (pregnancy).

EU EPAR Galvus

EU SmPC. Galvus



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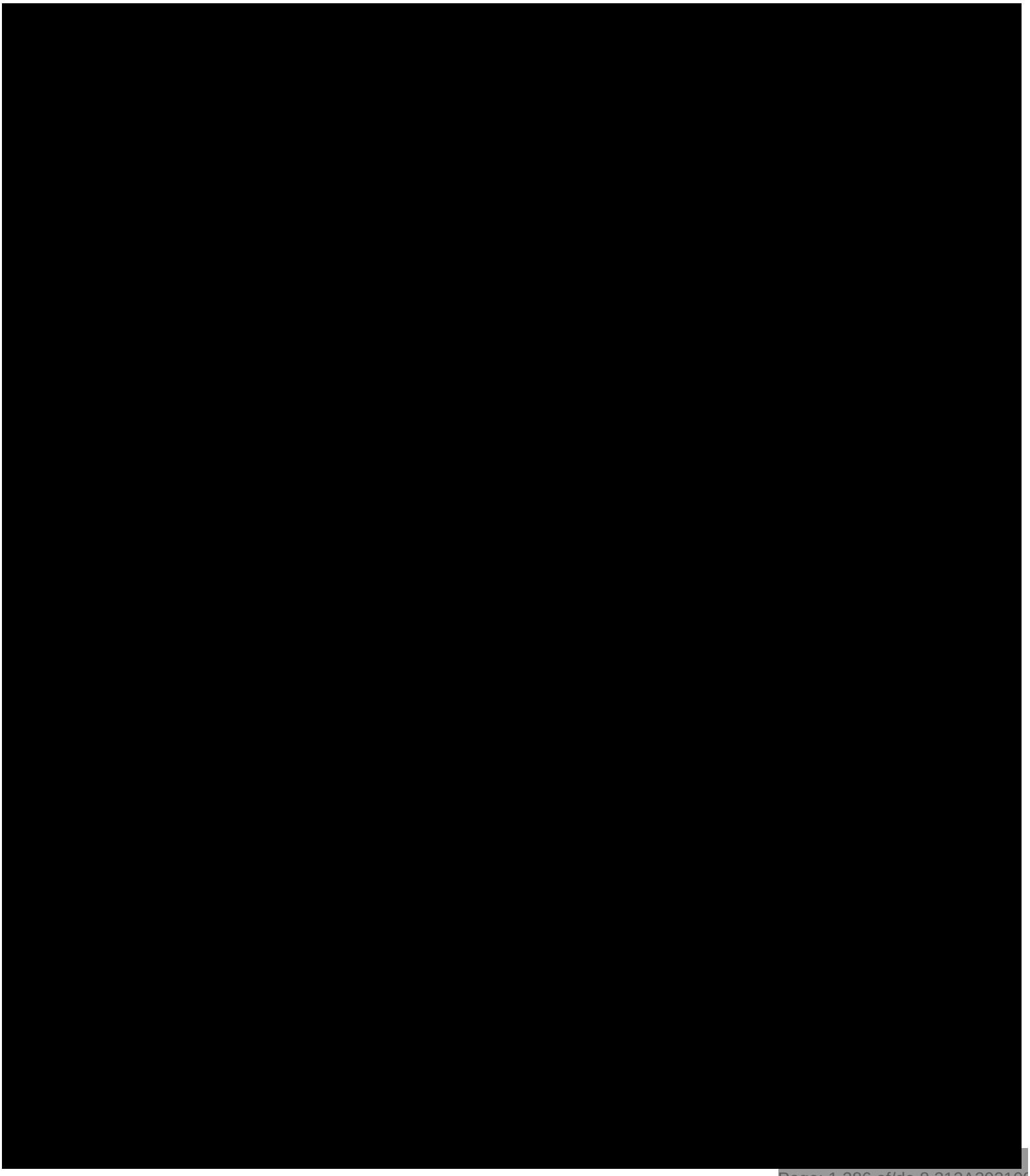

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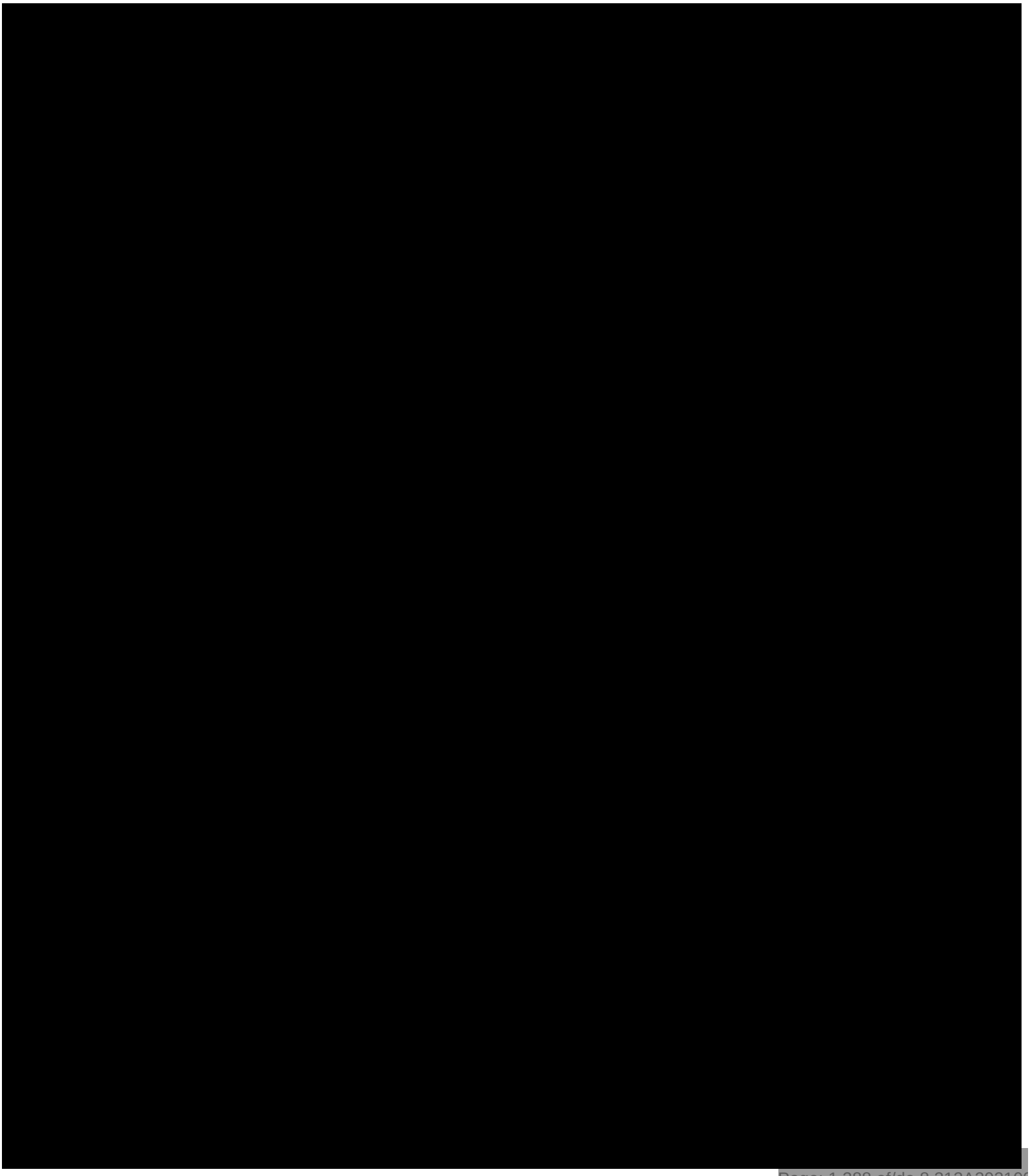

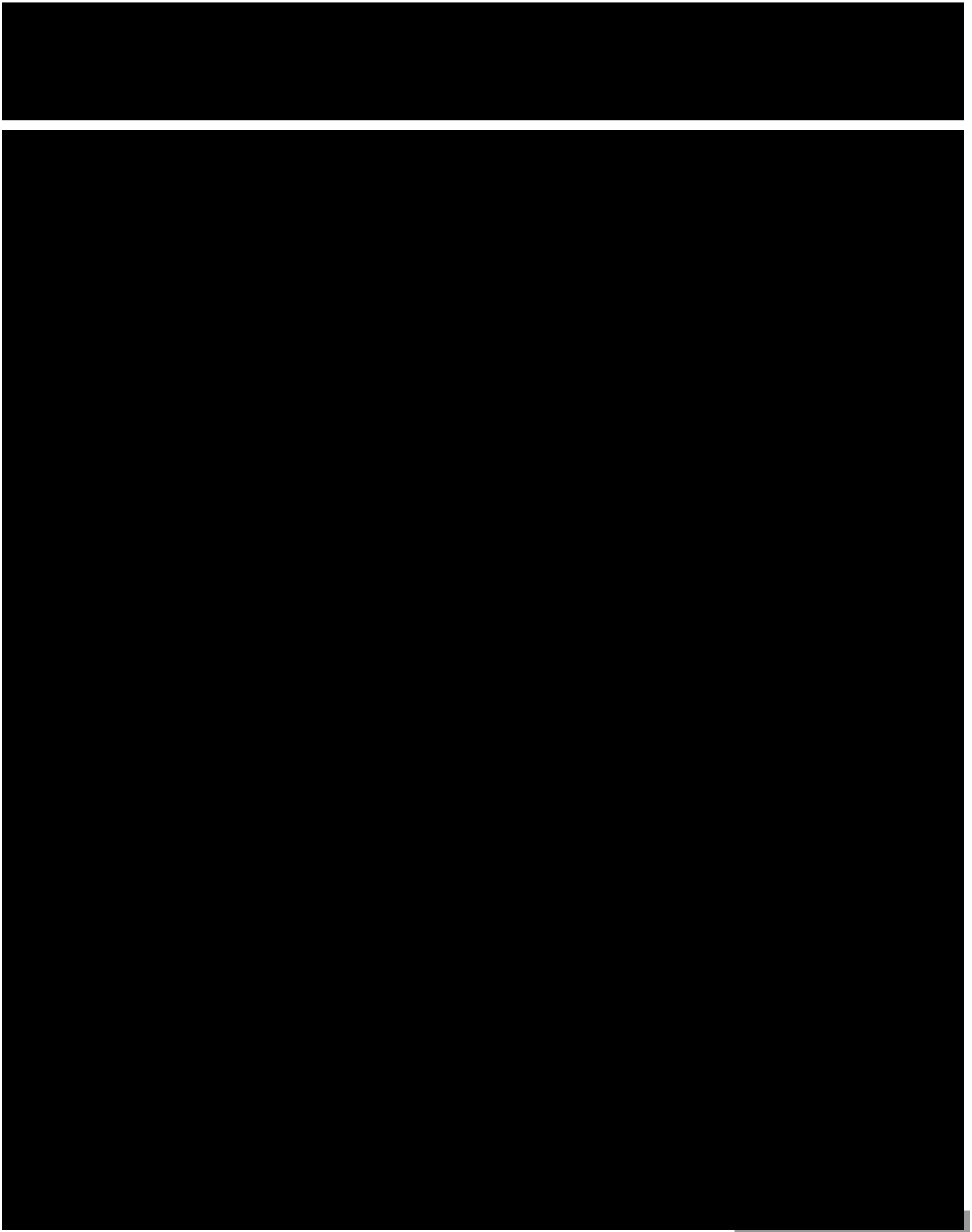

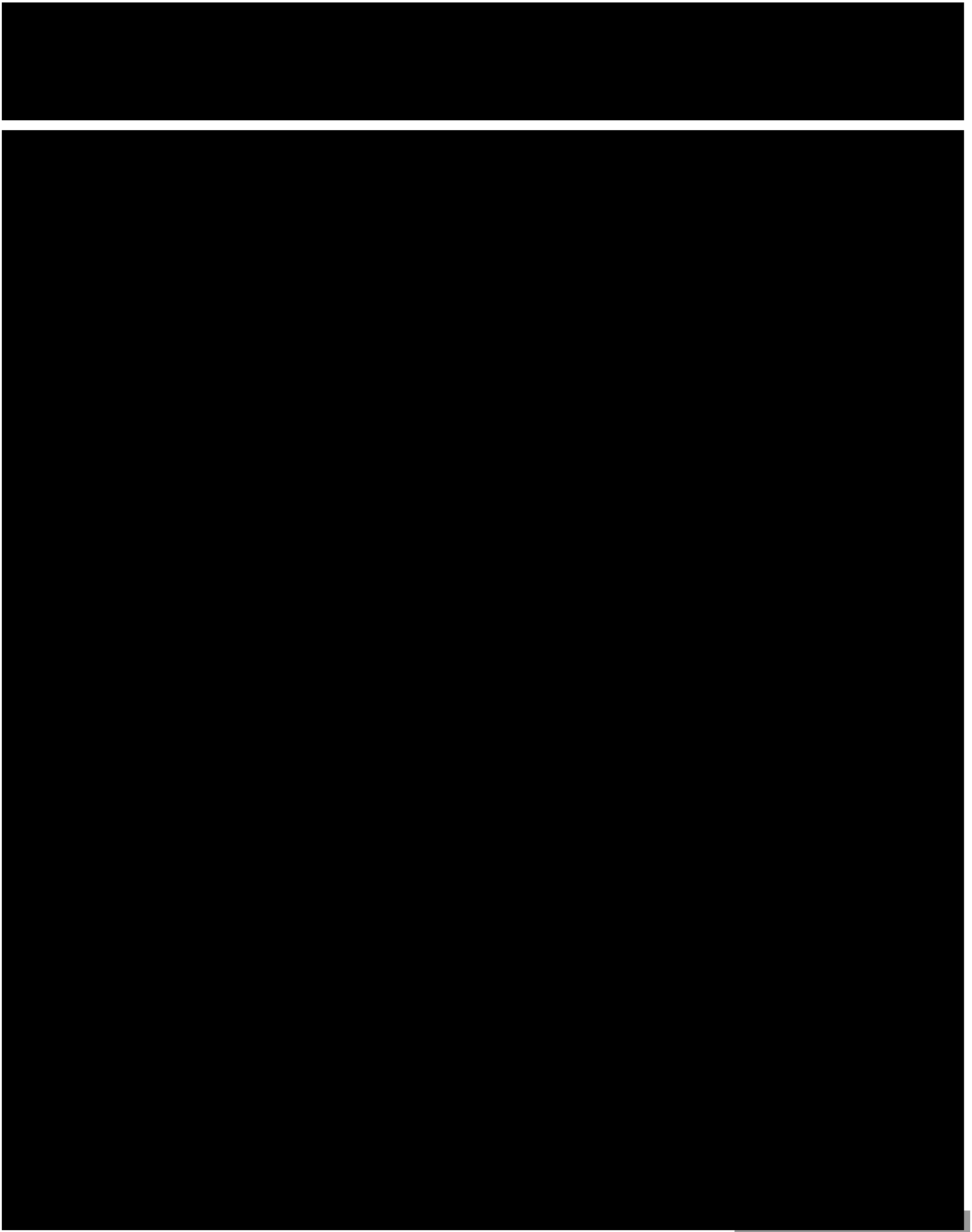

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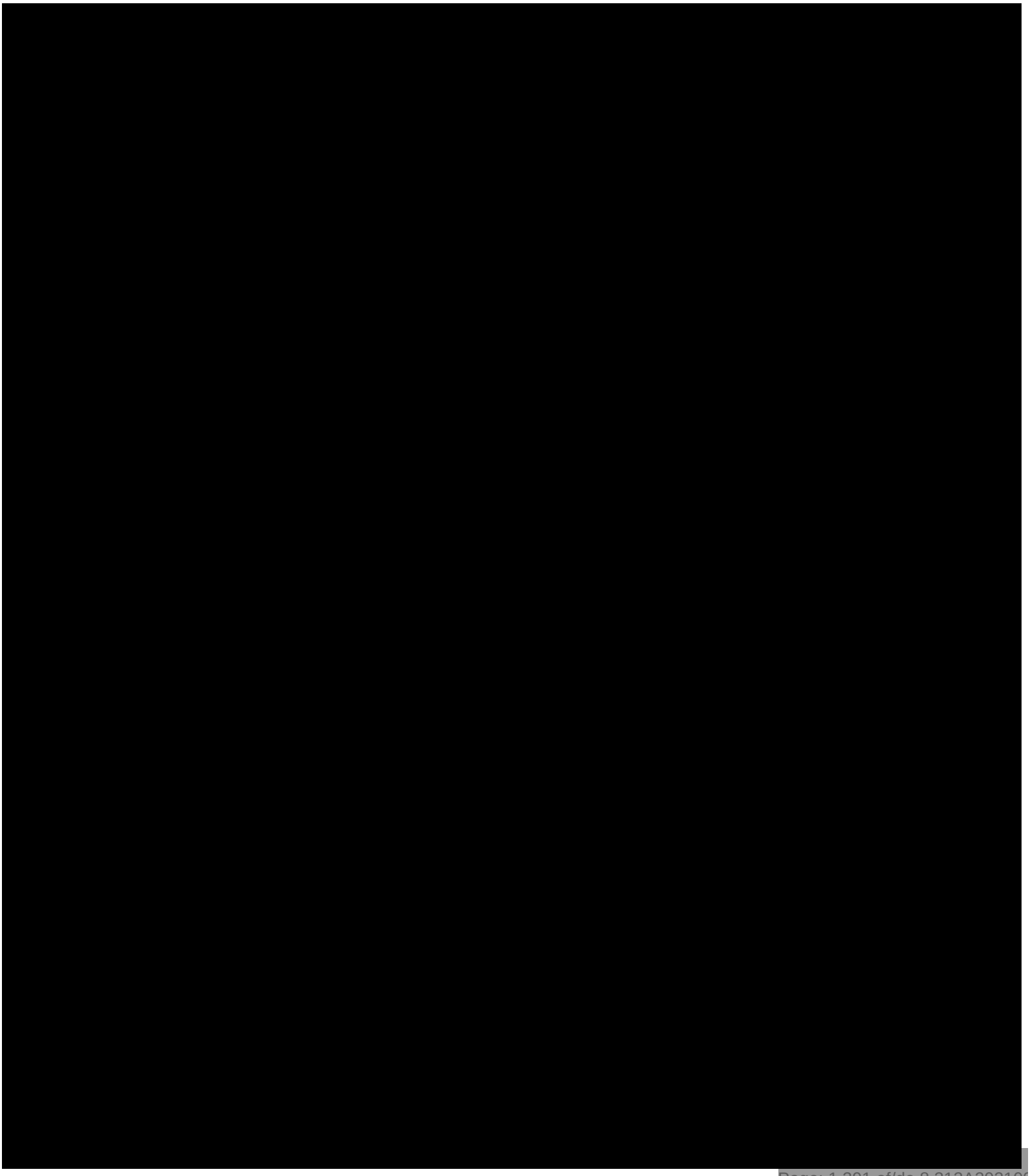

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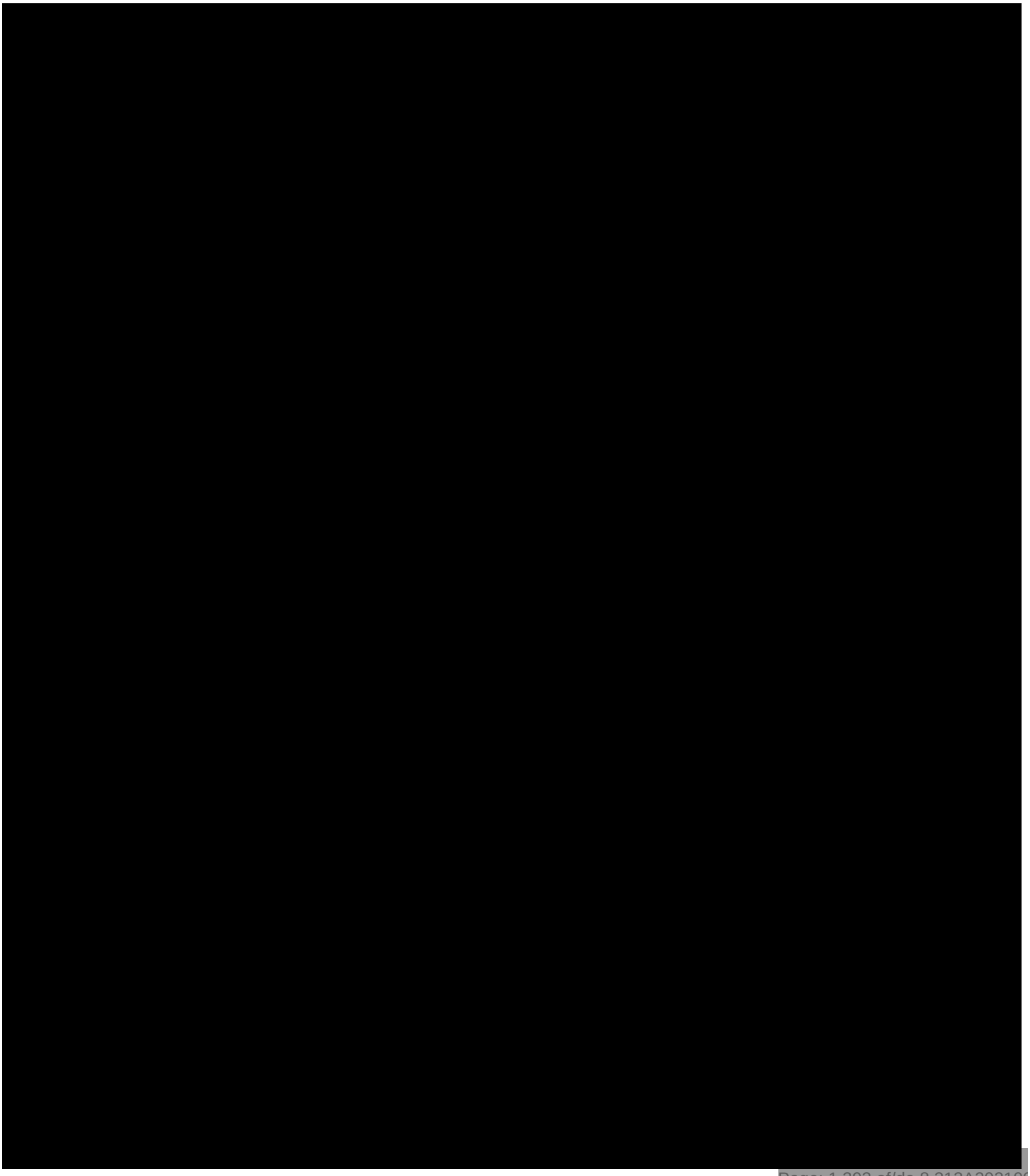

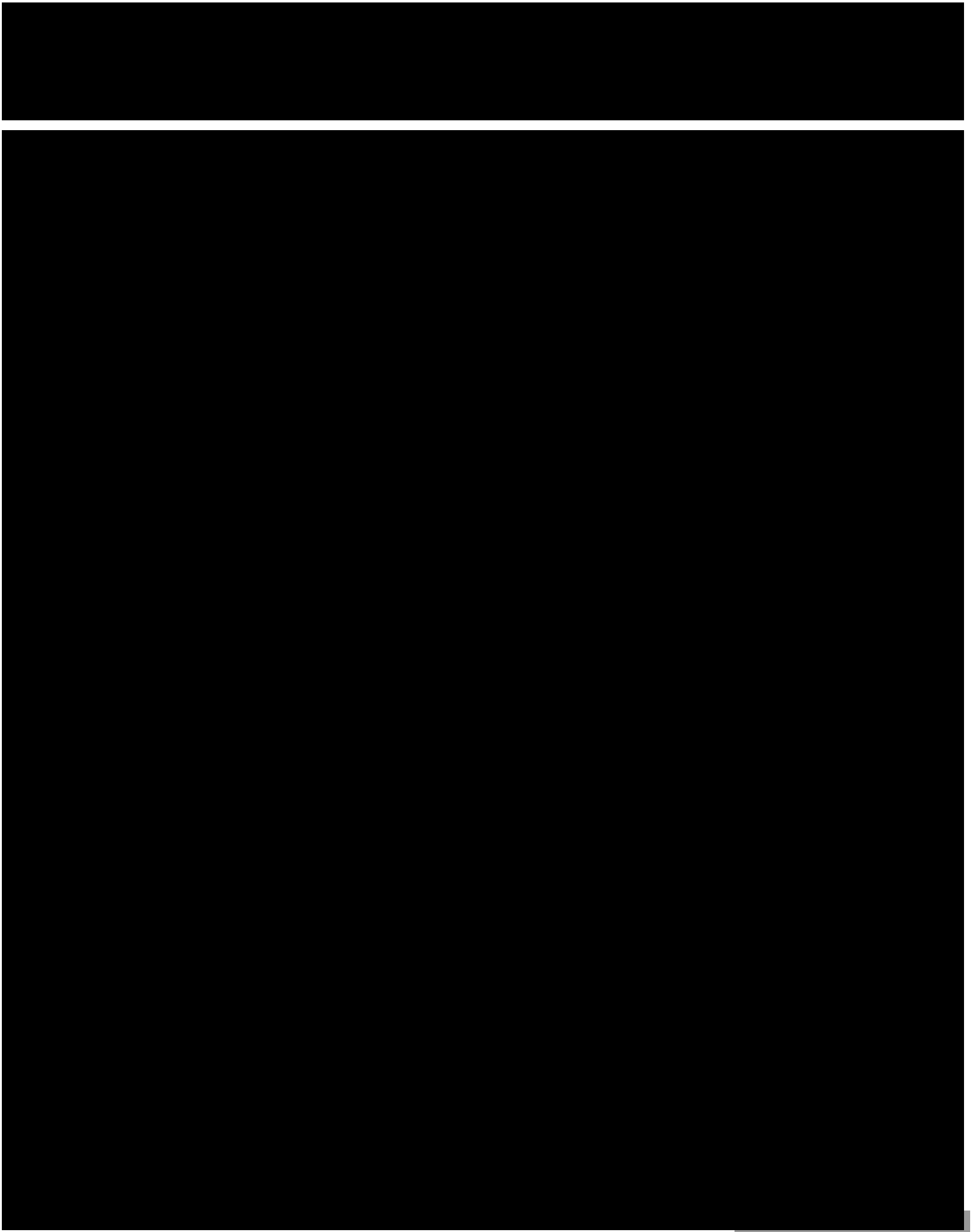

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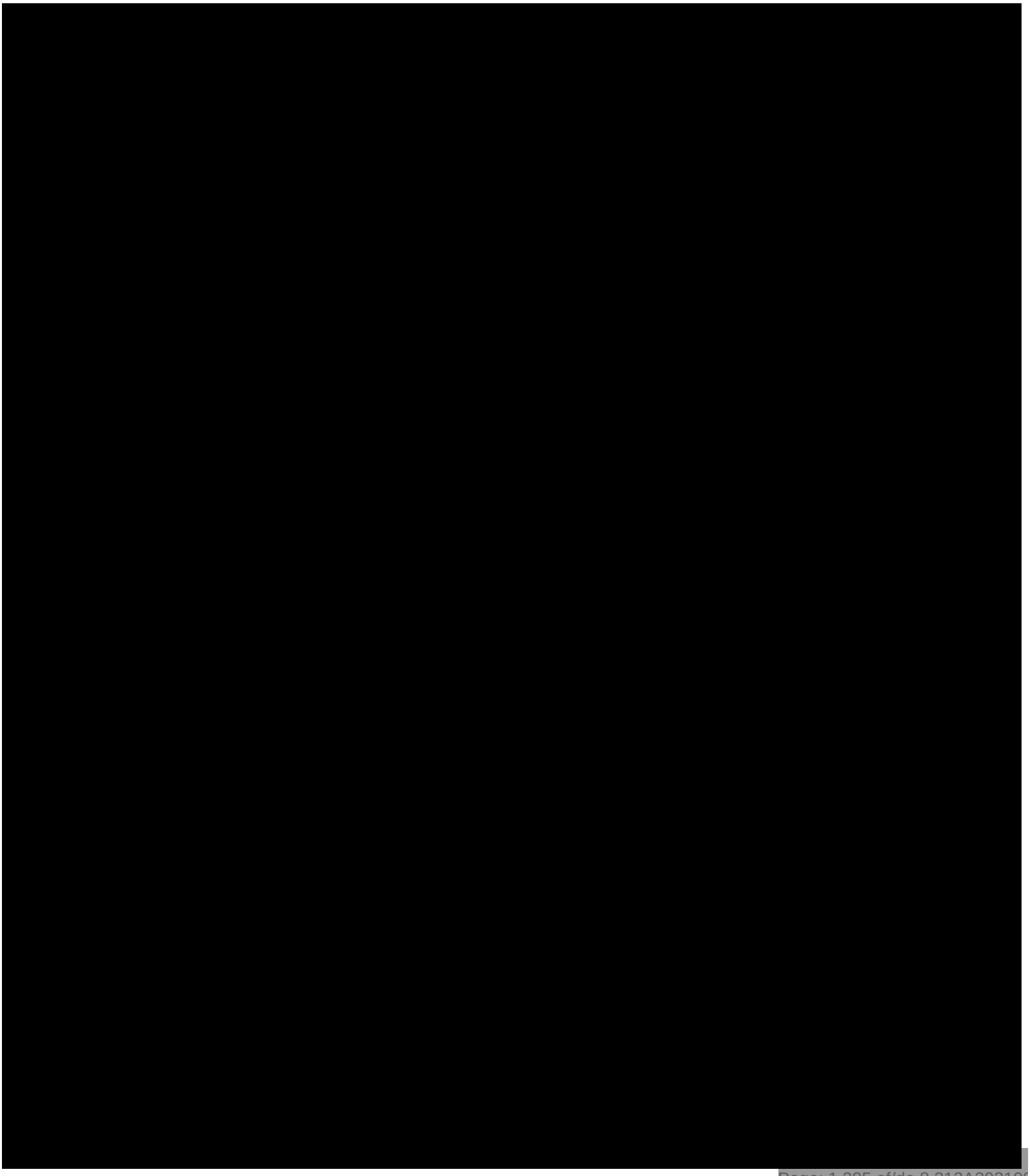

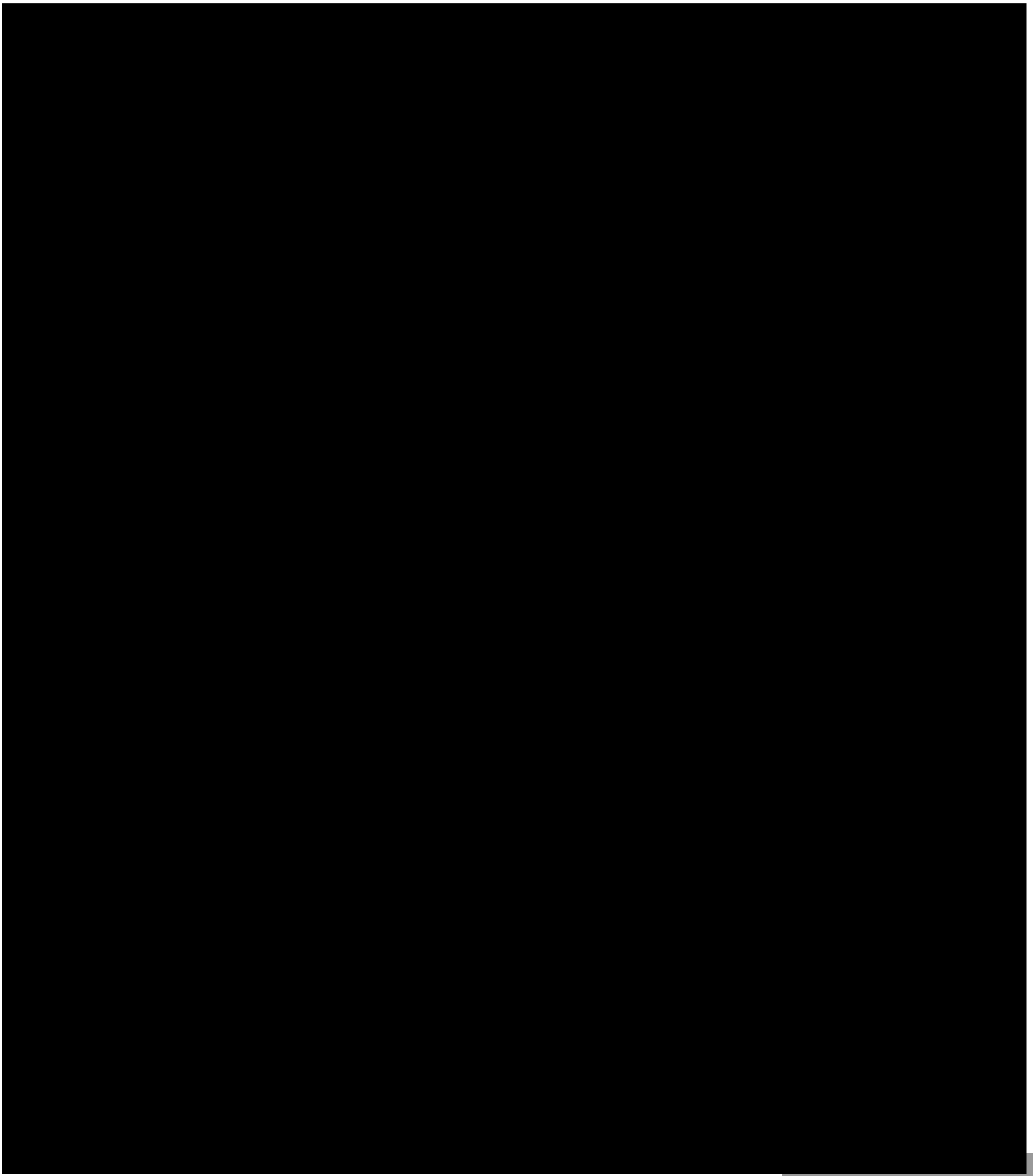

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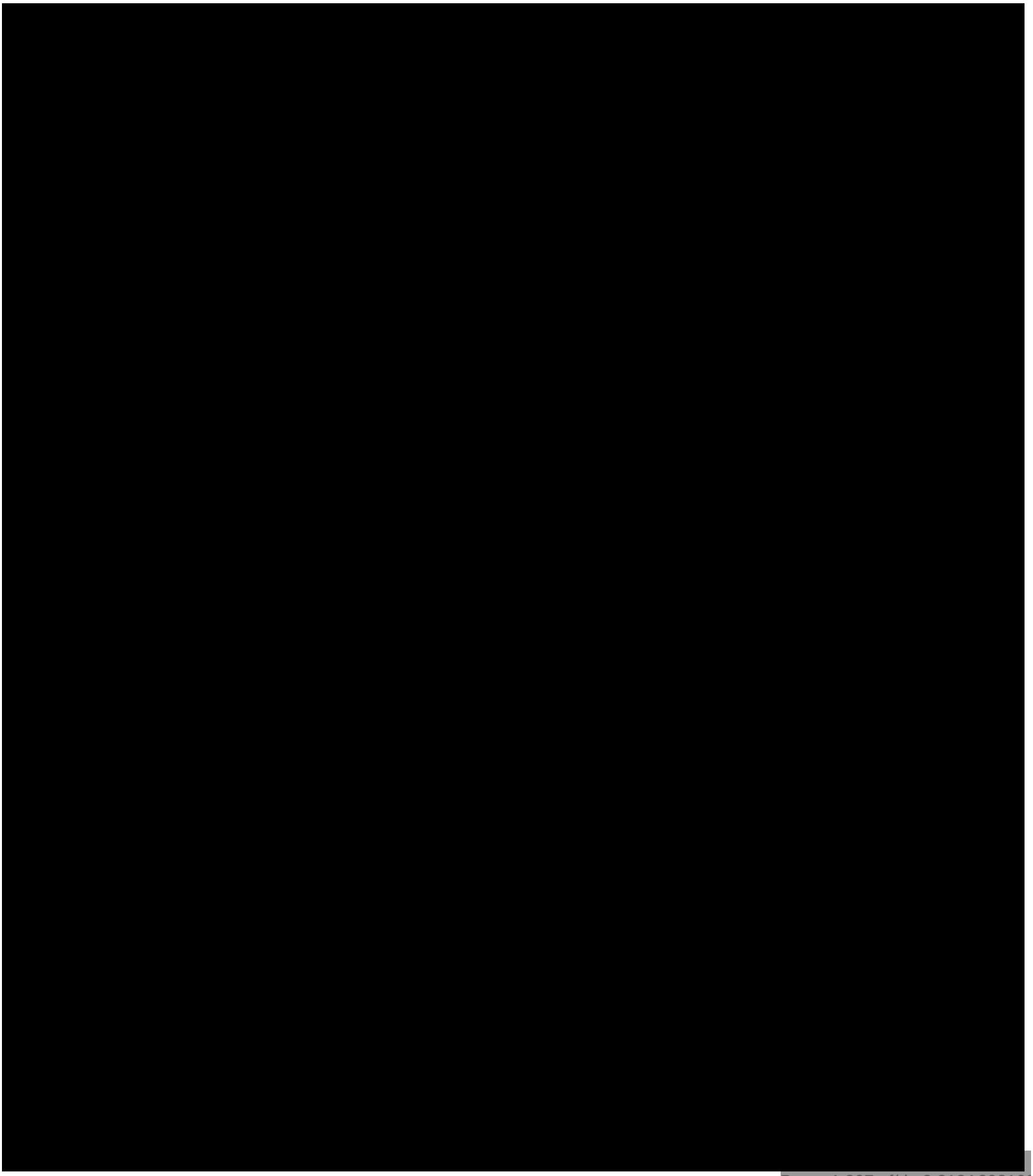

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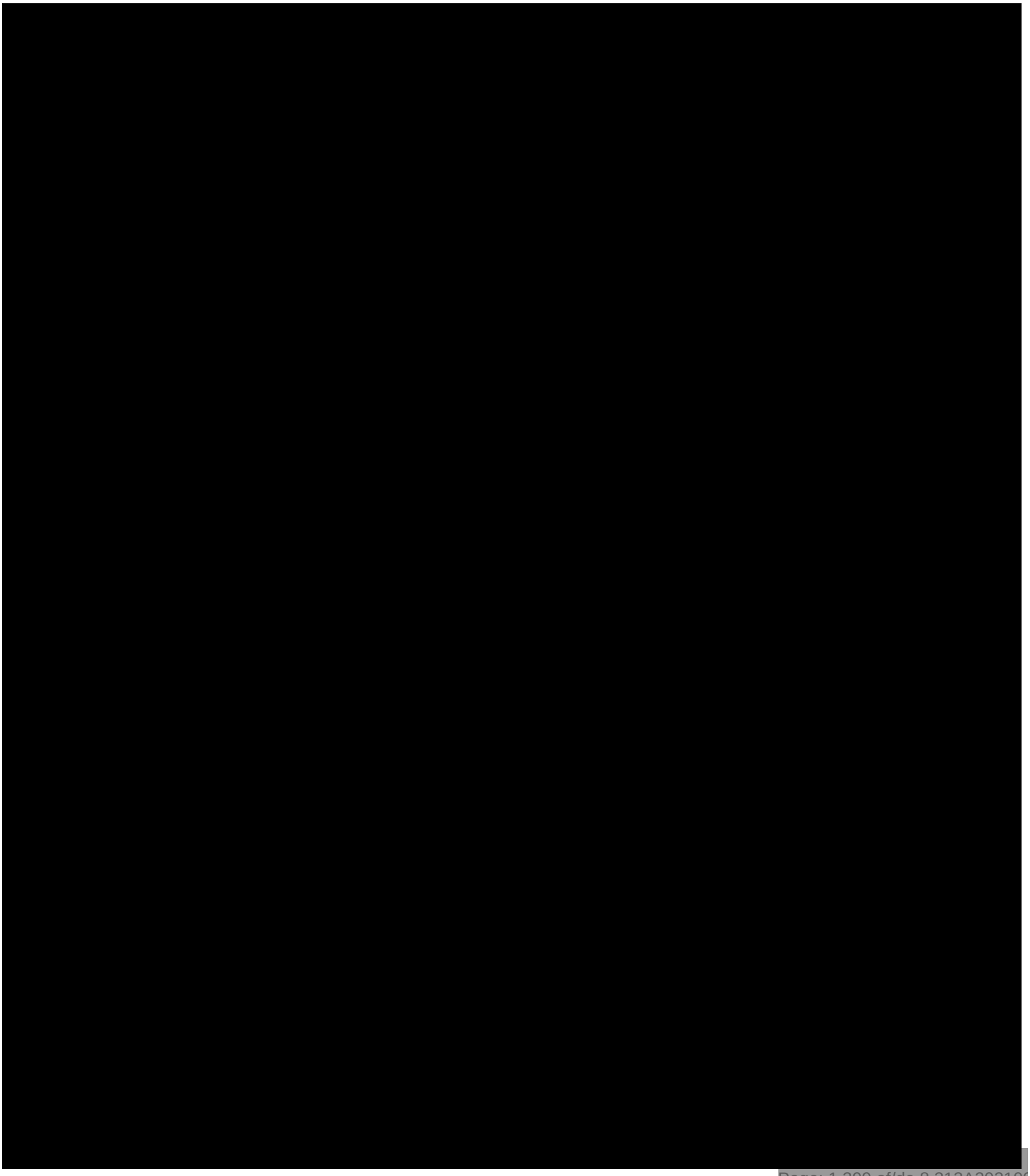

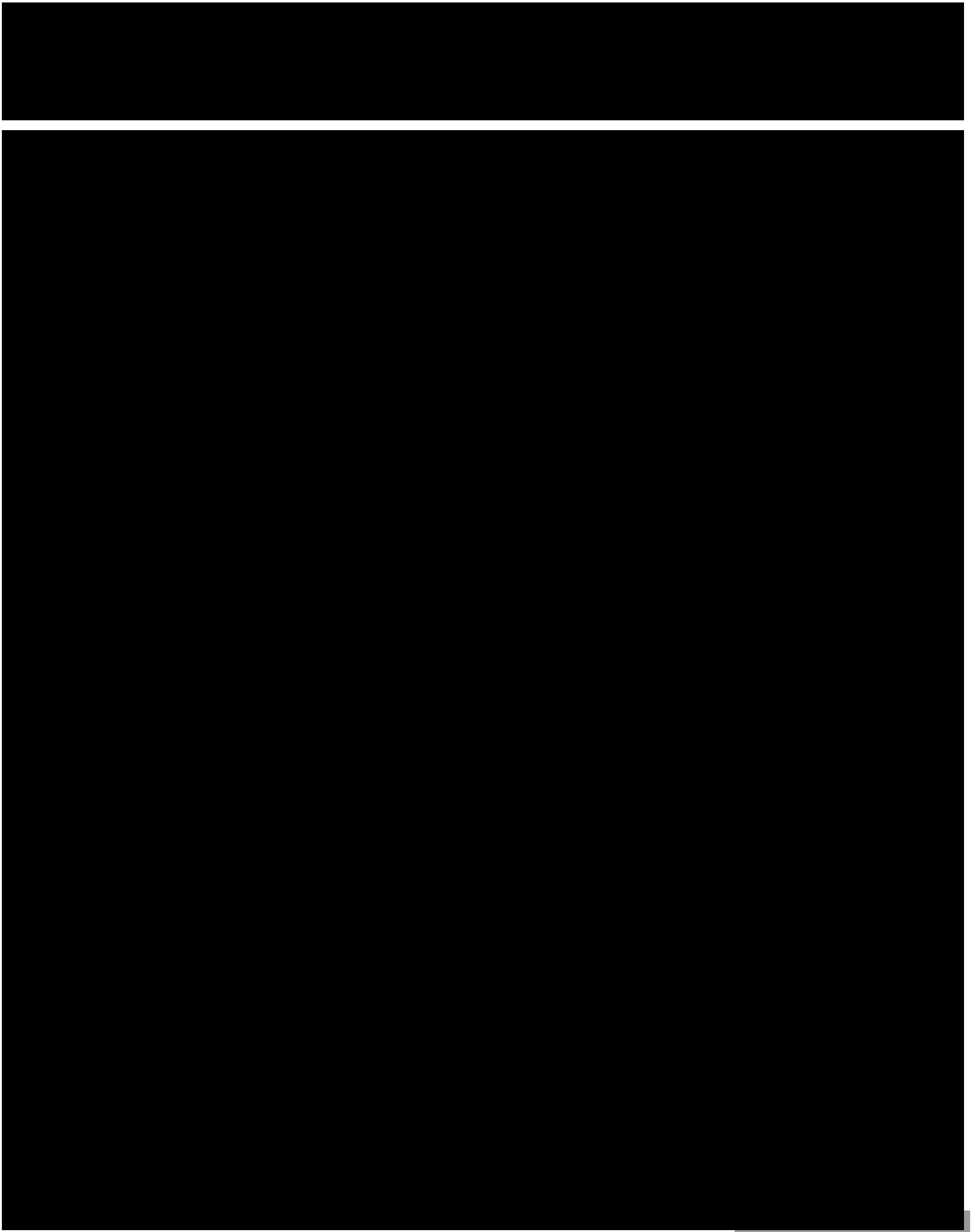

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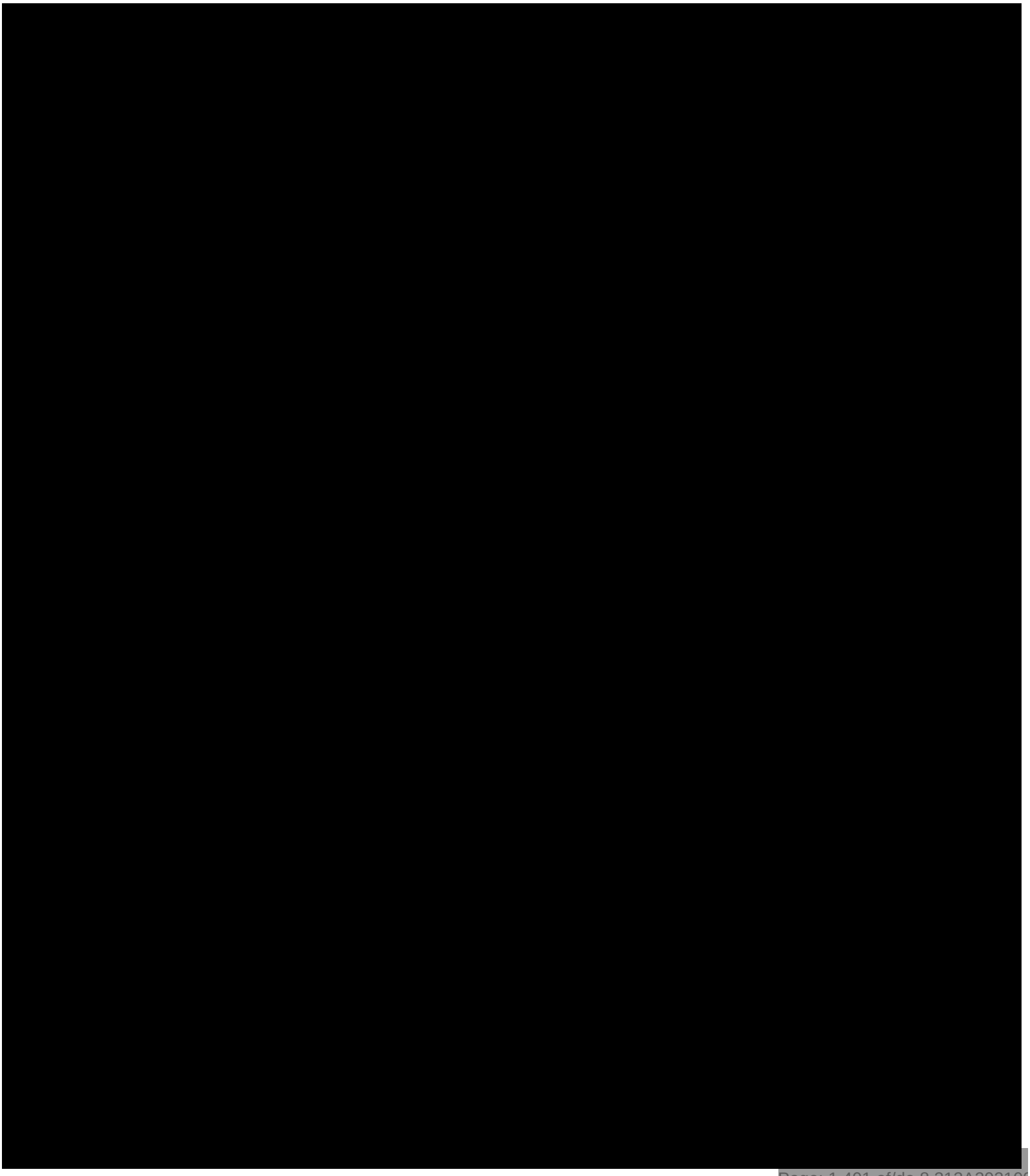

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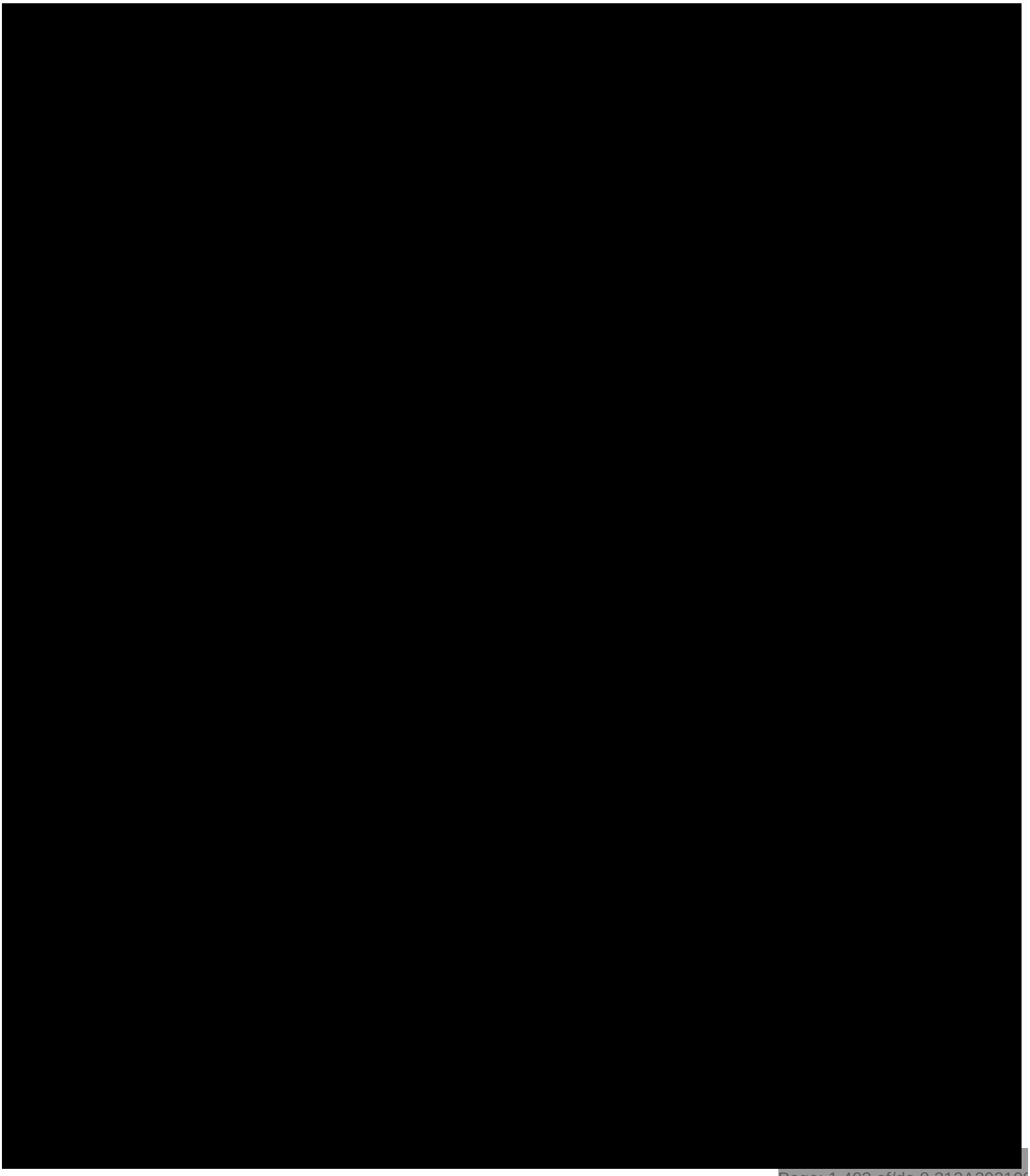

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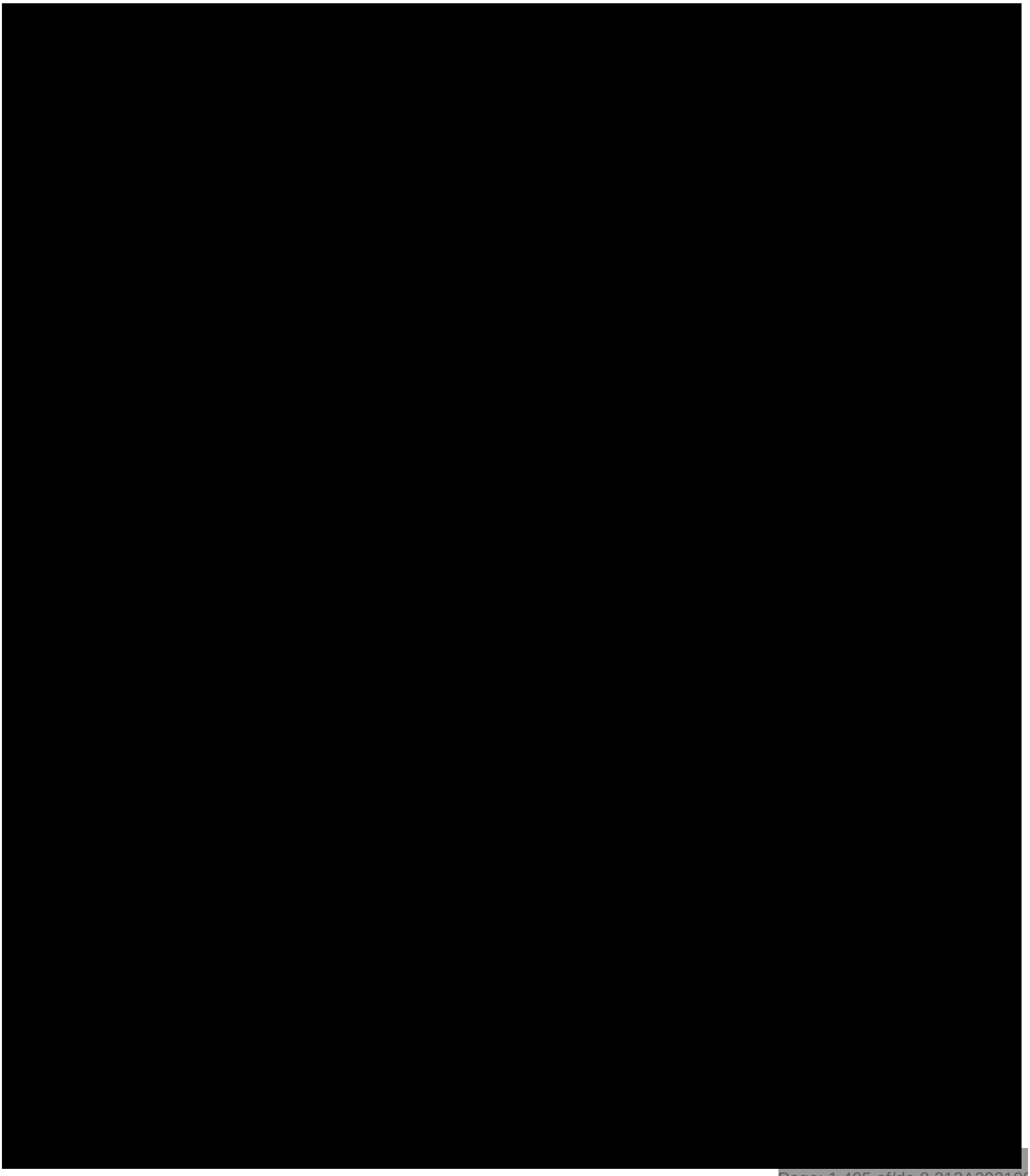

Ridgen, Patrick (HC/SC)

From: Patel, Shalu (HC/SC)
Sent: 2021-02-04 4:57 PM
To: [redacted]
Cc: [redacted] Akel, Sereen H (HC/SC); Panetta, Vincent (HC/SC); Alhaddad, Saj (HC/SC); Antonio, Christopher (HC/SC)
Subject: Final Meeting Minutes from Regulatory Strategy Overview Meeting for Novavax COVID-19 Vaccine, Control [redacted]

Dear [redacted]

[redacted]

Please confirm receipt of this email.

Regards,

Shalu Patel
(she / elle)

Senior Regulatory Affairs Officer
Biologic and Radiopharmaceutical Drugs Directorate
Health Products and Food Branch / Health Canada
shalu.patel@canada.ca / Tel: 613-462-8129 / Fax: 613-946-9520

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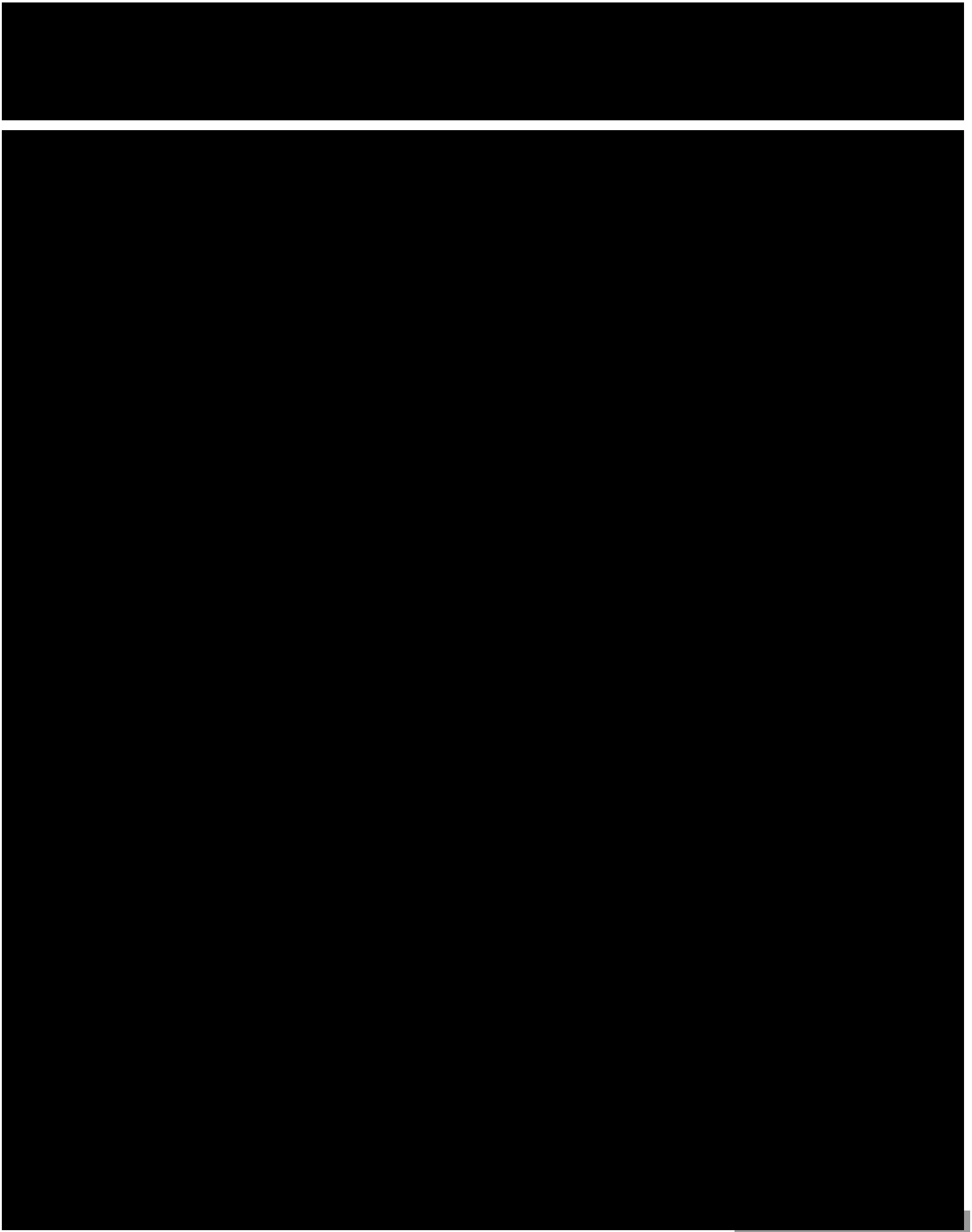

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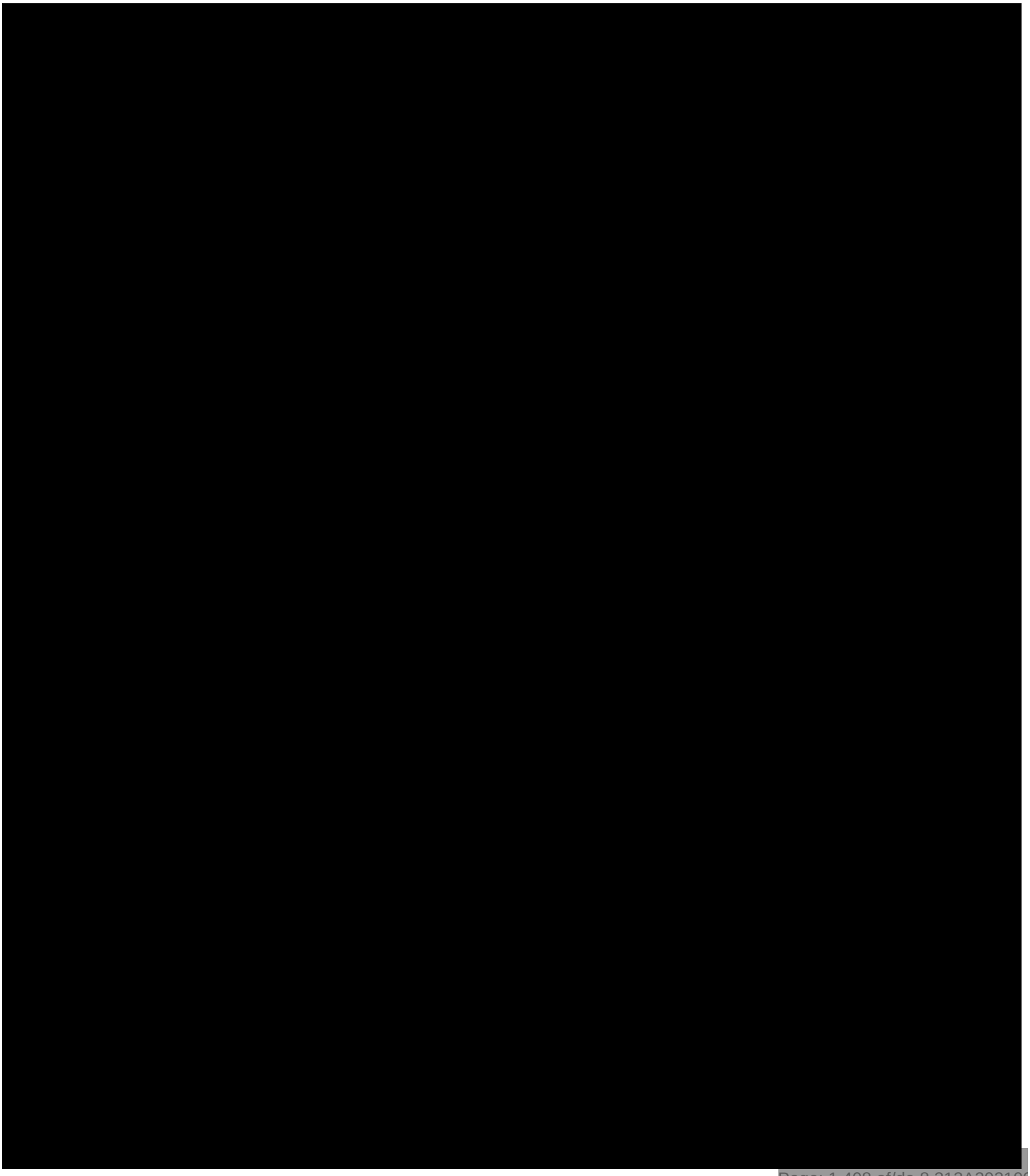

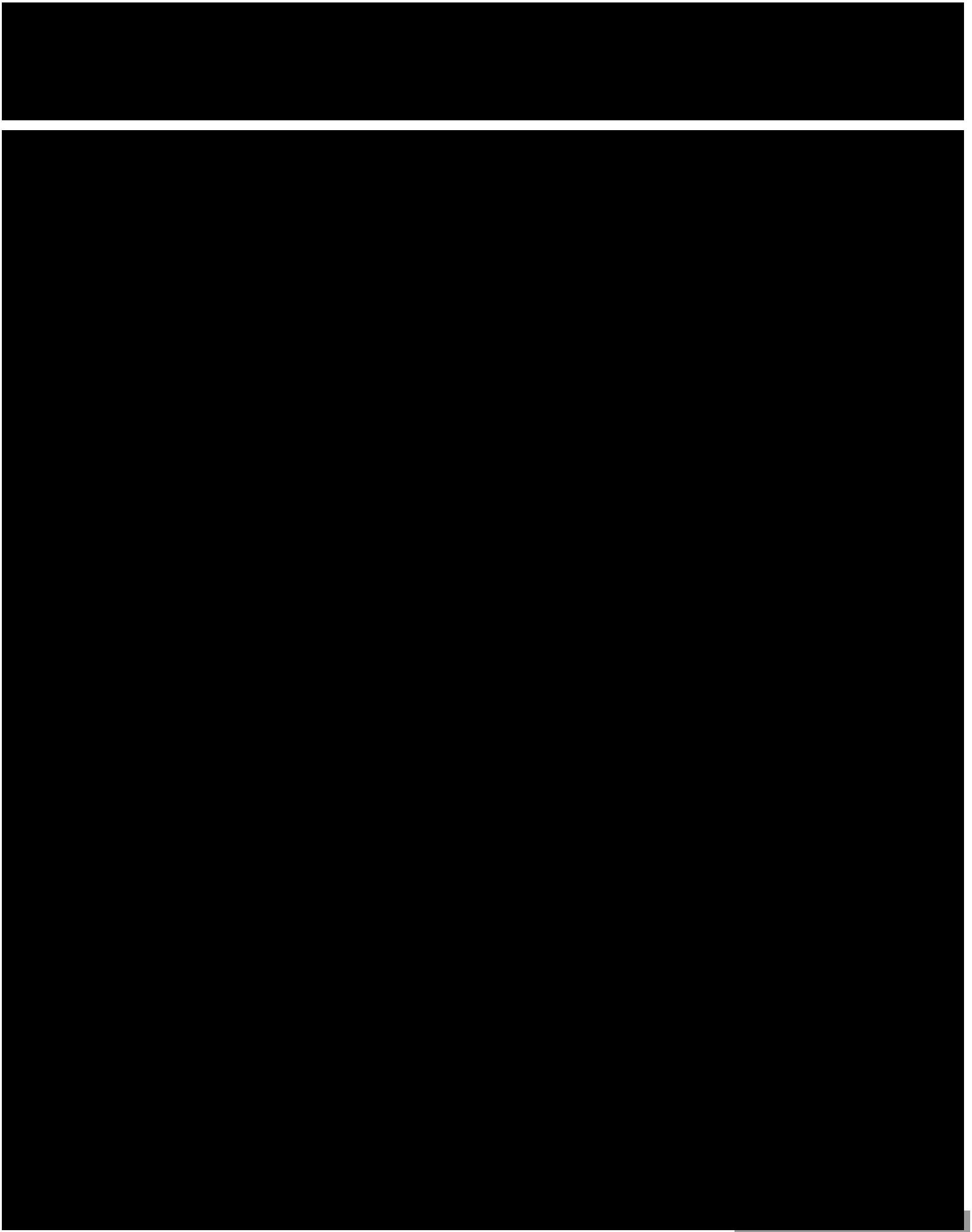

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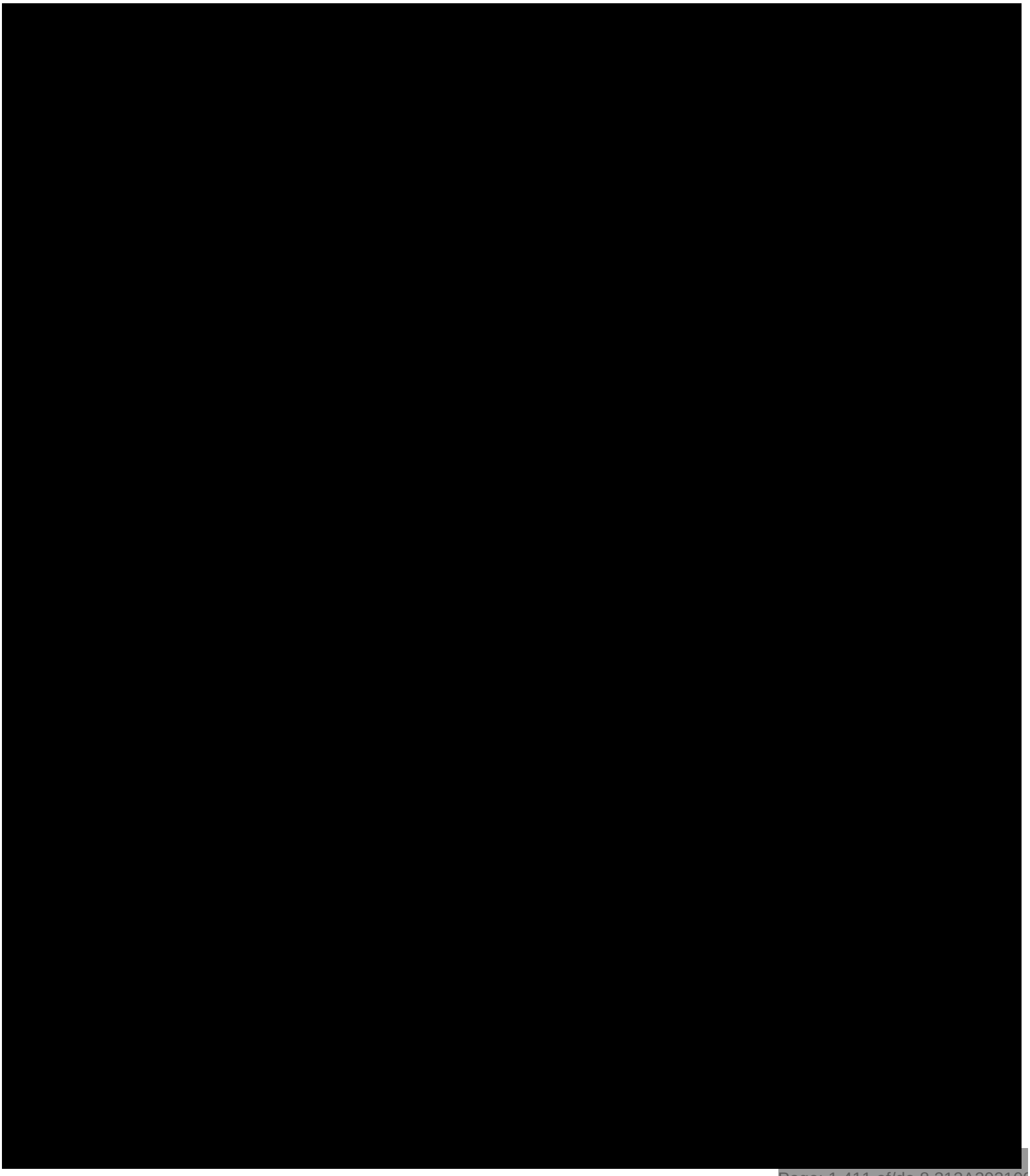

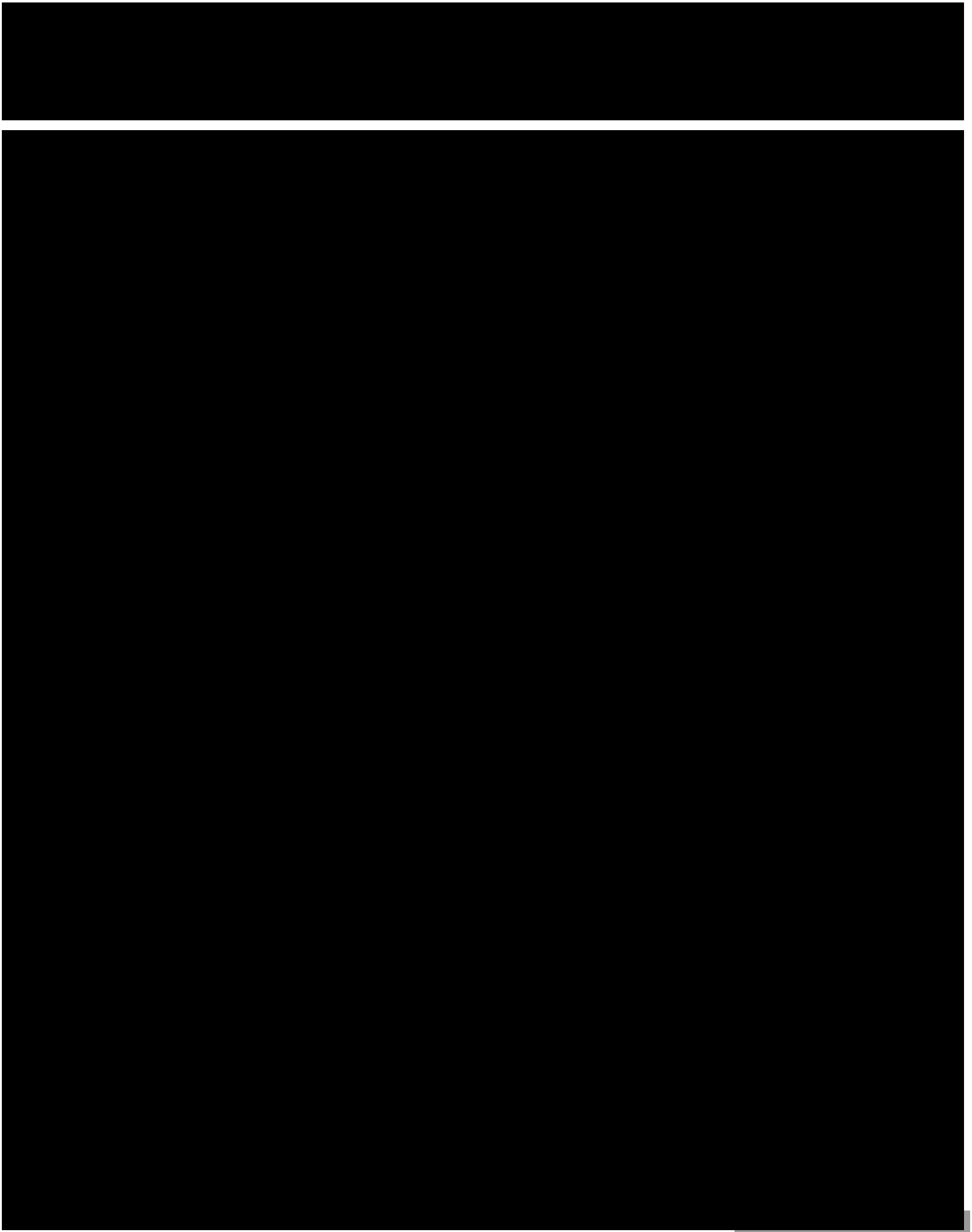

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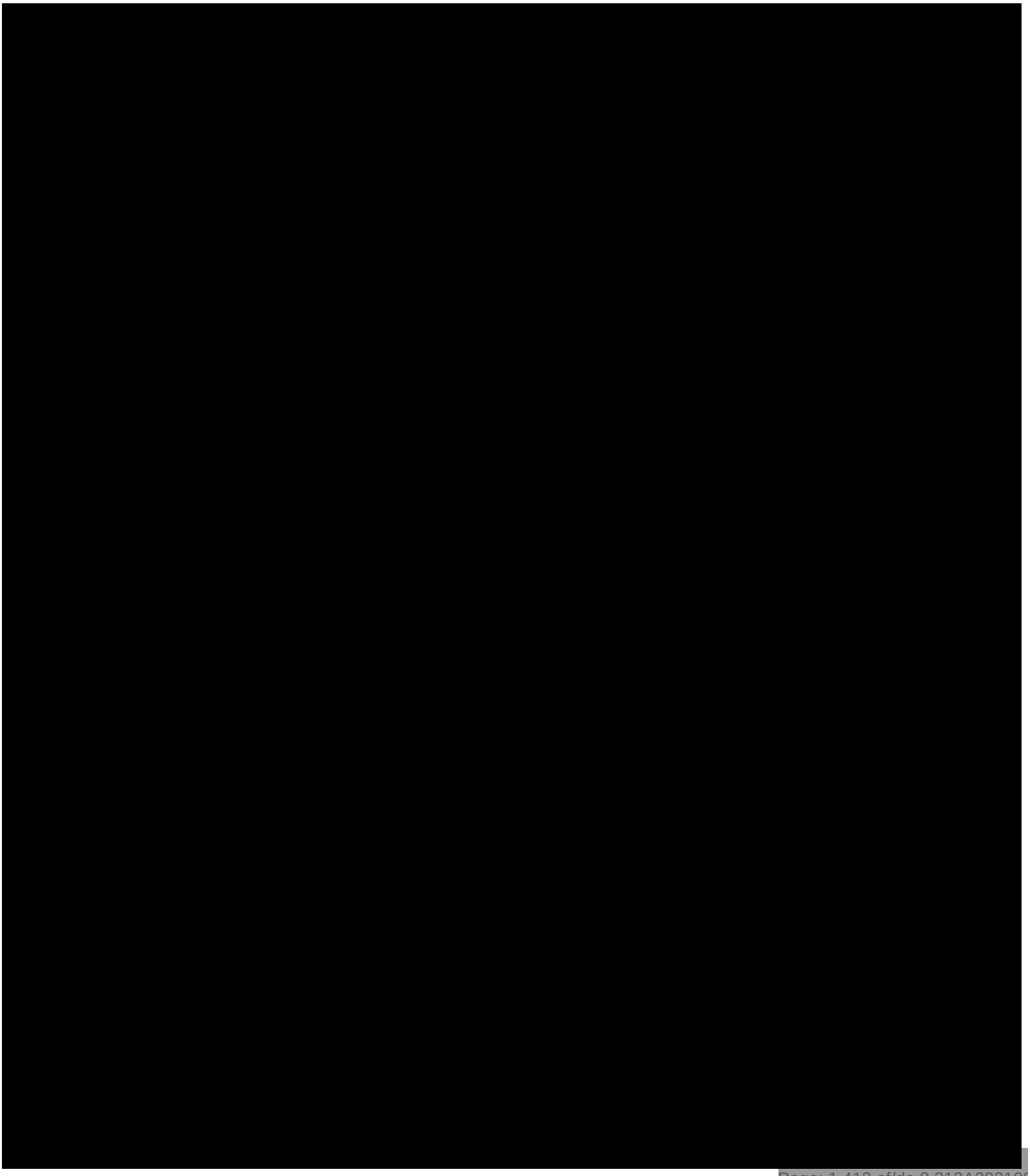

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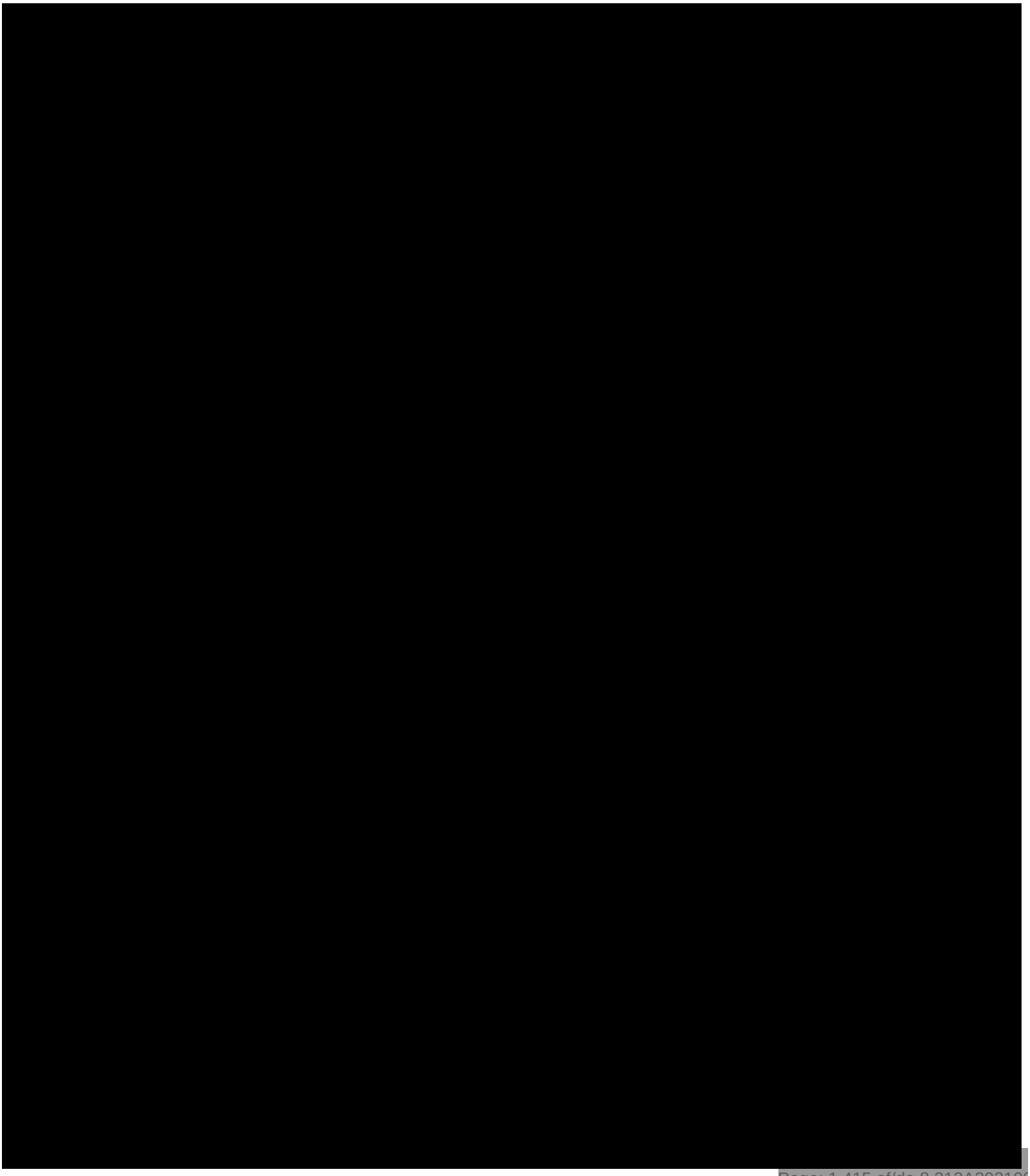

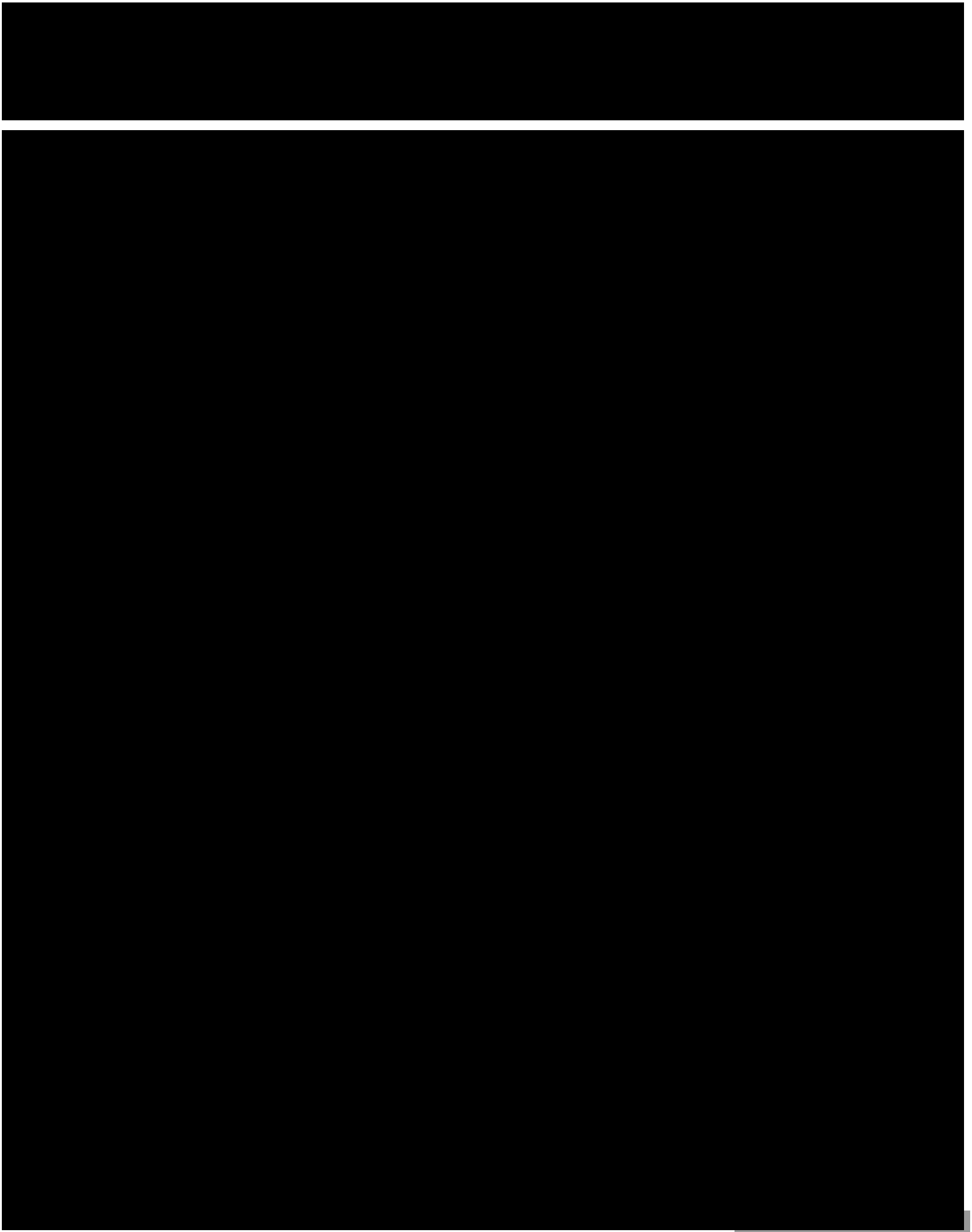

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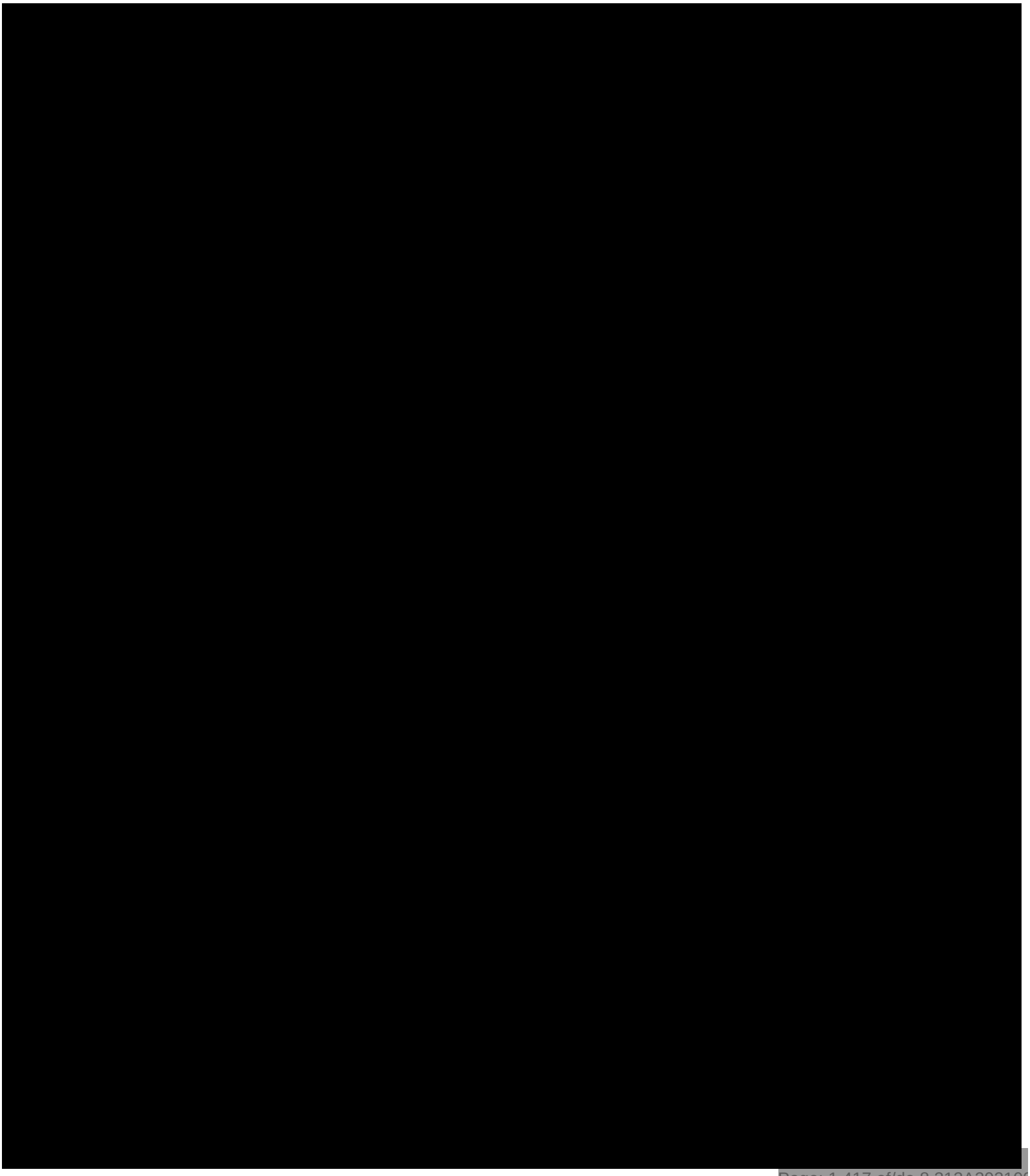

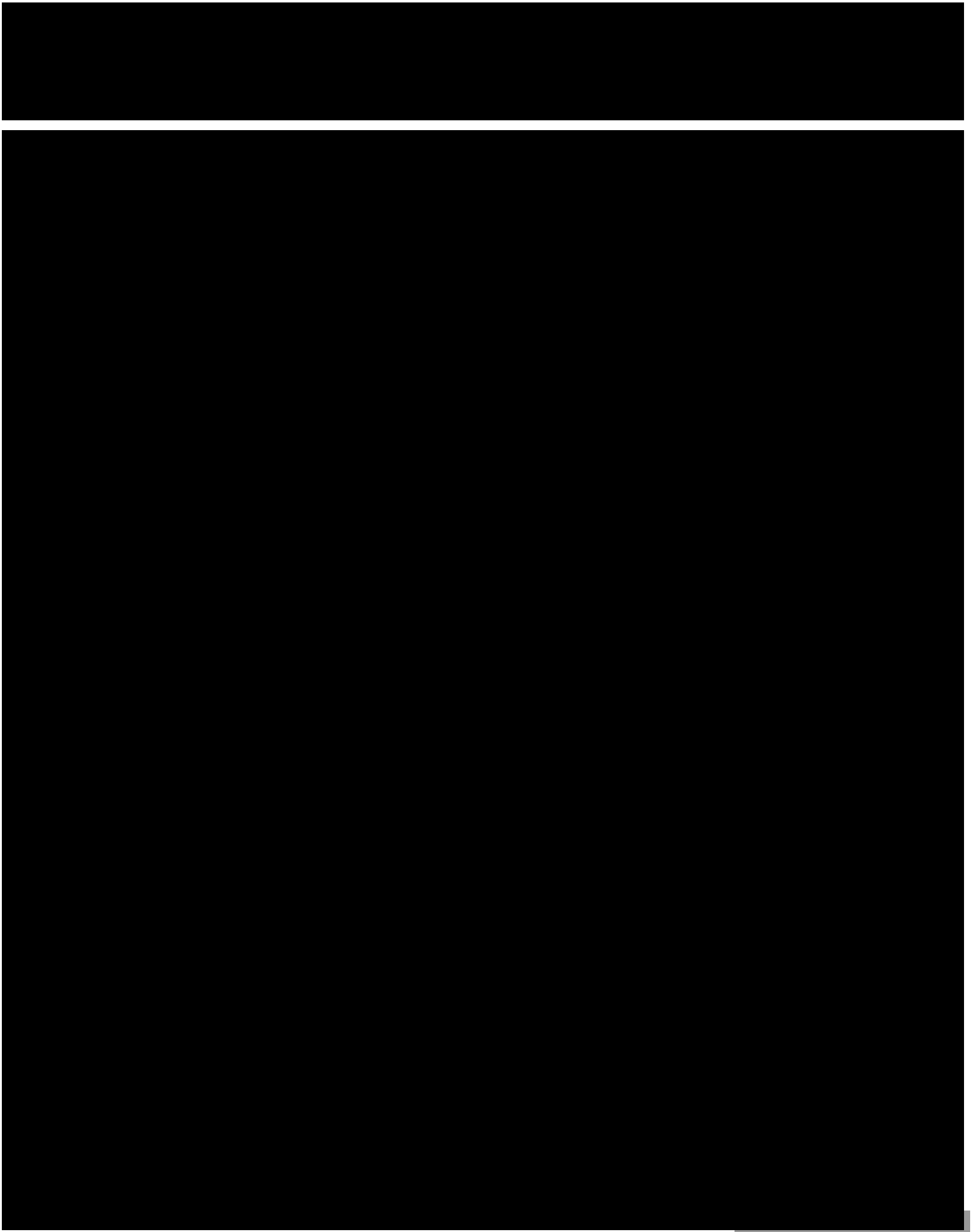

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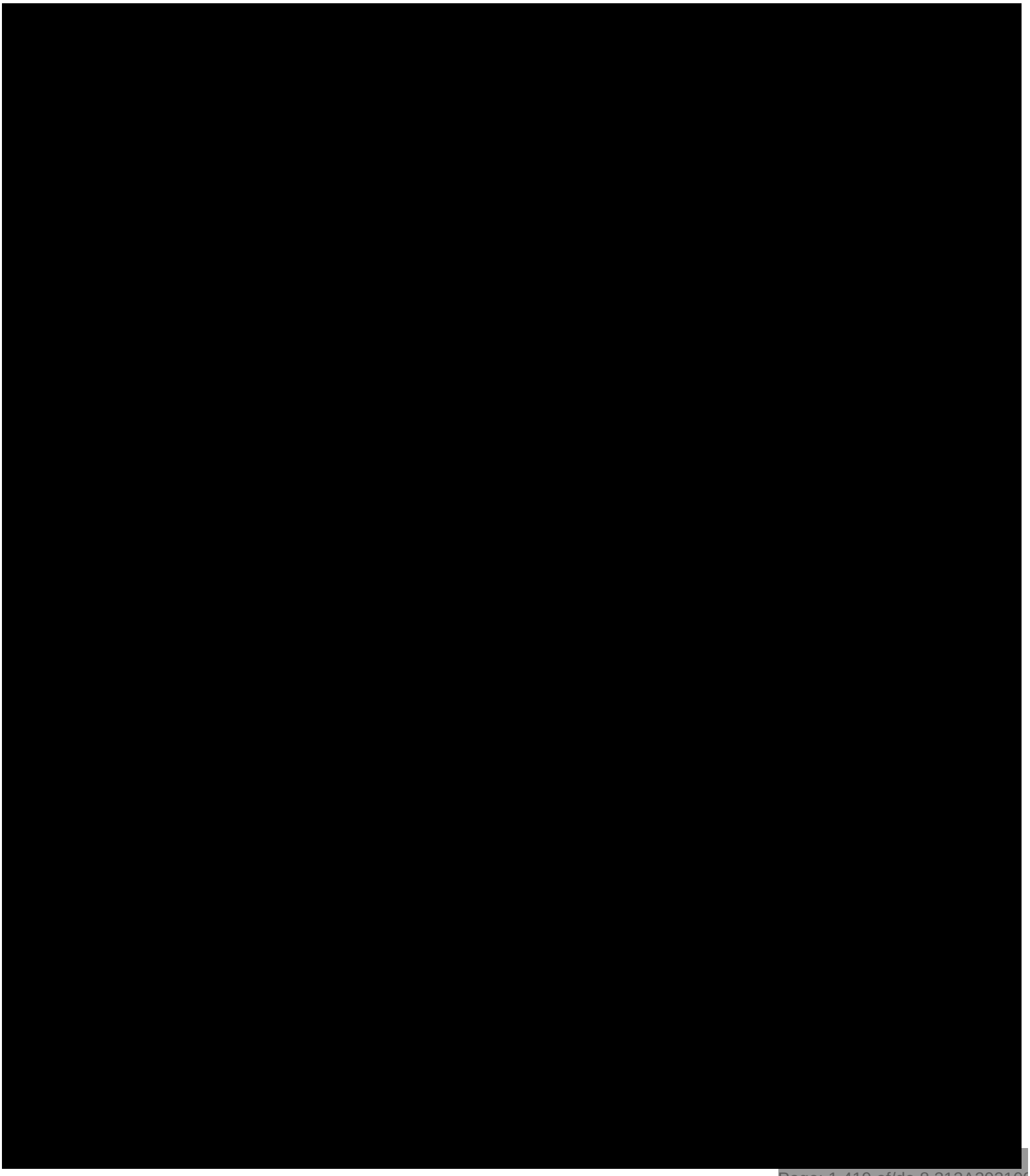

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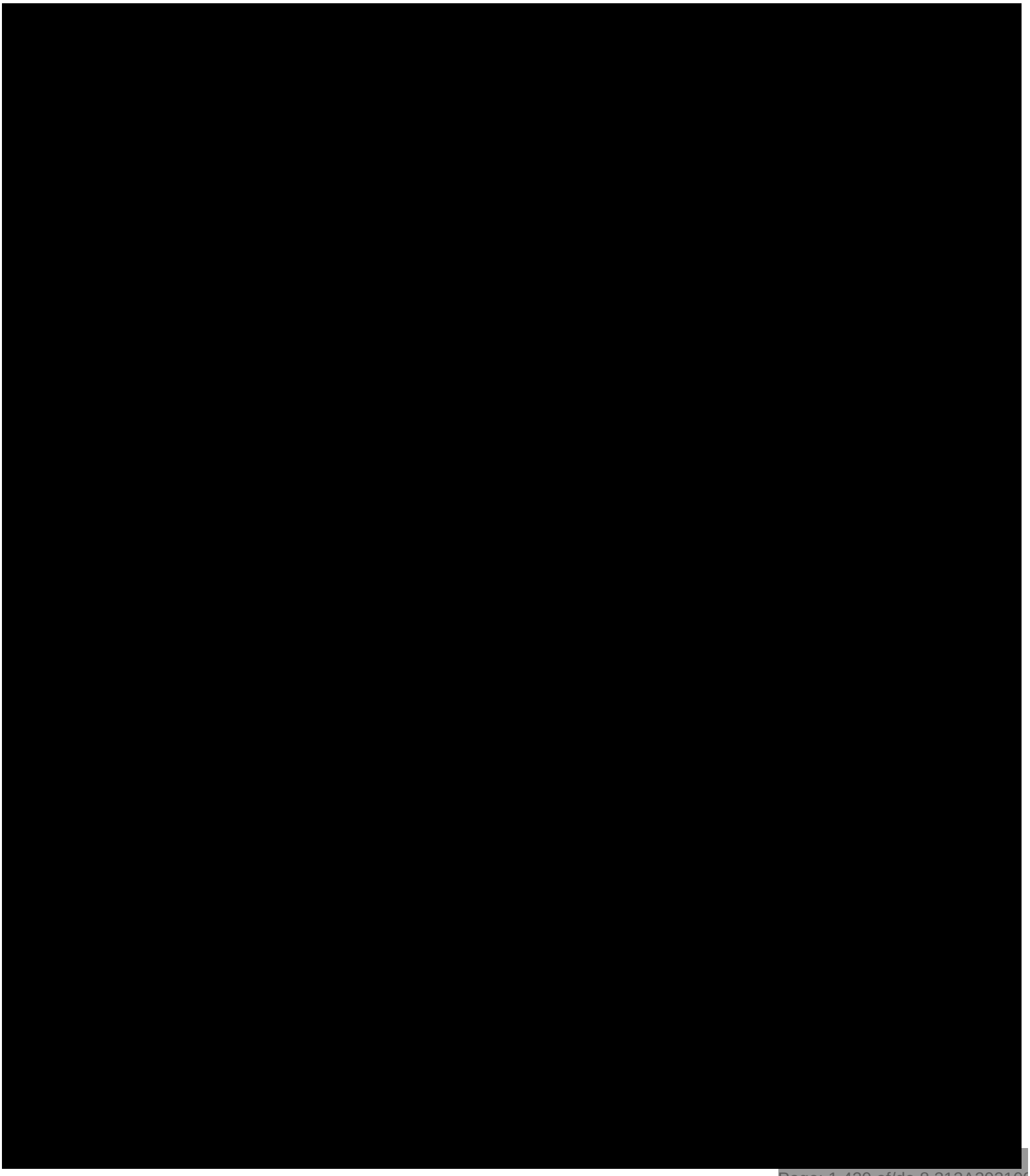

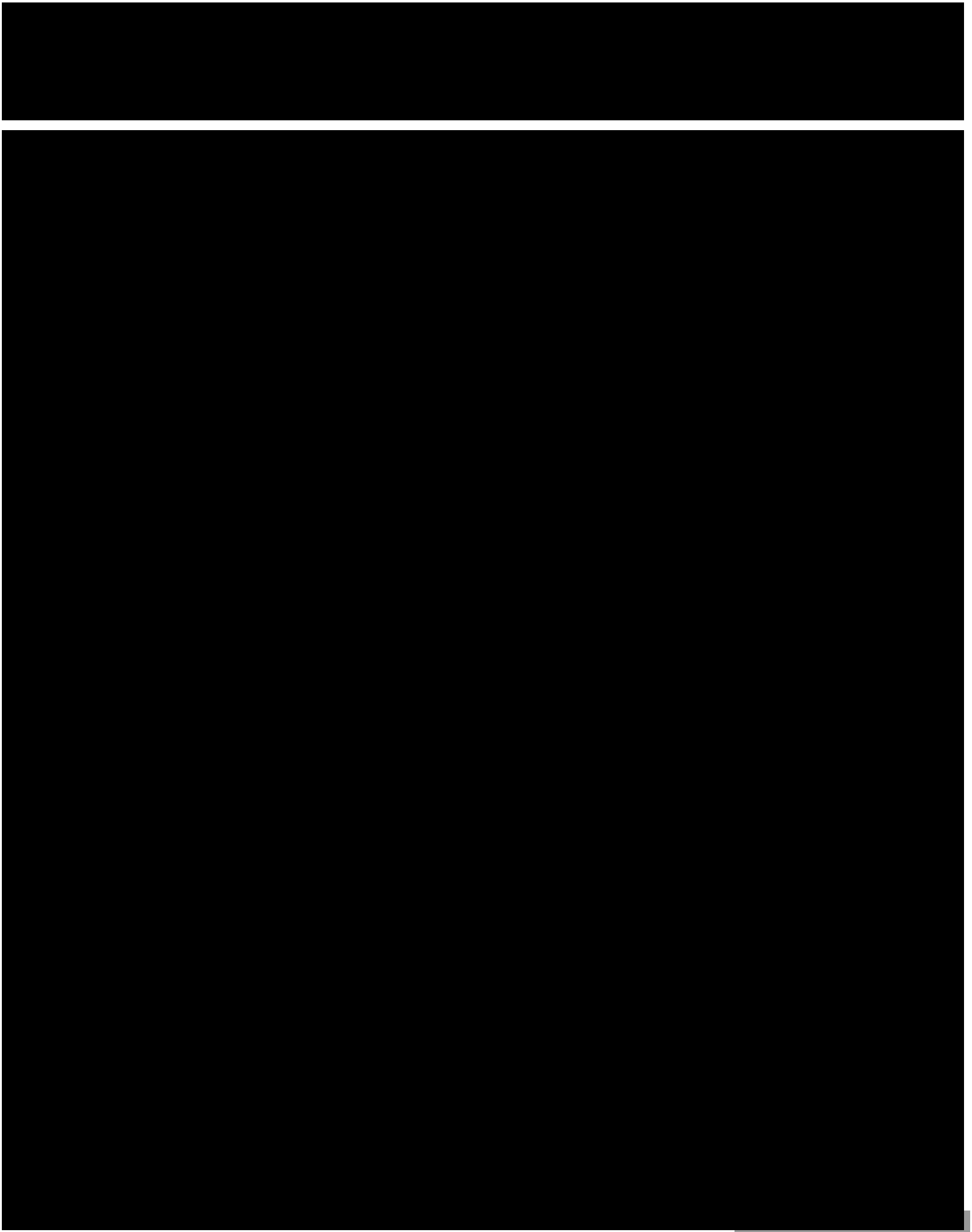

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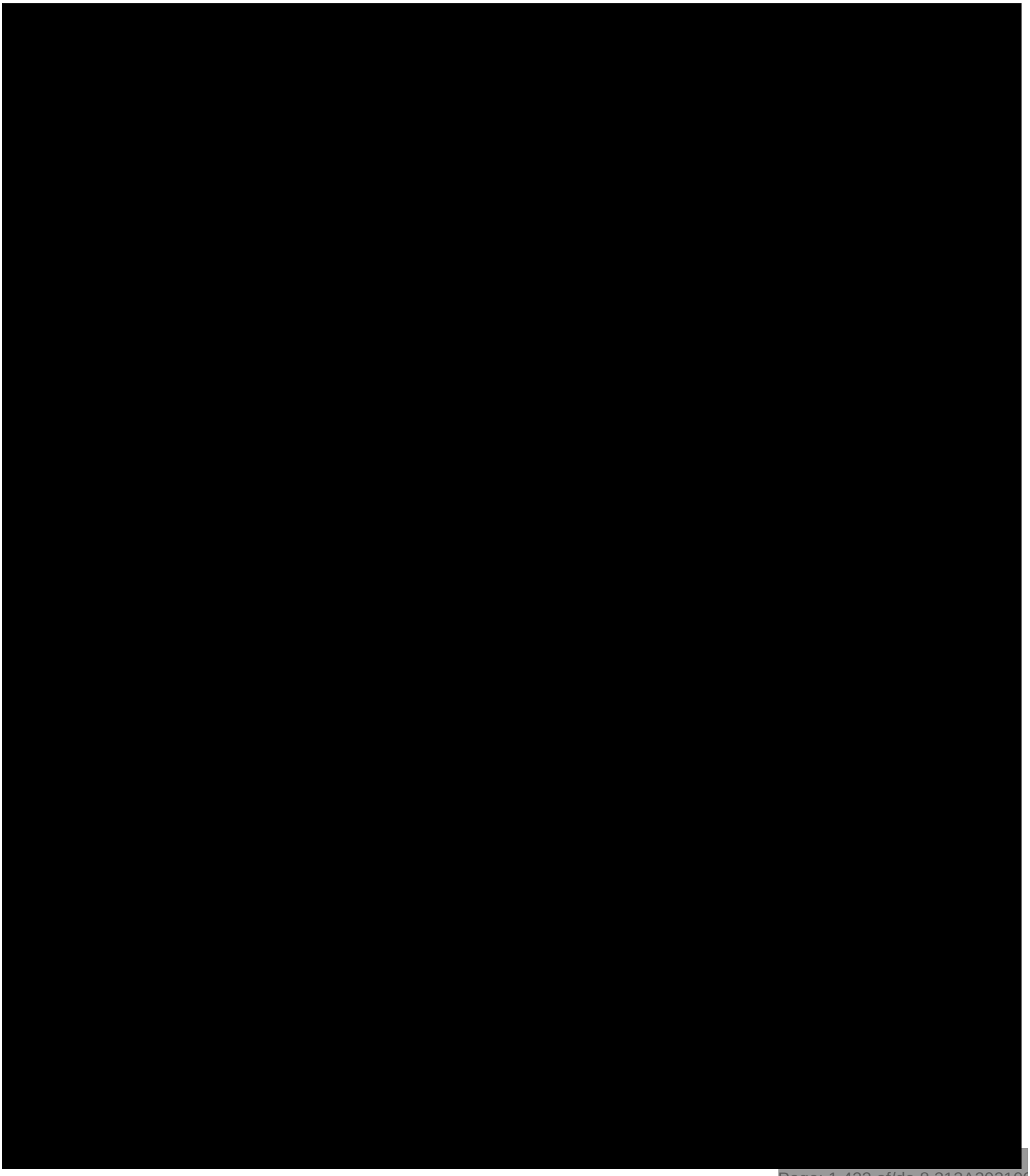

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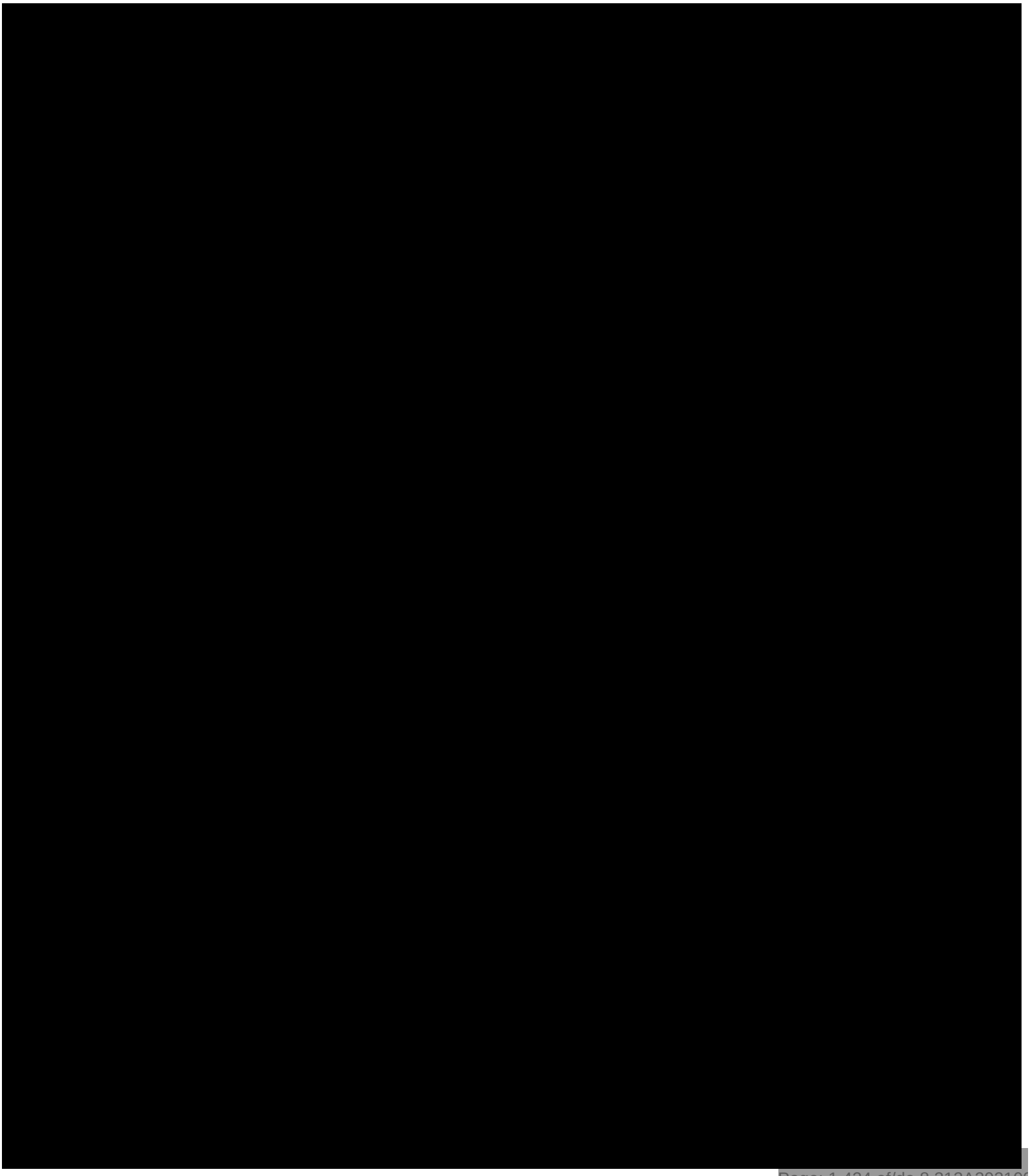

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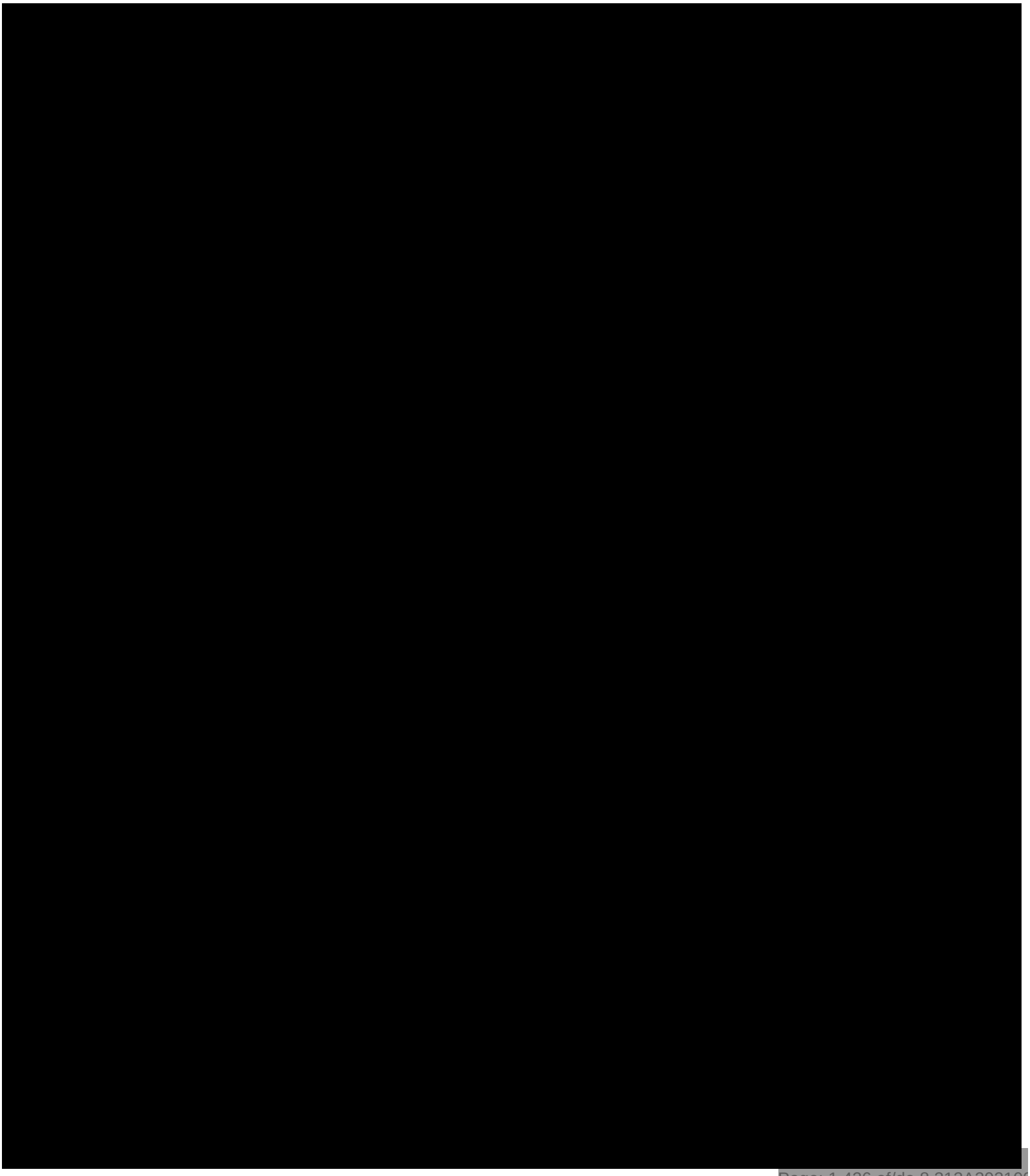

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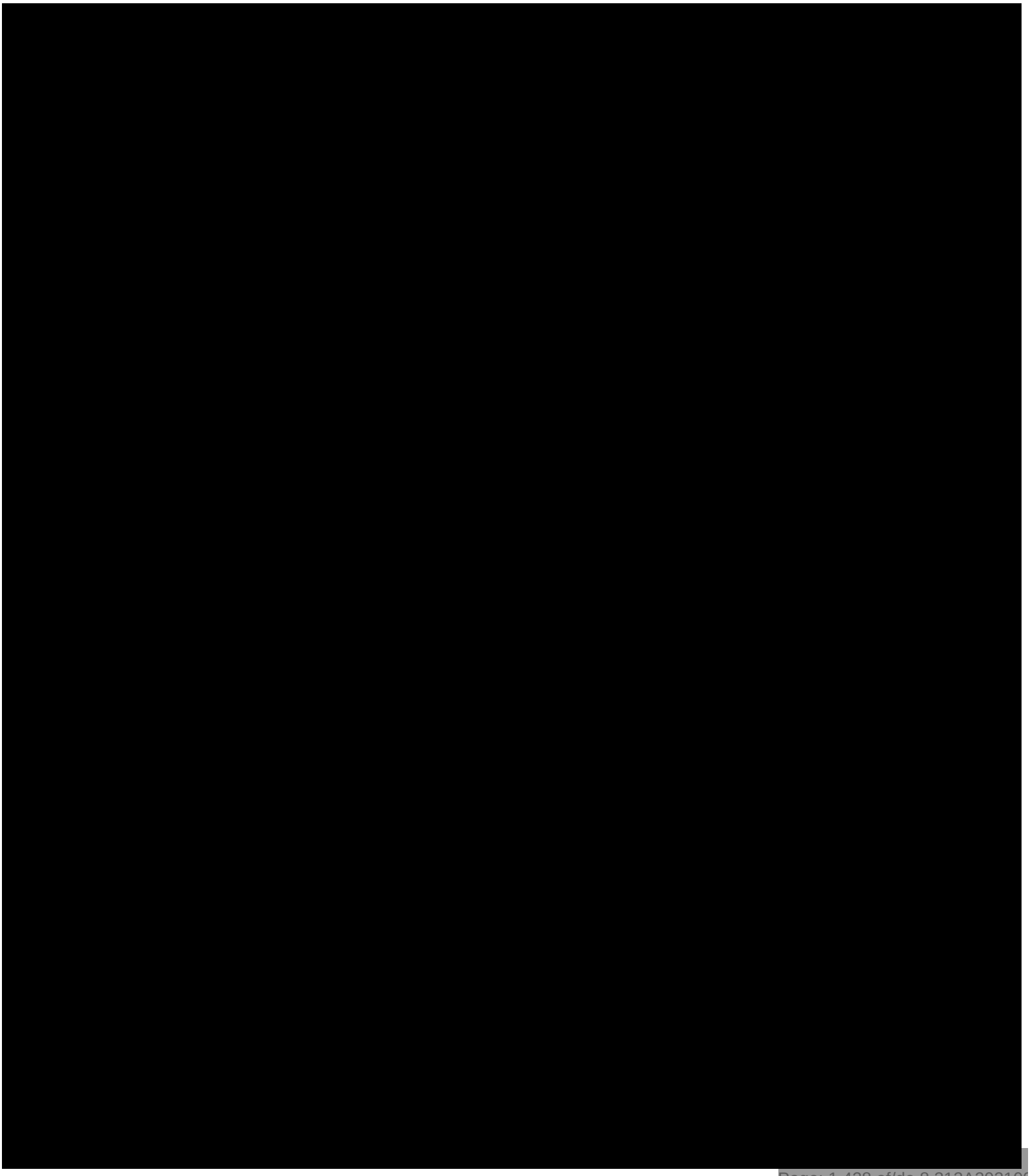

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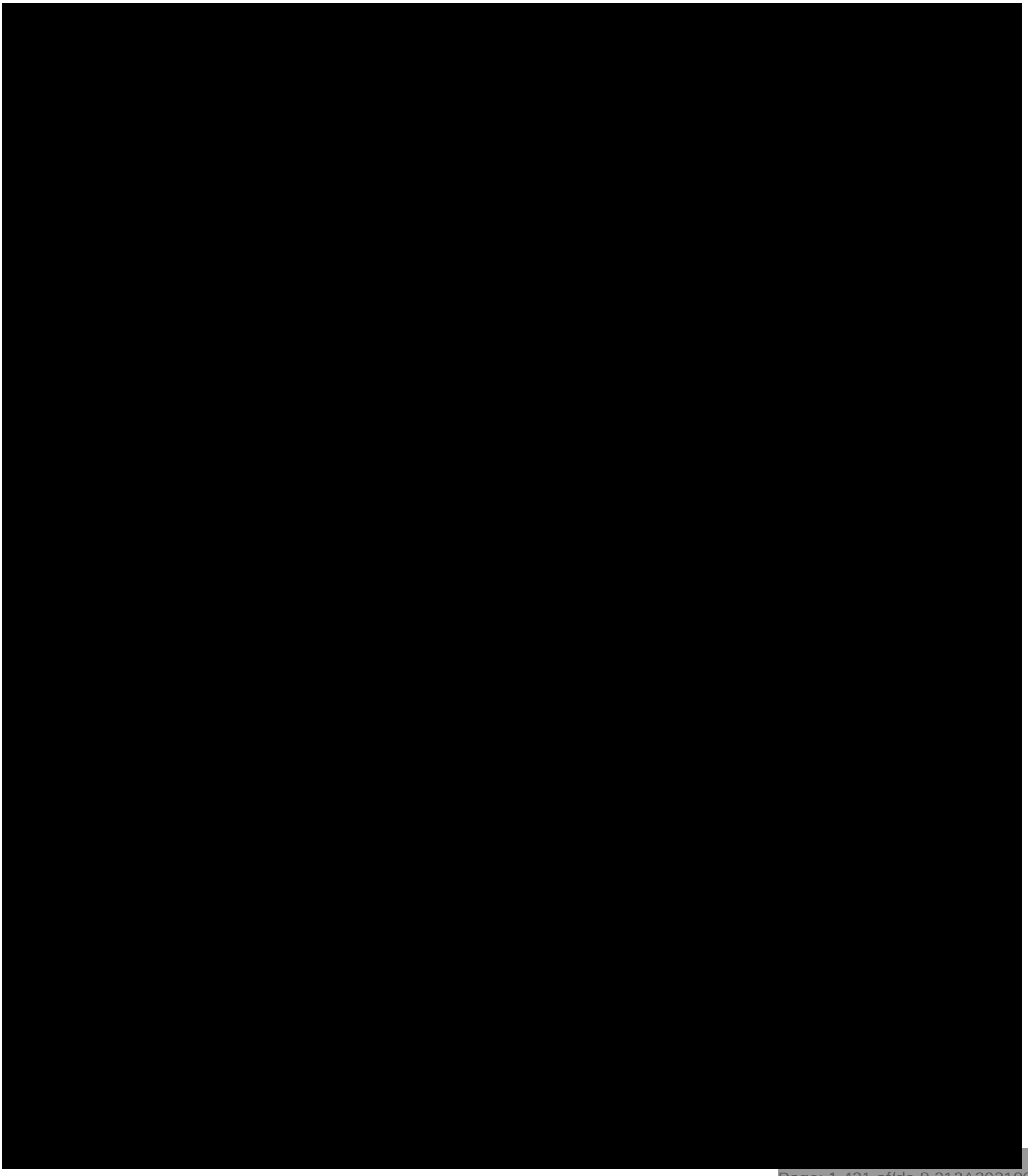

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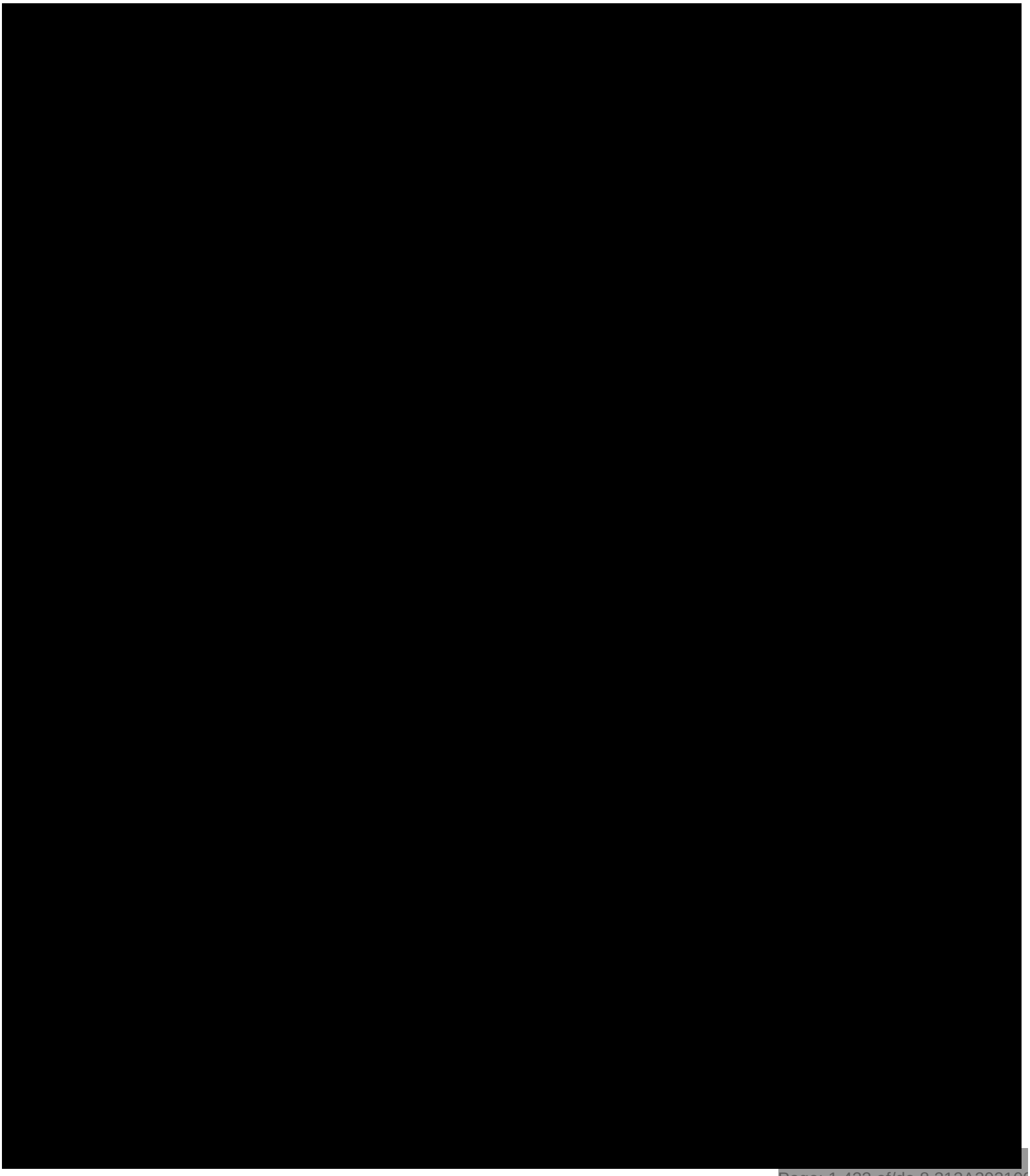

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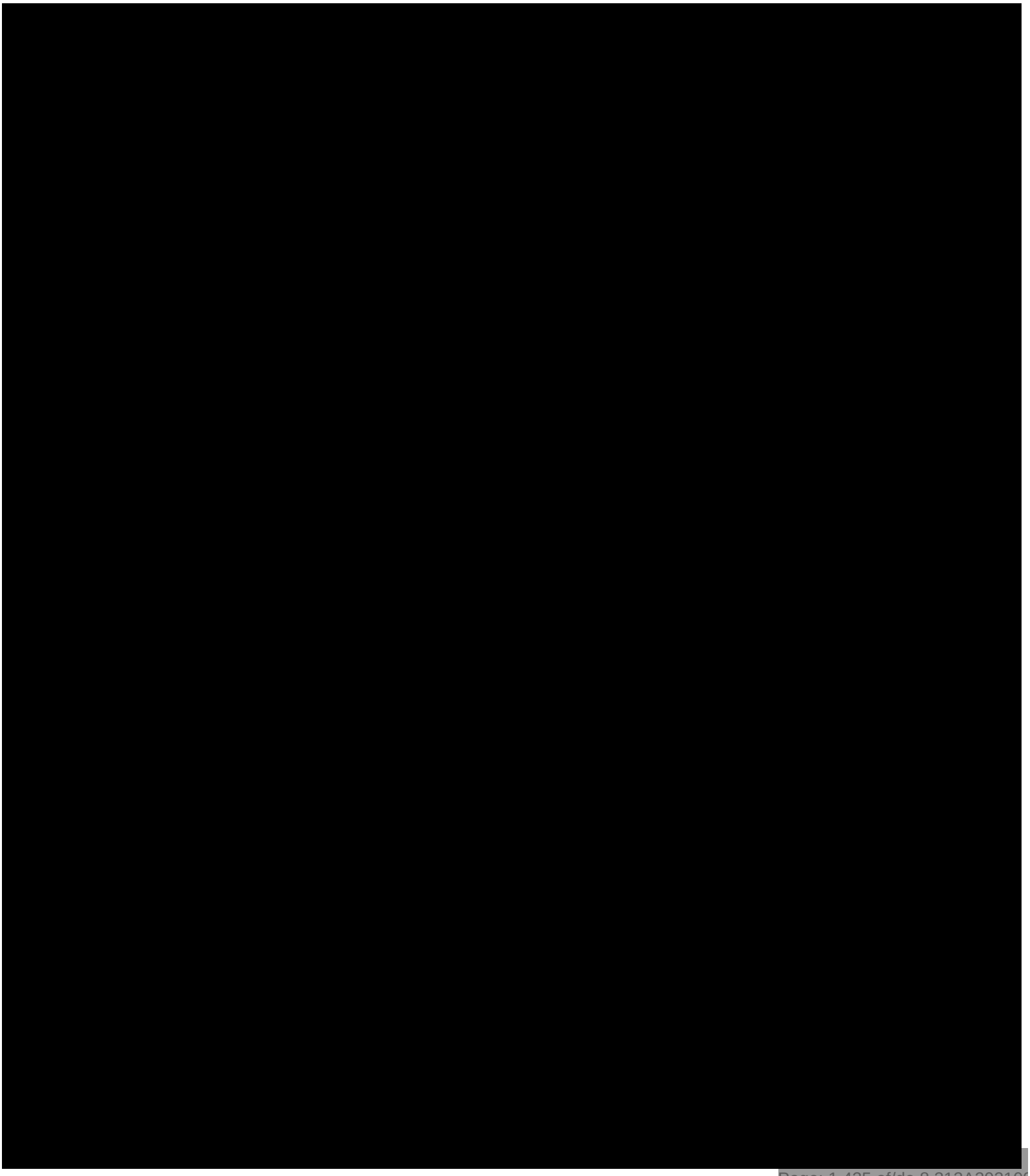

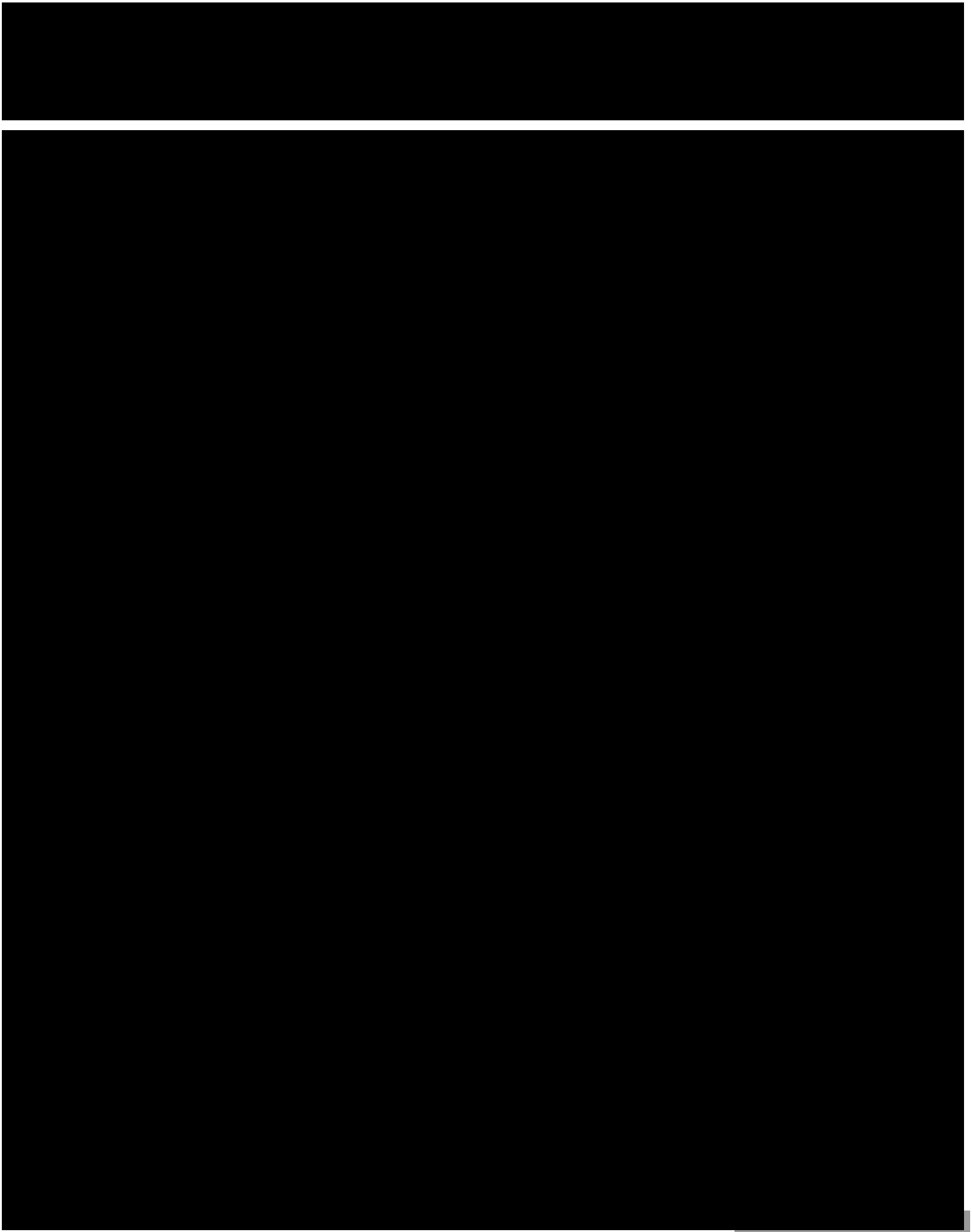

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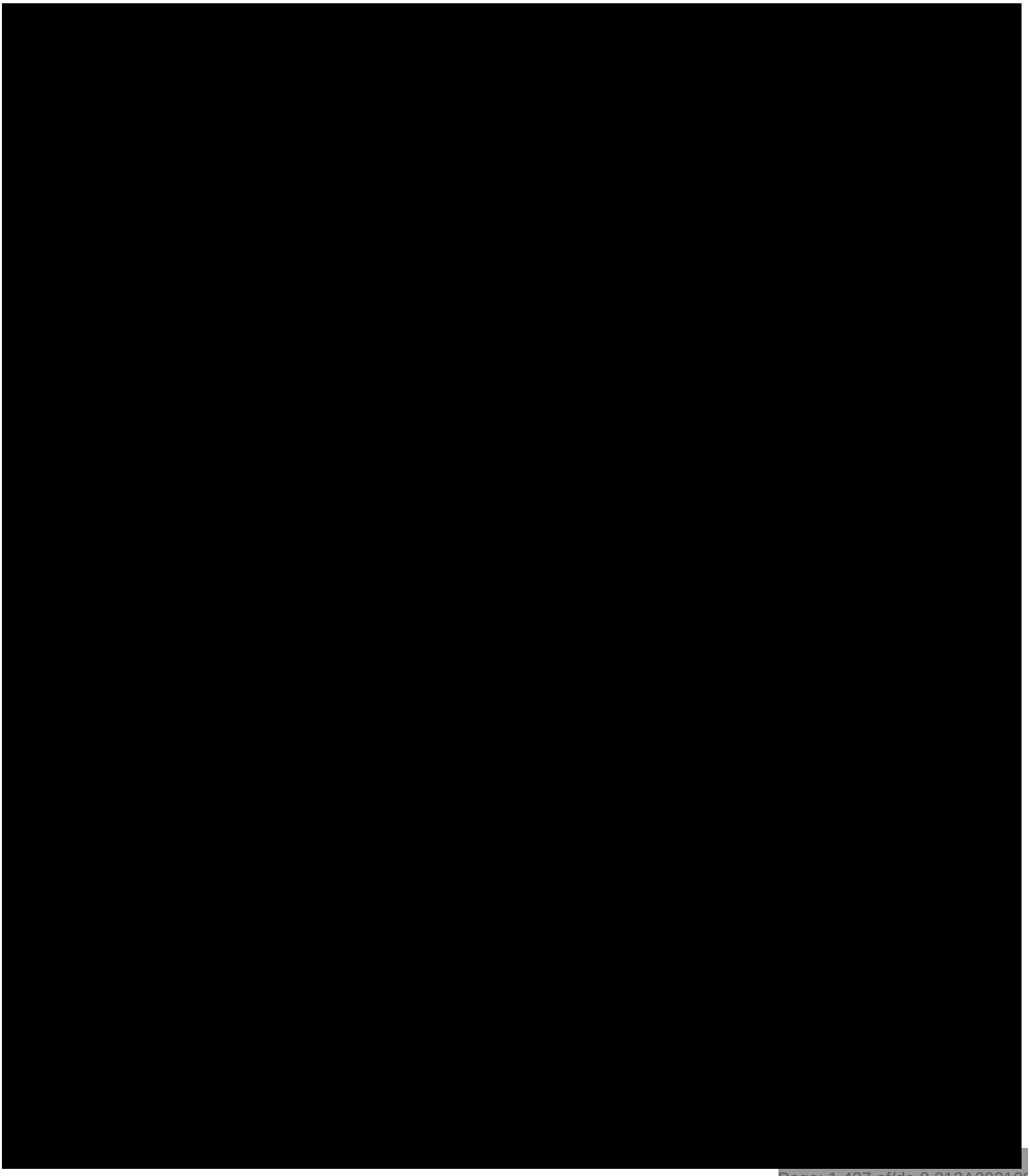

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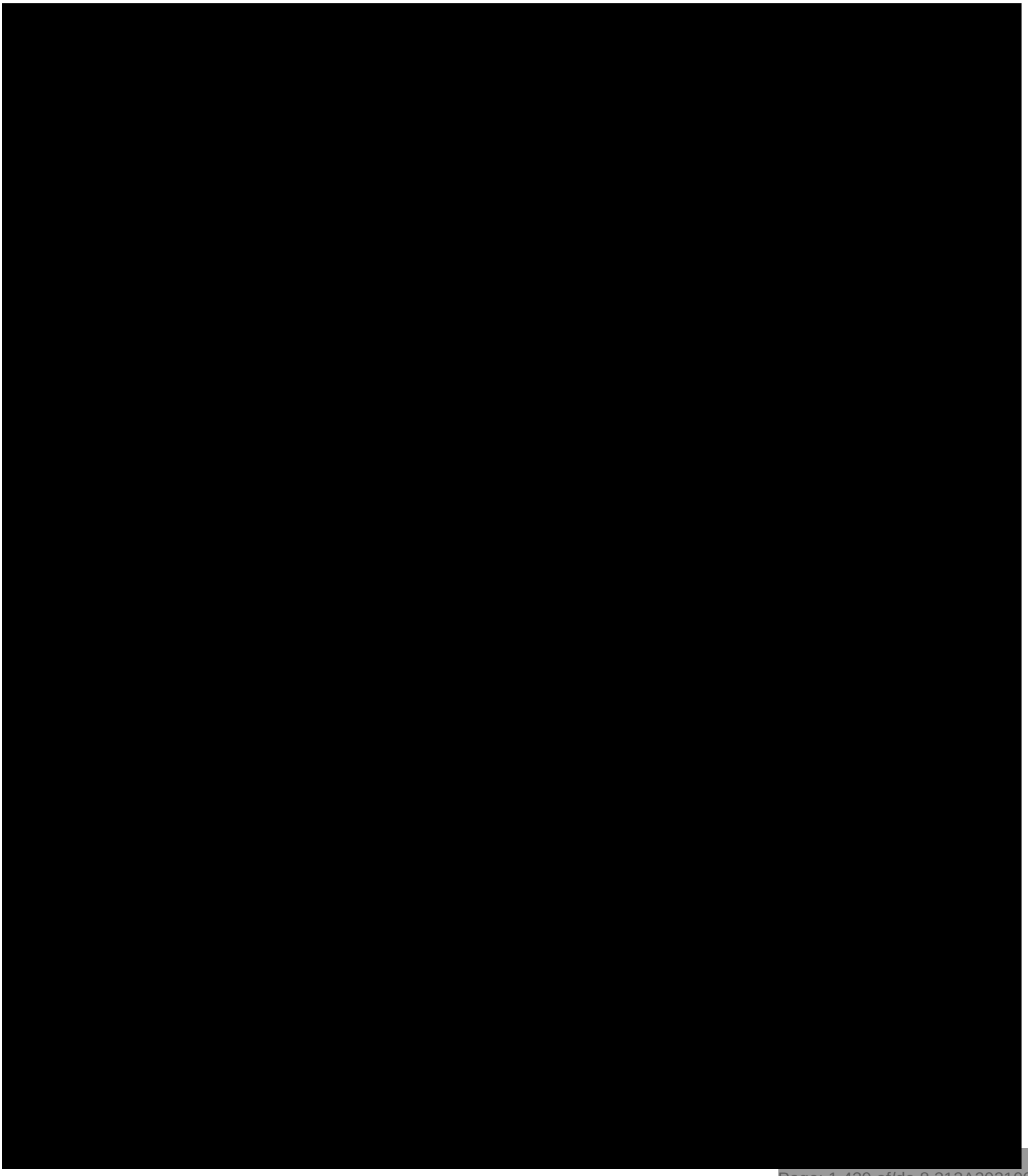

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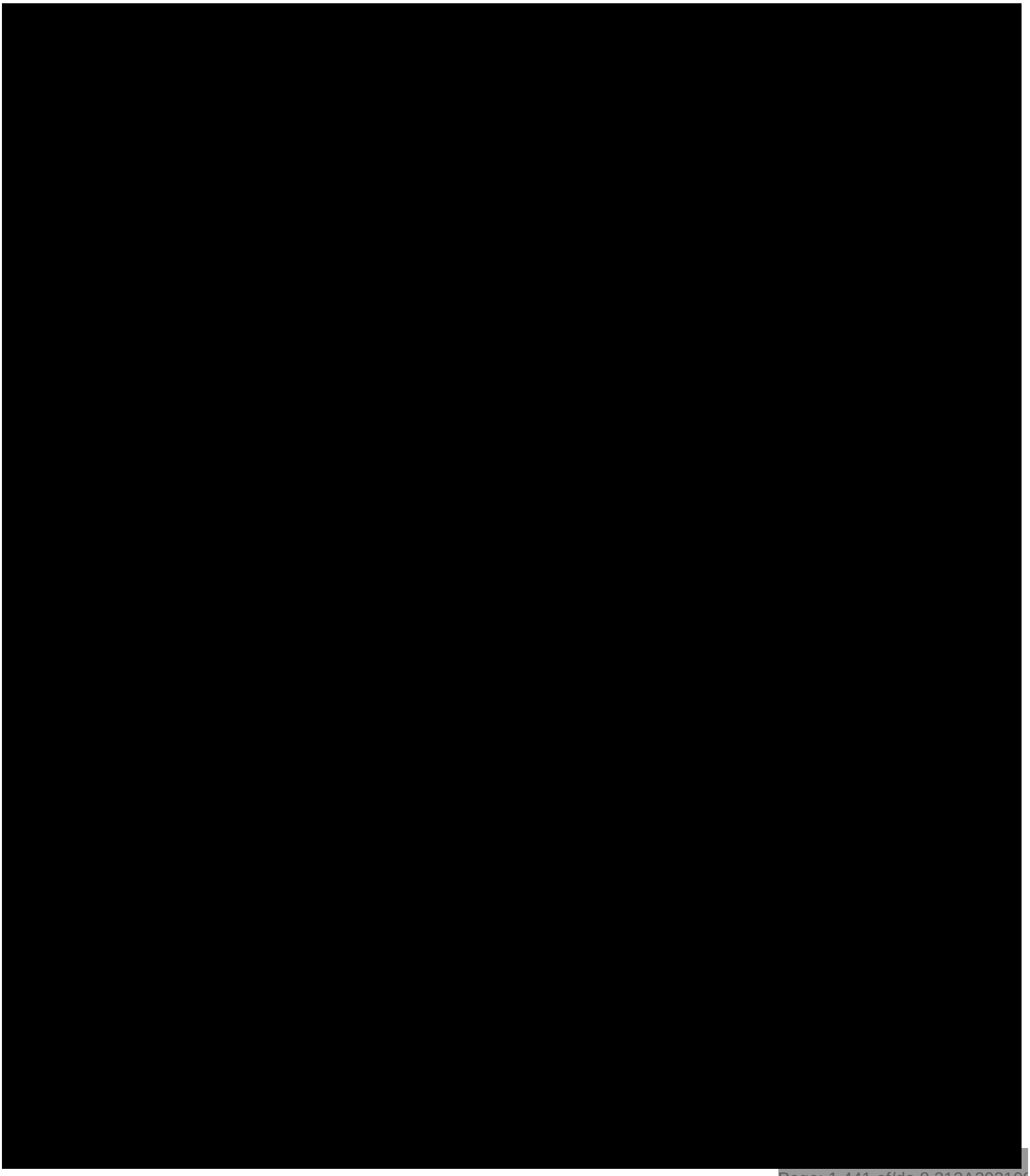

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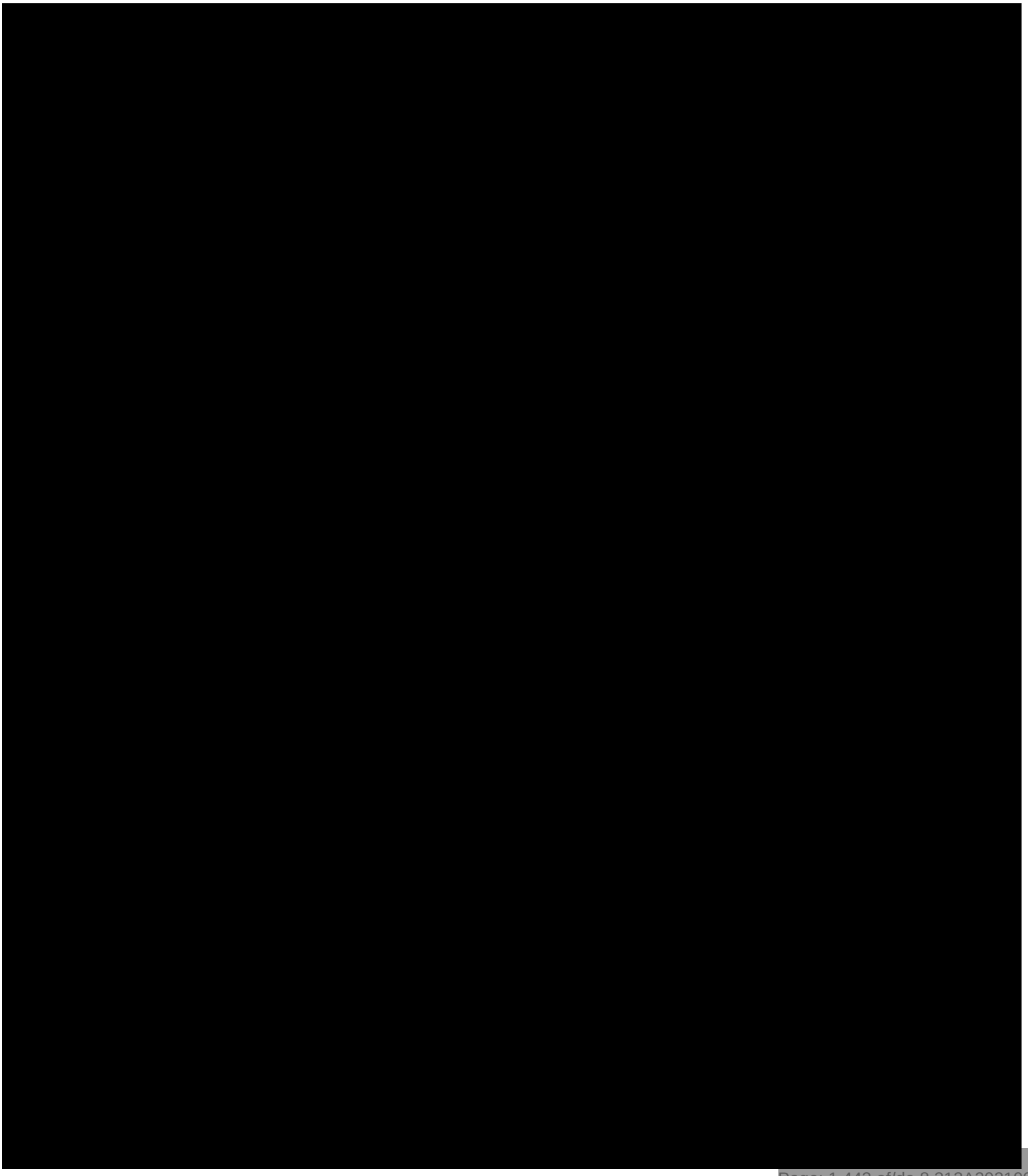

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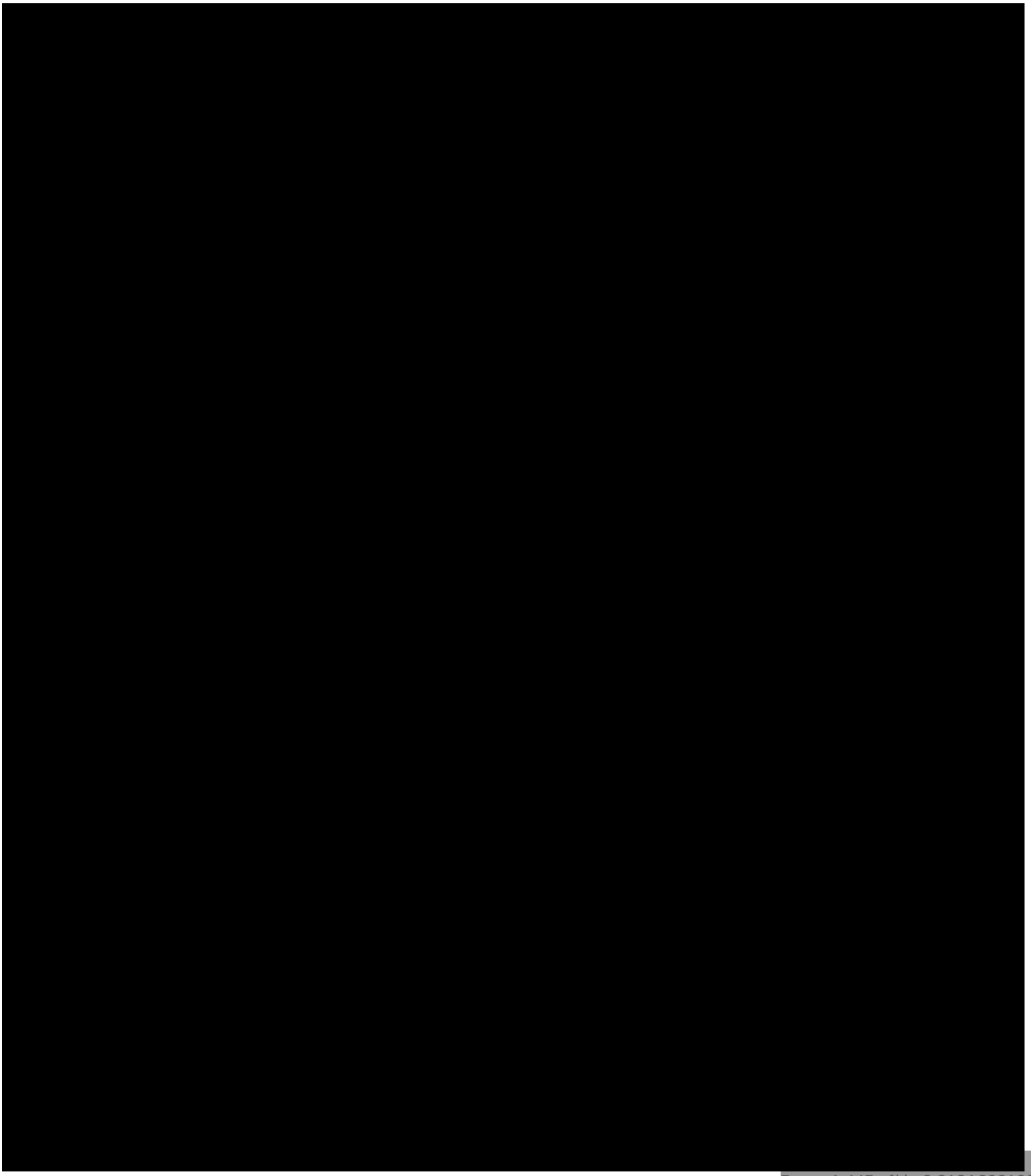

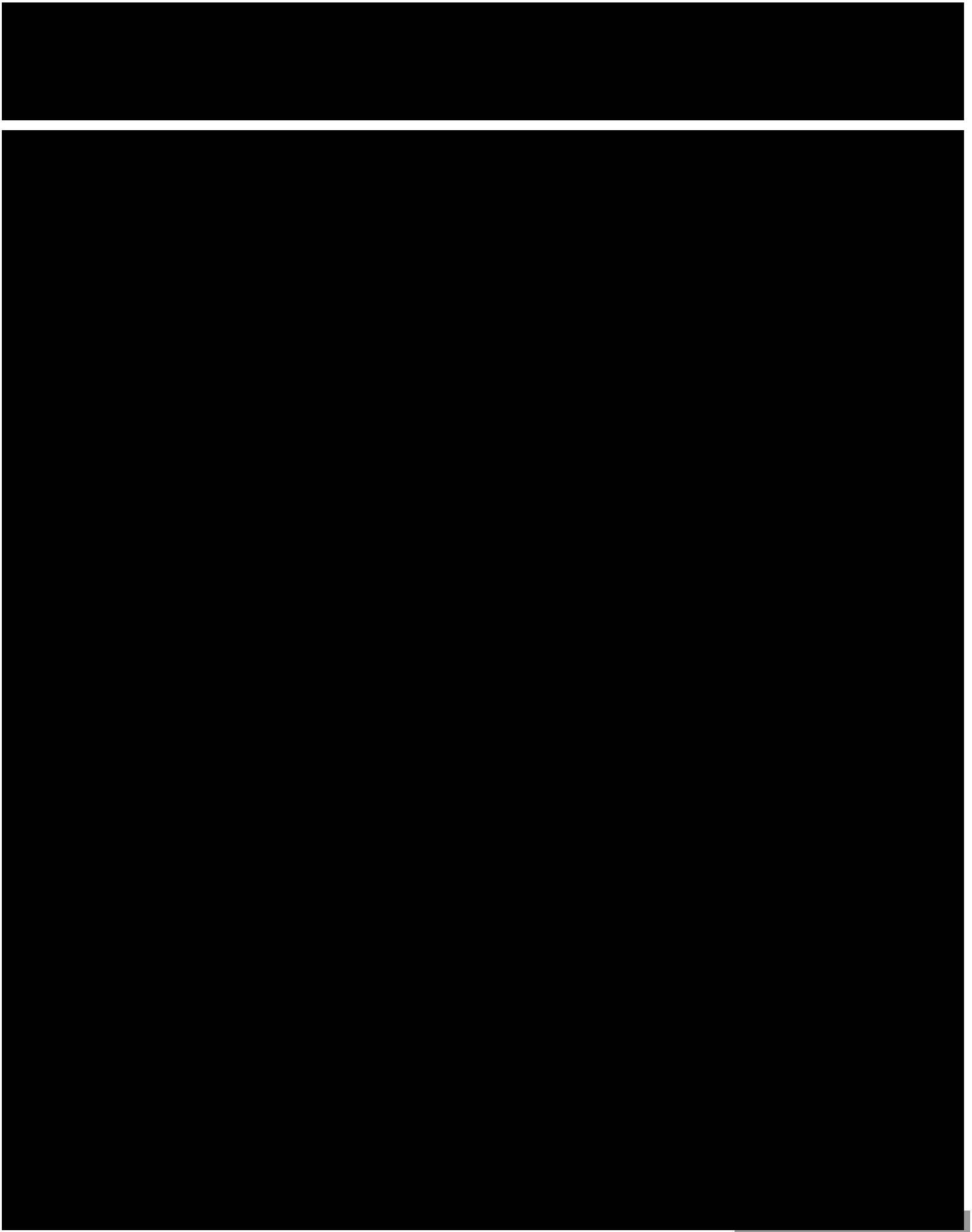

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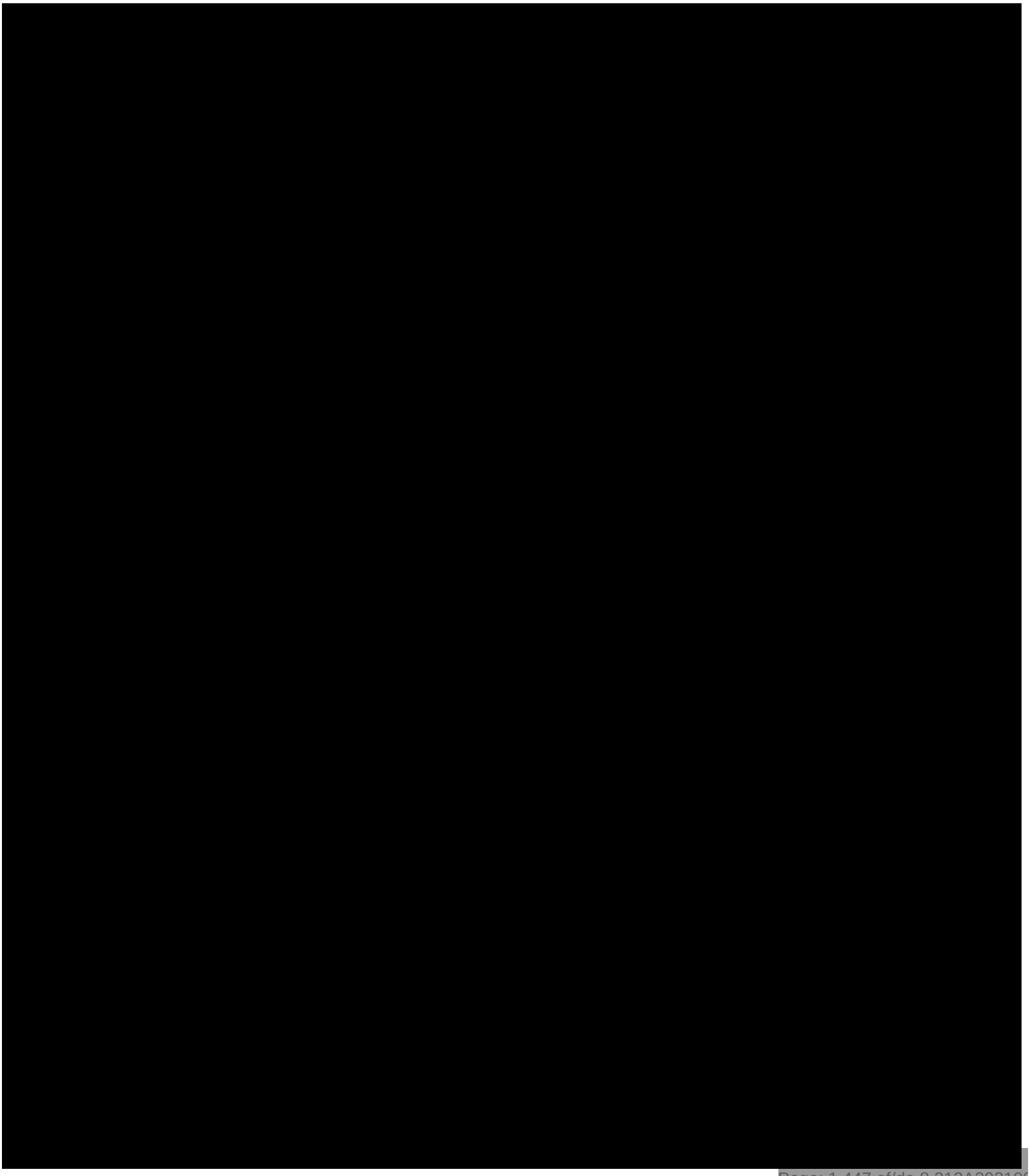

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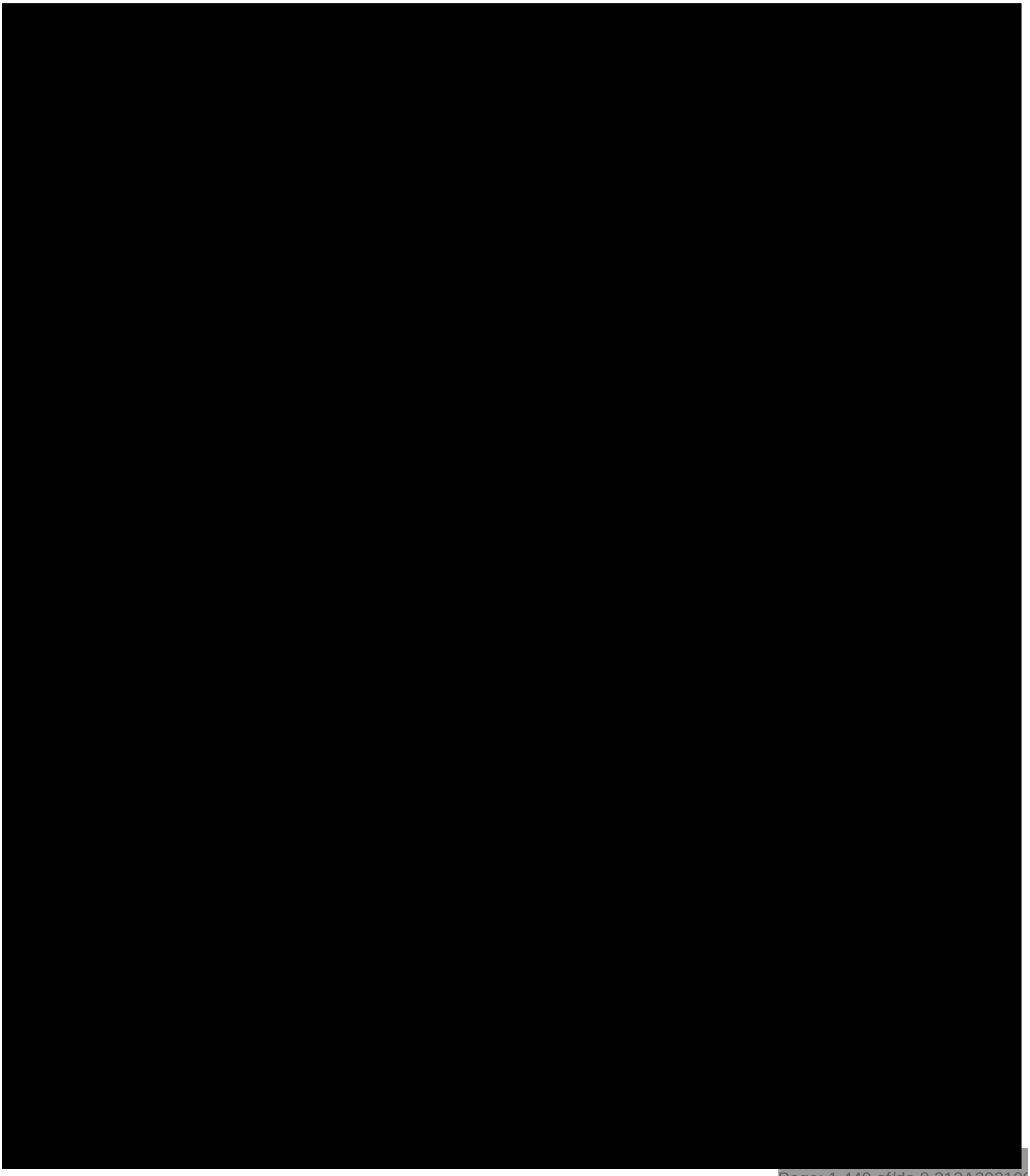

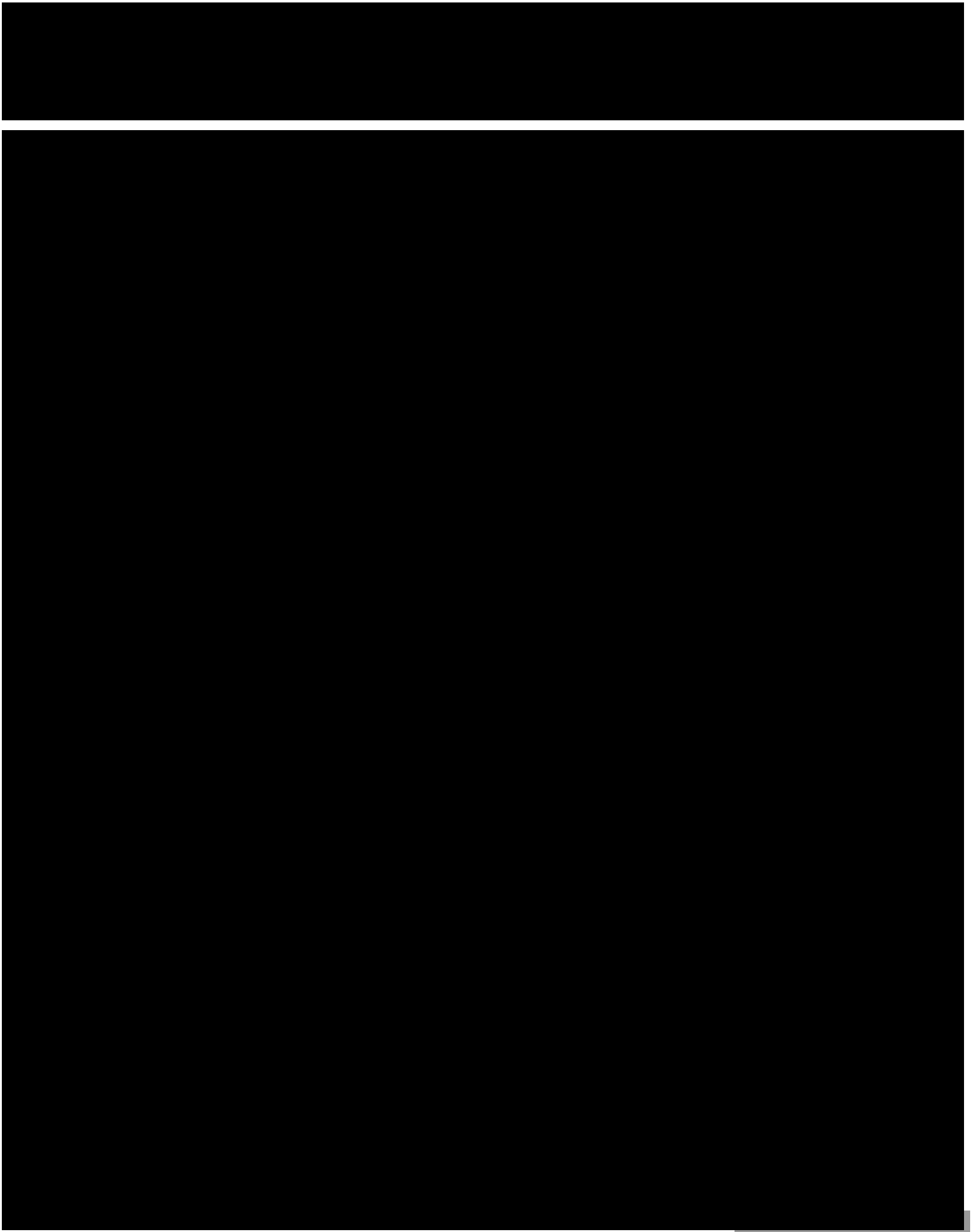

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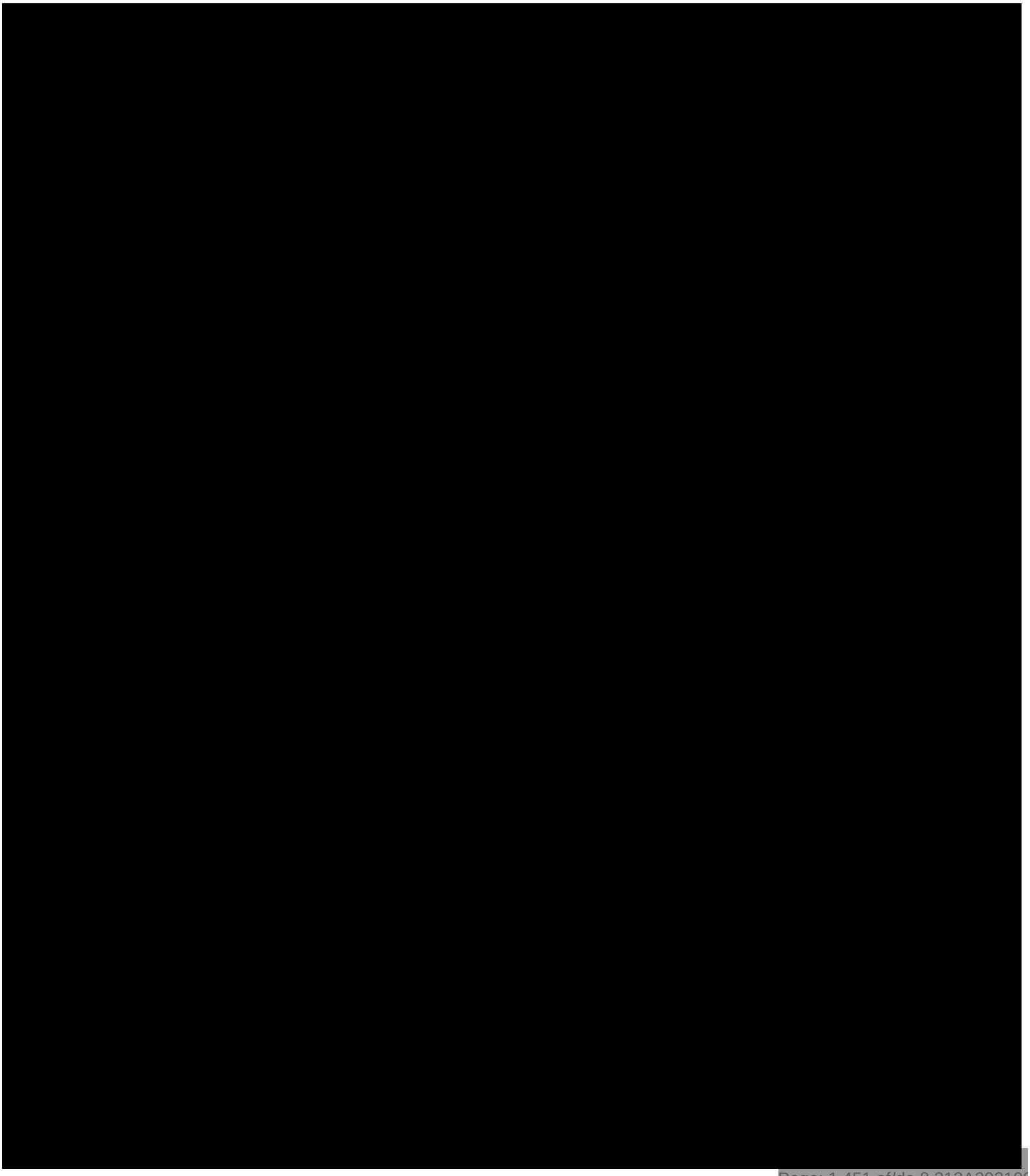

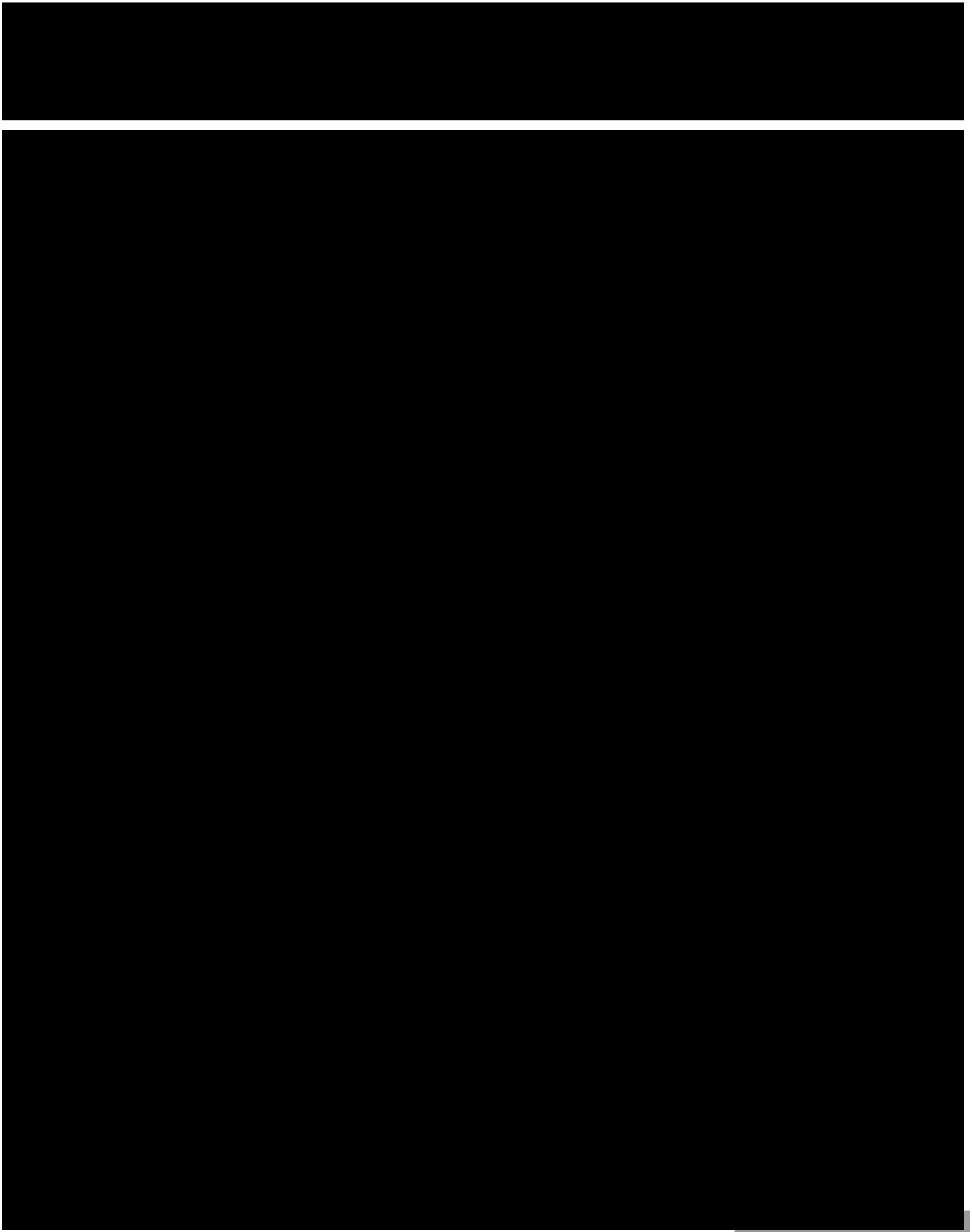

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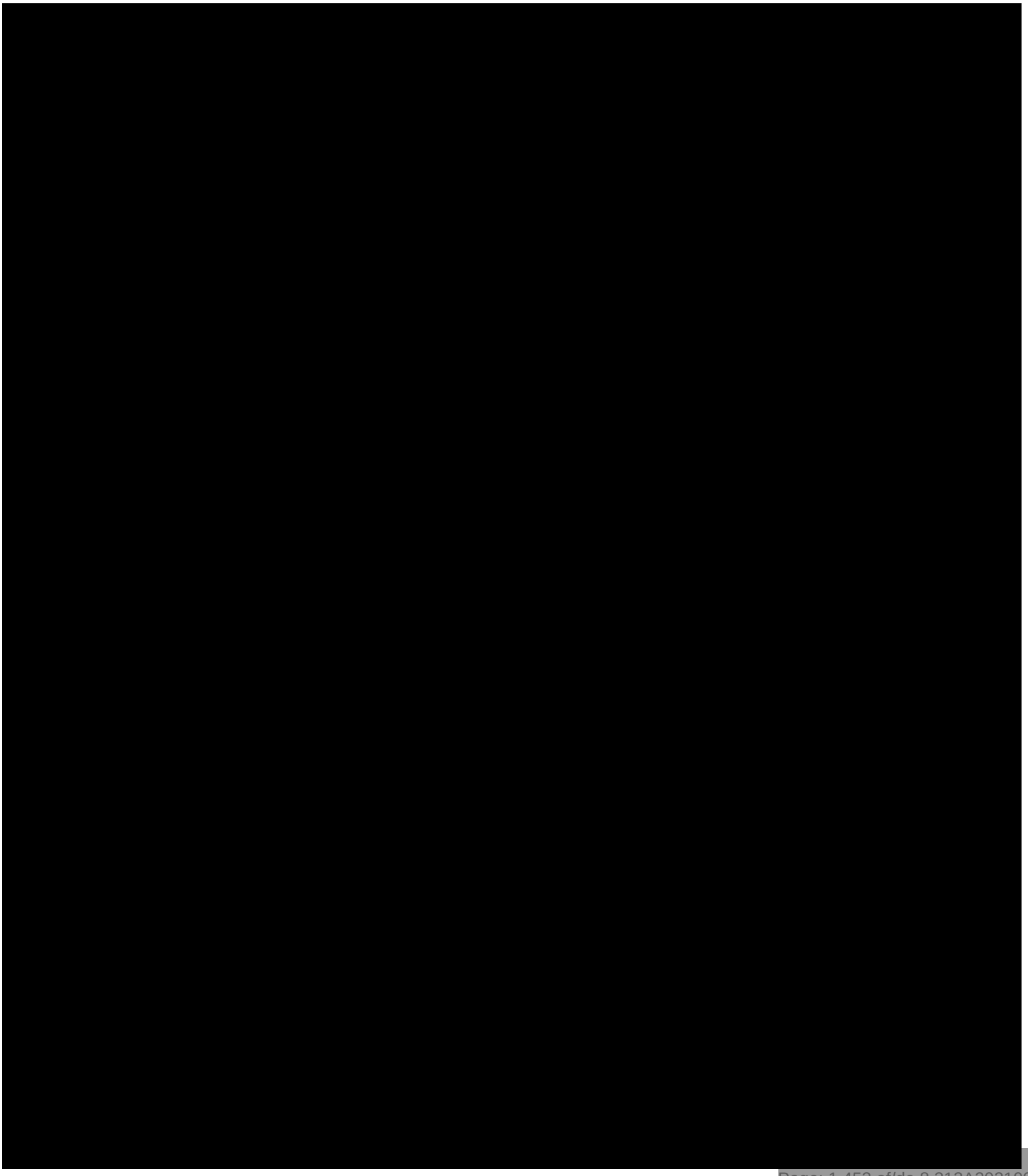

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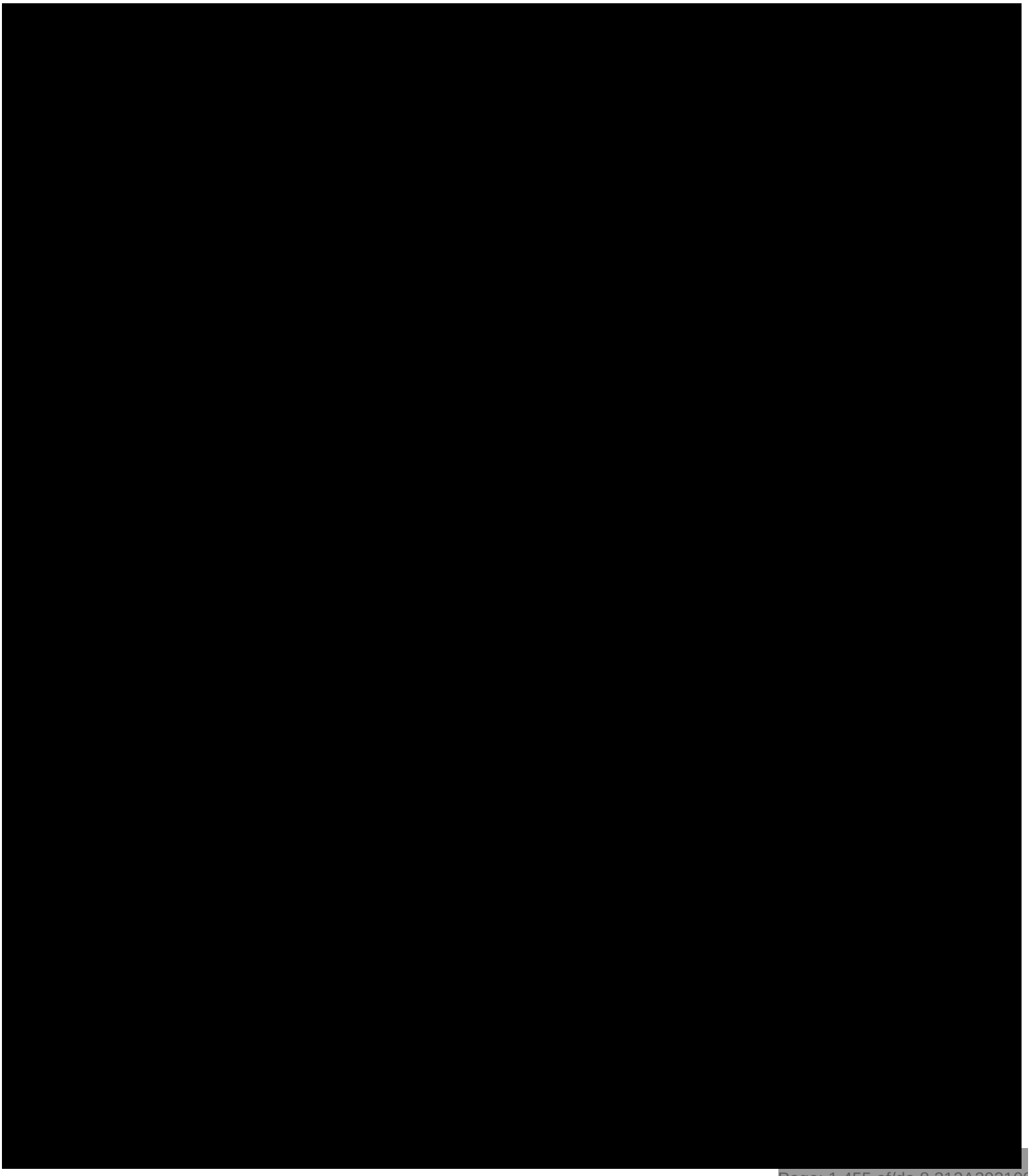

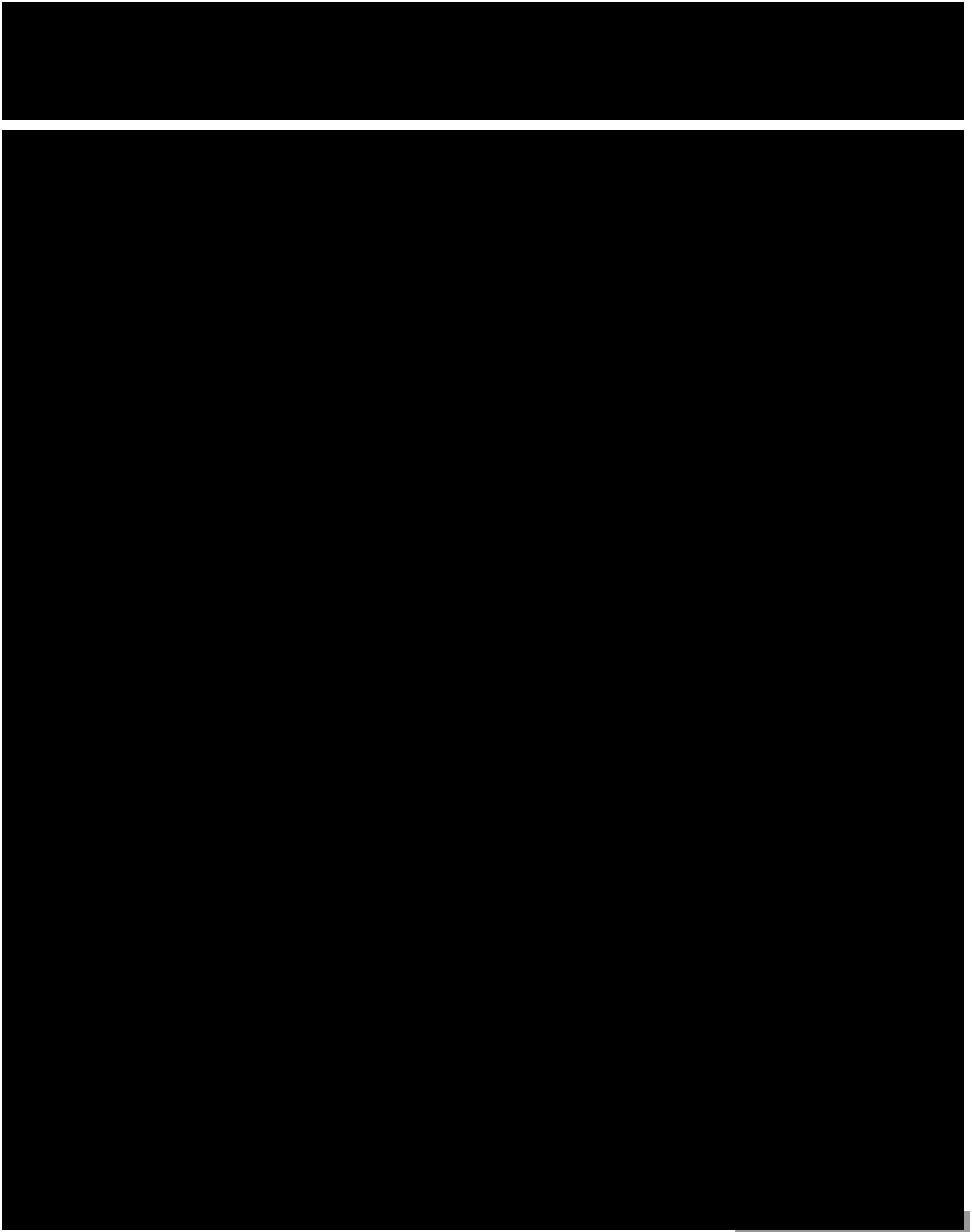

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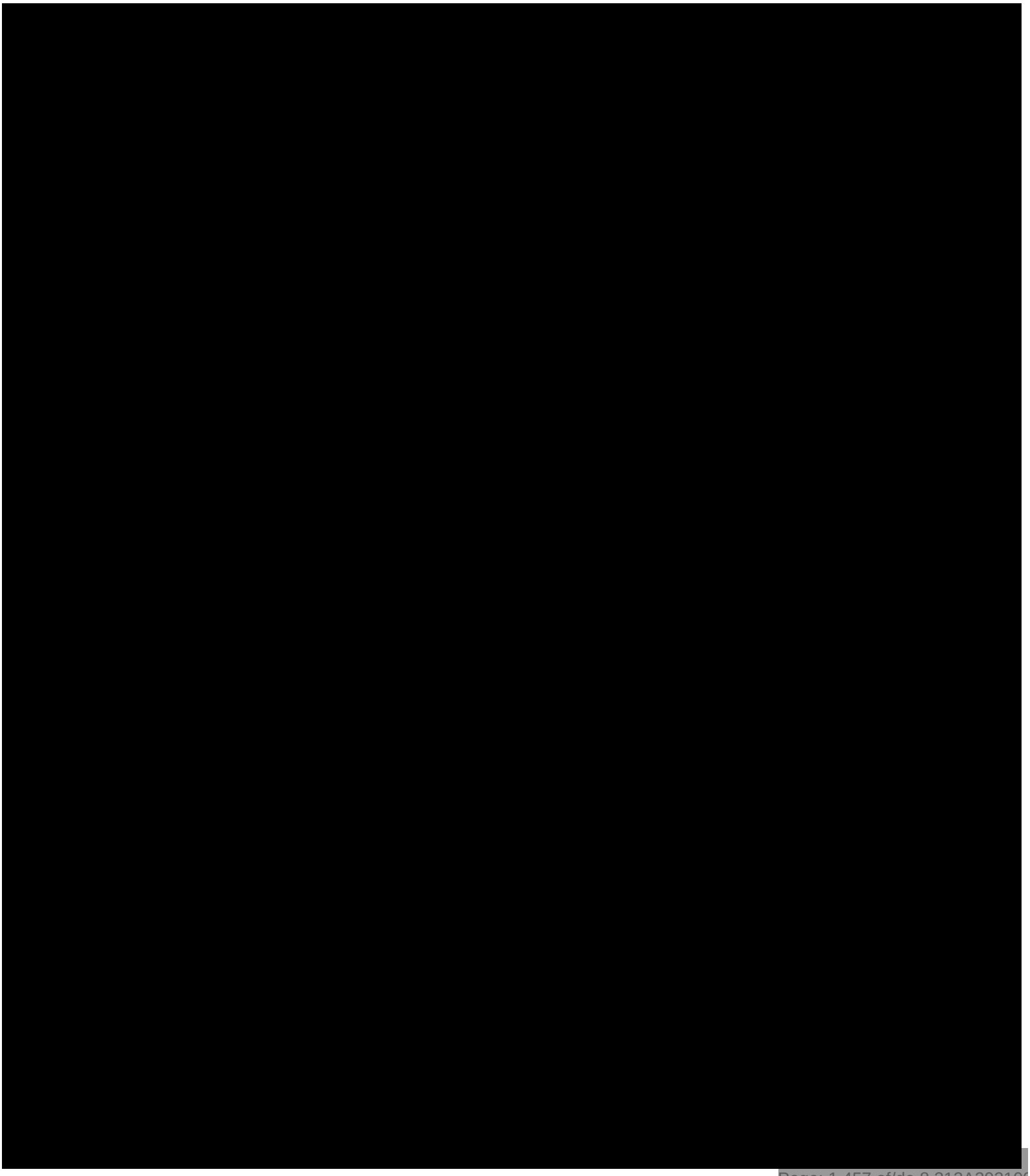

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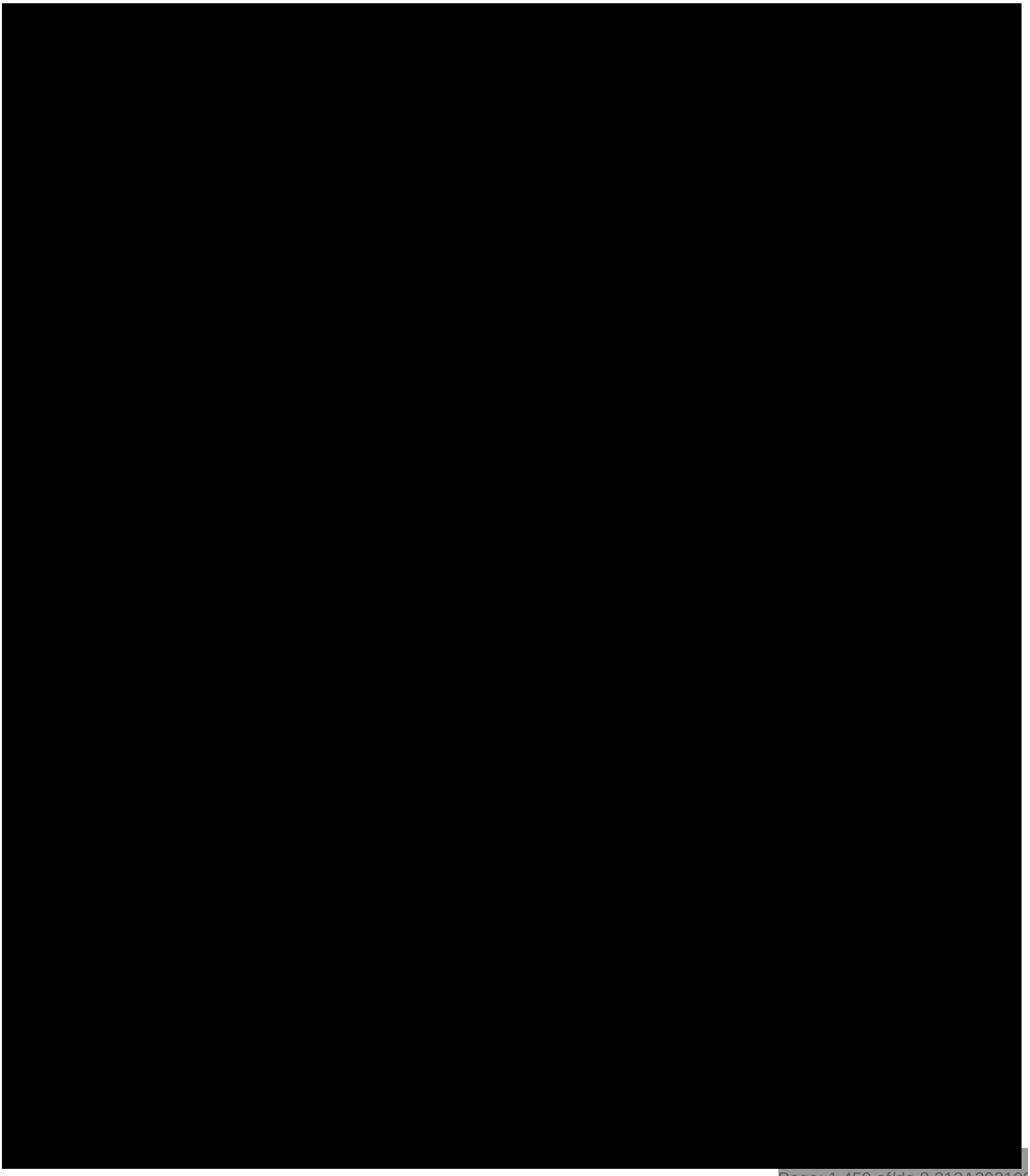

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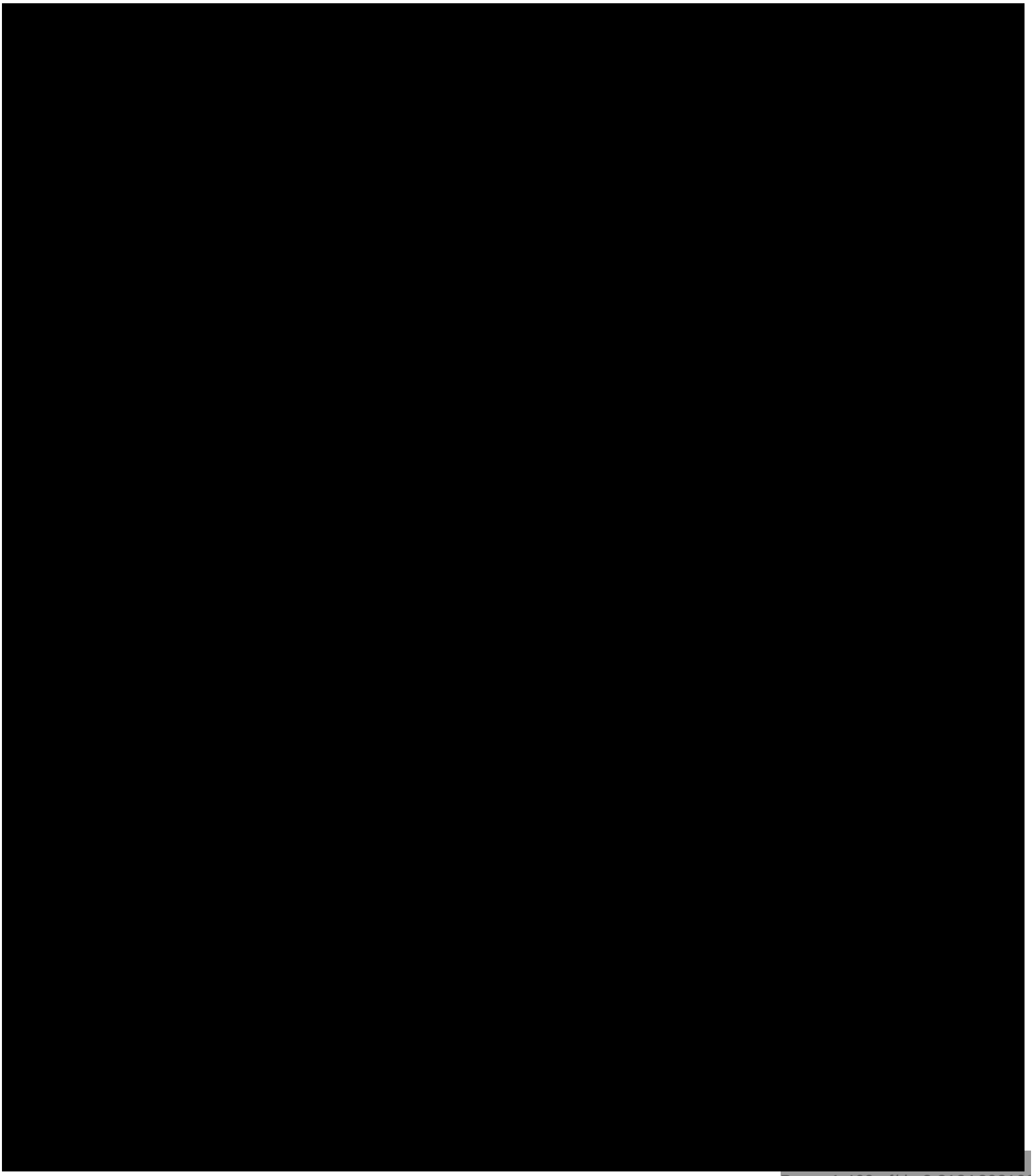

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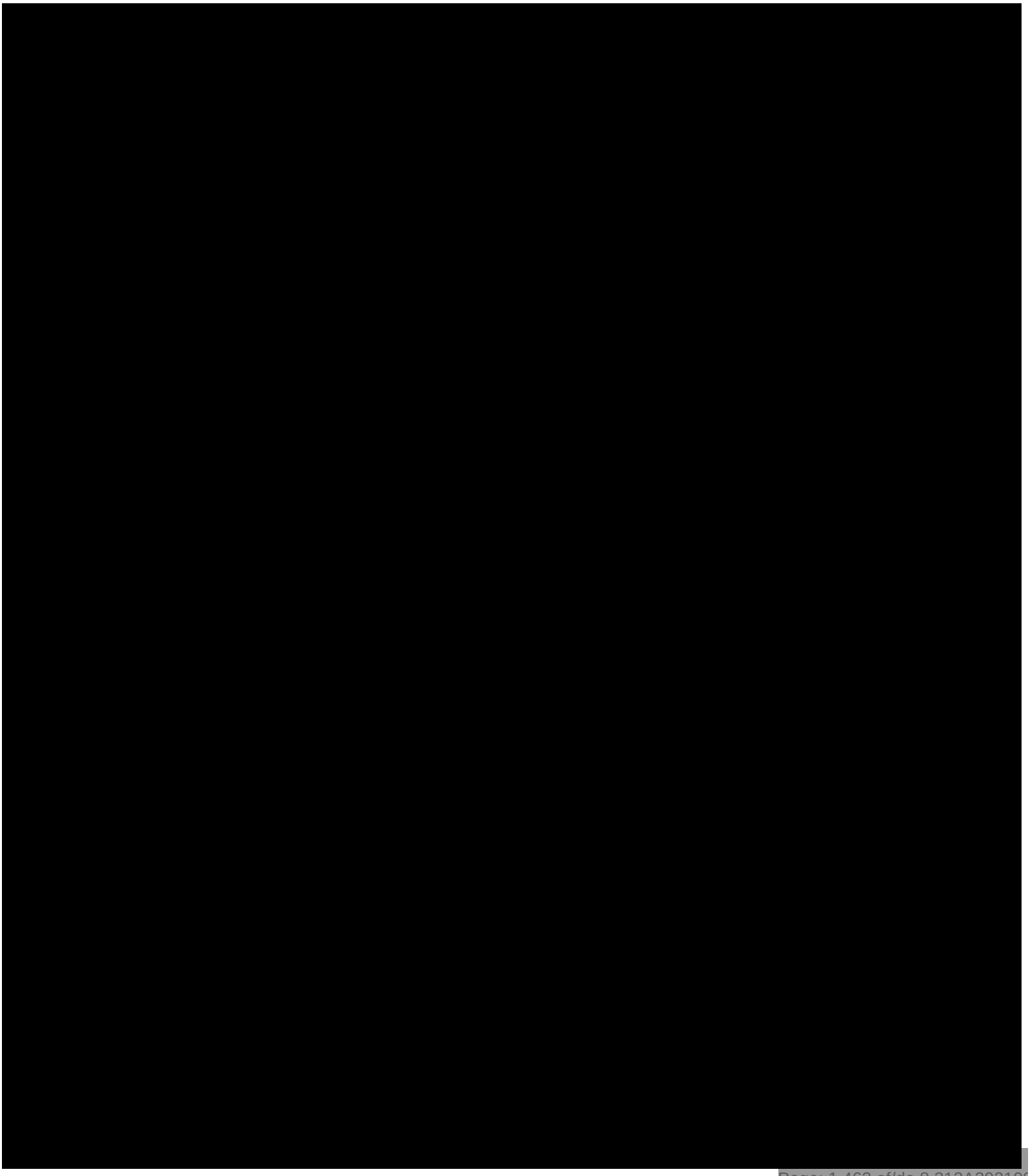

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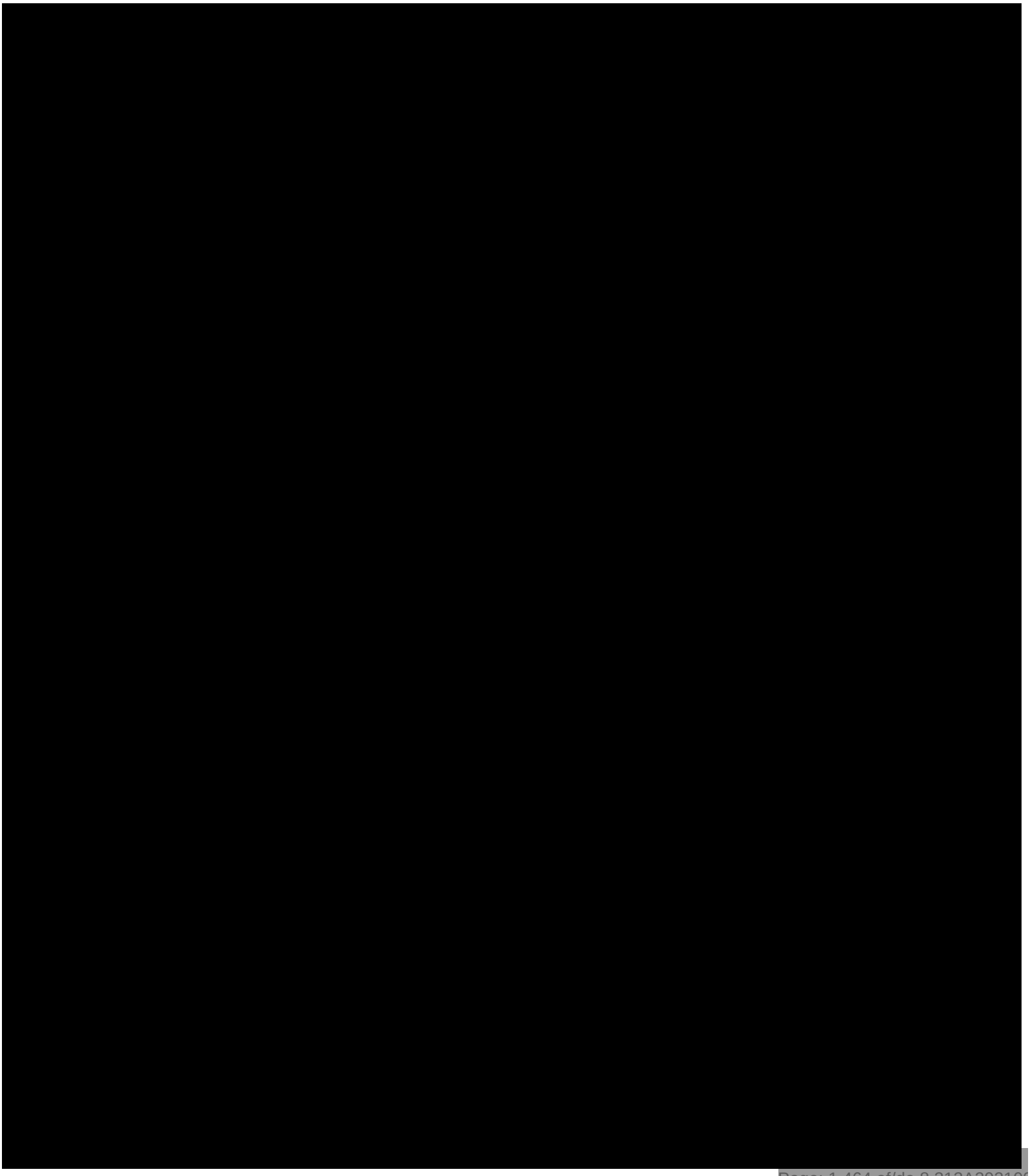

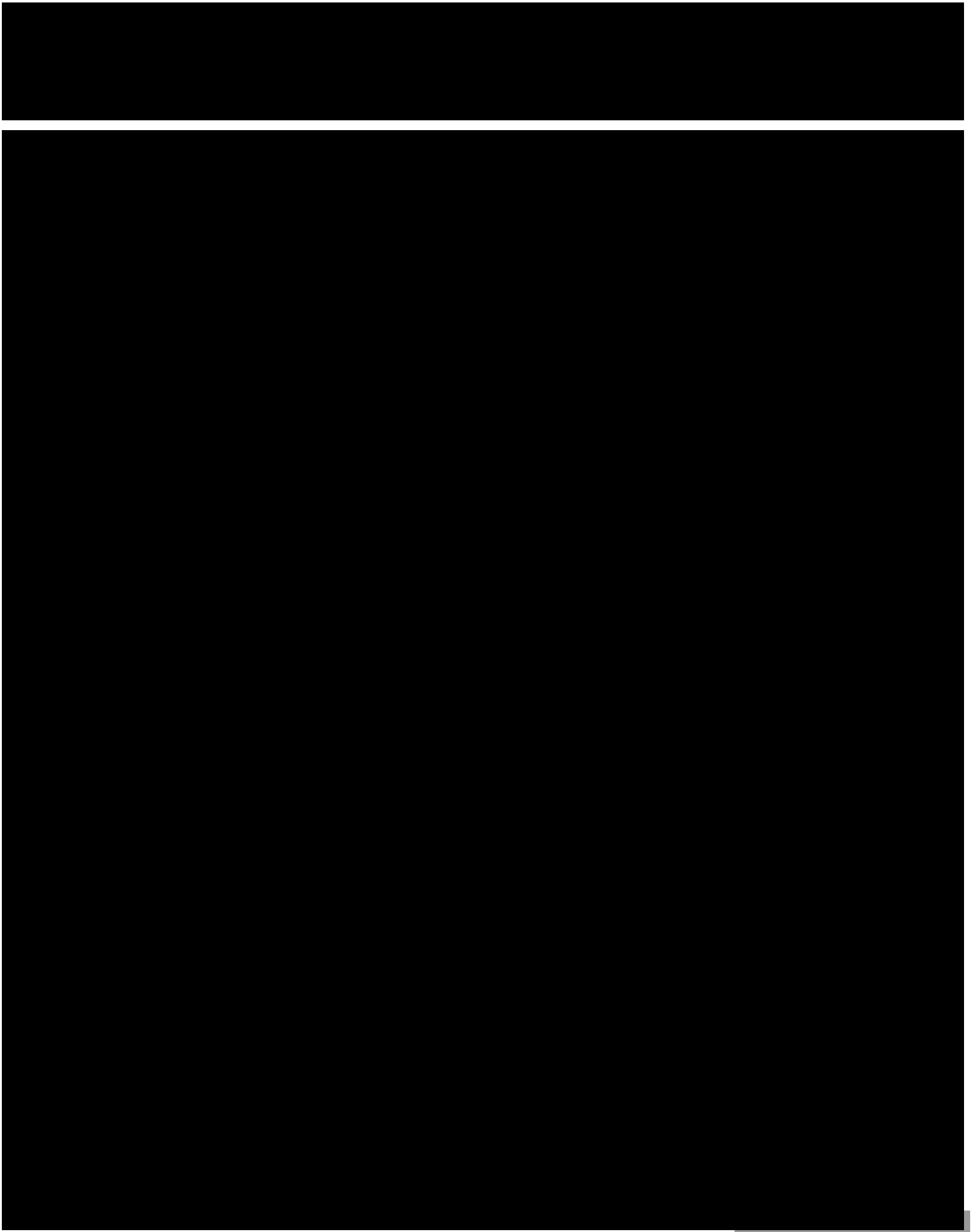

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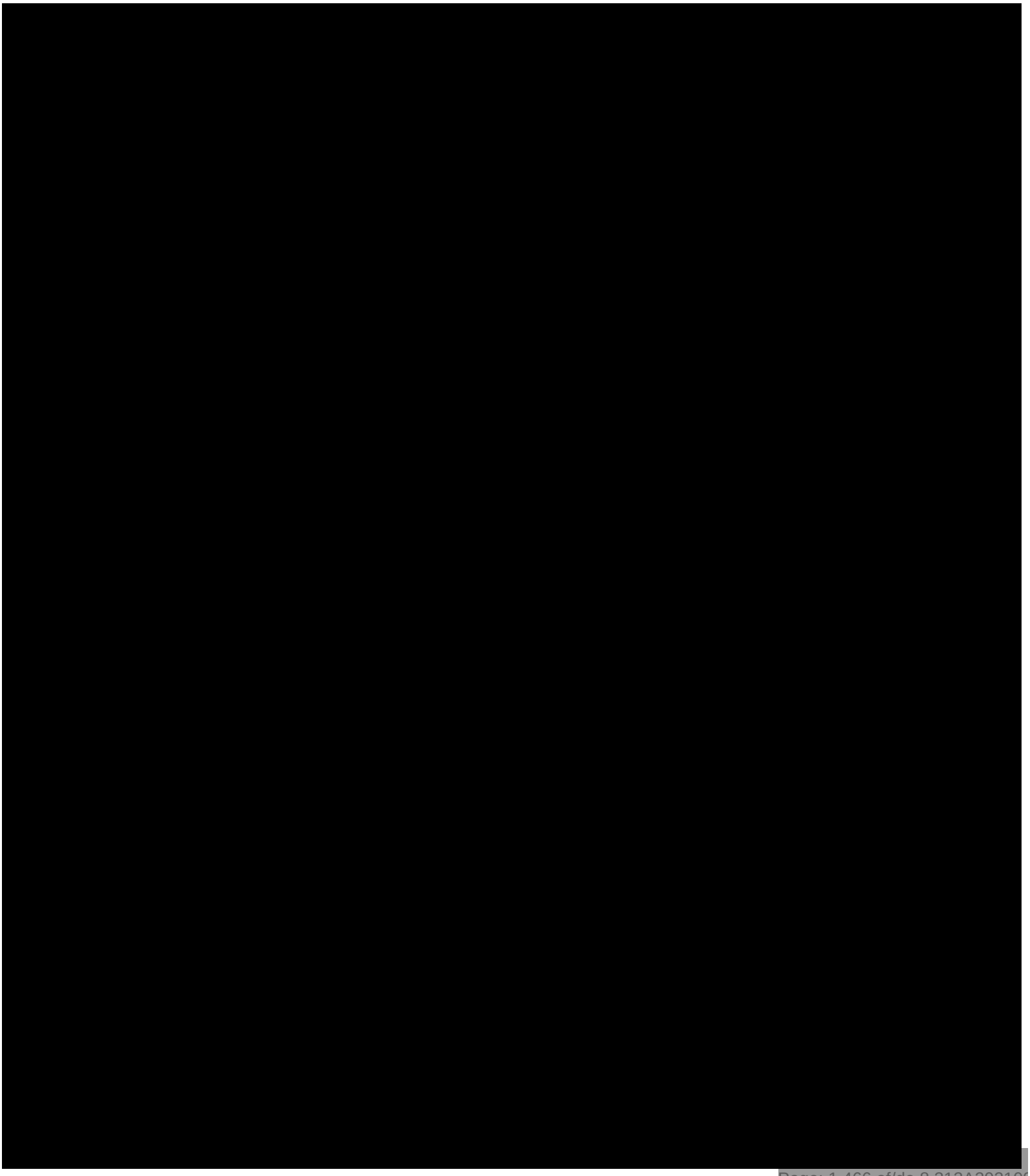

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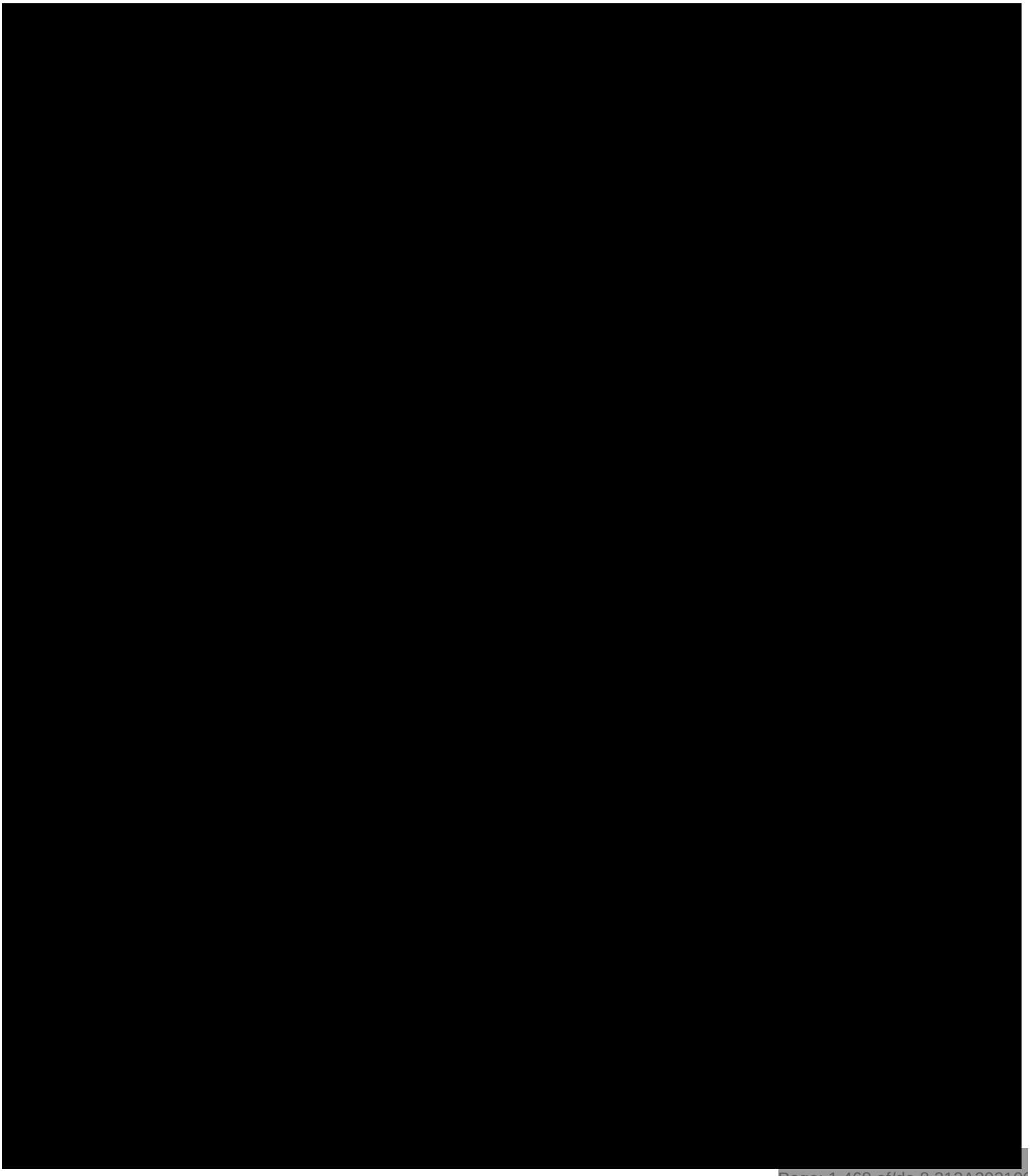

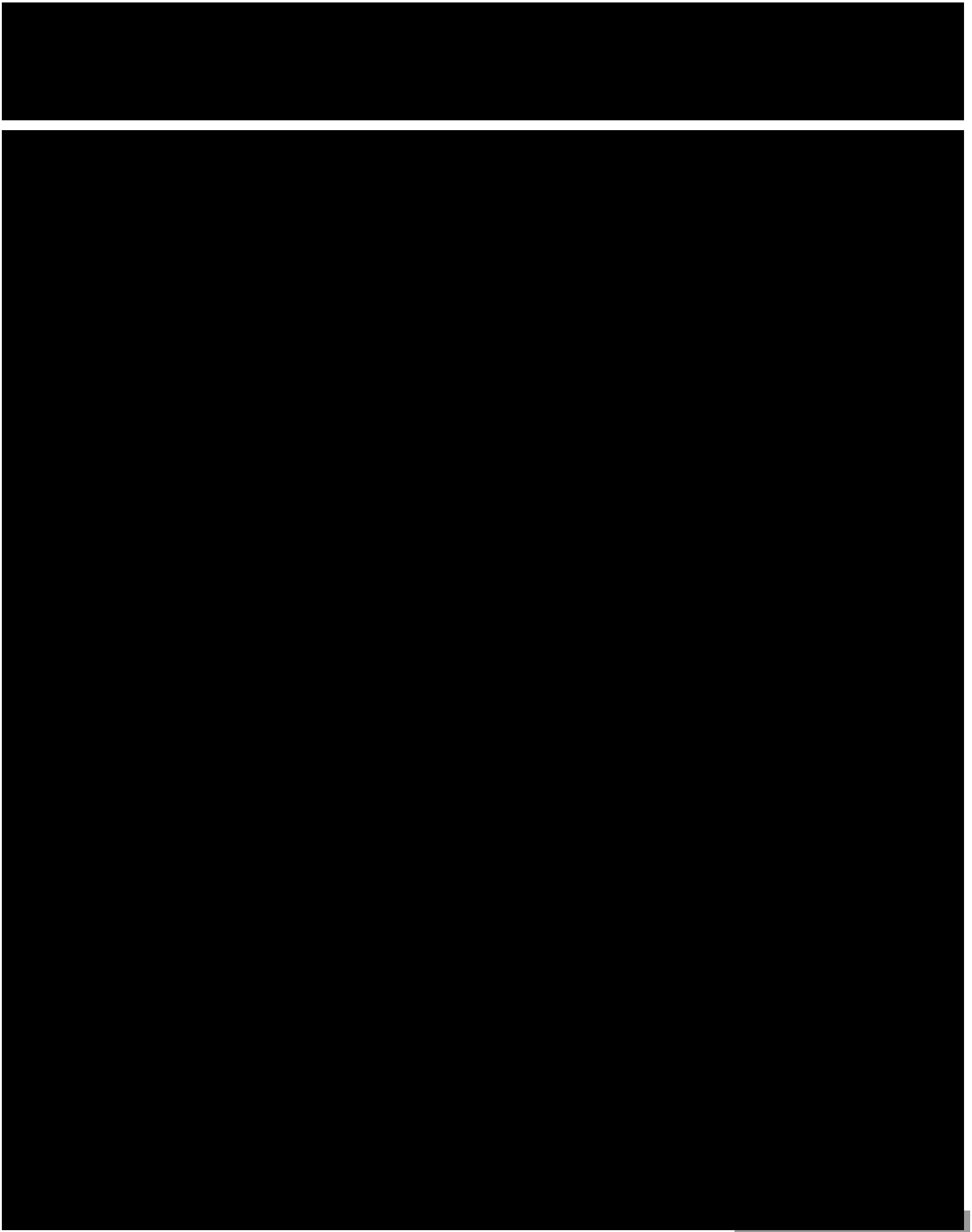

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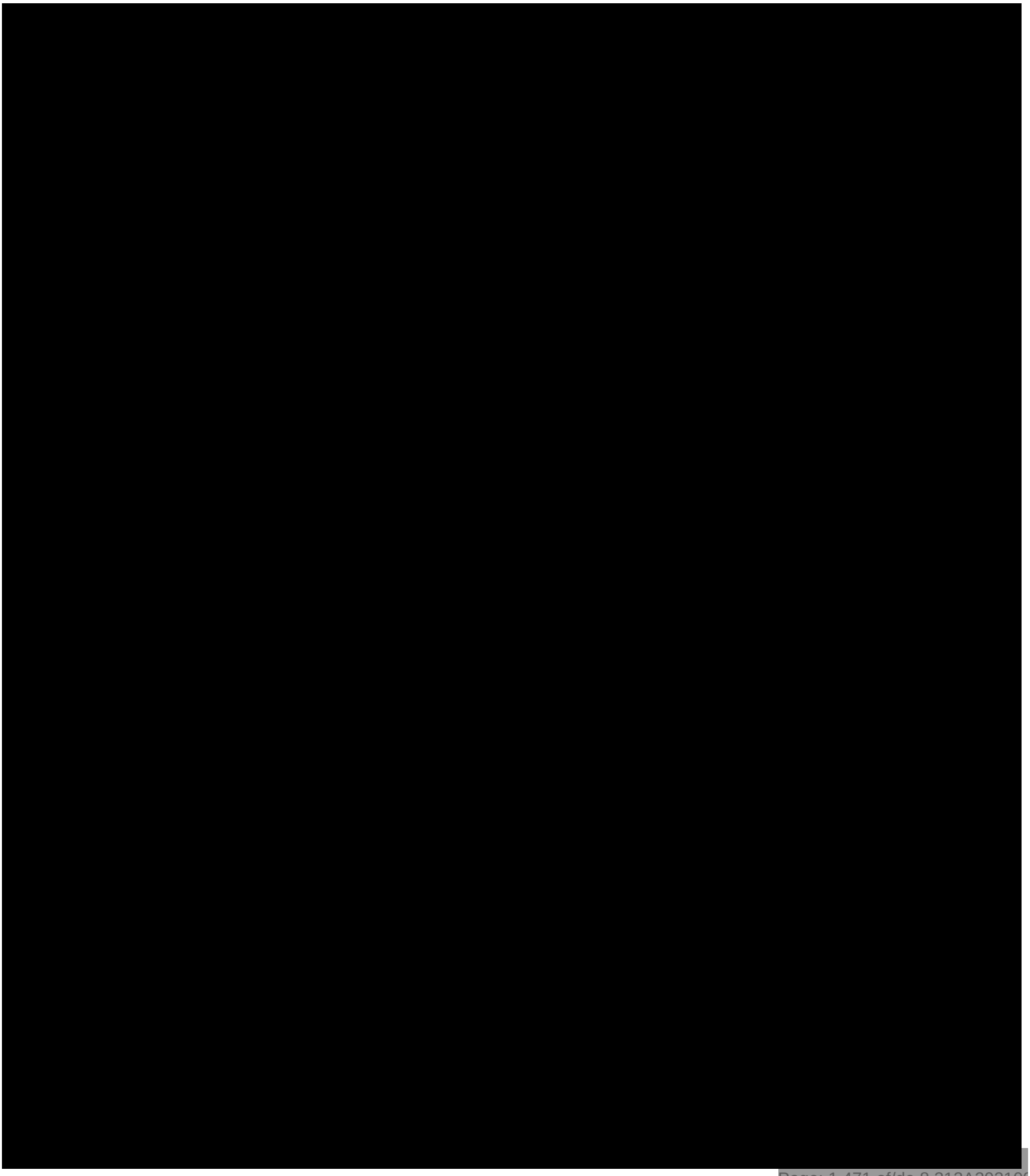

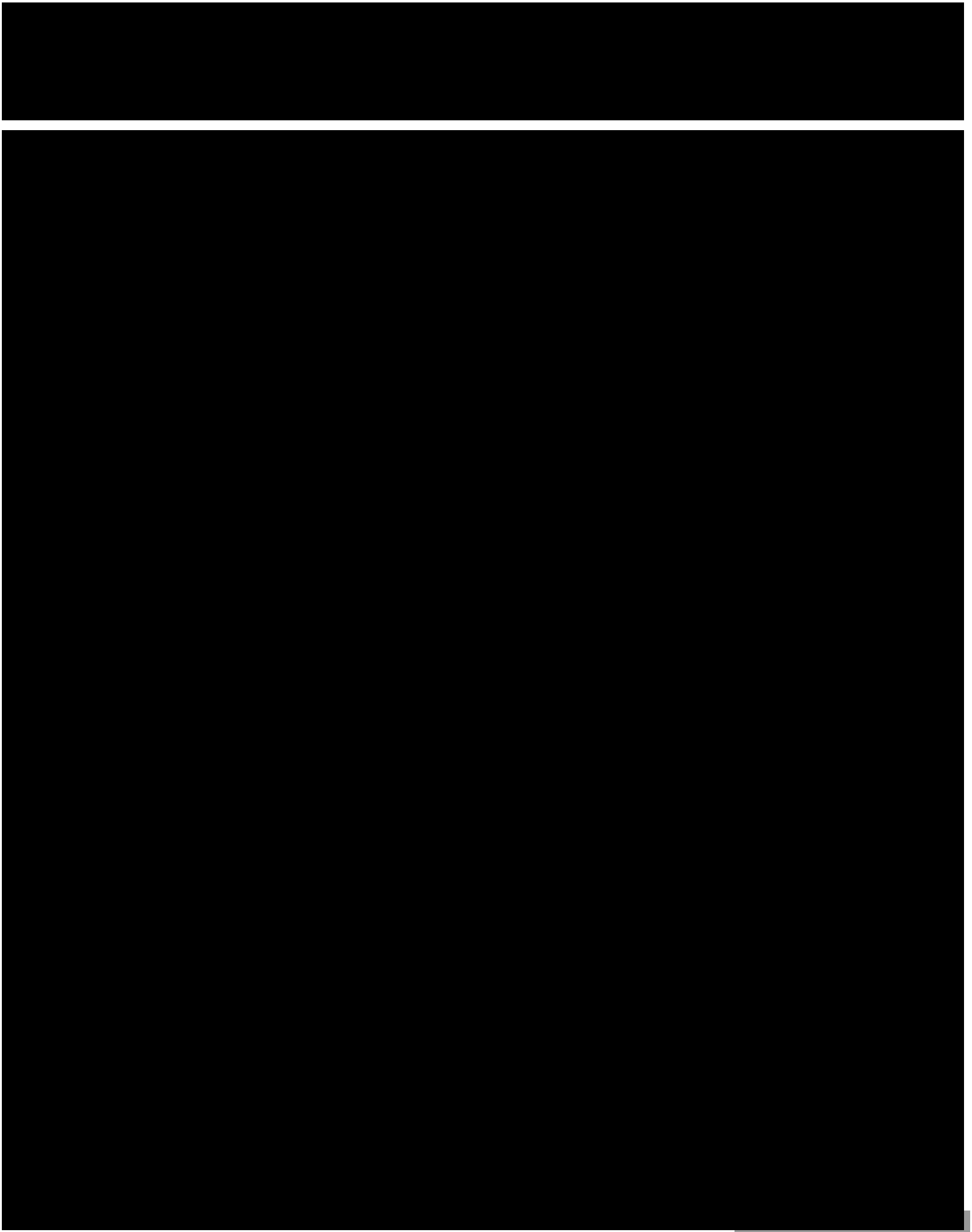

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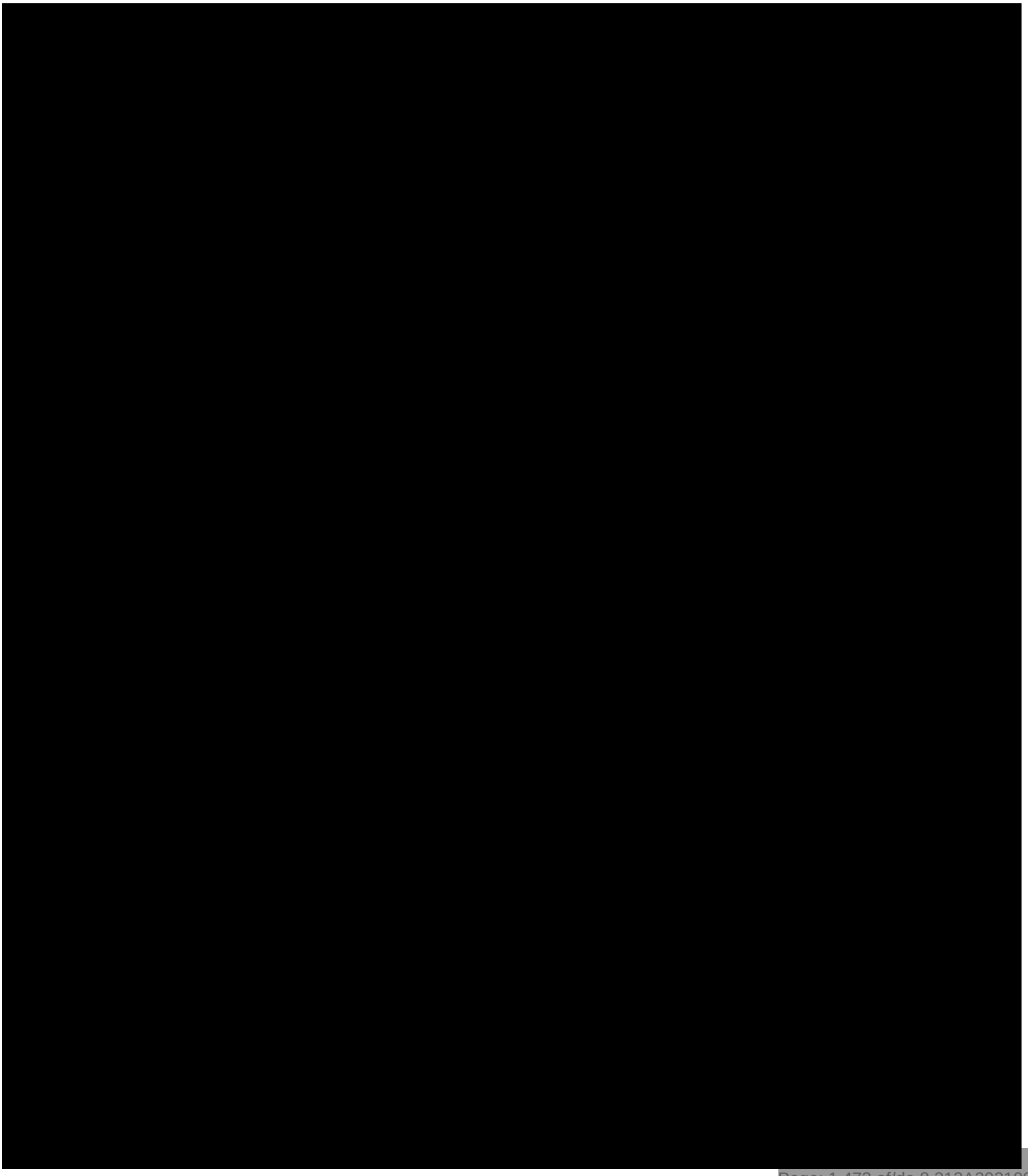

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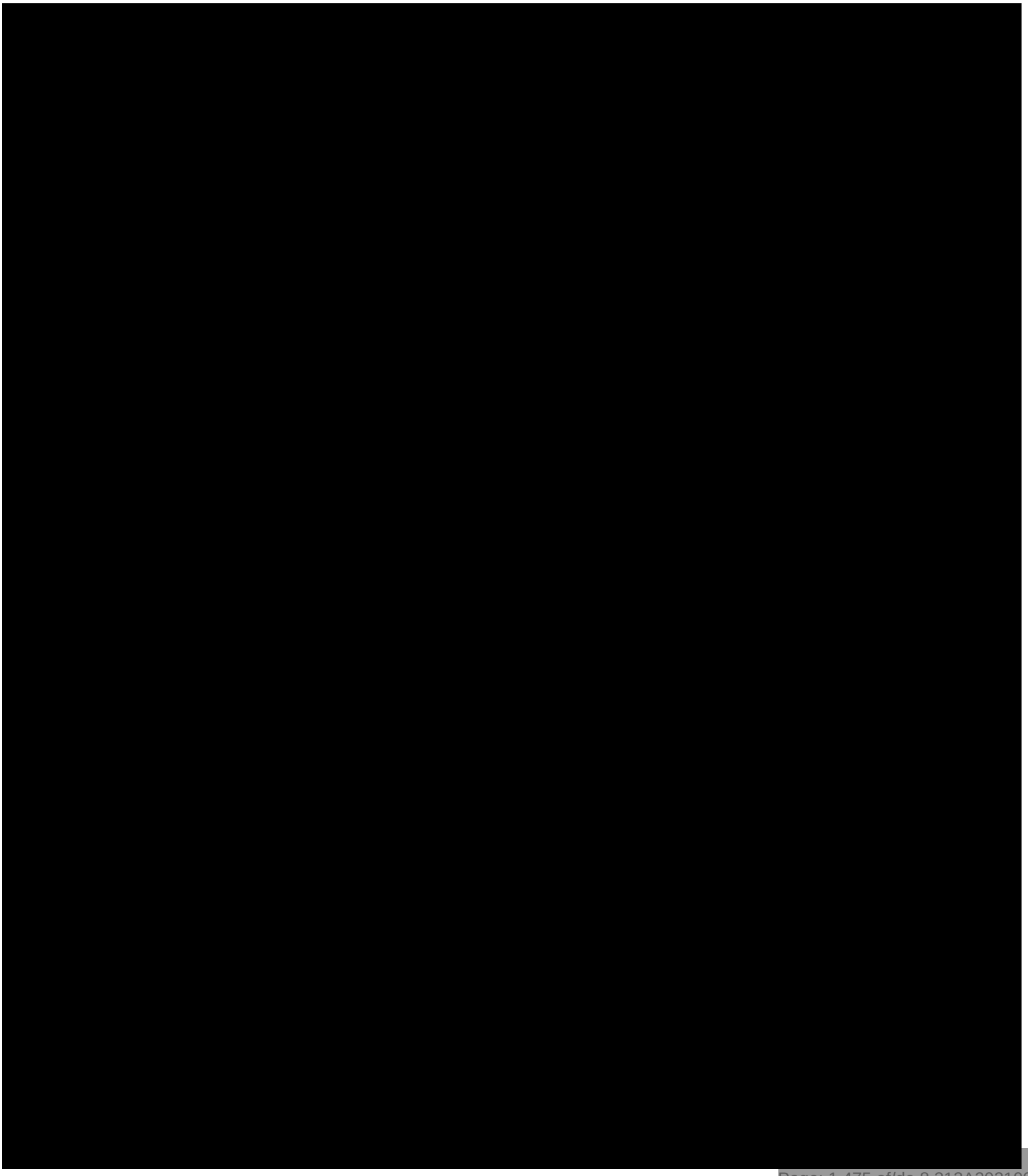

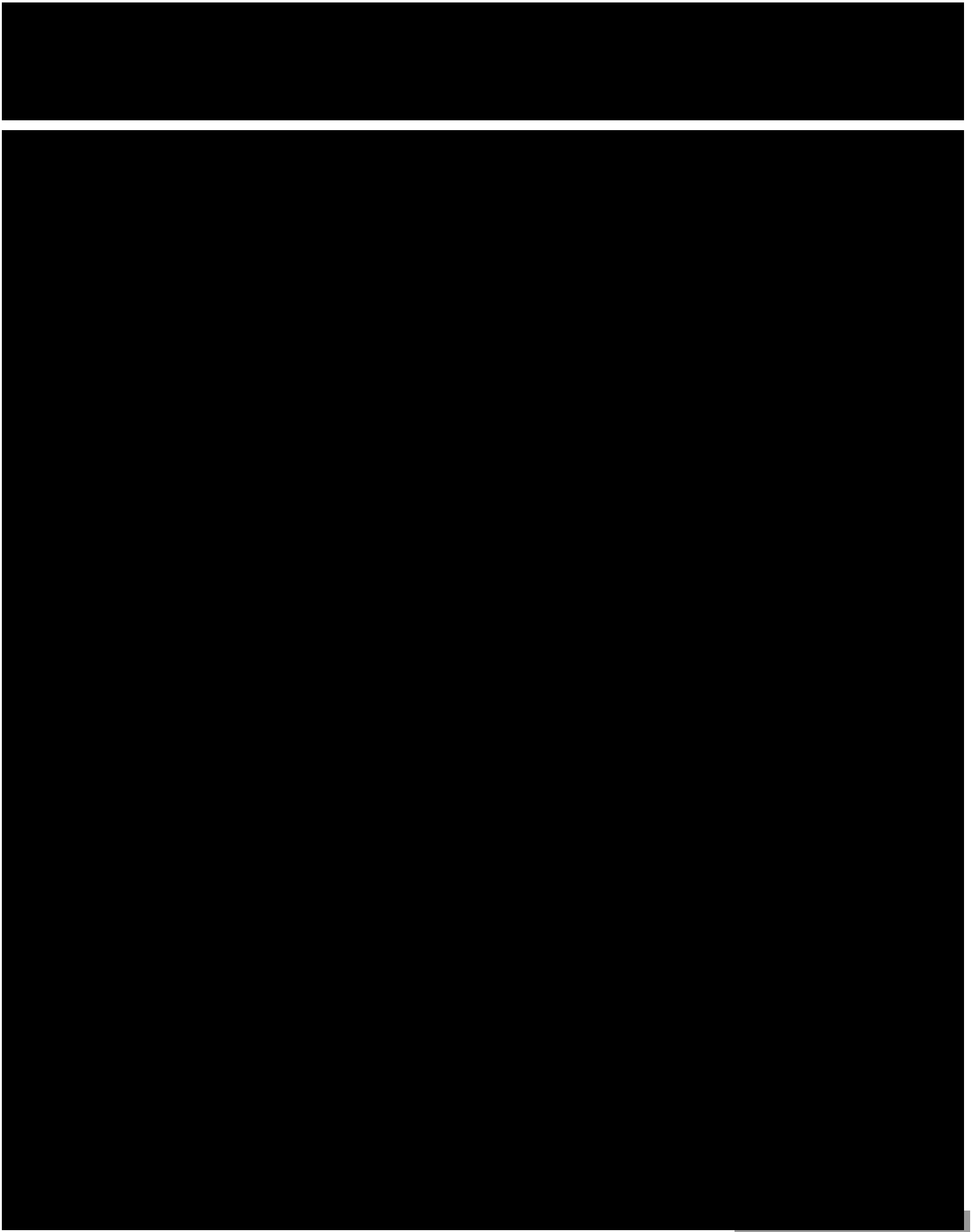

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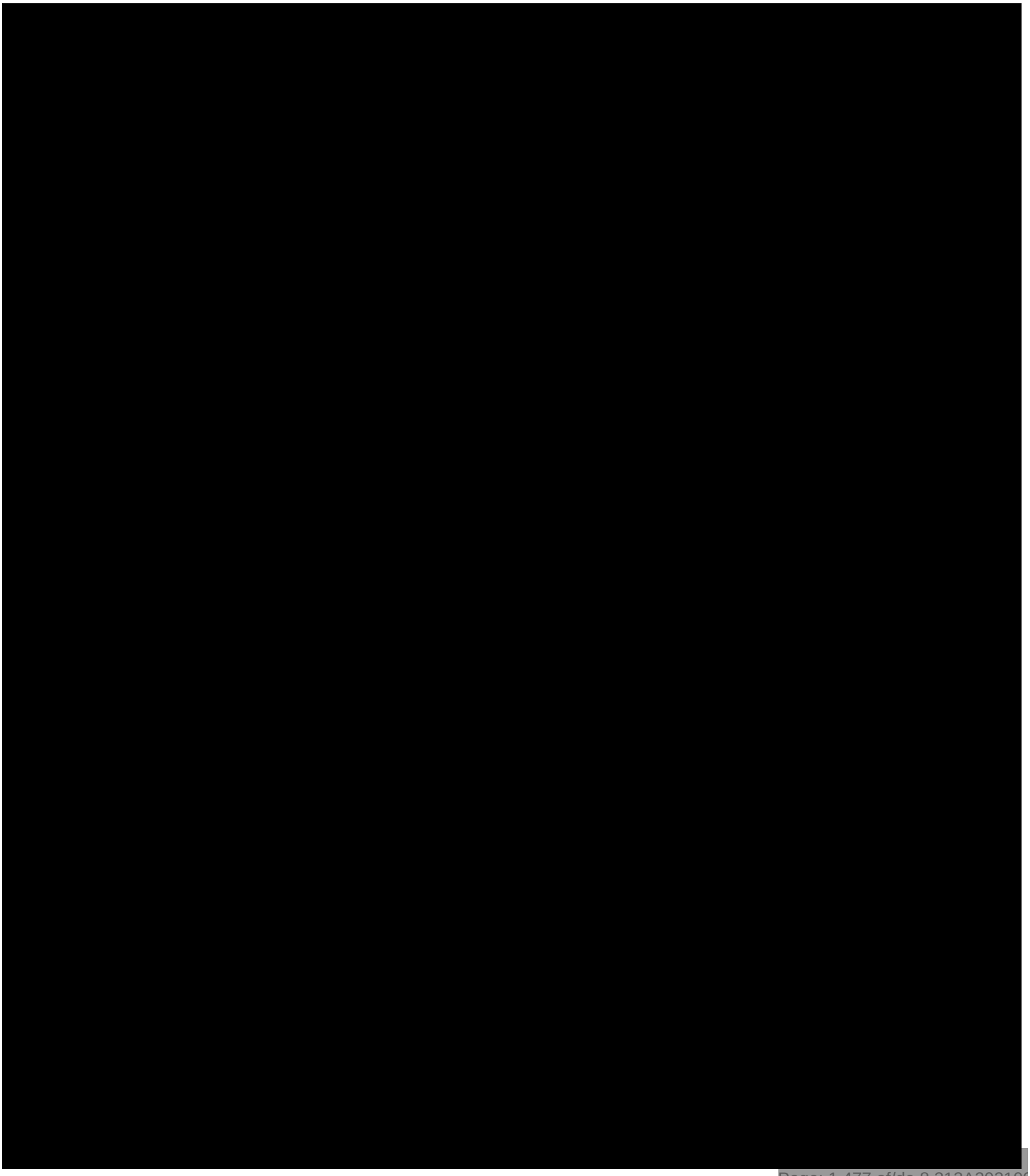

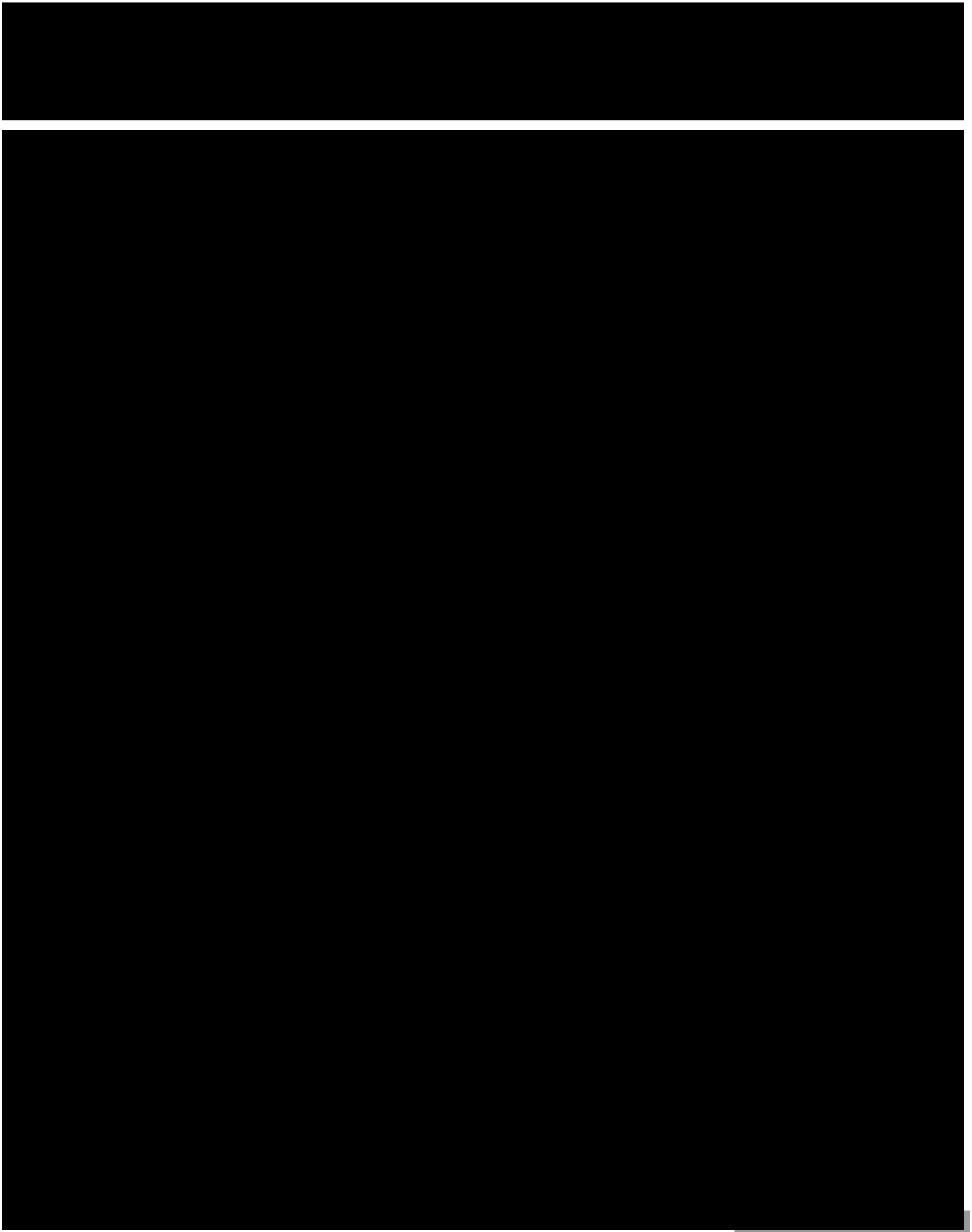

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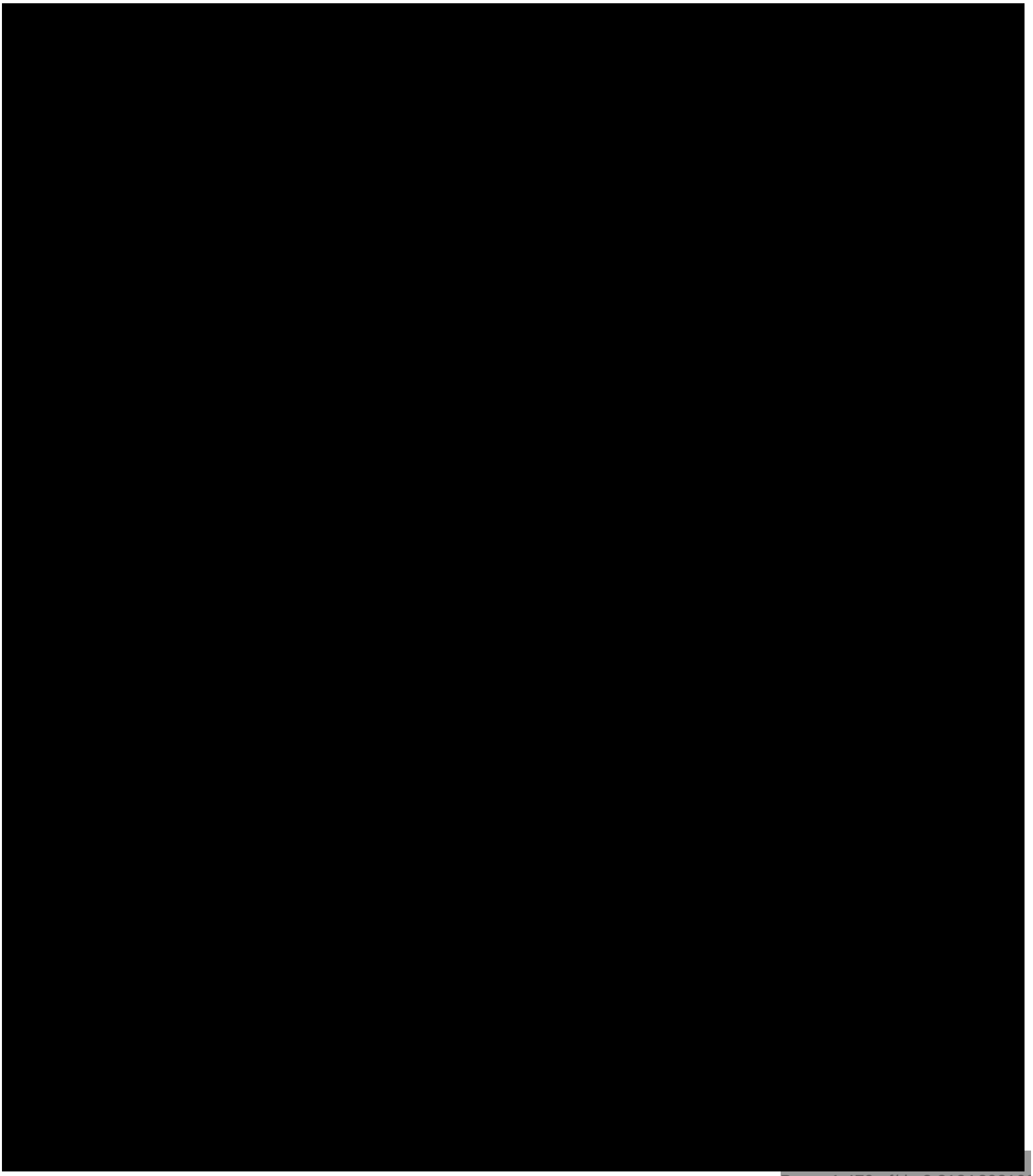

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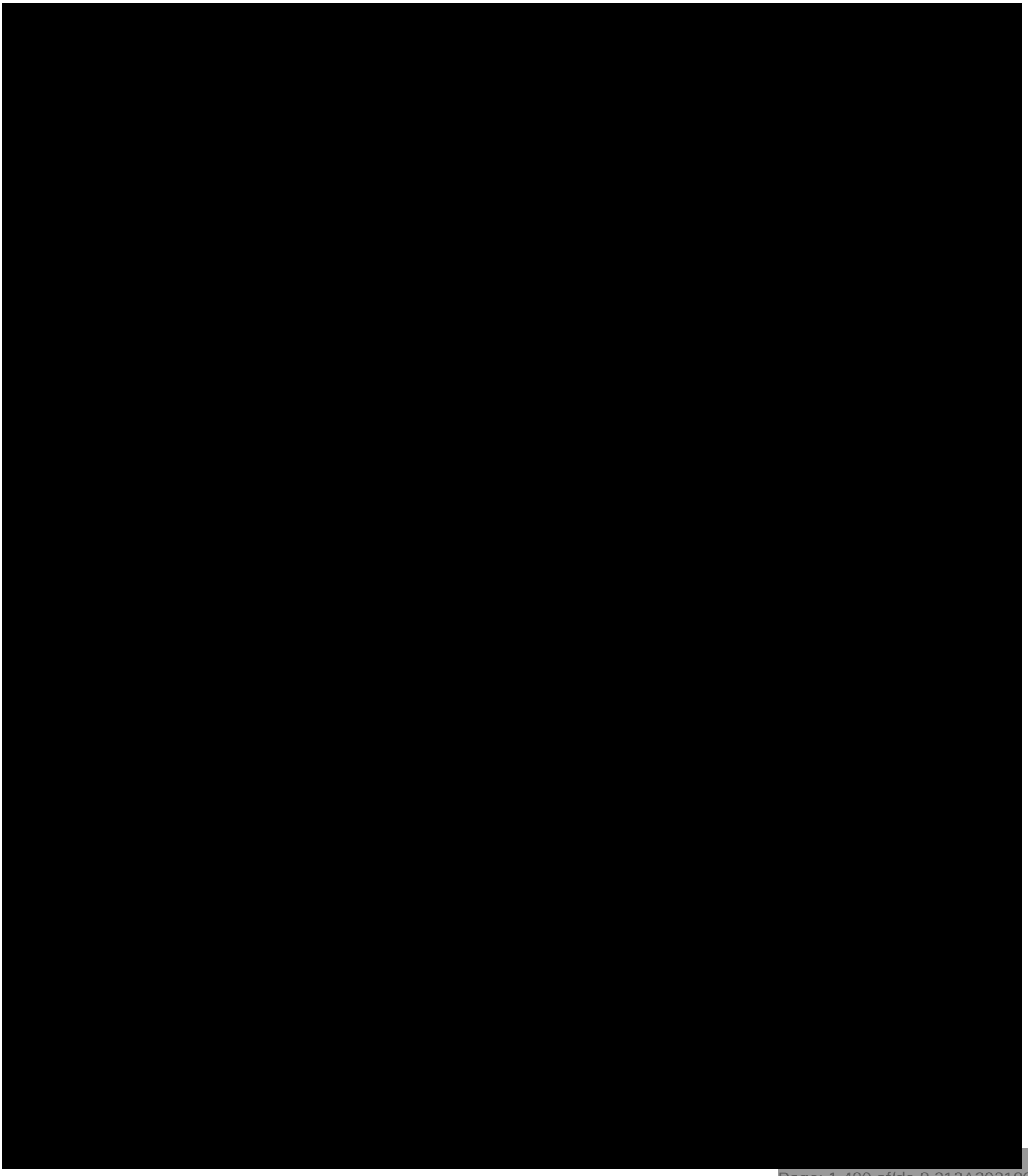

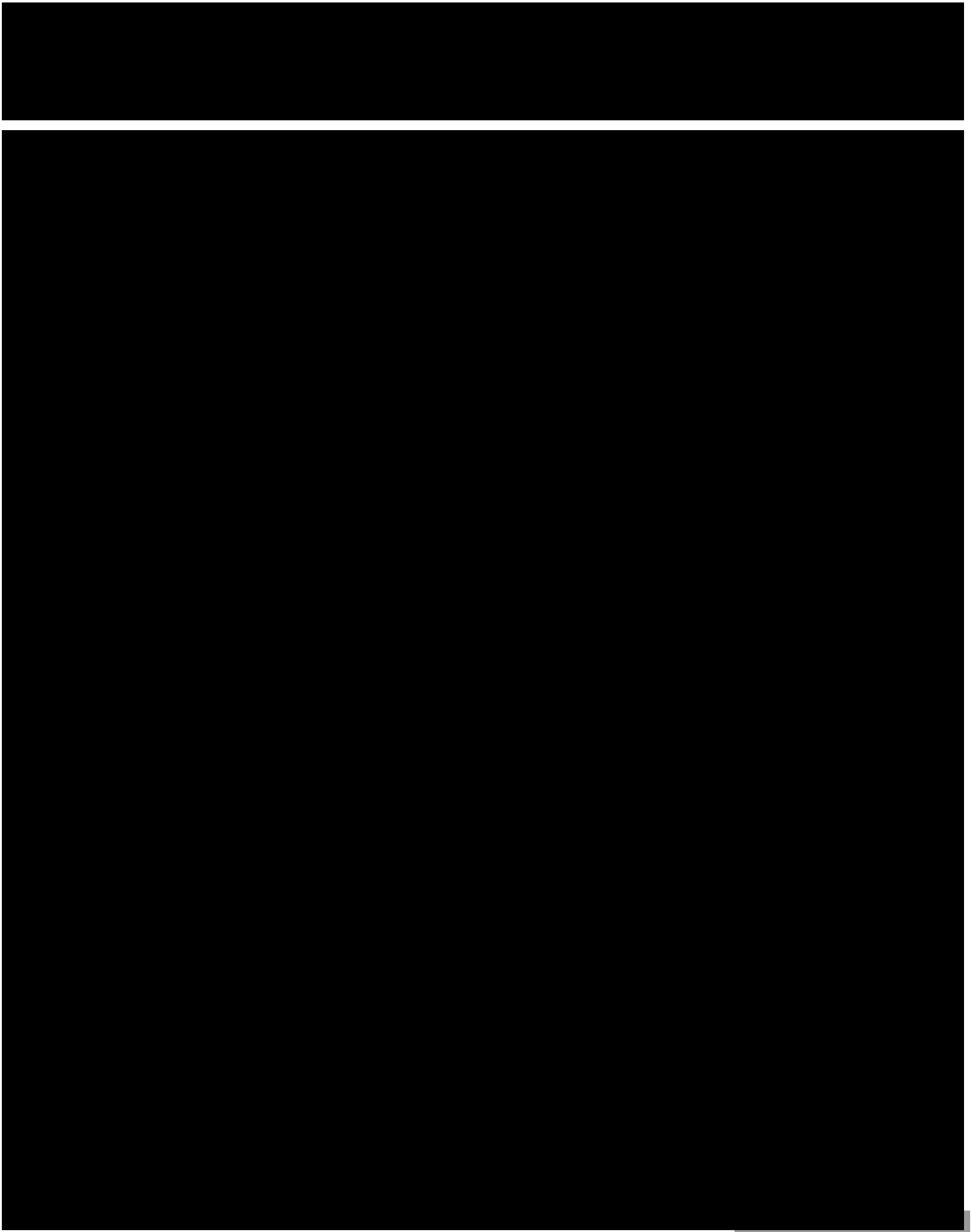

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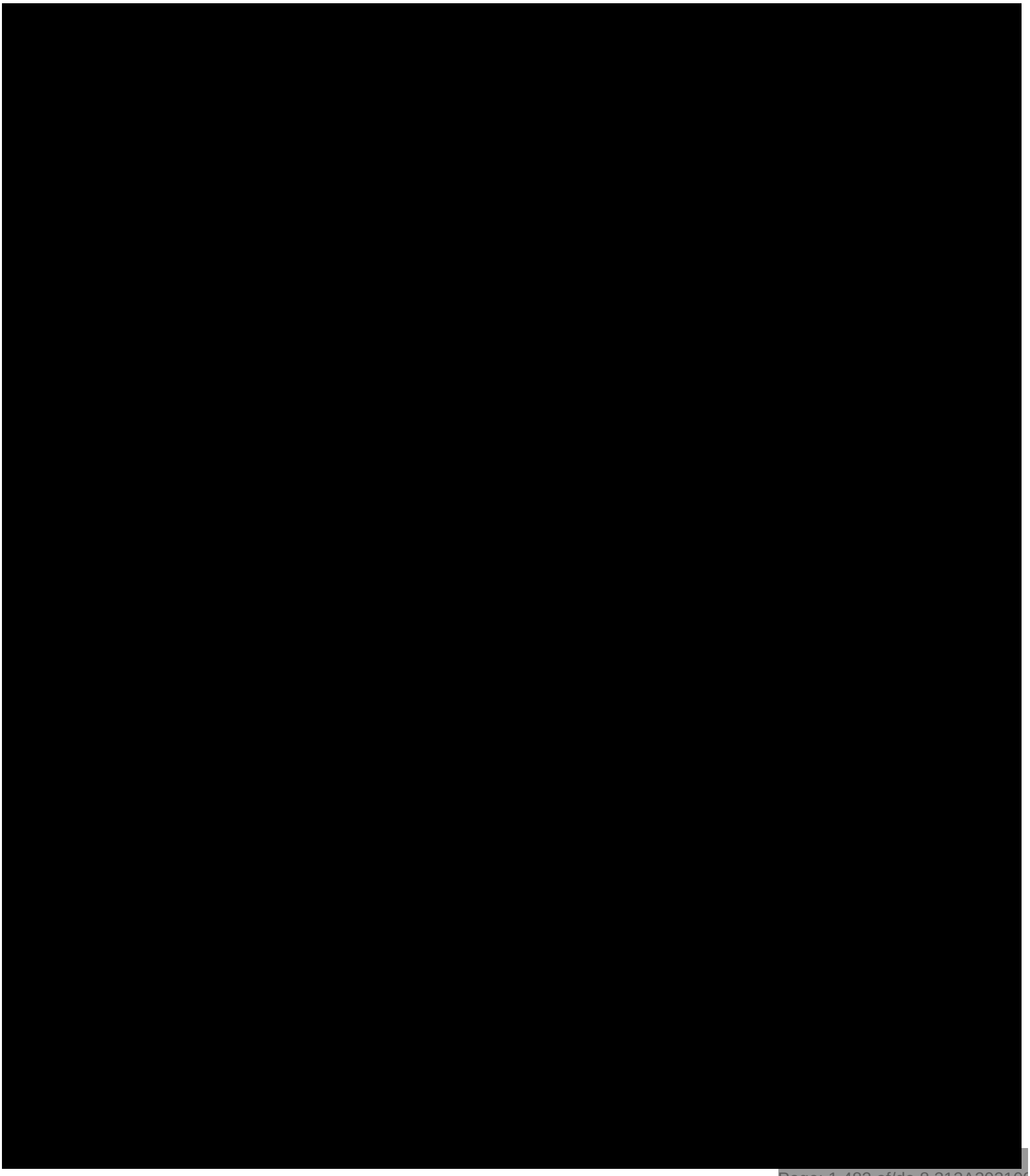

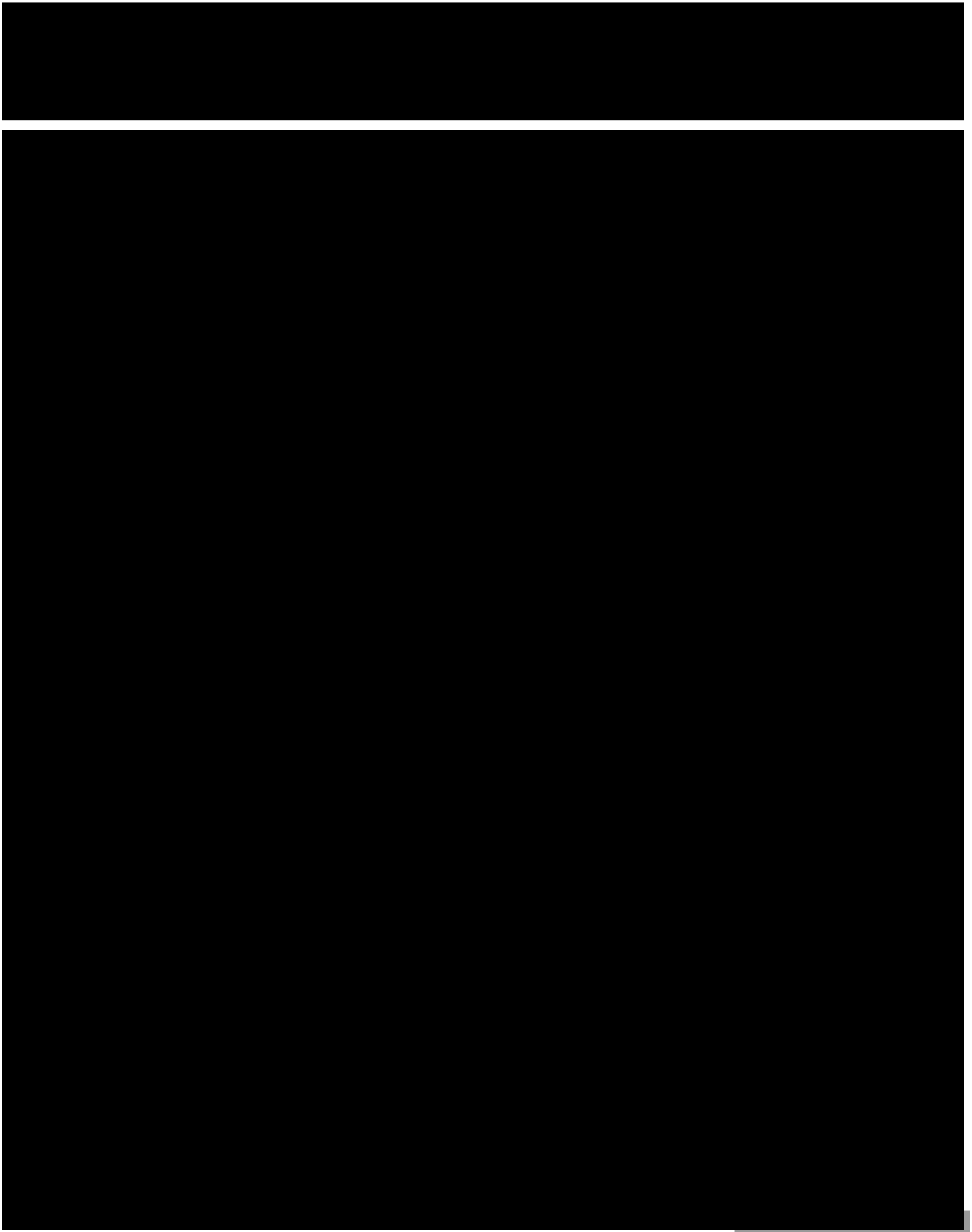

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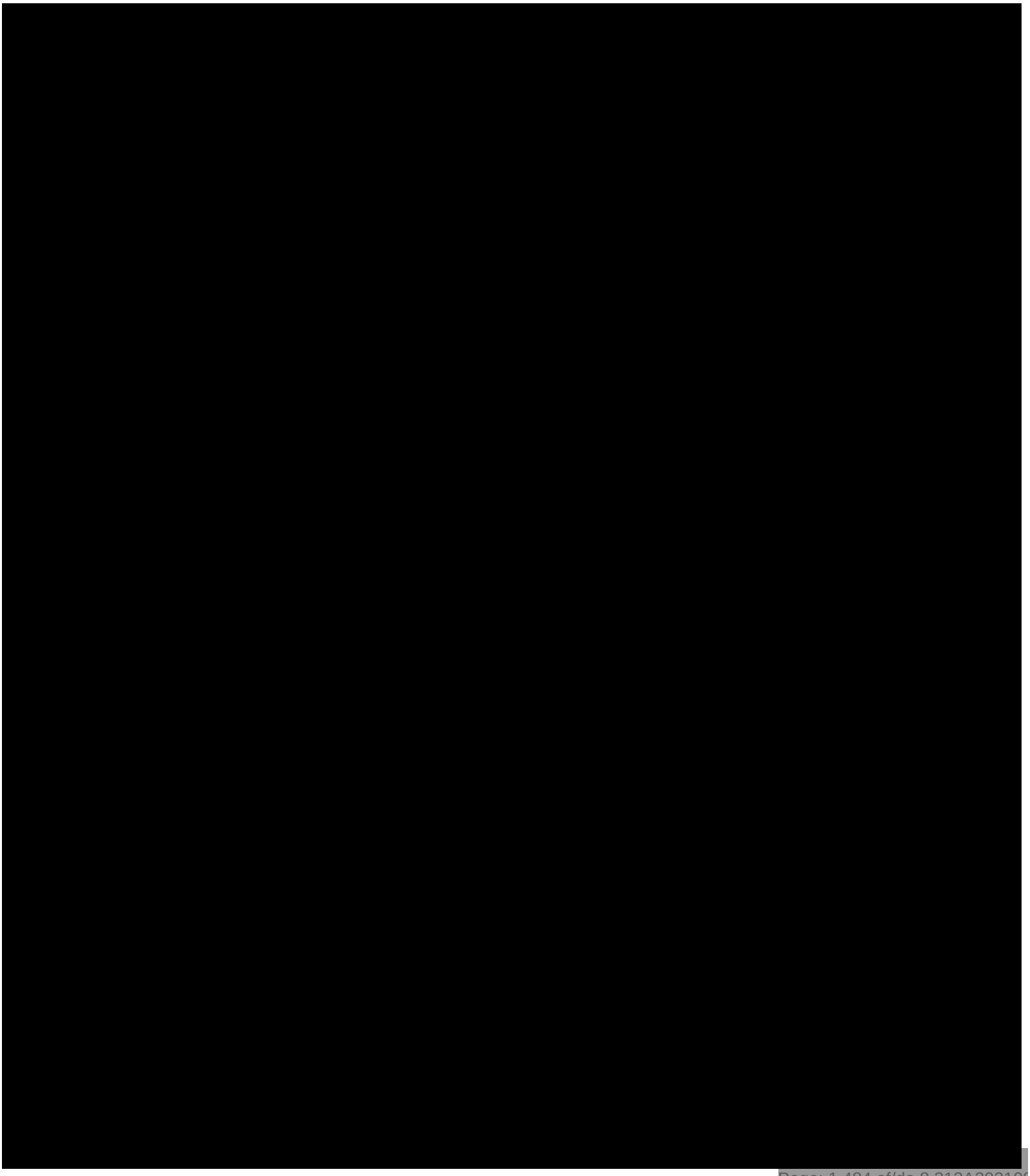

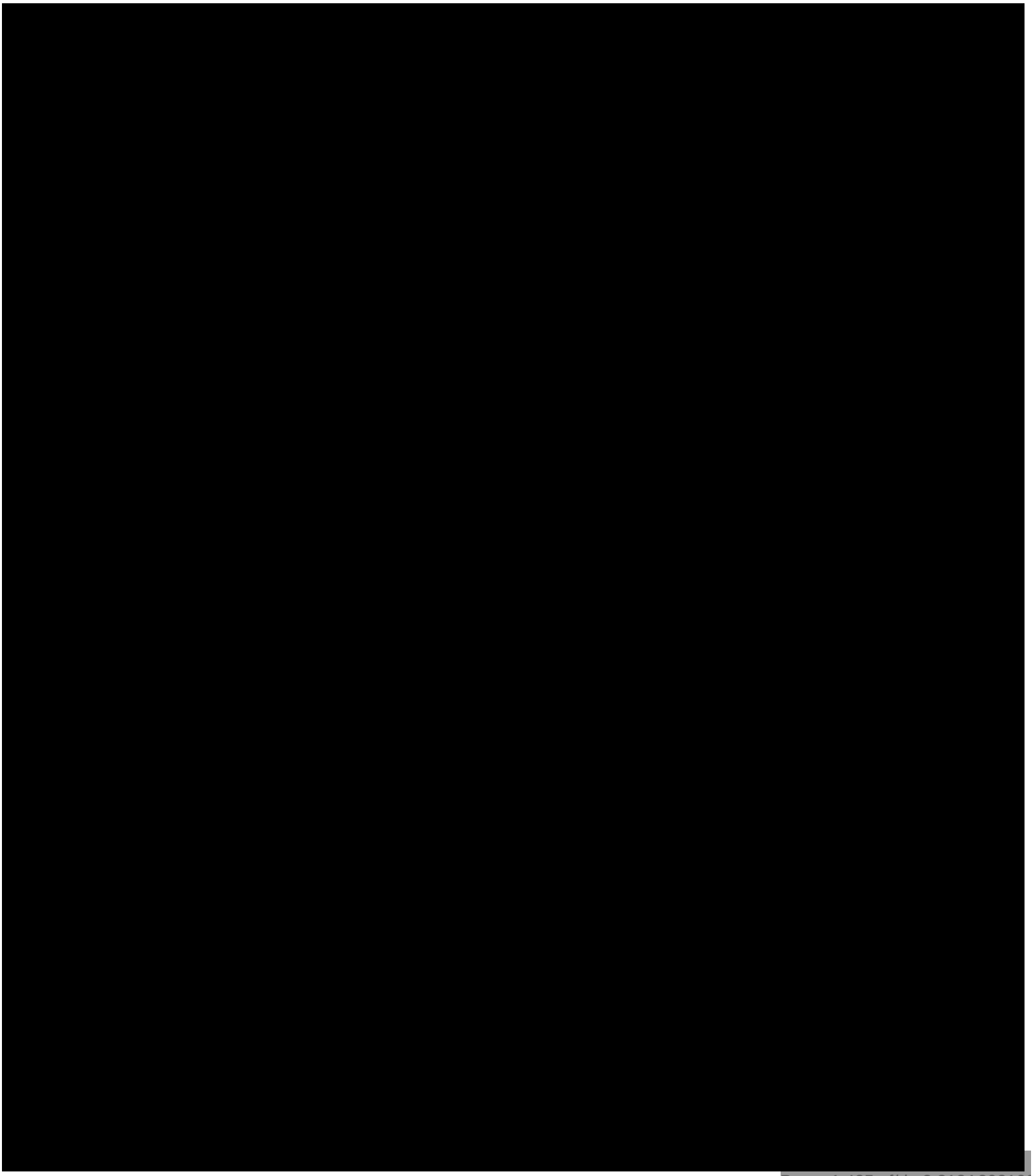

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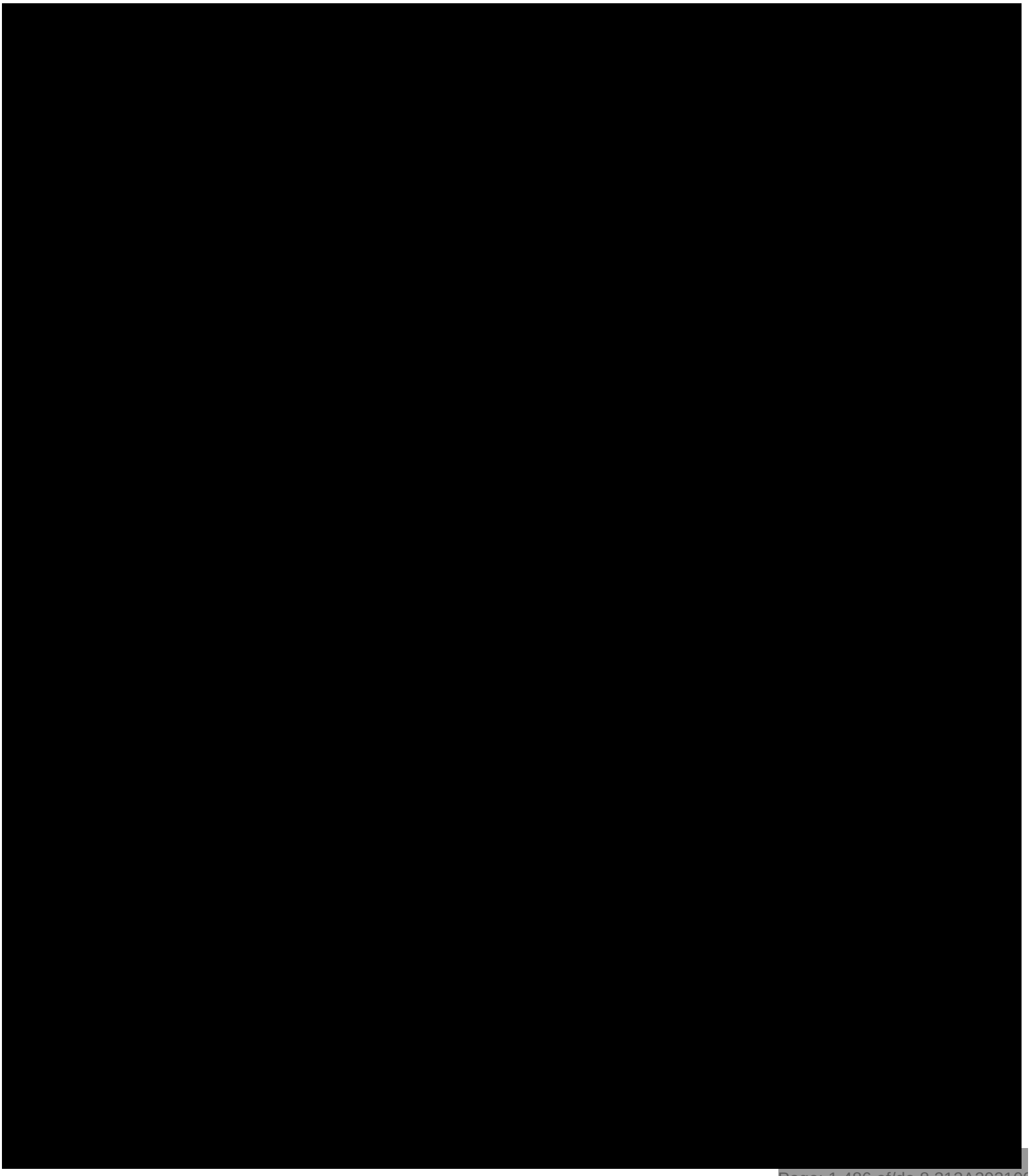

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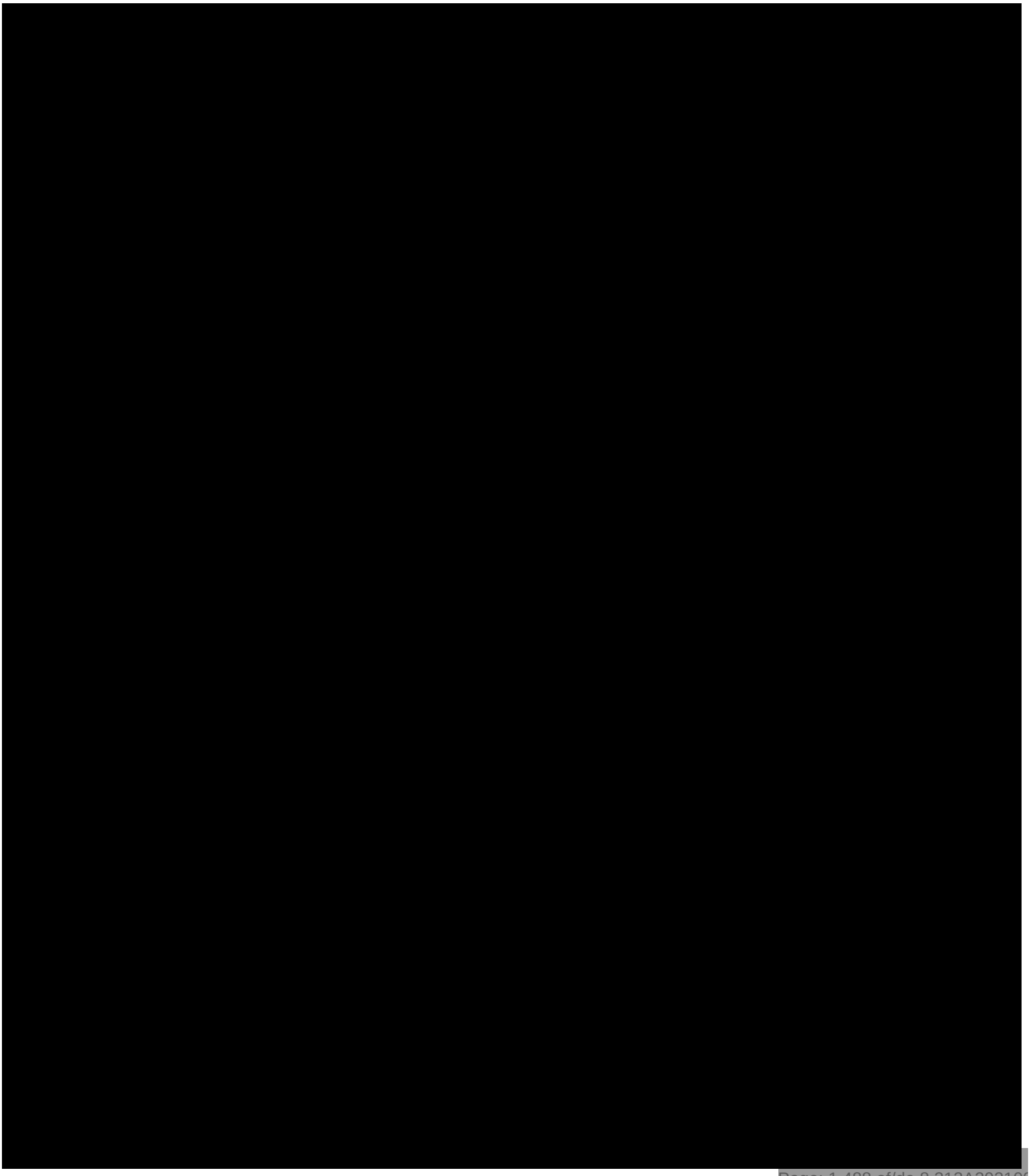

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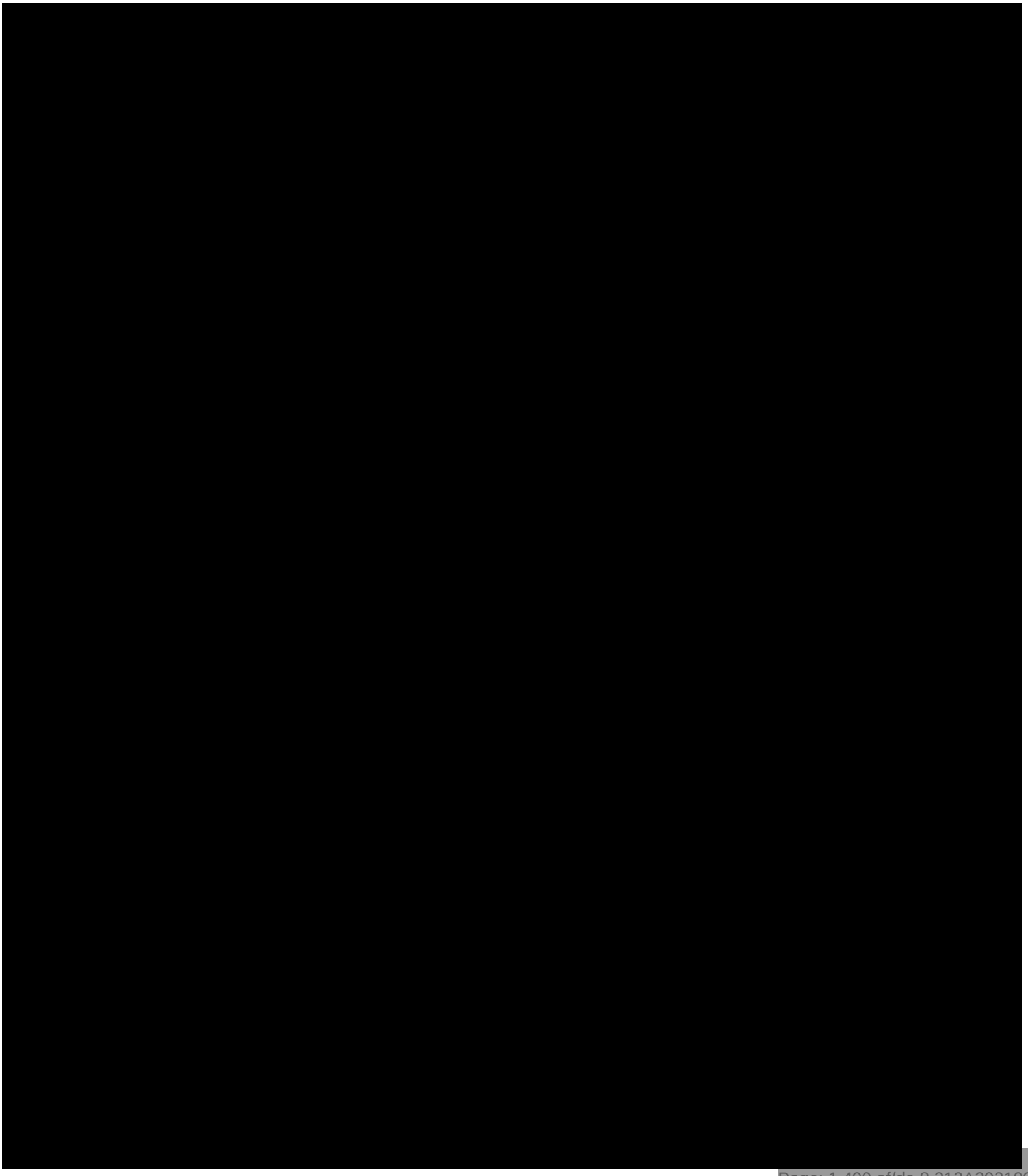

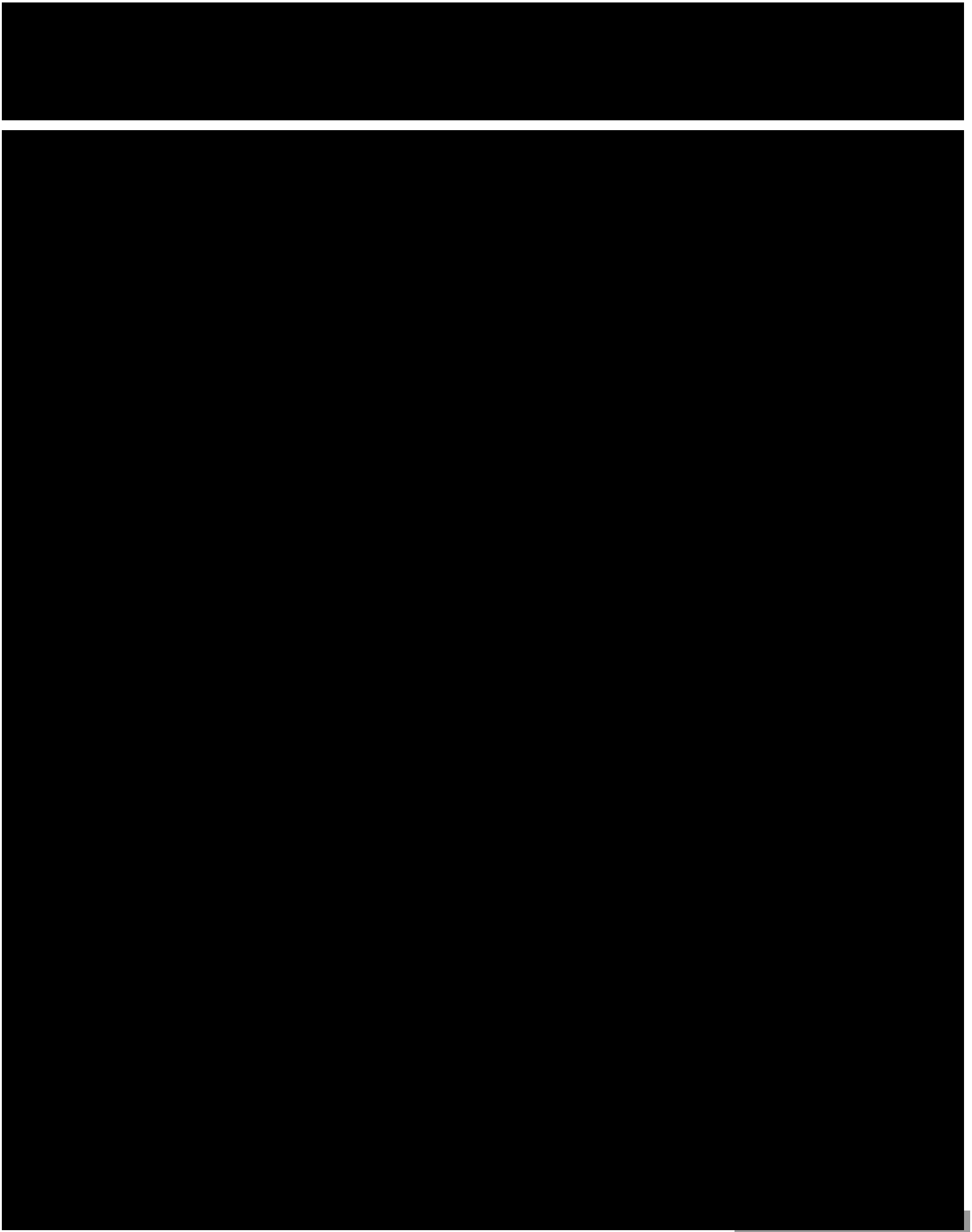

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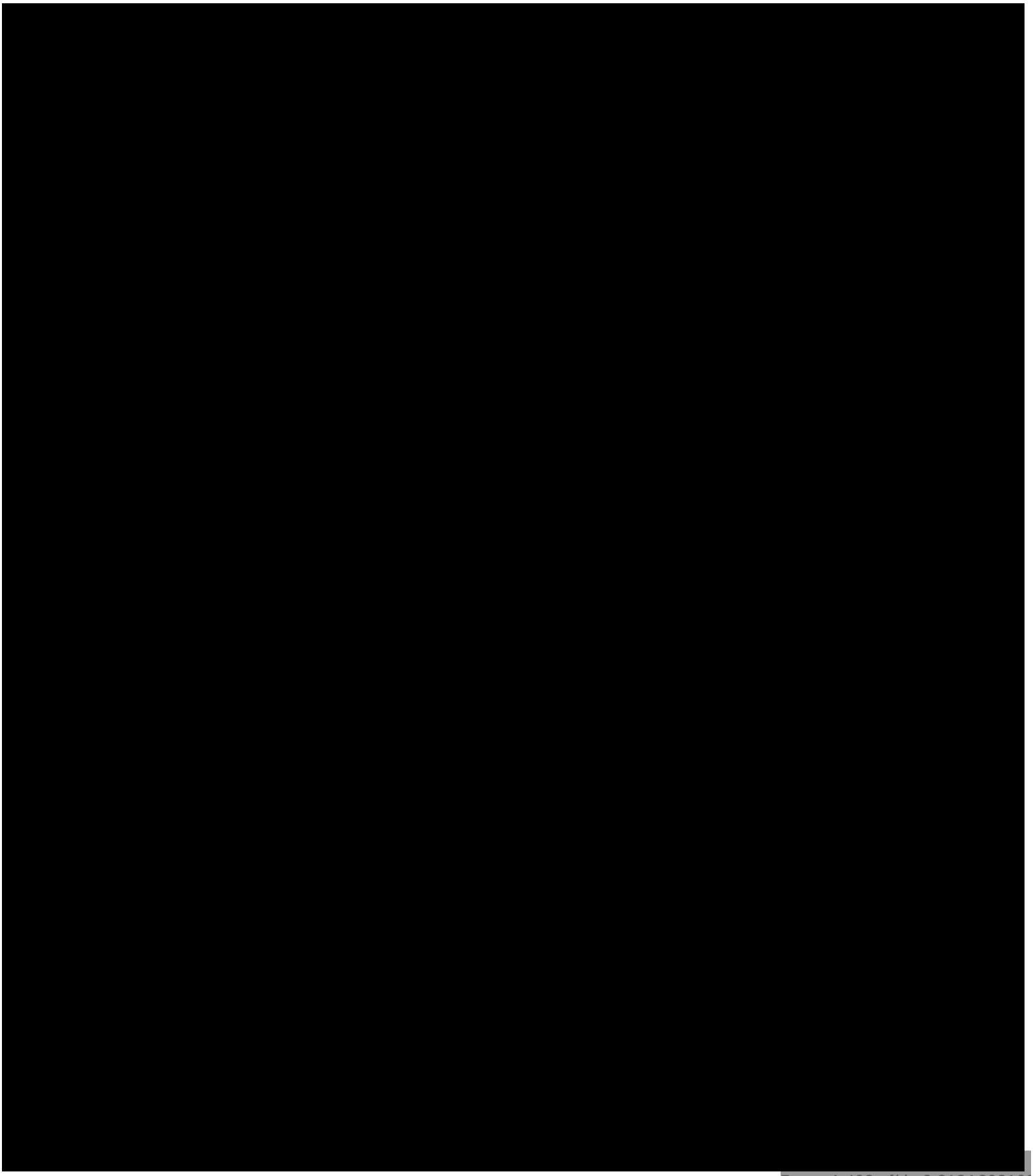

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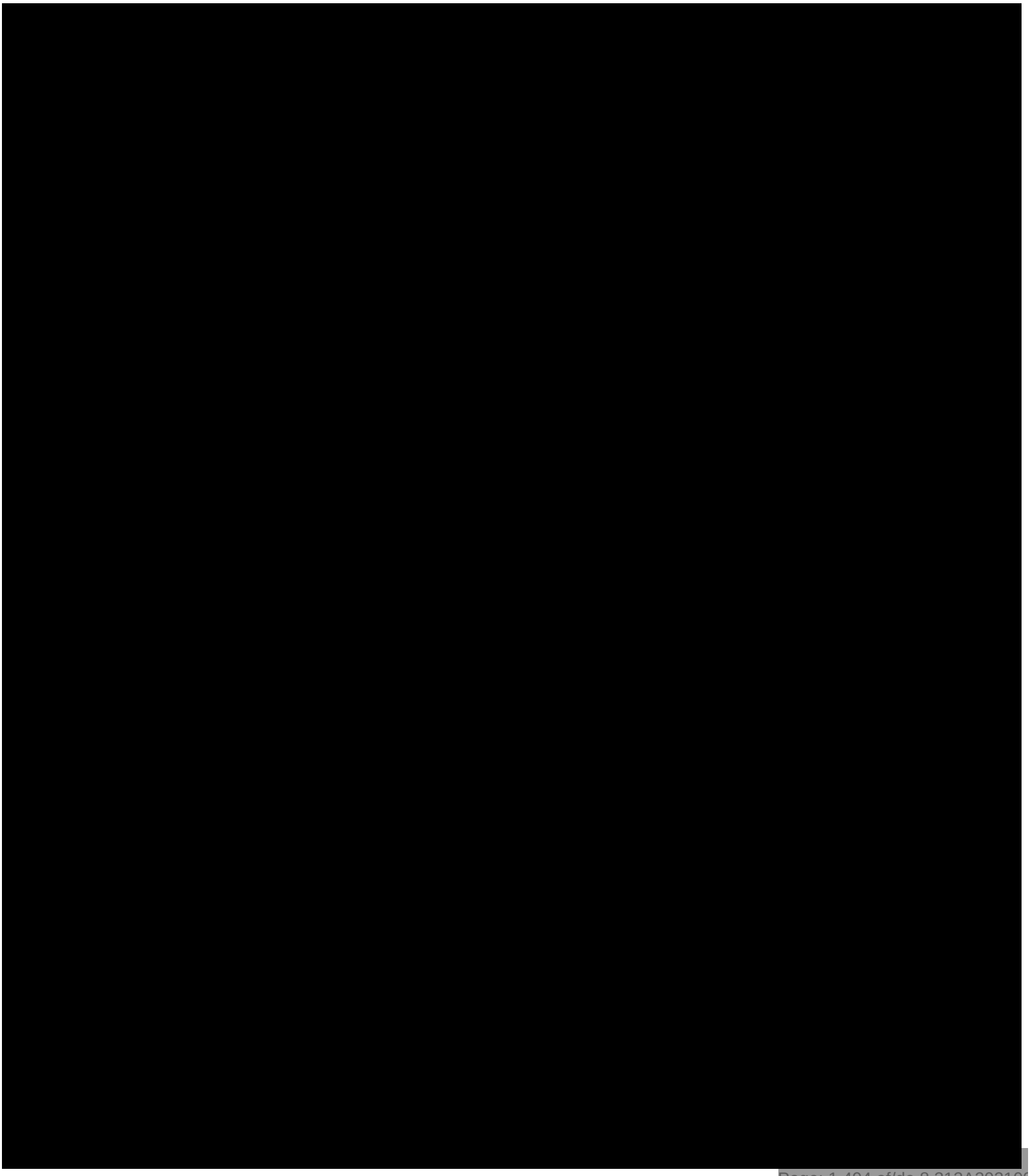

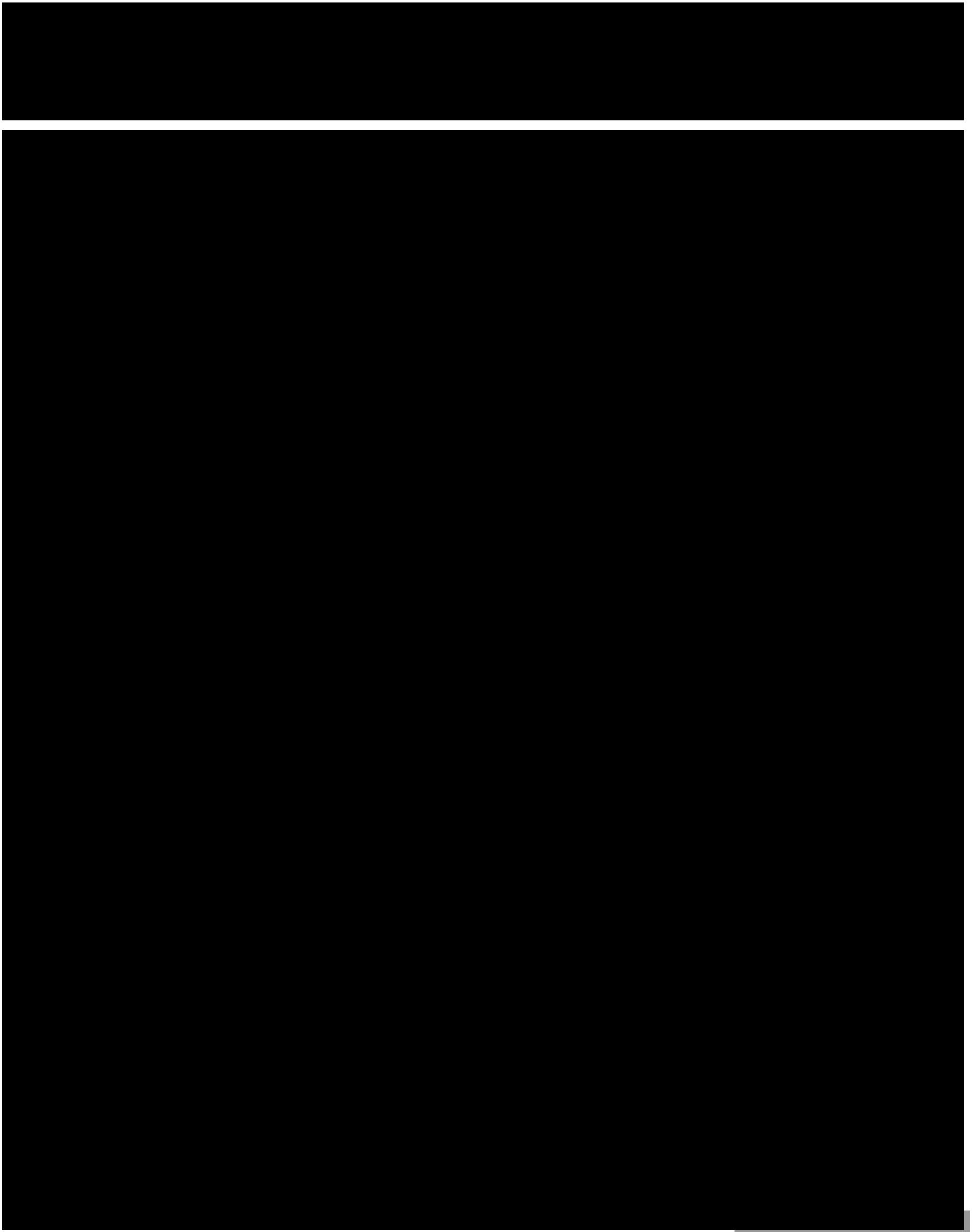

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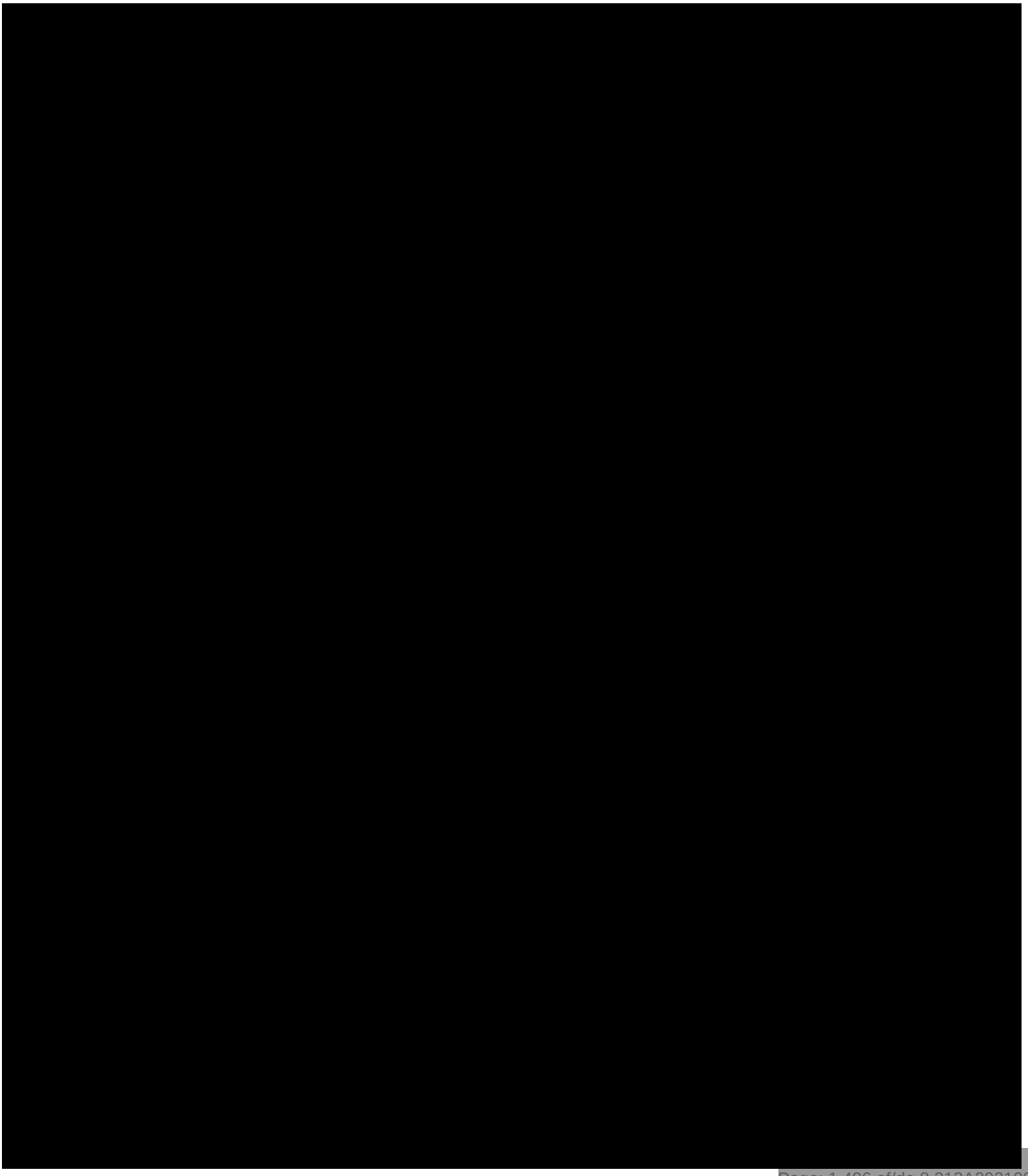

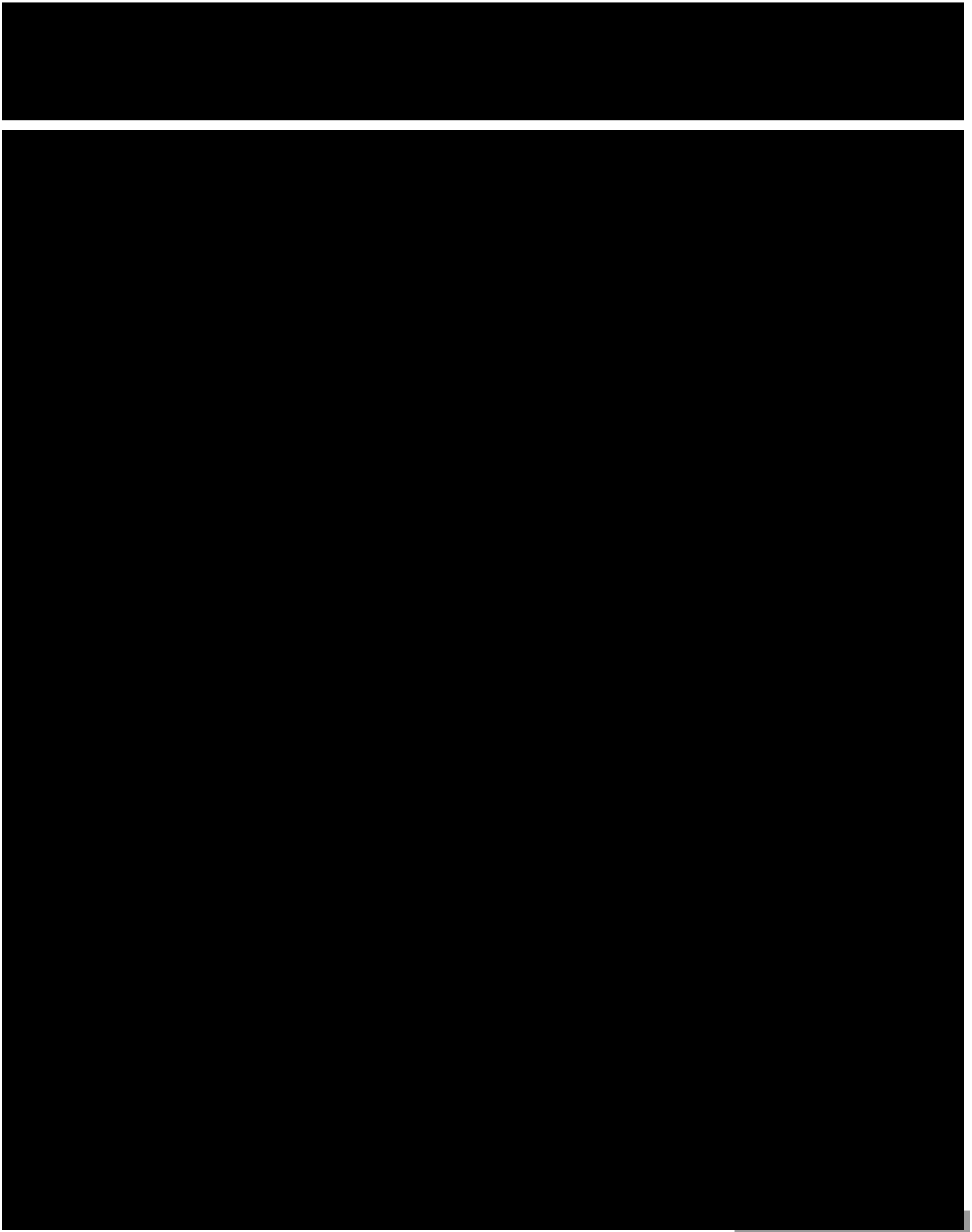

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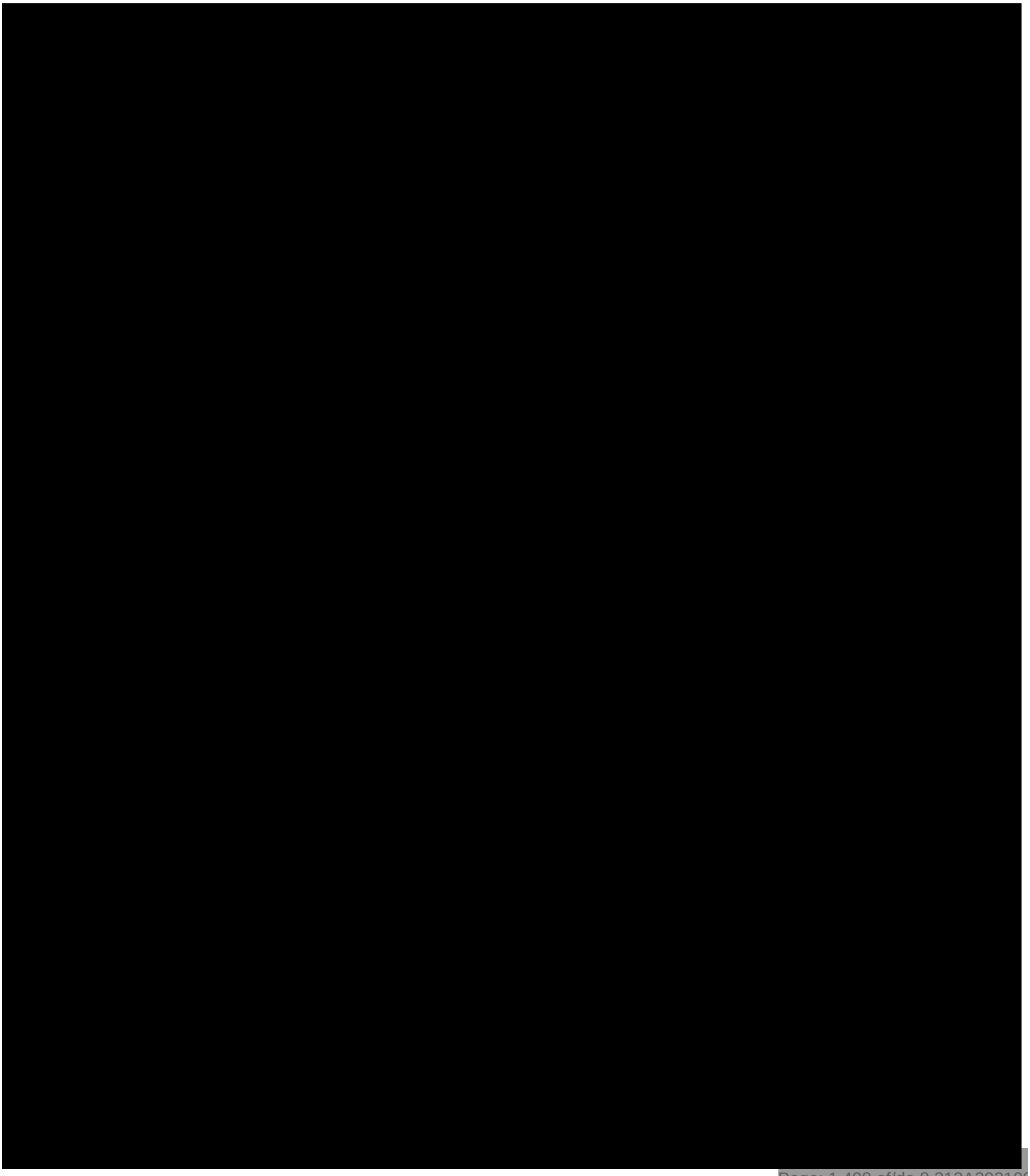

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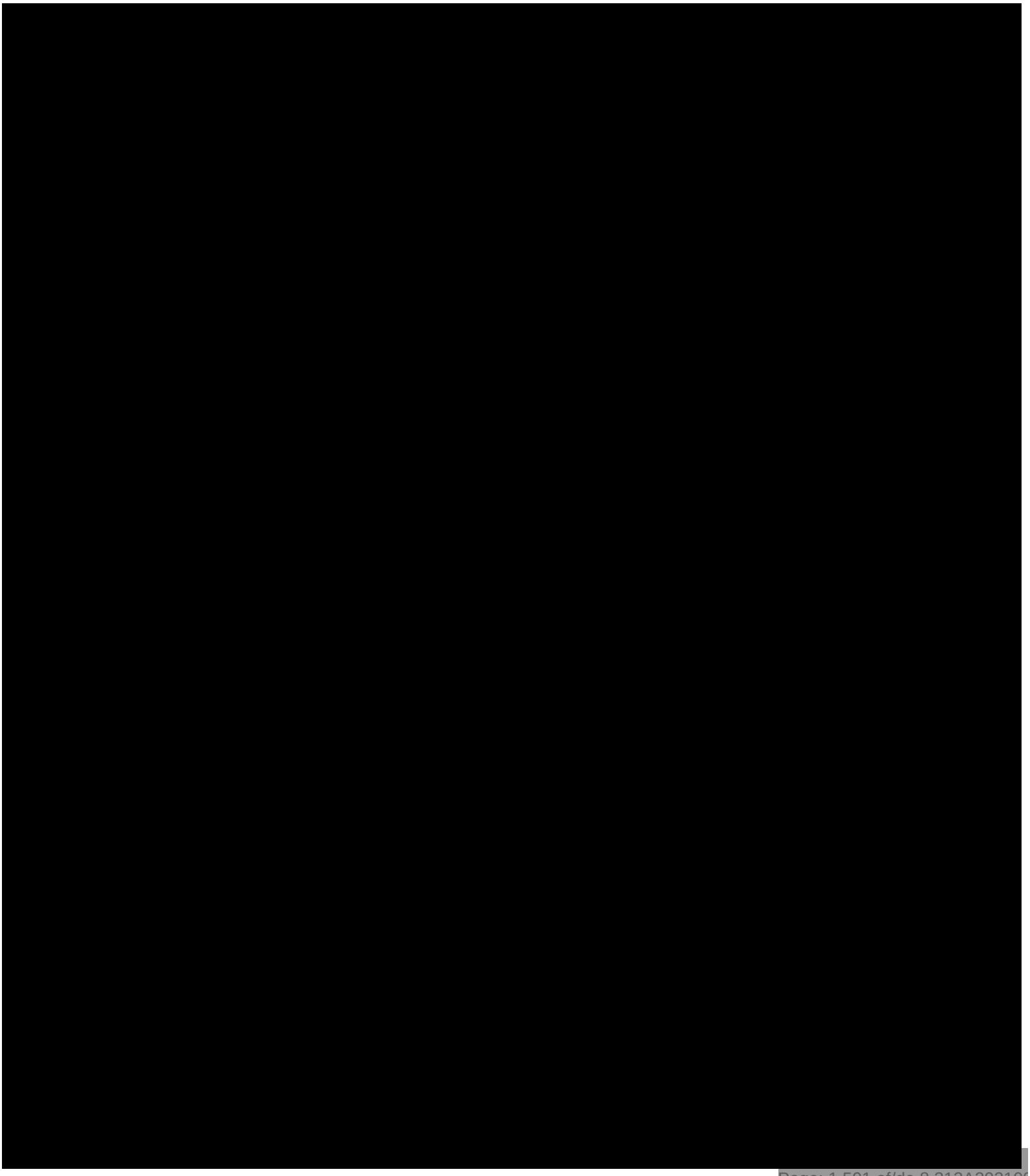

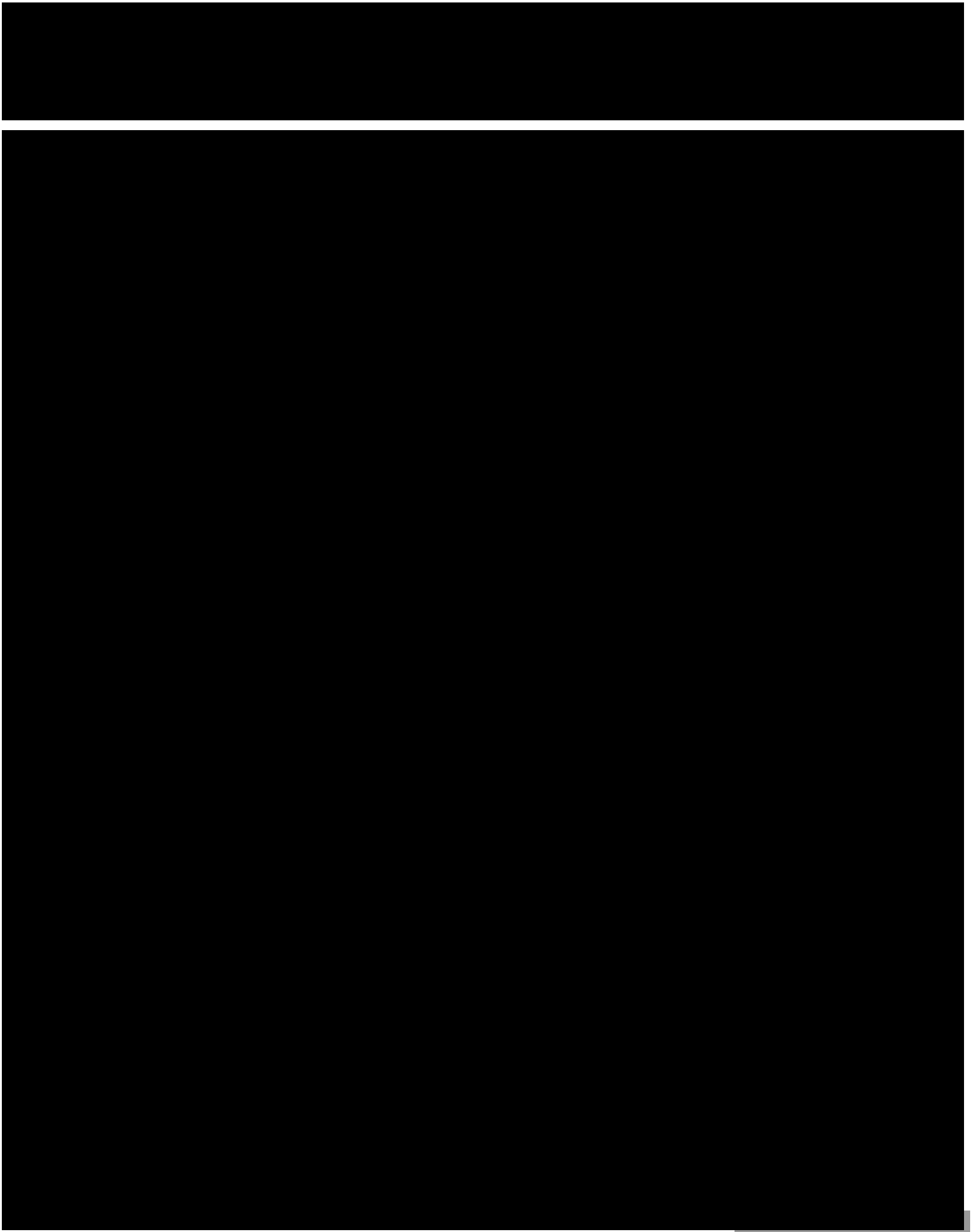

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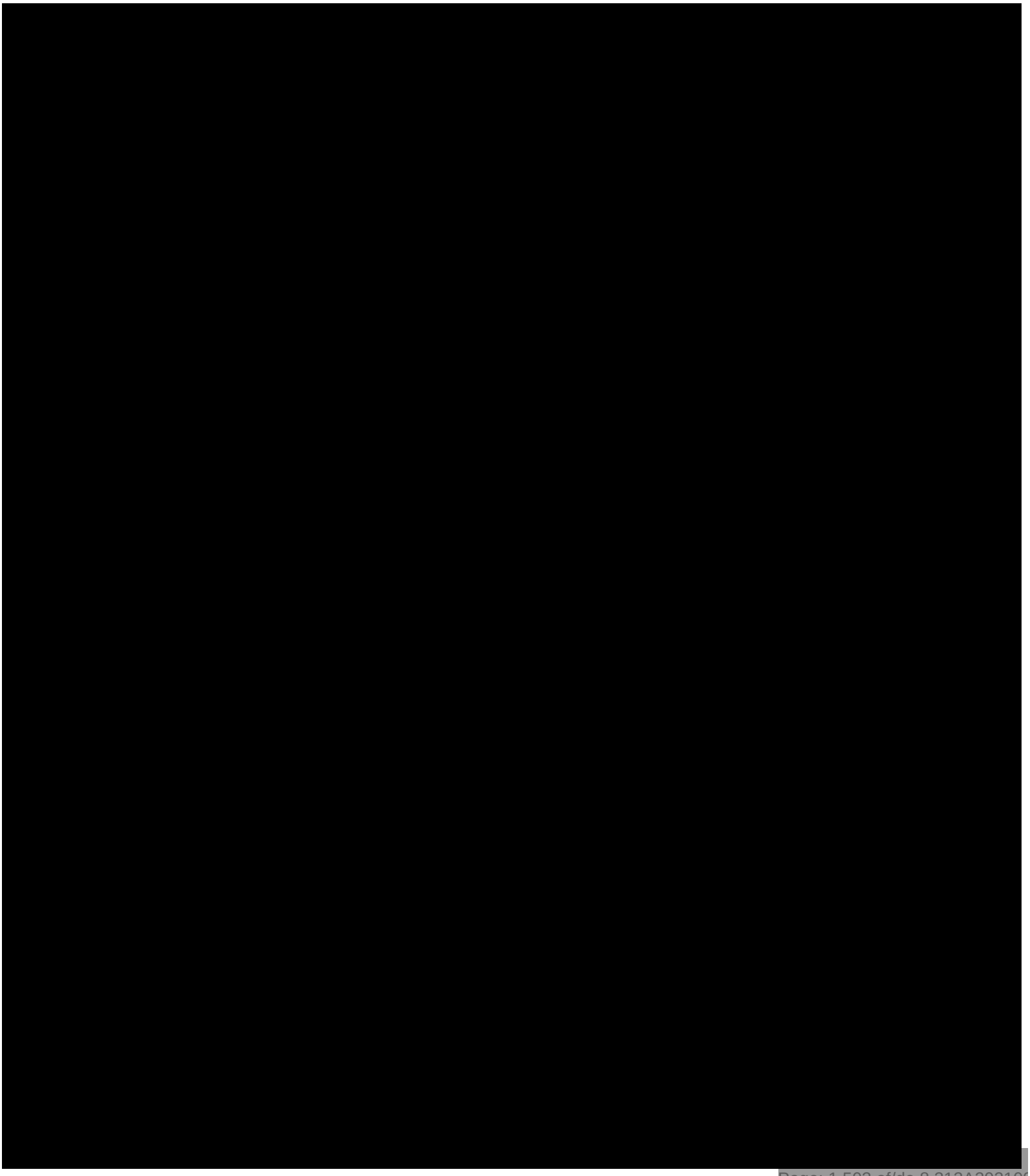

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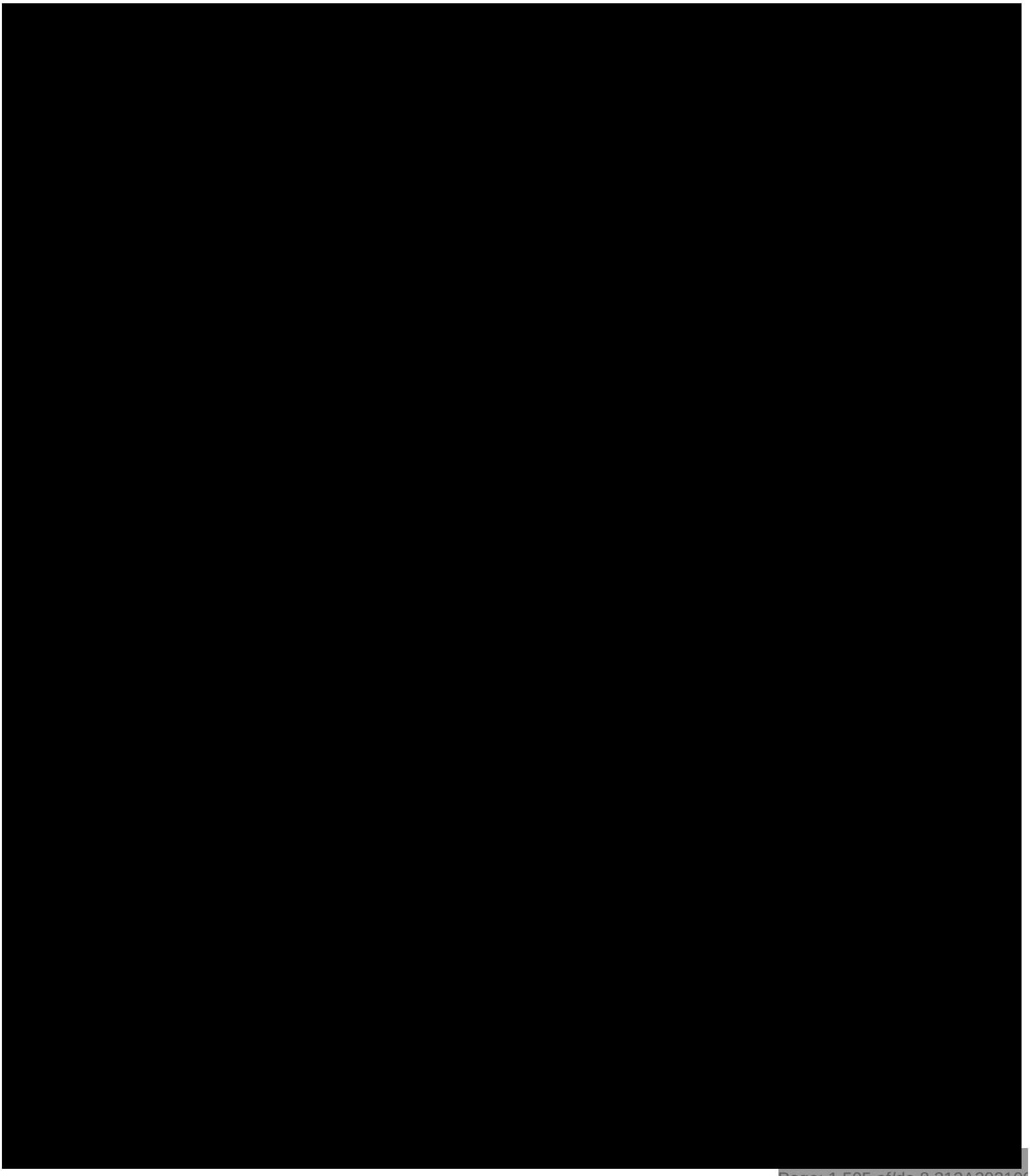

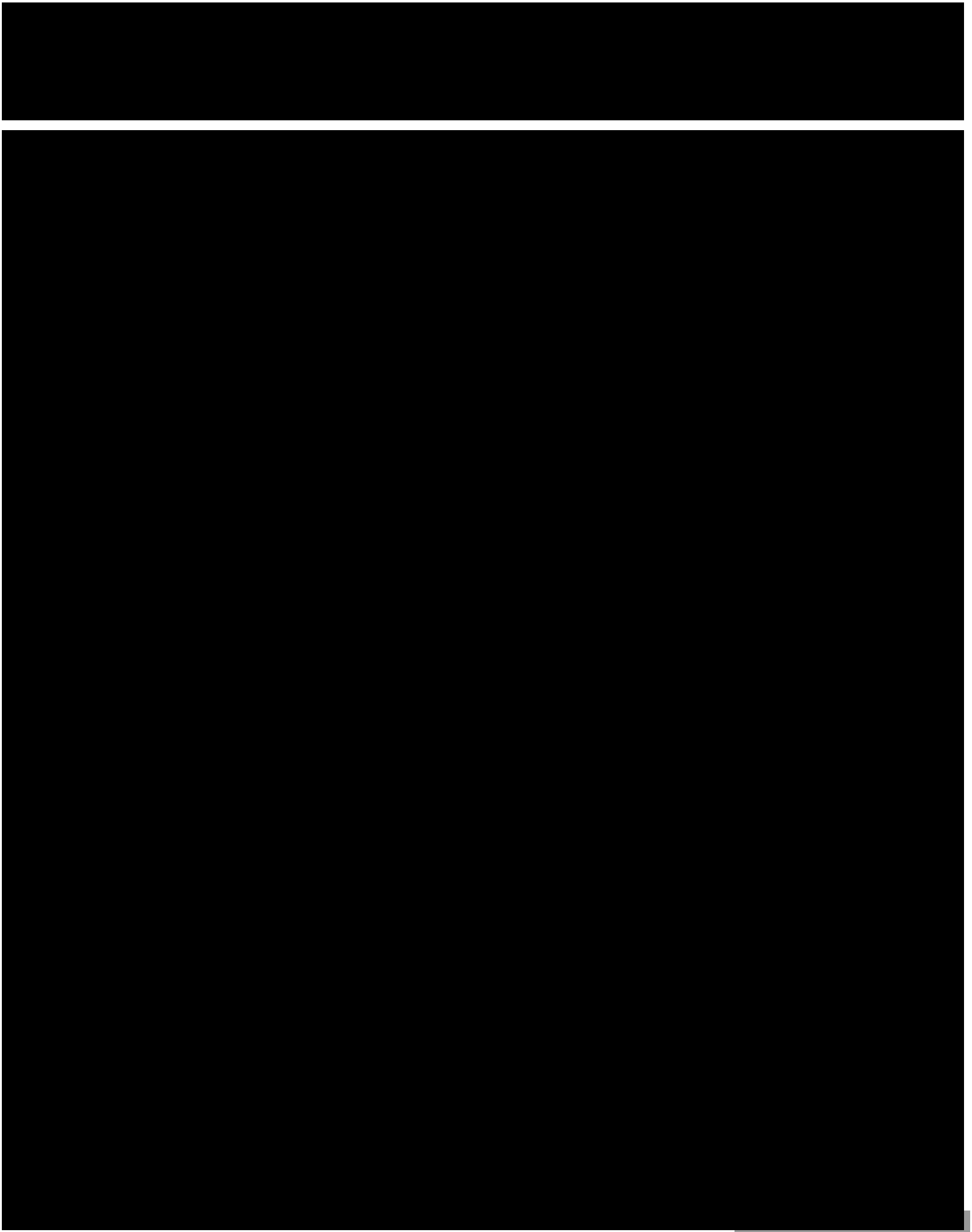

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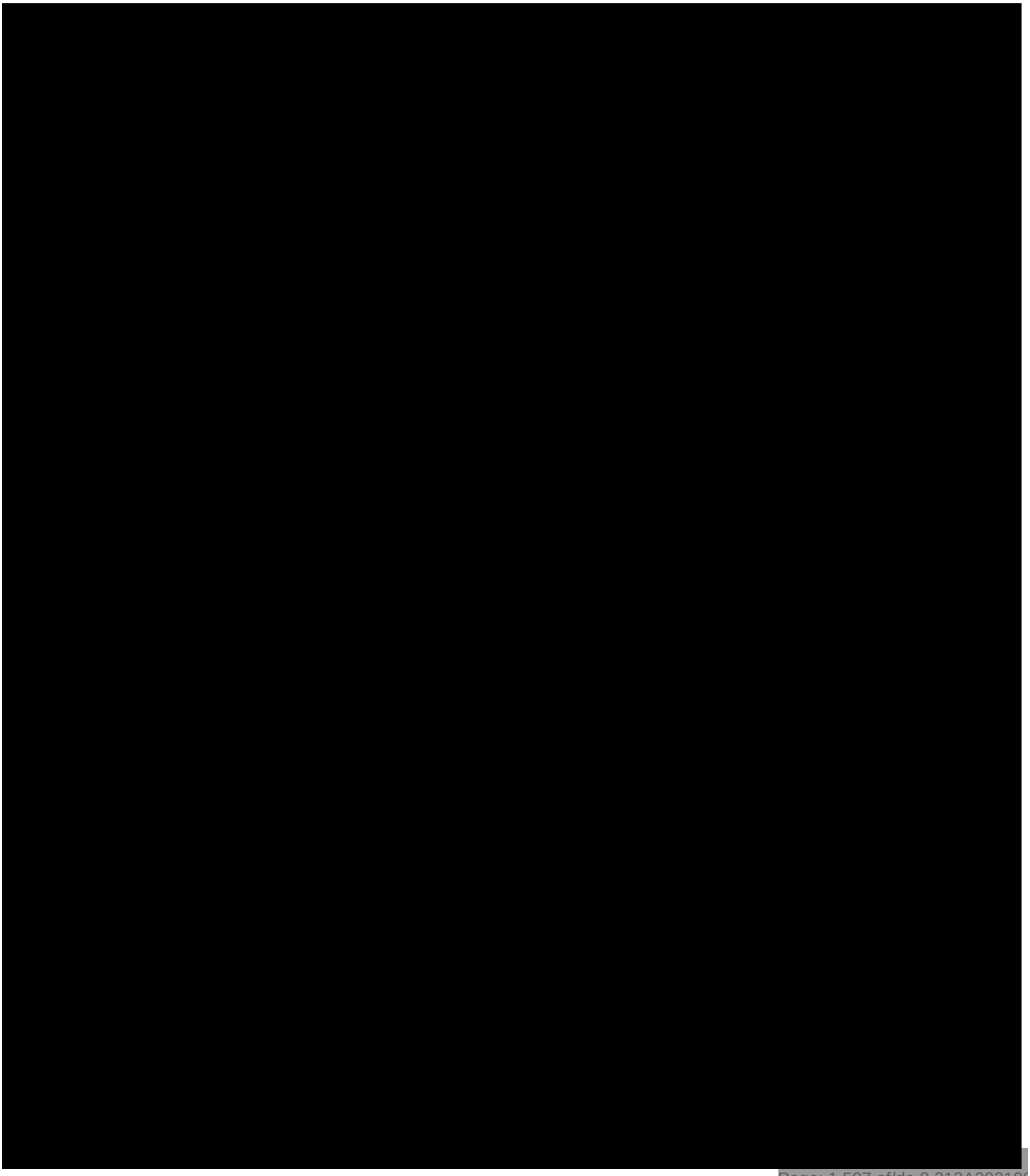

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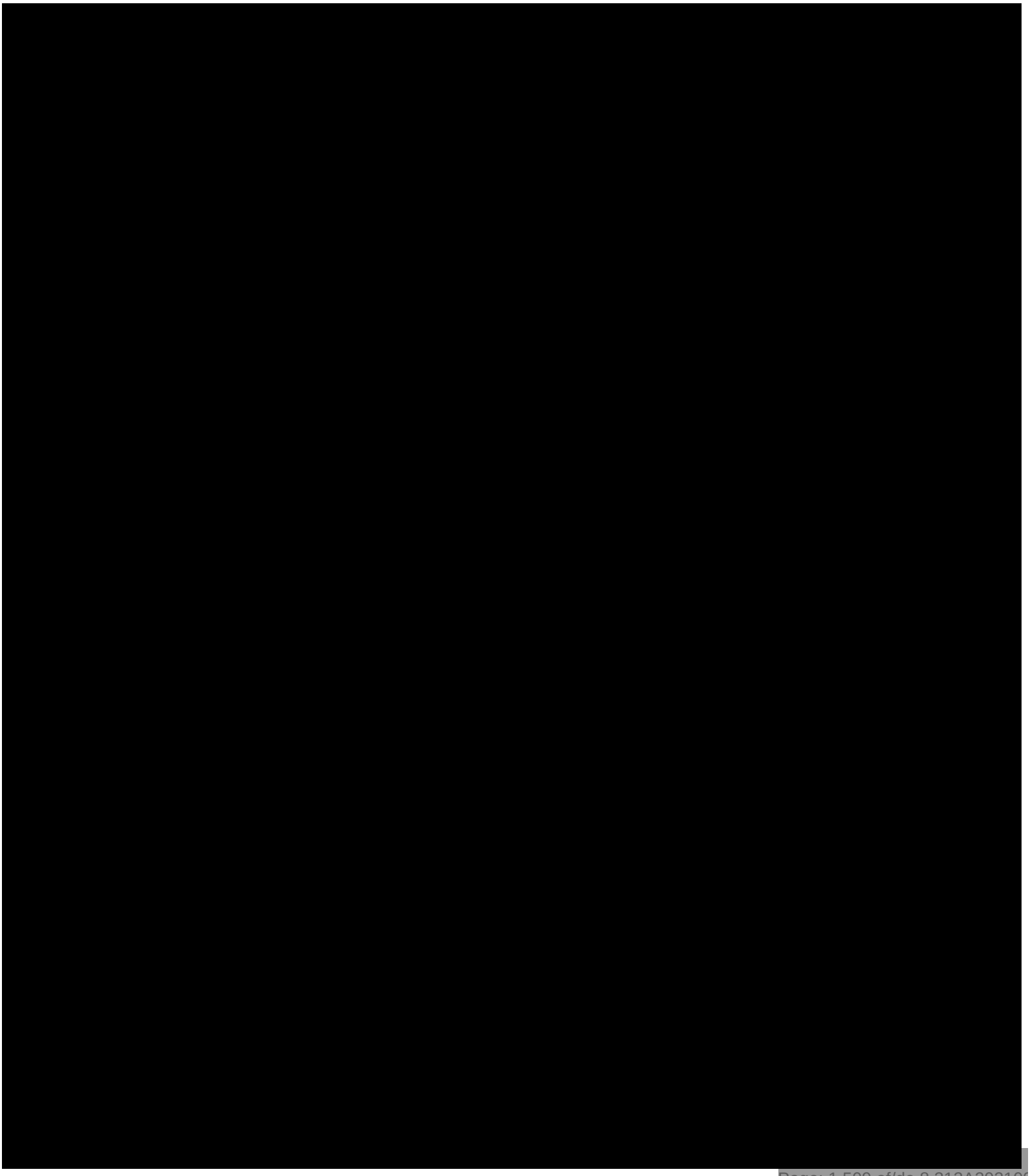

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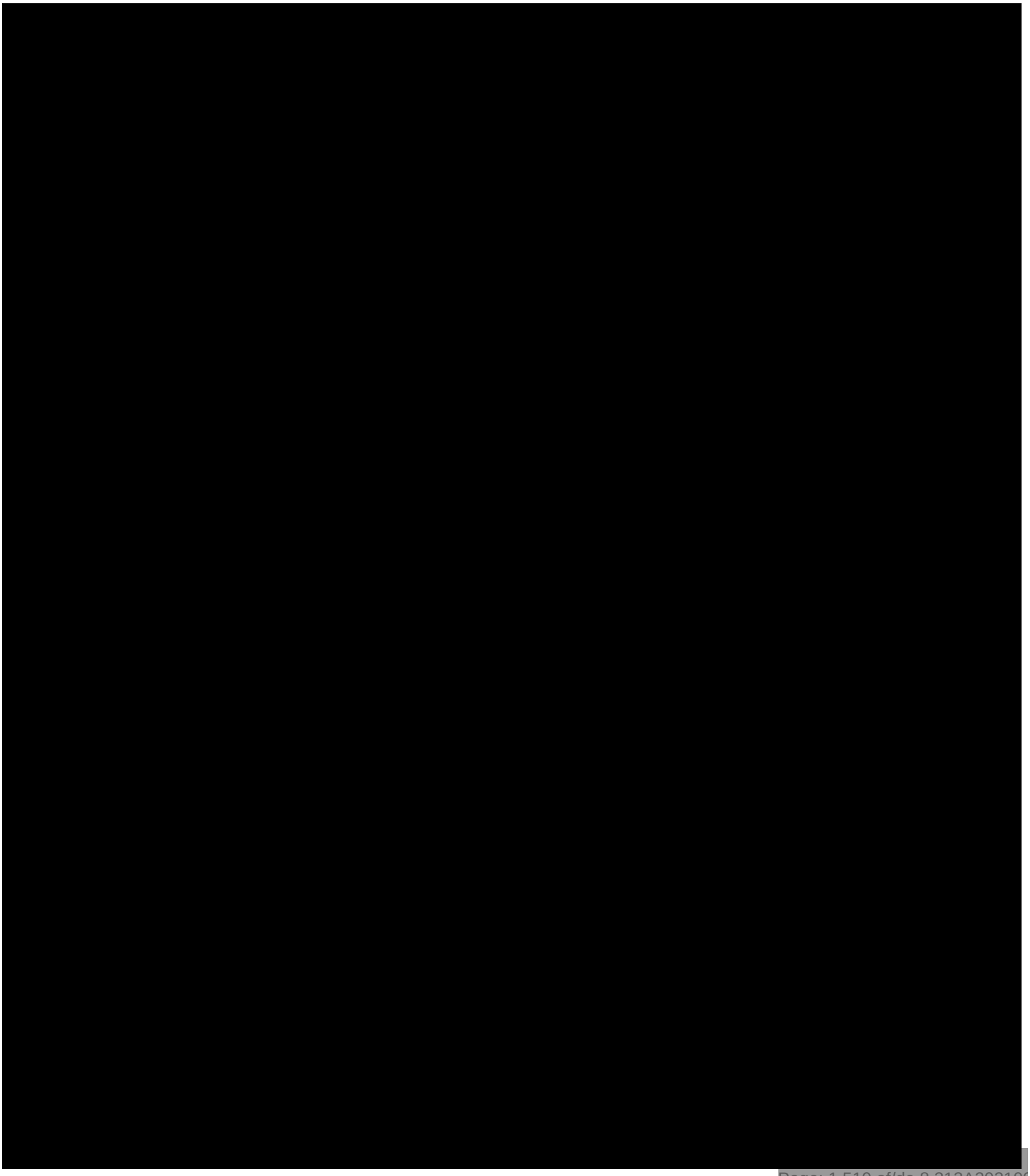

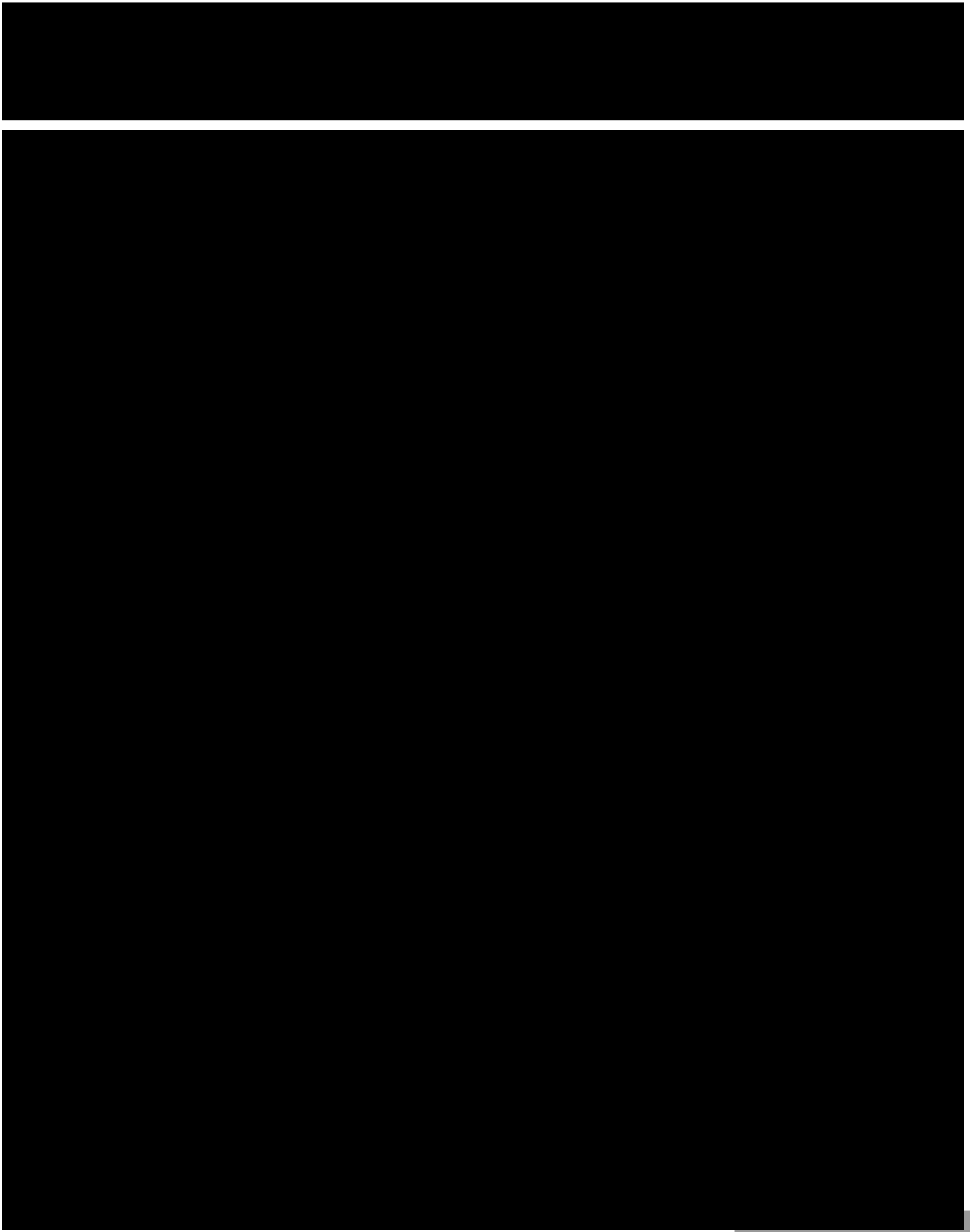

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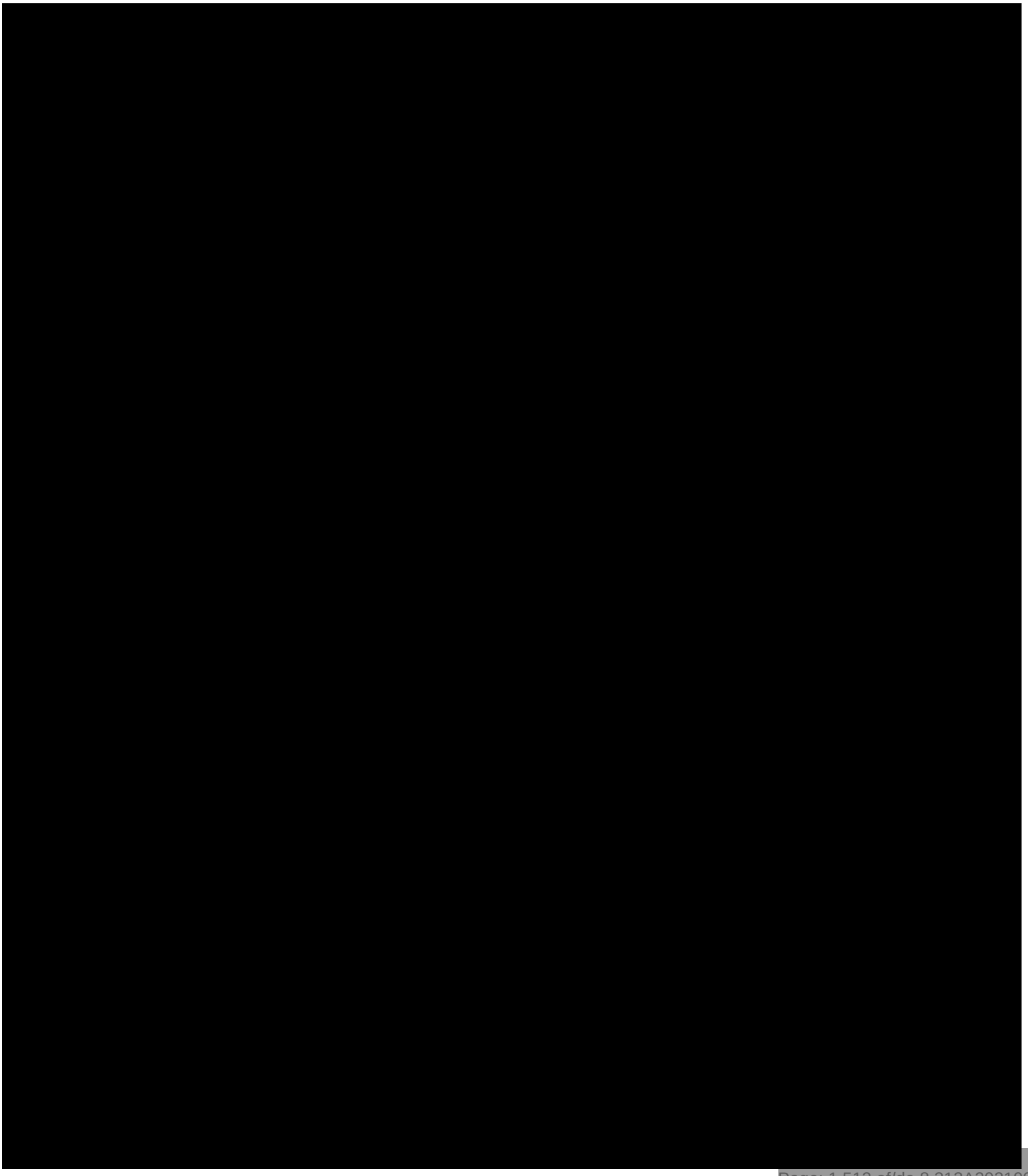

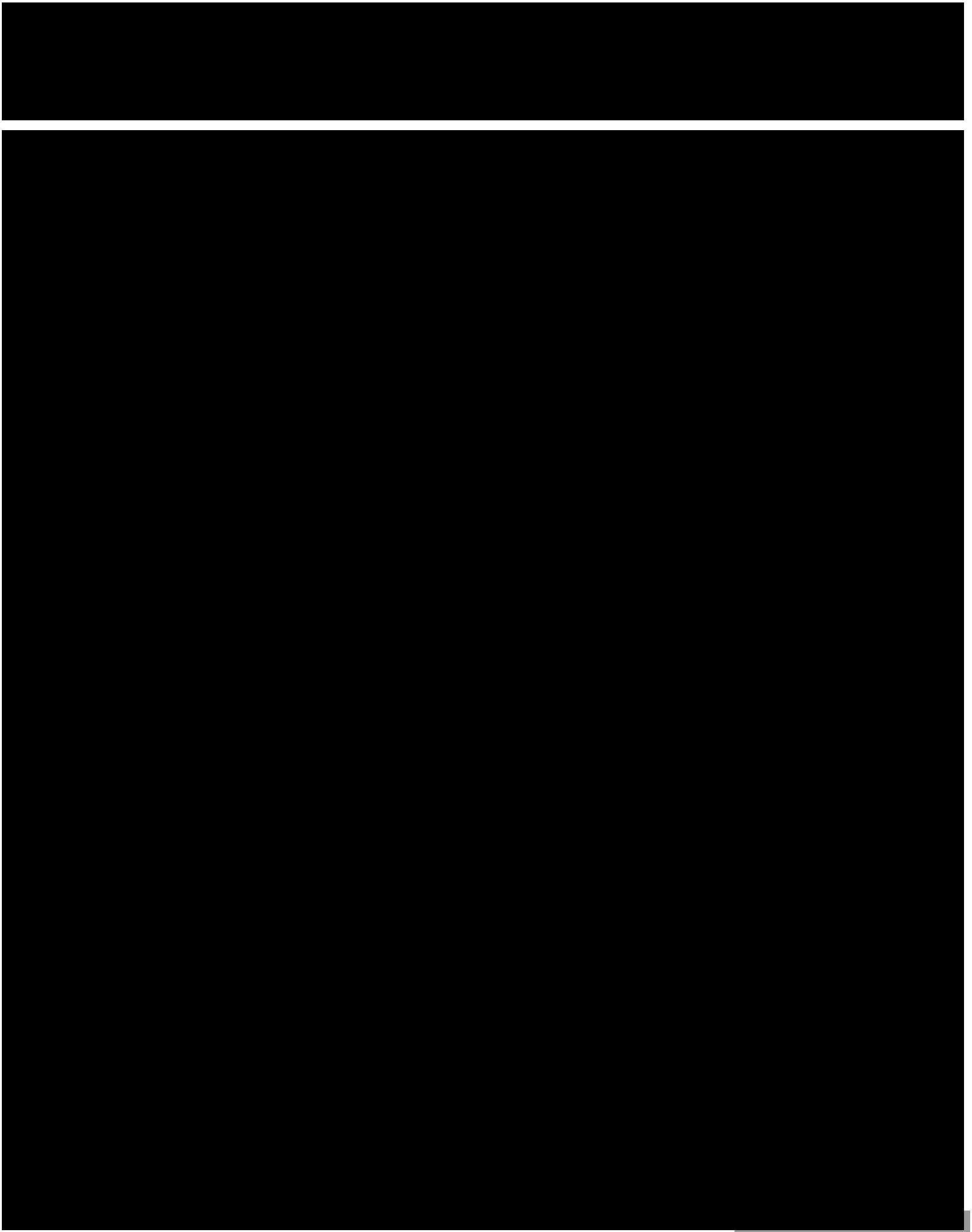

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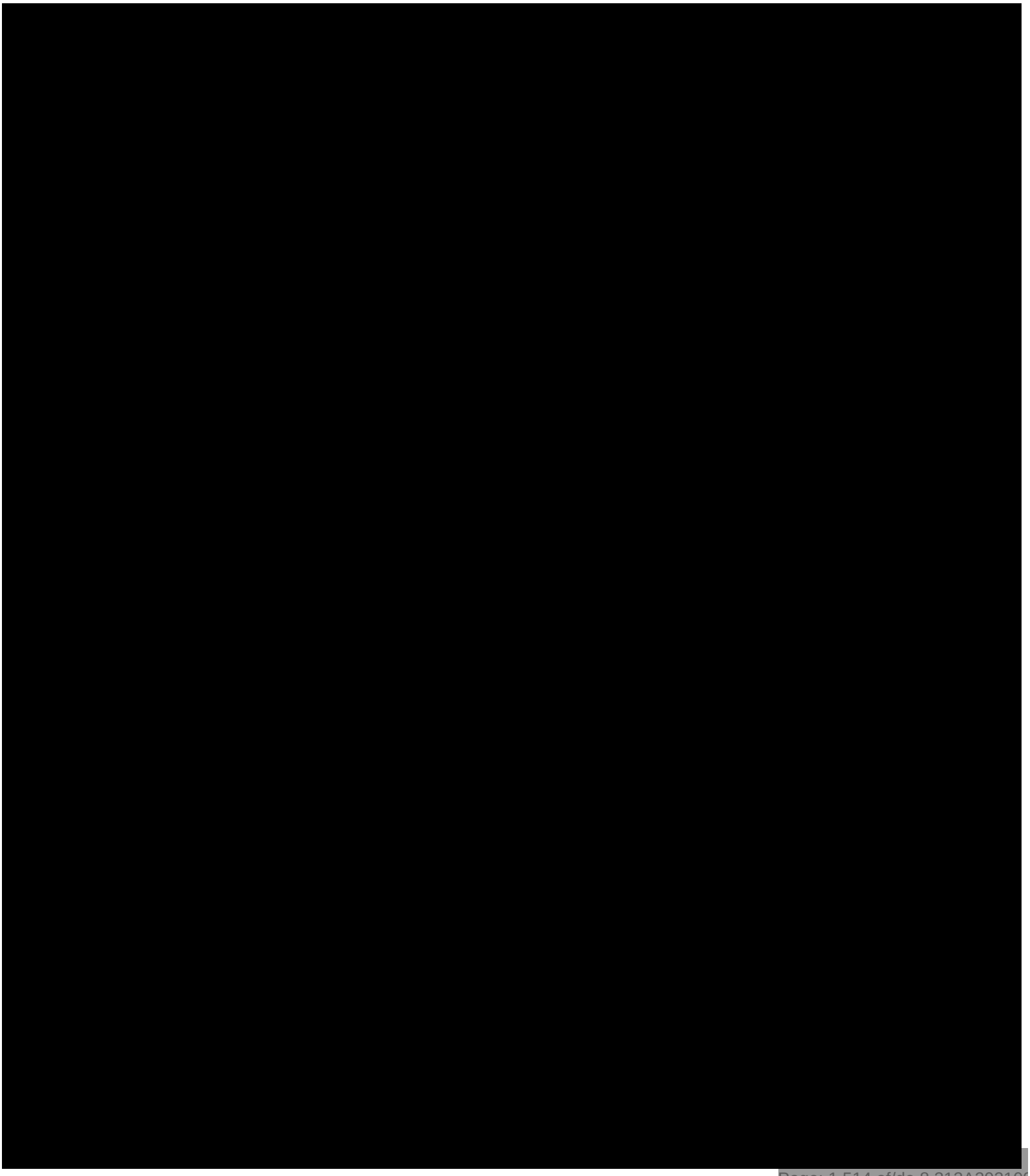

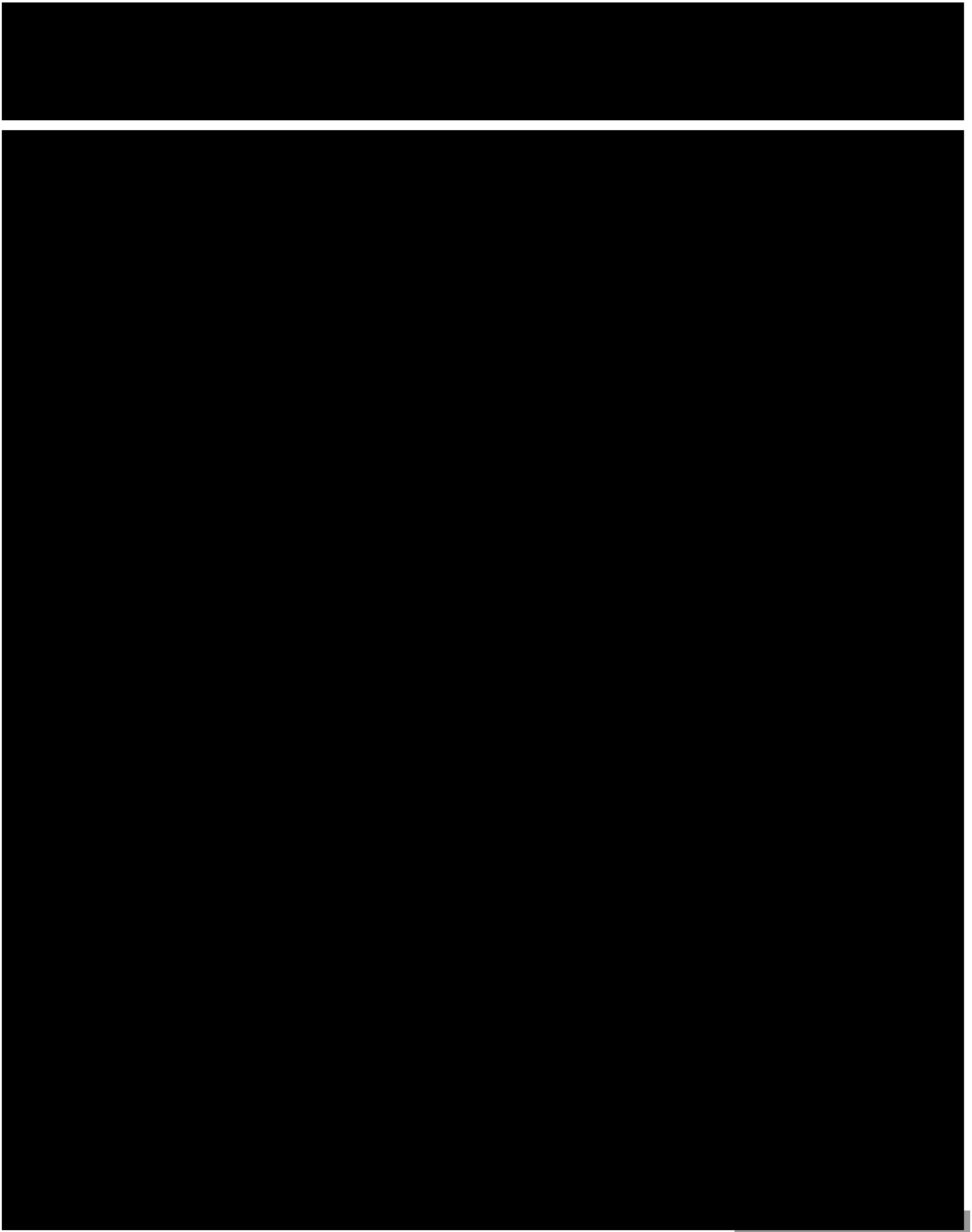

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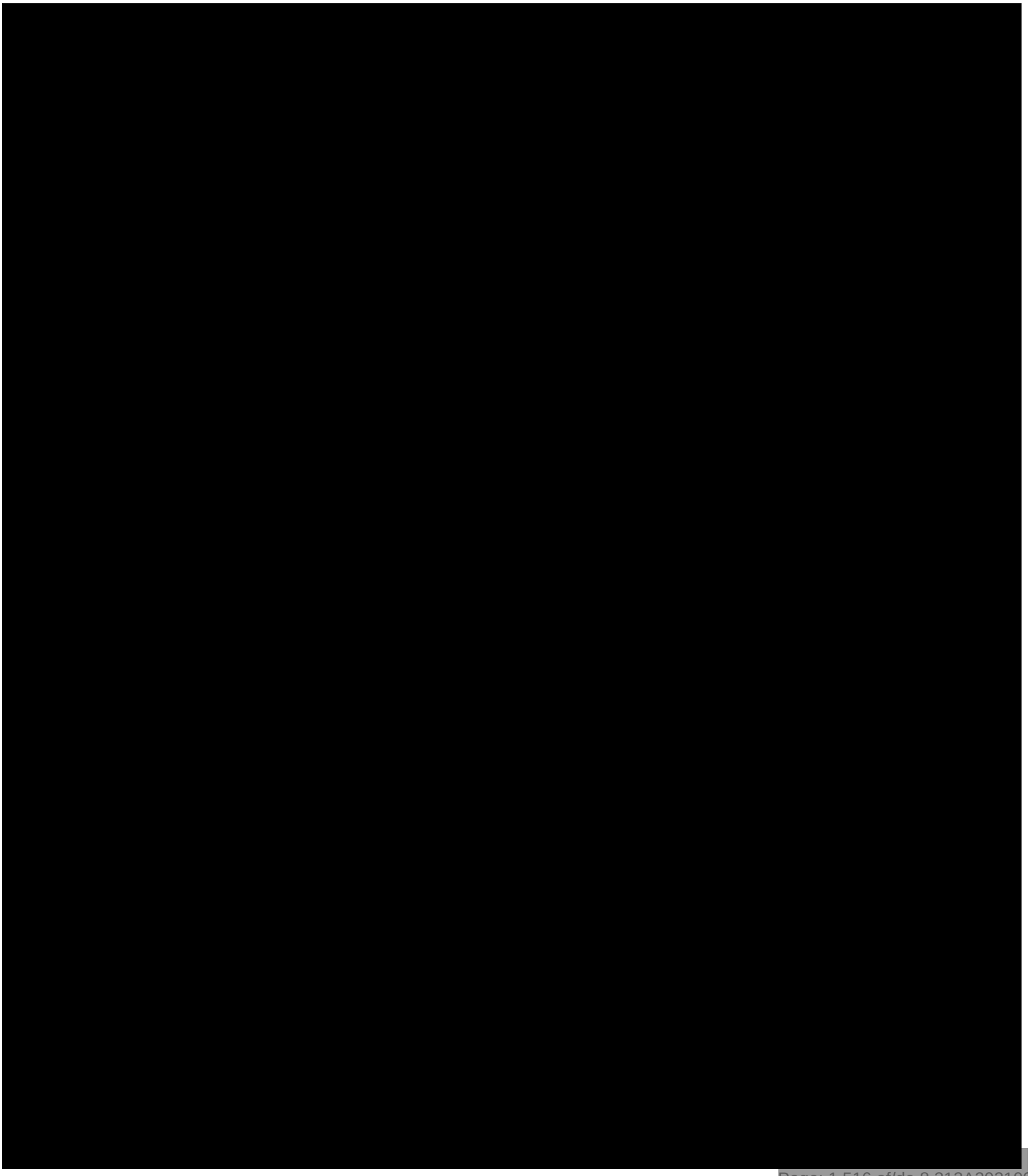

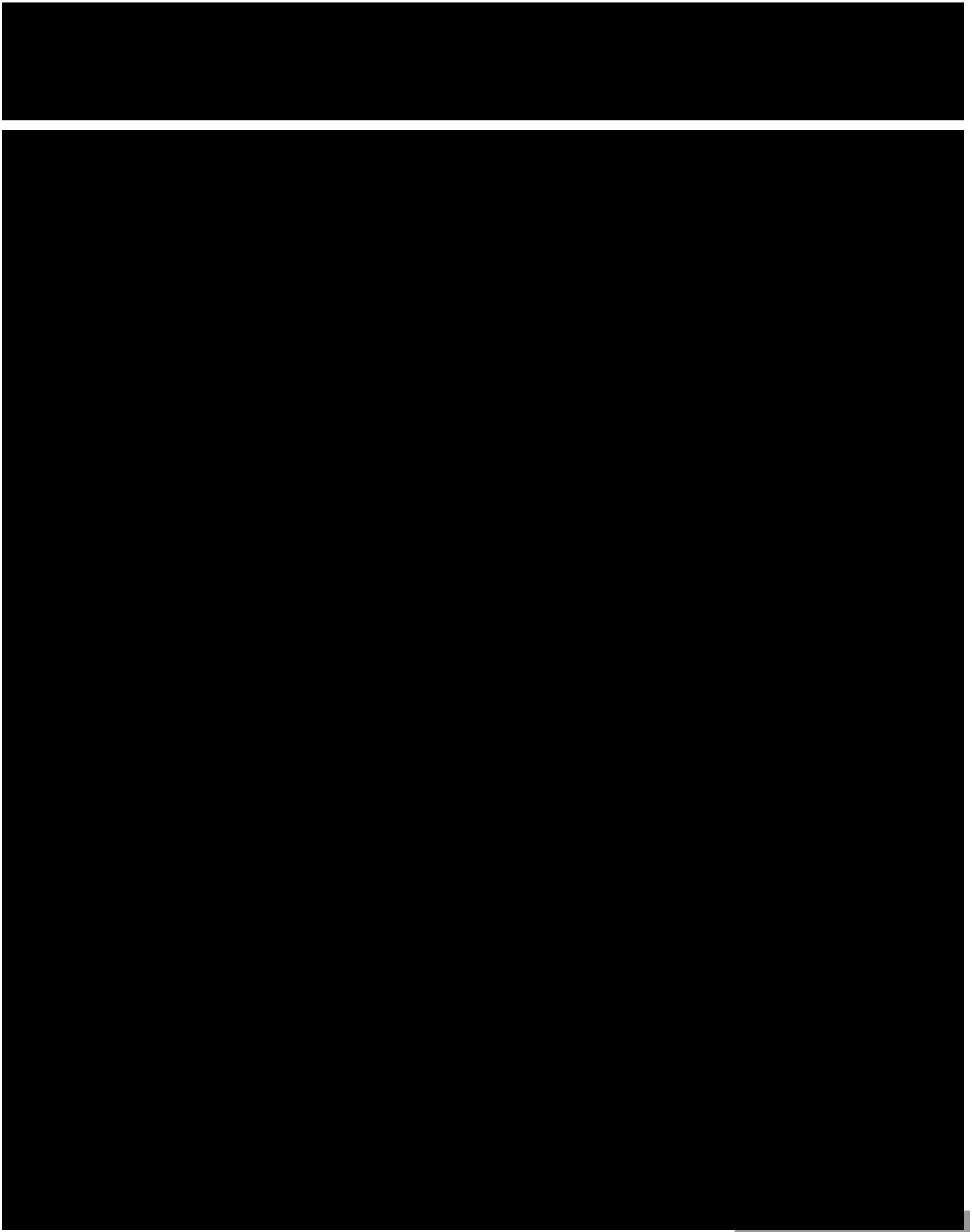

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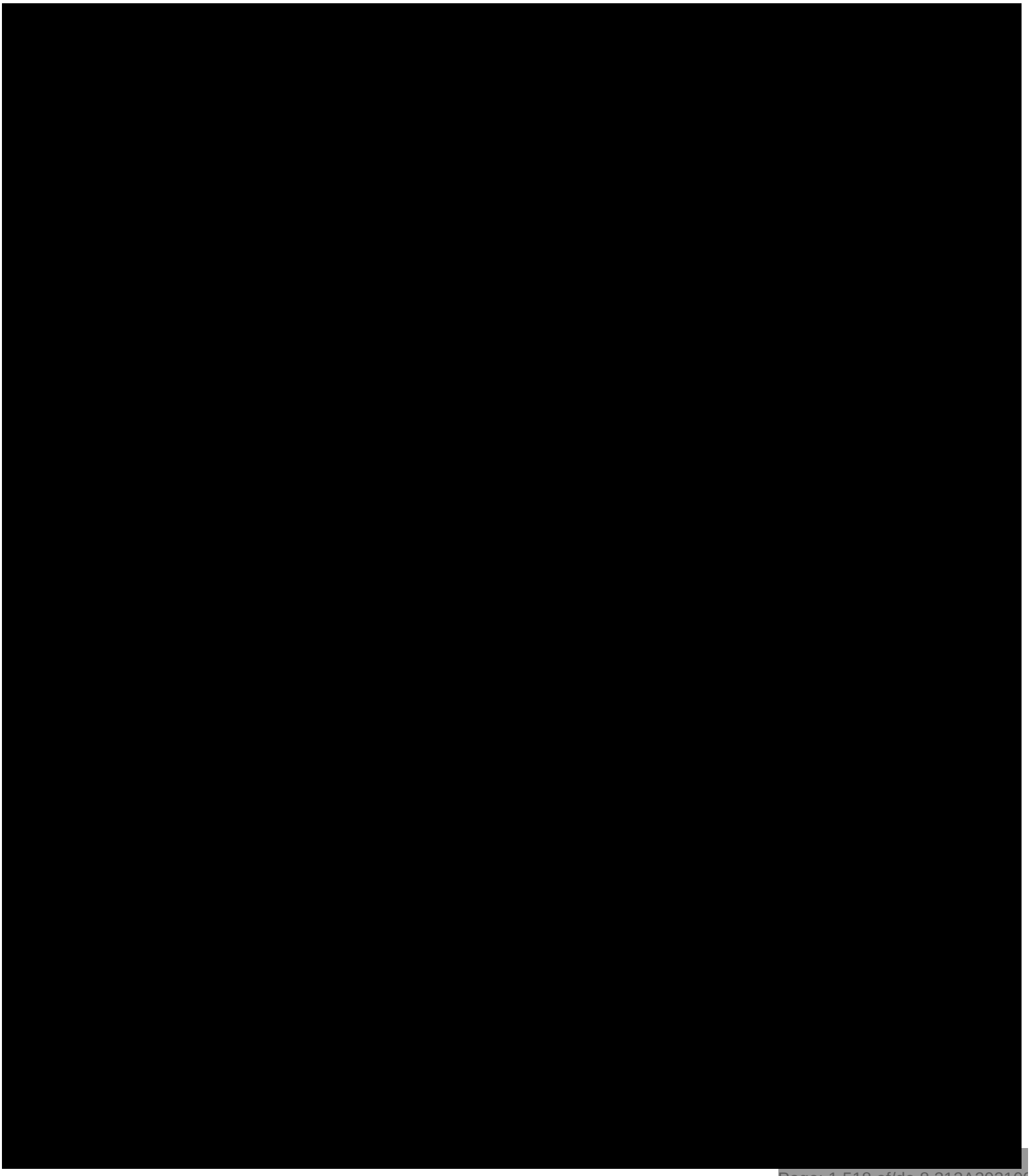

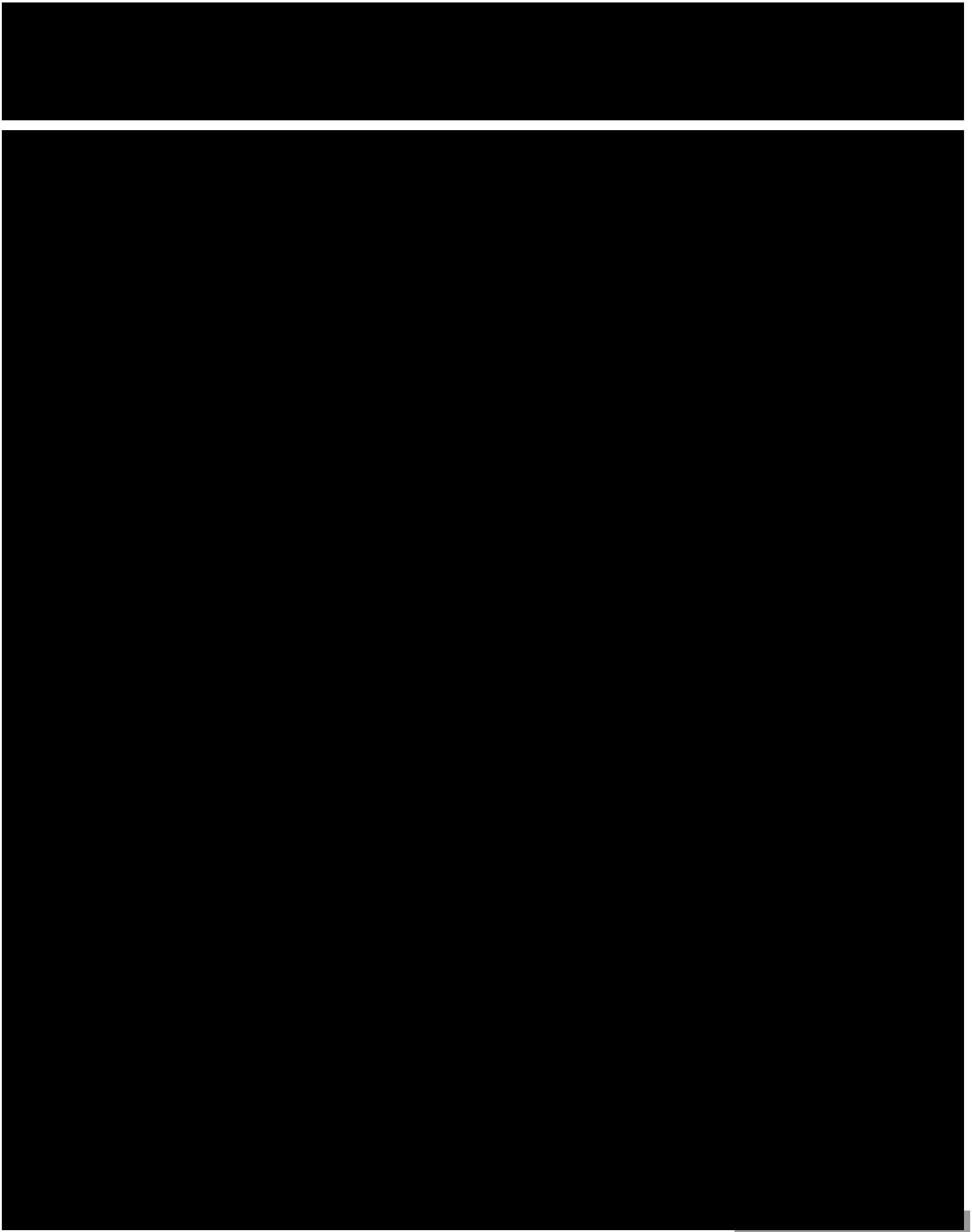

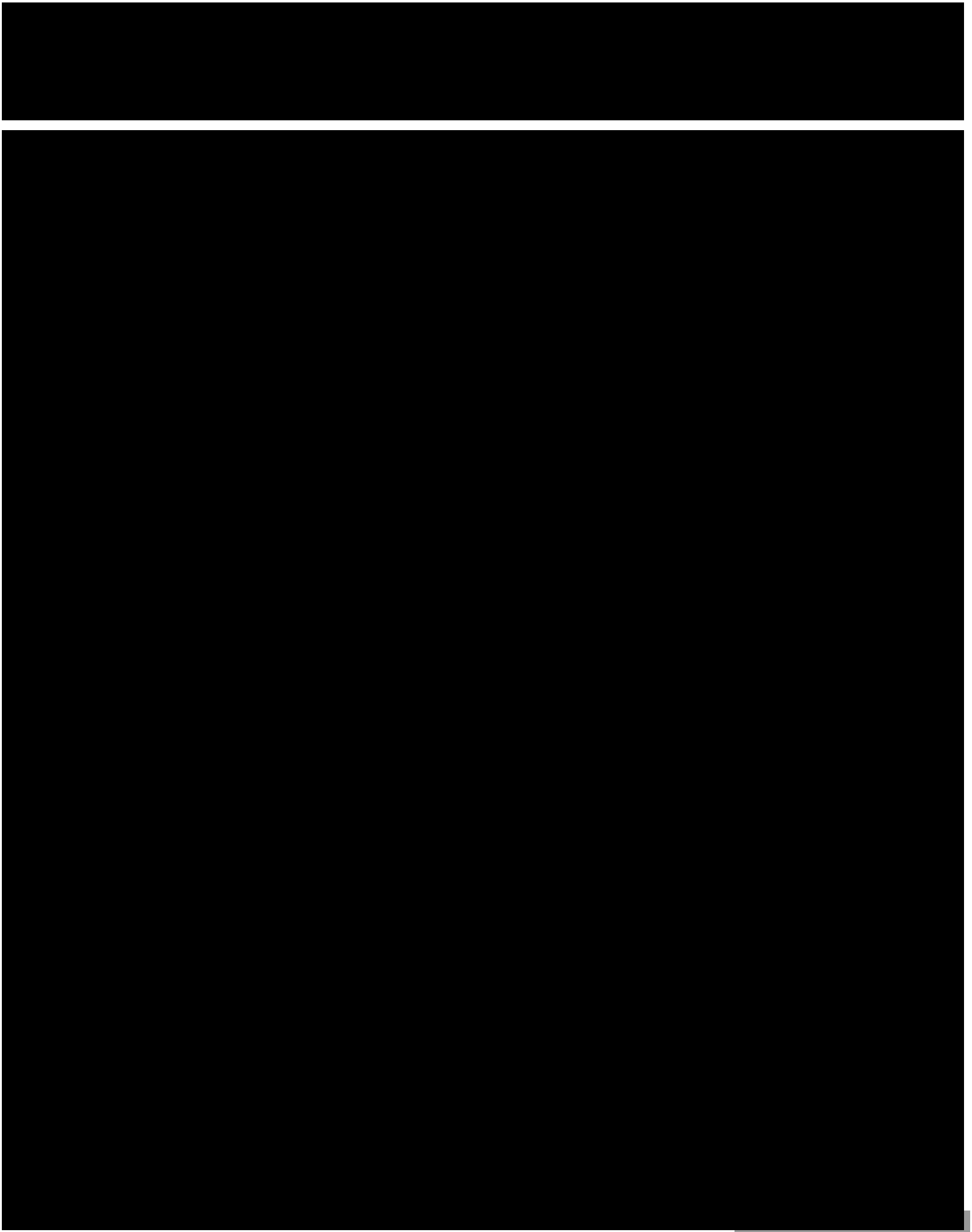

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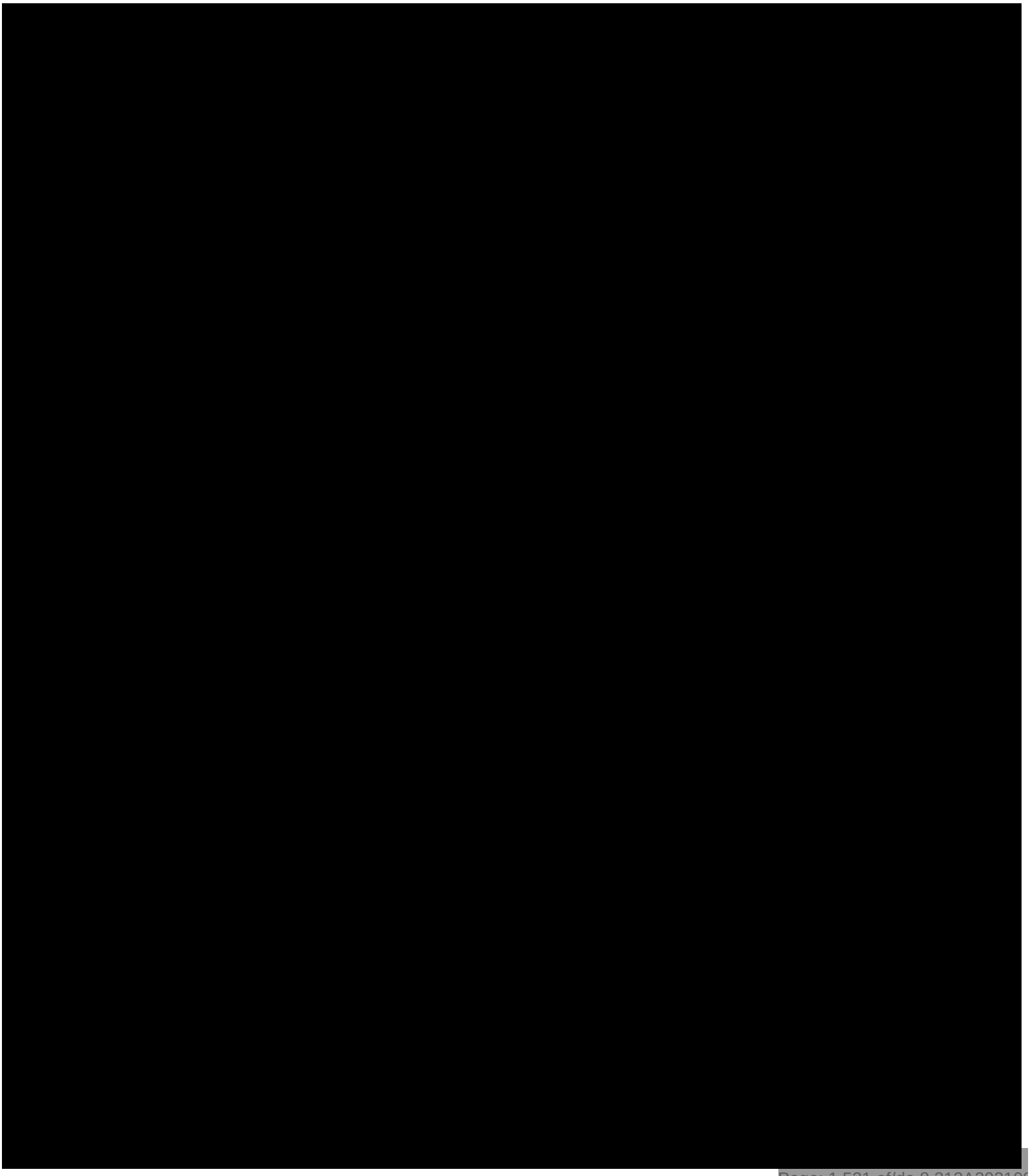

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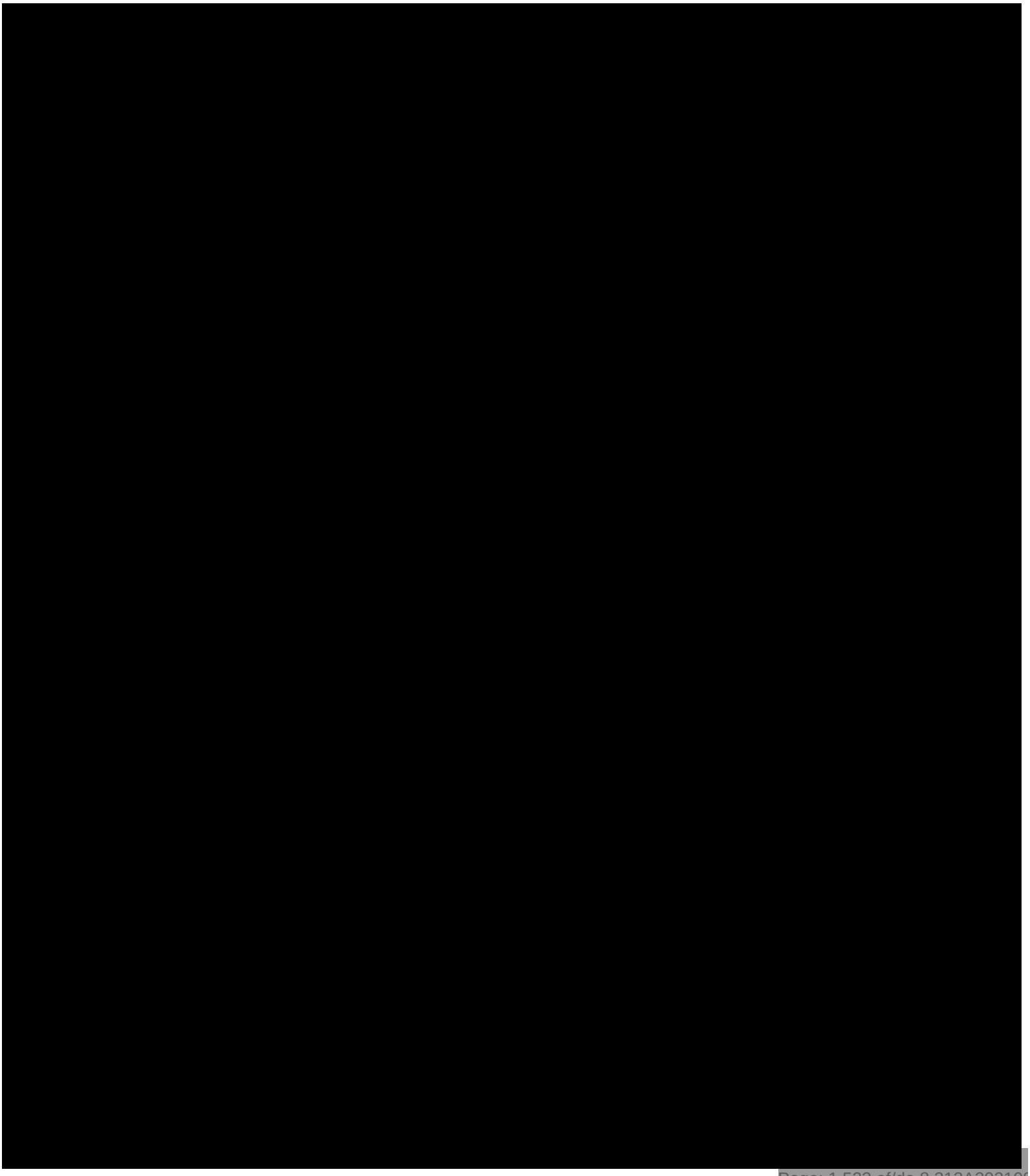

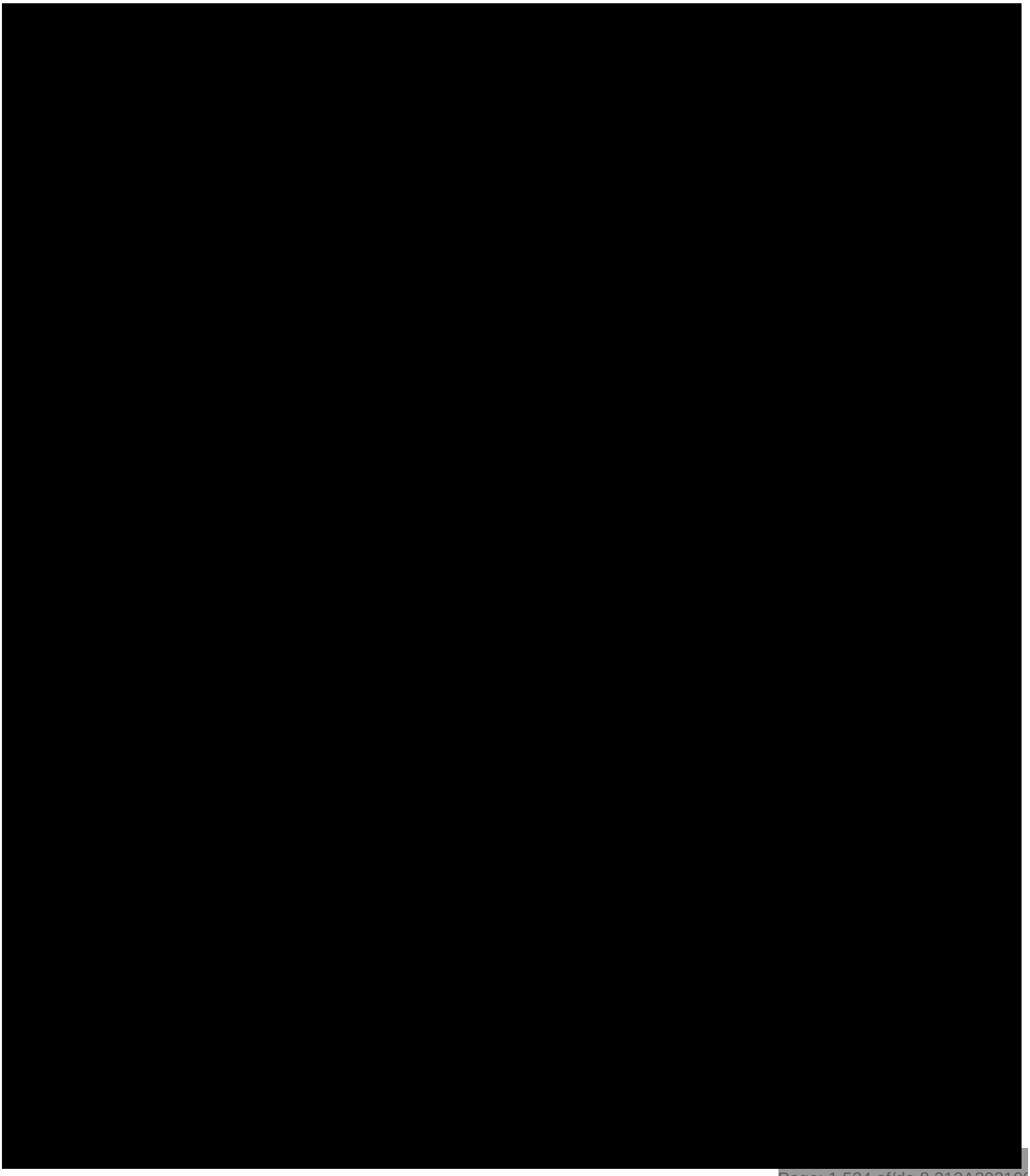

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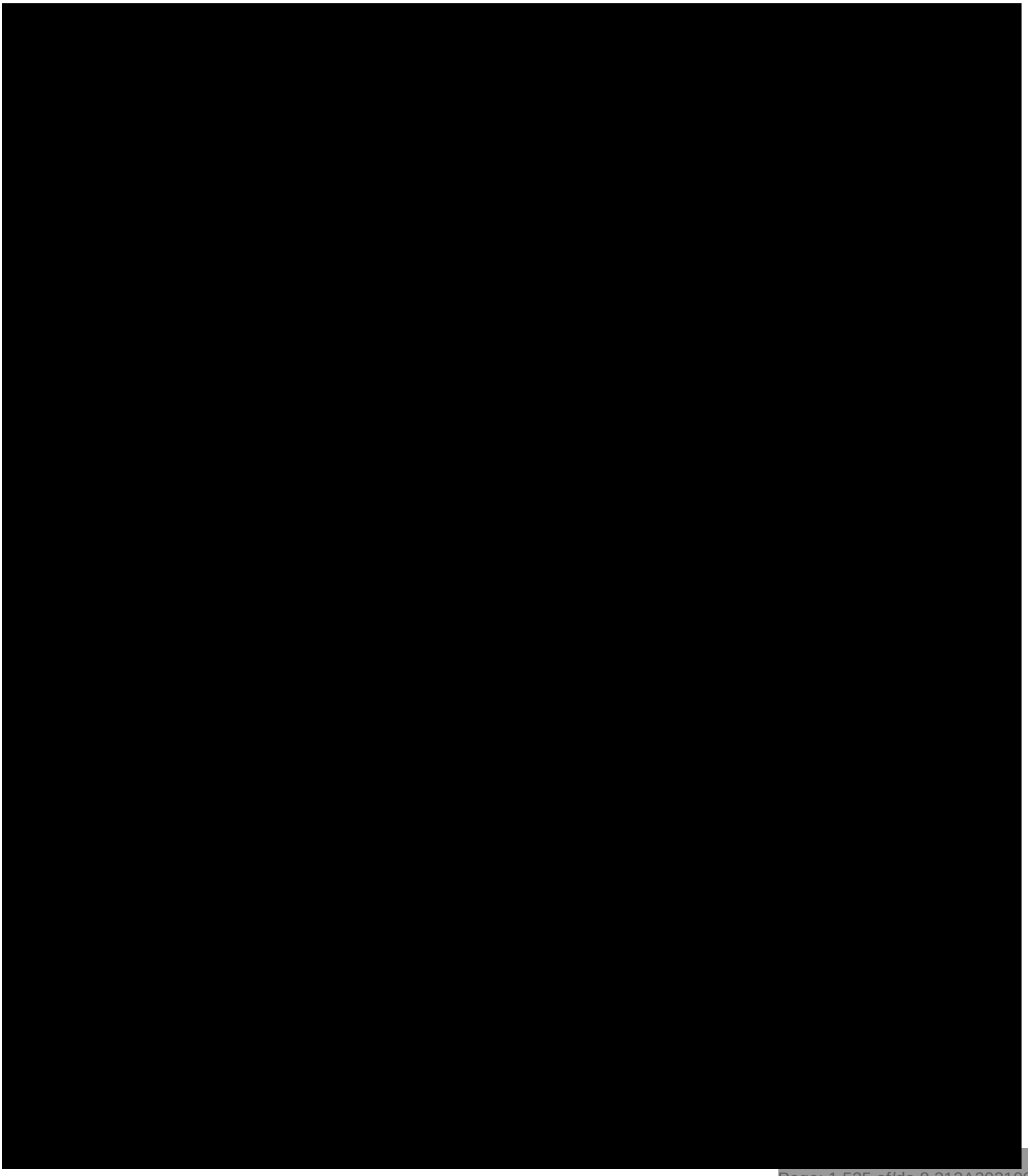

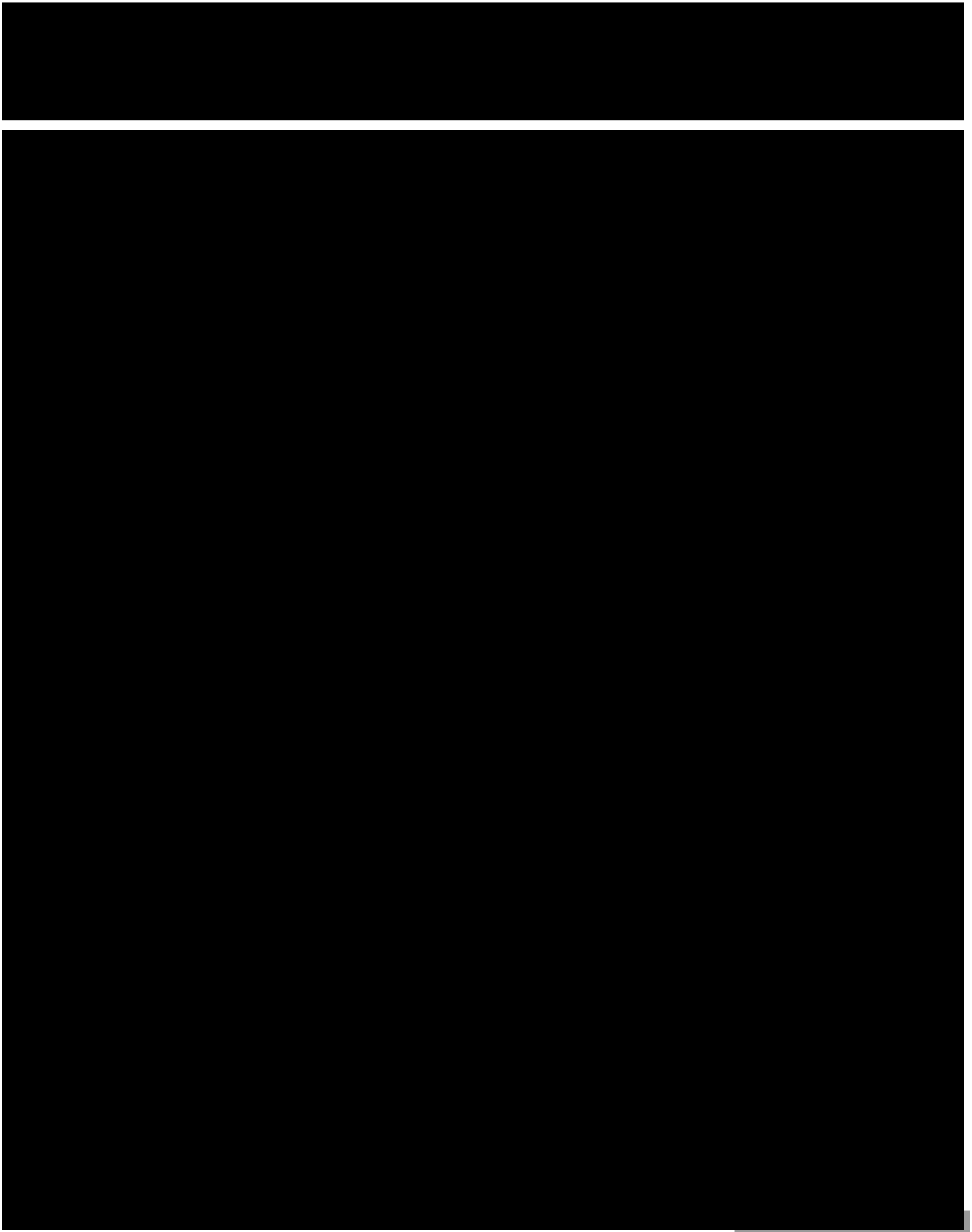

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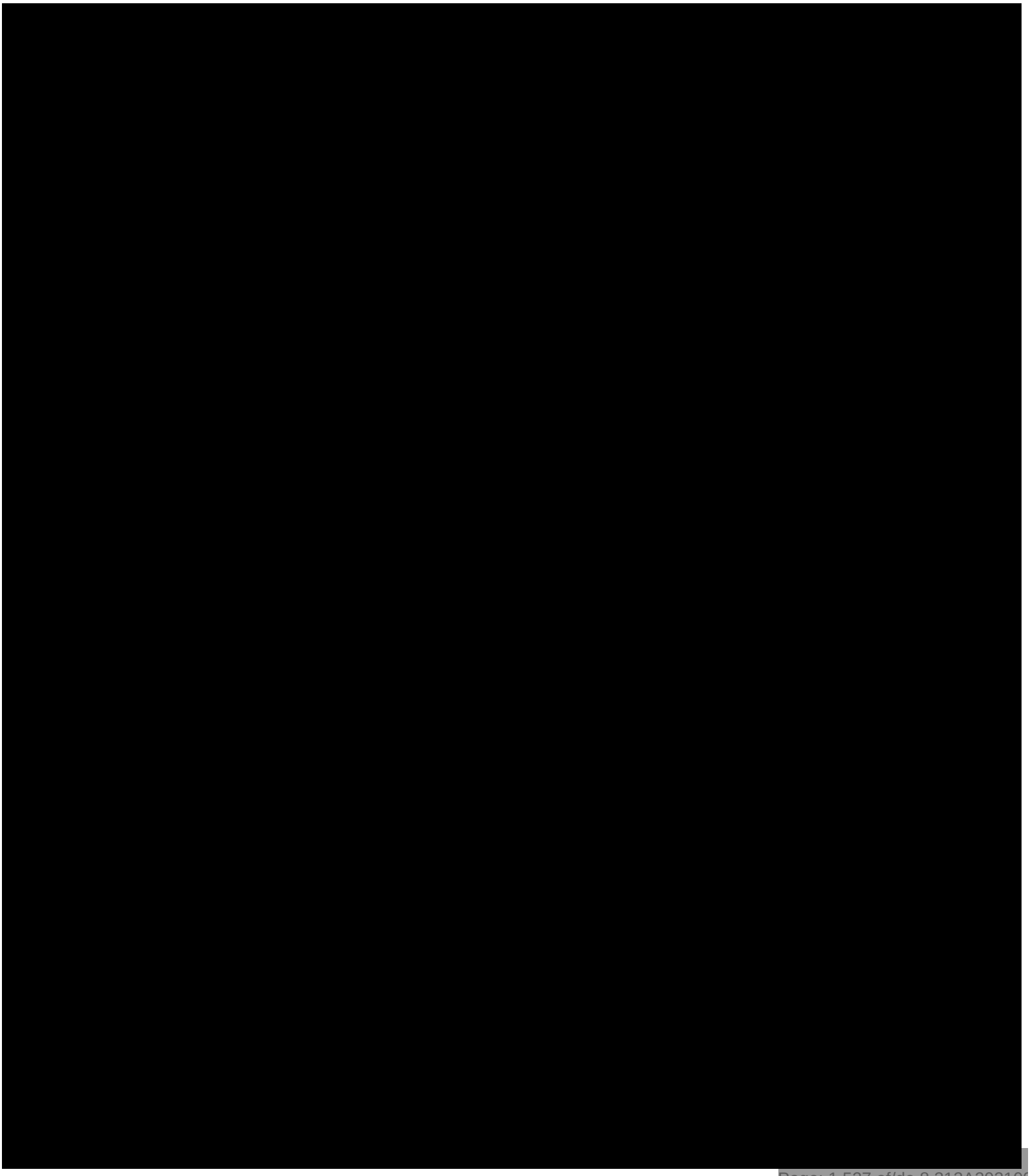

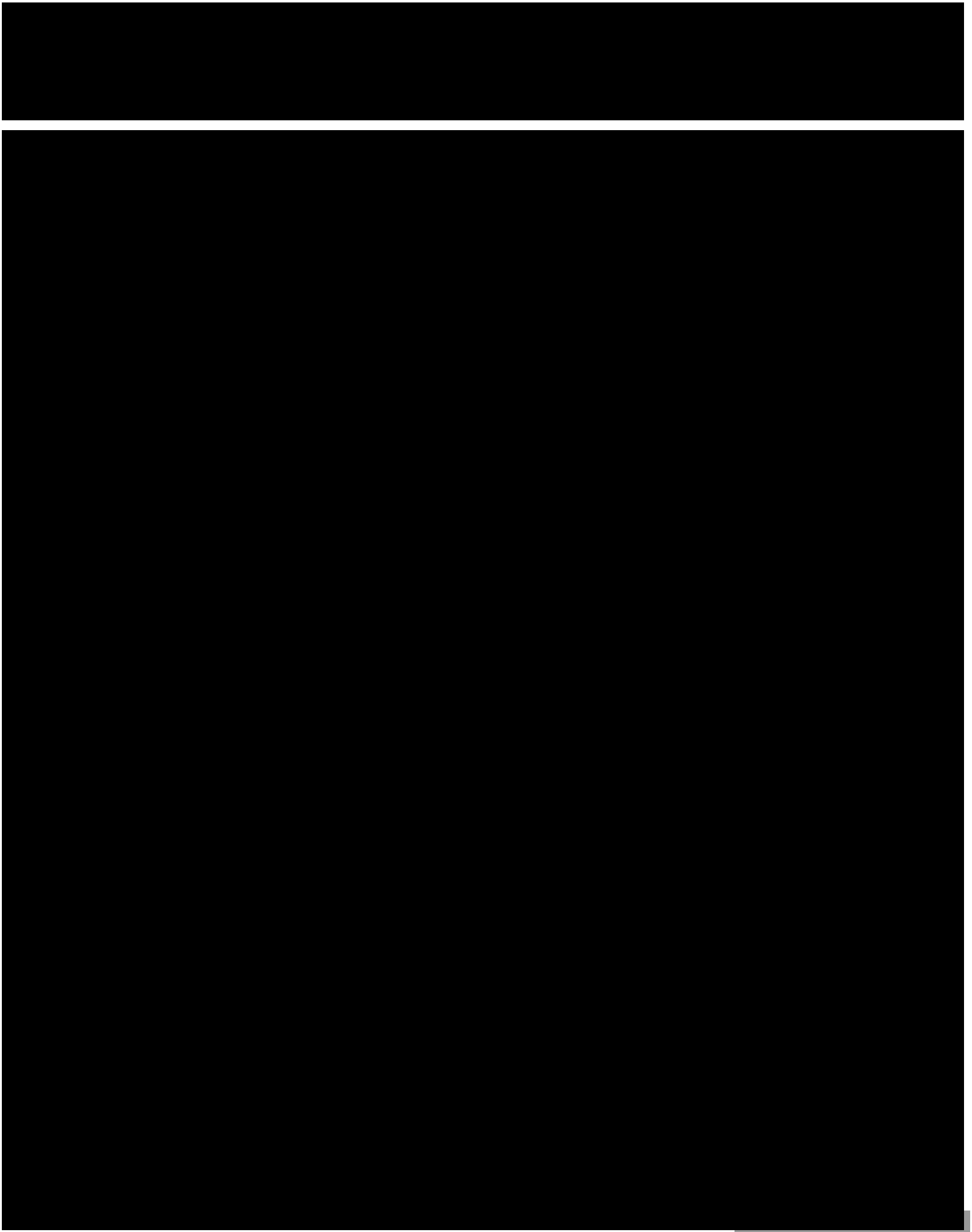

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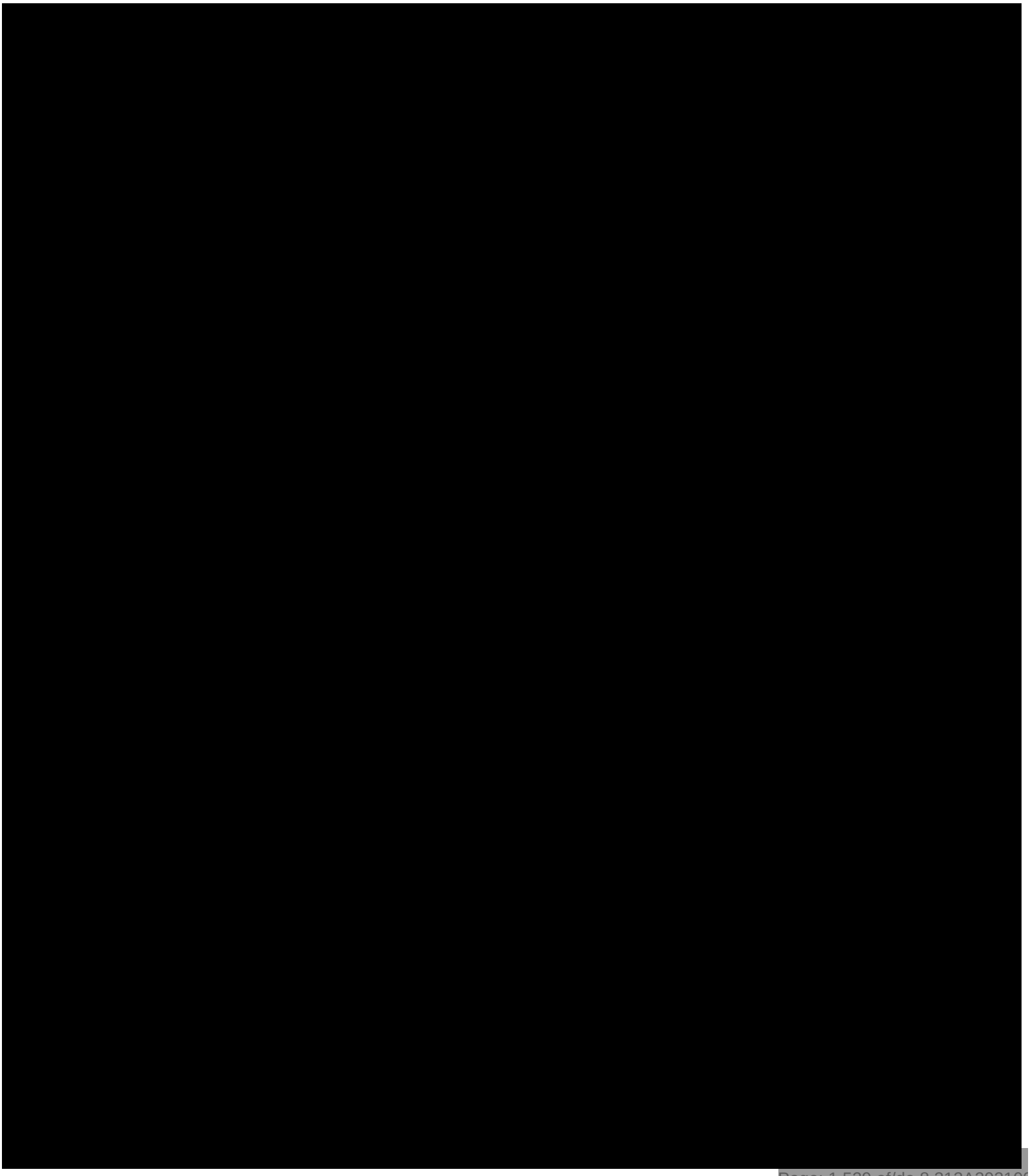

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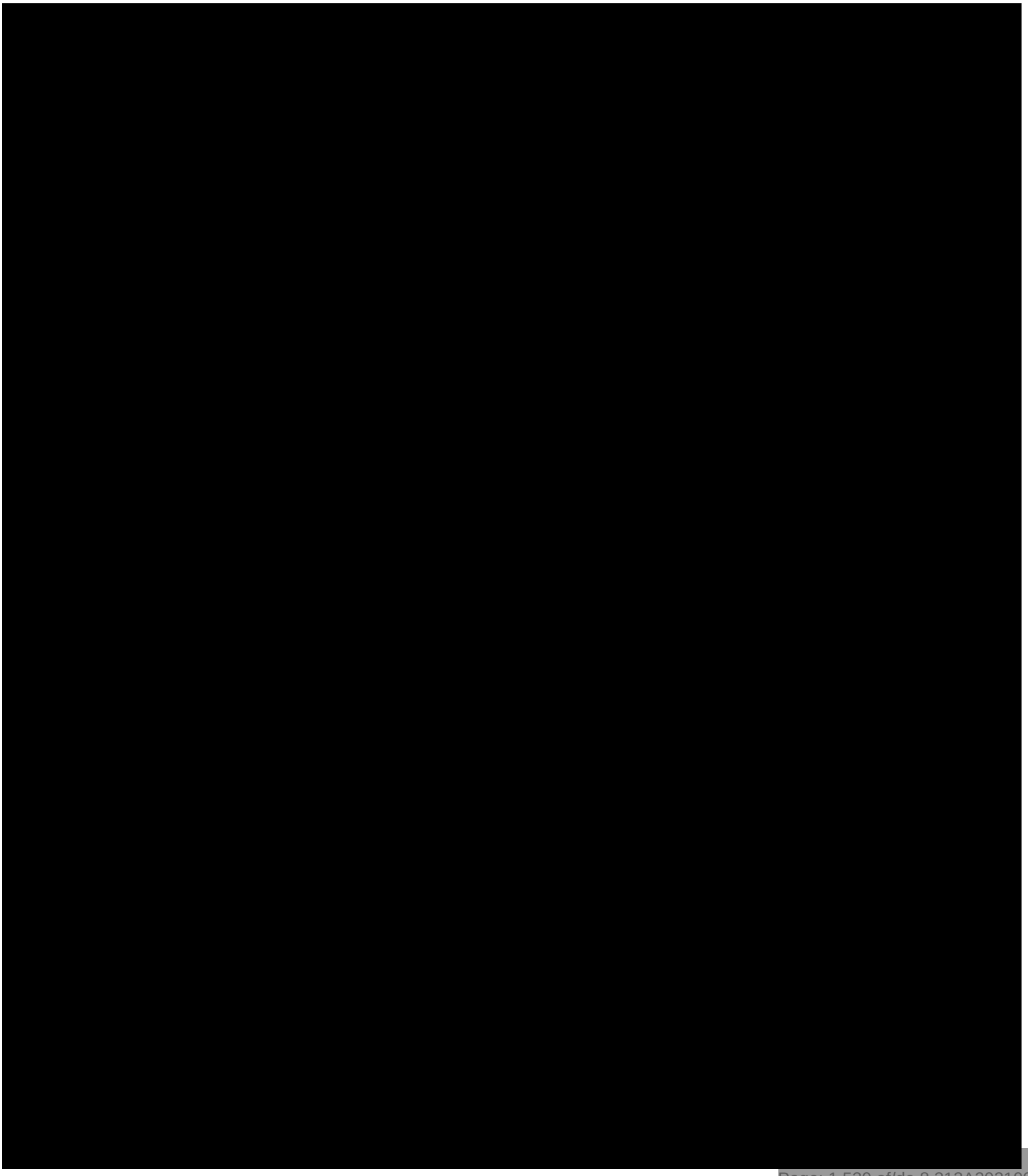

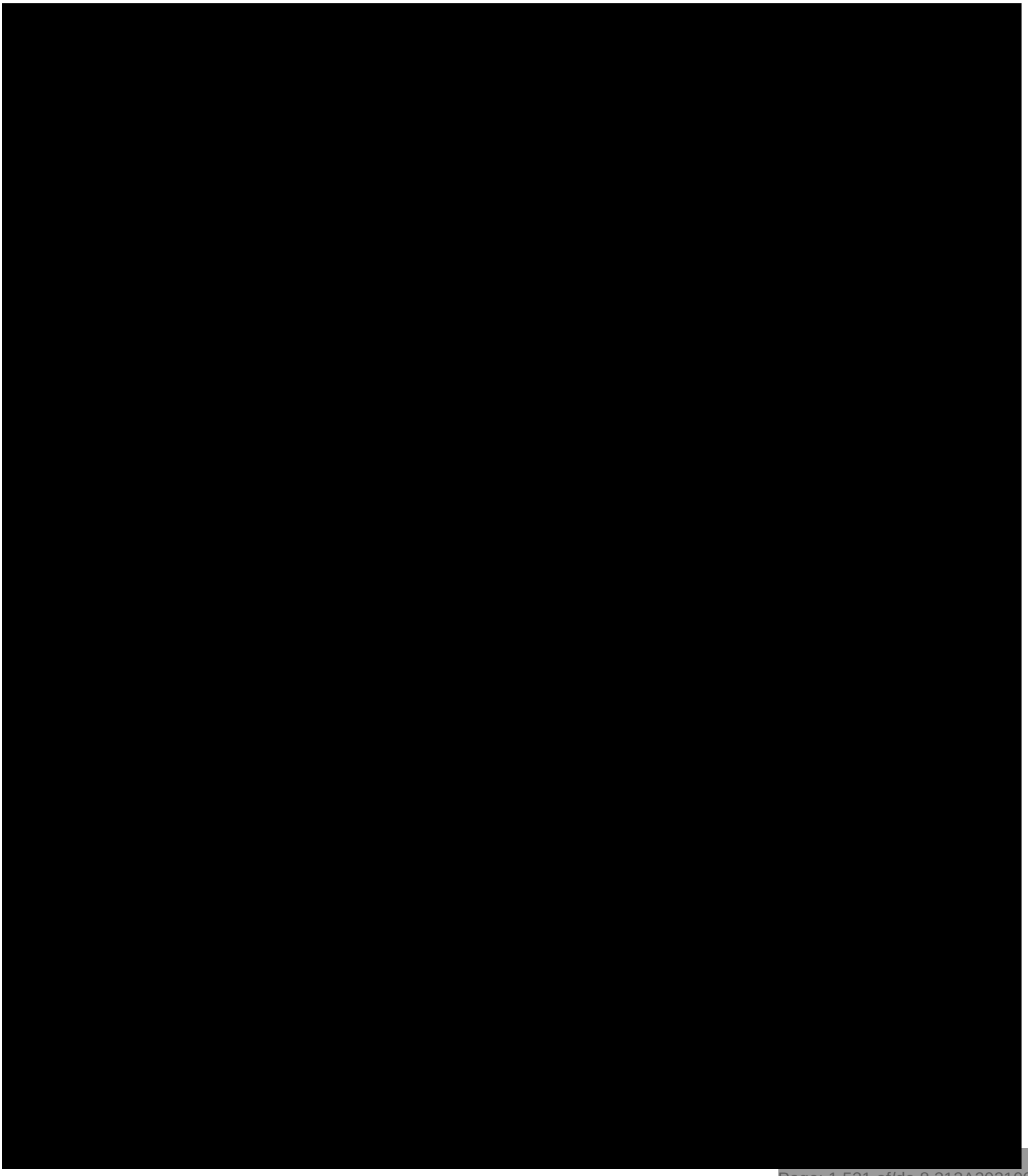

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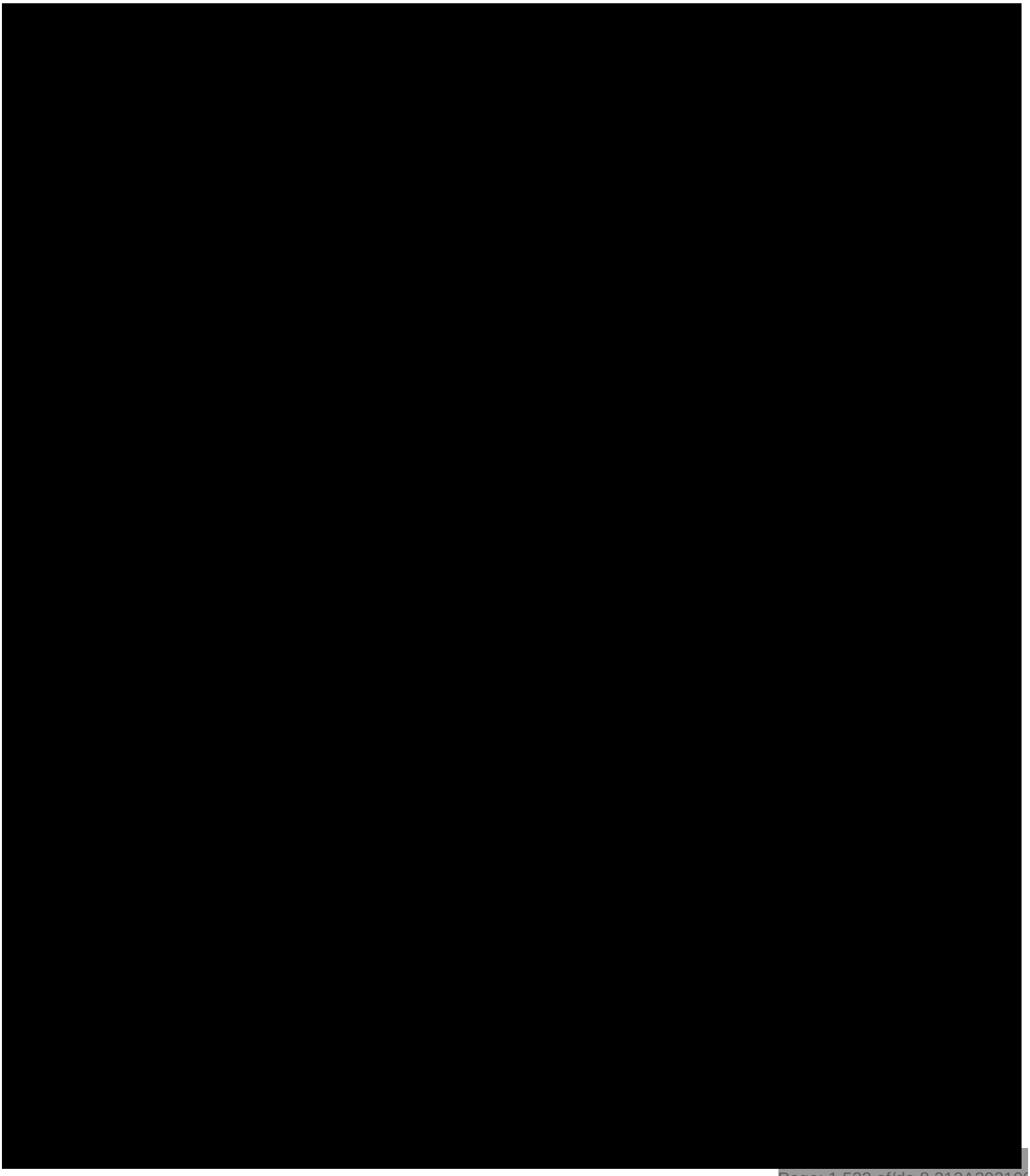

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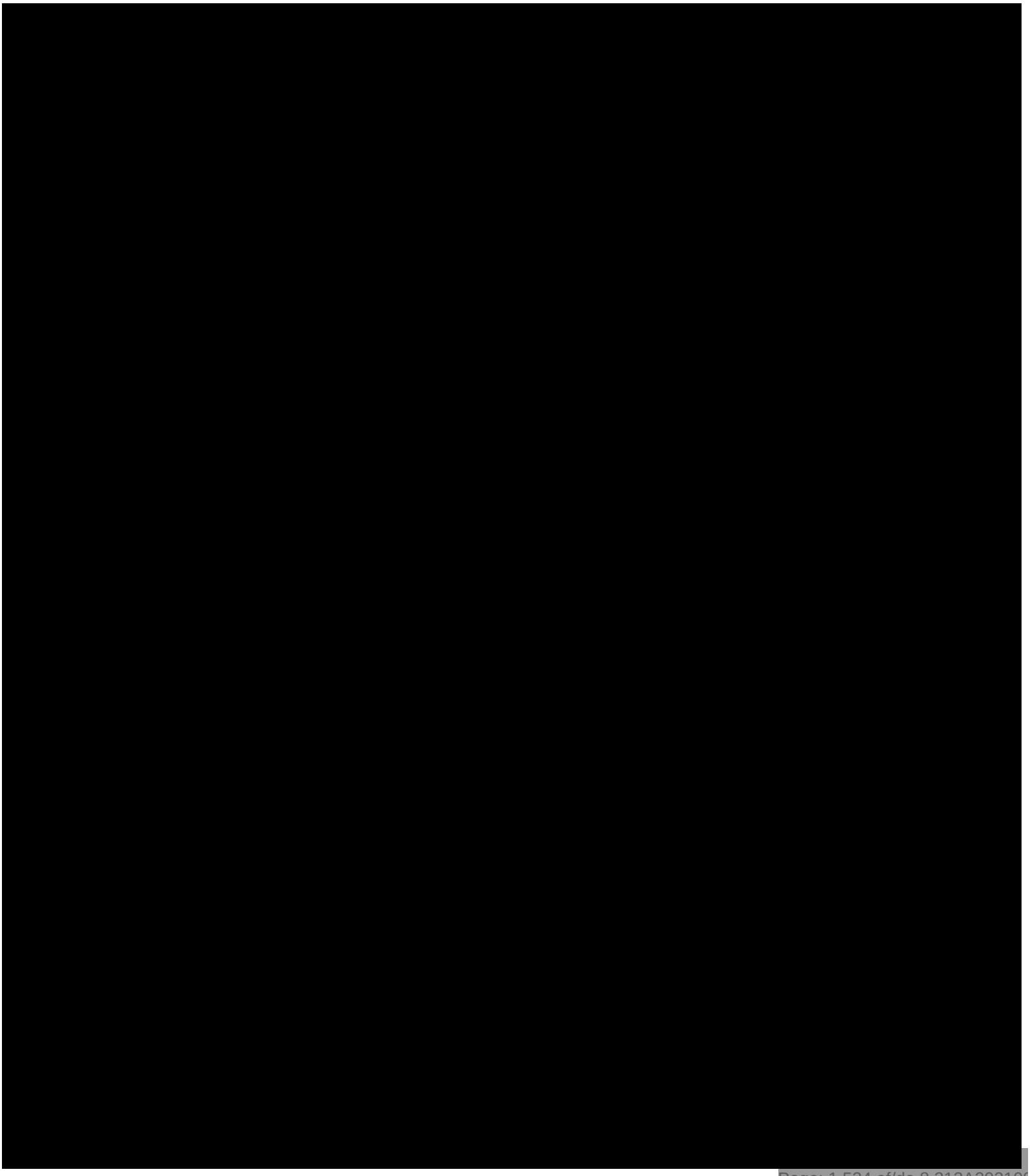

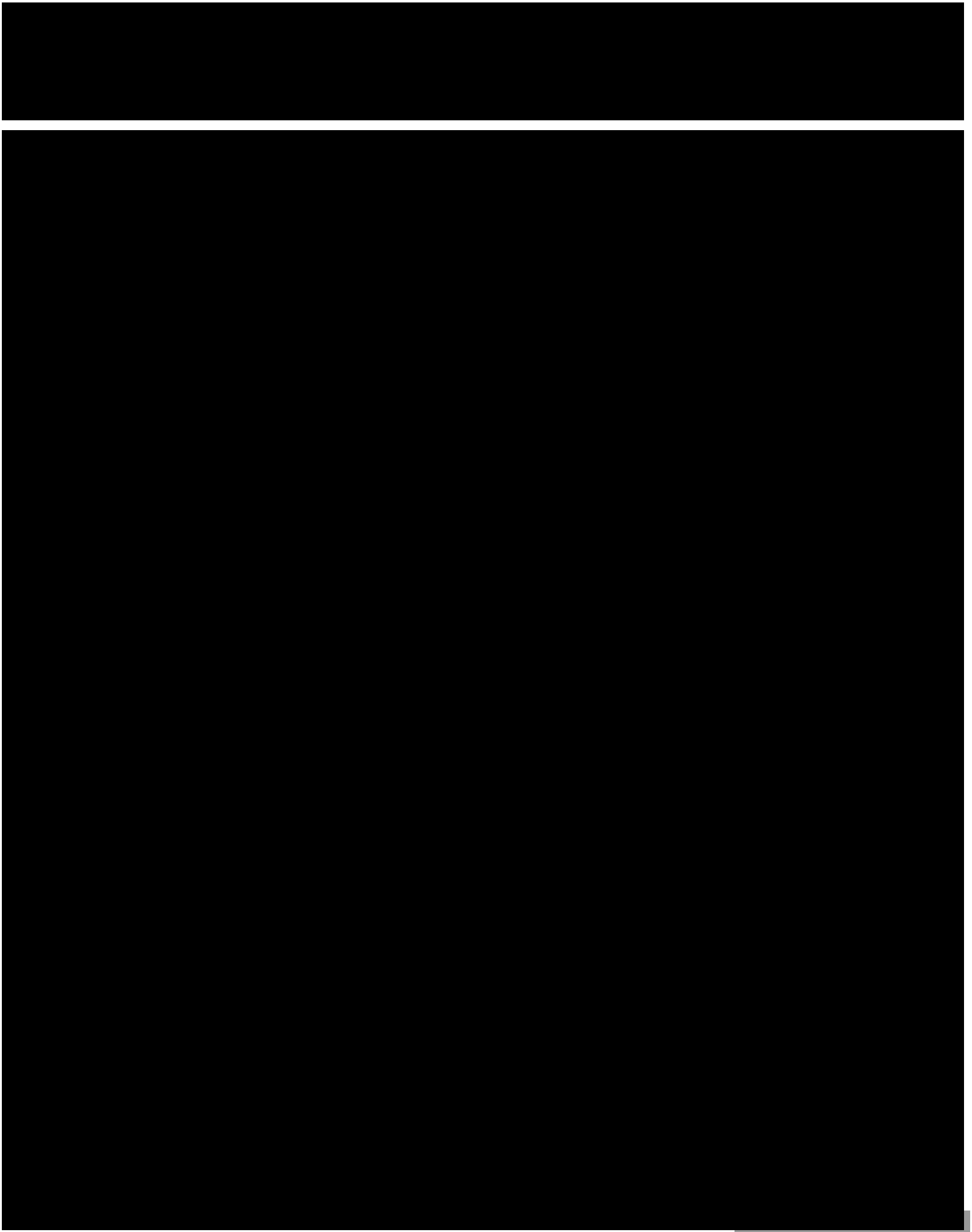

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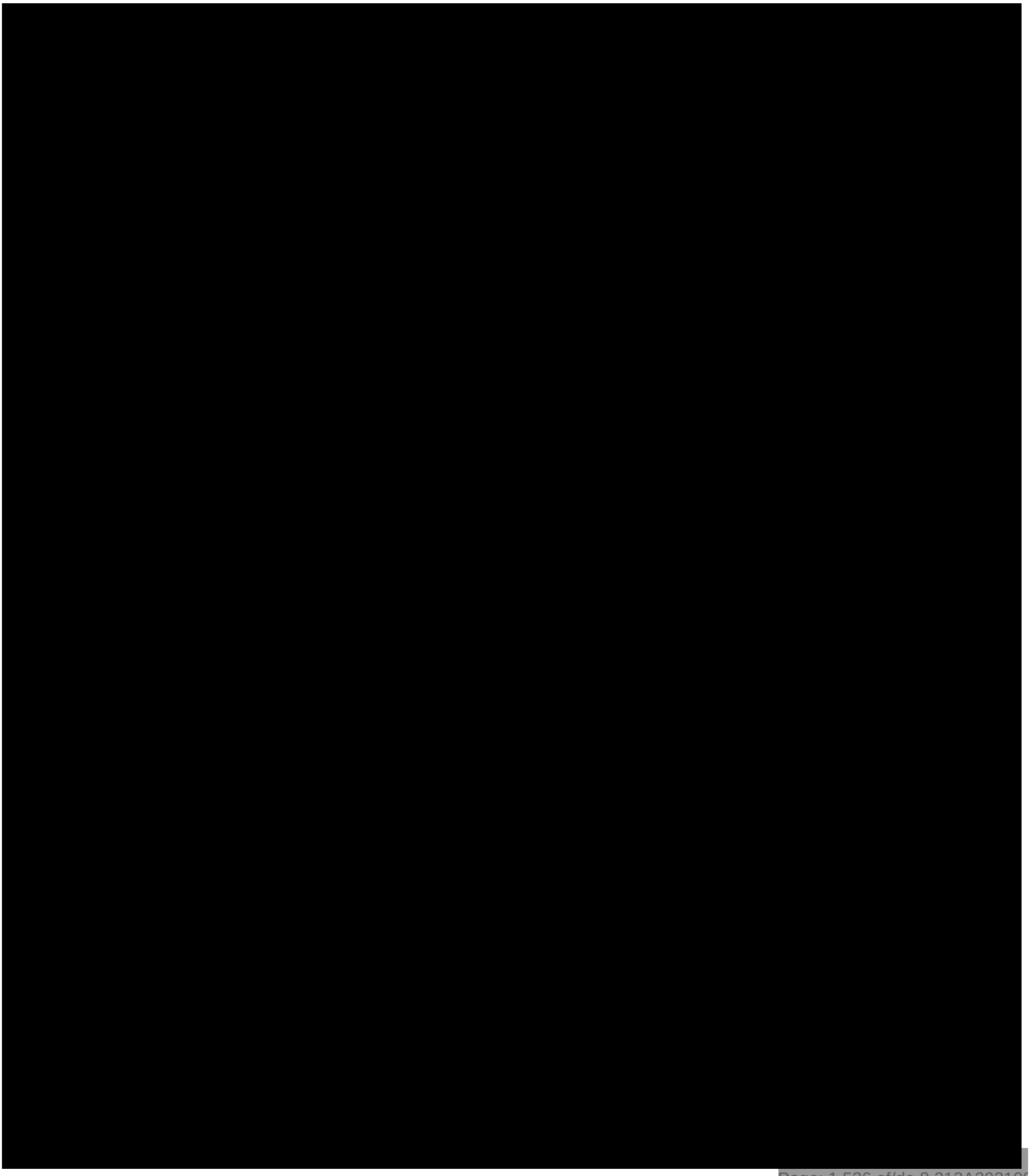

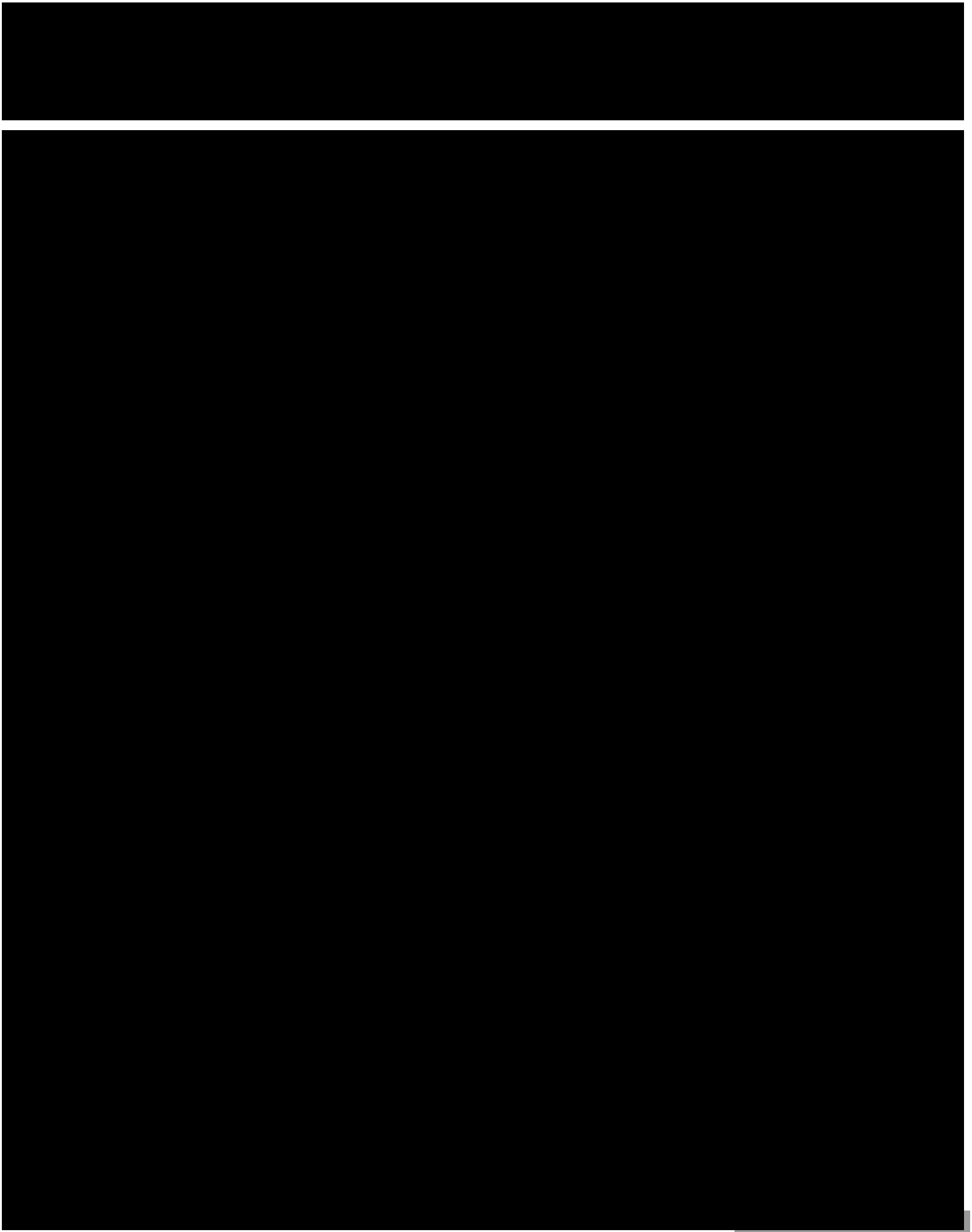

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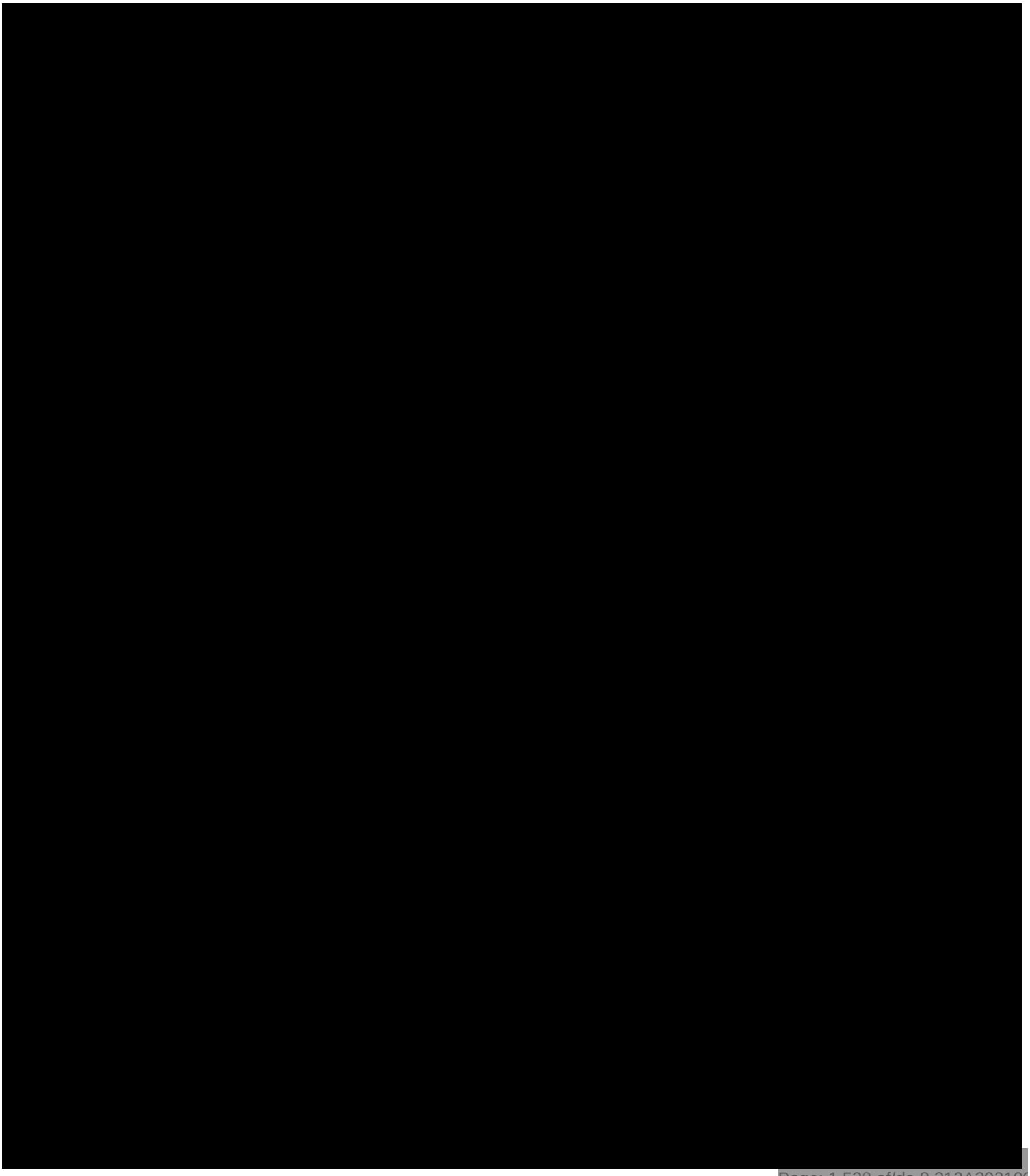

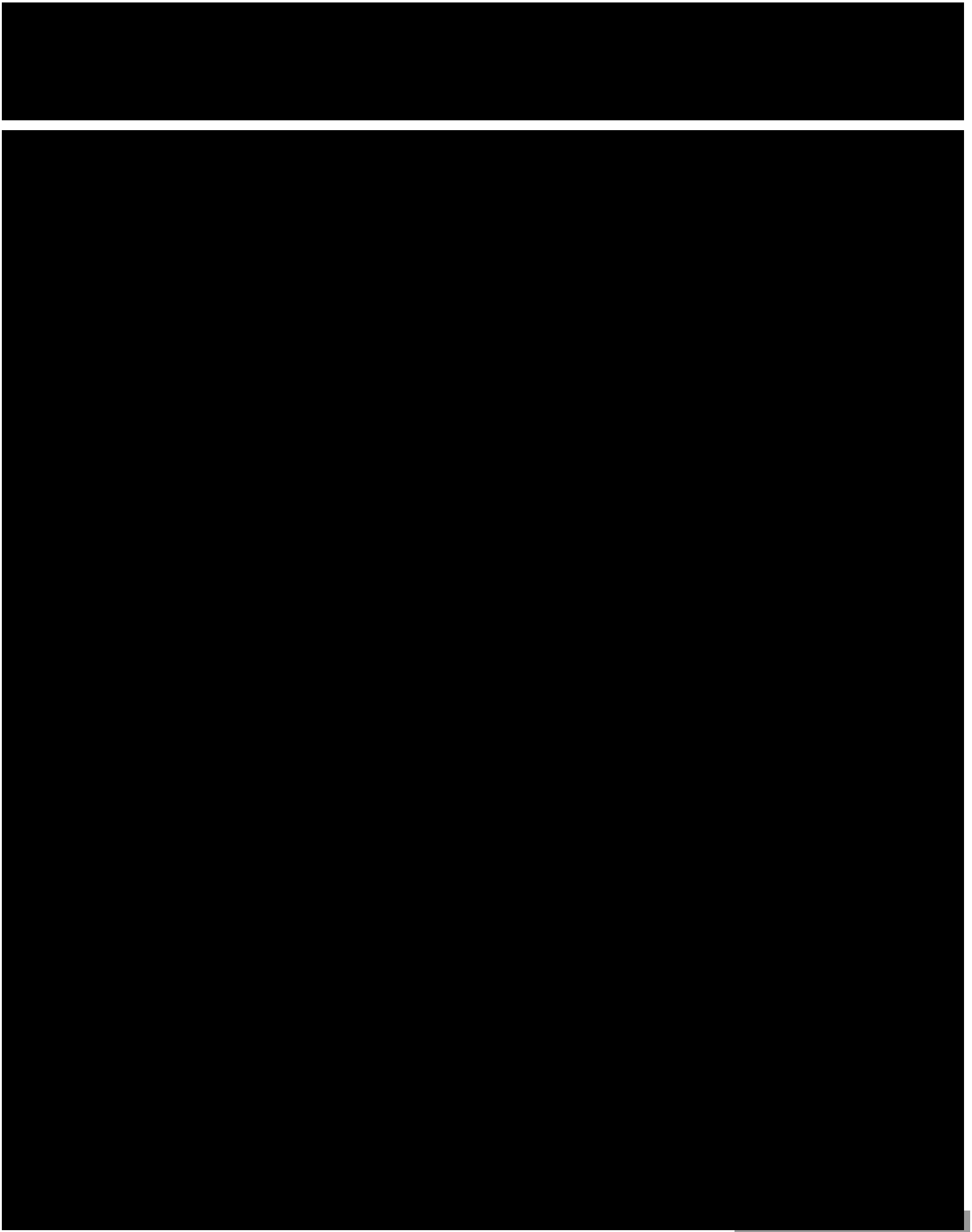

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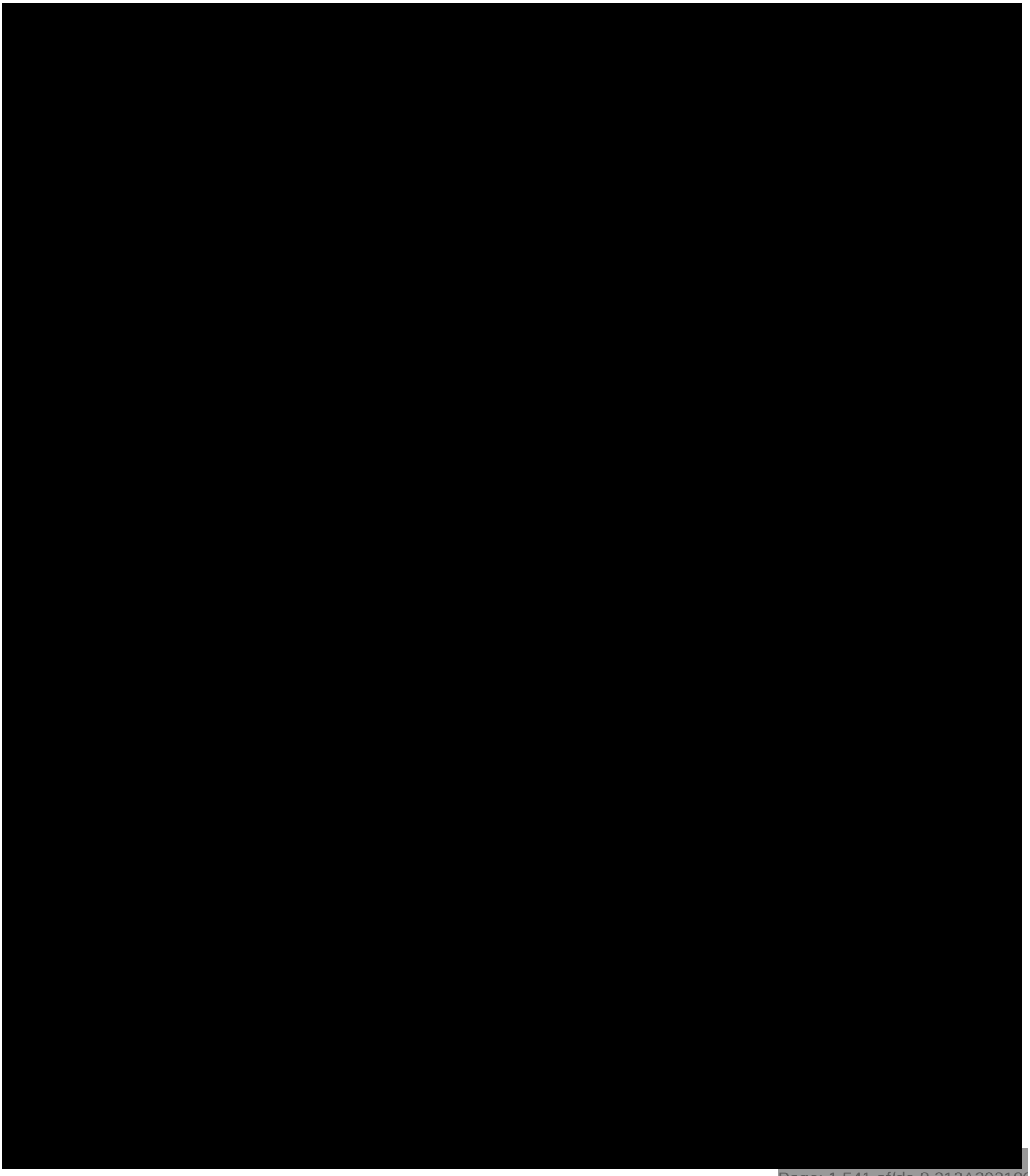

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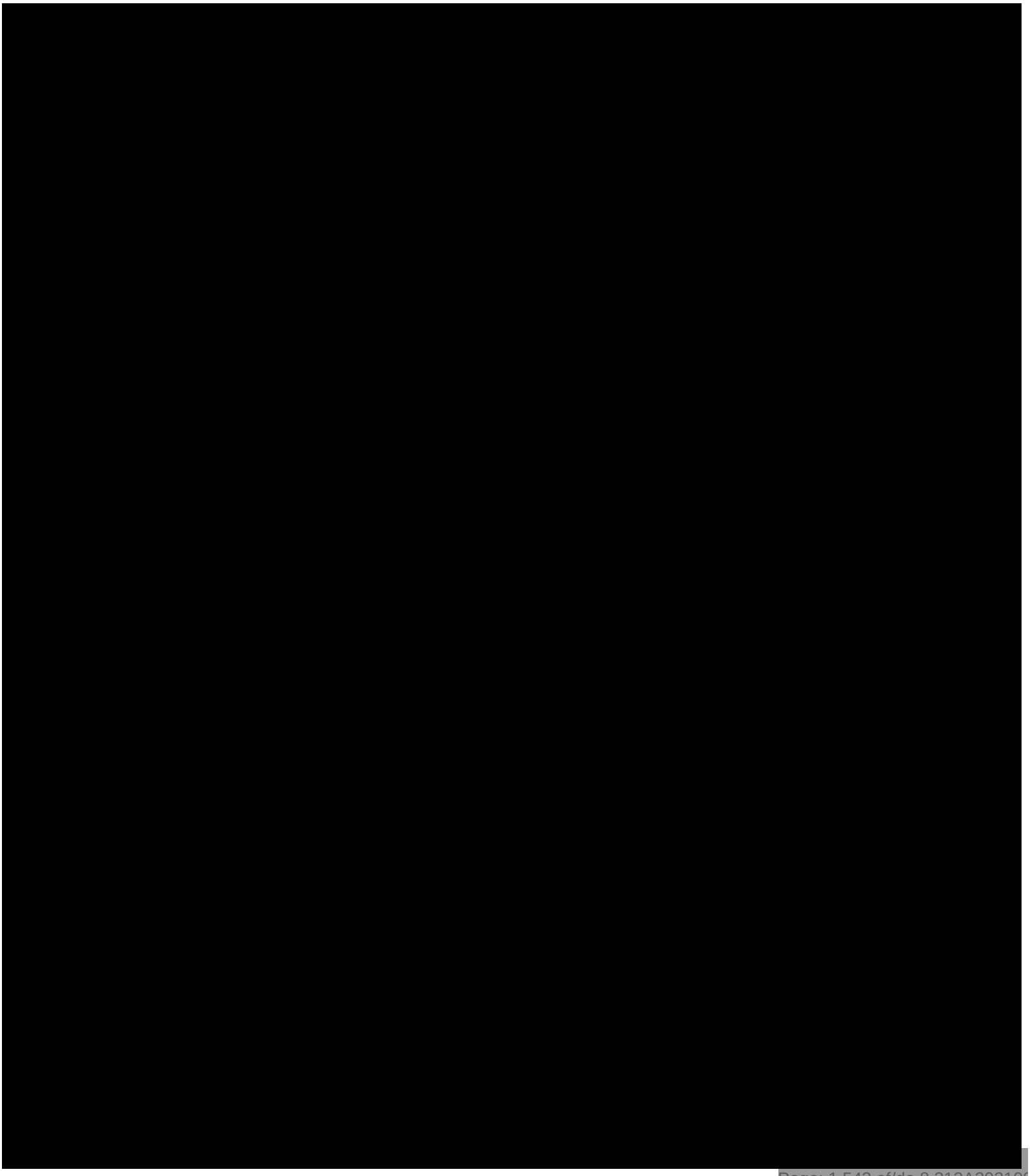

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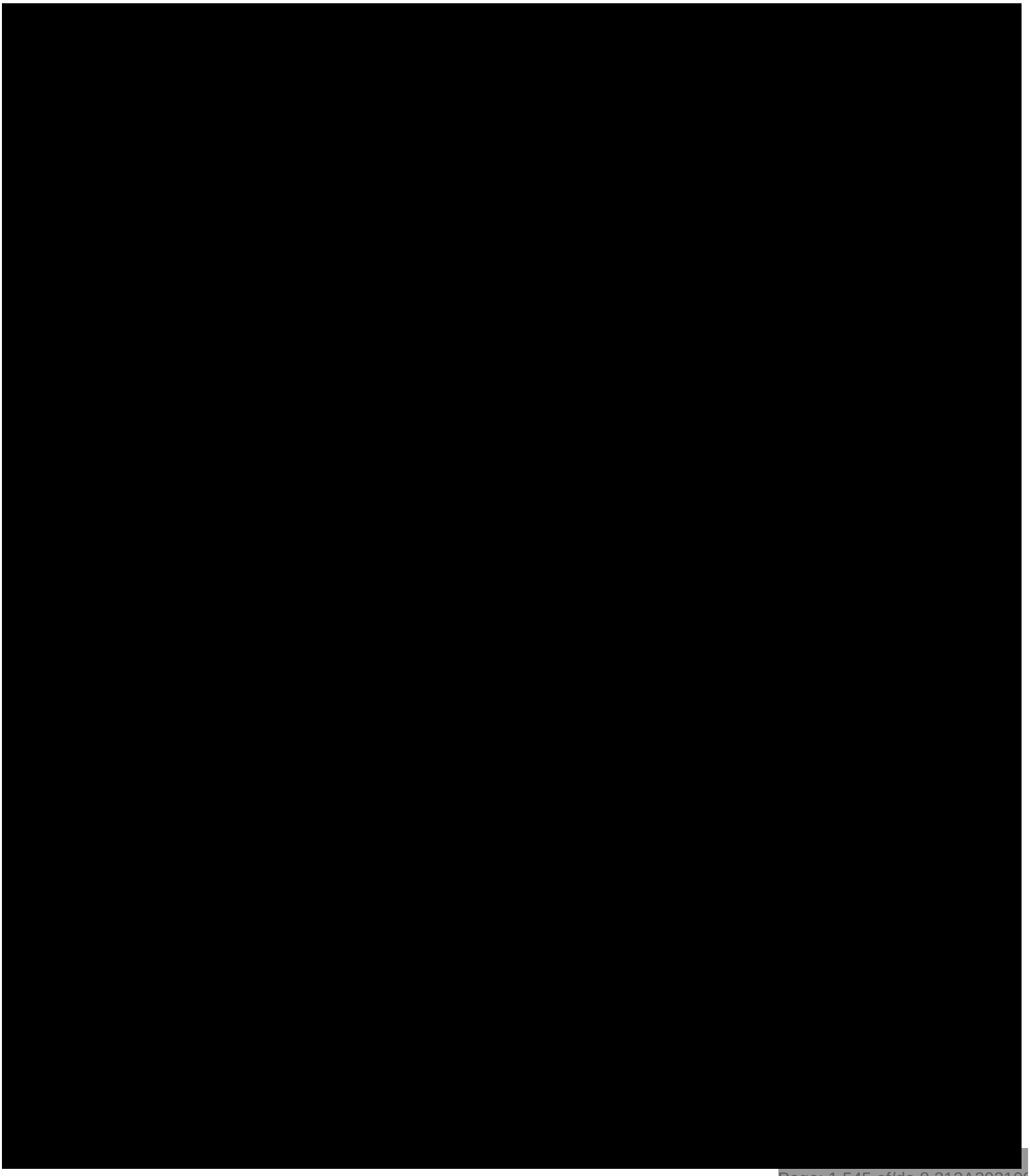

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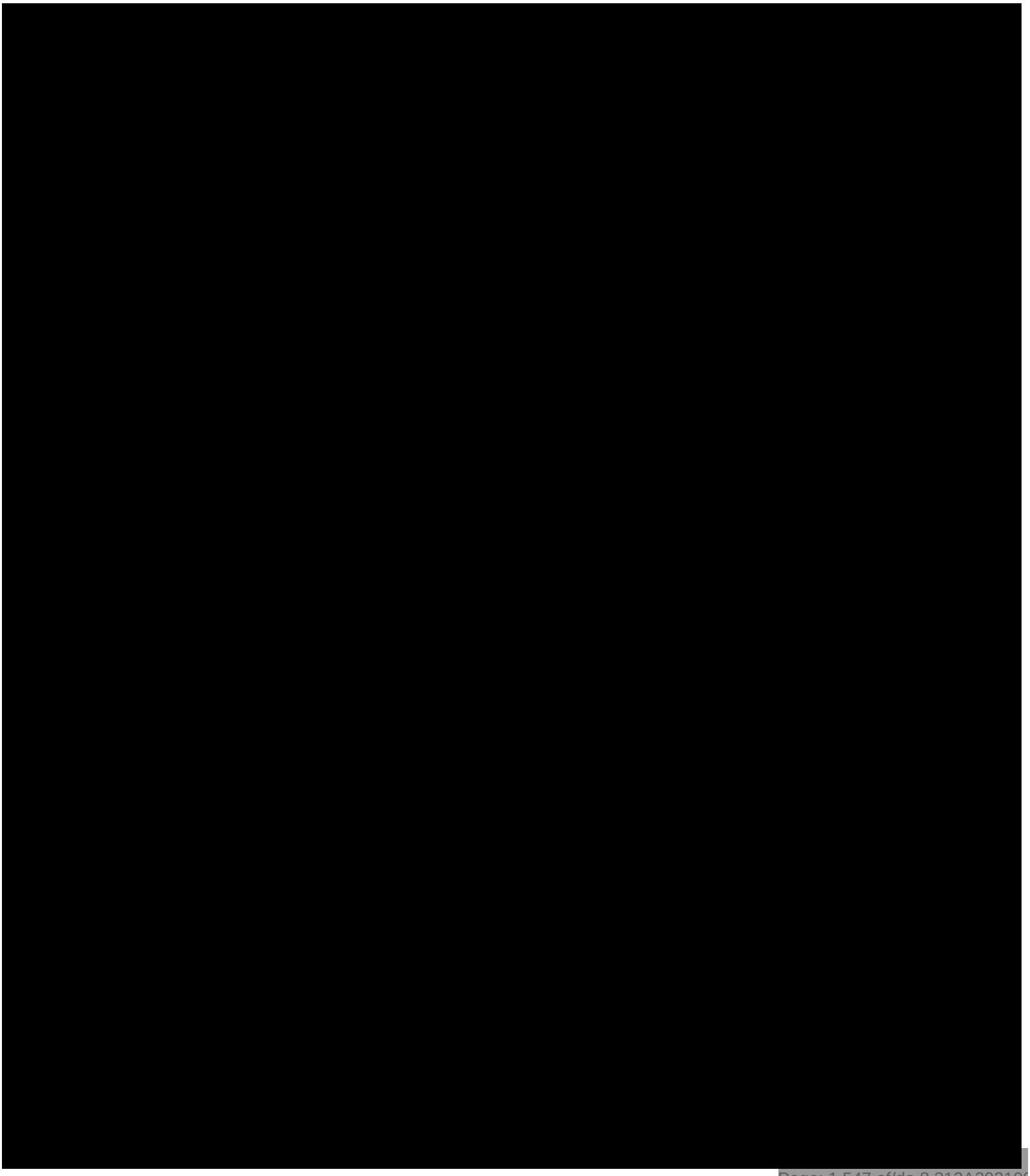

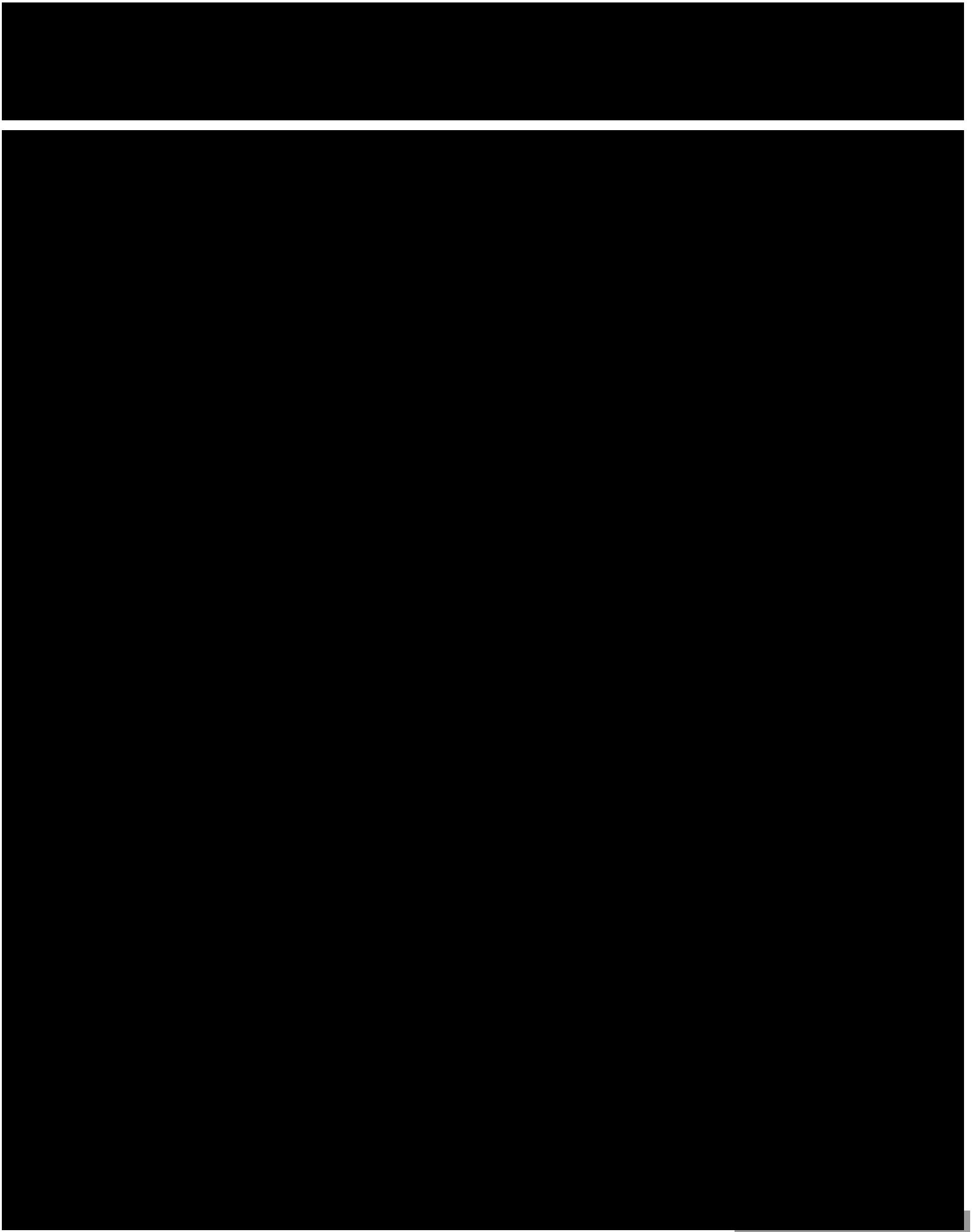

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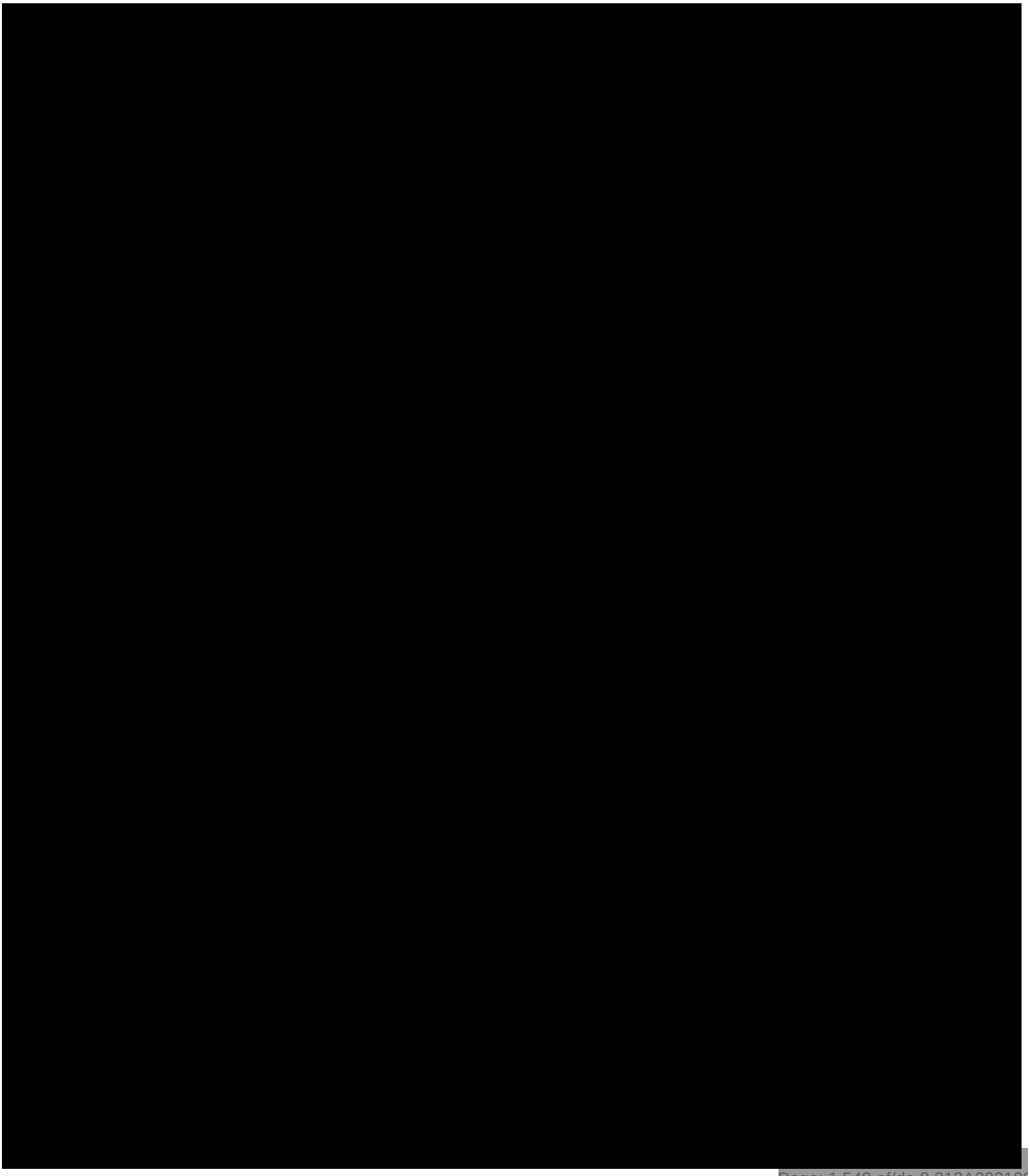

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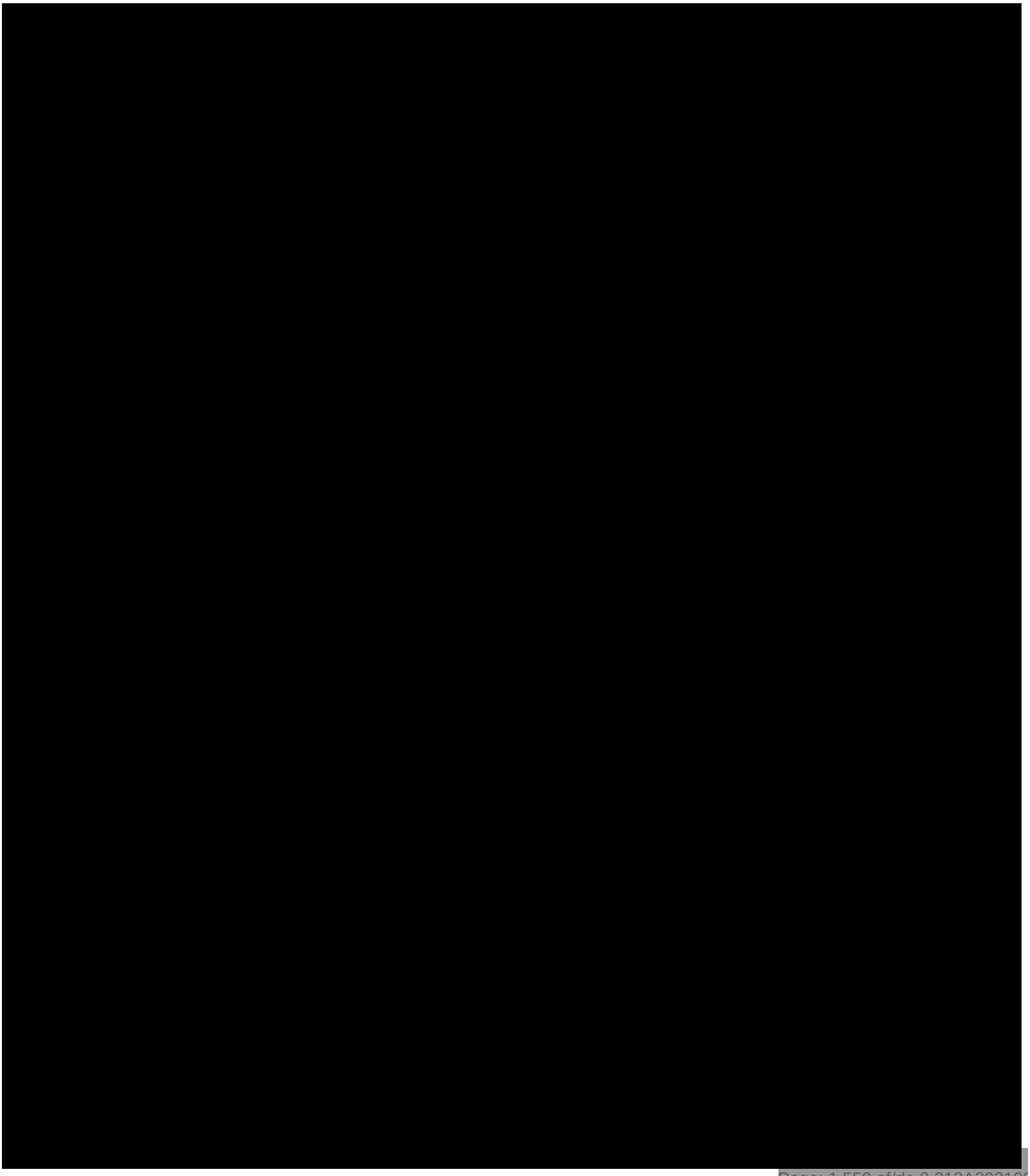

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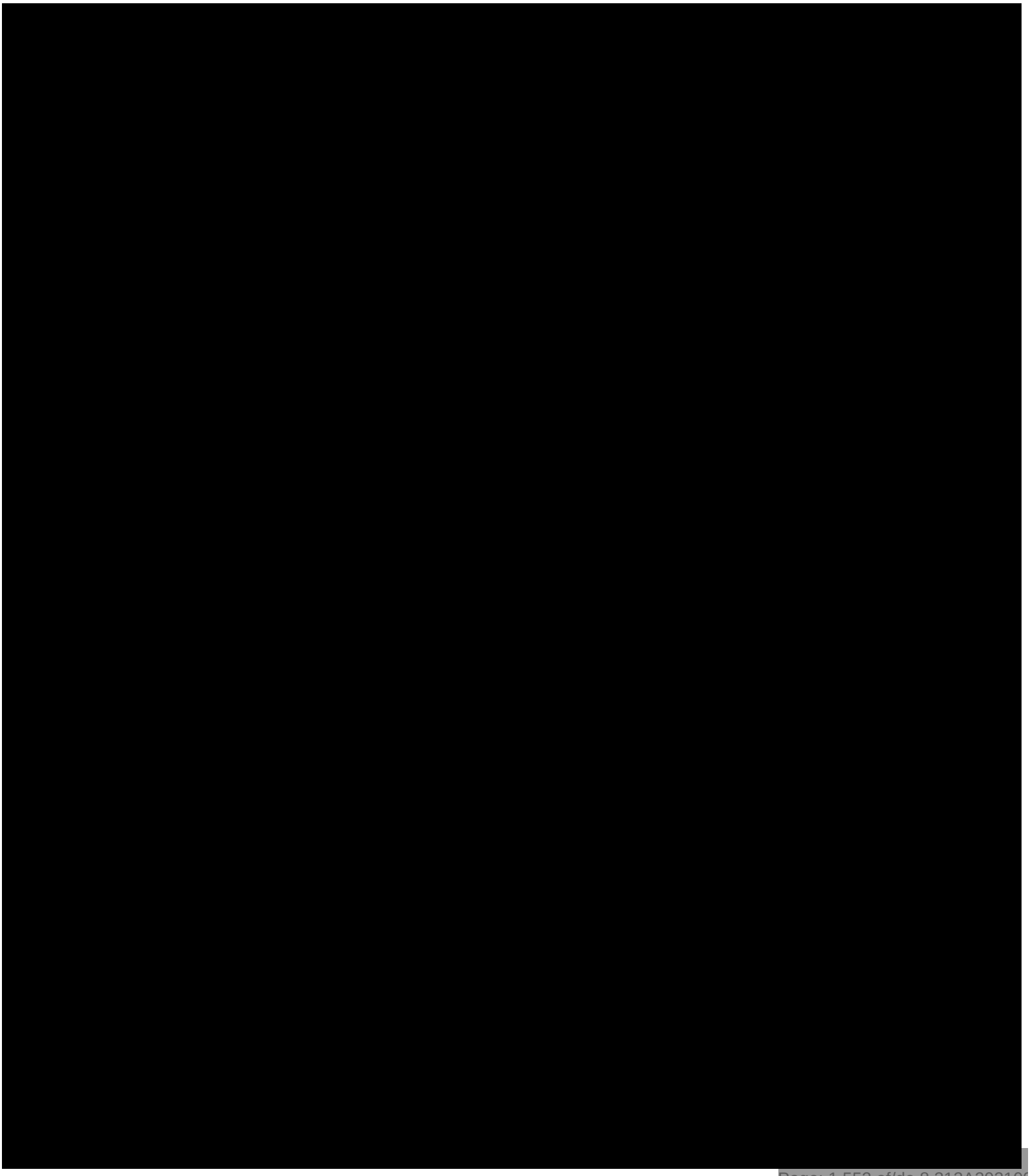

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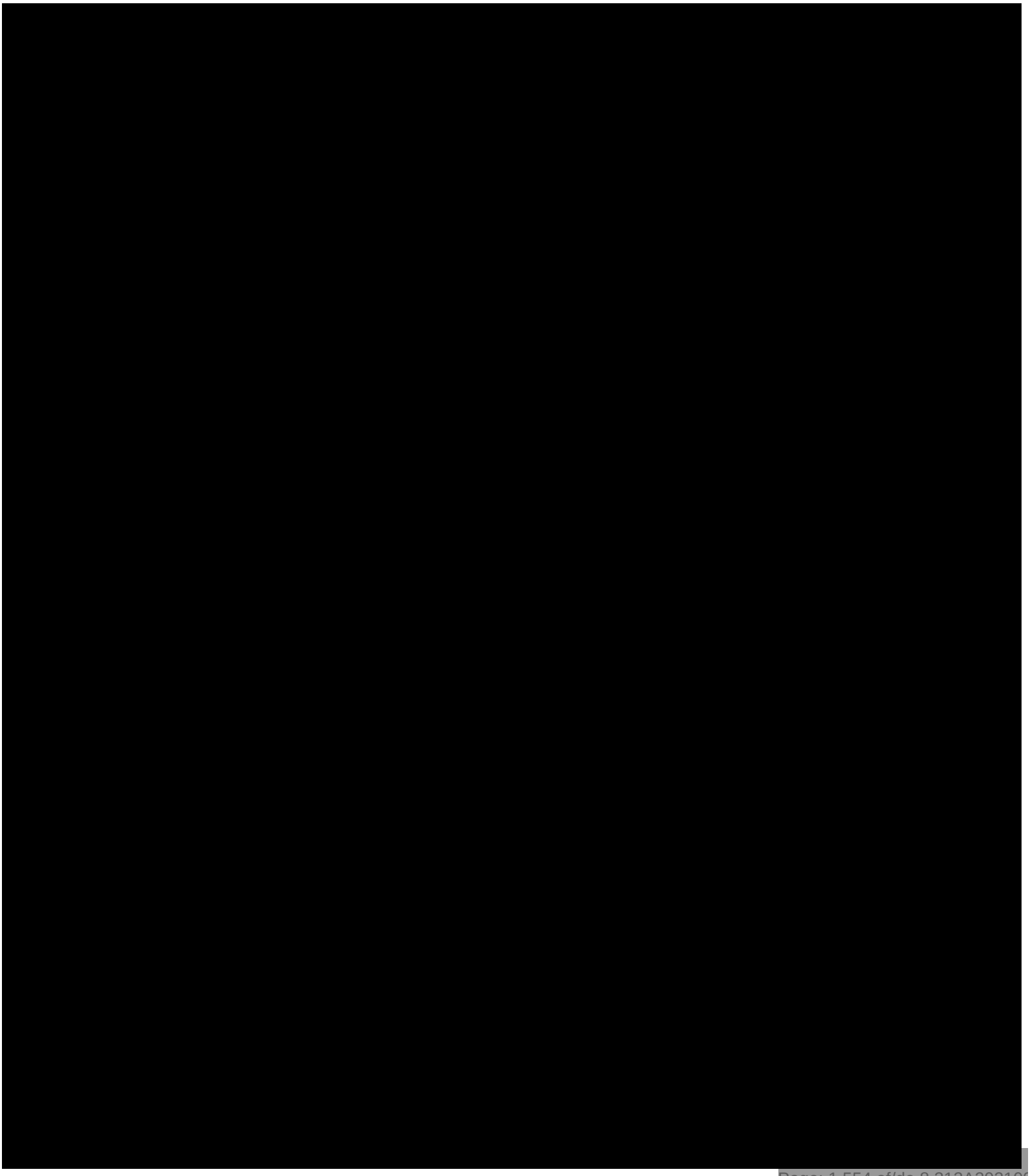

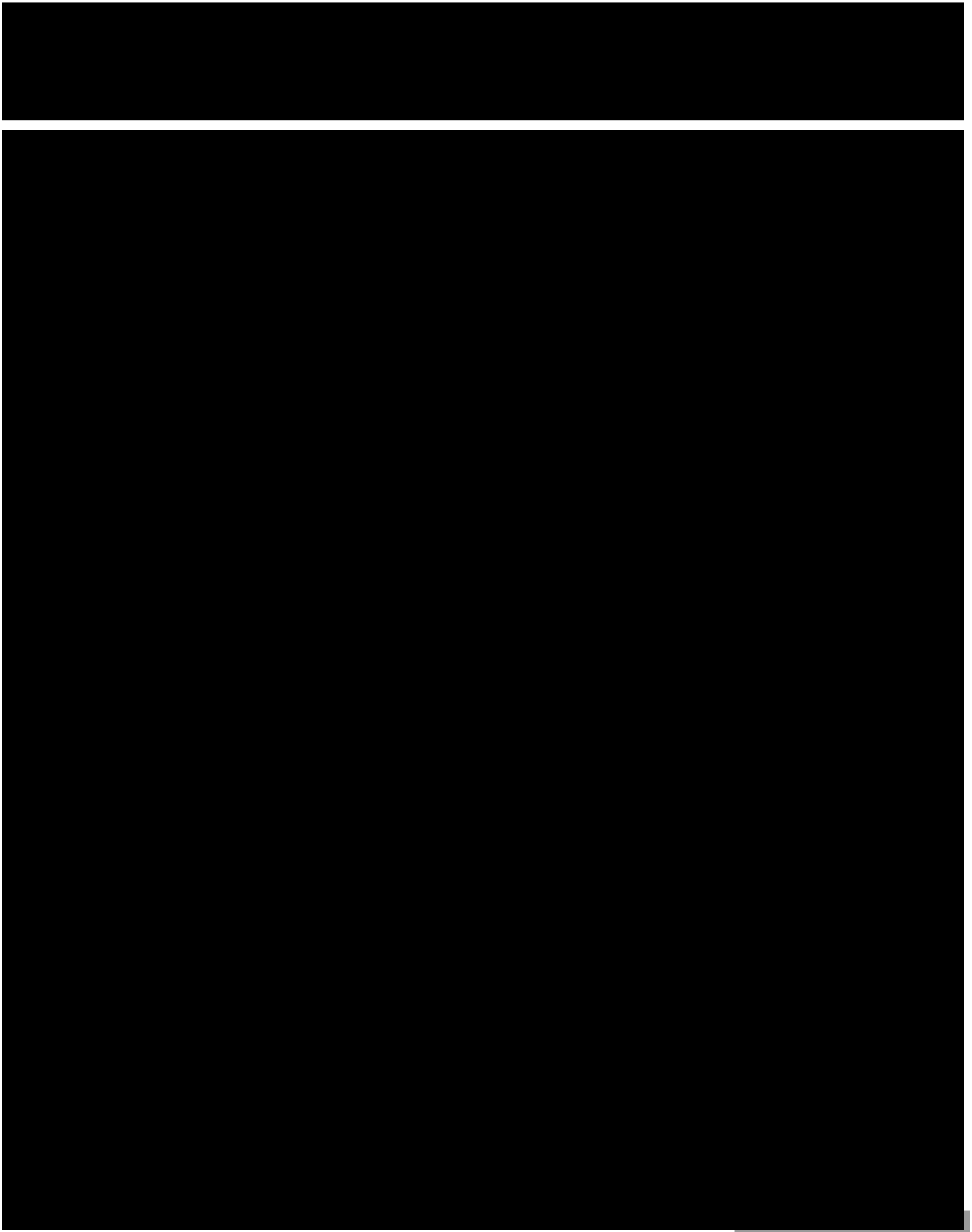

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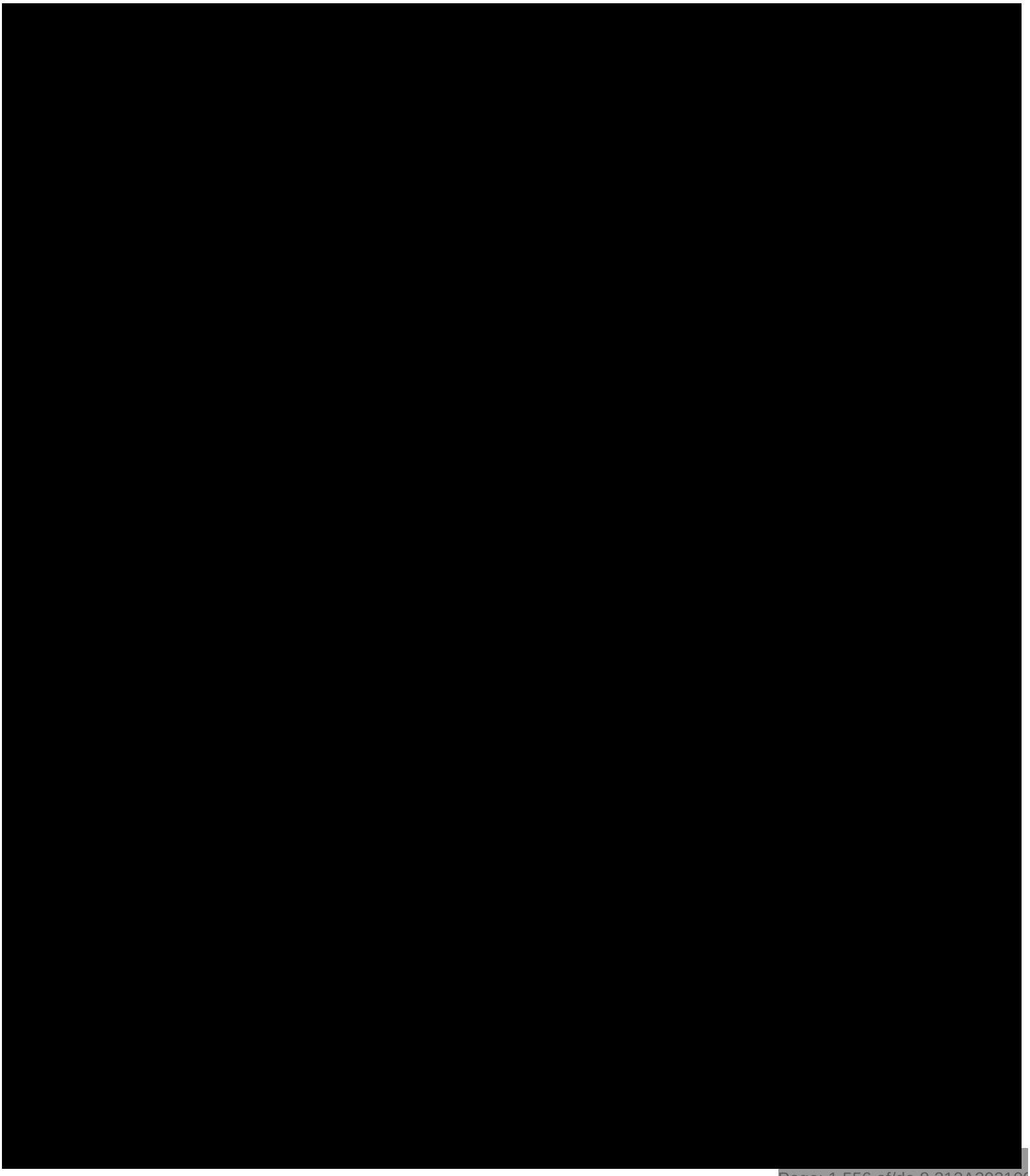

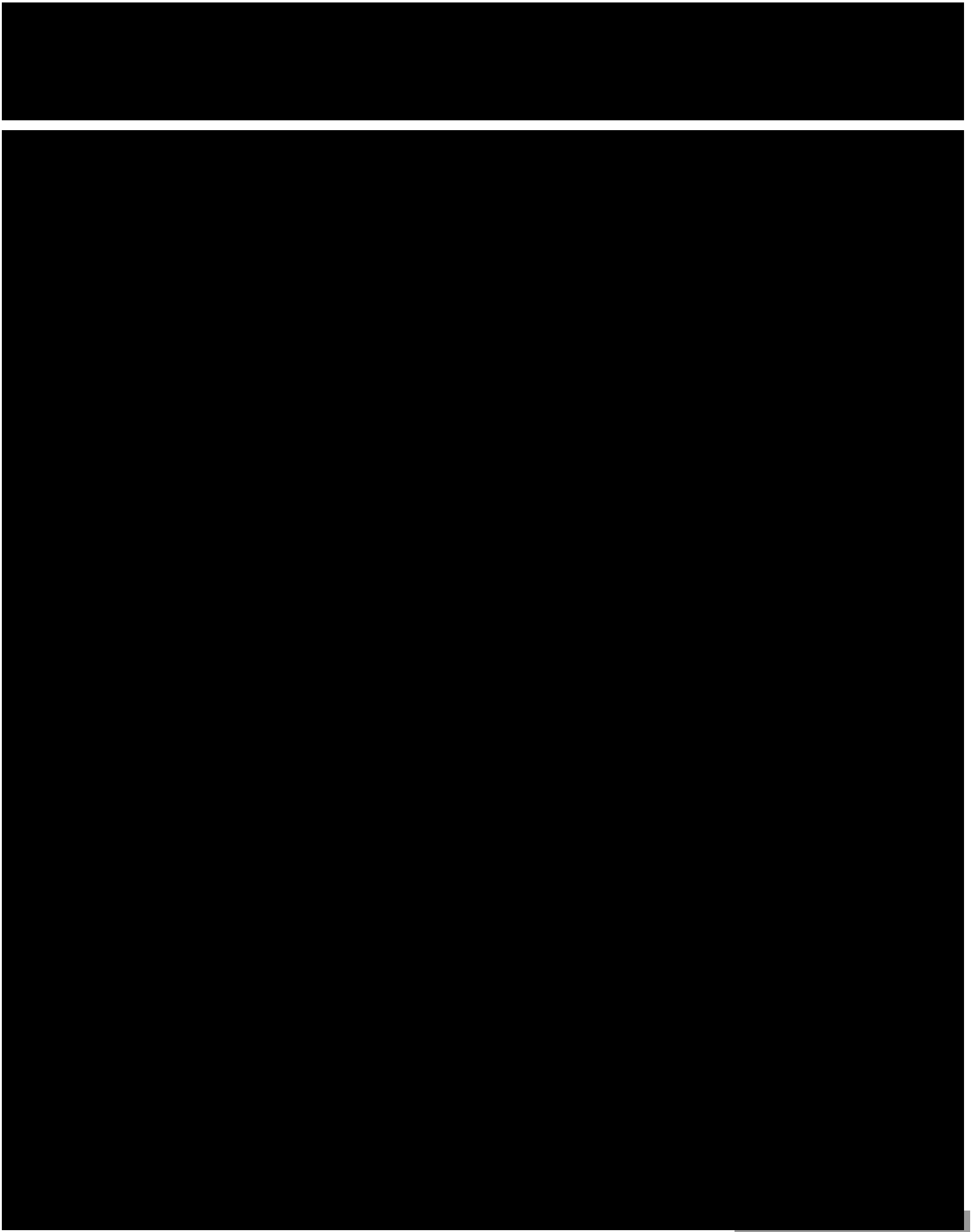

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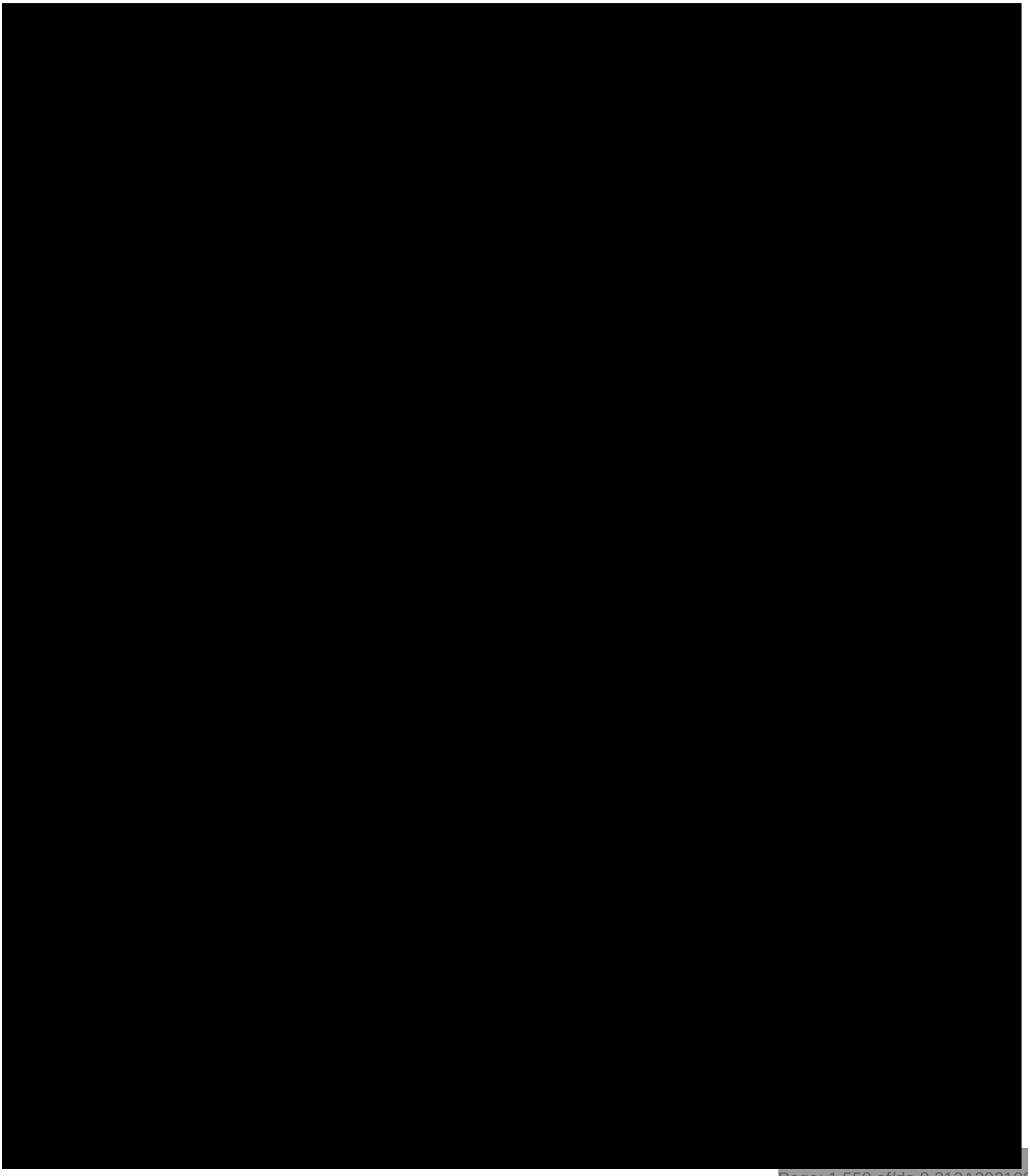

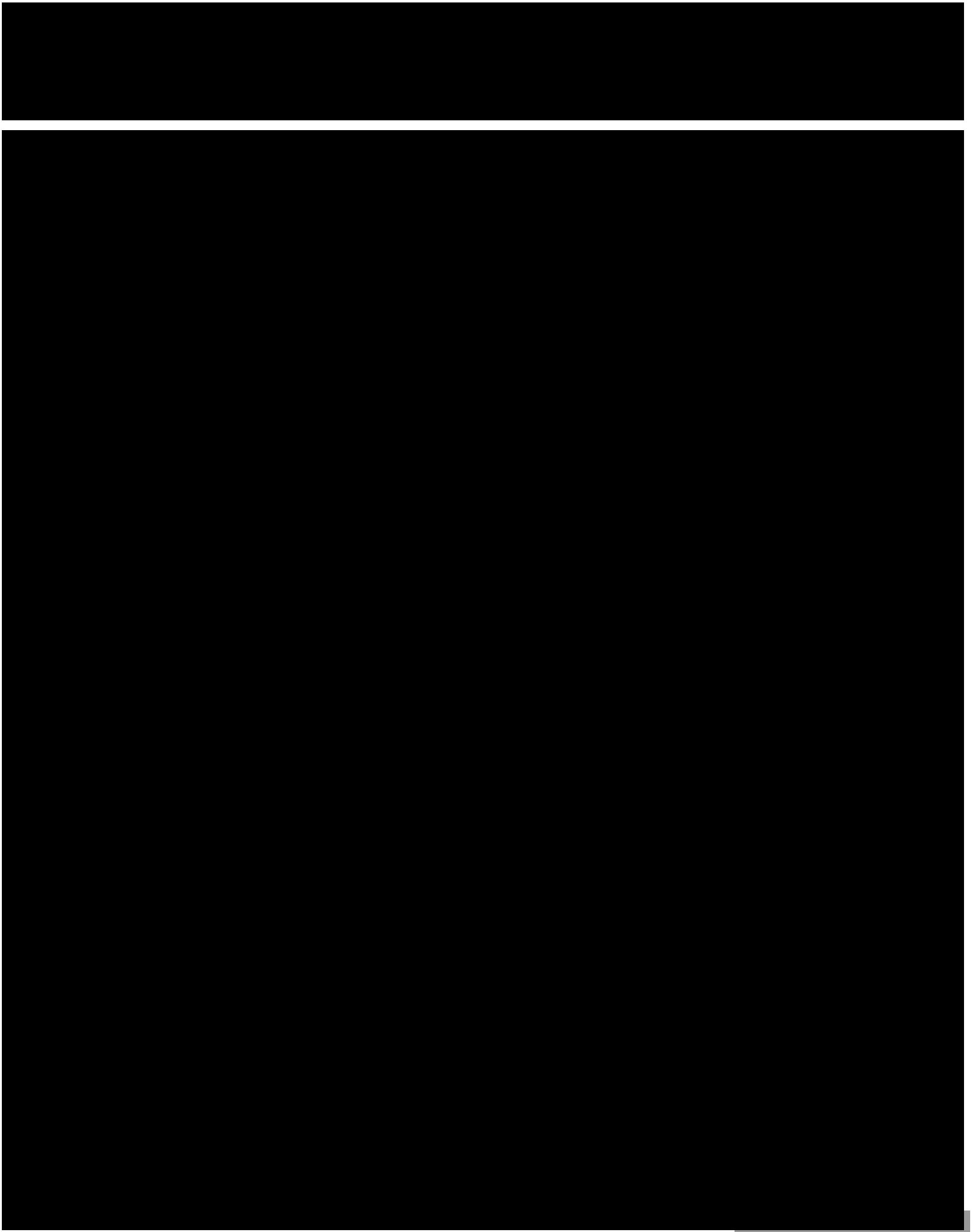

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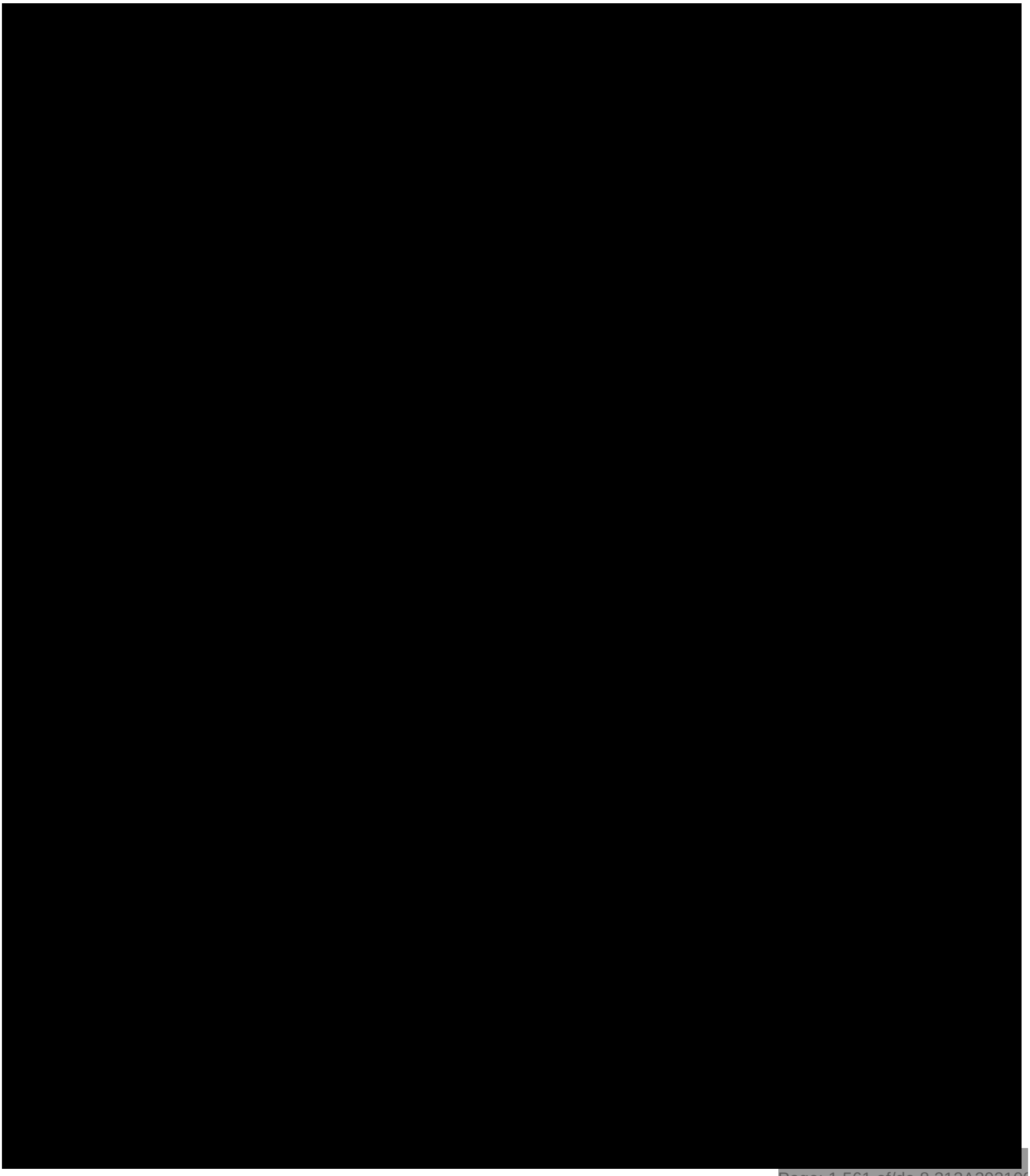

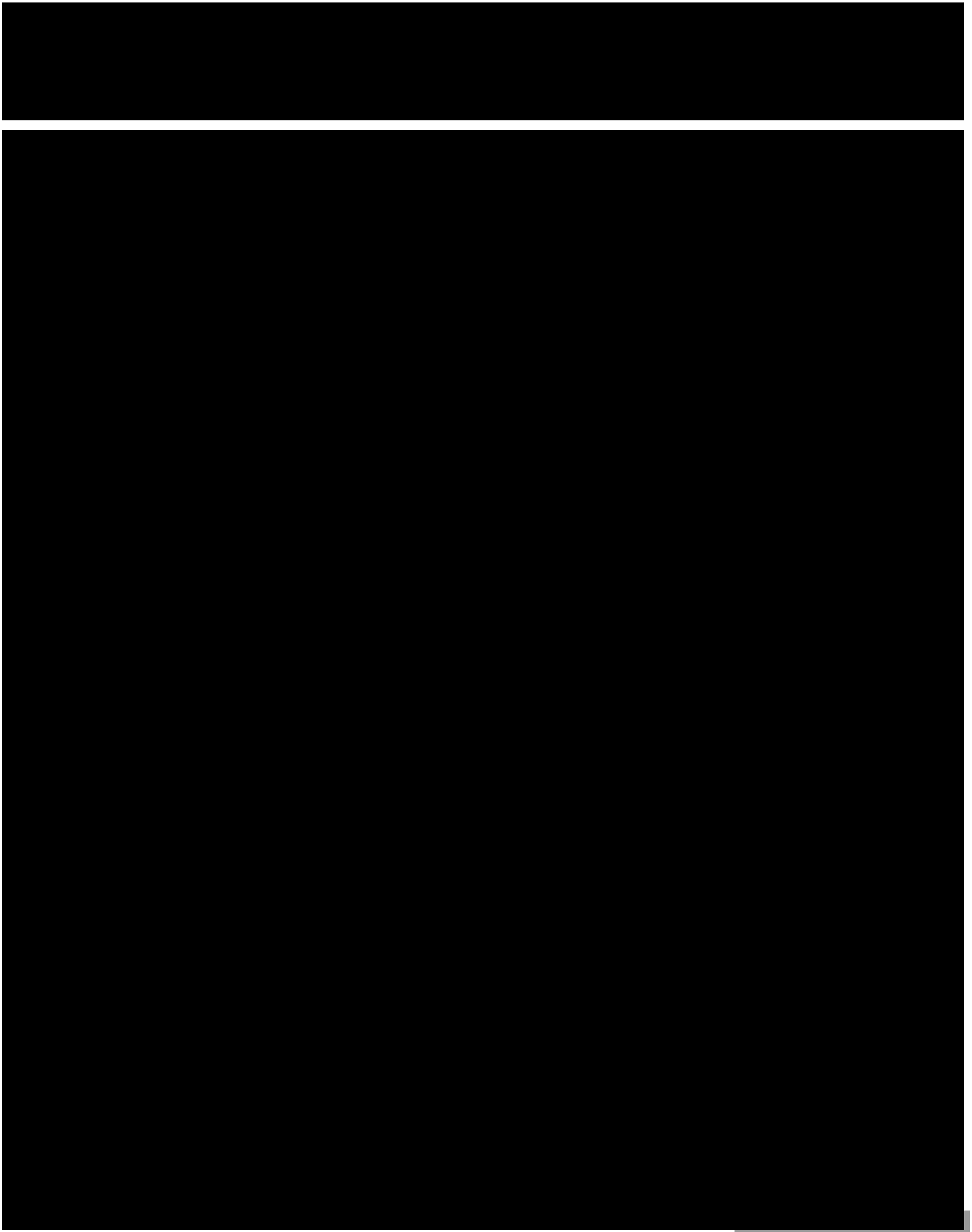

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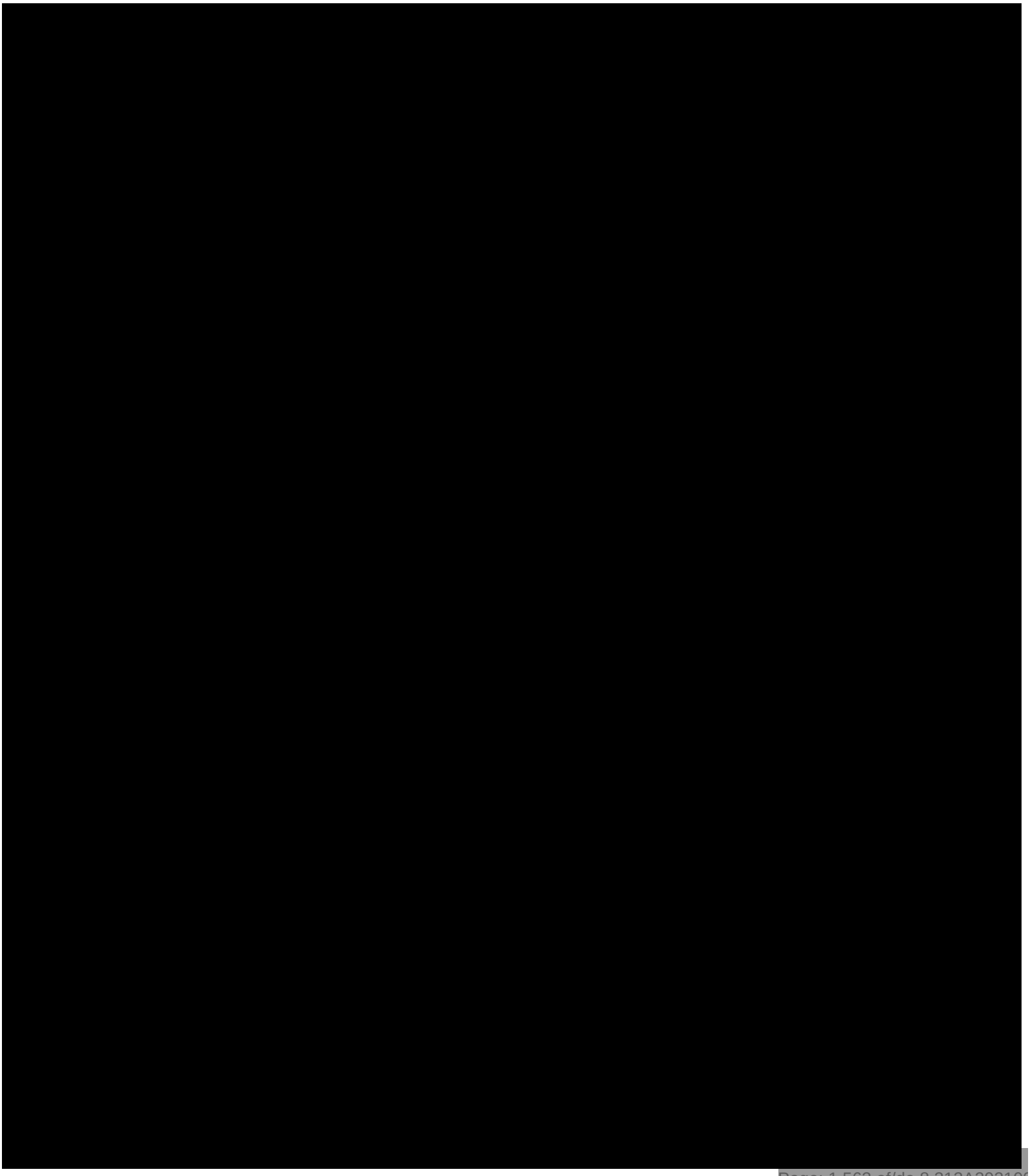

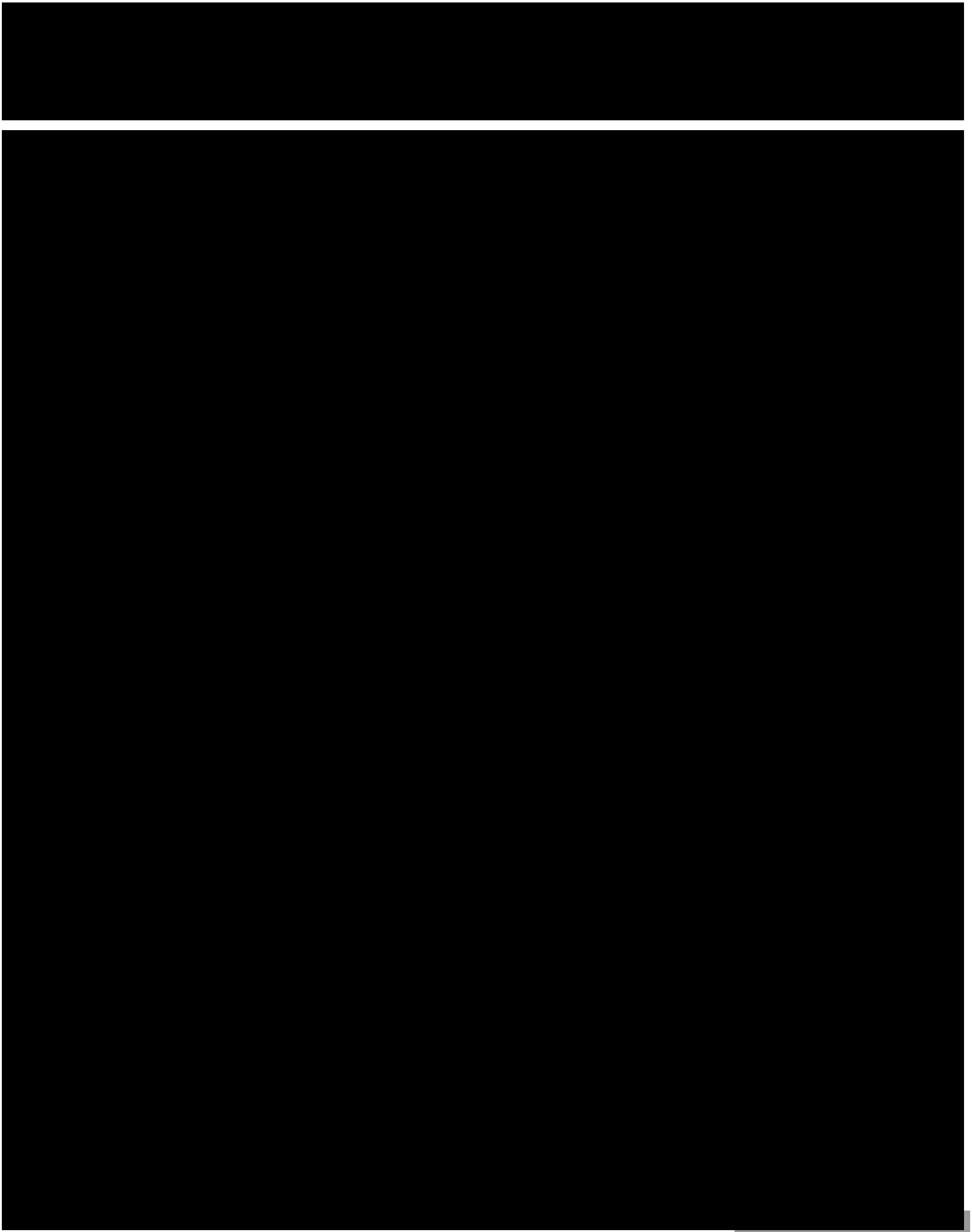

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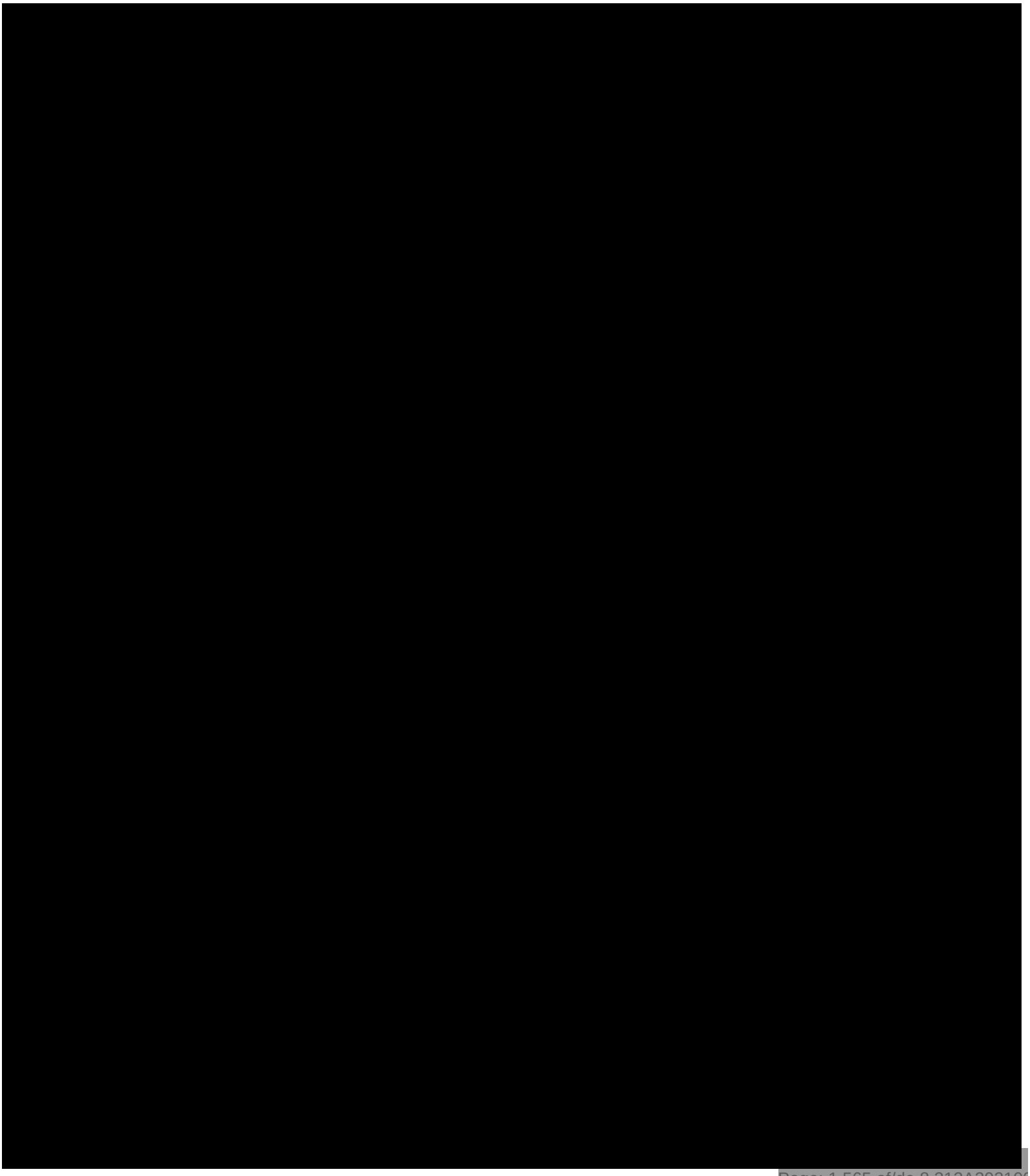

Ridgen, Patrick (HC/SC)

From: [redacted]
Sent: 2021-02-04 5:29 PM
To: Patel, Shalu (HC/SC)
Cc: [redacted] Akel, Sereen H (HC/SC); Panetta, Vincent (HC/SC); Alhaddad, Saj (HC/SC); Antonio, Christopher (HC/SC)
Subject: RE: Final Meeting Minutes from Regulatory Strategy Overview Meeting for Novavax COVID-19 Vaccine, Control [redacted]

Dear Shalu,

Thanks for confirming the minutes.

I do confirm receiving your email.

Thanks

[redacted] **MSc., RAC**
[redacted] REGULATORY AFFAIRS
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From: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Sent: Thursday, February 4, 2021 4:57 PM
To: [redacted]
Cc: [redacted] Akel, Sereen H (HC/SC) <sereenh.akel@canada.ca>; Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Antonio, Christopher (HC/SC) <christopher.antonio@canada.ca>
Subject: Final Meeting Minutes from Regulatory Strategy Overview Meeting for Novavax COVID-19 Vaccine, Control [redacted]

Dear [redacted]

[redacted]

Please confirm receipt of this email.

Regards,

Shalu Patel
(she / elle)

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WHO Technical Report Series, No. 927, 2005

Annex 1
WHO guidelines on nonclinical evaluation of vaccines

This document provides guidance to national regulatory authorities (NRAs) and vaccine manufacturers on the nonclinical evaluation of vaccines by outlining the international regulatory expectations in this area. It should be read in conjunction with the Guidelines on clinical evaluation of vaccines: regulatory expectations (1), in order to complete the understanding of the whole process of vaccine evaluation. Vaccines are a diverse class of biological products and their nonclinical testing programmes will depend on product-specific features and clinical indications. The following text has therefore been written in the form of guidelines rather than recommendations. Guidelines allow greater flexibility than recommendatisons with respect to specific issues related to particular vaccines.

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Introduction

Recent progress in biotechnology and basic immunology has led to the development of a broad range of novel vaccines raising exciting possibilities for the prevention of infectious diseases (*2*, *3*). Improvements to already licensed vaccines are also being considered; such improvements will lead to new products as well as to the introduction of new adjuvants. However, the complexity and novelty of these products presents scientific and regulatory challenges because criteria for their safety, potency and quality assessment may not exist. Product diversity and new approaches, technologies and methodologies develop over time; therefore, judgement based on the best science available should always form the basis for deciding on the type and extent of nonclinical evaluation for these products.

Although nonclinical evaluation plays an essential part in the overall development of vaccine candidates, there is at present limited guidance regarding nonclinical evaluation programmes for these products. In this guidance document, the general principles of nonclinical evaluation of vaccines are discussed, with particular attention being given to the regulatory expectations for new and novel vaccines.

Preclinical testing is a prerequisite to moving a candidate vaccine from the laboratory to the clinic and includes all aspects of testing, product characterization, proof of concept/immunogenicity studies and safety testing in animals conducted prior to clinical testing of the product in humans. Nonclinical evaluation, within the context of this document, refers to all in vivo and in vitro testing performed before and during the clinical development of vaccines. For example, nonclinical evaluation may be necessary when changes in the manufacturing process or product formulations are made or to further study potential safety concerns that may have arisen from phase I and II trials or that have been described in the literature for similar products.

1 General remarks

Nonclinical studies are aimed at defining the in vitro and in vivo characteristics of candidate vaccines including those relating to safety and immunogenicity. Nonclinical studies in animals are valuable tools for identifying possible risks to the vaccinees and helping to plan protocols for subsequent clinical studies in human subjects. However, in all cases, when safety testing in animals is performed, there should be a clear rationale for doing so and the study should be performed in

compliance with the national and international laws for the protection of laboratory animals (*4*), biosafety requirements (*5*) and with good laboratory practice (GLP) (*6*). However, there may be situations where full compliance with GLP is not possible. If the study, or part of the study, was not conducted in compliance with GLP, areas of noncompliance should be defined and a statement of the reason for noncompliance should be drawn up.

Potential safety concerns for a vaccine product include those due to inherent toxicities of the product, toxicities of impurities and contaminants, and toxicities that result from interactions between the vaccine components present in the vaccine formulation. In addition, the immune response induced by the vaccine may lead to toxic side-effects.

Despite efforts to maximize the predictive value of nonclinical toxicity studies there is always the possibility that not all risks are identified. The limitations of animal testing in reflecting clinical safety and efficacy in humans should be recognized as pathogenesis and immune responses are frequently species-specific. Moreover, potential safety concerns identified during animal testing may not necessarily indicate a problem in humans. However, any signal observed in nonclinical toxicity studies should be carefully addressed in human clinical trials and may require additional nonclinical testing. It should be noted that the absence of detectable toxicity in animal studies does not necessarily mean a vaccine will be safe in humans. Potential safety concerns related to specific types of vaccine candidate are considered in section 6.

The development and subsequent validation of in vitro tests for use as alternatives to nonclinical evaluation of vaccine candidates in animals is encouraged as it may lead to the improvement of nonclinical testing as well as to a reduction of animal usage.

The need for and extent of nonclinical testing will depend on the product under consideration. For example, for a product for which there is no prior nonclinical and clinical experience, nonclinical testing would be expected to be more extensive than for those vaccines previously licensed and used in humans. In some cases, it may not be necessary to perform preclinical safety studies prior to the initiation of phase 1 clinical trials. For example, in the case of transfer of technology, where access to the database of the originally developed vaccine is available, data from nonclinical bridging studies (e.g. physicochemical characterization and abbreviated in vivo studies) may be an acceptable basis for further development of the product.

Early communication between the vaccine manufacturer and the responsible national regulatory authority to agree on the requirements for and type of nonclinical testing is recommended.

1.1 *Scope*

For the purposes of this document, vaccines are considered to be a heterogeneous class of medicinal products containing immunogenic substances capable of inducing specific, active and protective host immunity against infectious disease.

Although most vaccines are being developed for pre- and post-exposure prophylaxis, in some cases, they may be indicated for therapeutic use against infectious diseases, e.g. human immunodeficiency virus (HIV), and human papillomavirus (HPV). Both prophylactic and therapeutic vaccines for infectious disease indications are considered in this document.

Vaccines for human use include one or more of the following: microorganisms inactivated by chemical and/or physical means that retain appropriate immunogenic properties; living microorganisms that have been selected for their attenuation whilst retaining immunogenic properties; antigens extracted from microorganisms, secreted by them or produced by recombinant DNA technology; chimeric microorganisms; antigens produced in vivo in the vaccinated host following administration of a live vector or nucleic acid or antigens produced by chemical synthesis in vitro. The antigens may be in their native state, truncated or modified following introduction of mutations, detoxified by chemical or physical means and/or aggregated, polymerized or conjugated to a carrier to increase immunogenicity. Antigens may be presented plain or in conjunction with an adjuvant, or in combination with other antigens, additives and other excipients.

Therapeutic vaccines for non-infectious diseases (e.g. certain cancer vaccines) and monoclonal antibodies used as immunogens (e.g. anti-idiotypic antibodies) are *not* considered here.

1.2 *Glossary*

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

Adjuvants
Substances that are intended to enhance relevant immune response and subsequent clinical efficacy of the vaccine.

Booster vaccination
Vaccination given at a certain time interval after primary vaccination to enhance immune responses and induce long-term protection.

Combination vaccine
A vaccine that consists of two or more antigens, either combined by the manufacturer or mixed immediately before administration and intended to protect against either more than one disease, or against one disease caused by different strains or serotypes of the same organism.

Genetically modified organism (GMO)
An organism or a microorganism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination. This definition covers microorganisms including viruses, viroids and cell cultures including those from animals, but does not cover naked recombinant DNA or naked recombinant plasmids.

Good clinical practice (GCP)
A standard for clinical studies that encompasses their design, conduct, monitoring, termination, audit, analyses, reporting and documentation and which ensures that the studies are scientifically and ethically sound and that the clinical properties (diagnostic, therapeutic or prophylactic) of the pharmaceutical product under investigation are properly documented.

Good laboratory practice (GLP)
A quality system concerned with the organizational process and the conditions under which nonclinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported. GLP principles may be considered as a set of criteria to be satisfied as a basis for ensuring the quality, reliability and integrity of studies, the reporting of verifiable conclusions and the traceability of data.

Good manufacturing practice (GMP)
A part of the pharmaceutical quality assurance which ensures that products are consistently produced and controlled according to the quality standards appropriate to their intended use and as required by the marketing authorization. In these guidelines, GMP refers to the current GMP guidelines published by WHO.

Immunogenicity
Capacity of a vaccine to induce antibody-mediated and/or cell-mediated immunity and/or immunological memory.

Nonclinical evaluation of vaccines
All in vivo and in vitro testing performed before and during clinical development of vaccines. The potential toxicity of a vaccine should be assessed not only prior to initiation of human trials, but throughout clinical development.

Plasmid
Double-stranded circular DNA molecules capable of replicating in bacterial cells.

Potency
The measure of biological activity, using a suitable quantitative biological assay, based on the attribute of the product that is linked to the relevant biological properties.

Preclinical evaluation of vaccine
All in vivo and in vitro testing carried out prior to the first testing of vaccines in humans. This is a prerequisite to the initiation of clinical trials and includes product characterization, proof of concept/immunogenicity studies and animal safety testing.

Preclinical toxicity study
A study designed with the primary purpose of demonstrating the safety and tolerability of a candidate vaccine product. The design of the preclinical toxicity study should meet the criteria outlined in the section on study design to be considered supportive of the intended clinical trial.

Primary vaccination
First vaccination or series of vaccinations given within a predefined period, with an interval of less than 6 months between doses, to induce clinical protection.

Product characterization
A full battery of physical, chemical and biological tests conducted for a particular product. These tests include, but are not limited to, in-process control testing, testing for adventitious agents, testing process additives and process intermediates, and lot release.

Protocol or study plan
A document that states the background, rationale and objectives of the nonclinical studies and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed.

Relevant animal model
An animal that develops an immune response similar to the expected human response after vaccination. It is acknowledged that species-specific differences in immune responses are likely. Ideally, the animal species chosen should be sensitive to the pathogenic organism or toxin under consideration.

Route of administration
The means by which the candidate vaccine product is introduced to the host. Possible routes of administration include the intravenous, intramuscular, subcutaneous, transcutaneous, intradermal, transdermal, oral, intranasal, intranodal, intravaginal and intrarectal routes.

Seroconversion
Predefined increase in antibody concentration, considered to correlate with the transition from seronegative to seropositive, providing information on the immunogenicity of a vaccine. If there are pre-existing antibodies, seroconversion is defined as a transition from a predefined low level to a significantly higher defined level, such as a fourfold increase in geometric mean antibody concentration.

Validation
The action of proving, in accordance with the principles of good manufacturing practice, that any procedure, process, equipment (including the computer software or hardware used), material, activity or system actually leads to the expected results.

2 Characterization of candidate vaccines

2.1 *Vaccine production*

The biological nature of the starting materials, the manufacturing process and the test methods needed to characterize batches of the product are important elements to be considered in the design and the interpretation of nonclinical testing of vaccines. Many vaccines are produced using prokaryotic or eukaryotic microorganisms and subtle changes in these organisms may radically affect the vaccine product. Therefore, the establishment of a seed-lot system is essential for vaccine production. Moreover, the quality, safety and potency of

these products are usually sensitive to changes in manufacturing conditions. The quality and safety of vaccine preparations cannot be assured solely by testing of the end-product, but depends on the strict control of the manufacturing process following the principles of good manufacturing practice (GMP) (*7*). This includes demonstration of the purity and quality of the starting material (raw materials and seeds), in-process control testing, testing for process additives and process intermediates and the development and establishment of lot release tests. Moreover, as the relationship between physical and chemical characteristics, and the immunogenicity and efficacy of these products is frequently not completely understood, biological characterization through the use of biological assays should always complement the physical and chemical product characterization. The development of appropriate laboratory methods to characterize a vaccine formulation with respect to its components, as well as its safety and potency, is a prerequisite to the clinical use of any new or novel vaccines against bacteria, viruses or parasites.

Consistency of production is essential, and the demonstration that the product does not differ from vaccine lots that have been shown to be safe and adequately immunogenic and protective in clinical studies is a crucial component of vaccine evaluation, licensing and batch release. For this reason, manufacturers should make every effort to characterize these clinical lots and if possible to keep some of these lots for future reference.

Where no appropriate animal model exists for testing potency or where direct serological or immunological correlates of clinical protection are not available, the challenge is to ensure that each production batch has the same protective efficacy as those batches shown to be protective in clinical trials. In such cases, emphasis is increasingly being placed on assuring the consistency of production using modern physical, chemical and immunological methods that enable characterization of some products to a degree of precision not previously possible.

The vaccine lots used in preclinical studies should be adequately representative of the formulation intended for use in the clinical investigation and, ideally, preclinical testing should be done on the same lot as that proposed for the clinical trials. If this is not feasible, then the lots studied should be comparable with respect to physicochemical data, stability and formulation.

At a minimum, candidate vaccines for clinical trials should be prepared under conditions of good manufacturing practice (GMP) for

clinical trial material (*8*). However full GMP will be required at the later stages of clinical development (*7*, *9*).

Any change proposed to the manufacturing process during vaccine development should be considered carefully to evaluate its impact on the quality, safety and efficacy of the vaccine and the possible need for additional nonclinical and clinical investigations.

Subsequent changes in production methods or scale-up following product licensure will necessitate further product characterization to demonstrate comparability with the original lot(s) used to demonstrate safety and efficacy of the product. The extent of comparability testing needed depends on the nature of the changes implemented (*10*). These changes should be documented and the national regulatory authority consulted. Regulatory authorities should clearly define and implement in their regulations what changes require only a notification and which changes require formal approval before implementation (*11*).

The procedures used in the characterization and control of existing licensed traditional vaccines are not likely to be applicable to newer products developed using state-of-the-art technology to protect against the same infection. For example, specific guidelines have been developed for the production and control of acellular pertussis vaccines that differ from those applied to whole cell pertussis vaccine (*12*). Likewise, the tests applied to the characterization and control of traditional inactivated cholera vaccine for parenteral use are not necessarily applicable to the new inactivated whole-cell cholera vaccine intended for oral administration, and an appropriate potency test for the oral vaccine needs to be developed.

2.2 *Potency*

Potency tests measure the biological activity of a vaccine but do not necessarily reflect the mechanism of protection in humans. Potency measurement is often used to verify the consistency of the manufacturing process. The initial concept of potency testing for vaccines was to quantify the biological activity of the vaccine in comparison with a reference preparation of known bioactivity, where the antigenic component(s) were not well-defined.

Classical challenge studies in animals immunized with the vaccine under consideration have been developed into routine potency assays (e.g. for diphtheria and tetanus toxoids). In the case of the whole-cell pertussis potency assay, which consists of intracerebral challenge of immunized and nonimmunized animals, a correlation was established with clinical protection in humans (*11*). Where no suitable animal

challenge model exists, potency is often based on measurement of immune responses, usually serological (e.g. influenza and hepatitis B vaccines).

More recently, recombinant DNA methodology and modern physicochemical techniques have resulted in the manufacture of highly purified products that can be better characterized than the classic biologicals. However, the ability to measure the "relevant" biological activity for such products may still be lacking. For these products, characterization using physicochemical parameters, such as amount of antigen, size of the antigen, protein content and others can be used as a measure of consistency, but not necessarily of the potency of a vaccine.

For live attenuated vaccines, the approach to potency measurement is generally different. The potency of live viral vaccines is usually based on titration of the minimum infective dose in cell culture or chicken embryos, which may be considered as a surrogate marker of potency, but not as a measure of potency itself. A similar approach is taken to the potency measurement of live attenuated bacterial vaccines, bacille Calmette–Guérin (BCG), and typhoid vaccine (live Ty21A oral), where the number of live organisms present is the measure of potency.

For vaccines that express inserts encoding heterologous vaccine antigens (vaccines based on viral or bacterial vectors), it is not sufficient to determine the "biological activity" of the entire construct by measuring colony forming units (CFU) or infectious titre. For these vaccines, the use of other methods such as the quantitation of the expression of the insert, or the evaluation of the effective dose (ED_{50}) of the vectored vaccine should be considered.

2.3 *Stability*

The evaluation of vaccine stability is complex, as they are very susceptible to inactivation by environmental factors. Potency, as defined in the glossary, should be measured as a part of the stability testing, except in those cases where potency testing based on biological activity is not possible. Physical and chemical product characterization should be included in the stability evaluation. For a product entering human clinical trials, sufficient data should be collected to support the stability of the product for the duration of the preclinical and clinical trial. In certain cases, accelerated stability data may be used to support preliminary data obtained at the normal storage temperature. Stability data to support licensure should be obtained under the proposed storage conditions and should be based on long-term,

real-time stability studies. Finally, the stability of standards and reference materials also needs to be considered to ensure that the procedures used to measure relevant parameters are reliably standardized.

2.4 *International and national guidelines*

The World Health Organization (WHO), through considerable international consultation, develops Recommendations and Guidelines on the production and control of vaccines and other important biologicals (*13*), and these form the basis for assuring the acceptability of products globally. These documents specify the need for appropriate starting materials, including seed lot system and cell banks; strict adherence to established protocols; tests for purity, potency, and safety at specific steps during production; and the keeping of proper records. Guidelines allow greater flexibility than Recommendations with respect to specific issues related to particular vaccines.

WHO also provides Guidelines on manufacturing establishments involved in vaccine production. Recommendations can be found in the WHO document on good manufacturing practice for biologicals (*7*). Particular attention should be given to developing documented standard operating procedures for both production processes and testing procedures. These should be introduced as early as possible during the development of a vaccine and be well established by the time phase III clinical studies are undertaken and an application for marketing authorization is filed. The basic principles for the production and control of vaccines are published in the WHO Technical Report Series (*7*, *14–18*). Specific WHO guidelines and recommendations for particular vaccines are also available and should be consulted where appropriate.

WHO Recommendations and Guidelines are intended to be scientific and advisory in nature and to provide guidance for national regulatory authorities and for vaccine manufacturers. These documents may be adopted by national health authorities as definitive national regulations or used as the basis of such regulations. They are also used as the basis for deciding the acceptability of vaccines for purchase by United Nations agencies such as the United Nations Children's Fund (UNICEF) for use in global immunization programmes. Regulatory requirements for vaccines and other biologicals are also produced by other bodies, such as the European Agency for the Evaluation of Medicinal Products (EMEA) and the US Center for Biologics Evaluation and Research (CBER) (*19*); these documents can be found on the appropriate web sites (www.emea.eu.int and www.fda.gov/cber). In addition, pharmacopoeial requirements, such as those of the

European Pharmacopoeia, are also established for vaccines and are available at www.pheur.org.

For newly developed products, specific WHO, national or pharmacopoeial requirements may not be available and a national regulatory authority will need to agree on specifications with the manufacturer on a case-by-case basis during the evaluation of products for clinical trials and for licensing. For some of these novel products general guidance on production and control from WHO can be found in relevant documents, such as those describing DNA and peptide vaccines (*14*, *16*), as well as recommendations on animal cell substrates used for production of biologicals (*14*).

In addition, information on how to assure the quality of biologicals in general and on procedures for approving manufacture and for setting up a national control laboratory, can be found in the relevant WHO guidelines (*17*, *18*). For a vaccine intended to be marketed worldwide, the development of which also involves much international collaboration, it will be essential to ensure consistency of a regulatory approach for novel products such as vaccines for HIV prevention (*19*).

2.5 *Batch release and independent laboratory evaluation*

The potential variability of methods for the production of biologicals has led to the establishment of national and international requirements to define procedures for assuring the quality of vaccines and for assessing consistency both among manufacturers and over long periods of time. Licensed vaccines are subject to independent batch release (review, testing and authorizing release of a batch of vaccine independent of the manufacturer) by a national regulatory authority or national control laboratory, before release on to the market. Independent evaluation entails at least an evaluation of a manufacturer's batch release data (protocol review), but in many instances it also includes independent laboratory testing in addition to that carried out by the manufacturer.

Batch or lot release tests are those tests chosen during full product characterization to demonstrate the purity, safety and potency of the product. Lot release testing provides one measure of assurance that a lot can be manufactured consistently. Validation and establishment of lot release tests and specifications is a process that continues throughout product development and should be finalized prior to licensure.

In some countries, samples of vaccine for clinical trials are required by the national regulatory authority, as a part of the approval process for clinical trials. Vaccine developers are encouraged to consult the

appropriate regulatory agency early on during the development of a vaccine.

2.6 *Standards and reference materials*

Standards and reference materials play a vital part in the licensing and quality control process, their role ranging from use in specific antigen recognition tests to assays of vaccine toxicity, immunogenicity and potency. The standardization of the methods used to evaluate vaccines, as well as those used to evaluate immune responses to vaccine antigens, is also vital so that results may be compared directly between laboratories both within and between countries, and between clinical trials.

WHO International Biological Standards and Reference Reagents are the primary standards in use worldwide. In addition, national regulatory authorities and manufacturers may establish secondary (regional, national), working standards for the purpose of testing vaccine quality on a lot-to-lot basis. Such standards should be calibrated against International Standards, when they exist. There is concern that different secondary standards may result in "drifting" from the International Standard. Production of secondary standards on a large scale (e.g. on a regional basis) reduces the number of secondary standards in use, and should improve accuracy of testing vaccine quality. For example, the European Department for the Quality of Medicines of the Council of Europe, has been active in establishing working standards for vaccines that are calibrated against the WHO International Standards, where appropriate. The complete list of WHO International Standards and Reference Reagents can be found on the WHO web site at: www.who.int/ biologicals.

3 Immunogenicity and other pharmacodynamic studies

A pharmacodynamic study for a vaccine product is generally conducted to evaluate the immunogenicity. However, a pharmacodynamic study may also extend to include the pharmacology of an adjuvant.

Immunization studies in animal models should be conducted because they may provide valuable "proof of concept" information to support a clinical development plan. In addition, immunogenicity data derived from appropriate animal models are useful in establishing the immunological characteristics of the product and may guide selection of the doses, schedules and routes of administration to be evaluated in clinical trials. Nonclinical immunogenicity studies should assess the relevant immune response, e.g. humoral and/or cell-mediated

immune response, induced in the vaccinated animals. Depending on the immune response induced, such studies may include an evaluation of seroconversion rates, geometric mean antibody titres, or cell-mediated immunity in vaccinated animals. Nonclinical studies should, where possible, be designed to assess relevant immune responses, including functional immune response (e.g. neutralizing antibodies, opsonophagocytic activity, etc.) leading to protection. These studies may also be designed to address interference between antigens and/or live viruses. If a vaccine consists of more than one defined antigen (e.g. acellular pertussis vaccine consisting of 3–5 protein products) the response to each antigen should be evaluated. Where appropriate, challenge/protection studies with the corresponding infectious agent may be conducted to confirm the relevance of the animal models. A primary concern in interpreting the data obtained from such studies should be to determine how closely the animal model resembles the disease and immune response in humans. It should be recognized that animal models frequently fail to predict immunogenicity and efficacy in humans.

4 Toxicity assessment

The nonclinical safety assessment of vaccines needs to be viewed in the context of the evolving field of vaccine development. Thus, judgement based on the best science available should always form the basis for any decisions regarding the need for nonclinical safety studies, types of study and study designs. Similarly, scientific judgement should be applied to the interpretation of data from preclinical studies, regarding the risk–benefit ratio, animal model, dosing etc. For example, the observation of hypersensitivity reactions in an animal model may not necessarily preclude proceeding to clinical trials, but may indicate the necessity for careful monitoring of a particular clinical parameter.

Section 4.1 provides a general framework for designing a preclinical toxicity study for a vaccine. The parameters set out in this section are considered the minimum necessary for a safety assessment prior to the initiation of clinical trials in humans, in situations where preclinical safety studies are deemed necessary. As the design of any toxicity study is product-specific and based on indications, modifications to the framework outlined below may be necessary in response to particular product features, availability of animal models, methodologies, etc.

Section 4.2 provides additional considerations for performing special toxicity assessments that may be required on a case-by-case basis.

4.1 *Basic toxicity assessment*

4.1.1 *Study design*

The preclinical toxicity study should be adequate to identify and characterize potential toxic effects of a vaccine to allow investigators to conclude that it is reasonably safe to proceed to clinical investigation. The parameters to be considered in designing animal toxicology studies are the relevant animal species and strain, dosing schedule and method of vaccine administration, as well as timing of evaluation of end-points (e.g. sampling for clinical chemistry, antibody evaluation and necropsy). The route of administration should correspond to that intended for use in the clinical trials. When the vaccine is to be administered in human clinical trials using a particular device, the same device should be used in the animal study, where feasible (e.g. measles aerosol vaccine in the monkey model). Potential toxic effects of the product should be evaluated with regard to target organs, dose, route(s) of exposure, duration and frequency of exposure, and potential reversibility. The toxicity assessment of the vaccine formulation can be done either in dedicated-stand alone toxicity studies or in combination with studies of safety and activity that have toxicity end-points incorporated into the design. The study should also include an assessment of local tolerance.

4.1.2 *Animal species, sex, age and size of groups*

Data to be recorded on the animals used for toxicity testing should include information on the source, species and animal husbandry procedures (e.g. housing, feeding, handling and care of animals). In general, the use of outbred animals is recommended. The health of the animal will need to be evaluated in accordance with acceptable veterinary medical practice to ensure that animals are free of any condition that might interfere with the study. For instance, individual housing of laboratory animals may be required to minimize the risk of cross-infection.

Where possible, the safety profile of a product should be characterized in a species sensitive to the biological effects of the vaccine being studied. Ideally, the species chosen should be sensitive to the pathogenic organism or toxin. The animal species used should develop an immune response to the vaccine antigen. In general, one relevant animal species is sufficient for use in toxicity studies to support initiation of clinical trials. However, there may be situations in which two or more species may be necessary to characterize the product, for example where the mechanism of protection induced by the vaccine is not well understood (for example, intranasal influenza vaccine and intranasal measles vaccine).

In addition, when species-specific or strain-specific differences in the pharmacodynamics of the product are observed, it may be necessary to address the nonclinical safety of the product in more than one safety study and in more than one animal model.

The size of the treatment group depends on the animal model chosen. The number of animals used in studies using non-human primates would be expected to be less than that in studies that used rodents. For small animal models, e.g. rats and mice, it is recommended that approximately 10 males + 10 females per group be studied.

In general, the approximate age at the start of the study for rodents is 6–8 weeks, and for rabbits, 3–4 months.

4.1.3 *Dose, route of administration and control groups*

The toxicity study should be performed using a dose that maximizes exposure of the animal to the candidate vaccine and the immune response induced, for example, peak antibody response. In general, an evaluation of the dose–response is not required as part of the basic toxicity assessment and the lethal dose does not have to be determined. However, pilot dose–response studies may be conducted to determine which dose induces the highest antibody production in the animal model. If feasible, the highest dose (in absolute terms) to be used in the proposed clinical trial should be evaluated in the animal model. However, the dose is sometimes limited by the total volume that can be administered in a single injection, and guidelines on animal welfare should be followed. In such cases, the total volume may be administered at more than one site using the same route of administration. Alternatively, a dose that exceeds the human dose on a mg/kg basis and that induces an immune response in the animal model may be used. In such cases, the factor between human and animal dose should be justified.

The number of doses administered to the test animals should be equal to or more than the number of doses proposed in humans. To better simulate the proposed clinical usage, vaccine doses should be given at defined time intervals rather than as daily doses; the dosing interval used in the toxicity study may be shorter (e.g. an interval of 2–3 weeks) than the proposed interval in clinical trials in humans. The dosing interval in nonclinical trials may be based on the kinetics of the primary and secondary antibody responses observed in the animal model. A single-dose study may be performed in situations in which vaccine-induced antibodies are expected to neutralize a live viral vector, thus limiting the expression of the gene of interest (e.g. anti-adenovirus immune response), or when immune responses induced in

animals are expected to react with species-specific proteins present in the vaccine formulation (e.g. human recombinant cytokines used as adjuvants).

The route of administration should correspond to that intended for use in the human clinical trials. If toxic effects are observed in safety studies using a particular route of administration (e.g. intranasal), further toxicity studies using a different route of administration (e.g. intravenous) may be helpful in understanding the full spectrum of toxicity of the product.

The study design should include a negative control group(s) to evaluate a baseline level of treatment. If appropriate, active control groups (e.g. vaccine formulation without antigen) may also be included in the study. The study should include an additional treatment group of animals to be killed and evaluated as described below at later time-points after treatment, to investigate the reversibility of any adverse effects observed during the treatment period and to screen for possible delayed adverse effects.

4.1.4 *Parameters monitored*

Toxicity studies should address the potential of the product for causing local inflammatory reactions, and possible effects on the draining lymph nodes, systemic toxicity and on the immune system. A broad spectrum of information should be obtained from the toxicity studies. Parameters to be monitored should include daily clinical observations, weekly body weights and weekly food consumption. During the first week of administration frequent measurements of body weight and food consumption are recommended, if feasible, as these are sensitive parameters indicating "illness". Interim analysis of haematology and serum chemistry should be considered approximately 1–3 days following the administration of the first and last dose and at the end of the recovery period. Haematology and serum chemistry analyses should include, at the minimum, an evaluation of relative and absolute differential white blood cell counts (lymphocytes, monocytes, granulocytes, abnormal cells) and albumin/globulin ratio, enzymes and electrolytes. In some cases, it may also be useful to evaluate coagulation parameters, urine samples and serum immunoglobulin classes. Data should be collected not only during treatment, but also following the recovery phase (e.g. 2 weeks or more following the last dose) to determine persistence, and look at exacerbation and/or reversibility of potential adverse effects.

At study termination, final body weights (after a period of fasting) should be measured. Terminal blood samples should be collected and

serum chemistry, haematology and immunological investigations should be done as described in the preceding paragraph. The immune response induced by the candidate vaccine should be assessed in order to confirm that the relevant animal model has been selected. A complete gross necropsy should be conducted and tissues collected and preserved, gross lesions should be examined and organ weights recorded (*23*). Histopathological examinations of tissues should be performed and special attention paid to the immune organs, i.e. lymph nodes (both local and distant from site of administration), thymus, spleen, bone marrow and Peyer's patches or bronchus-associated lymphoid tissue, as well as organs that may be expected to be affected as a result of the particular route of administration chosen. Histopathological examinations should always include pivotal organs (e.g. brain, kidneys, liver and reproductive organs) and the site of vaccine administration. The choice of tissues to be examined (ranging from a short list limited to immune and pivotal organs to a full list as provided in the Appendix) will depend on the vaccine in question, and the knowledge and experience obtained from previous nonclinical and clinical testing of the vaccine components. For example, full tissue examination will be required in the case of novel vaccines for which no prior nonclinical and clinical data are available. Therefore, the list of tissues to be tested should be defined on a case-by-case basis, following consultation with the relevant regulatory authority. Data should be reported in full listing the original collection of values, and summarized.

4.1.5 *Local tolerance*

The evaluation of local tolerance should be conducted either as a part of the repeated dose toxicity study or as a stand-alone study. Tolerance should be determined at those sites that come into contact with the vaccine antigen as a result of the method of administration, and also at those sites inadvertently exposed (e.g. eye exposure during administration by aerosol) to the vaccine. More details have been published elsewhere (*24*).

If abnormalities are observed in the basic toxicity study outlined in section 4.1., further studies may be necessary to evaluate the mechanism of the toxic effect.

4.2 ***Additional toxicity assessments***

4.2.1 *Special immunological investigations*

In certain cases, the results from evaluations of immune response from nonclinical and clinical studies, or from data on natural disease, may indicate immunological aspects of toxicity, e.g. precipitation of

immune complexes, humoral or cell-mediated immune response against antigenic determinants of the host itself as a consequence of molecular mimicry or exacerbation of the disease (e.g. inactivated measles vaccine). In such cases, additional studies to investigate the mechanism of the effect observed might be necessary.

Great similarity of vaccine determinants and host molecules could cause autoimmune reactions induced by molecular mimicry (*26*). Therefore, any vaccine antigen whose characteristics might mimic those of a host antigen should be treated with caution, even though it is recognized that molecular mimicry does not necessarily predispose to autoimmunity.

Because considerable efforts may be required in selecting and developing relevant animal models to address the above issues, caution should be exercised and a strong rationale provided when developing vaccines for diseases associated with autoimmune pathology.

If data suggest that the pathogen against which the vaccine is directed may cause autoimmune pathology, studies may be needed to address this concern on a case-by-case basis, if an appropriate animal model exists.

It should be noted that observations of biological markers for autoimmune reactions are not necessarily linked to pathogenic consequences. For instance, the presence of autoimmune antibodies does not necessarily indicate the induction of autoimmune disease (*25*).

When hypersensitivity reactions induced by the antigen(s), adjuvants, excipients or preservatives are of concern, additional investigations may be warranted.

4.2.2 *Developmental toxicity studies*

Developmental toxicity studies are usually not necessary for vaccines indicated for immunization during childhood. However, if the target population for the vaccine includes pregnant women and women of childbearing potential, developmental toxicity studies should be considered, unless a scientific and clinically sound argument is put forward by the manufacturer to show that conducting such studies is unnecessary. For a preventive vaccine, reproductive toxicity assessments are generally restricted to prenatal and postnatal developmental studies, because the primary concern is any potential untoward effect on the developing embryo, fetus or newborn. The need to conduct fertility and post-weaning assessments should be considered on a case-by-case basis. The animal model chosen should develop

an immune response to the vaccine, which is usually determined by serum antibody measurements. In addition, it is important to evaluate maternal antibody transfer by measuring vaccine-induced antibody in cord or fetal blood to verify exposure of the embryo or fetus to maternal antibody. The route of administration should mimic the clinical route of administration. Ideally, the maximal human dose should be administered to the test animal. If it is not possible to administer the full human dose, e.g. limitations on the total volume that can be administered, or if local toxicity is observed that may result in maternal stress, a dose that exceeds the human dose on a mg/kg basis and is able to induce an immune response in the animal should be used.

To assess any potential adverse effects of the vaccine during the period of organogenesis, the gestating animal is usually exposed to the vaccine during the period from implantation until closure of the hard palate and end of gestation defined as stages C, D and E in the ICH S5a document (*27*). Because of the relatively short gestation period of most animal models used, pre-mating treatment is frequently required to ensure maximal exposure of the embryo or fetus to the vaccine-induced immune response. For a preventive vaccine, the number of doses administered depends on the time of onset and duration of the response. Booster immunizations may be necessary at certain times during the period of gestation to maintain a high level of antibody throughout the gestation period and to expose the developing embryo to the components of the vaccine formulation. End-points include, but are not limited to, viability, resorptions, abortions, fetal body weight and morphology. The reader is referred to other publications for guidance on end-points used to evaluate potential toxic effects of the product on development of the embryo or fetus (*27*). It is also recommended that a period of postnatal follow-up of pups from birth to weaning be incorporated in the study design to assess normality of growth, body weight gain, suckling activity and viability. Studies should therefore be designed so that test groups are divided into subgroups. Half of the animals should be delivered by Caesarean section and the other half allowed to deliver their pups without surgical intervention.

4.2.3 *Genotoxicity and carcinogenicity studies*

Genotoxicity studies are normally not needed for the final vaccine formulation. However, they may be required for particular vaccine components such as novel adjuvants and additives. If needed, the in vitro tests for mutations and chromosomal damage should be done prior to first human exposure. The full battery of tests for genotoxicity may be performed in parallel with clinical trials (*28*).

Carcinogenicity studies are not required for vaccine antigens. However, they may be required for particular vaccine components such as novel adjuvants and additives.

4.2.4 *Safety pharmacology*

The purpose of safety pharmacology is to investigate the effects of the candidate vaccine on vital functions. If data from nonclinical and/or human clinical studies suggest that the vaccine (e.g. one based on specific toxoids) may affect physiological functions (e.g. central nervous system, respiratory, cardiovascular and renal functions) other than those of the immune system, safety pharmacology studies should be incorporated into the toxicity assessment. Useful information on this topic can be found in the *Note for Guidance on safety pharmacology studies for human pharmaceuticals* (*29*).

4.2.6 *Pharmacokinetic studies*

Pharmacokinetic studies (e.g. for determining serum or tissue concentrations of vaccine components) are normally not needed. The need for specific studies should be considered on a case-by-case basis (e.g. when using novel adjuvants or alternative routes of administration) and may include local deposition studies that would assess the retention of the vaccine component at the site of injection and its further distribution (e.g. to the draining lymph nodes). Distribution studies should be considered in the case of new formulations, novel adjuvants or when alternative routes of administration are intended to be used (e.g. oral or intranasal).

5 Special considerations

5.1 *Adjuvants*

Adjuvants may be included in vaccine formulations or co-administered with vaccines to enhance the immune responses to particular antigen(s), or to target a particular immune response. It is important that the adjuvants used comply with pharmacopoeial requirements where they exist, and that they do not cause unacceptable toxicity.

Adjuvant activity is a result of many factors and the immune response obtained with one particular antigen/adjuvant formulation cannot, as a rule, be extrapolated to another antigen. Individual antigens vary in their physical and biological properties and antigens may interact differently with an adjuvant. Adjuvants must be chosen according to the type of immune response desired and they must be formulated with the antigen in such a way that distribution of both is optimized to ensure availability to the relevant lymphatic tissues. The route of

administration of the vaccine is also an important factor influencing the efficacy and safety of an adjuvant.

The effect of the adjuvant should be demonstrated in preclinical immunogenicity studies. If no toxicological data exist for a new adjuvant, toxicity studies of the adjuvant alone should first be performed. In general, assessment of new or novel adjuvants should be undertaken as required for new chemical entity (*30–32*). These data may be obtained by the vaccine manufacturer or by the producer of the adjuvant. In addition to assessing the safety of the adjuvant by itself it is also important to assess whether the combination of antigen and adjuvant exerts a synergistic adverse effect in the animal model (*33*, *34*). When species-specific proteins (e.g. cytokines) are used as novel adjuvants, the issue of species-specific response should be considered.

When evaluating the safety profile of the combination of adjuvant and vaccine, the formulation proposed for clinical use should be used.

Compatibility of the adjuvant(s) (e.g. lack of immune interference) with all antigenic components present in the vaccine should be evaluated.

If applicable, adsorption of all antigenic components present in the vaccine should be shown to be consistent on a lot-to-lot basis. Potential desorption of antigen during the shelf-life of the product should be performed as a part of stability studies, the results reported and specifications set, as this may affect not only immunogenicity, but also the toxicity profile of the product.

It should be noted that no adjuvant is licensed in its own right, but only as a component of a particular vaccine.

5.2 *Additives (excipients and preservatives)*

Where a new additive is to be used, for which no toxicological data exist, toxicity studies of the additive alone should first be performed and the results documented according to the guidelines for new chemical entities (*31*). The compatibility of a new additive with all vaccine antigens should be documented together with the toxicological profile of the final vaccine formulation under consideration in animal models as outlined in section 4.

5.3 *Vaccine formulation and delivery device*

The vaccine formulation (i.e. liquid form, capsules or powder), as well as the delivery device, may have an impact on the uptake of

the vaccine, its effectiveness and safety. Ideally, the delivery device and vaccine formulation tested in an animal safety study should be identical to those intended to be used clinically. However, animal models in which delivery devices intended for clinical use can be tested may not be available. In these instances, in order to develop an appropriate animal model, it may be necessary to conduct pilot studies to define and optimize the conditions for drug delivery in the animal model before it can be used to assess the preclinical safety of the product.

5.4 *Alternative routes of administration*

When using a vaccine formulation administered by alternative routes (e.g. intranasal, oral, intradermal, rectal and intravaginal routes), it can be assumed that their potency, relevant immunogenicity, tolerability, toxicity, and long-term safety may differ from that of products delivered by the parenteral route. Thus, when different routes of administration are proposed, nonclinical safety studies may have to be conducted using vaccine formulation and/or adjuvant alone in a suitable animal model to address the specific safety concerns associated with vaccine administration by these routes. Particular issues relevant to vaccines administered using alternative routes that may need to be considered are discussed below.

5.4.1 *Animal models*

A special consideration for vaccines administered by alternative routes should be the anatomy and physiology of the site of vaccine administration of the particular animal model chosen and its accessibility for the administration of the vaccine. For example, for intranasally administered products, the species chosen should ideally be receptive to spray administration of the product. In general, rabbits and dogs are useful test models for use of spray devices; however, their olfactory bulbs are highly protected and special techniques would be required to ensure that the test product reached this organ. Although mice and rats are useful models, intranasal administration to these species presents technical difficulties. Intranasal administration to non-human primates may be preferable, if they are susceptible to the infectious agent in question.

Depending on the level of concern regarding a particular route of administration or when there are species-specific differences between the animal models in their sensitivity to the candidate vaccine, it may be necessary to address the preclinical safety of the product in more than one safety study and in more than one animal model.

5.4.2 *Dose*

As the optimal dose derived from studies using the parenteral route of administration may differ from the dose used for alternative route(s) of administration, dose-finding studies may need to be conducted for a particular route of administration. Also, consideration should be given to the total volume of the vaccine administered as it may affect the outcome of the safety study. For example, intranasal administration of more than 5 µl of test preparation per nostril to a mouse would result in the test preparation being swallowed, rather than being adsorbed by the nasal mucosa.

5.4.3 *End-points*

The toxicity end-points would include those described in section 4 and may include additional outcome measures that would depend on the route of administration and specific concerns associated with the particular route and target organ. For example, if there is concern about the potential passage of vaccine components to the brain following intranasal administration, immunohistology and "in situ" methods and/or neurological assays and examinations may be necessary. For vaccines administered by inhalation, outcome measures may include pulmonary function tests and data on histopathology of the lungs. Considerable efforts may be required to develop appropriate methods to address potential safety concerns associated with the use of new routes of administration.

5.4.4 *Immunogenicity assessment*

The development of appropriate assays for measuring mucosal immune responses is critical for vaccines that are expected to function as mucosal immunogens because serological assays alone may not reflect the relevant immune response for a mucosal vaccine. Thus, in addition to measuring serological responses, it may be necessary to evaluate T cell responses, antibody-secreting cells and cytokine production. In addition, assays may need to be developed to assess the induction of local and systemic responses at sites distant from administration of the vaccine antigen.

6 Specific considerations for particular types of vaccines

In addition to the testing strategies outlined in sections 3, 4 and 5, studies may be necessary to address specific safety concerns associated with particular product types using suitable in vitro and in vivo test methods. The specific testing requirements for live attenuated and combination vaccines are discussed below. Detailed information regarding the production and control of other types of vaccine is available in the WHO guidance documents for production and con-

trol (13), and should be consulted. For example, in the recently developed guidelines for DNA (16) and synthetic peptide vaccines (18, 35), as well as for particular vaccines such as Hib conjugated vaccine (26), the issues relevant for nonclinical testing are discussed and should be considered in the development of an appropriate design for the nonclinical study of the vaccine in question.

6.1 *Live attenuated vaccines*

An assessment of the degree of attenuation, and the stability of the attenuated phenotype, are important considerations for the nonclinical testing programme of a live attenuated vaccine. Laboratory markers of attenuation are invaluable for this purpose. These markers should be capable of distinguishing the attenuated vaccine from fully virulent wild-type strains and, ideally, of detecting partial reversion to full virulence. To assess the stability of the attenuation phenotype, the vaccine may be passaged under production conditions beyond the maximum passage number to be used for production. Stability of attenuation may also be assessed by passage under conditions that are outside the conditions to be used for vaccine production. For example, higher or lower temperatures may exert selection pressure for reversion to virulence. The marker(s) of attenuation may subsequently be used to qualify new vaccine seed preparations and to monitor the effect of any significant changes in production conditions of the attenuated phenotype.

If the wild-type organism is neurotropic, or if passages through neural tissue have been used in the attenuation of a virus vaccine, then a test for neurovirulence should be performed at least at the level of the vaccine seed. A neurovirulence test is not necessarily required for all live attenuated vaccines. The specifications for an appropriate neurovirulence test depend on the organism under test and should be capable of distinguishing the attenuated vaccine from fully virulent wild-type strains and, ideally, of detecting partial reversion to full virulence. Specific reference preparations may be needed for this purpose. Neurovirulence tests in small animal models may be acceptable.

If the live attenuated vaccine is based on a genetically modified organism, then an environmental risk assessment may be required as part of the preclinical evaluation. An investigation into the possible shedding of vaccine organisms following administration contributes to the environmental risk assessment. For all live attenuated vaccines, information on the likelihood of exchange of genetic information with non-vaccine strains may be required and suitable nonclinical tests may be designed to provide data for this purpose.

6.2 *Combined vaccines*

New combinations produced either by formulation or at the time of reconstitution of antigens or serotypes should be studied for appropriate immunogenicity in an animal model, if available, before initiation of human clinical trials (*36*, *37*). Combined antigens should be examined by appropriate physicochemical means to evaluate possible changes to antigen properties on combination, such as degree of adsorption to aluminium adjuvants, as well as stability of the combination.

The immune response to each of the antigens in the vaccine should be assessed, including the quality of response and any potential interference and incompatibilities between combined antigens. It is preferable to study a new combination in comparison with the individual antigens in animals to determine whether augmentation or diminution of response occurs.

The need to evaluate the safety of the new combination in an animal model should be considered on a case-by-case basis. Such evaluation is likely to be necessary if there is concern that combining antigens and/or adjuvants may lead to problems of toxicity (e.g. novel adjuvant).

Similar consideration for nonclinical testing will also apply to cases where a new candidate single-component vaccine is developed from an already licensed combined vaccine (e.g. monovalent oral polio vaccine versus trivalent oral polio vaccine).

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References

1. WHO guidelines for clinical evaluation of vaccines: regulatory expectations. In: *WHO Expert Committee on Biological Standardization. Fifty-second Report*. Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 924 Annex 1).
2. *Biological standardization and control. A scientific review commissioned by the UK National Biological Standards Board*. Geneva, World Health Organization, 1997 (WHO/BLG/97.1).
3. *Biotechnology and world health. Risks and benefits of vaccines and other medical products produced by genetic engineering. Proceedings of a WHO meeting*. Geneva, World Health Organization, 1997 (WHO/VRD/BLG/97.01).
4. *WHO Manual of laboratory methods for testing vaccines used in the WHO Expanded Programme on Immunization*. Geneva, World Health Organization, 1997, Annex 1 (WHO/VSQ/97.04).
5. World Health Organization. *Laboratory biosafety manual*, 2nd ed. (revised) Geneva, World Health Organization, 2003.
6. *OECD principles on Good Laboratory Practice* (revised 1997). Paris, Organisation for Economic Co-operation and Development, 1997 (ENV/MC/CHEM (98) 17).
7. Good manufacturing practices for biological products. In: *WHO Expert Committee on Biological Standardization. Forty-second Report.* Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 822):20–30.
8. Good manufacturing practice: supplementary guidelines for the manufacture of the investigational pharmaceutical products for clinical trials in humans. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations: Thirty-Fourth Report.* Geneva, World Health Organization, 1996, Annex 7 (WHO Technical Report. Series, No. 863).
9. Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second*

Report. Geneva, World Health Organization, 1992 Annex 1 (WHO Technical Report Series, No. 823).

10. *Note for guidance on comparability of medicinal products containing biotechnology-derived proteins as drug substance*. London, Committee for Proprietary Medicinal Products, 2000 (CPMP/BWP/3207/00).

11. European Commission Regulations No. 541/95, 542/95, 1146/98 and 1069/98.

12. Griffiths E. Efficacy of whole-cell pertussis vaccine. In: Wardlaw AC, Parton R, eds. *Pathogenesis and immunity in pertussis*. Chichester, Wiley, 1988: pp. 353–374.

13. Recommendations and guidelines for biological substances used in medicine and other documents. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 910):99–102.

14. Requirements for the use of animal cells as *in vitro* substrates for the production of biologicals. In: *WHO Expert Committee on Biological Standardization. Forty-seventh Report*. Geneva, World Health Organization, 1998, Annex 1 (WHO Technical Report Series, No. 878).

15. *Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products*. Geneva, World Health Organization, 2003 (WHO/BCT/QSD/03.01).

16. Guidelines for assuring quality of DNA vaccines. In: *WHO Expert Committee on Biological Standardization. Forty-seventh Report.* Geneva, World Health Organization, 1998, Annex 3 (WHO Technical Report Series, No. 878).

17. Guidelines for assuring the quality of pharmaceutical and biological products prepared by recombinant DNA technology. In: *WHO Expert Committee on Biological Standardization. Forty-first Report*. Geneva, World Health Organization, 1991, Annex 3 (WHO Technical Report Series, No. 814).

18. Guidelines for the production and quality control of synthetic peptide vaccines. In: *WHO Expert Committee on Biological Standardization. Forty-eighth Report*. Geneva, World Health Organization, 1999, Annex 1 (WHO Technical Report Series, No. 889).

19. *Guidance for industry: content and format of chemistry, manufacturing and controls information and establishment description information for a vaccine or related product*. *Federal Register*, 1999, **2**:518–519 (Center for Biologics Evaluation and Research, US Food and Drug Administration).

20. Guidelines for national authorities on quality assurance for biological products. In: *WHO Expert Committee on Biological Standardization. Forty-second Report.* Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 822):31–46.

21. Regulation and licensing of biological products in countries with newly developing regulatory authorities. In: *WHO Expert Committee on Biological Standardization. Forty-fifth Report.* Geneva, World Health Organization, 1995 (WHO Technical Report Series No. 858):21–35.

22. Scientific considerations for the regulation and clinical evaluation of HIV/AIDS preventive vaccines: report from a WHO–UNAIDS Consultation 13–15 March 2001, Geneva Switzerland. *AIDS*, 2002, **16**:W15–W25.

23. *Note for guidance on repeated dose toxicity*. London, Committee for Proprietary Medicinal Products, 1999 (CPMP/SWP/1042/99).

24. *Note for guidance on non-clinical local tolerance testing of medicinal products.* London, Committee for Proprietary Medicinal Products, 2000 (CPMP/SWP/2145/00).

25. **Wraith DC, Goldman M, Lambert PH.** Vaccination and autoimmune disease: what is the evidence? *Lancet*, 2003, **362**:1659–1666.

26. Recommendations for *Haemophilus influenzae* type b conjugate vaccines. In: *WHO Expert Committee on Biological Standardization. Forty-ninth Report.* Geneva, World Health Organization, 2000 (WHO Technical Report Series, No. 897).

27. *Note for guidance for reproductive toxicology: detection of toxicity to reproduction for medicinal products*. London, Committee for Proprietary Medicinal Products (CPMP/ICH/386/95).

28. *Note for guidance on genotoxicity: a standard battery for genotoxicity testing of pharmaceuticals*. London, Committee for Proprietary Medicinal Products, 1995 (CPMP/ICH/174/95).

29. *Note for guidance on safety pharmacology studies for human pharmaceuticals*. London, Committee for Proprietary Medicinal Products (CPMP/ICH/539/00).

30. ICH M3(M) *Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals*. London, Committee for Proprietary Medicinal Products, 2000 (CPMP/ICH/286/95 modification).

31. *Guidance for industry: nonclinical studies for development of pharmaceutical excipients*. Draft. September 2002.

32. *Note for guidance on excipients, antioxidants and antimicrobial preservatives in the dossier for application for marketing authorisation of a medicinal product.* London, Committee for Proprietary Medicinal Products, 2003 (CPMP/QWP/419/03).

33. *Note for guidance on preclinical pharmacological and toxicological testing of vaccines*. London, Committee for Proprietary Medicinal Products, 1998 (CPMP/SWP/465/95).

34. **Goldenthal KL, Cavagnaro JA, Alving CR, Vogel FR.** Safety evaluation of vaccine adjuvants: National Cooperative Vaccine Development Meeting Working Group. *AIDS Research and Human Retroviruses*, 1993, **9**(suppl 1):S47–S51.

35. *Guidance for industry for the submission of chemistry, manufacturing, and controls information for synthetic peptide substances*. Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, 1994.

36. **Verdier F, Patriarca C, Descotes J.** Autoantibodies in conventional toxicity testing. *Toxicology*, 1997, **119**:51–58.

37. *Guidance for industry for the evaluation of combination vaccines for preventable diseases: production, testing and clinical studies*. US Food and Drug Administration, 1997.

38. *Note for guidance on pharmaceutical and biological aspects of combined vaccines*. London, Committee for Proprietary Medicinal Products, 1999 (CPMP/BWP/477/97). Geneva, World Health Organization, 2003.

Appendix

List of tissues to be collected in a repeated dose toxicity study

adrenal glands

aorta

bone (femur) and articulation

bone (sternum) with bone marrow

bone marrow smears[1]

brain

bronchi (main-stem)

caecum

colon

duodenum

epididymides

eyes

heart

ileum

injection site(s) (a sample should be taken from the area of injection)

jejunum

kidneys and ureters

larynx

liver

lungs

lymph node (mandibular)

lymph node (mesenteric)

mammary gland

oesophagus

optic nerves

[1] Bone marrow smears should be prepared at the scheduled necropsy for all animals including any moribund animals killed during the study. The smears should be fixed in methanol and then stained by the May-Grunwald-Giemsa method.

ovaries and oviducts
pancreas
parathyroid glands
Peyer's patches
pituitary gland
prostate
rectum
salivary glands (mandibular, parotid, sublingual)
sciatic nerves
seminal vesicles
skeletal muscle
skin
spinal cord (cervical, thoracic, lumbar)
spleen
stomach
testes
thymus
thyroid glands
tongue
trachea
ureters
urinary bladder
uterus (horns + cervix)
vagina
all gross lesions

Annex 2

Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines

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Guidelines published by WHO are intended to be scientific and advisory in nature. Each of the following sections constitutes guidance for national regulatory authorities (NRAs) and for manufacturers of biological products. If an NRA so desires, these Guidelines may be adopted as definitive national requirements, or modifications may be justified and made by the NRA. It is recommended that modifications to these Guidelines are made only on condition that such modifications ensure that the product is at least as safe and efficacious as that prepared in accordance with the guidance set out below.

Introduction

These Guidelines are intended to provide guidance to NRAs and manufacturers on the nonclinical and initial clinical evaluation of vaccine adjuvants and adjuvanted vaccines by outlining international regulatory expectations in this area. The Guidelines should be read in conjunction with existing WHO guidelines on nonclinical (*1*) and clinical (*2*) evaluation of vaccines. There is substantial diversity among vaccine adjuvants and adjuvanted vaccines and their nonclinical and clinical testing programmes will depend upon product-specific features and their clinical indications. Therefore, the following text is written in the form of WHO Guidelines instead of Recommendations. Guidelines allow greater flexibility than Recommendations with respect to specific issues related to particular adjuvanted vaccines.

Over the past decades, strategies and approaches for the development and delivery of vaccine antigens have been expanded. Some of these antigens are weakly immunogenic and require the presence of adjuvants for the induction or enhancement of an adequate immune response. Vaccines with aluminium-based adjuvants have been used extensively in immunization programmes worldwide and a significant body of safety information has accumulated for them (*3*, *4*). As the knowledge of immunology and the mechanisms of vaccine adjuvant action have developed, the number of vaccines containing novel adjuvants being evaluated in clinical trials has increased. Vaccines containing adjuvants other than aluminium-containing compounds have been authorized for use in many countries (e.g. human papillomavirus and hepatitis B vaccines), and a number of vaccines with novel adjuvants are currently under development, including, but not limited to, vaccines against human immunodeficiency virus (HIV), malaria and tuberculosis, as well as new-generation vaccines against influenza and other diseases. However, the development and evaluation of adjuvanted vaccines present regulatory challenges. Vaccine manufacturers and regulators have questions about the type of information and extent of data that would be required to support proceeding to clinical trials with adjuvanted vaccines and to eventual authorization.

Existing WHO guidelines on nonclinical evaluation of vaccines (*1*) provide valuable general guidance; however, they provide limited information specifically related to new adjuvants and adjuvanted vaccines. Some of the issues addressed here are also discussed in national or regional guidance documents (*5*, *6*). Given the importance and the complexity of the issues, this updated and more extensive guidance on the nonclinical and preclinical testing of adjuvants and adjuvanted vaccines should allow manufacturers and regulators to proceed in an efficient manner on the critical path towards development and licensure of adjuvanted vaccines indicated for the control of diseases with an important global public health impact.

Background

Over the past decades, there have been a number of international workshops and meetings in which the issues covered by these WHO Guidelines have been discussed (*7–12*). To address the need for additional international guidance on nonclinical evaluation of adjuvanted vaccines, a consultation was organized by WHO on 7–8 September 2011 in Rockville, Maryland, United States, to initiate the process of developing new WHO guidance on the subject. The consultation was attended by experts from academia, NRAs, national control laboratories and industry involved in the research, manufacture and approval of adjuvanted vaccines from countries around the world. The purpose was to review the scientific information and available data and to discuss and identify the issues to be considered for the development of such international guidance. On 27–28 November 2012, WHO organized an informal consultation at its headquarters in Geneva, Switzerland attended by academics, researchers, vaccine manufacturers and regulators involved in the evaluation of adjuvanted vaccines, to review draft WHO Guidelines prepared by the drafting group and to seek consensus on key regulatory issues. The approaches to nonclinical and initial clinical evaluation of vaccine adjuvants and adjuvanted vaccines discussed in this document are a result of the efforts of this and other international working groups.

Scope

This document addresses regulatory considerations related to the nonclinical and initial clinical evaluation of adjuvanted vaccines. The goal of this document is to provide consistent and harmonized guidance on nonclinical testing approaches to support the use of candidate adjuvanted vaccines in all stages of clinical development and ultimately for marketing authorization of the product. However, each NRA may determine the regulatory requirements applicable for adjuvanted vaccines to be marketed and used in their country.

Vaccine adjuvants are substances or combinations of substances that are used in conjunction with a vaccine antigen to enhance (e.g. increase, accelerate, prolong and/or possibly target) or modulate to a different type (e.g. switch a Th1 immune response to a Th2 response, or a humoral response to a cytotoxic T-cell response) the specific immune response to the vaccine antigen in order to enhance the clinical effectiveness of the vaccine (see "Terminology" section below). For the purposes of this document, the term "adjuvant" includes formulations that contain one individual adjuvant as well as adjuvant combinations that contain multiple adjuvants. These WHO Guidelines specifically address vaccine adjuvants that are either separate substances that are mixed with vaccine antigens and administered at the same time and location as the vaccine antigen, or immunostimulatory

moieties that are engineered by recombinant DNA technology to be an inherent part of the antigen molecule (e.g. fusion proteins) or the immunogen (e.g. vectored vaccines). In this context, it should be noted that no vaccine adjuvant is authorized in its own right, but only as a component of a particular adjuvanted vaccine. This document does not deal with the carrier proteins that are covalently linked to polysaccharide antigens in conjugate vaccines. Also, the immune enhancing properties that are intrinsic to certain vaccine antigen preparations, such as the naturally occurring adjuvant activity of whole-cell pertussis vaccines, are not considered "adjuvants" within this document.

This document covers adjuvanted vaccines used in both prophylactic and therapeutic indications against infectious diseases. Nevertheless, some of the principles outlined below may be applicable to the nonclinical and initial clinical testing of adjuvanted therapeutic vaccines for other indications as well (e.g. cancer).

Nonclinical evaluation, within the context of this document, refers to all in vivo (in animal) and in vitro testing performed before and during the clinical development of adjuvanted vaccines and includes product characterization, proof-of-concept and immunogenicity studies, as well as safety testing in animals. Preclinical testing specifically refers to the nonclinical testing done prior to initiation of any human testing and is a prerequisite to movement of a candidate adjuvanted vaccine from the laboratory to the clinic. Thus, for the remainder of this document, the term "preclinical" will be used only when referring specifically to the nonclinical evaluation done prior to the first-in-human clinical trials.

Many regulatory agencies, in addition to defining an adjuvant based on its immune-enhancing biological activity, provide a regulatory and/or legal classification for the adjuvant component of a vaccine (e.g. excipient, active ingredient or constituent material). It is possible that depending on the particular definition used by the regulatory authority, additional testing may be required. These regulatory and legal issues are specific for each regulatory authority and are beyond the scope of this document.

General considerations

Adjuvants have been used for decades to enhance the immune response to vaccine antigens (*7*). Possible benefits of administering antigens in conjunction with adjuvants include the induction of long-term protection, better targeting of effector responses, induction of long-term memory, reduction of the antigen amount and/or the number of vaccine doses needed for a successful immunization and optimization of the immune response for populations with poor responsiveness. For certain complex diseases, stimulation of cell-mediated immune responses appears to be critical, and adjuvants can be employed to

optimize a desired immune response, such as the induction of cytotoxic or helper T lymphocyte responses. In addition, certain adjuvants can be used to promote antibody responses in a relevant immunoglobulin class or at mucosal surfaces.

Successful preclinical evaluation of adjuvanted vaccines, including physicochemical characterization, proof-of-concept testing in animals, and toxicity testing, is an important step towards their clinical development. In addition, studies in animals are valuable tools to help select a safe dose, schedule and route of administration, and to identify unexpected or potential adverse effects for specific monitoring in clinical trials. Safety concerns include potential inherent toxicities of the vaccine antigen and/or adjuvant, potential toxicities of any impurities and contaminants, and potential toxicities due to interactions of the components present in the final formulation. The regulatory considerations for adjuvanted vaccines are similar to those for vaccines in general, with additional issues being considered that are unique to novel adjuvants. For the purposes of these WHO Guidelines, a novel adjuvant is defined as an adjuvant that has not been included in a licensed vaccine.

Throughout this document, guidance is provided related to the evaluation of new adjuvants and adjuvanted vaccines, to include:

- unlicensed adjuvanted vaccines;
- antigens and adjuvants that have been included in licensed vaccines, but for which the production process has undergone significant changes;
- previously licensed products that have undergone major formulation changes (e.g. a change in adjuvant or addition or removal of one of the components);
- previously licensed products given by a new route of administration.

Where appropriate, considerations specific to the evaluation of novel adjuvants will be provided.

The established benefits and increased availability of adjuvants have stimulated an interest in transferring adjuvant production technology from one adjuvant or adjuvanted vaccine manufacturer to another. As stated above, adjuvants are not approved in their own right. In the context of vaccines against infectious diseases, adjuvants may only exist as components in licensed vaccines that consist of specific antigen/adjuvant combinations. Thus, each new adjuvanted vaccine is considered a new entity that will require appropriate physicochemical characterization and nonclinical and clinical evaluations. However, in cases of technology transfer, existing data from similar antigen and adjuvant components and/or adjuvanted vaccines held by the original manufacturer can provide important information to guide and potentially accelerate the nonclinical and clinical studies (e.g. data from adjuvant-alone study arms). The need for and

extent of nonclinical testing will depend on the adjuvanted vaccine under consideration; manufacturers are encouraged to consult with the NRA regarding the nonclinical testing needed.

Vaccine adjuvants have been divided broadly into two main types – those known as vaccine delivery systems, which enhance the delivery of the antigen to the local lymph node, and those known as immunostimulators, although this division has become less clear since some delivery systems are now known to have direct immune stimulatory effects in addition to their ability to enhance the delivery of the antigen to the local lymph node. Delivery systems include, but are not limited to, particles, carriers, emulsions and liposomes. Immunostimulators in general include substances that enhance the immune response to vaccine antigens by activating the innate immune system, which usually sets off a cascade of events including, but not limited to, increased antigen uptake into antigen-presenting cells, increased release of stimulatory molecules such as cytokines and increased localization of the antigen in the local lymph node. Immunostimulators may include cytokines or other substances that are generally described as "immune potentiators" because they exert direct effects on immune cells.

Adjuvants also can be classified according to their source (e.g. synthetic or microbial-derived), mechanism of action and physical or chemical properties. A list of the most commonly described adjuvant classes, with specific examples, is provided in Appendix 1. It should be noted that a given vaccine adjuvant may be a combination adjuvant (see "Terminology" section below) that consists of multiple types of adjuvants and thus can fall into more than one of the listed categories.

Terminology

The definitions given below apply to the terms used in these WHO Guidelines. They may have different meanings in other contexts.

Adjuvanted vaccine: the complete formulation that includes one or more antigens, an adjuvant(s), and any additives (which may include, for example, excipients or preservatives), the administration of which is intended to stimulate the immune system to result in an immune response that leads to the prevention or treatment of an infection or infectious disease.

First-in-human trial: for the purposes of this document, this refers to the first evaluation in human subjects. Most commonly, the first-in-human clinical trials are carried out in small numbers of healthy and immunocompetent adults to test the properties of a vaccine, its tolerability and, if appropriate, clinical laboratory and pharmacological parameters. These trials are considered phase I trials (*2*) and are primarily concerned with safety.

Good laboratory practice (GLP): a quality system concerned with the organizational process and the conditions under which nonclinical health and environmental safety studies are planned, performed, monitored, recorded,

archived and reported. GLP principles may be considered as a set of criteria to be satisfied as a basis for ensuring the quality, reliability and integrity of studies, the reporting of verifiable conclusions and the traceability of data (*1*, *13*).

Good manufacturing practice (GMP): a part of the pharmaceutical quality assurance which ensures that products are consistently produced and controlled according to the quality standards appropriate to their intended use and as required in the marketing authorization. In these Guidelines, GMP refers to the current GMP guidance published by WHO (*14*, *15*).

Immunogenicity: the capacity of a vaccine/adjuvanted vaccine to induce antibody-mediated immunity, cell-mediated immunity and/or immunological memory.

In vitro studies: refers to studies that are conducted in a laboratory environment using components (e.g. serum, cells or tissues) that were originally obtained from a living organism.

In vivo studies: refers to studies that are conducted with living organisms.

Nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines: nonclinical testing includes all in vivo and in vitro testing performed before and in parallel with the clinical development of adjuvanted vaccines. Nonclinical testing includes product characterization, proof-of-concept studies and animal in vivo/in vitro toxicity testing. The potential toxicity of an adjuvanted vaccine should be defined not only prior to initiation of human trials, but throughout clinical development, if appropriate (see also the definition of preclinical evaluation of vaccine adjuvants and adjuvanted vaccines).

Novel adjuvant: a novel adjuvant is an adjuvant that has not been contained in a licensed vaccine.

Potency: a measure of biological activity, using a suitably quantitative biological assay, based on an attribute of the product (e.g. adjuvanted vaccine) that is believed to be linked to the relevant biological properties. Other measures of potency (e.g. physicochemical analyses) may be appropriate based on the nature of the products (e.g. polysaccharides).

Preclinical evaluation of vaccine adjuvants and adjuvanted vaccines: preclinical testing refers specifically to the nonclinical testing (see definition of nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines) done prior to the first-in-human clinical trials. Preclinical evaluation is a prerequisite to the initiation of clinical trials.

Process intermediates: the antigen(s) and the adjuvant(s) used to produce the formulated adjuvanted vaccine.

Product characterization: a full battery of physical, chemical and biological tests conducted for a particular product (e.g. adjuvanted vaccine). These tests include, but are not limited to, in-process control testing, testing for adventitious agents, testing of process additives and process intermediates, and lot-release testing (*1*).

Proof-of-concept studies: proof-of-concept studies as discussed in this document include the in vivo and in vitro nonclinical testing conducted to evaluate the immune response to the adjuvanted vaccine, the enhancement of the immune response to the antigen by the adjuvant and/or the demonstration of the resulting protection against challenge with the infectious agent targeted by the adjuvanted vaccine. For therapeutic vaccines, proof-of-concept studies would include, when possible, studies to evaluate the capacity to control or ameliorate disease and/or clear infection.

Protocol or study/trial plan: a document that states the background, rationale and objectives of the nonclinical study or clinical trial, and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed (*1*).

Raw materials: ingredients used to produce process intermediates.

Route of administration: the means by which the candidate adjuvanted vaccine is introduced to the recipient. Routes of administration for adjuvanted vaccines may include, for example, the intramuscular, subcutaneous, transcutaneous (with or without scarification), intradermal, oral, intranasal, inhaled (aerosol), intravenous, intranodal, intravaginal or intrarectal routes.

Safety: the relative freedom from direct or indirect harmful effect to animals or persons by a product when appropriately administered, taking into consideration the character of the product in relation to the condition of the recipient at the time.

Vaccine adjuvants: substances or combinations of substances that are used in conjunction with a vaccine antigen to enhance (e.g. increase, accelerate, prolong and/or possibly target) or modulate to a different type (e.g. switch a Th1 immune response to a Th2 response or a humoral response to a cytotoxic T-cell response) the specific immune response to the vaccine antigen in order to enhance the clinical effectiveness of the vaccine. It may be any of the types of substances identified as examples of adjuvants in Appendix 1. The term "adjuvant" is used throughout the document to include adjuvants that exist as one individual substance as well as combination adjuvants that consist of multiple adjuvants and sometimes other additives.

Vaccine and adjuvanted vaccine: the complete formulation that includes an antigen (or an immunogen, e.g. a plasmid DNA vaccine) and any additives such as adjuvants, excipients or preservatives, the administration of which is intended to stimulate the immune system to result in an immune response to the vaccine antigen leading to the prevention or treatment of an infection or infectious disease. When the vaccine contains an adjuvant, it may be referred to as an adjuvanted vaccine.

Vaccine antigen: the active ingredient in a vaccine (or generated by a vaccine) against which a specific immune response is raised. The vaccine antigen may be a live, attenuated preparation of bacteria, viruses or parasites; inactivated

(killed) whole organisms; crude cellular fractions or purified antigens, including recombinant proteins (i.e. those derived from recombinant DNA expressed in a host cell); polysaccharides and conjugates formed by covalent linkage of polysaccharides to components such as mutated or inactivated proteins and/or toxoids, synthetic antigens, or heterologous proteins expressed by plasmid DNA or viral or bacterial vectors. It may also be a combination of the antigens or immunogens listed above.

Part A. Manufacturing and quality considerations for the nonclinical and clinical evaluation of vaccine adjuvants and adjuvanted vaccines

Adjuvanted vaccine manufacturers are encouraged to discuss with the NRA the extent of the manufacturing and quality-related information necessary to support the intended use of the antigen, the adjuvant and the adjuvanted vaccine. The extent of information necessary to evaluate and assure the consistent safety and effectiveness of adjuvanted vaccines will vary with the phase of nonclinical and clinical investigation. Similarly, the nature and extent of the manufacturing controls needed to achieve, and testing needed to demonstrate, appropriate adjuvanted vaccine quality differ not only among the various phases of product development (that is, research, pilot, investigational and commercial manufacture) but also among the various phases of clinical evaluation.

A.1 Production, characterization and quality assurance of lots to be used in nonclinical pharmacology studies

It is generally accepted that nonclinical pharmacology studies (e.g. the proof-of-concept and mechanism-of-action studies) may be done as non-GLP studies, and that they are often conducted with research or pilot-scale lots of antigen, adjuvant and/or adjuvanted vaccine formulations. Also, these studies are often dose-optimization studies in which the antigen and adjuvant components may be provided in two separate containers to allow for the mixing of different amounts of each component prior to administration, and the generation of data that support the proposed dose of antigen and adjuvant to be used in the investigational adjuvanted vaccine. While the level of characterization of the lots of antigen and adjuvant used in these exploratory studies may be less extensive than those to be used in the nonclinical toxicology and clinical studies, the same raw materials should be used, where possible, in their preparation, and the source and any testing of the raw materials – for example, purity and assessment of levels of metal ions (such as copper) in aluminium-containing compounds – should be documented. Ideally, the lots of antigen and adjuvant used to formulate the final

product should be manufactured by the same process as the lots to be tested in the nonclinical toxicology studies. The general quality of the adjuvanted vaccine components (that is, antigen and adjuvant intermediates) used in the nonclinical pharmacology studies should be adequately characterized preliminarily. As the relationship between physical and chemical characteristics of the adjuvanted vaccine and its components and the immunogenicity and efficacy of the adjuvanted vaccine is not completely understood in many cases, biological characterization (i.e. through the use of biological assays) should complement the physical and chemical characterization of the intermediates and the adjuvanted vaccine (see section A.2 and Table 2.1).

A.2 Production, characterization and quality assurance of lots to be used in nonclinical toxicology studies and first-in-human clinical trials

Ideally, the lots of the antigen, the adjuvant, and the adjuvanted vaccine used in the nonclinical toxicology studies should be the same lots as those proposed for use in the first-in-human trials; these lots should be manufactured in compliance with the GMPs that are appropriate for phase I clinical trial materials (*16*, *17*). Additionally, the quality and stability of the antigen, adjuvant and final adjuvanted vaccine formulation should be characterized adequately prior to, if not in parallel with, their use in a toxicology study (see section A.2.1 and Table 2.1).

If use of the same lots is not feasible, the lots used for the nonclinical toxicology studies should be comparable to those proposed for use in the first-in-human trials with respect to manufacturing process, physicochemical data, formulation and stability. Where there are significant differences in the manufacture of the antigen or the adjuvant (or in the formulation of the adjuvanted vaccine) to be used in the nonclinical toxicology studies and the first-in-human clinical trial, a detailed description of the differences should be provided. This information will allow the NRA to evaluate the potential impact of such changes on the safety of the adjuvanted vaccine and to determine whether or not the differences are sufficient to warrant the conduct of additional toxicology studies to support the safety of the proposed clinical use.

With respect to the control and testing of adjuvanted vaccine lots manufactured for use in first-in-human clinical trials, emphasis should generally be placed on elements that assure the safety of subjects. This usually includes identification and control of the raw materials used to manufacture the antigen and the adjuvant. For this reason, Certificates of Analysis, with test specifications and results indicated, should be provided for ingredients that are acquired from contract suppliers for use in manufacturing the adjuvanted vaccine. For some adjuvanted vaccines, additional considerations related to the manufacturing and testing of the vaccine adjuvant and its individual components may be needed

to provide assurance that the adjuvant is manufactured consistently and has a consistent composition. This may apply particularly when one or more of the components of the adjuvant is biological in nature, when the vaccine contains a complex adjuvant mixture, or when the antigens are adsorbed to mineral salts or gels. Therefore, it is important to use established quality control procedures that ensure the consistent manufacture of adjuvants and antigens to be used in the preparation of adjuvanted vaccines. The antigen and adjuvant, or formulated adjuvanted vaccine, used in the first-in-human trial should be manufactured under GMPs that are appropriate for phase I clinical trial materials (*16*, *17*). Compliance with GMPs will ensure that the lots of antigen, adjuvant and adjuvanted vaccine are consistently manufactured and controlled to the quality standards appropriate to their intended use. Compliance with all aspects of GMPs will be required at the later stages of clinical development (*14*, *15*) as discussed below (see section A.3 and Table 2.1).

The clinical lot(s) of adjuvanted vaccine, or separate lots of antigen and adjuvant if provided in separate final containers, should be demonstrated to be stable for the duration of the clinical trial. Additionally, if the adjuvant is provided in a separate container (e.g. vial or syringe) to be used to reconstitute or be added to the antigen prior to vaccine administration, a detailed description of the procedure for mixing the components should be provided. A clear statement of the appropriate time and conditions for storage of the individual components and the final adjuvanted vaccine should be provided. Also, the appearance of the adjuvanted vaccine after mixing should be described, and stability data to support the storage of the adjuvanted vaccine up to the time of administration should be provided.

A.2.1 Analytical testing of adjuvant, antigen and adjuvanted vaccine

A detailed description of the adjuvant, antigen and adjuvanted vaccine should be provided and include information regarding the characterization conducted to assure the quality (e.g. identity, purity, sterility) and quantity of the antigen and adjuvant as well as the potency of the adjuvanted vaccine. It should be demonstrated that the adjuvant does not adversely affect the potency of the antigen upon mixing. In addition, information on the methods of manufacture and testing for the intermediates and final product, together with their preliminary release specifications, should be provided. Although it is not necessary to have validated methods for testing the lots of antigen and adjuvant or adjuvanted vaccine to be used in nonclinical toxicology studies and first-in-human clinical trials, the scientific background should justify the choice of the testing methods and the selected preliminary specifications. It is recommended that the NRA be consulted when designing analytical protocols appropriate for establishing the identity and quantity of the antigen(s), adjuvant(s) and any additives. It is important to

assess attributes of each of the antigen and the adjuvant components that may be relevant for adjuvant activity and adjuvanted vaccine potency. Additionally, the properties of the antigen and the adjuvant that are most indicative of stability, both when stored individually and as a formulated final adjuvanted vaccine, should be identified.

Assays used for characterization of the adjuvant may or may not be related to its mode of action, but should be adequate to ensure consistency of adjuvant production and to evaluate adjuvant stability. These may include, for example, assays for appearance, particle size distribution, presence of aggregates and pH for the adjuvant, and the amount of aluminium and degree of antigen adsorption for a vaccine adsorbed to an aluminium-containing compound. Analytical methods to evaluate the antigen and the adjuvant in an adjuvanted vaccine should be developed and validated as adjuvanted vaccine product development and clinical evaluation proceed. If relevant, the methods to be developed for characterization purposes should include, where possible, methods to assess compatibility and/or physical interactions between the antigen and adjuvant (and between the components of the adjuvant, if a combination adjuvant is used). Validation of these methods should be completed if they are intended for quality control batch release during later-stage clinical development or commercial distribution.

A quality-control test evaluating the potency of the final adjuvanted vaccine should be developed as one of the assays to assess consistency of manufacture. Depending on the type of potency assessment conducted on the adjuvanted vaccine and the requirements of the NRA, the assessment may or may not reflect the contribution of the adjuvant to the potency of the adjuvanted vaccine. If it does not, it will be important to conduct assessments of the identity and content of the adjuvant in the final adjuvanted vaccine. Also, the purity and sterility of the final adjuvanted vaccine will need to be assessed to ensure its safety. If the adjuvant or adjuvanted vaccine is tested for endotoxin via the Limulus amoebocyte lysate (LAL) test method, evidence that the adjuvant or adjuvanted vaccine does not interfere with the LAL test (e.g. data from lipopolysaccharide spiking experiments with and without adjuvant) should be provided, as certain adjuvants, such as cationic liposomes, may interfere with the LAL test method. If interference is observed, alternative tests (e.g. pyrogen test or macrophage-activation test) should be investigated.

If the final adjuvanted vaccine consists of co-packaged antigen and adjuvant, where each is provided in a separate container to be mixed prior to administration, both the antigen and the adjuvant should be evaluated prior to mixing for relevant parameters, such as identification, purity and sterility. In addition, the potency of the antigen and the content of the adjuvant per dose should be assessed. Also, where feasible, evidence should be provided as mentioned previously to demonstrate that the adjuvant does not adversely affect the potency of the final adjuvanted vaccine. Thus, the potency of the extemporaneously mixed,

adjuvanted vaccine formulation should be demonstrated. For some adjuvanted vaccines (e.g. aluminium-adsorbed vaccines), it may not be possible, depending on the nature of the potency assay, to evaluate the potency of the final formulated vaccine by certain assays. In this case, the determination of the potency of the antigen alone prior to adsorption may be recommended as well as the development of an in vivo method for potency assessment of the final formulation.

Consultation with the NRA is recommended to discuss both the need for and design of the quality control test known as the innocuity, general safety, or abnormal toxicity test for the adjuvanted vaccine. Additionally, if a particular NRA requires such a test for a formulated adjuvanted vaccine, it should be clarified whether only the antigen or both the antigen and adjuvant are to be tested when provided in separate final containers. While some regulatory authorities and WHO no longer require this test to be performed on a routine basis once the consistency of production has been established, some have further questioned the relevance of this test (*18–20*). In some countries there is a legal requirement to conduct an innocuity test with the objective of assessing the potential introduction of extraneous impurities into the final adjuvanted vaccine; however, this is not considered a toxicity test. If the innocuity test is required, and the investigational adjuvant or adjuvanted vaccine does not pass the innocuity test when administered according to the prescribed protocol, which is typically volume based and administered by the intraperitoneal route, it will be necessary to define the appropriate dose and route of administration for the adjuvanted vaccine. The manufacturer of the vaccine will need to provide justification for a modification of the innocuity test in regulatory submissions. Such modifications should be discussed with the NRAs. In the countries where the innocuity test is still necessary, once test data from many lots have been accumulated, and consistency of production has been well established to the satisfaction of the NRA, it may be possible to request an exemption from conduct of the innocuity test as part of routine lot-release testing.

A.3 Information required for later-stage clinical trials

In general, in the course of adjuvanted vaccine product development, the analytical technology and methodology is developed in parallel with the clinical investigations. As the adjuvanted vaccine product development and clinical evaluation proceed, the quality control and quality assurance of the antigen and adjuvant should be refined. When clinical trials to collect safety and efficacy data to support licensure are initiated, the manufacturing processes should be demonstrated to be consistent and validated, and a detailed description with appropriate validation information should be provided for all analytical procedures (except for those that are from an official pharmacopeial compendium) (*14*, *15*). If a national or international standard is not yet available for a particular

antigen, adjuvant or adjuvanted vaccine, the manufacturer should establish its own primary reference material during later-stage clinical trials.

A minimum of three consecutive lots of each of the antigen and the adjuvant intermediates (or final containers if provided separately) and formulated adjuvanted vaccine should be manufactured and tested for purposes of demonstrating consistency of manufacture of the vaccine antigen, the adjuvant and the formulated adjuvanted vaccine. Any changes in the manufacture or formulation should be carefully assessed to determine if such changes directly or indirectly affect the quality or safety of the adjuvanted vaccine. When analytical data from tests conducted on the adjuvanted vaccine demonstrate that the antigen, adjuvant or adjuvanted vaccine manufactured before and after such changes is not comparable, additional qualification and/or bridging studies should be undertaken to support the safety of the materials proposed for continued clinical evaluation.

To ensure that appropriate stability data are collected during later stage clinical trials of the adjuvanted vaccine, a stability protocol to be used for the formal stability studies should be developed for the antigen, the adjuvant and the adjuvanted vaccine. Stability programmes should be designed to monitor the chemical, physical, biological and microbiological stability of the antigen, the adjuvant, and the adjuvanted vaccine throughout the clinical testing programme. The properties of each antigen and adjuvant that are most indicative of stability, both when stored individually and as a mixed final adjuvanted vaccine, should be identified as stability evaluations proceed (as mentioned in section A.2.1). If it is determined that degradation products accumulate from either the antigen or the adjuvant over the shelf-life of the adjuvanted vaccine, these should be evaluated during stability testing of the final product. It is recommended that the NRA be consulted to determine whether additional suitable nonclinical toxicological testing should be undertaken to confirm their safety. Additional guidance on stability testing of vaccines can be found in WHO Guidelines on stability evaluation of vaccines (*21*).

Part B. Rationale for the use of the adjuvant

Adjuvant activity is a result of multiple factors and an adjuvant-mediated enhancement of the immune response to one vaccine antigen, as a rule, cannot be extrapolated to the enhancement of the immune response to another antigen. Individual antigens vary in their physical, biological and immunogenic properties and antigens may have different needs for immunological help from an adjuvant (*5*). Manufacturers should justify the choice of the adjuvant based on the immune response desired, which may include effects on the magnitude, the breadth and/or the type of immune response to specific antigens and on the safety profile. In addition, adjuvants are also used in antigen dose-sparing strategies with the aim of

increasing the availability and supply of vaccines – for example, under emergency situations of an influenza pandemic (*22*) or as a strategy to decrease the cost of the vaccine (e.g. use of inactivated poliovirus vaccine for polio eradication) (*23*).

Many advances in the understanding of innate immunity have begun to provide insights into the immunological mechanisms of adjuvant action. Many of the immunostimulatory adjuvants are recognized by various members of the toll-like receptor (TLR) family, a subclass of pathogen-recognition receptors, while other adjuvants may target other families of pathogen-recognition receptors that could prove to be important in shaping the adaptive immune response. Furthermore, there are complex regulatory interactions between the many families of innate receptors and other signalling pathways. Within this framework, the activities exerted by adjuvants include, but are not limited to, the facilitation of: (a) mobilization of antigen-presenting and/or polymorphonuclear cells; (b) antigen uptake and presentation of the antigen(s) in the vaccine by antigen-presenting cells; (c) secretion of proteins by antigen-presenting cells; (d) recruitment, targeting and activation of antigen-specific cells; (e) modulation of activities that regulate the ensuing immune responses; and/or (f) protection of the antigen from degradation and elimination.

The scientific rationale supporting the benefit of adding the adjuvant and the choice of specific adjuvant(s) should be provided by the adjuvanted vaccine manufacturer. Before evaluating a particular adjuvant in combination with an antigen in a clinical trial, it is recommended that data from in vitro and/or in vivo studies be generated to support the rationale for including the specific adjuvant in the vaccine formulation and for selecting the dose range of adjuvant to be tested. In the ideal case, the mode of action of the selected adjuvant as well as the mechanism of the enhanced immune response would be well understood prior to the initiation of later-stage clinical development. When the mode of adjuvant action is not well defined, supplemental in vivo or in vitro data (as discussed in sections B.1 and B.2, respectively) may be provided in addition to the pivotal toxicity study to support the added benefit of the adjuvant to the immune response induced by the adjuvanted vaccine as well as the safety of the adjuvanted vaccine.

B.1 In vivo proof-of-concept studies

Data from proof-of-concept studies, including data from early studies conducted to evaluate optimal antigen/adjuvant formulations, can provide important information with regard to the characteristics of the adjuvanted vaccine. These data include evidence for the need for the adjuvant, the type and magnitude of the immune responses induced (i.e. innate immunity, or humoral and cellular immunity), and the functional capacity of the immune response to either protect against disease (i.e. prophylactic vaccine) or ameliorate an existing infectious disease (i.e. therapeutic vaccine) when a relevant nonclinical disease model

is available. These pilot or exploratory studies designed to identify and screen adjuvanted vaccine formulations may be non-GLP-compliant; however, they may identify unknown or potential adverse effects, and provide crucial information for the design of GLP-compliant toxicity studies. In addition, in vivo proof-of-concept studies may provide the scientific justification for manufacturing changes and for optimization of adjuvanted vaccine formulation, dose and route of administration during the clinical development of the adjuvanted vaccine product.

It is recommended that proof-of-concept studies to support the use of an adjuvant be carried out to evaluate vaccine formulations with and without the adjuvant. Depending on the specific antigen and/or adjuvant being considered, possible examples of these types of studies include:

- evaluation of humoral immune responses with regard to magnitude (e.g. mean titre or concentration), quality (e.g. affinity or avidity), and functional activity (e.g. neutralizing activity);
- evaluation of cellular immune responses including assessment of the induction of specific types of cellular responses (e.g. examining Th1 or Th2 cytokine profiles, or testing for the induction of cytotoxic T cells);
- evaluation of protective or therapeutic responses against the relevant pathogen using appropriate animal or in vitro disease models and/or evaluation of functional immune responses (e.g. neutralizing activity, serum bactericidal or opsonophagocytic antibody titres);
- evaluation of duration of (*24*) and extent of cross-protection provided by the induced immune response (*25*, *26*).

These studies will contribute to the elucidation of the adjuvant mode of action and may provide indication of the adjuvant-specific immune modulatory effects. In addition, these studies may assist in the interpretation of nonclinical safety studies and the identification of potential adverse effects to be monitored during clinical development. The development of in vitro model systems, particularly those using human cells, is recommended when possible, as they may provide additional relevant information to elucidate the mechanism of action of the adjuvant (see section B.2).

B.2 In vitro supporting studies

Functional in vitro bioassays may also provide helpful insight in understanding the mode of action of a particular adjuvant, and may provide valuable supplemental and complementary data to animal studies. This is particularly important when there are limitations to the animal models, such as species-specific differences (e.g. in TLRs). Antigen-presenting cells or other immune cells are widely used to assess and monitor the direct or indirect effects of adjuvants by measuring activation parameters (such as changes in the expression of cell

surface molecules and the pattern of cytokine secretion), and more recently such human cells have been used to develop in vitro assays that may be predictive of adjuvant safety in vivo (*27*). More complex tissue culture systems, containing a mixture of human immune cells mimicking lymphoid tissue, are being explored with the aim of evaluating human immune responses in vitro (*28*).

Part C. Considerations for selection of the animal species for nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines

Investigations of the properties that influence the safety and pharmacological activity of the adjuvant and the adjuvanted vaccine require the use of appropriate animal species. The animal species used for pharmacological and safety evaluations should be chosen carefully and justified. For ethical reasons, it is desirable to apply the 3Rs concept of "Replace Reduce Refine" to minimize the use of animals in research where scientifically appropriate (*29*). Both manufacturers and staff at the NRA or national control laboratory are encouraged to further develop in vitro assays and to evaluate their suitability for the control of vaccines (*30*).

C.1 Selection of animal species for nonclinical pharmacology studies

For the purpose of this document, the nonclinical pharmacological activity of an adjuvanted vaccine is defined as the ability of the adjuvanted vaccine to induce and/or modify an immune response in an animal species. Factors influencing the selection of a particular animal species include, but are not limited to, the vaccine antigen, the adjuvant chosen, the type of immunity (i.e. cell-mediated or humoral) to be induced and the route of administration. It is recommended that proof-of-concept studies be undertaken using an animal species in which: (a) an immune response to the vaccine antigen is developed; and (b) the immune response to the antigen is enhanced by the adjuvant through a mechanism similar to that expected in humans (e.g. TLRs known to be targeted by the adjuvant are present in the species, and enhanced humoral and/or cellular immunity is observed). However, it is acknowledged that species-specific differences in the immune responses induced in the animal species compared to the human are likely. Proof-of-concept studies most commonly are conducted in several animal species, including both naive and pre-exposed animals. In addition to evaluating the immune response induced by the vaccine antigen alone and in the presence of the adjuvant, the mechanism of action of the adjuvant in the absence of the vaccine antigen should also be evaluated.

If the adjuvanted vaccine is a therapeutic vaccine for an infectious disease indication, where feasible, disease animal models may need to be developed to

study the pharmacological activity of the adjuvanted vaccine and its effect on the disease. For preventive adjuvanted vaccines, the use, when available, of an animal species sensitive to the human pathogen may provide important insight into the mechanism of protection from the disease (e.g. the ferret model for human influenza).

Nonclinical pharmacology studies may be conducted under non-GLP compliant conditions. It is advisable to incorporate into the study design toxicological end-points to guide the design of GLP-compliant nonclinical safety studies. It is sufficient to conduct these studies in small animal species if it can be demonstrated that the animal species chosen is relevant and responsive to the vaccine antigen and the adjuvant when given by the intended route of administration. Nonhuman primates should be used only if no other relevant animal species is available.

C.2 Selection of animal species for nonclinical safety studies

When selecting the animal species for nonclinical safety studies, it is important to document the pharmacological activity of the vaccine in the presence and absence of adjuvant in that species. It is recommended that manufacturers conduct nonclinical safety studies in compliance with GLPs (see section D.2 and Table 2.1) and using an animal species in which an immune response to the vaccine antigen is developed and, ideally, the immune response to the antigen is enhanced by the adjuvant through a similar mechanism as expected in humans. It is not necessary, however, to conduct the nonclinical safety study in the same animal species used for proof-of-concept or nonclinical pharmacology studies (see sections B.1 and C.1). Nonhuman primates should be used only if no other relevant animal species is available. In situations where no animal species is available that is responsive to the adjuvanted vaccine, the choice of the animal species should be justified. In some circumstances, the use of in vitro model systems, particularly those using human cells, to evaluate the toxicity of the adjuvanted vaccine may provide additional supplementary information to assist in interpreting toxicity data (*27*).

It is highly recommended that the animal species chosen is one for which relevant and sufficient historical control data exist. Analysis and interpretation of data from the toxicity studies commonly includes a comparison with the inactive control (e.g. saline control) in the same study. However, historical control data from the same laboratory in which the study was conducted and for animals of comparable age and from the same species and/or strain may provide additional information. When historical control data are used, the data should be provided to the NRA.

The route of administration used in the toxicity study should correspond to that intended for use in the clinic. Also, when the adjuvanted vaccine is to be

administered in the clinic using a particular device, the same device should be used in the animal study, where feasible. For example, a small rodent species may not be an appropriate choice for nonclinical evaluation of a vaccine that is to be delivered intranasally because some of the inoculum could be delivered to the lungs. In this case, a larger animal or one with nasal surface area, anatomy and physiology similar to that of humans would be more appropriate.

Use of a single species is generally acceptable (see section D.2). This approach has commonly been accepted based primarily on pragmatic considerations – for example, the ability to predict the human immune response may be limited due to the species specificity of the response in animals to the antigen, the adjuvant or both.

C.3 Limitations of animal studies

The limitations of using animals to characterize the pharmacological and safety profile of an adjuvant or adjuvanted vaccine are acknowledged. The ability to predict the human immune response based on pharmacological studies in an animal may be limited due to the species specificity of the response to the antigen, the adjuvant, or both. Similarly, local and systemic adverse effects observed in a nonclinical safety study may not be directly translatable to the clinic. In addition, rare and/or late-onset adverse events that may occur in human subjects as a result of adjuvanted vaccine administration may not be observed in animal studies. Nevertheless, these studies offer the best currently available tools to evaluate the preclinical safety and pharmacology of adjuvanted vaccines.

D. Nonclinical safety assessment in animals

D.1 General remarks

Safety concerns for products such as vaccines include the potential inherent toxicities of the antigen and other vaccine components, as well as potential toxicities due to interactions of the components present in the final formulation. For adjuvanted vaccines, these concerns include the possibility that the immune-modulatory and/or inflammatory response induced may lead to undesired toxic side effects. Additionally, some adjuvants may elicit elevated levels of proinflammatory cytokines and other mediators of toxicity, irrespective of the immune response against the antigen.

Safety assessments in animal studies are valuable tools to help define an acceptable adjuvant/antigen ratio and a safe dose, as well as to identify unknown or potential adverse effects that should be taken into consideration for further product development or to be monitored in future clinical trials. The type of studies and the timing in relation to the clinical programme are presented in section D.2.

D.2 Toxicity studies of vaccine adjuvants and final adjuvanted vaccine formulations

The preclinical toxicity studies of the final adjuvanted vaccine formulation should be adequate to identify and characterize potential adverse effects of the vaccine in order to conclude that it is reasonably safe to proceed to first-in-human clinical investigation. As the mechanism of action of the adjuvant and/or adjuvanted vaccine formulation is often not fully understood, the toxicity studies should be designed to evaluate a broad spectrum of parameters due to the uncertainty of the in vivo effects and associated outcomes. Toxicity studies should be designed to mimic the intended route of administration in the clinic and to evaluate local reactogenicity (e.g. injection-site inflammation) and systemic toxicity (i.e. toxicity that occurs at sites distant from the site of initial administration). Pivotal toxicity studies should use the intended final formulation and dose of the adjuvanted vaccine (see section A.2) and should be conducted in compliance with GLPs.

When properly designed, conducted and interpreted, and when no major safety signals are revealed in the study results, one repeated-dose toxicity study in one relevant species should be sufficient. However, if there are significant manufacturing or formulation changes during product development, additional animal toxicity studies may be recommended to confirm that the safety profile of the product has not been changed. Also, throughout the clinical programme, additional animal toxicity studies (e.g. developmental and reproductive toxicity studies) may be necessary to investigate any adverse events observed in clinical trials or to support the use of the vaccine in a special population.

While comprehensive toxicity evaluations of the final adjuvanted vaccine formulation are considered essential, the advantages and limitations of toxicity studies with adjuvant alone have been discussed extensively in previous meetings and workshops (*7–11*). A comprehensive toxicity assessment of the adjuvant alone in animals (or of individual evaluations of its multiple components, if it is a combination adjuvant) may not be needed as a separate programme. However, to enable the interpretation of immunogenicity and safety studies of the adjuvanted vaccine, a study arm receiving adjuvant alone may be included in the repeated-dose toxicity studies (see section D.2.2) that are part of the comprehensive toxicity evaluations of the final adjuvanted vaccine formulation.

D.2.1 Safety pharmacology studies

The purpose of a safety pharmacology study is to investigate the effects of the candidate vaccine on vital functions. Although not usually required, safety pharmacology studies may be recommended by the NRA in some cases. For example, if data from nonclinical and/or human clinical studies suggest that the adjuvanted vaccine may affect physiological functions other than the immune

system (e.g. the central nervous system, respiratory or cardiovascular system, renal function or body temperature) then safety pharmacology studies should be incorporated into the safety assessment programme.

D.2.2 Repeated-dose toxicity studies

This section highlights important considerations regarding the study design for pivotal toxicity studies that should be conducted with the same vaccine formulation intended to be used in clinical trials (see section A.2). If more than one dose of an antigen or adjuvant is to be evaluated in the clinical study, the formulation containing the highest dose (i.e. the "worst case") should be included in the pivotal toxicity studies. Single-dose toxicity studies on the final formulated vaccine product, which are applicable to small-molecule chemical medicines, are usually not needed in accordance with *Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals: M3(R2)* (*31*). Acute effects of administering a vaccine can also be monitored in repeated-dose toxicity studies if they are adequately designed (e.g. an evaluation is conducted after the first administration). Alternatively, acute effects can be assessed in a single-dose design as part of a local tolerance study. For a study intended to support a first-in-human clinical trial, the number of animals studied per sex, group and time interval should be sufficient to allow meaningful scientific interpretation of the data generated. The size of the treatment group will depend on the animal species chosen; i.e. the number of animals included in studies using non-rodents (e.g. miniature pigs) would be expected to be fewer than the number included in studies using rodents. For mice and rats, it is recommended that at least 10 animals of each sex per group be used for the necropsy at the end of the treatment interval, and at least 5 animals of each sex per group be used for the necropsy at the end of the recovery period. For rabbits, it is recommended that at least five animals of each sex per group for each time interval be used. In general, the approximate age for rodents should be 6–8 weeks, and for rabbits, 3–4 months, at the start of the study.

D.2.2.1 Dose, dosing regimen and controls

Dose–response evaluation for the adjuvanted vaccine is generally not required as part of the basic toxicity assessment, given that, in most cases, dose–response assessment was explored in nonclinical pharmacology studies. For adjuvanted vaccines, the toxicity study should be performed using the highest anticipated human dose (in absolute terms) of the final adjuvanted vaccine to be used in the proposed clinical trial, where feasible. Ideally this dose provides optimal exposure of the animal to the candidate vaccine and the immune response induced. However, in the case of a novel adjuvant, it may be advisable to include additional (lower and higher) doses of the adjuvanted vaccine formulation or

adjuvant alone in order to identify a safe dose that could be used in a first-in-human clinical trial.

If the dose to be administered is limited by the total volume that can be administered in a single injection, guidelines for animal welfare should be followed (*32*). In such cases, the total volume may need to be administered at multiple sites using the same route of administration; however, it should be noted that the evaluation of local reactogenicity might be less reliable in such cases.

For adjuvanted vaccines intended to be given repeatedly, the number of doses administered to the animals in repeated-dose toxicity studies should equal or exceed the number of doses proposed in humans. However, in many cases, the studies are designed to include one dose more than planned for the clinical trial to allow for the possible inclusion of an additional dose in the clinical trial. To simulate the proposed clinical usage, vaccine doses should be given as episodic doses, but the dosing interval used in the toxicity study may be reduced (e.g. to 2 weeks or 3 weeks) compared with the proposed clinical dosing interval (which usually is greater than 2 weeks to 3 weeks). The nonclinical dosing interval should be based primarily on the kinetics of the primary and secondary antibody response observed in the animal study.

In general, the study design should include a negative control group that receives an inert placebo, such as saline, to evaluate a baseline level of treatment, and an adjuvant-alone arm to aid in the interpretation of safety data from the adjuvanted vaccine. Also, the treatment groups in the study should include a sufficient number of animals for evaluation (as described in section D.2.2.3) at later time points after treatment to evaluate the reversibility of adverse effects observed during the treatment period and to detect potentially delayed adverse effects.

D.2.2.2 Route of administration

The route of administration should correspond to that intended for use in the clinical trials. When the vaccine will be administered in human clinical trials using a particular device, the same device should be used in the animal study, where feasible.

D.2.2.3 End-points in toxicity studies

The following section discusses end-points that are especially relevant and important in the evaluation of adjuvanted vaccines in repeated-dose toxicity studies using the final vaccine formulation. In general, potential adverse effects of the adjuvanted vaccine should be evaluated in repeated-dose studies with regard to target organs (see Appendix 2), dose, route(s) of exposure, duration and frequency of exposure, and potential reversibility of observed toxic effects.

D.2.2.3.1 *Parameters for monitoring of systemic toxicity*

Toxicity studies, repeated-dose toxicity studies in particular, should address the potential for systemic toxicity including, but not limited to, the systemic effects on the immune system. A broad spectrum of information should be obtained from the toxicity study, and both in-life and postmortem data should be collected. This routinely includes careful monitoring of body weight and food consumption, body temperature, histopathology, clinical chemistry, haematology, coagulation parameters and acute phase reactants. In addition, the immune response should be evaluated in a group of treated animals to confirm that the anticipated immune response occurred during the toxicity study. A detailed description of the assay(s) used should be provided with the toxicity study results.

While the standard in-life parameters routinely assessed for general pharmaceuticals (e.g. overall health, body weight and food consumption) are appropriate, it is important to note that for adjuvanted vaccines more frequent (e.g. daily) measurements of body weight and food consumption are recommended, especially during the first week after the administration of each dose as these parameters are very sensitive in detecting systemic toxicity effects. After the first week, body weights may be collected less frequently (e.g. 2–3 times each week). Body temperature should also be evaluated prior to, and 3–8 h and 24 h after each dose. If there is an increase in temperature, additional measurements should be taken every 24 h until the values return to baseline. Interim analyses of haematology and serum chemistry should be considered within approximately 1–3 days following the first and last dose administration, and at the end of the recovery period; in addition, the collection of a predosing sample is recommended. Coagulation parameters should be included routinely; in some cases, evaluation of urine samples and serum immunoglobulin classes may be of value. Additionally, it is recommended that species-appropriate acute phase reactants (e.g. C reactive protein) be measured in the toxicity study prior to immunization, at time points following the administration of the adjuvant or adjuvanted vaccine that have been demonstrated to reflect peak elevations in the acute phase reactants being evaluated (commonly 24–48 h), and after a recovery phase of 7 days. When measuring acute phase reactants, the choice of the animal species may determine which proteins can be measured as these reactants vary among species (*33*). The data discussed above should be collected not only prior to and during the treatment phase, but also following the treatment-free (recovery) phase (i.e. 2 or more weeks following the last dose) to determine persistence, exacerbation and/or reversibility of potential adverse effects.

Postmortem data, including data from gross necropsy (with tissue collection and preservation, including gross lesions and organ weights), should be collected within 3 days following the last dose and following the above-mentioned recovery period (e.g. 2 or more weeks following the last dose) (*1*). At study termination, final body weights (following overnight fasting) should be

obtained. Terminal blood collection and analysis should include serum chemistry, haematology, and coagulation parameters as well as an immune-response evaluation. Histopathological examinations should always include pivotal organs (brain, lung, heart, kidneys, liver, reproductive organs), and the site of adjuvant or adjuvanted vaccine administration. Special attention should be paid to the immune organs – i.e. lymph nodes (draining and distant to the application site), thymus, spleen, bone marrow, and Peyer's patches or bronchus-associated lymphoid tissue – as well as organs that may be primarily affected due to the particular route of administration. The extent of the list of tissues to be examined (i.e. the full tissue list as provided in Appendix 2 versus the reduced list mentioned above, which is limited to the immune system and pivotal organs) will depend on the adjuvant or adjuvanted vaccine in question, as well as on the experience and knowledge obtained through previous nonclinical and clinical testing of the vaccine's components. Additionally, any known target organs of the adjuvant or adjuvanted vaccine should be evaluated. For novel adjuvants and adjuvanted vaccines containing a novel adjuvant, it is recommended that the full tissue list be evaluated.

D.2.2.3.2 *Parameters for monitoring of local reactogenicity*

Local toxicities should be determined at the site(s) of adjuvant or adjuvanted vaccine administration and any other sites that come into contact with the adjuvant or adjuvanted vaccine components as a result of the method of administration. Local toxicity studies of intramuscularly administered vaccines should preferably be conducted in animals with sufficient muscle mass to test the full human dose of the final vaccine formulation.

Injection site reaction after inoculation should be scored using a prospectively defined system (e.g. the modified Draize test) (*34*) along with an assessment of any vesiculation, ulceration, severe eschar formation and other manifestations of significant toxicity (e.g. limb impairment).

The site of administration and any other site that comes in contact with the adjuvant or adjuvanted vaccine (e.g. eye exposure during aerosol administration, or digestive tract after oral administration) should also be evaluated histopathologically. In addition, a description of cellular infiltrates based on routine histological staining, if present, should be reported as part of the postmortem evaluation, as well as any manifestation of tissue damage at the site of injection and surrounding anatomic structures (e.g. sciatic nerves, nasal cavities or olfactory bulb).

D.2.3 Developmental and reproductive toxicity

Because vaccination programmes may include women of childbearing potential, it is important to consider the need for developmental and reproductive toxicity studies. As is the case for general toxicity, the use of a novel adjuvant may require

adding an adjuvant-alone arm to the reproductive toxicity studies. However, the study design is also dependent on the intended clinical use of the vaccine. For example, vaccination may be given early in pregnancy to protect the mother at risk, or might be given later in pregnancy to induce passive immunization to protect the infant directly from birth.

In general, the administration of one or several additional doses during organogenesis (i.e. implantation to closure of the hard palate) is recommended in order to evaluate the potential, direct embryotoxic effects of the components of the vaccine formulation, and, depending on the animal model, to allow maternal antibody to transfer to the progeny during pregnancy or the lactation period. Depending on the adjuvant, there may be concern about an adjuvant-induced systemic inflammatory response, such as fever, which may adversely affect early pregnancy (e.g. implantation or placental growth) (*35*). In these cases, it is recommended to include in the study design an additional treatment group to evaluate the effect of adjuvant on early pregnancy parameters. Rather than dosing this treatment arm prior to mating, it is recommended to dose animals post-mating and prior to implantation (e.g. post-mating day 1). Considering the short gestational period of the animal species that are most frequently used, it may be necessary to administer priming doses to the animals several days or weeks prior to mating in order to elicit a peak antibody response during the period of organogenesis.

End-points in embryo-fetal/perinatal-postnatal toxicity studies include, but are not limited to, viability, abortions, number of resorptions, fetal body weight, morphology, preweaning development and growth, as well as survival incidence and developmental landmarks. For details on such studies, please see the United States Food and Drug Administration's *Guidance for industry: considerations for developmental toxicity studies for preventive and therapeutic vaccines for infectious disease indications* (*36*) and WHO guidelines on nonclinical evaluation of vaccines (*1*).

In most cases, the developmental and reproductive toxicity studies can be performed in parallel to the clinical trials. However, some NRAs require that women of childbearing potential be excluded from large-scale late-stage clinical trials that are conducted prior to the completion of developmental and reproductive toxicity studies; other NRAs require the use of appropriate birth control methods for women of childbearing potential that are included in clinical trials. Further considerations can be found in *Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals: M3(R2)* (*31*).

D.2.4 Biodistribution studies

Adjuvants are expected to exert their action locally in close connection to the antigen. However, biodistribution studies can be helpful in understanding the

distribution of the adjuvant following injection. The feasibility of and need for such biodistribution studies should be evaluated on a case-by-case basis.

D.2.5 Genotoxicity and carcinogenicity studies

Genotoxicity studies are normally not needed for the final vaccine formulation (*1*). However, a standard battery of genotoxicity studies is generally recommended for most novel adjuvants that are (or contain) new chemical entities (*31*, *37*). Based on previous experience, carcinogenicity studies are generally not needed for adjuvants or adjuvanted vaccines.

D.2.6 Toxicity studies of adjuvant alone

As noted in the introduction to section D.2, comprehensive toxicity assessment of the adjuvant alone in animals may be included as part of the study design with the adjuvanted vaccine. However, evaluation of the adjuvant alone can be important for novel adjuvants that have not been studied previously or will be used in multiple different vaccine formulations. In the case of a novel adjuvant or combination adjuvant, it may be advisable to include additional (lower and higher) doses of the adjuvant component(s) in order to identify a safe dose that could be used in a first-in-human clinical trial, as well as safety signals that should be monitored in the proposed clinical trial.

Although not usually required, safety pharmacology studies may be recommended in some cases to demonstrate that a novel adjuvant has no adverse effects on physiological functions (e.g. on the central nervous system, or the respiratory or cardiovascular system, renal function, and body temperature). If needed, such evaluations could also be included as a specific arm with the adjuvant alone in the repeated-dose toxicity study of the intended final vaccine formulation (*1*, *38*). It is expected that these studies would be conducted before initiating first-in-human clinical trials.

D.2.7 Summary of recommendations regarding timing of studies

In general, the guidance provided in this document regarding the timing of studies in relation to clinical trials is consistent with that of other guidance documents (*31*). A repeated-dose toxicology study (including safety pharmacology end-points, if needed) should be conducted before the first-in-human clinical trial. It may be important to conduct some studies with adjuvant alone (e.g. systemic toxicity and genotoxicity, when needed as discussed in sections D.2.5 and D.2.6) prior to initiation of clinical trials (*31*). Developmental toxicology studies should be performed prior to initiation of any clinical study to be conducted in pregnant women – i.e. for those vaccines specifically developed for use in pregnancy. For vaccines indicated for females of childbearing potential, subjects can be enrolled in clinical trials provided that appropriate precautions are taken to

avoid vaccination during pregnancy, such as pregnancy testing and use of birth control. For these products, developmental toxicity studies (section D.2.3) may be performed in parallel to the clinical study.

D.3 Additional considerations

Additional studies for safety assessment have been considered for the specific situation in which the target population for a vaccine containing a novel adjuvant includes very young subjects – such as neonates. At this time, however, there is insufficient knowledge about suitable animal models to evaluate whether neonates with an immature immune system would adequately respond to adjuvanted vaccines or whether the adjuvant could modify the neonatal immune system in an undesirable way. Modified immune responses to vaccination also have been observed in elderly populations; however, there also is insufficient knowledge about animal models to evaluate the response to adjuvants and adjuvanted vaccines in the ageing population. Further research to improve methods that can be used for the nonclinical evaluation of adjuvanted vaccines that are targeted for neonatal and elderly populations is encouraged.

Thus far, there is no compelling clinical evidence that adjuvants are causally related to the induction of autoimmune phenomena (or autoimmune disease) or hypersensitivity in humans (*4*). Although there has been interest in developing animal models that could be used to screen adjuvants and adjuvanted vaccines for induction of autoimmunity or hypersensitivity, such models do not currently exist. Therefore, no recommendations can be made at this time regarding specific nonclinical studies that should be conducted. These are complex and multifactorial conditions; further research is needed to identify additional biomarkers related to autoimmunity and hypersensitivity phenomena.

Part E. Considerations for first-in-human clinical trials

As with the nonclinical safety assessment considerations, the first-in-human trial considerations for new adjuvanted vaccines are similar to those for non-adjuvanted vaccines (*2*); however, some issues unique to the clinical evaluation of vaccines with novel adjuvants may need to be considered. The initial clinical trials of adjuvanted vaccines are usually intended to: (a) determine the subjects' tolerability to the range of doses of antigen and adjuvant, and the dosing regimen that may be needed for later immunogenicity and clinical end-point trials; and (b) to aid in the collection of information on the nature of the adverse reactions that can be expected. This section provides guidance on the points to consider when transitioning from nonclinical to clinical testing of adjuvanted vaccines as signals observed in nonclinical studies can aid in the design of the first-in-human clinical trials. This section is intended to supplement the information

provided in the WHO Guidelines on clinical evaluation of vaccines: regulatory expectations (*2*).

Although there are limitations in the ability of animal and in vitro studies to predict safety in humans, all of the relevant nonclinical data, including the information on the pharmacologically active dose and the full toxicological profile of the adjuvanted vaccine, should be considered when designing the first-in-human trials. These data may aid in the selection of a safe starting dose, schedule, and route of administration, and in the identification of potential adverse effects for specific monitoring in the first-in-human clinical trial. A summary of such data from the nonclinical studies with the adjuvanted vaccine, and any available clinical data from similar or related adjuvanted vaccines, should be provided to support the acceptability of the proposed first-in-human clinical trial design. If, for example, dose-limiting toxicity was observed with the adjuvanted vaccine in the animal studies and the studies were repeated with lower doses to identify a dose that was without adverse effect in animals, it would be important to point that out and to summarize the specific adverse effects observed in the nonclinical studies.

Manufacturers should provide a rationale and scientific support for the use of an adjuvant in their vaccine. This could include information supporting the "added benefit" of the adjuvant derived from nonclinical studies (e.g. in vitro assays and/or proof-of-concept studies in animal models, including relevant challenge models when available) conducted prior to the initiation of clinical trials. In addition, it is recommended that the early clinical evaluations of an adjuvanted vaccine be designed to include the evaluation of both antigen-alone and adjuvanted vaccine arms to demonstrate the added benefit of the adjuvant; such data may include, for example, evidence of enhanced immune responses or antigen sparing.

If the safety of the adjuvanted vaccine was evaluated in appropriately designed toxicology studies that were conducted in line with the recommendations outlined above, and if there were no adverse effects observed in the toxicology studies conducted, the human dose tested in the toxicology studies may be acceptable as the starting dose in the first-in-human trials. However, such clinical trials are often designed as dose-escalating studies where the antigen and/or the adjuvant are given at escalating doses. With this in mind, given the limitations of the animal studies, it may be prudent to consider using a safety factor (a safety factor of 10 has been used historically) and to divide the human dose tested in the toxicology studies by the safety factor to find the recommended starting dose, and then escalate the dose from there. While it is anticipated that the adjuvant may have an antigen-sparing effect, the first-in-human trials should be designed to attempt to establish whether the adjuvant is needed and, if so, the minimum dose of adjuvant that is necessary to achieve adequate immunogenicity.

Although an inactive control (placebo) group may not be required in the first-in-human trial of an adjuvanted vaccine, the inclusion of a group receiving an inactive control, such as inert saline placebo, in early-phase clinical trials will enhance interpretation of the initial safety data through control for placebo effects and circulating community-acquired illnesses. It is recommended that the inclusion of an adjuvant-alone arm be discussed with the relevant NRA as some regulatory authorities recommend that such arms be avoided for ethical reasons; in those cases, an antigen-alone control arm may be preferred.

As with first-in-human trials of non-adjuvanted vaccines, those for adjuvanted vaccines are usually conducted in a limited number of healthy, adult volunteers (e.g. aged 18–50 years) with safety as the primary objective. The number of subjects enrolled in these first-in-human clinical trials typically ranges from 20 to 80 subjects; however, depending on the study design, the formulation of adjuvanted vaccine to be studied, and other relevant factors, a lower or higher number of subjects may be enrolled. To aid in the overall risk/benefit evaluation of the adjuvanted vaccine, the subject population should be clearly defined by inclusion and exclusion criteria, and the subjects should be closely monitored for safety. The clinical protocol should contain a safety monitoring plan with details of active post-vaccination monitoring, and predefined toxicity criteria for assessing the severity of clinical and laboratory parameters (*39*). In addition, the plan for increasing the dose of antigen and adjuvant, with predefined stepwise criteria for doing so, should be included in the clinical protocol. Also, it is recommended, especially when a novel adjuvant is used, that safety monitoring be extended through 12 months following the last vaccination (where the last follow-up may be accomplished by a telephone call). In this regard, it is recommended that serum specimens be banked where possible for potential future assessment in the event of a serious adverse event, a new-onset medical condition, or an adverse event of special interest that develops later in the course of the first-in-human clinical trial.

Any safety data based on experience with the same adjuvant formulated with other vaccine antigens, if available, may assist in developing the safety monitoring plan for the adjuvanted vaccine. However, since the mode of action in humans for the adjuvant in the specific adjuvanted vaccine to be evaluated in the first-in-human trial is usually unknown, and adjuvants may exhibit a range of properties that induce complex immune responses, it is recommended that subjects in first-in-human trials of adjuvanted vaccines be asked about specific adverse events. This may include, for example, inquiries on local reactions (e.g. pain, redness, swelling, granuloma formation, abscess, necrosis and regional lymphadenopathy), systemic reactions (e.g. fever, nausea, diarrhoea, and malaise), immune-mediated toxicity (e.g. cytokine release, immune suppression and autoimmune disease), and teratology. Examples of

adverse events of "special interest" may include neuroinflammatory disorders (e.g. optic neuritis and transverse myelitis), musculoskeletal and connective tissue diseases (e.g. rheumatoid arthritis, systemic lupus erythematosus and Wegener granulomatosis), and gastrointestinal disorders (e.g. Crohn disease and ulcerative colitis). Additionally, targeted laboratory assessments (e.g. C reactive protein, fibrinogen, antinuclear antibody, antineutrophil cytoplasmic antibodies, and rheumatoid factor) may aid in the evaluation of adverse events and medical conditions.

Table 2.1

Points to consider for the manufacturing and quality information to be provided for pharmacology studies, toxicology studies[a] and first-in-human trials

Considerations	Comment on information needed, by type of study		
	Pharmacology	Toxicology[a]	First-in-human trials
Quality information regarding raw materials[b]	Information regarding purity and source of raw materials is important	Information regarding purity and source of raw materials is important	Information regarding purity and source of raw materials is important
Production of intermediates and adjuvanted vaccine	Production of intermediates and adjuvanted vaccine may be small scale	Production of intermediates and adjuvanted vaccine may be small scale; ideally, the lots used for the toxicology study should be the same as those that will be used in the first-in-human trials (or the lots should be comparable to the lots that will be used in the first-in-human trials in terms of the manufacturing process and the controls)	Production of intermediates and adjuvanted vaccine may be small scale, but control of manufacture is important; intermediates and adjuvanted vaccine should be manufactured in compliance with the appropriate good manufacturing practices

Table 2.1 *continued*

Considerations	Comment on information needed, by type of study		
	Pharmacology	Toxicology[a]	First-in-human trials
Presentation	Adjuvanted vaccine components (or antigen and adjuvant intermediates) often are provided in separate containers to be mixed prior to use	Adjuvanted vaccine may be provided as a premixed formulation or as two components (in separate containers) to be mixed prior to administration	Adjuvanted vaccine may be provided as a premixed formulation or as two components (in separate containers) to be mixed prior to administration
Characterization	Characterization of material may not be extensive; usually general quality information (e.g. composition, purity, potency[c, d]) is provided	Material should undergo considerable characterization to include, for example, information on purity, physicochemical characteristics and potency;[c, d] also, stability should be assessed	Material should undergo considerable characterization to include, for example, information on purity, physicochemical characteristics and potency;[c, d] also, stability should be assessed

[a] Toxicology studies should be compliant with GLPs (see "Terminology" section above).

[b] Ideally, the raw materials should be the same throughout all of the studies: pharmacology, toxicology and first-in-human trials.

[c] If a potency assay has been developed for the adjuvanted vaccine, such information should be provided. Alternatively, testing the antigen for potency, and the adjuvant for identity and content, is recommended.

[d] If the adjuvanted vaccine is provided premixed in one container, it should be tested for potency. However, in some cases, the potency assessment of the adjuvanted vaccine may require multiple types of tests (e.g. in the case of aluminium-adsorbed vaccines). In these cases, the determination of potency and amount of antigen present in the antigen intermediate preparation prior to adsorption (as well as the completeness of adsorption) may be recommended in addition to an in vivo method to assess the potency of the adjuvanted vaccine.

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References

1. WHO guidelines on nonclinical evaluation of vaccines. In: *WHO Expert Committee on Biological Standardization. Fifty-fourth report*. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 927), Annex 1.
2. Guidelines on clinical evaluation of vaccines: regulatory expectations. In: *WHO Expert Committee on Biological Standardization. Fifty-second report*. Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 924), Annex 1.
3. Global Advisory Committee on Vaccine Safety, June 2012. *Weekly Epidemiological Record*, 2012, 87:281–287.
4. Ahmed SS et al. Assessing the safety of adjuvanted vaccines. *Science Translational Medicine*, 2011 3(93):93rv2 (doi: 10.1126/scitranslmed.3002302).
5. Committee for Medicinal Products for Human Use. *Guideline on adjuvants in vaccines for human use*. London, European Medicines Agency, 2005 (EMEA/CHMP/VEG/134716/2004) (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003809.pdf, accessed 26 June 2013).
6. *Guideline for nonclinical studies of preventive vaccines for infectious diseases: notification of yakushokushinsahatsu No. 0527-1 May 27*. Tokyo, Japan, Ministry of Health, Labour and Welfare, 2010 (Supplemental Information).
7. Global Advisory Committee on Vaccine Safety, 10–11 June 2004. *Weekly Epidemiological Record*, 2004, 79:269–272.
8. *Workshop on: non-clinical safety evaluation of preventive vaccines: recent advances and regulatory considerations*, vol. I. Arlington, VA, Center for Biologics Research and Review, United States Food and Drug Administration, 2002 (http://www.fda.gov/downloads/biologicsbloodvaccines/newsevents/workshopsmeetingsconferences/transcriptsminutes/ucm054459.pdf, accessed 26 June 2013).
9. van der Laan JW et al. Nonclinical testing of vaccines: report from a workshop. *Drug Information Journal*, 2009, 43:97–107.
10. *Workshop on adjuvants and adjuvanted preventive and therapeutic vaccines for infectious disease indications*. Arlington, VA, Center for Biologics Research and Review, United States Food and Drug Administration, 2008 (http://www.fda.gov/downloads/biologicsbloodvaccines/newsevents/workshopsmeetingsconferences/ucm095708.pdf, accessed 26 June 2013).
11. Mastelic B et al. Mode of action of adjuvants: implications for vaccine safety and design. *Biologicals*, 2010, 38:594–601.
12. Sun Y, Gruber M, Matsumoto M. Overview of global regulatory toxicology requirements for vaccines and adjuvants. *Journal of Pharmacological and Toxicological Methods*, 2012, 65:49–57.
13. *Handbook: good laboratory practice (GLP): quality practices for regulated non-clinical research and development*, 2nd ed. Geneva, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, 2009 (http://www.who.int/tdr/publications/documents/glp-handbook.pdf, accessed 26 June 2013).

14. Good manufacturing practices for biological products. In: *WHO Expert Committee on Biological Standardization. Forty-second report*. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 822), Annex 1.

15. Good manufacturing practices: main principles for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth report*. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 3.

16. Good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996 (WHO Technical Report Series, No. 863), Annex 7.

17. *Guidance for industry: CGMP for phase 1 investigational drugs*. Rockville, MD, United States Food and Drug Administration, 2008 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070273.pdf, accessed 26 June 2013).

18. Cussler K. A 4R concept for the safety testing of immunobiologicals. *Developments in Biological Standardization*, 1999, 101:121–126.

19. Gupta RK. Is the test for abnormal toxicity, general safety or innocuity necessary for vaccines? *Vaccine*, 1996, 14(17–18):1718.

20. Halder M. Three Rs potential in the development and quality control of immunobiologicals. *ALTEX*, 2001, 18(Suppl. 1):S13–S47.

21. Guidelines on stability evaluation of vaccines. In: *WHO Expert Committee on Biological Standardization. Fifty-seventh report*. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 962), Annex 3.

22. Friede M et al. WHO initiative to increase global and equitable access to influenza vaccine in the event of a pandemic: supporting developing country production capacity through technology transfer. *Vaccine*, 2011, 29(Suppl. 1):A2–A7.

23. Verdijk P, Rots NY, Bakker WA. Clinical development of a novel inactivated poliomyelitis vaccine based on attenuated Sabin poliovirus strains. *Expert Review of Vaccines*, 2011, 10:635–644.

24. Giannini SL et al. Enhanced humoral and memory B cellular immunity using HPV16/18 L1 VLP vaccine formulated with the MPL/aluminium salt combination (AS04) compared to aluminium salt only. *Vaccine*, 2006, 24:5937–5949.

25. De Vleeschauwer AR et al. Efficacy of an AS03A-adjuvanted split H5N1 influenza vaccine against an antigenically distinct low pathogenic H5N1 virus in pigs. *Vaccine*, 2012, 30:5557–5563.

26. Stephenson I et al. Cross-reactivity to highly pathogenic avian influenza H5N1 viruses after vaccination with nonadjuvanted and MF59-adjuvanted influenza A/Duck/Singapore/97 (H5N3) vaccine: a potential priming strategy. *Journal of Infectious Diseases*, 2005, 191:1210–1215.

27. Zaitseva M et al. Use of human MonoMac6 cells for development of in vitro assay predictive of adjuvant safety in vivo. *Vaccine*, 2012, 30:4859–4865.

28. Ma Y et al. Assessing the immunopotency of Toll-like receptor agonists in an in vitro tissue-engineered immunological model. *Immunology*, 2010, 130:374–387.

29. Shin J et al. International regulatory requirements for vaccine safety and potency testing: a WHO perspective. *Procedia in Vaccinology*, 2011, 5:164–170.

30. Guidelines for independent lot release of vaccines by regulatory authorities. In: *WHO Expert Committee on Biological Standardization. Sixty-first report*. Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 978), Annex 2.

31. *Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals*. Tripartite Harmonised Guideline M3(R2). Geneva, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2009.
32. Diehl KH et al. A good practice guide to the administration of substances and removal of blood, including routes and volumes. *Journal of Applied Toxicology*, 2001, 21:15–23.
33. Kushner I, Mackiewicz A. The acute phase response: an overview. In: Mackiewicz A, Kushner I, Baumann H, eds. *Acute phase proteins: molecular biology, biochemistry, and clinical applications*. Boca Raton: CRC Press, 1993:3–19.
34. Draize JH, Woodard G, Calvery HO. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *Journal of Pharmacology and Experimental Therapeutics*, 1944, 82:377–390.
35. Herberts C et al. New adjuvanted vaccines in pregnancy: what is known about their safety? *Expert Review of Vaccines*, 2010, 9:1411–1422.
36. *Guidance for industry: considerations for developmental toxicity studies for preventive and therapeutic vaccines for infectious disease indications*. Center for Biologics Evaluation and Research, United States Food and Drug Administration, 2006 (http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm092170.pdf, accessed 26 June 2013).
37. *Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use*. Tripartite Harmonised Guideline S2(R1). Geneva, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2011.
38. *Safety pharmacology studies for human pharmaceuticals*. Tripartite Harmonised Guideline S7A. Geneva, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2000.
39. *Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials*. Center for Biologics Evaluation and Research, United States Food and Drug Administration, 2007 (http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf, accessed 26 June 2013).

Appendix 1

Examples of classes of adjuvants

The following main classes of adjuvants (see section on "Scope" and section 2 above) are currently used in licensed vaccines or are being investigated. The list is an updated version of the list of adjuvants developed by the European Medicines Agency, Committee for Medicinal Products for Human Use (*1*). For each category, representative examples are provided.

Classification of adjuvants

- **Mineral salts or gels** – for example, aluminium hydroxide, aluminium phosphate gels or calcium phosphate gels.
- **Oil-in-water and water-in-oil emulsions, amphiphilic molecules and surfactant-based formulations** – for example, Novartis' MF59 (microfluidized detergent-stabilized oil-in-water emulsion); QS-21 (purified saponin, which is derived from plants); GlaxoSmithKline's AS03 adjuvant (an oil-in-water emulsion plus α-tocopherol); and SEPPIC's Montanide ISA 51 and Montanide ISA 720.
- **Particulate adjuvants** – for example, liposomes; virosomes (unilamellar liposomal vehicles incorporating influenza haemagglutinin); DC Chol (a lipoidal immunostimulator able to self-organize into liposomes); immune-stimulating complexes known as ISCOMS (structured complexes of saponins and lipids) and CSL's Iscomatrix (the iscom without the incorporated antigen); and biopolymers such as Poly(lactide-co-glycolide) (PLGA).
- **Pathogen-associated molecular patterns (natural and synthetic)** – for example, low-toxicity versions of LPS, including monophosphoryl lipid A (MPL or MPLA) and RC-529 (a synthetic acylated monosaccharide); Detox adjuvant (an oil drop emulsion of MPL plus *Mycobacterium phlei* cell-wall skeleton); OM-174 (lipid A derivative); CpG motifs (synthetic oligodeoxynucleotides containing immunostimulatory CpG motifs); bacterial flagellin genetically fused with an antigen; bacterial toxins that have been genetically modified to provide nontoxic adjuvant effects such as modified heat-labile enterotoxin (LT) and cholera toxin (CT); and synthetic dsRNA such as Poly IC, Poly ICLC (also known as Hiltonol), and poly I:poly C12U (known as Ampligen).

- **Endogenous human immunostimulators** – for example, cytokines such as human granulocyte-macrophage colony-stimulating factor (hGM-CSF) or human interleukin-12 (hIL-12) that may be administered as proteins or as plasmid preparations (DNA sequences contained in DNA vaccine vectors that promote gene expression and are capable of inducing and/or promoting an immune response against an antigen in vaccine recipients).
- **Inert vehicles** – for example, gold particles.
- **Adjuvants derived from inulin** – for example, Vaxine's delta inulin (a plant-derived polysaccharide also known as Advax).
- **Combination adjuvants or adjuvant systems** consisting of combinations of vaccine-delivery systems and immunostimulatory agents that may result in more effective delivery of the immunostimulatory adjuvant as well as the antigen – for example, AS01 (liposomes, MPL and QS-21), AS02 (an oil-in-water emulsion plus MPL and QS-21), AS03 (an oil-in-water emulsion plus α-tocopherol), AS04 (MPL and aluminium hydroxide), AS15 (liposomes, MPL, QS-21 and a CpG oligodeoxynucleotide), glucopyranosyl lipid adjuvant-stable emulsion (GLA-SE) (a synthetic acylated monosaccharide in a stable oil-in-water emulsion) and CAF01 (liposomes, a quaternary ammonium lipid and a synthetic analogue of a mycobacterial lipid).

Reference

1. Committee for Medicinal Products for Human Use. *Guideline on adjuvants in vaccines for human use*. London, European Medicines Agency, 2005 (EMEA/CHMP/VEG/134716/2004) (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003809.pdf, accessed 26 June 2013).

Appendix 2

Tissue samples to be collected for a repeated-dose toxicity study

This is a comprehensive list of the tissues that should be evaluated for local and systemic toxicity in repeated-dose toxicity studies; some additional tissues have been included to represent those specifically targeted by adjuvanted vaccines. This is an updated version of a list developed initially by WHO for vaccines (*1*) that was broadened and harmonized by the European Medicines Agency, Committee for Medicinal Products for Human Use (*2*) and the Society of Toxicologic Pathology (*3*).

Samples should be collected from the following tissues. The type of tissue to be collected depends upon the species used for testing.

adrenal glands

aorta (thoracic)

bone (femur) with articulation

bone (sternum) with bone marrow

bone marrow smears[1]

brain

bronchi (main stem)

caecum

colon

diaphragm

duodenum

epididymides

eyes

gall bladder

Harderian glands

heart

ileum

injection site(s) (a sample should be taken from the area of injection)

jejunum

kidneys

lachrymal glands (from the main body and subconjunctival part)

larynx

liver

lungs

lymph nodes that drain the injection site

lymph nodes that do not drain the injection site (e.g. mandibular or mesenteric)

mammary gland

nasal–oropharyngeal cavity (depending on the vaccine and adjuvant)

[1] Bone marrow smears should be prepared for all animals at the time of necropsy, including from any moribund animals killed during the study. The smears should be fixed in methanol and then stained using the May-Grunwald-Giemsa method.

nasal tissue (skull/nasal cavity)
oesophagus
optic nerves
ovaries
oviducts
pancreas
parathyroid glands
Peyer's patches
pituitary gland
prostate
rectum
salivary glands (mandibular, parotid and sublingual)
sciatic nerves
seminal vesicles
skeletal muscle
skin
spinal cord (cervical, thoracic and lumbar)
spleen
stomach
testes
thymus
thyroid glands
tissues with macroscopic observations (a sample should be taken from any and all tissues with macroscopic observations)
tongue
trachea
ureters
urinary bladder
uterus (from the body, horns and cervix)
vagina

References

1. WHO guidelines on nonclinical evaluation of vaccines. In: *WHO Expert Committee on Biological Standardization. Fifty-fourth report*. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 927), Annex 1.
2. Committee for Medicinal Products for Human Use. *Guideline on repeated dose toxicity*. London, European Medicines Agency, 2010 (EMEA/CHMP/SWP/1042/99 Rev. 1 Corr.) (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500079536.pdf, accessed 26 June 2013).
3. Bregman CL et al. Recommended tissue list for histopathologic examination in repeat-dose toxicity and carcinogenicity studies: a proposal of the Society of Toxicologic Pathology (STP). *Toxicologic Pathology*, 2003, March–April, 31(2):252–253 (http://www.ncbi.nlm.nih.gov/pubmed/12696587, accessed 22 February 2014).

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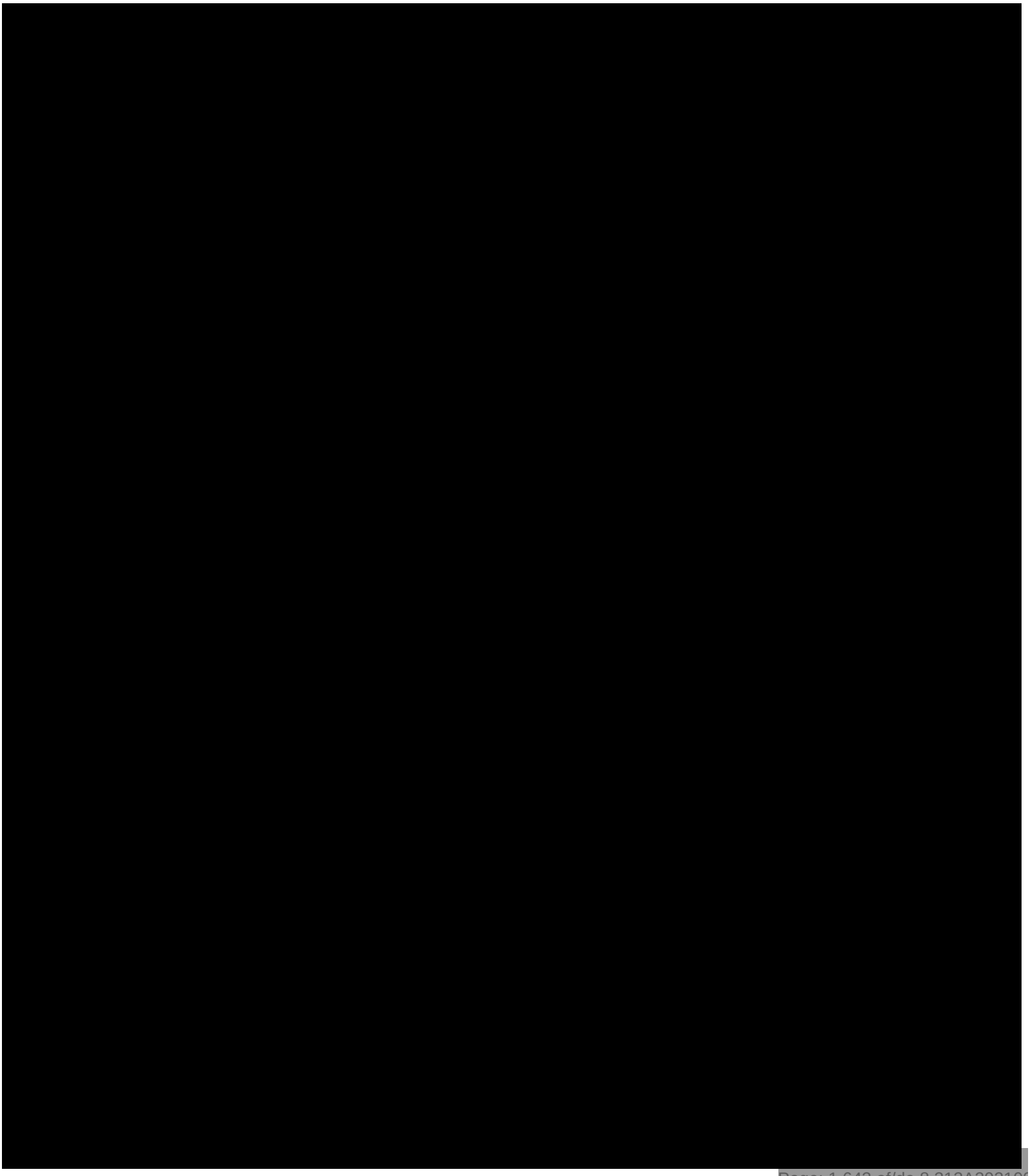

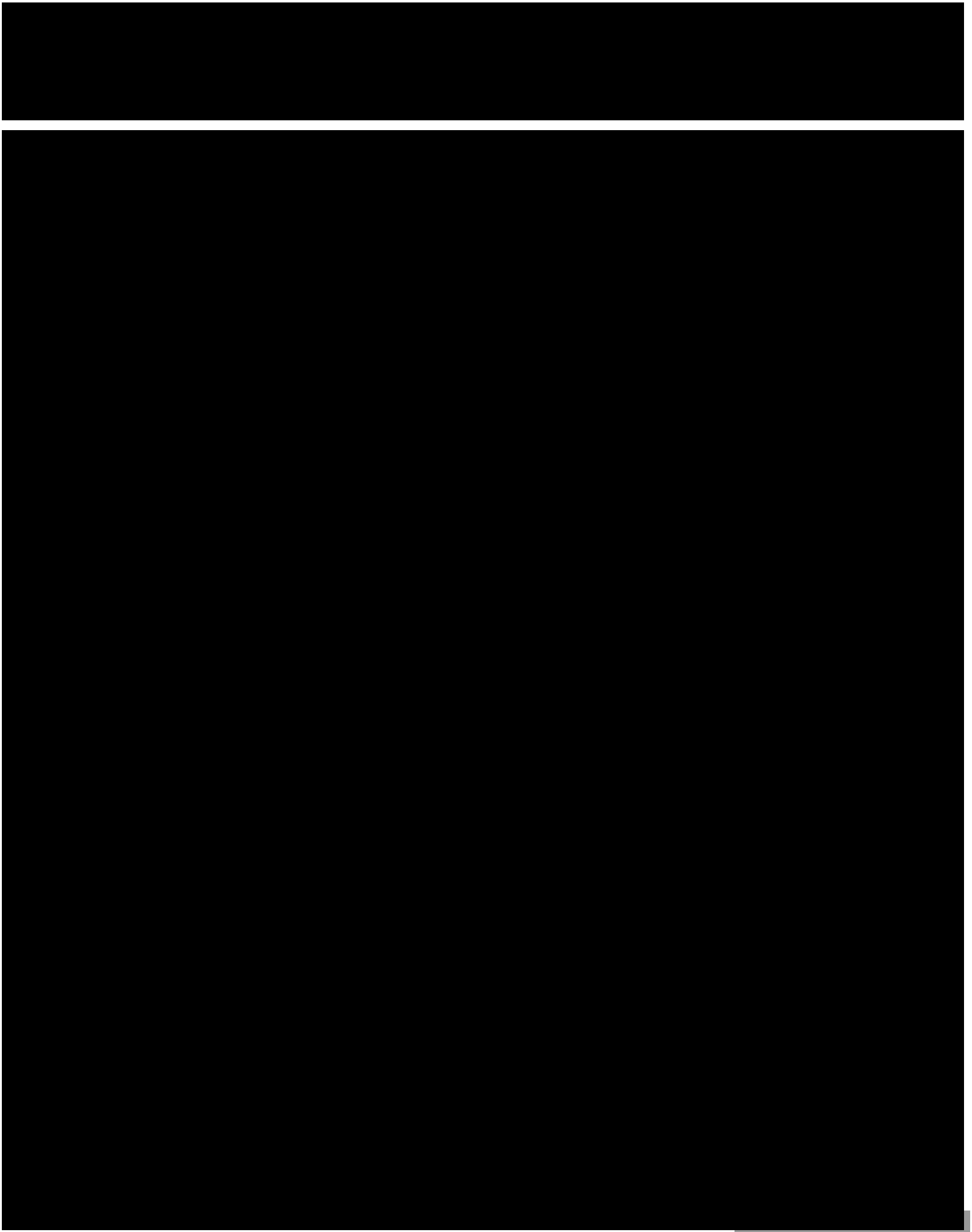

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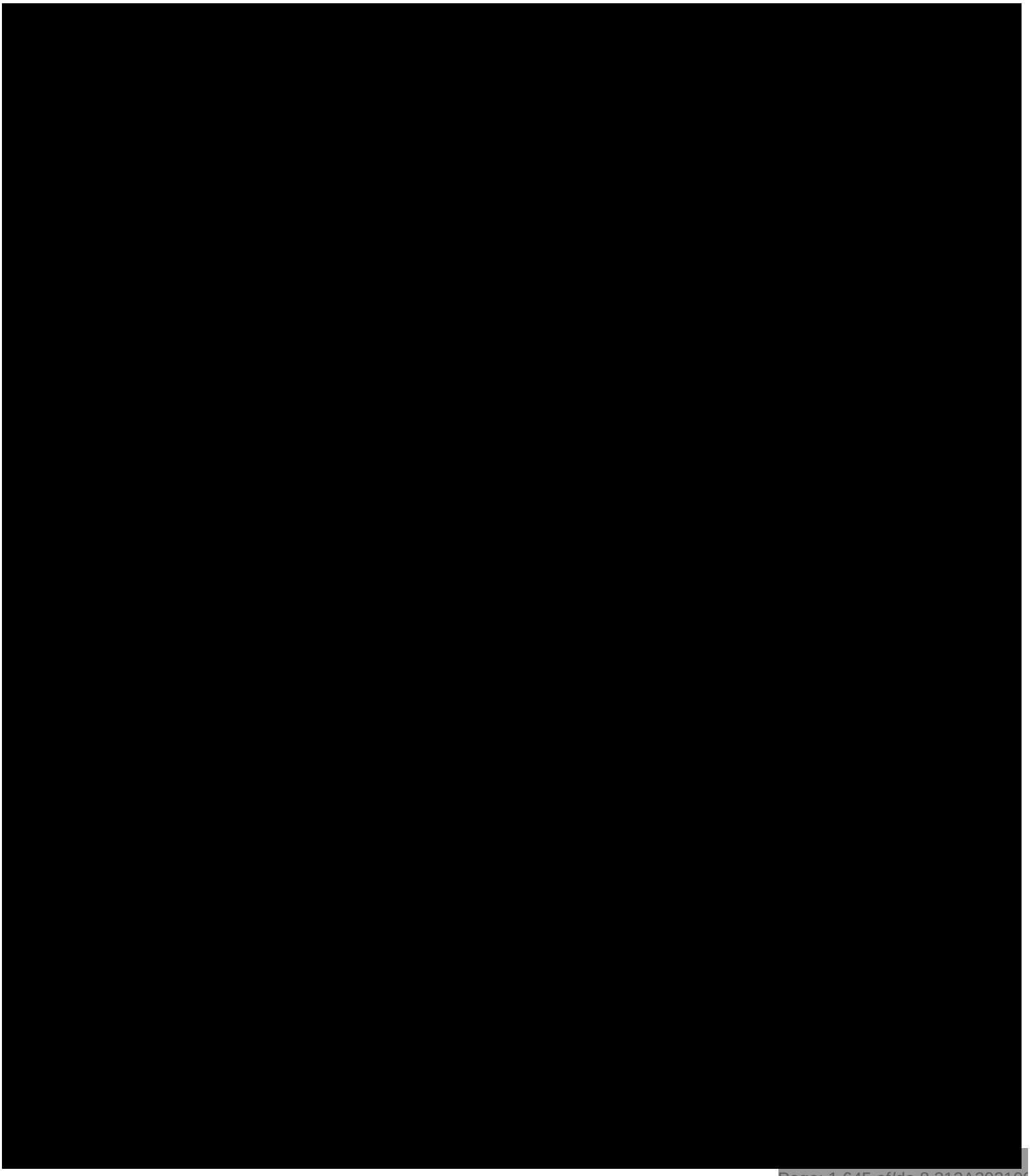

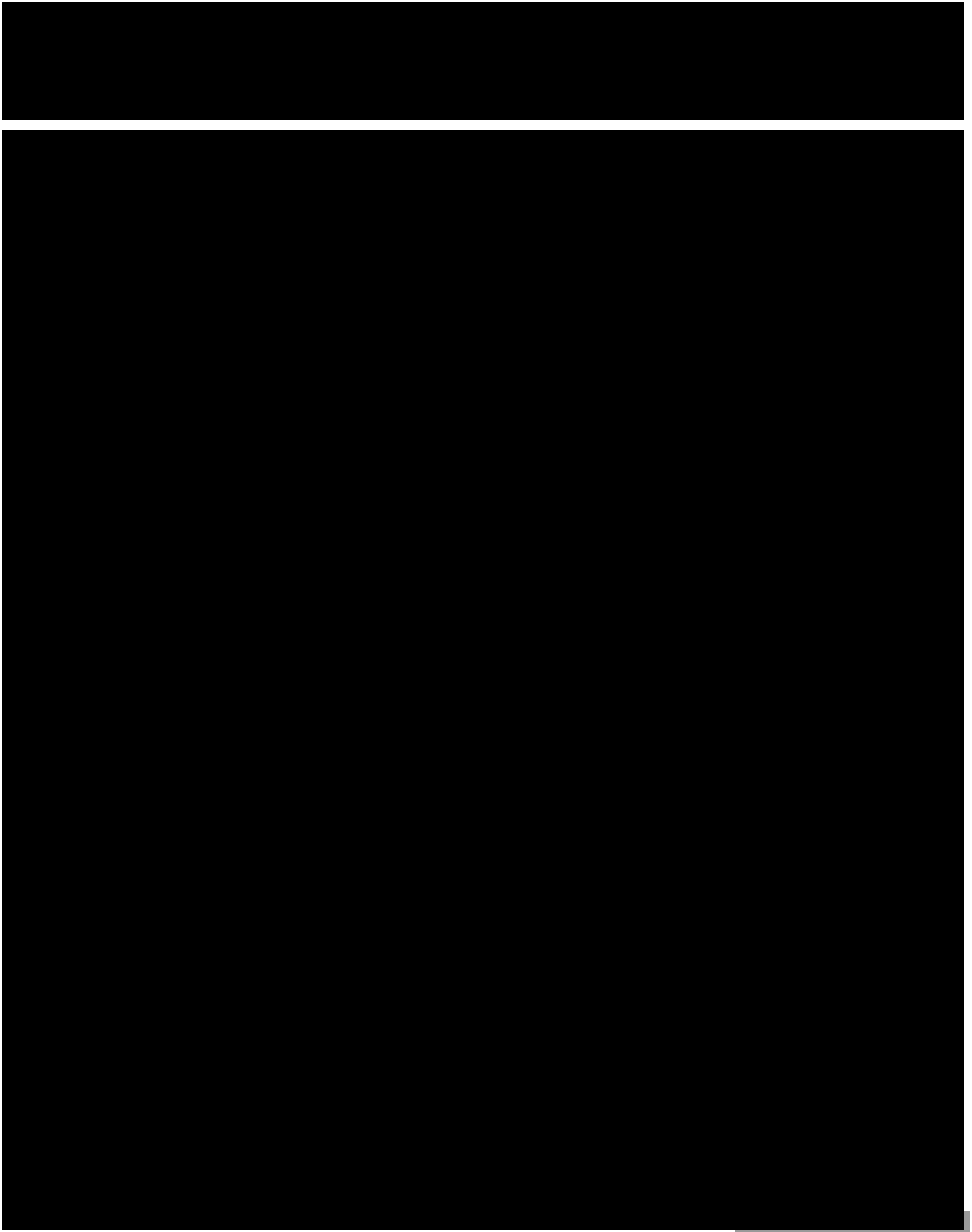

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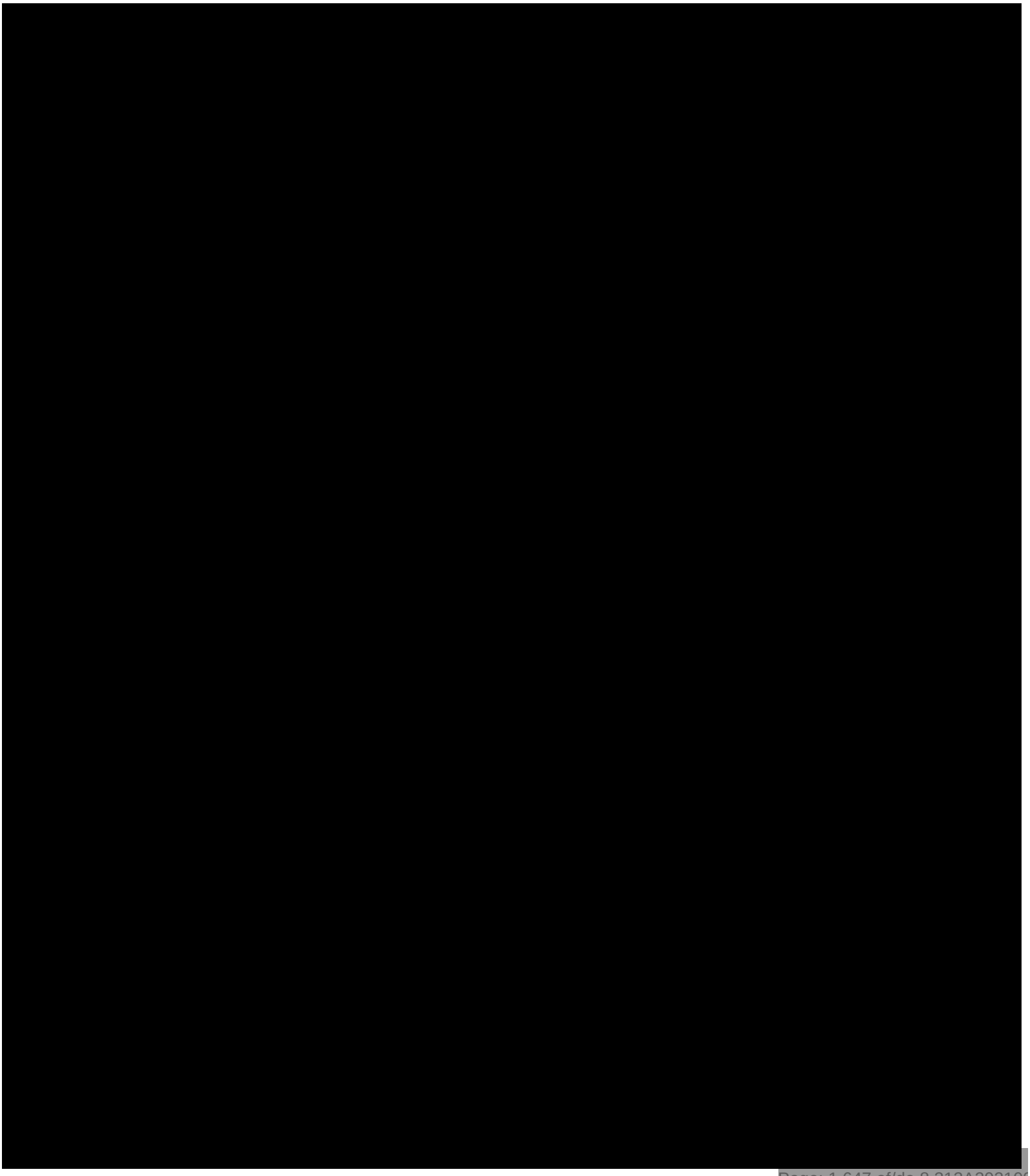

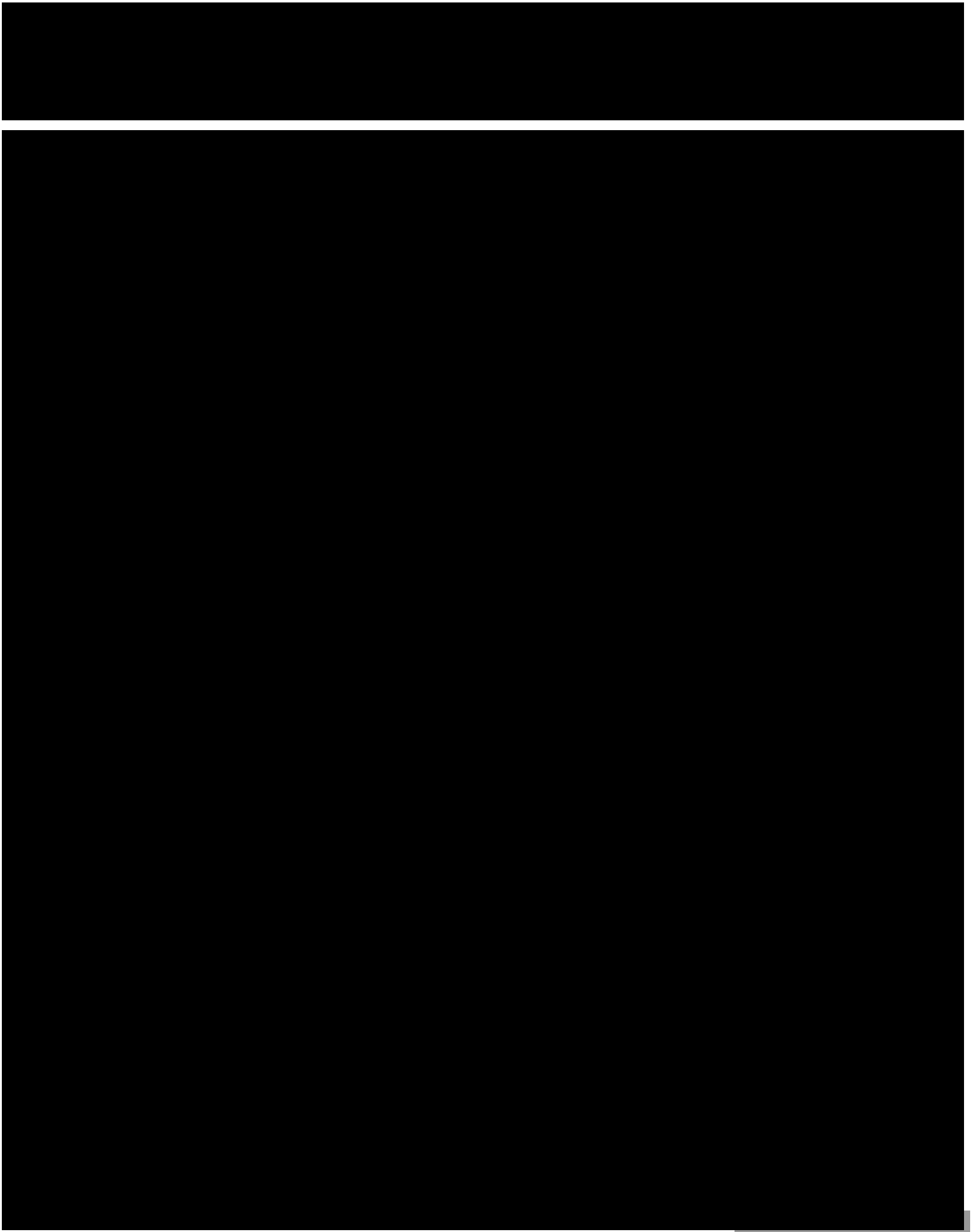

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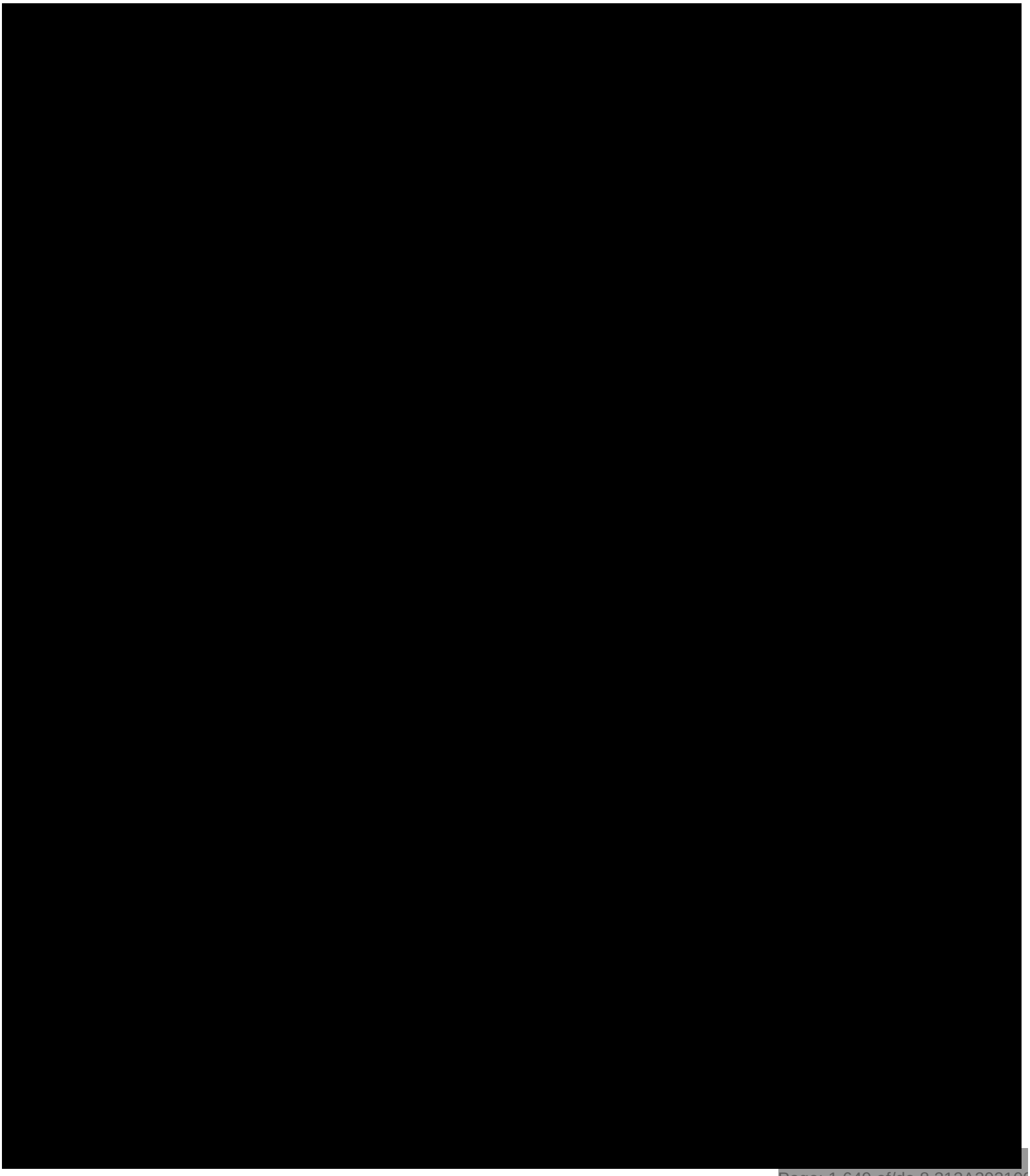

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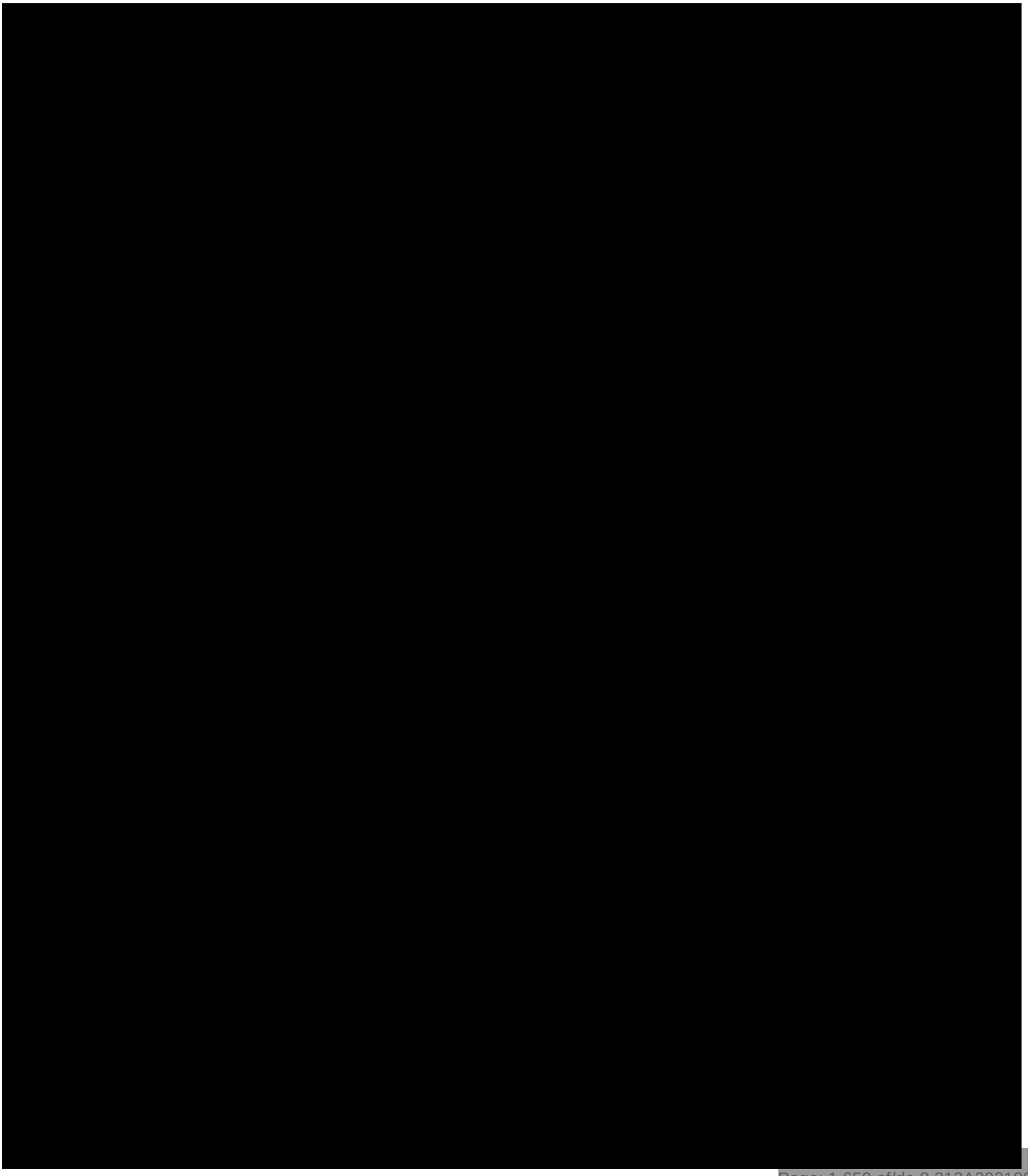

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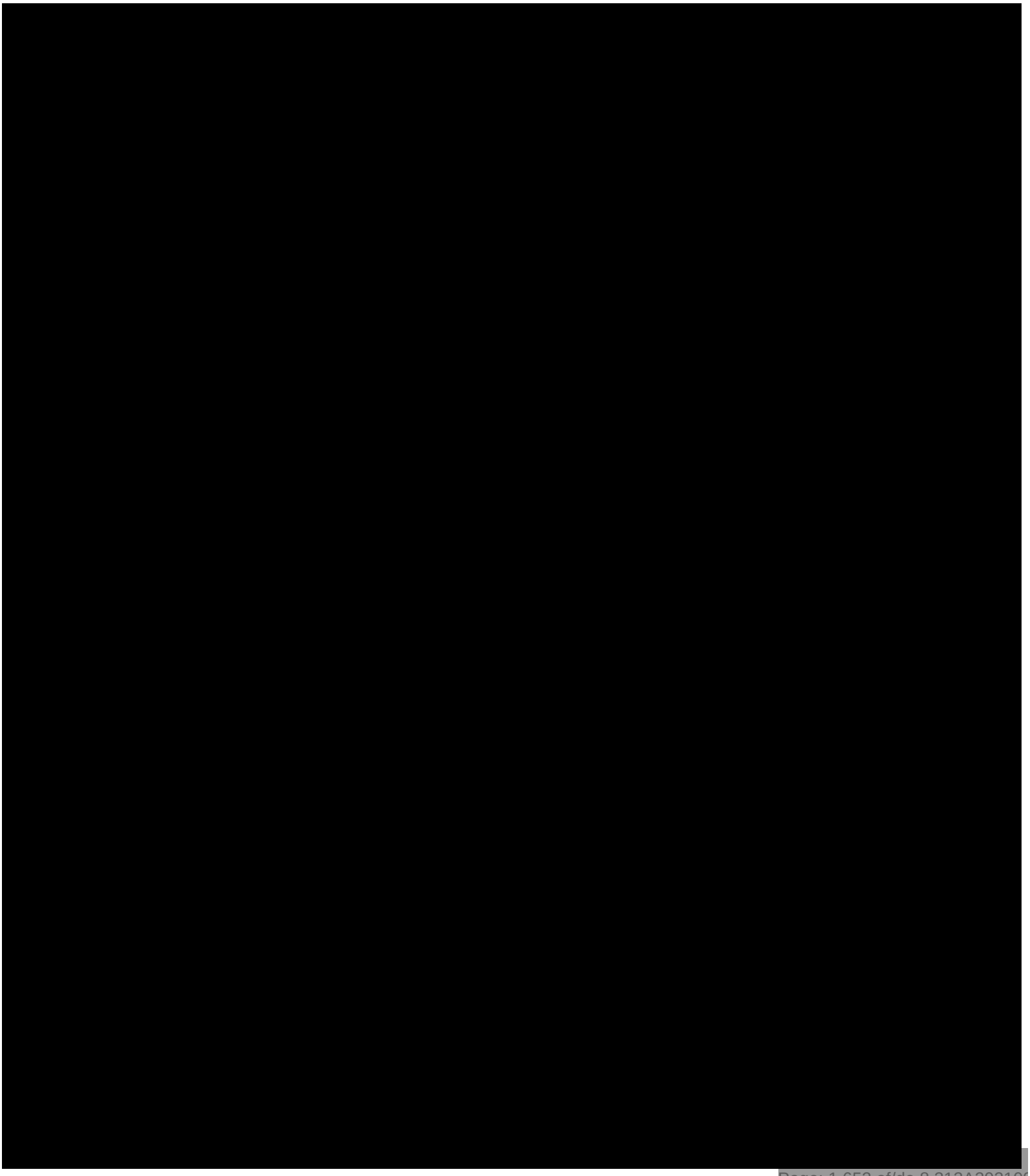

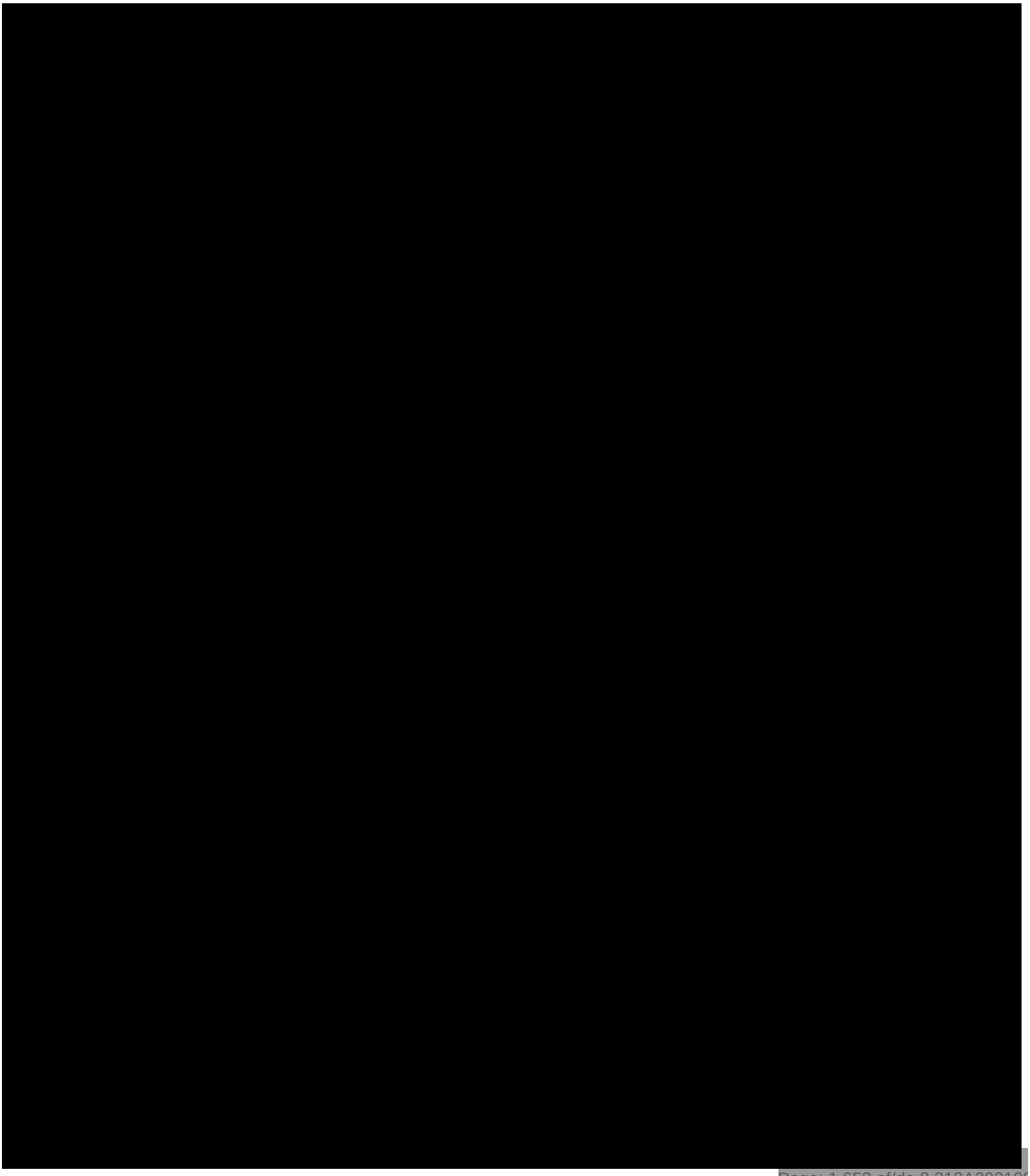

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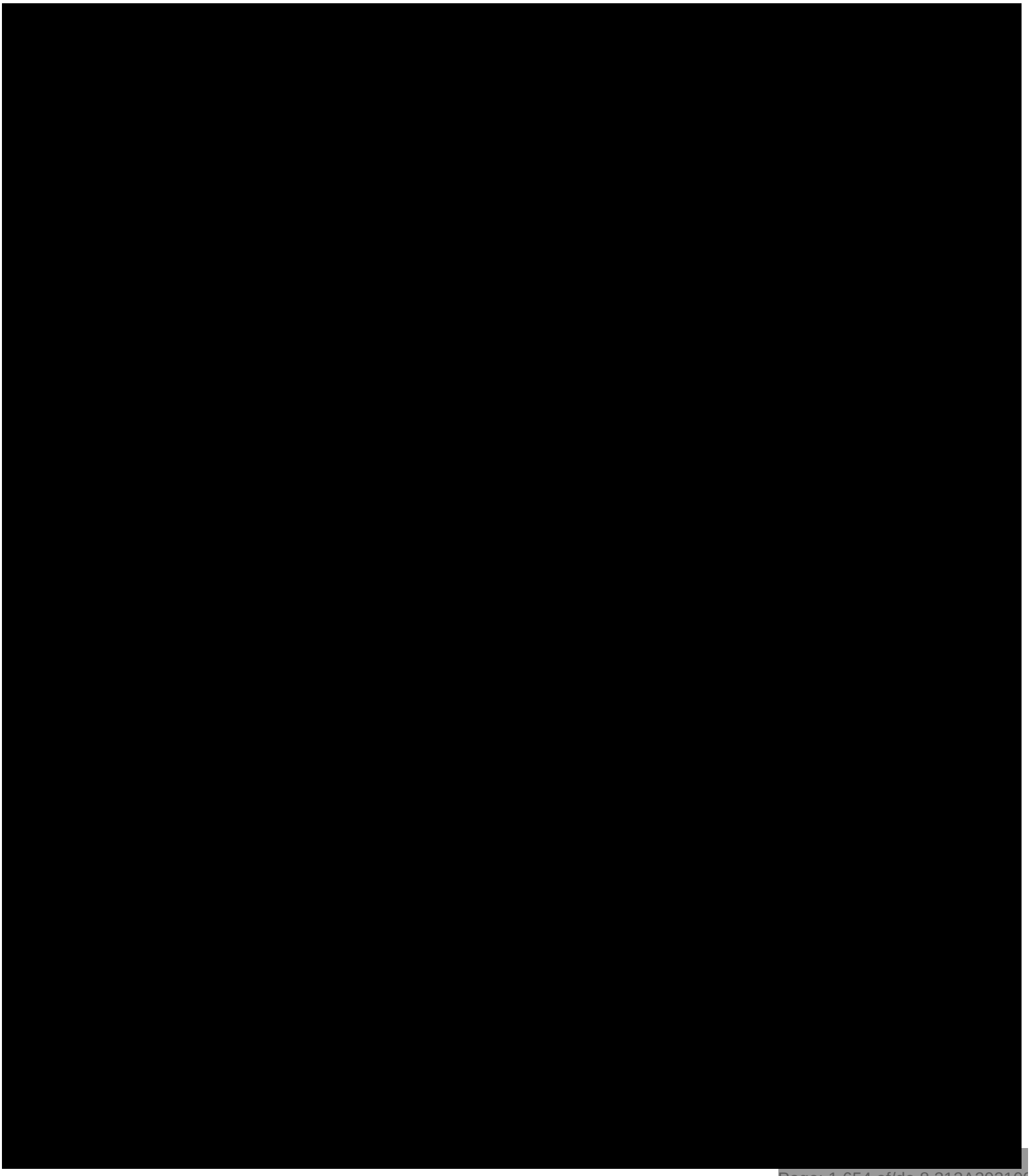

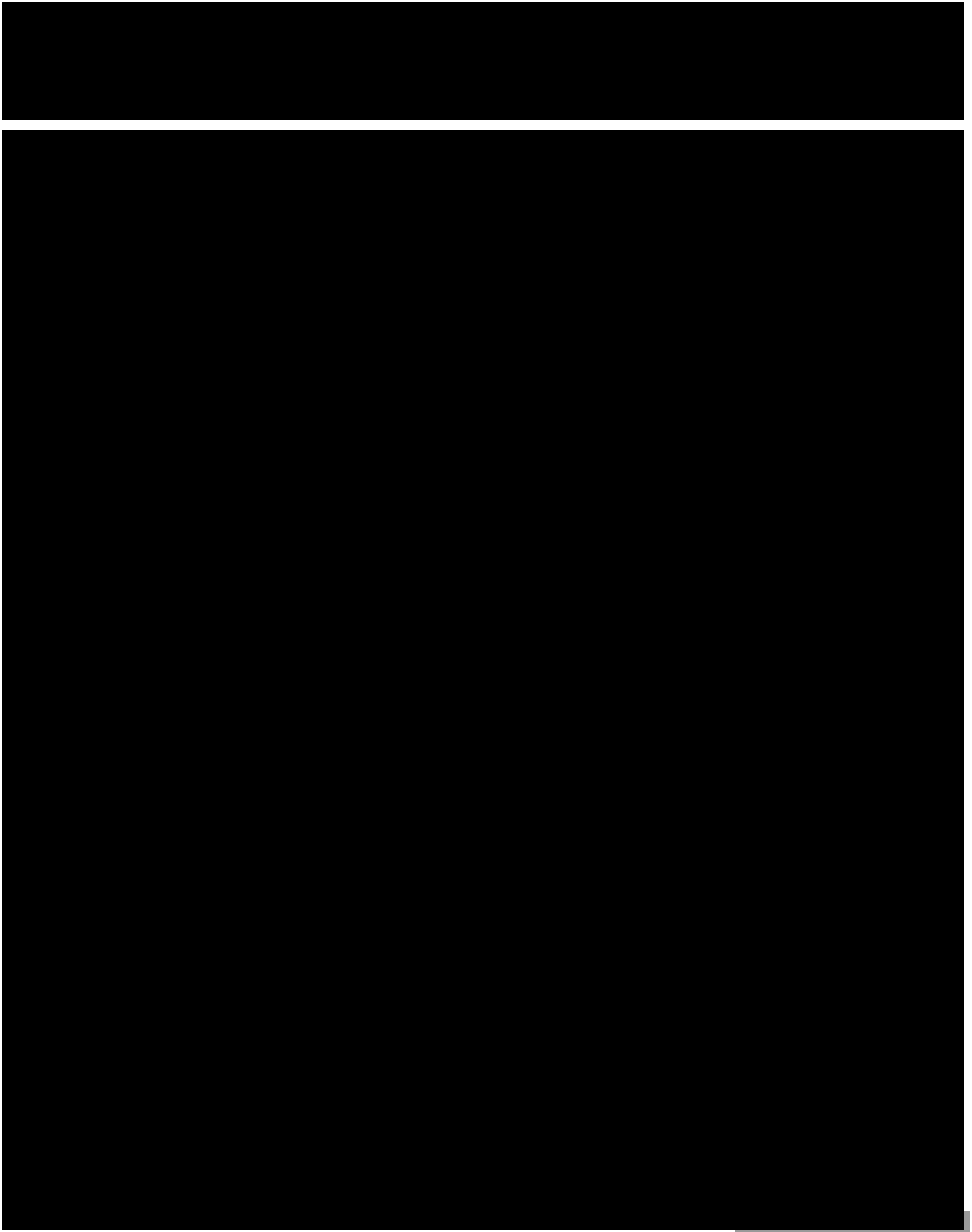

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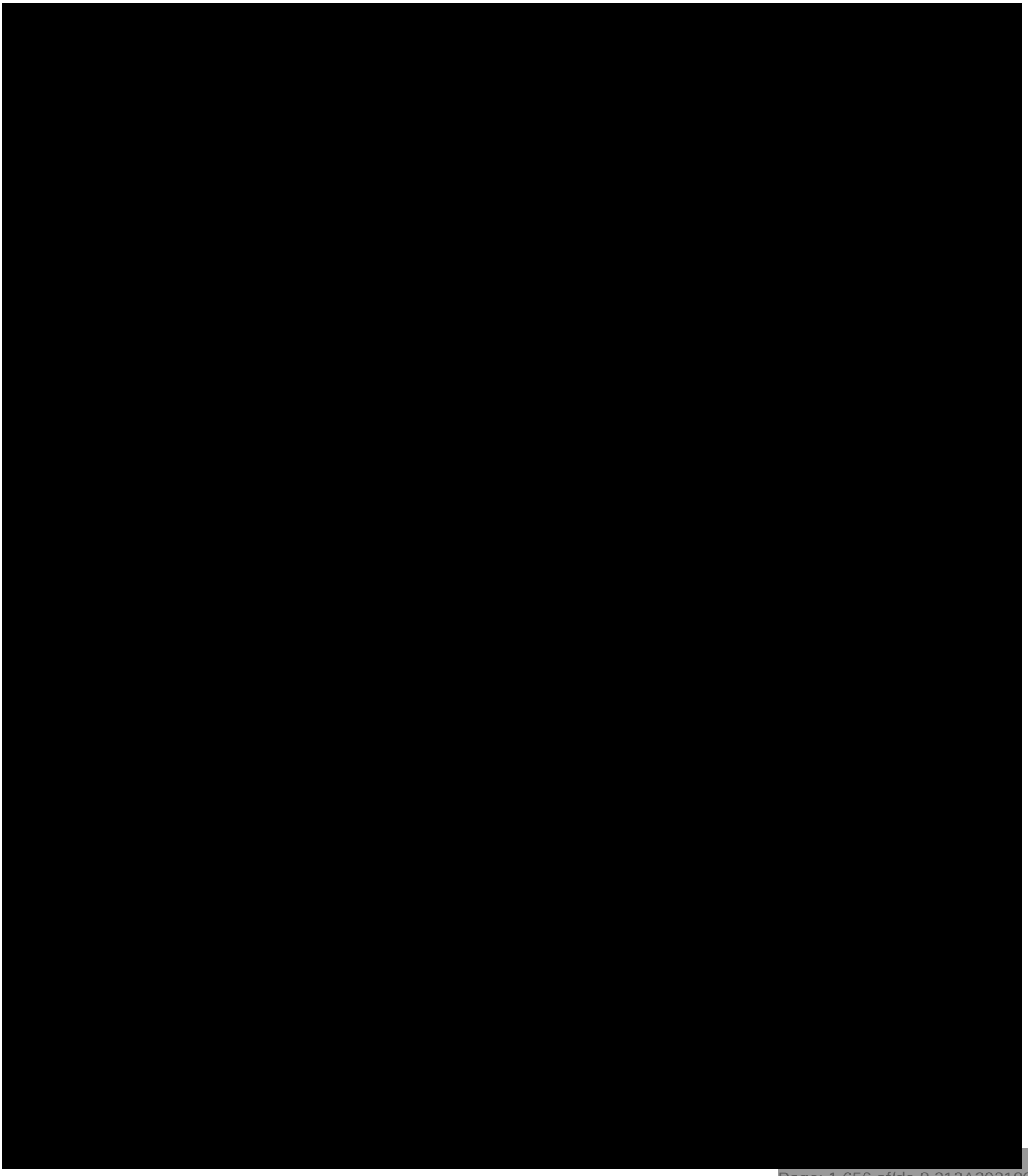

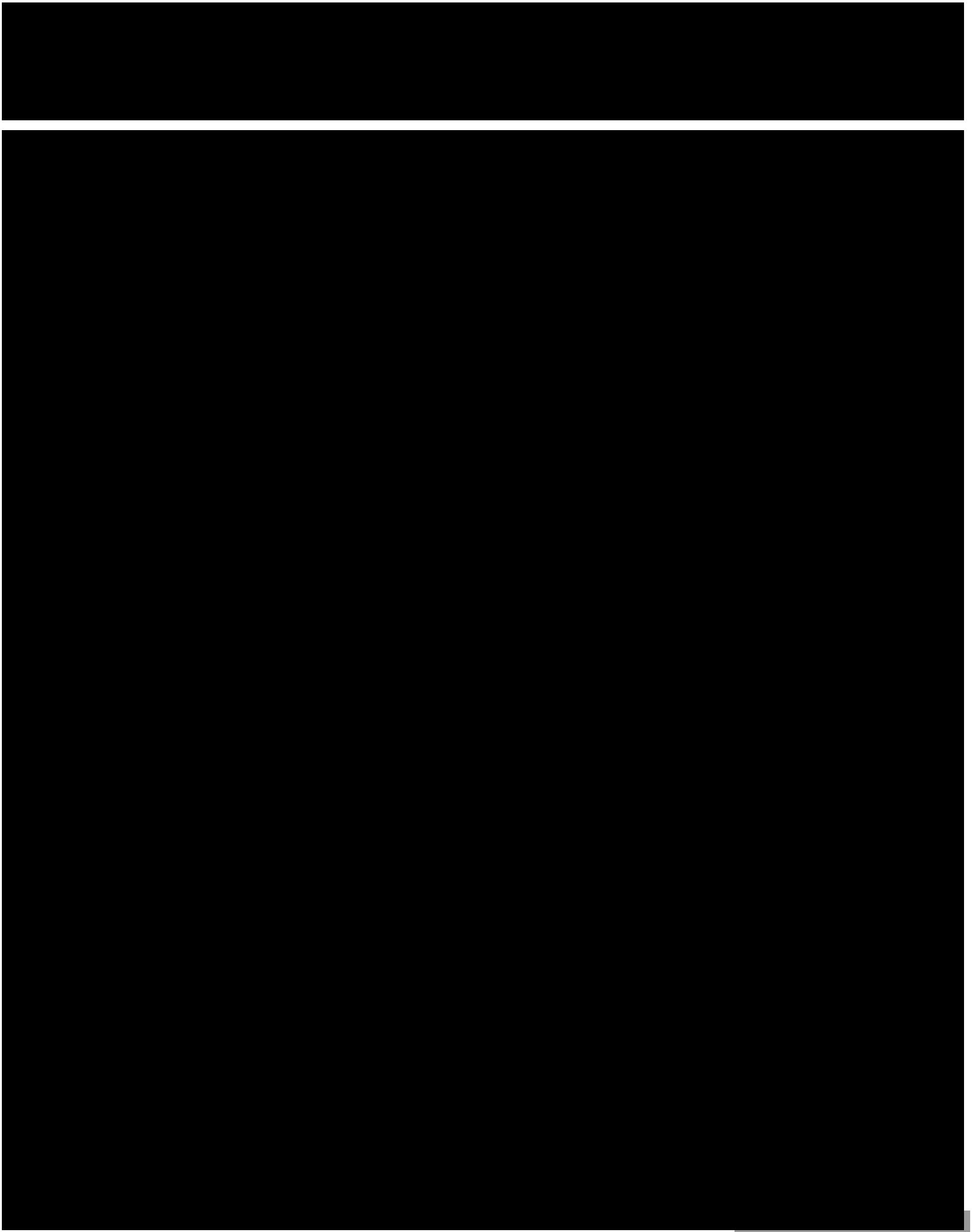

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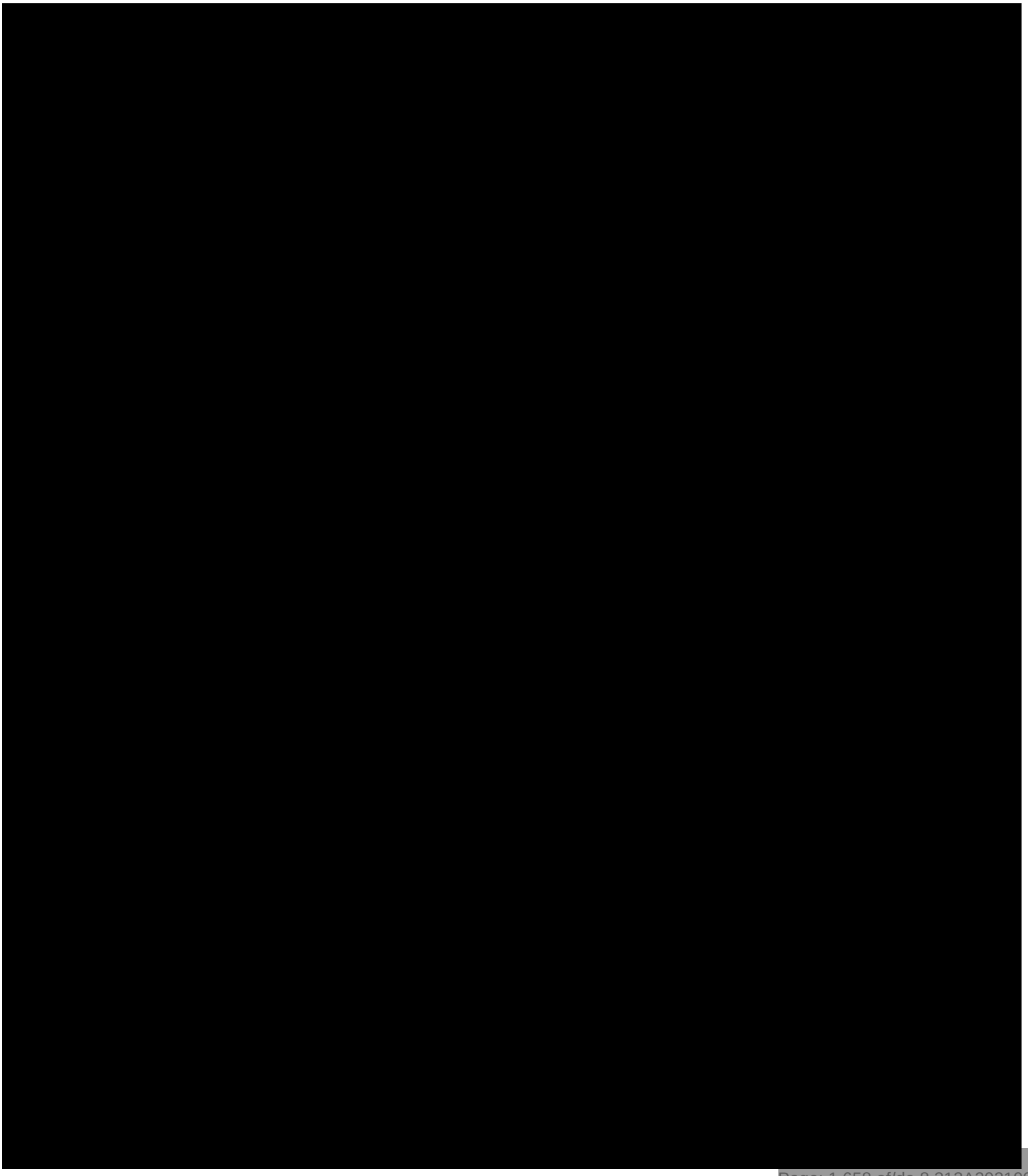

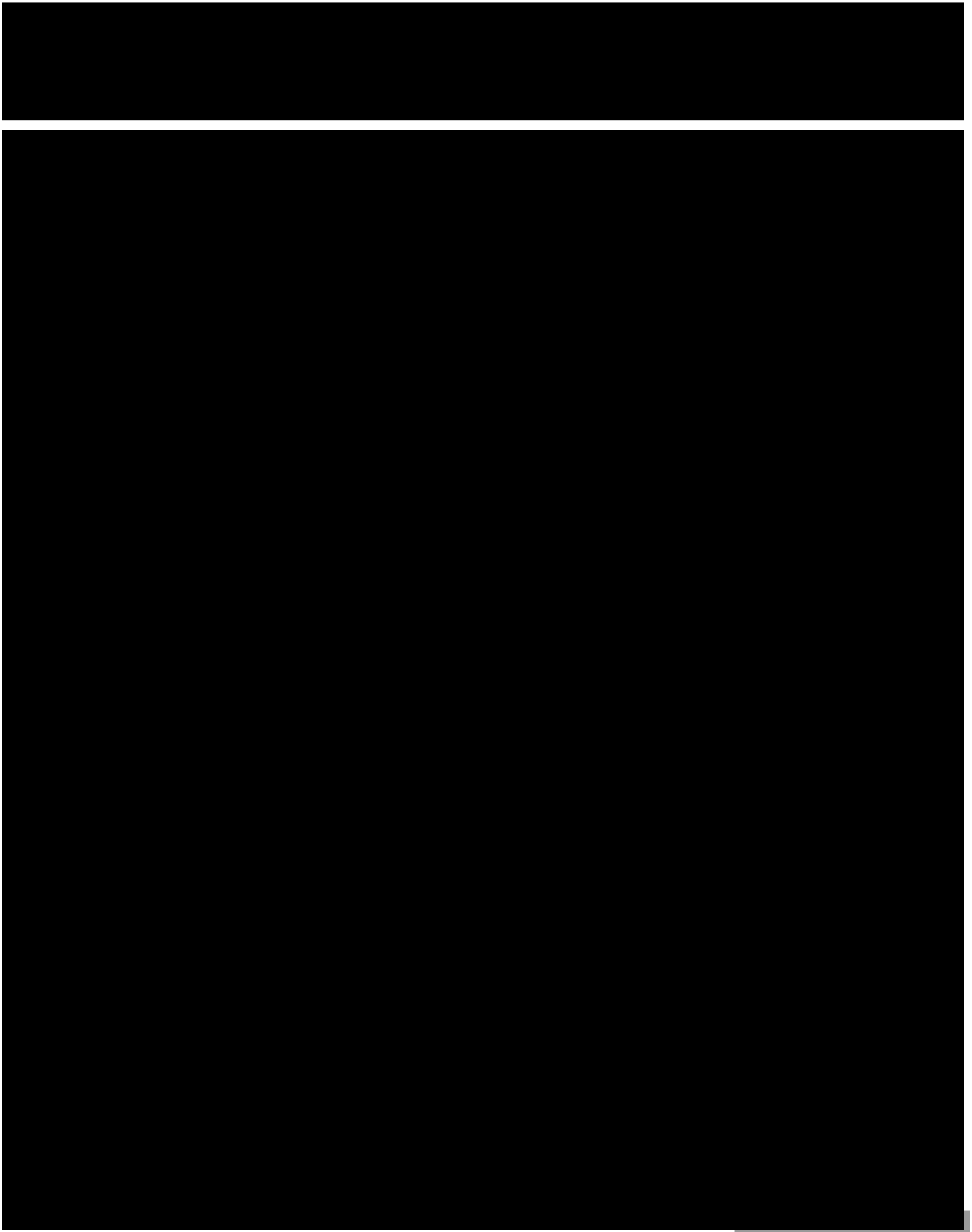

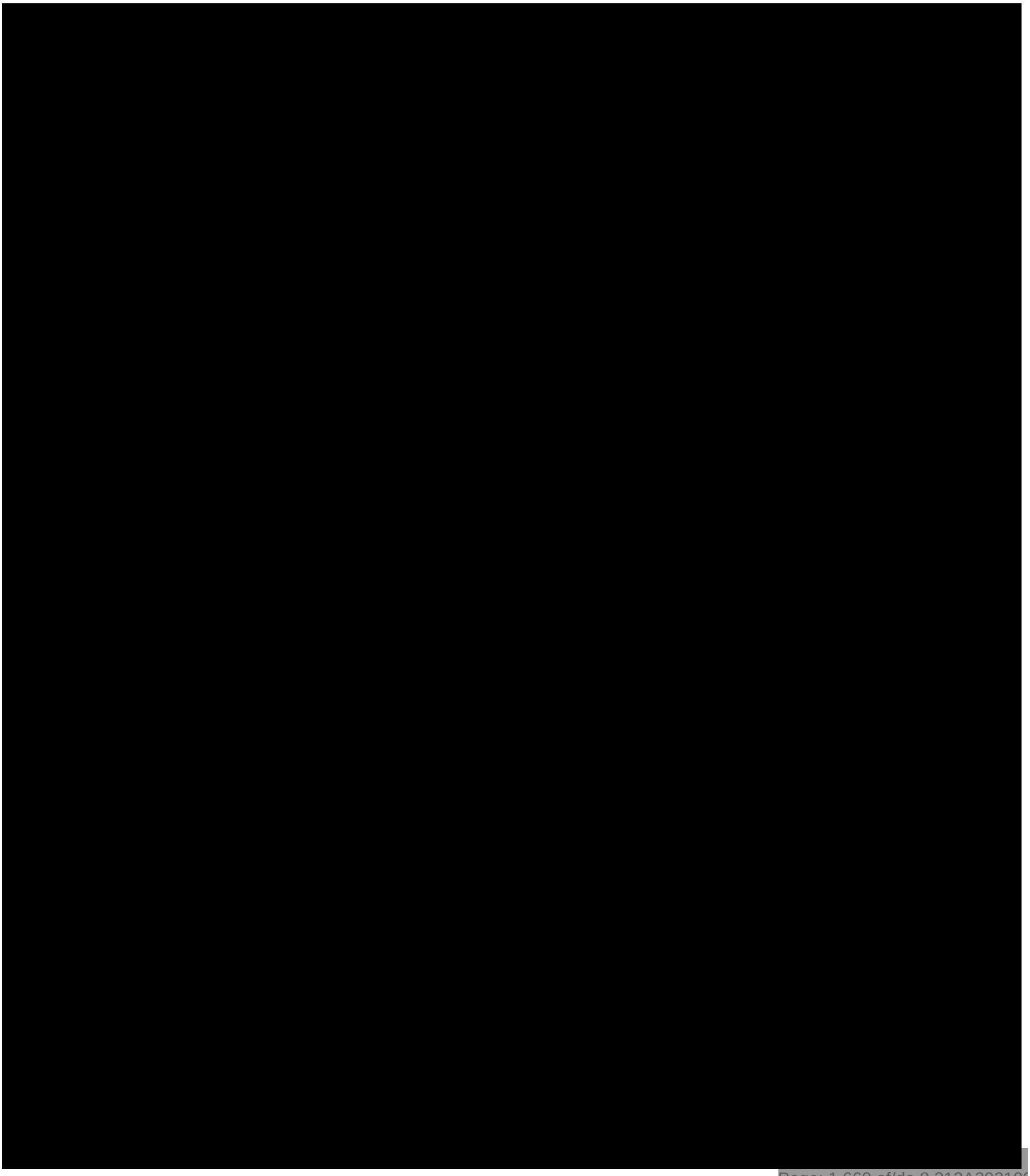

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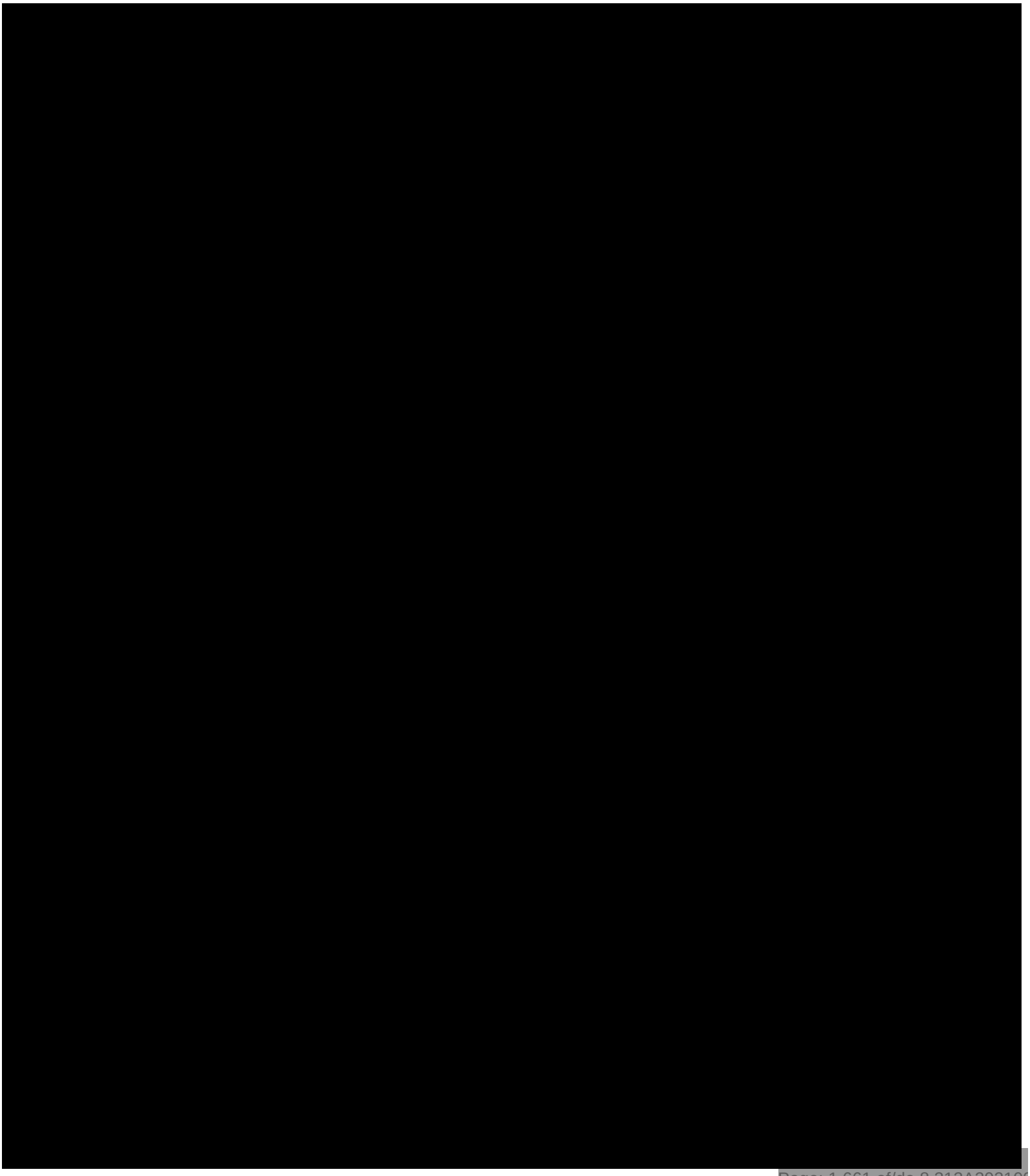

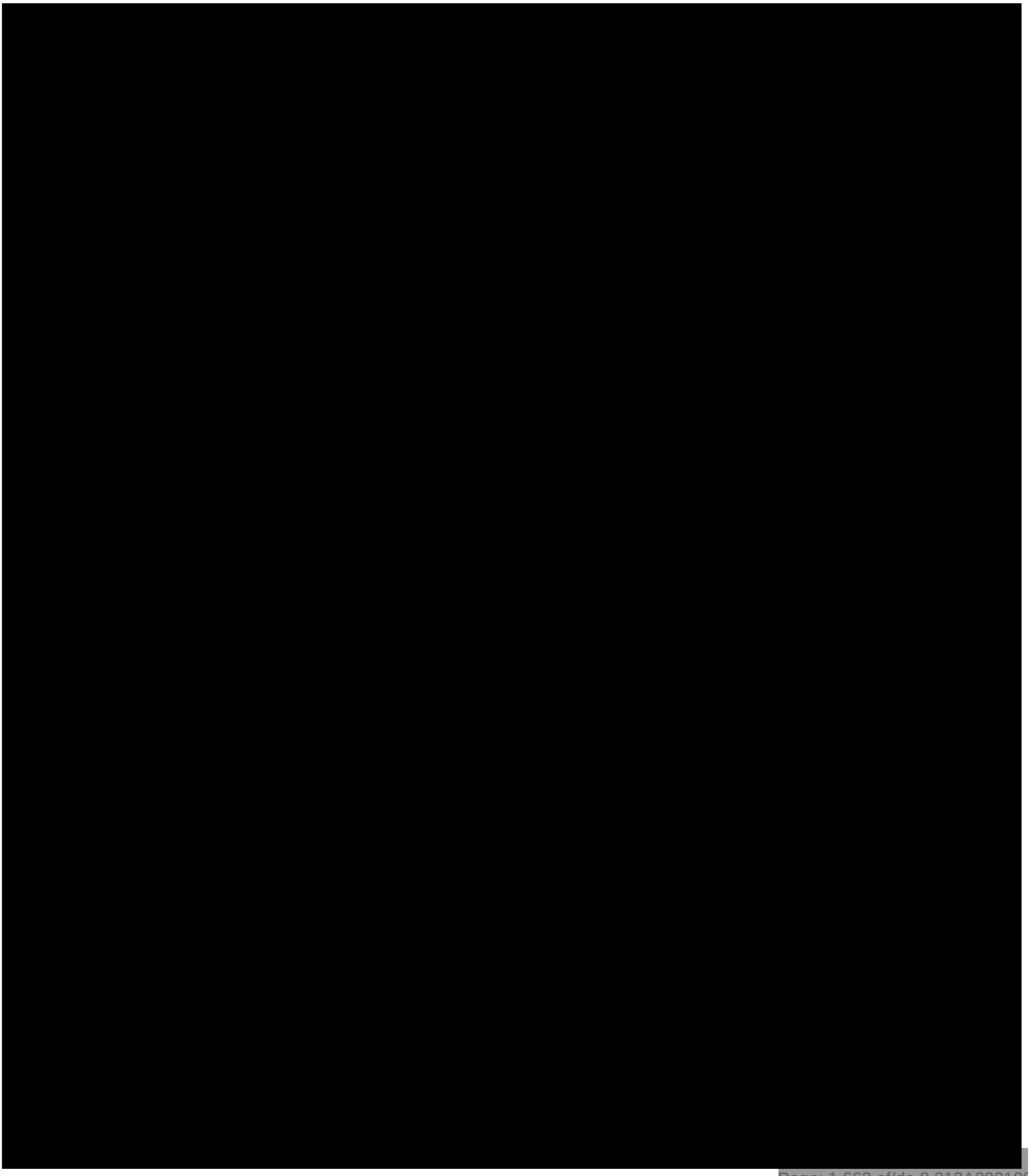

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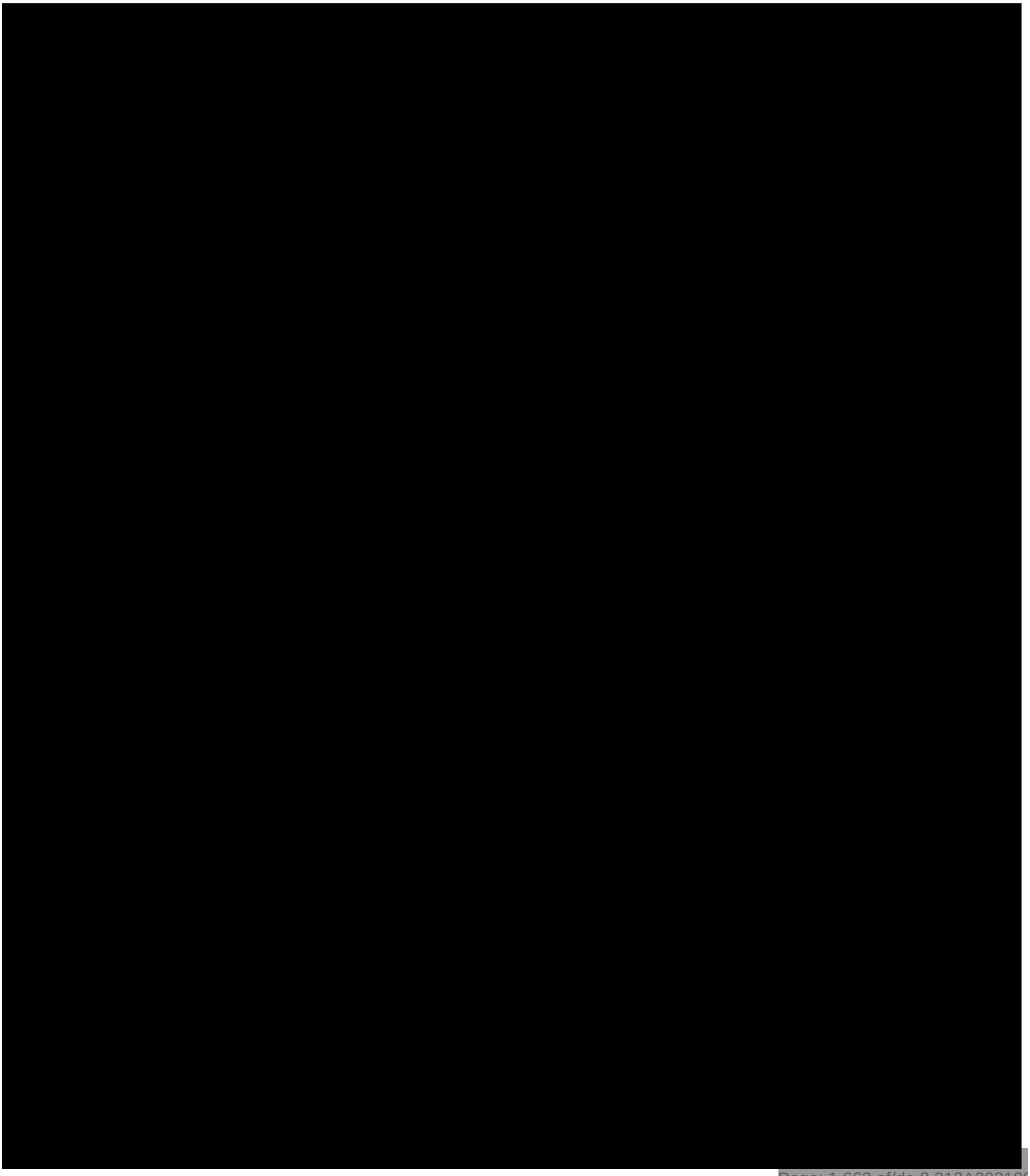

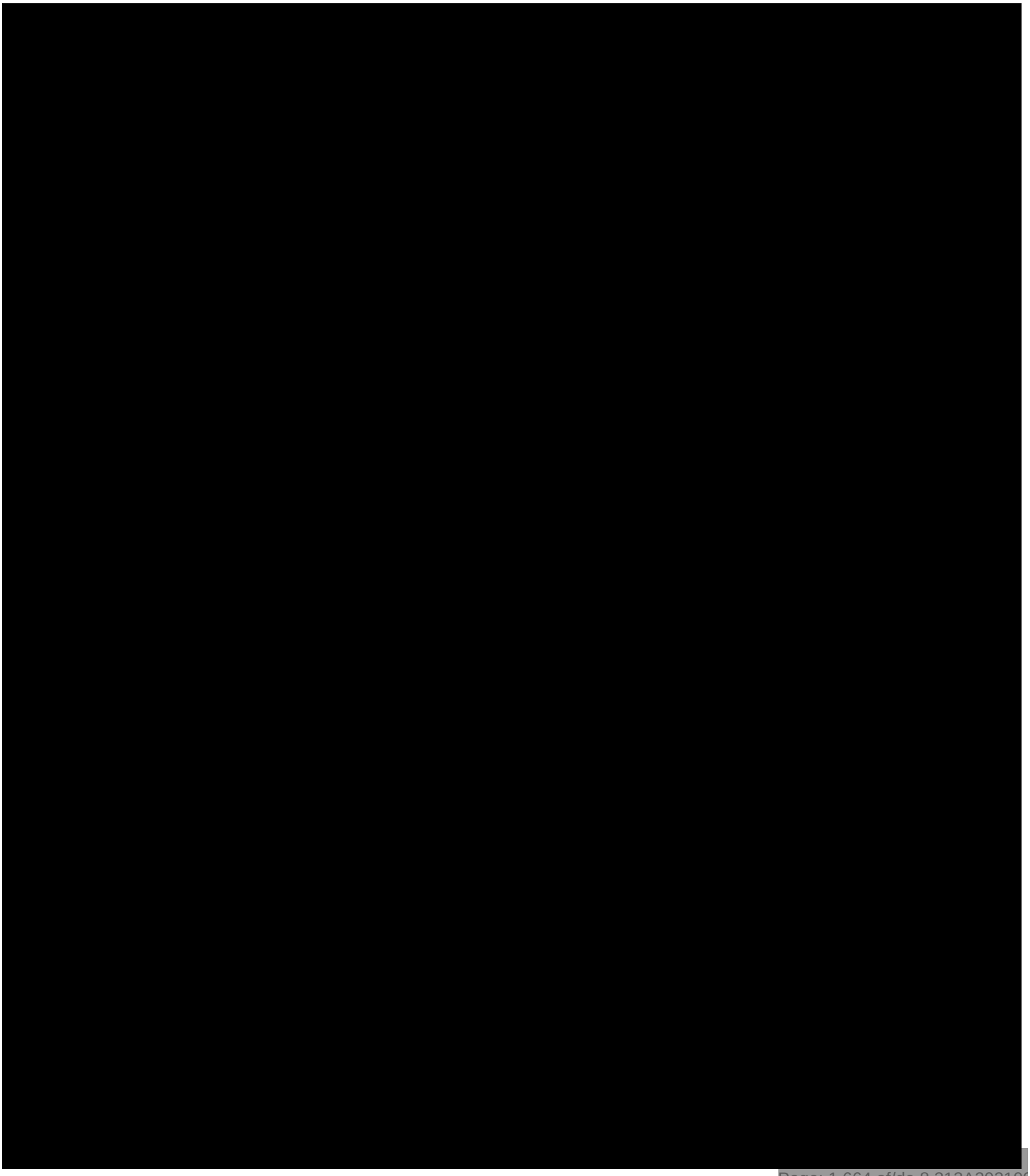

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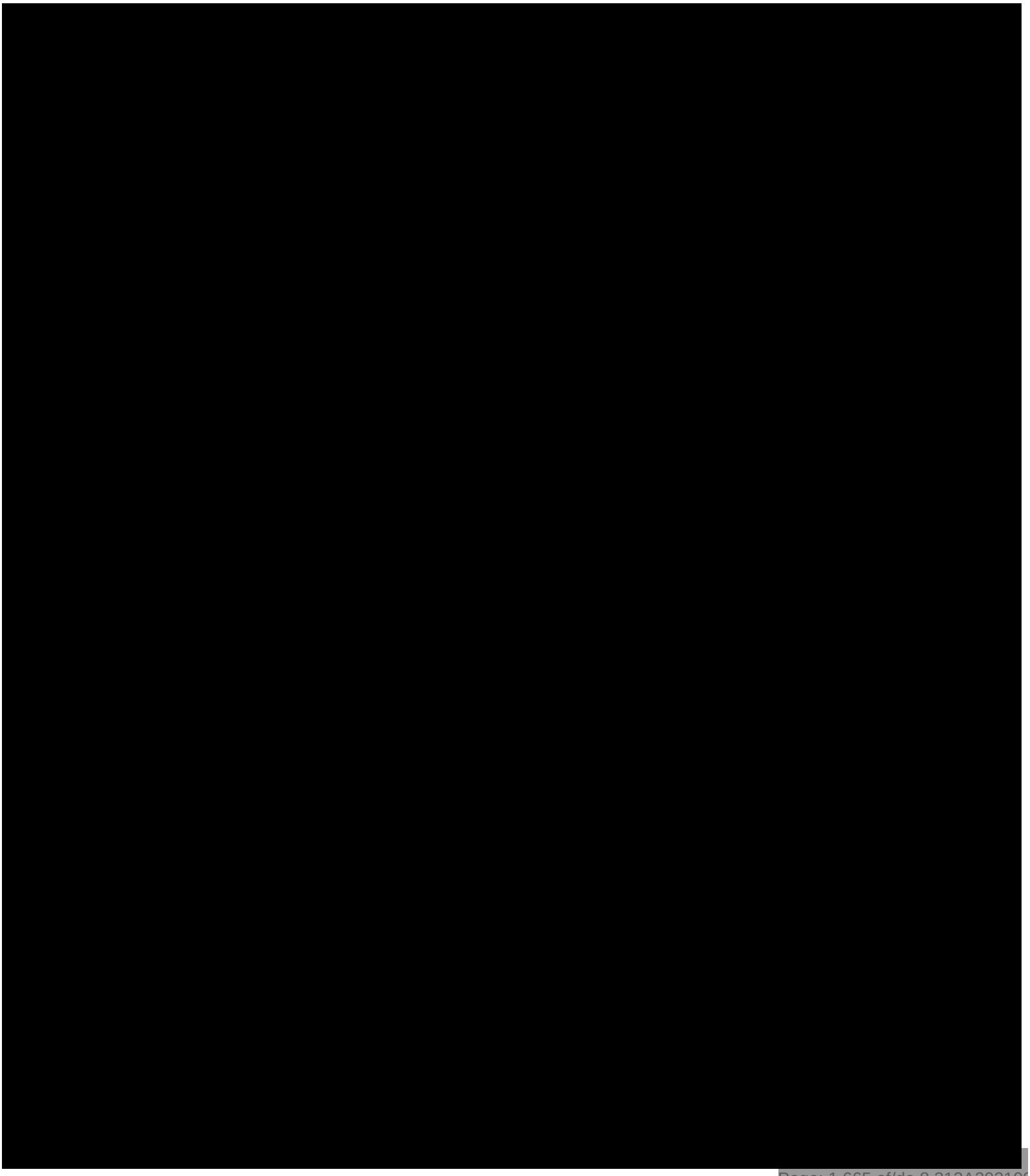

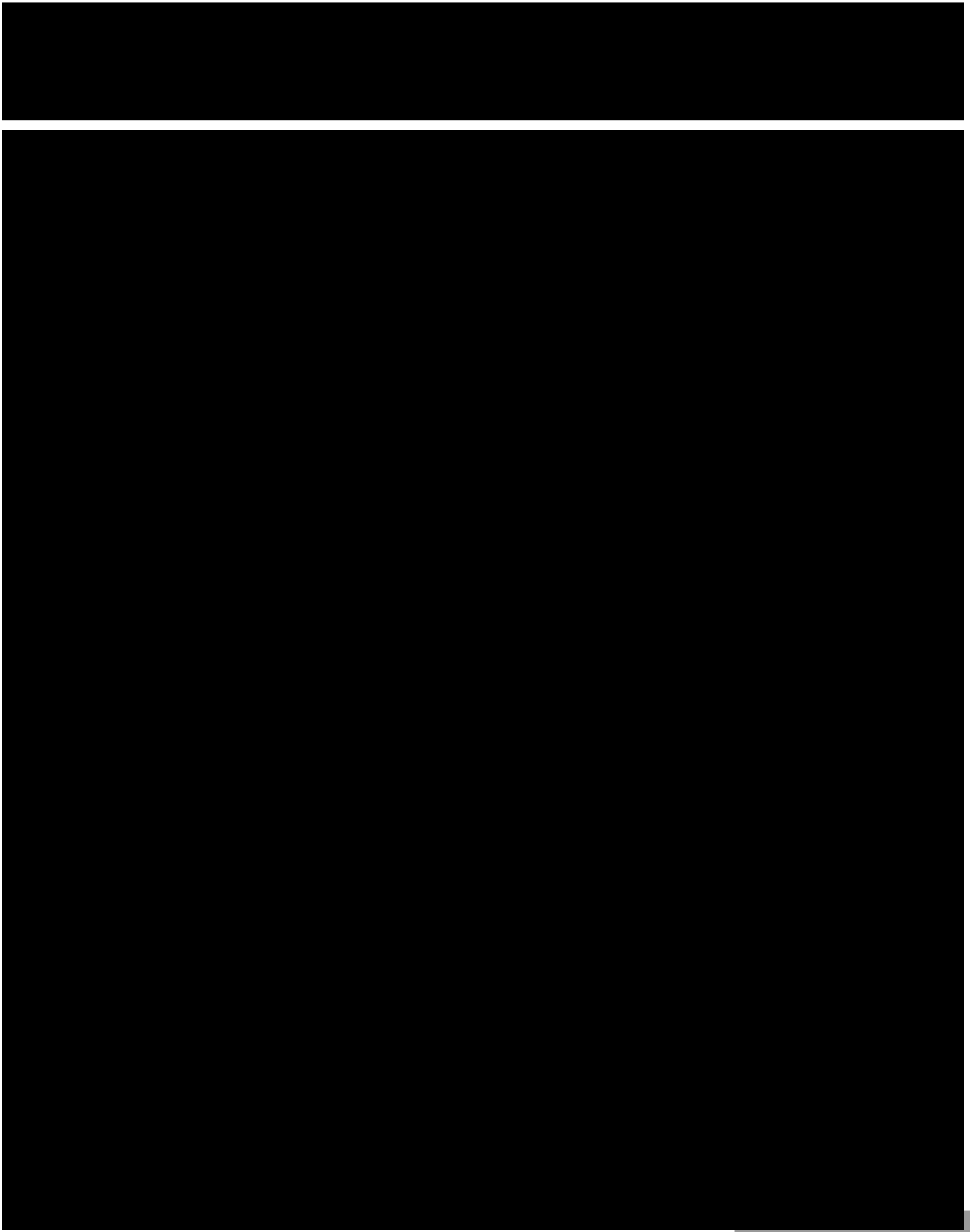

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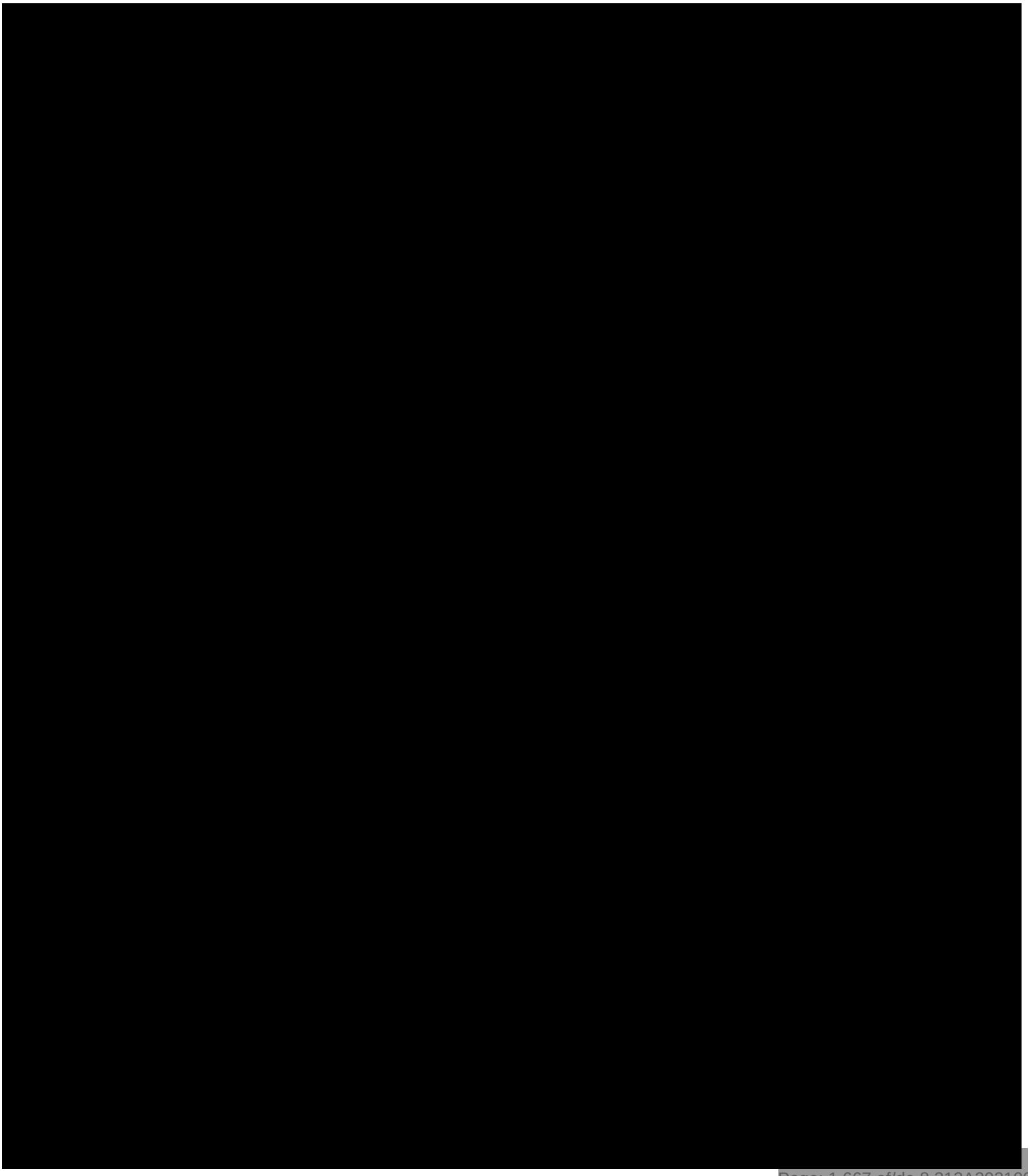

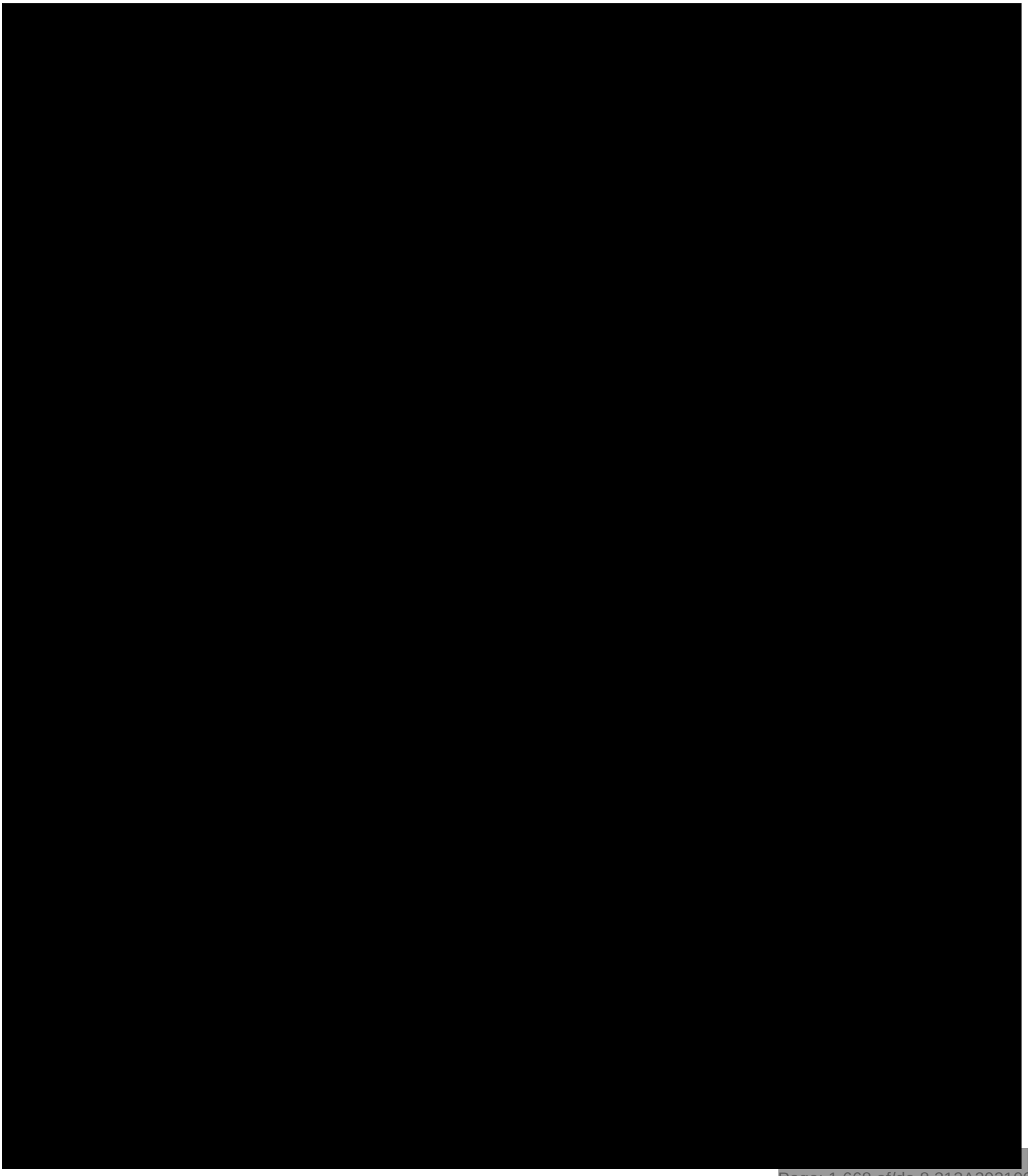

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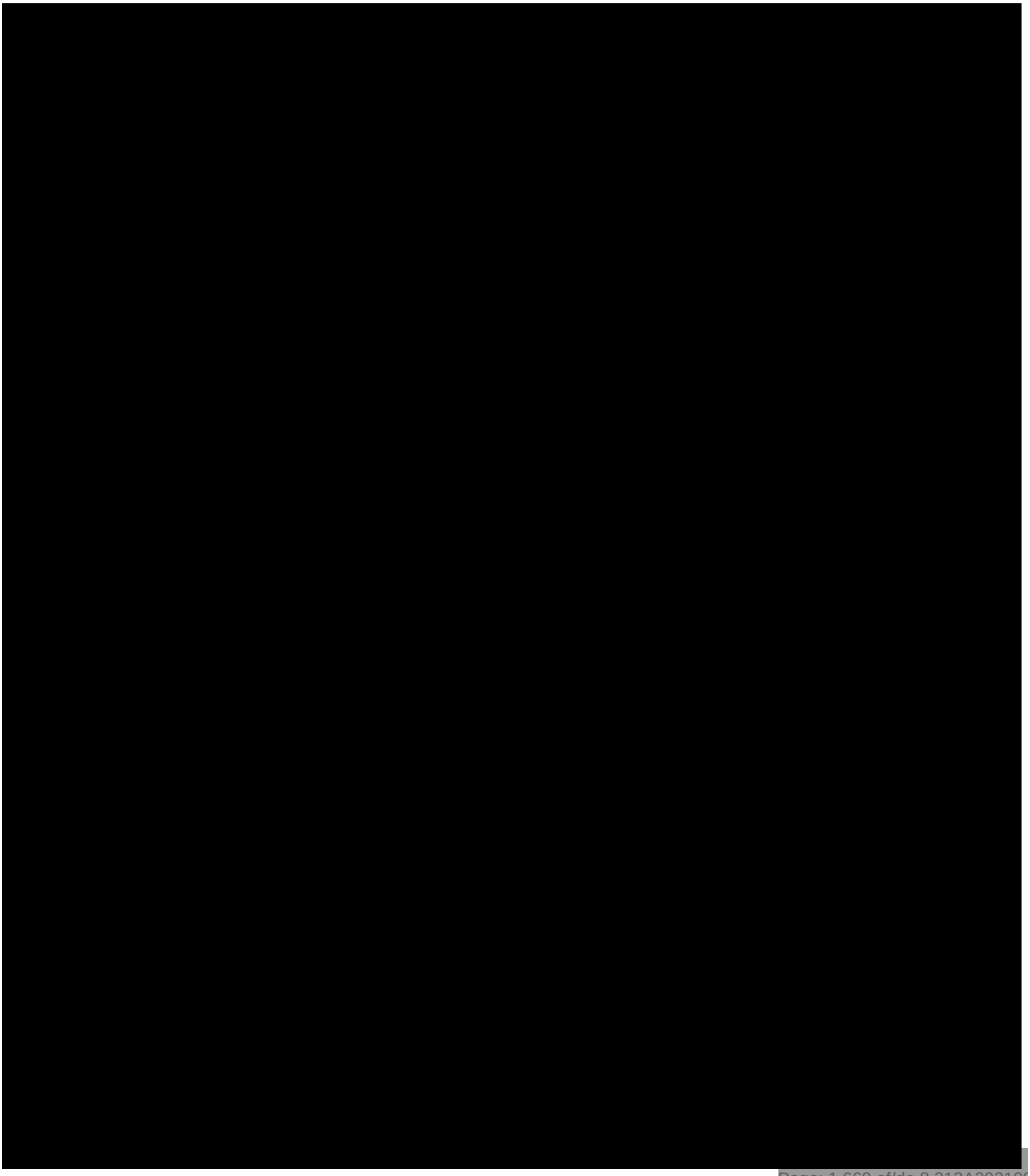

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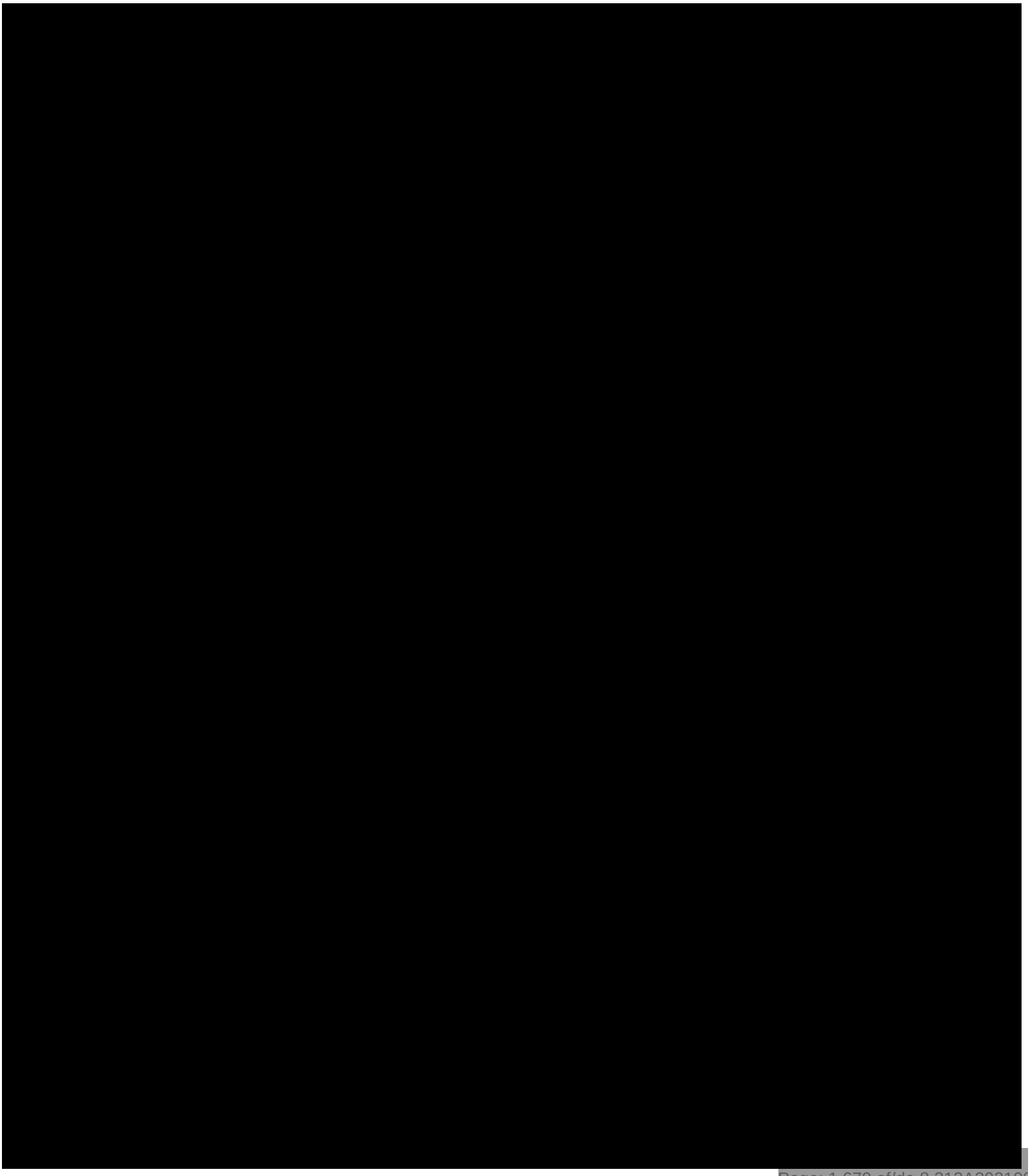

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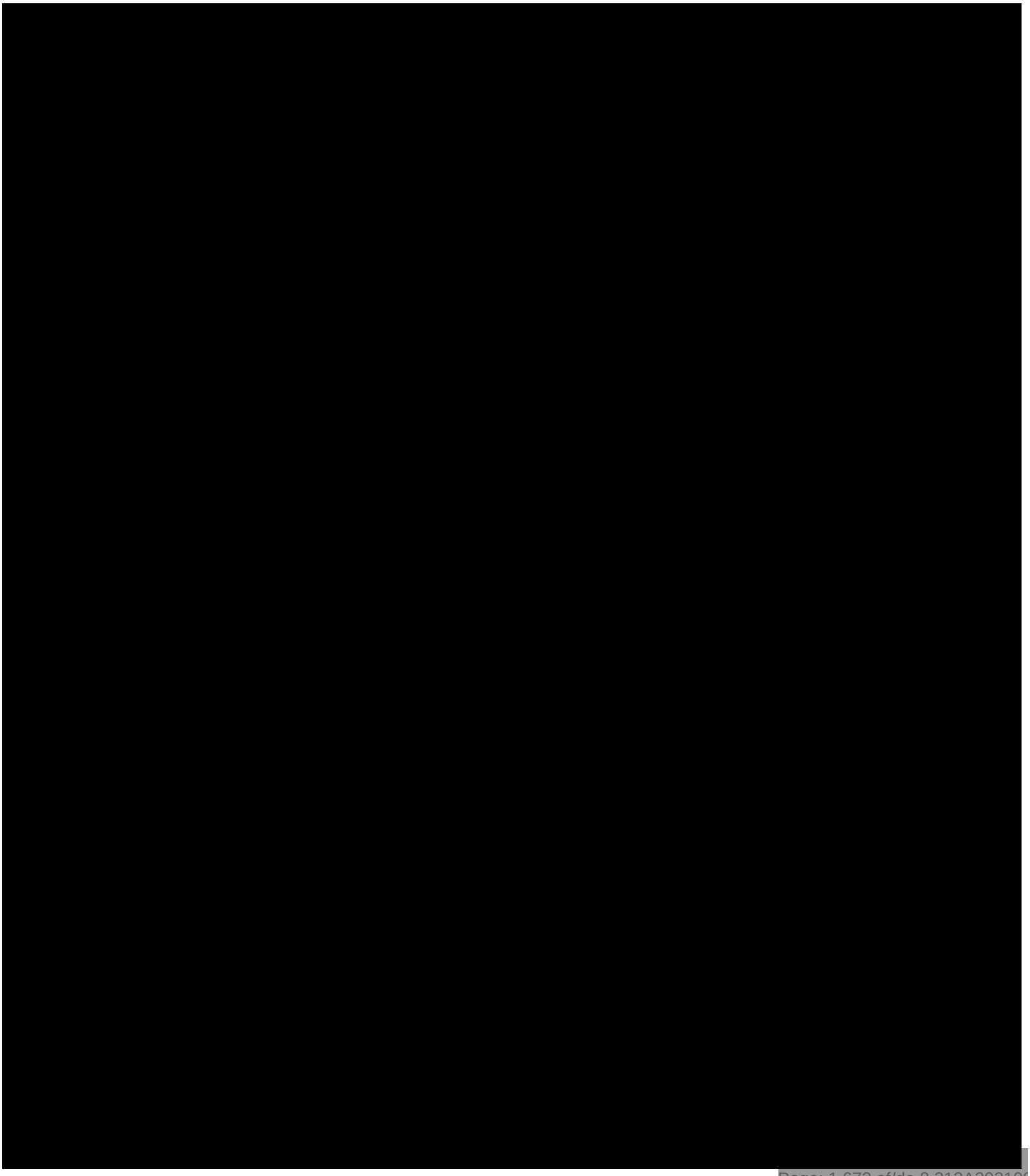

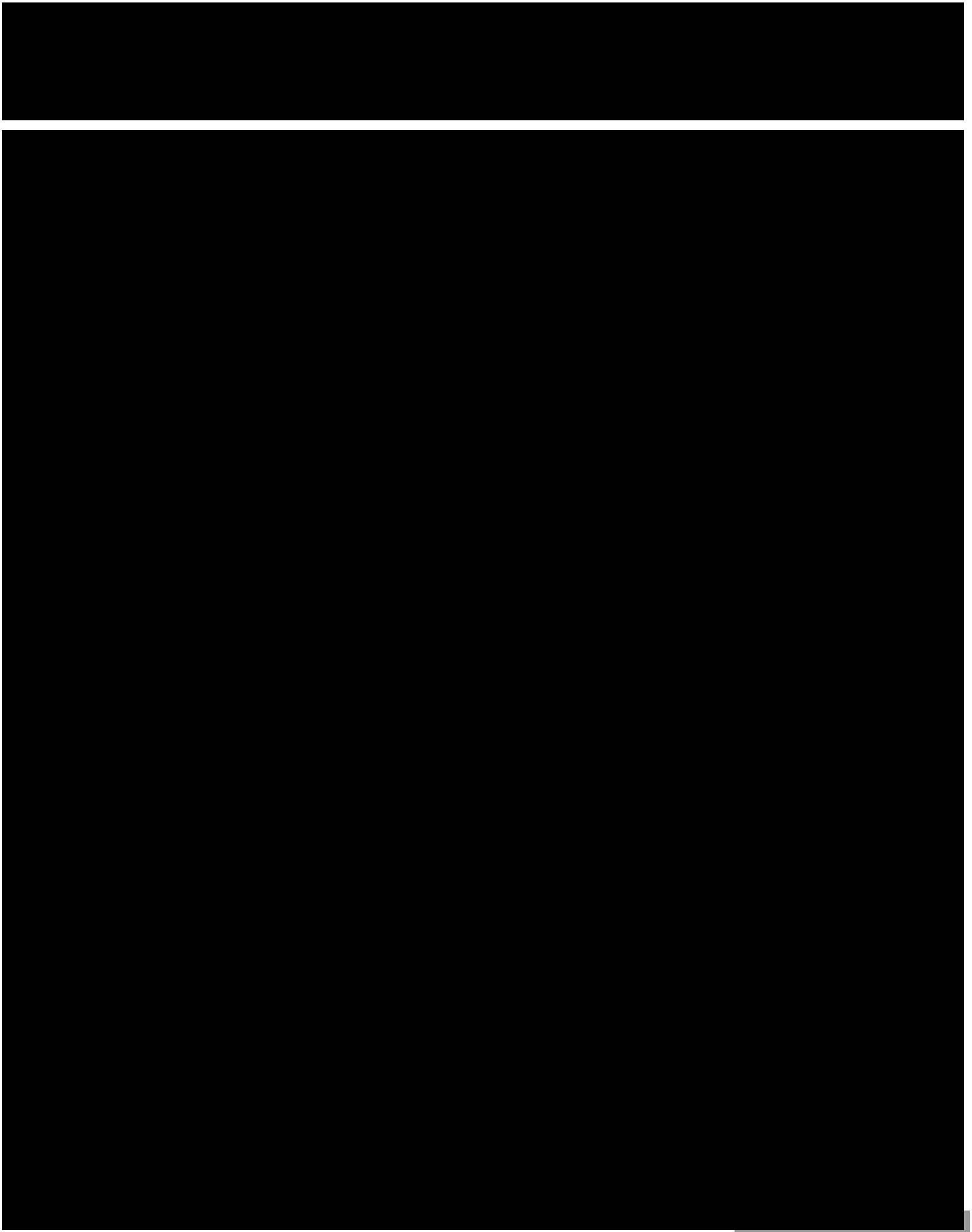

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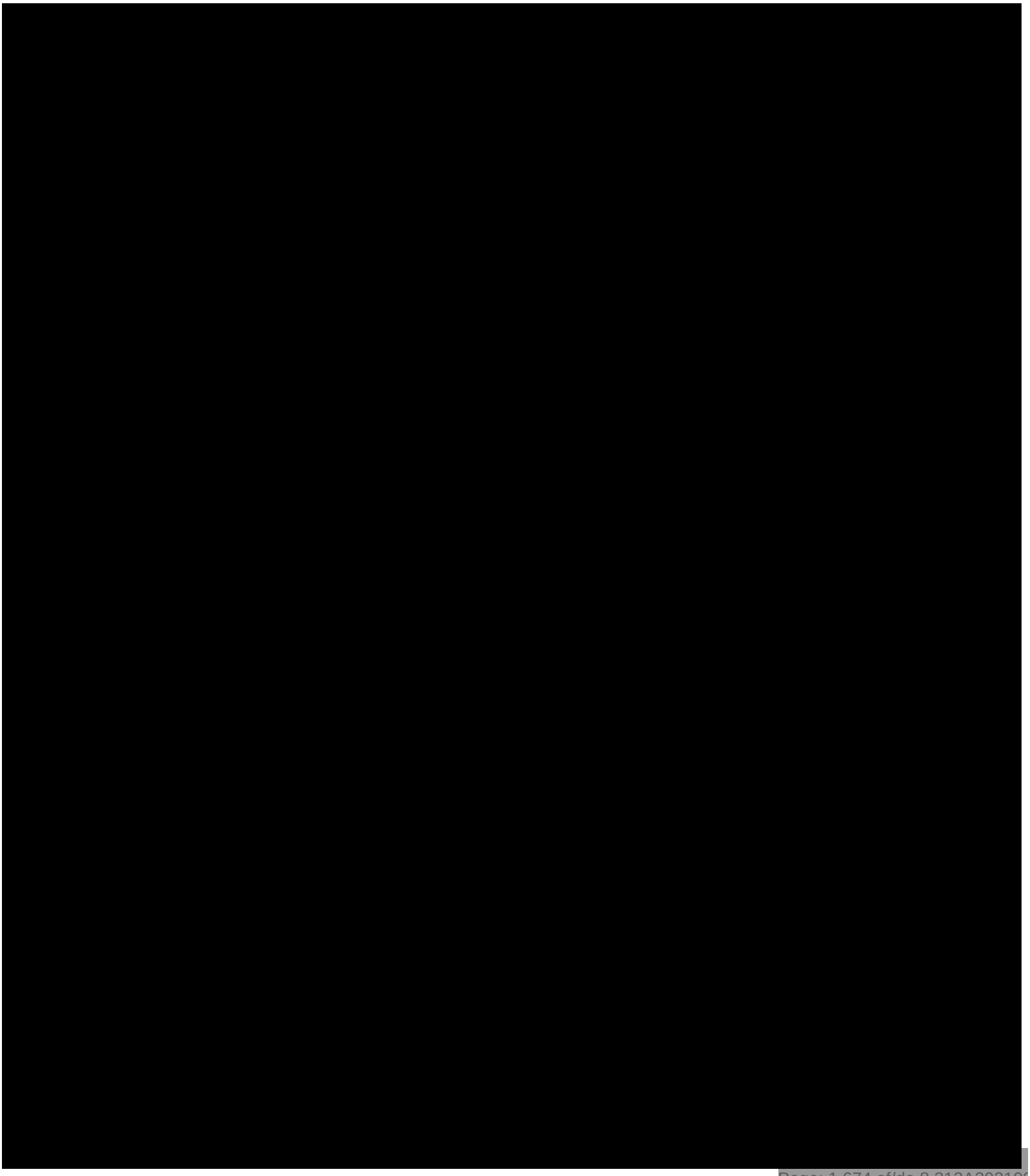

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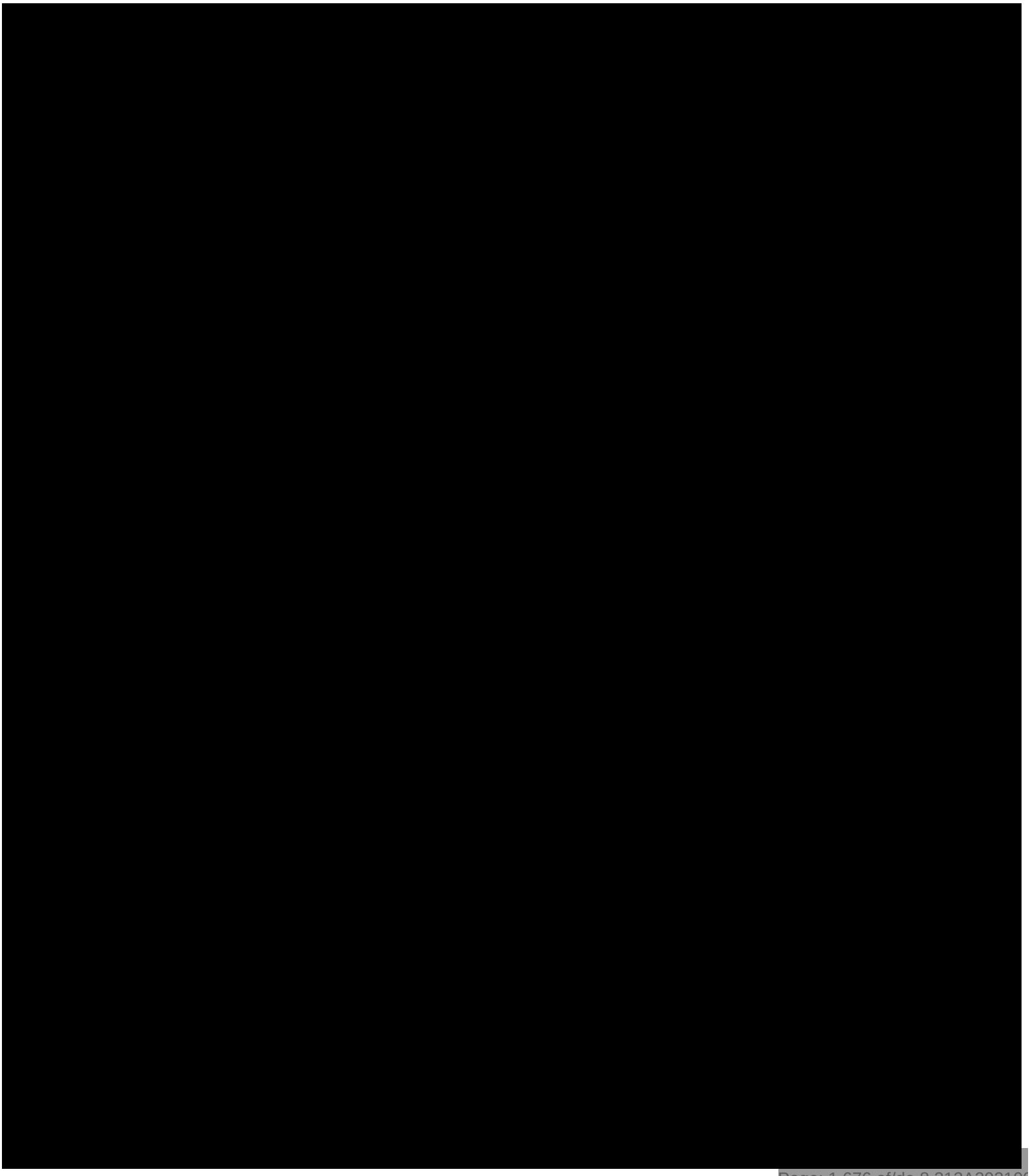

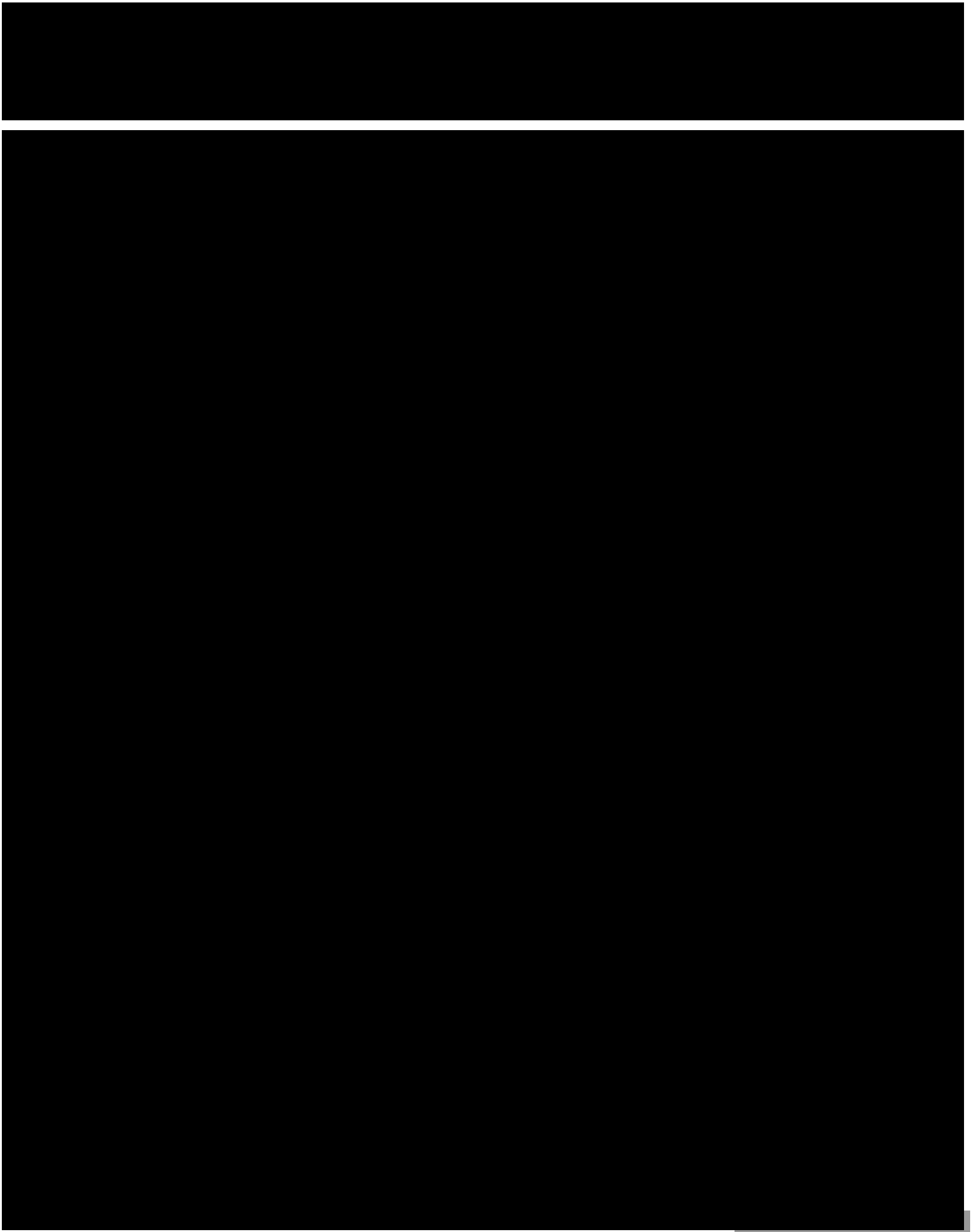

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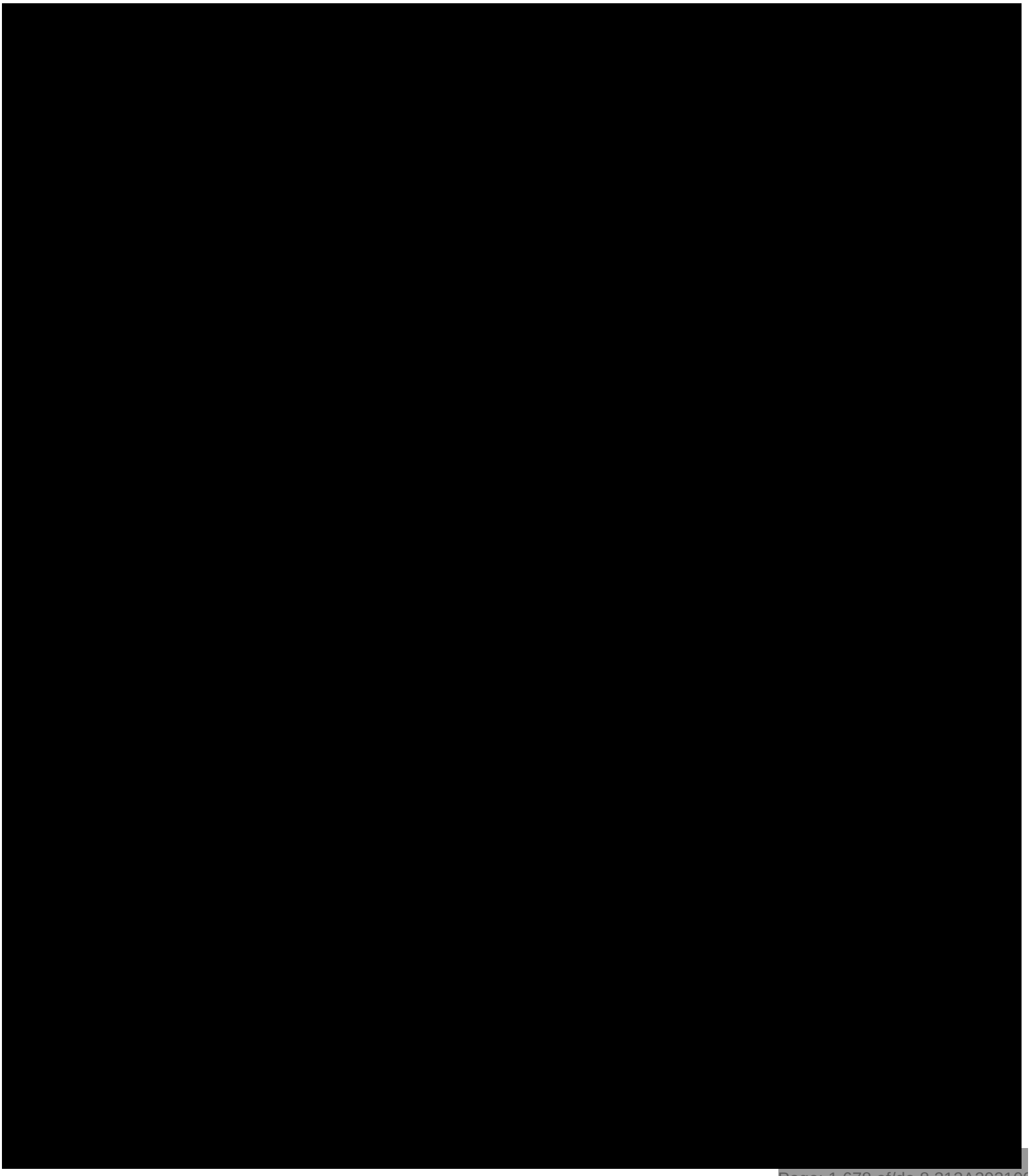

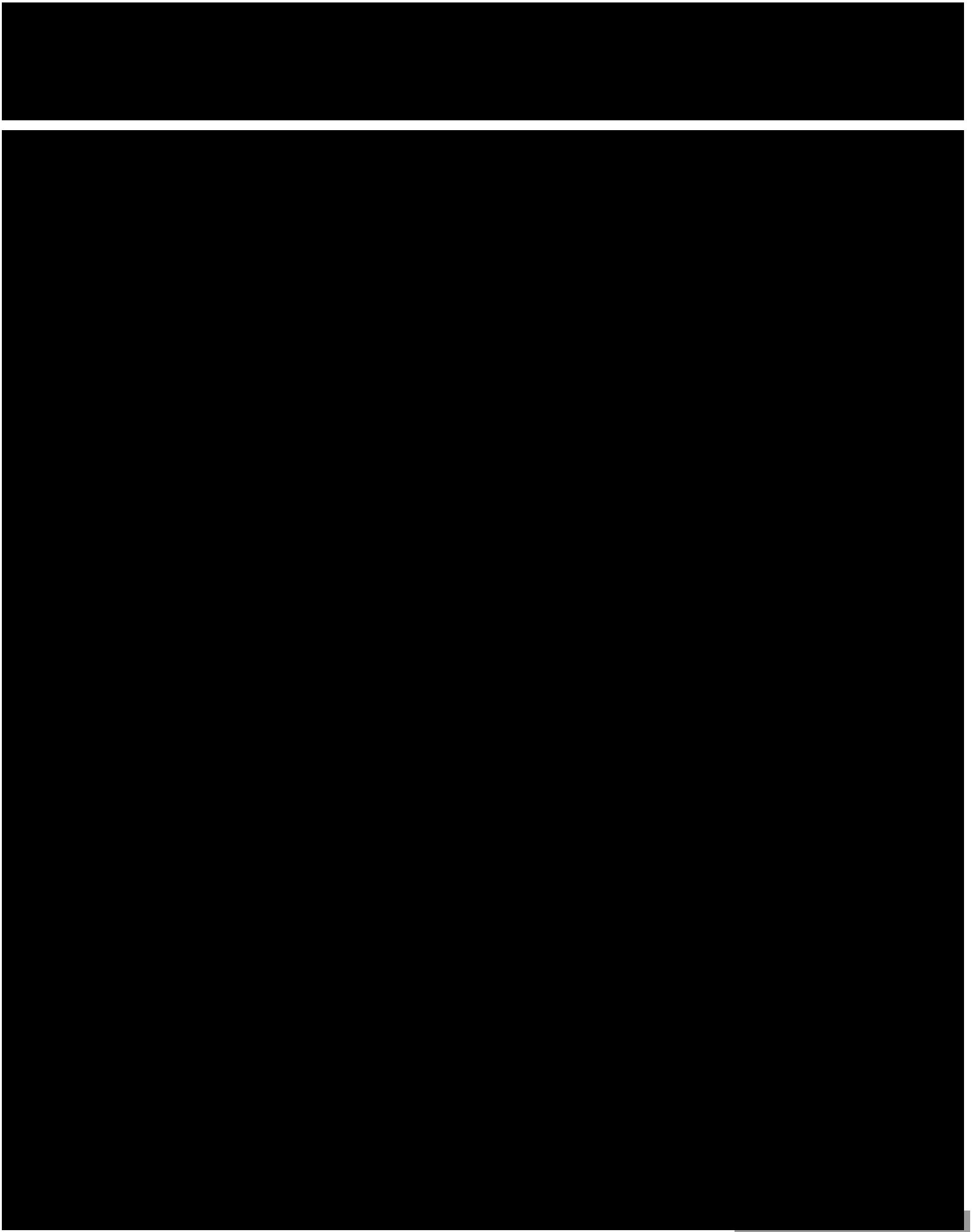

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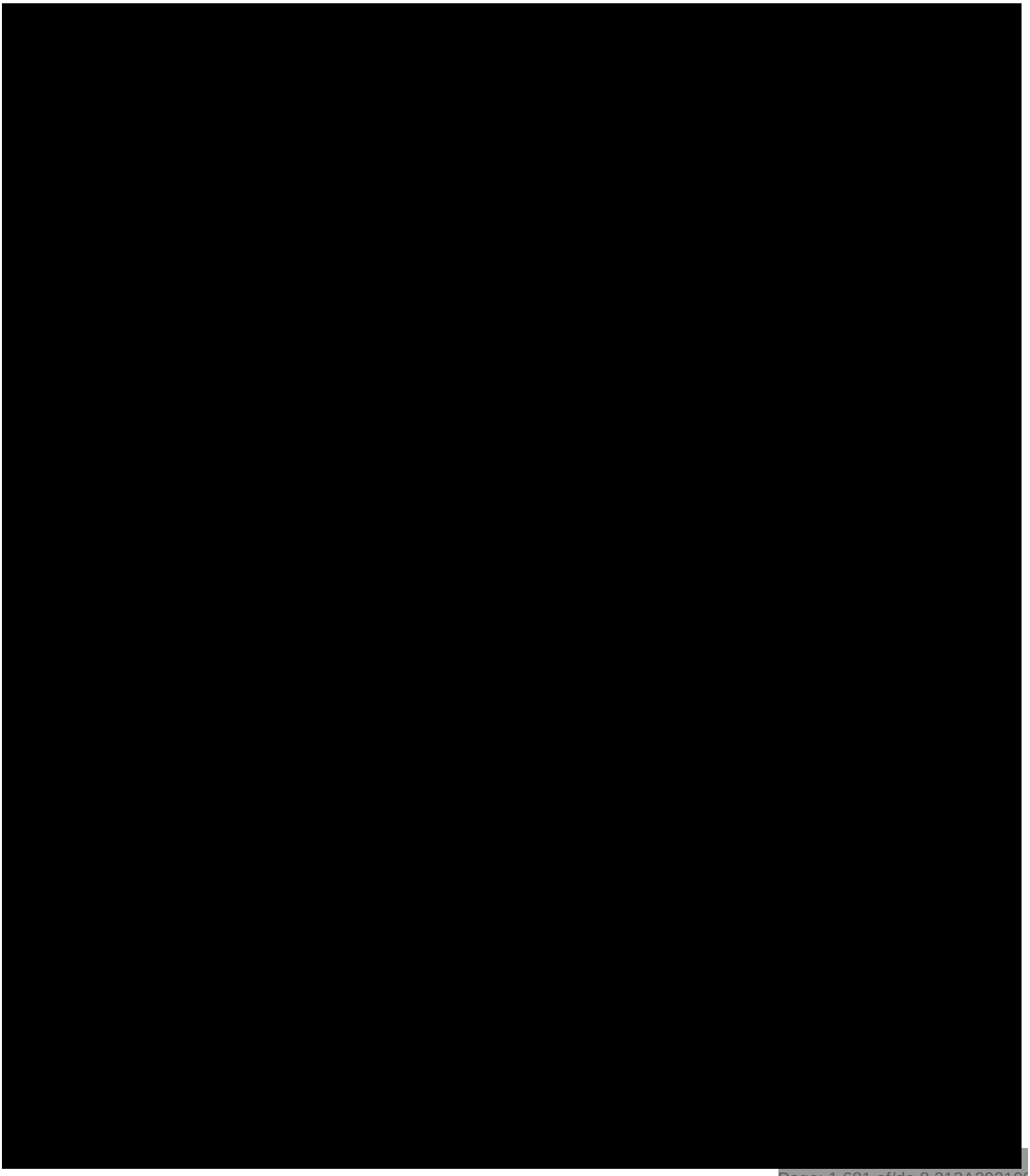

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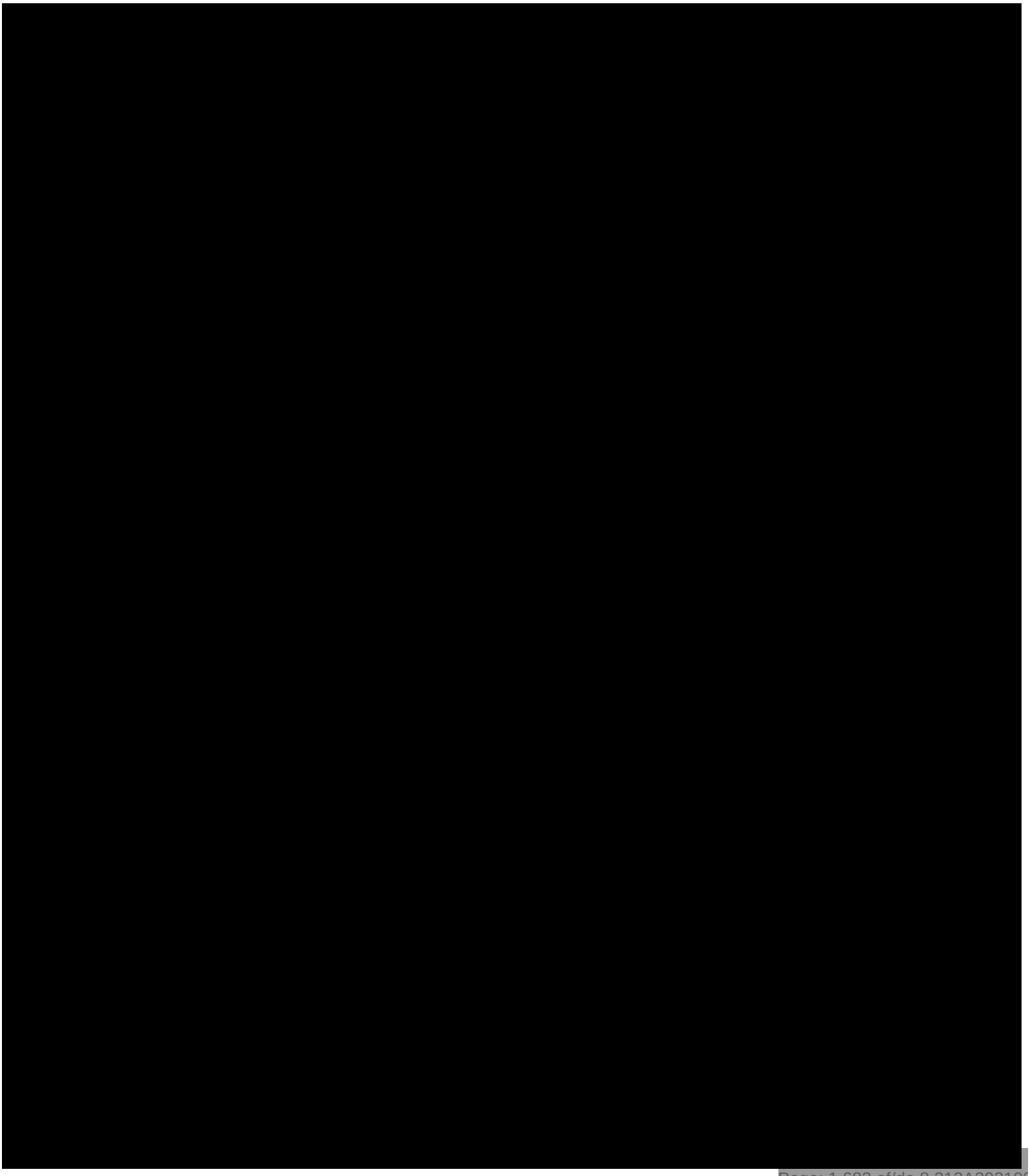

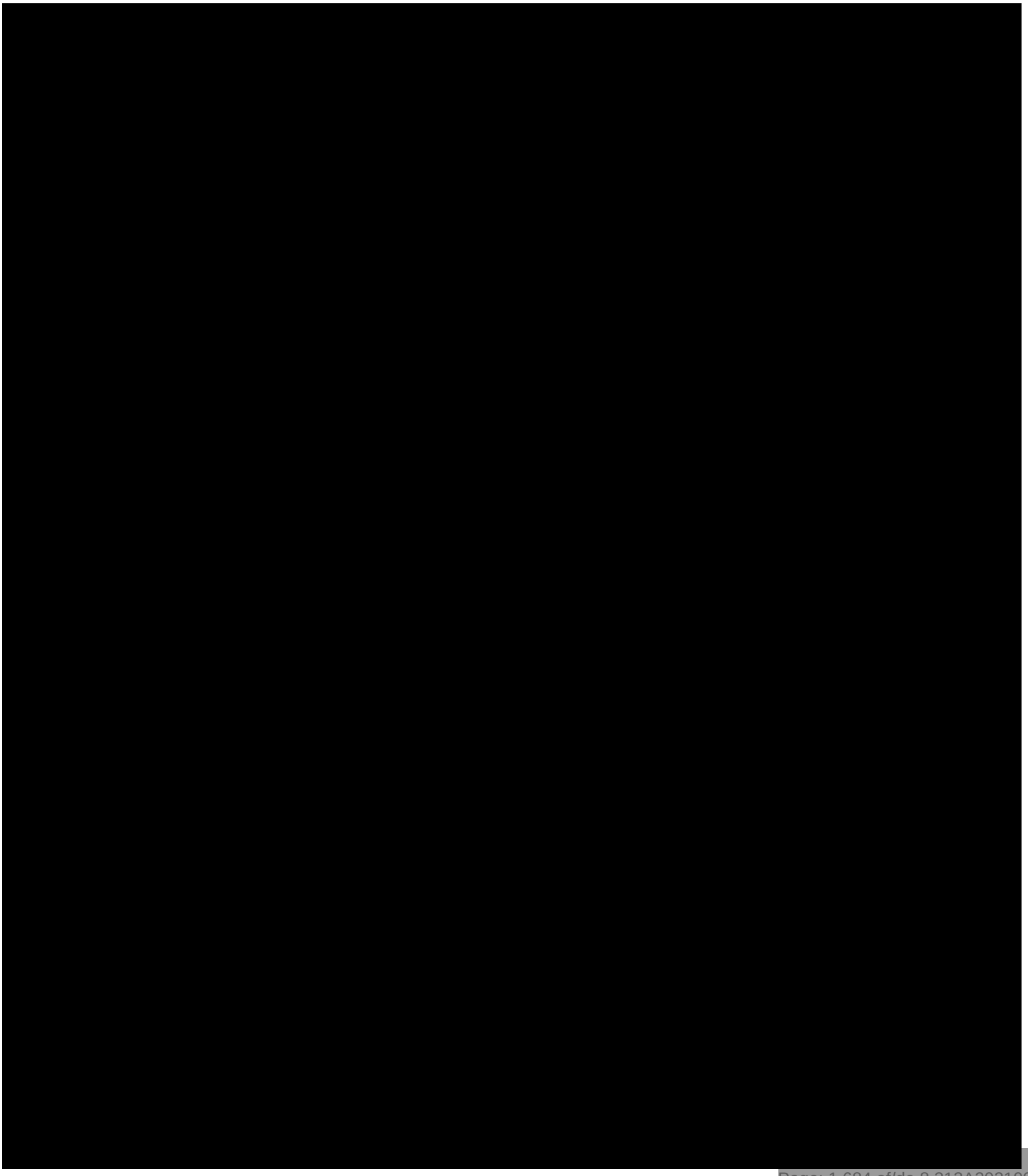

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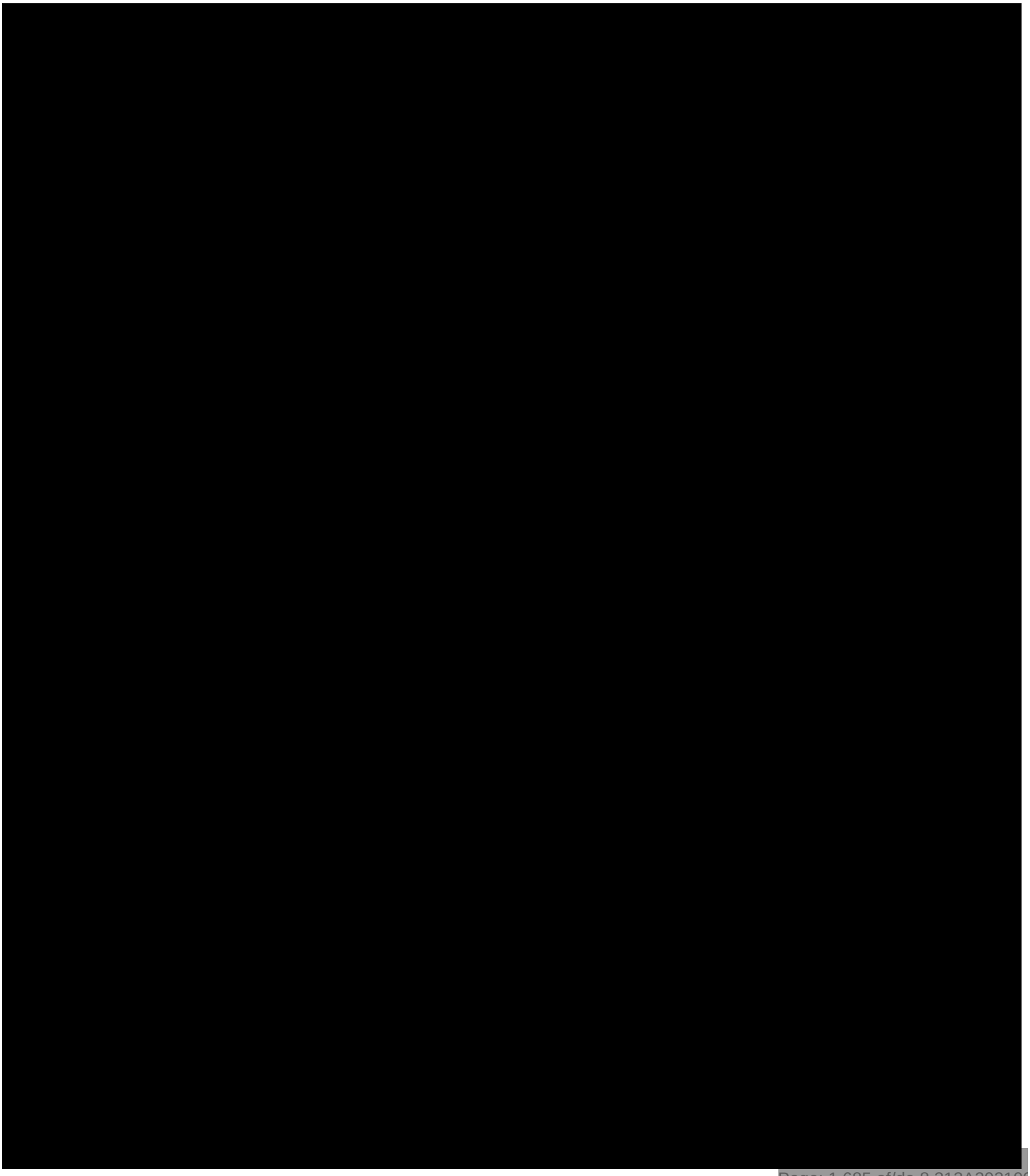

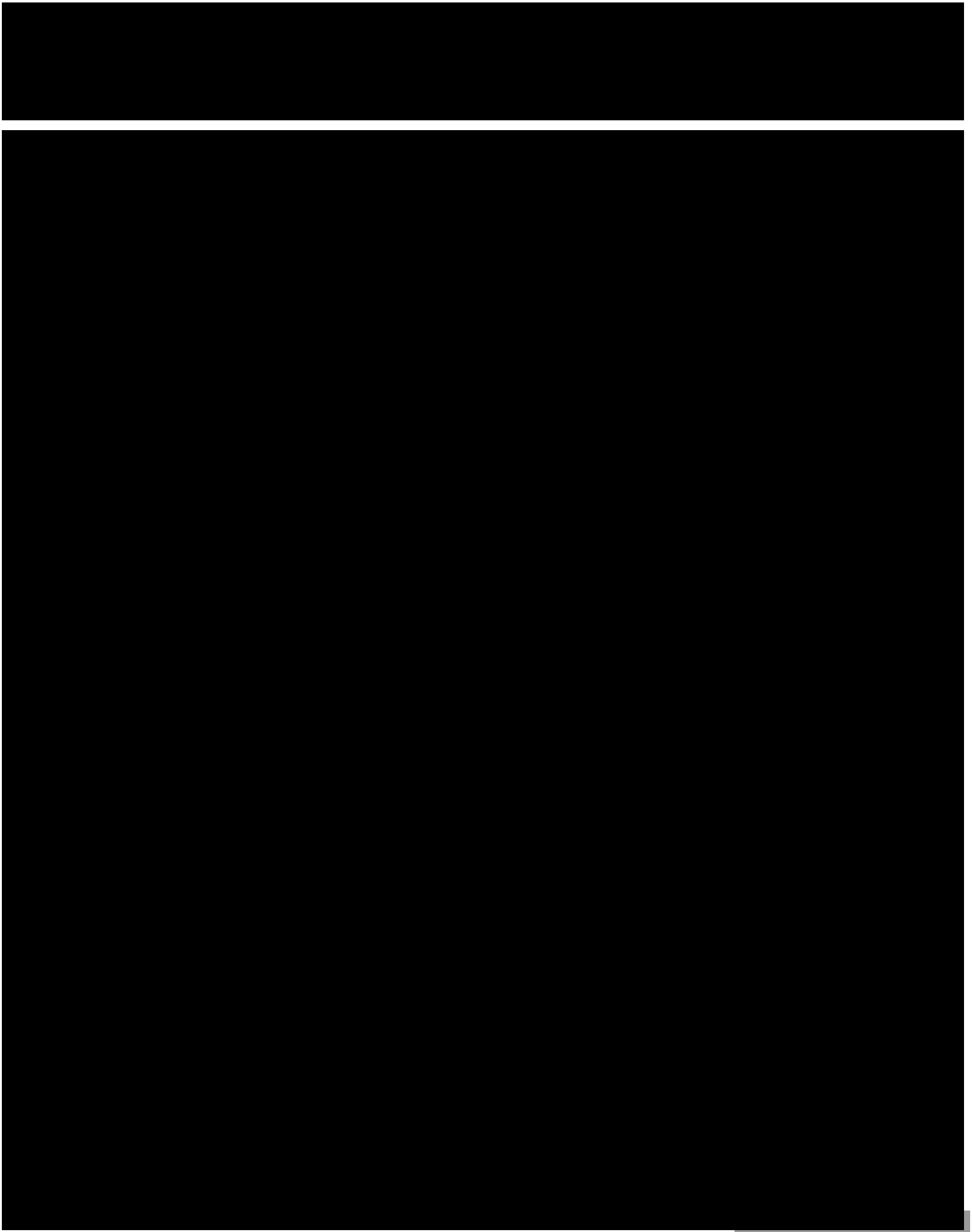

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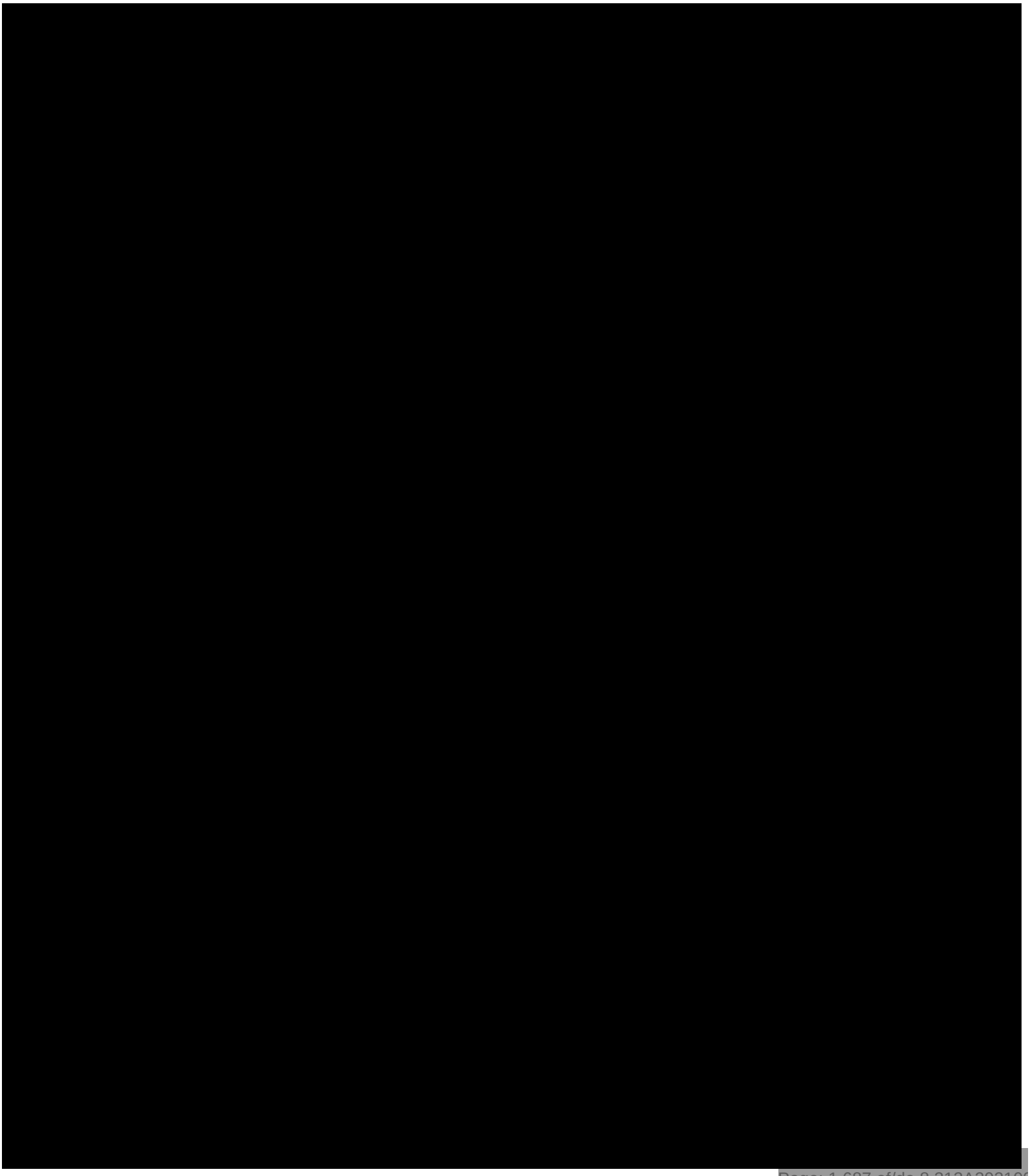

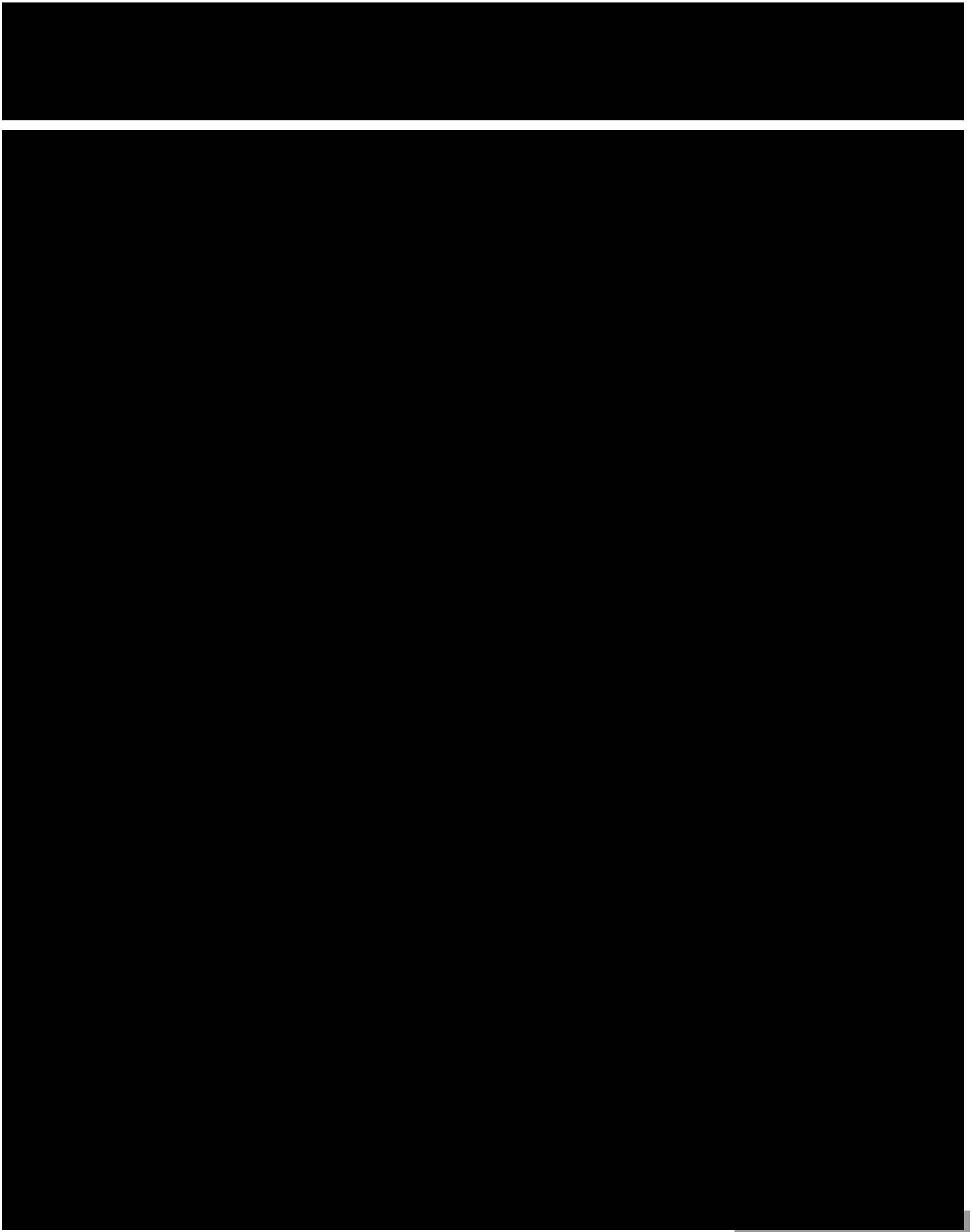

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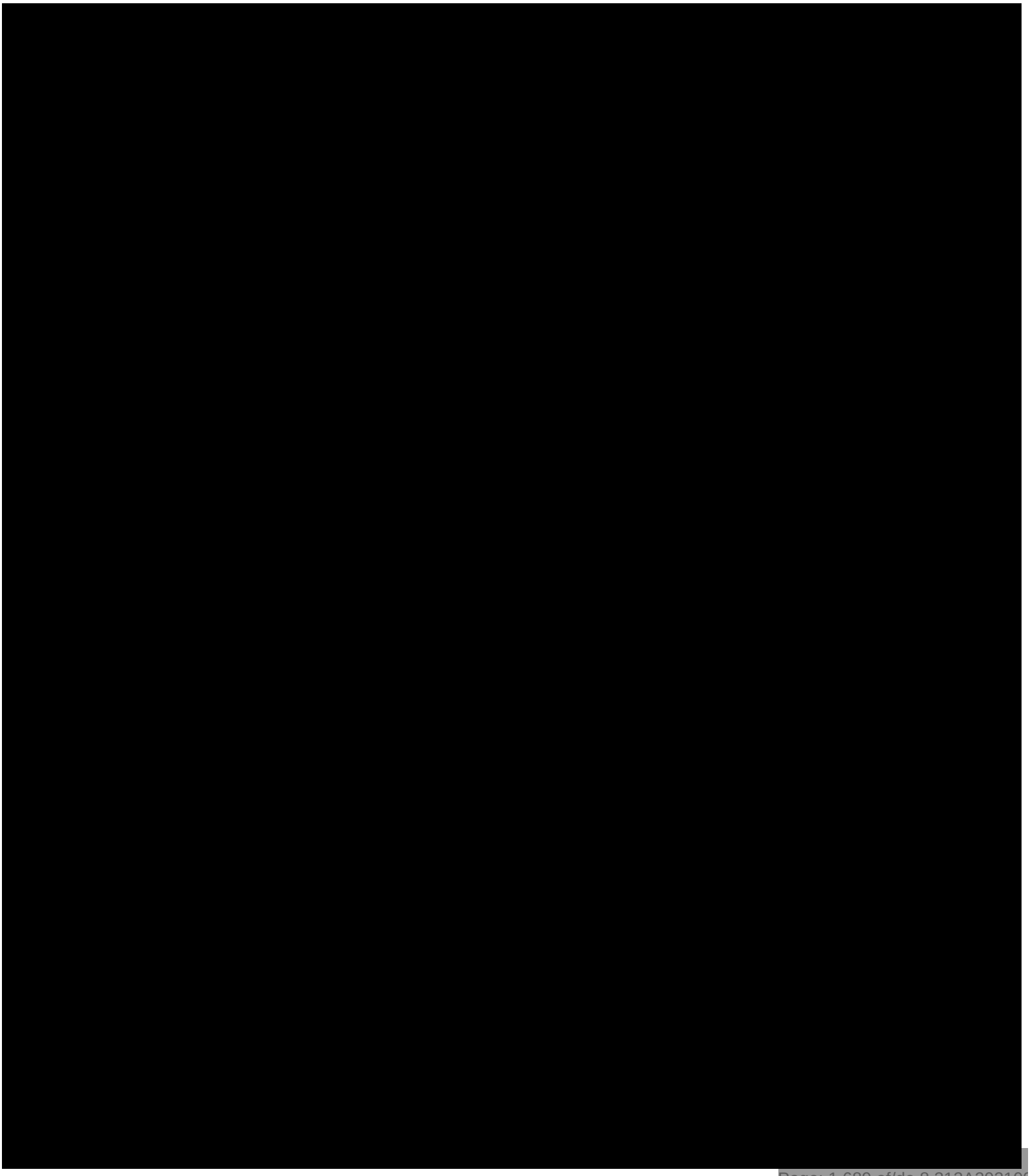

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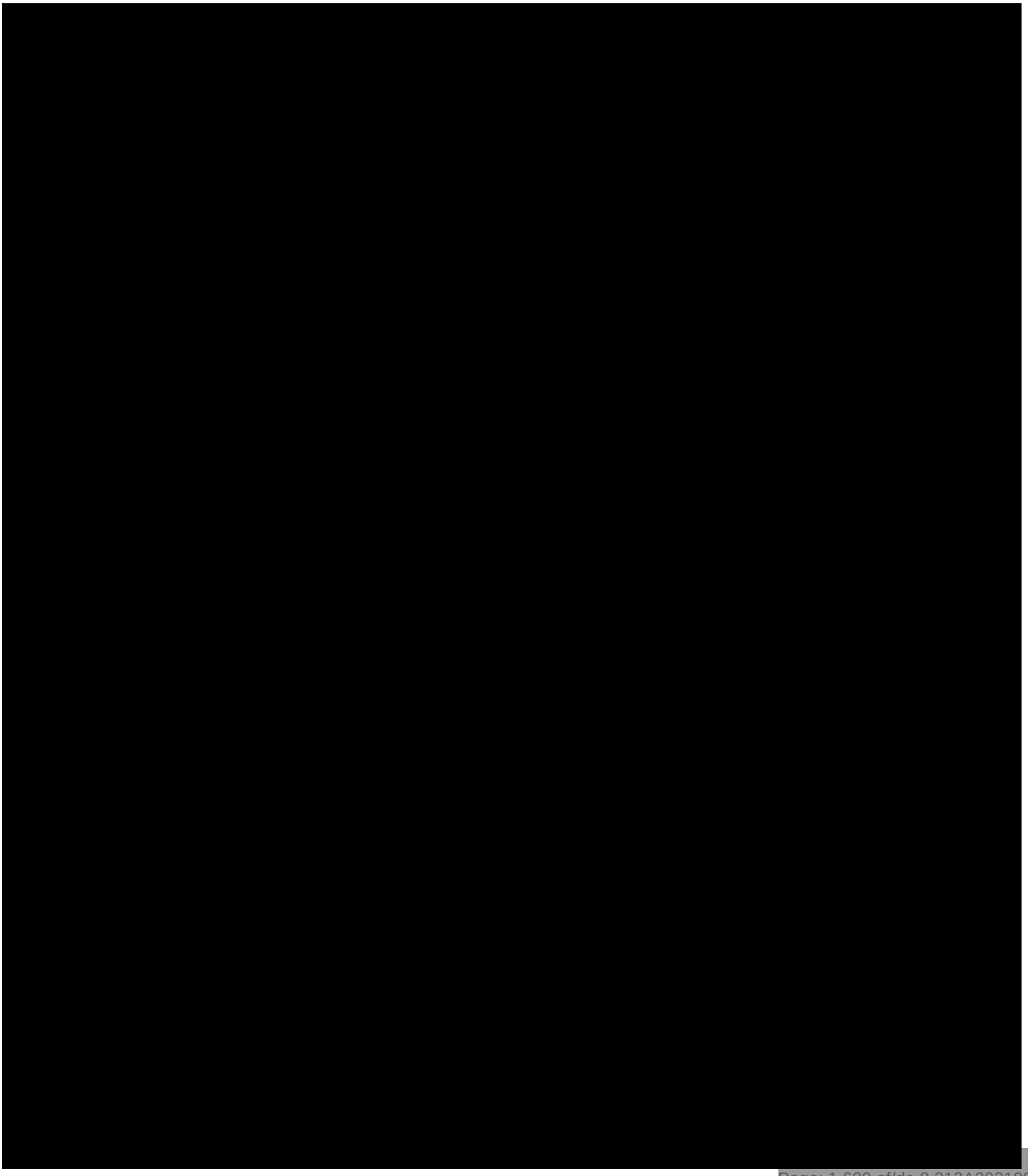

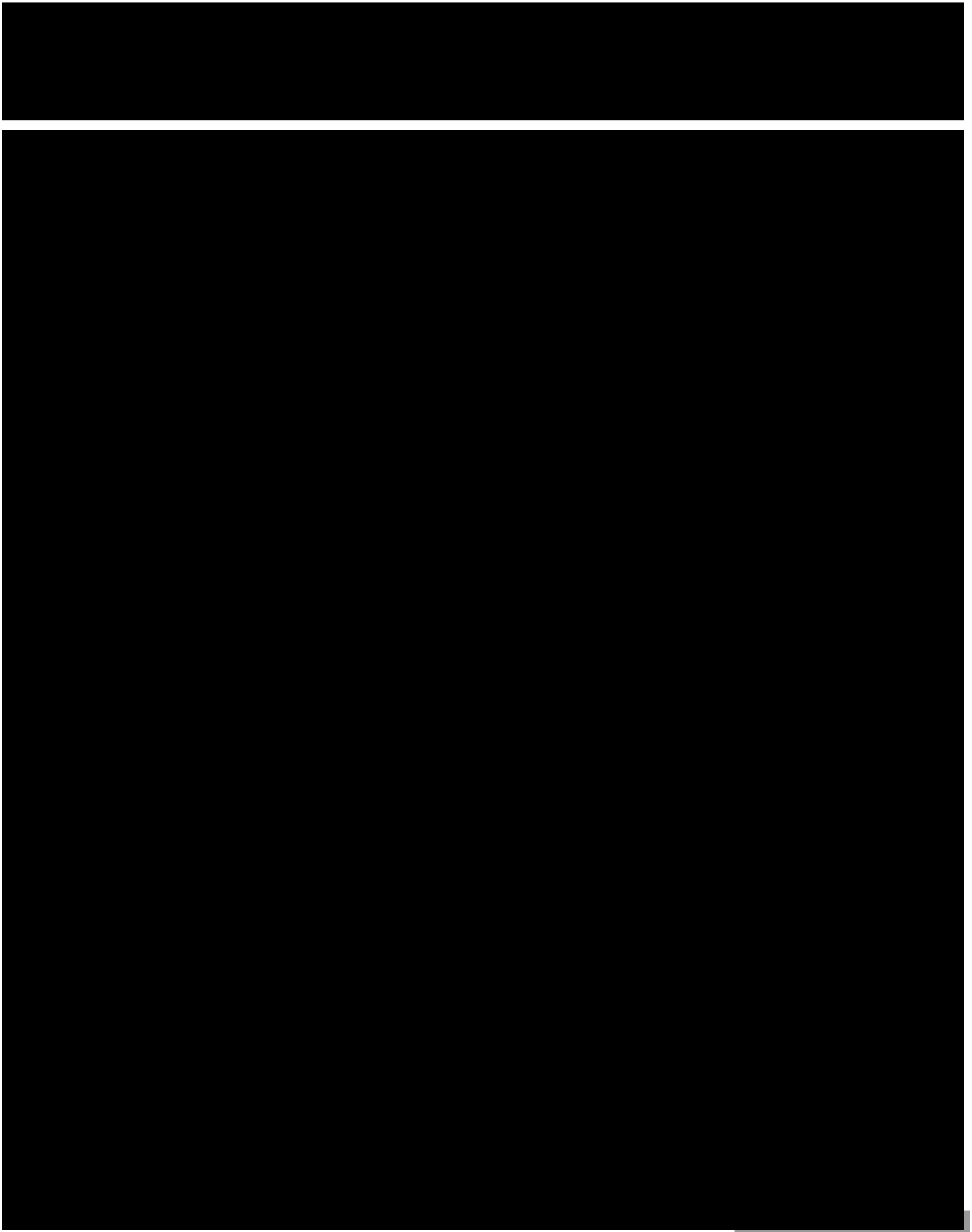

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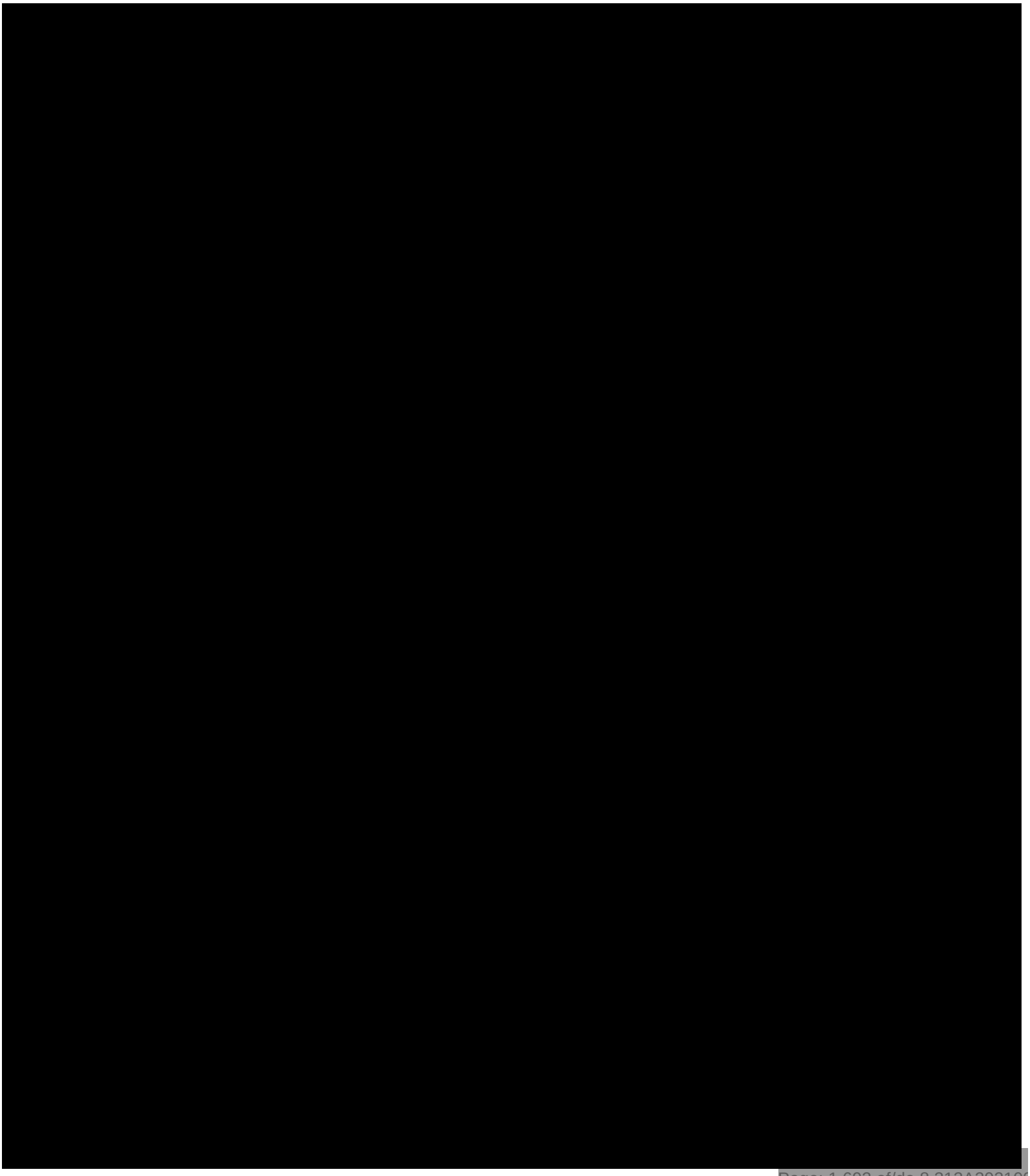

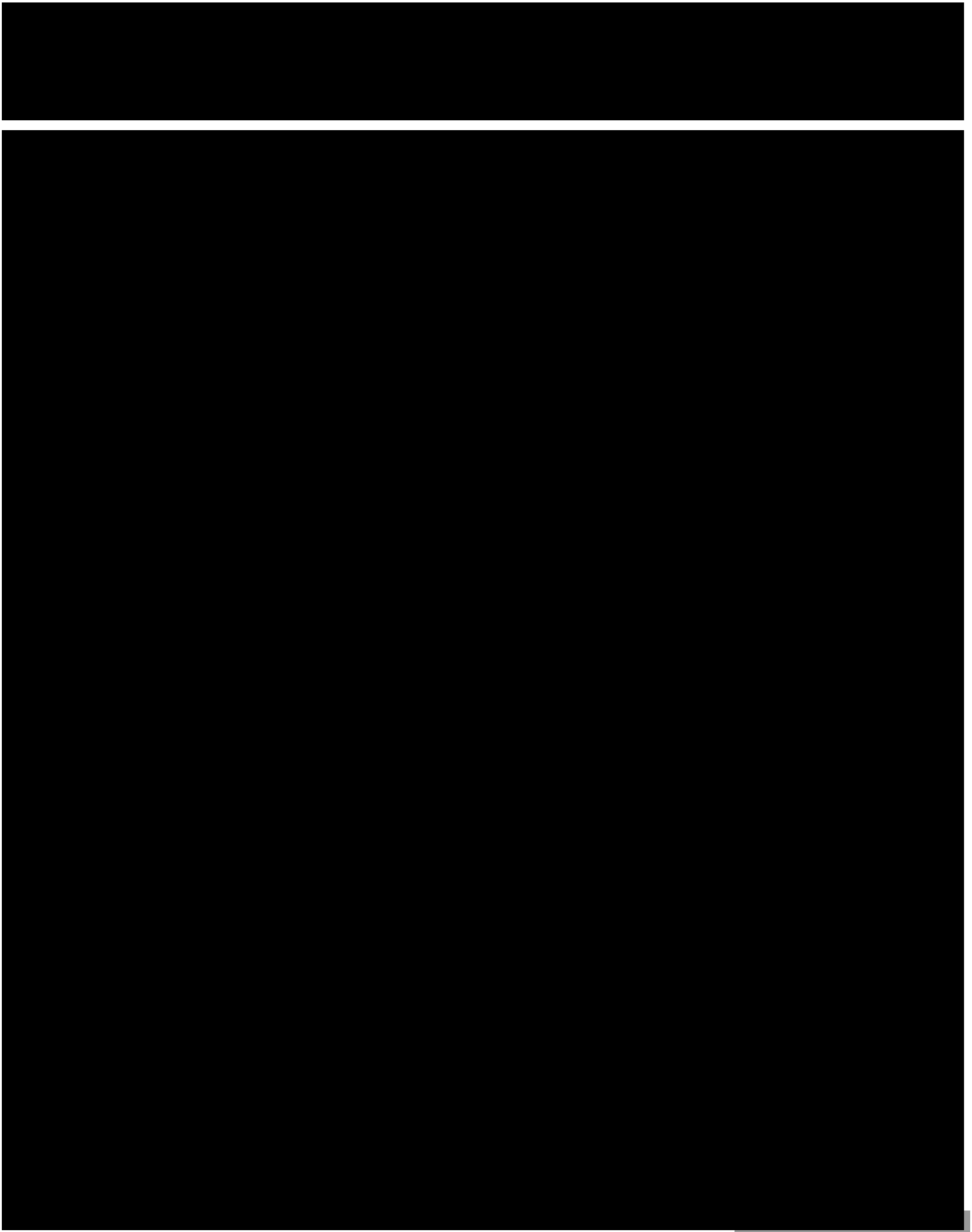

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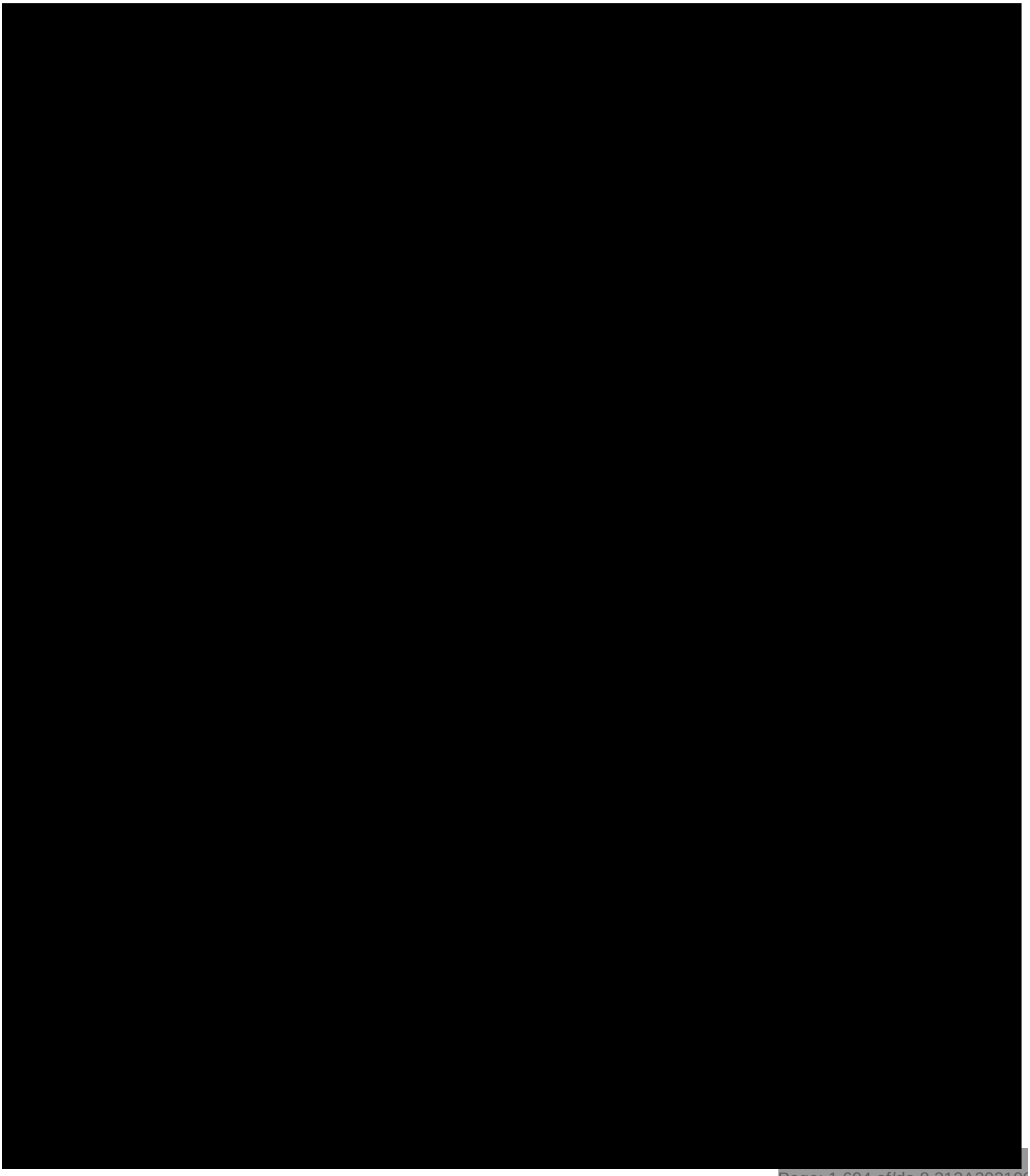

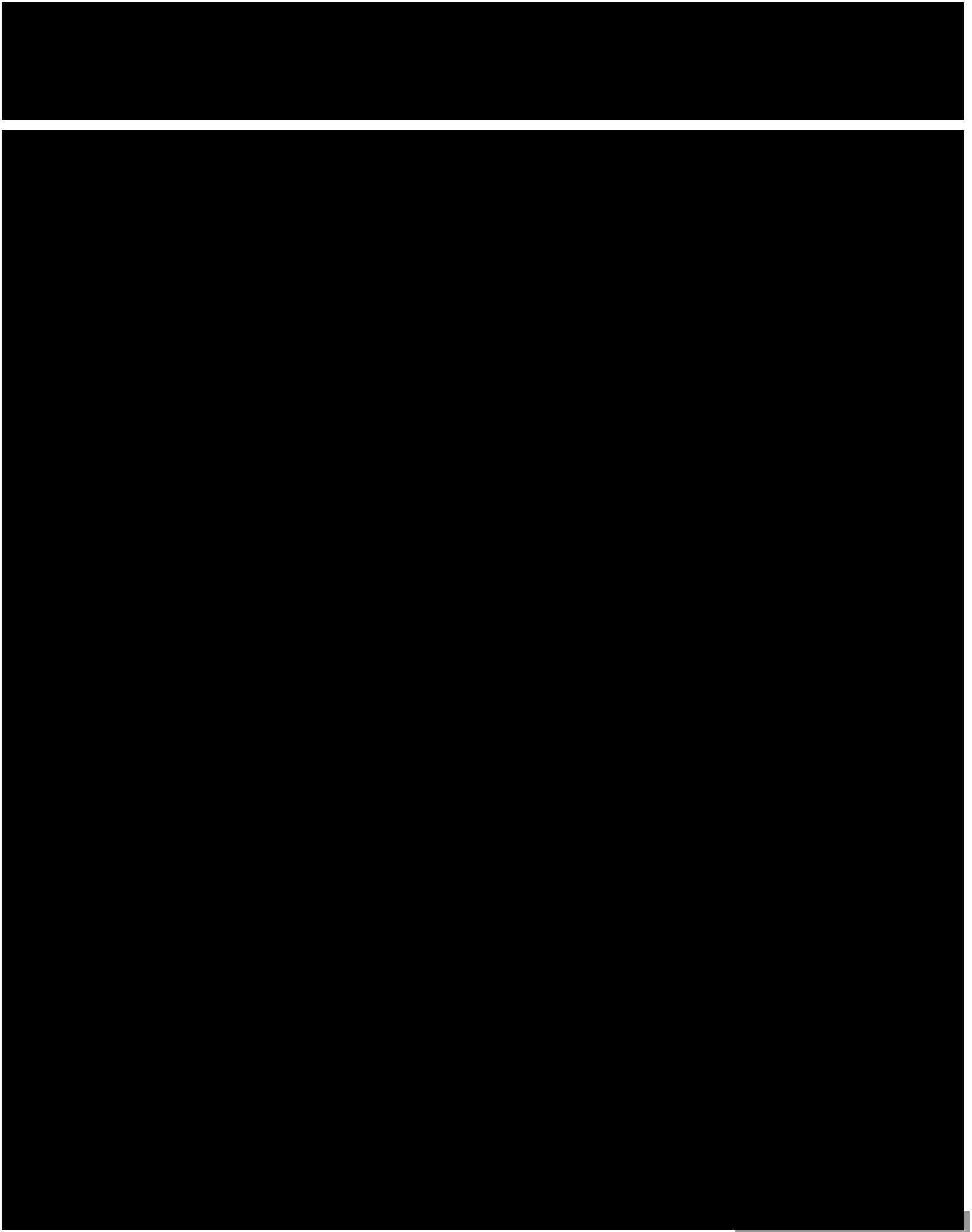

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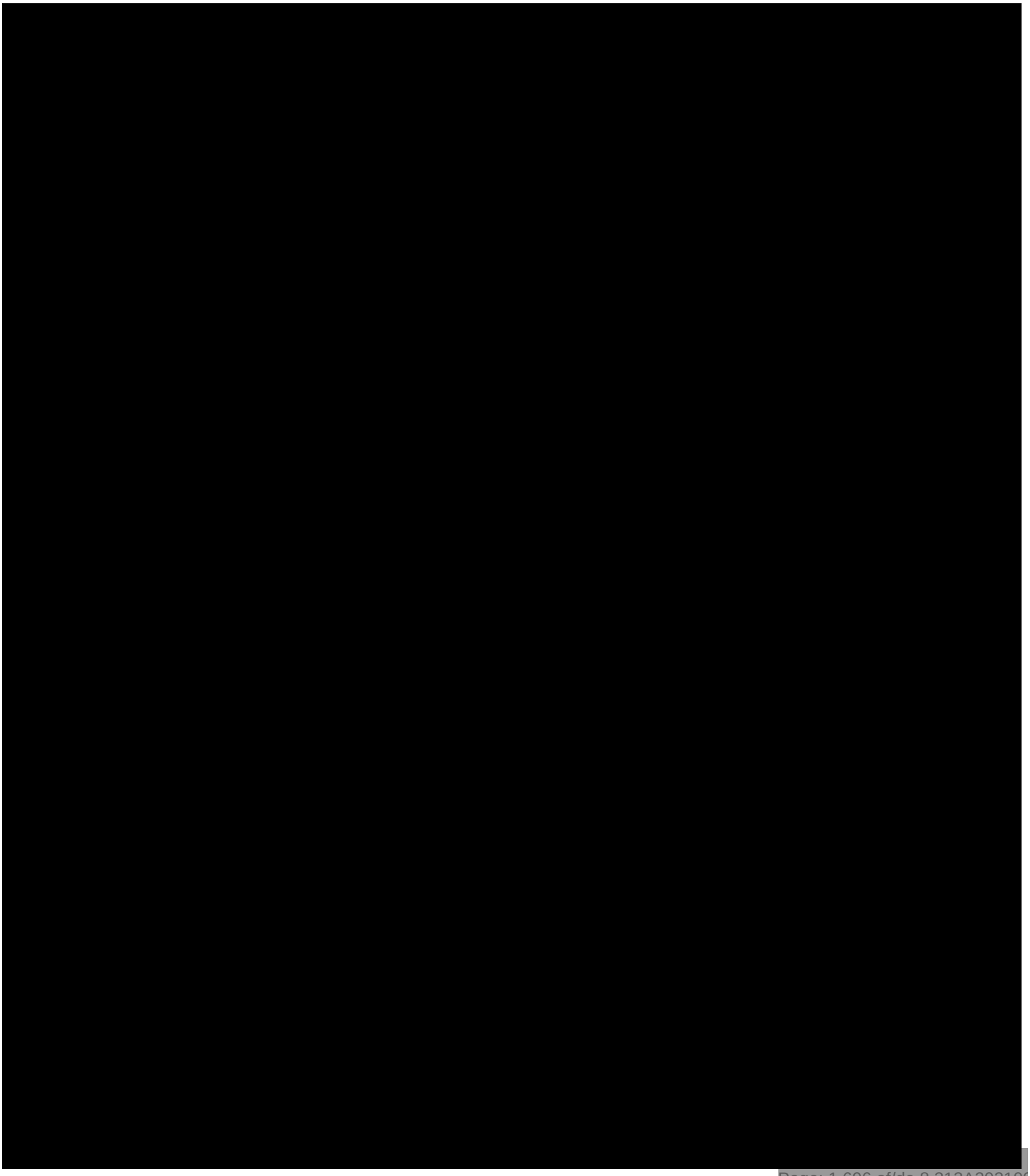

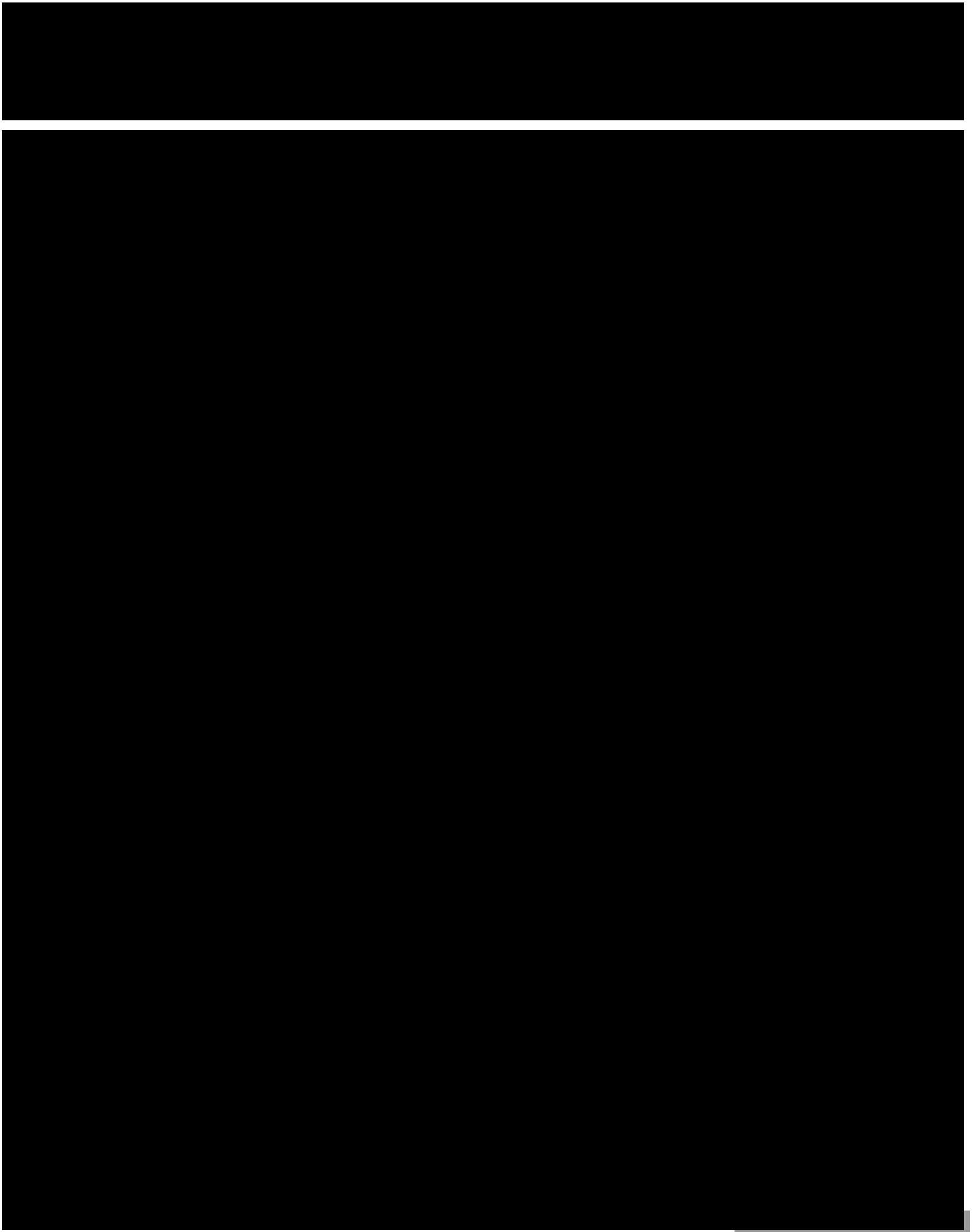

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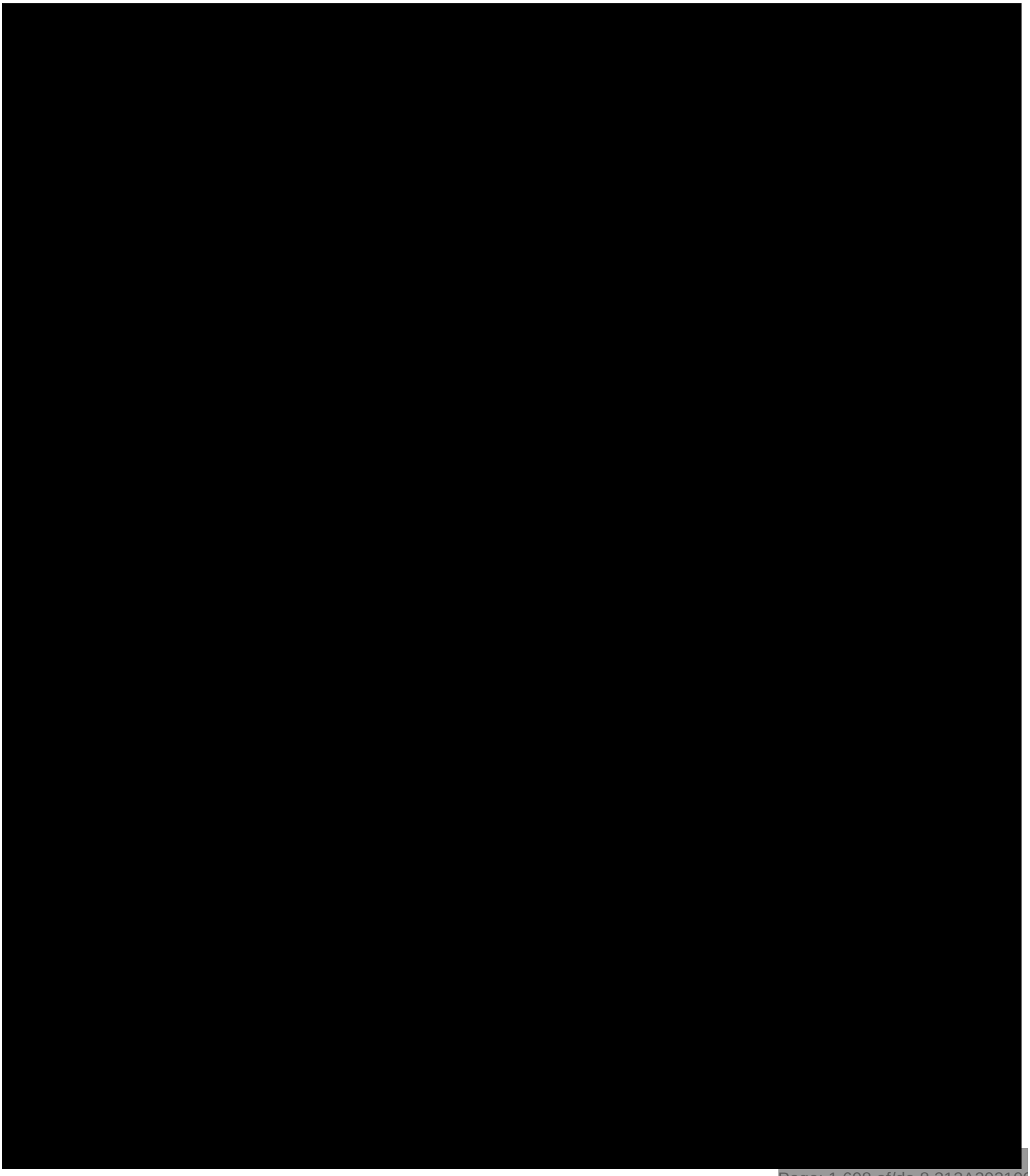

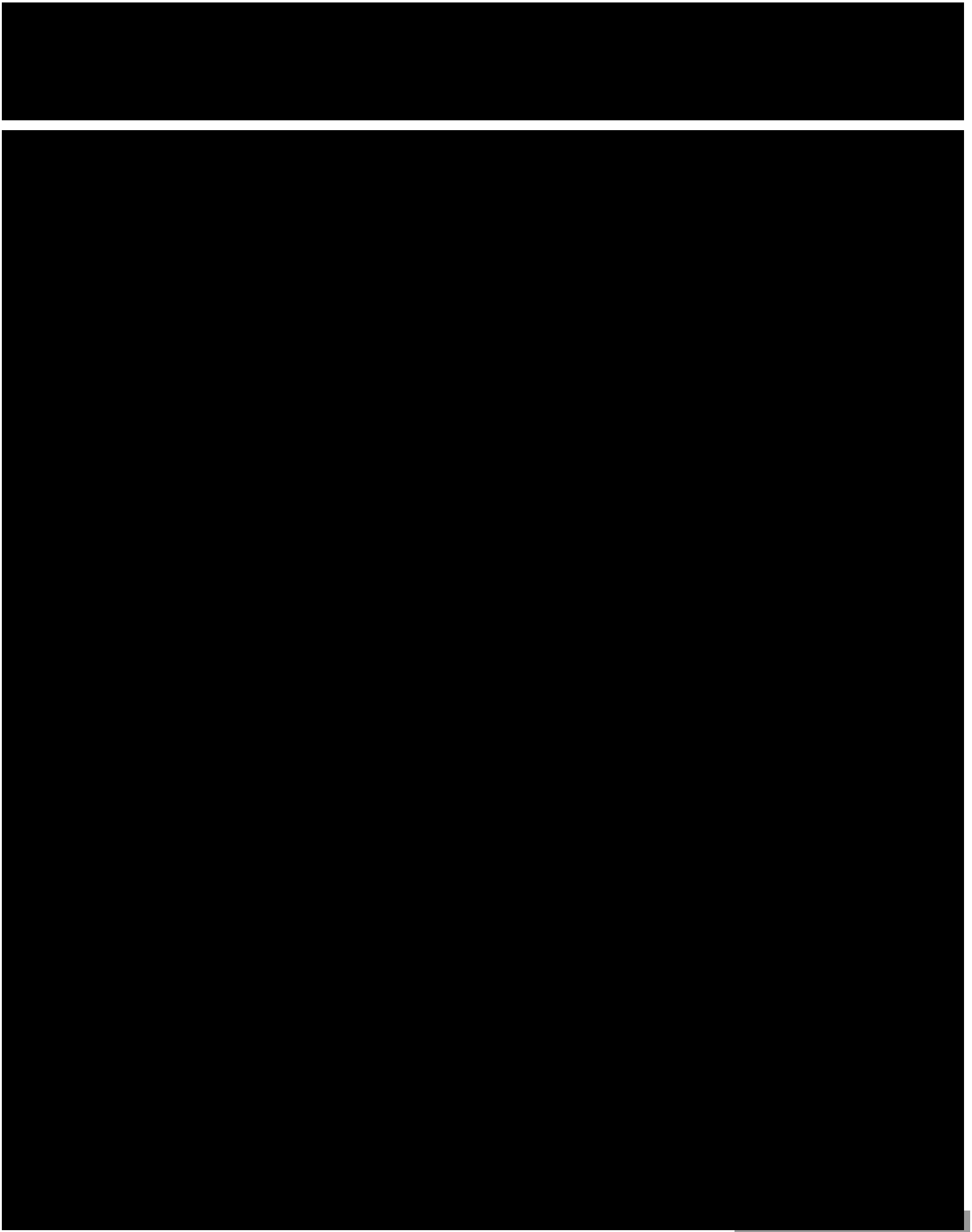

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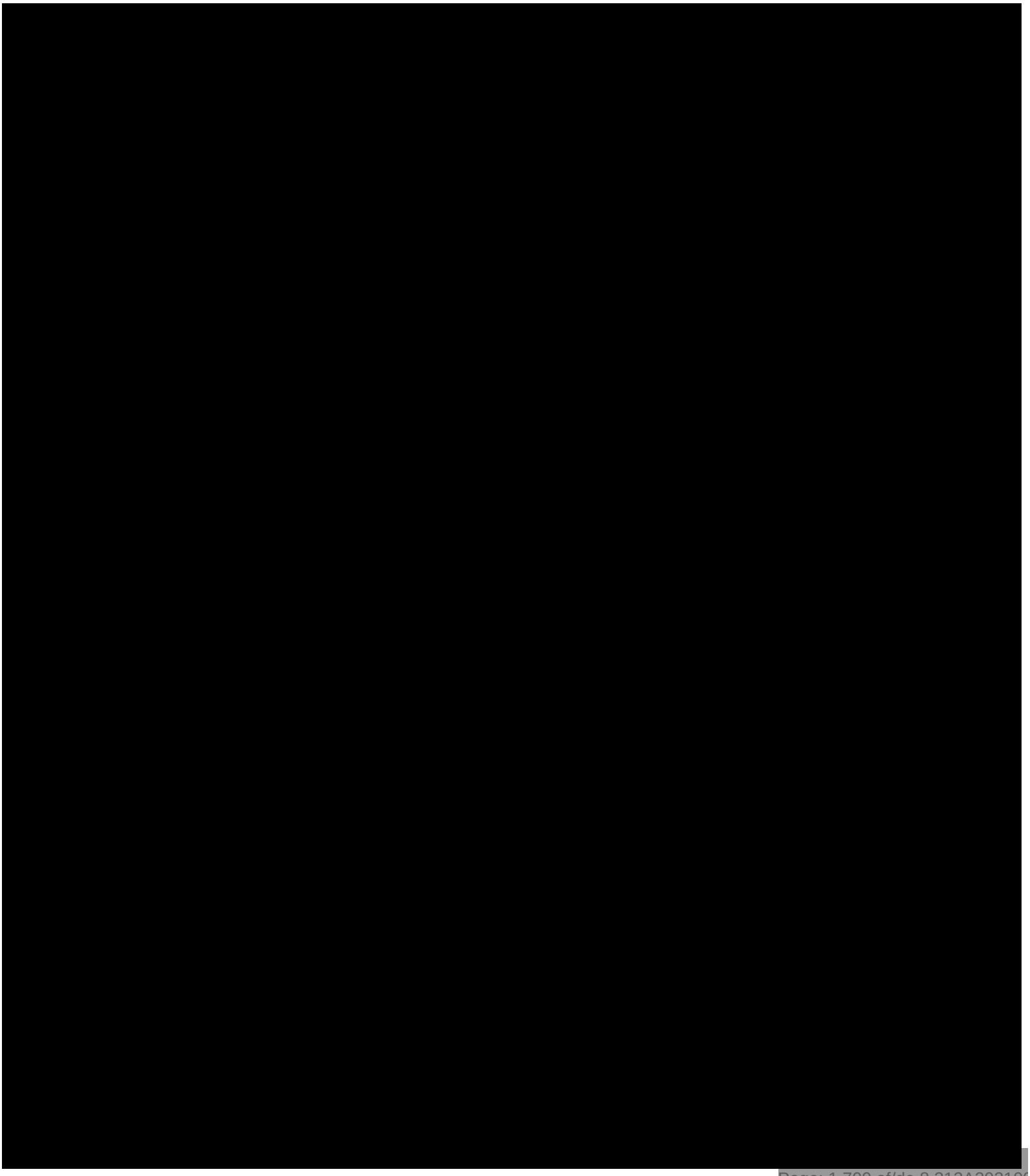

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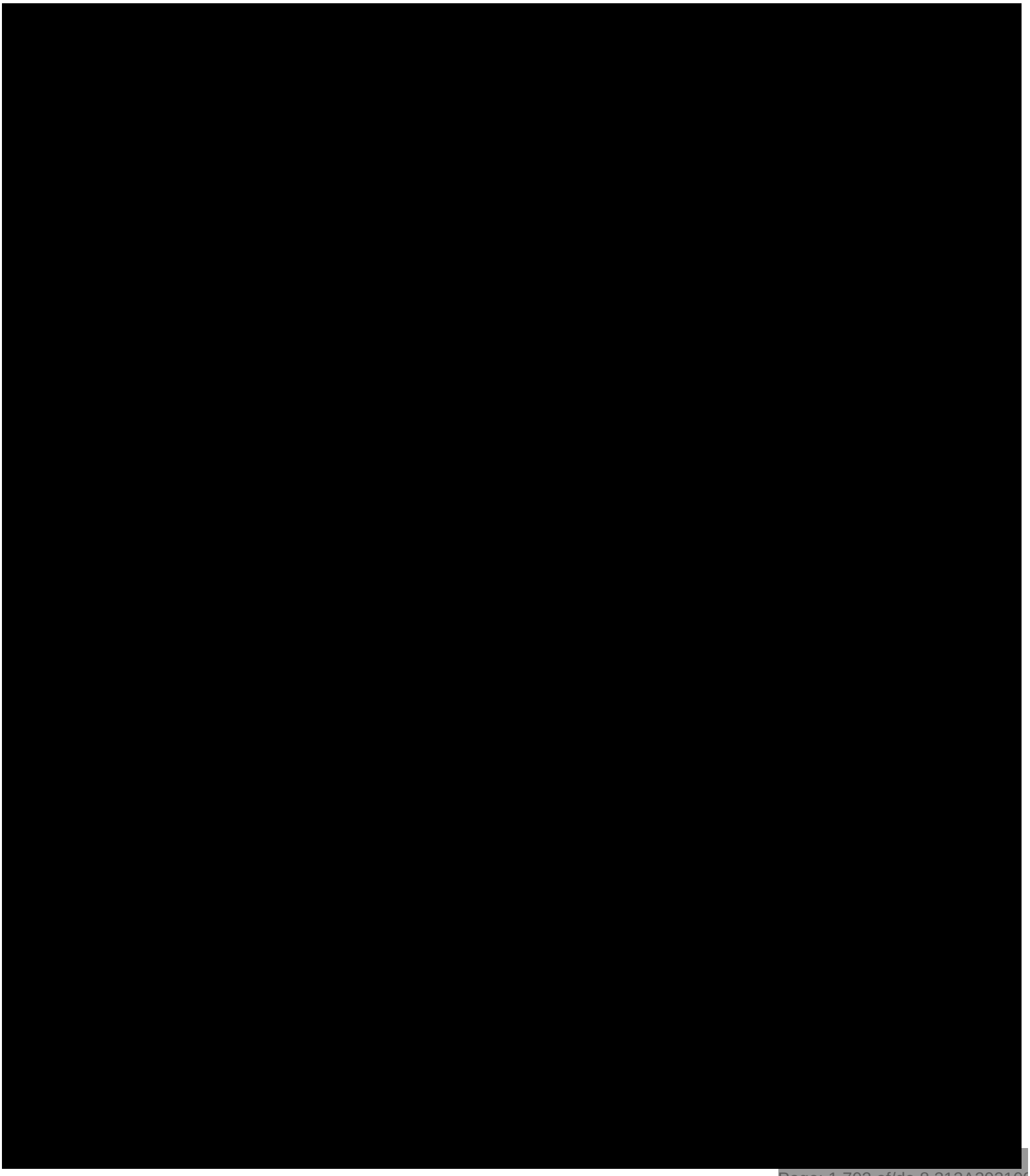

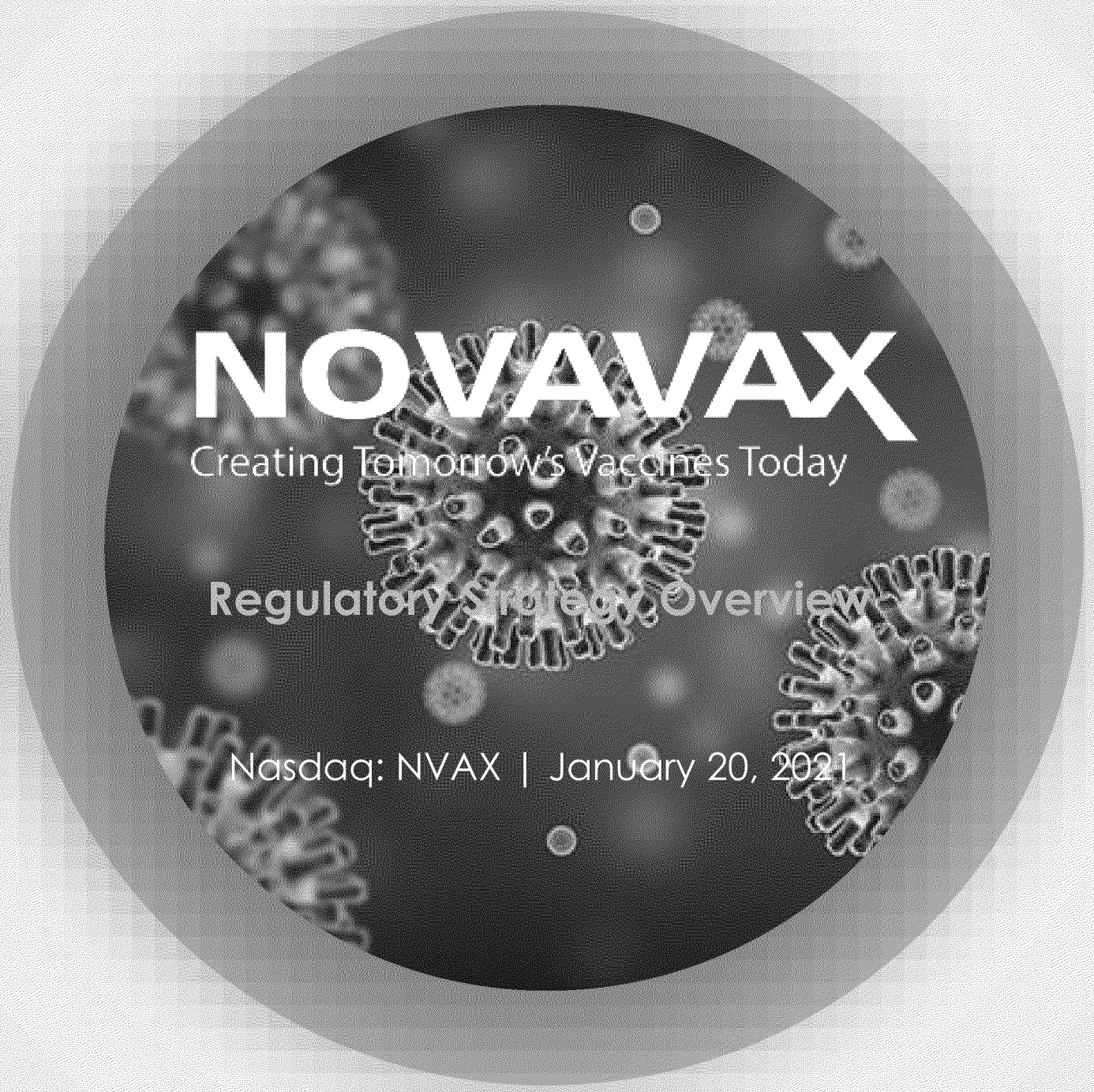

NOVAVAX

Creating Tomorrow's Vaccines Today

Regulatory Strategy Overview

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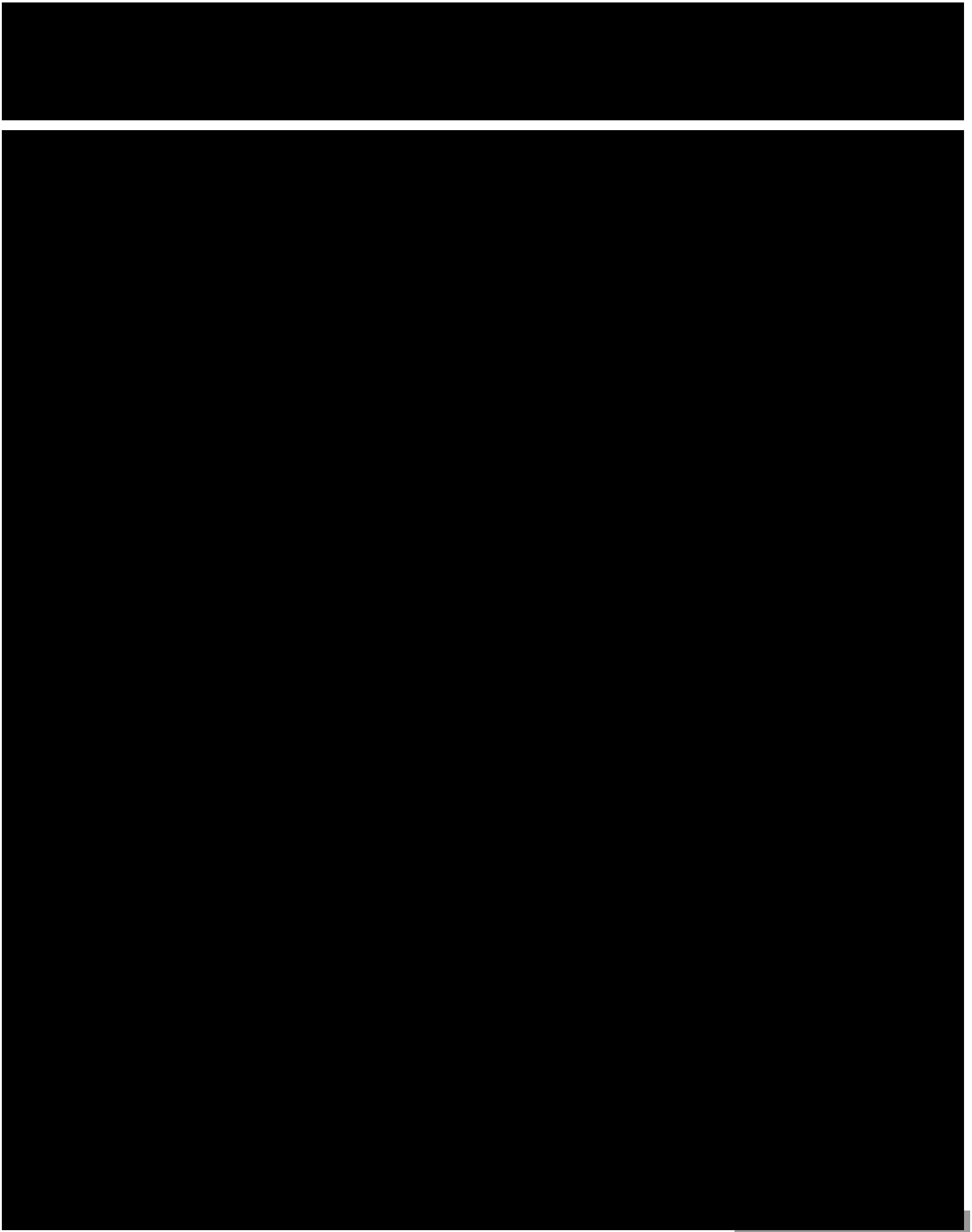

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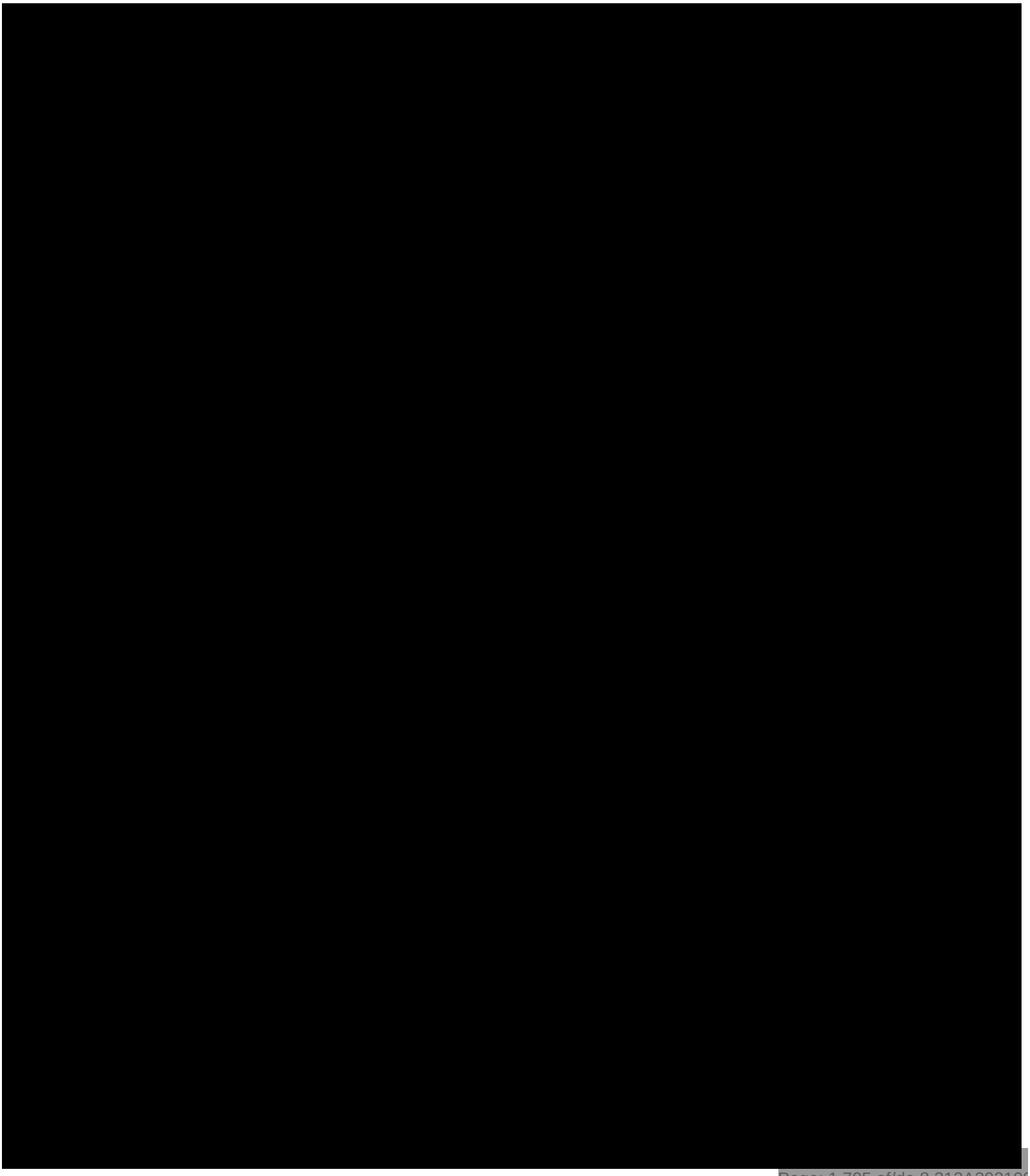

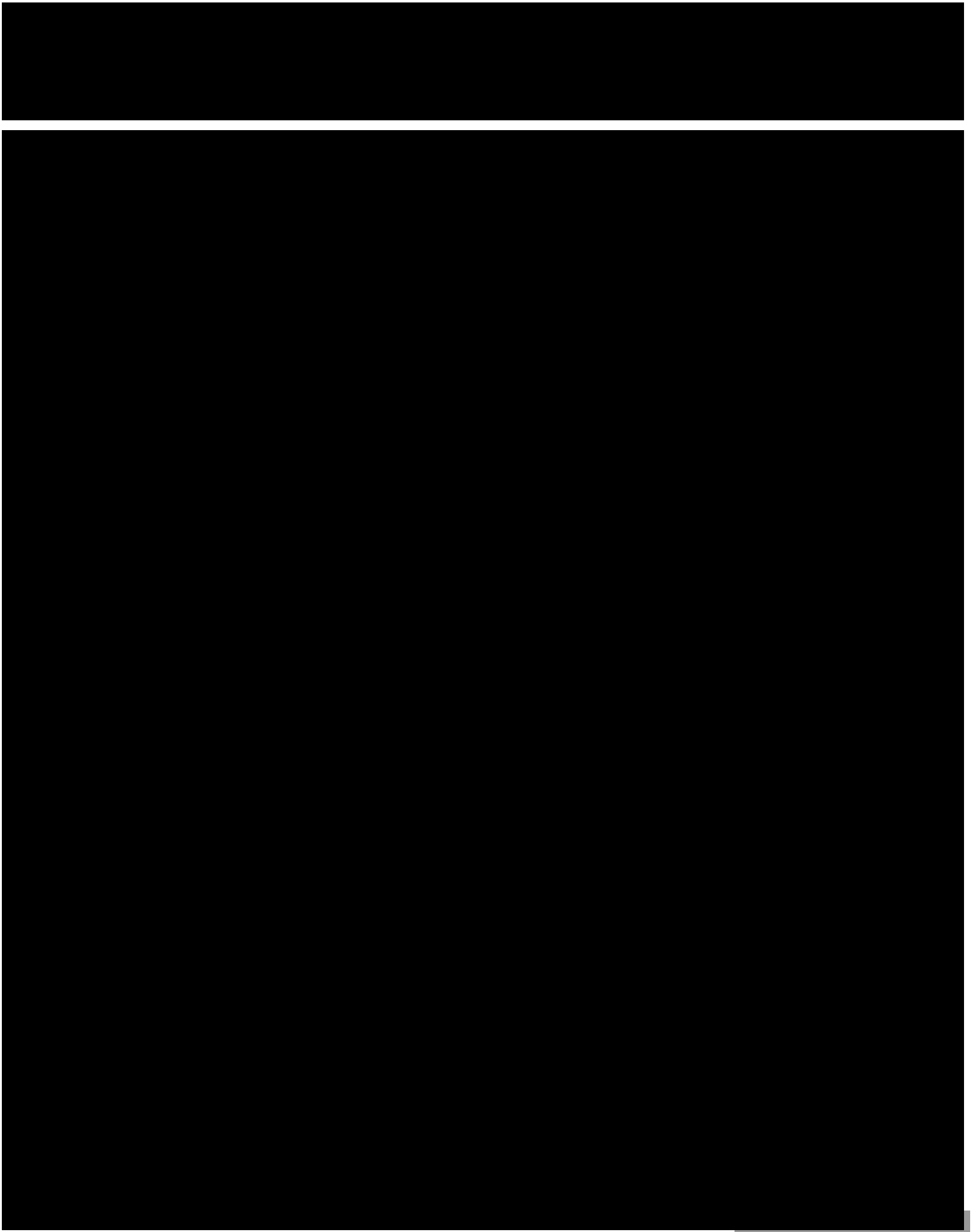

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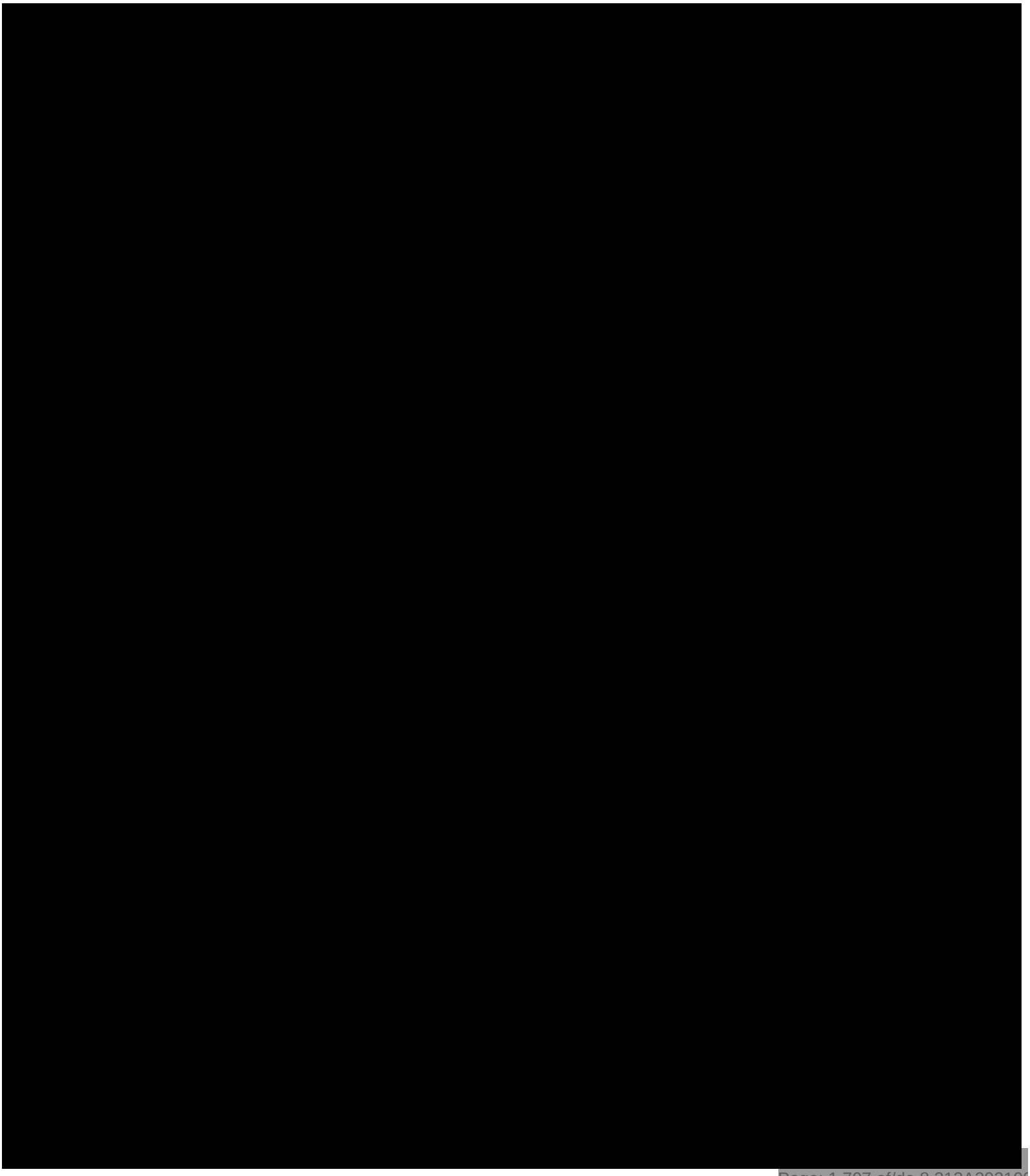

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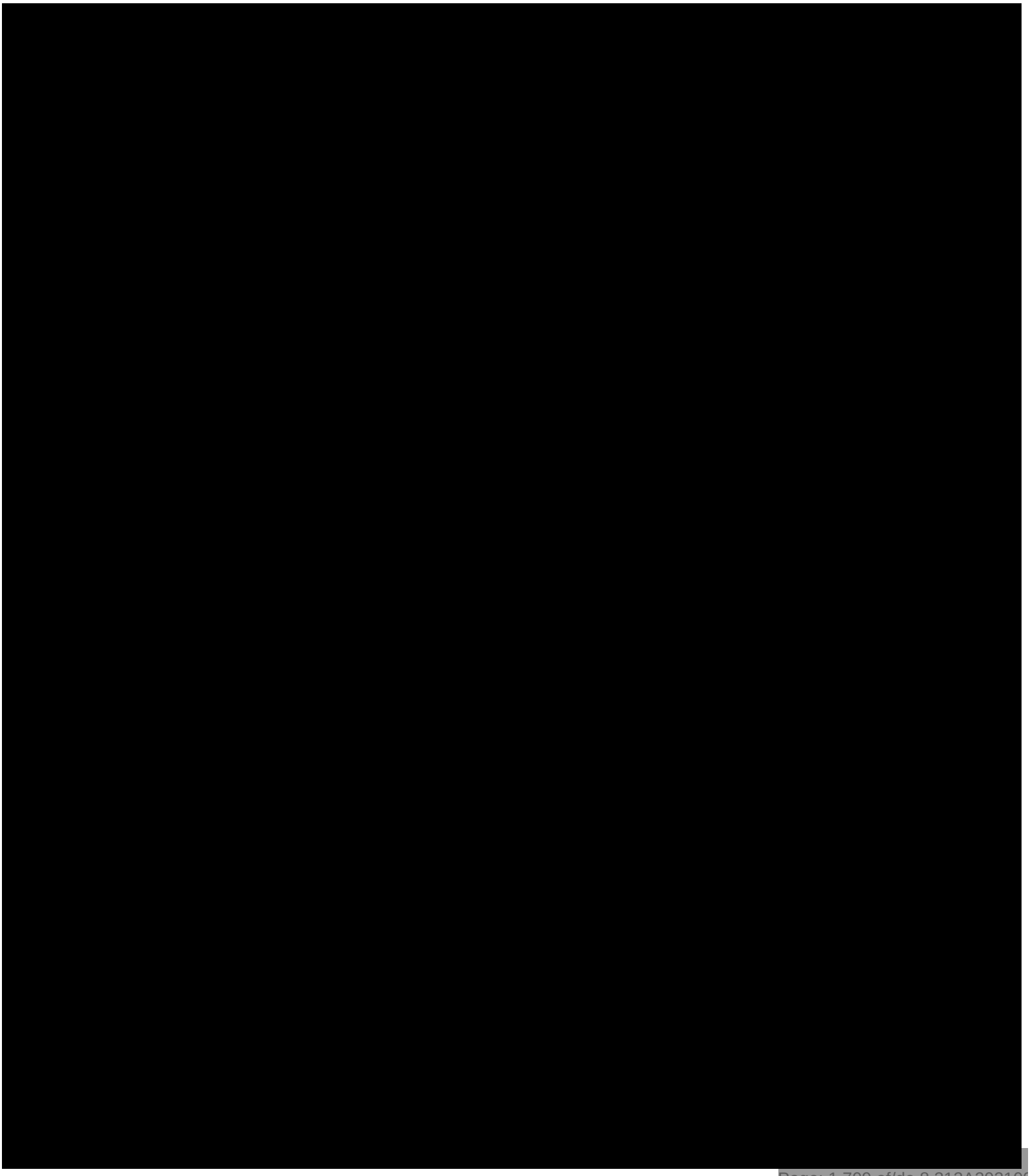

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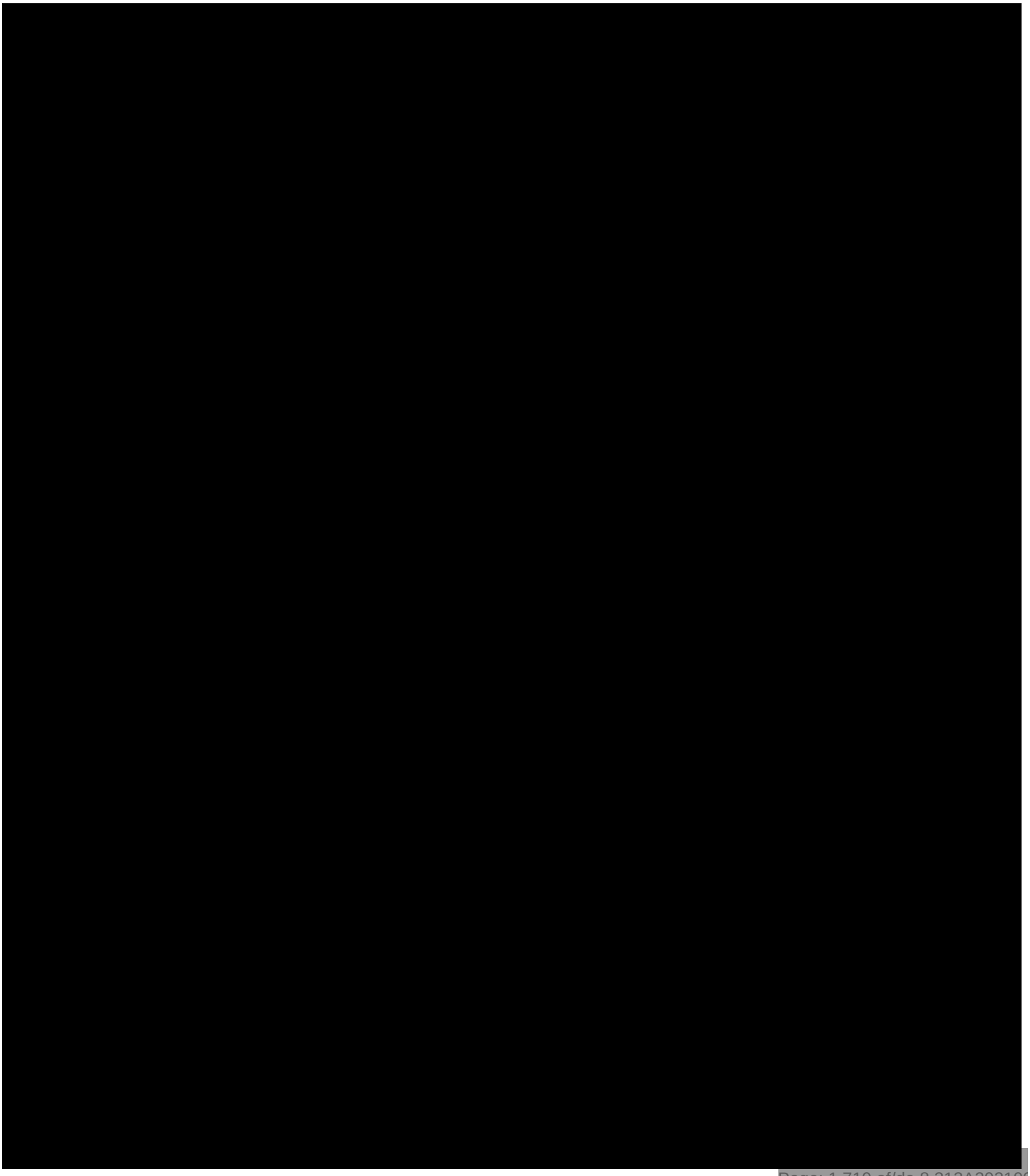

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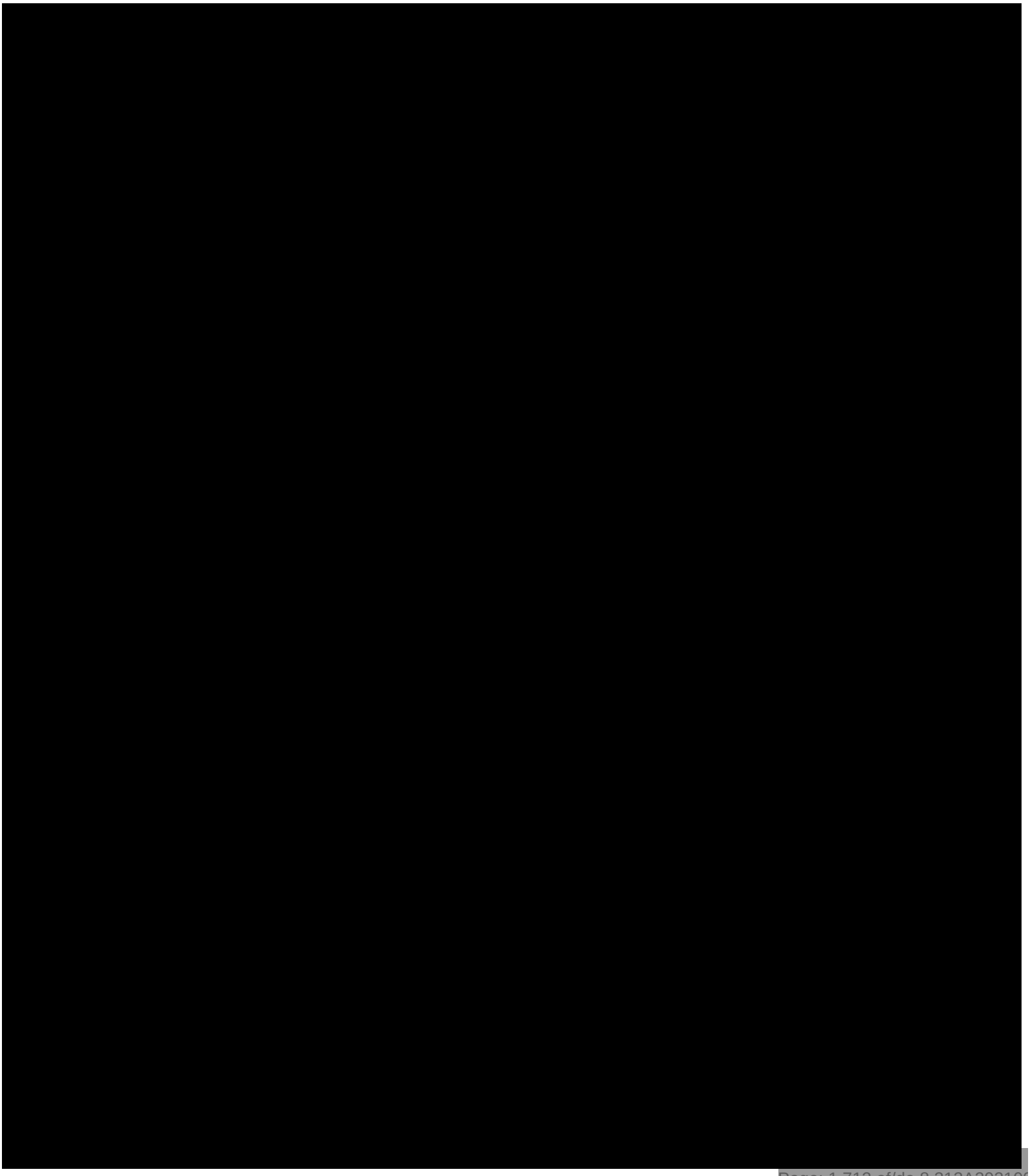

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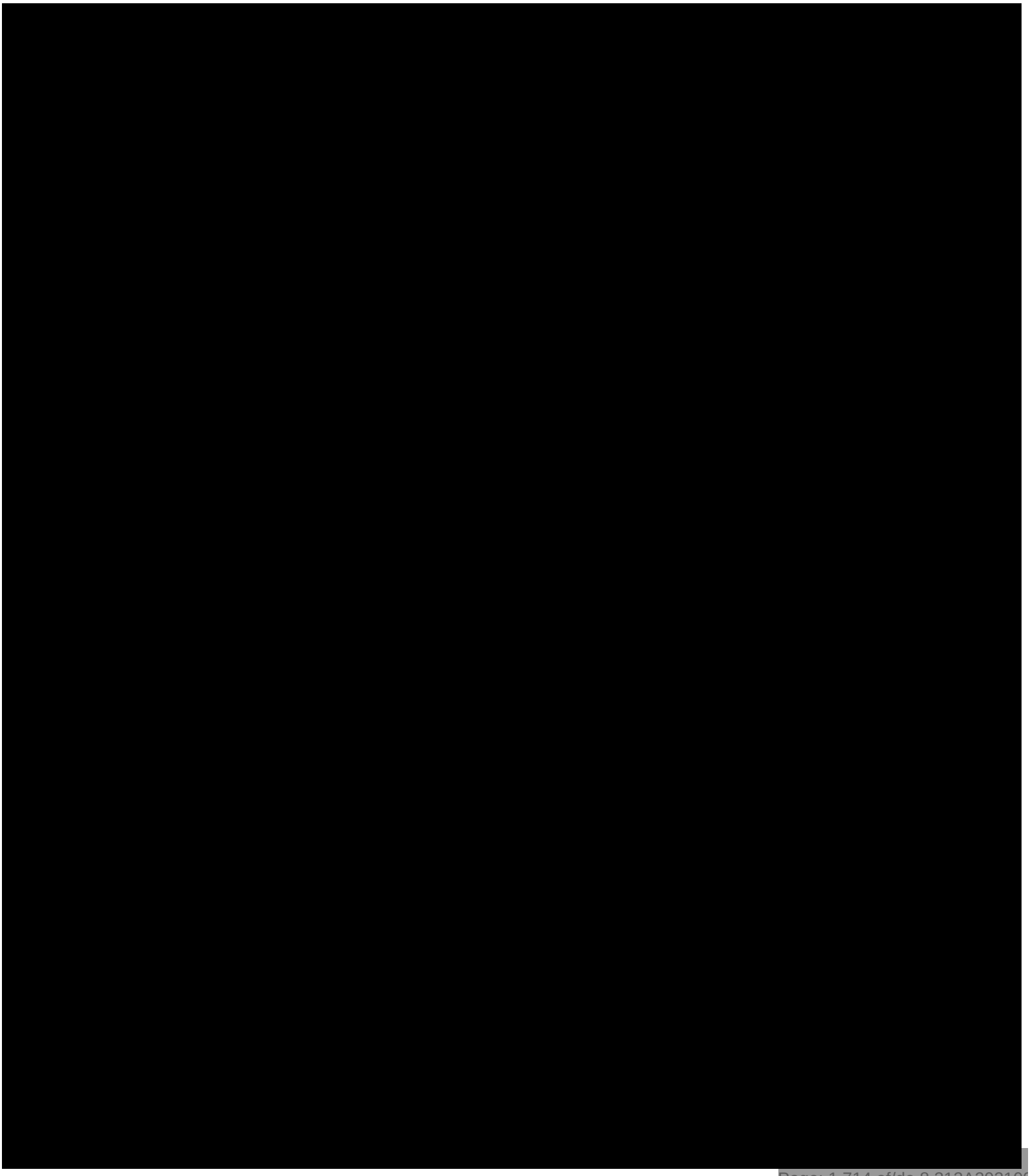

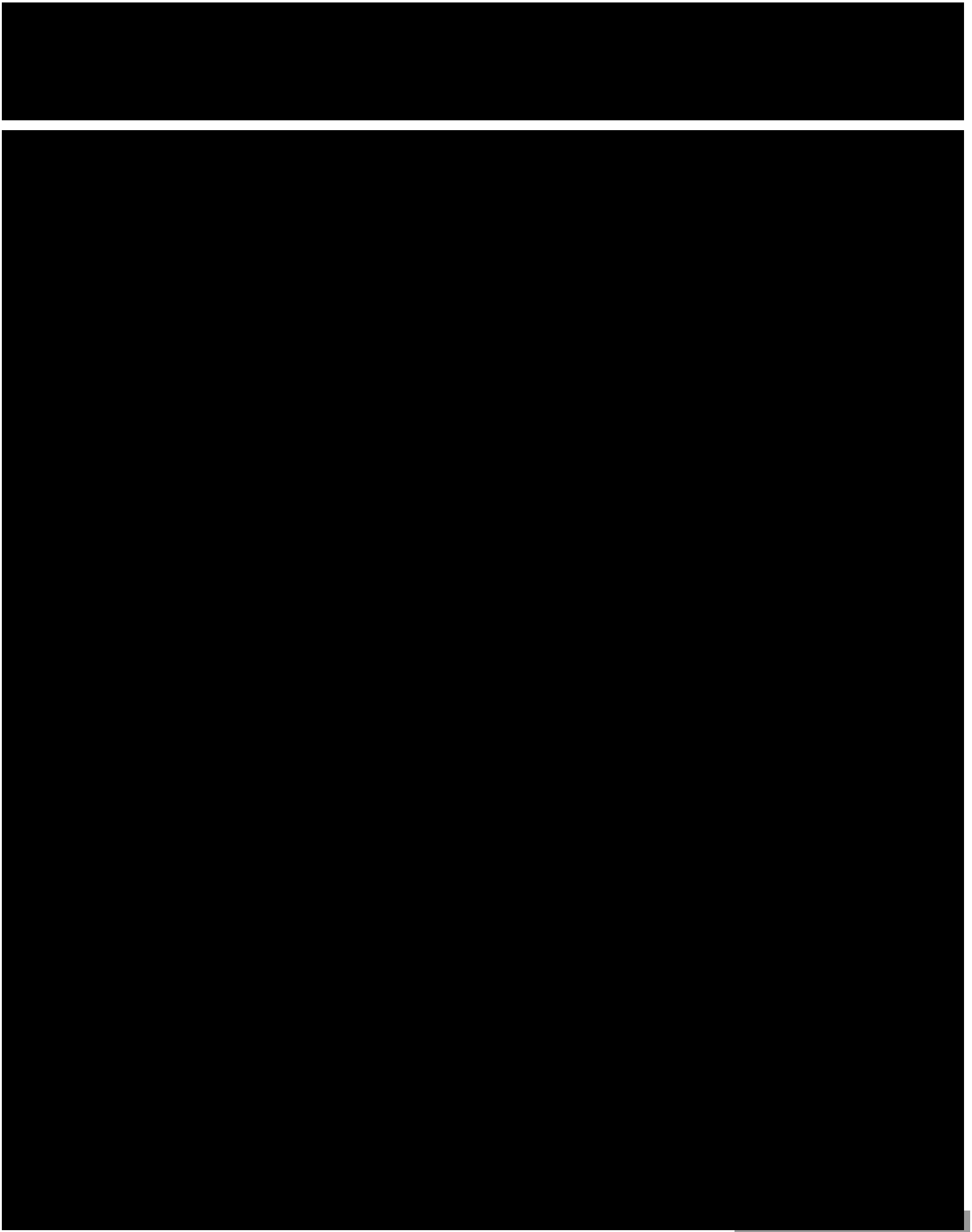

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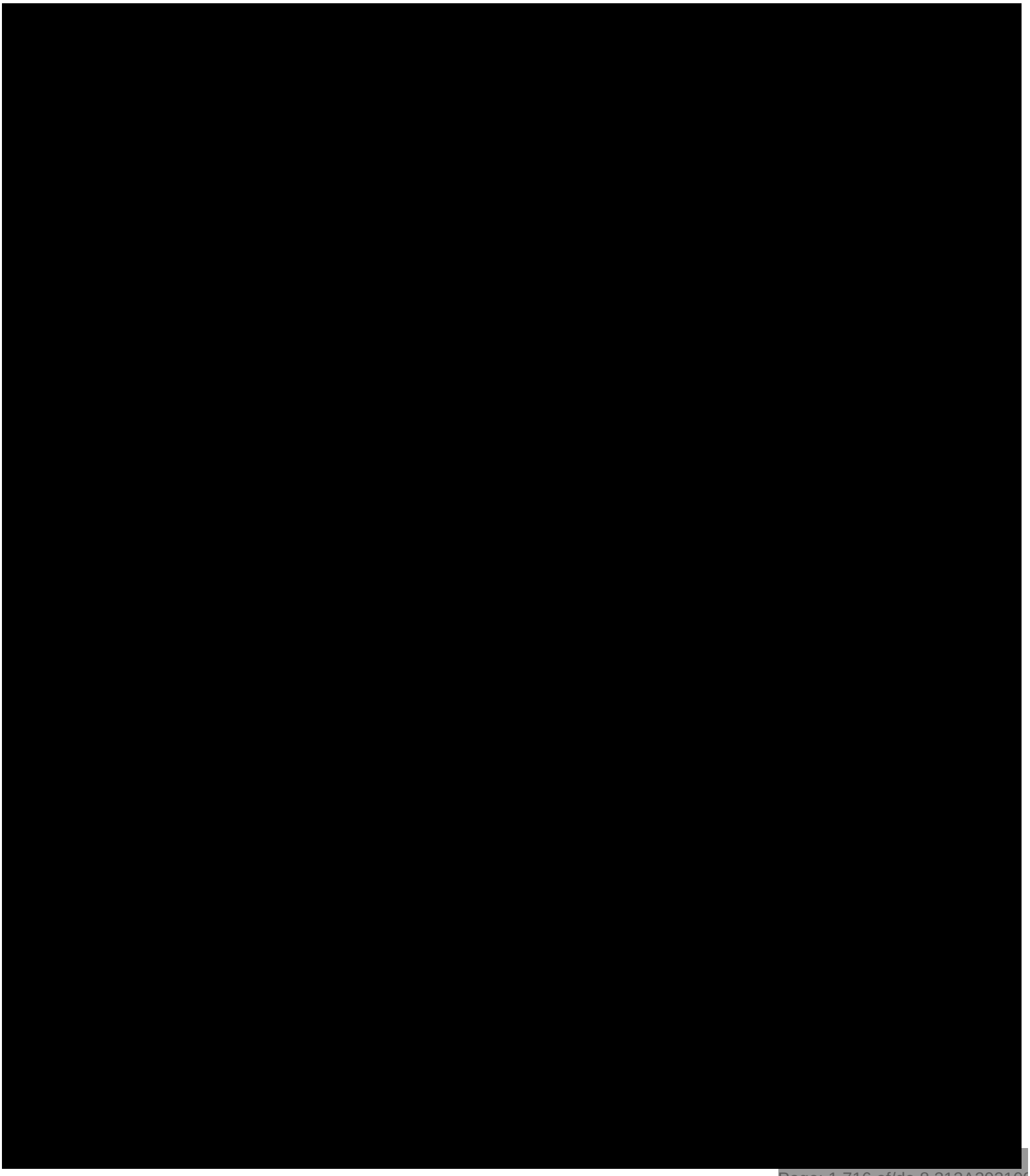

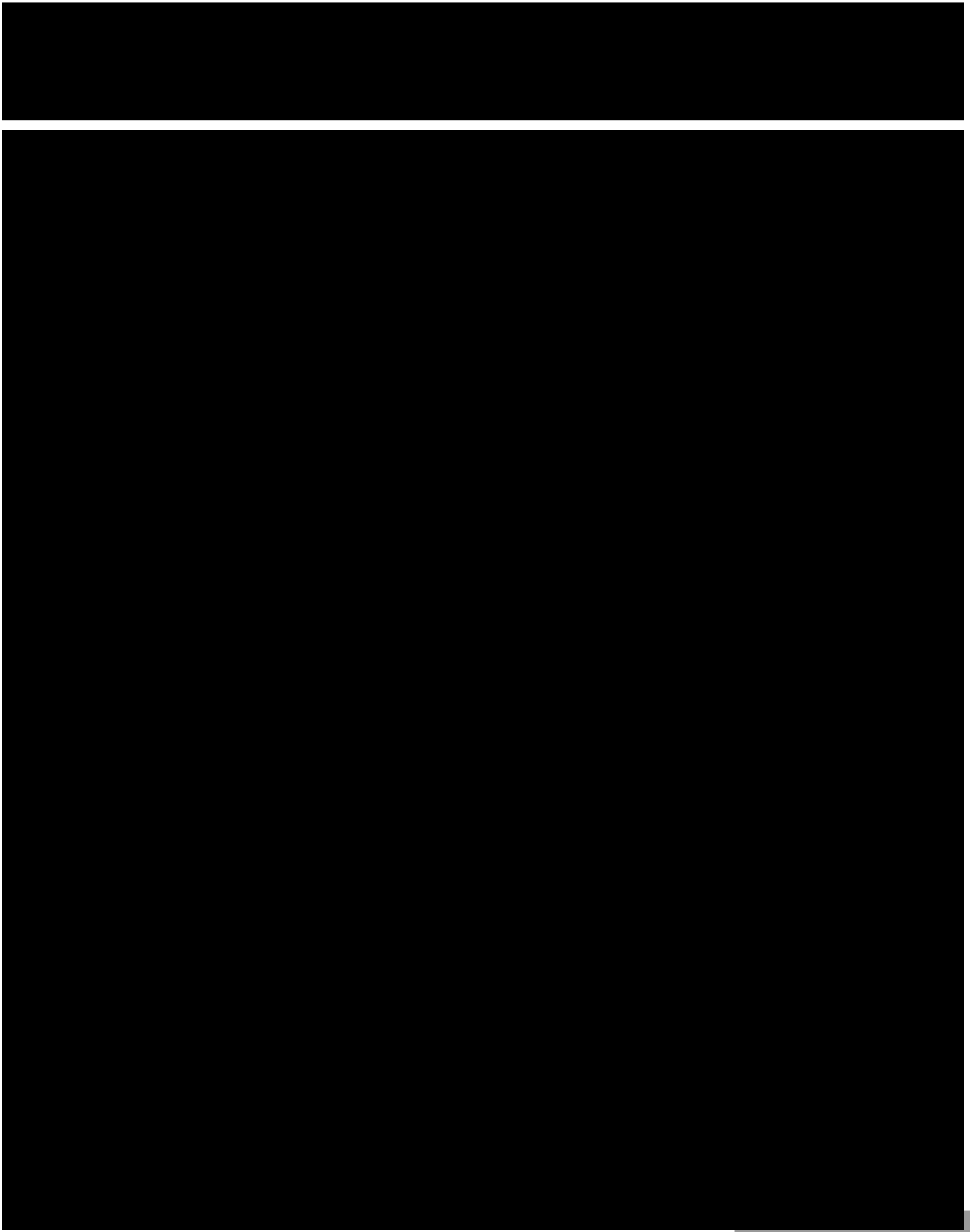

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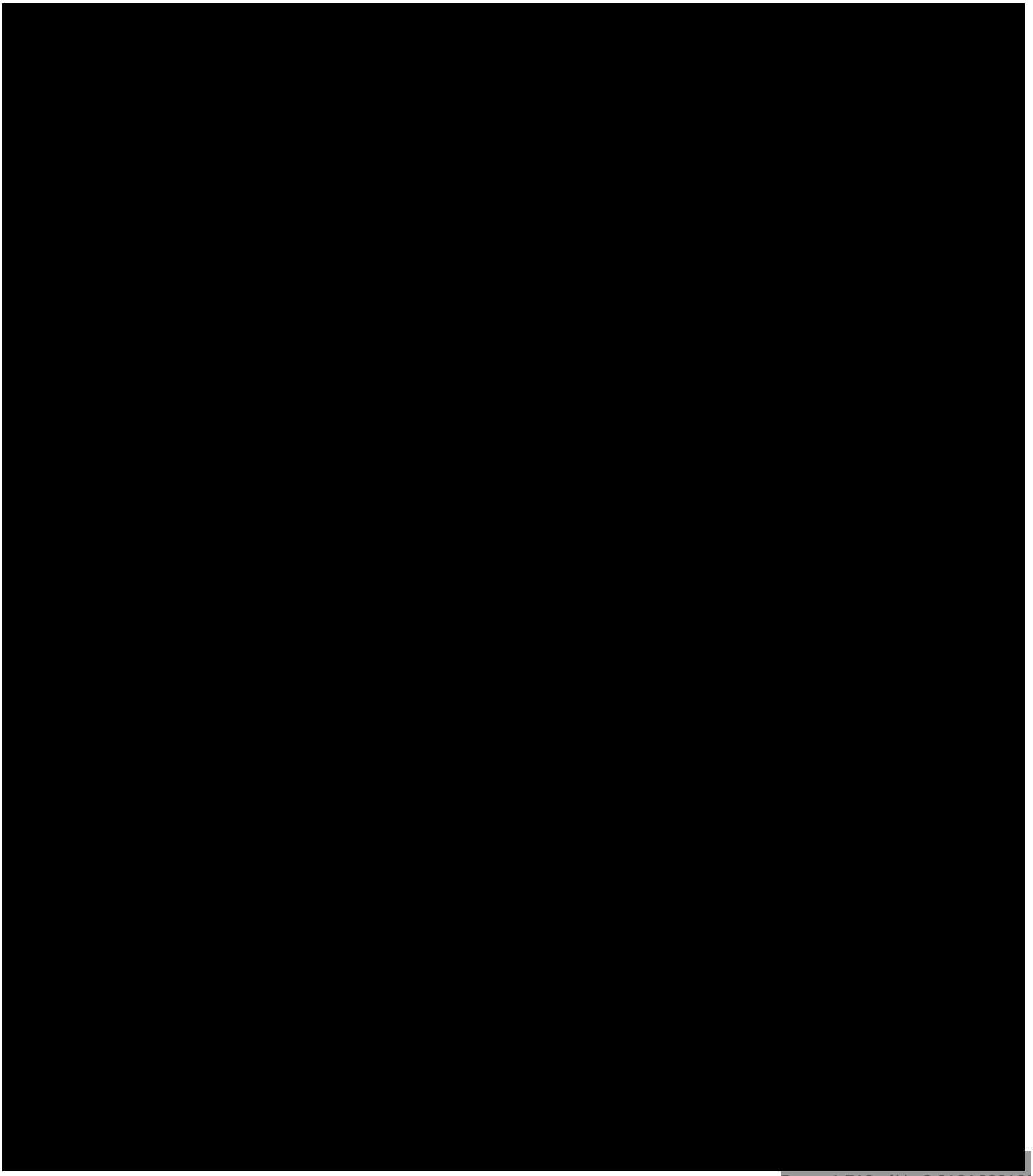

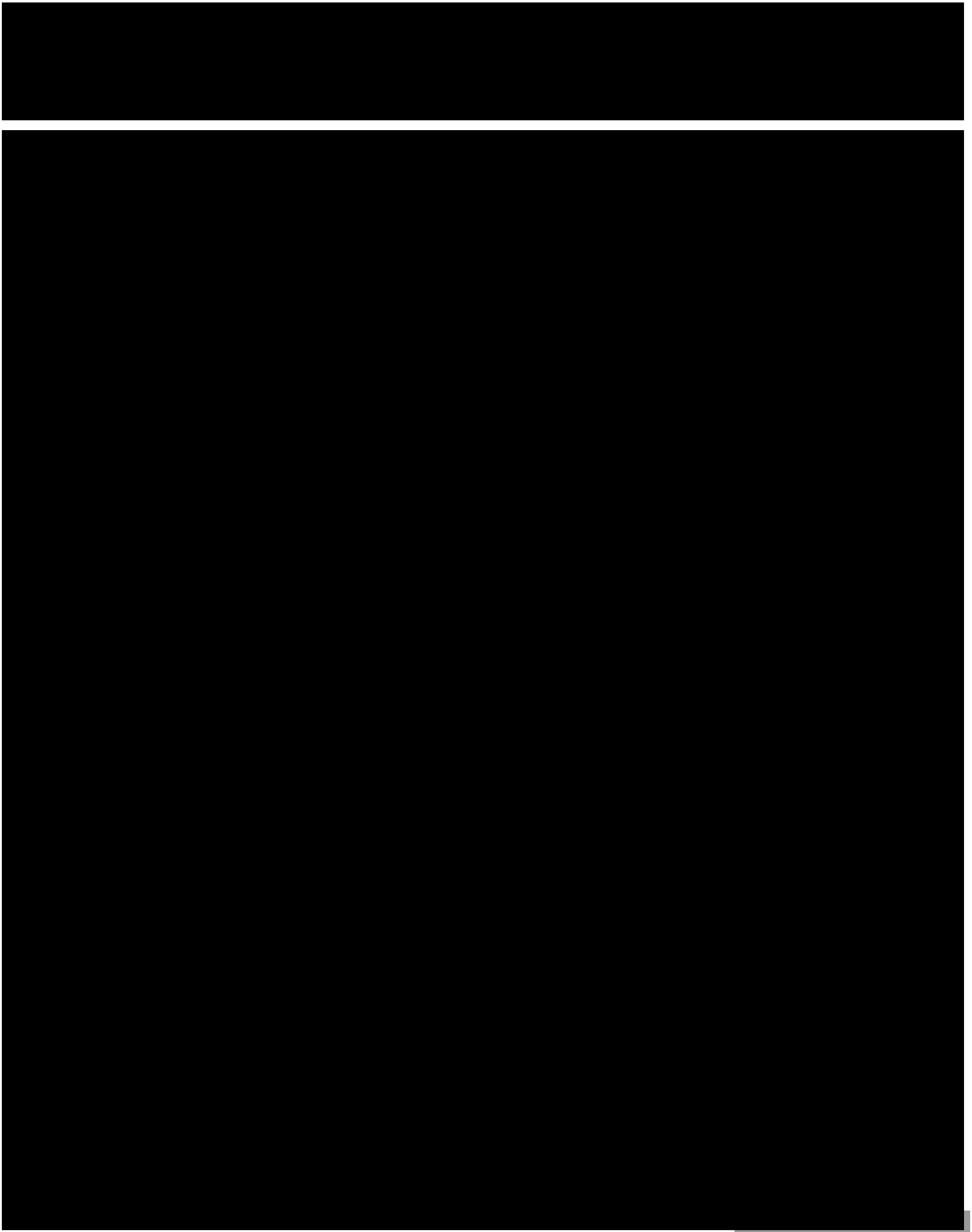

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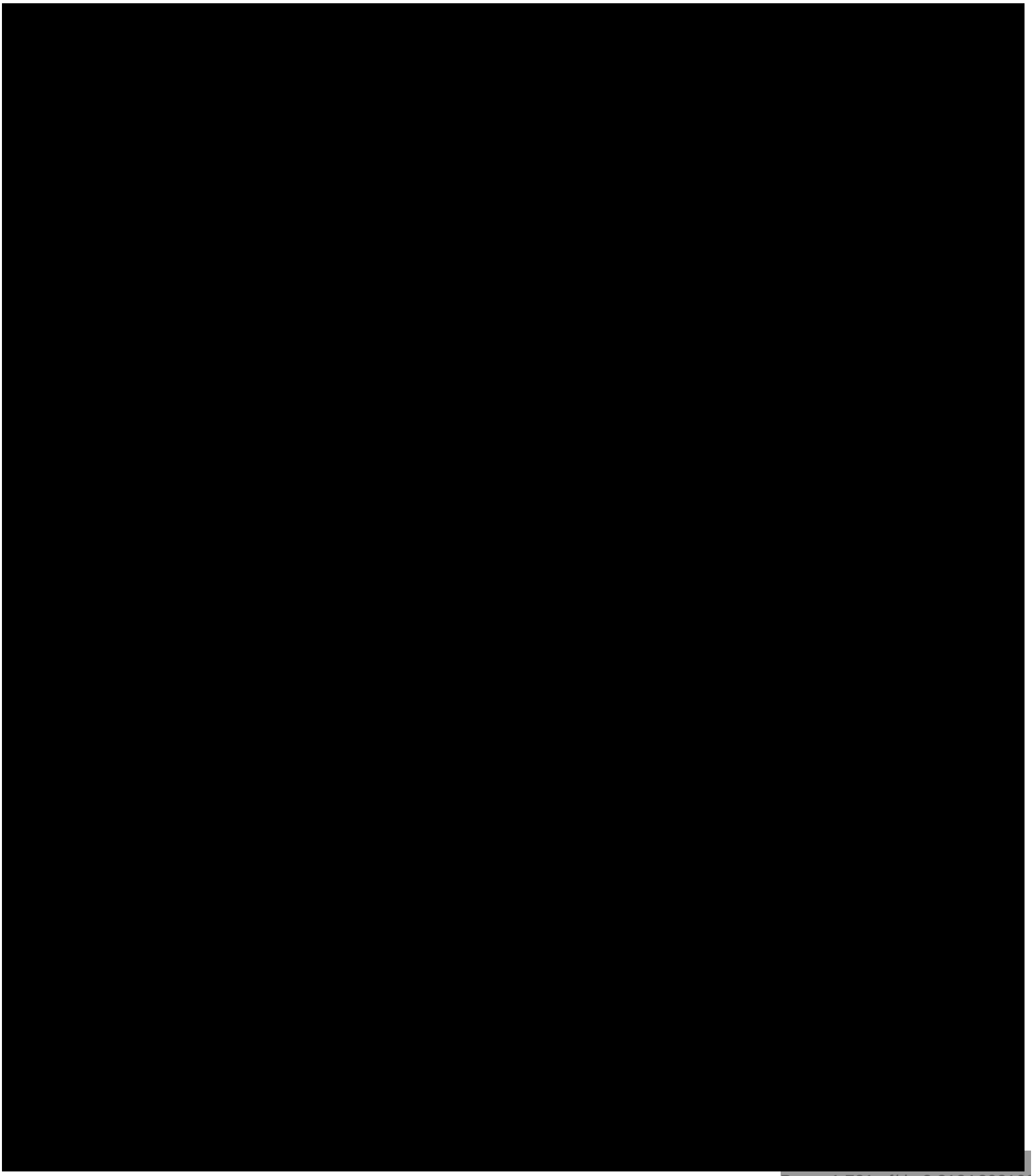

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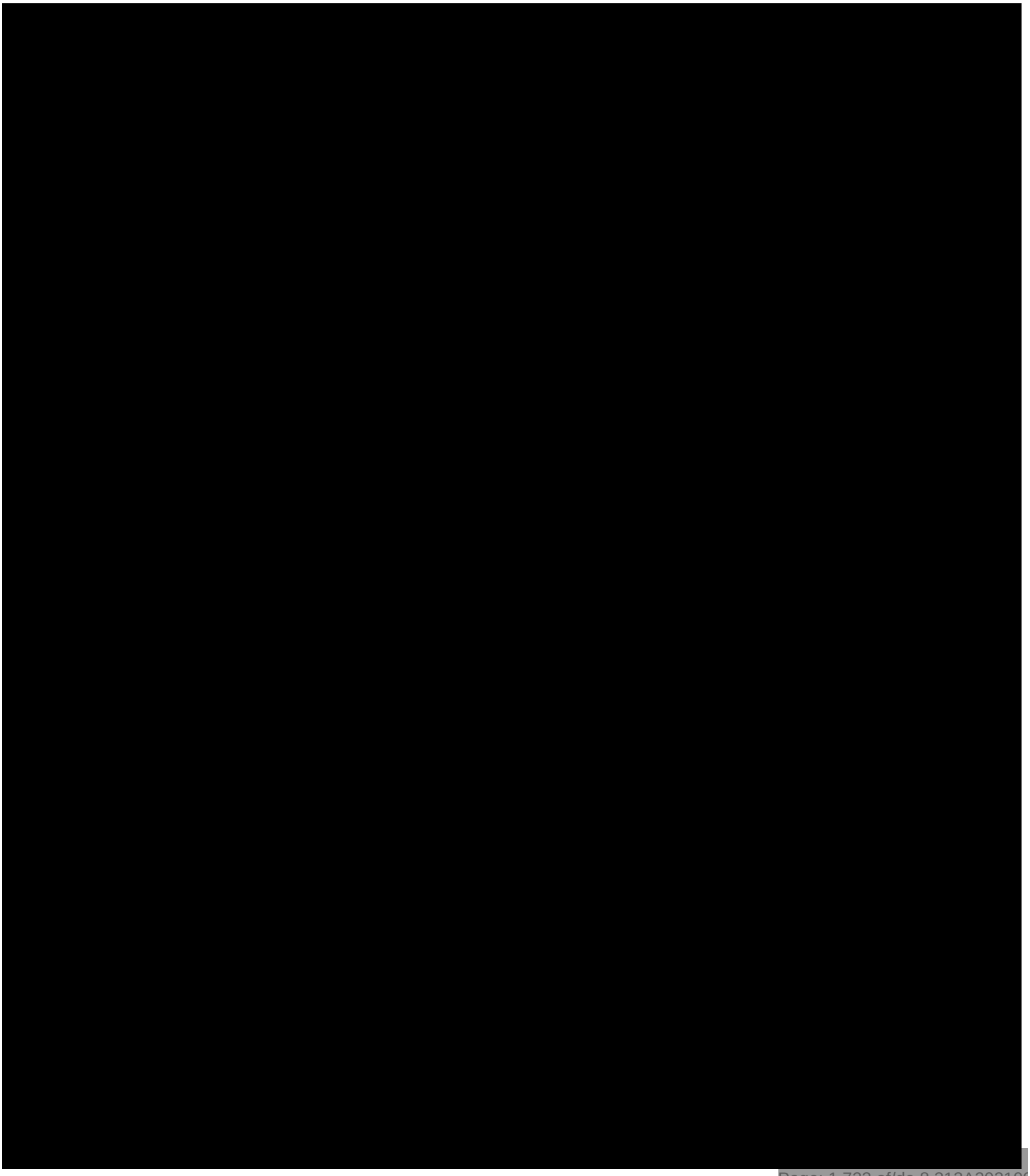

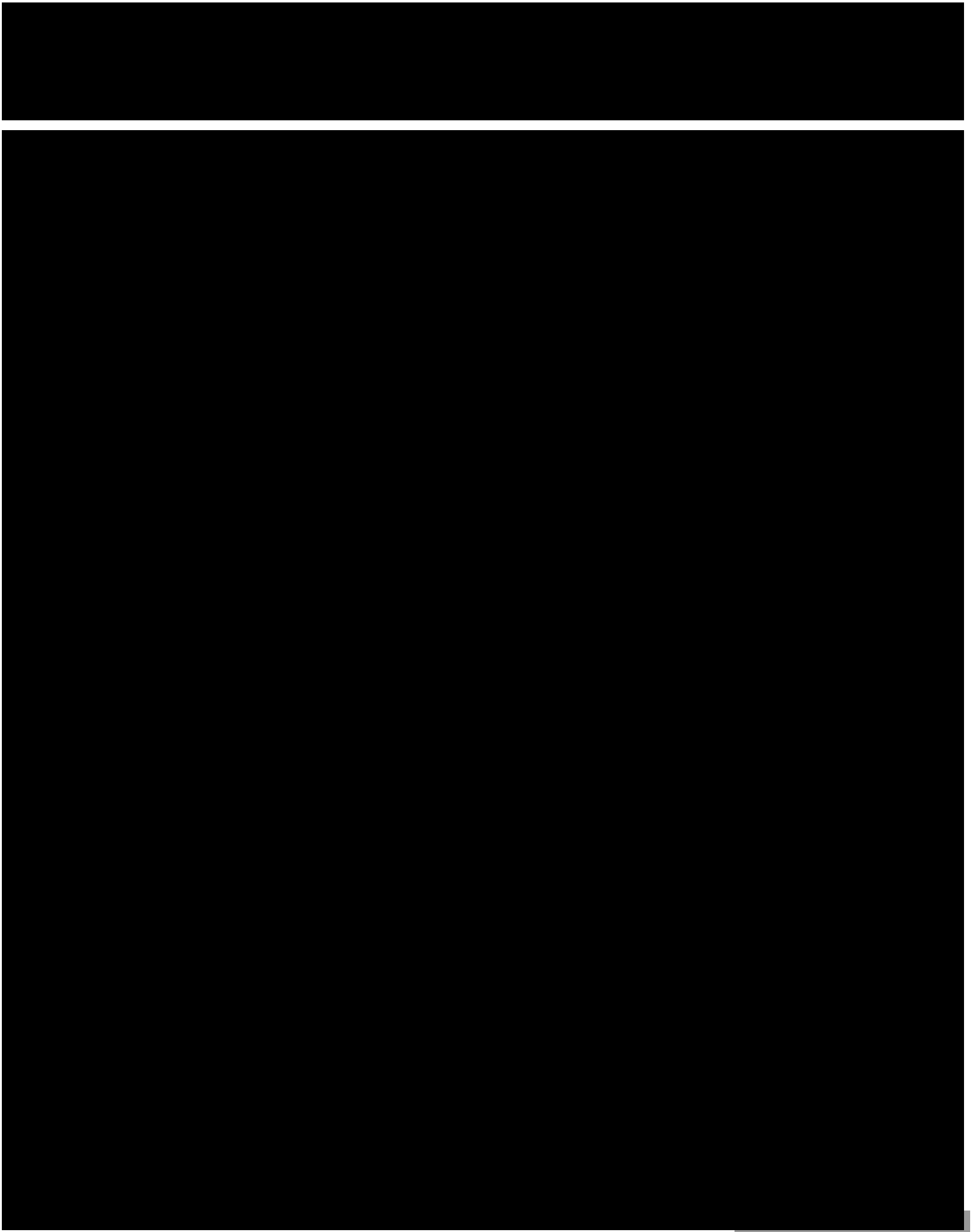

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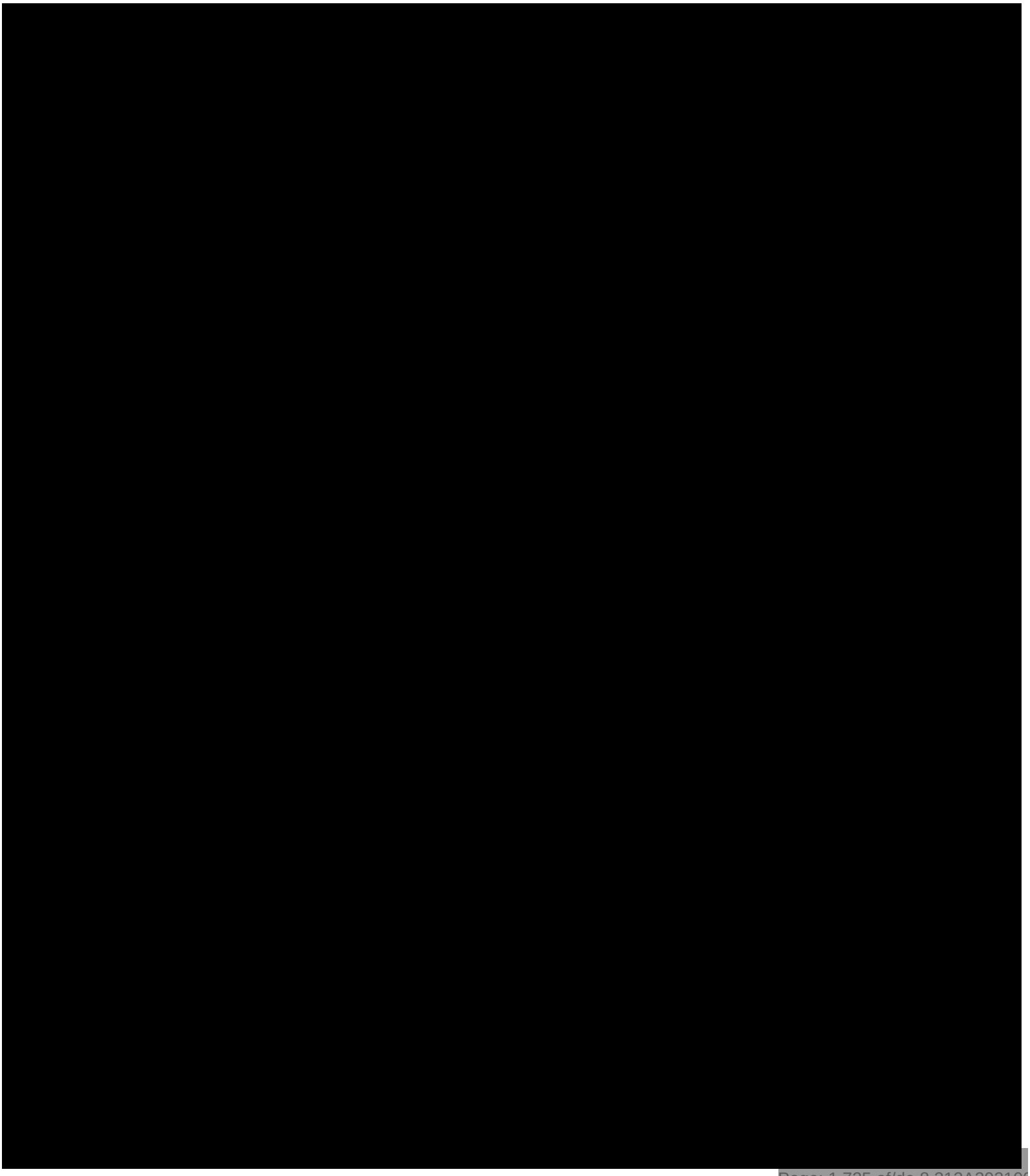

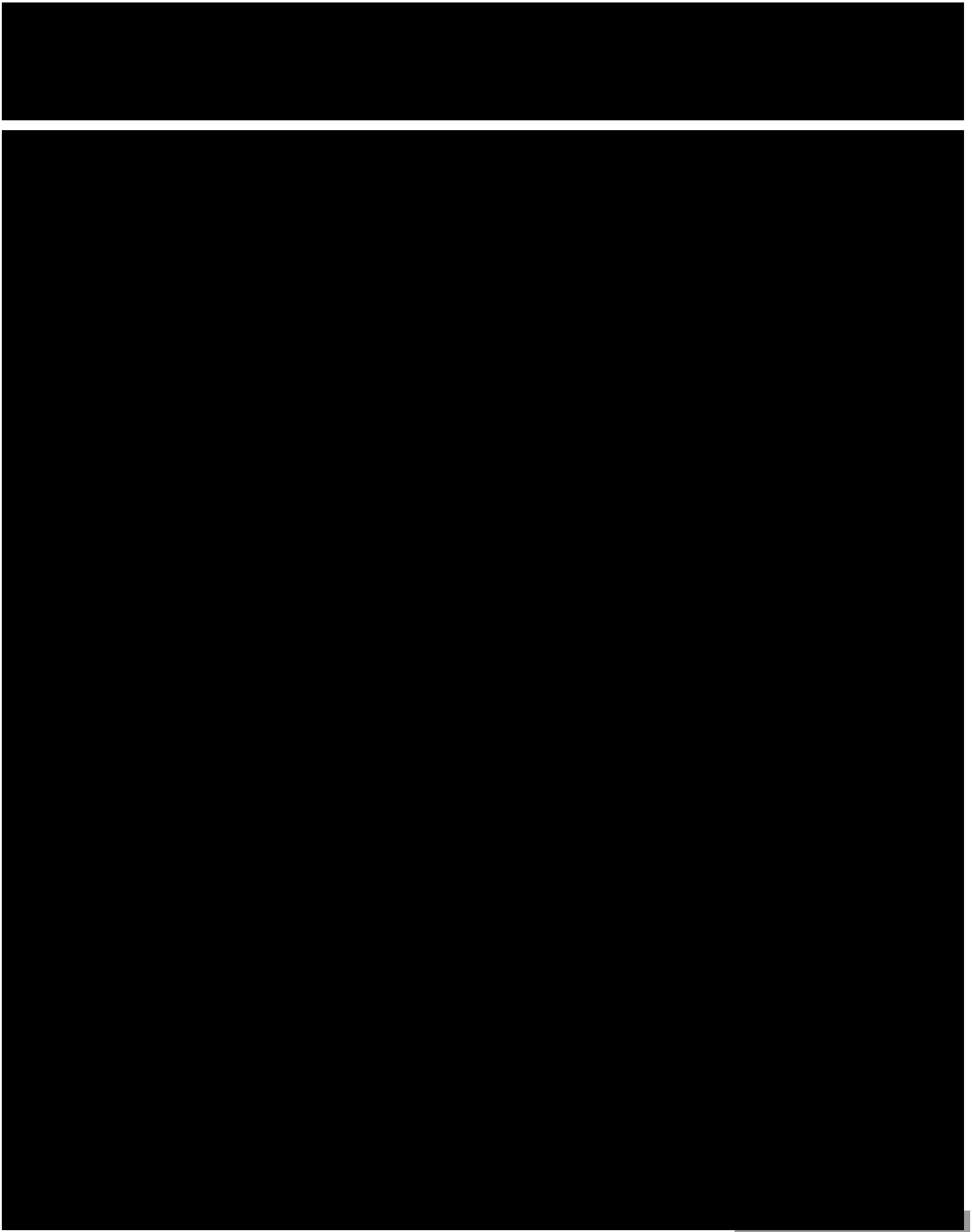

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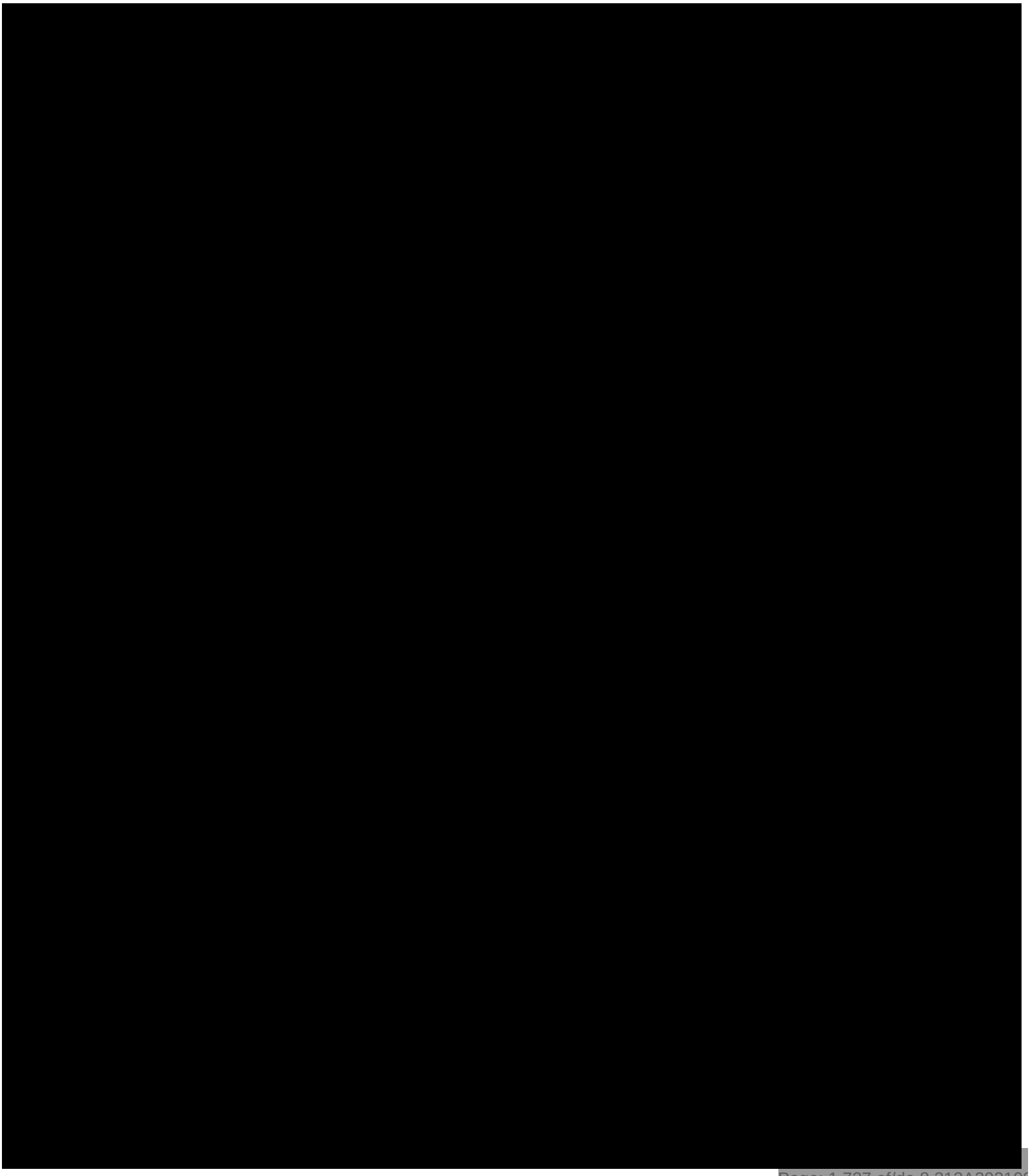

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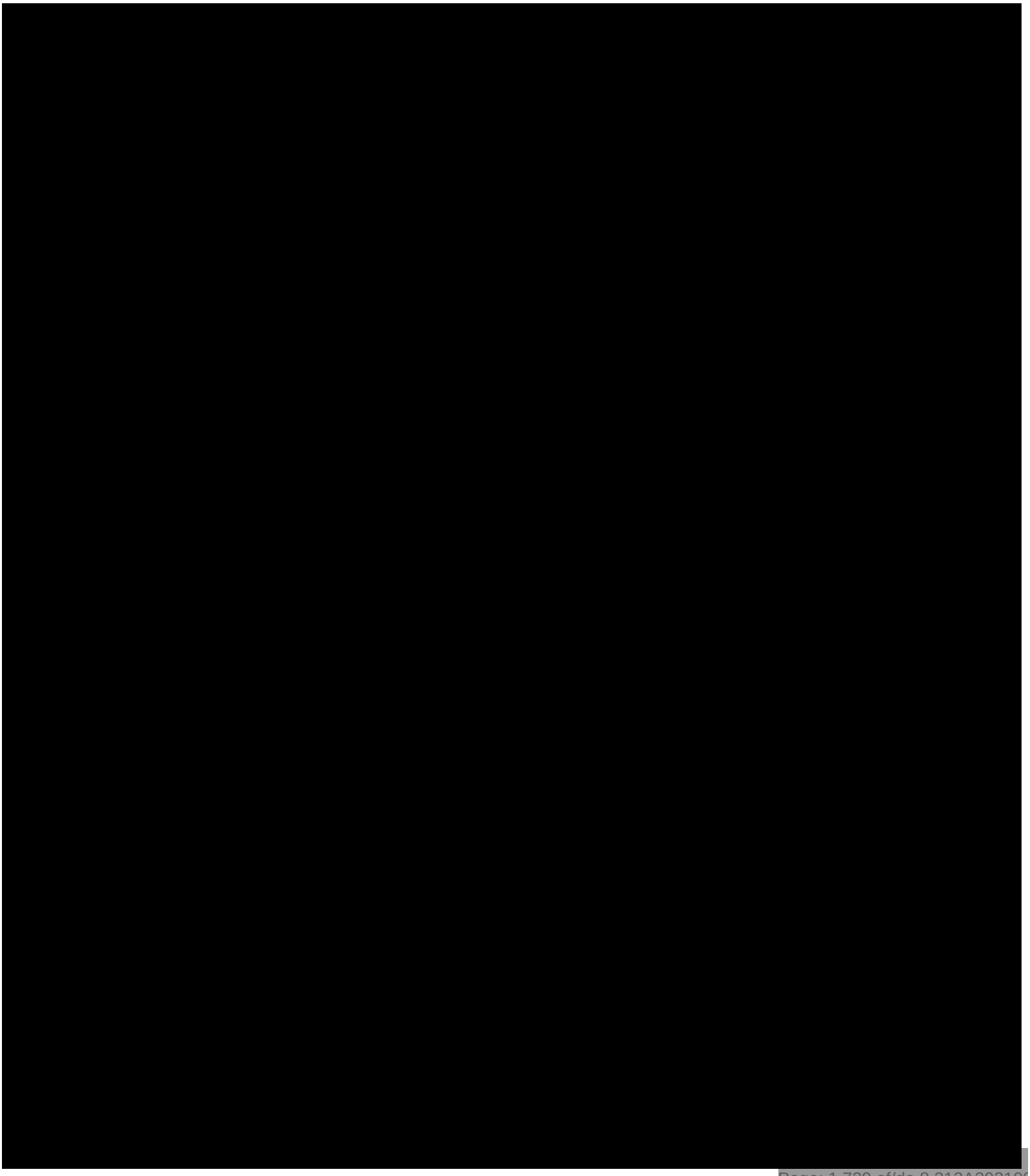

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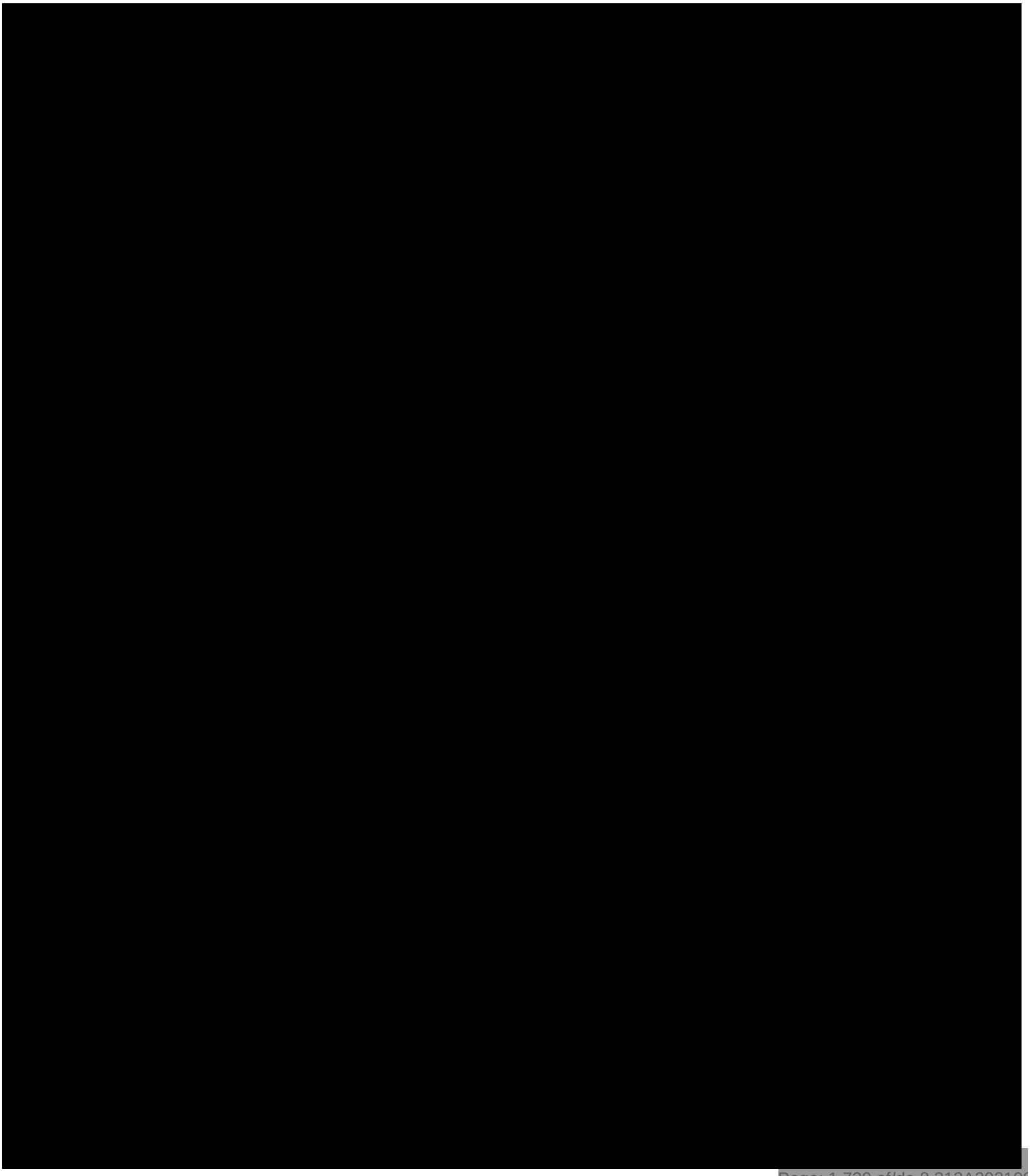

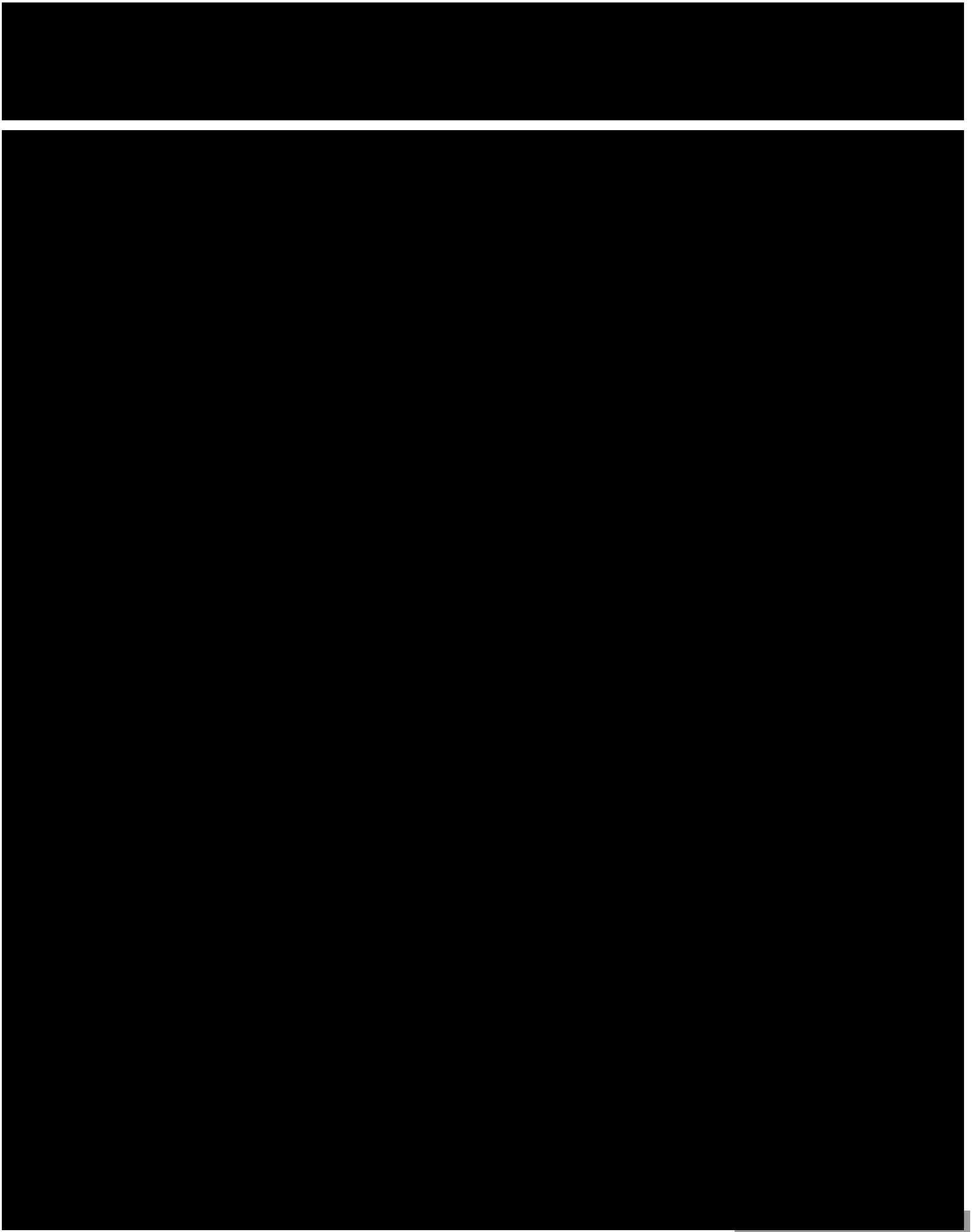

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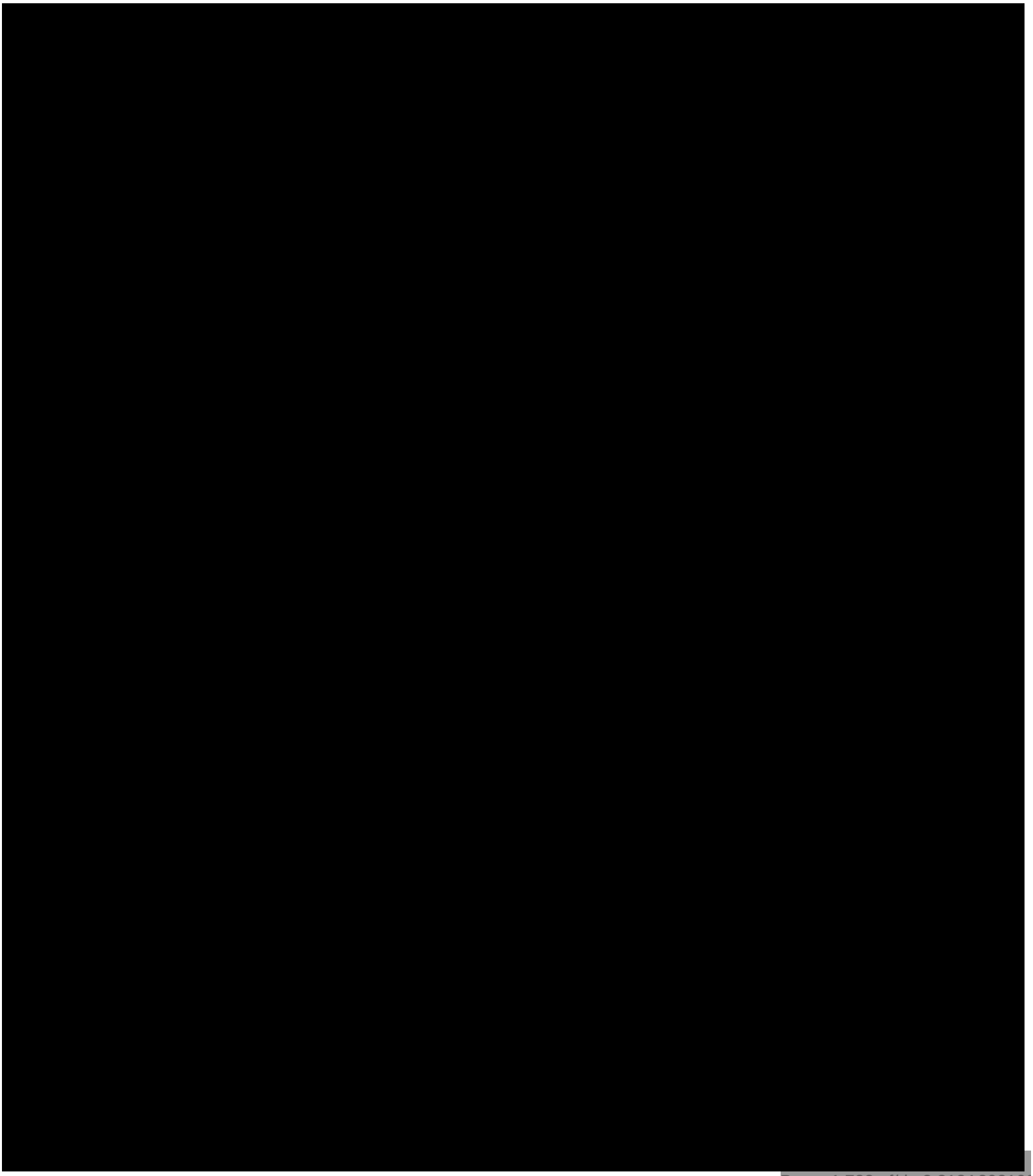

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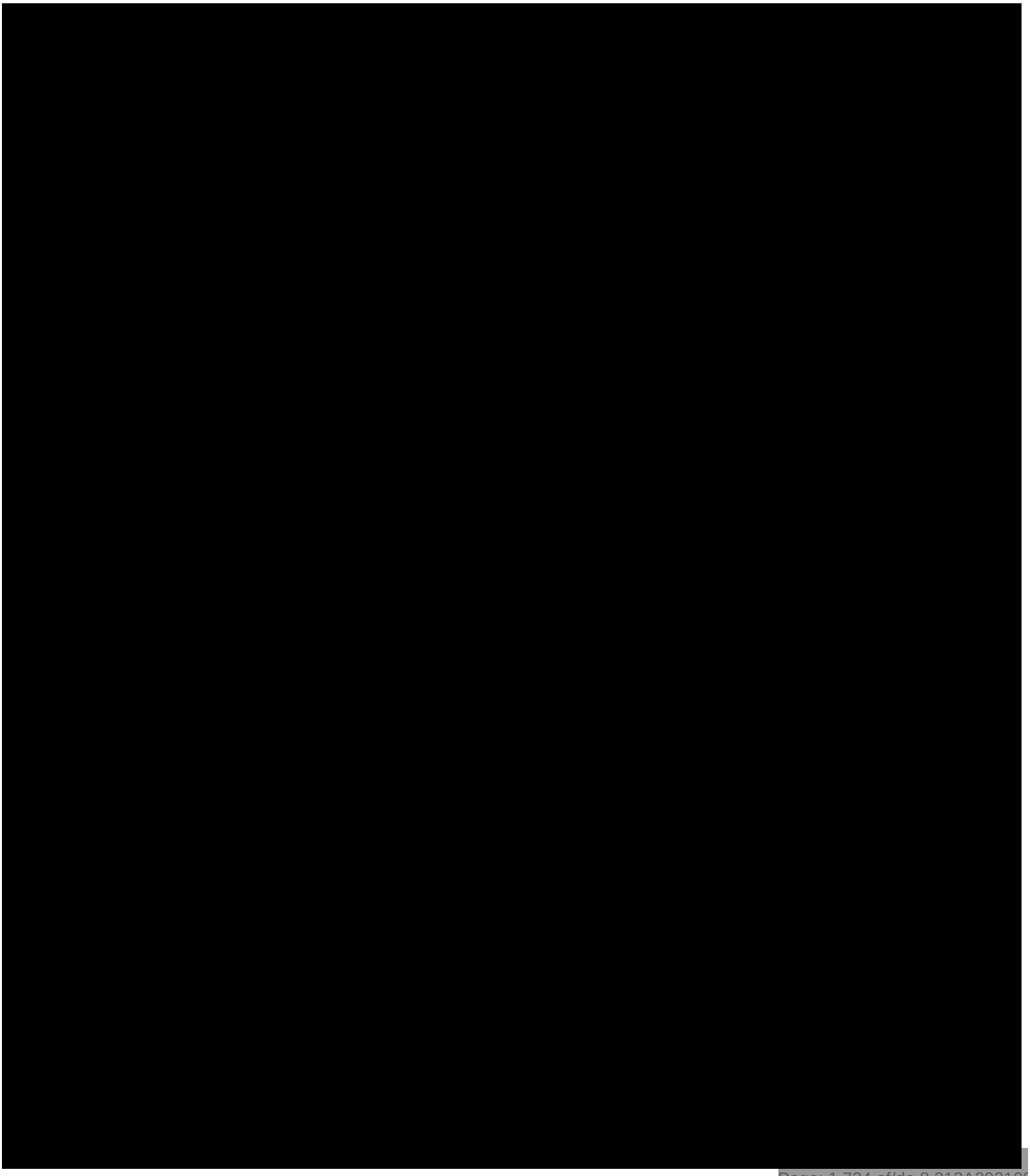

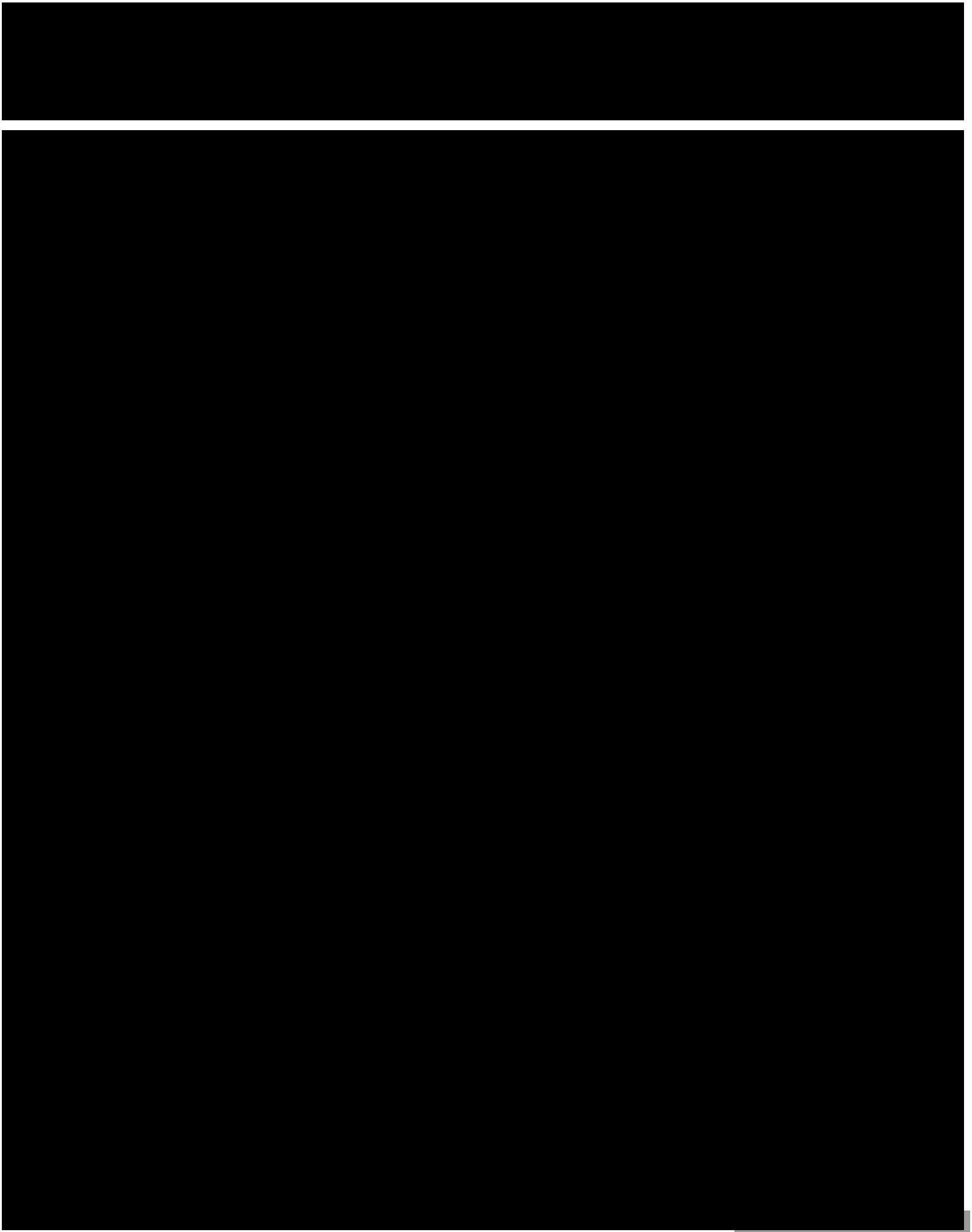

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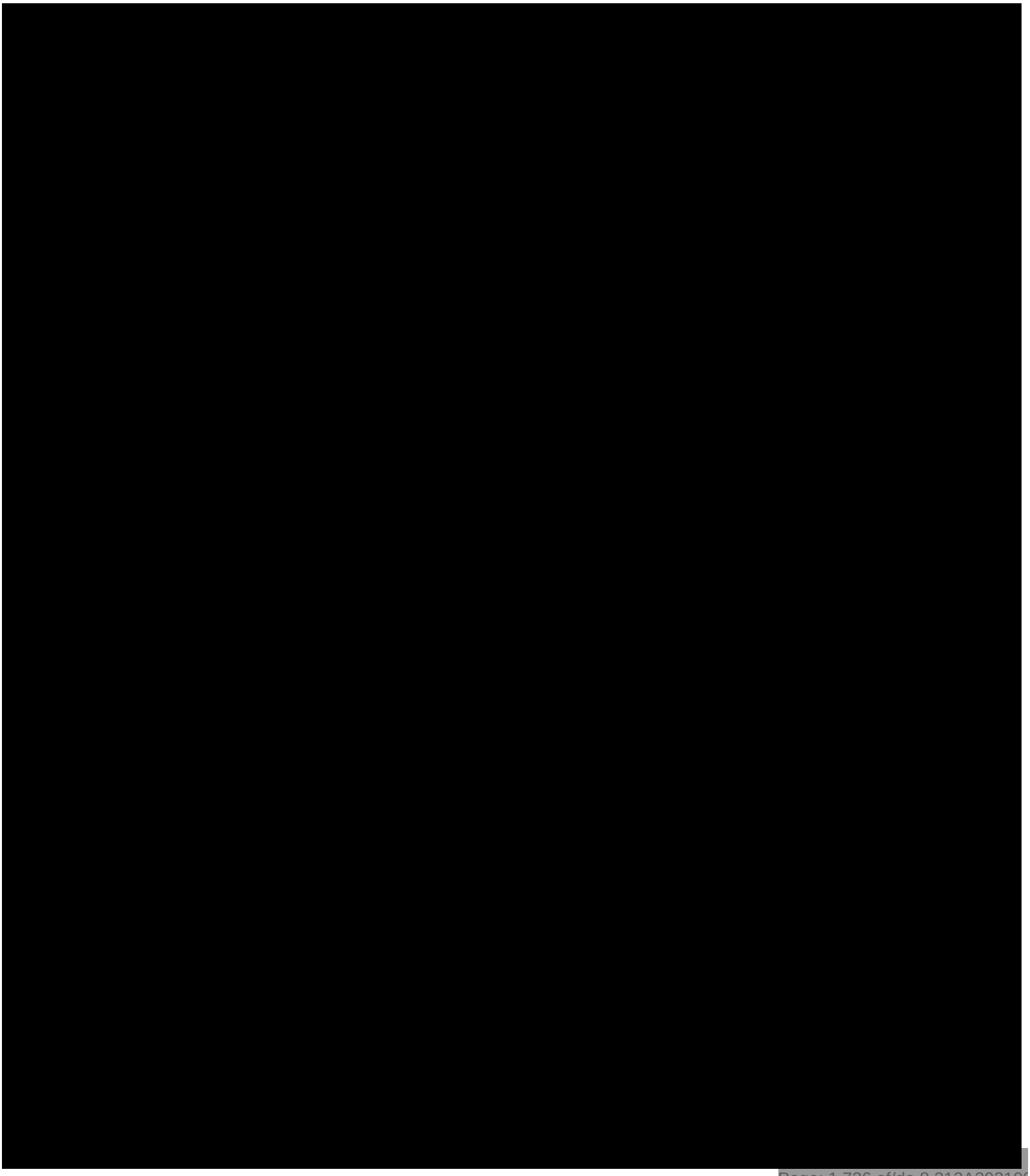

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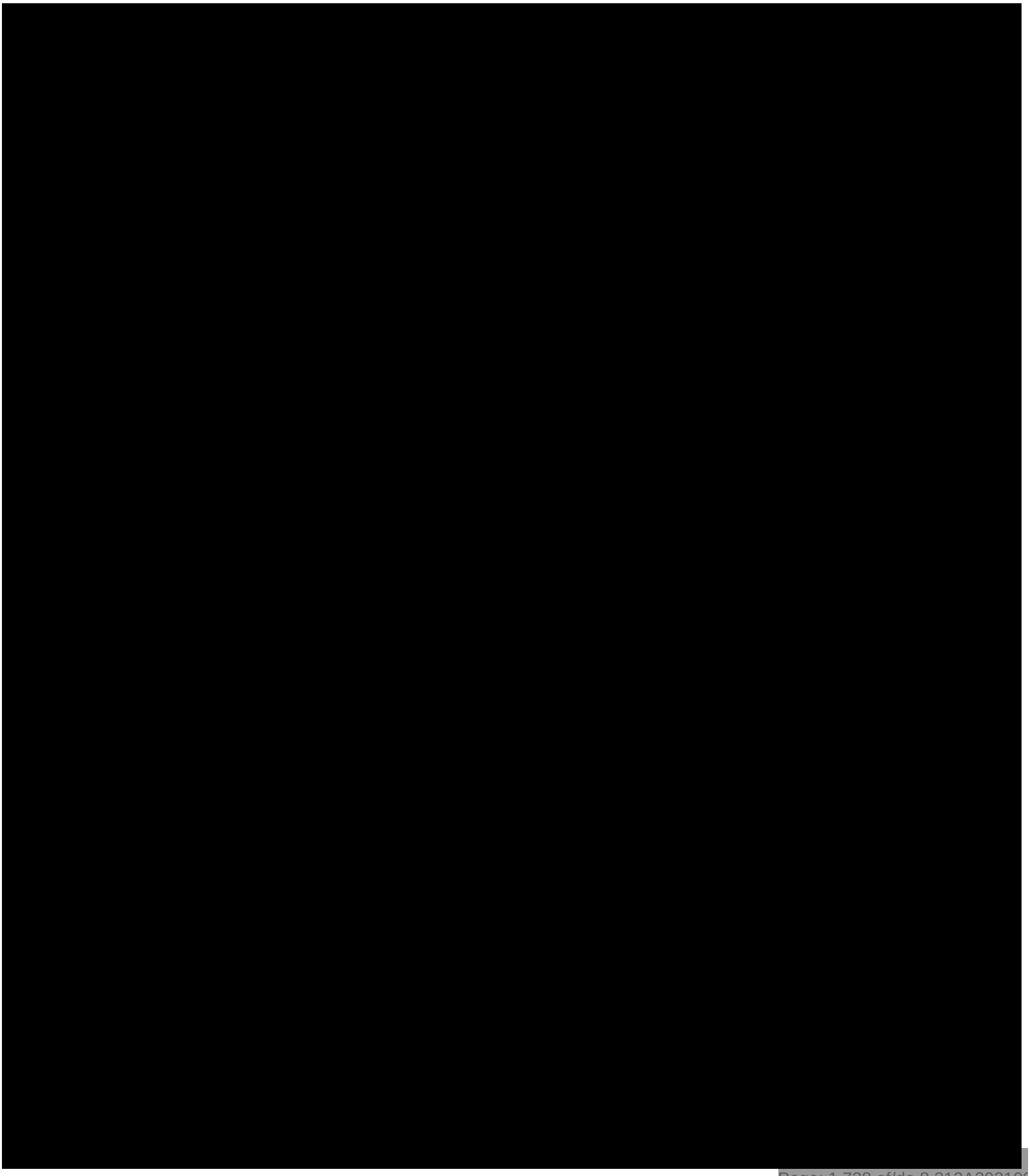

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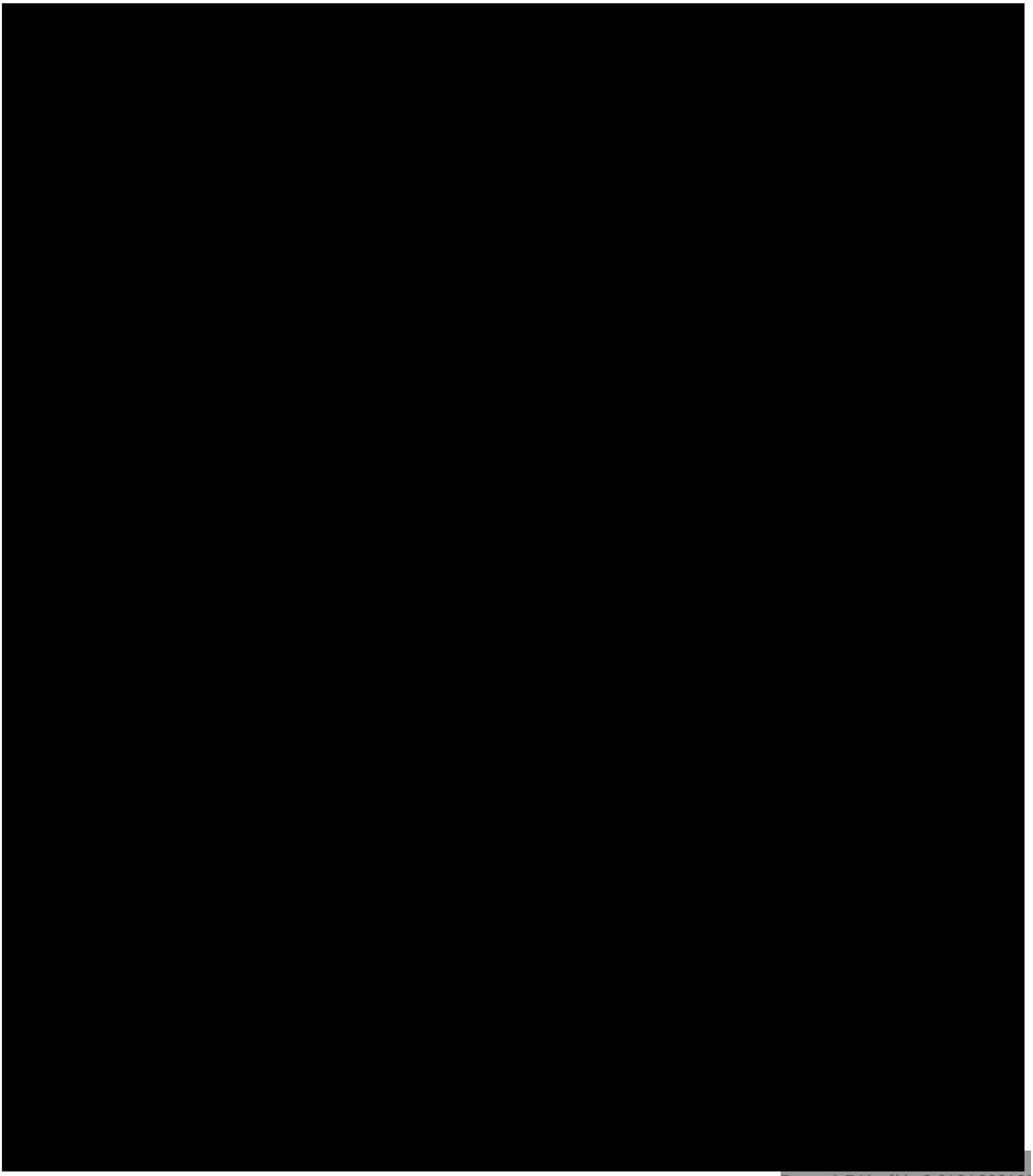

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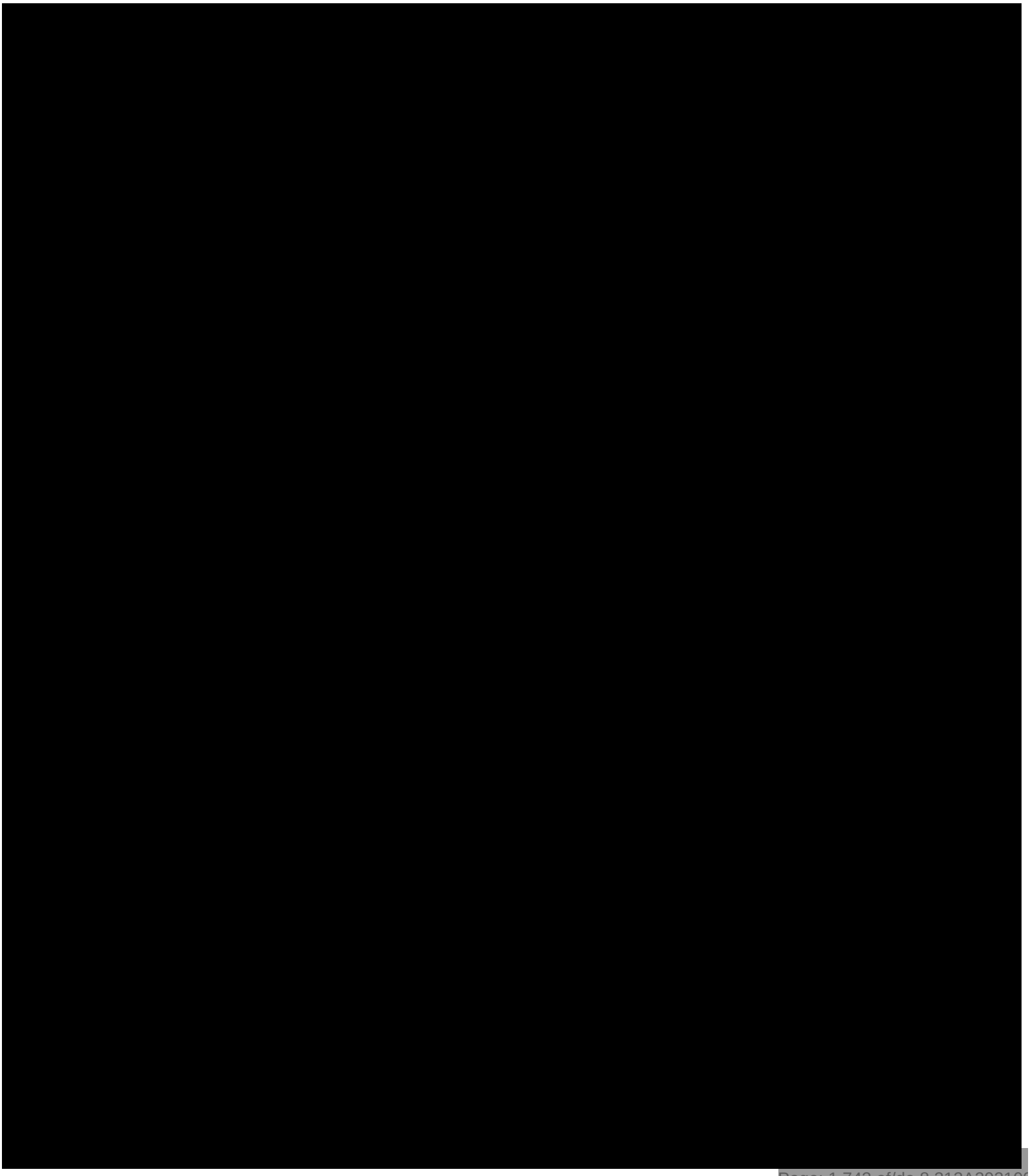

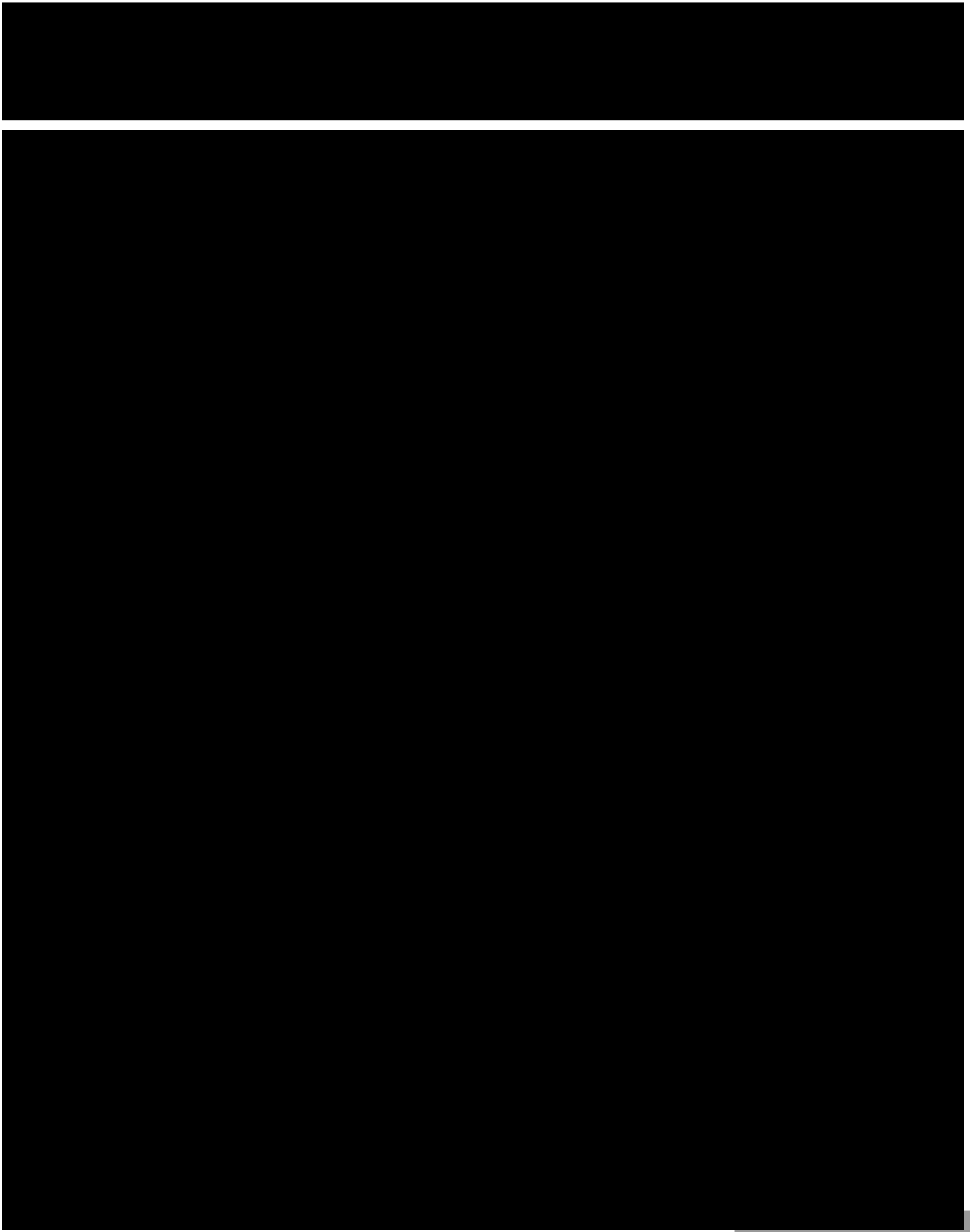

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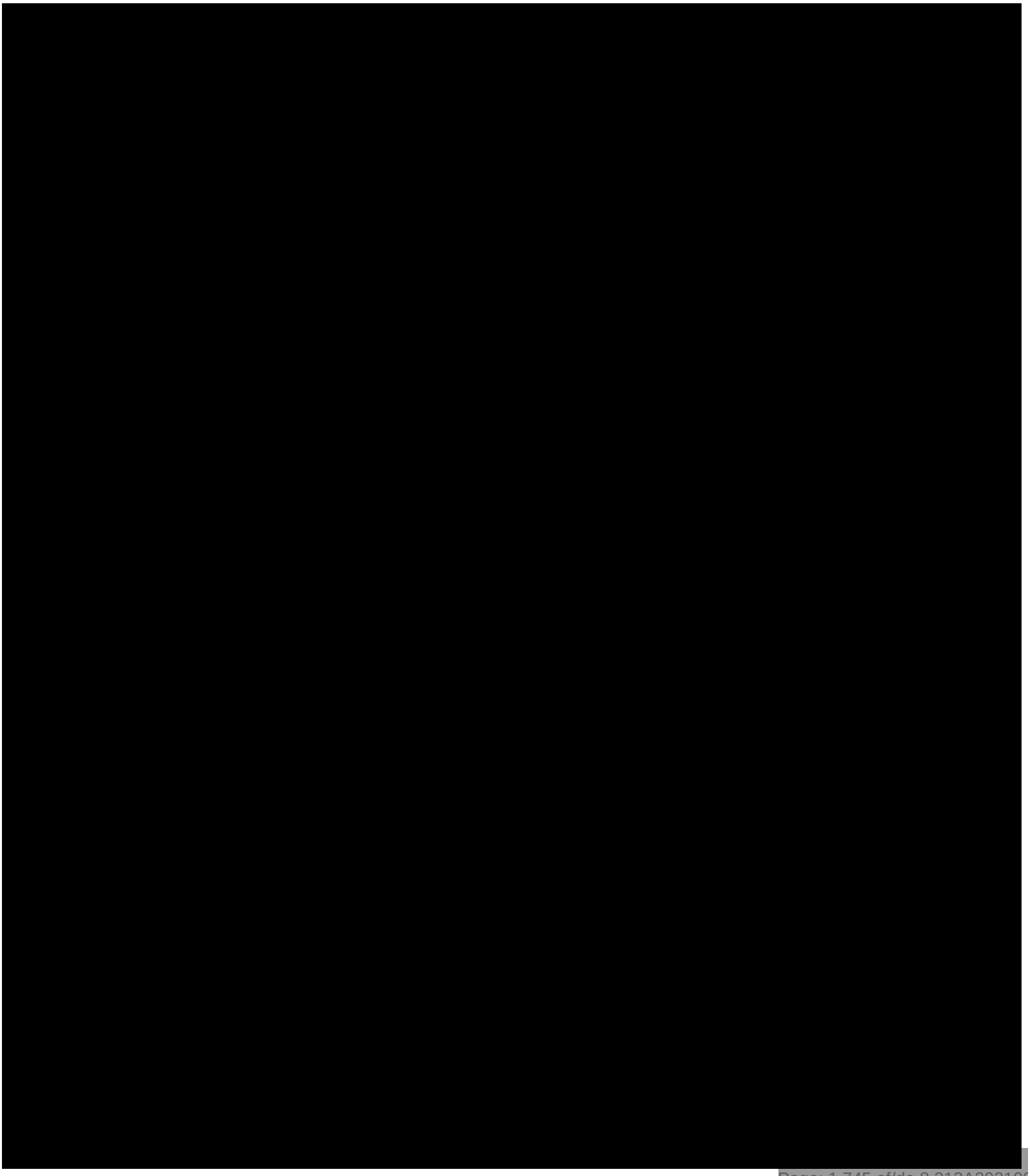

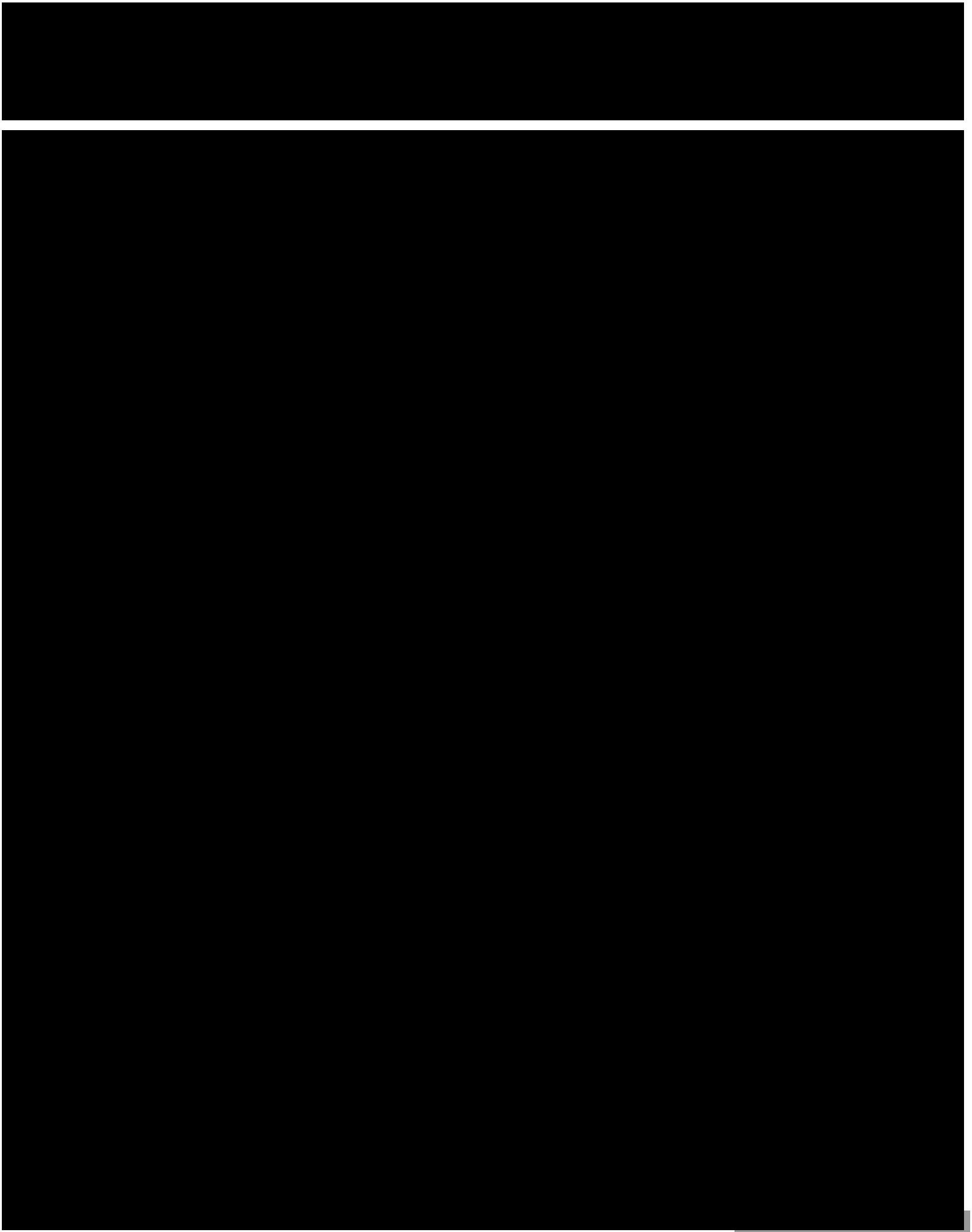

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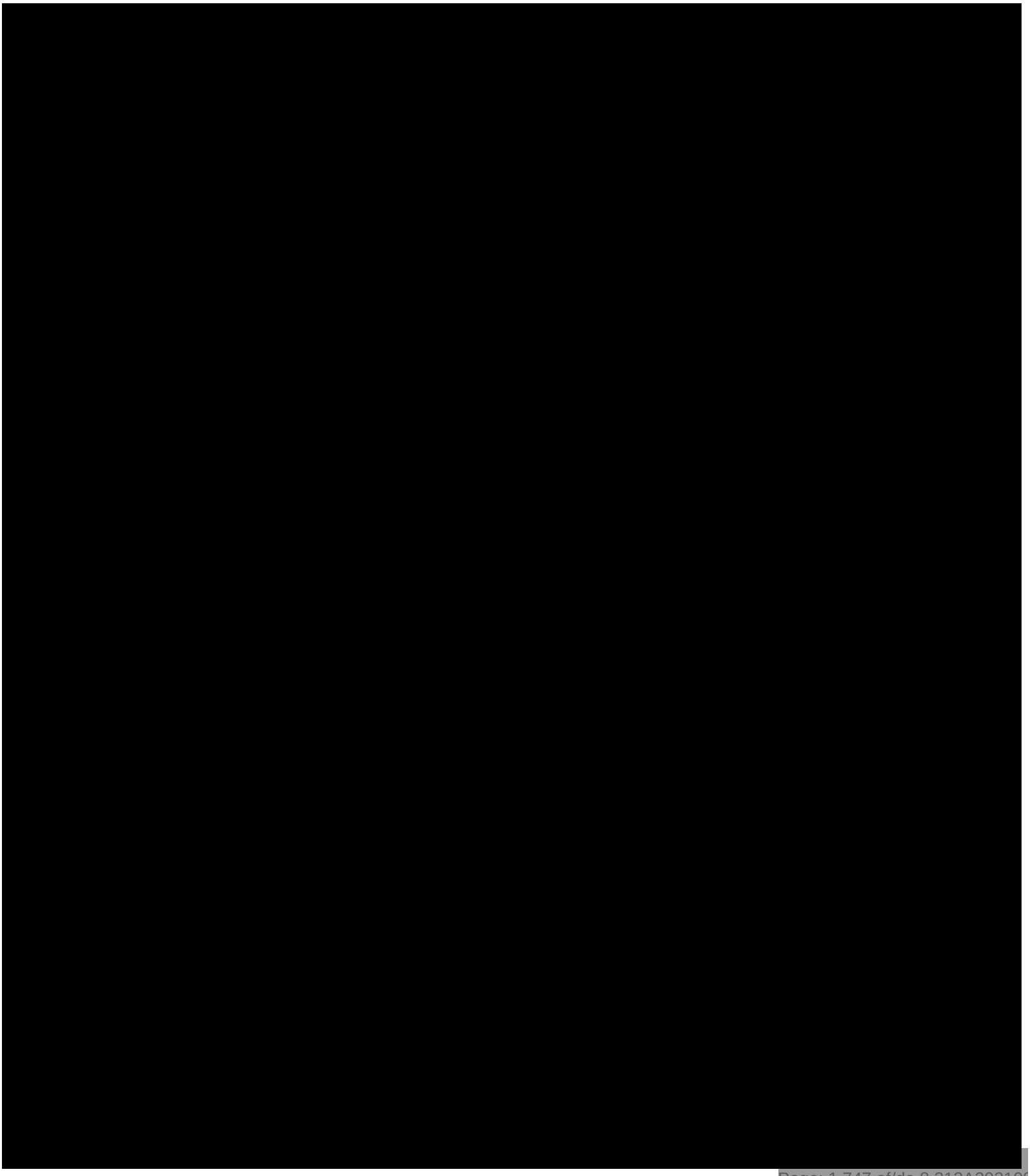

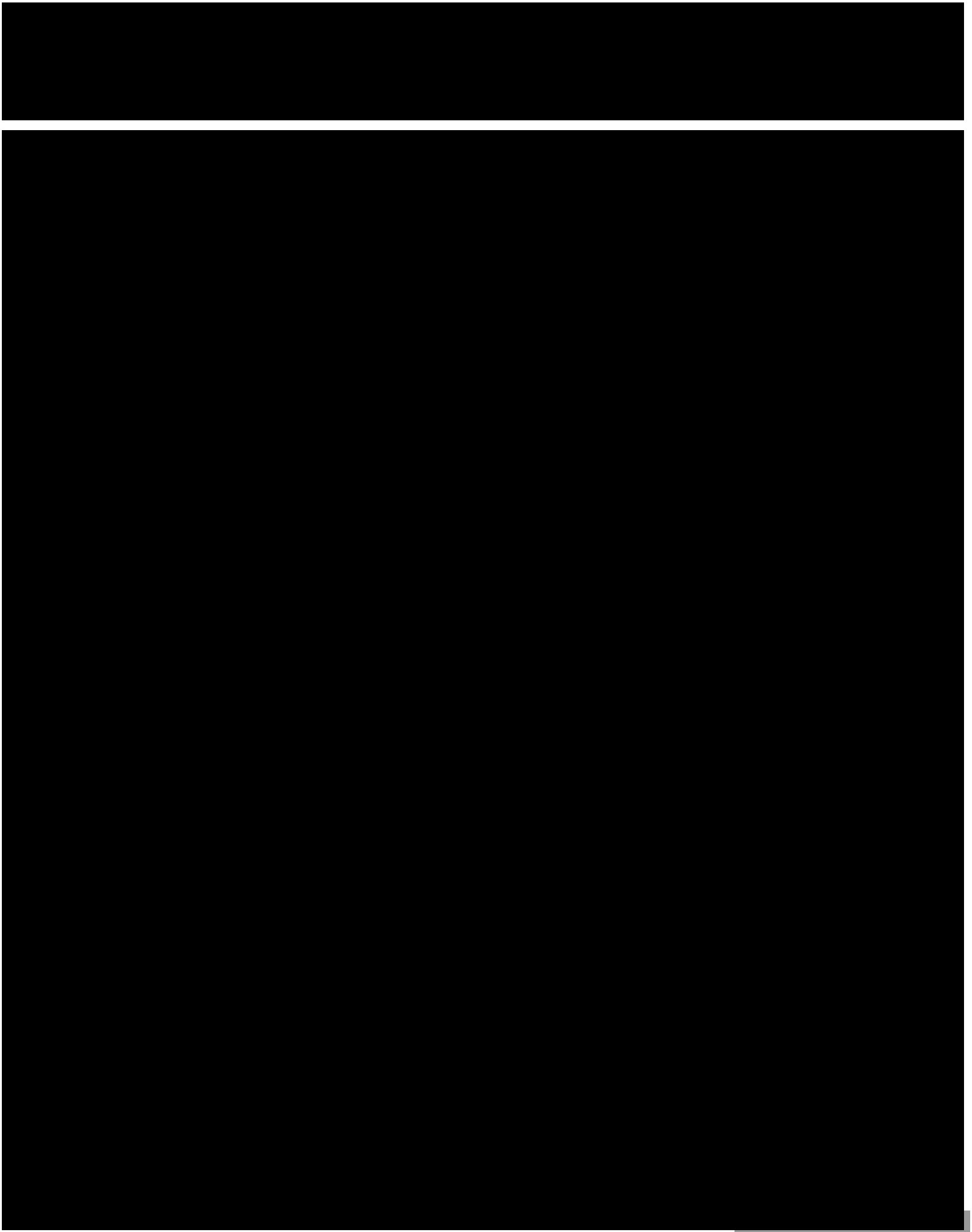

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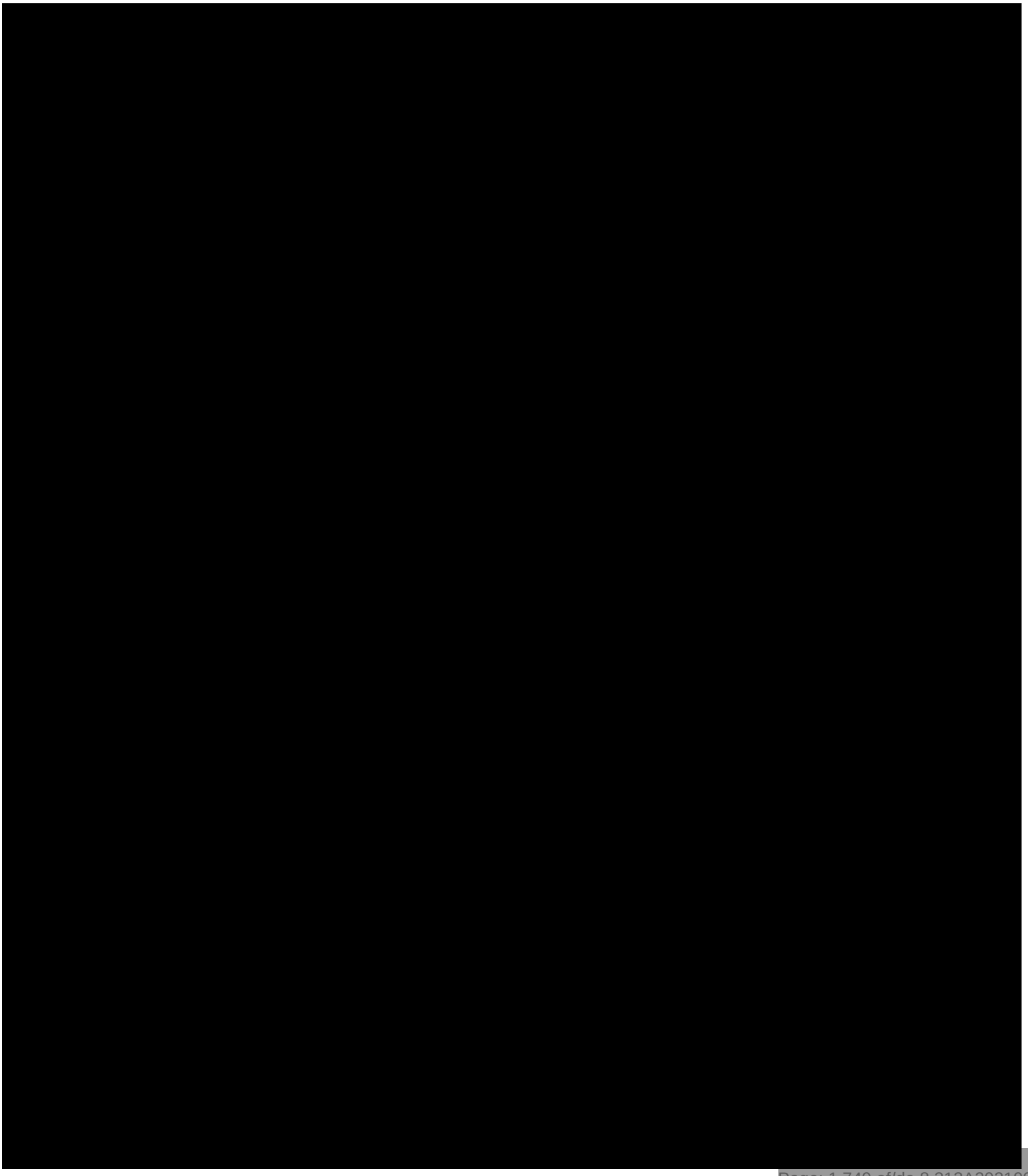

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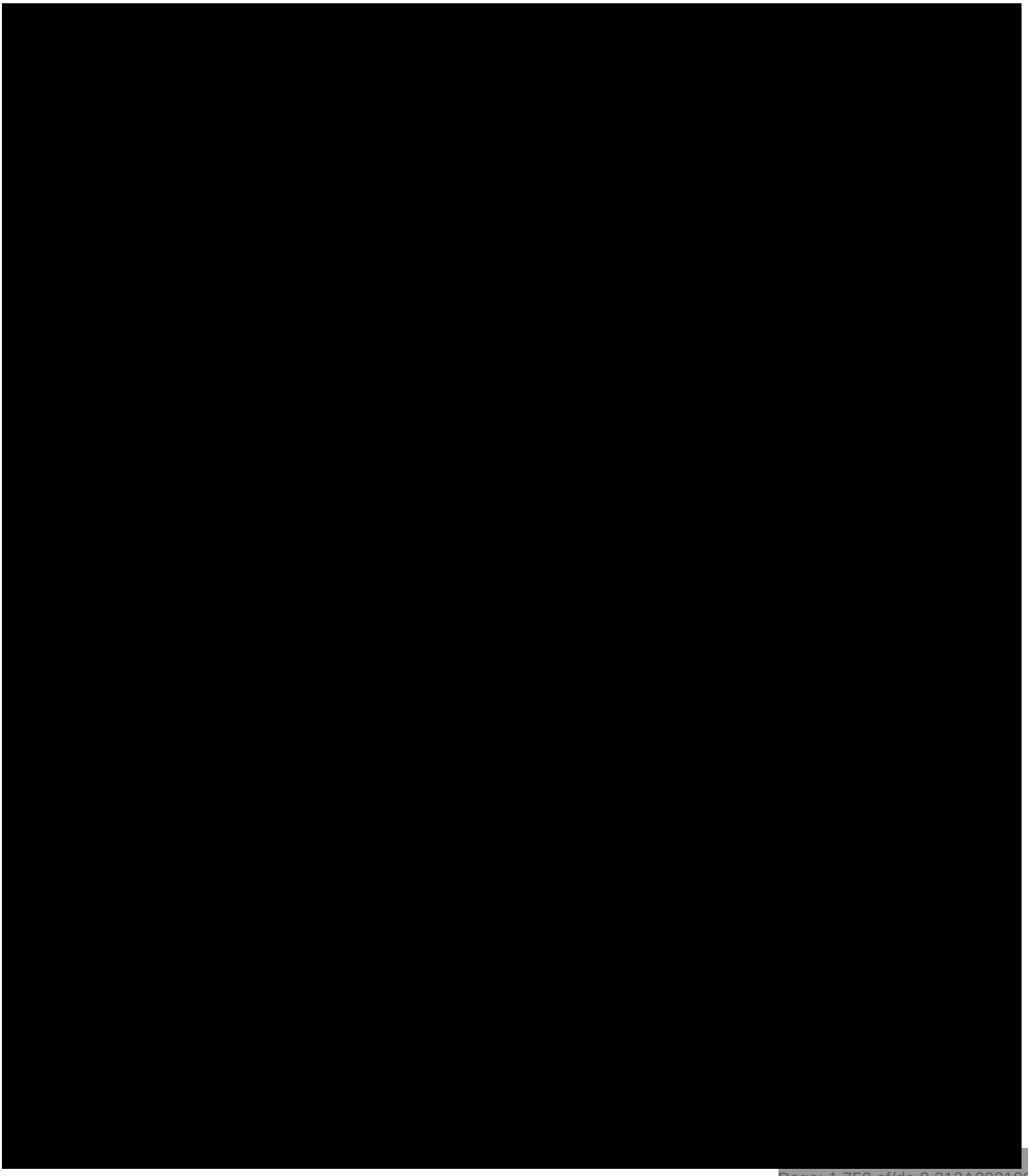

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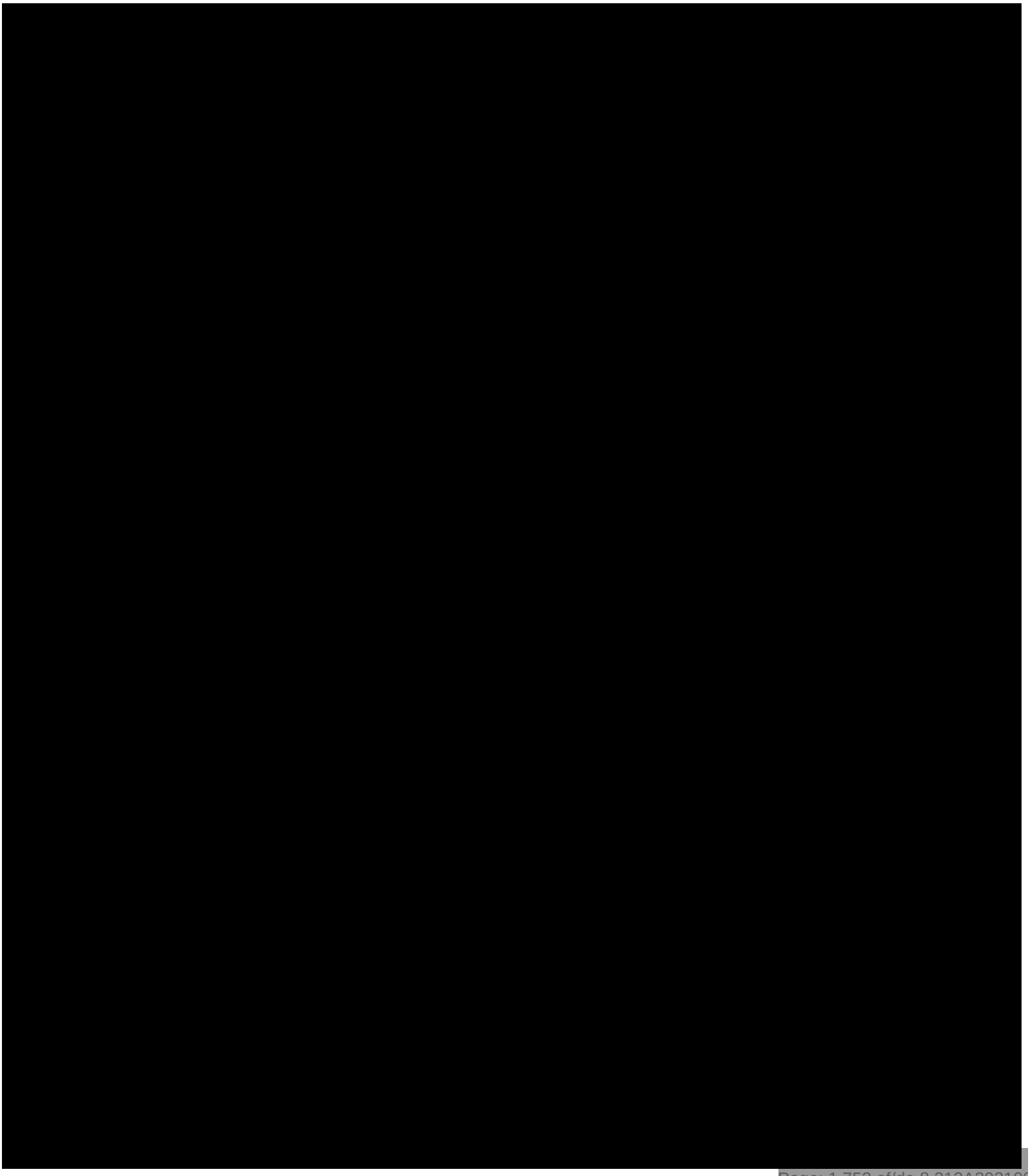

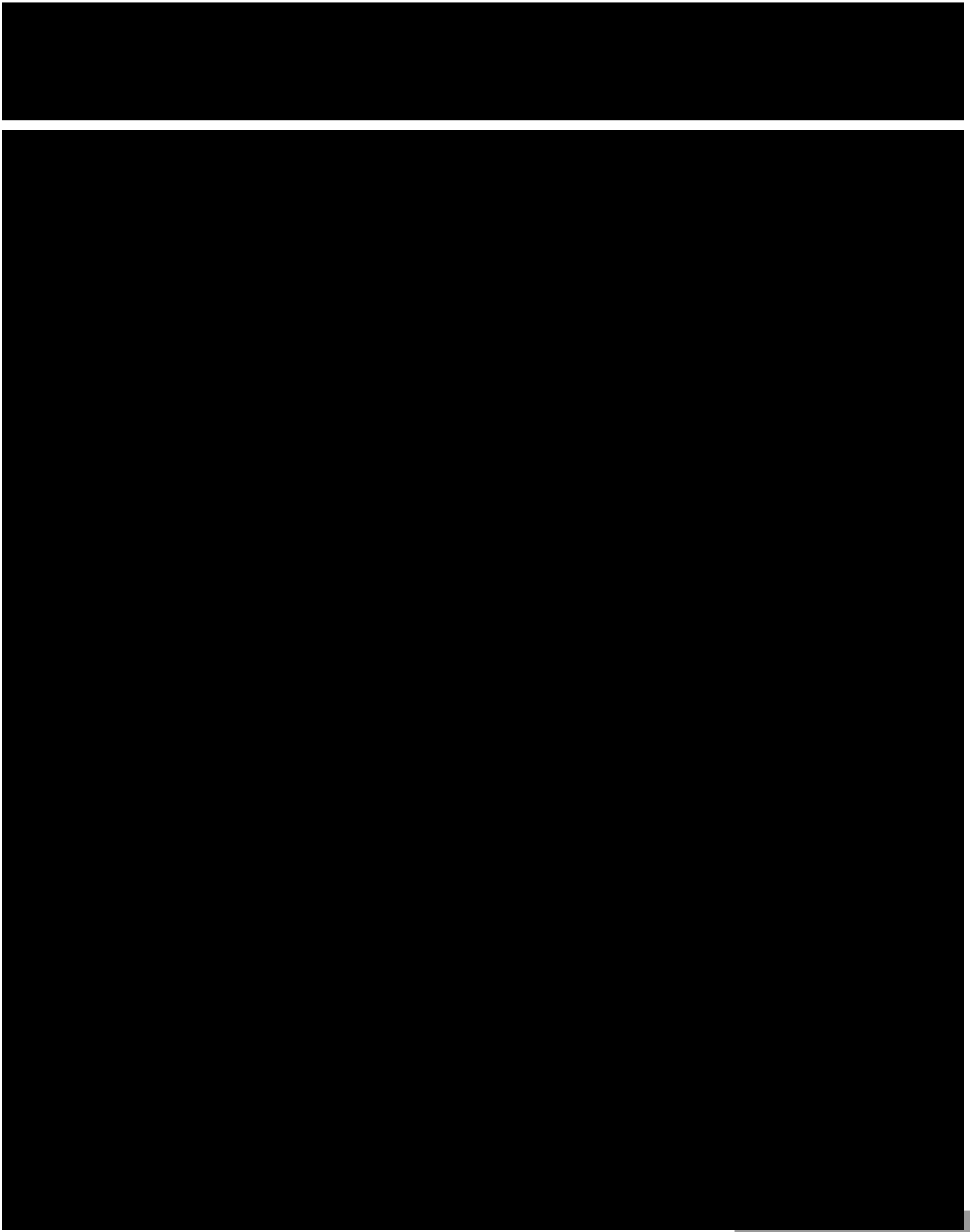

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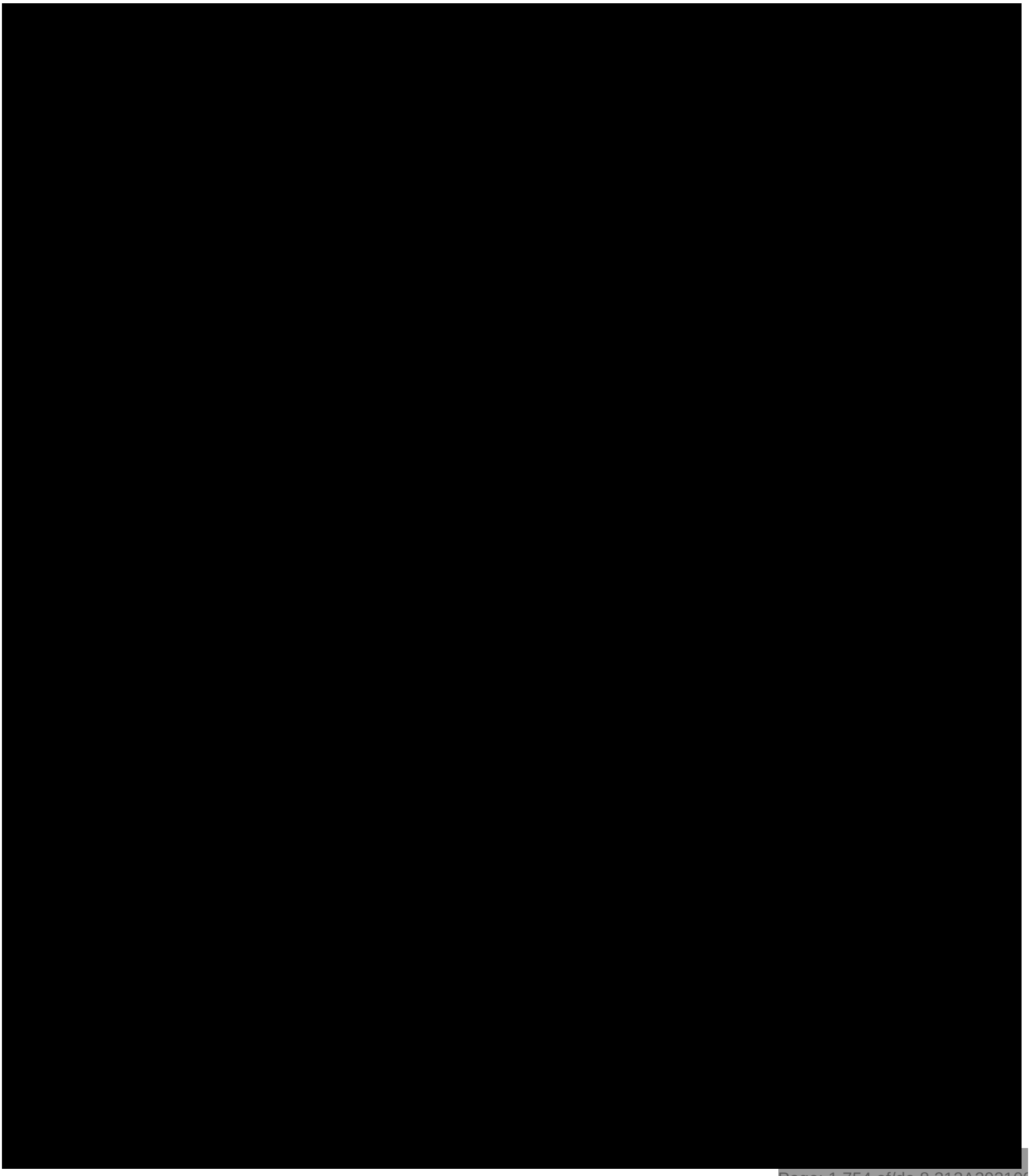

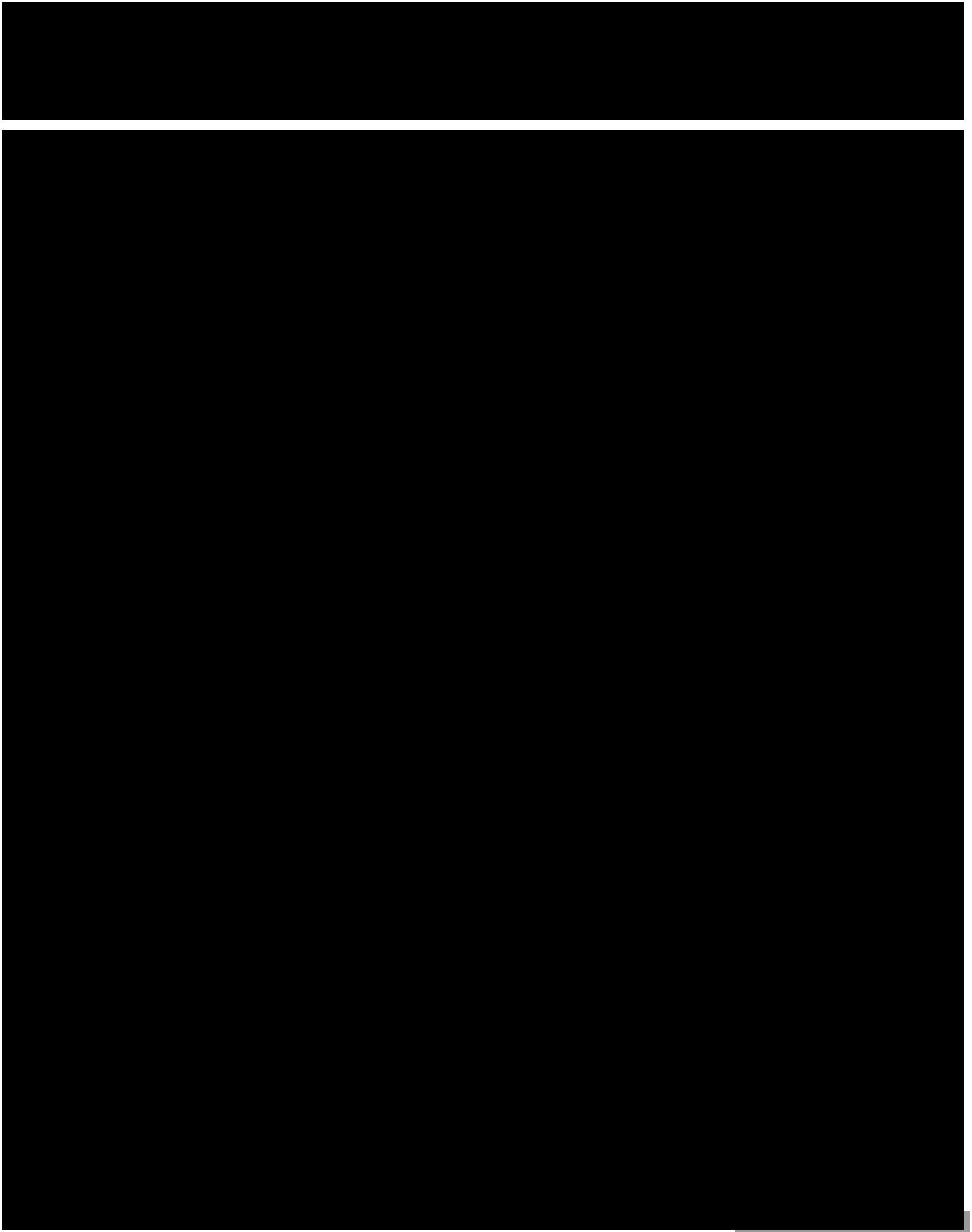

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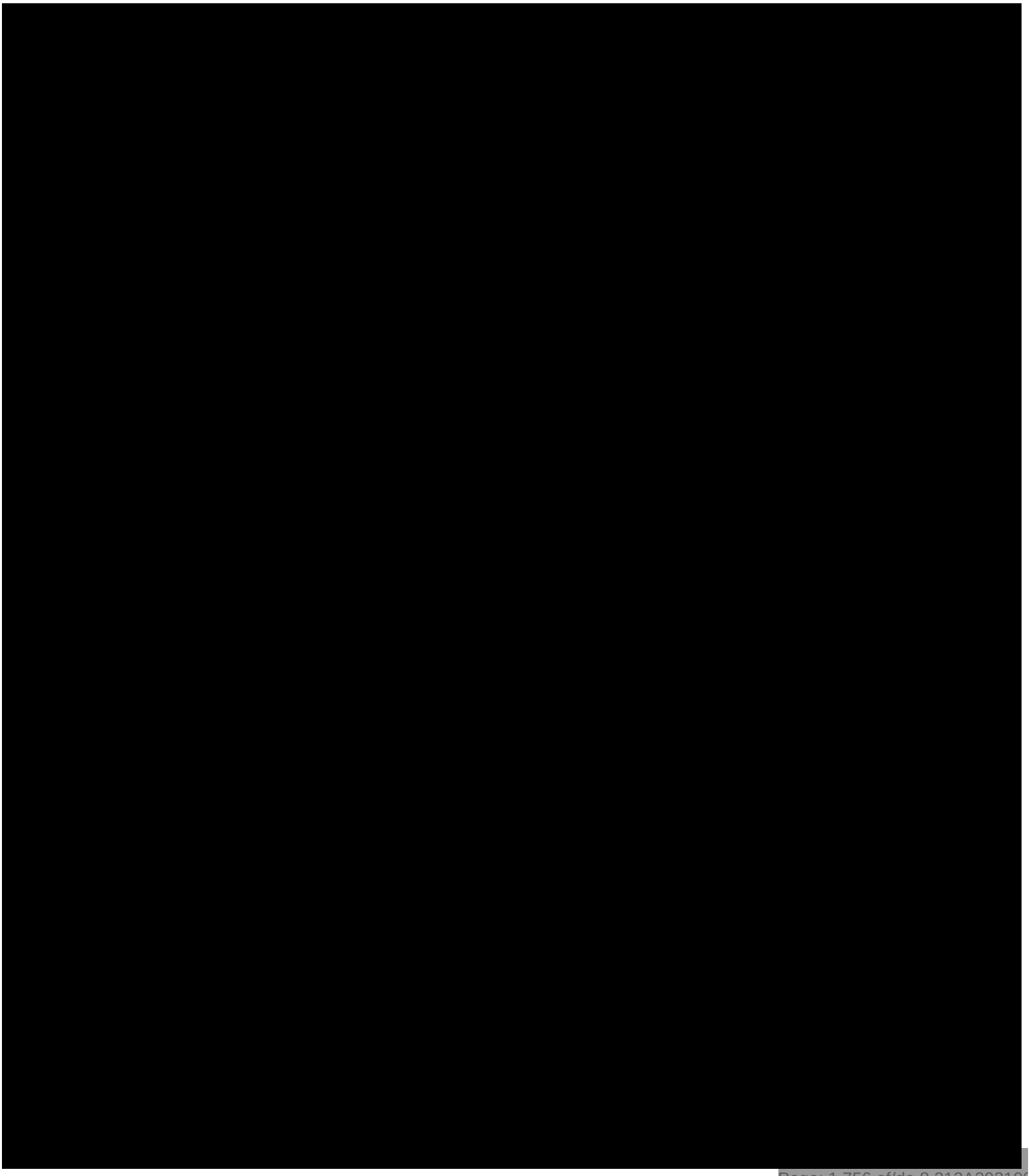

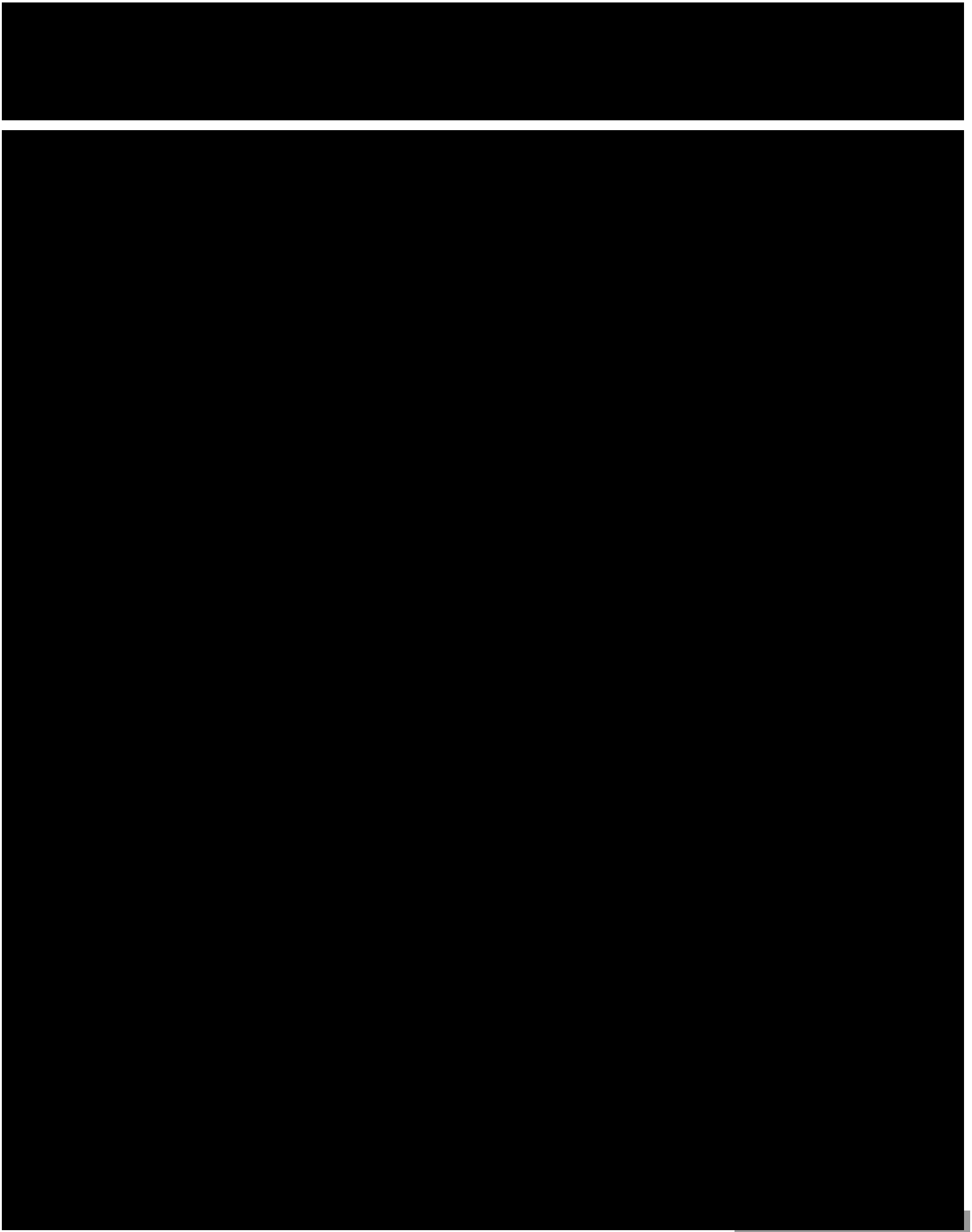

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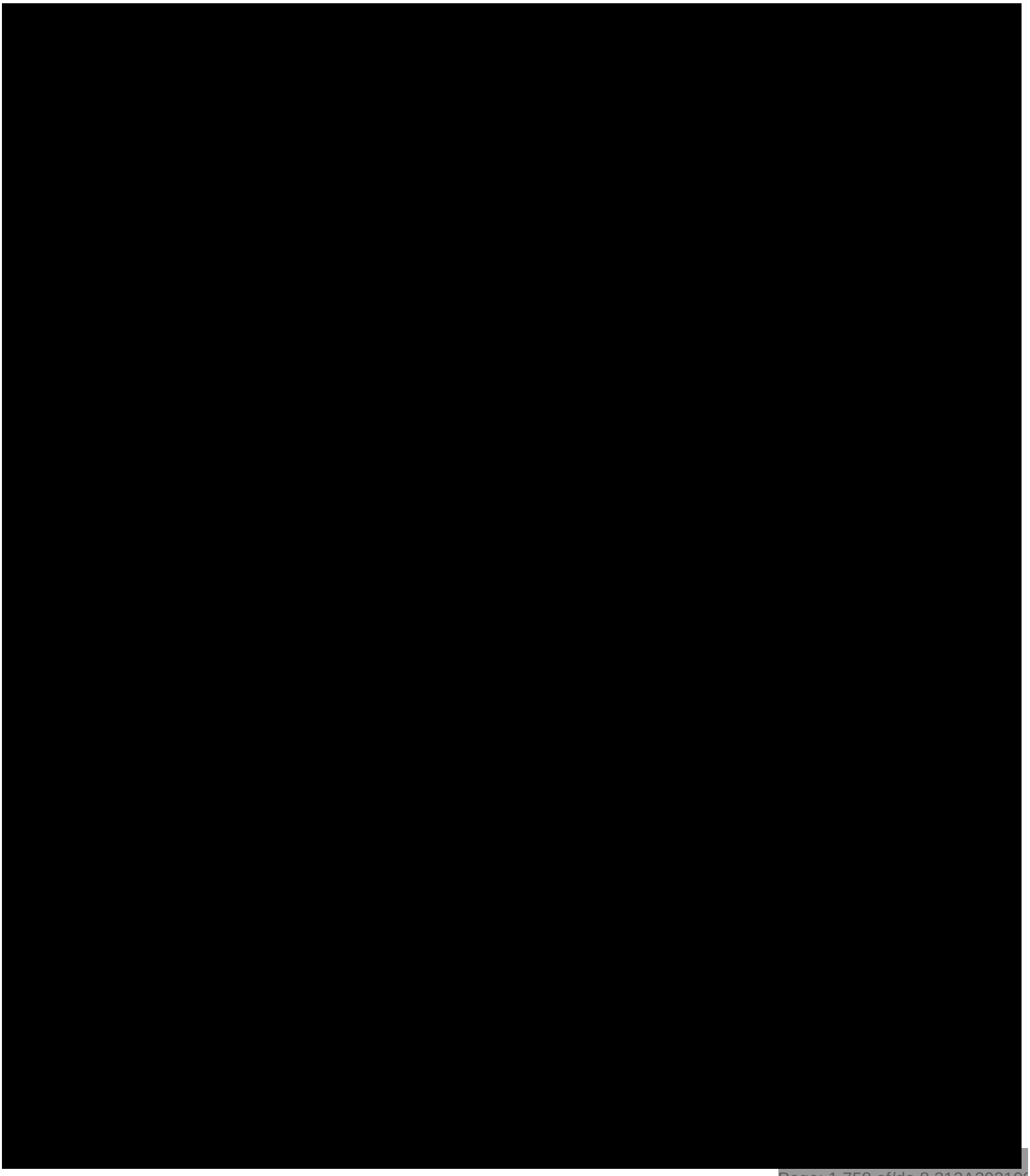

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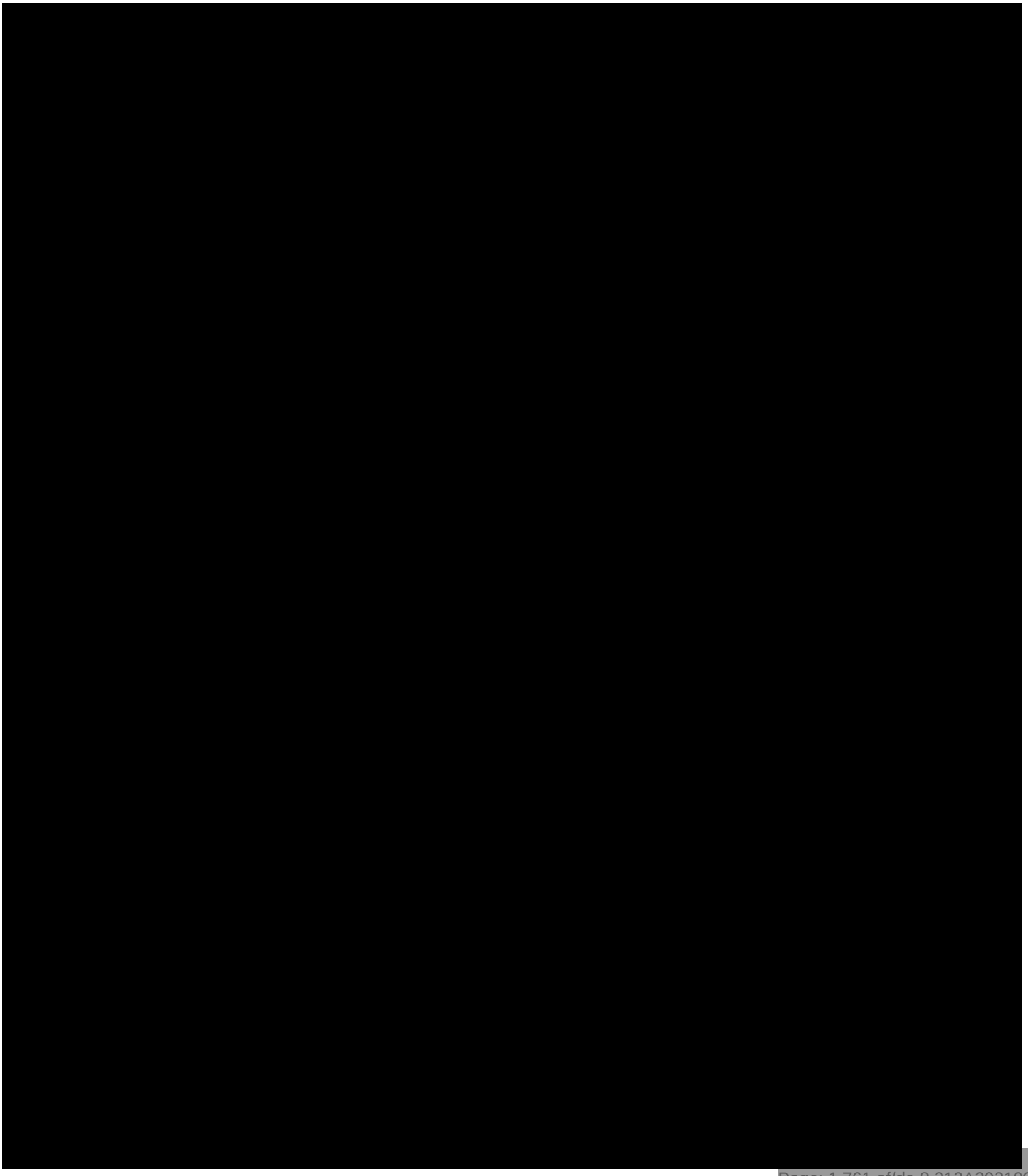

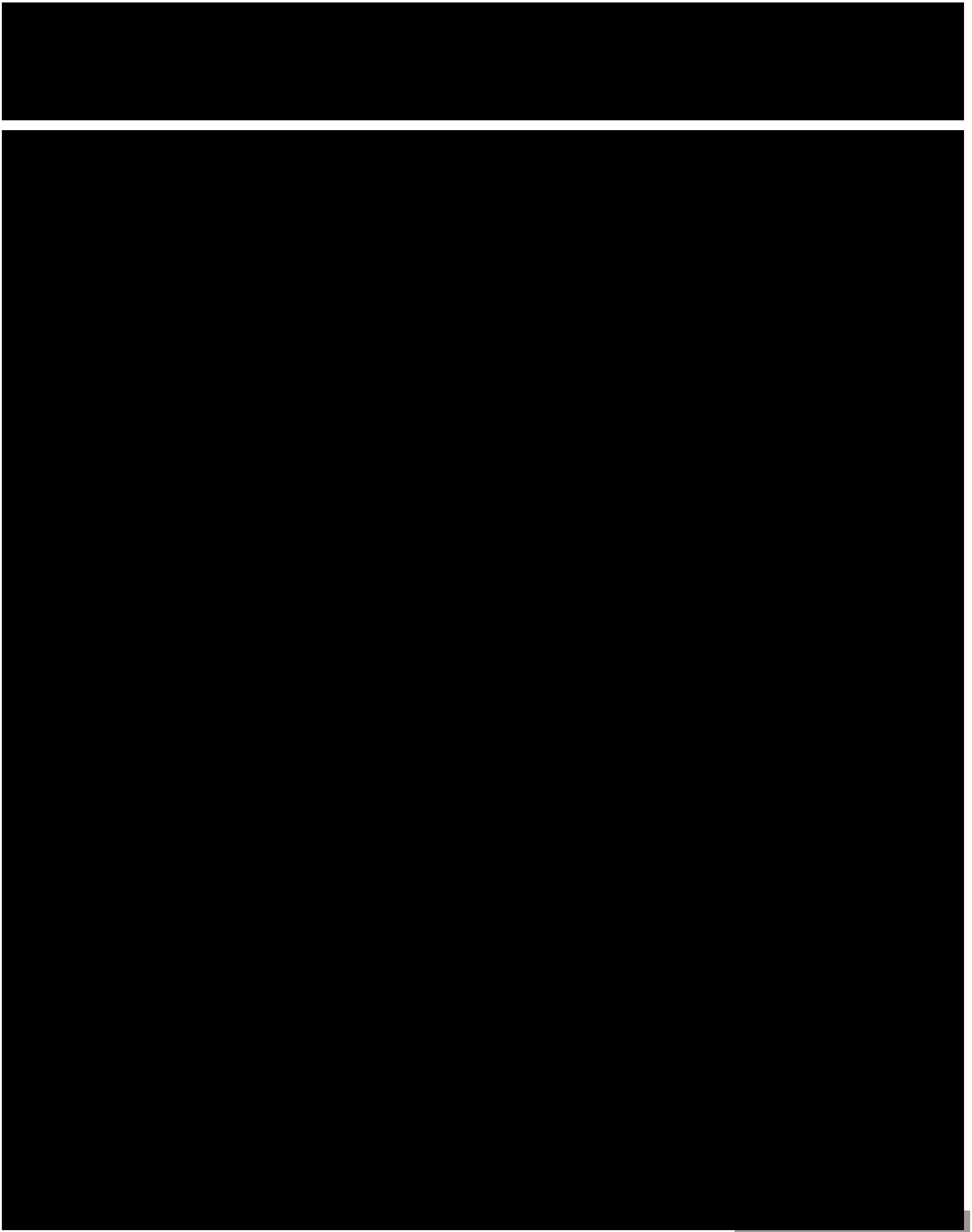

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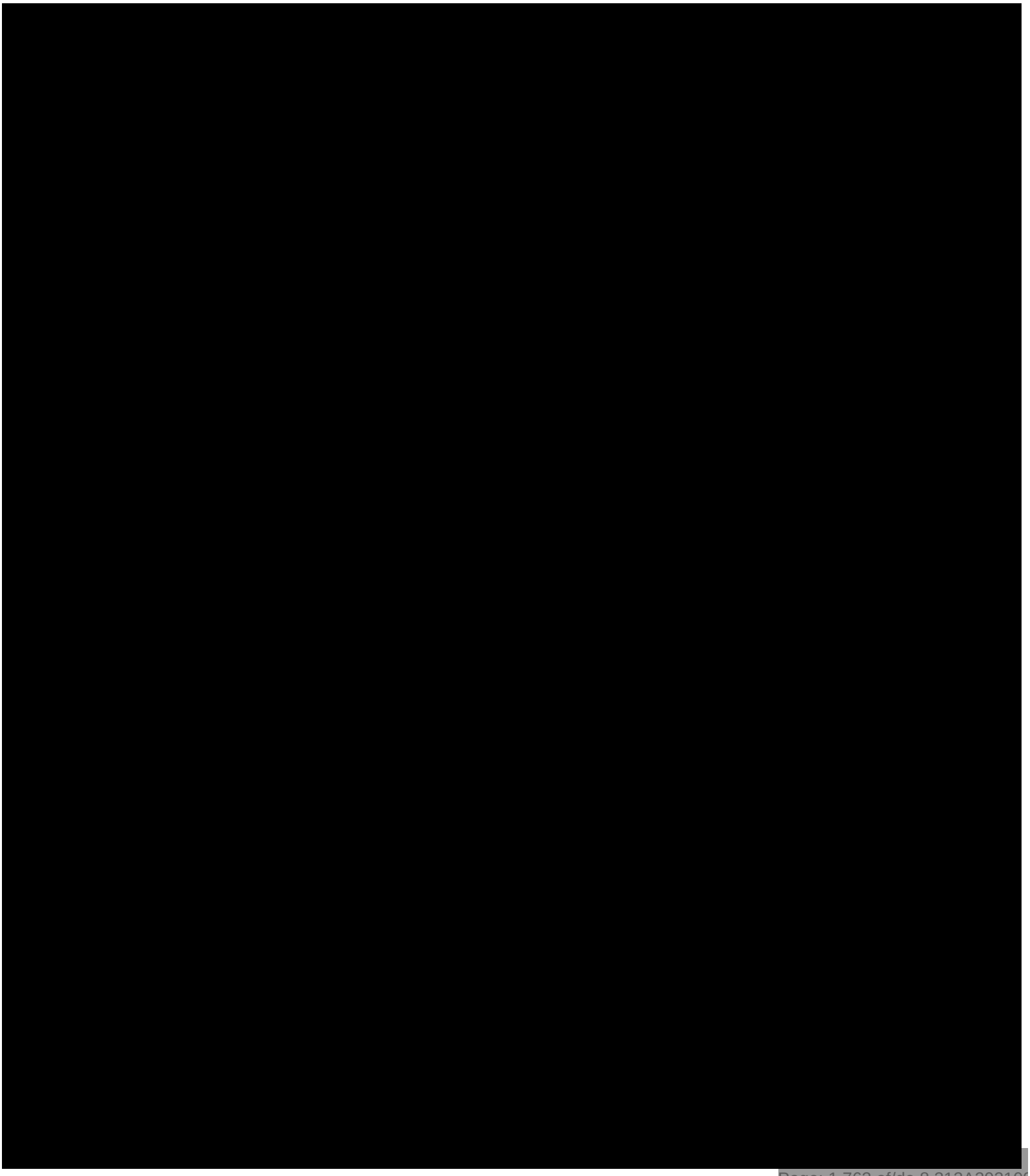

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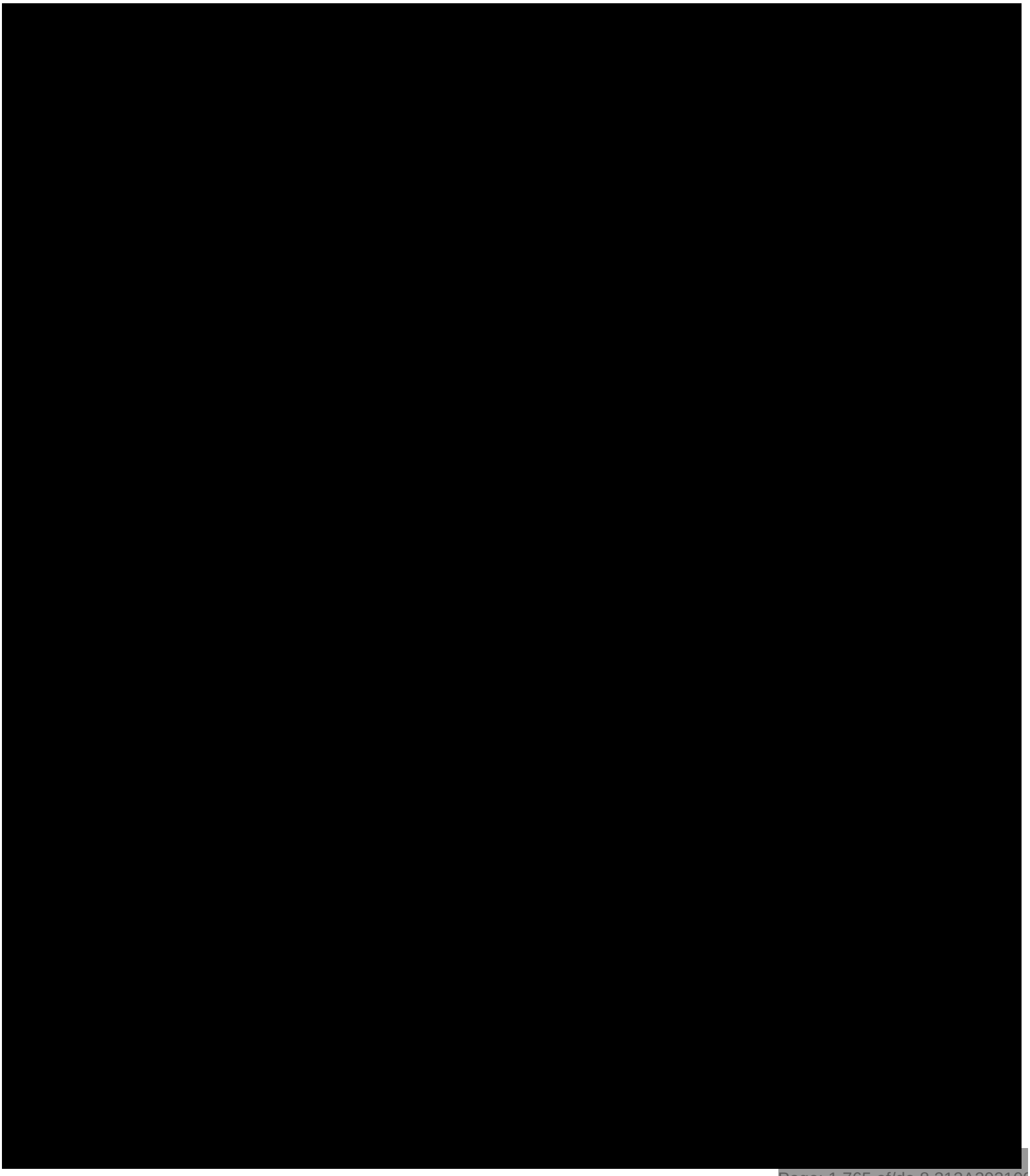

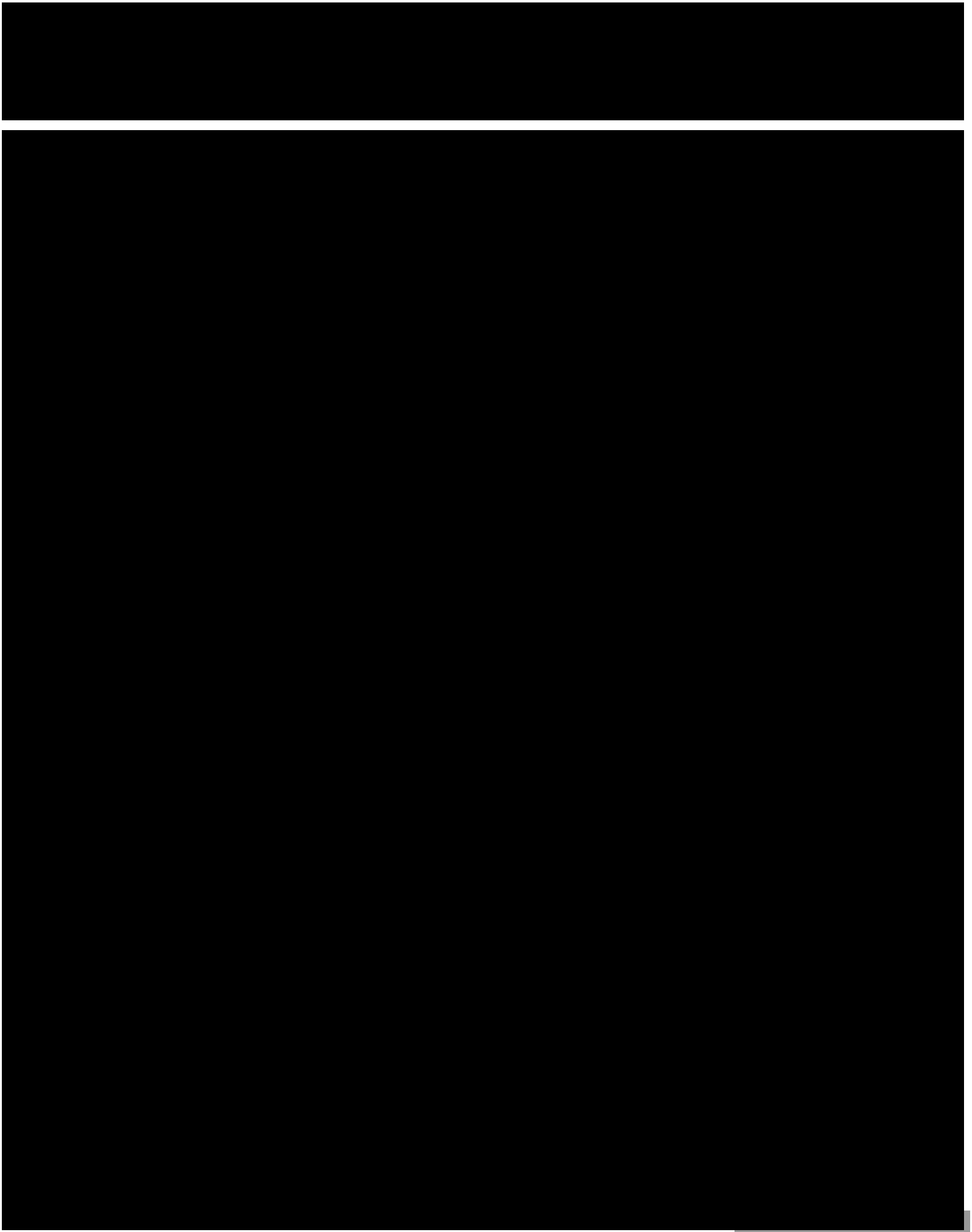

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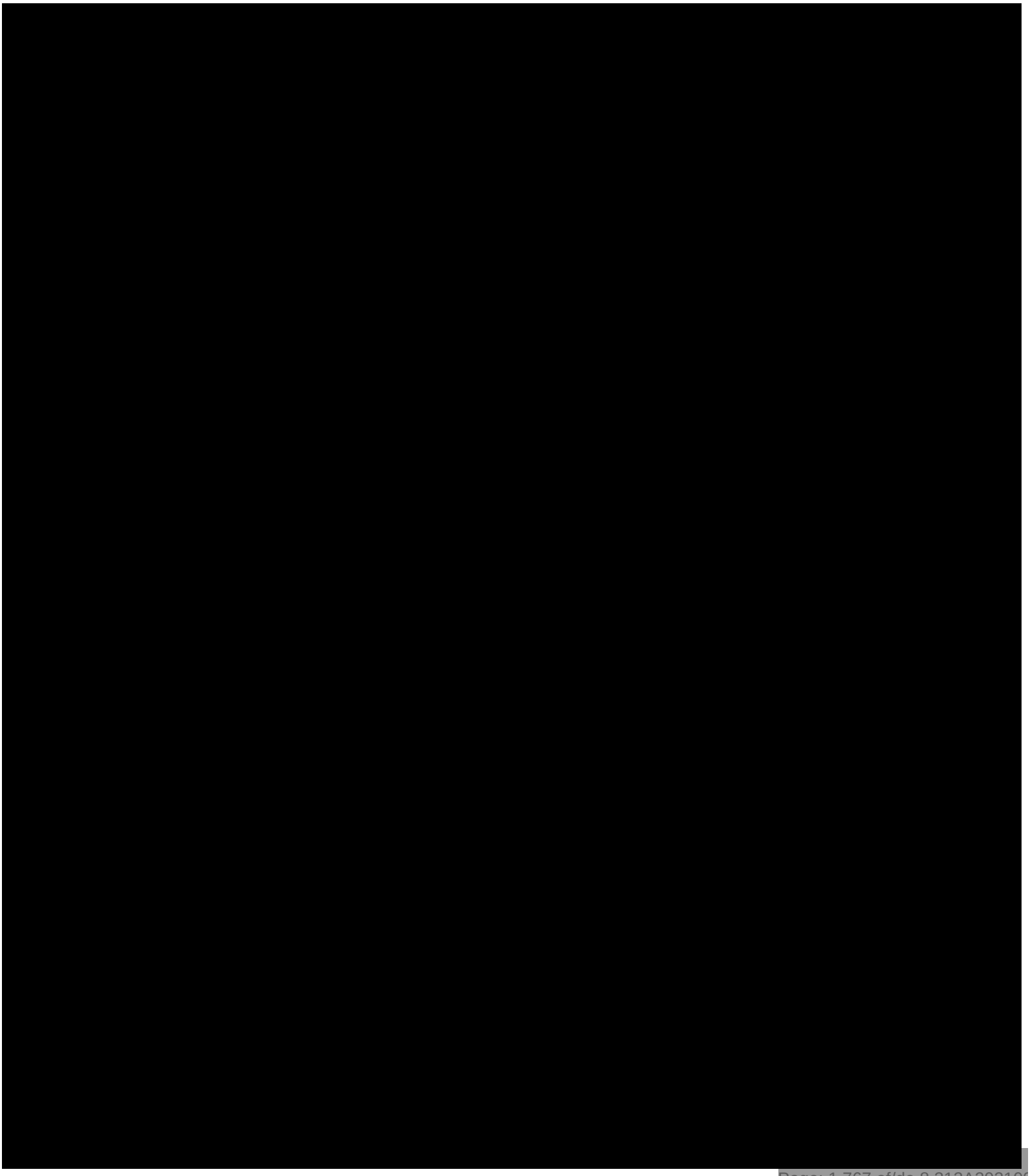

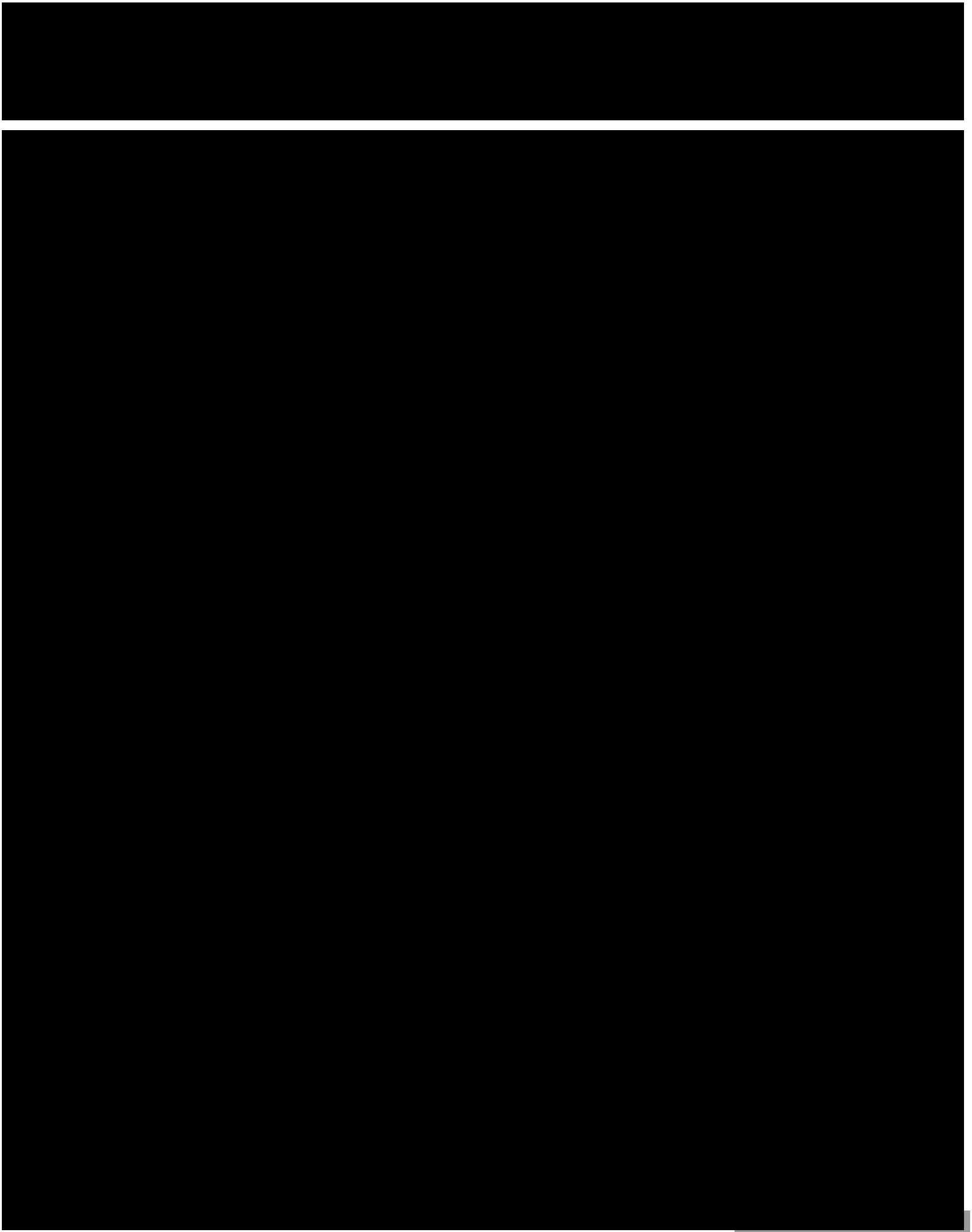

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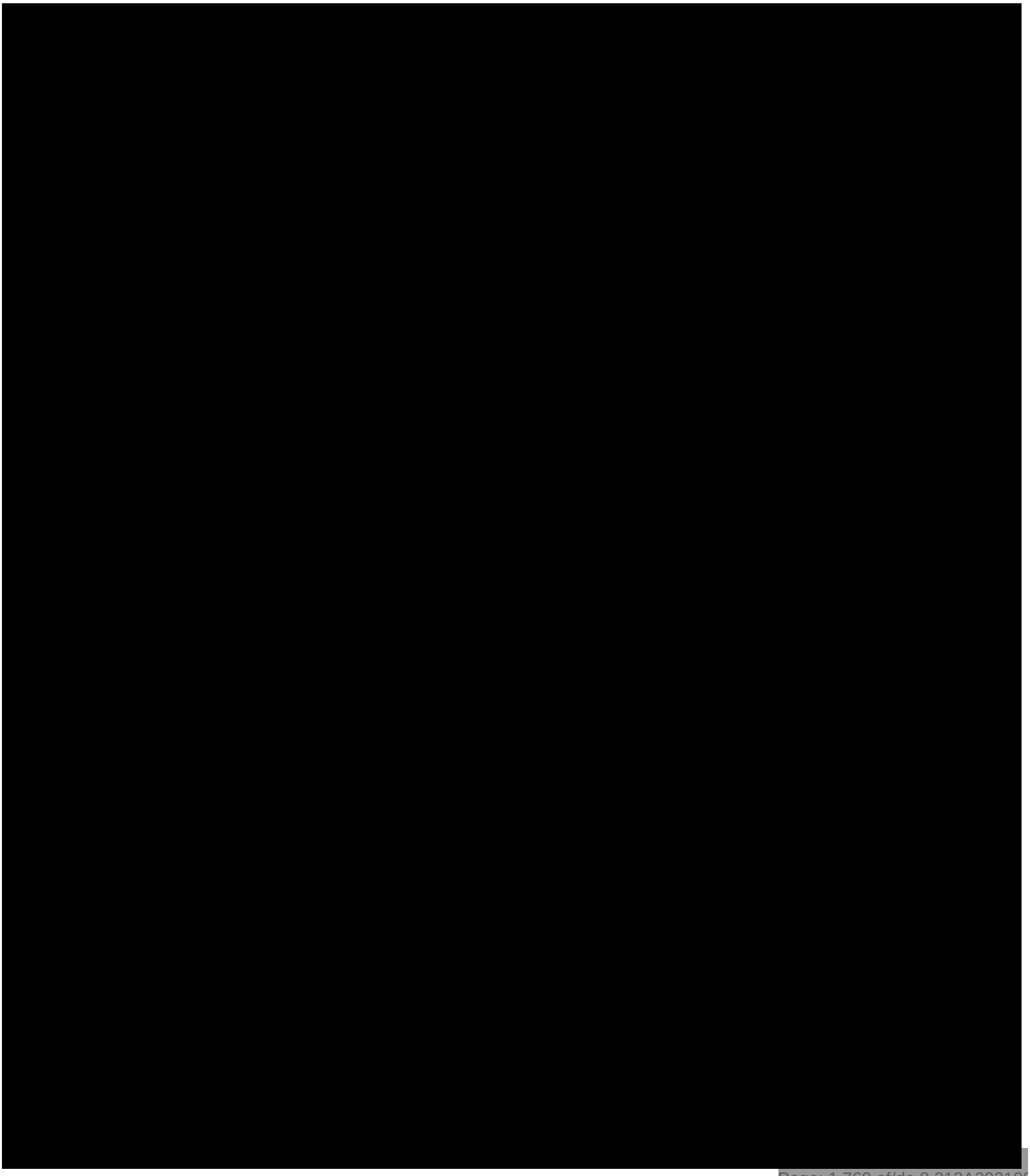

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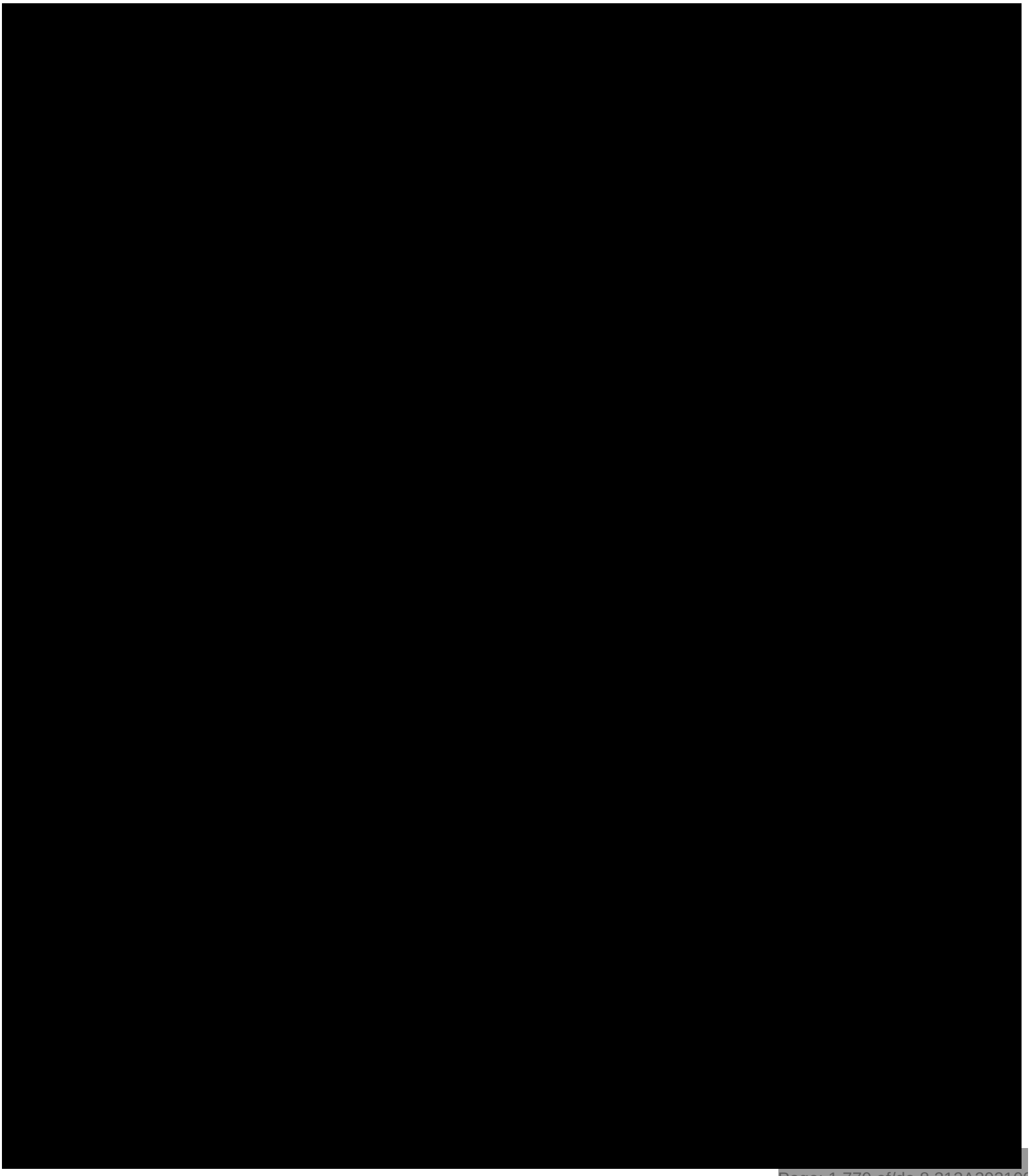

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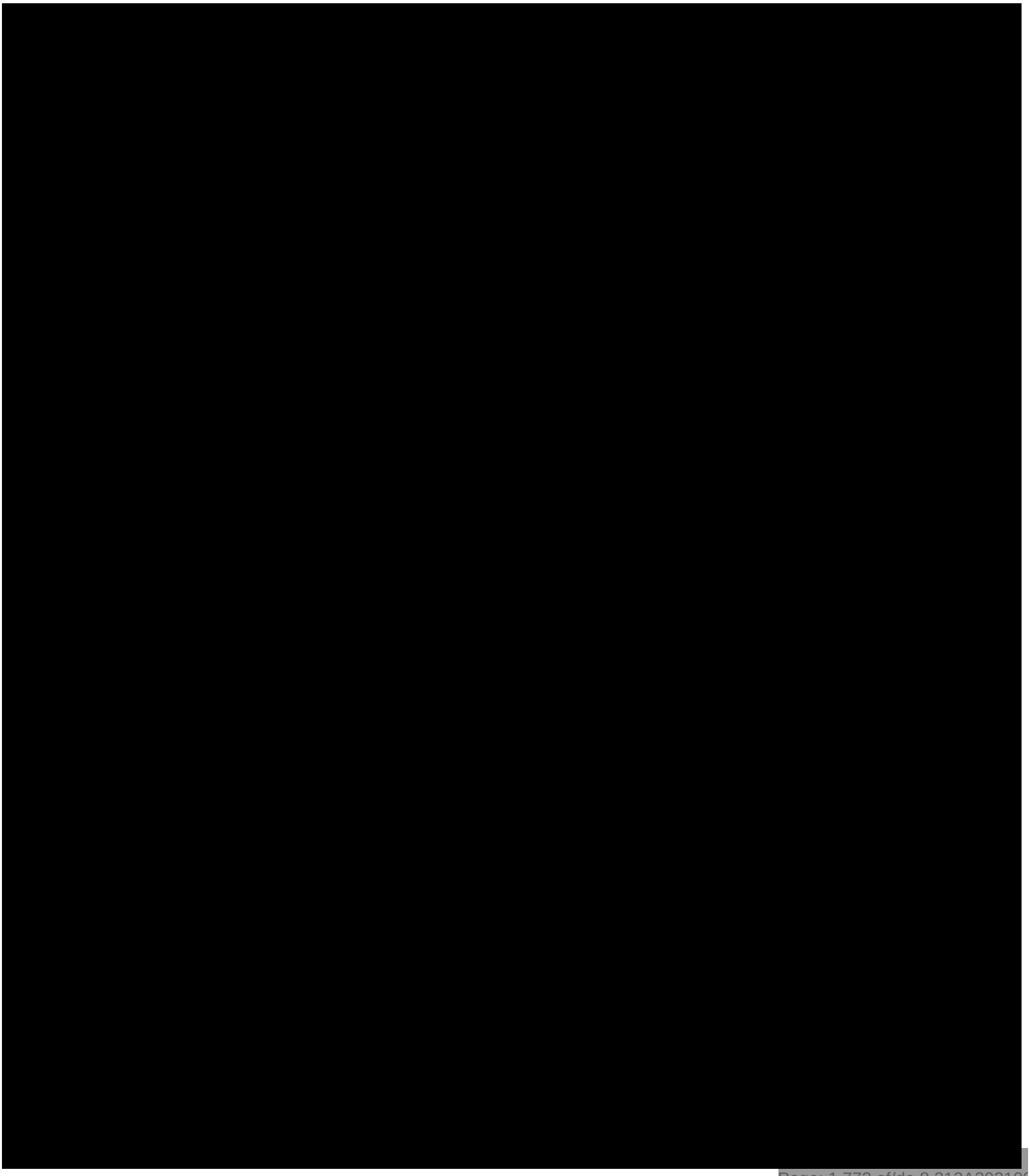

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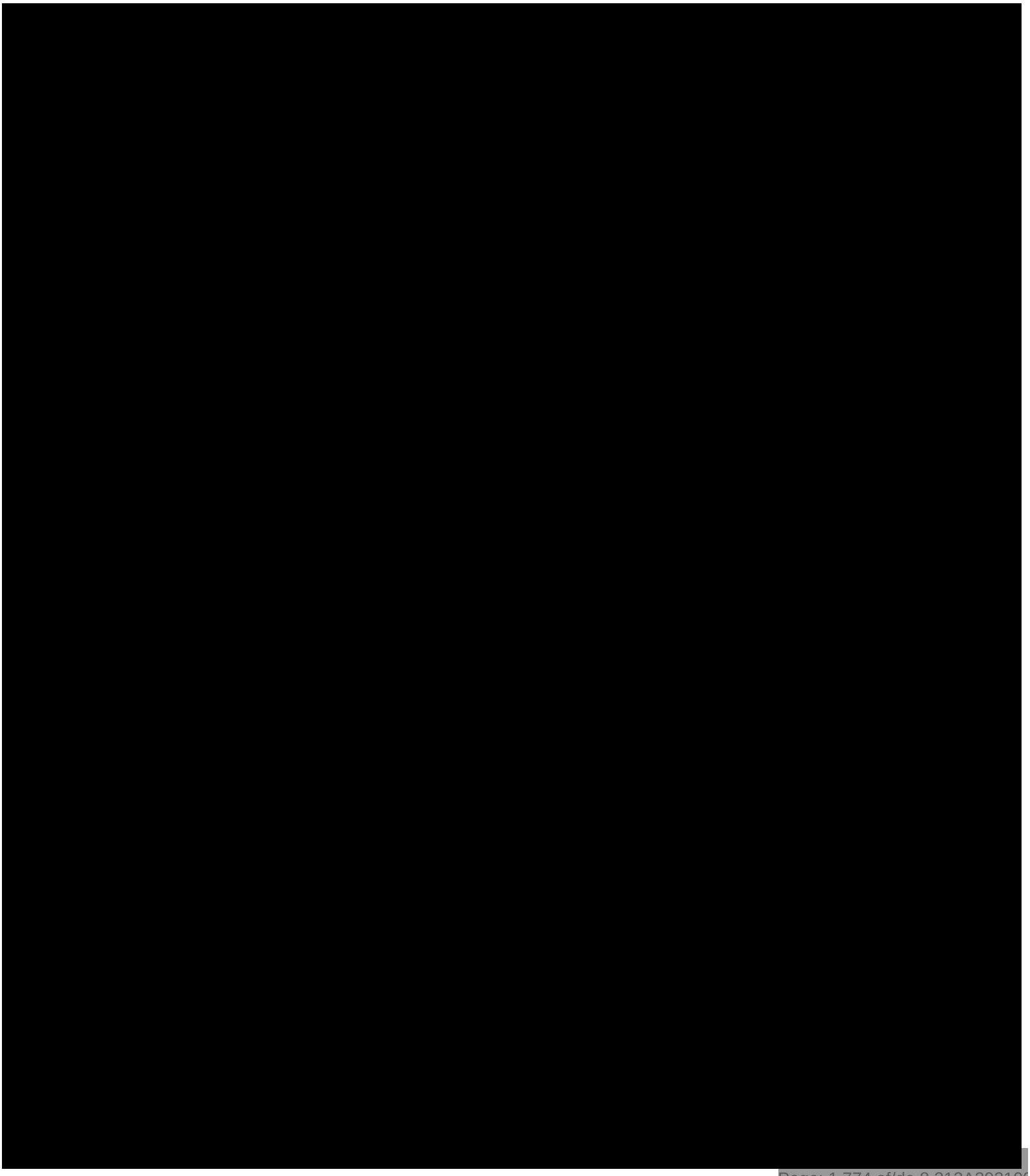

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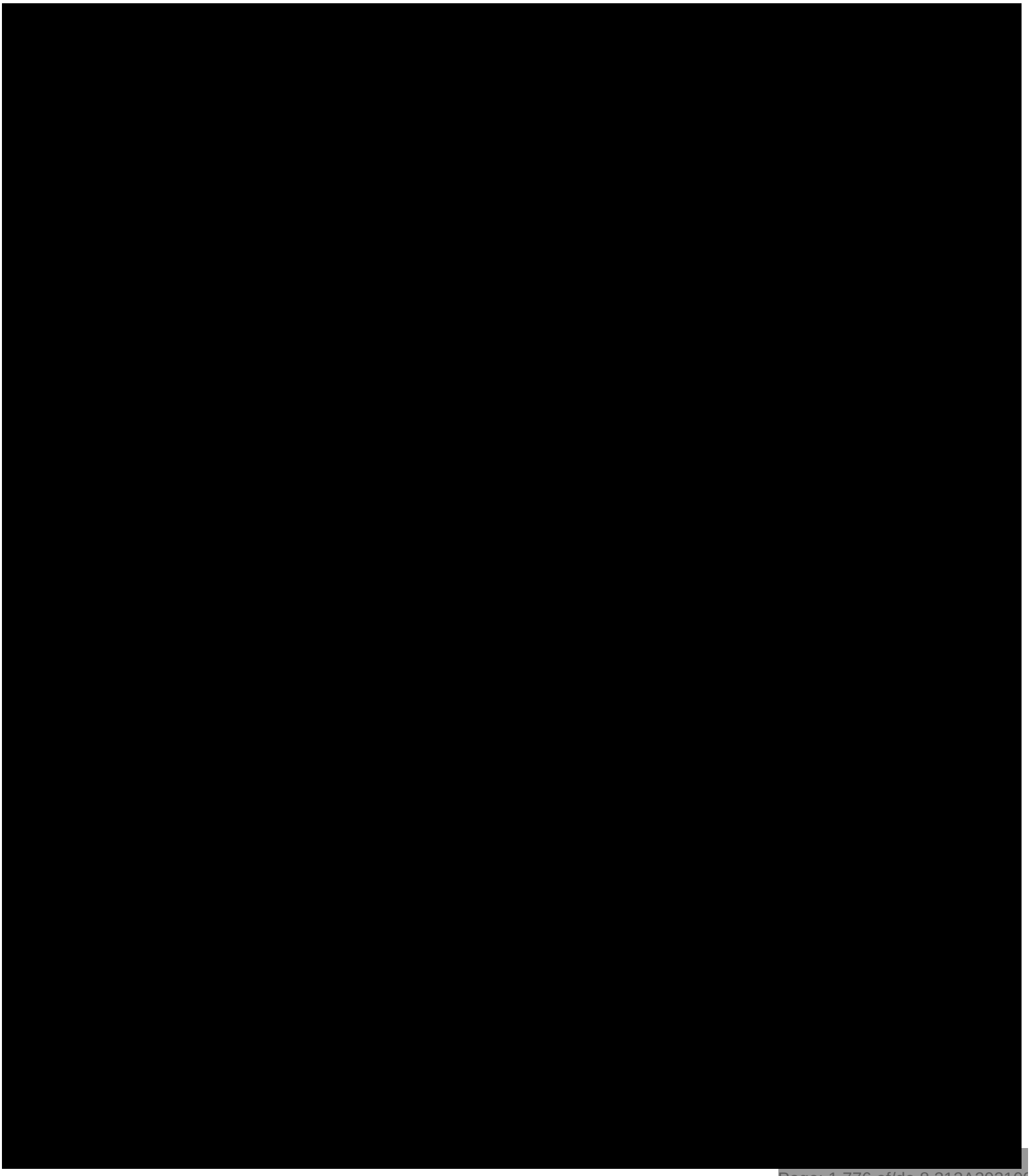

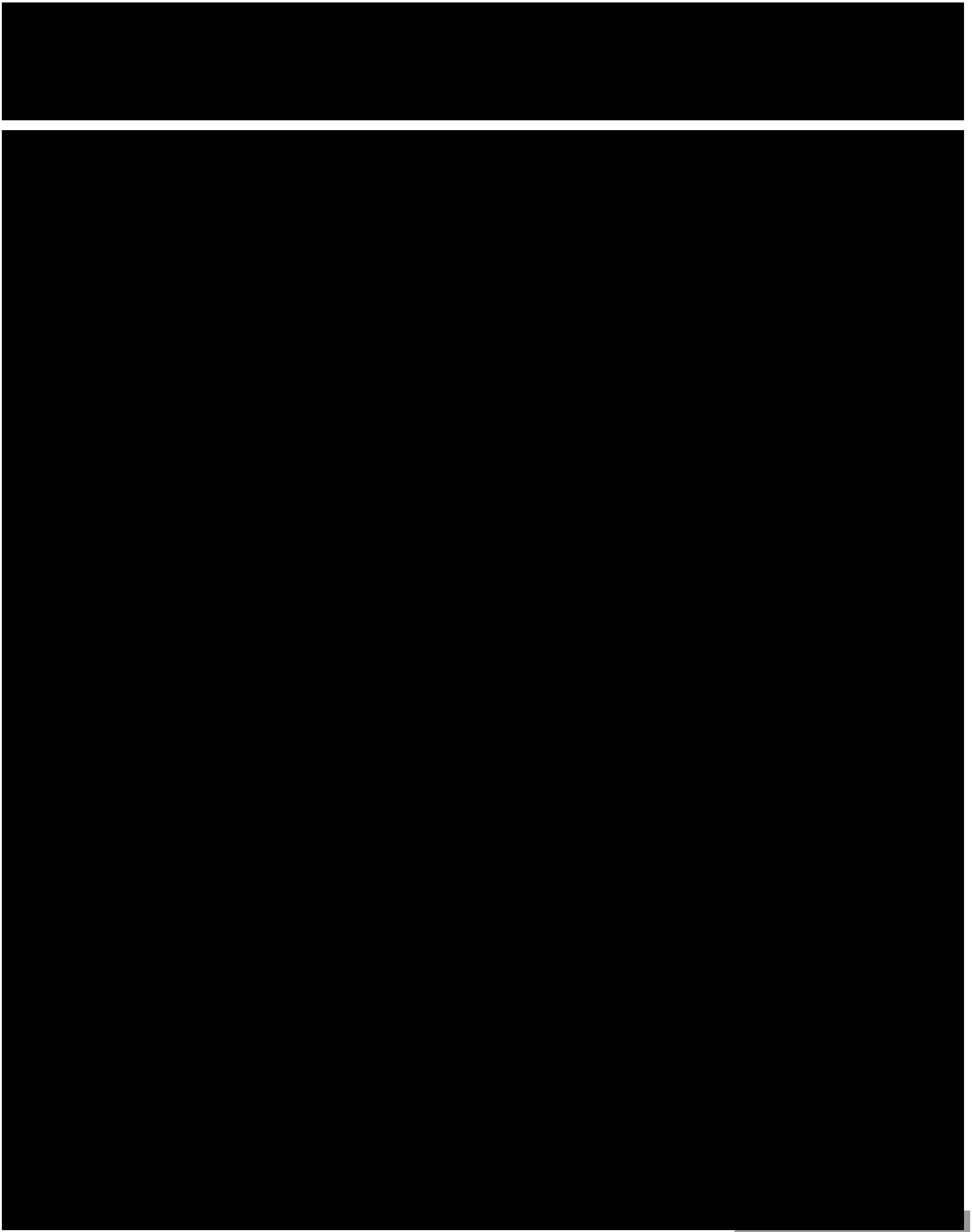

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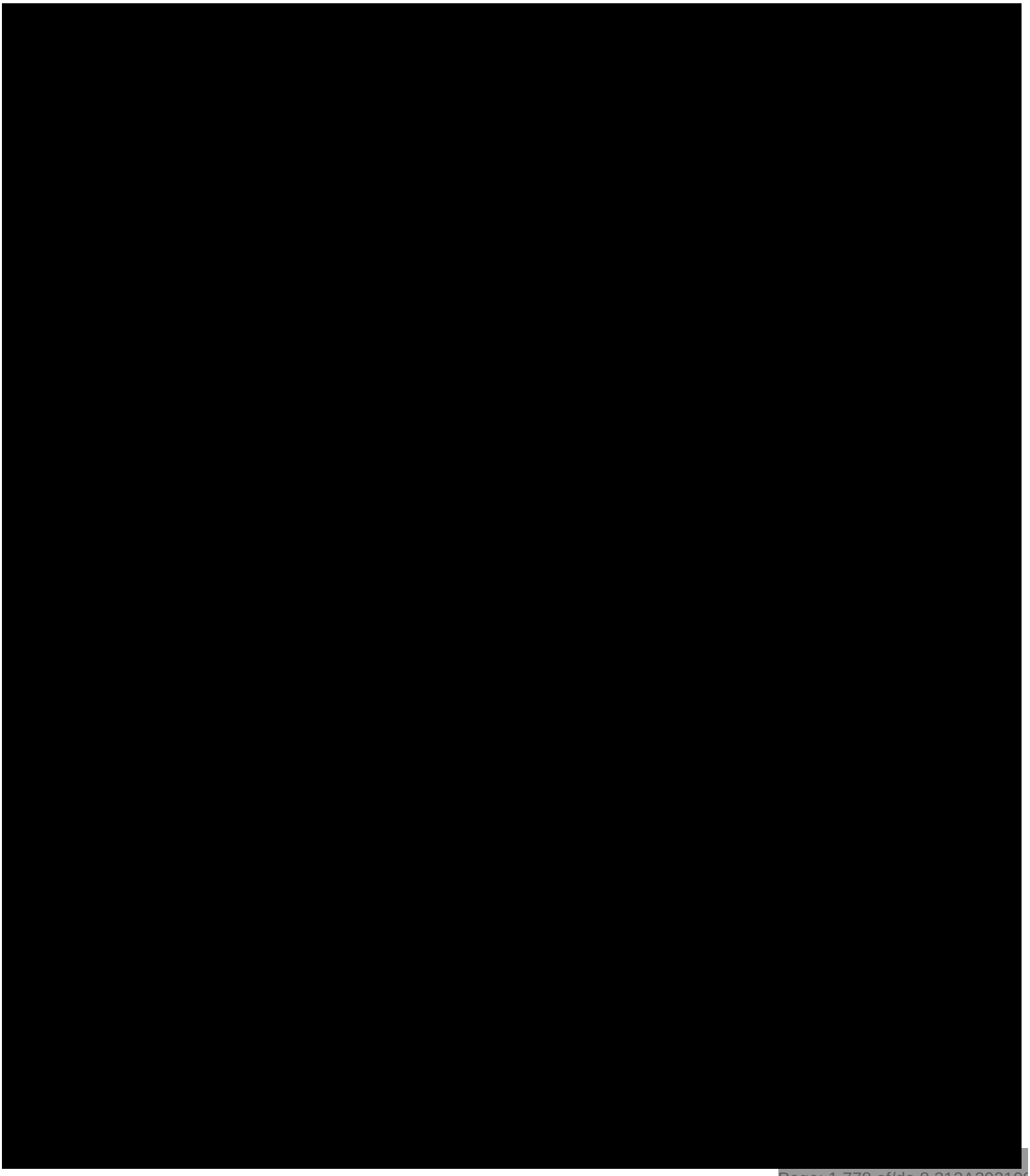

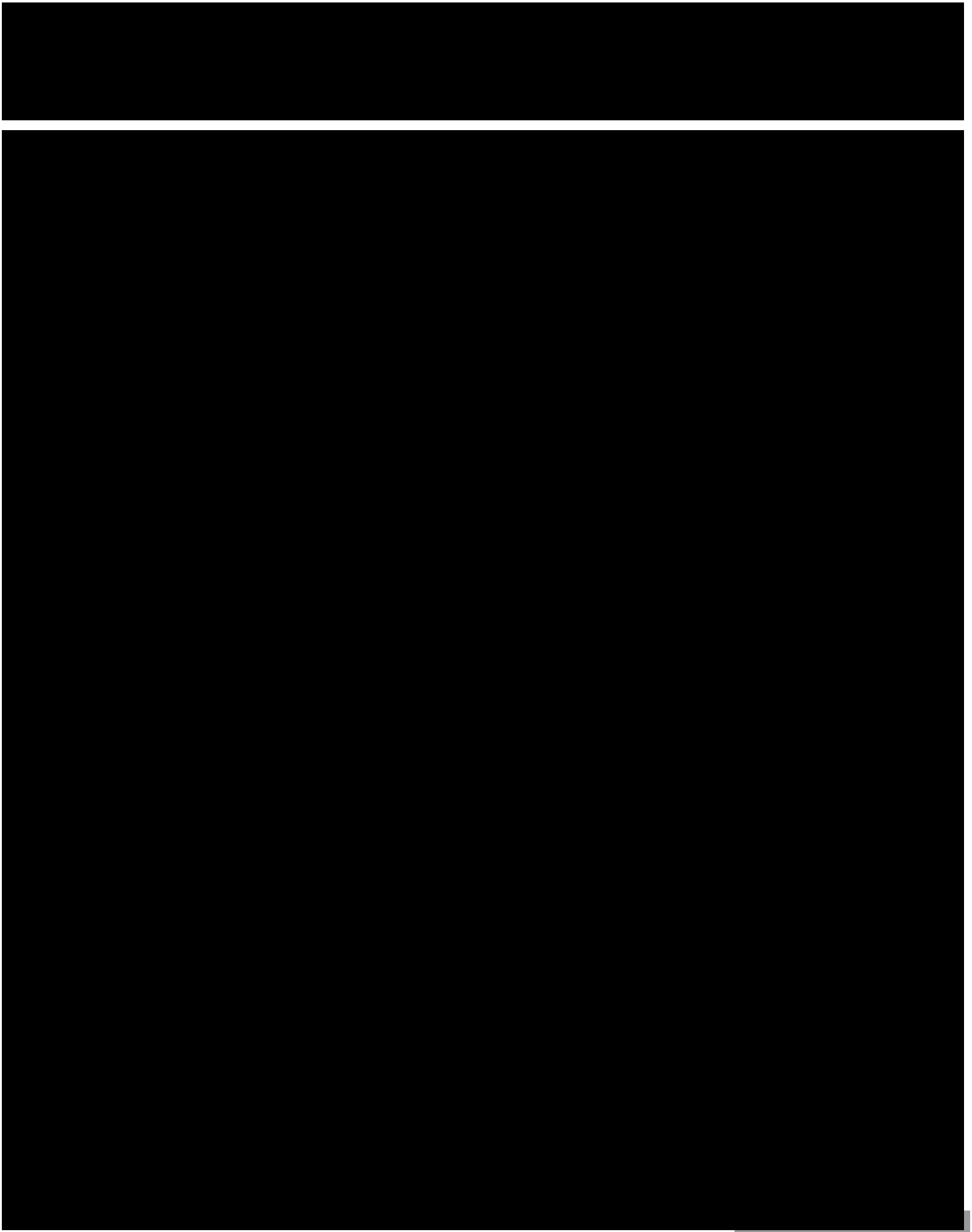

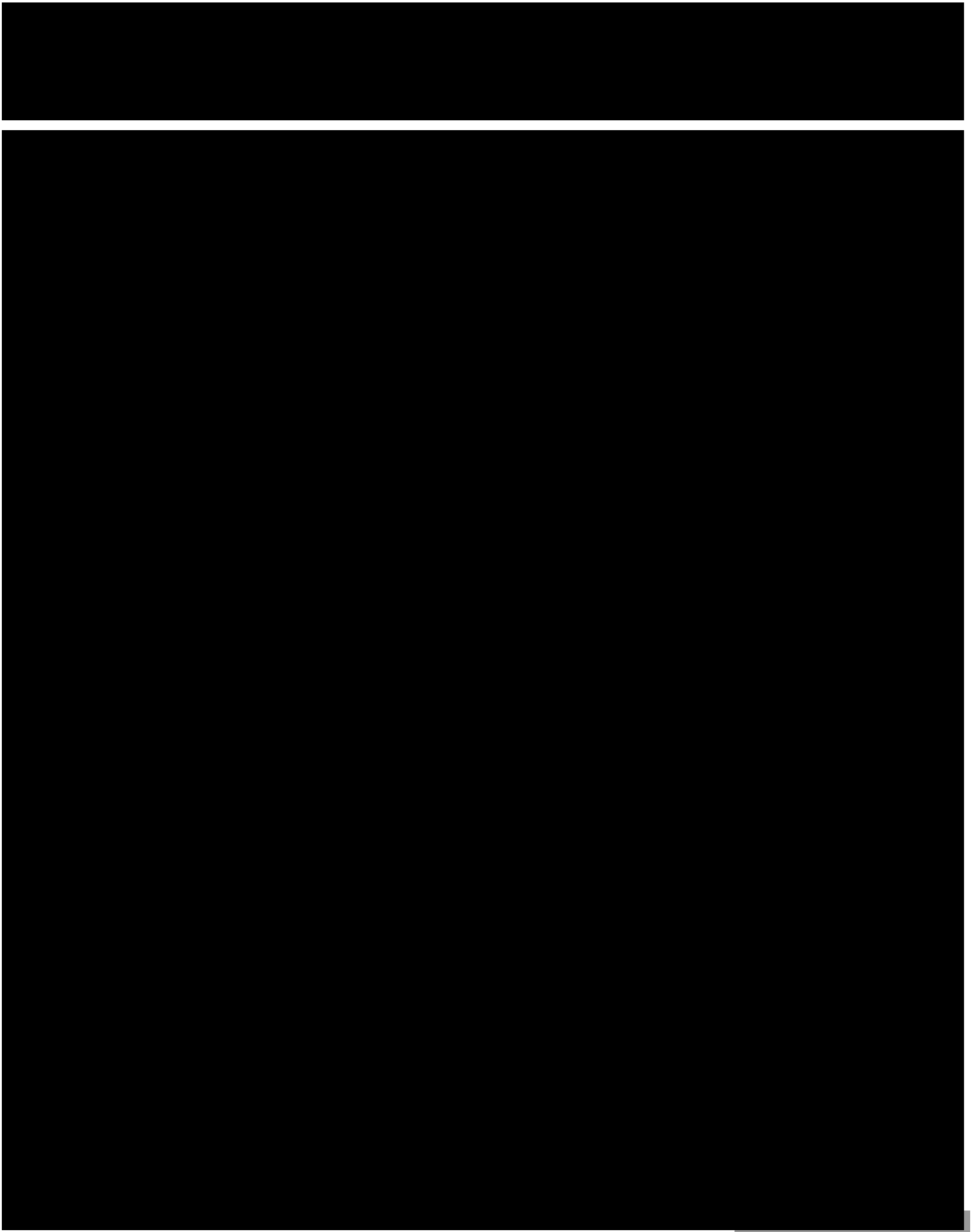

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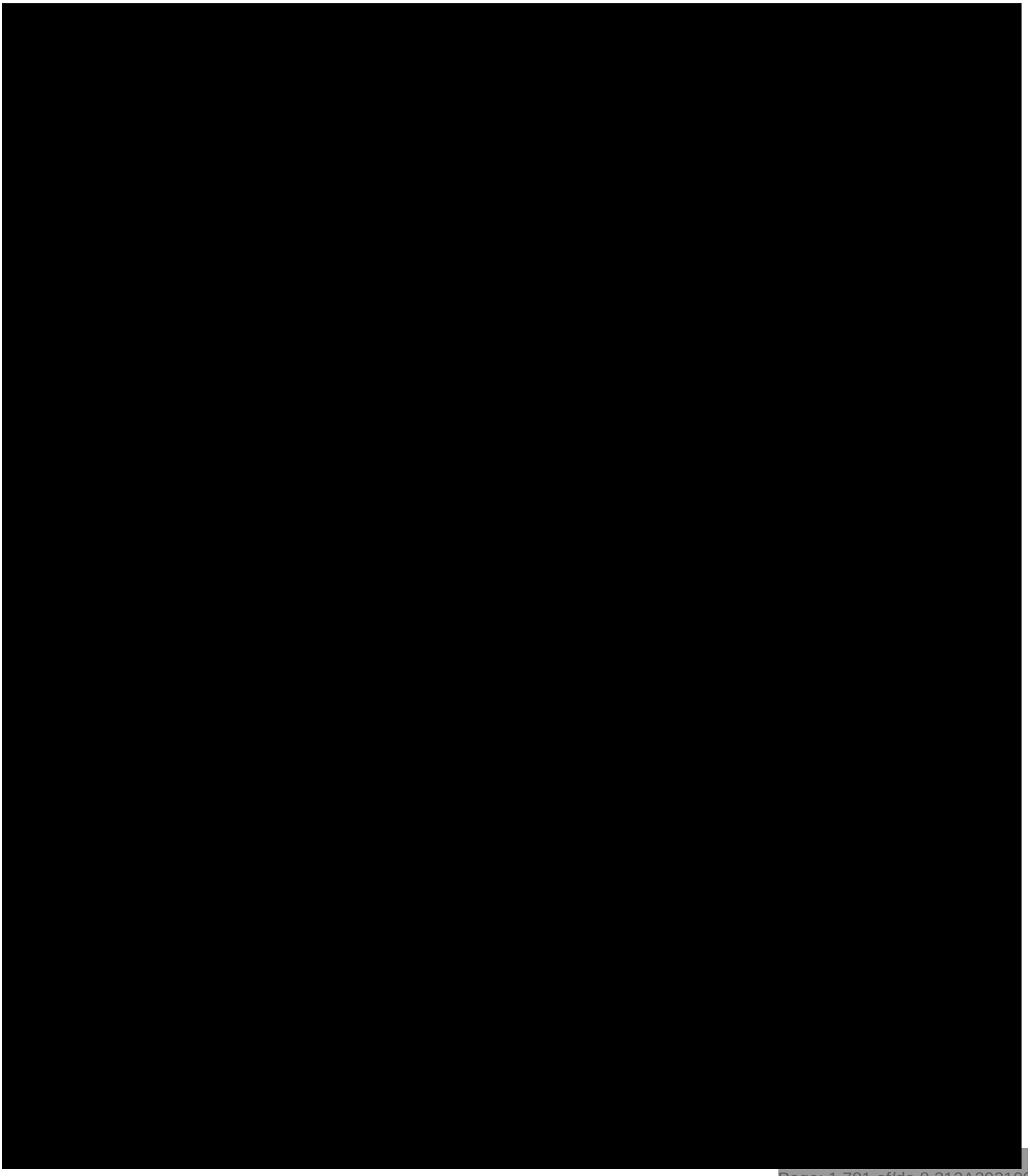

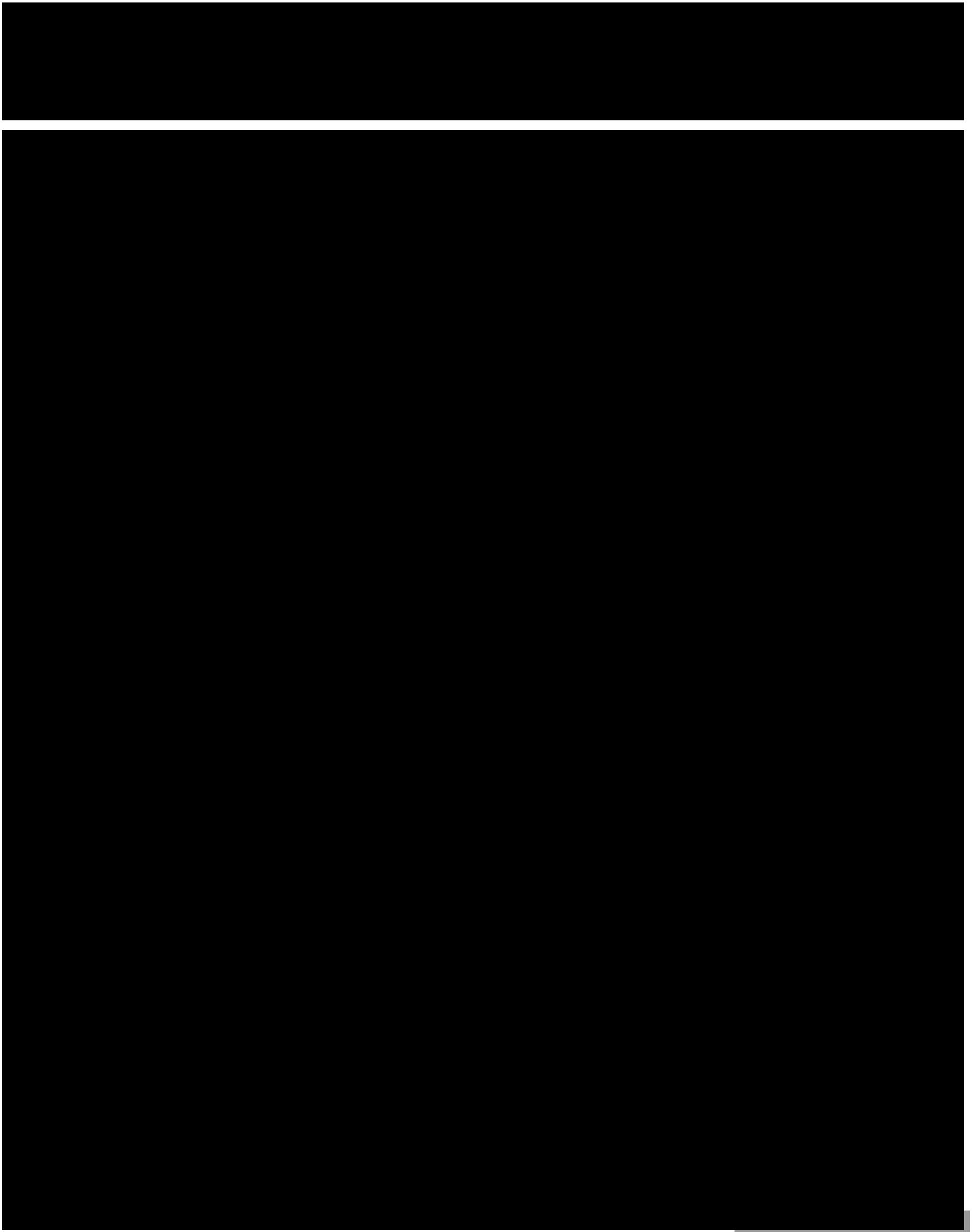

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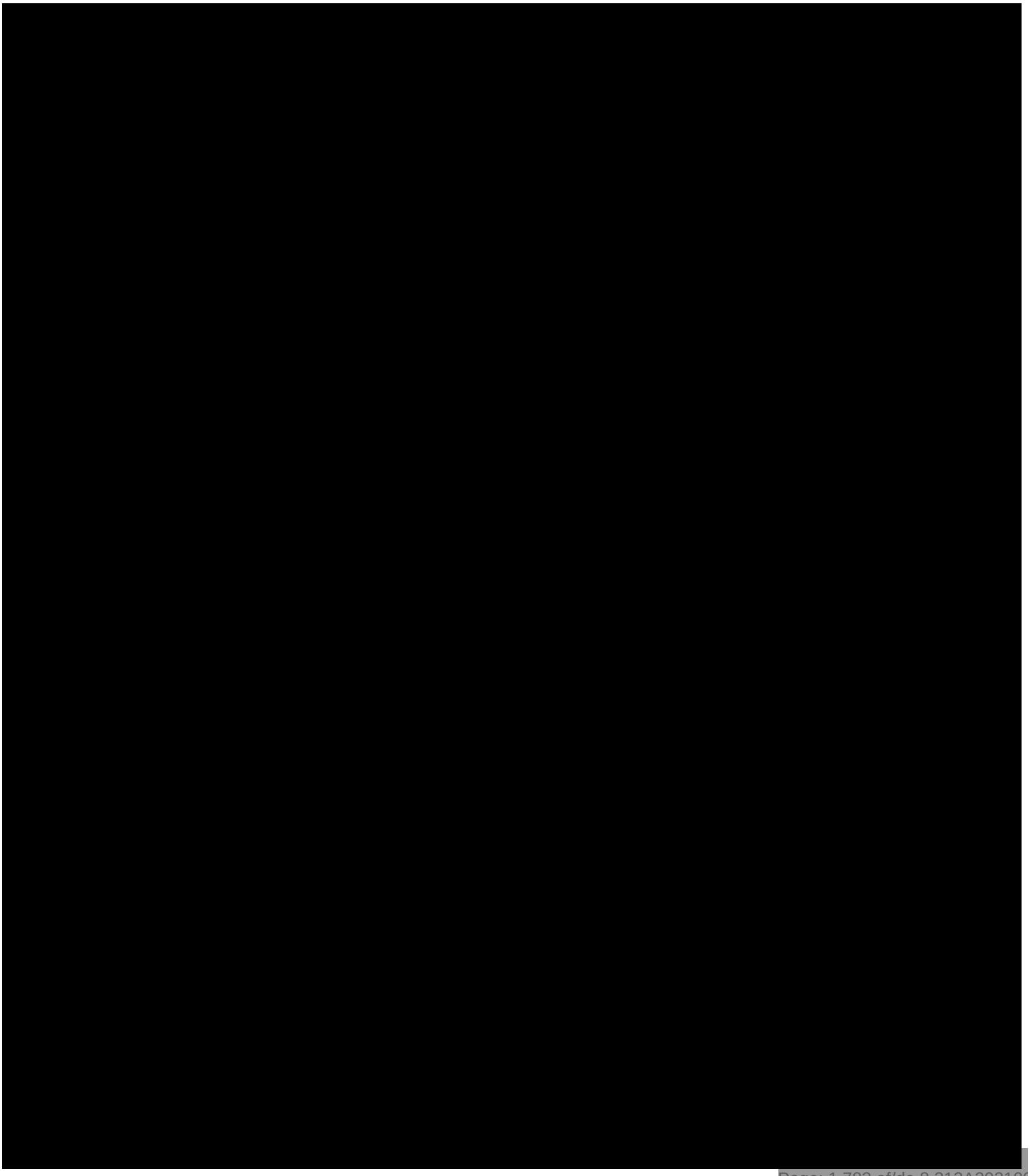

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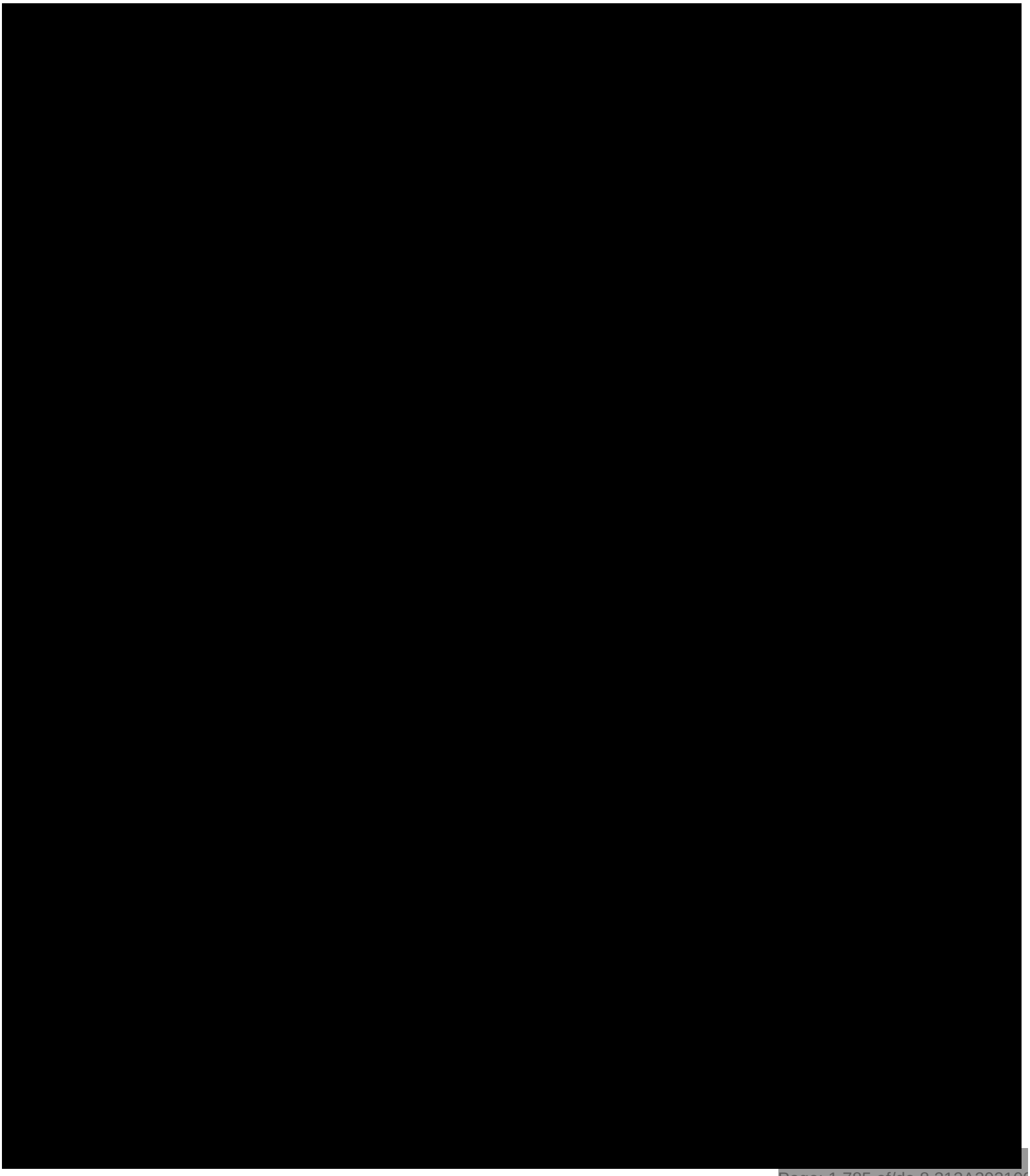

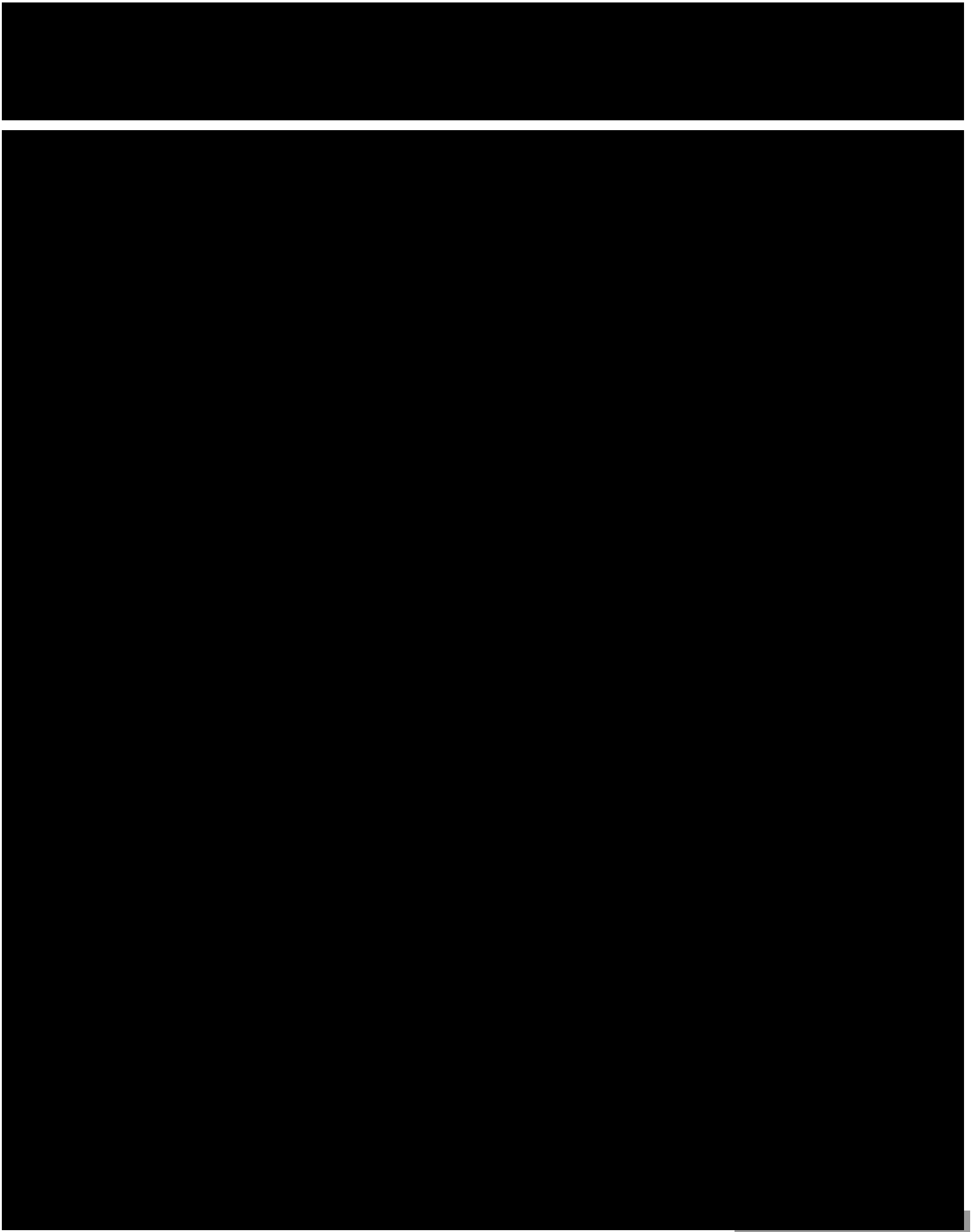

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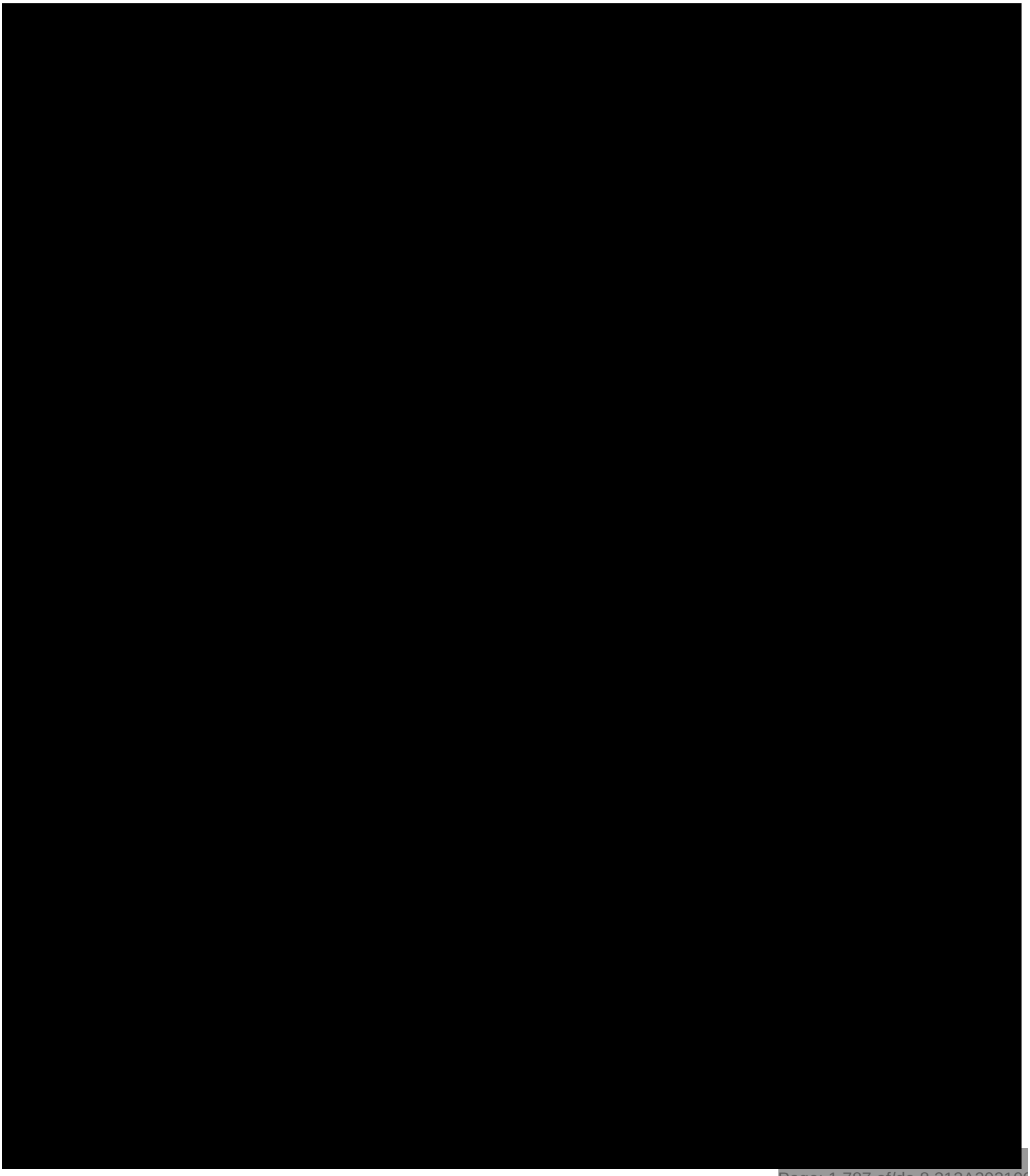

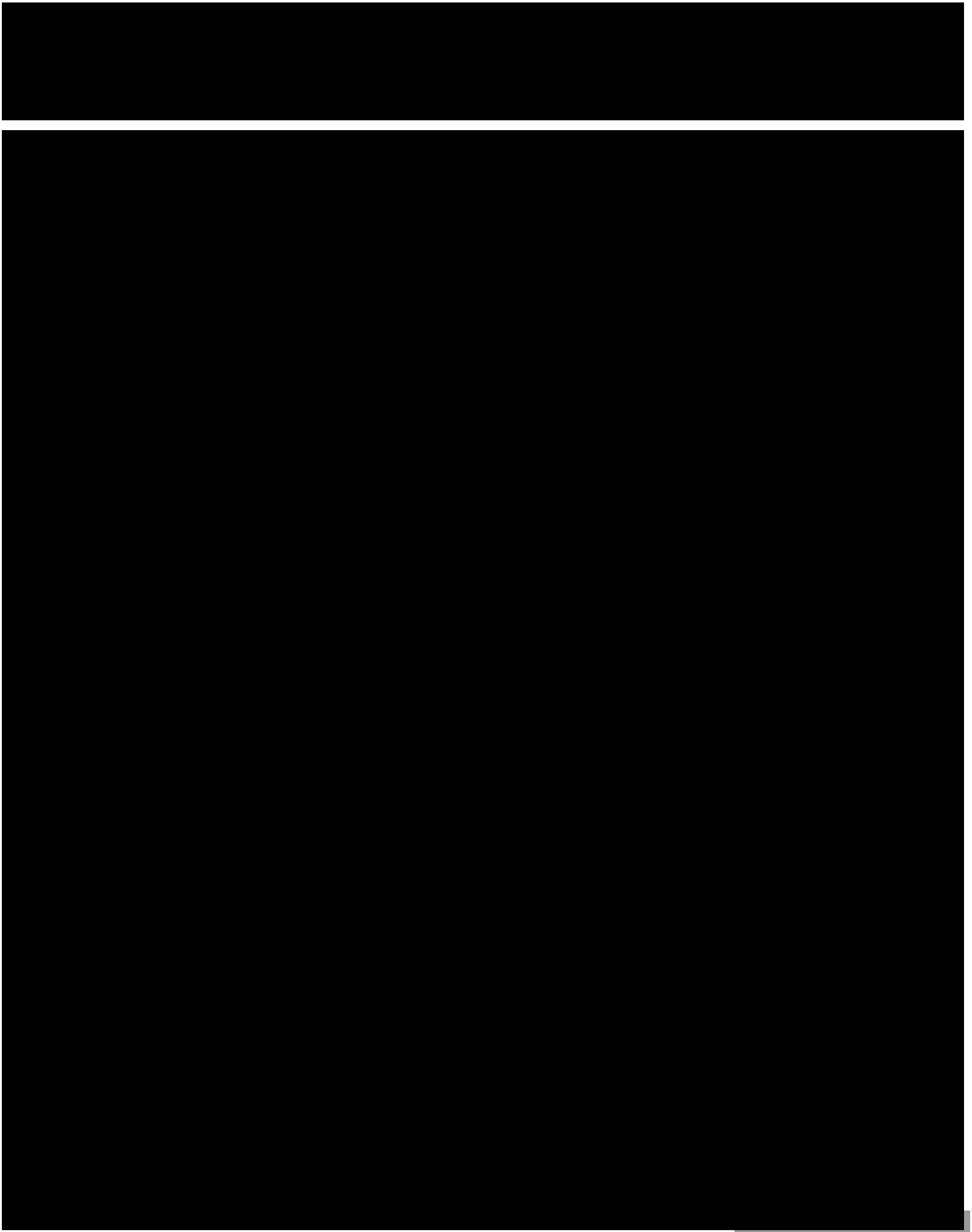

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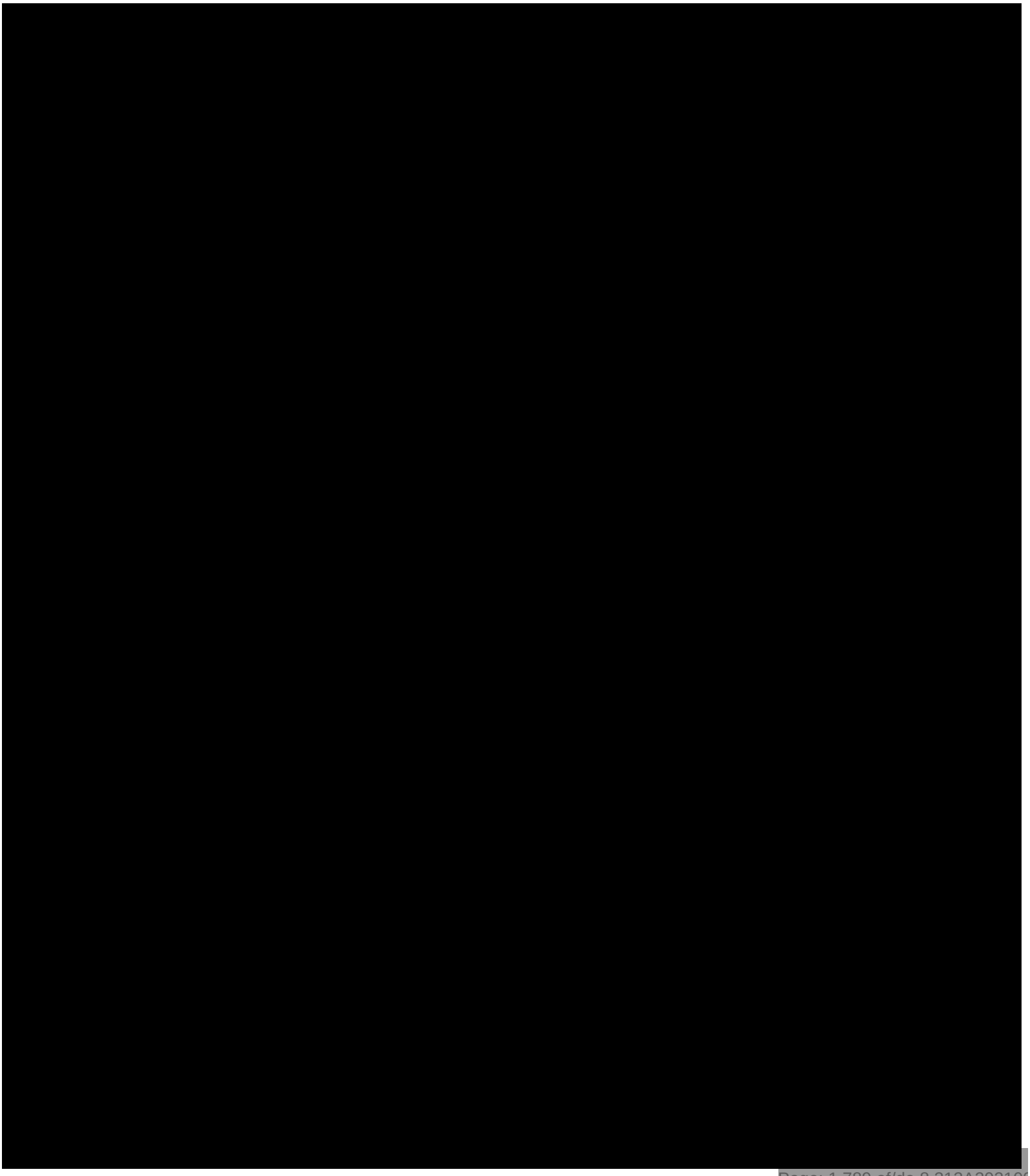

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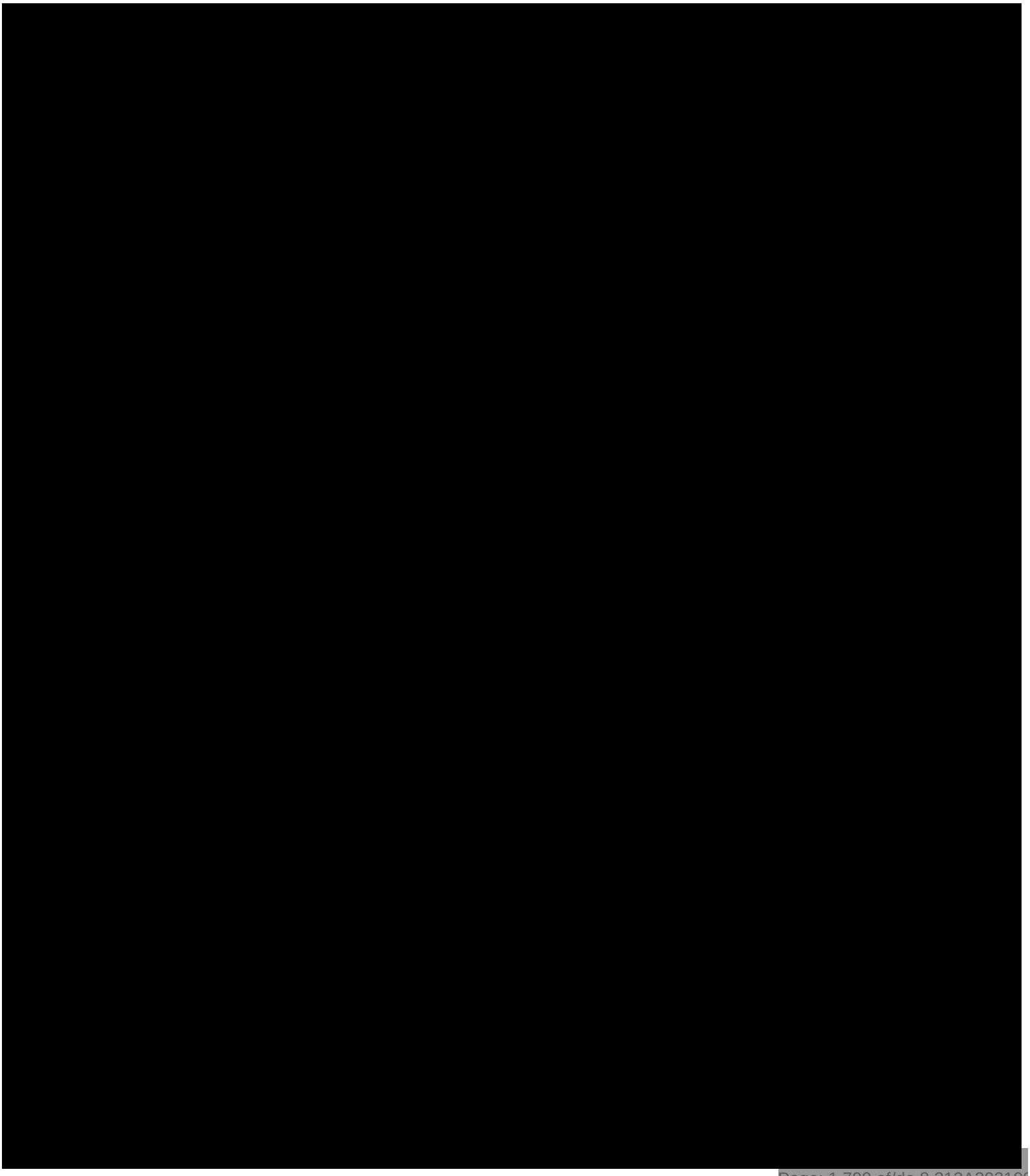

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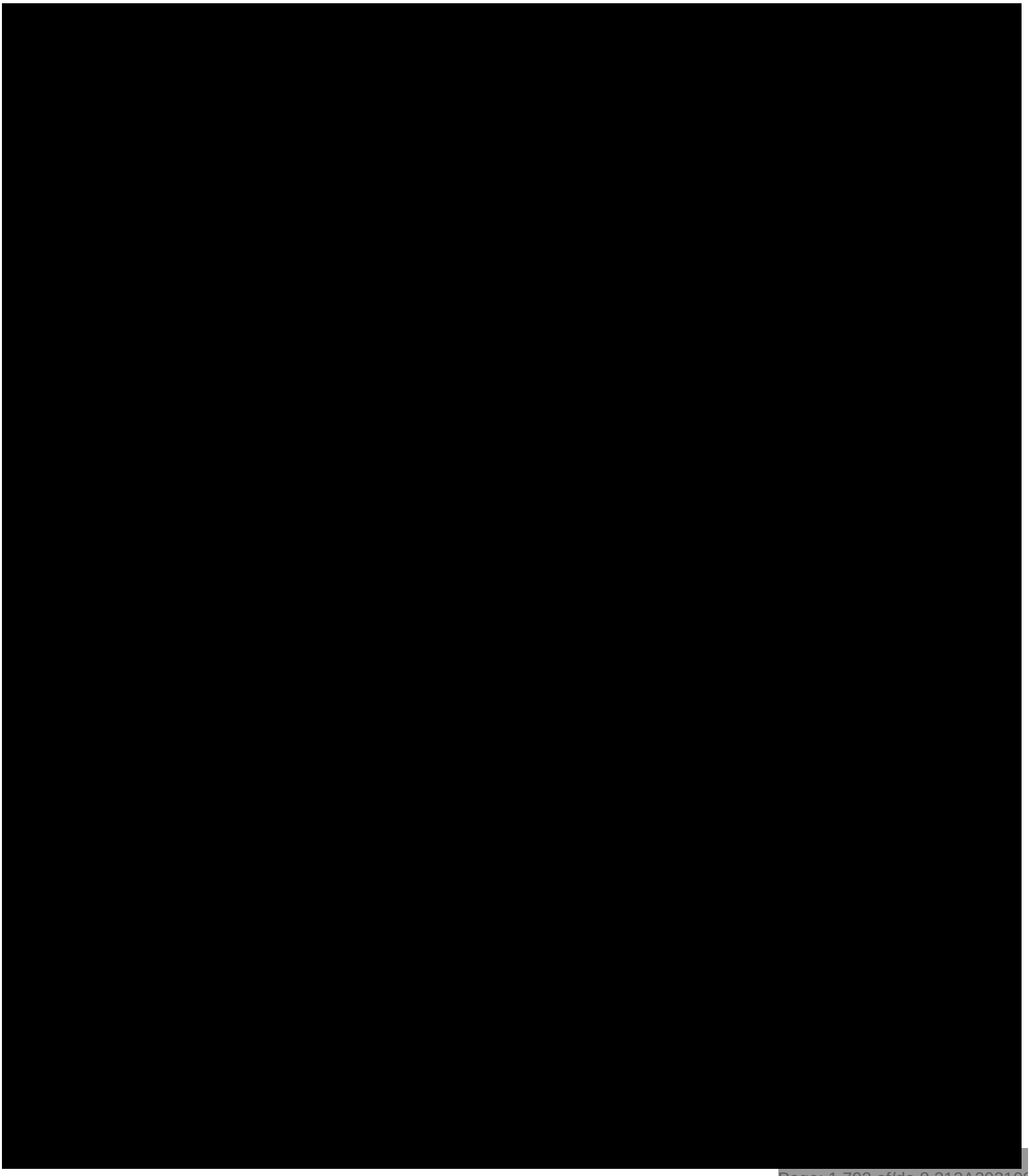

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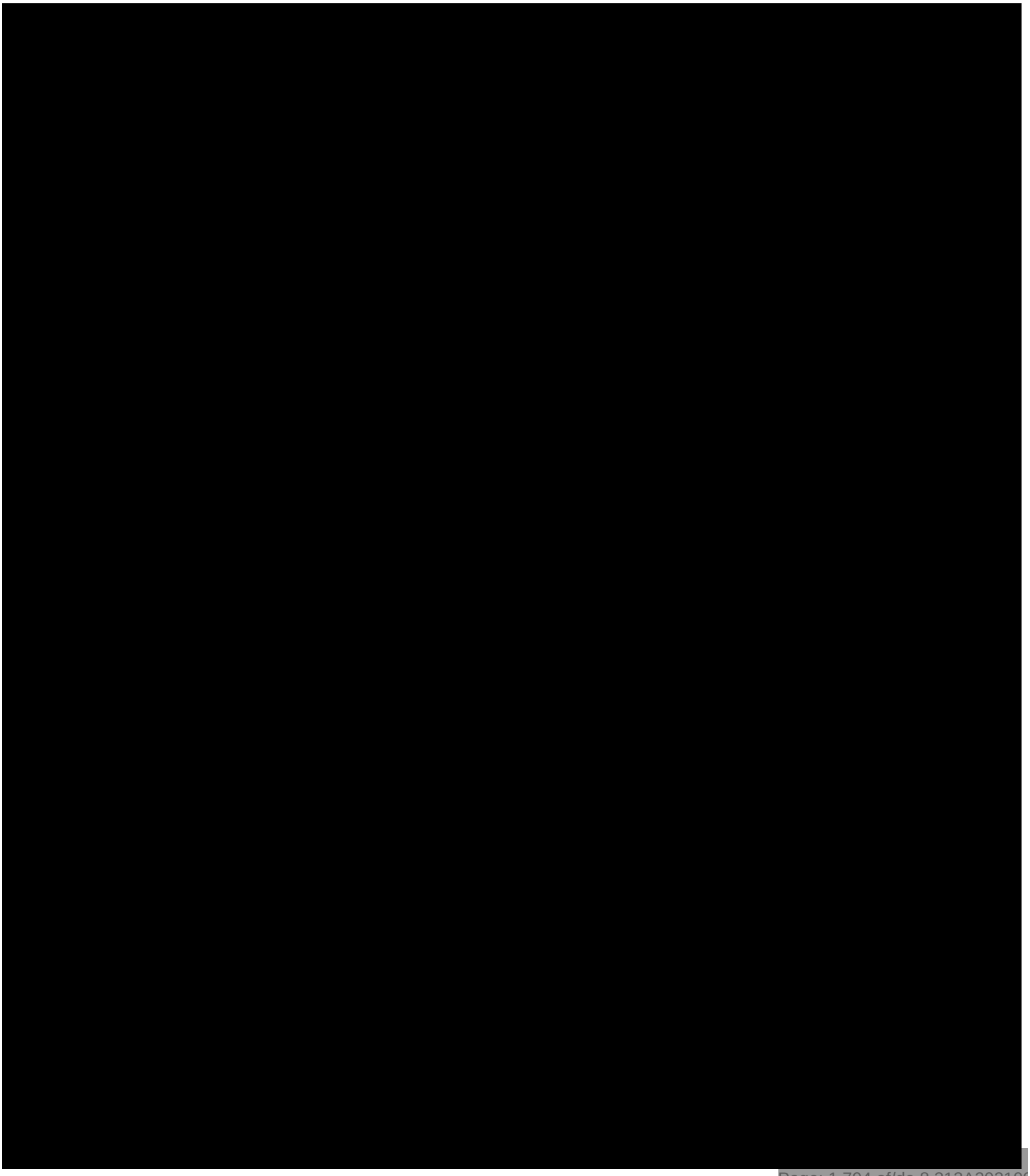

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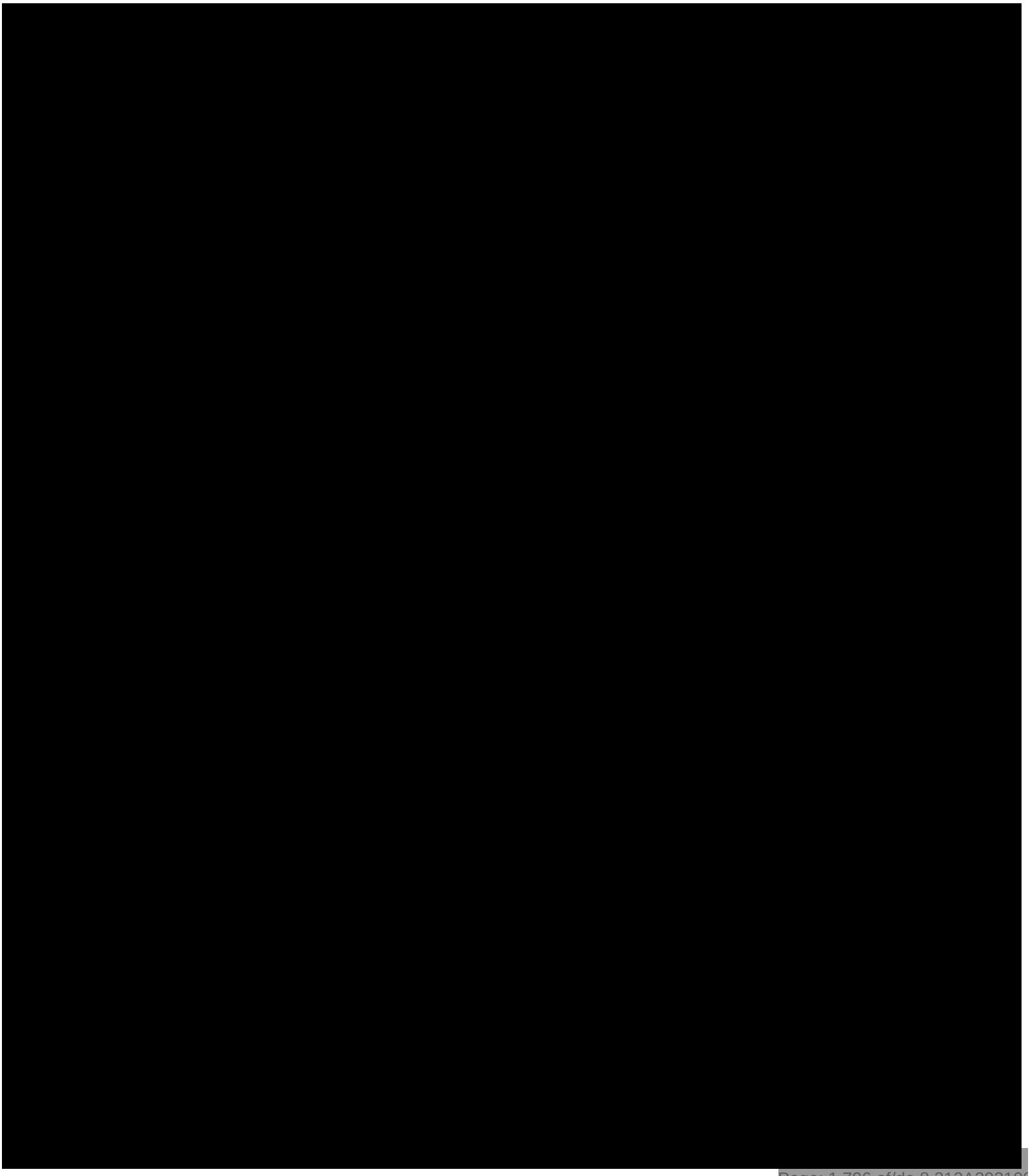

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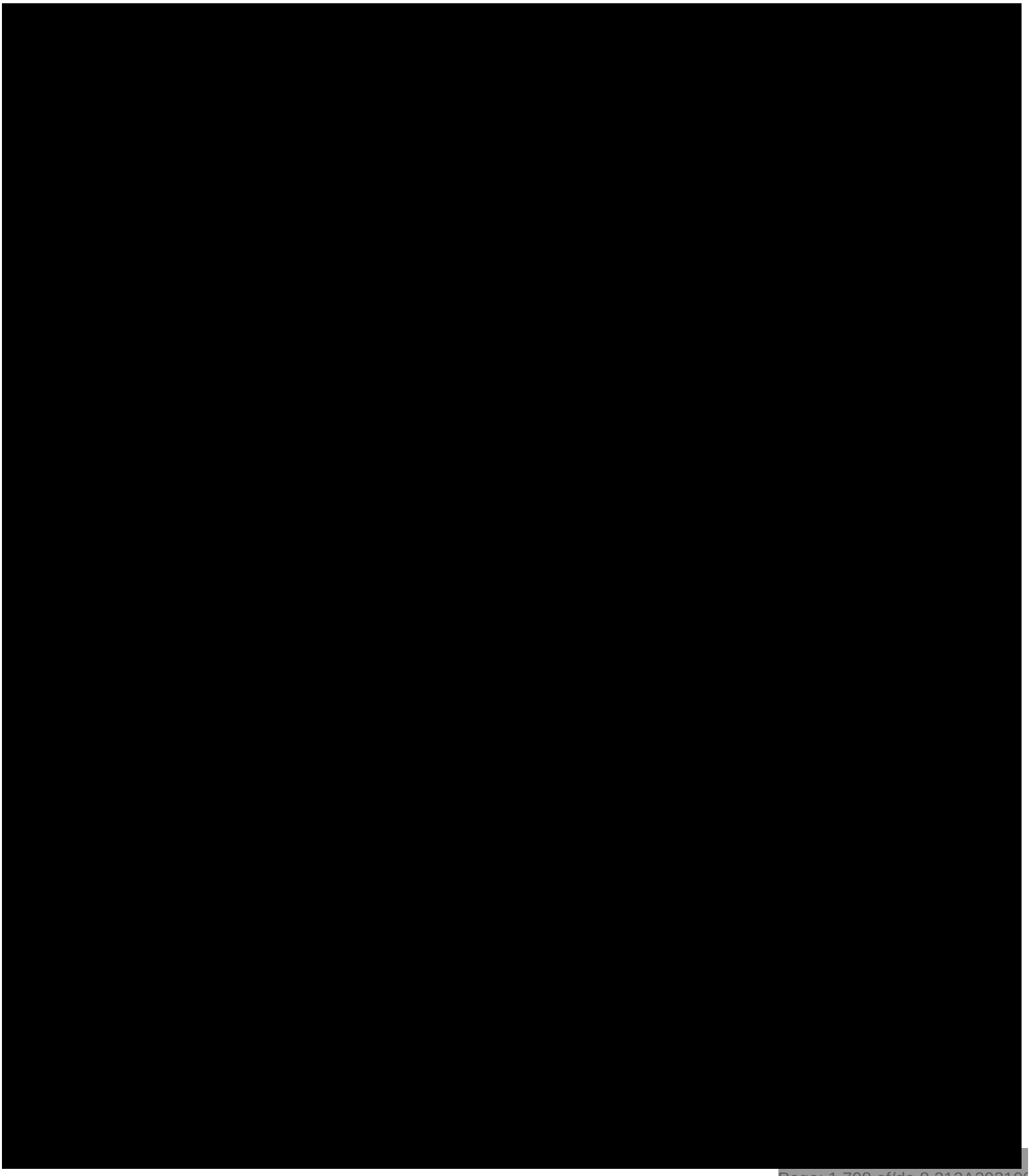

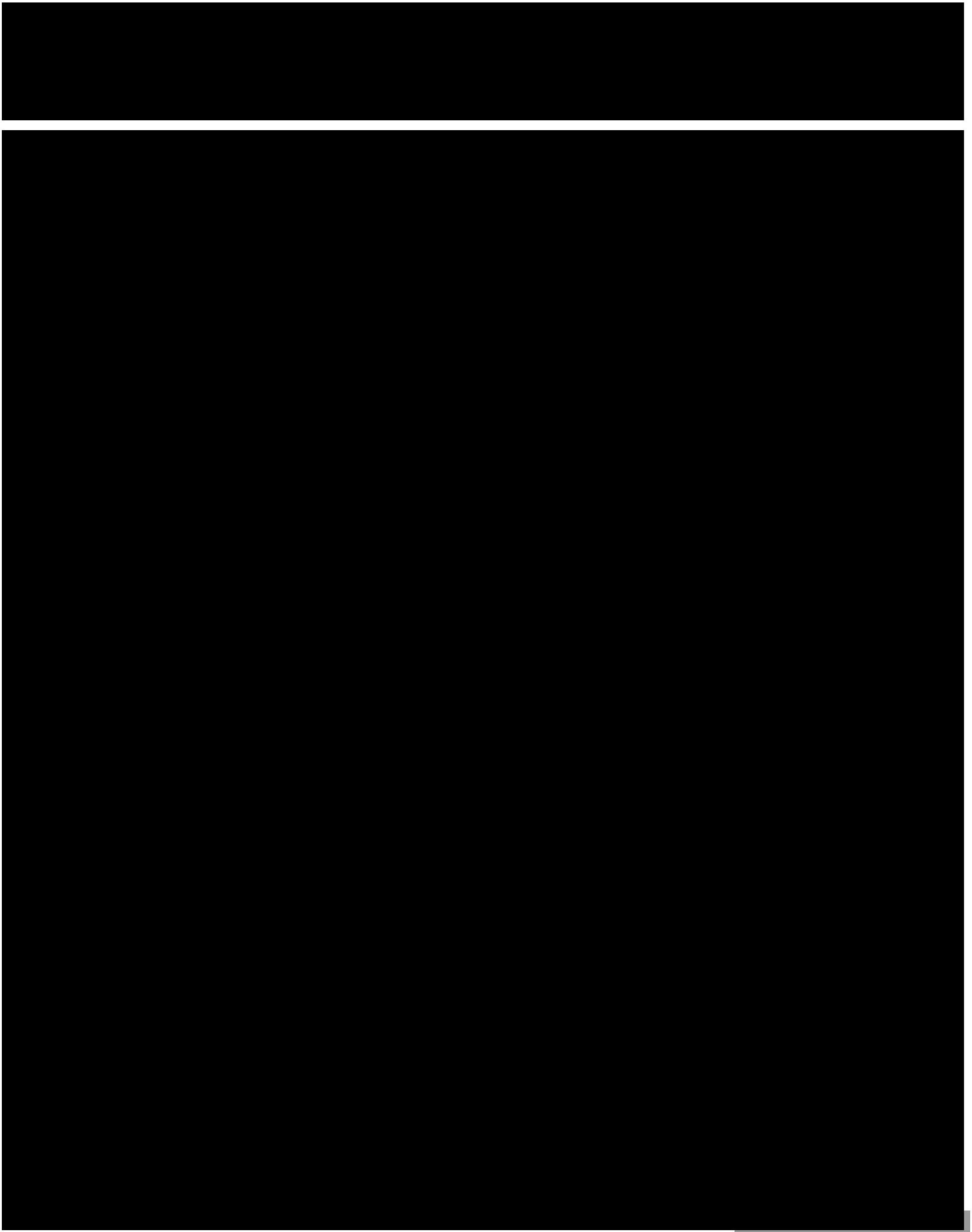

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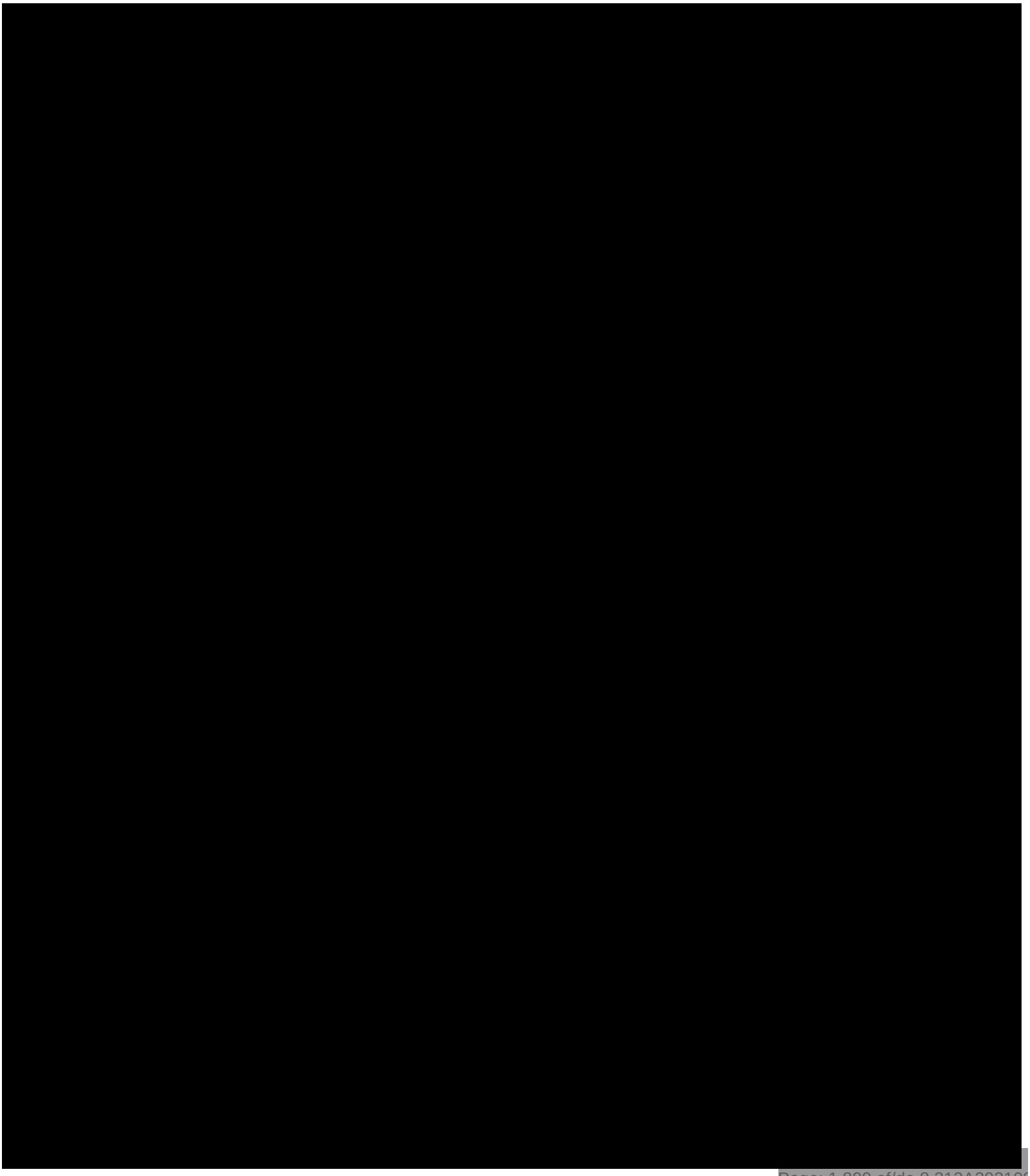

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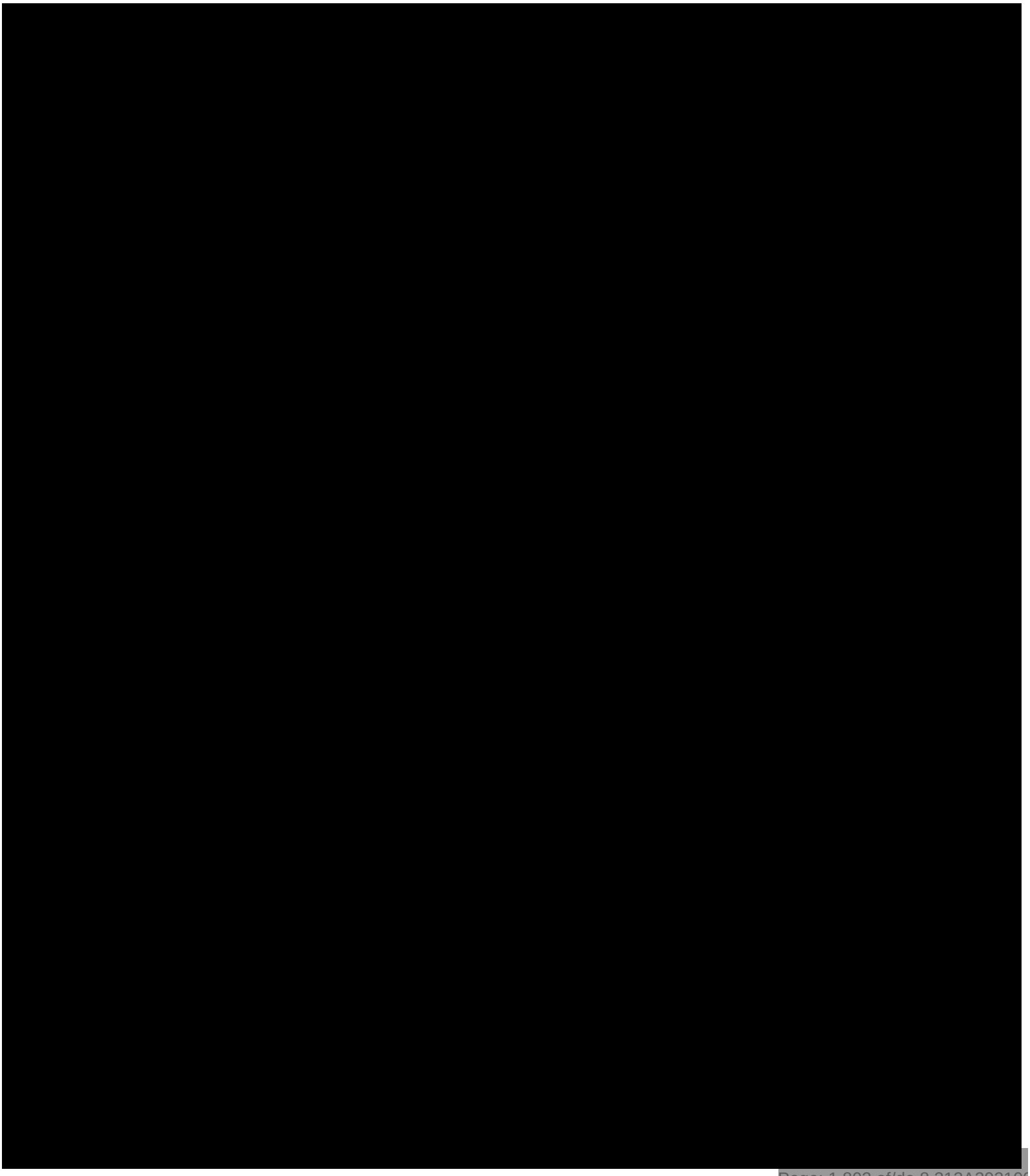

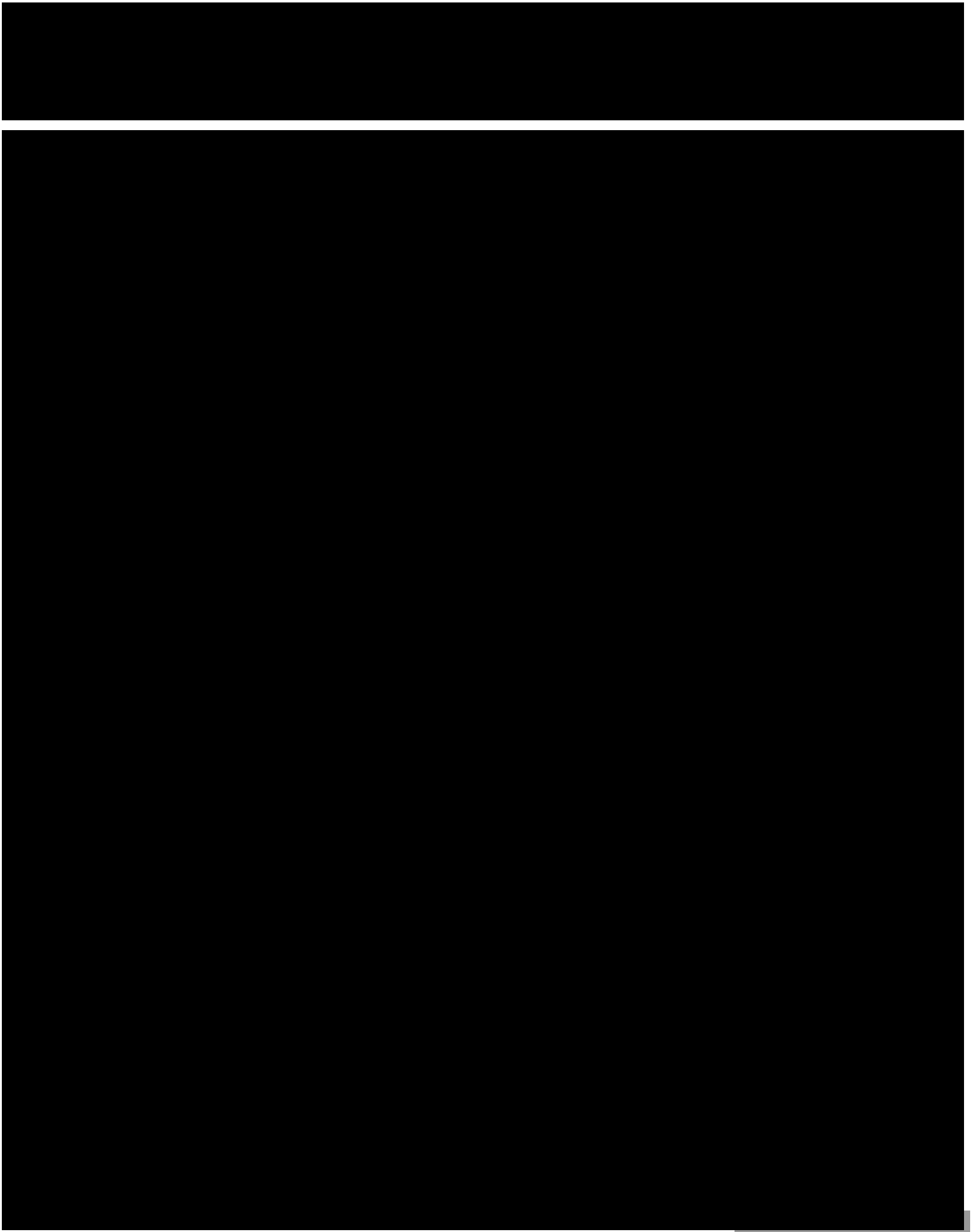

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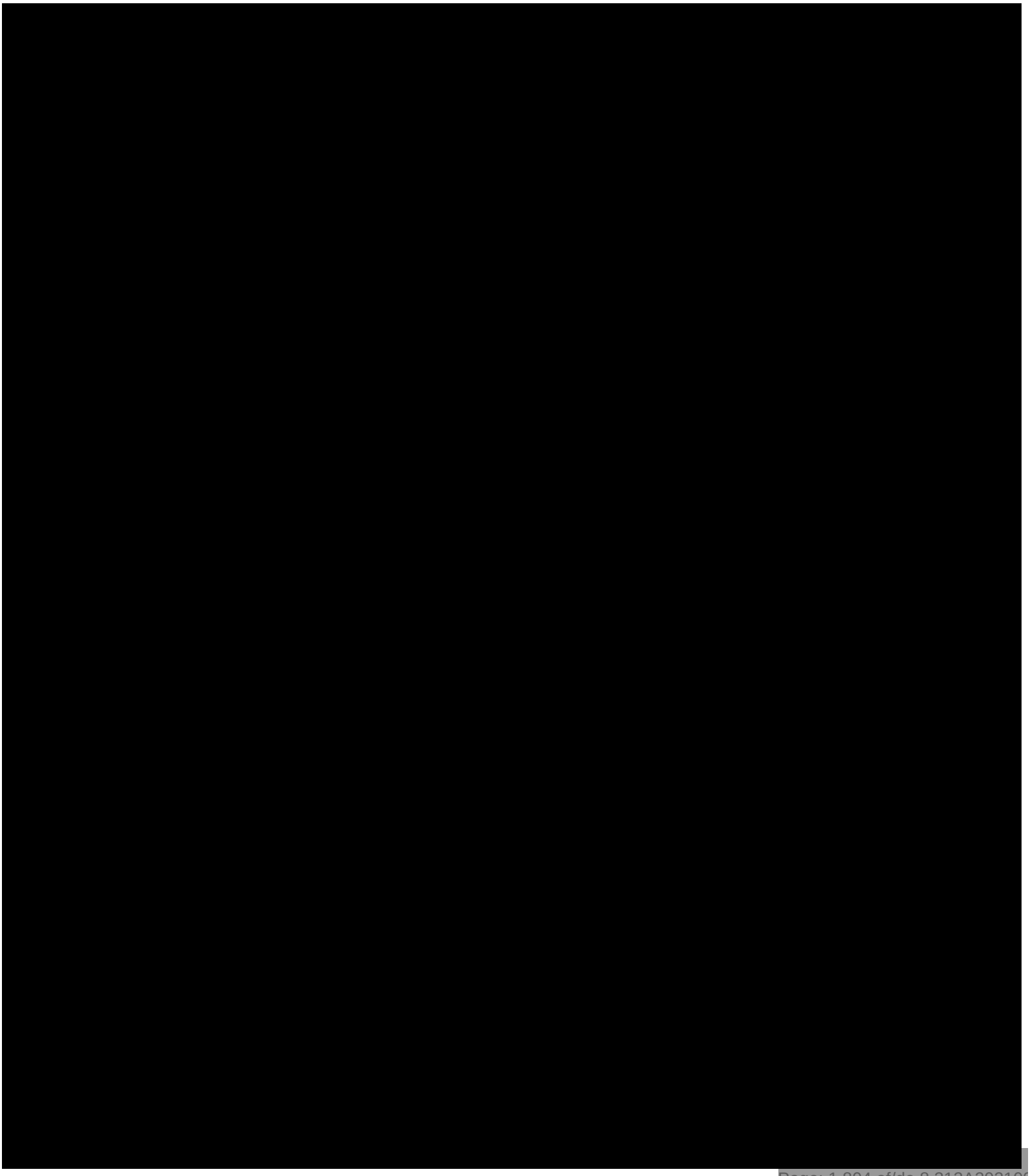

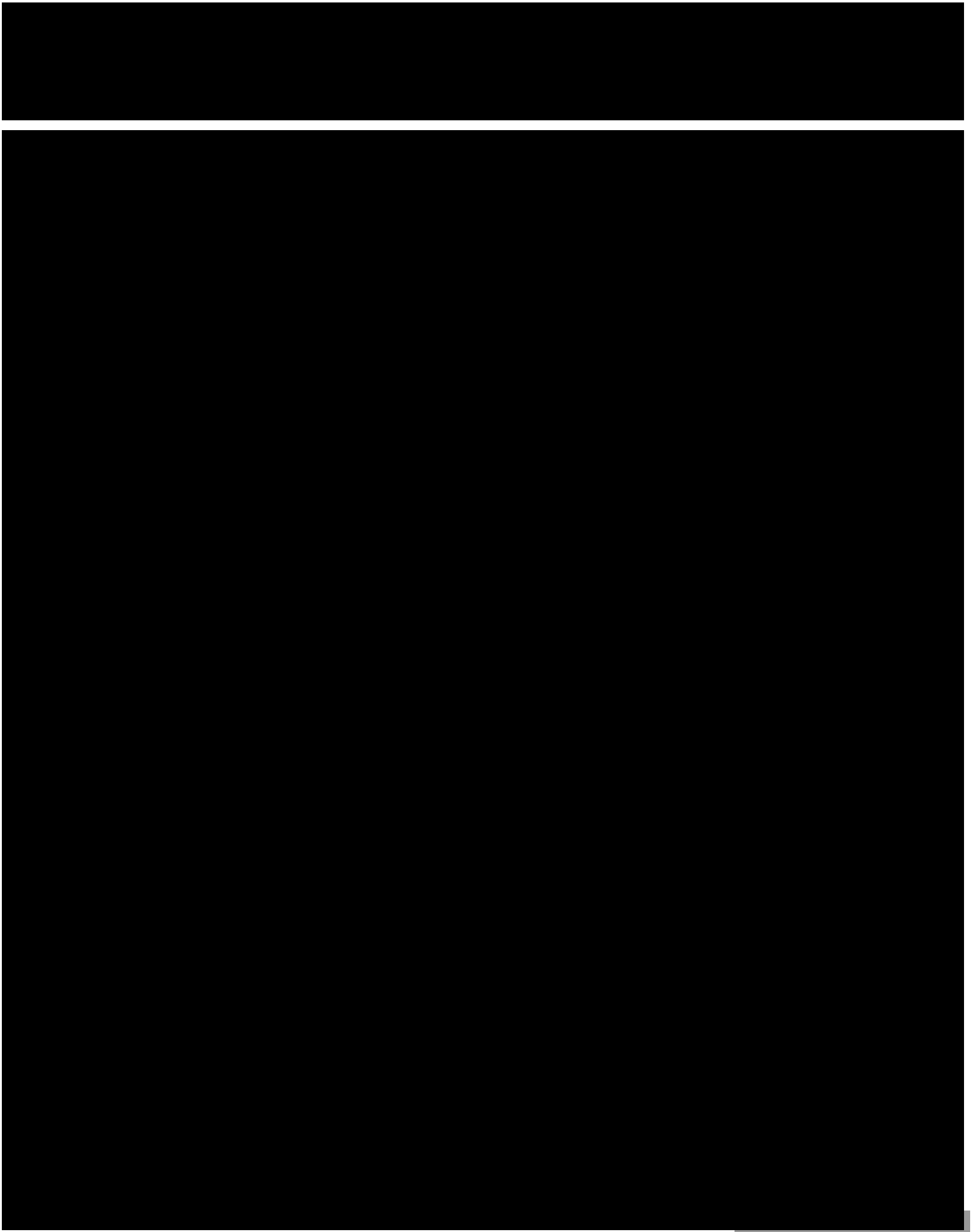

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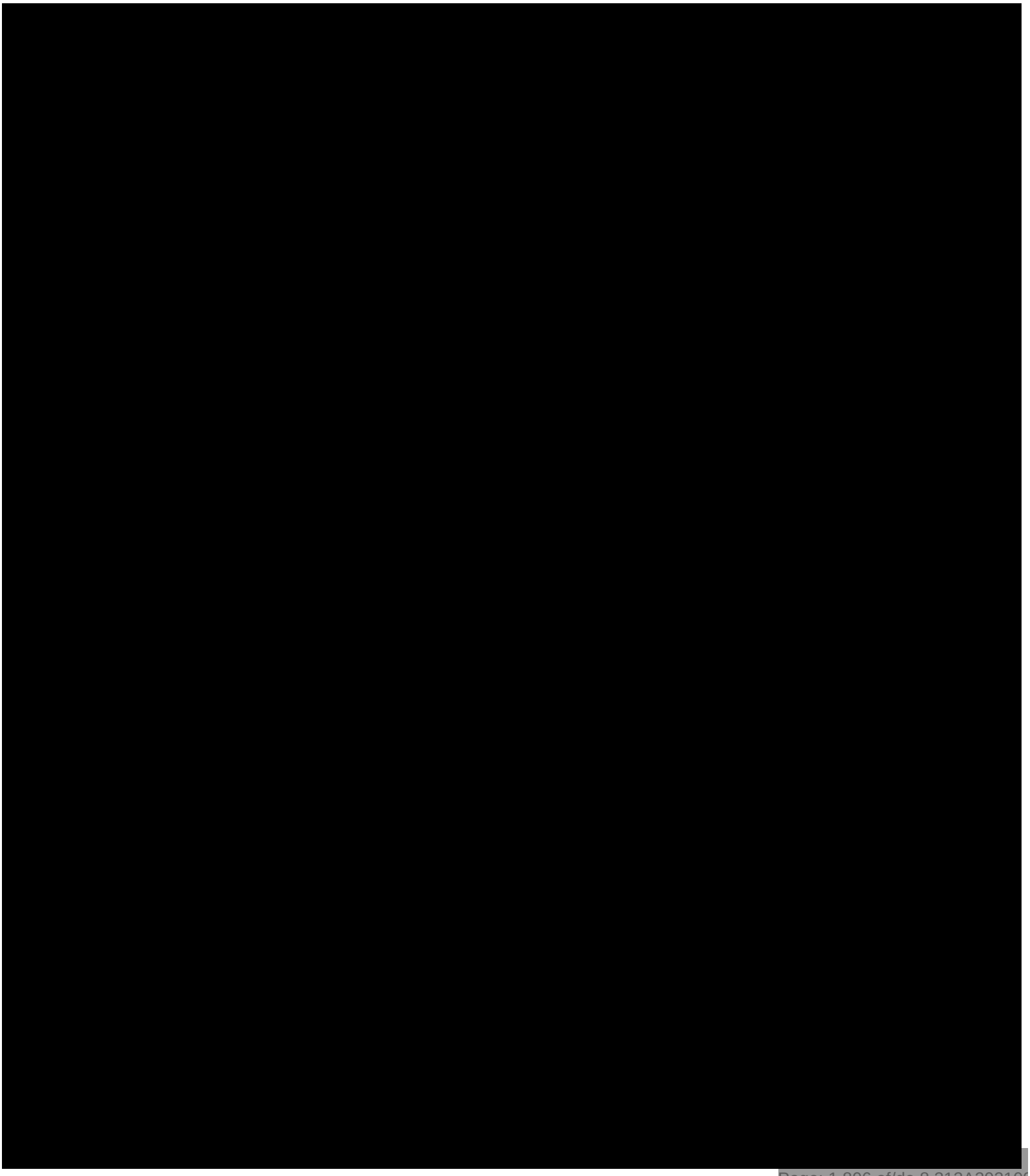

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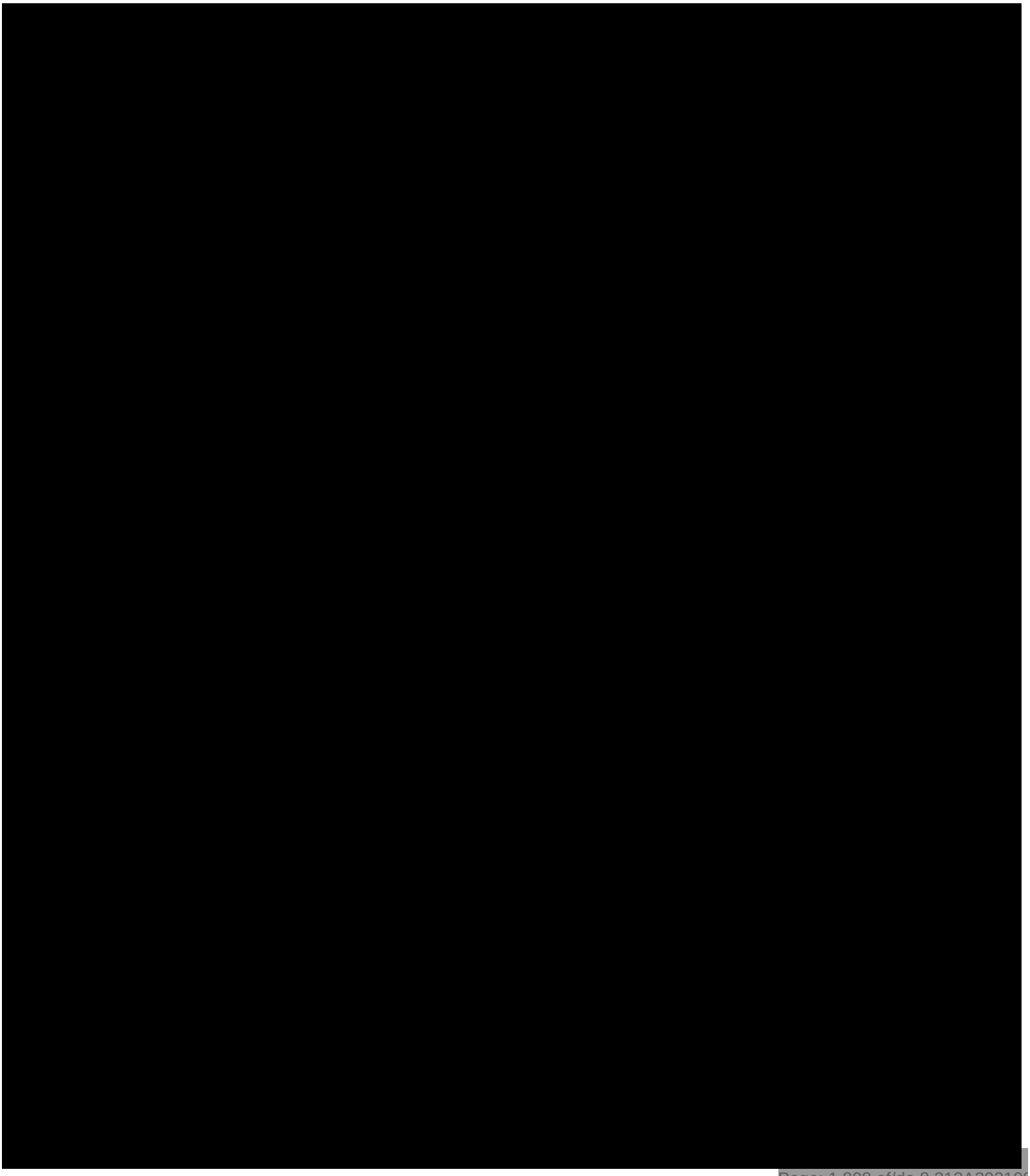

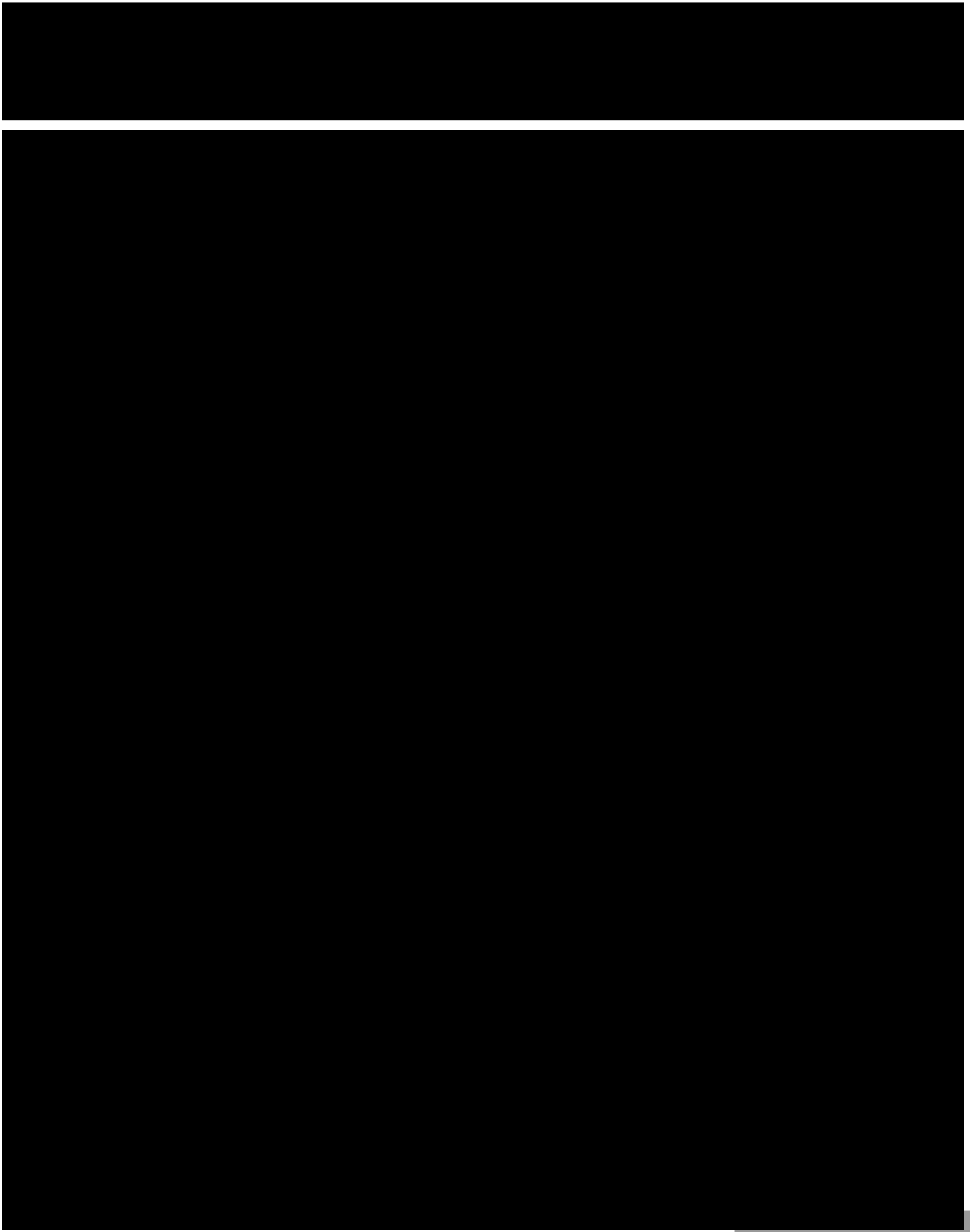

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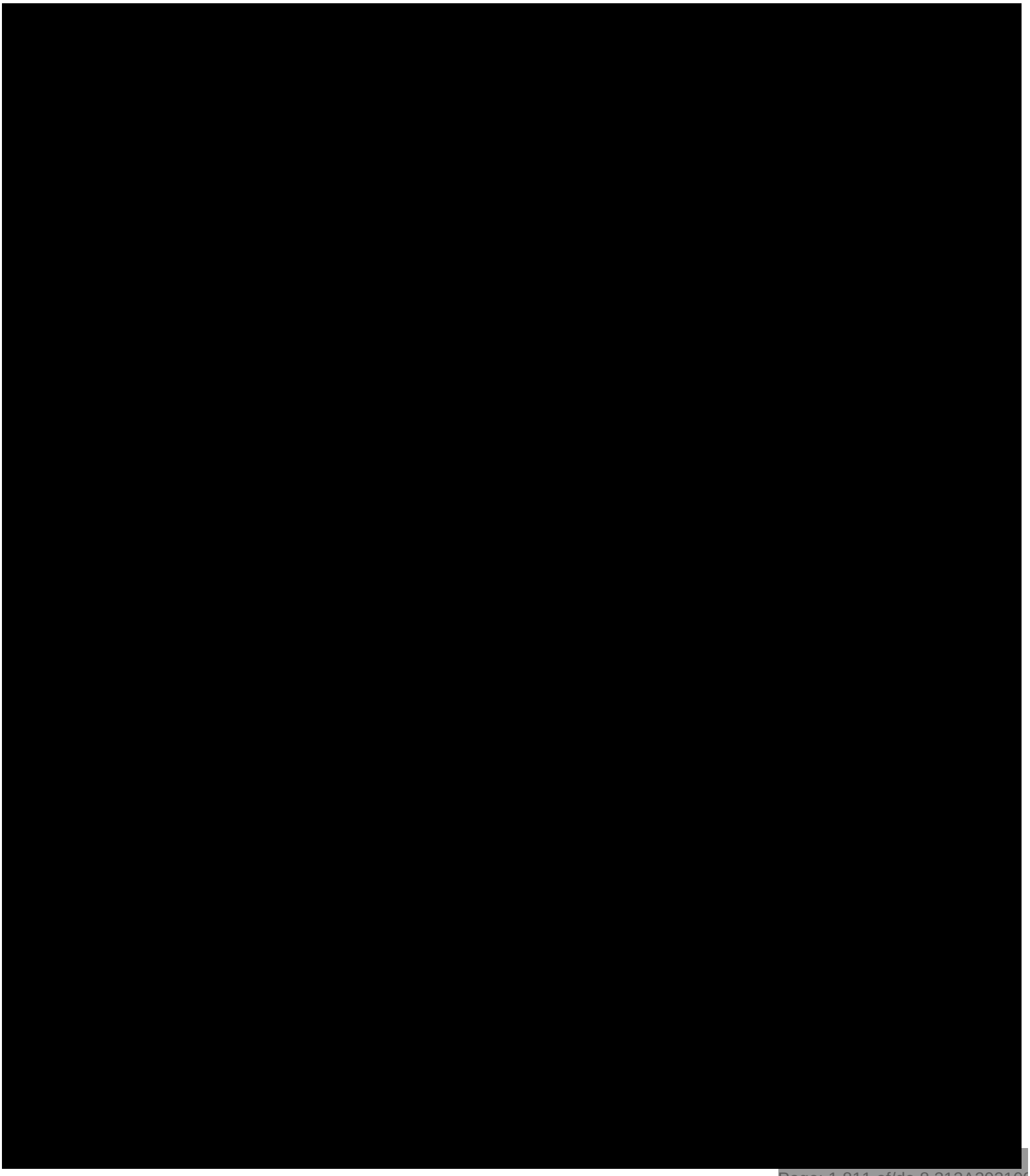

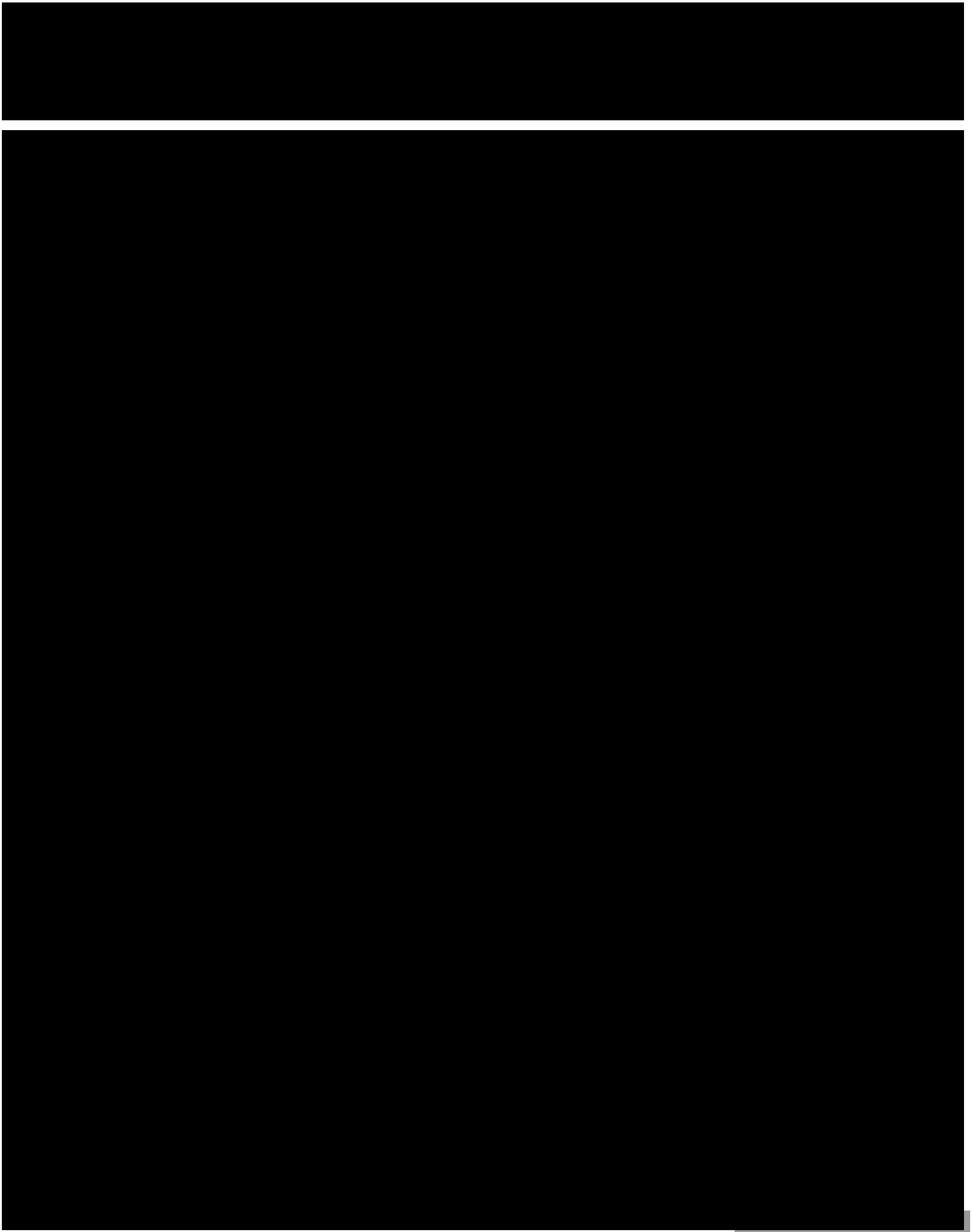

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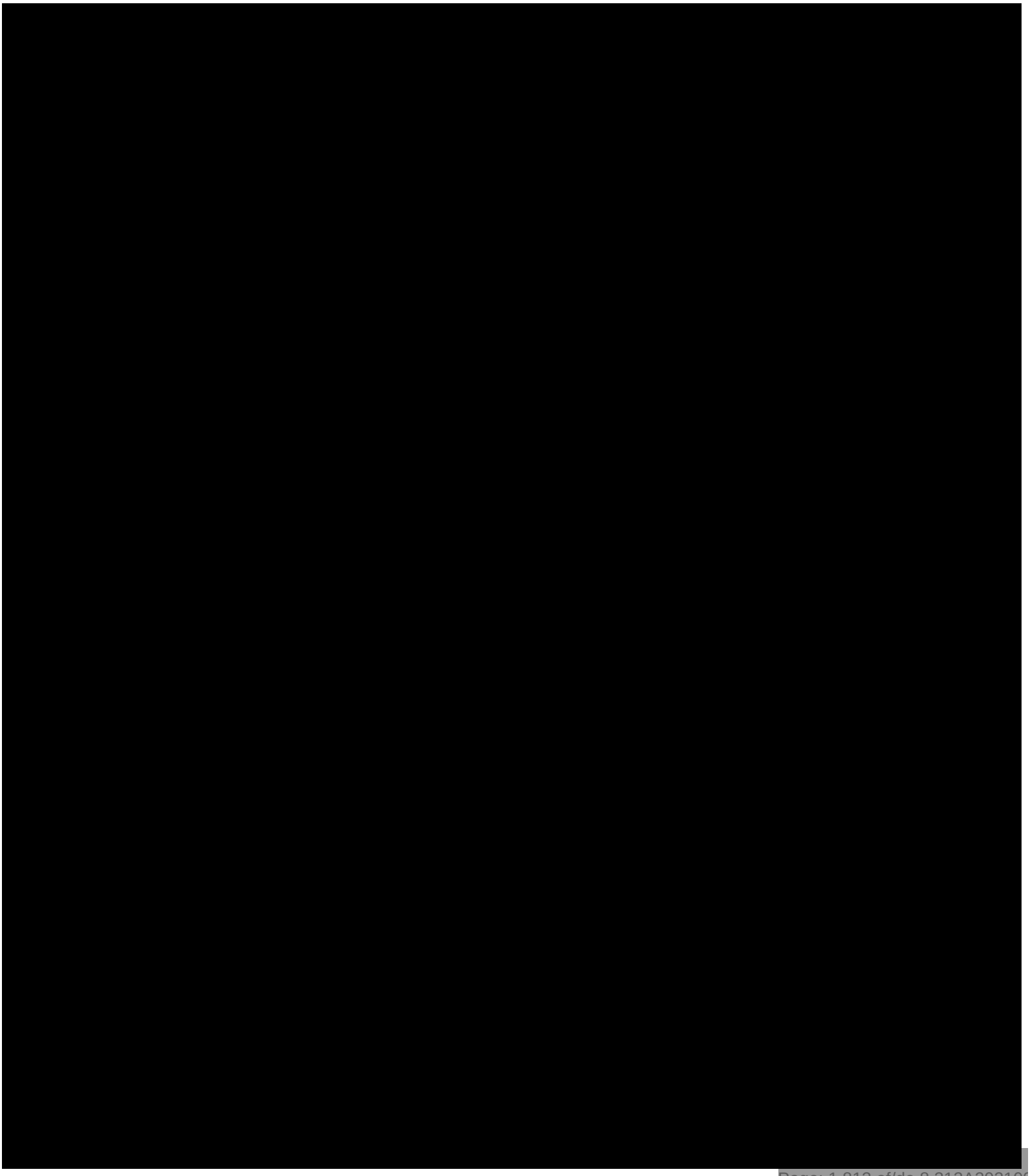

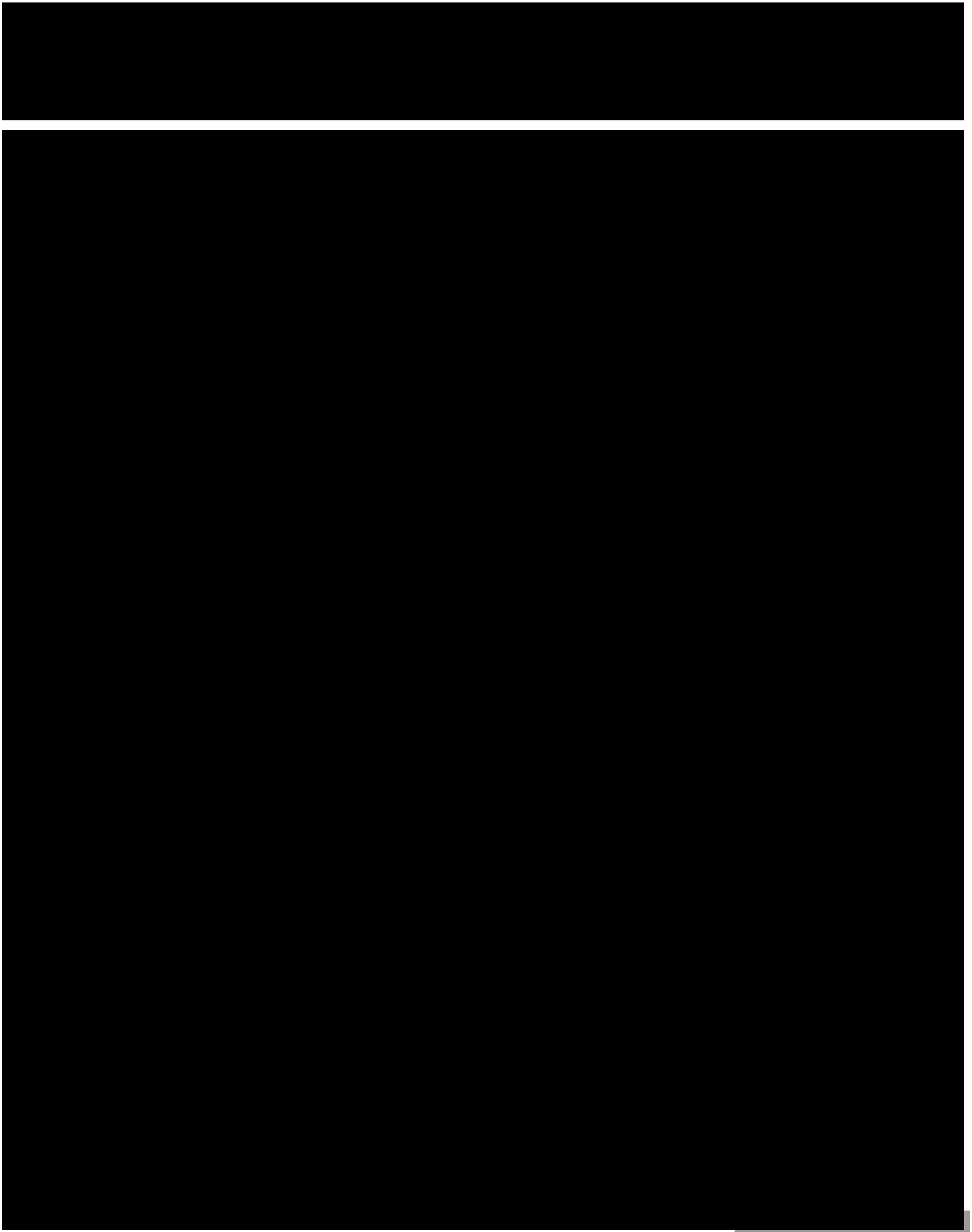

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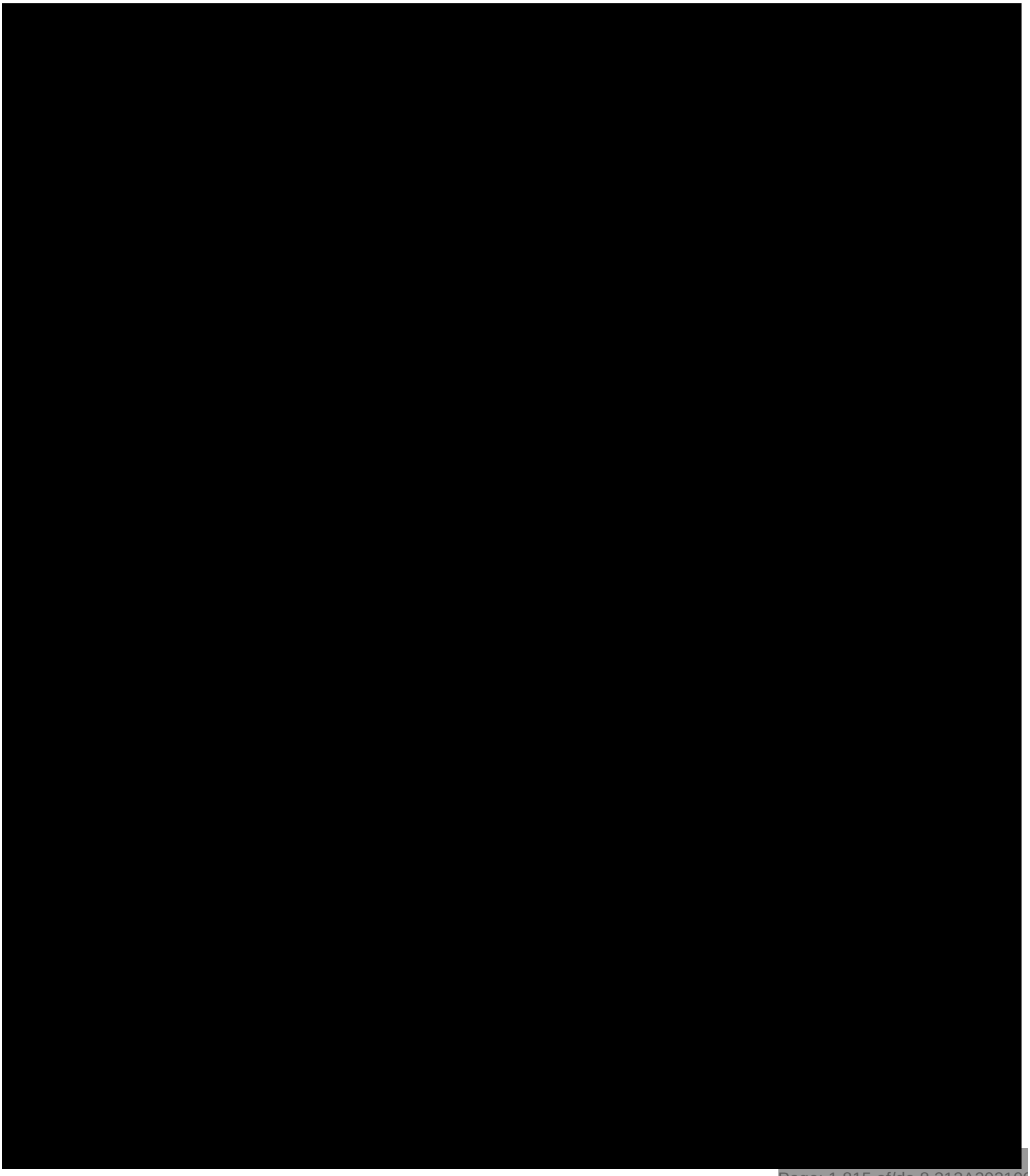

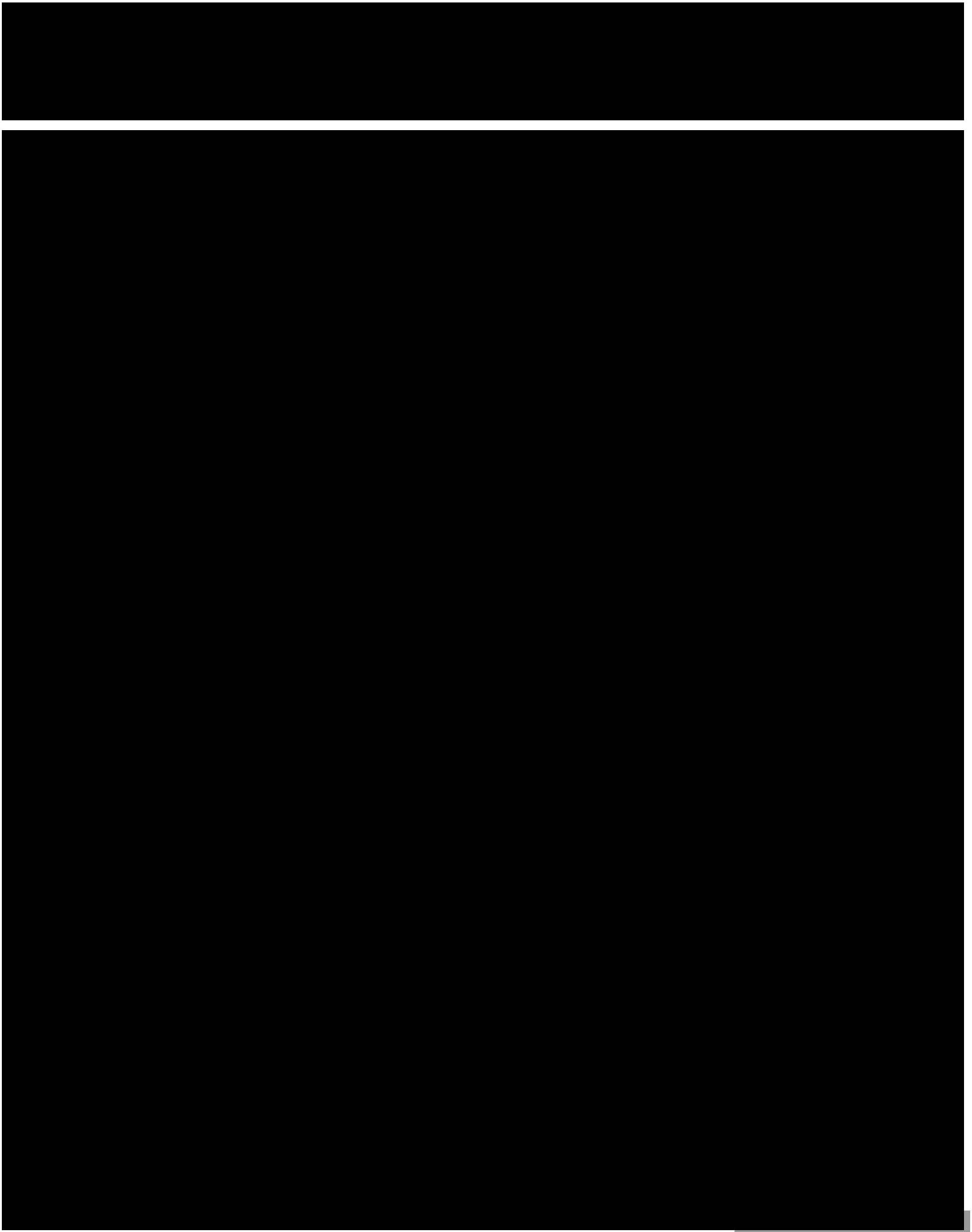

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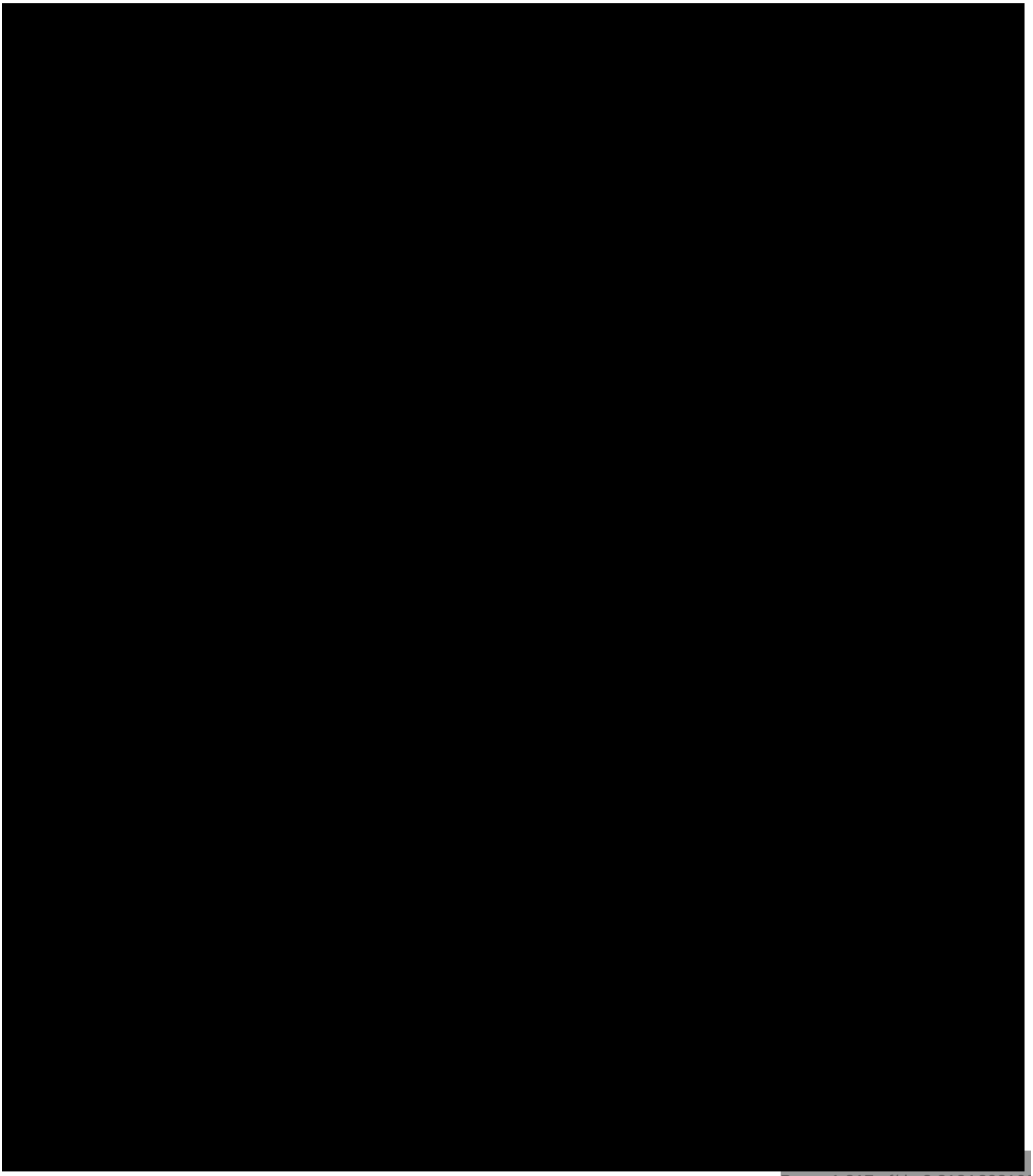

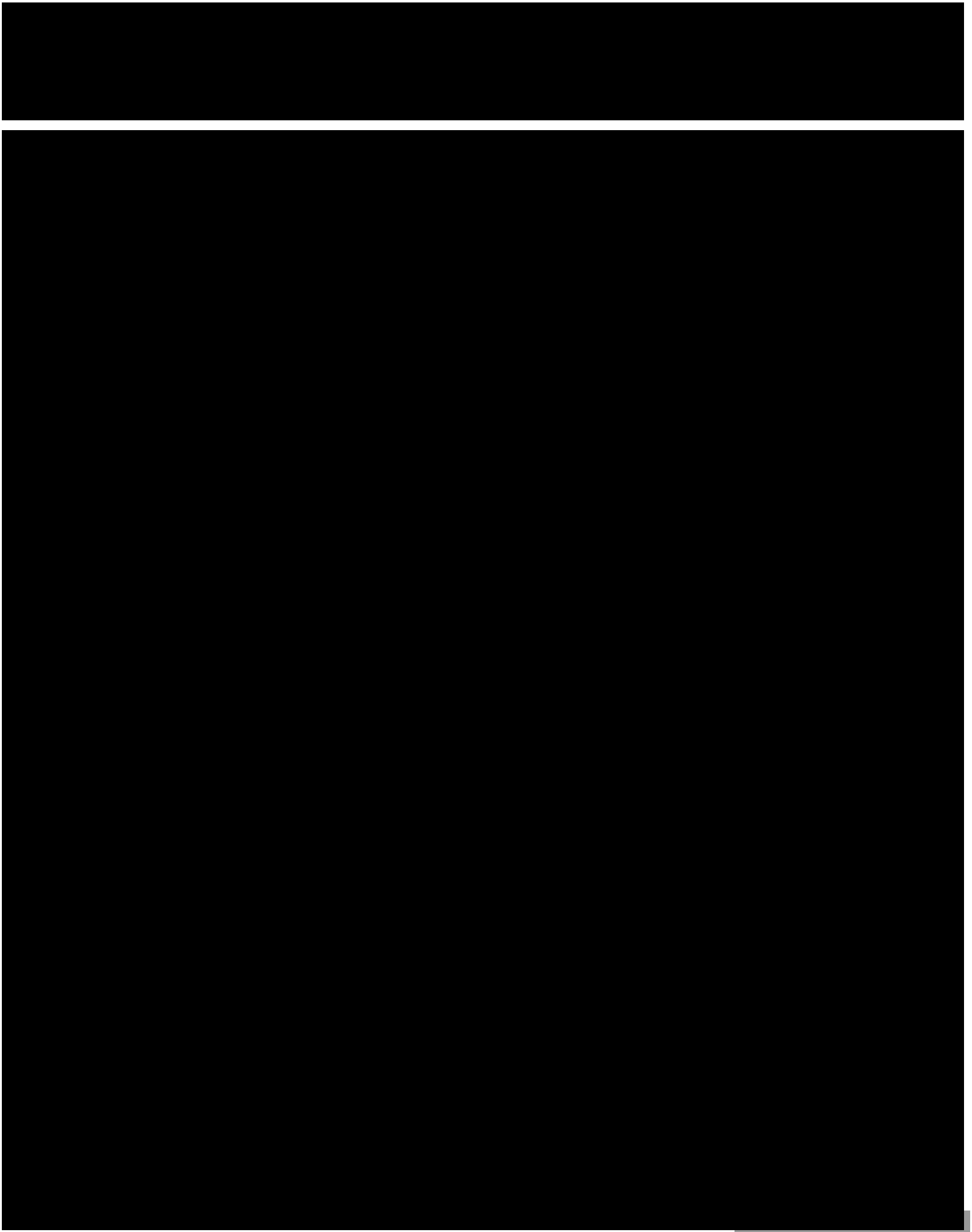

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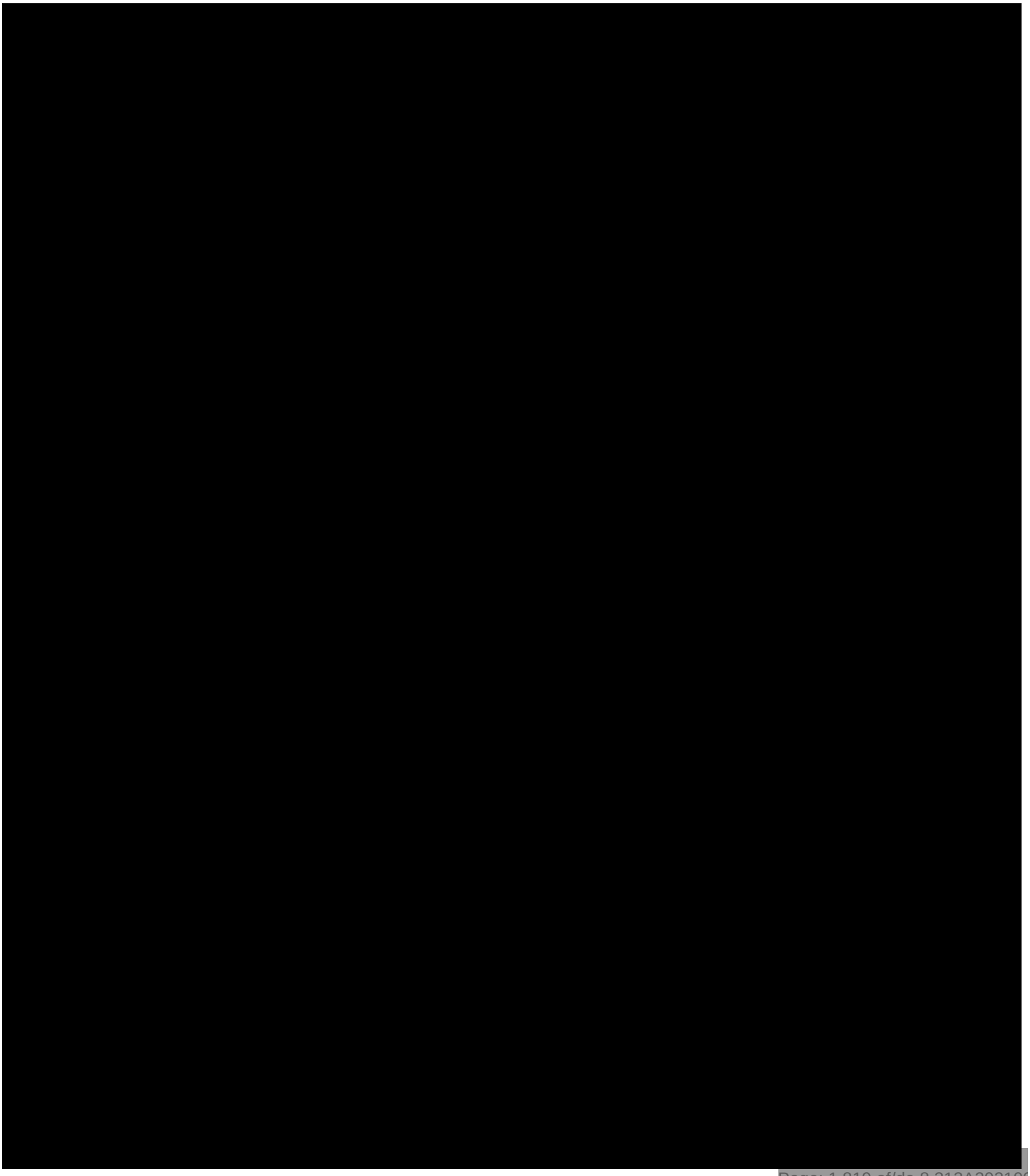

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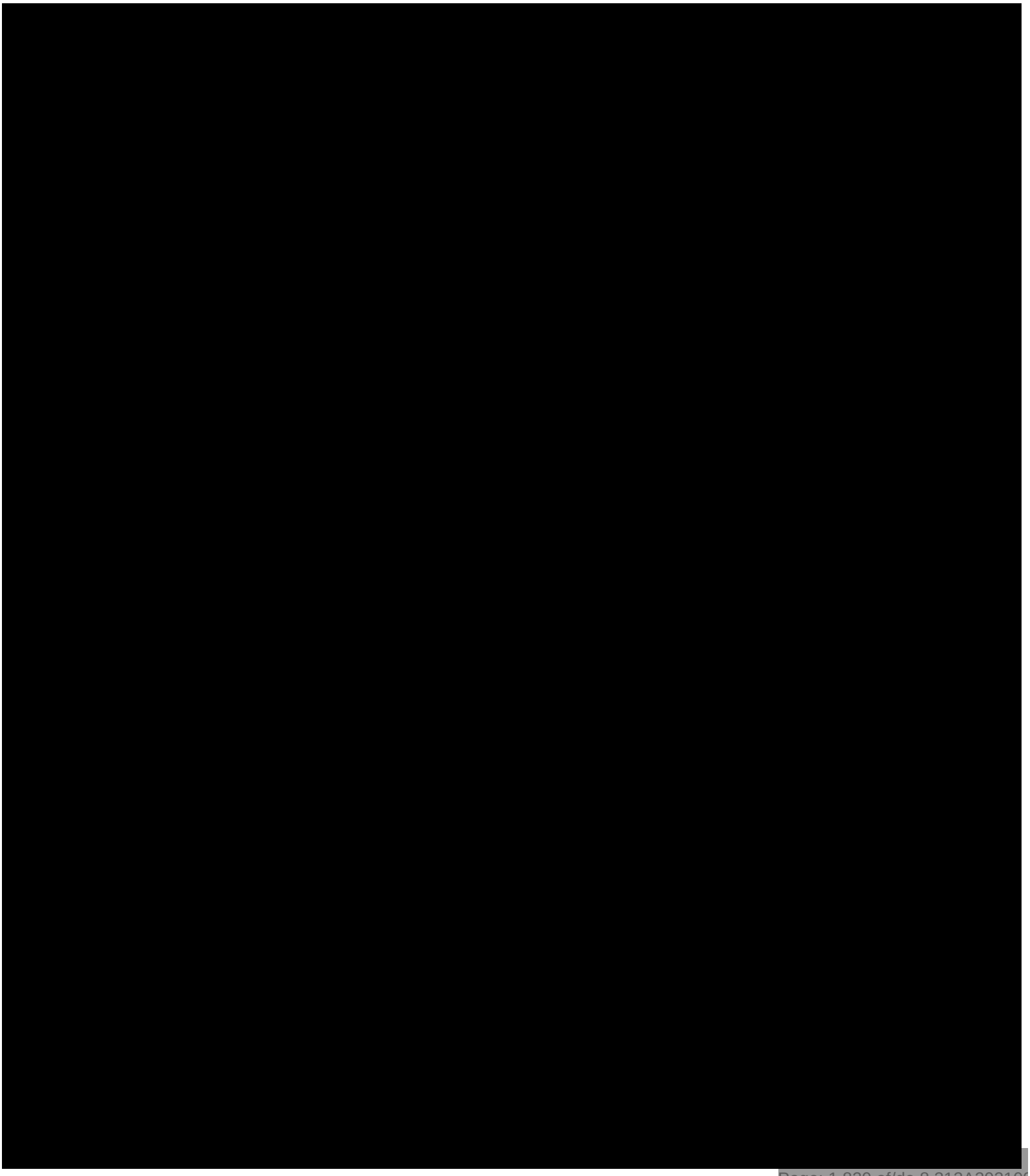

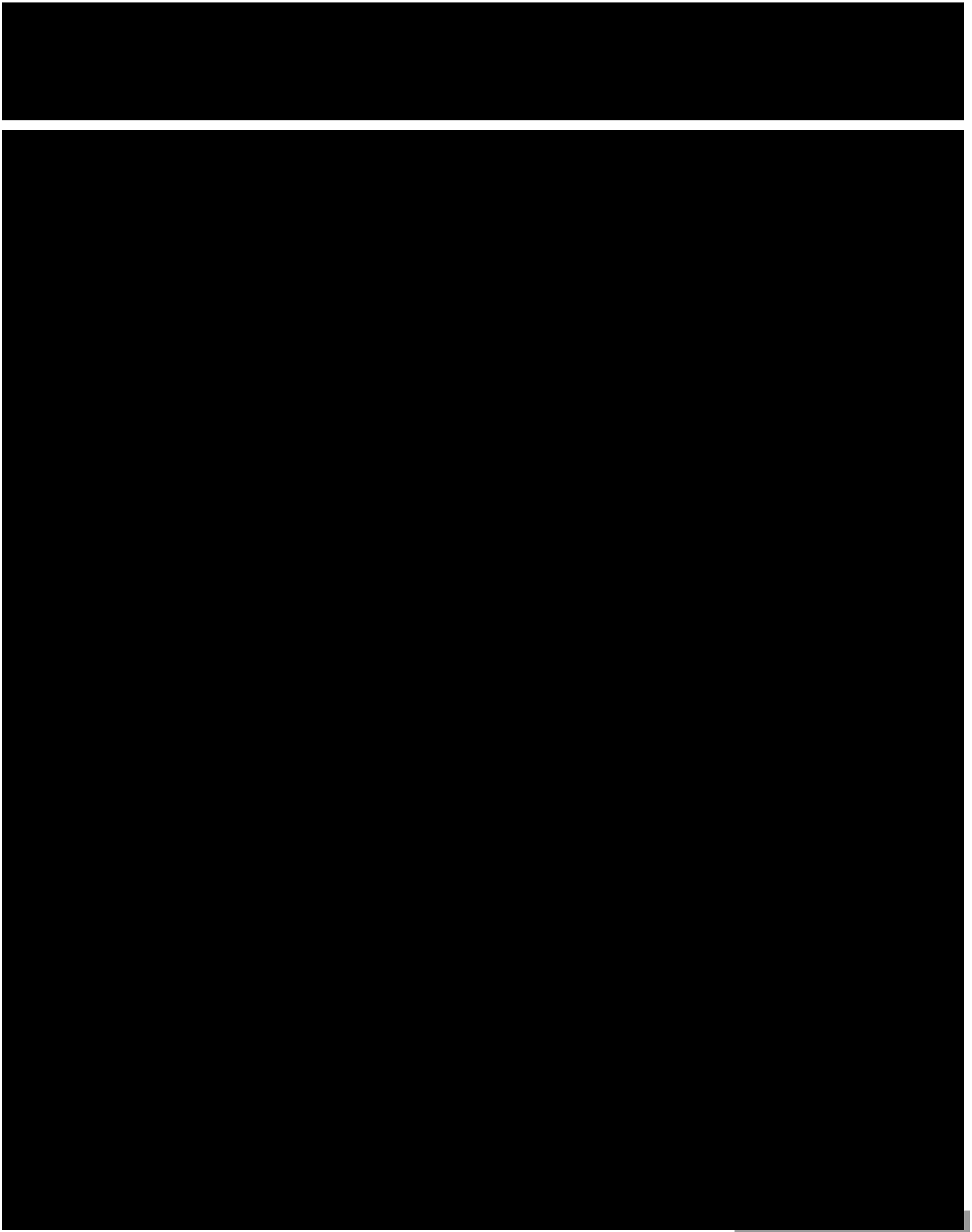

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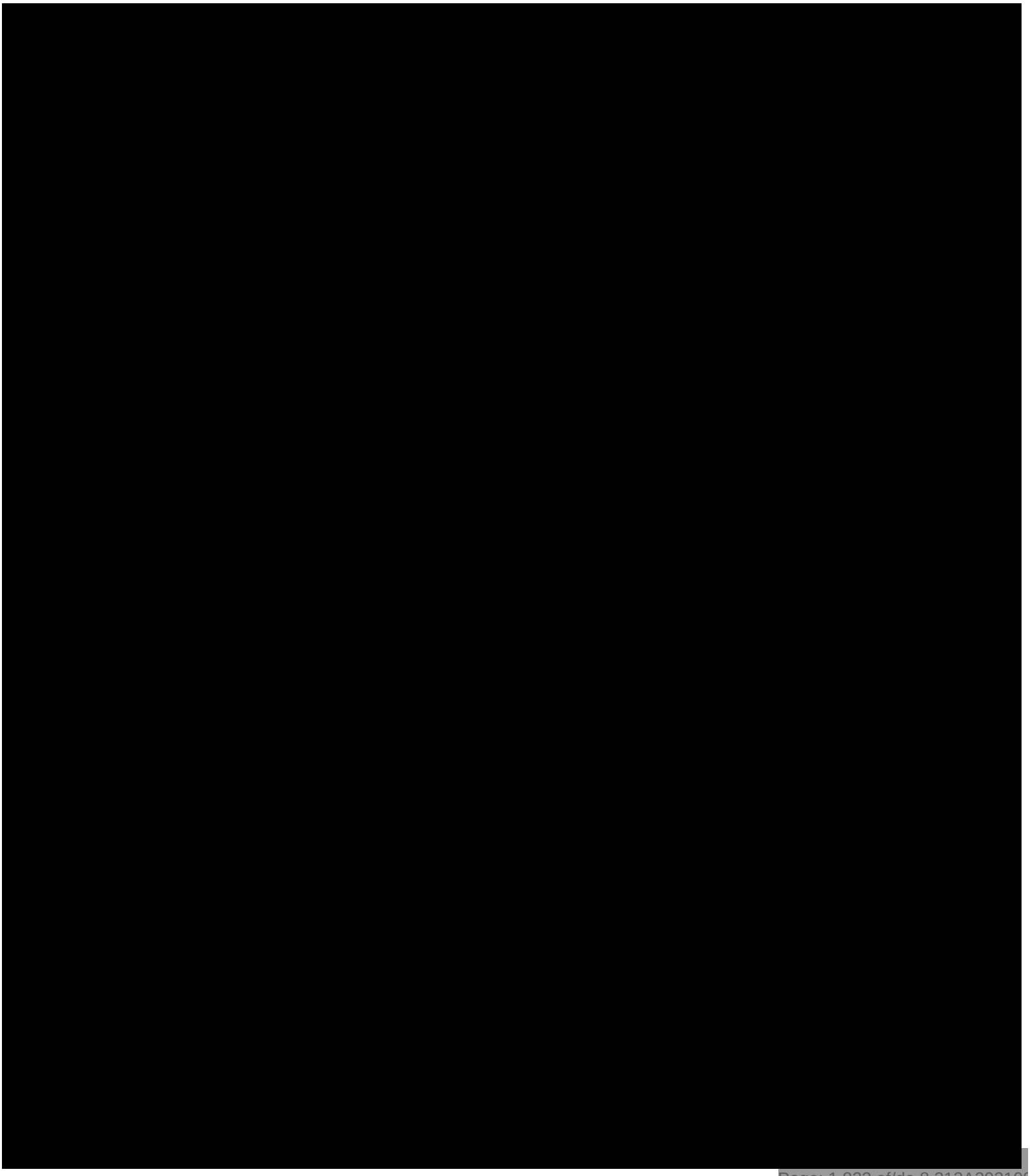

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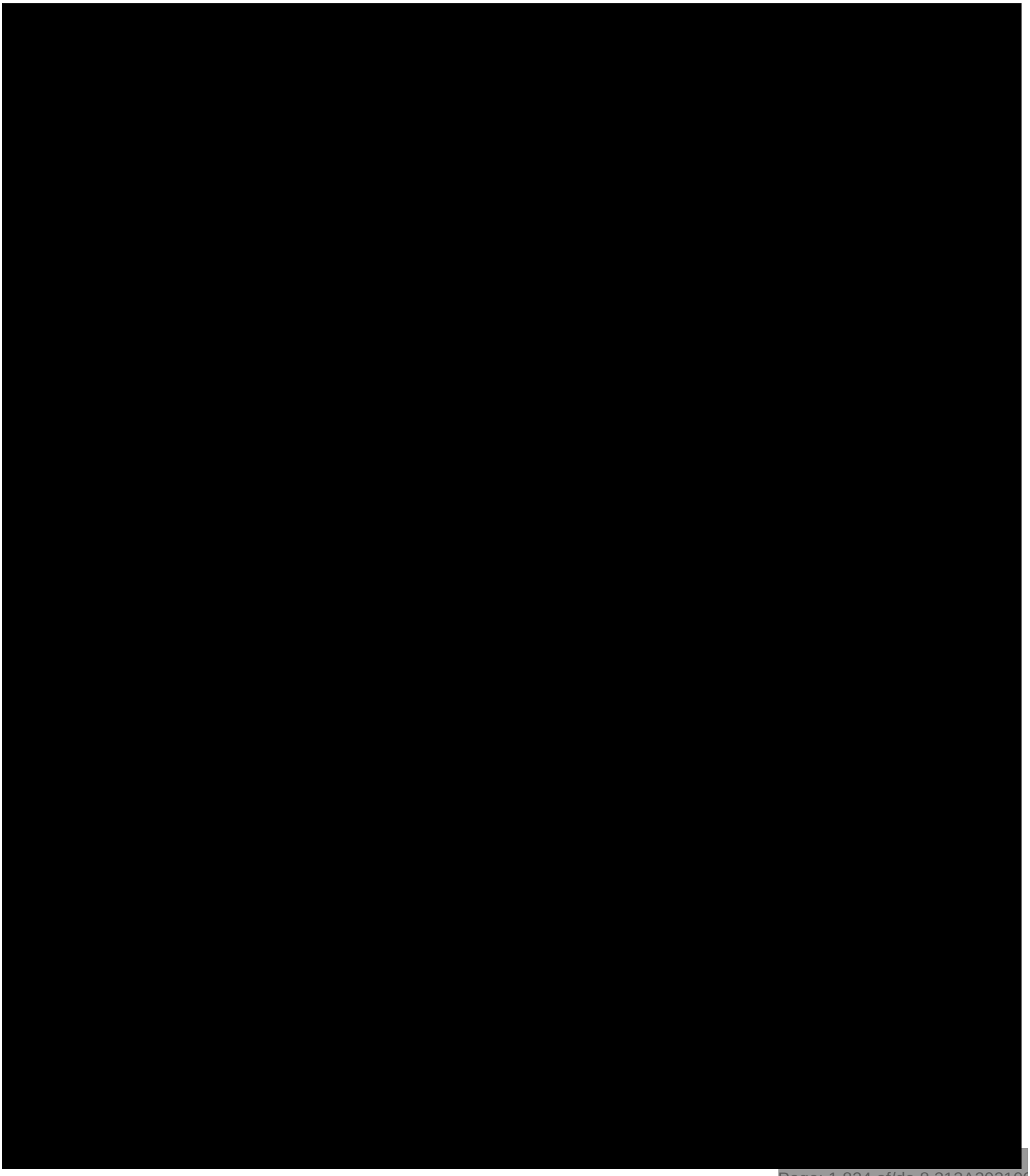

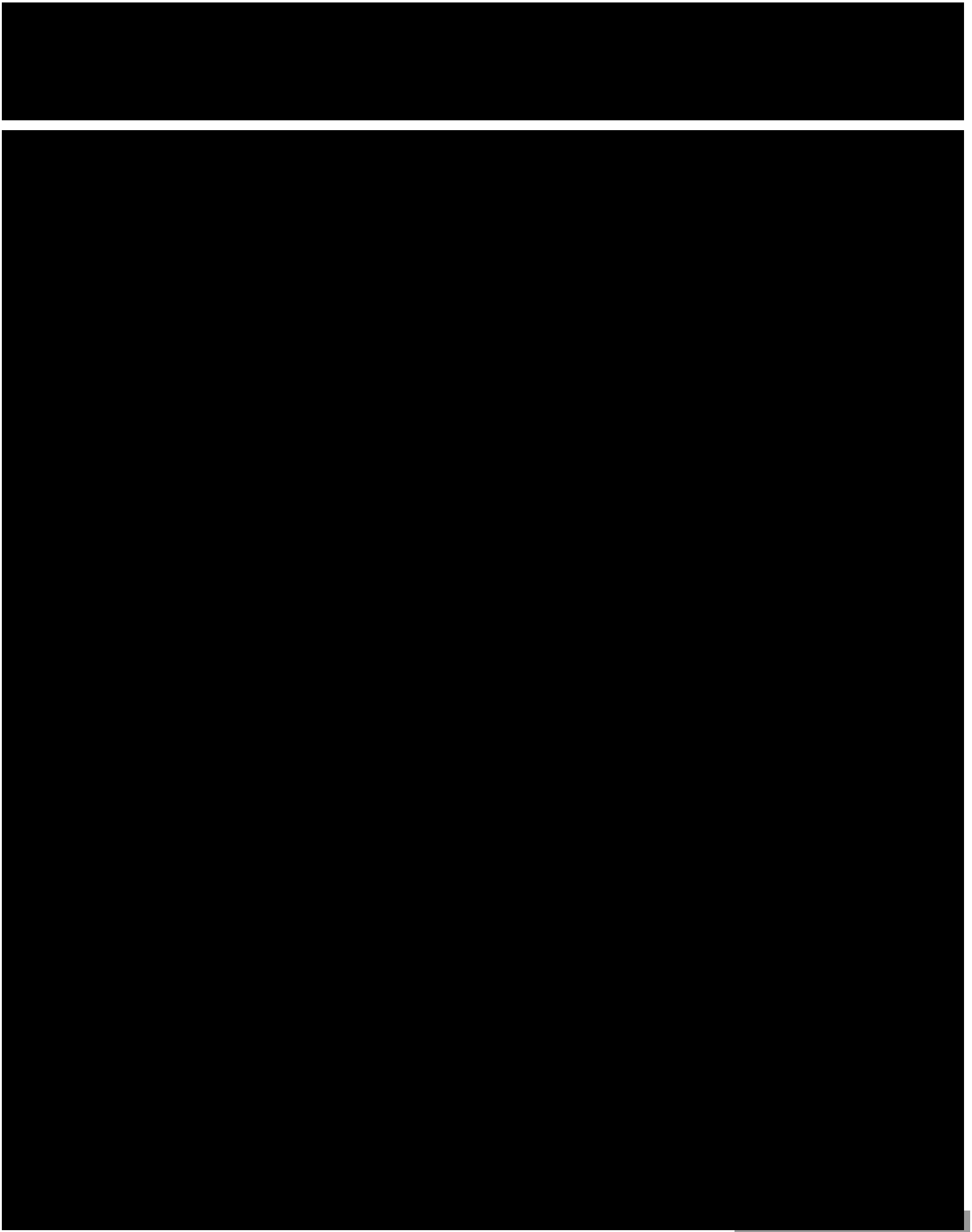

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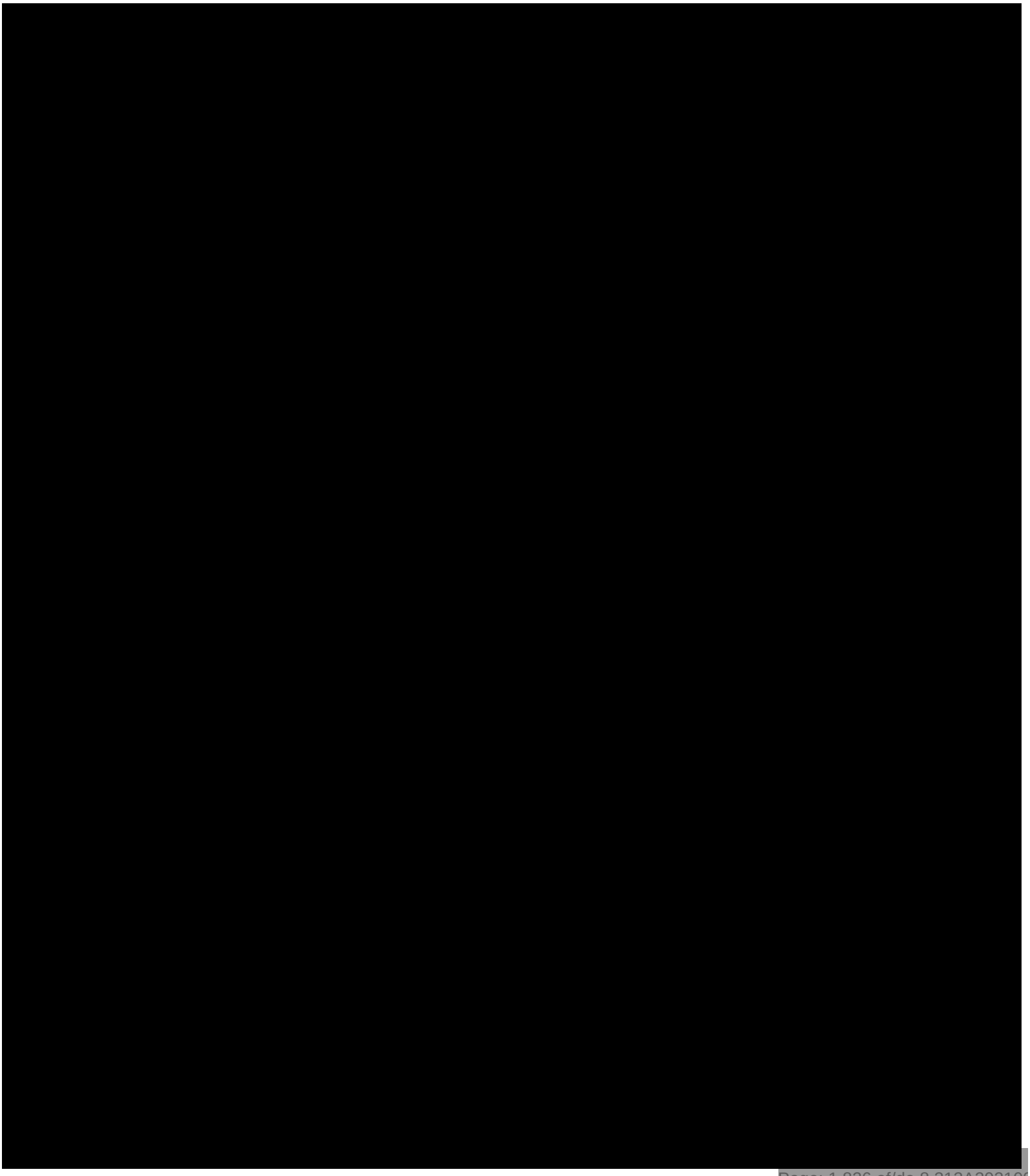

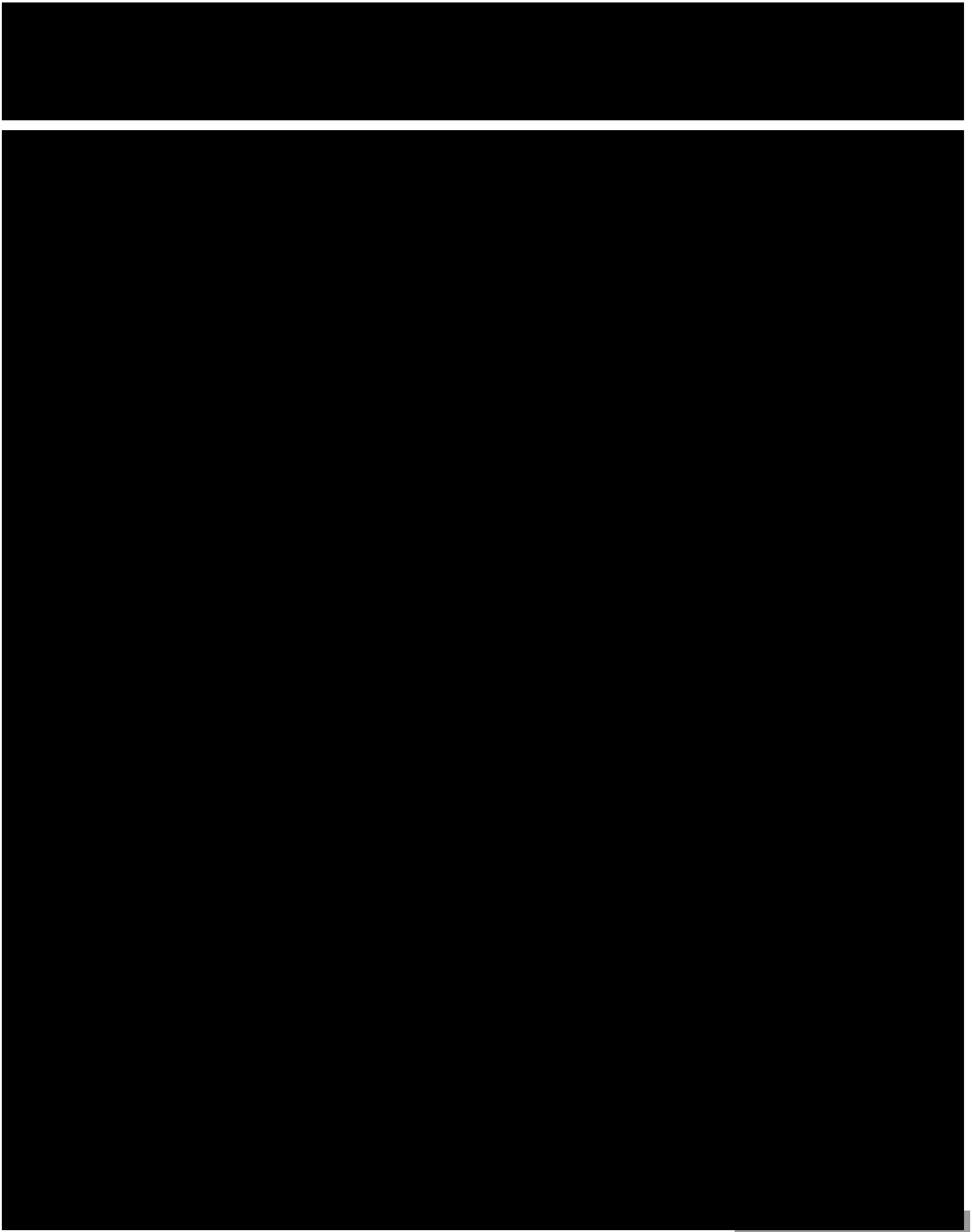

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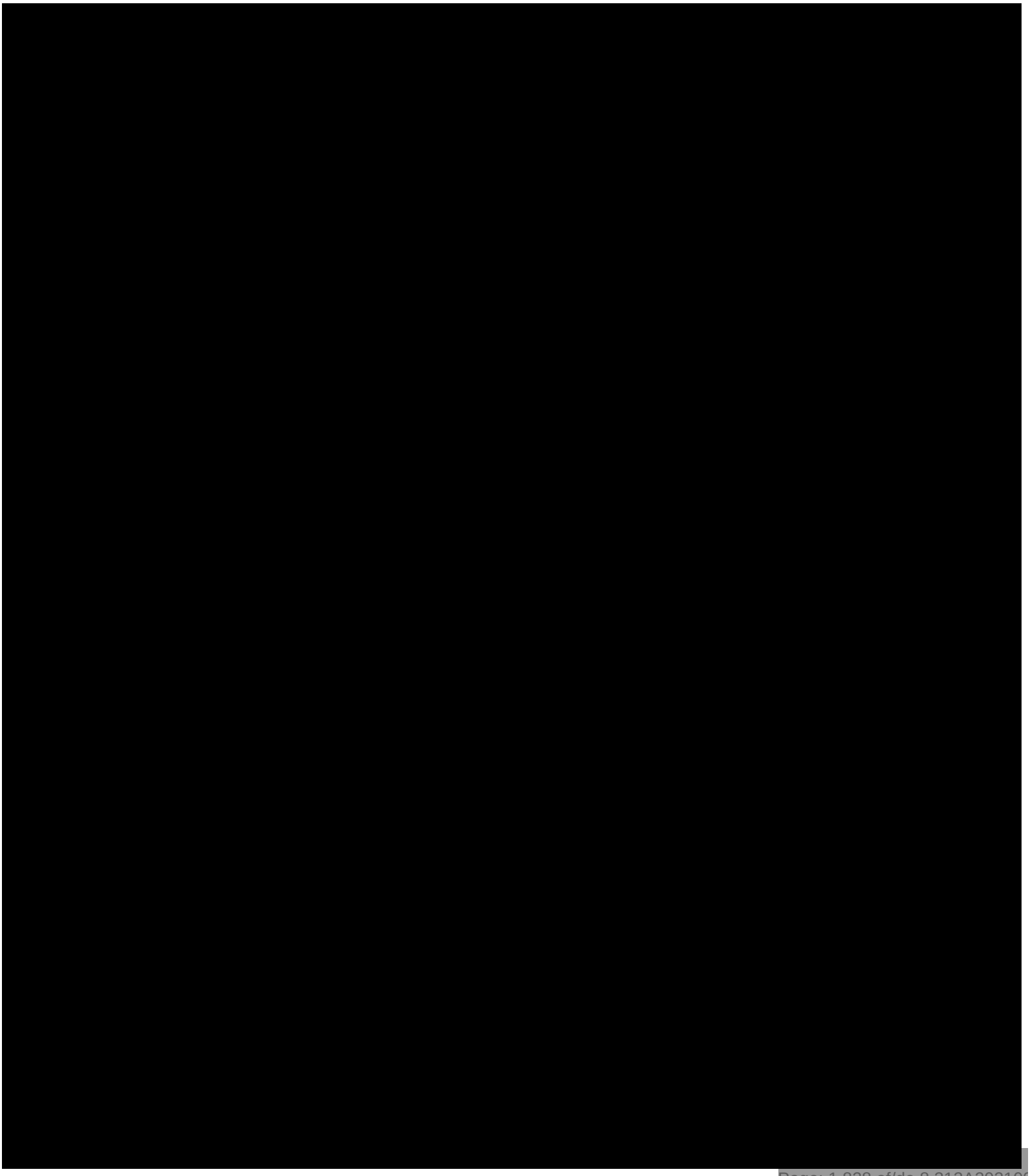

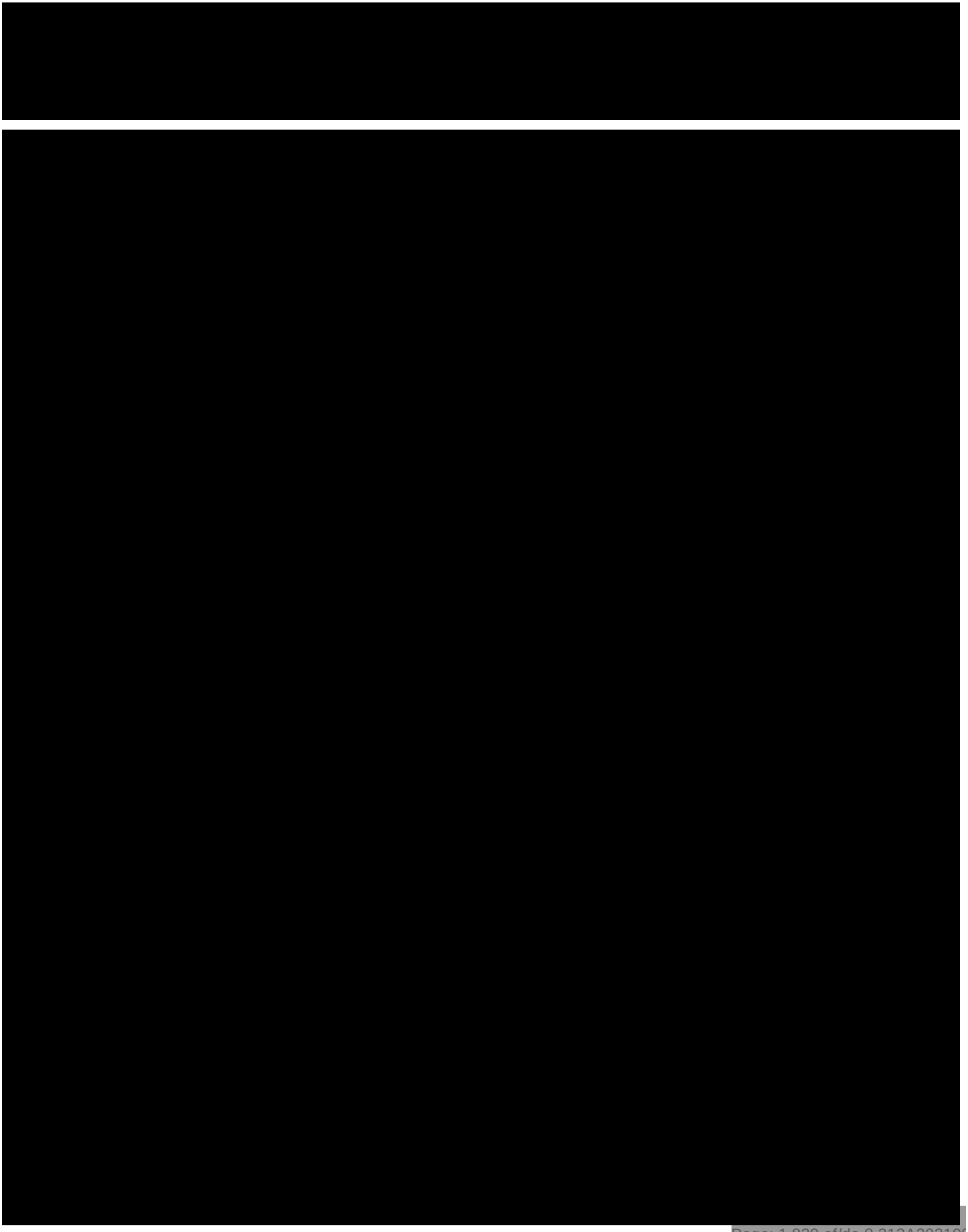

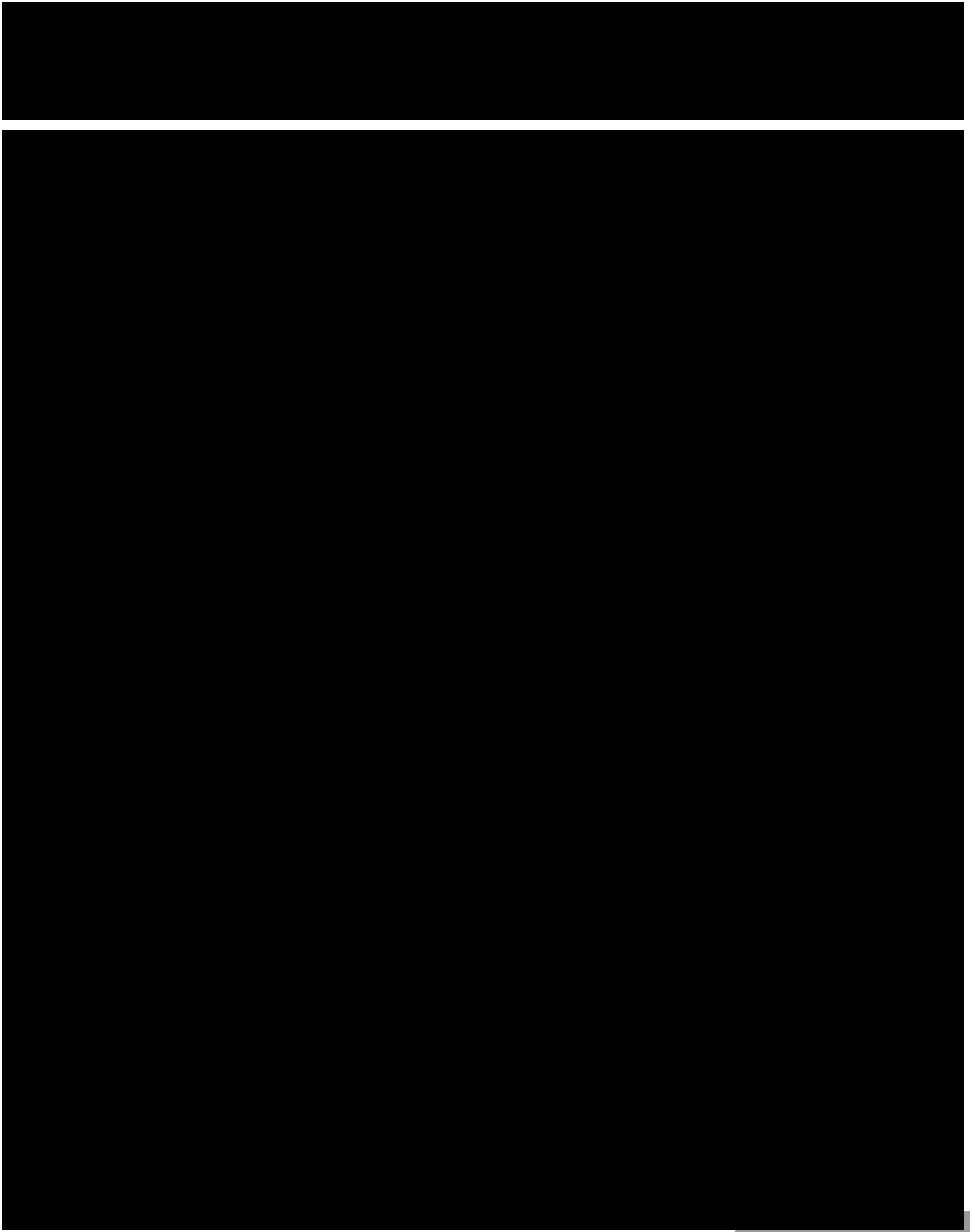

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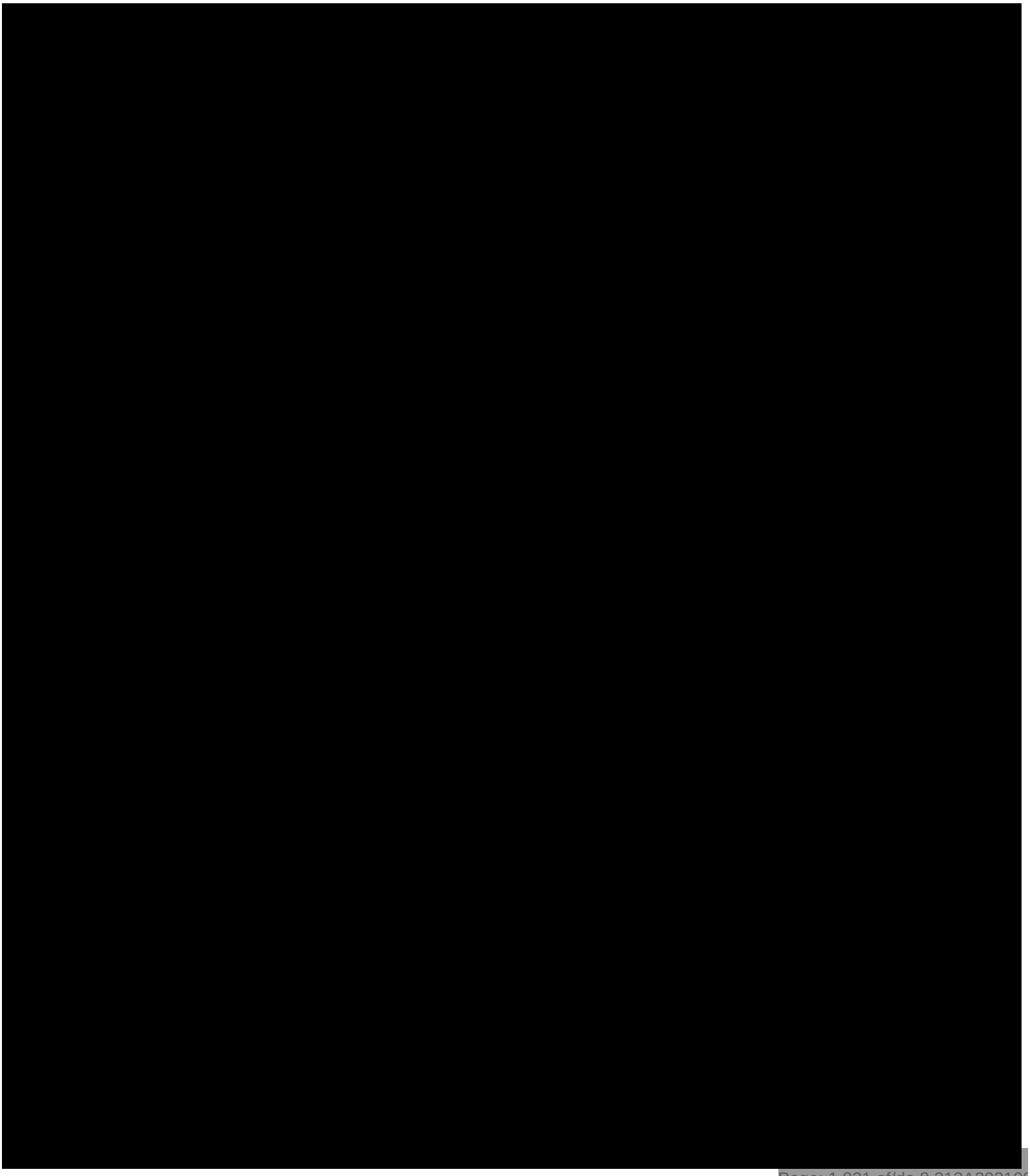

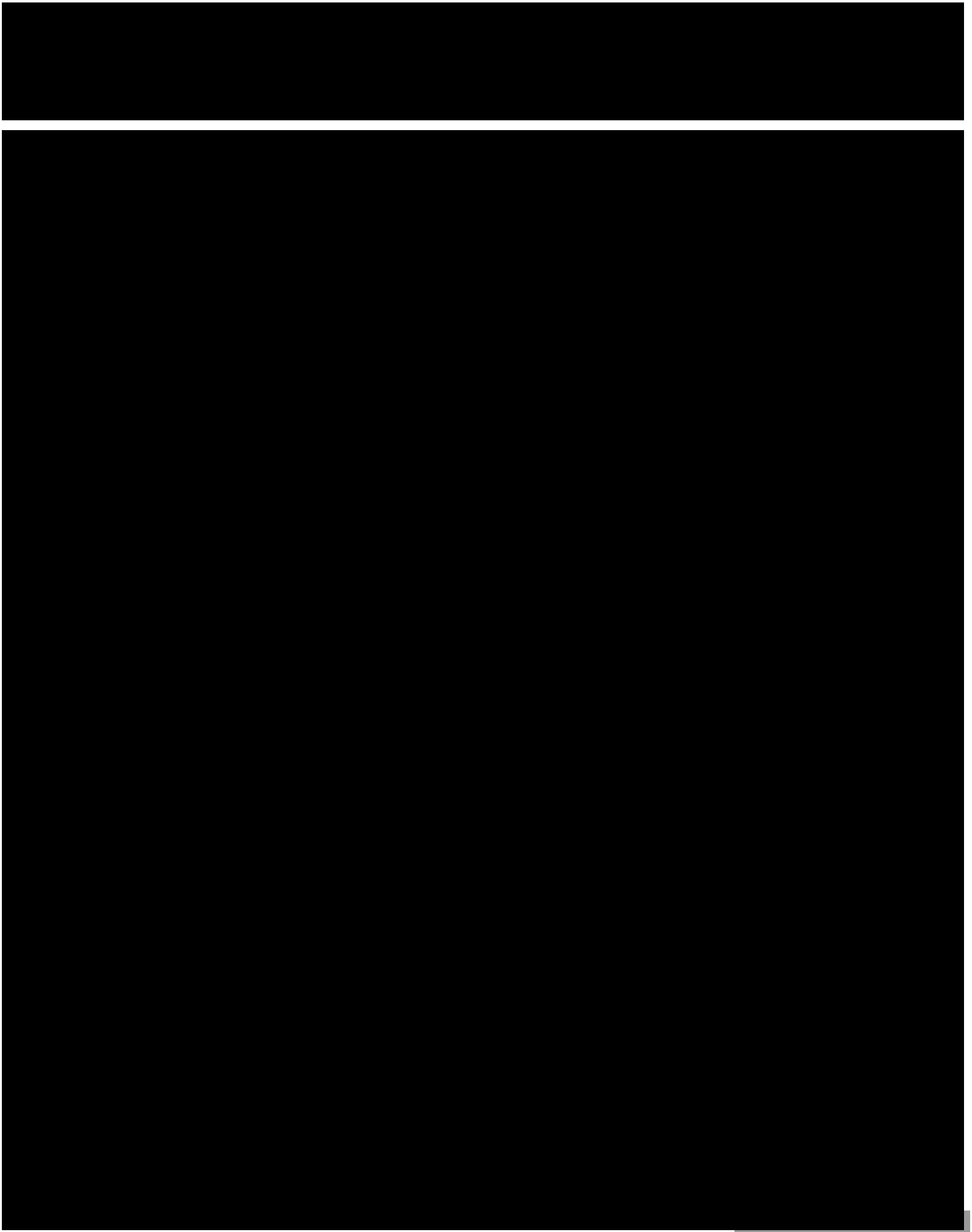

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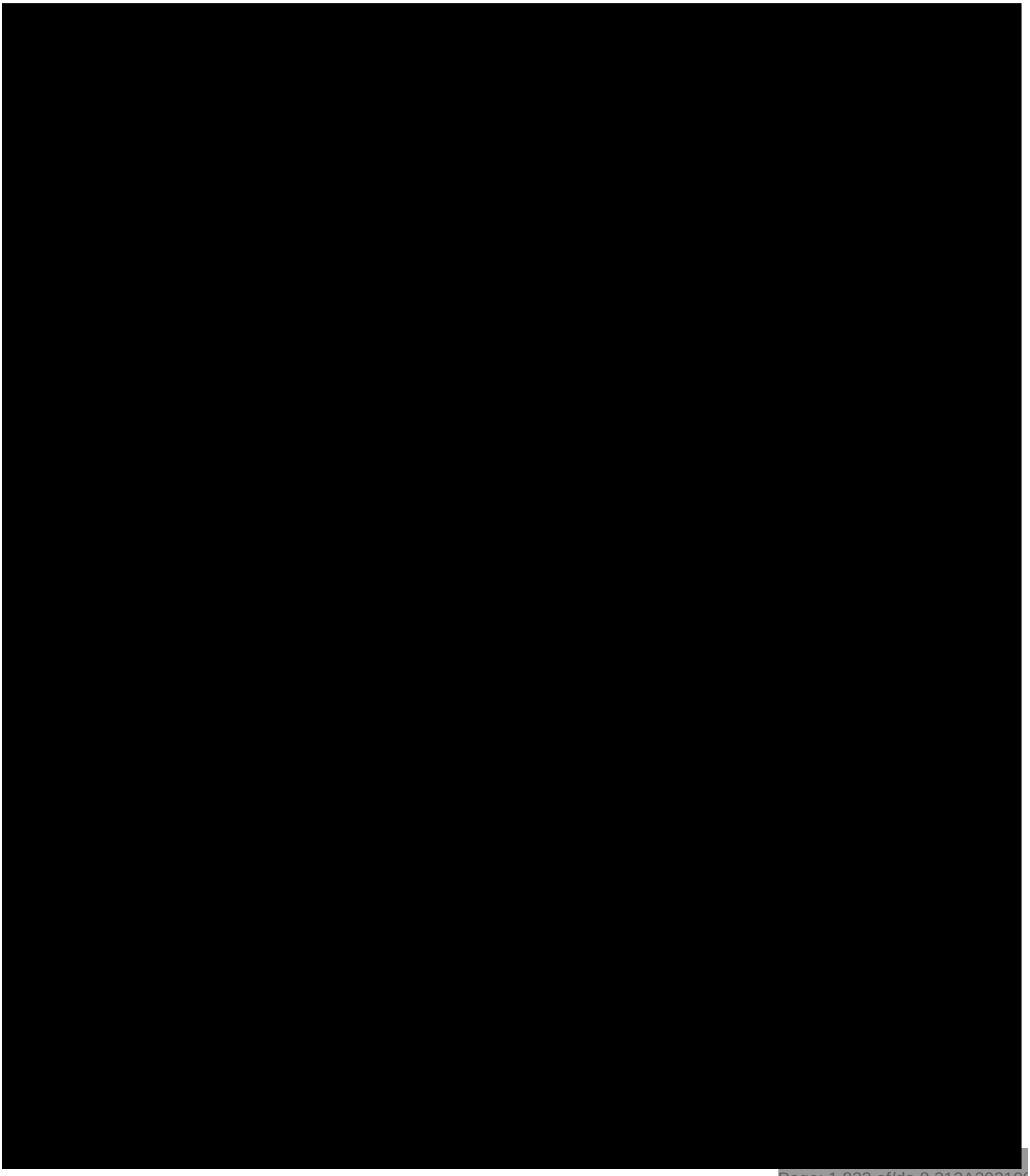

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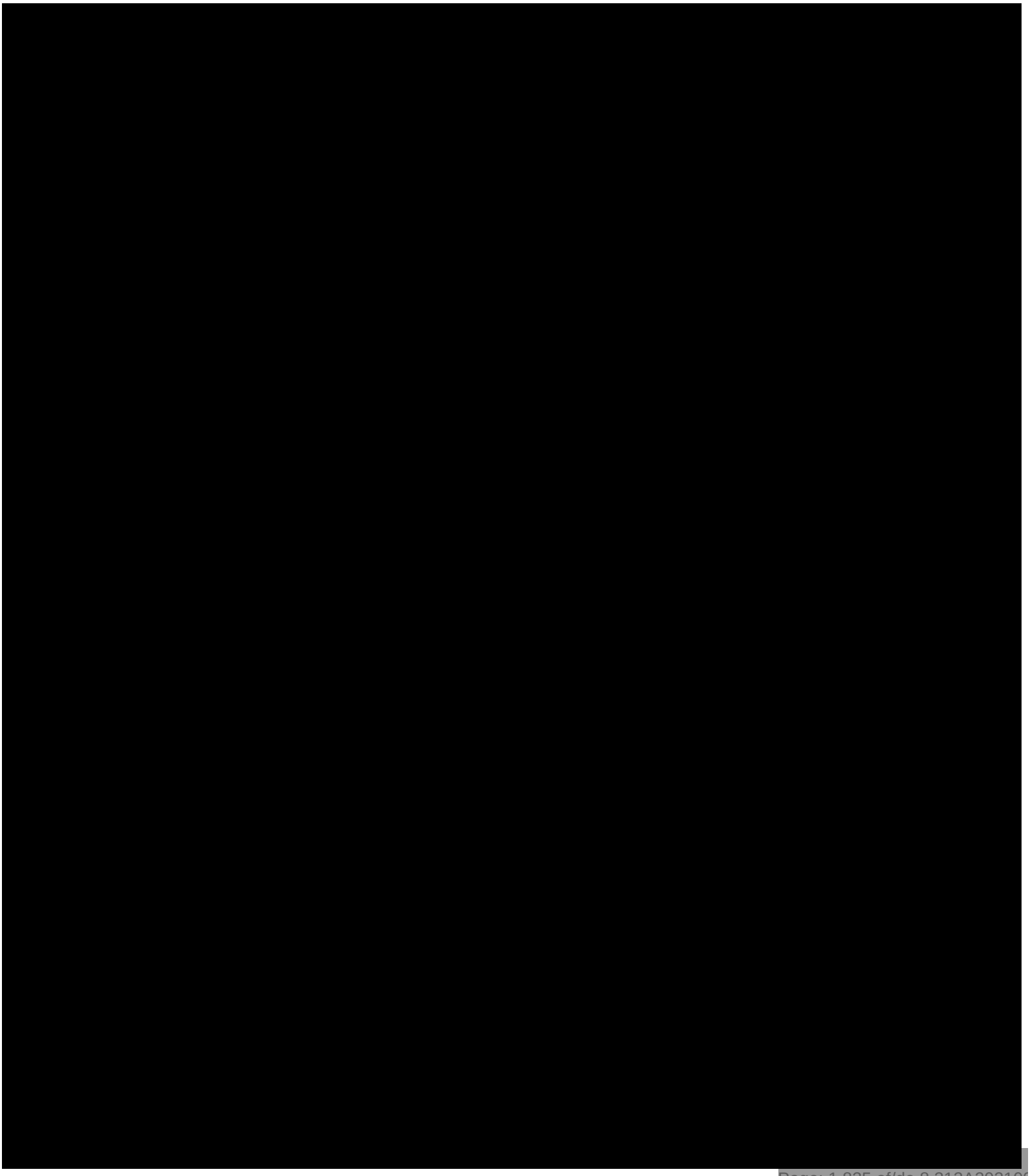

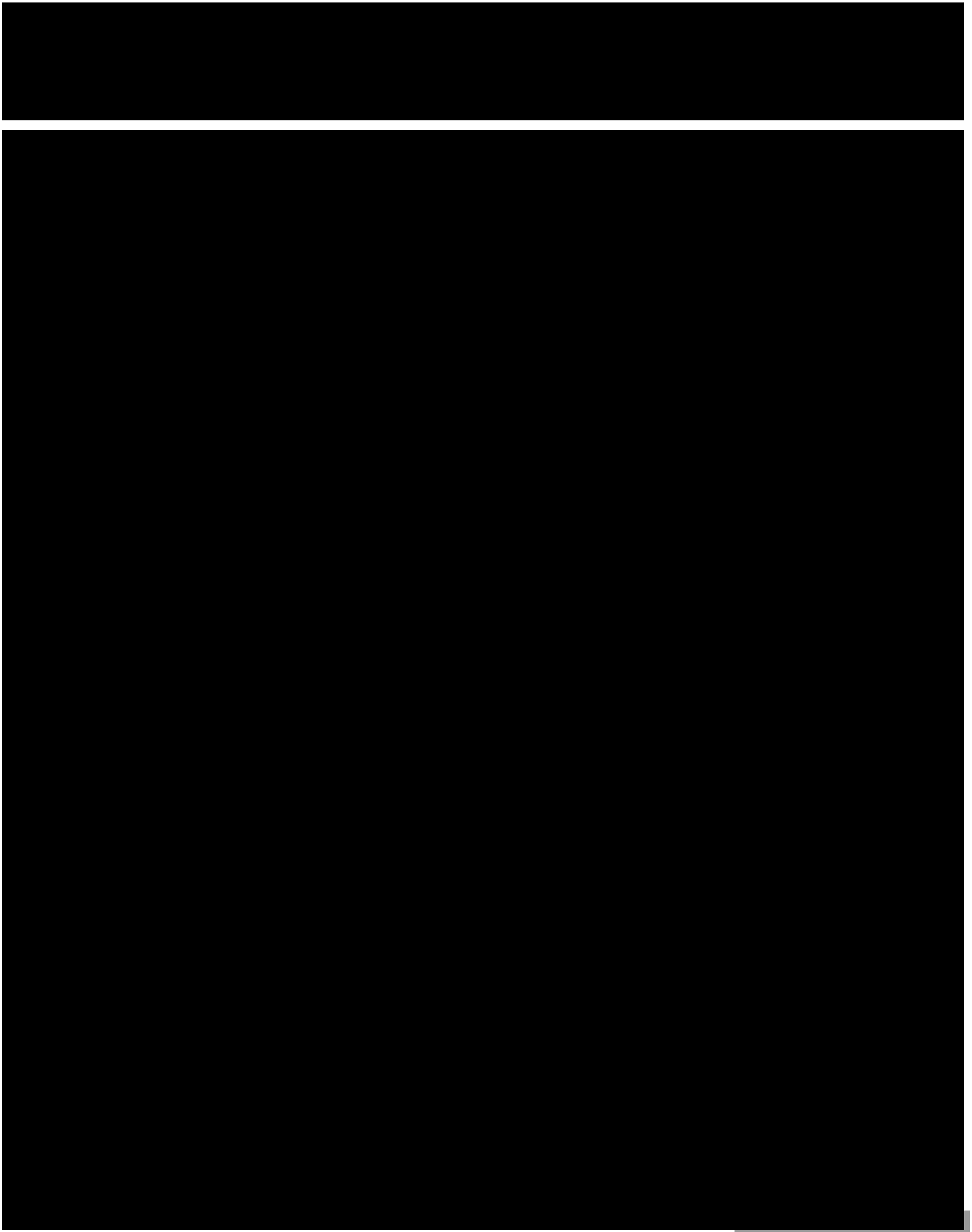

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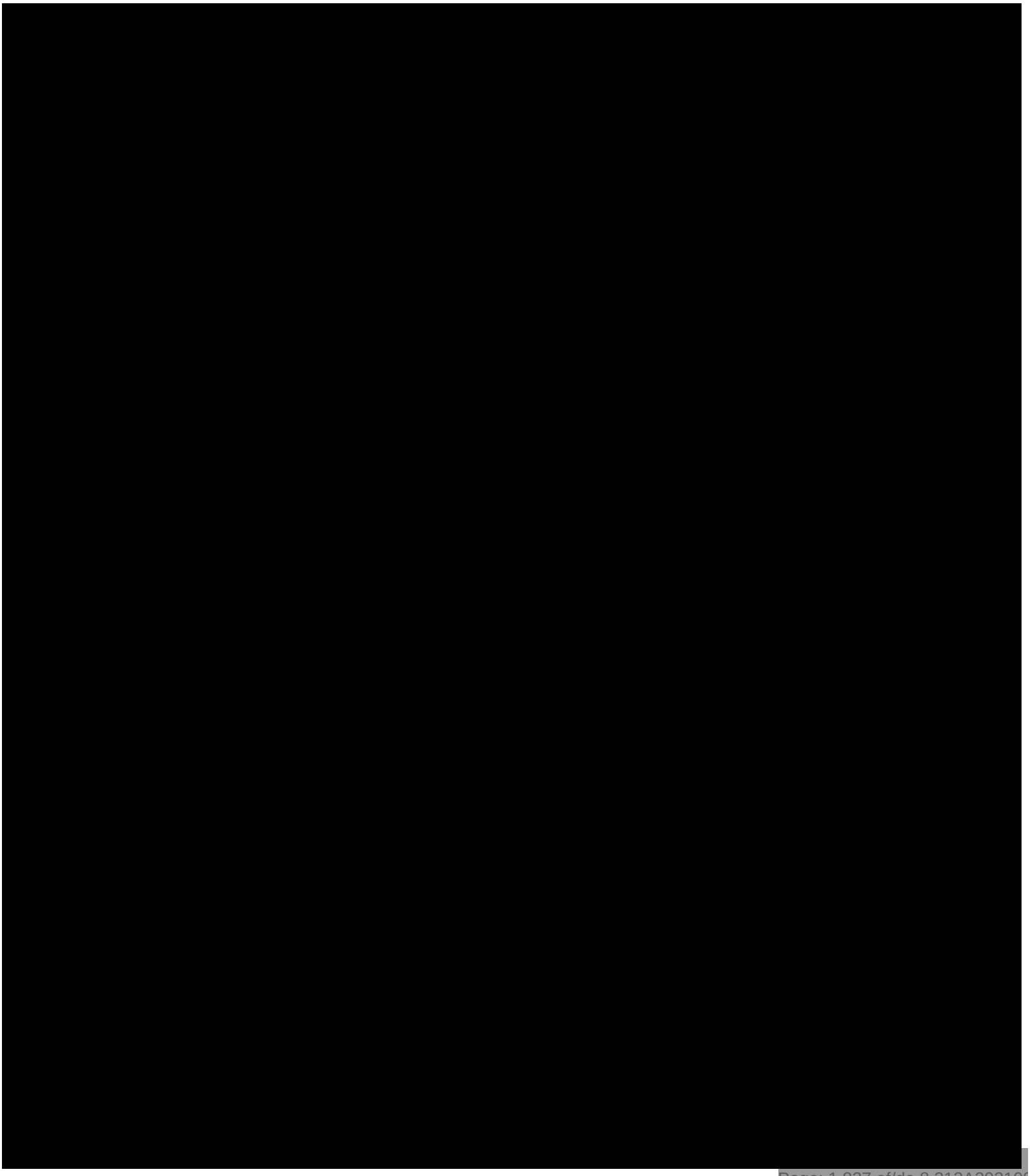

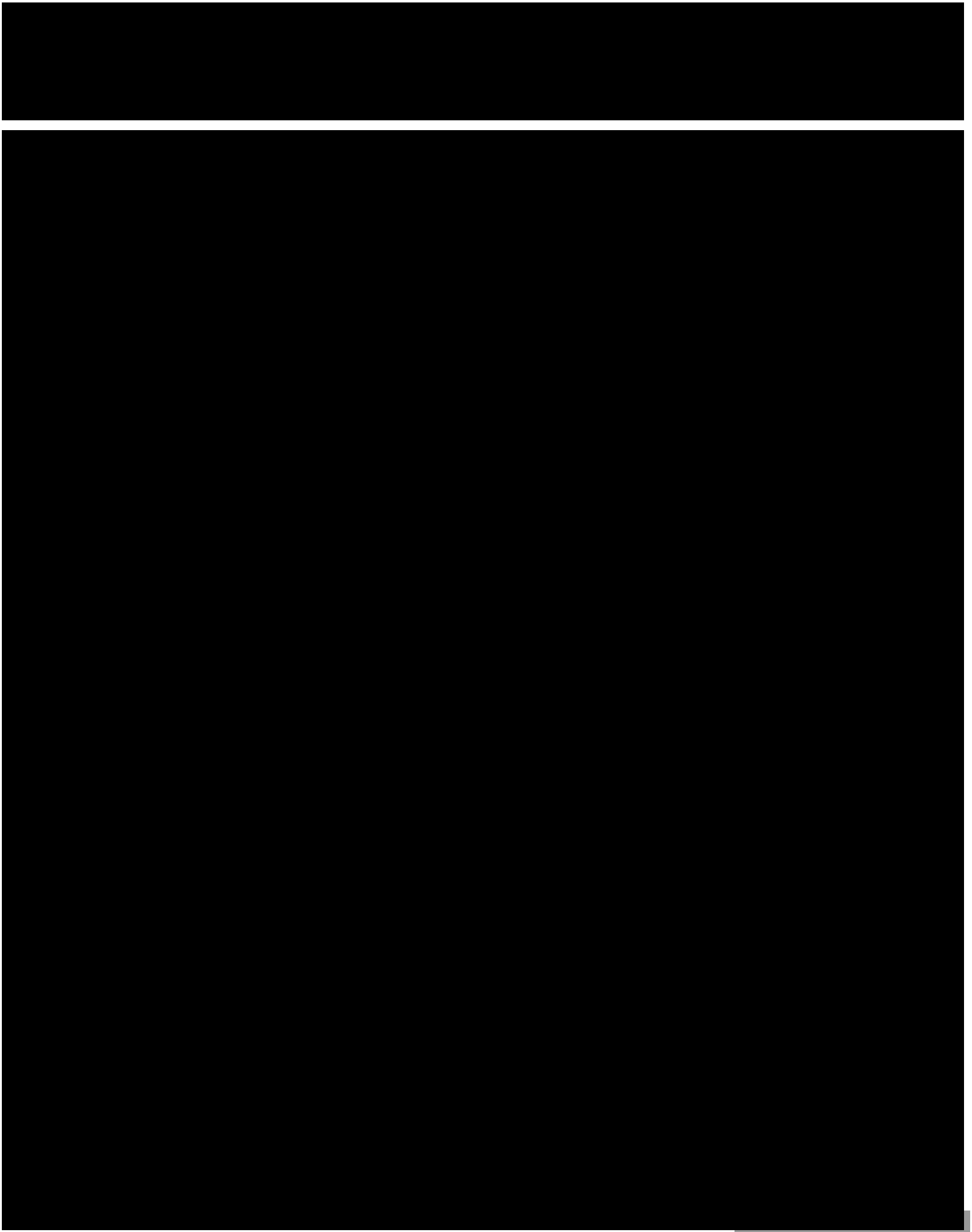

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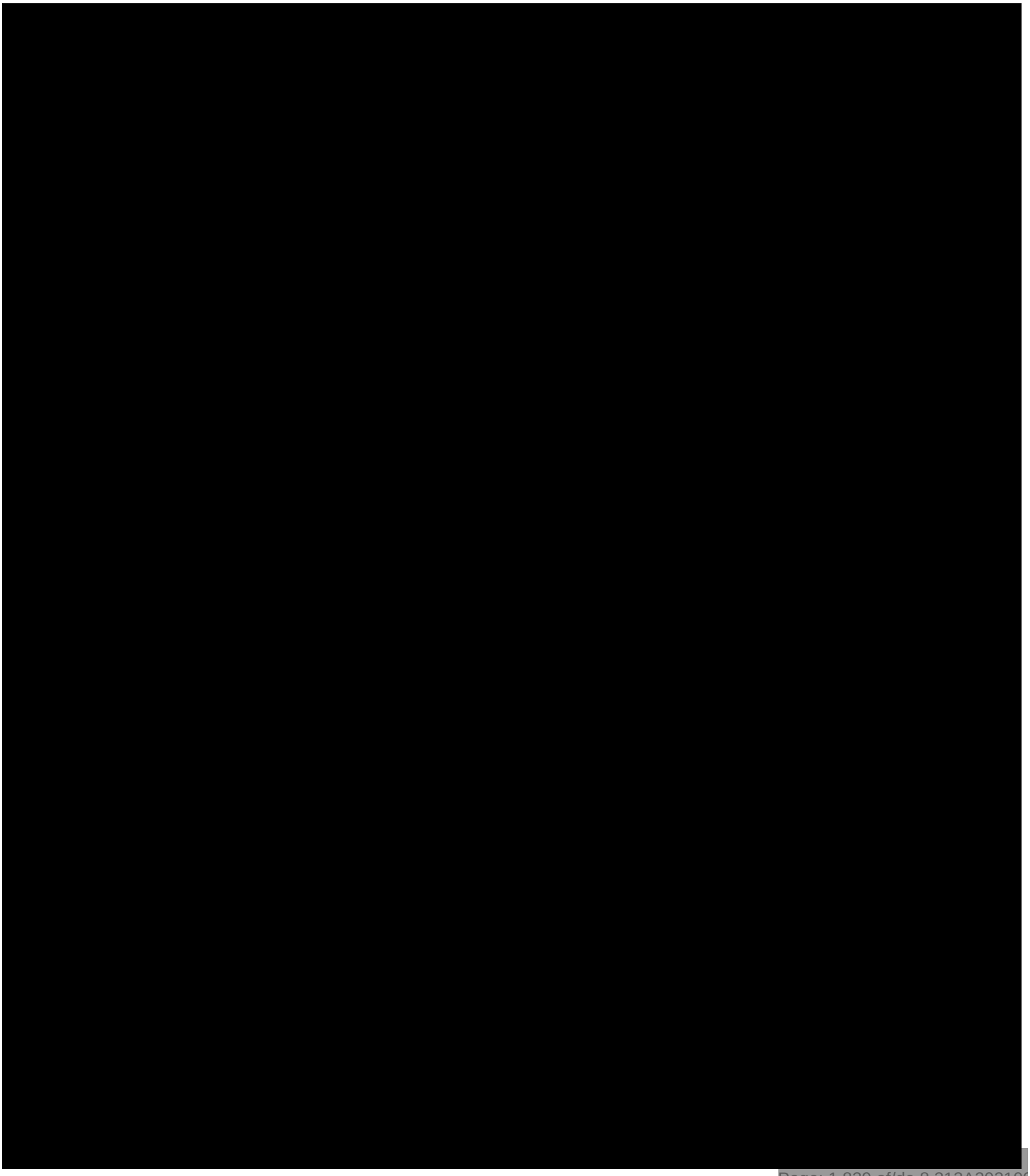

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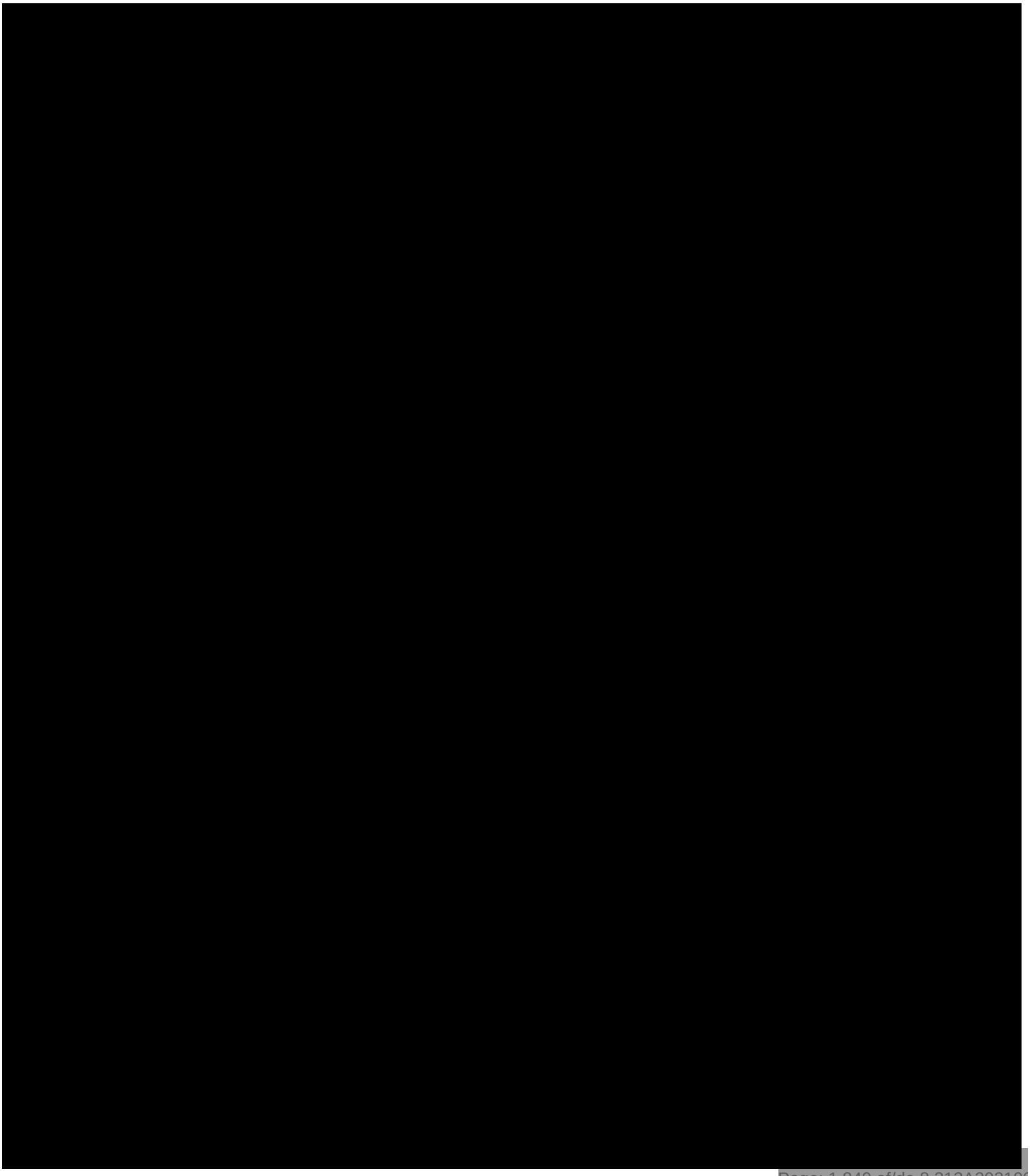

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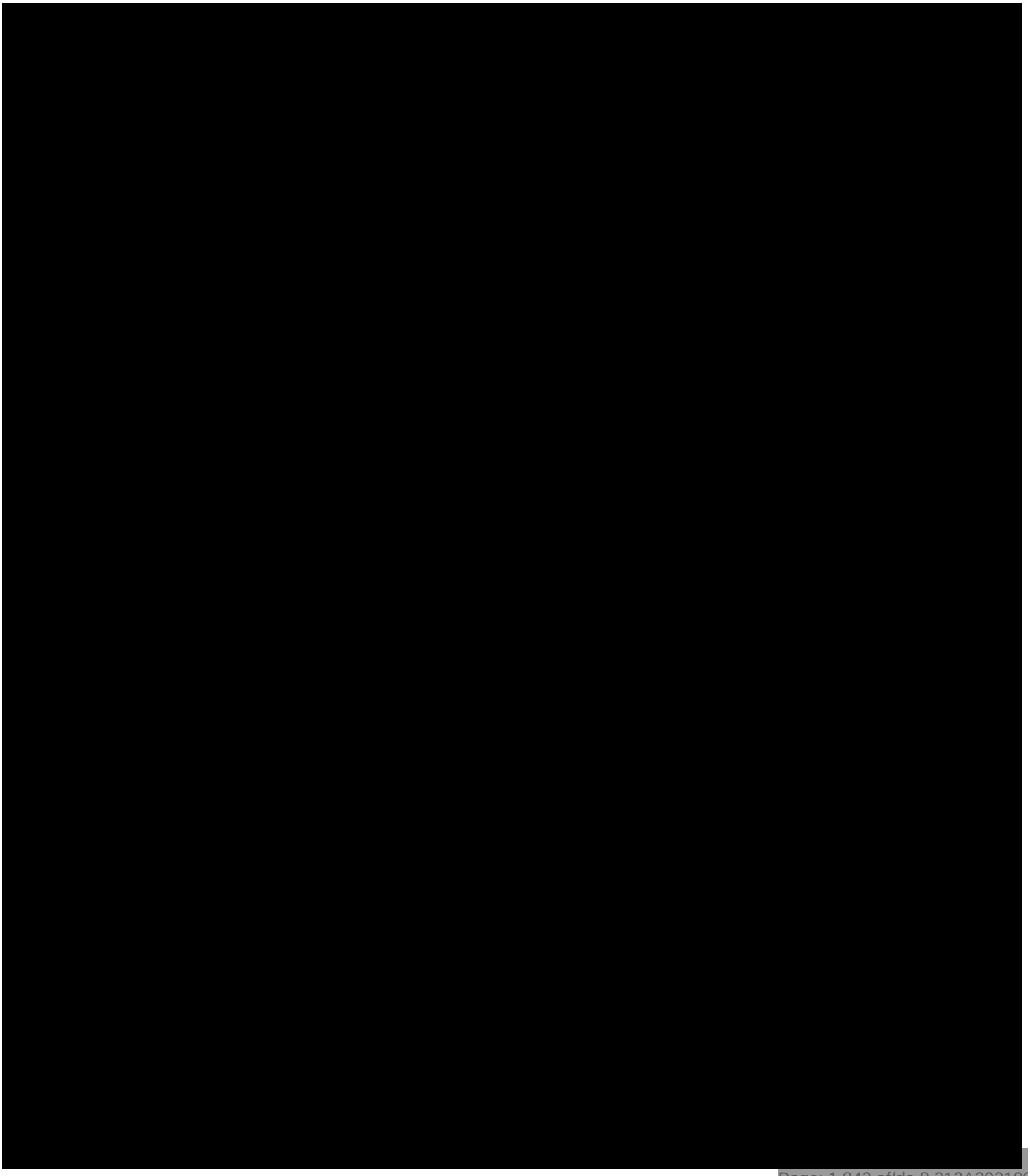

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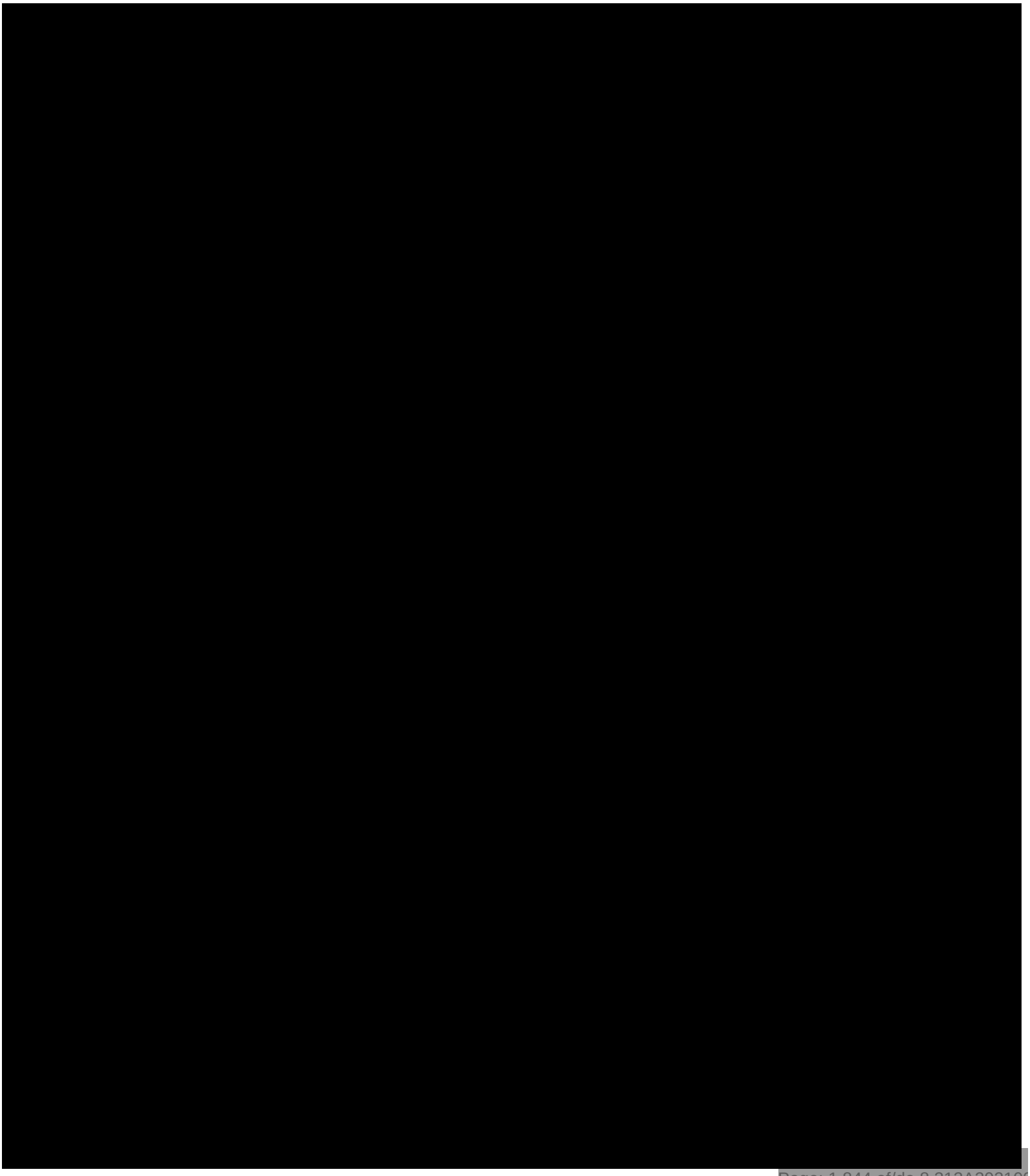

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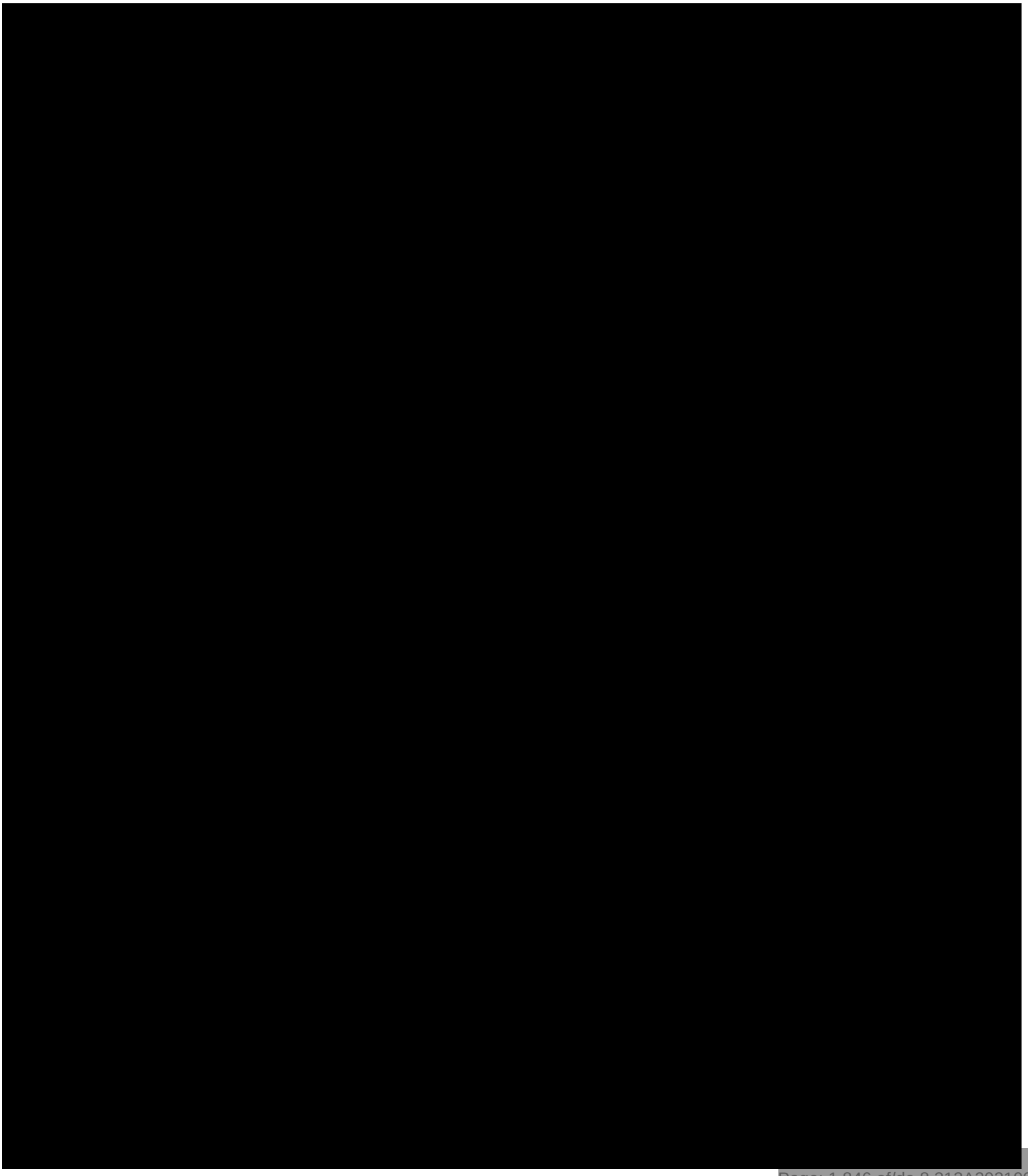

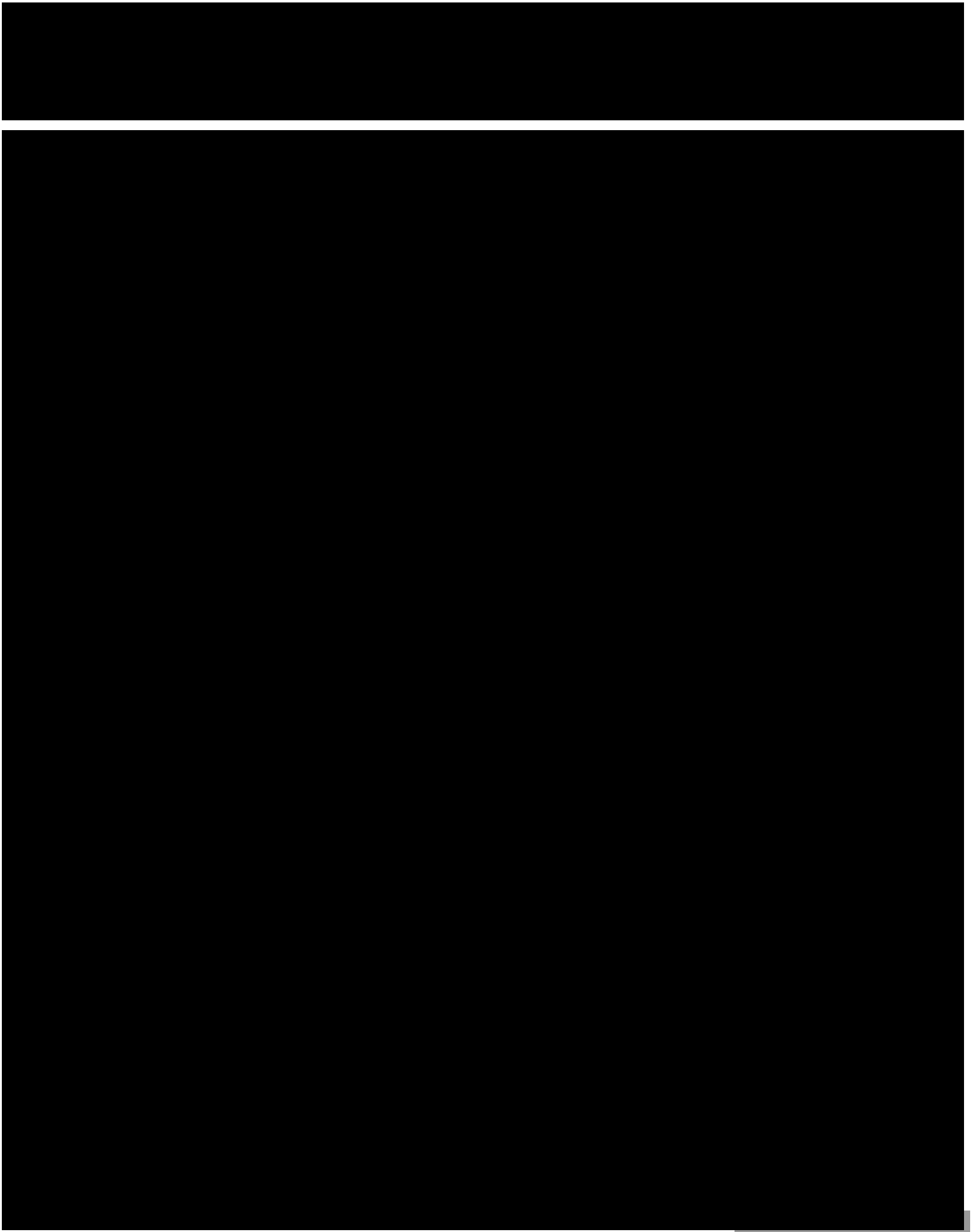

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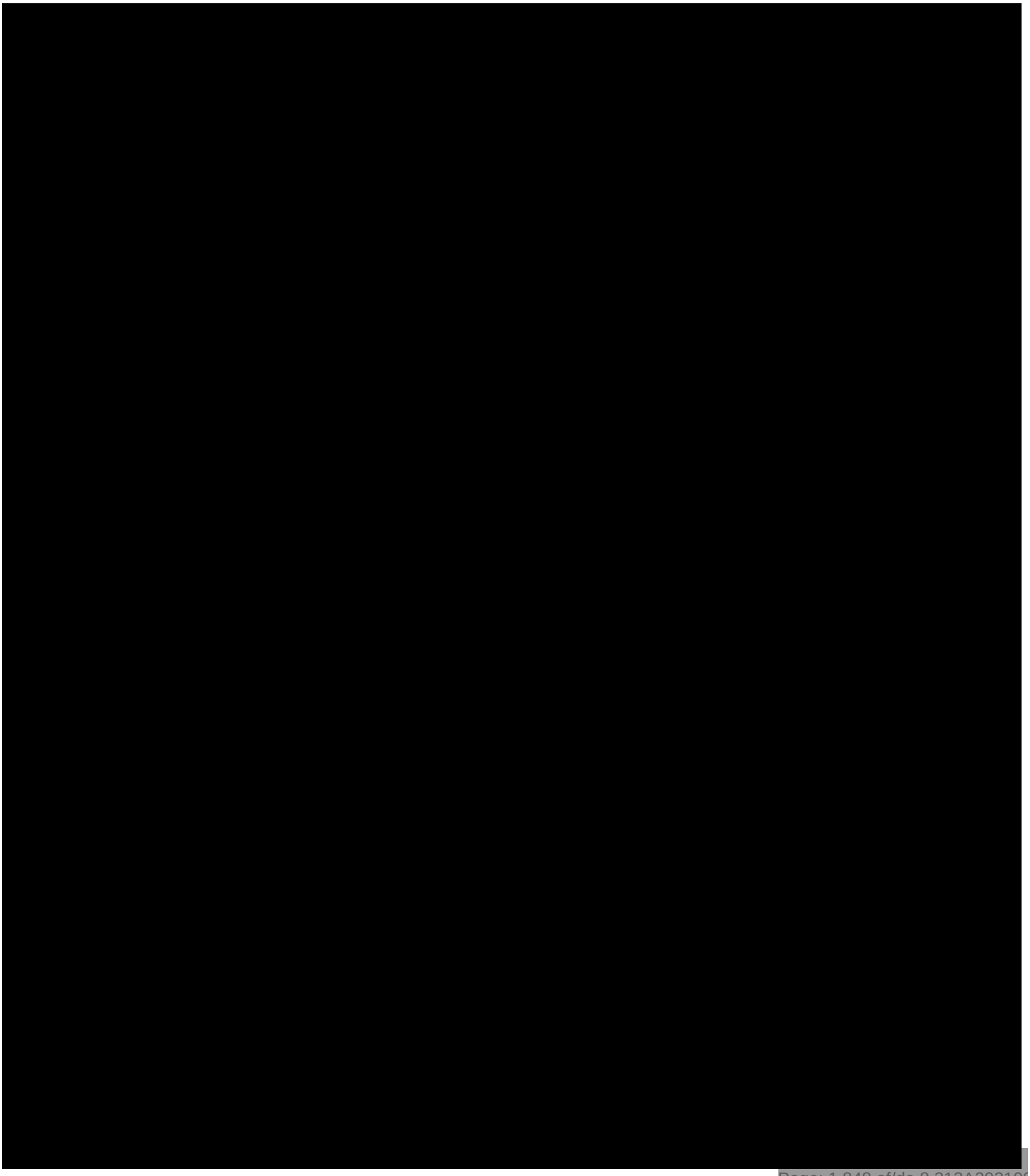

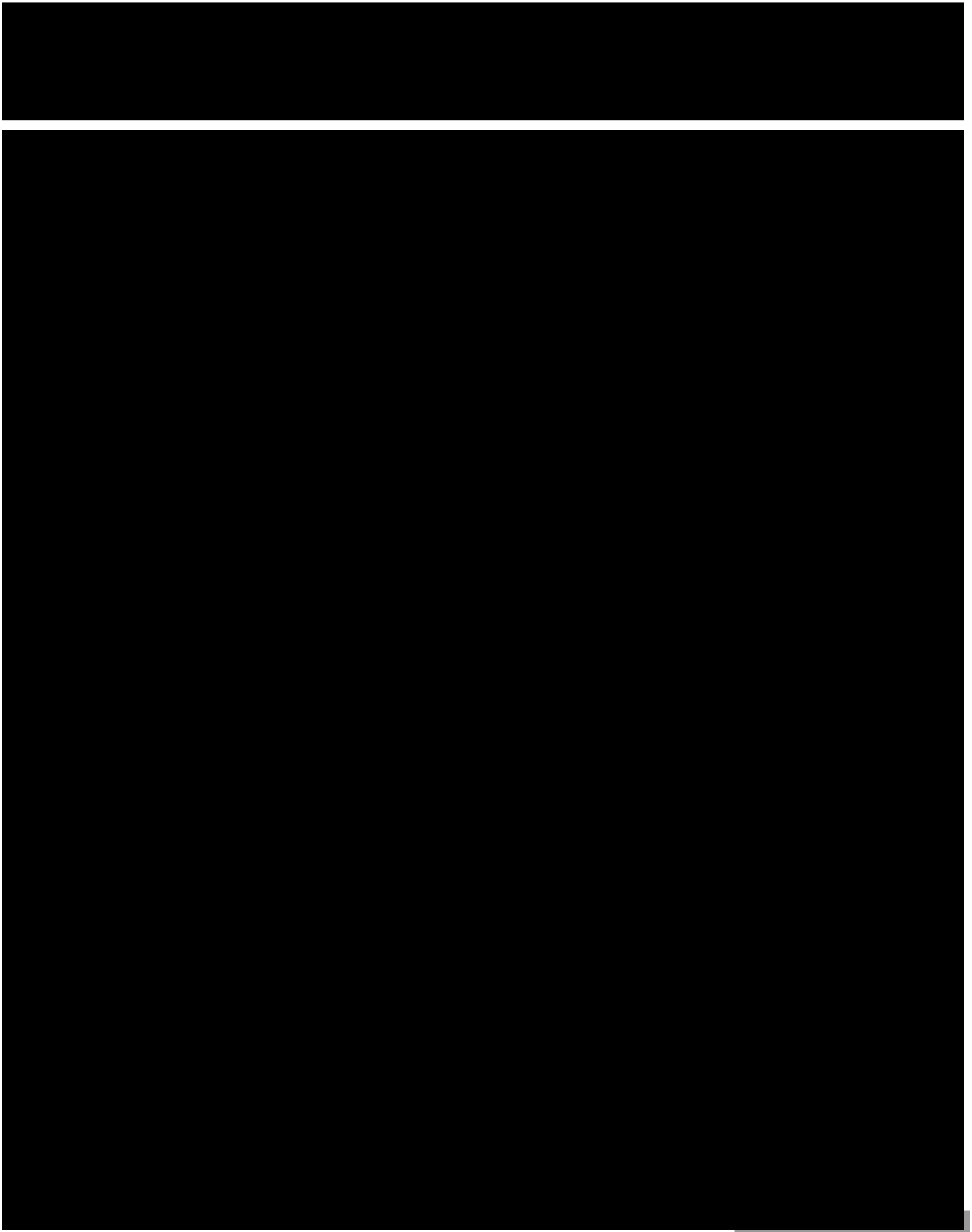

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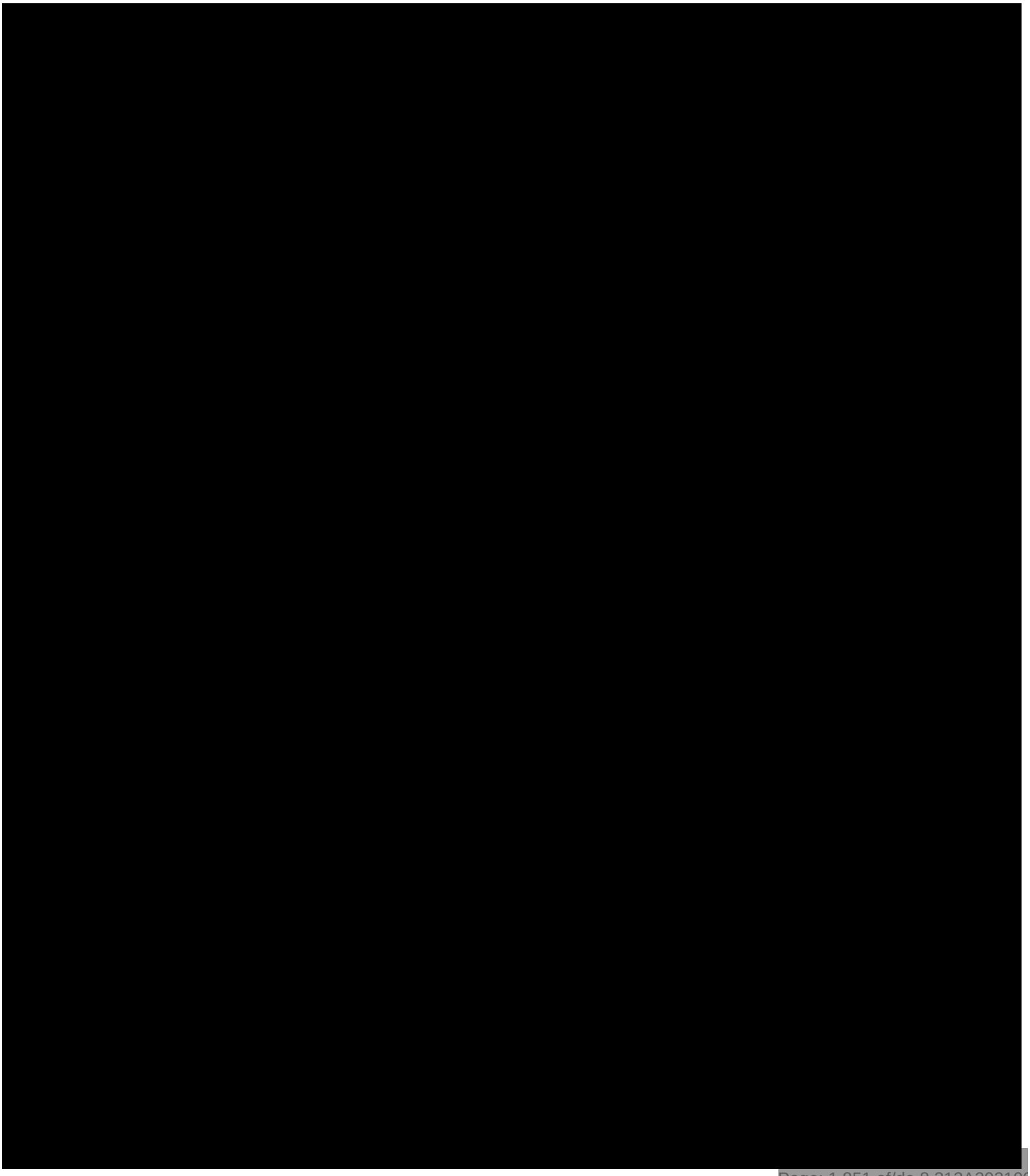

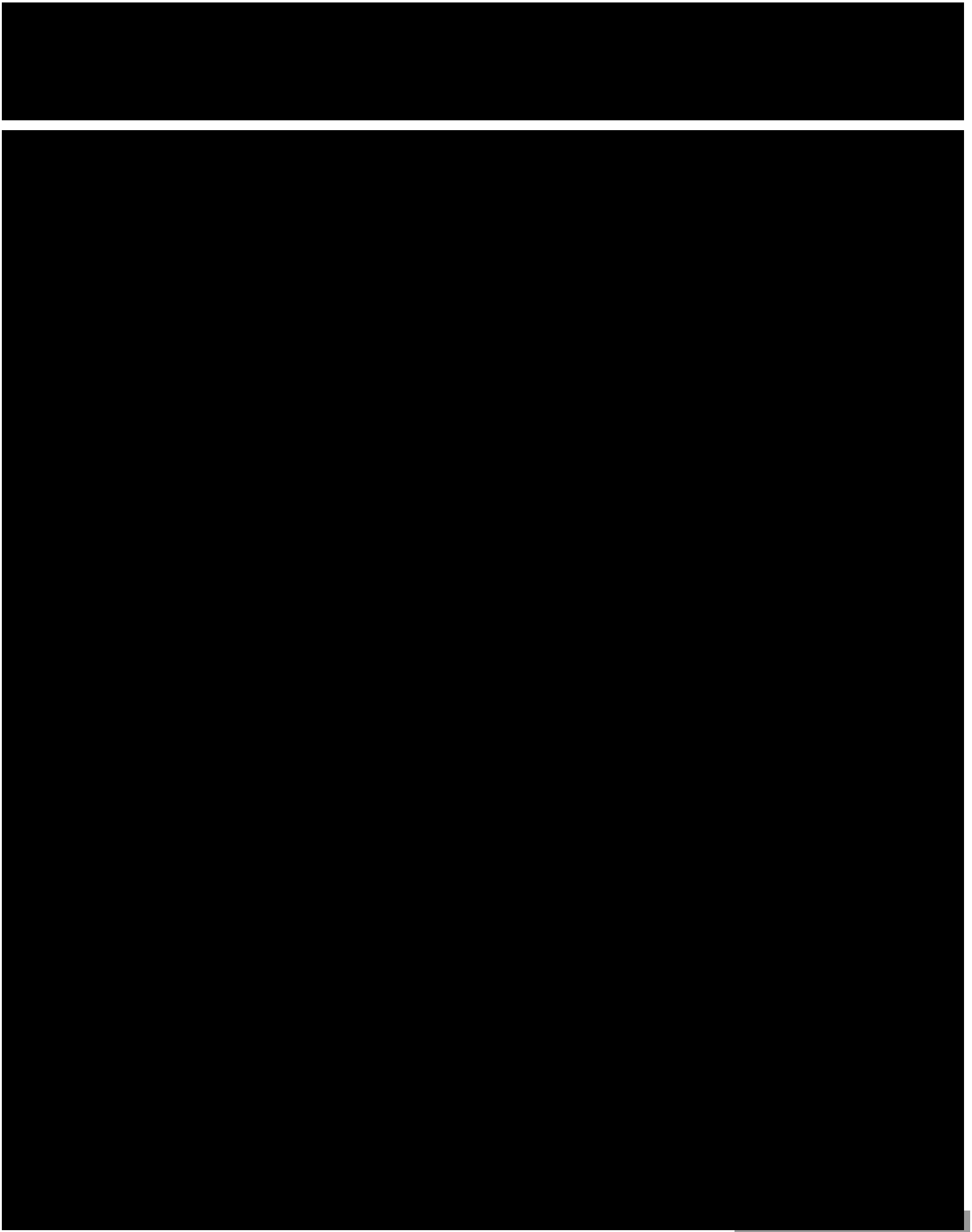

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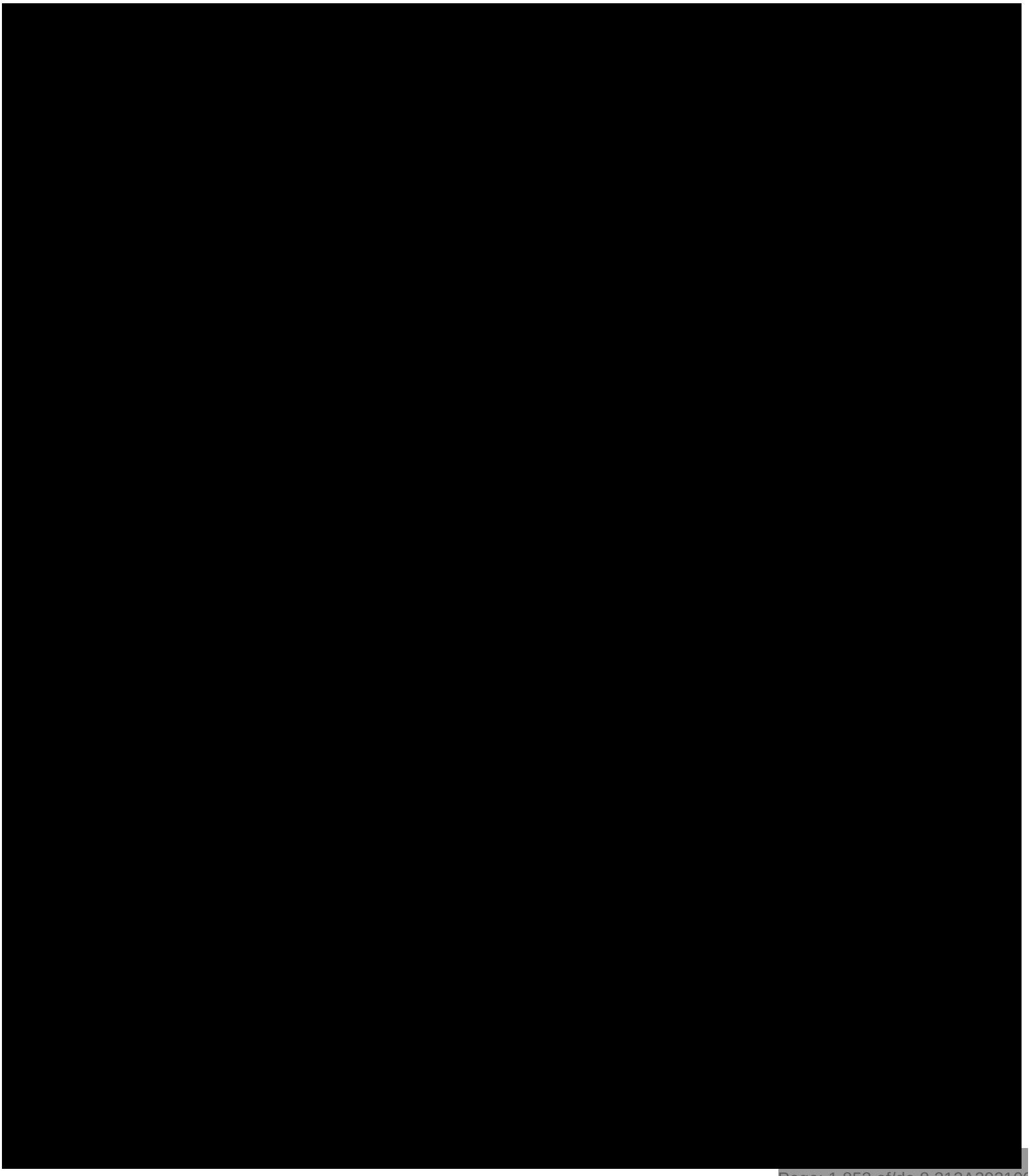

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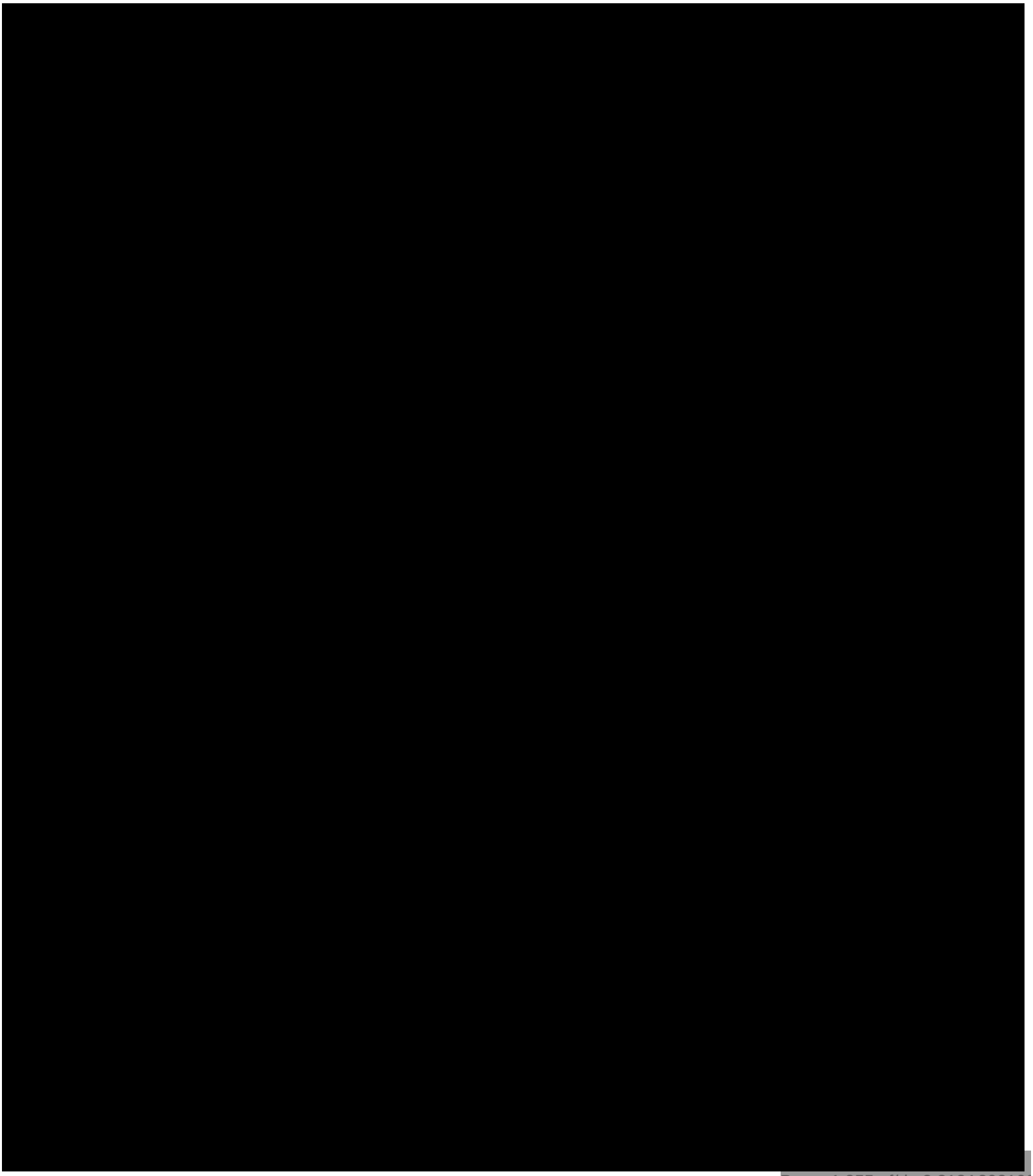

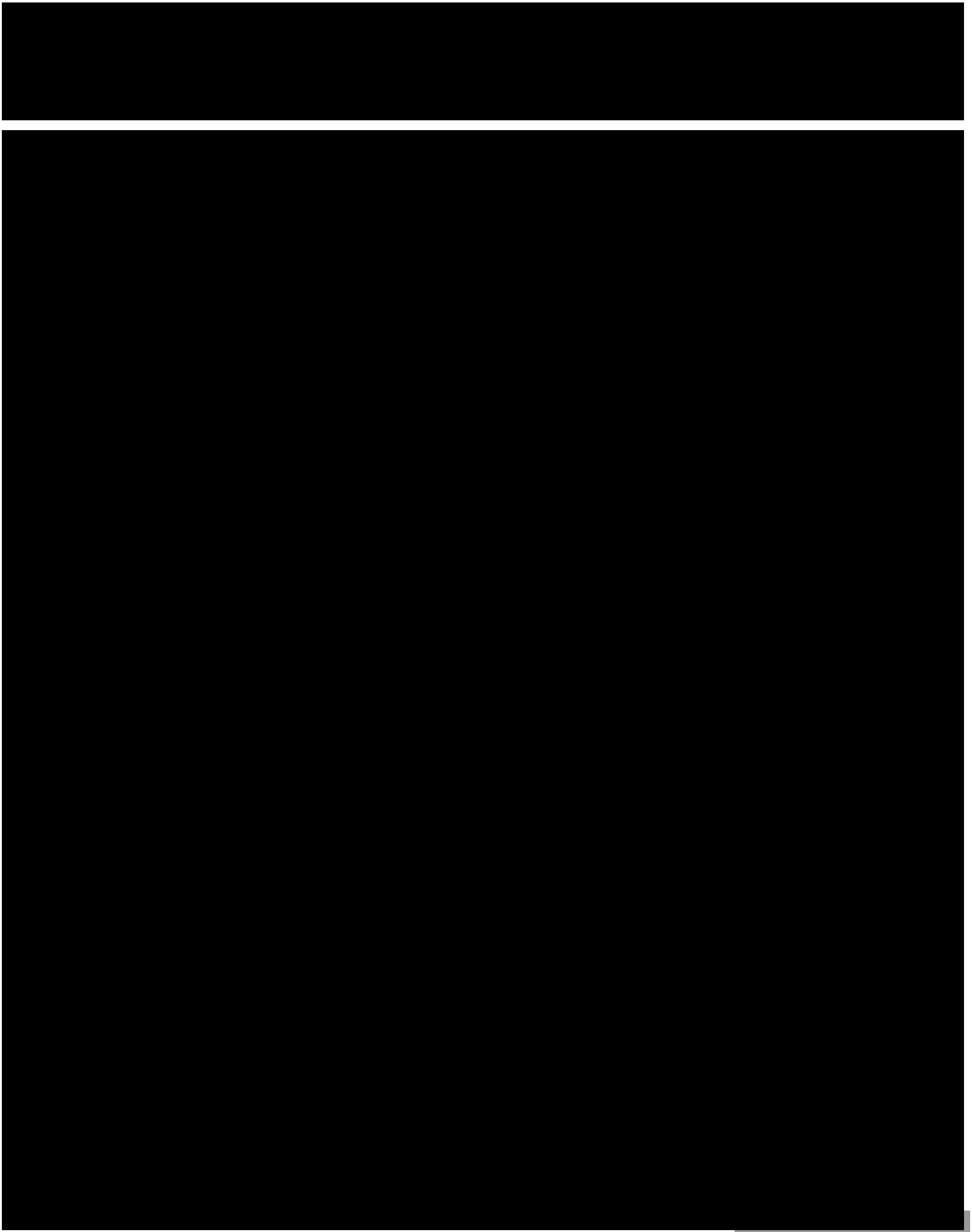

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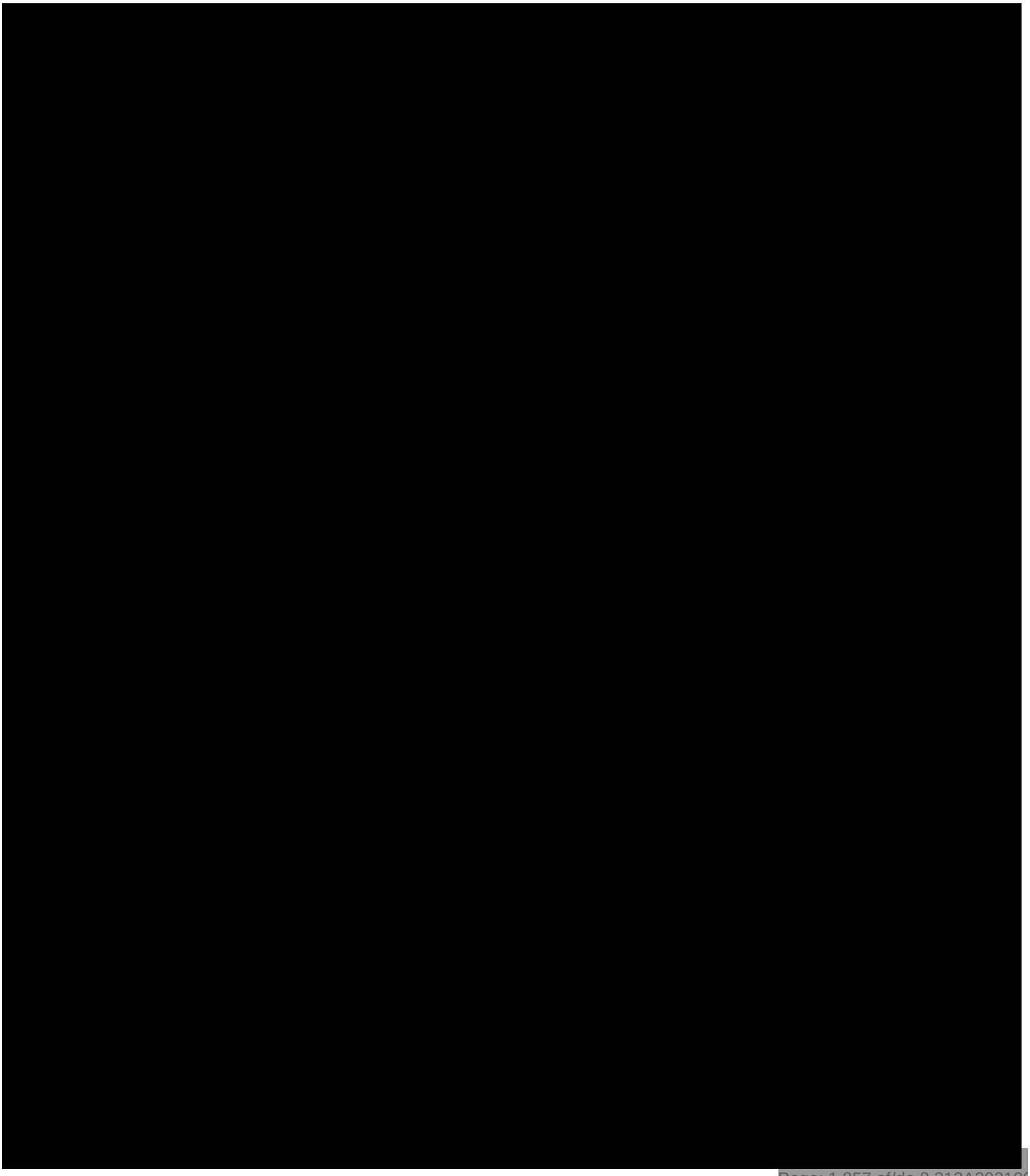

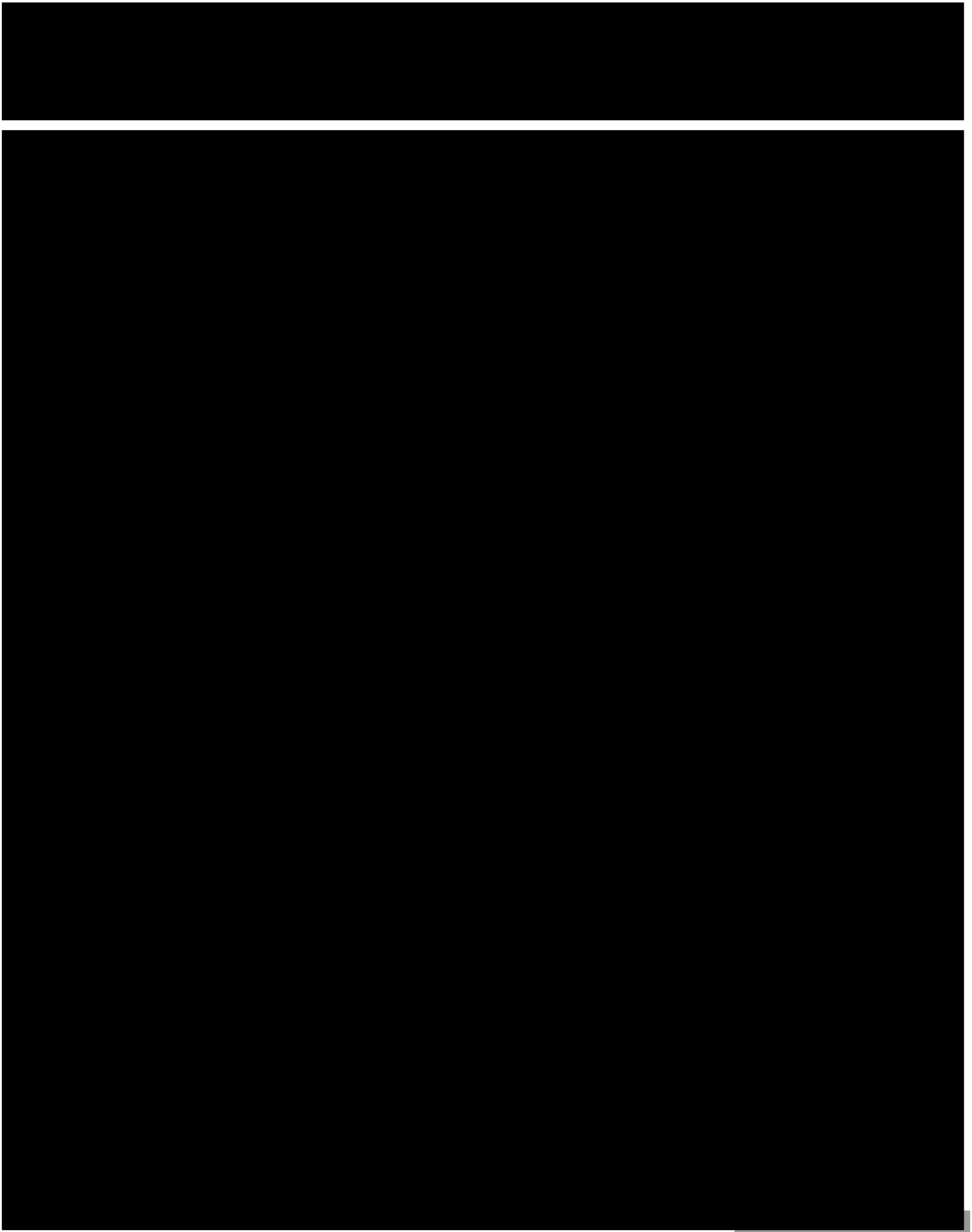

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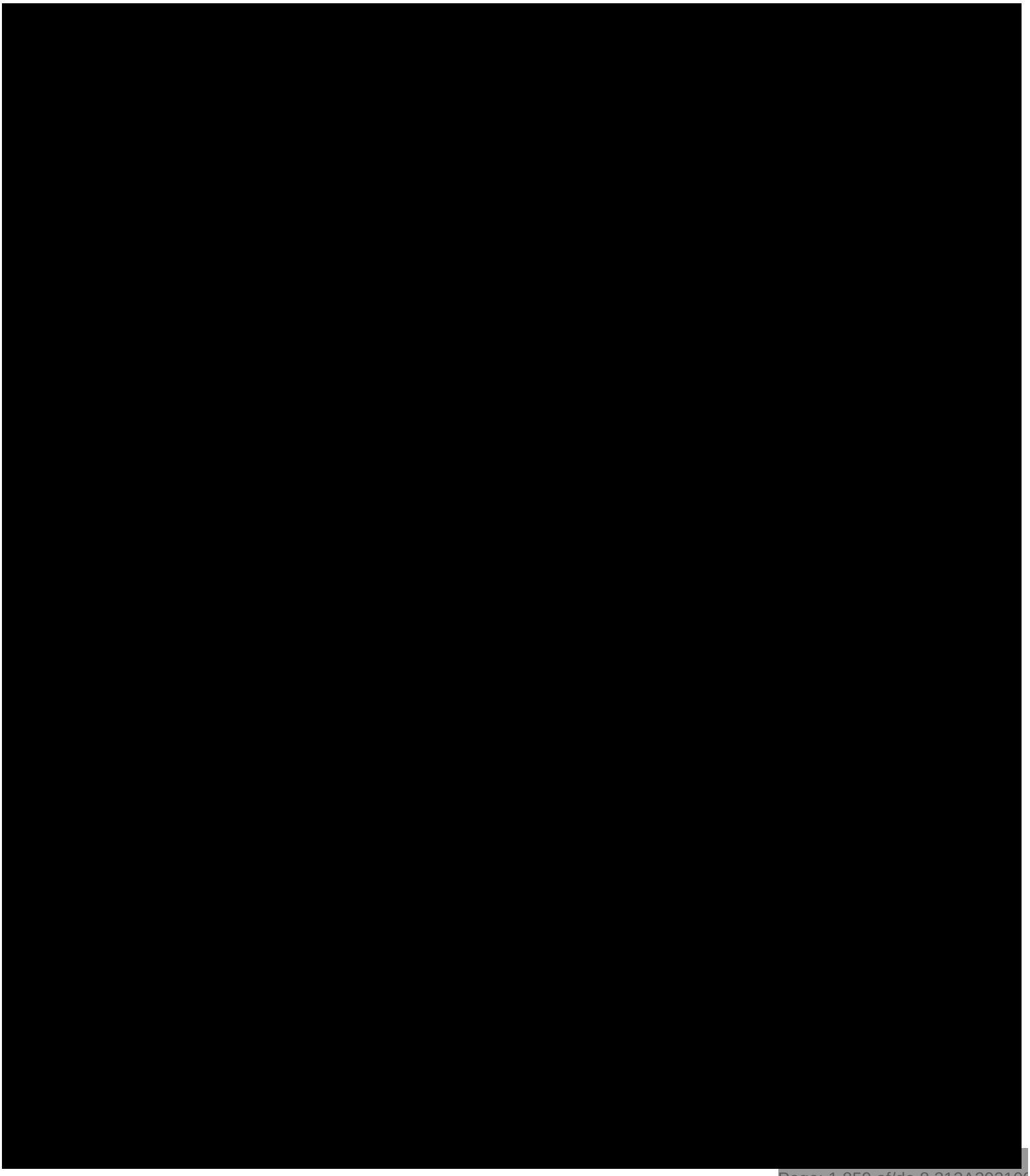

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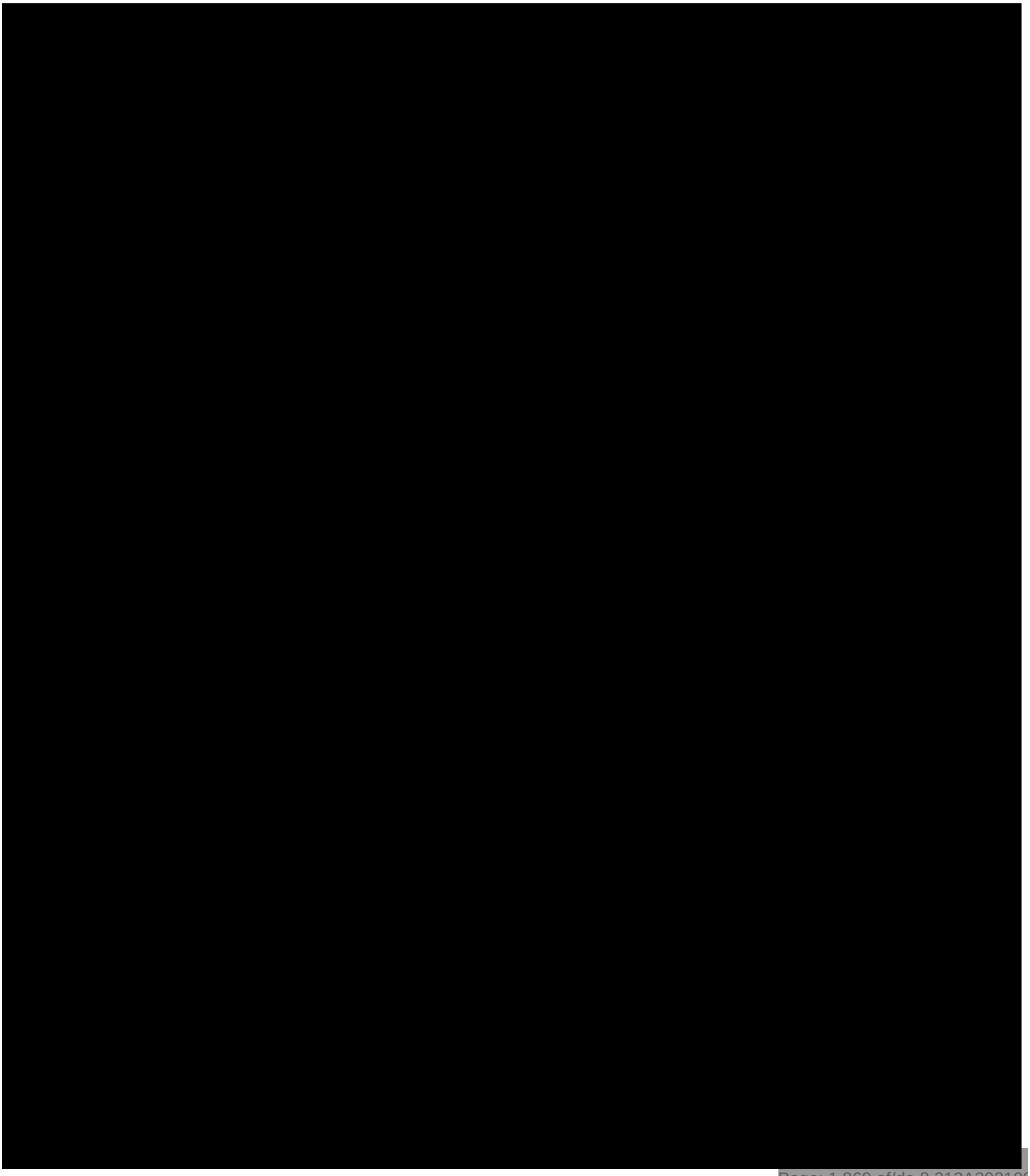

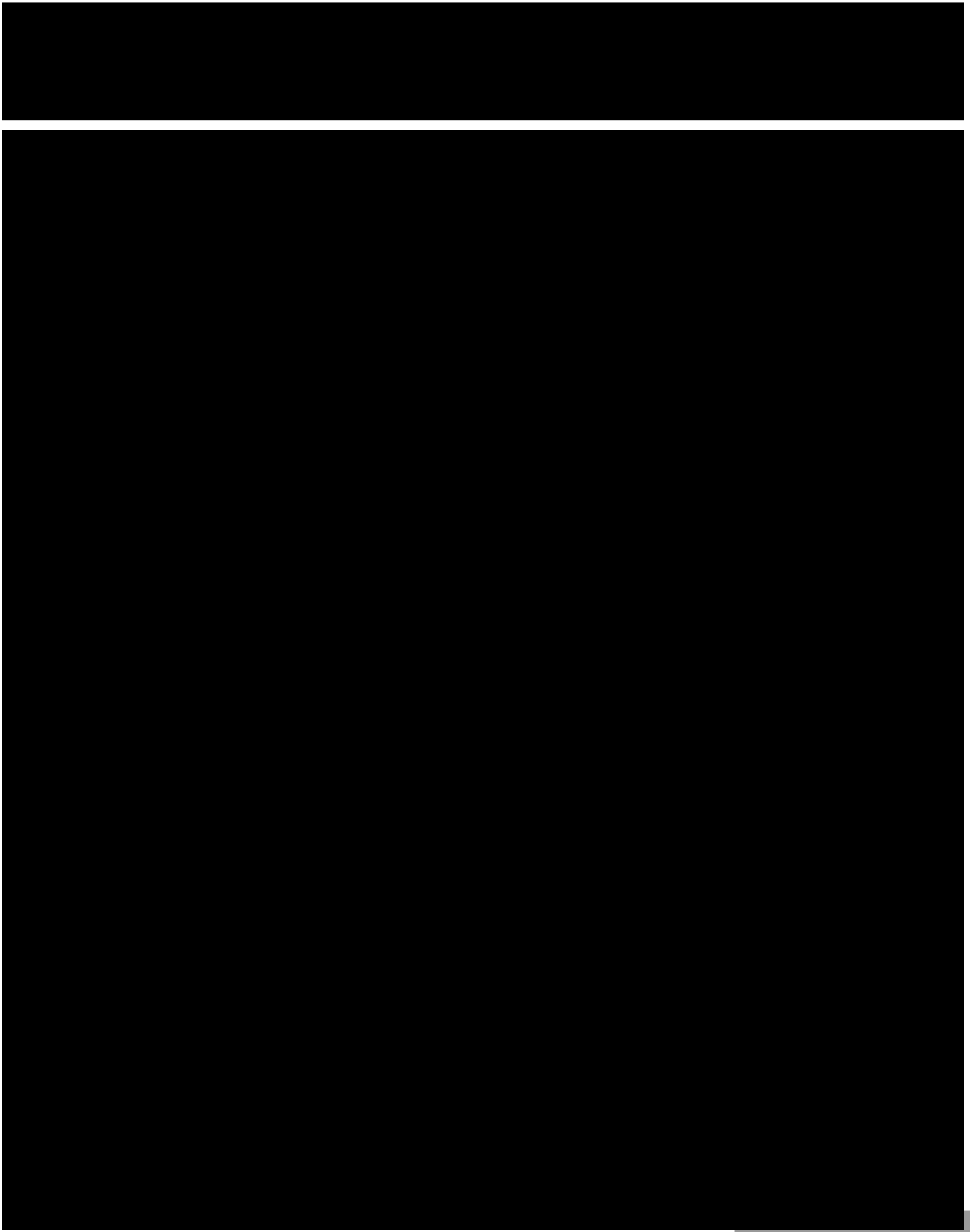

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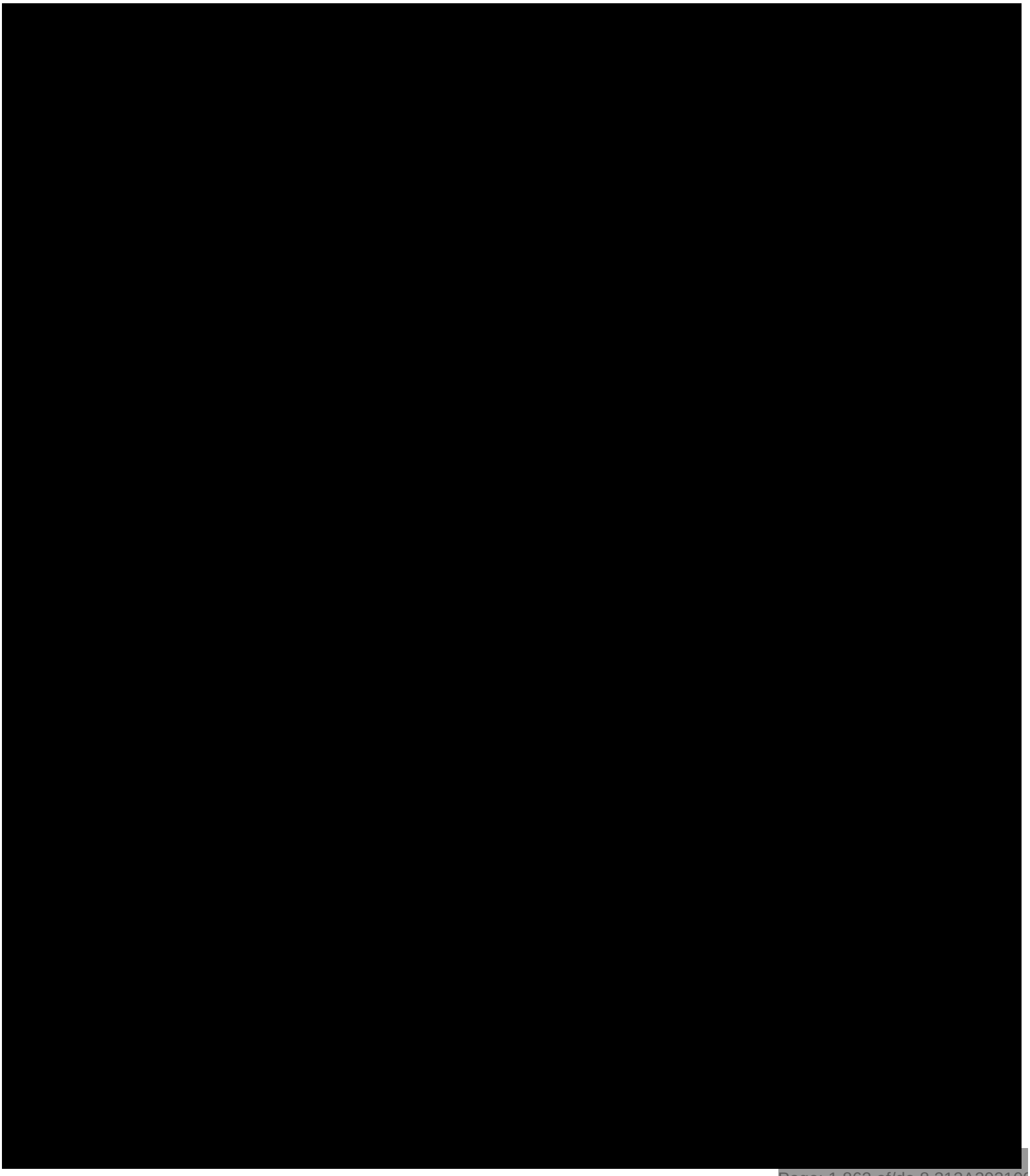

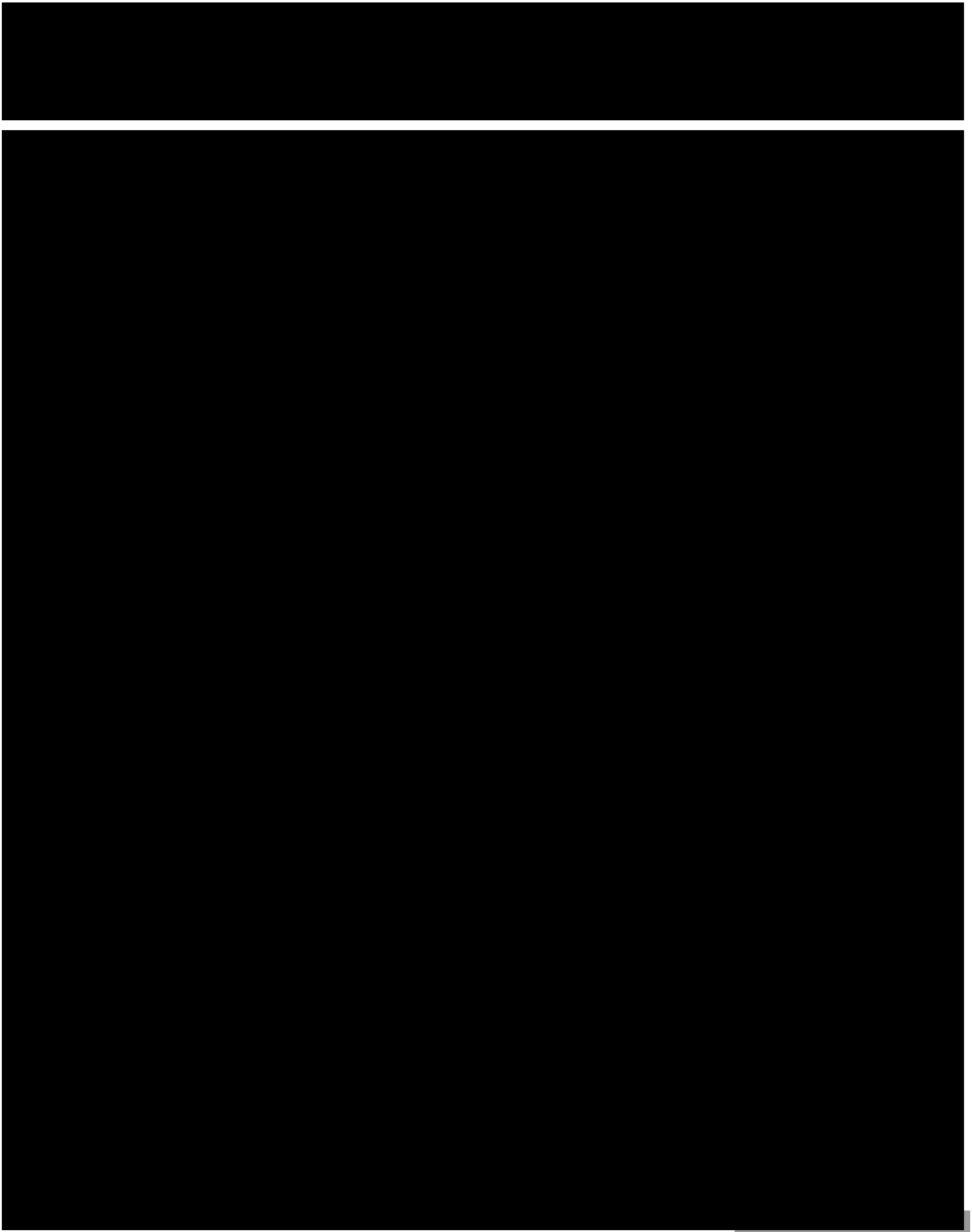

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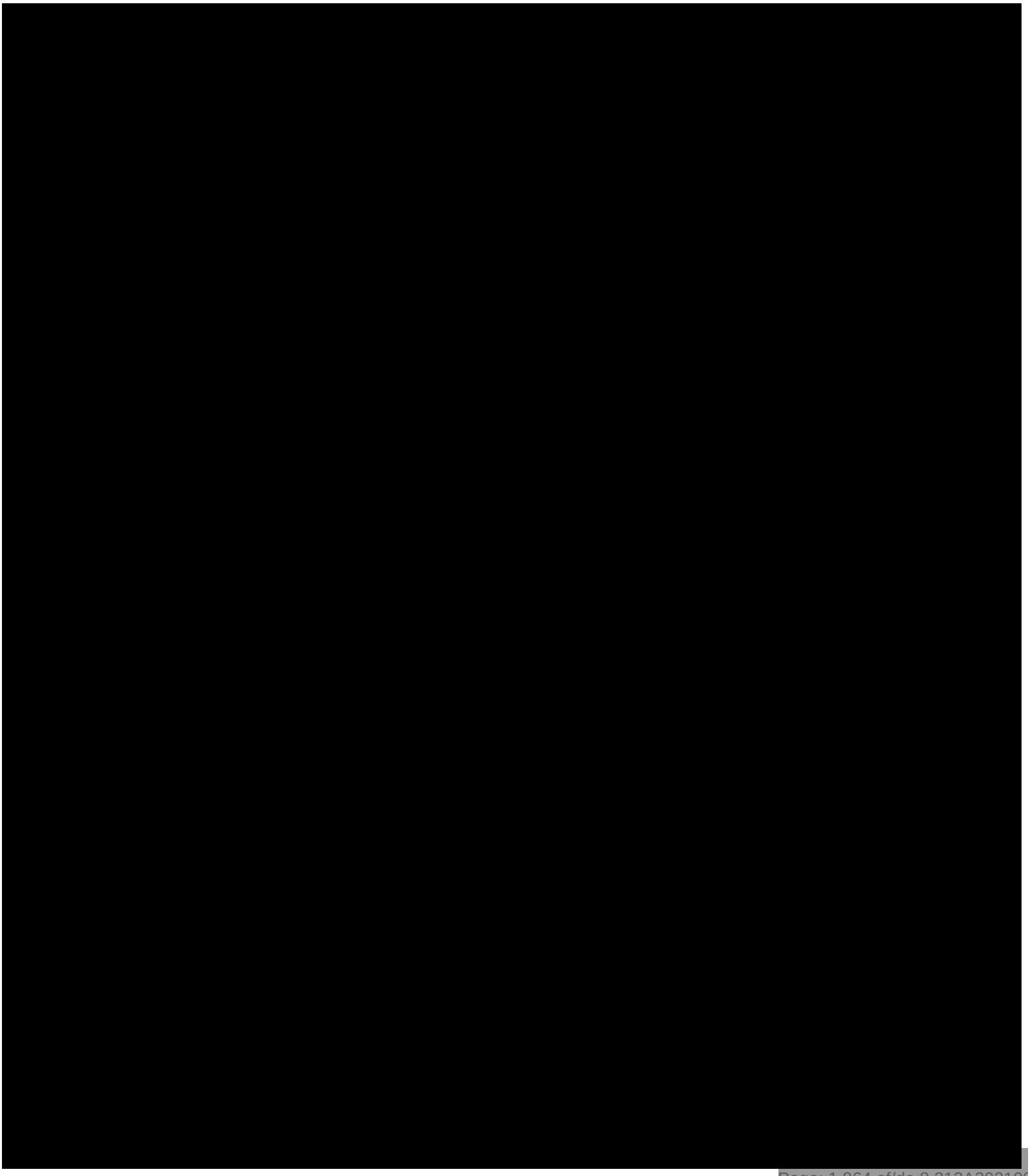

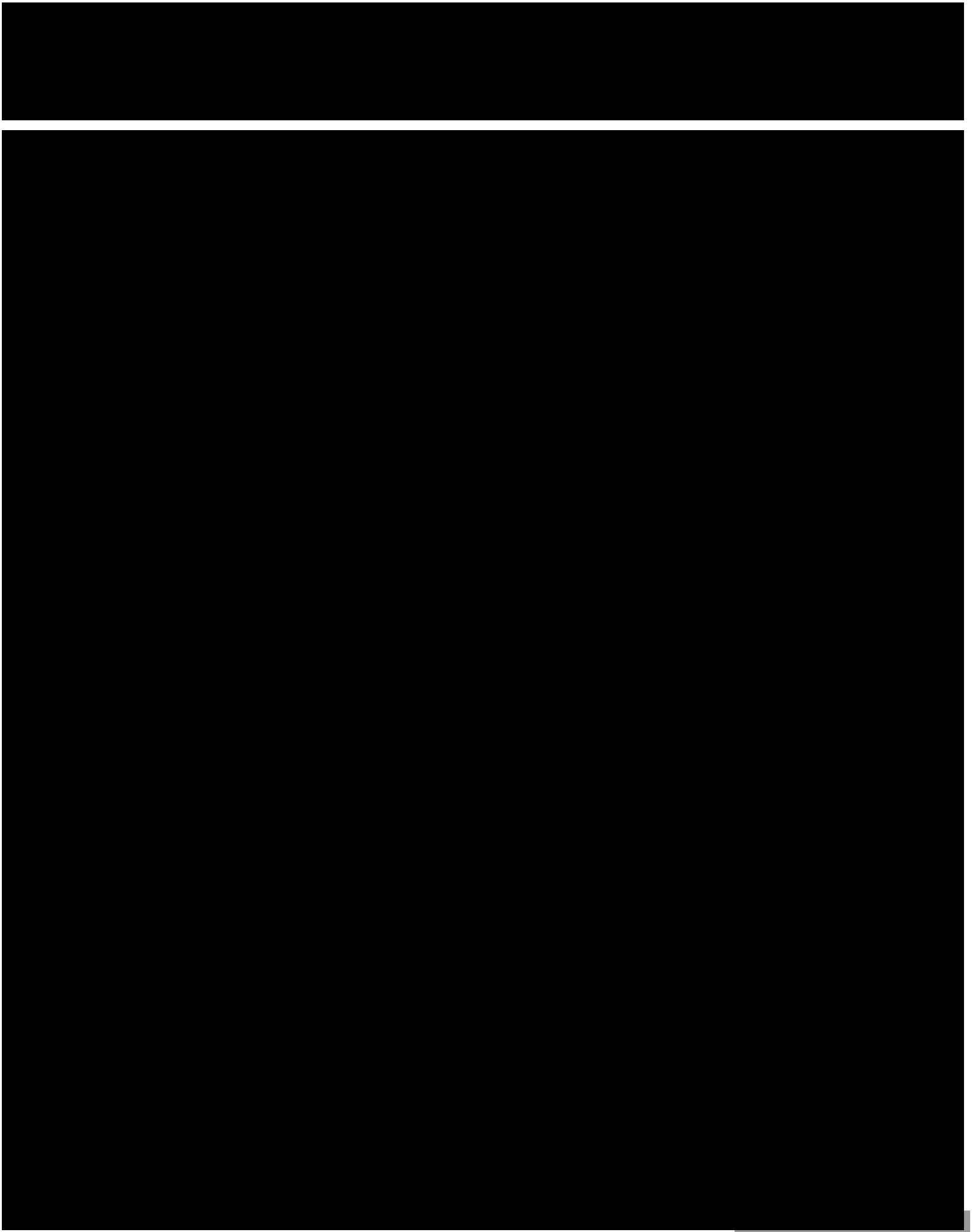

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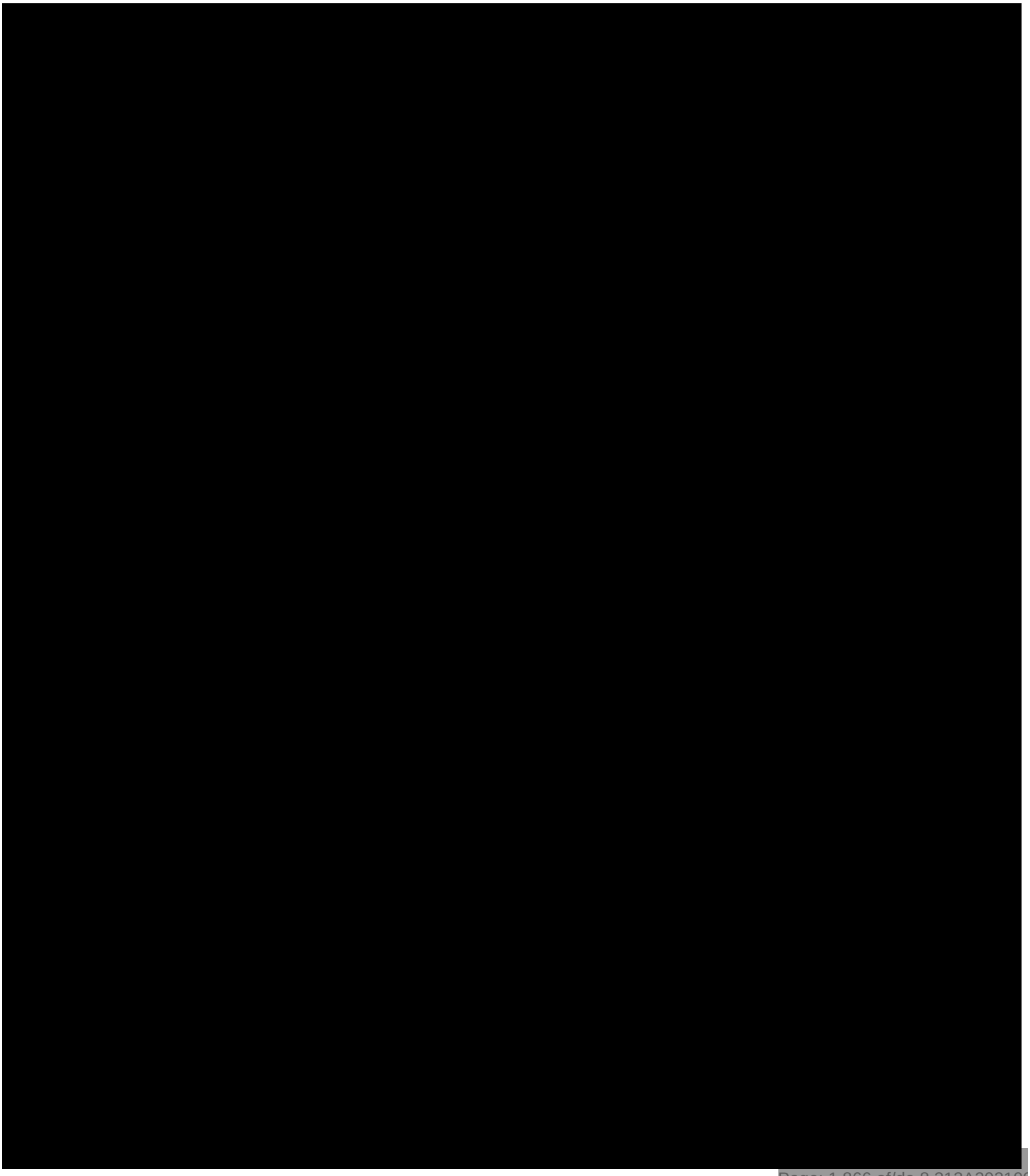

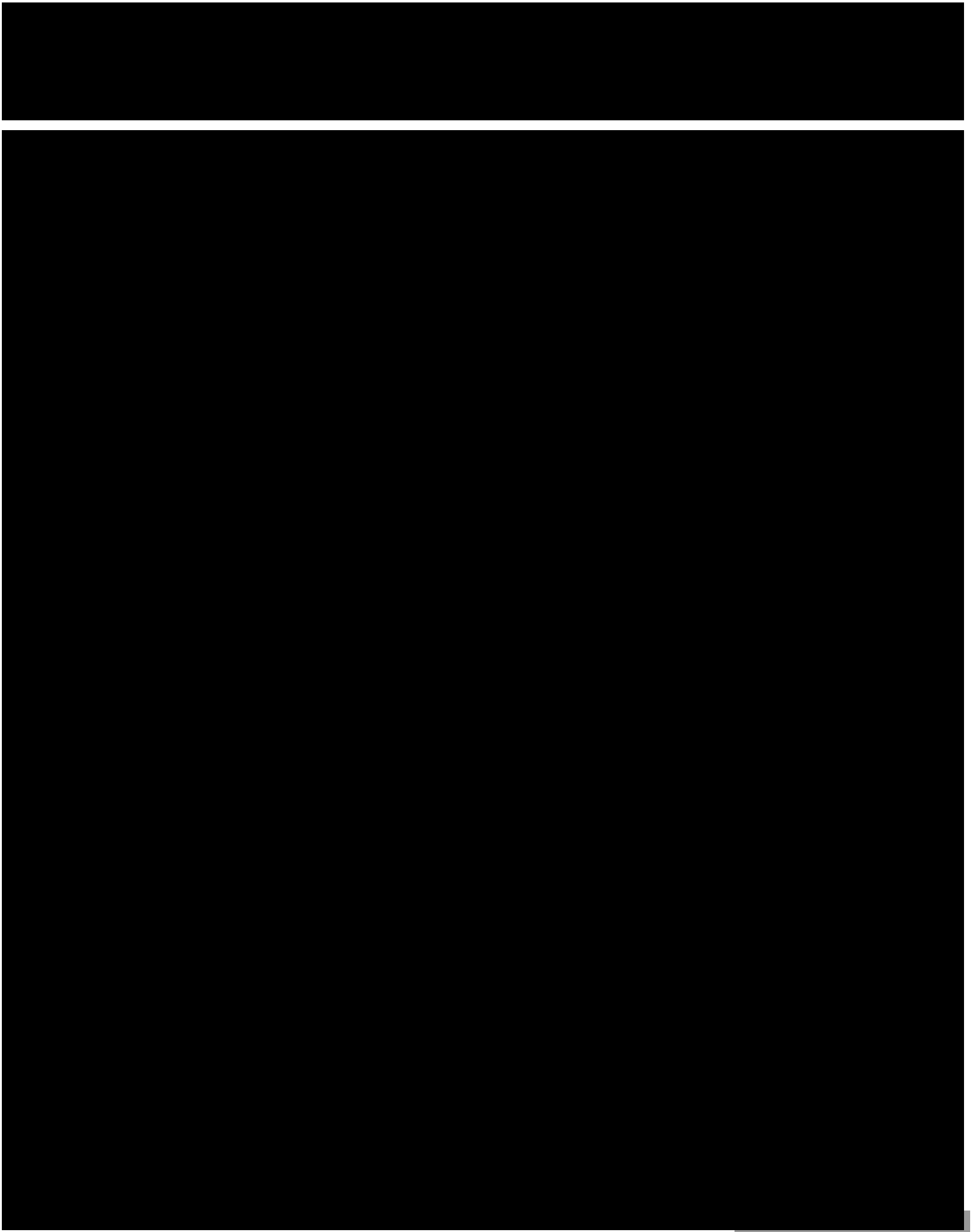

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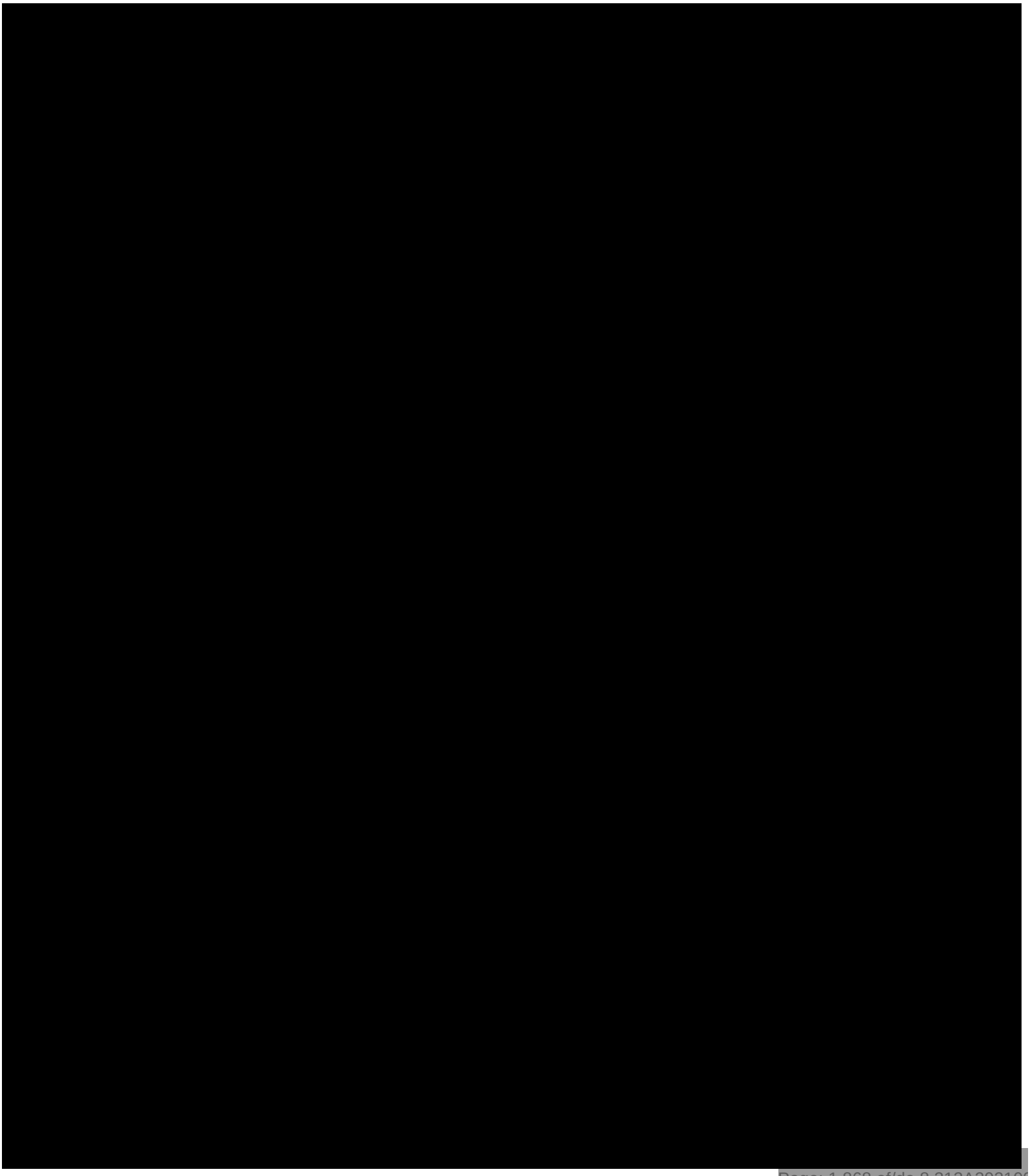

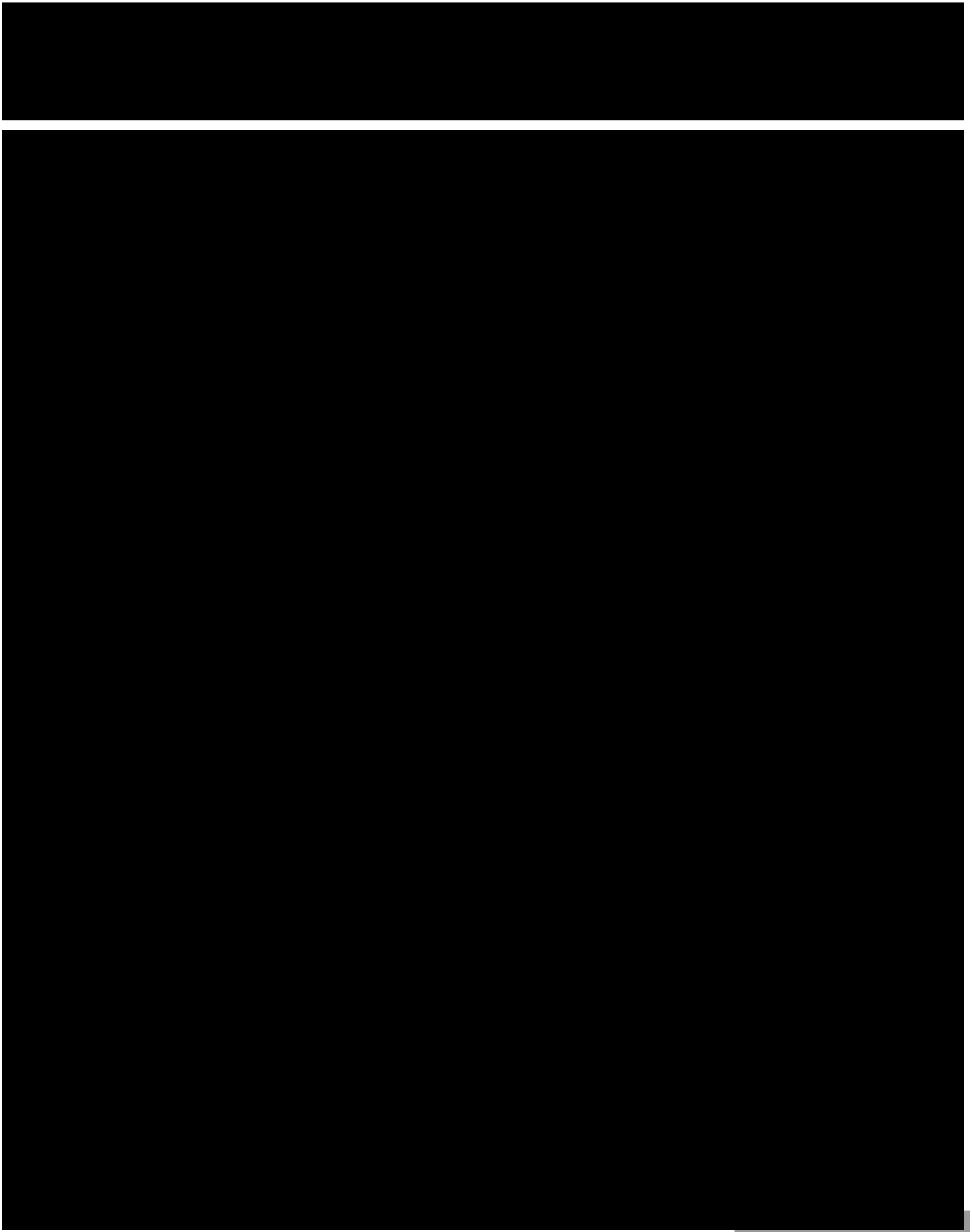

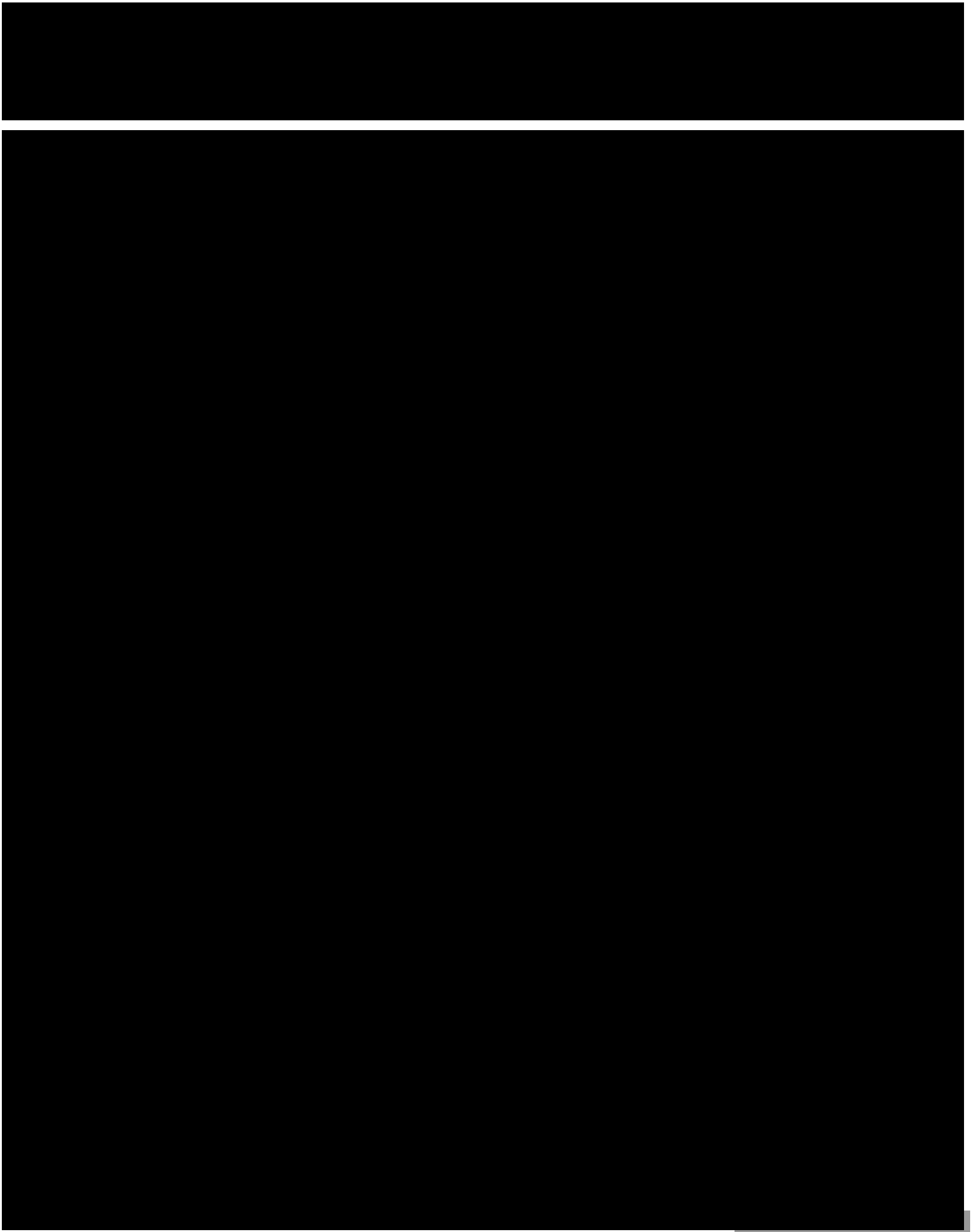

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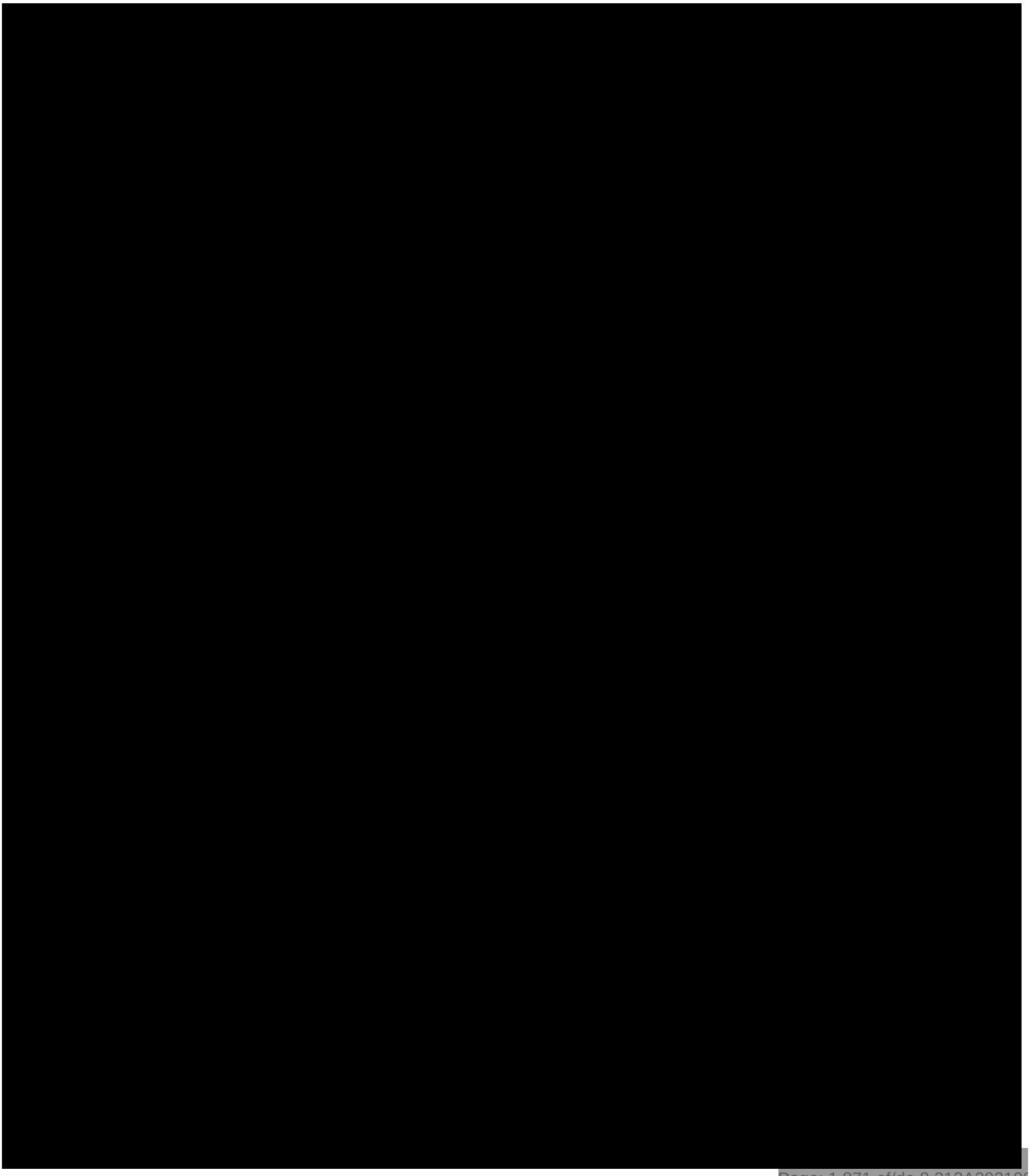

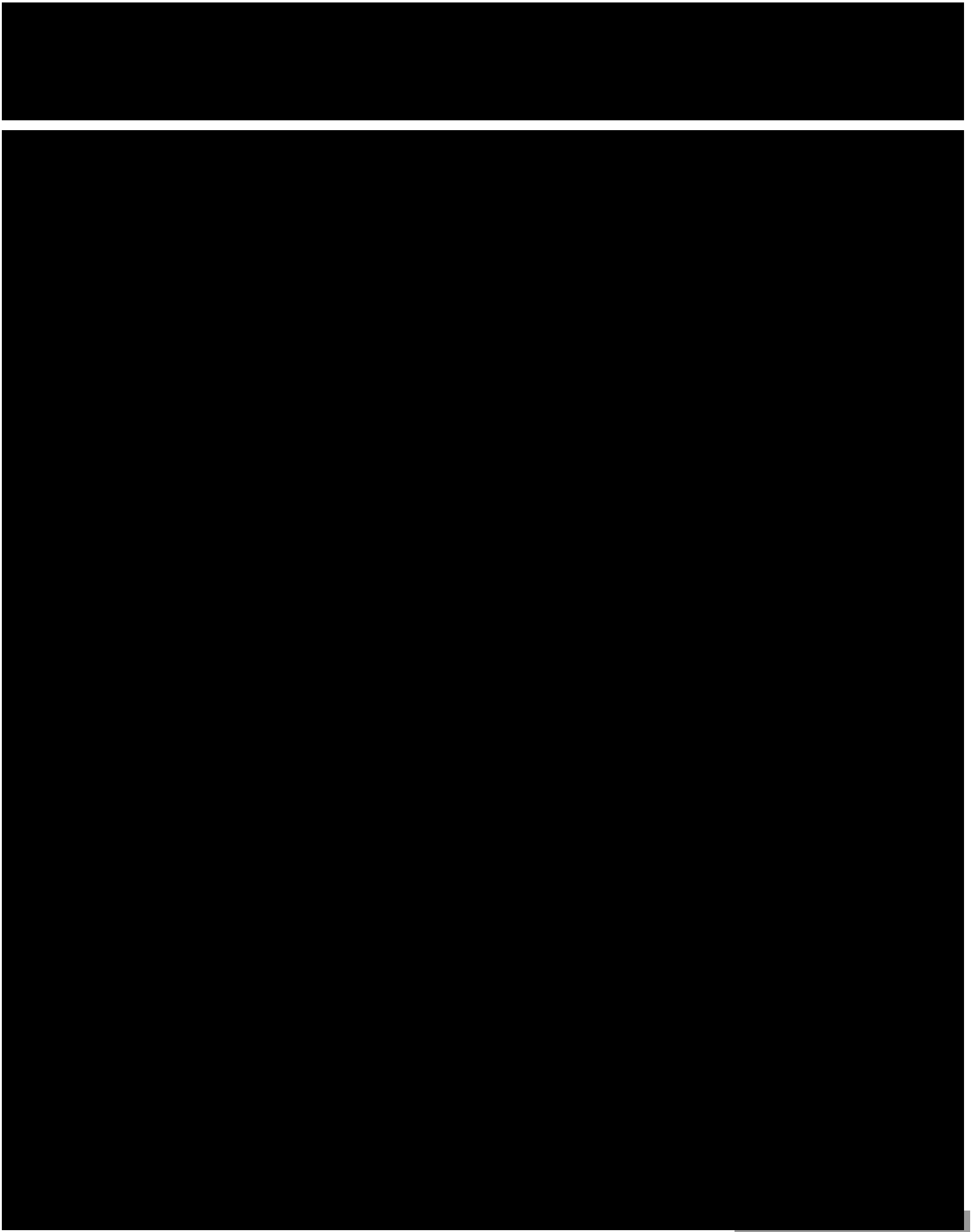

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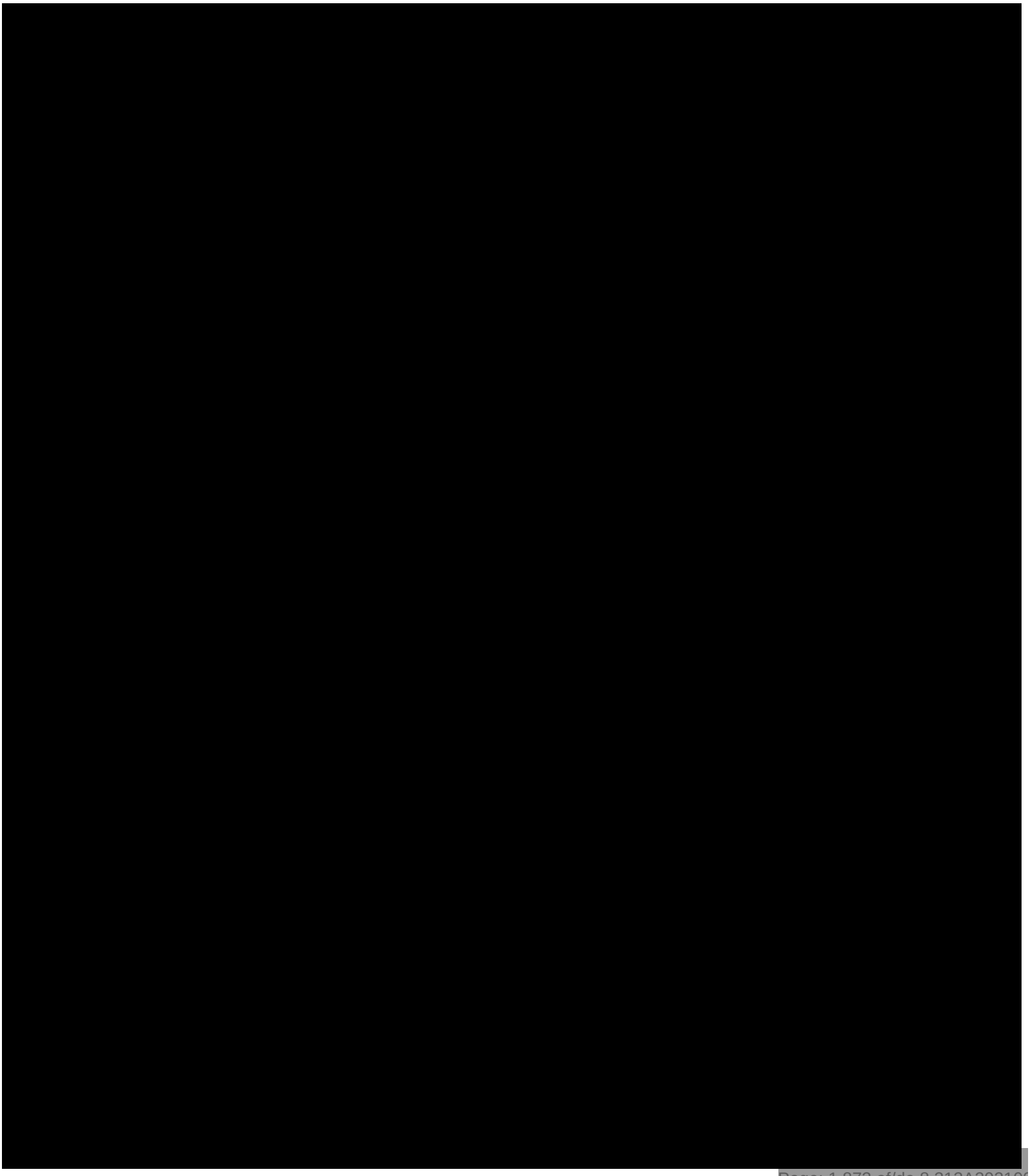

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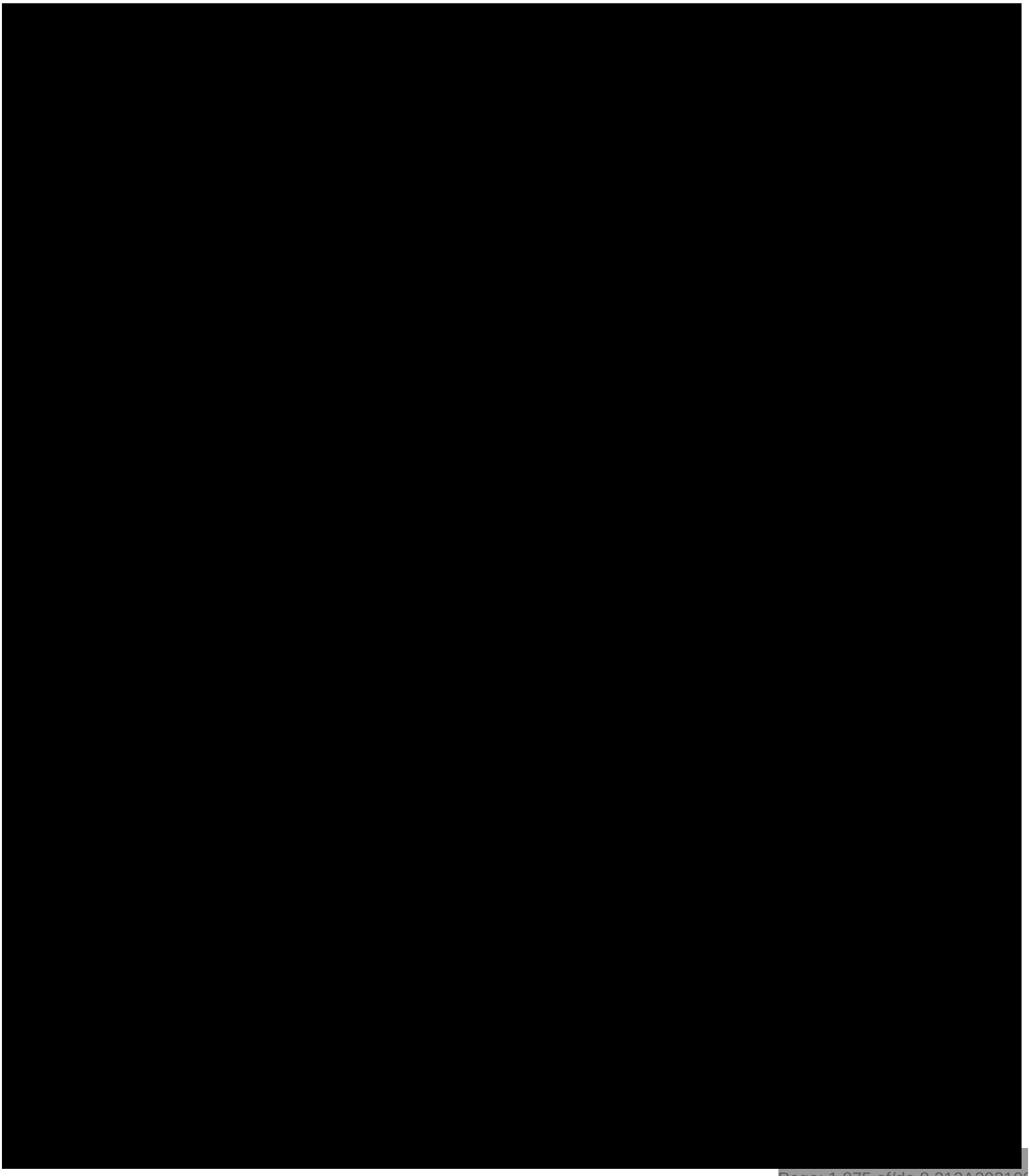

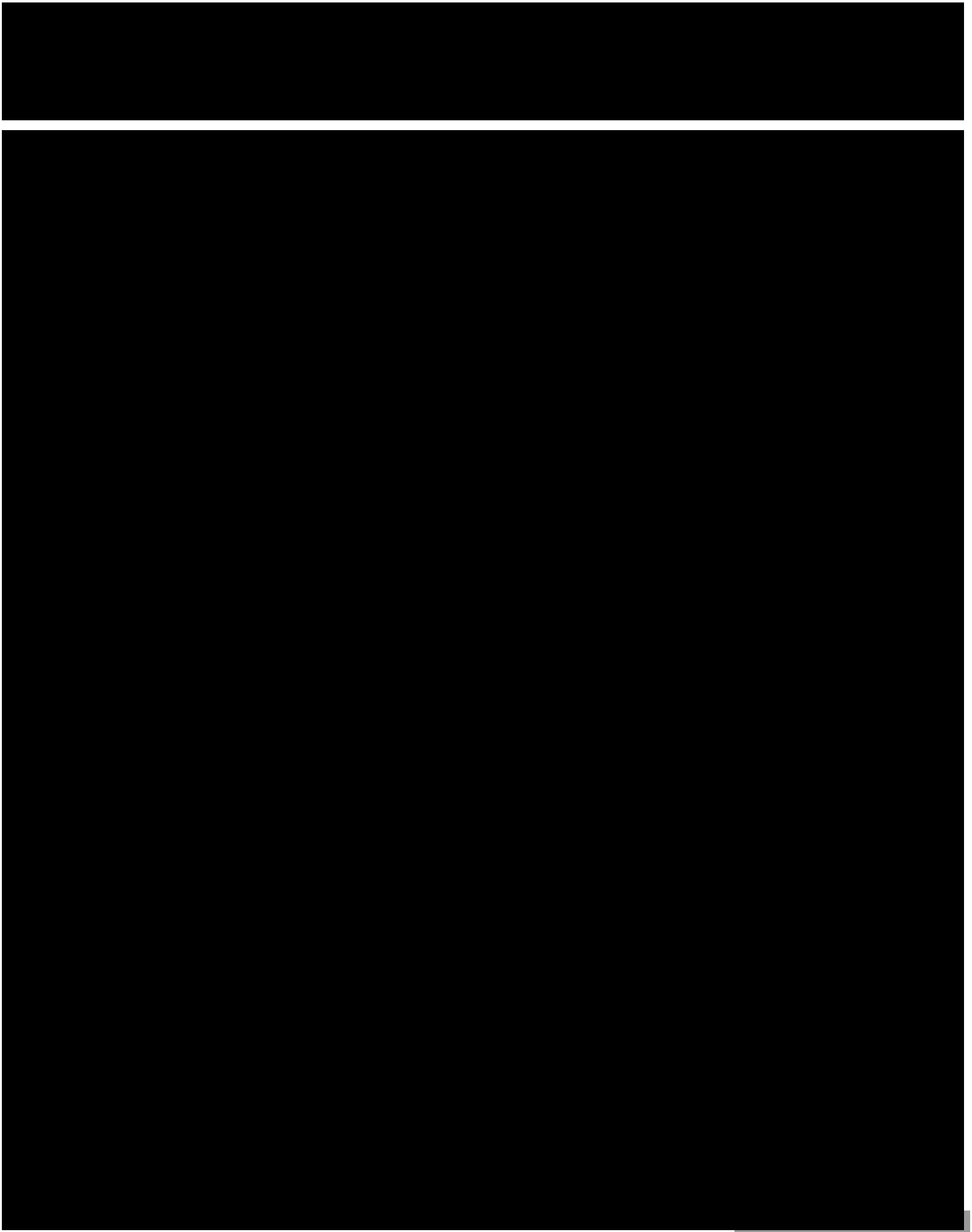

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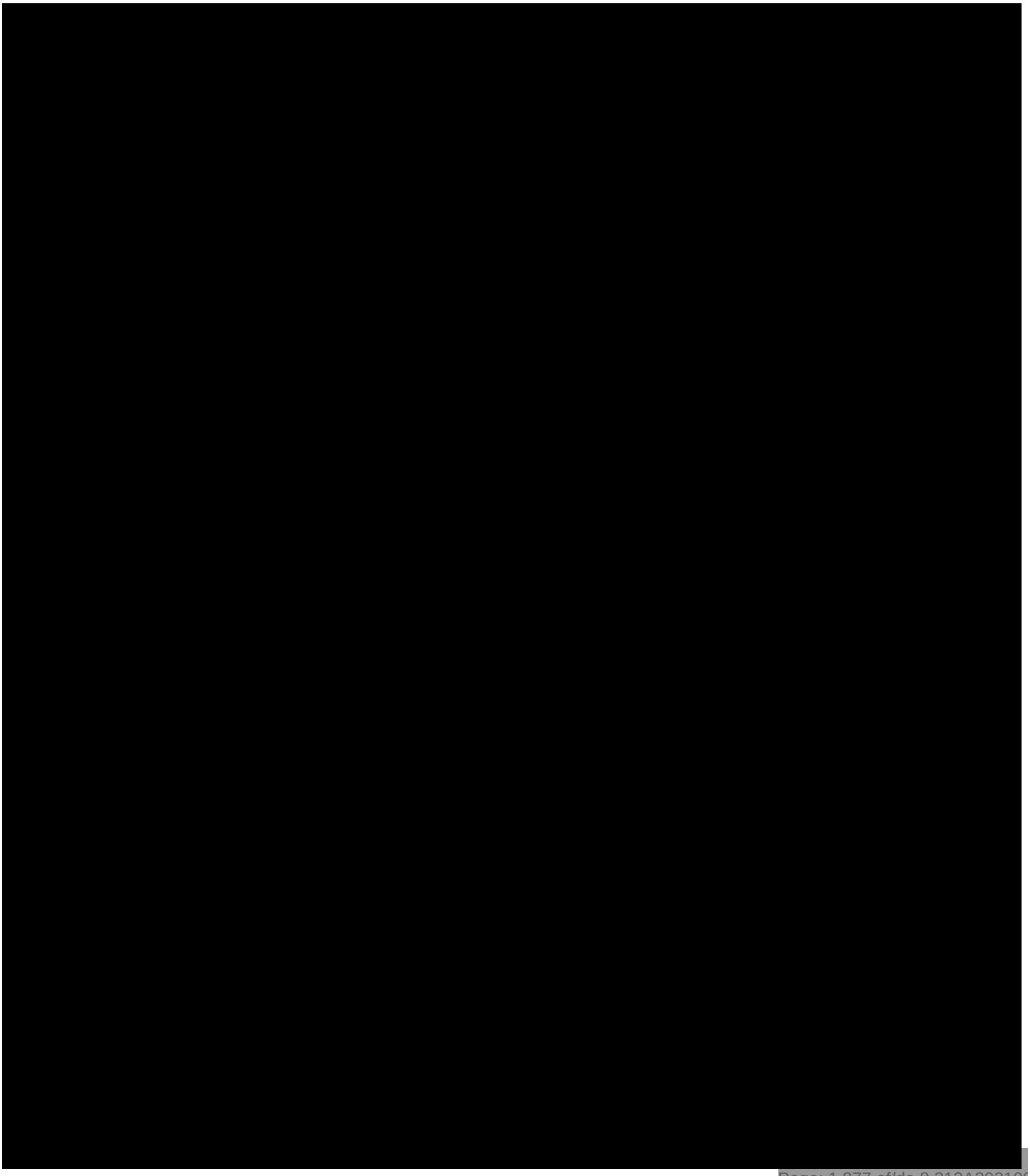

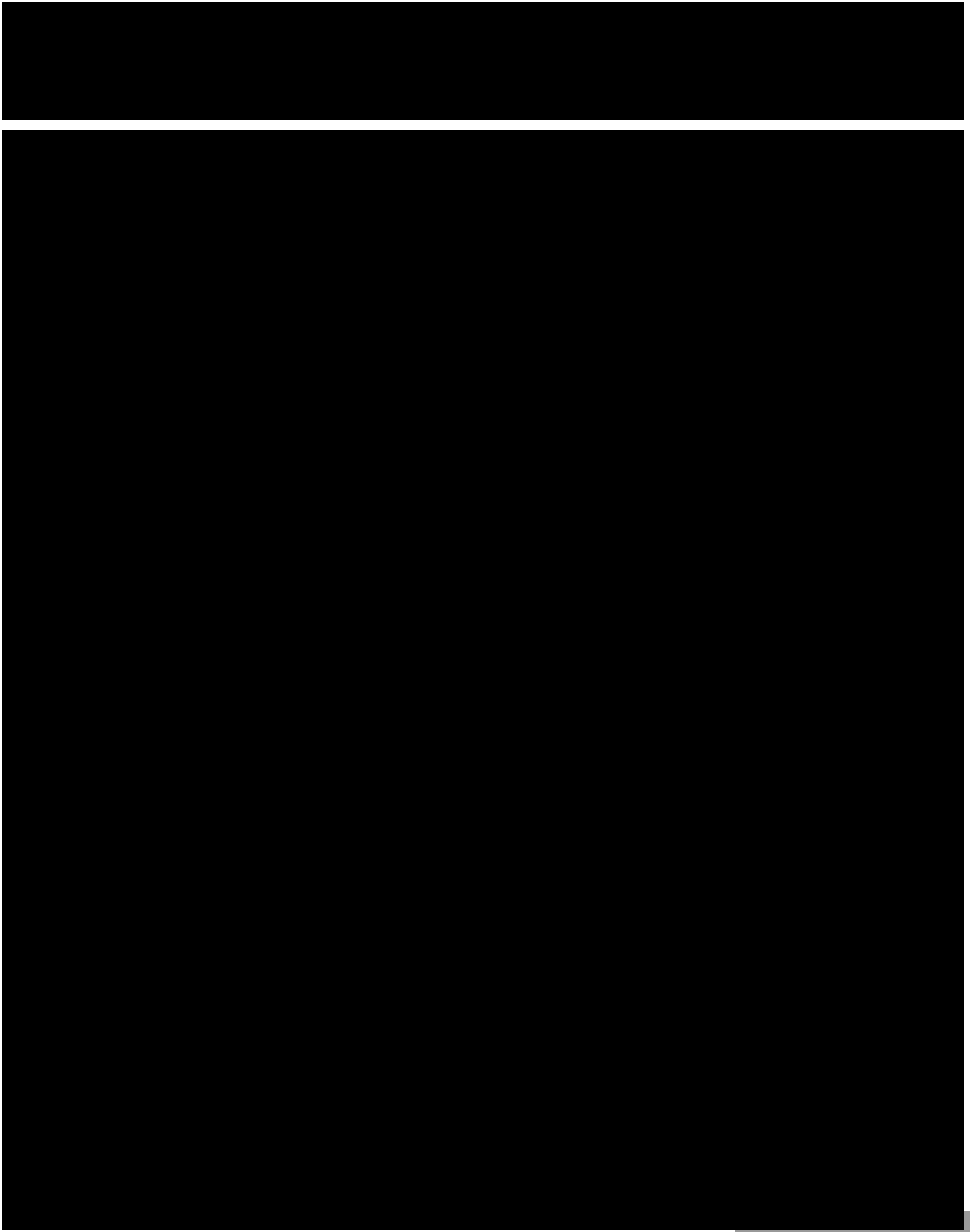

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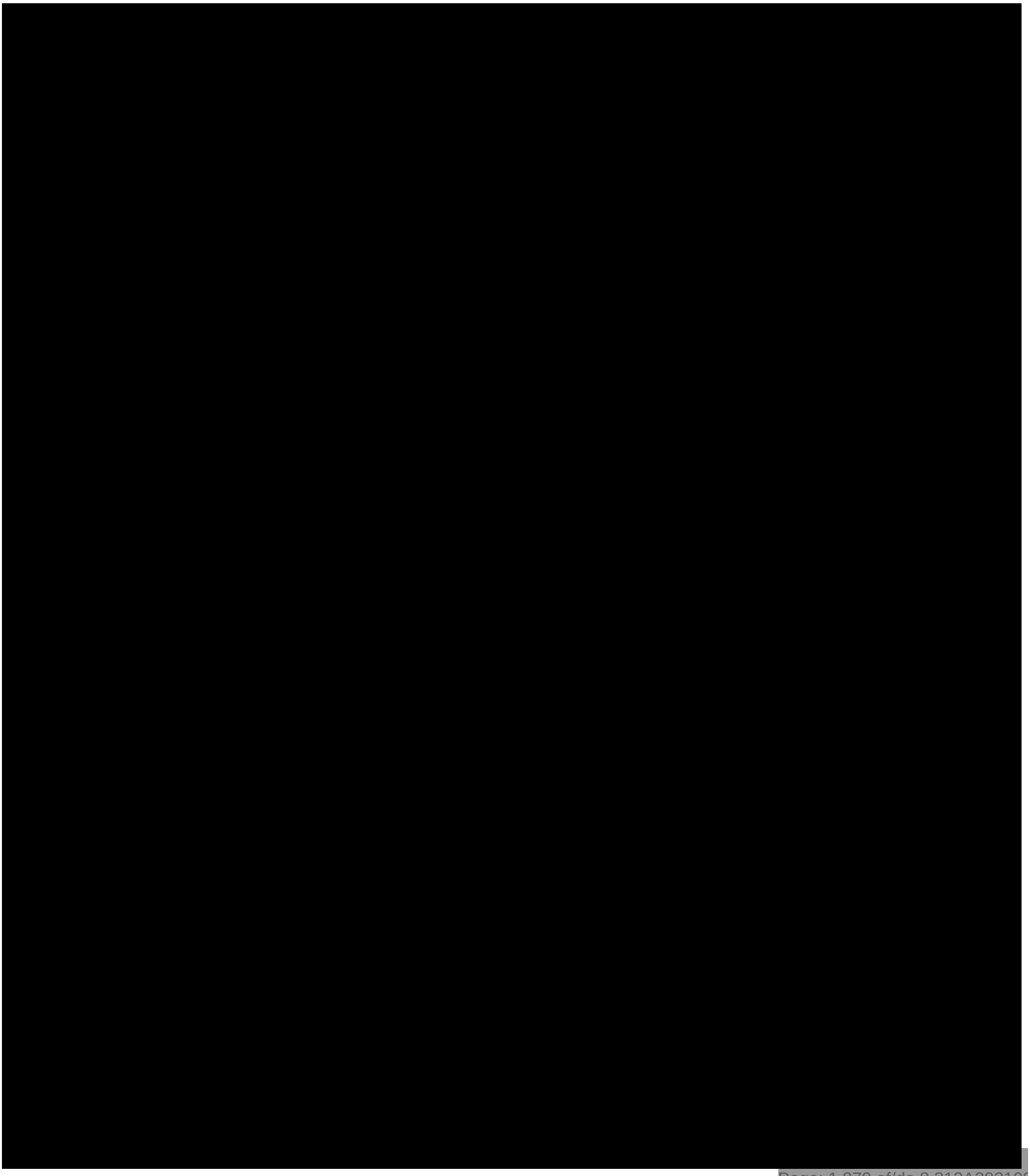

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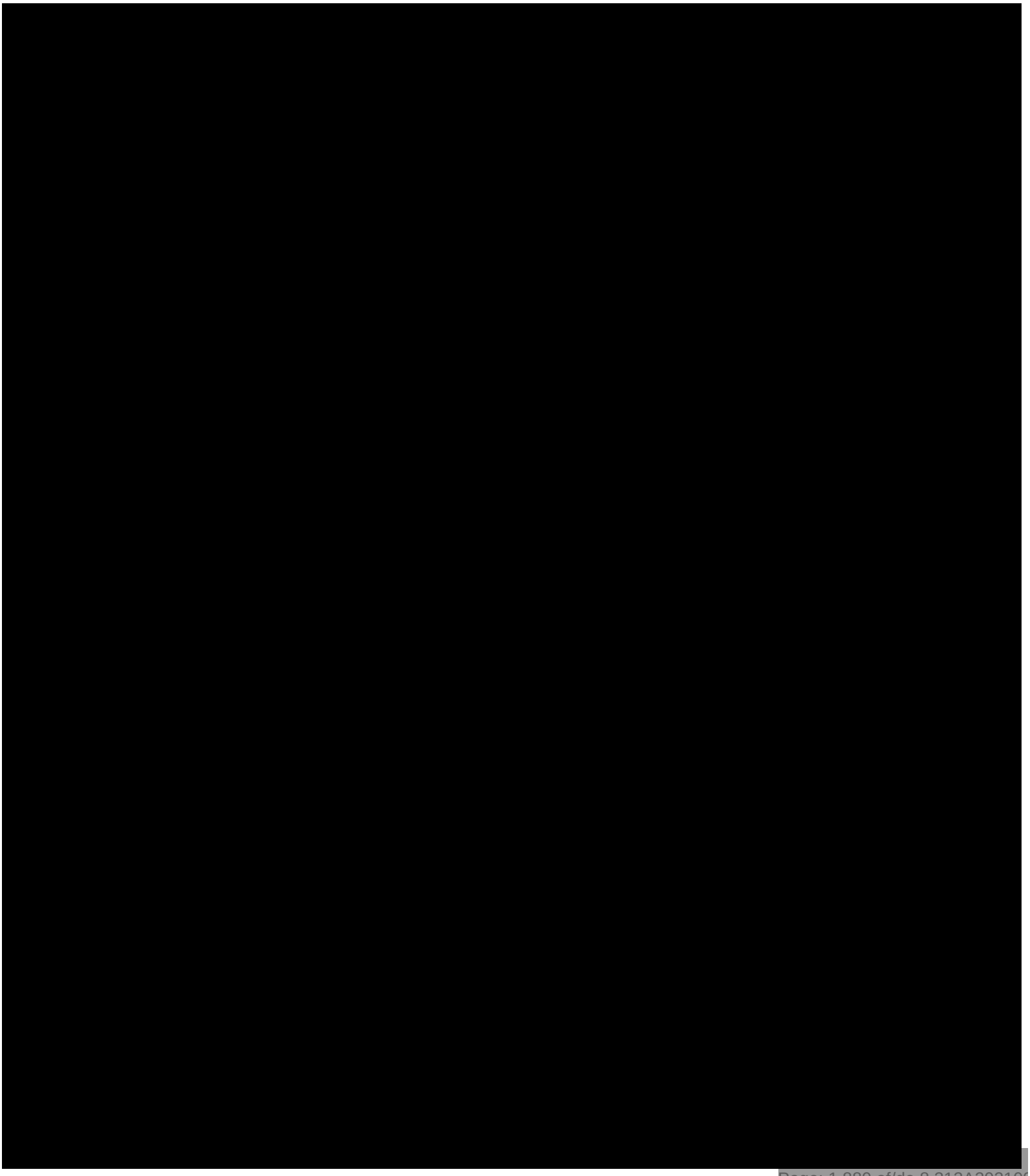

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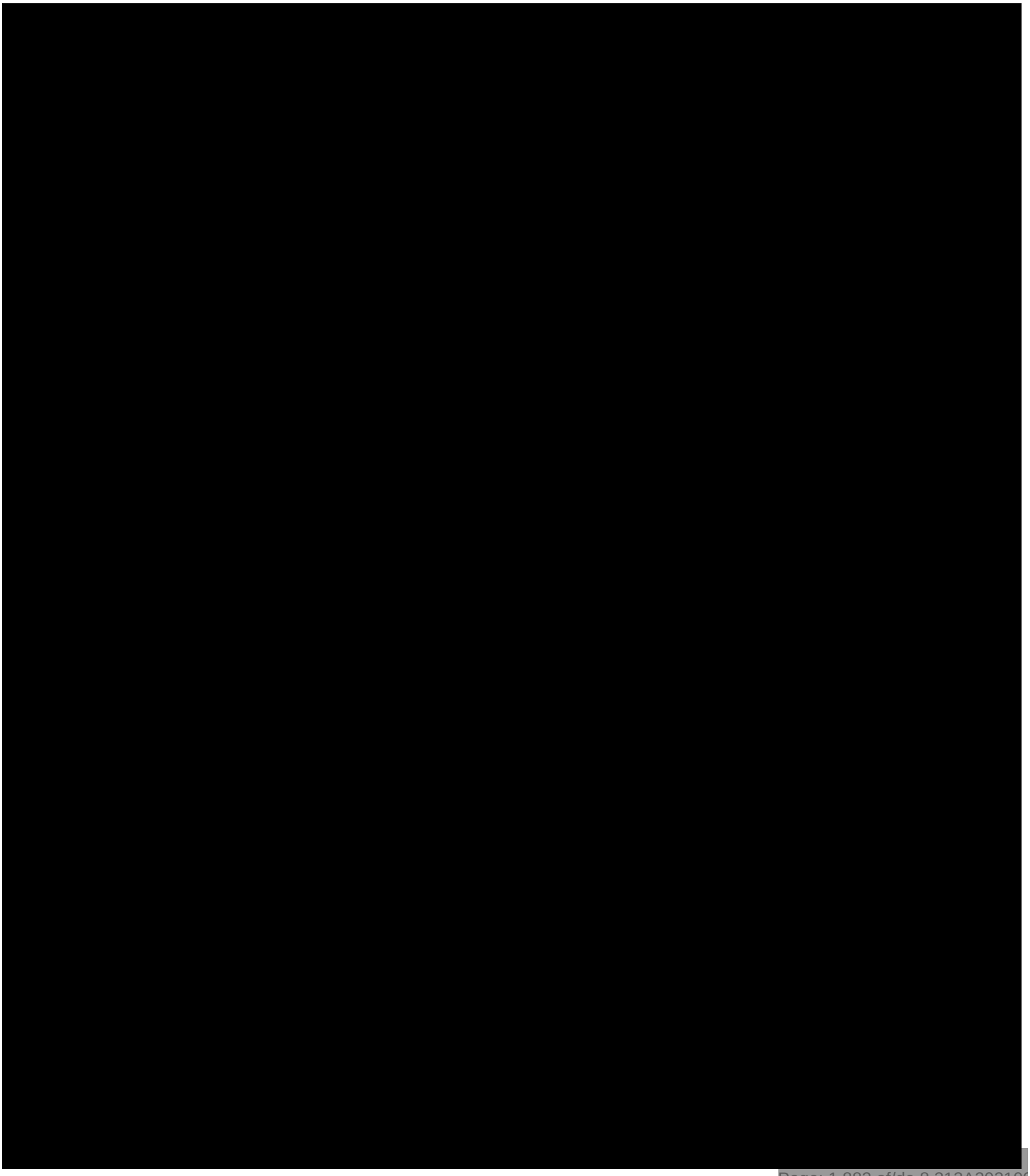

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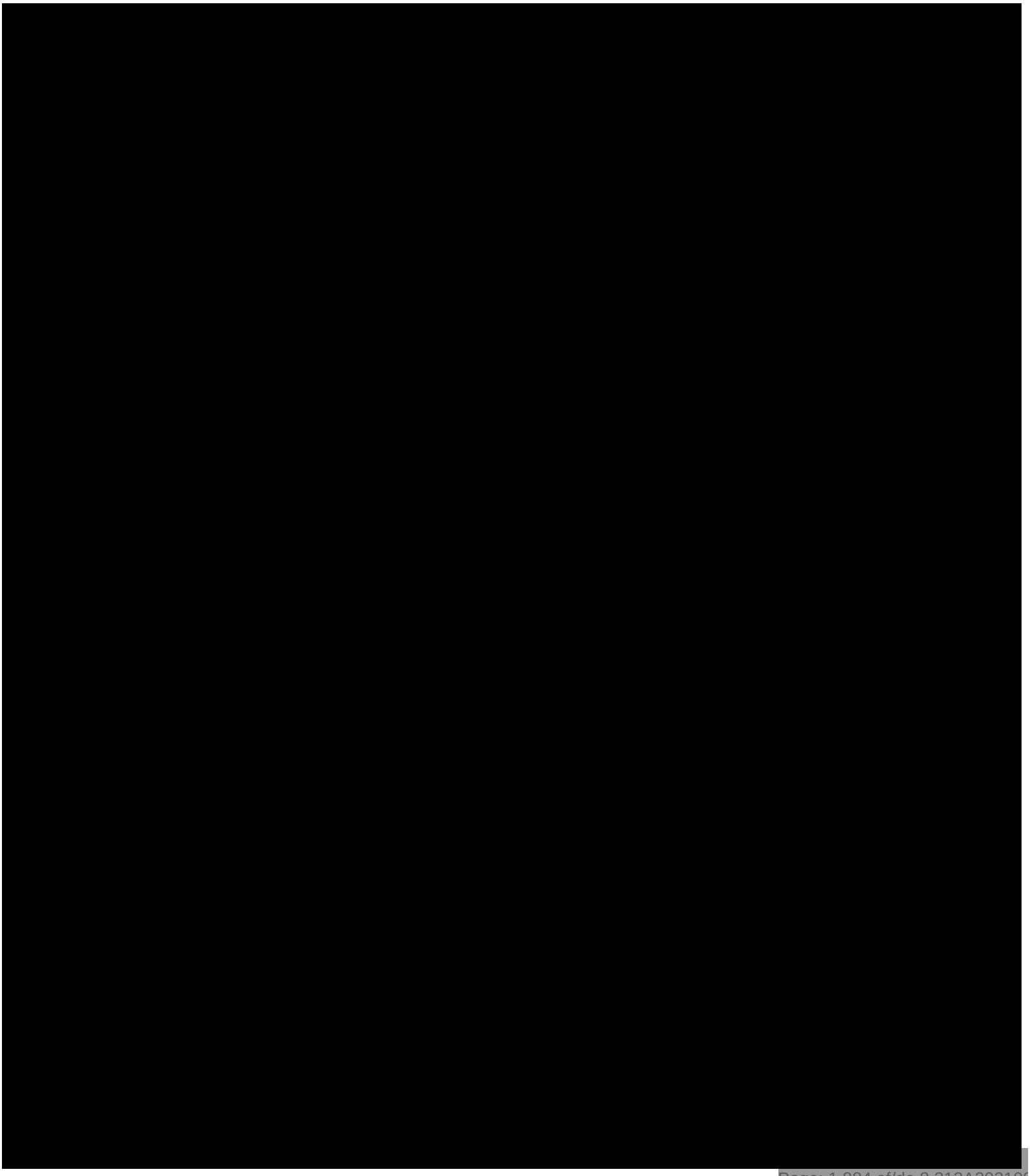

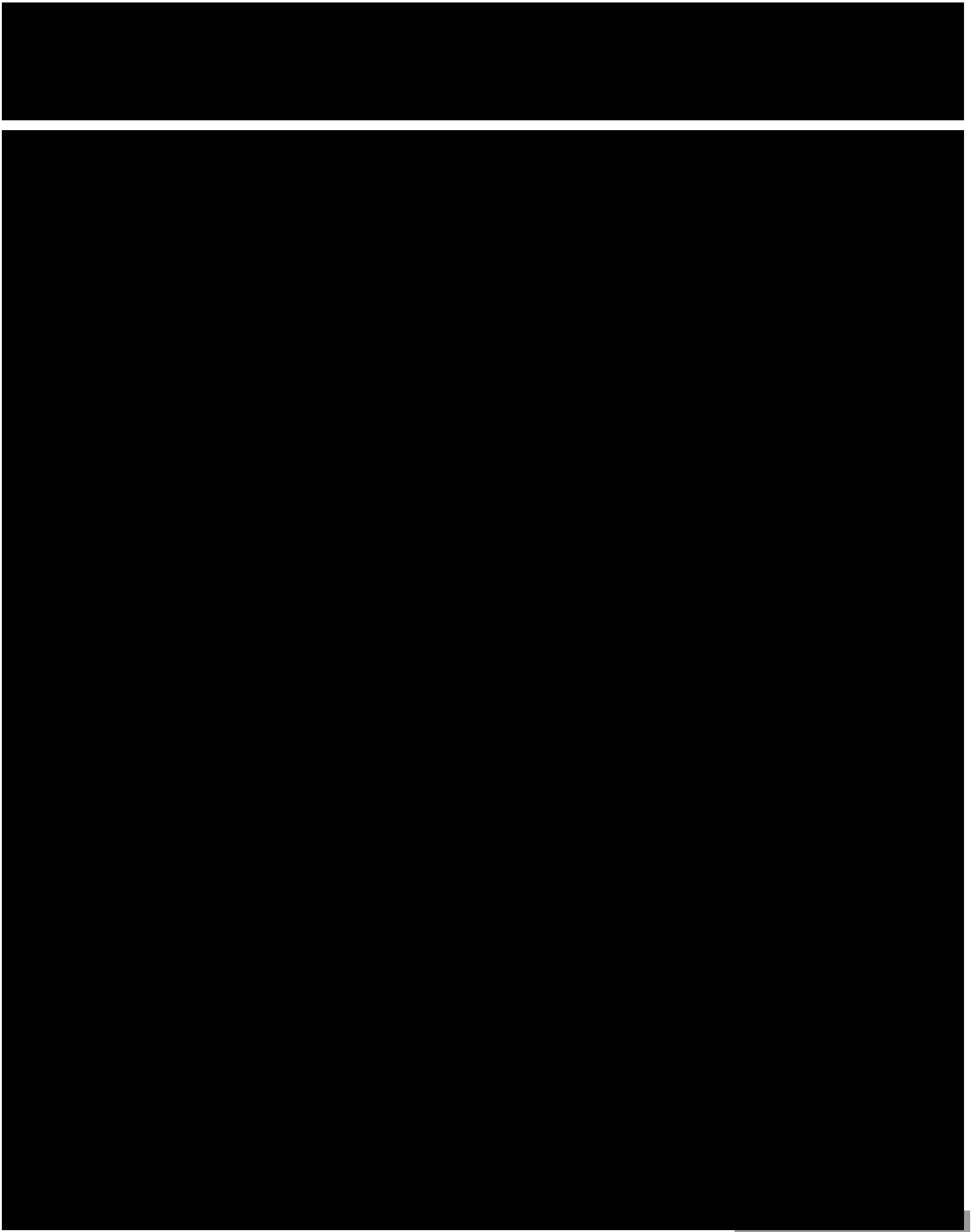

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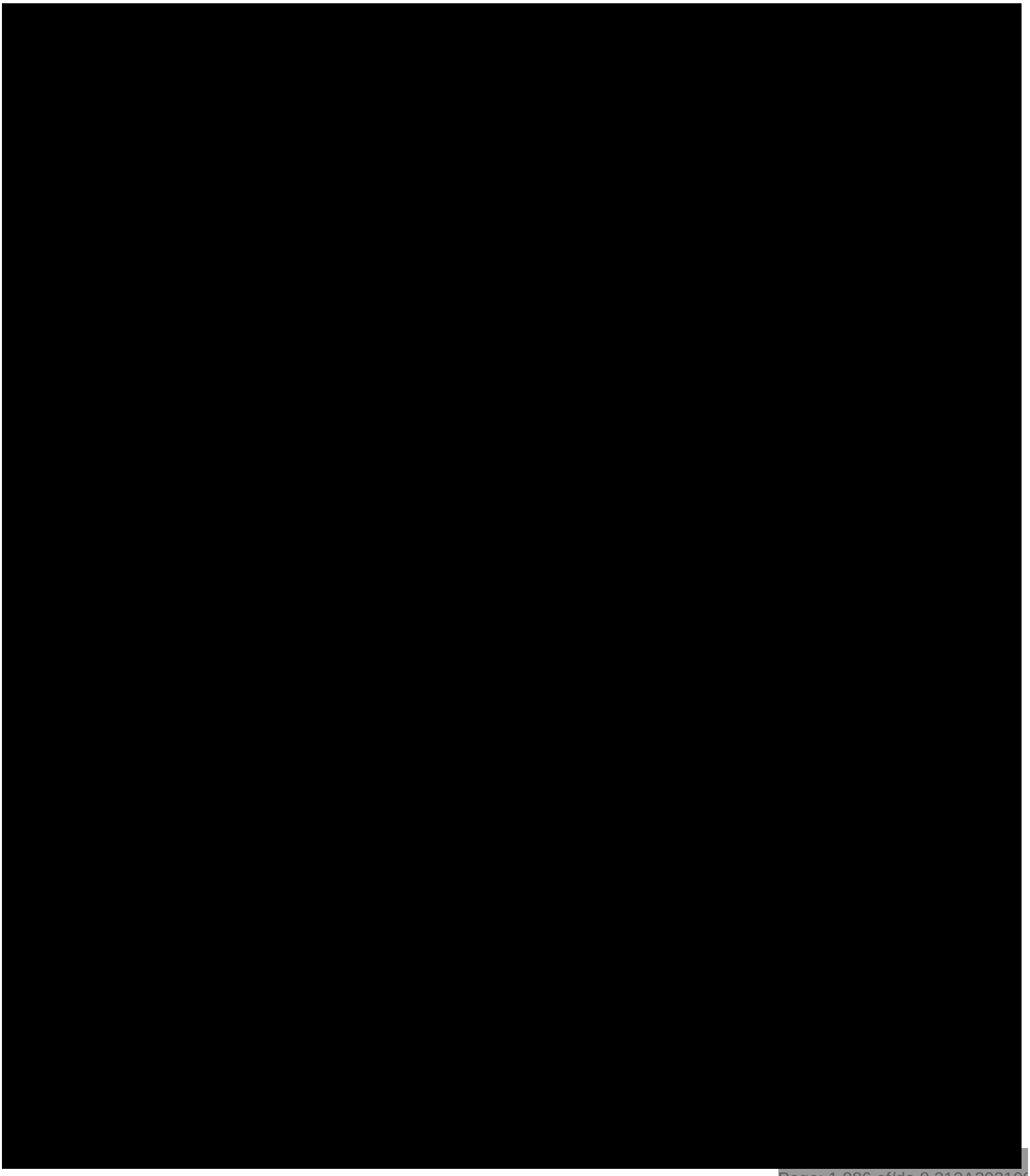

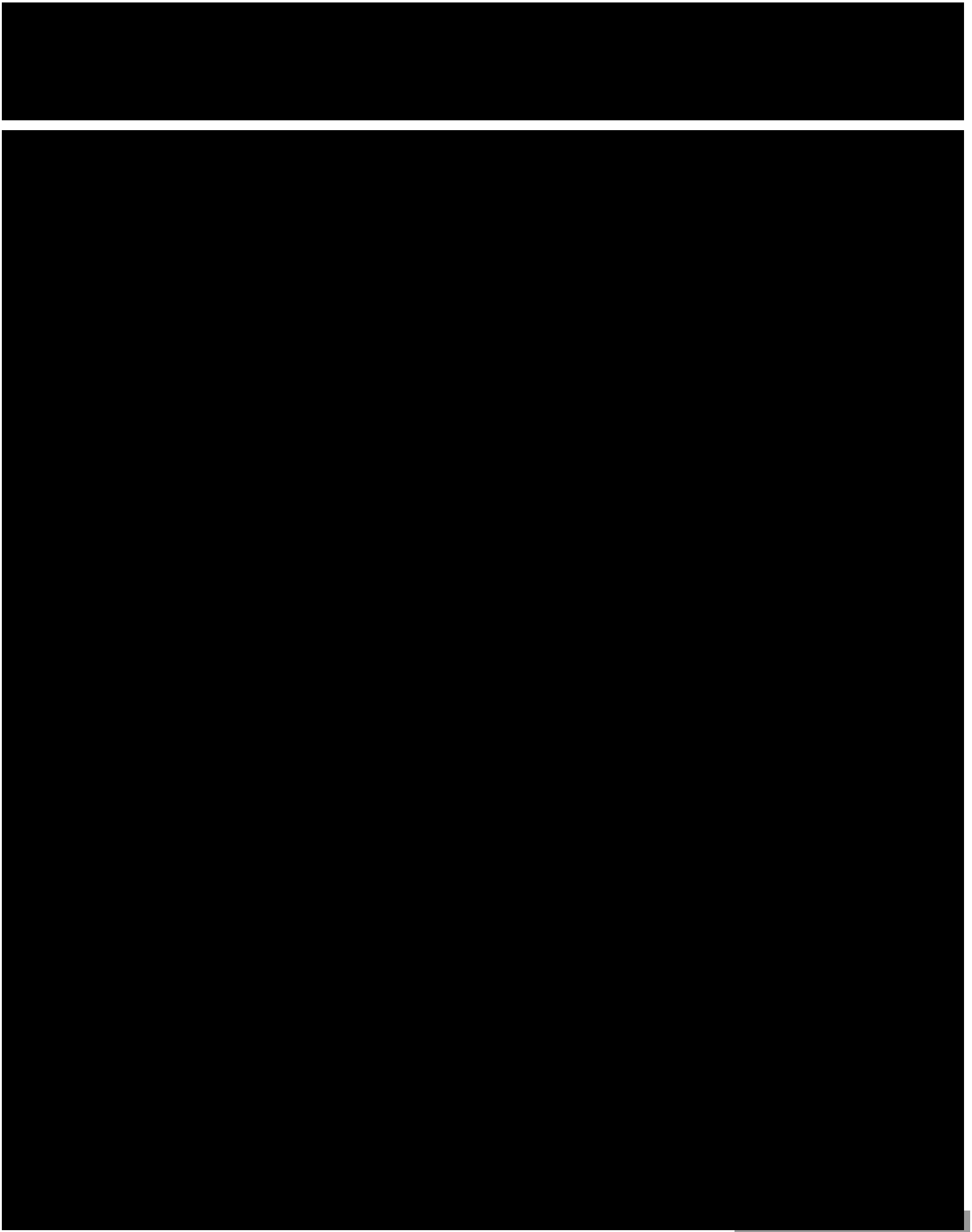

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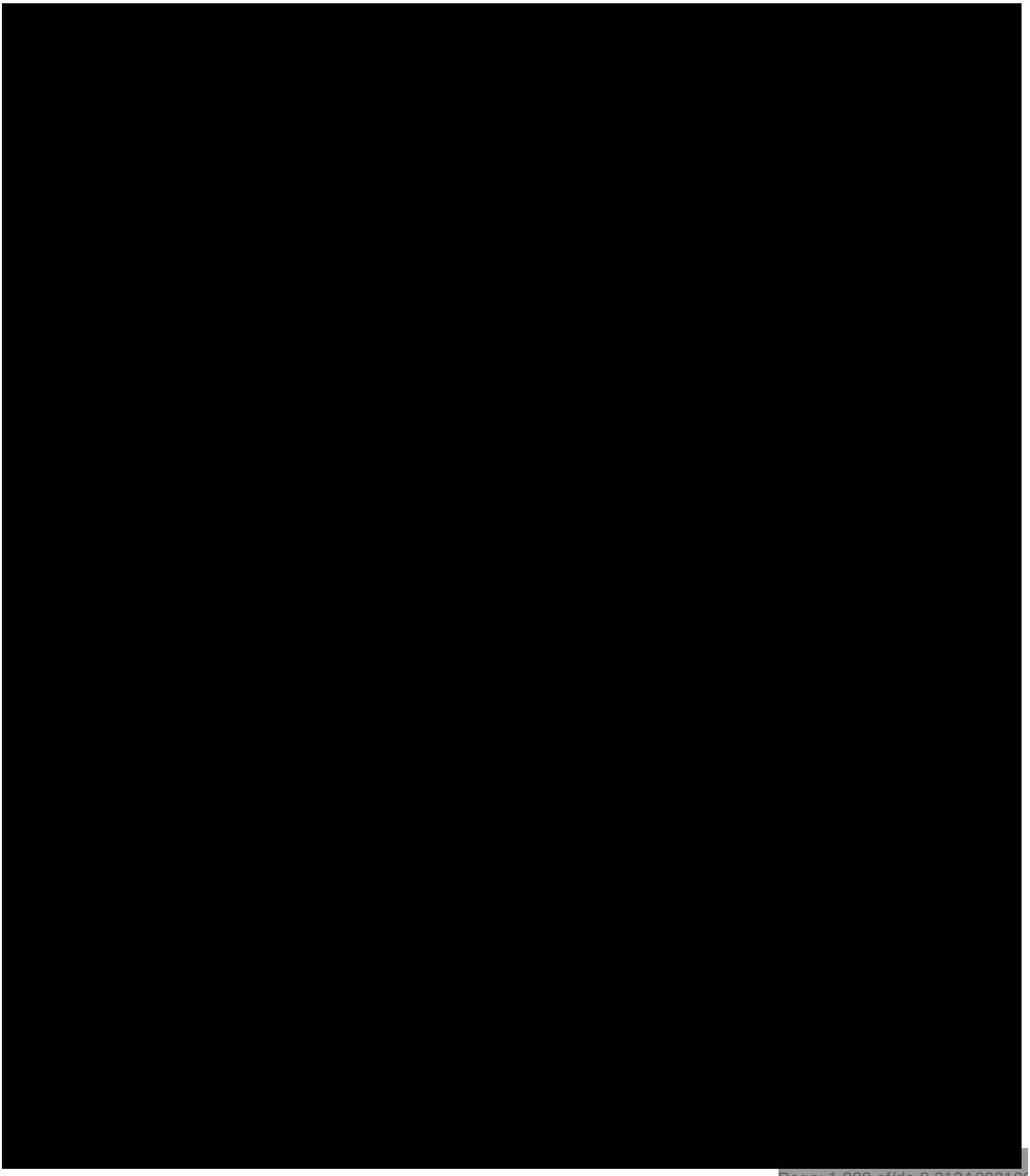

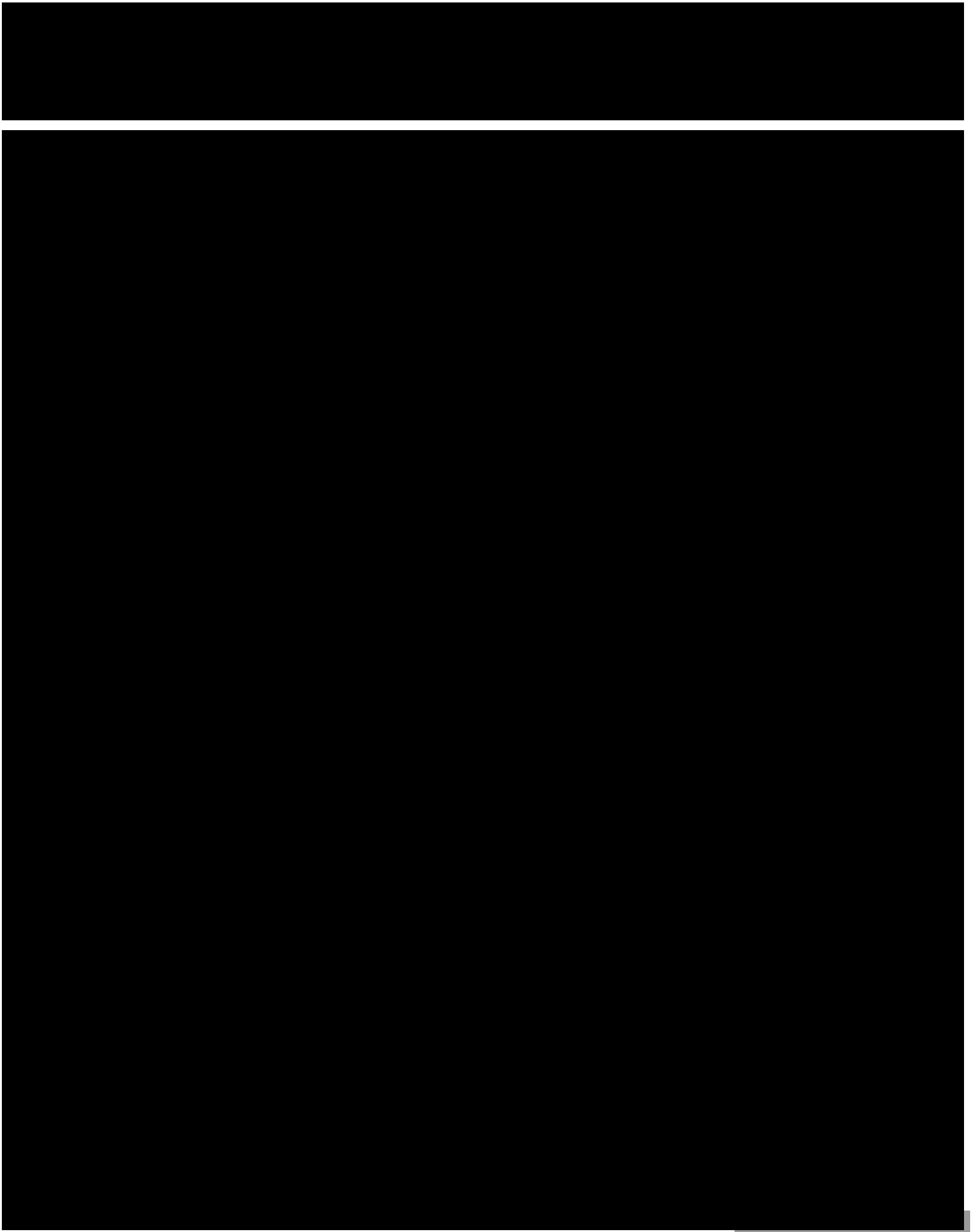

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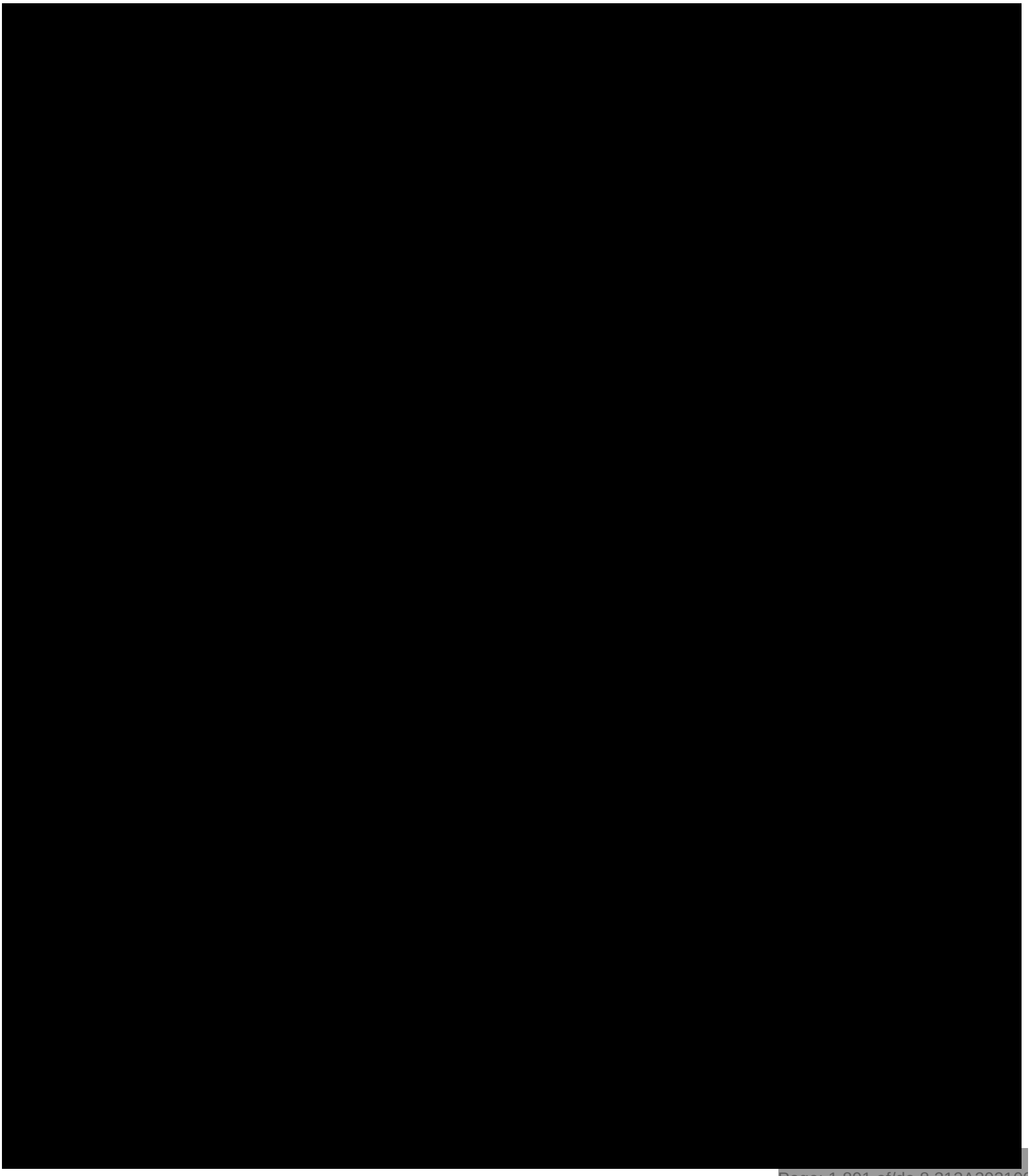

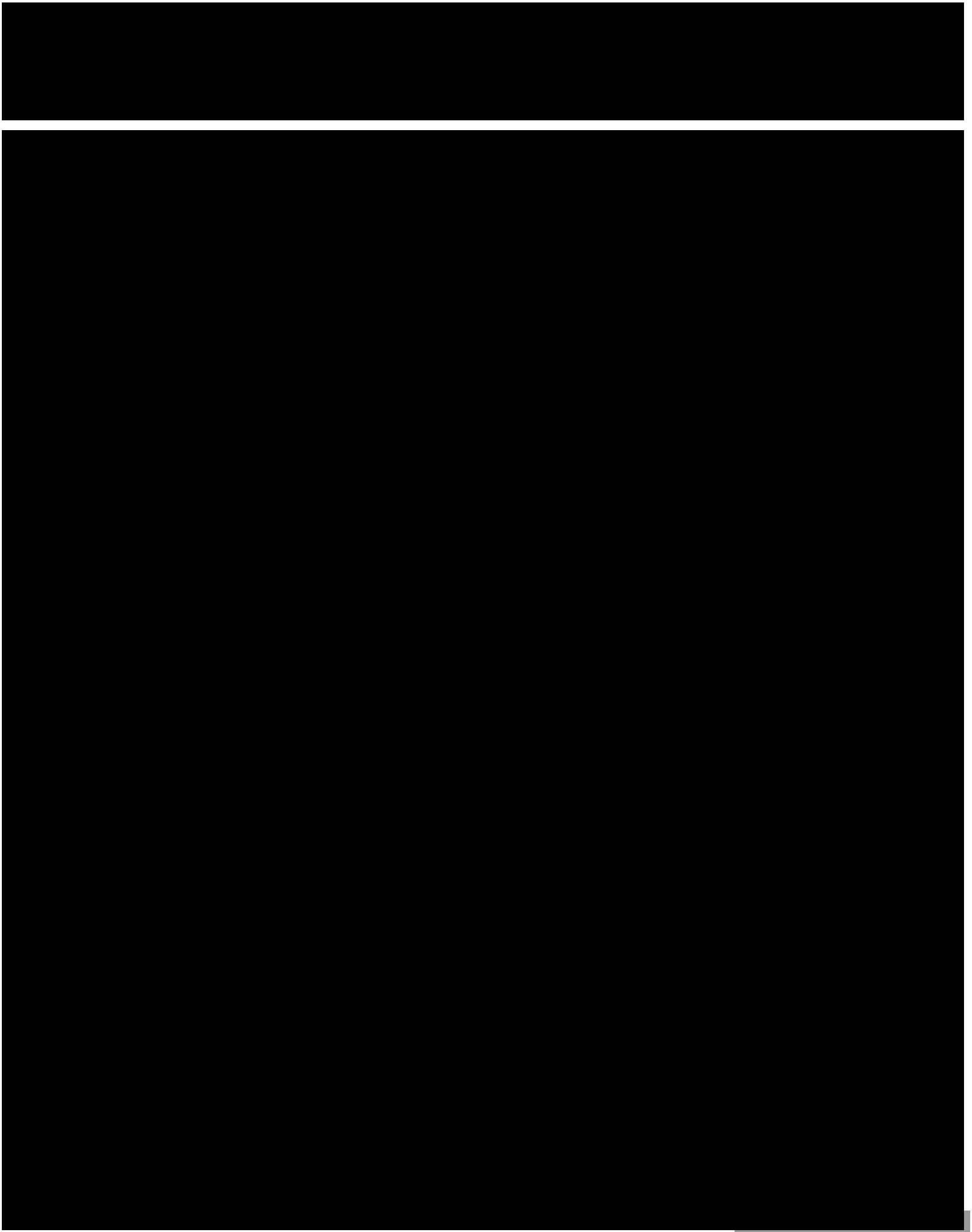

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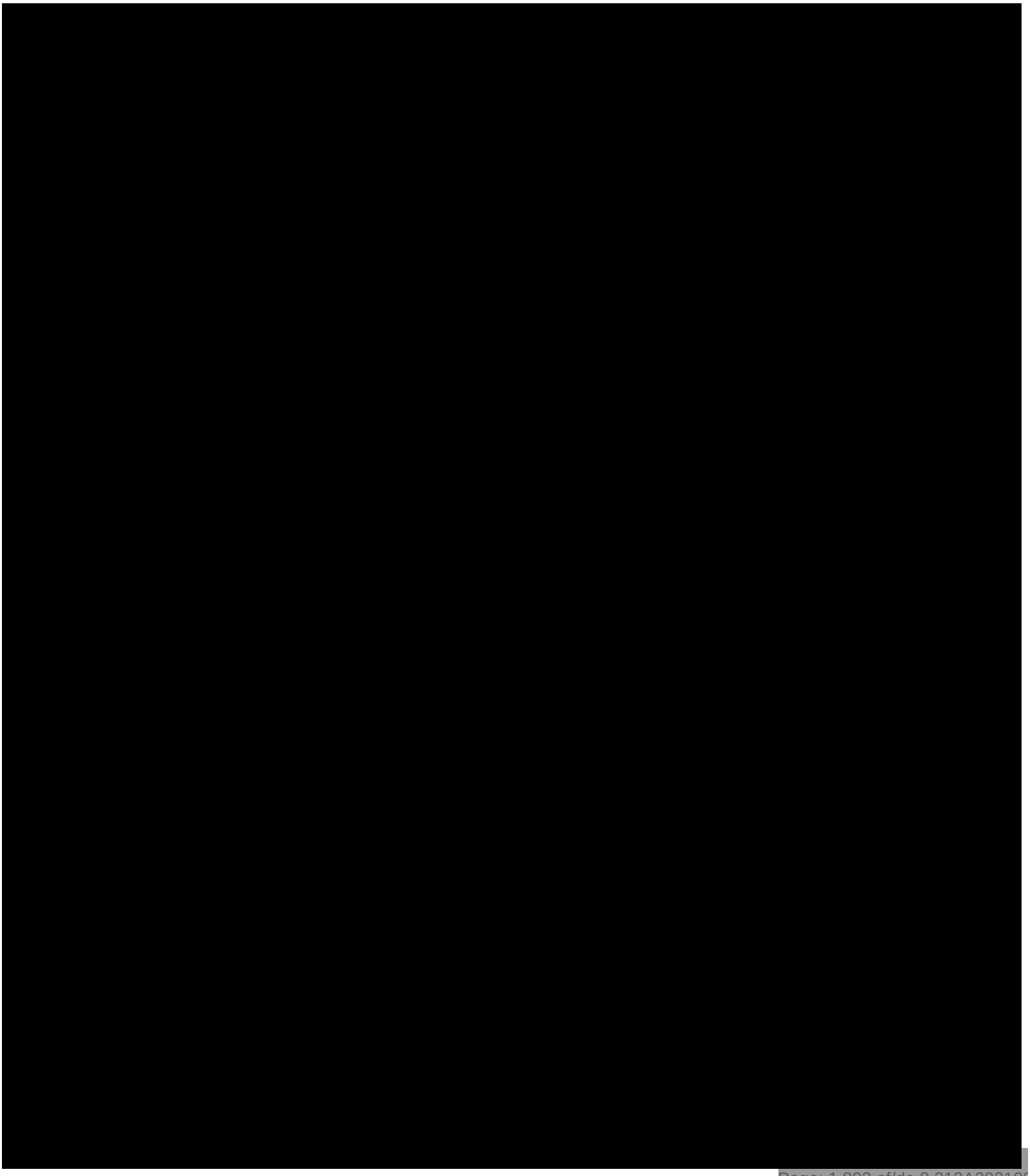

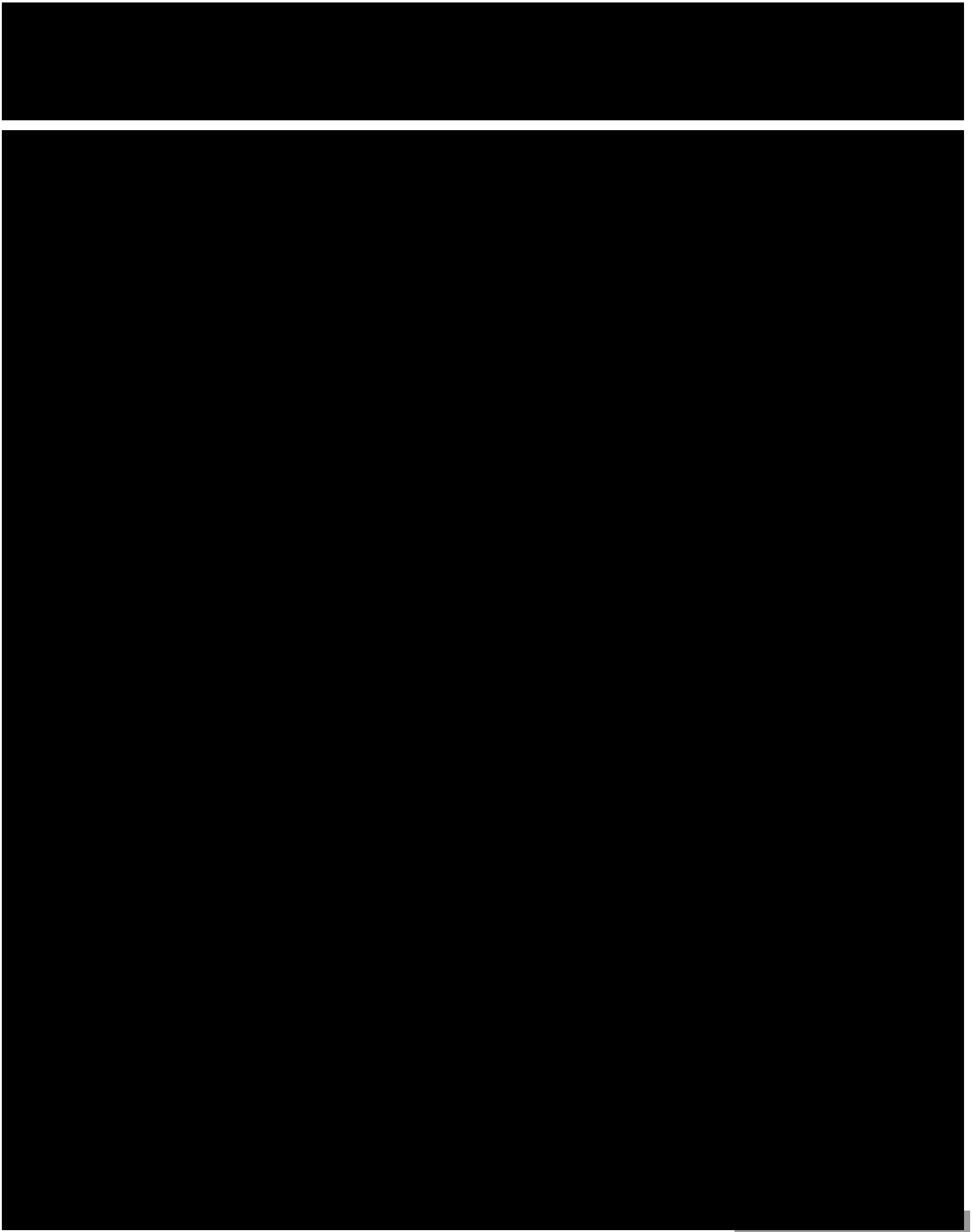

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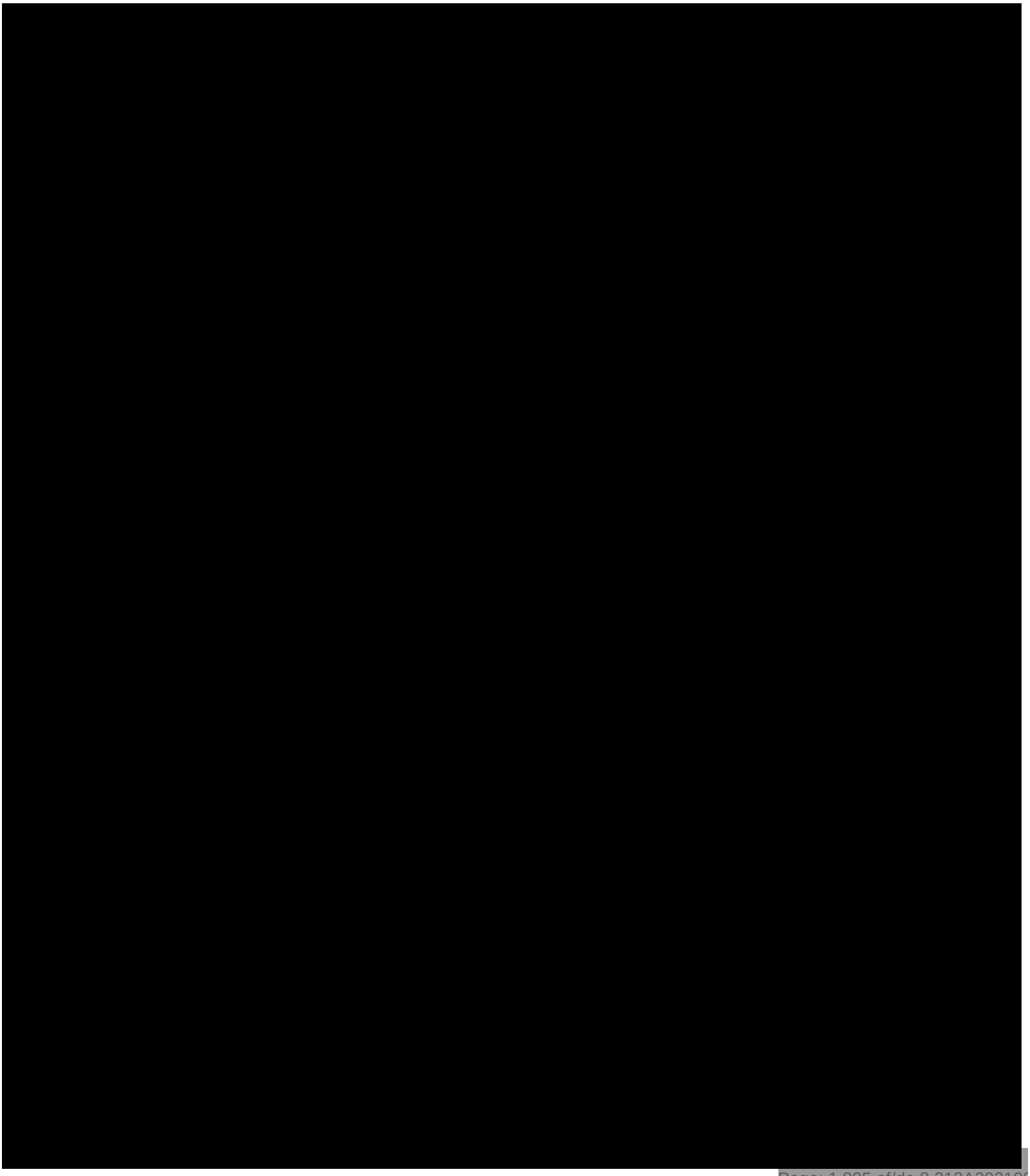

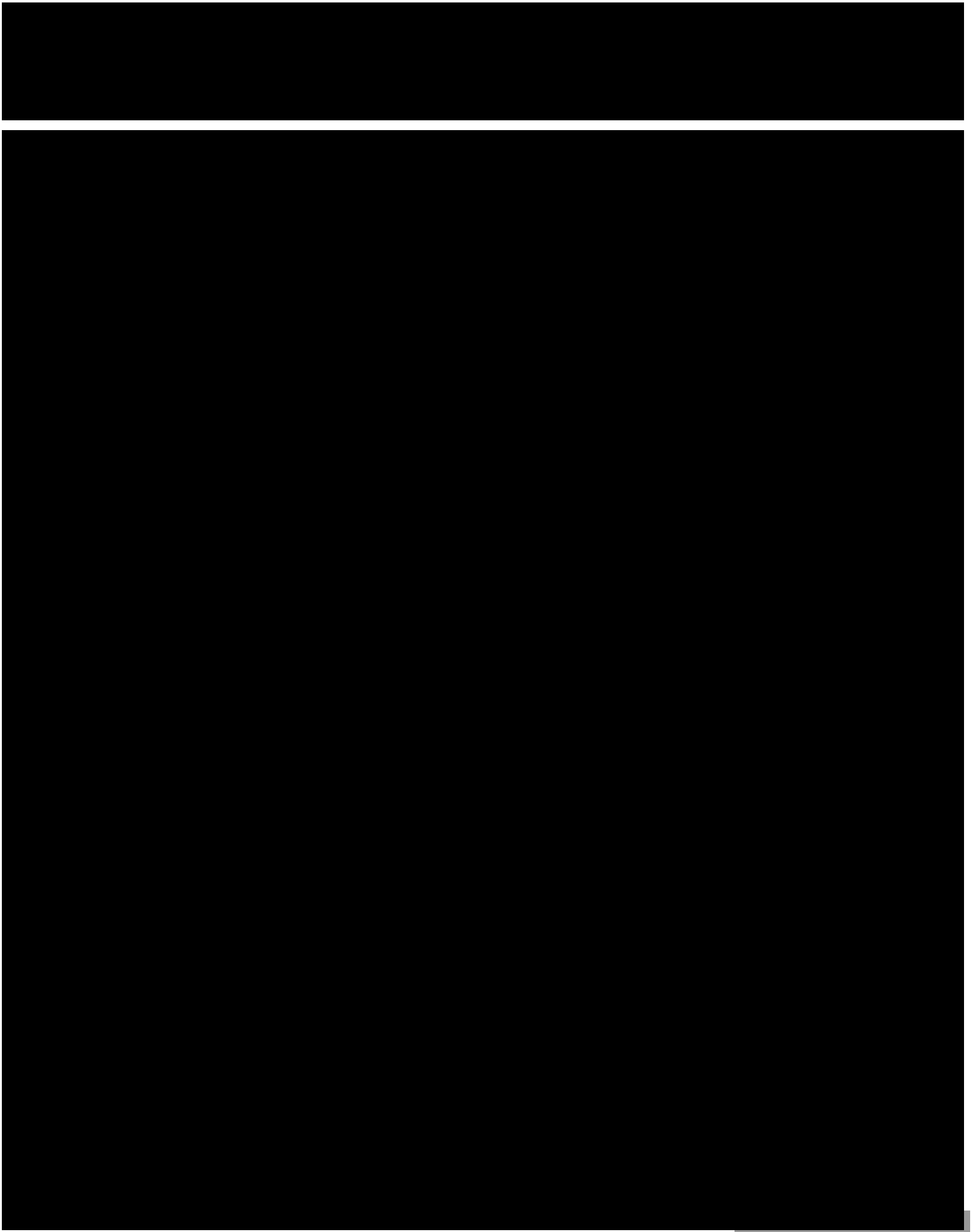

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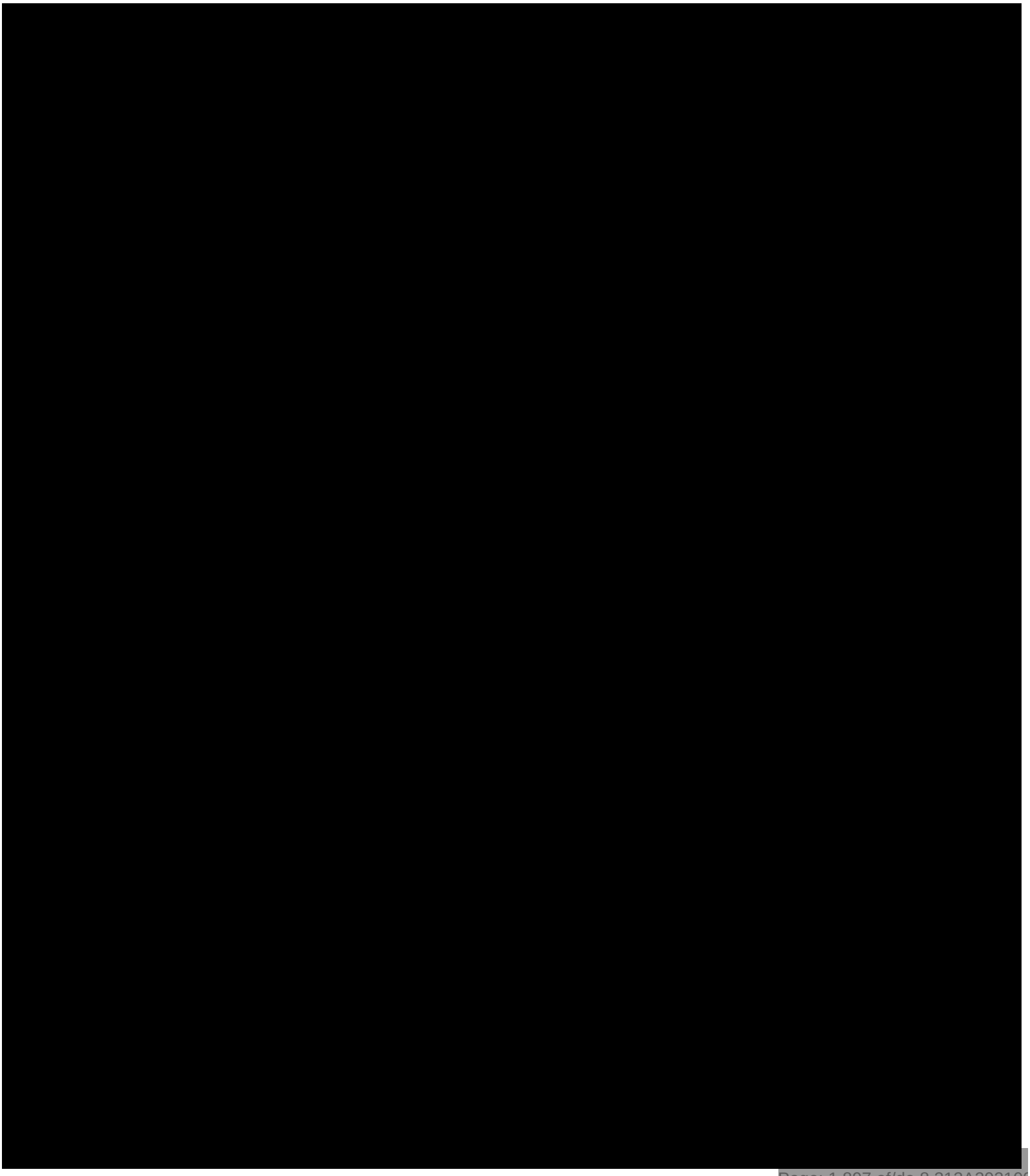

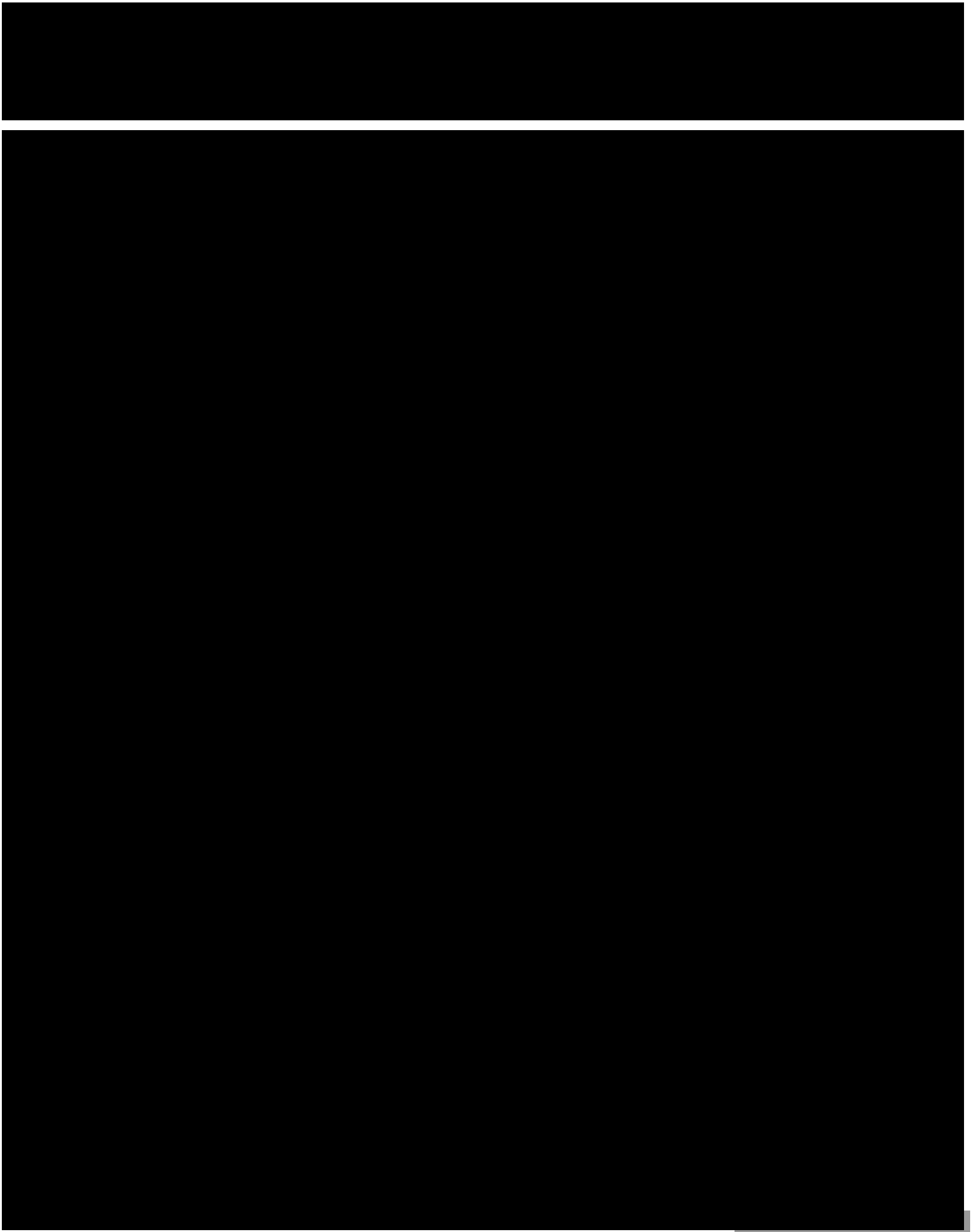

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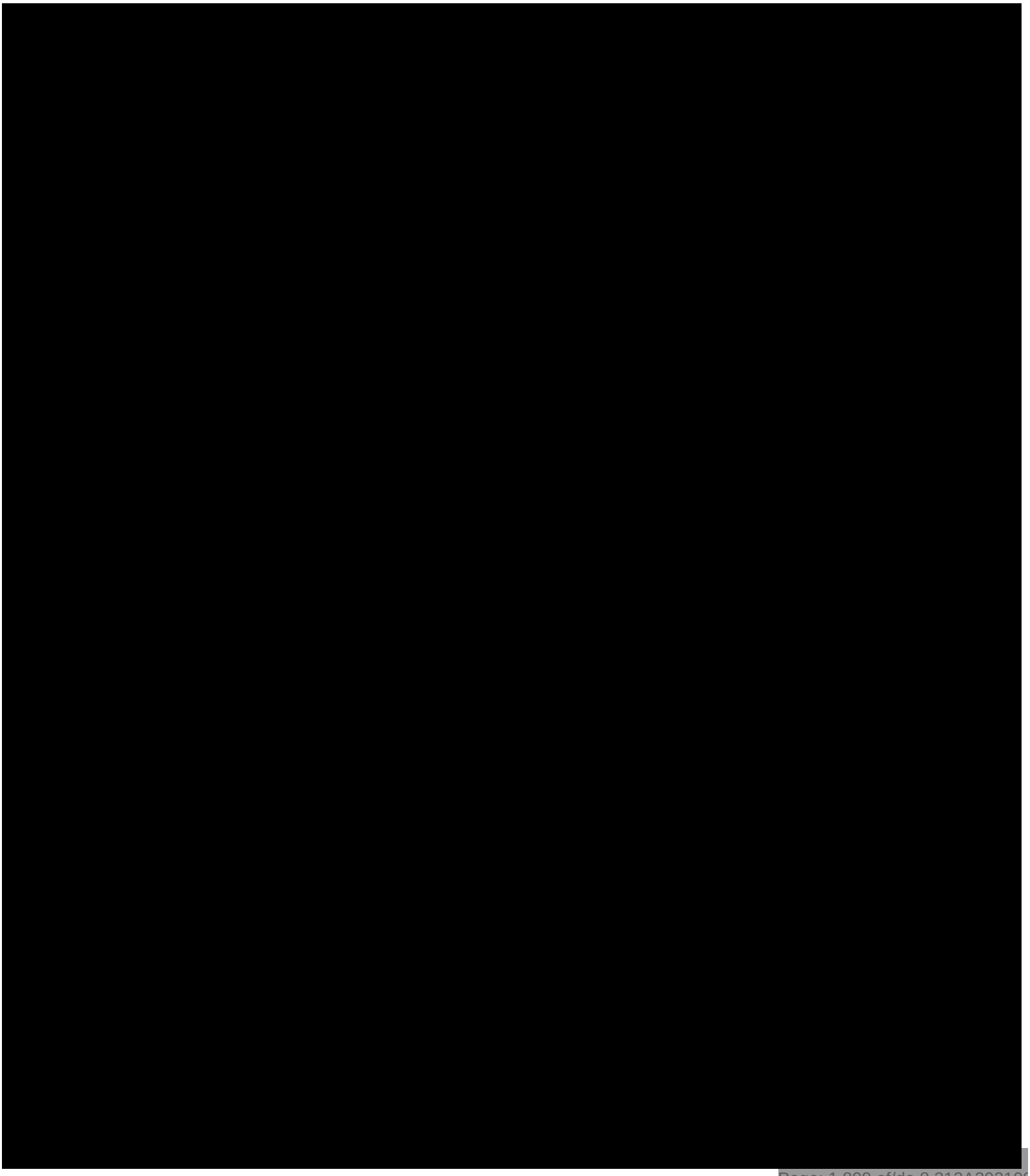

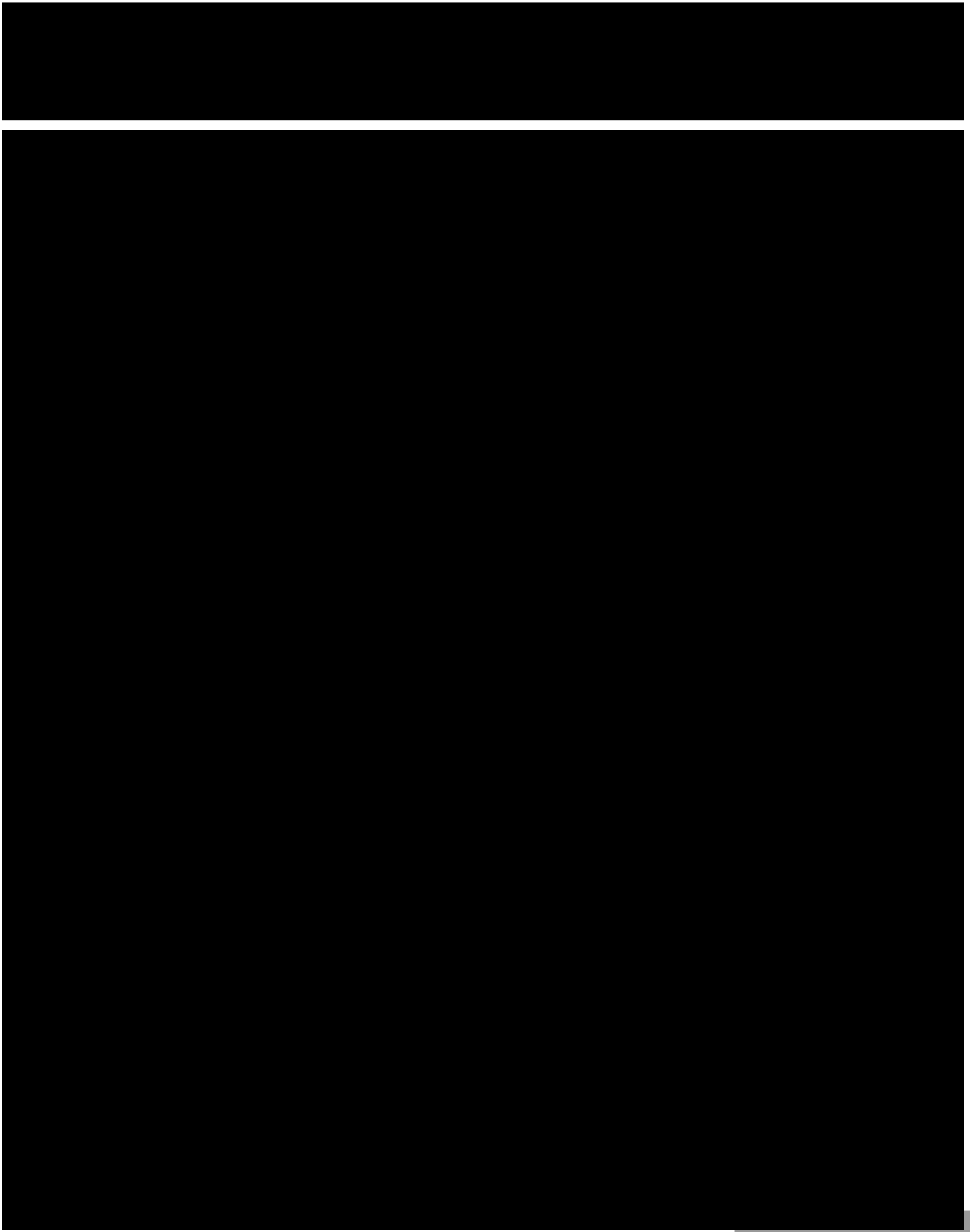

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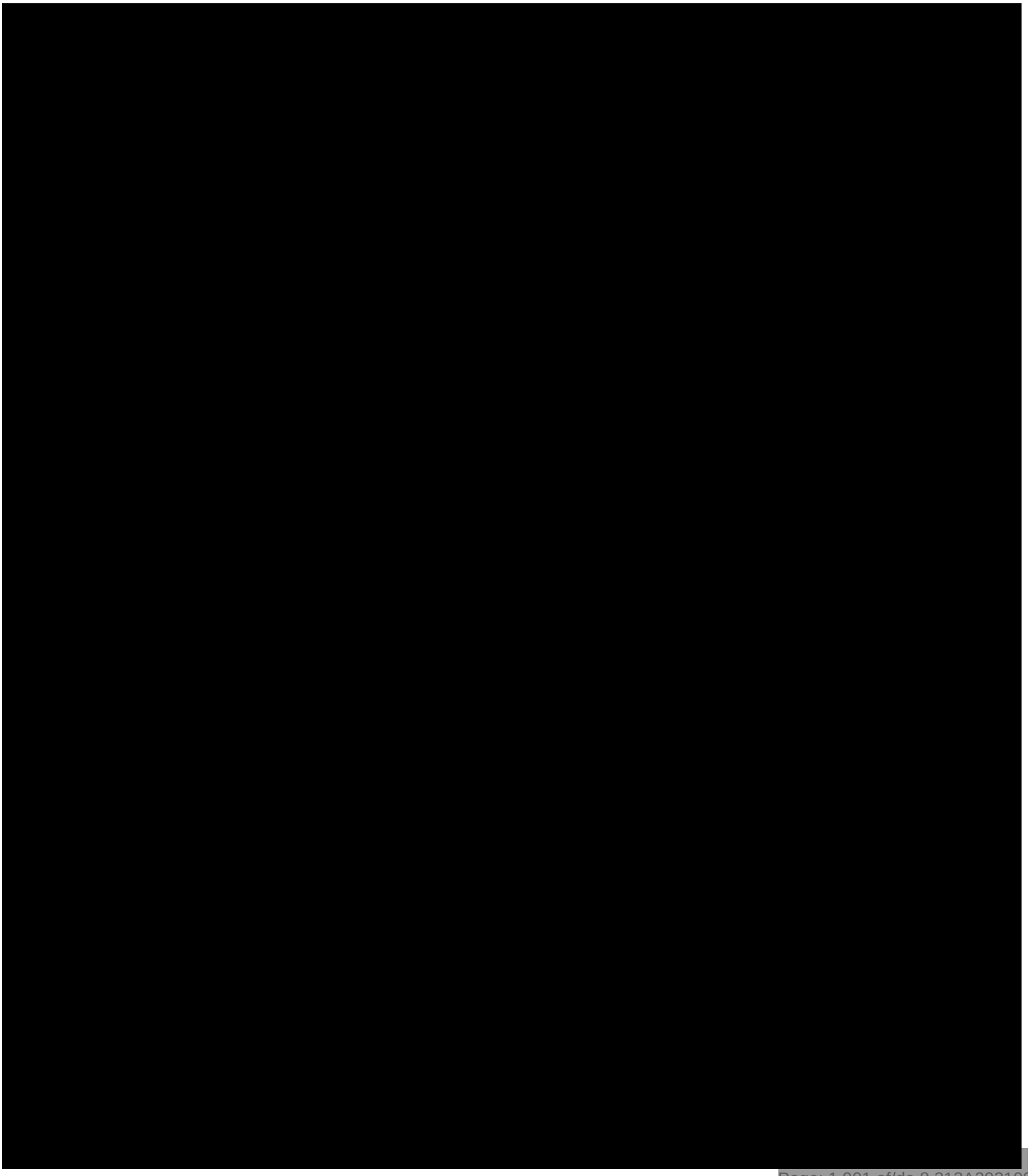

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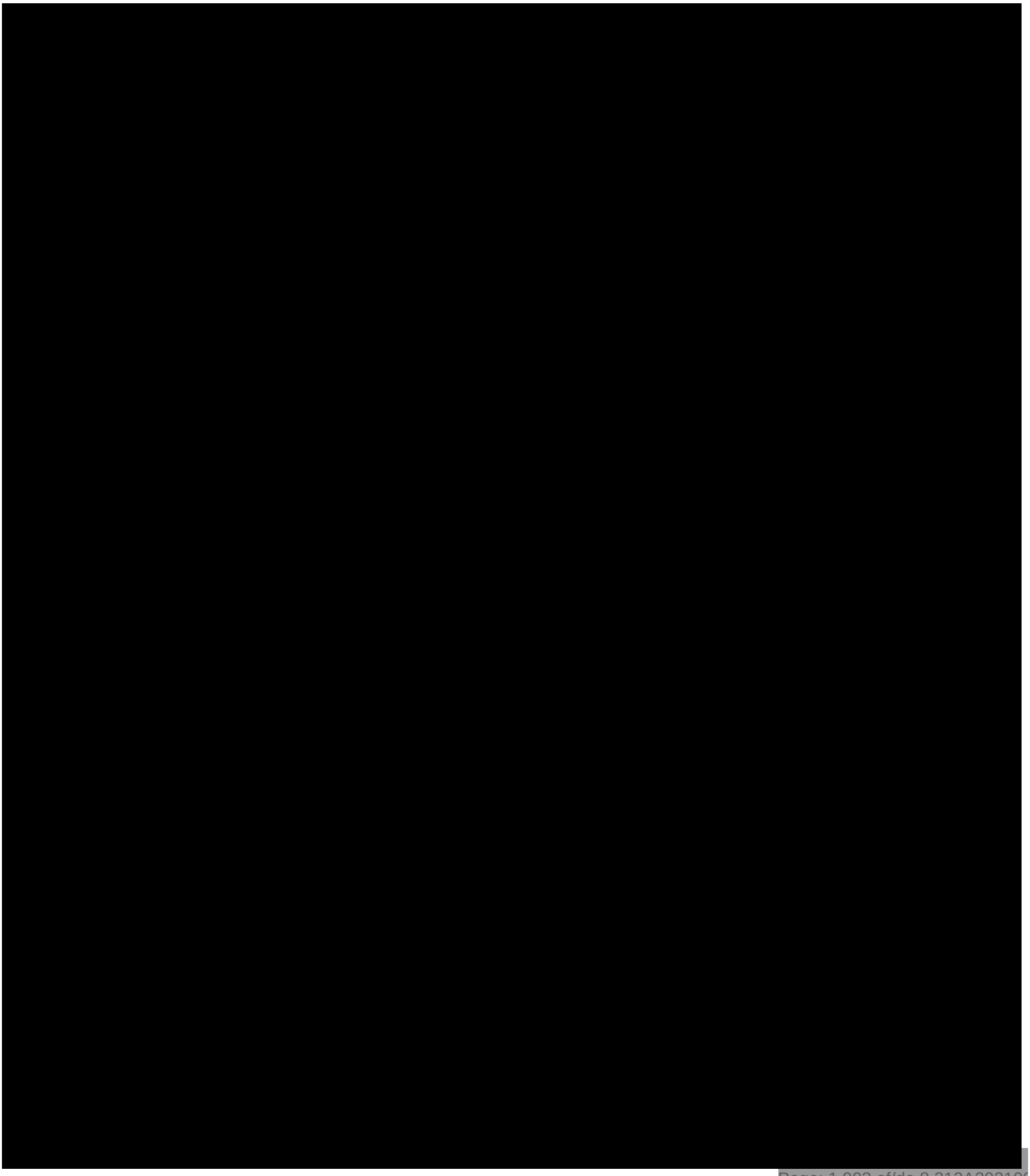

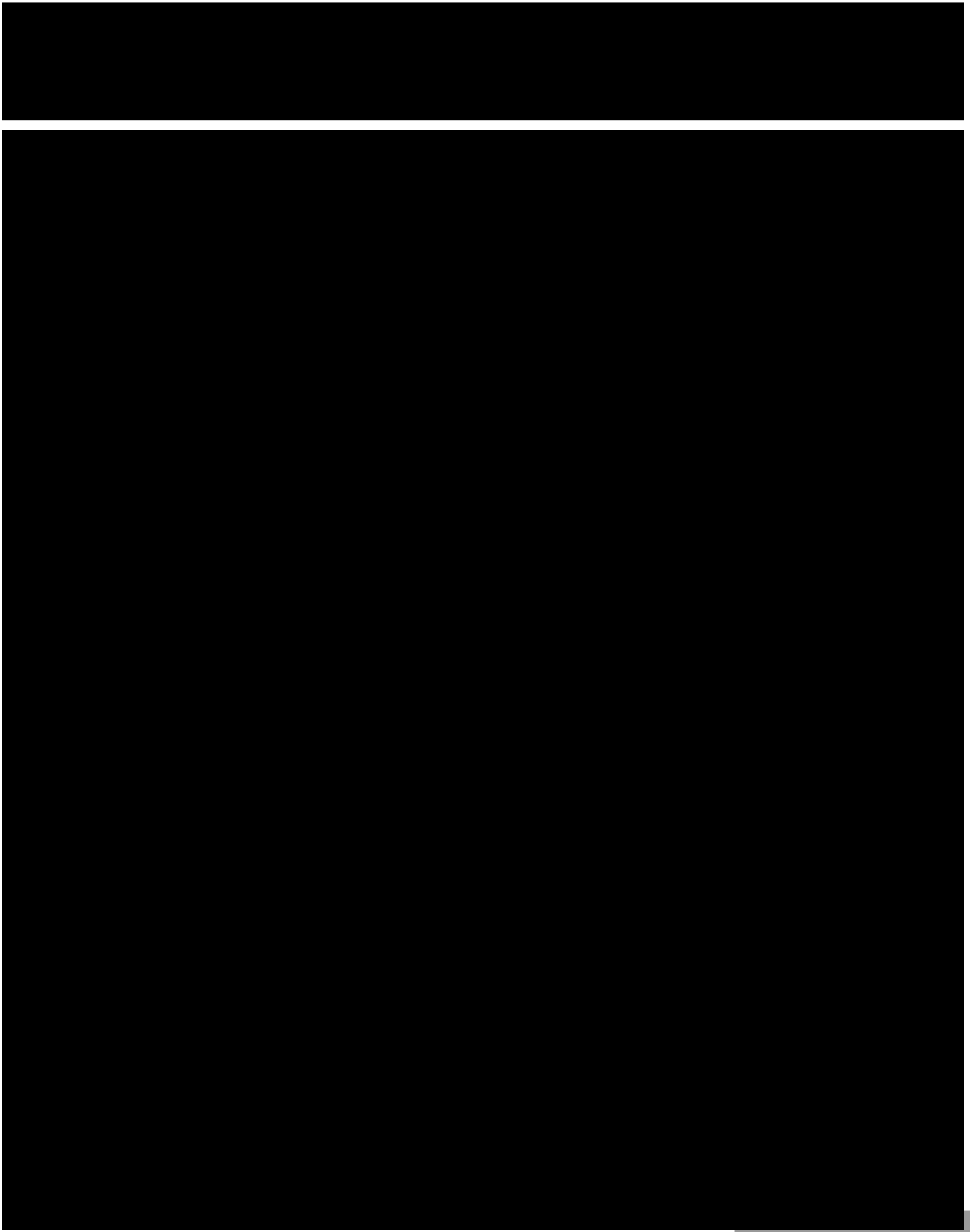

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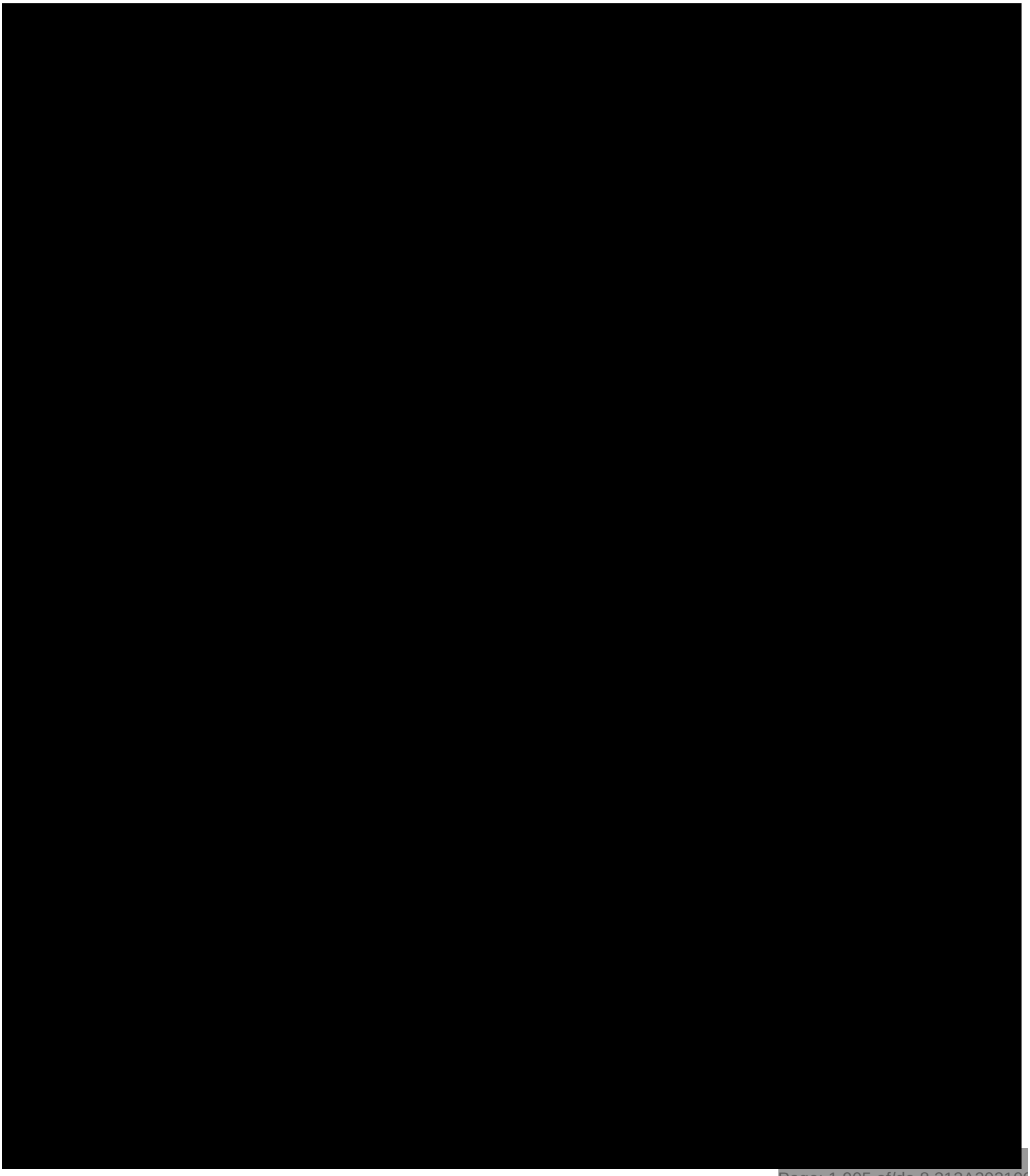

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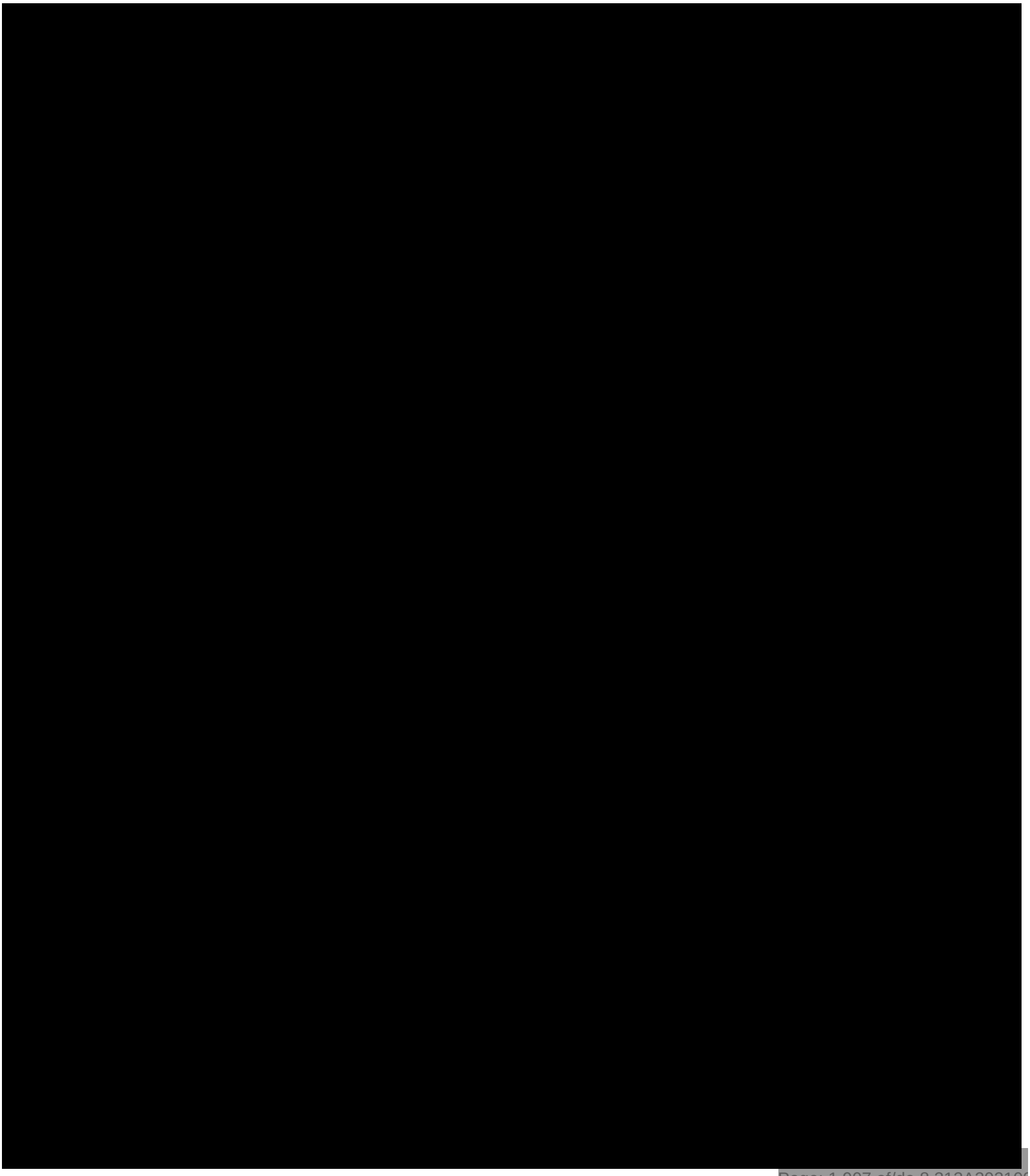

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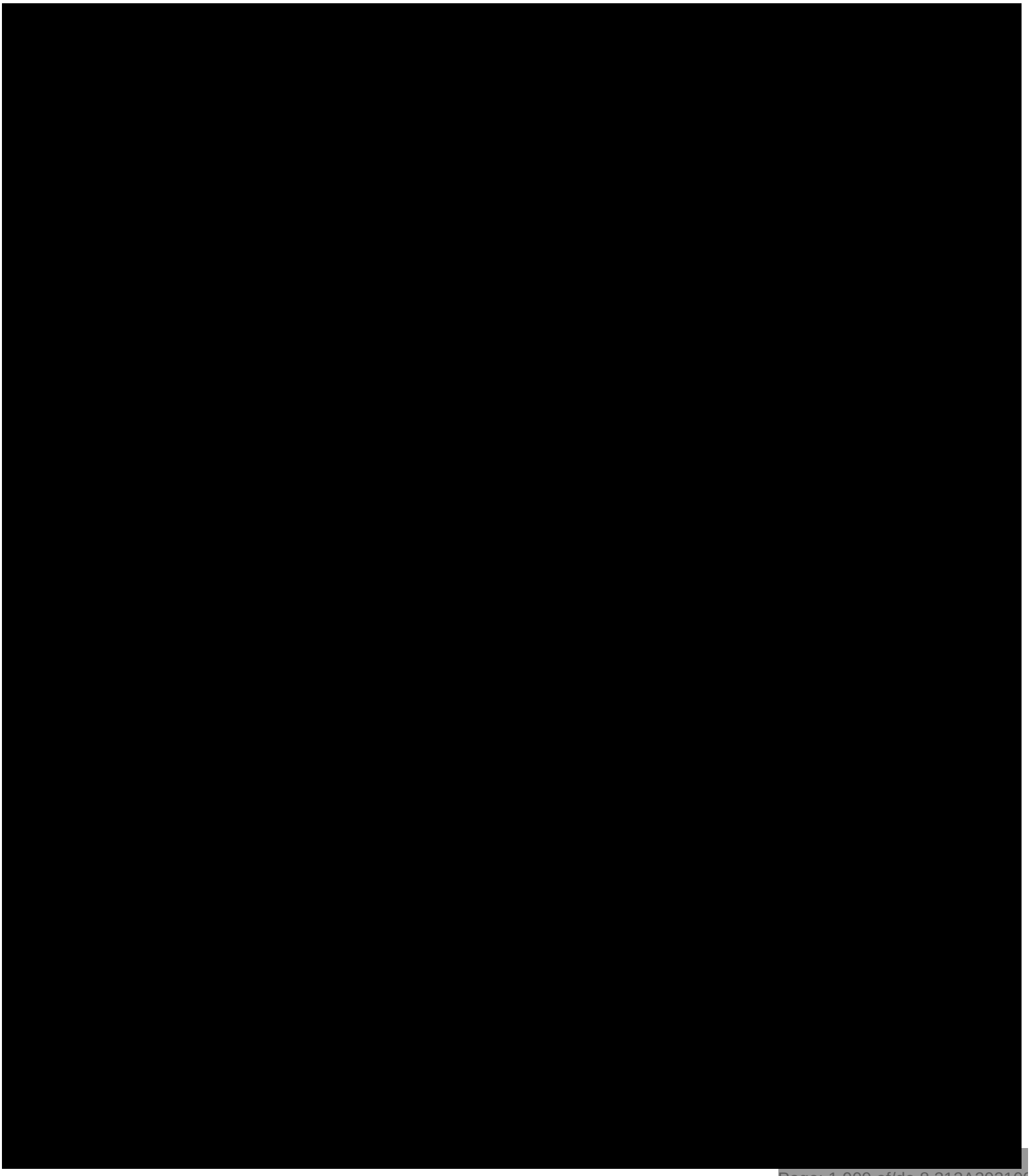

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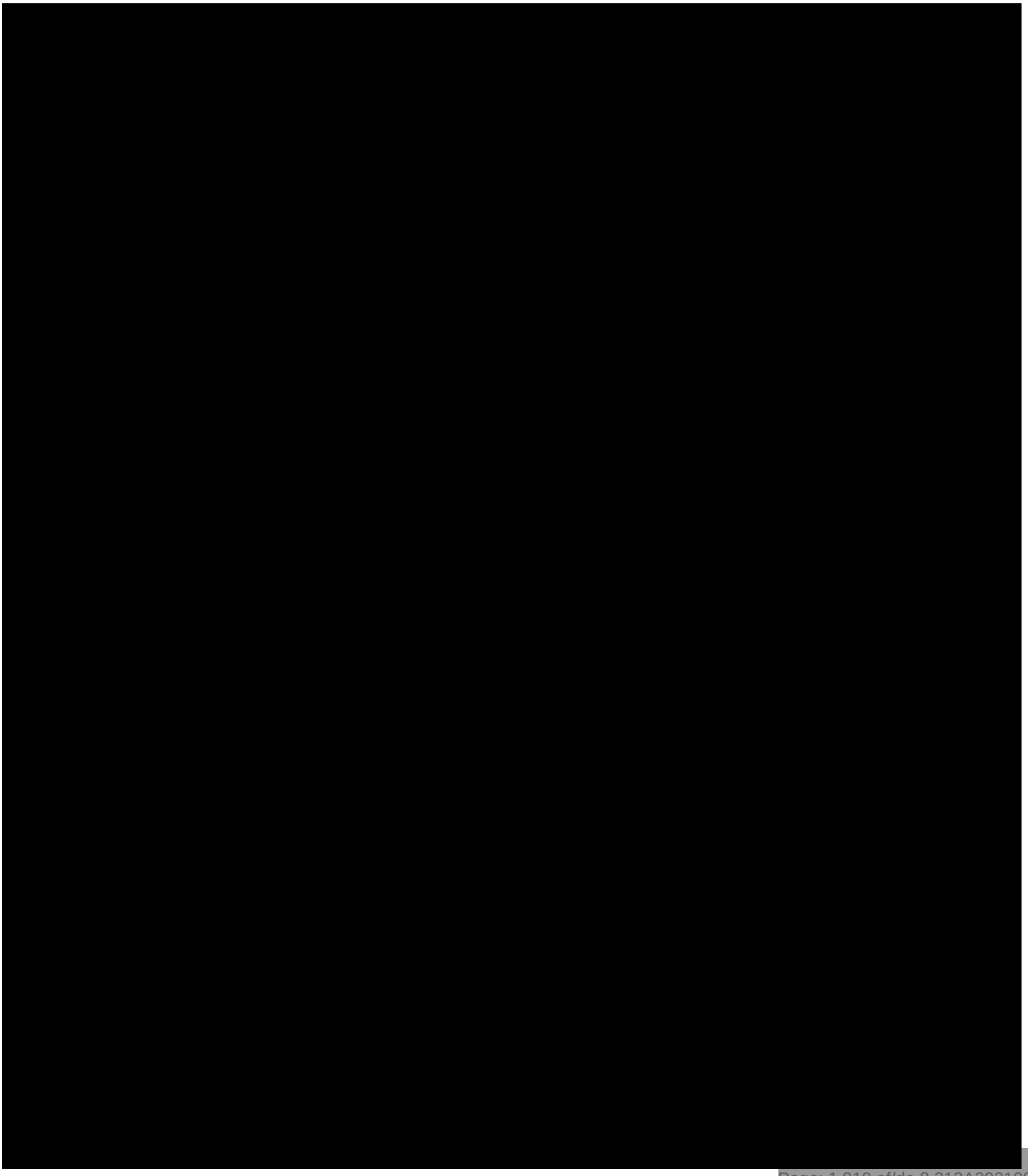

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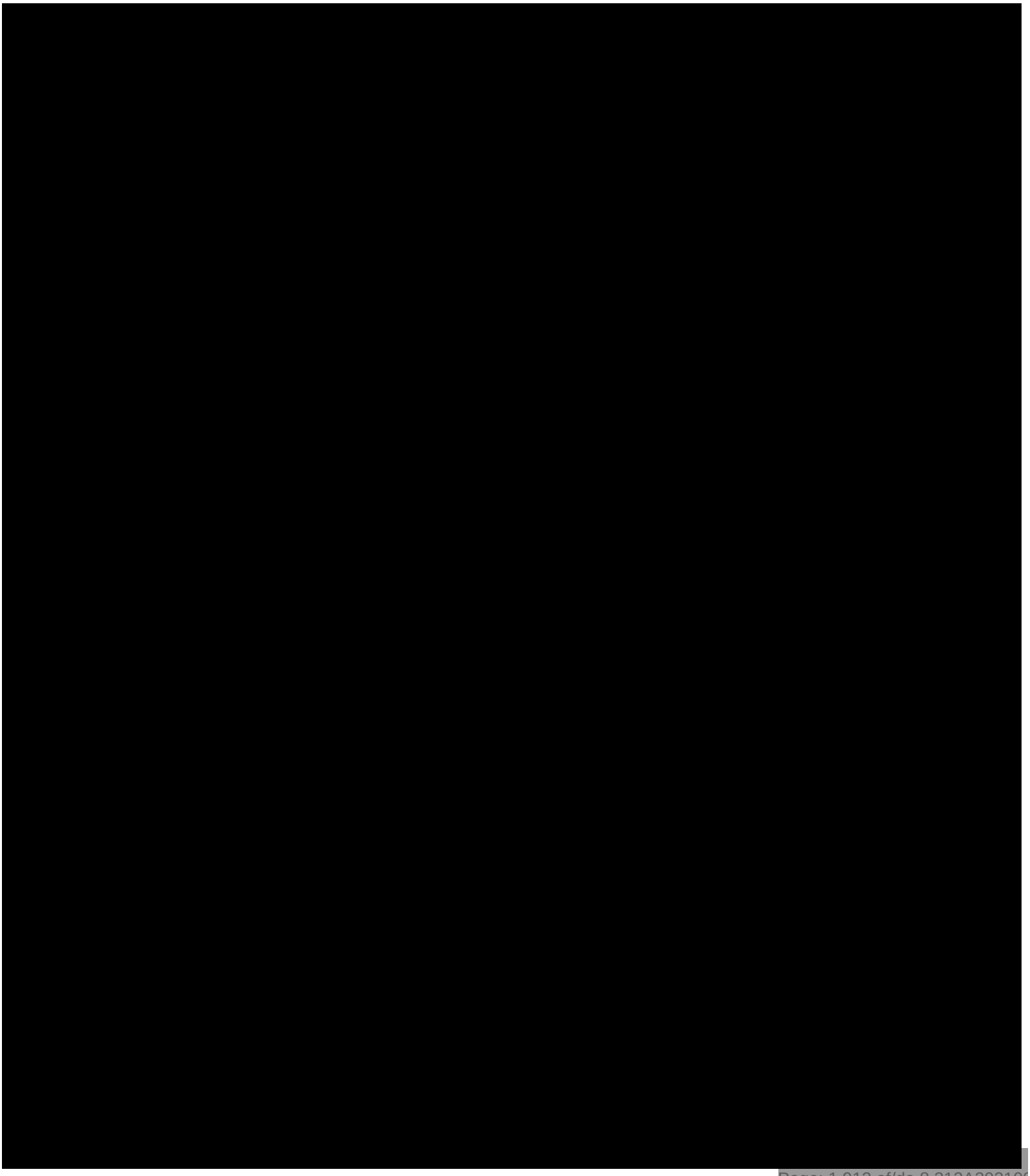

DRUG SUBMISSION APPLICATION FORM FOR: HUMAN, VETERINARY OR DISINFECTANT DRUGS AND CLINICAL TRIAL APPLICATION/ATTESTATION

* denotes a mandatory field
+ denotes a field with validation error or missing data

External Link to the Guidance Document

*5. Product Class

Human

*Type of Human Submission

COVID-19 Interim Order Application(COV19) (Not applicable for Clinical Trial Applications)

6. Number of Original Volumes, Compact Discs, and Duplicates

Original Volumes | Compact Discs | Duplicates

7. Schedule and/or Prescription Status

Schedule D

*8. Brand or Proprietary or Product Name (should be the same as the brand name on the product label)

TBC

*9. Proper, Common or Non-Proprietary Name

Novavax COVID-19 Vaccine (SARS-CoV-2 rS with Matrix-M1 Adjuvant)

10. Company Code (if assigned)

Does the product fall under the Controlled Drugs and Substances Act (CDSA)?

PART 1 - MANUFACTURER/SPONSOR INFORMATION

A) MANUFACTURER/SPONSOR MAILING ADDRESS

*11. Company Name

Novavax Inc.

*12. Street/Suite

21 Firstfield Road

*13. City - Town	*15. Country	*14. State	*16. ZIP Code
Gaithersburg	United States	Maryland	20878

MANUFACTURER/SPONSOR CONTACT

*Salutation	*Given Name	Initials	*17. Surname	*21. Title	*20. Language
Ms.	[redacted]		[redacted]	[redacted]	English

*18. Telephone No.	Ext.	19. Fax No.	*22. Email
[redacted]			[redacted]

B) CONTACT MAILING ADDRESS (For THIS Drug Submission)

☐ Same as A Above (that is Manufacturer/Sponsor Mailing Address)

*23. Company Name

PPD Development, LP

*24. Street/Suite/P. O. Box

3900 Paramount Parkway

*25. City - Town	*27. Country	*26. State	*28. ZIP Code
Morrisville	United States	North Carolina	27560-7200

Contact (for THIS Drug Submission)

☐ Same as A Above (that is Manufacturer/Sponsor Contact)

*Salutation	*Given Name	Initials	*29. Surname	*33. Title	*32. Language
[redacted]	[redacted]		[redacted]	[redacted]	English

*30. Telephone No.	Ext.	31. Fax No.	*34. Email
[redacted]		919-456-4148	PPD-HCsubmissions@ppd.com

C) REGULATORY MAILING ADDRESS

☒ Same as A Above (that is Manufacturer/Sponsor Mailing Address)

Regulatory Contact

☐ Same as A Above (that is Manufacturer/Sponsor Contact)

*Salutation	*Given Name	Initials	*41. Surname	*45. Title	*44. Language
[redacted]	[redacted]		[redacted]	[redacted]	English

*42. Telephone No.	Ext.	43. Fax No.	*46. Email
[redacted]		919-456-4148	PPD-HCsubmissions@ppd.com

D) CANADIAN IMPORTER MAILING ADDRESS

E) ADDRESS TO WHICH THE DRUG NOTIFICATION FORM (DNF)/ NOTICE OF COMPLIANCE (NOC) IS TO BE SENT (SELECT AT LEAST ONE OF THE OPTIONS)

[redacted]

F) Third Party Submission

*Will this submission be signed/filed by a third party on behalf of the manufacturer/sponsor? [redacted]

53. RELATED SUBMISSIONS (REFERRED TO IN THIS SUBMISSION)

PART 2 - DRUG PRODUCT FORMULATION INFORMATION

Copy Drug Product Formulation

2.01

54. & 61. PROPOSED SHELF LIFE AND CONTAINER TYPE, PACKAGE SIZE

		Shelf Life		Temp. Range	
*Container Type	*Package Size	Years	Months	Min. Celsius	Max. Celsius
[redacted]					

55. Please indicate the country(ies) of manufacture for this drug product.

*Country of Manufacture [redacted]
*Country of Manufacture
*Country of Manufacture

56. MEDICINAL (ACTIVE) INGREDIENT(S)

Chemical Abstracts Service No.	*Active Ingredient Name	Standard	*Strength	*Units
	NVX-CoV2373	[redacted]		

Per	*Calculated as Base?	*Animal/Human Source?	*Nanomaterial?
	[redacted]		

57. NON-MEDICINAL INGREDIENT(S)

Copy an Ingredient

58. ANIMAL AND/OR HUMAN SOURCED MATERIAL(S) USED AT ANY STAGE IN THE MANUFACTURE OF THE DRUG

*60. Dosage Form [redacted]

*62. Therapeutic/Pharmacological Classification: Novavax COVID-19 Vaccine (SARS-CoV-2 rS with Matrix-M1 Adjuvant)

63. ROUTE OF ADMINISTRATION*

[redacted]

64. Drug Product* [redacted]

65. Drug Use*

- [x] Human [redacted]
- [ ] RadioPharmaceutical
- [ ] Veterinary
- [ ] Disinfectant

*66. Is this a Non-Prescription drug to which one or more Schedule A claims apply? [redacted]

*67. Proposed Indication/Use: Active immunization for the prevention of mild, moderate, and severe coronavirus diseases 2019 (COVID-19) caused by SARS-CoV-2 [redacted]

*68. Proposed Dosage (by age/species - include maximum daily dose) [redacted]

*69. Draft of Proposed Canadian Labels (inner and outer) enclosed? [redacted]

*Package Insert enclosed? [redacted]

Health Canada / Santé Canada

NAME OF AUTHORIZED SIGNING OFFICIAL

I, the undersigned certify that the information and material included in this drug submission application are accurate and complete.

*Salutation	*74. Given Name	Initials	*75. Surname	*78. Title
[redacted]	[redacted]		[redacted]	[redacted]

*79. Telephone No.	Ext.	80. Fax No.
[redacted]		919-456-4148

○ Digital ID	◉ Image Signature

76. Signature	[redacted]	77. Date (YYYY-MM-DD)	2021-01-28

81. Company Name	PPD Development, LP

Health Canada / Santé Canada

Appendix 2 - for All Applications

Template Authorization for a Third Party to Sign/File a Drug Submission Application on Behalf of the Manufacturer/ Sponsor

AUTHORIZED THIRD PARTY

*Third Party Company Name

PPD Development, LP

*Third Party Person

[redacted]

AUTHORIZATION

I authorize [redacted] of PPD Development, LP to file a drug submission application for TBC on behalf of Novavax Inc.

*Salutation	*Given Name	Initials	*Surname	*Title
[redacted]	[redacted]		[redacted]	[redacted]

Signature [redacted]

Date (YYYY-MM-DD) 2021-01-28

Company Name: Novavax Inc.

Health Canada Use Only

1. Submission No.		2. Responsible Area	
3. File Number		4. Date of Receipt	

From: [redacted]
To: Patel, Shalu (HC/SC); [redacted]
Cc: Panetta, Vincent (HC/SC)
Subject: RE: URGENT: COVID-19 Interim Order Application Control [redacted]
Date: 2021-06-22 12:31:35 PM
Attachments: image001.png
image002.png
image003.png
image004.png
image005.png

Dear Shalu

[redacted]

Regards

[redacted]
REGULATORY AFFAIRS

PPD
929 North Front Street
Wilmington, NC 28401-3331
[redacted]
www.ppdi.com
www.ppd.com/regulatory-affairs

Early Development | Clinical Development | Laboratories | Post-Approval | Consulting

---

From: Patel, Shalu (HC/SC) <shalu.patel@canada.ca>
Sent: Tuesday, June 22, 2021 11:53 AM
To: [redacted]
Cc: Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>
Subject: URGENT: COVID-19 Interim Order Application Control [redacted]
Importance: High

Dear [redacted]

[redacted] Novavax COVID-19 Vaccine (SARS-CoV-2 rS with Matrix-M1 Adjuvant), COVID-19 Interim Order Application Control [redacted]

Please confirm receipt of this email.

Kind regards,

Shalu Patel

Senior Regulatory Affairs Officer
Biologic and Radiopharmaceutical Drugs Directorate
Health Products and Food Branch / Health Canada
shalu.patel@canada.ca / Tel: 613-462-8129 / Fax: 613-946-9520

Agente principale des affaires réglementaires
Direction des médicaments biologiques et radiopharmaceutiques
Direction générale des produits de santé et des aliments / Santé Canada
shalu.patel@canada.ca / Tél: 613-462-8129 / Fax: 613-946-9520

Regulatory Transaction Template: Regulatory Enrolment Process (REP) (Version: 4.2.4)

Company Identifier	Dossier Type	Dossier Identifier	Date Last Saved
[redacted]	Biologic	[redacted]	2021-06-04

Regulatory Information

Product Name: SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 RECOMBINANT SPIKE PROTEIN NANOPARTICLE VACCINE (SARS-COV-2 RS) WITH MATRIX-M1 ADJUVANT
Was this regulatory activity approved for priority review? [redacted]
Was this regulatory activity approved for NOC/C review? [redacted]
Is this regulatory activity an Administrative Submission or does this regulatory activity contain an administrative component? [redacted]

Transaction Details

Transaction Details Record

Control Number: [redacted]
Regulatory Activity Lead: Biological
Regulatory Activity Lead Description:
Biological: Includes all regulatory activities and transactions under the Biologics and Radiopharmaceutical Drugs Directorate (BRDD) mandate (biologics/radiopharmaceuticals).
Regulatory Activity Type: COV19 (COVID-19 Interim Order Application)
Regulatory Transaction Description: Rolling Information - Rolling Submission – Clinical Roll # 3

Are new or revised fees associated with this transaction? Please identify fees when applying for remission. No

Contact for THIS Regulatory Activity

Regulatory Activity Contact for THIS transaction

A. Company Information:

Is the contact for this regulatory activity a third party corresponding on behalf of the manufacturer/sponsor? Yes

- If the regulatory activity type is COV19, COV19A, NDS, SNDS, ANDS, SANDS, SNDS-C, SANDS-C, NC, EUNDS, EUSNDS, EUANDS, EUSANDS, DINA, DINB, DIND, DINF, PDC, PDC-B, then a Third Party Authorization letter is required within the initial transaction of the regulatory activity.
- If the contact changed, a new letter of authorization is required.
- If the contact did not change, another third party authorization letter is not required under the same control#.

Company Name (Full Legal Name)
PPD Development, LP

B. Address Information:

3900 Paramount Parkway
Morrisville, North Carolina, United States of America
27560

C. Company Representative:

Job Title [redacted] Regulatory Affairs

Language of Correspondence English

First Name [redacted]

Initials

Last Name [redacted]

Phone Number [redacted] **Ext**

Fax Number 9194564148

Email [redacted]

Routing Identifier

☒ **I confirm that the above regulatory activity contact information is valid.**

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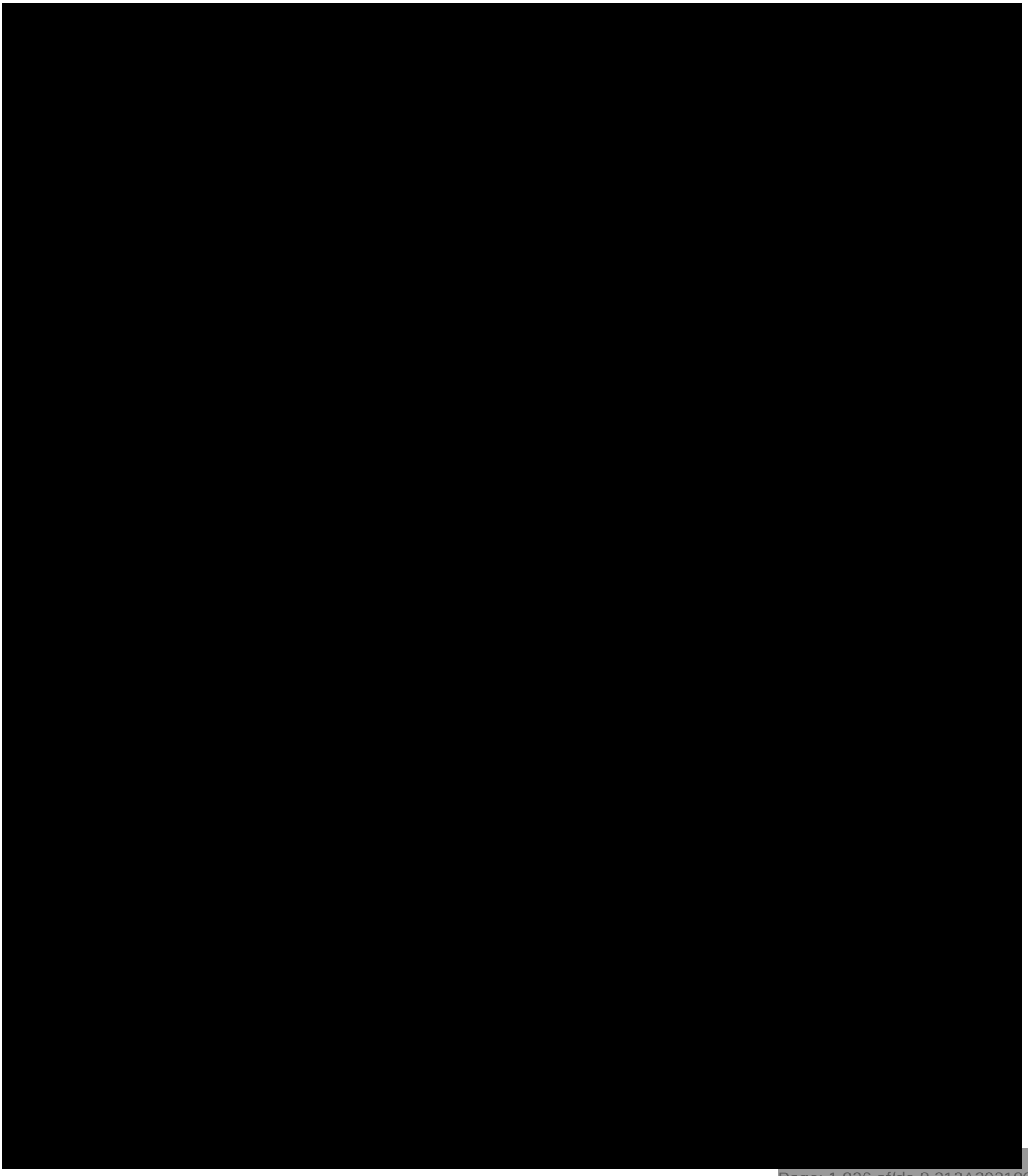

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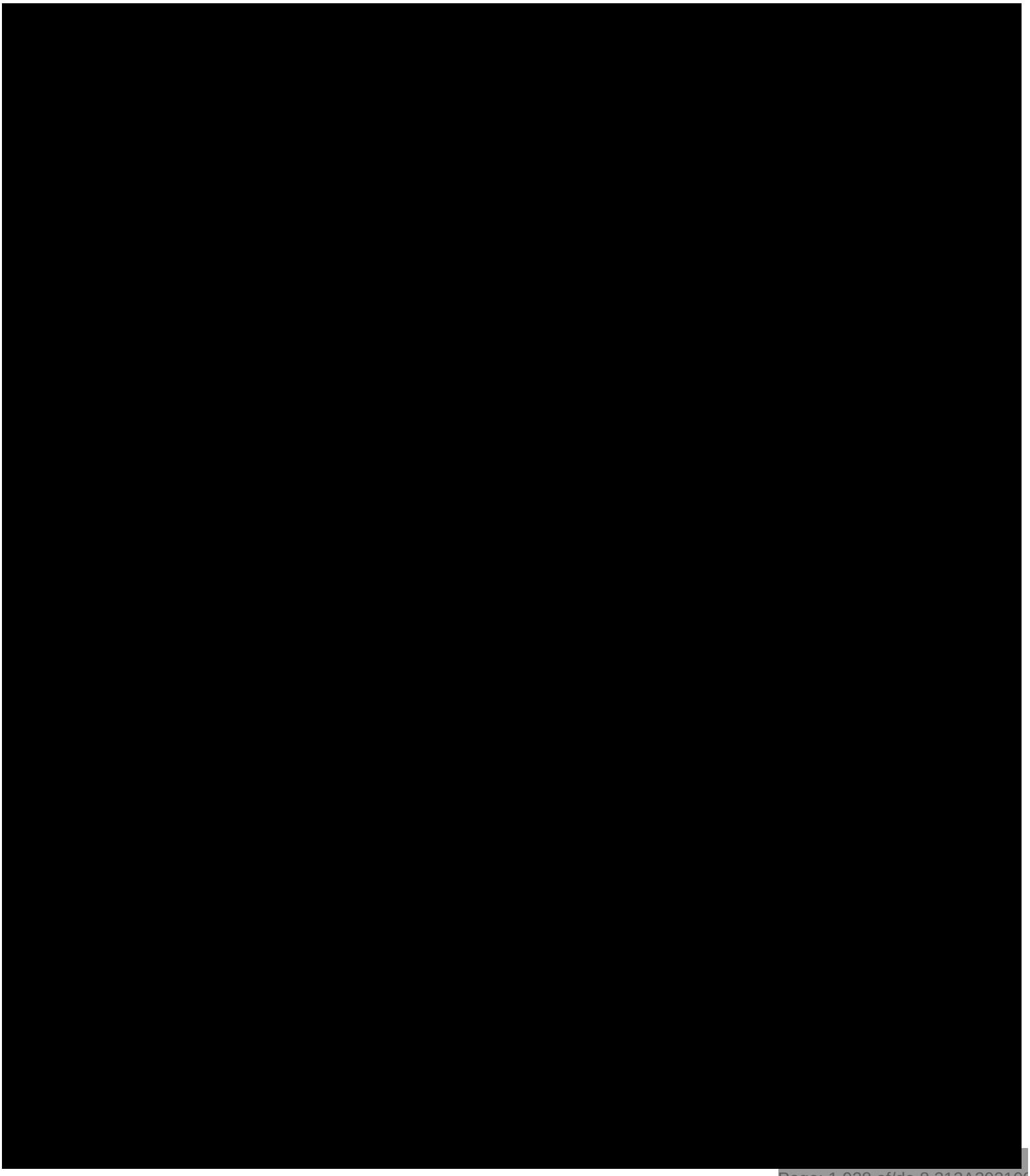

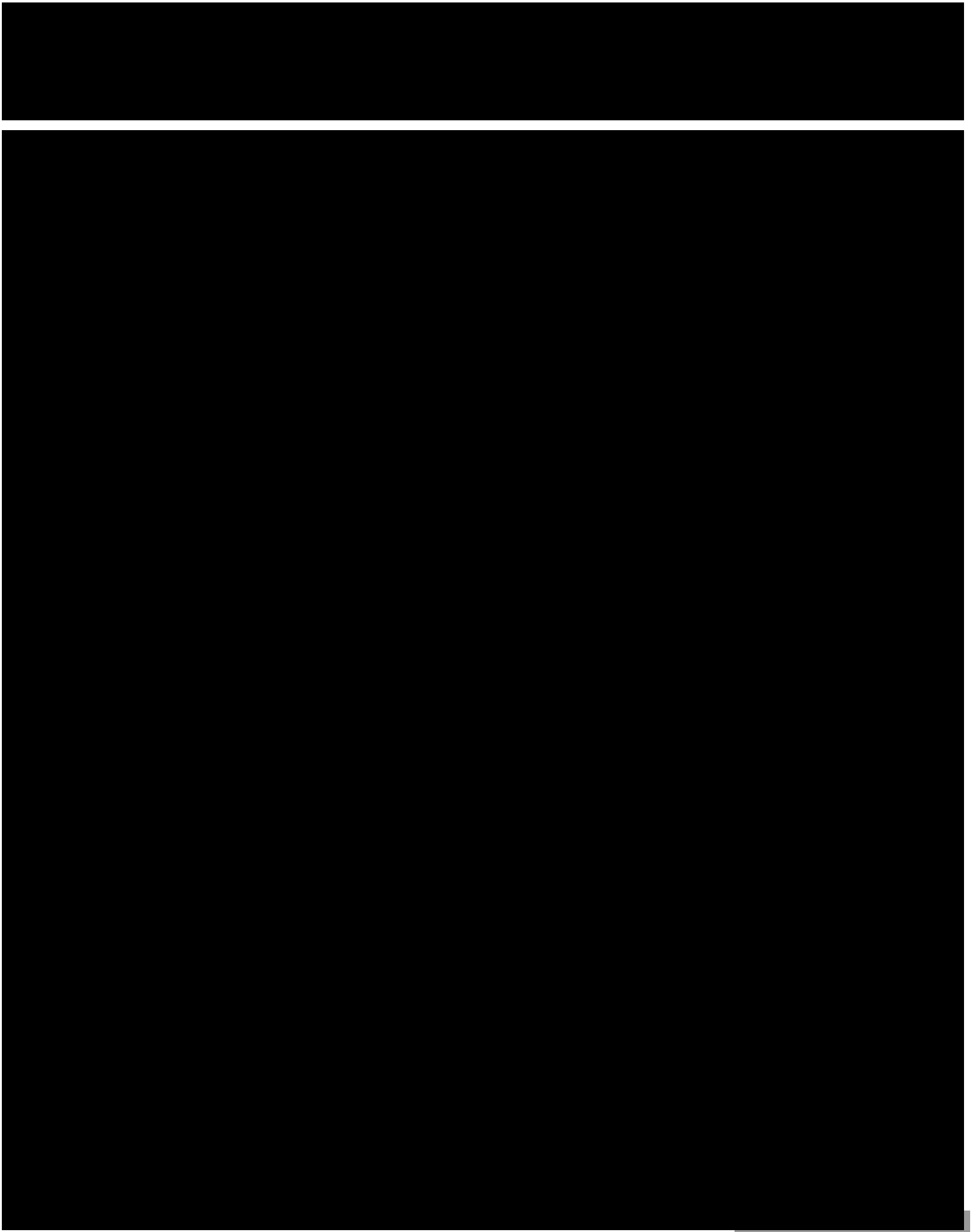

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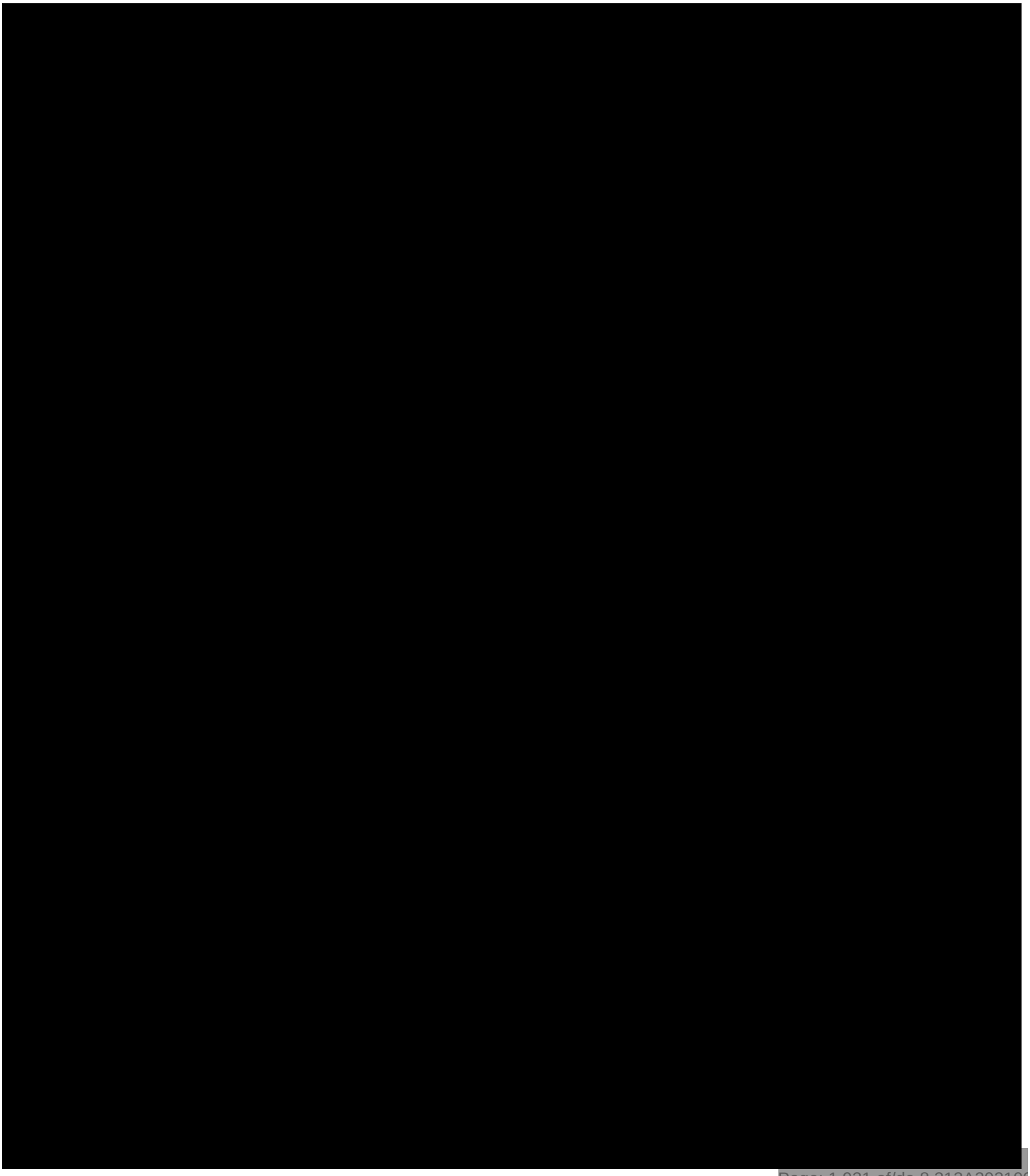

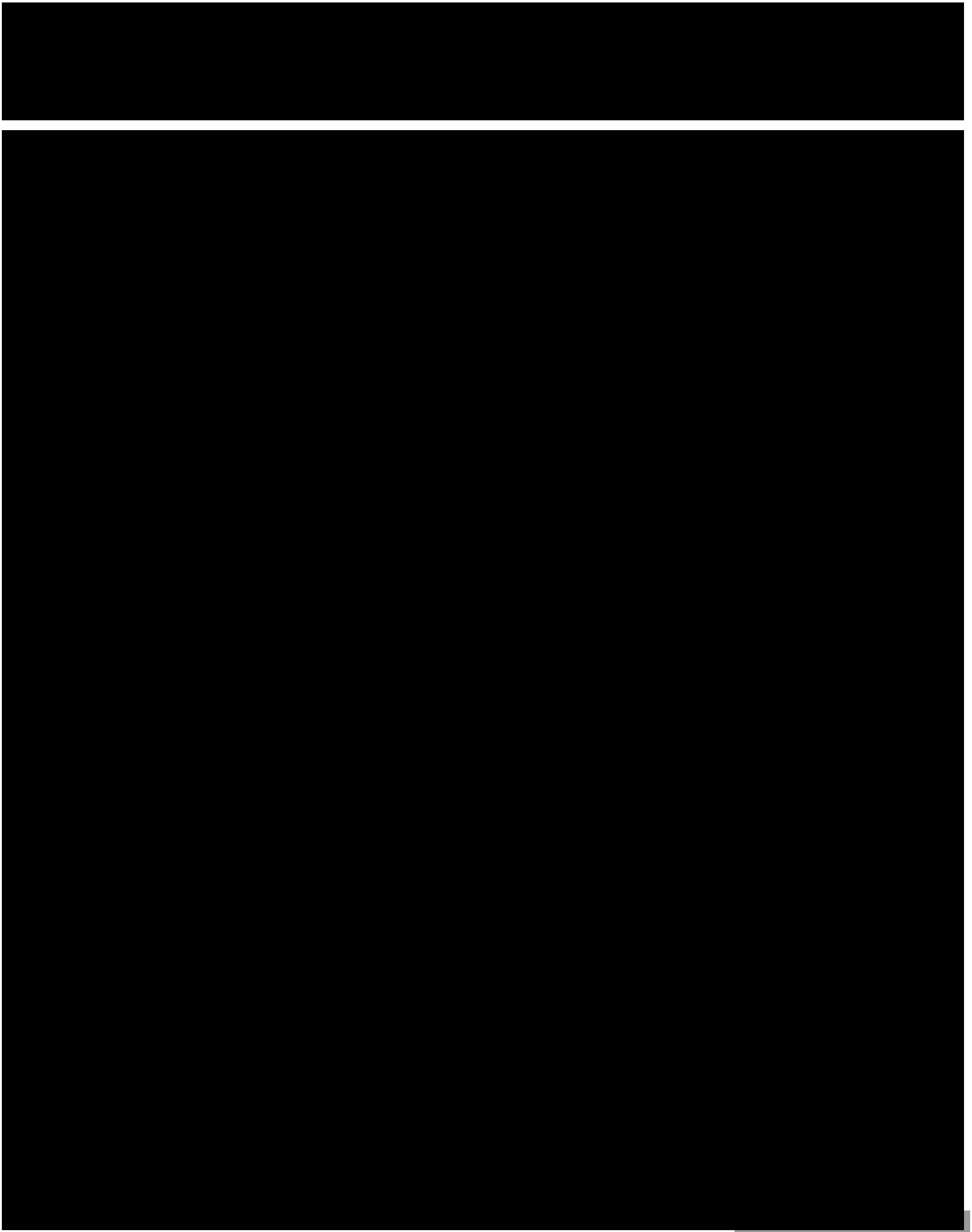

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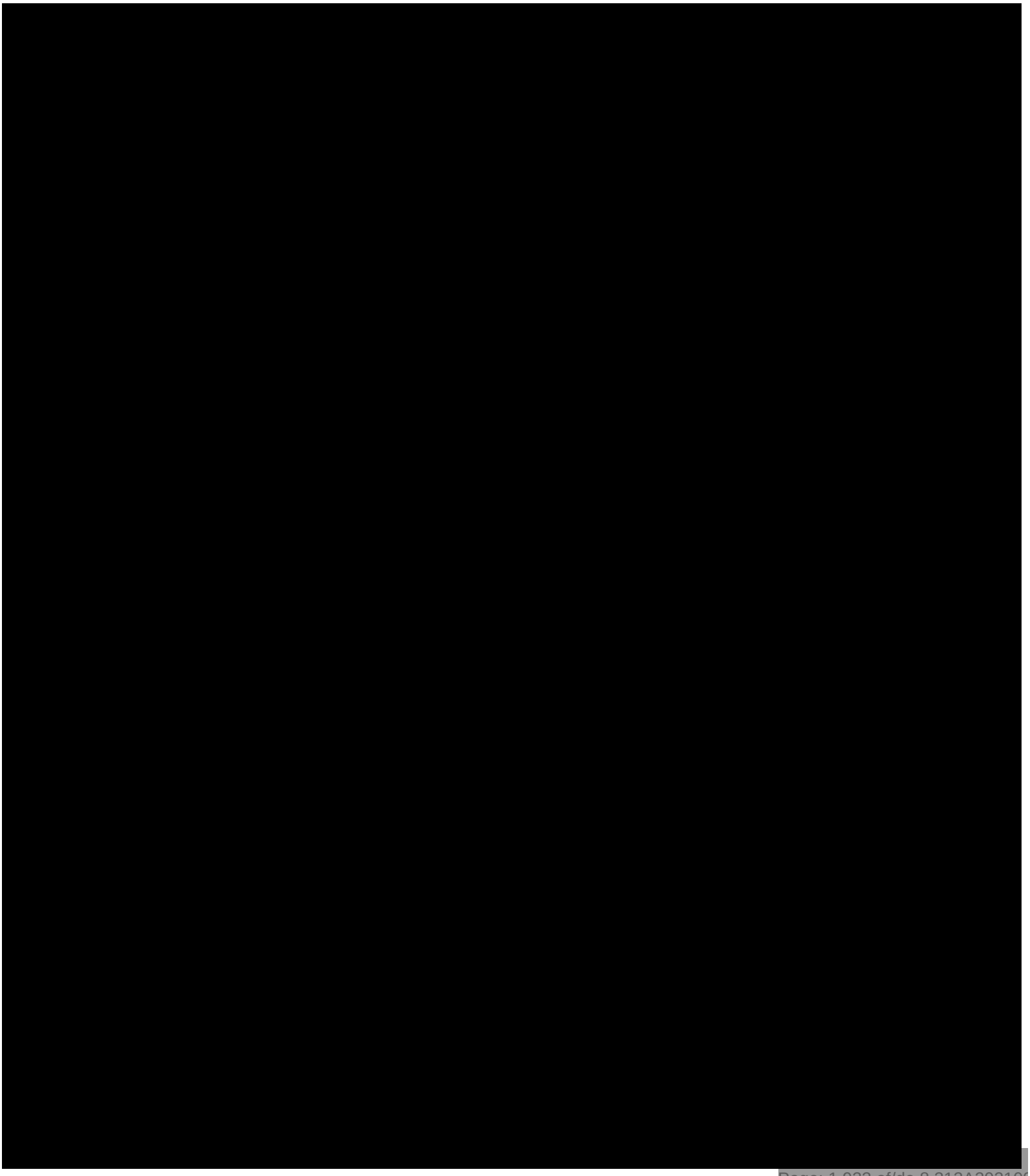

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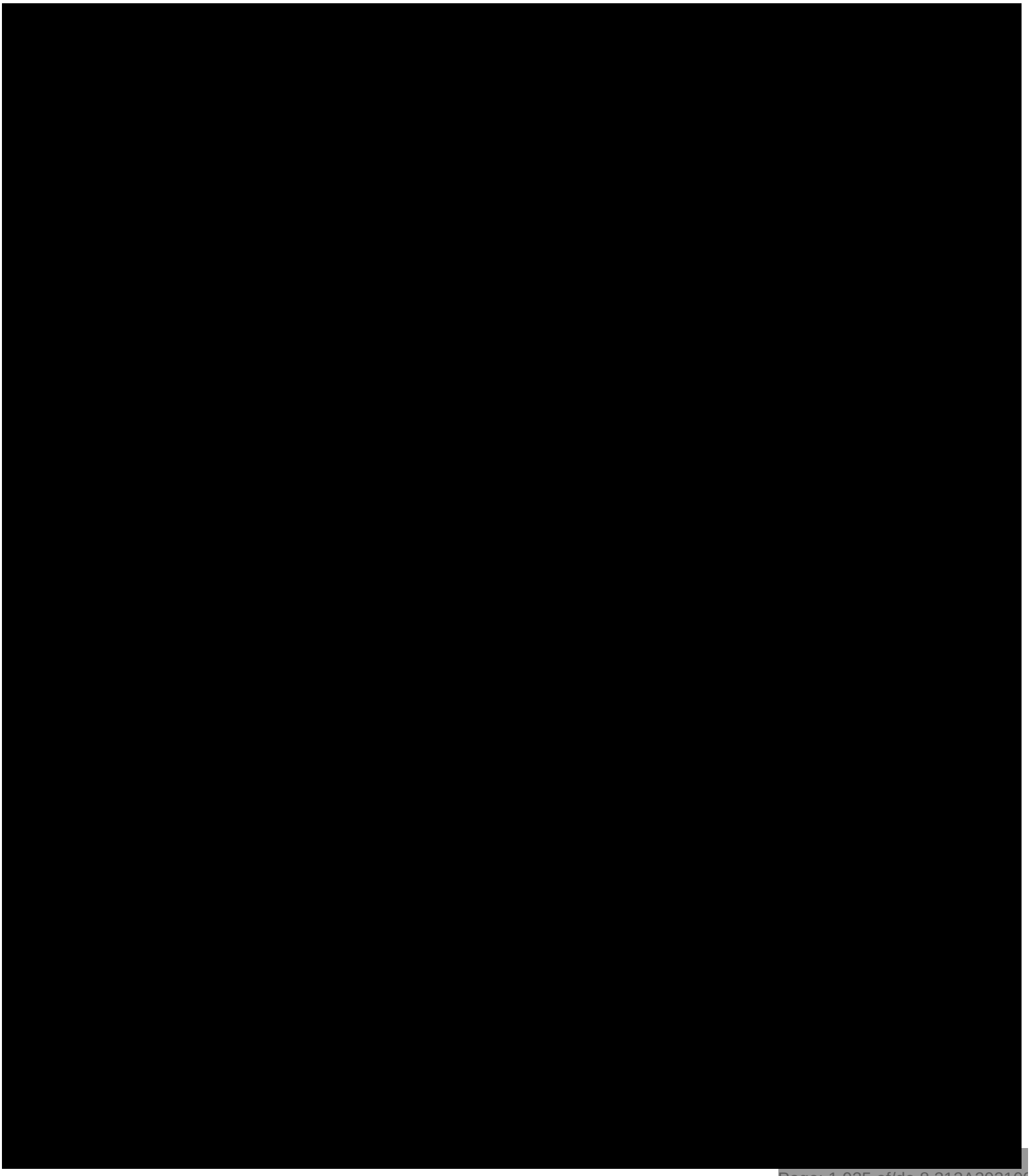

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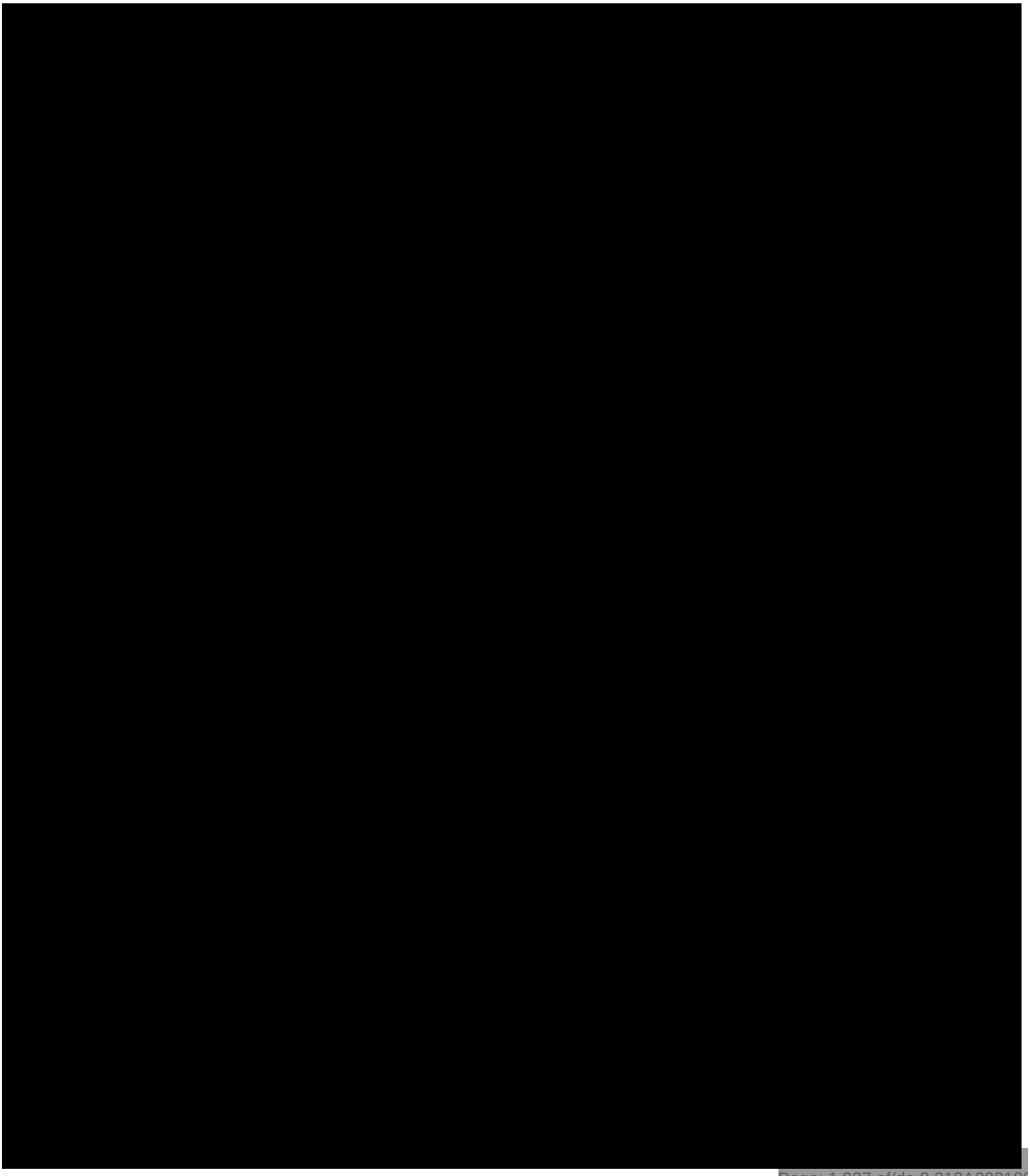

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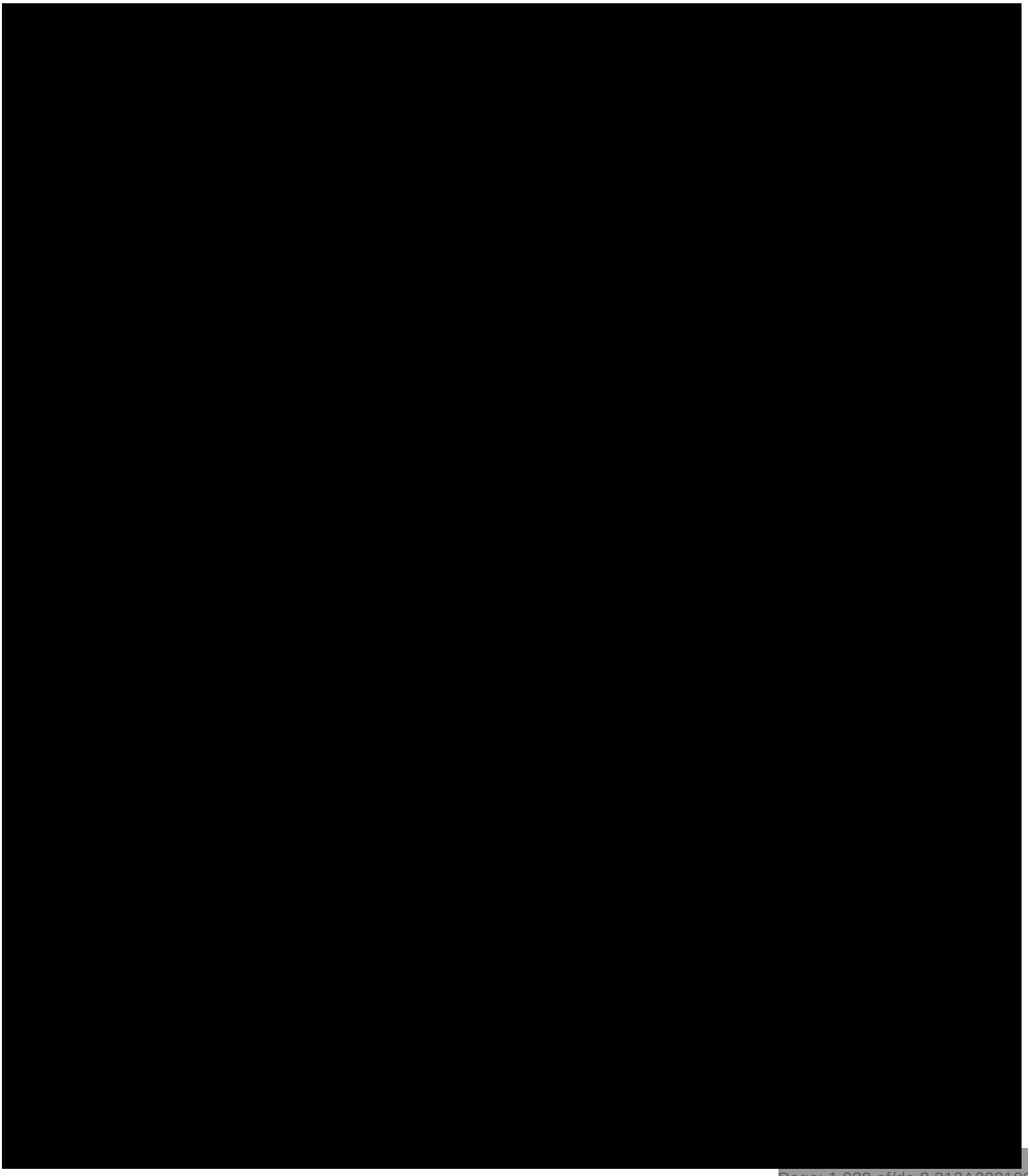

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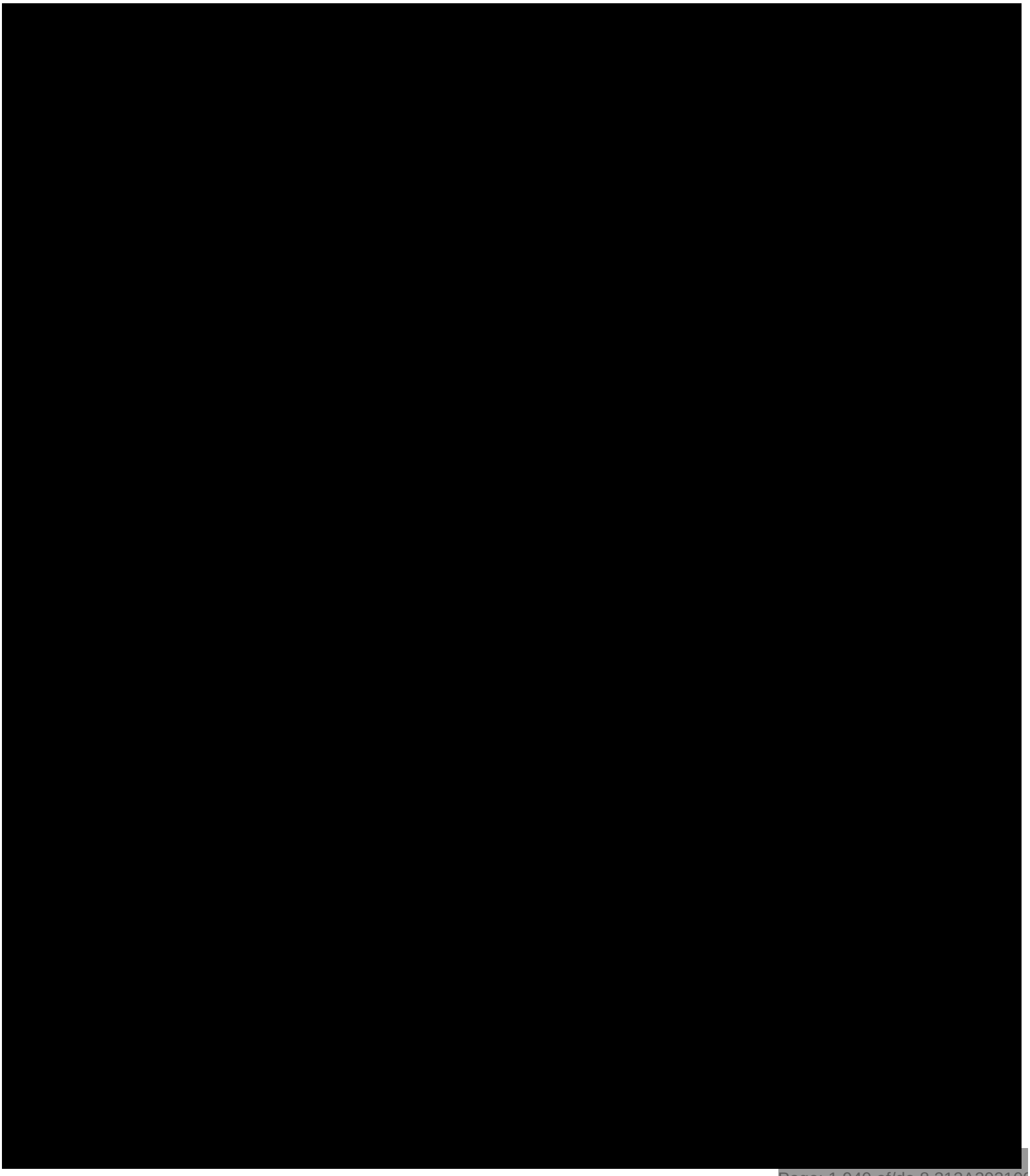

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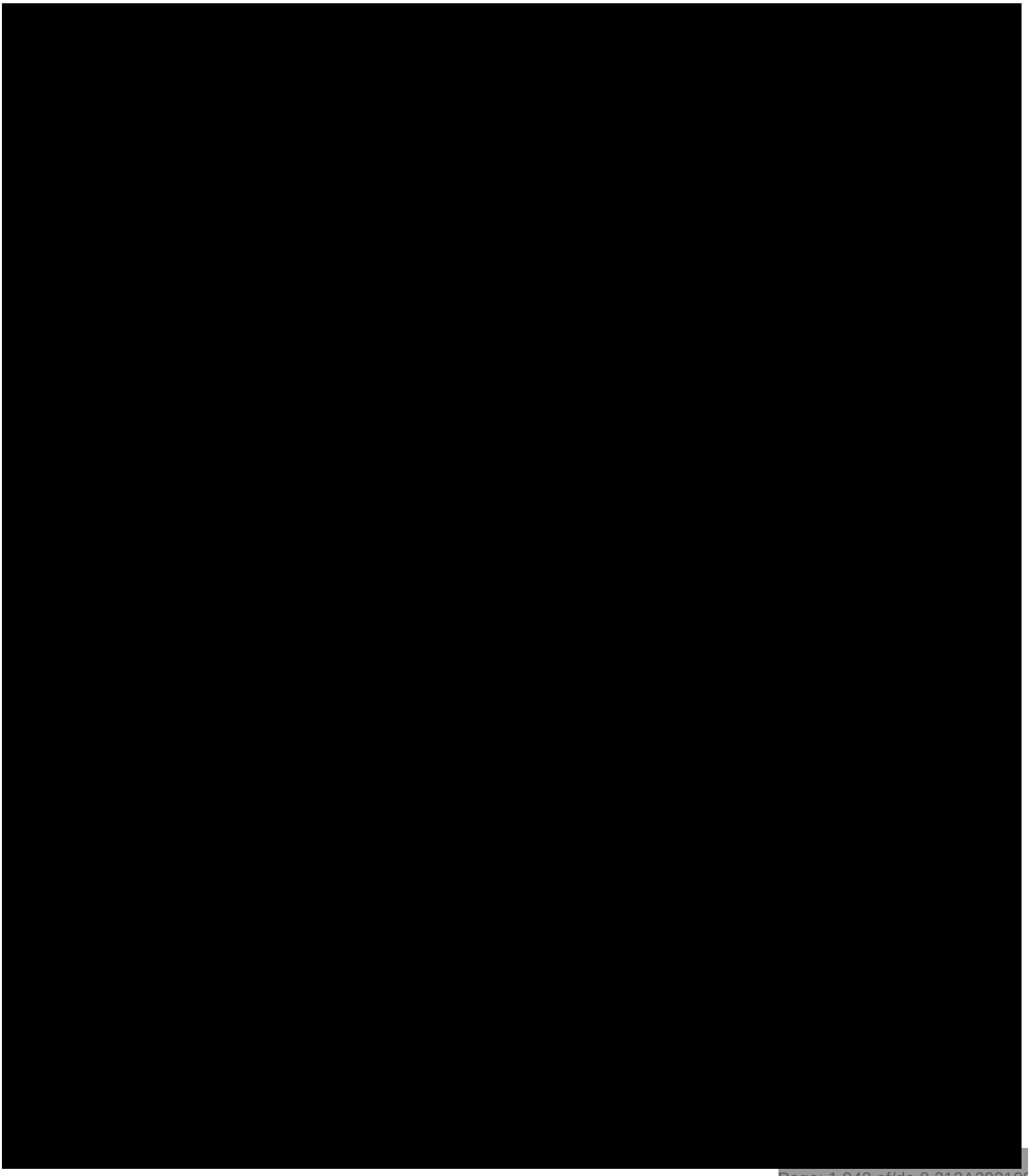

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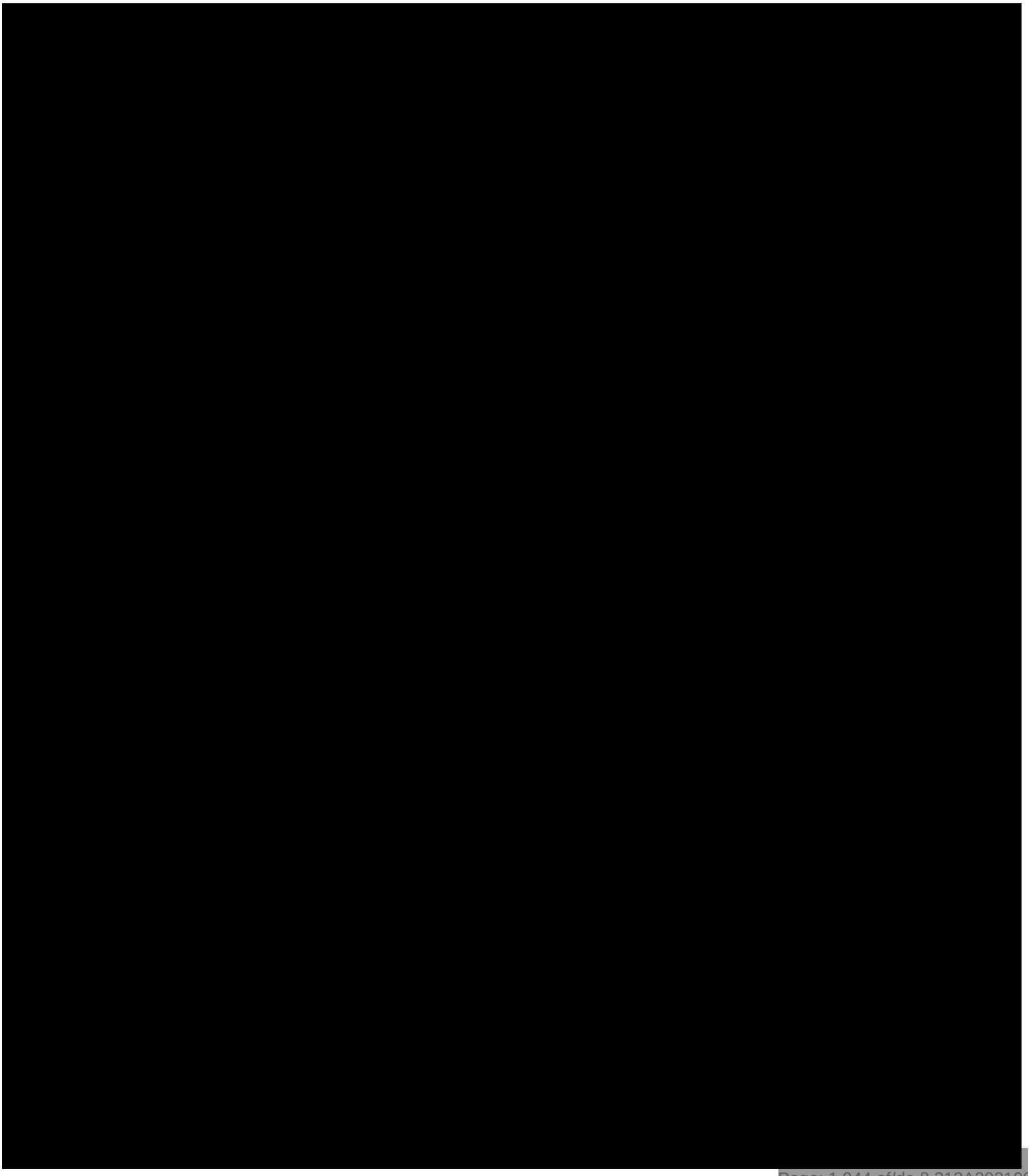

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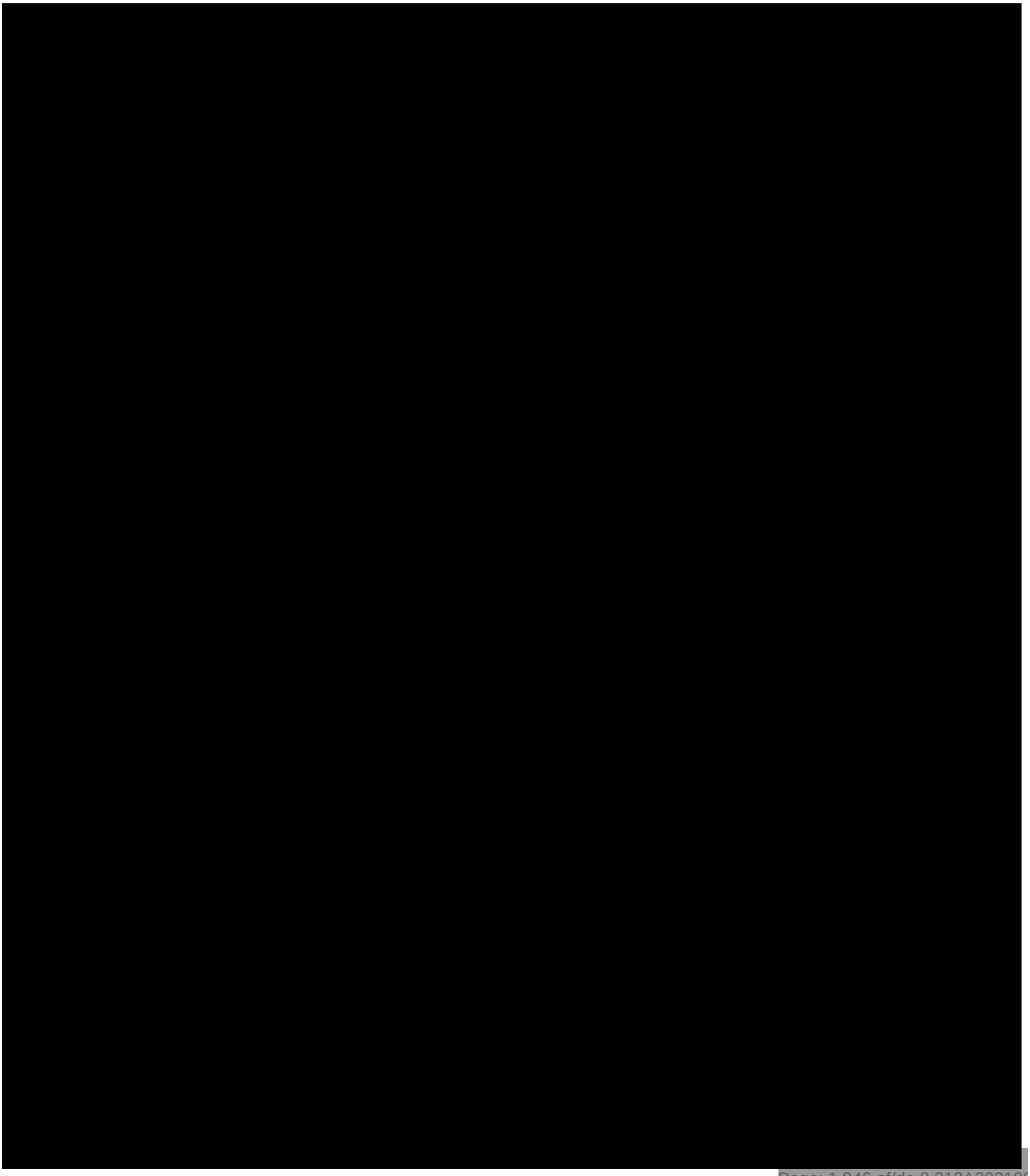

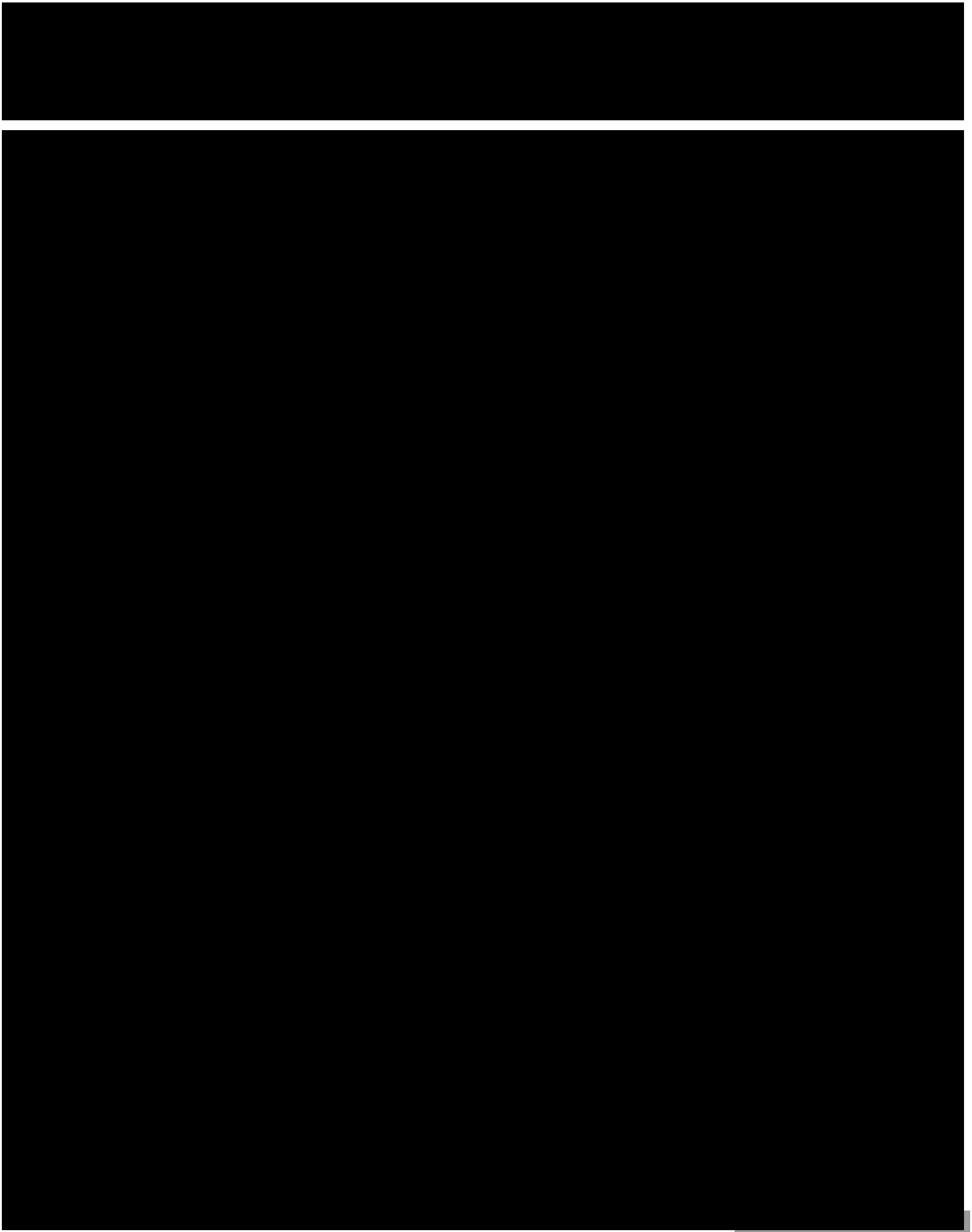

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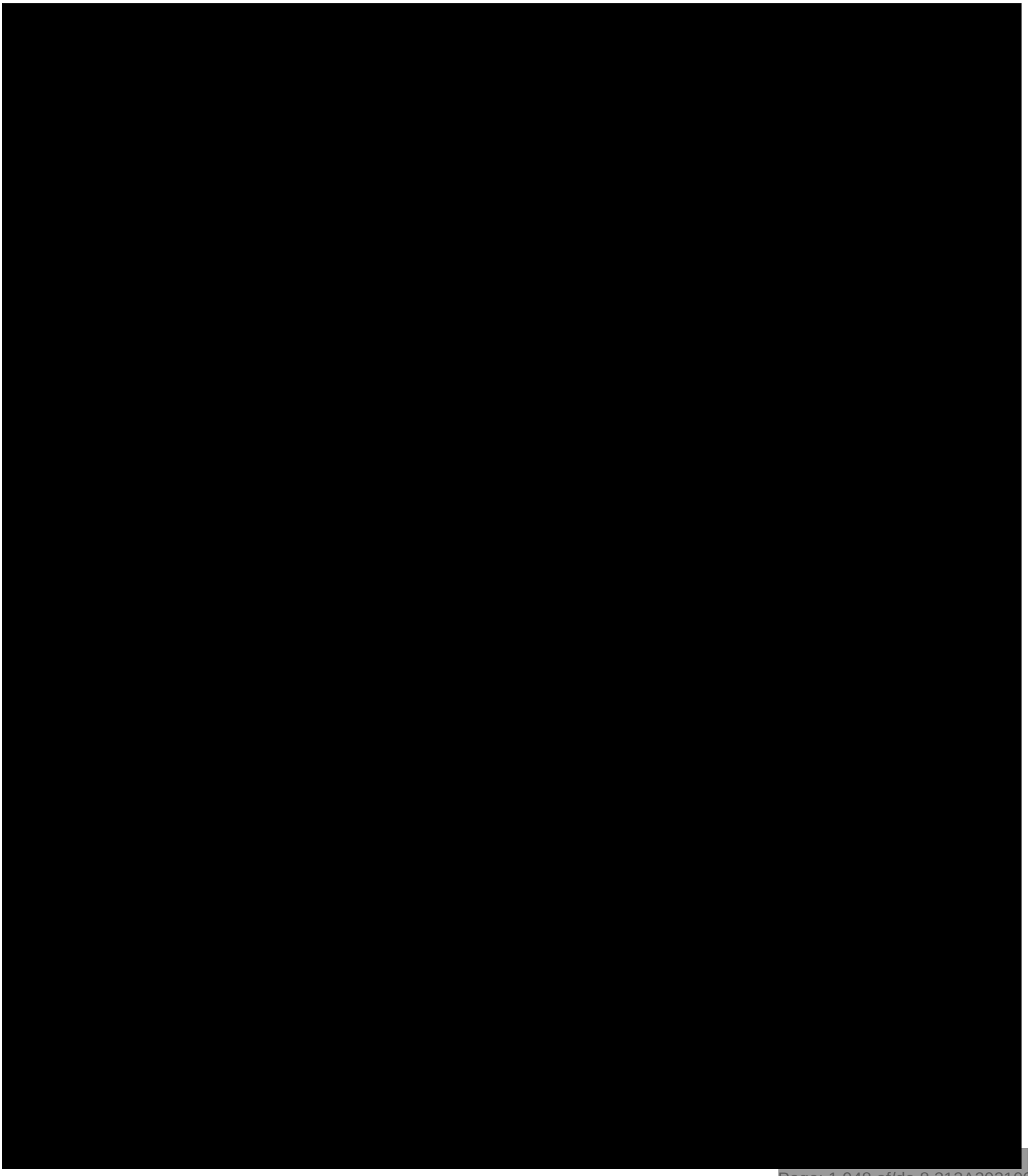

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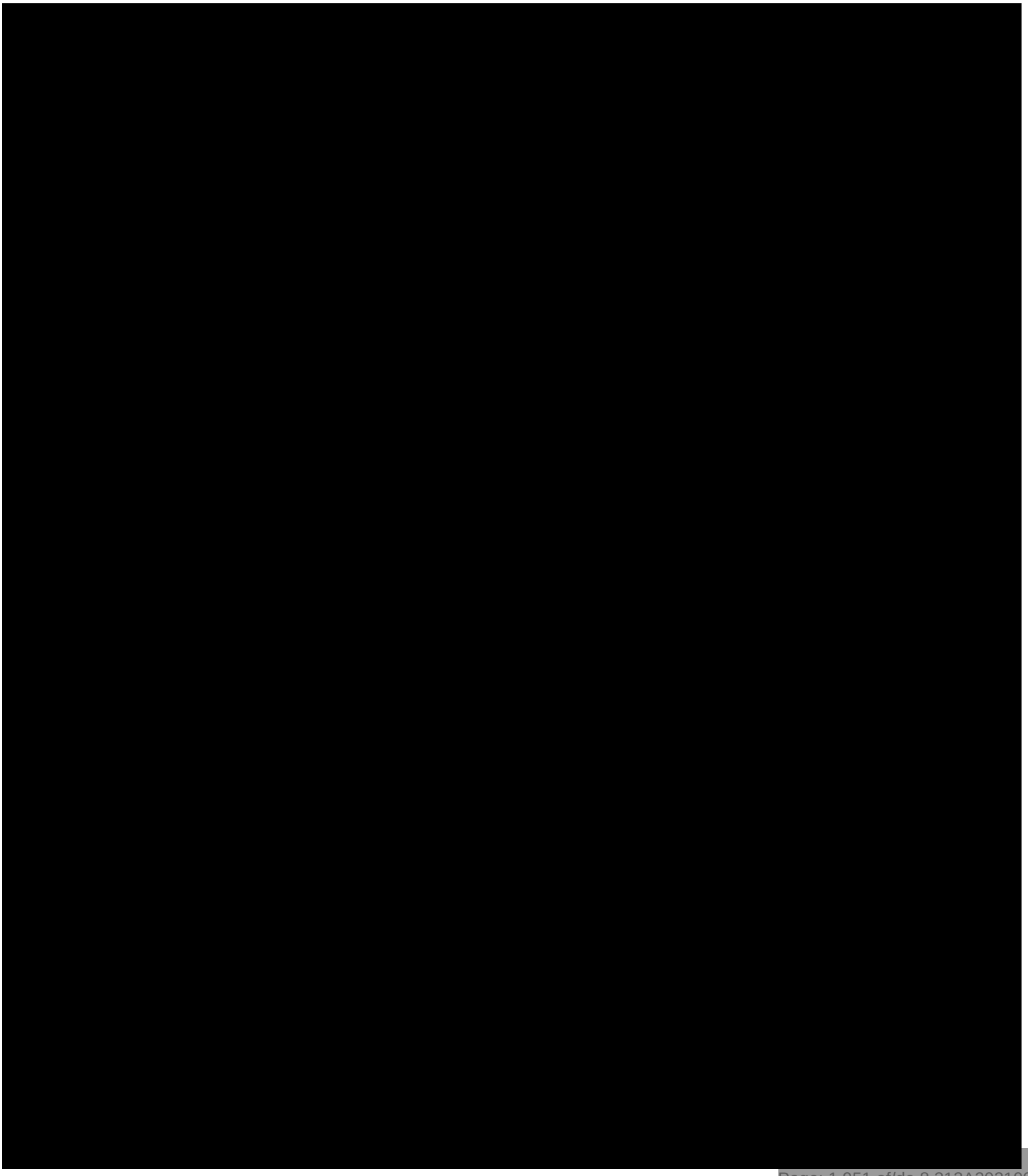

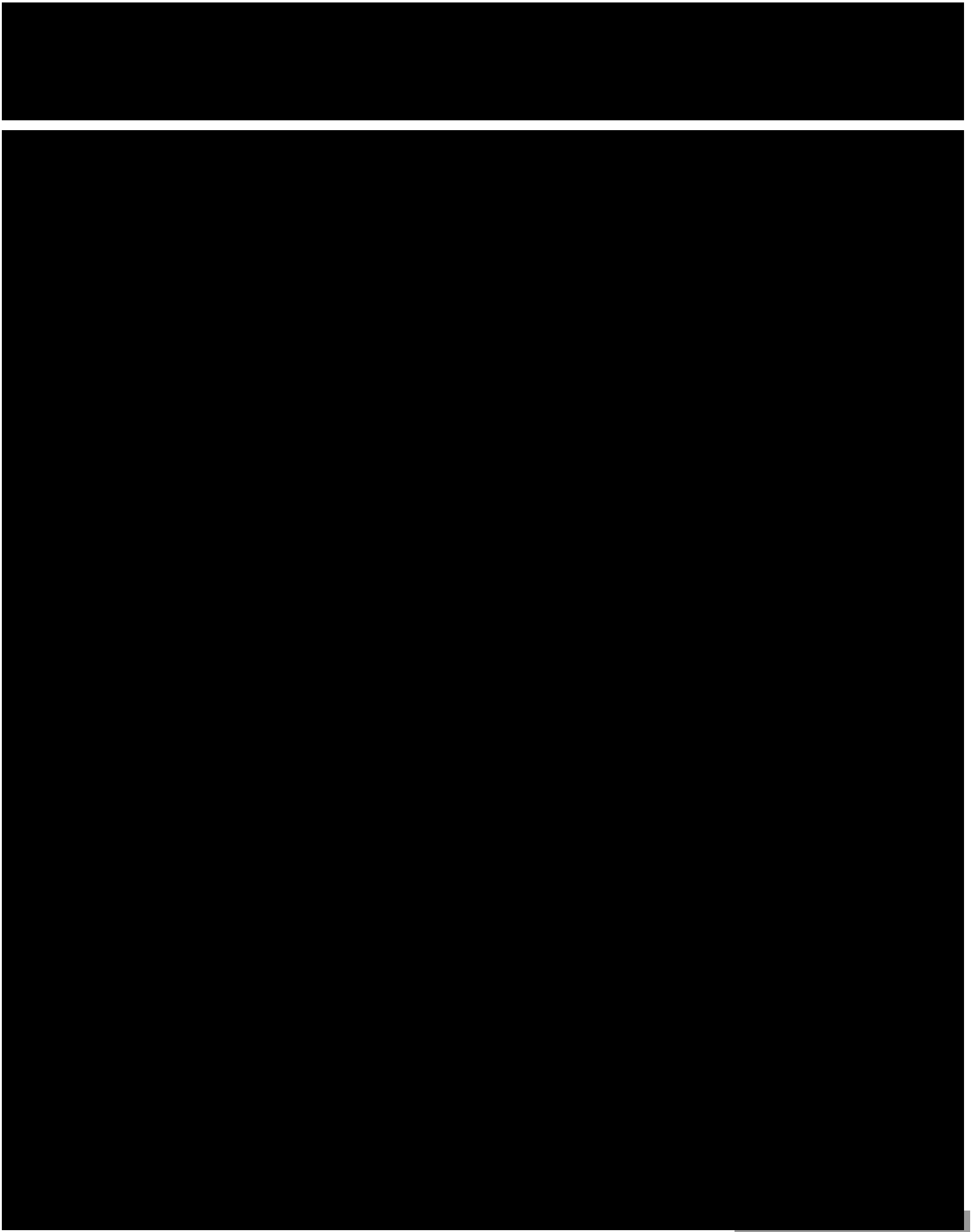

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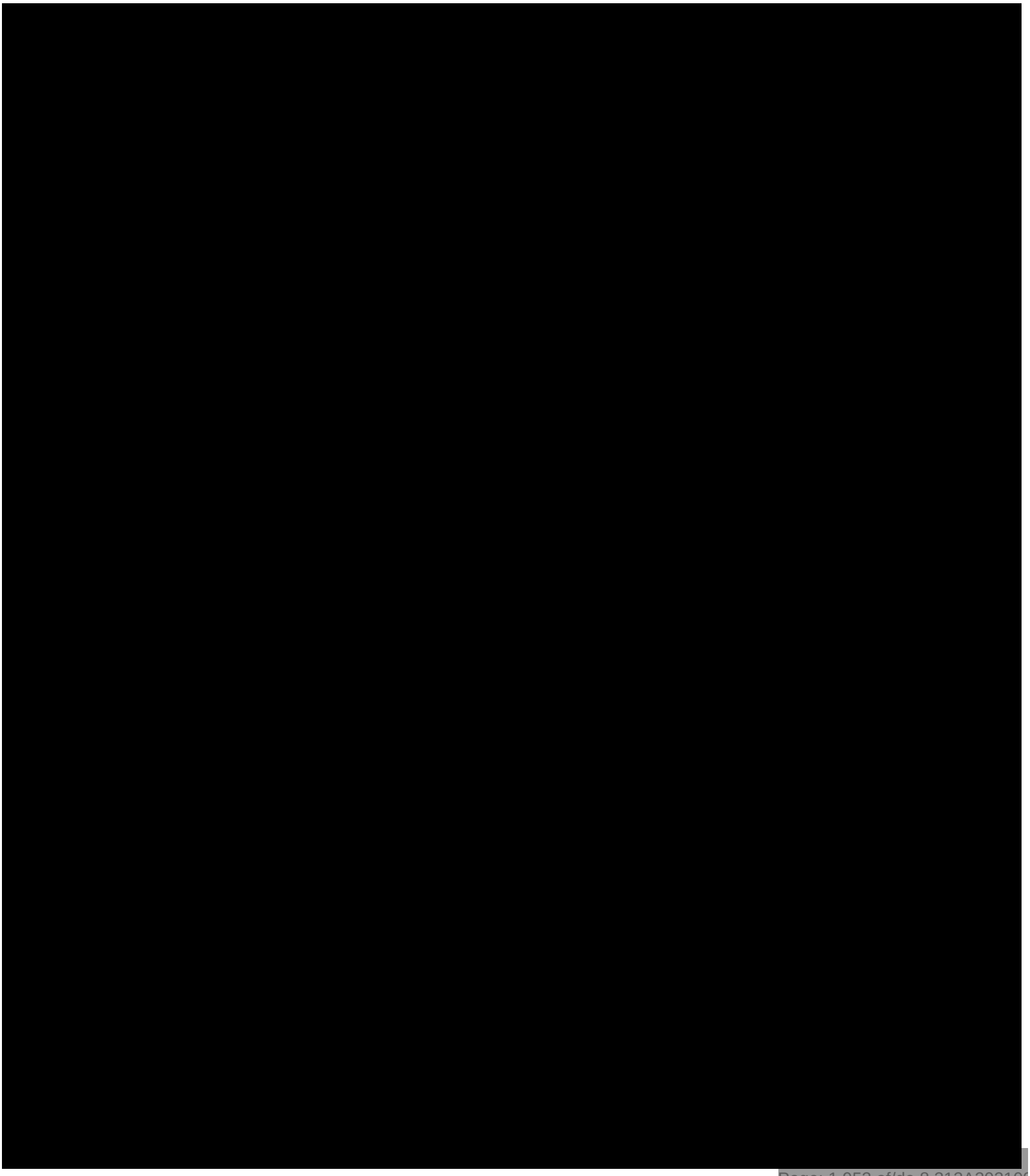

Consent to share regulatory information

Product Name: Novavax COVID-19 vaccine

The undersigned hereby acknowledges and gives consent to the sharing of assessment reports and information in relation to the application:

☑ with all Access Consortium agencies*:_____

☑ with U.S. Food and Drug Administration (USFDA): _____

☑ with European Medicines Agency (EMA): _____

Name of Authorised Signing Official: [redacted]

Title, Company: [redacted] Regulatory Affairs, Novavax Inc.

Signature**: [redacted]

Date: April 28, 2021

* The Access Consortium comprises the medicines regulatory agencies from the following jurisdictions: Australia (Therapeutic Goods Administration (TGA)), Canada (Health Canada (HC)), Singapore (Health Sciences Authority (HSA)), Switzerland (Swissmedic (SMC)) and United Kingdom (Medicines and Healthcare products Regulatory Agency (MHRA))

** Signatures (including digital/electronic versions, where permitted) must comply with the legal requirements of the jurisdiction(s)

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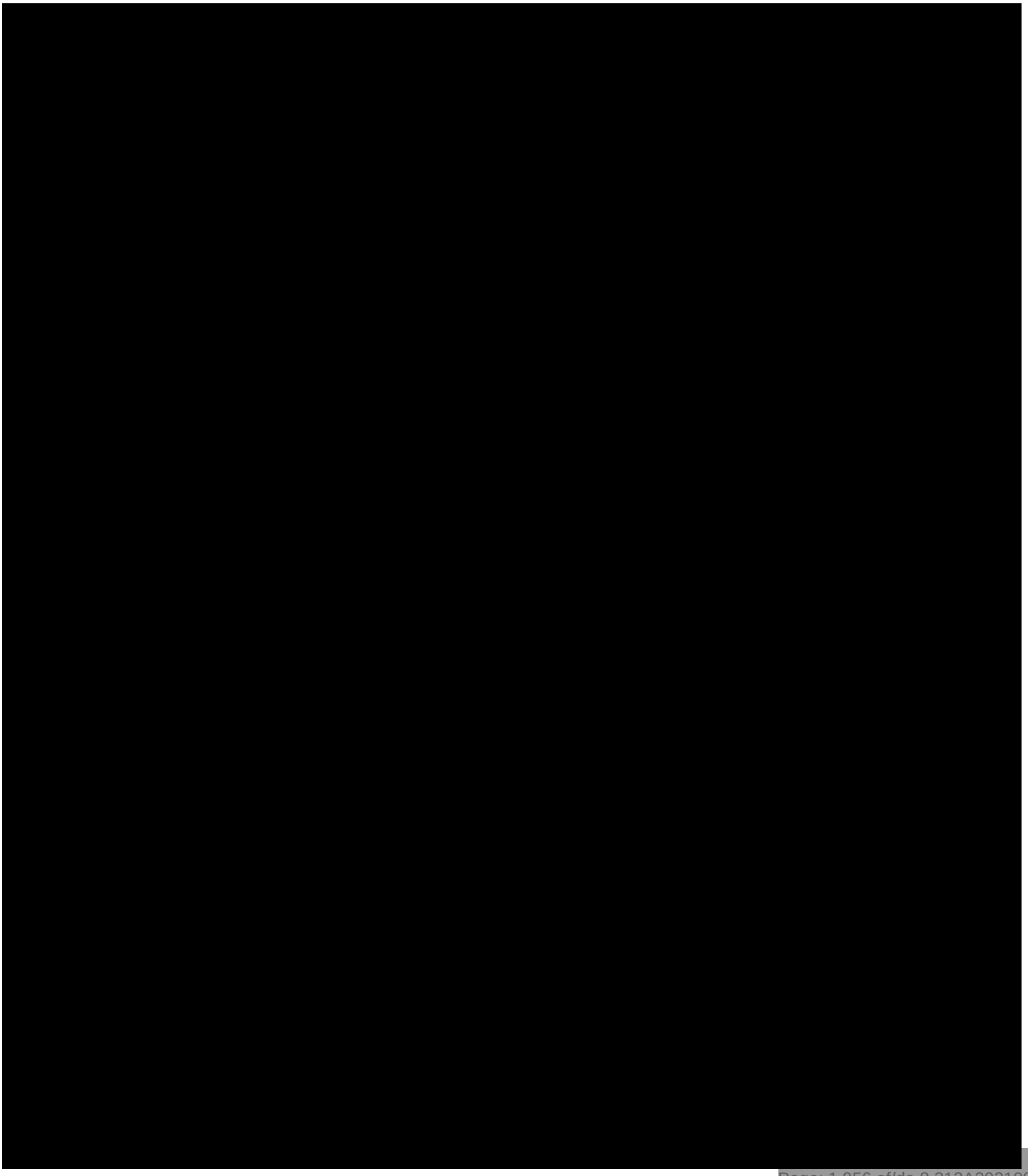

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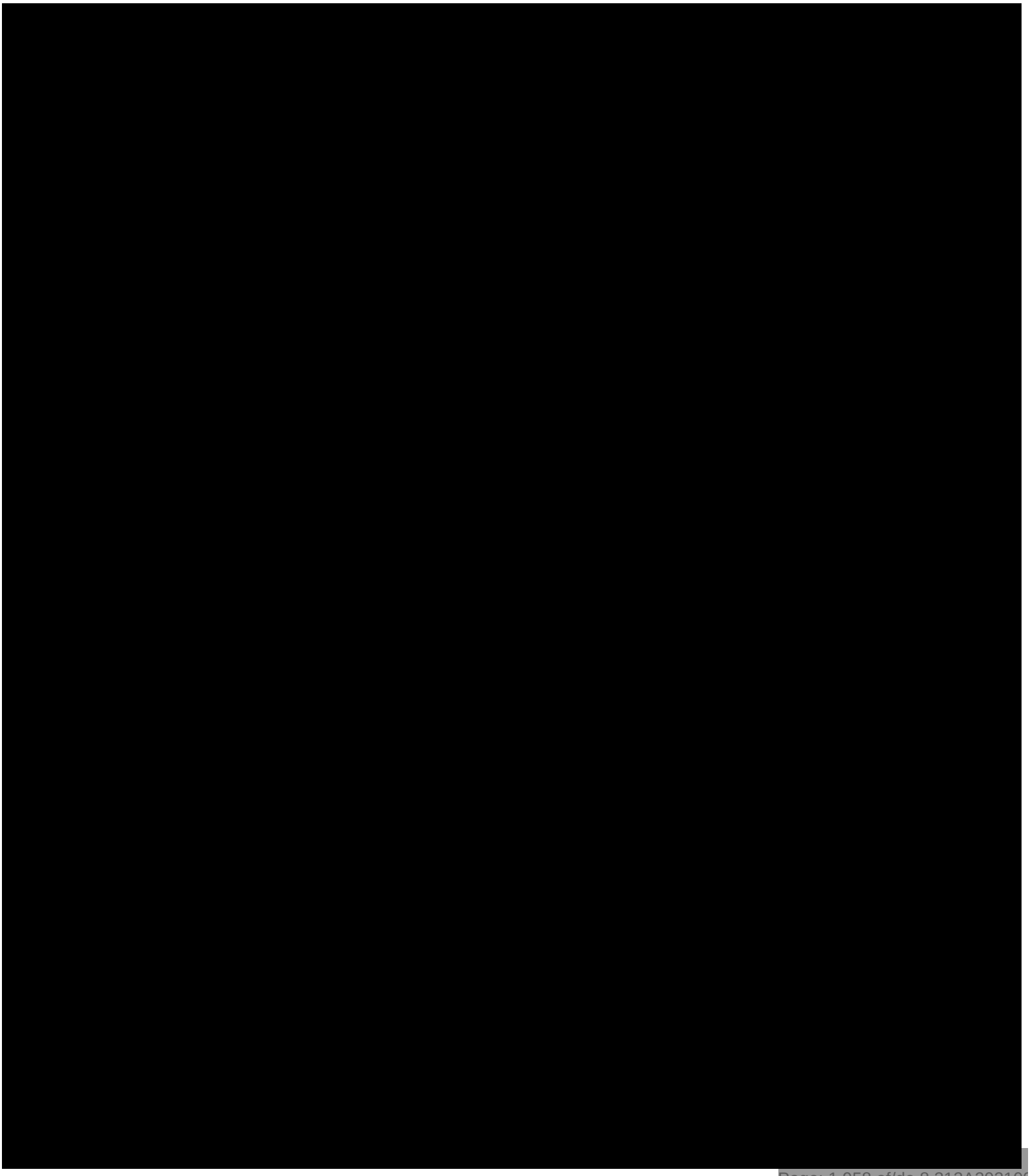

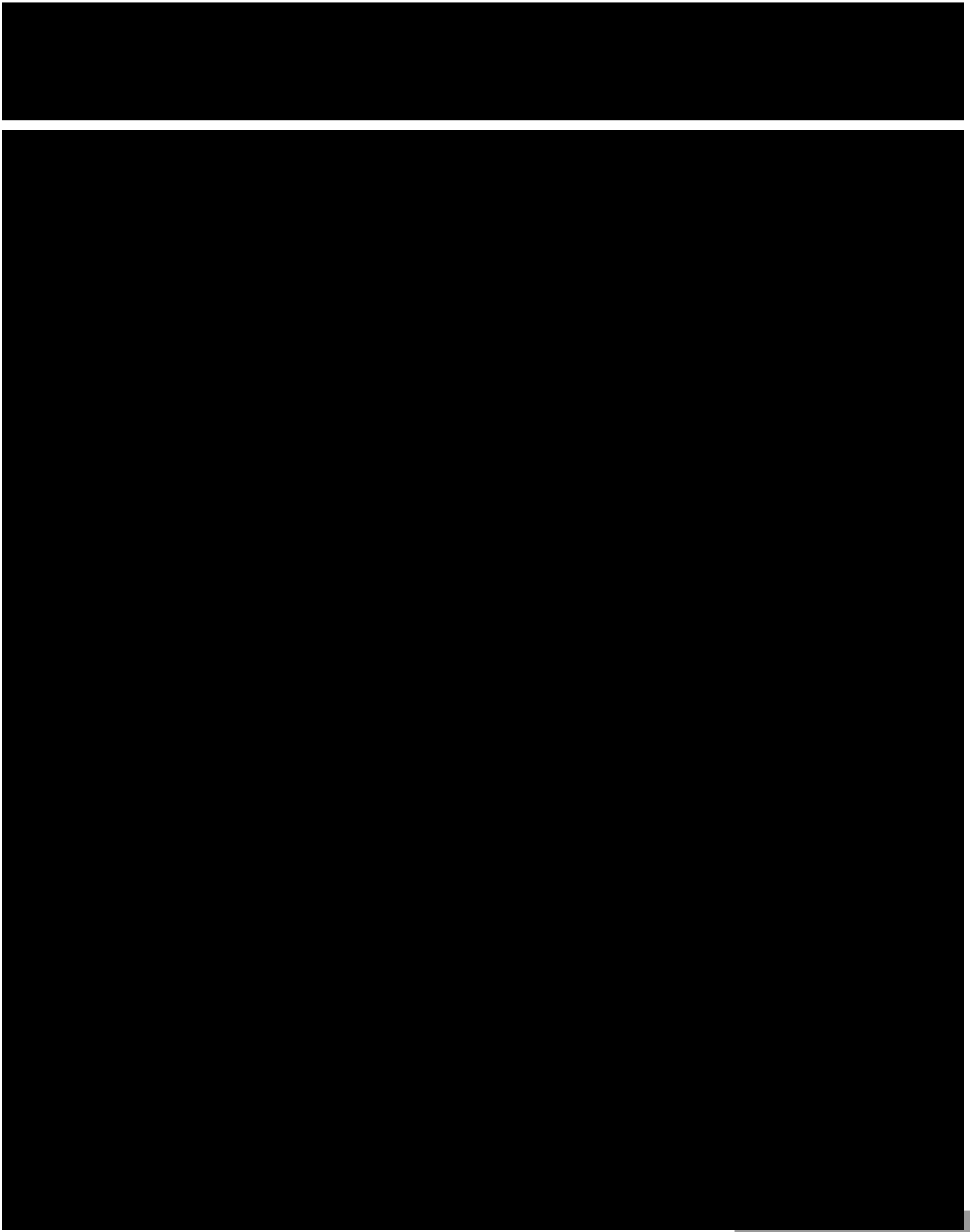

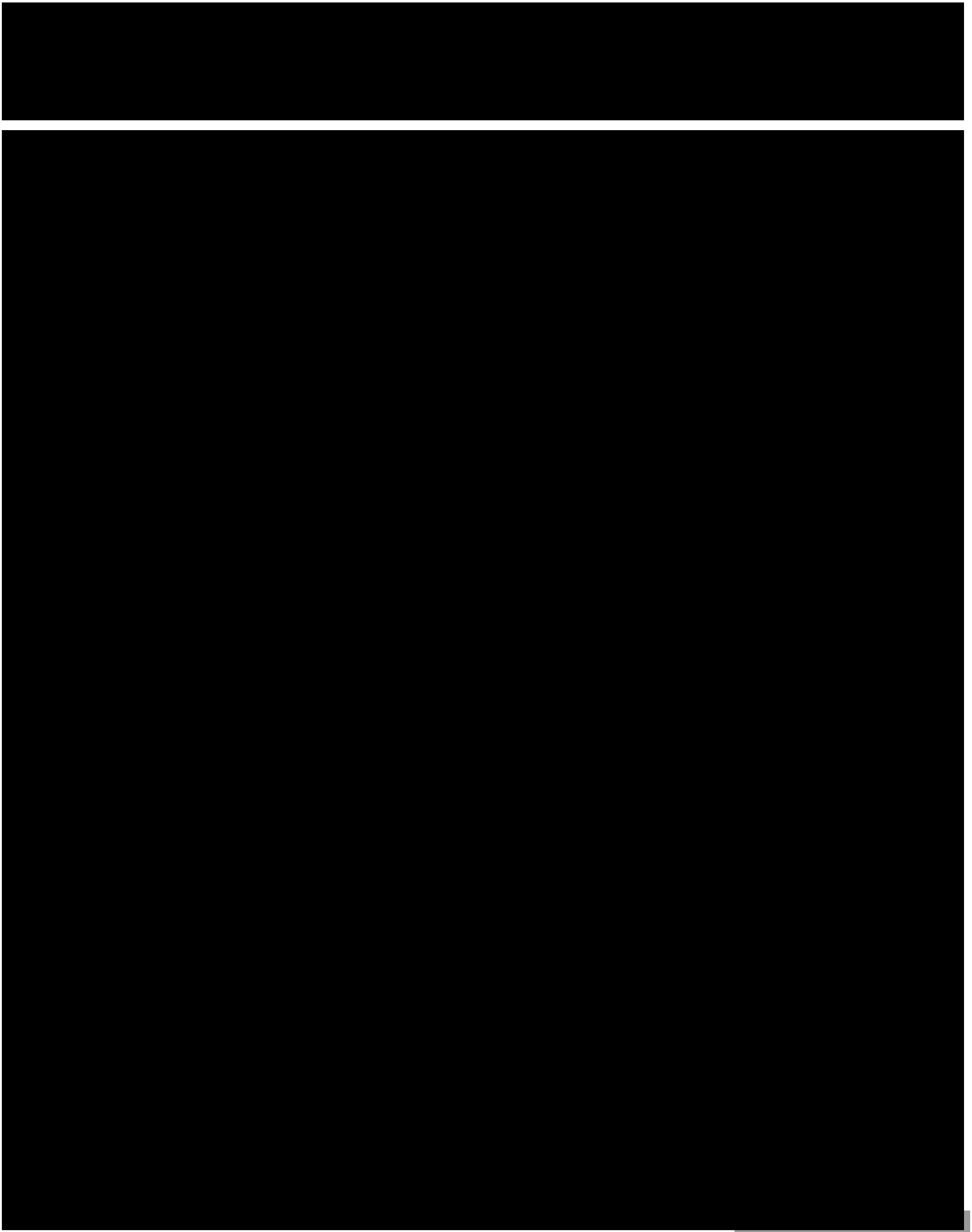

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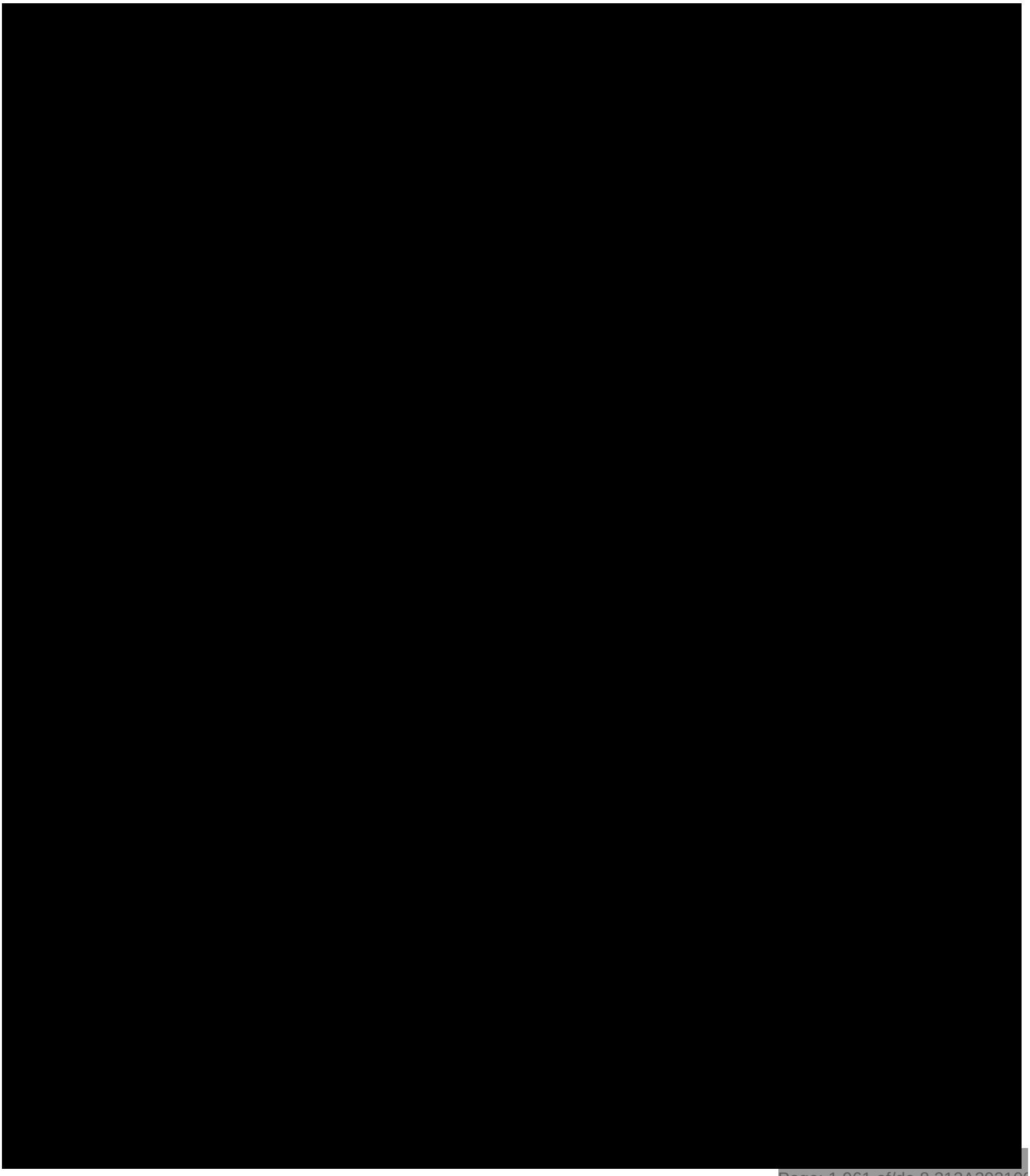

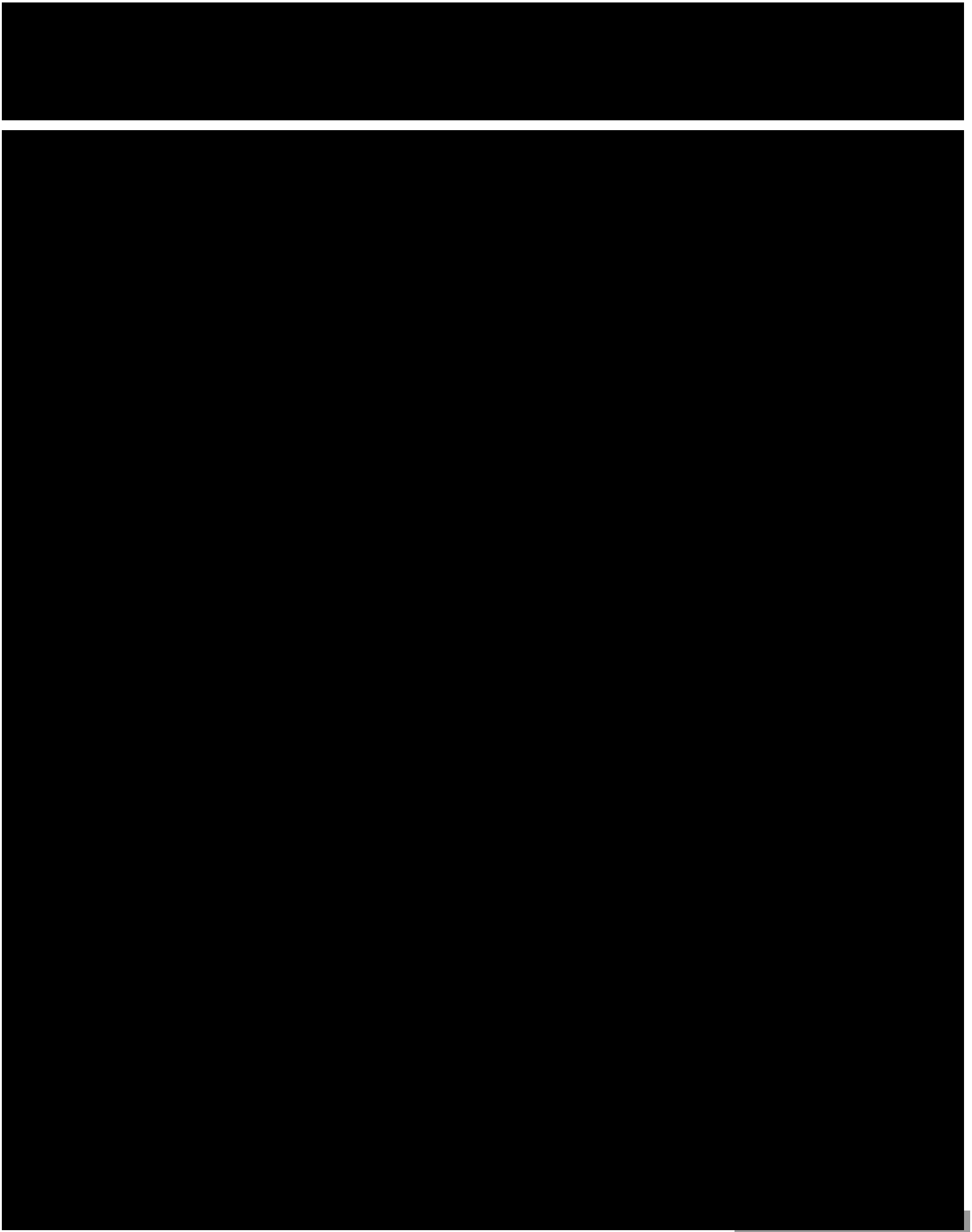

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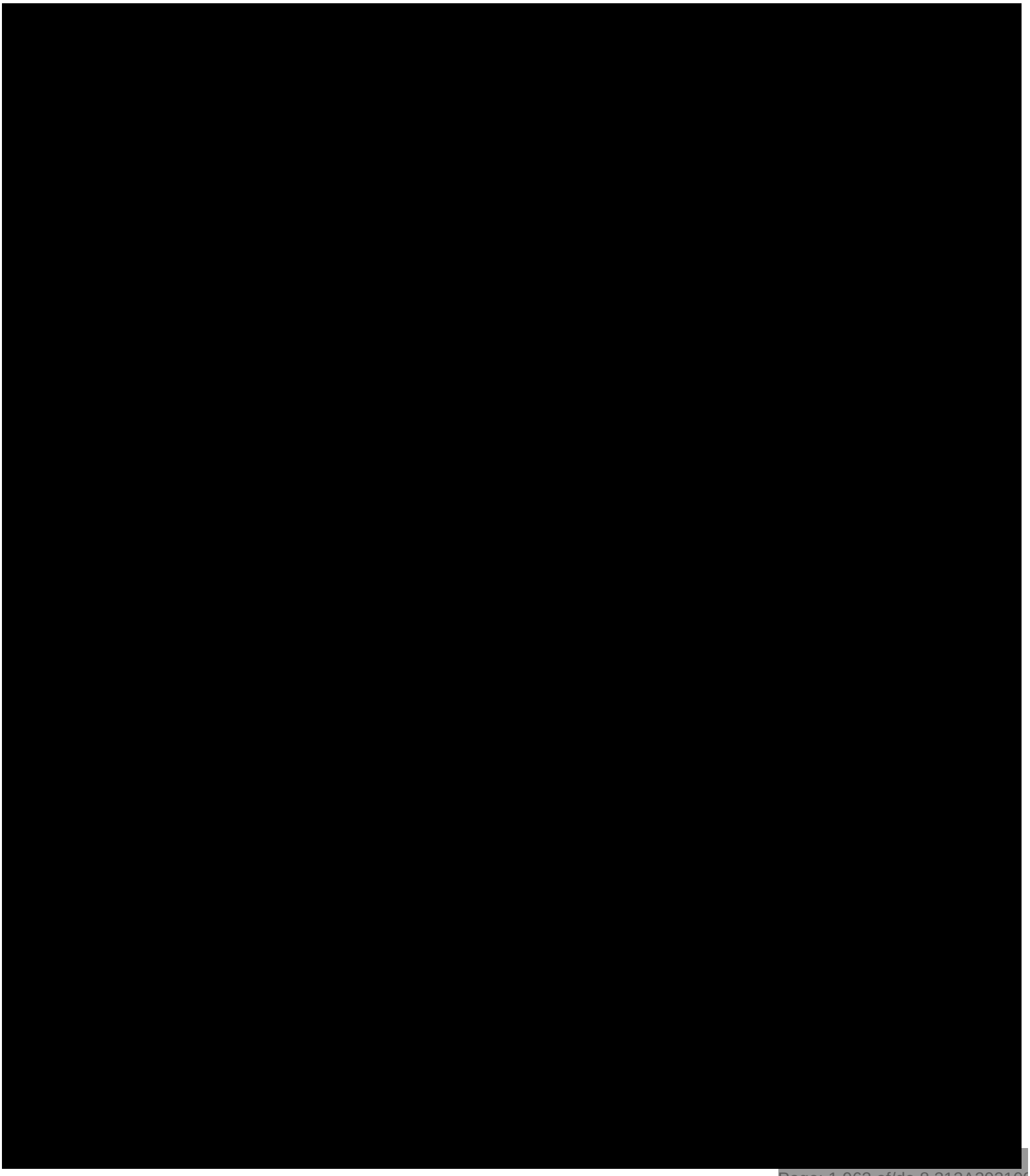

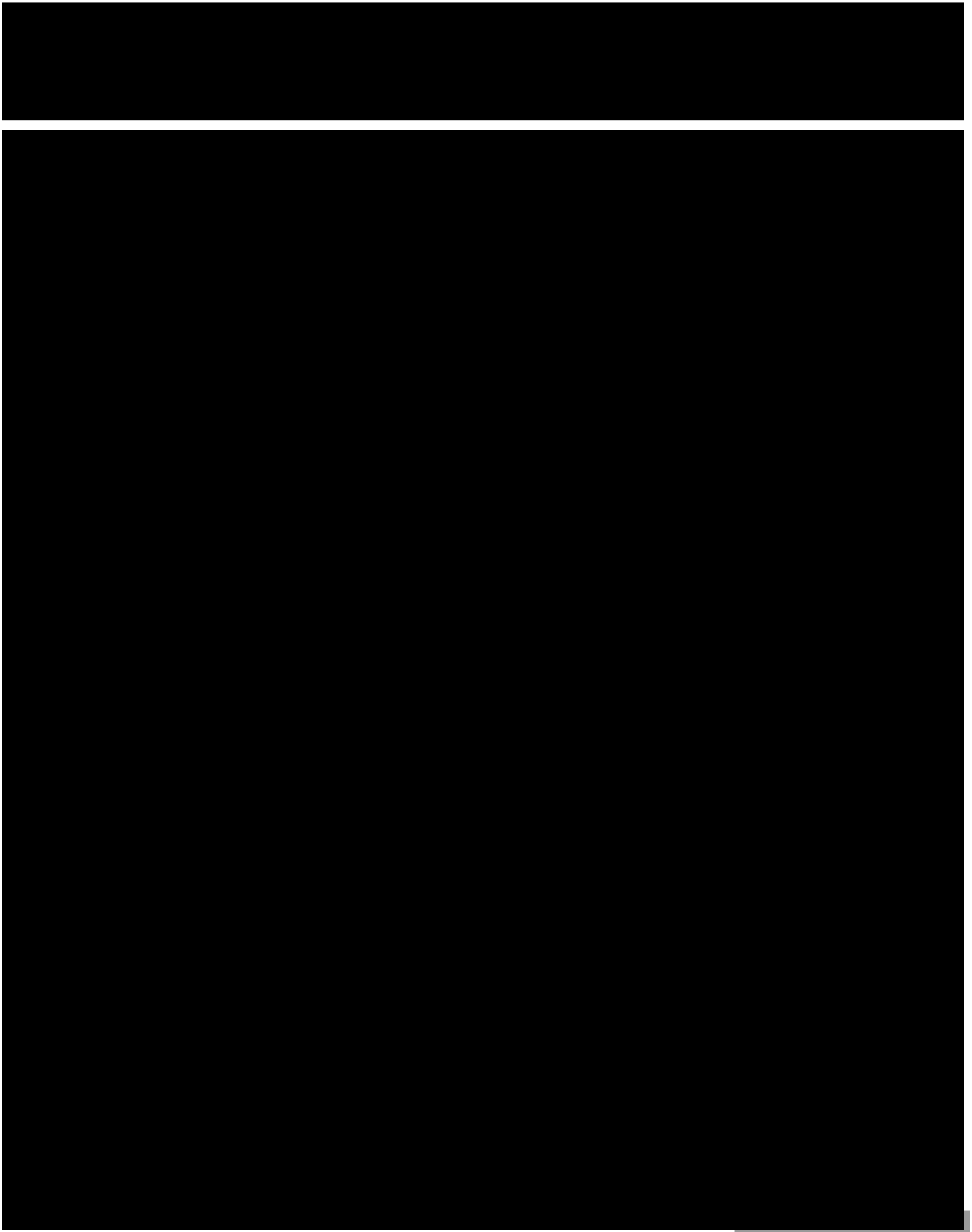

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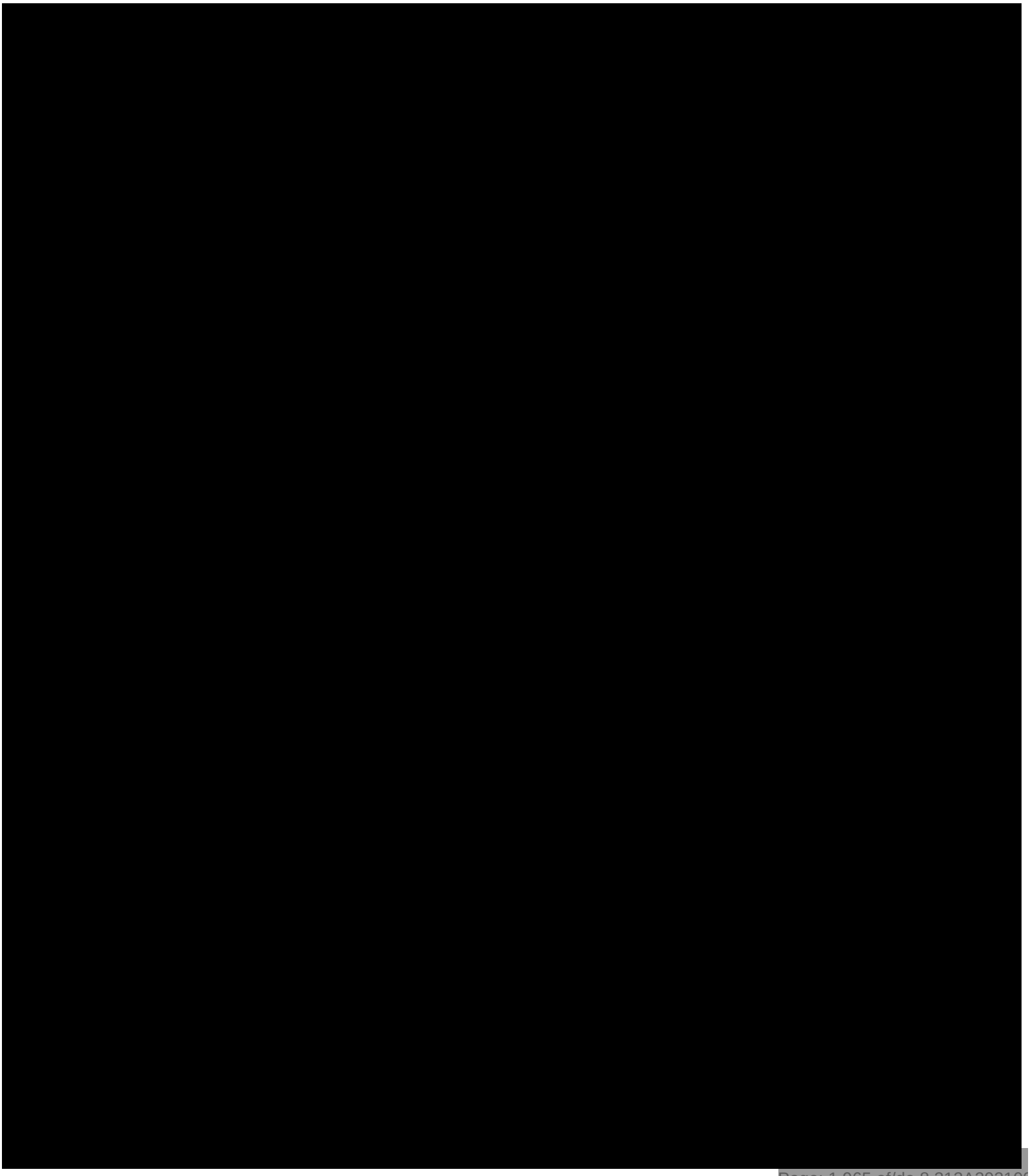

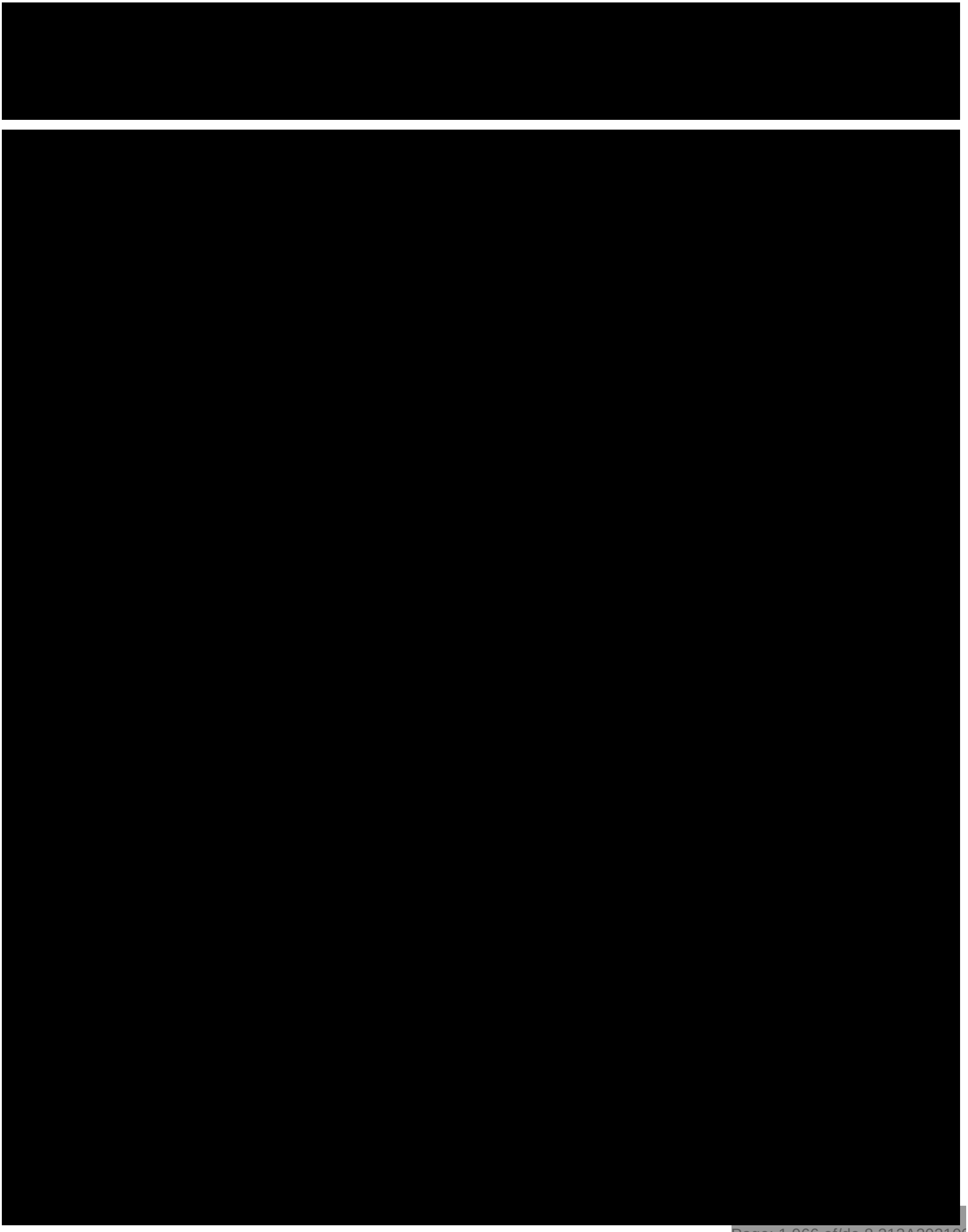

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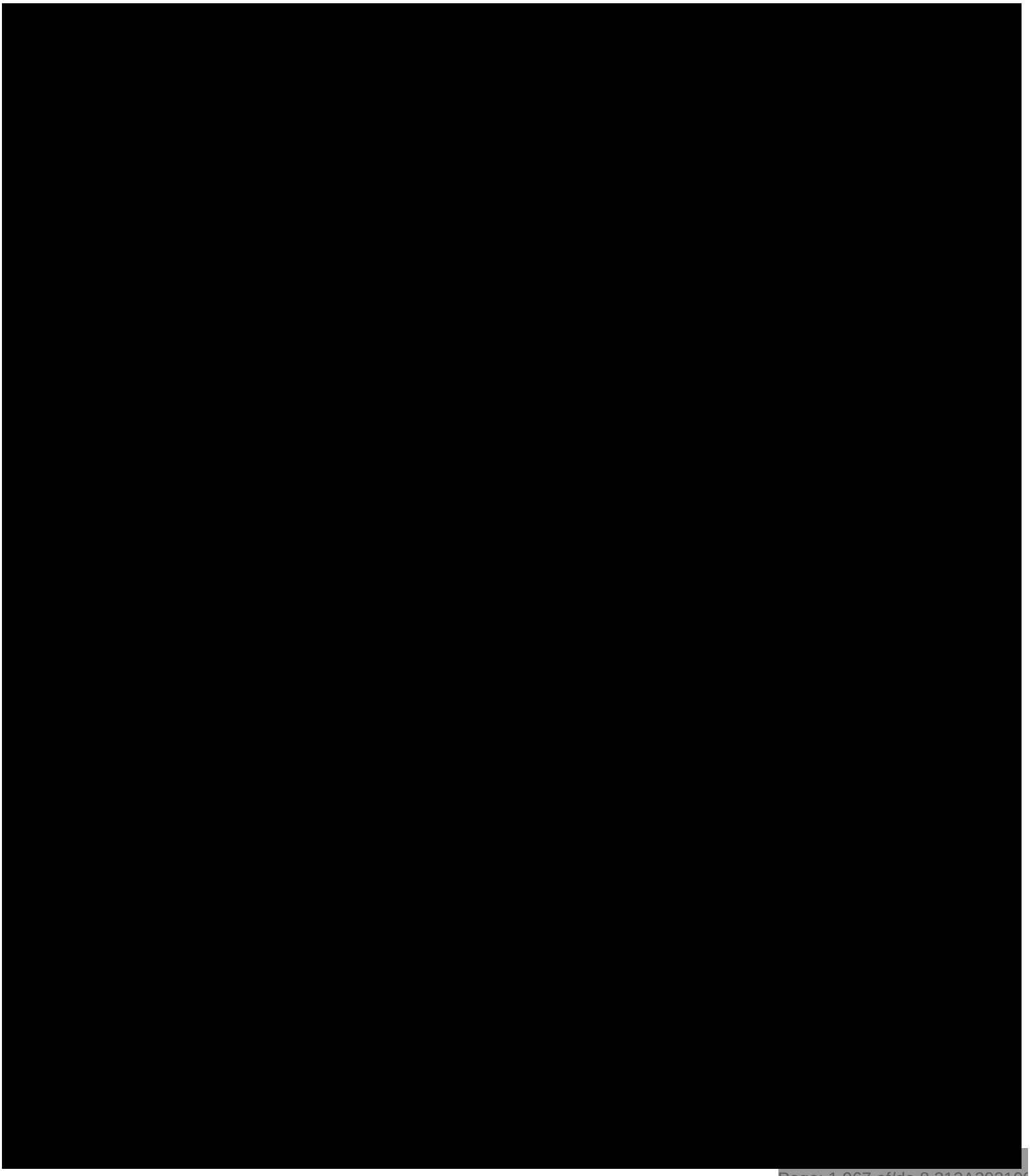

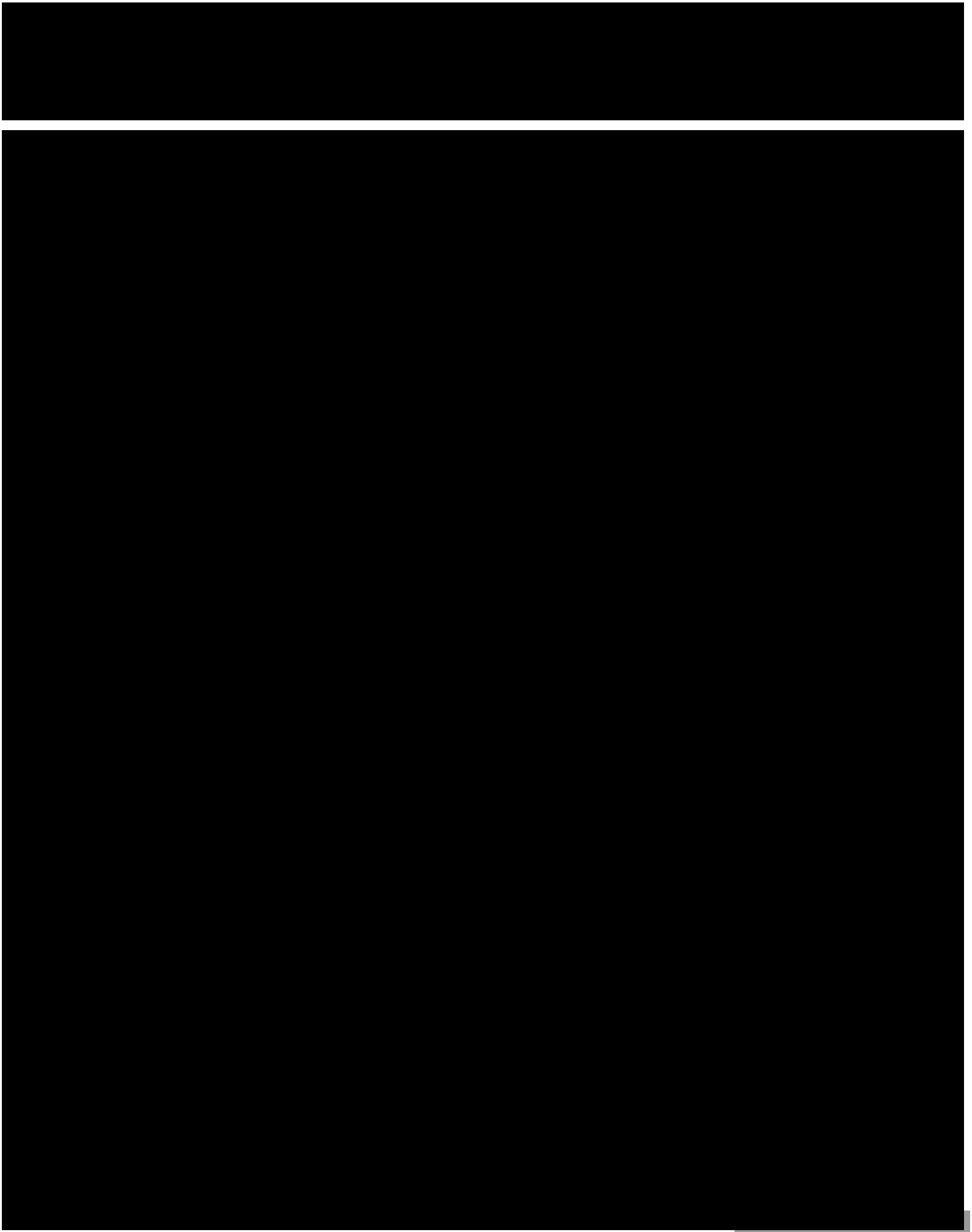

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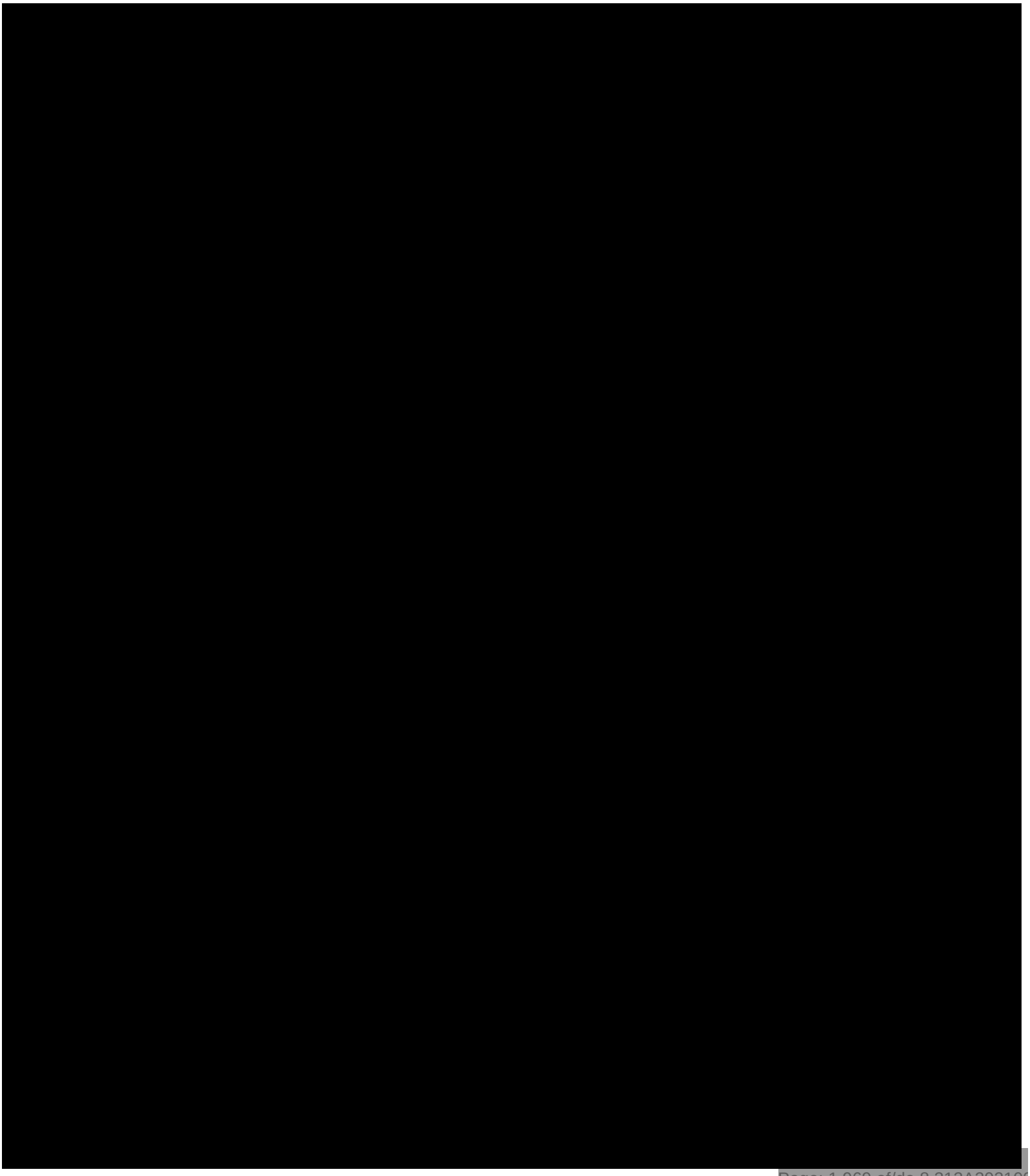

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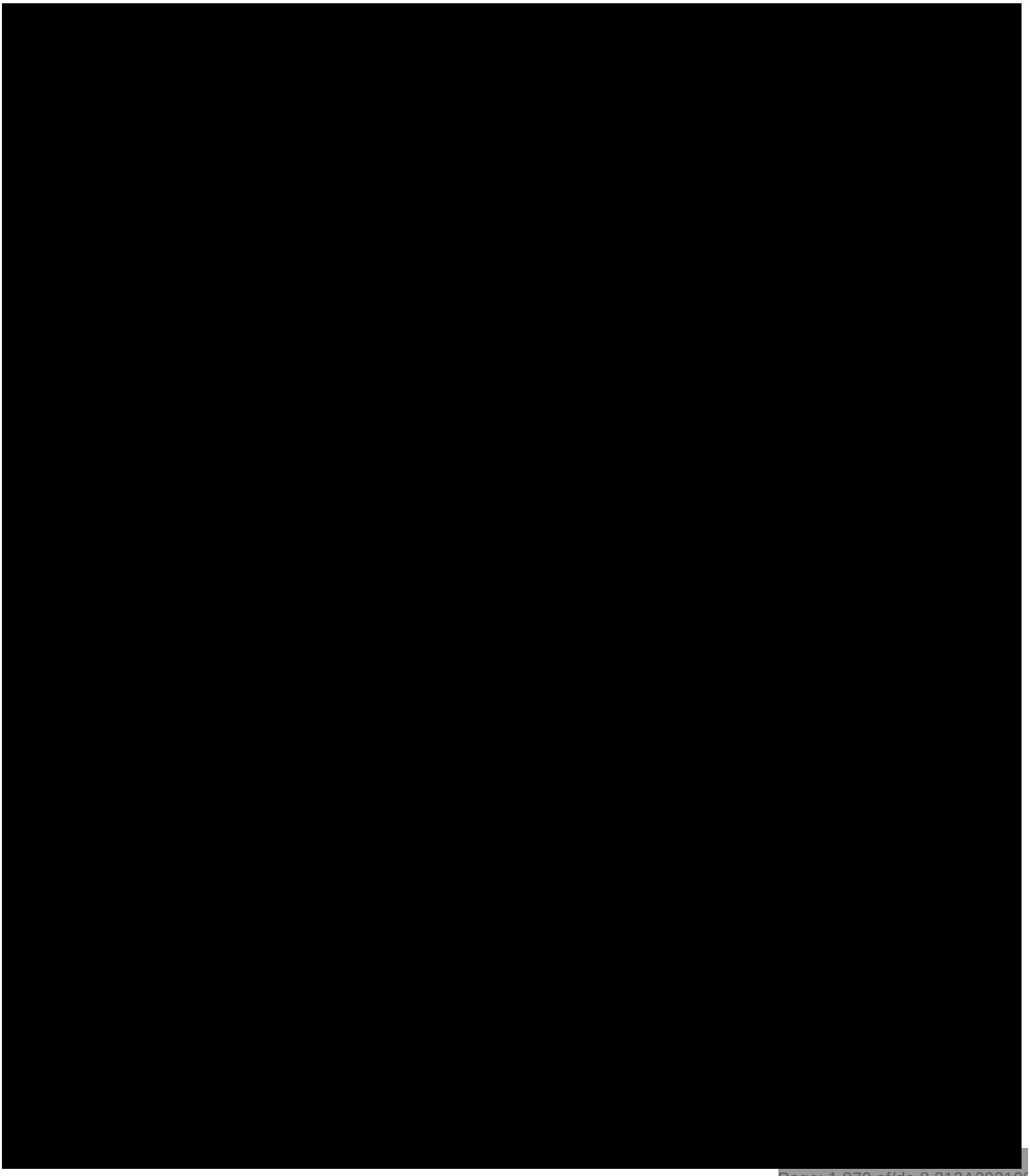

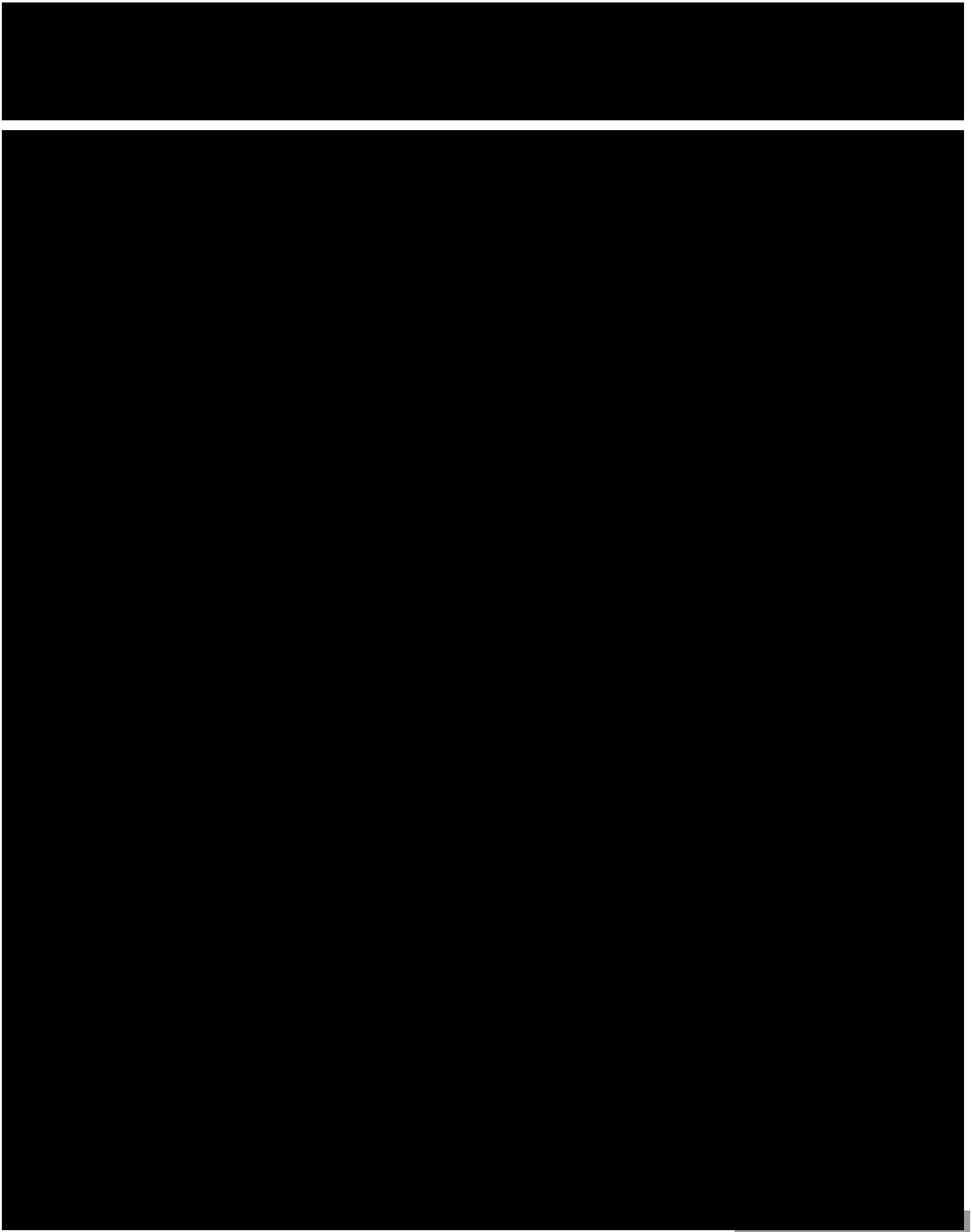

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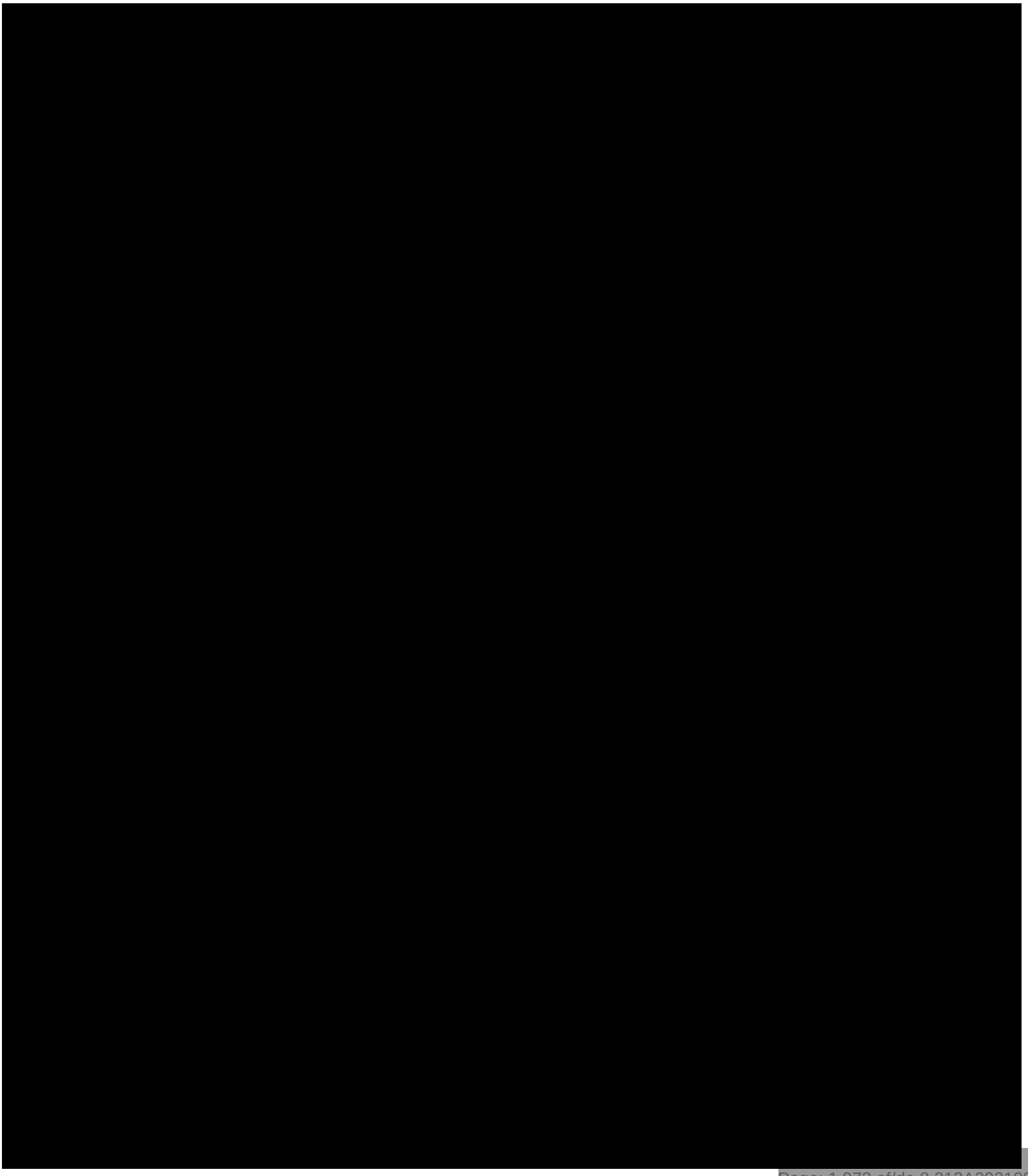

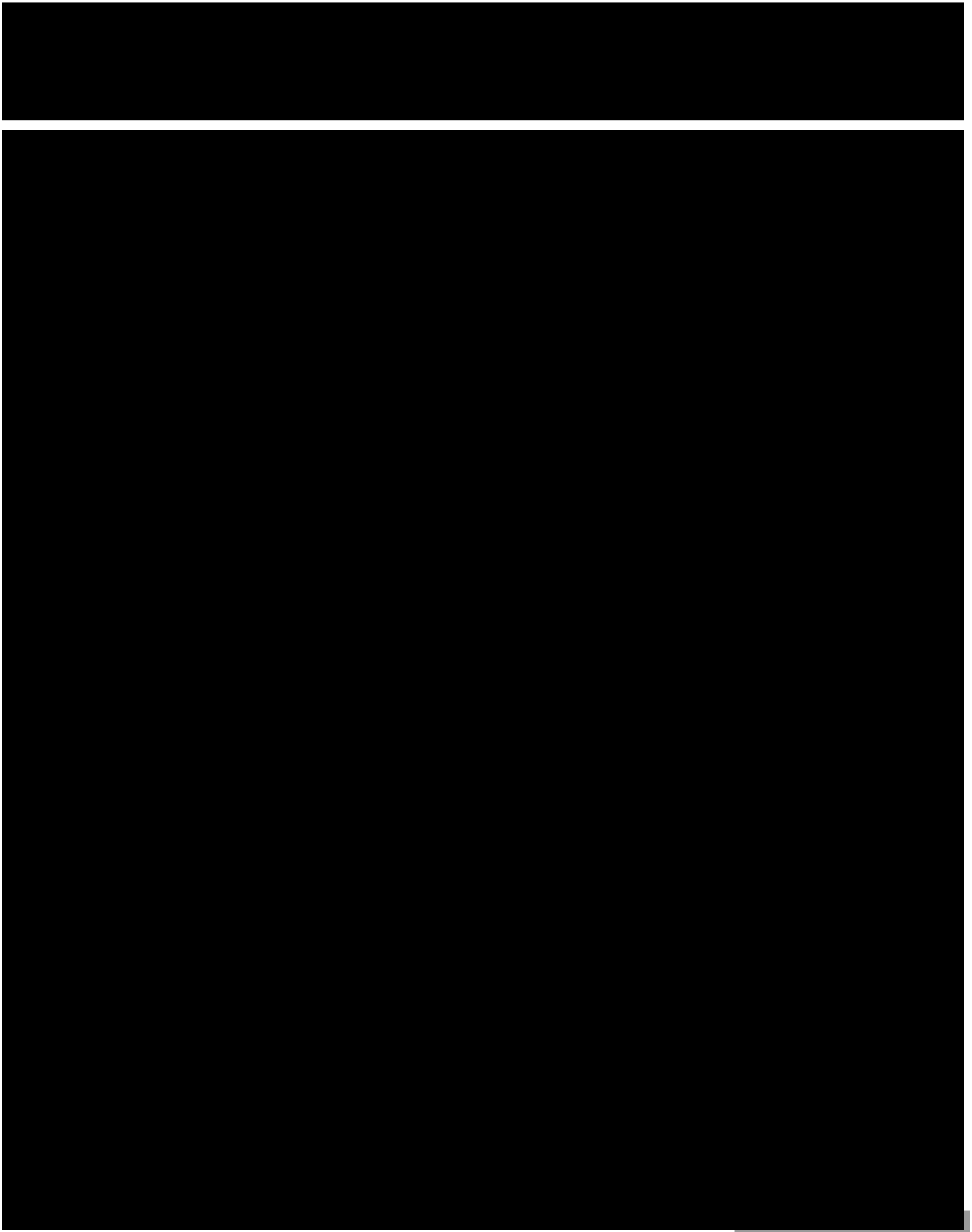

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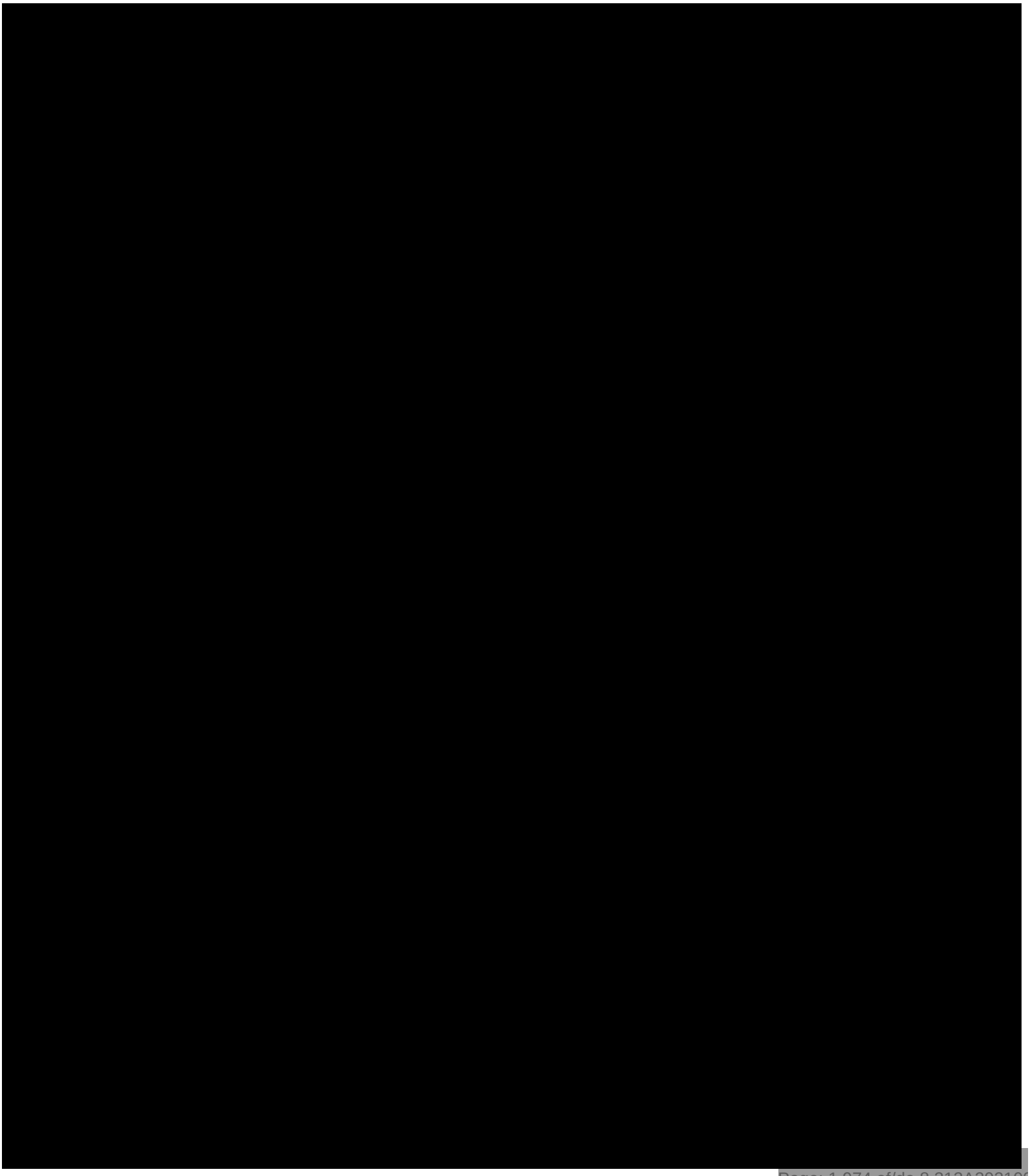

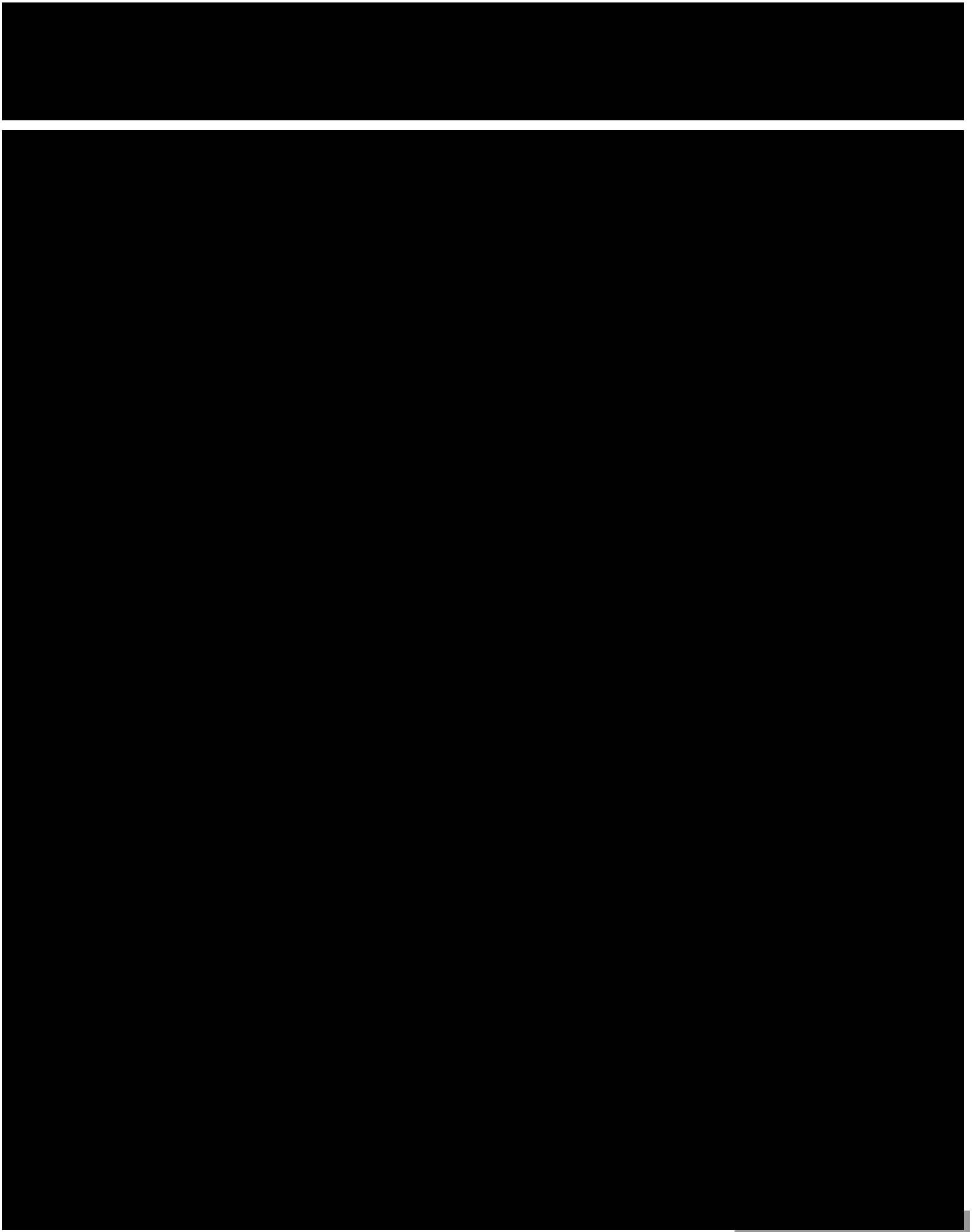

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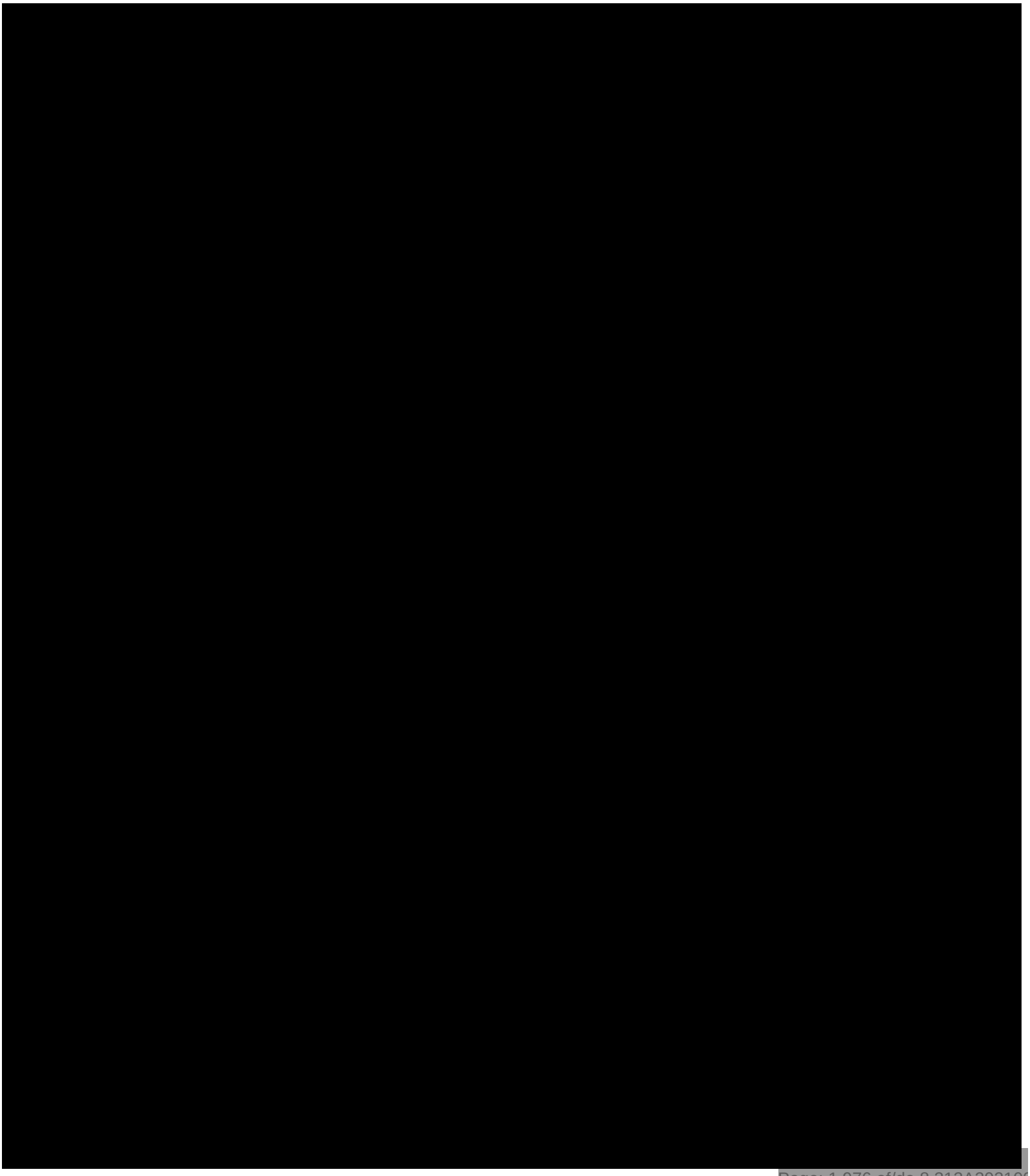

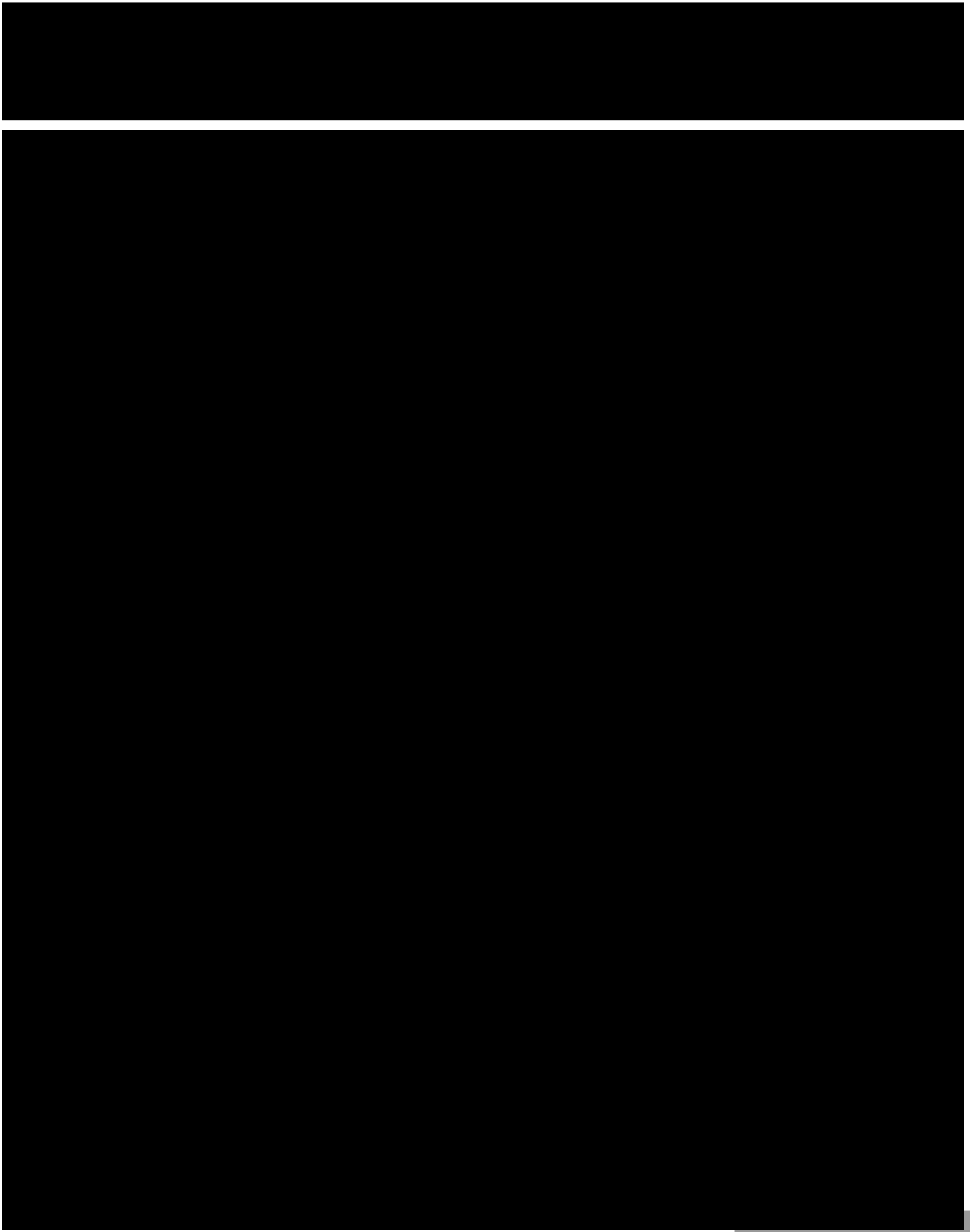

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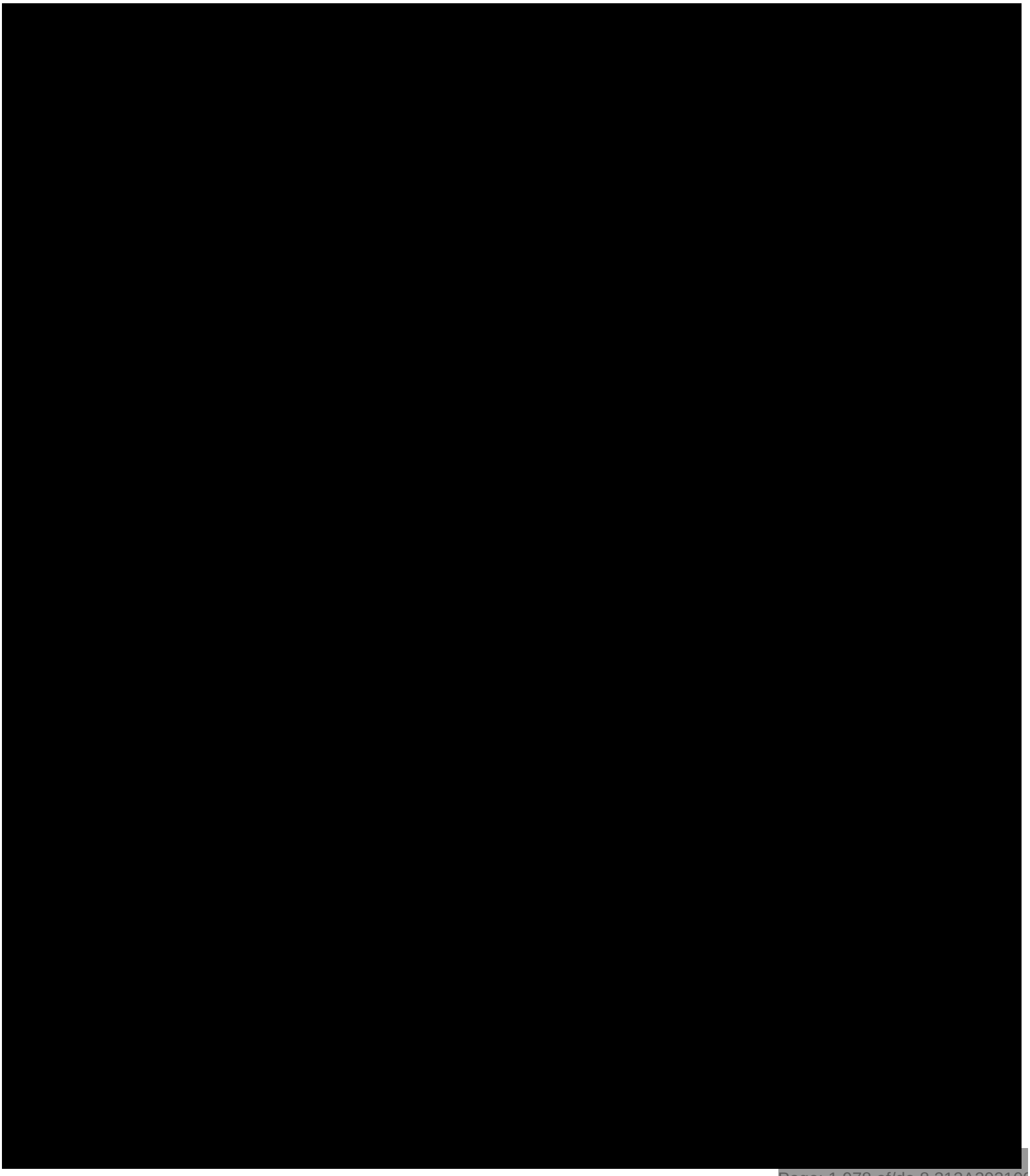

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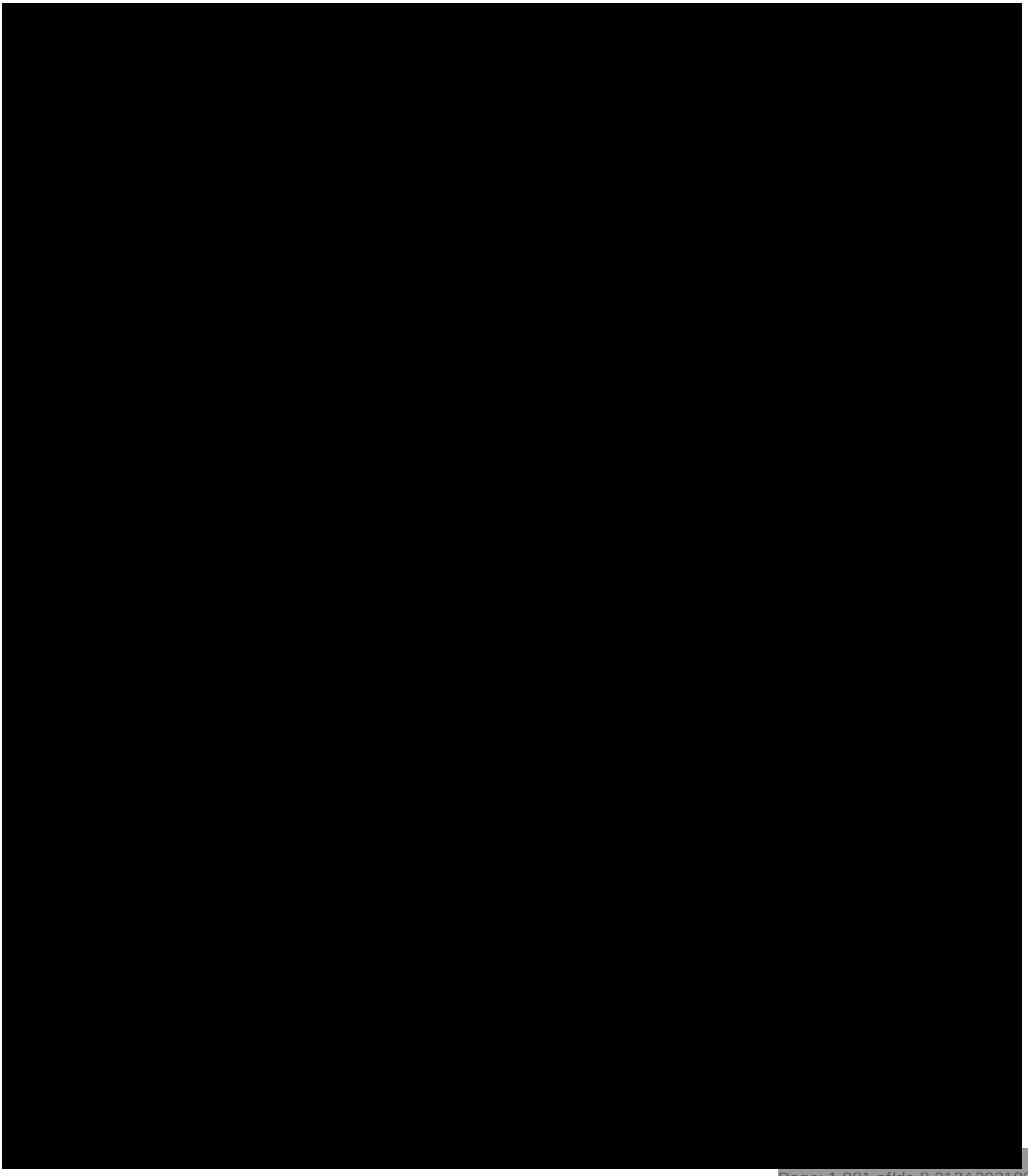

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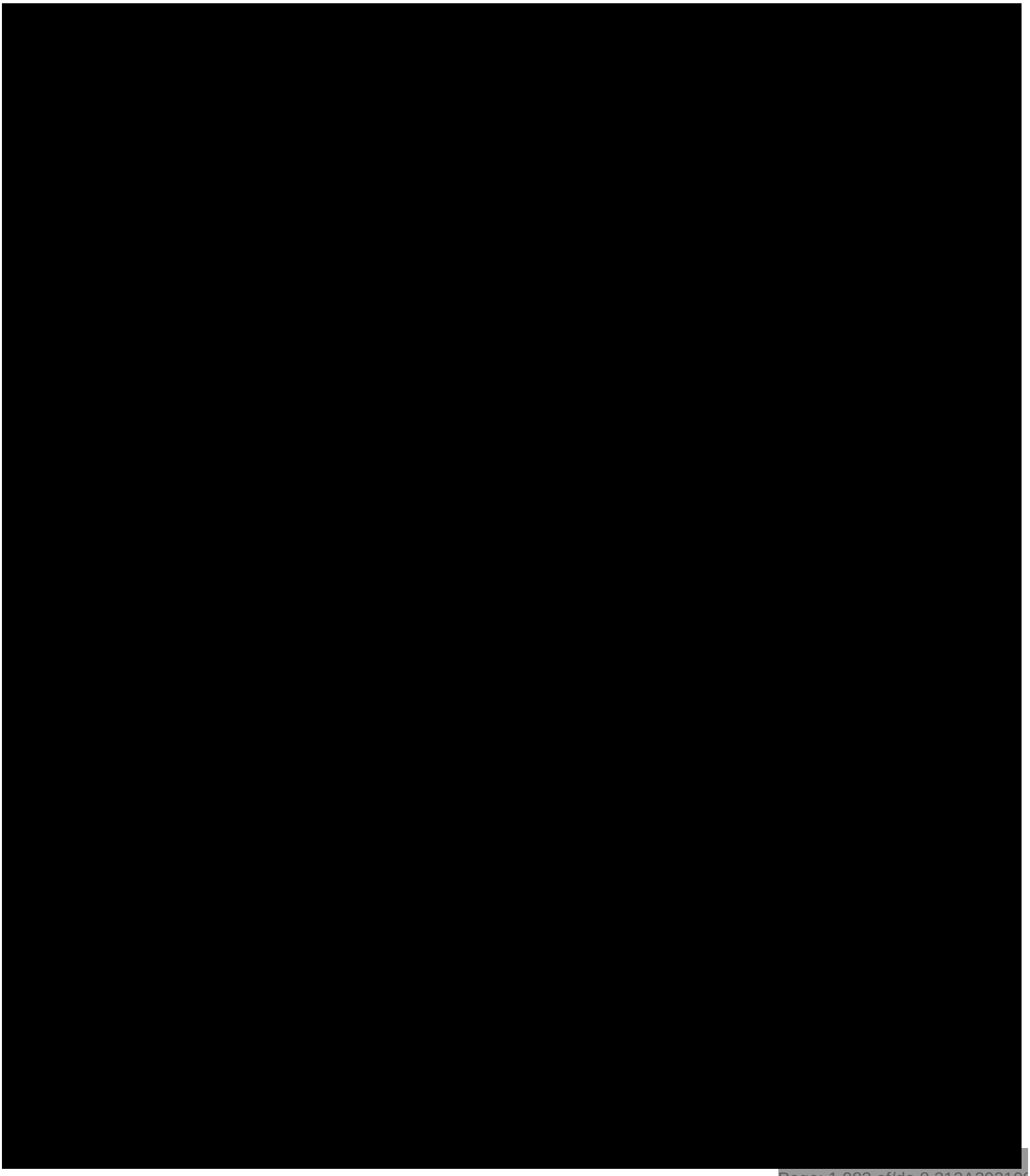

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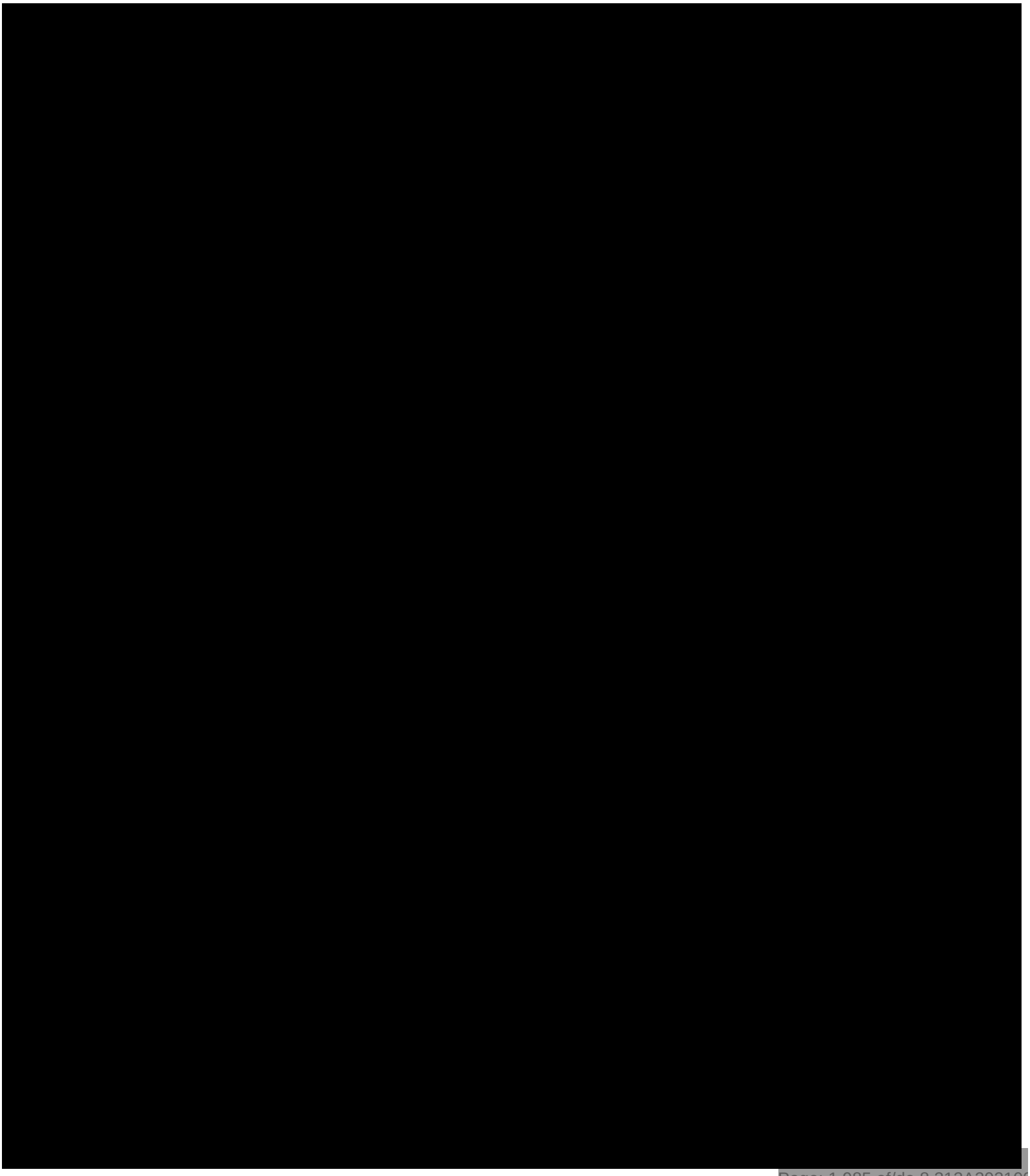

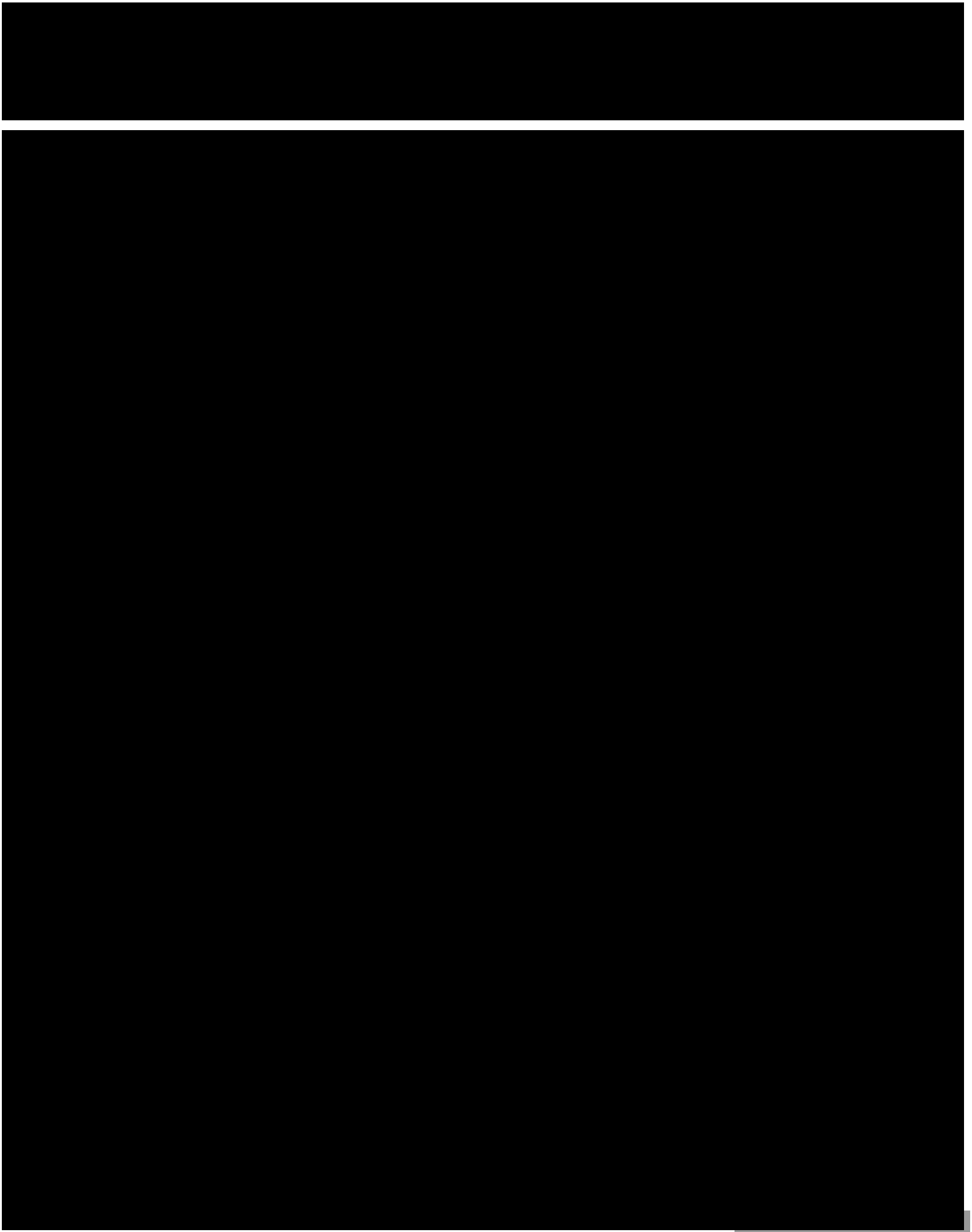

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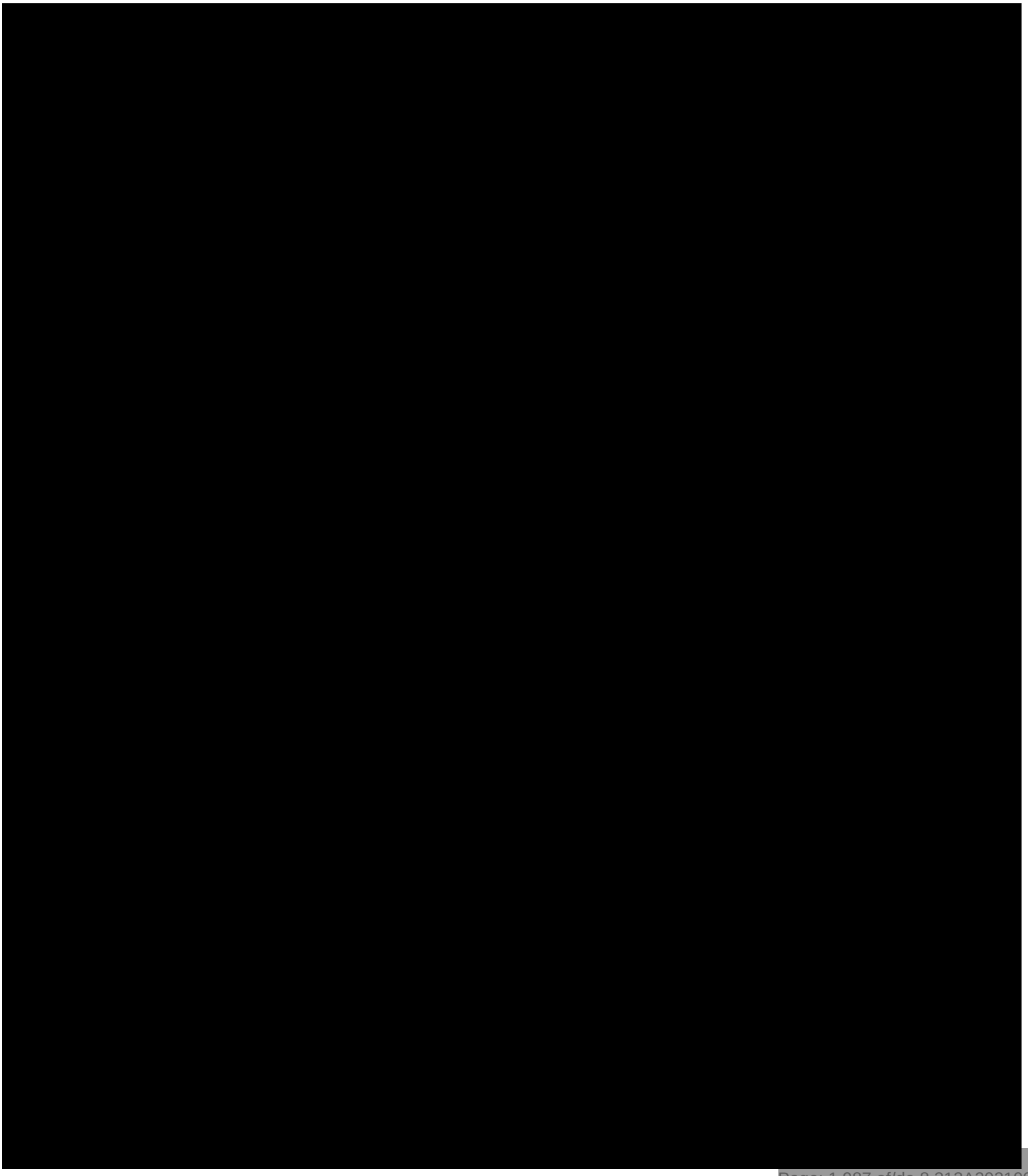

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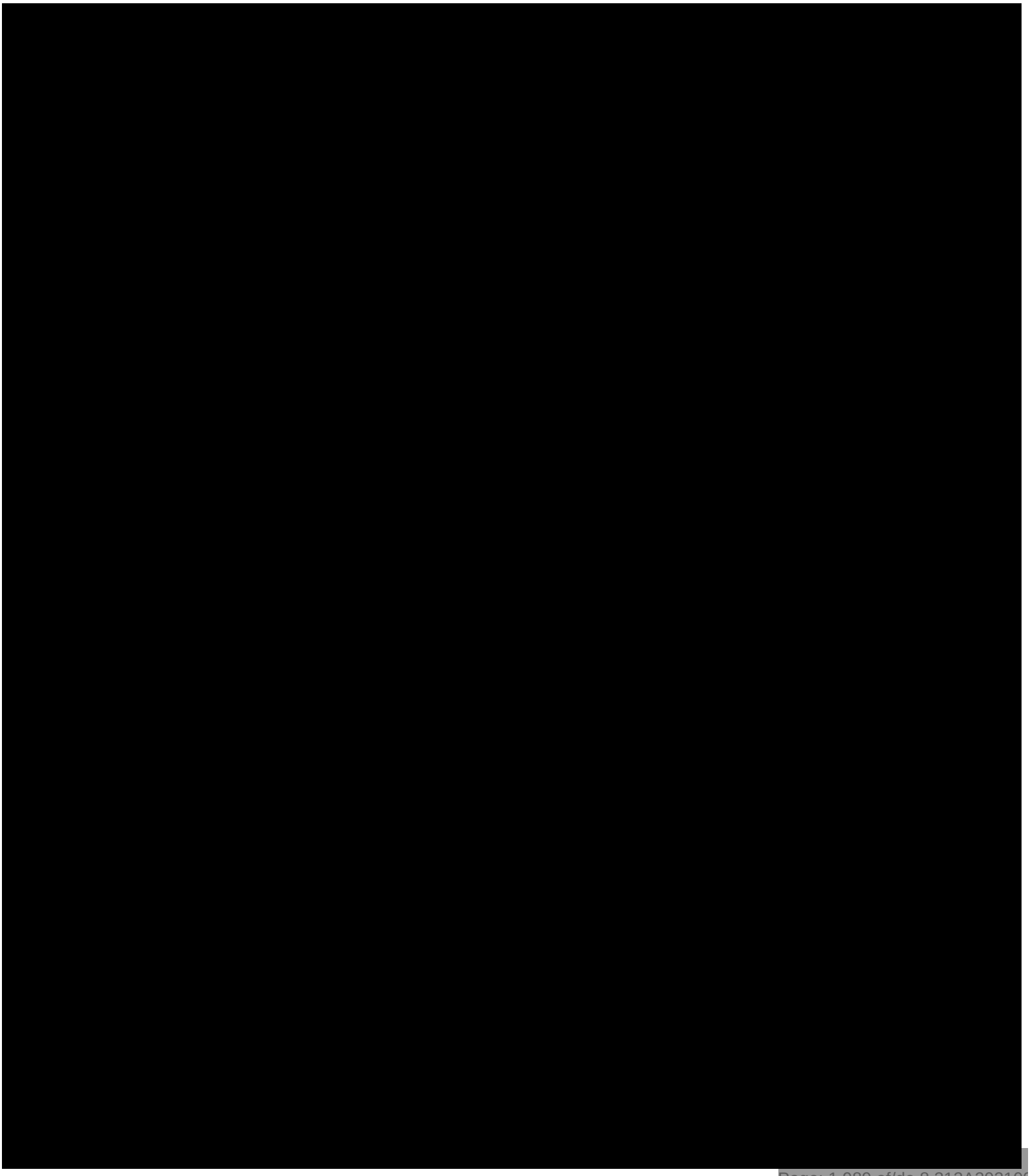

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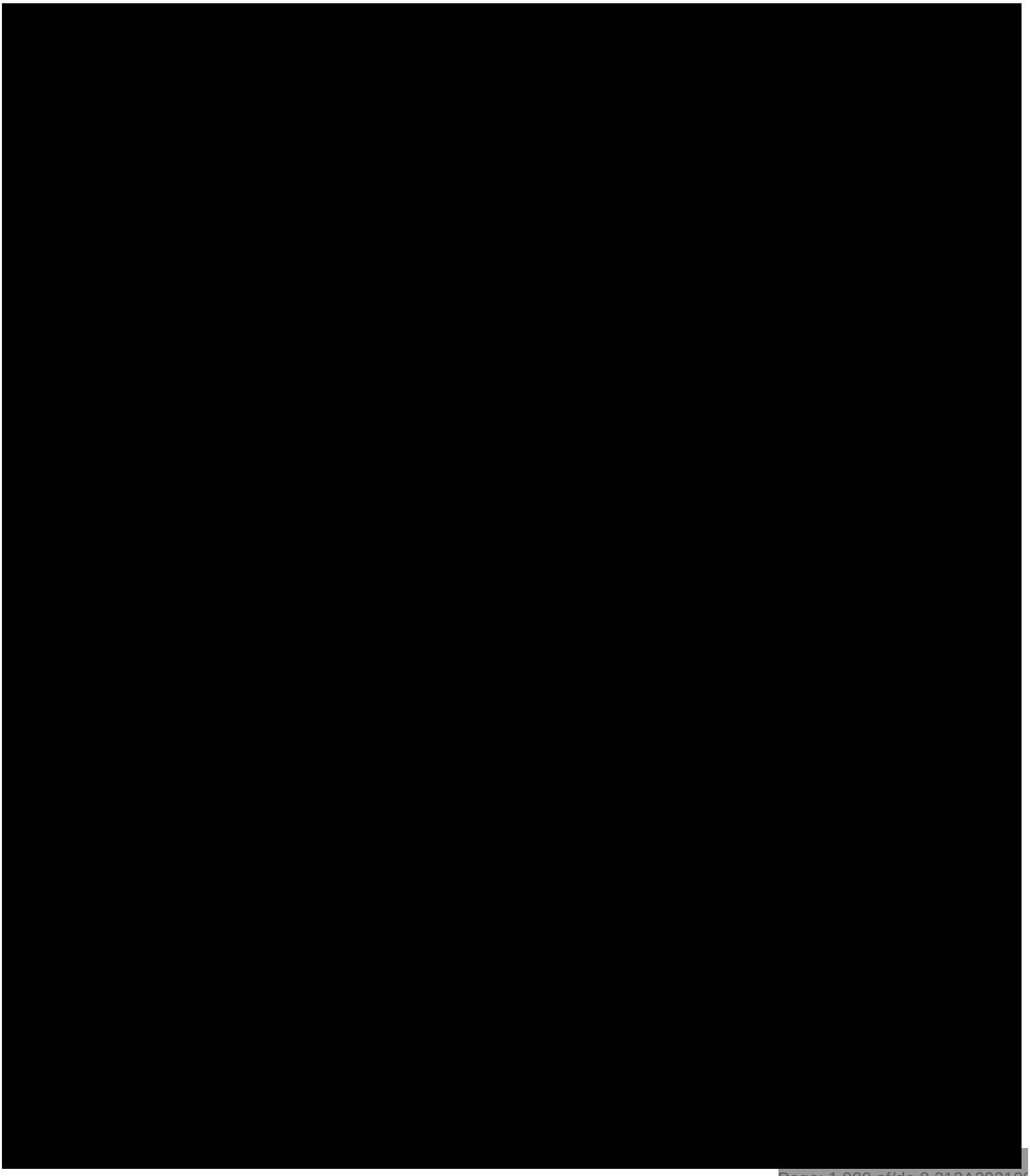

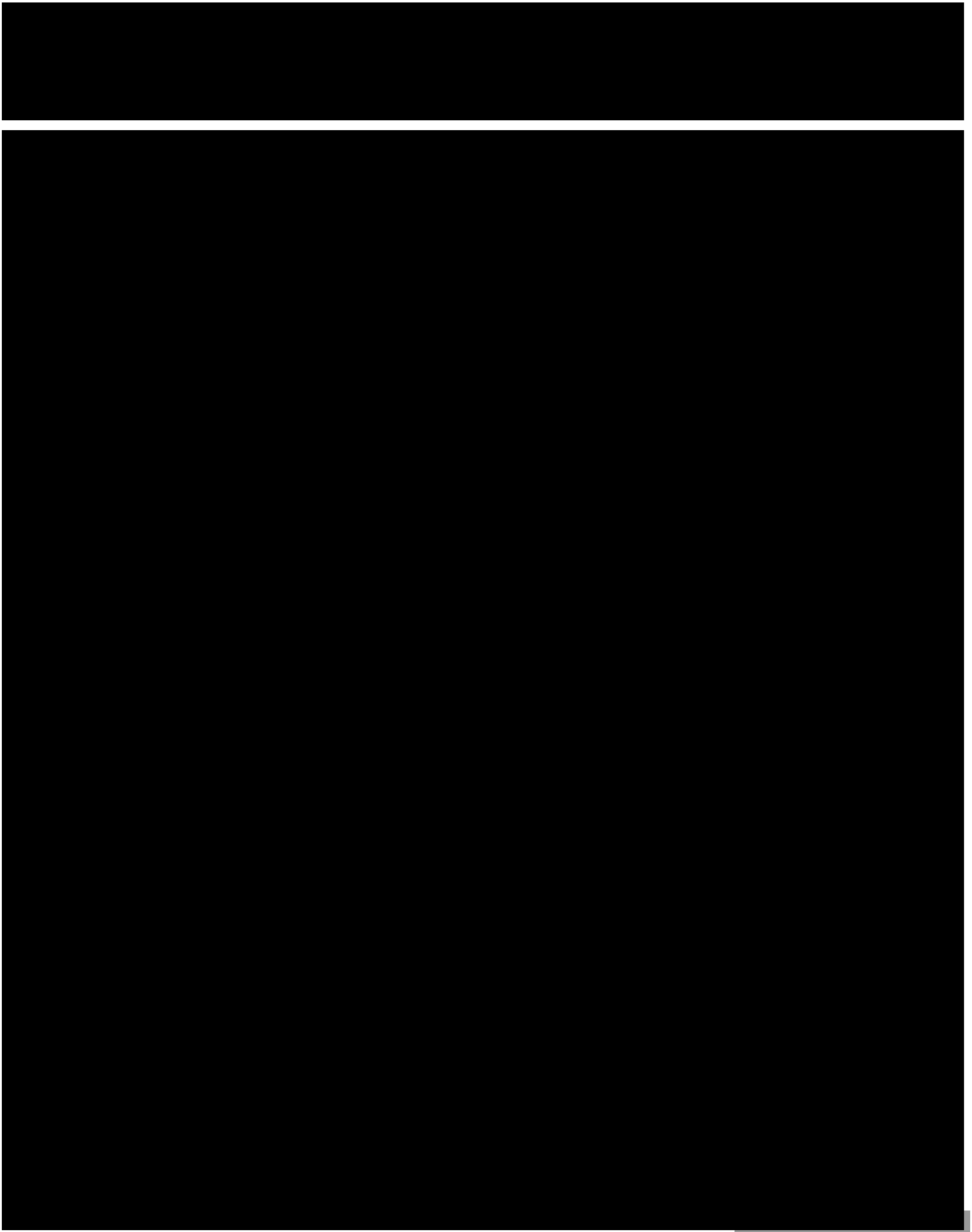

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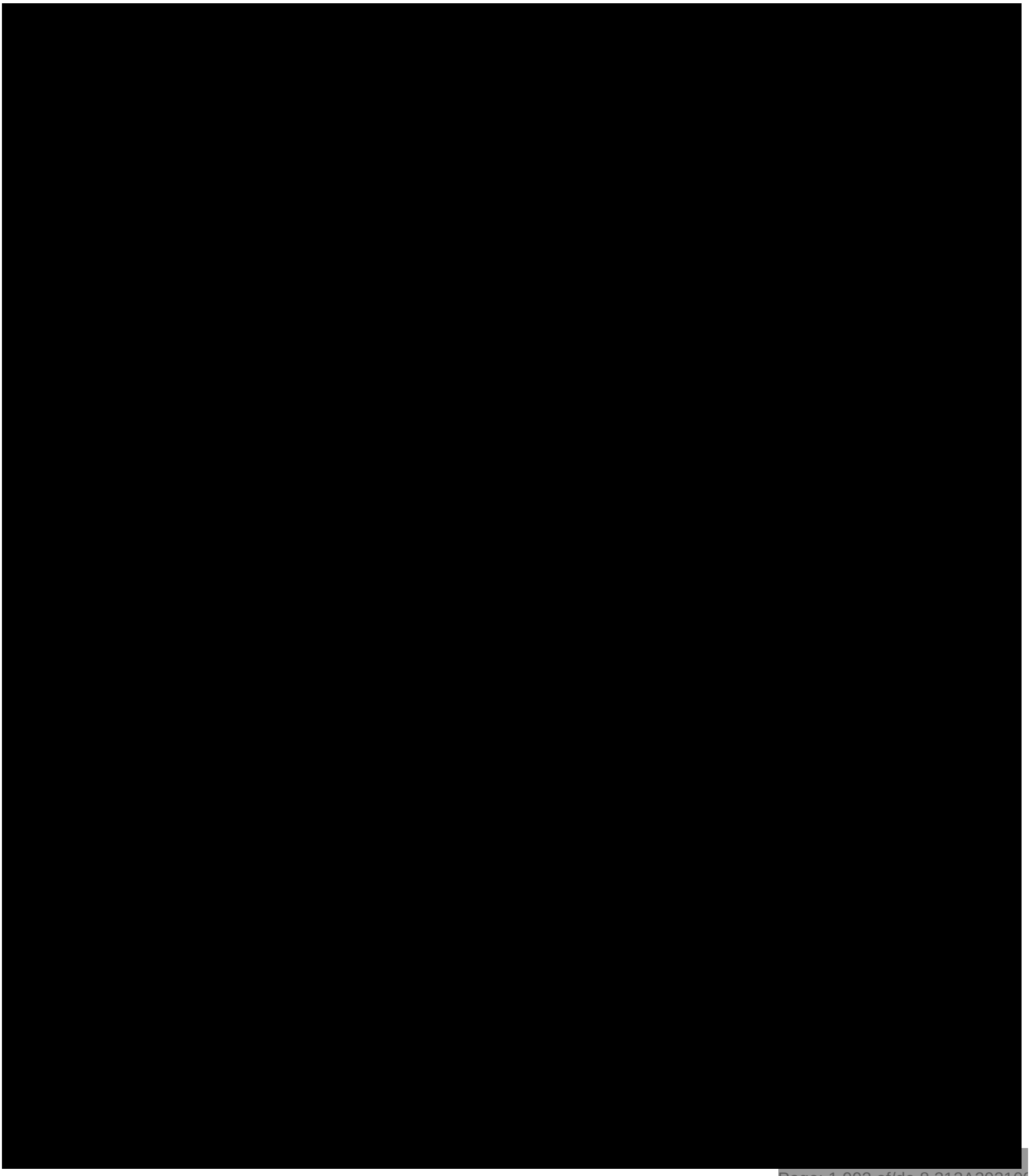

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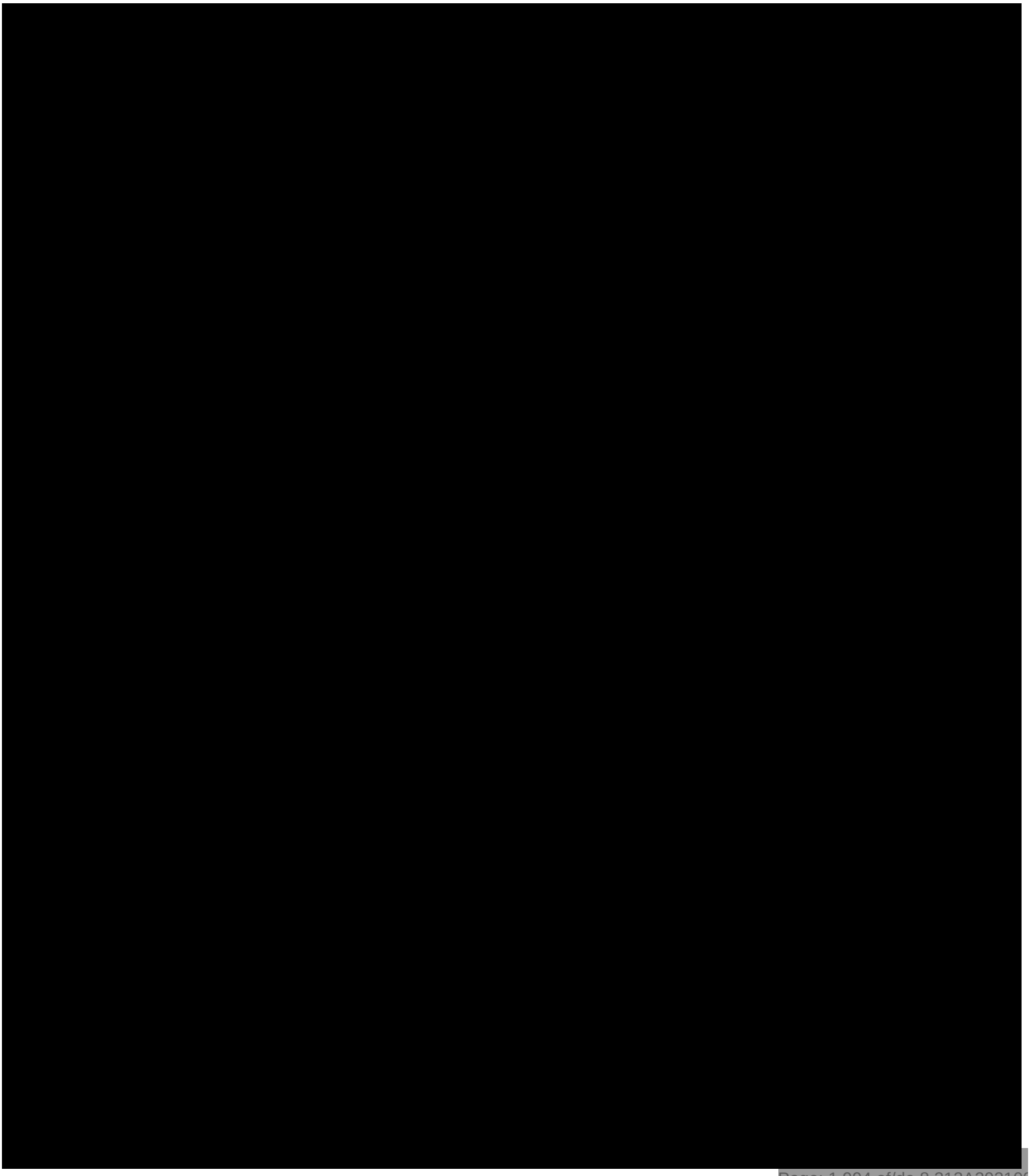

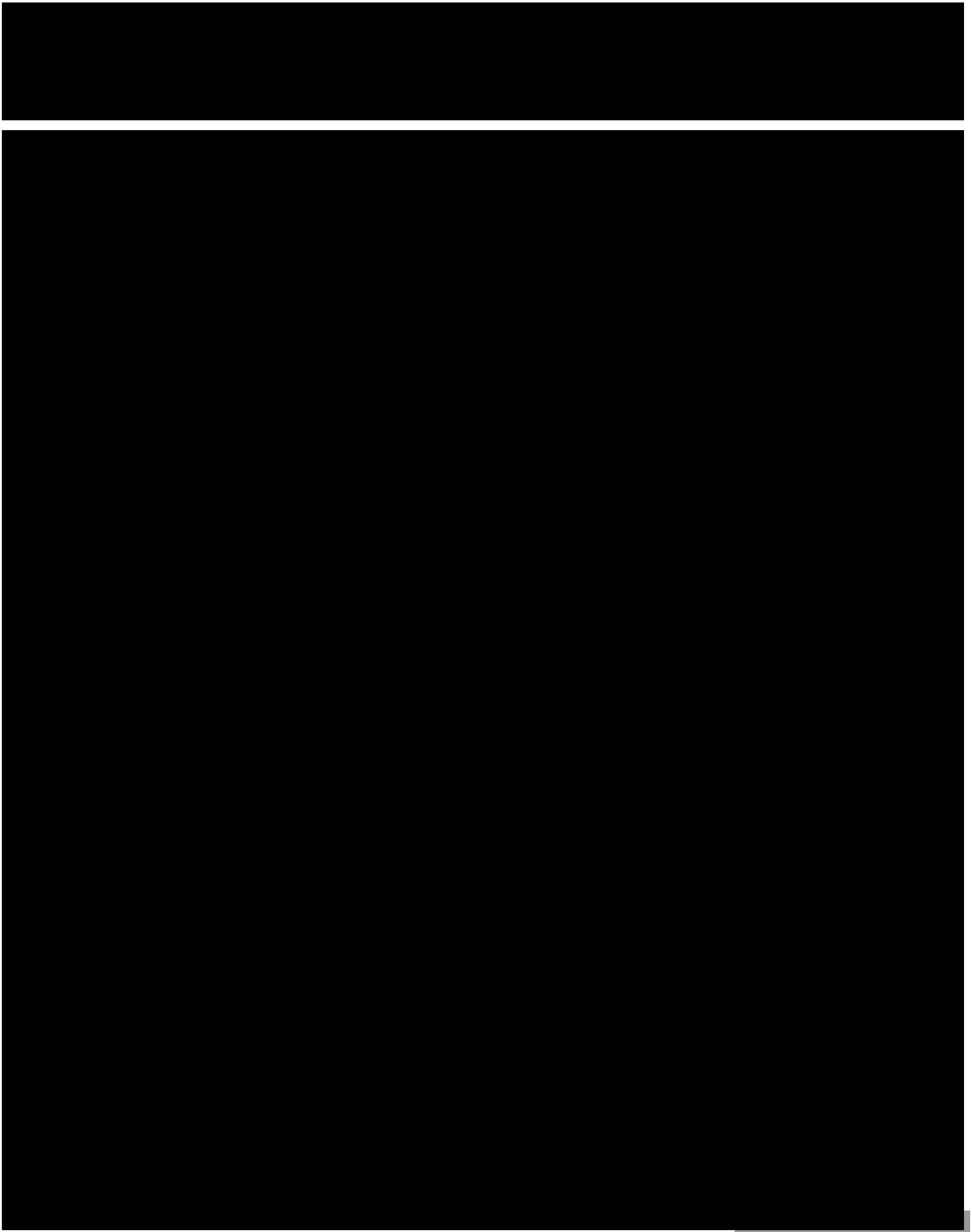

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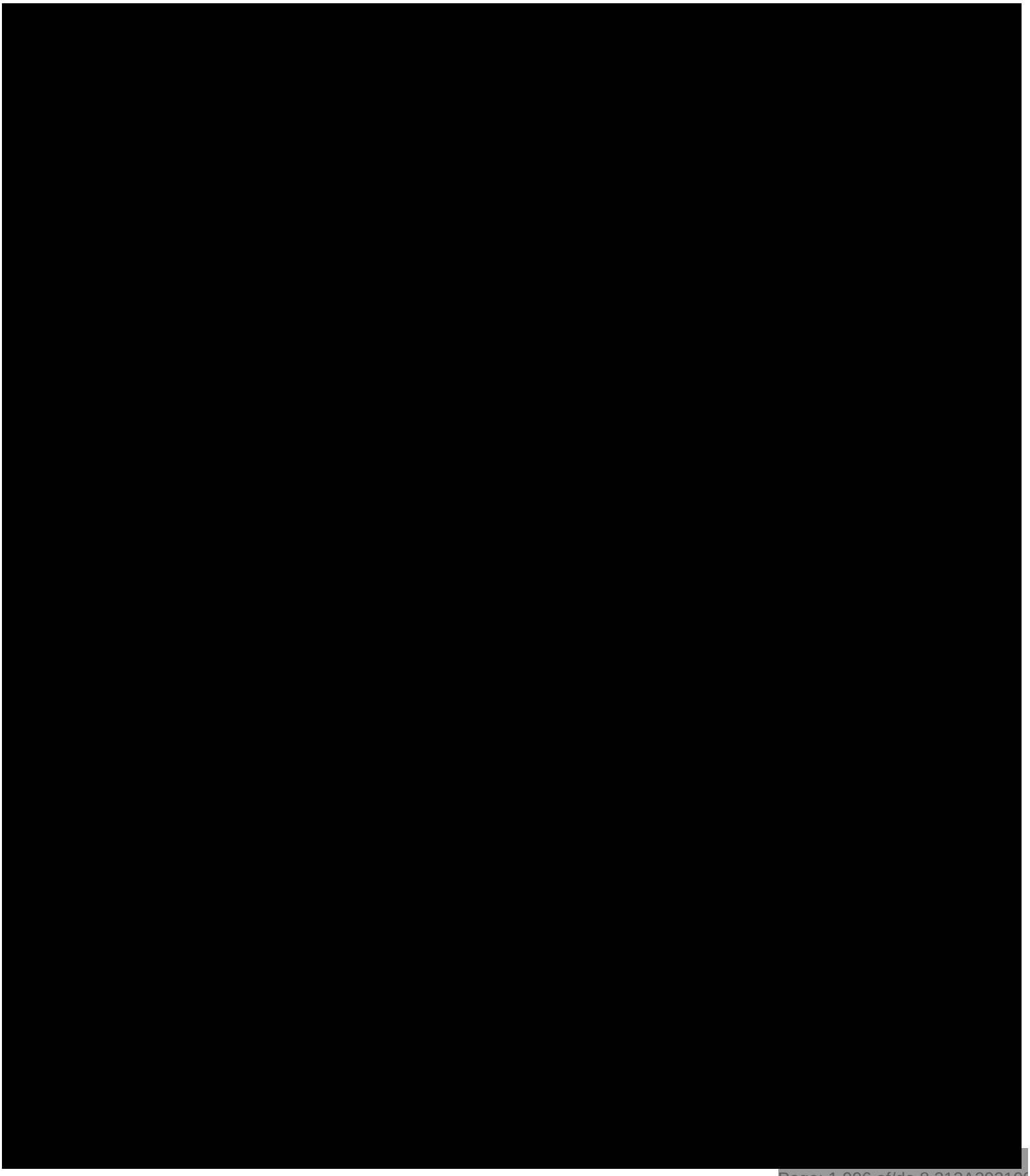

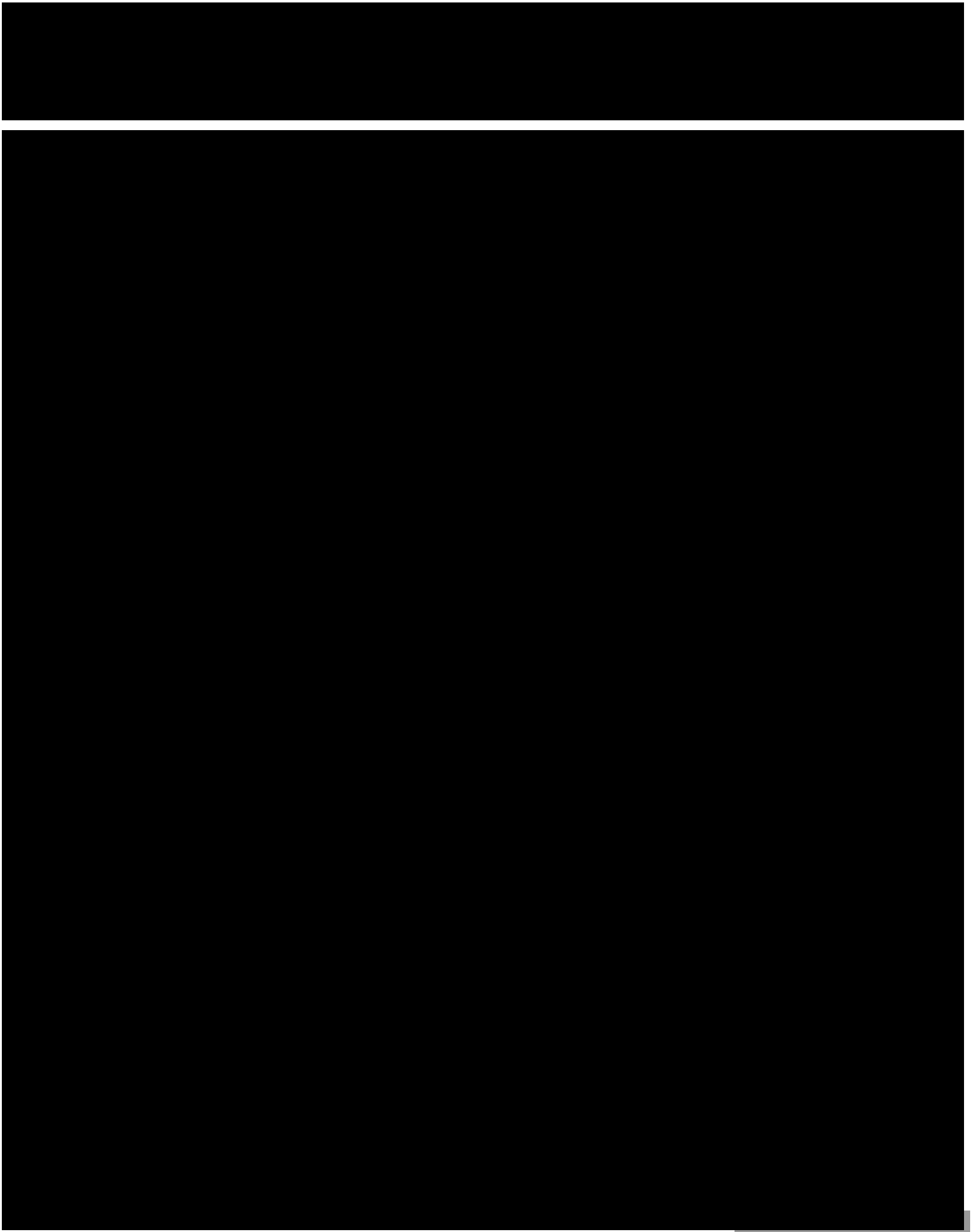

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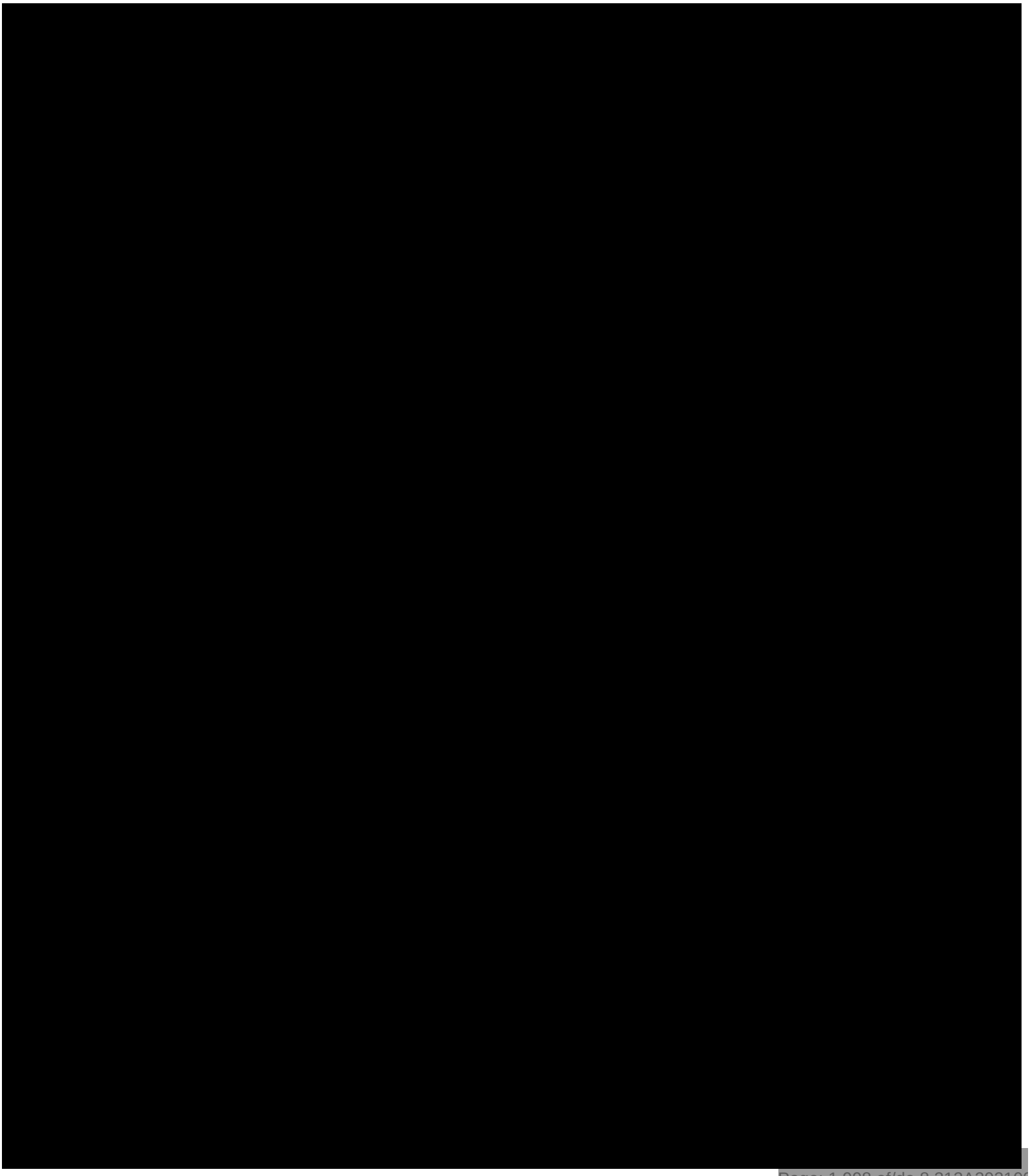

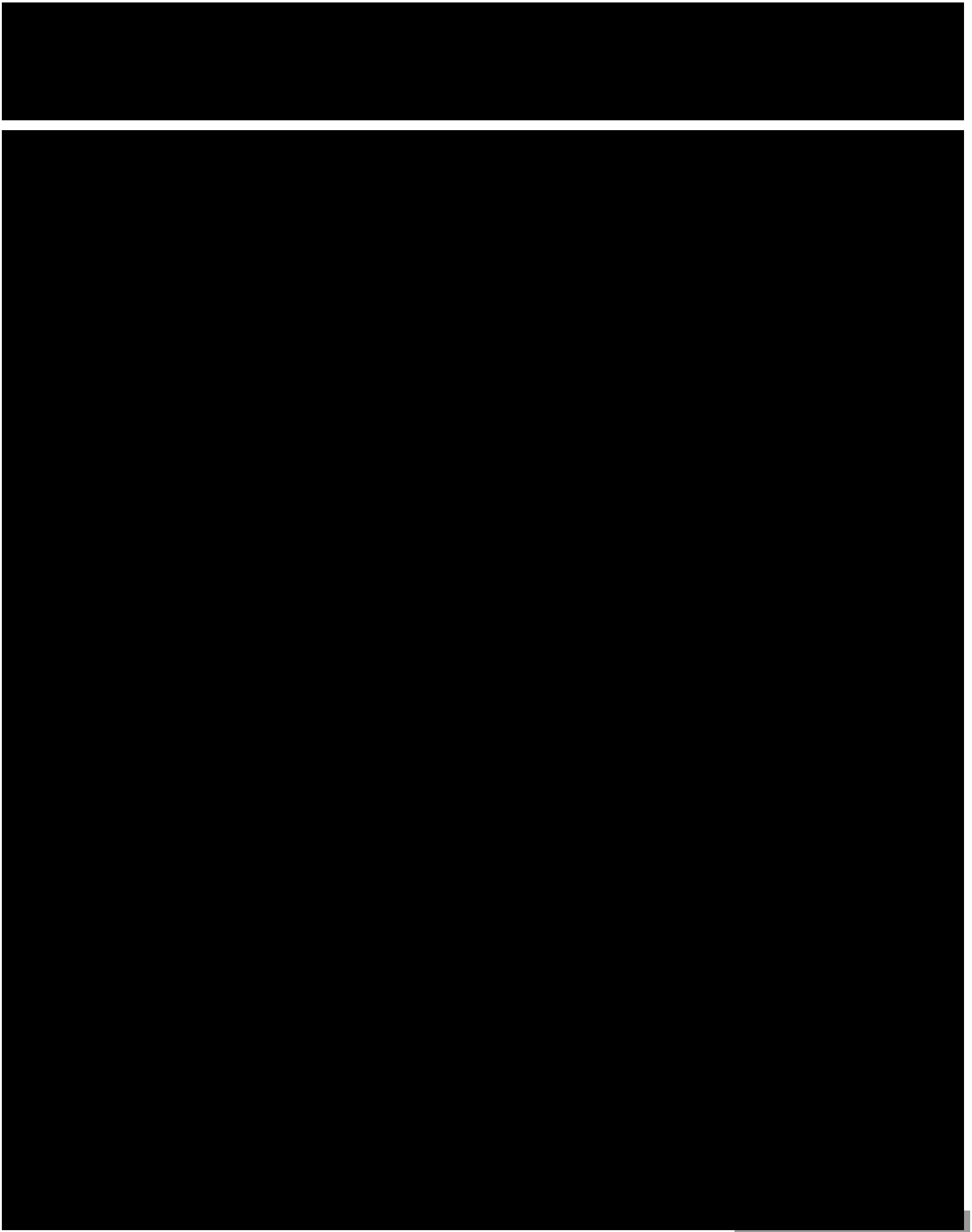

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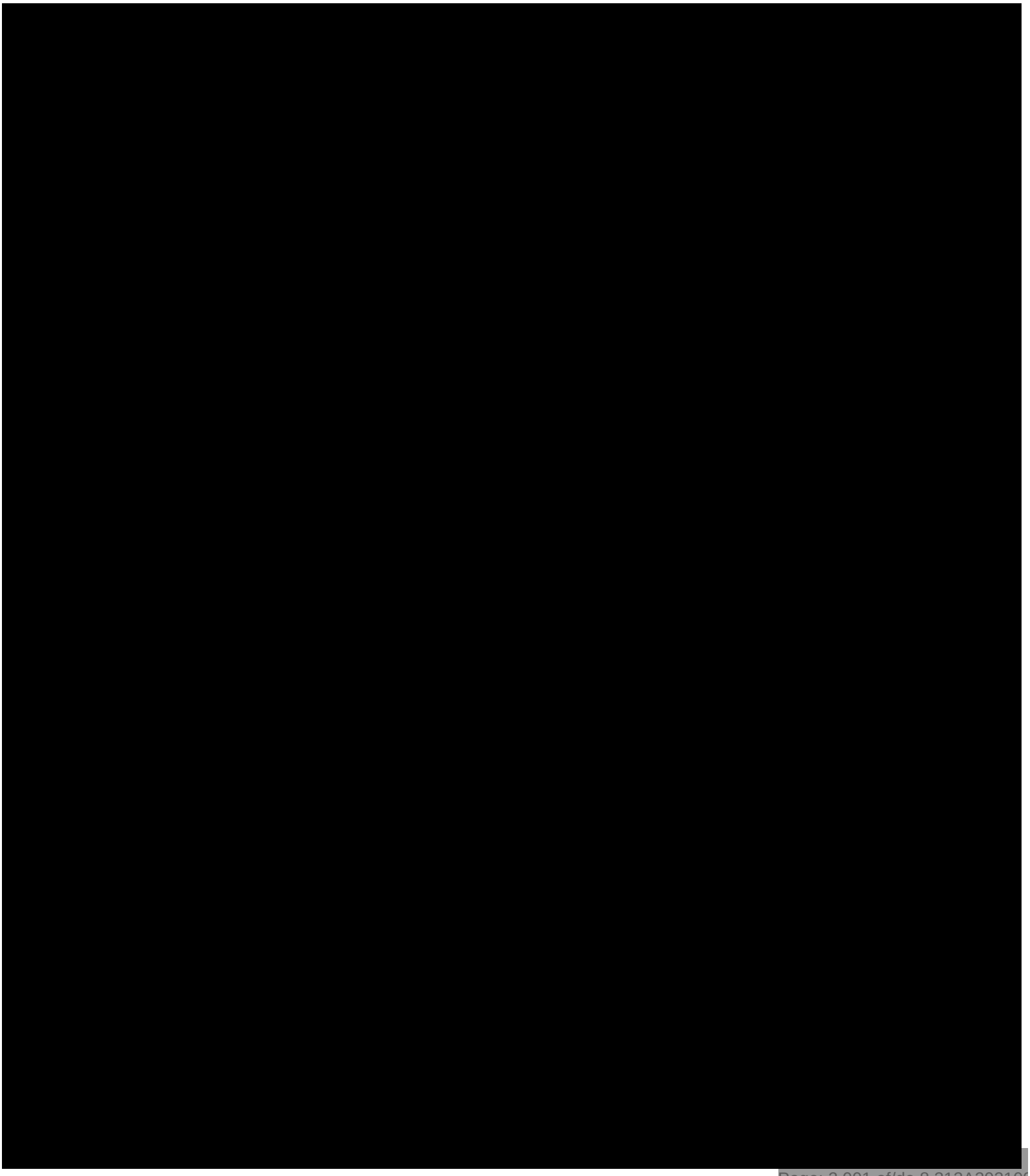

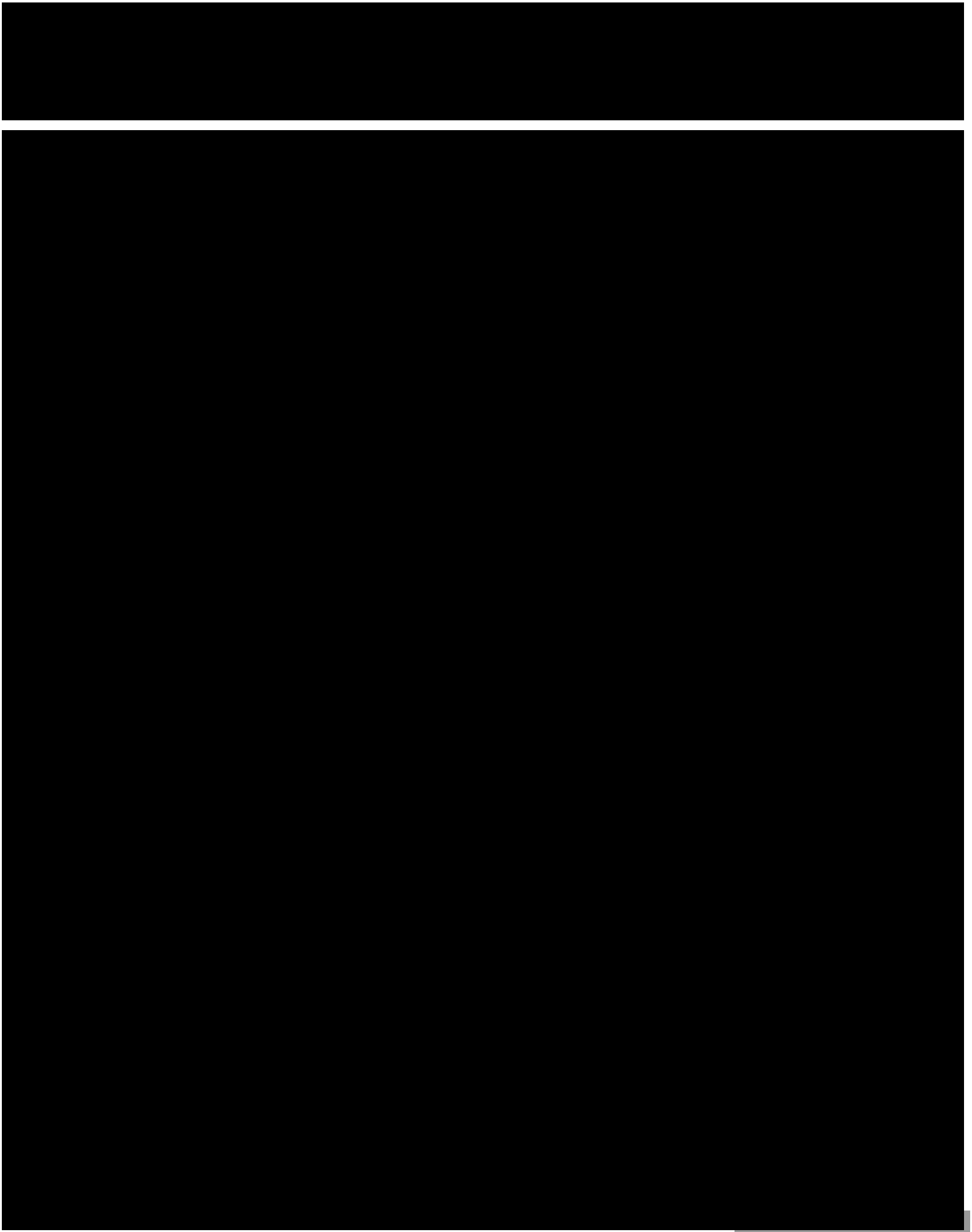

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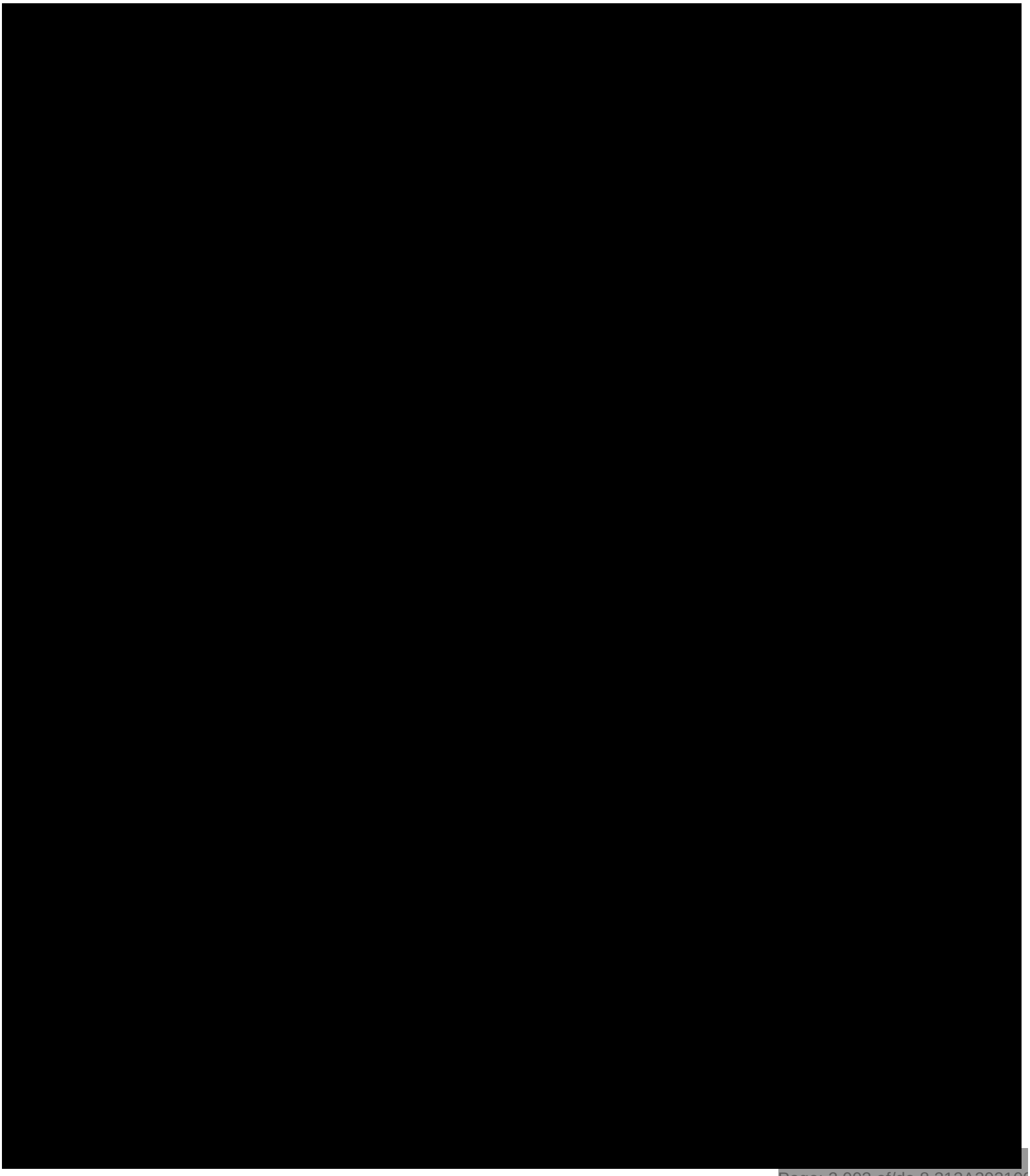

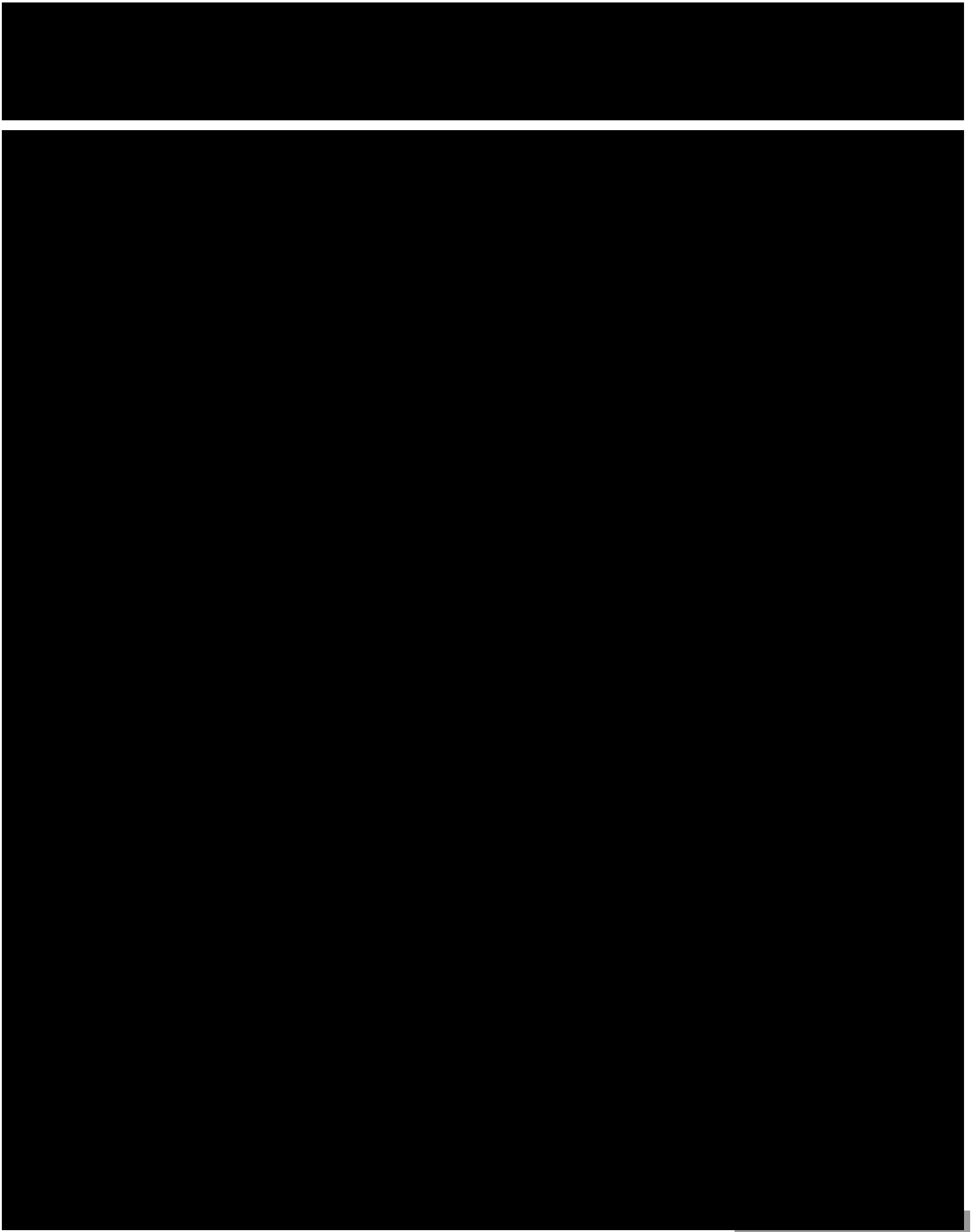

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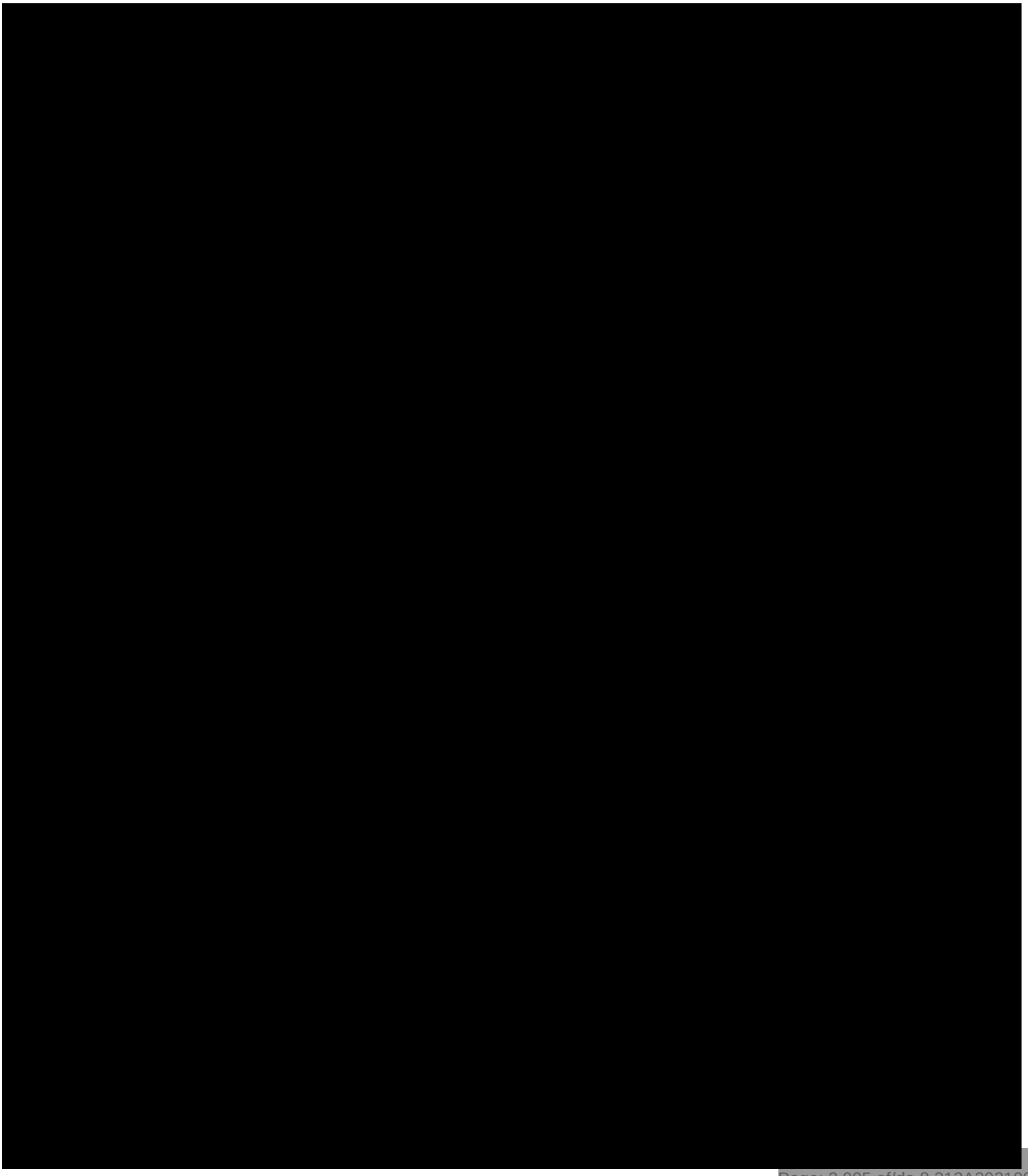

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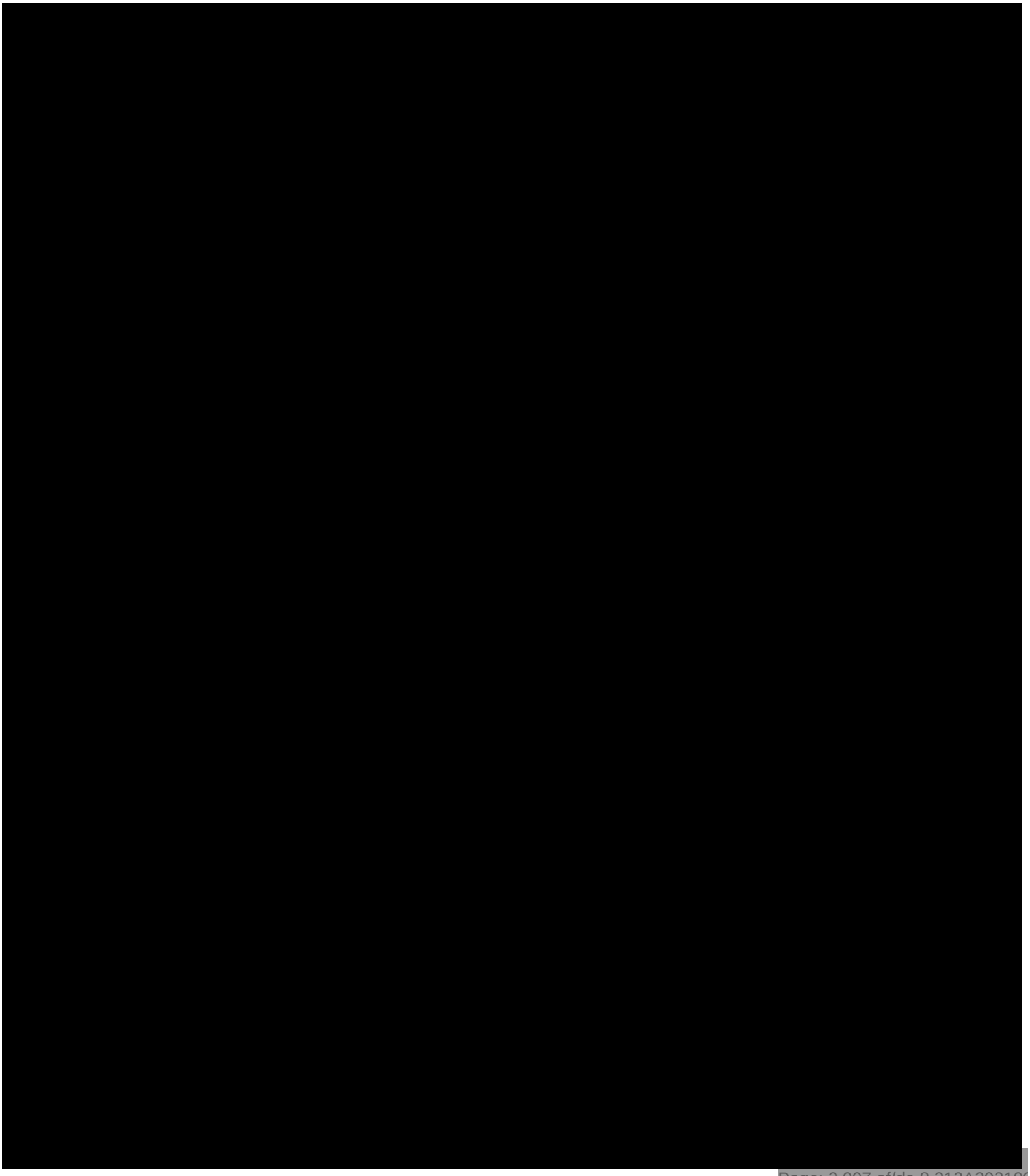

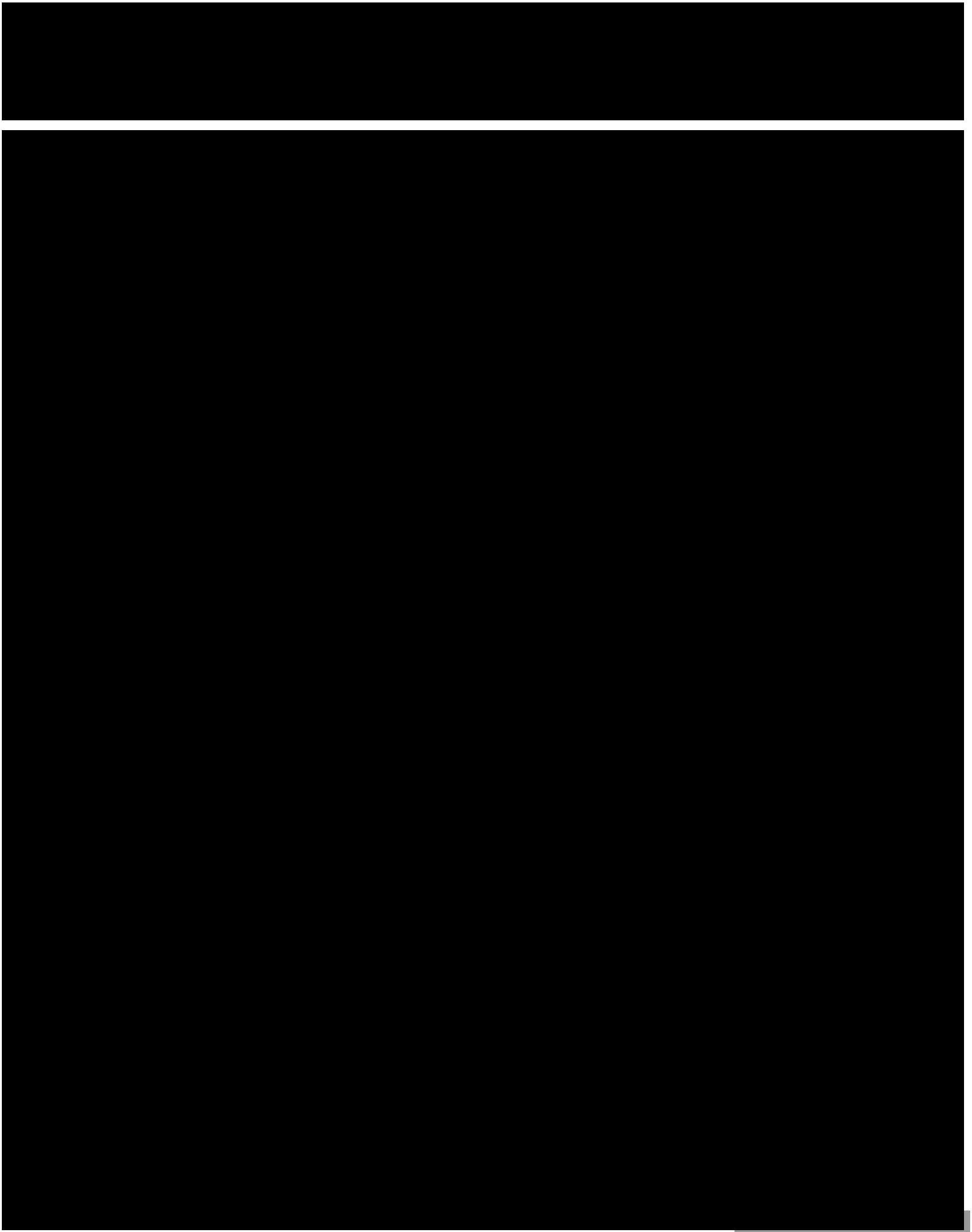

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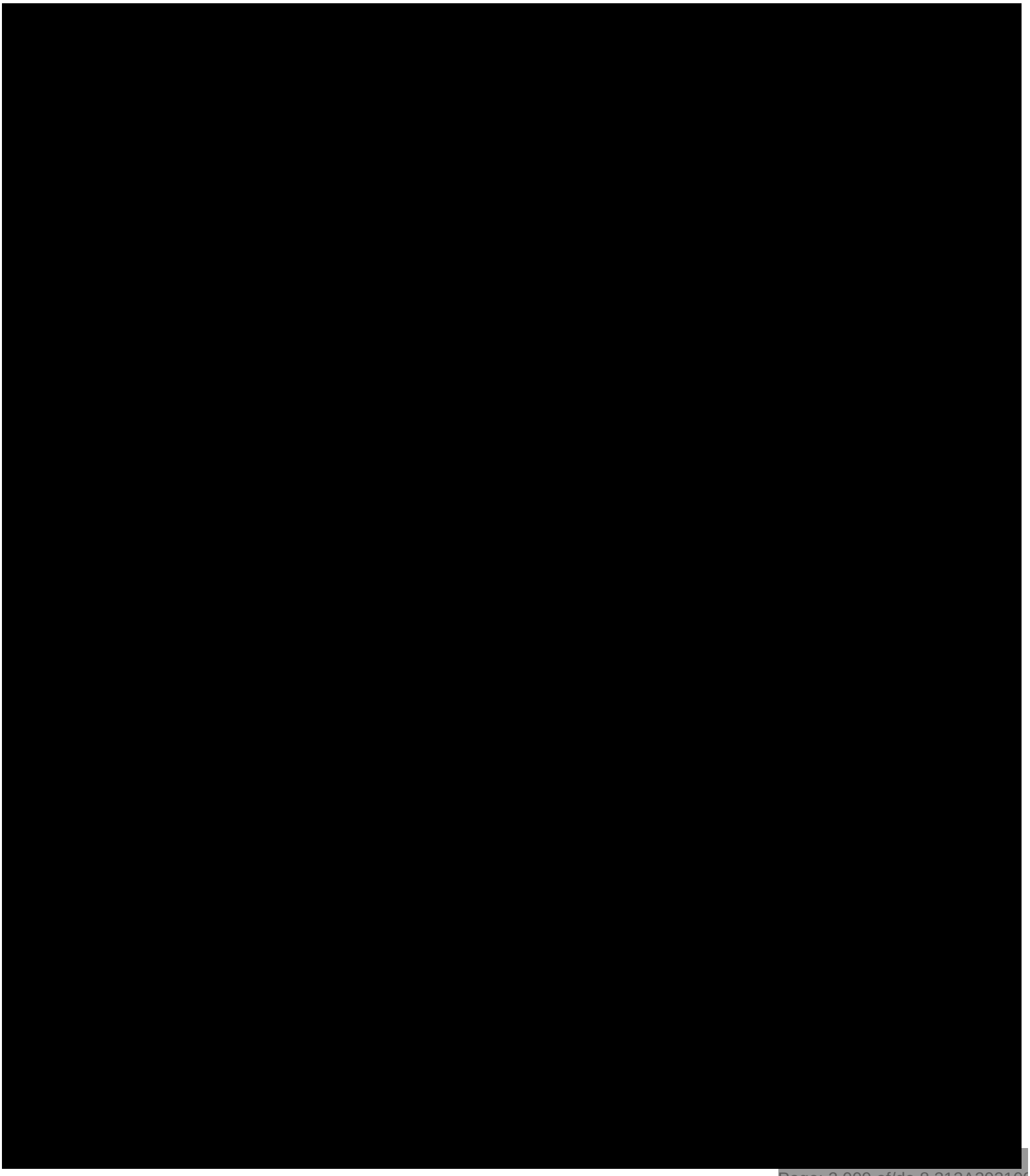

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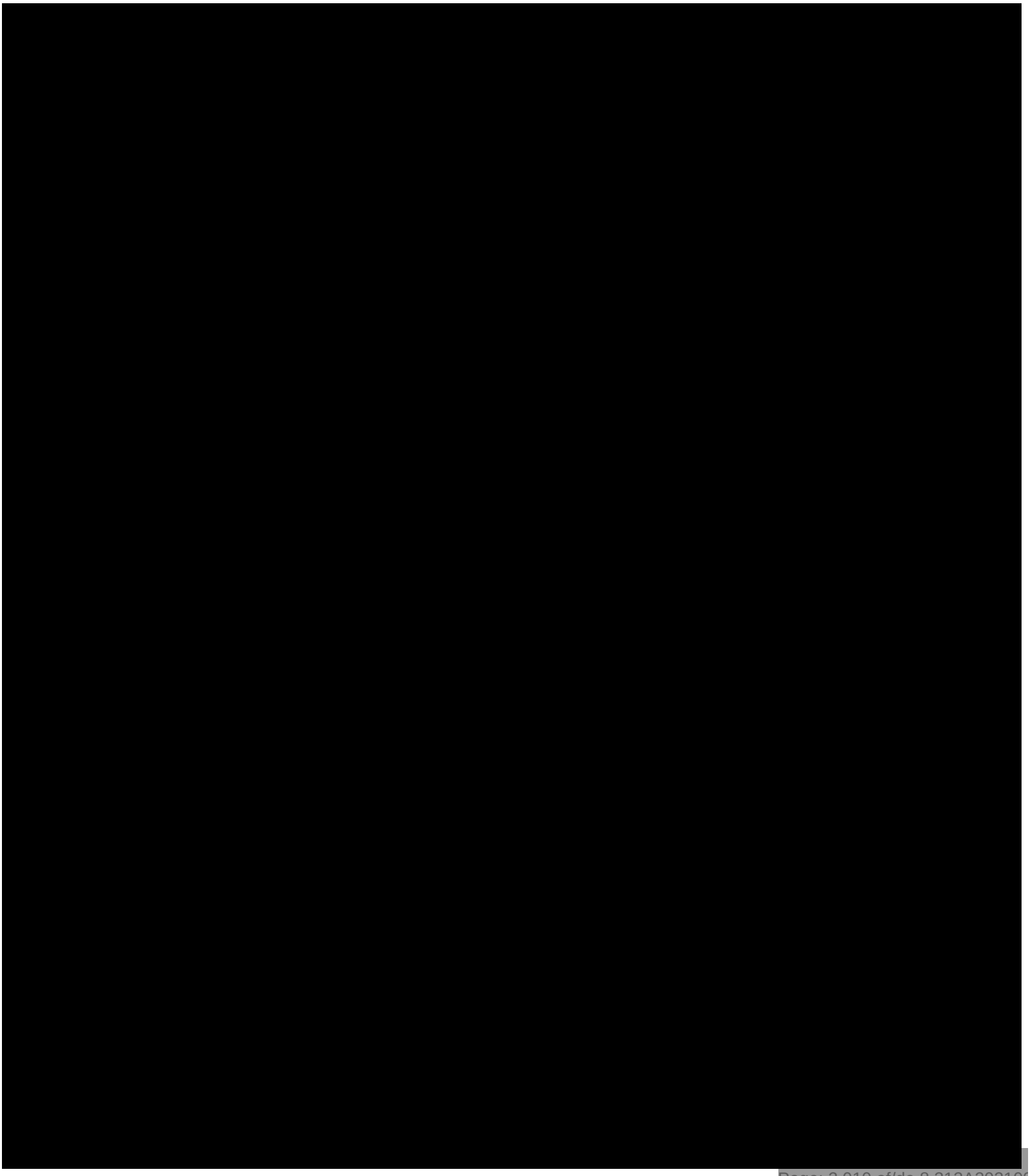

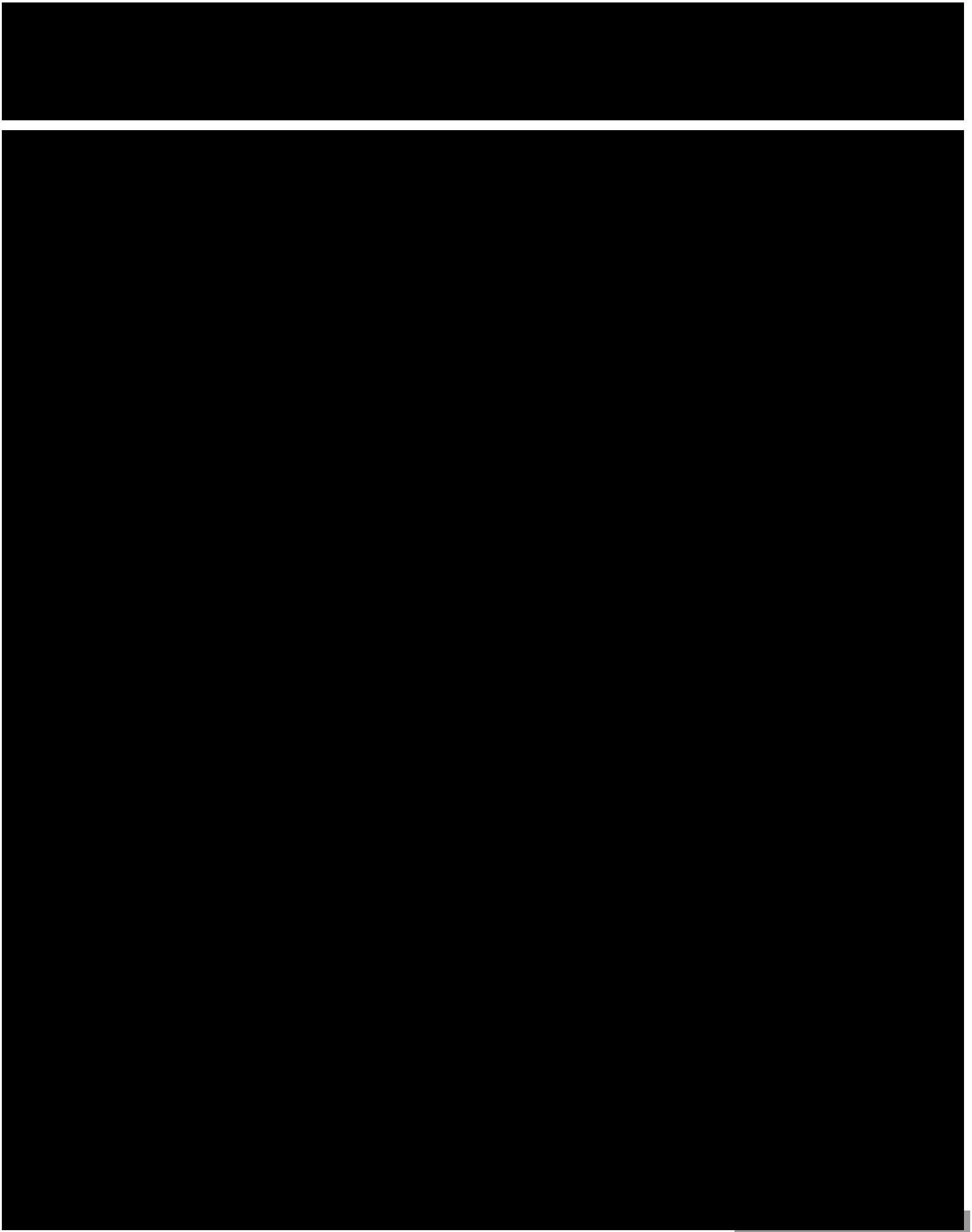

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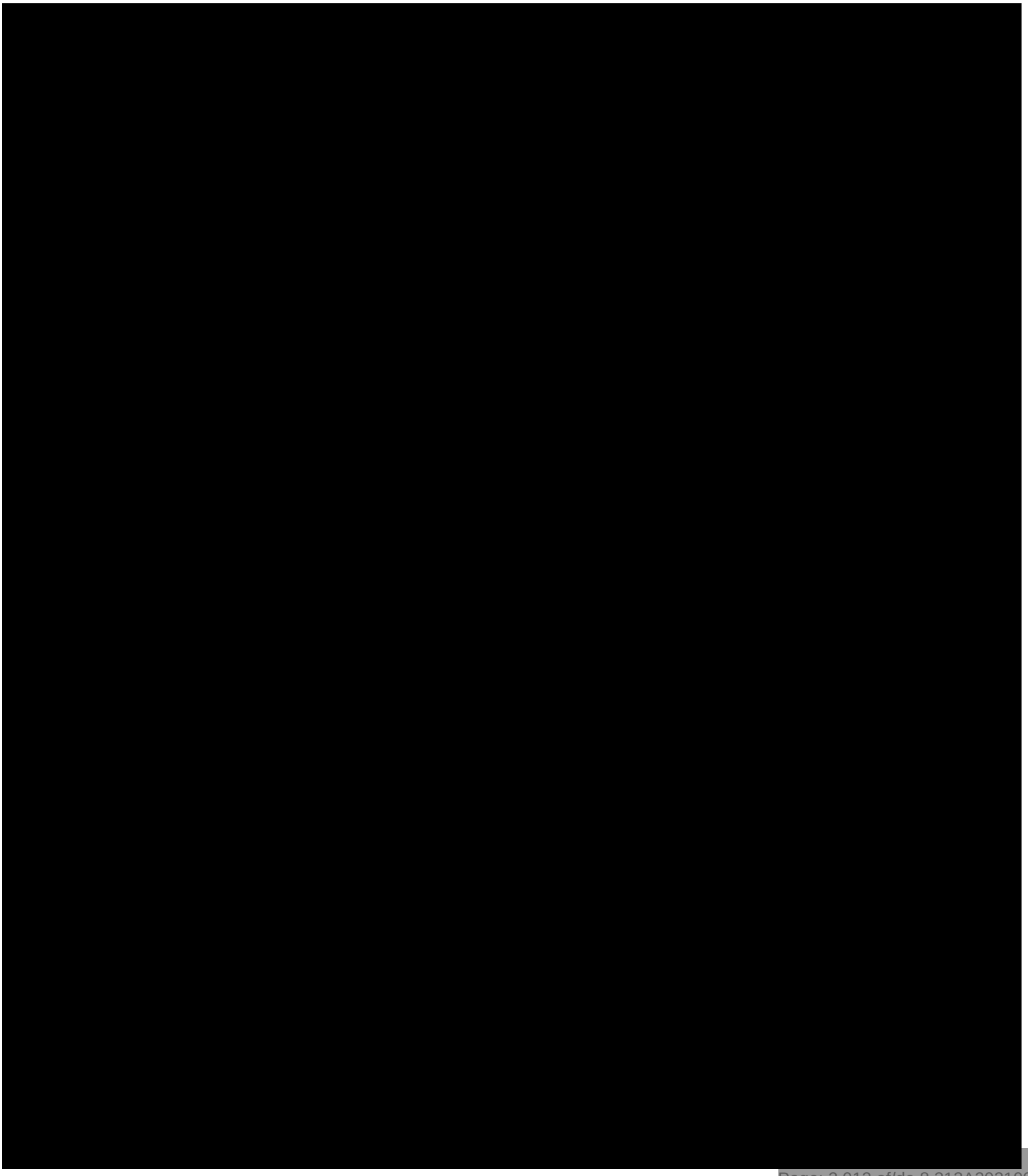

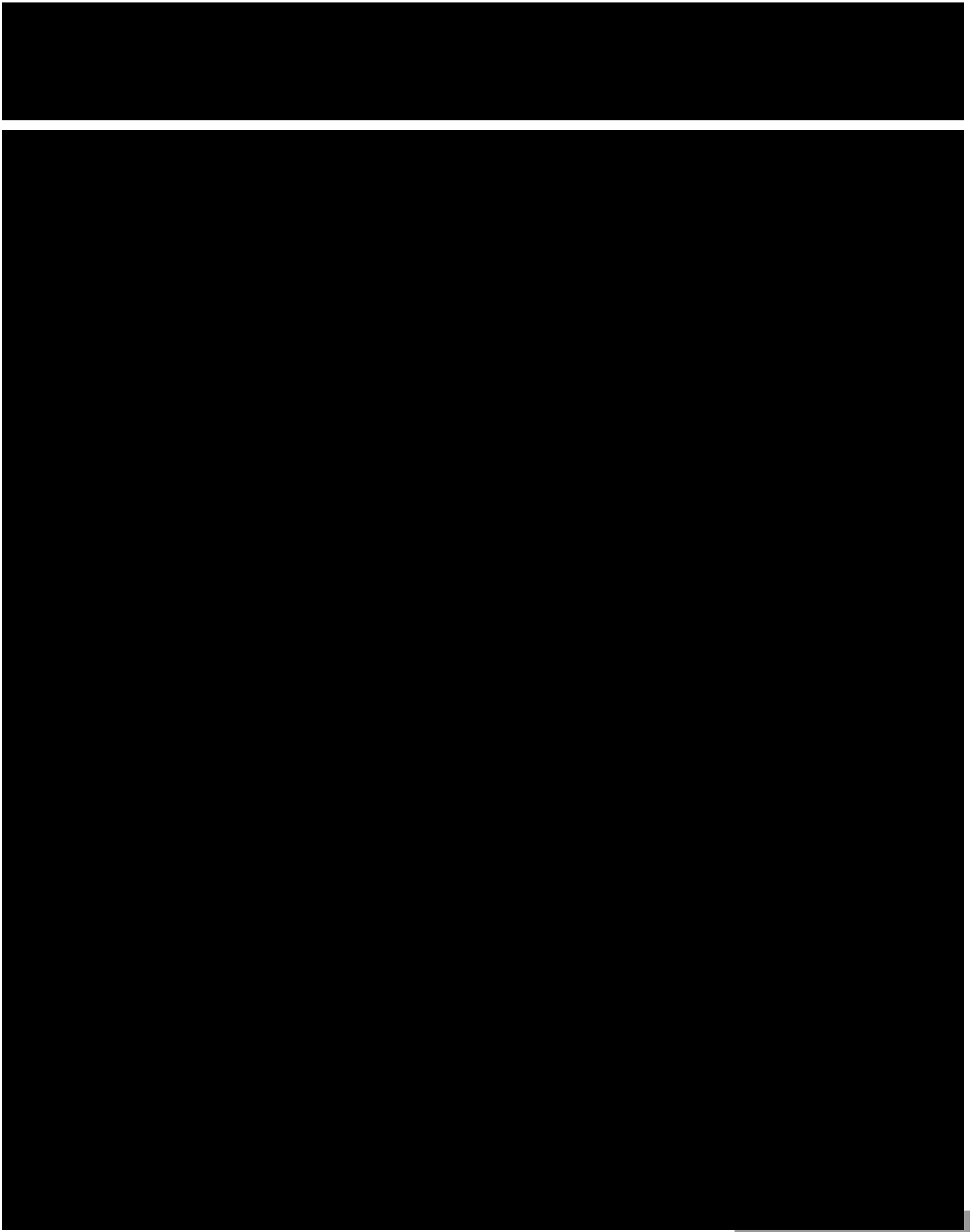

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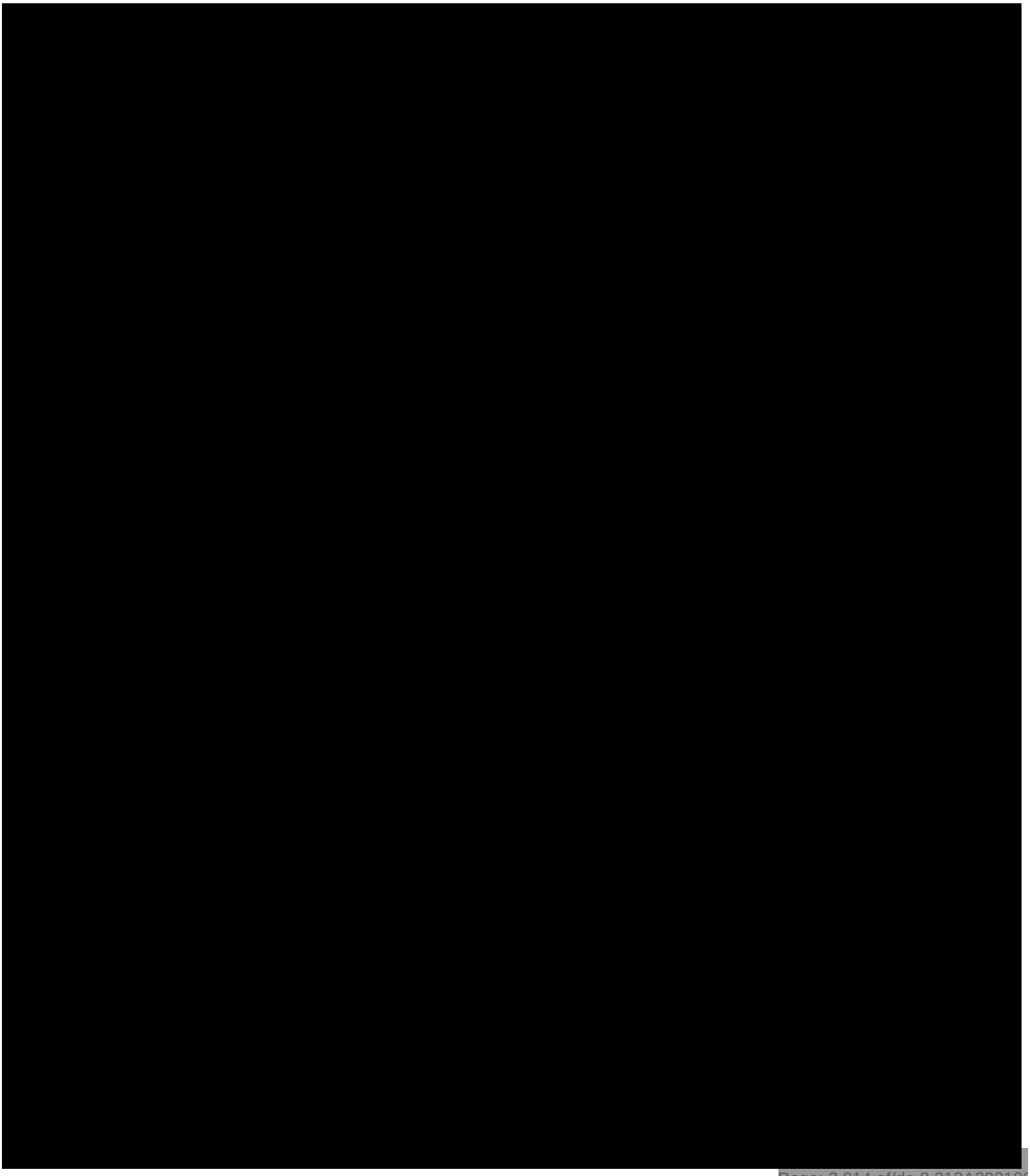

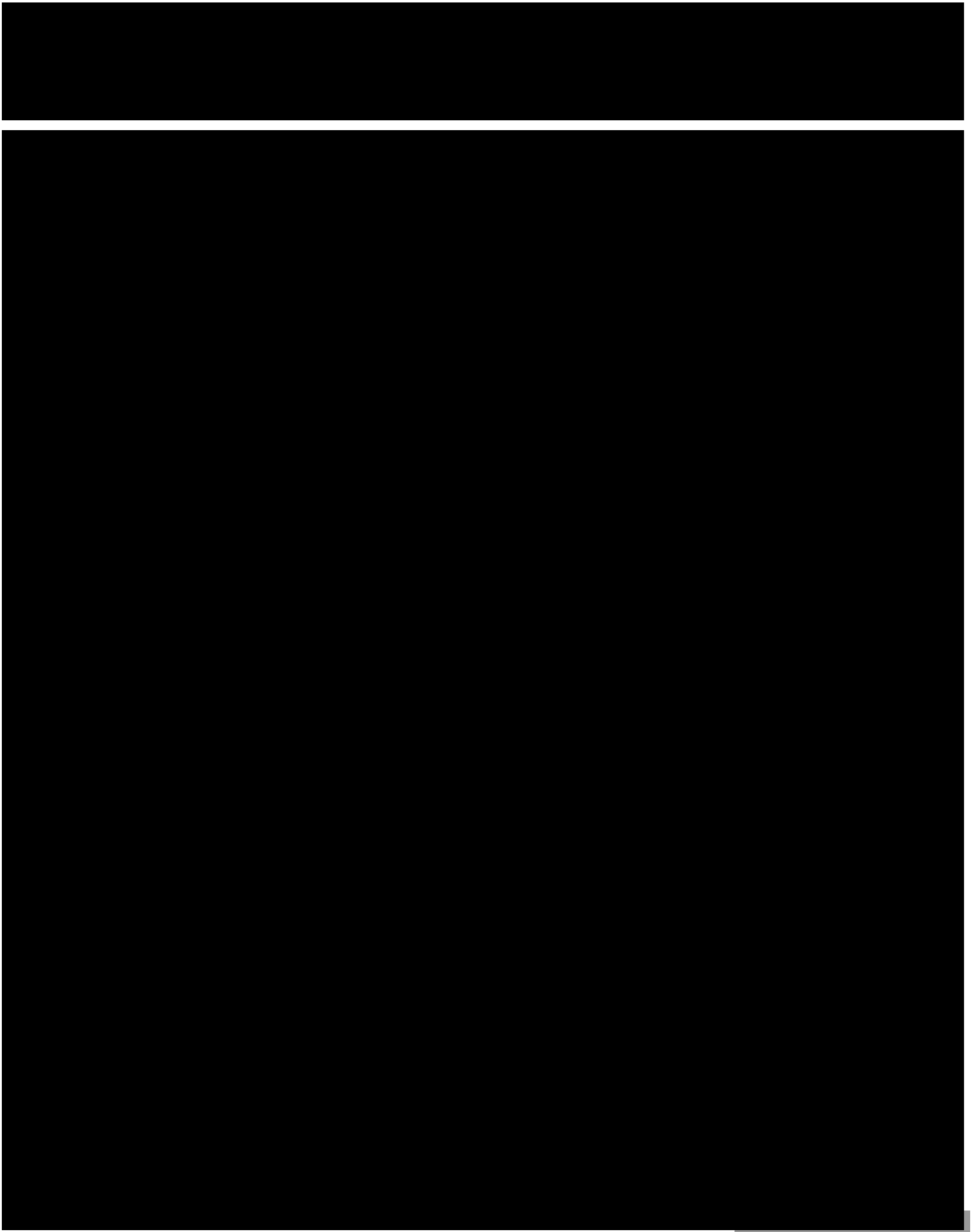

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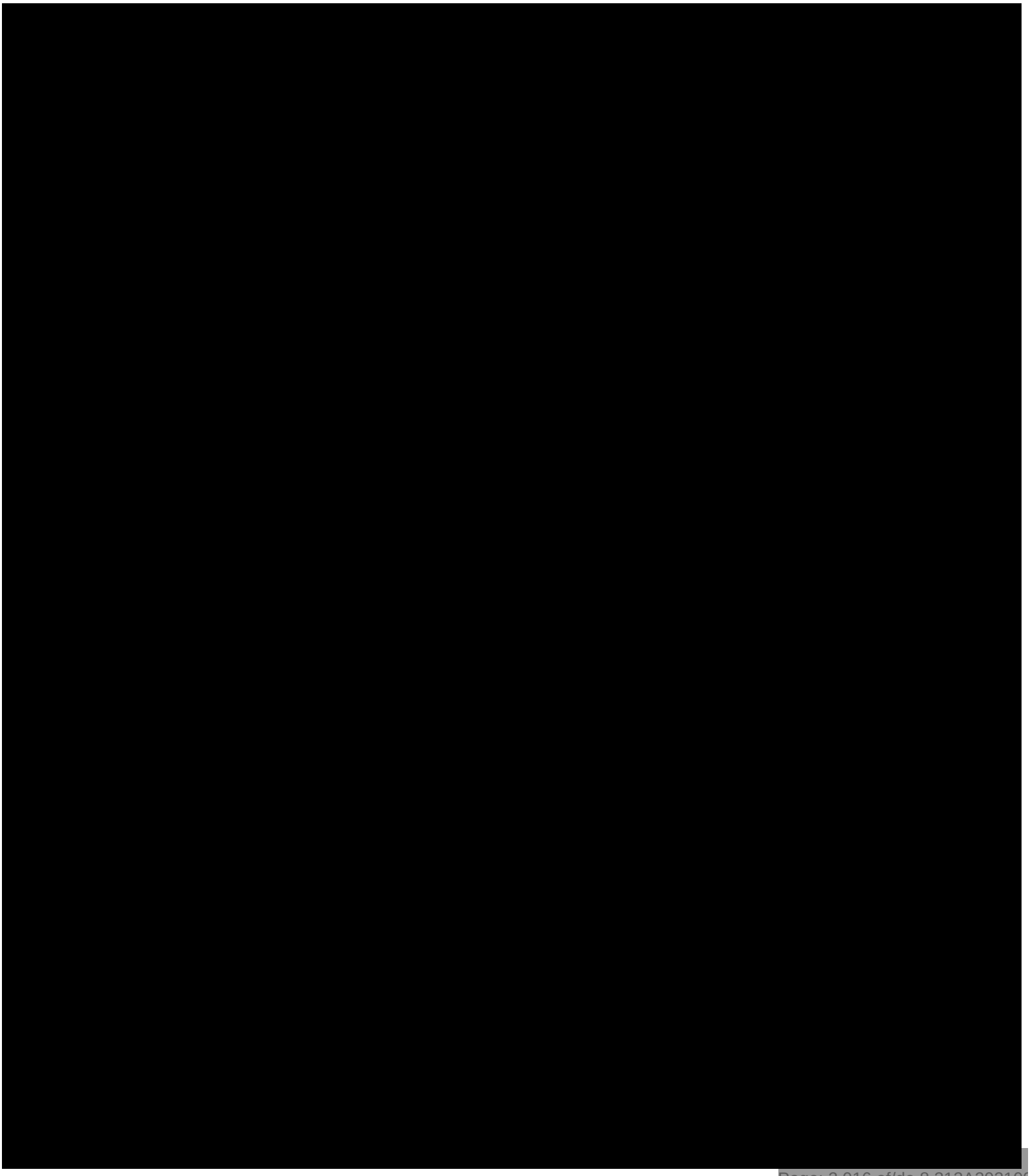

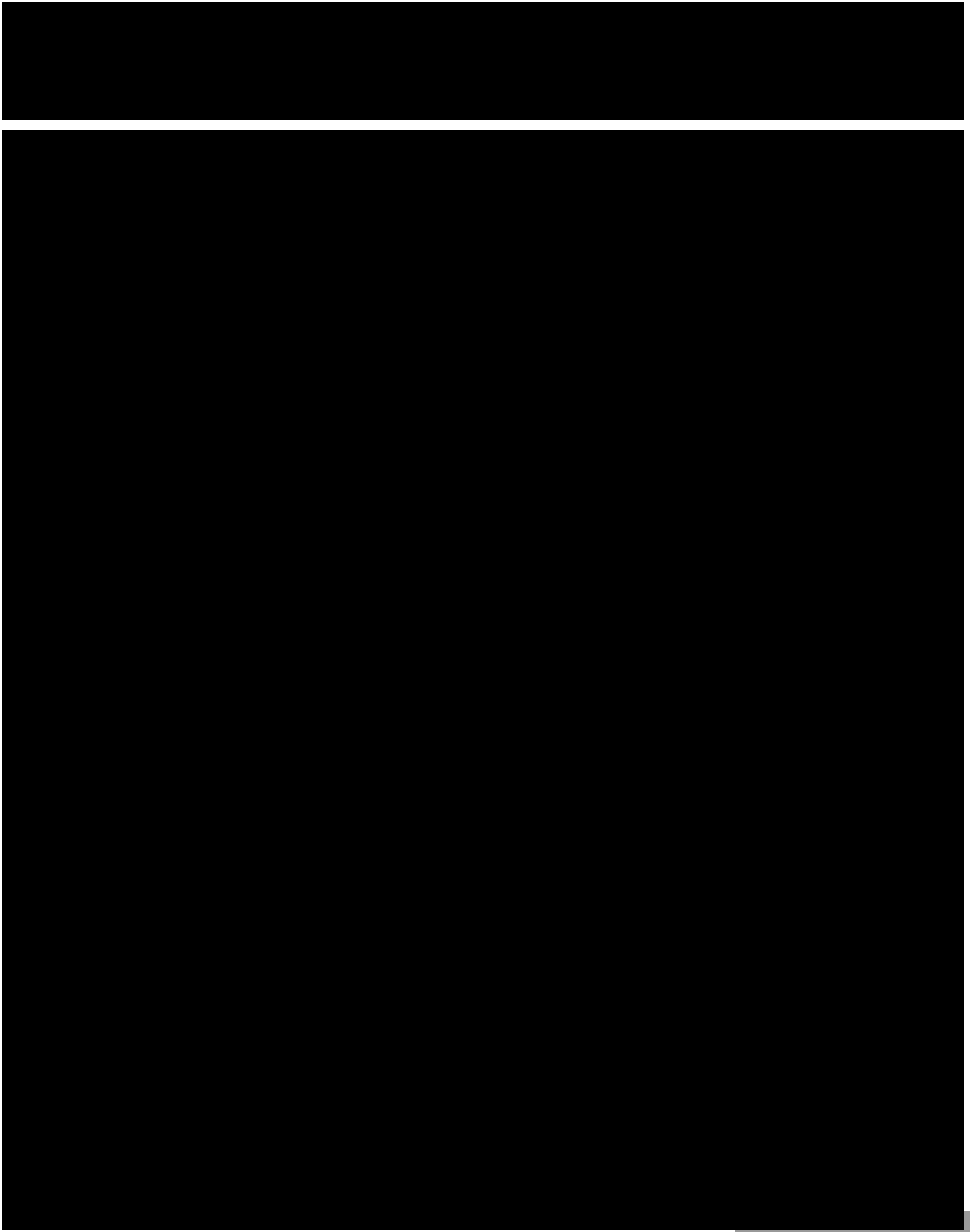

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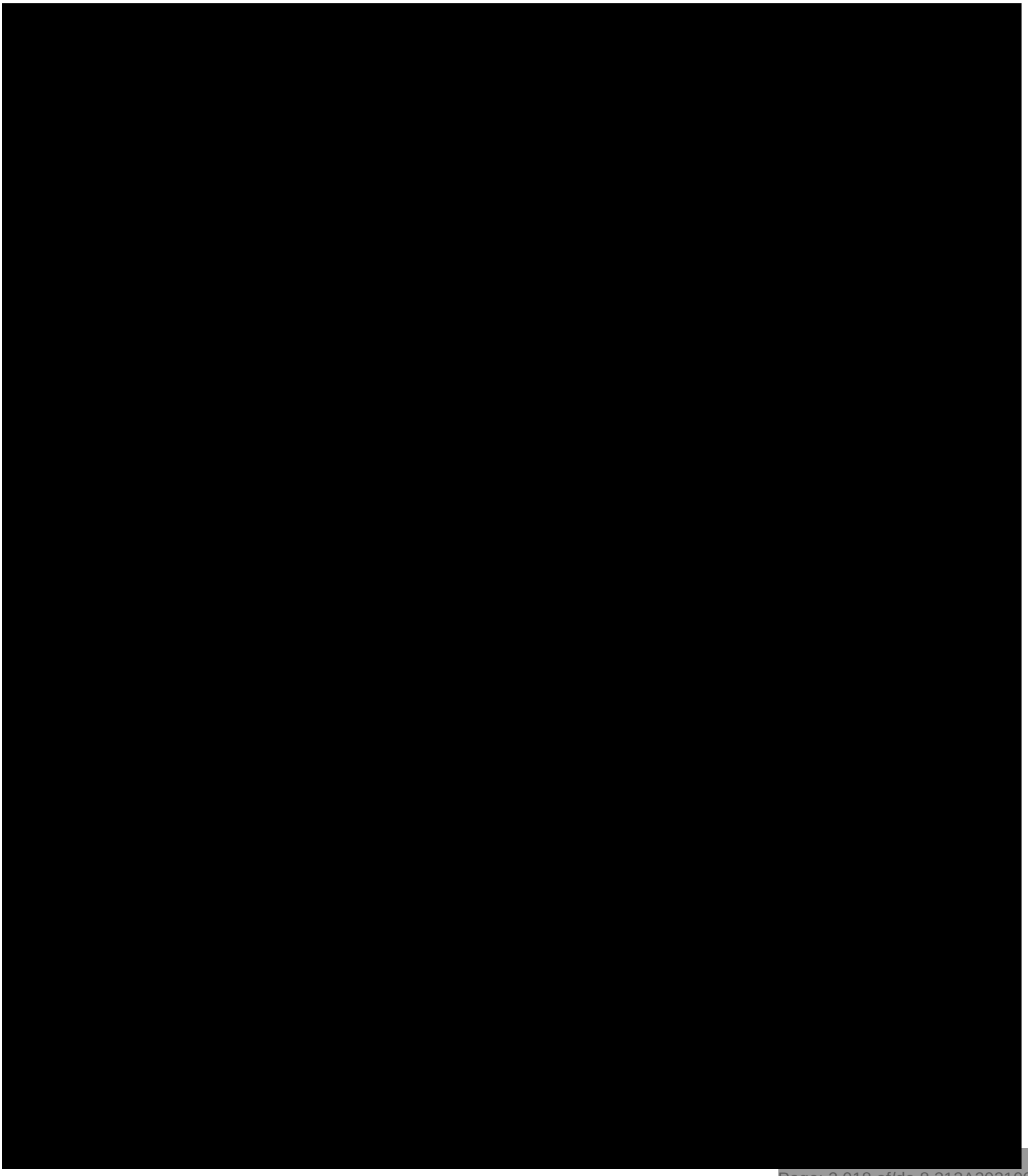

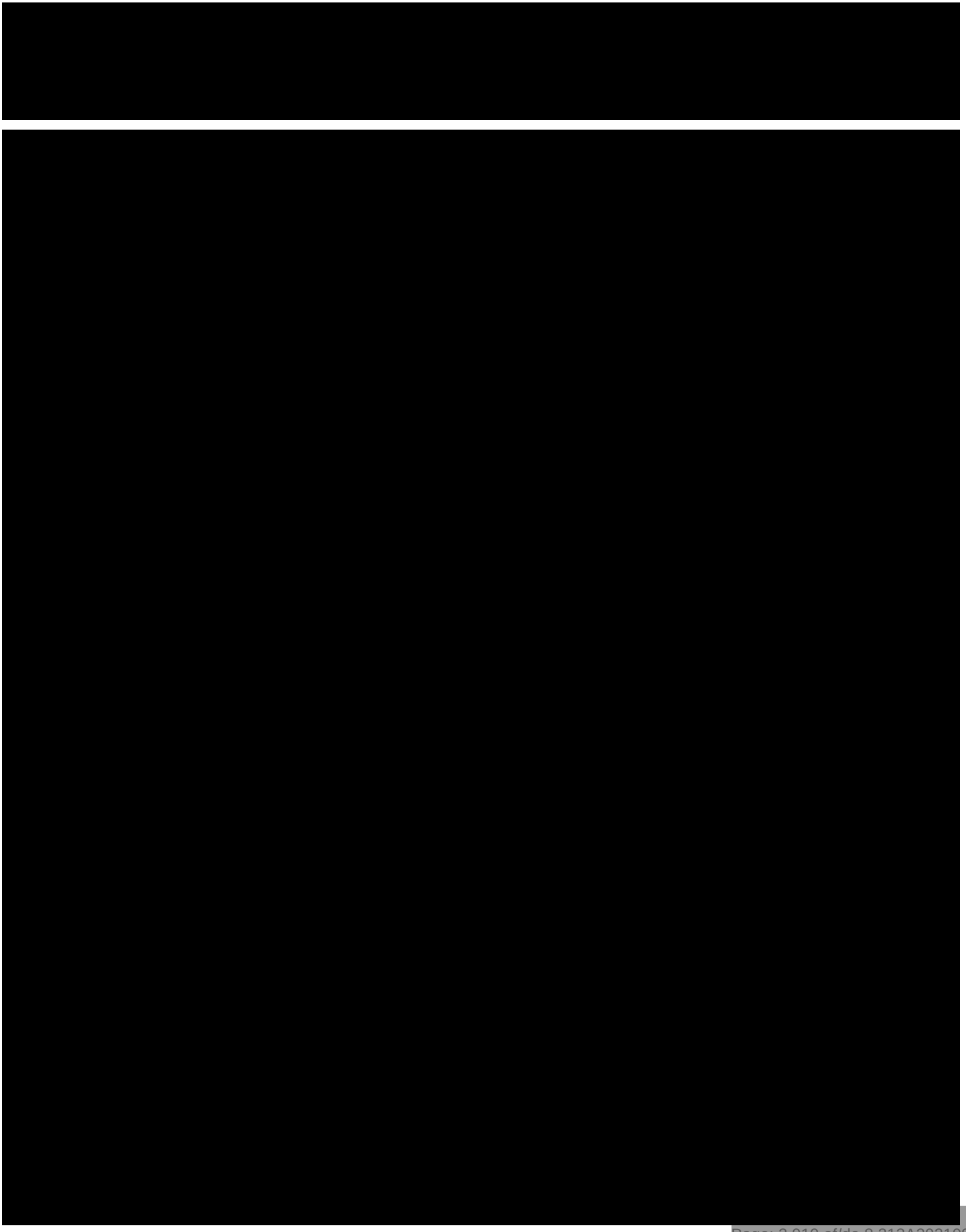

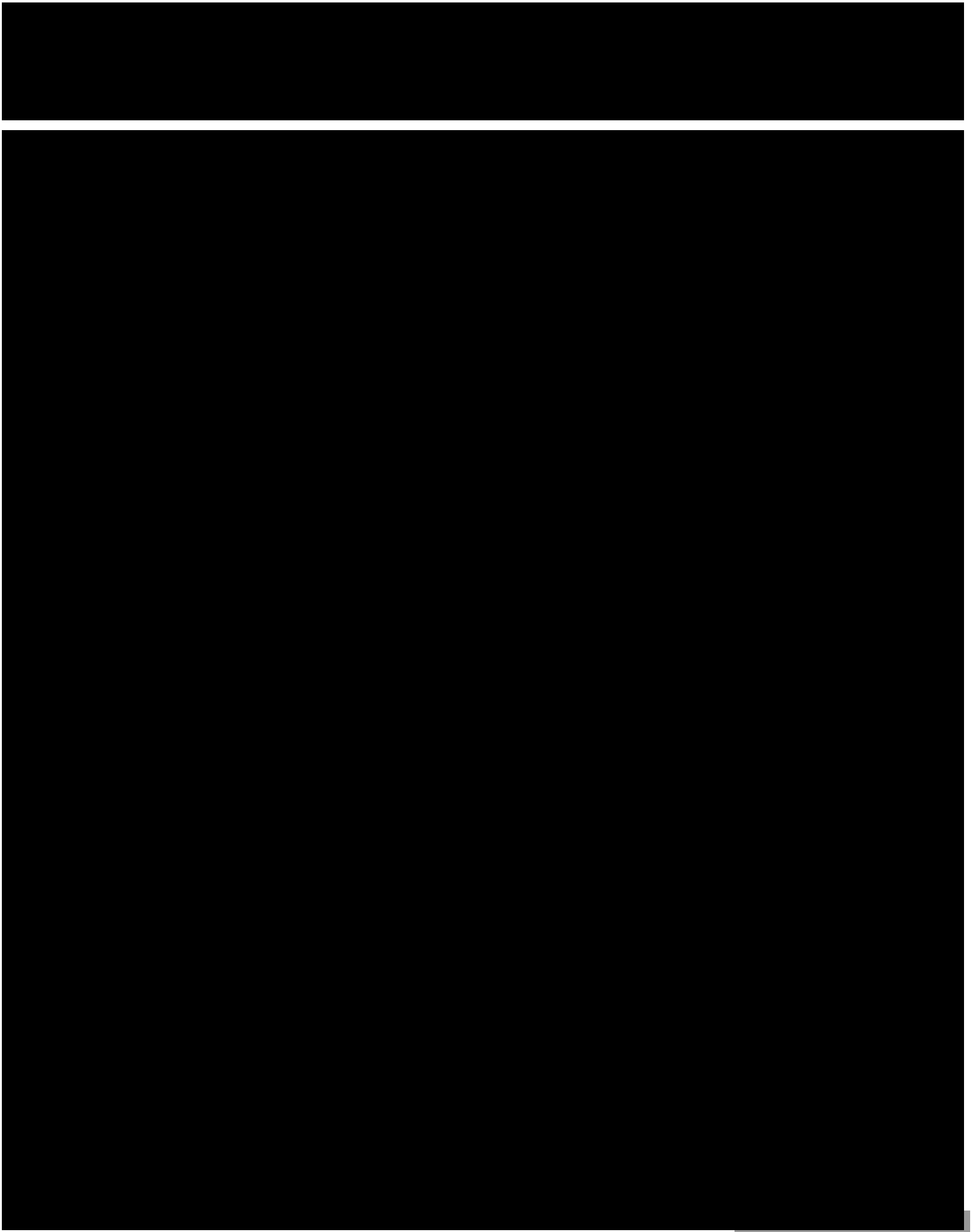

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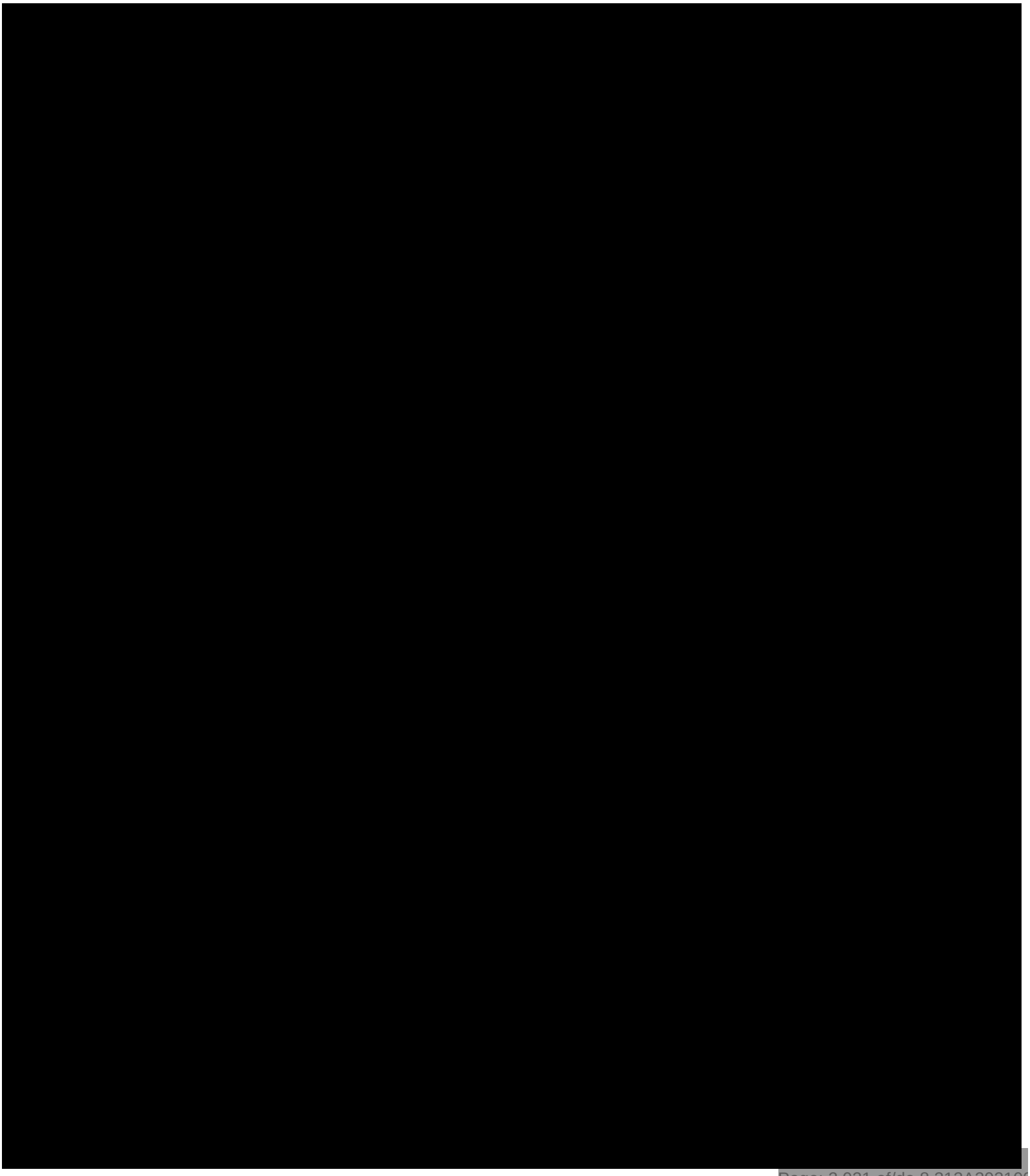

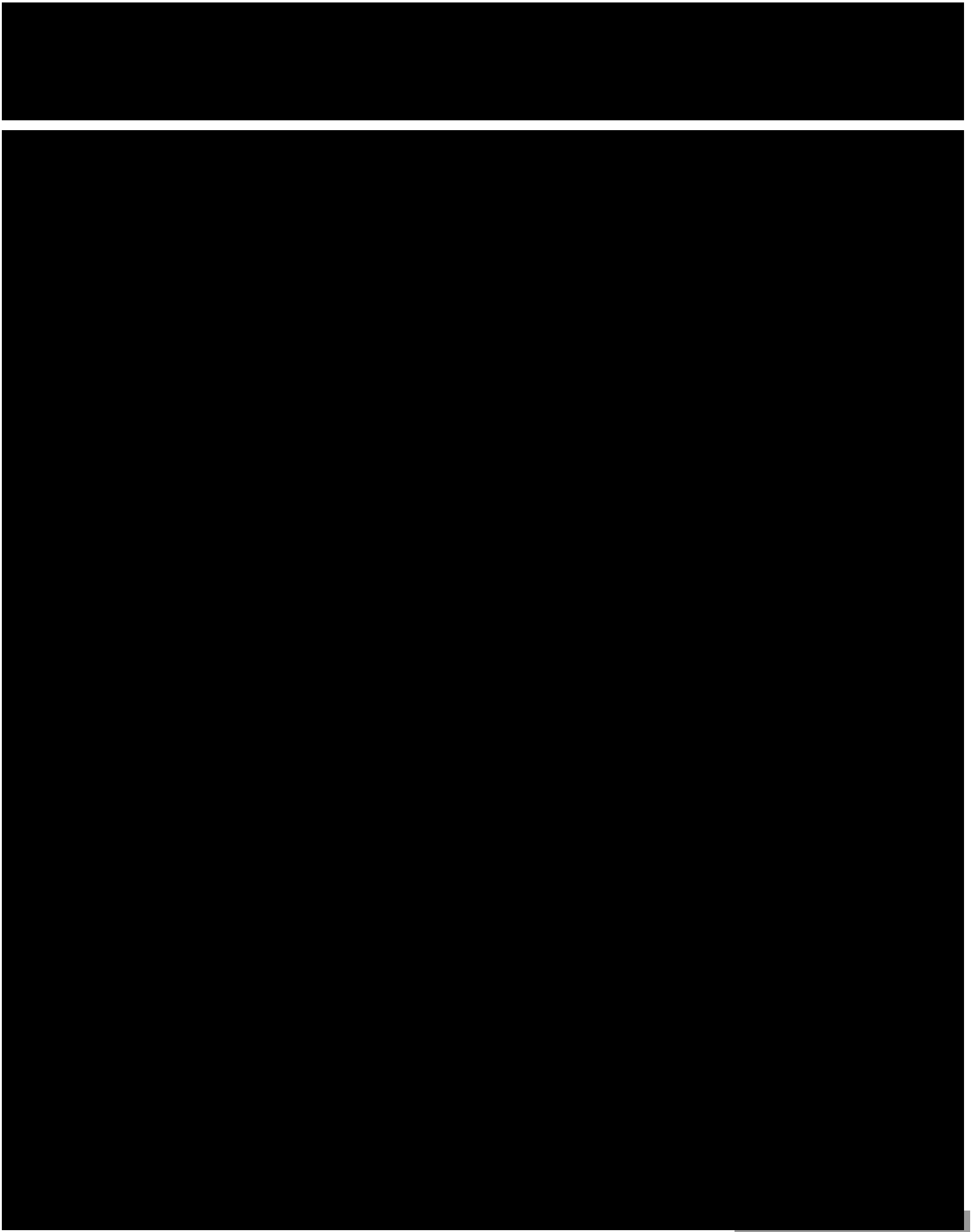

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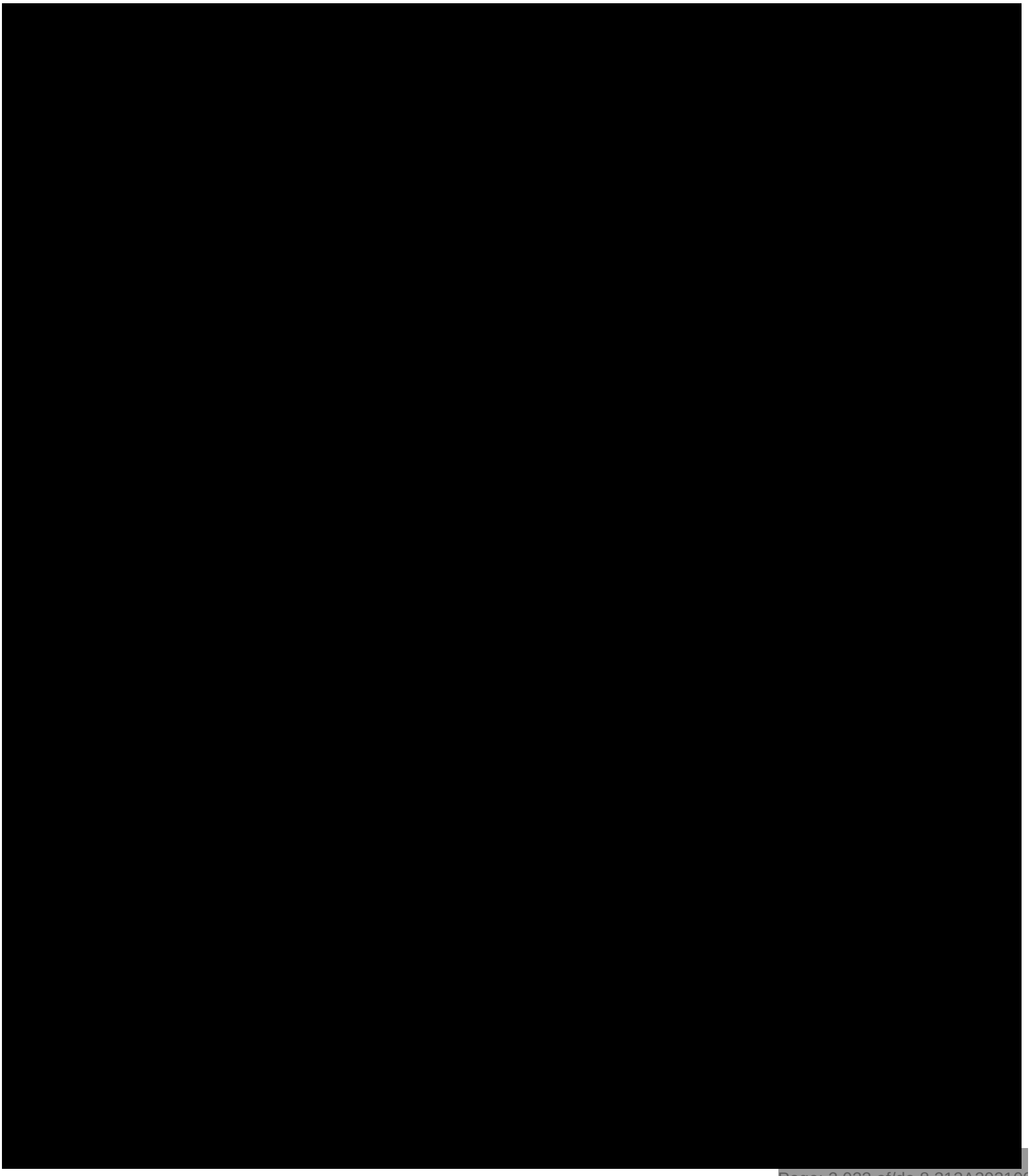

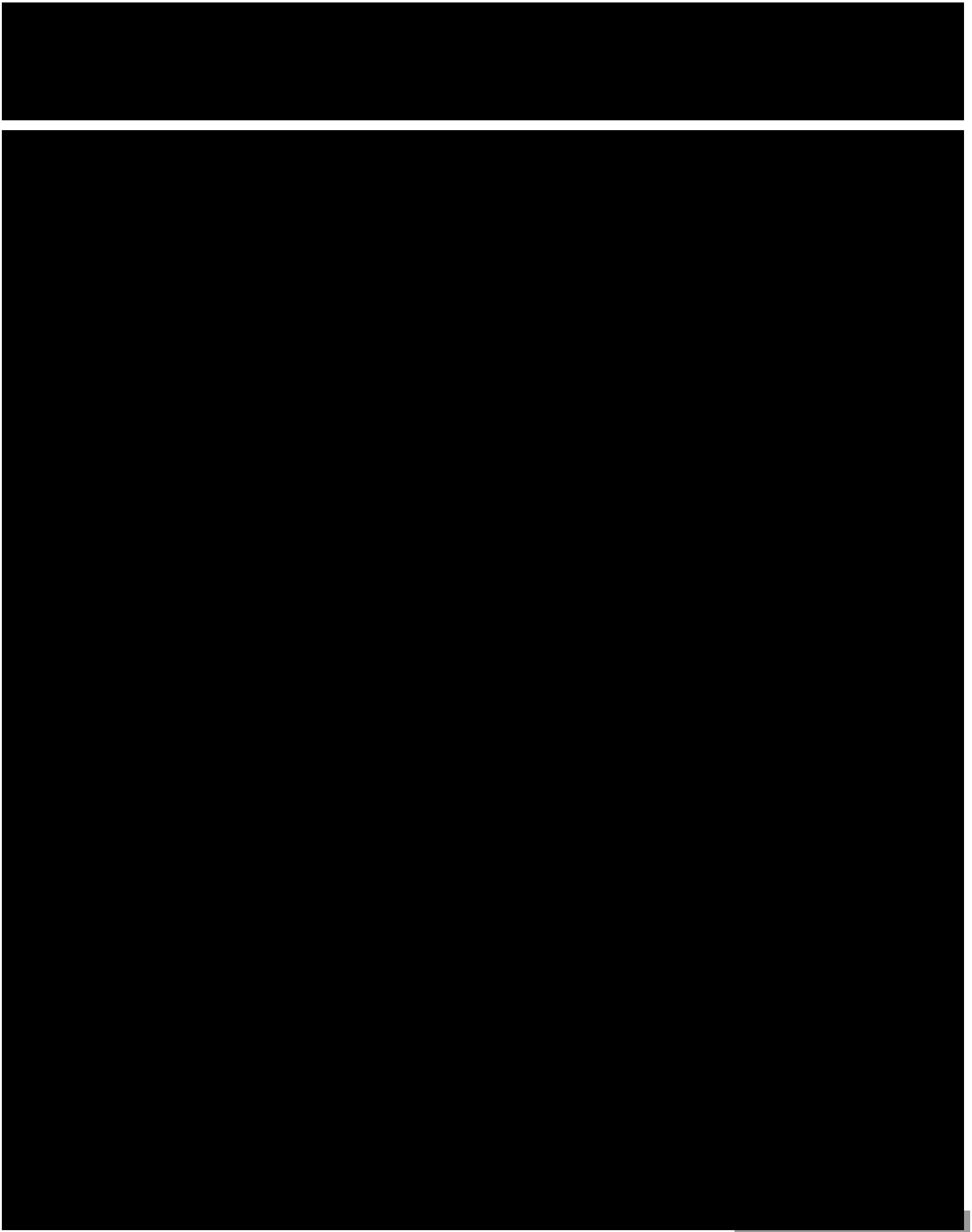

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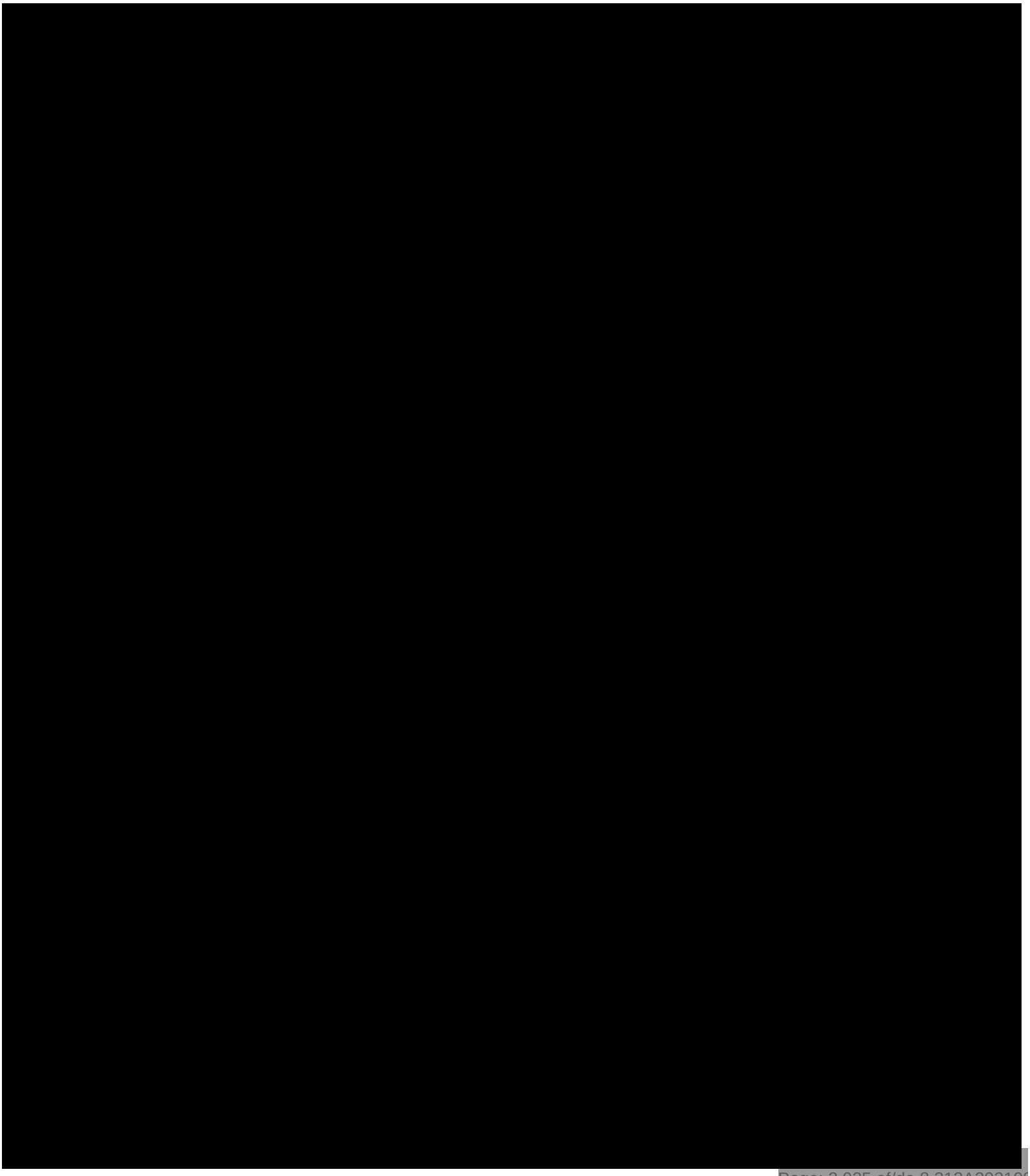

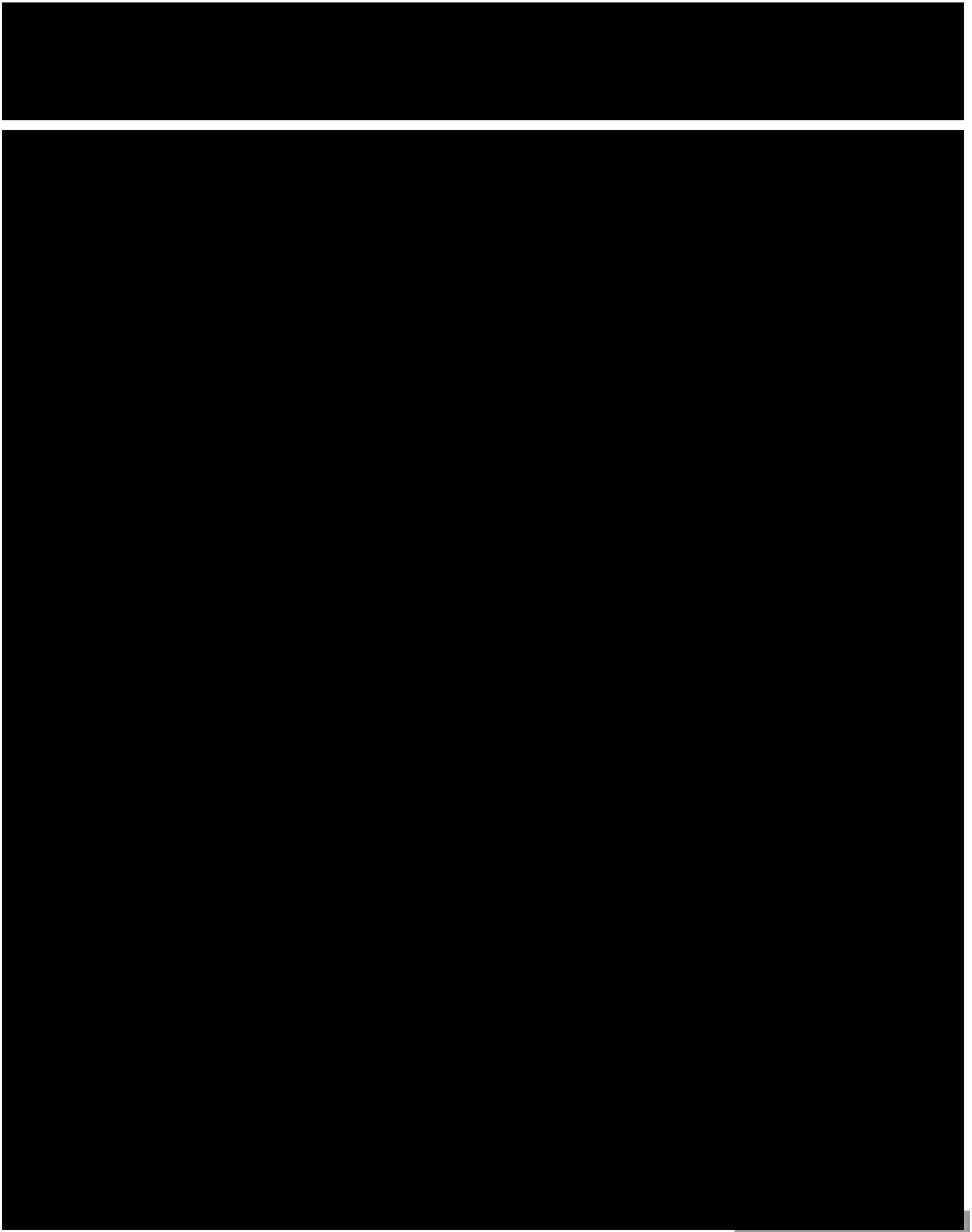

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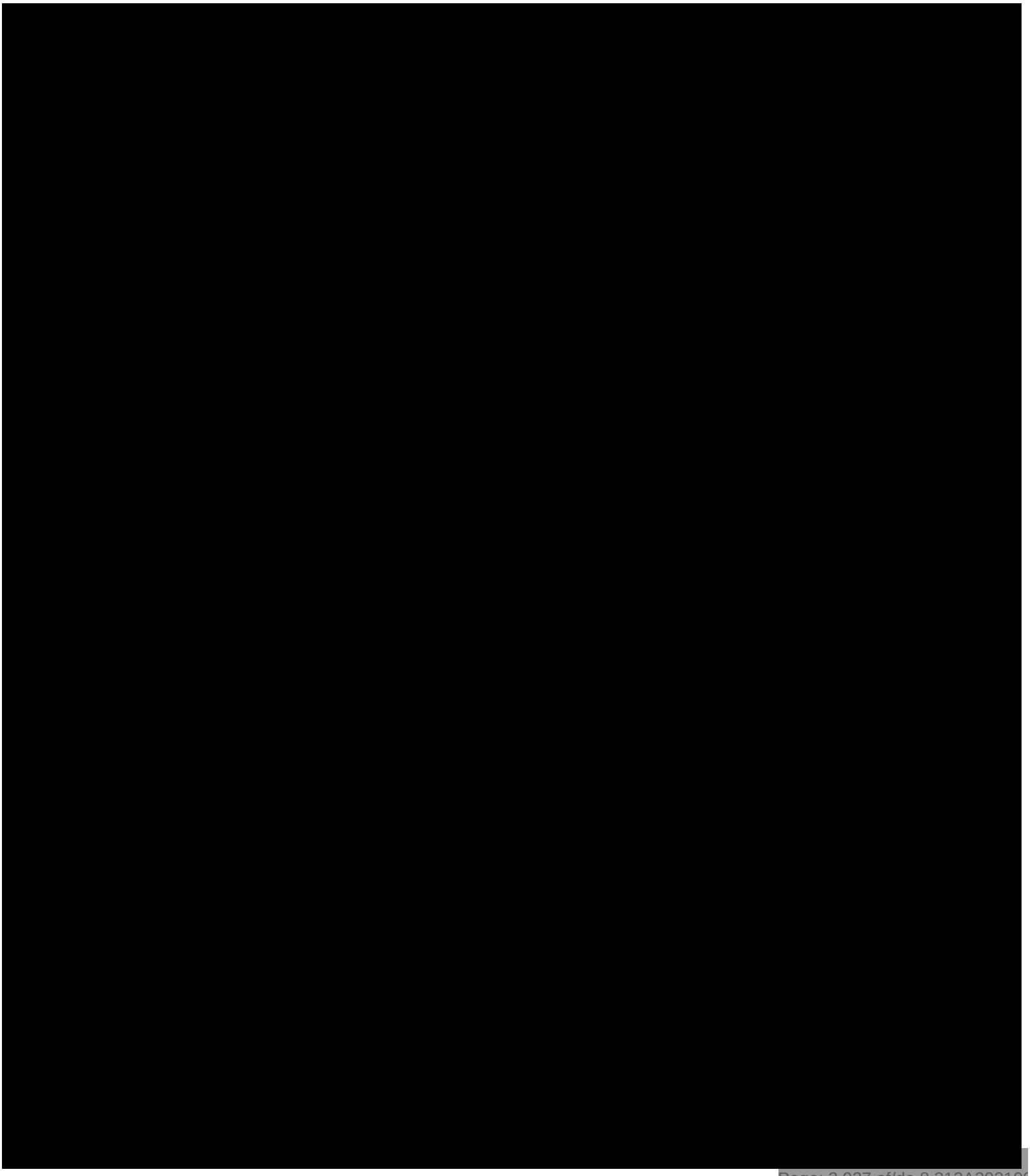

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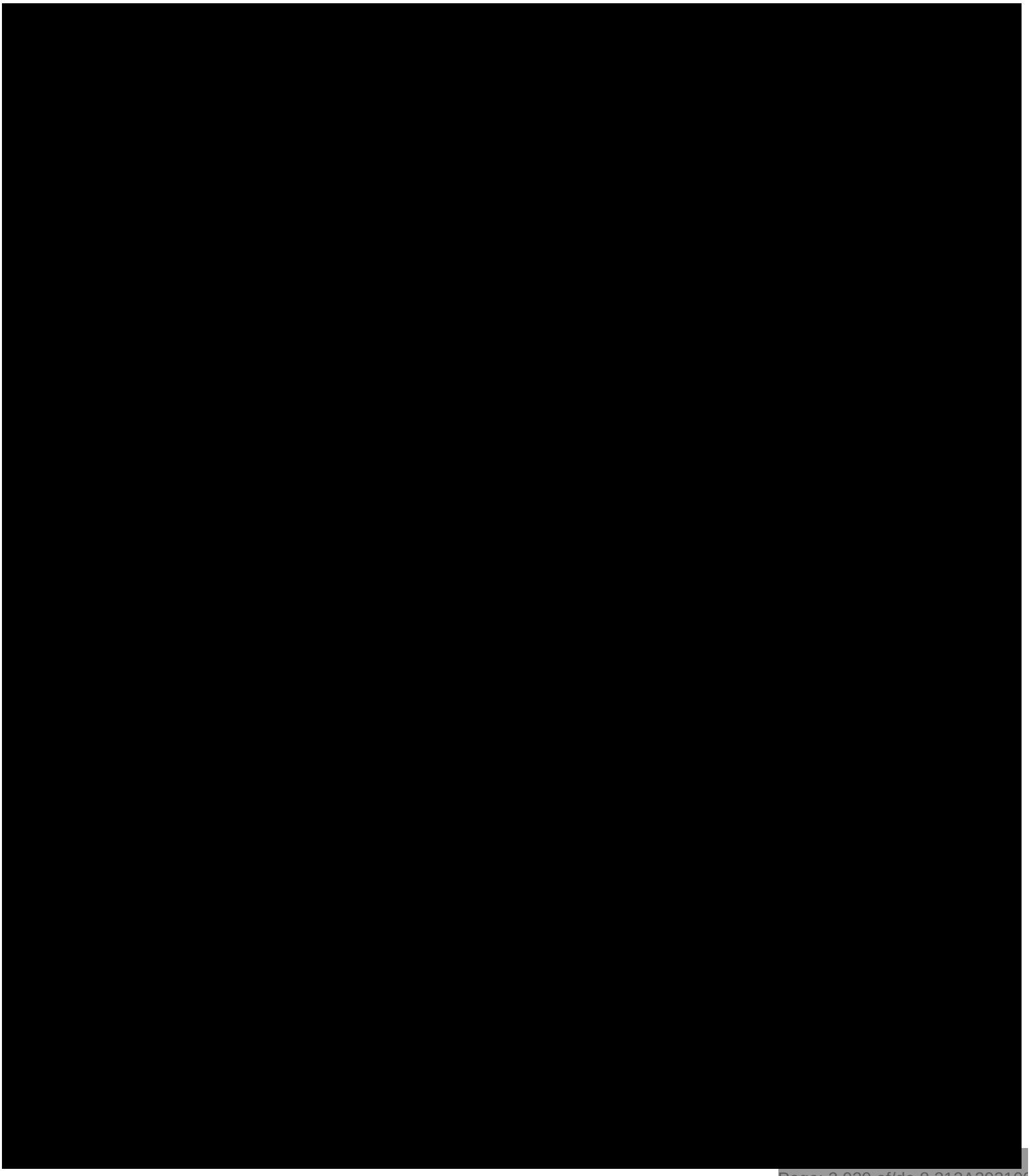

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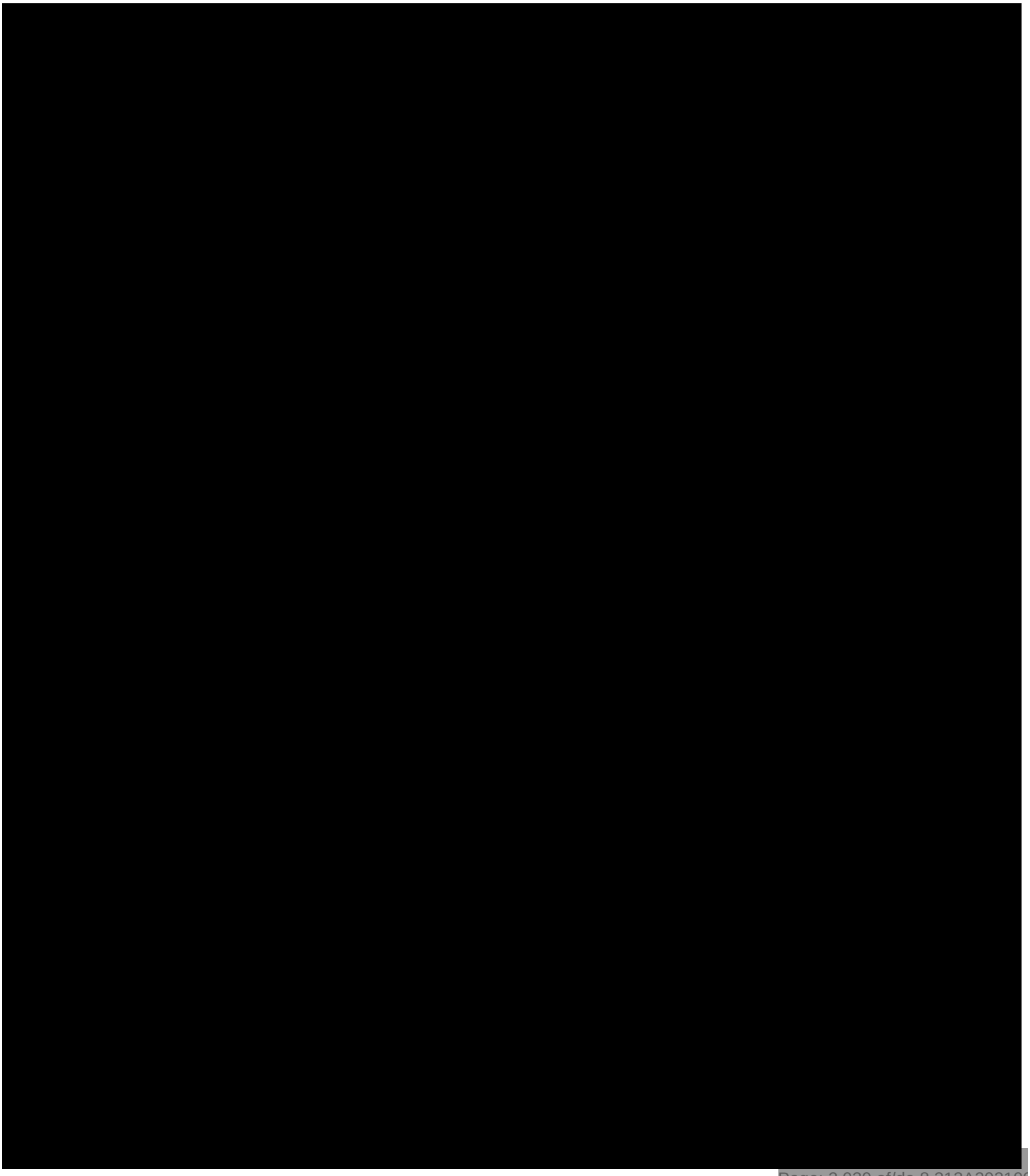

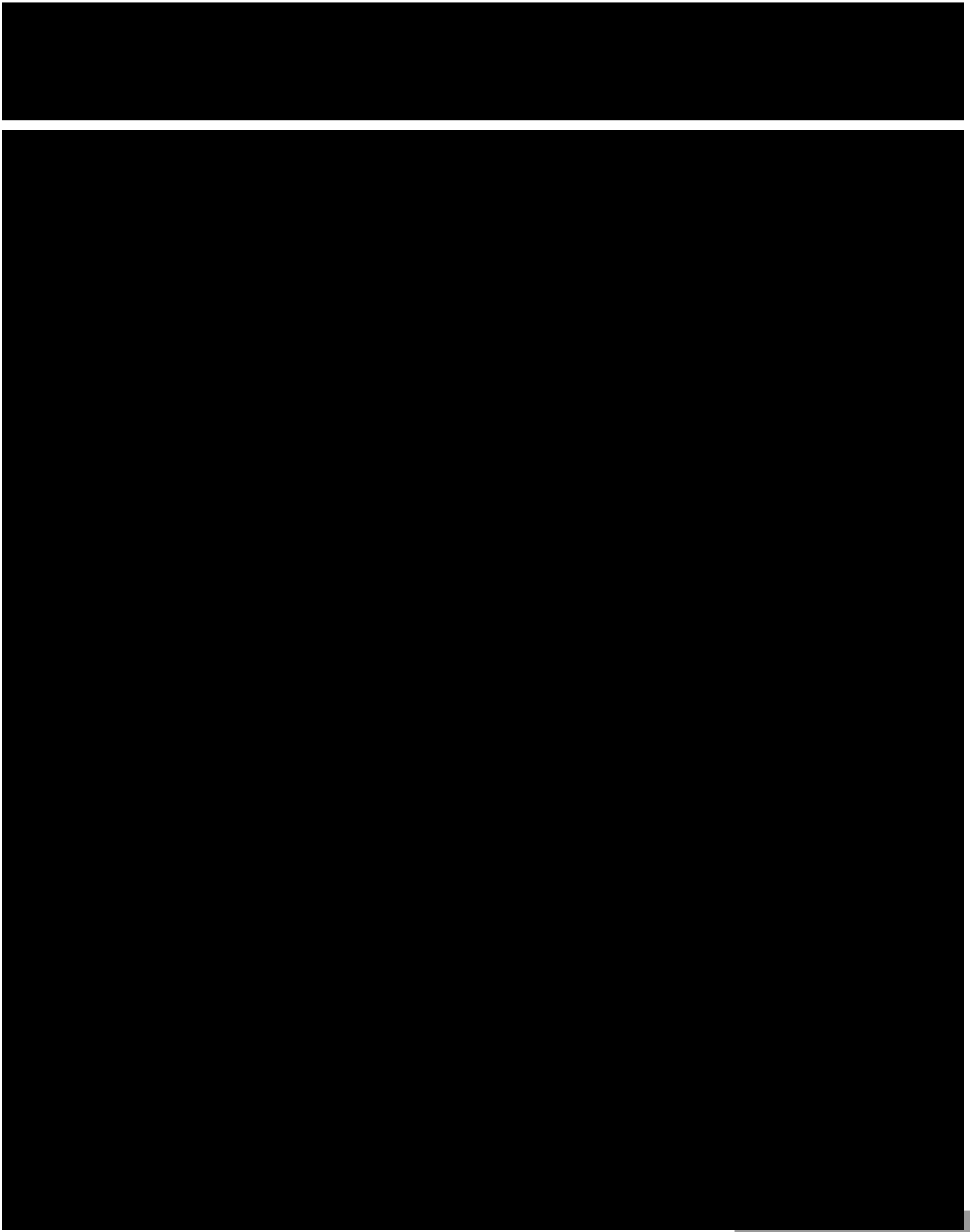

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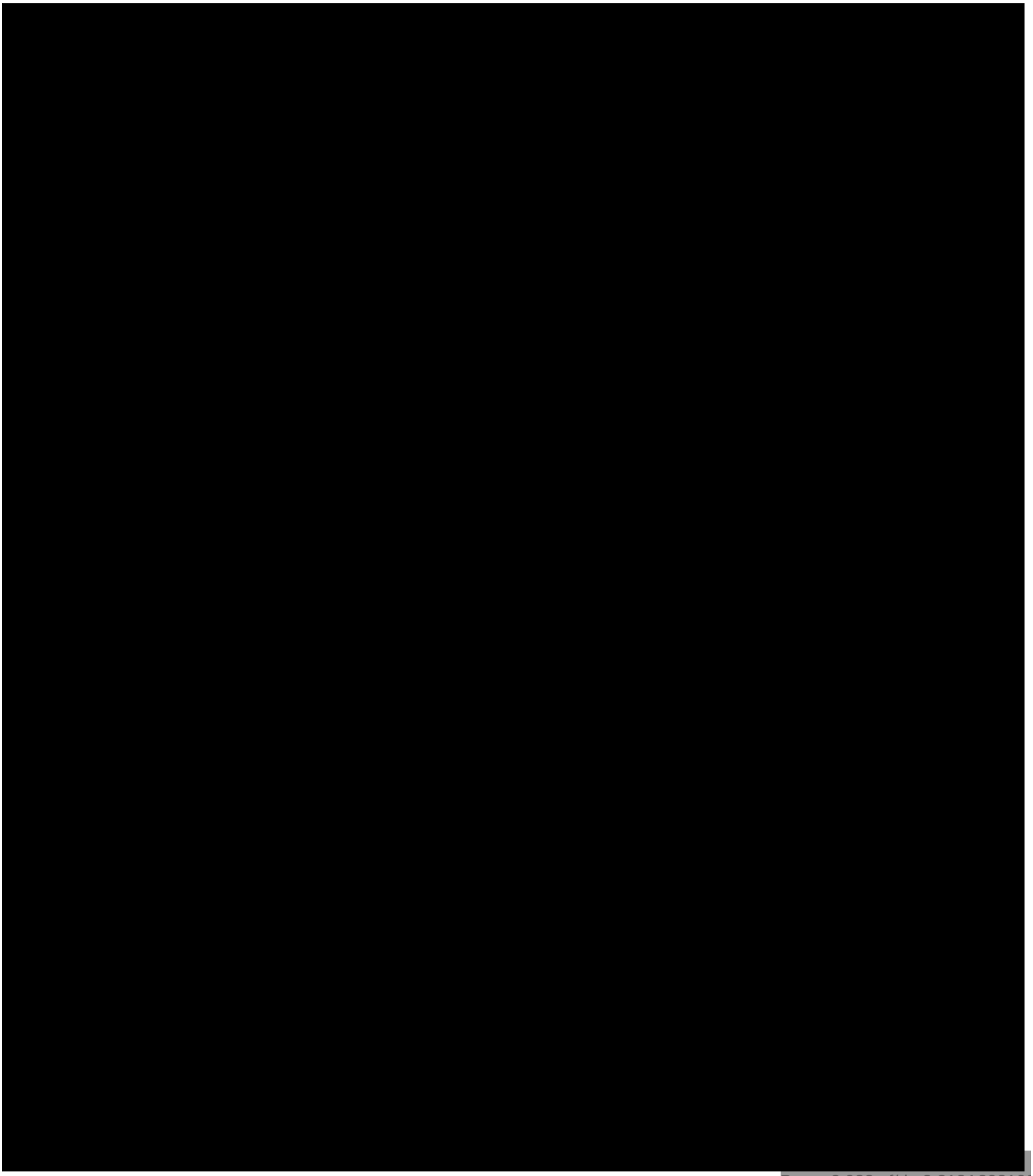

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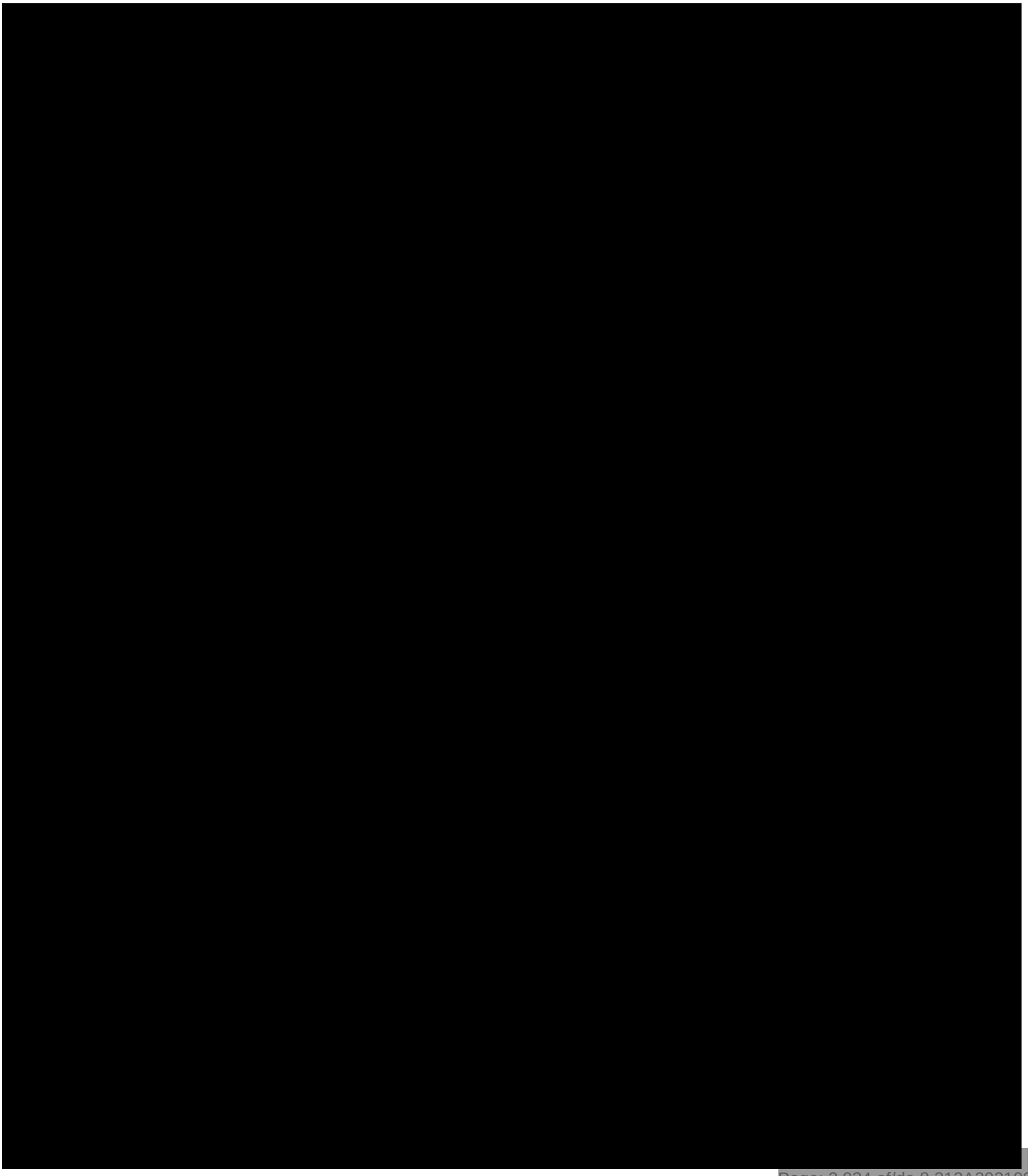

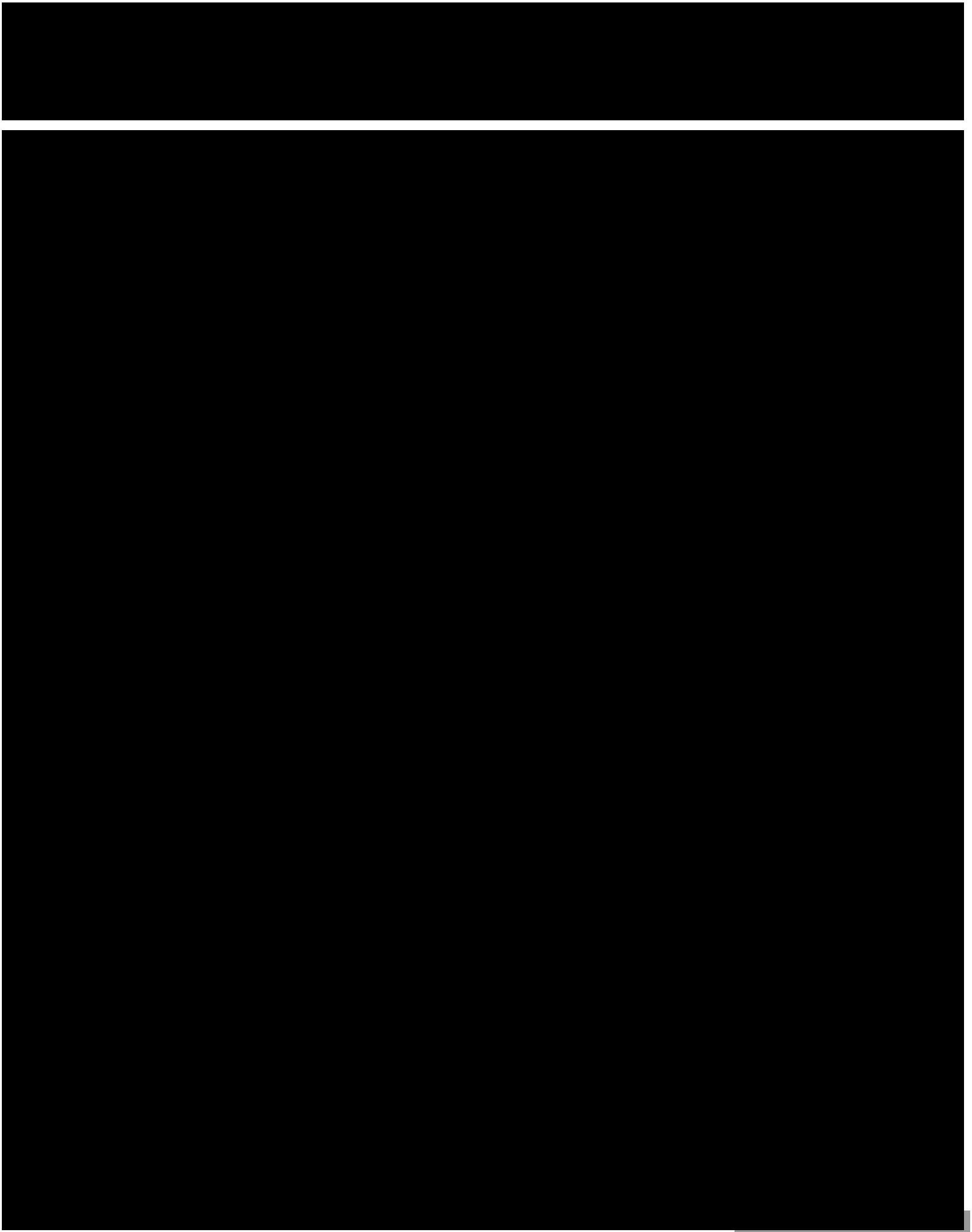

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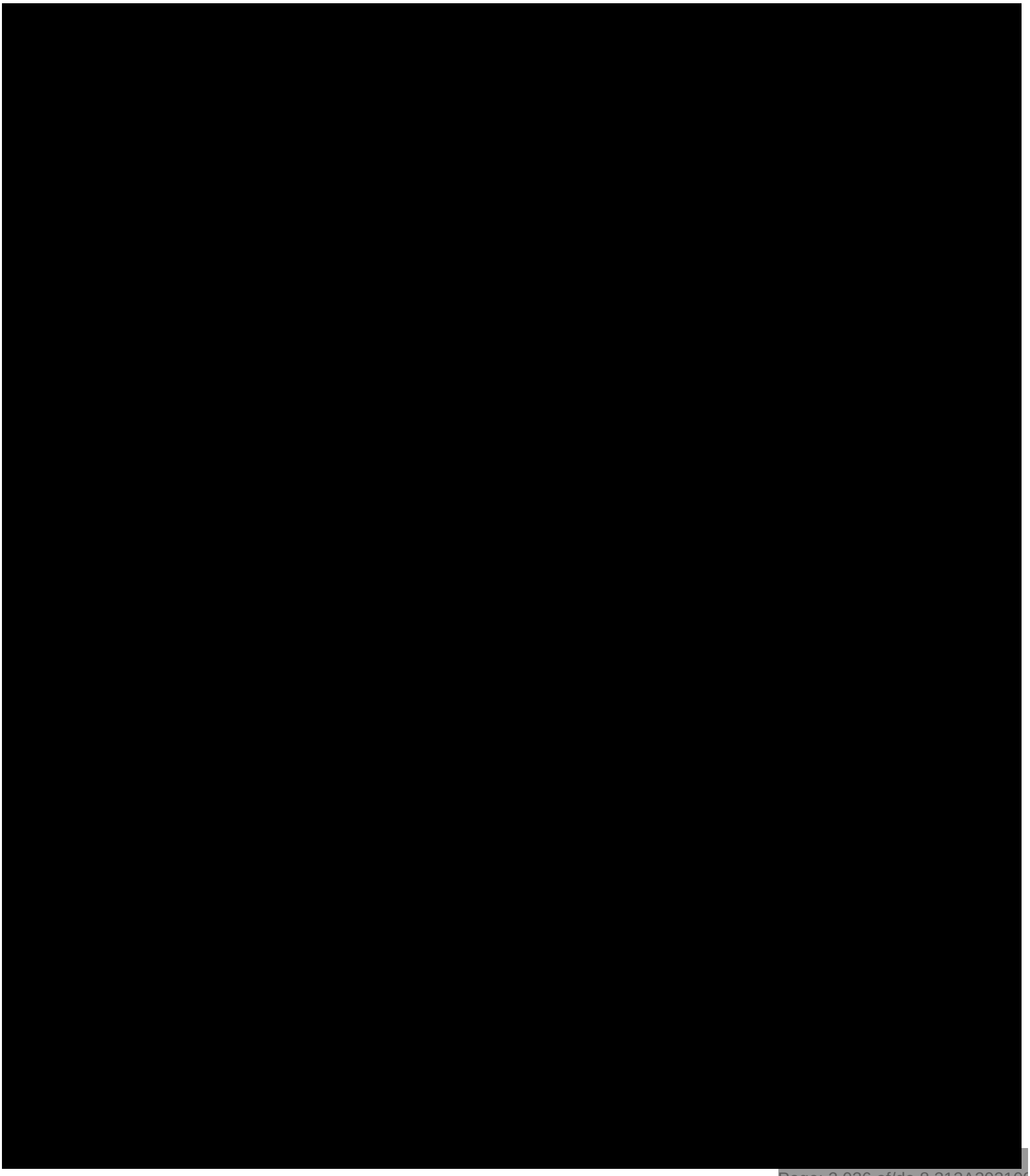

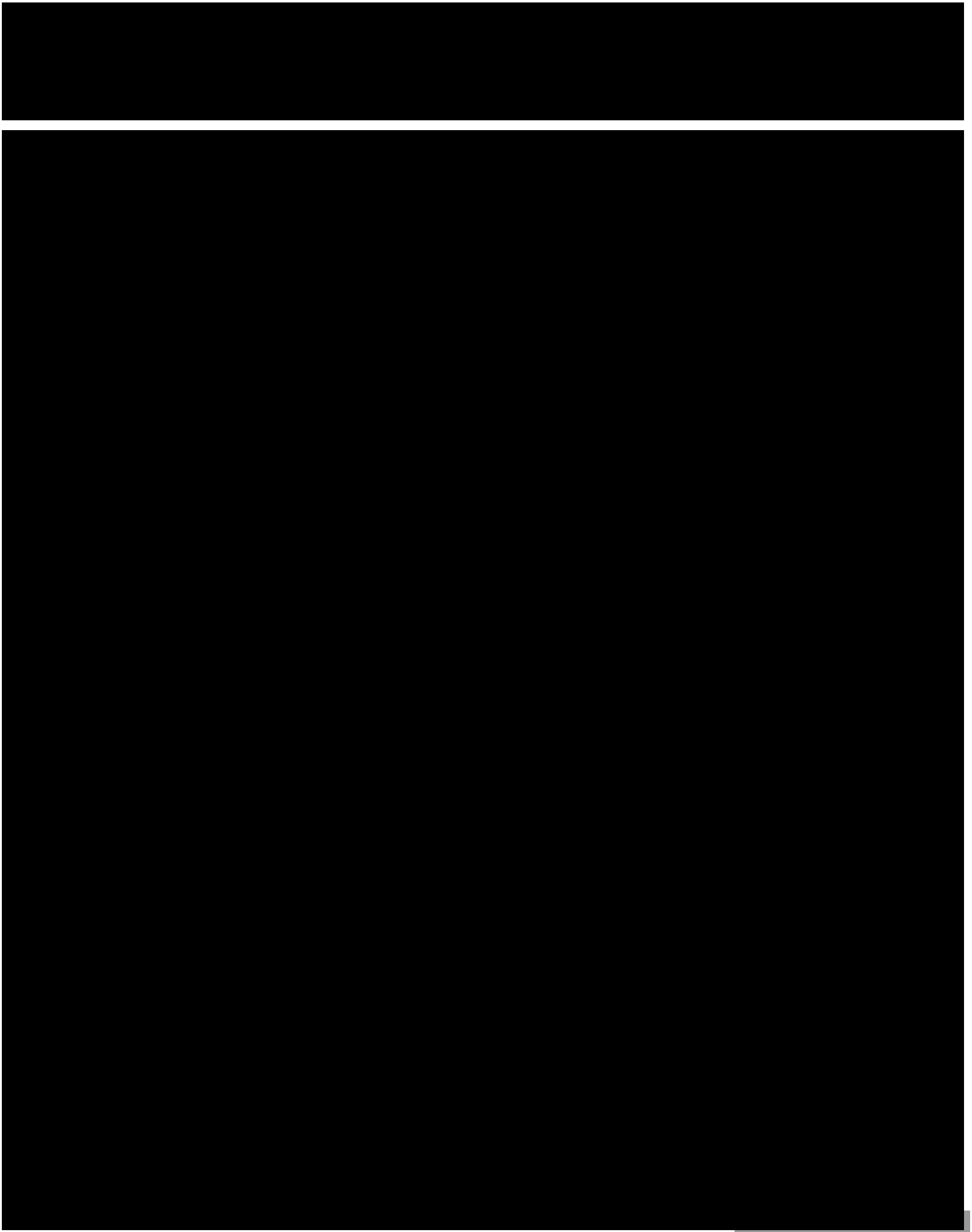

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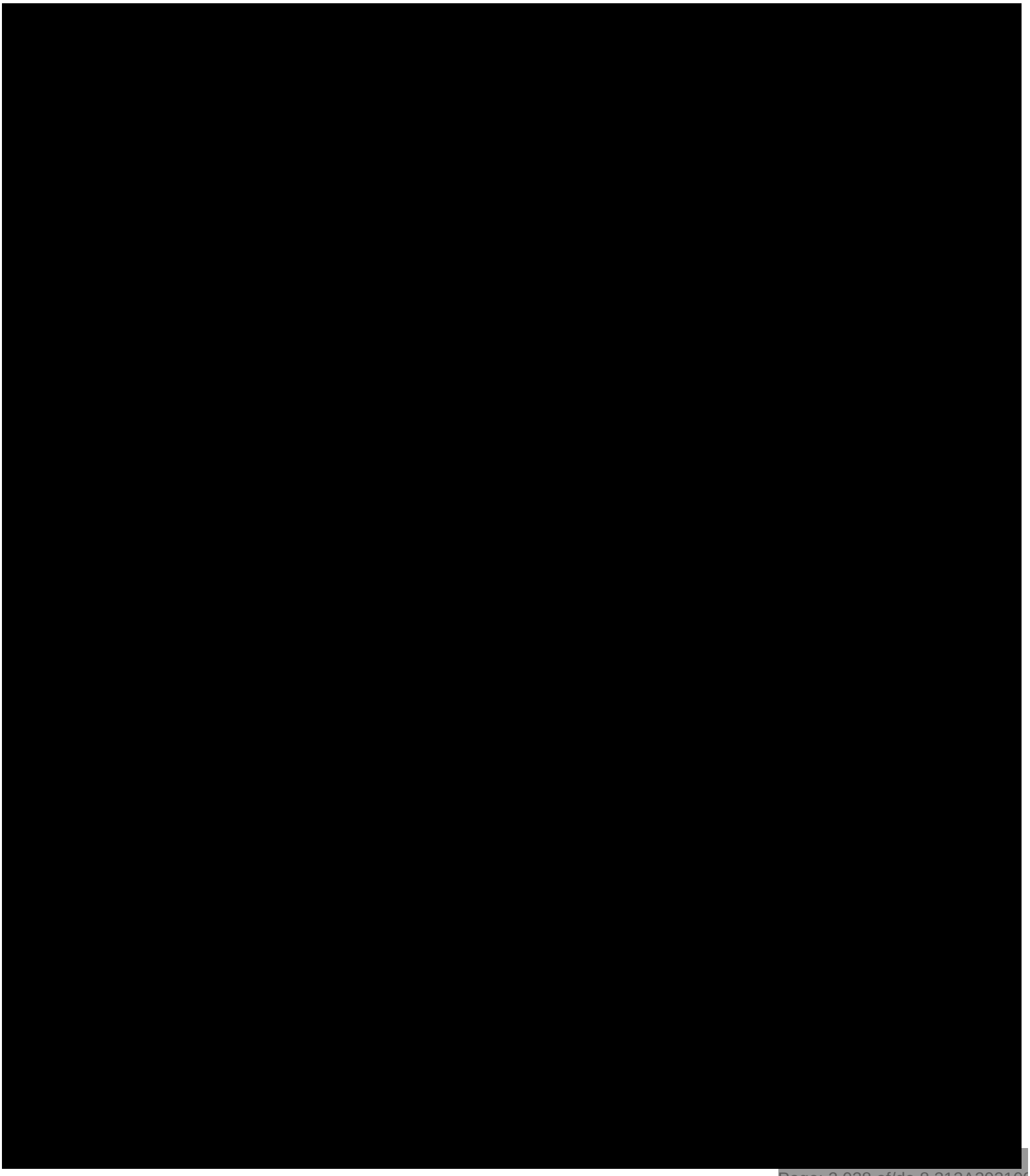

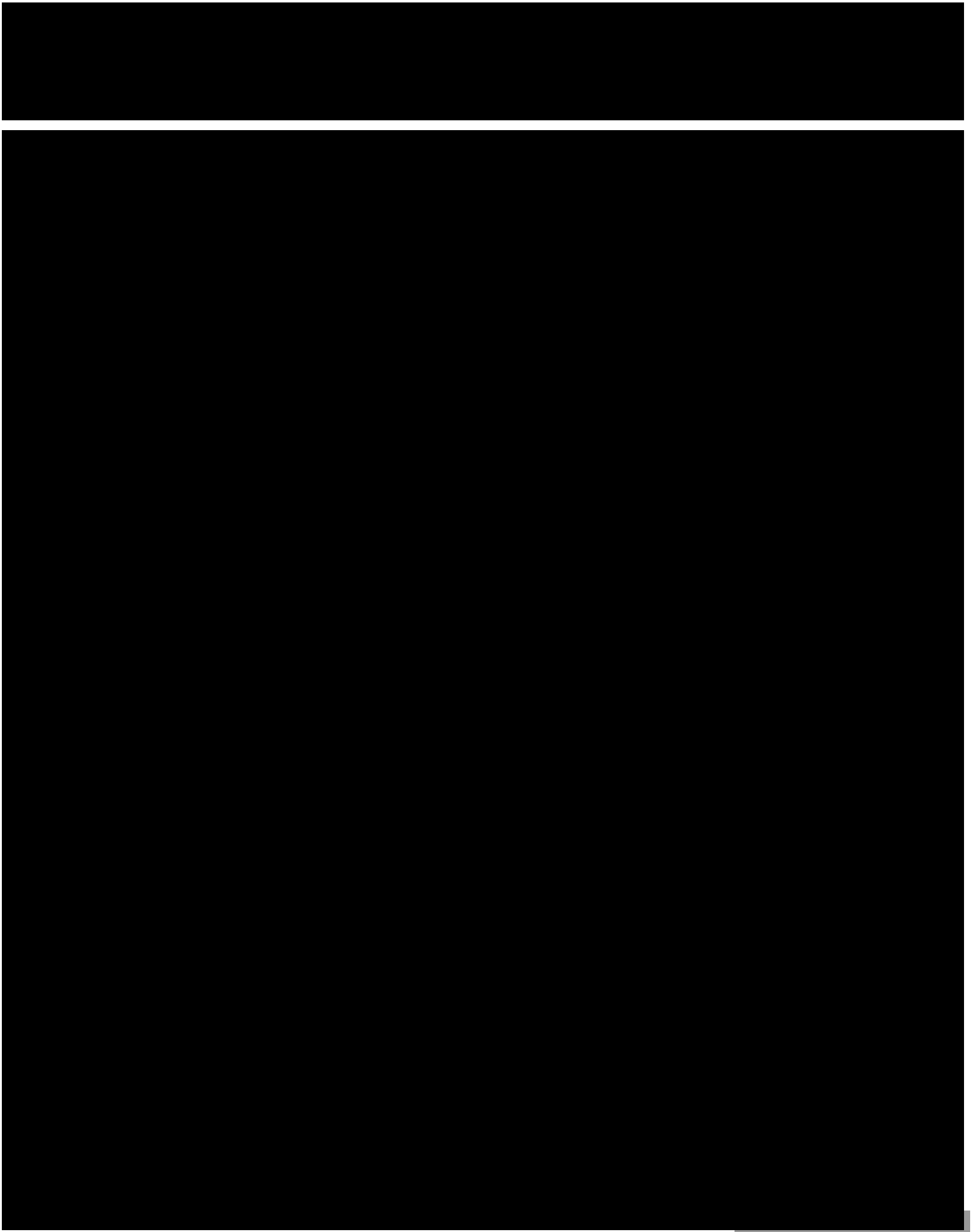

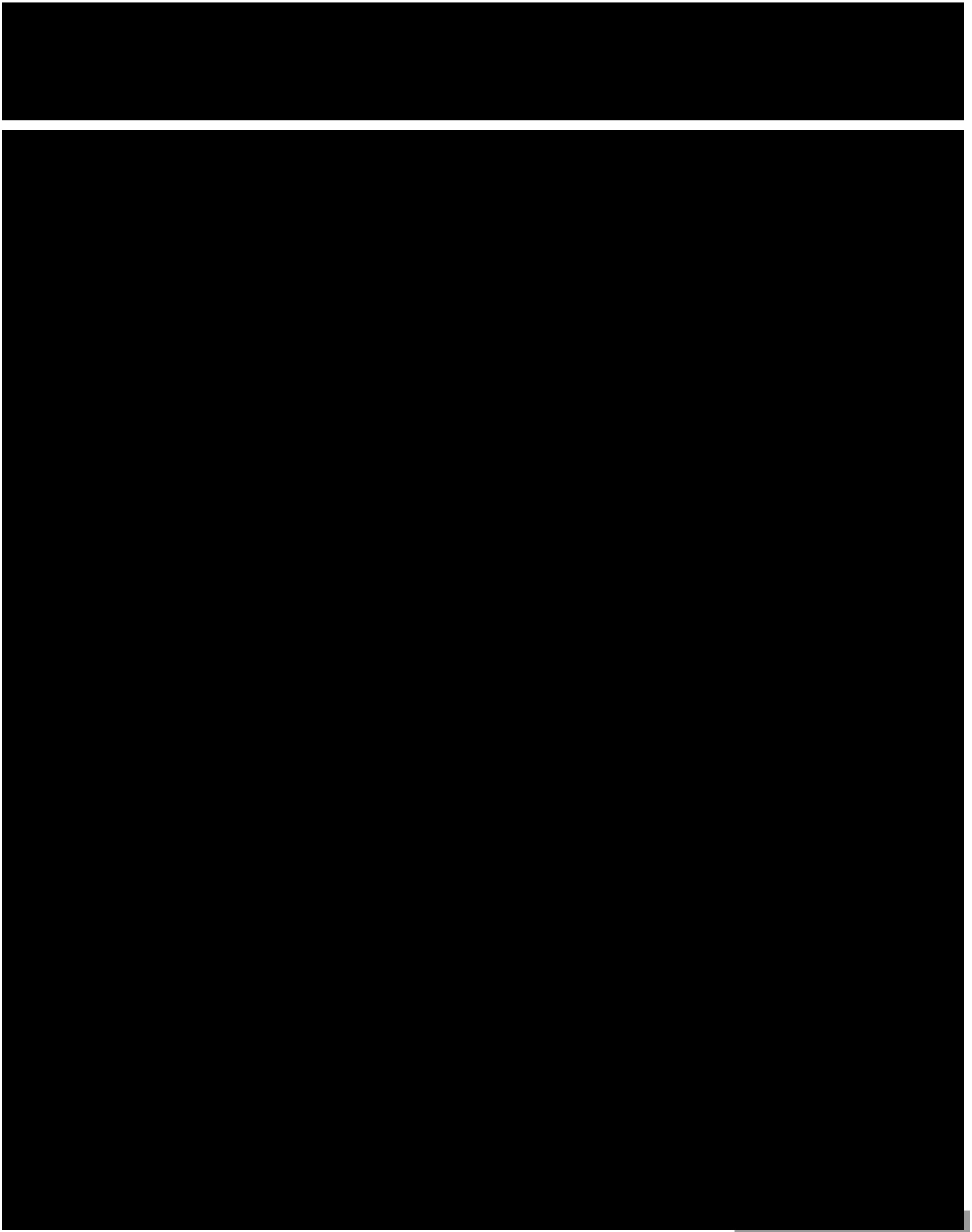

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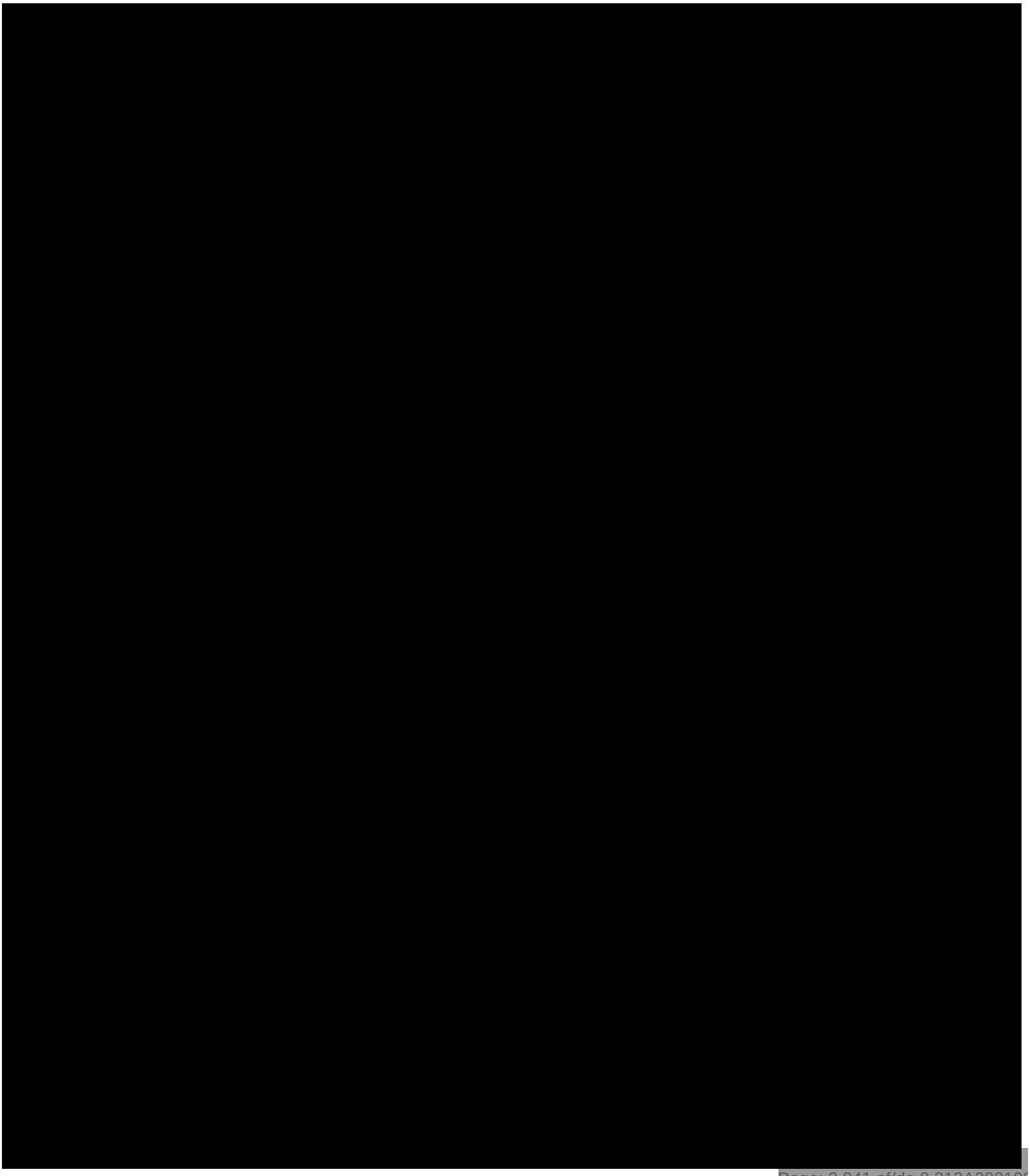

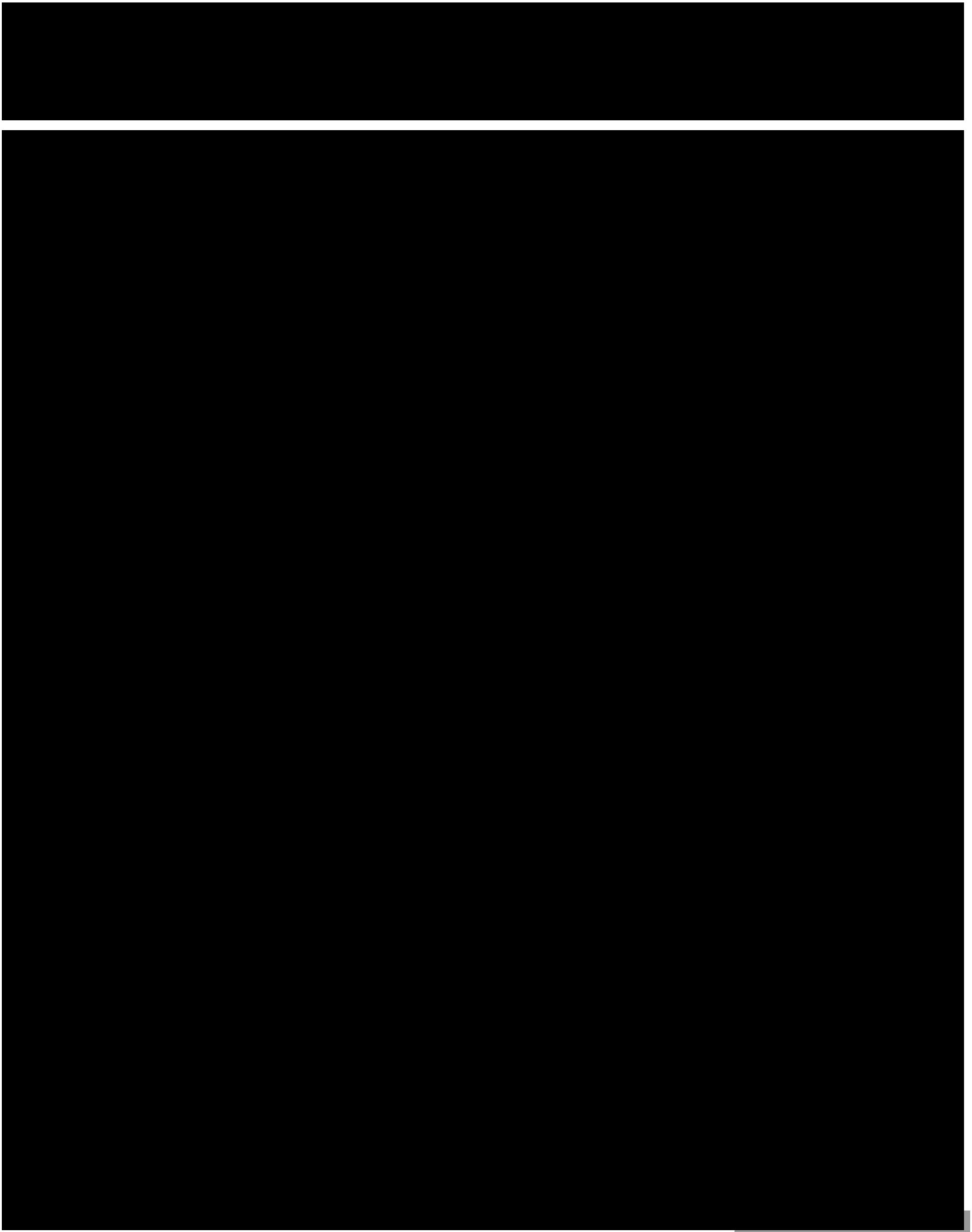

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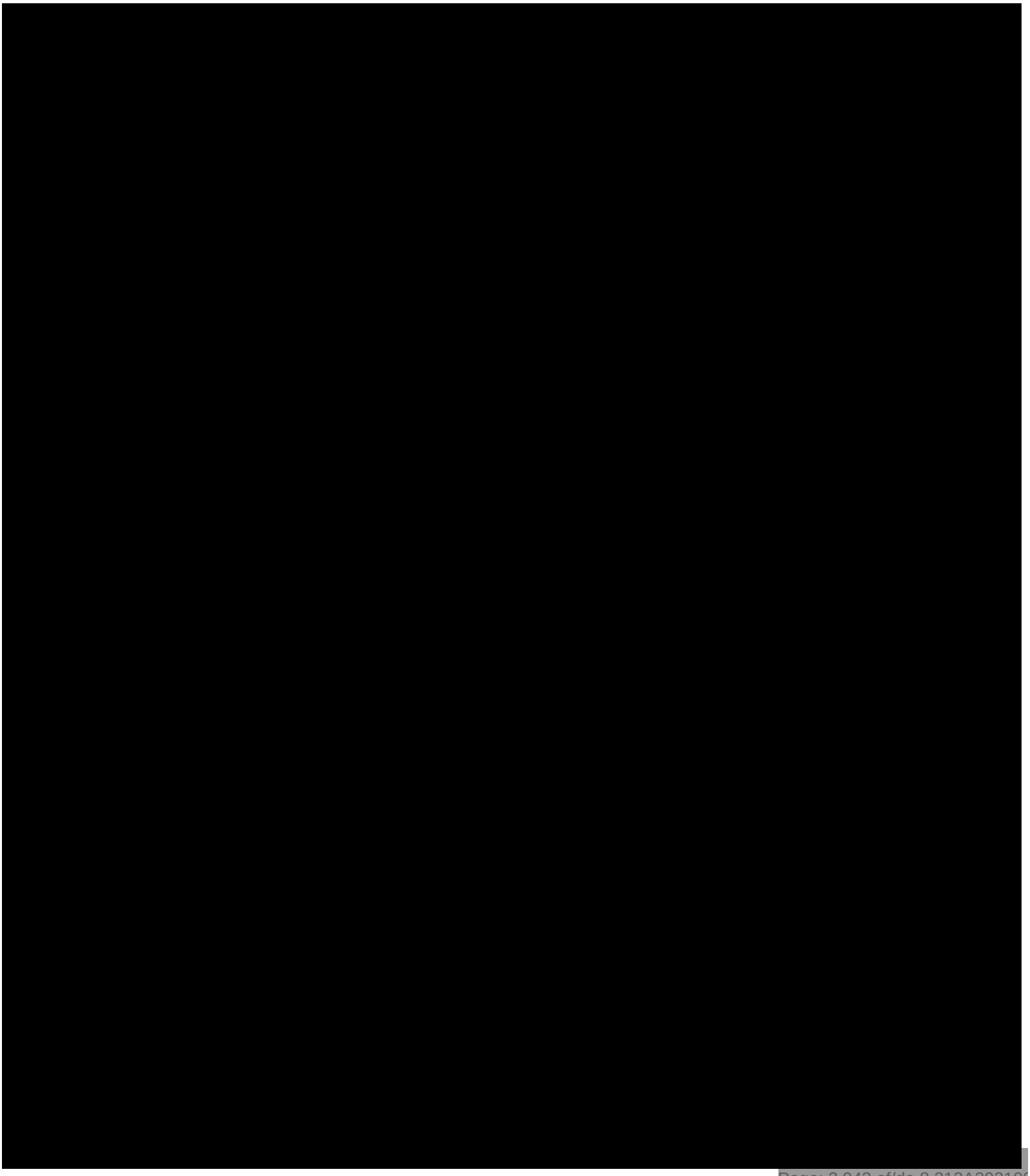

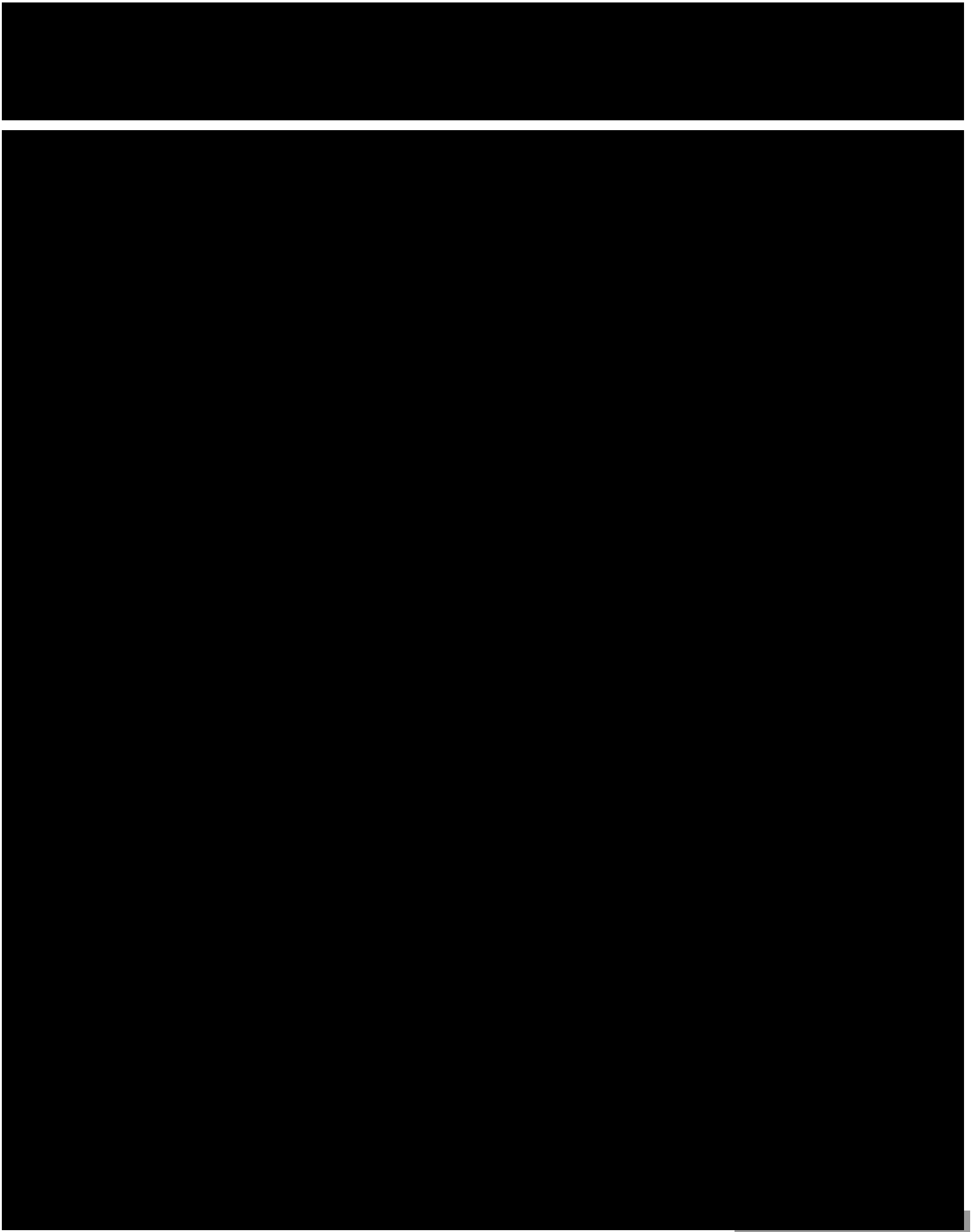

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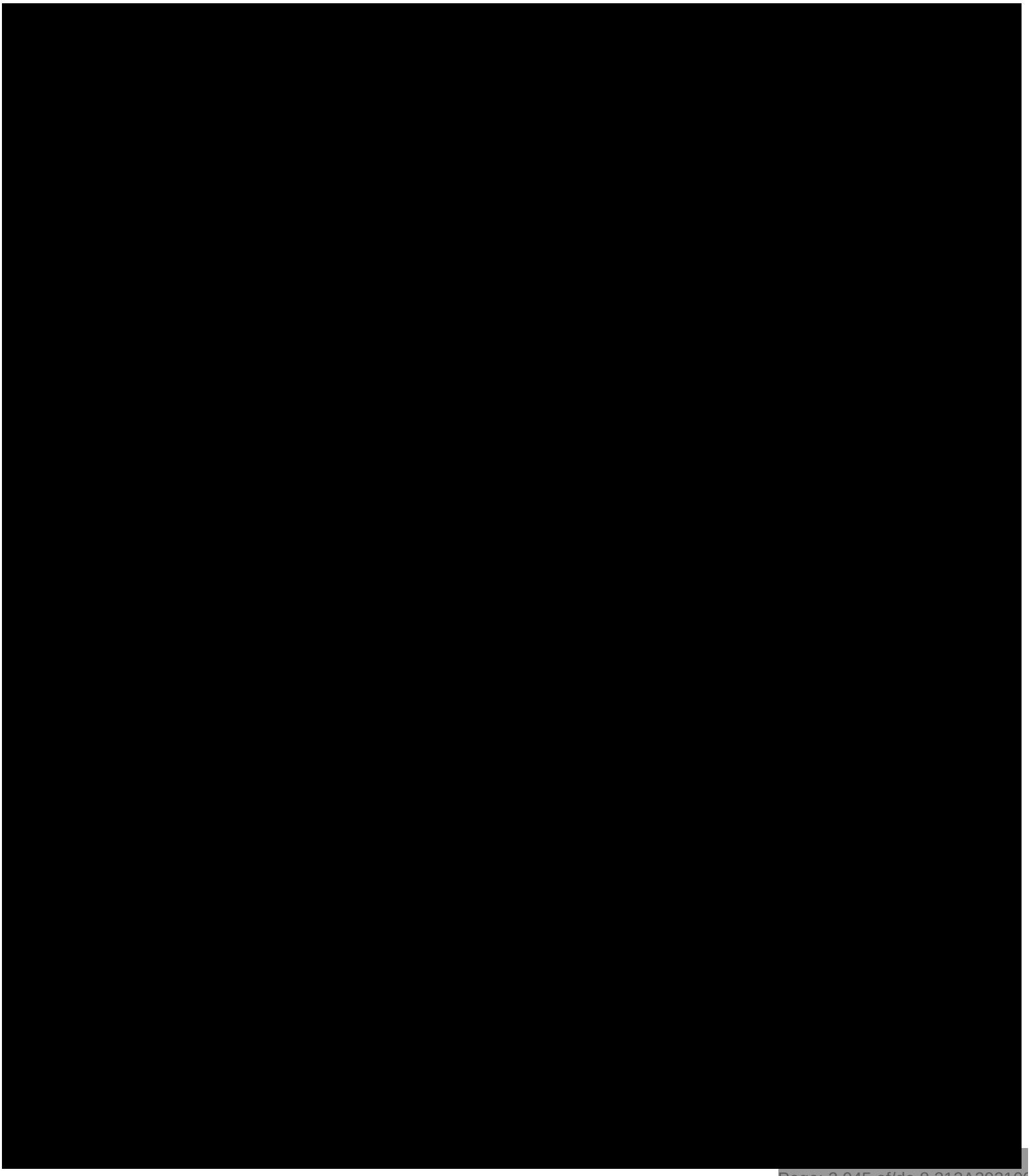

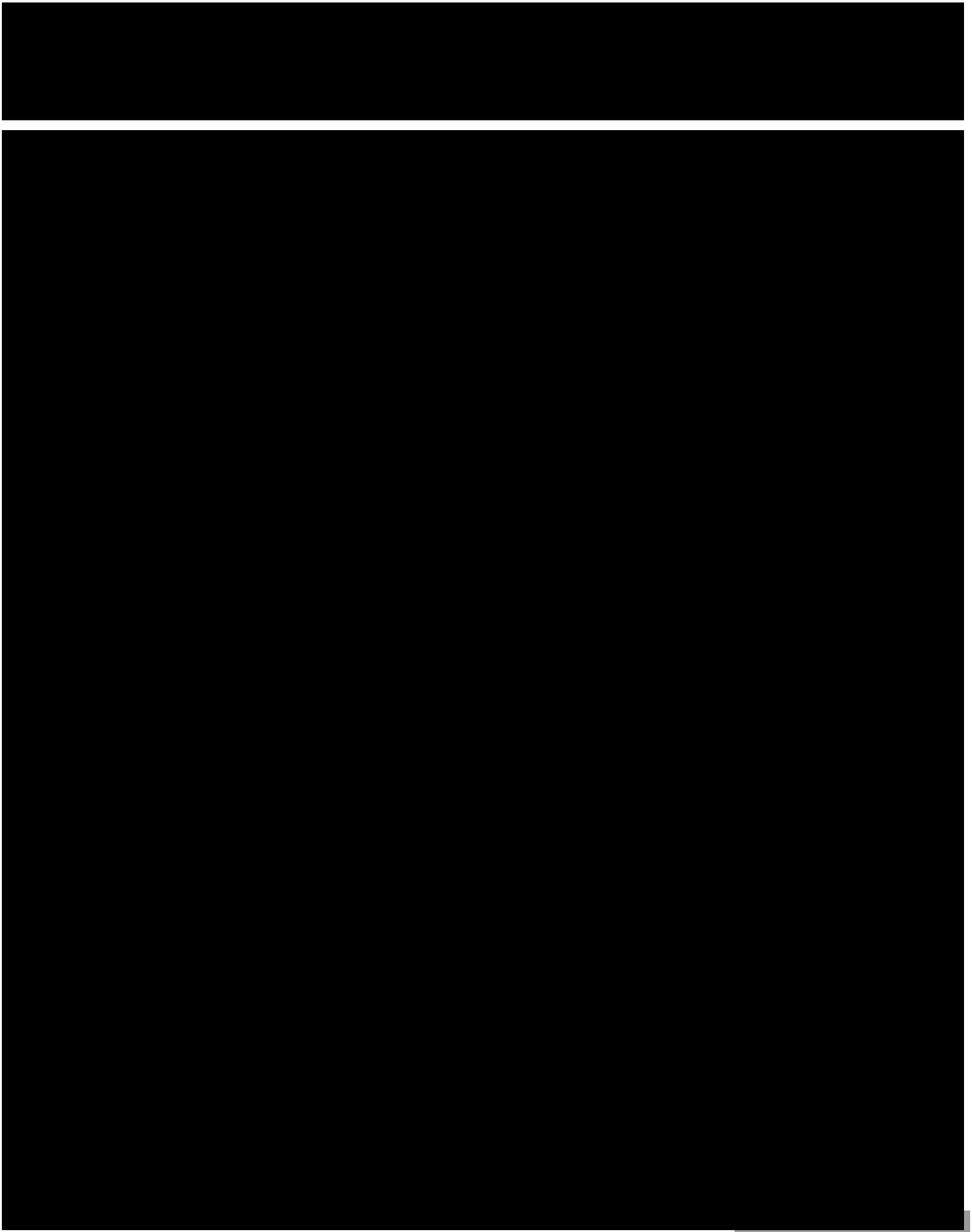

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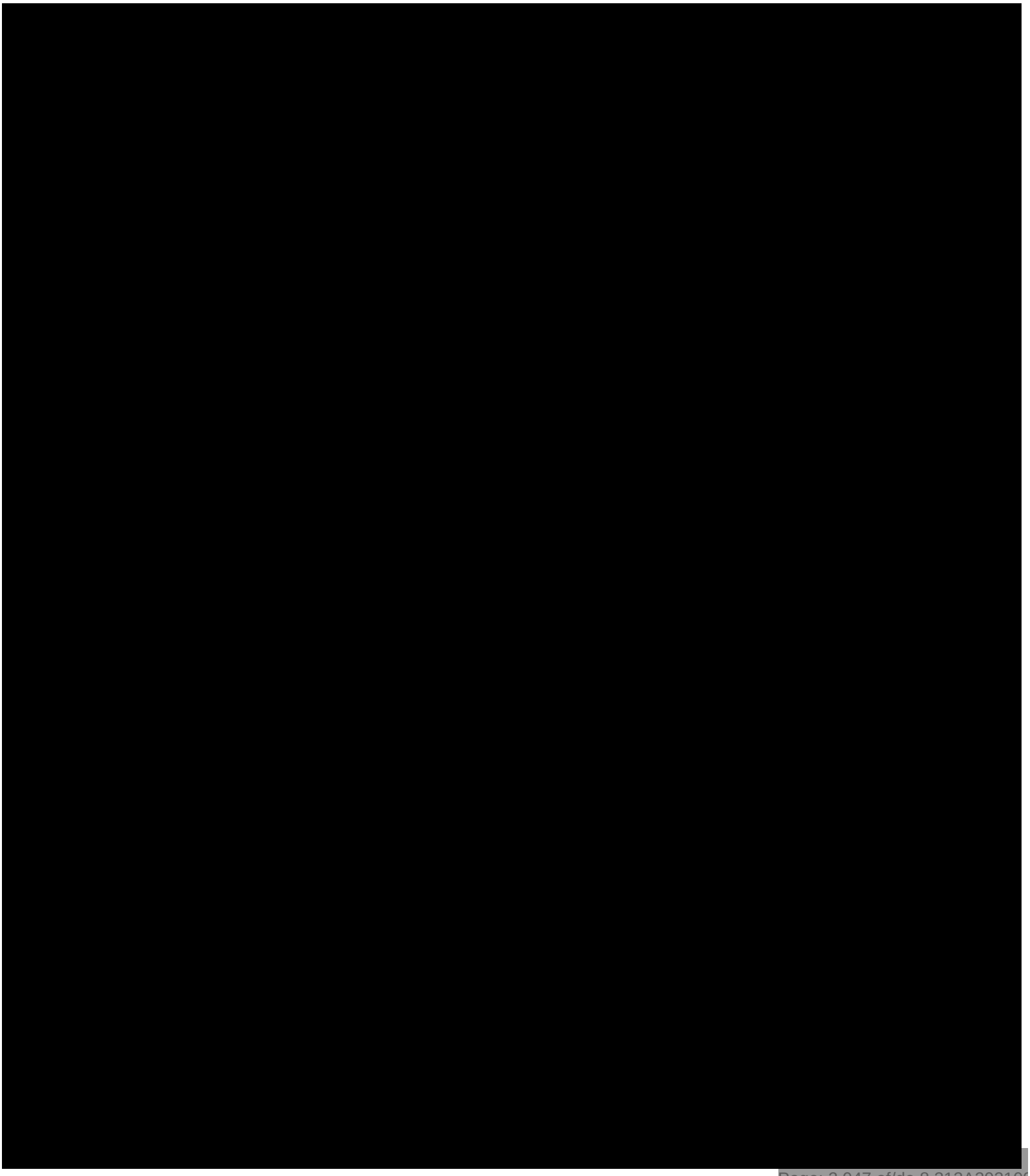

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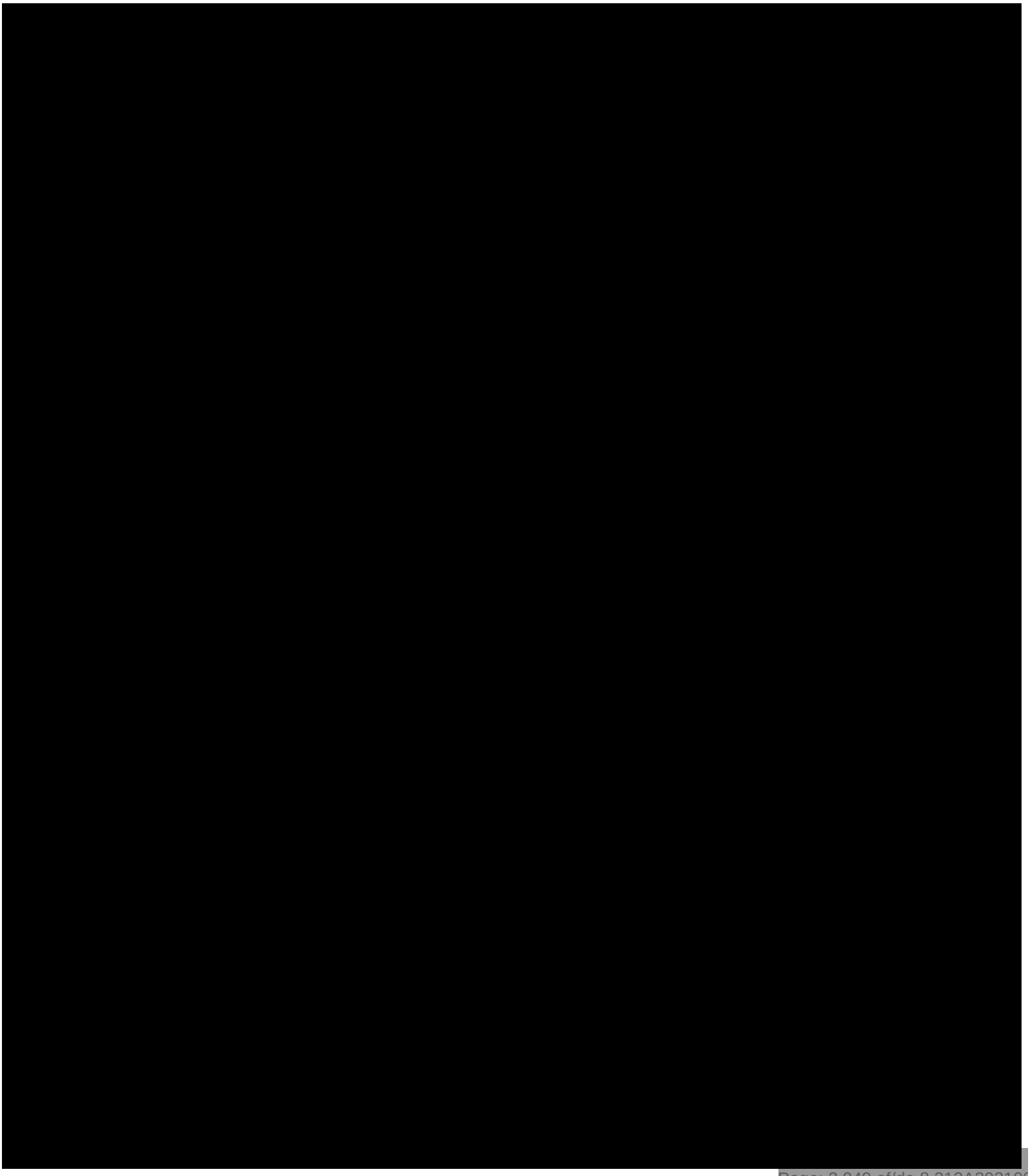

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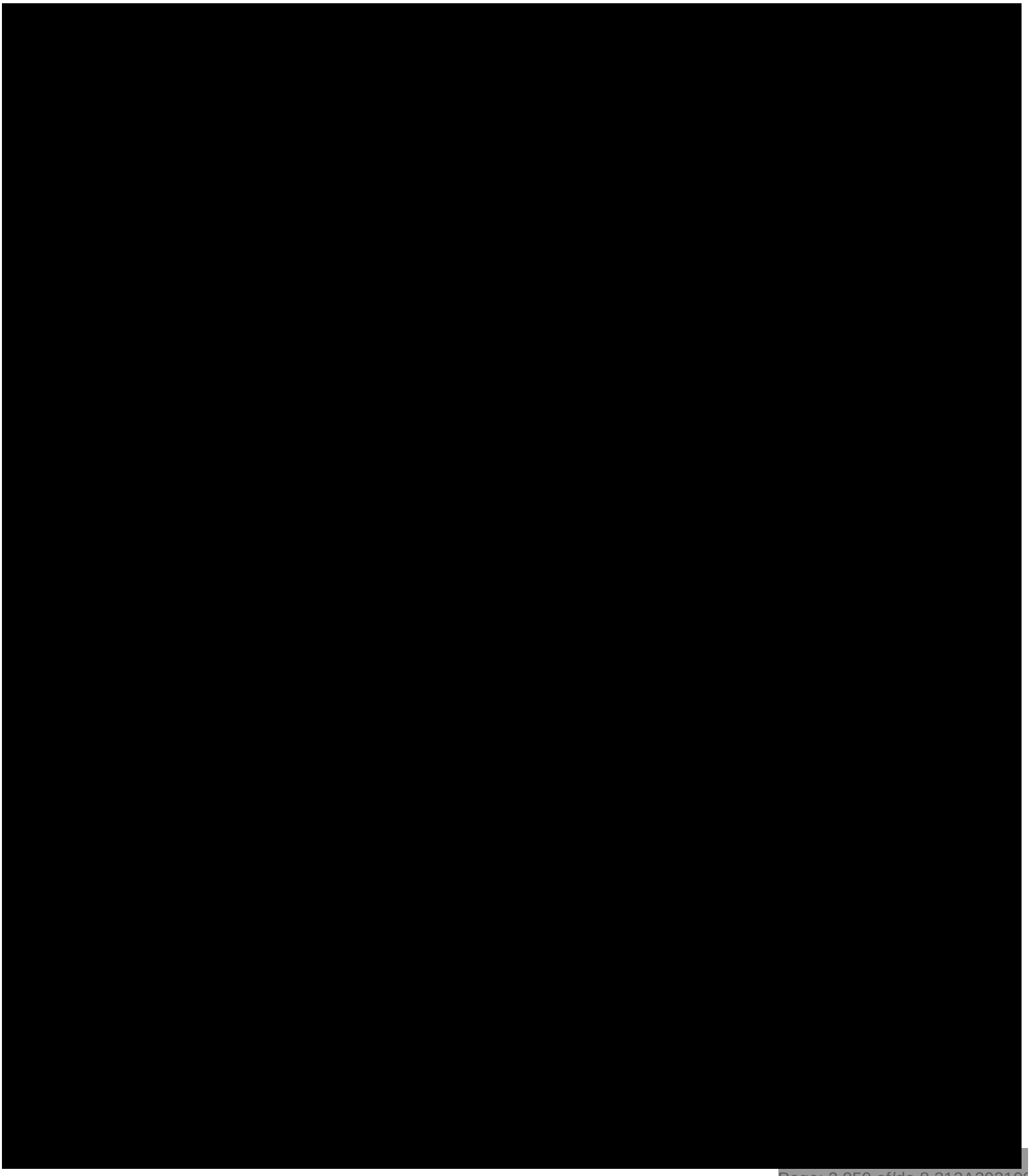

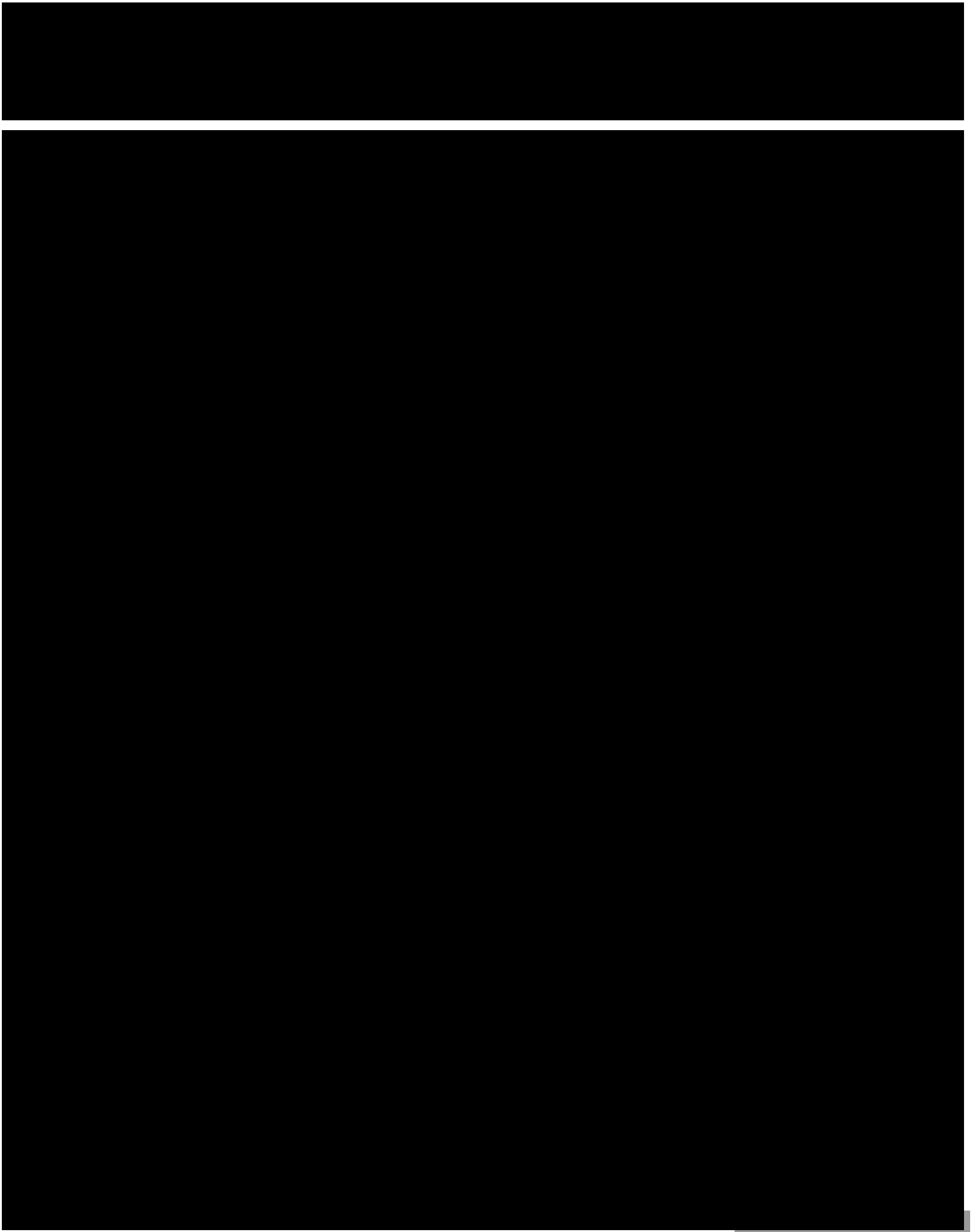

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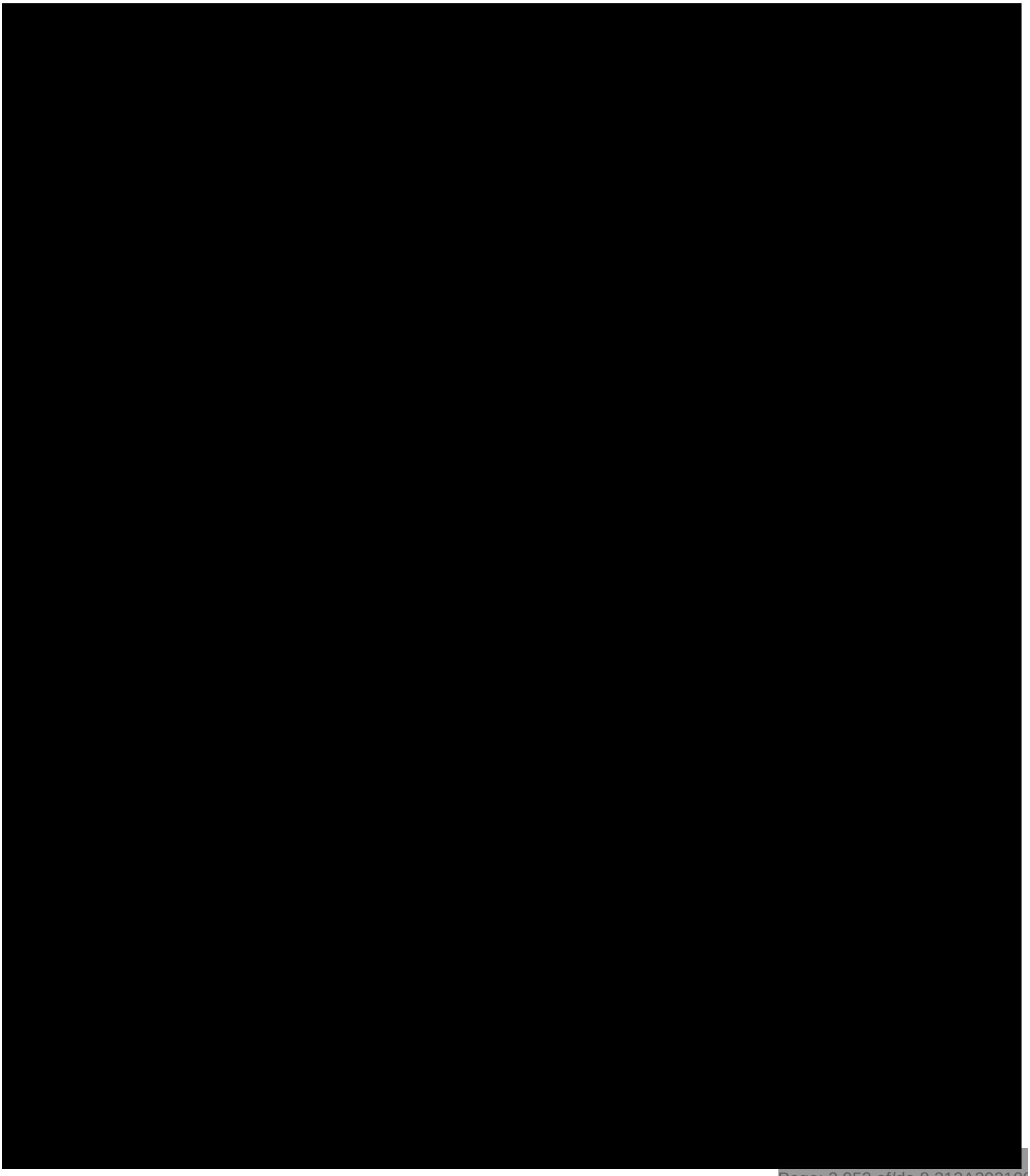

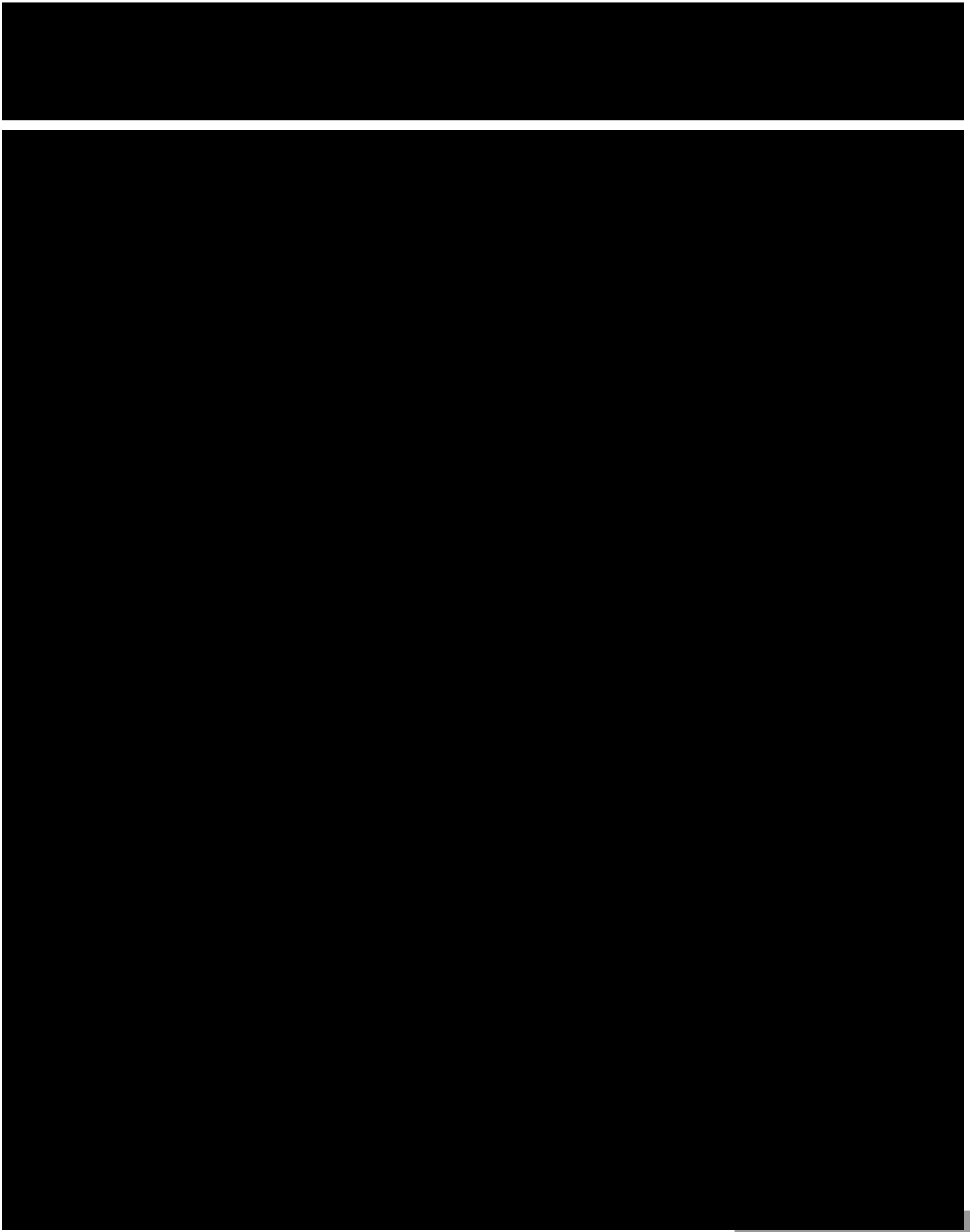

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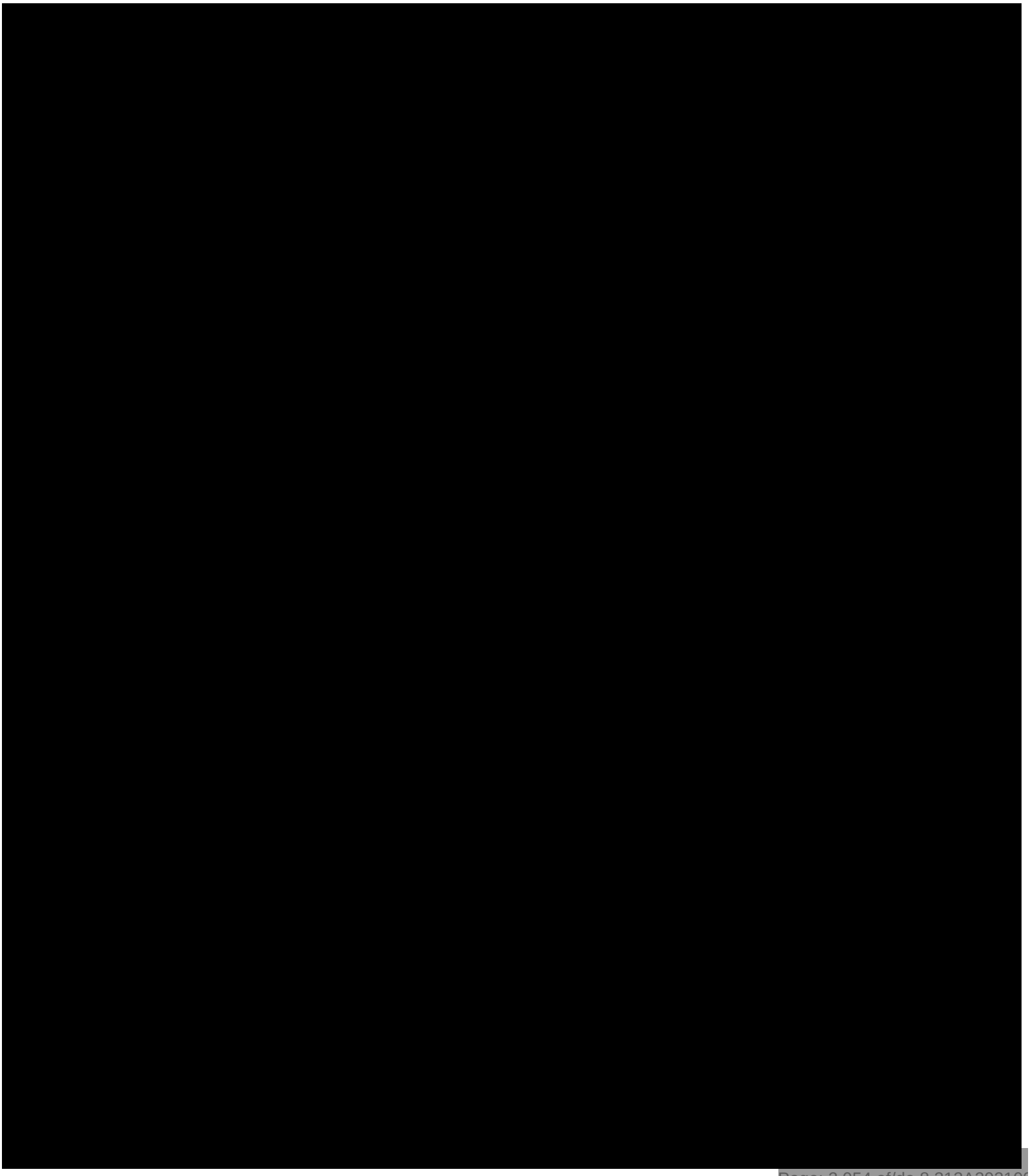

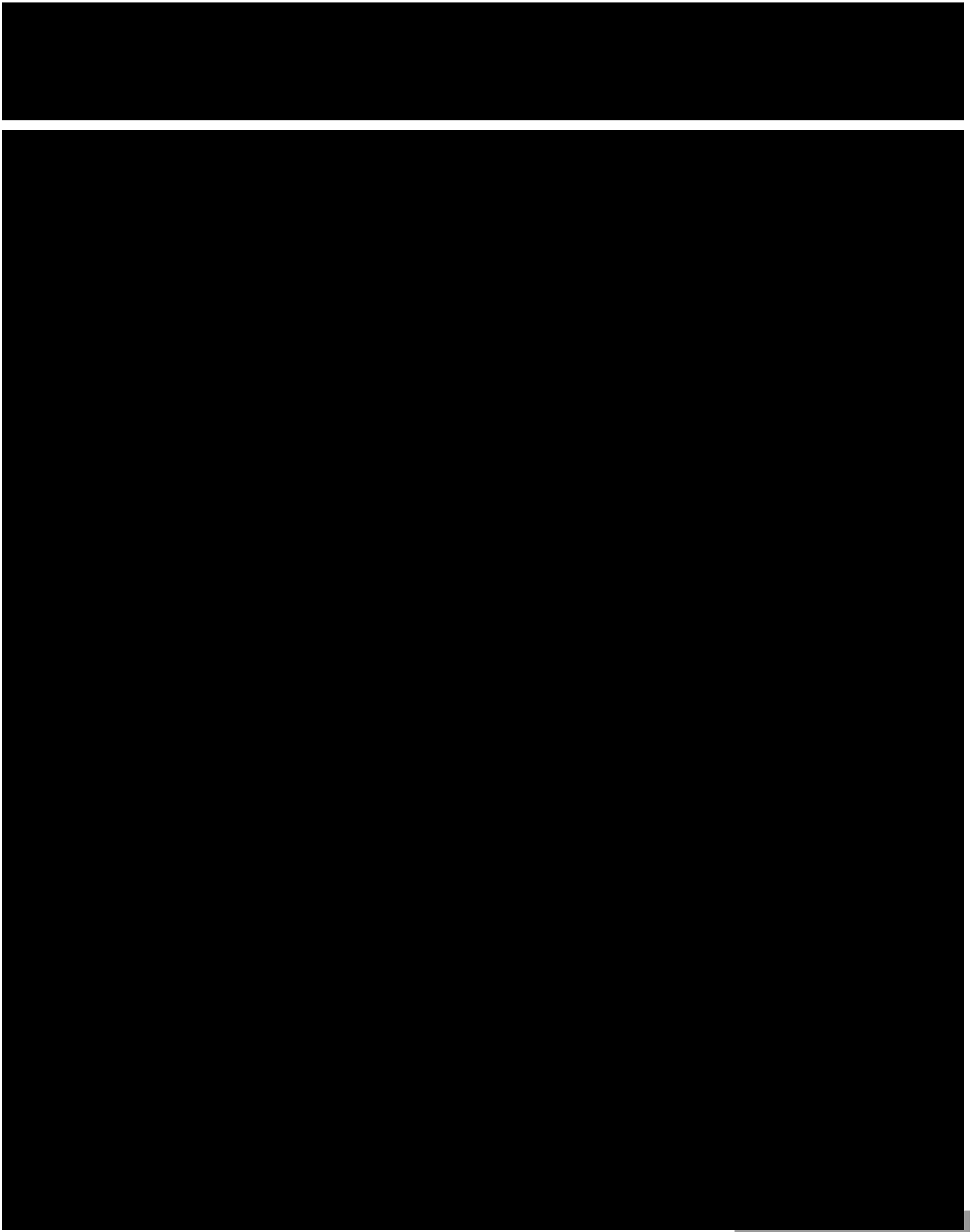

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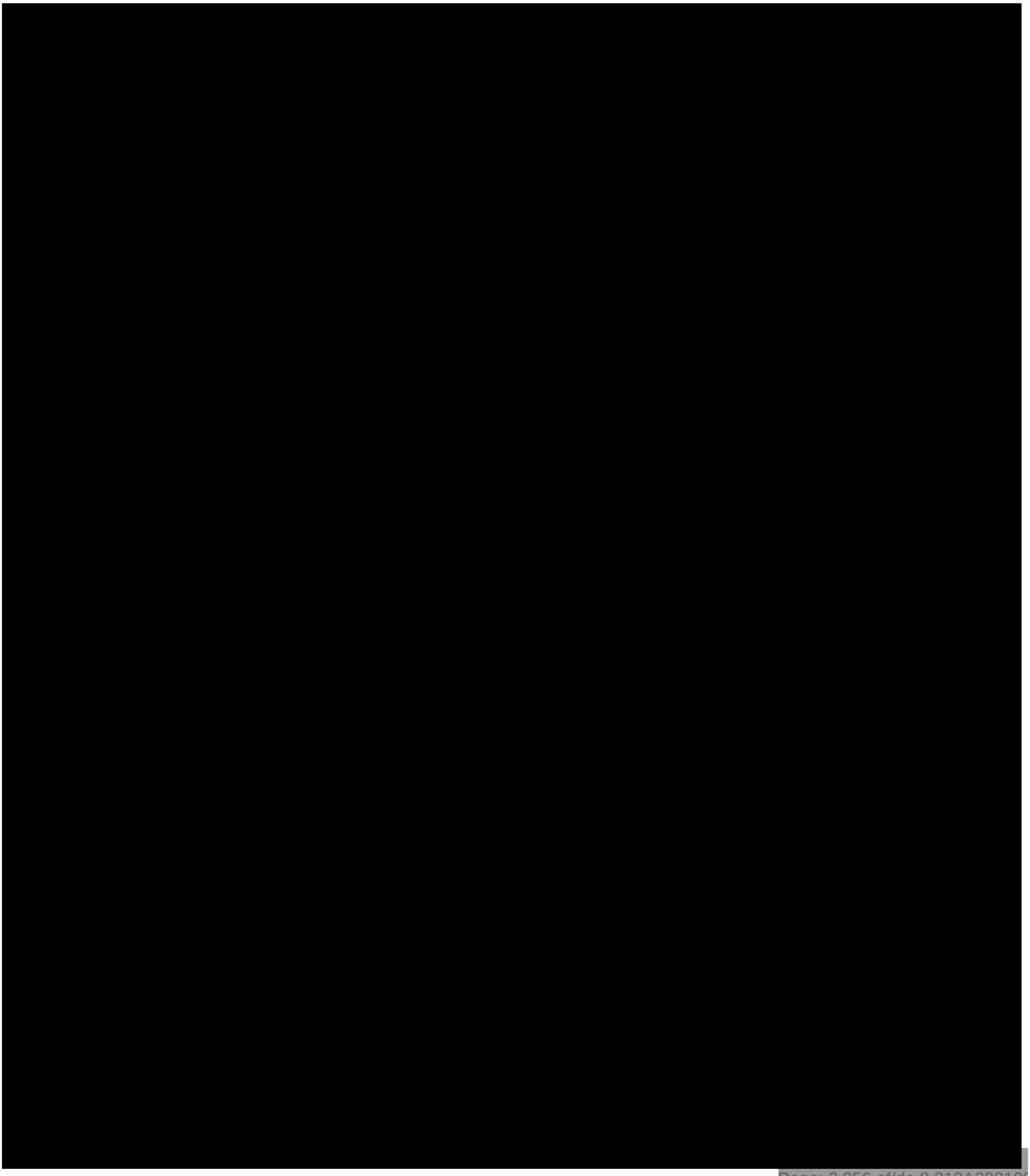

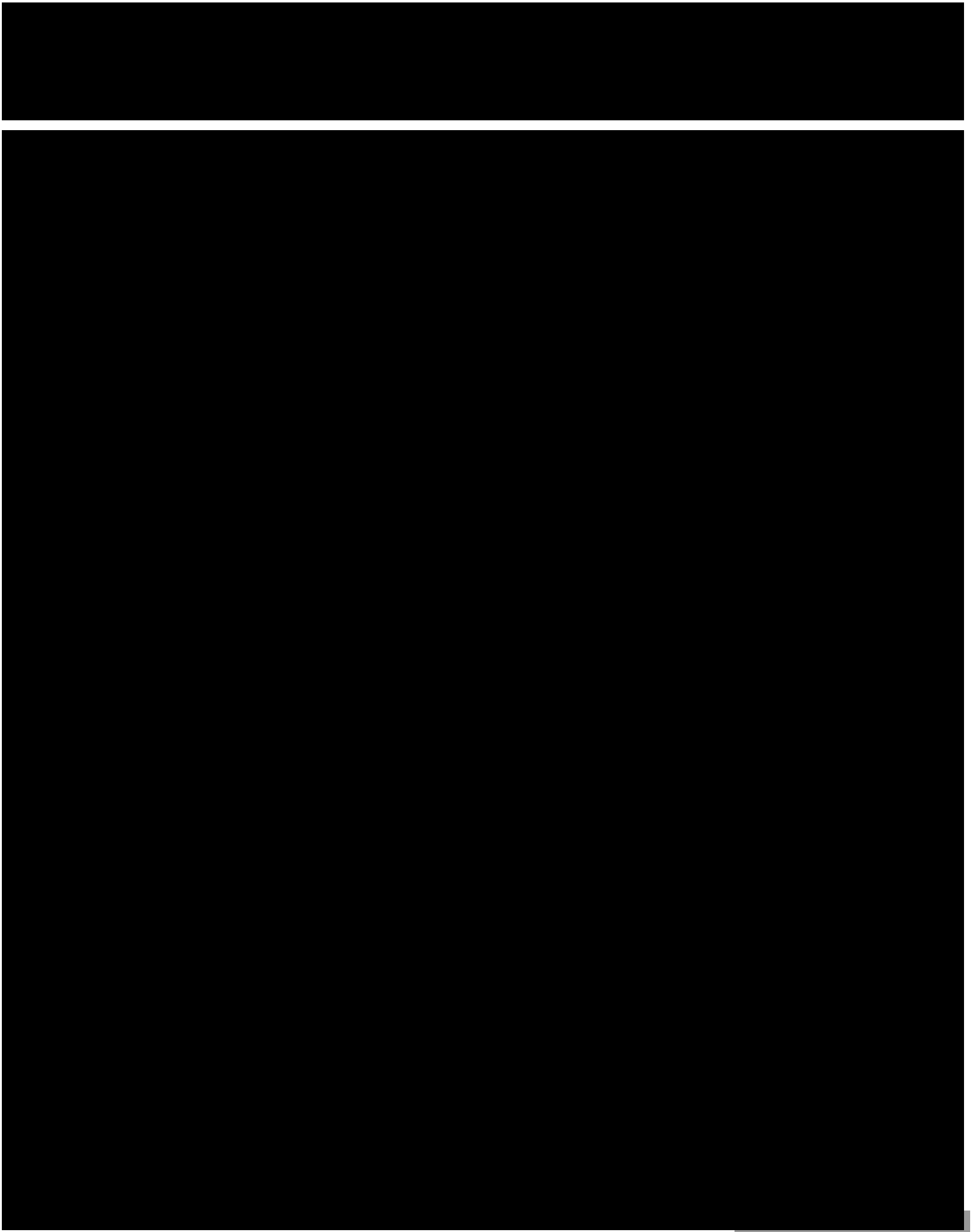

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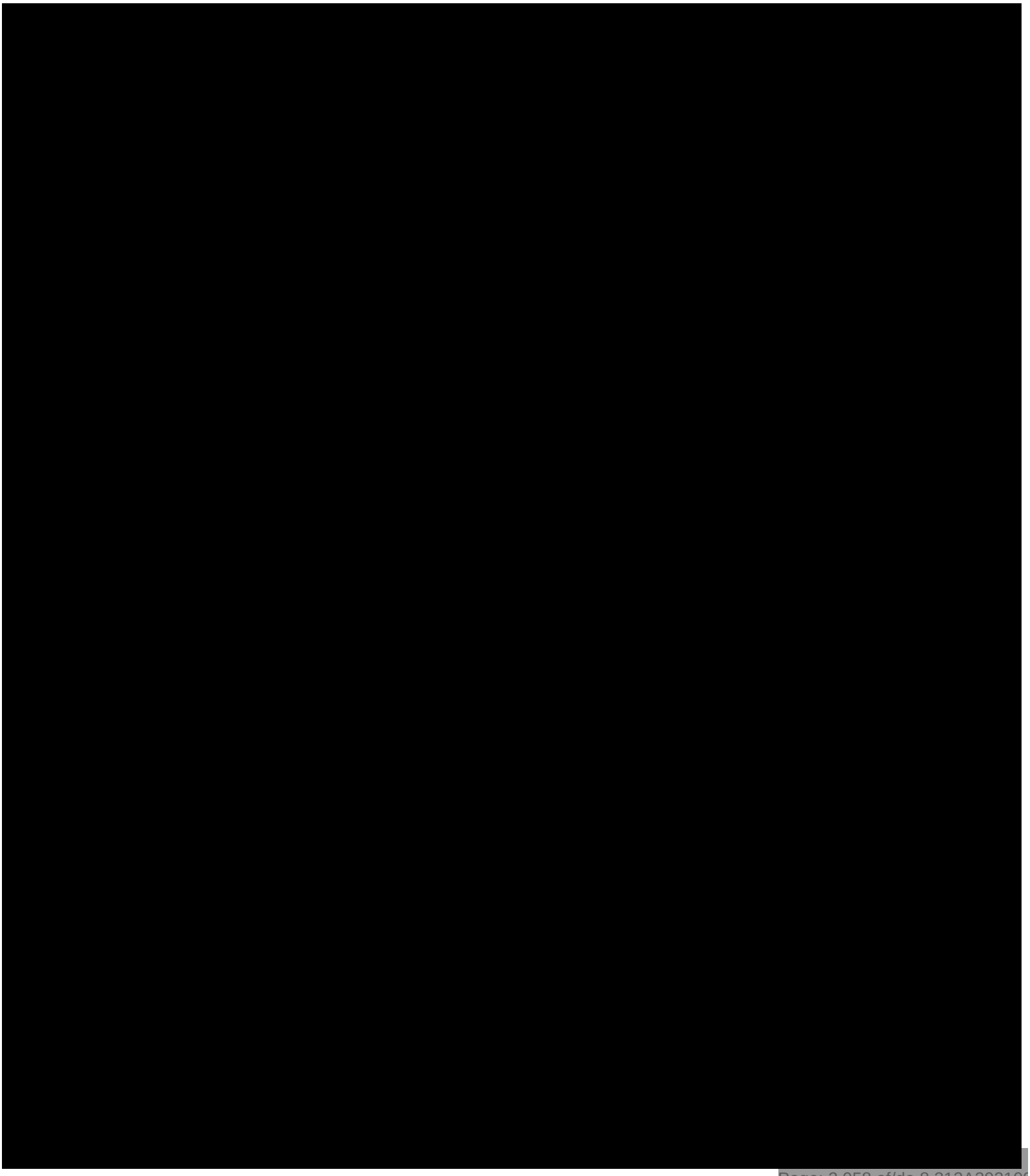

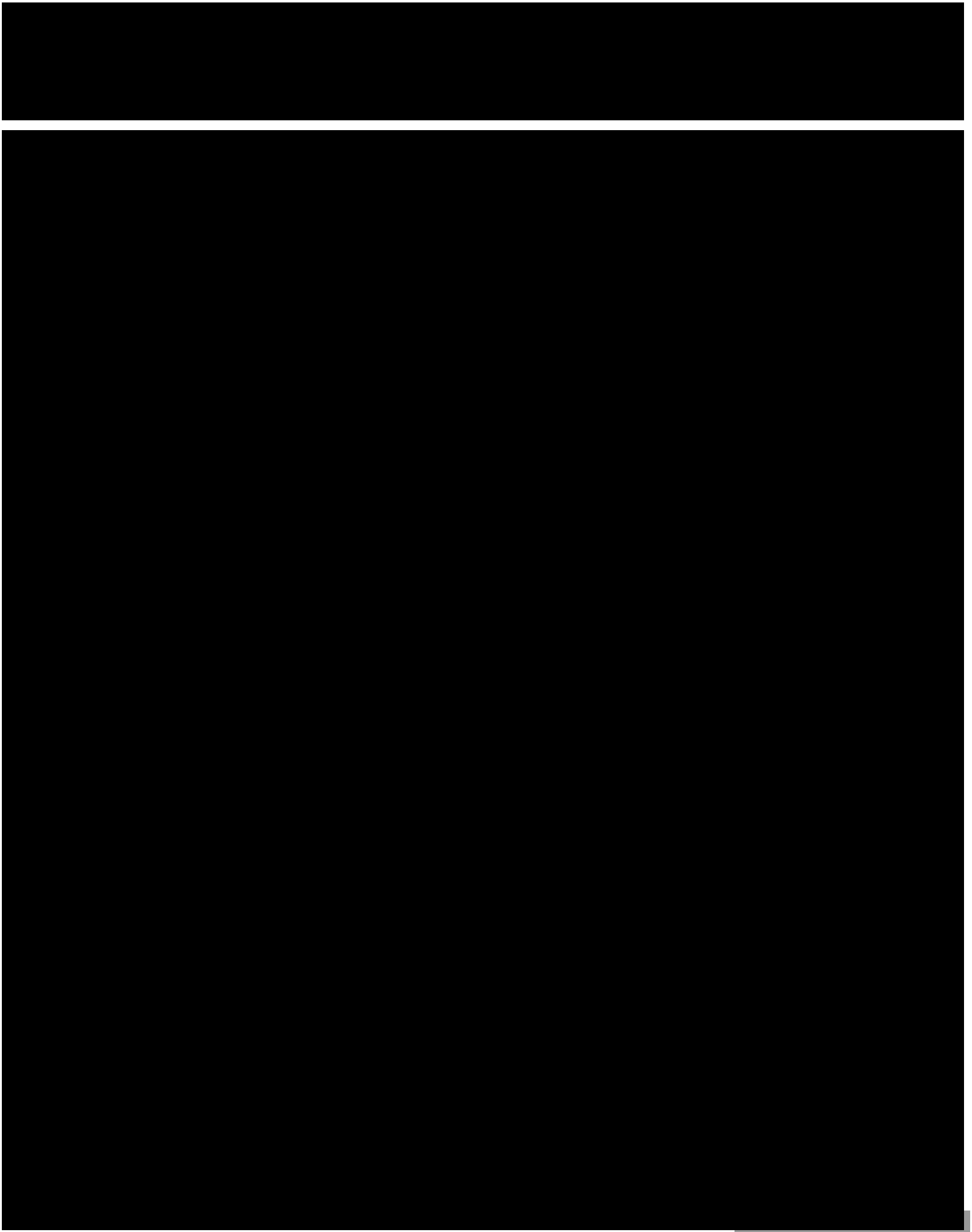

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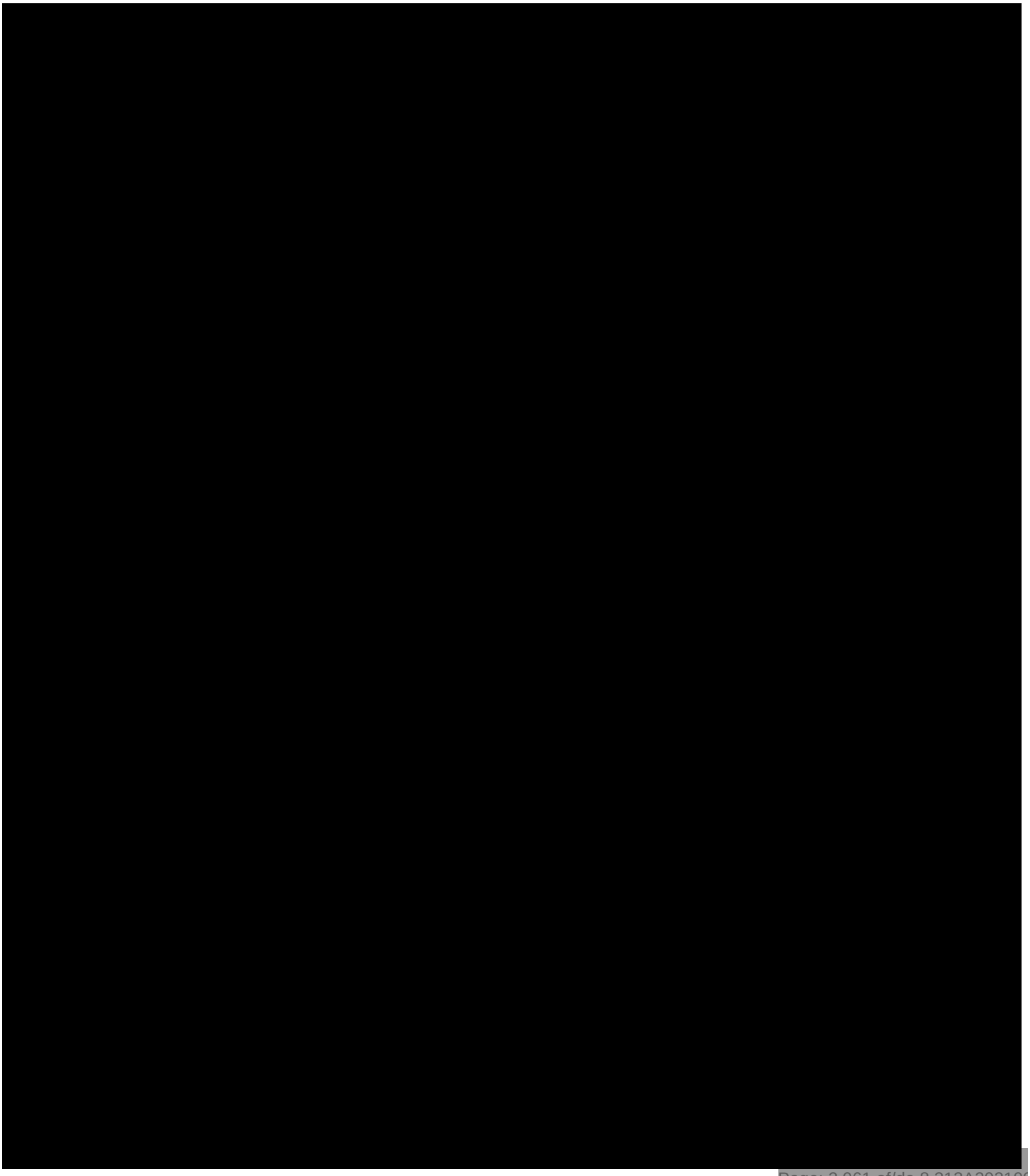

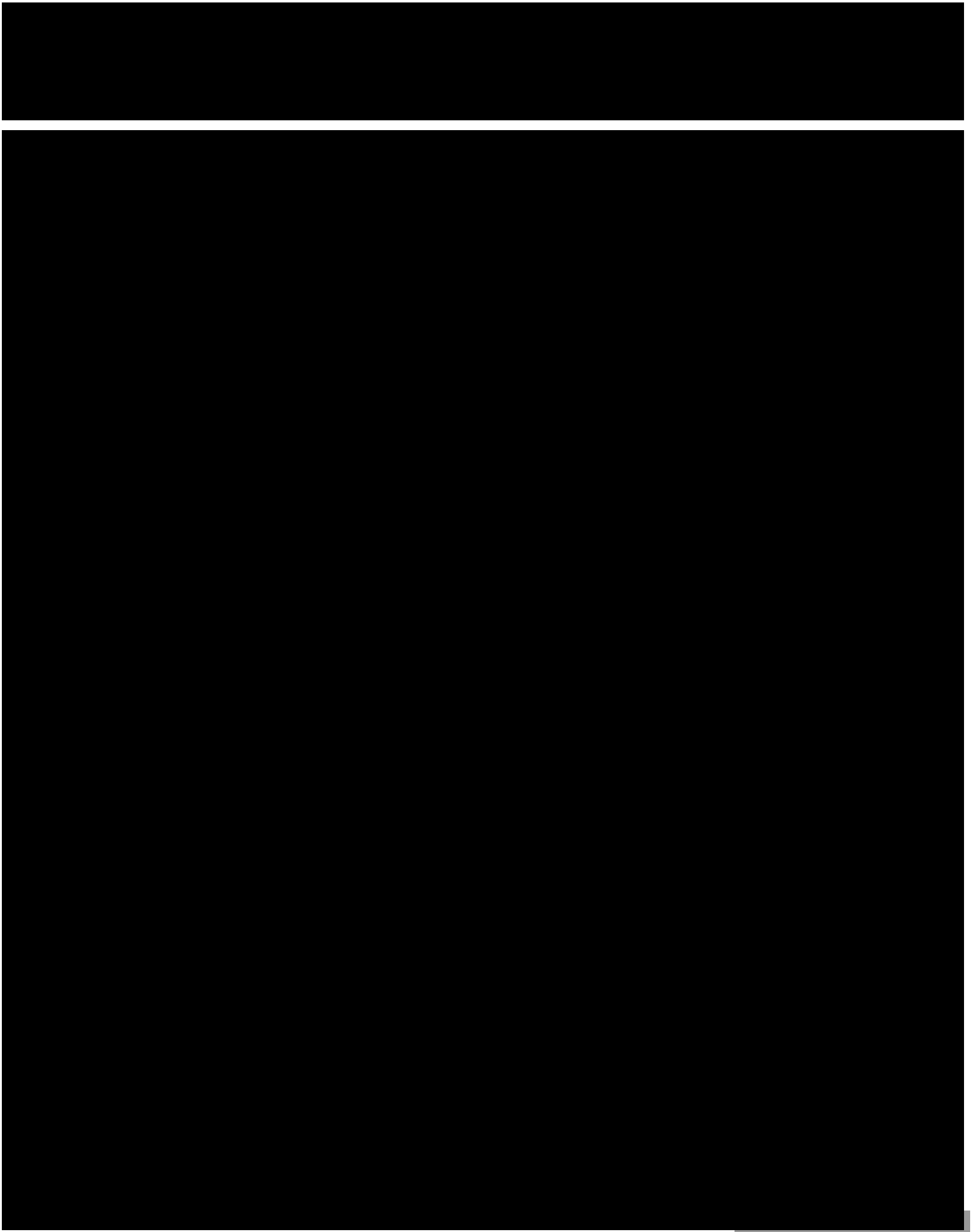

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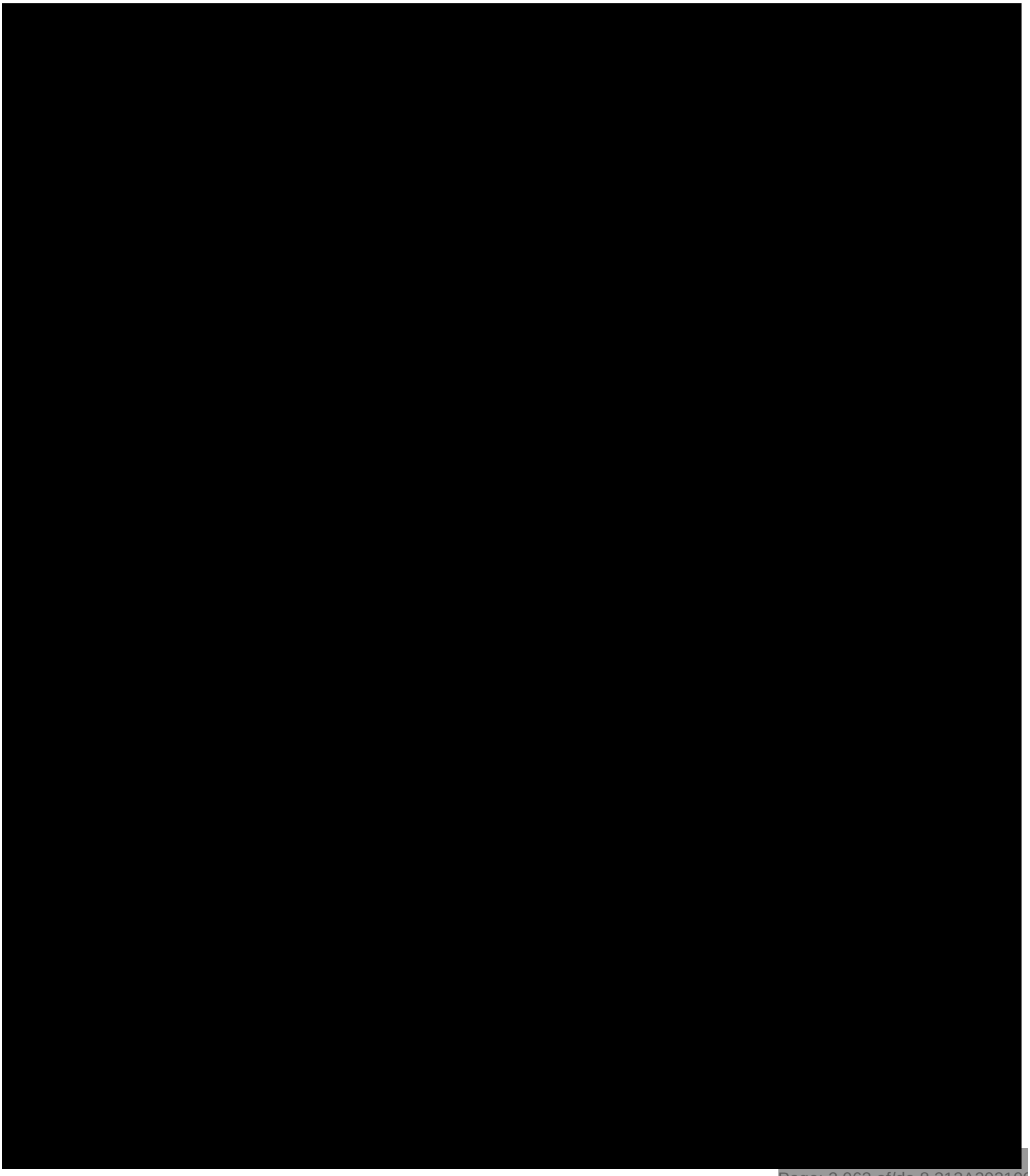

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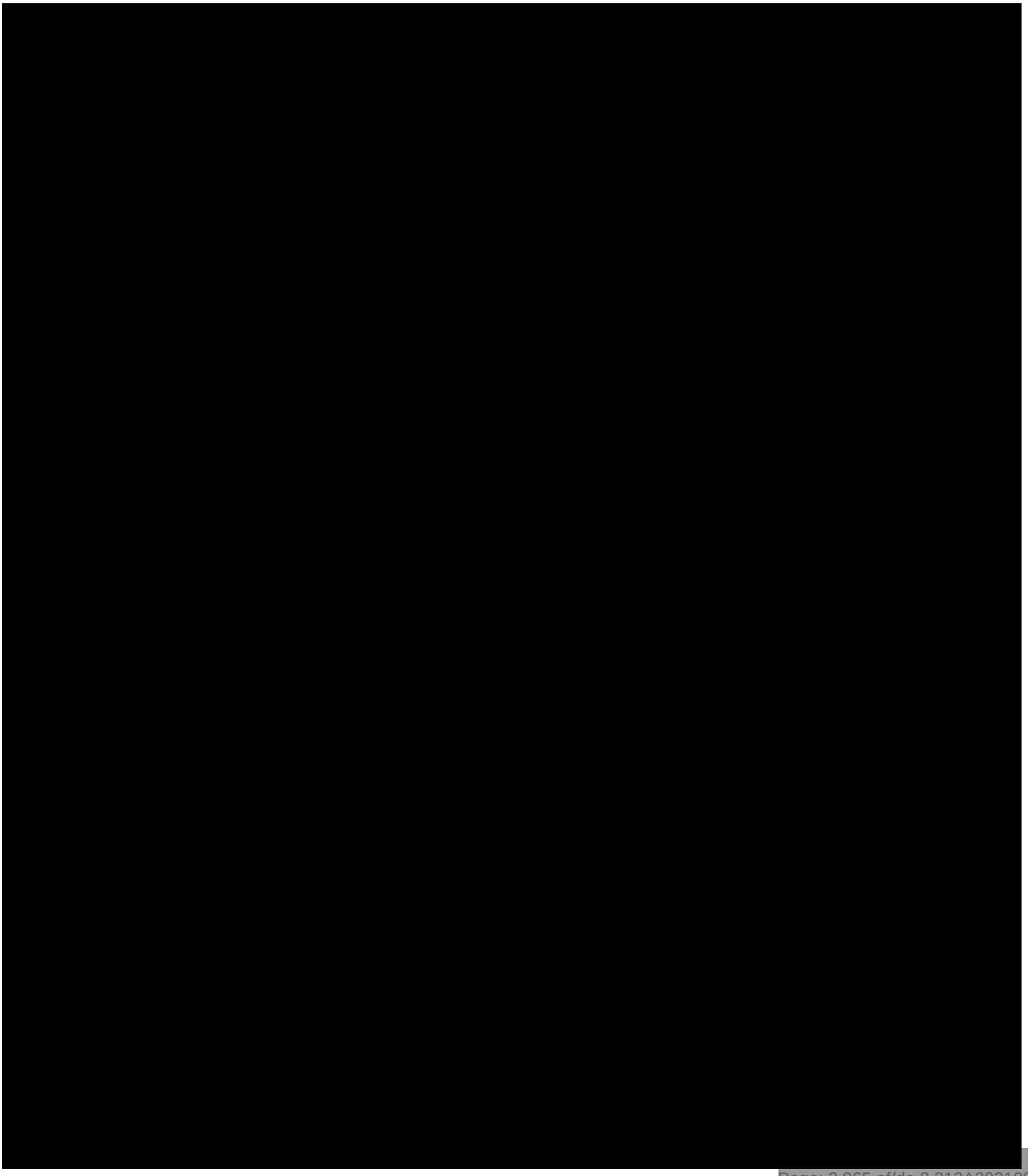

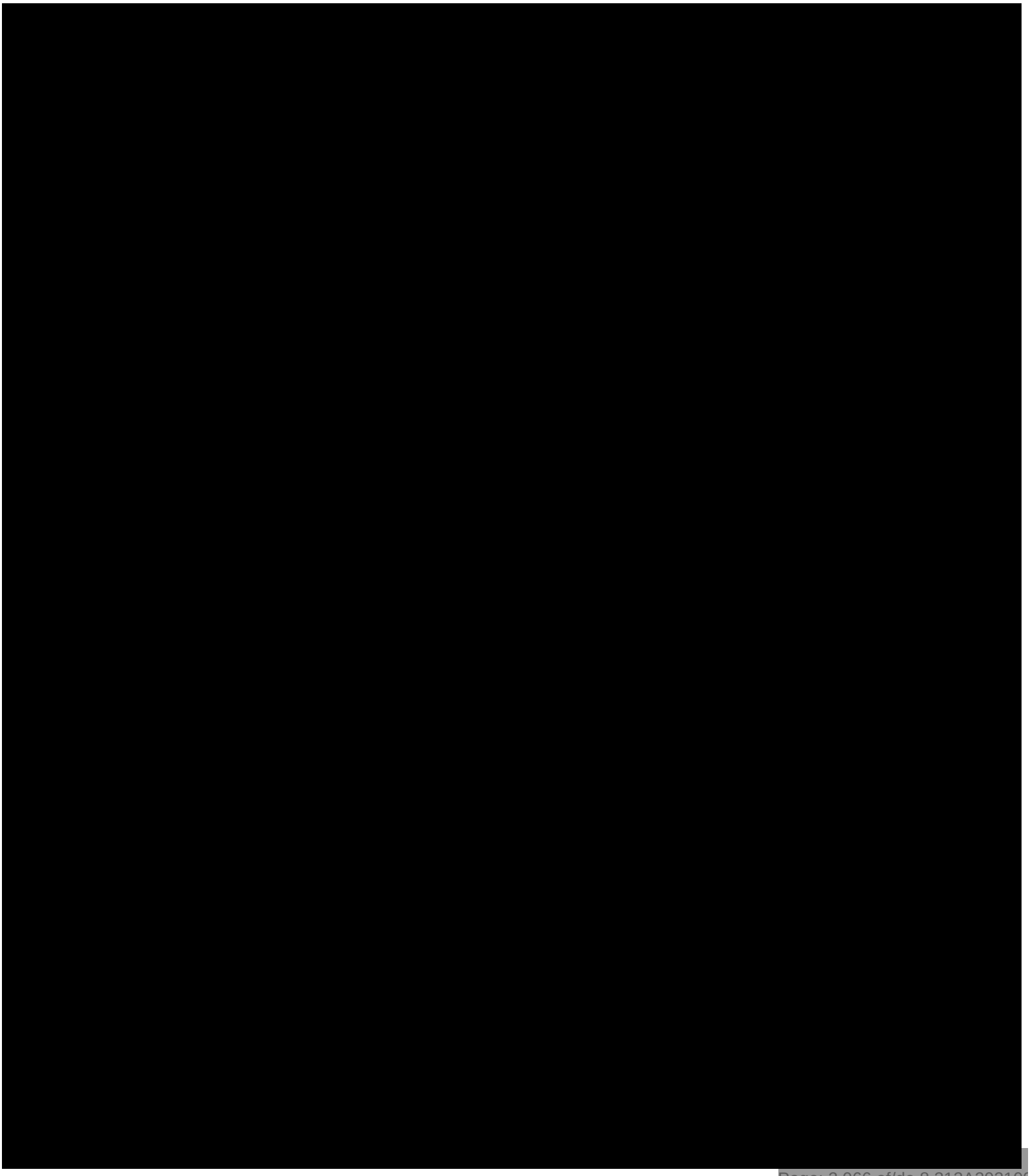

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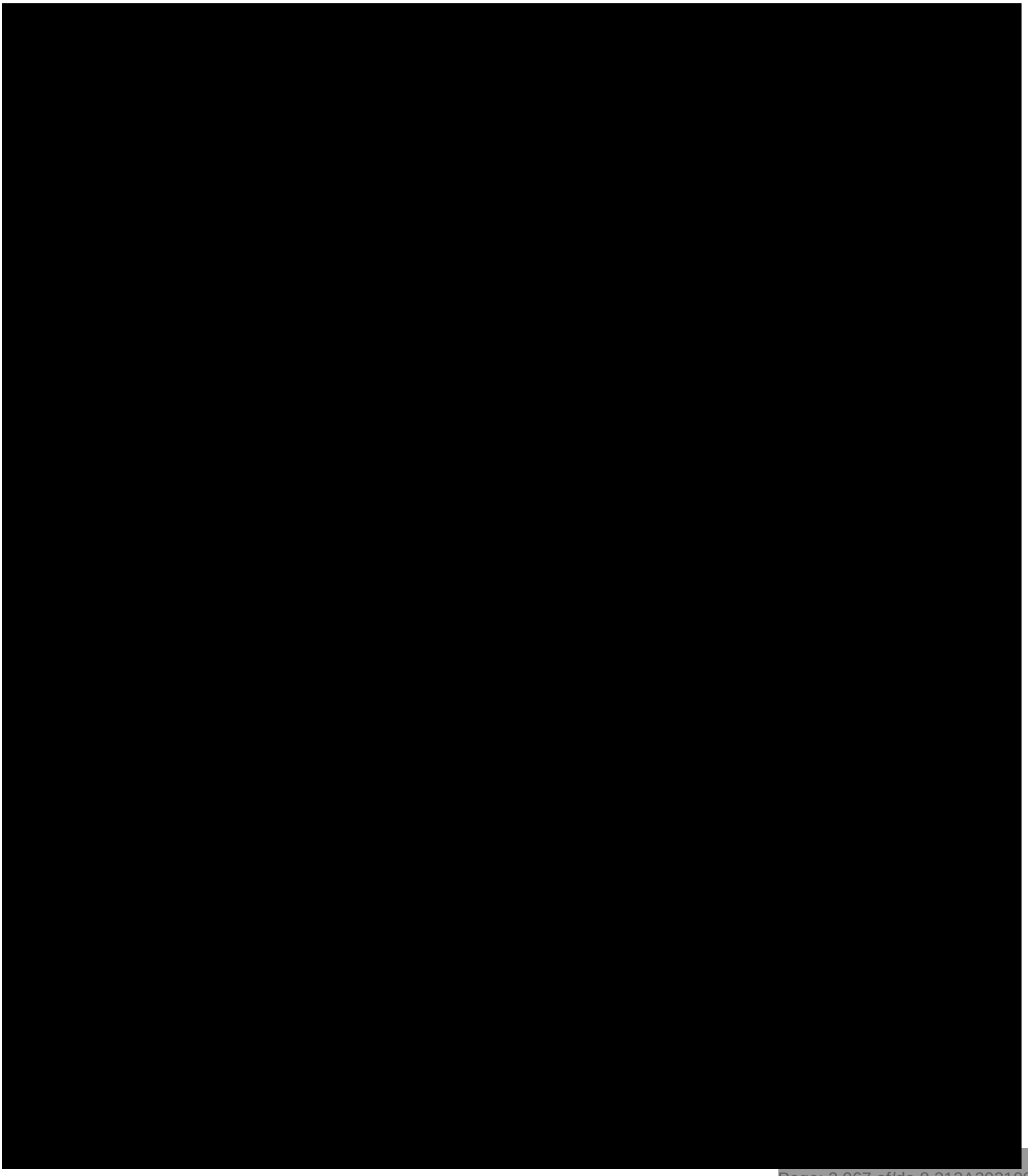

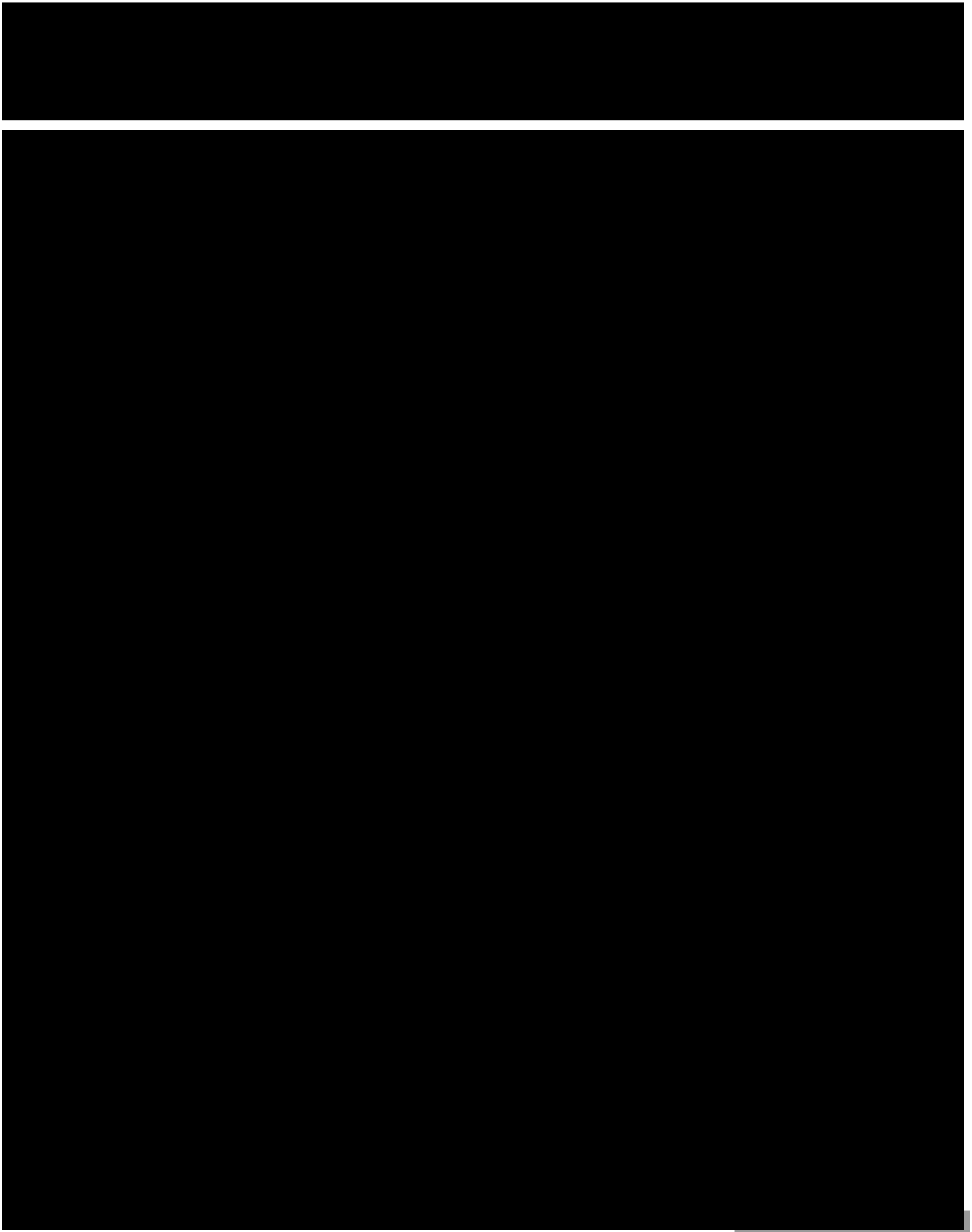

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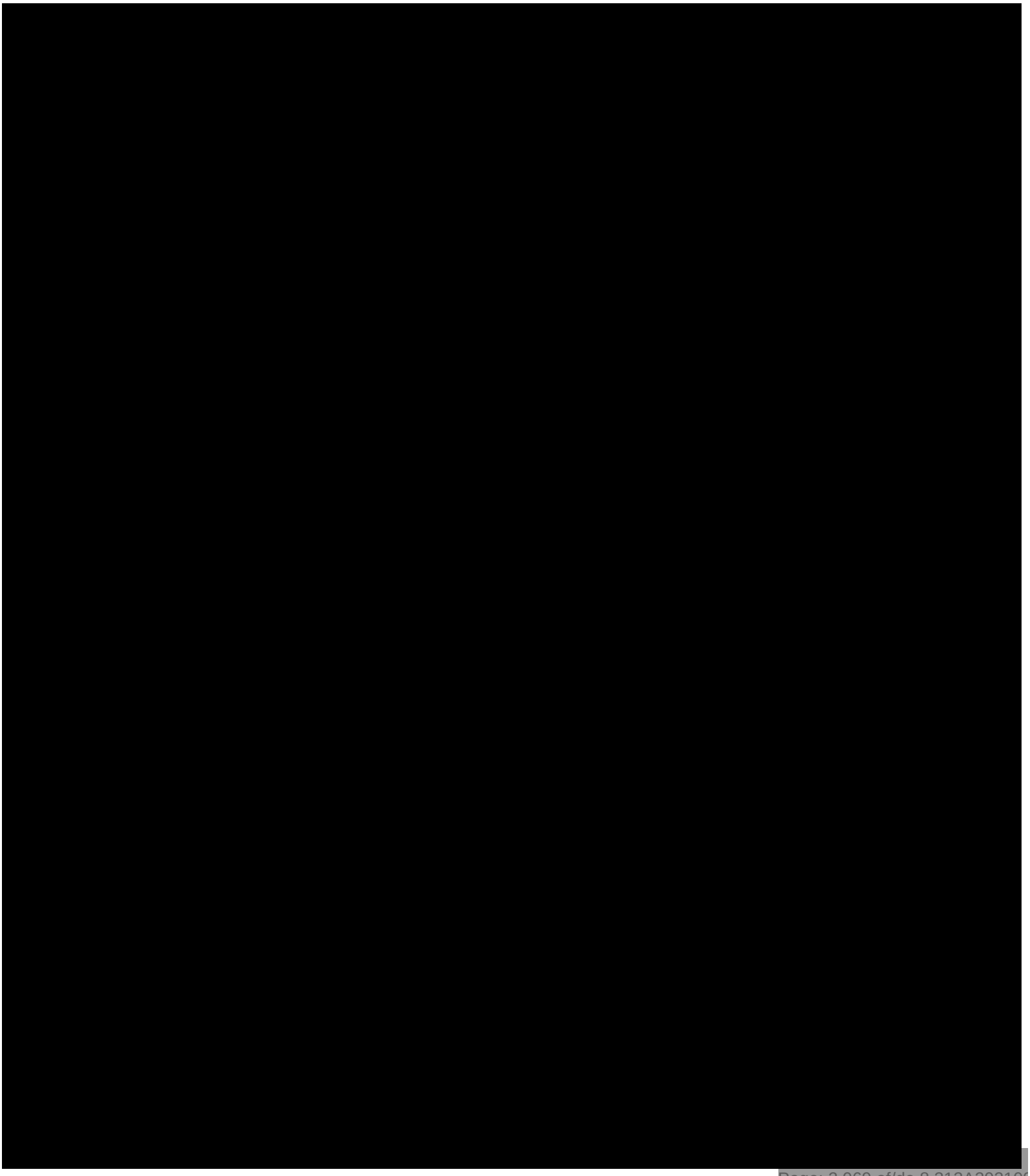

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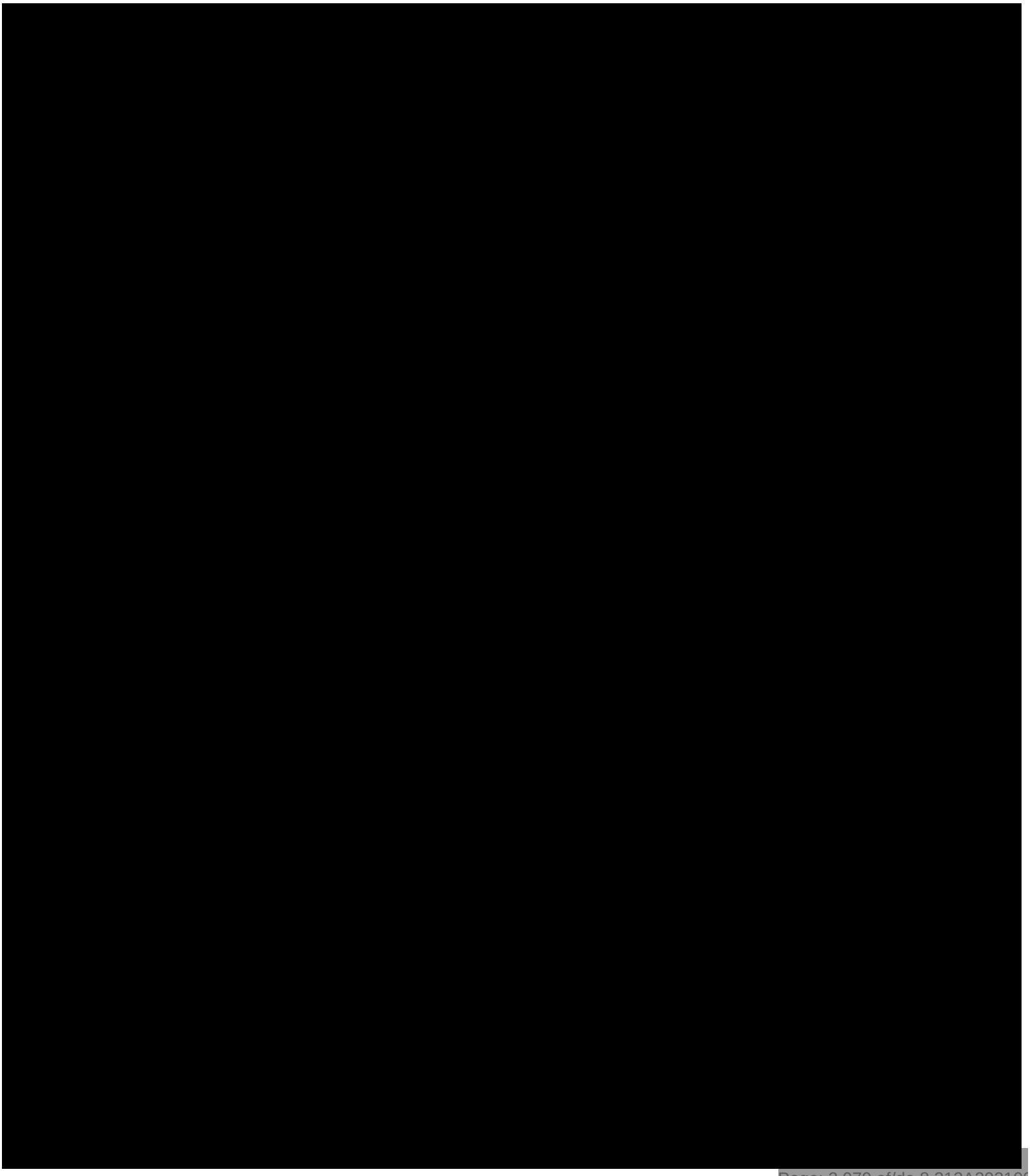

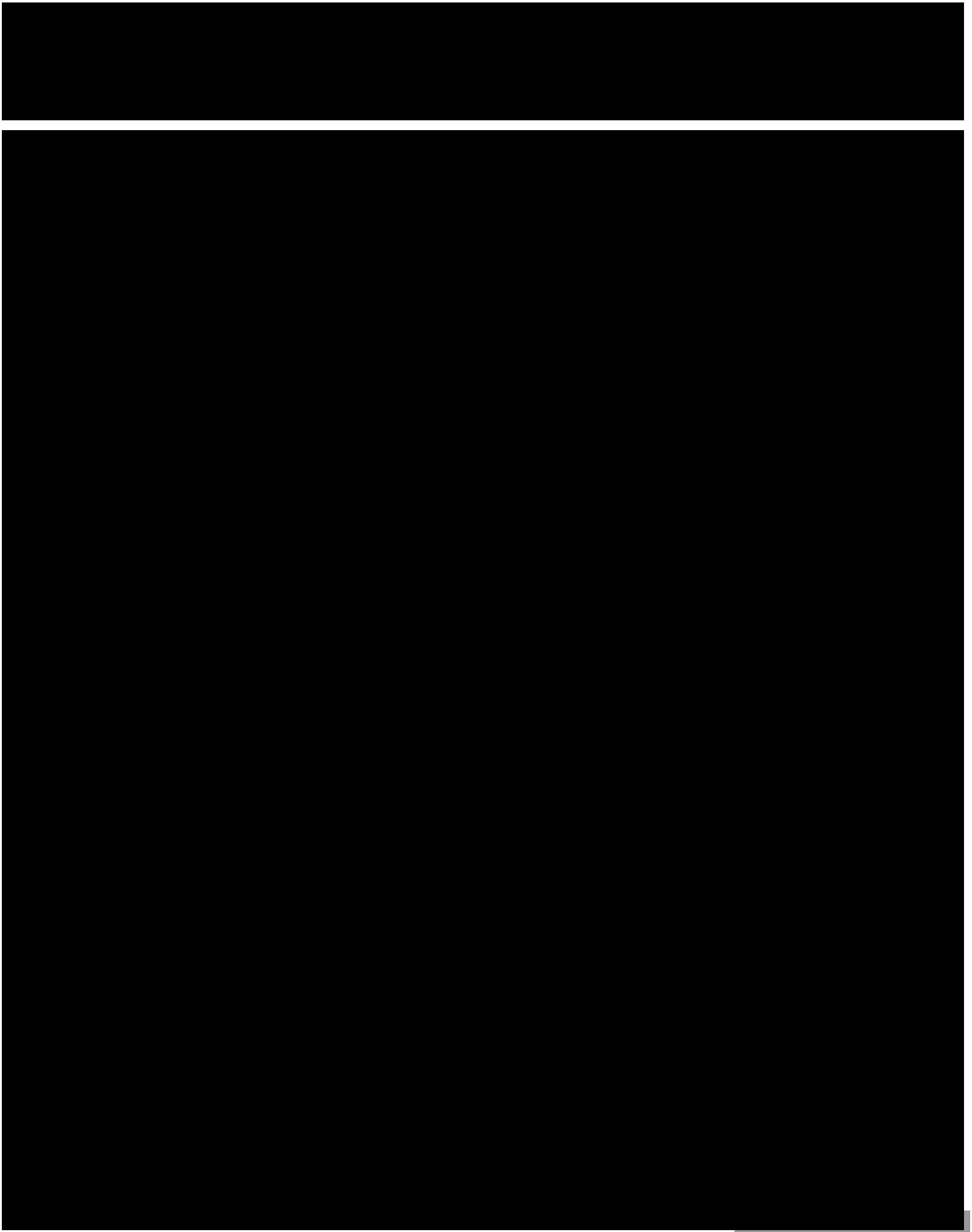

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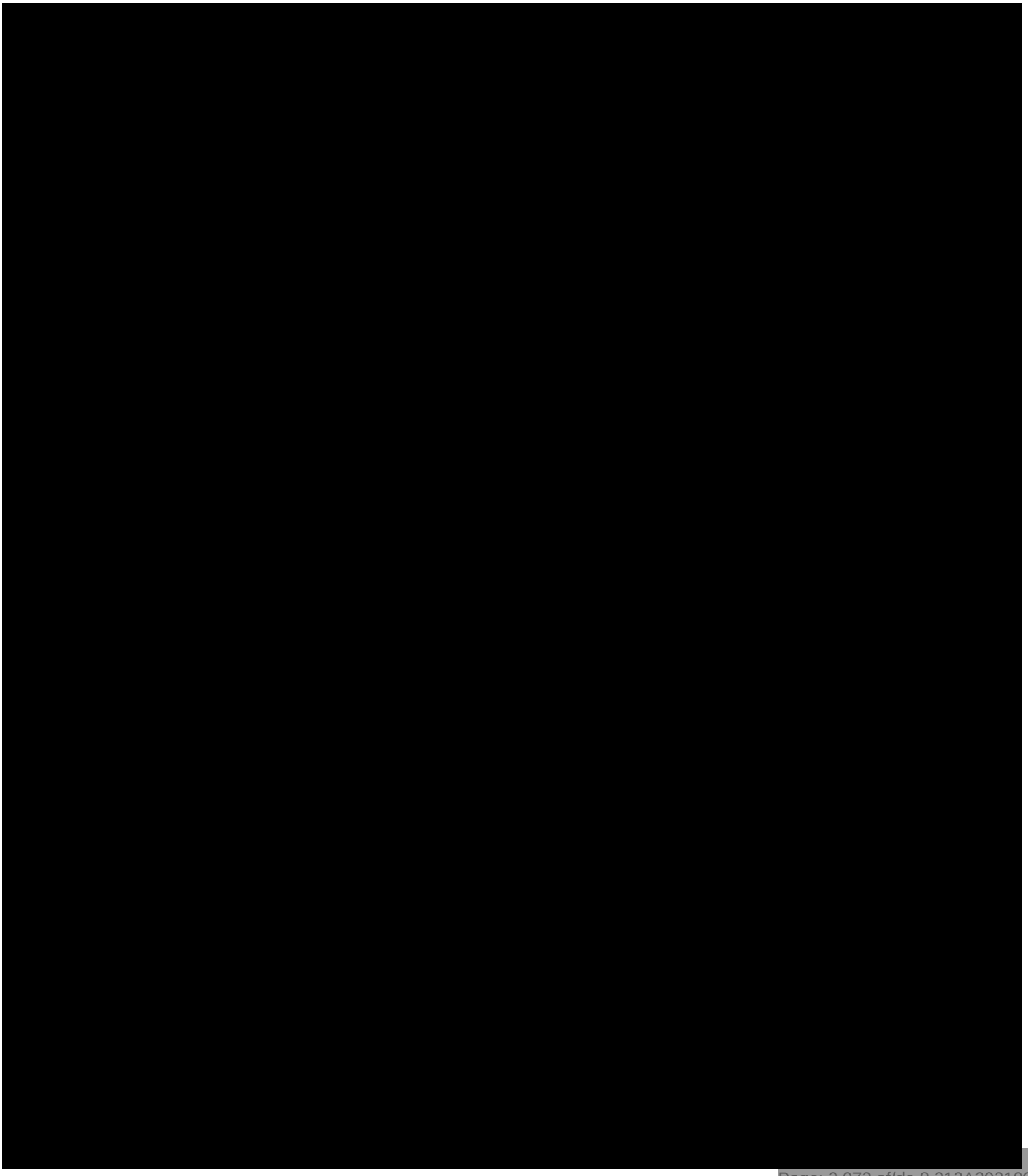

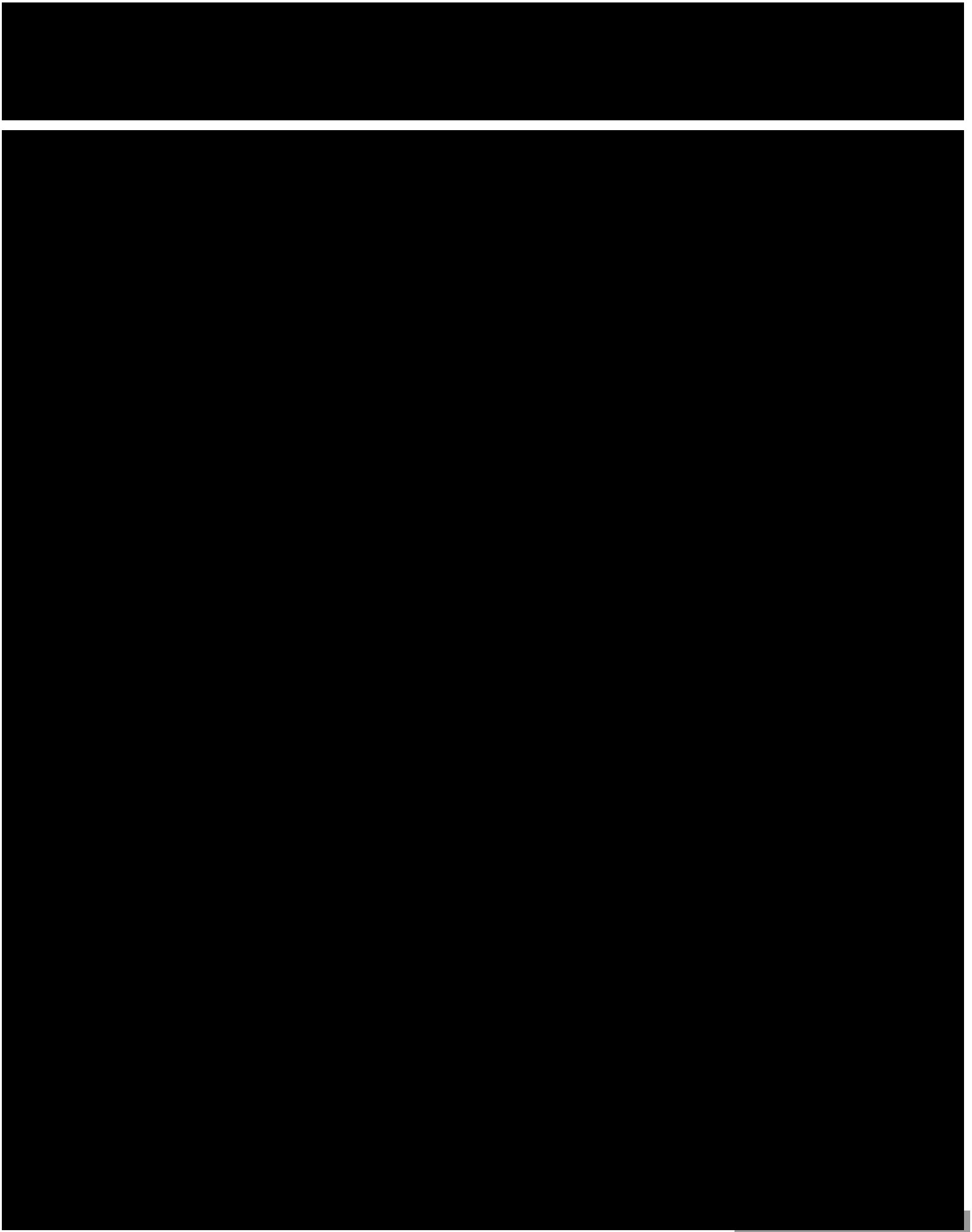

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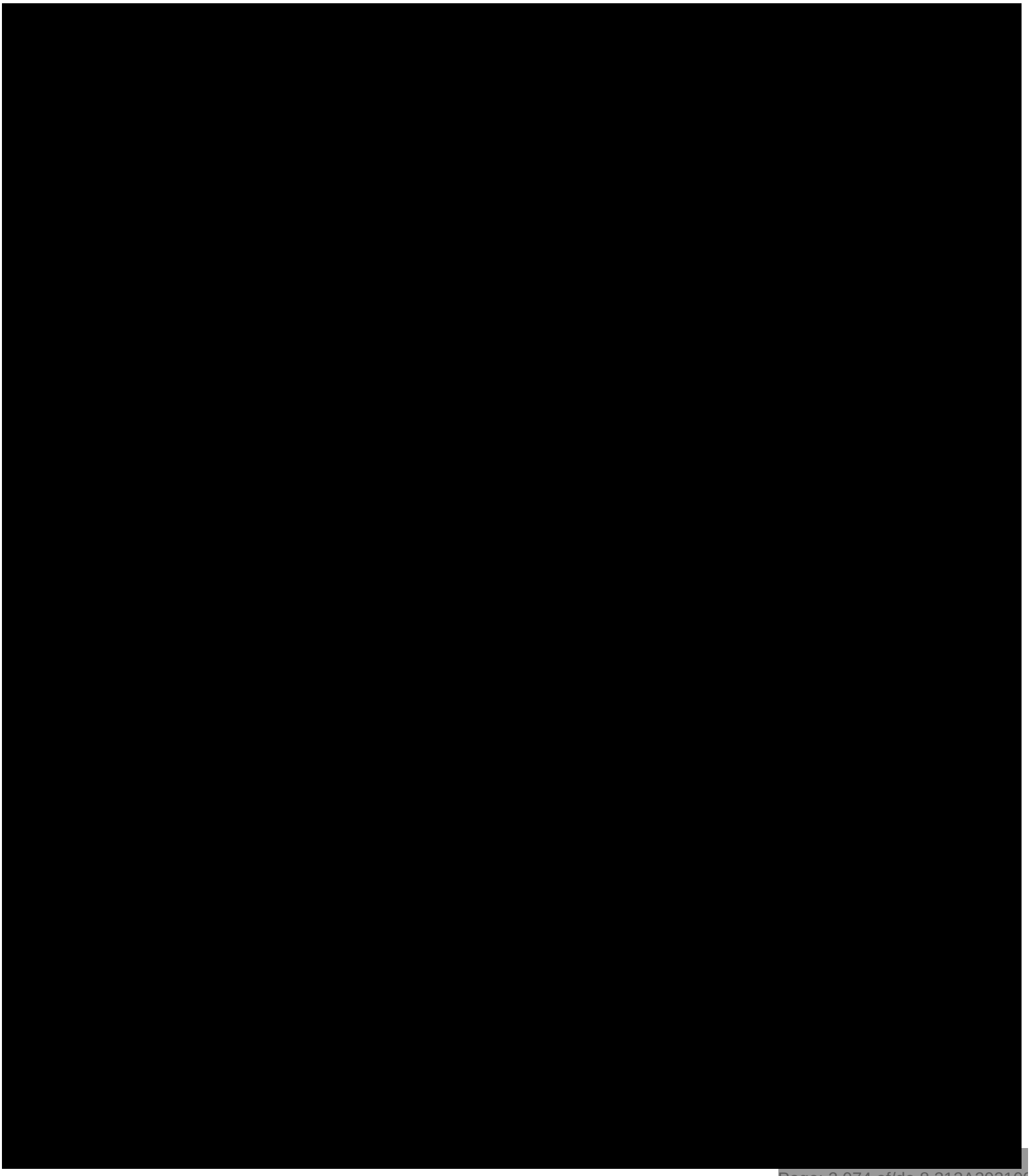

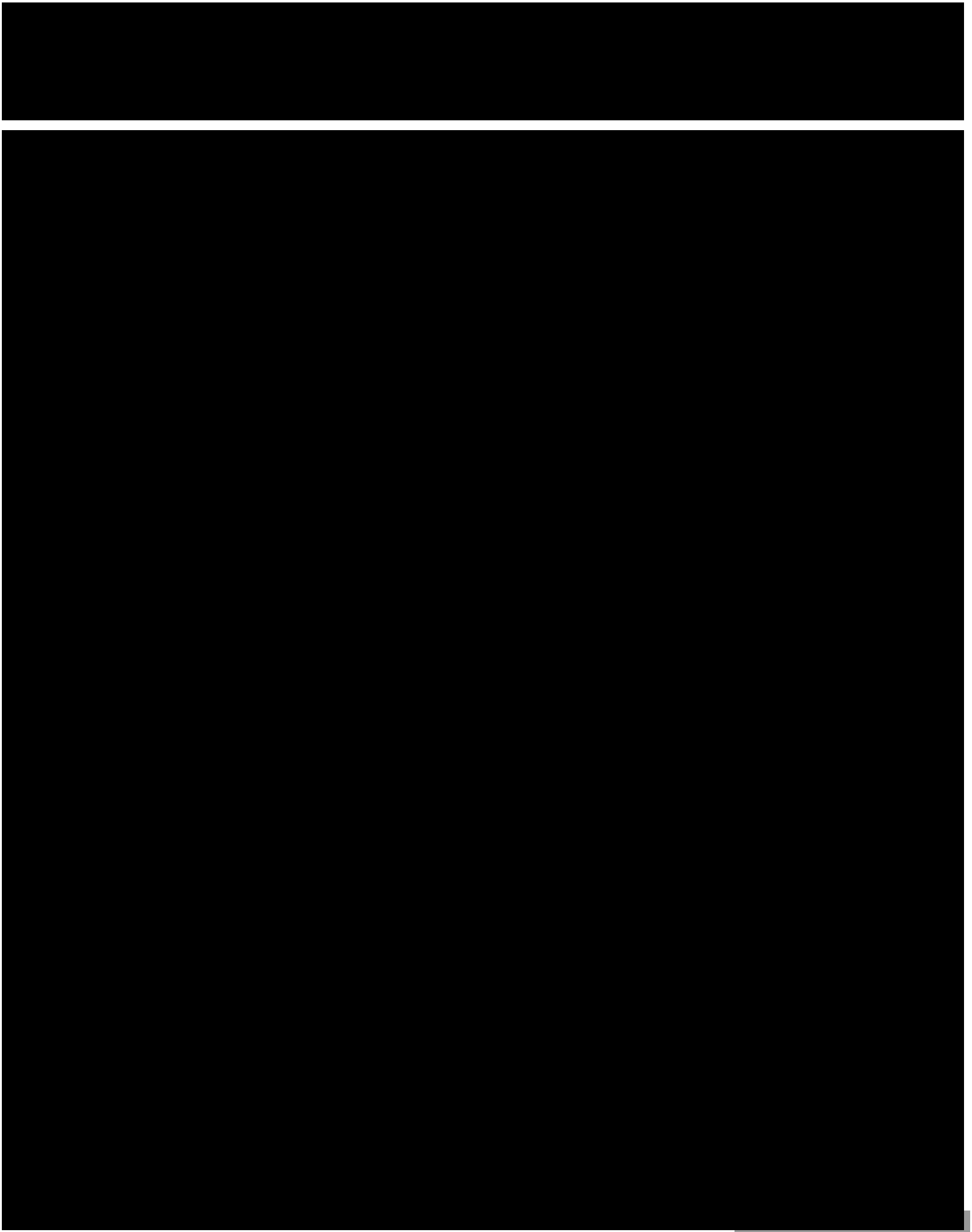

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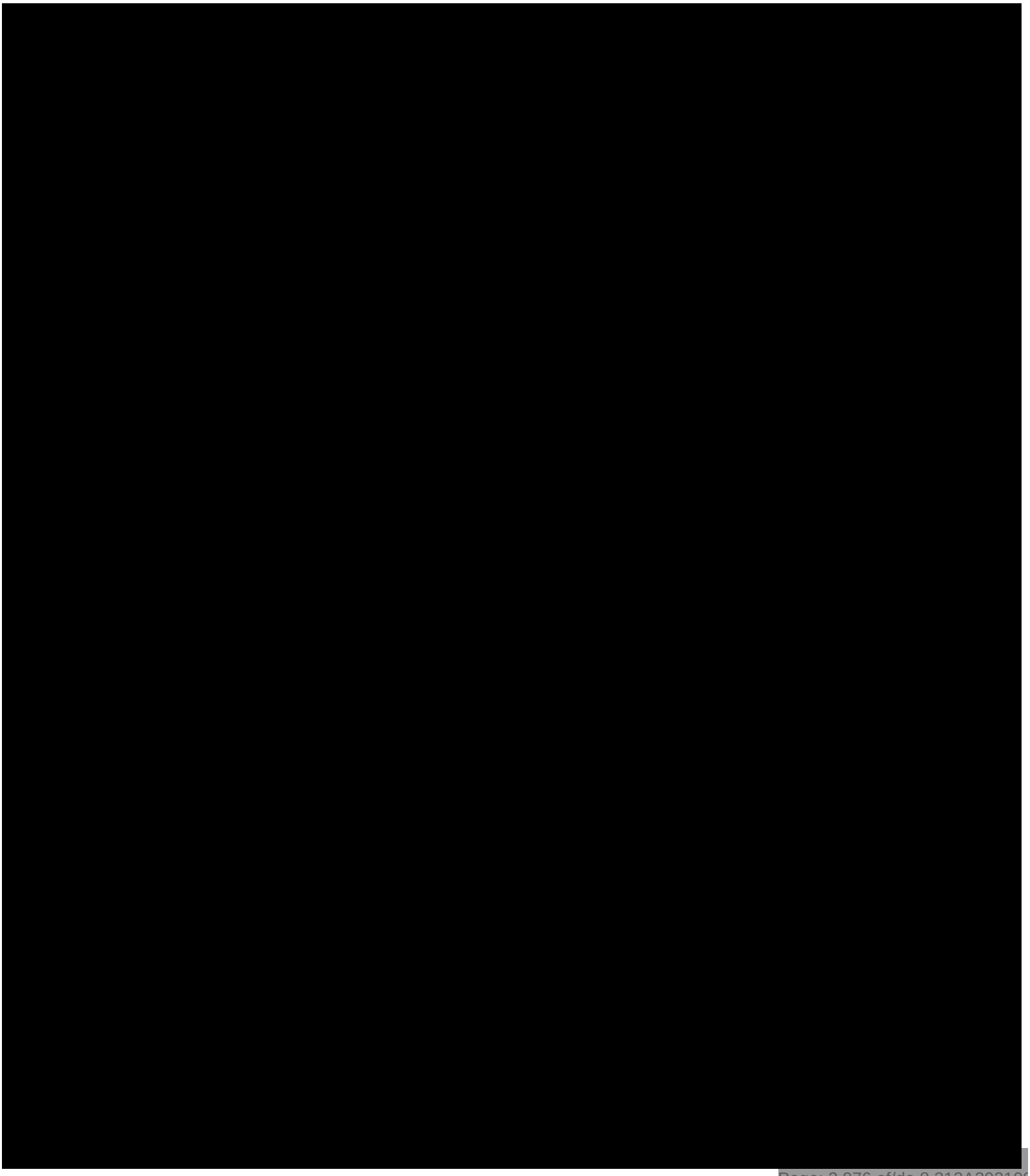

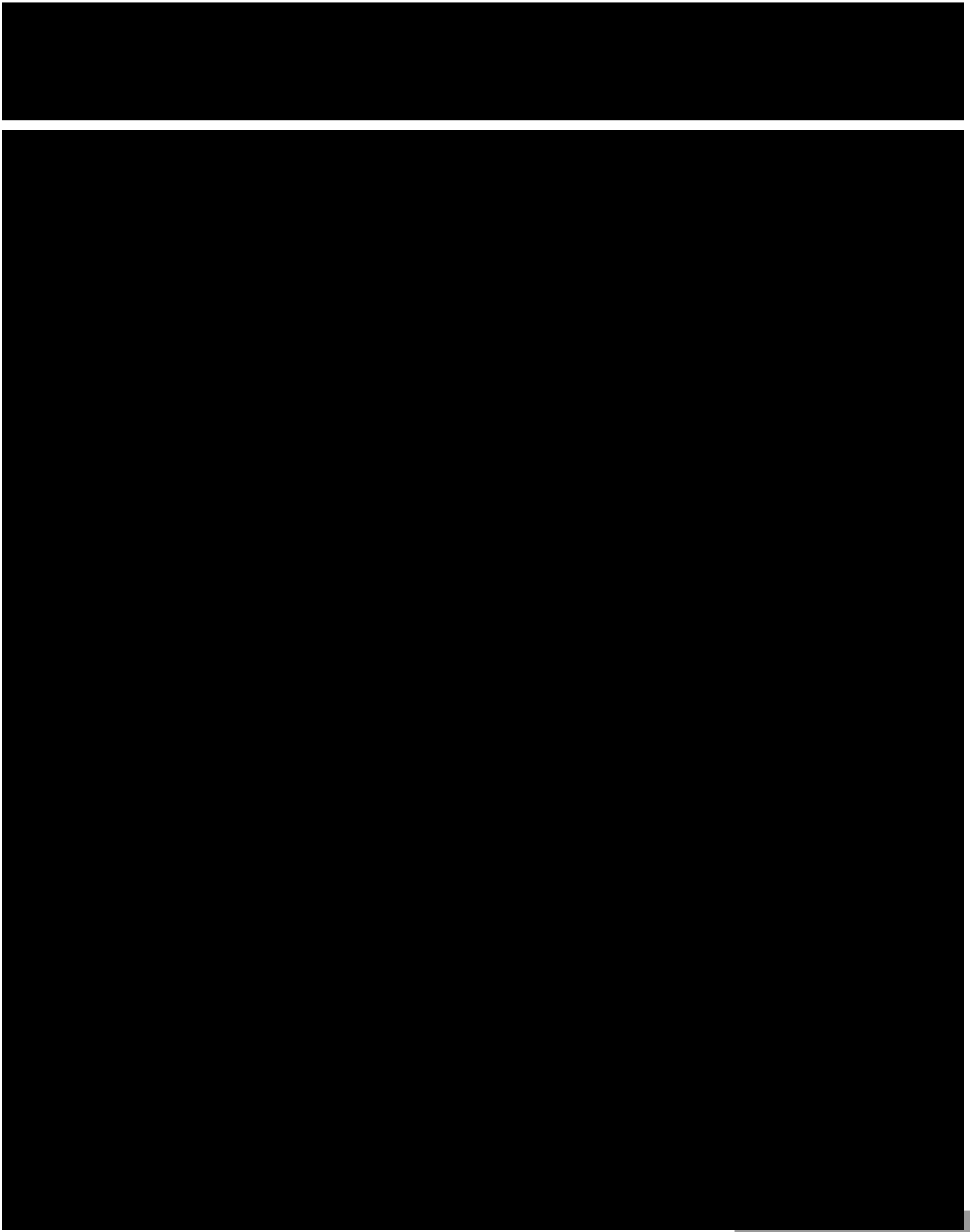

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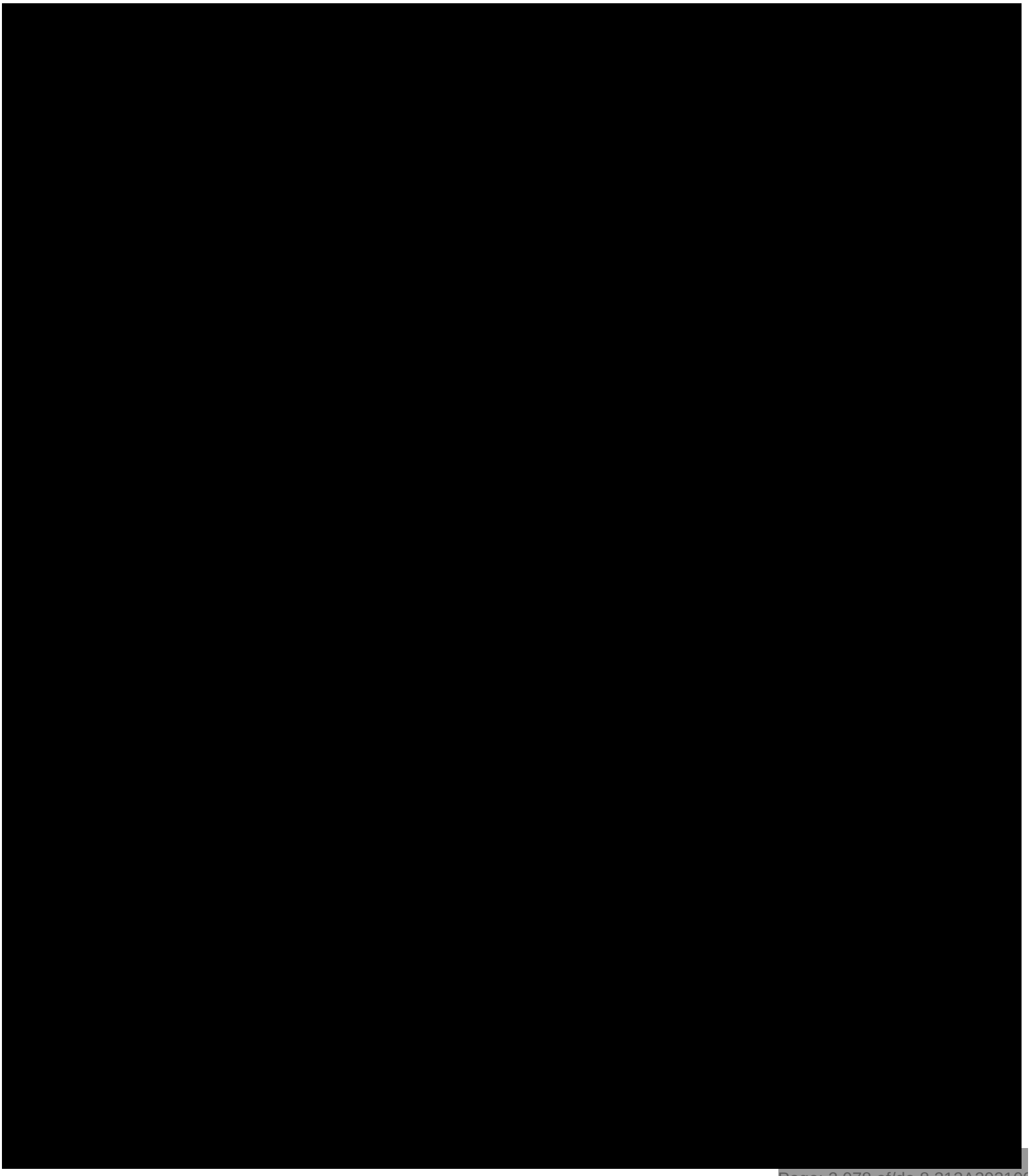

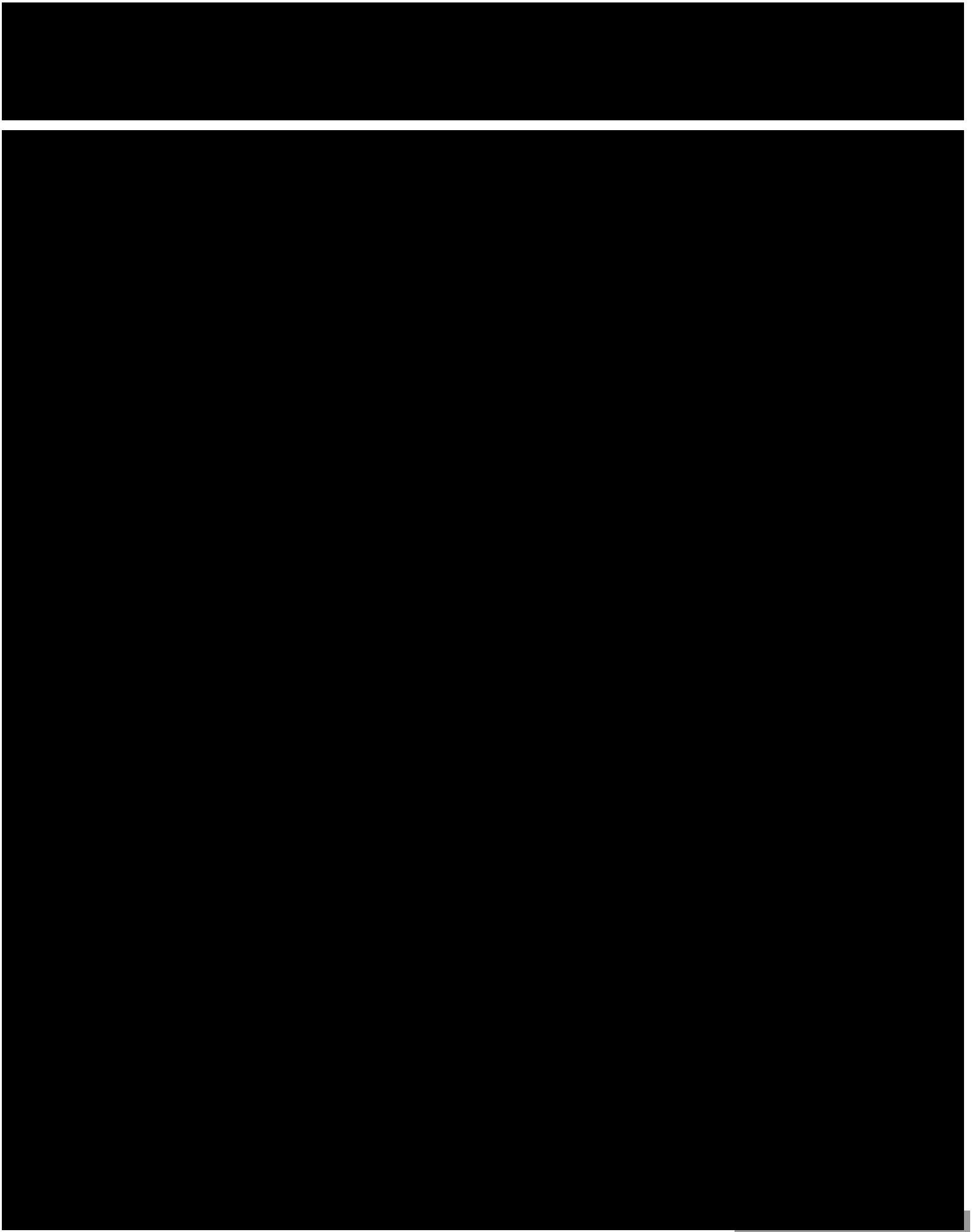

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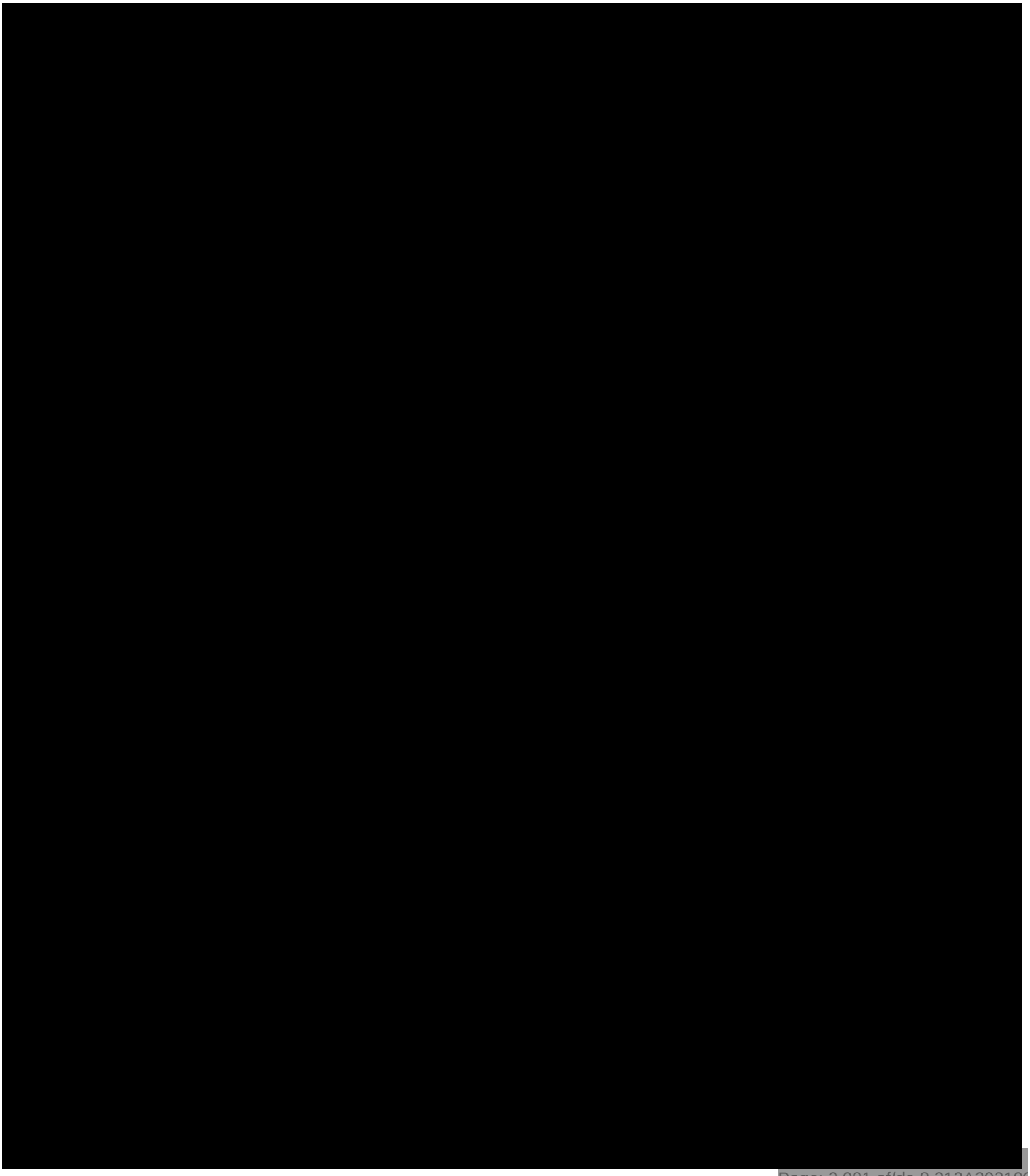

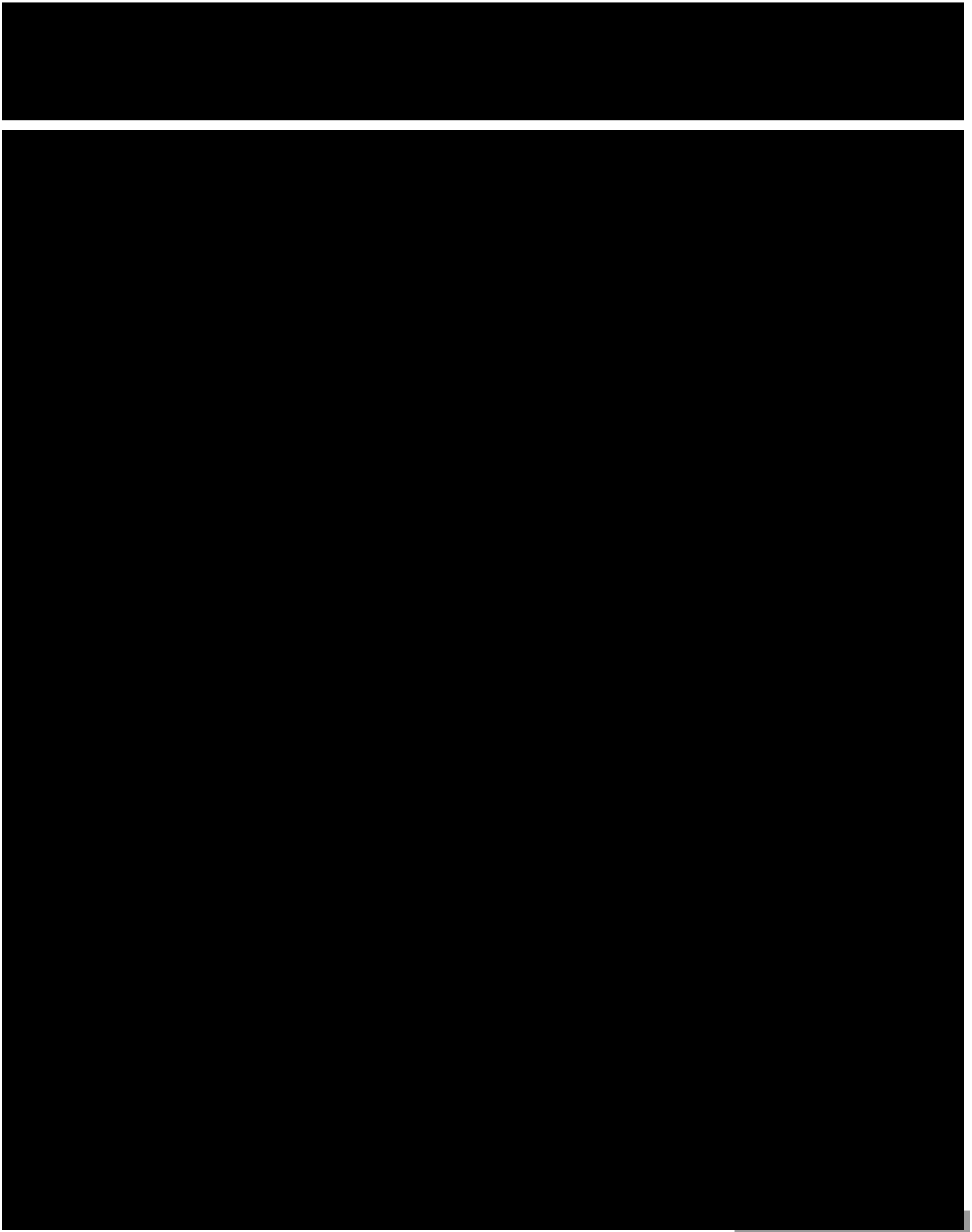

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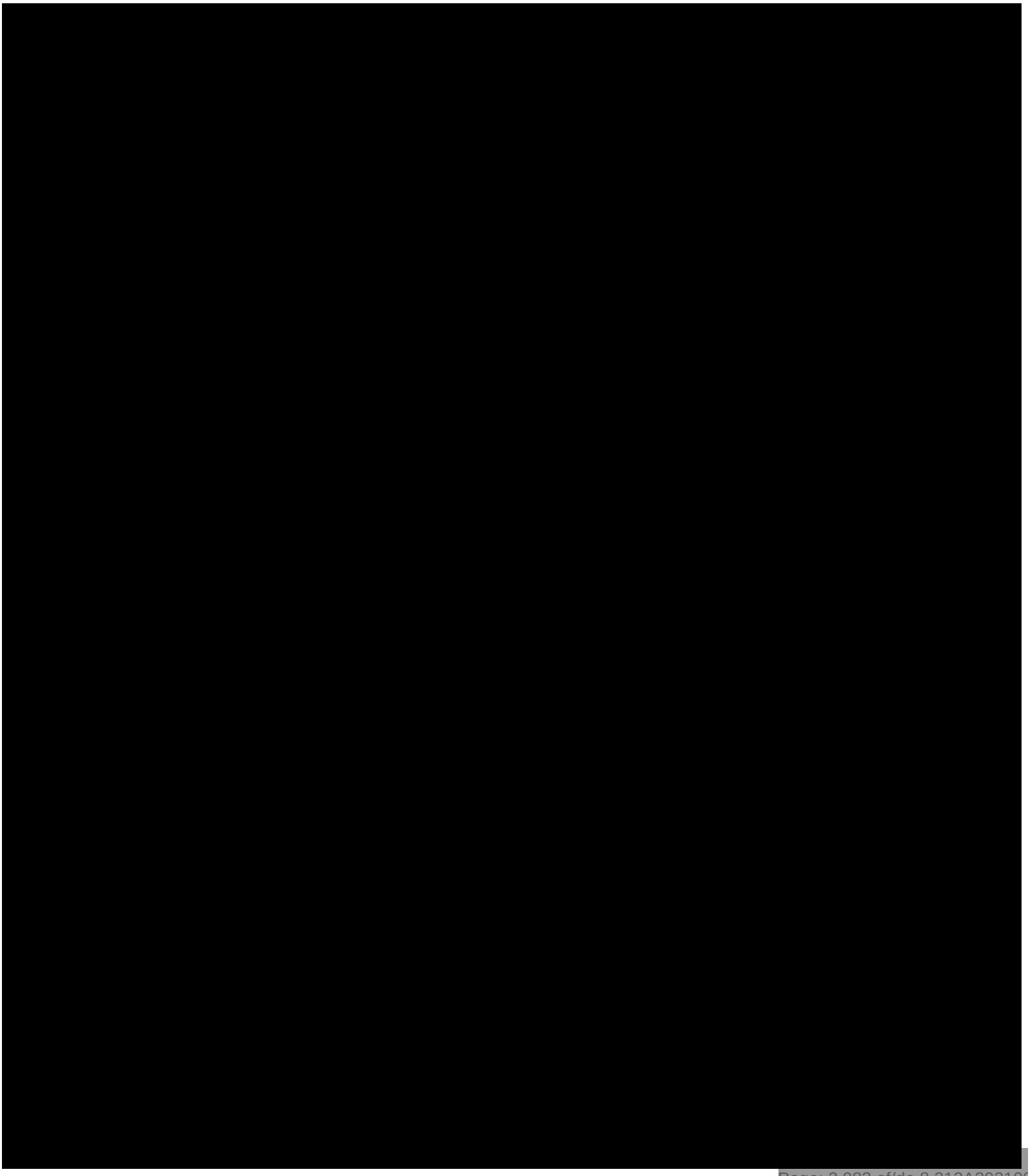

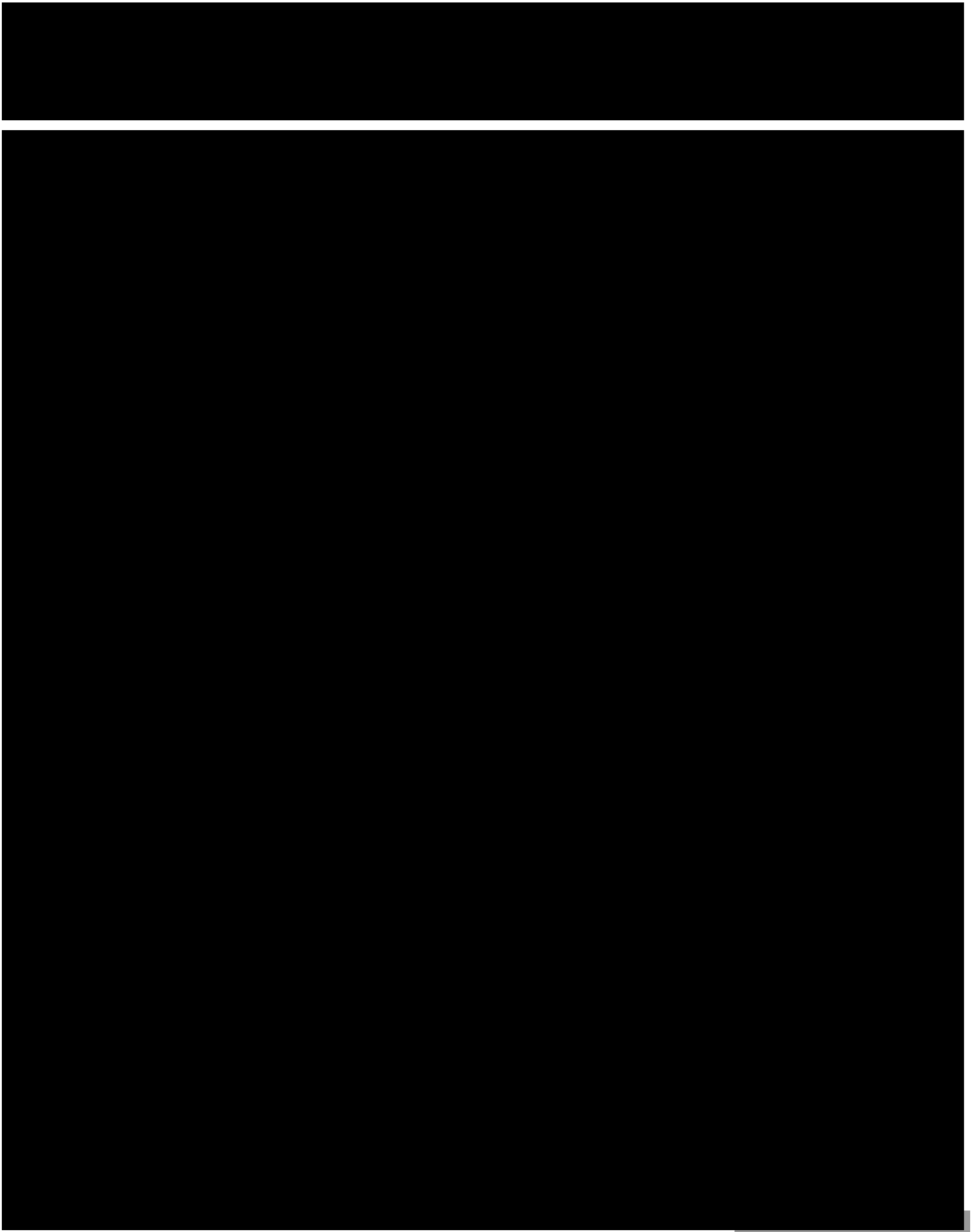

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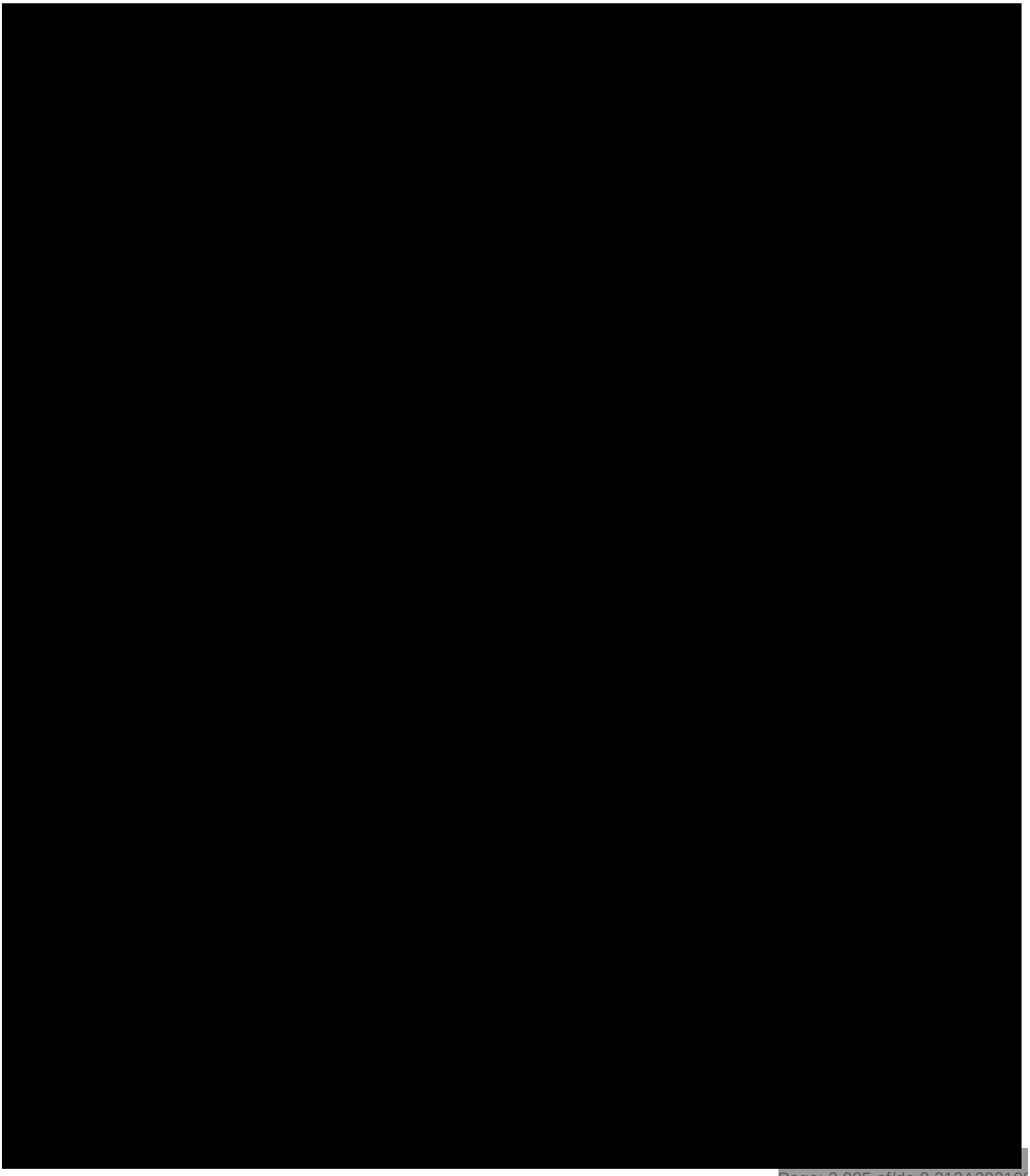

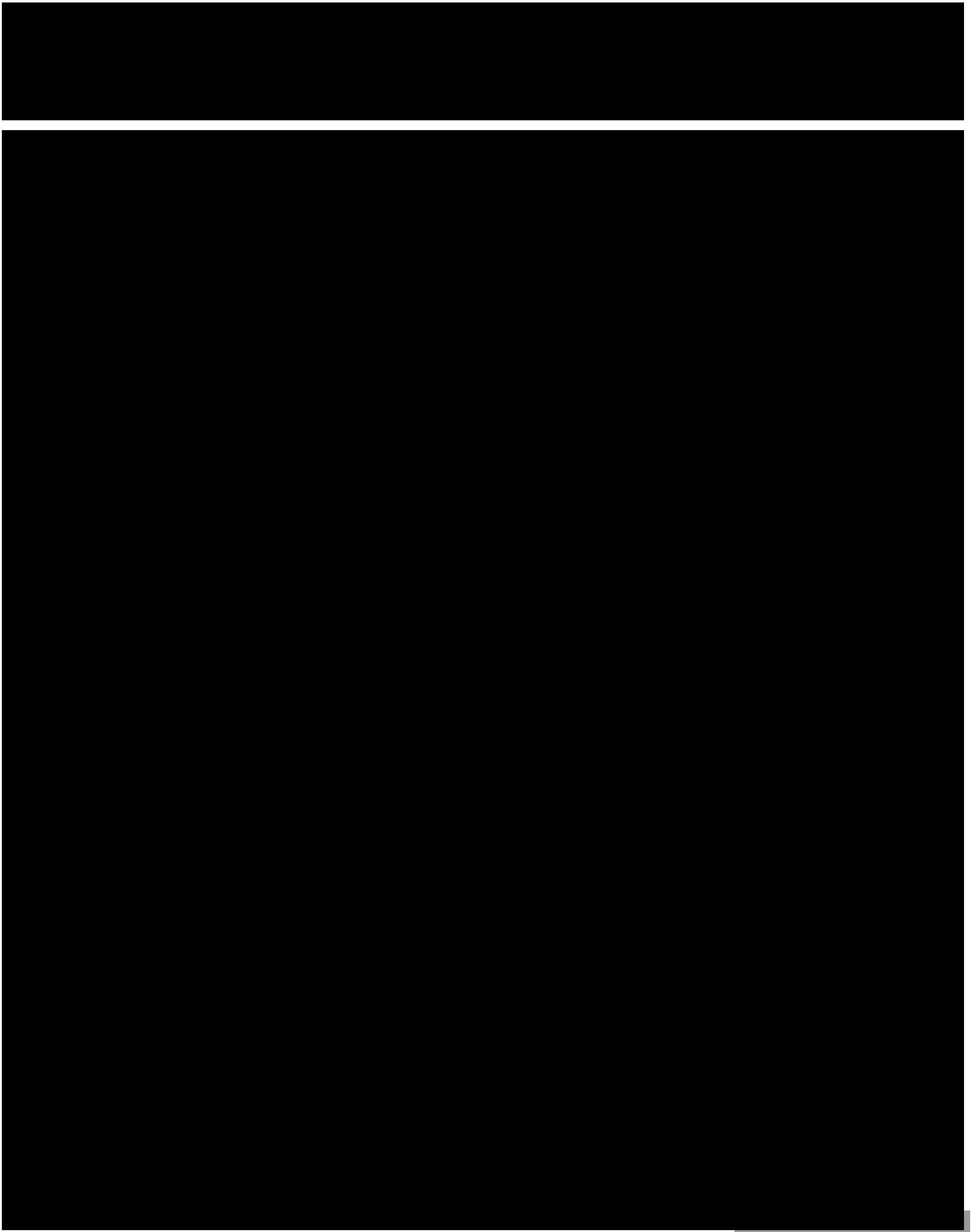

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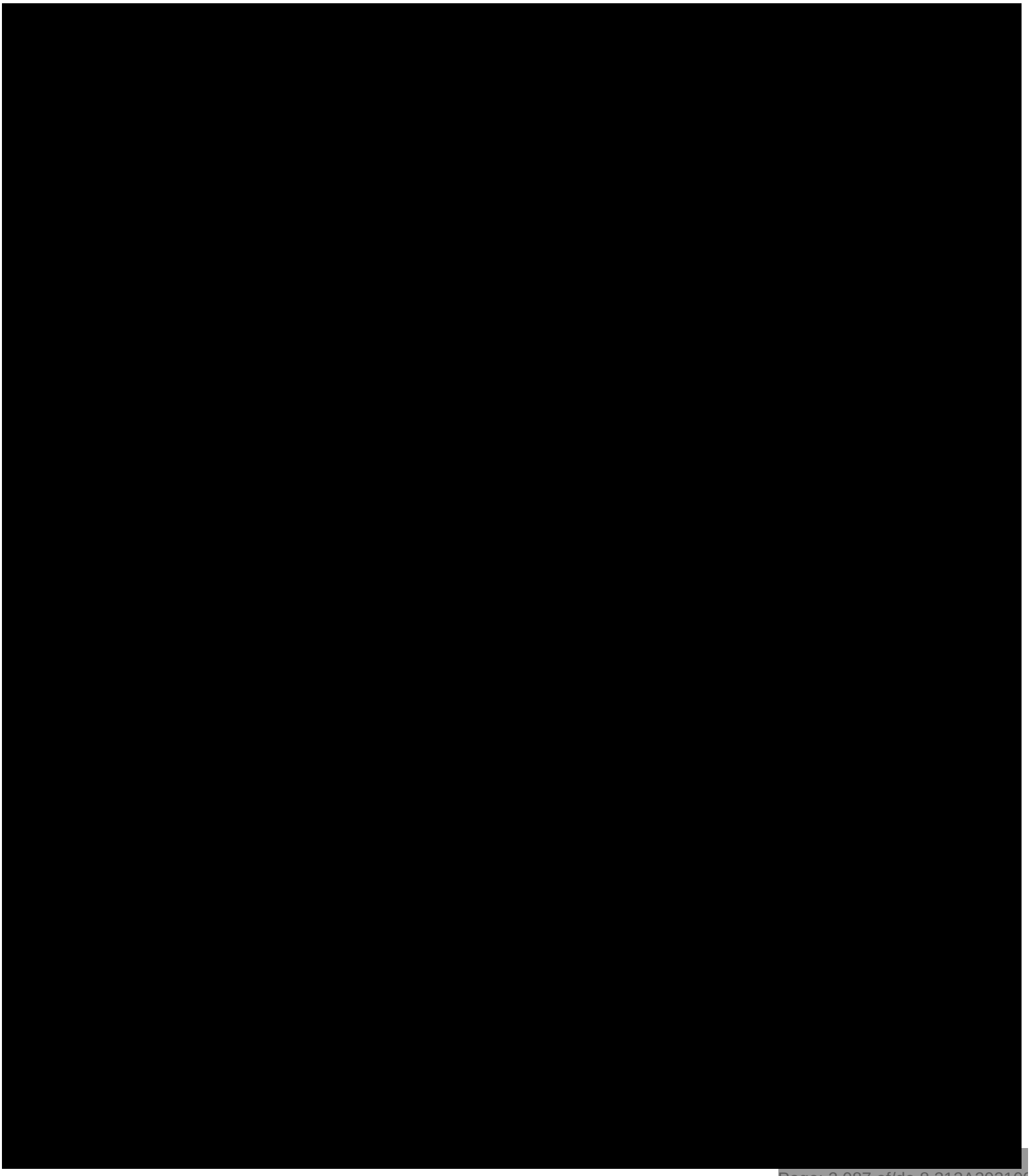

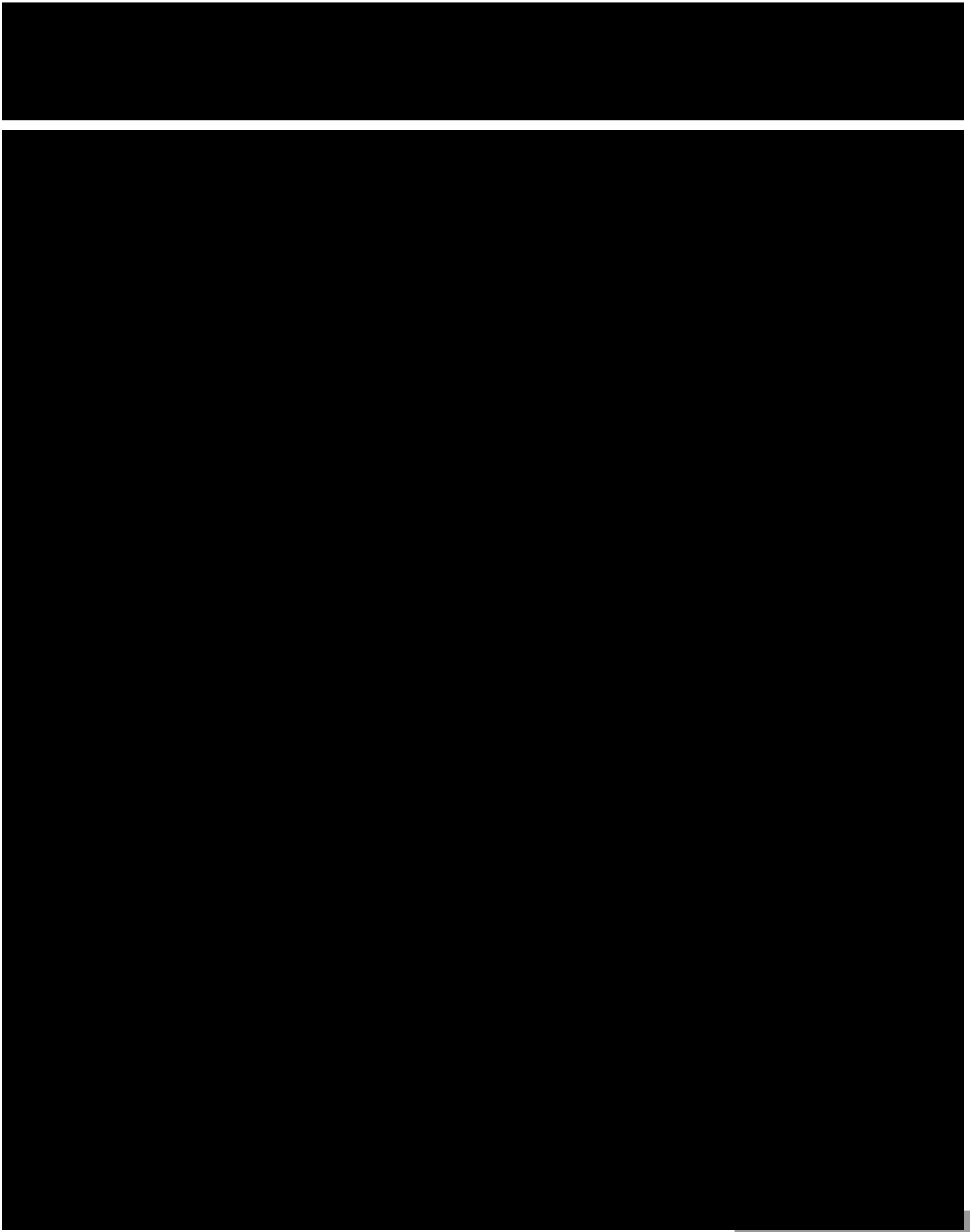

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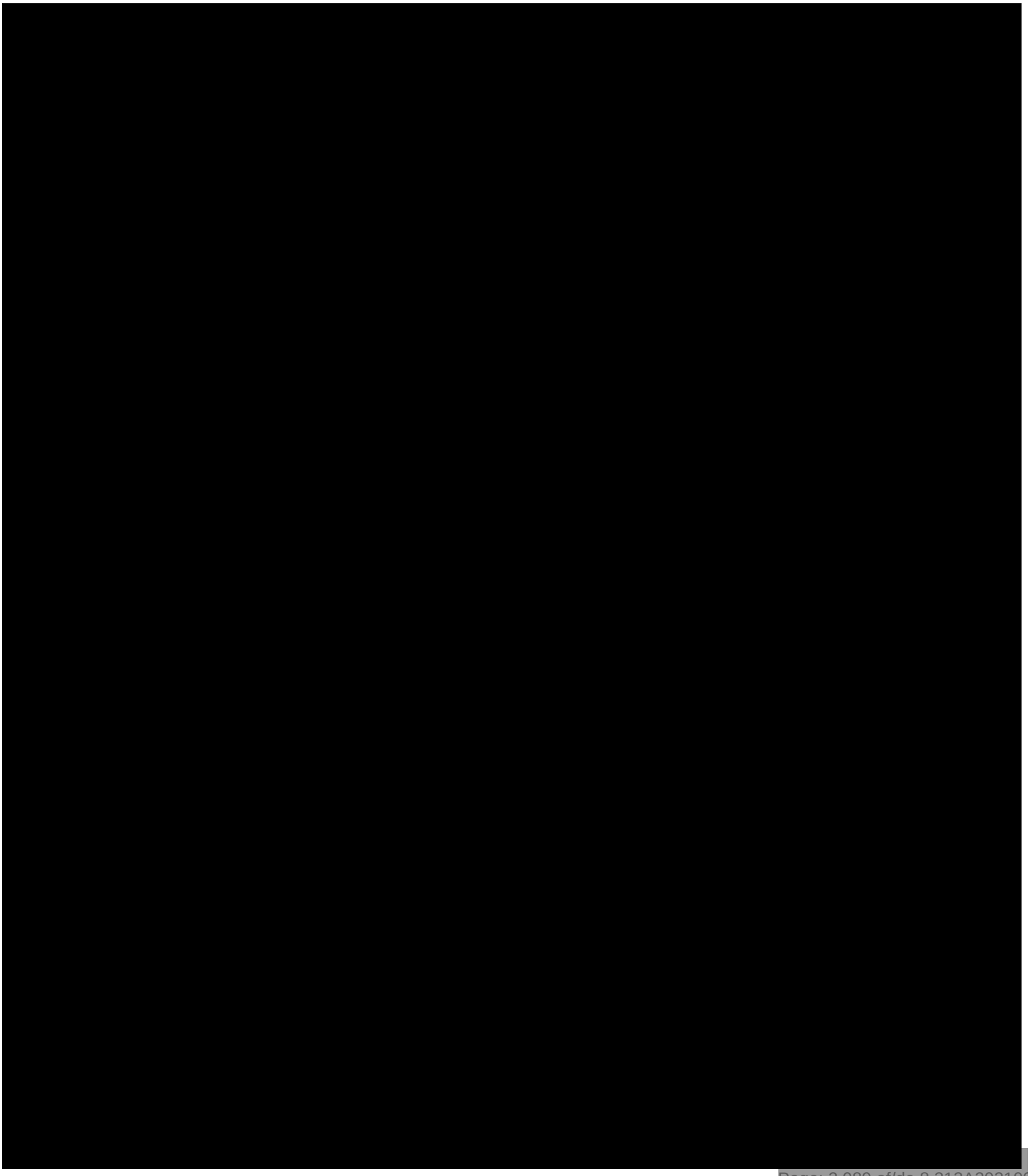

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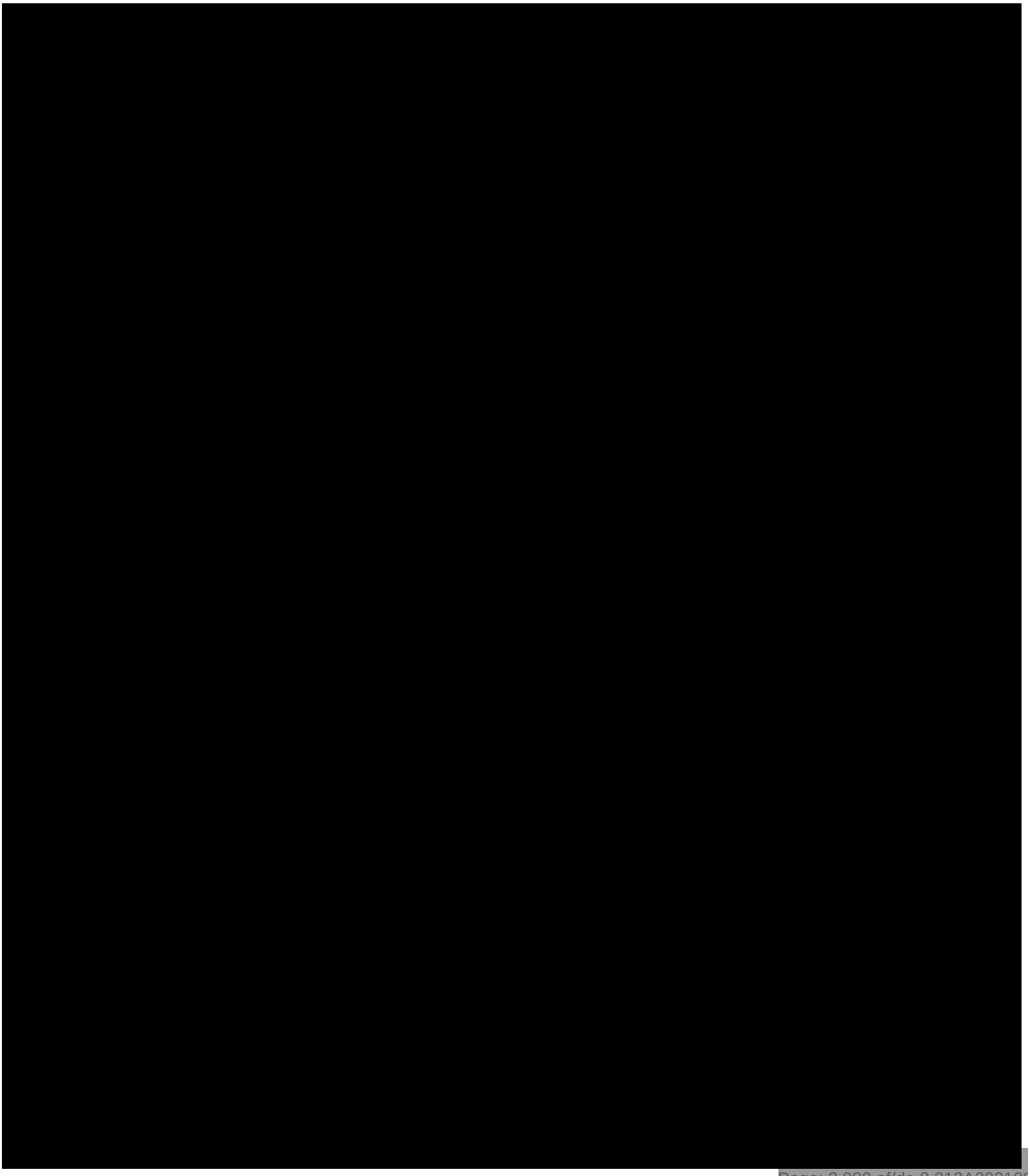

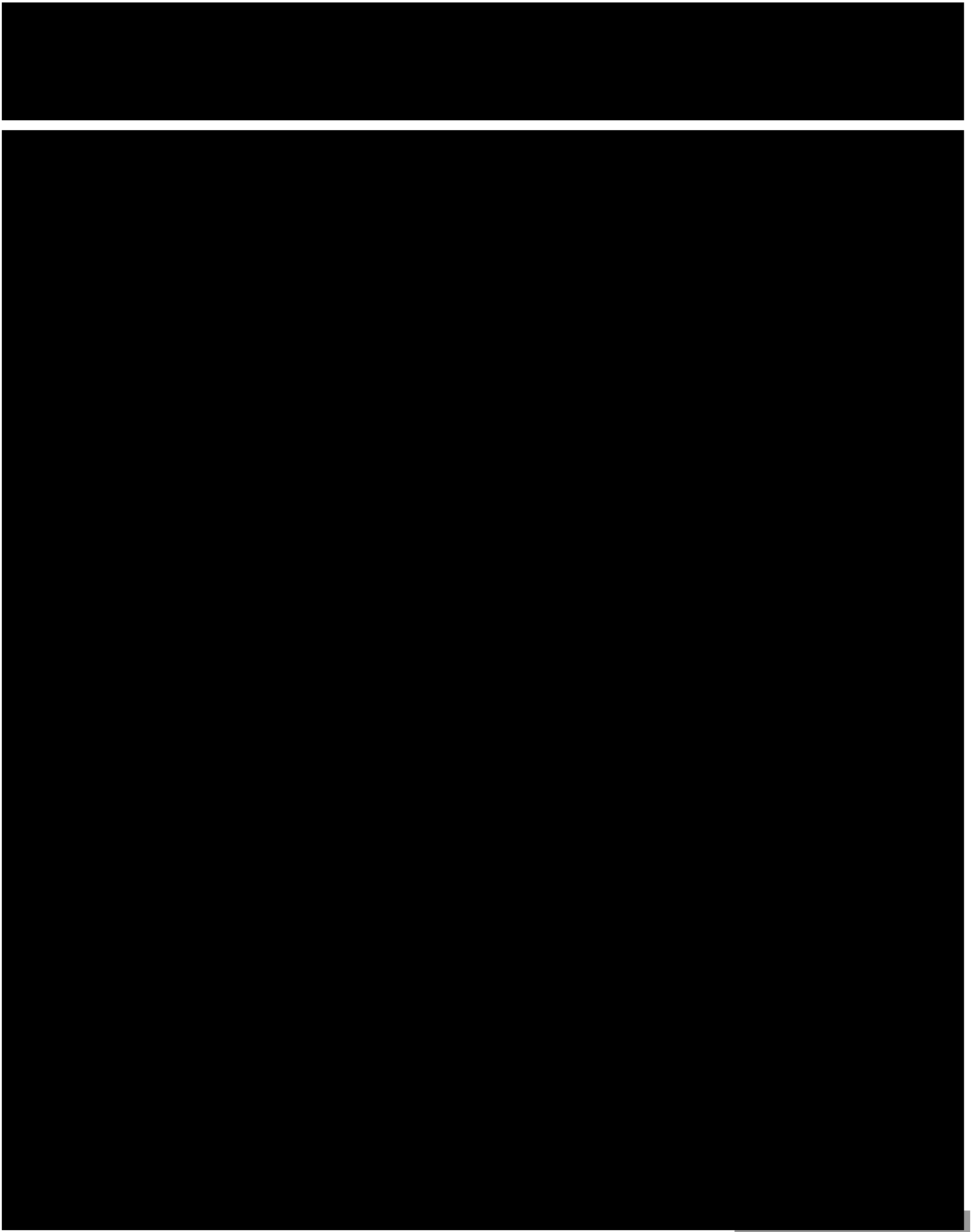

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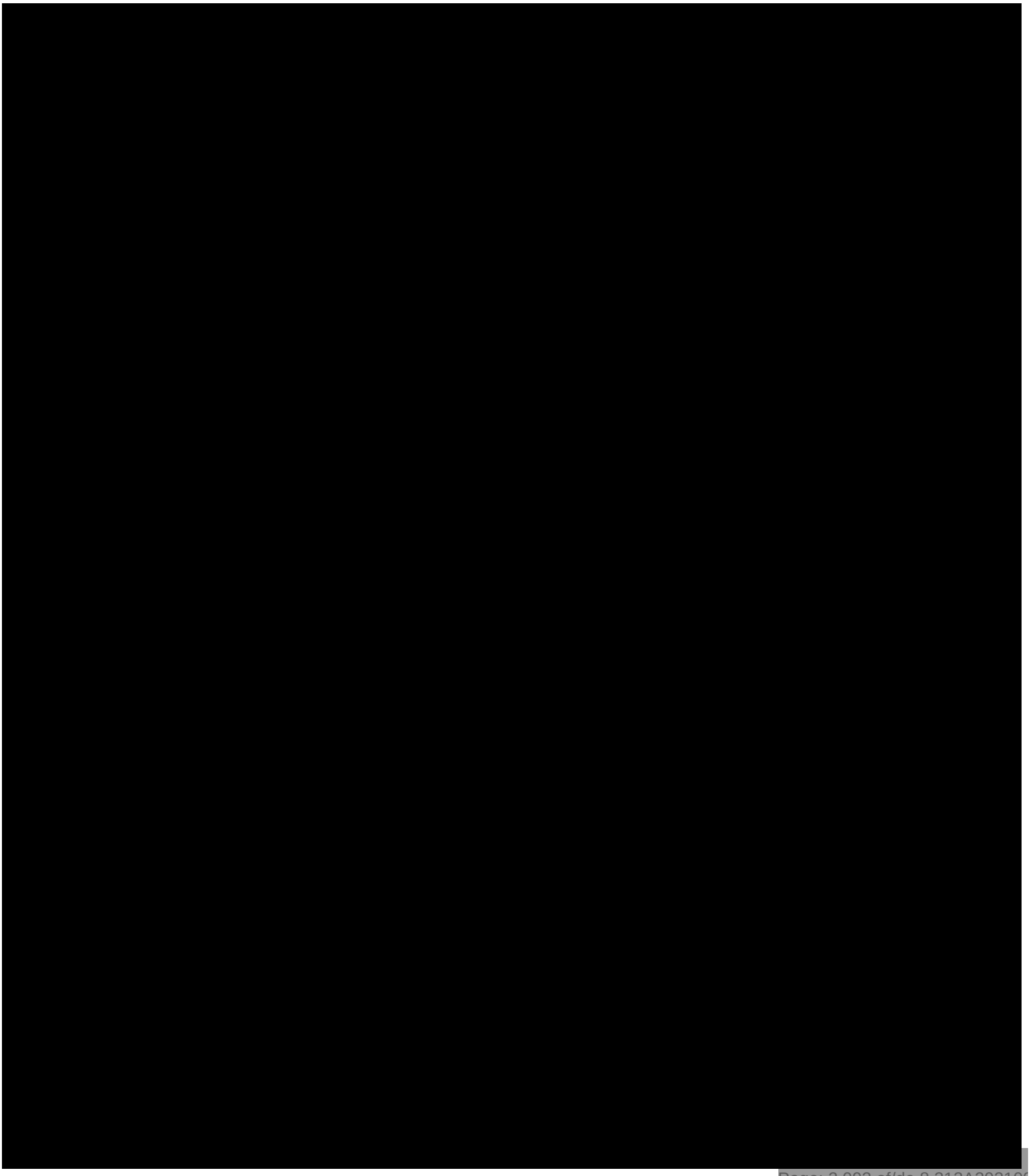

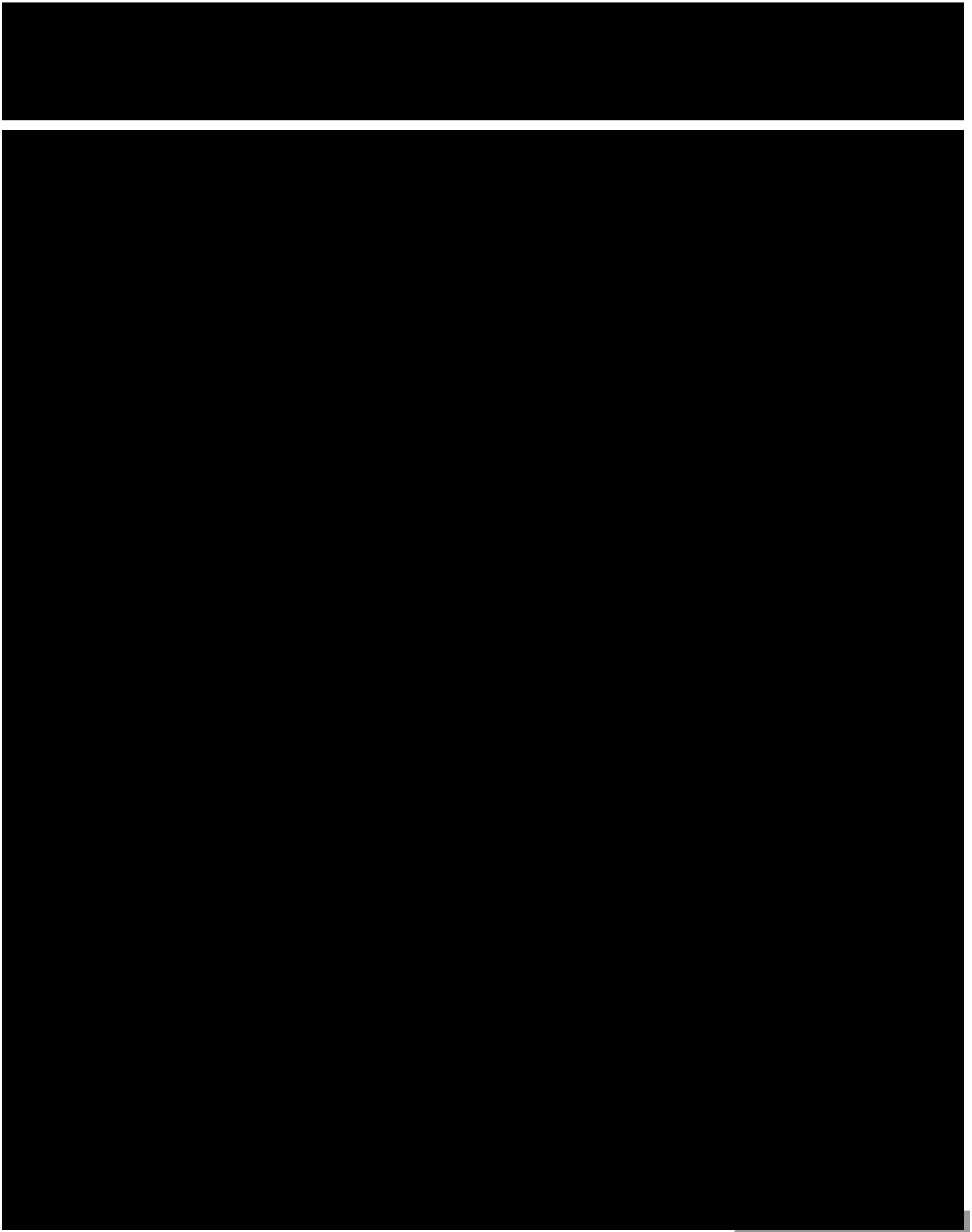

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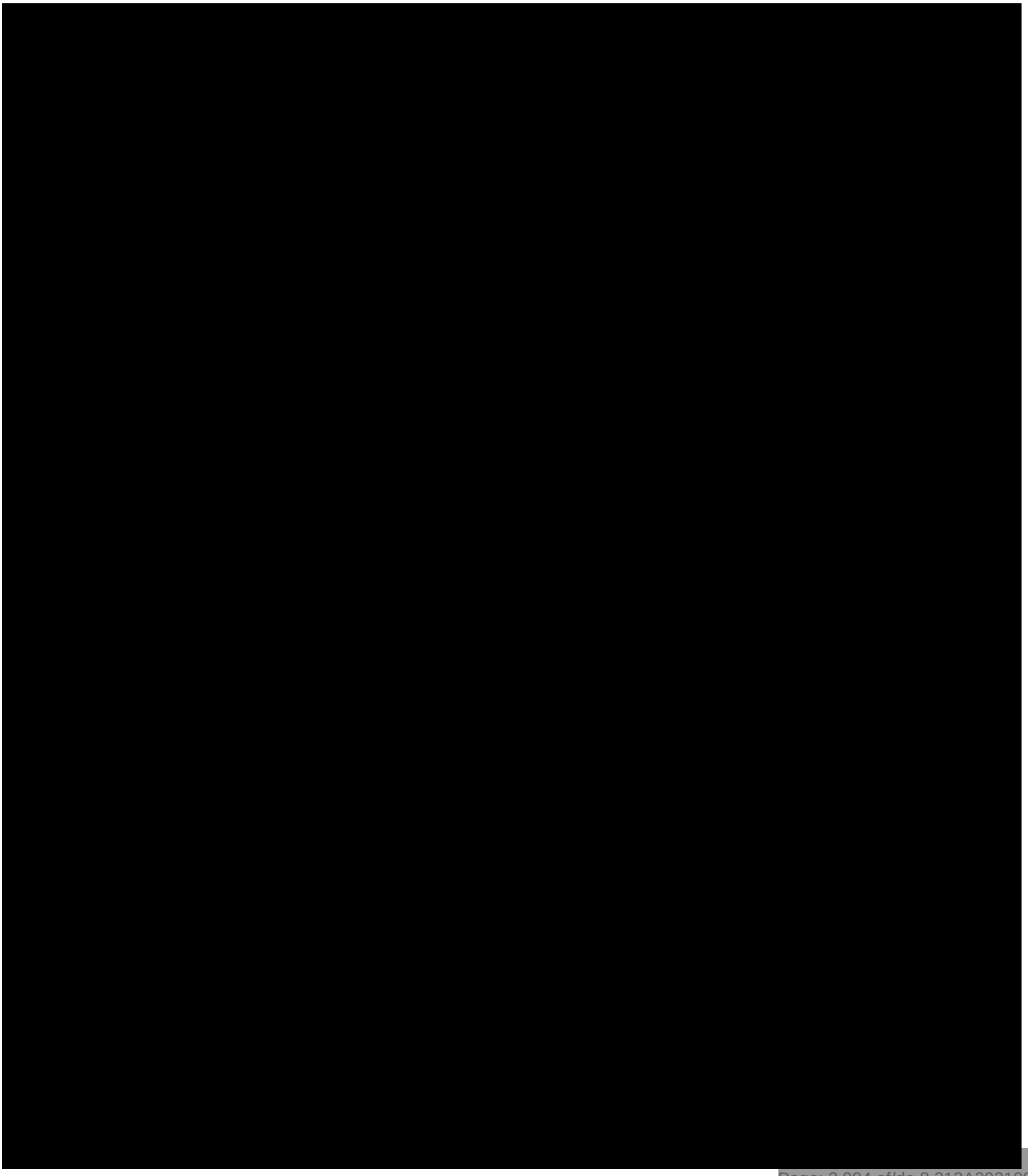

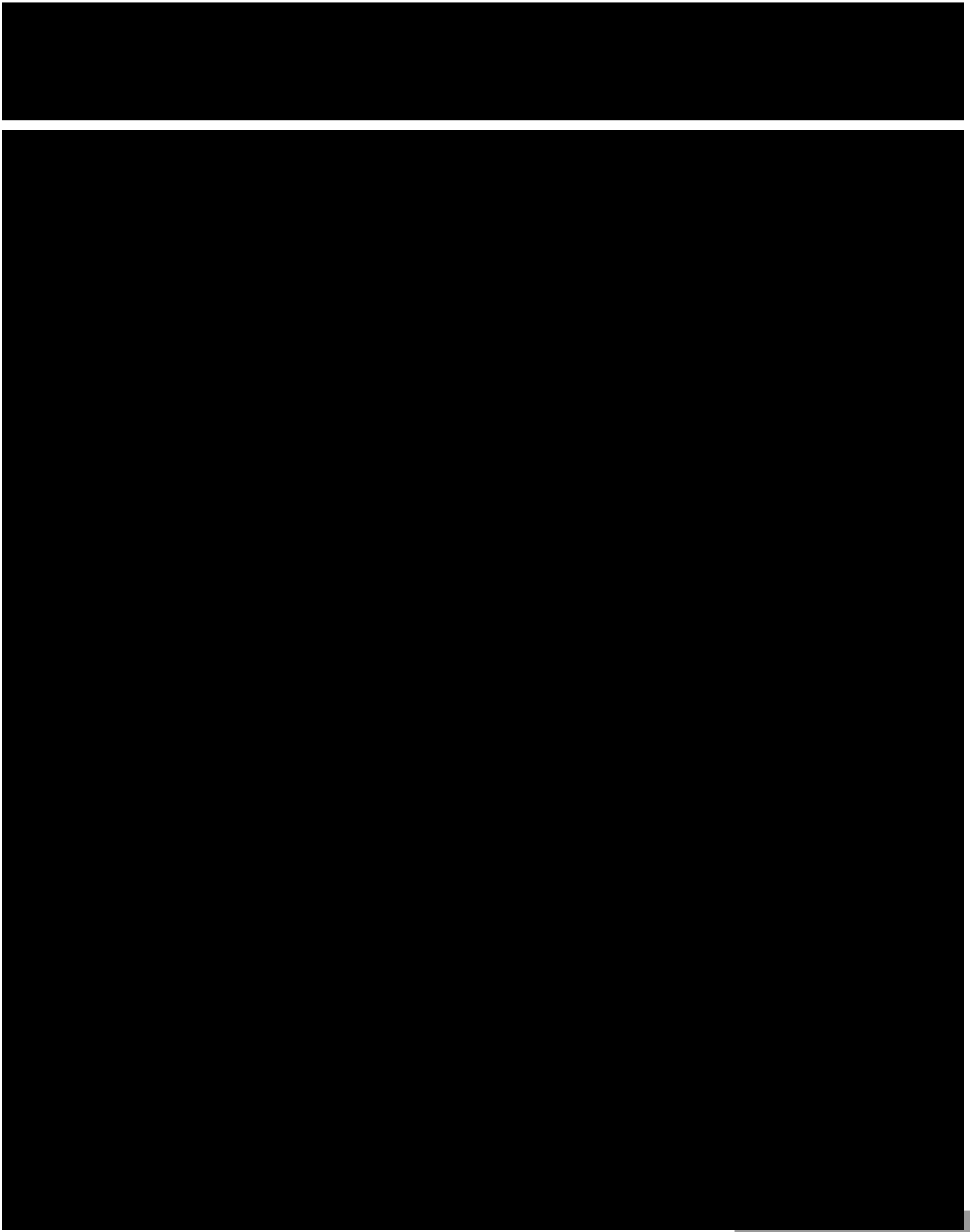

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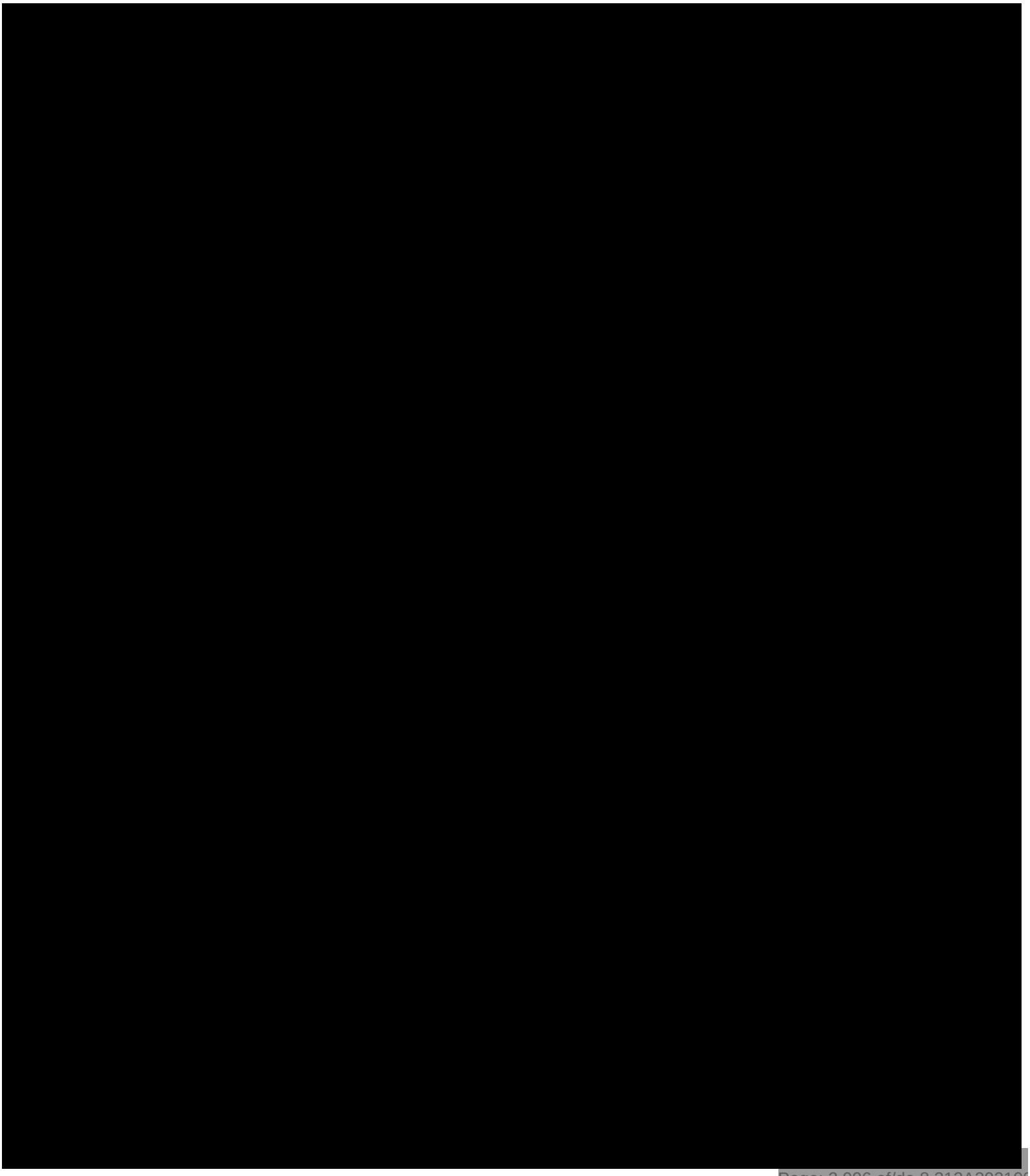

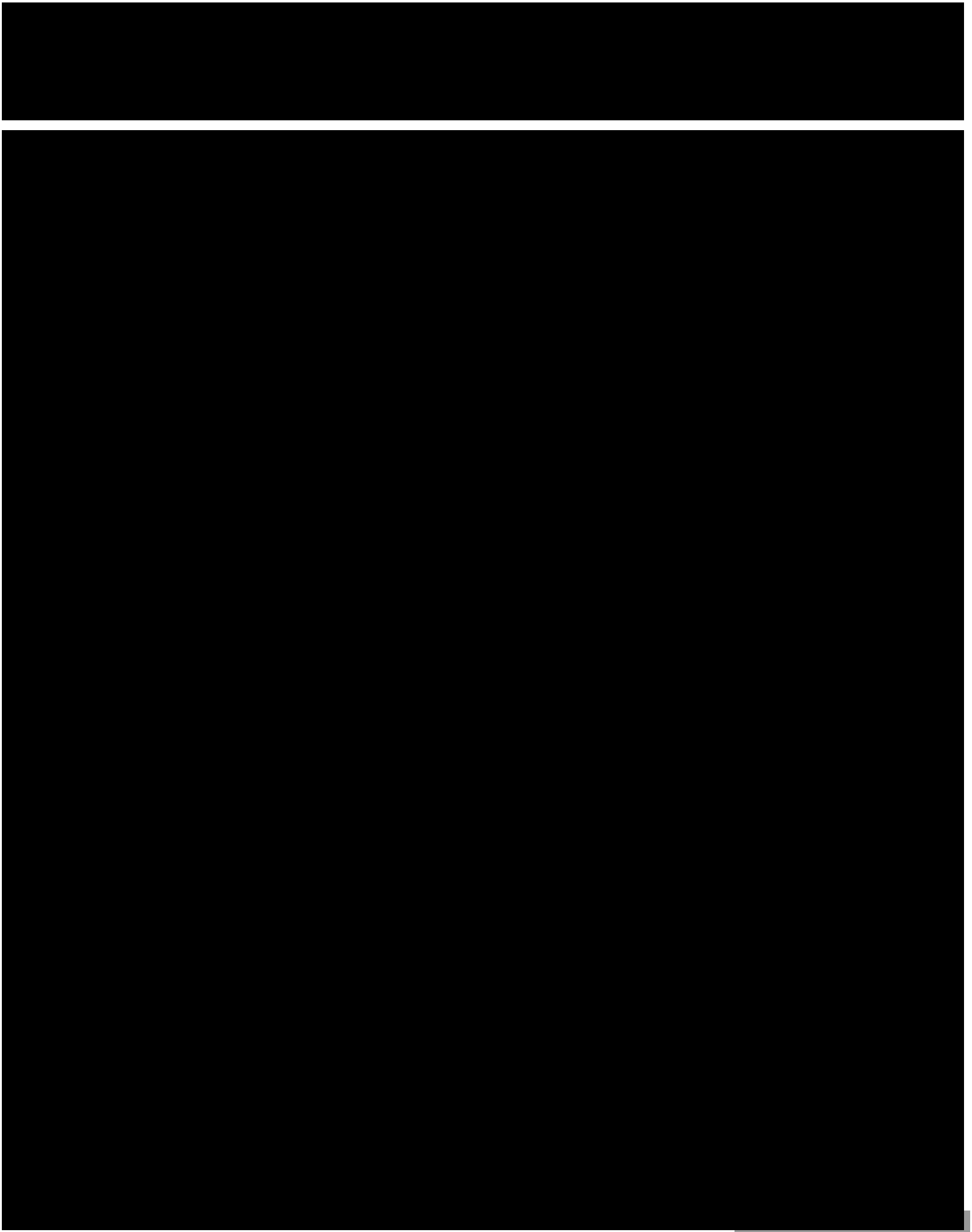

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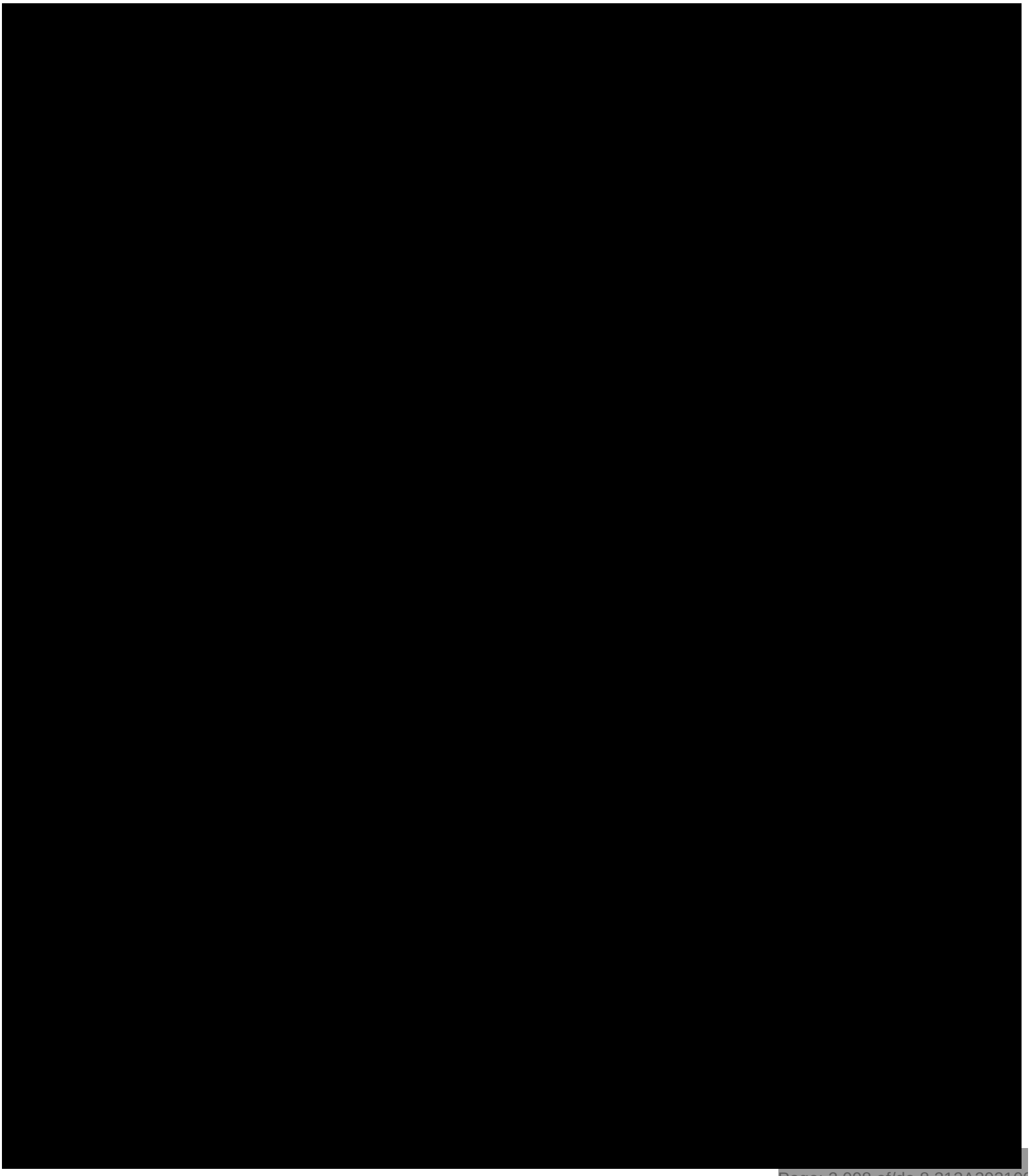

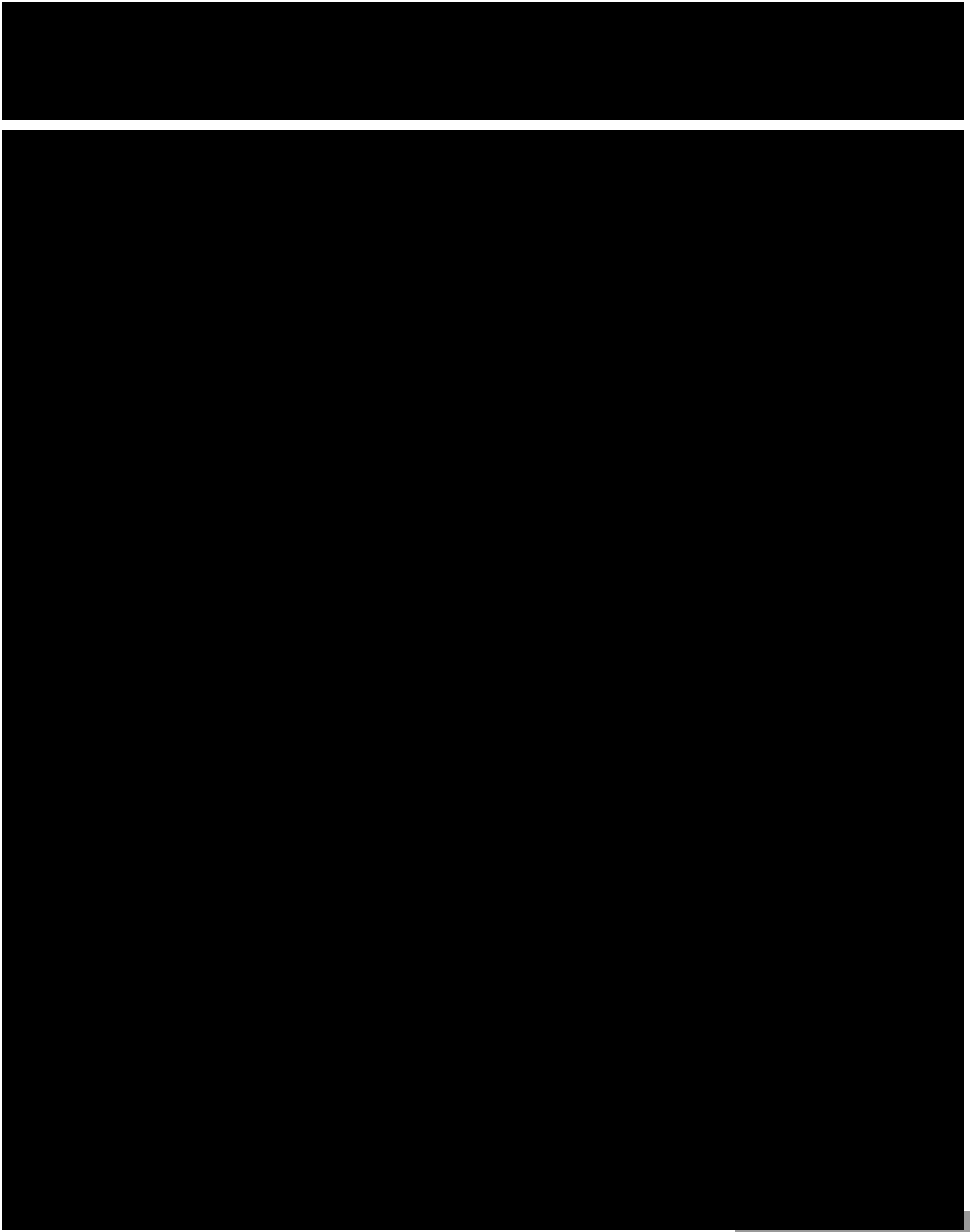

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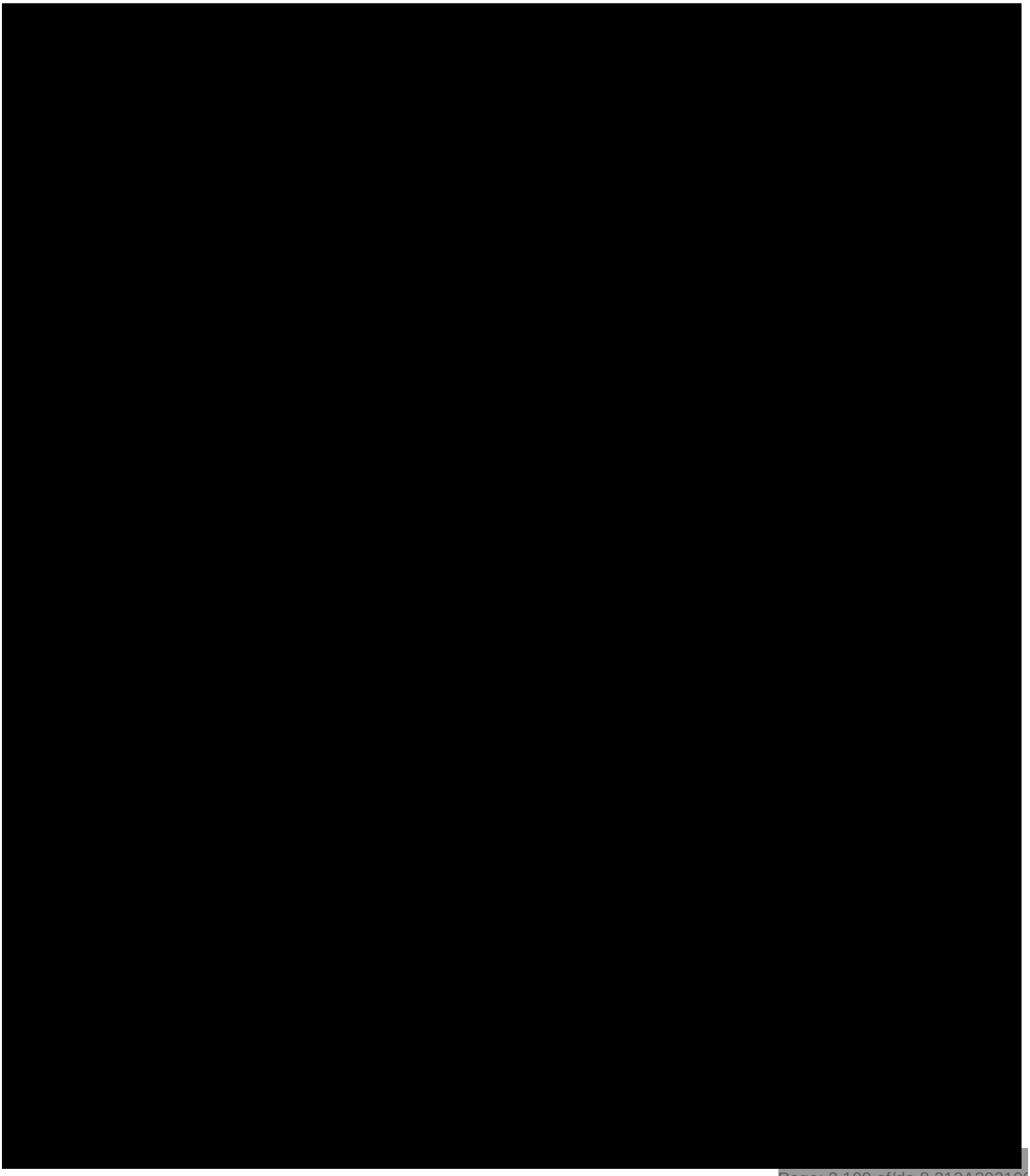

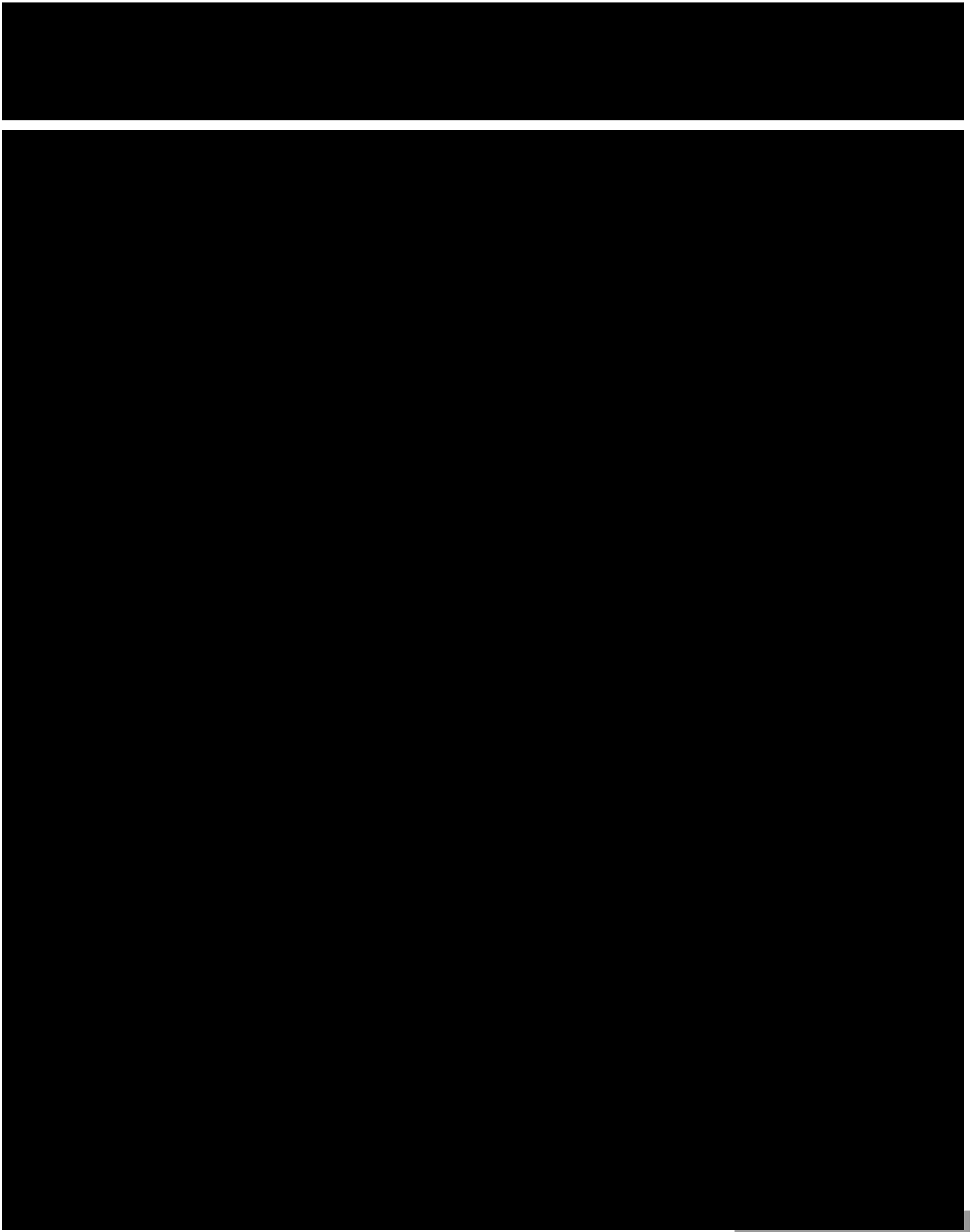

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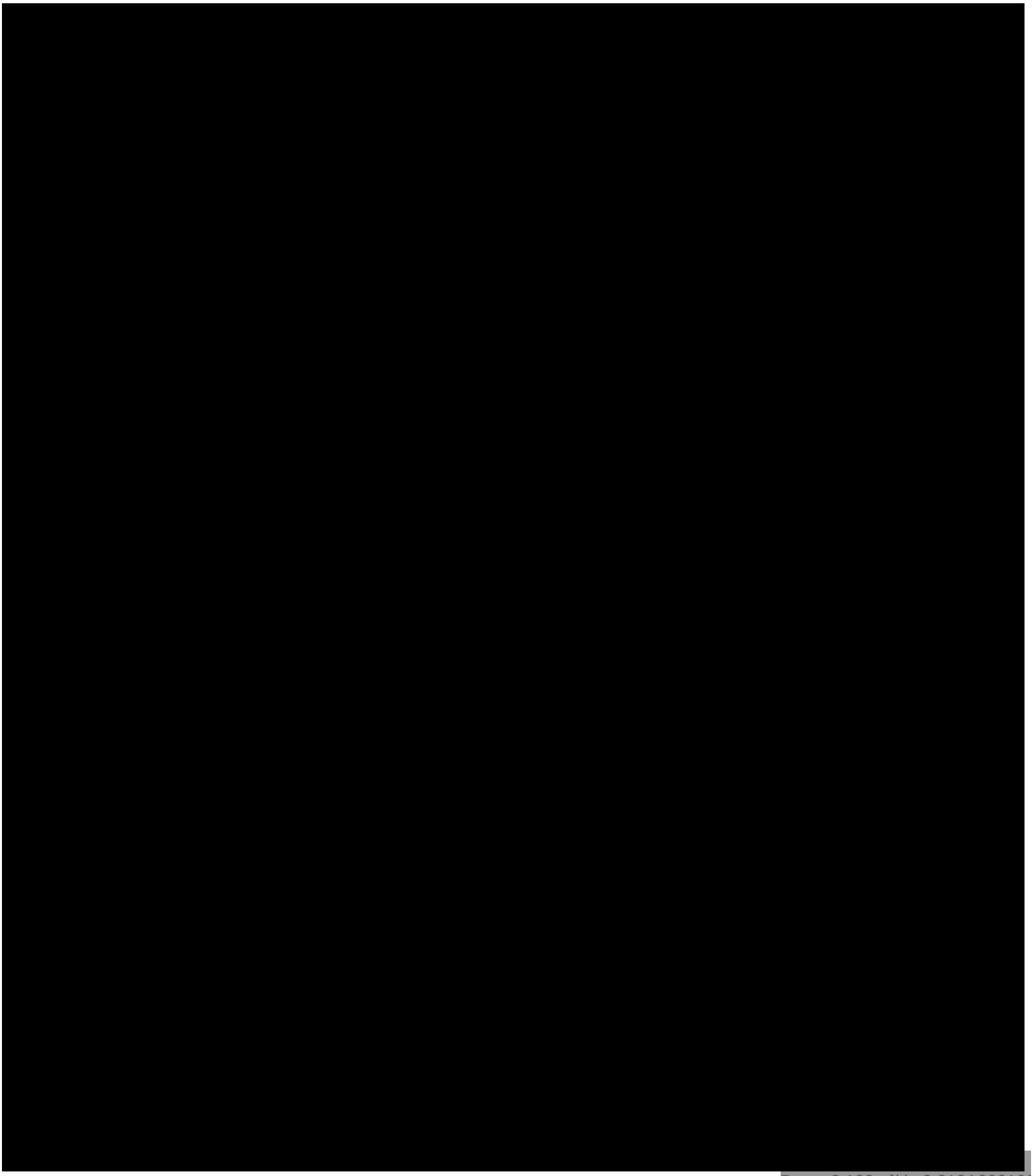

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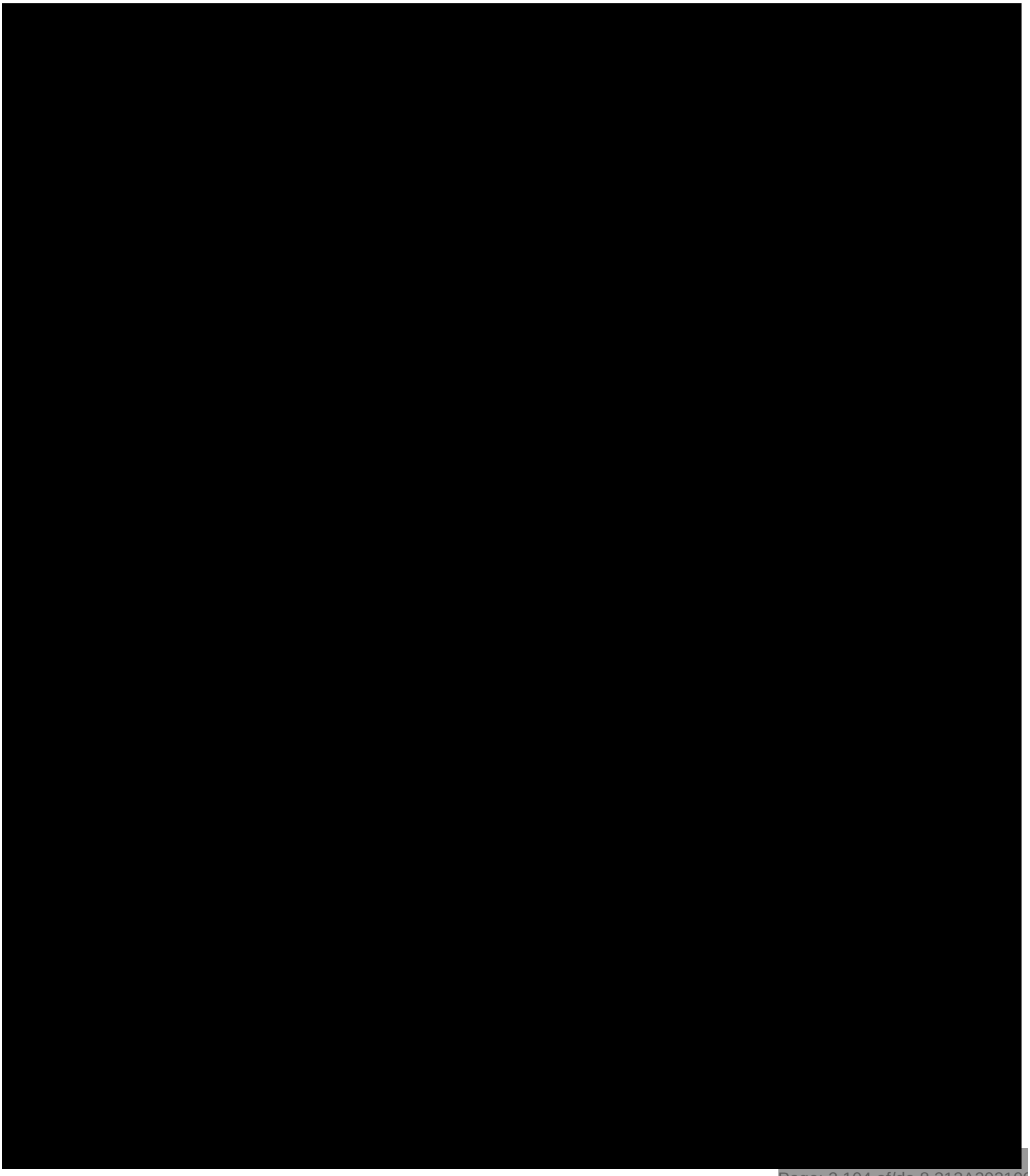

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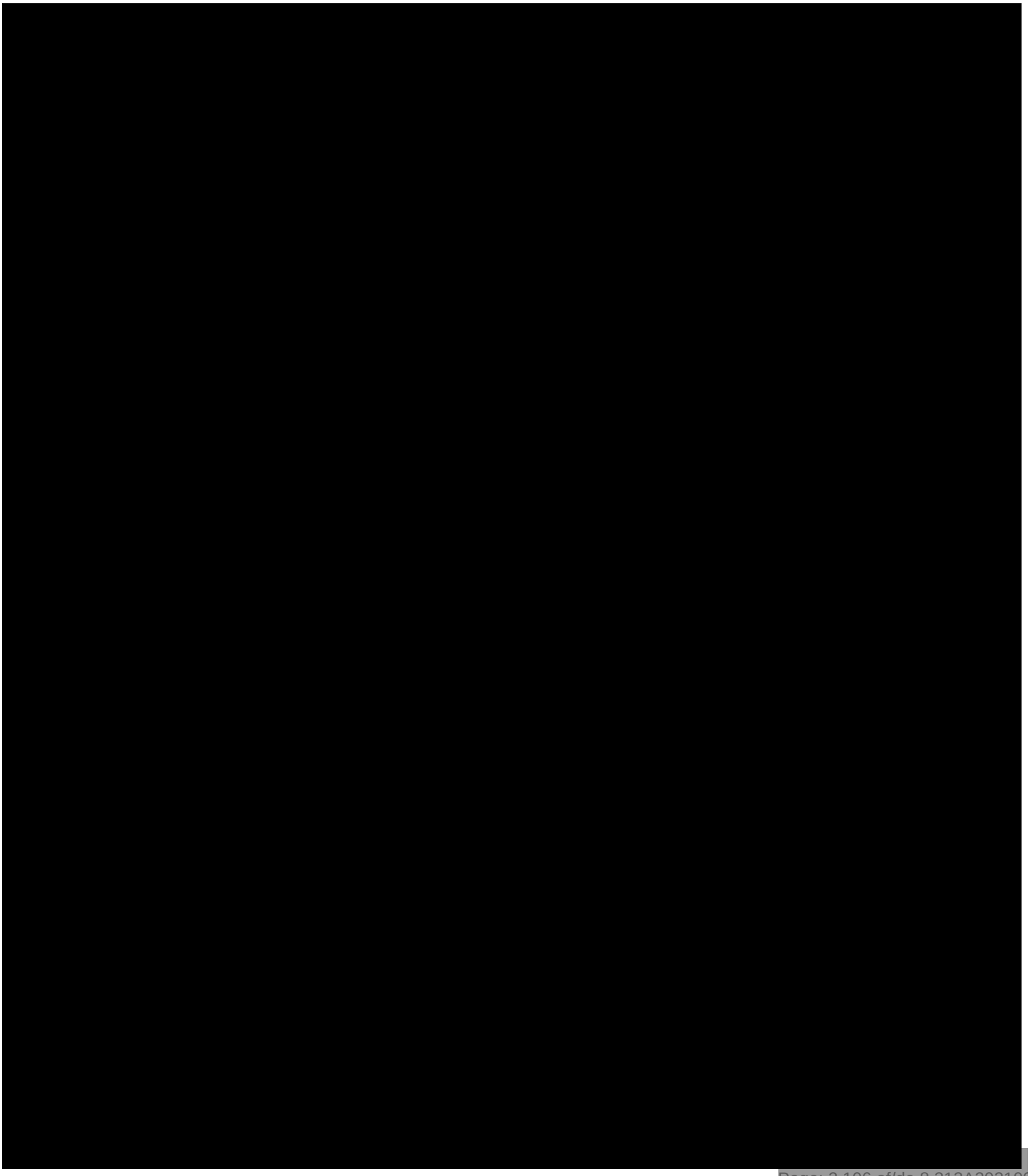

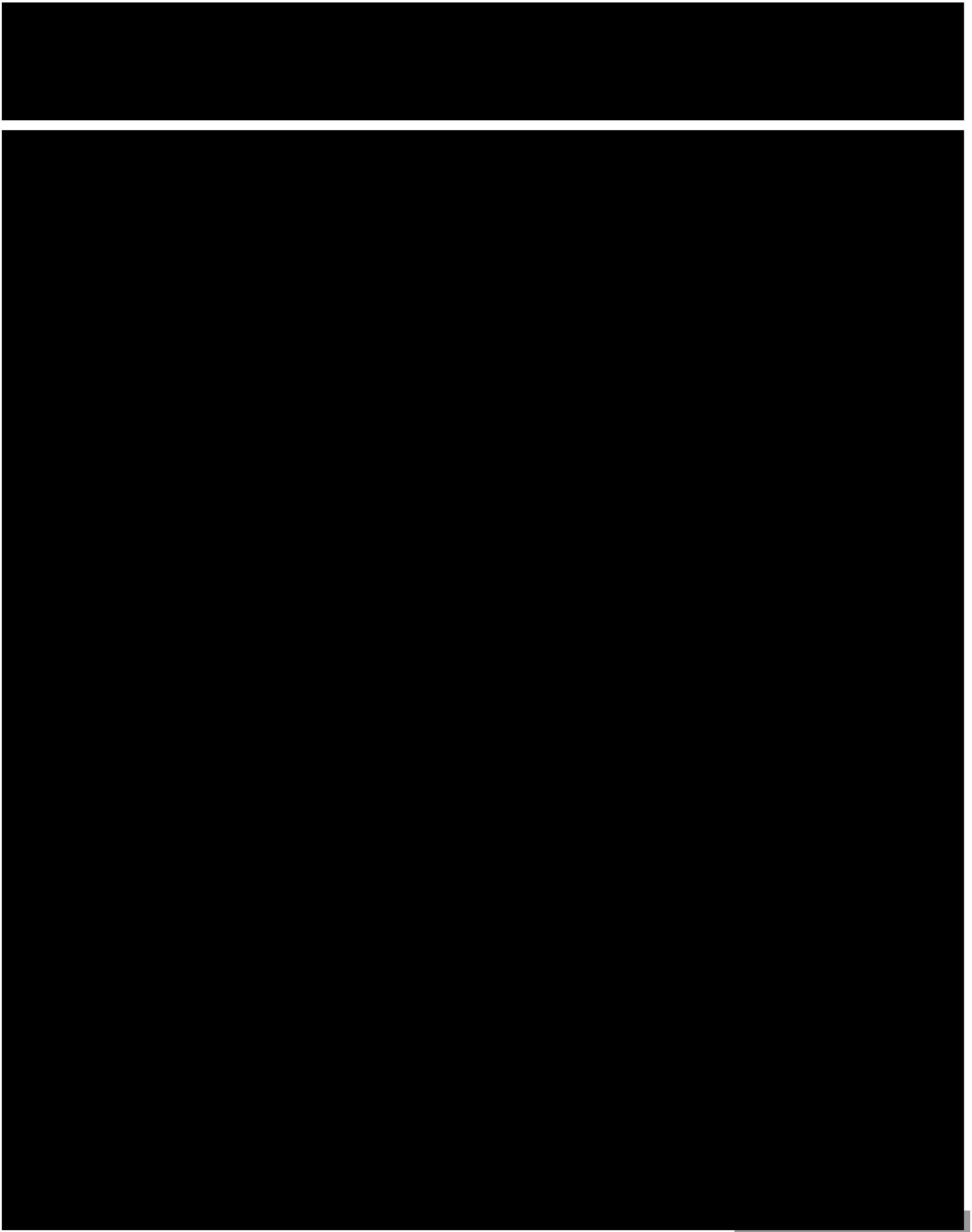

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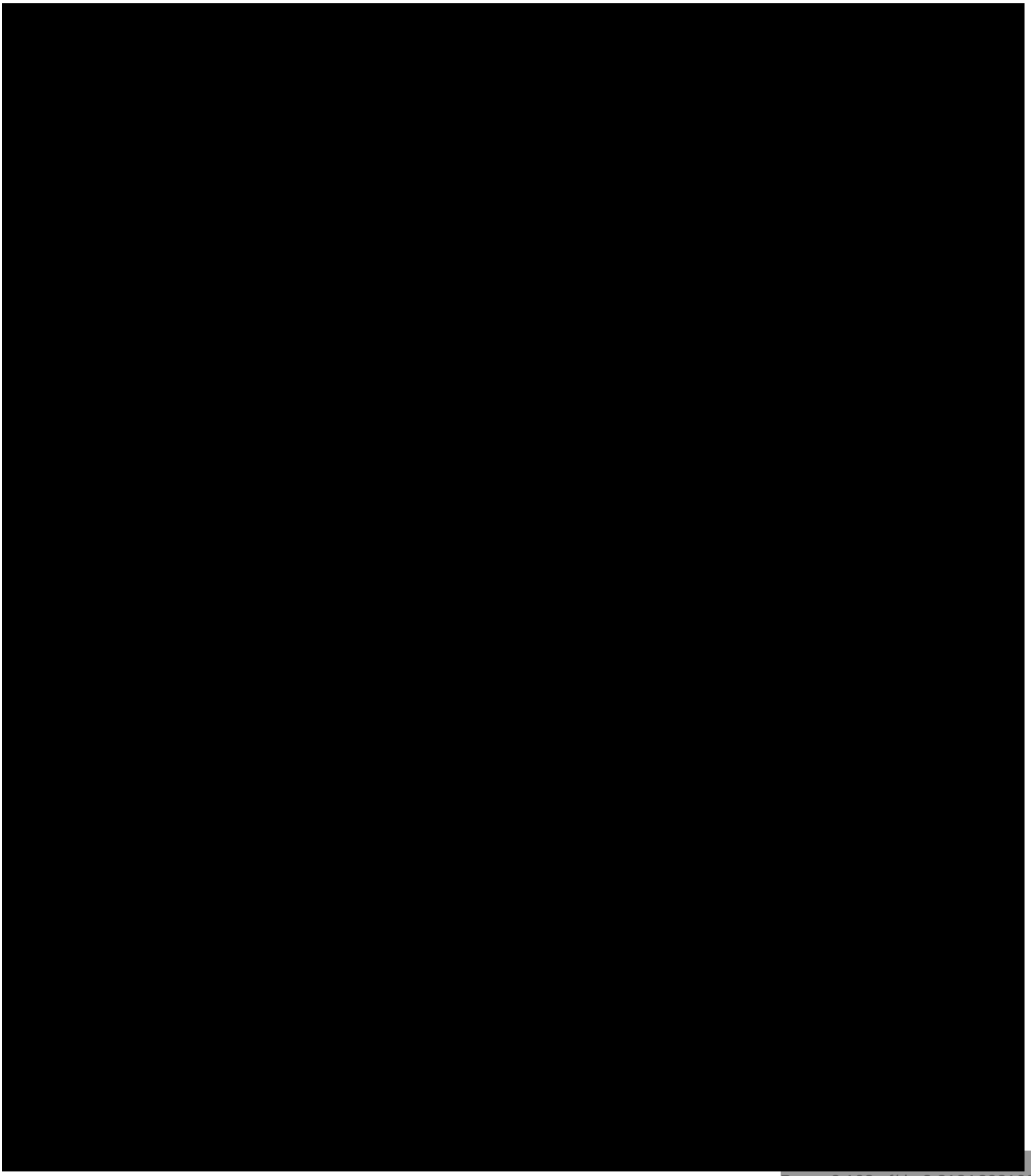

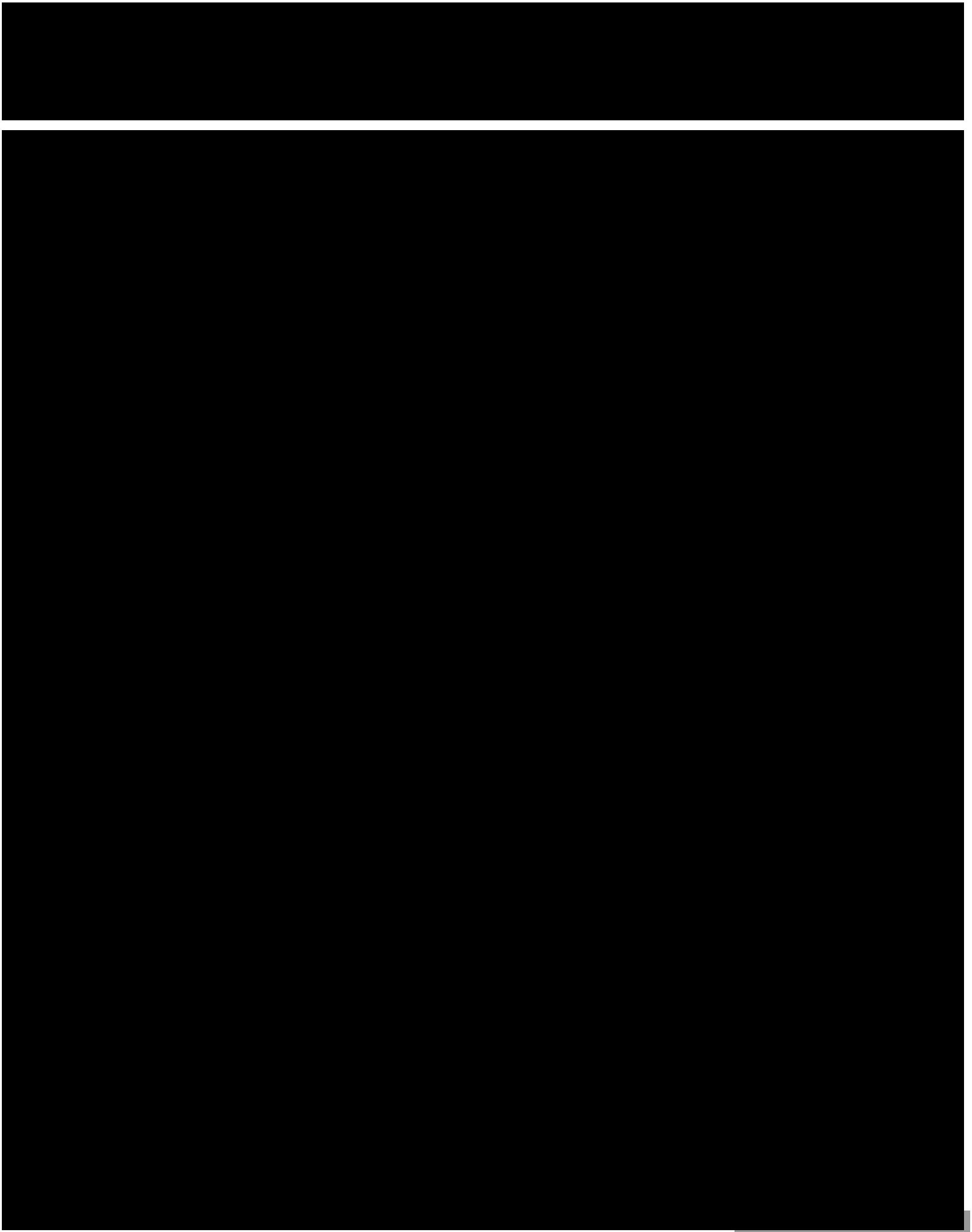

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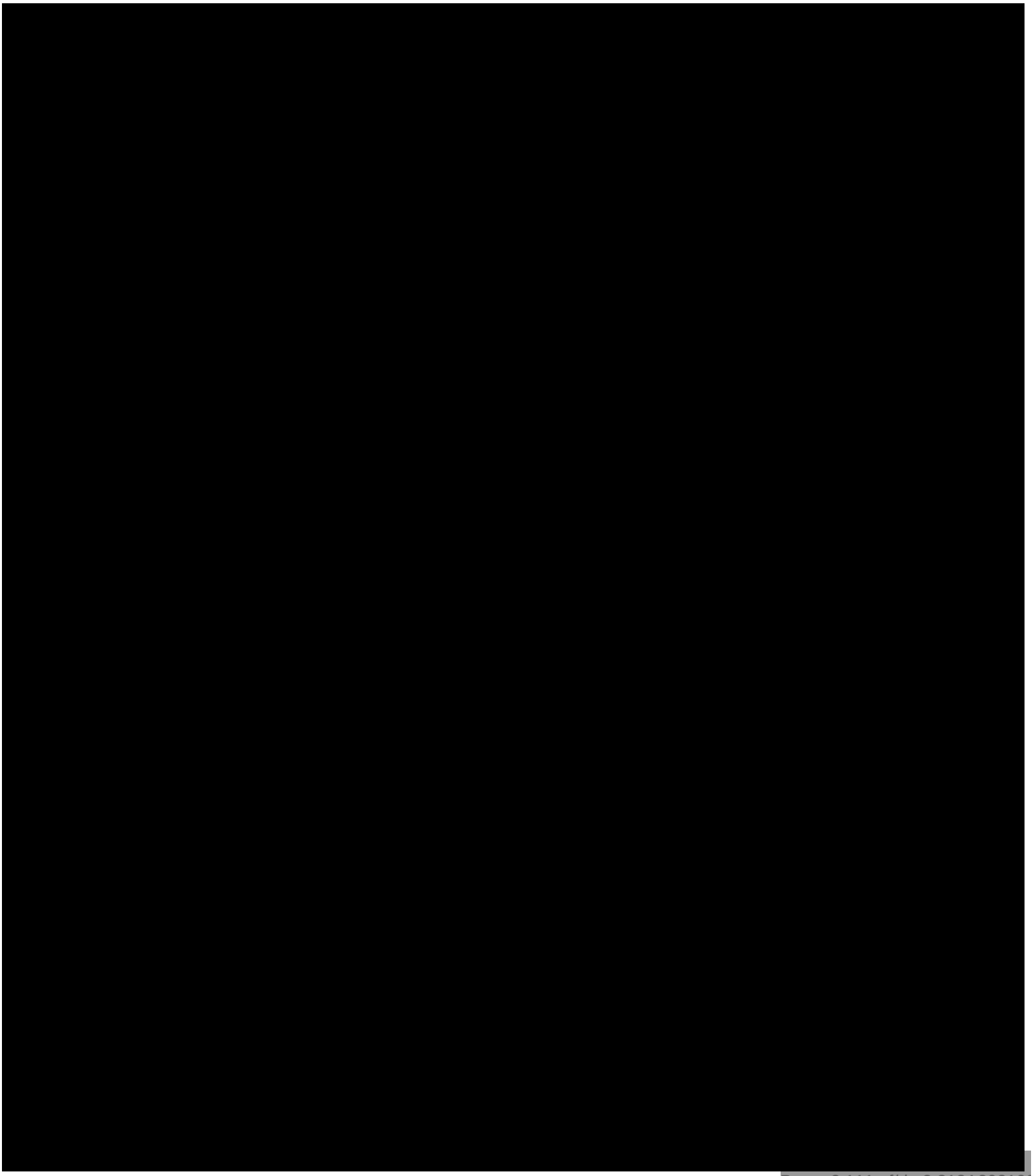

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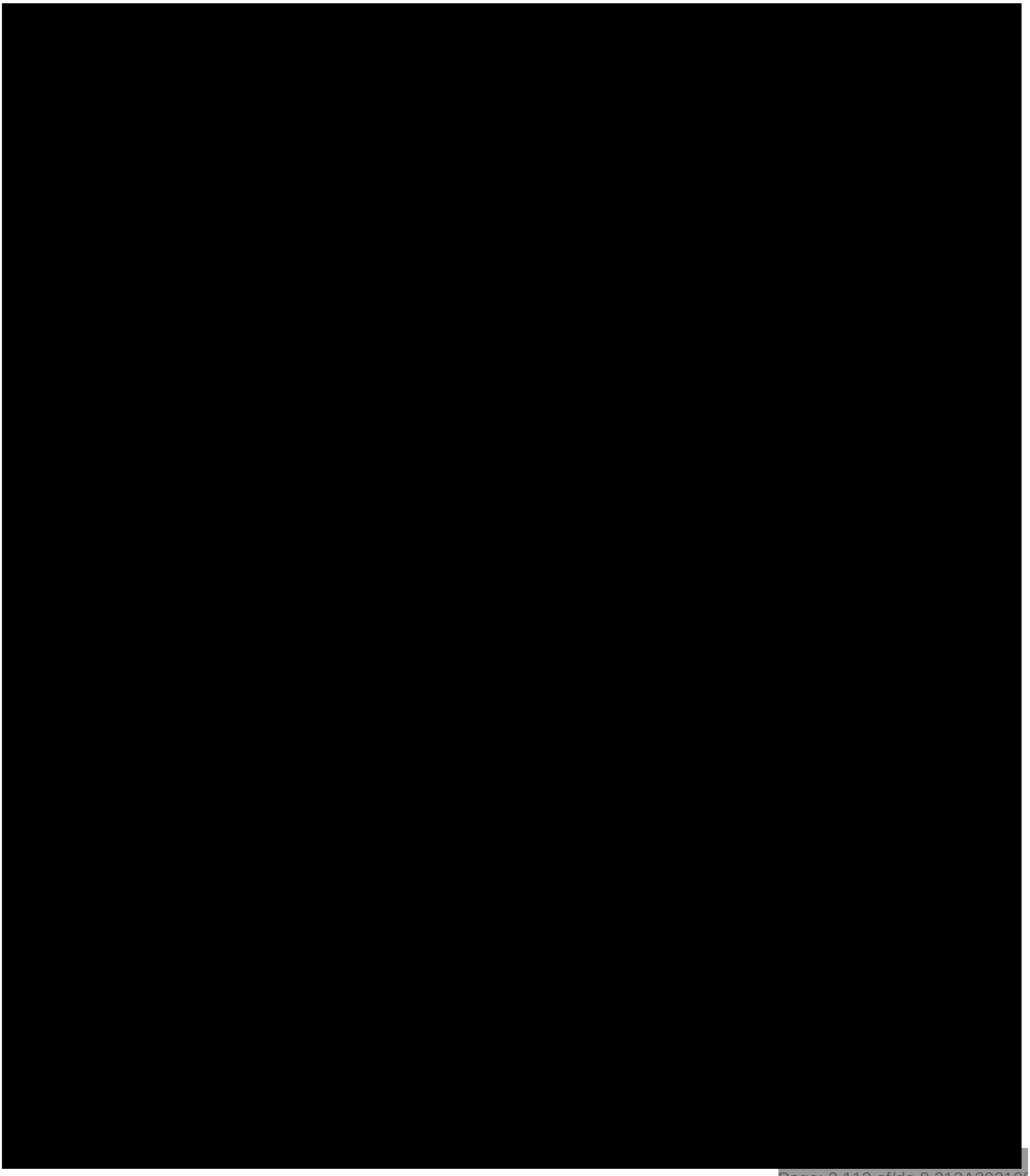

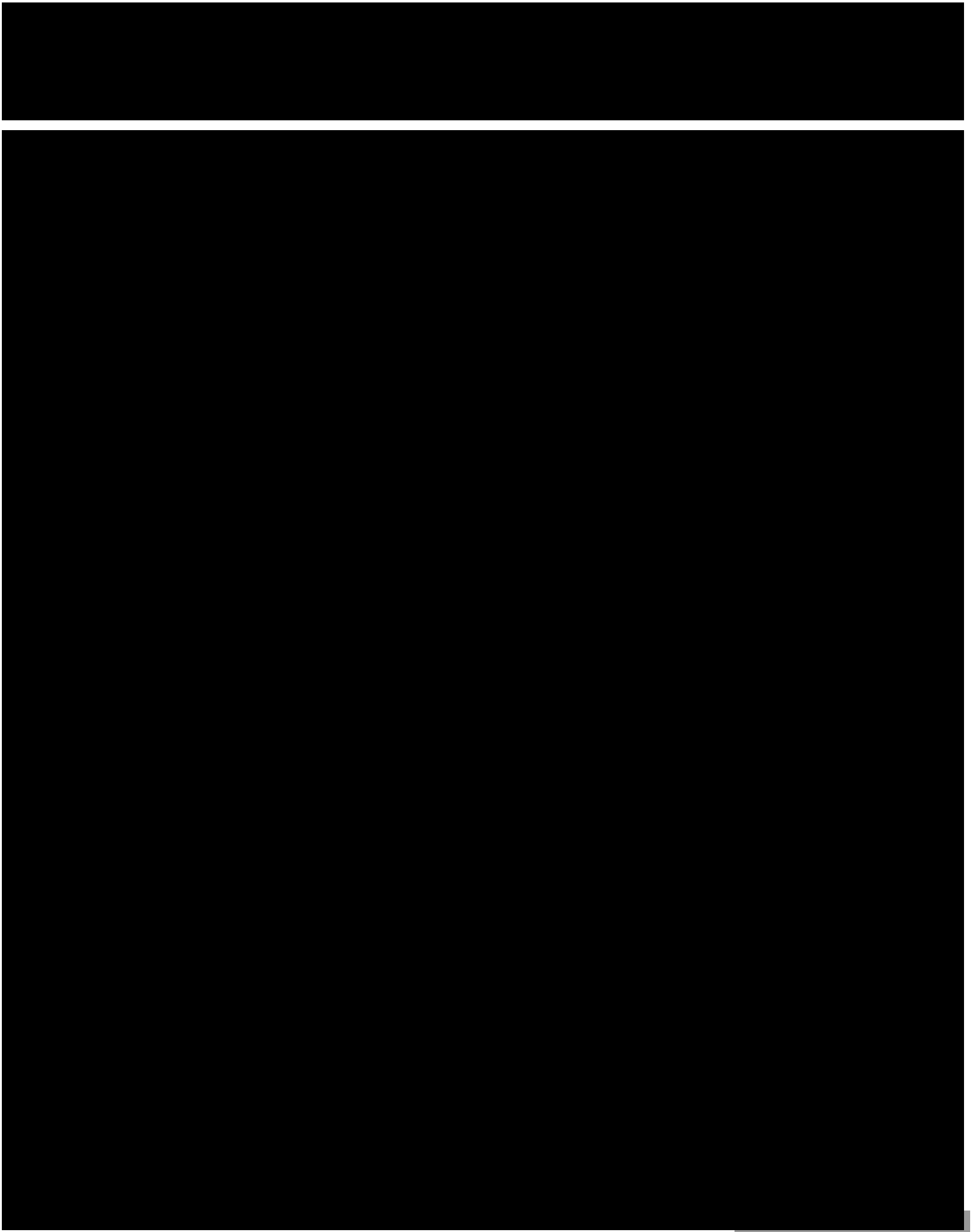

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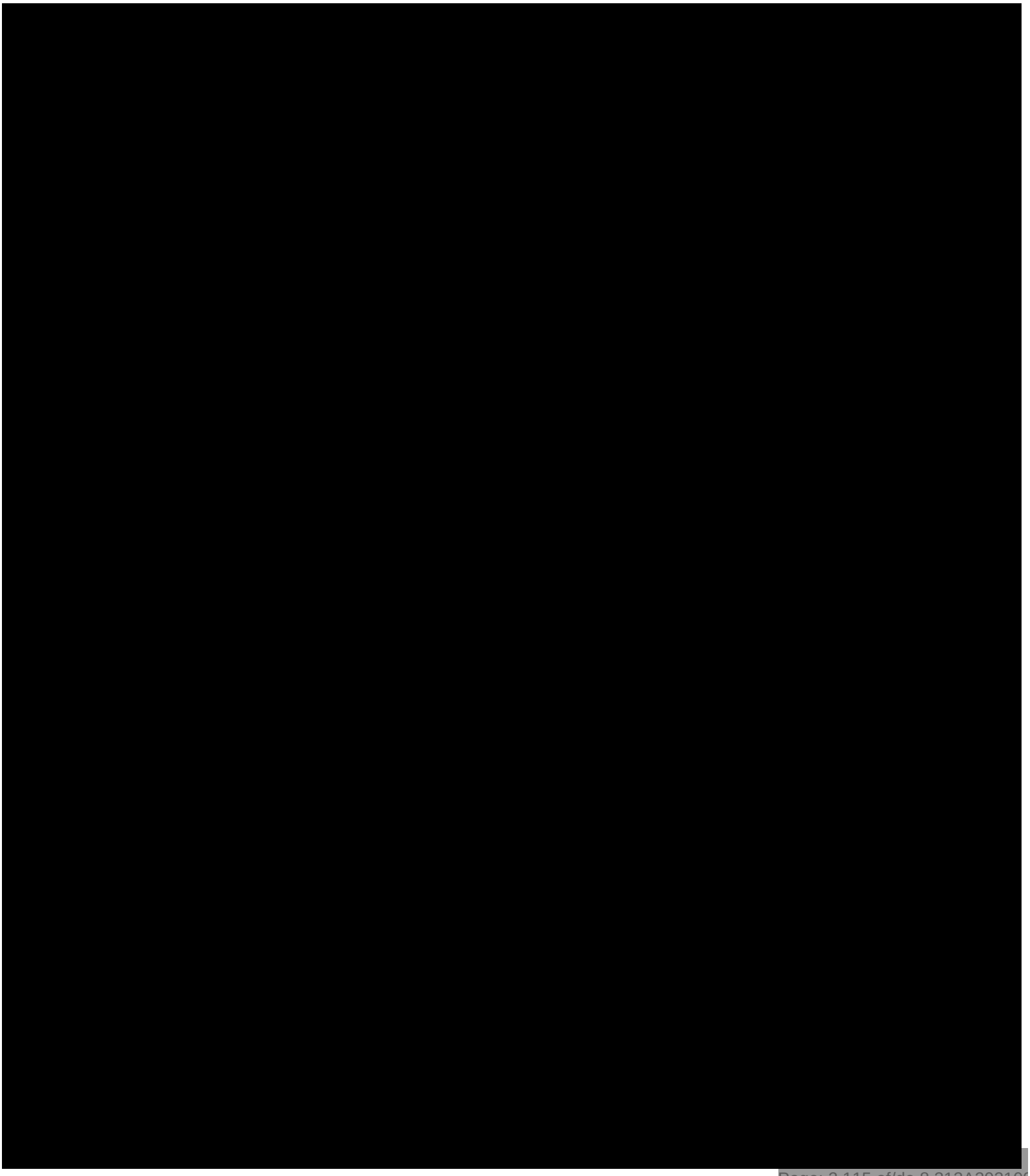

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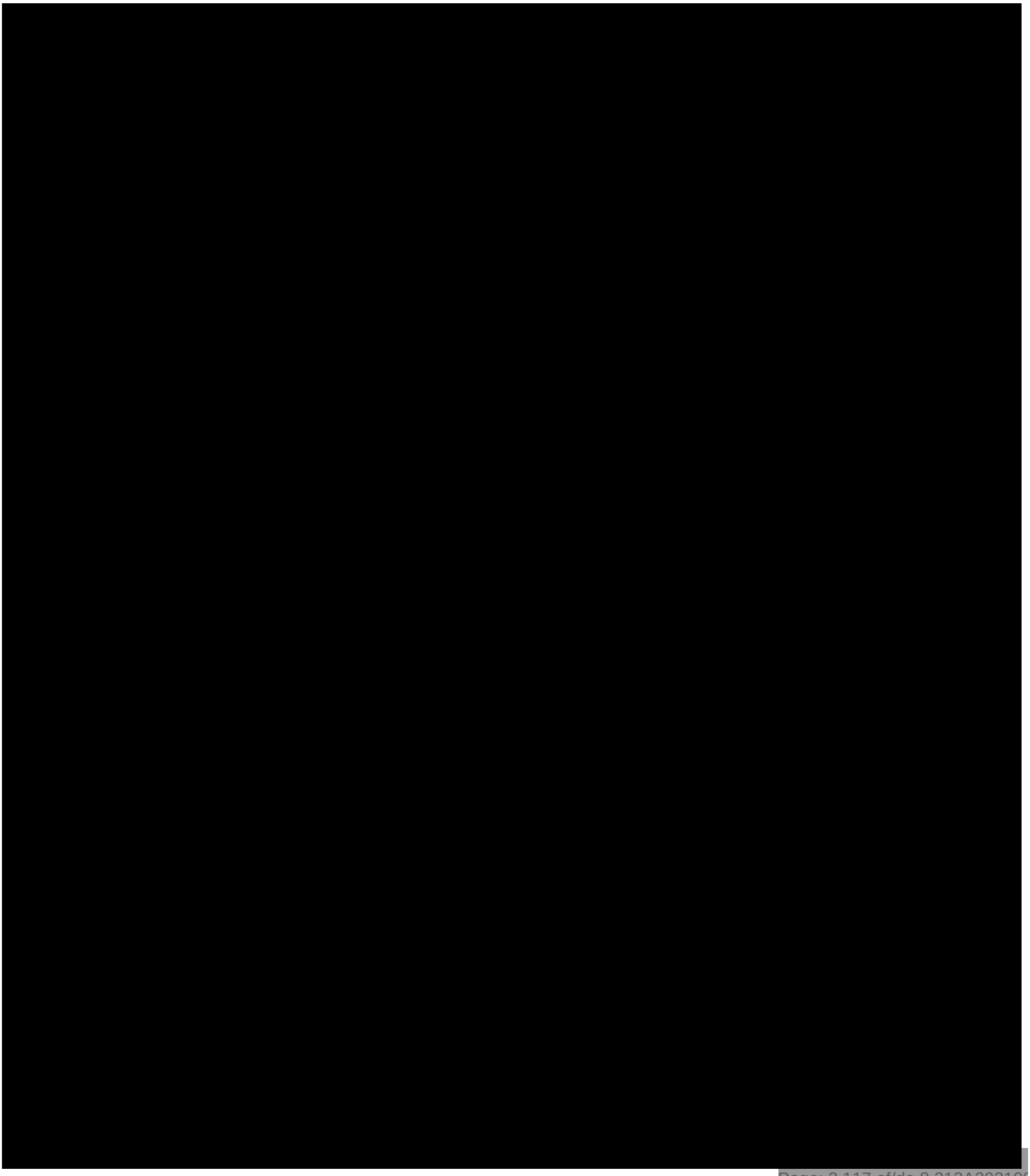

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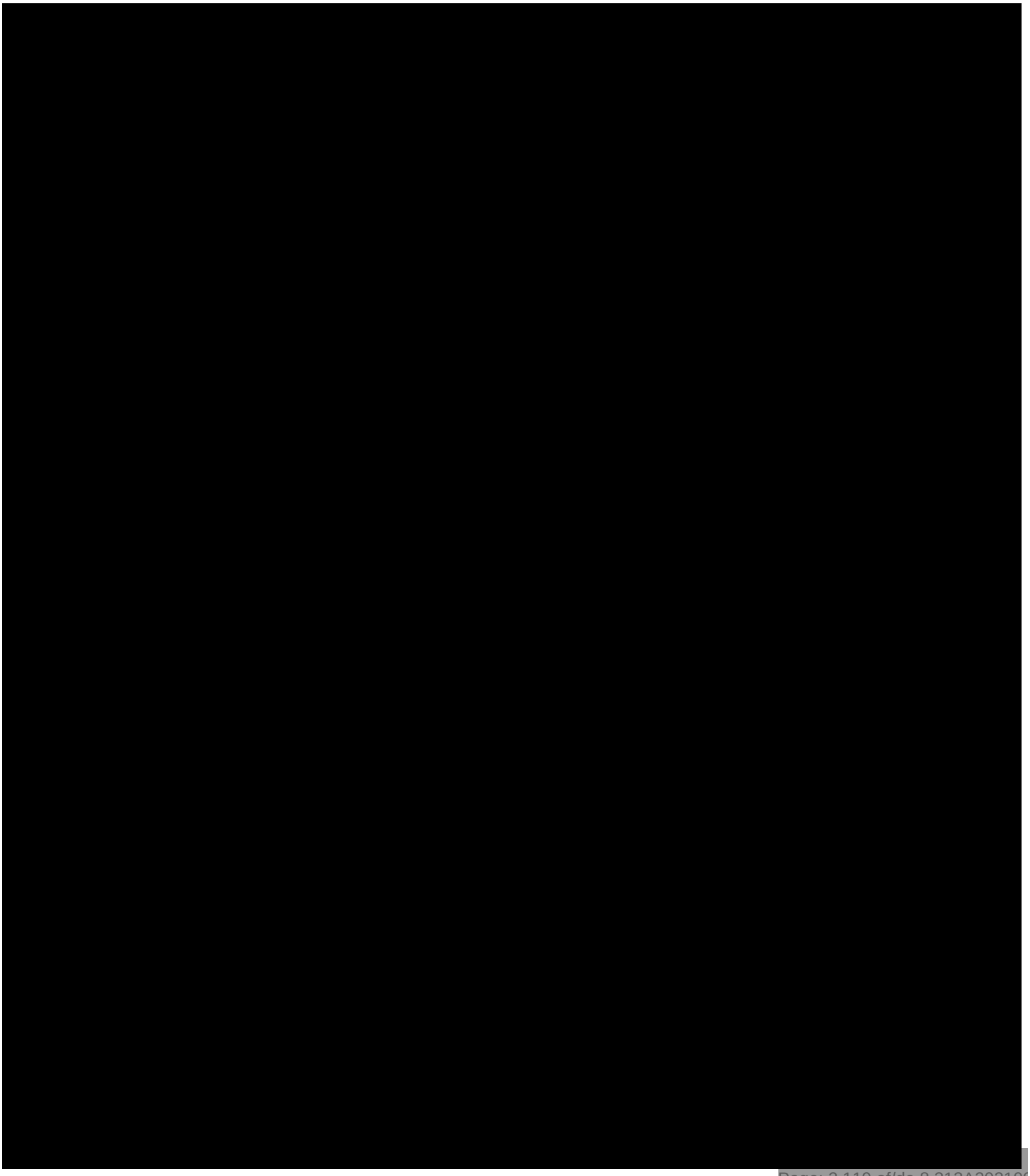

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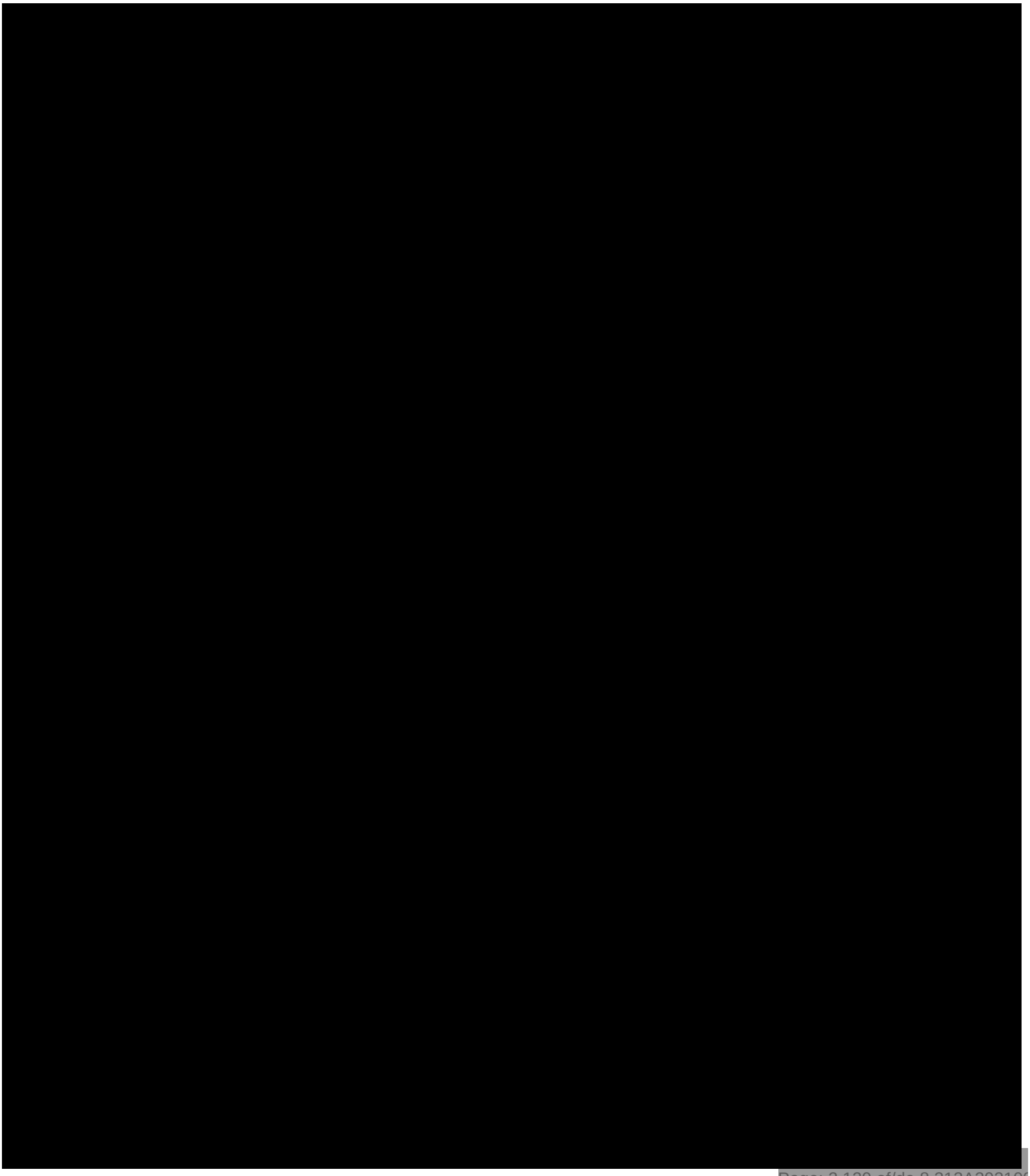

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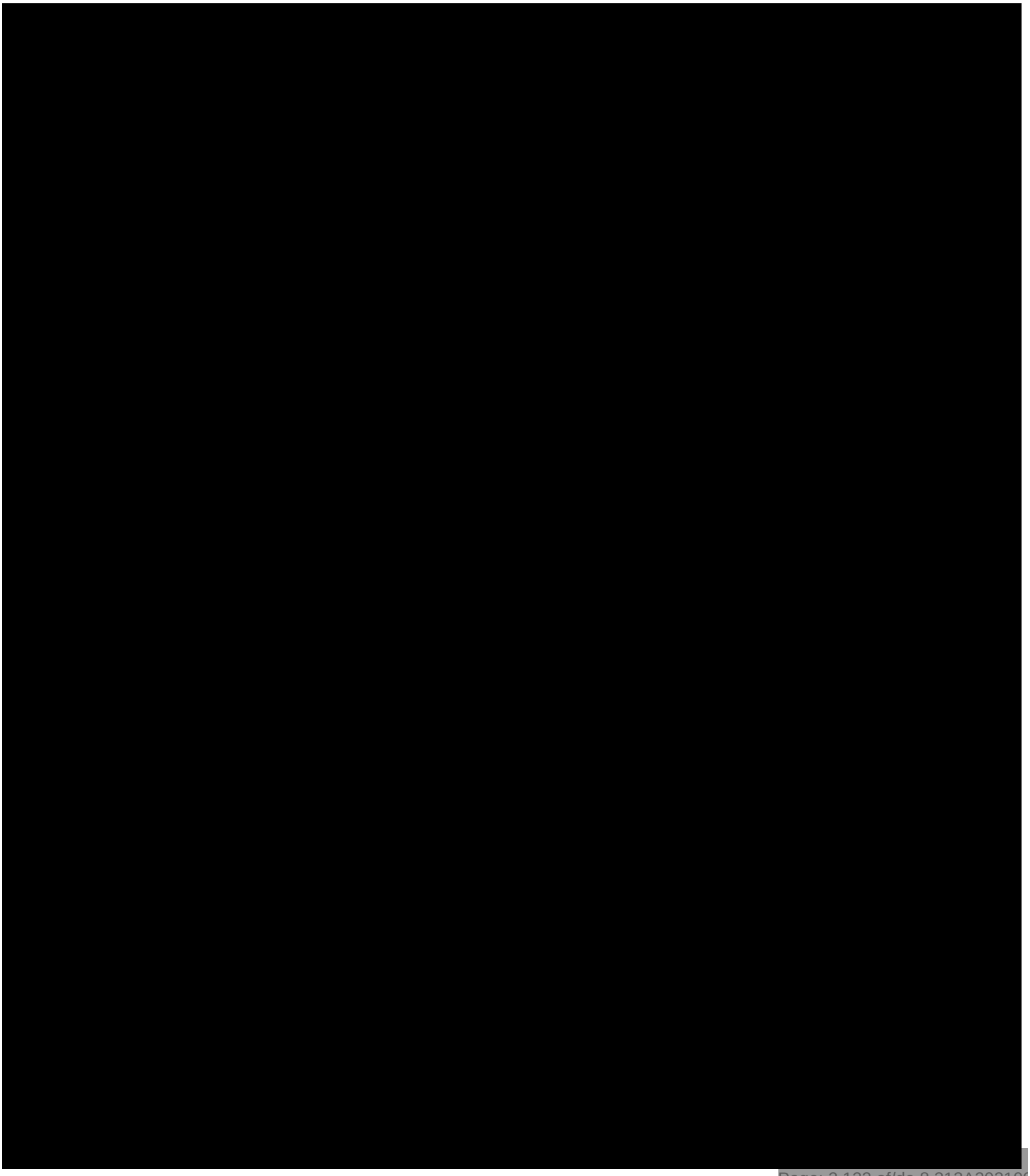

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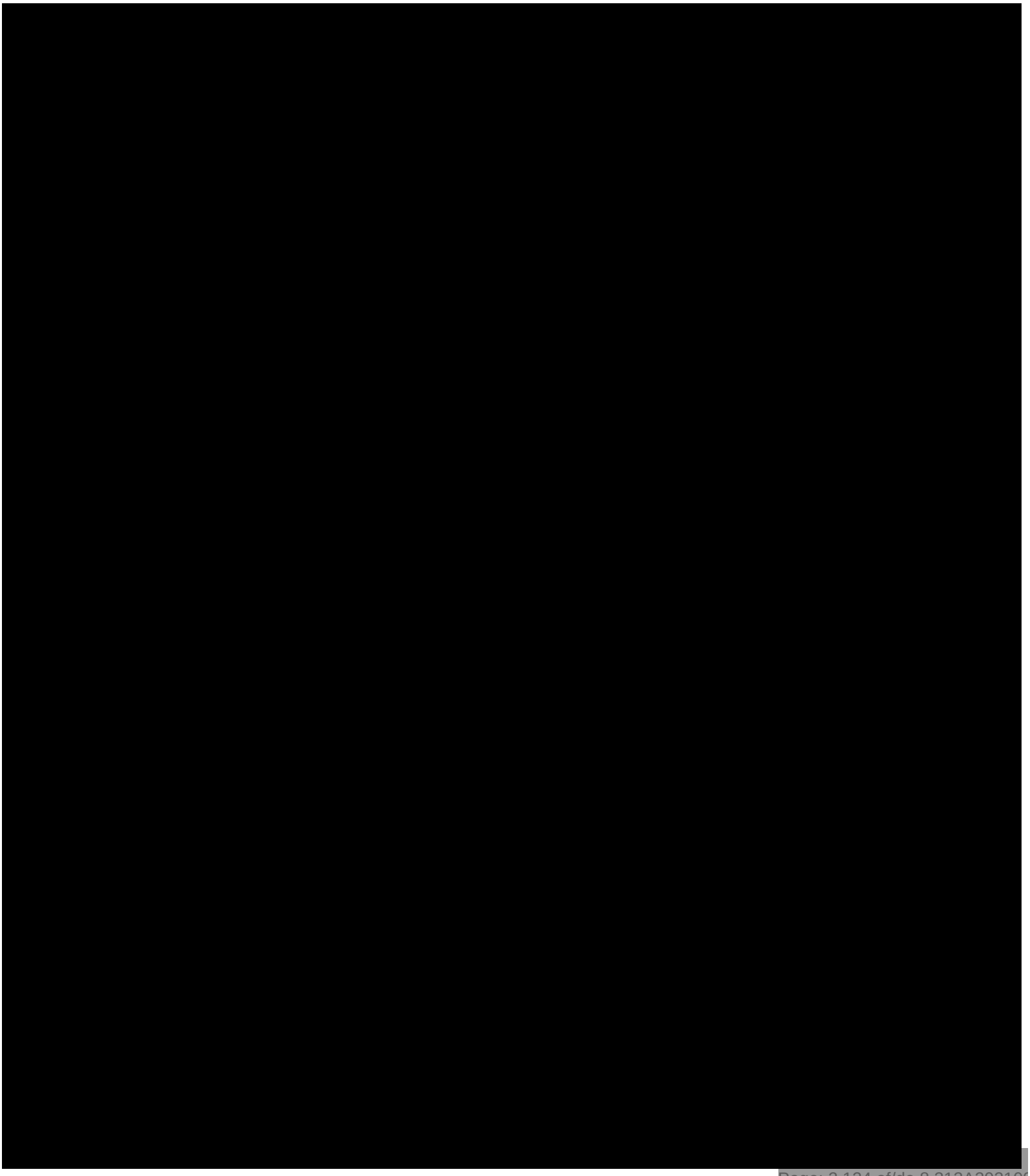

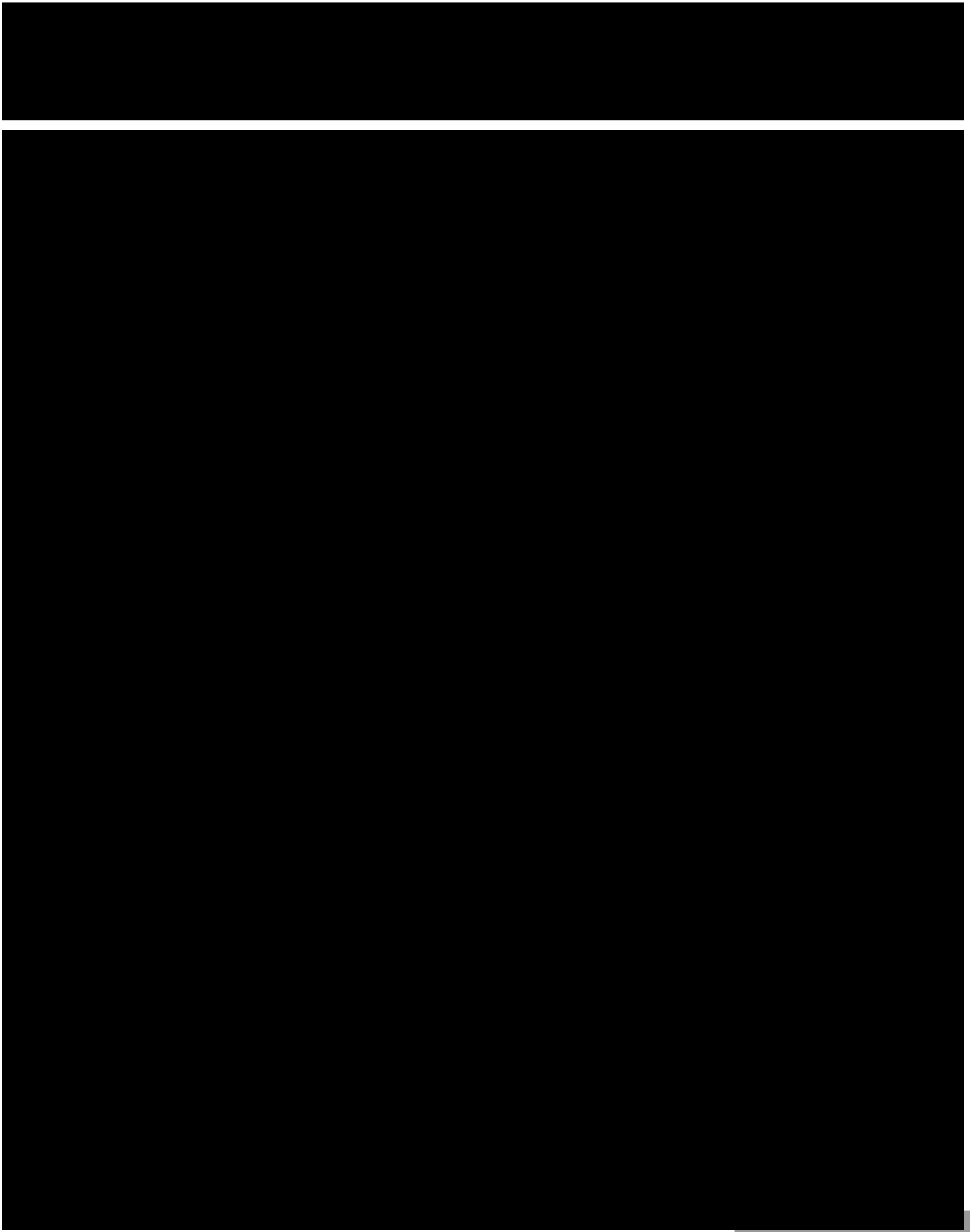

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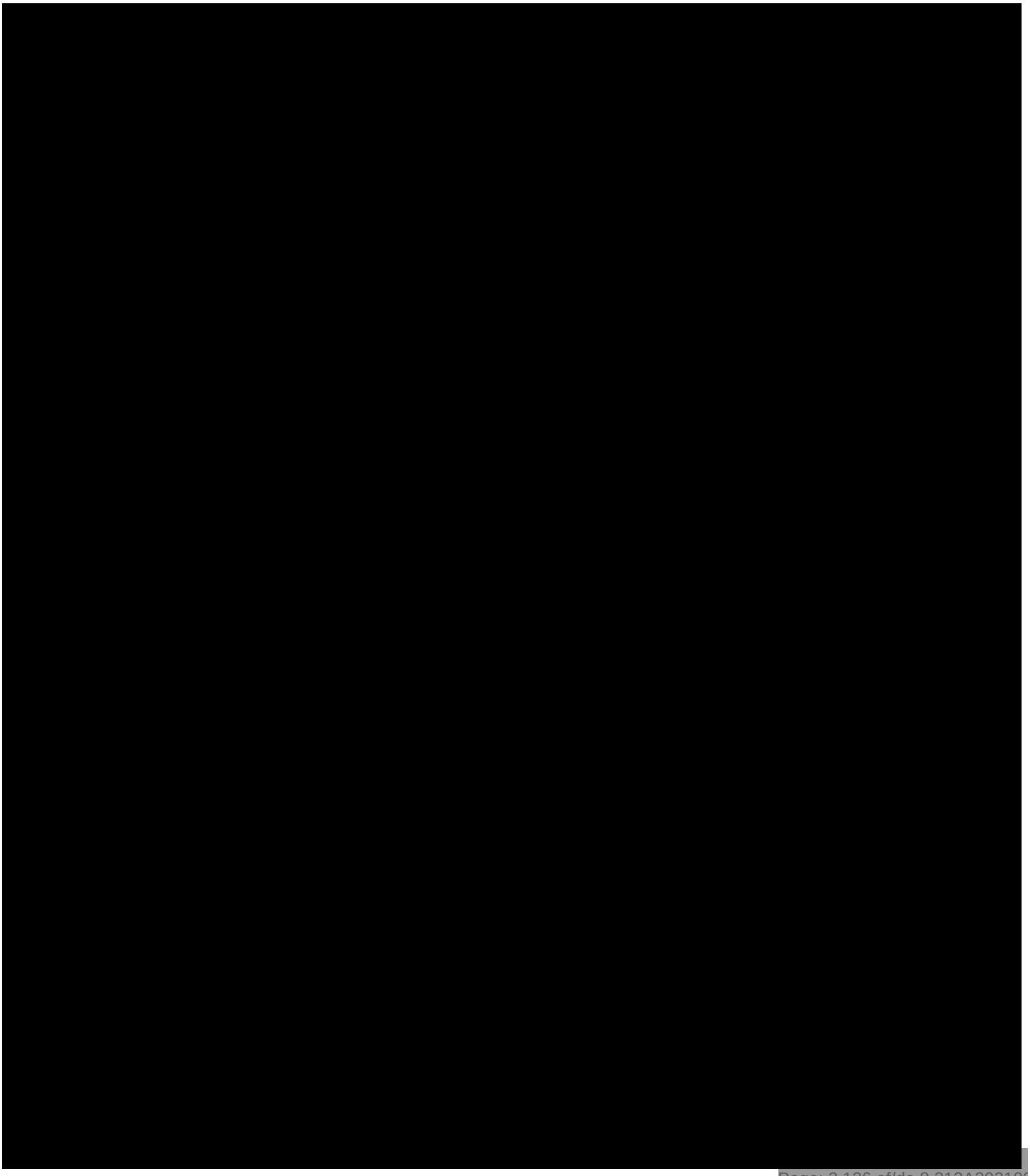

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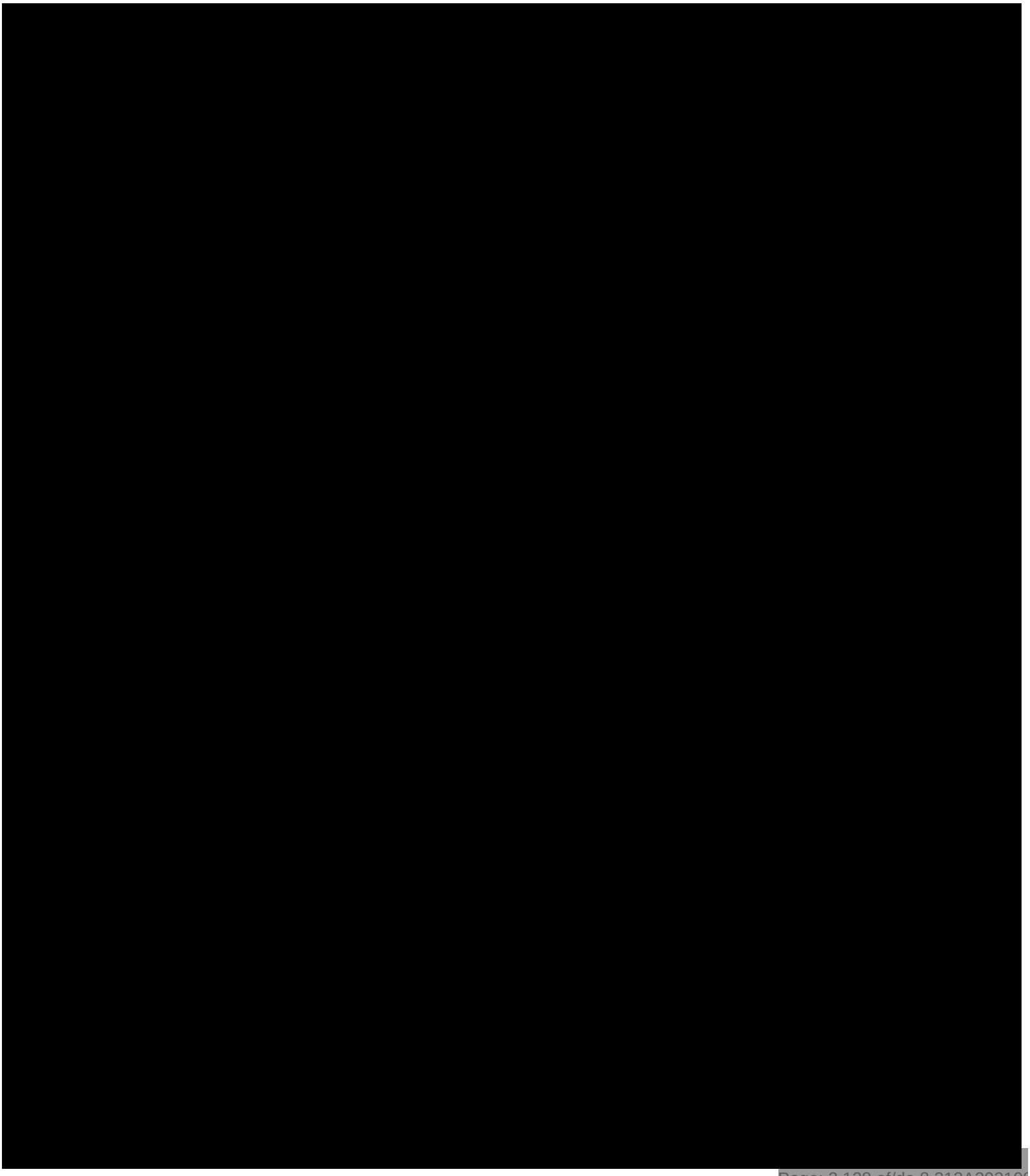

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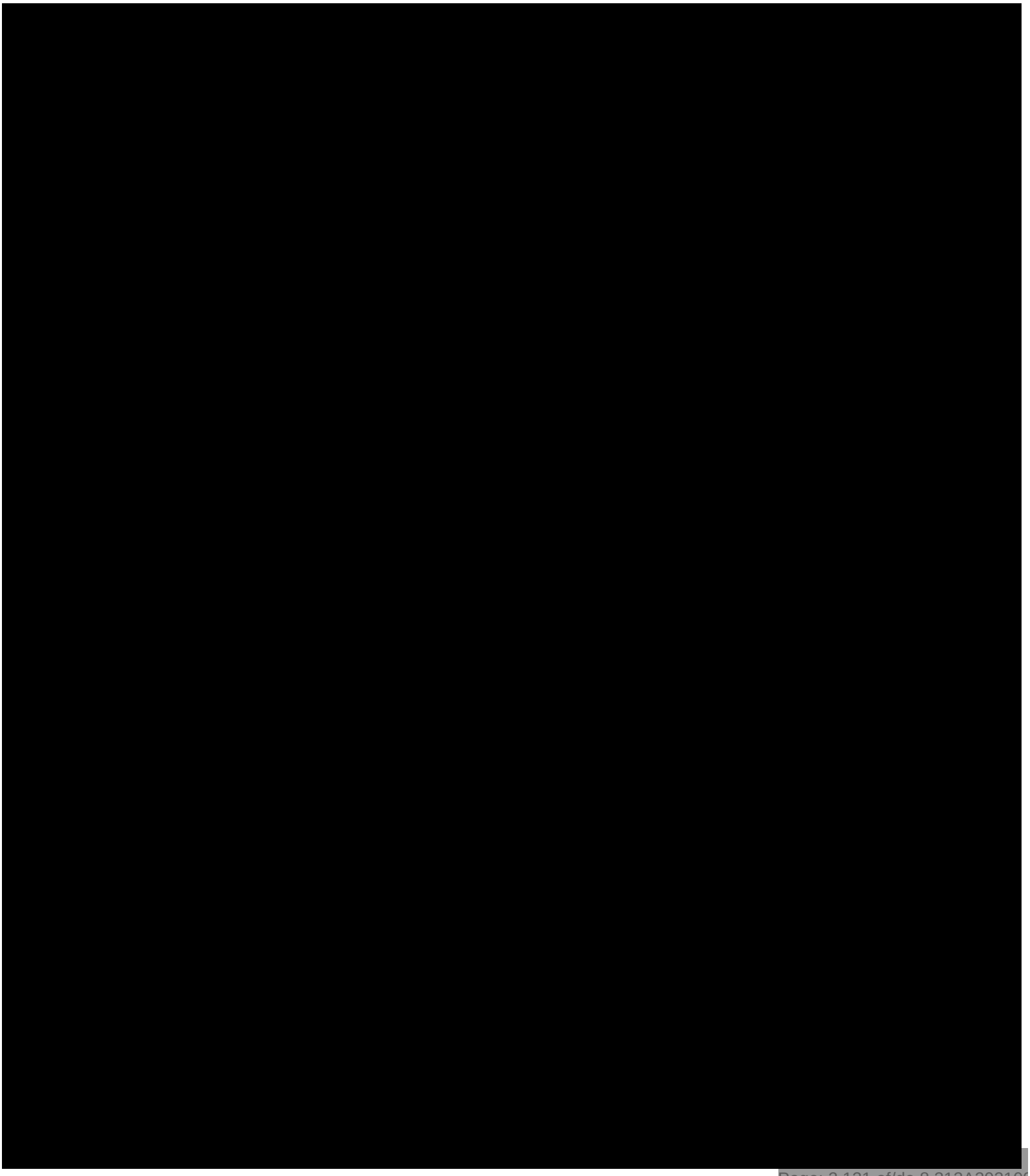

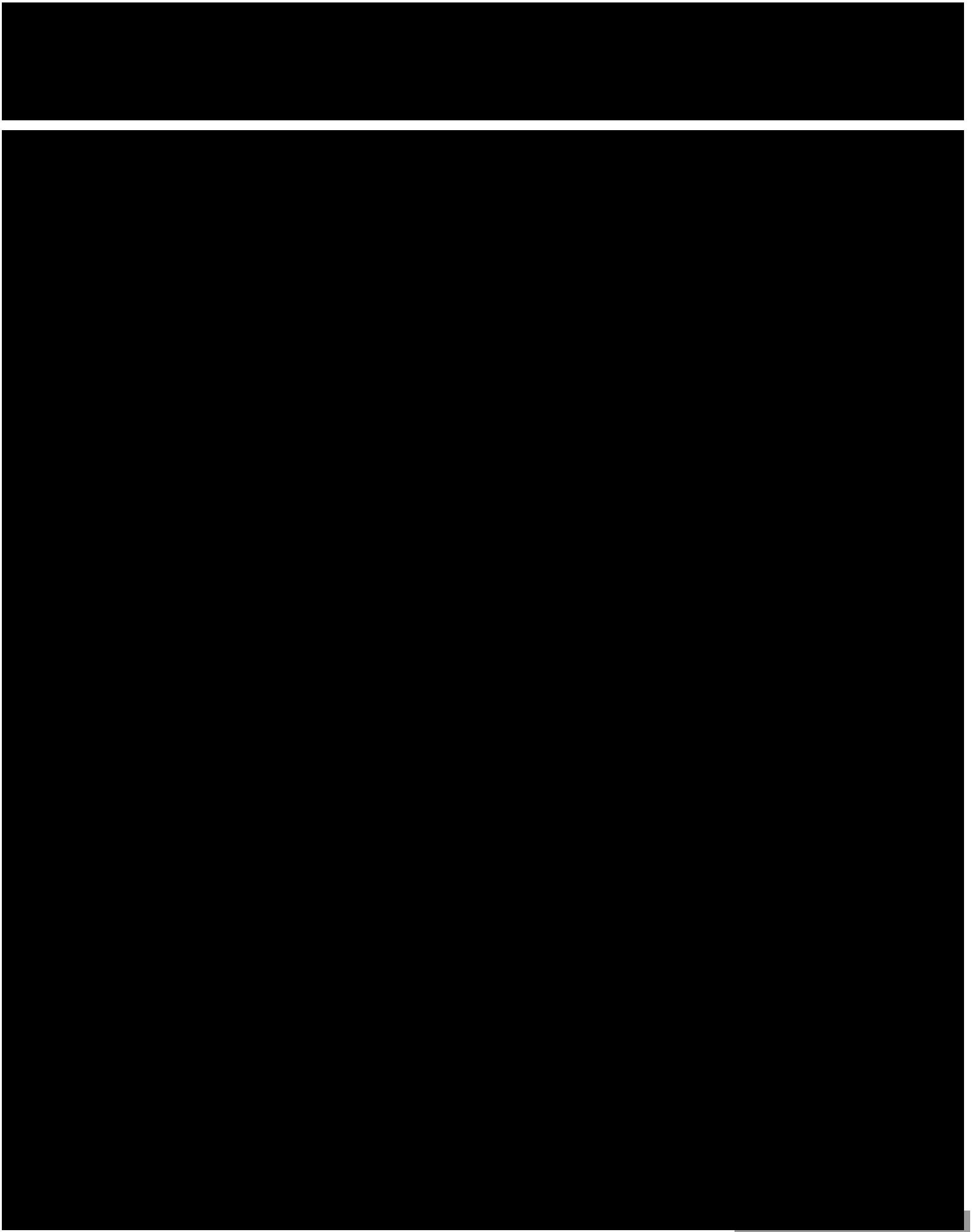

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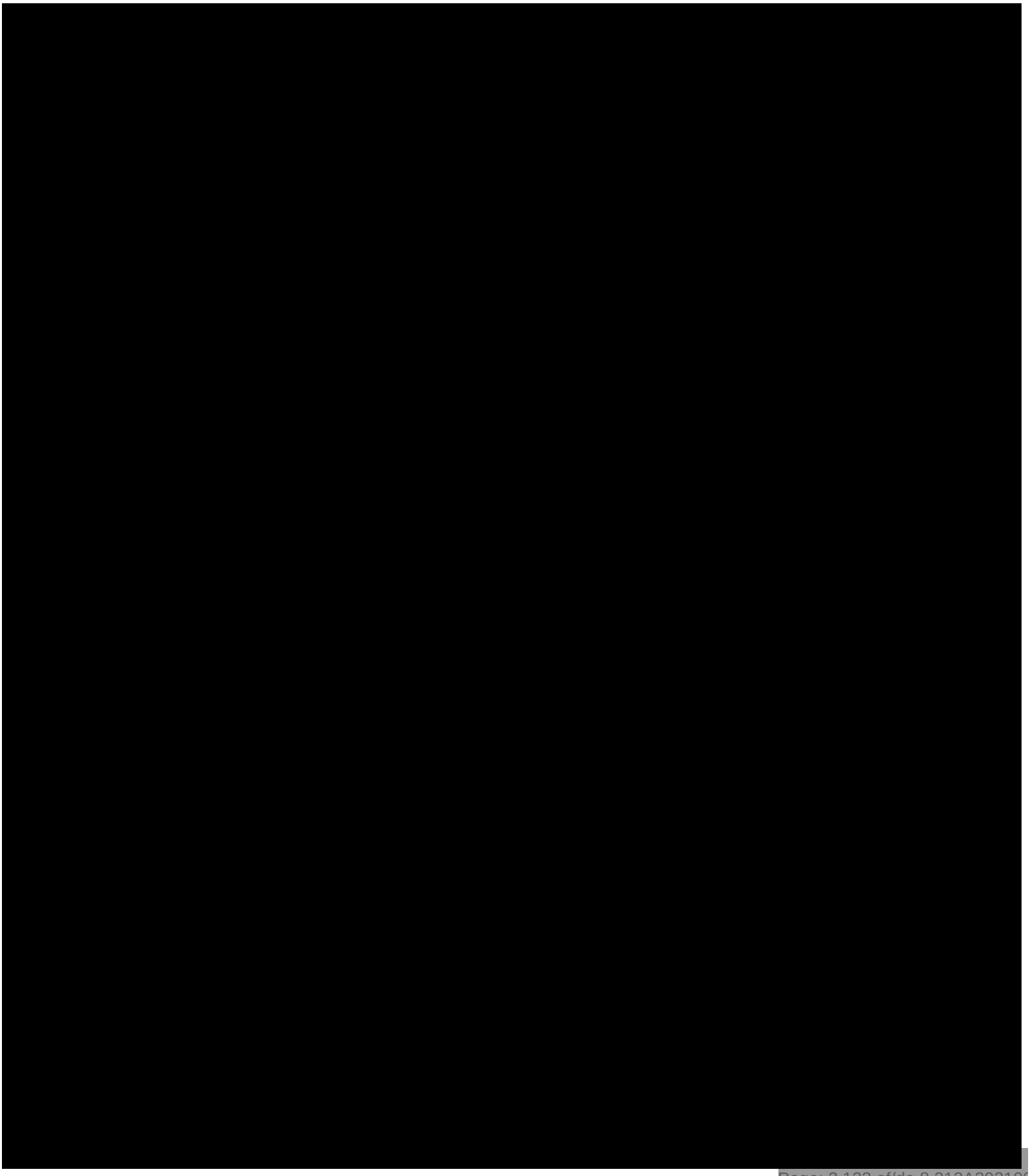

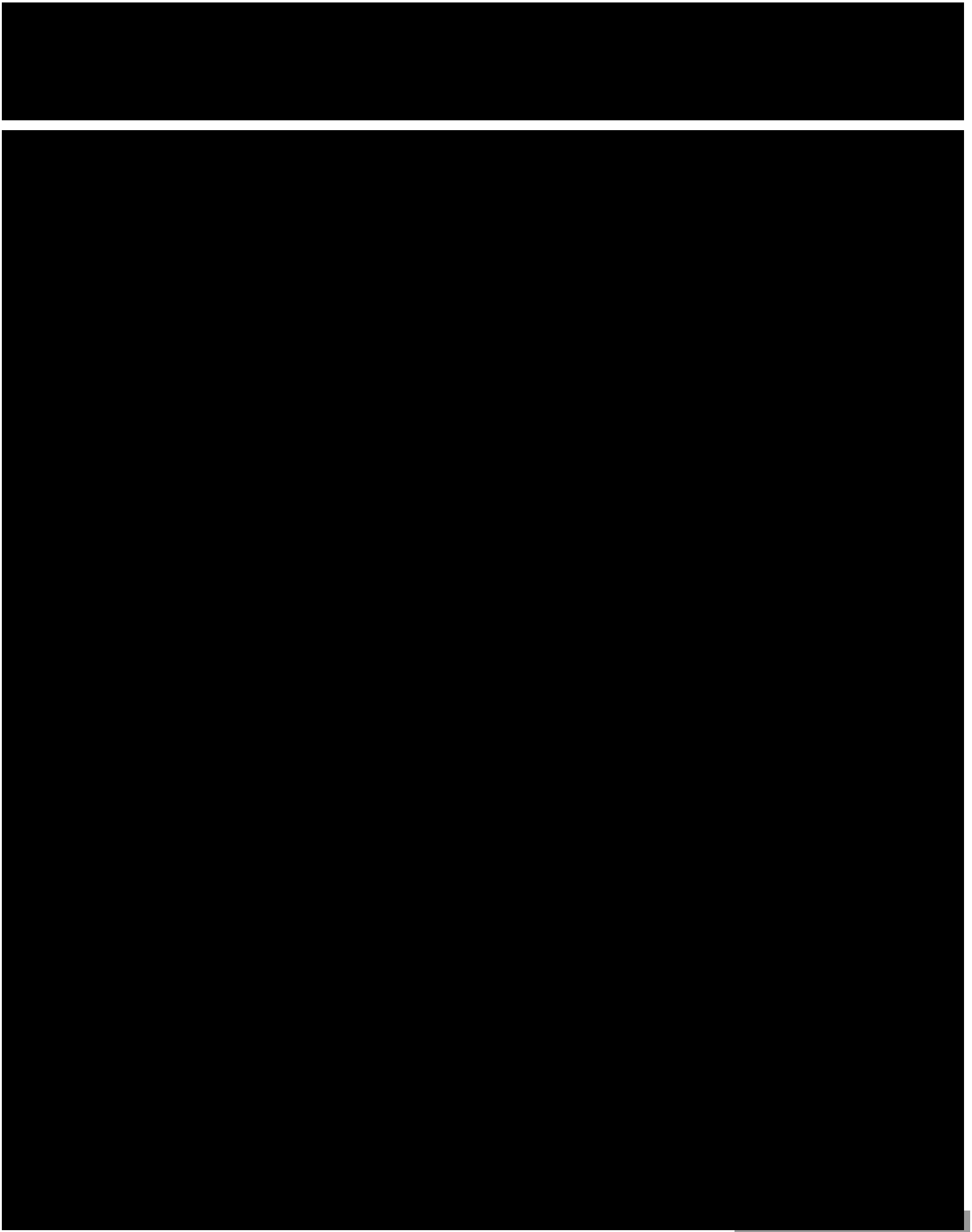

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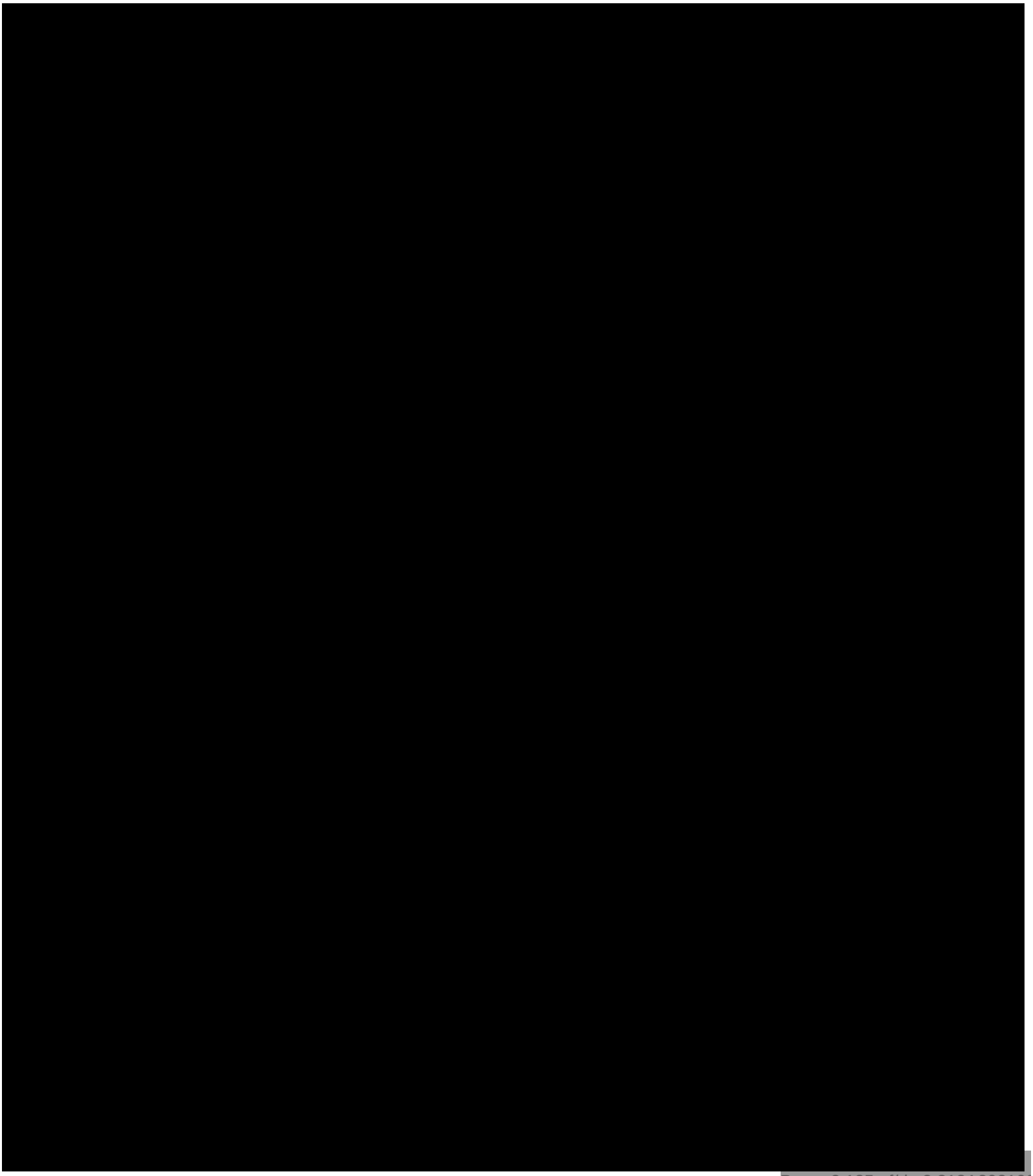

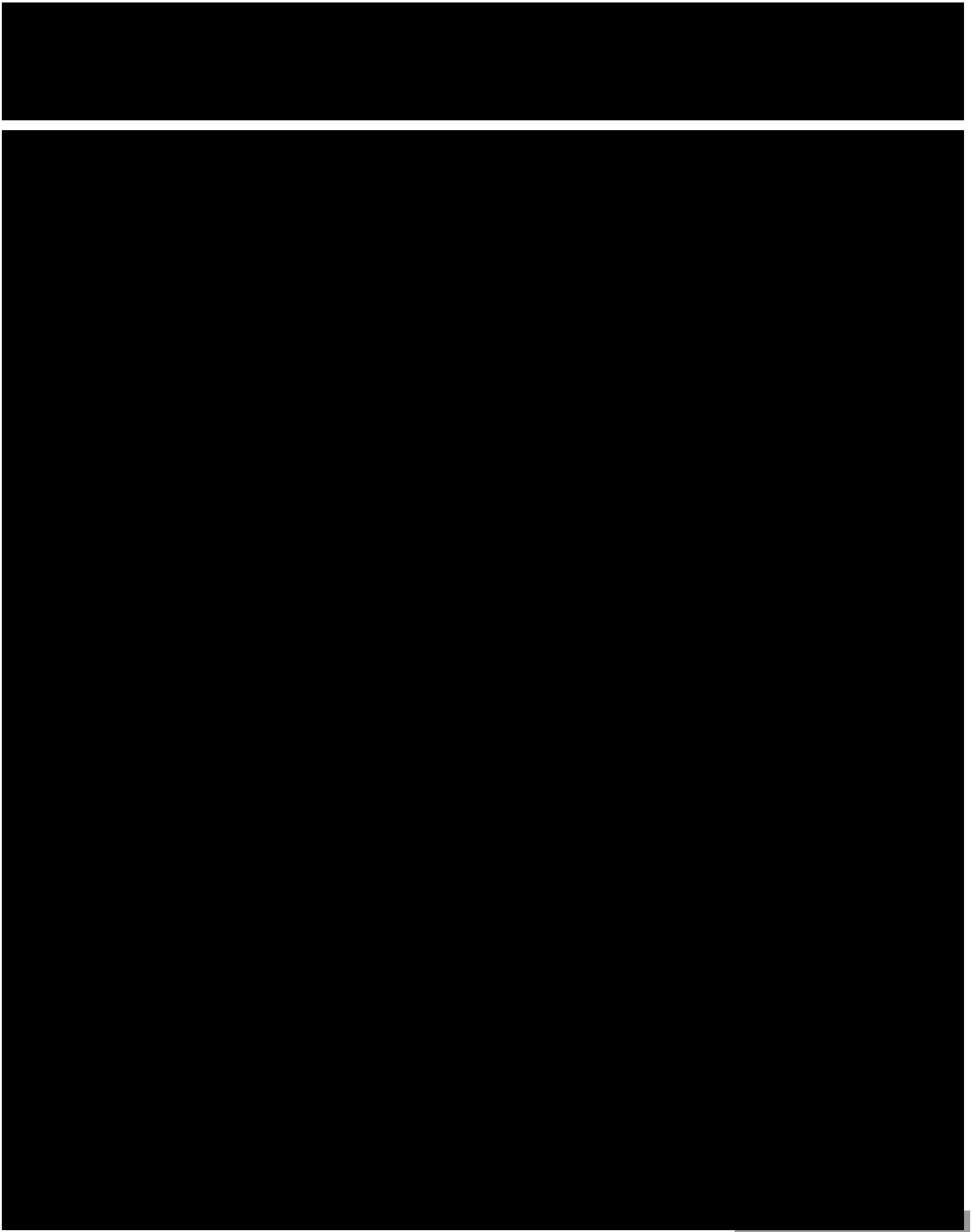

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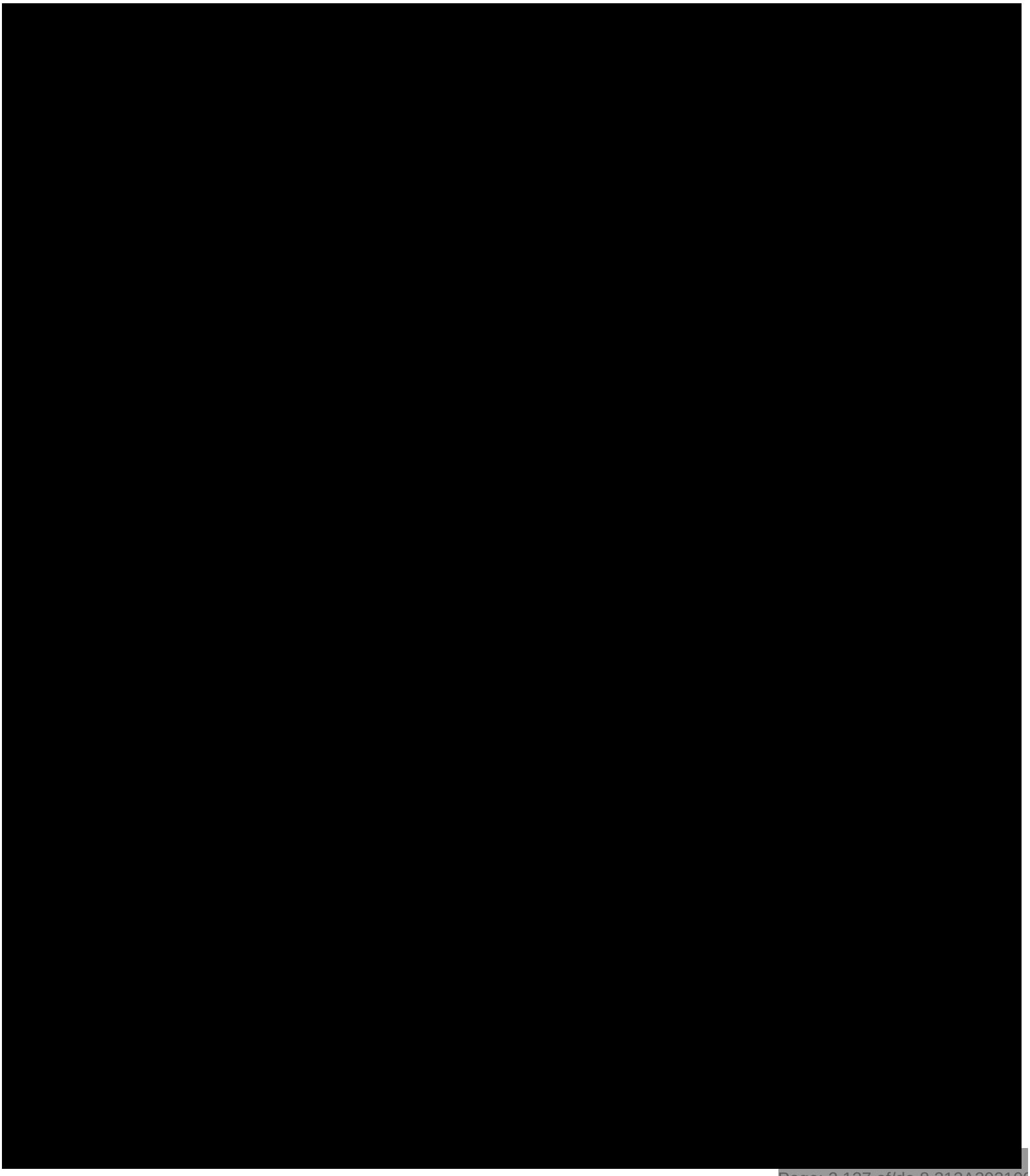

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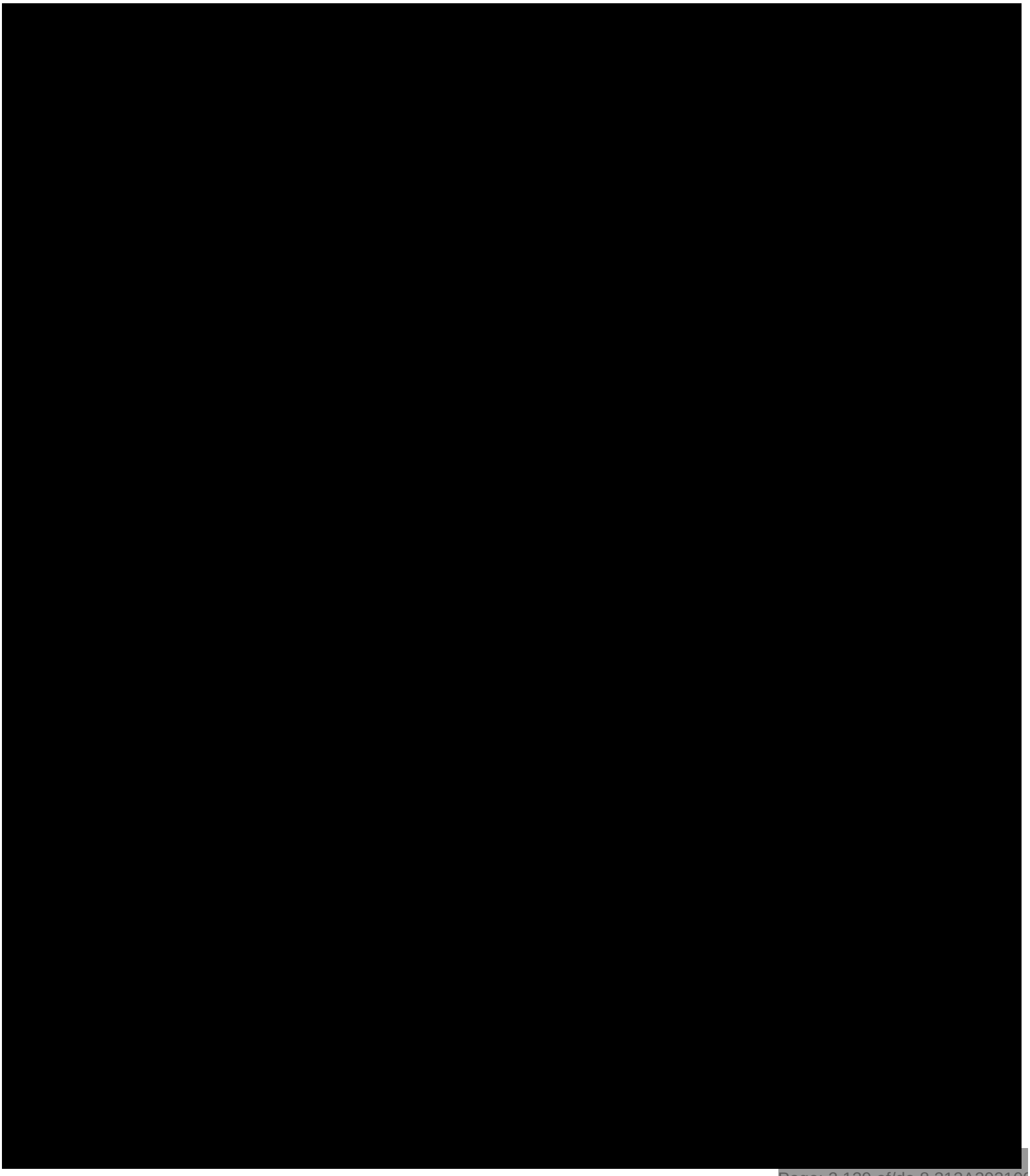

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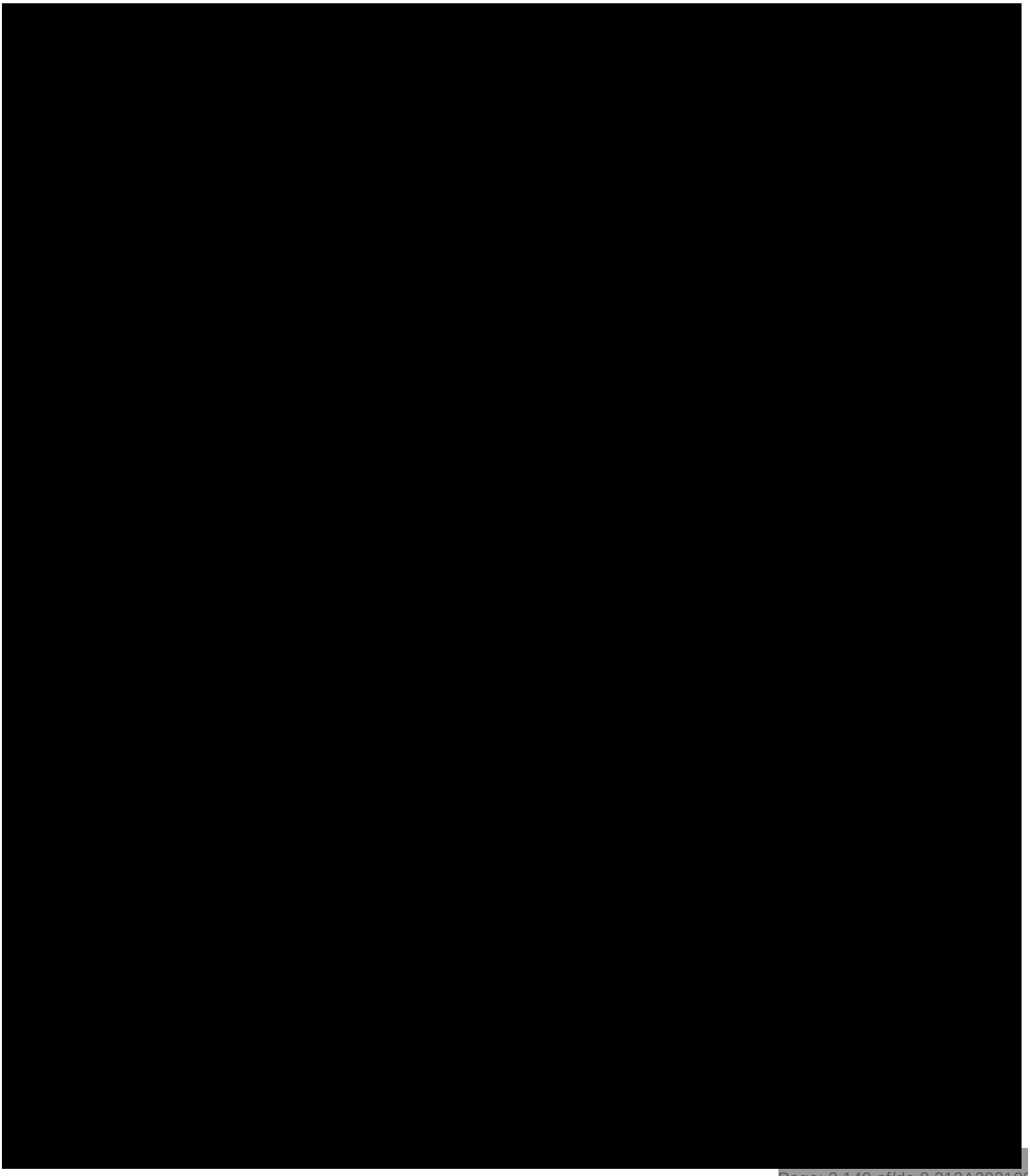

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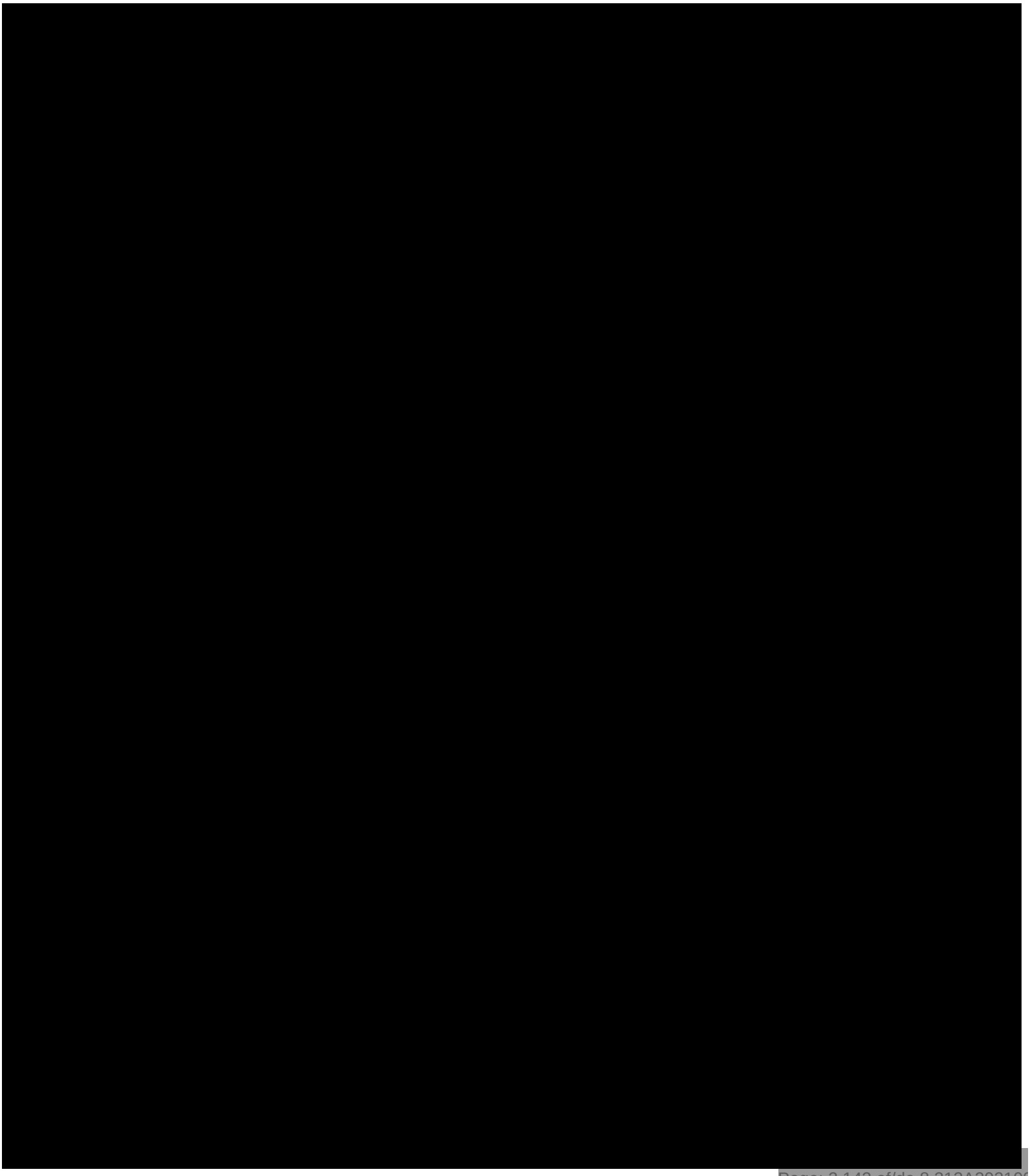

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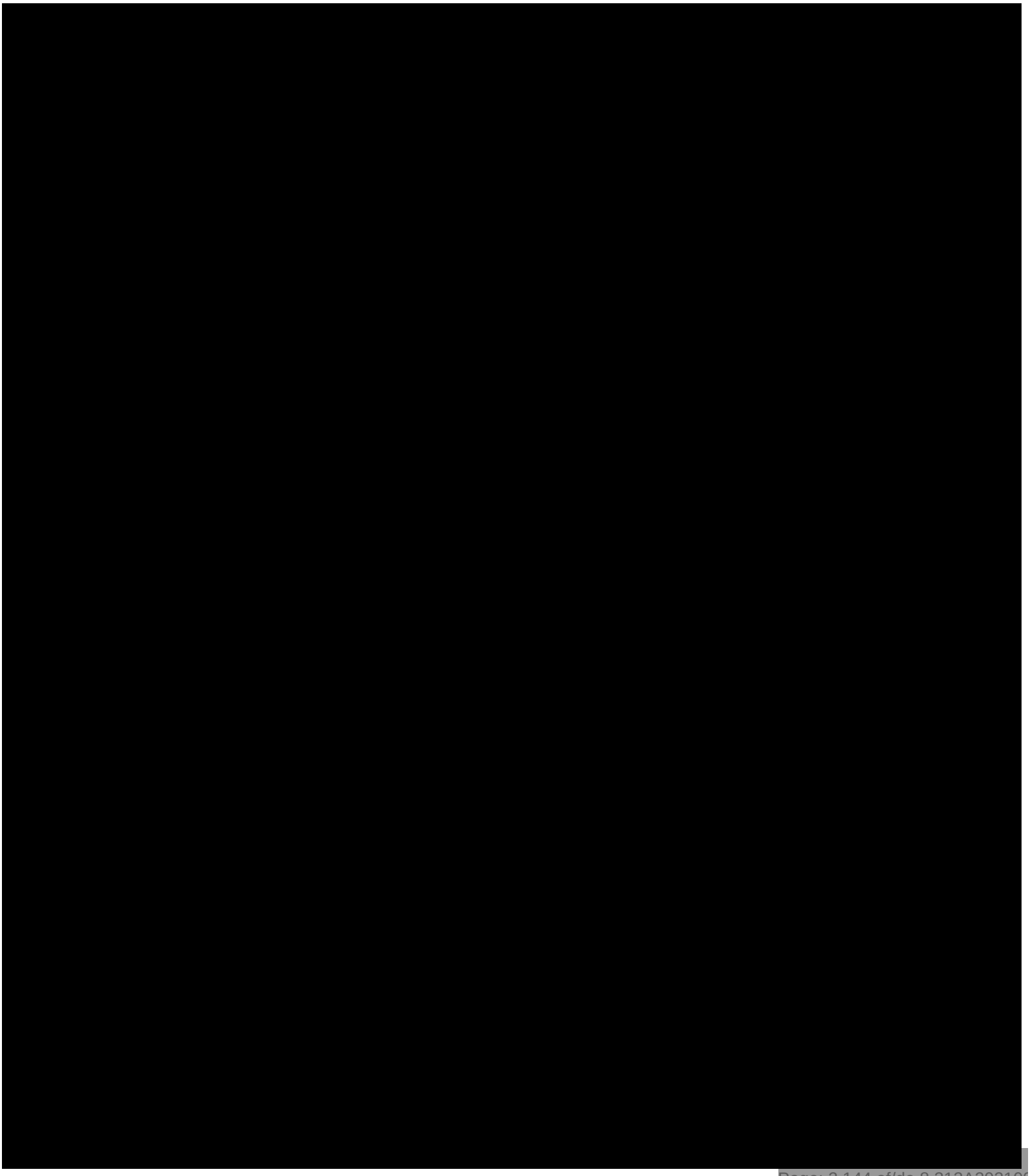

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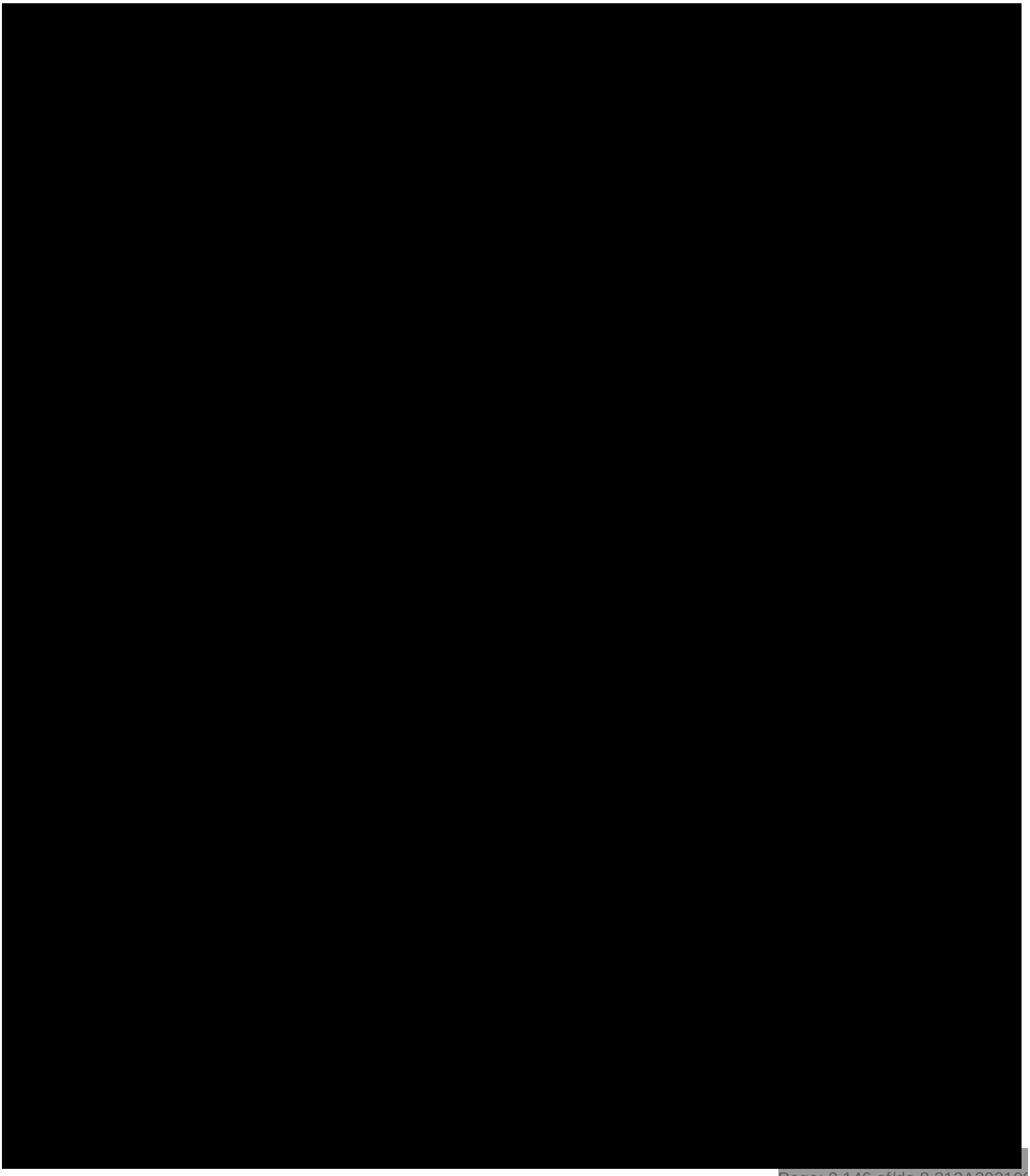

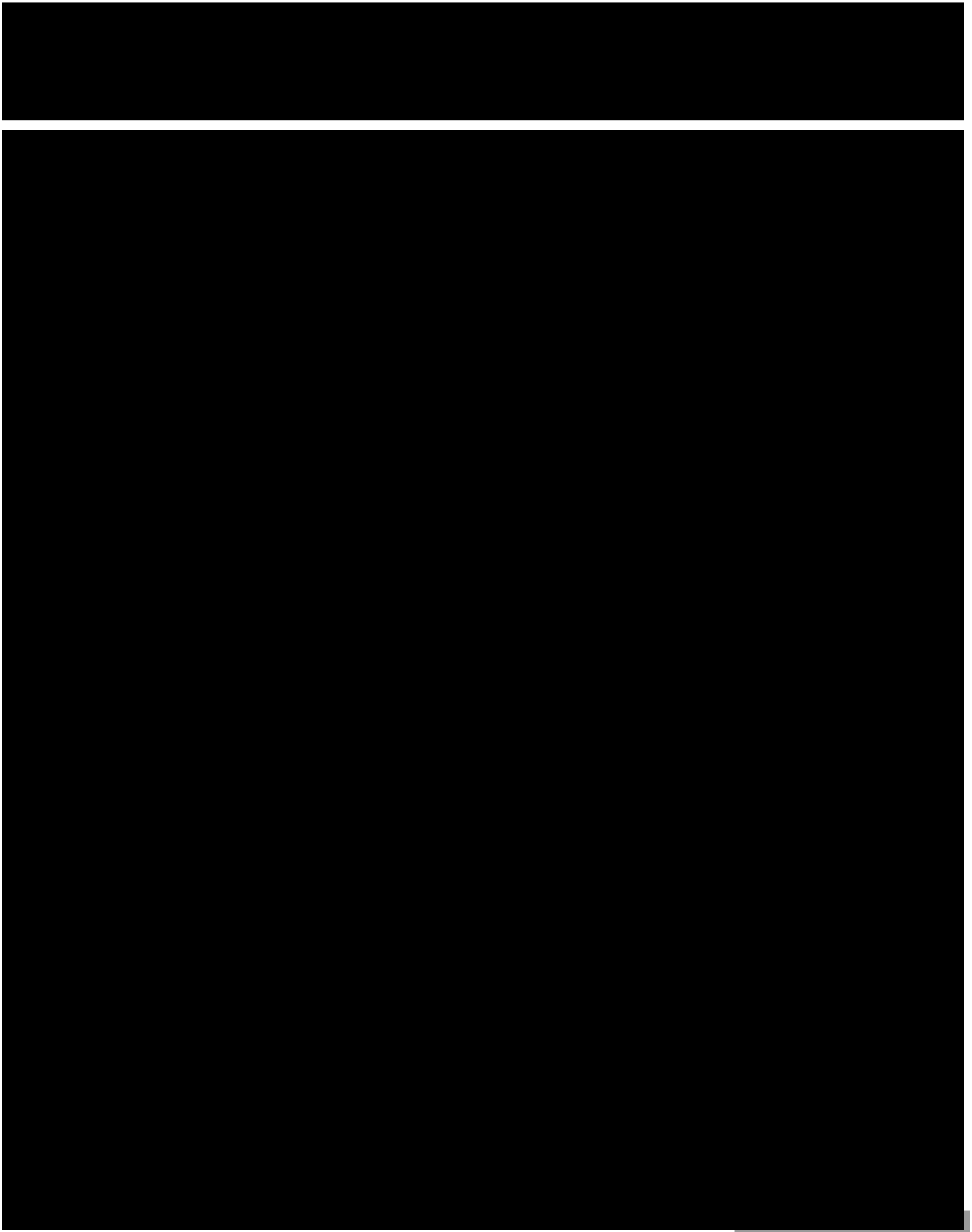

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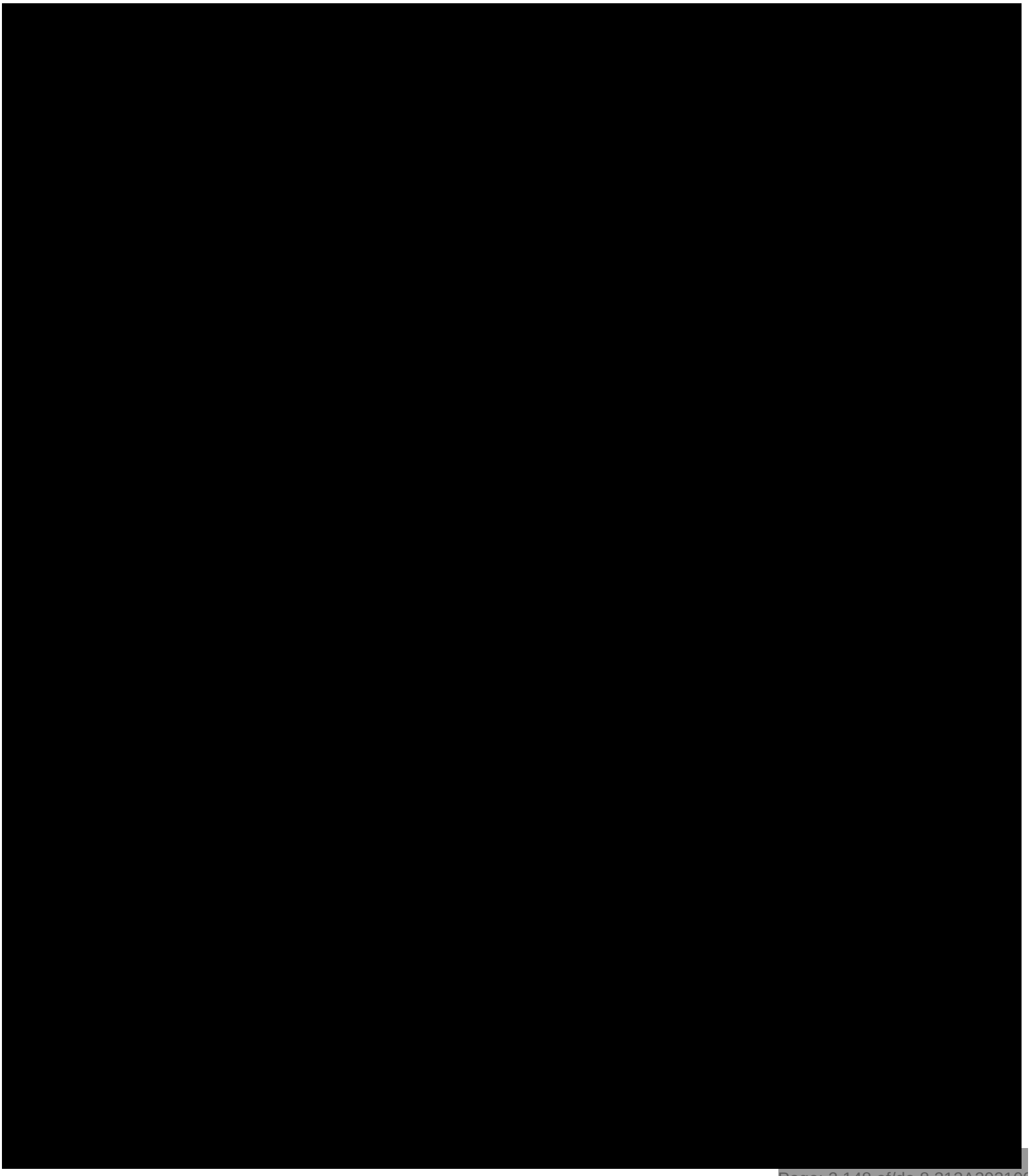

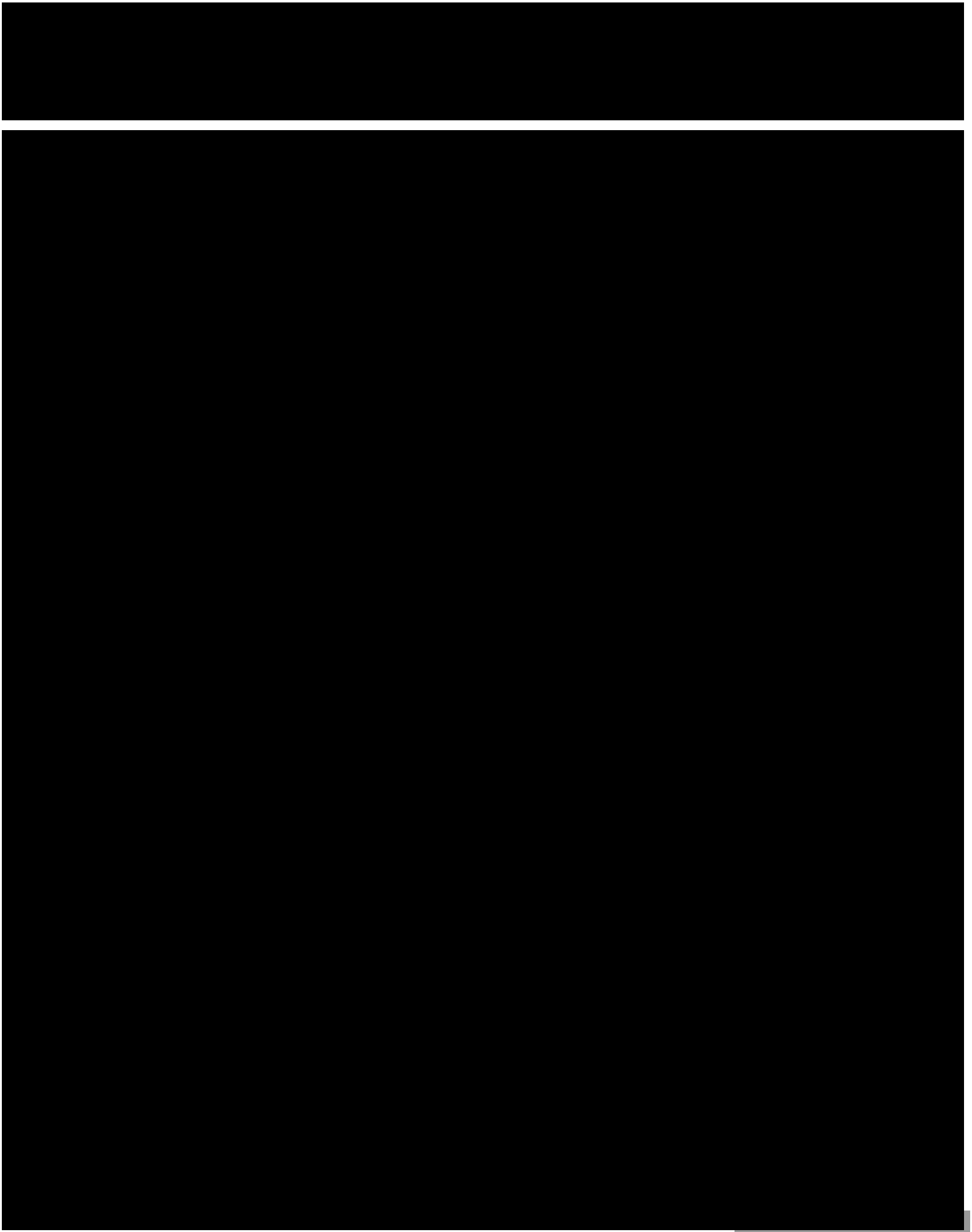

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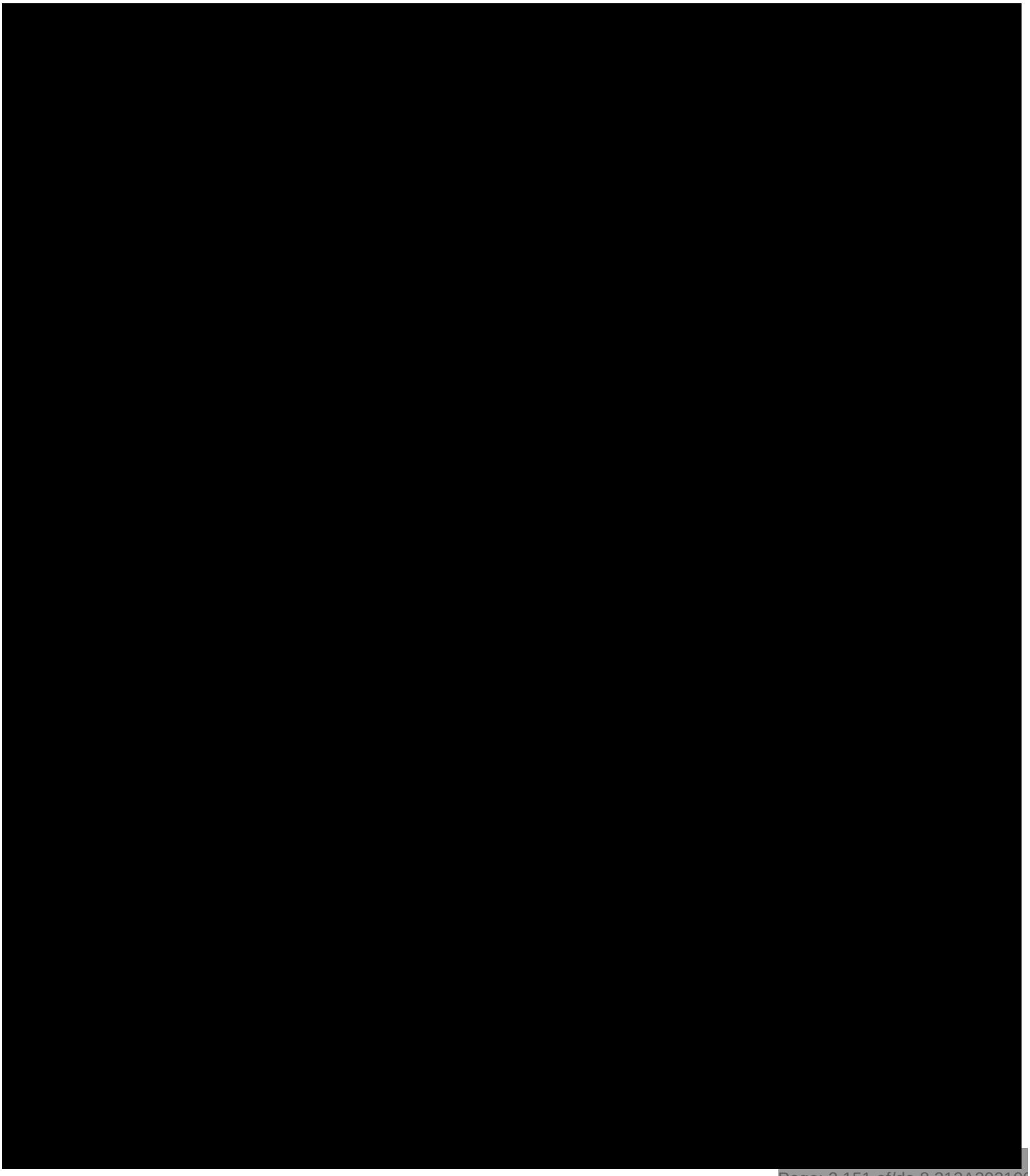

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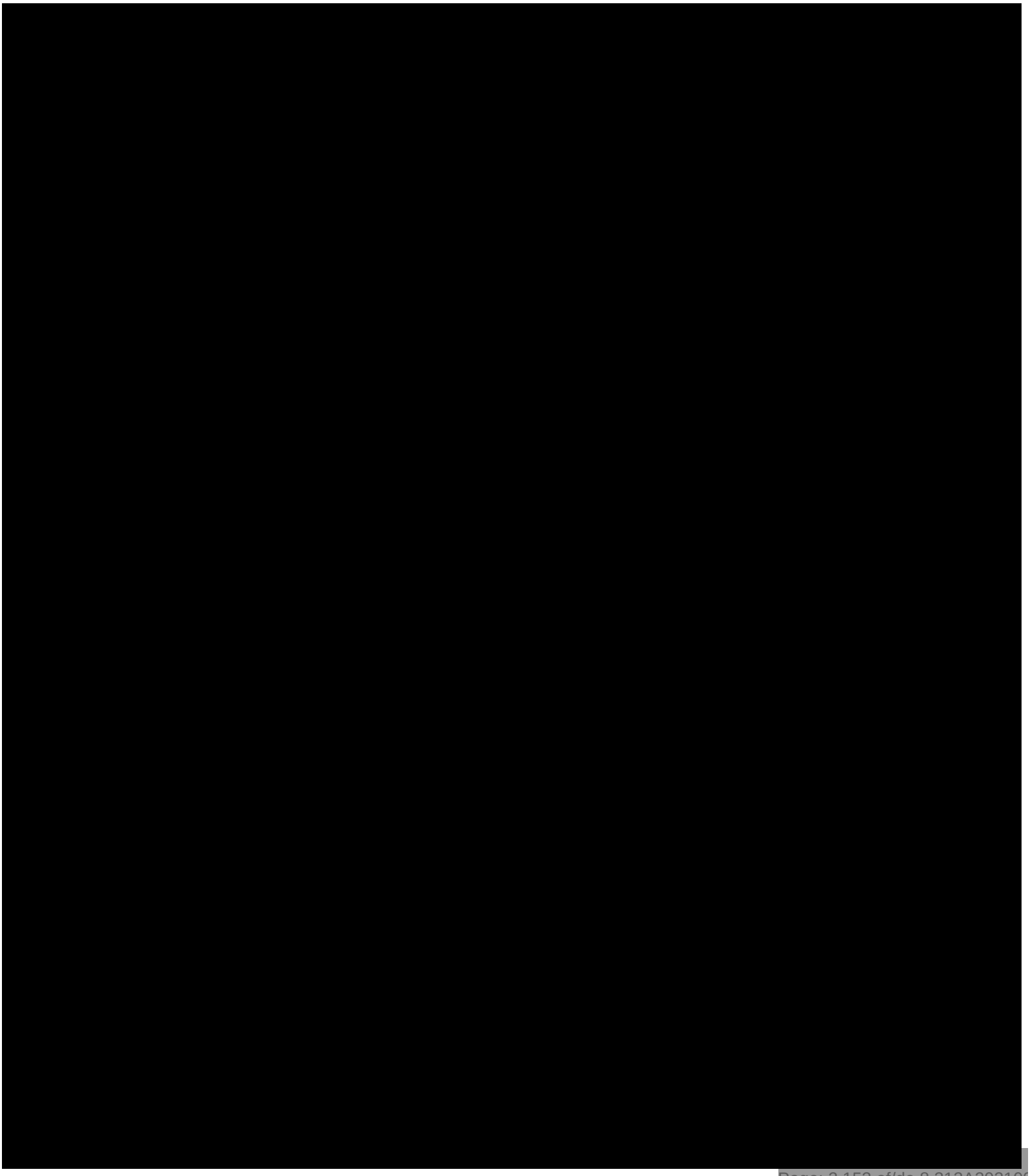

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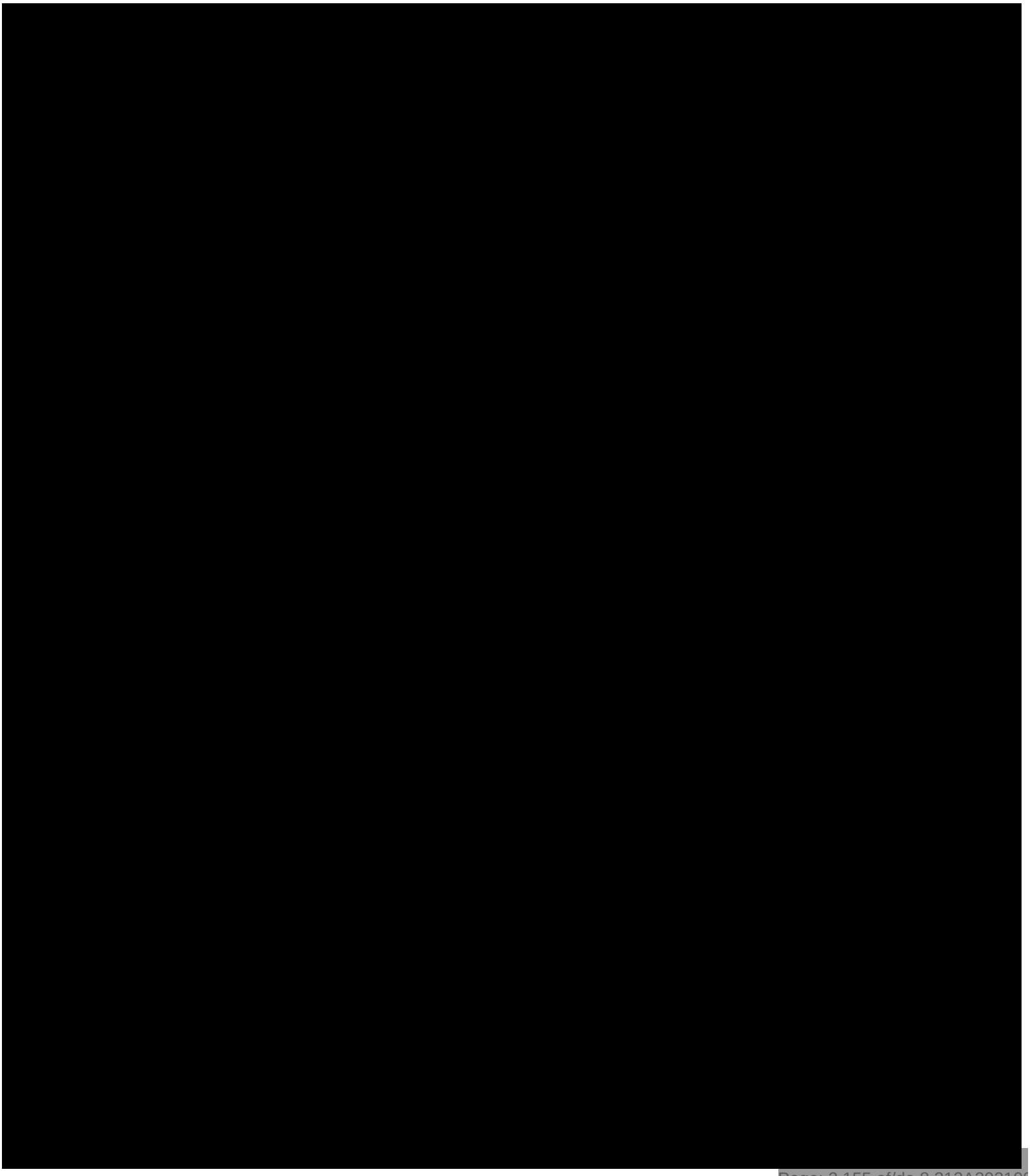

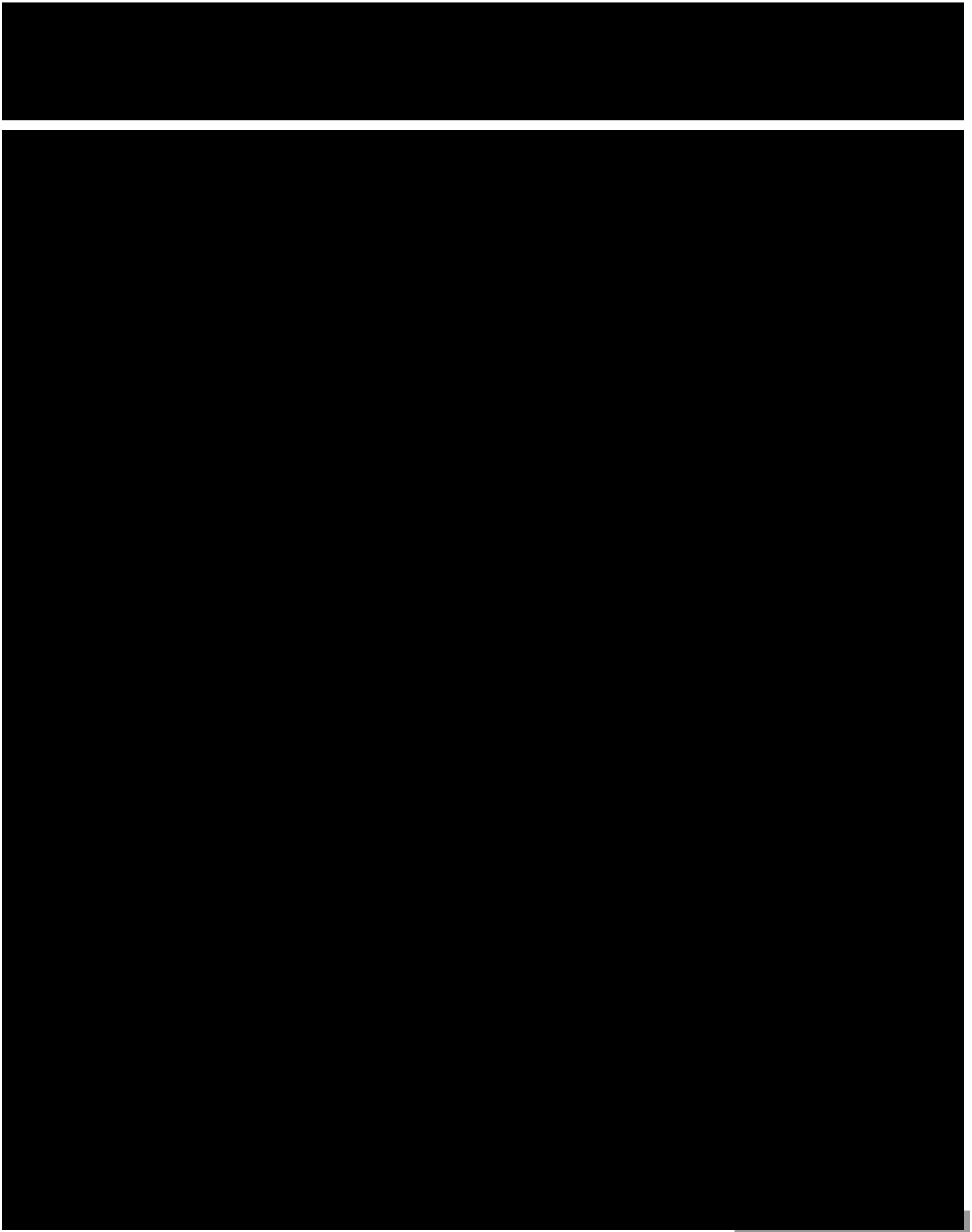

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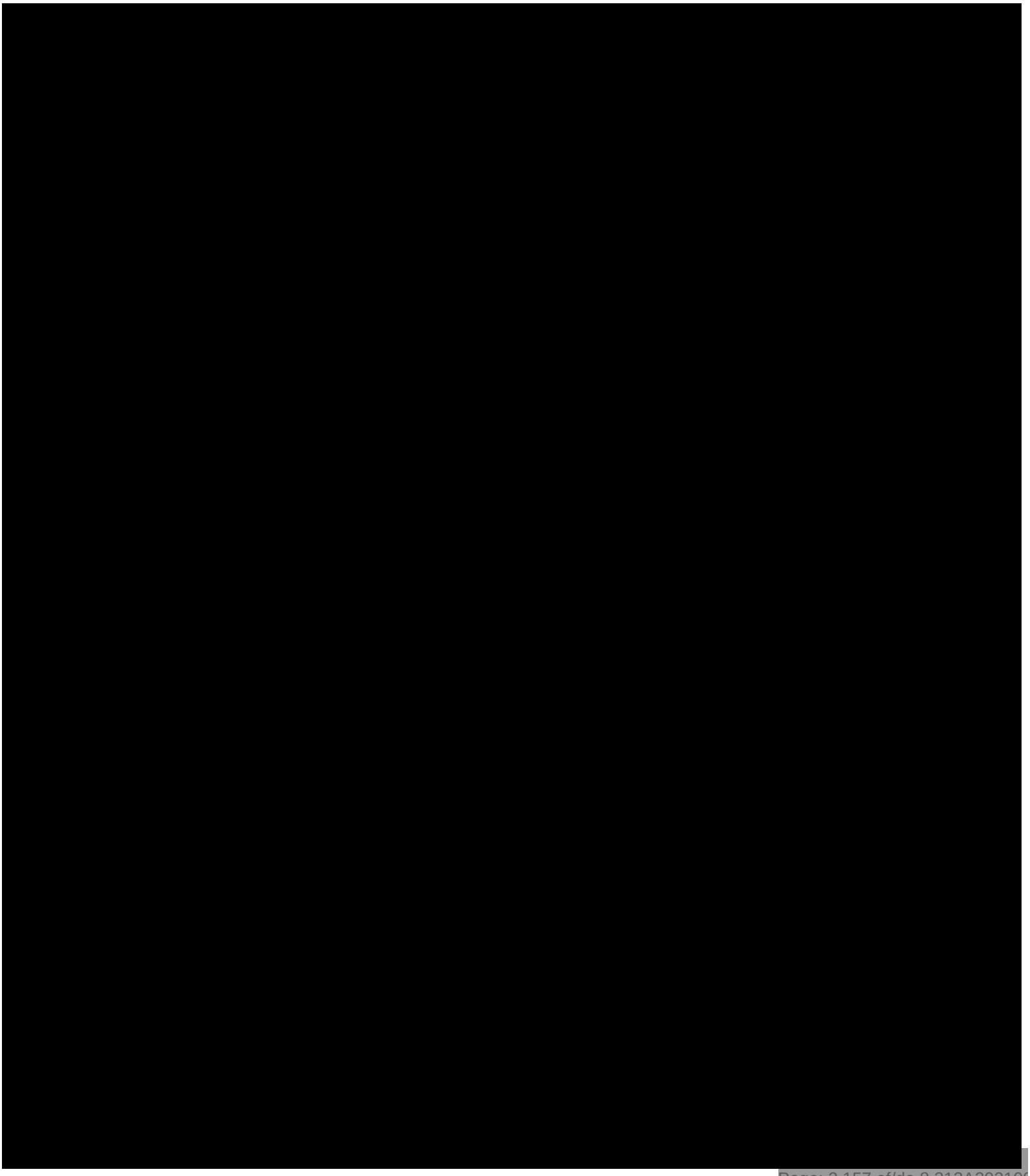

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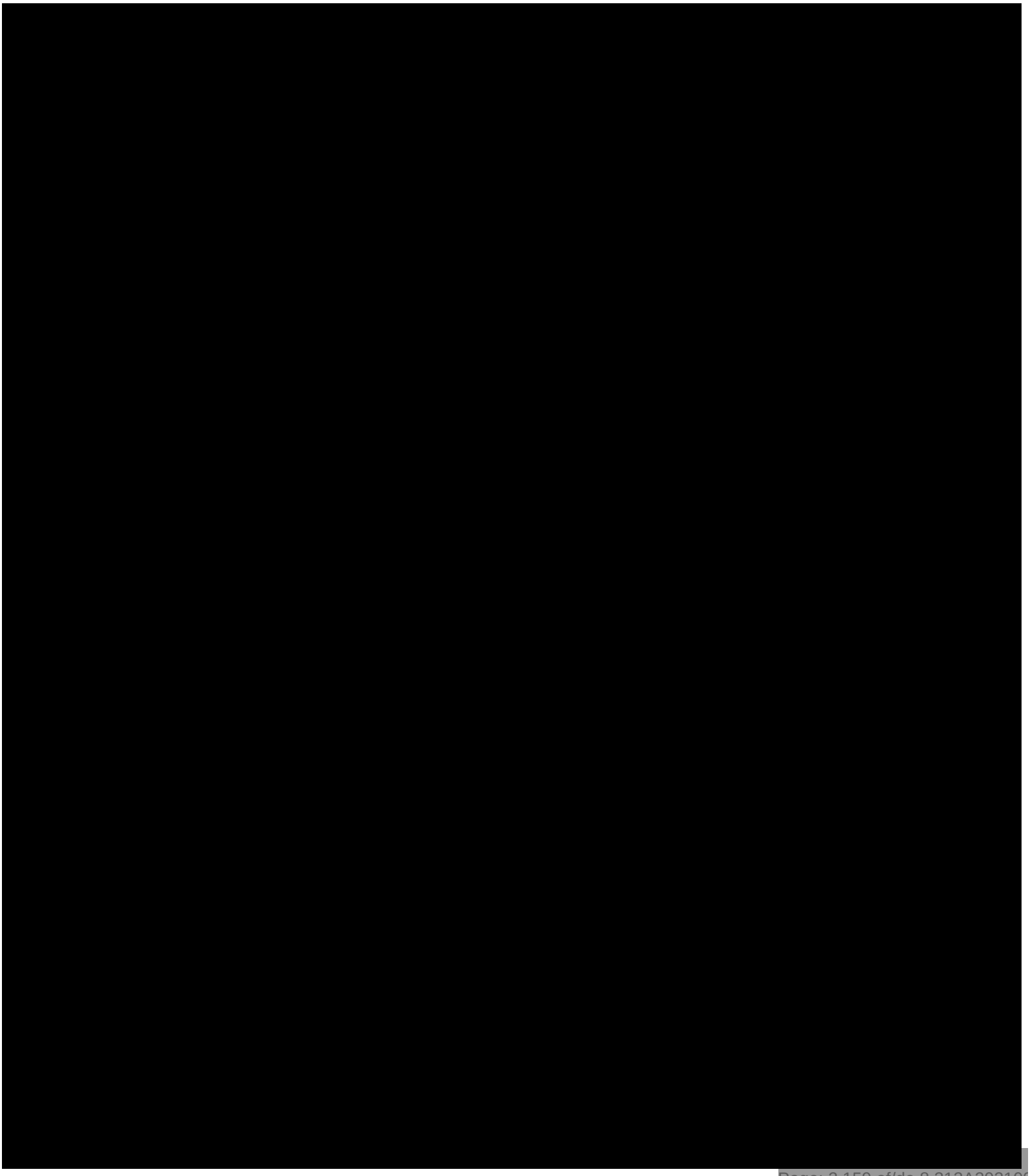

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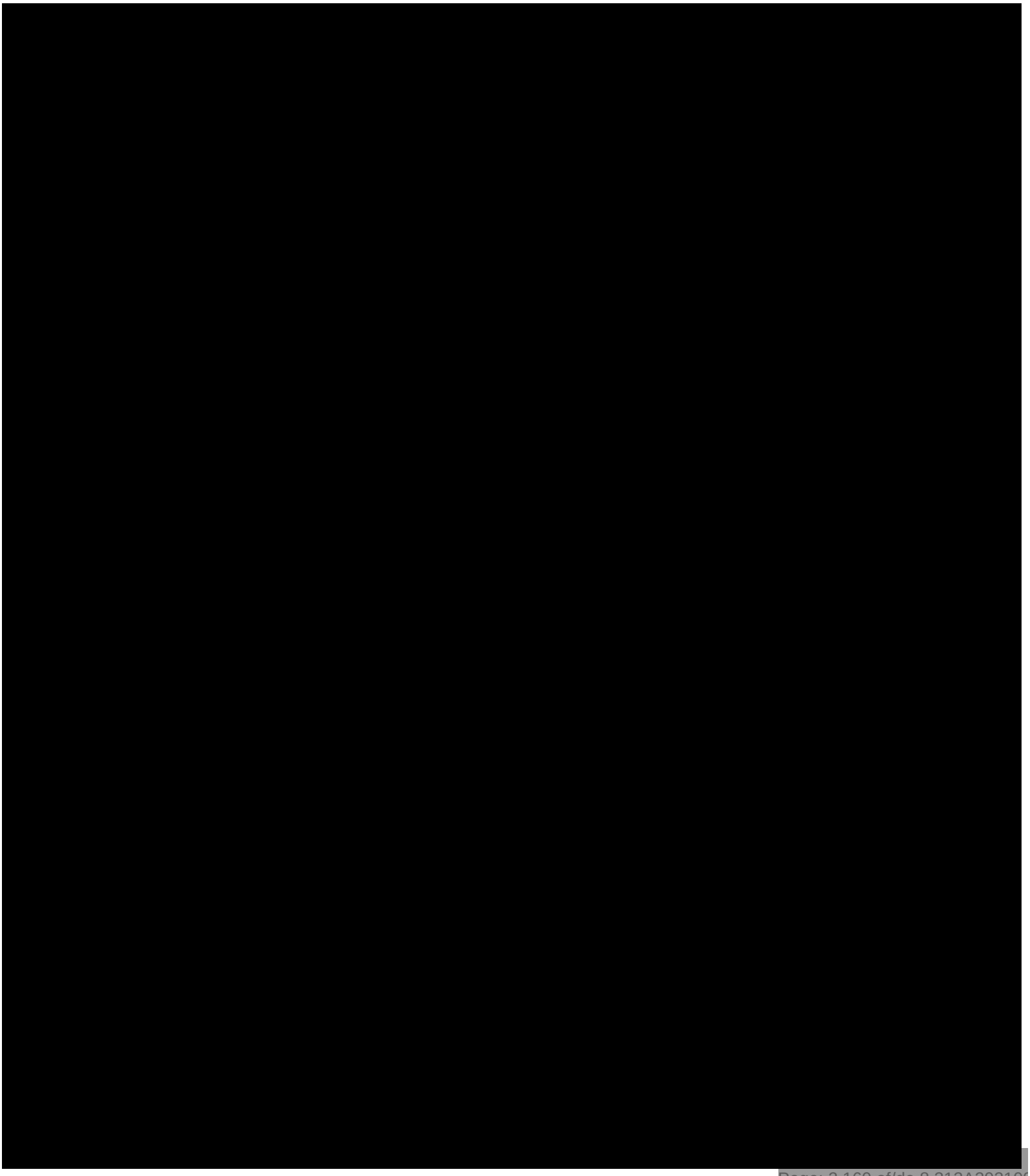

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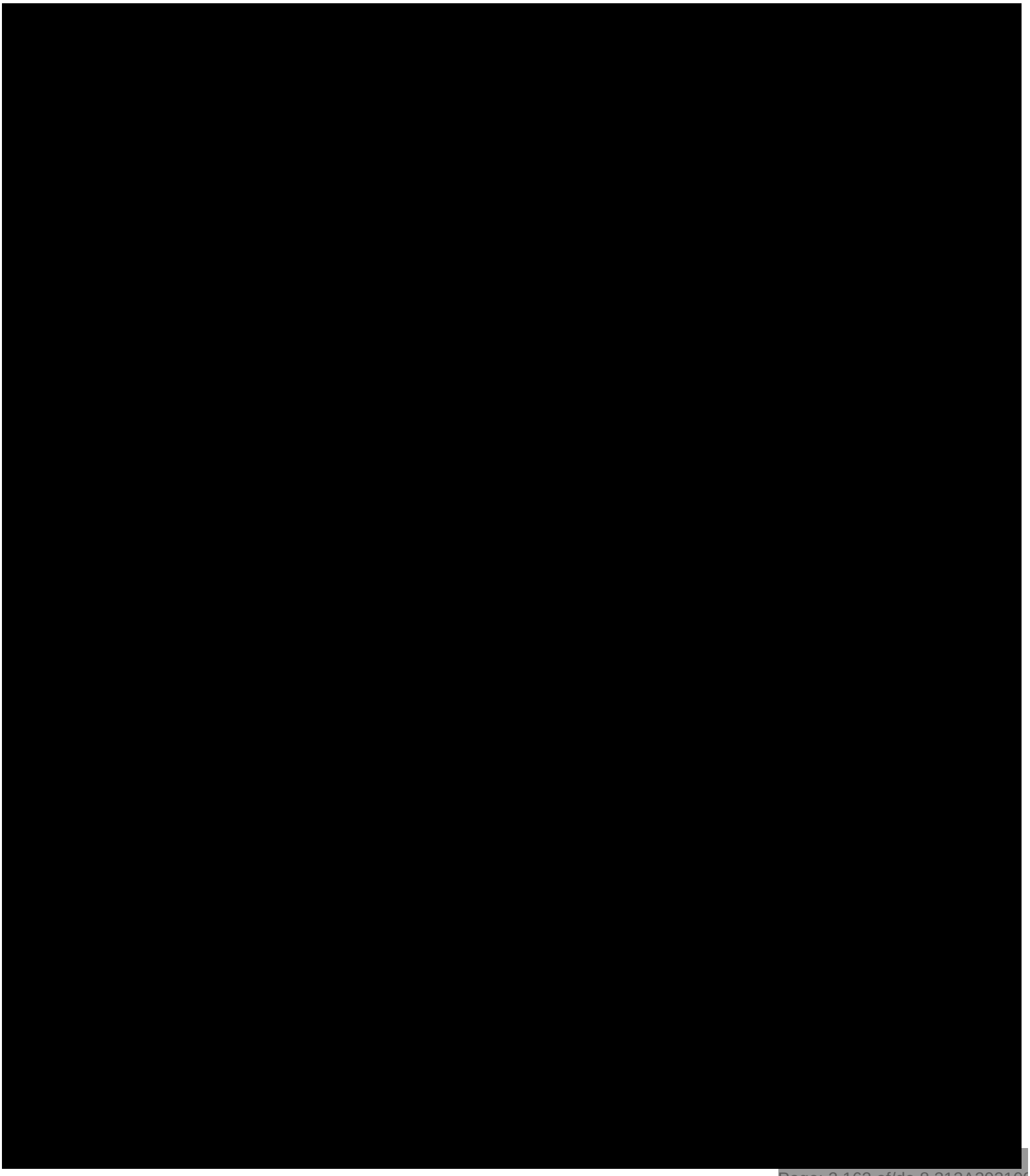

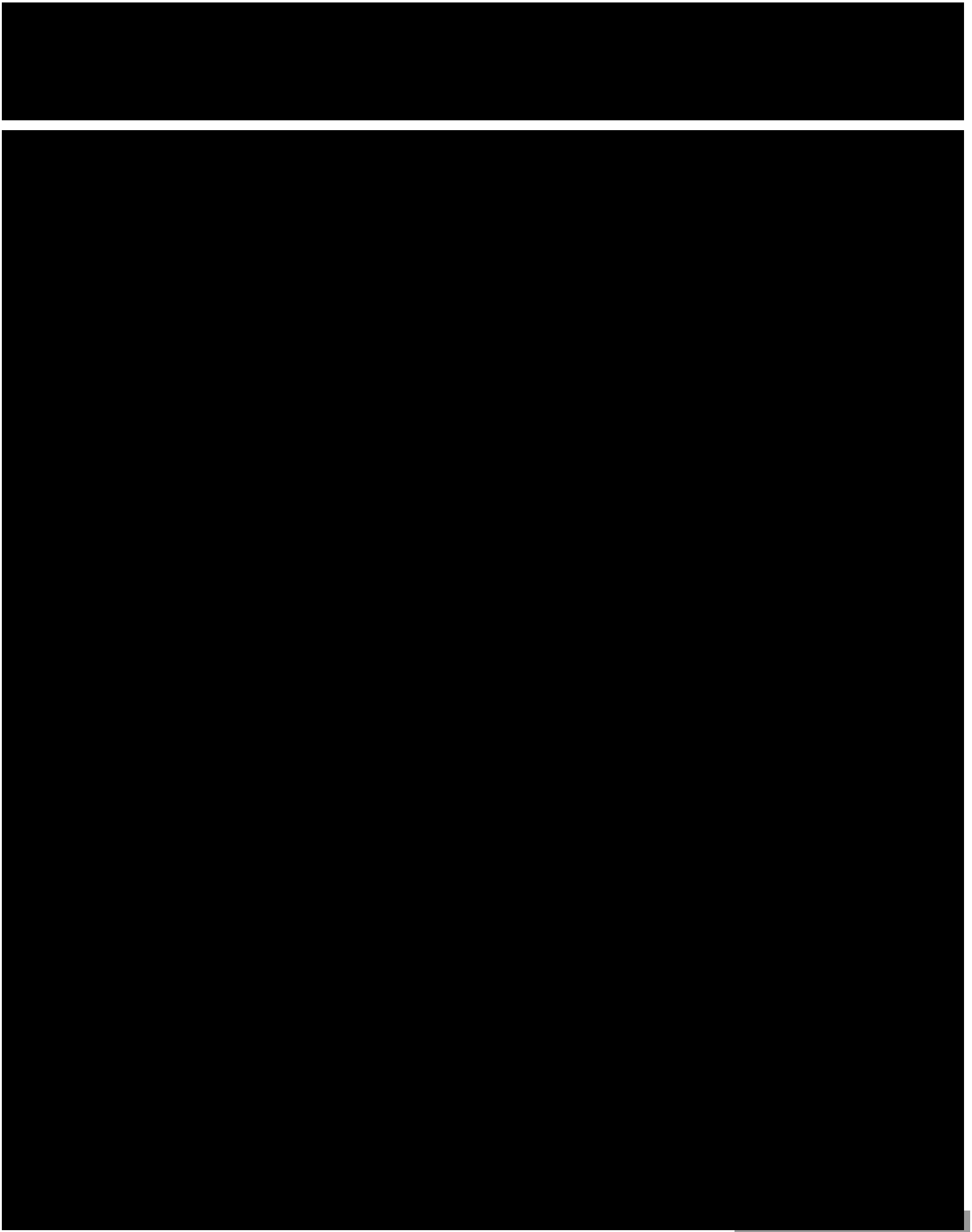

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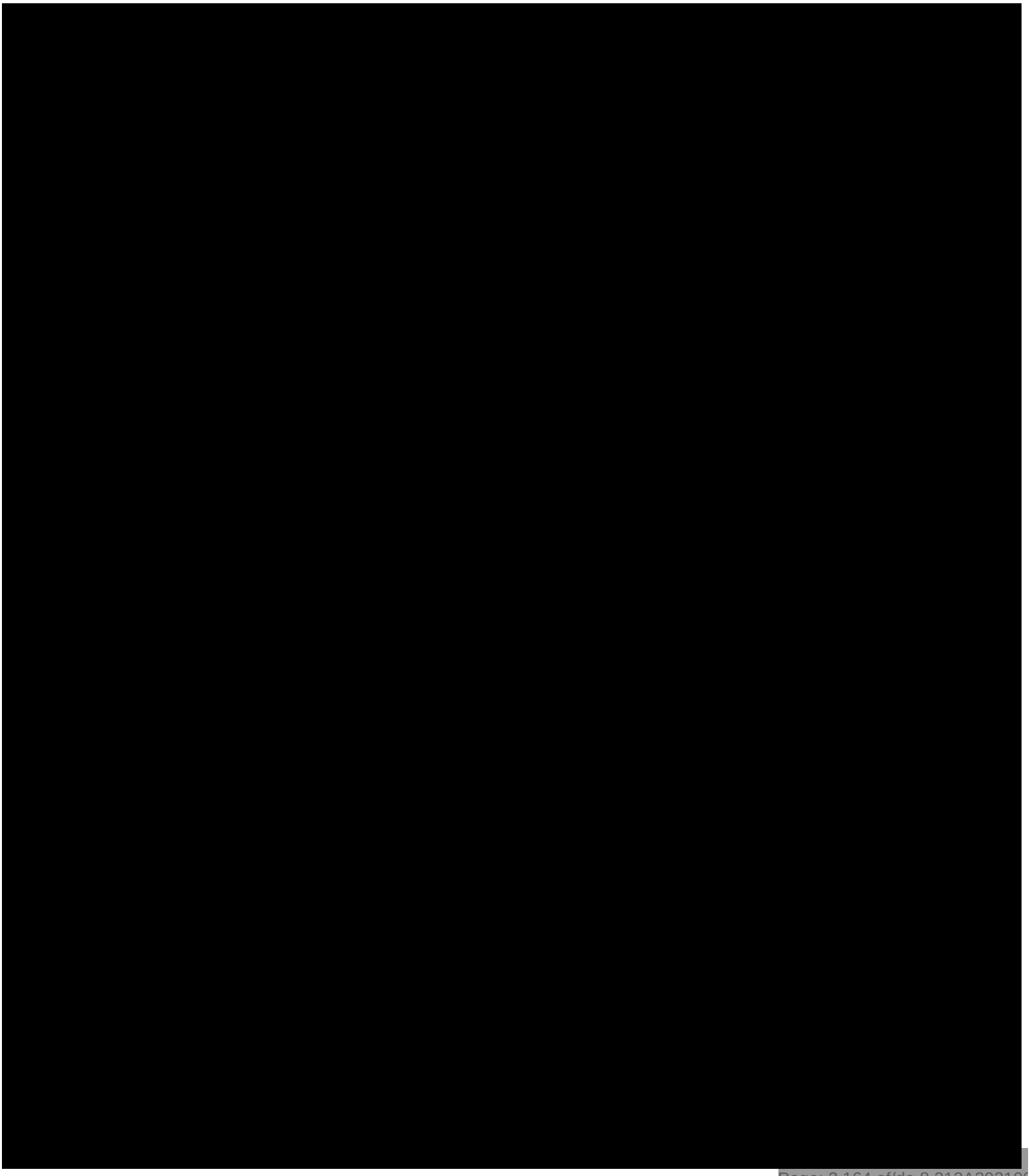

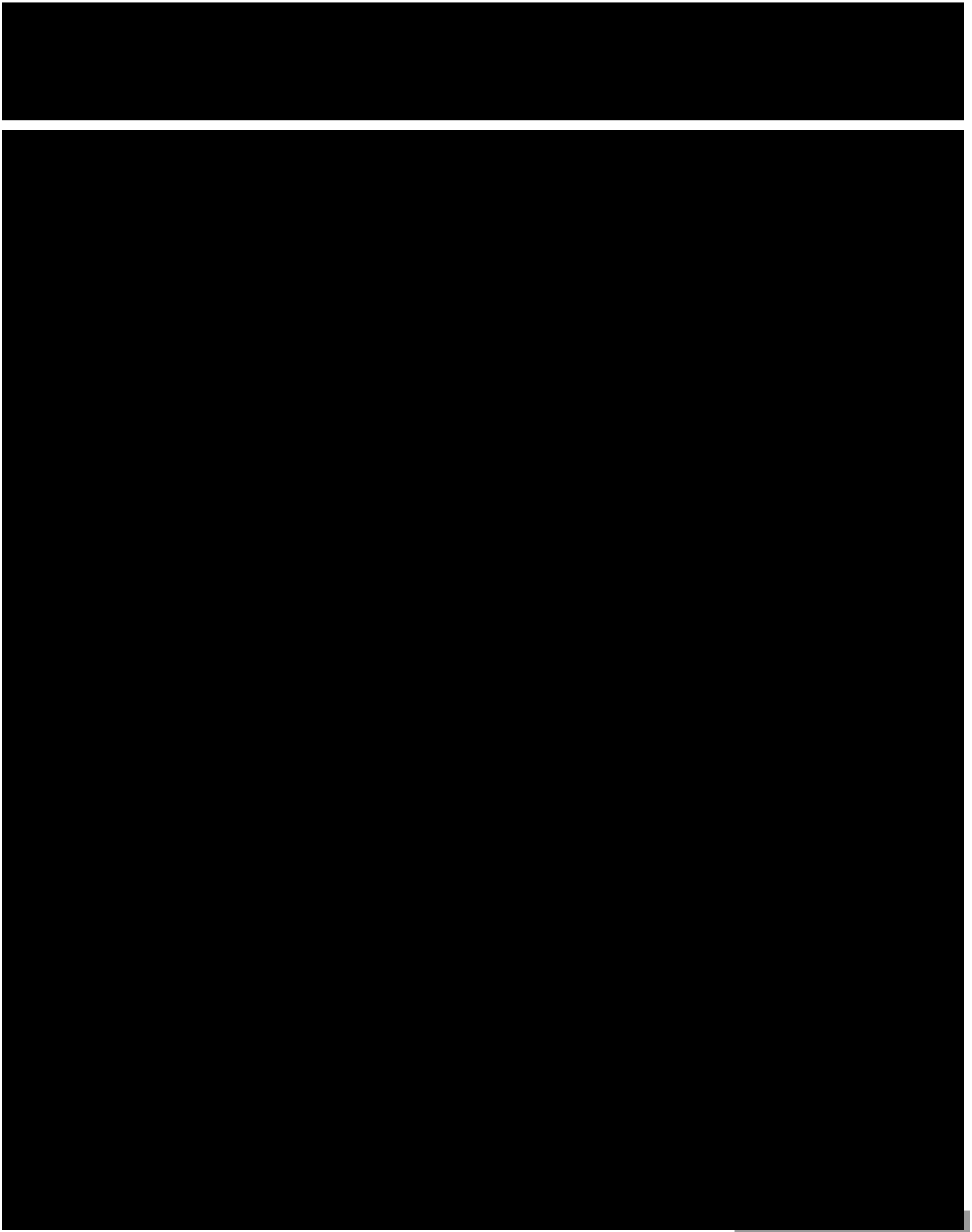

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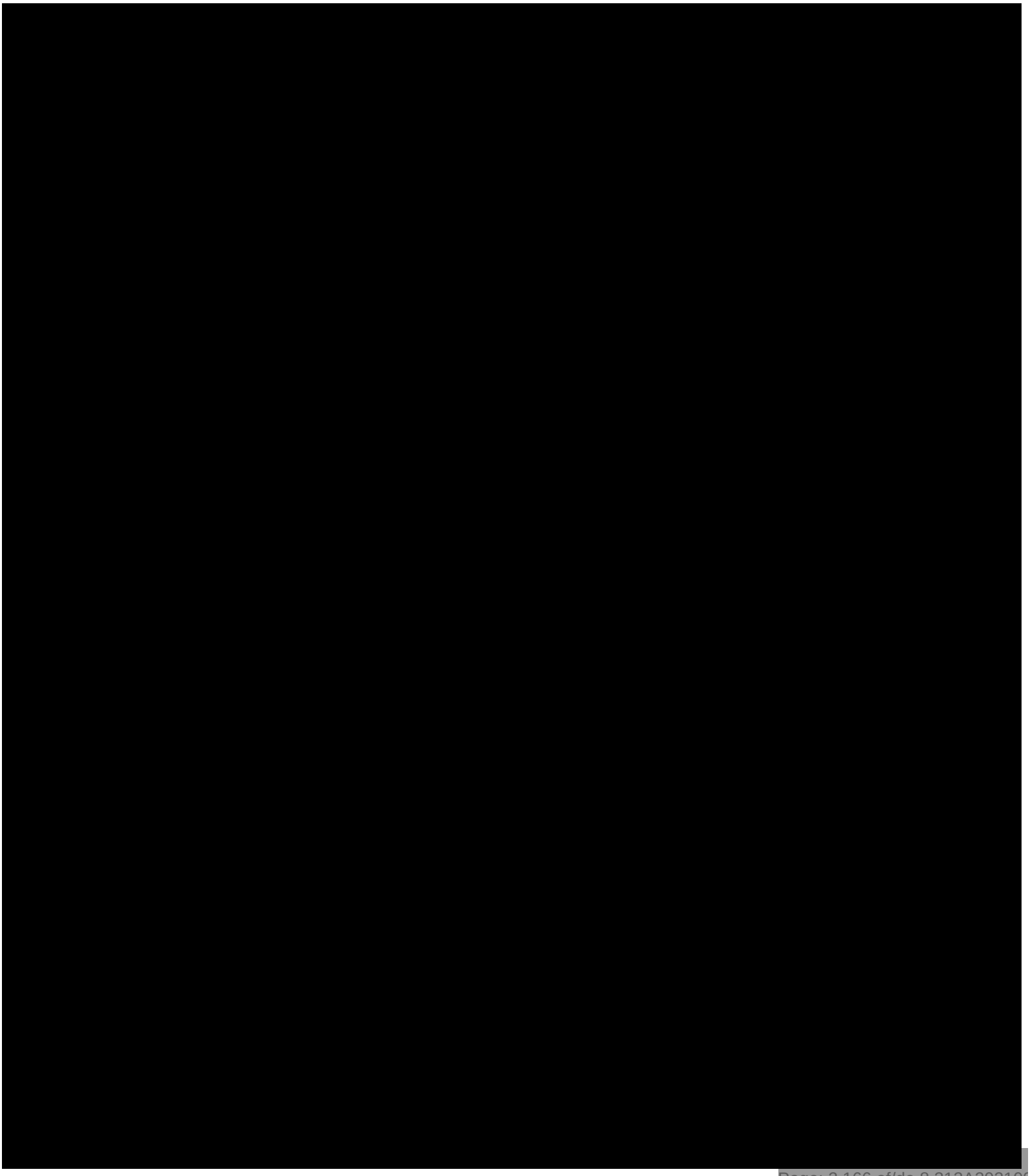

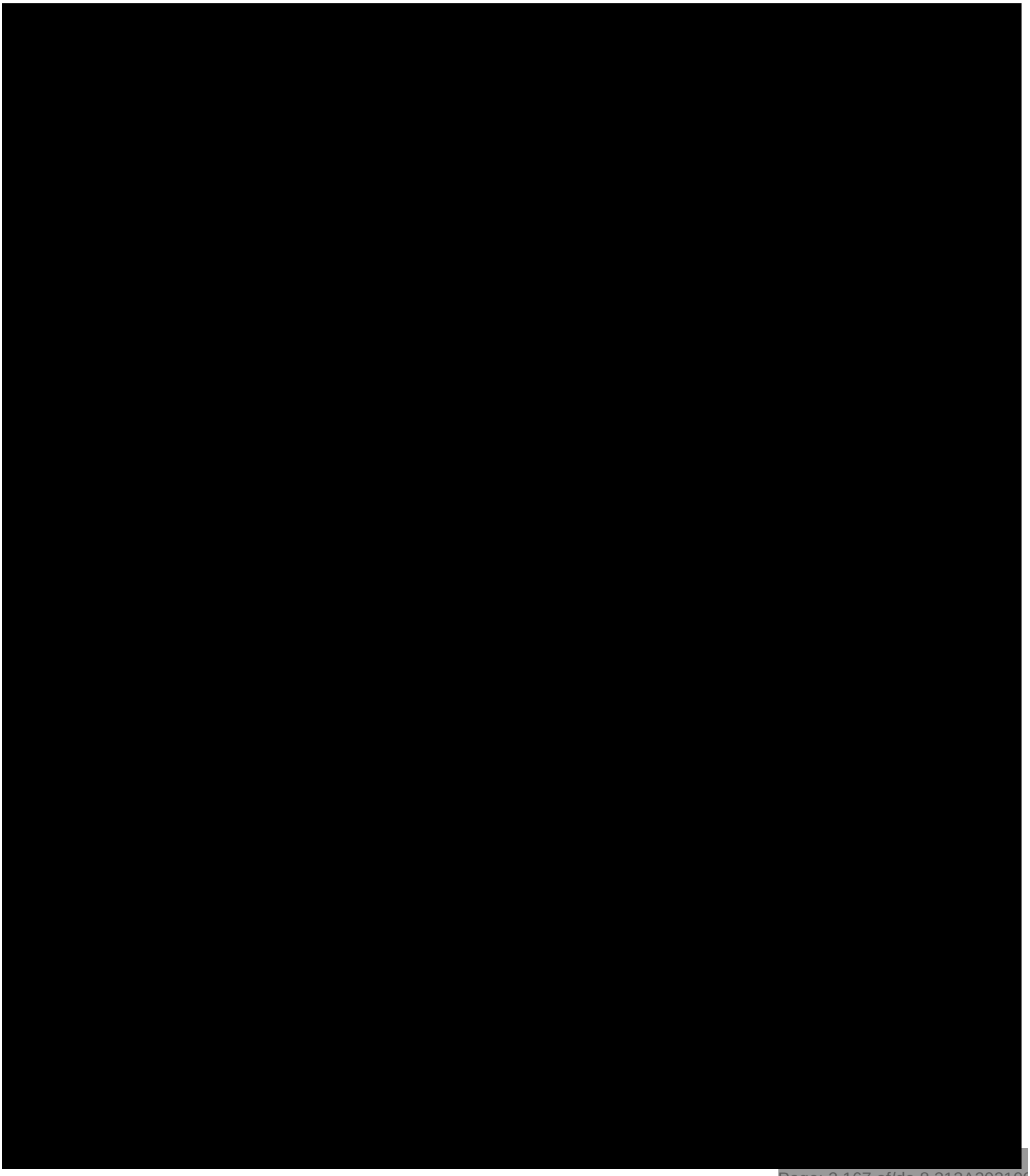

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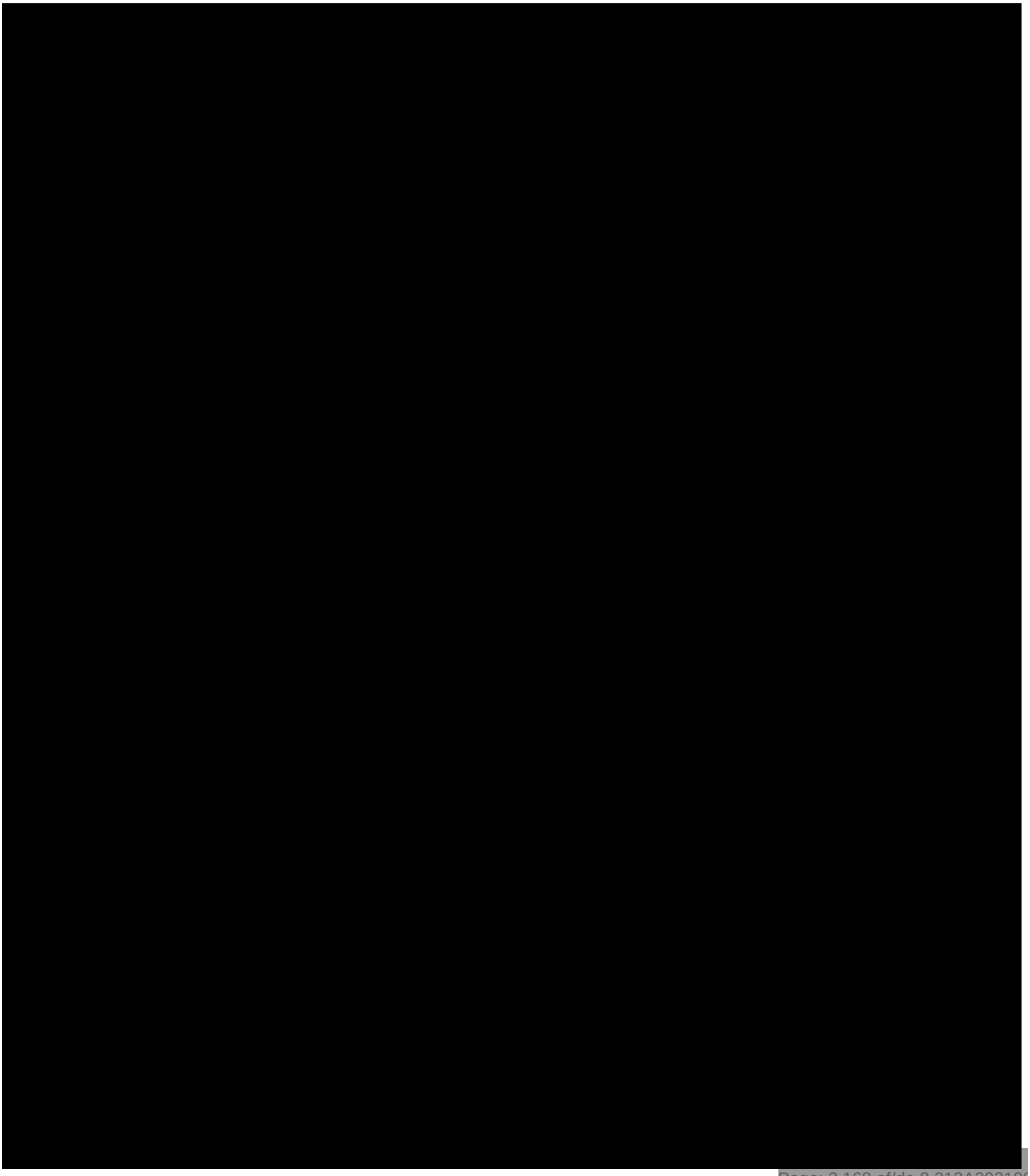

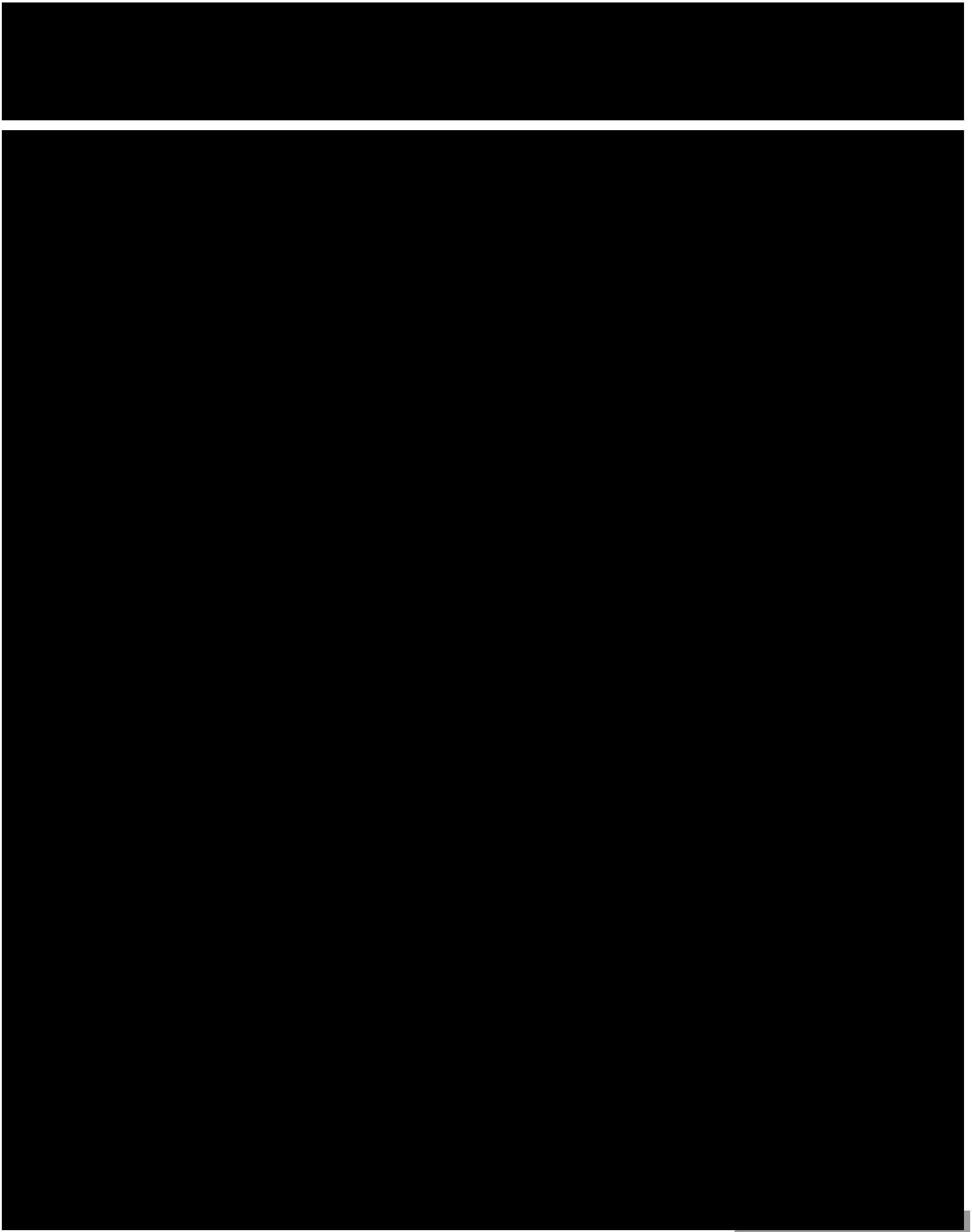

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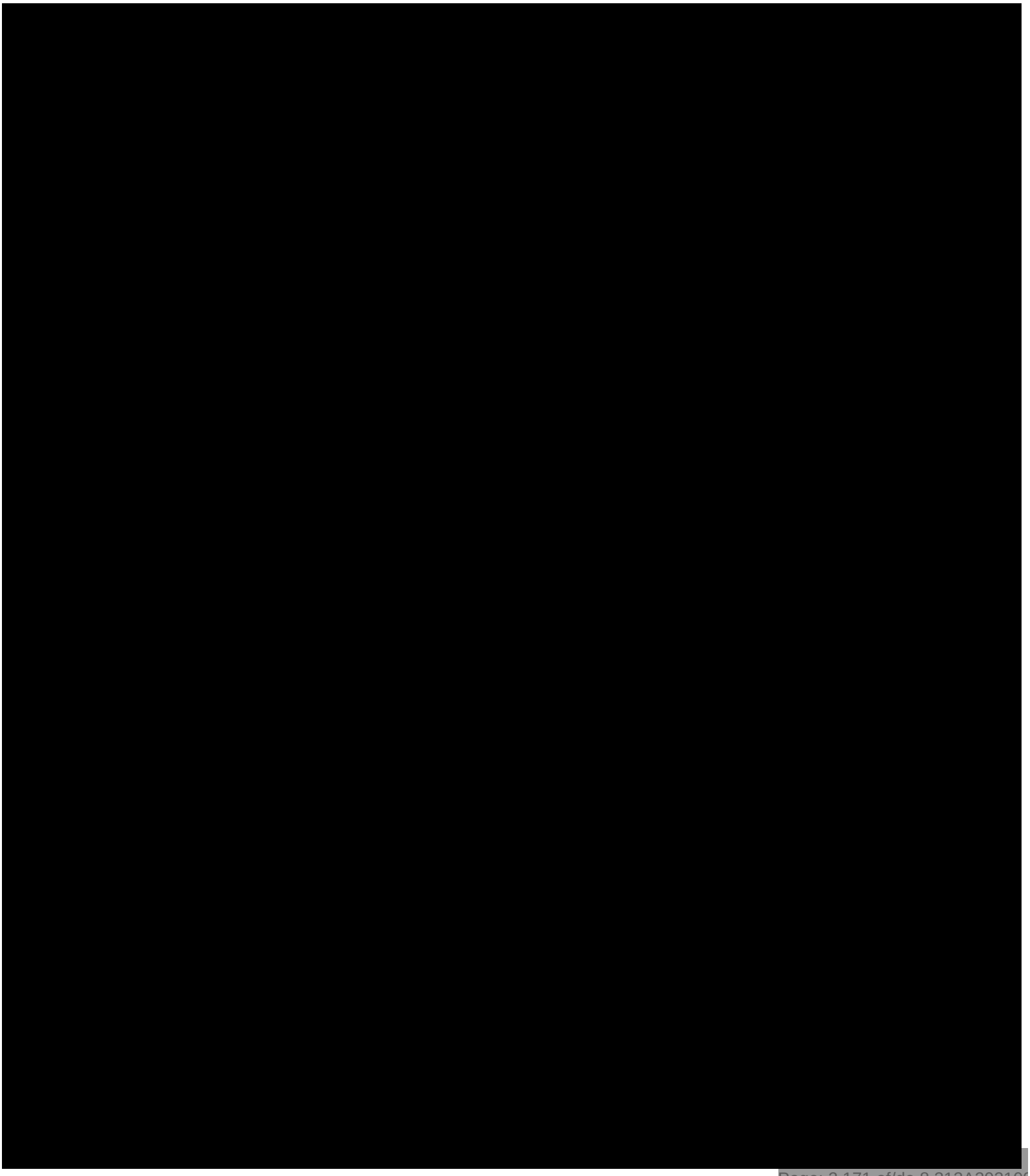

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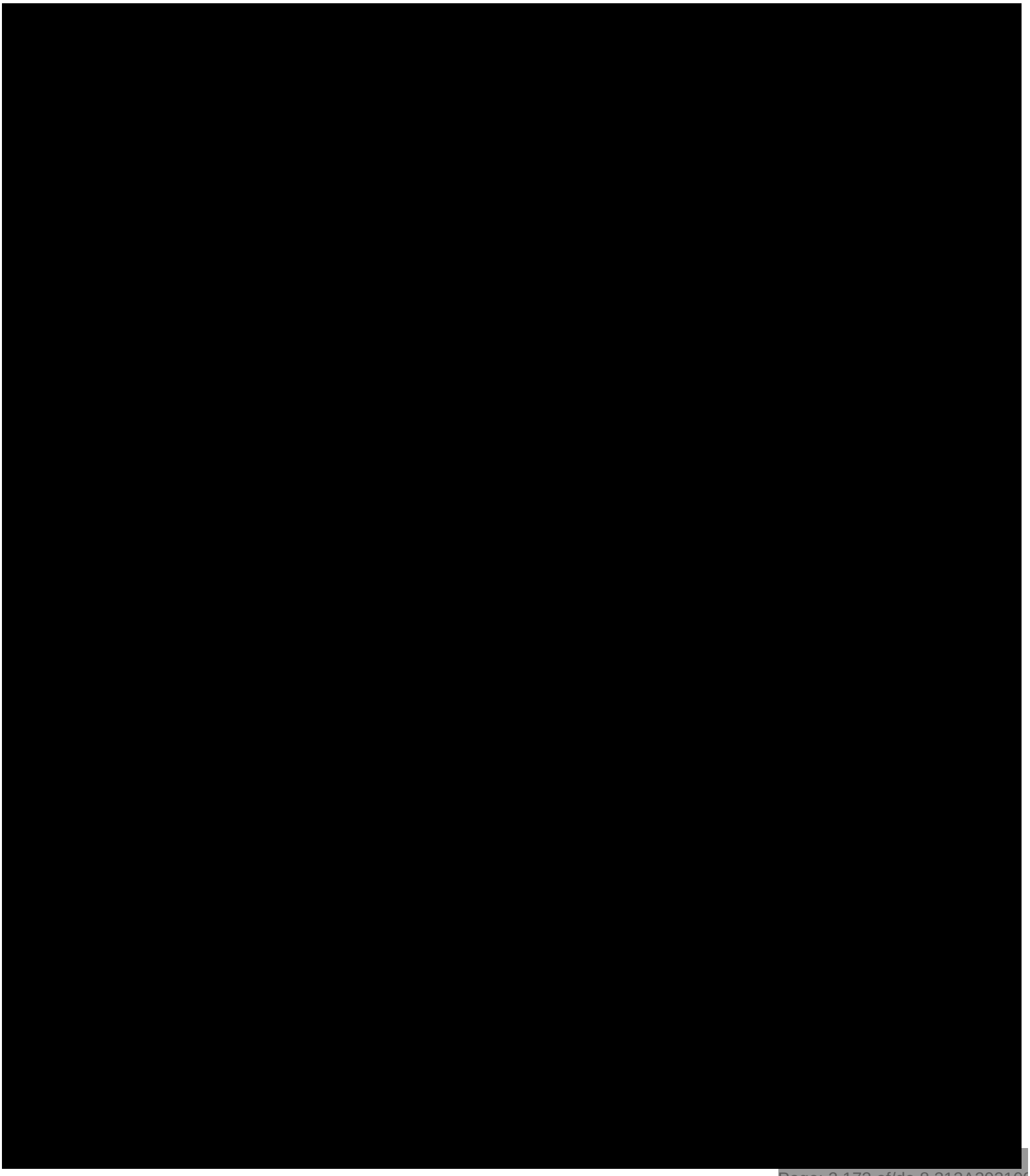

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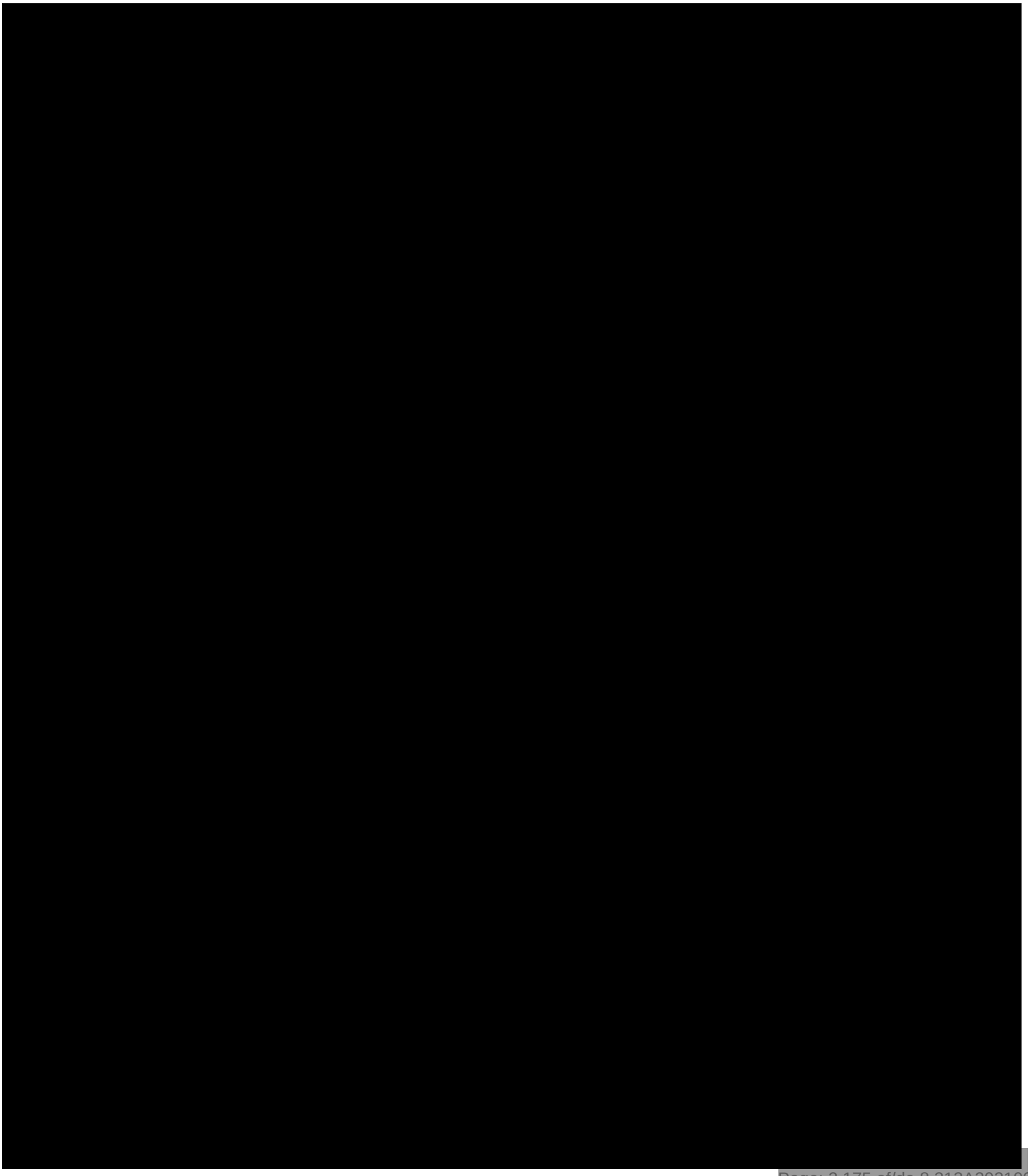

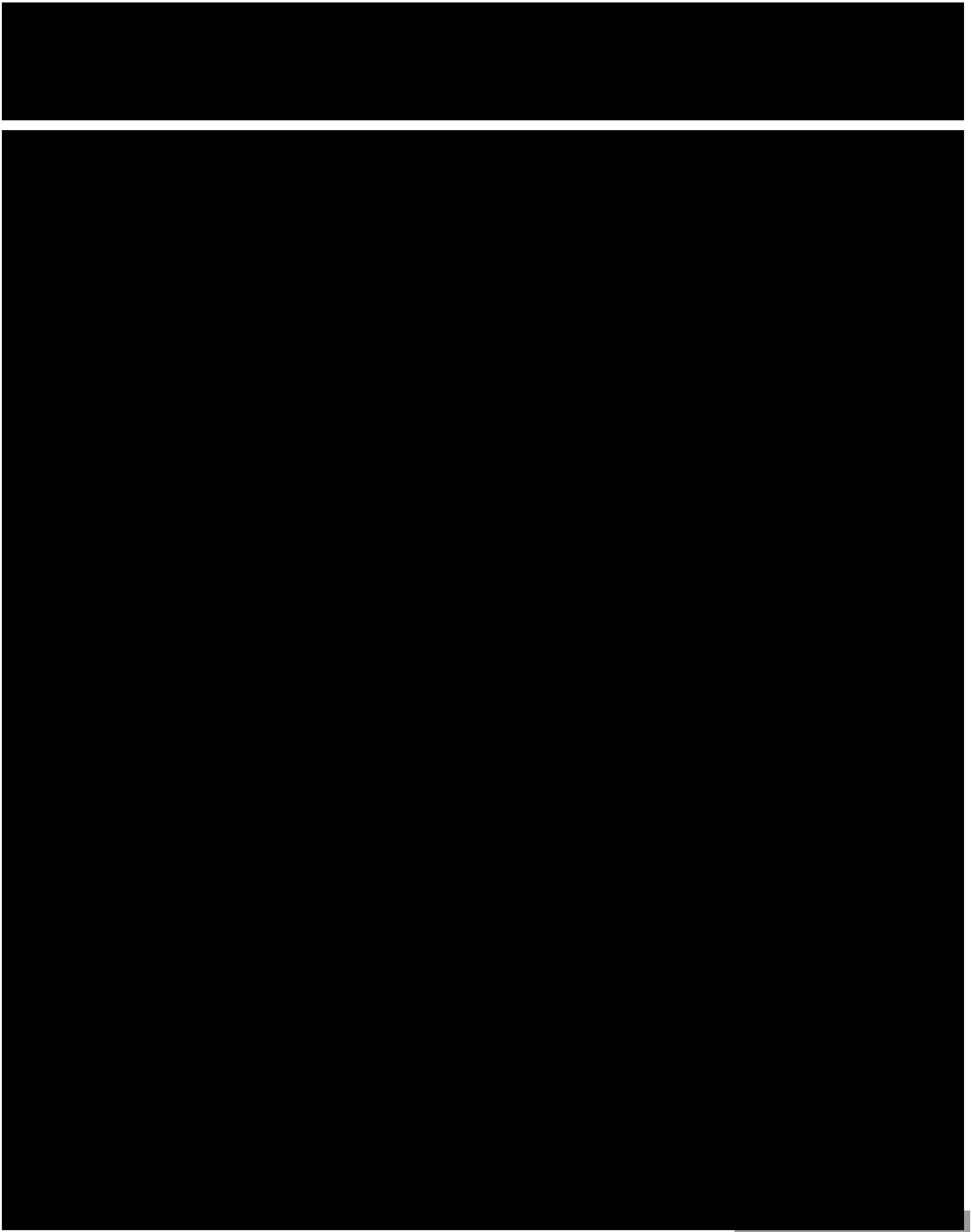

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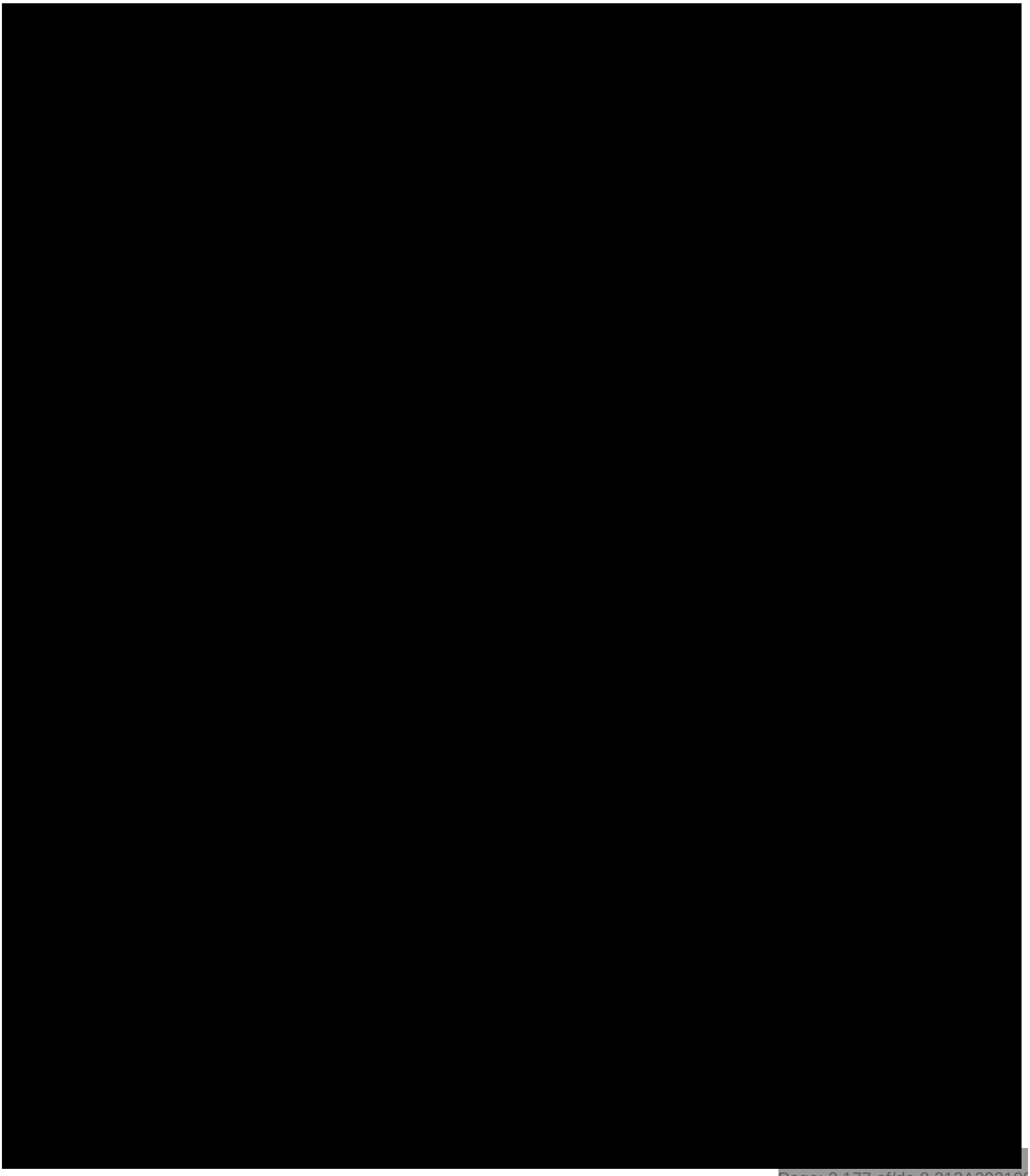

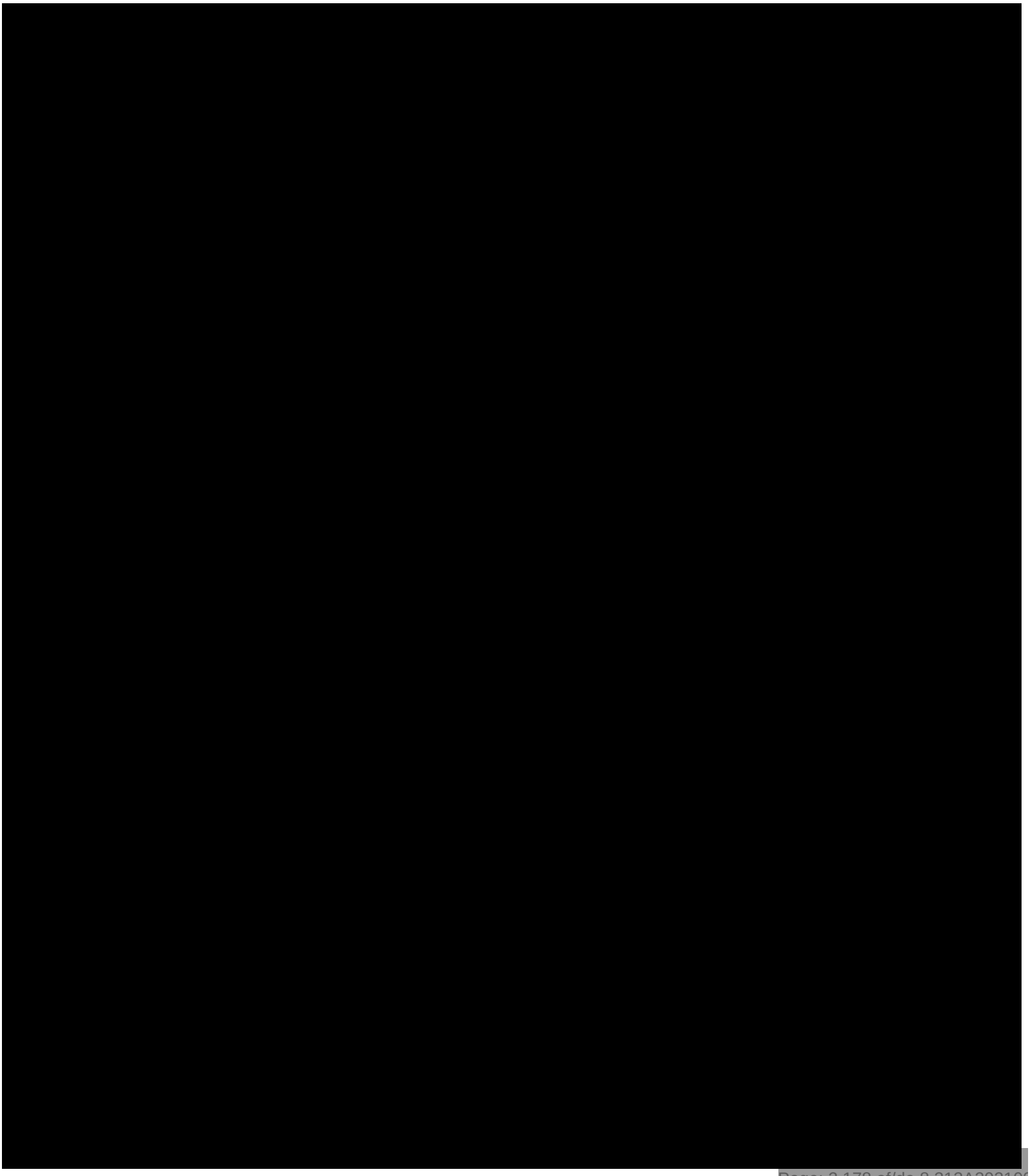

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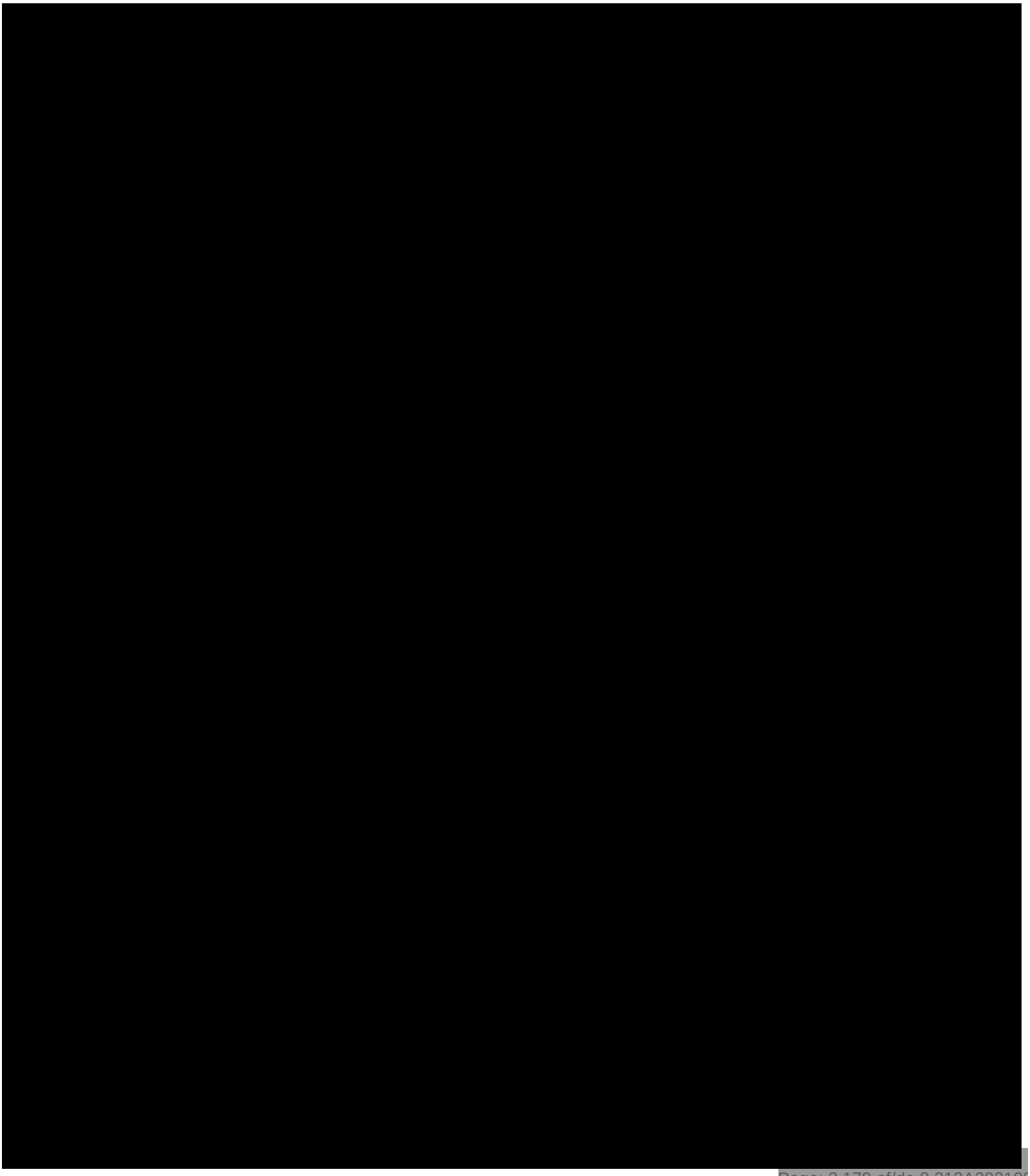

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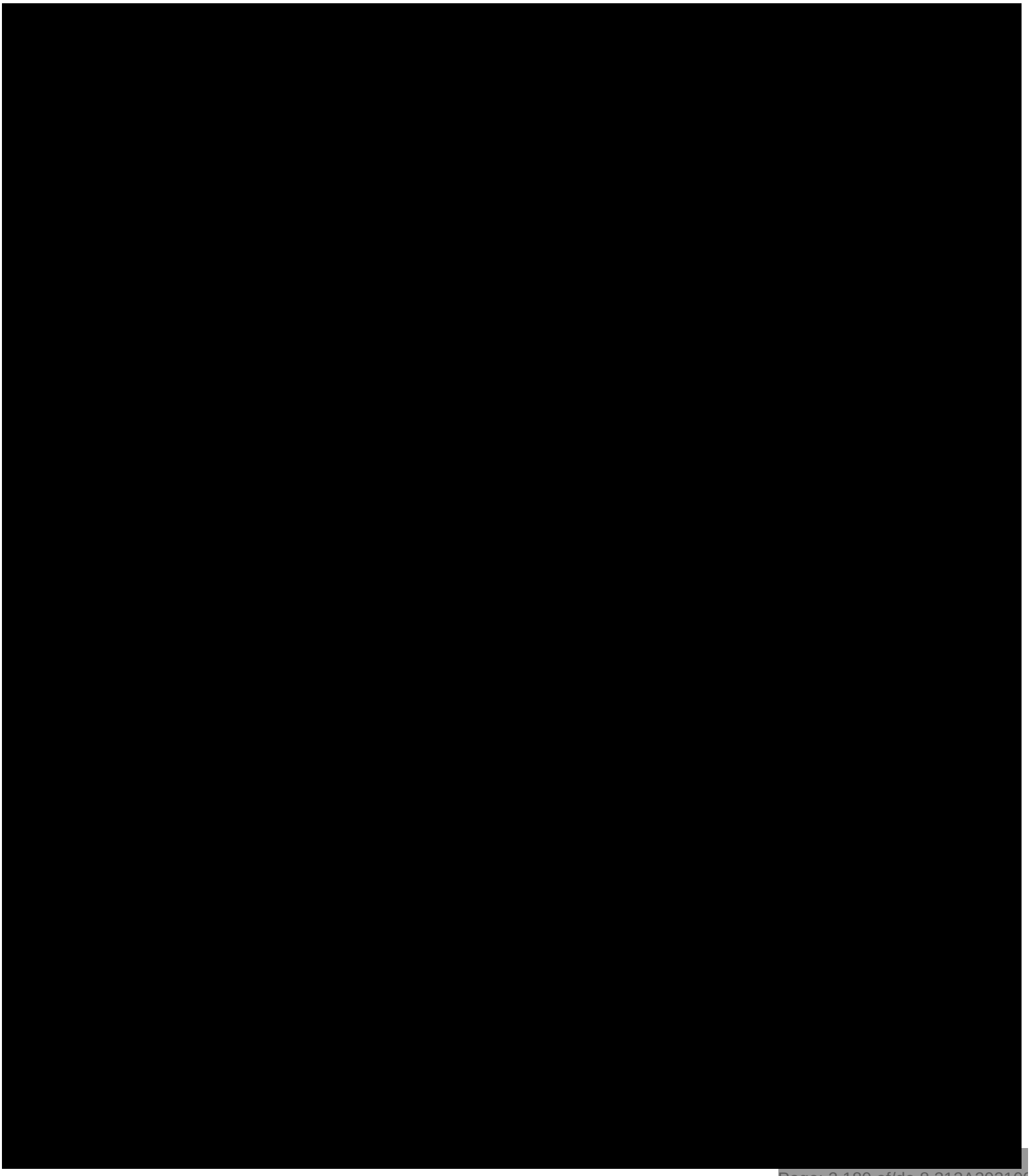

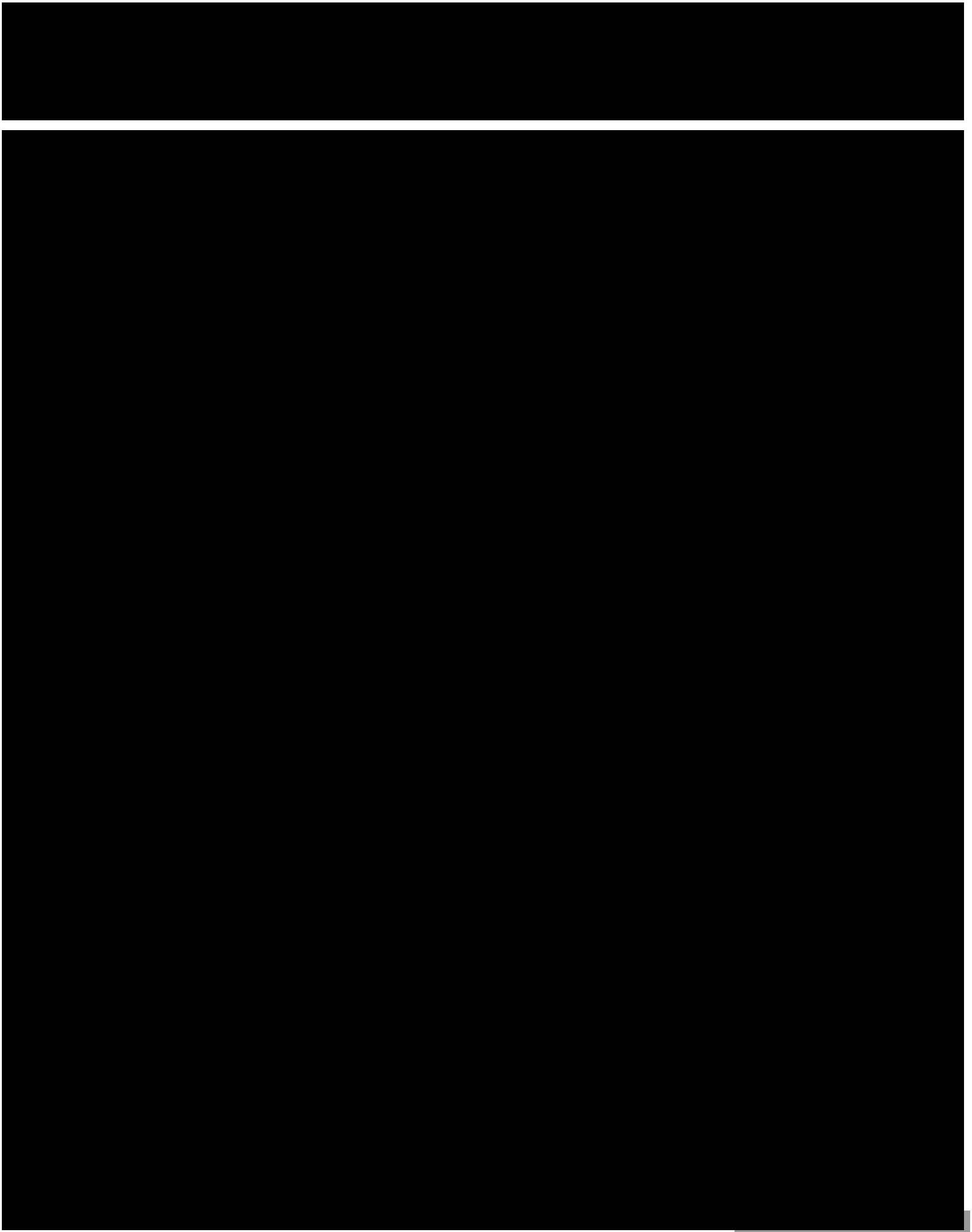

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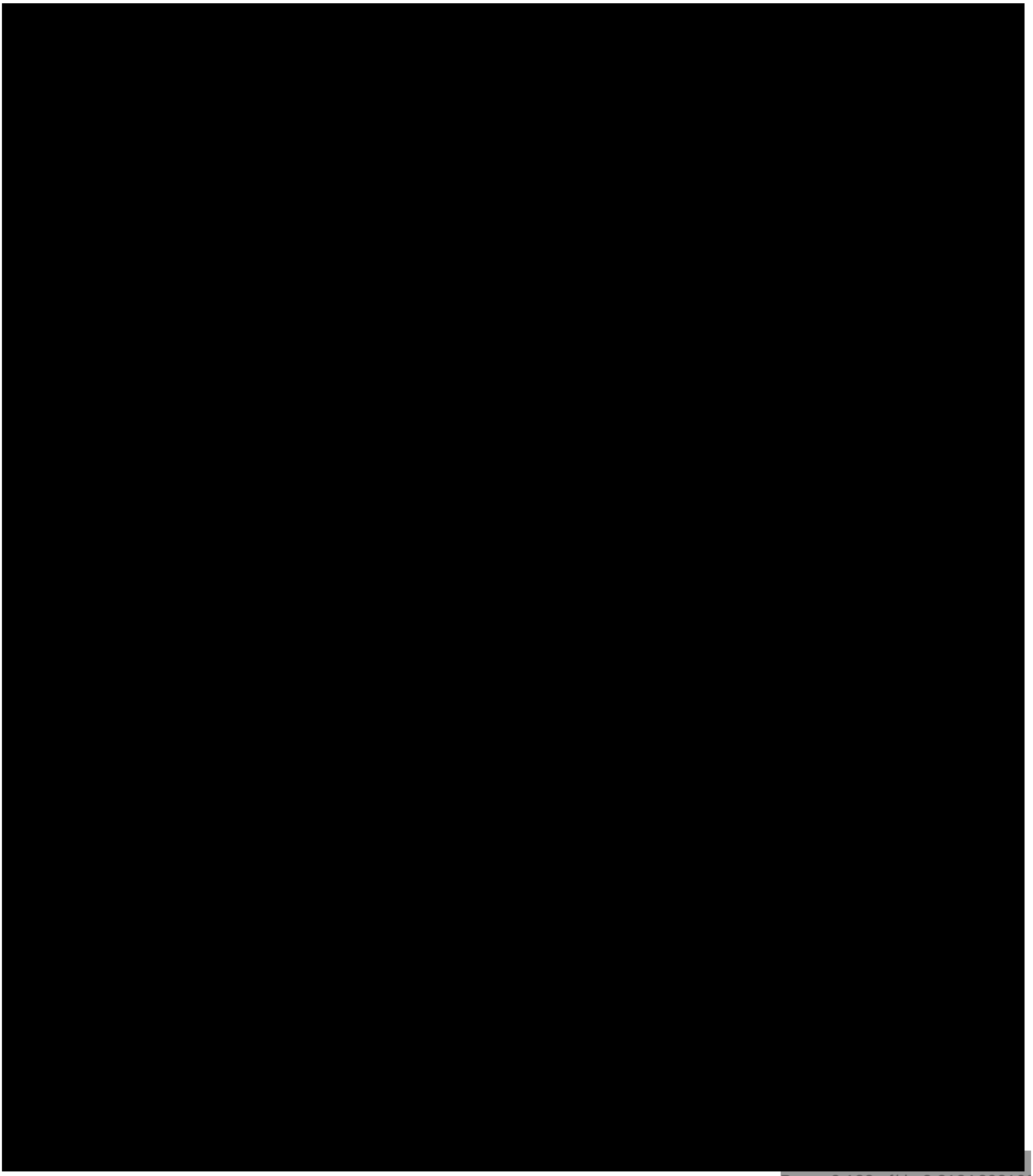

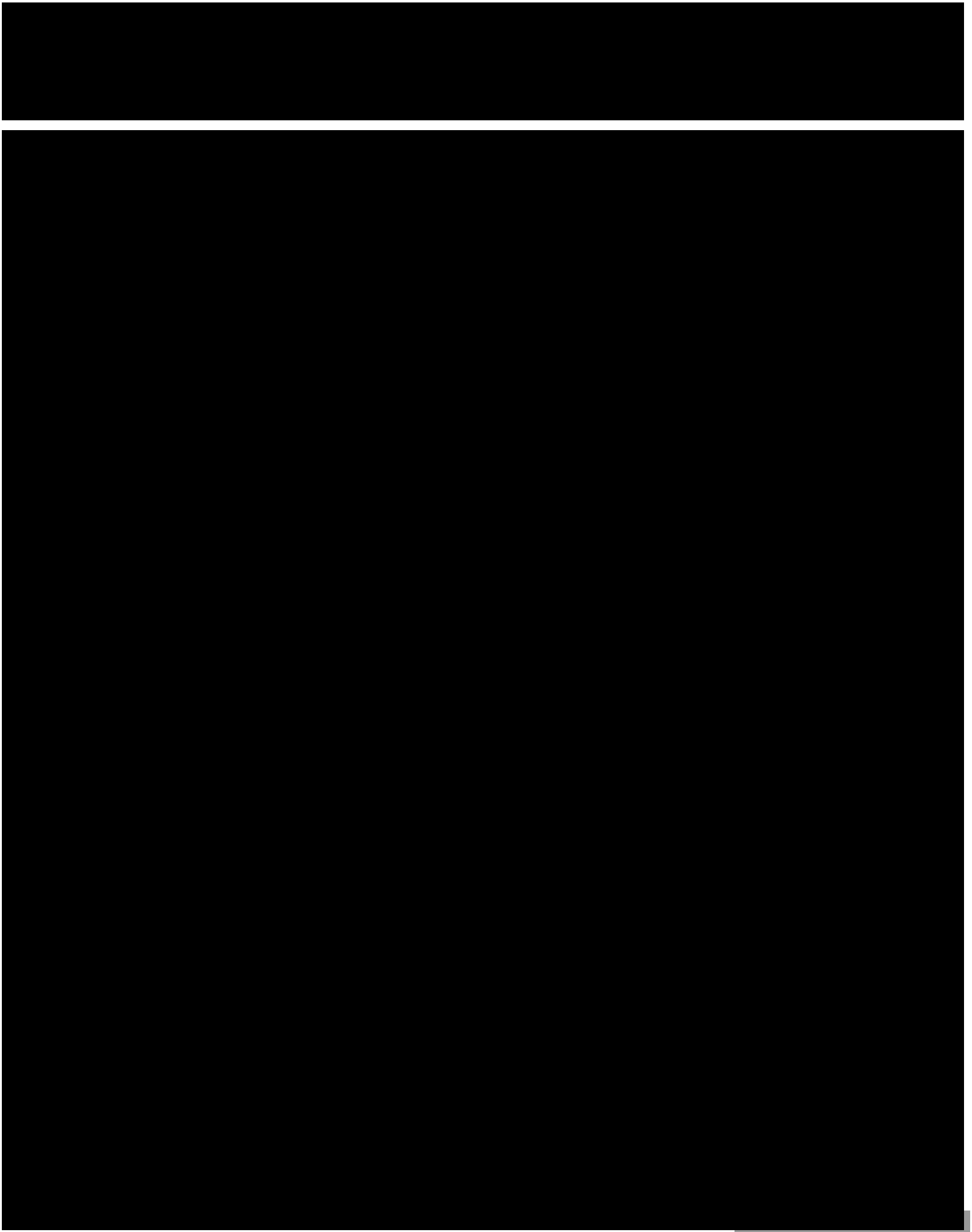

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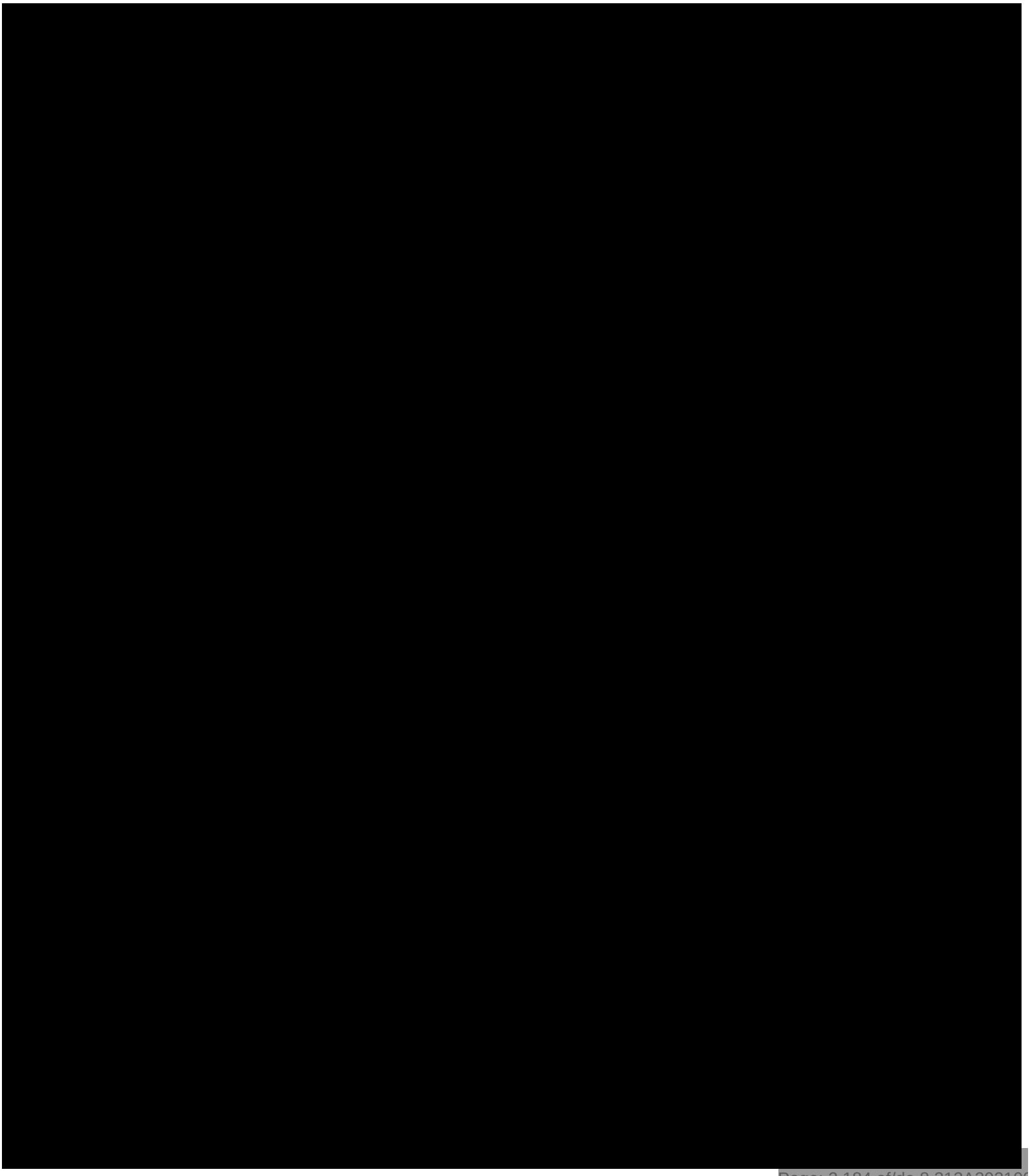

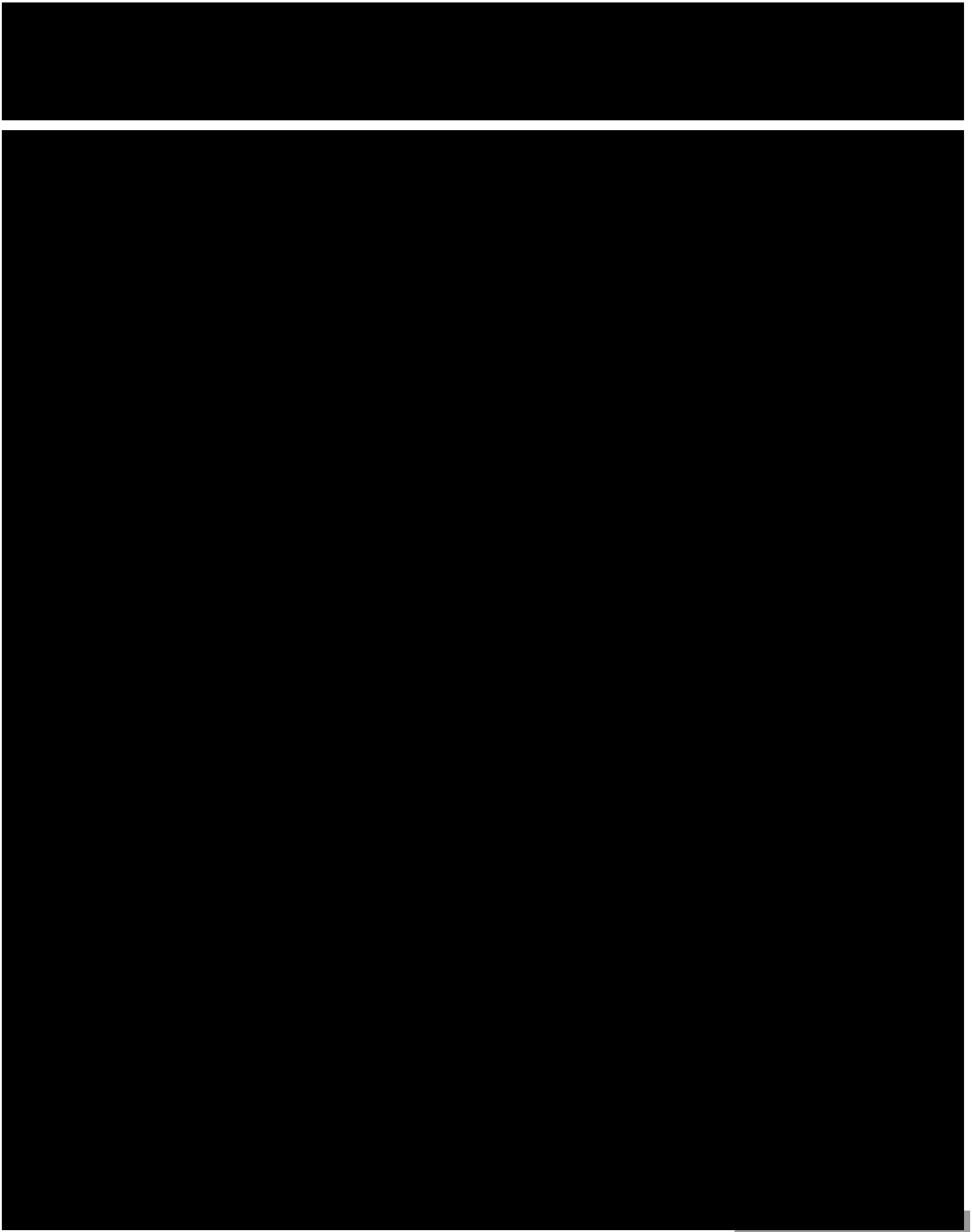

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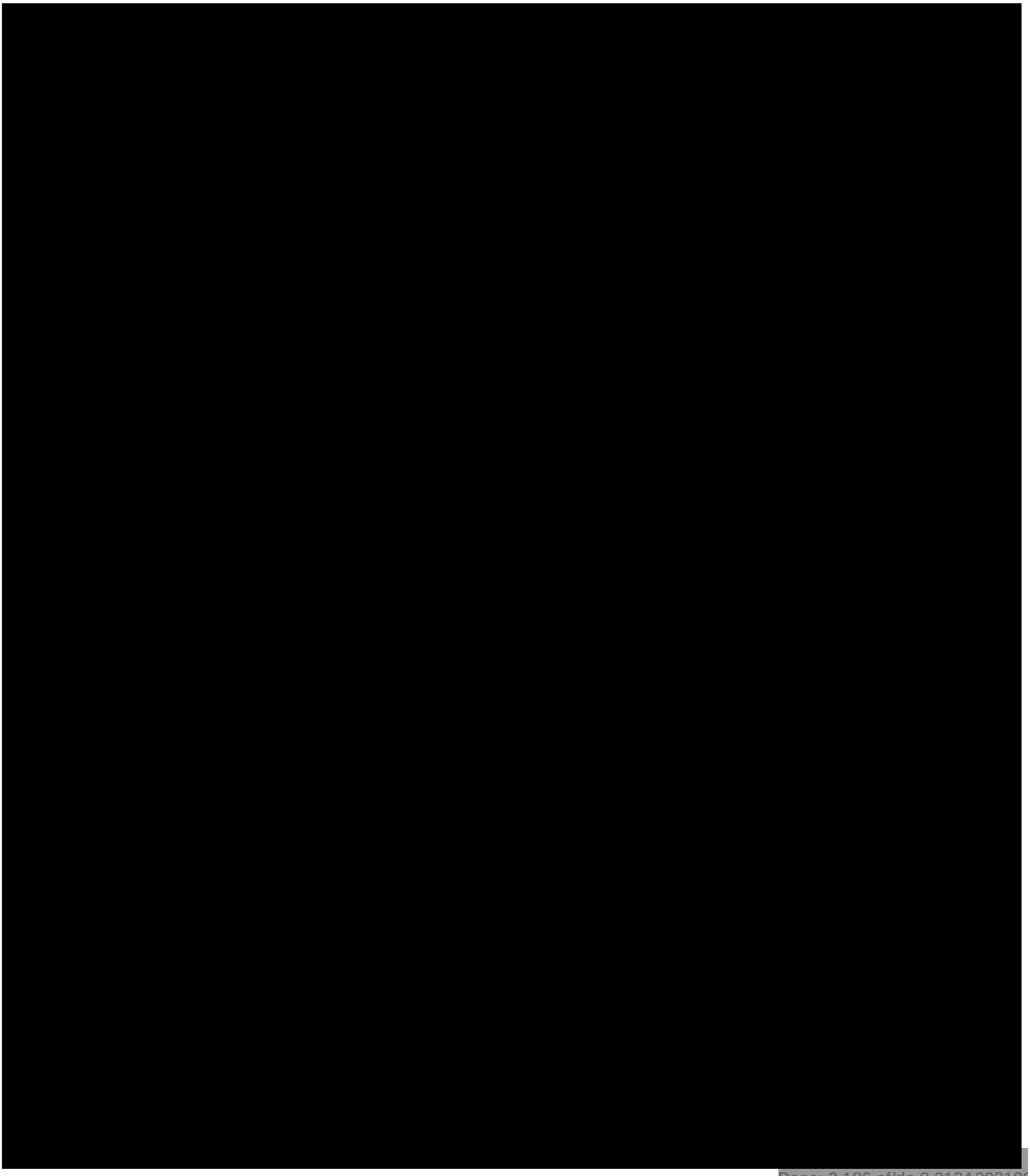

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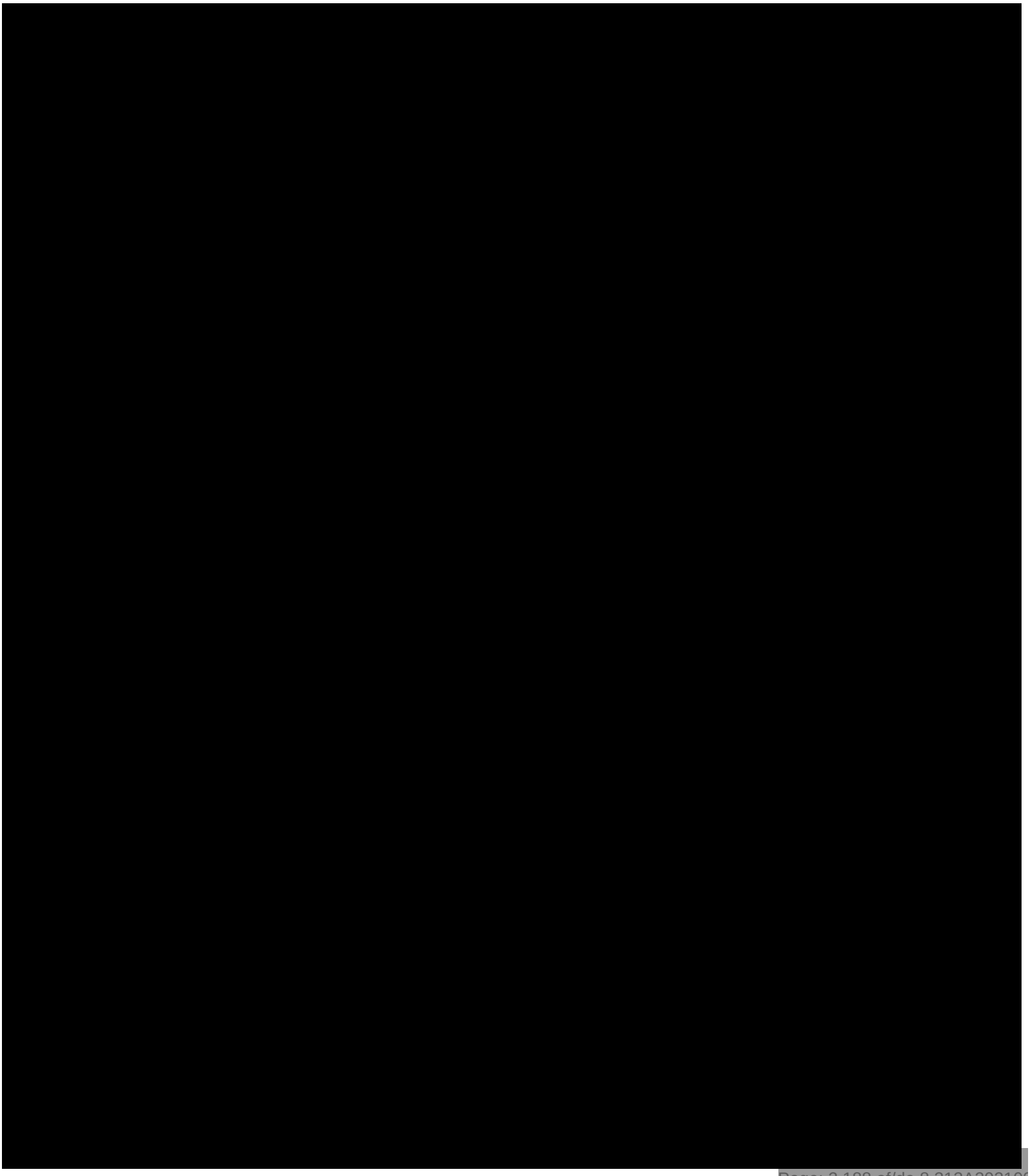

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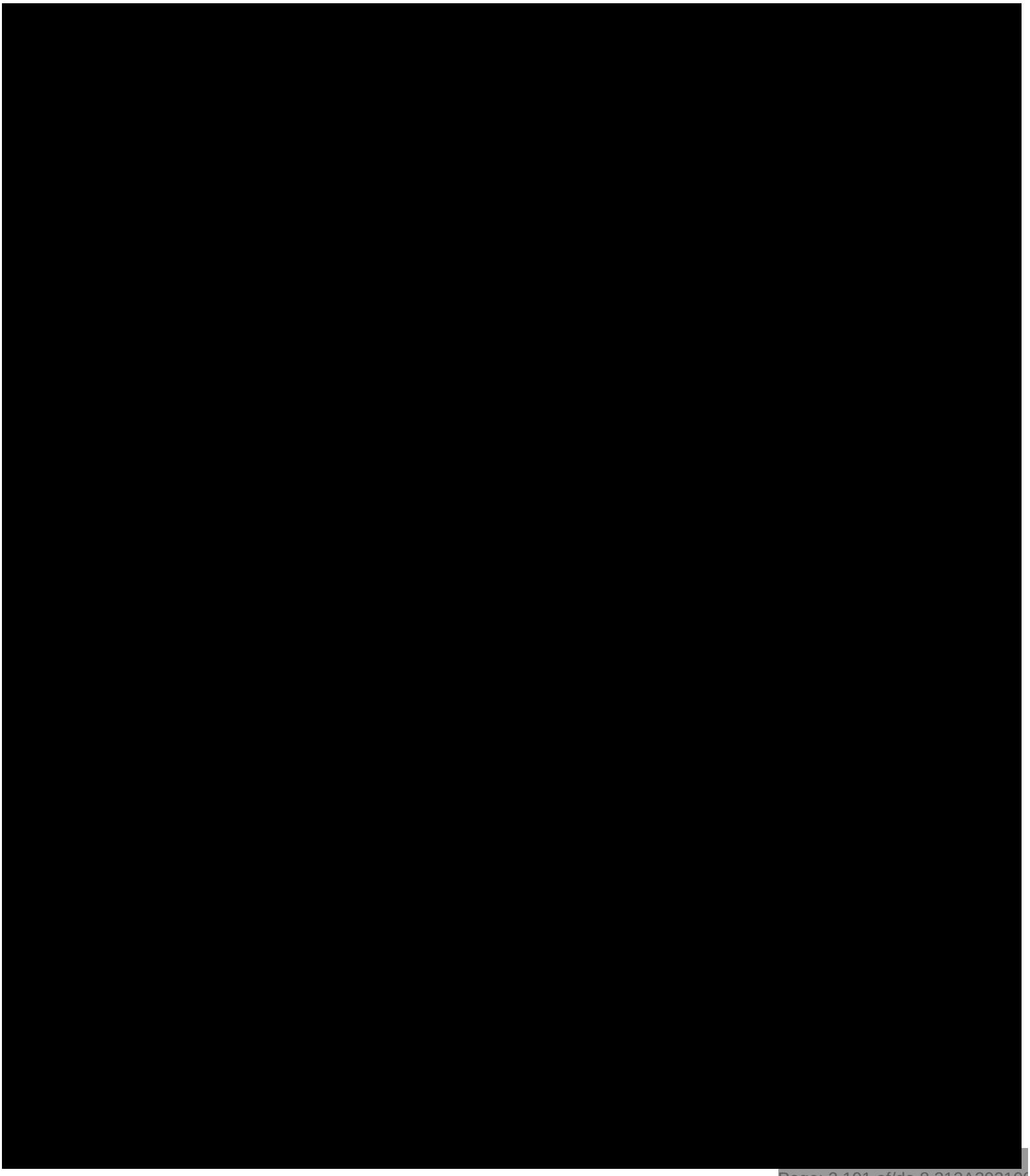

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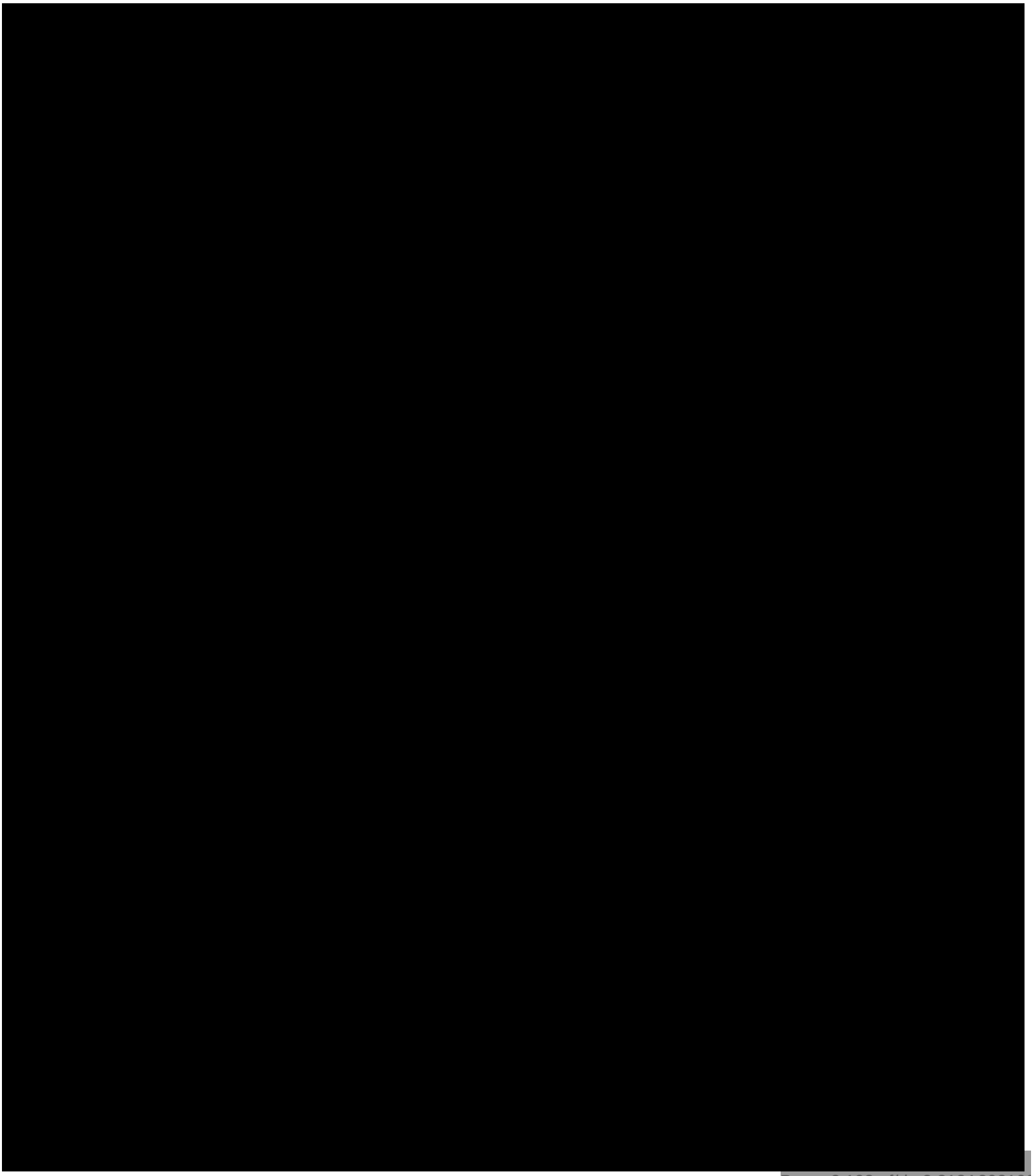

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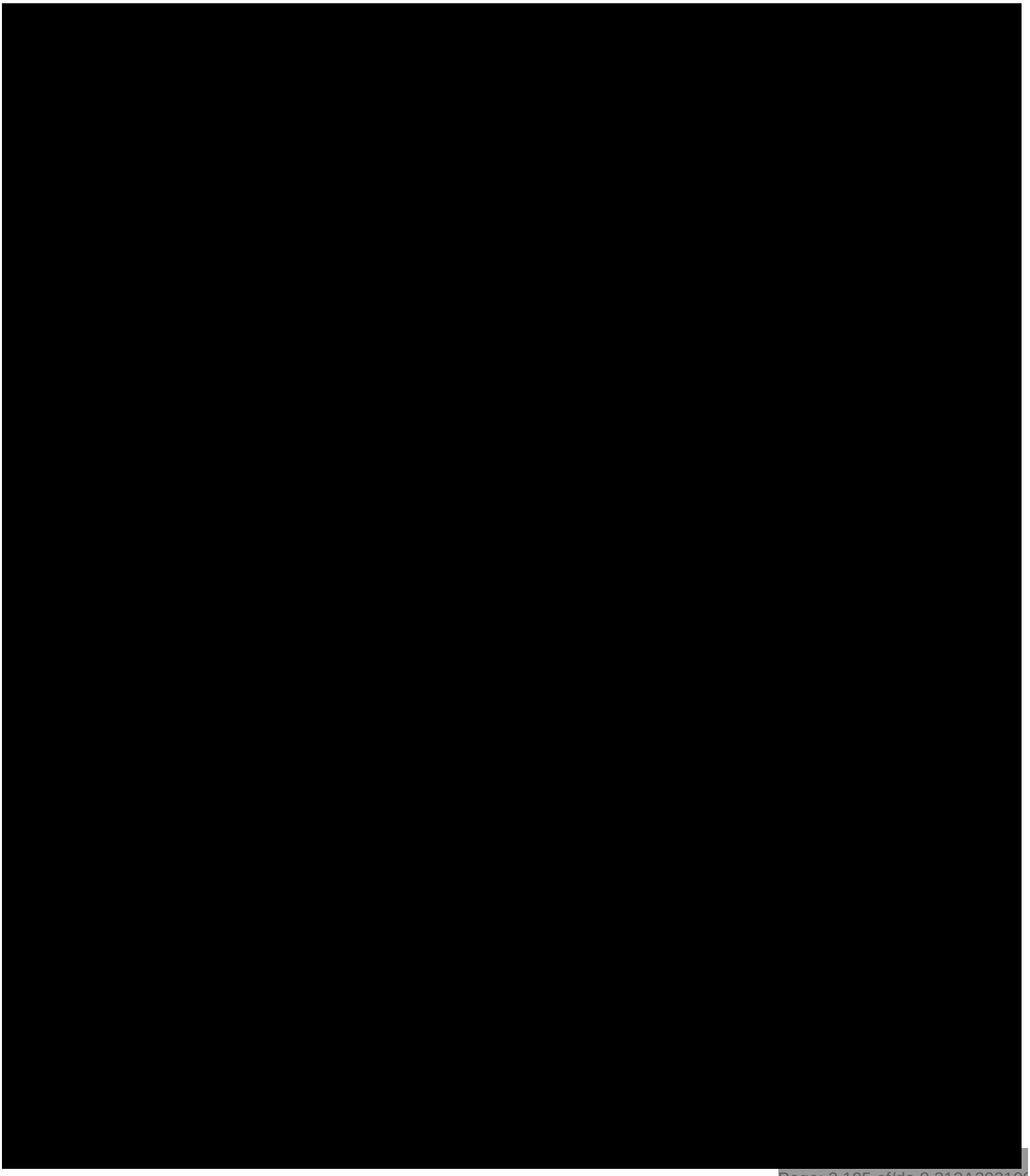

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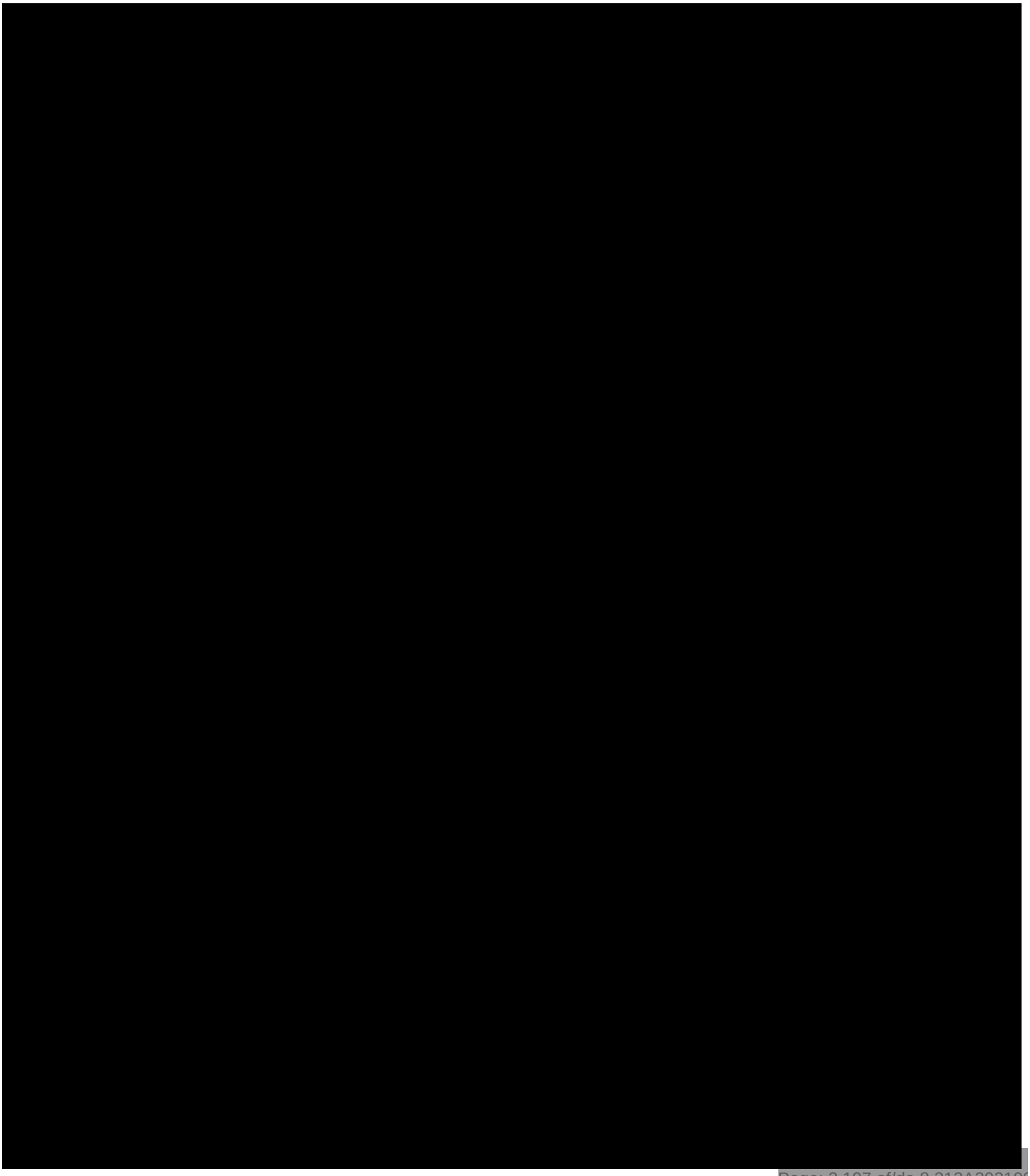

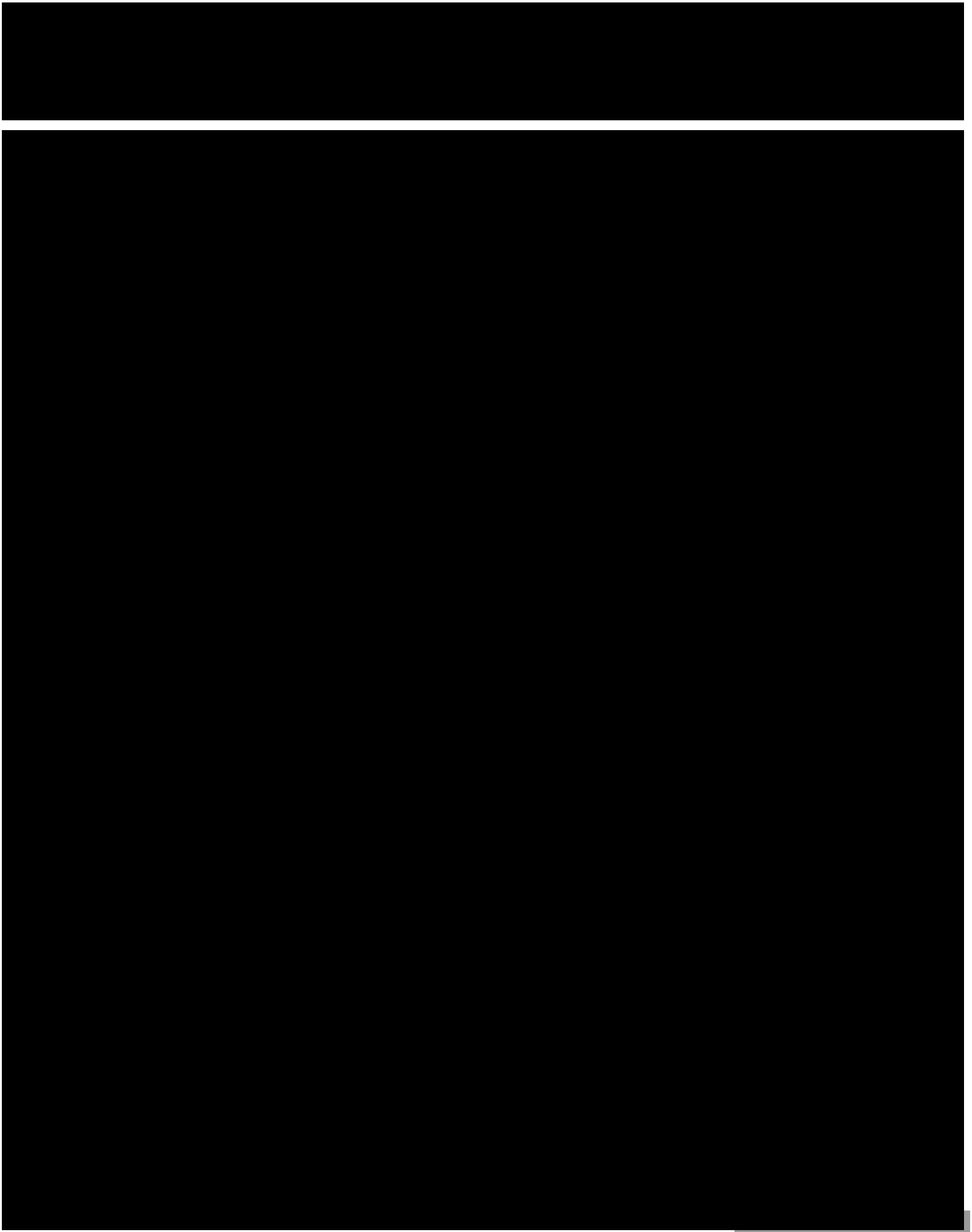

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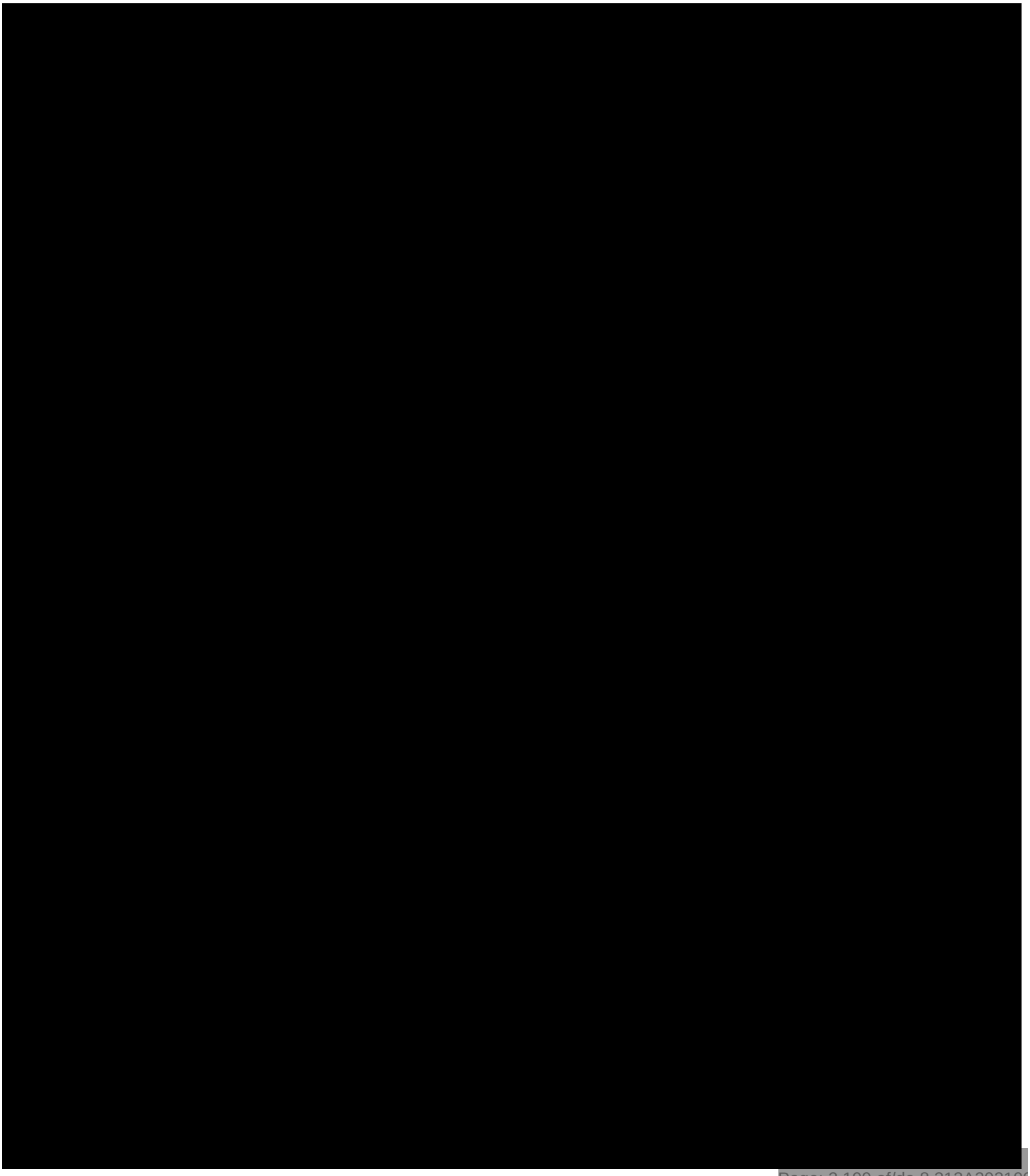

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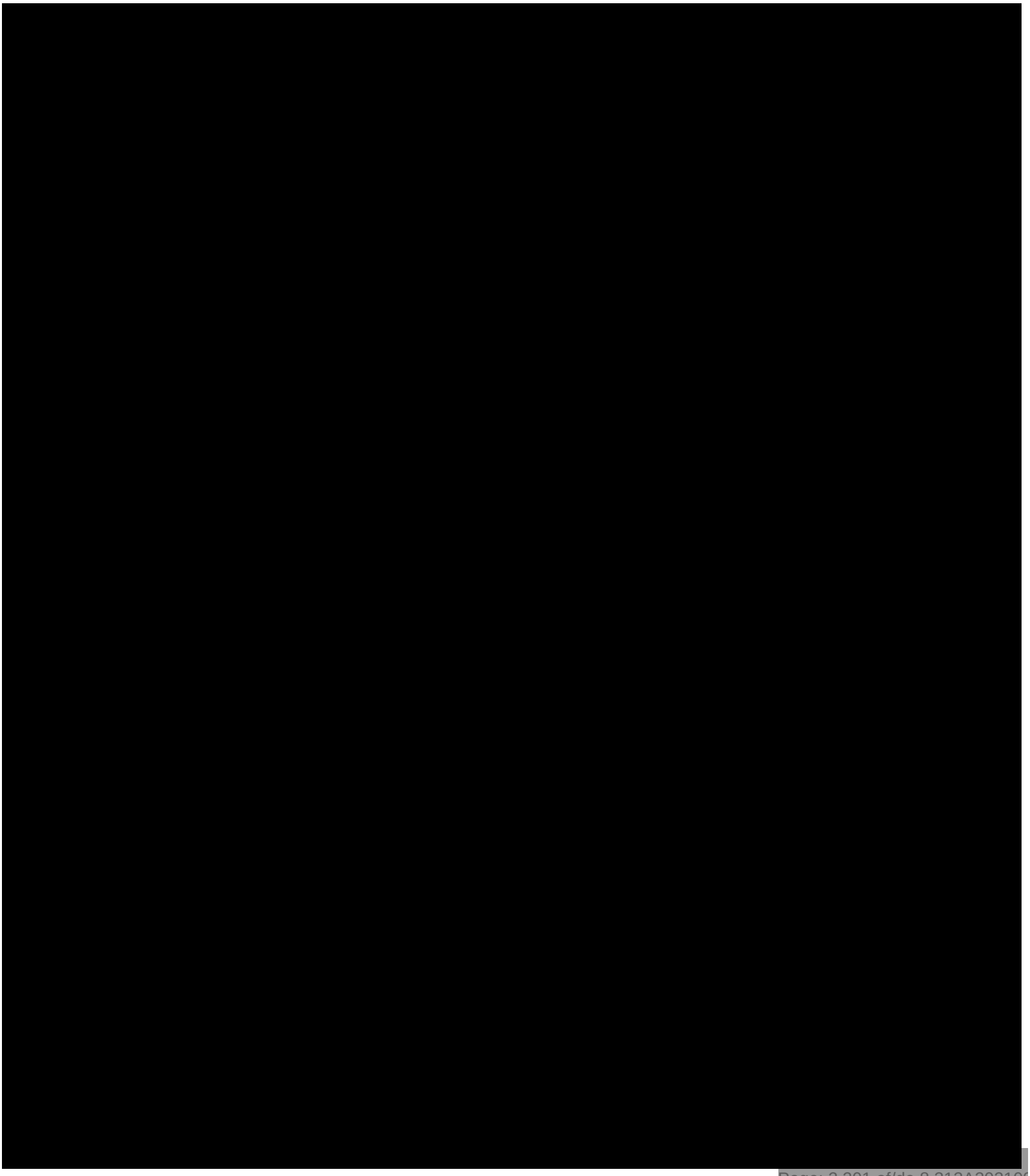

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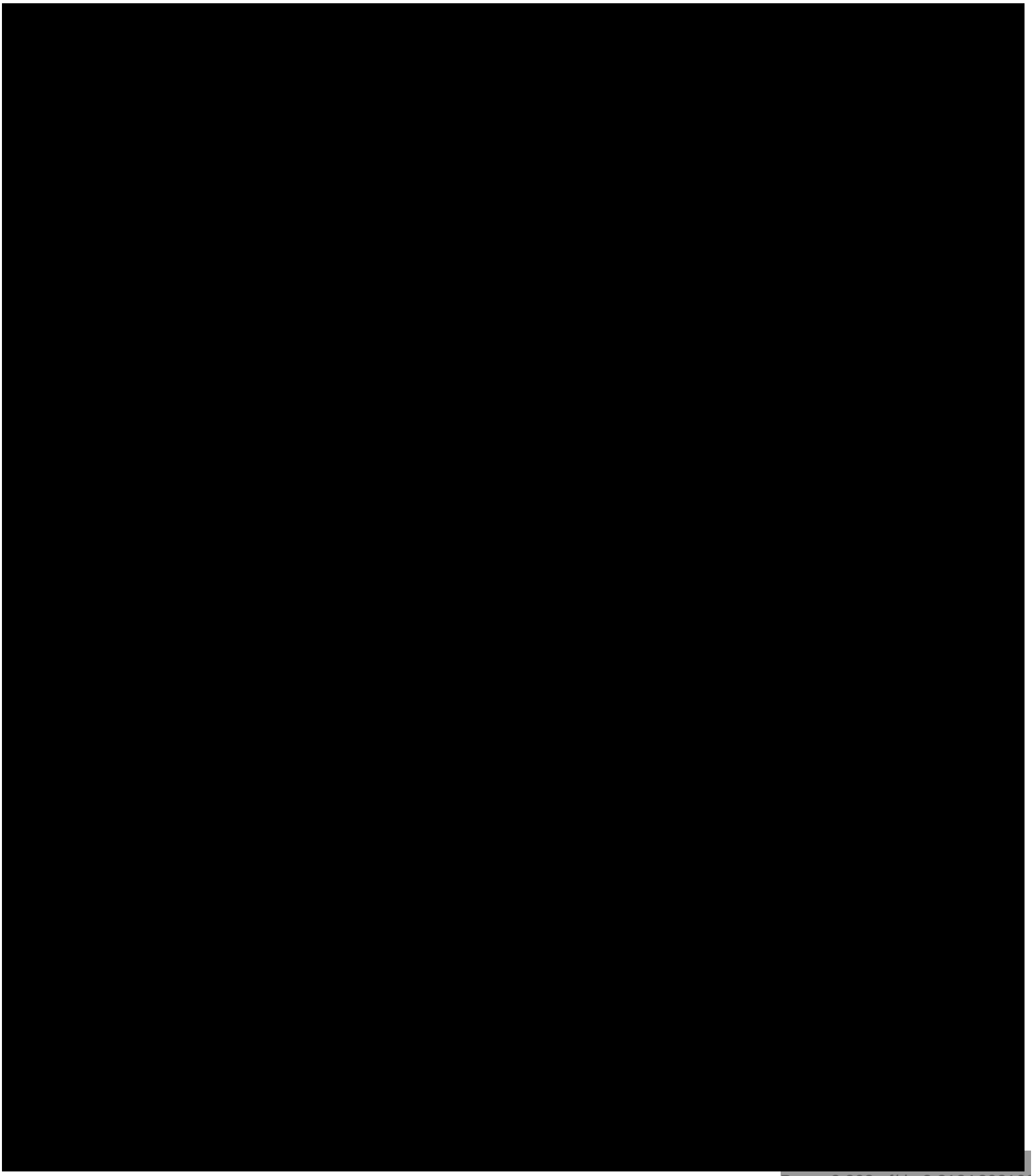

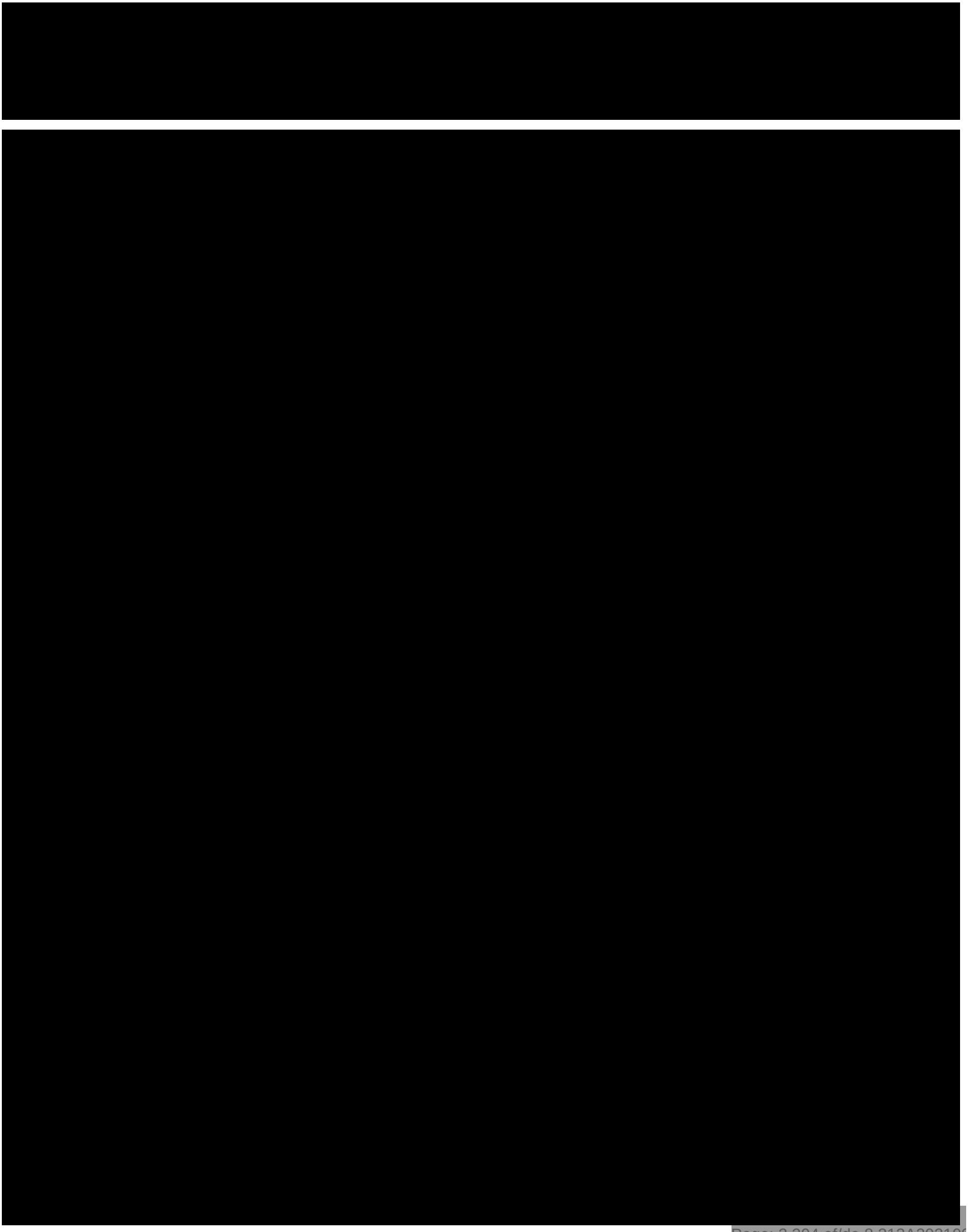

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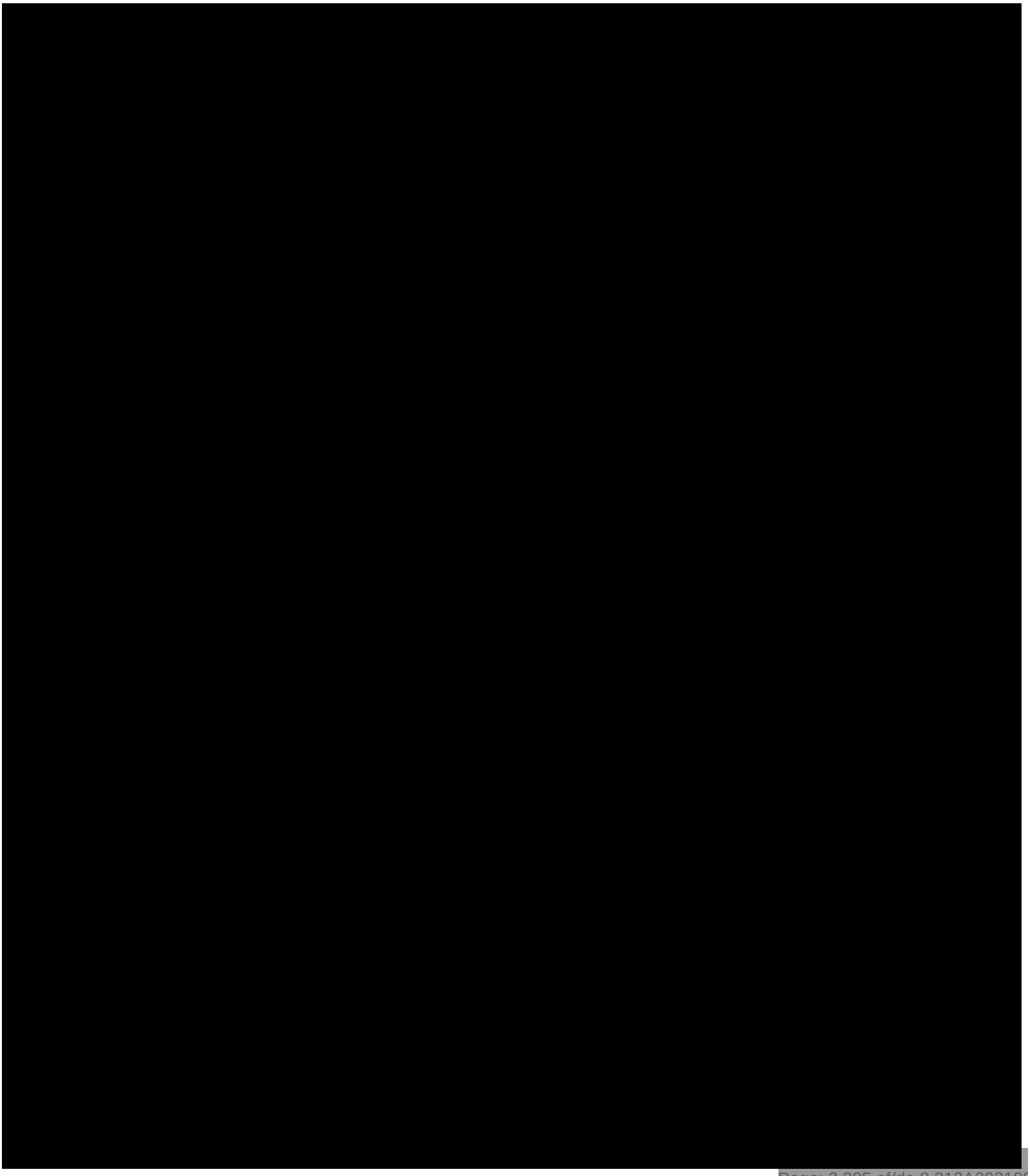

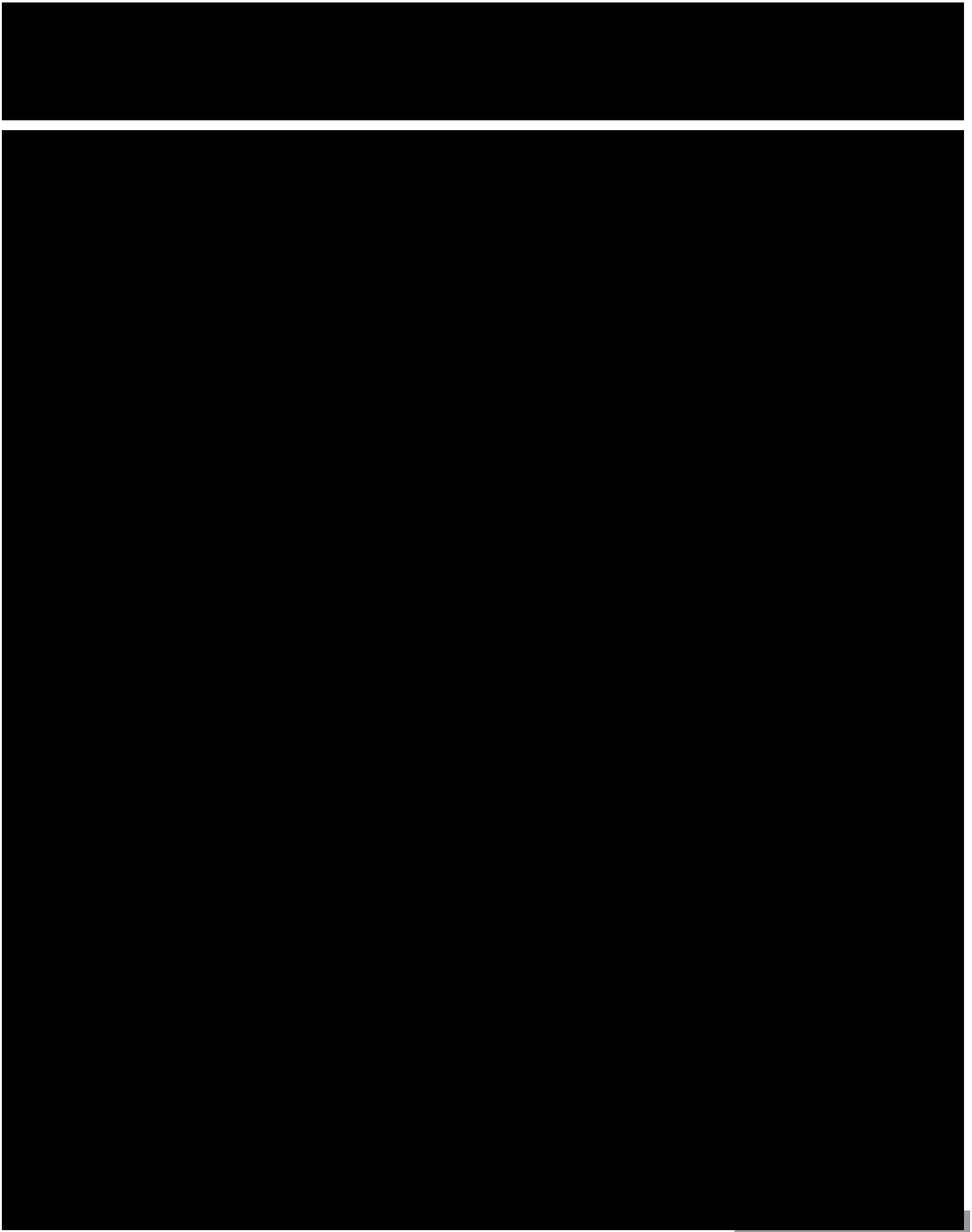

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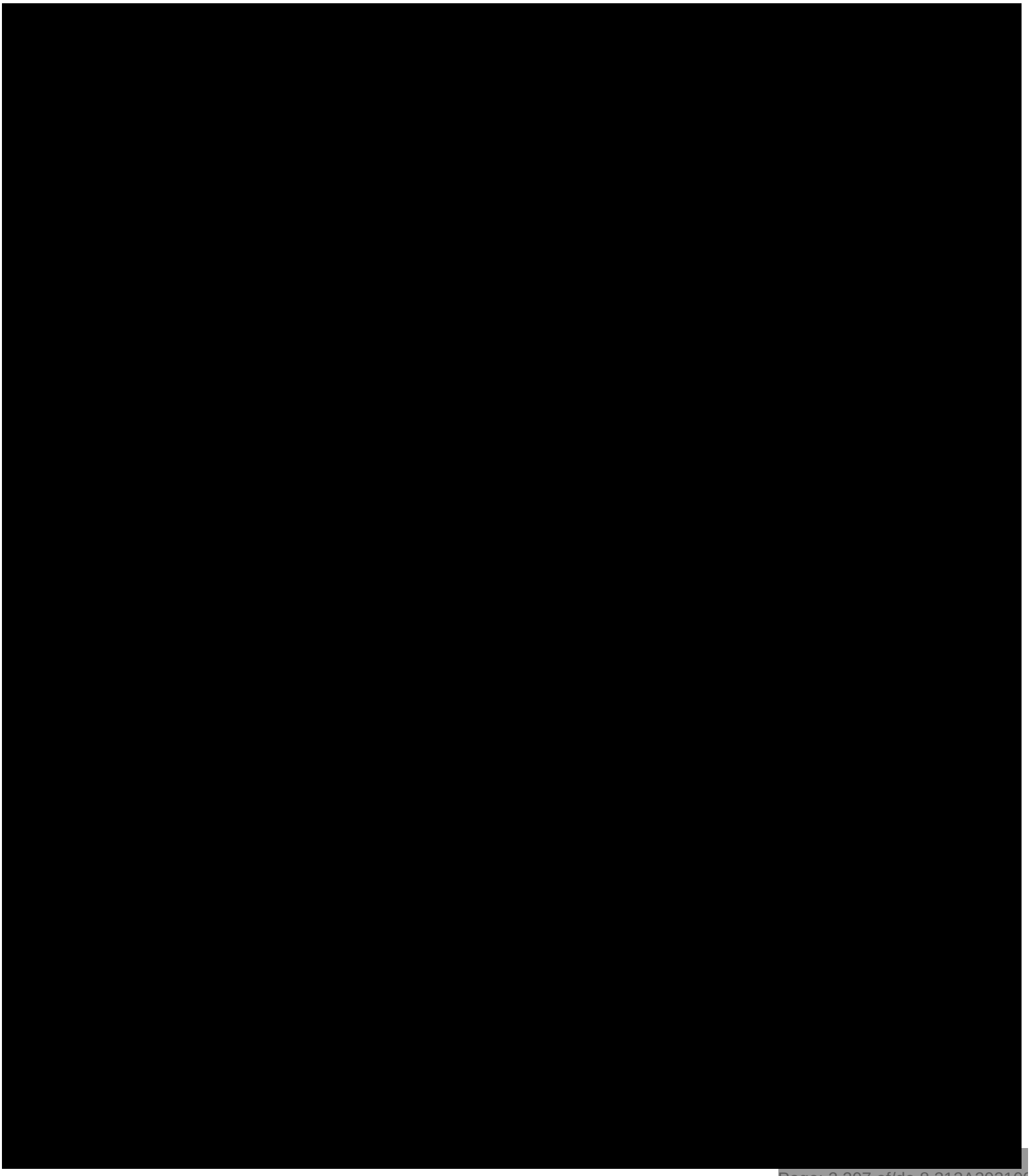

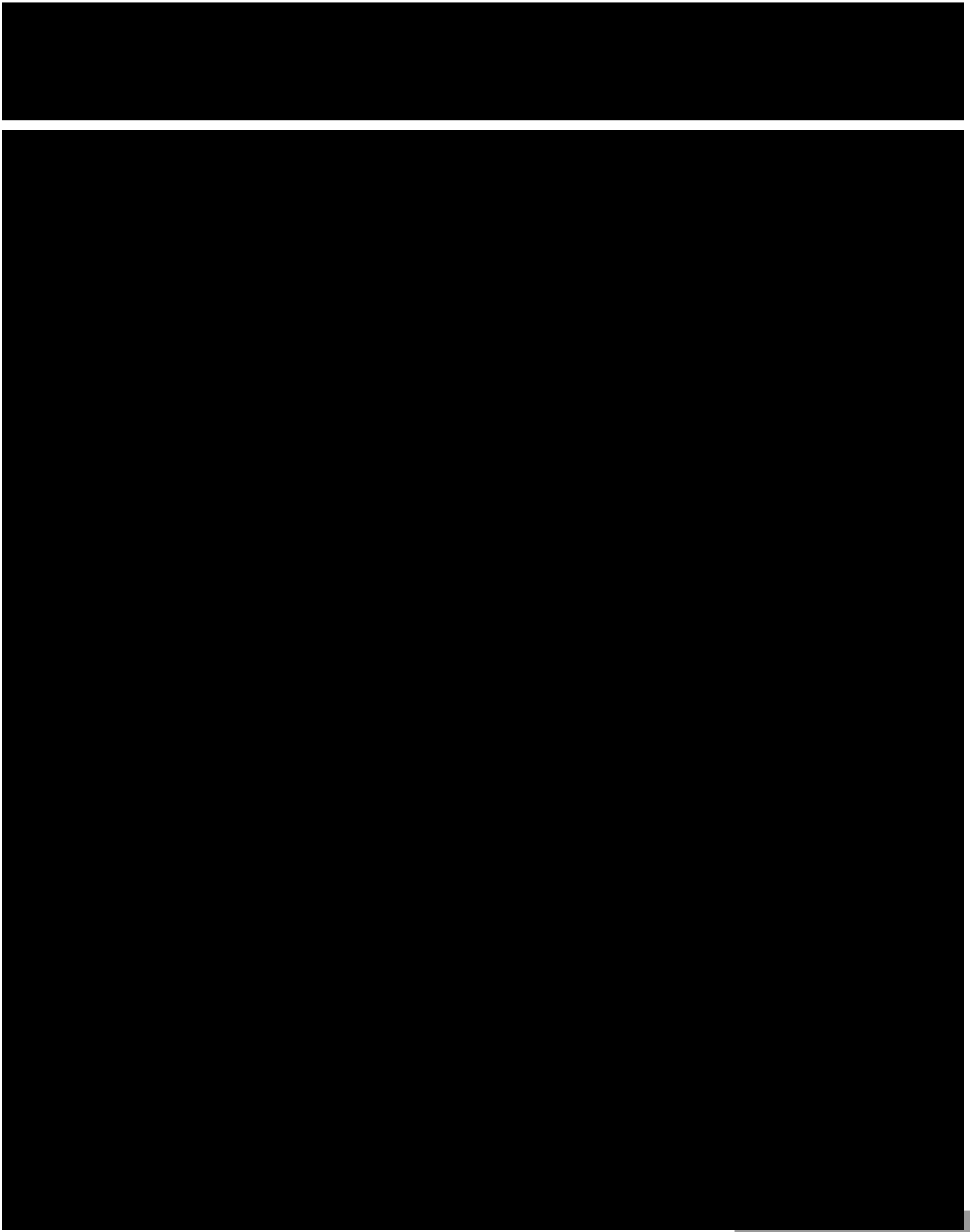

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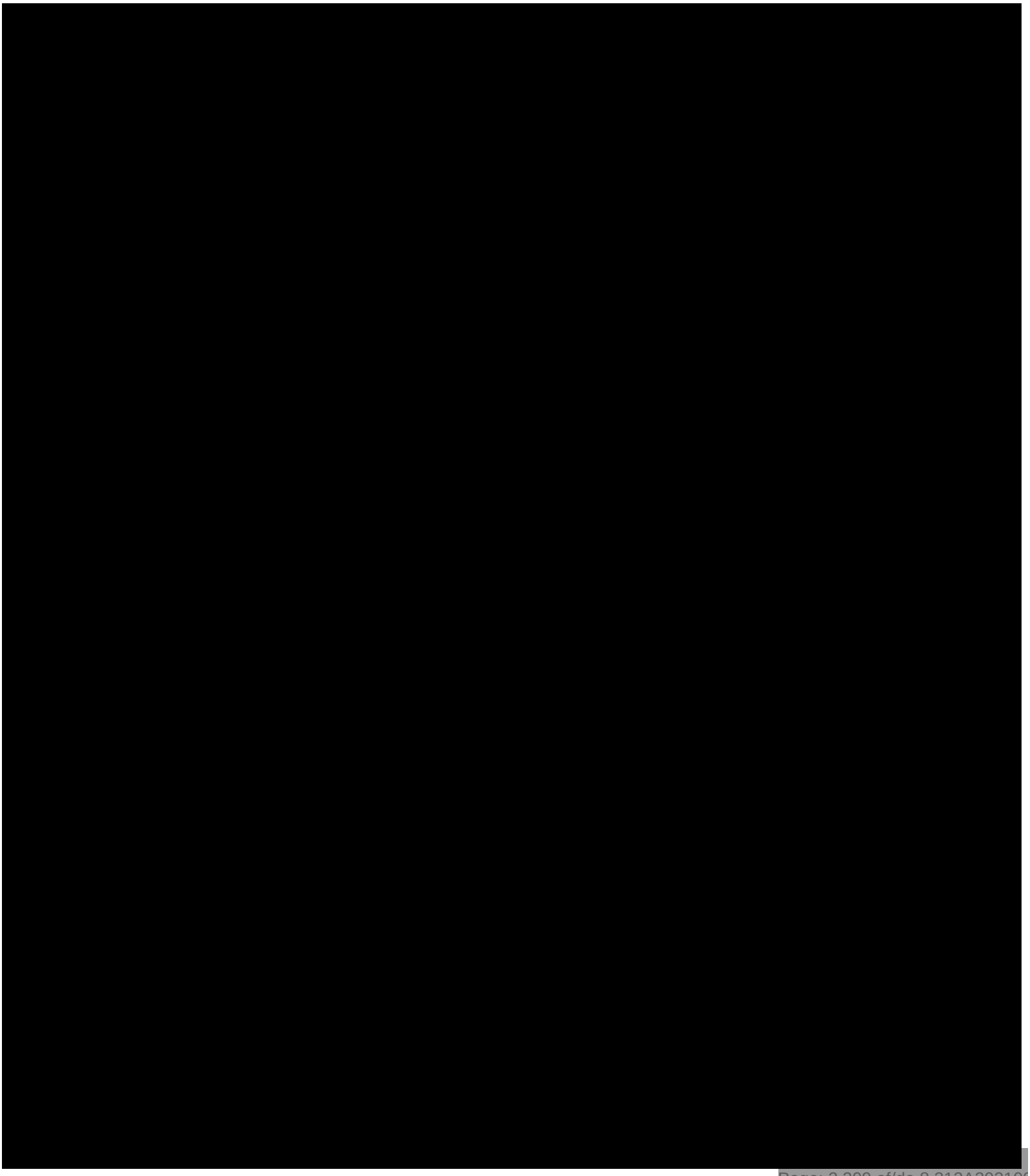

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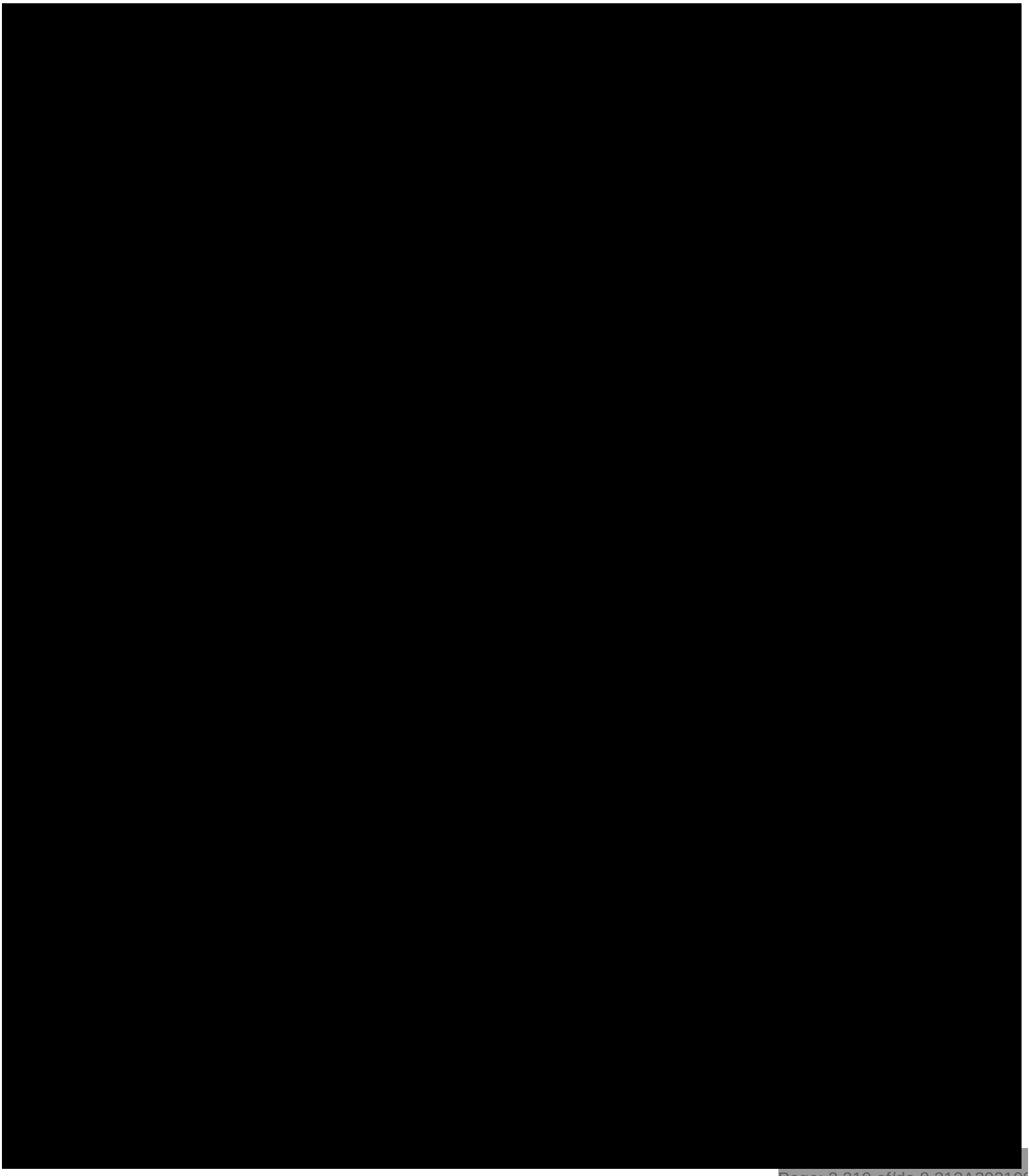

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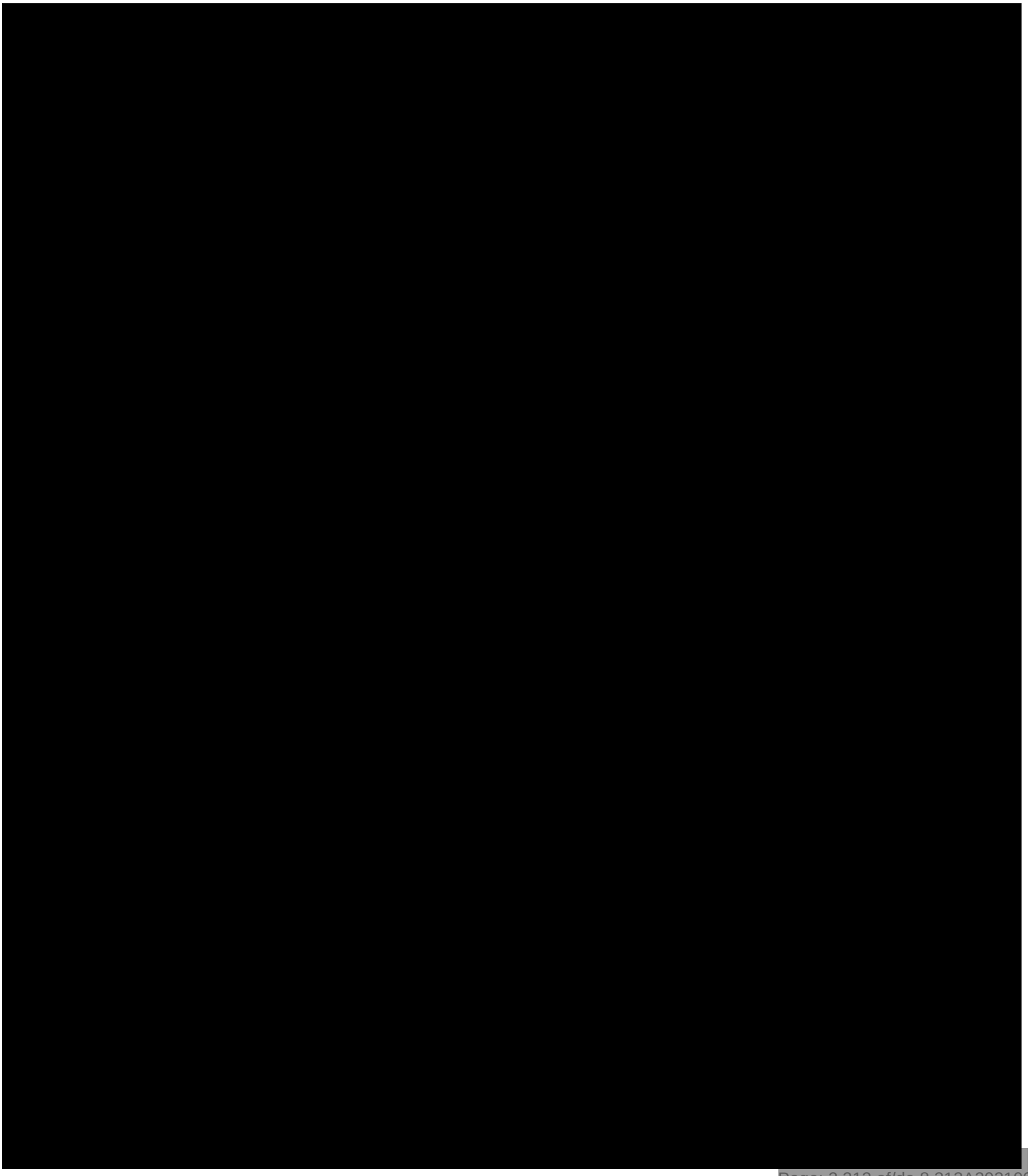

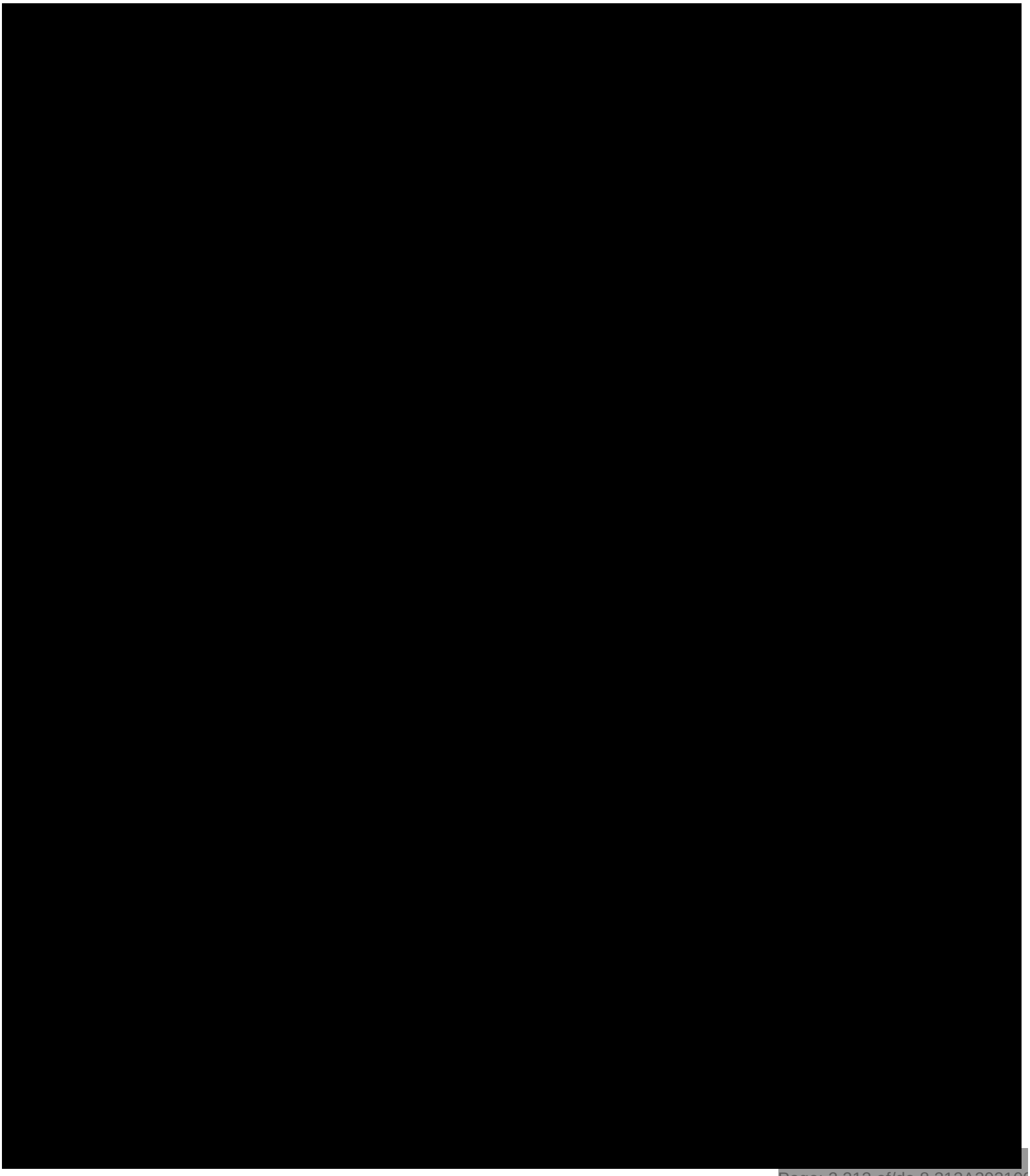

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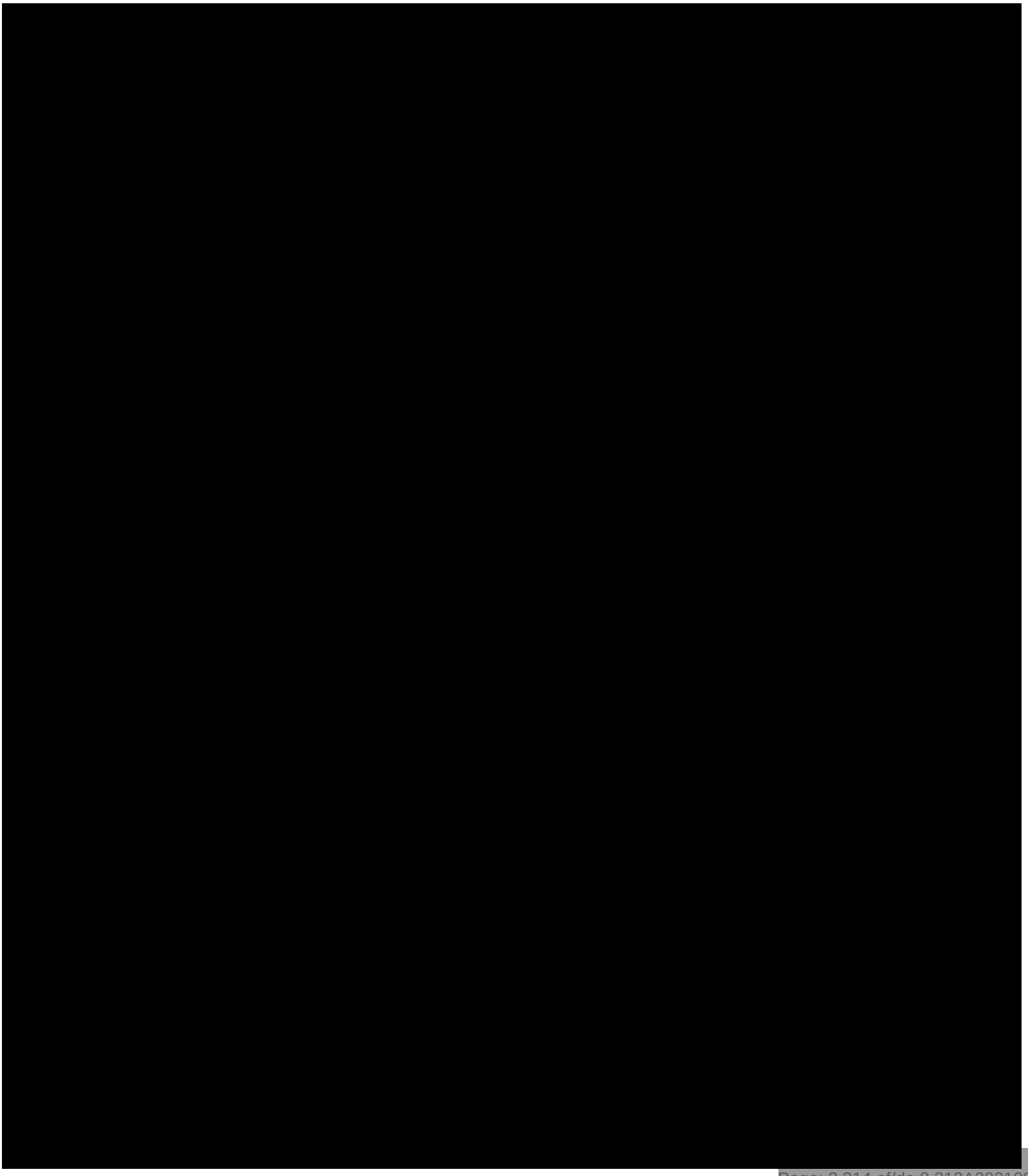

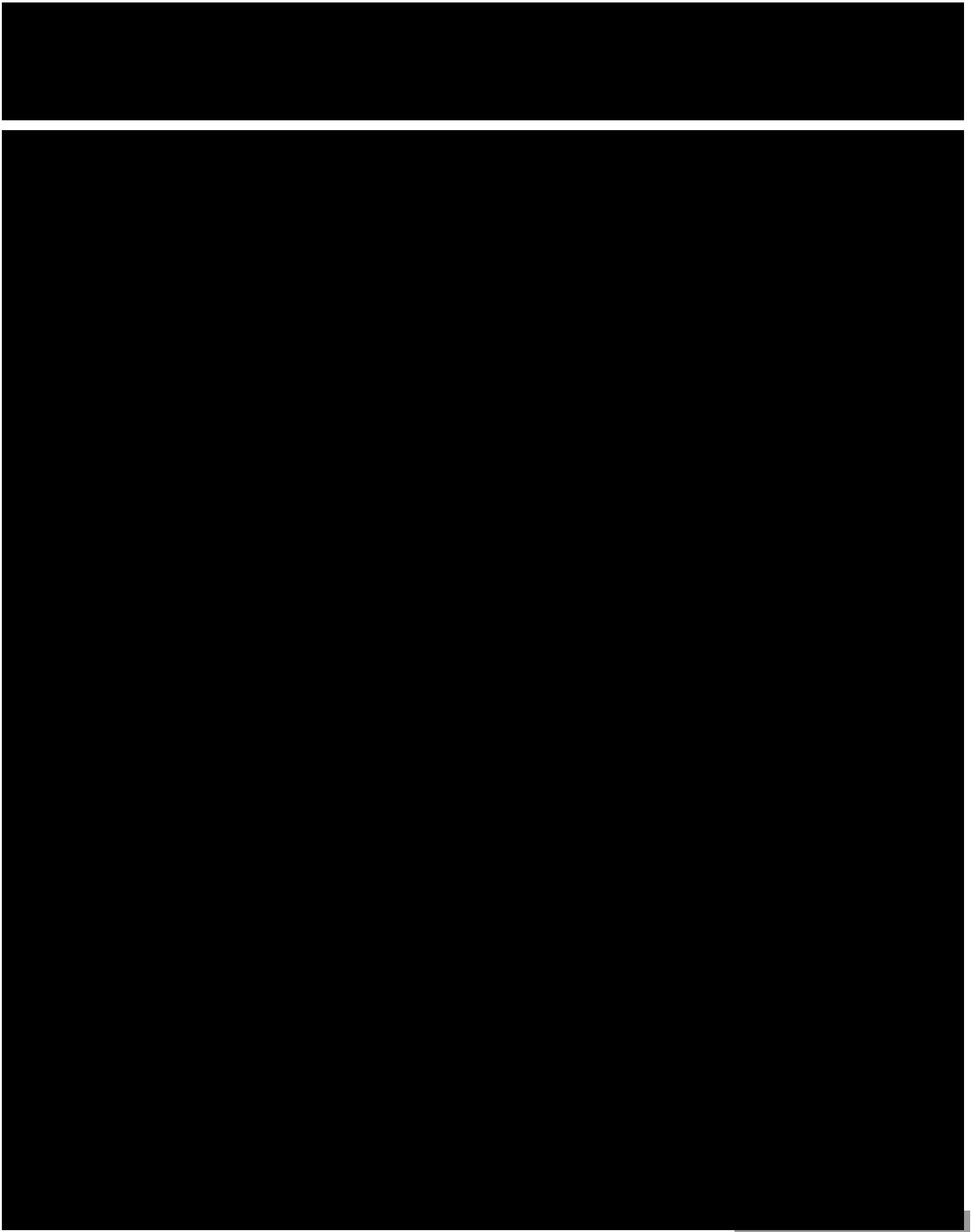

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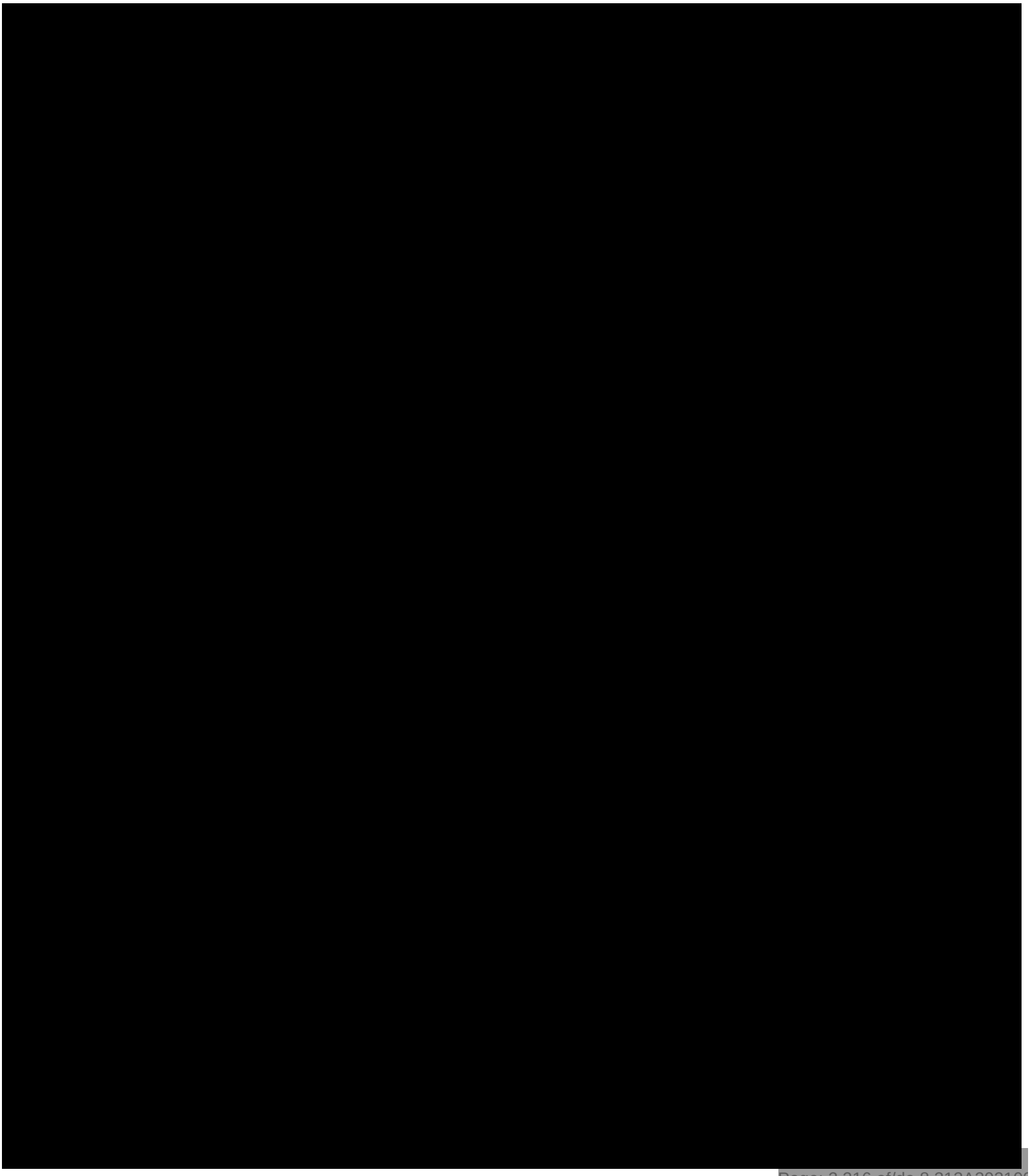

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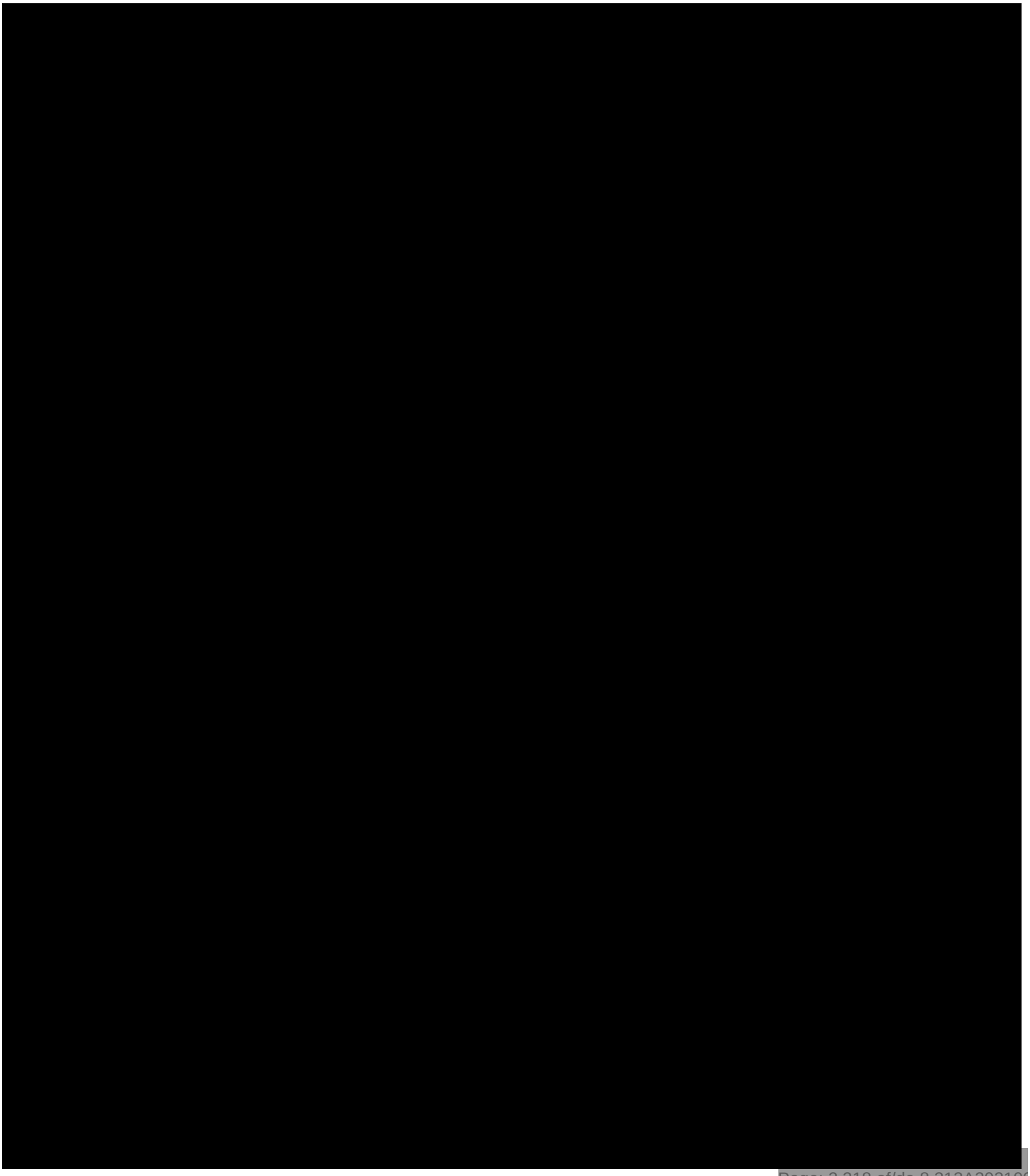

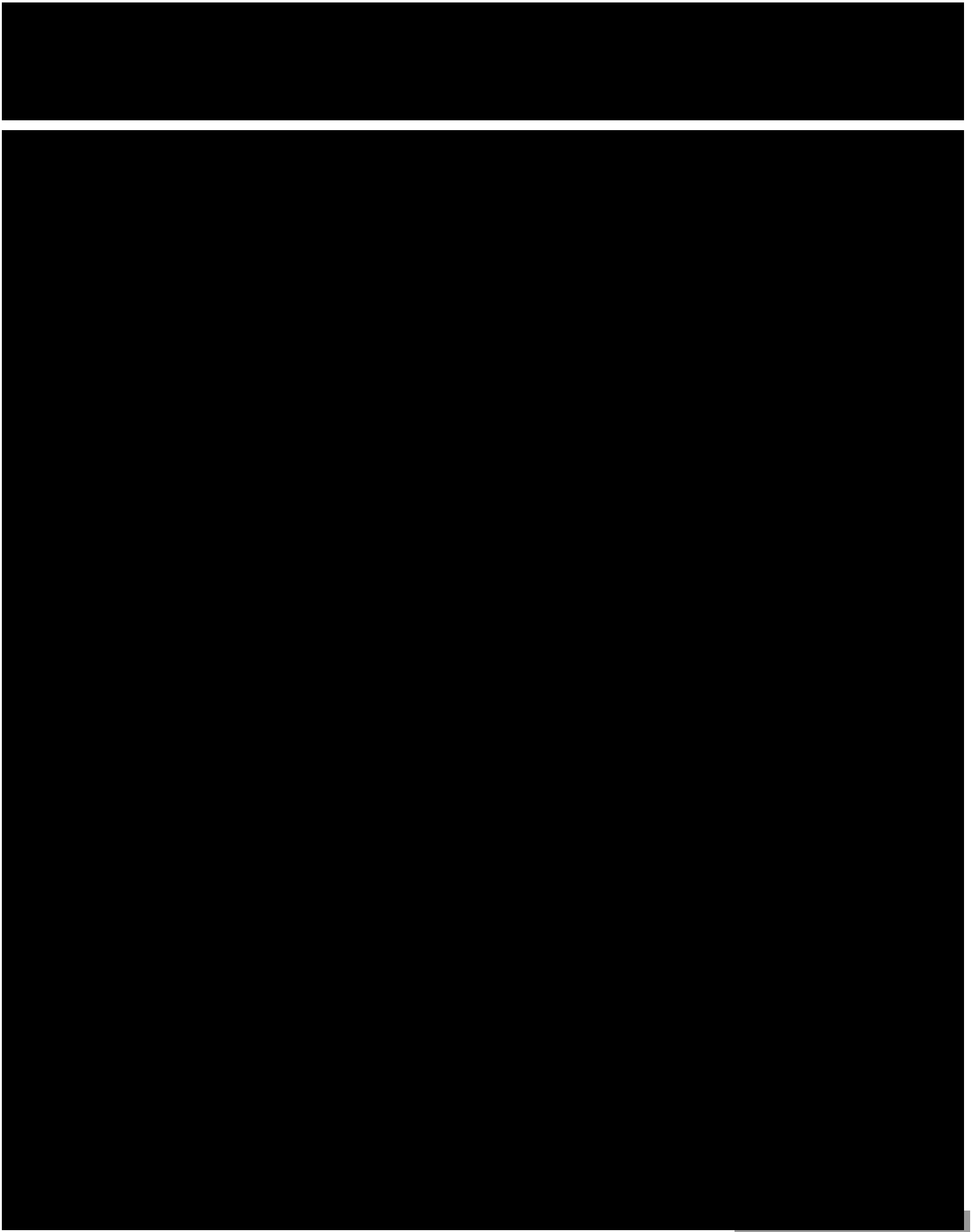

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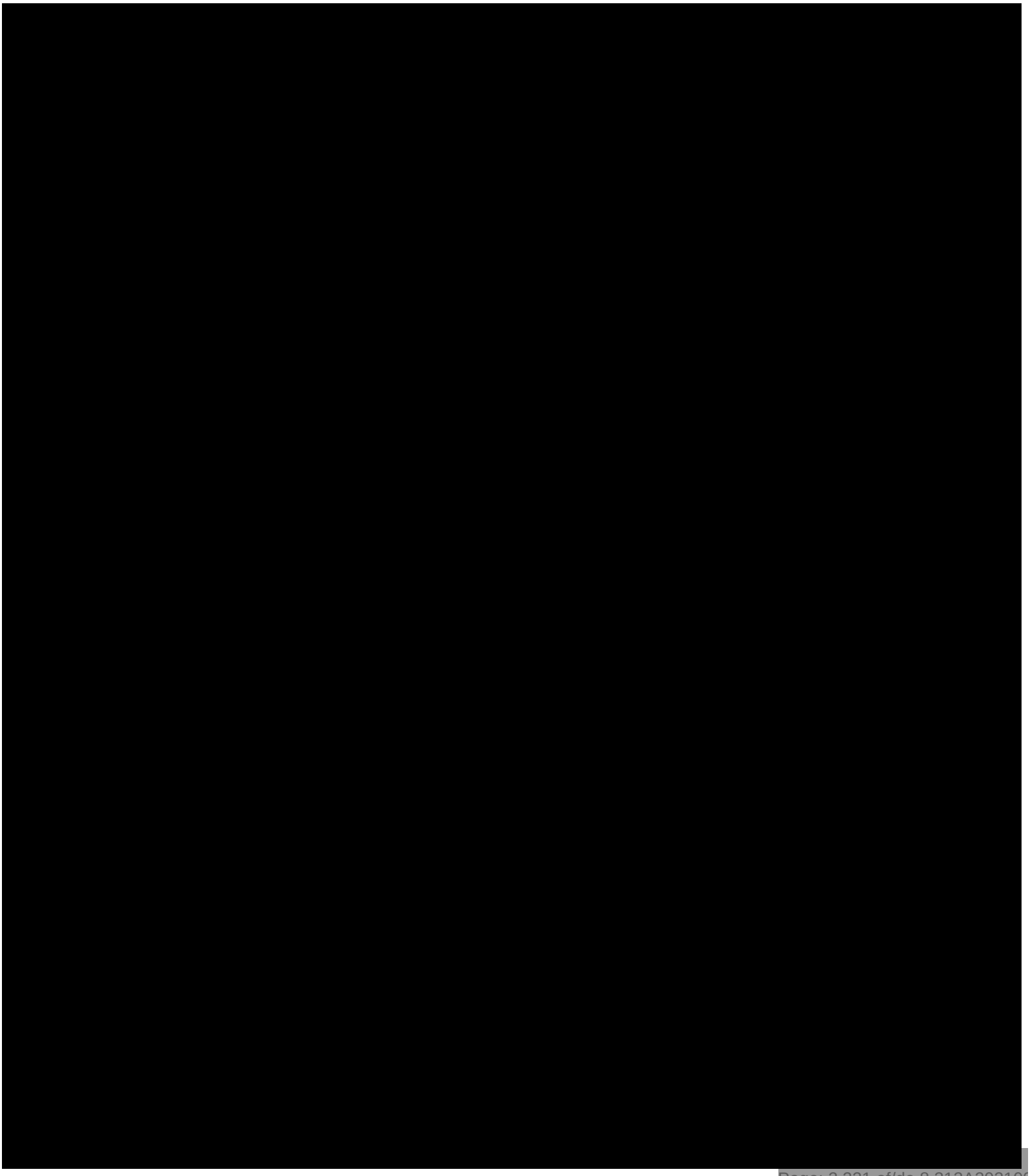

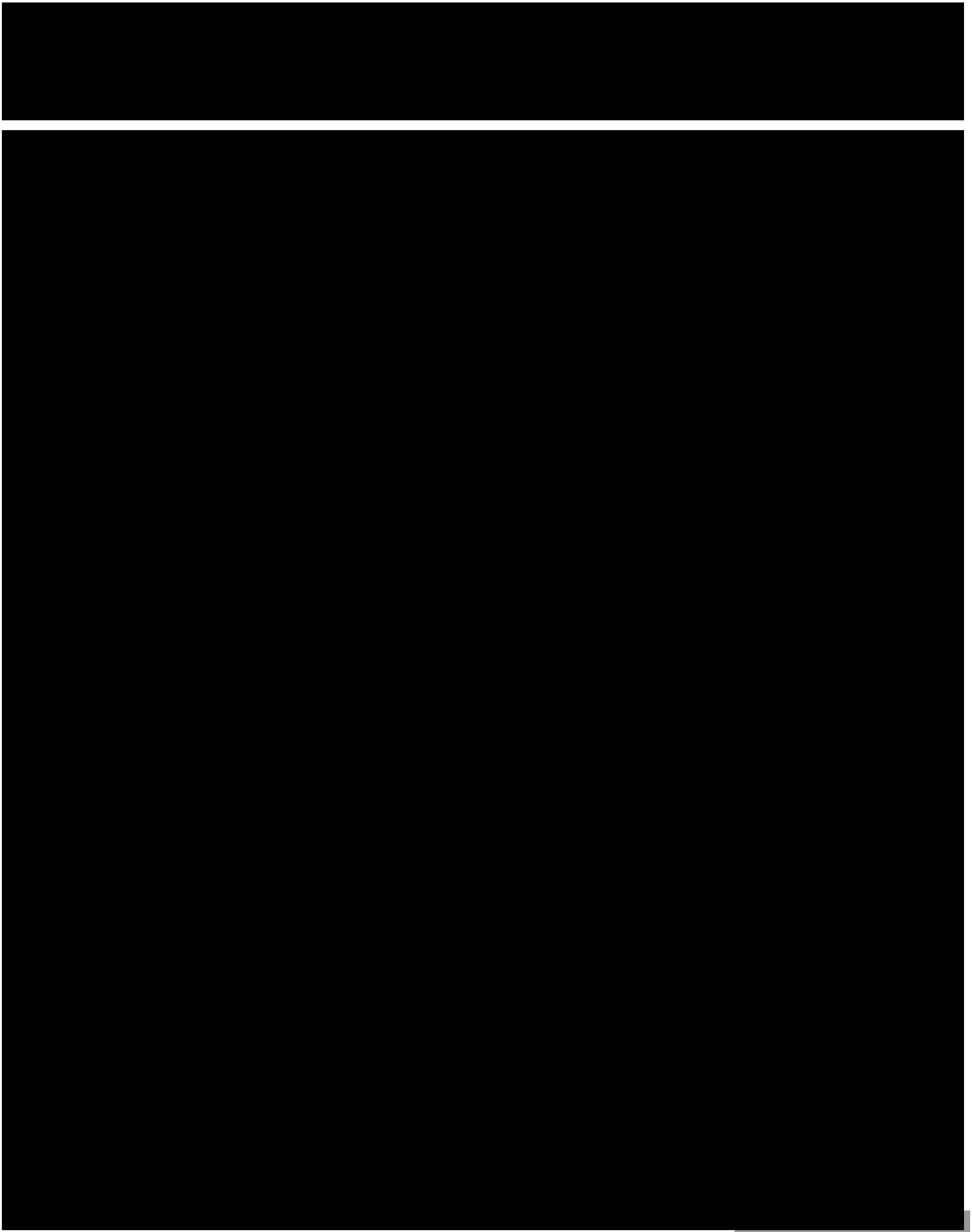

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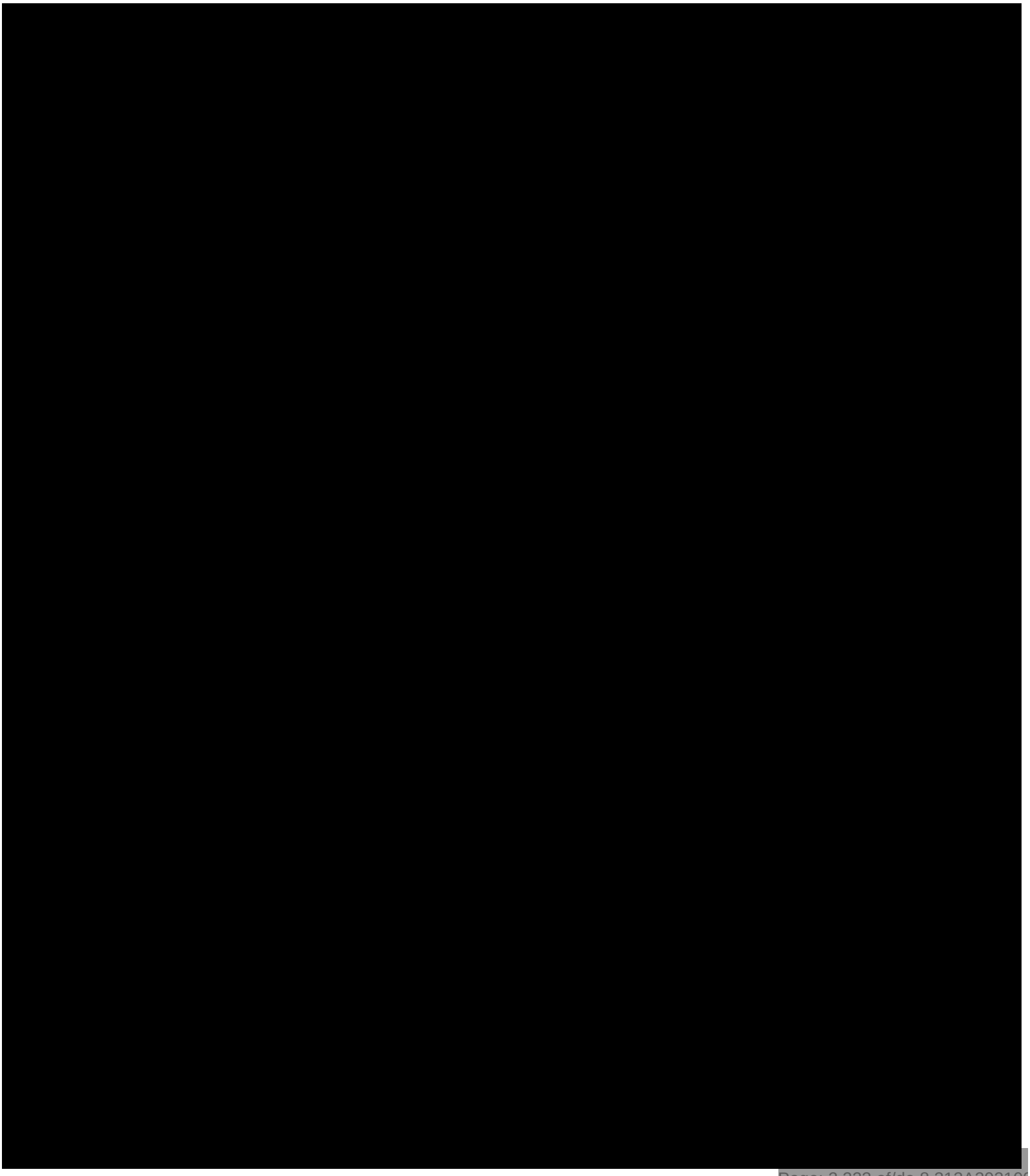

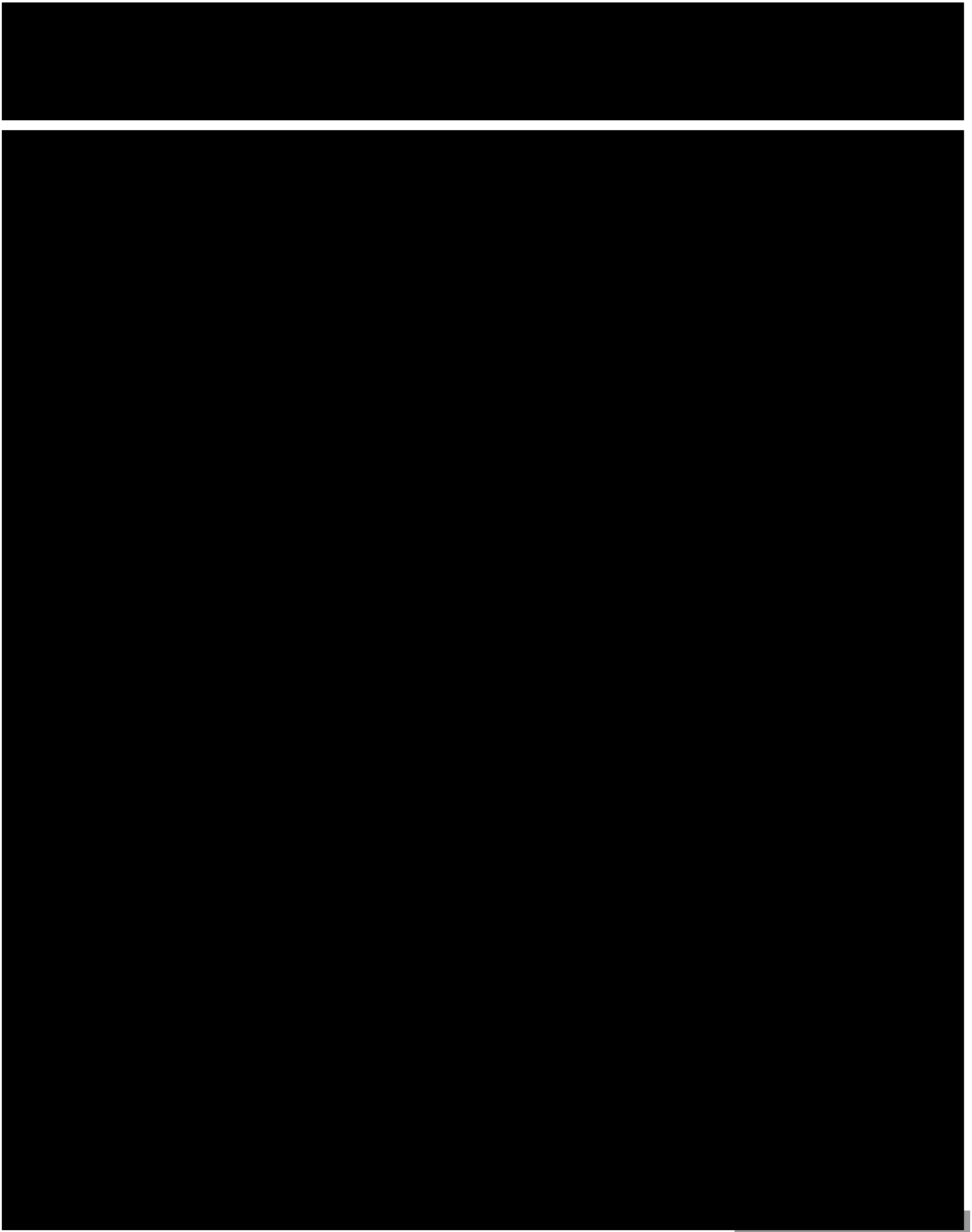

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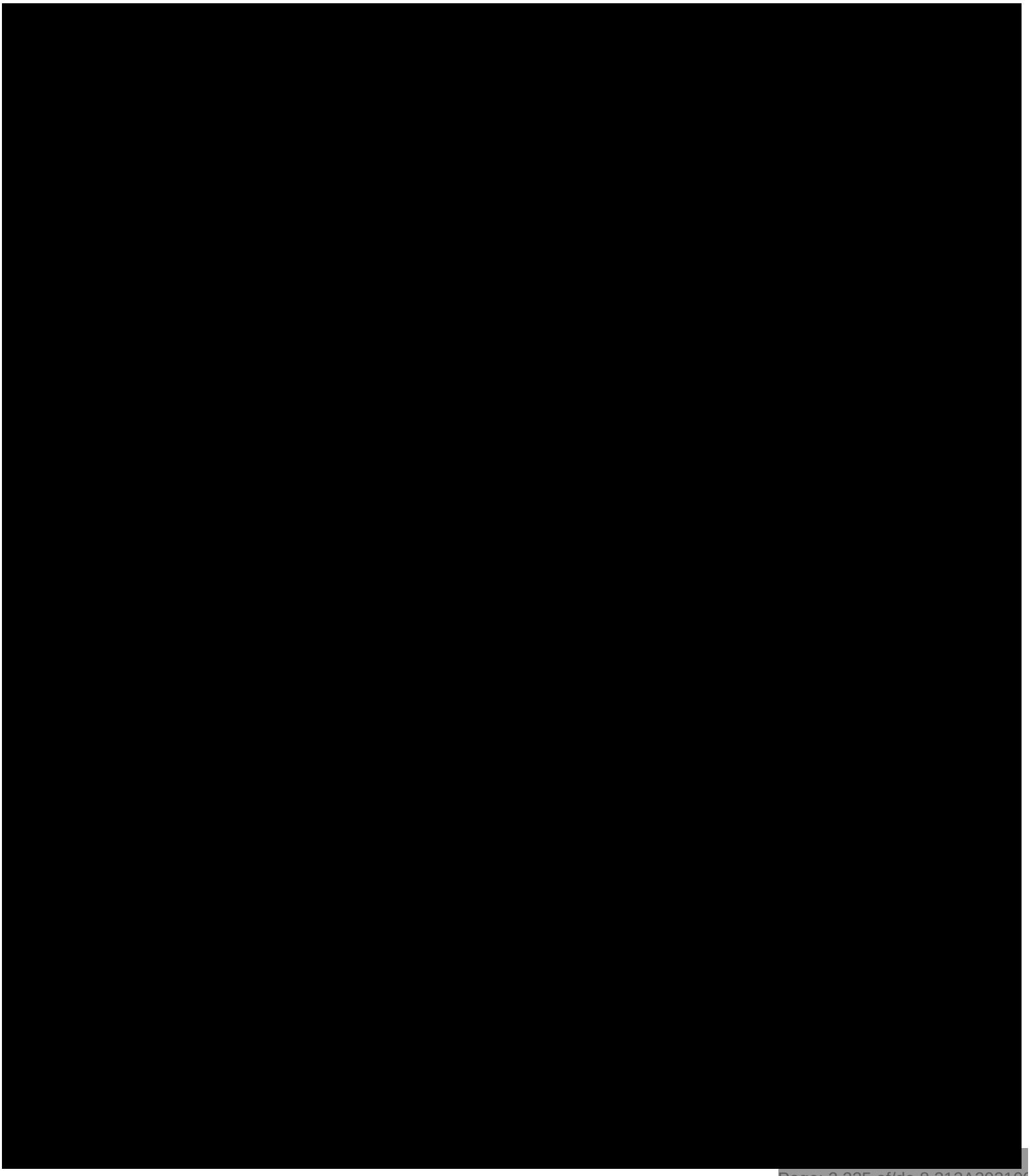

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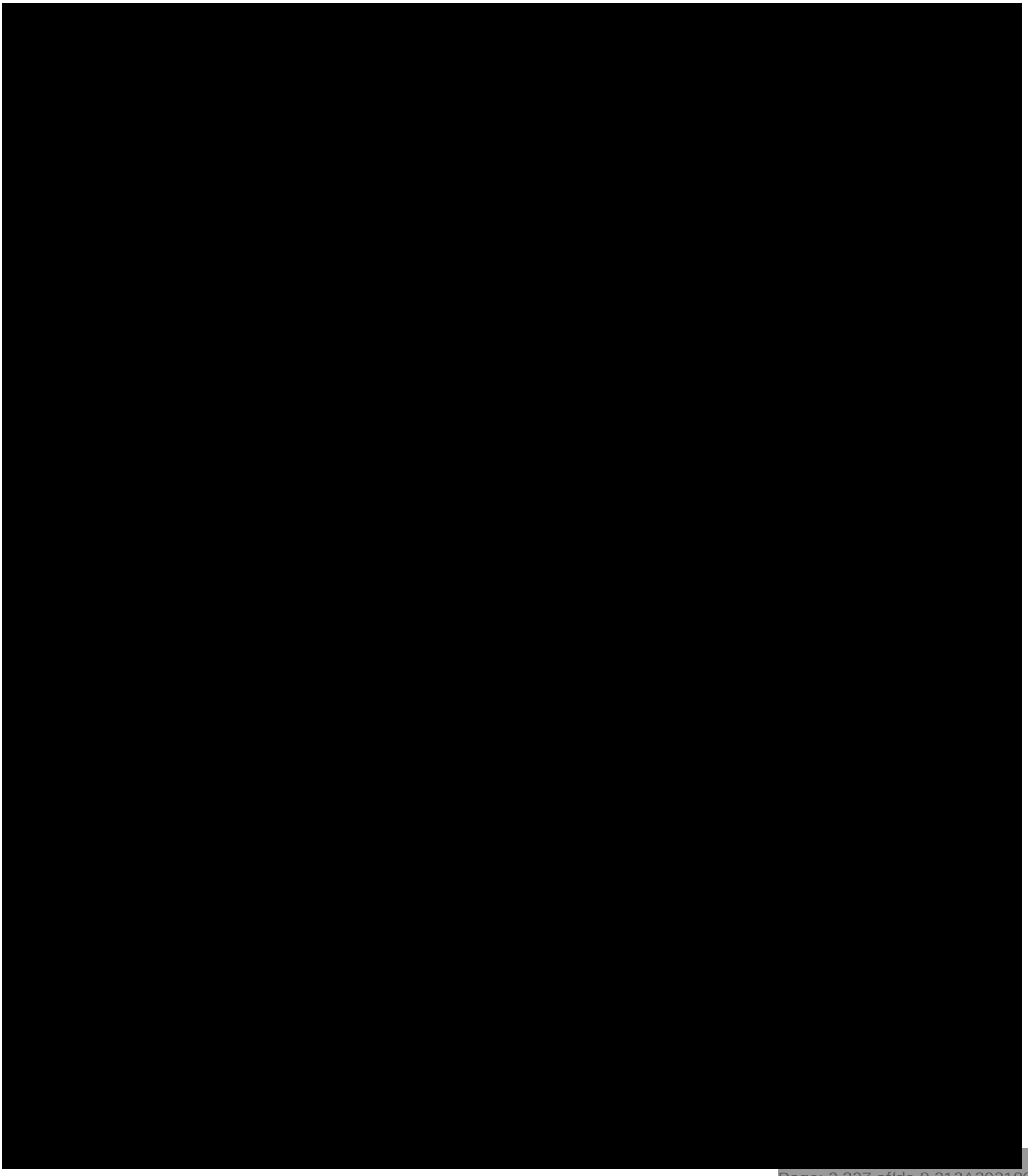

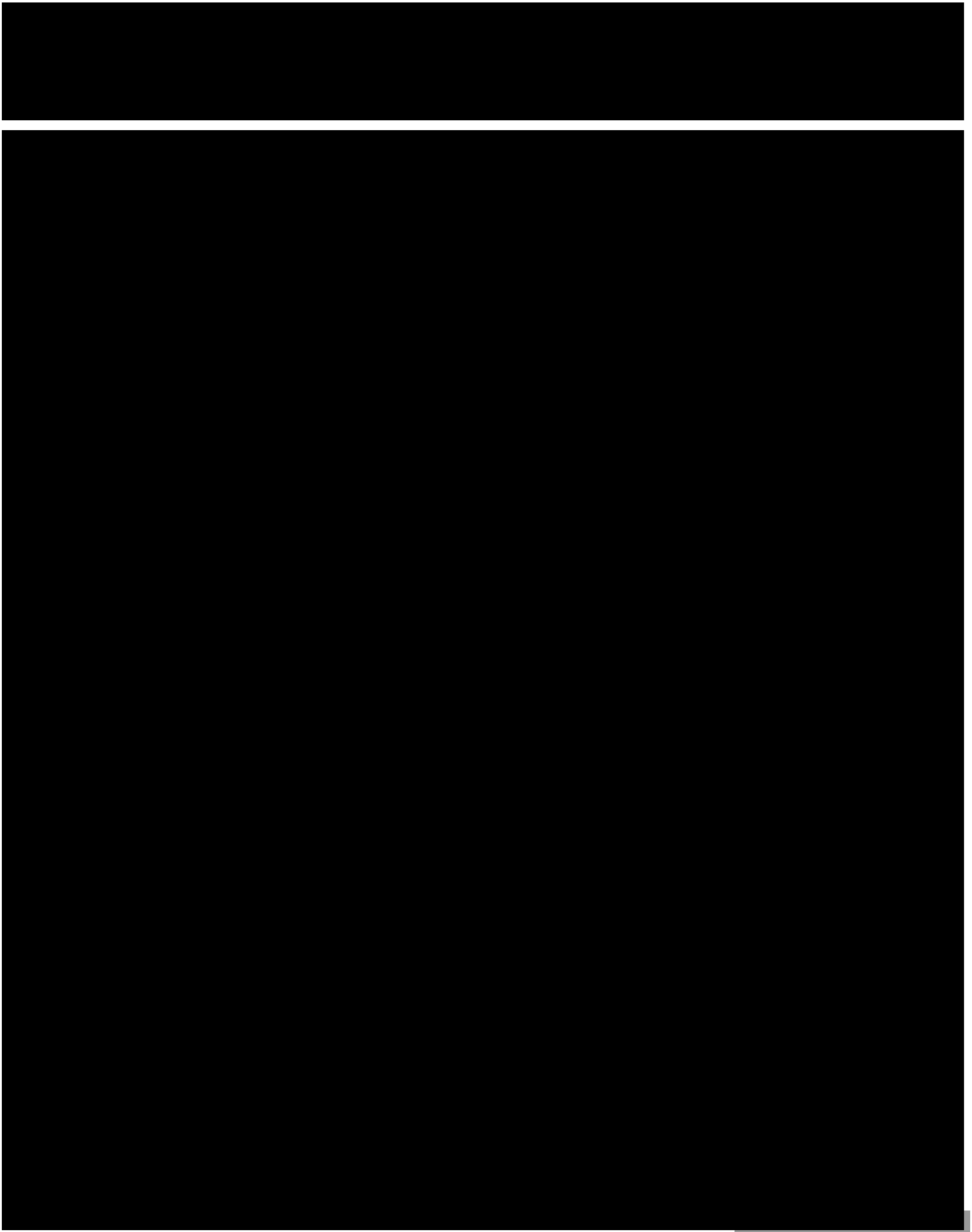

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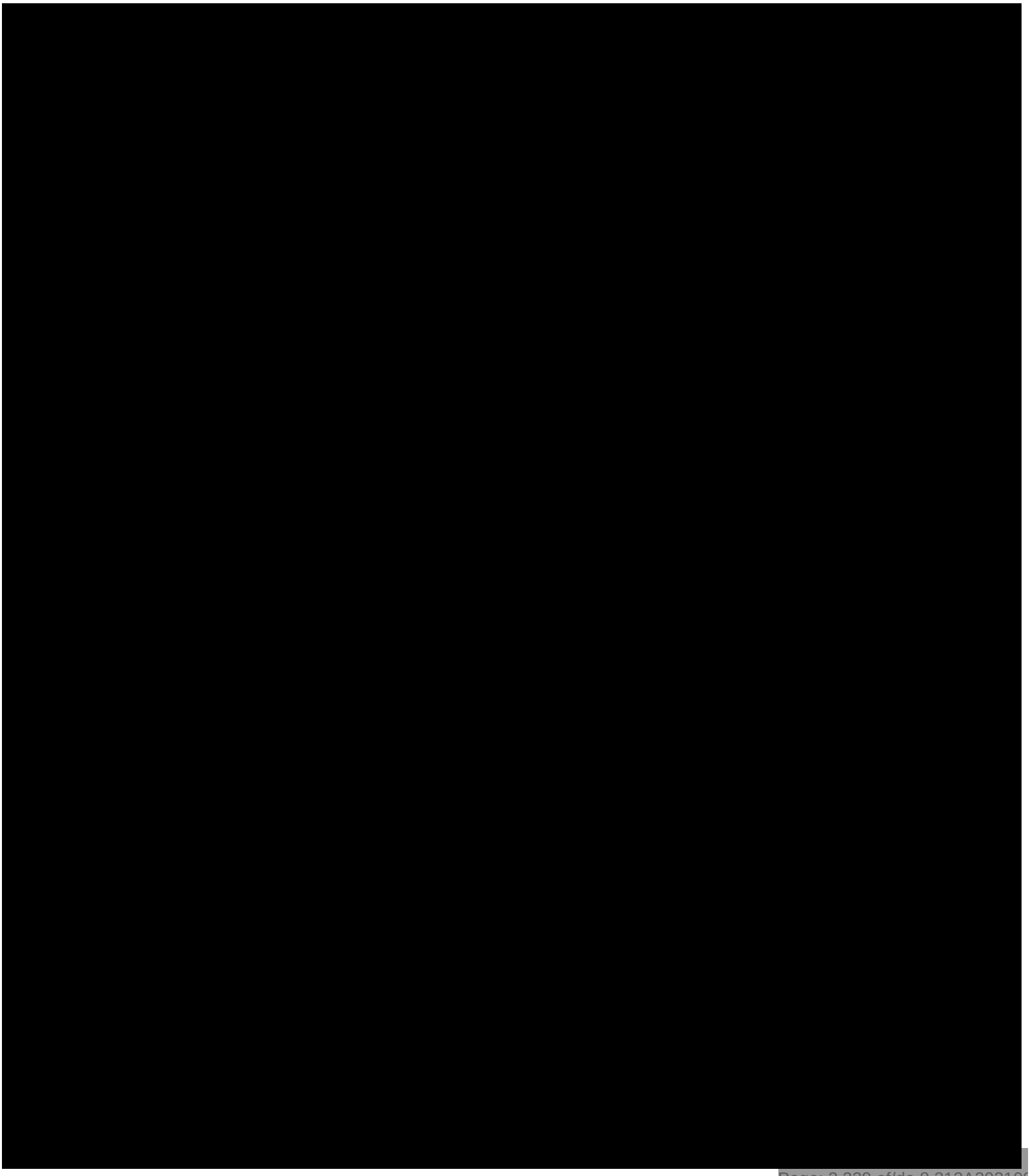

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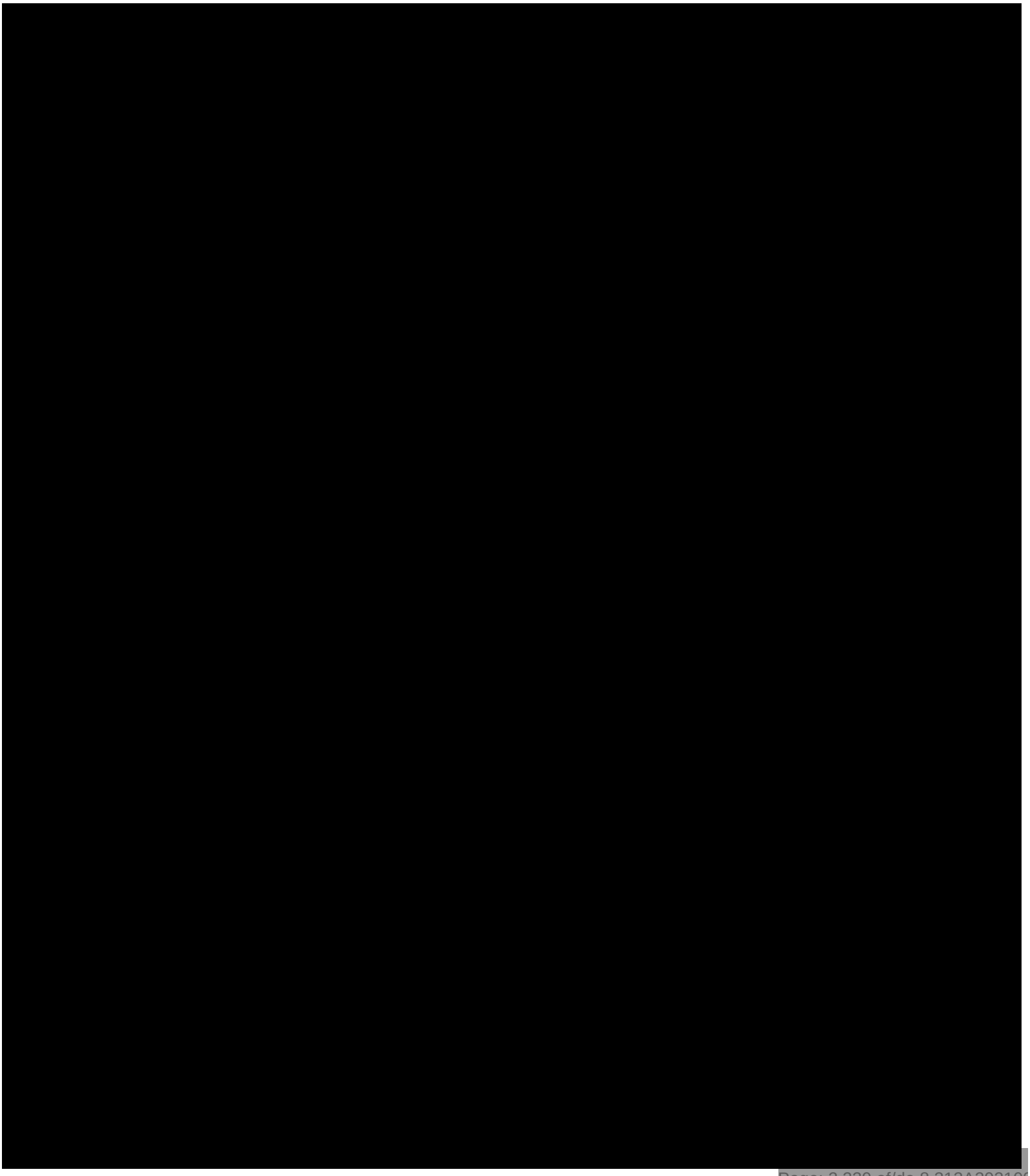

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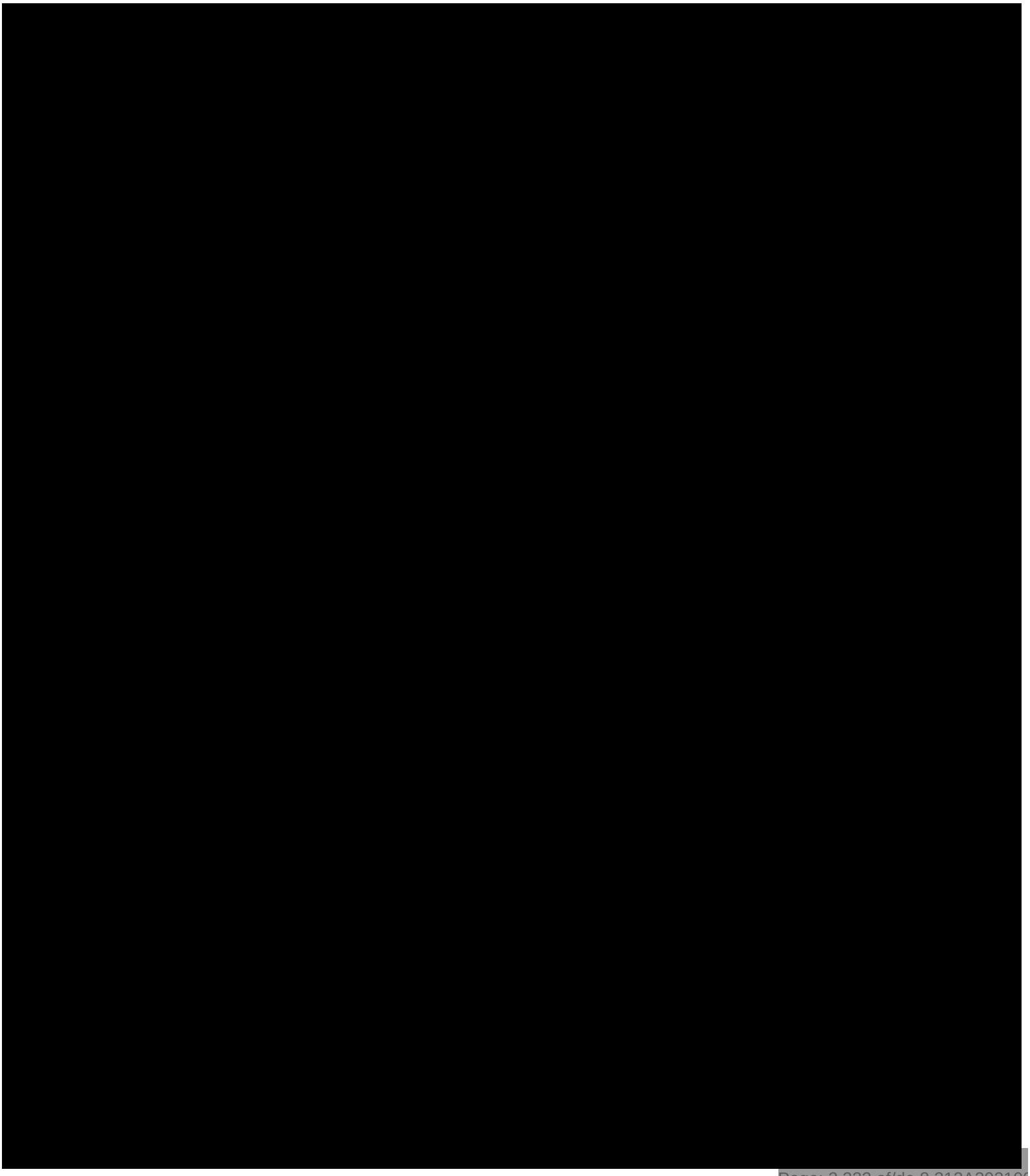

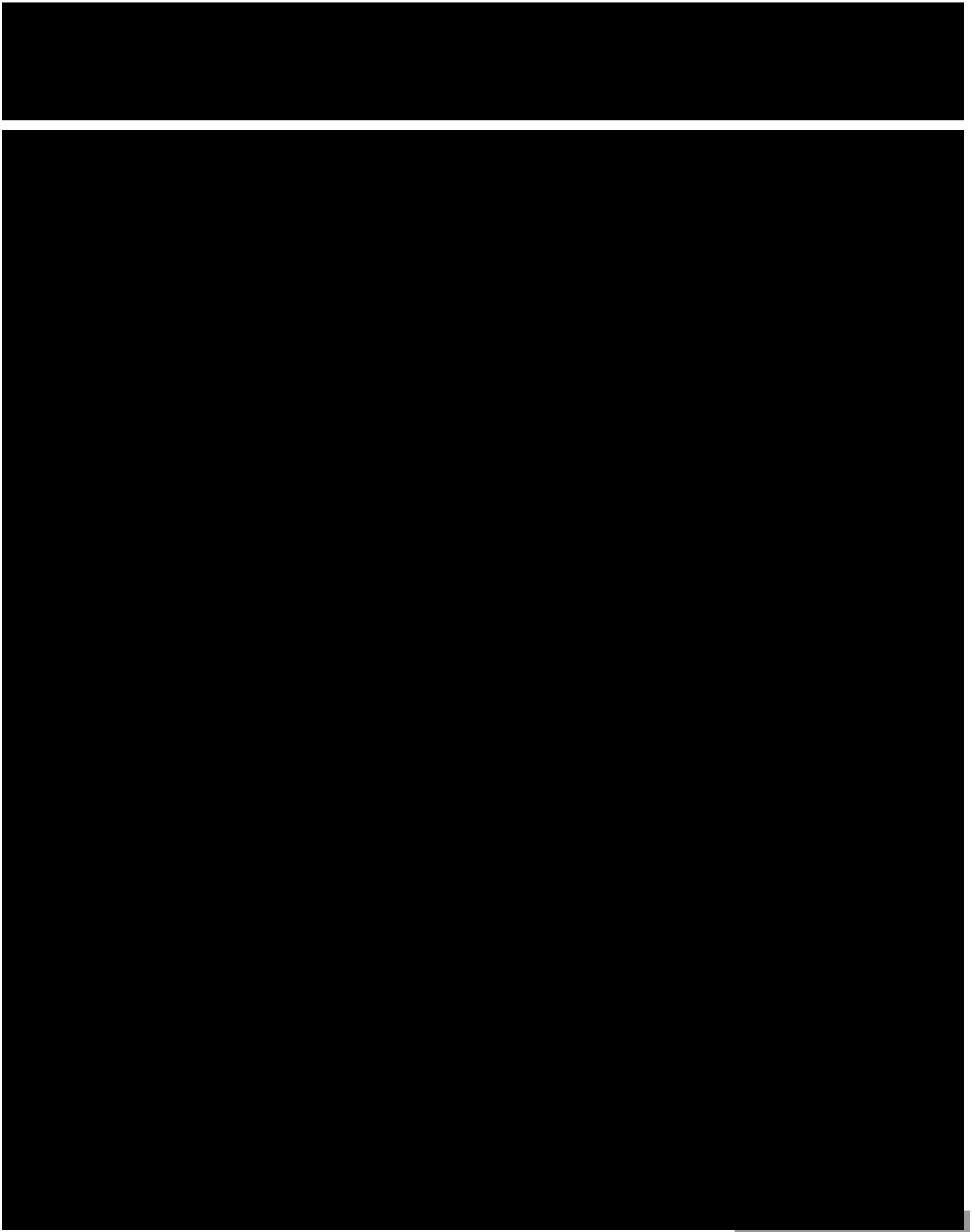

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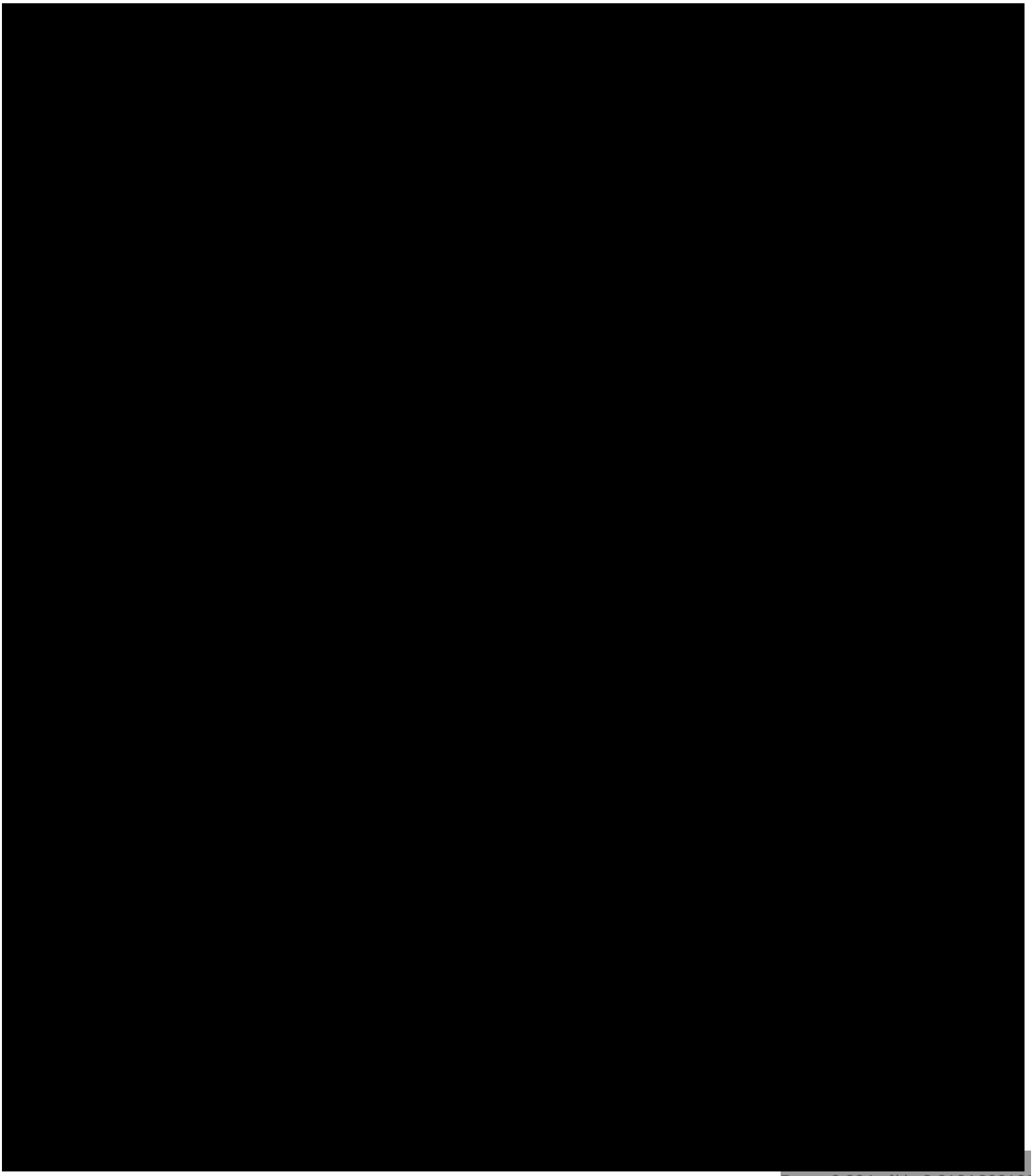

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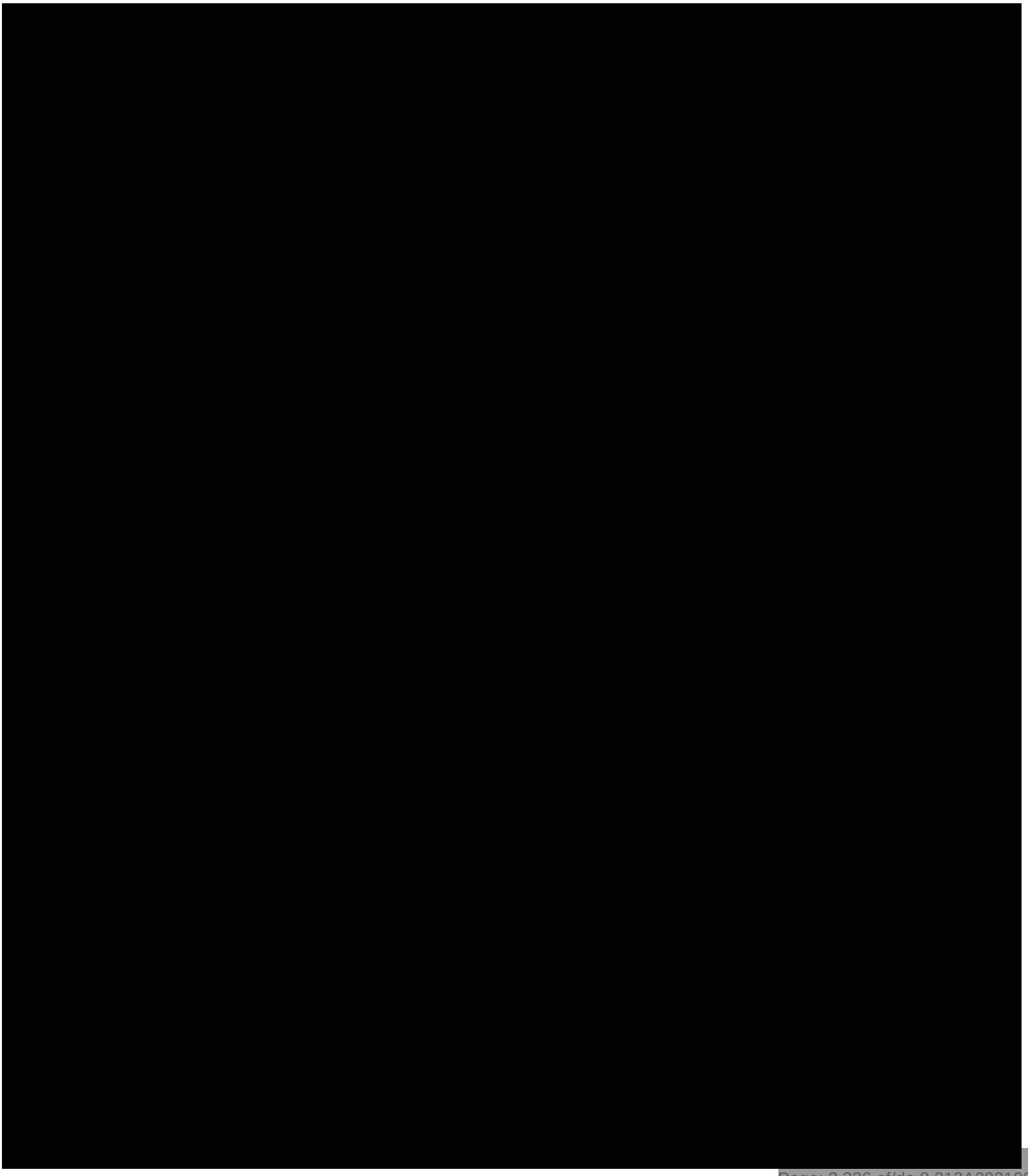

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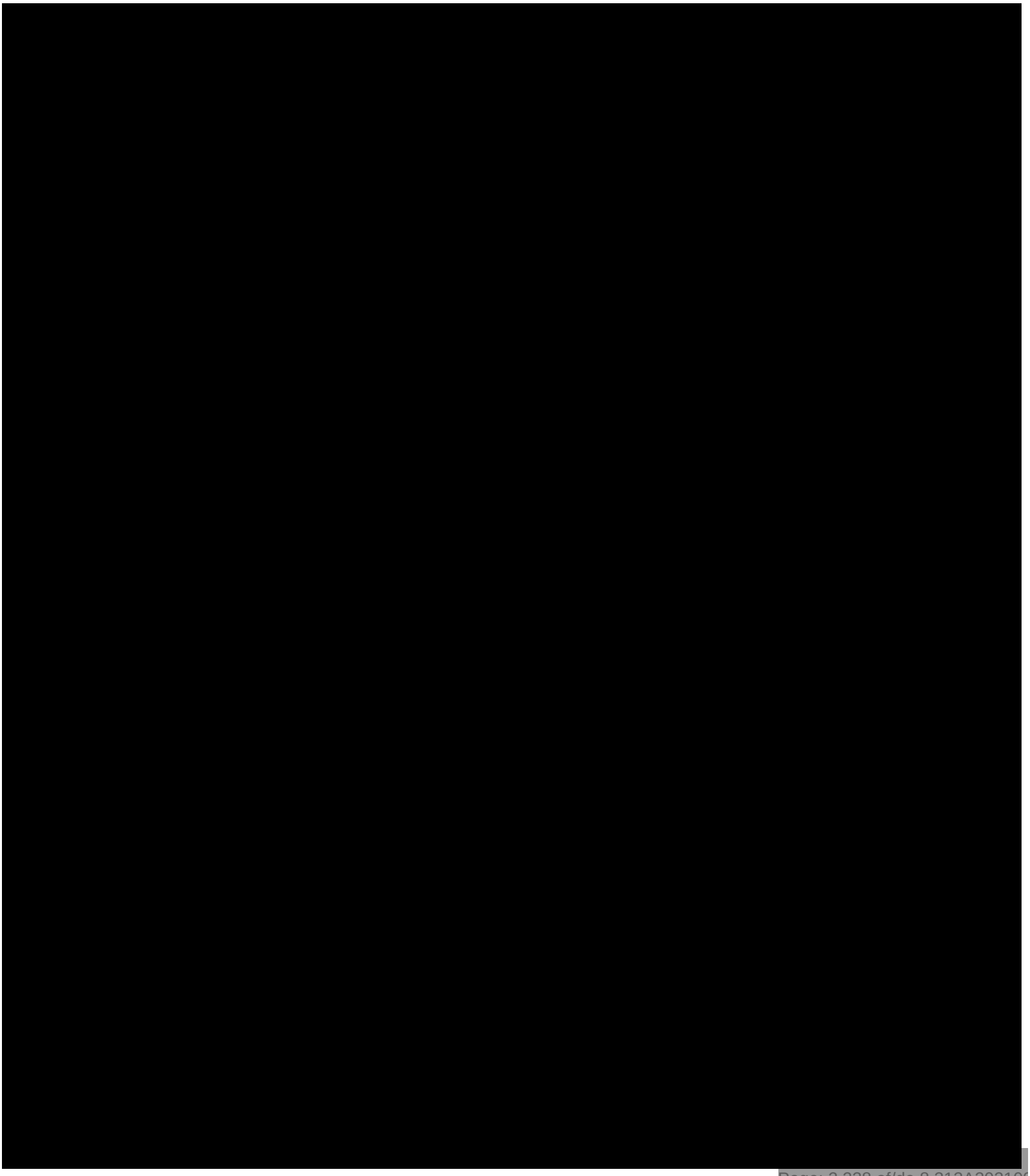

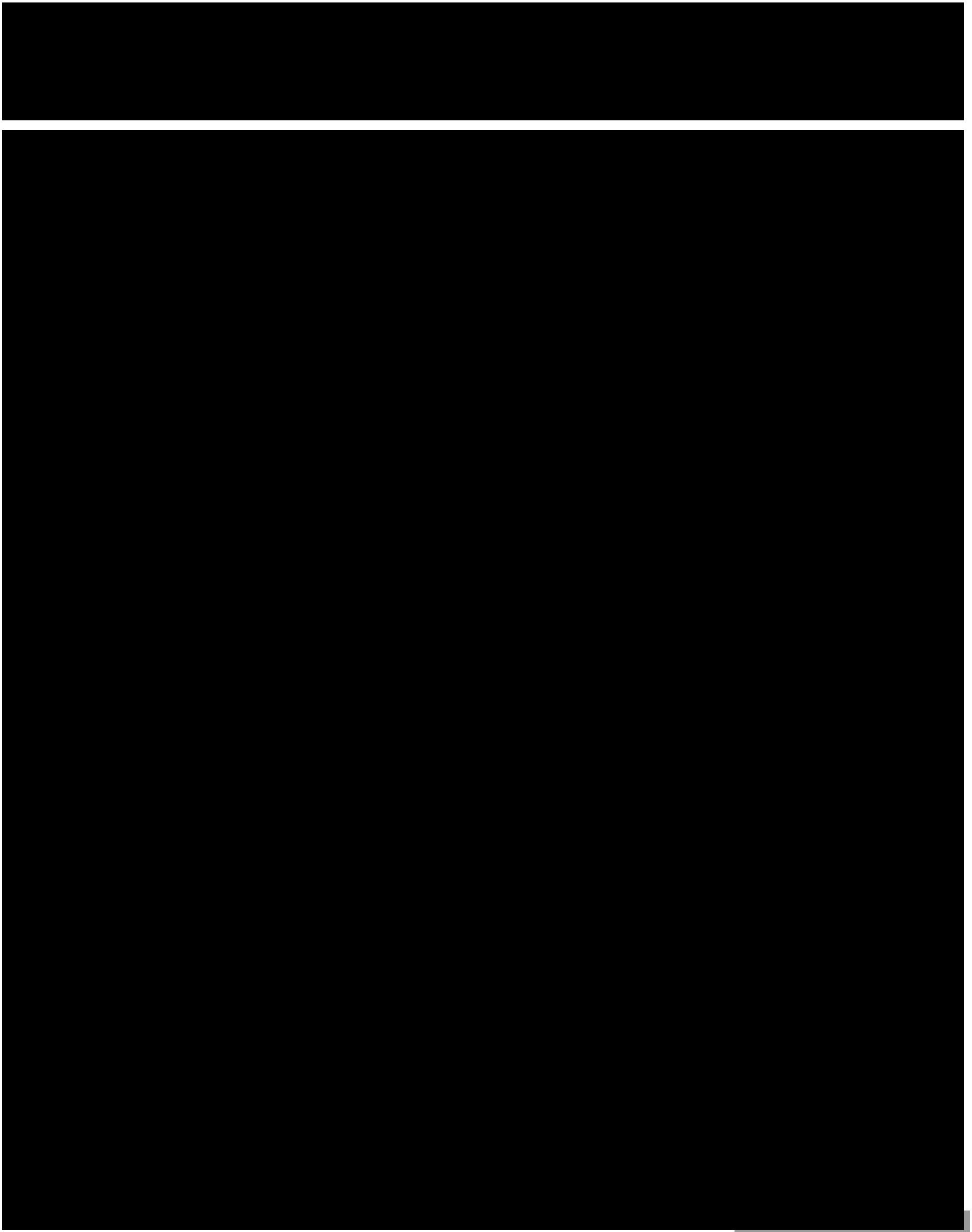

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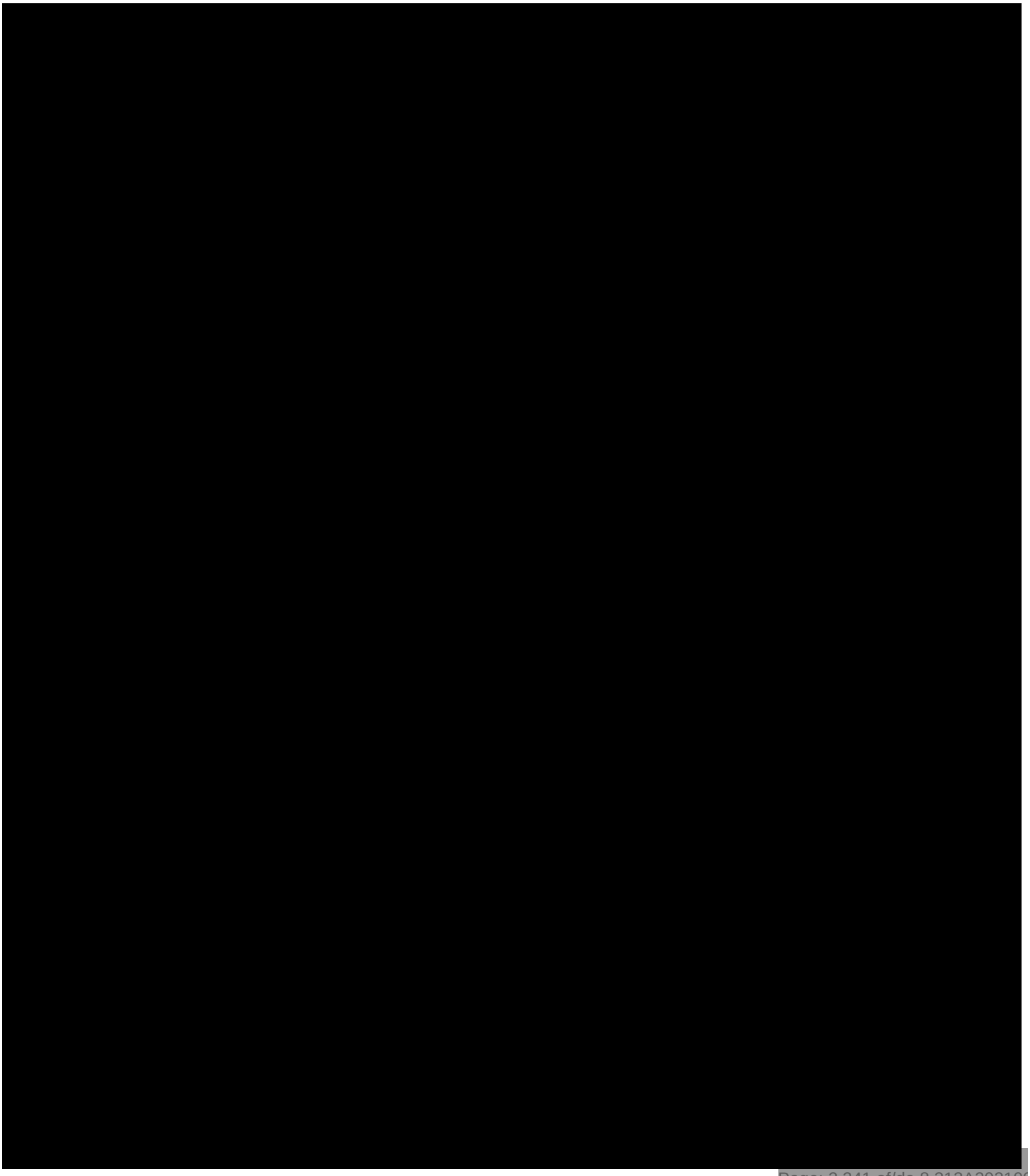

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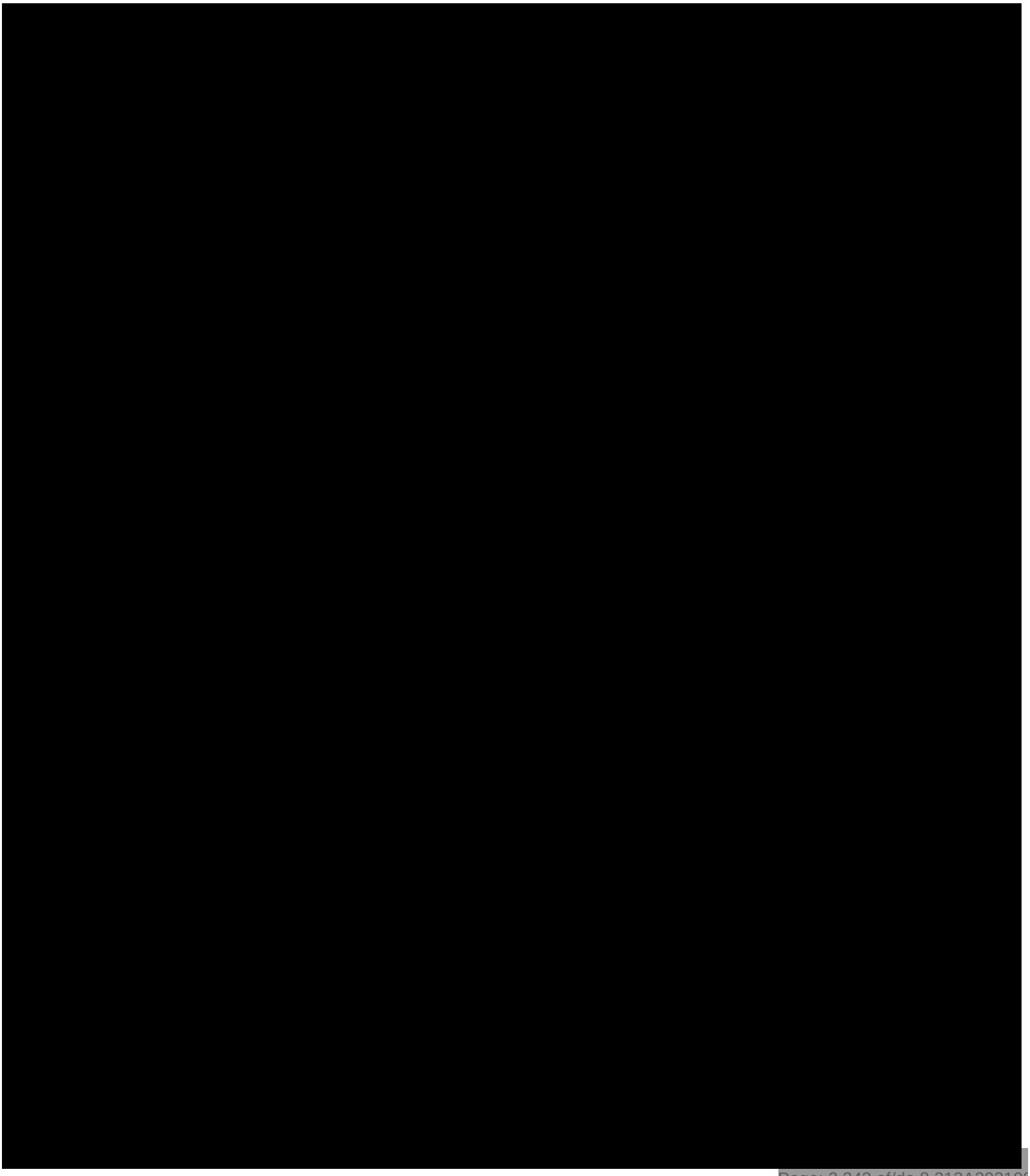

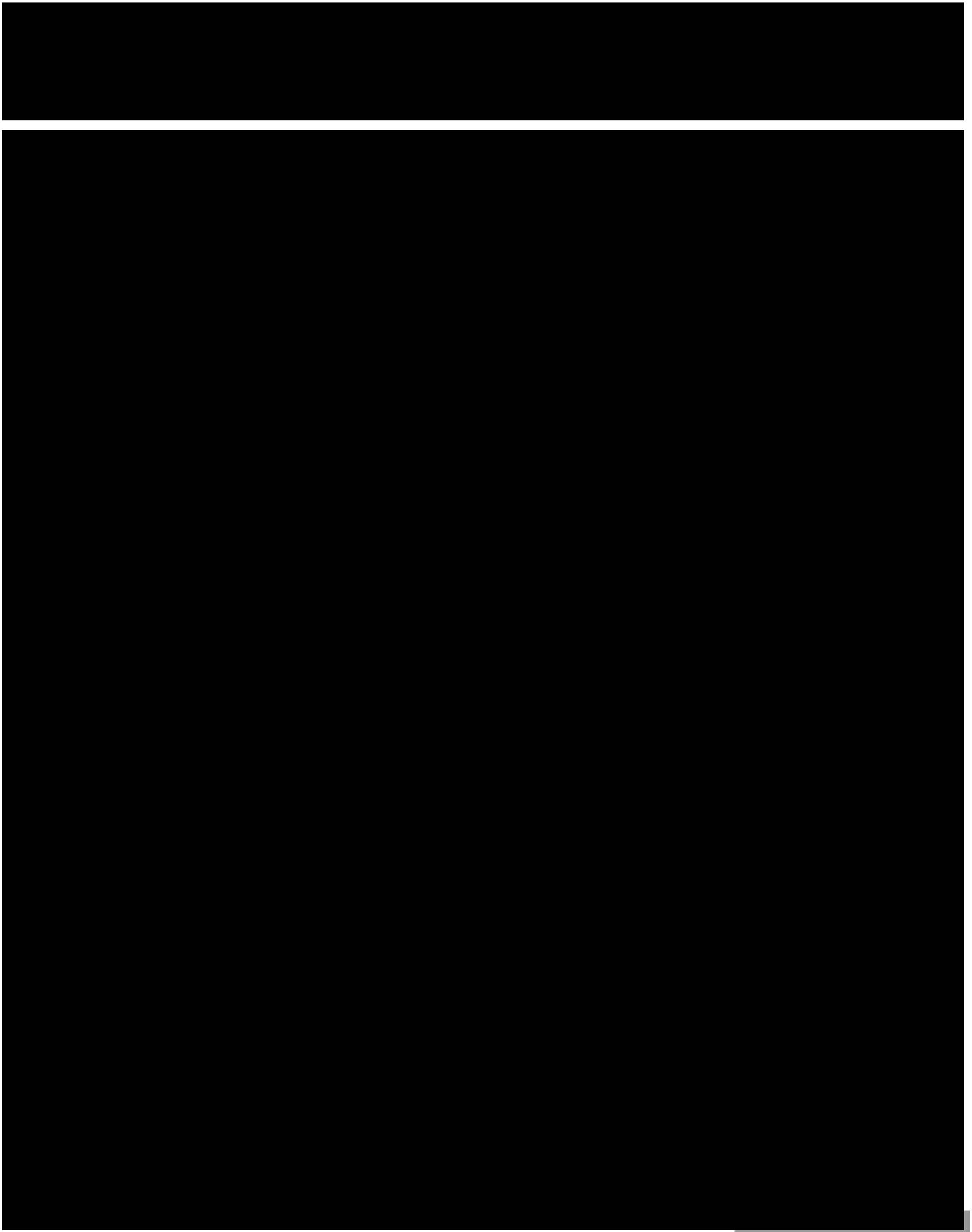

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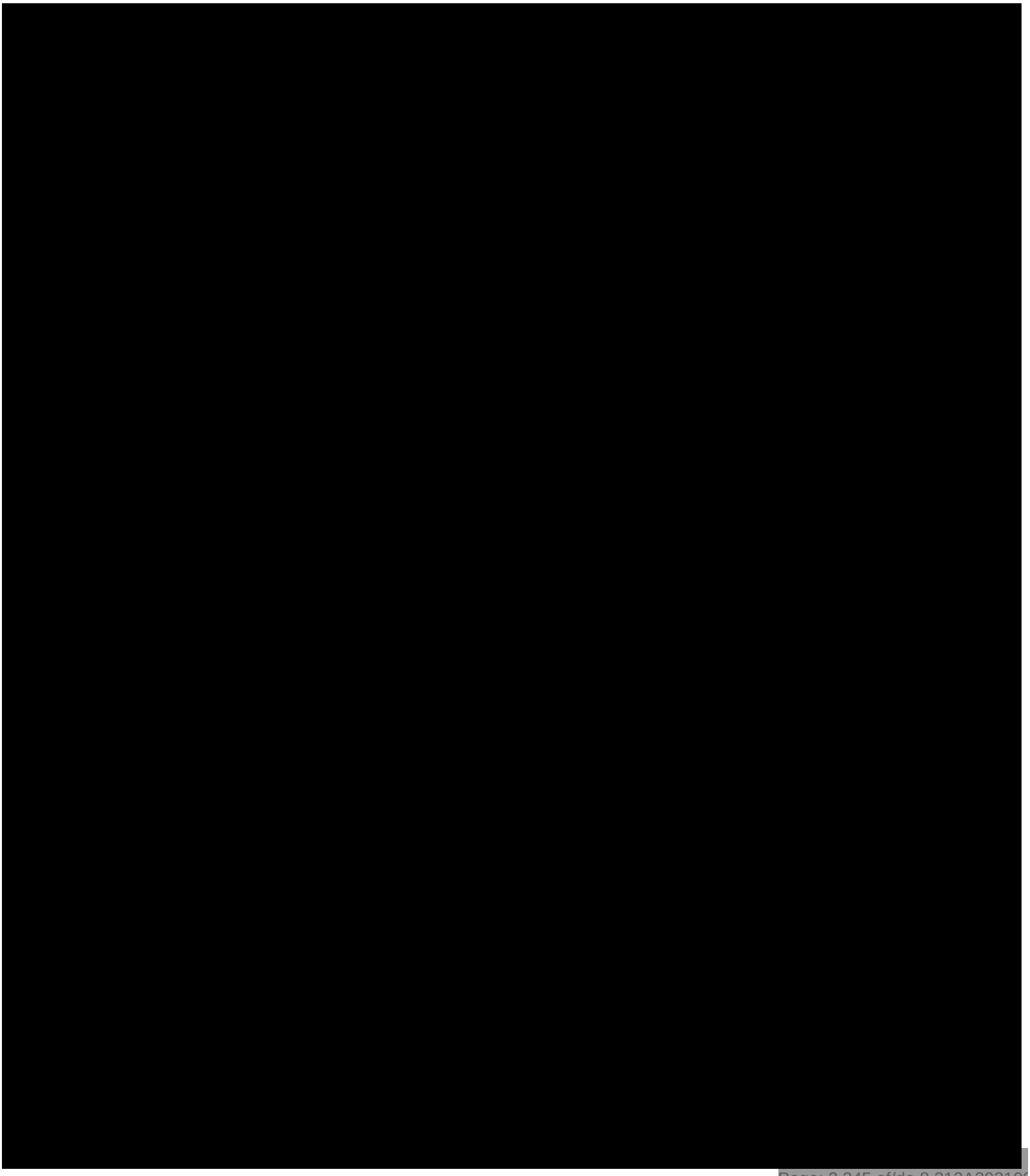

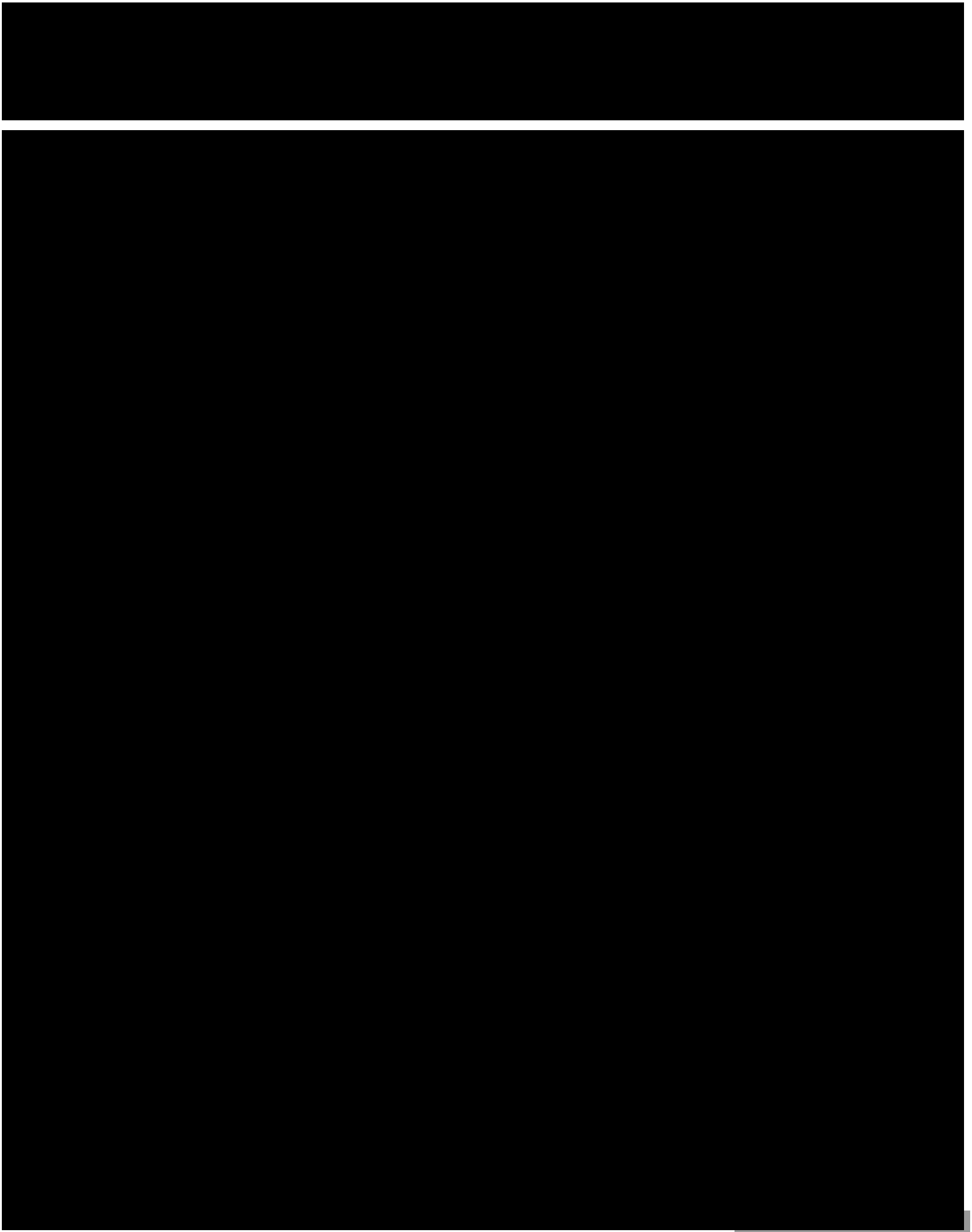

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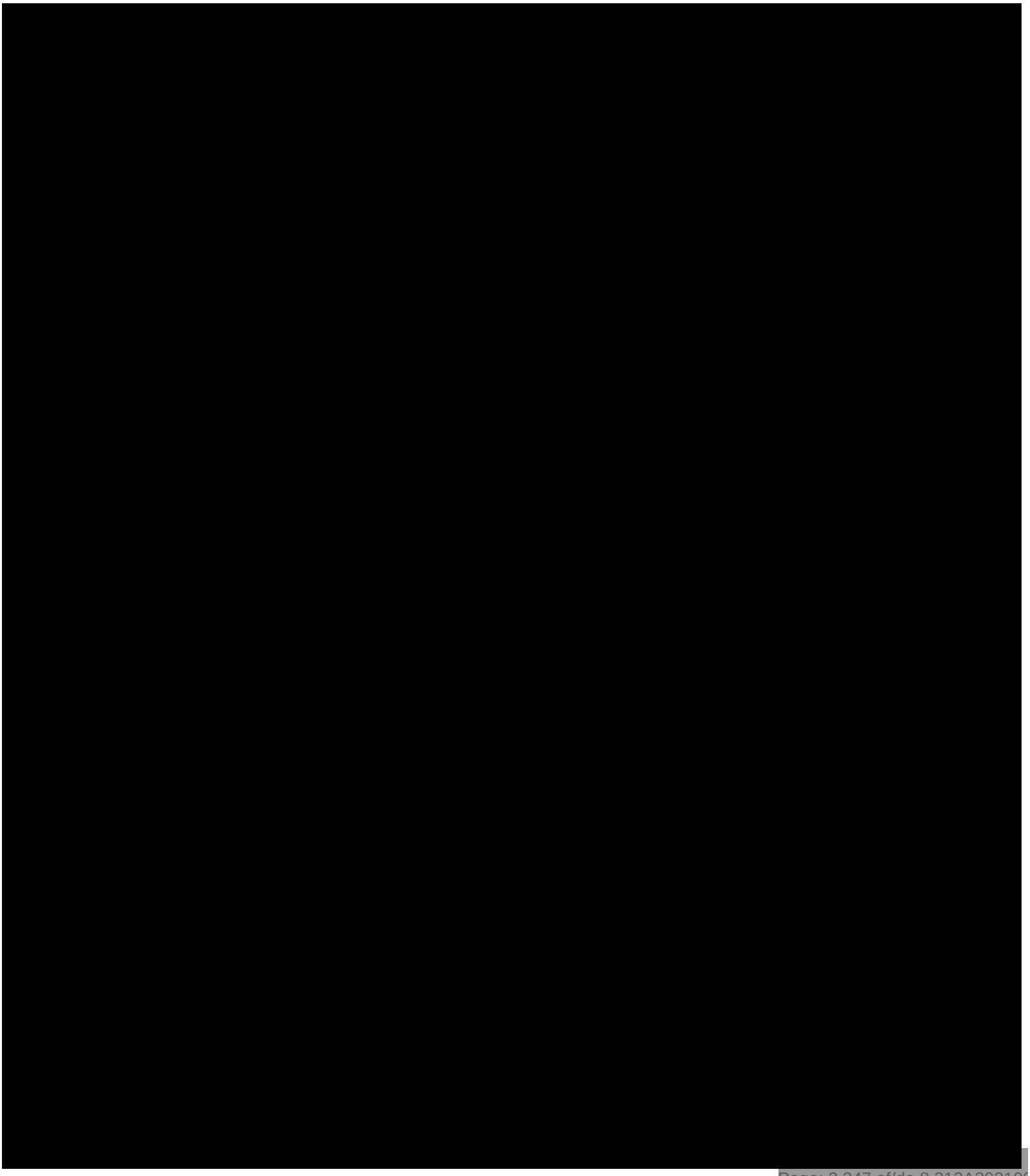

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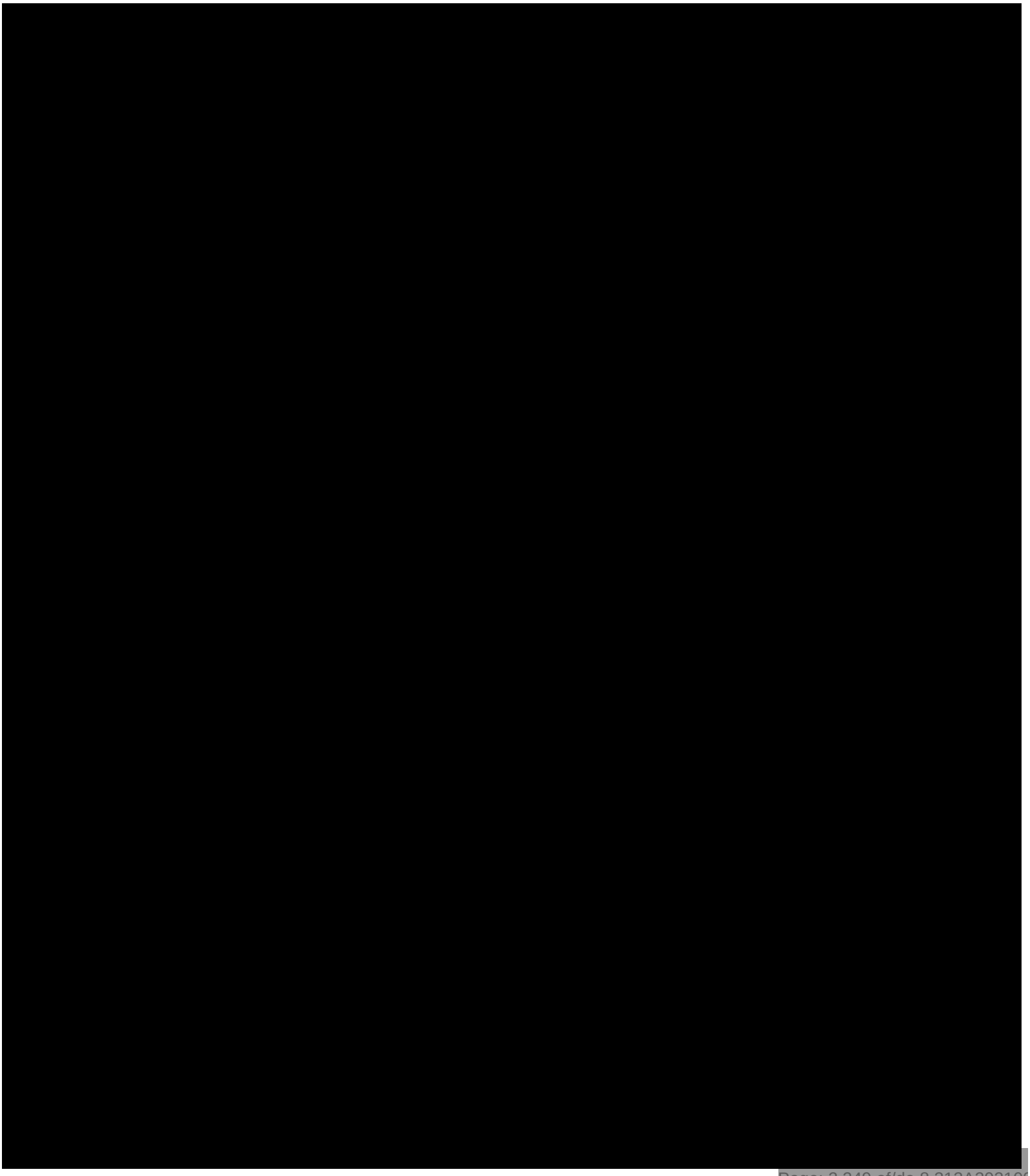

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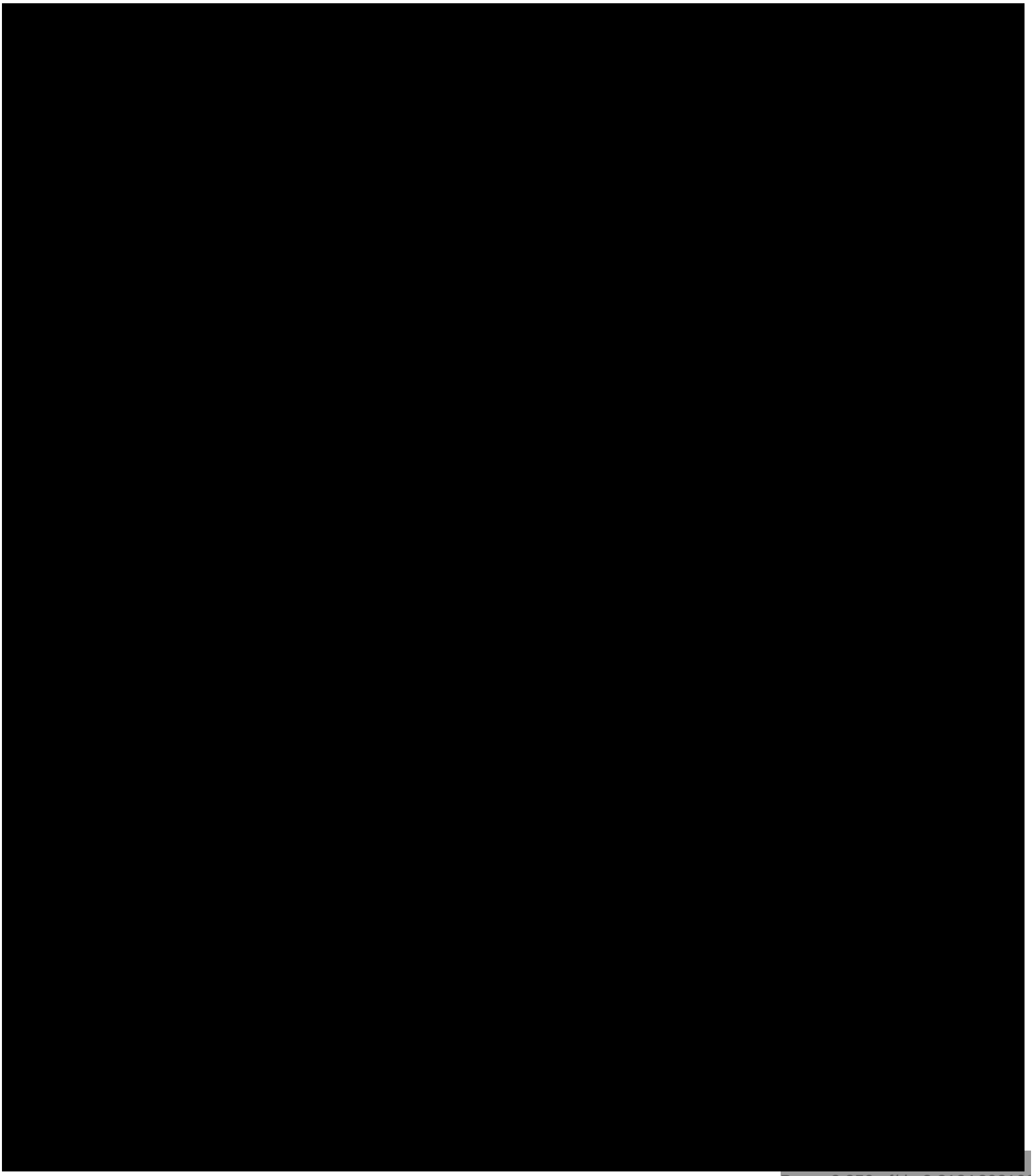

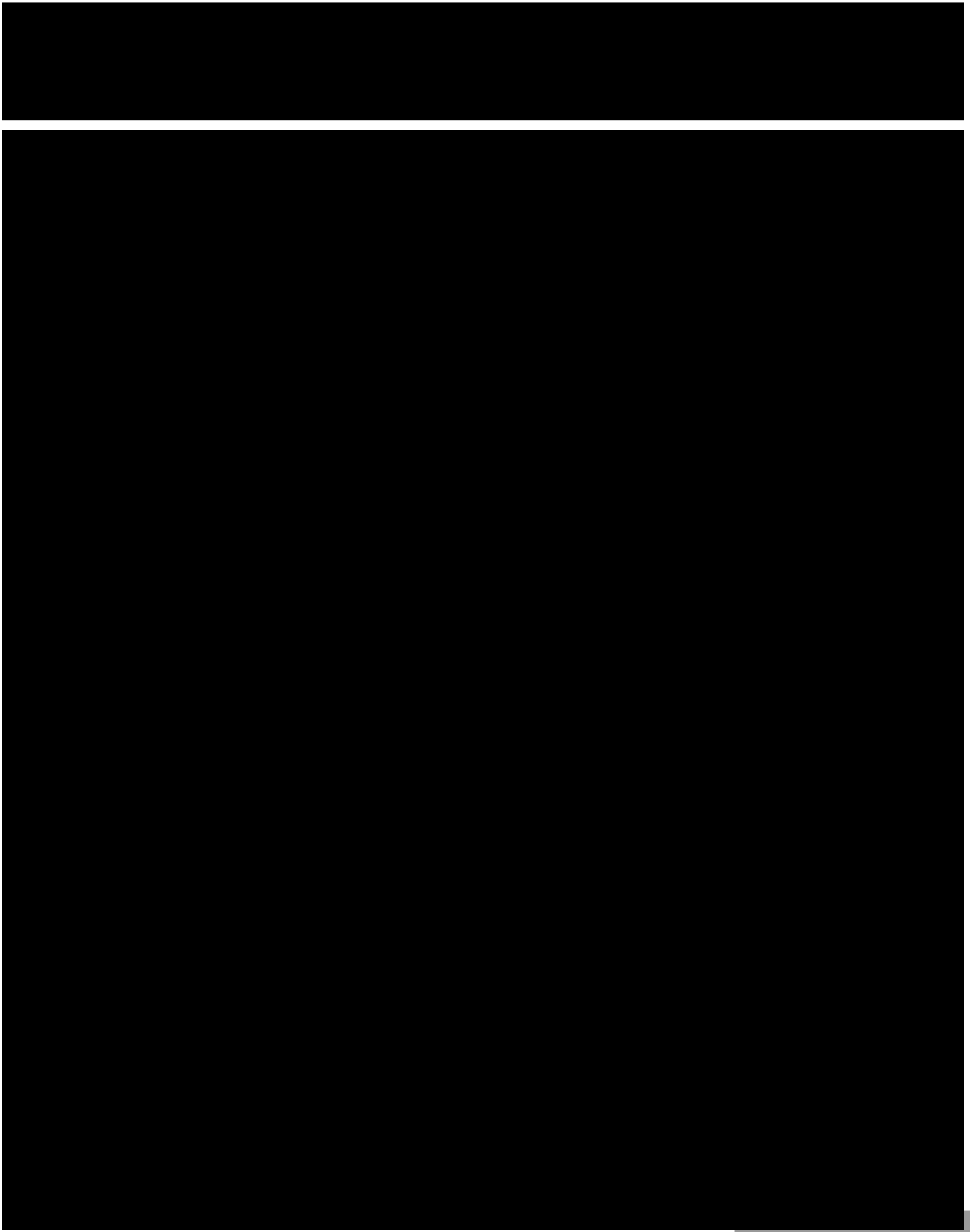

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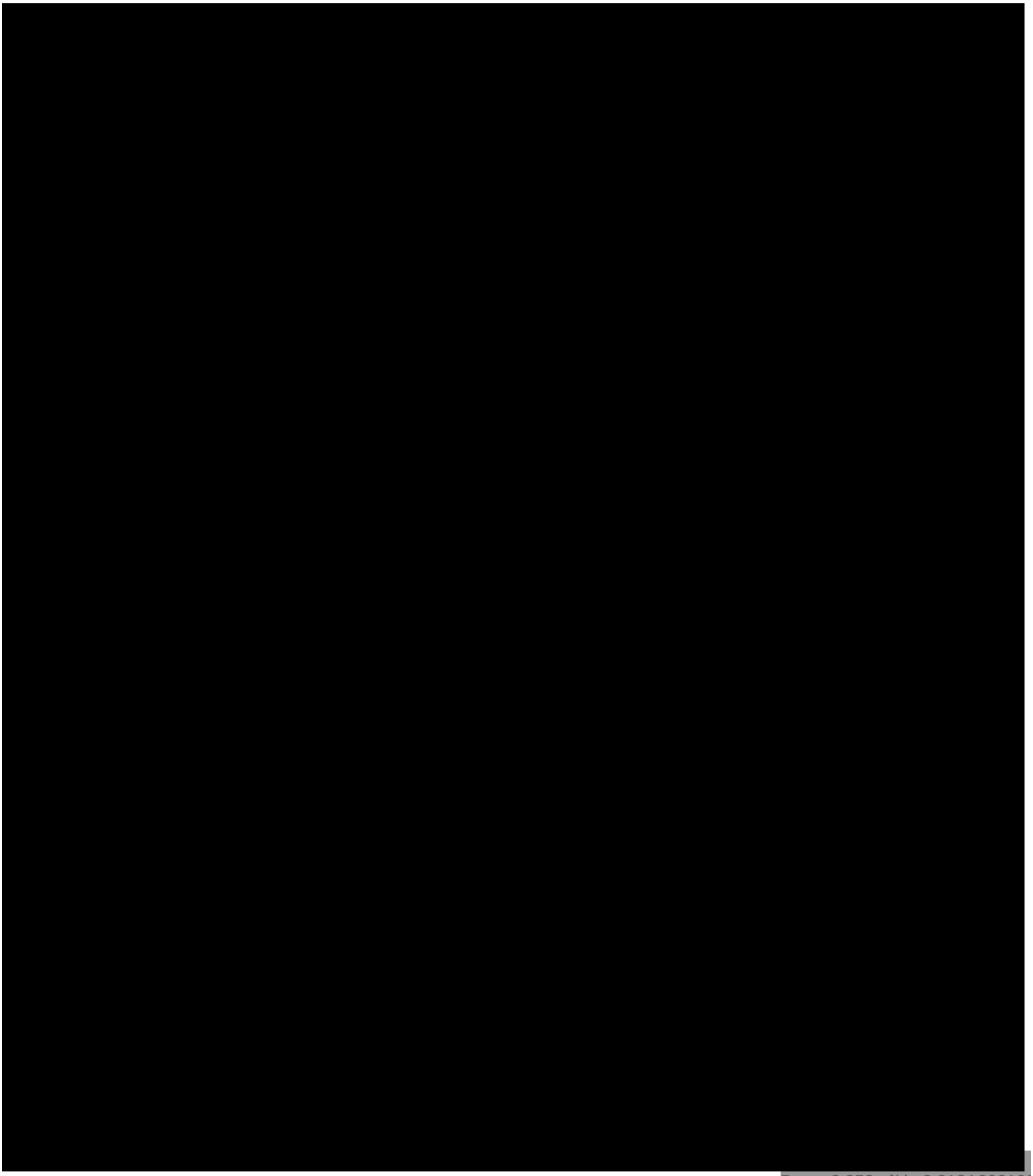

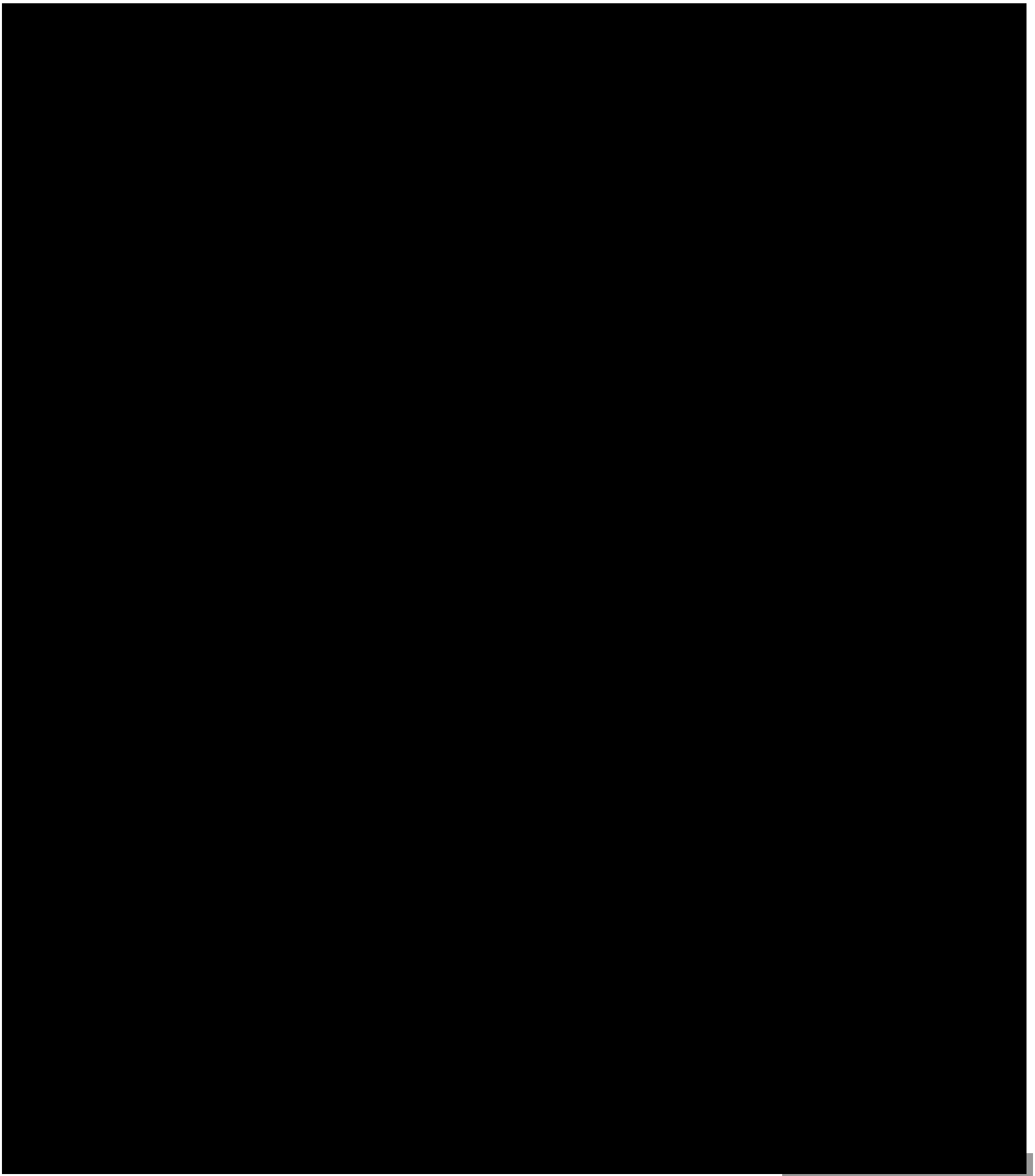

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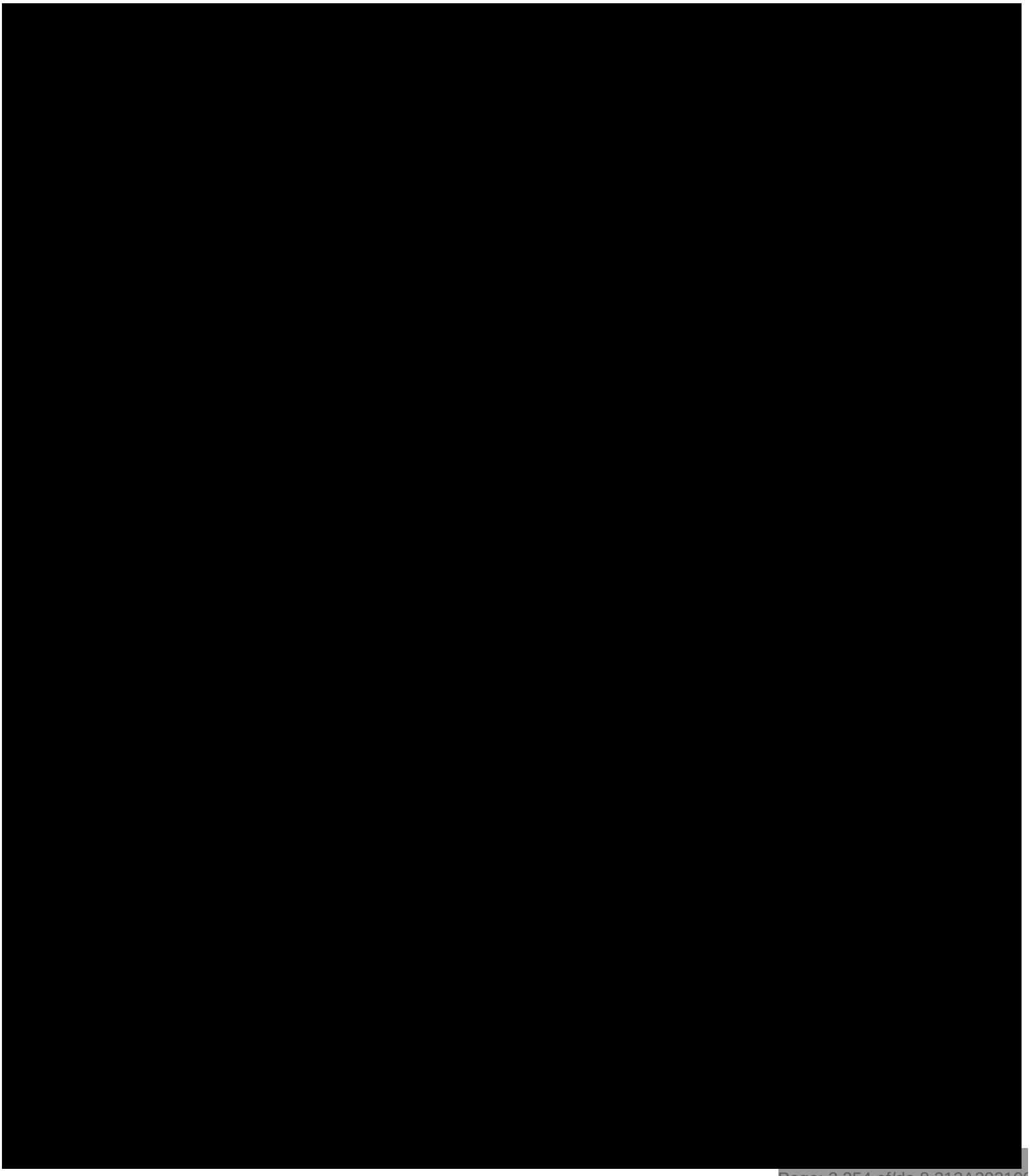

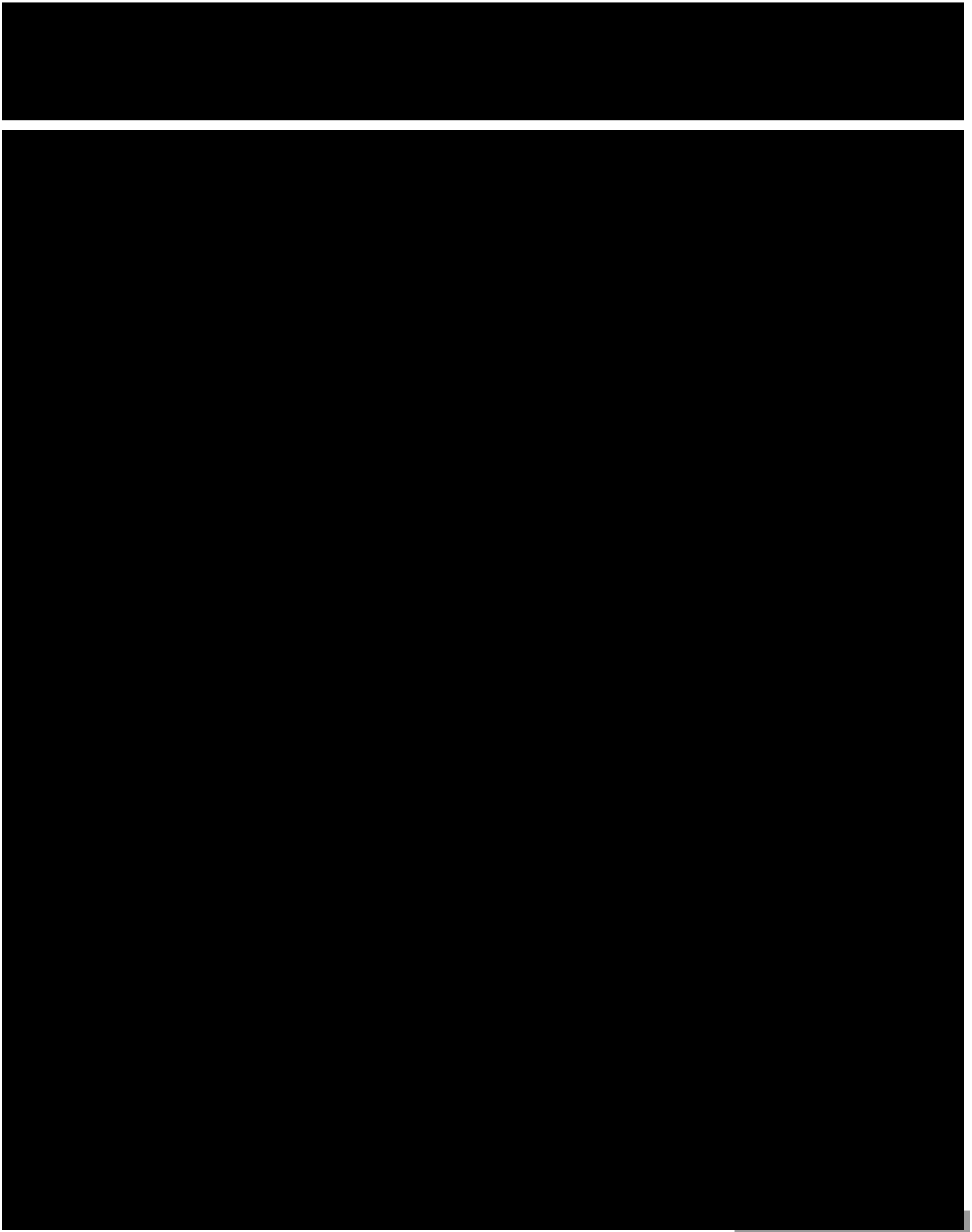

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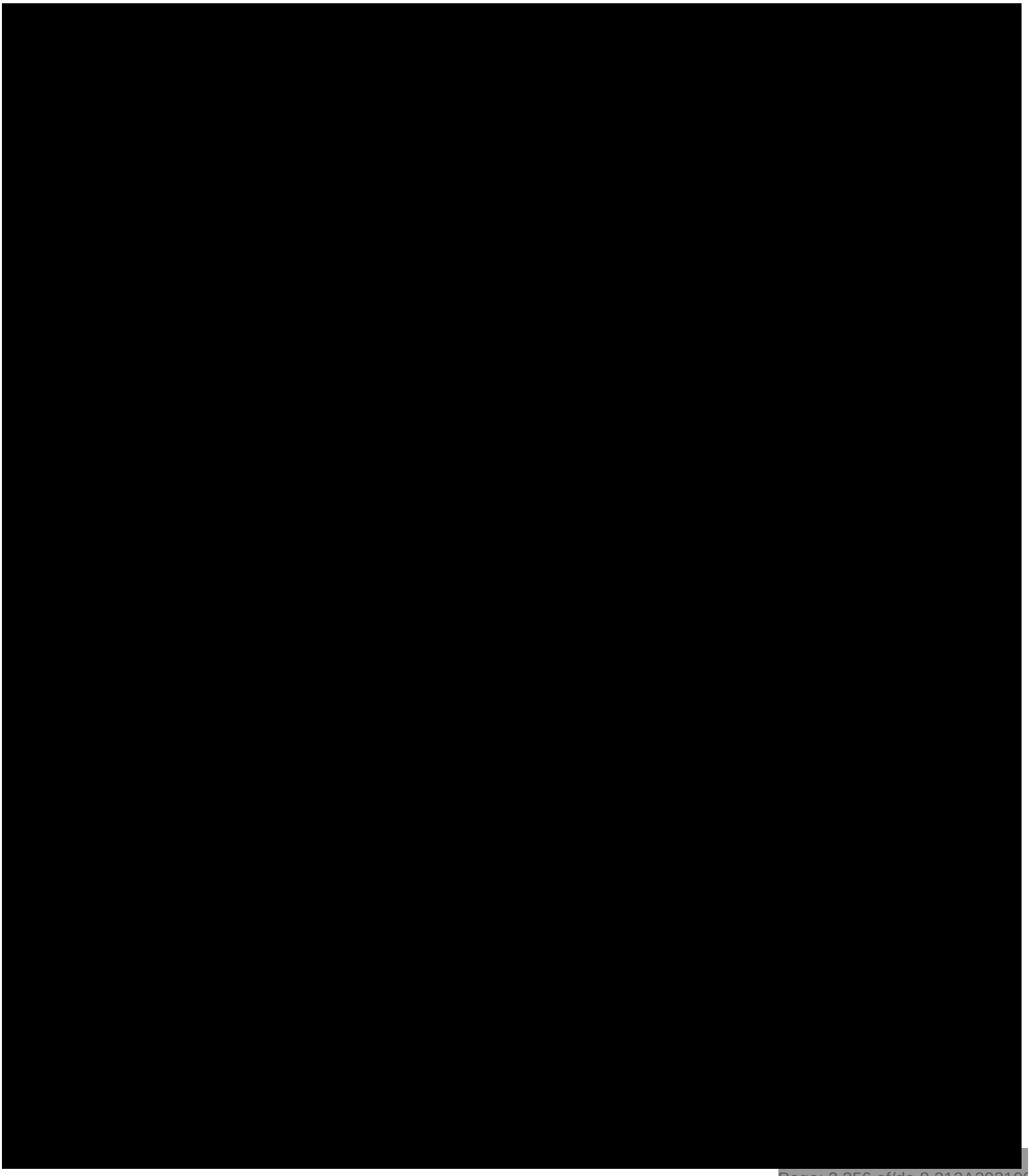

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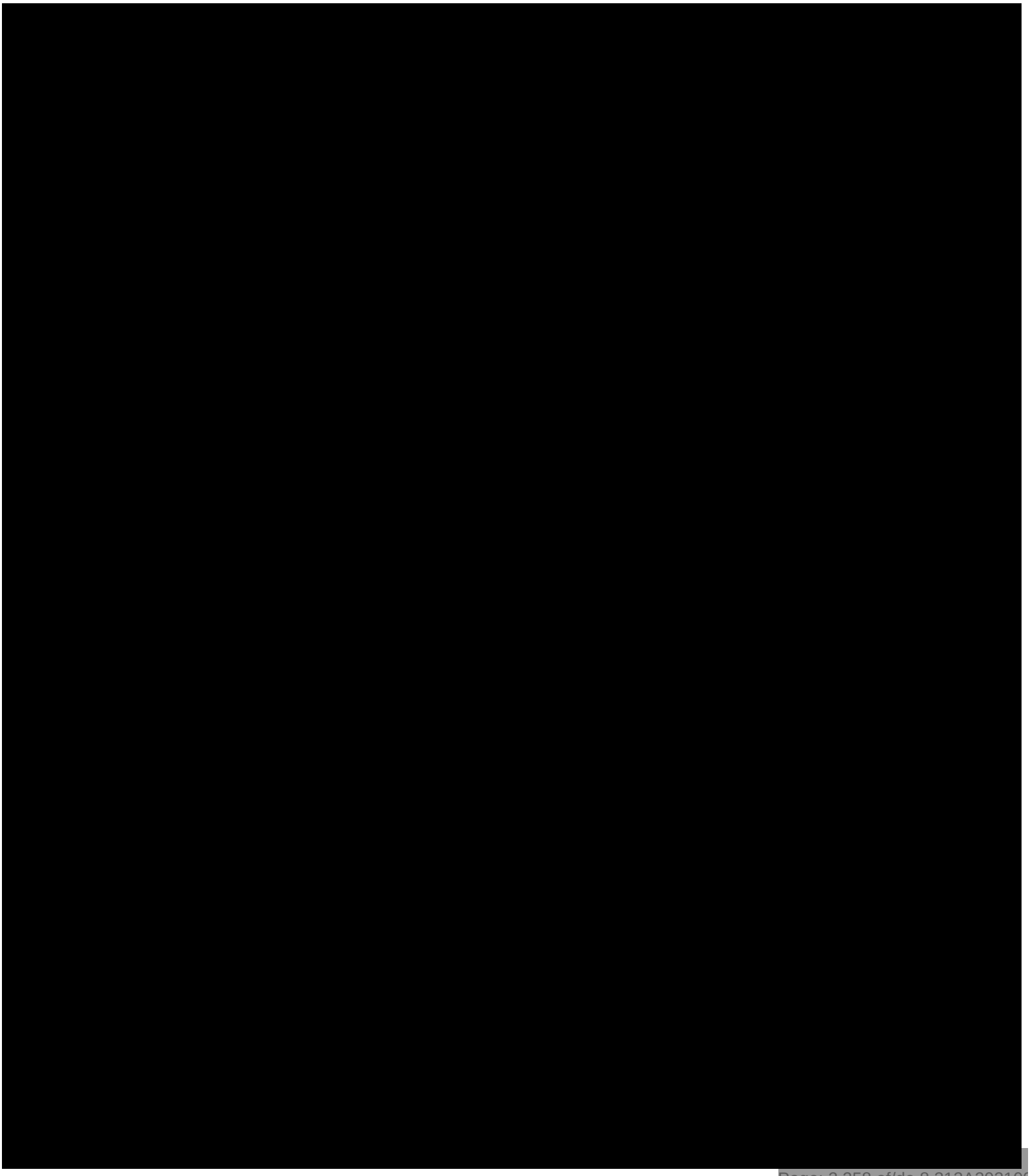

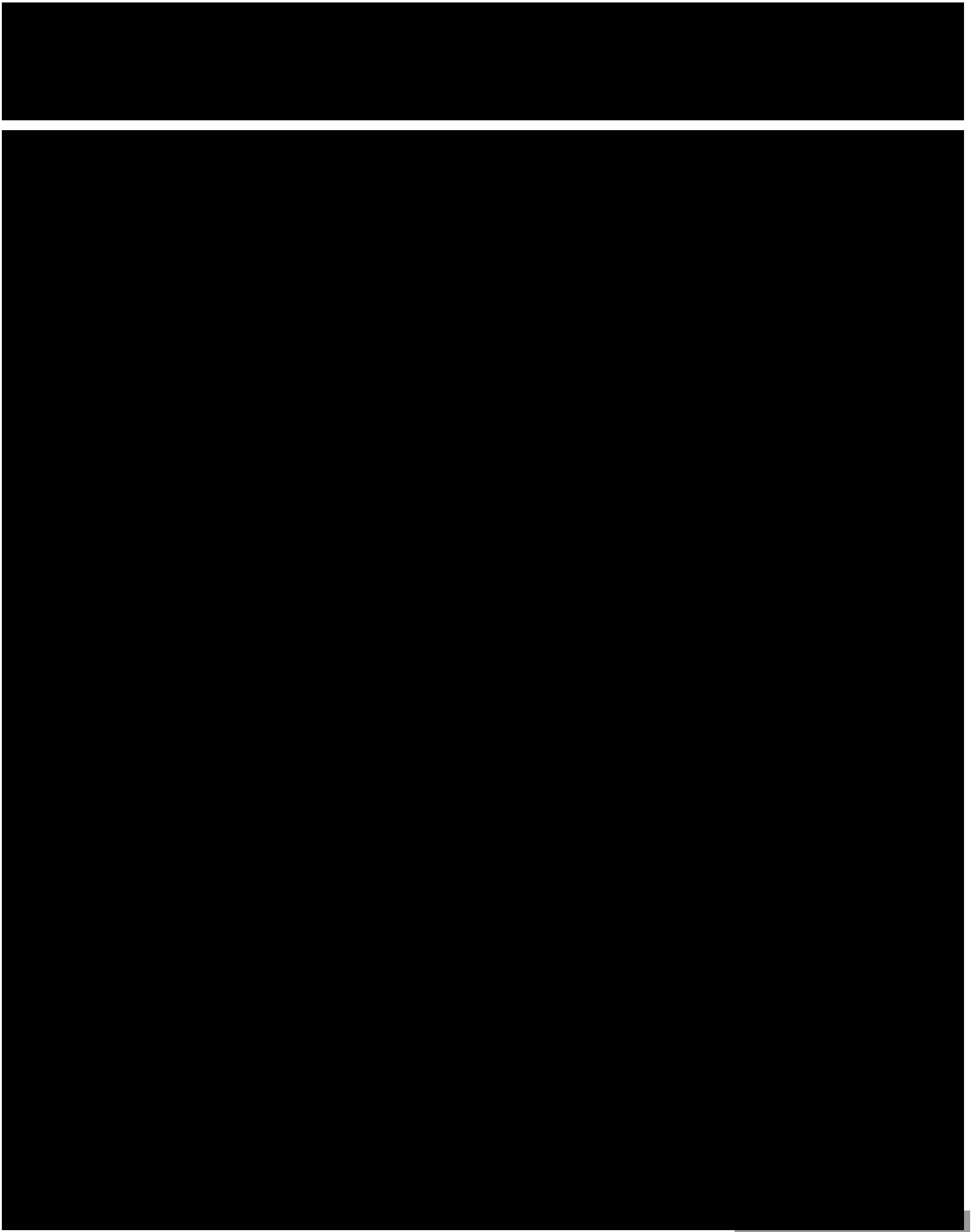

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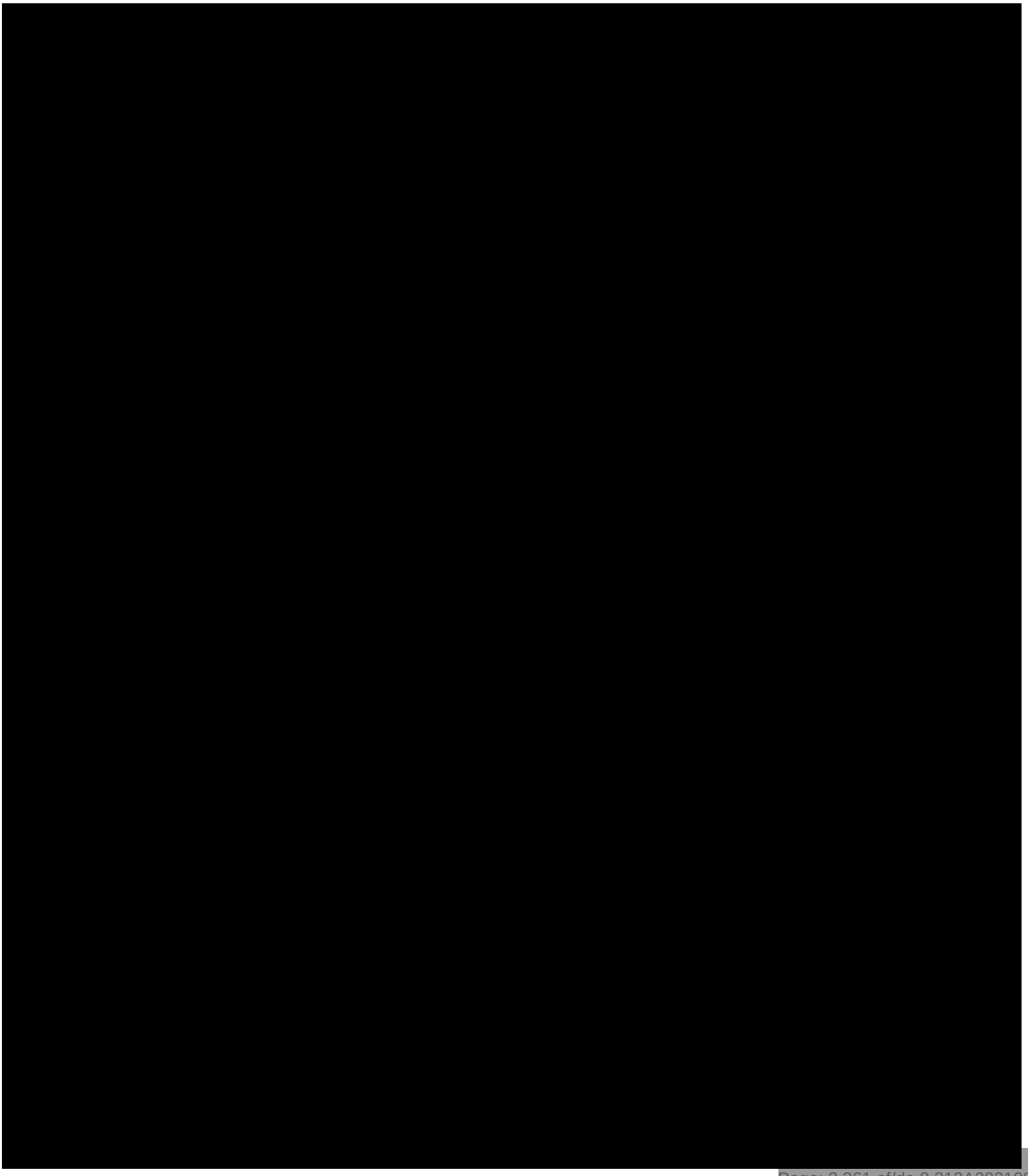

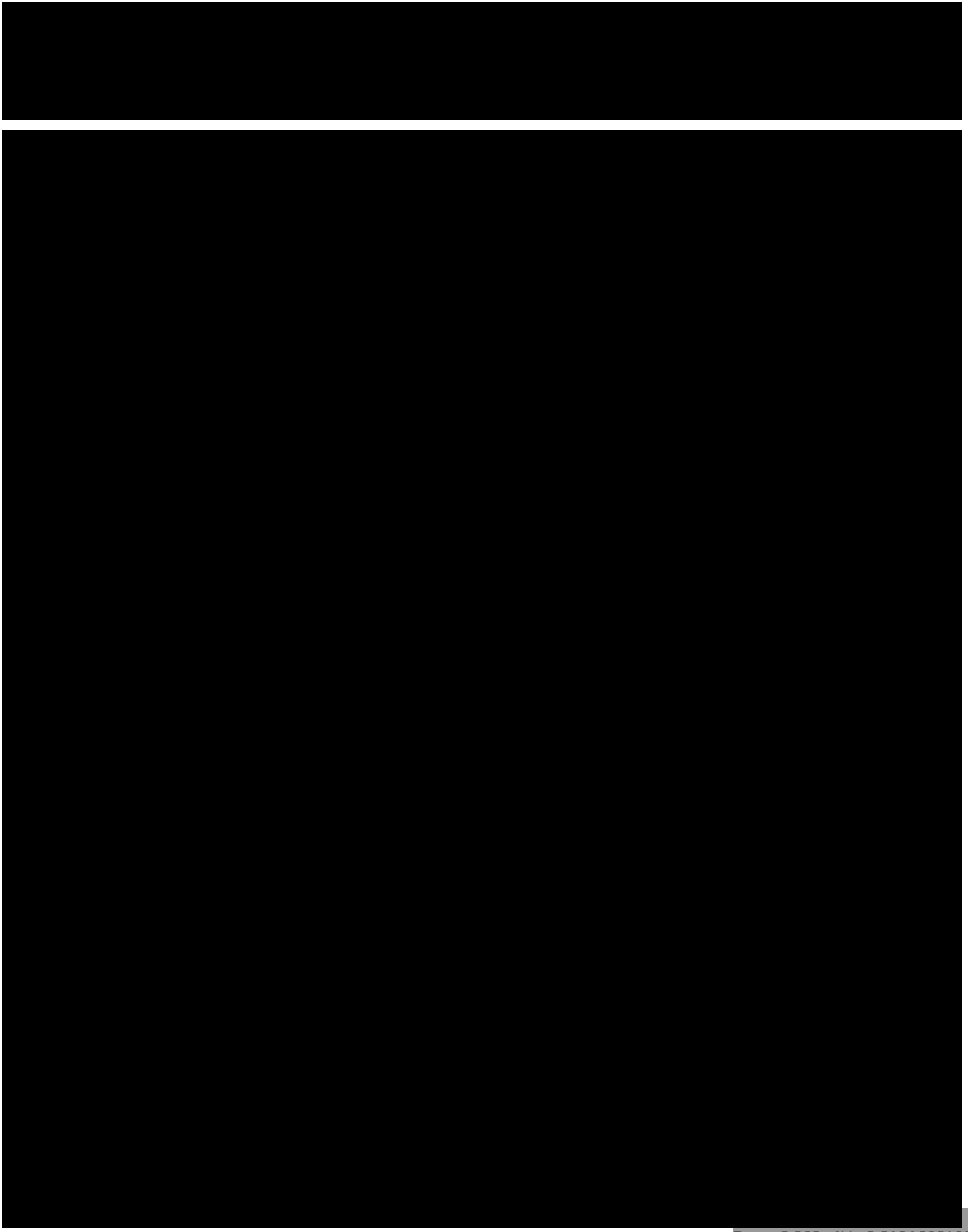

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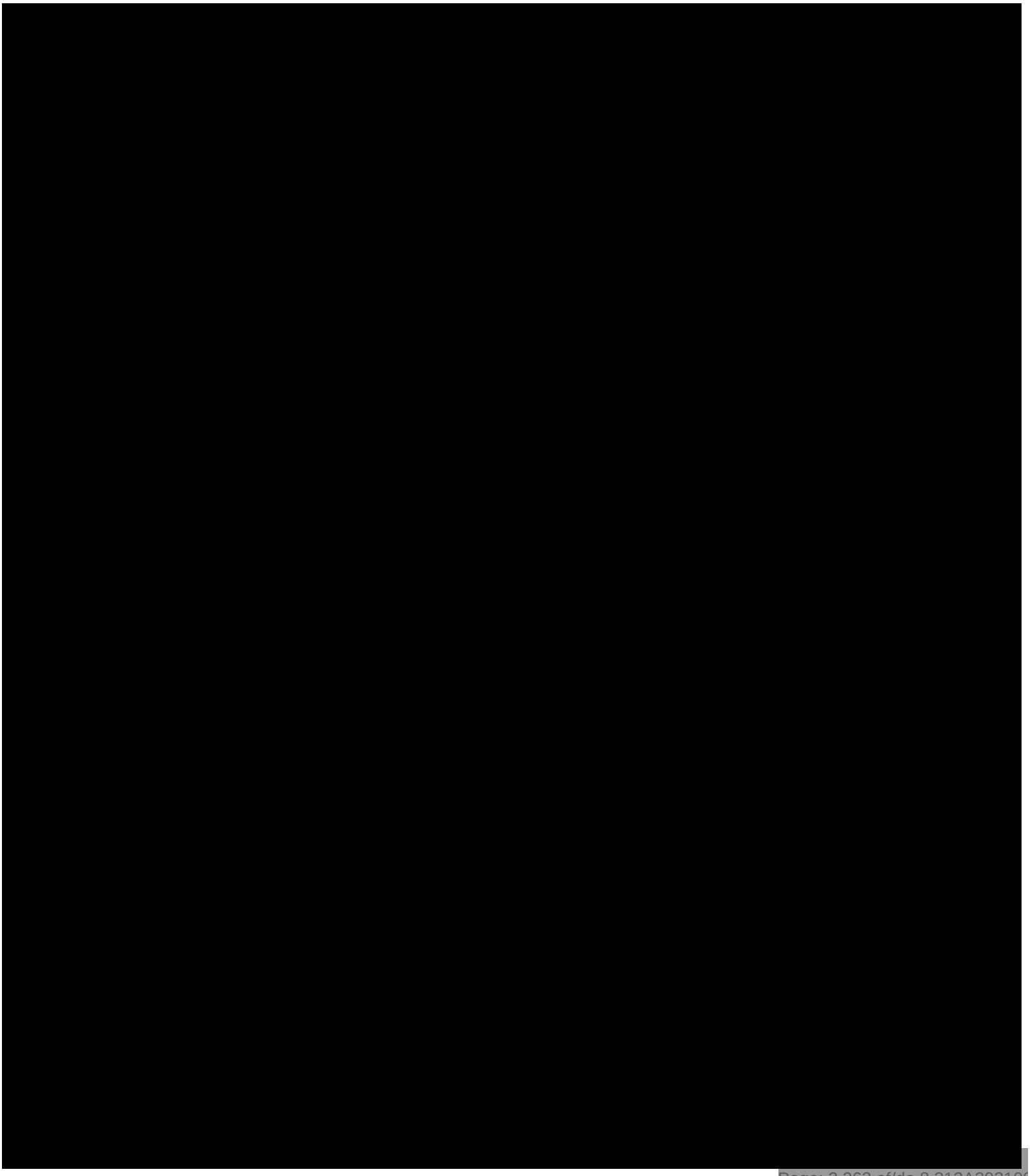

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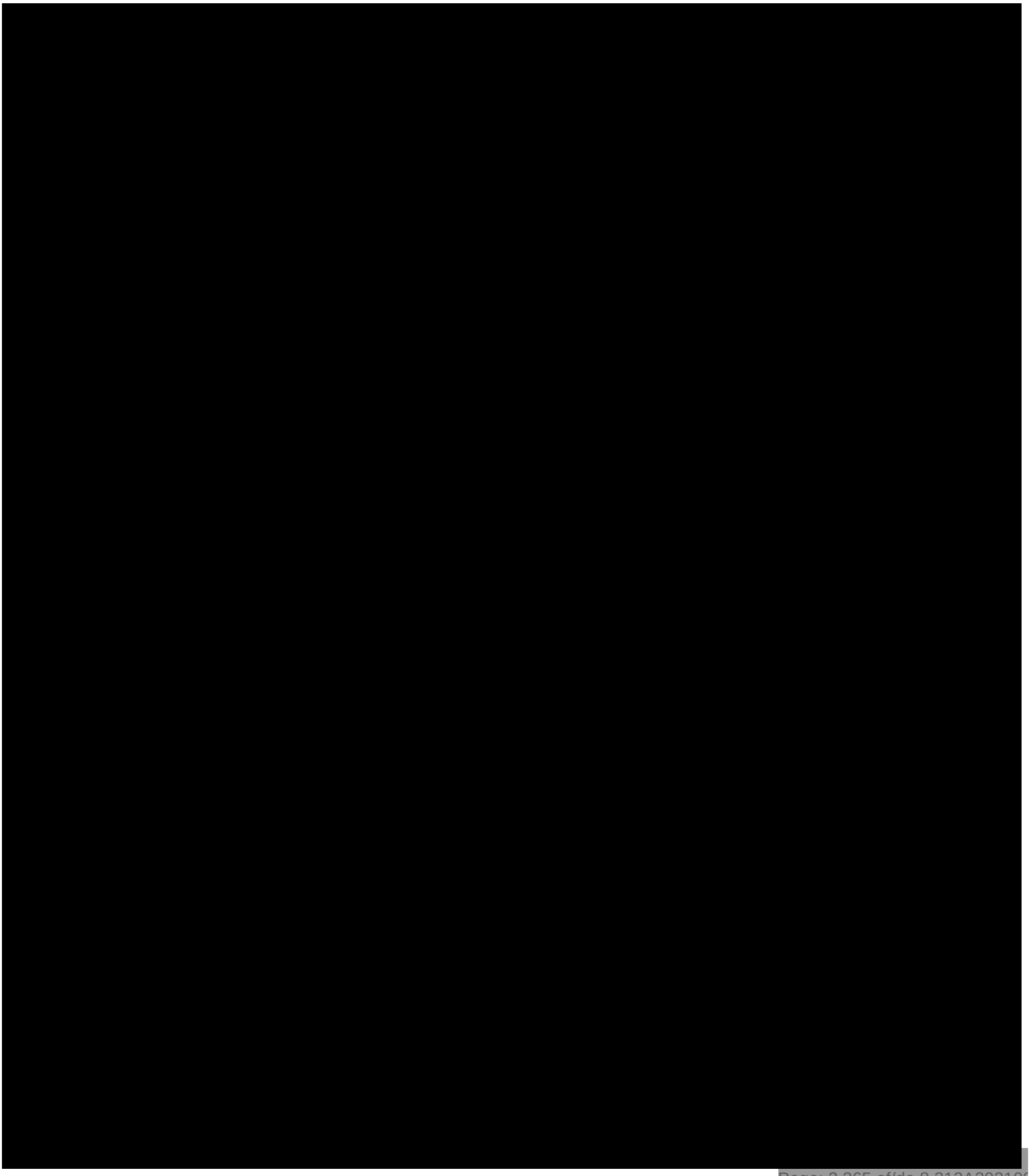

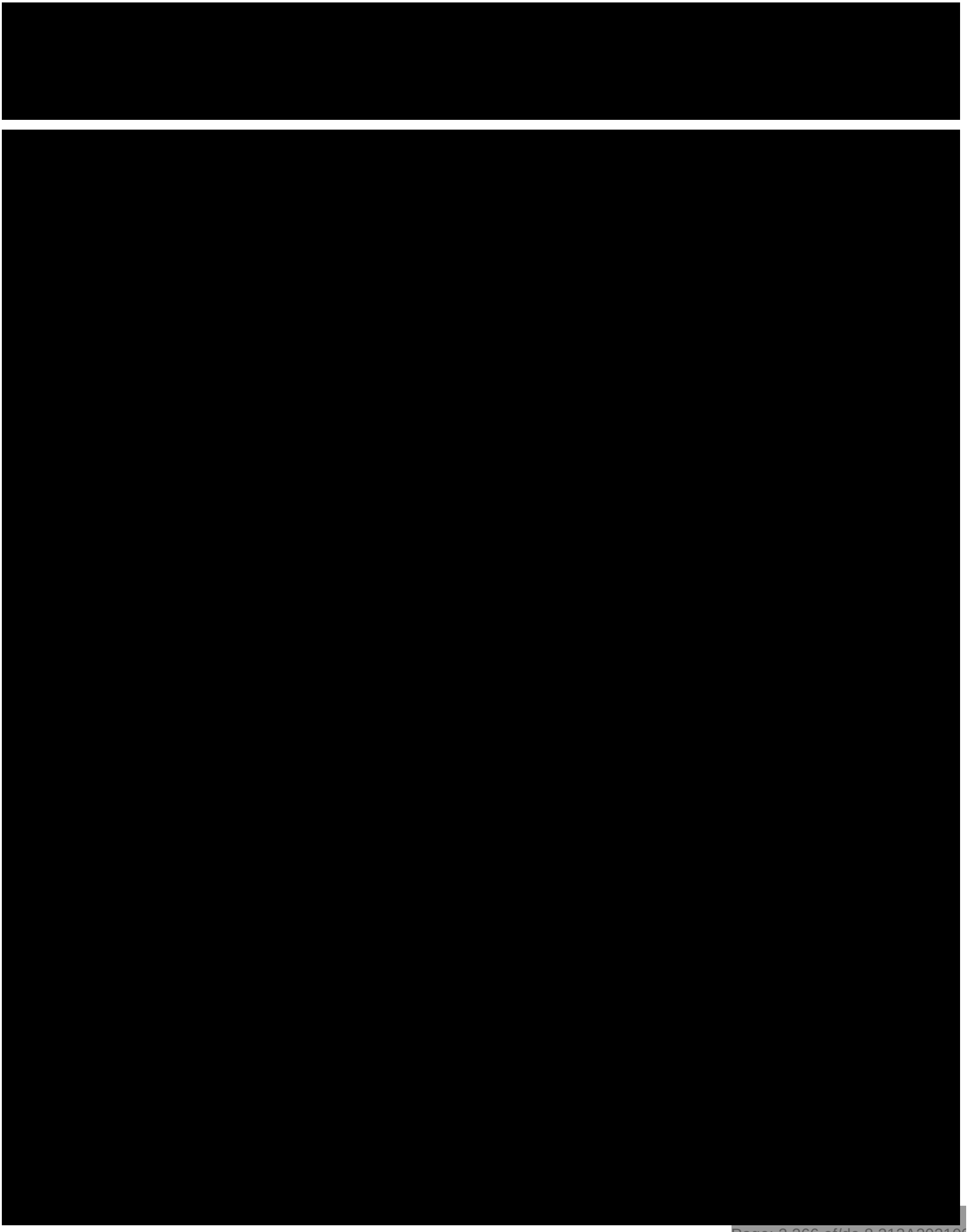

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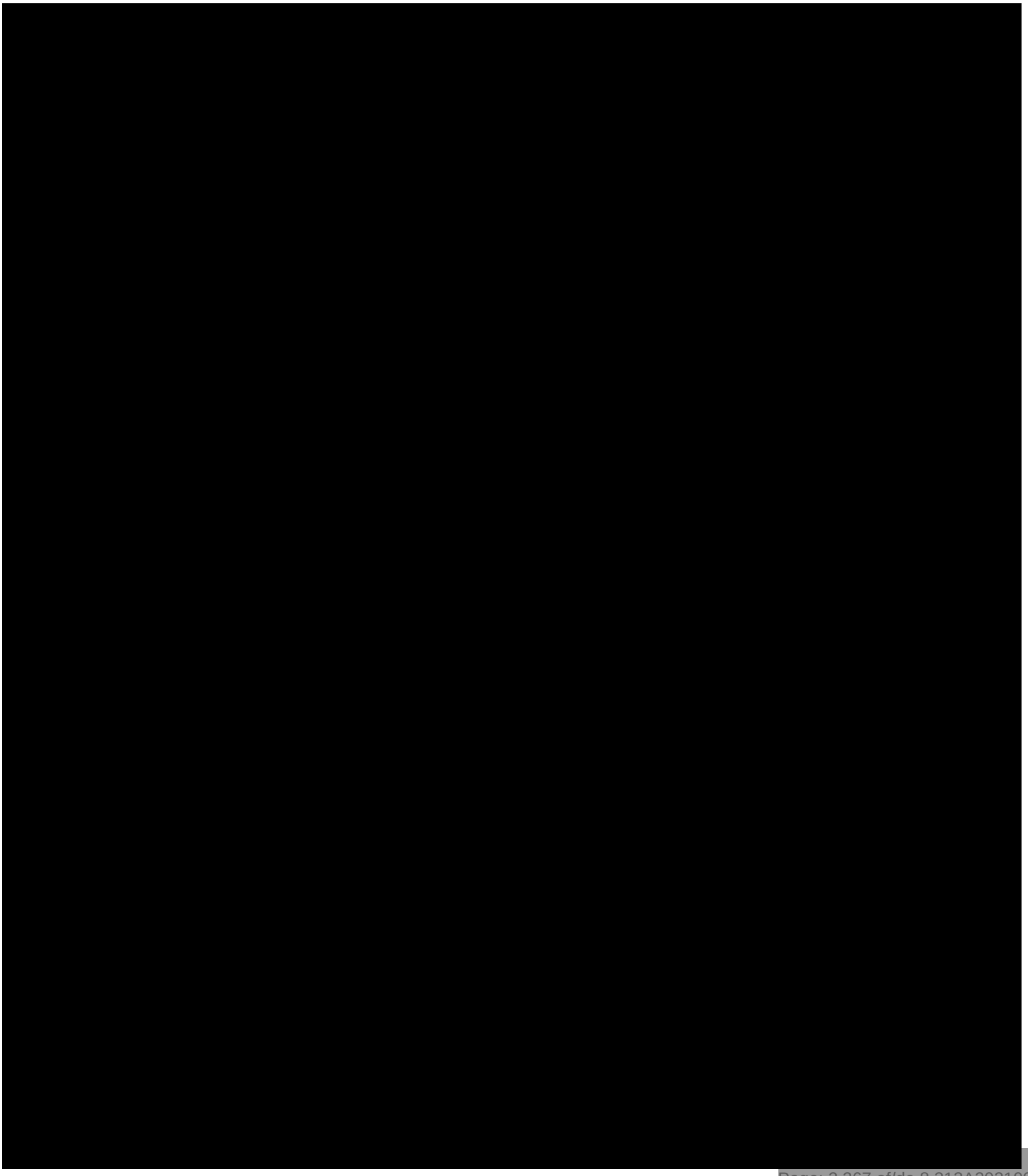

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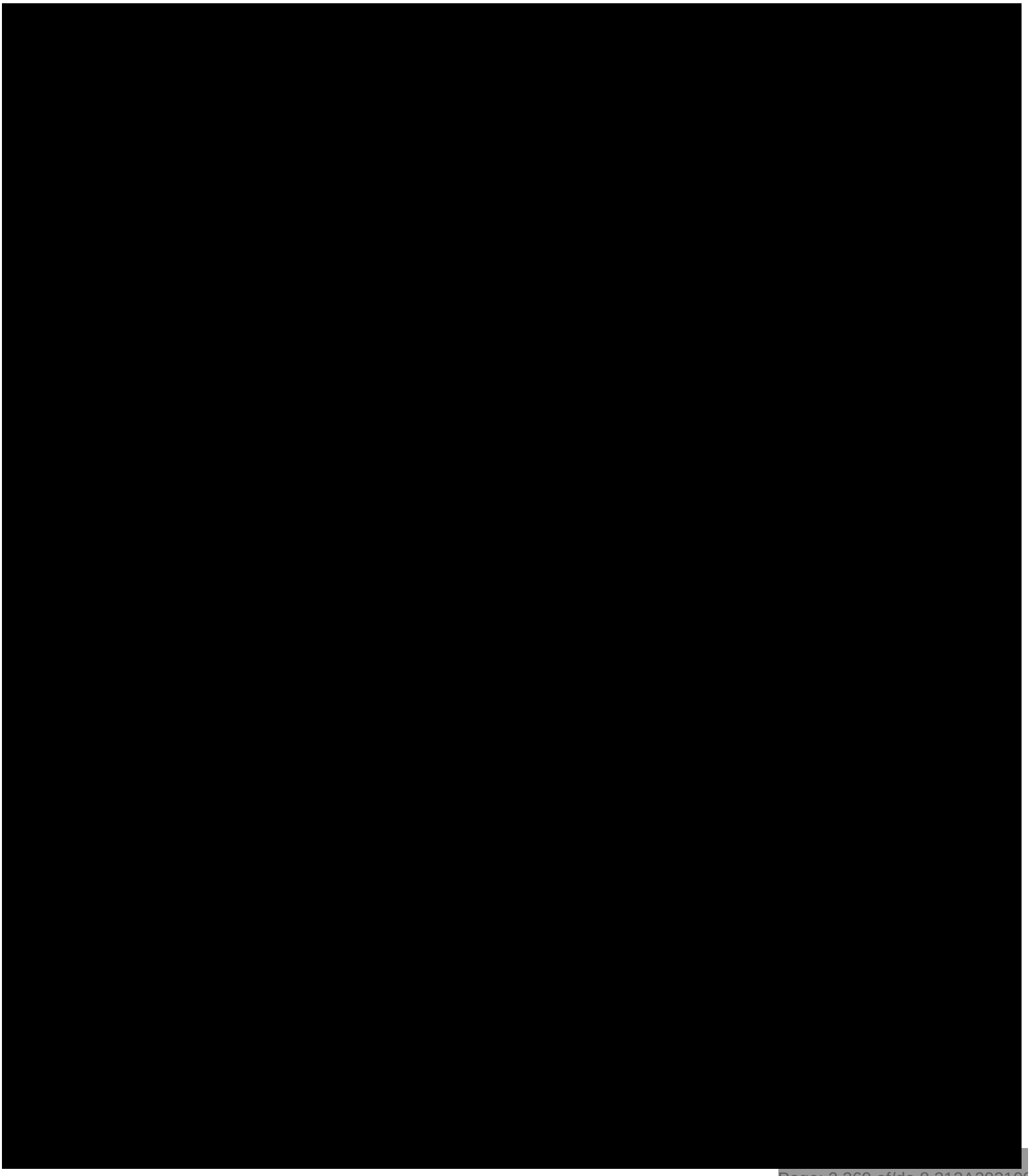

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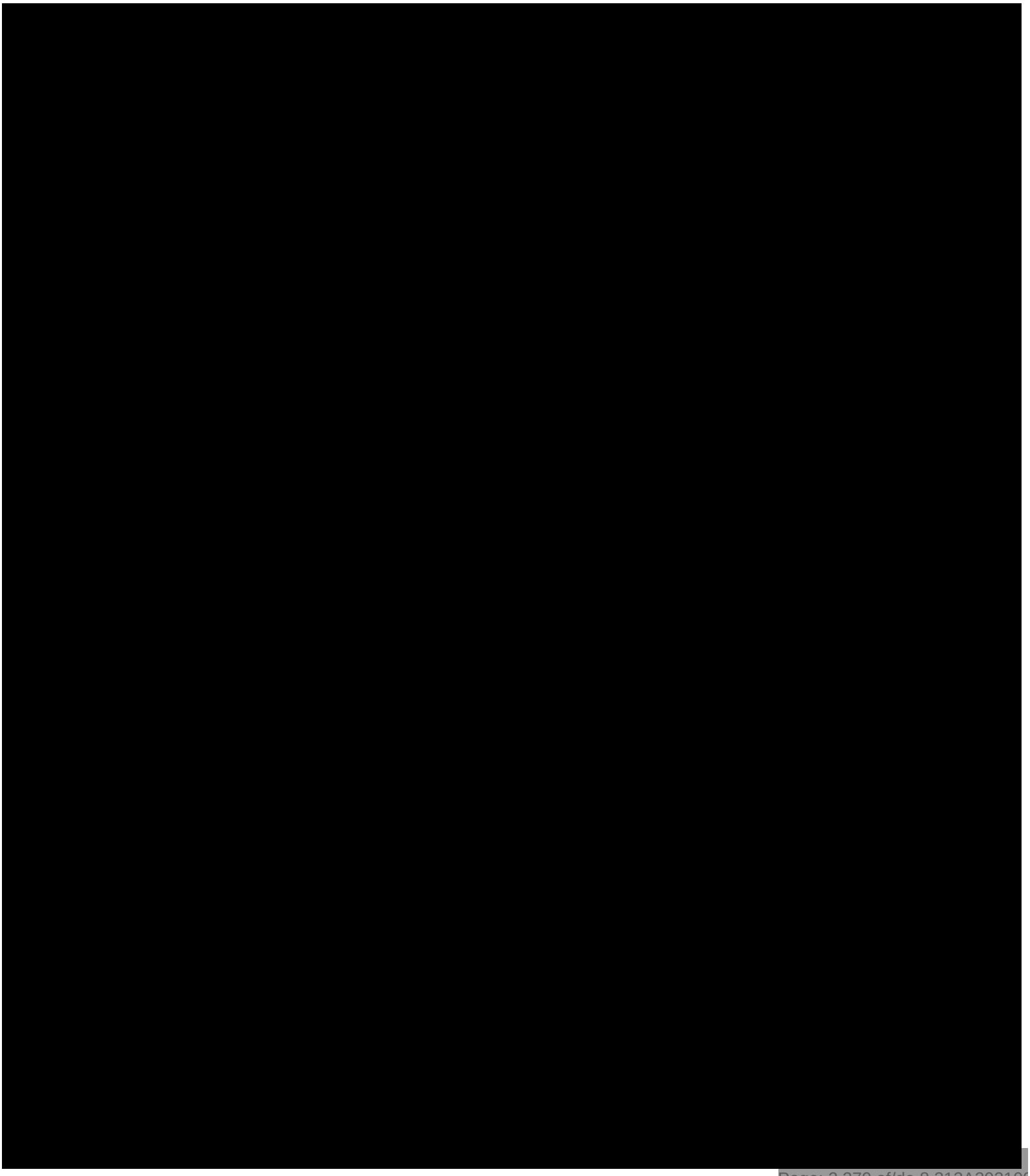

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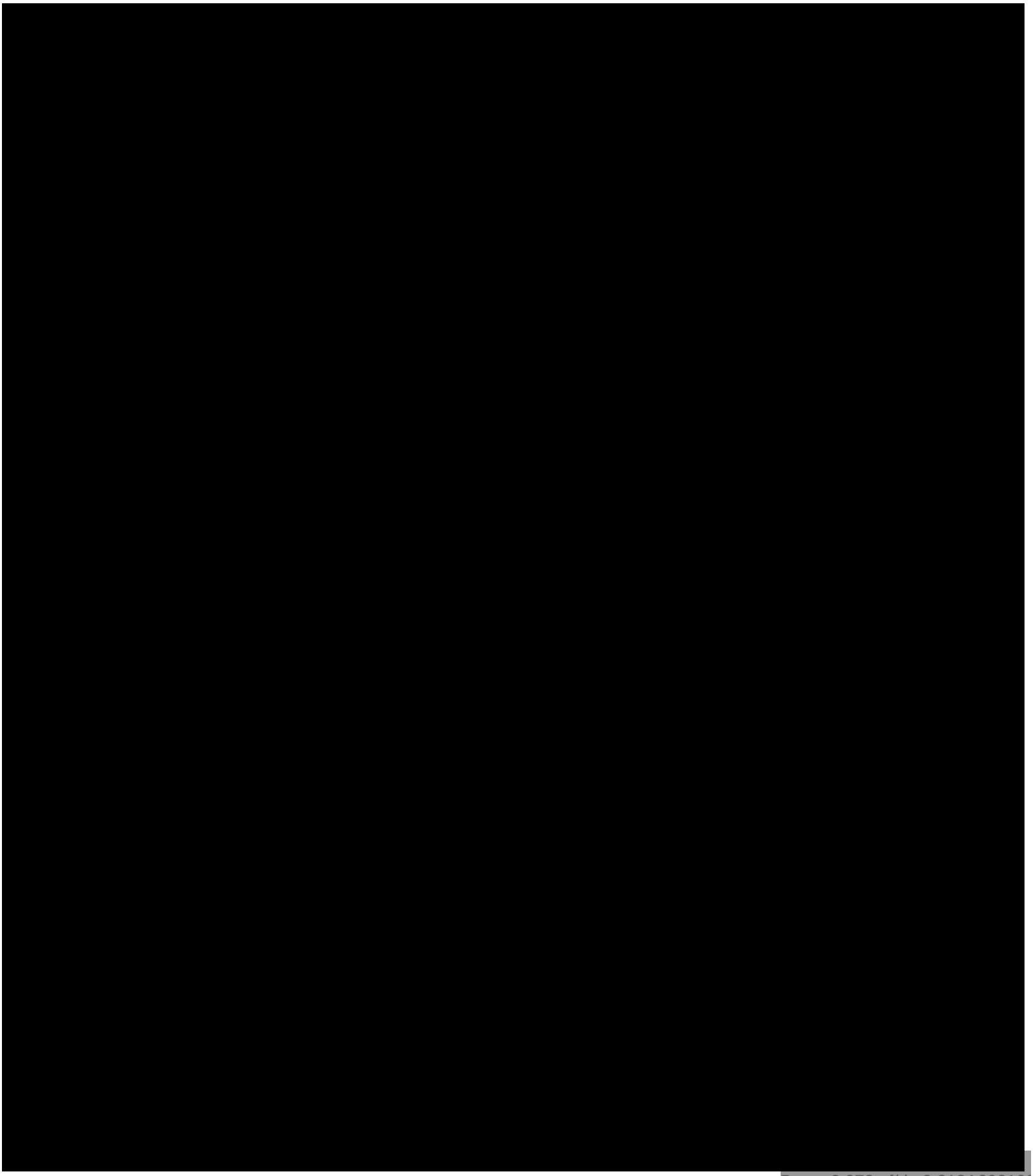

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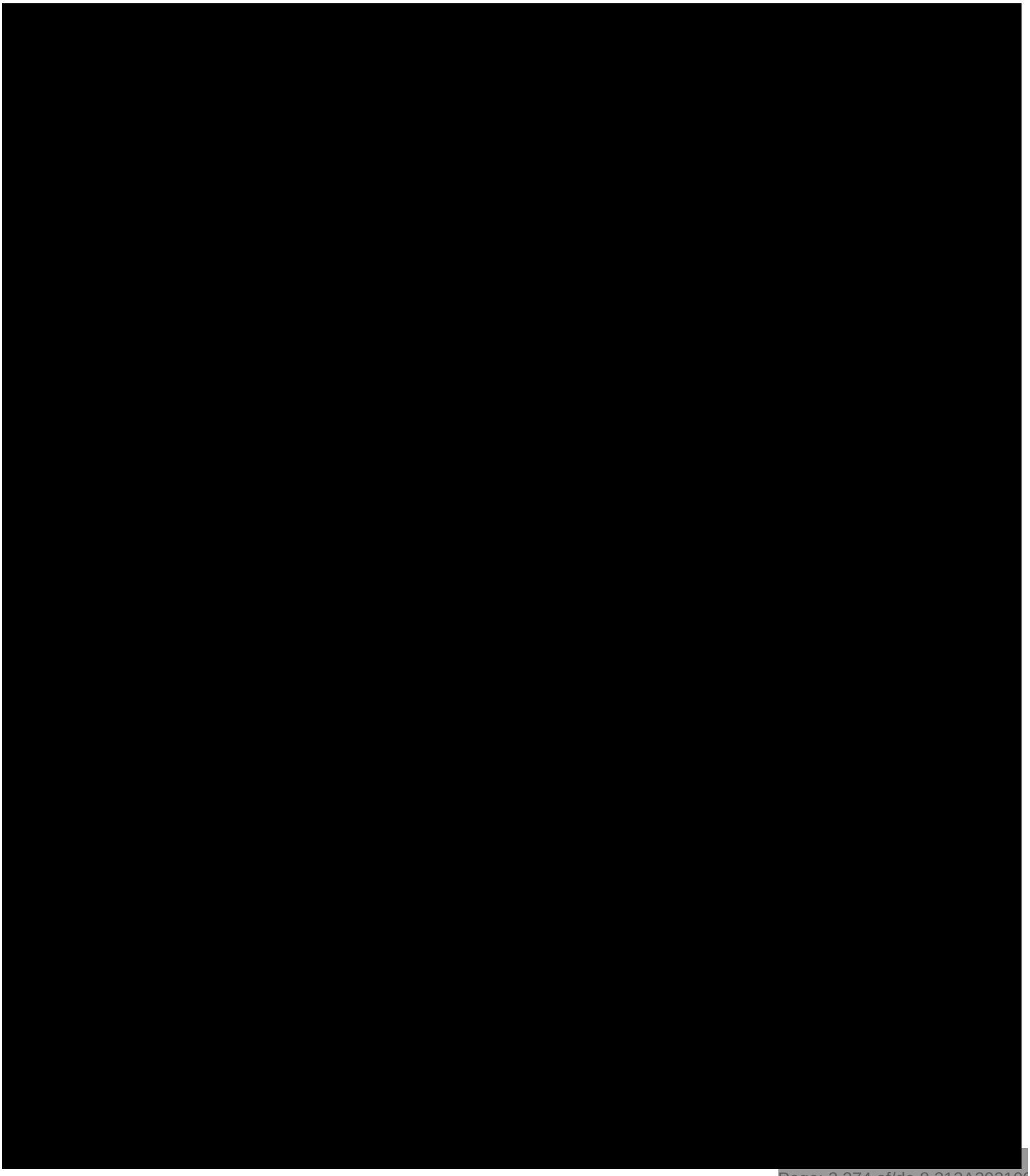

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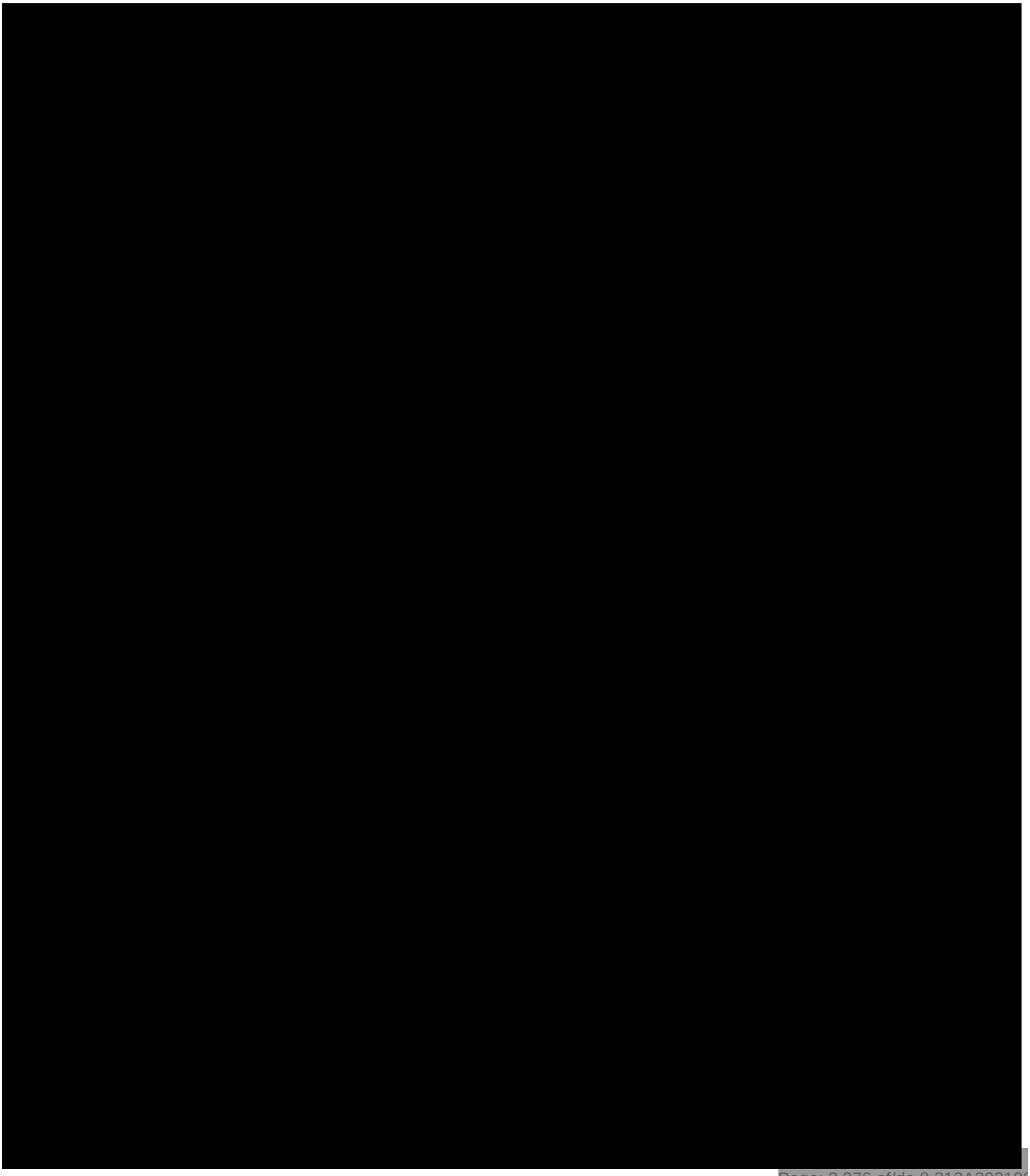

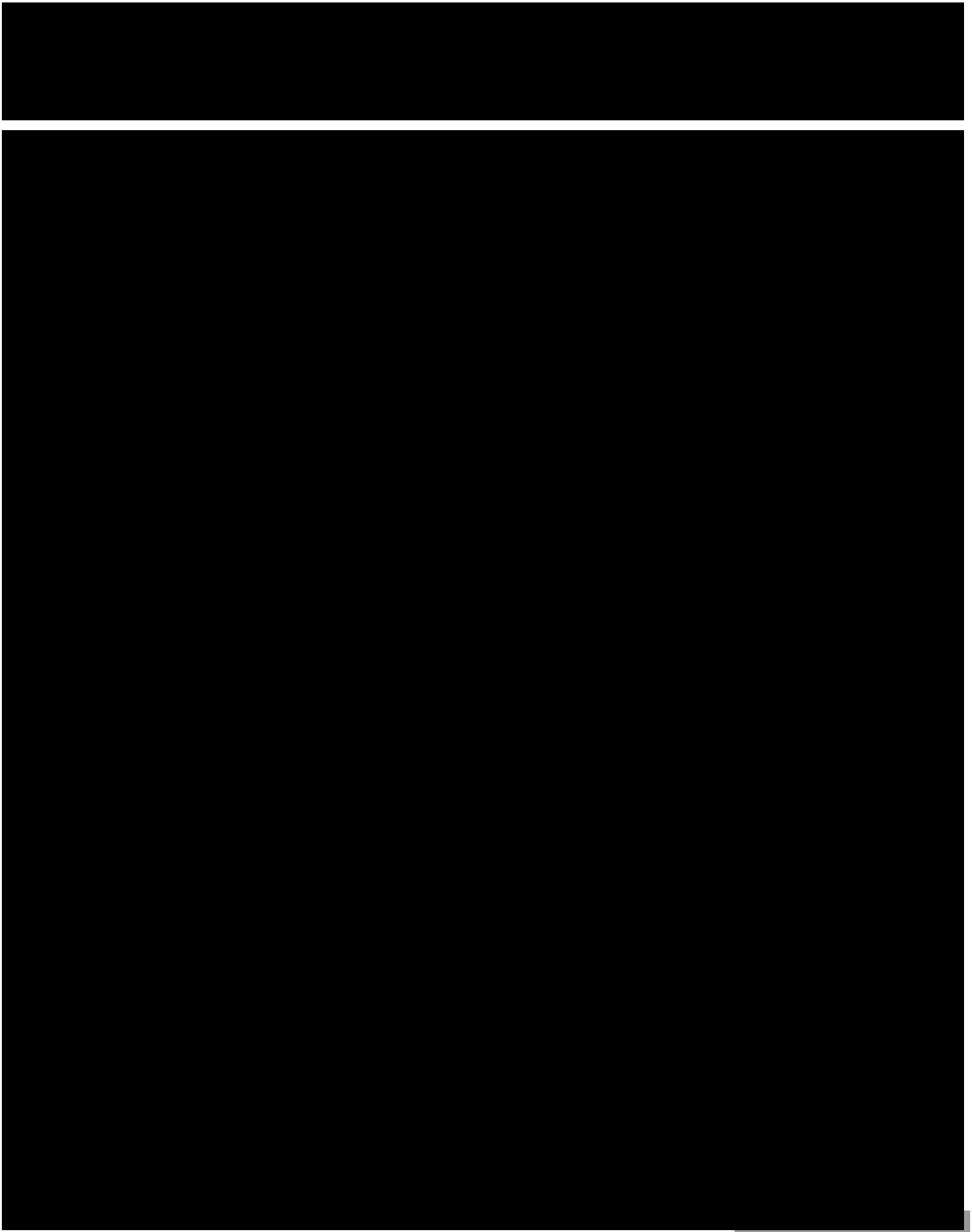

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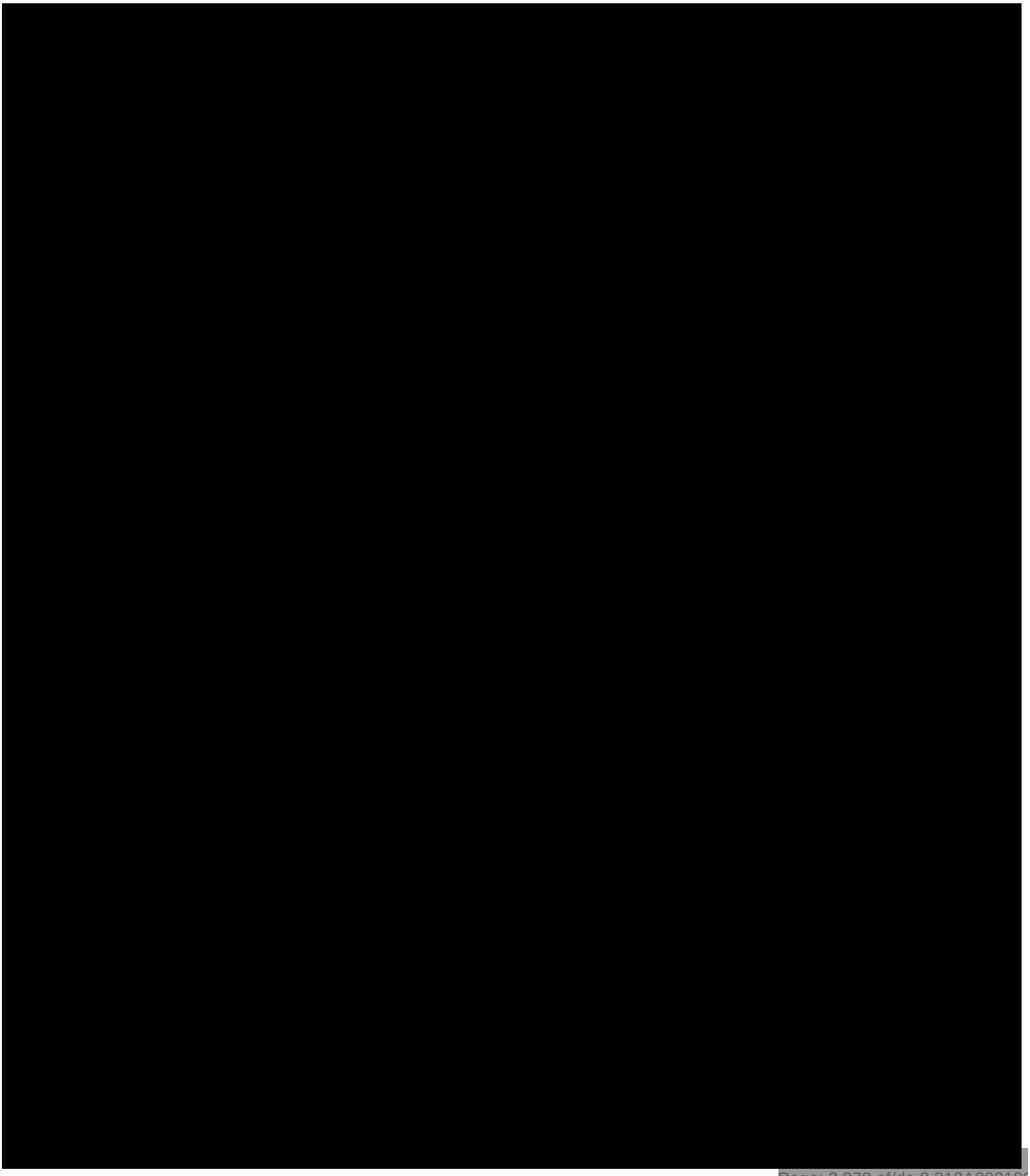

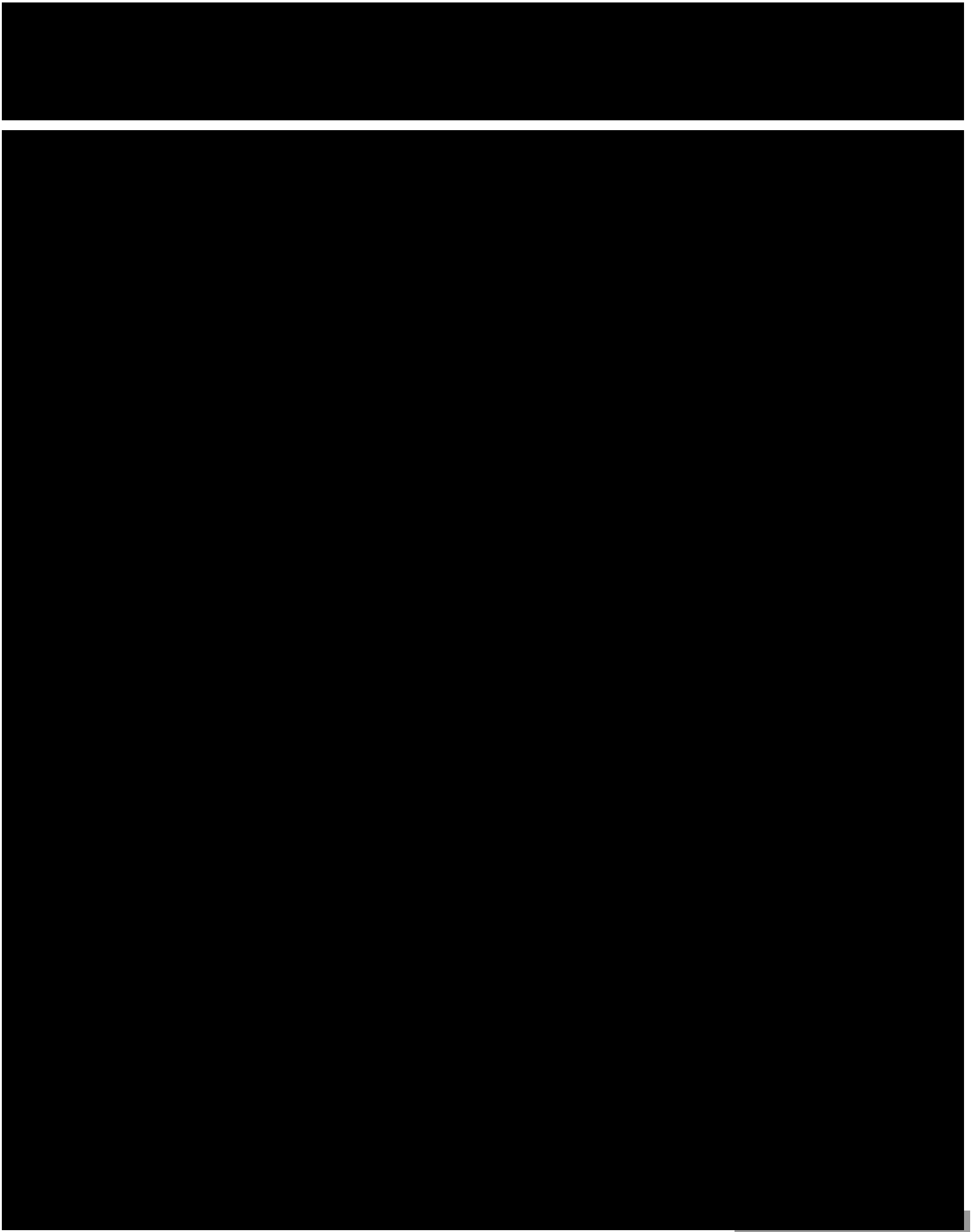

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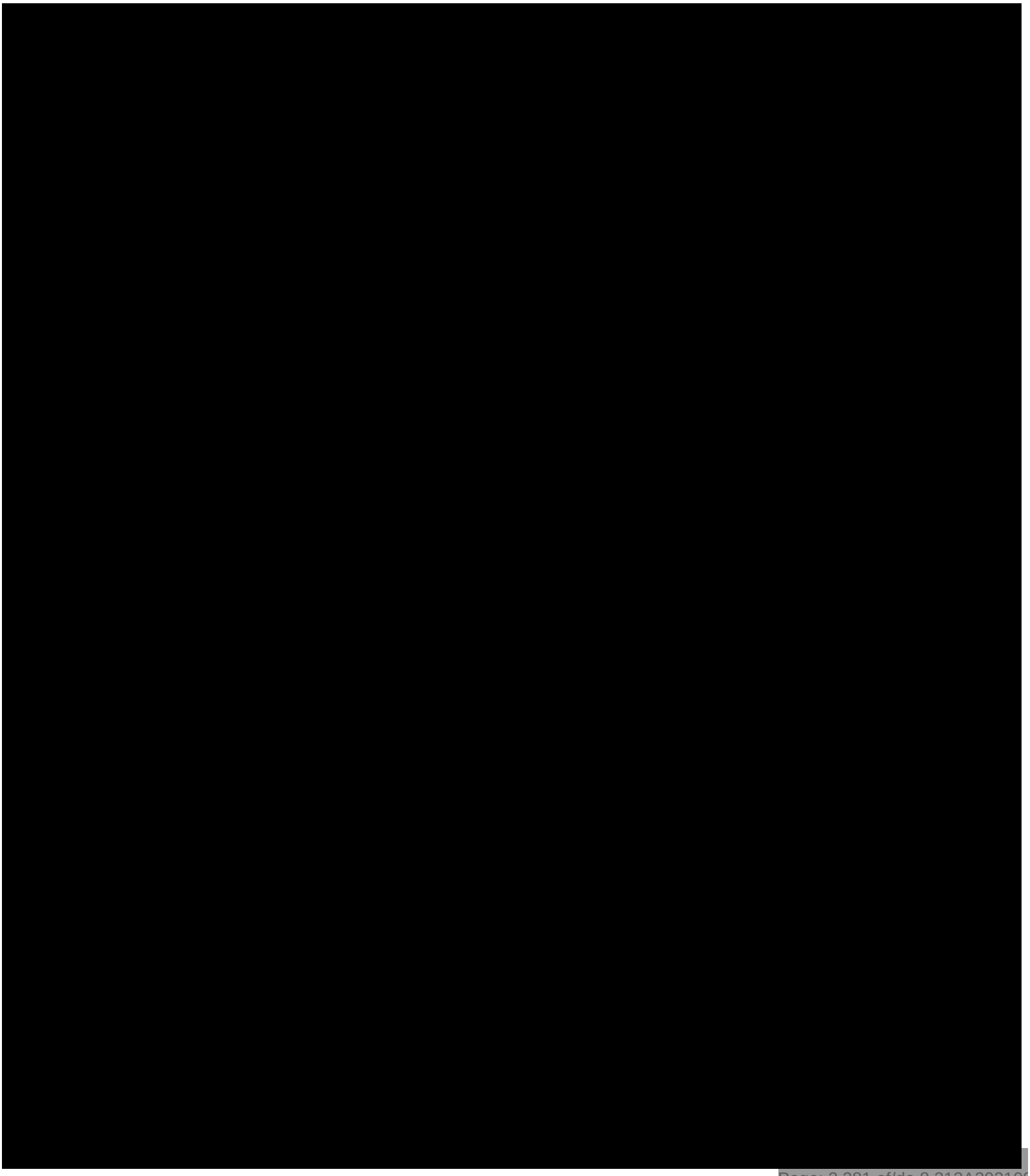

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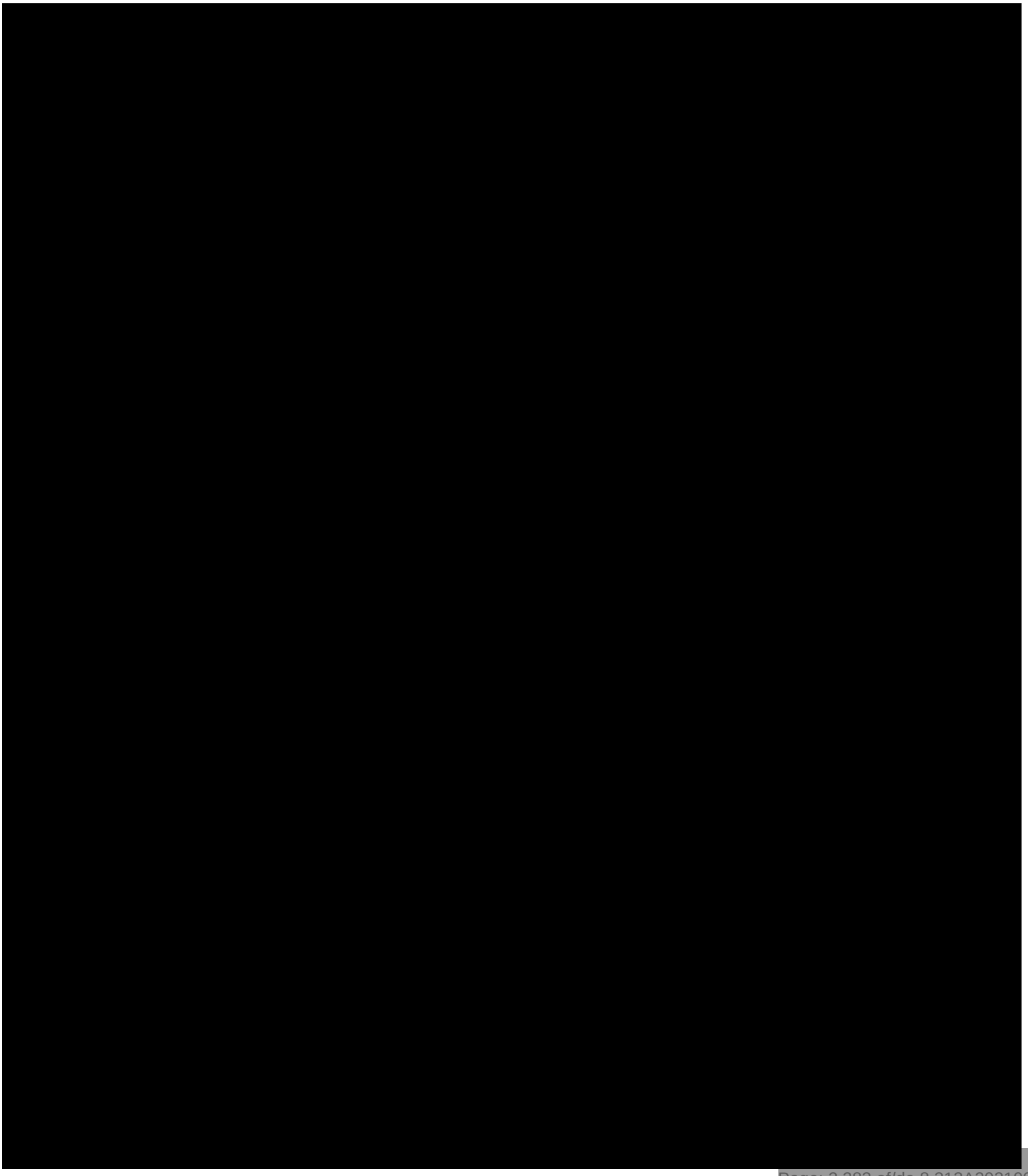

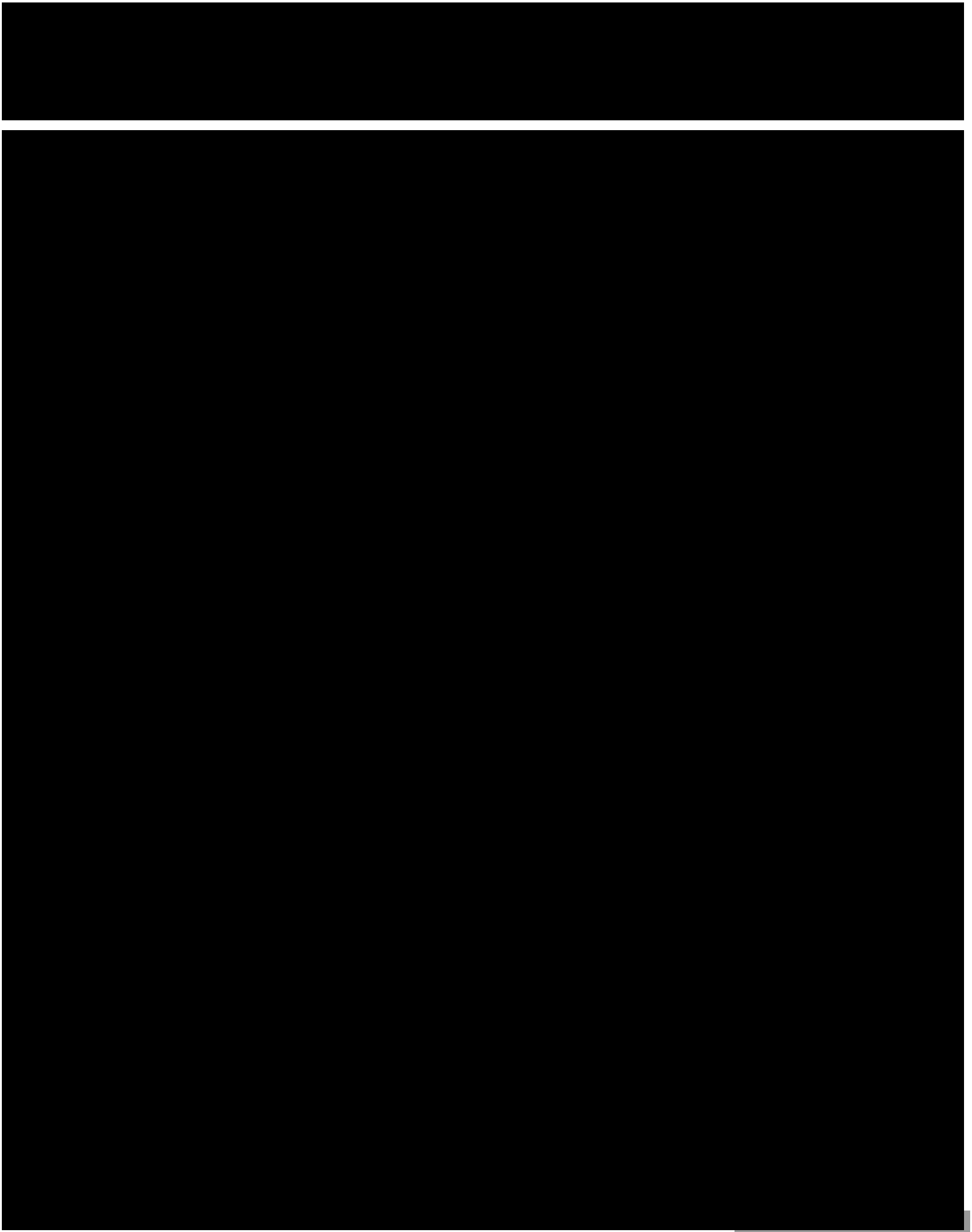

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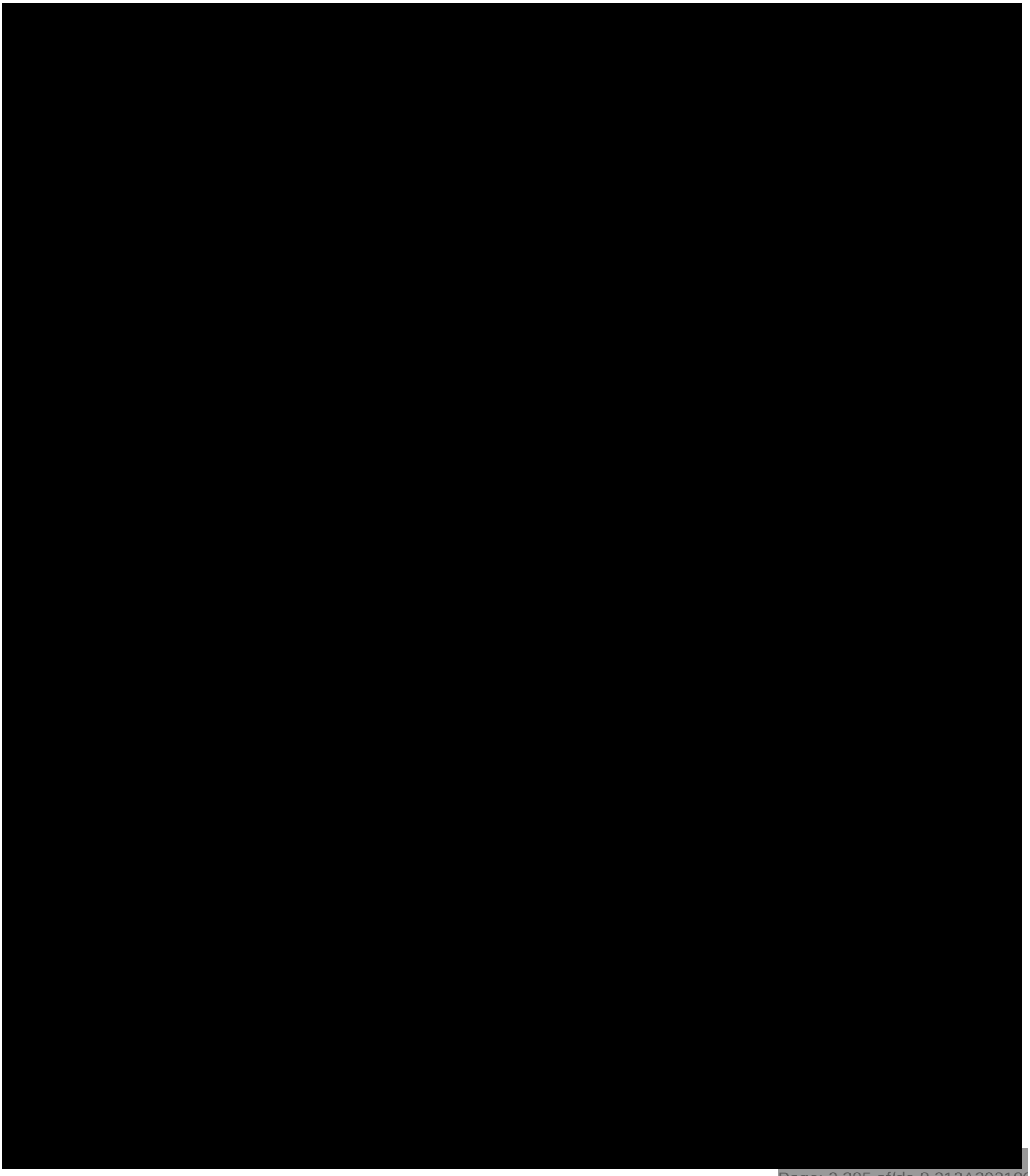

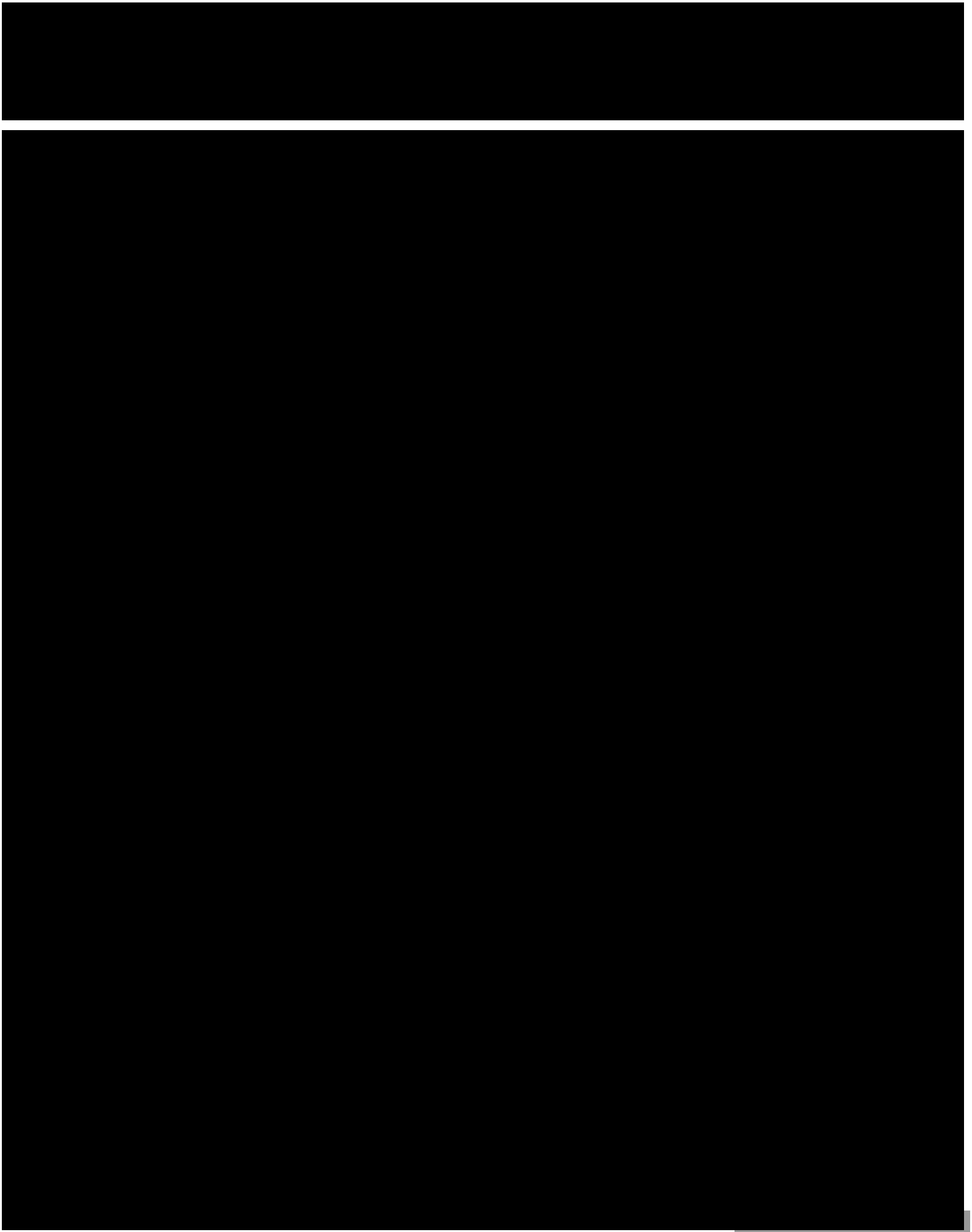

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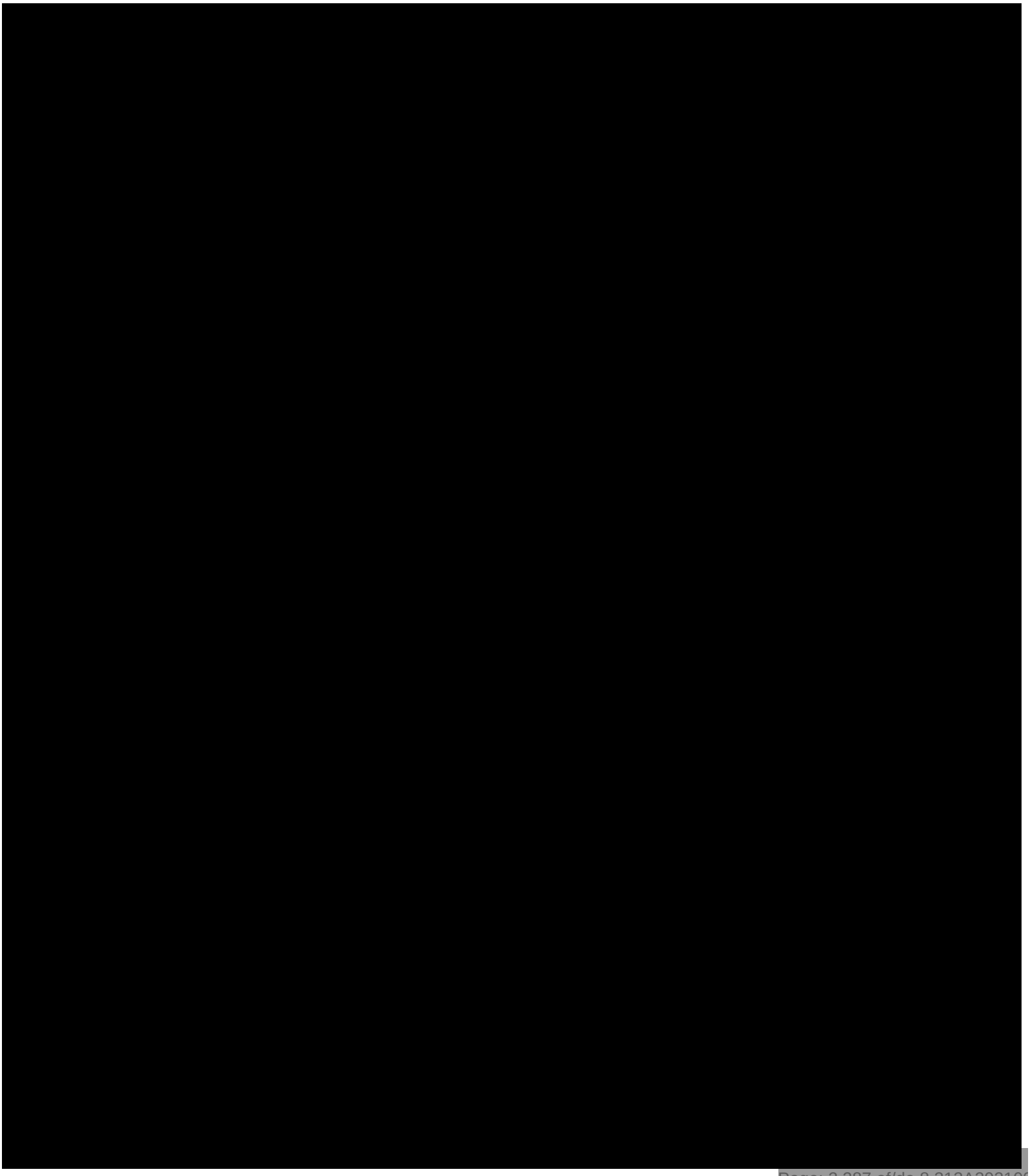

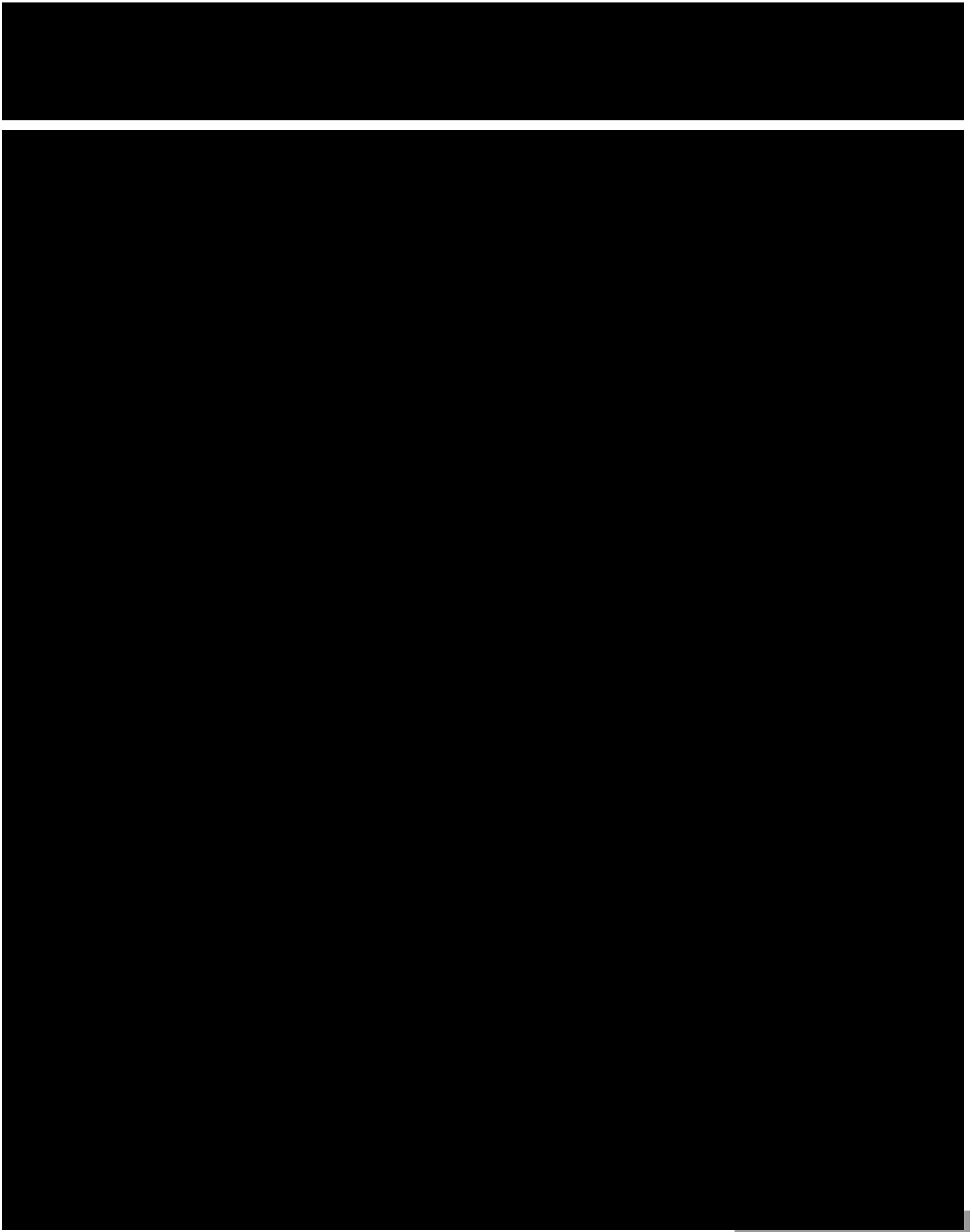

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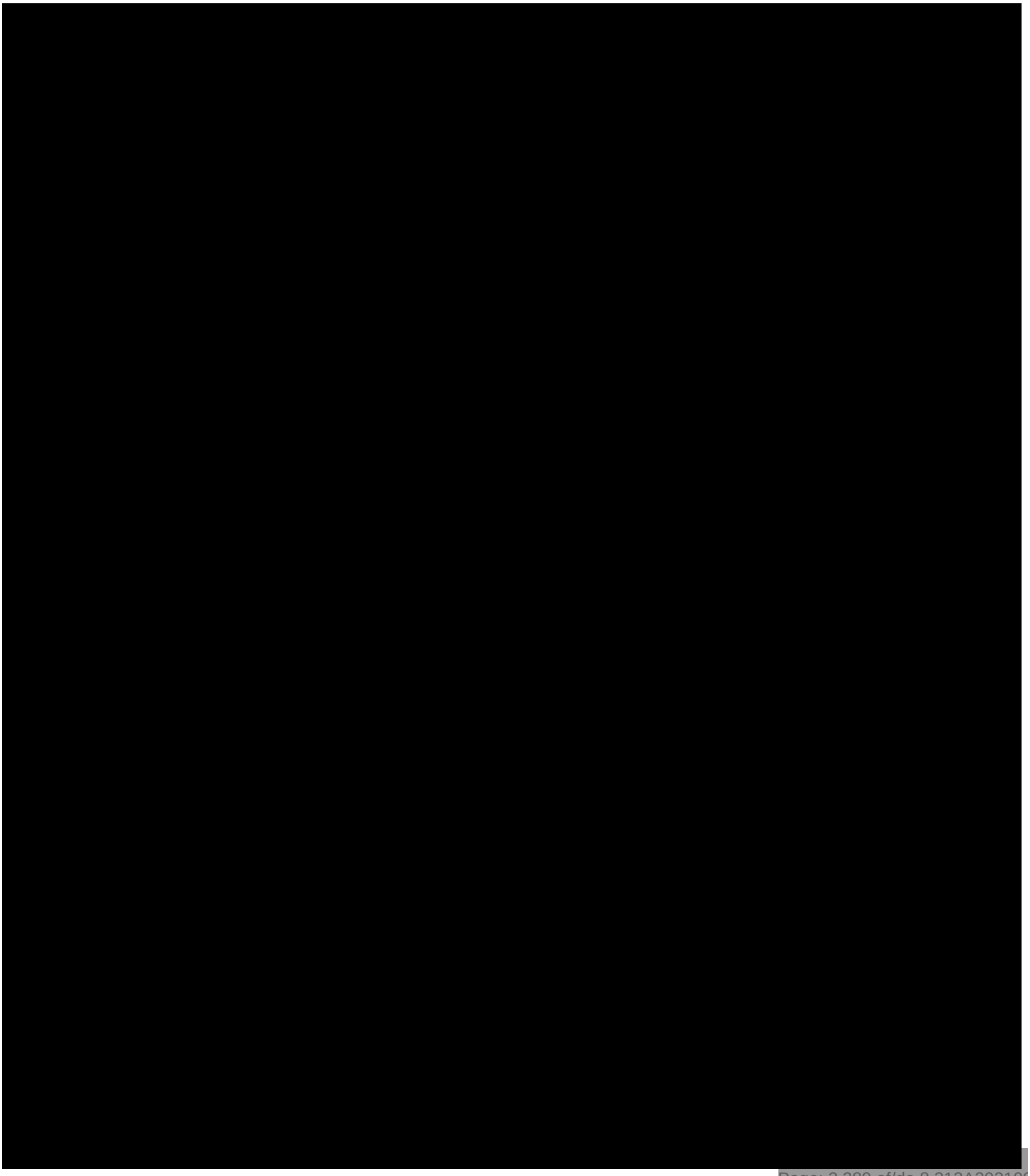

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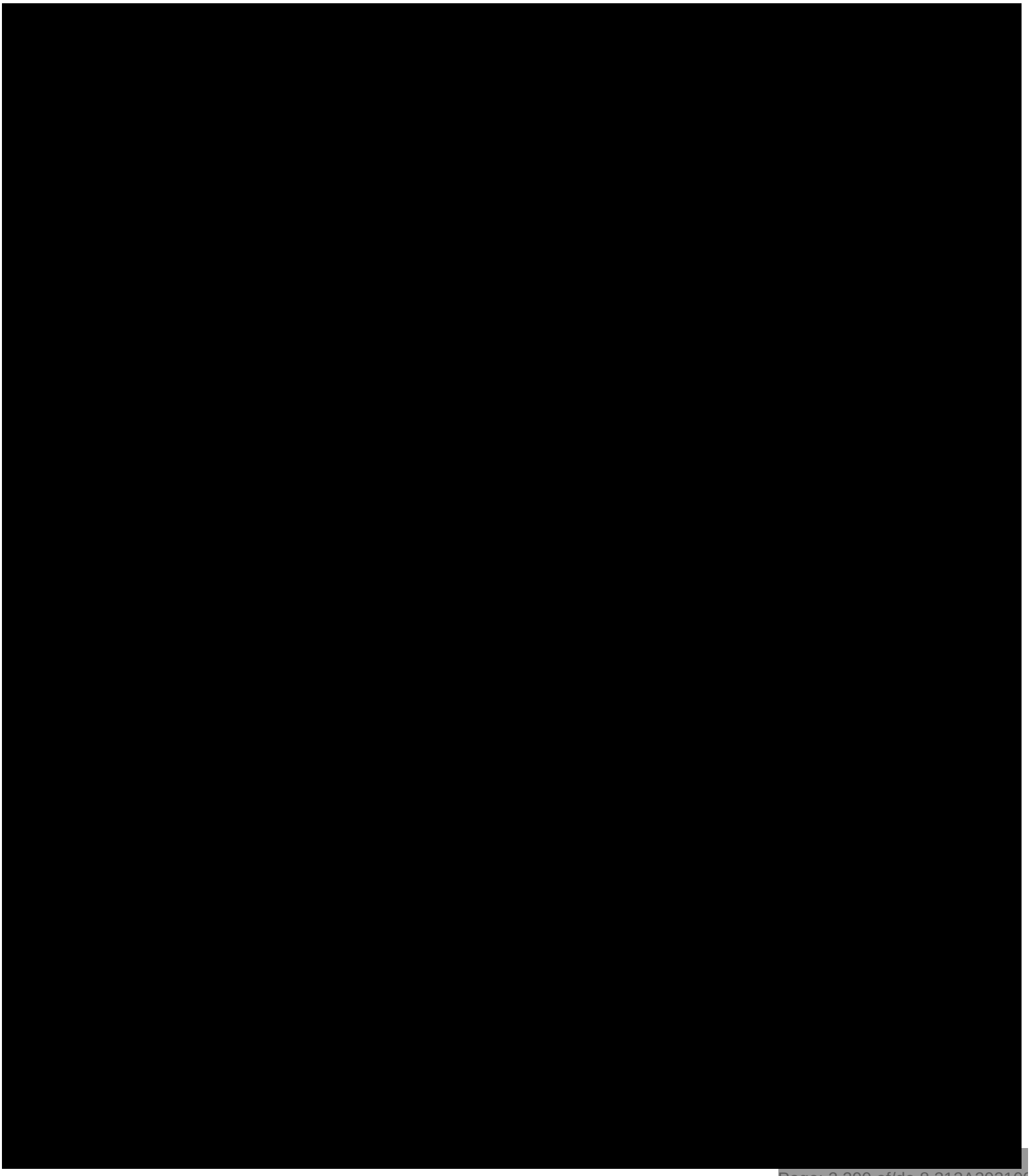

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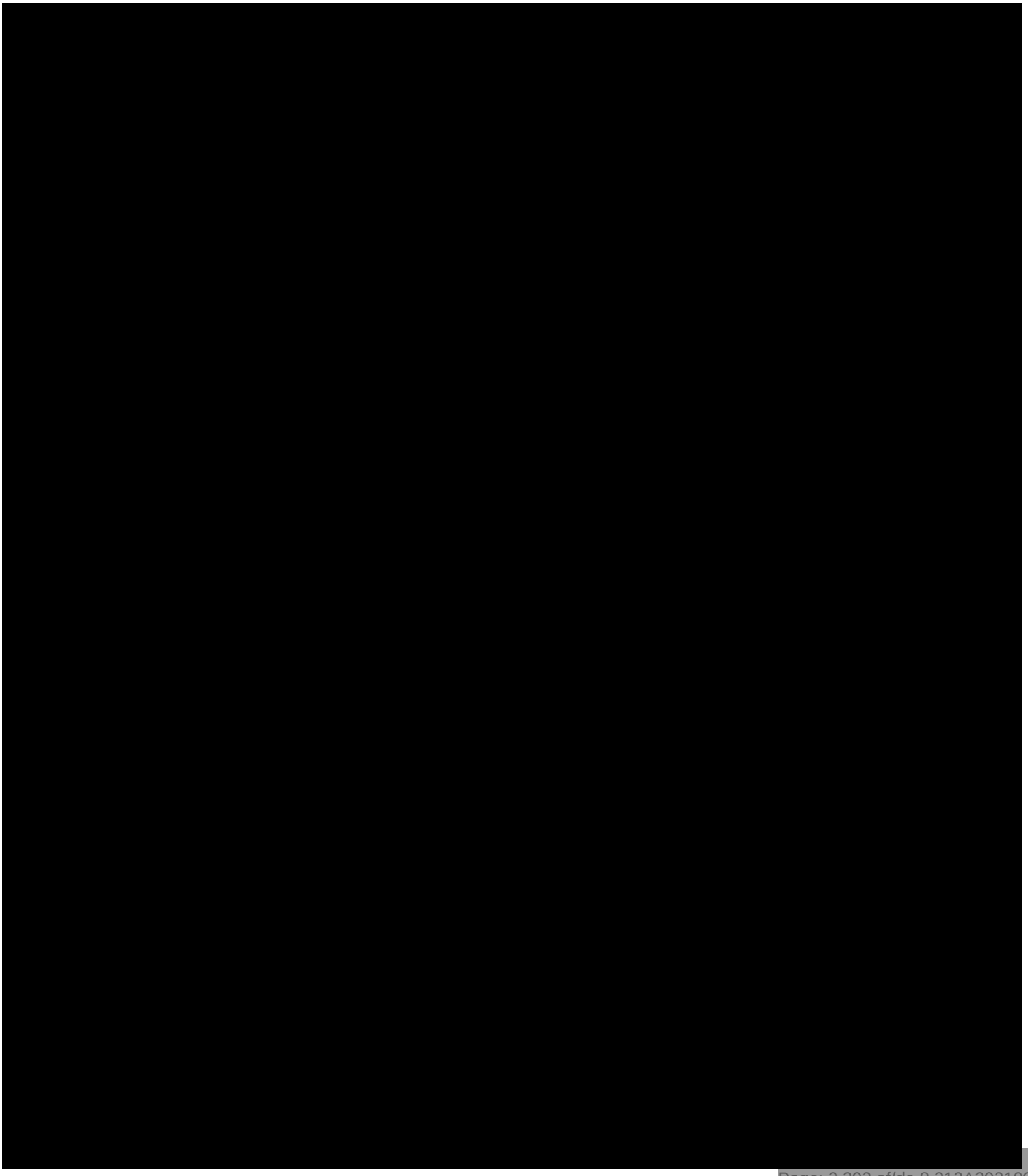

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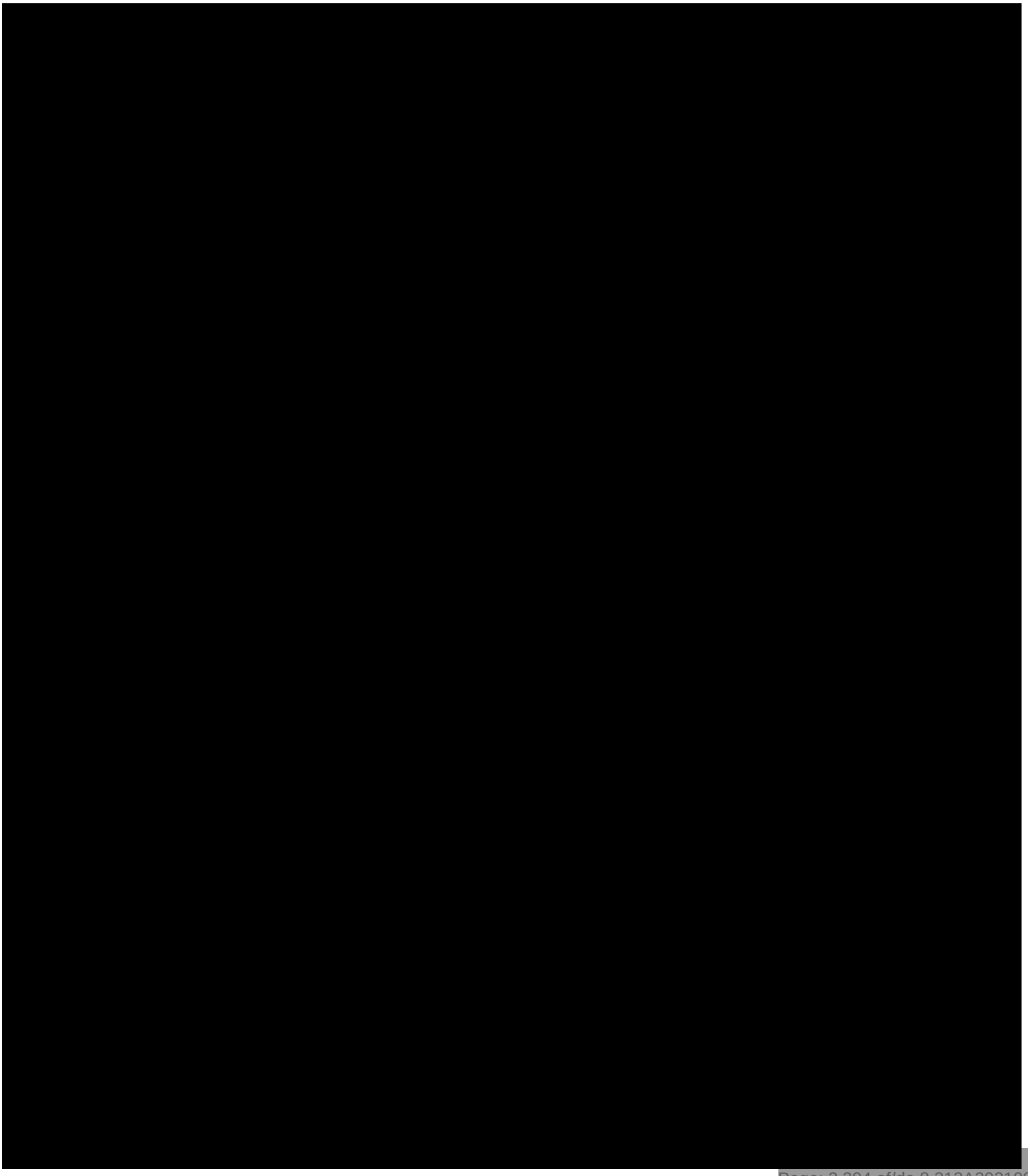

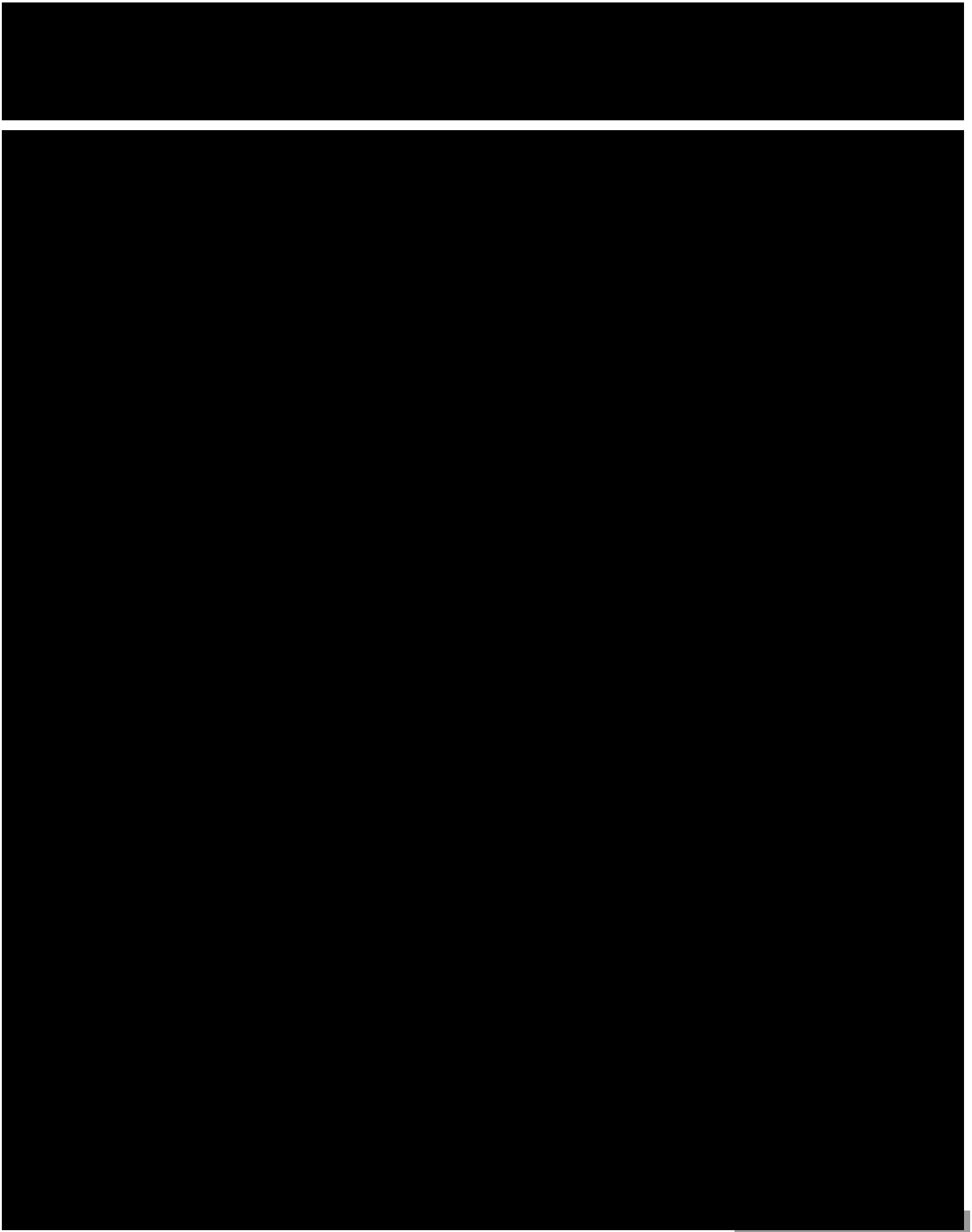

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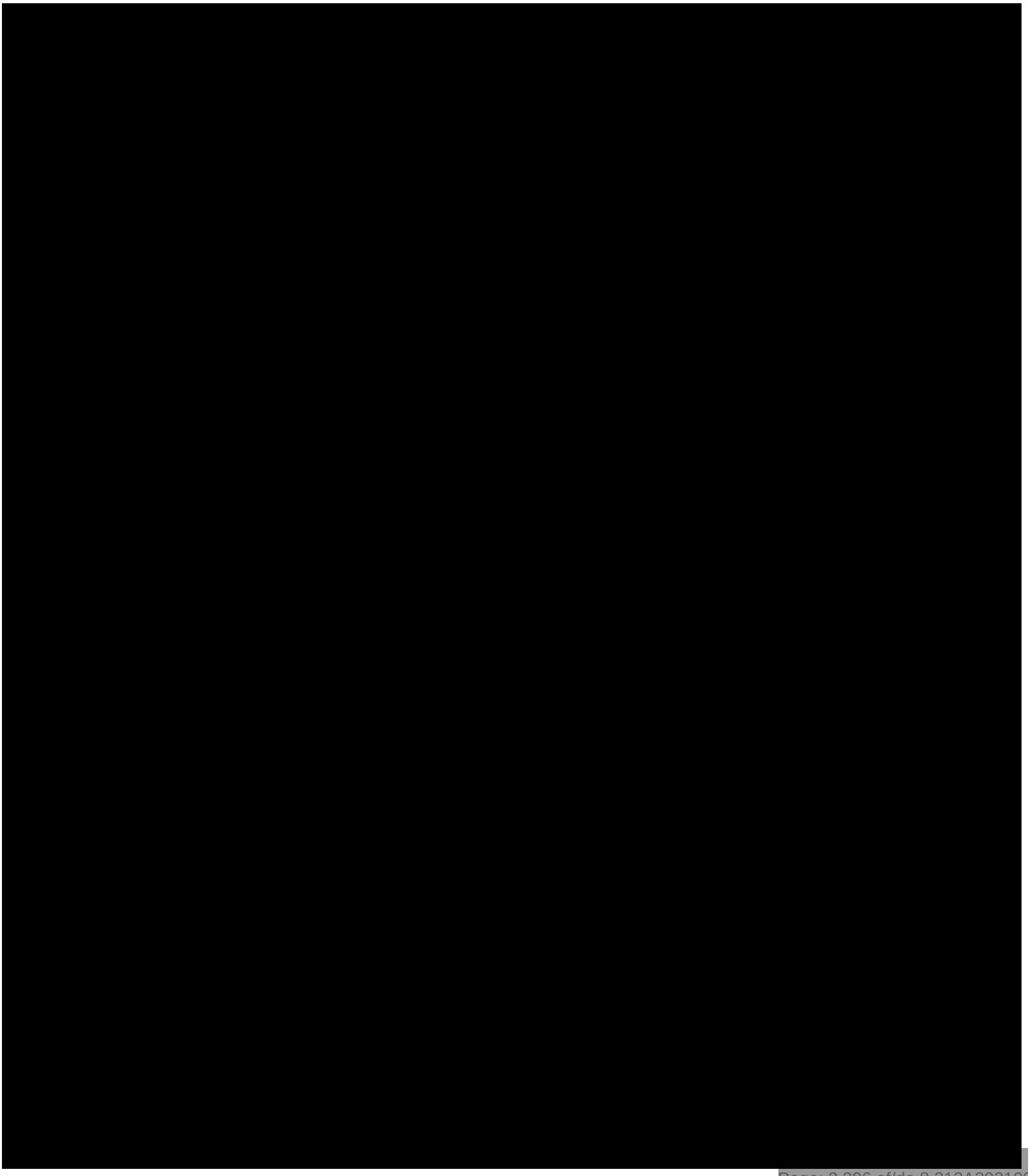

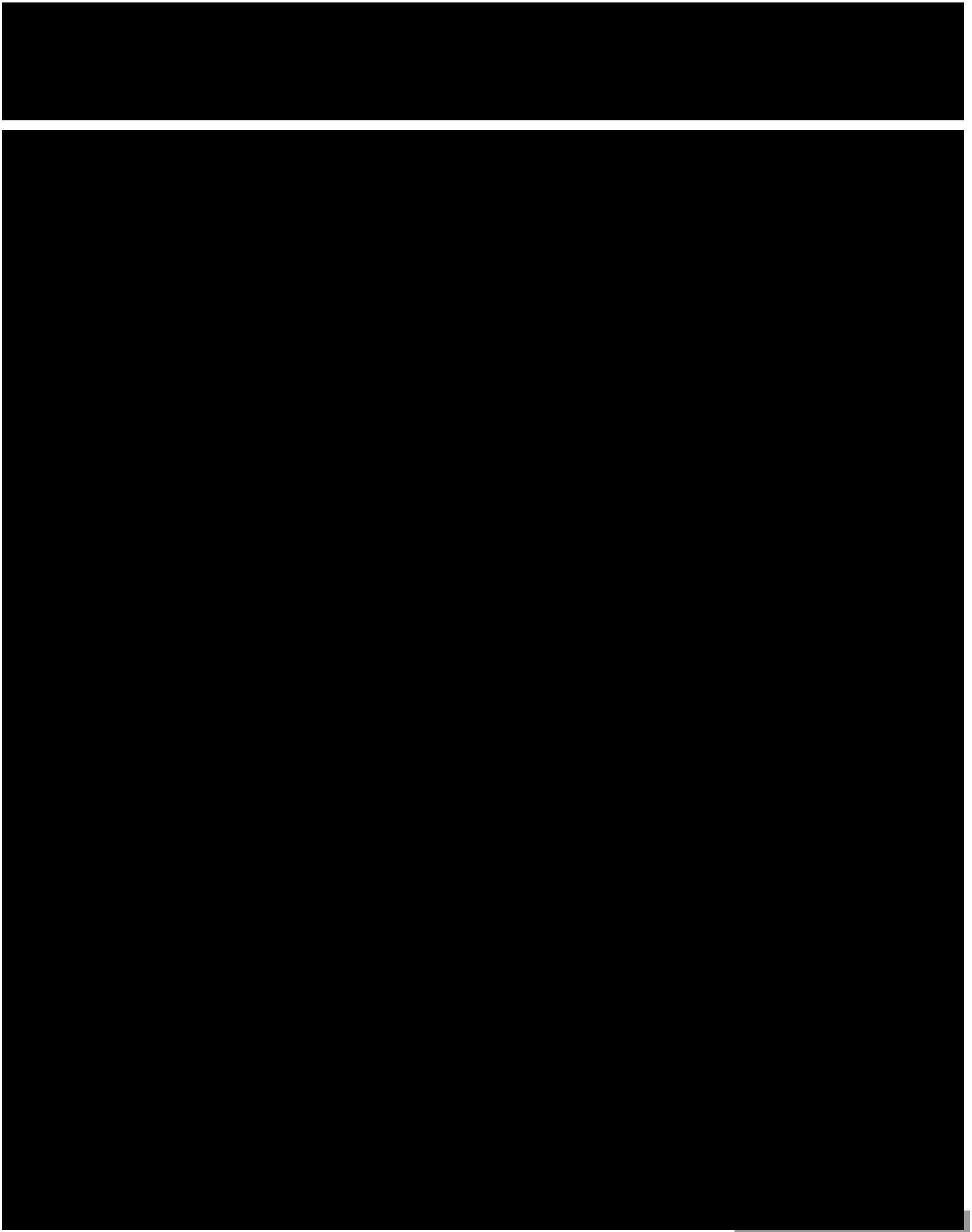

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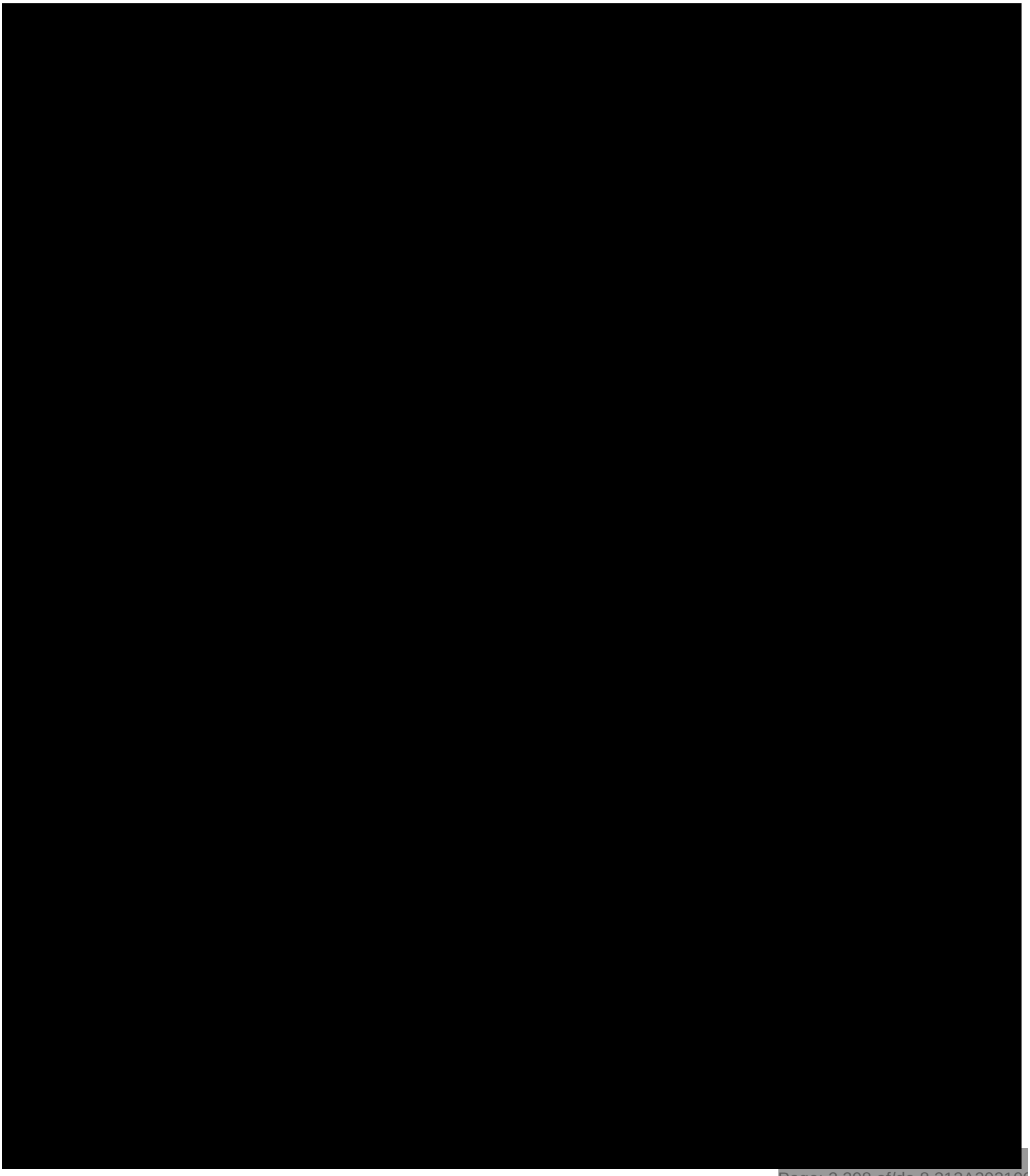

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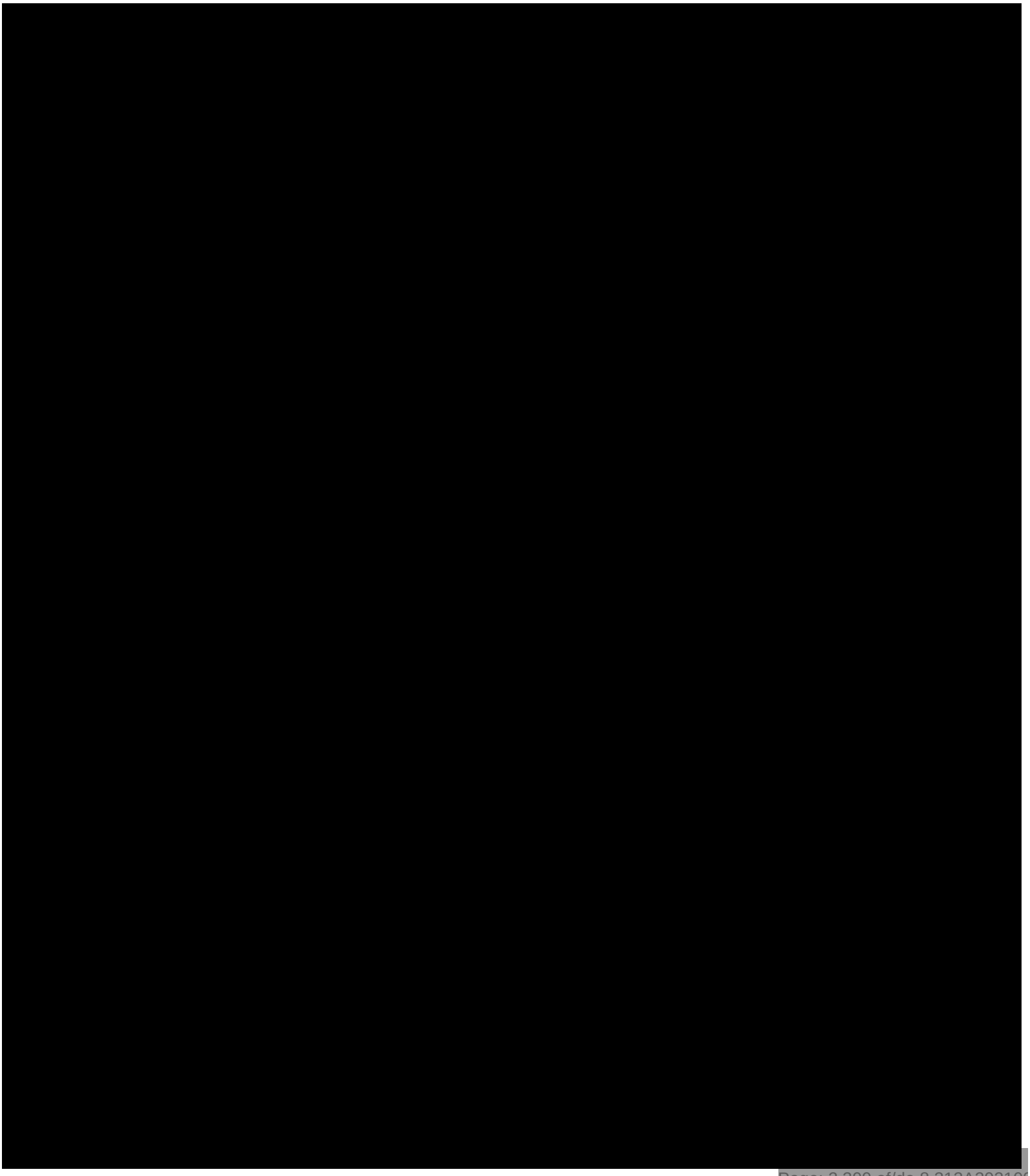

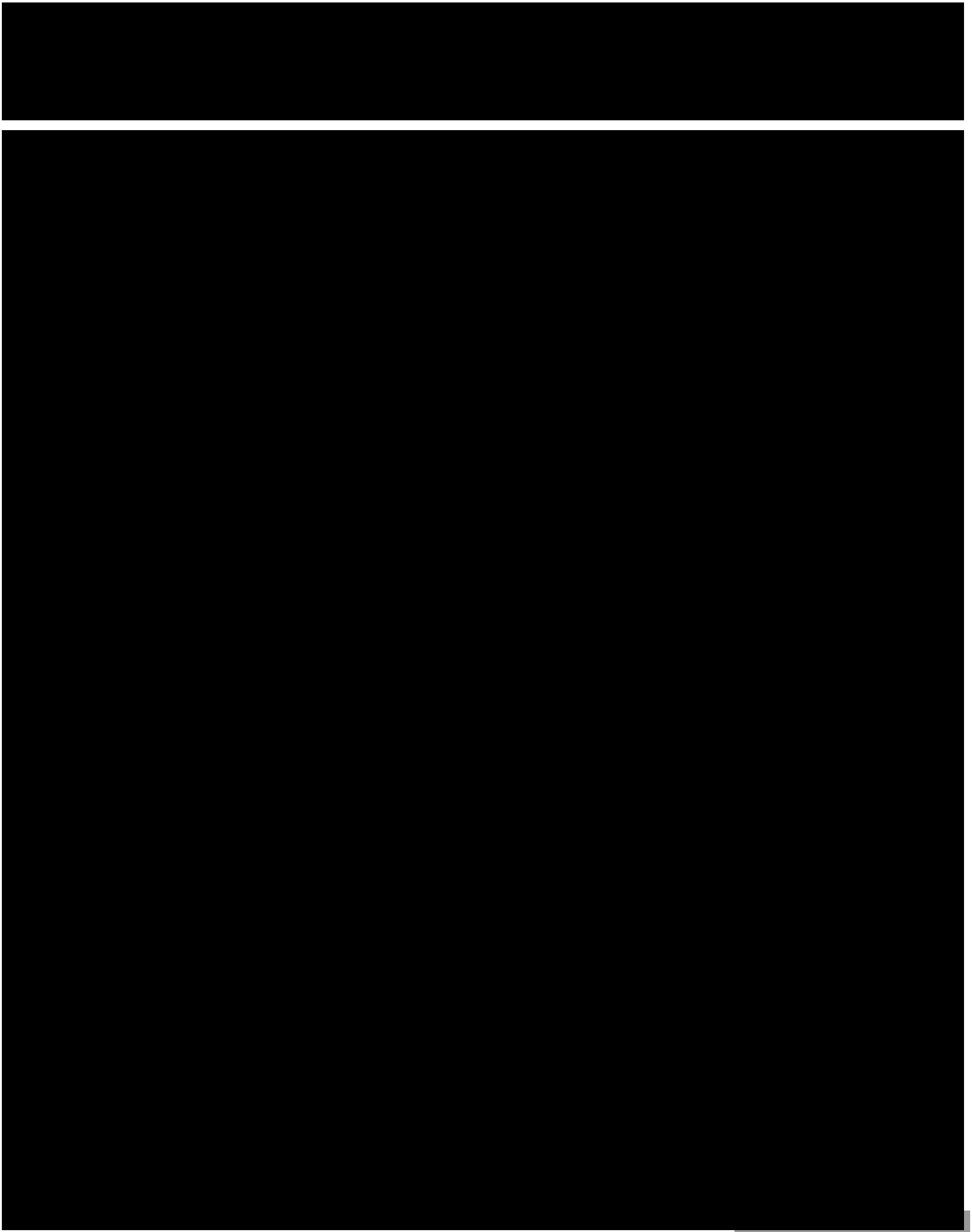

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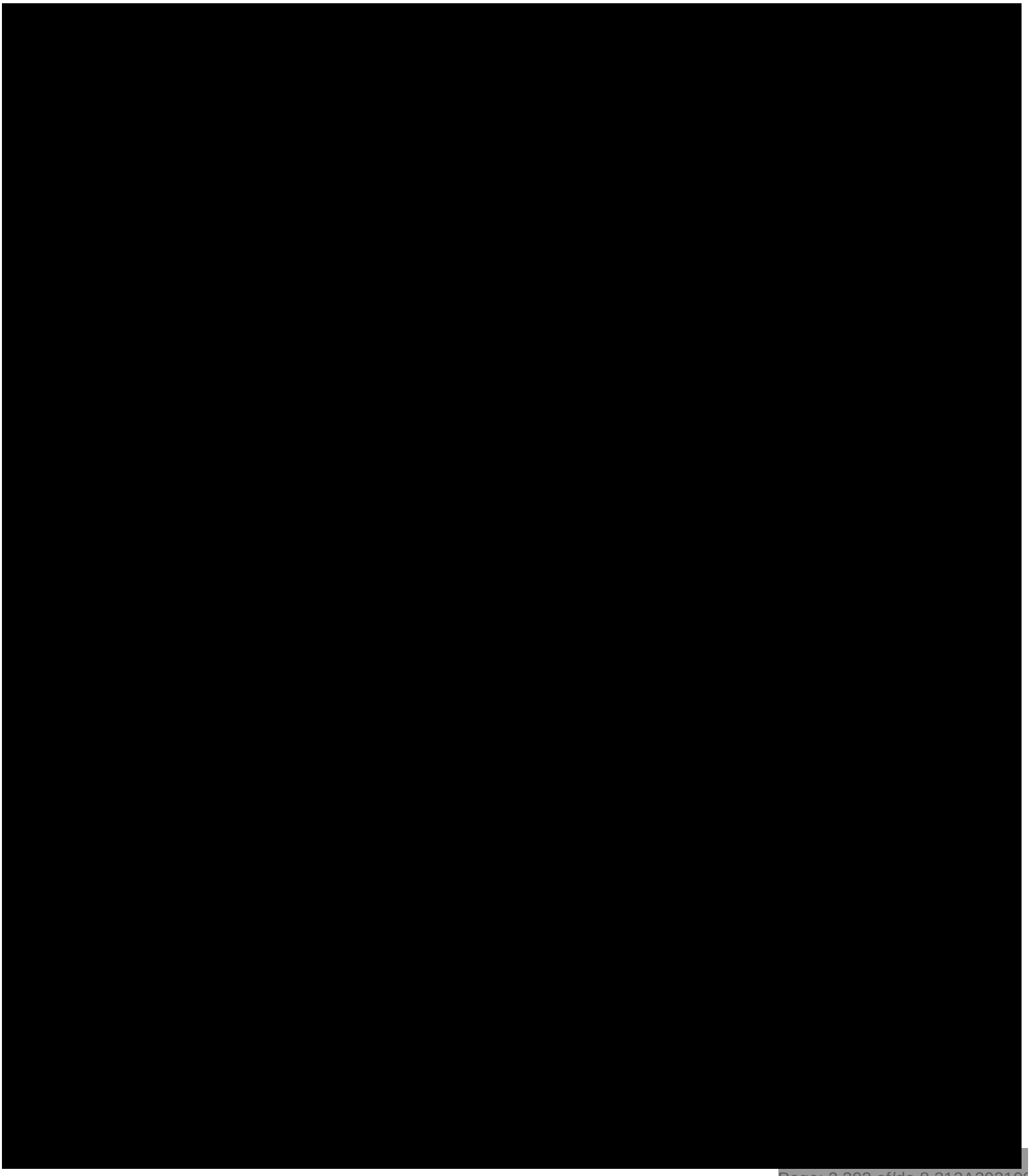

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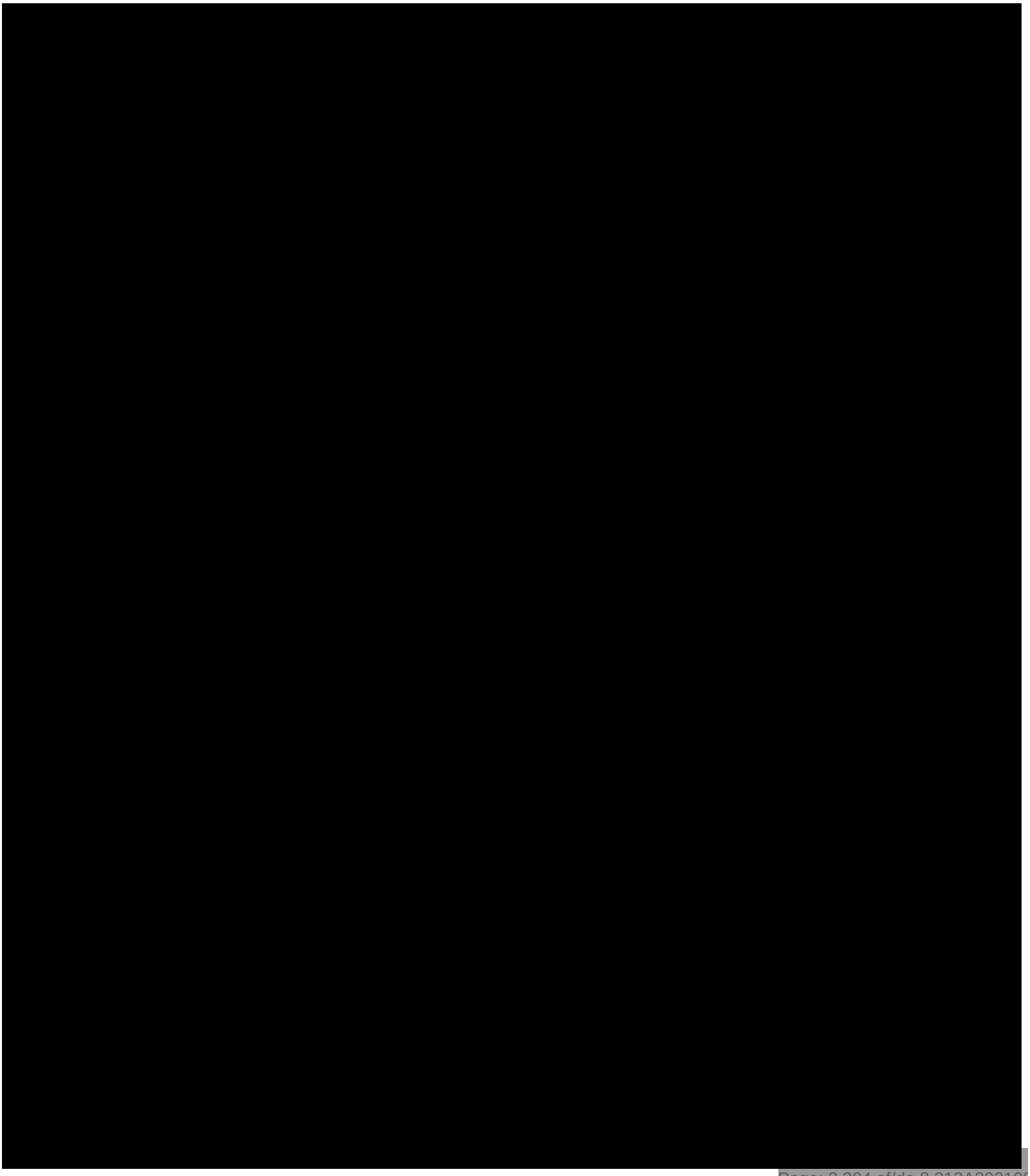

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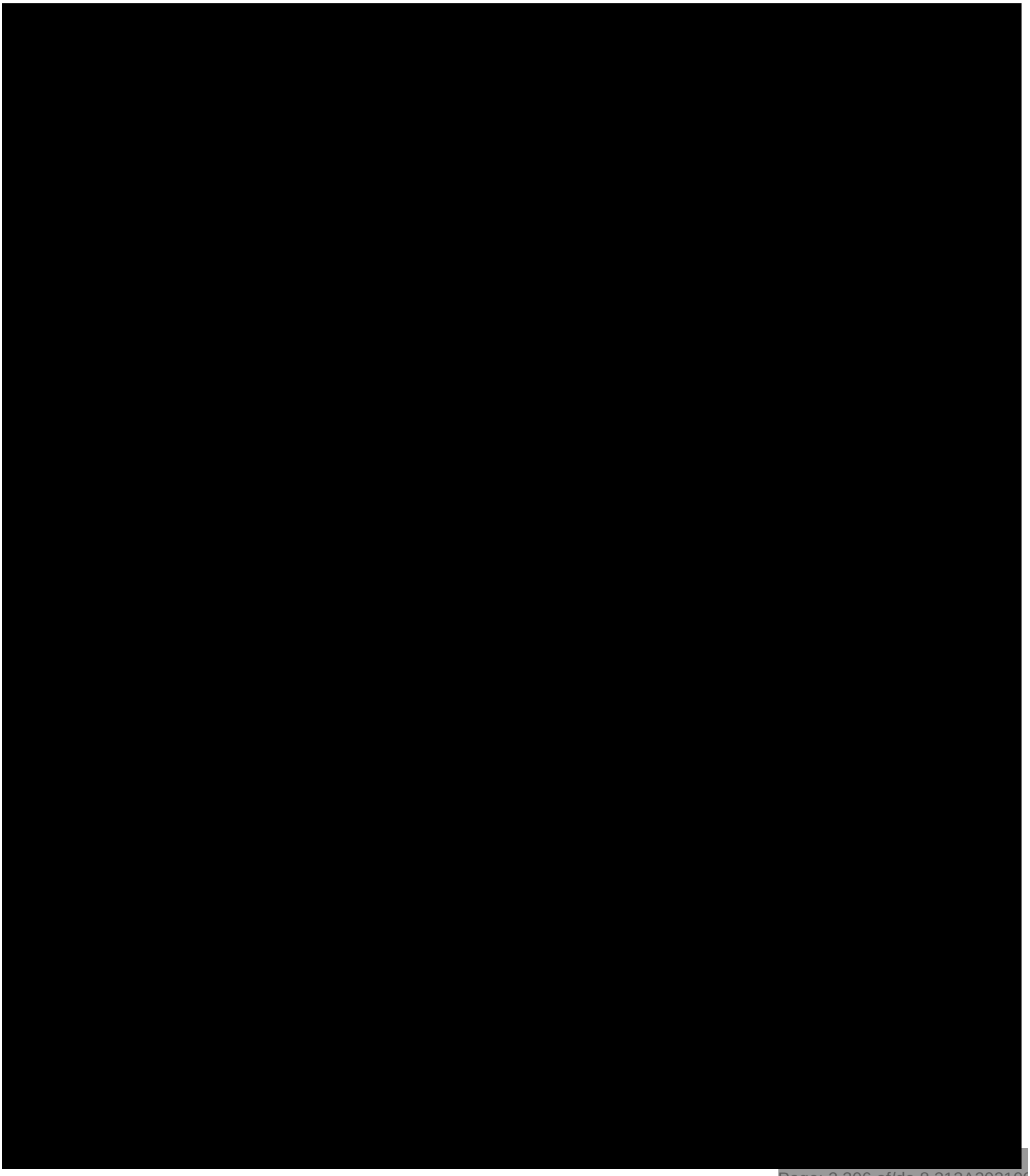

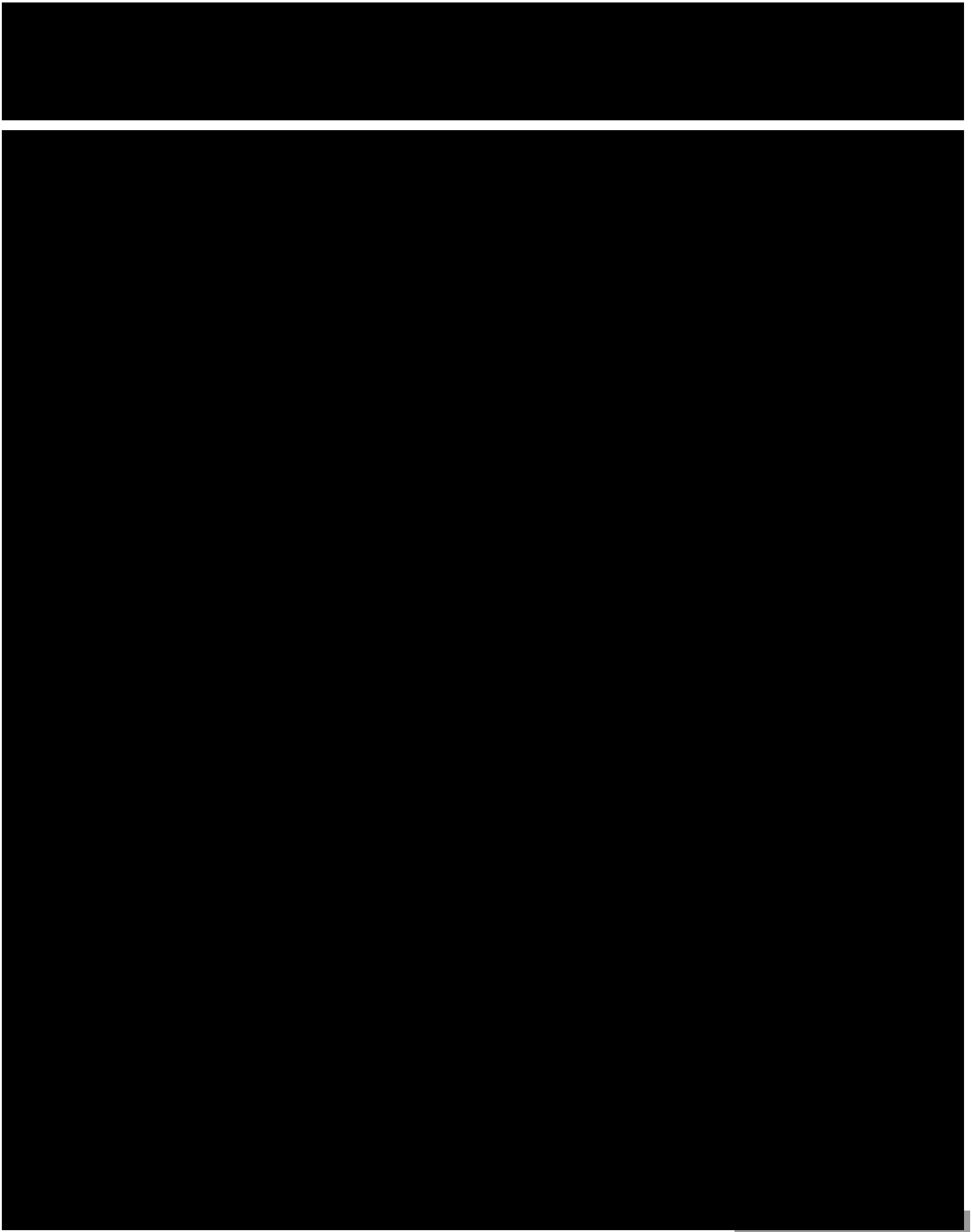

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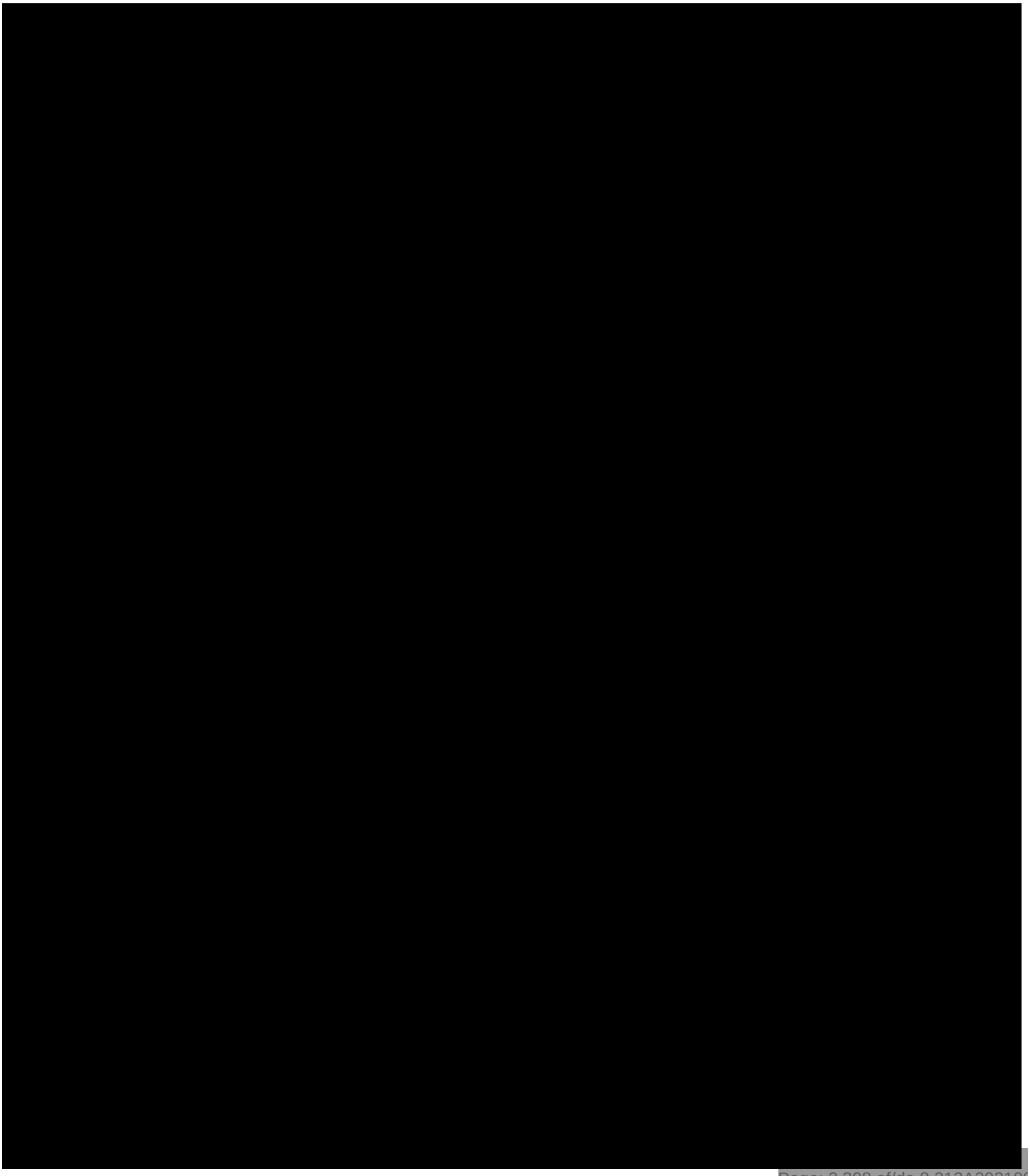

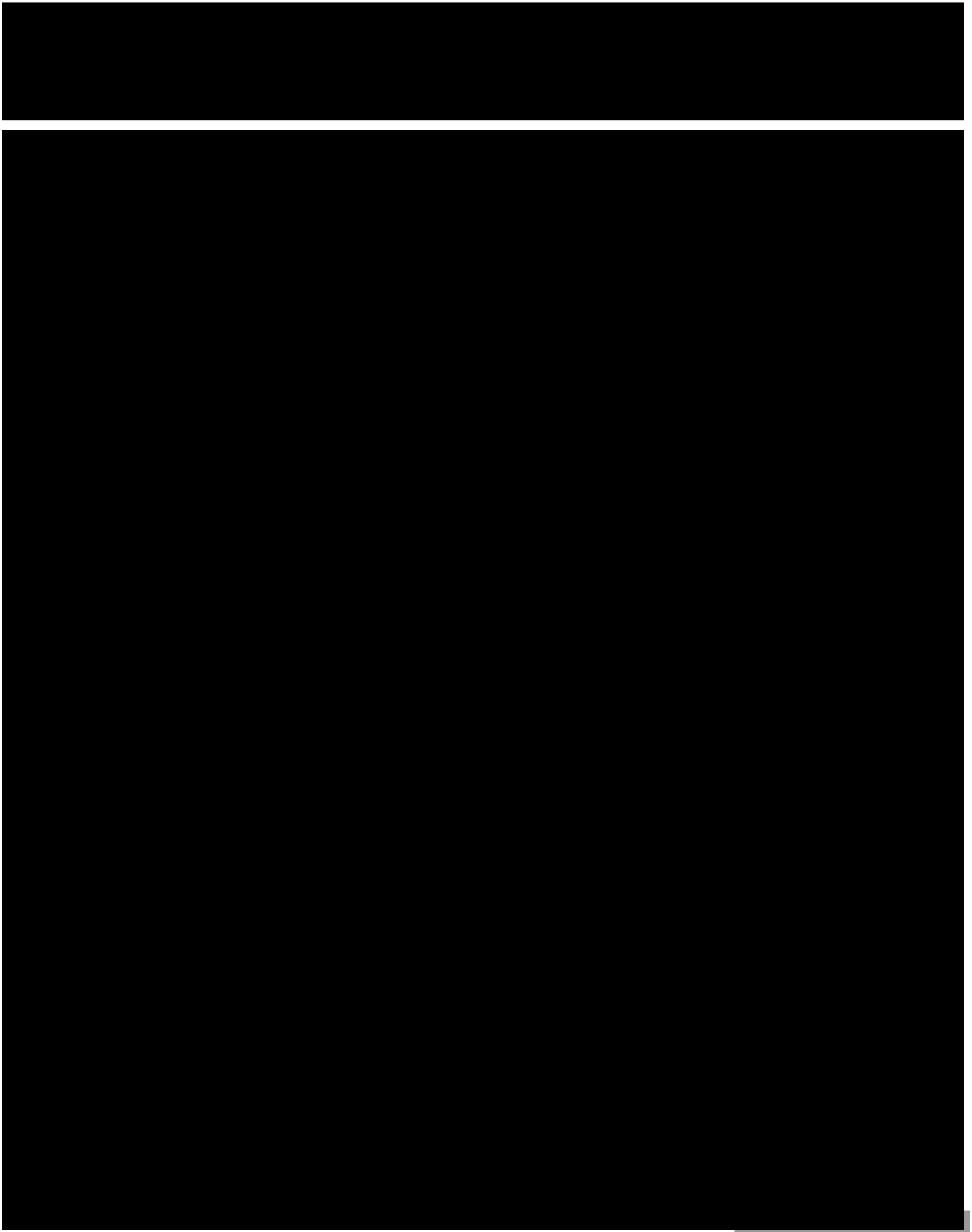

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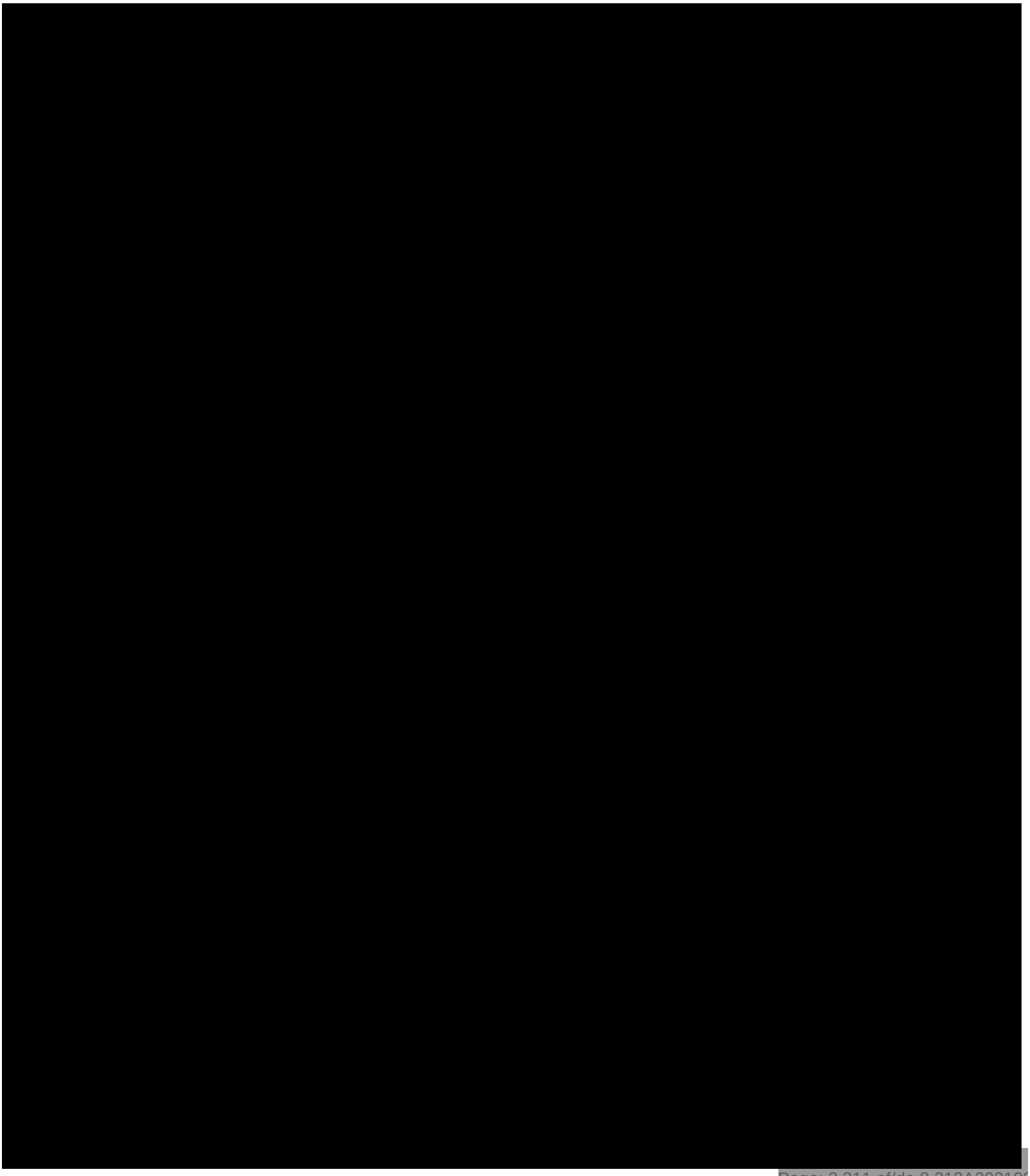

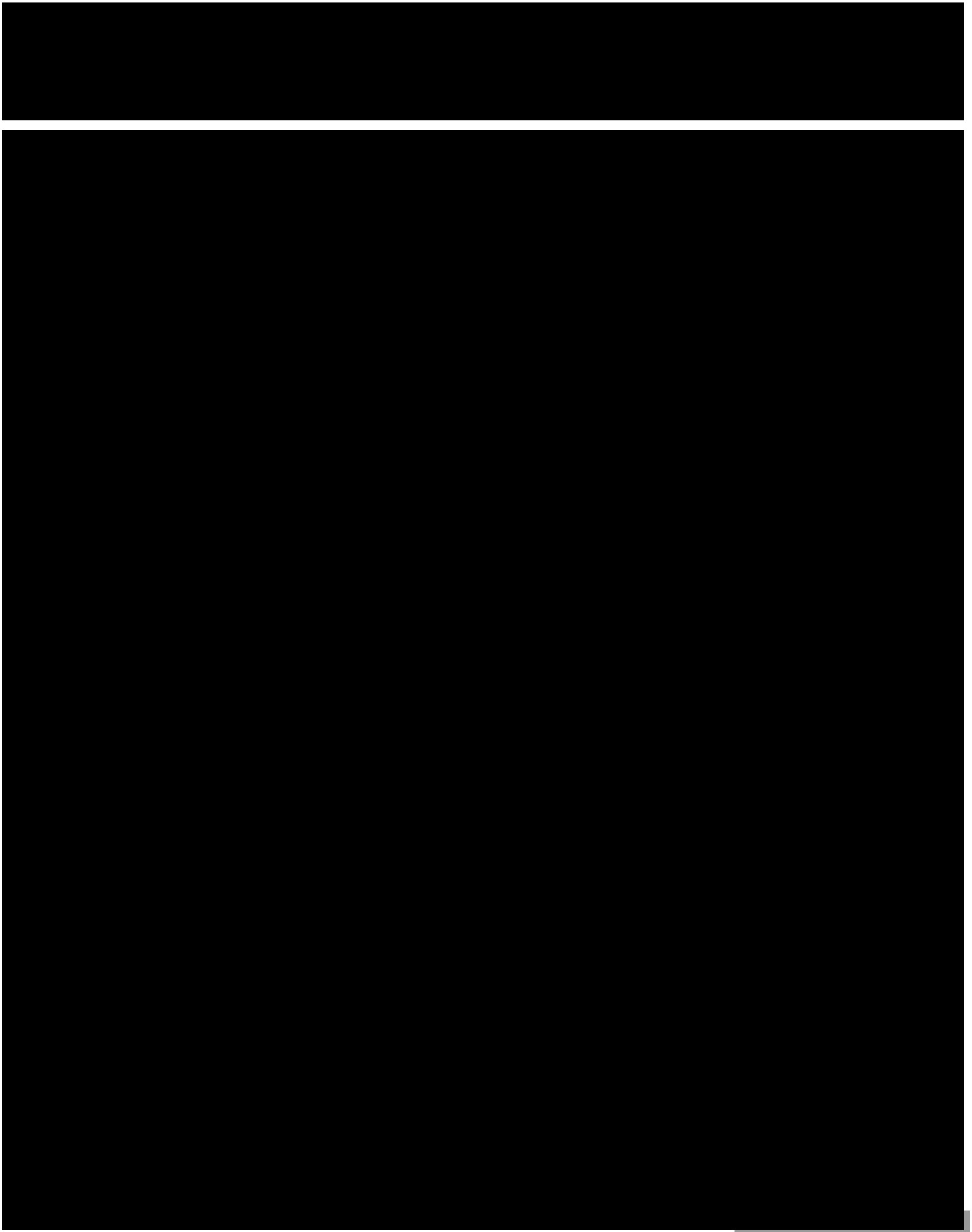

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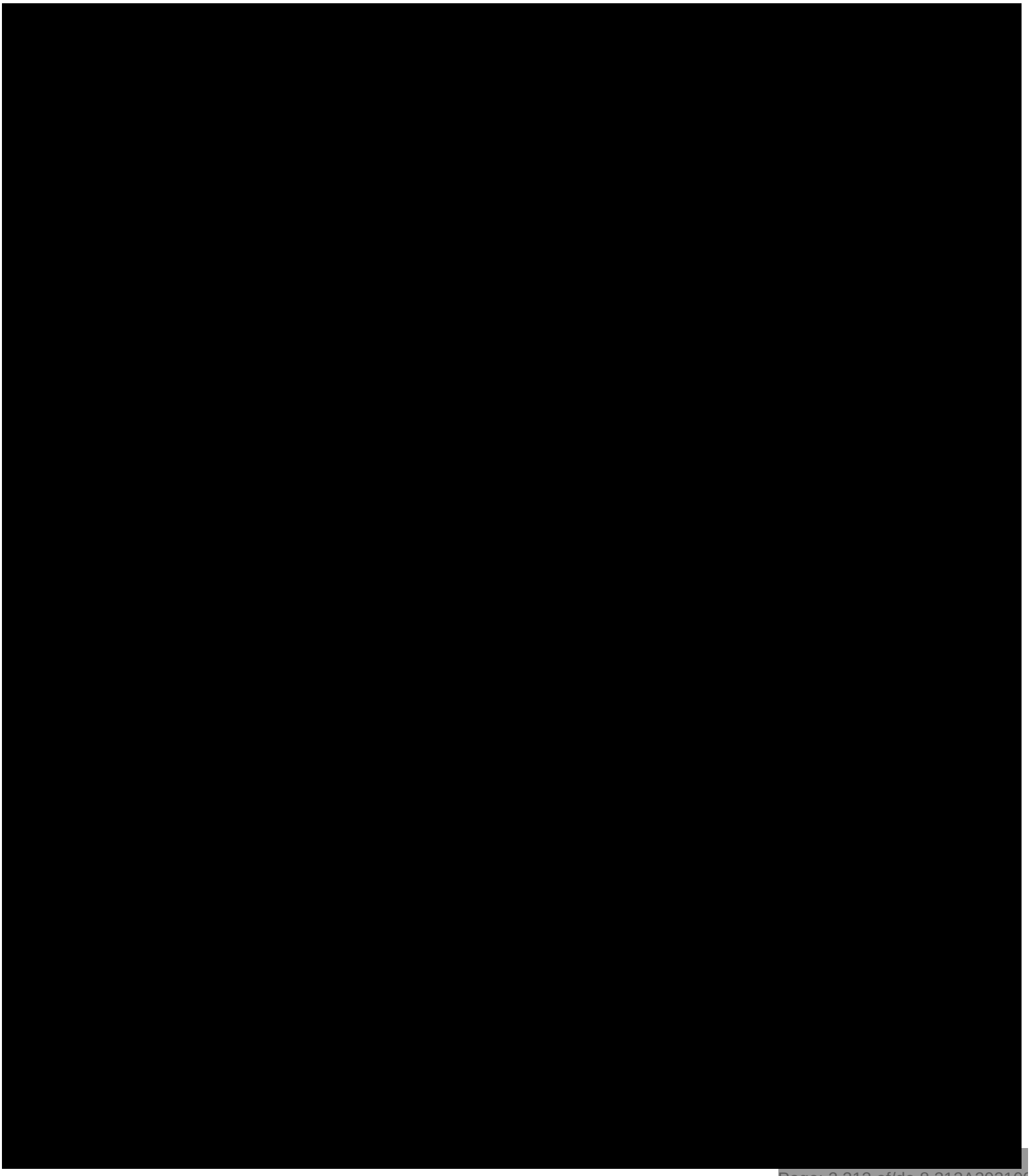

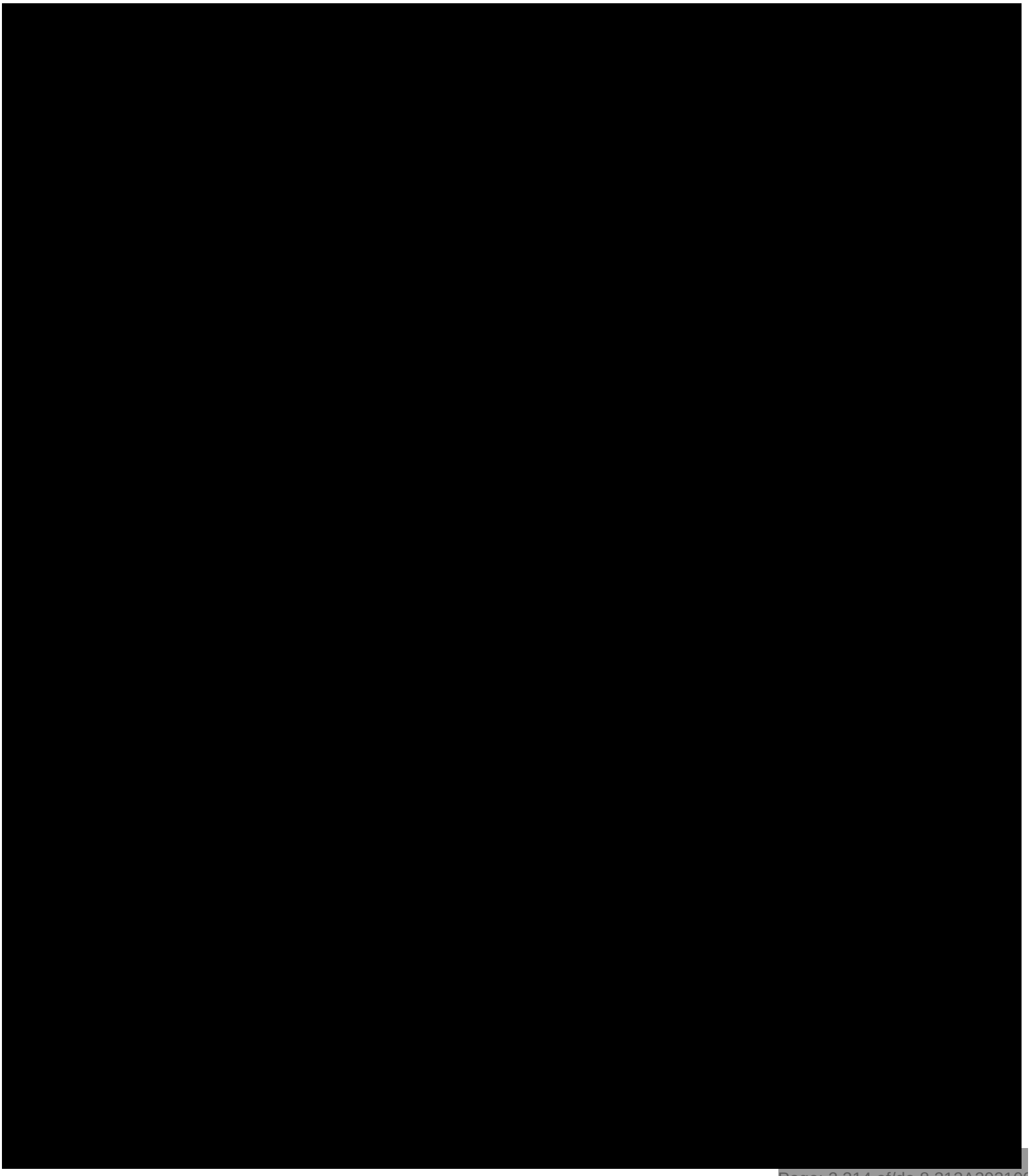

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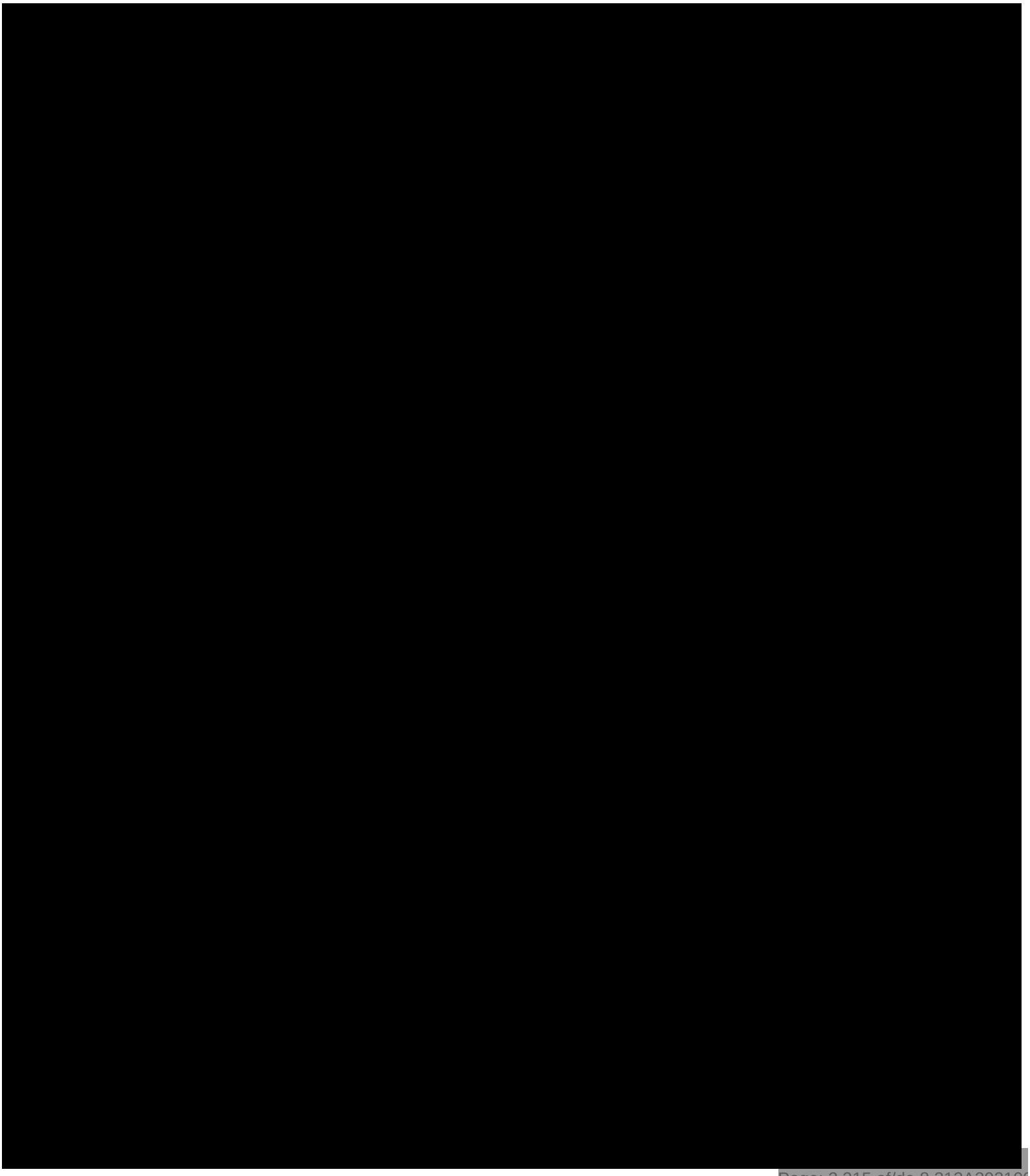

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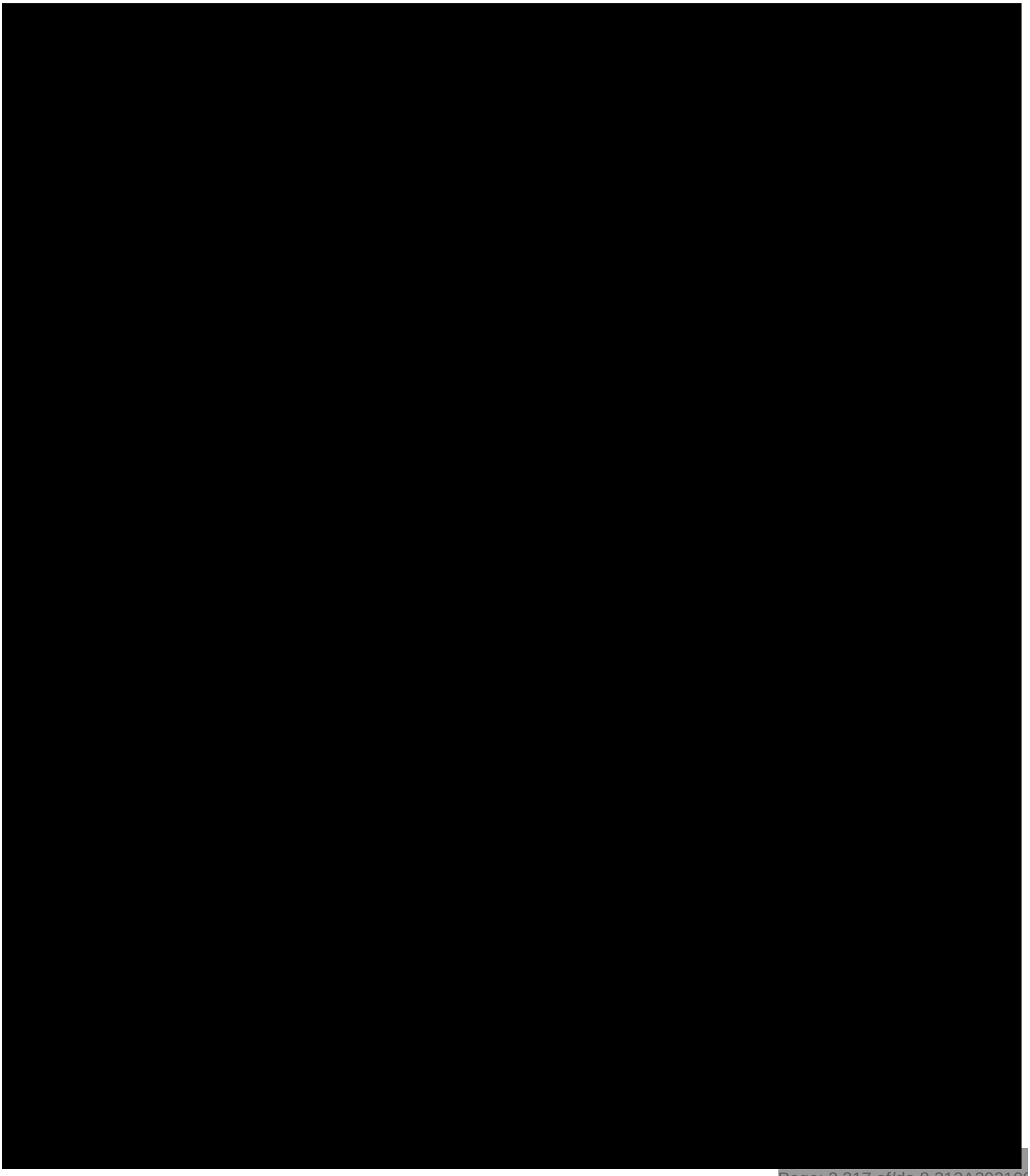

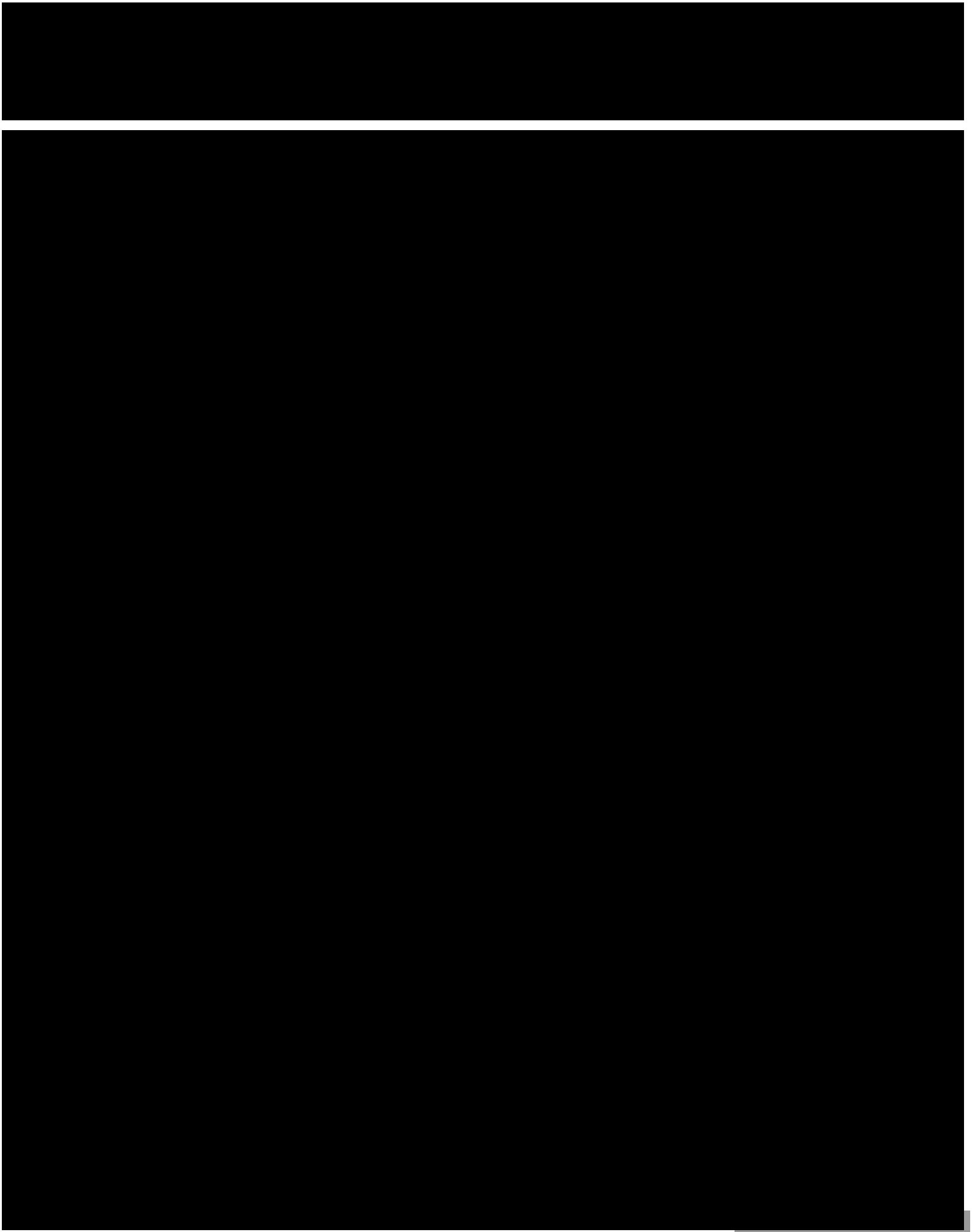

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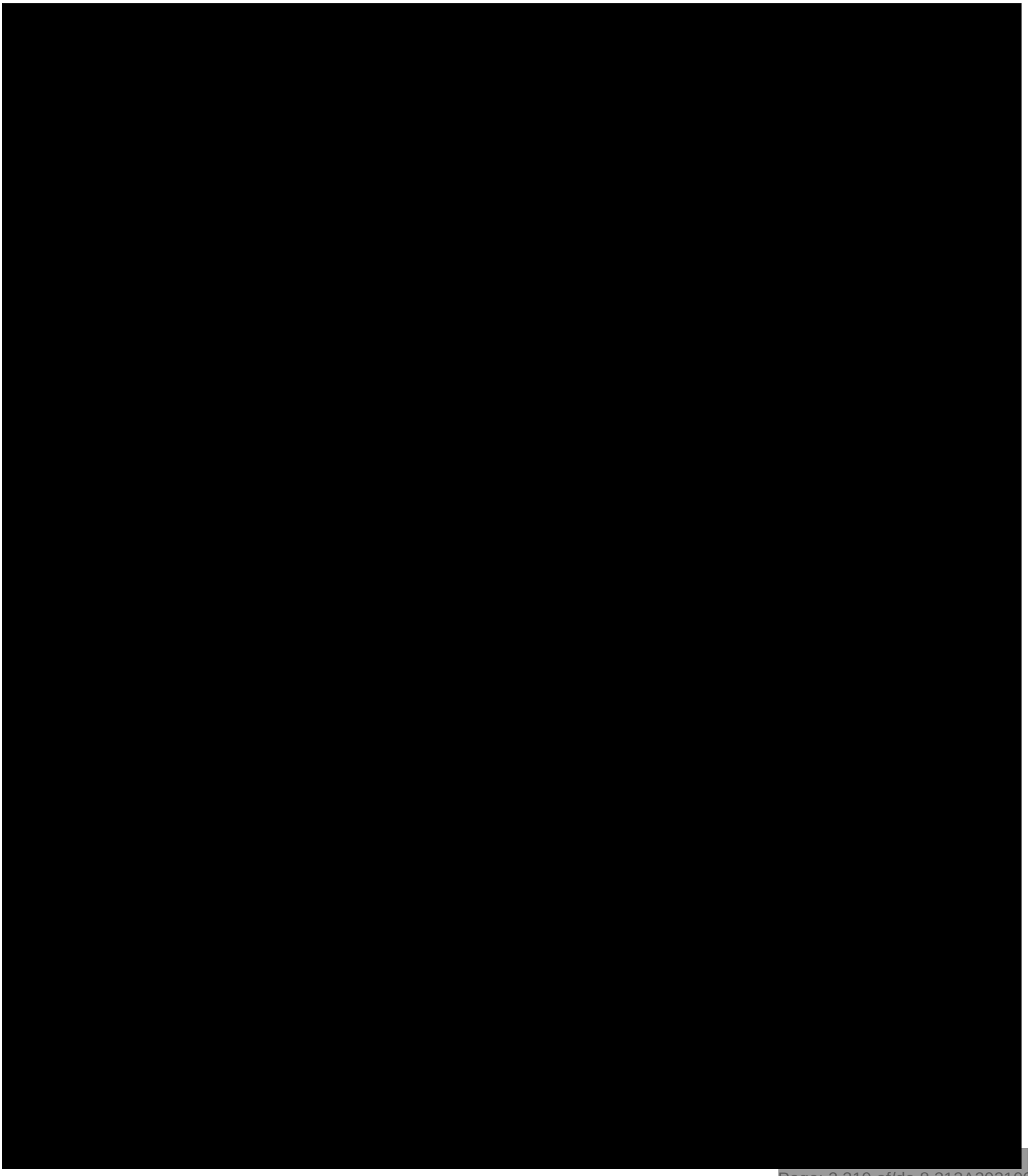

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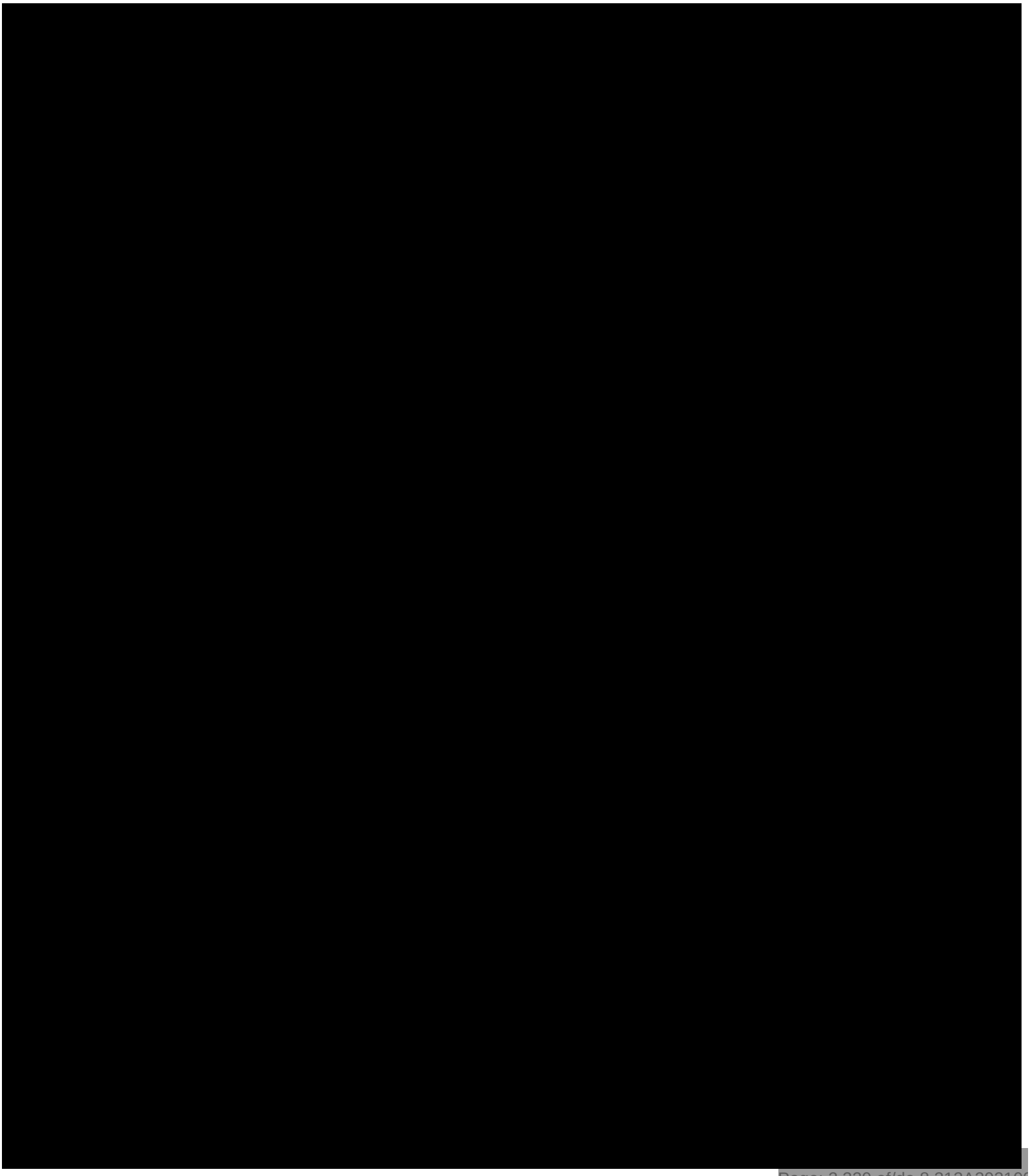

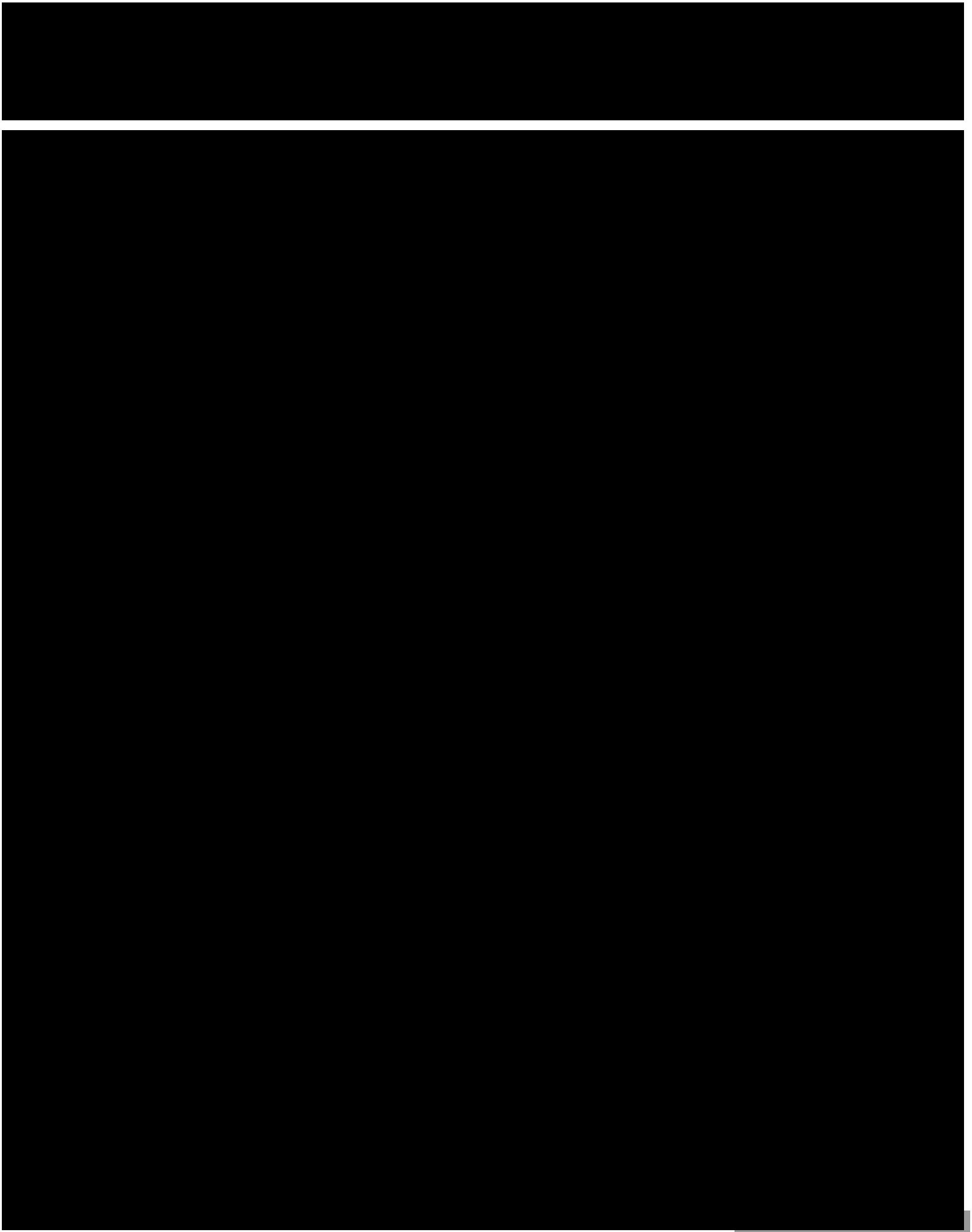

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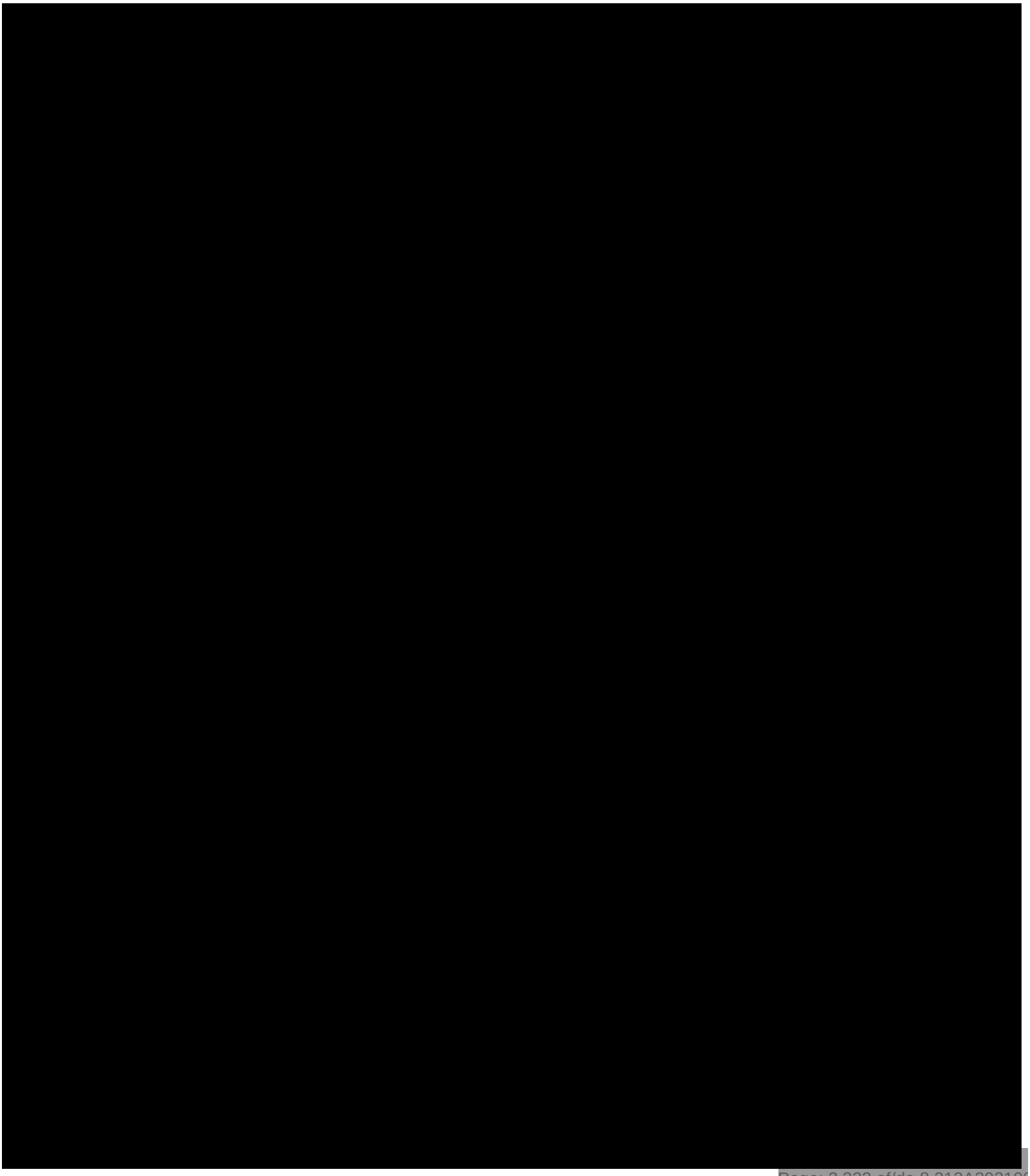

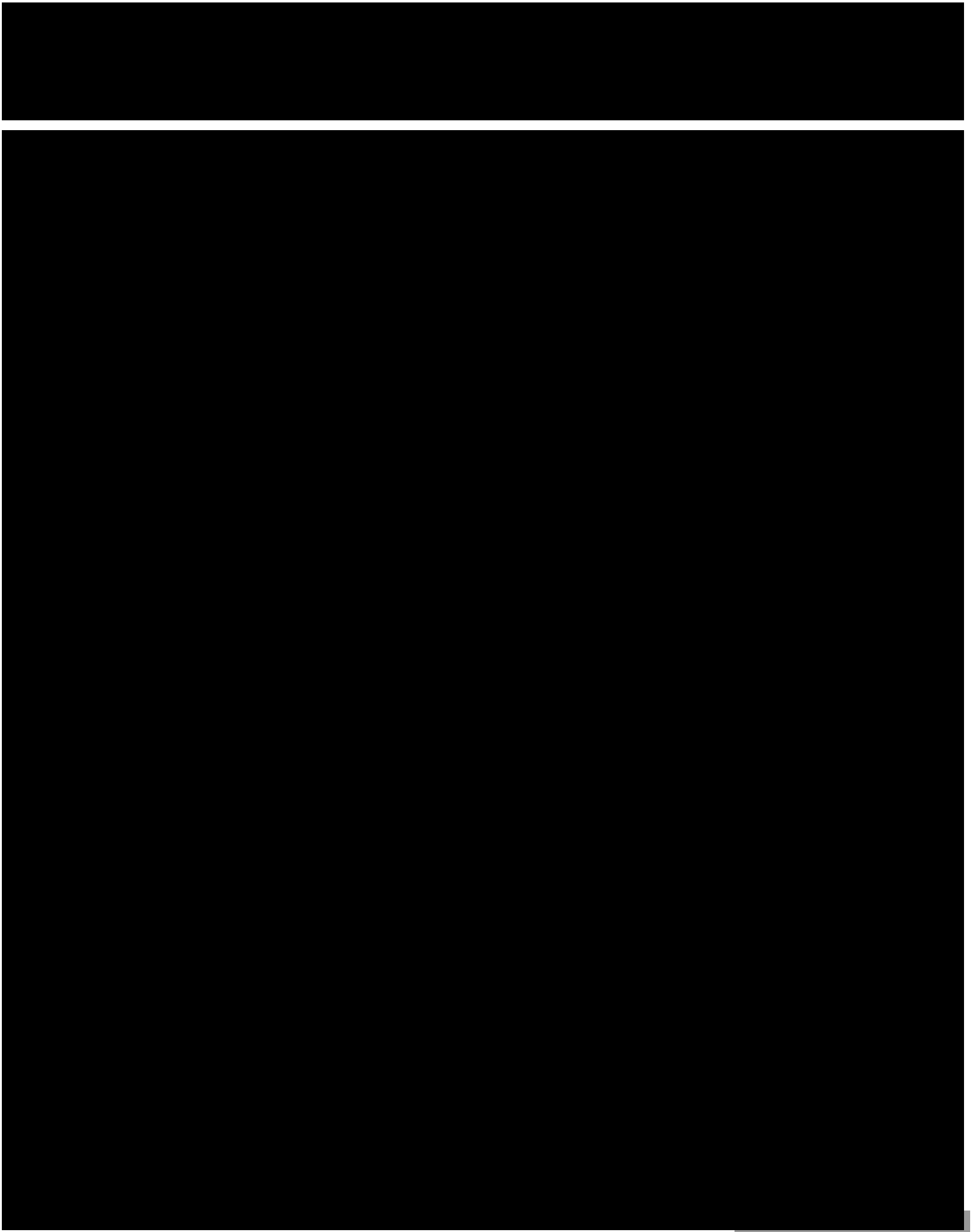

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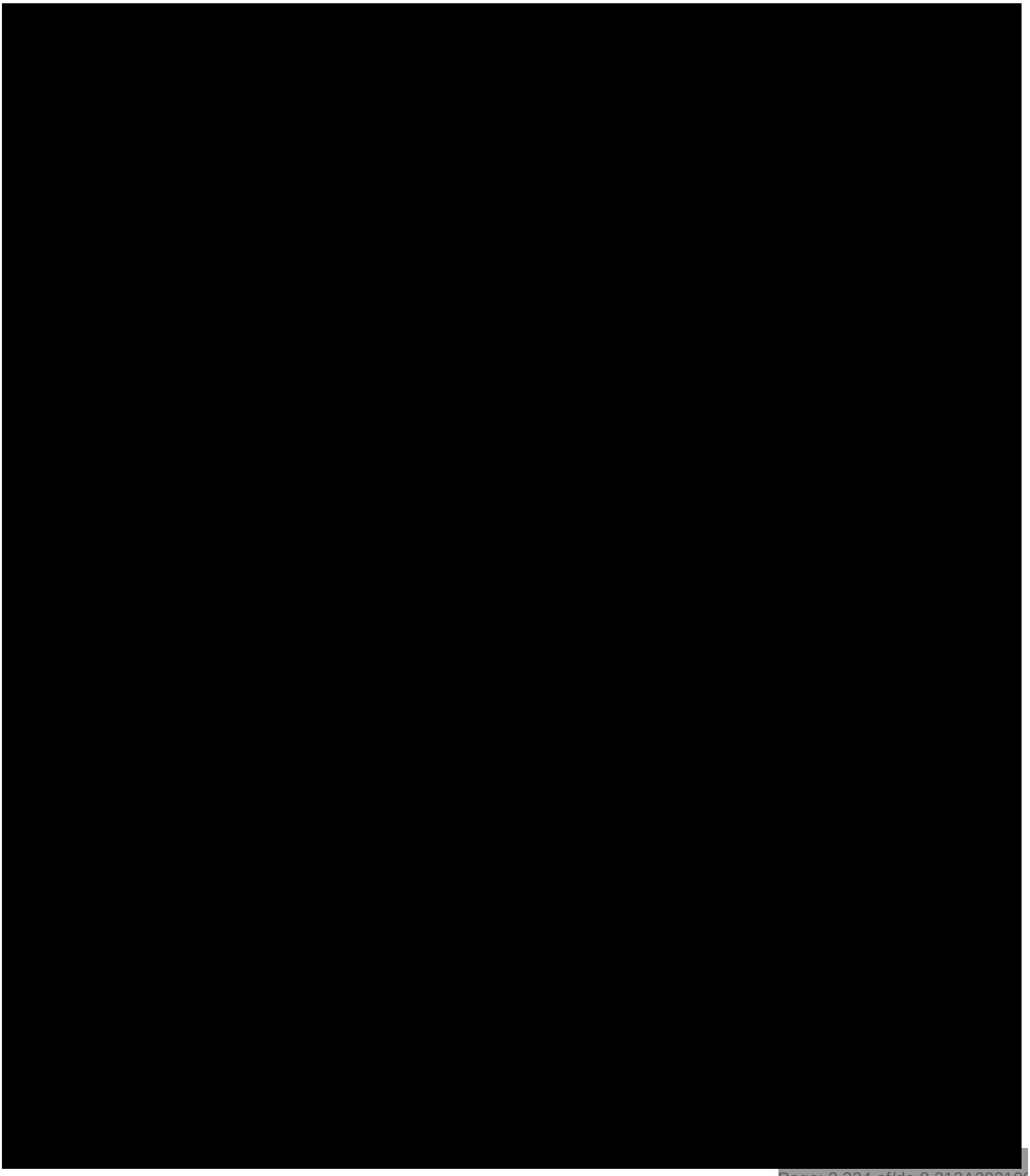

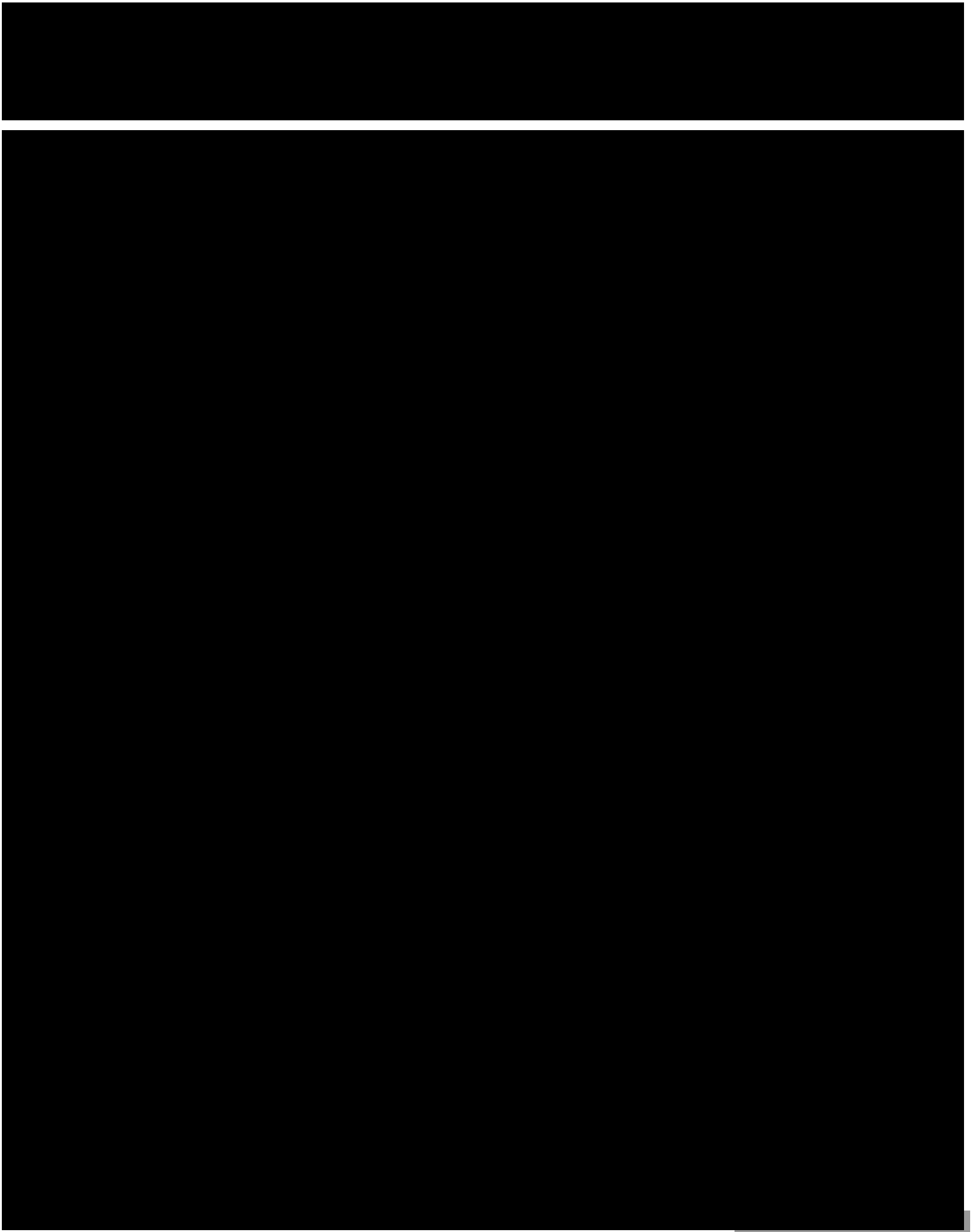

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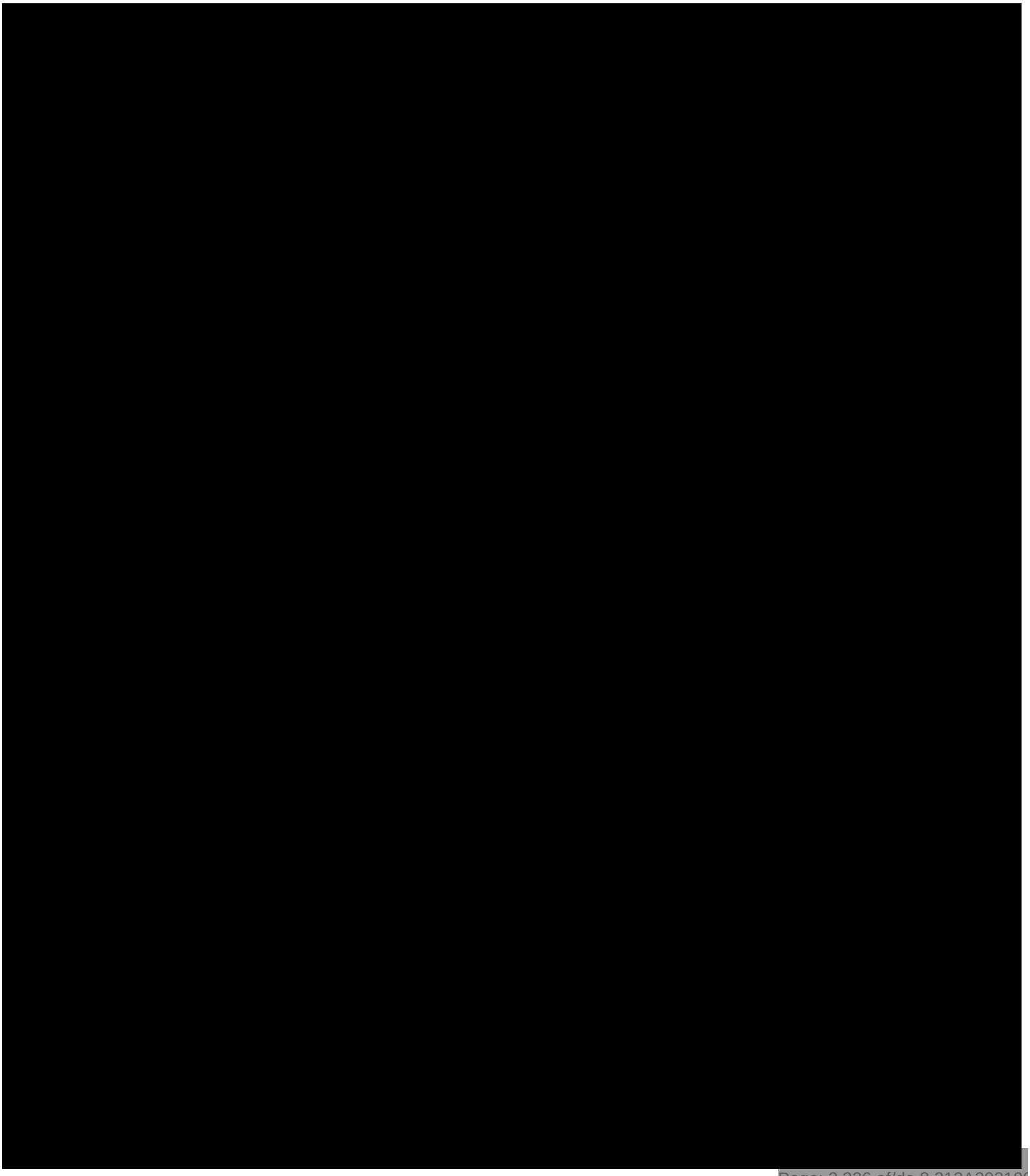

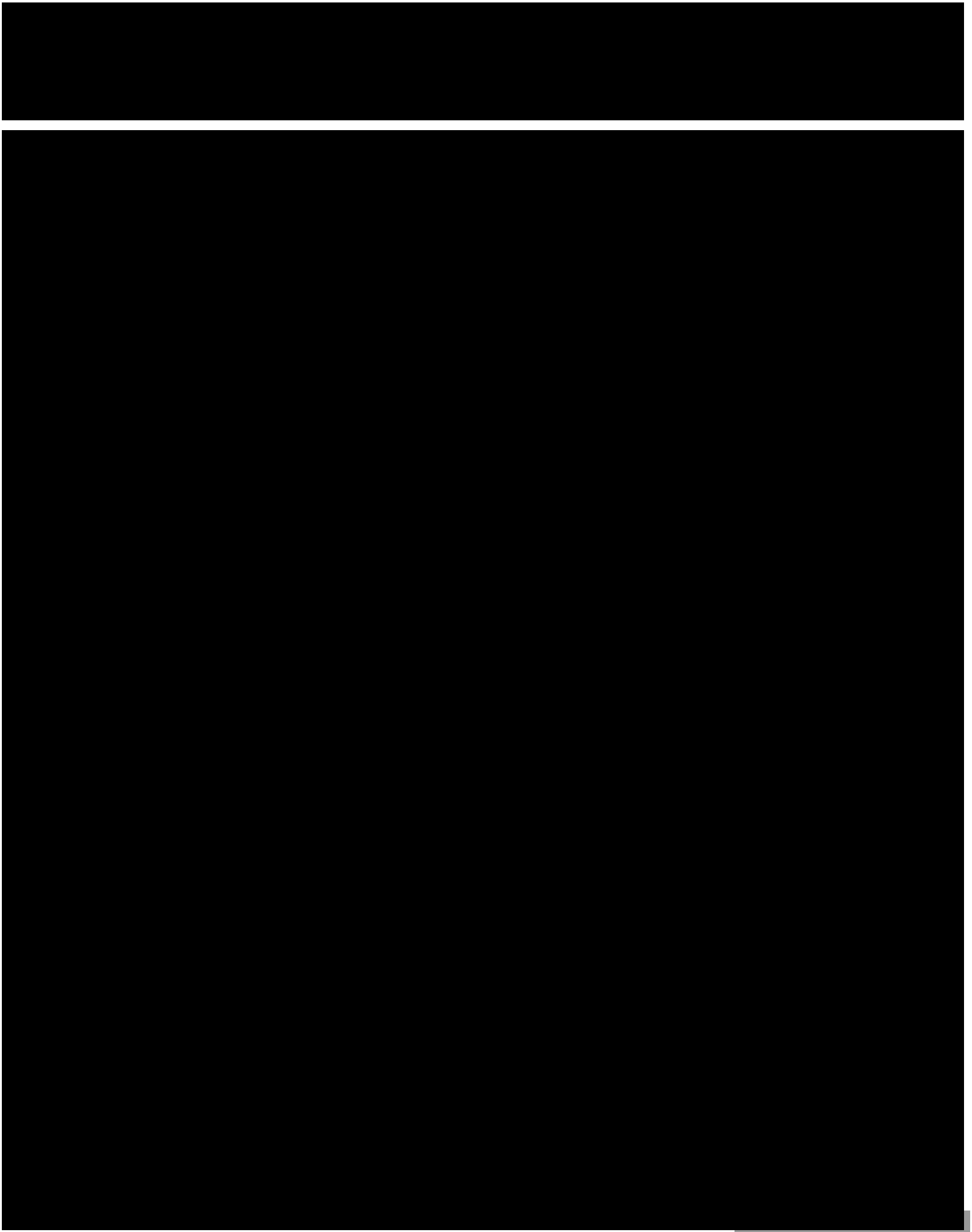

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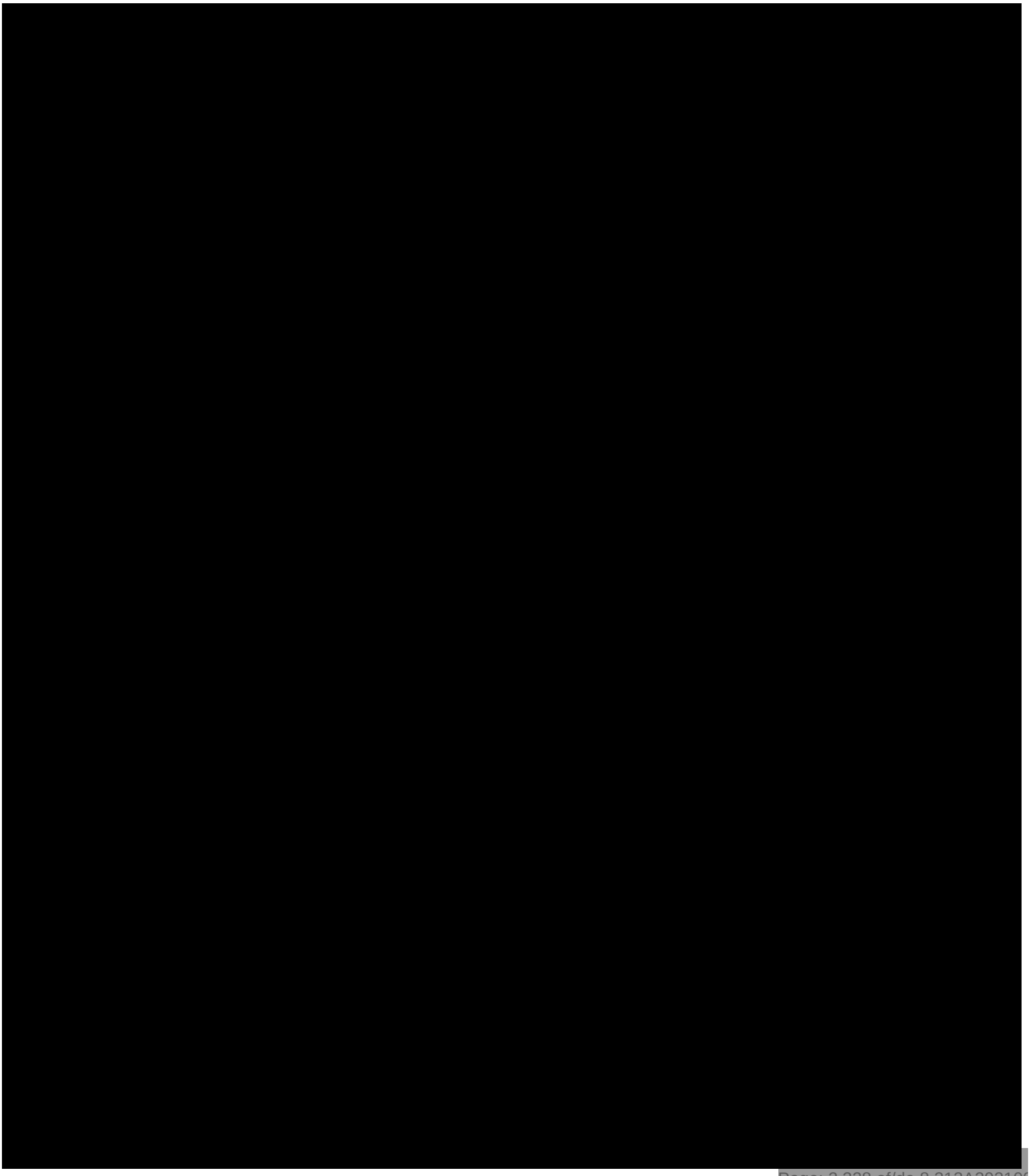

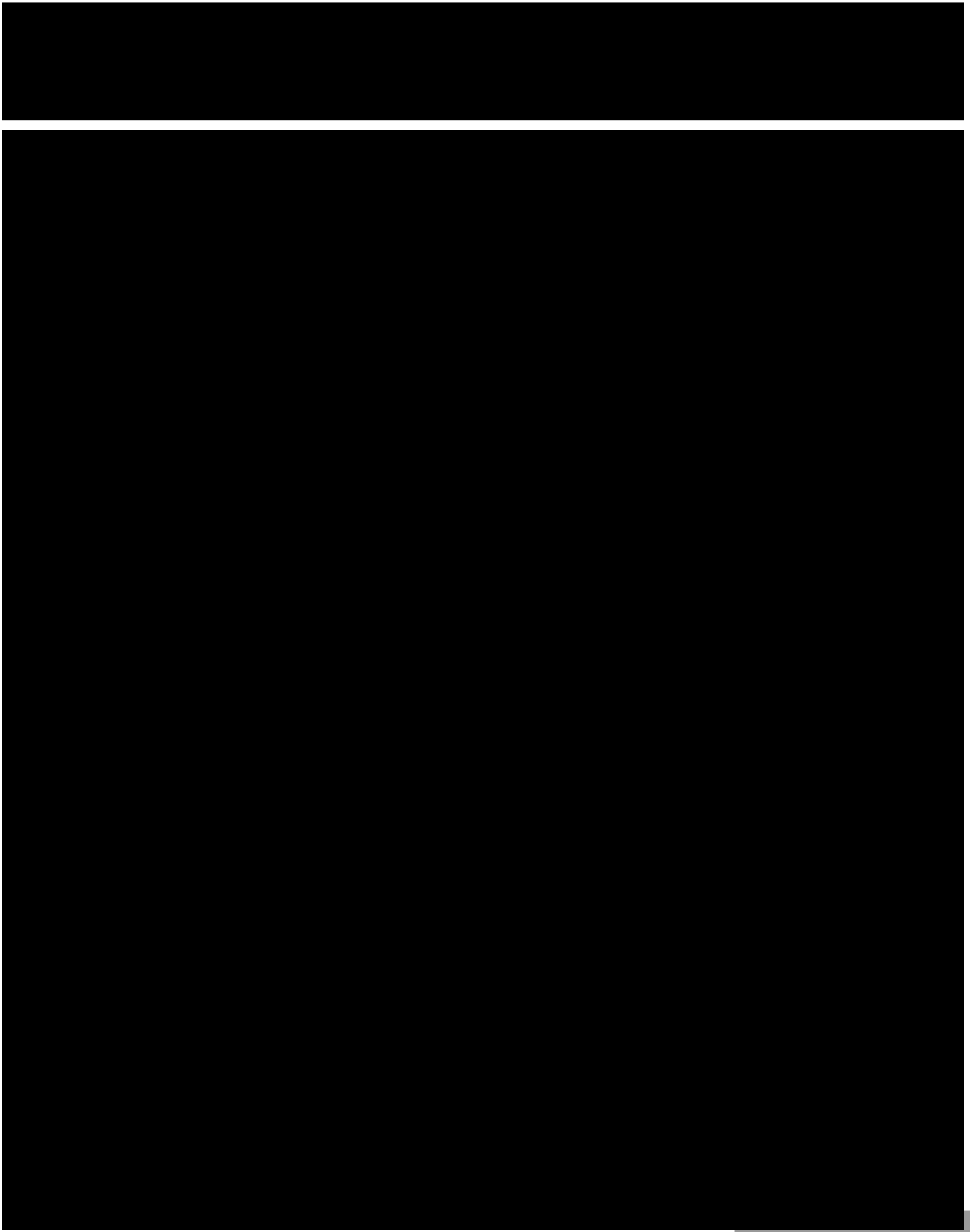

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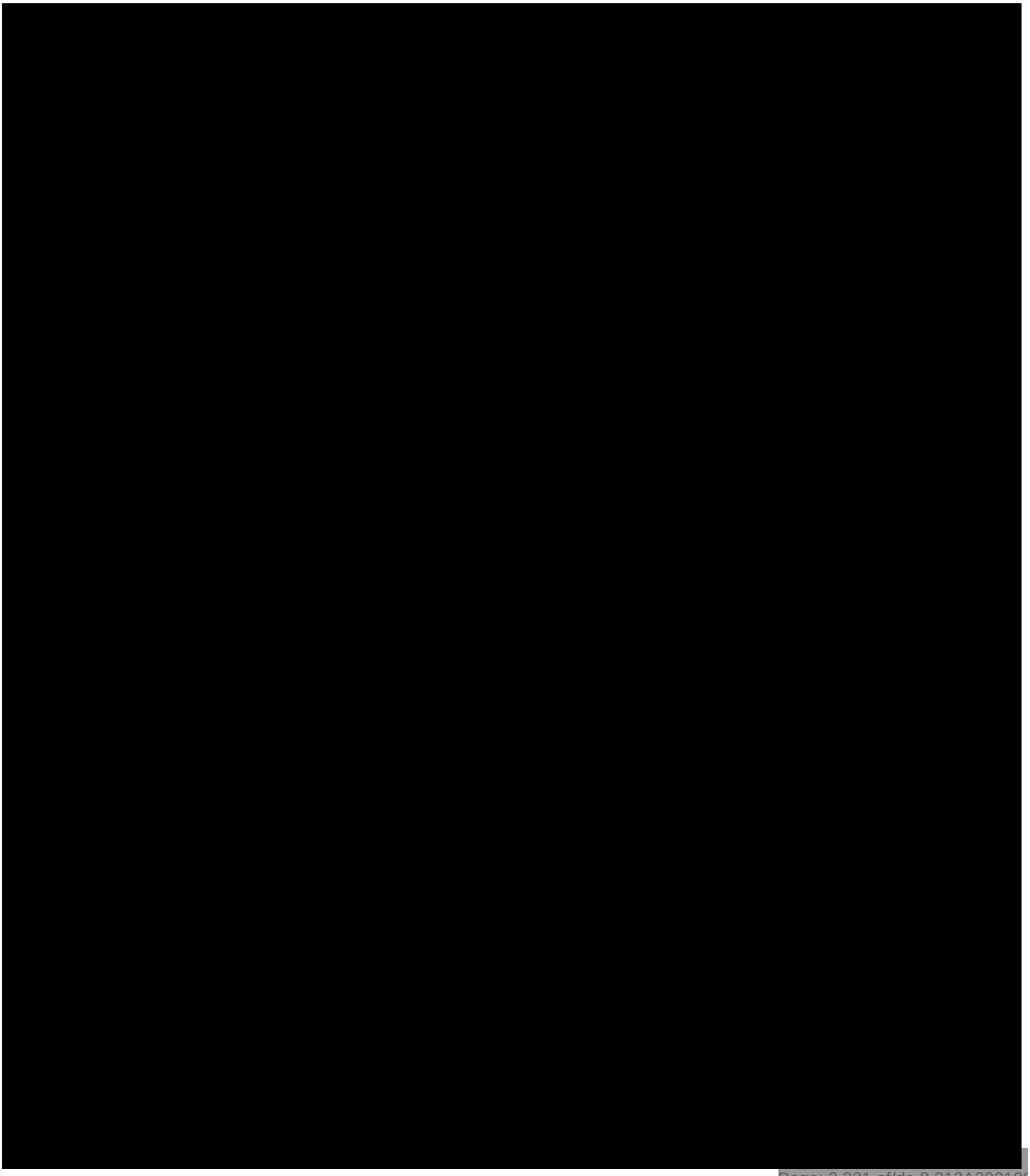

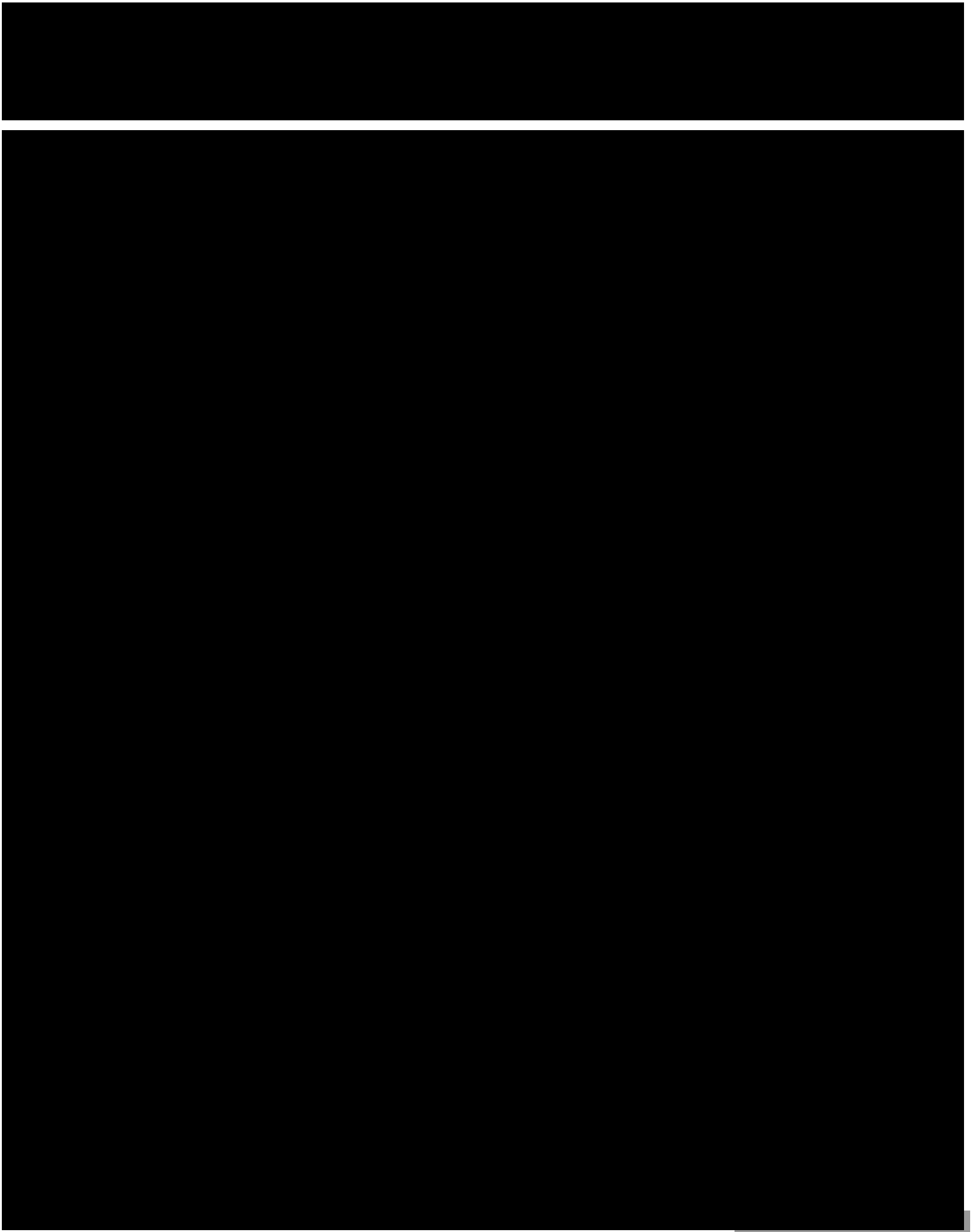

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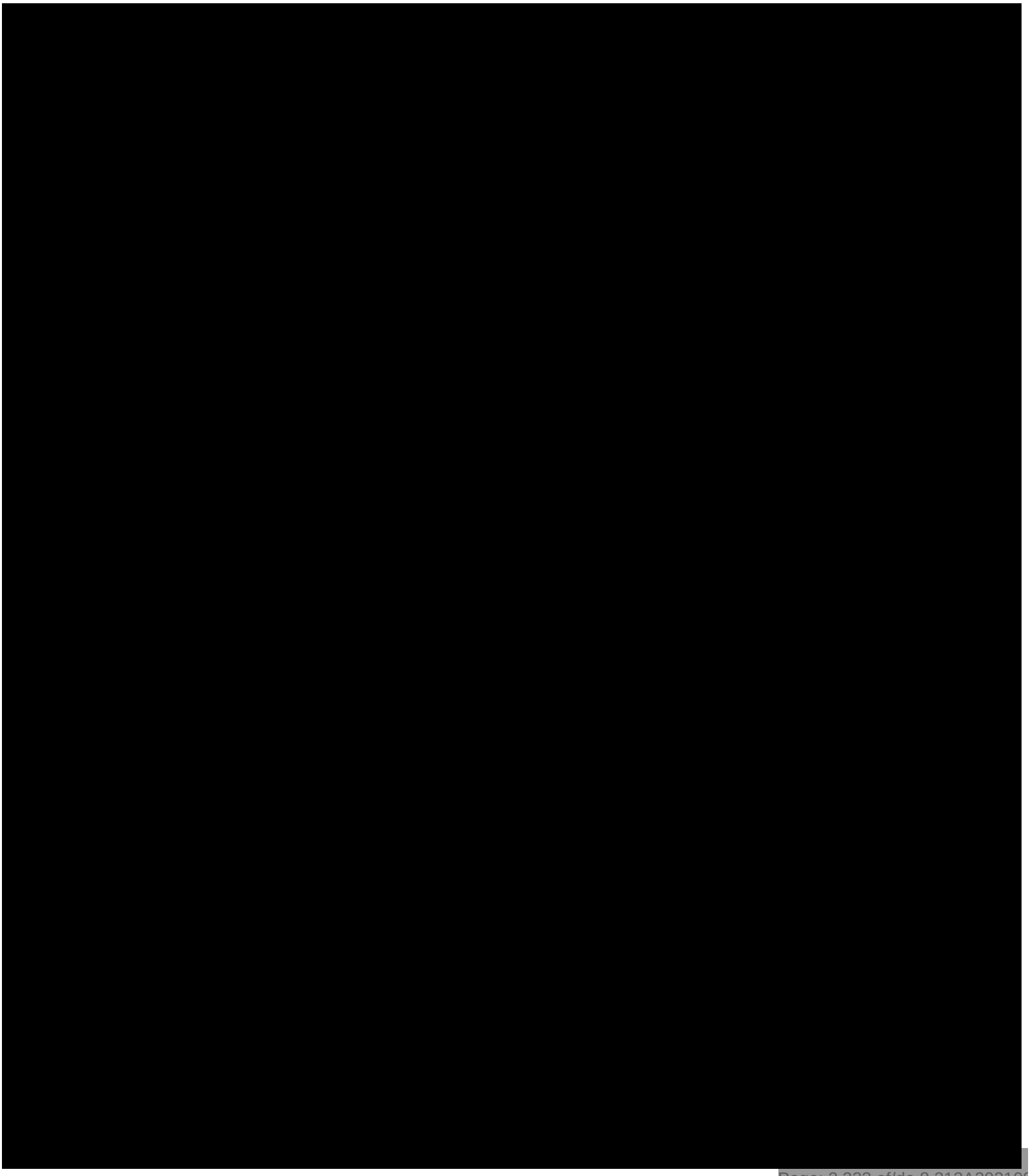

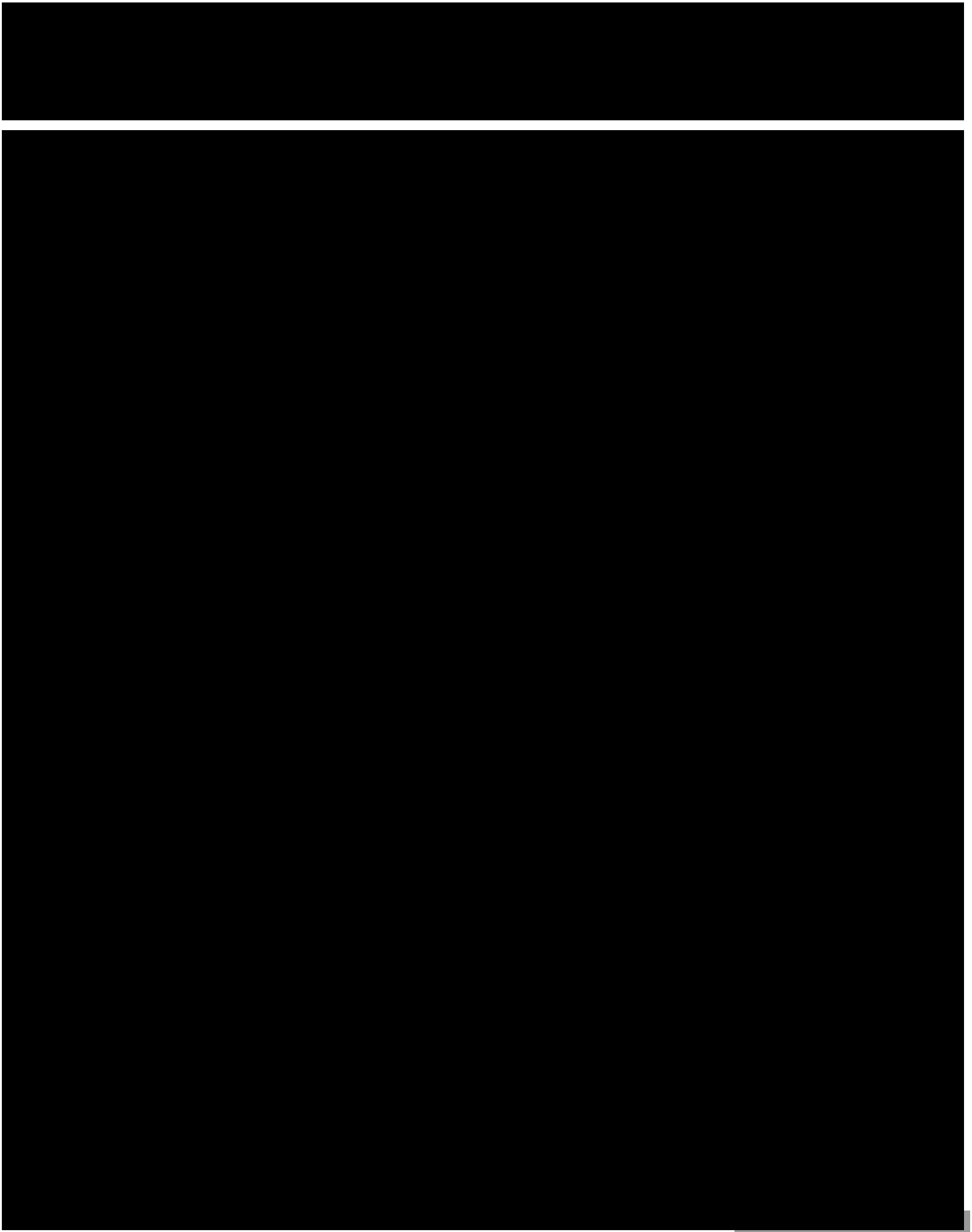

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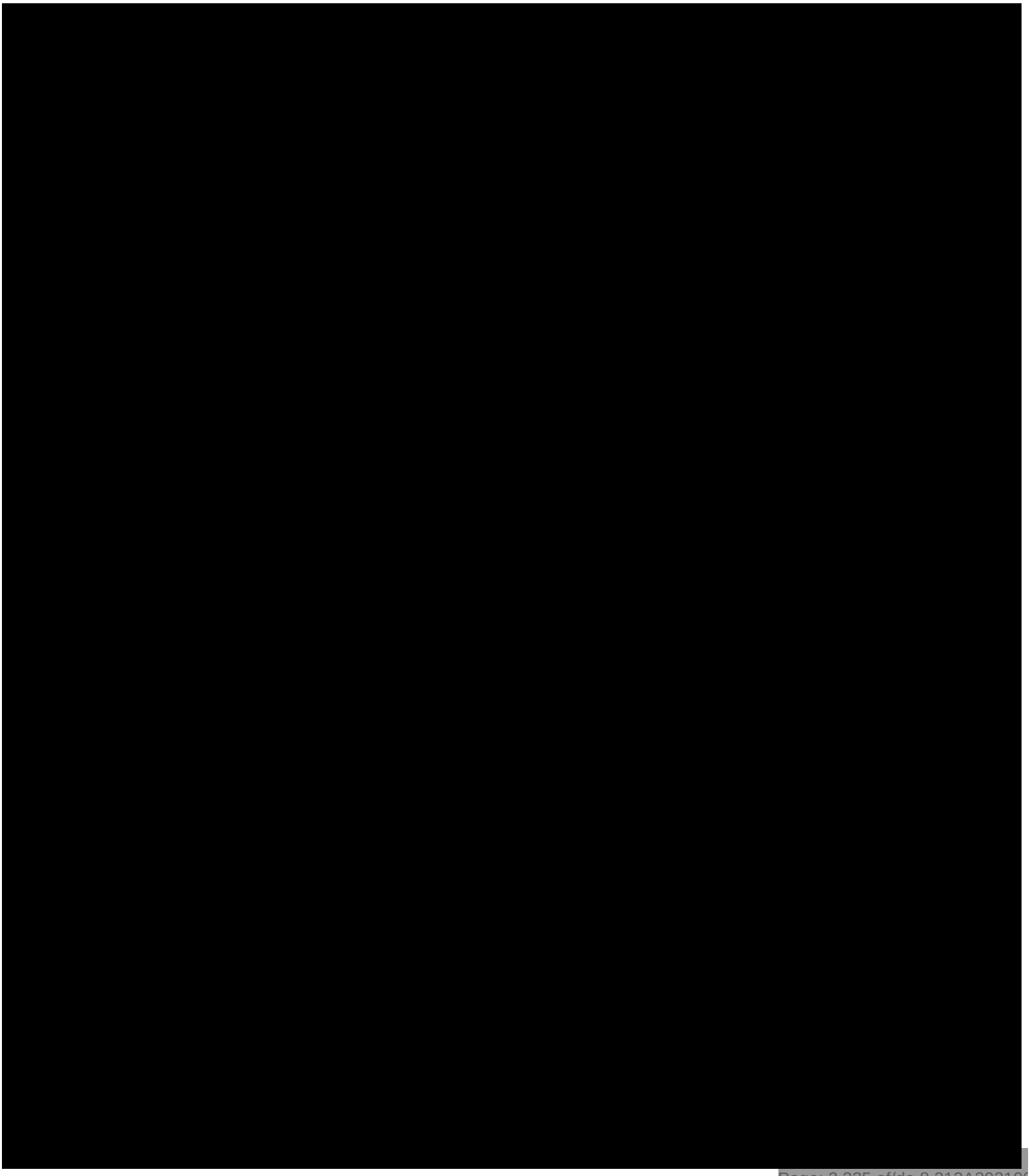

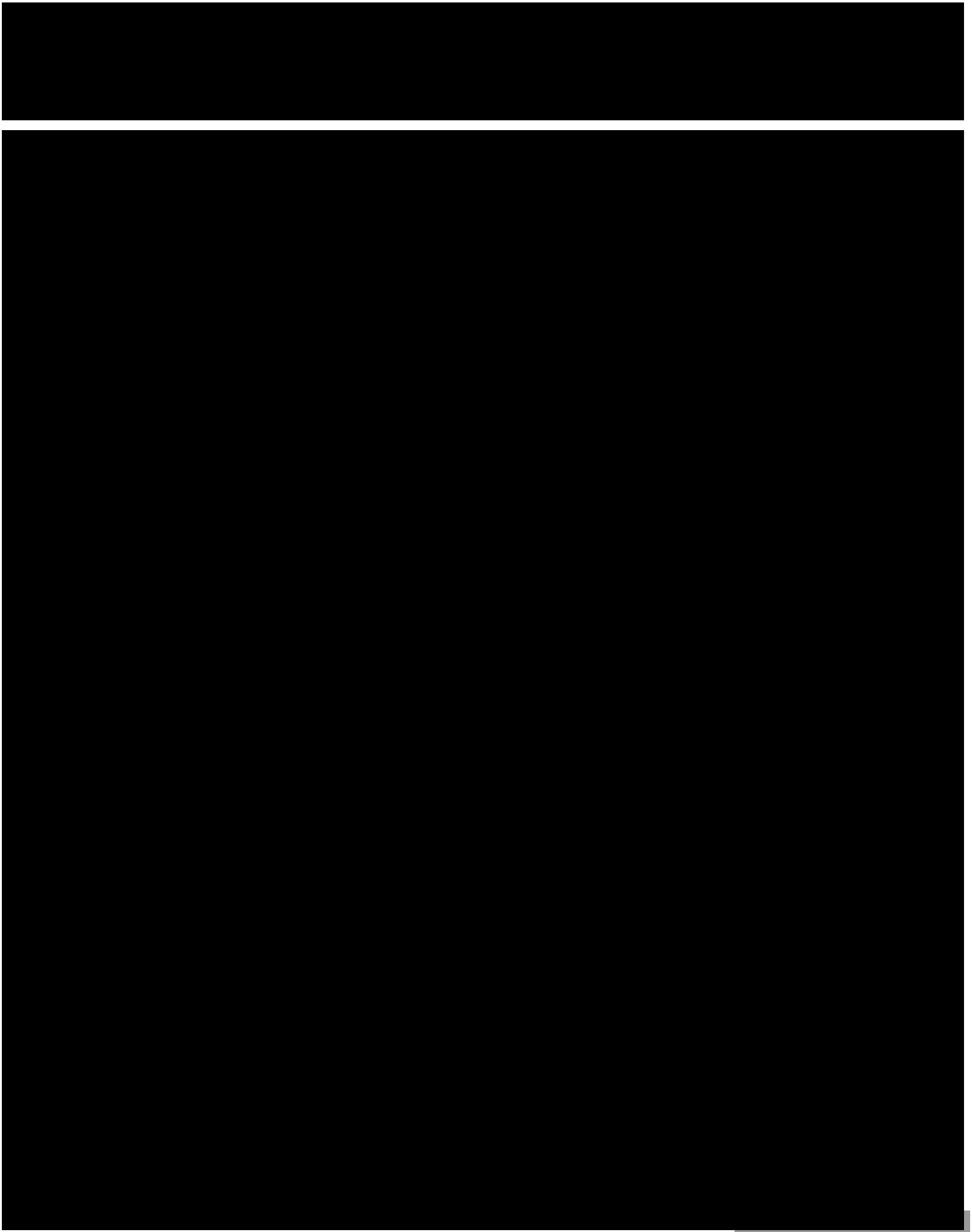

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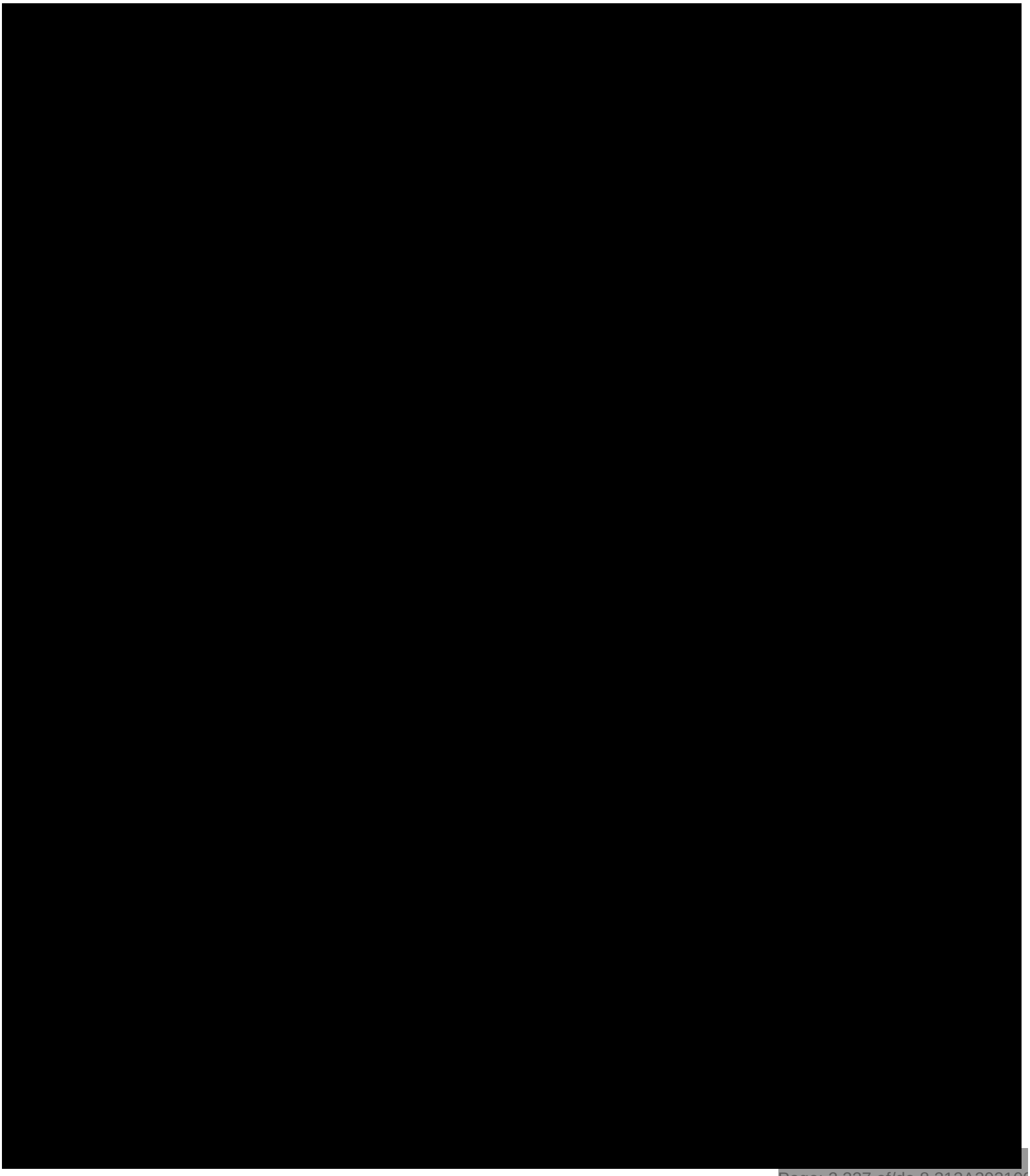

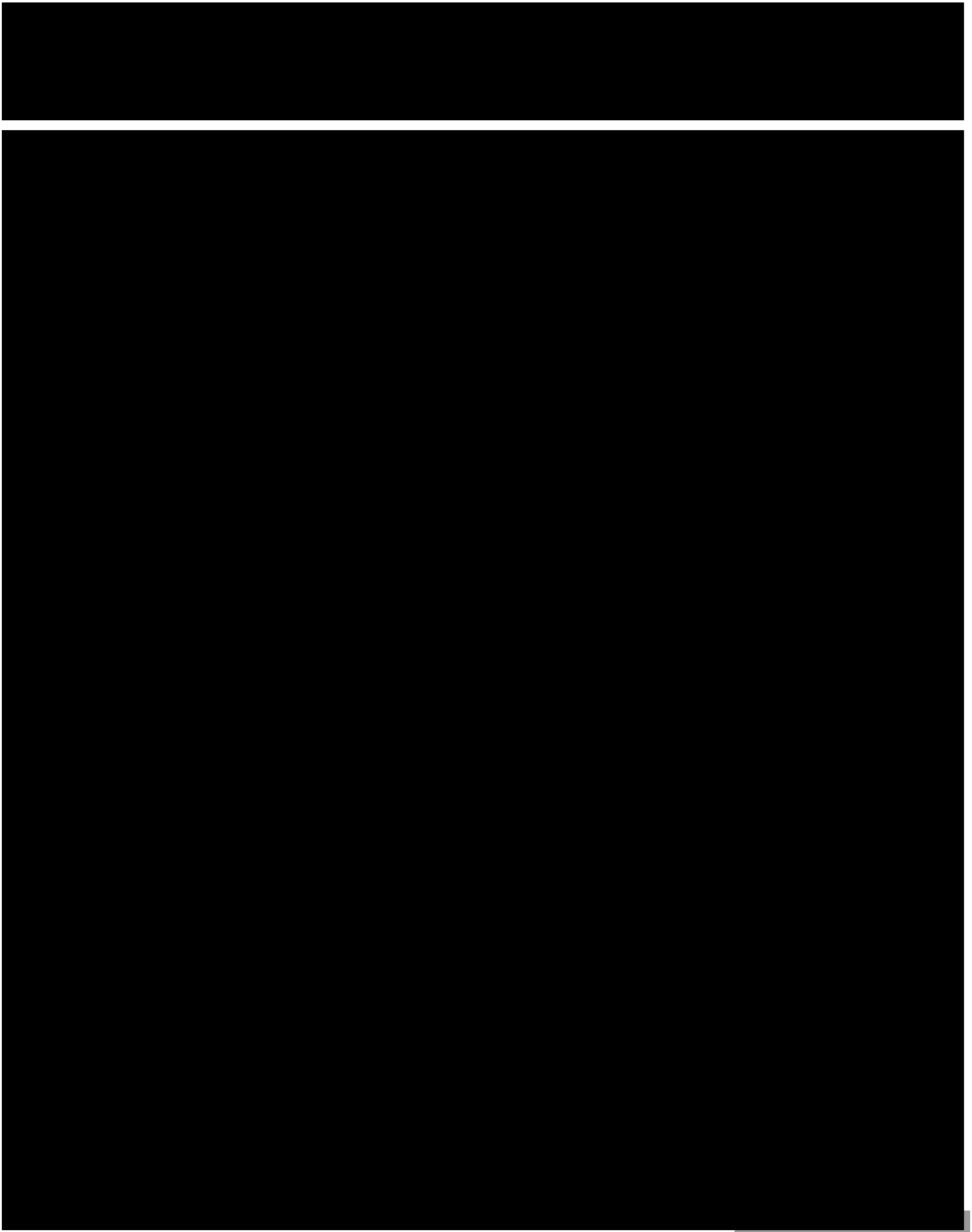

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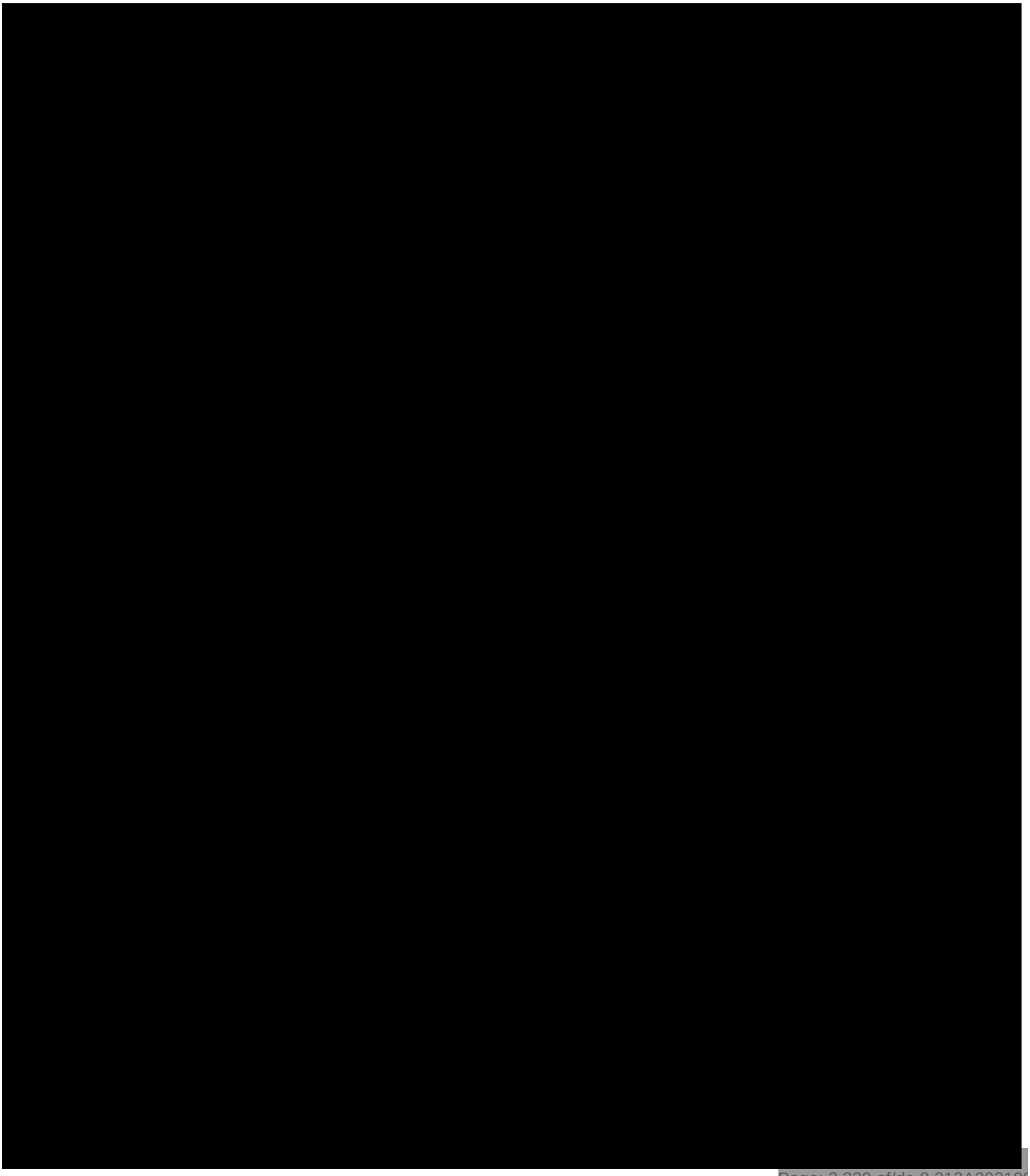

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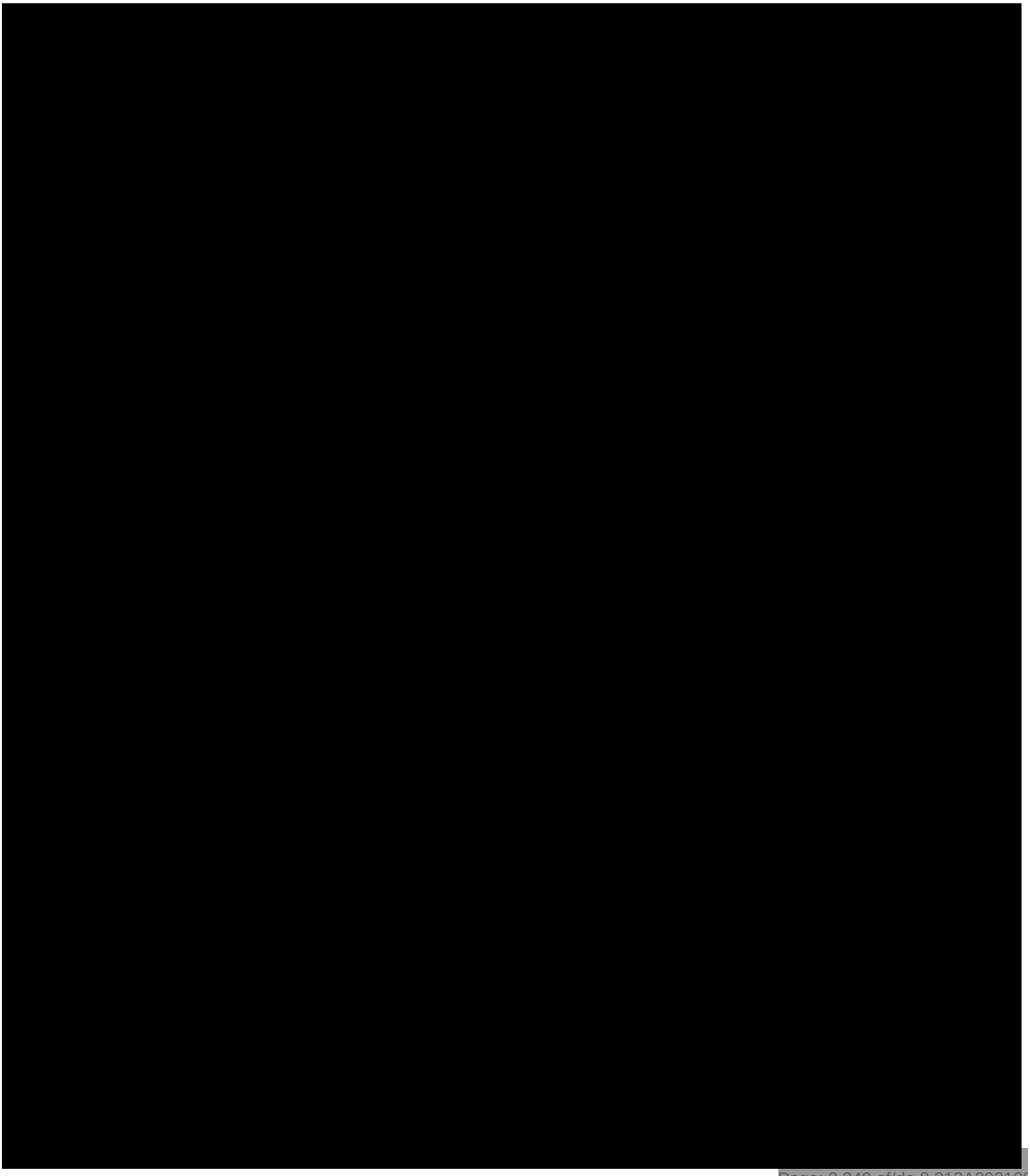

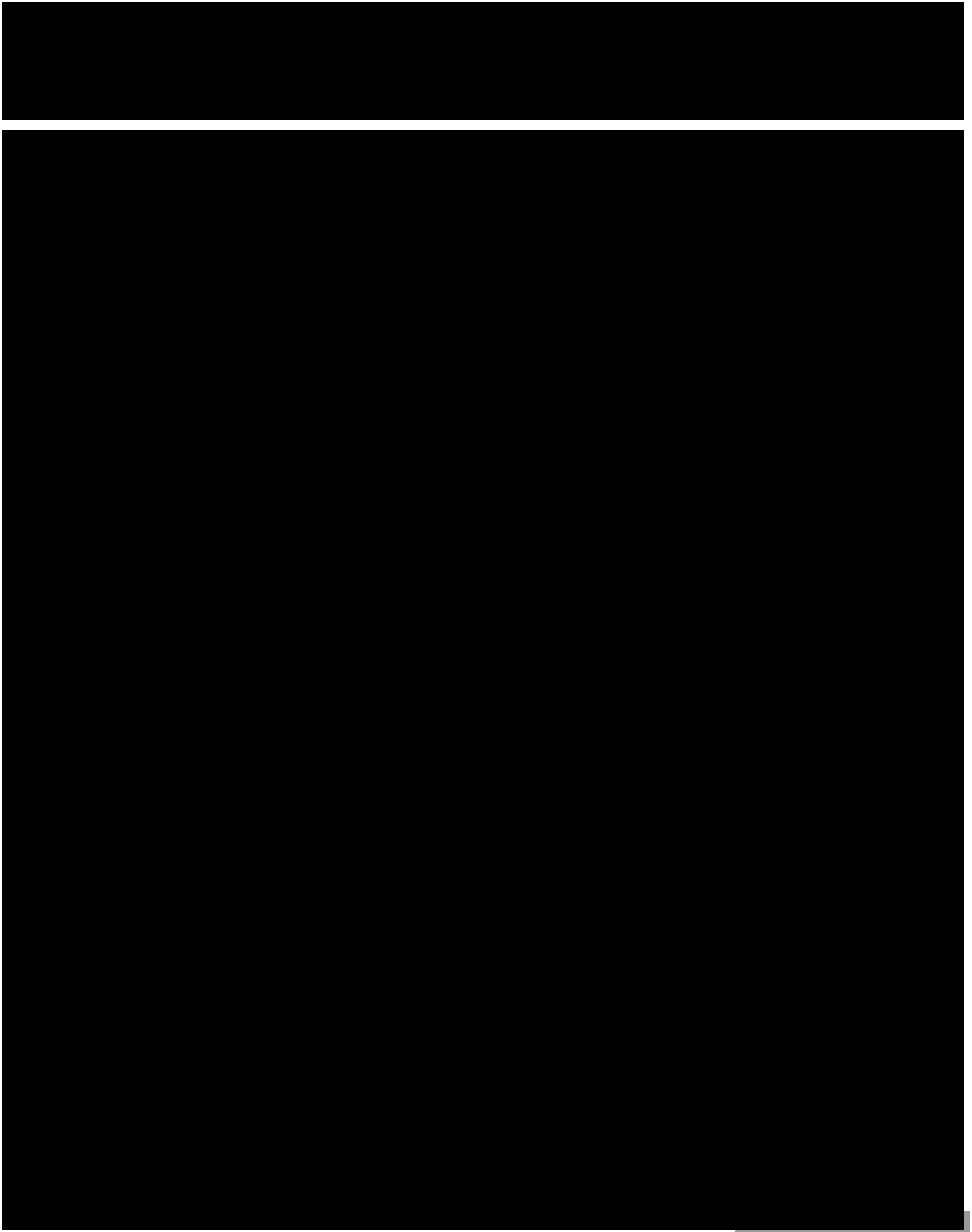

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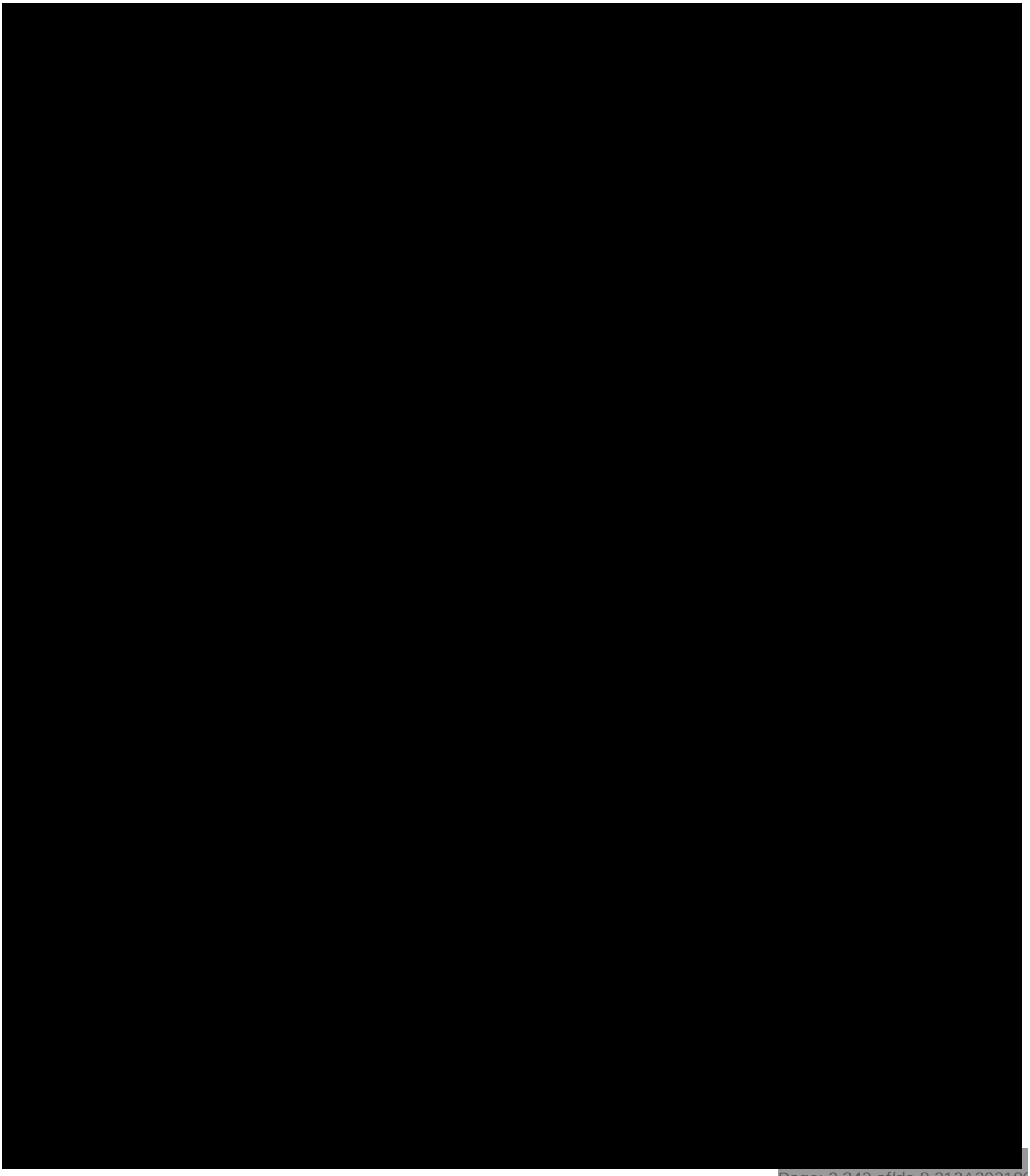

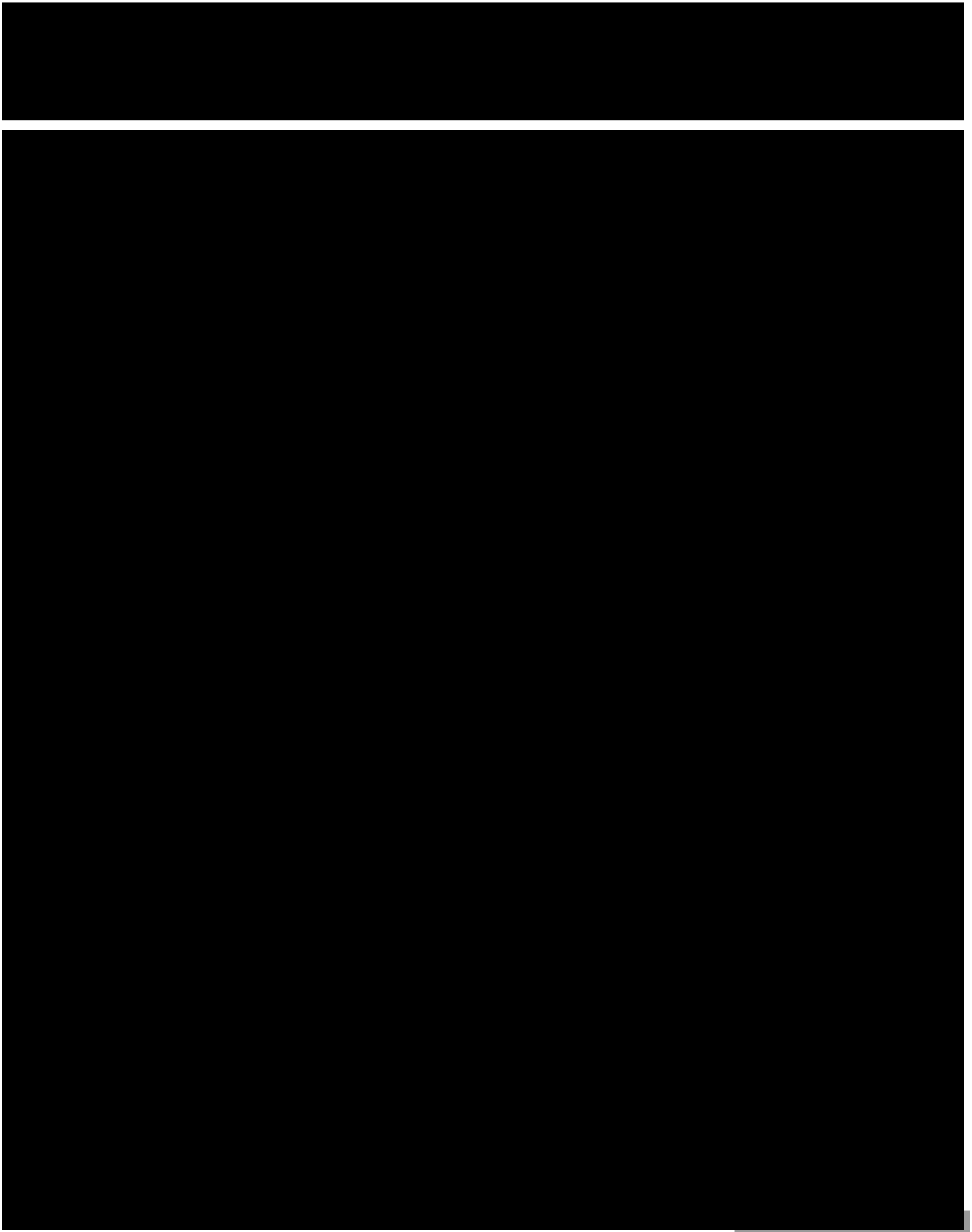

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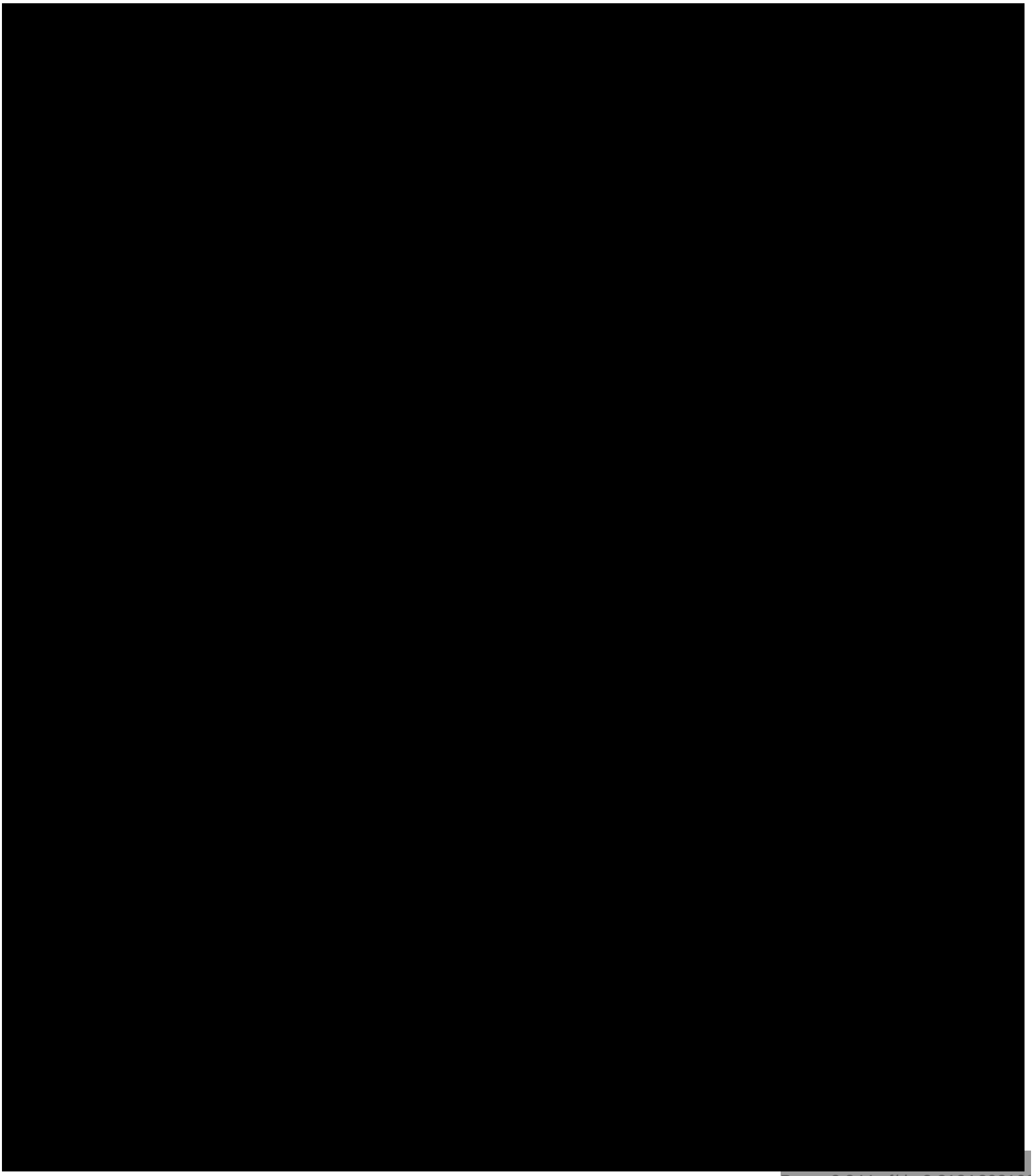

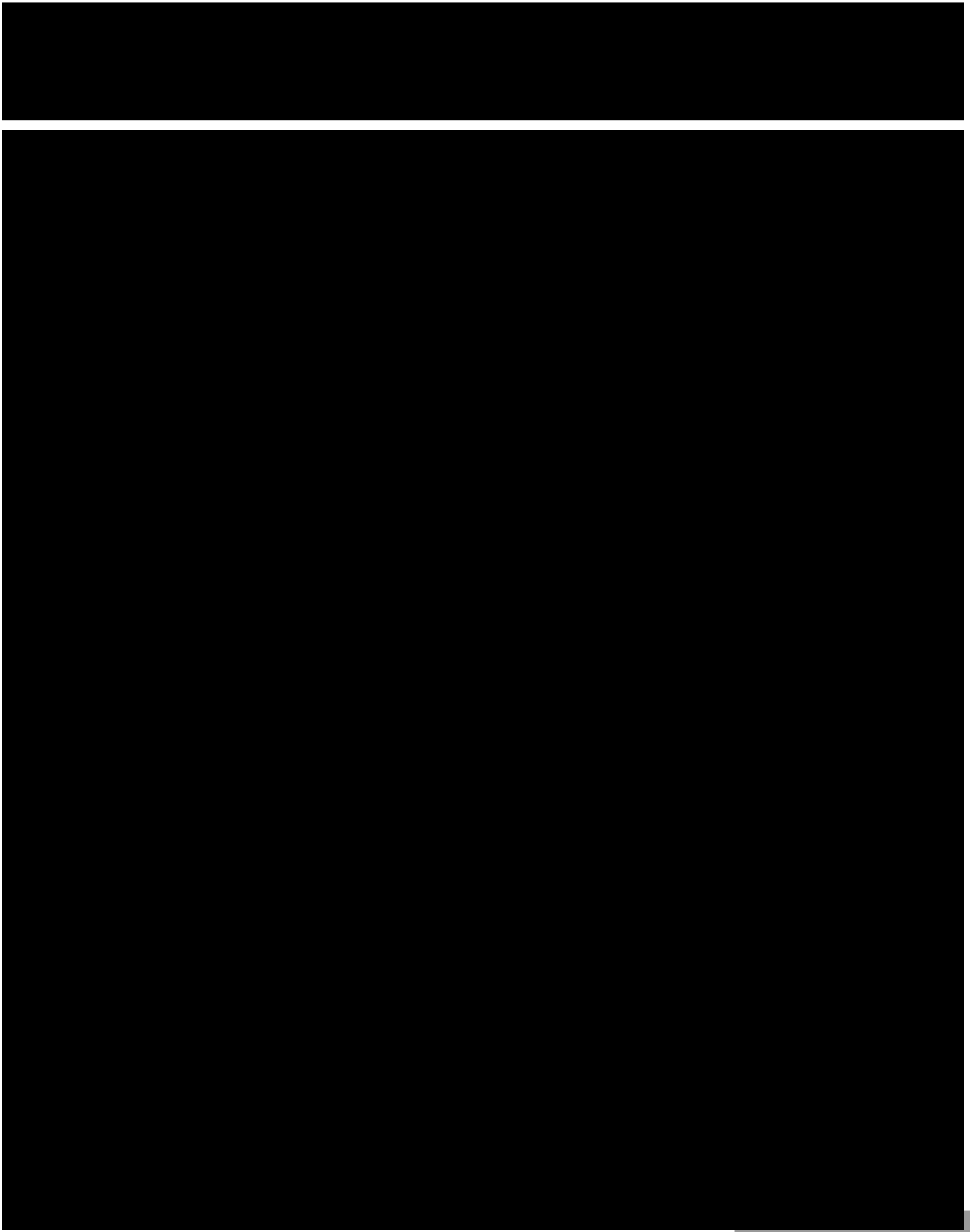

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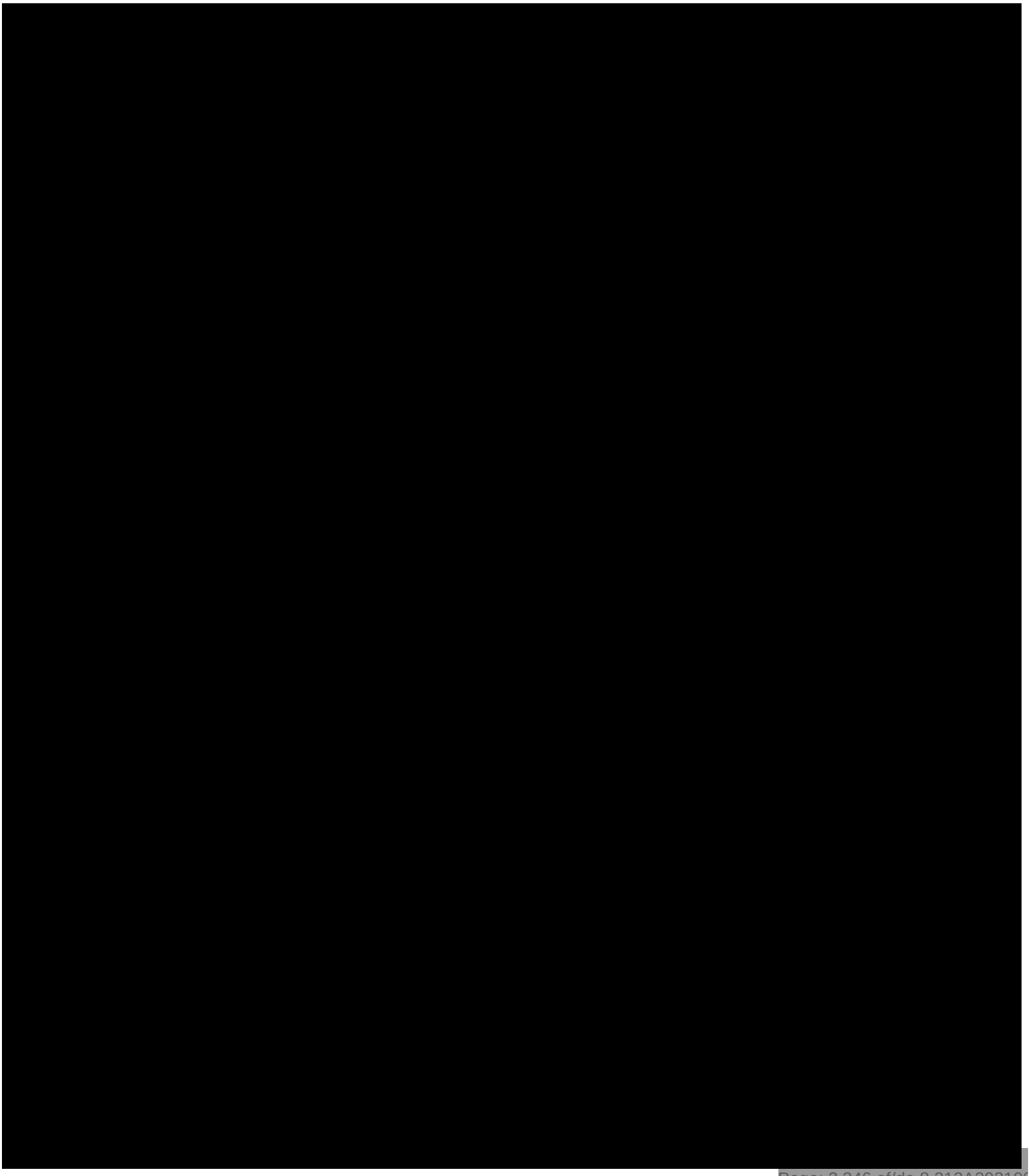

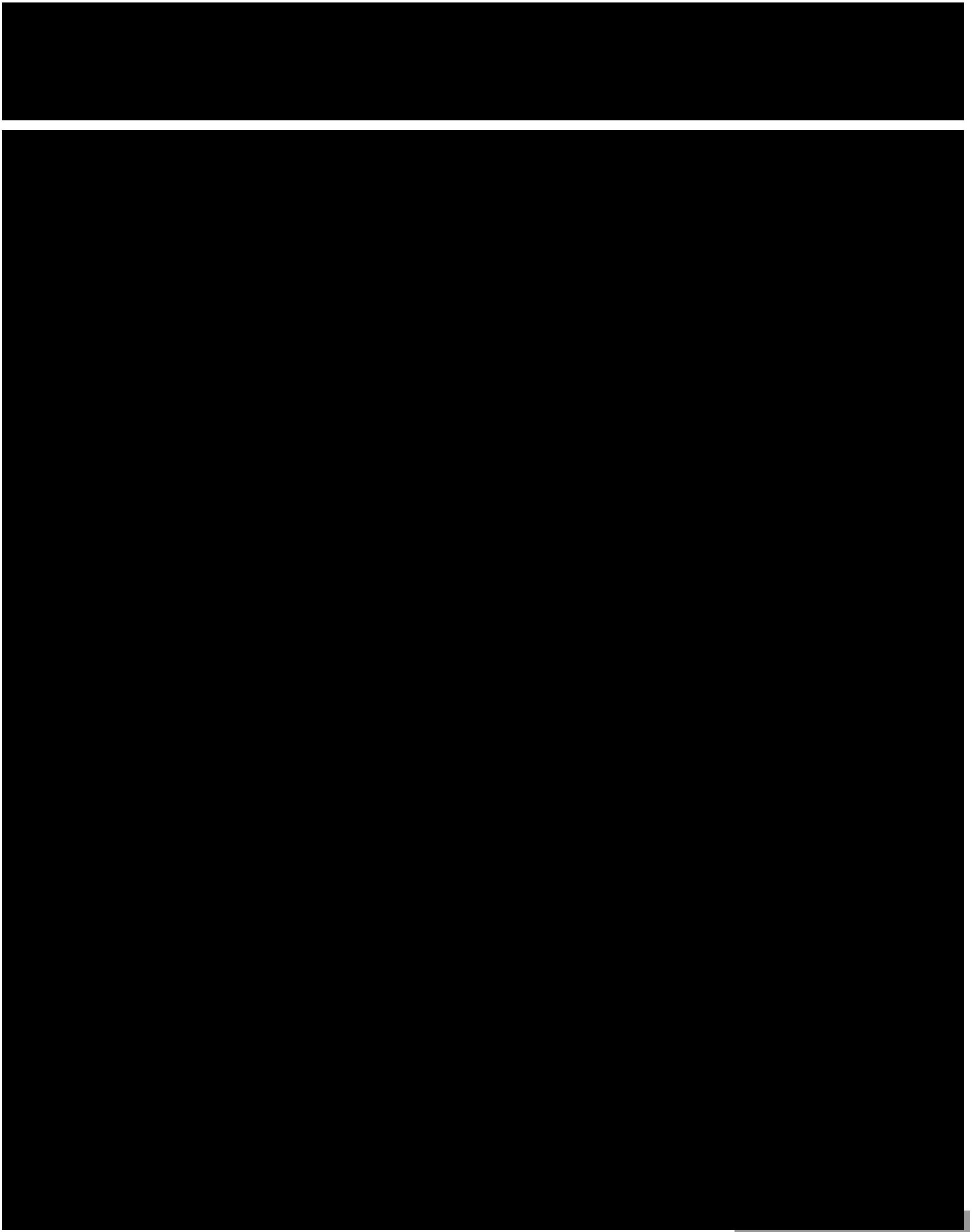

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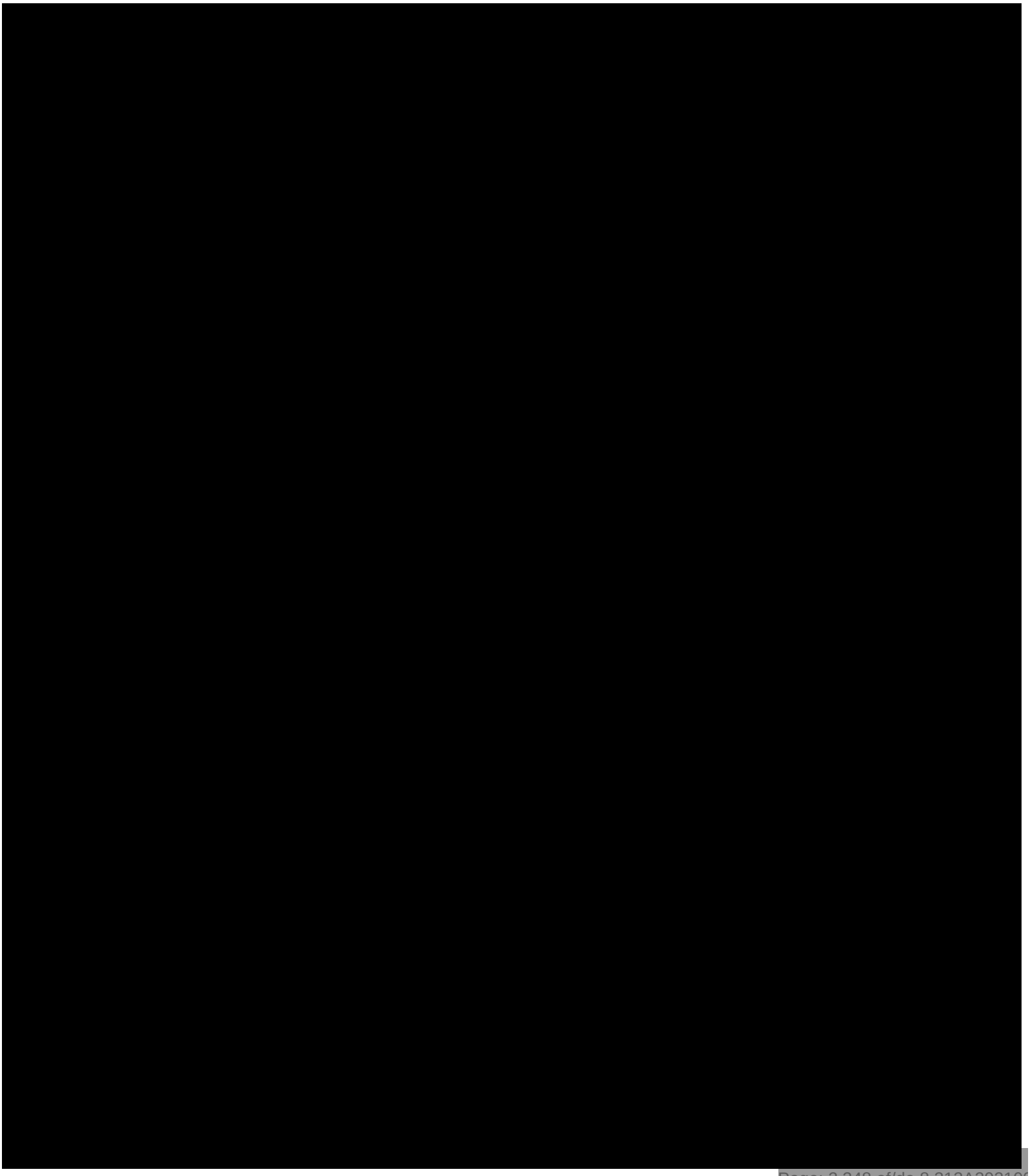

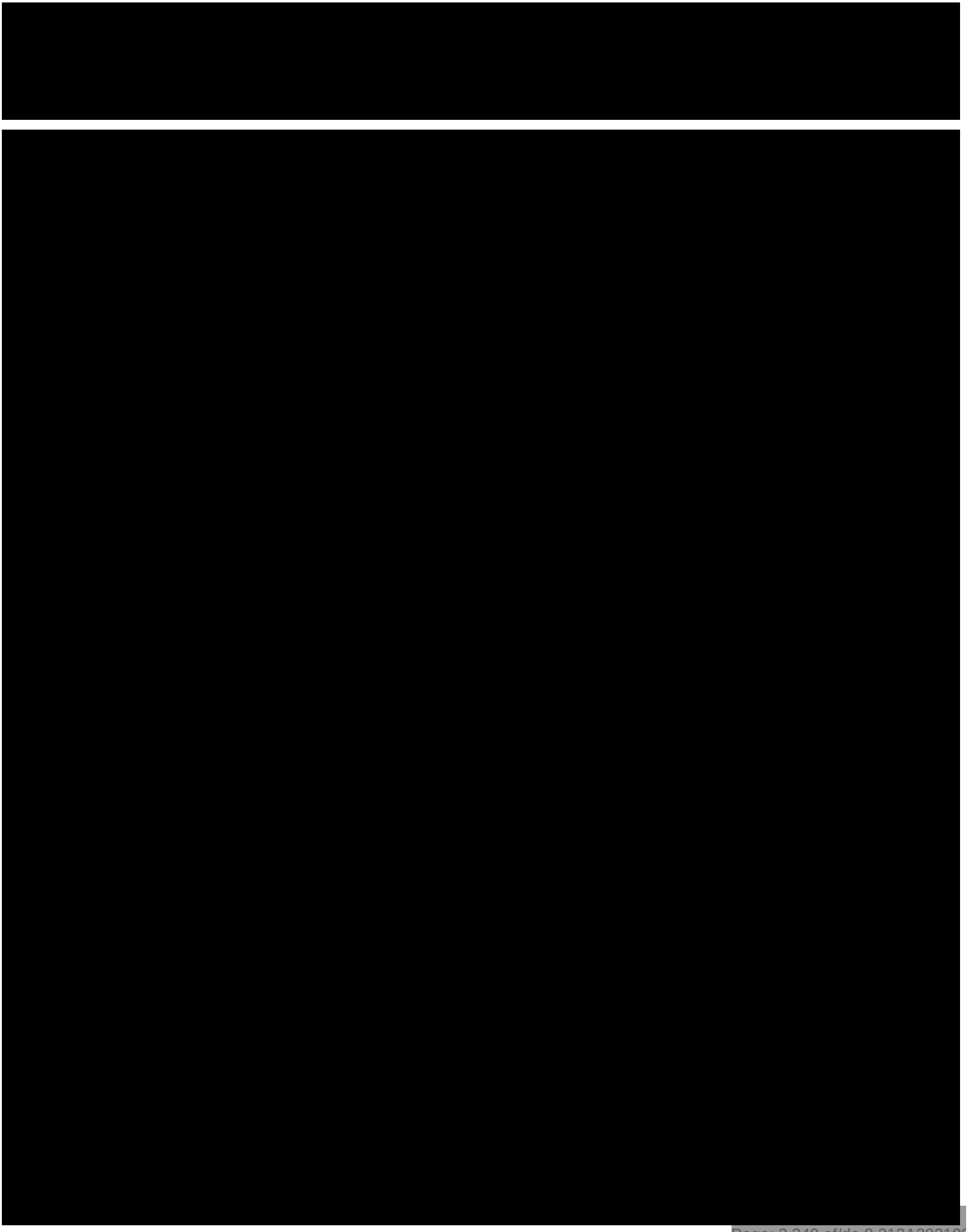

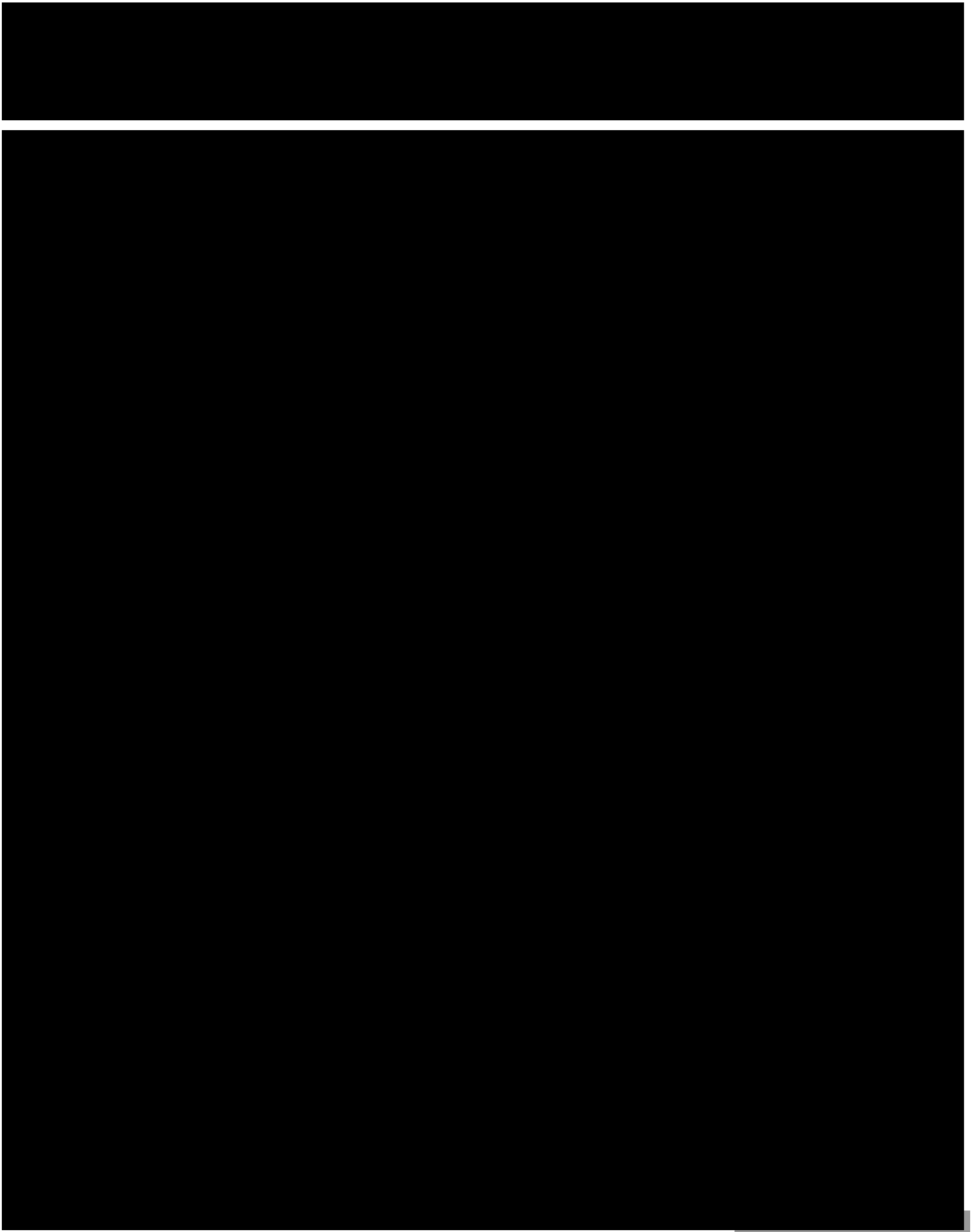

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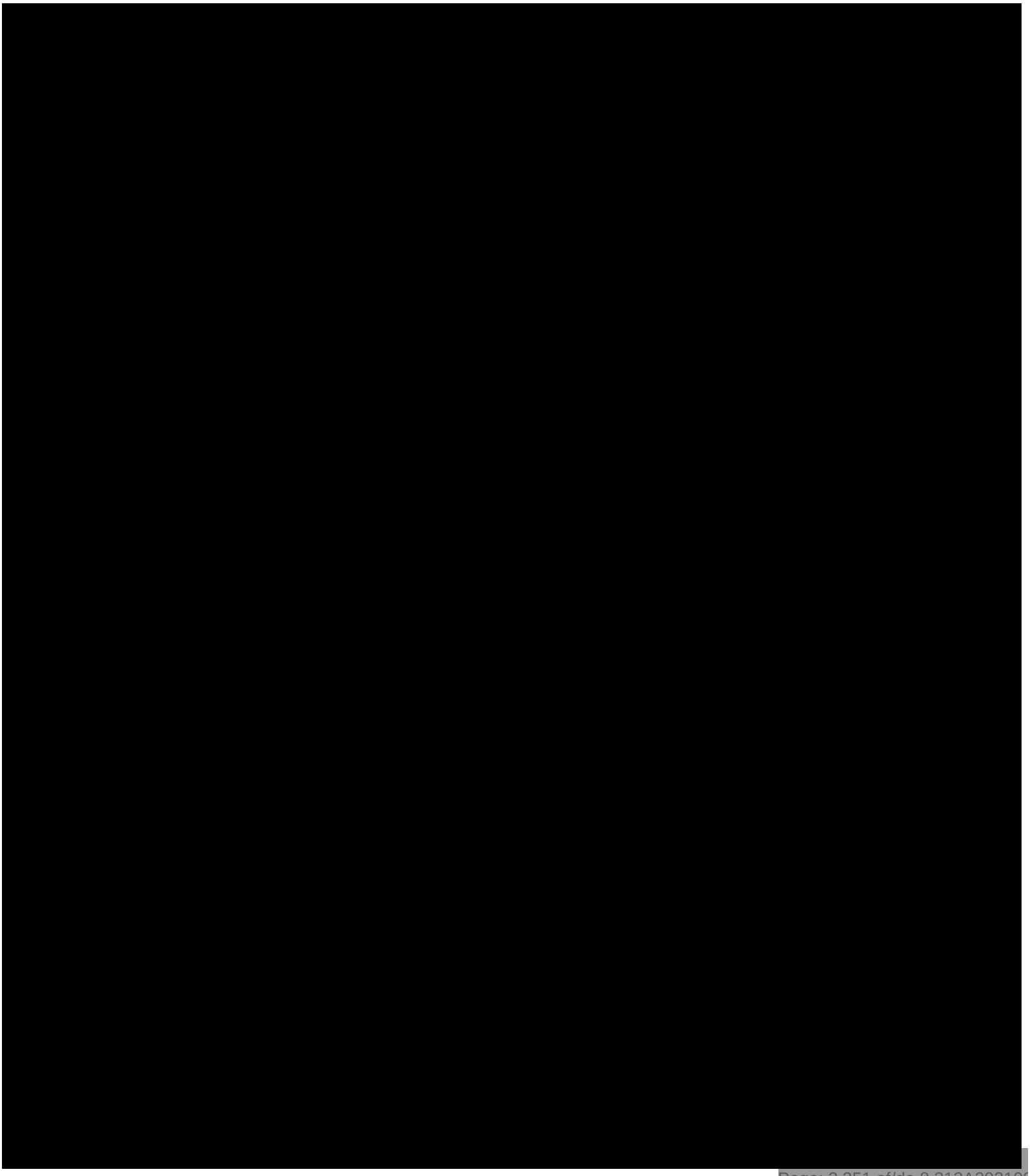

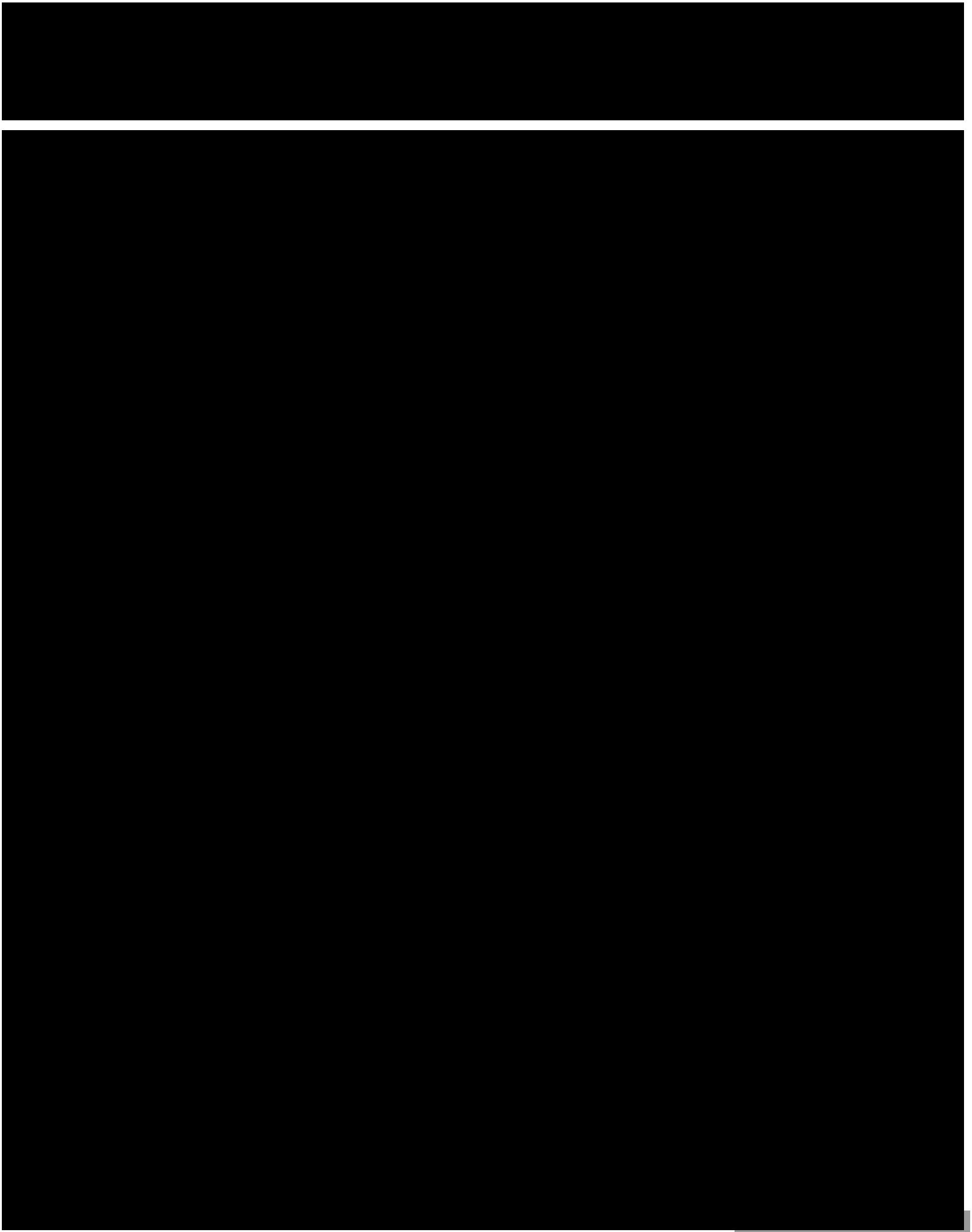

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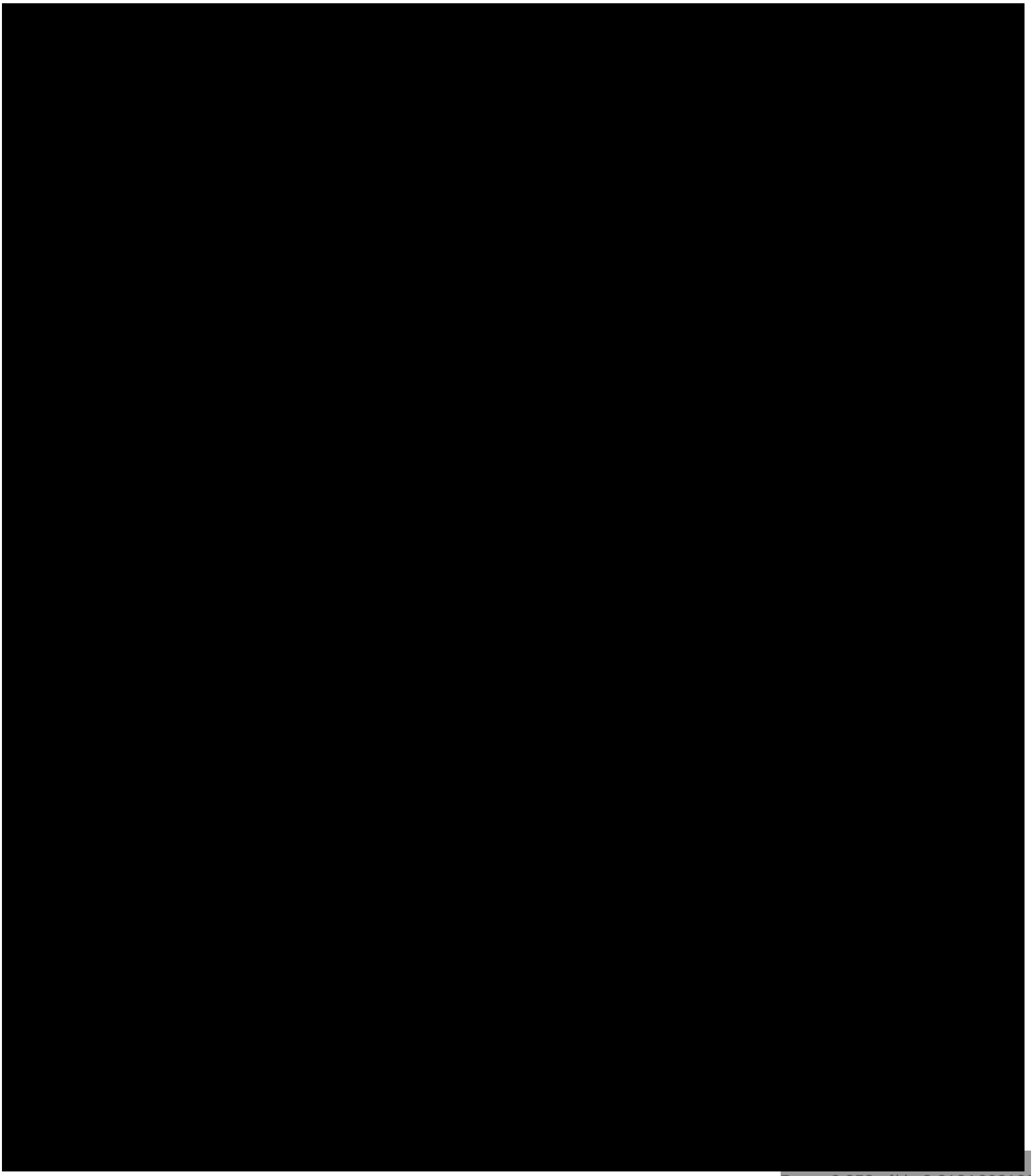

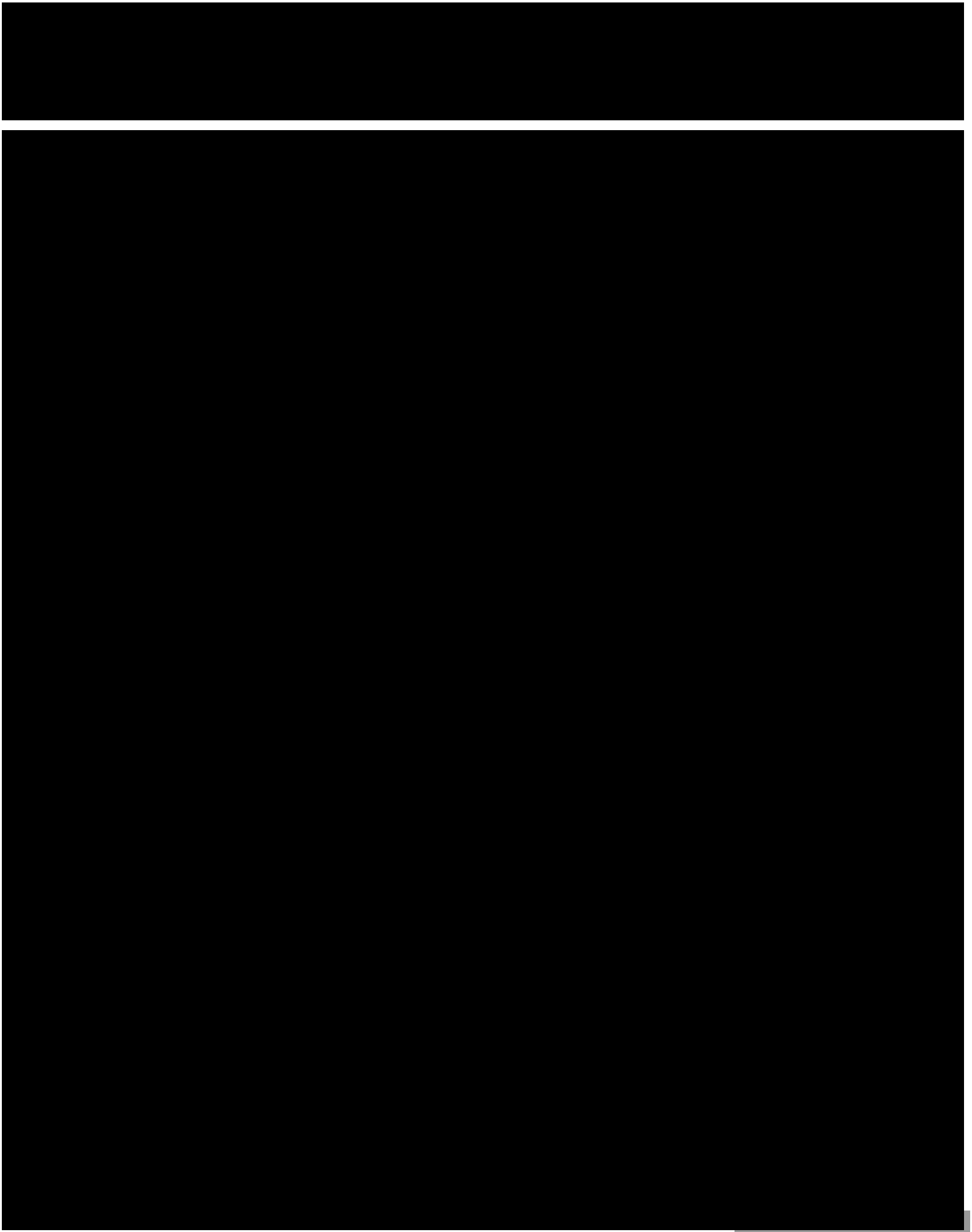

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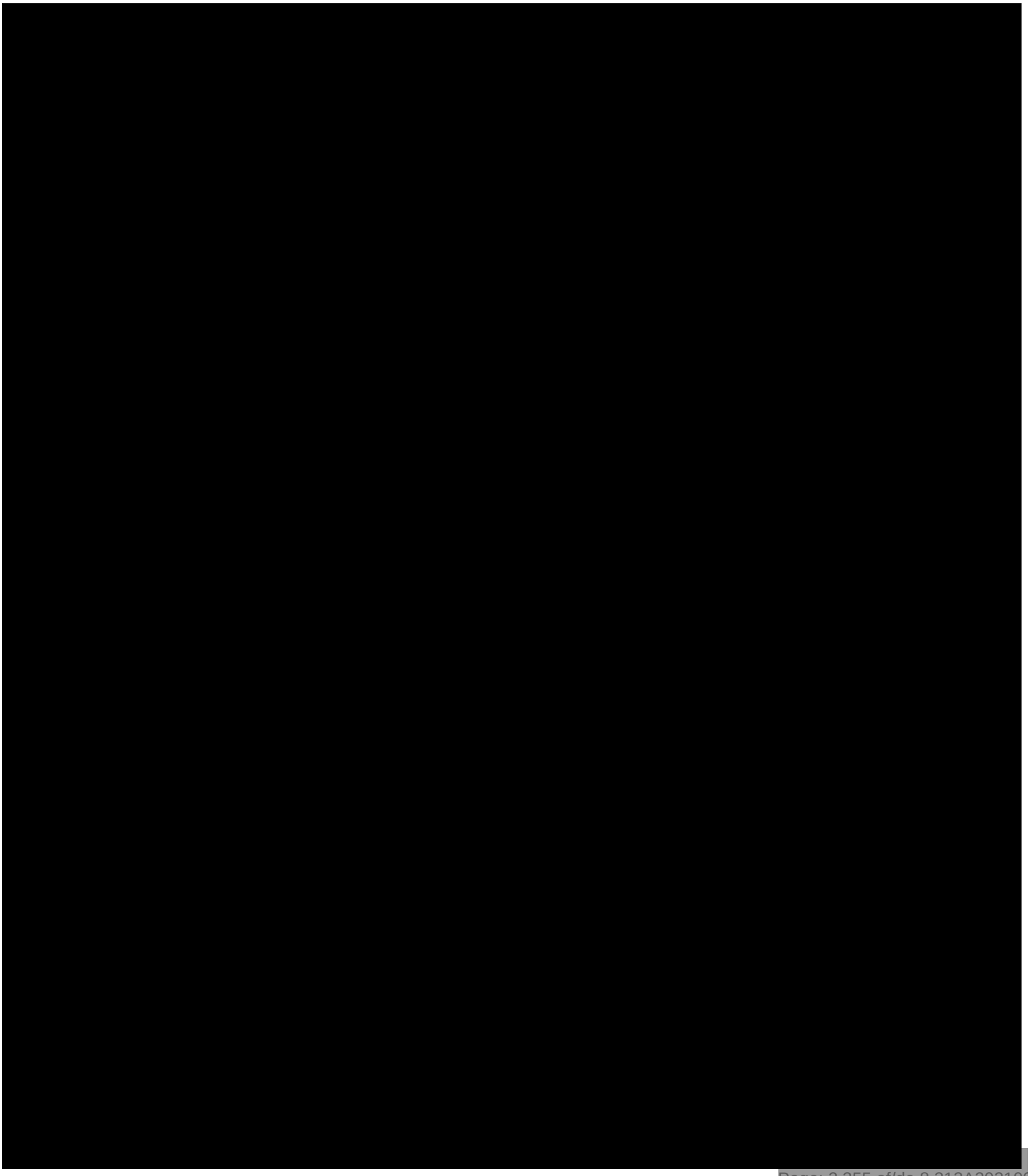

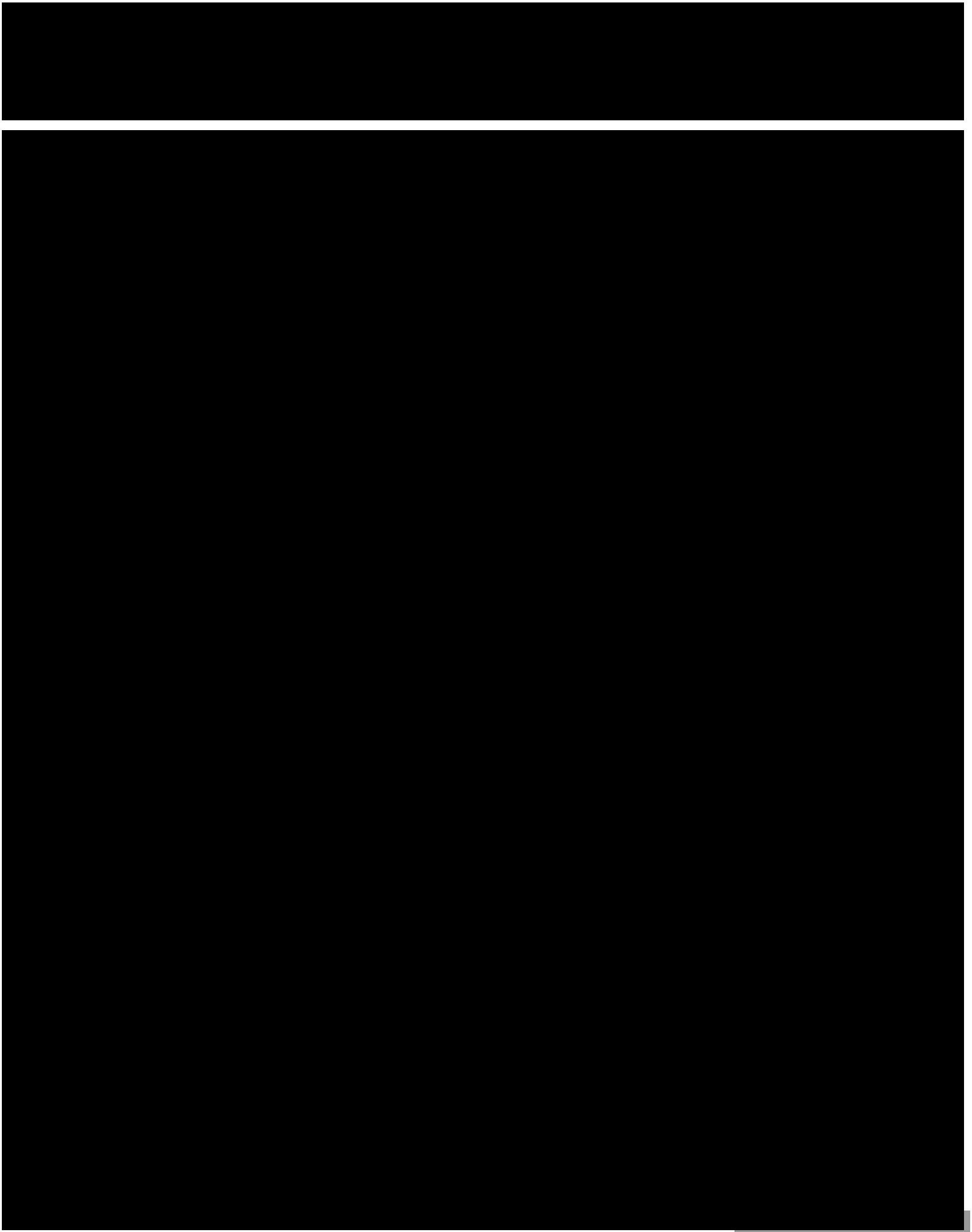

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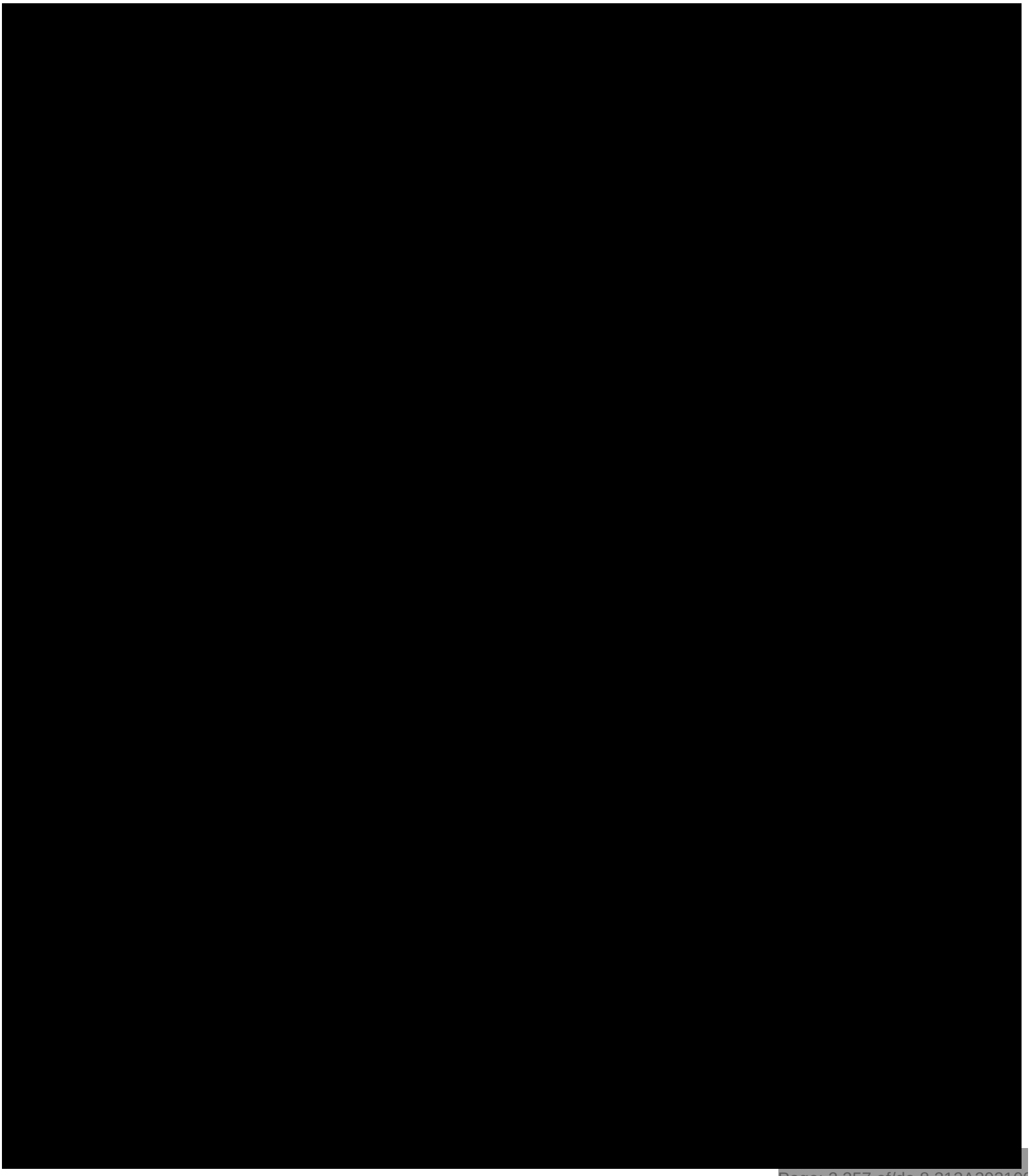

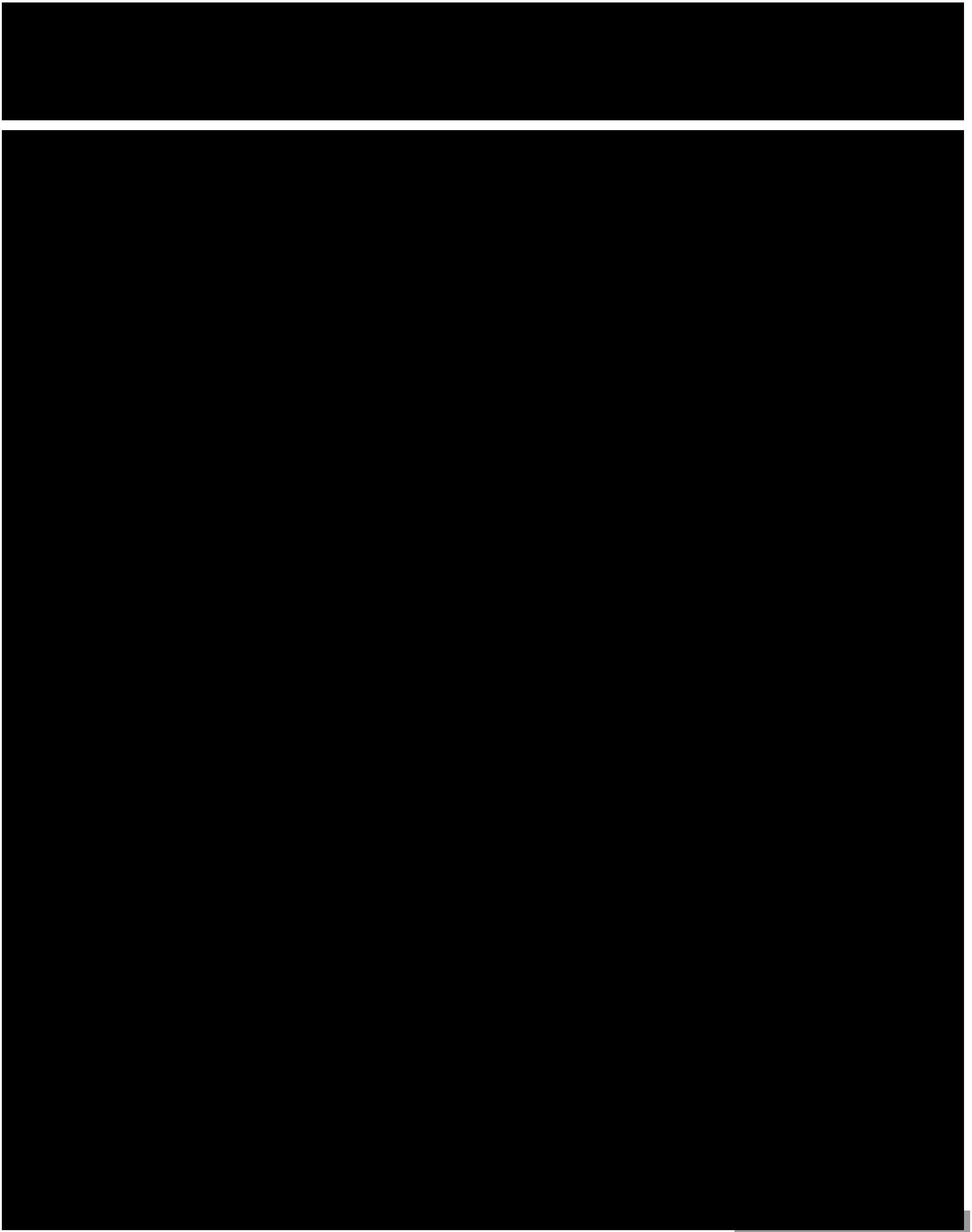

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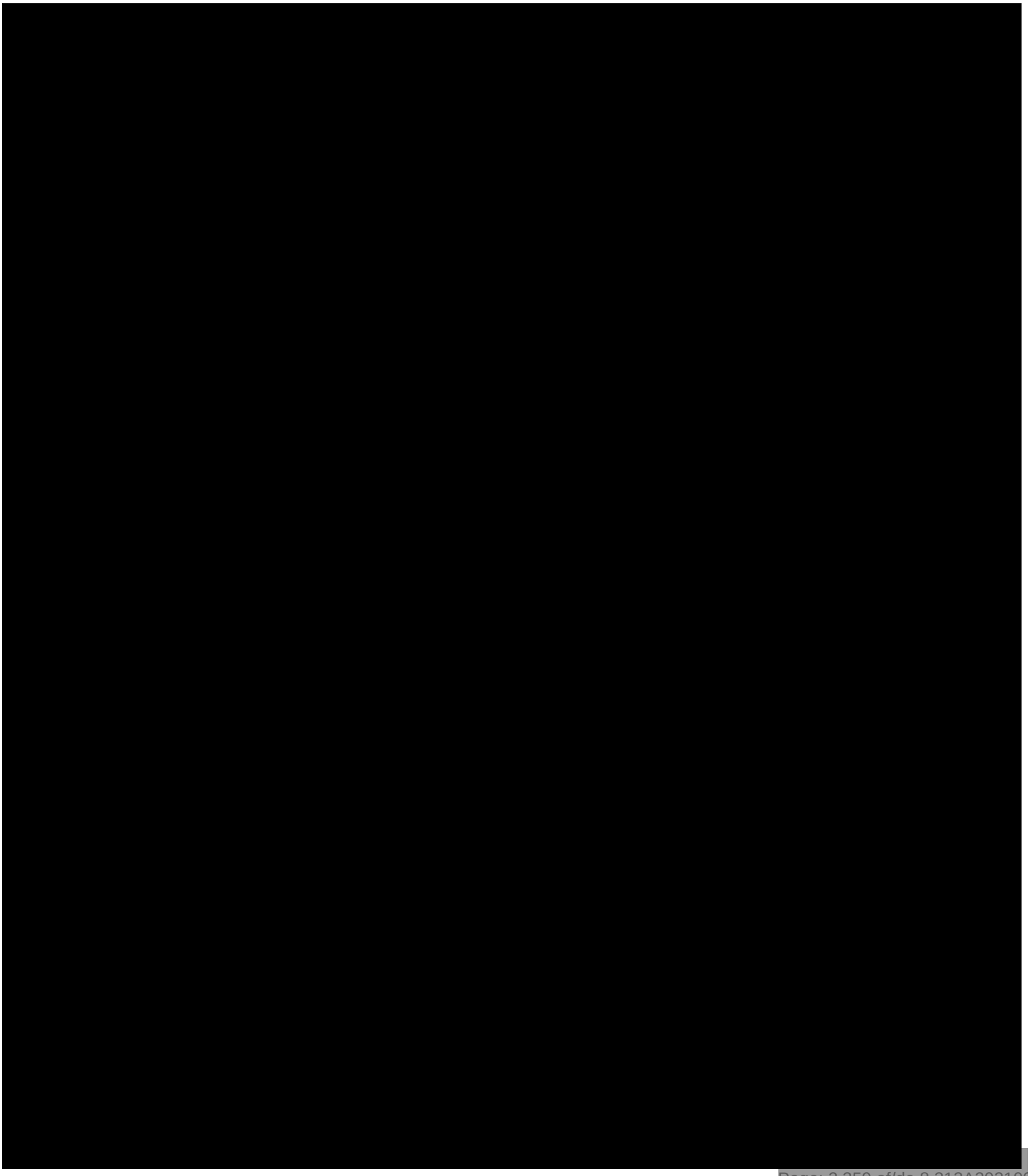

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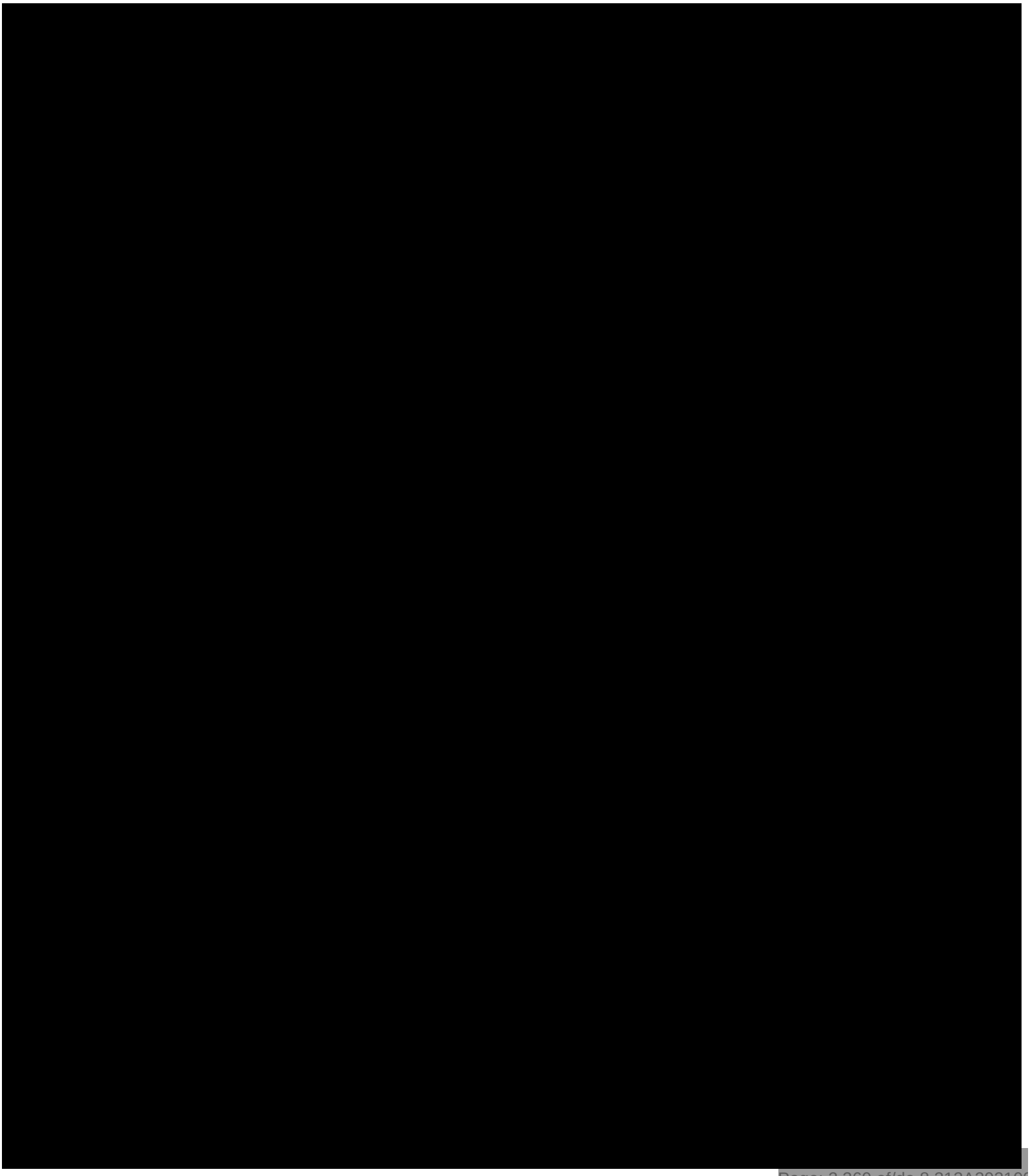

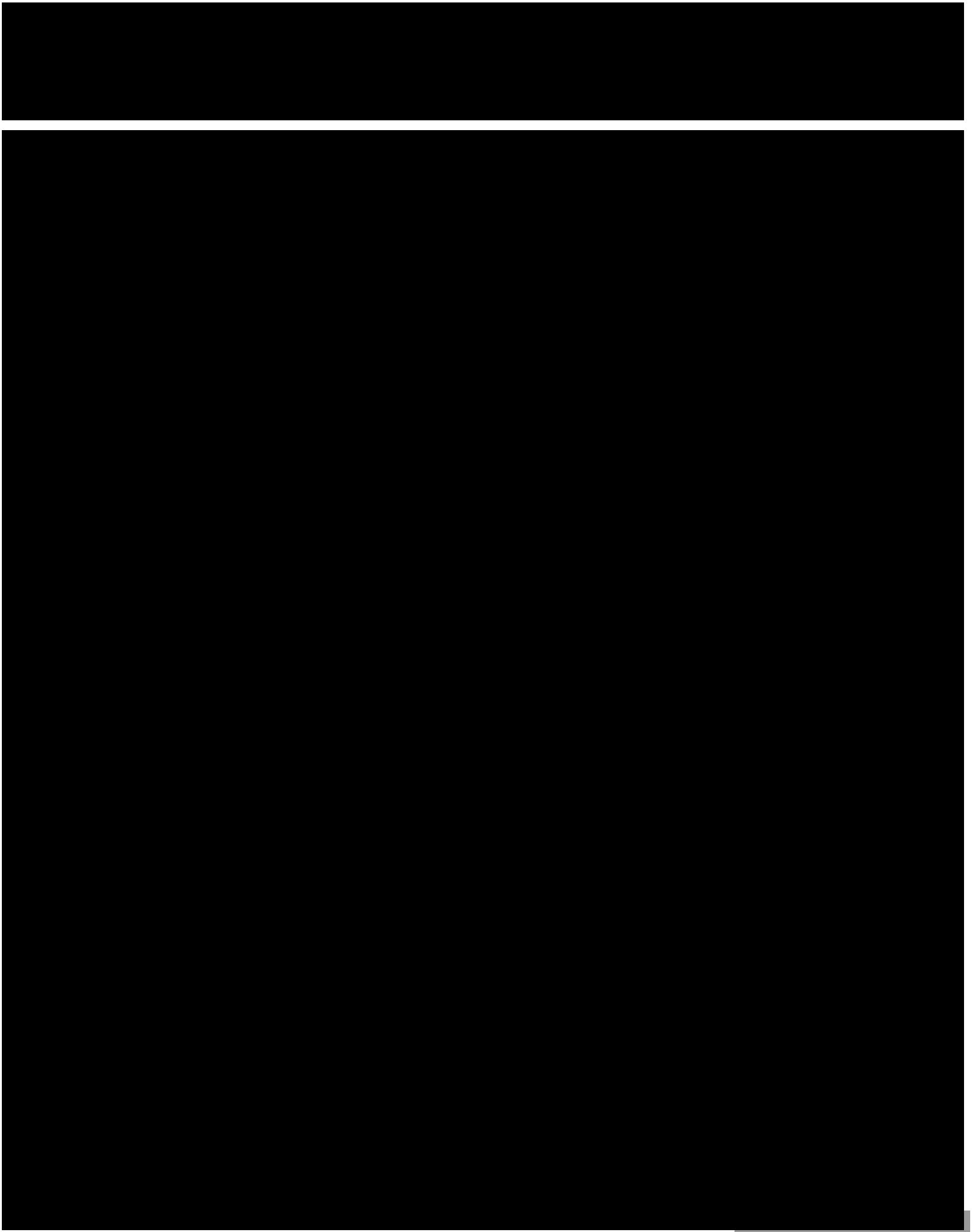

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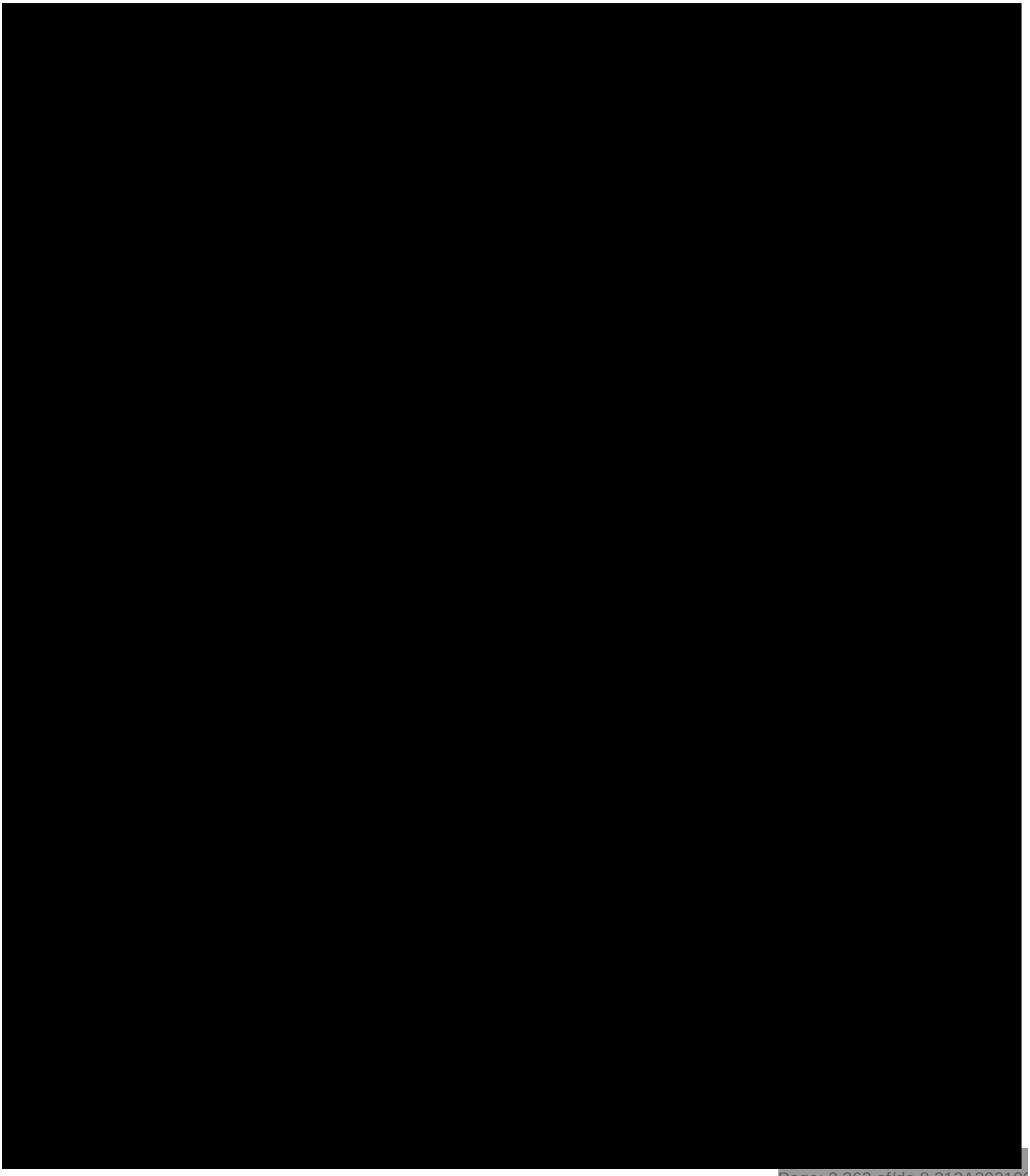

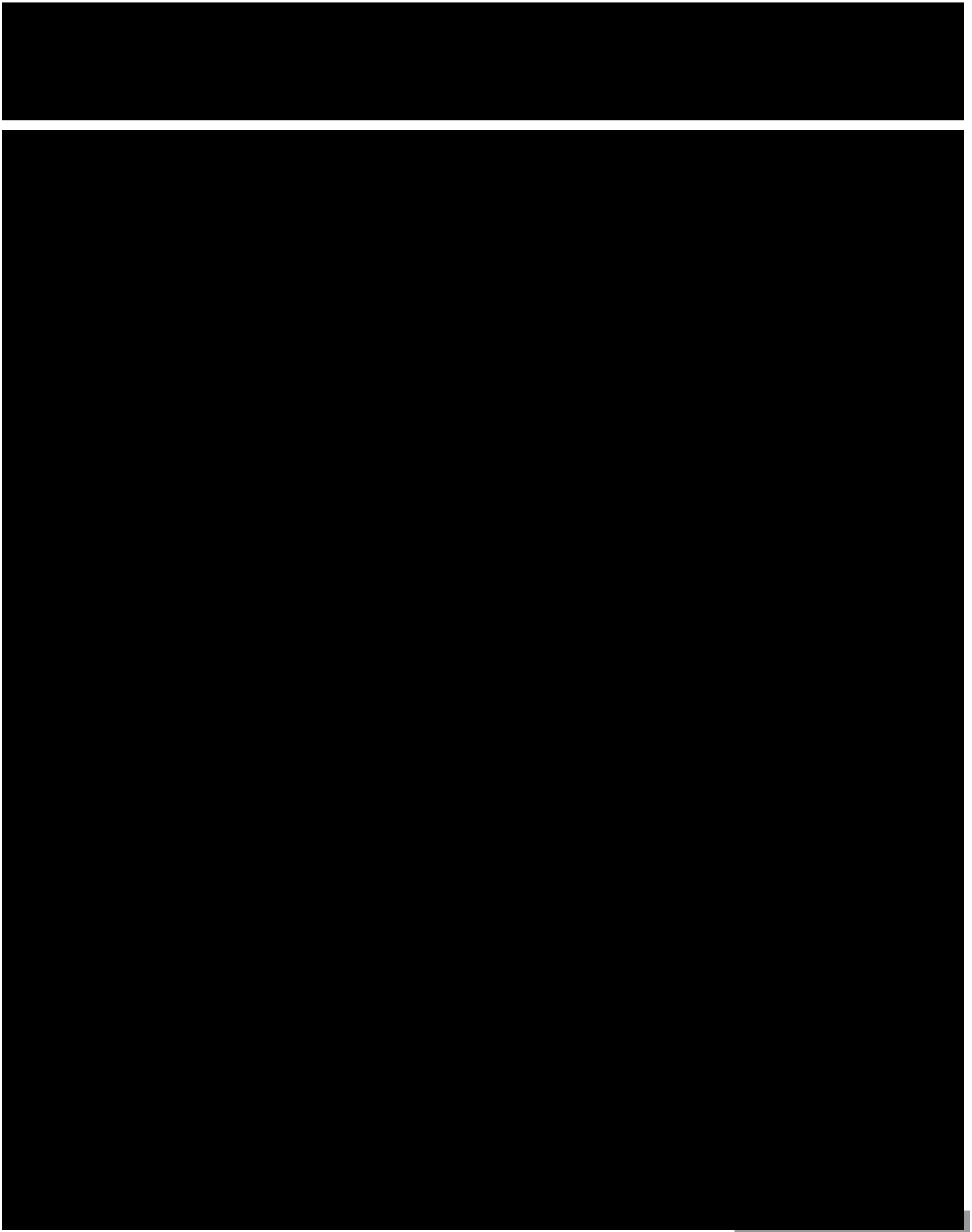

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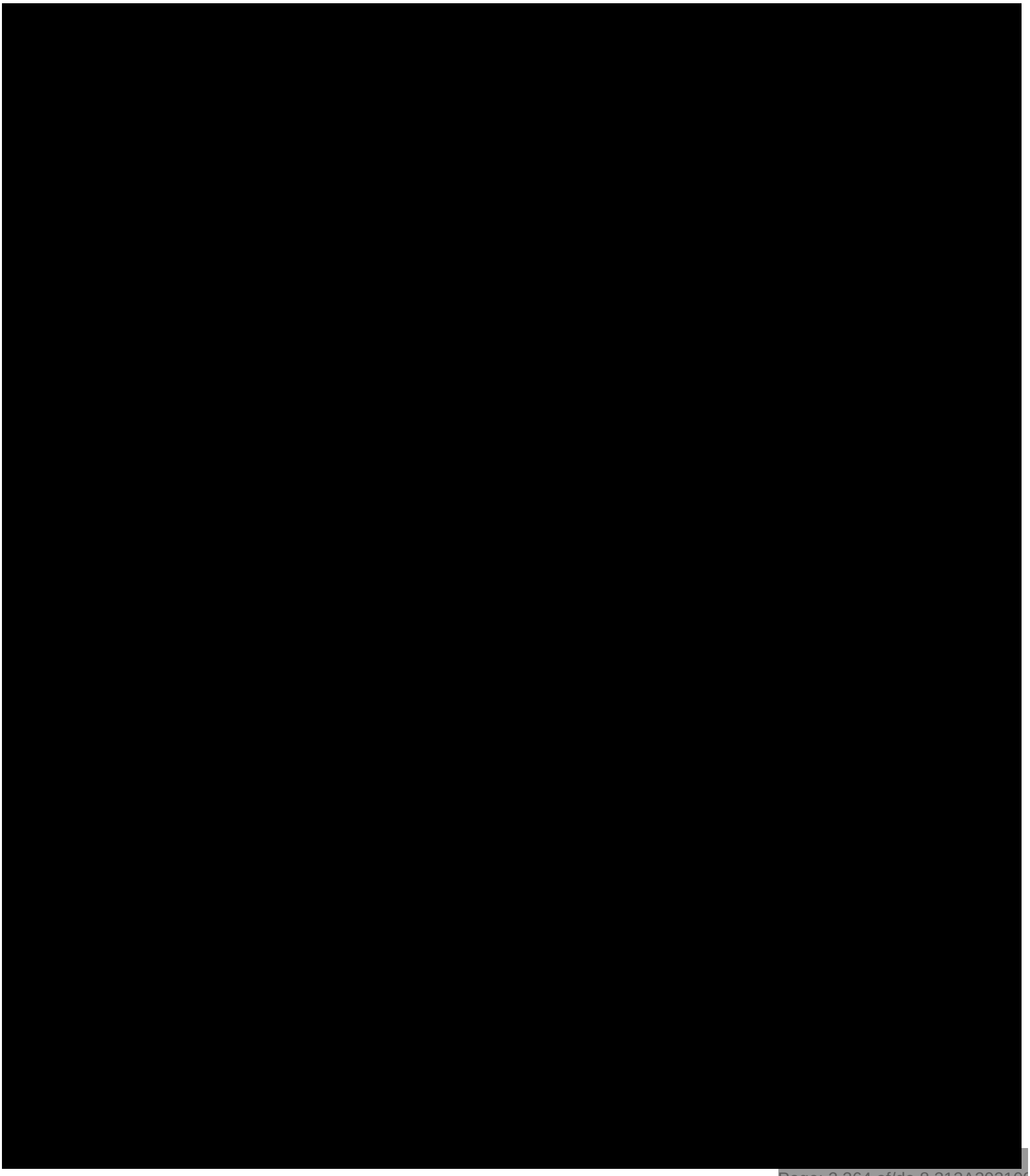

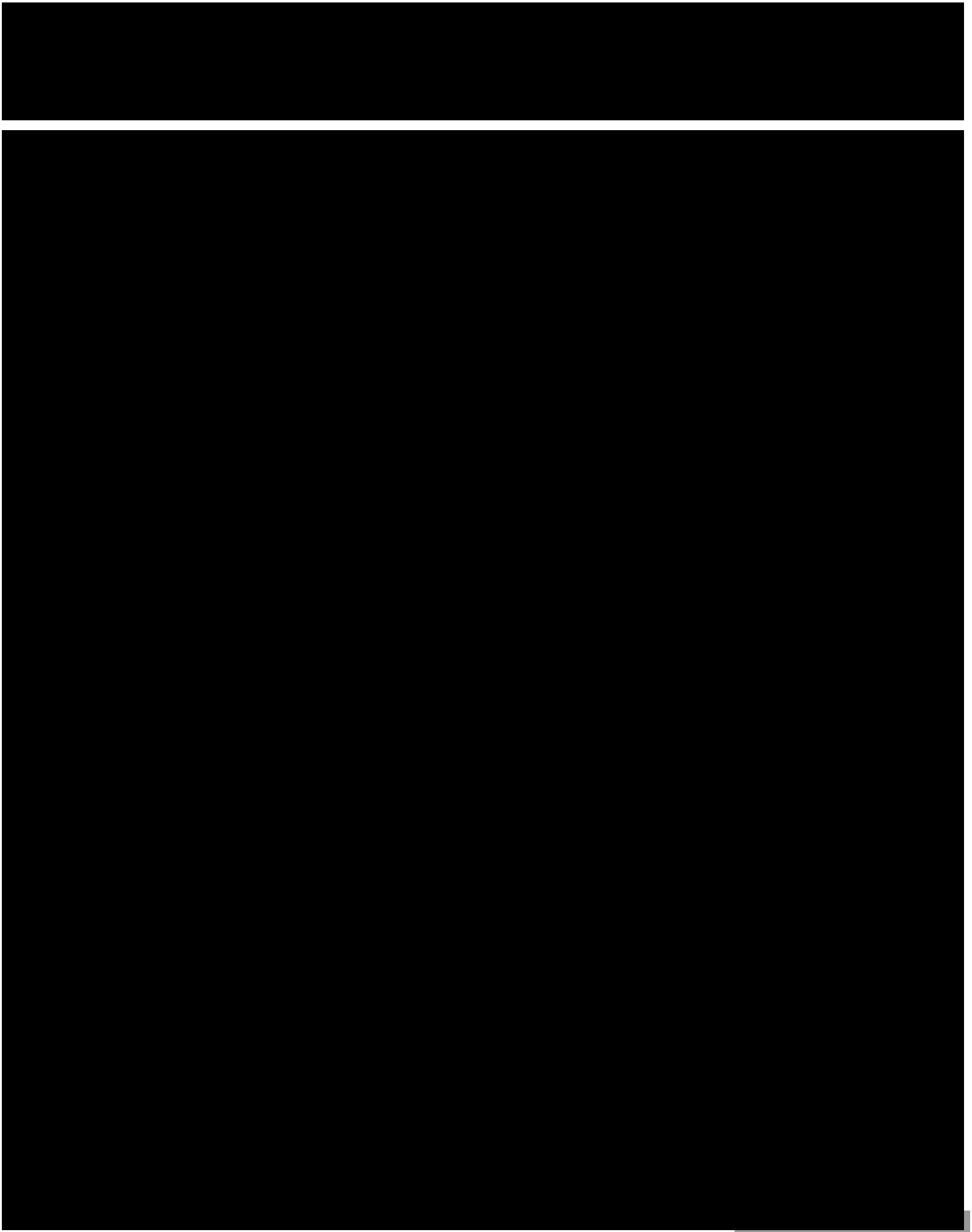

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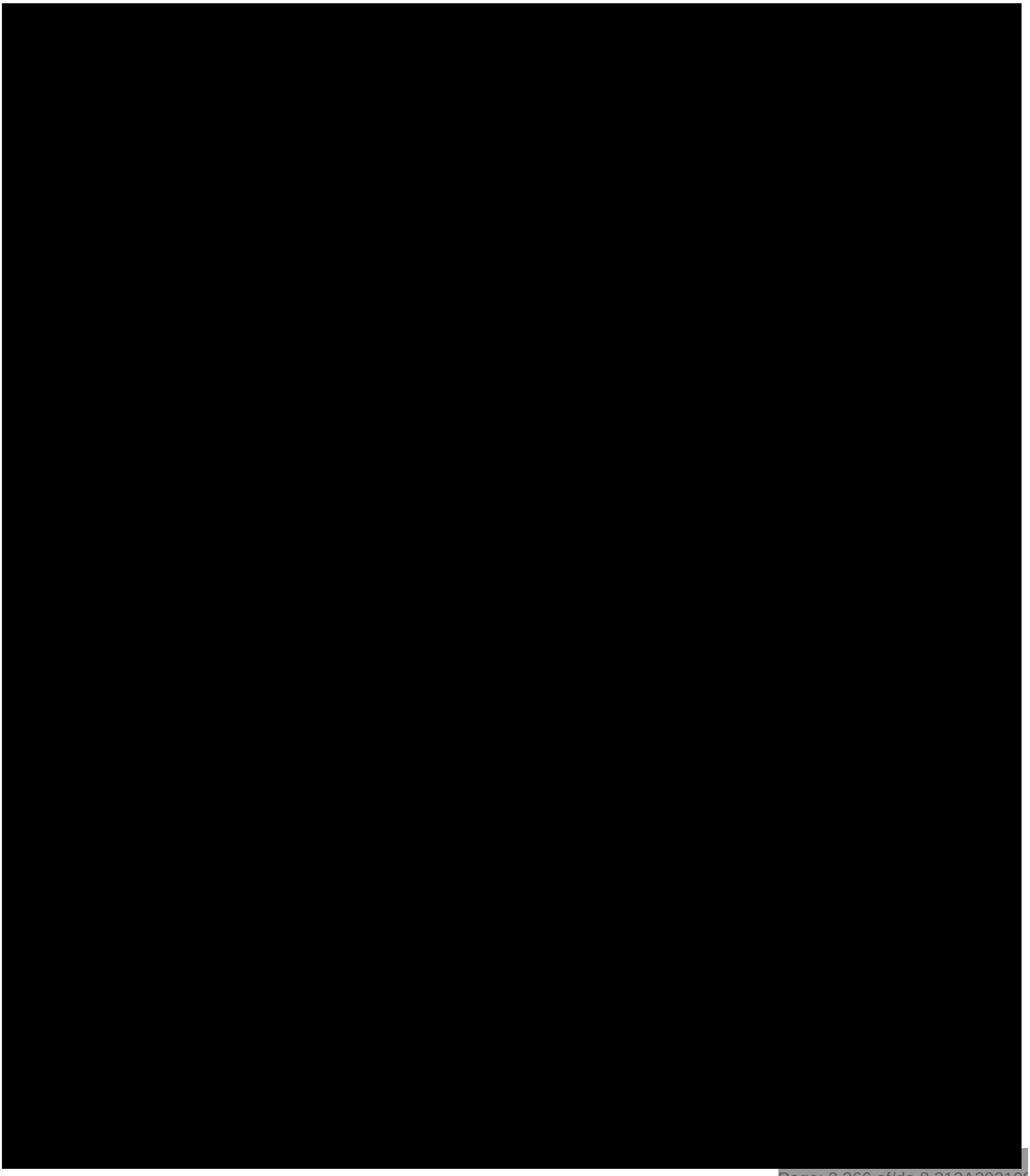

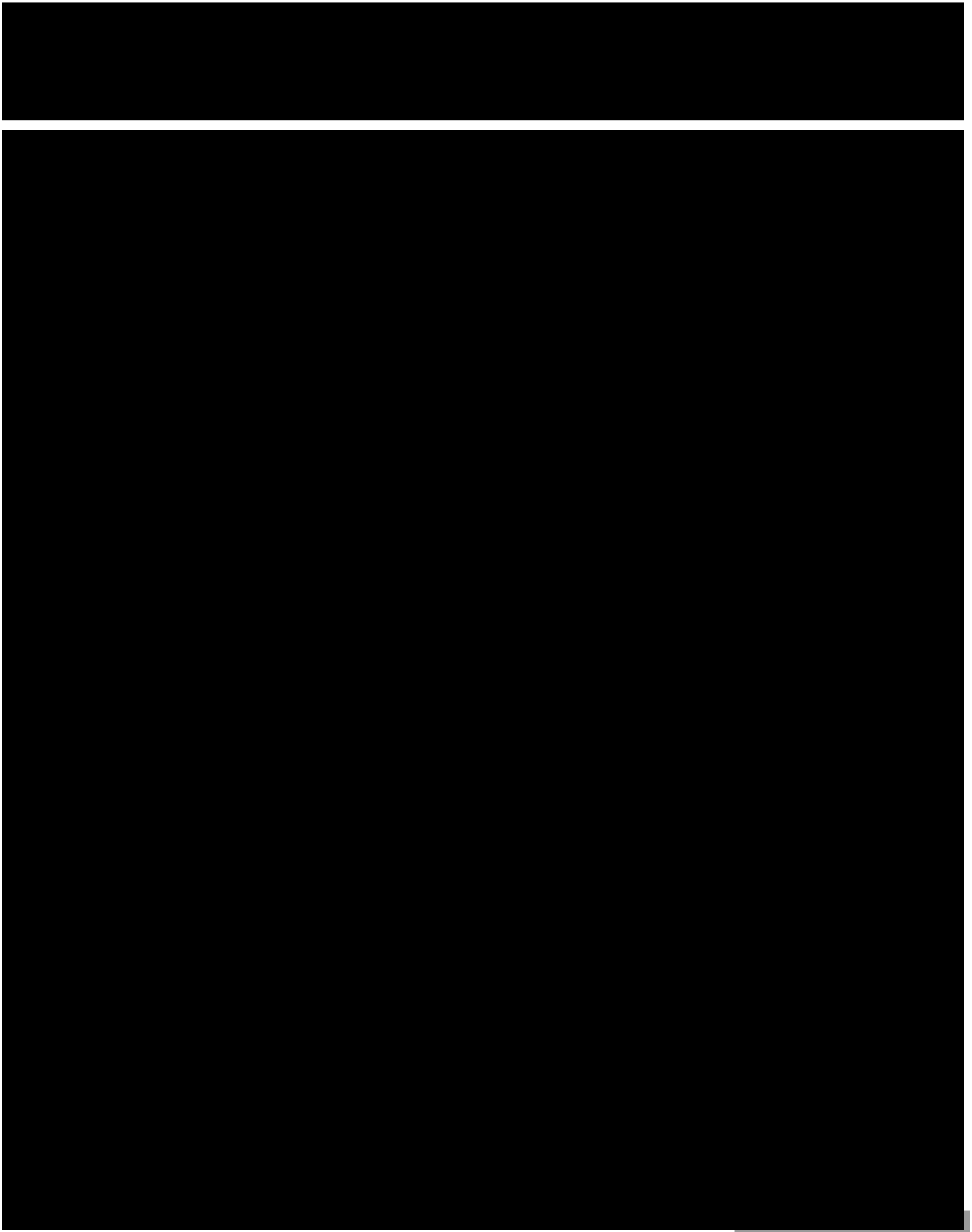

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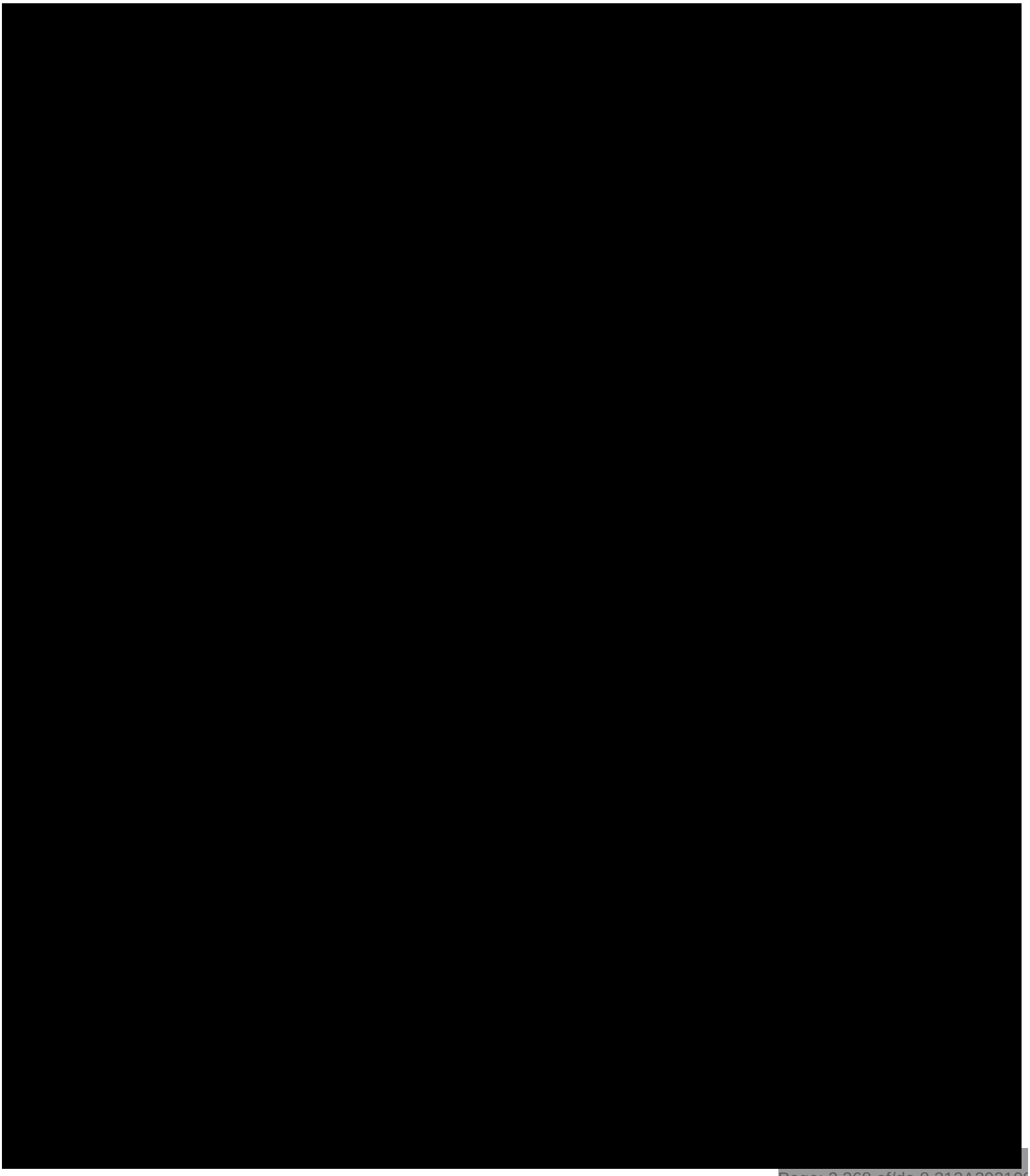

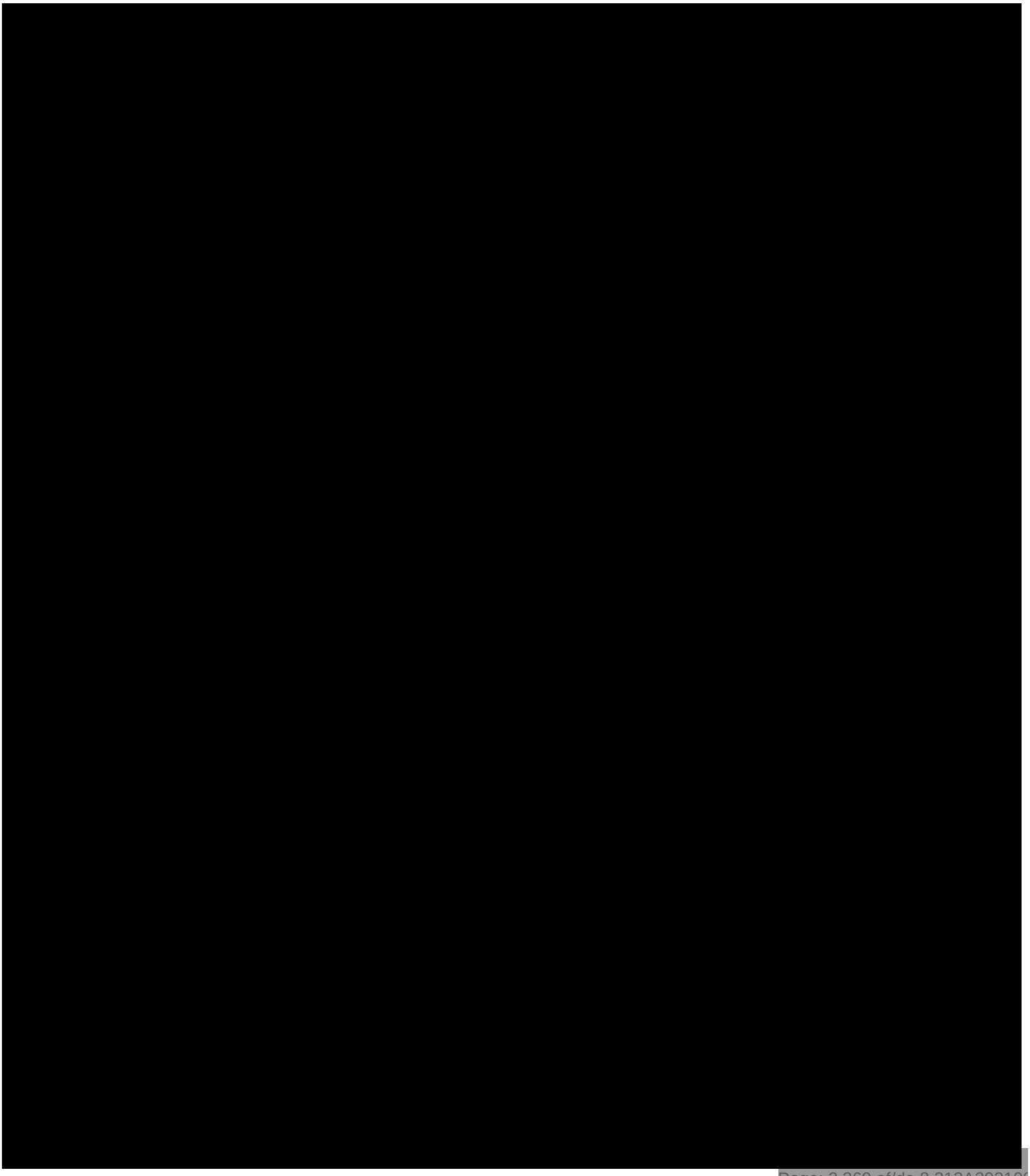

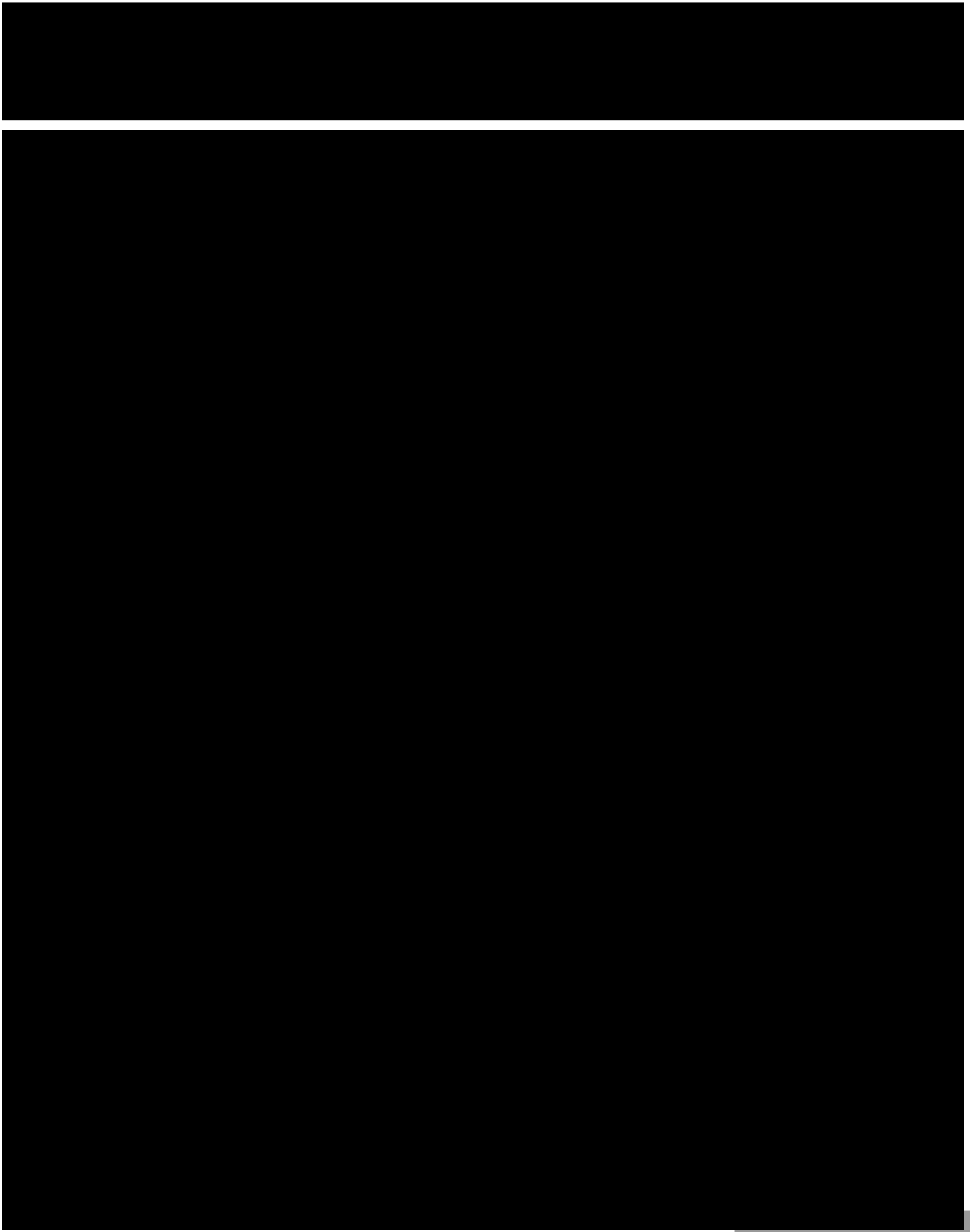

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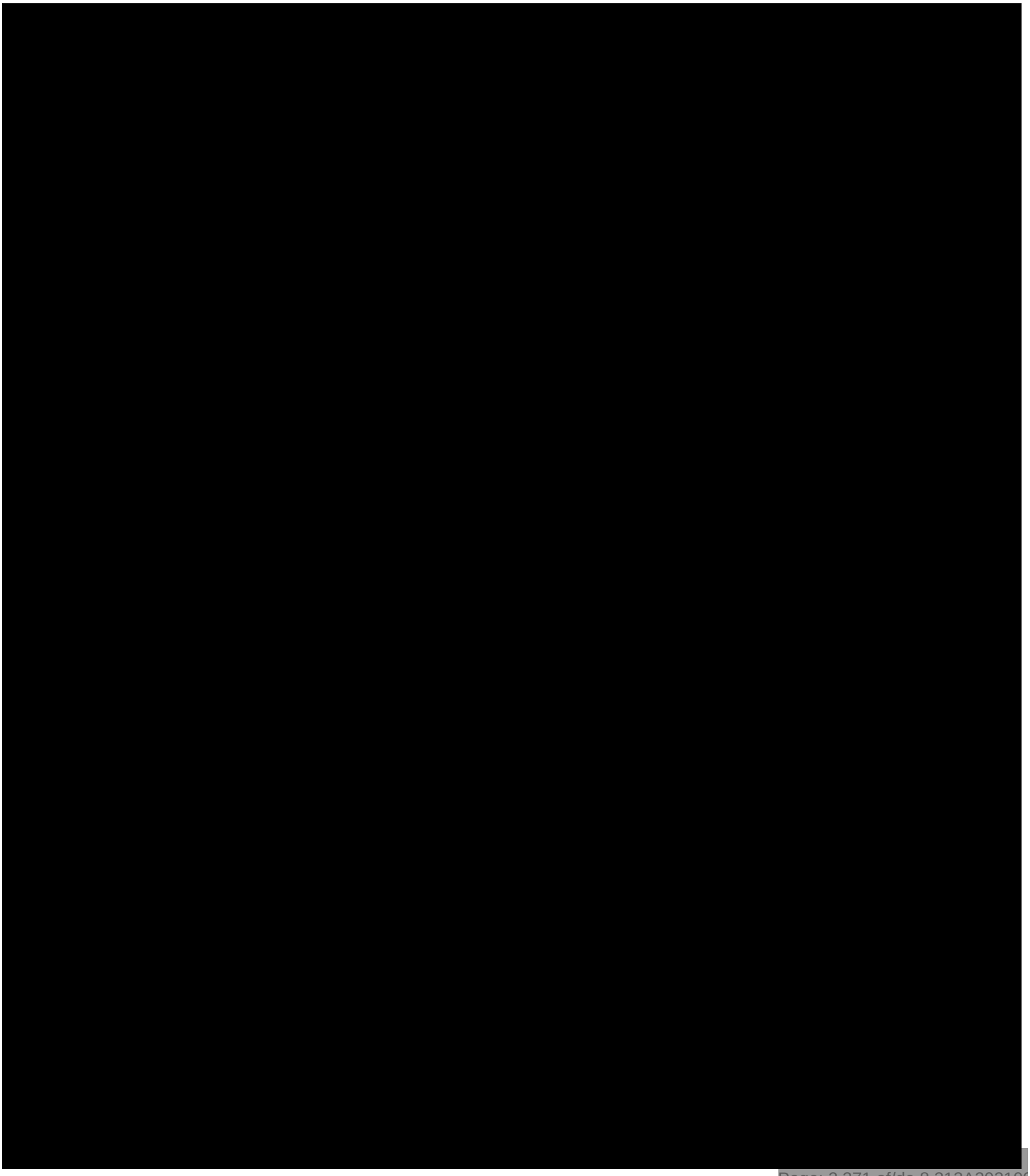

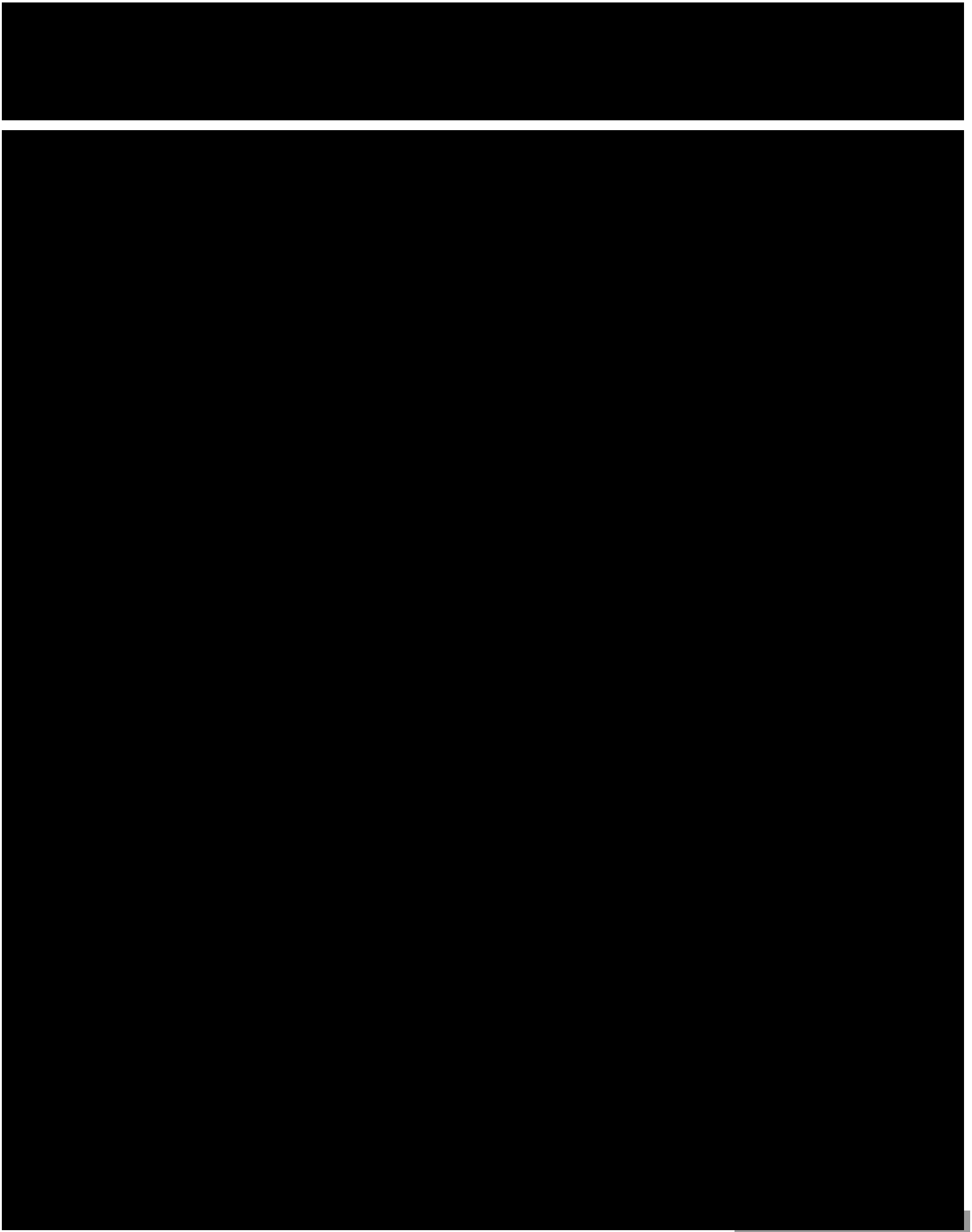

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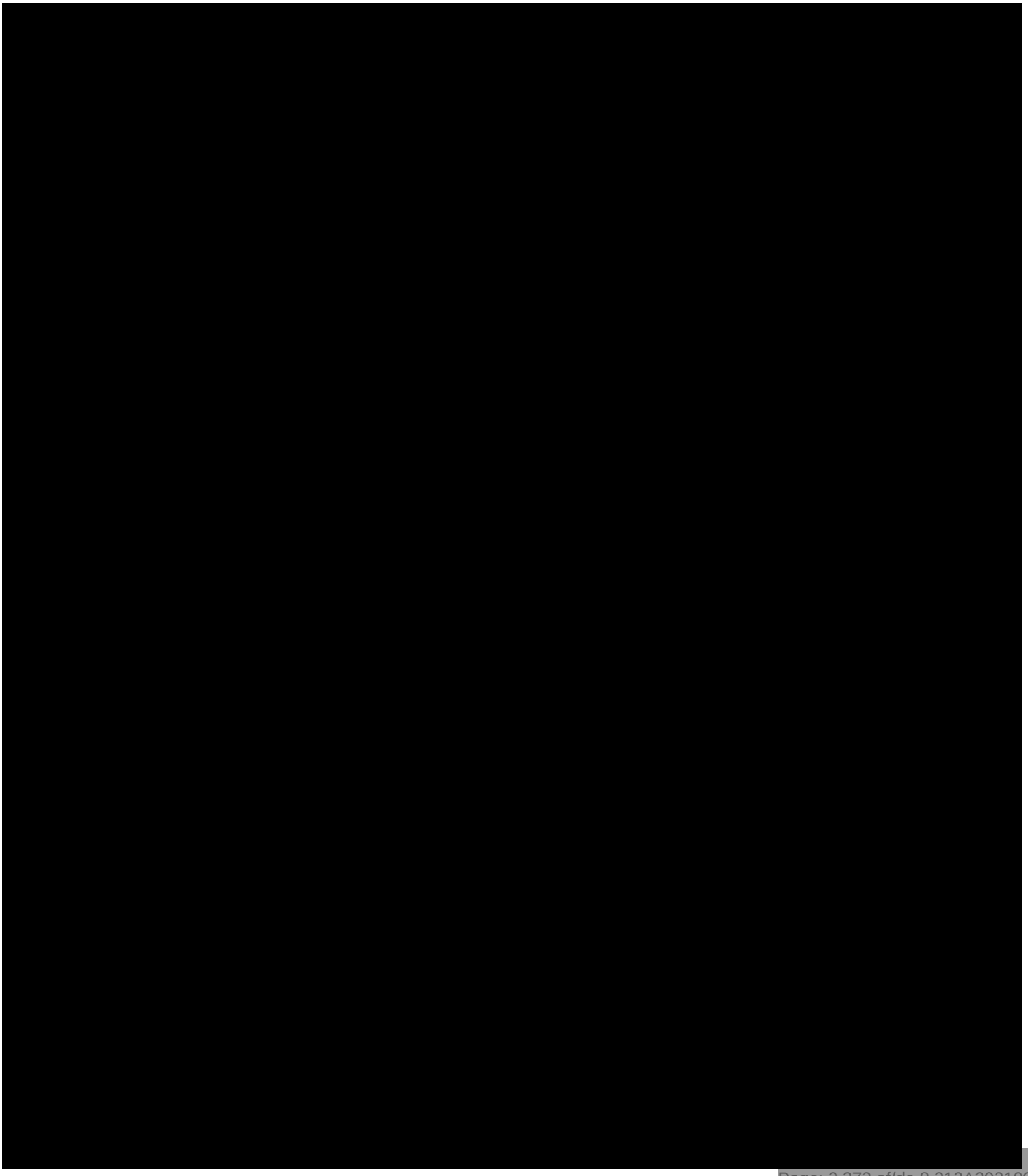

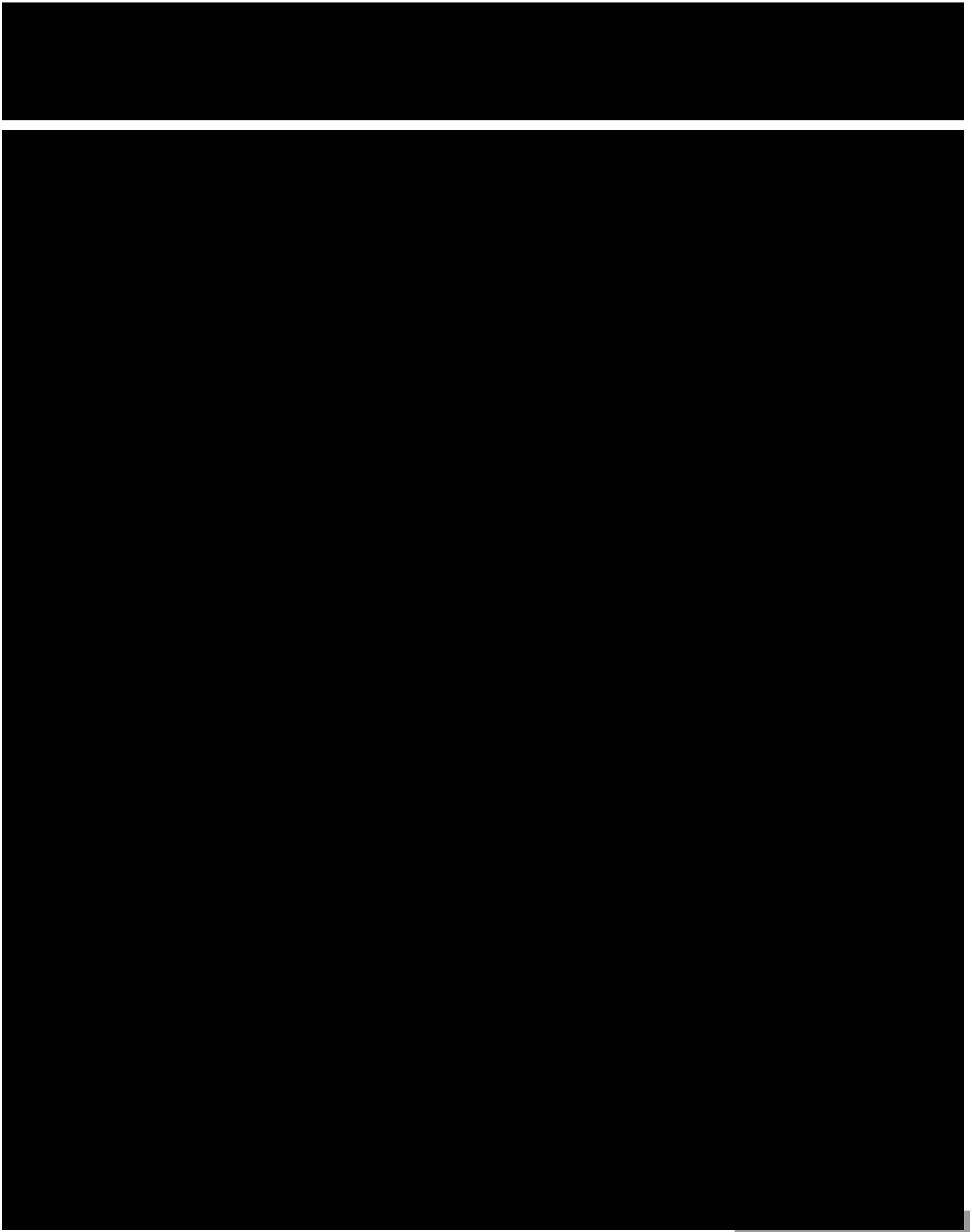

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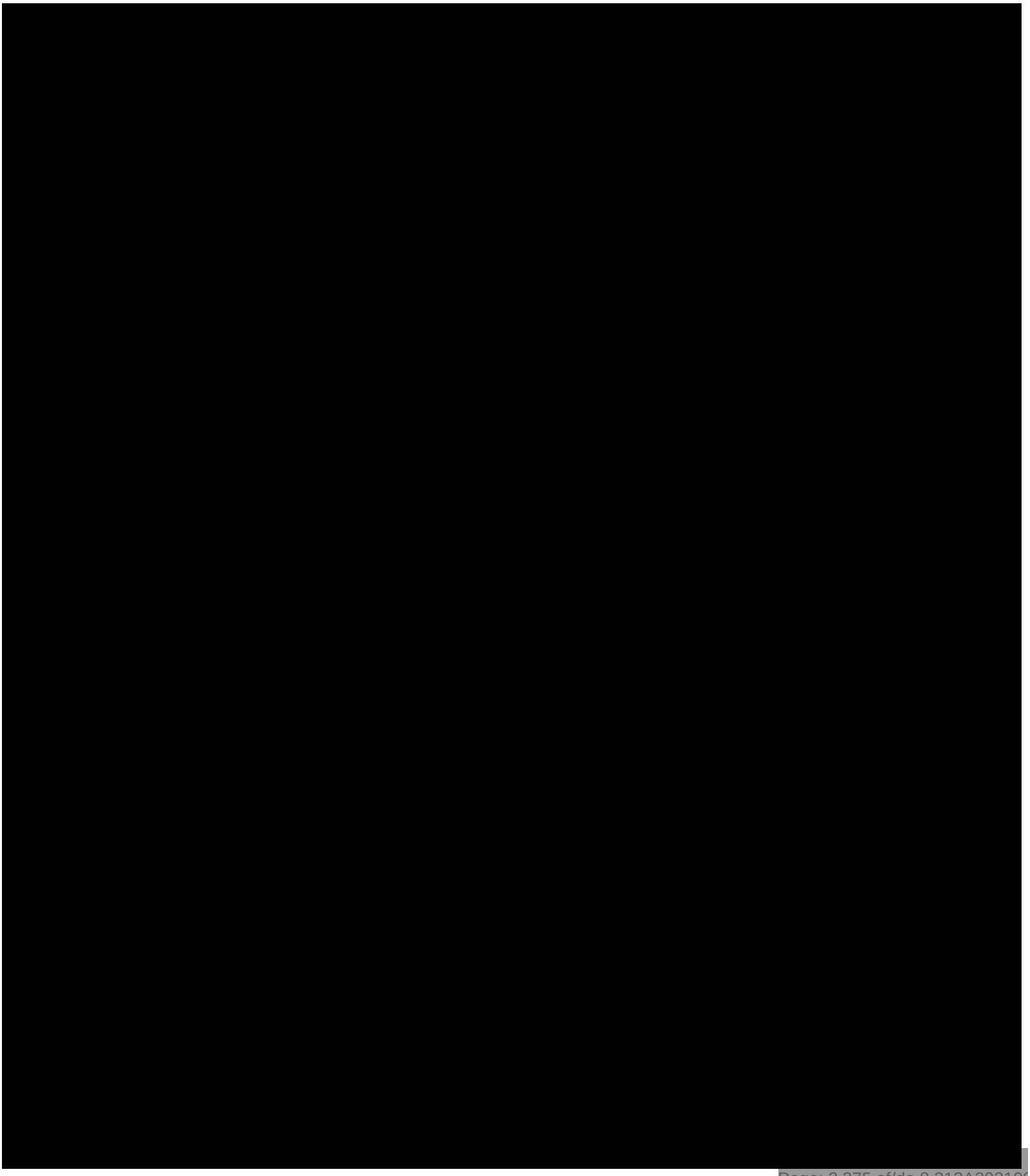

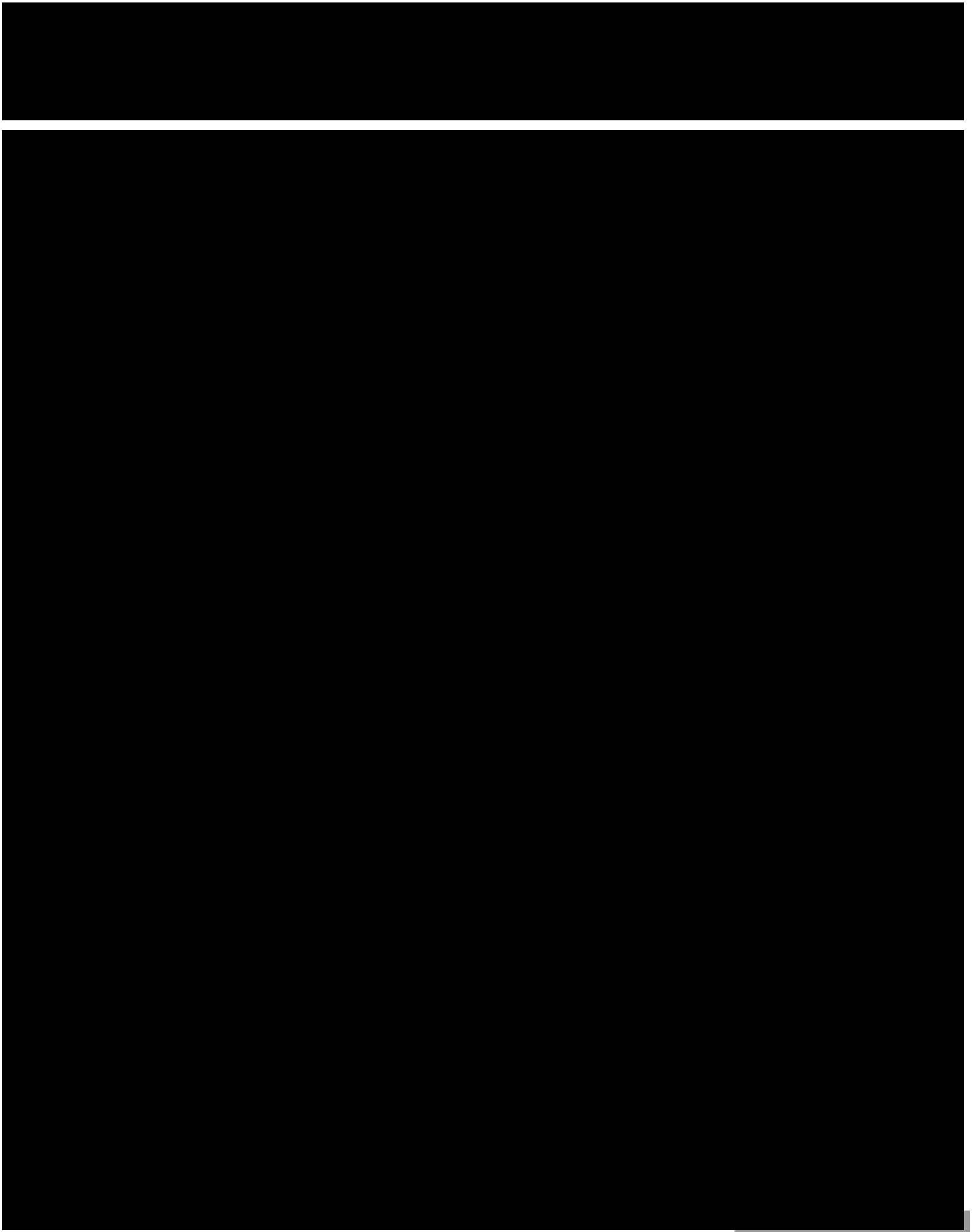

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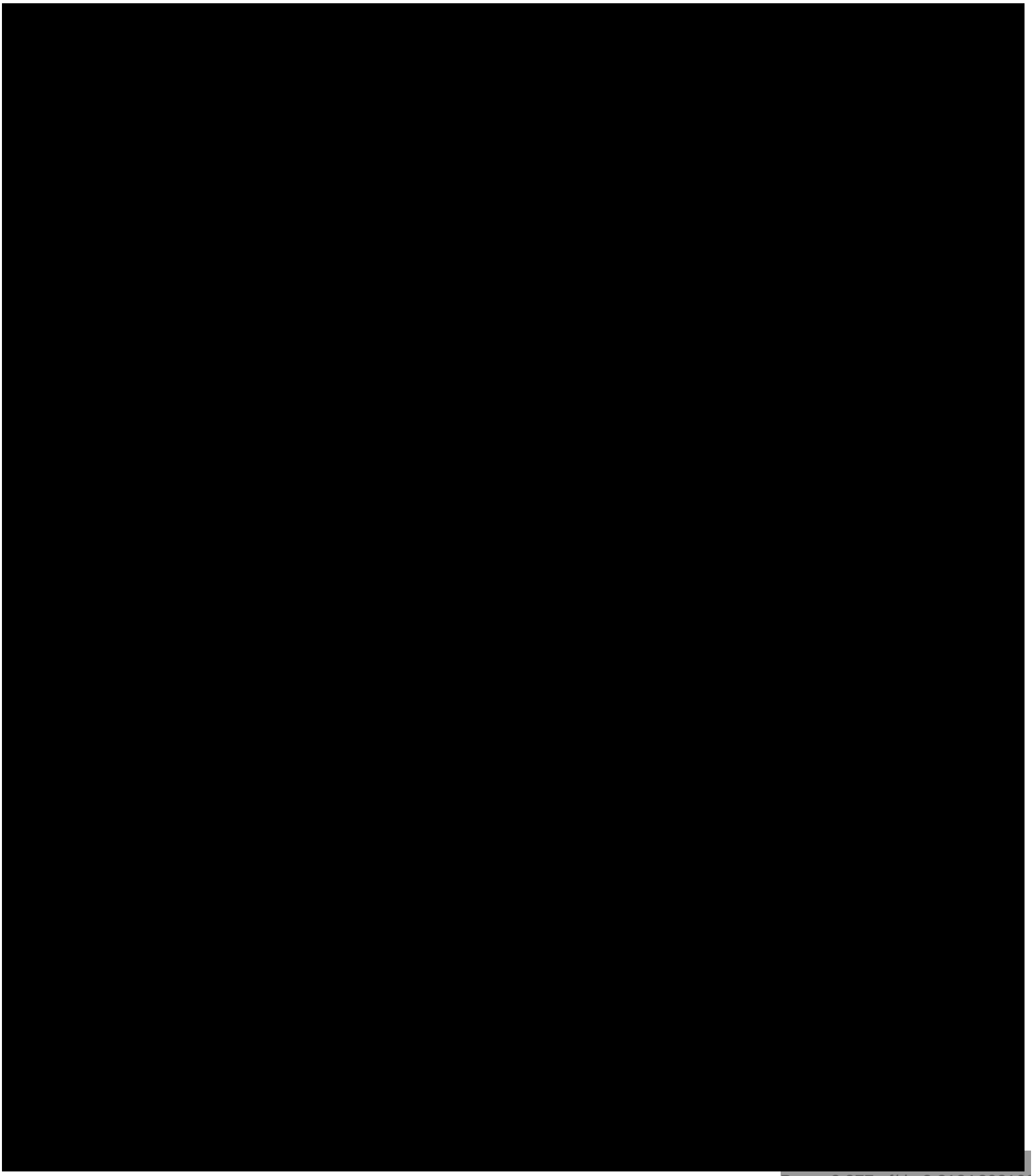

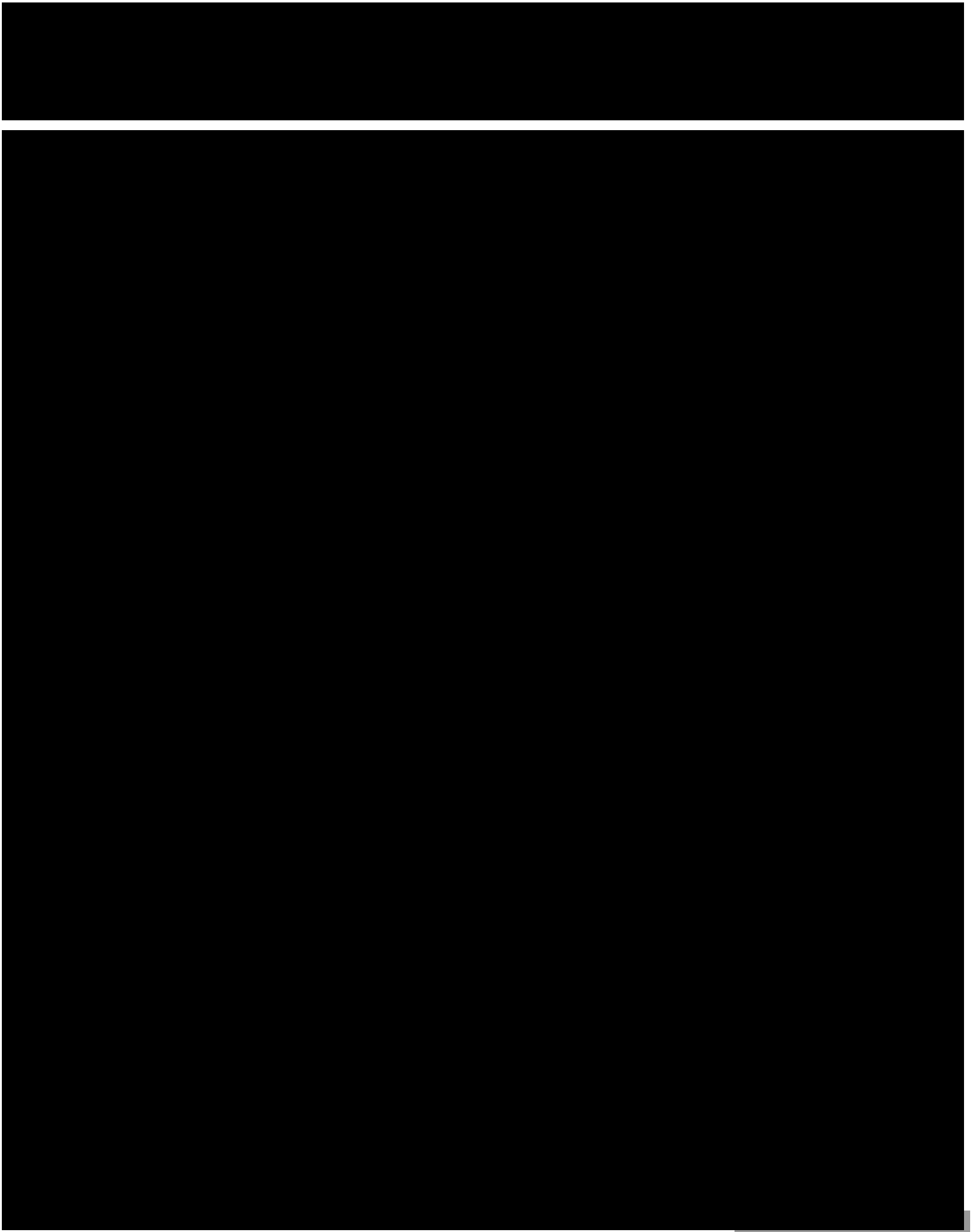

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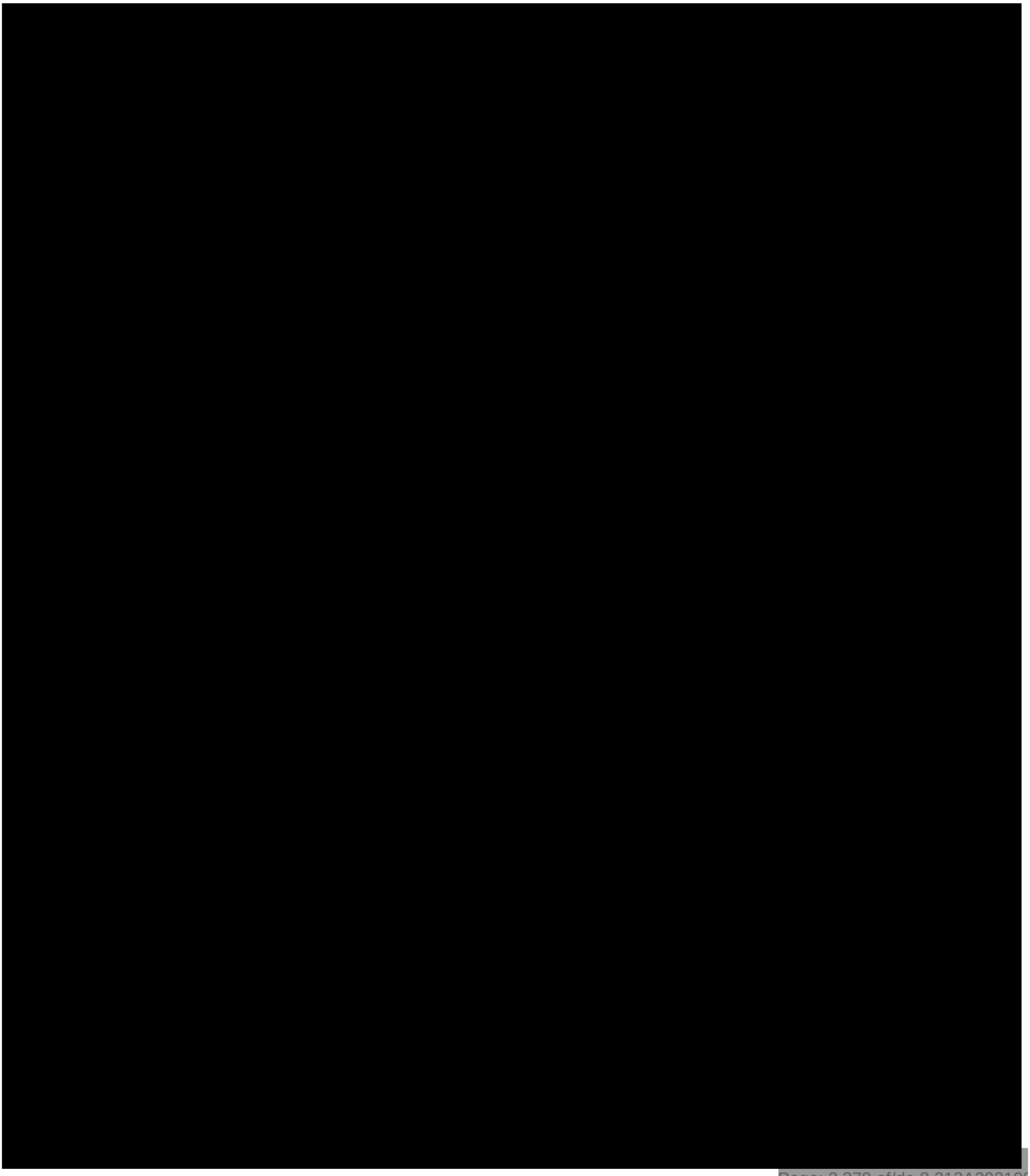

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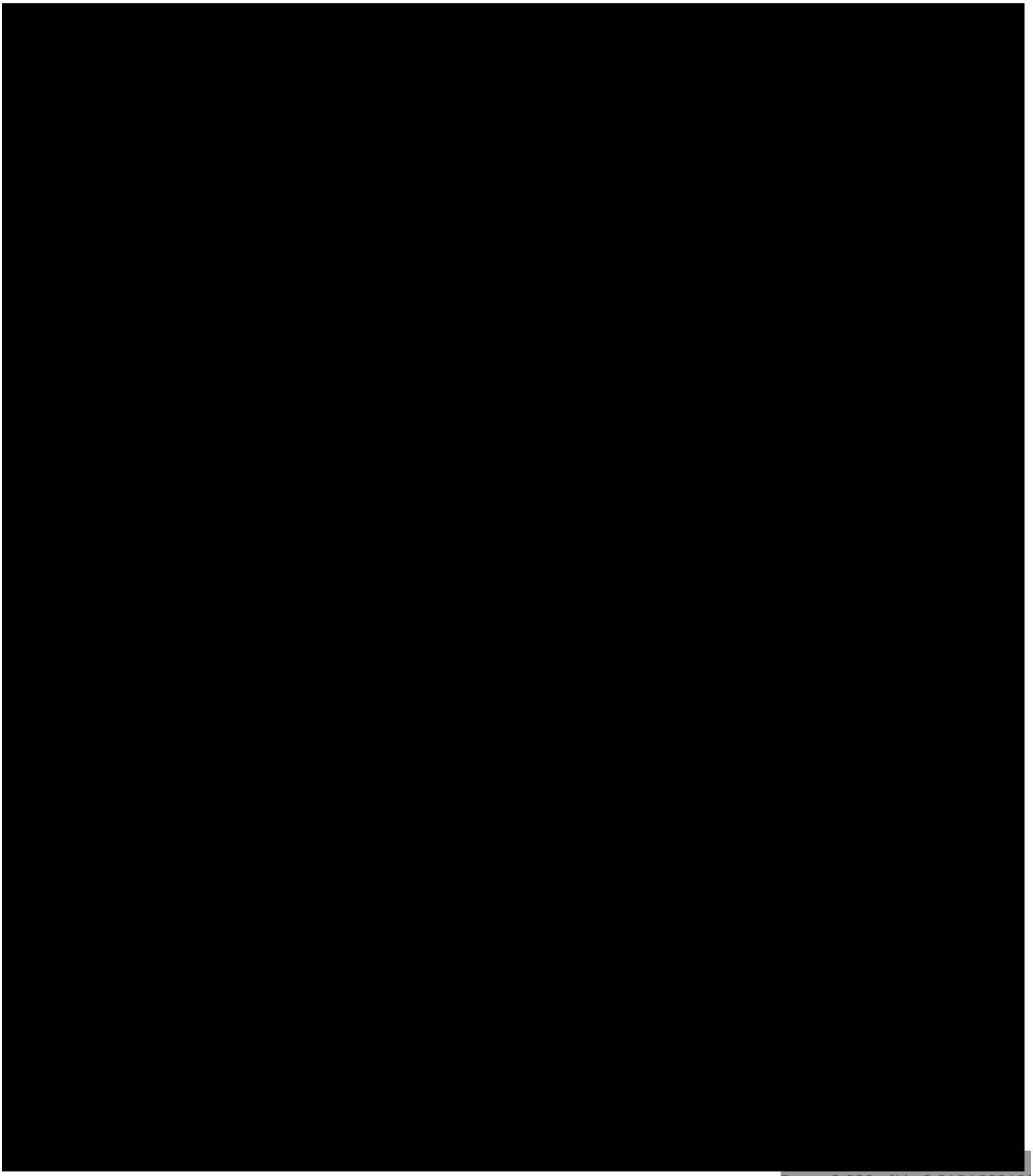

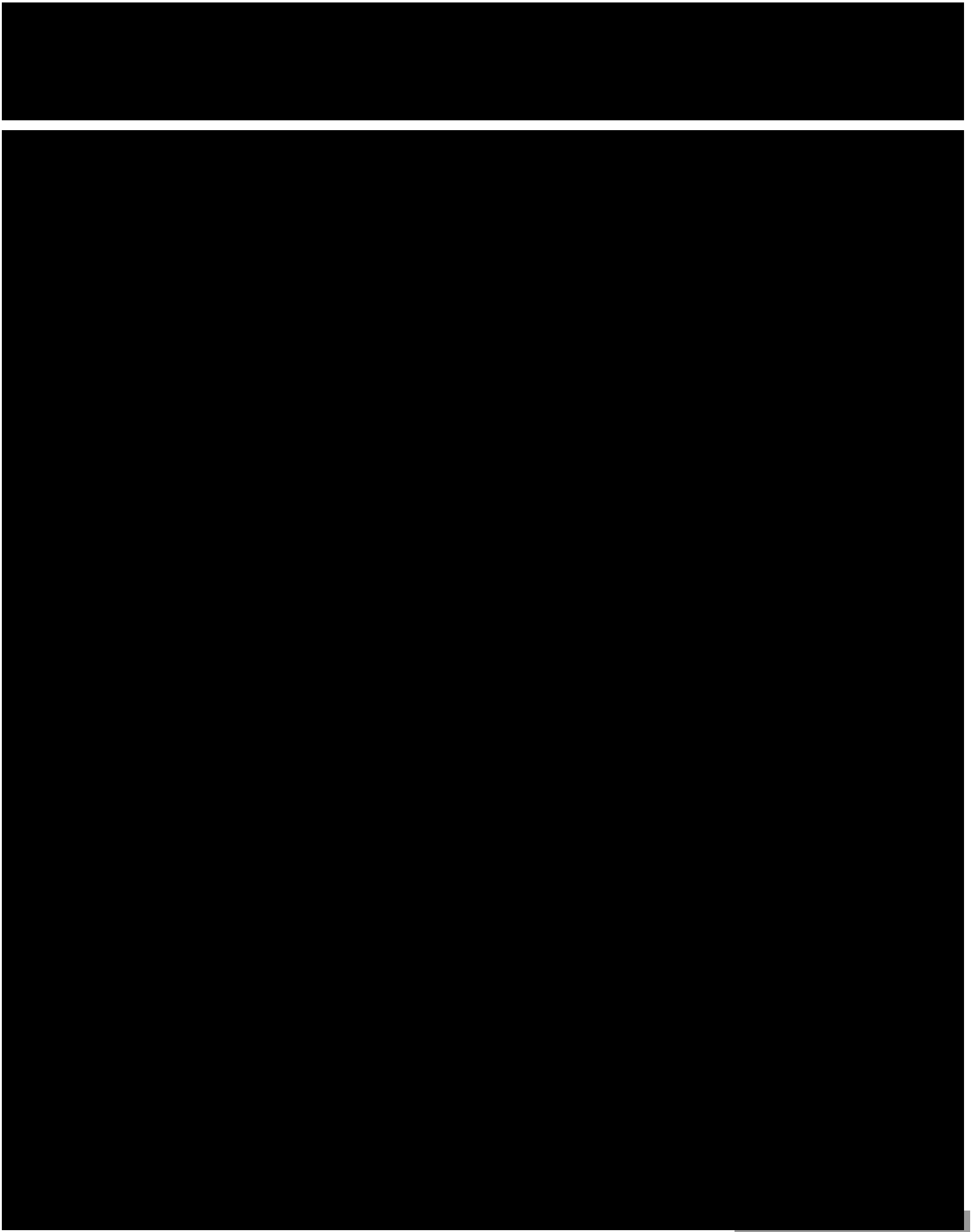

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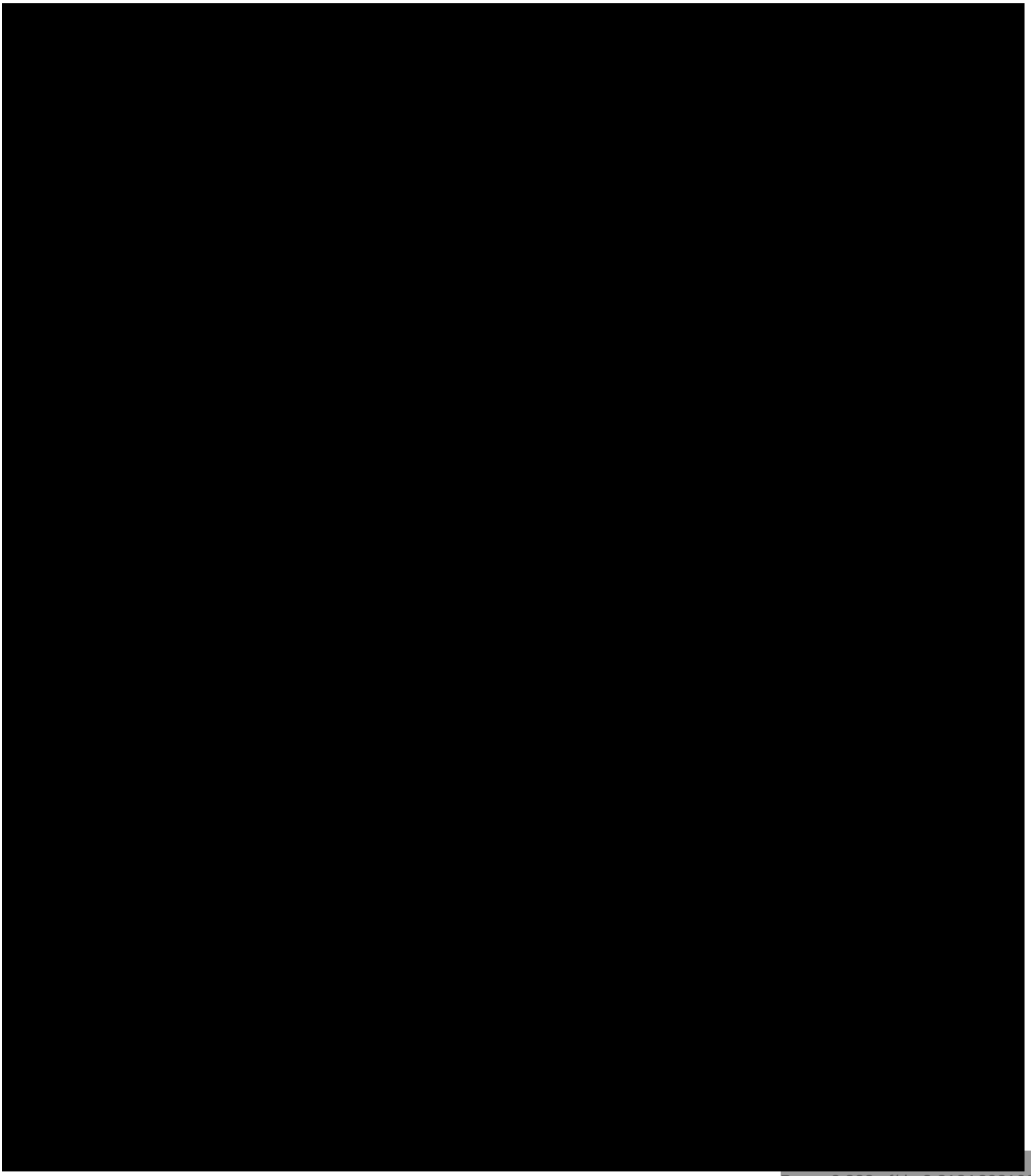

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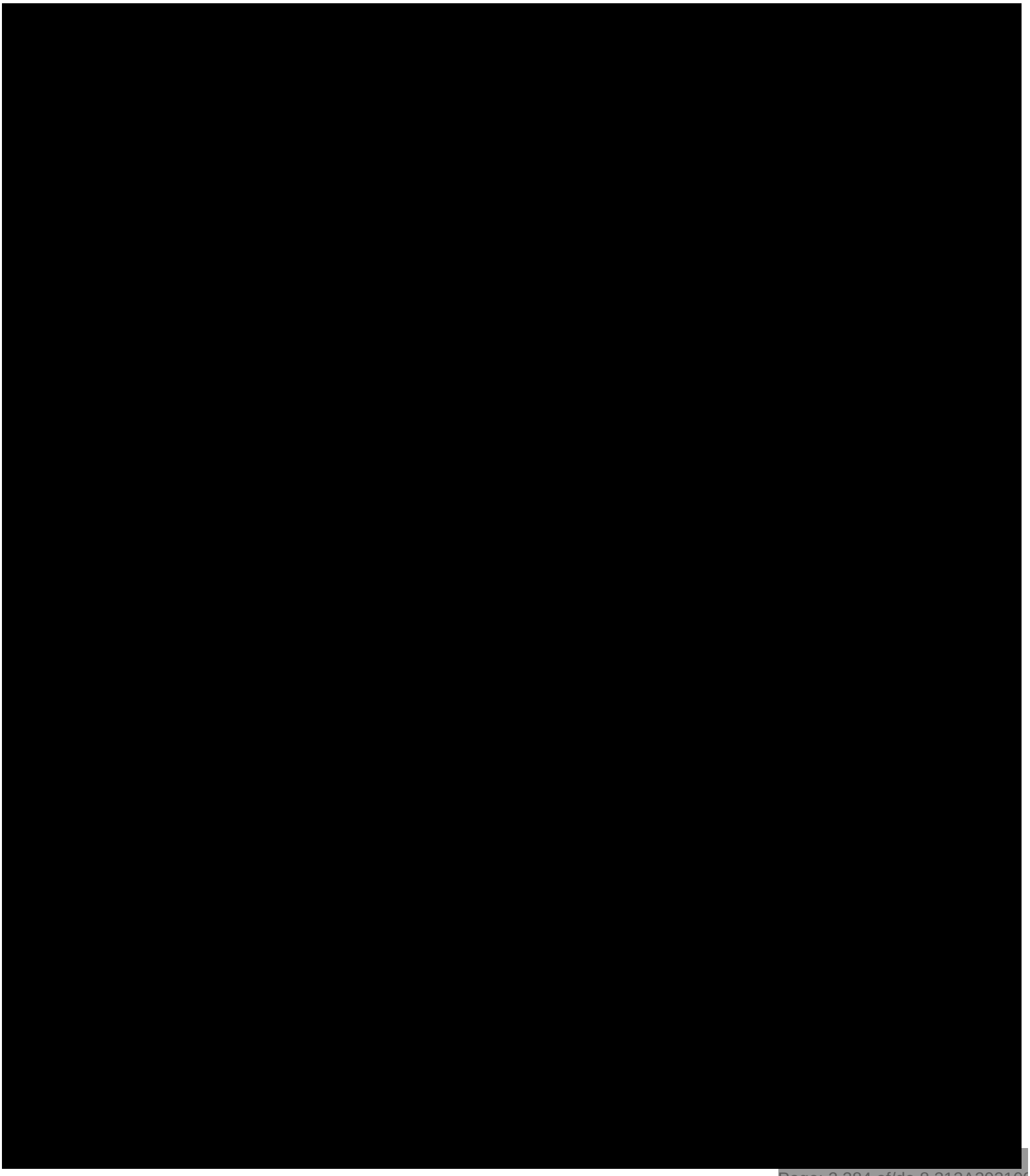

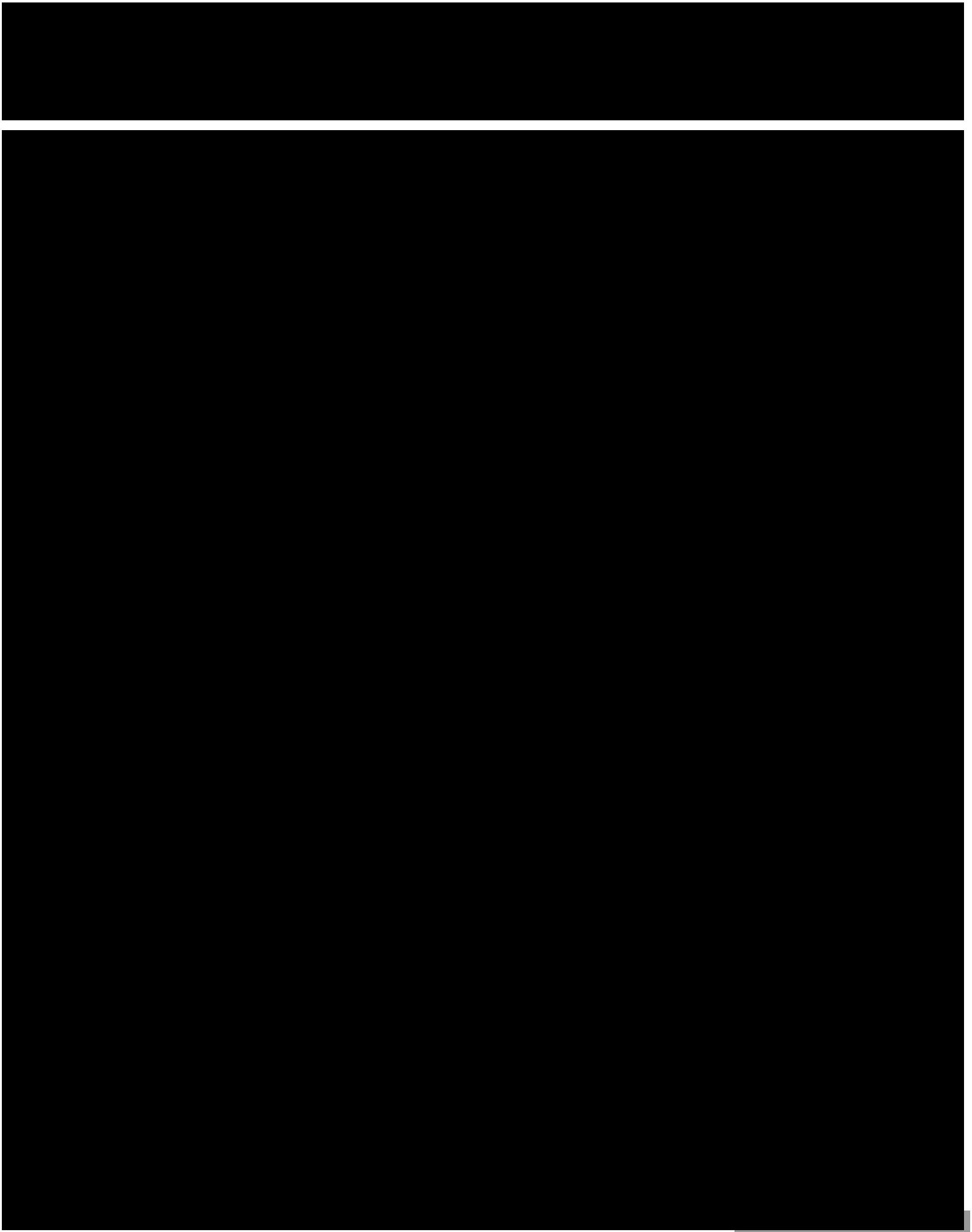

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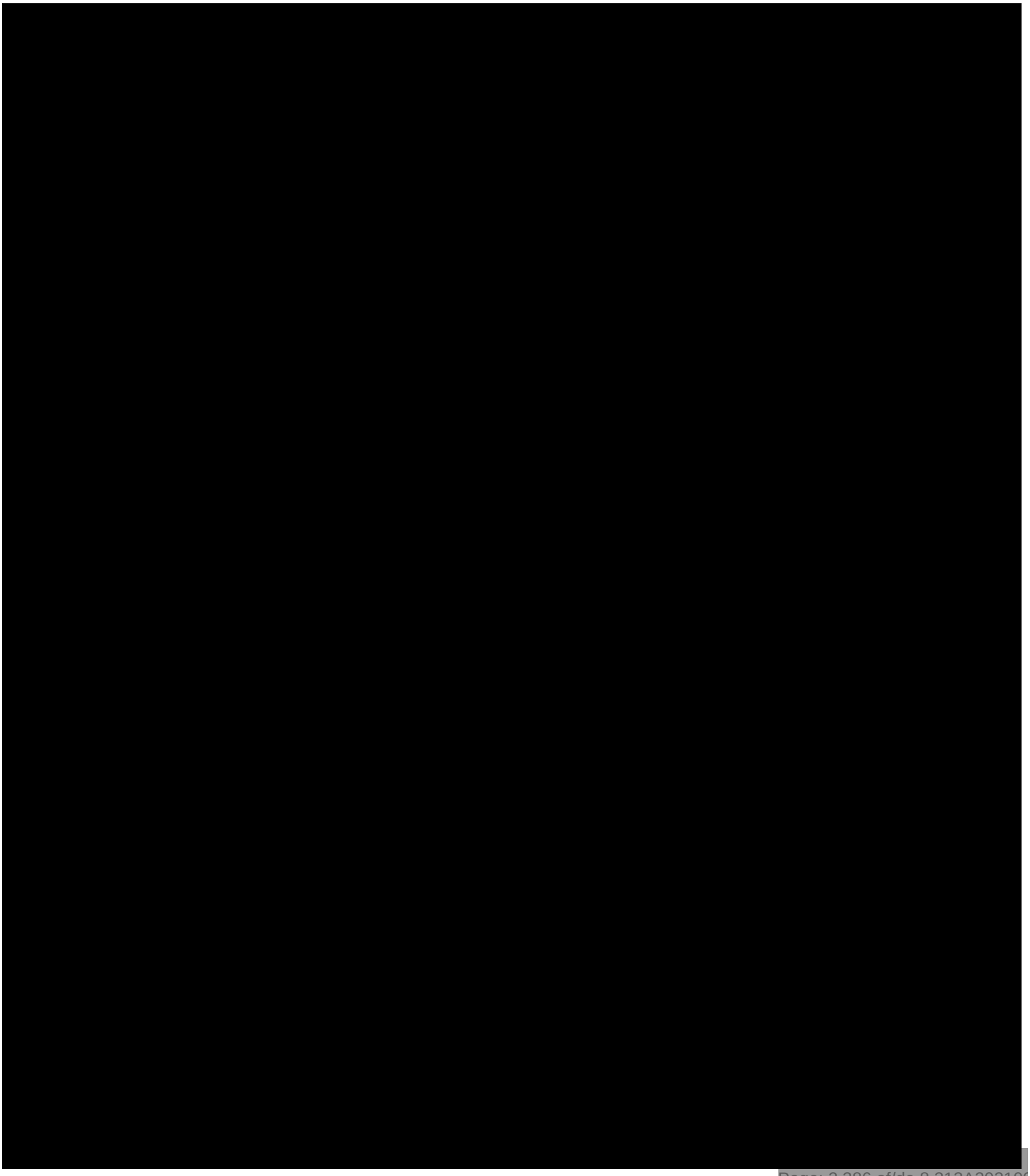

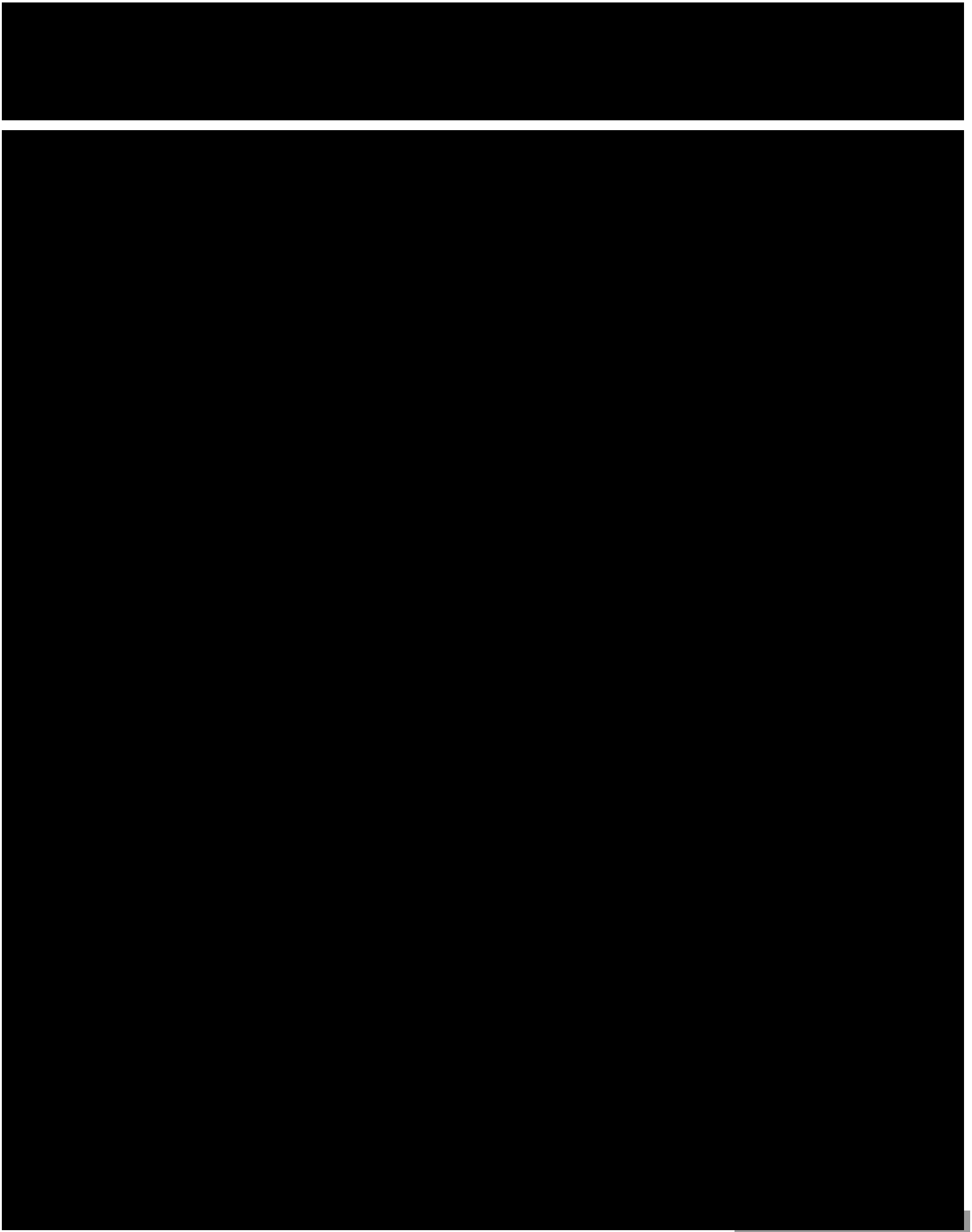

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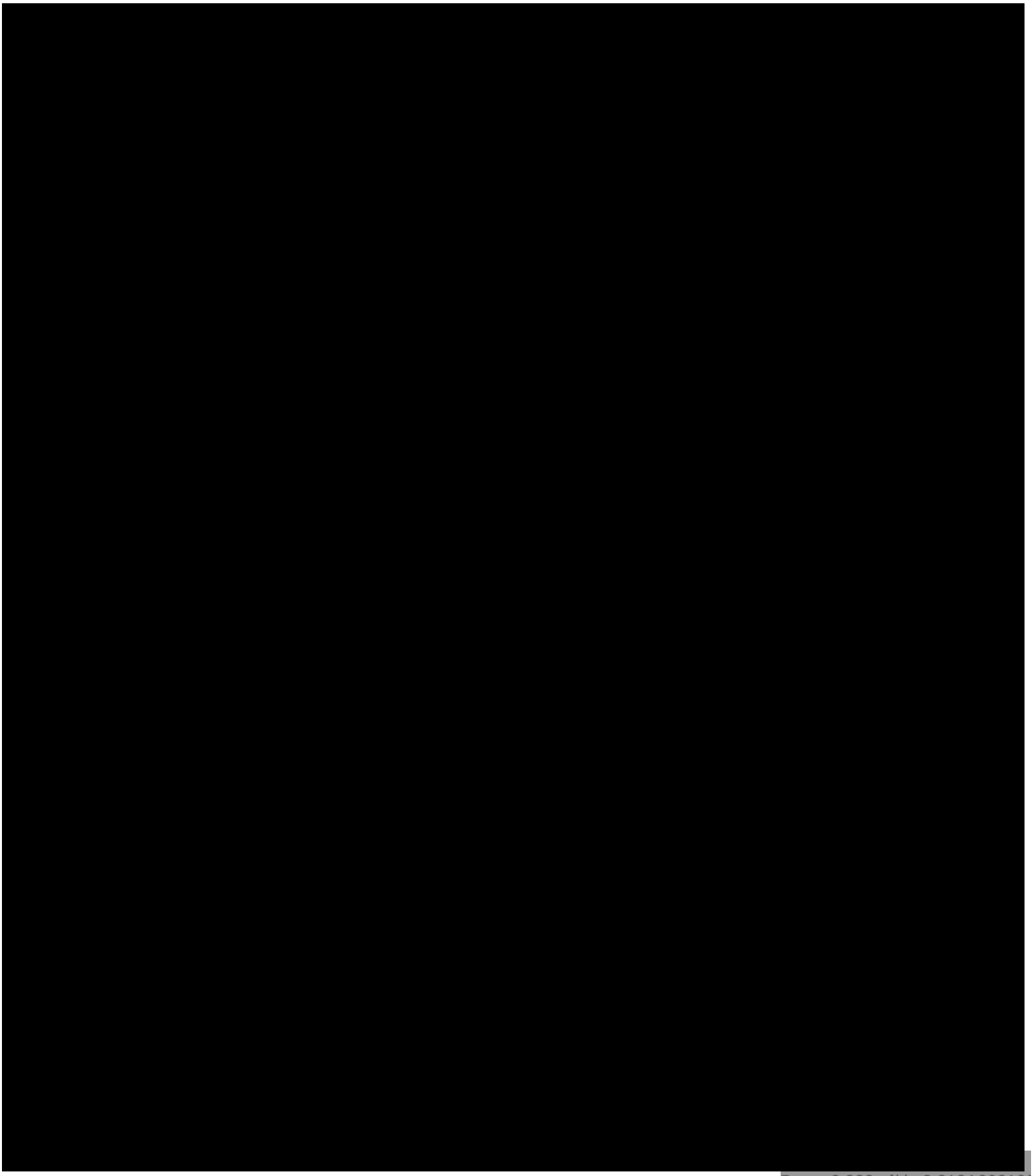

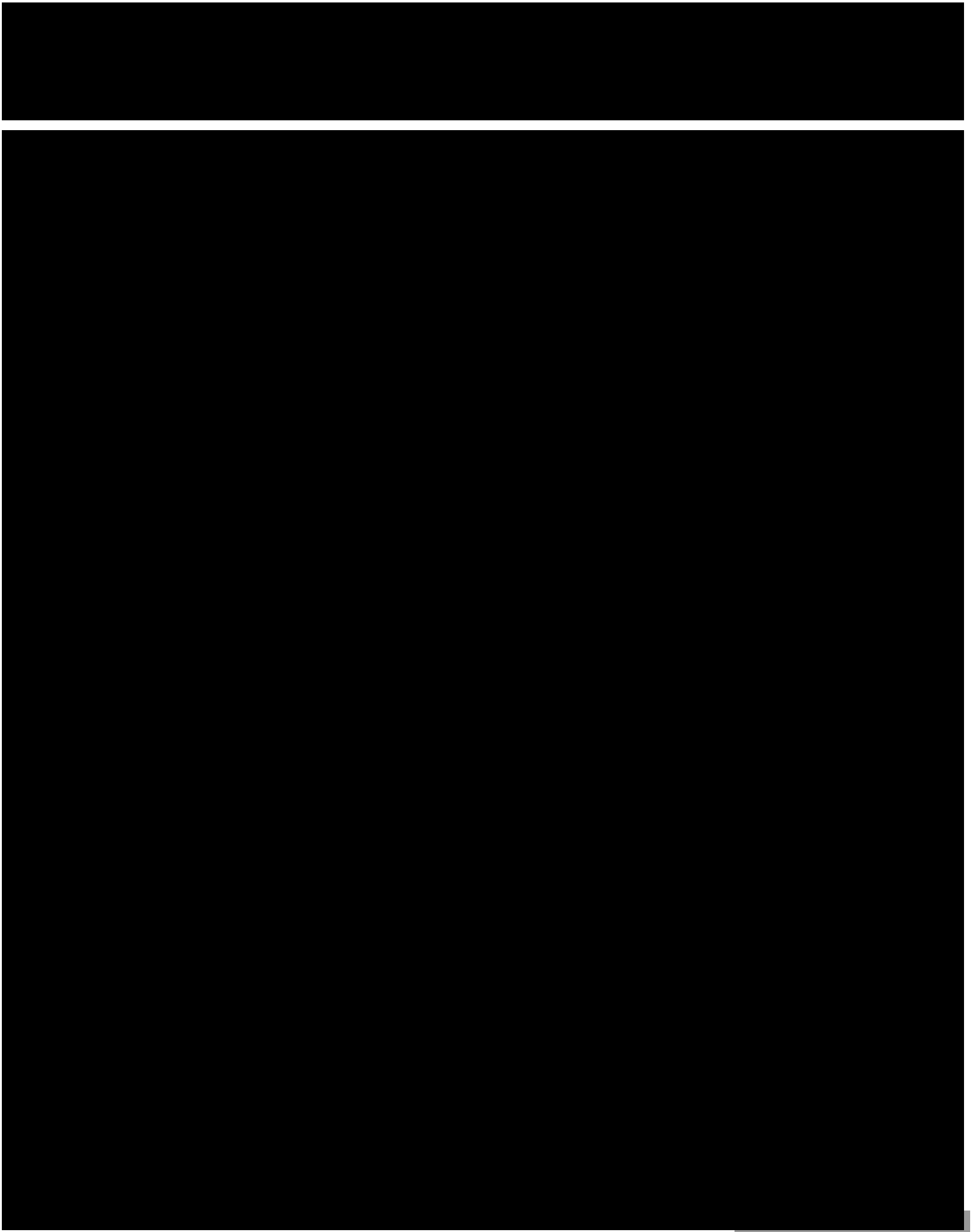

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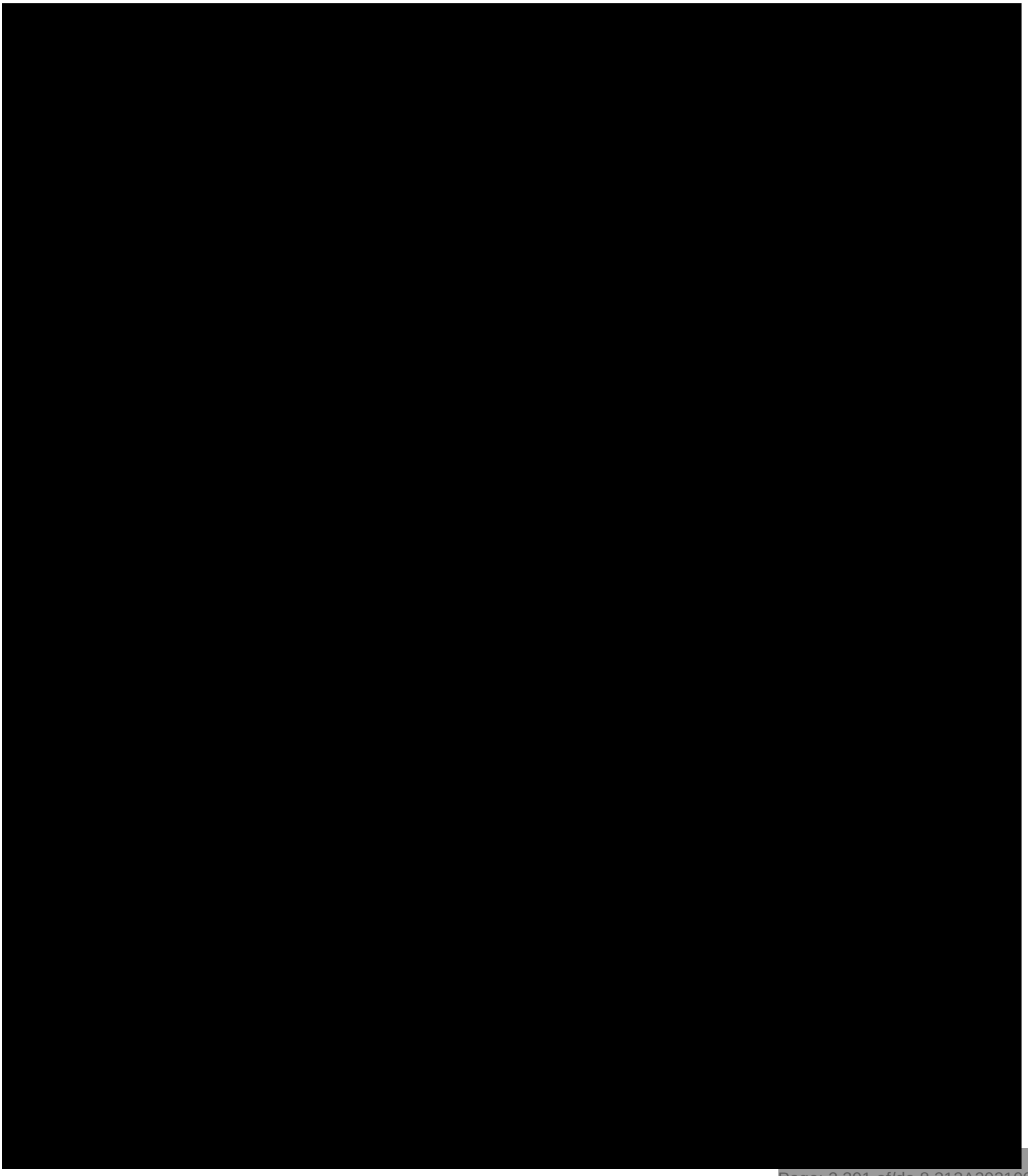

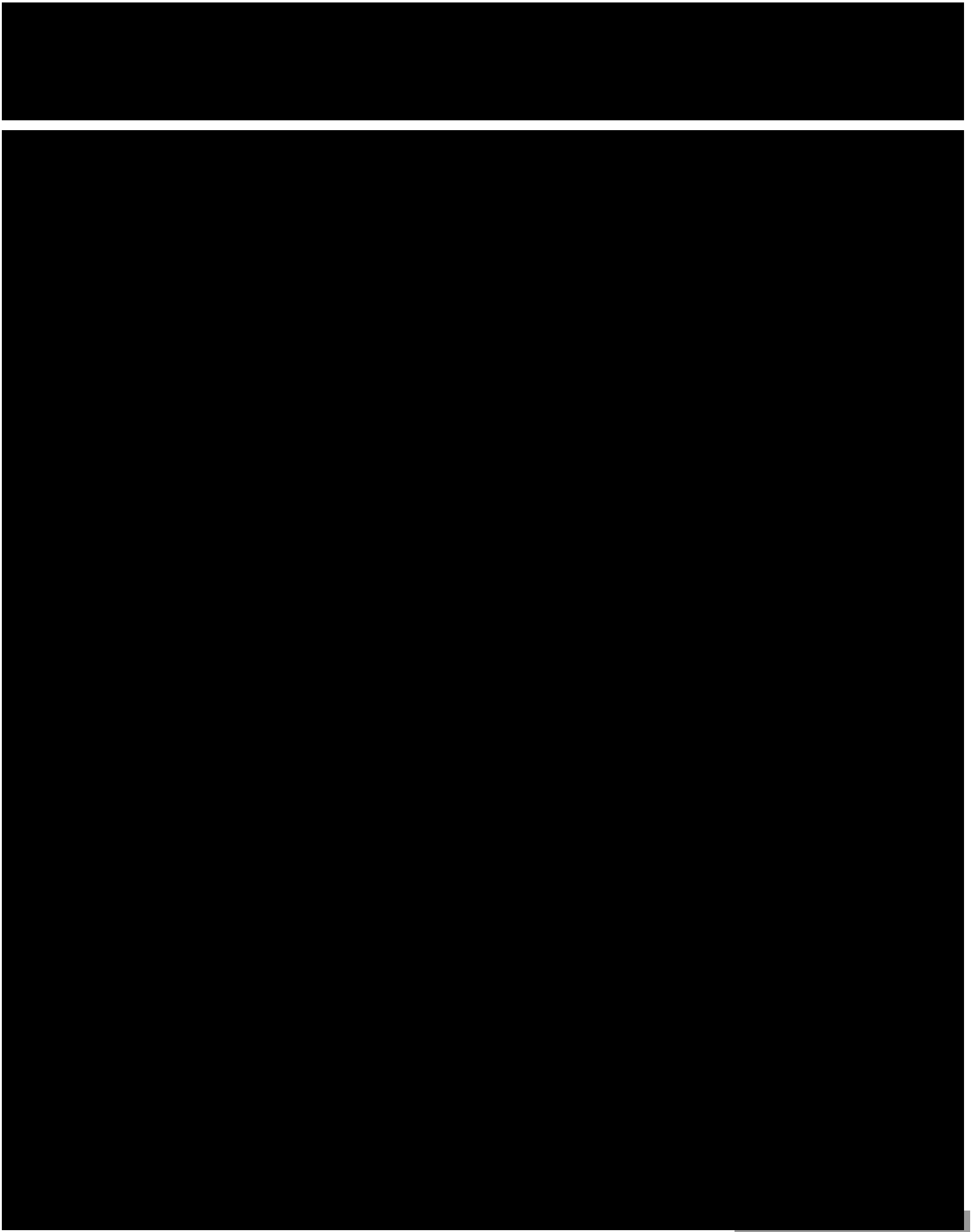

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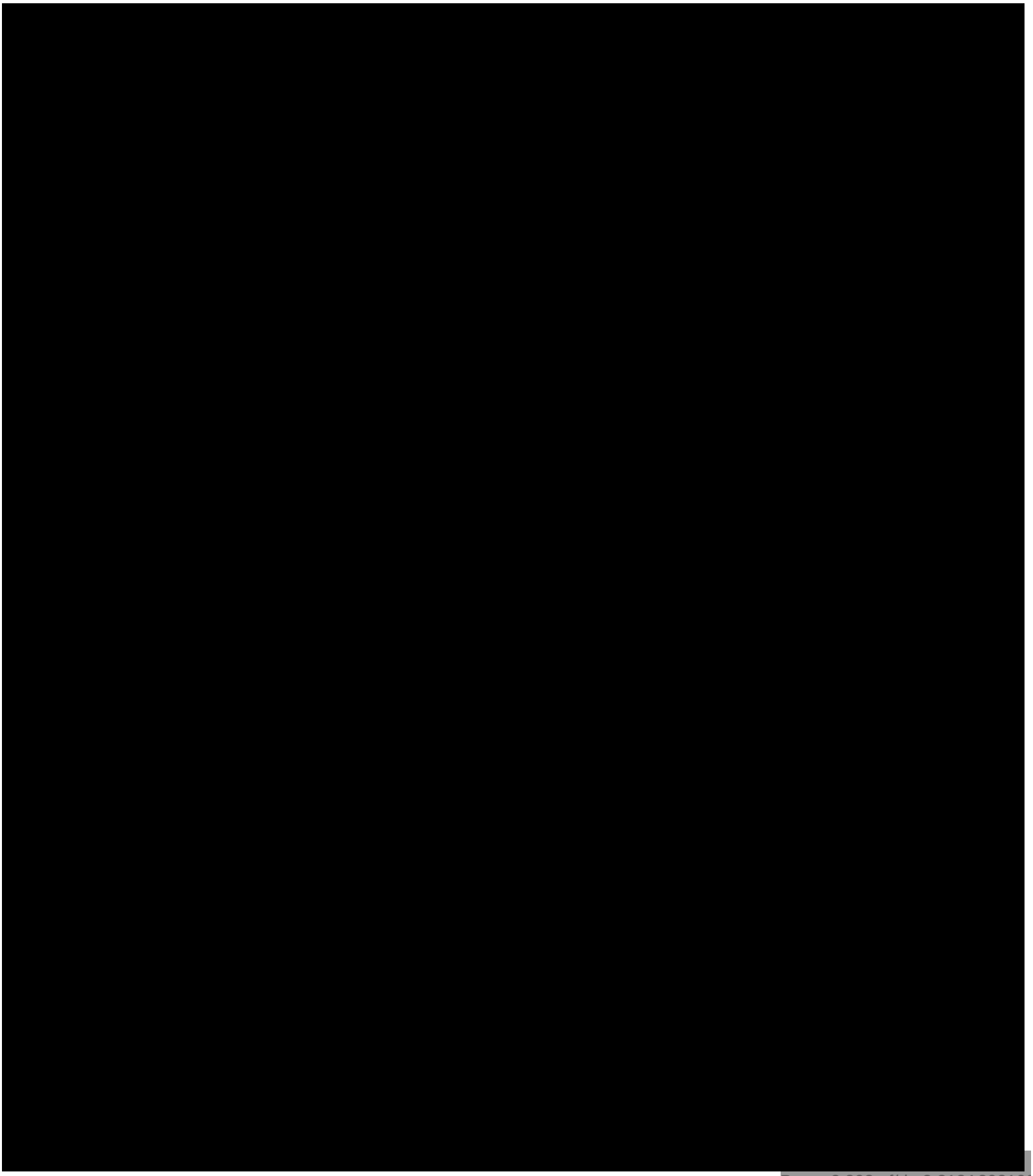

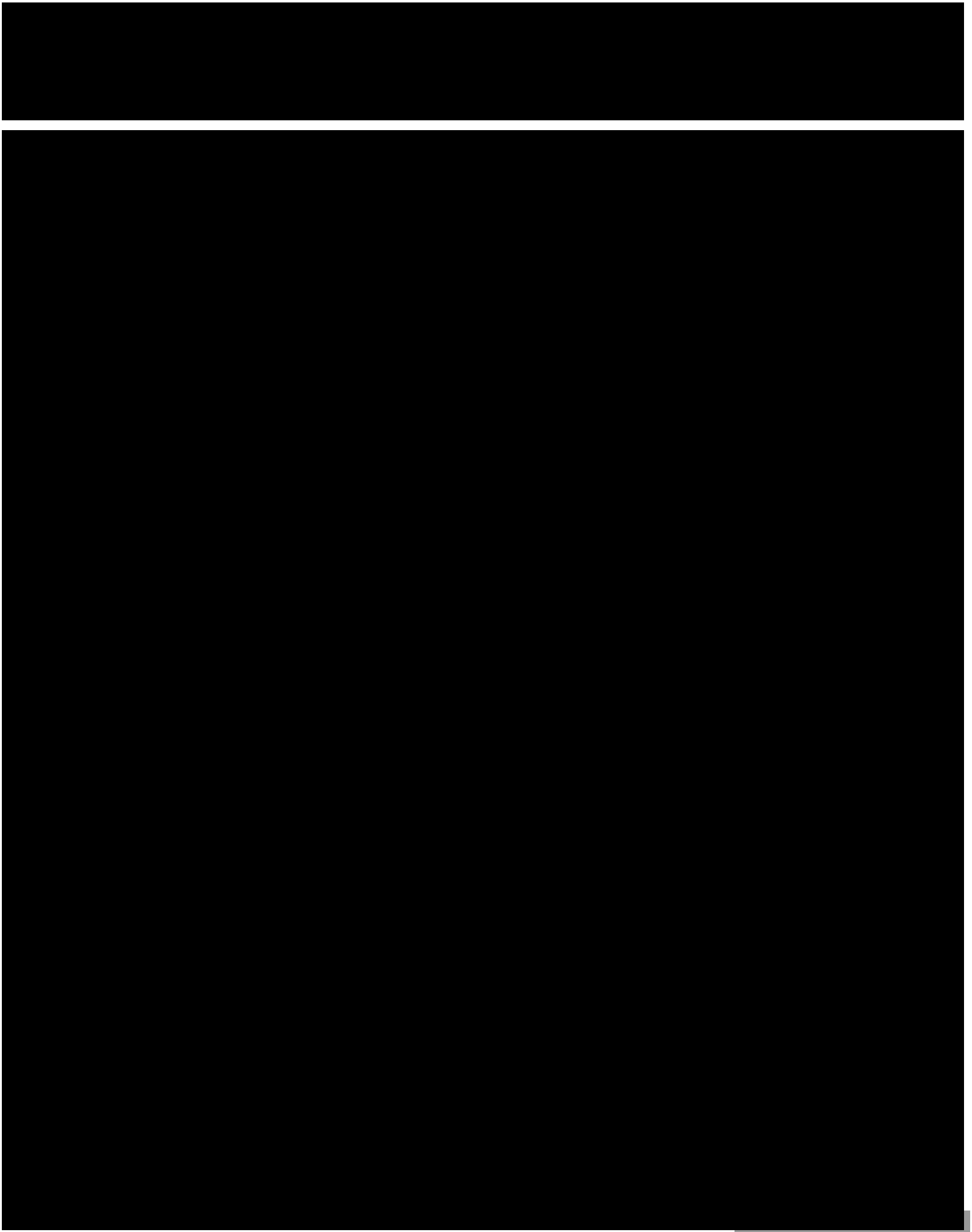

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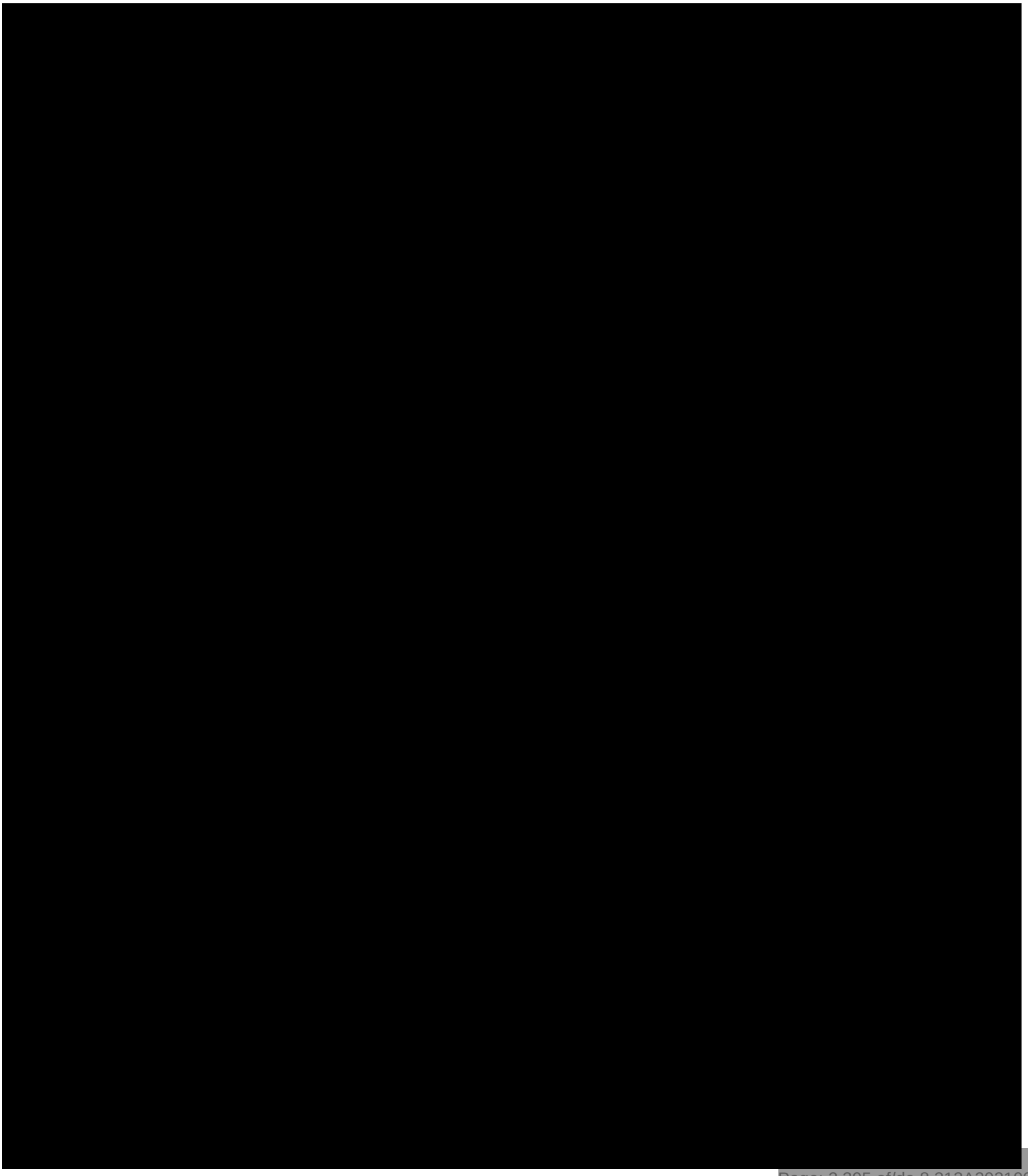

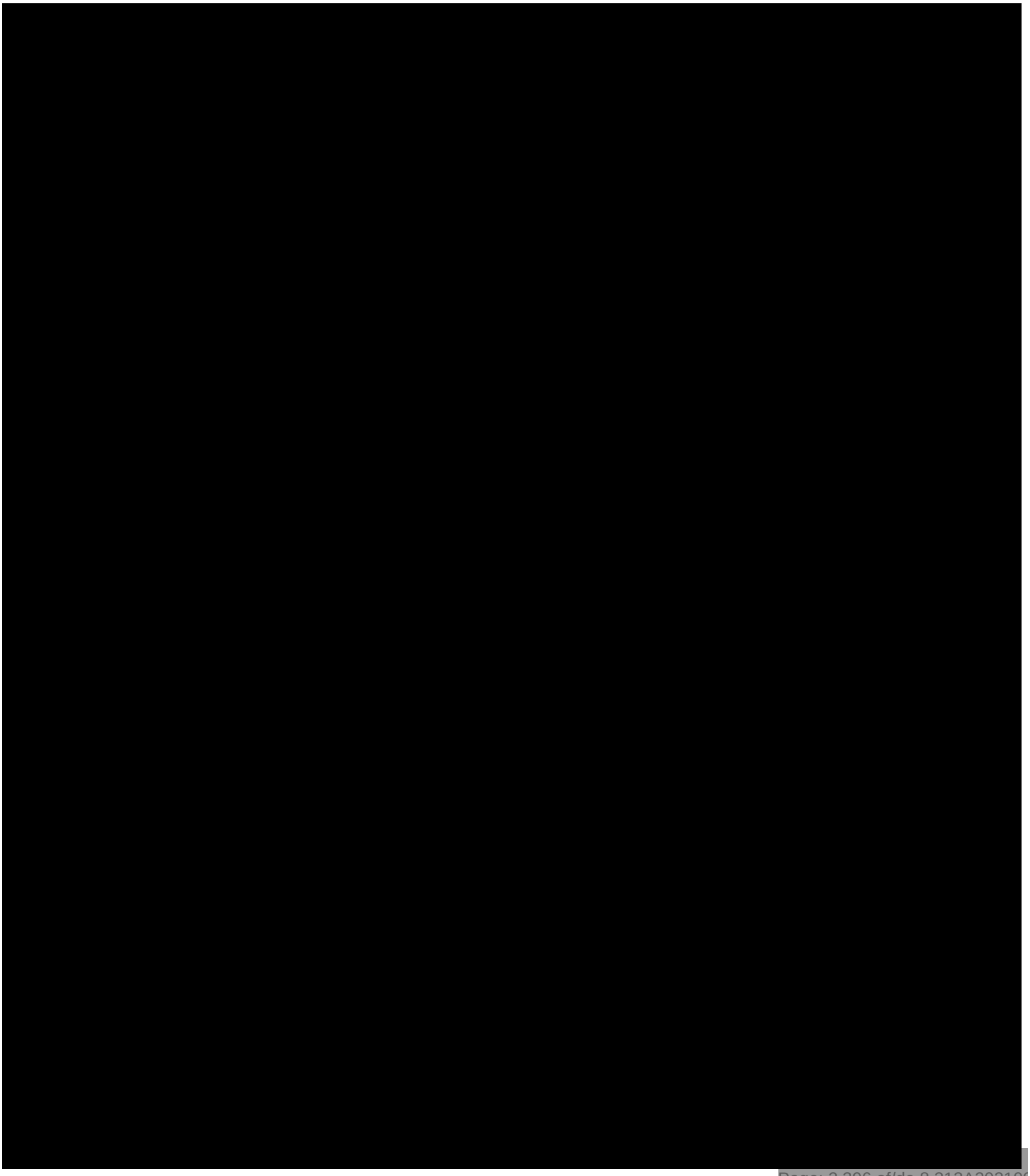

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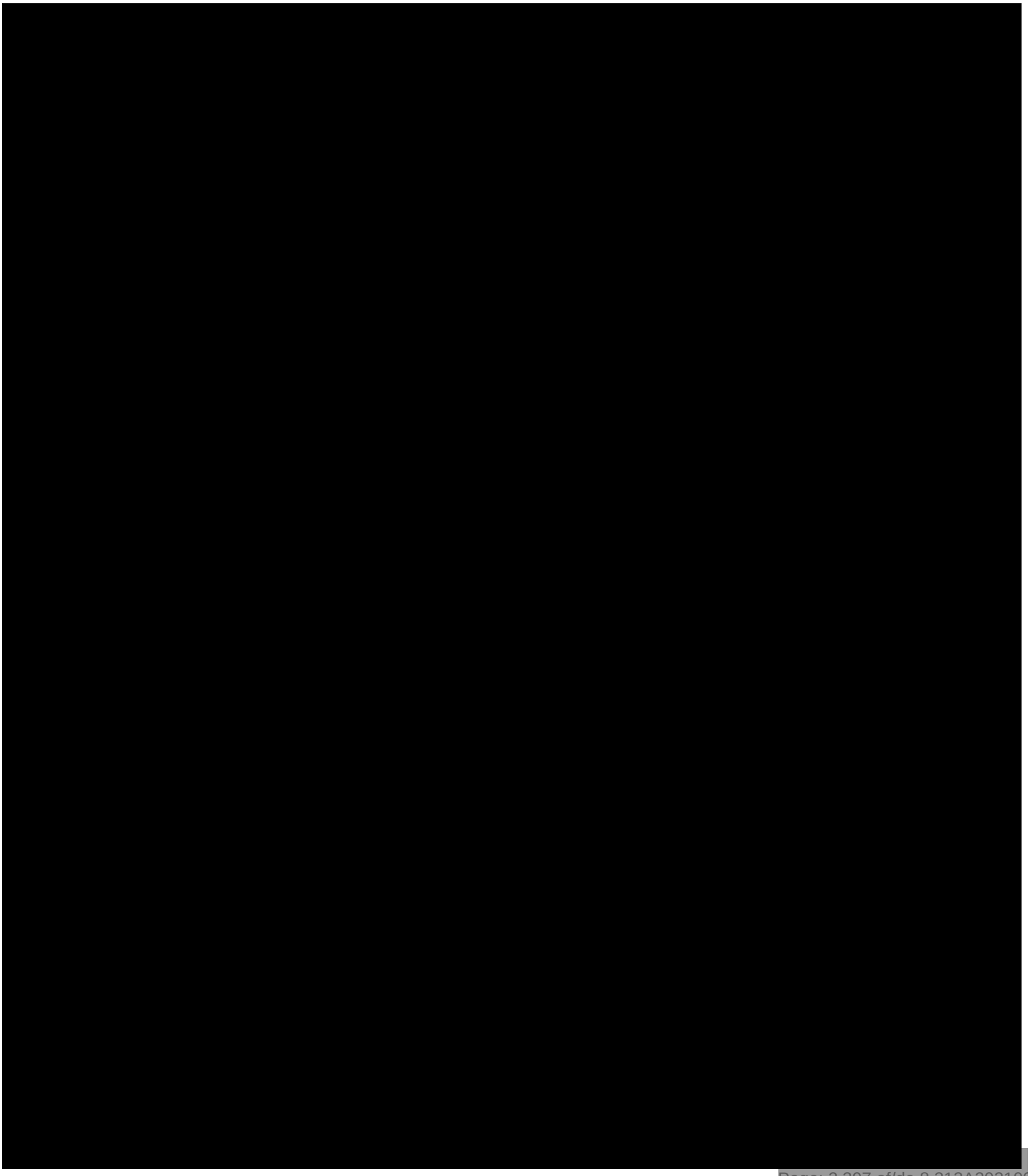

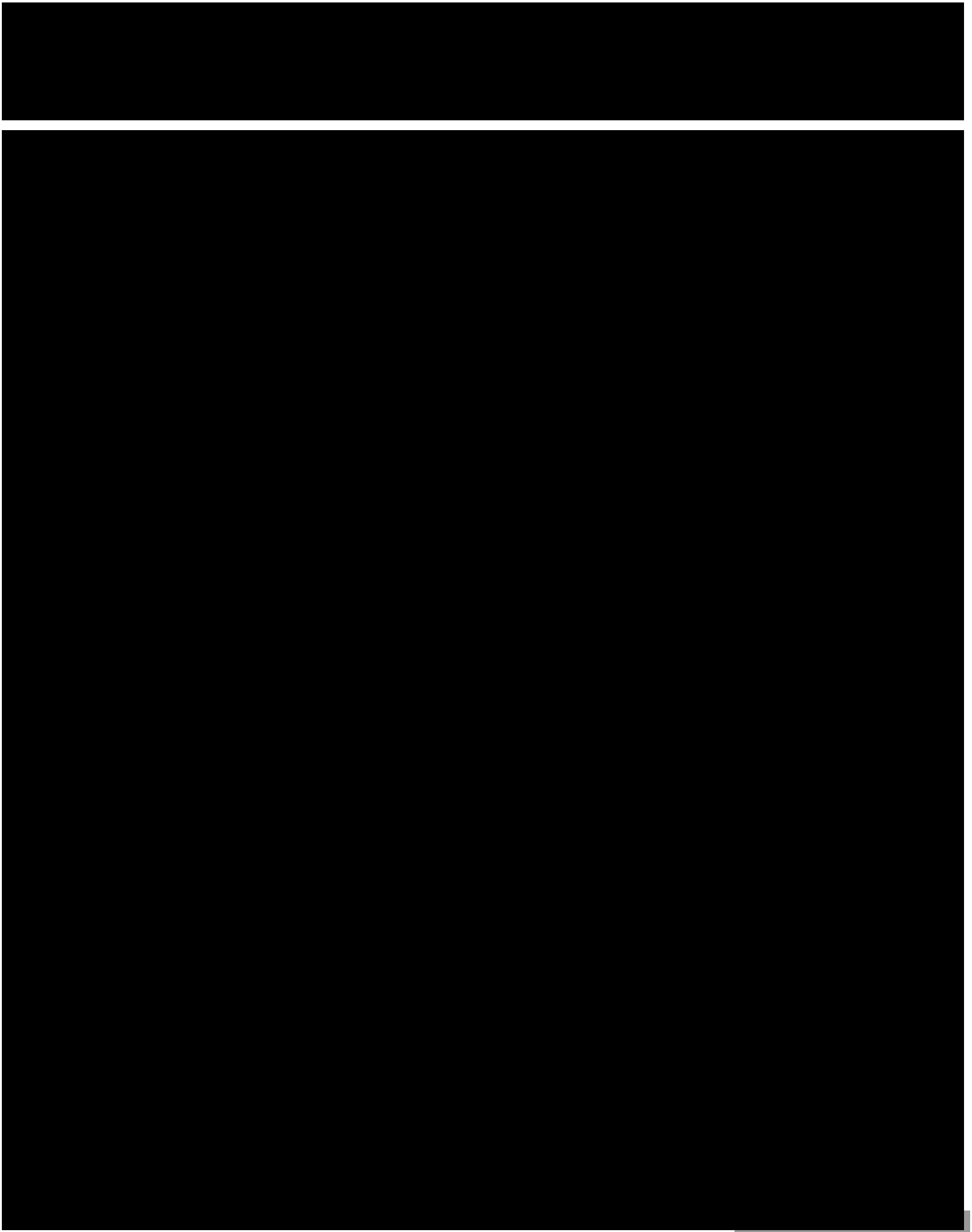

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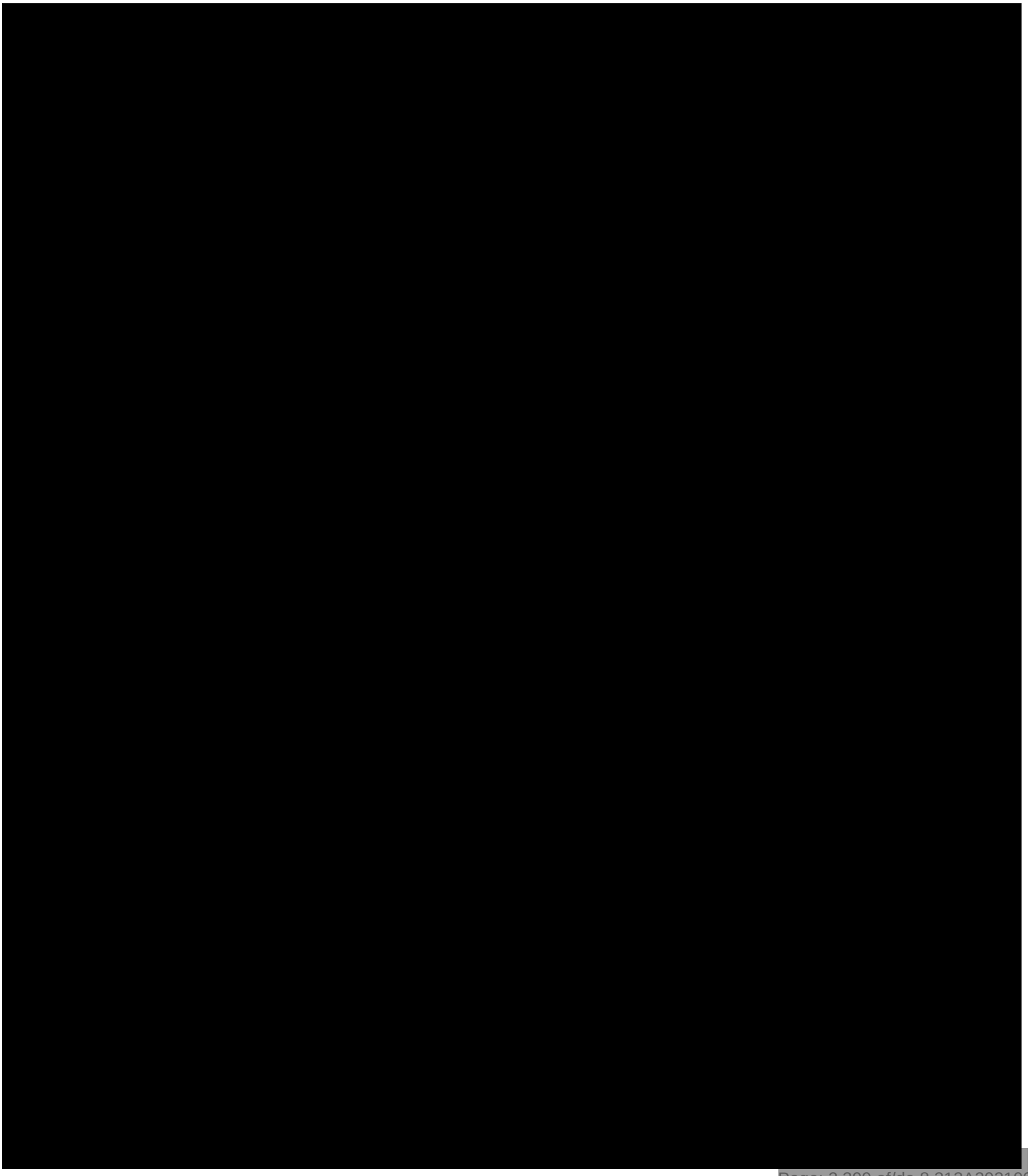

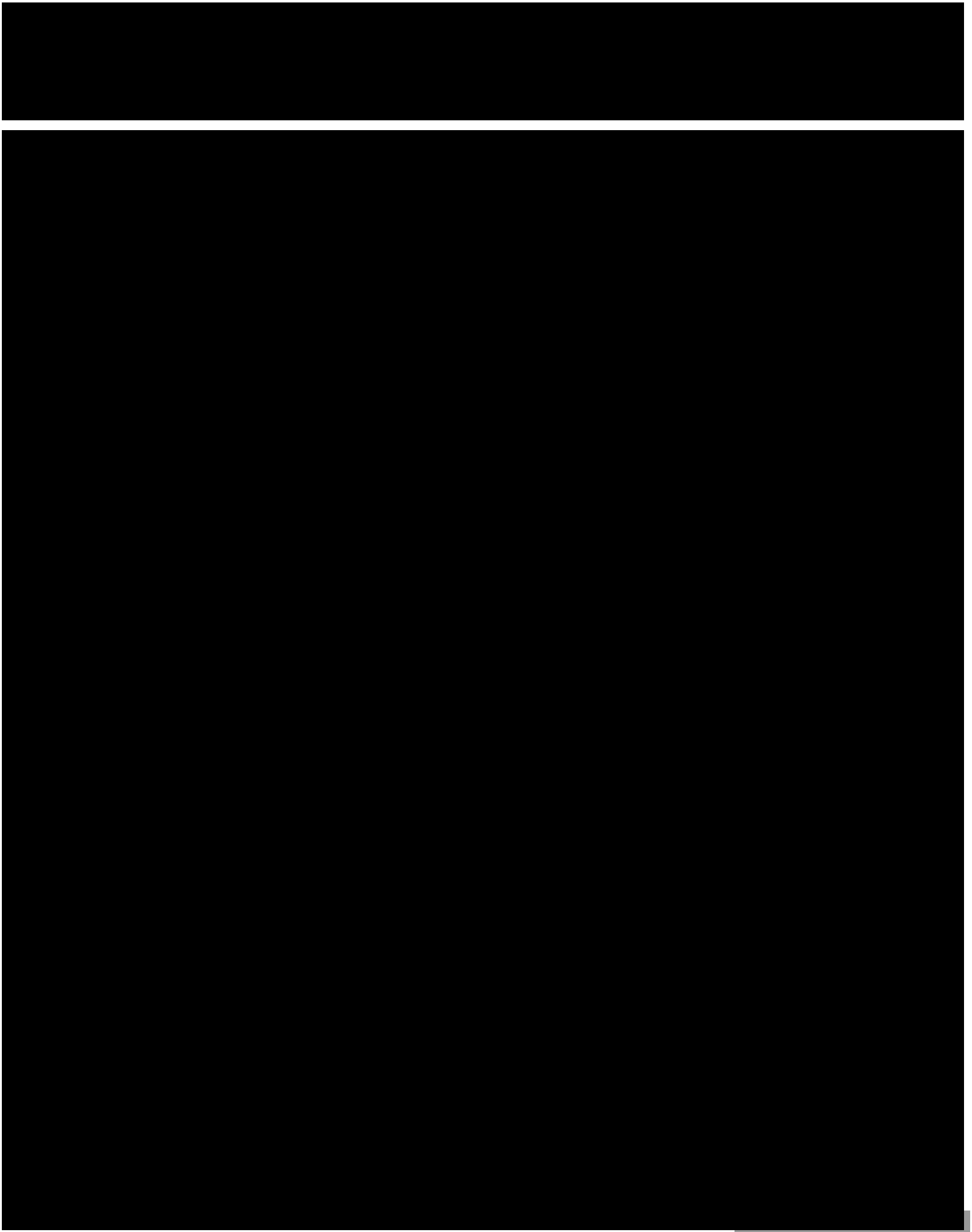

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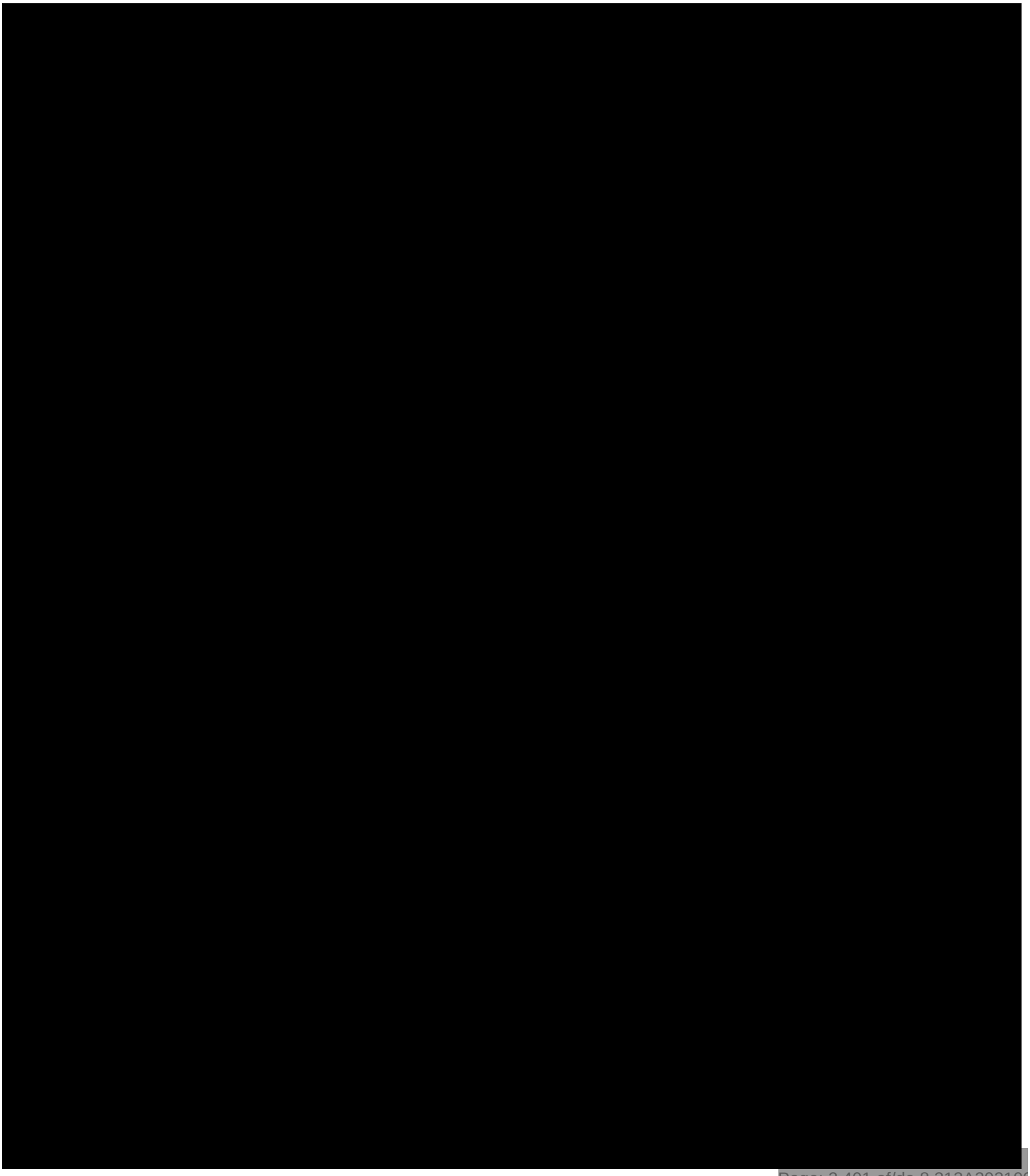

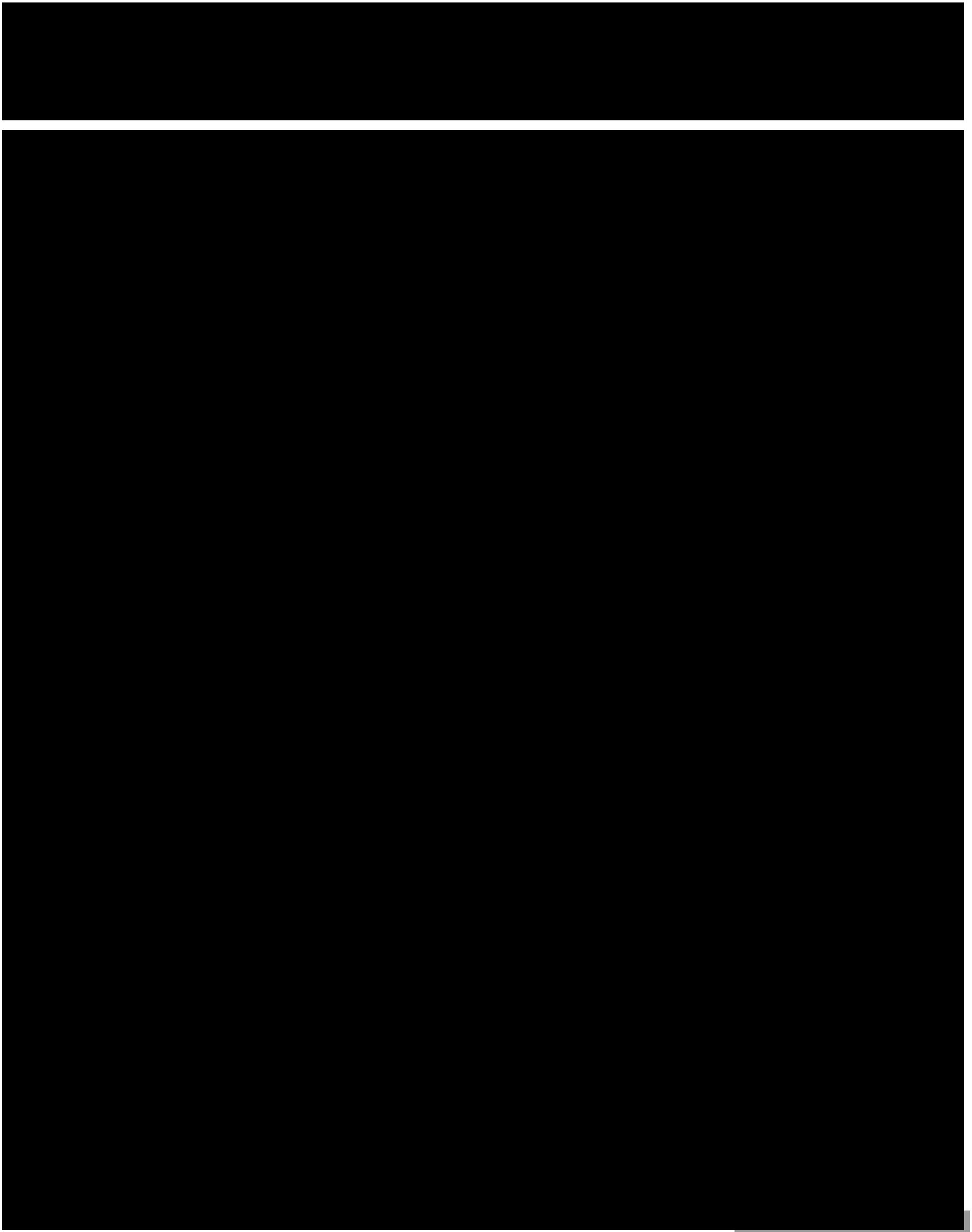

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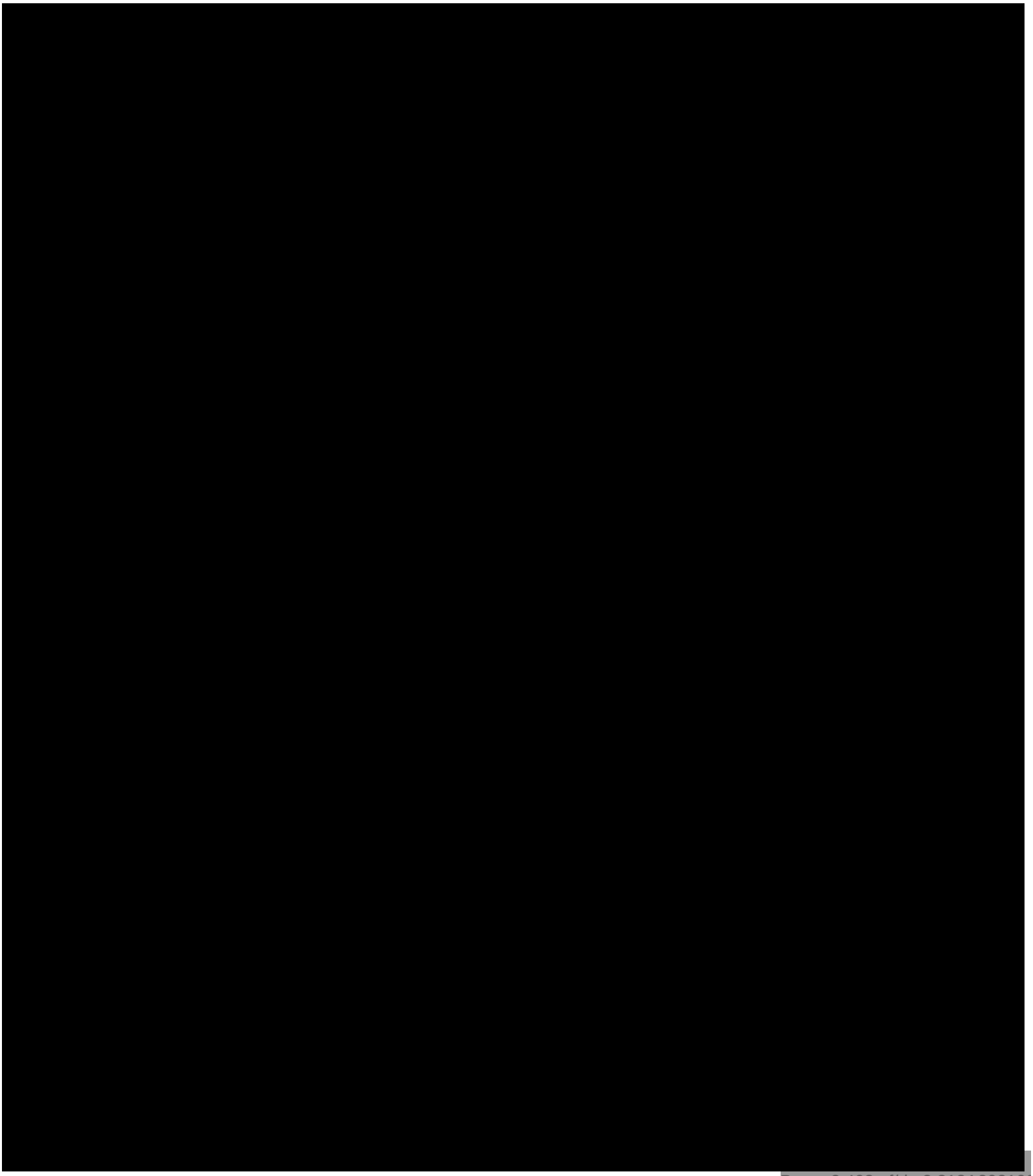

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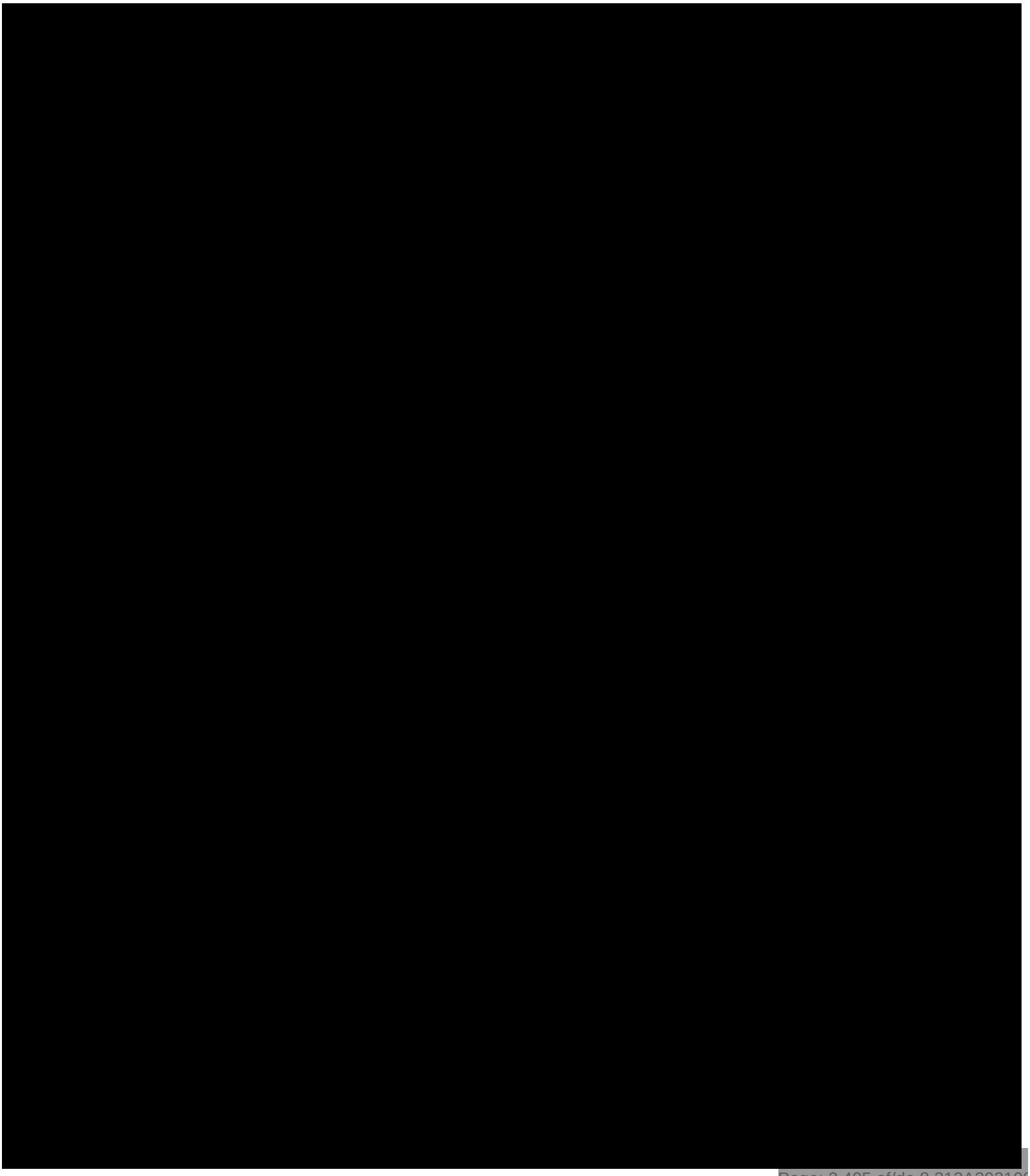

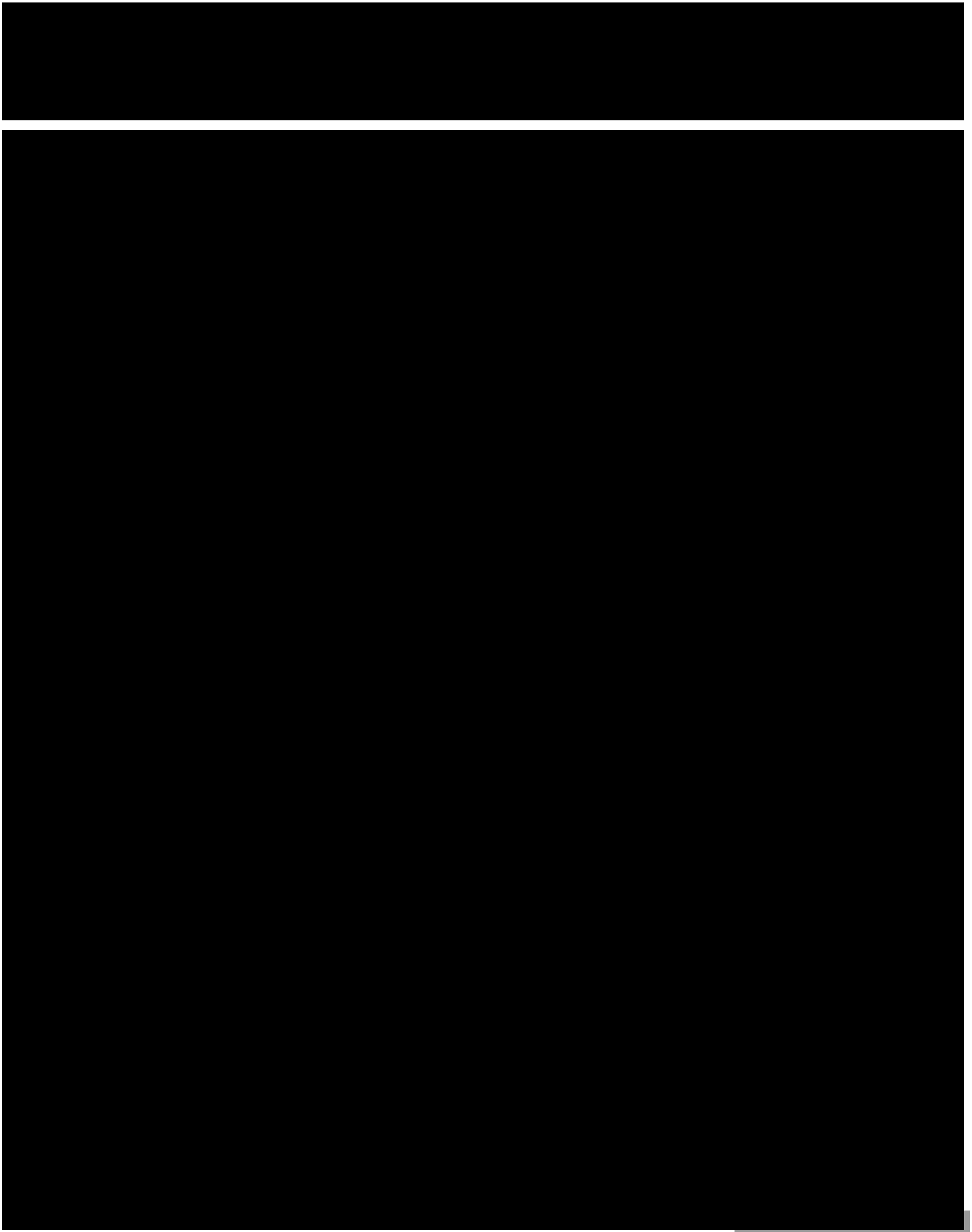

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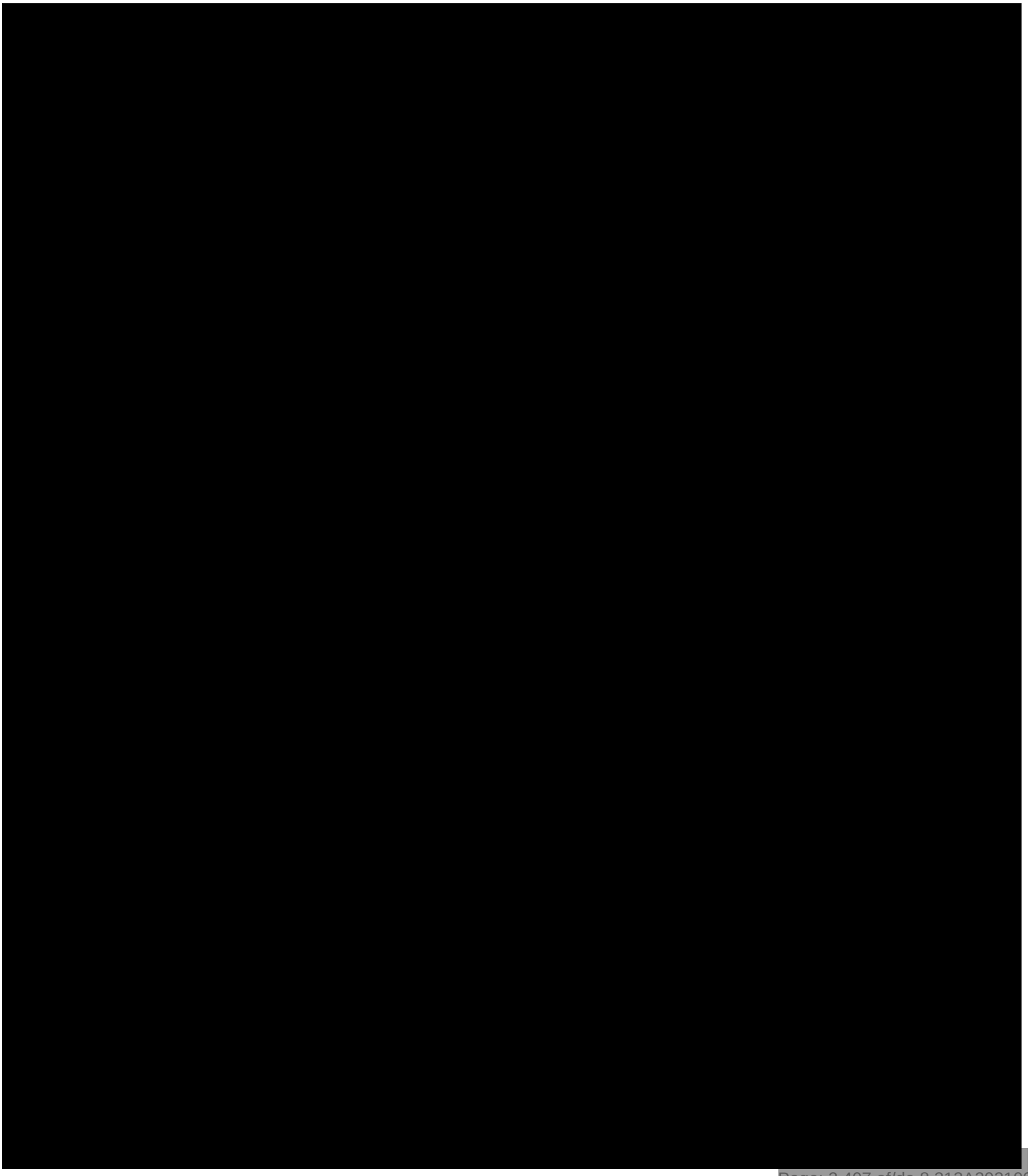

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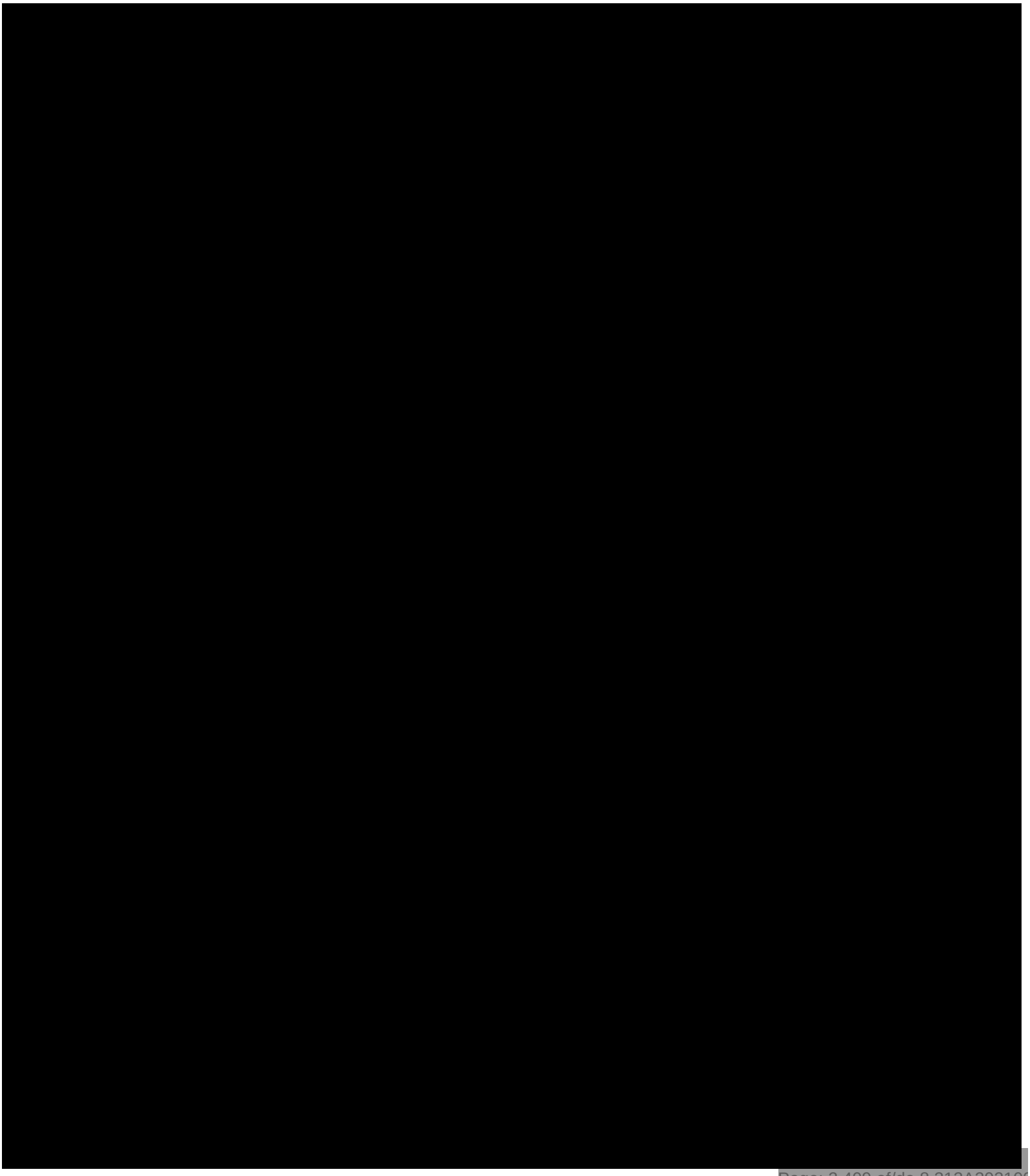

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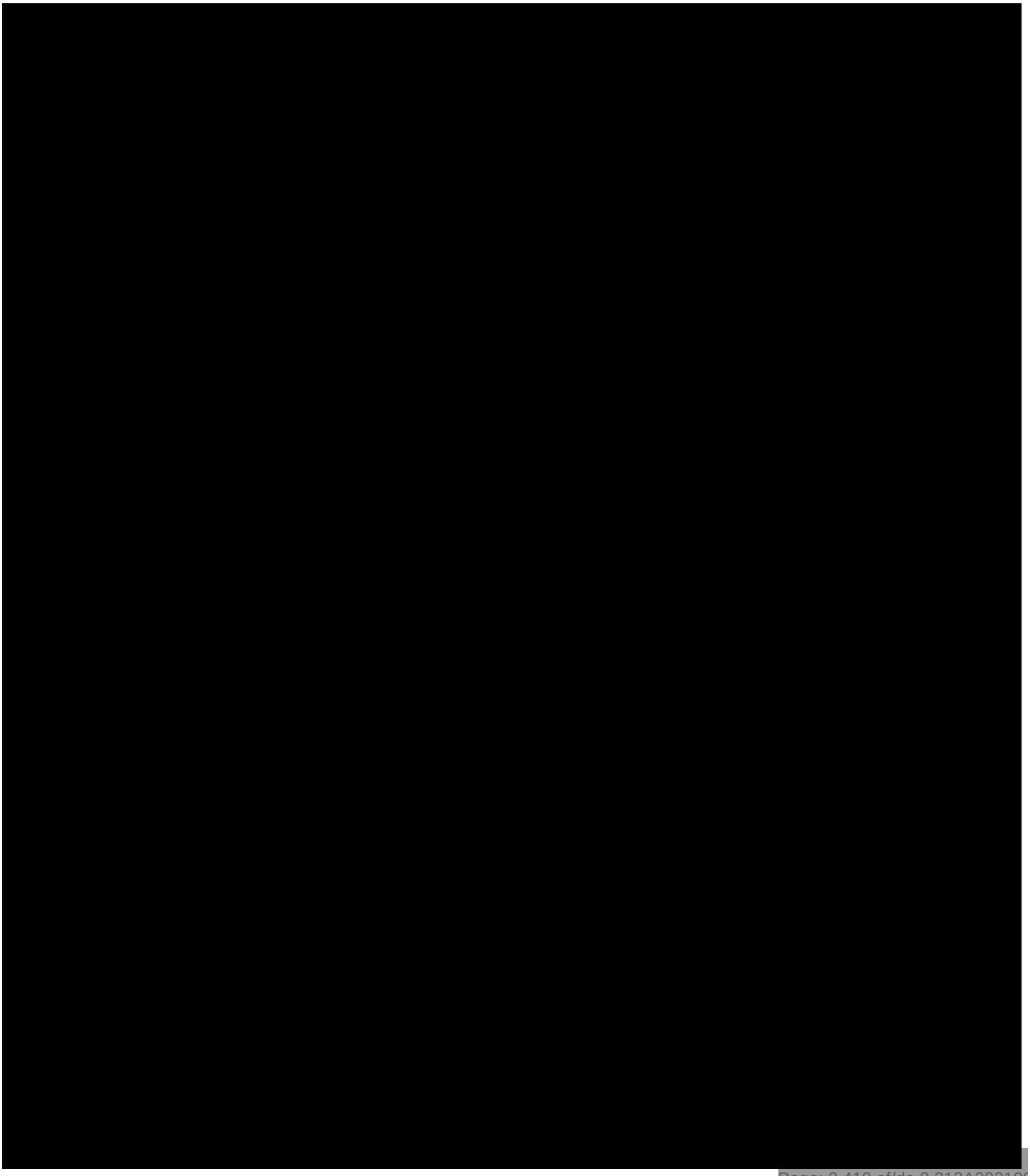

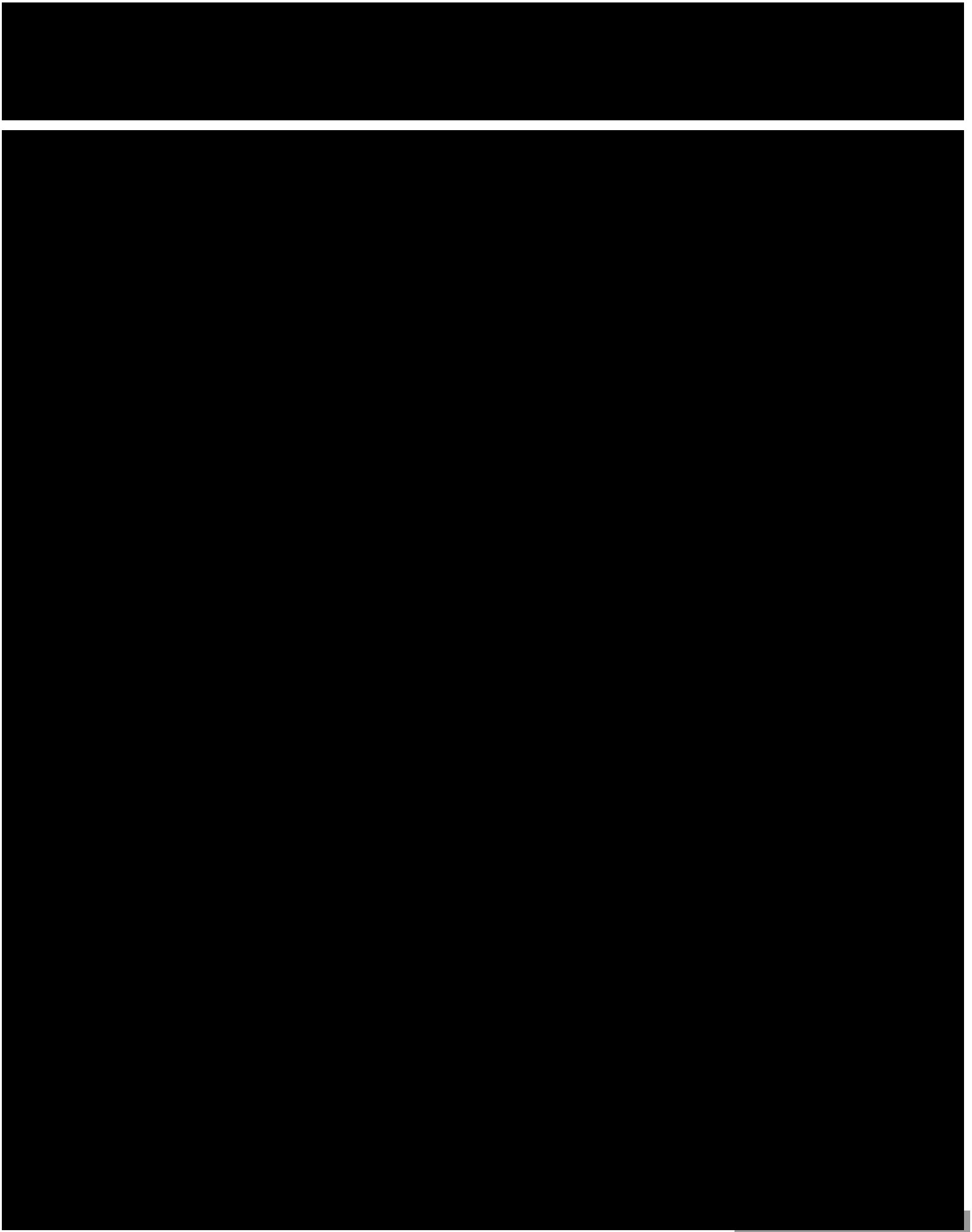

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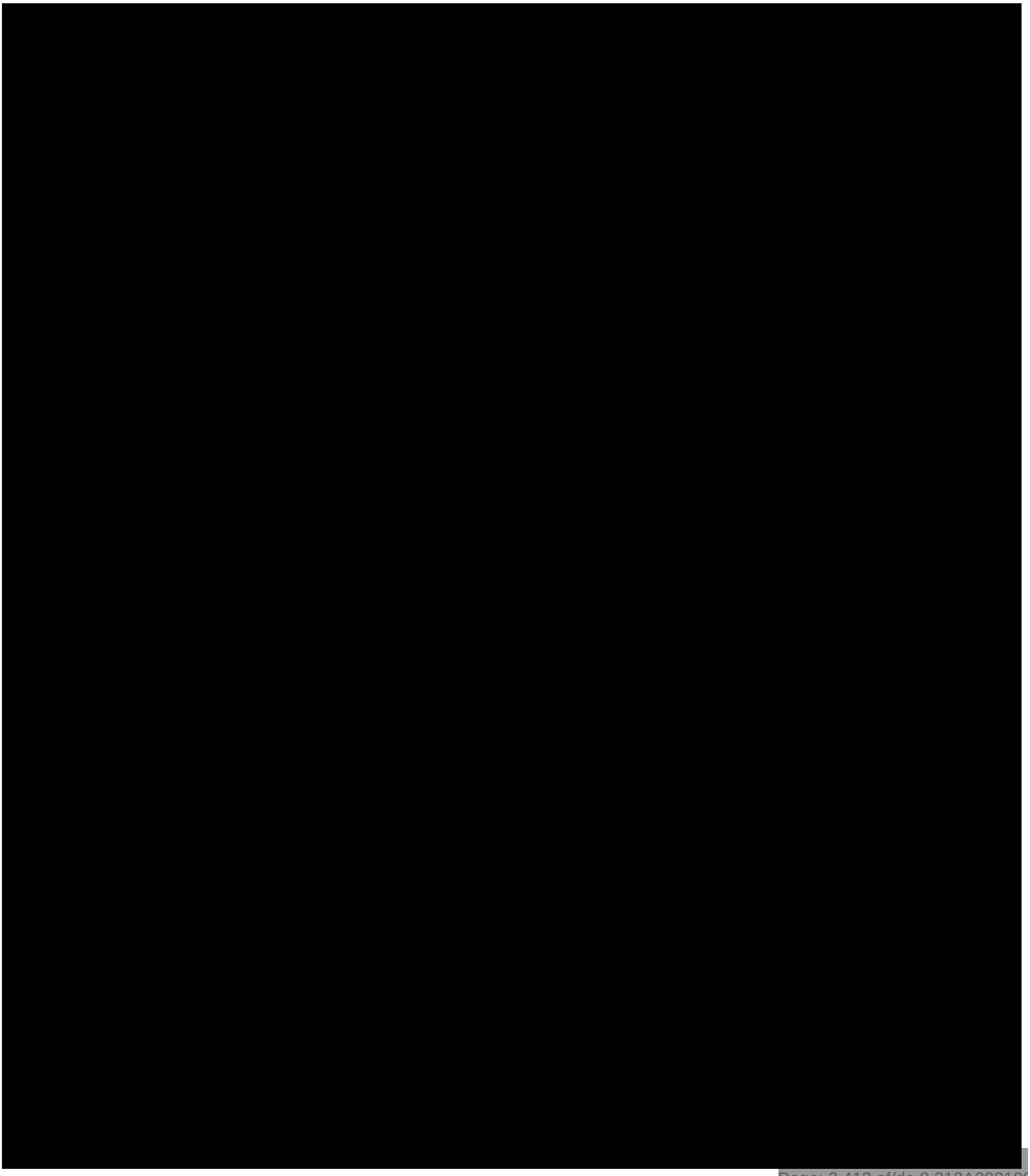

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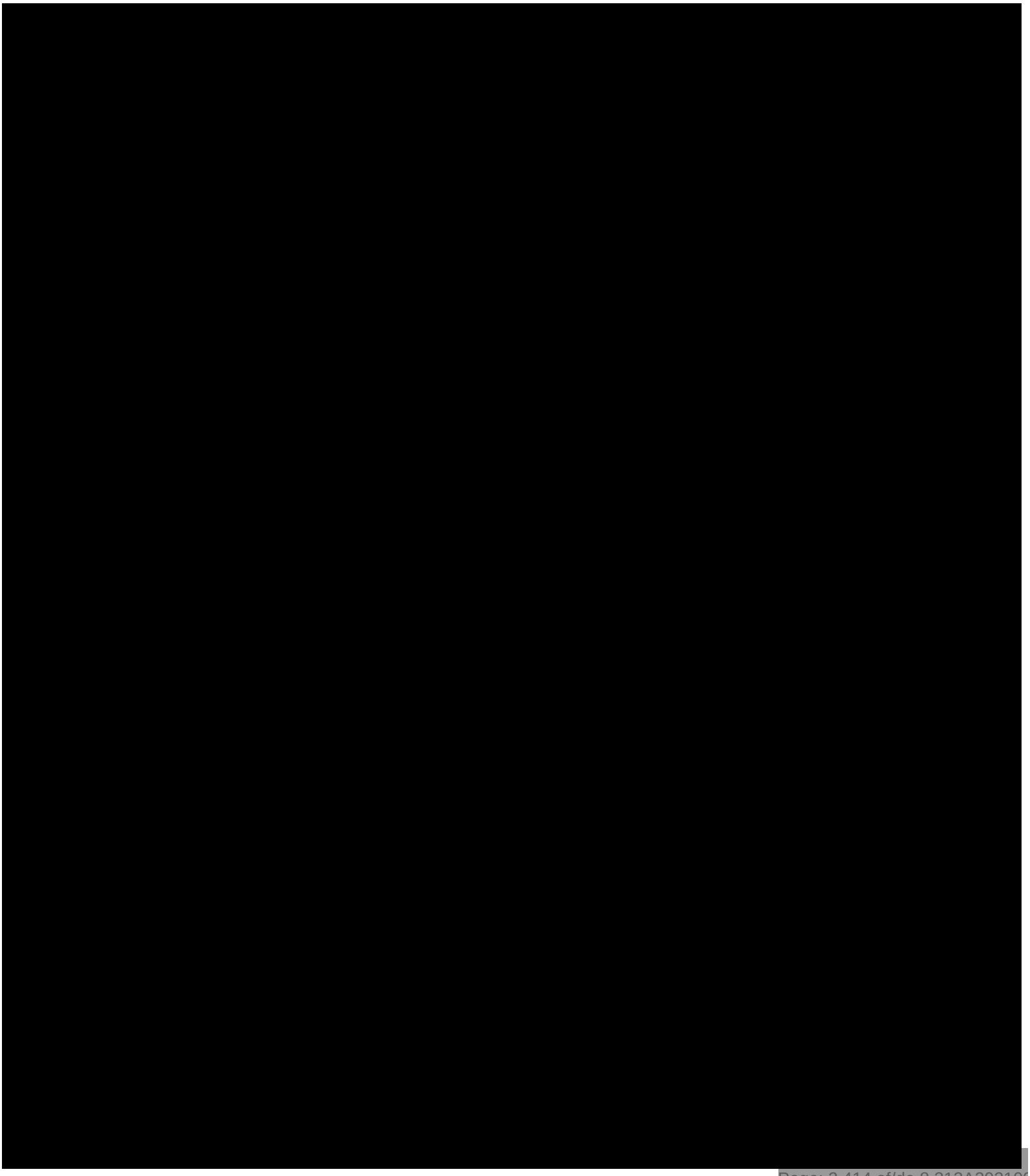

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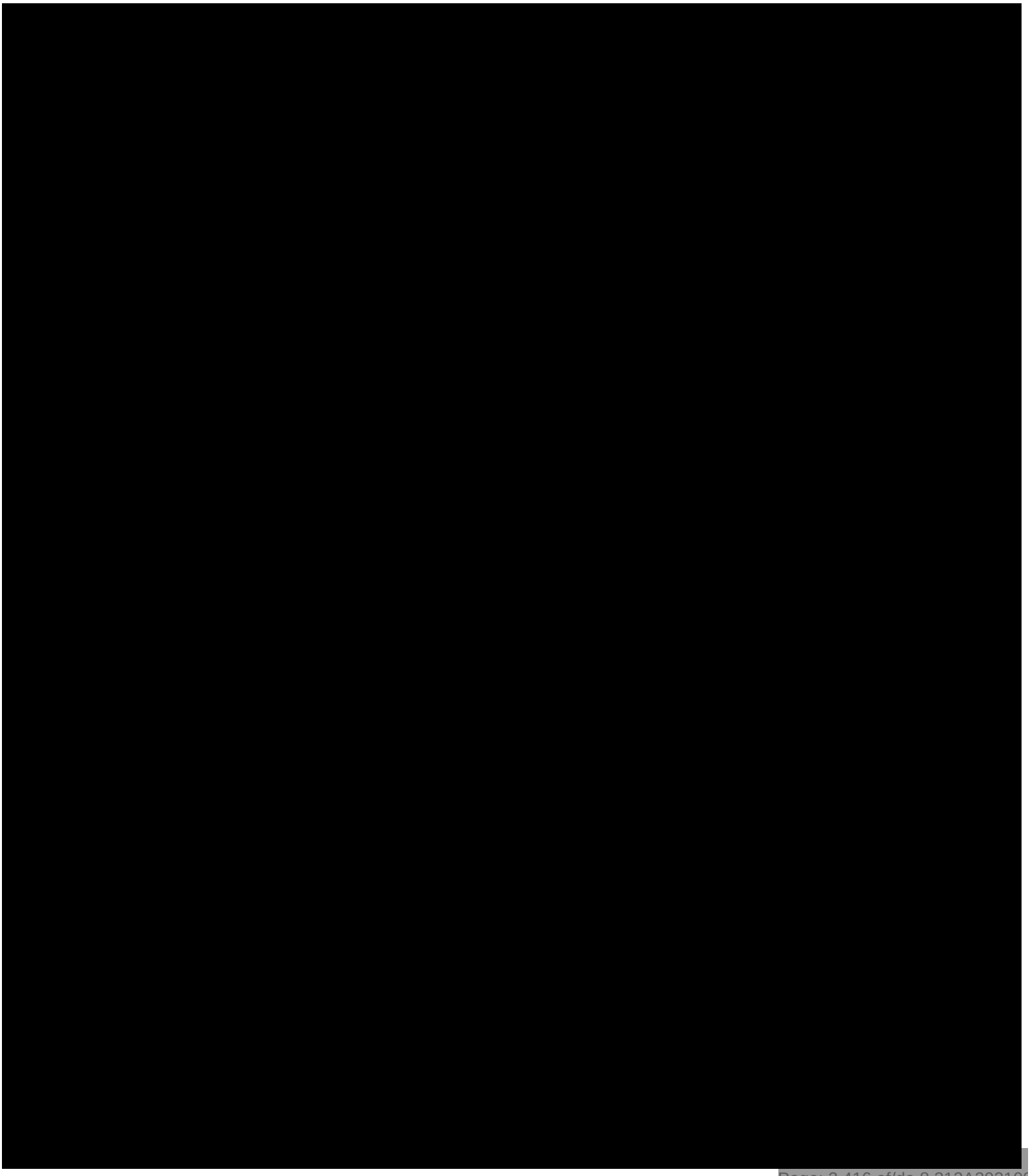

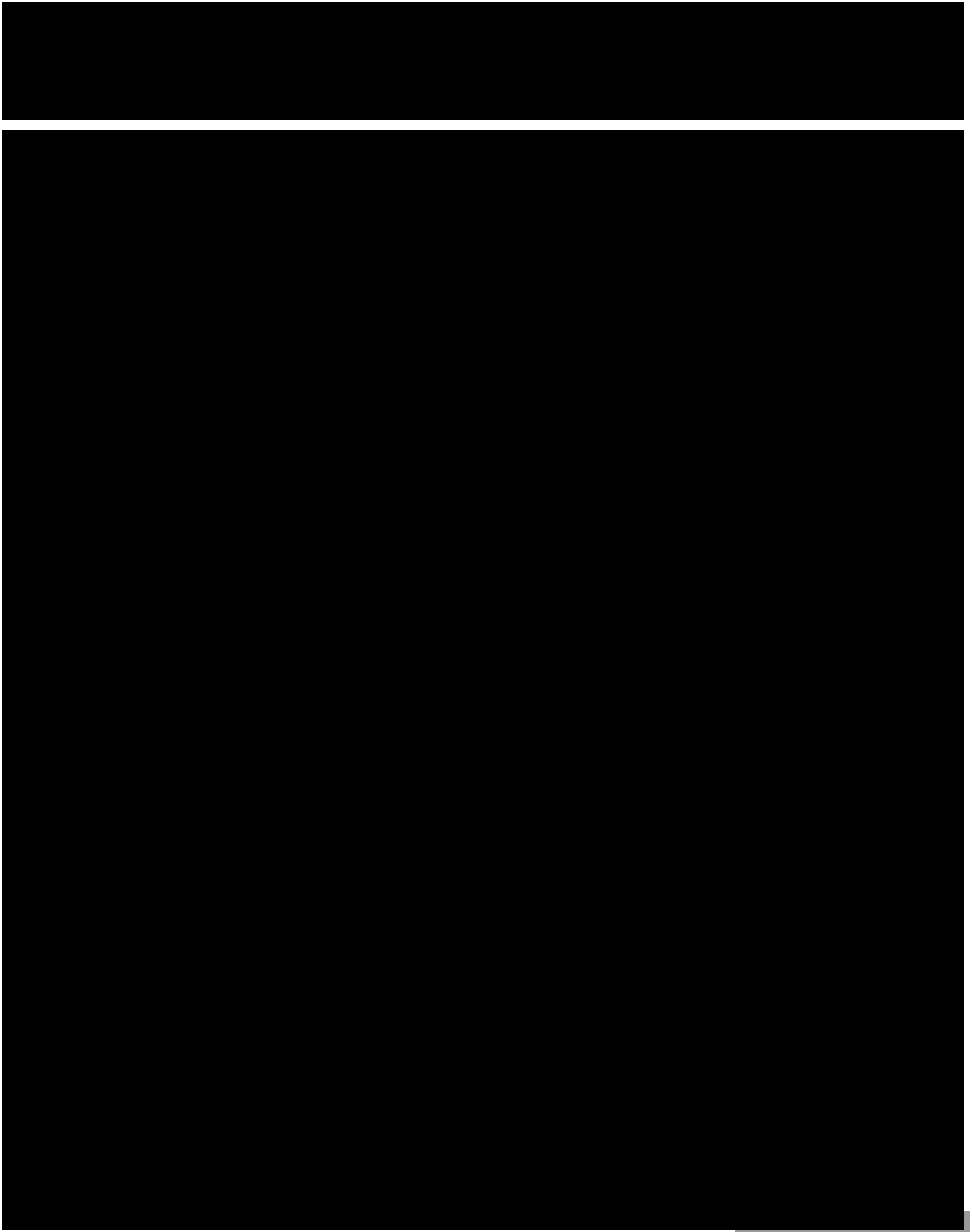

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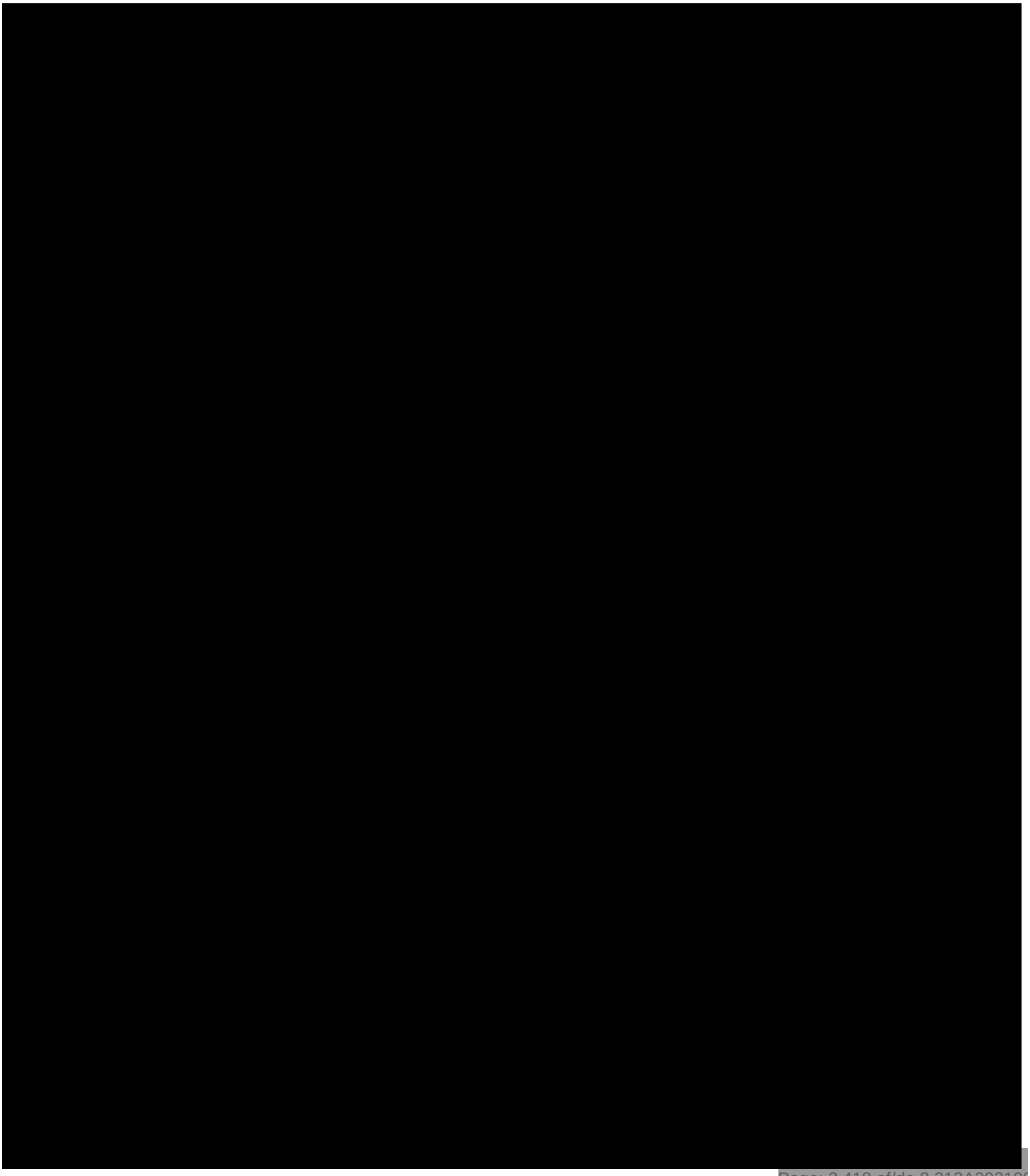

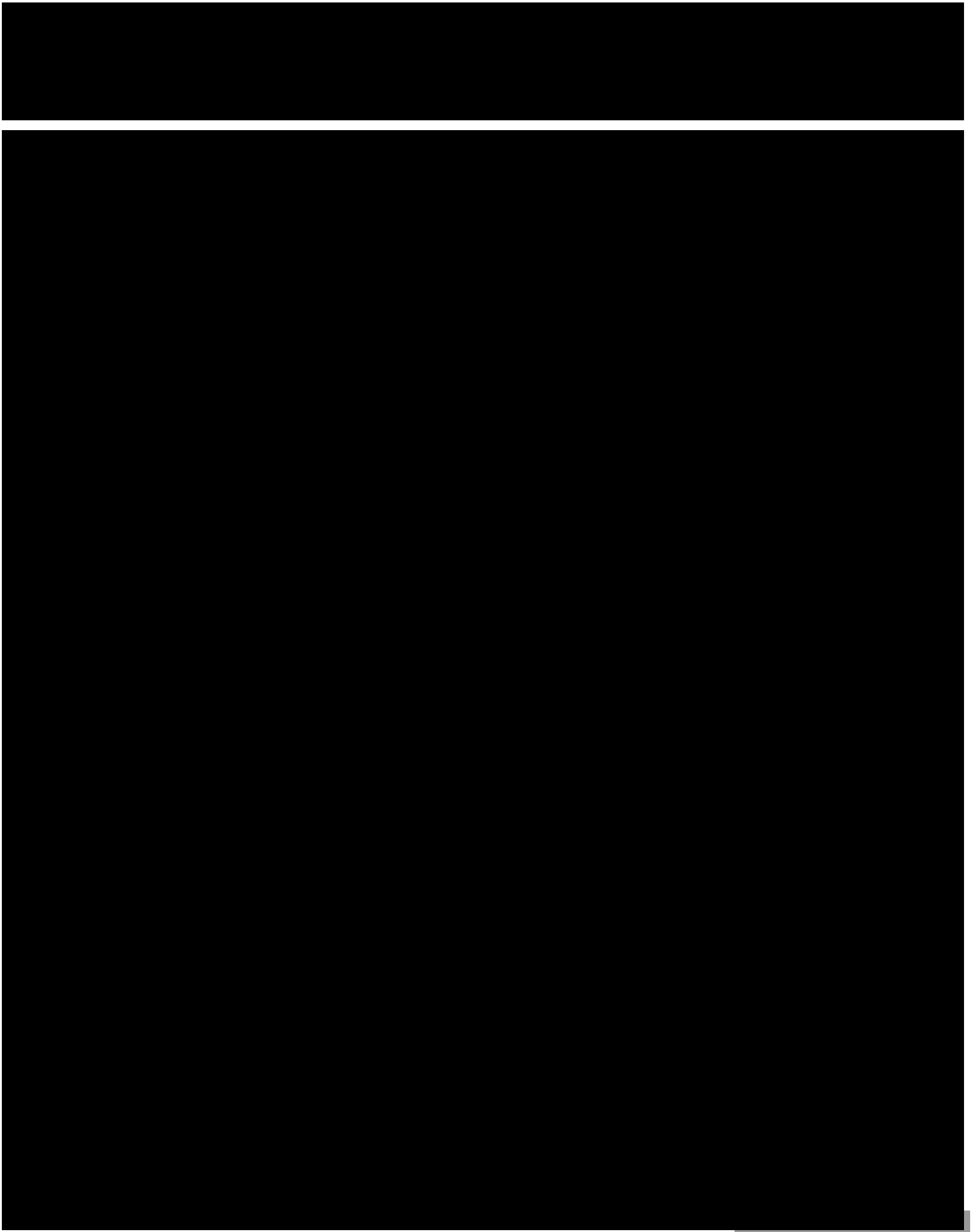

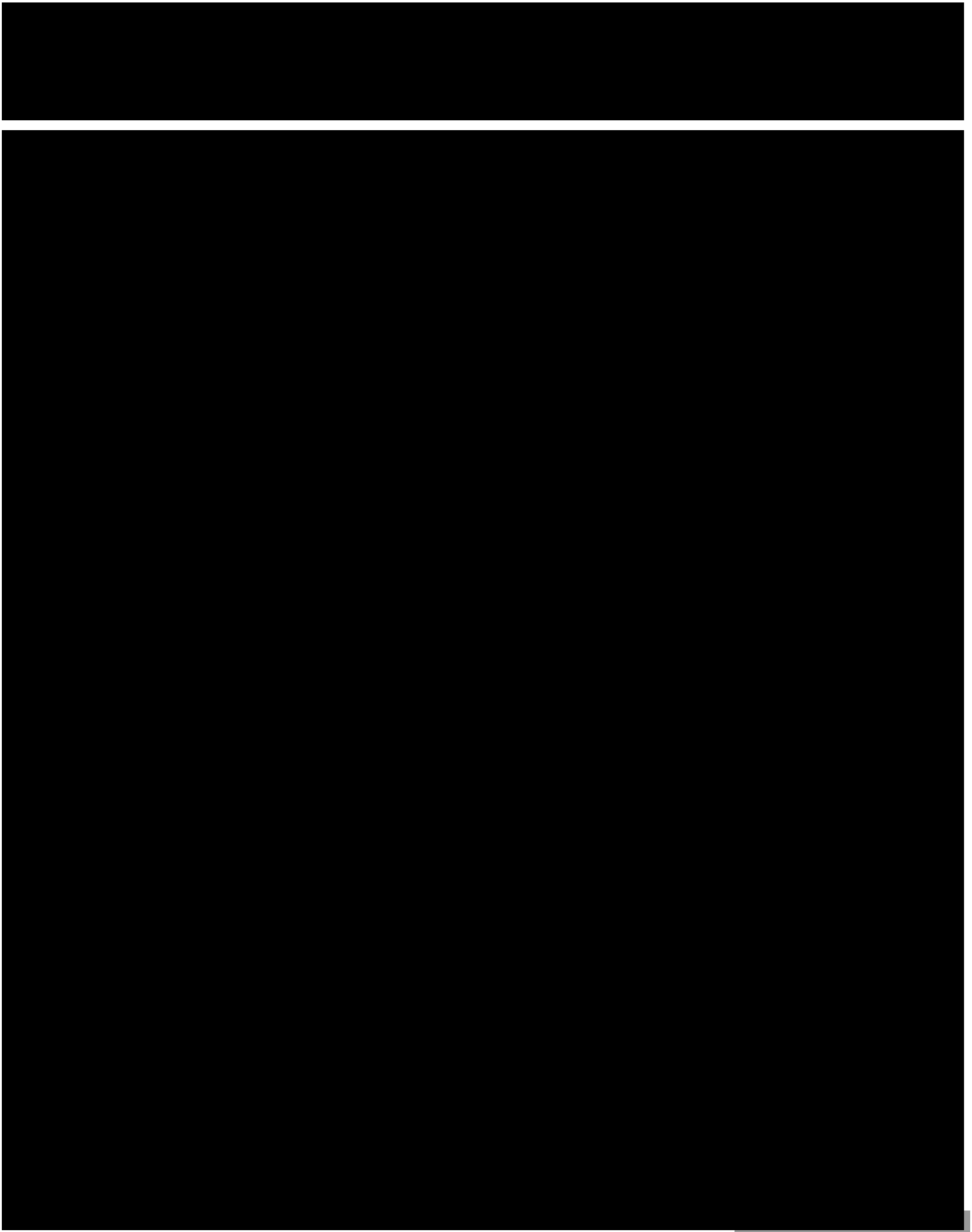

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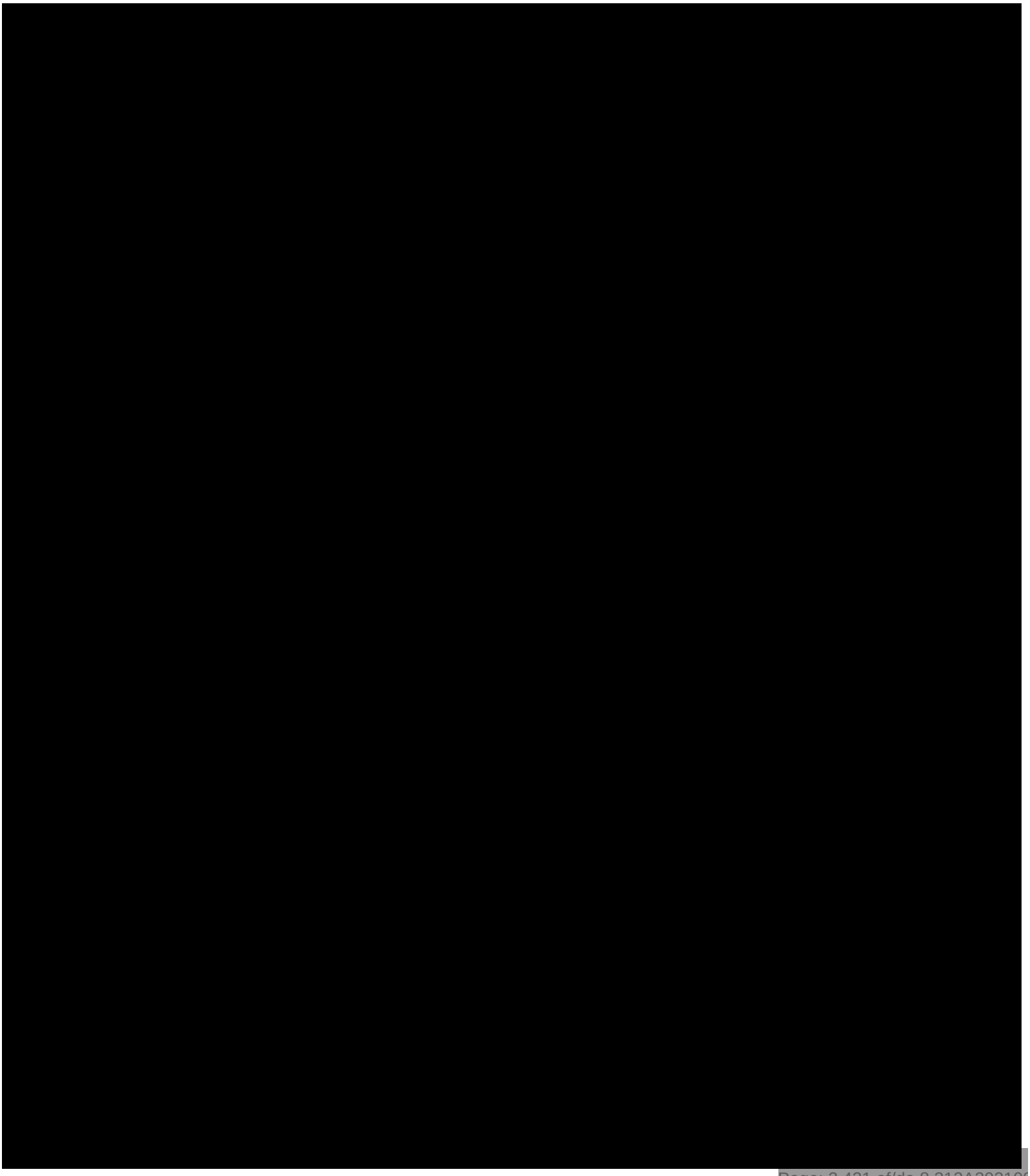

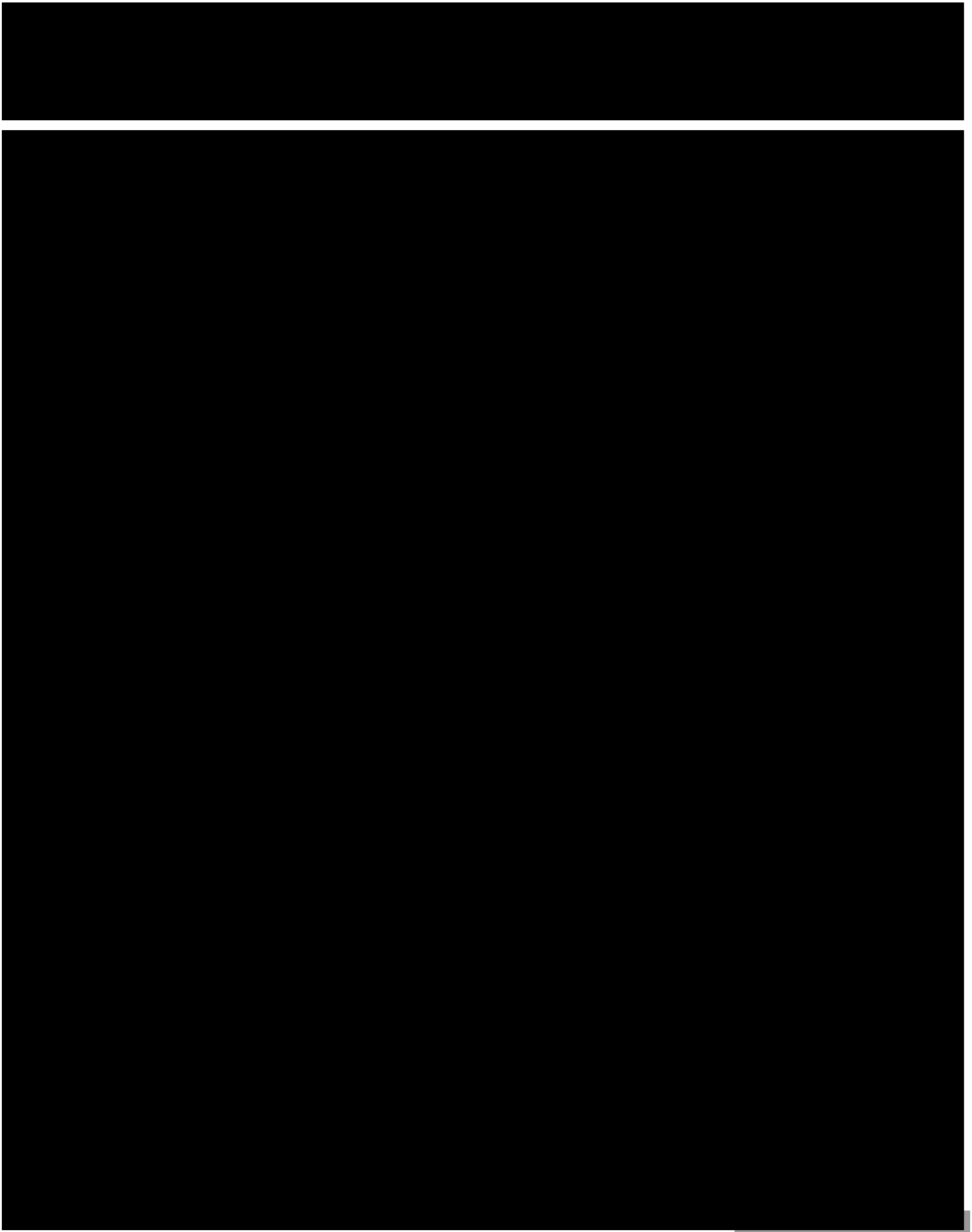

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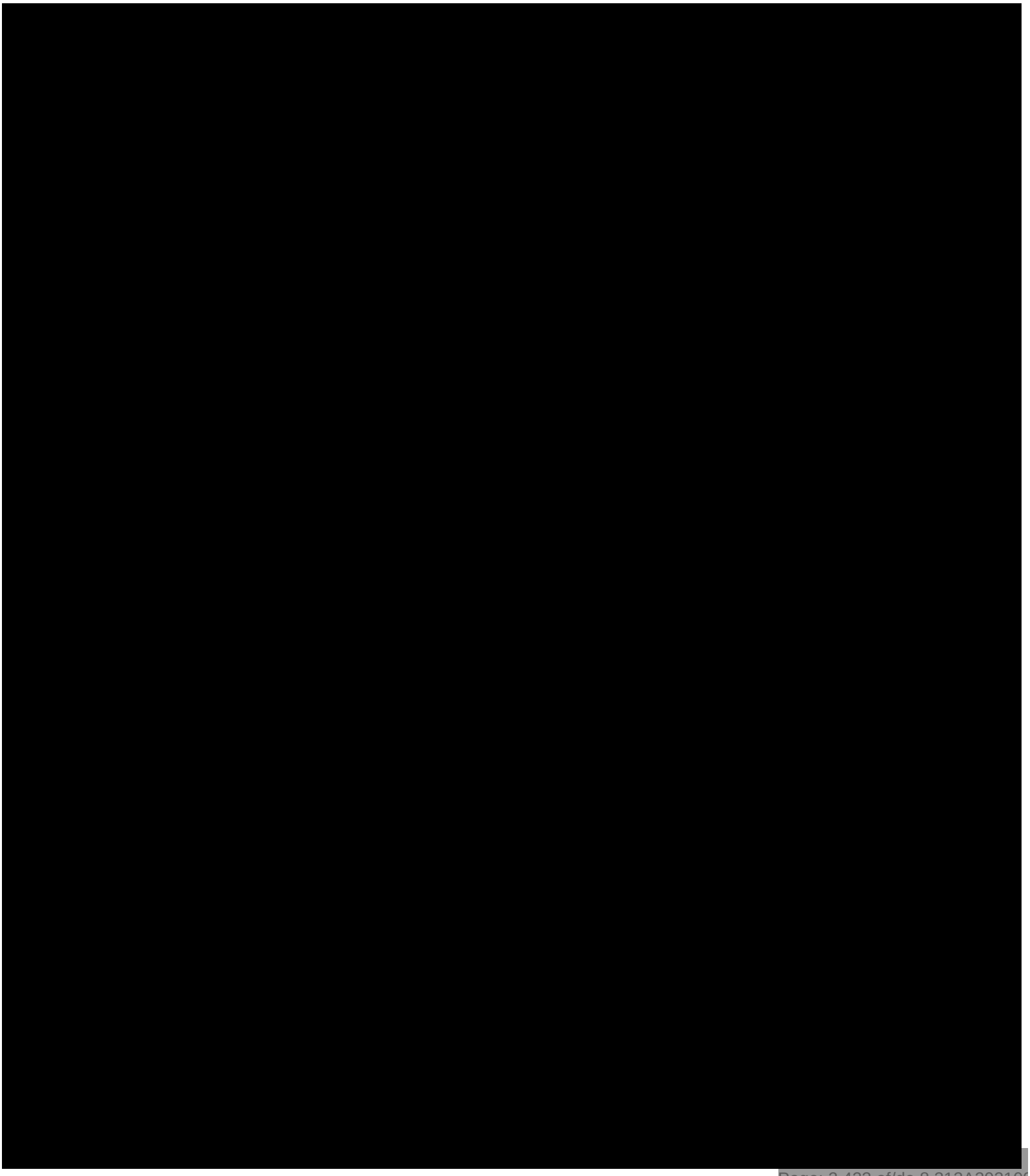

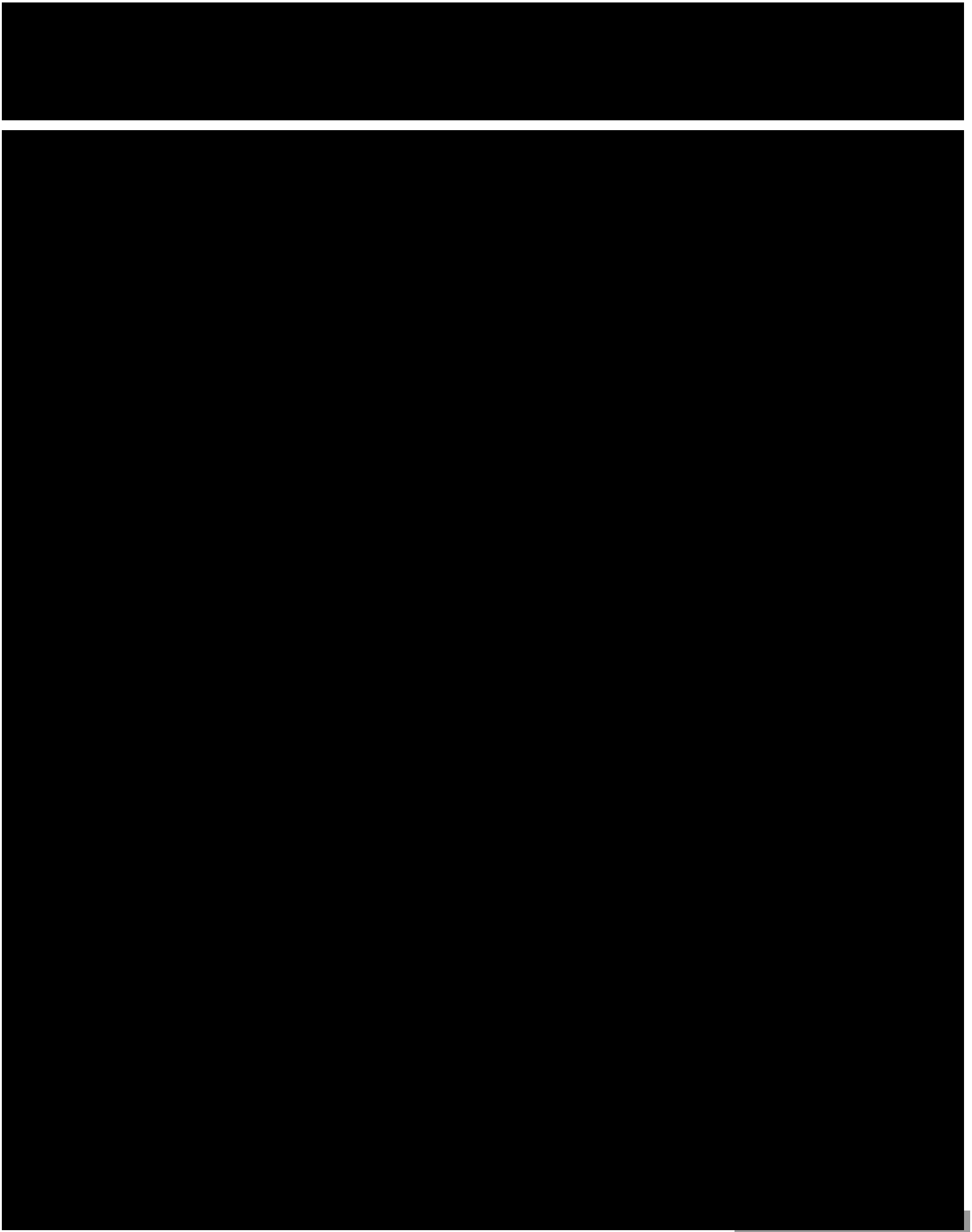

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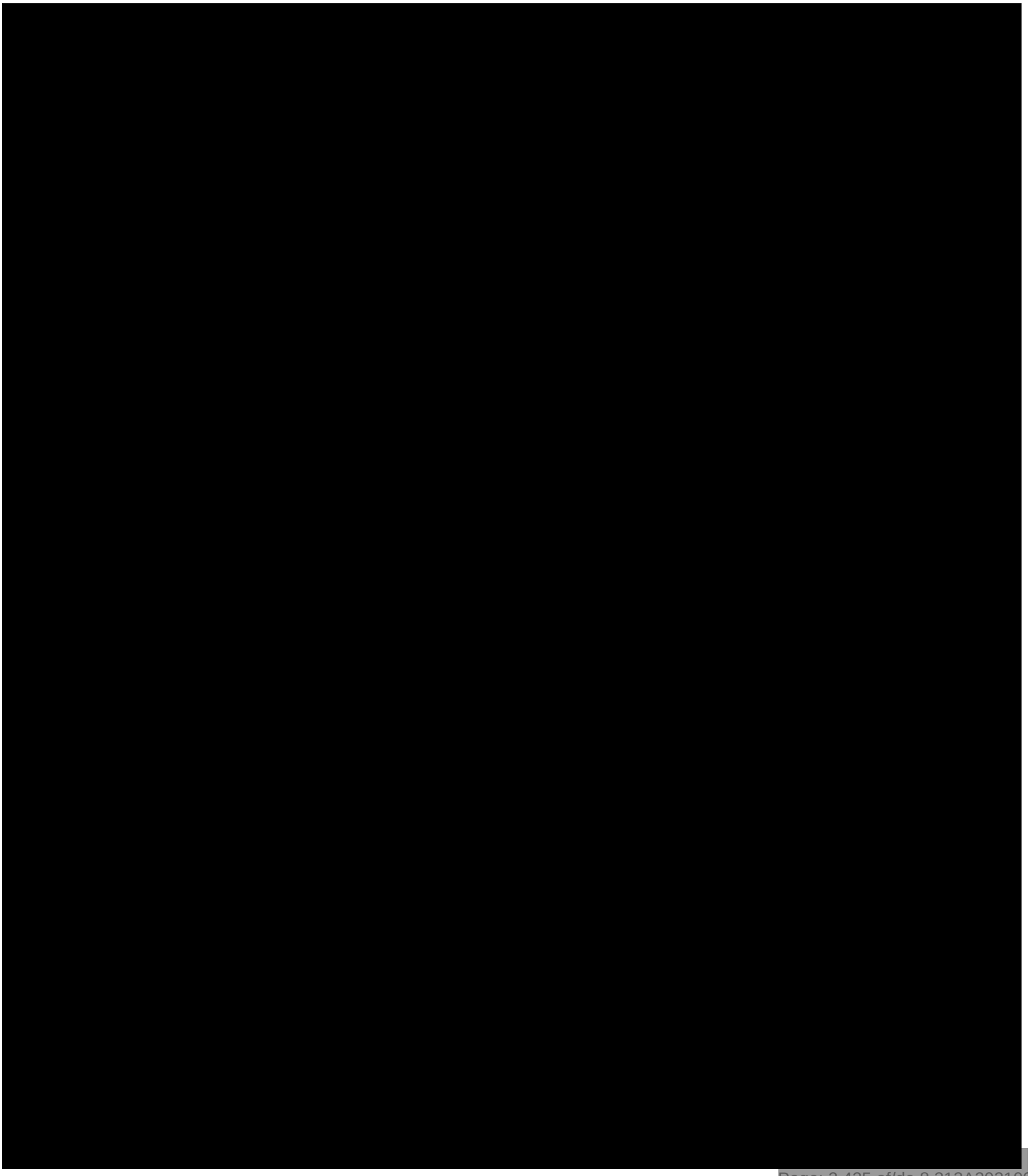

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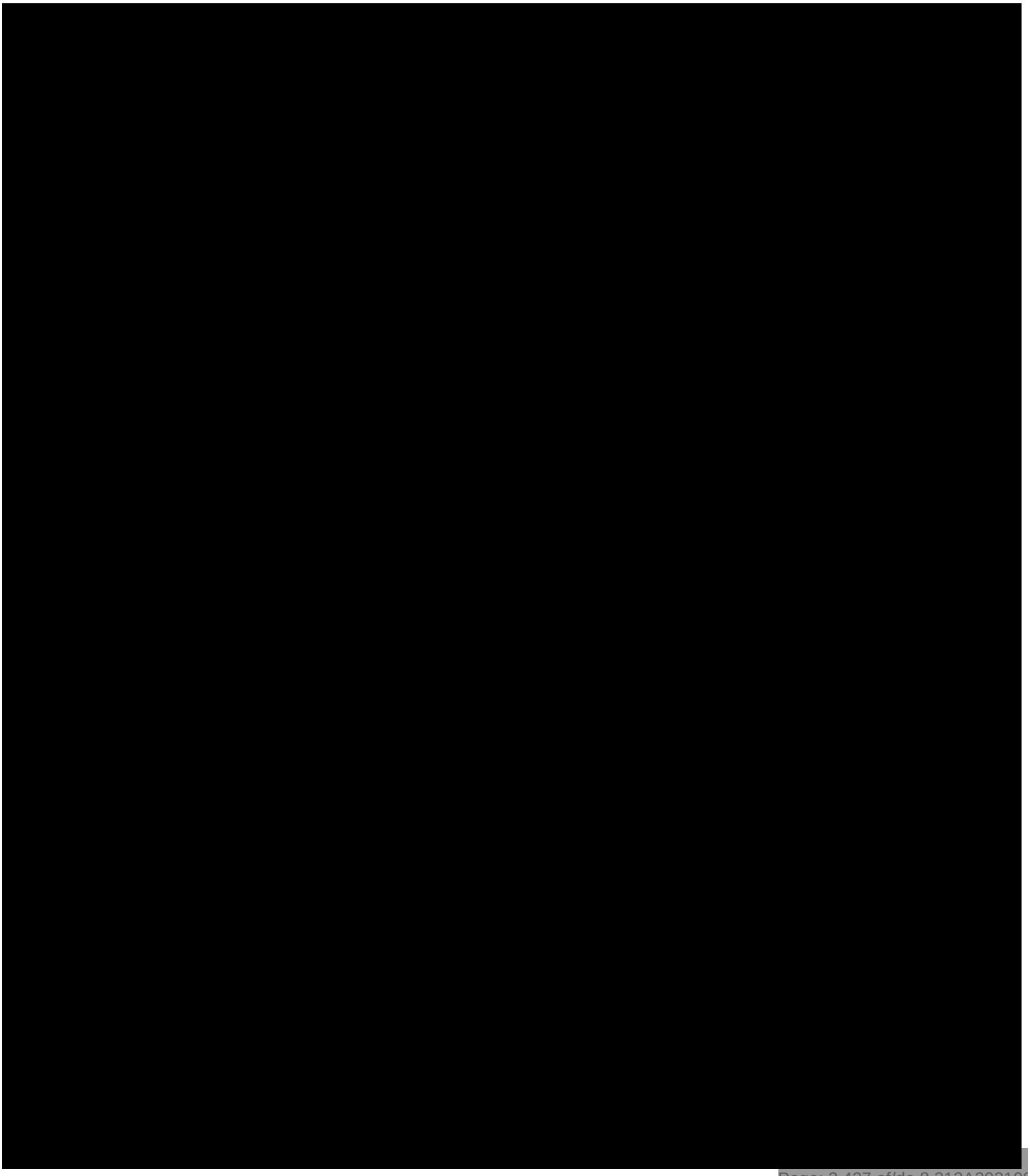

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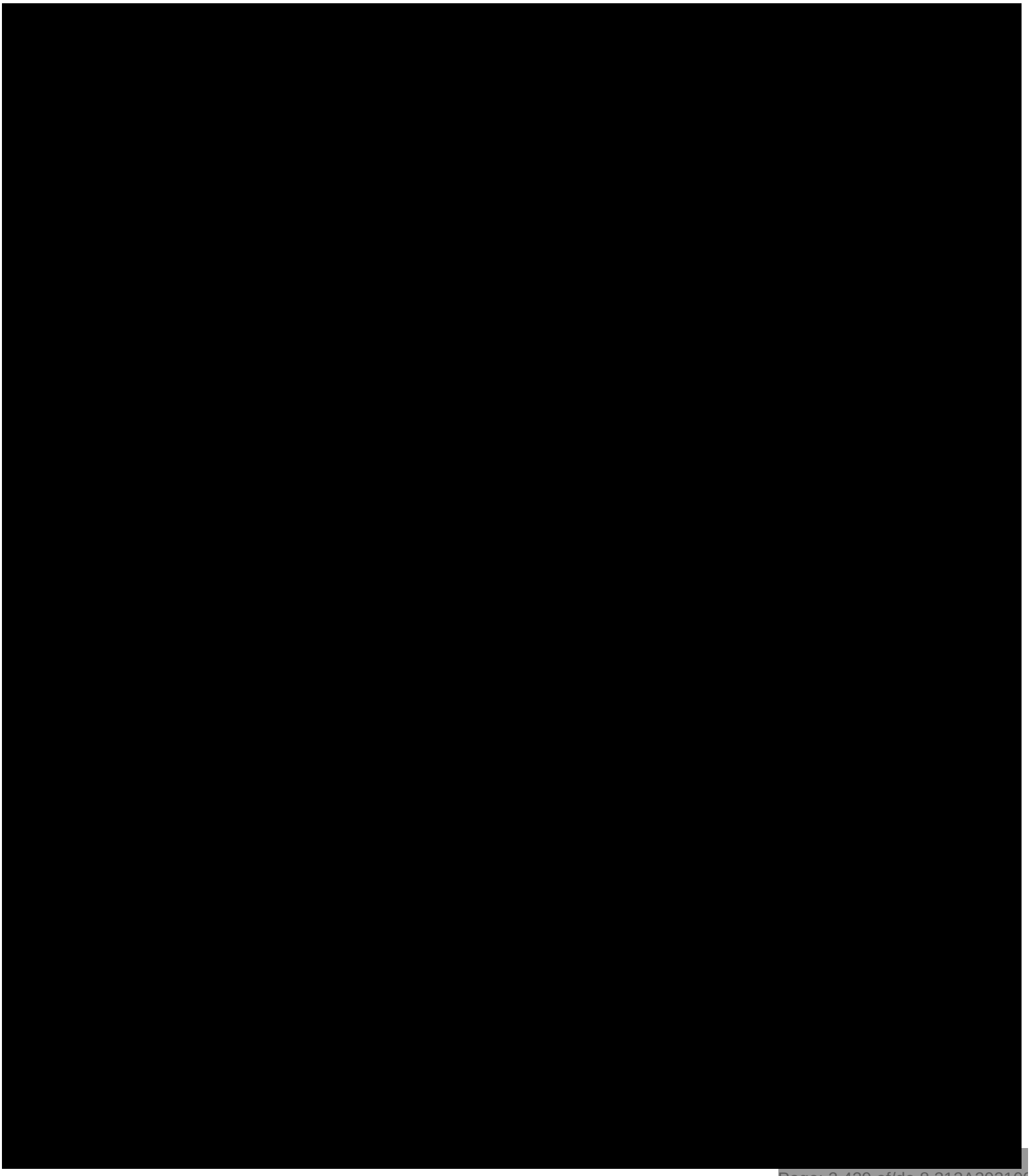

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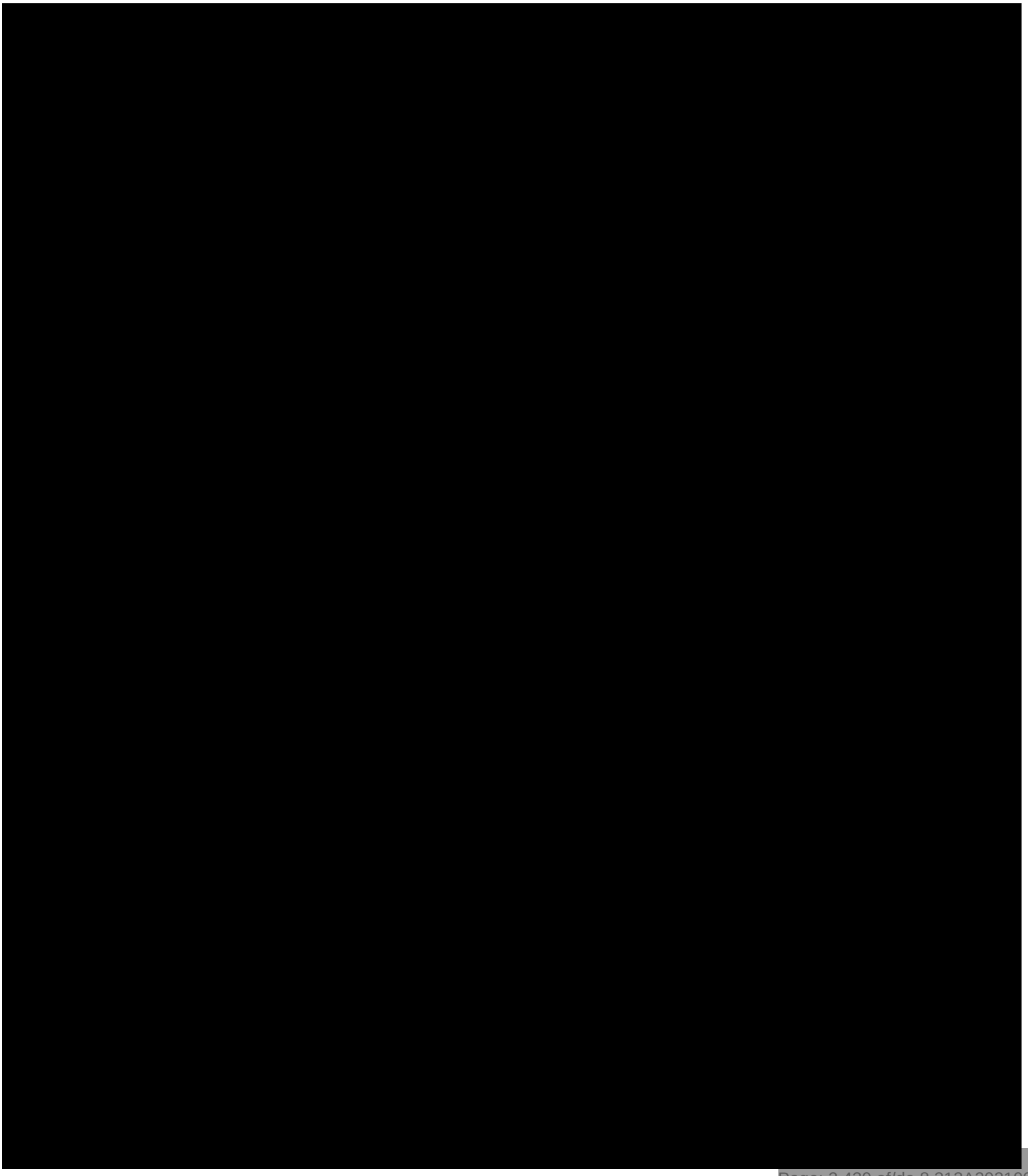

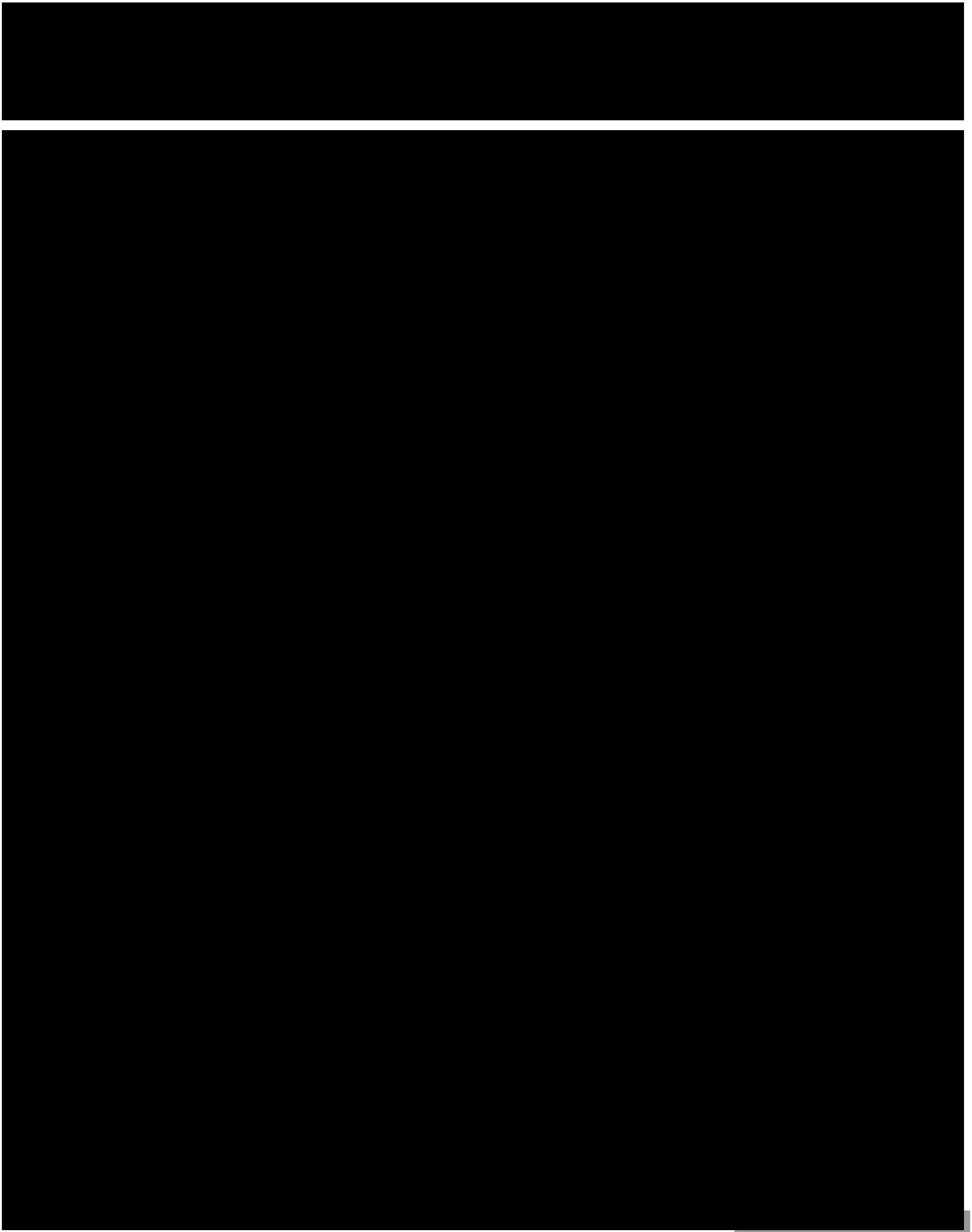

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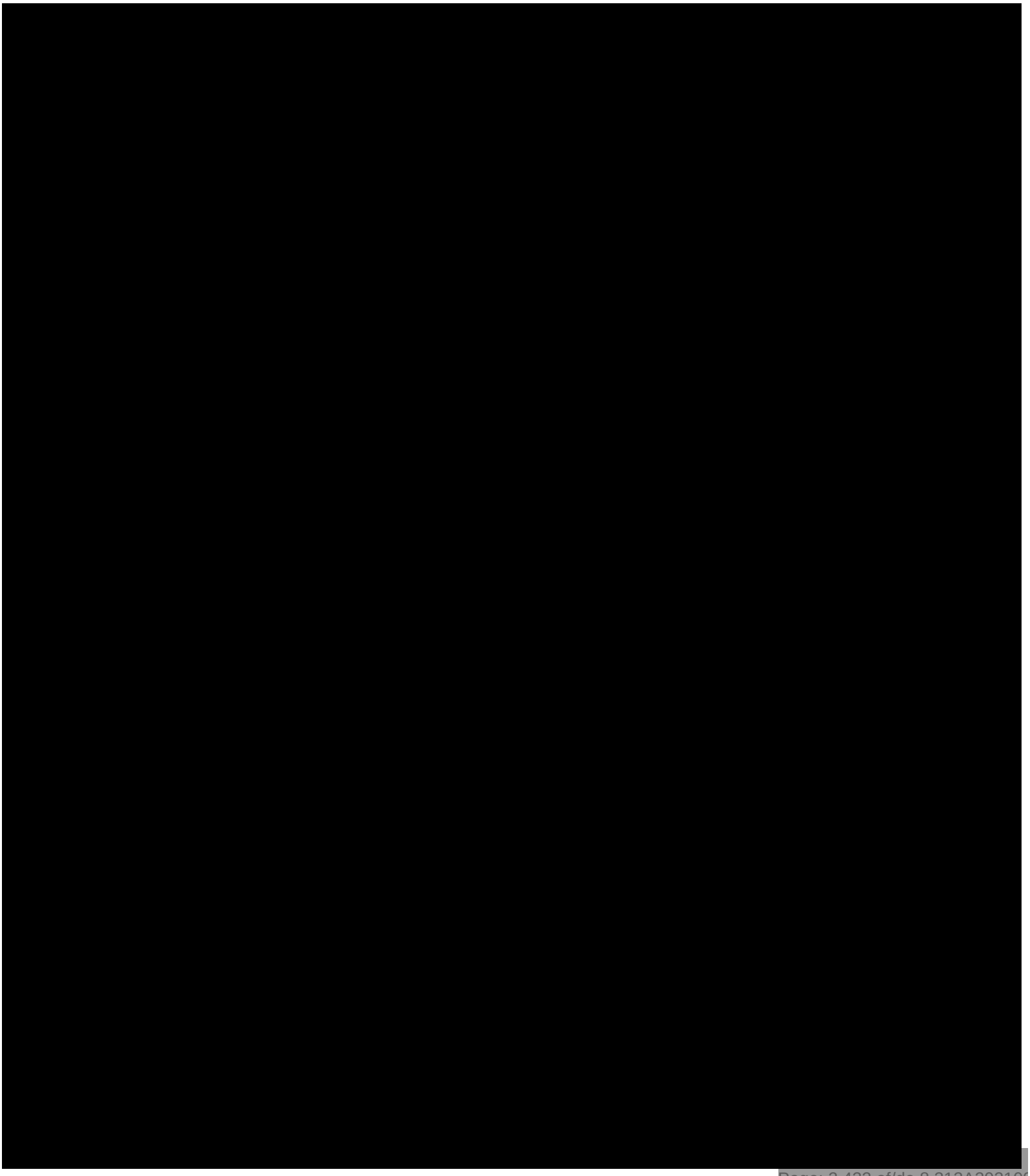

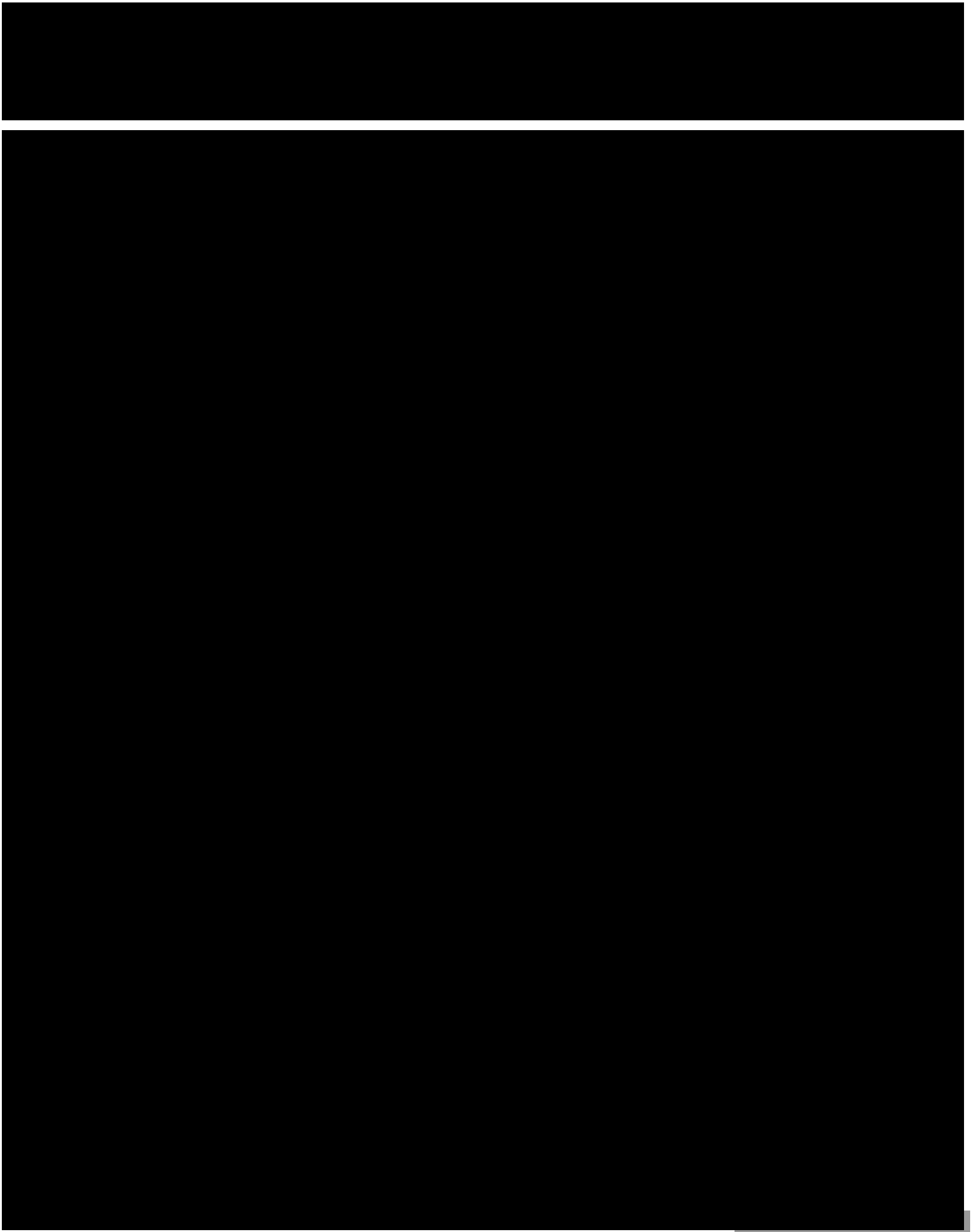

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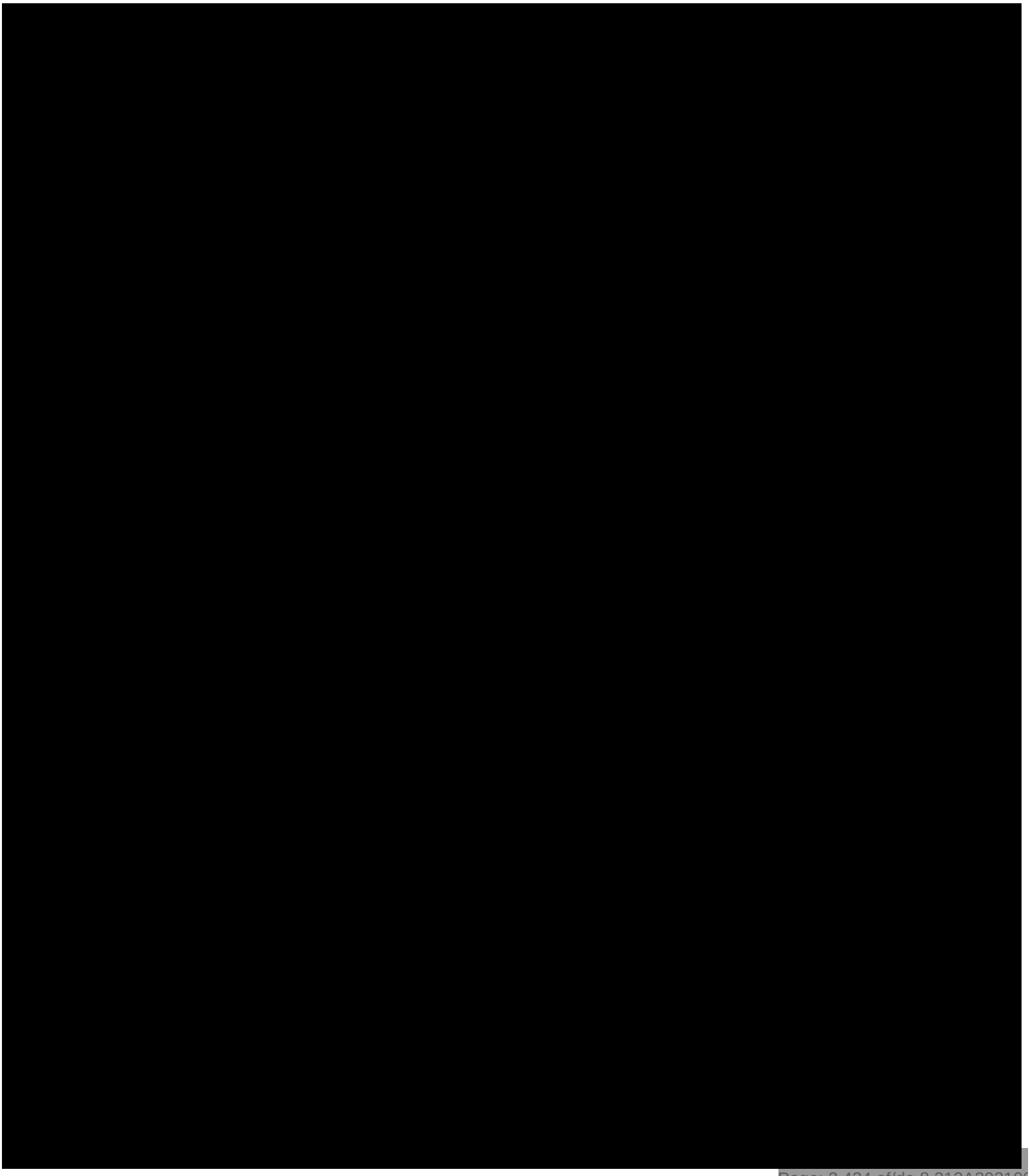

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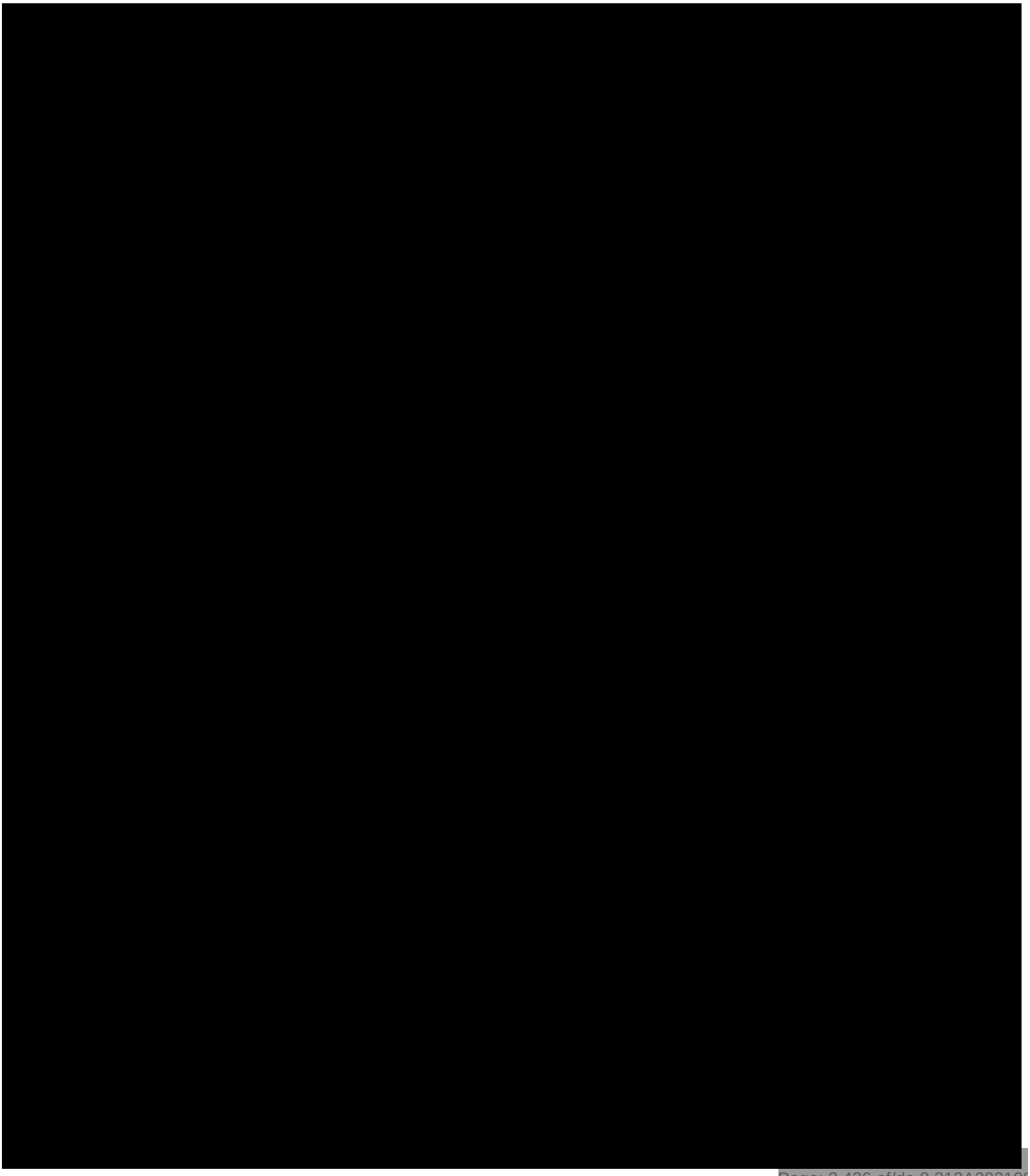

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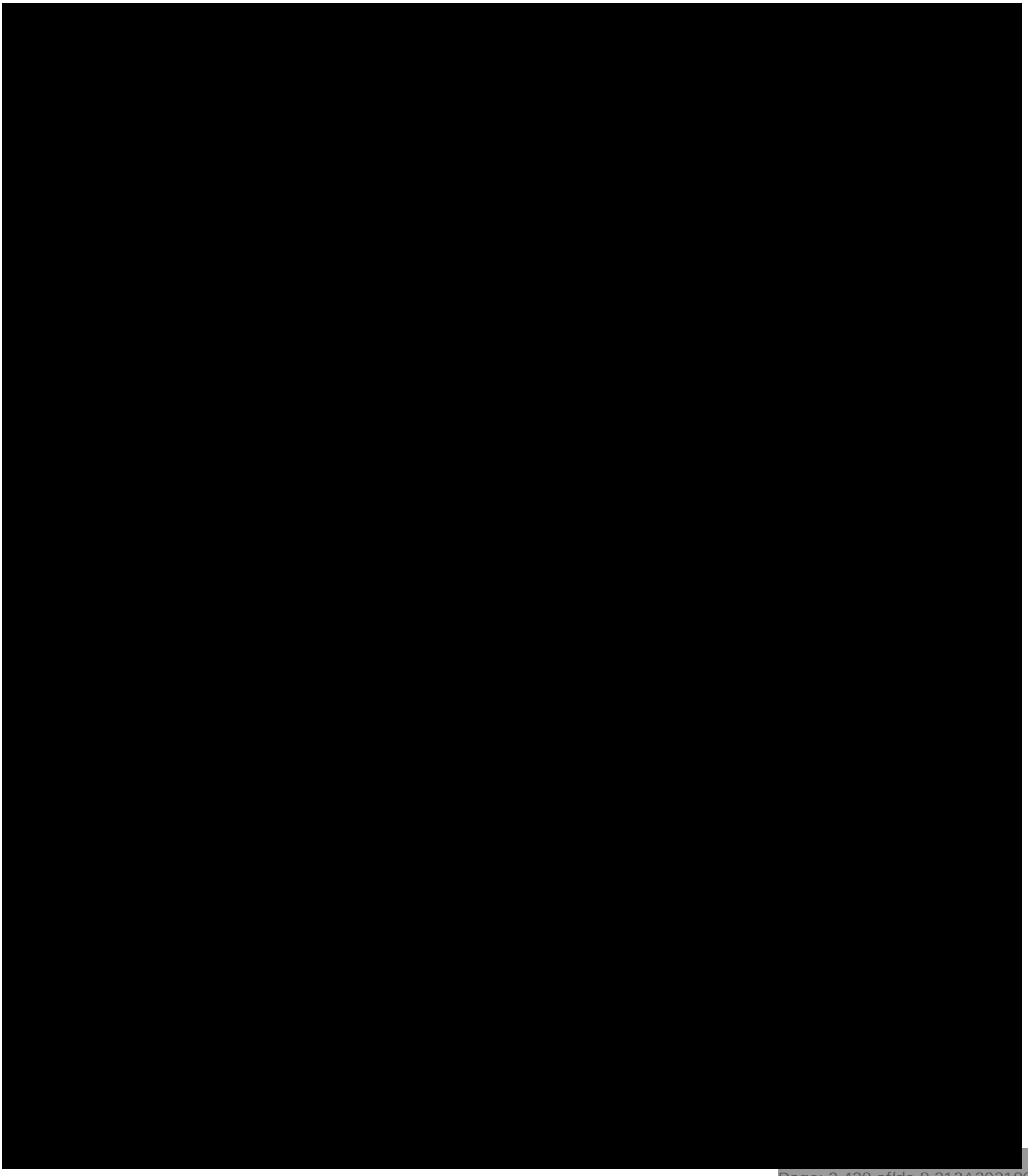

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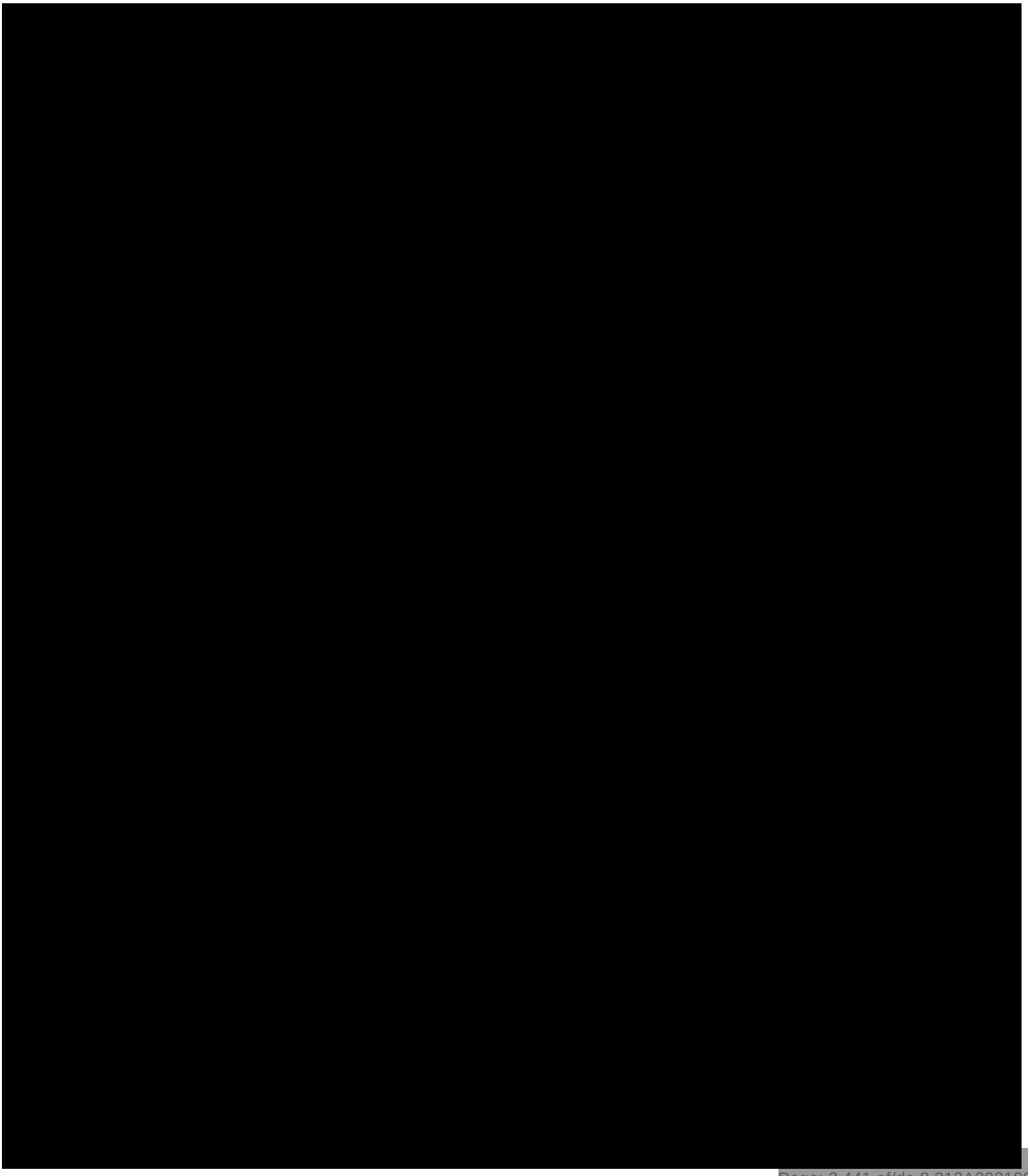

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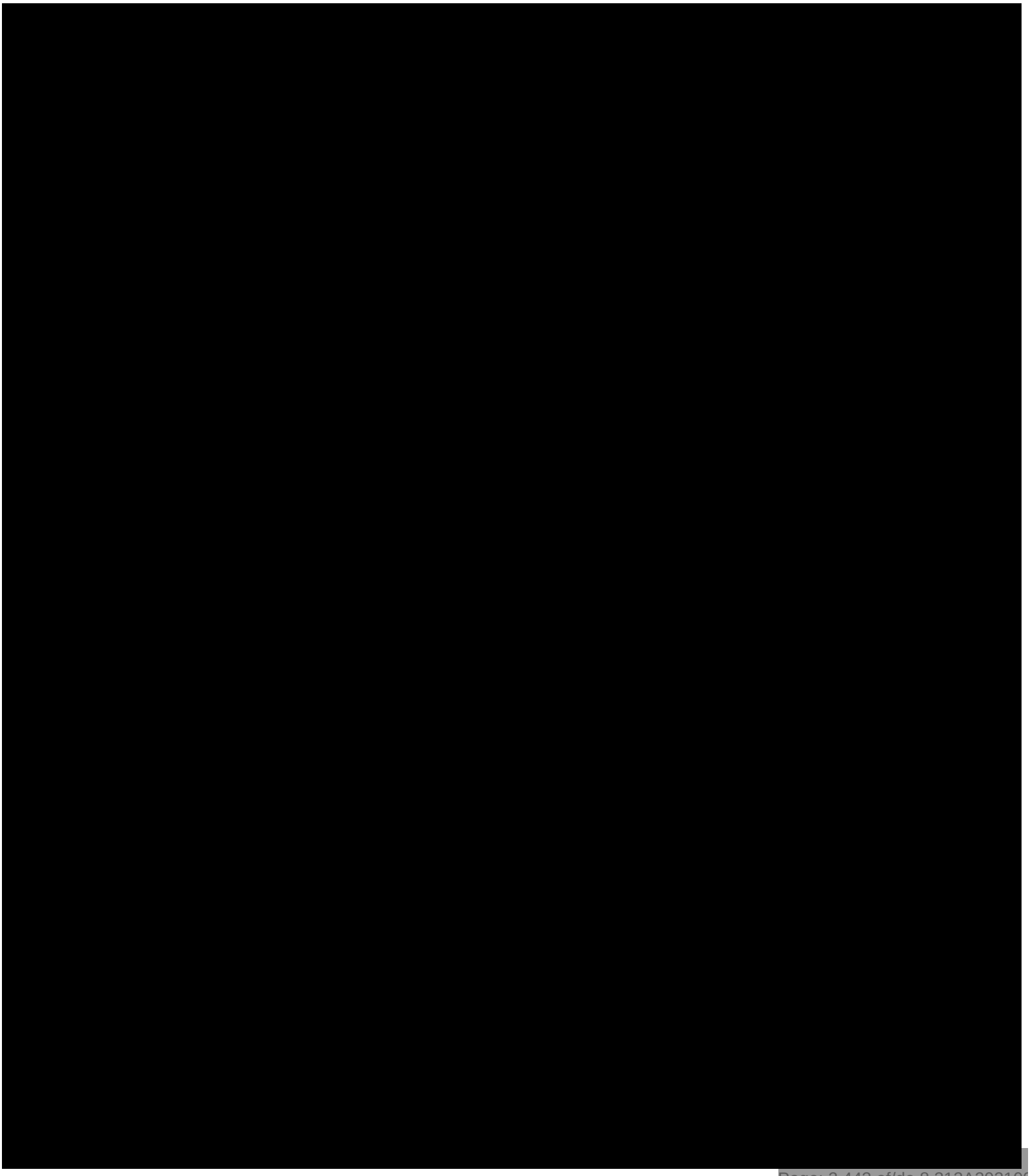

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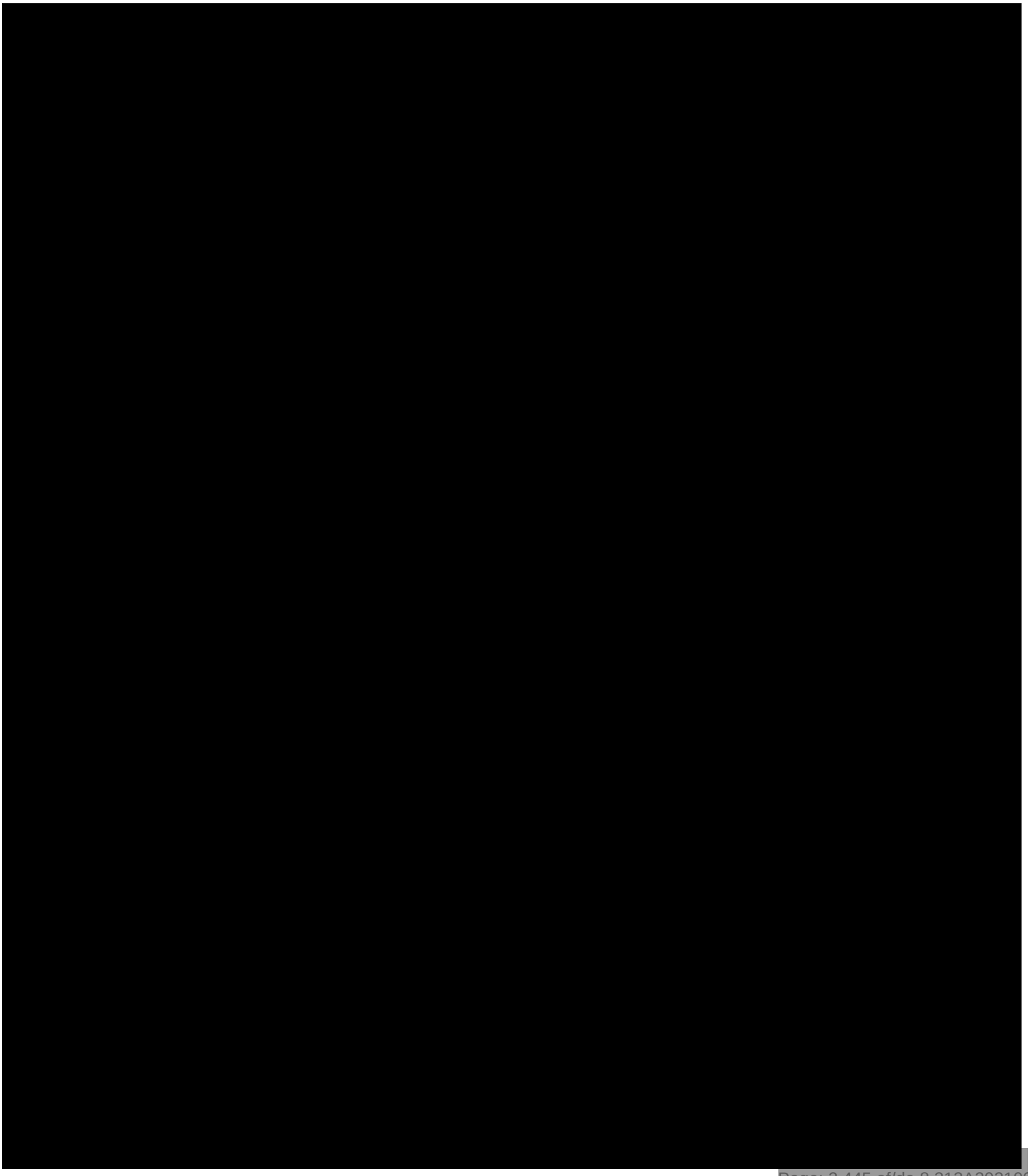

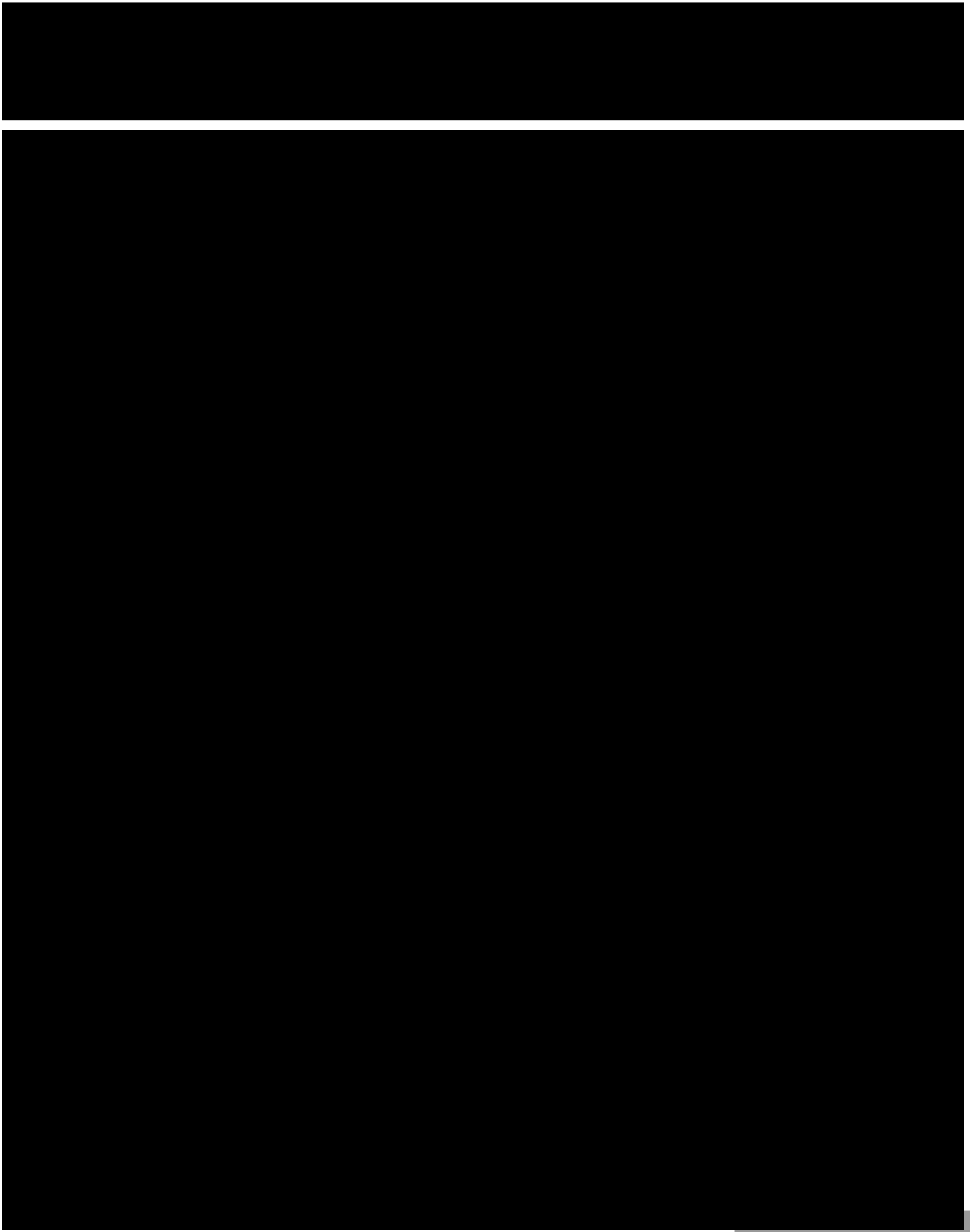

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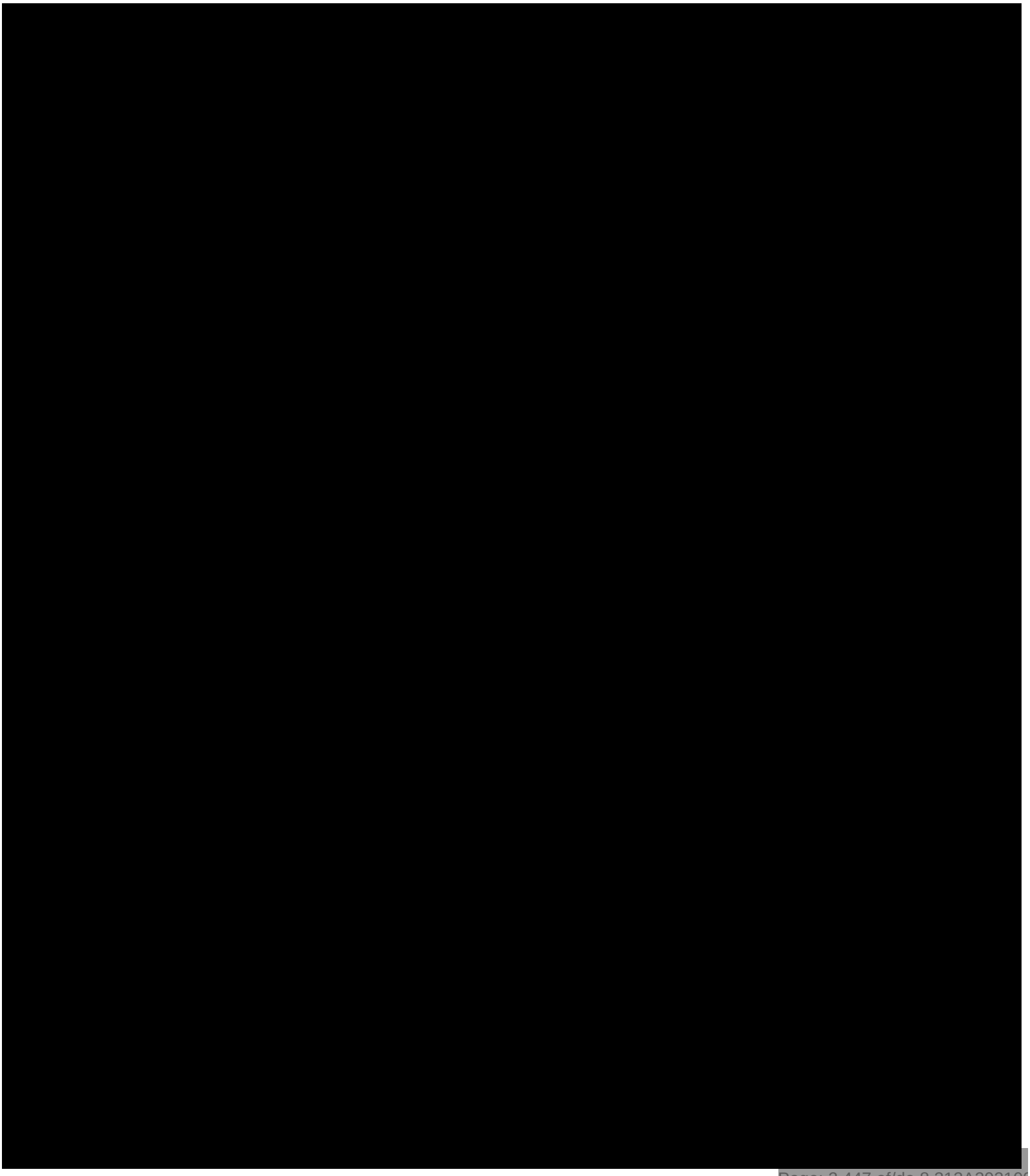

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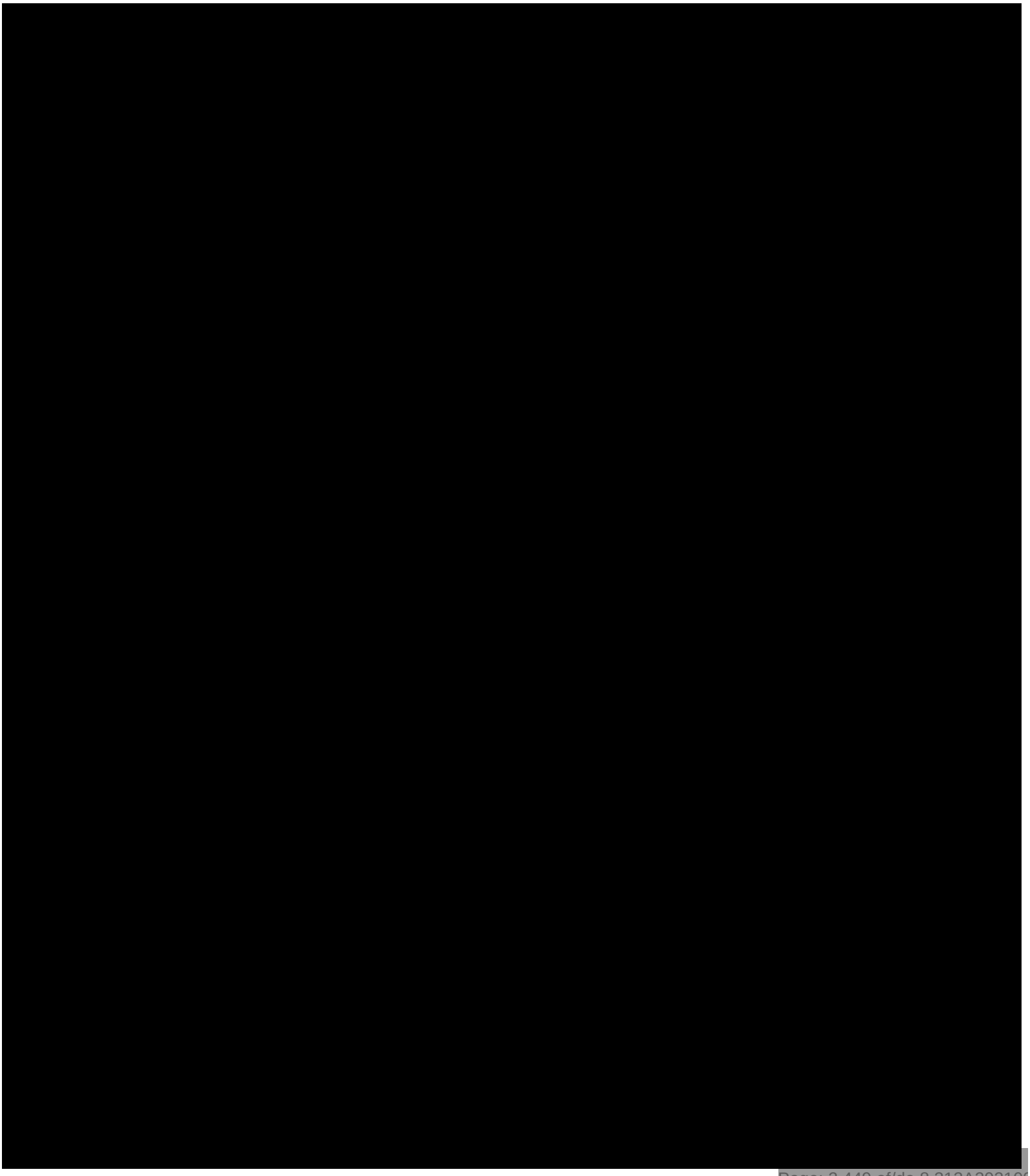

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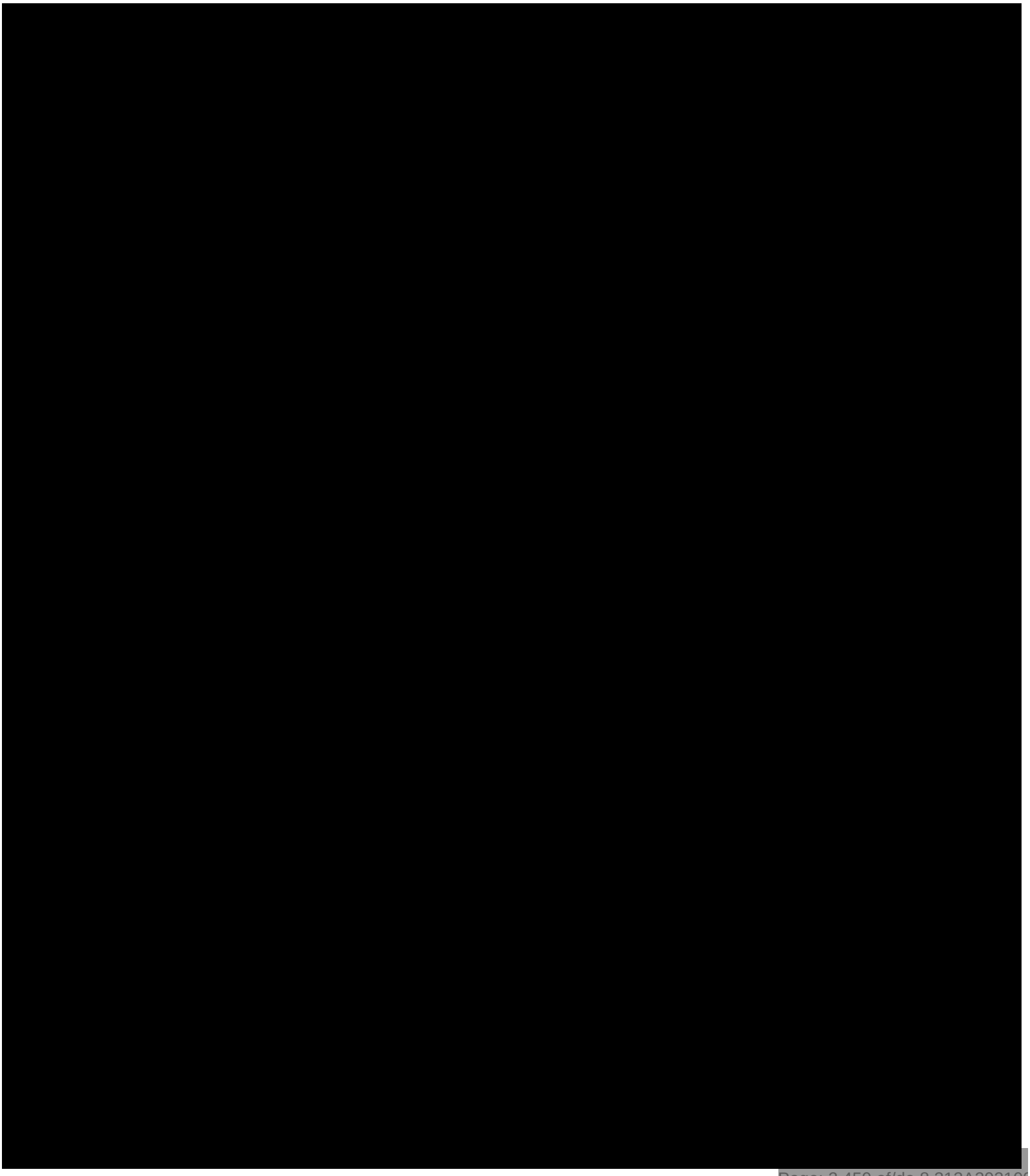

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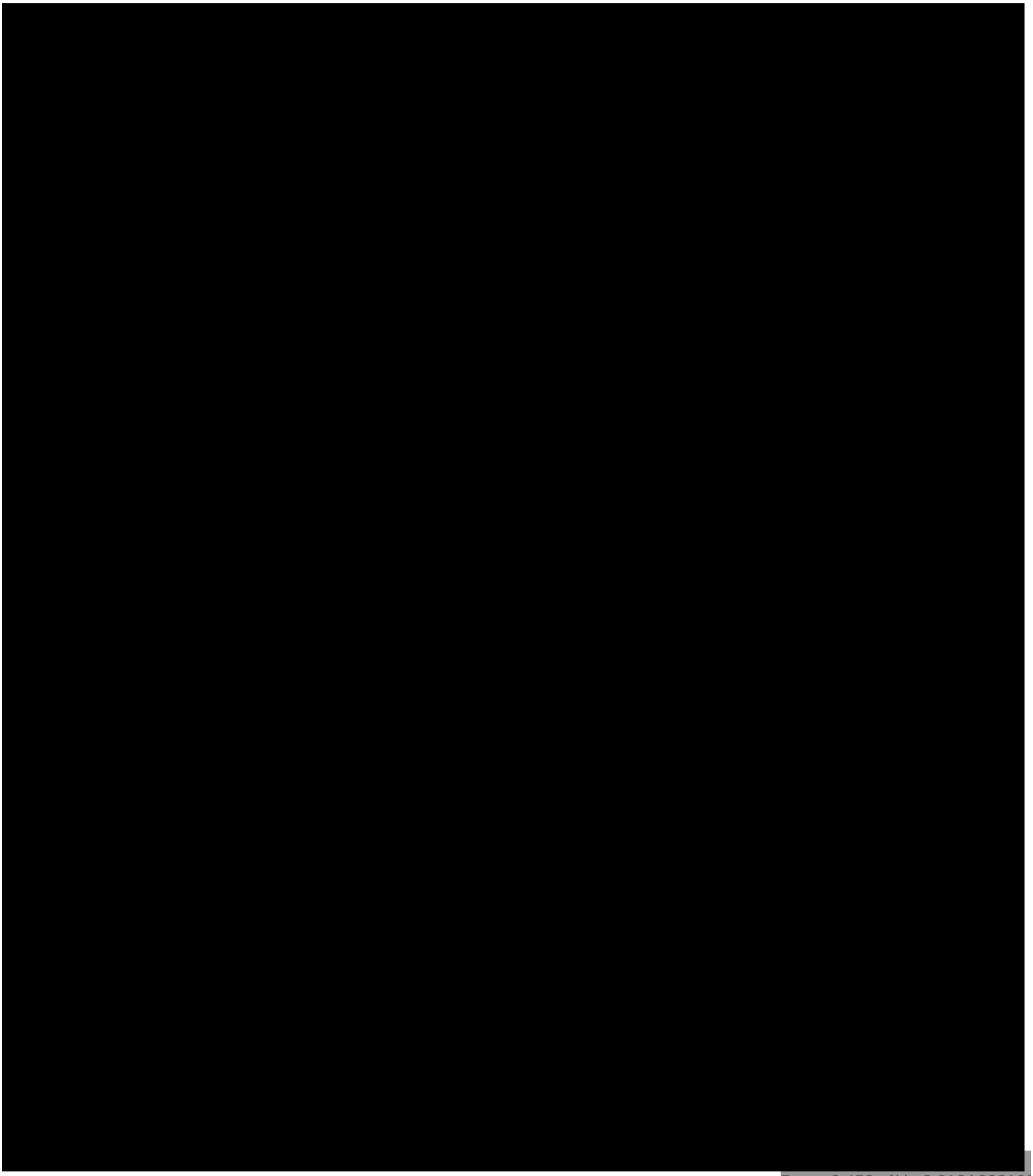

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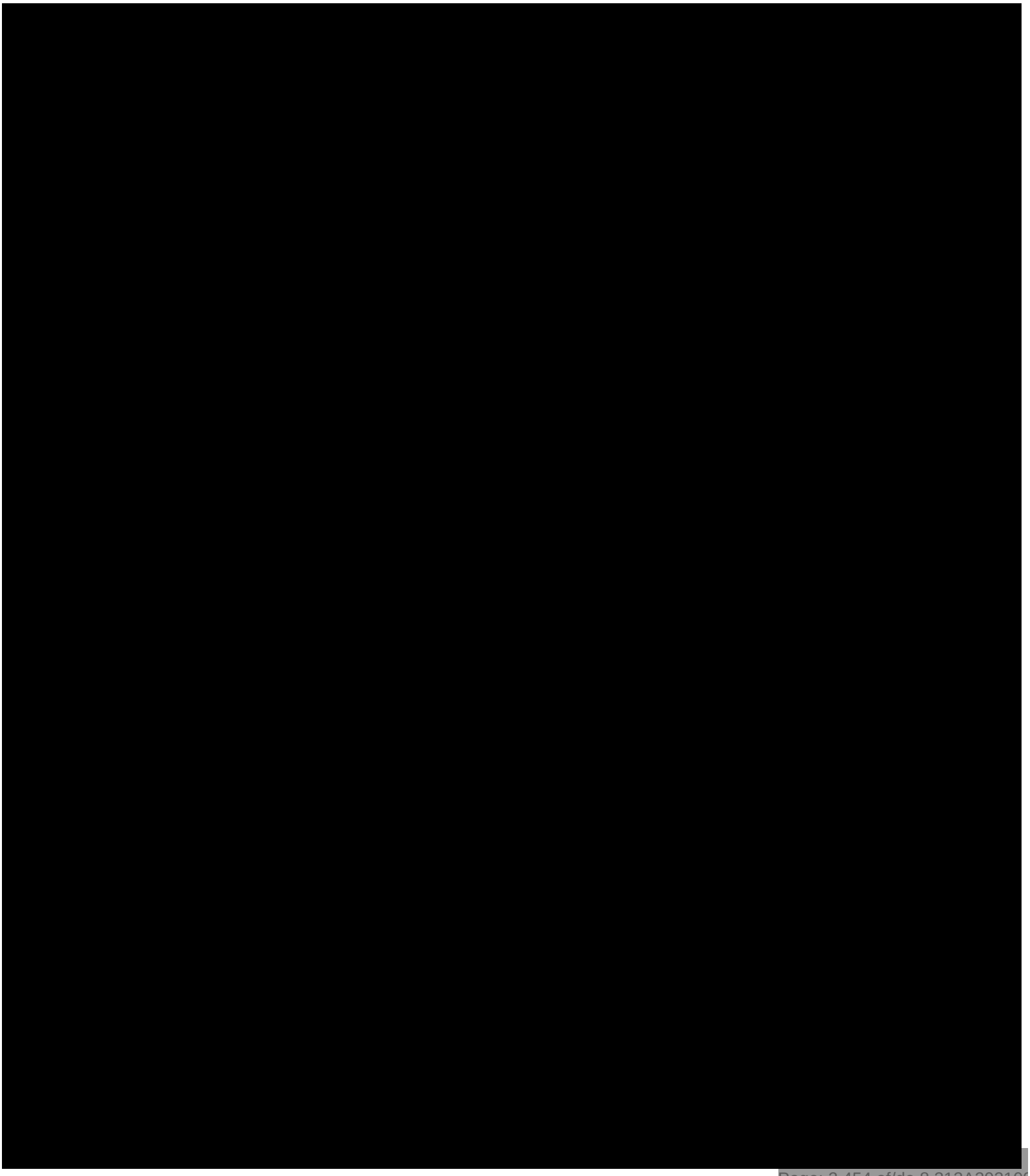

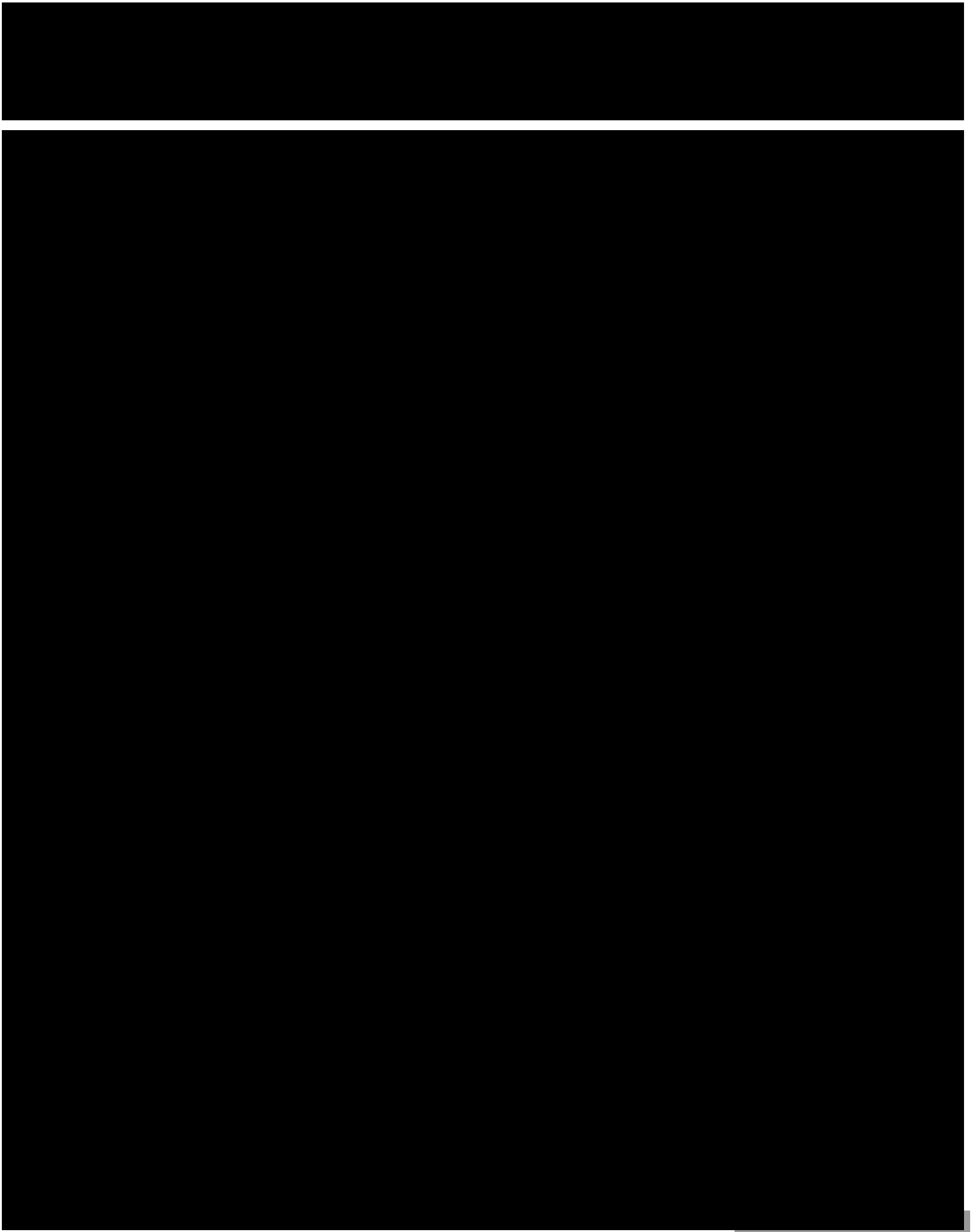

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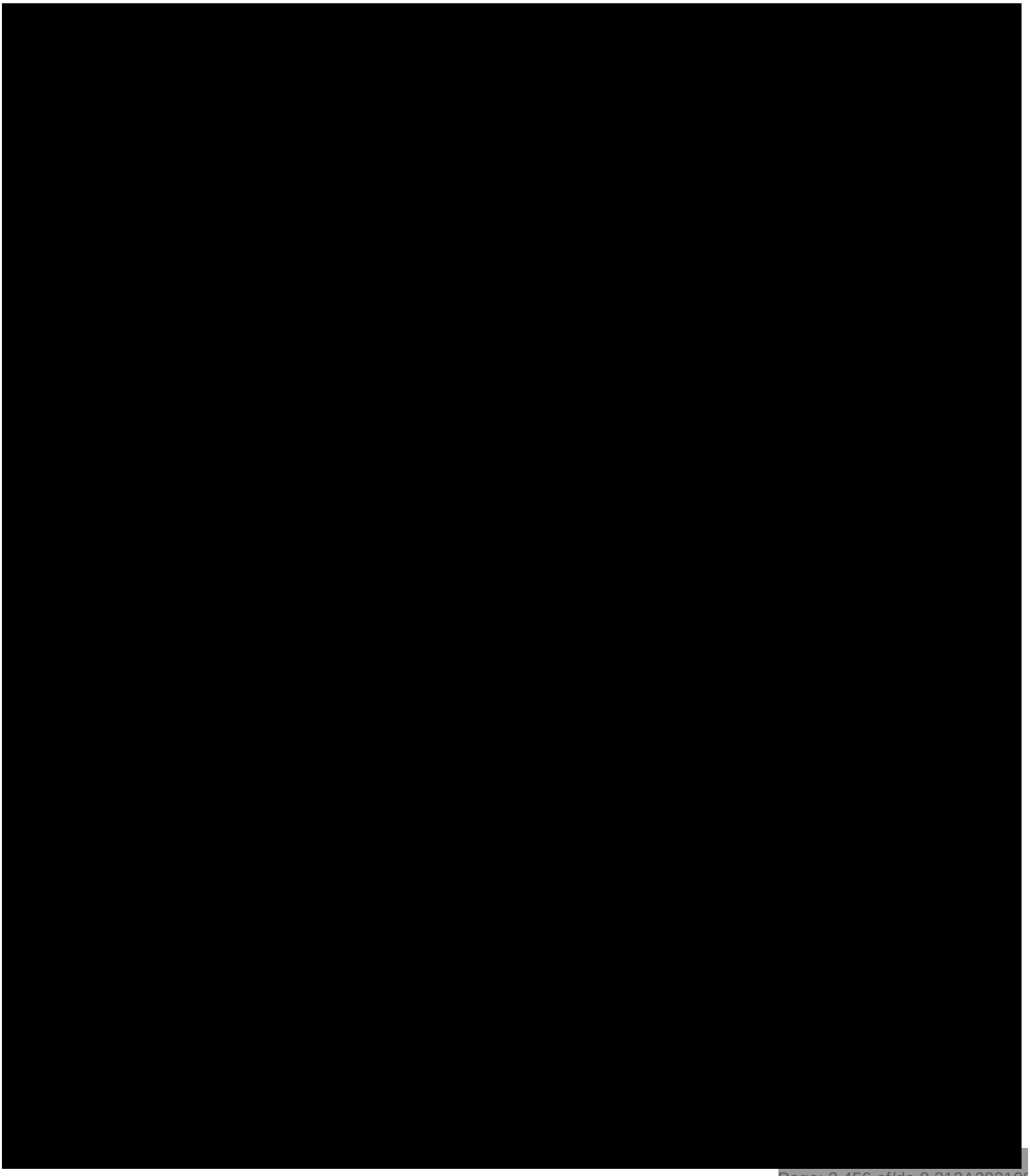

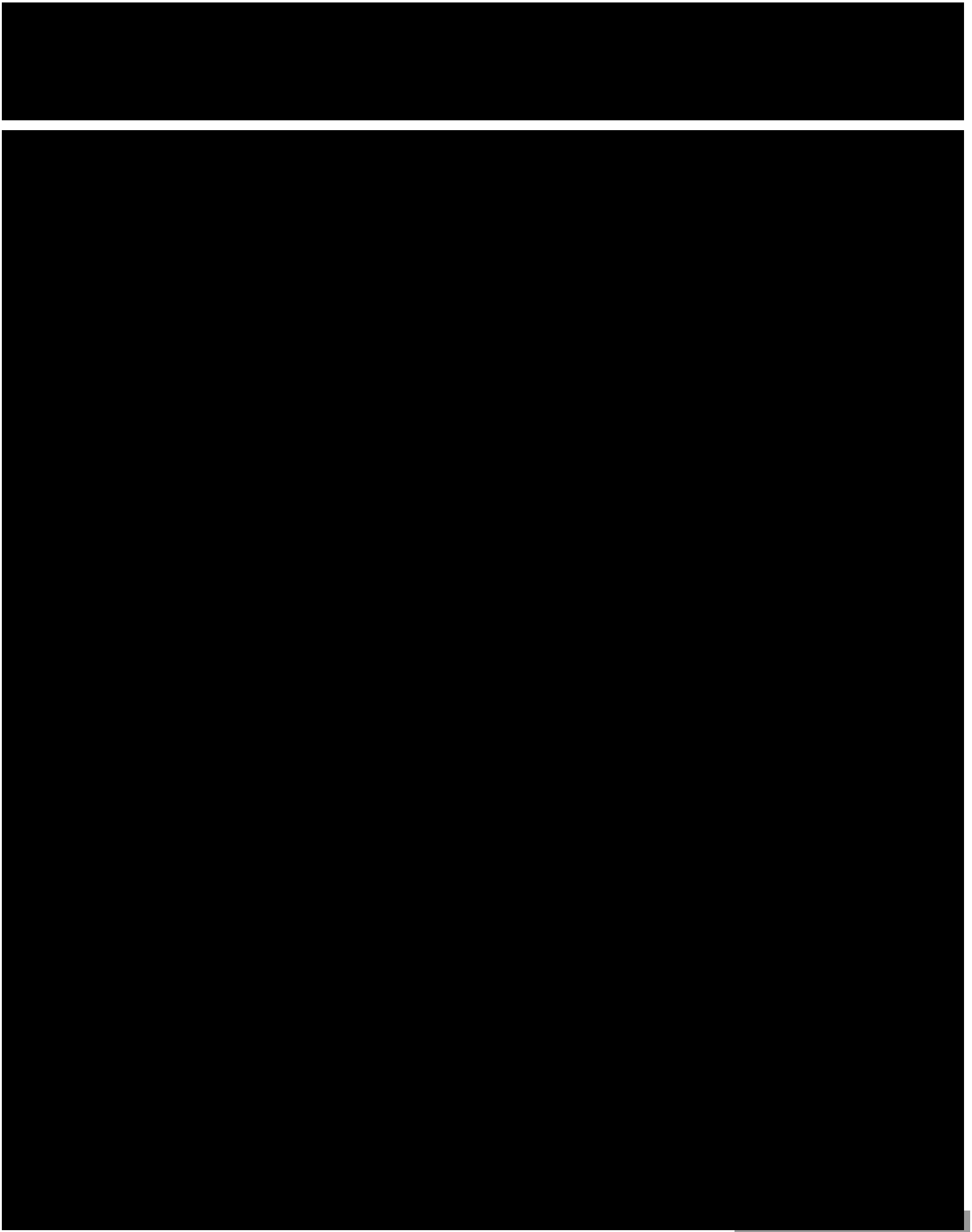

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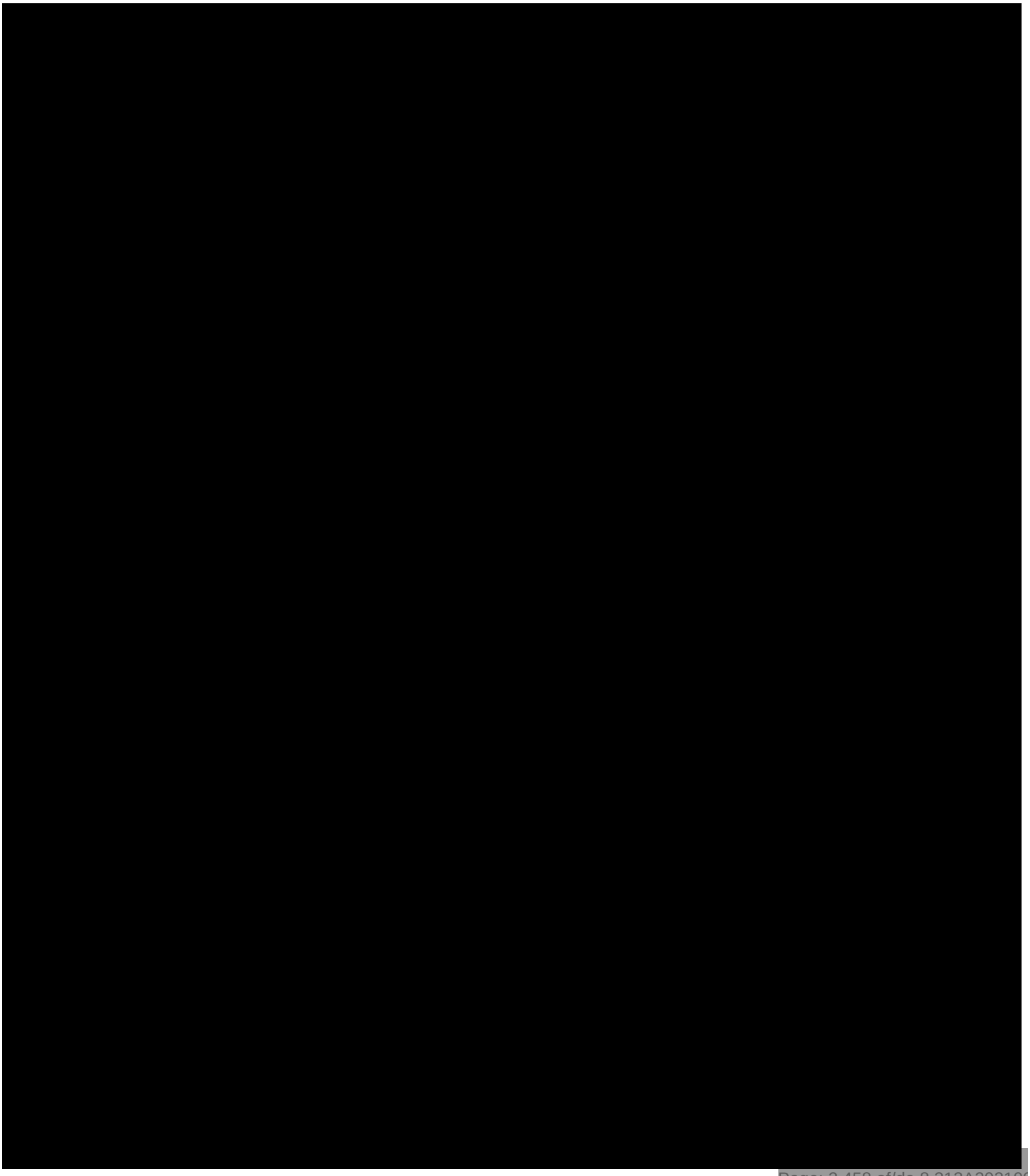

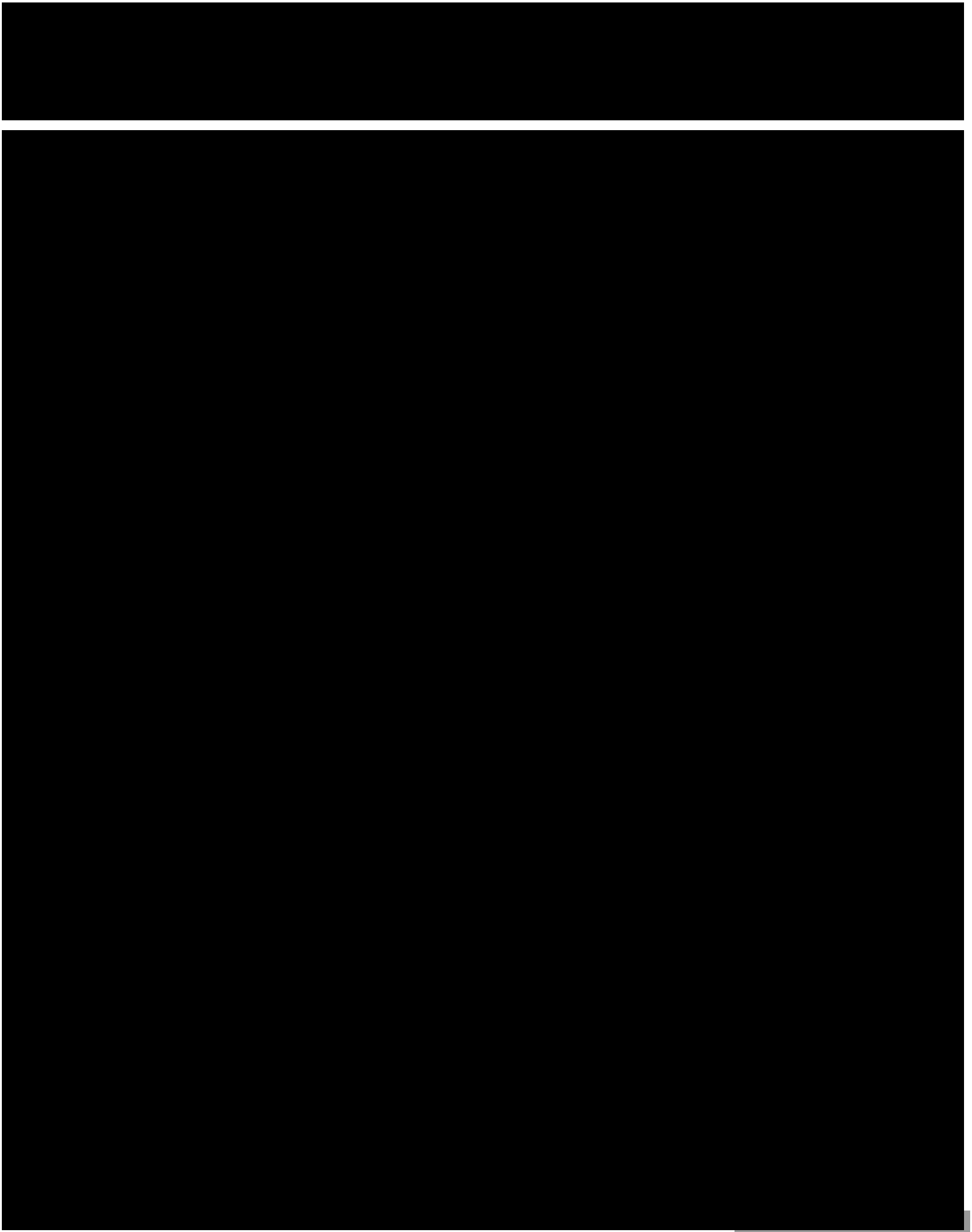

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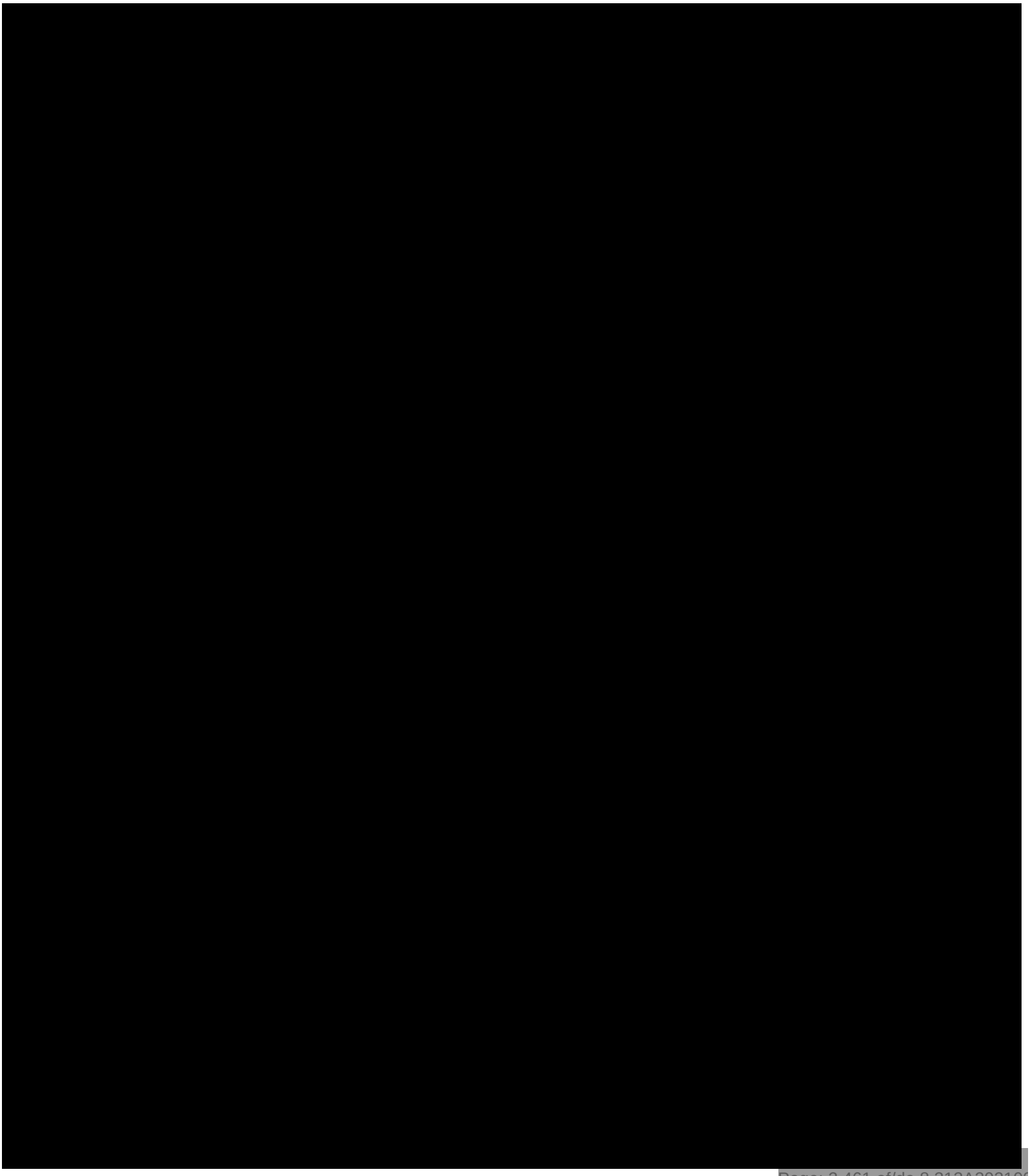

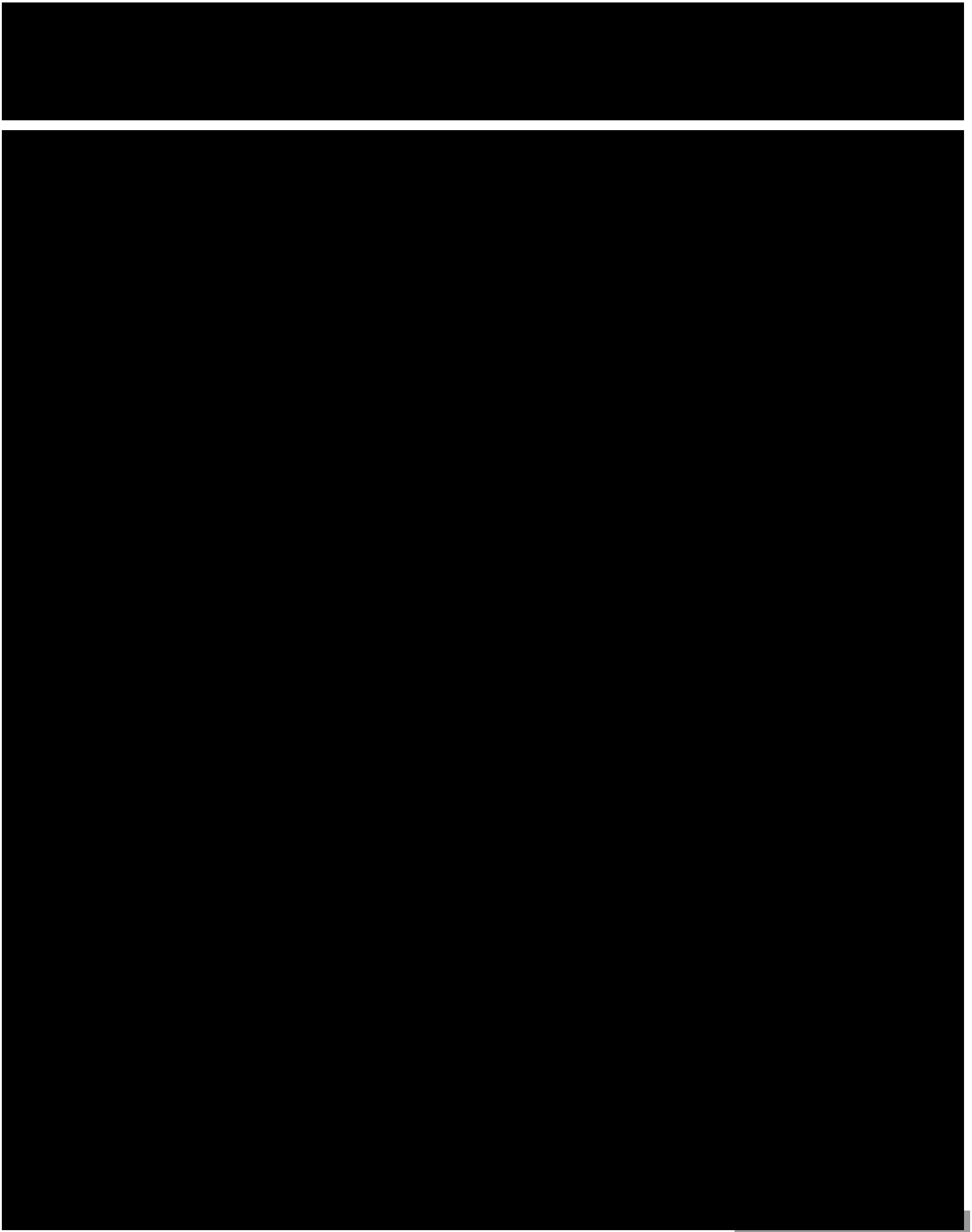

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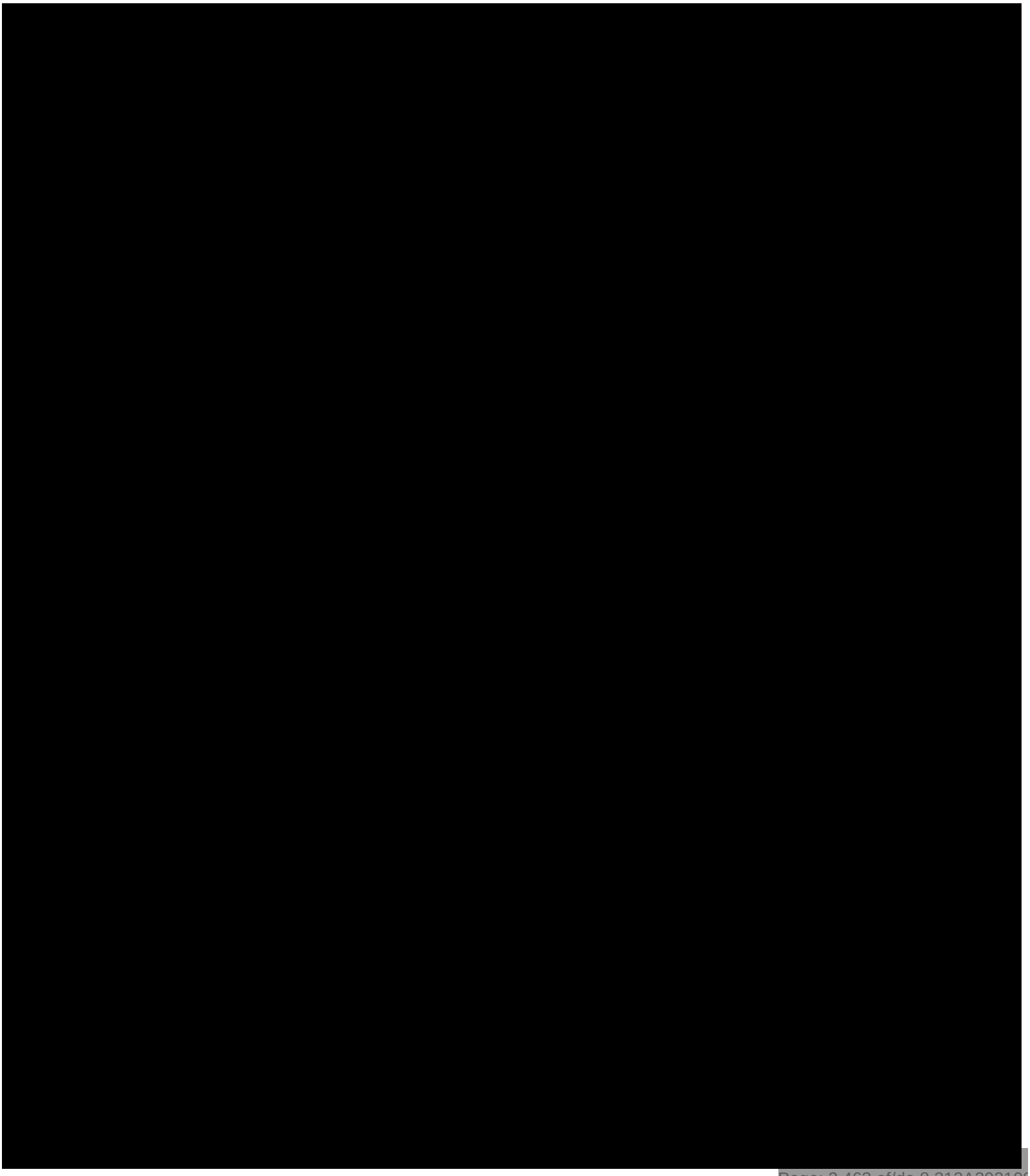

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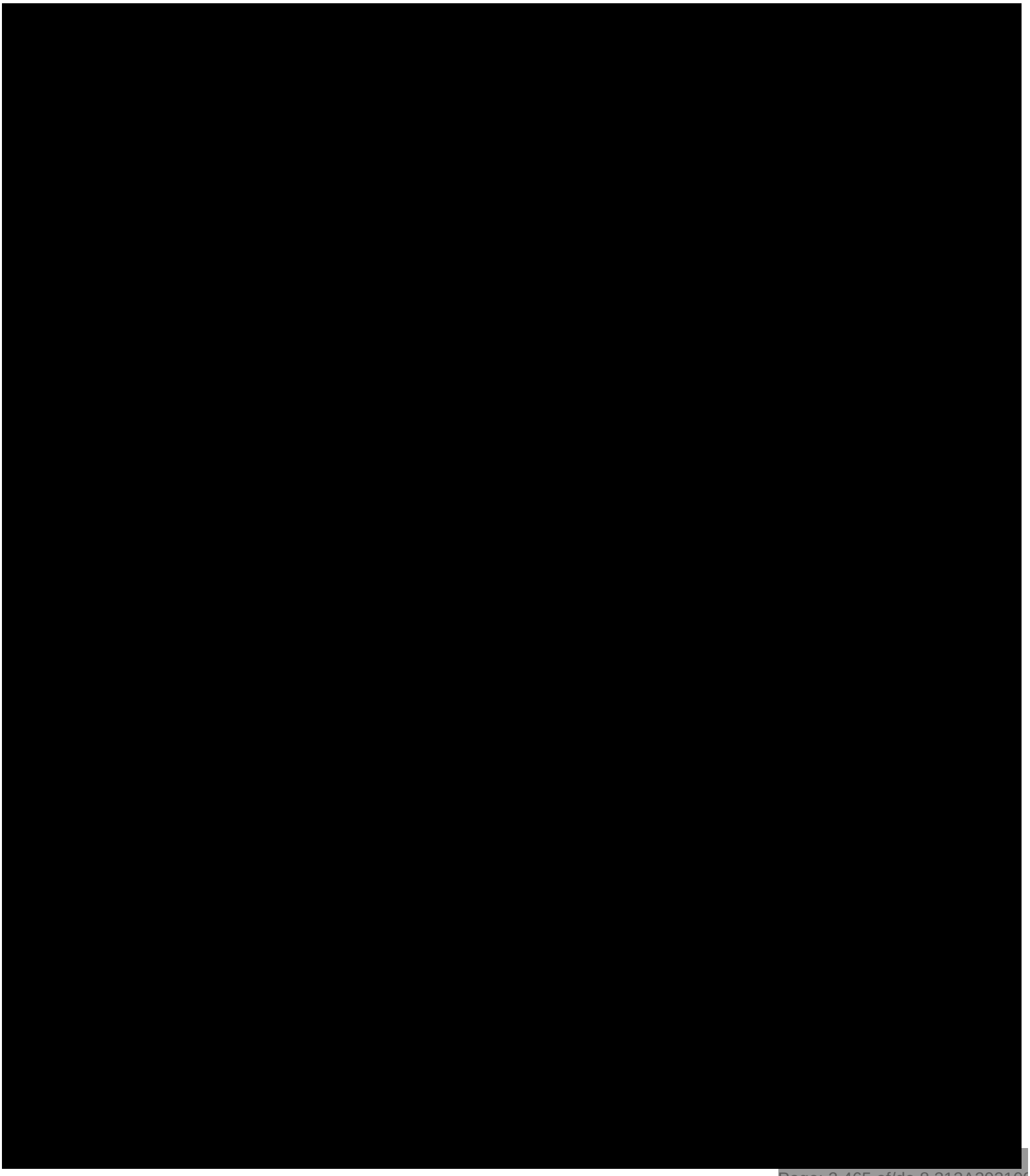

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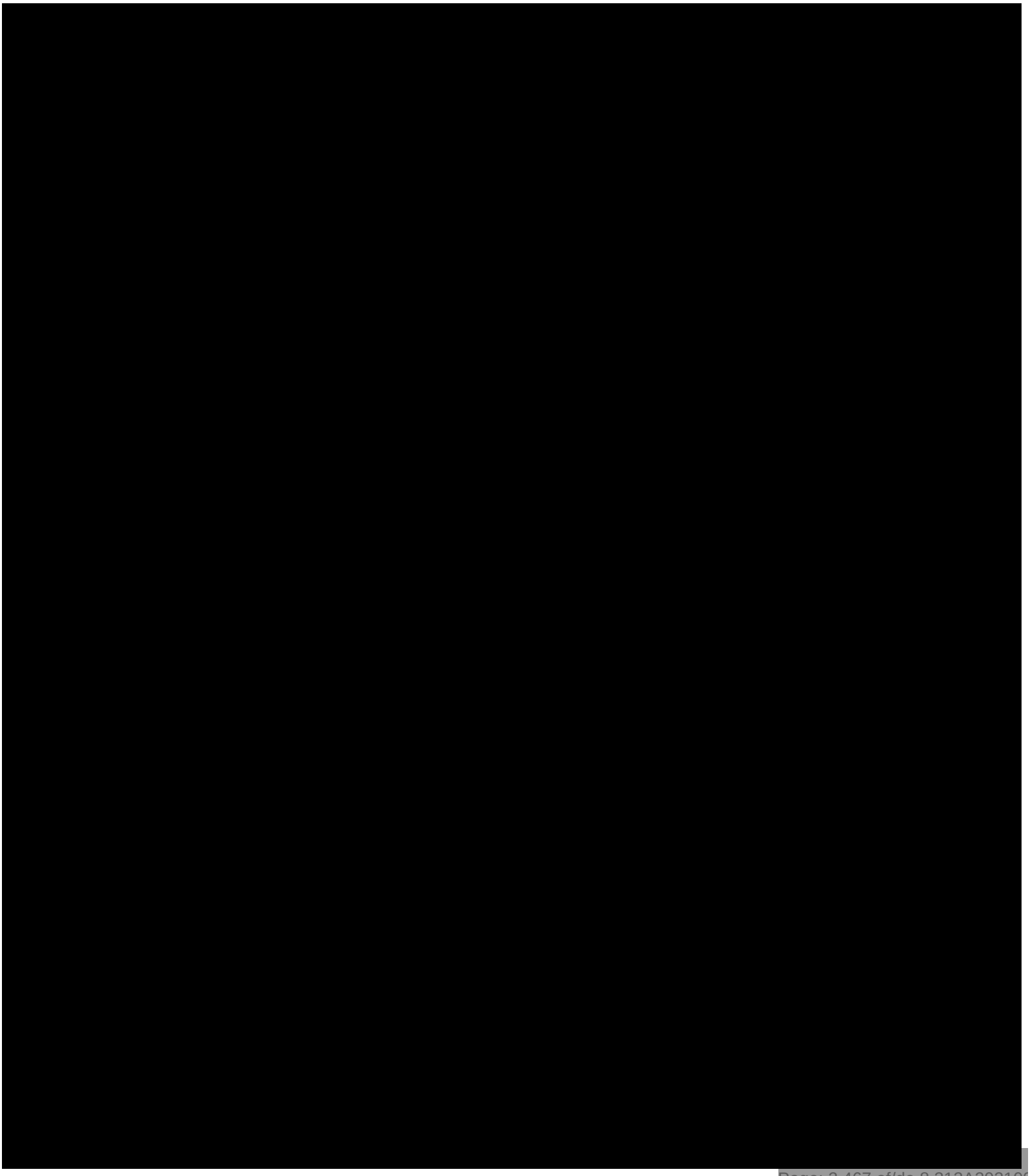

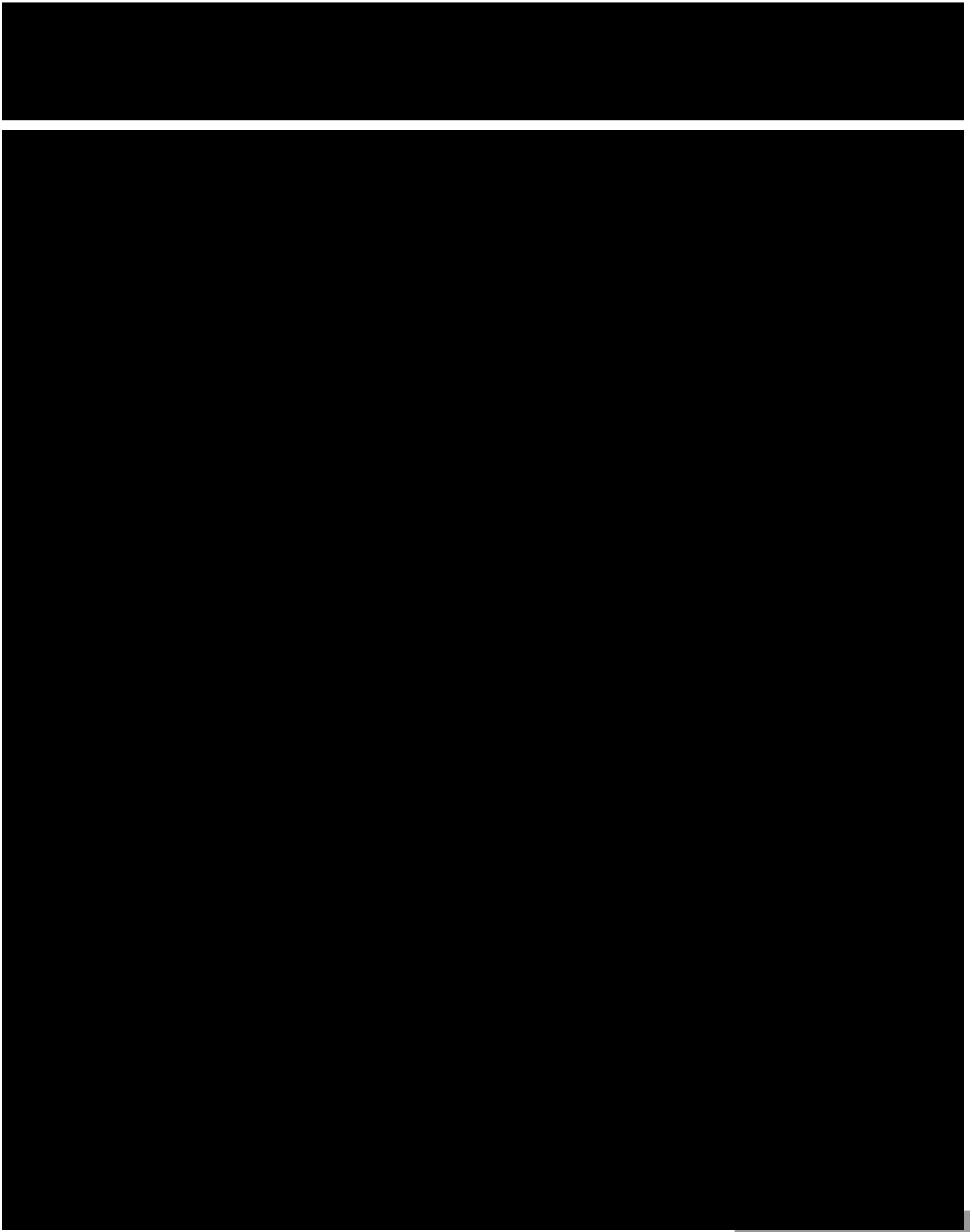

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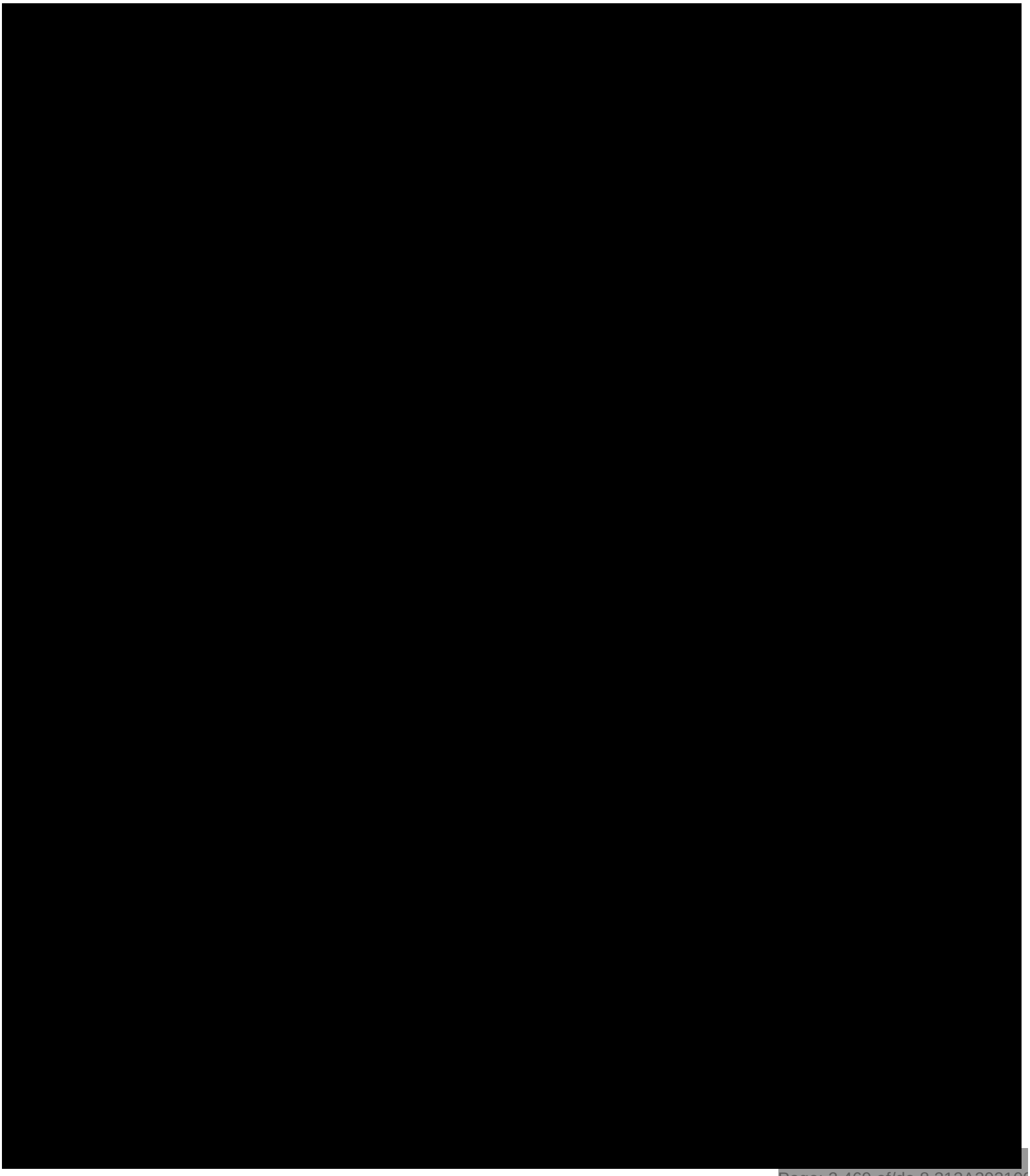

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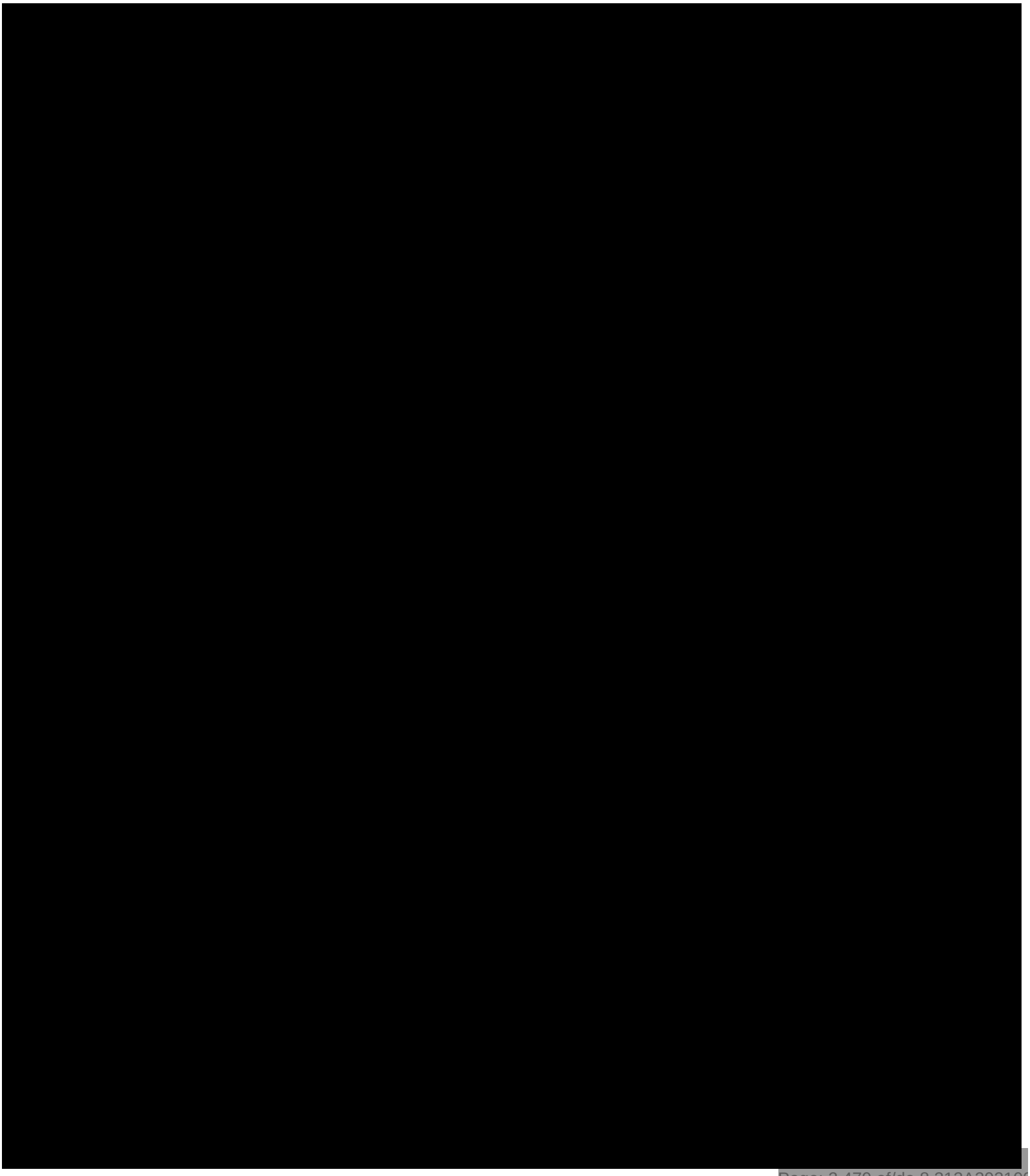

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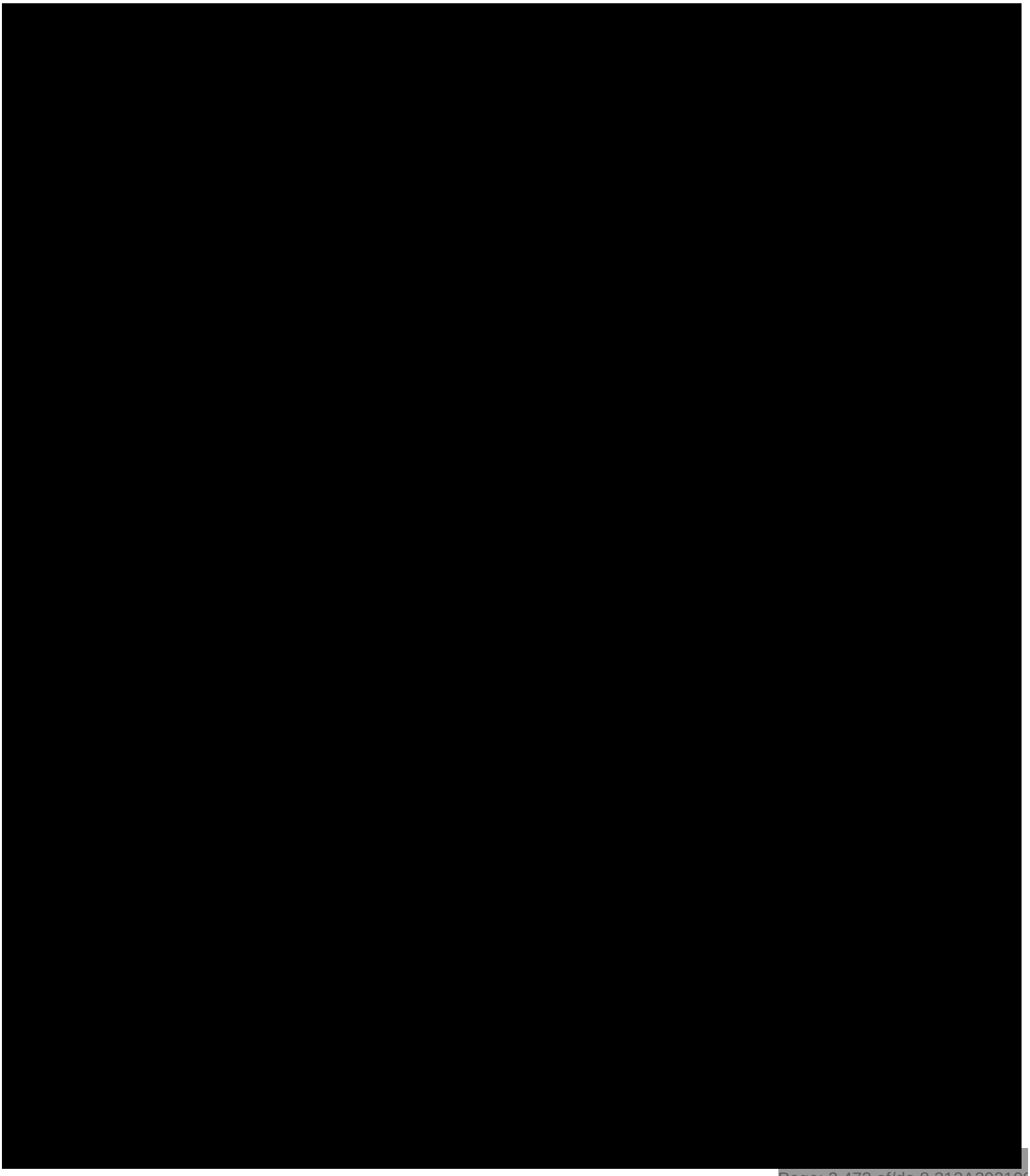

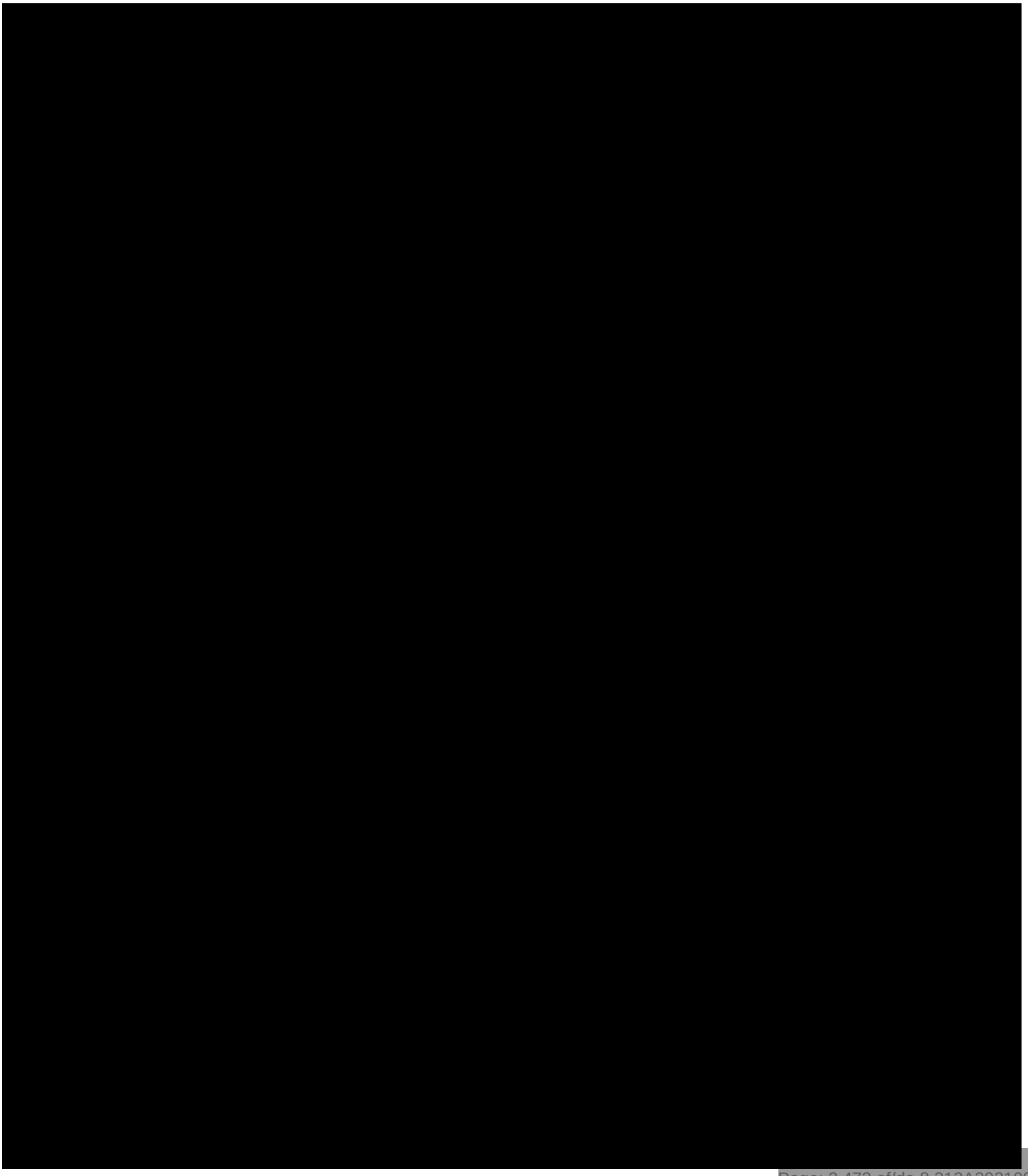

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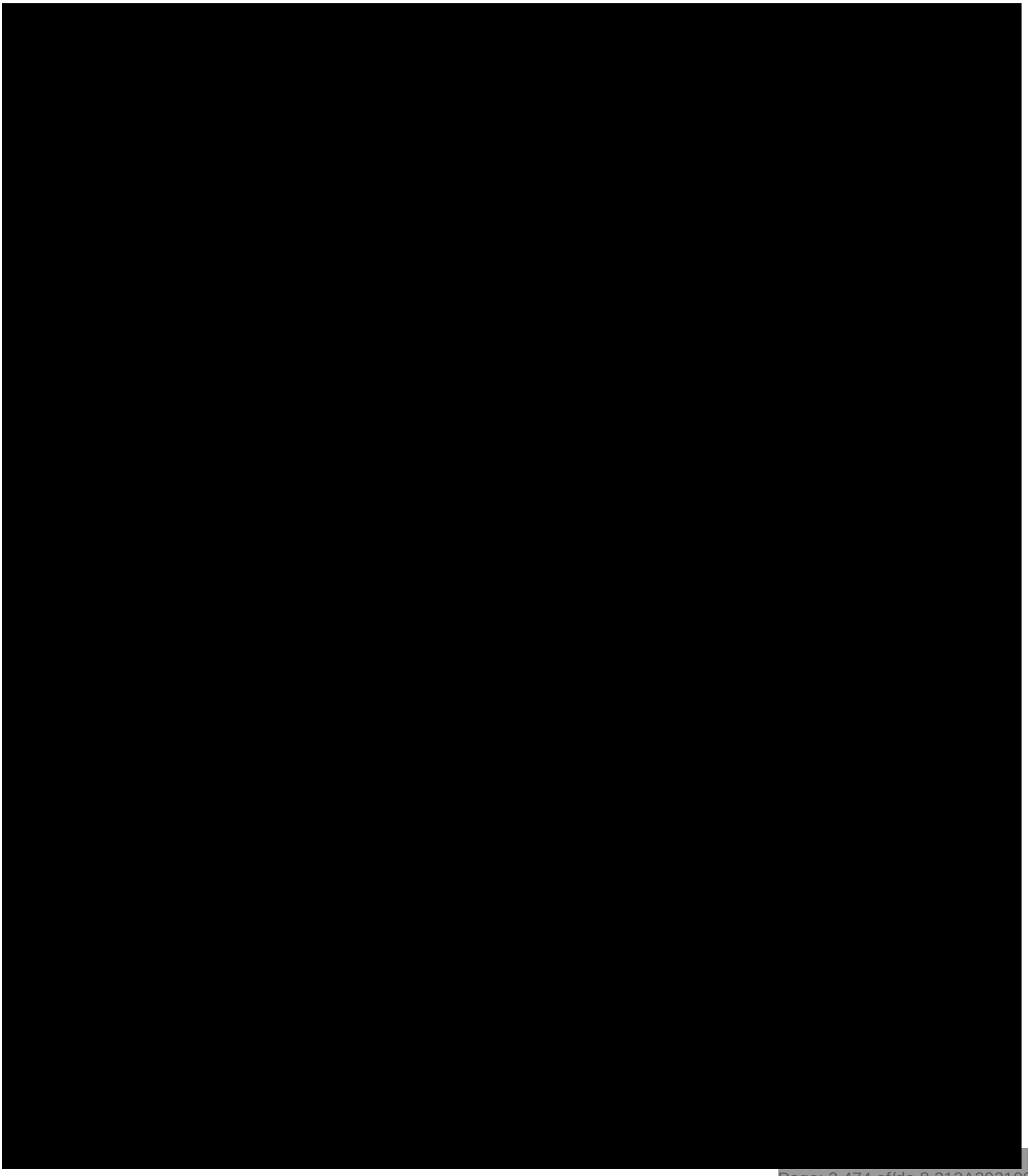

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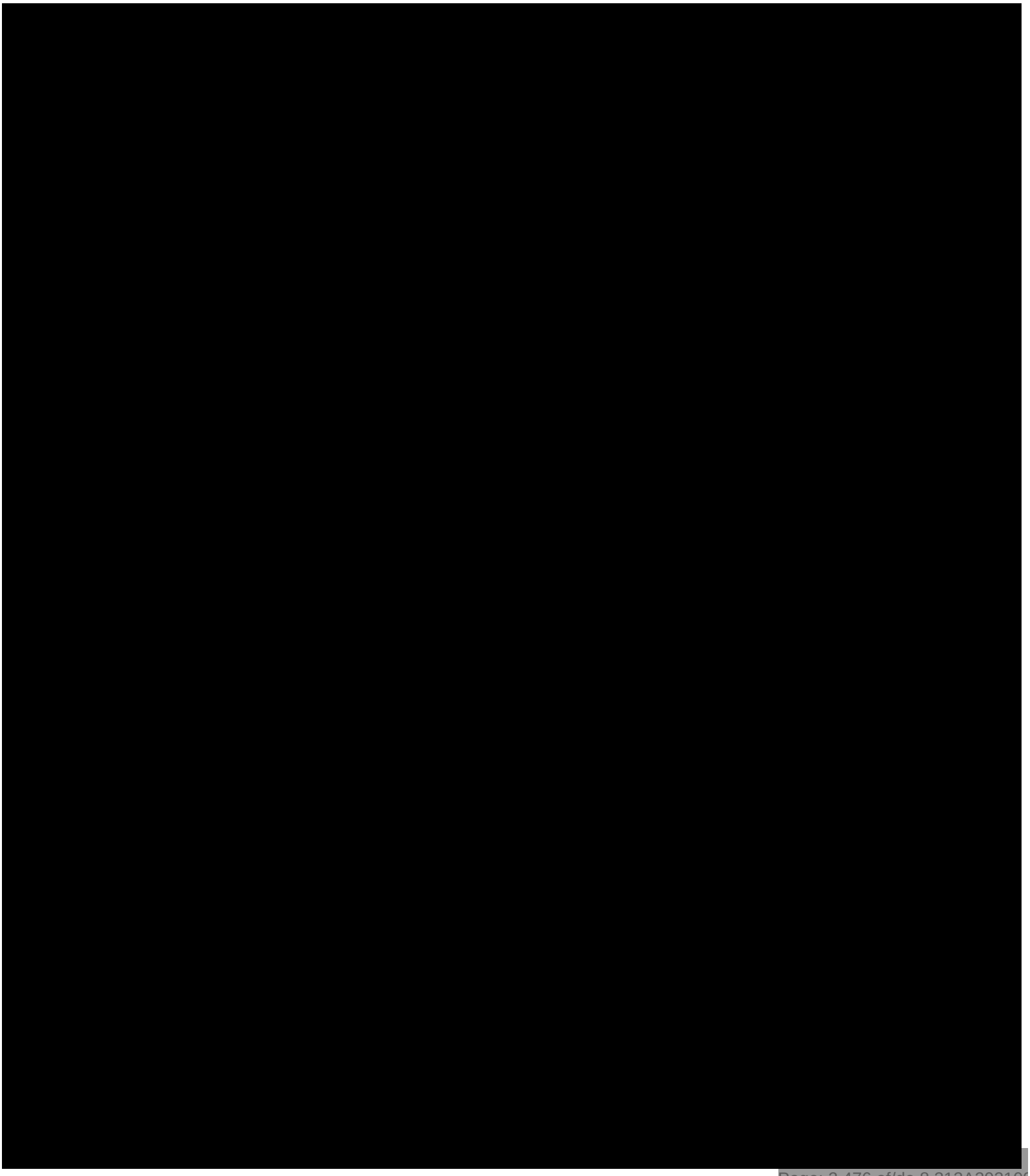

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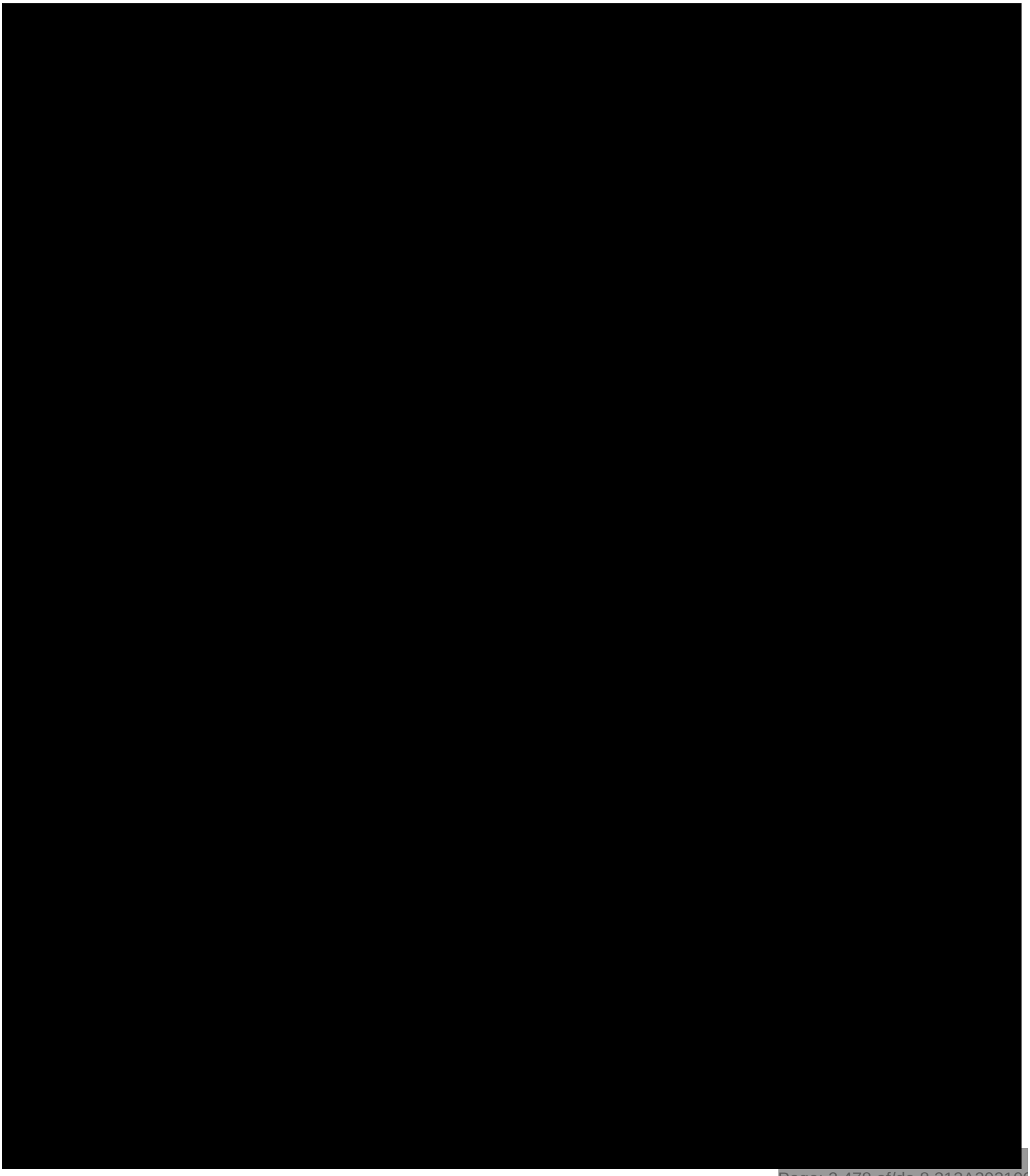

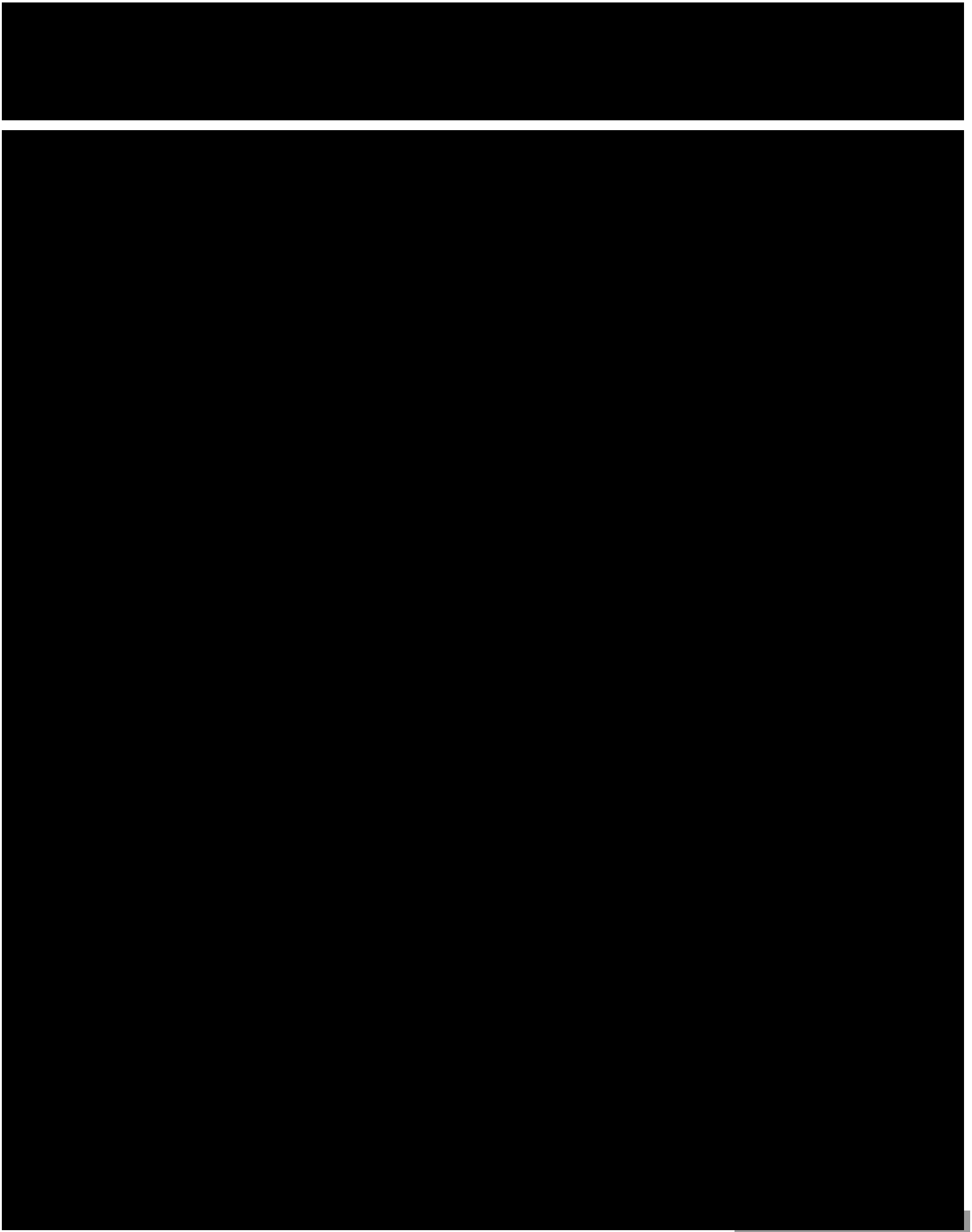

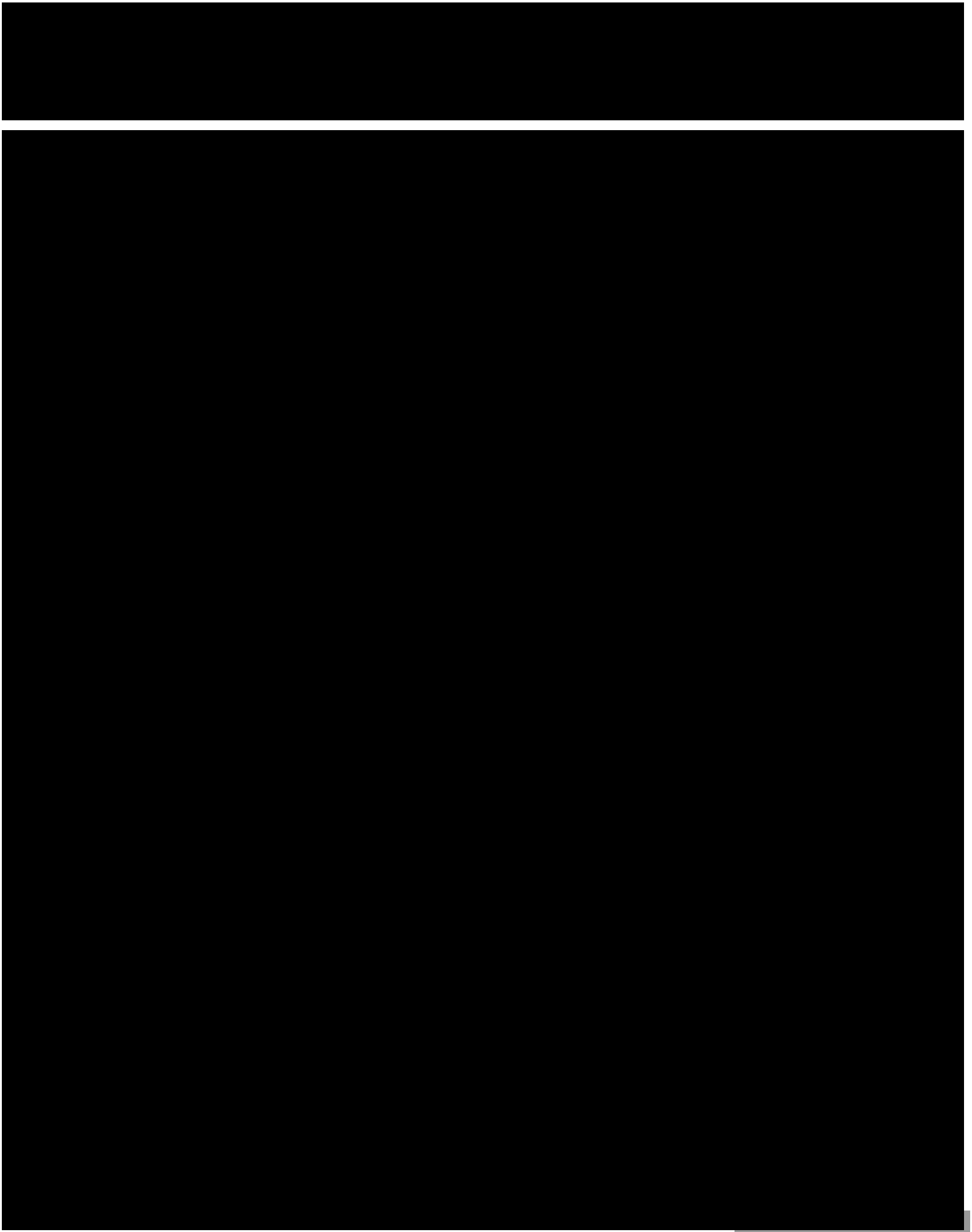

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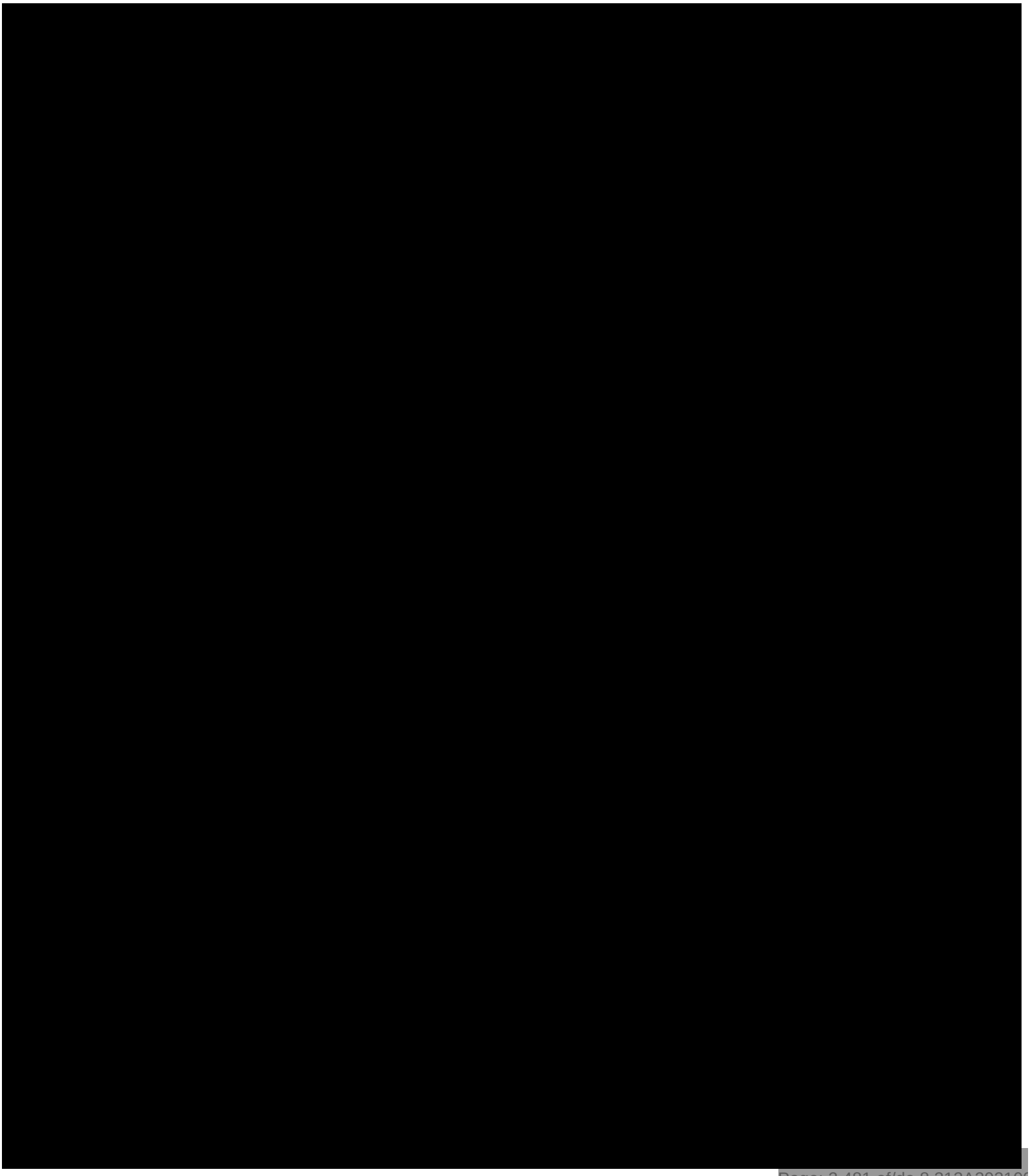

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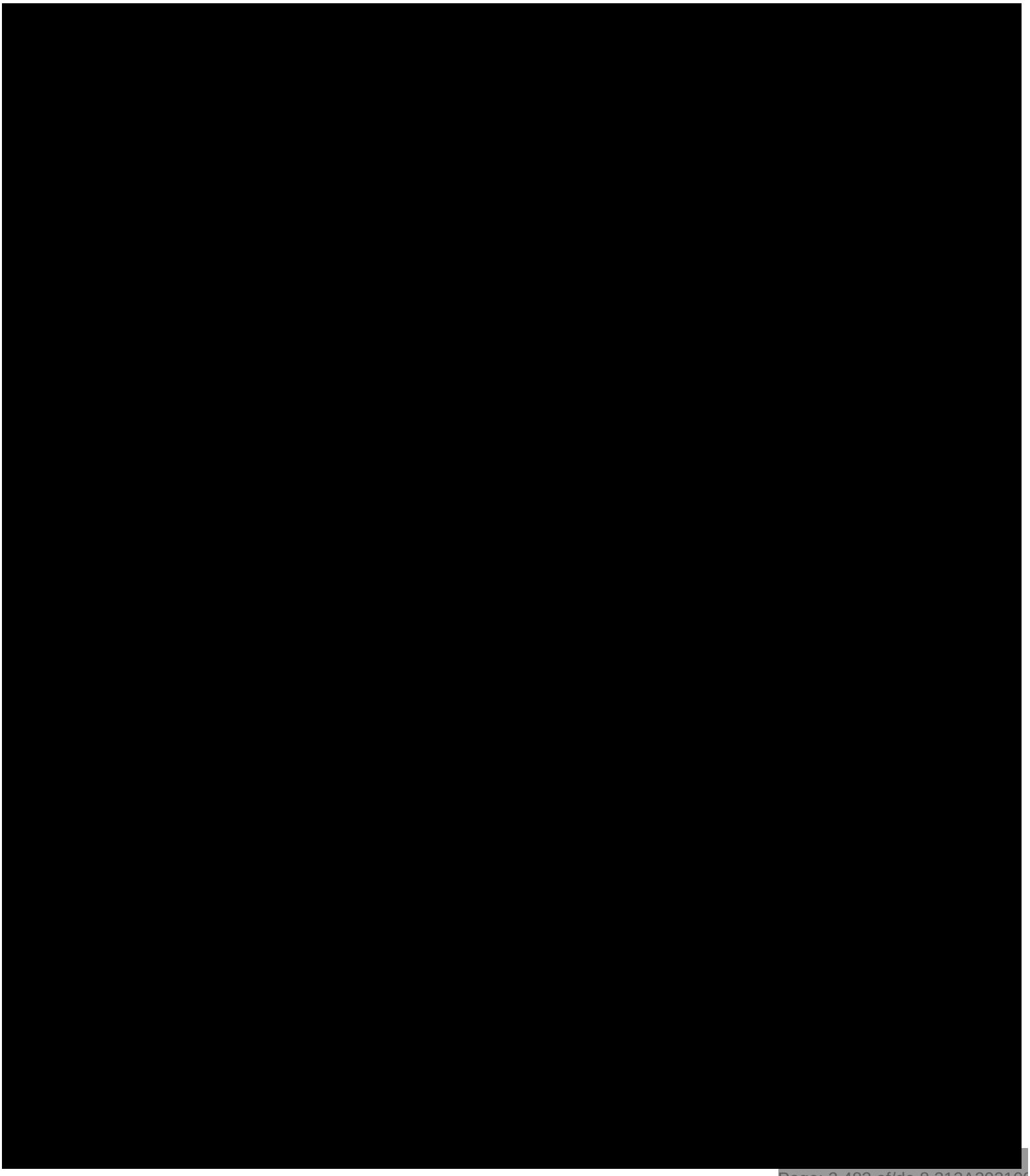

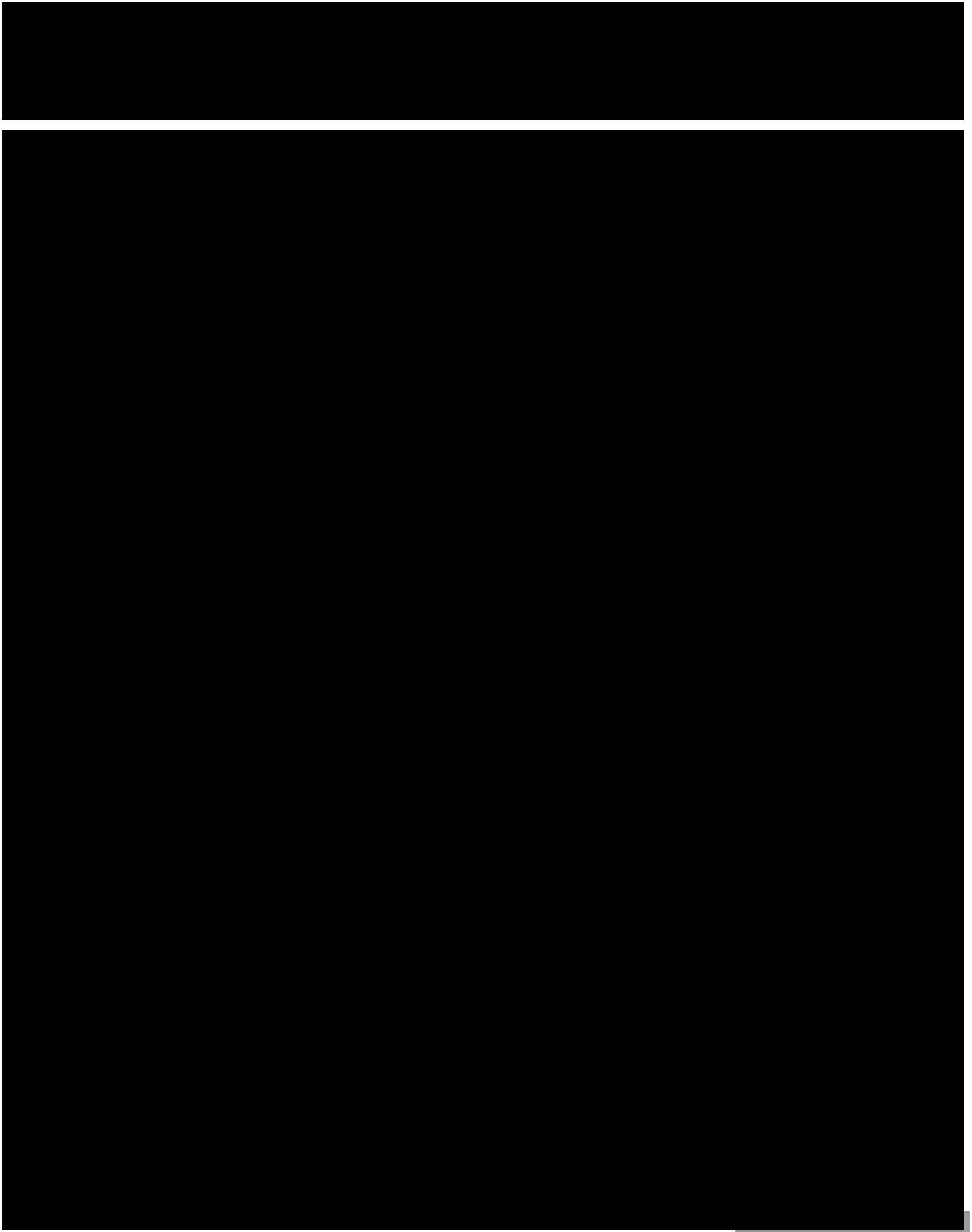

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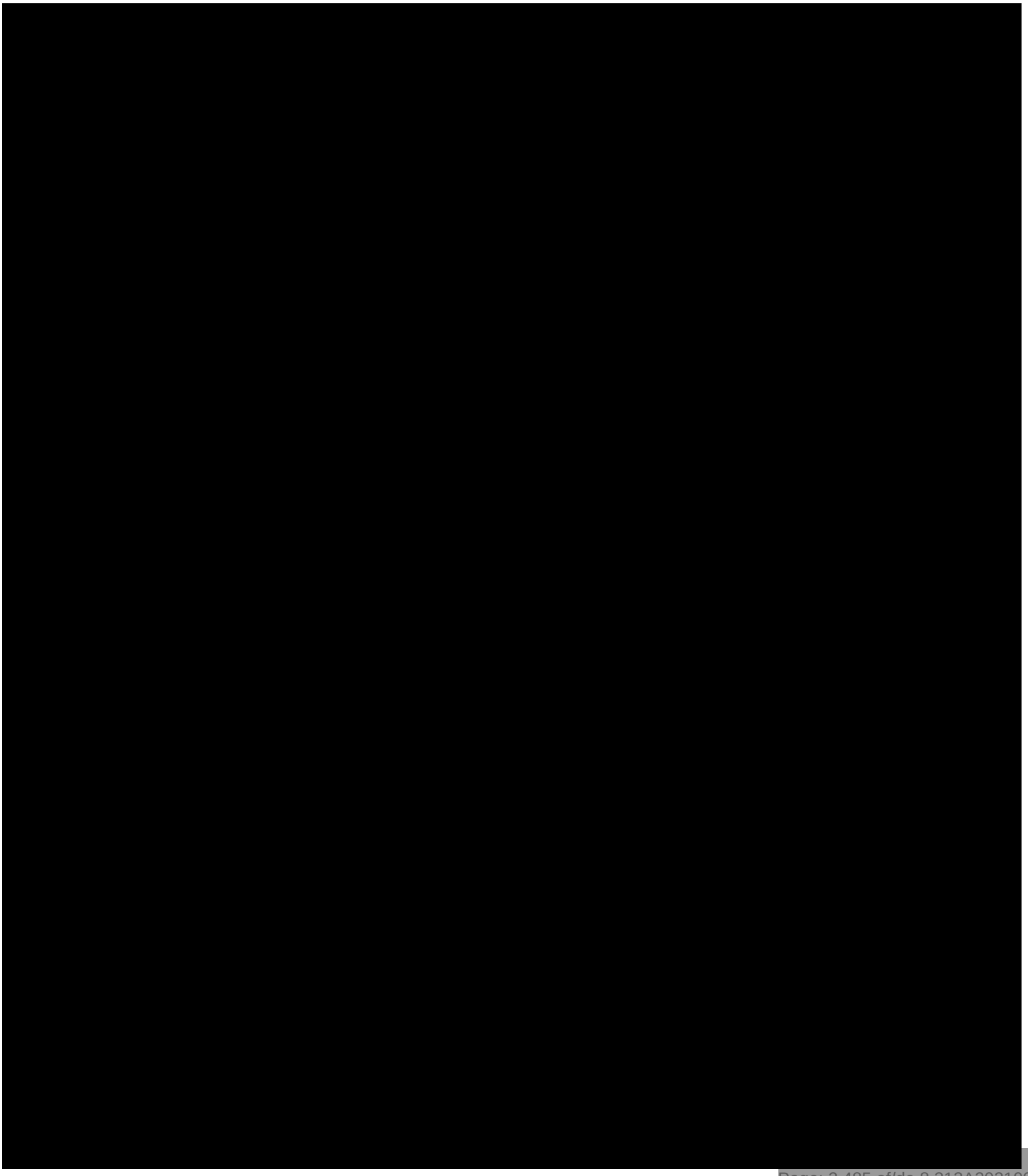

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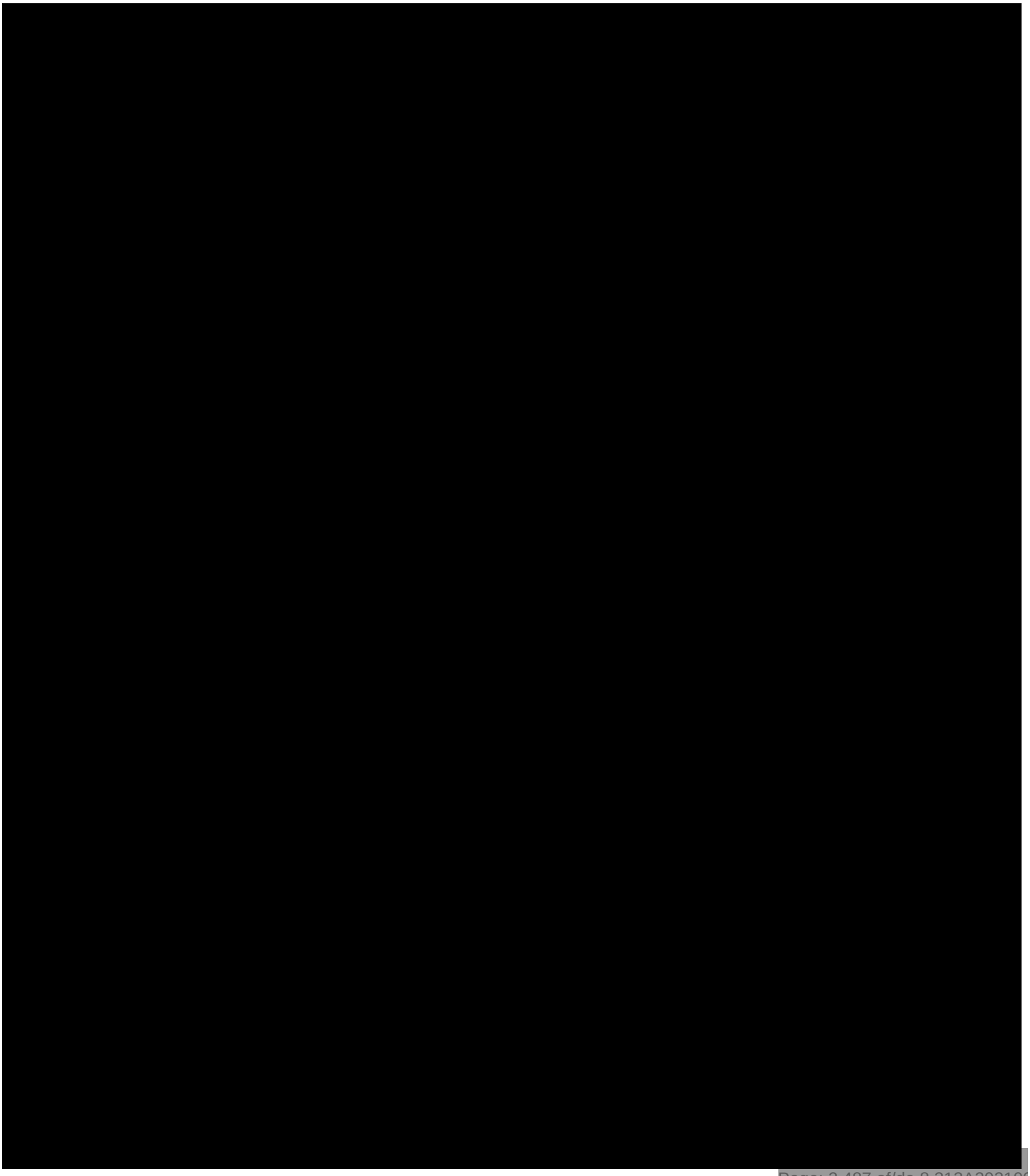

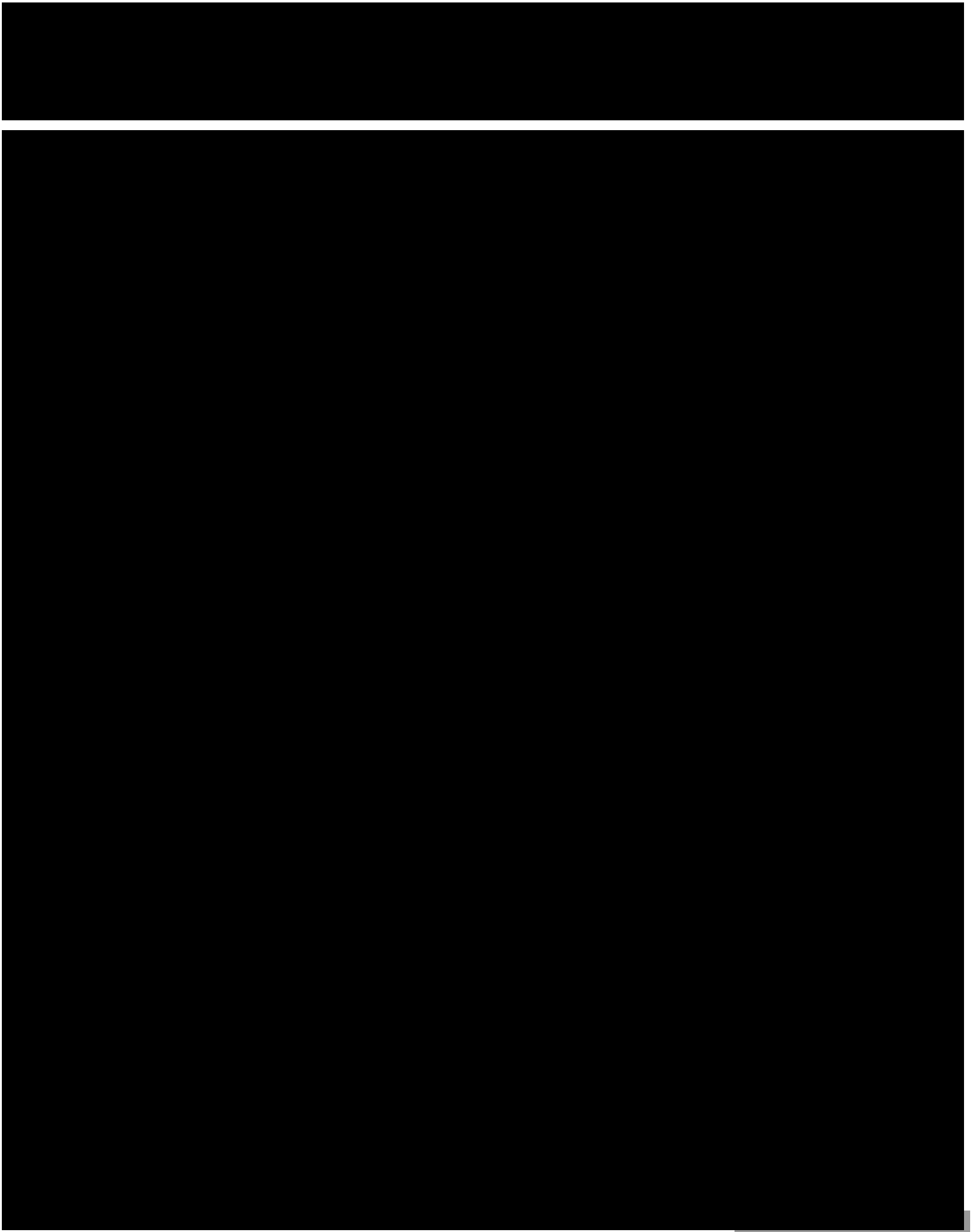

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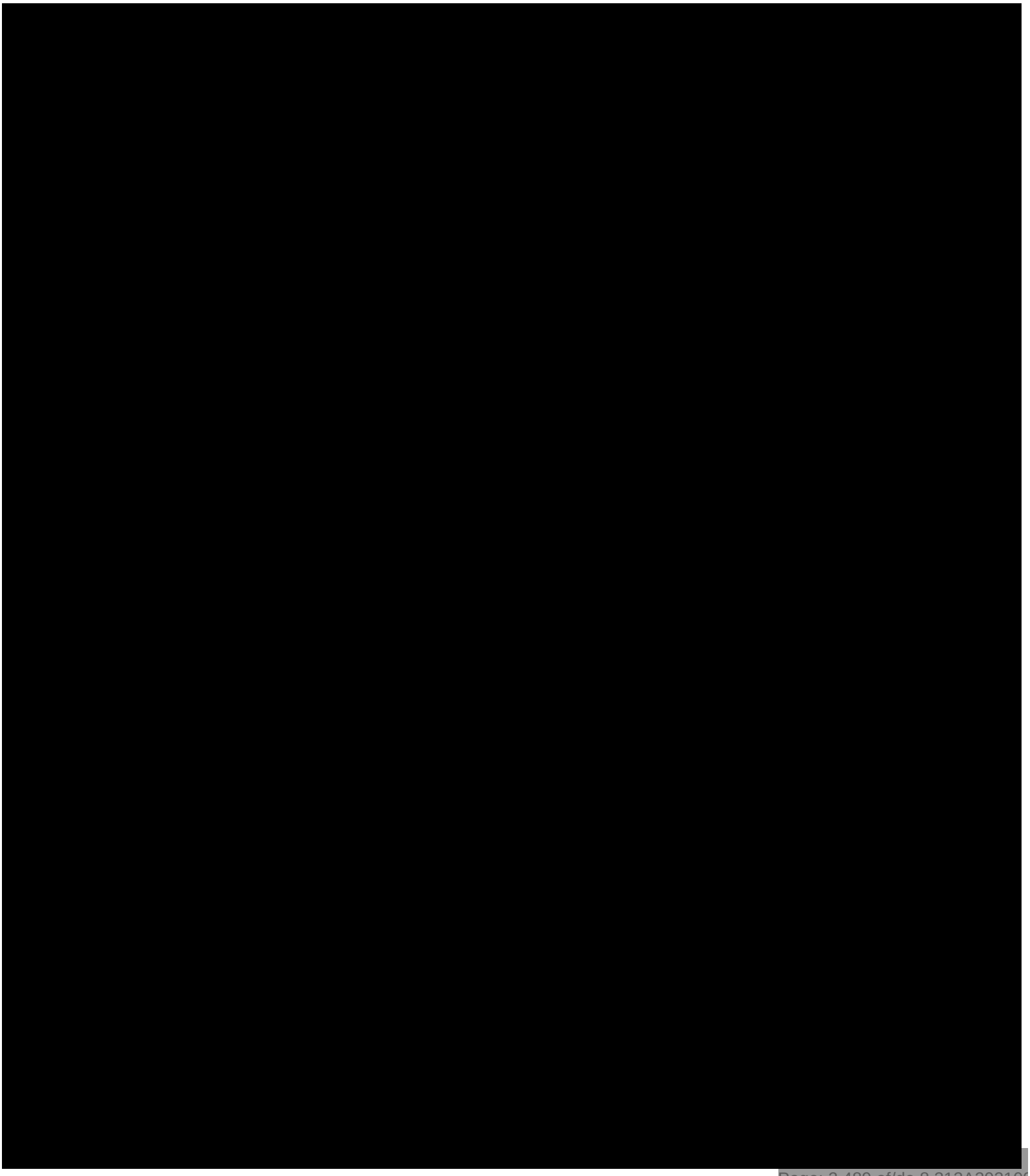

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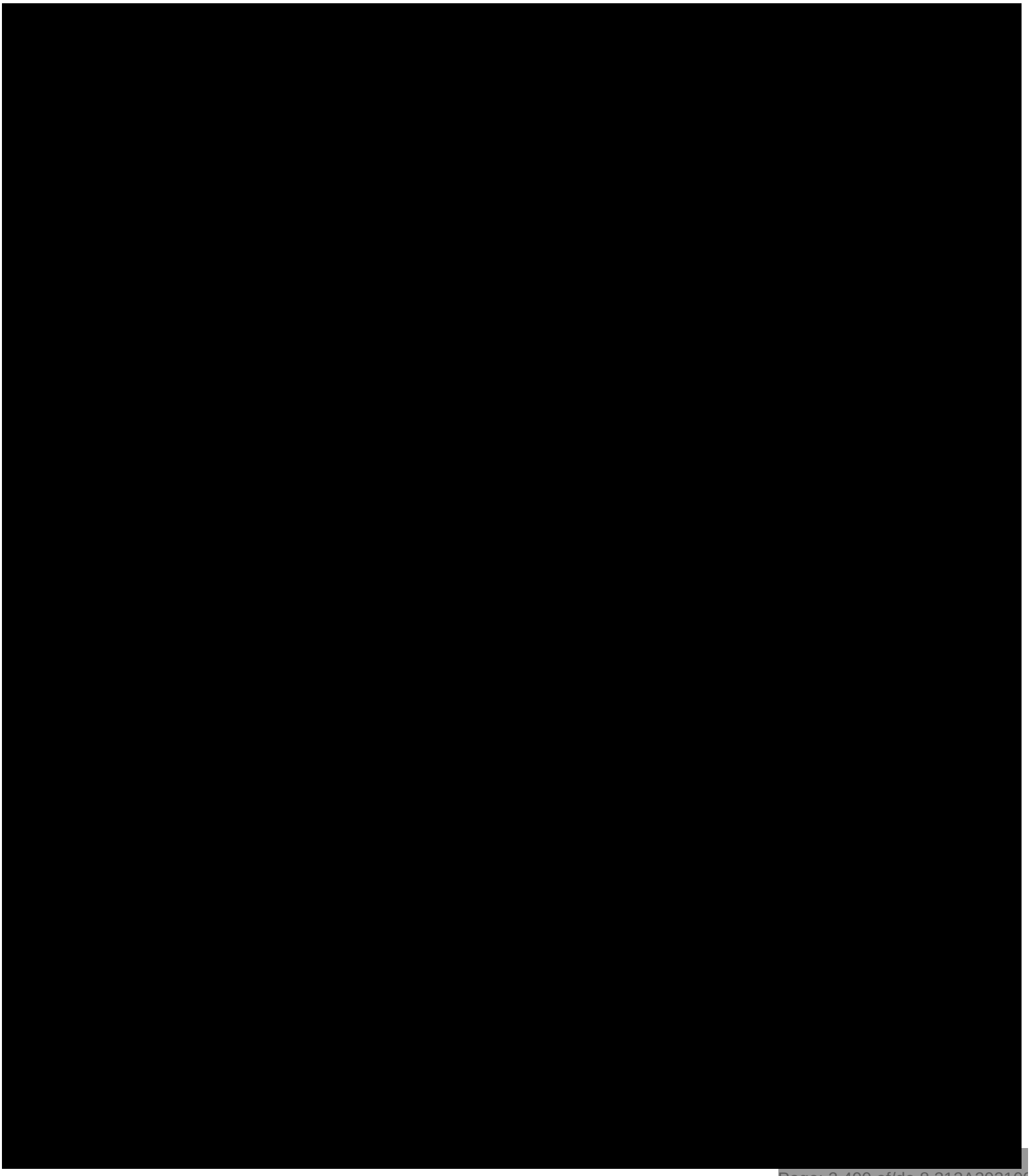

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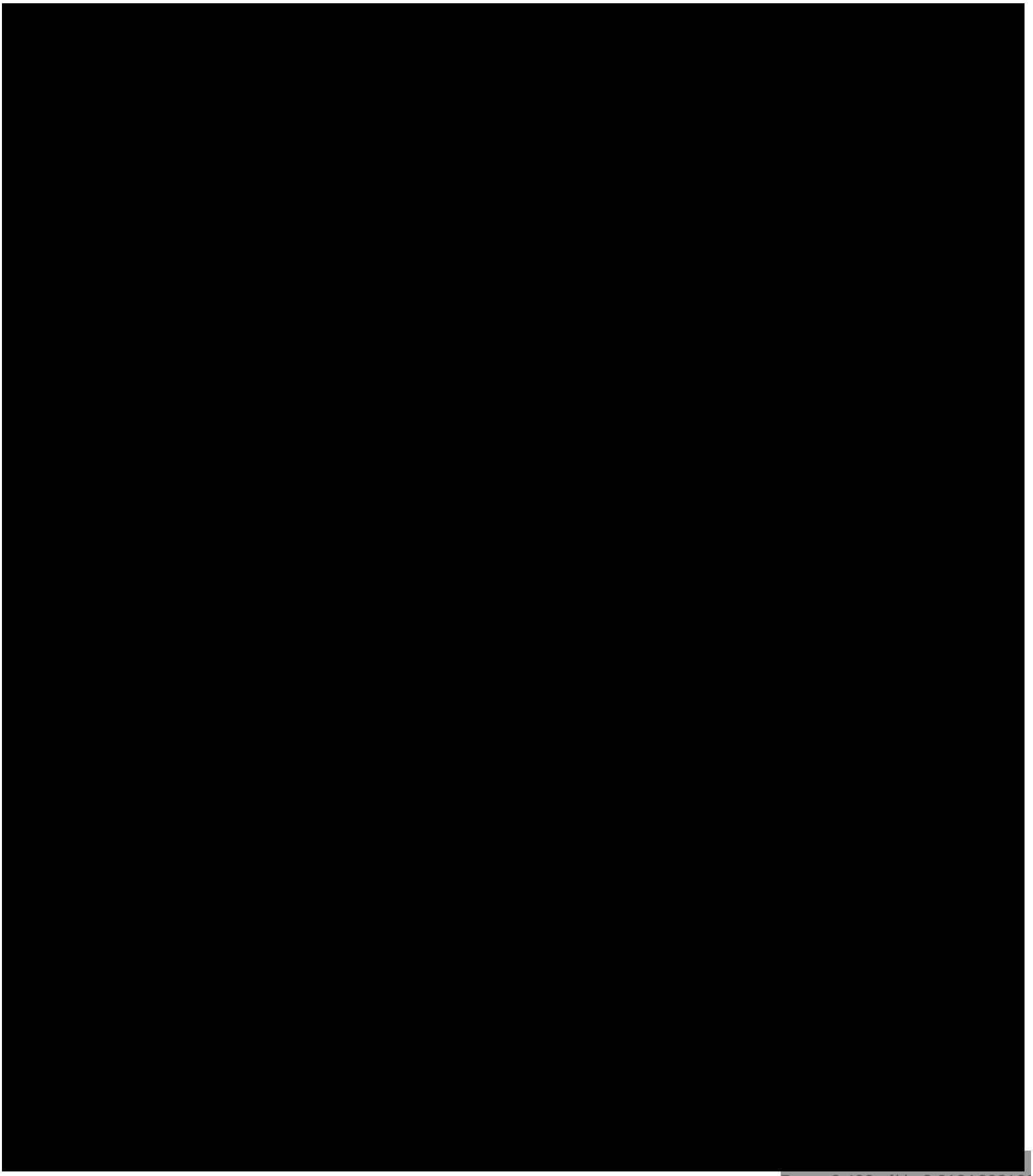

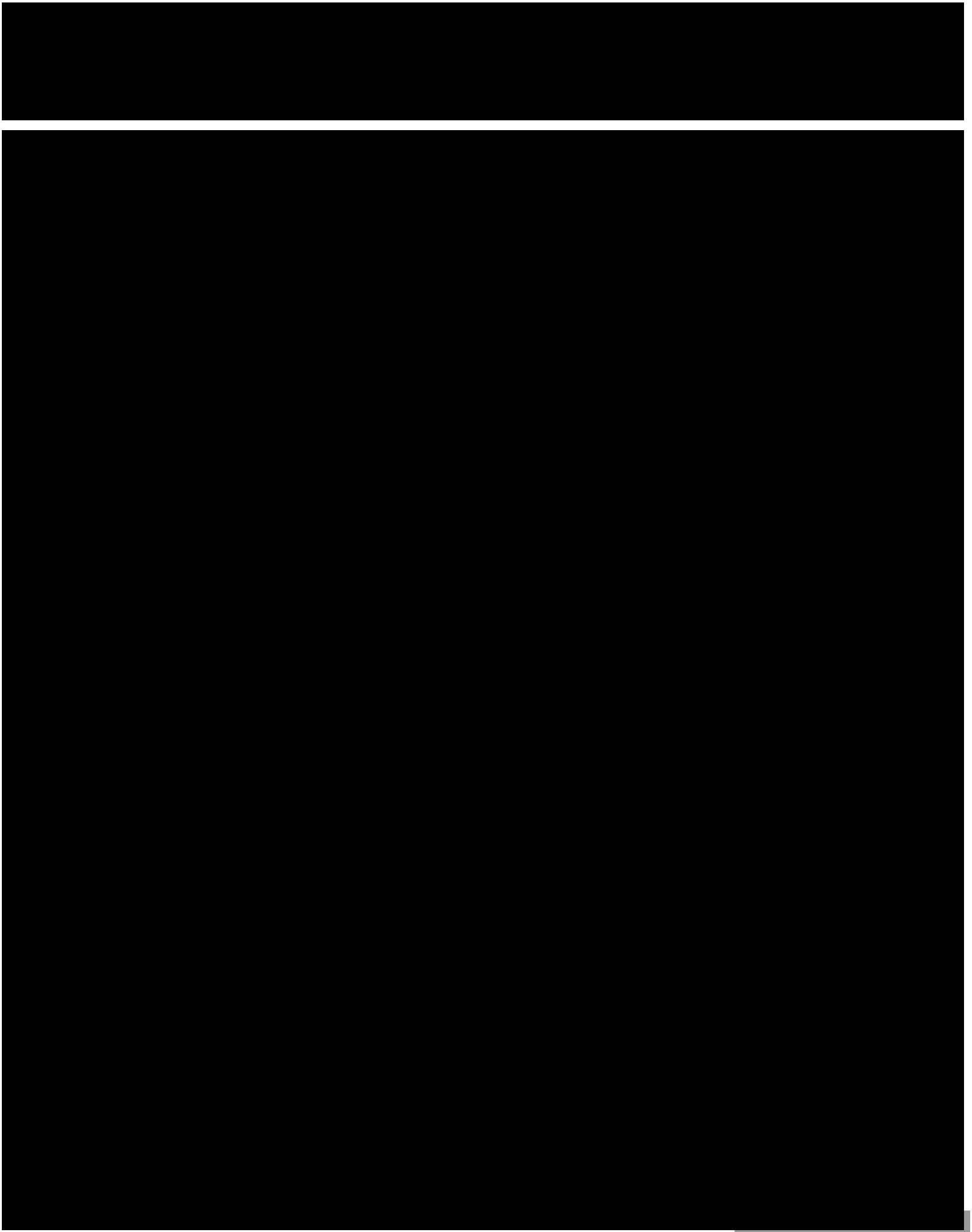

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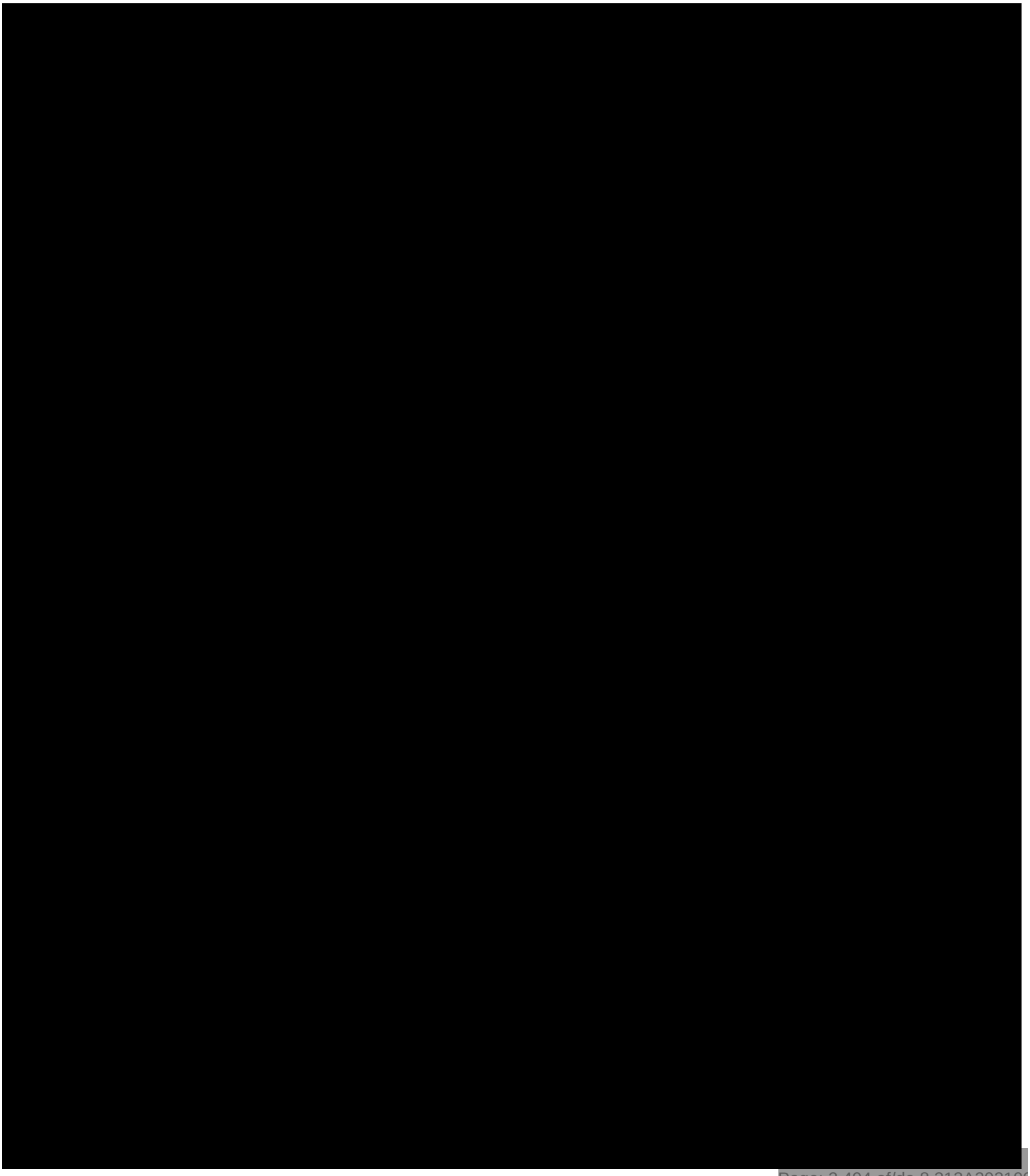

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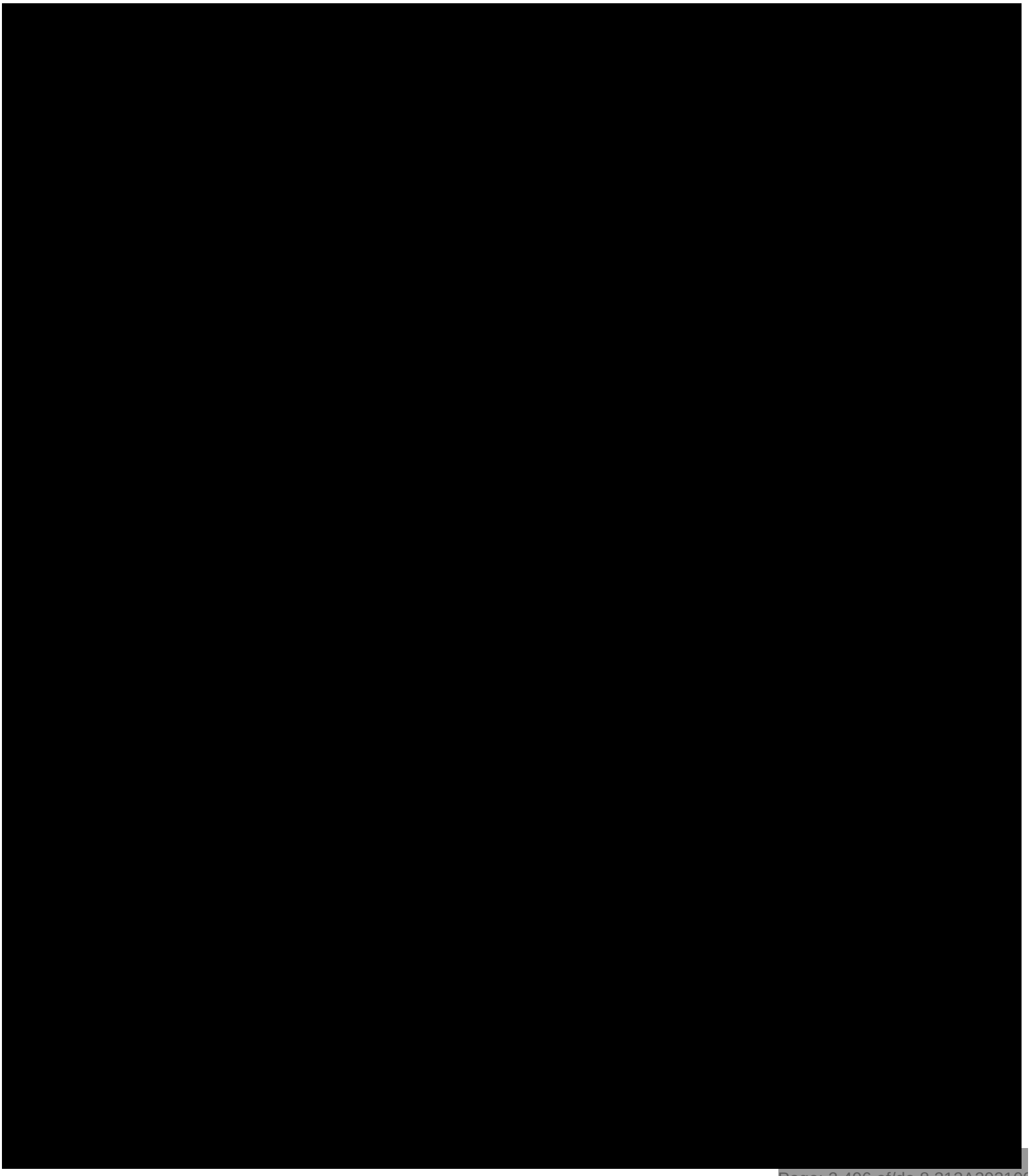

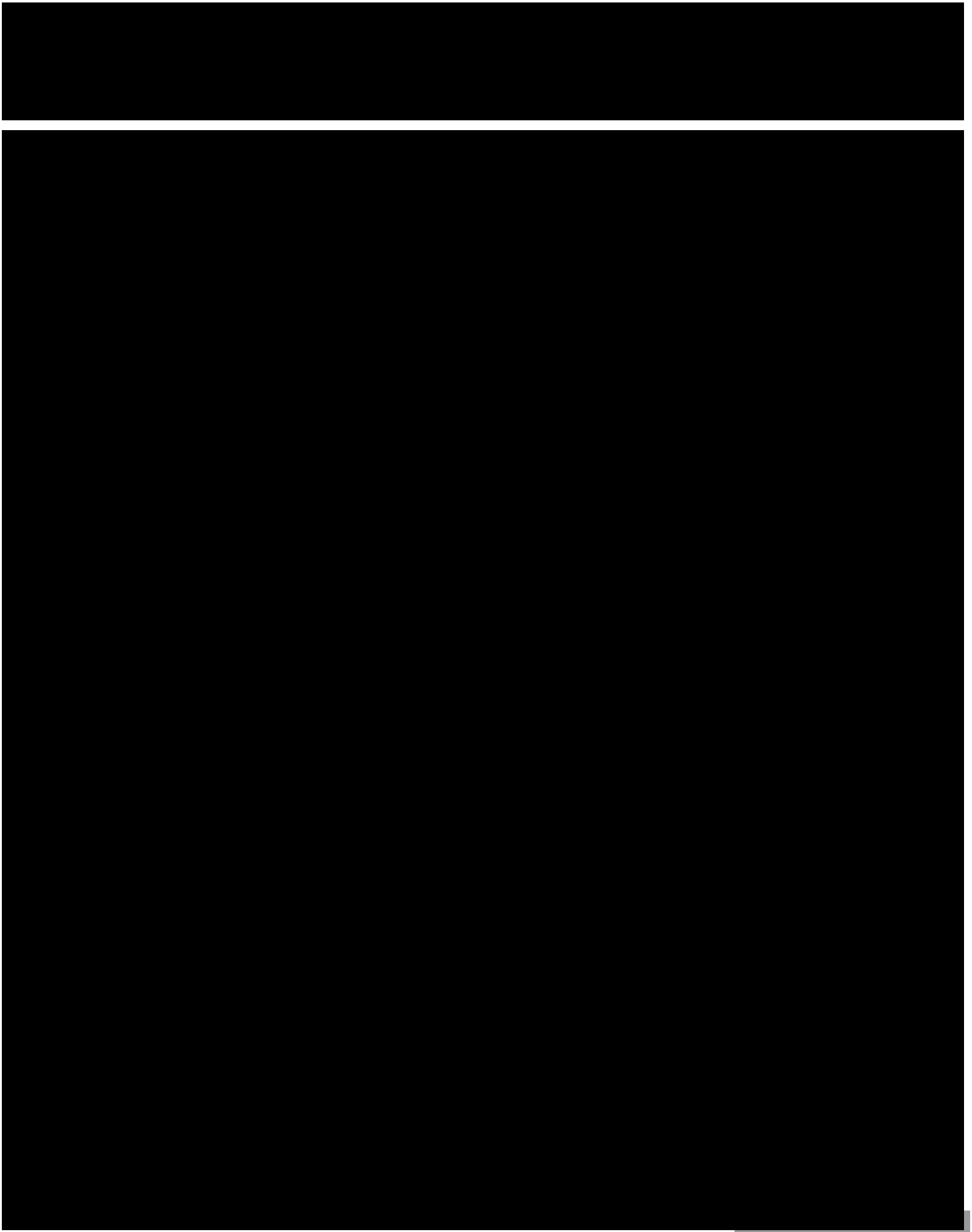

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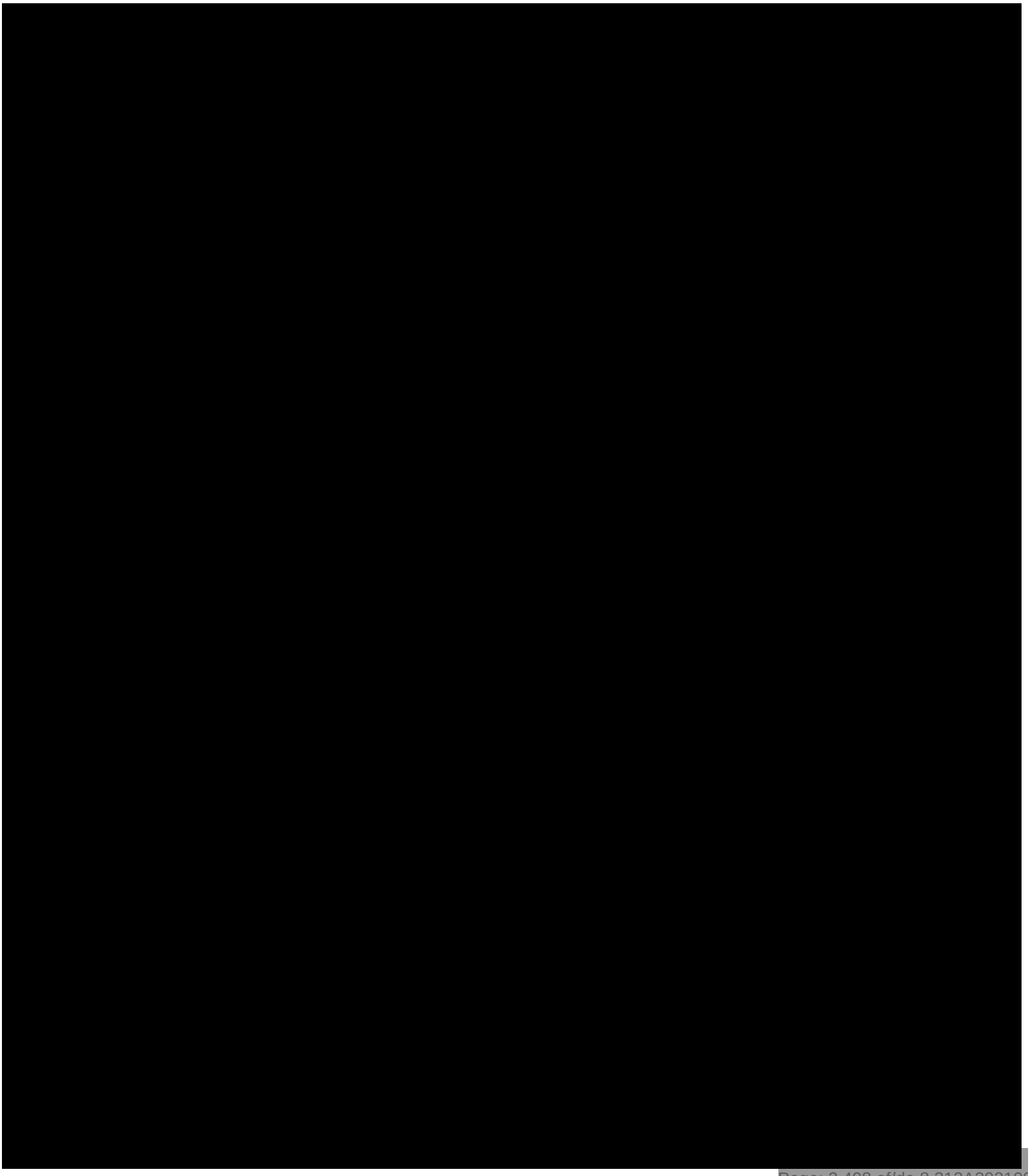

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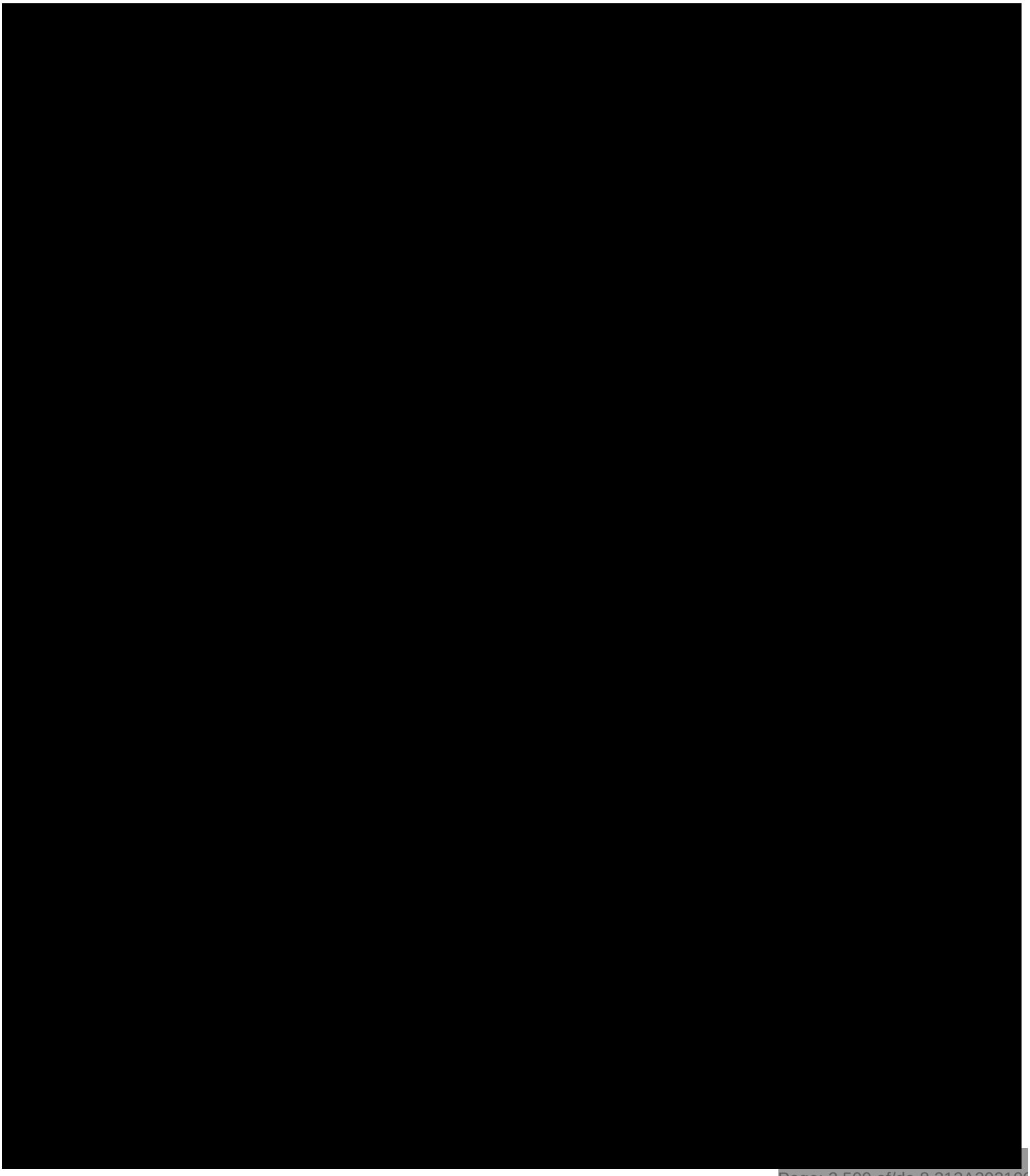

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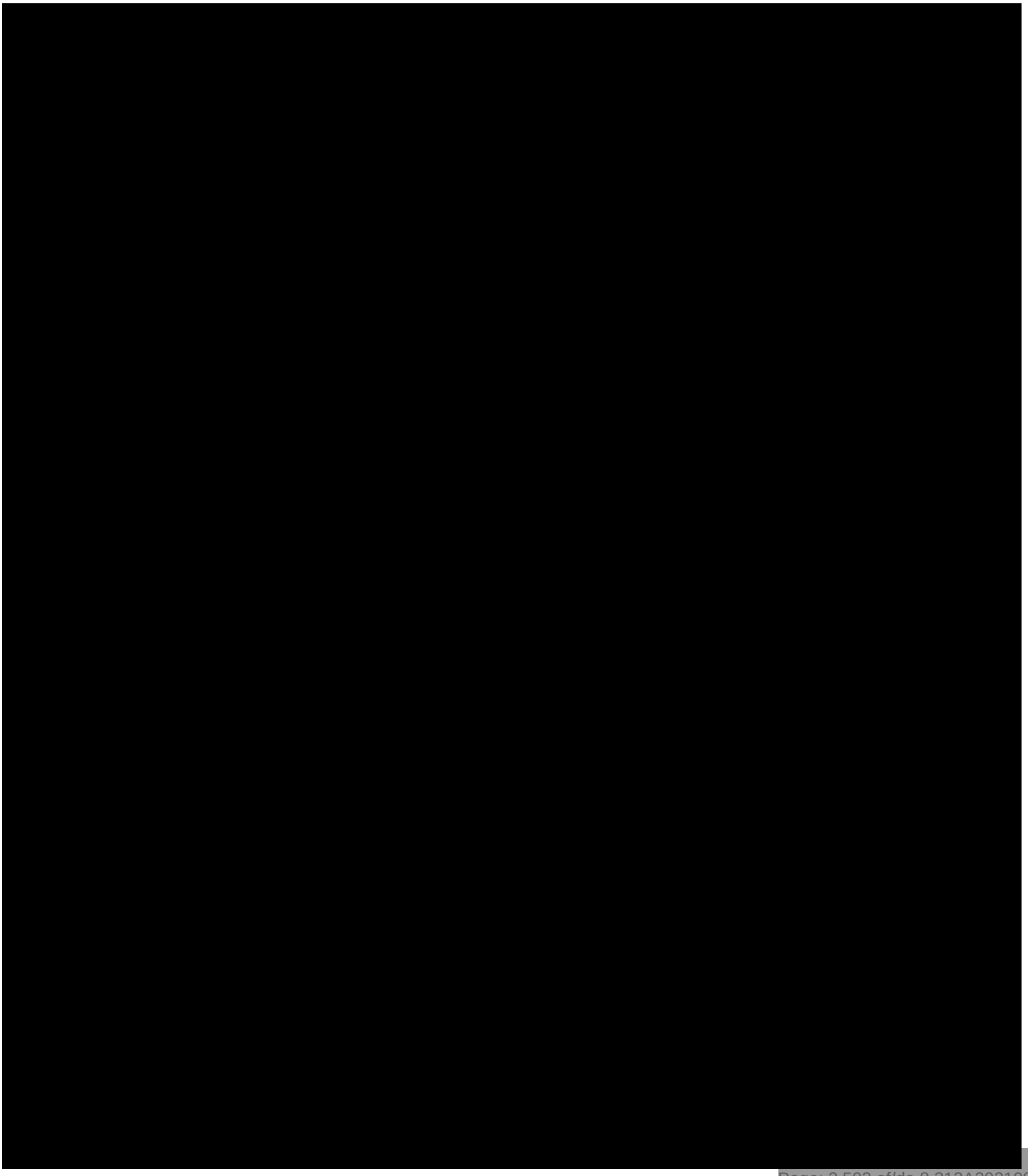

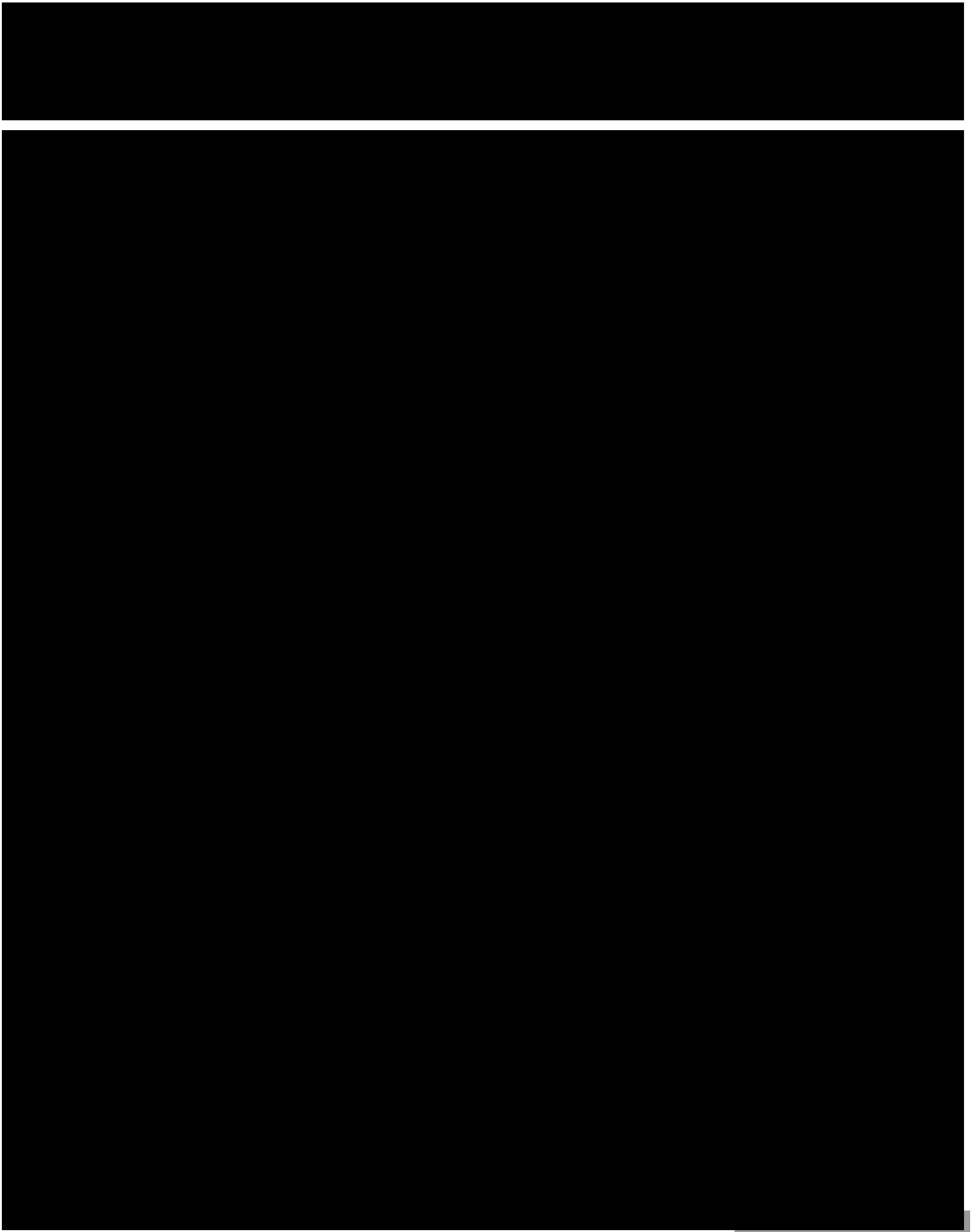

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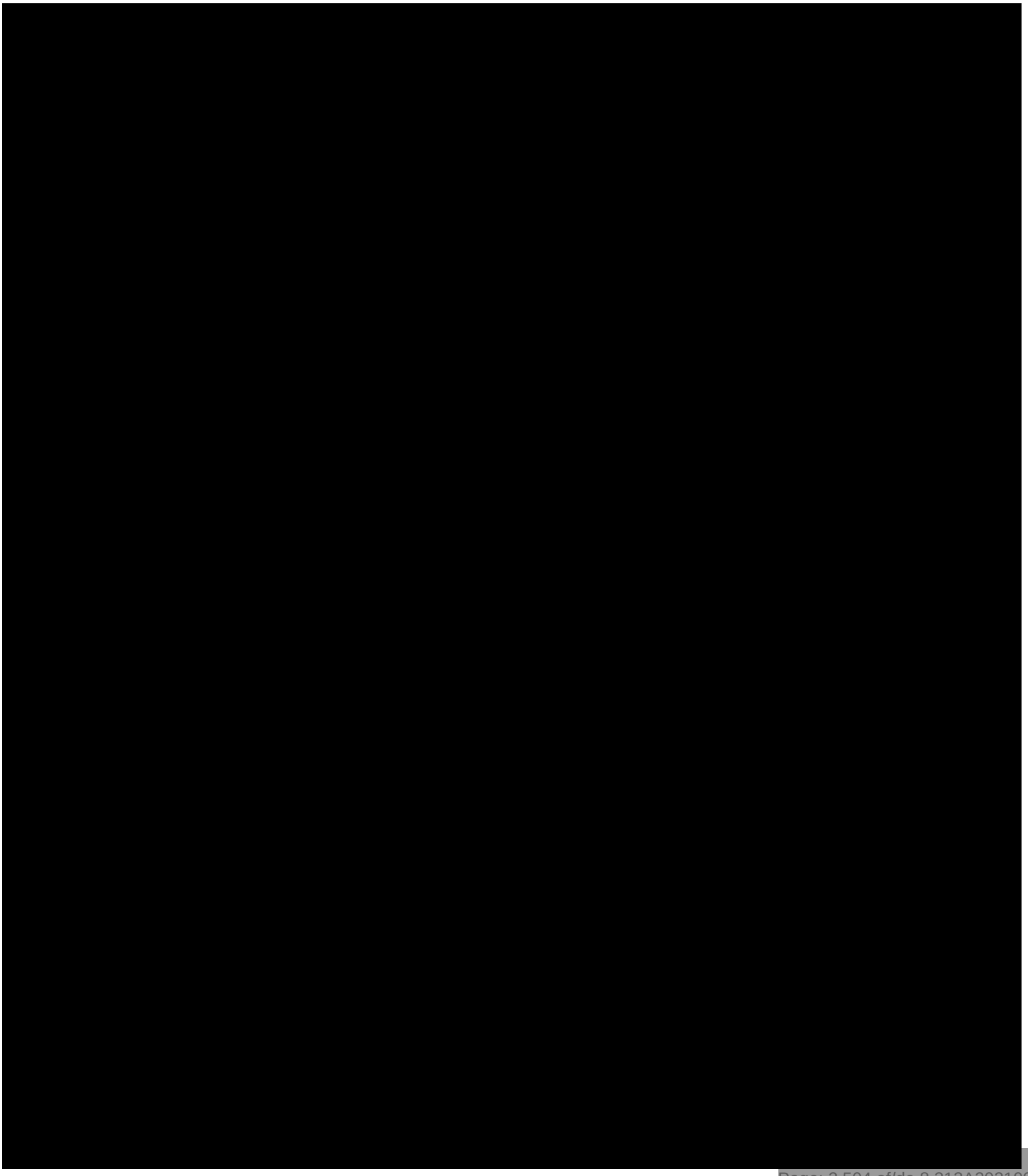

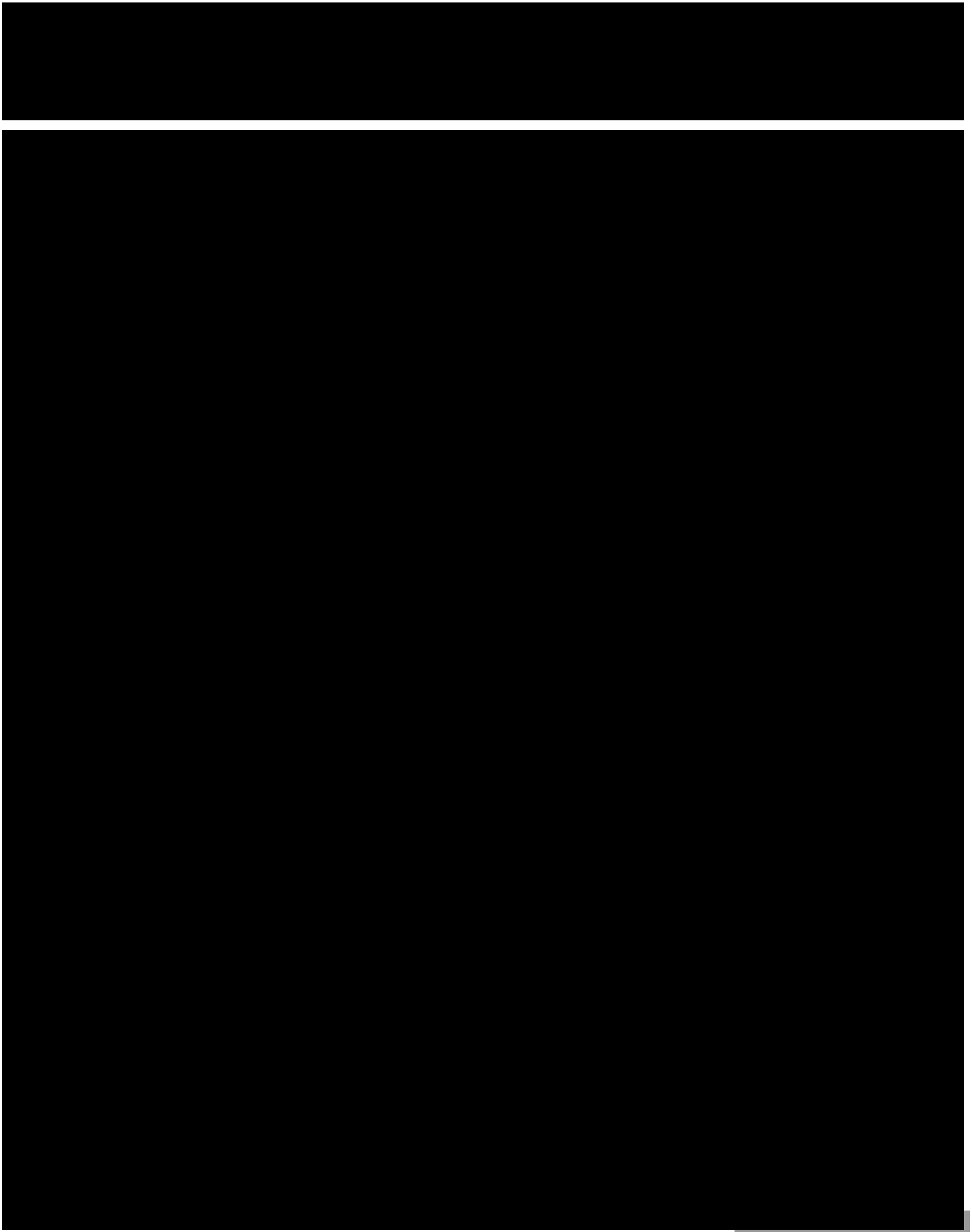

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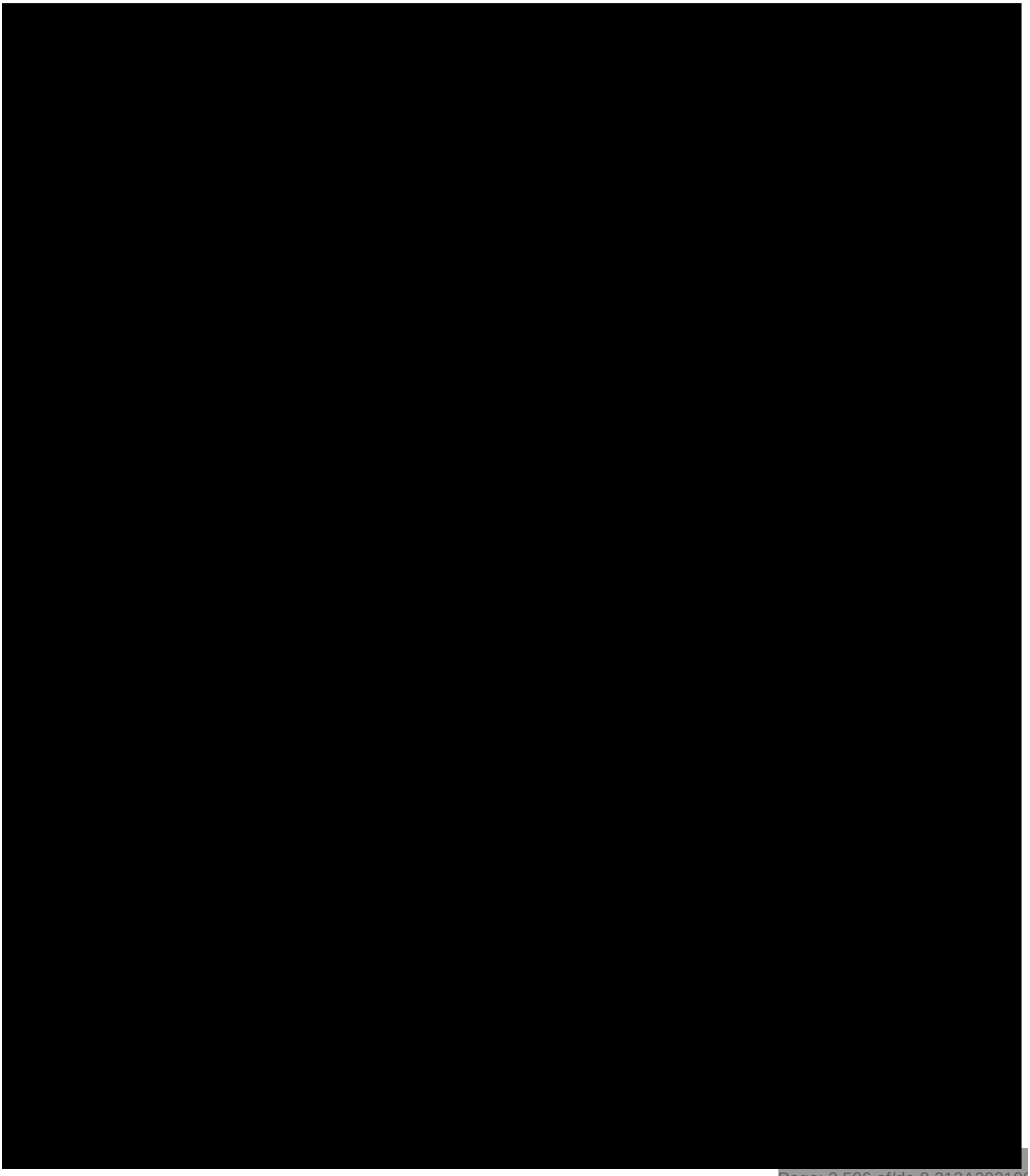

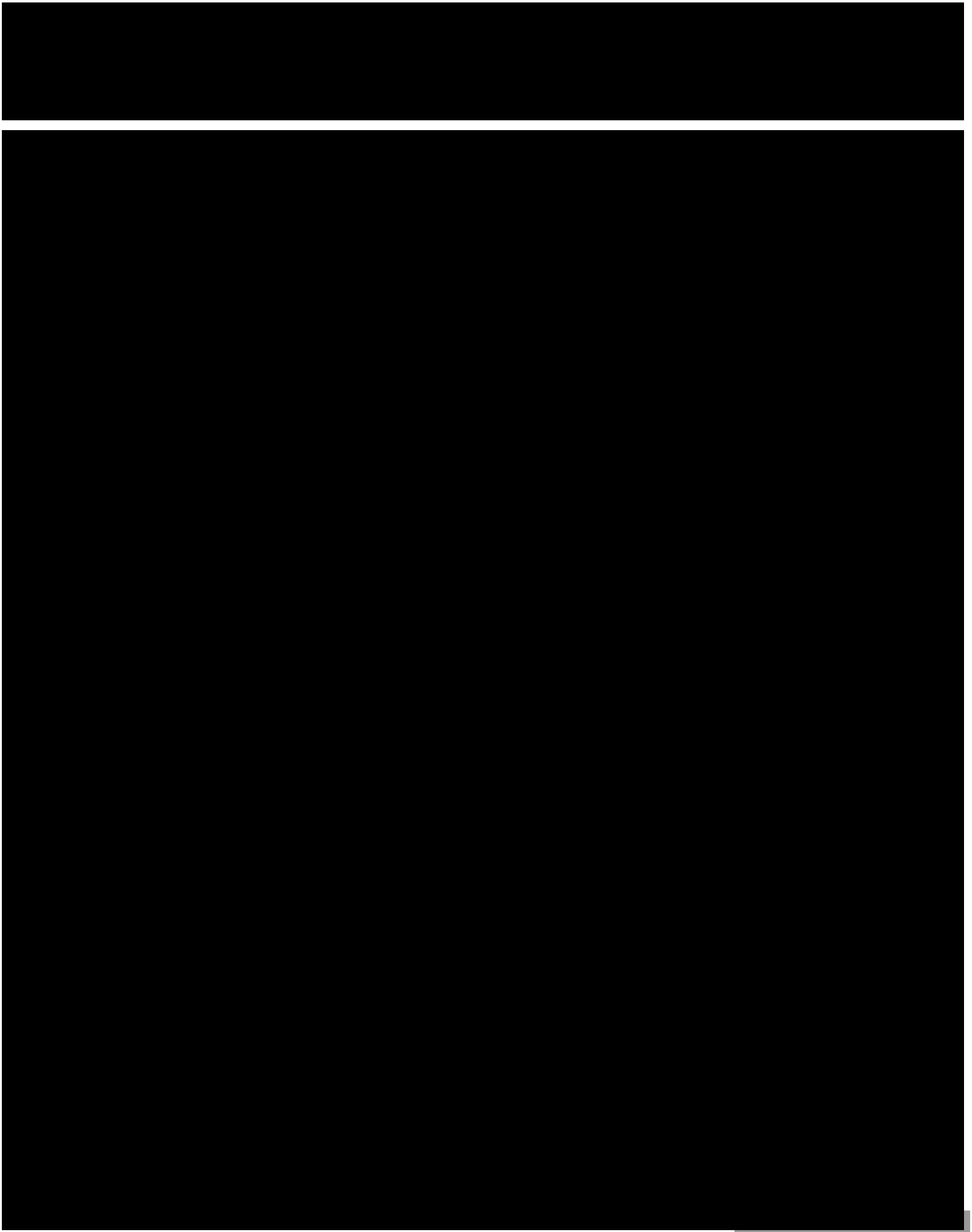

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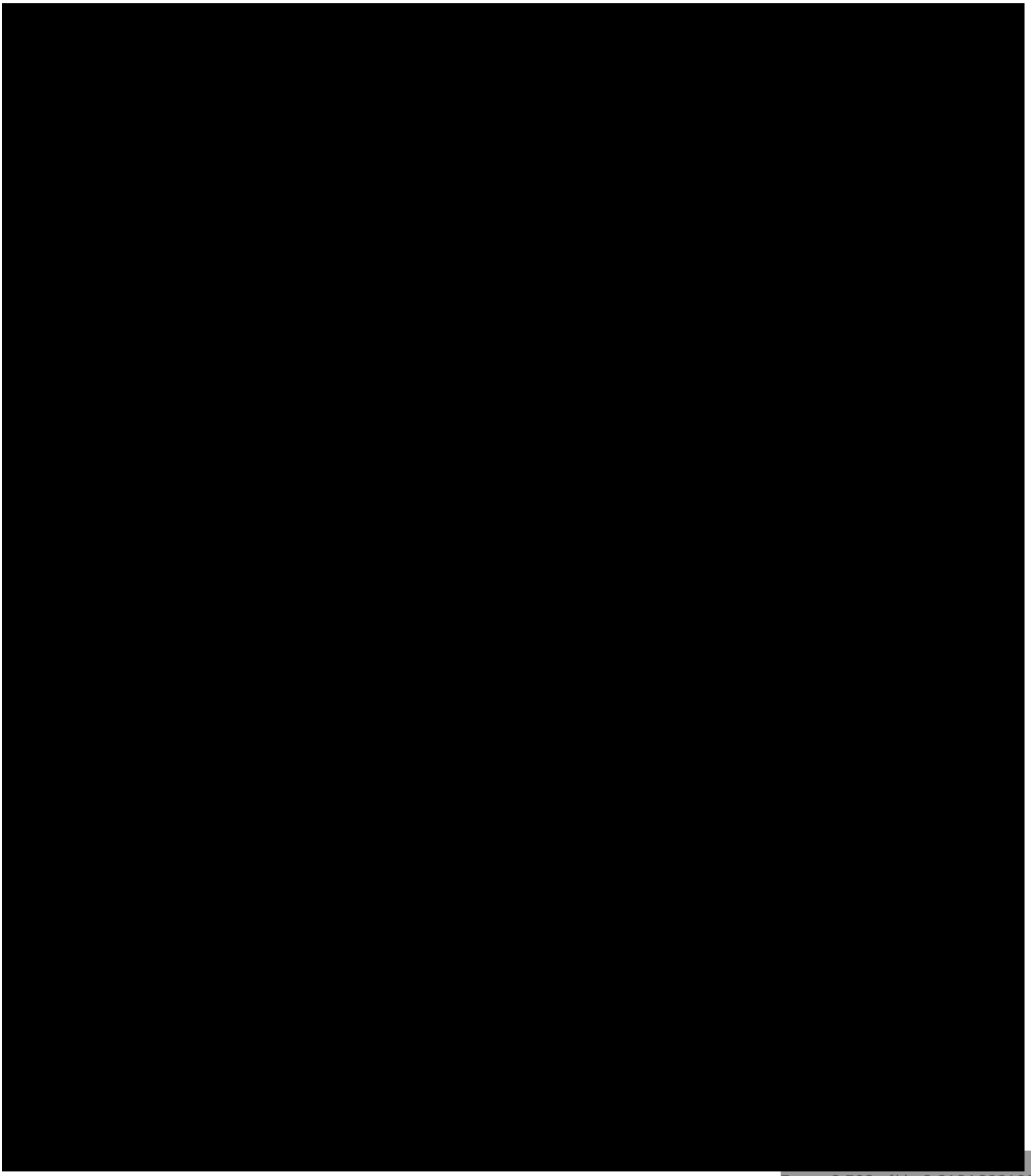

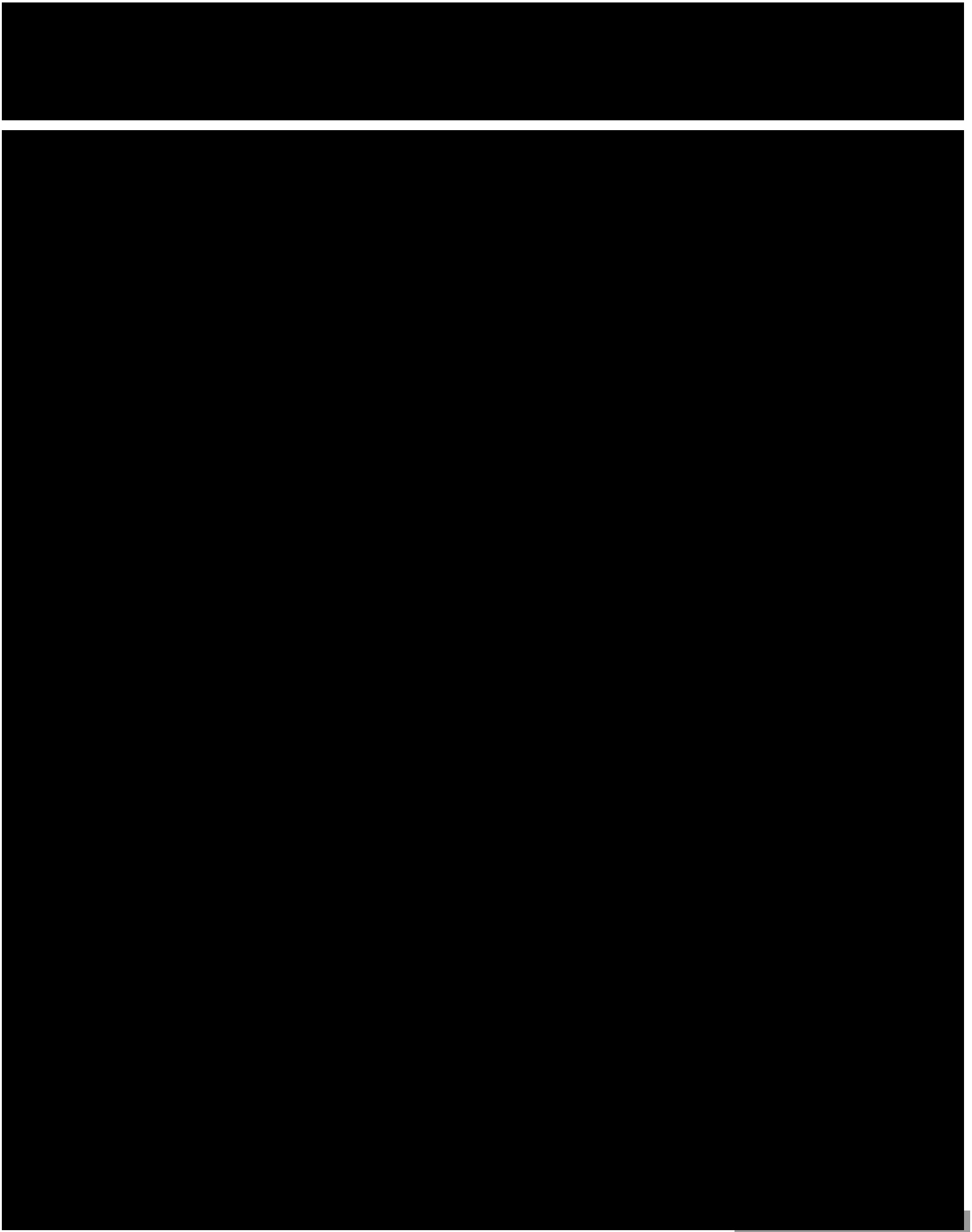

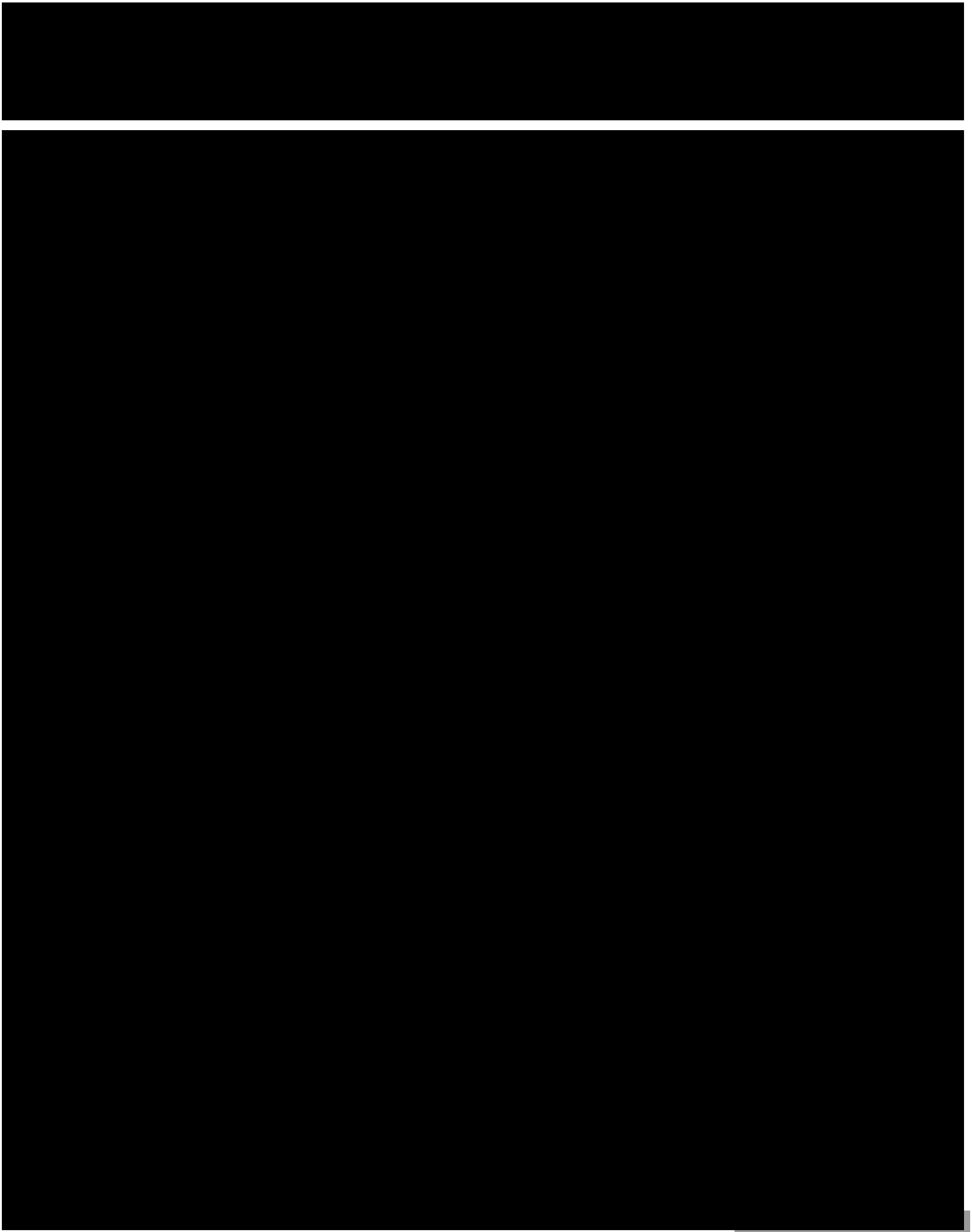

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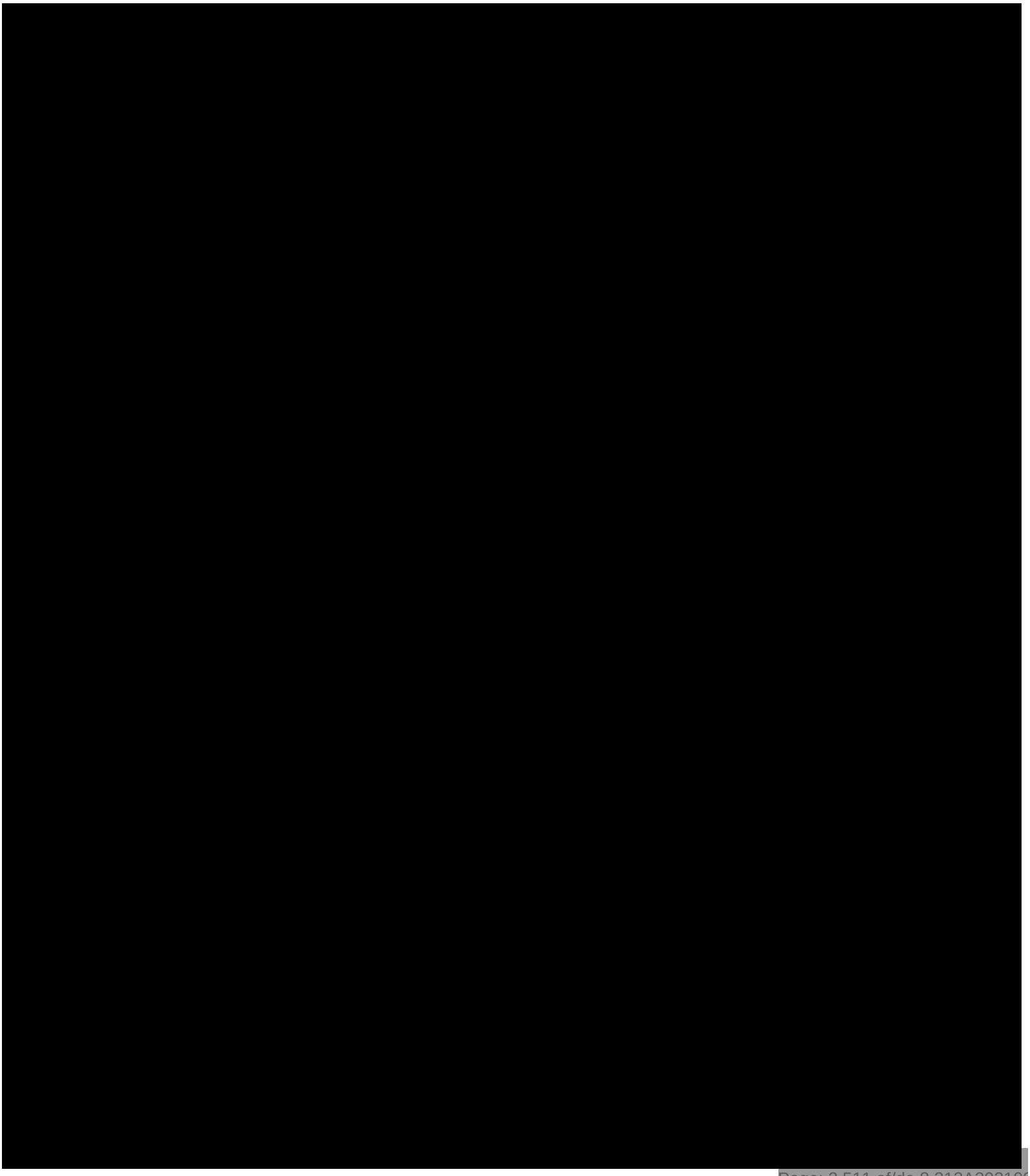

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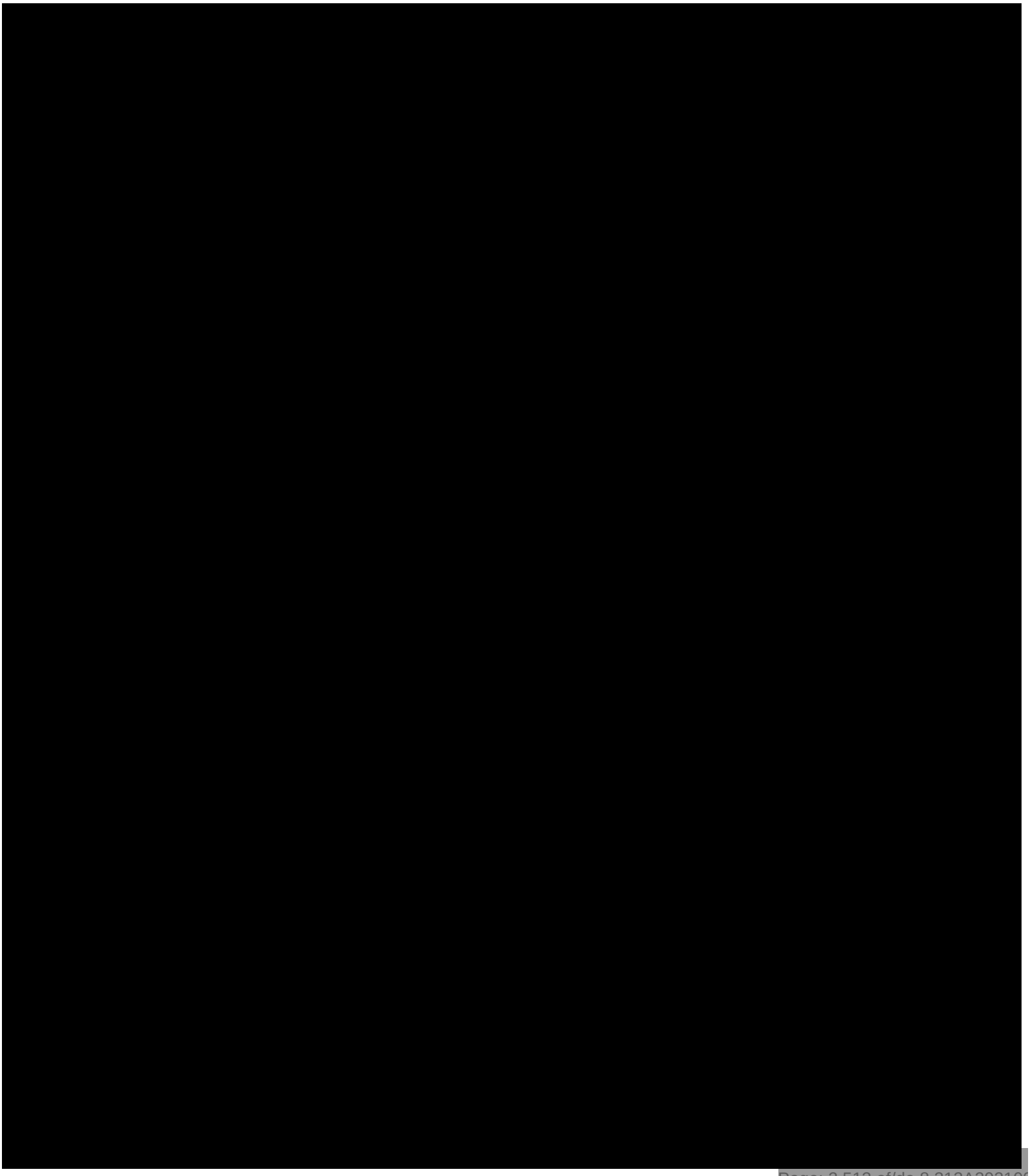

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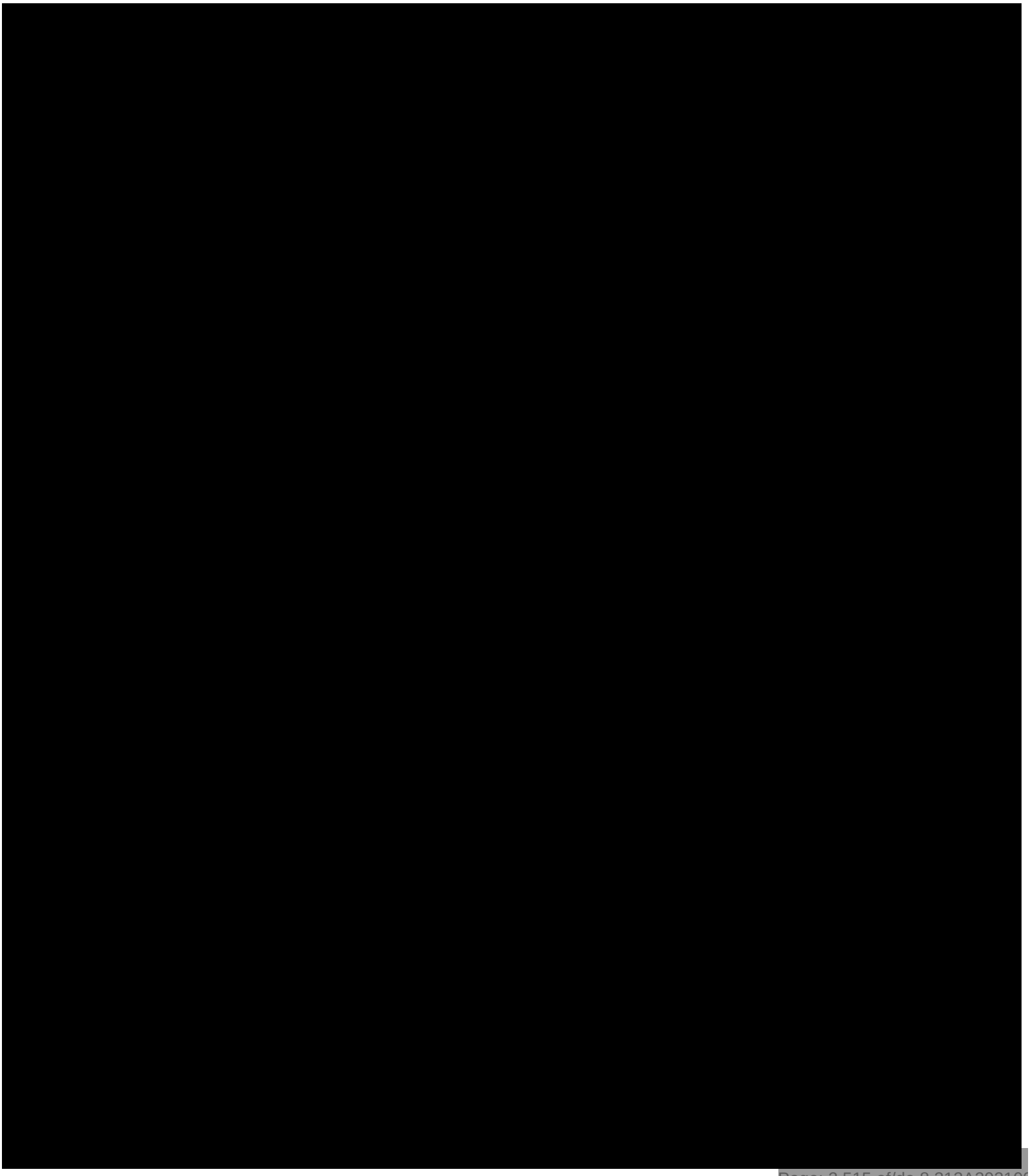

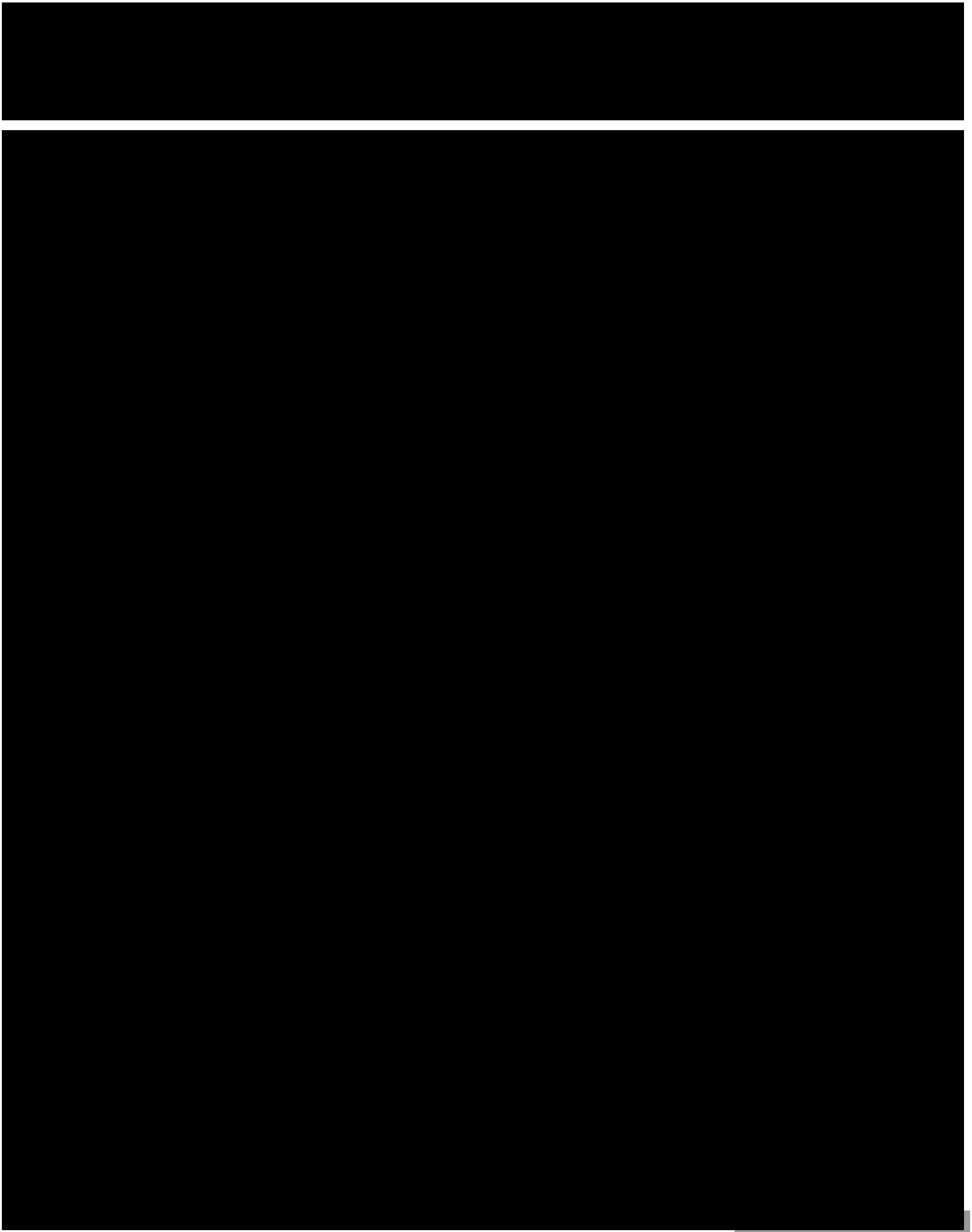

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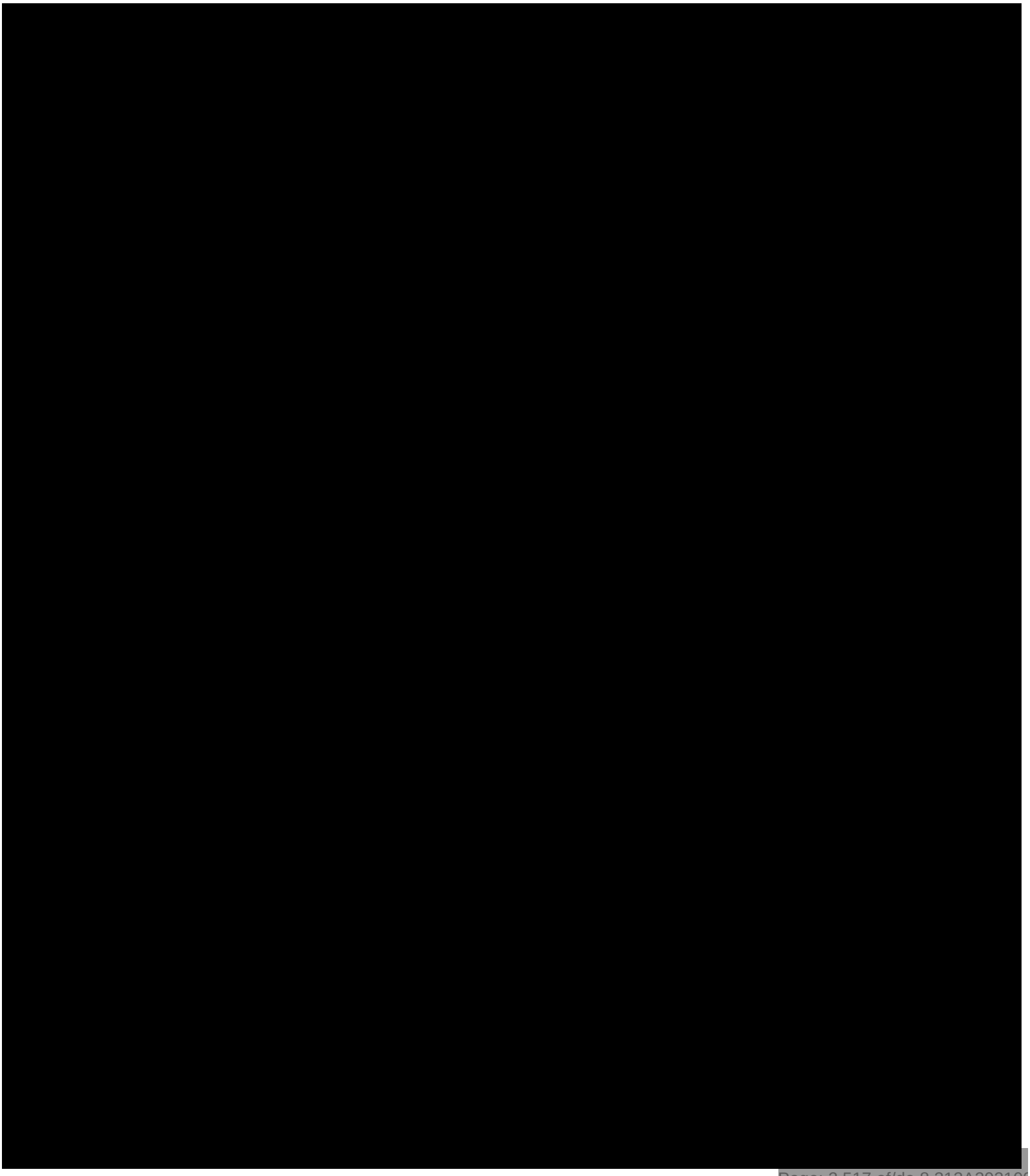

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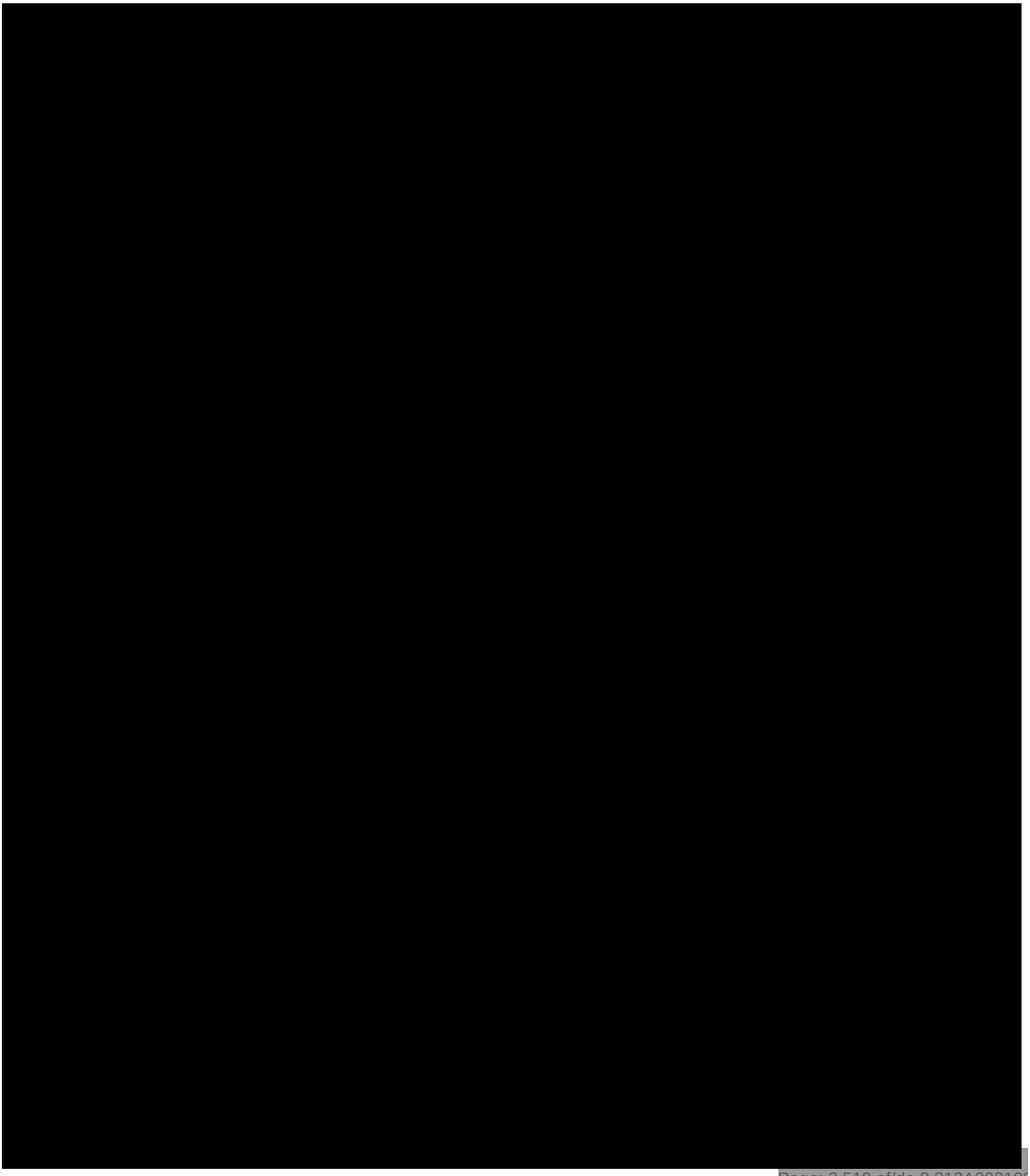

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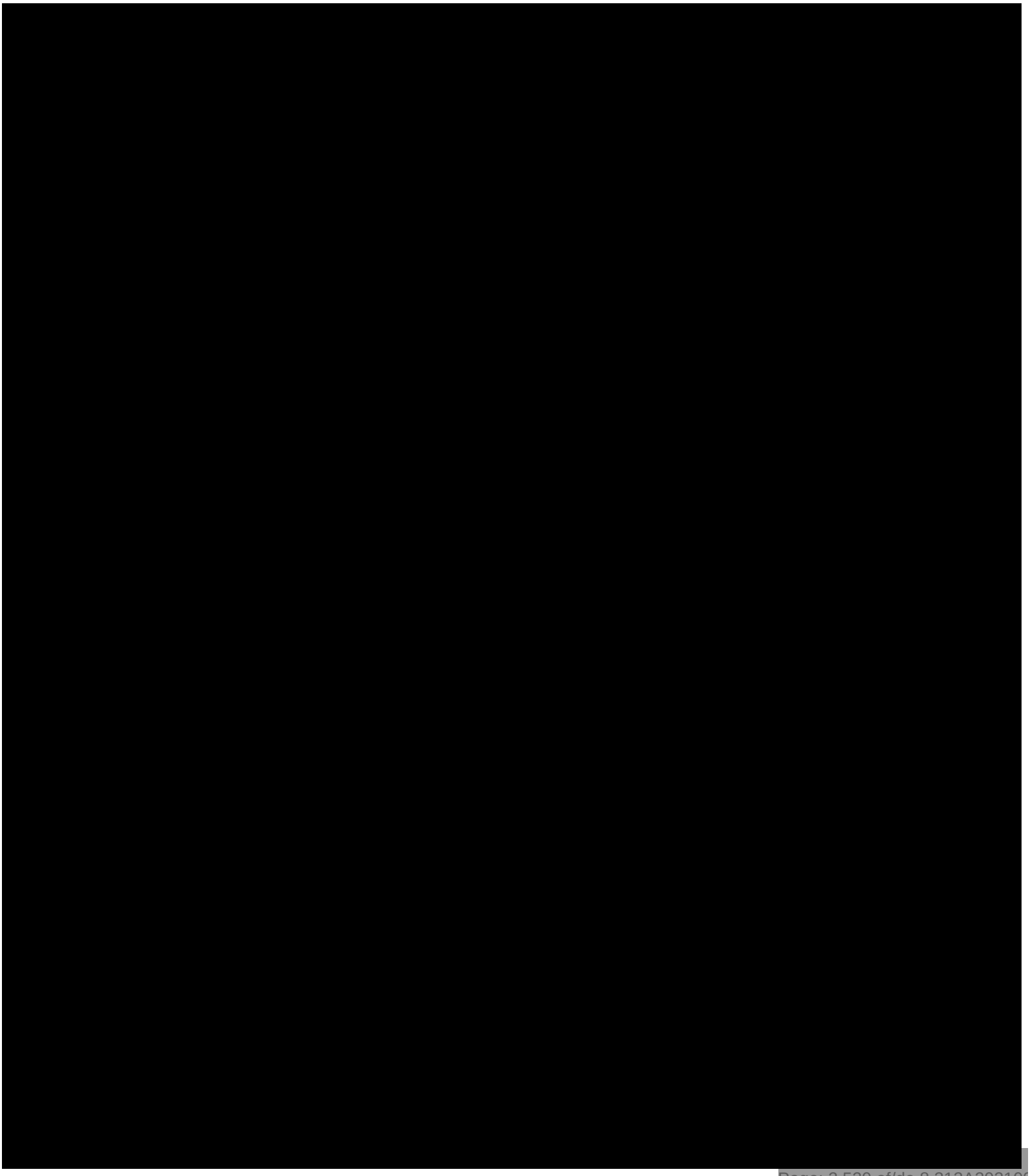

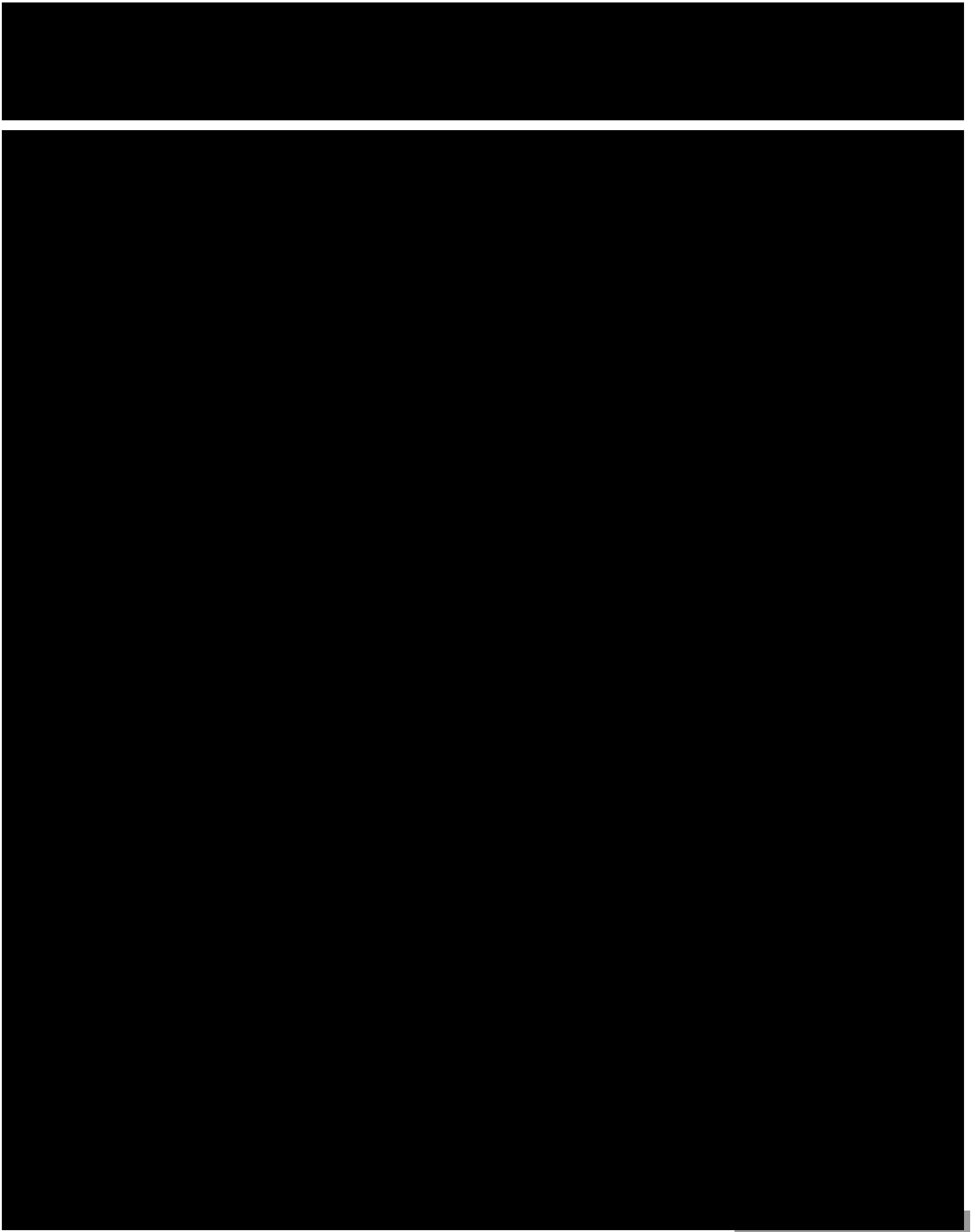

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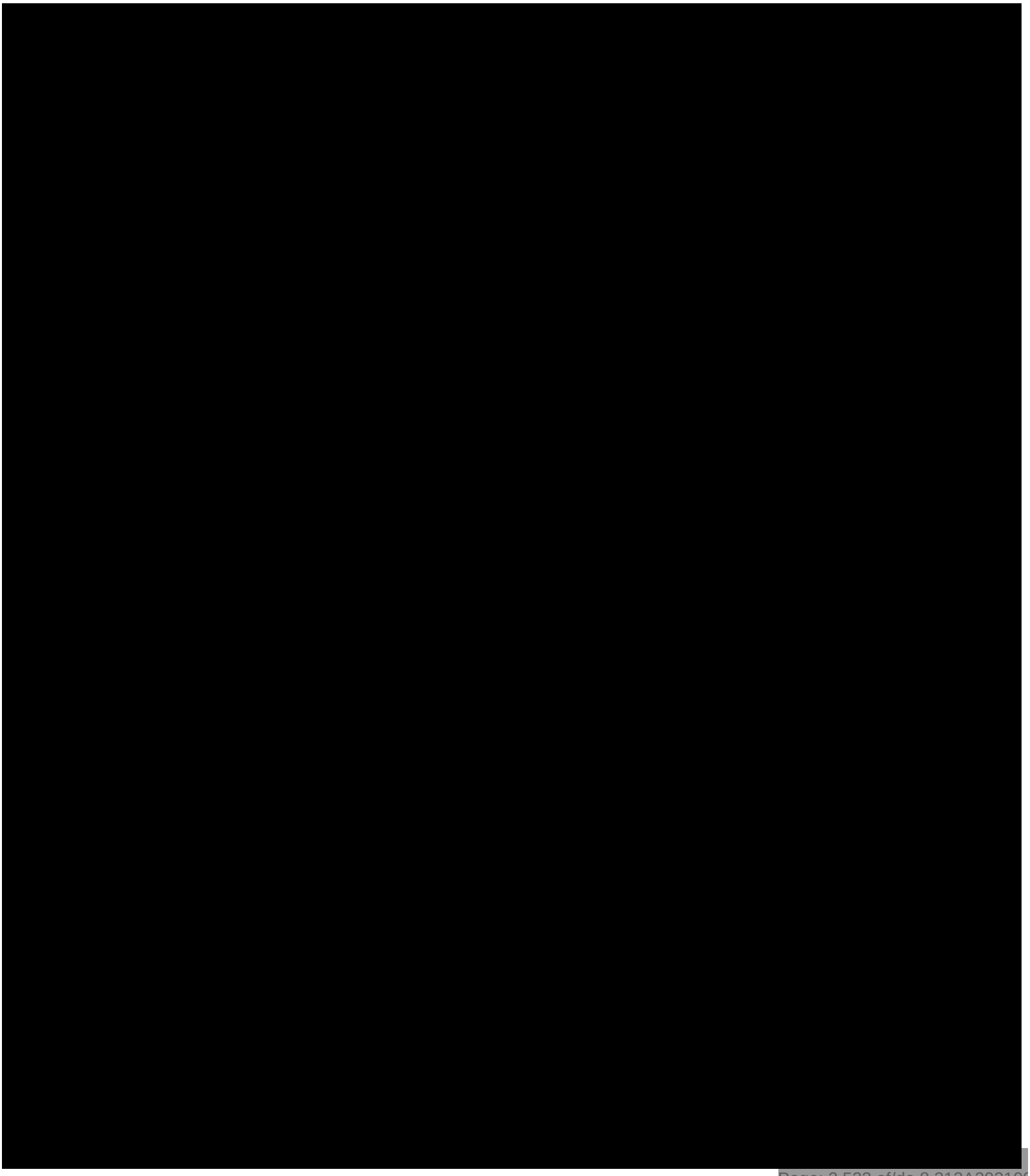

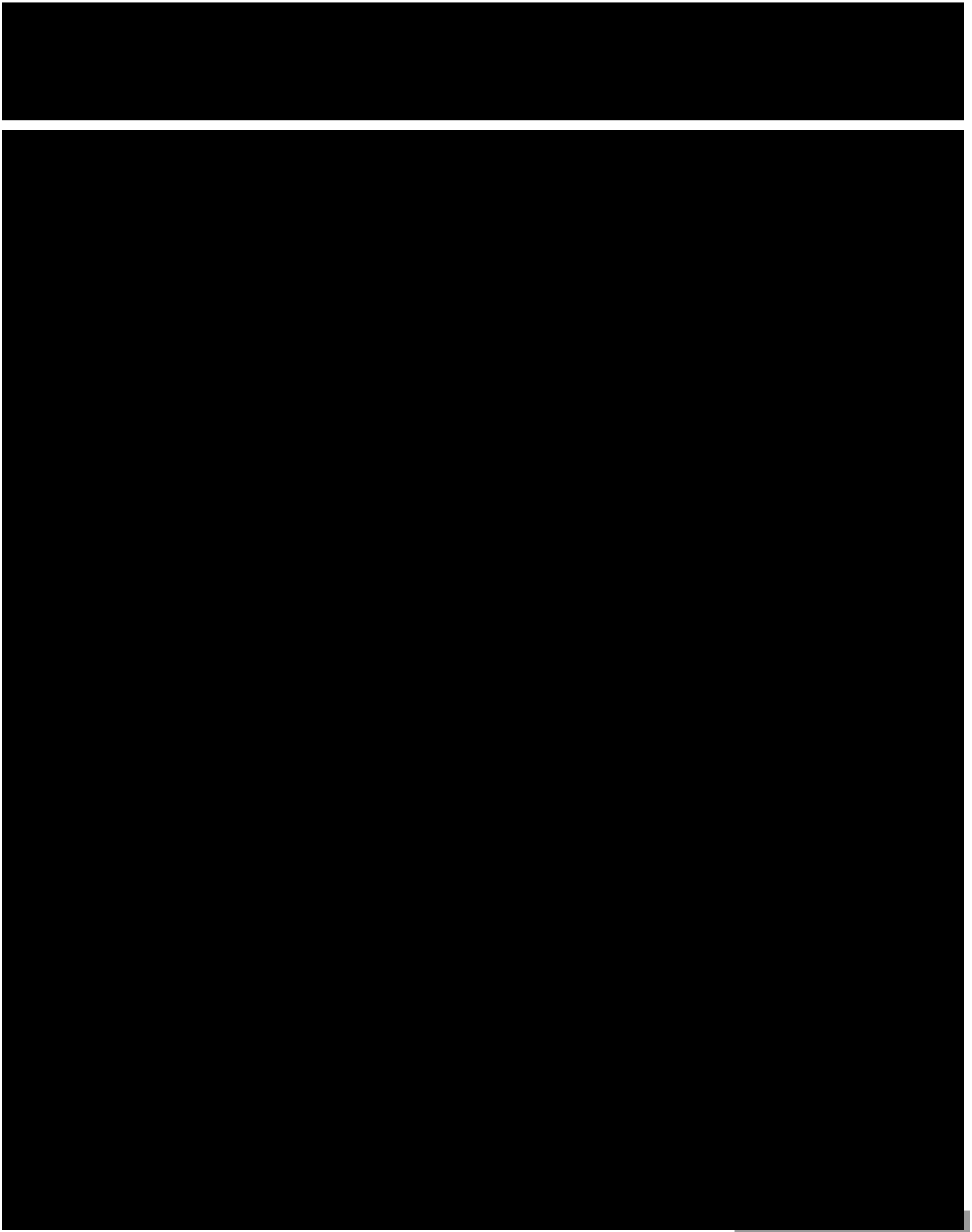

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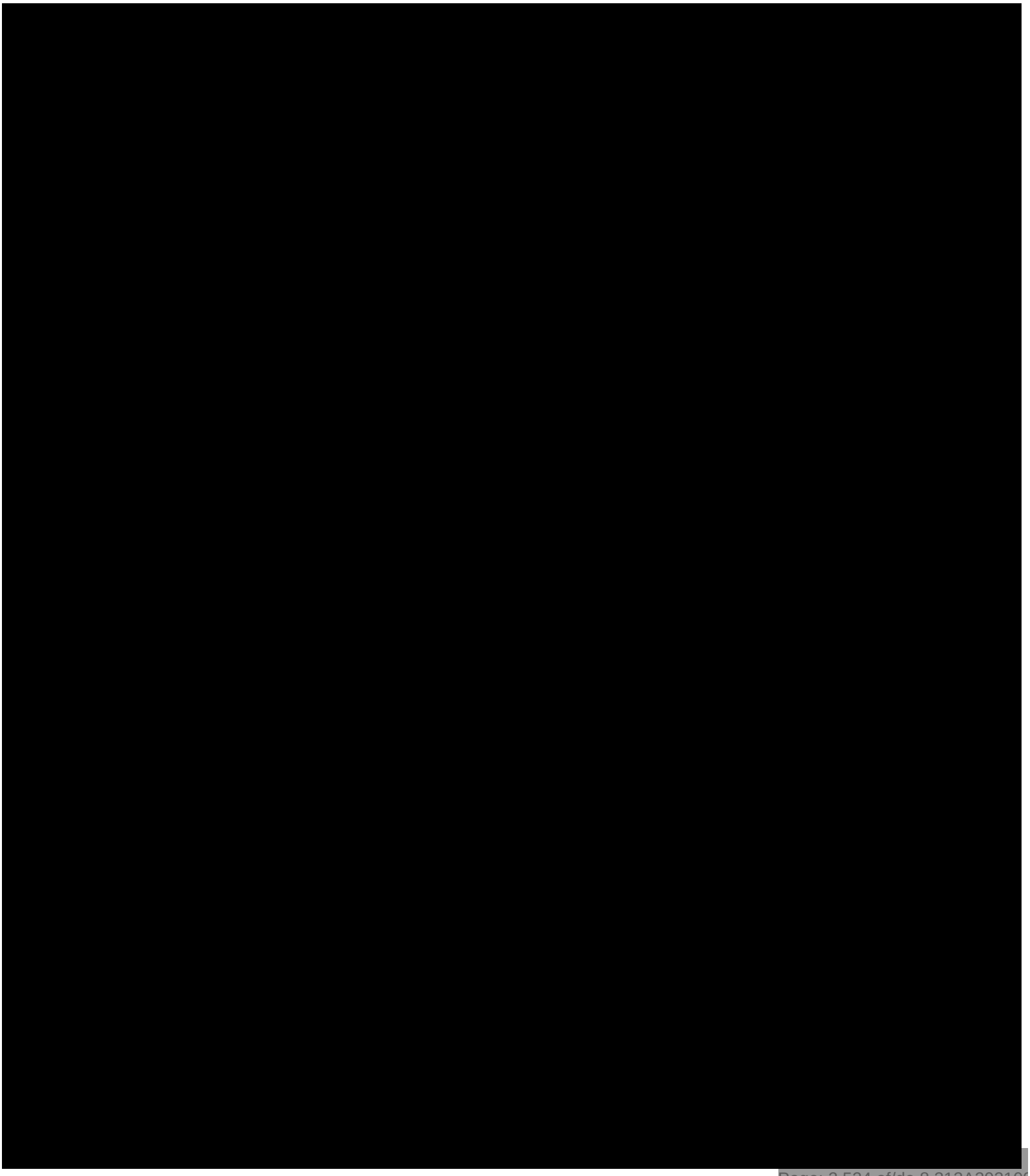

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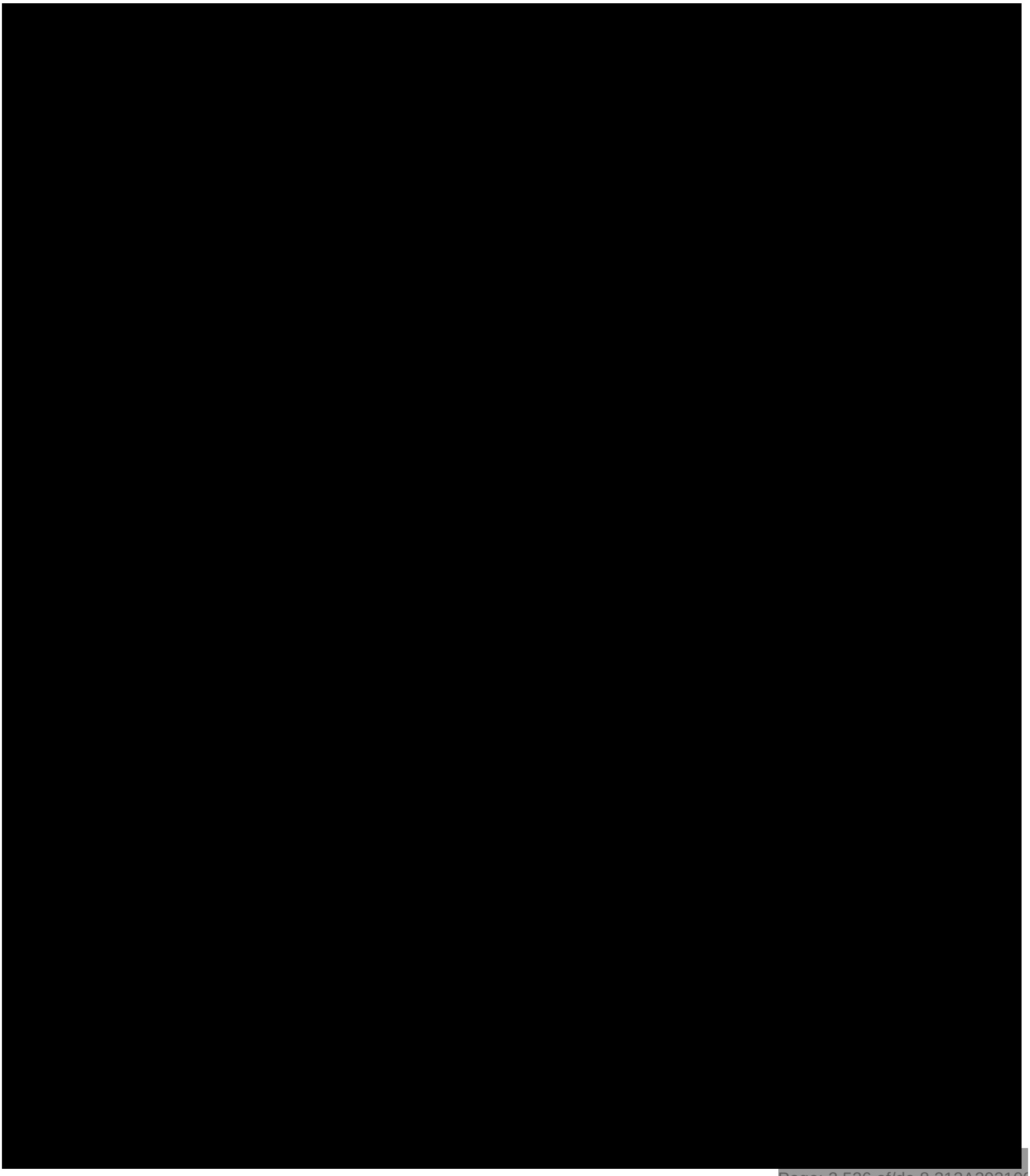

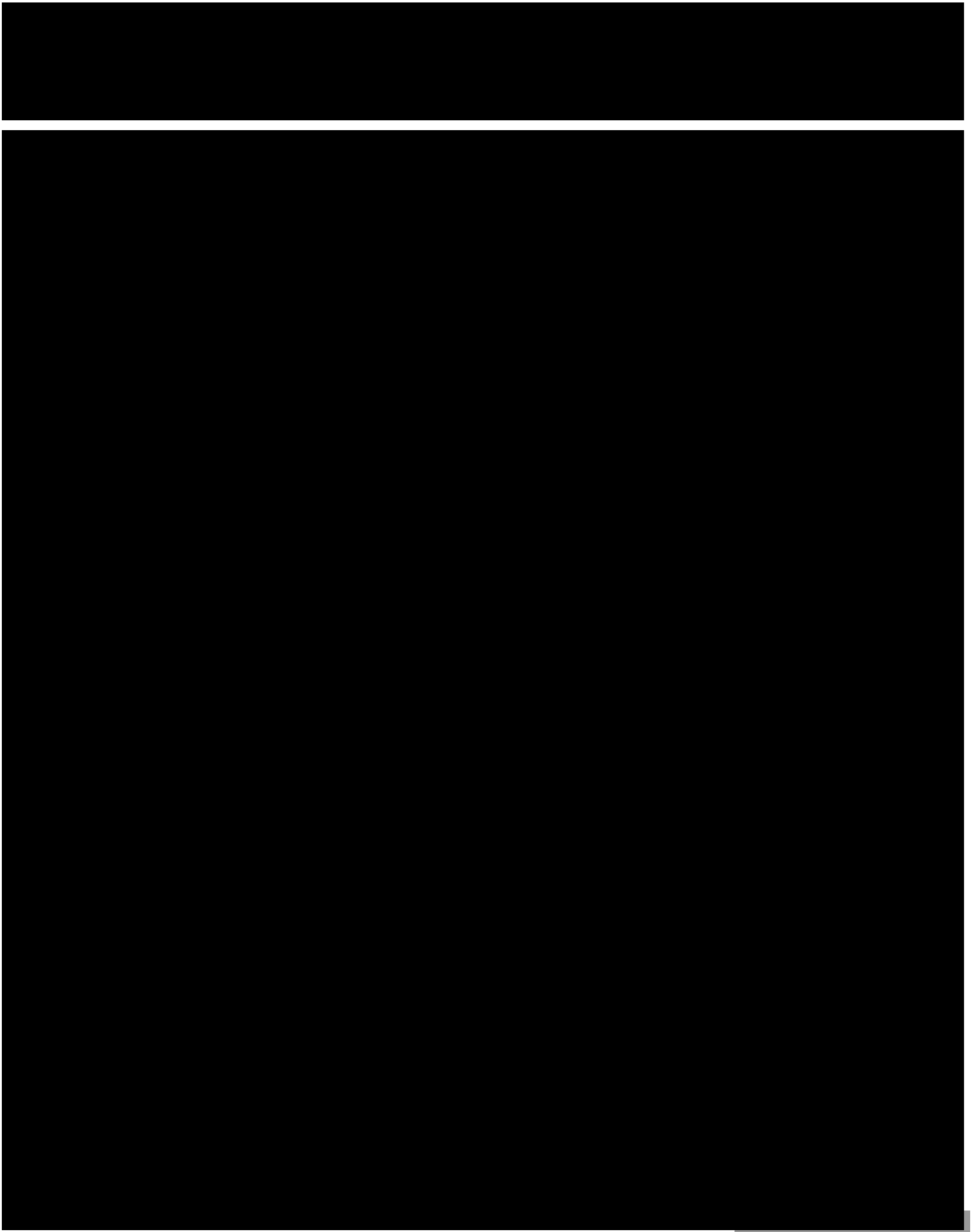

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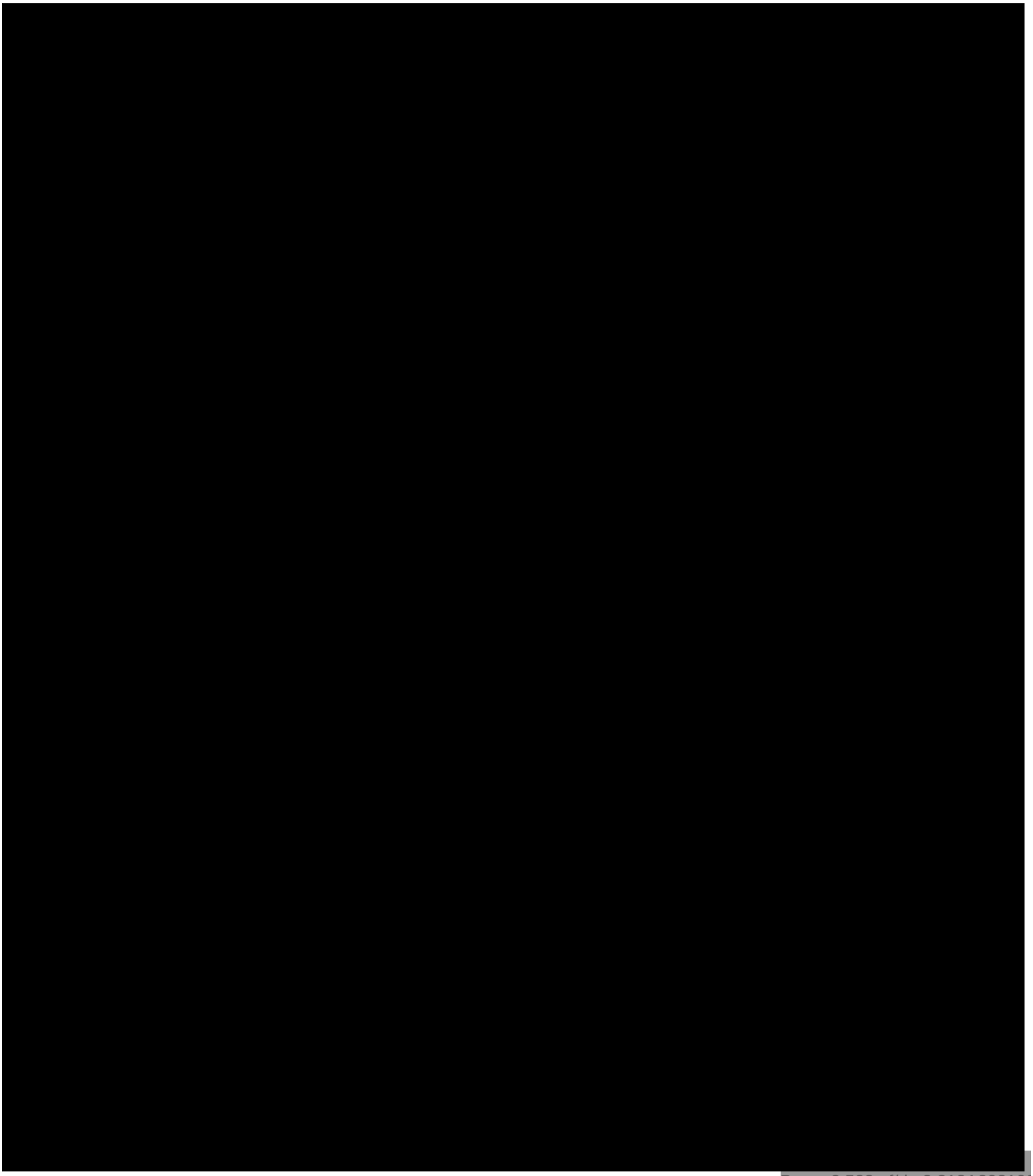

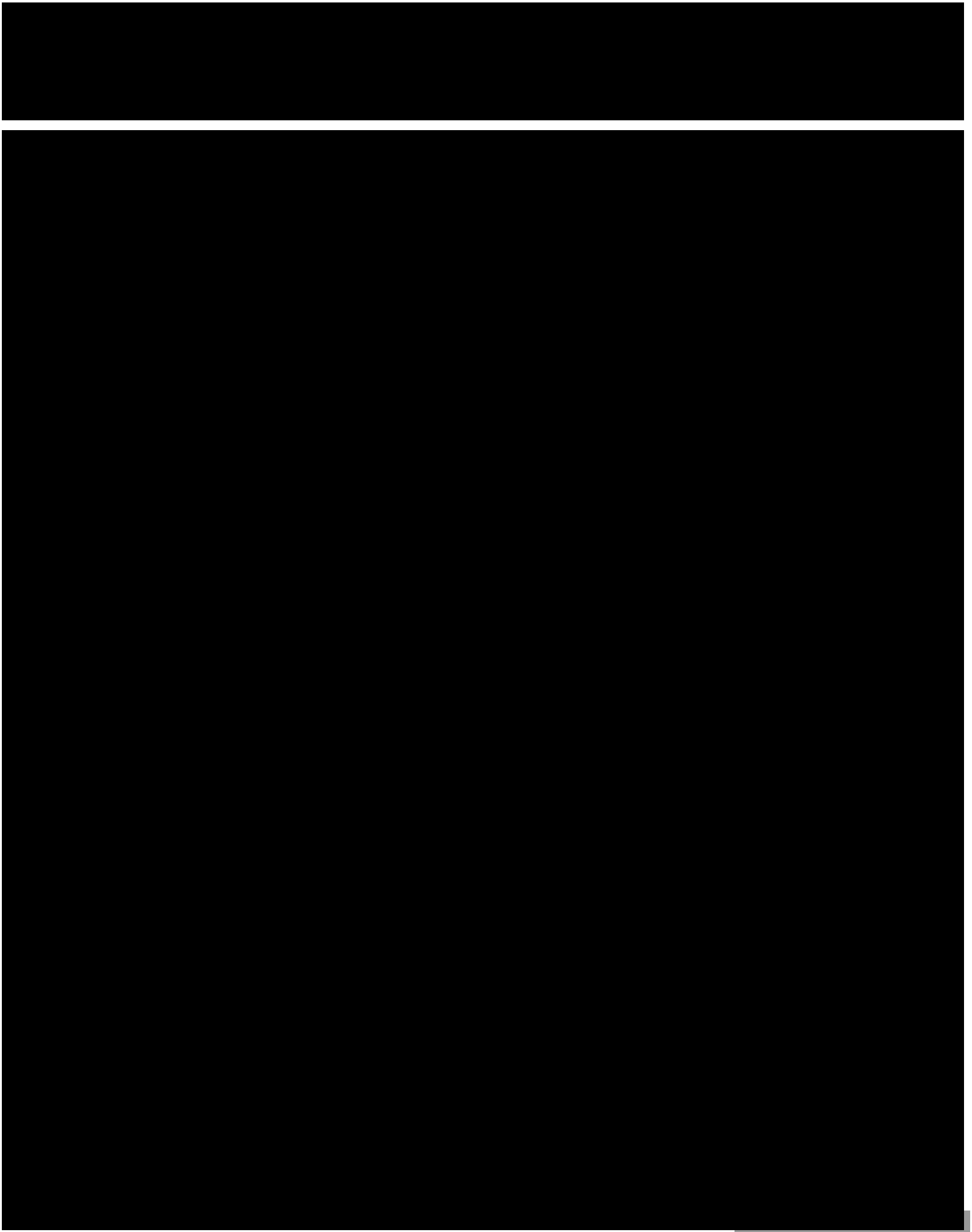

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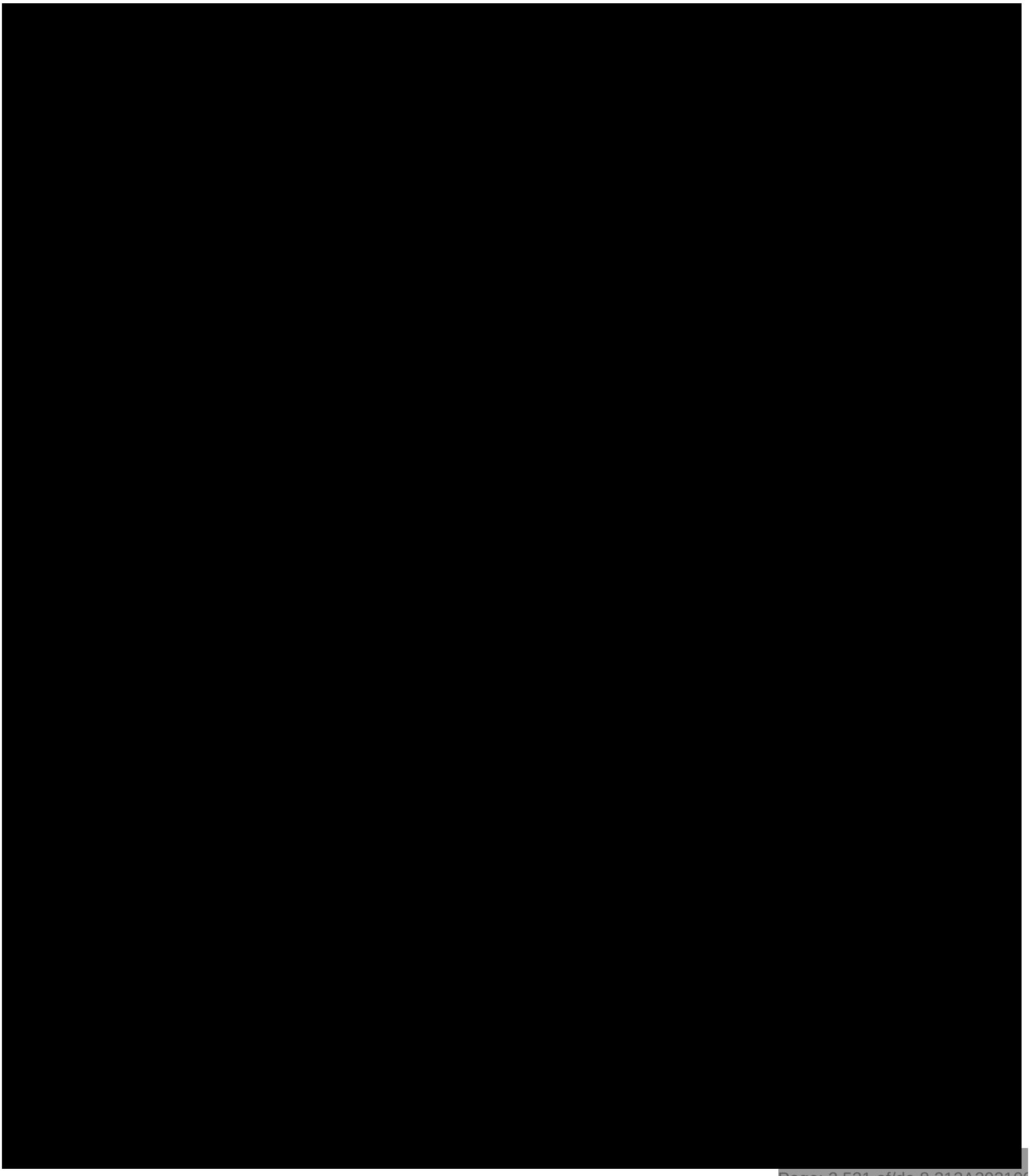

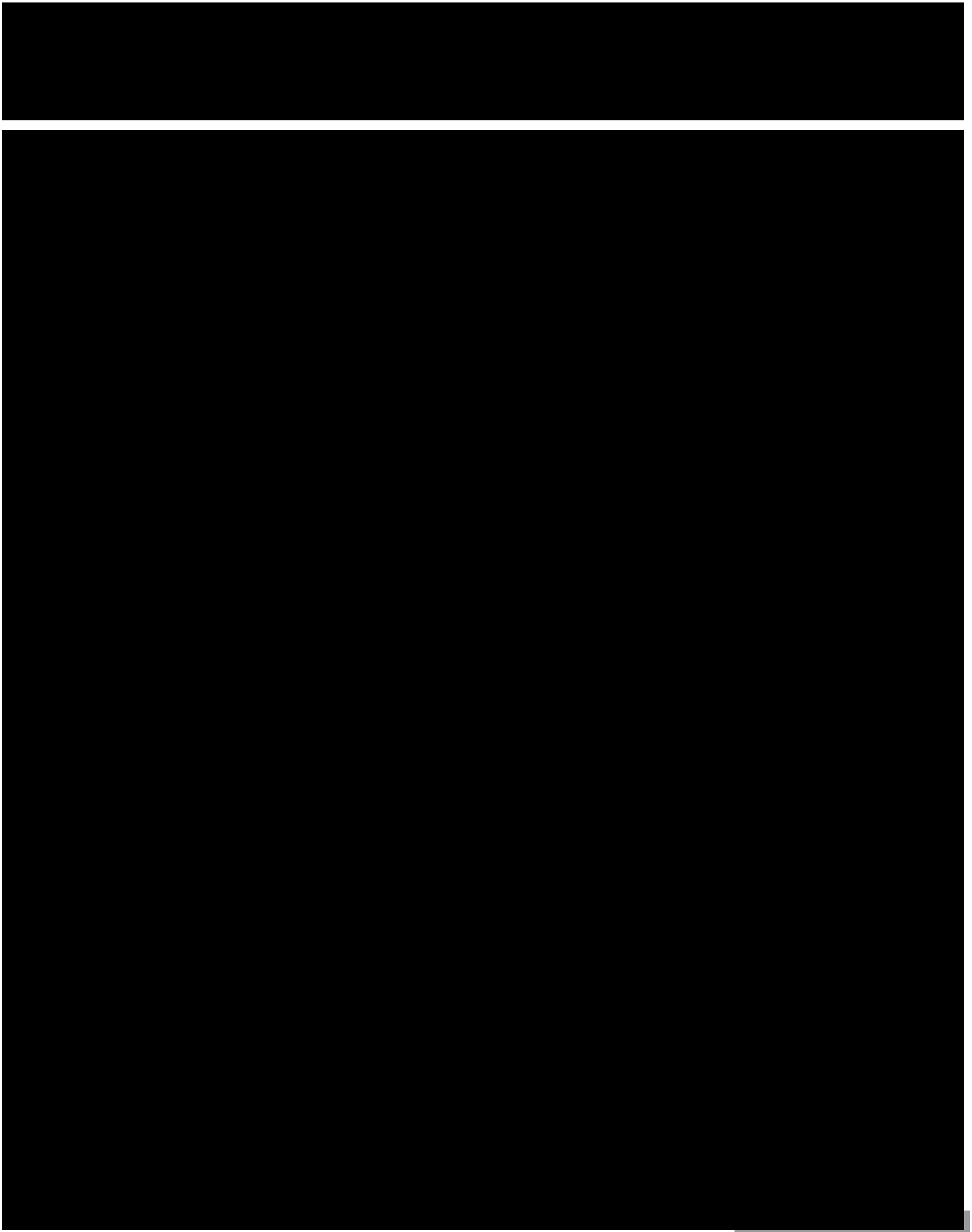

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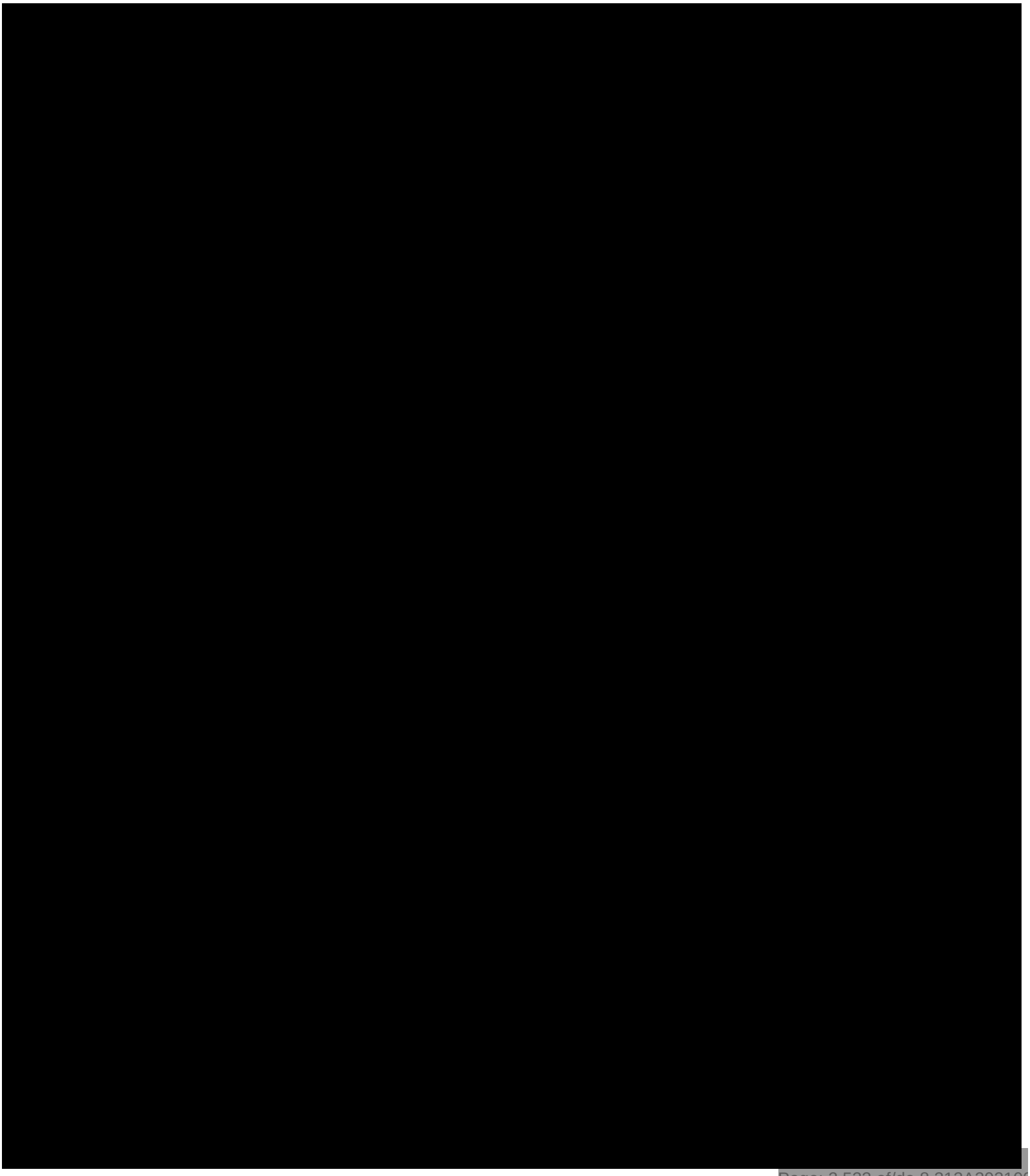

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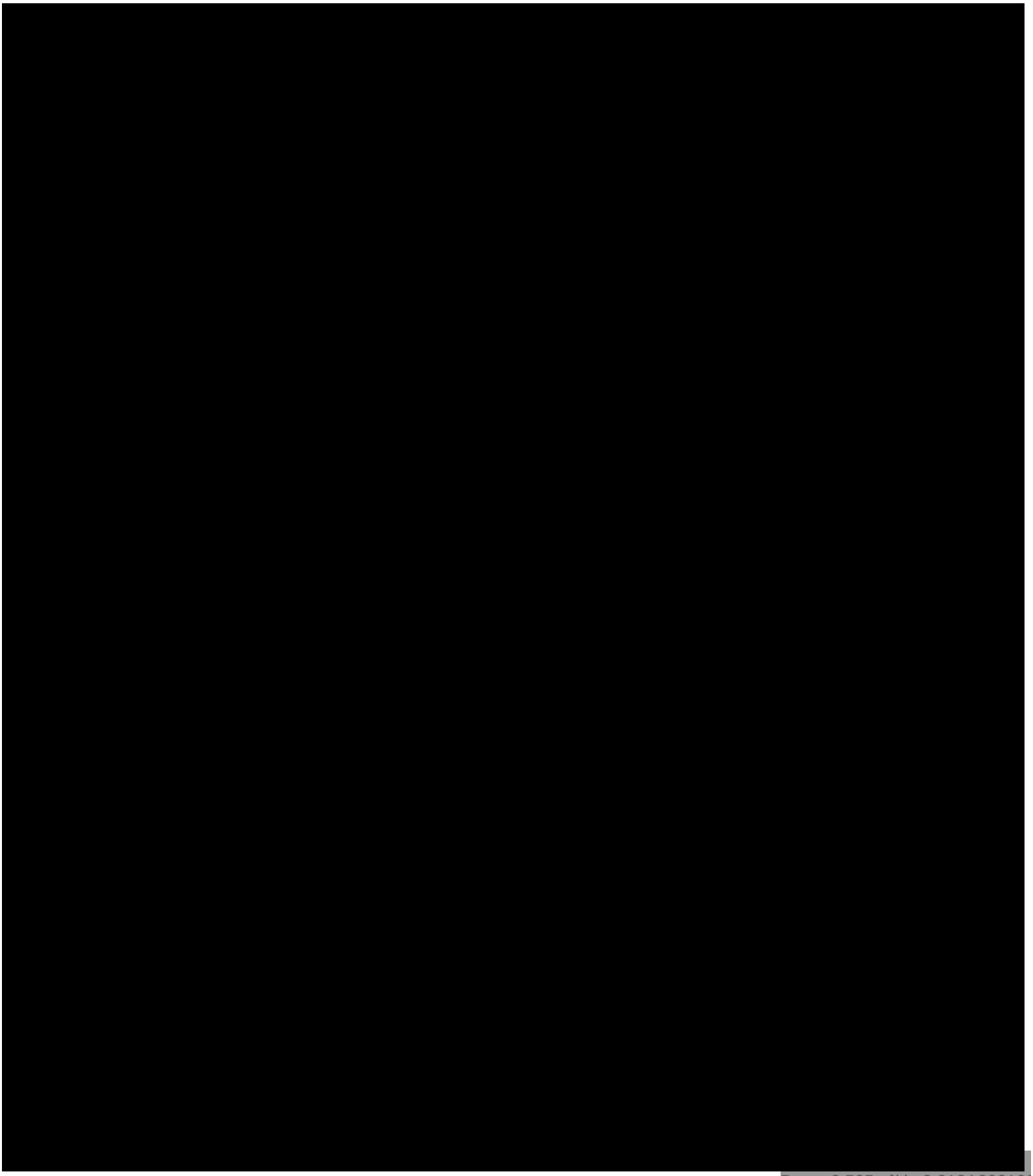

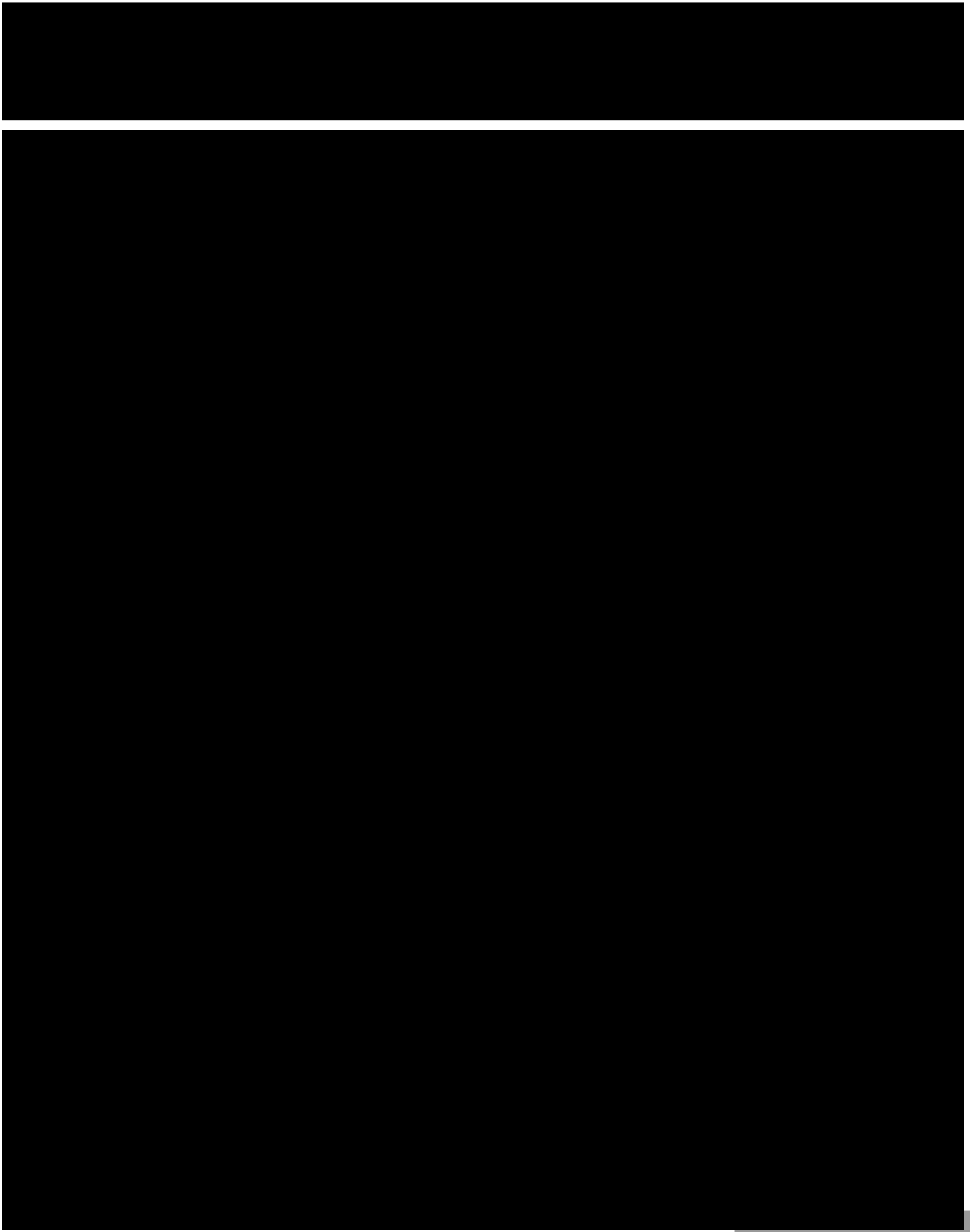

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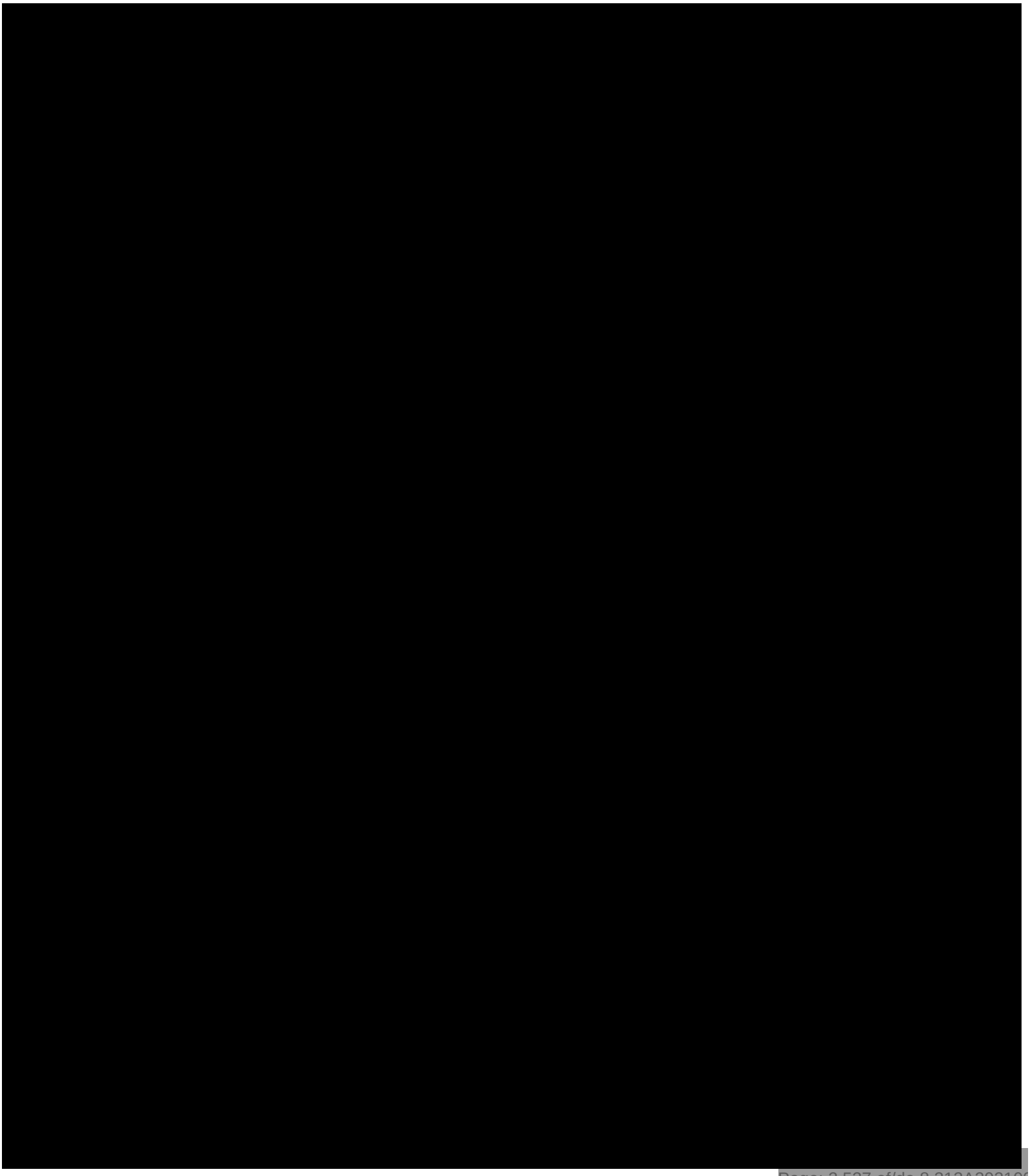

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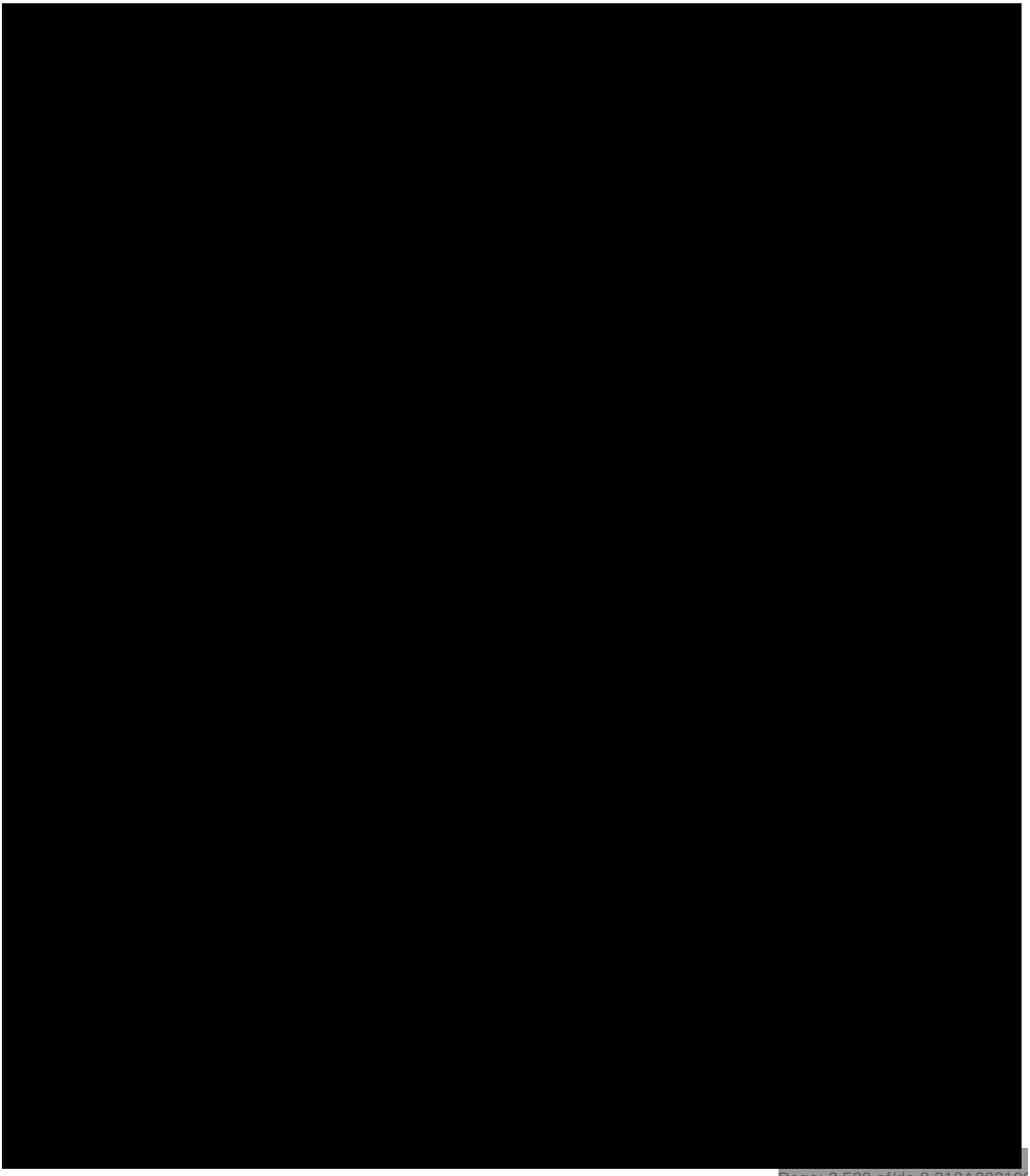

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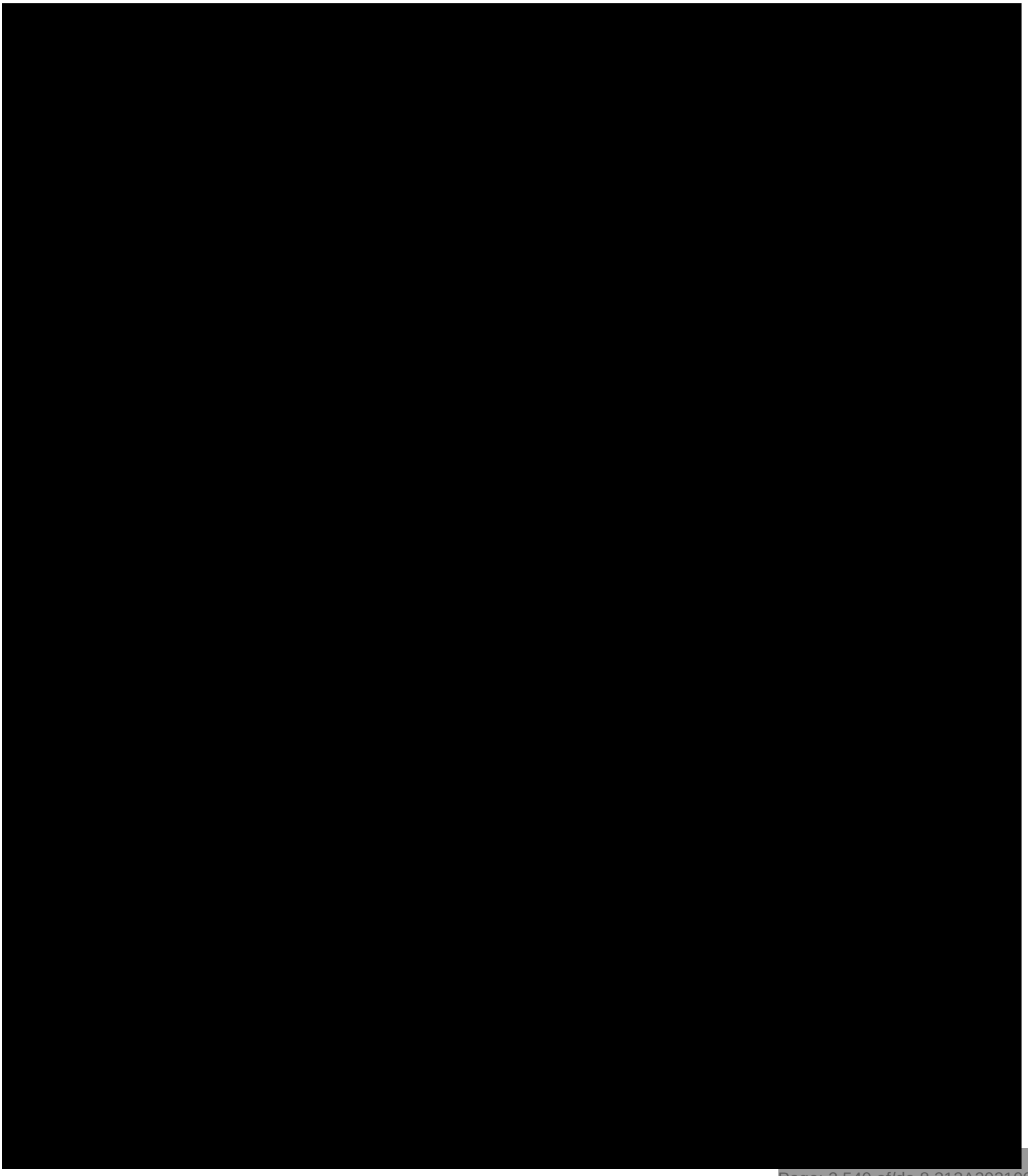

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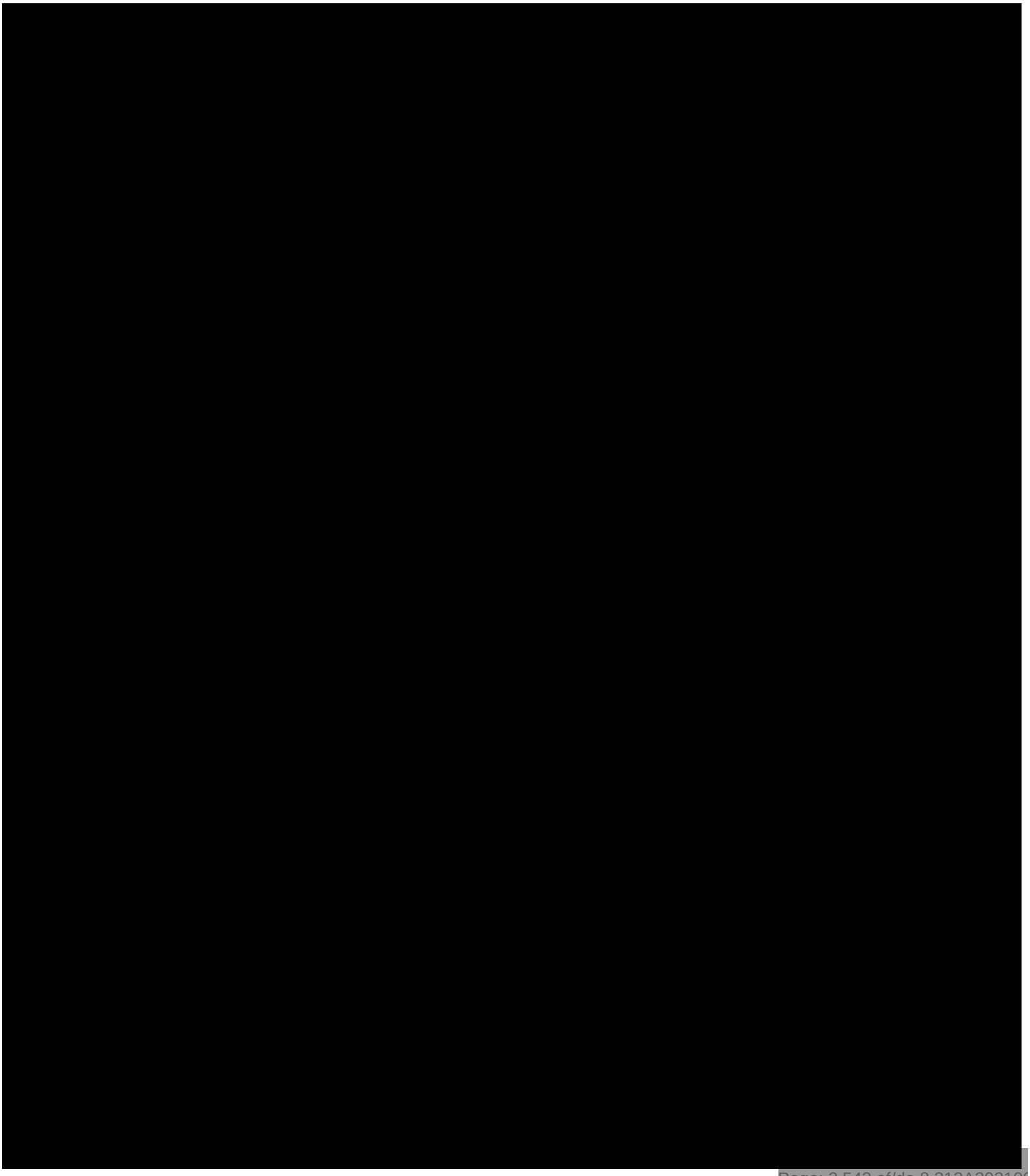

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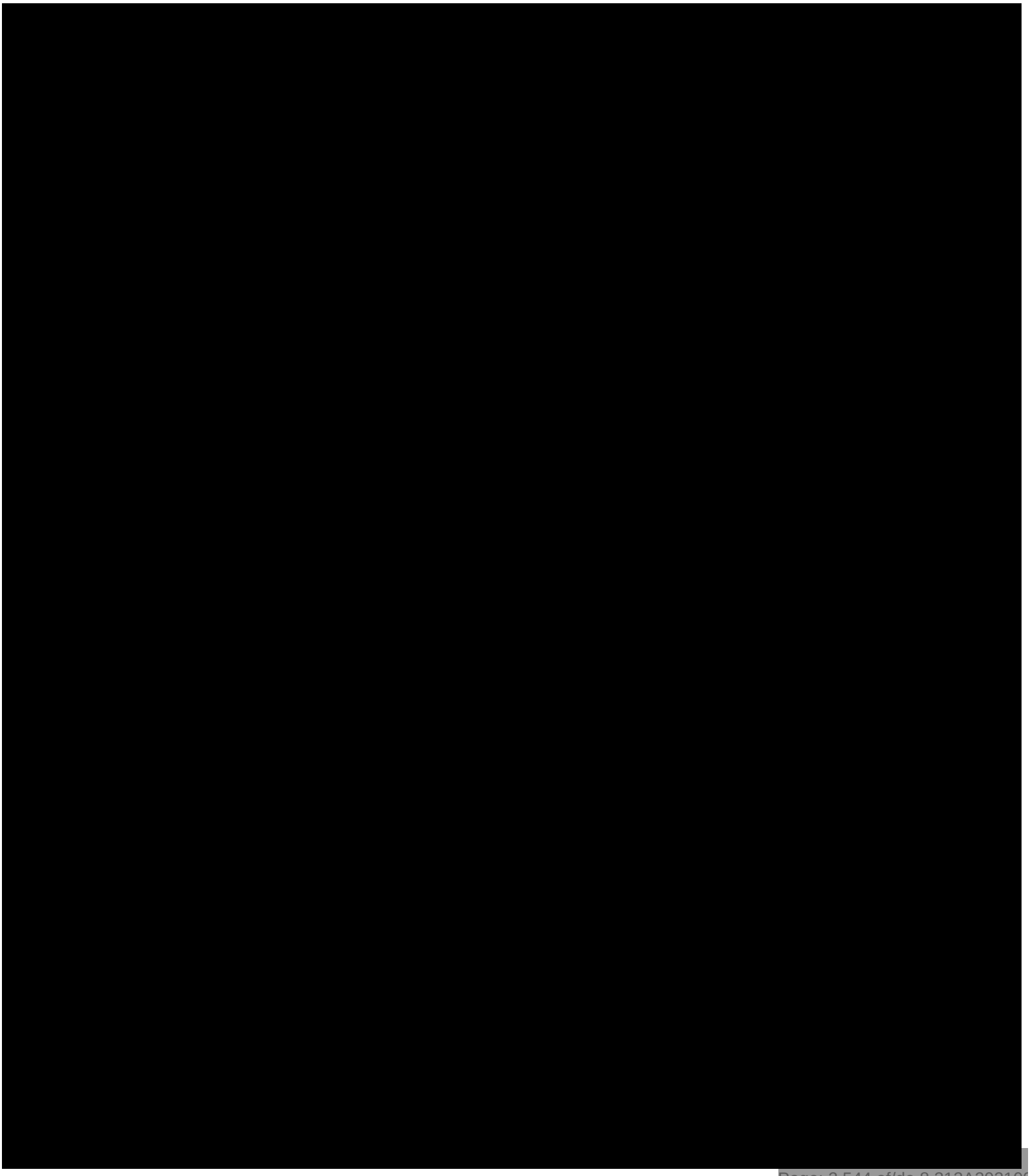

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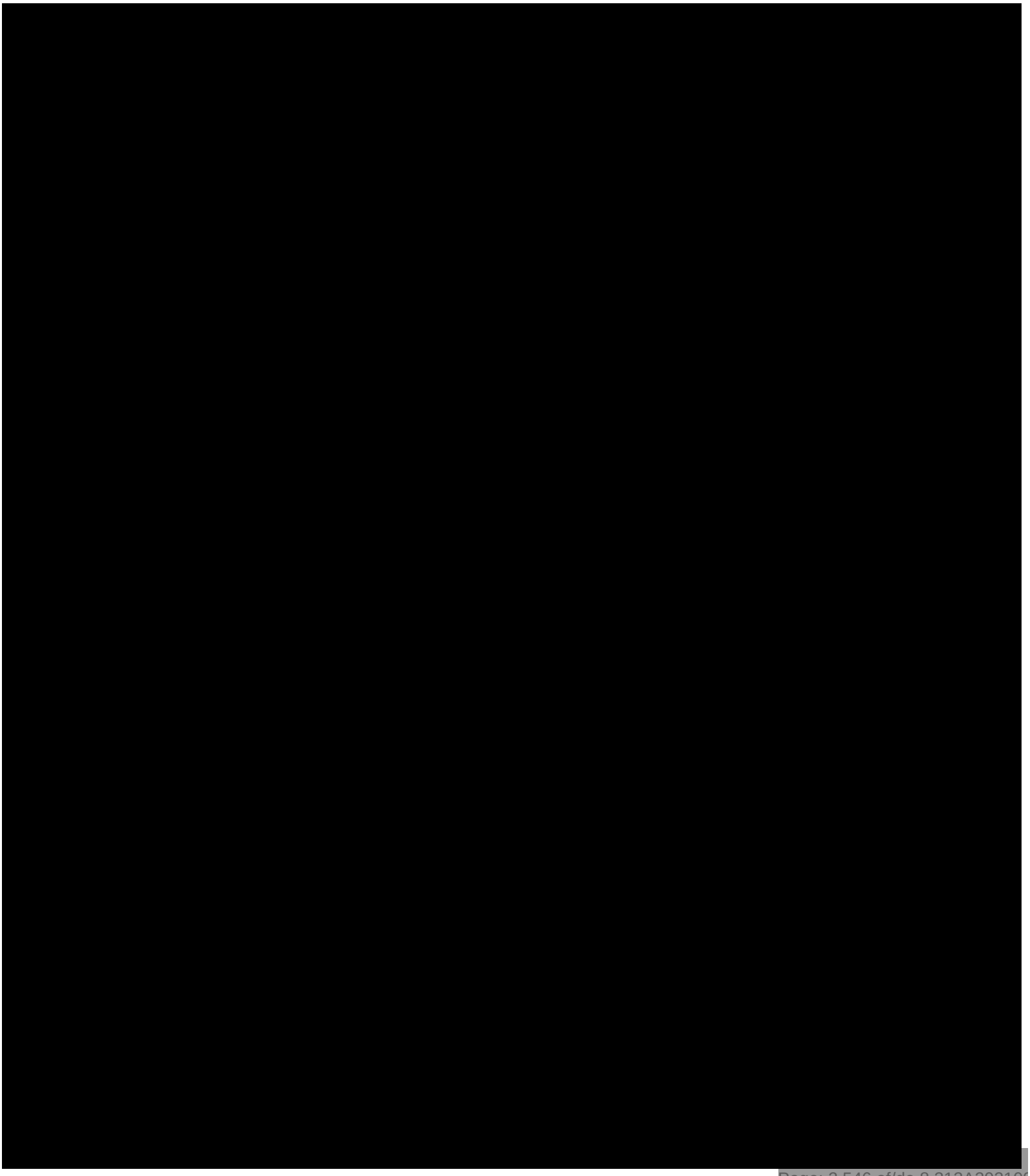

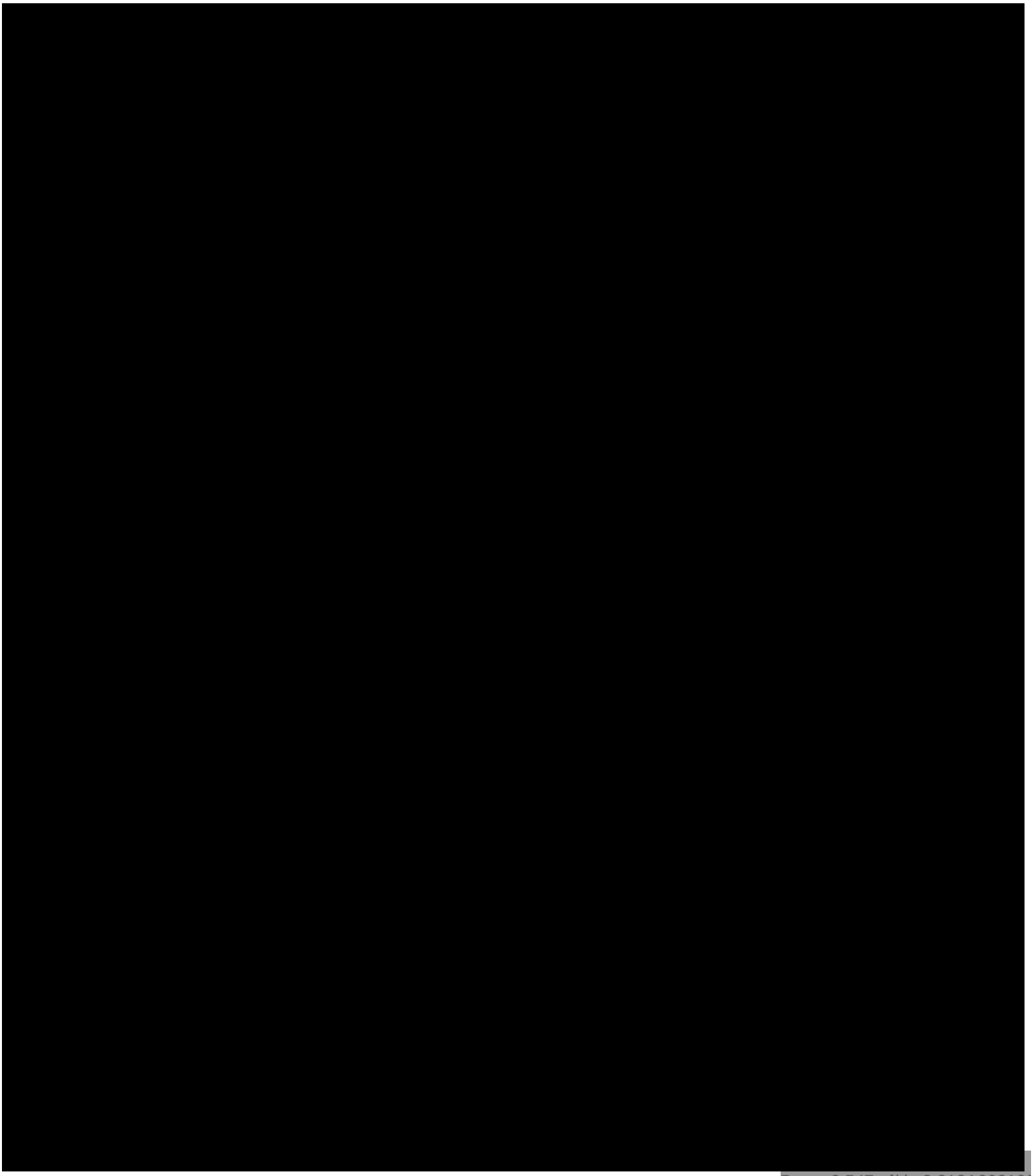

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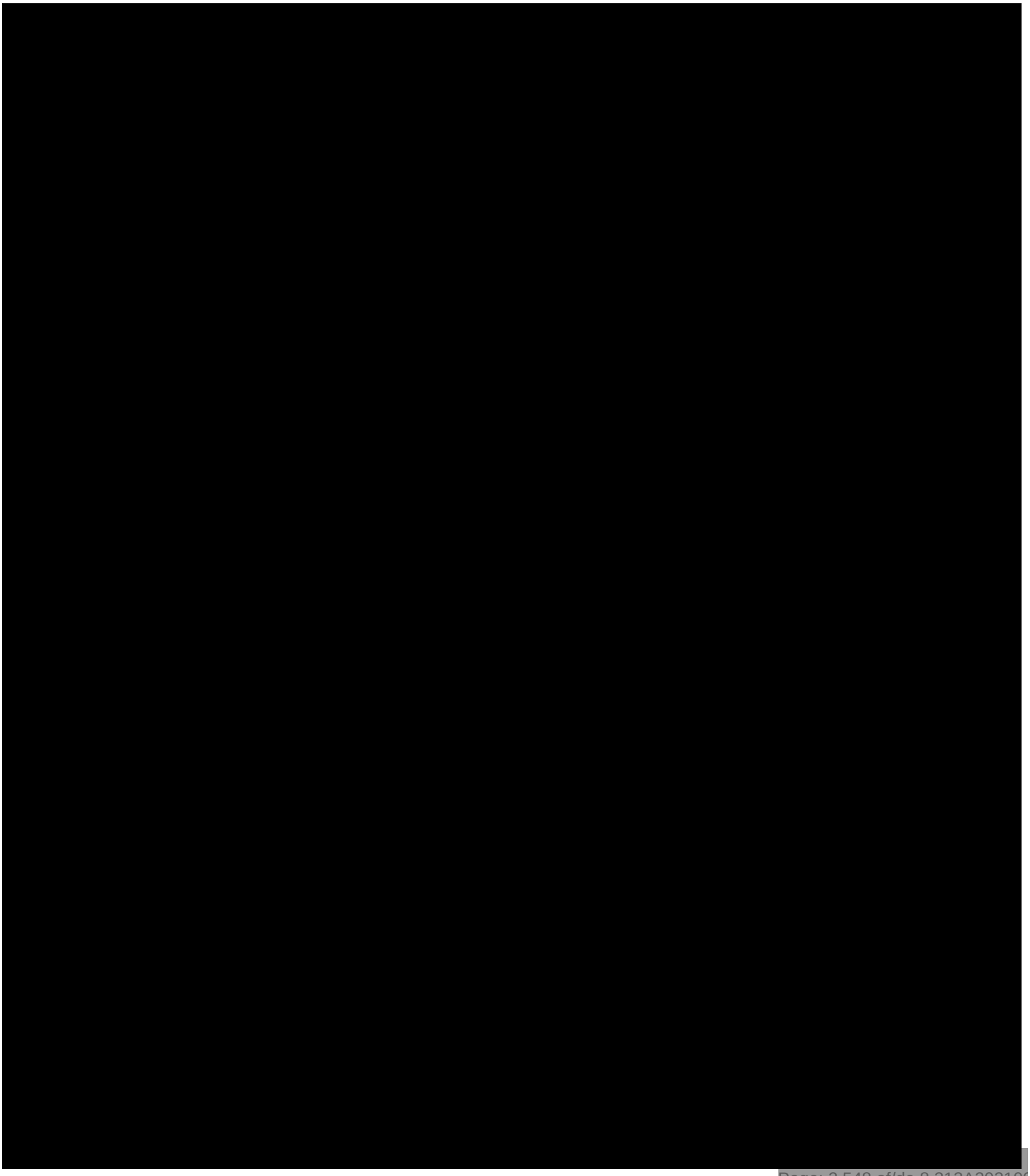

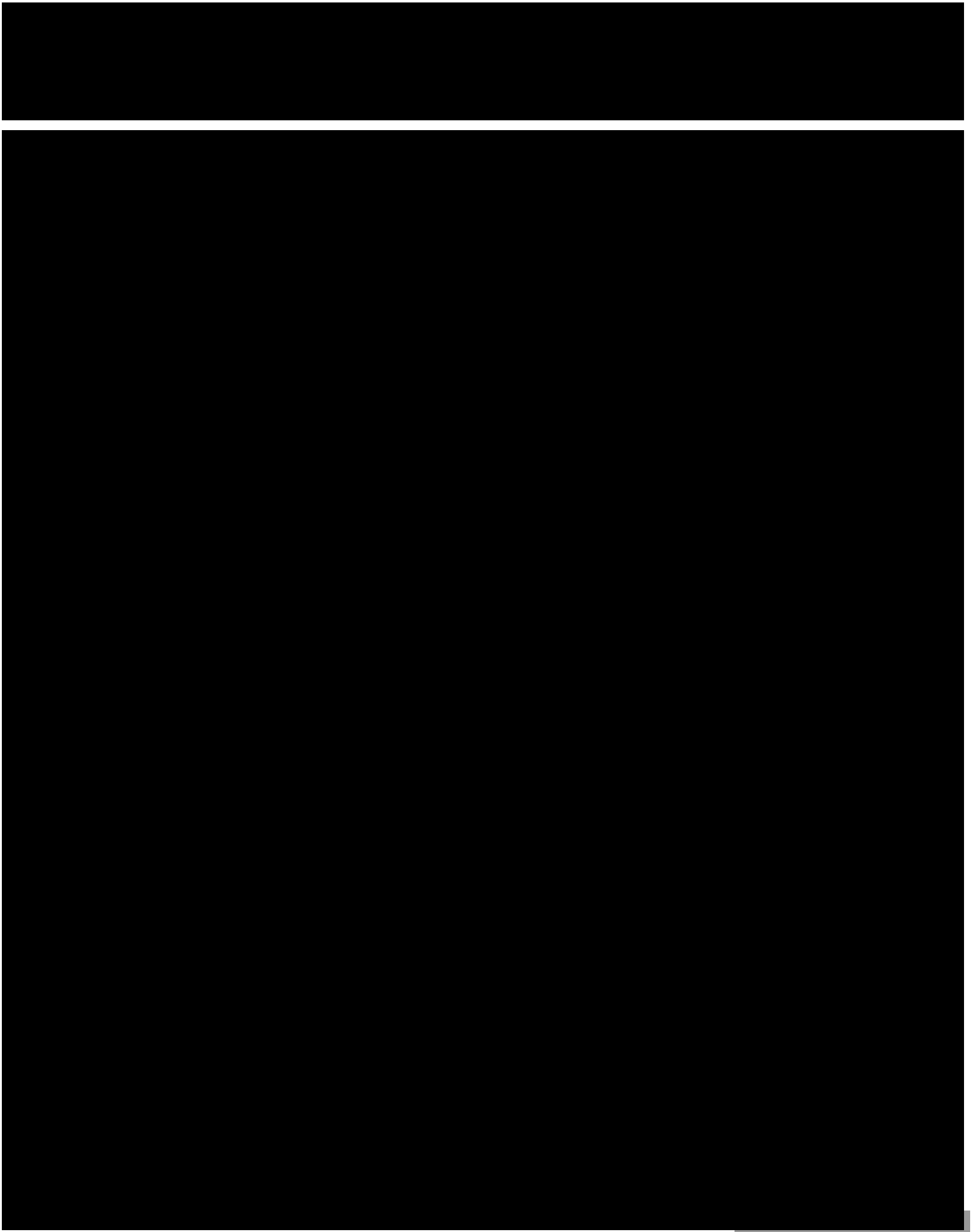

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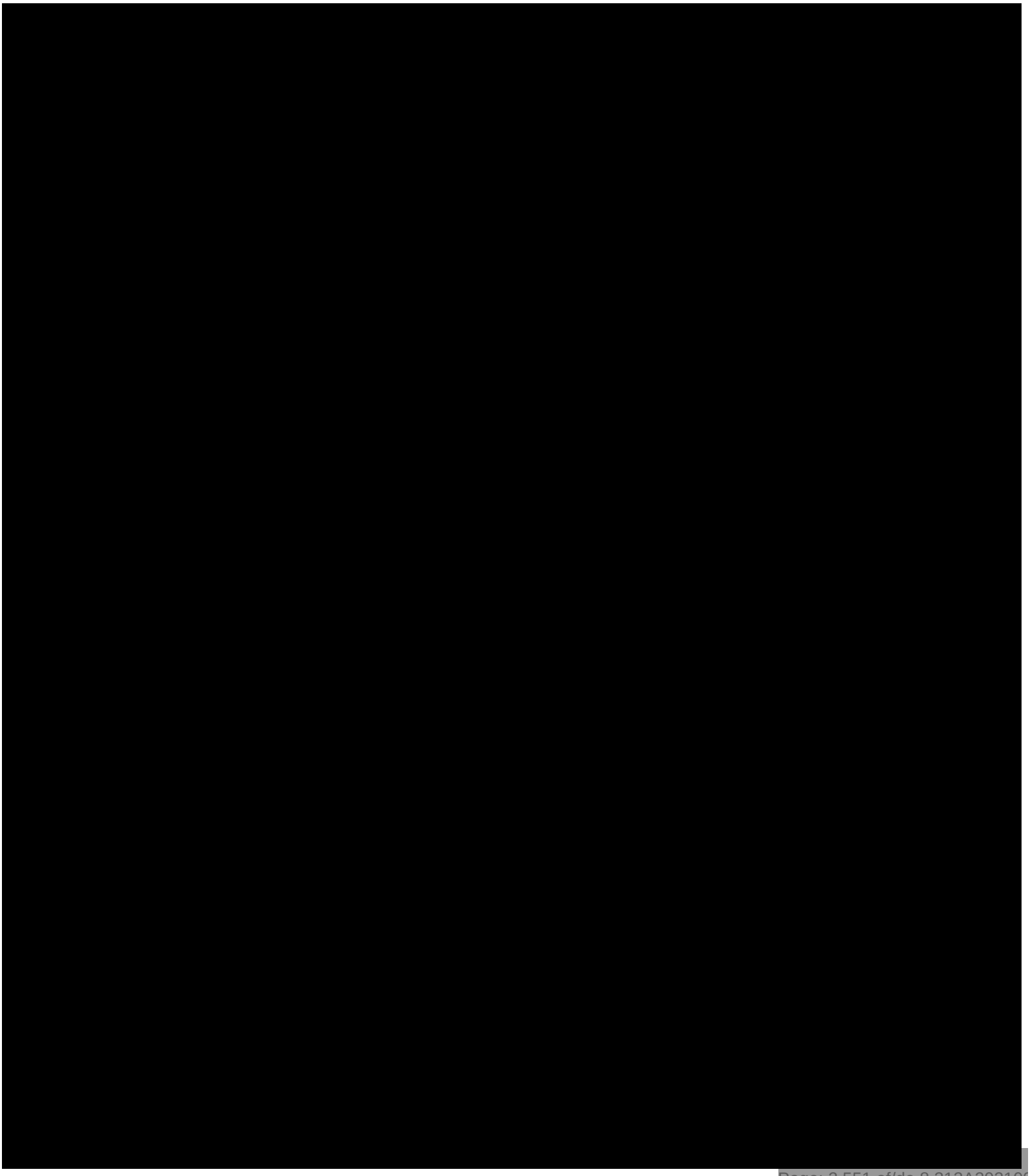

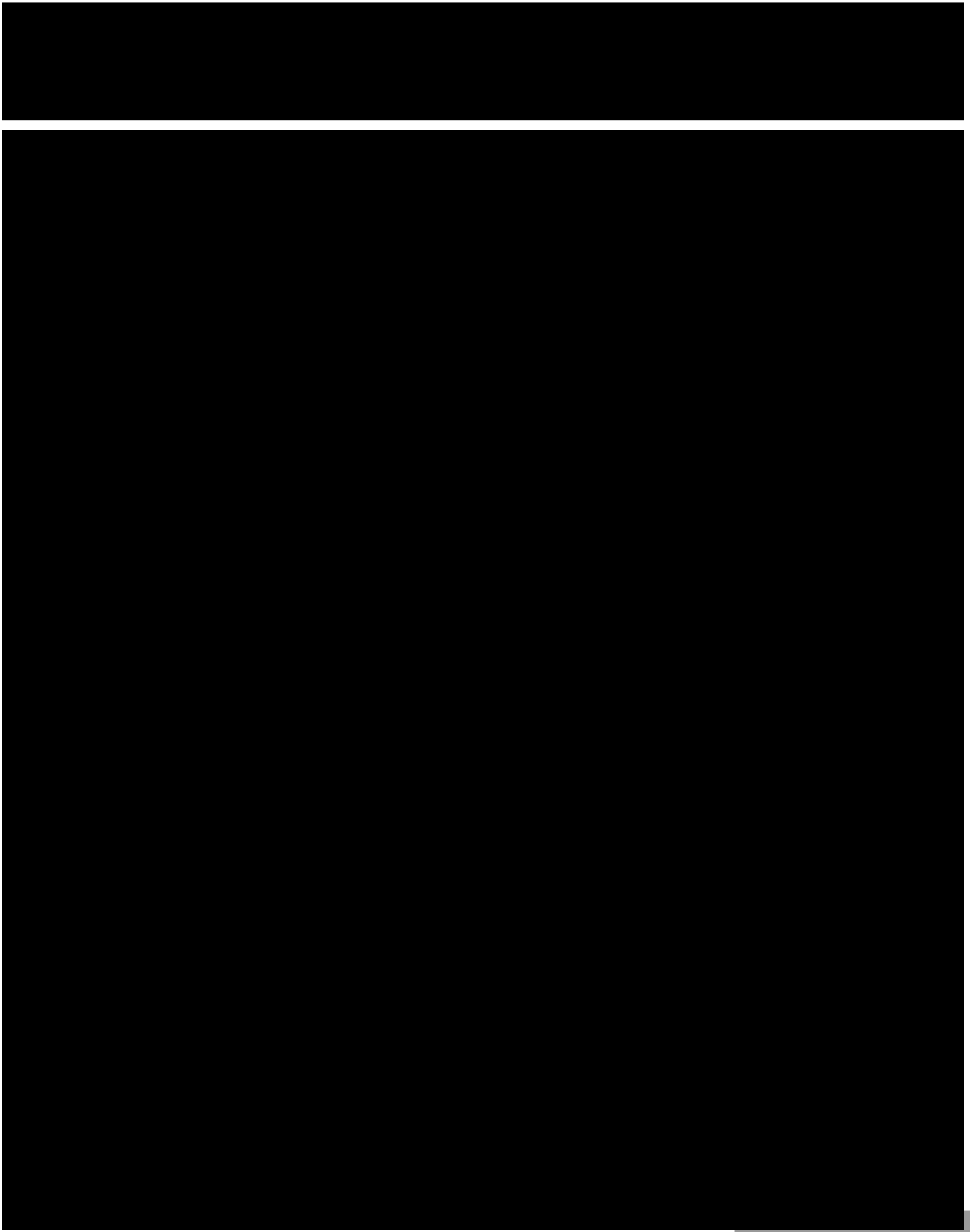

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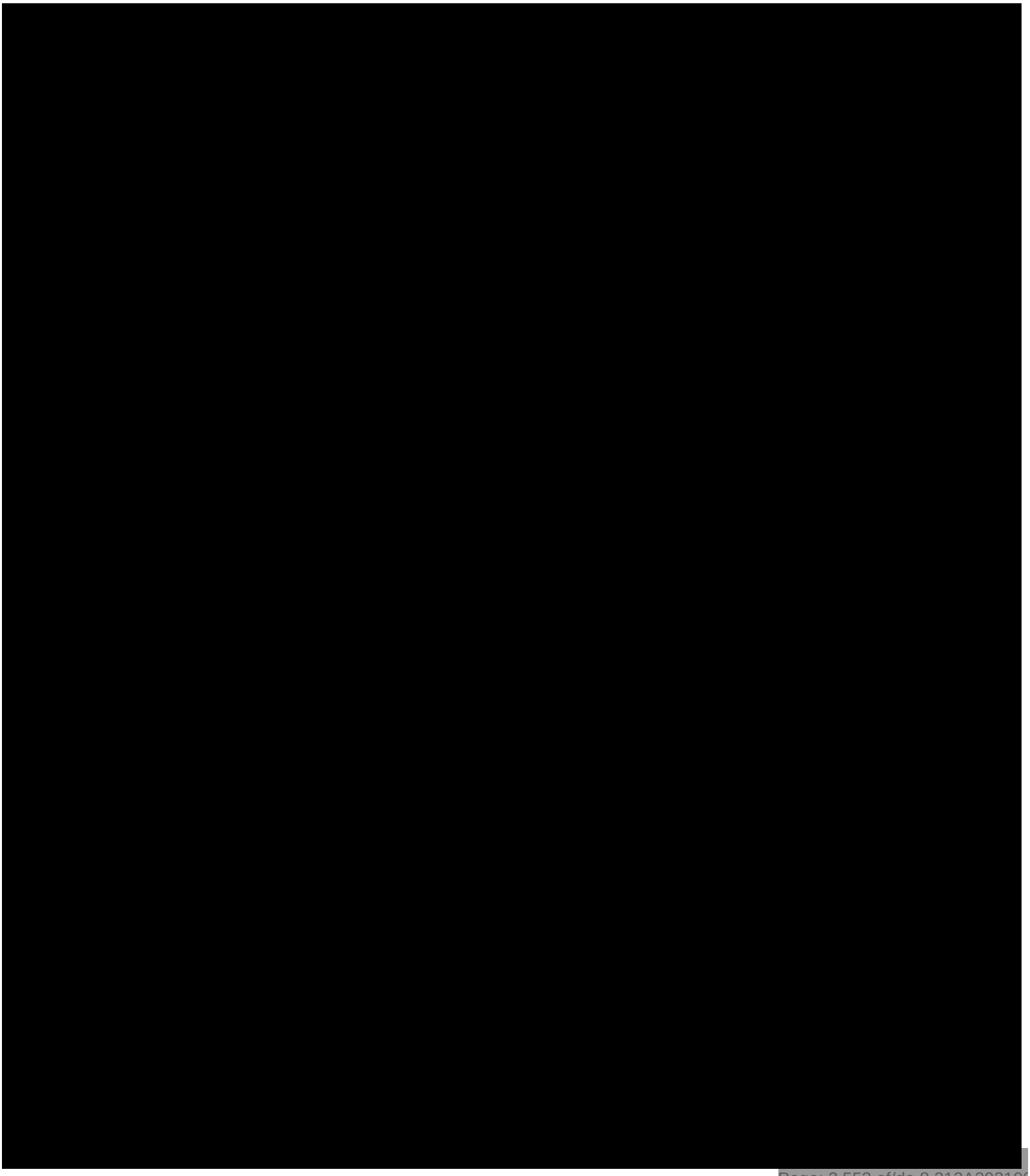

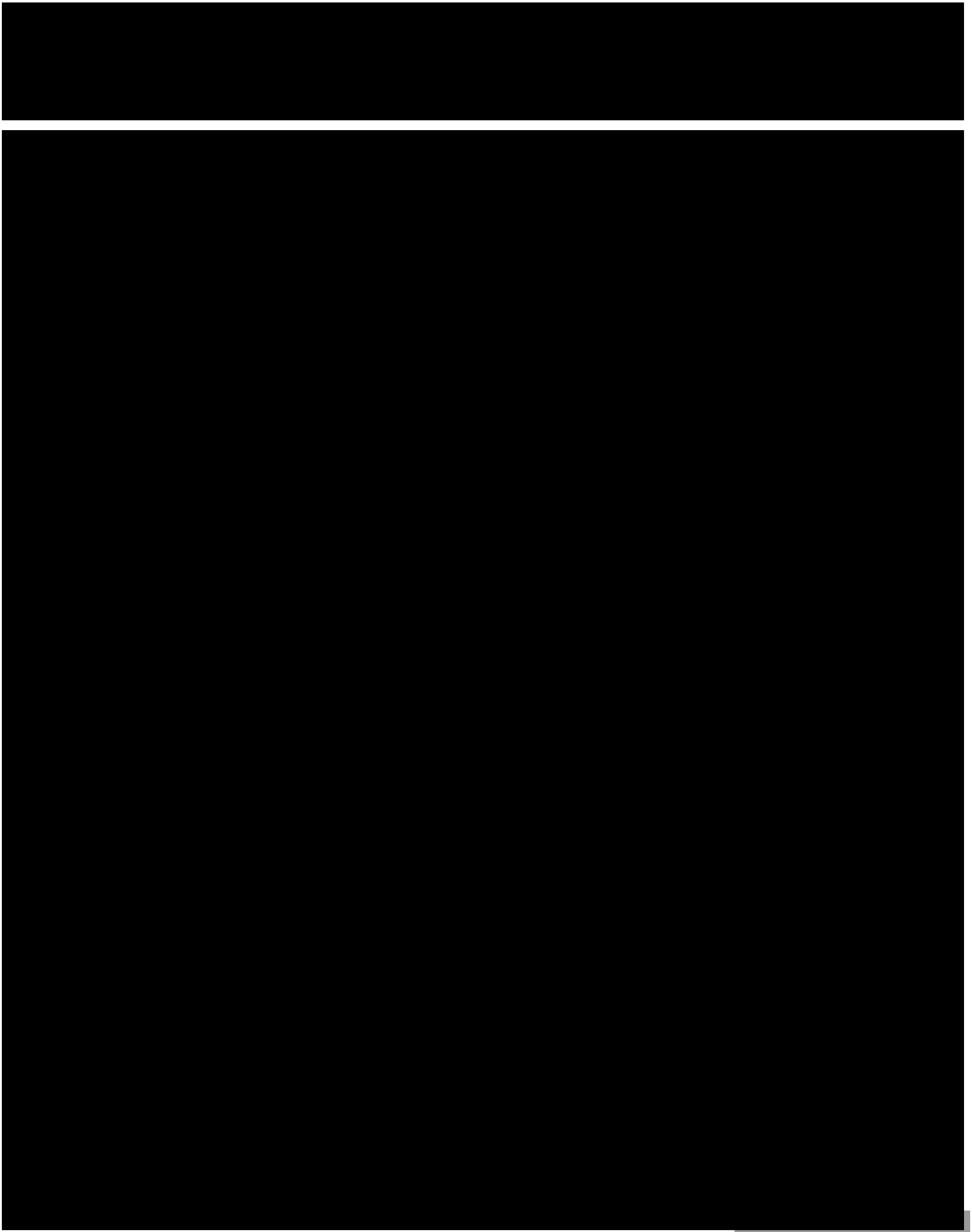

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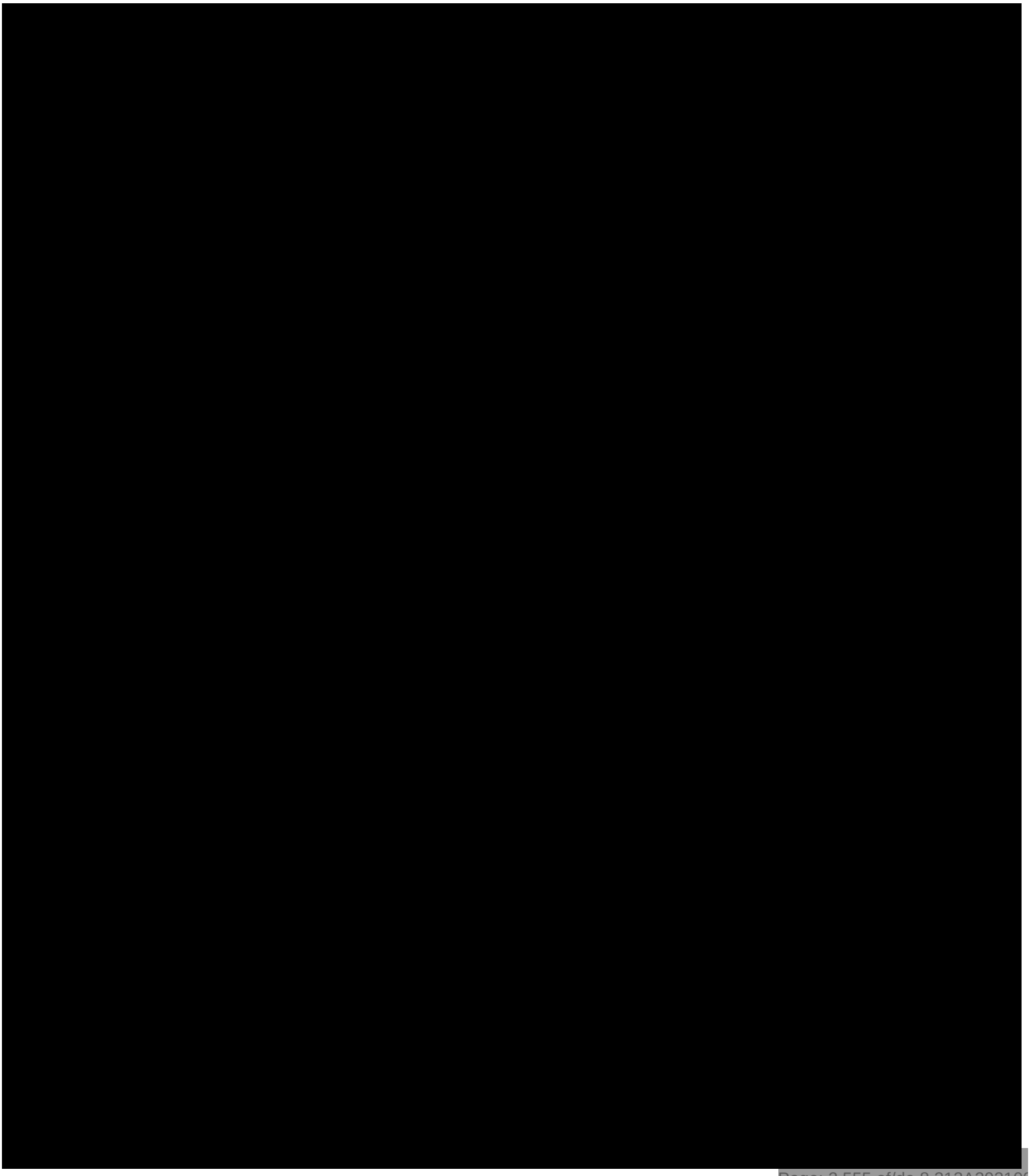

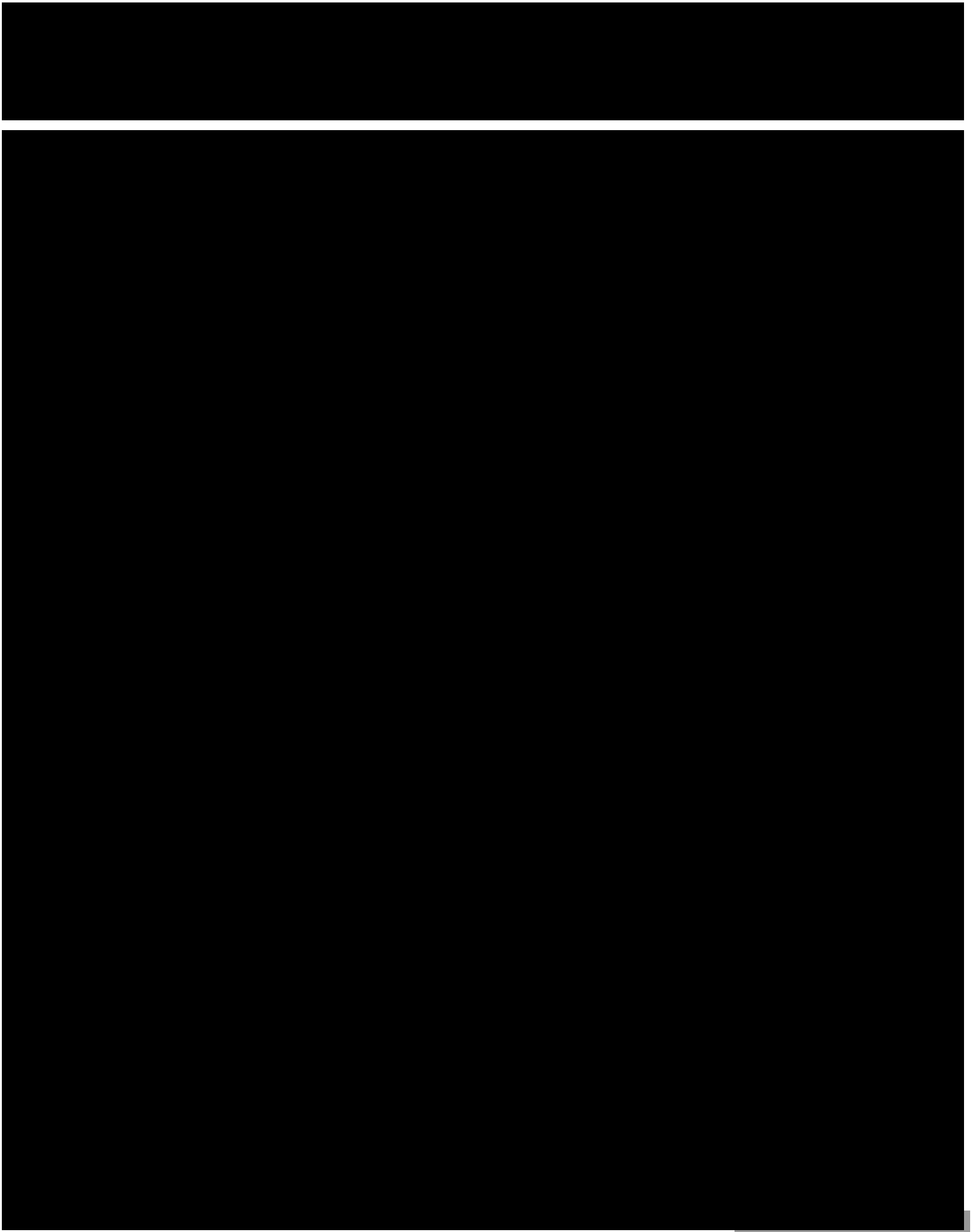

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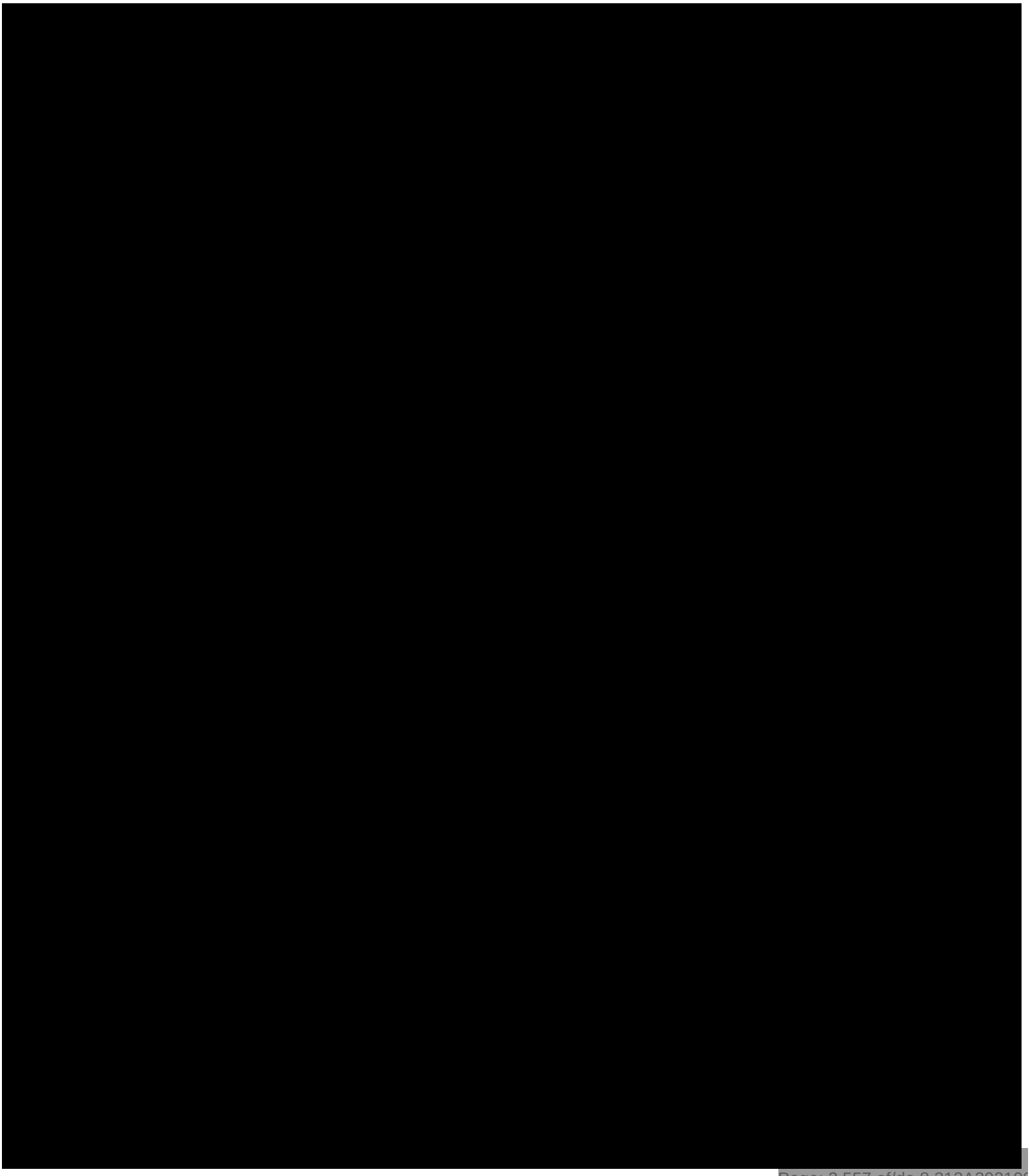

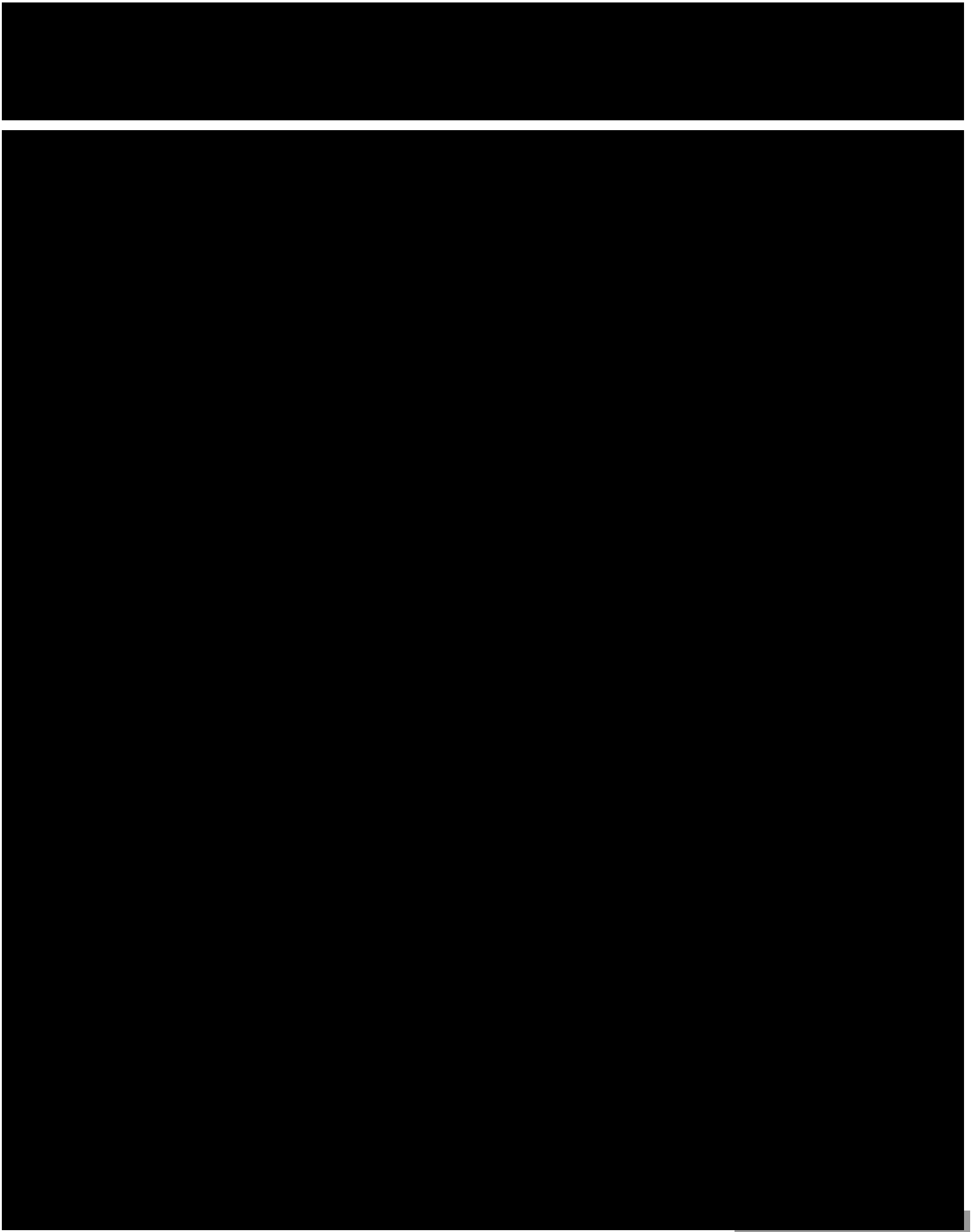

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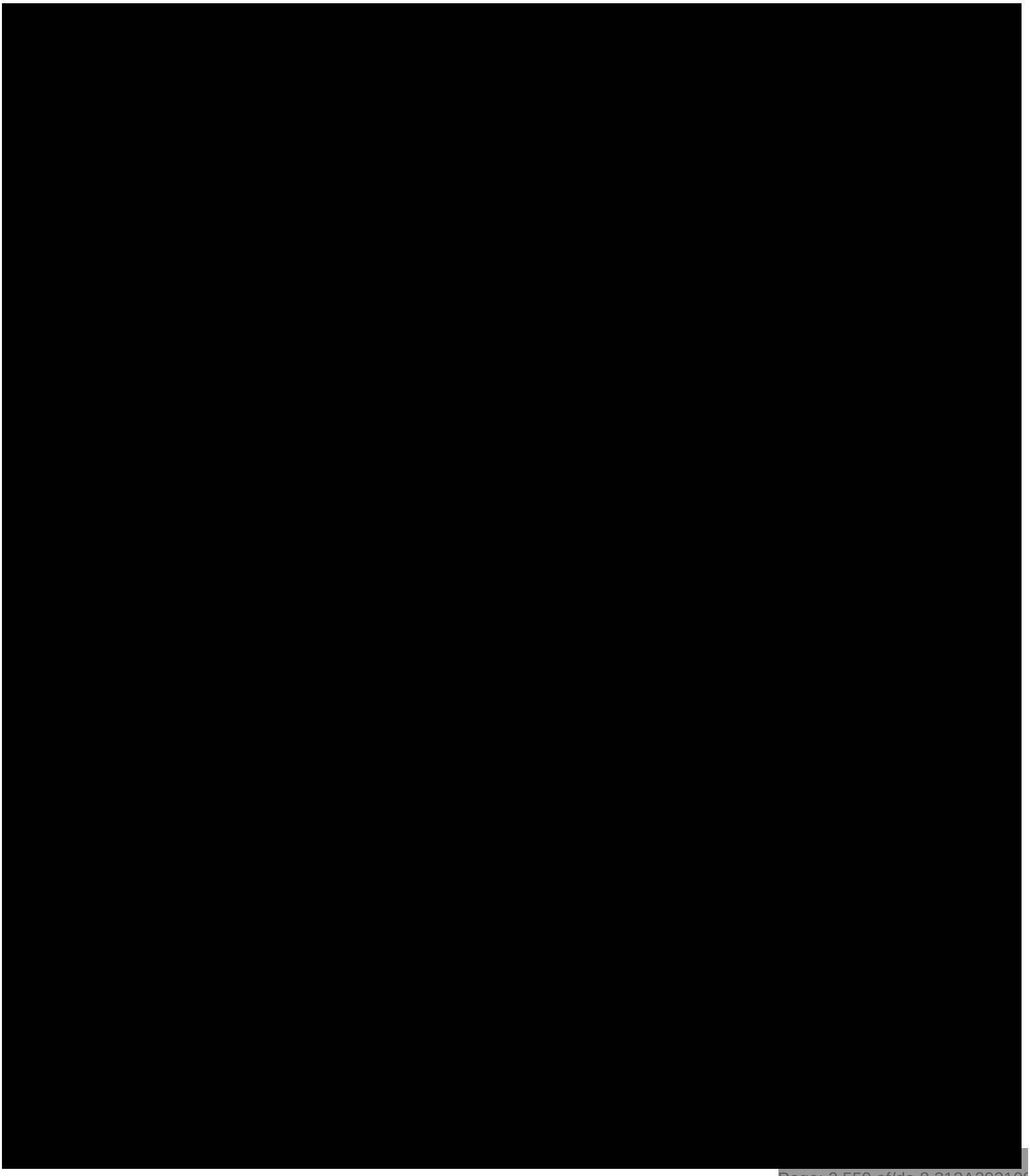

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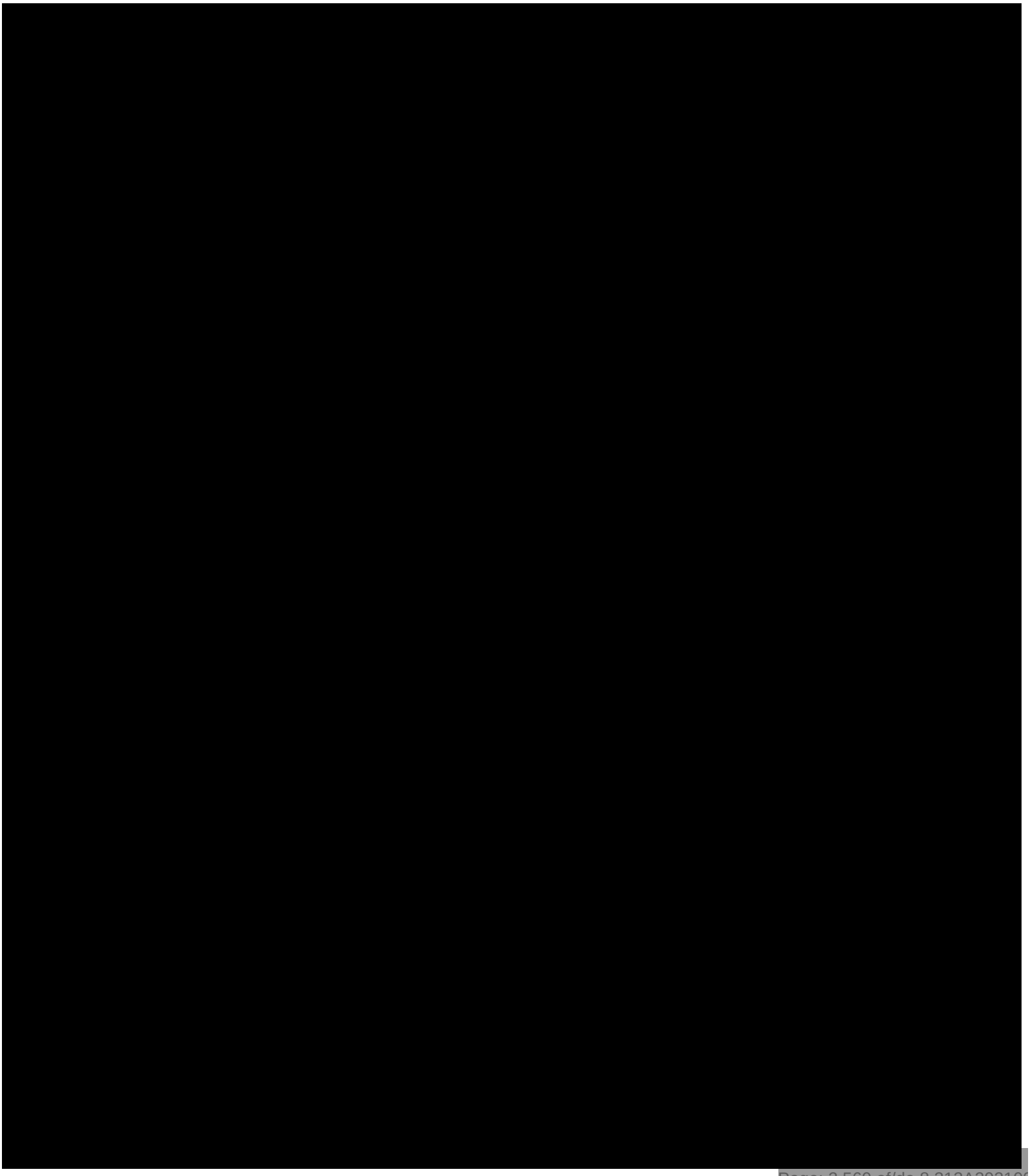

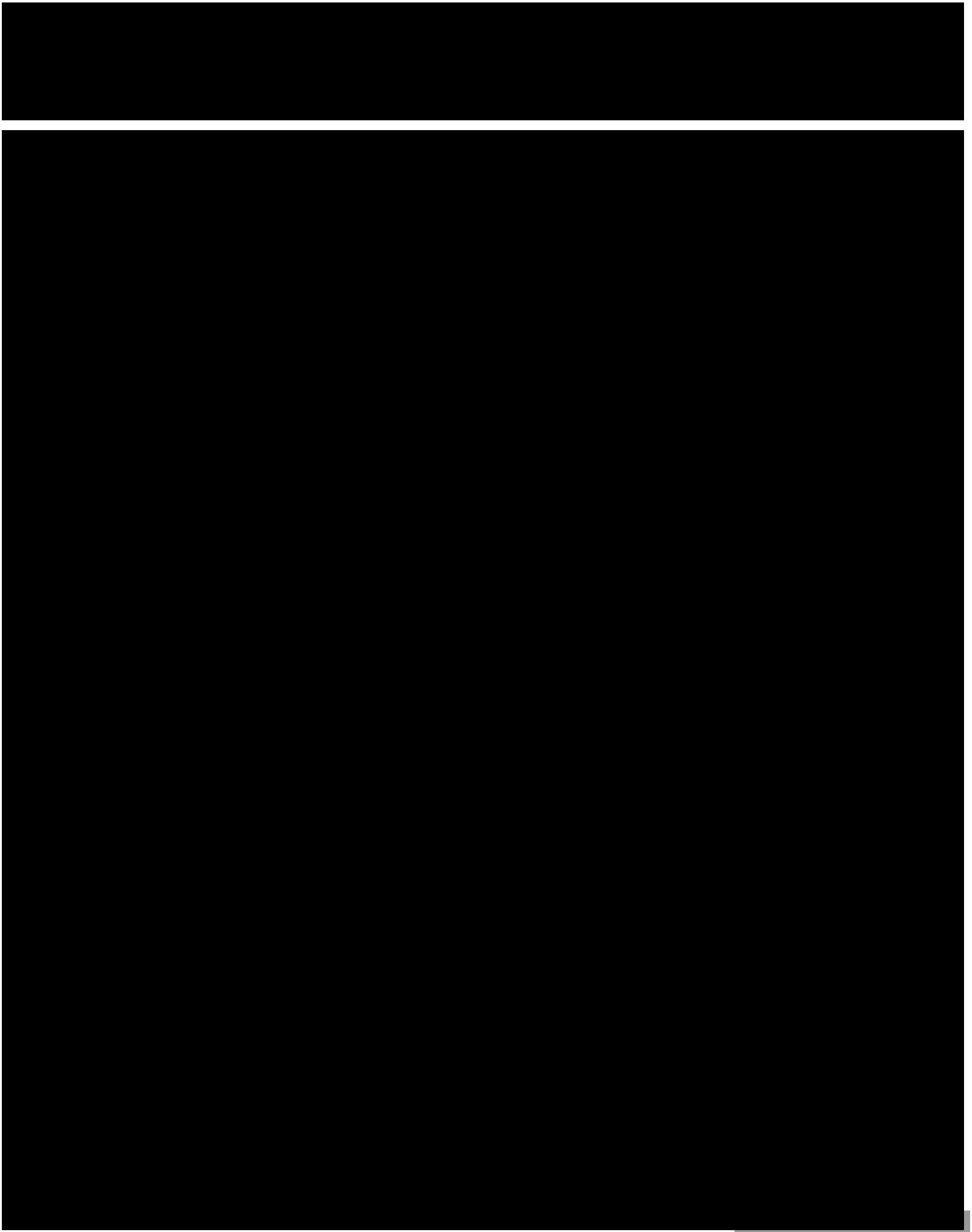

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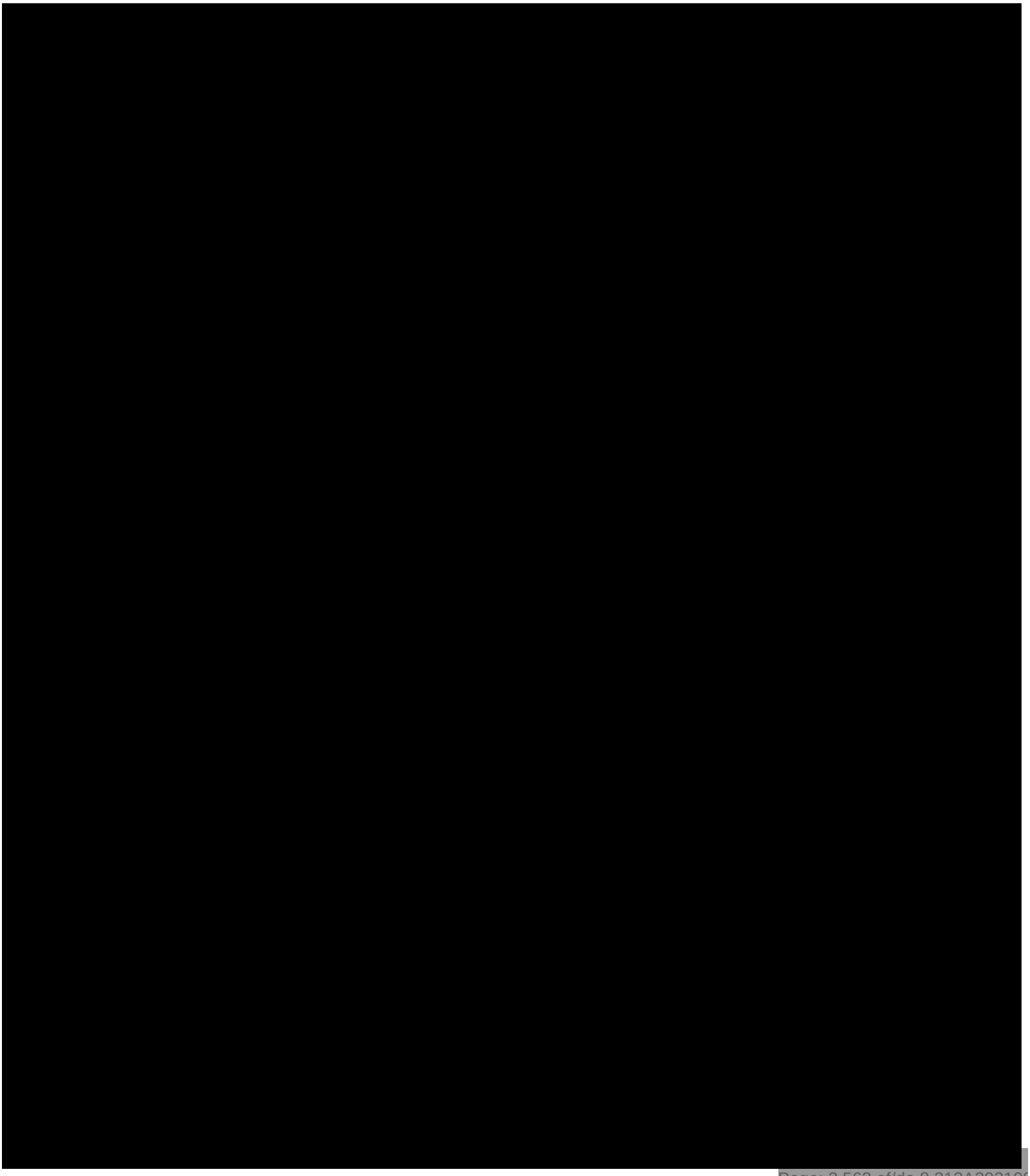

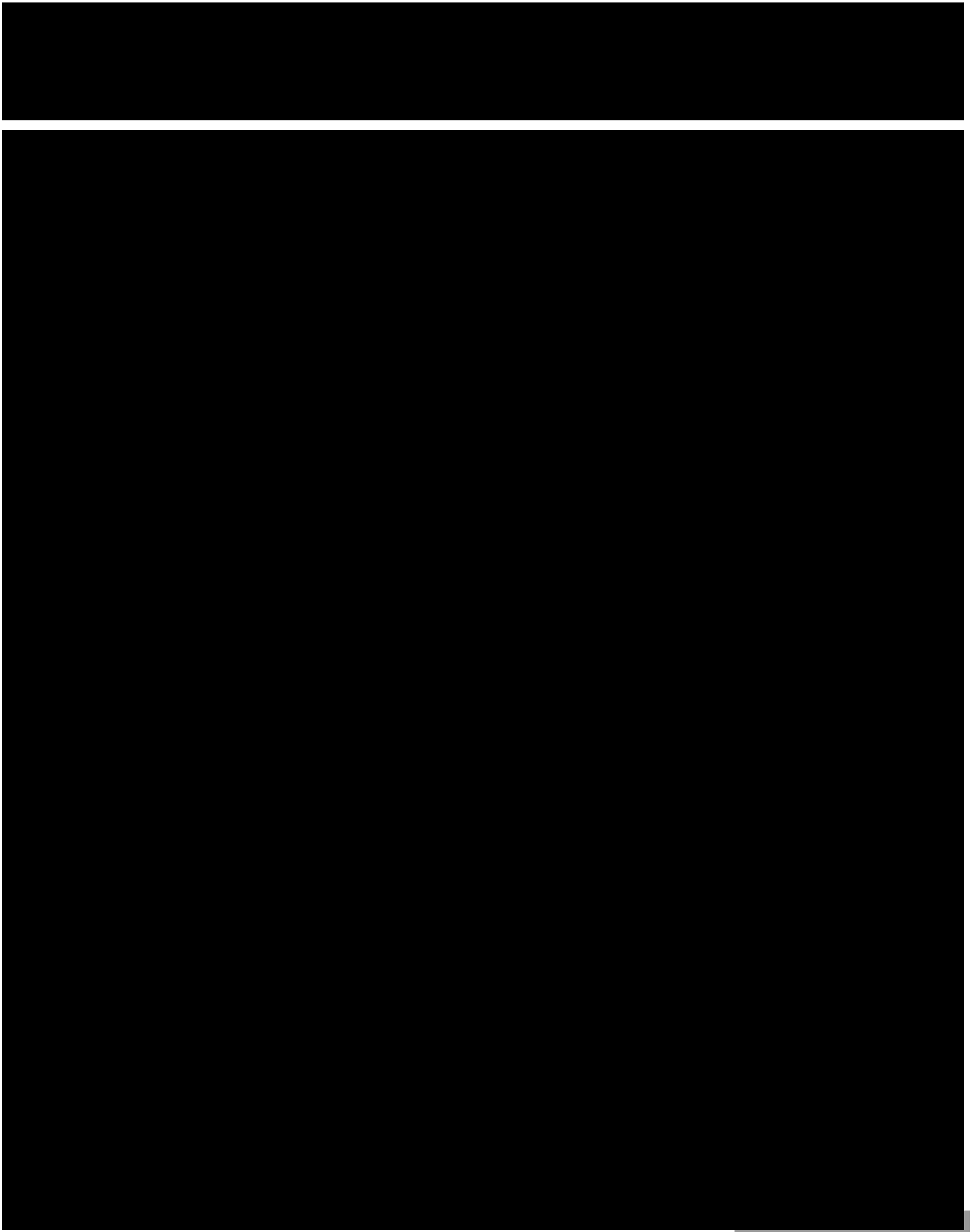

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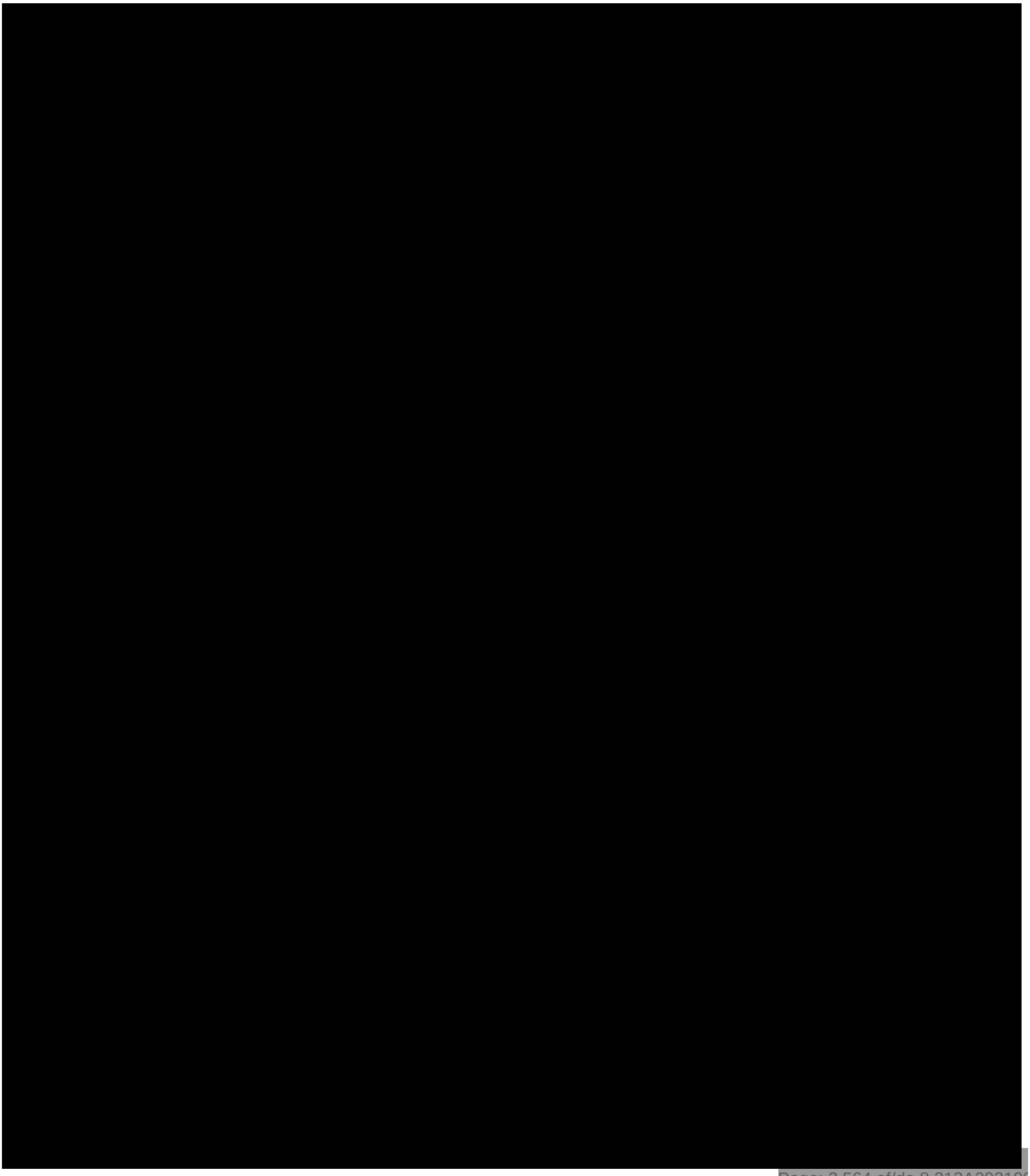

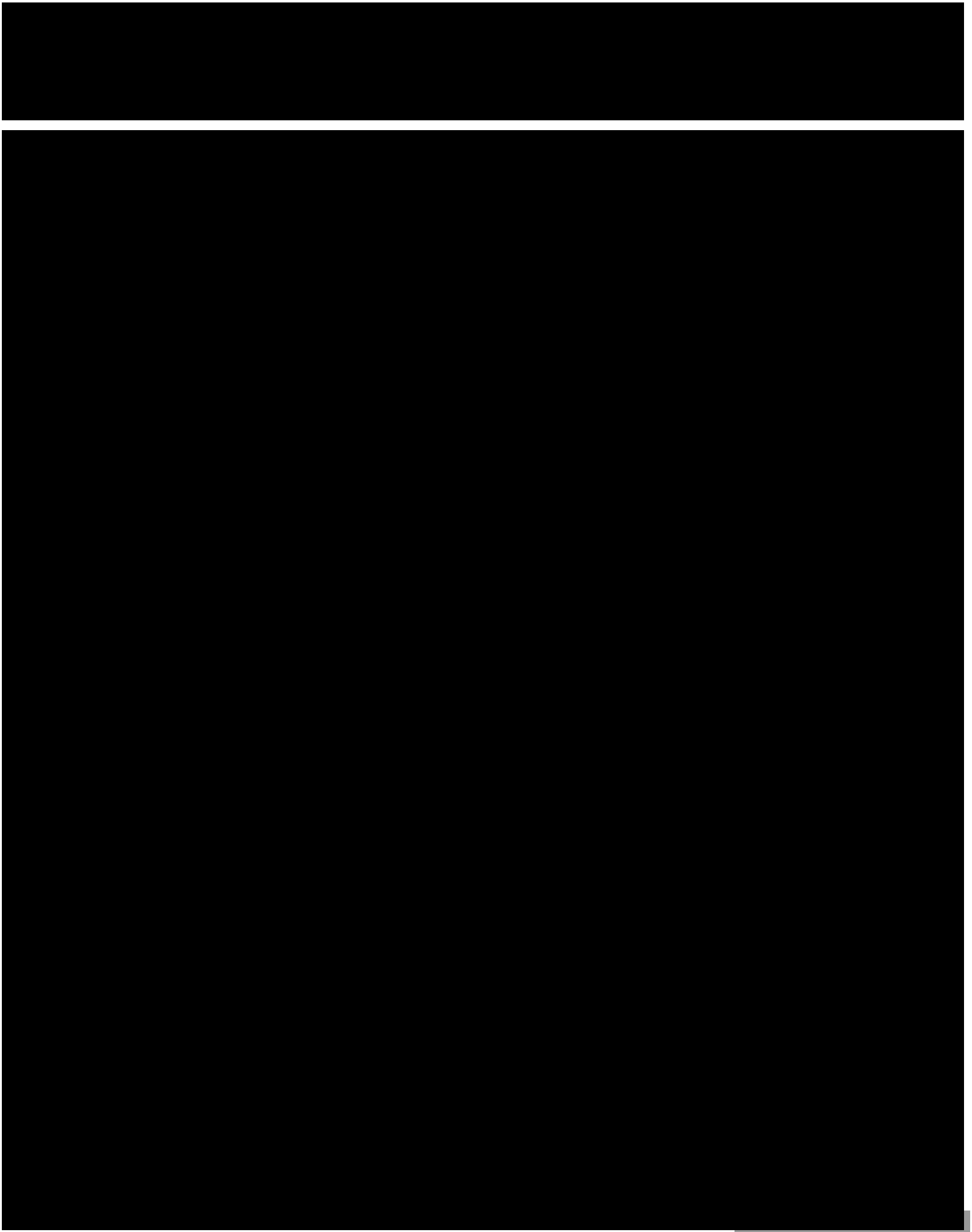

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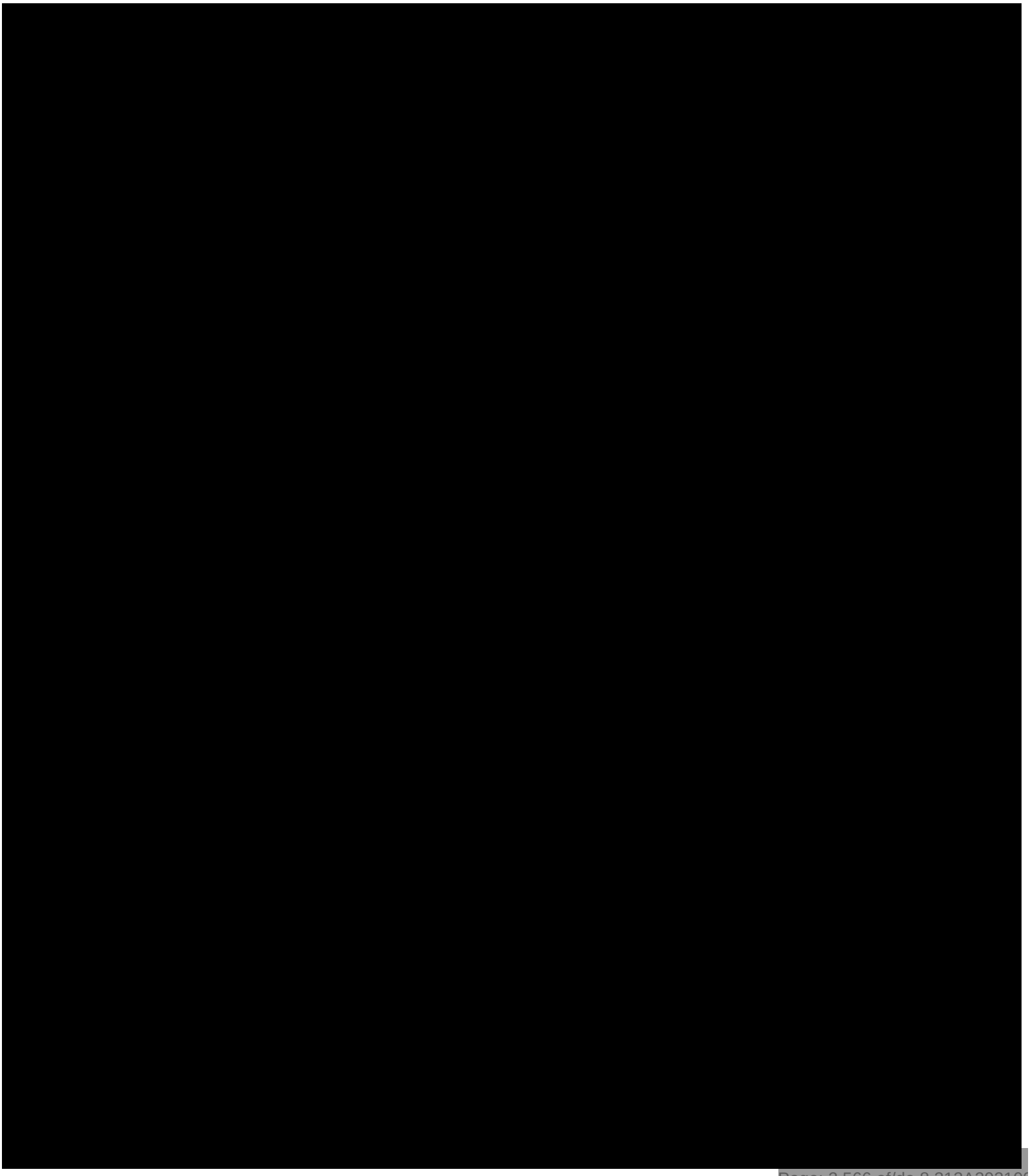

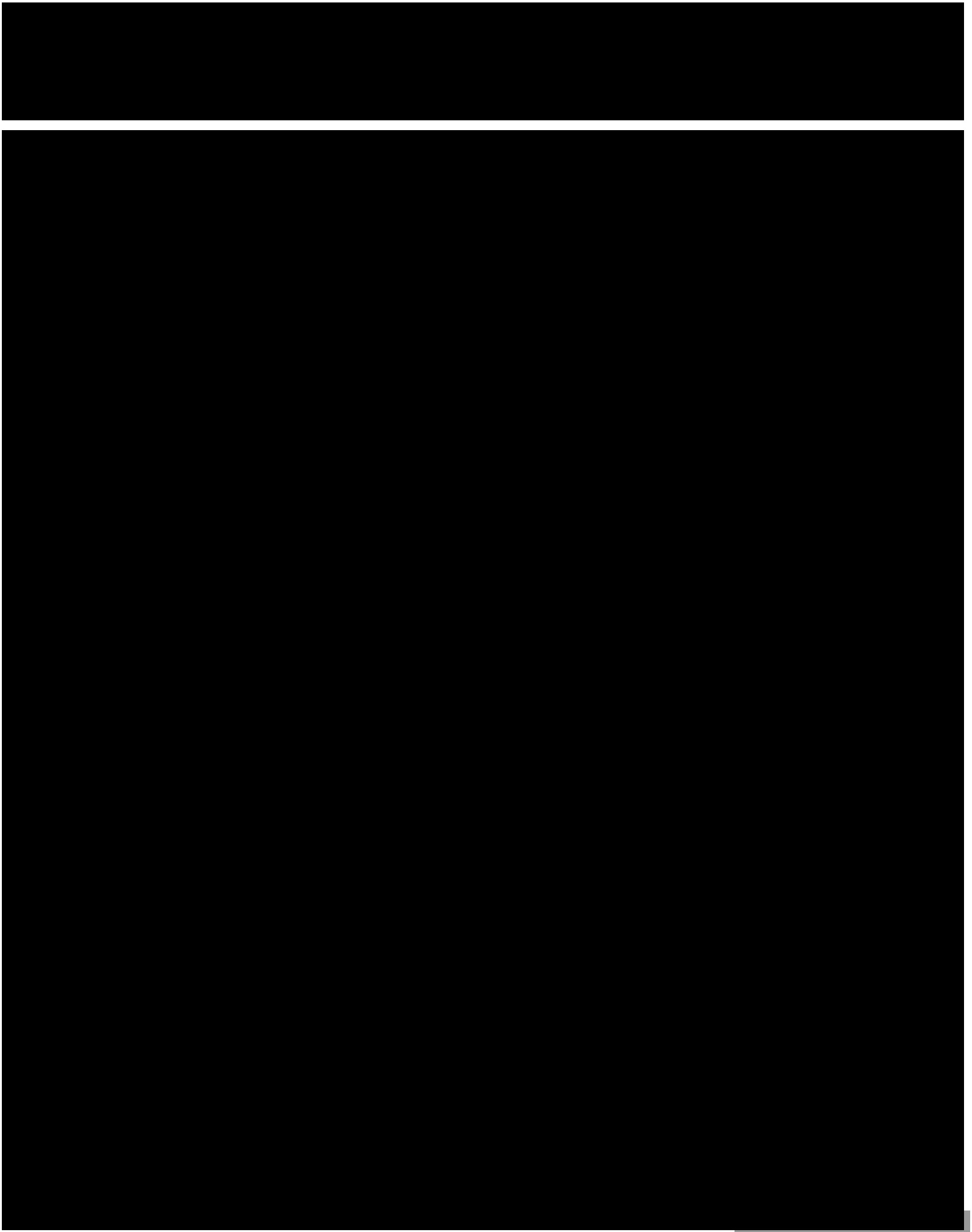

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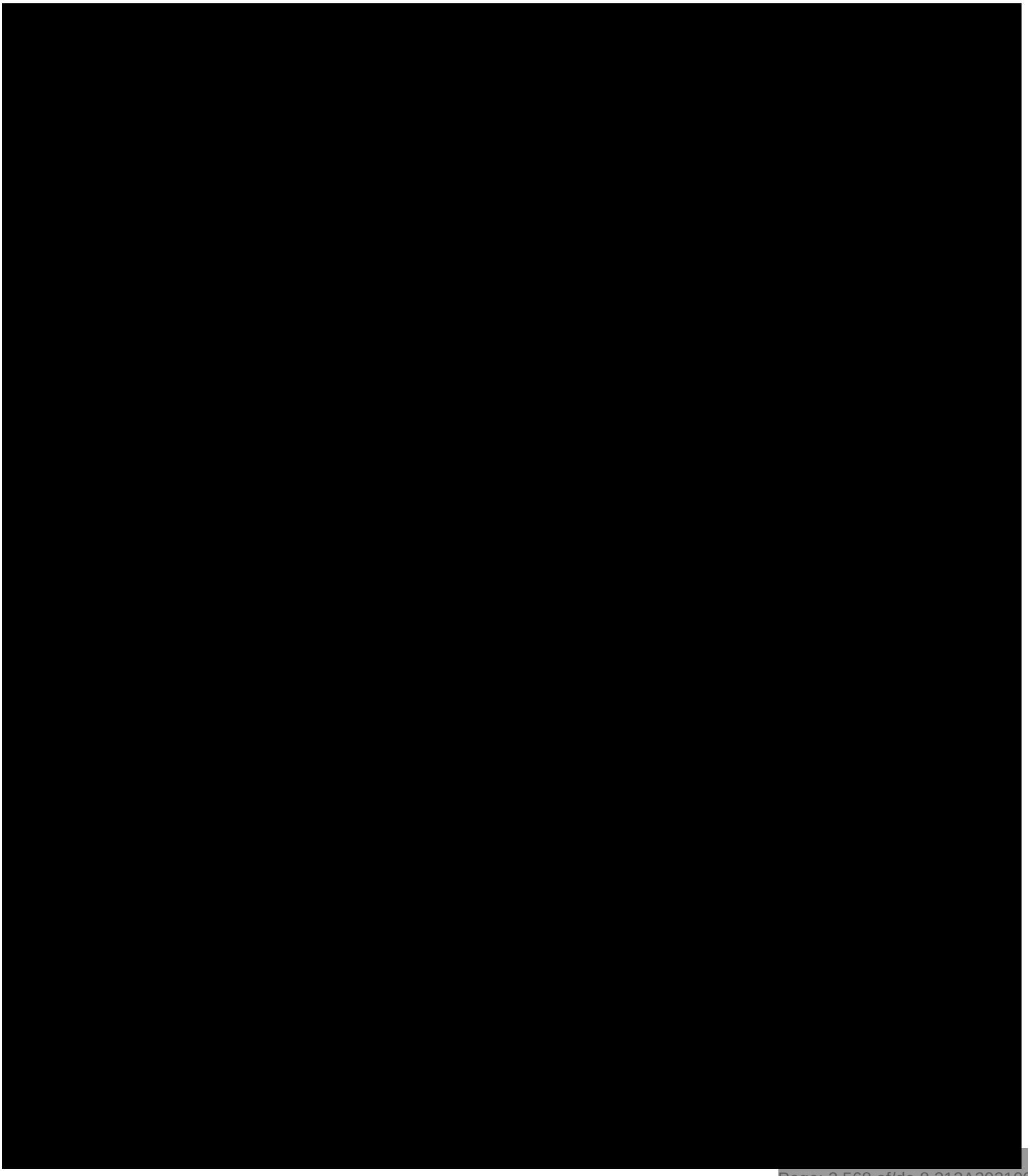

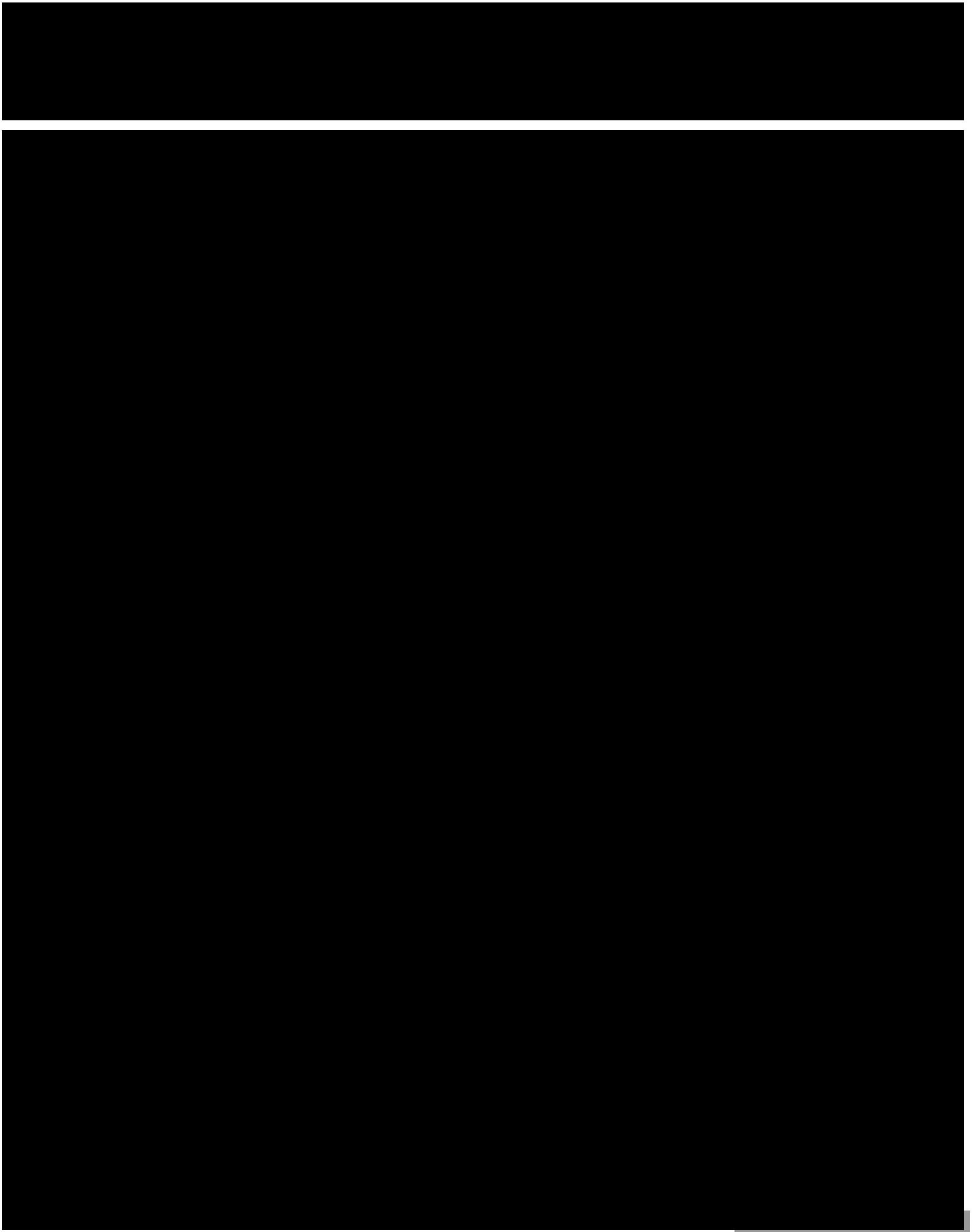

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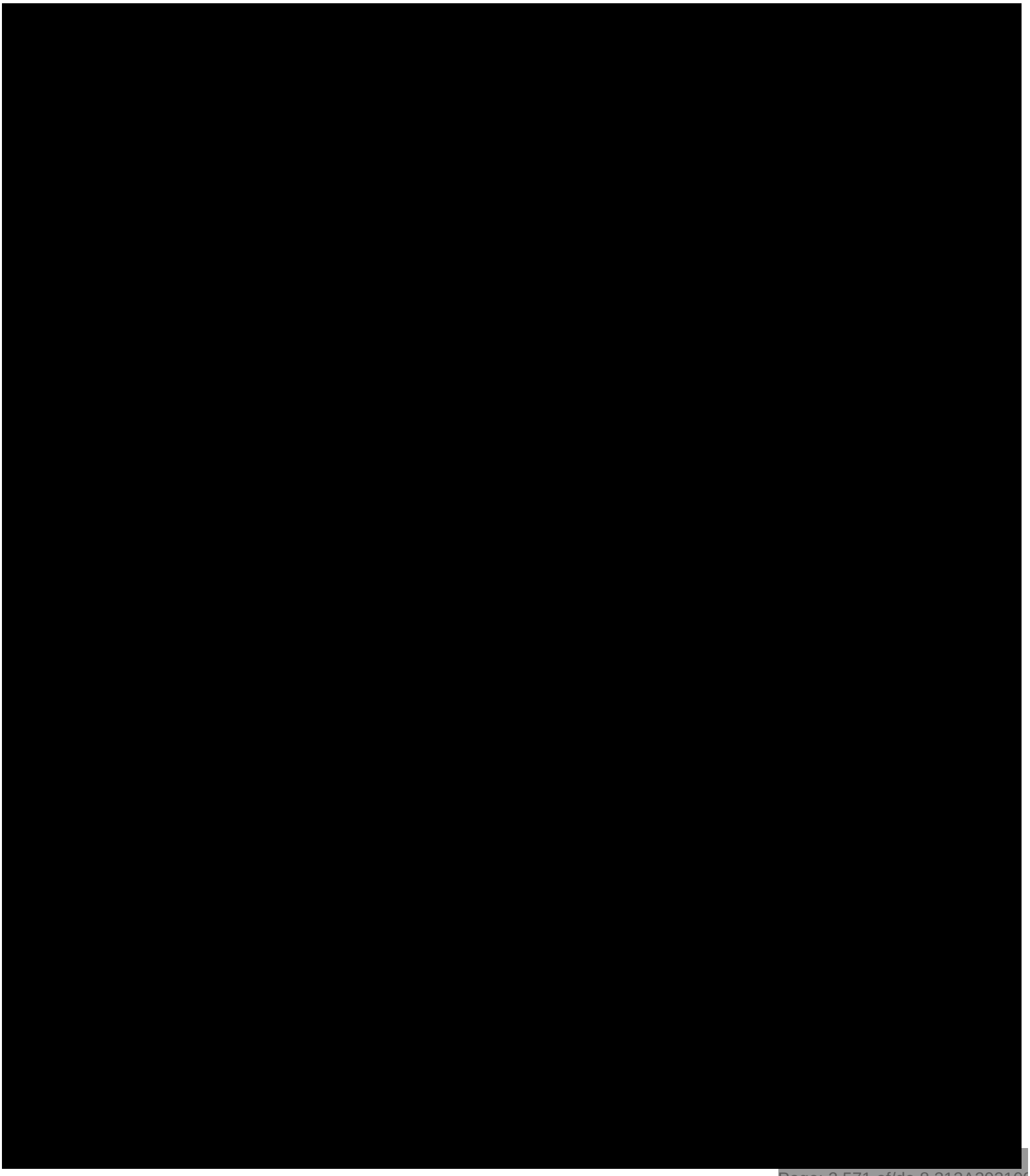

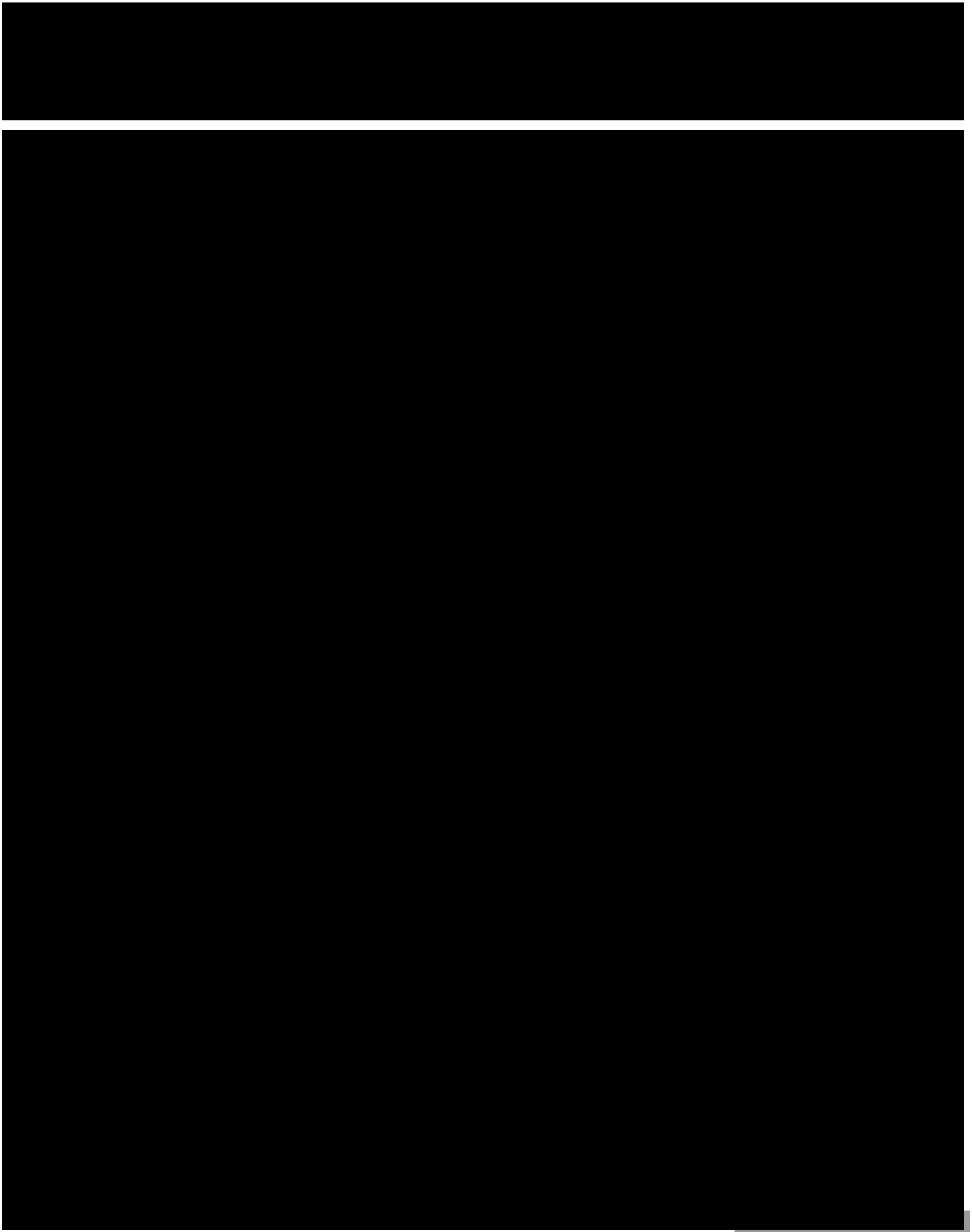

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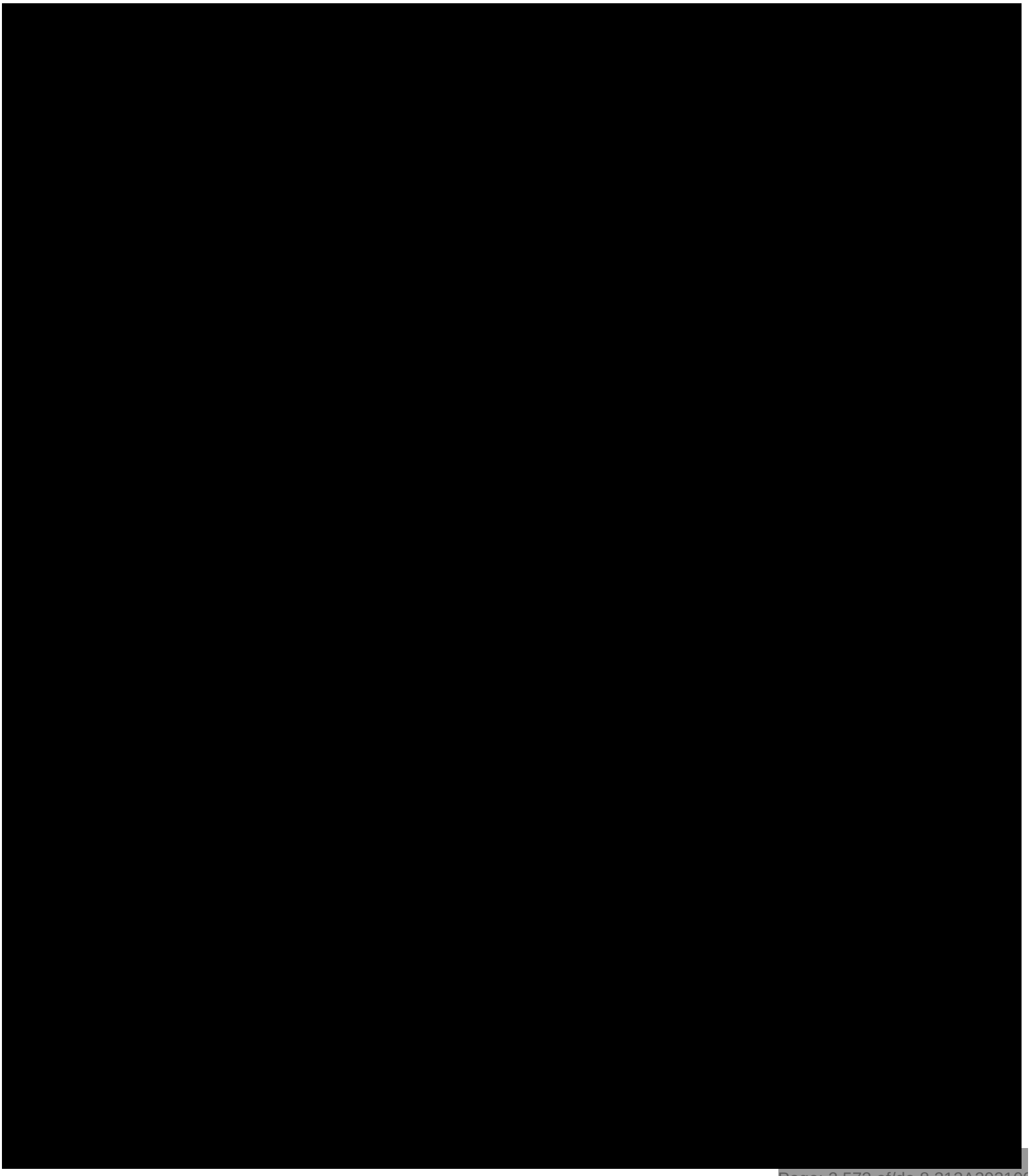

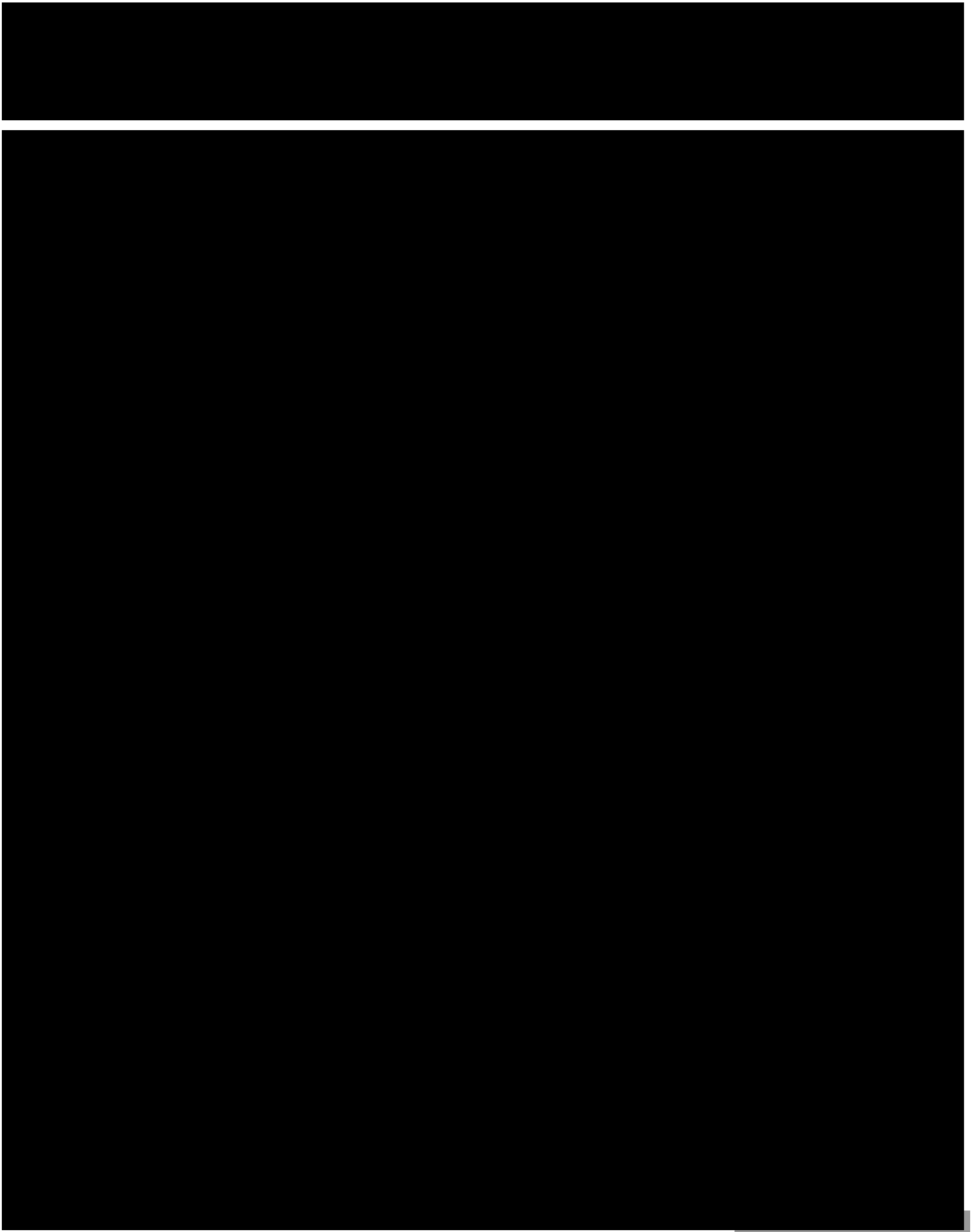

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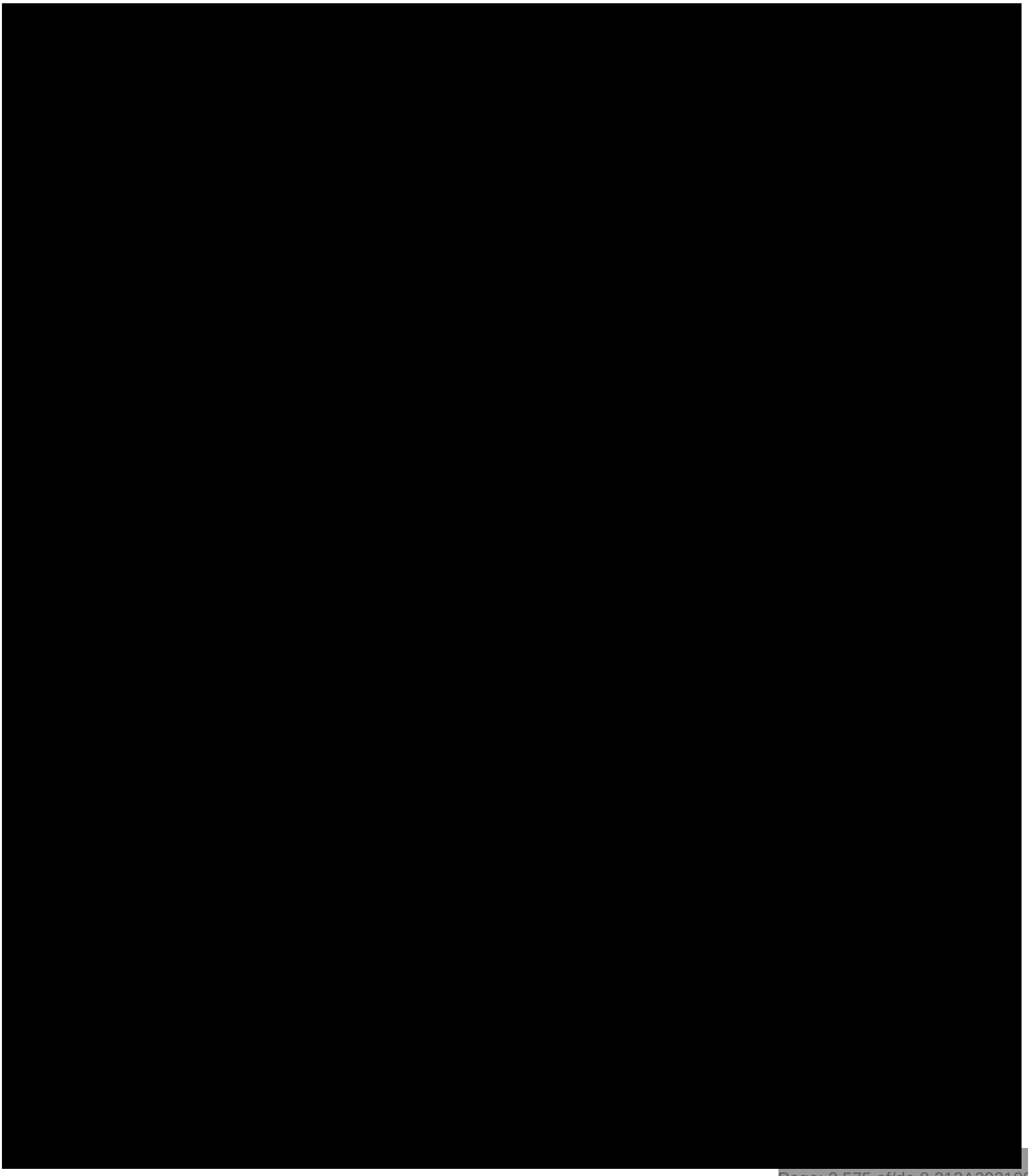

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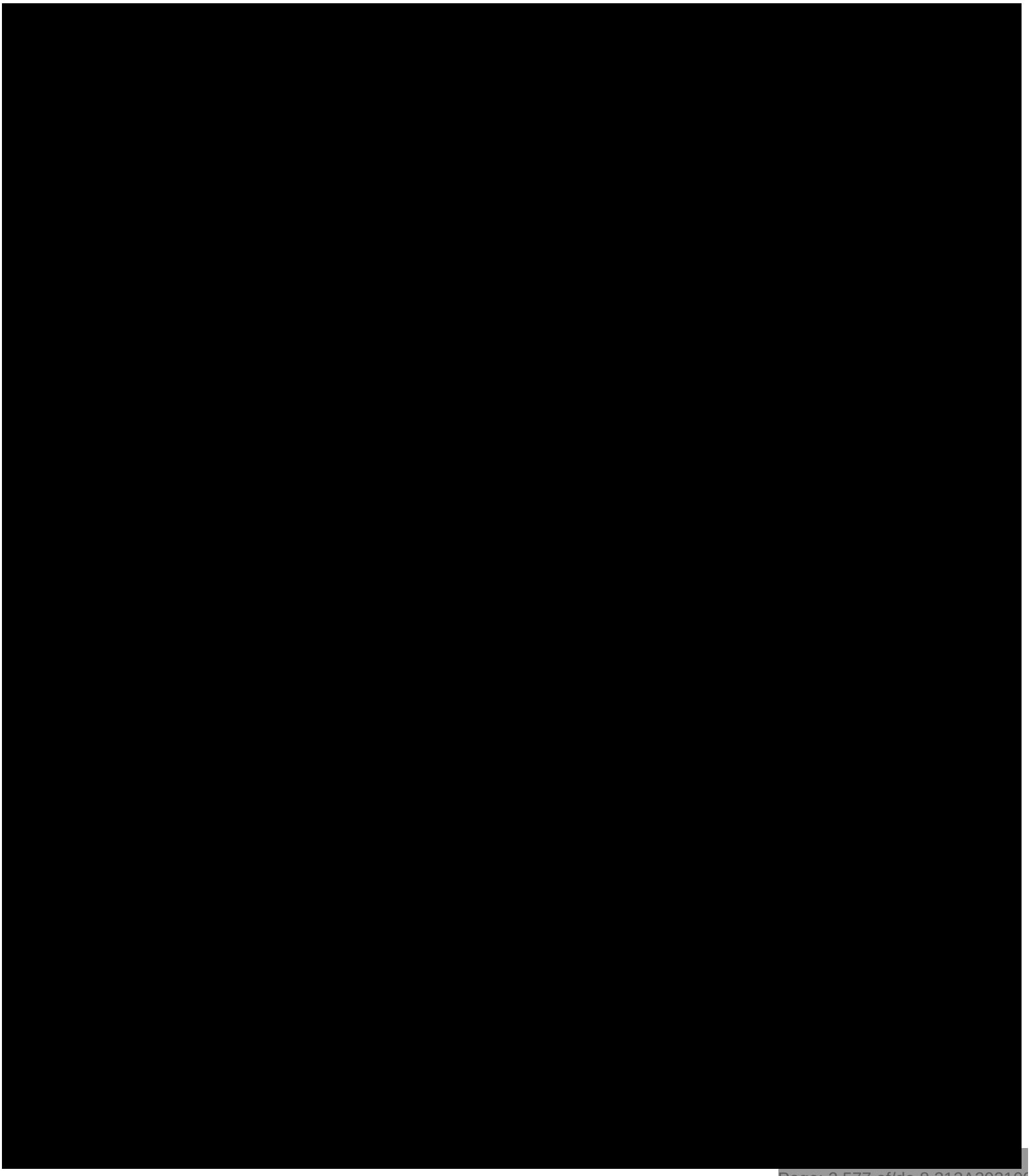

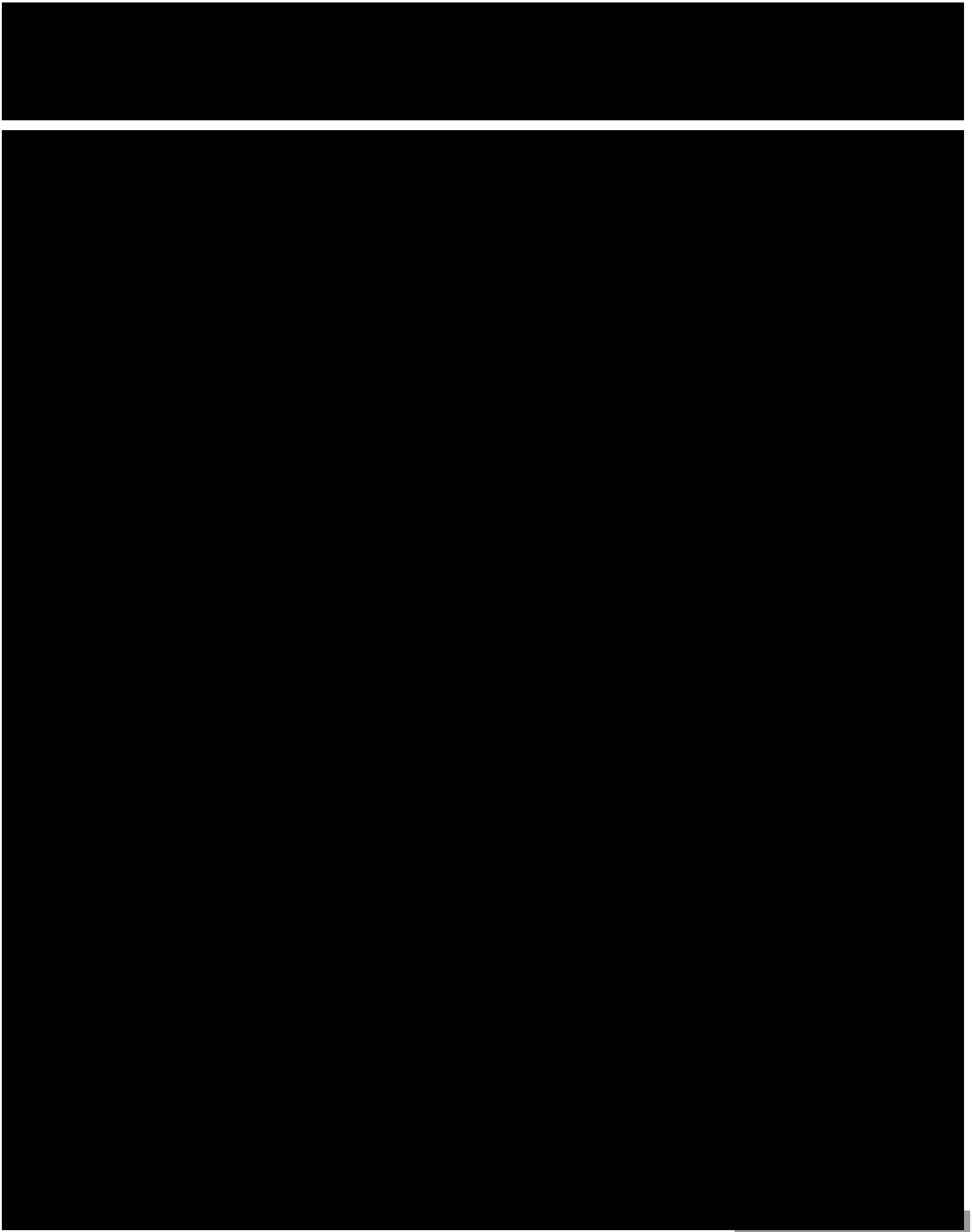

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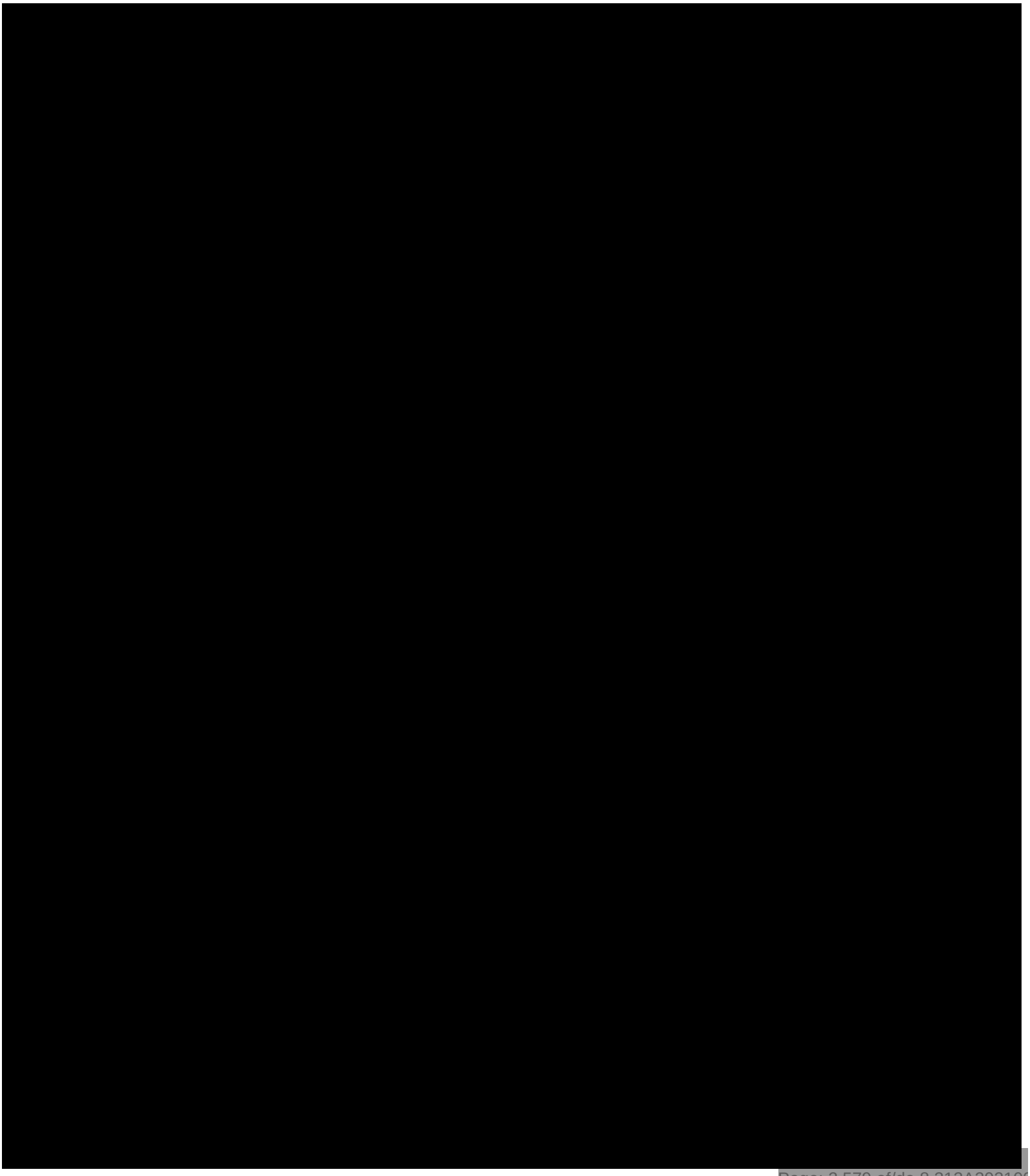

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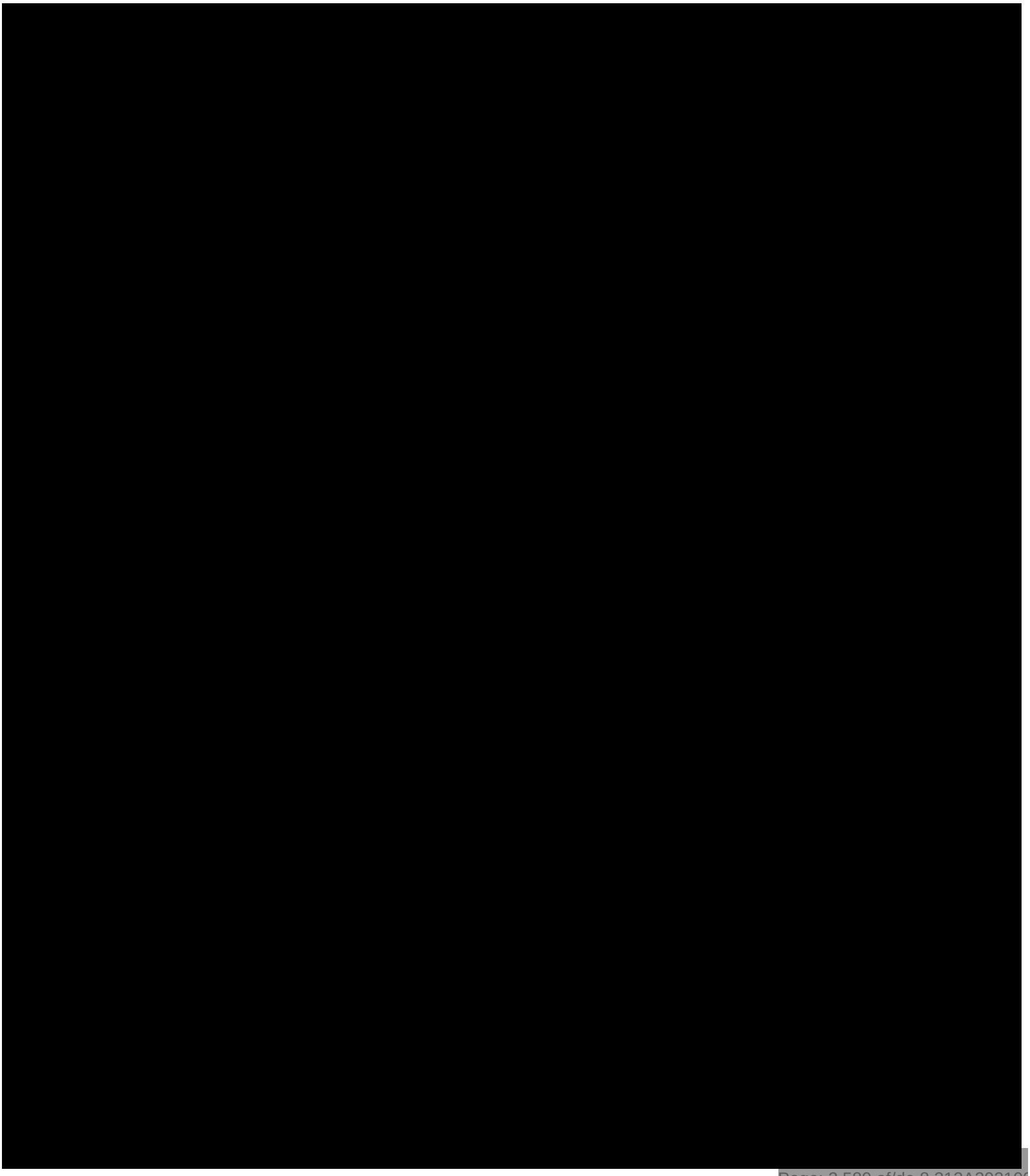

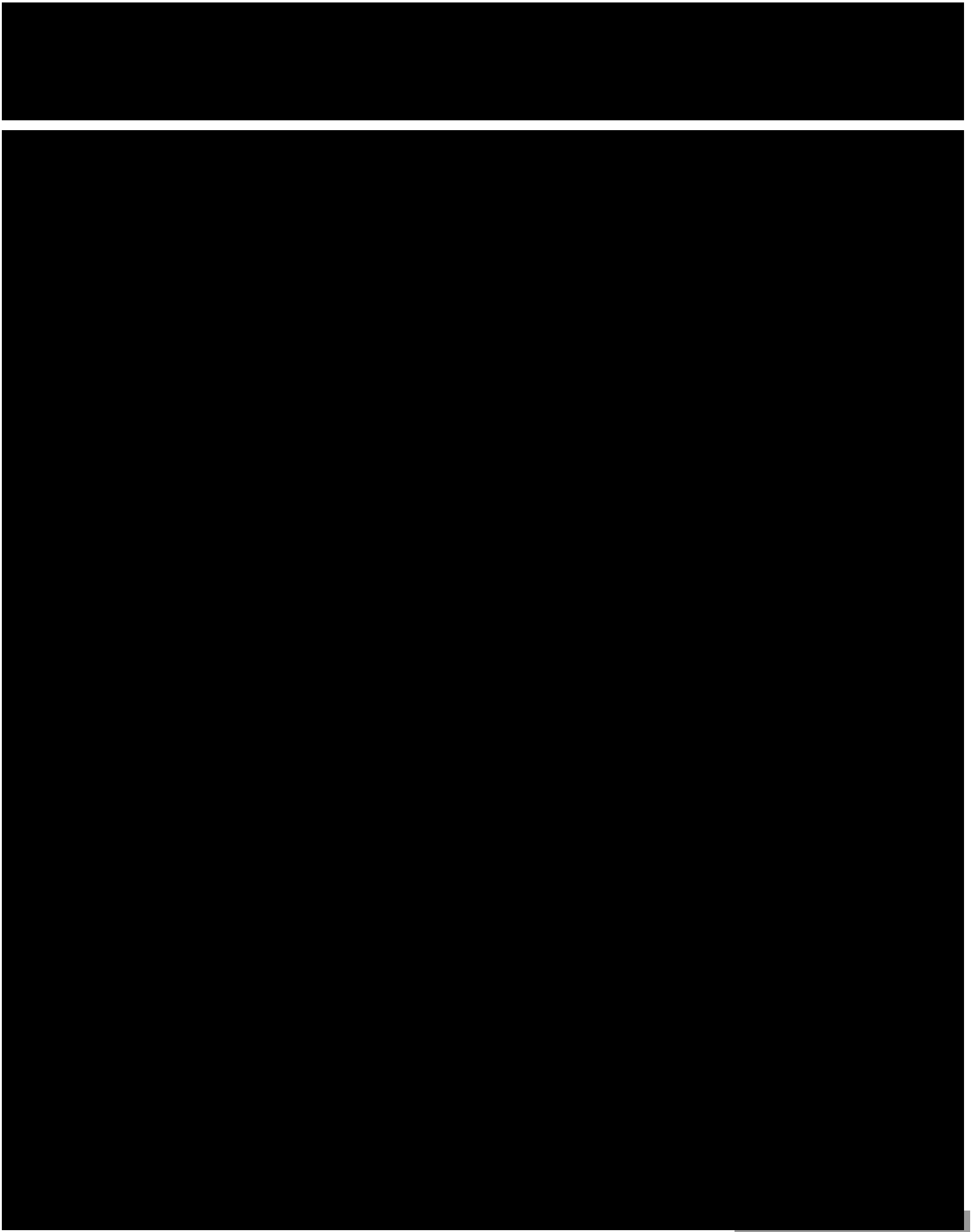

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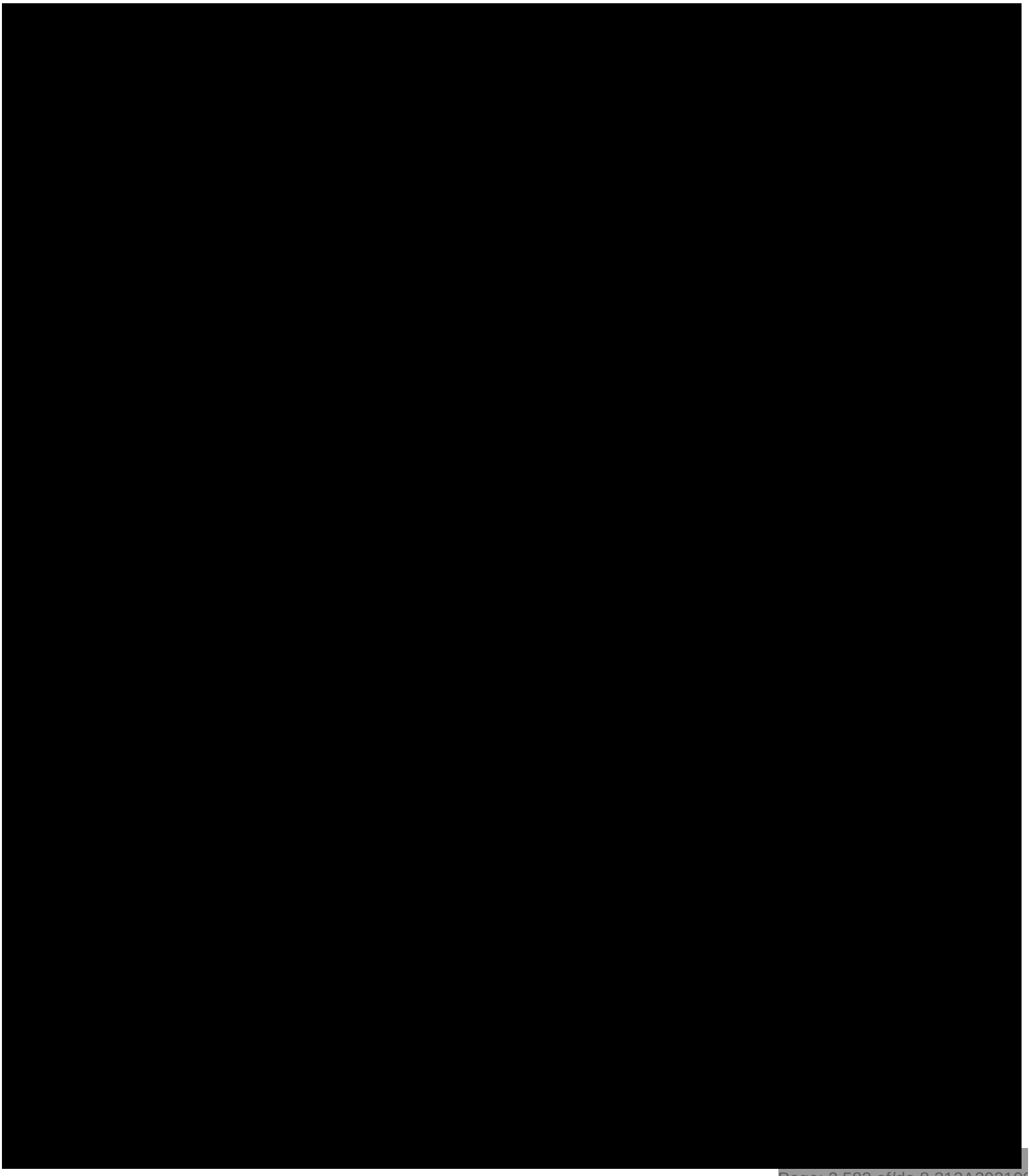

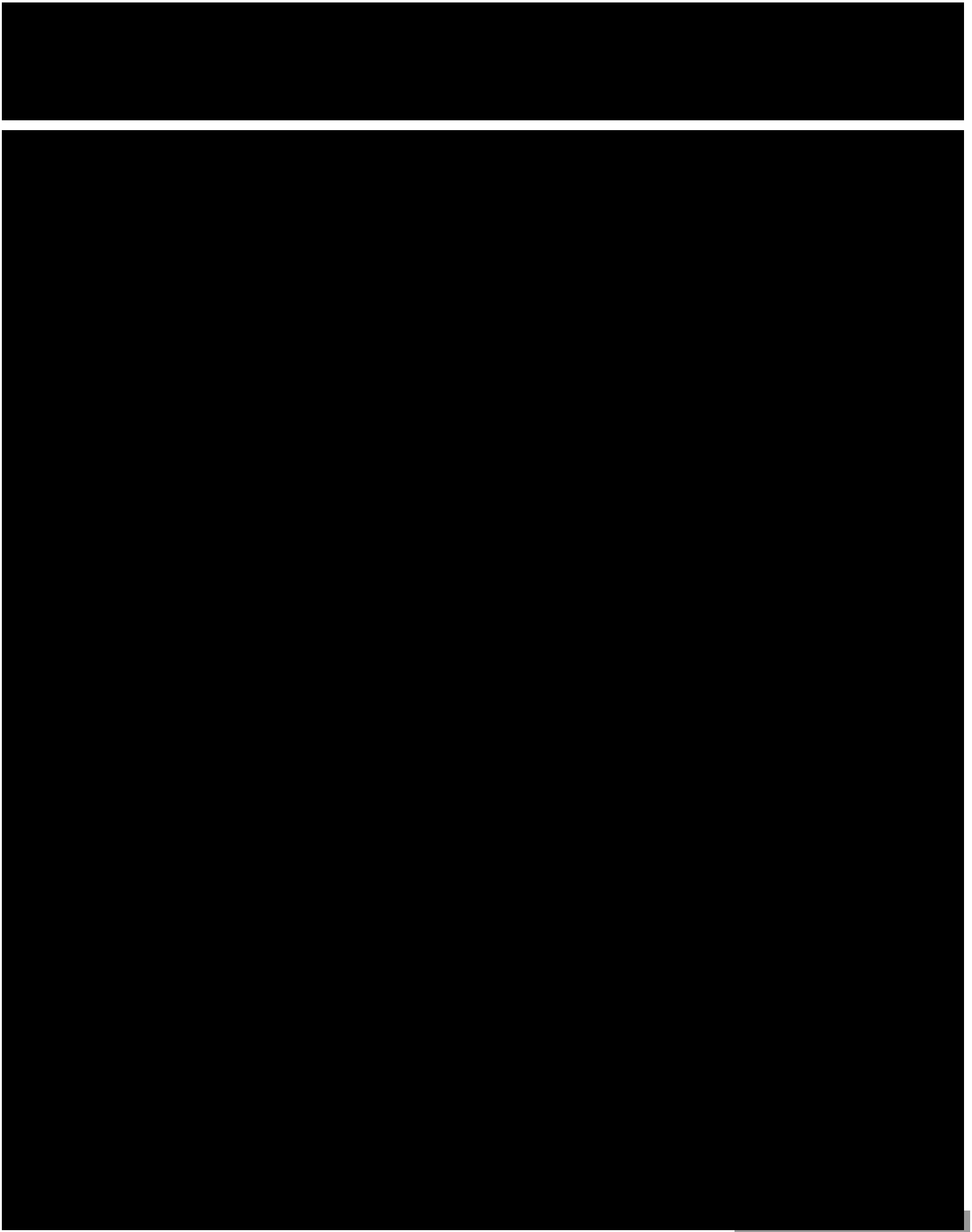

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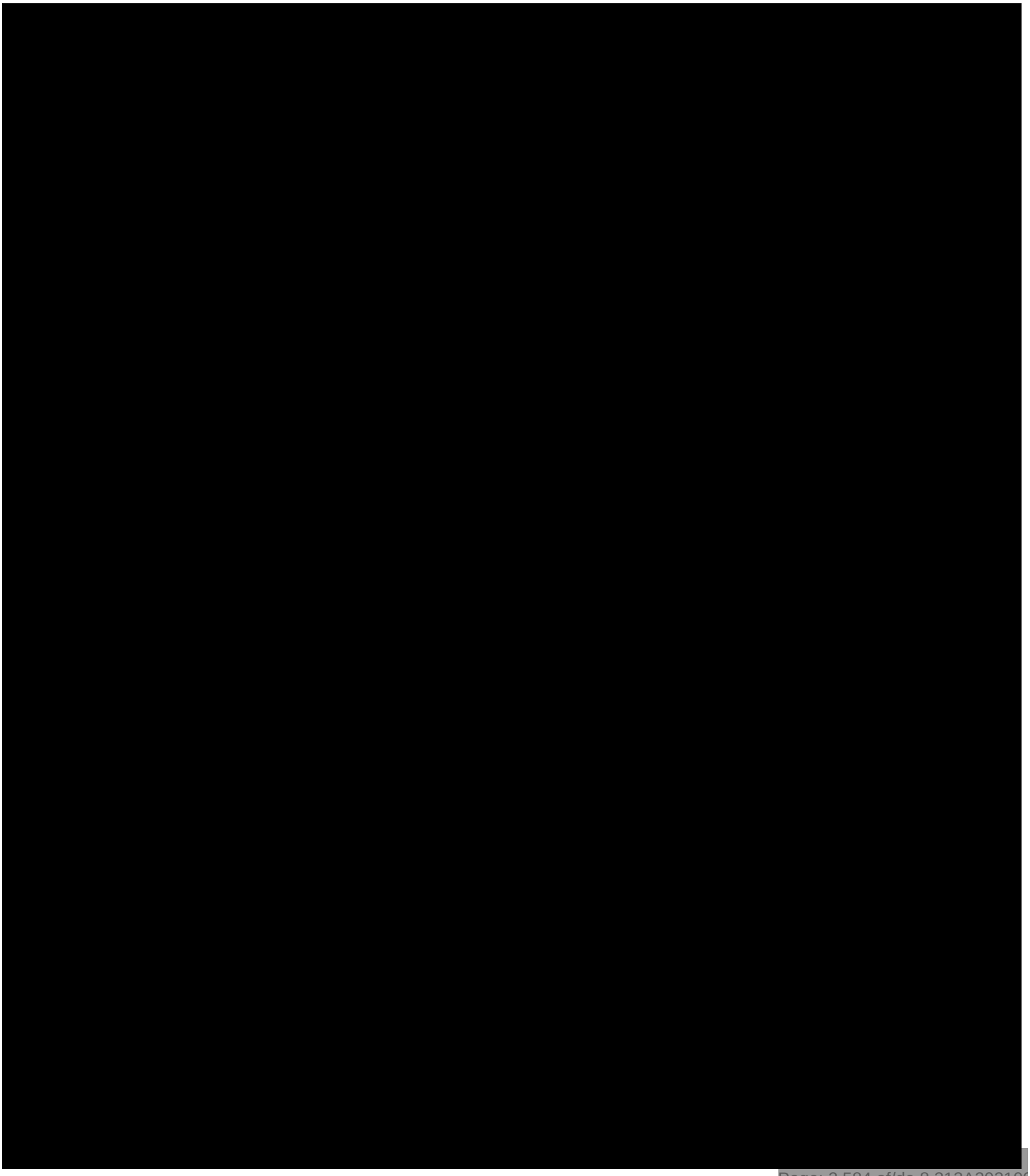

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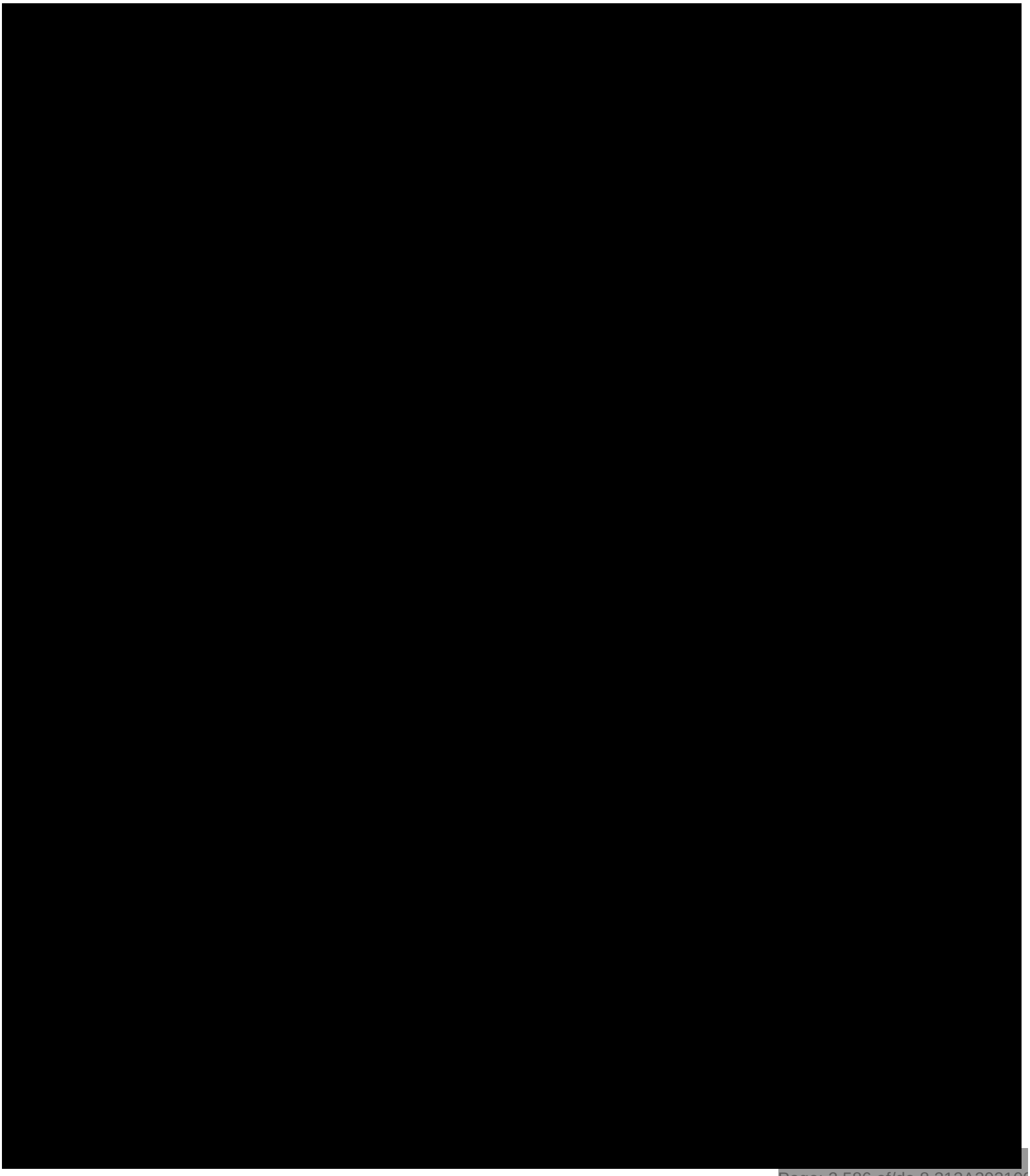

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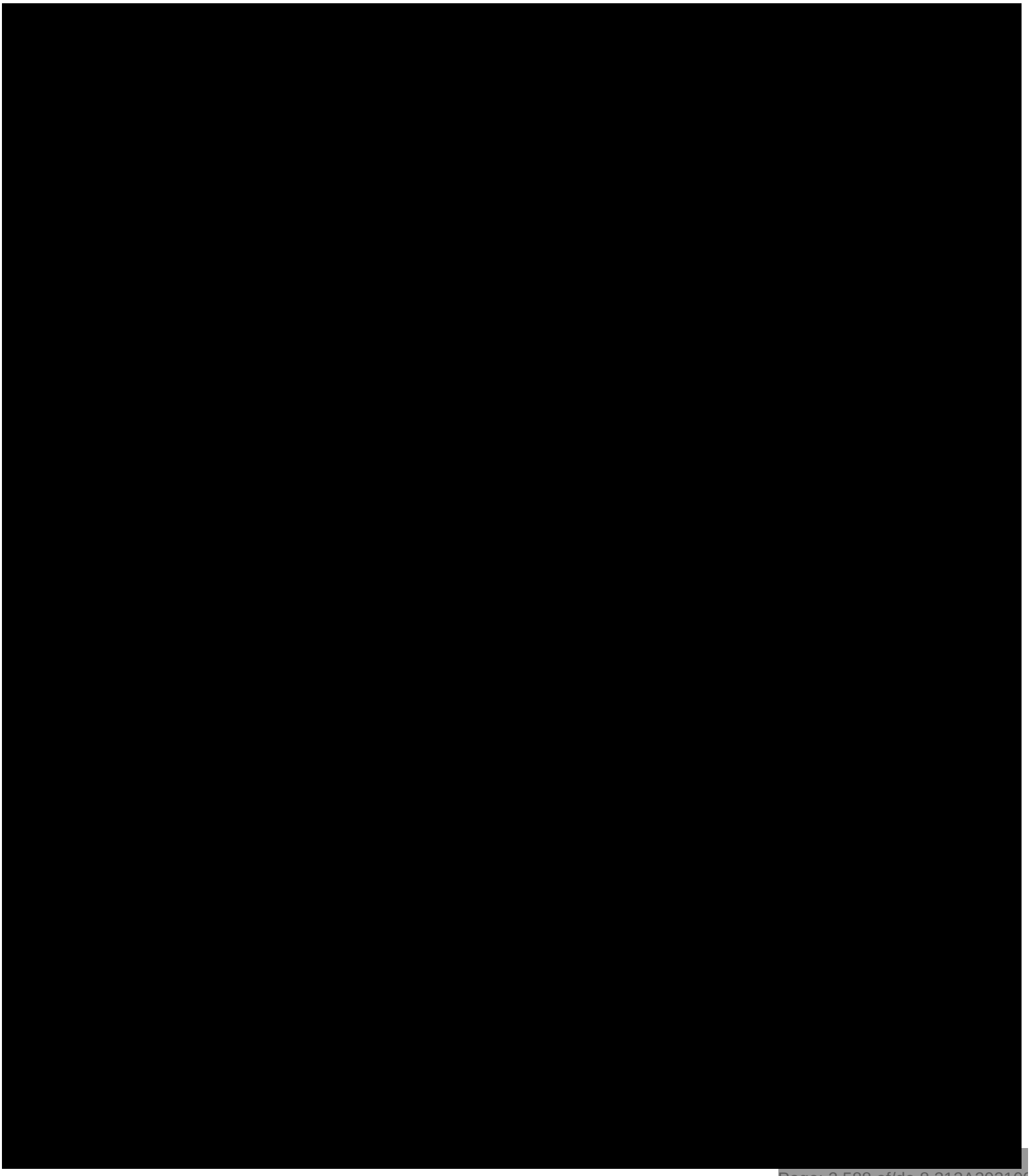

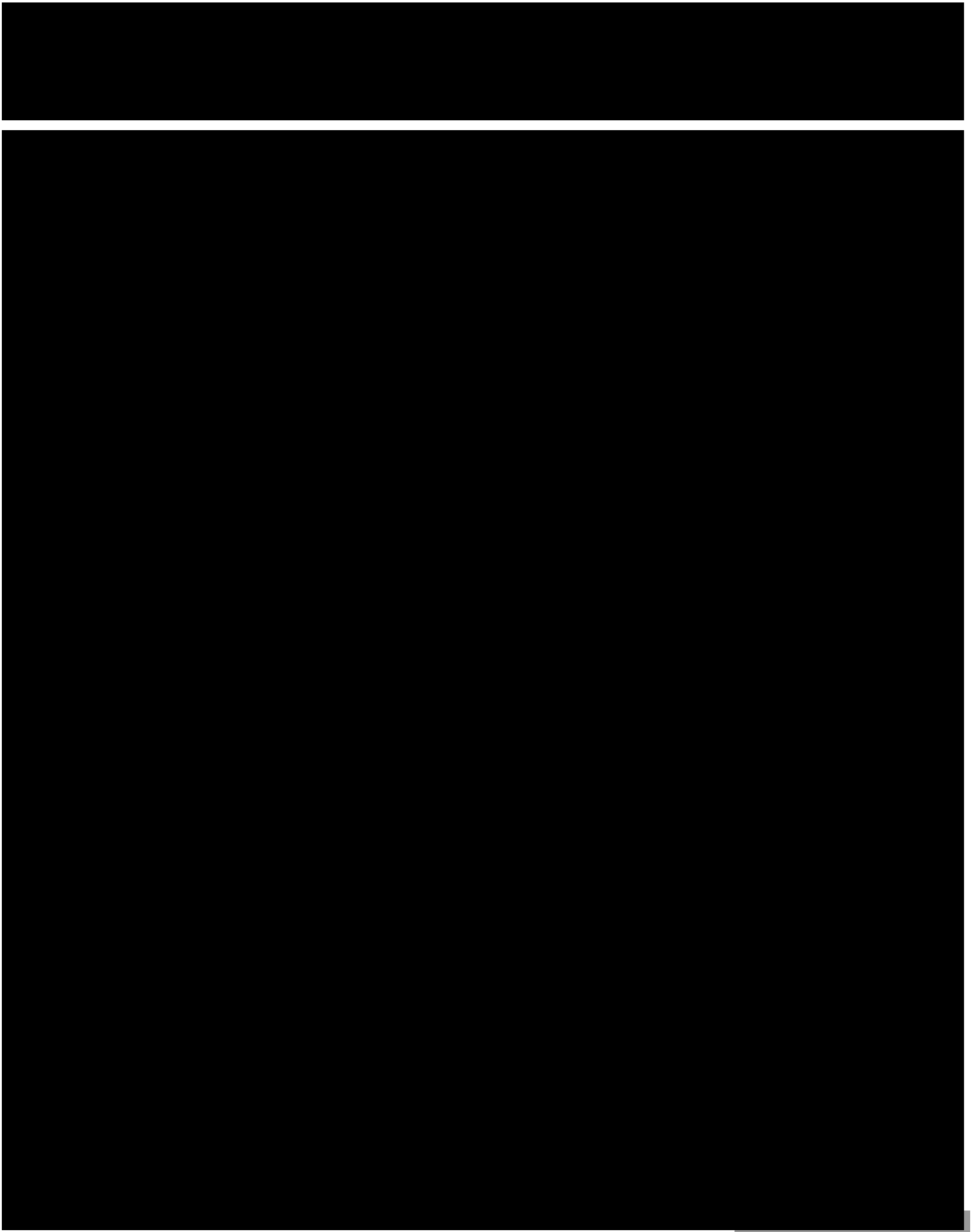

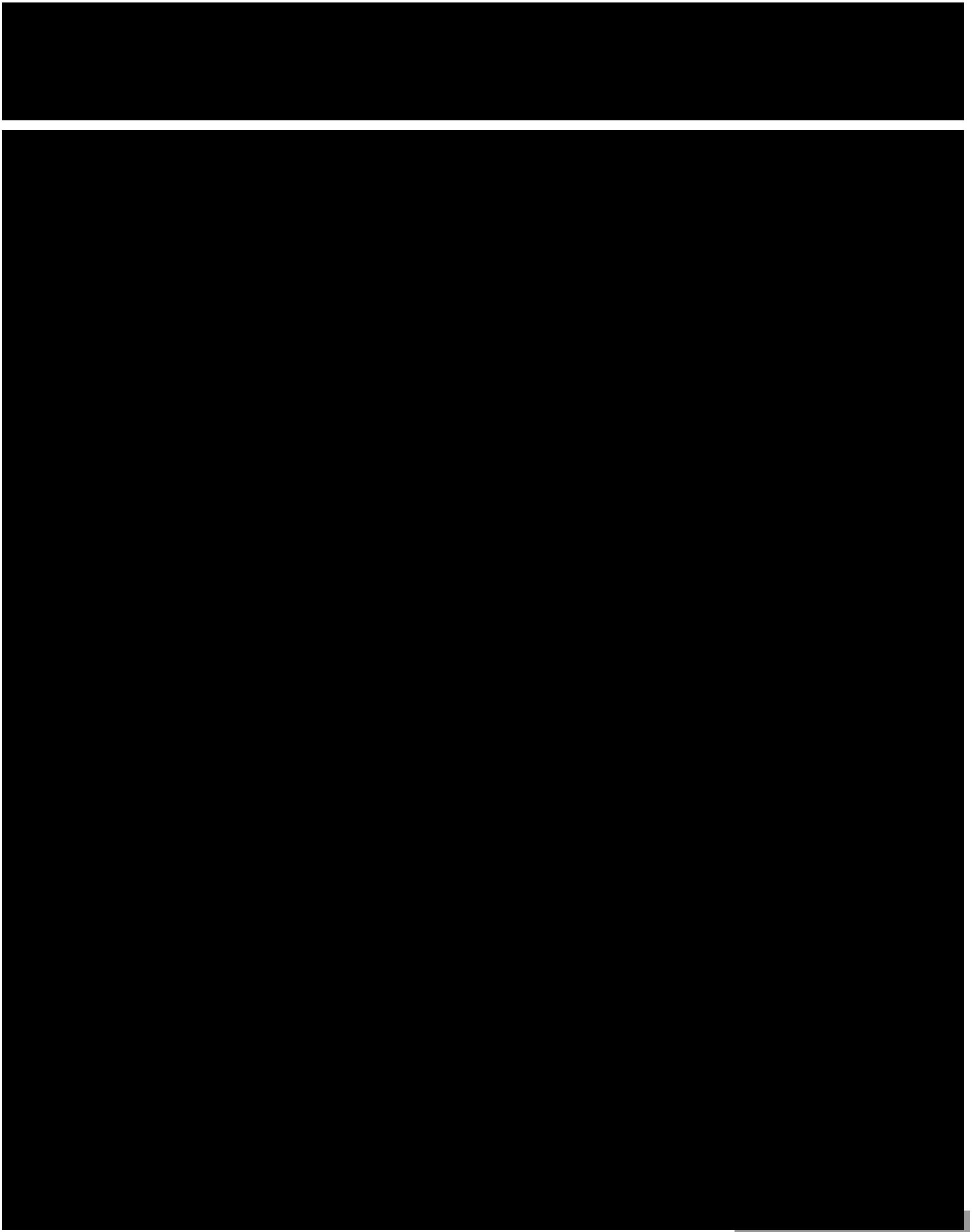

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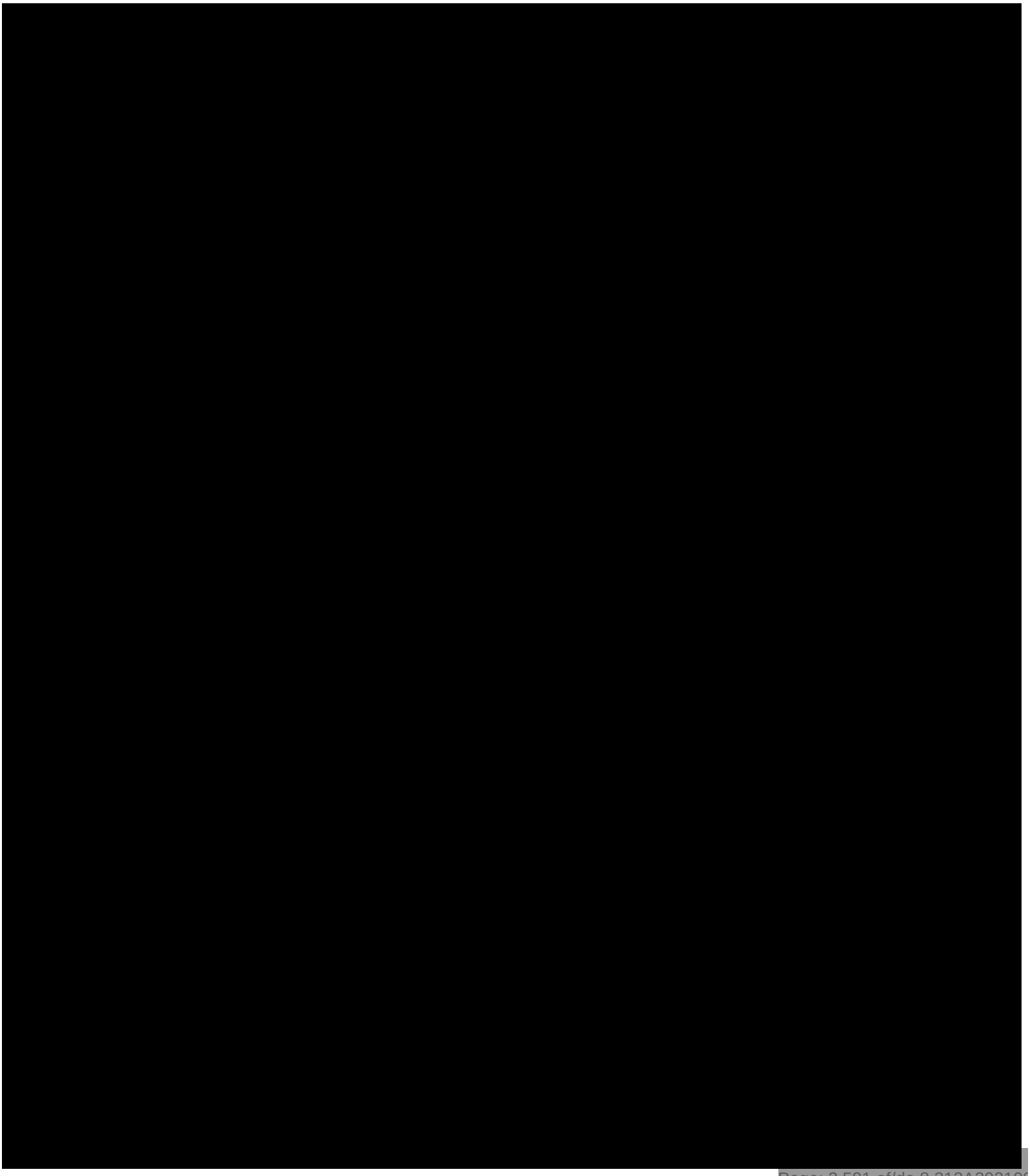

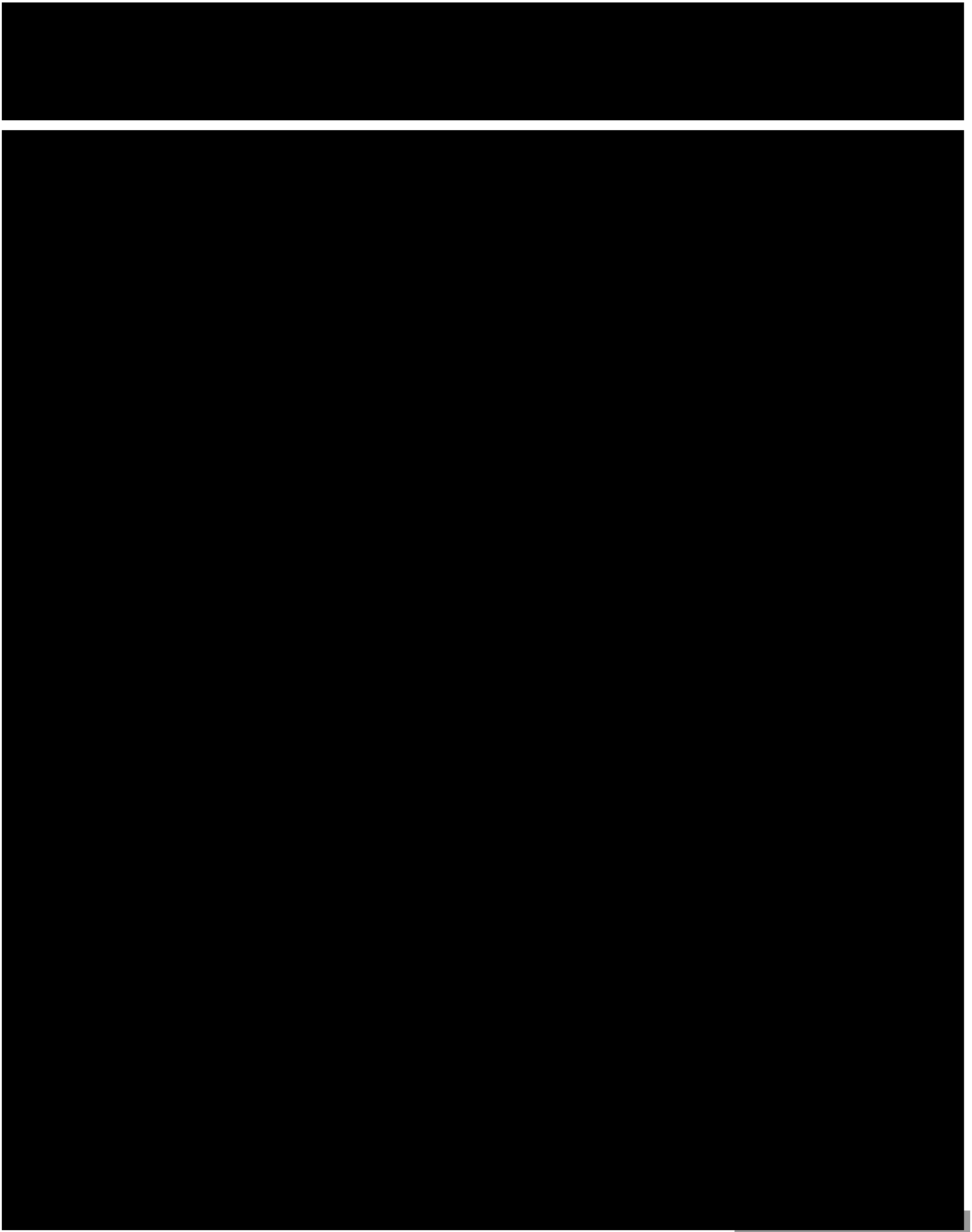

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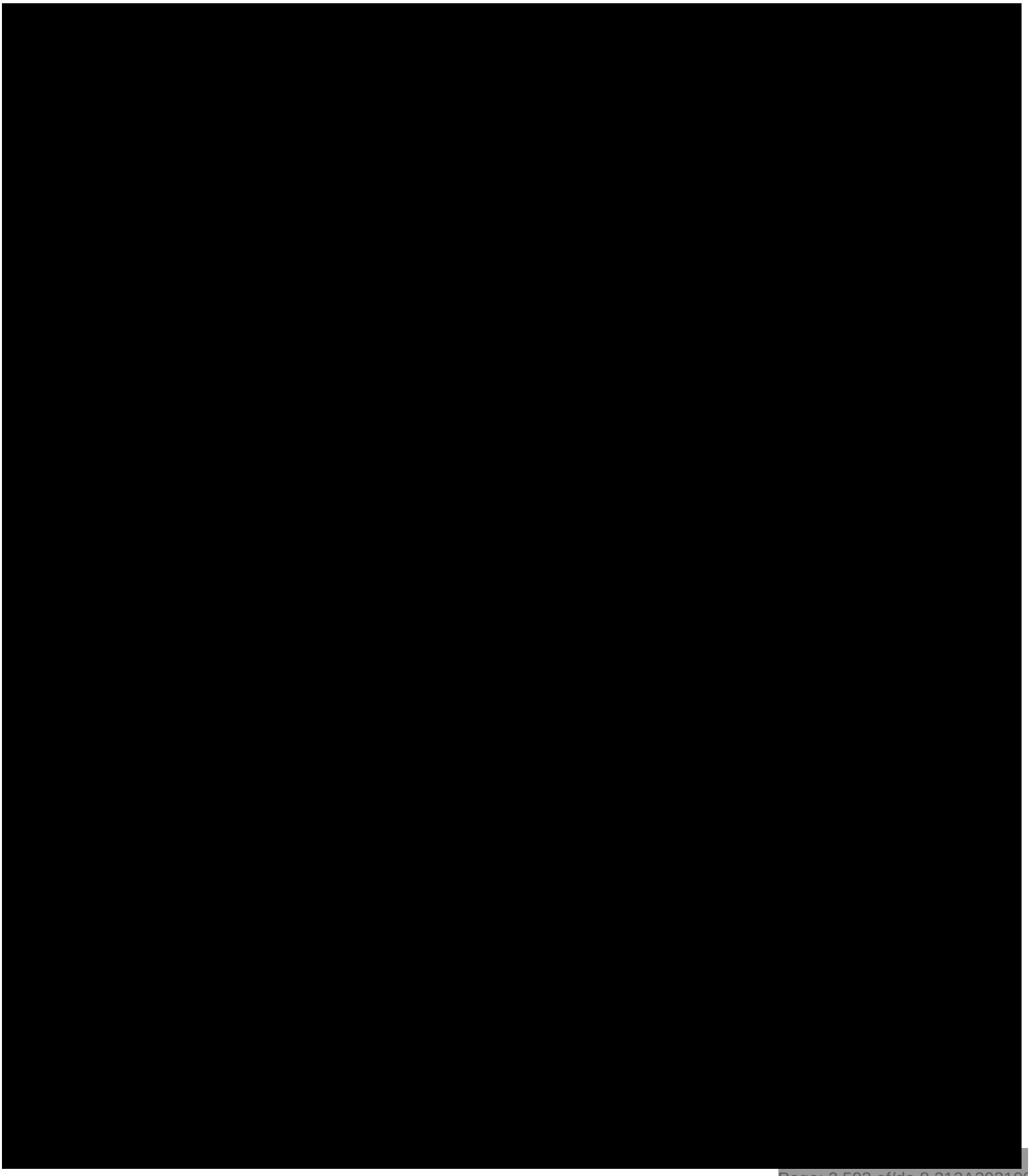

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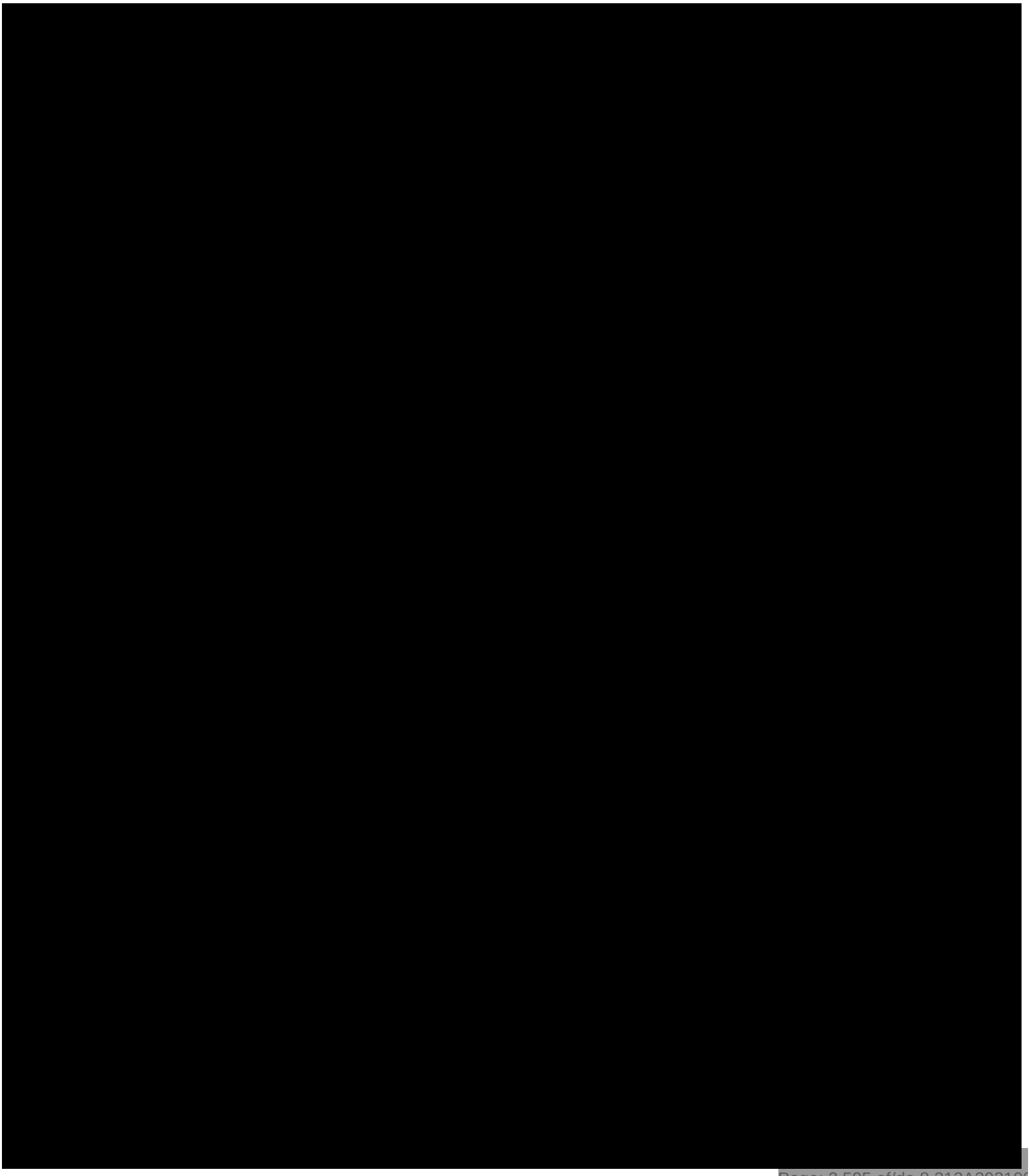

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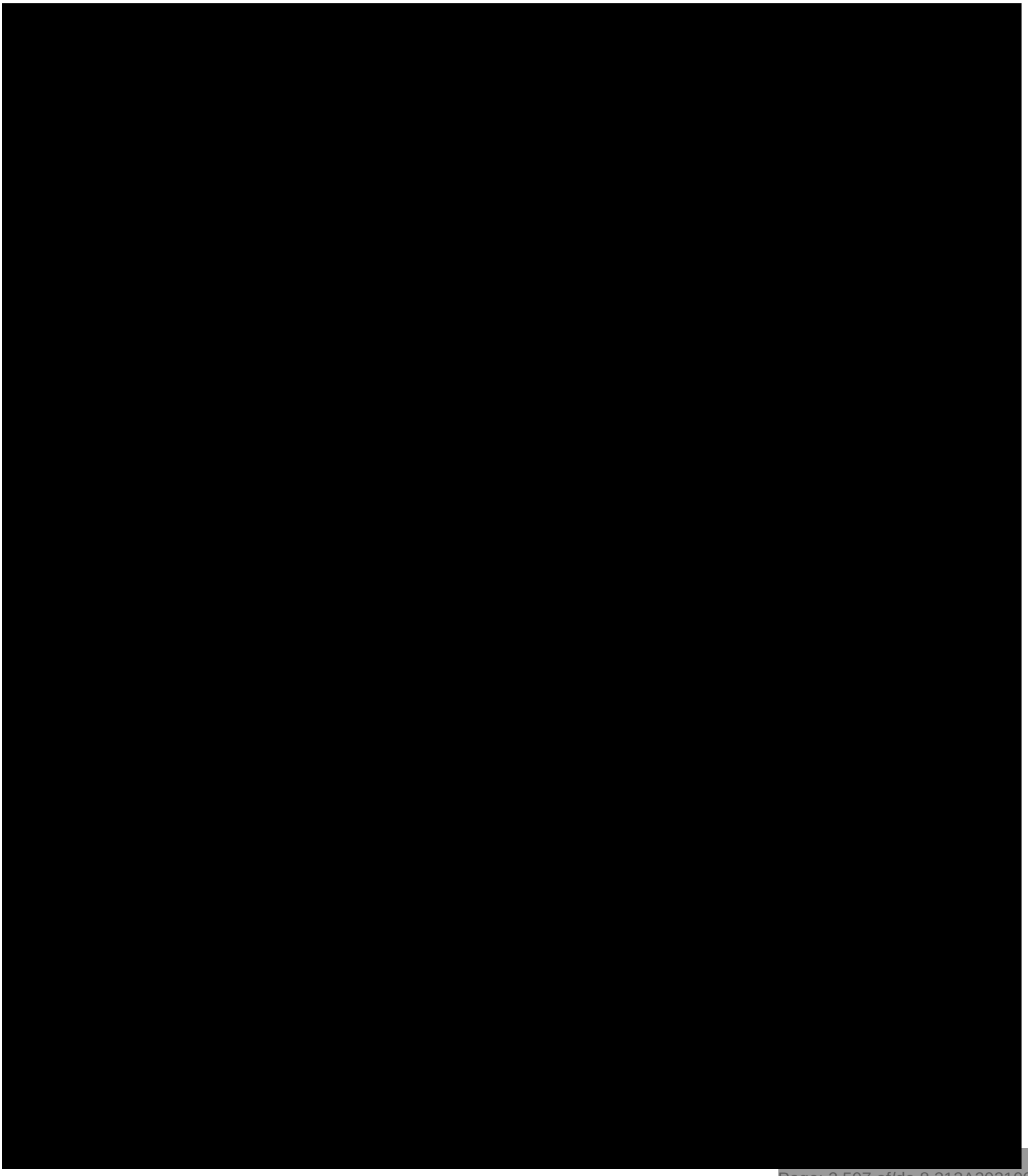

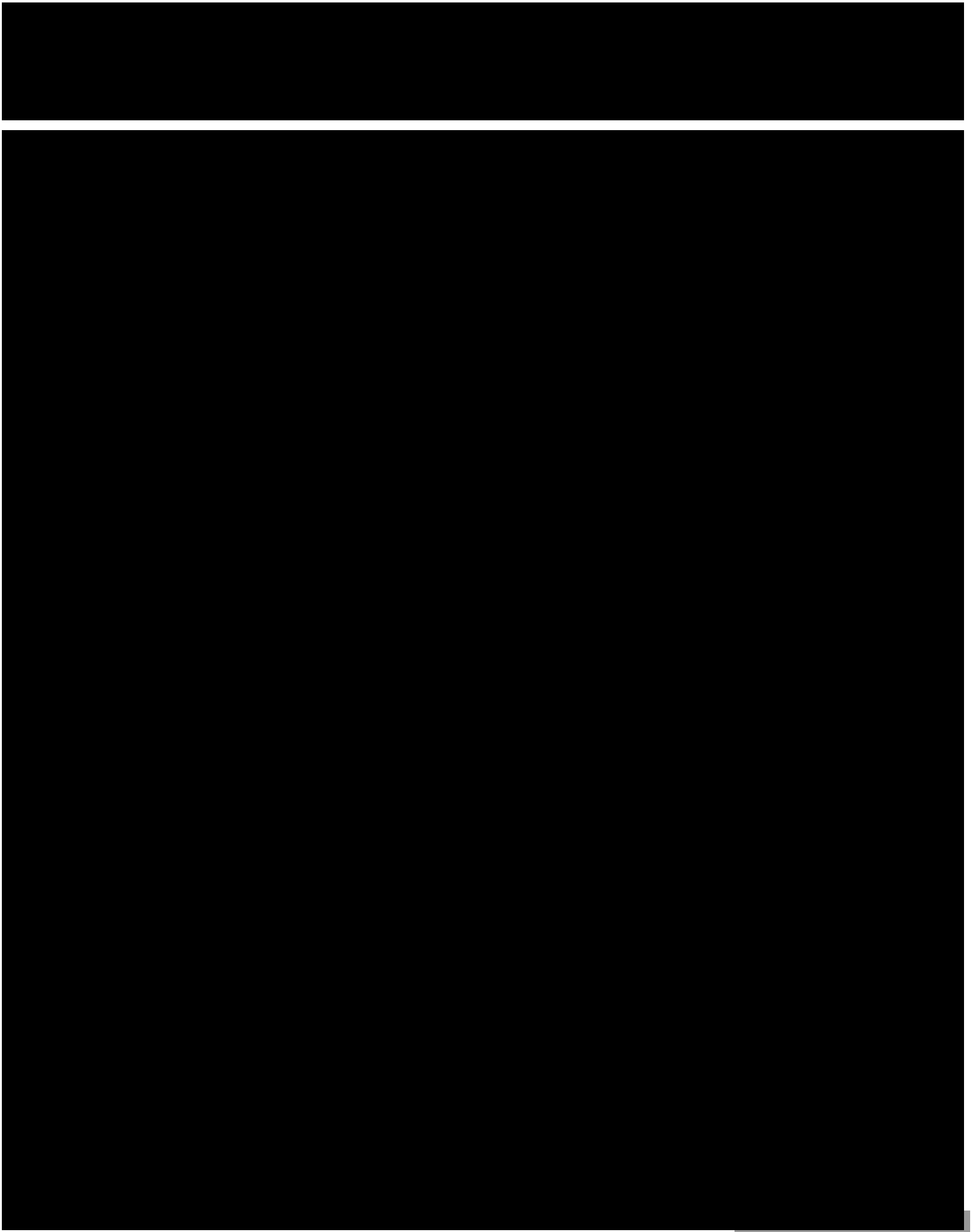

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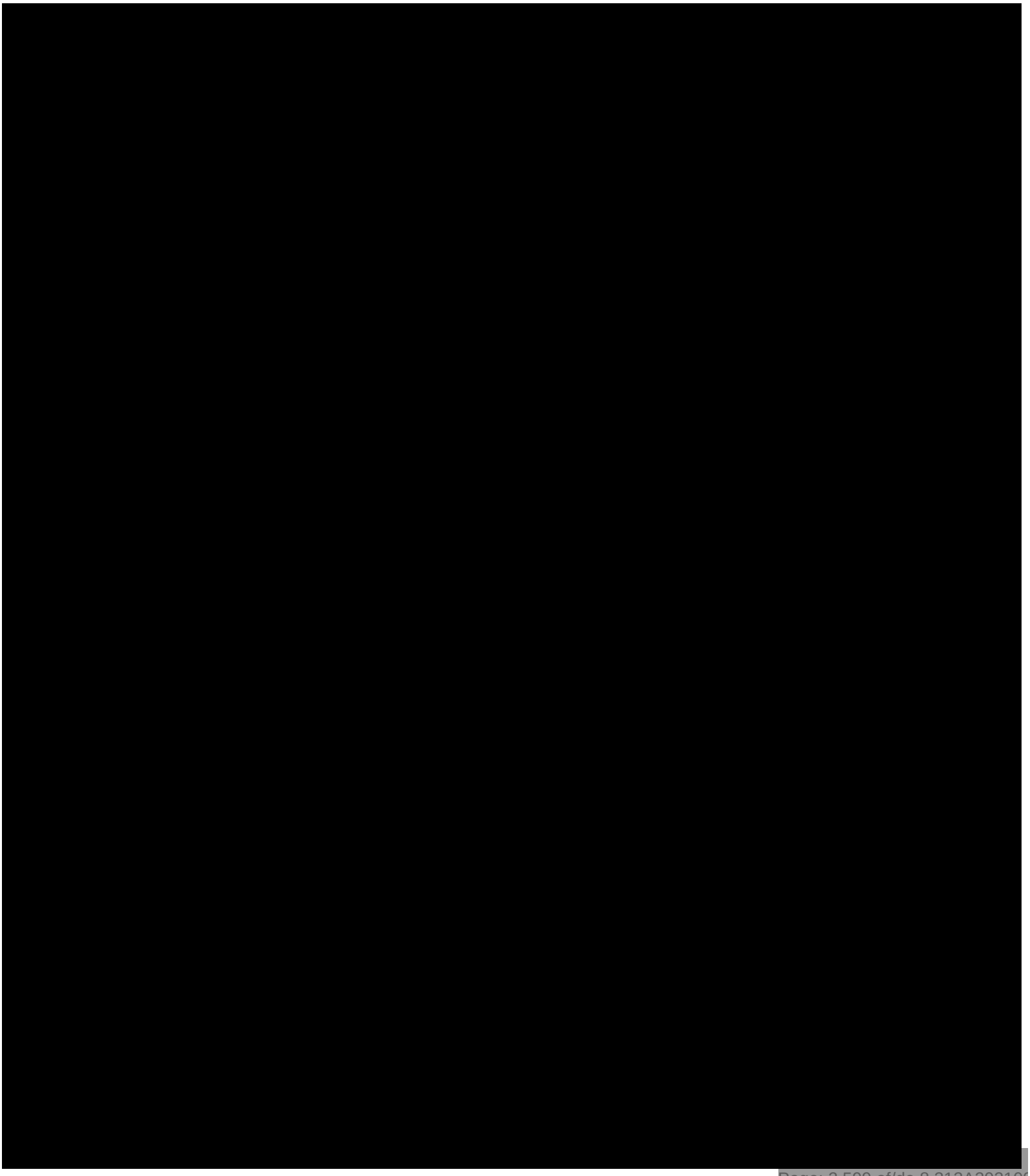

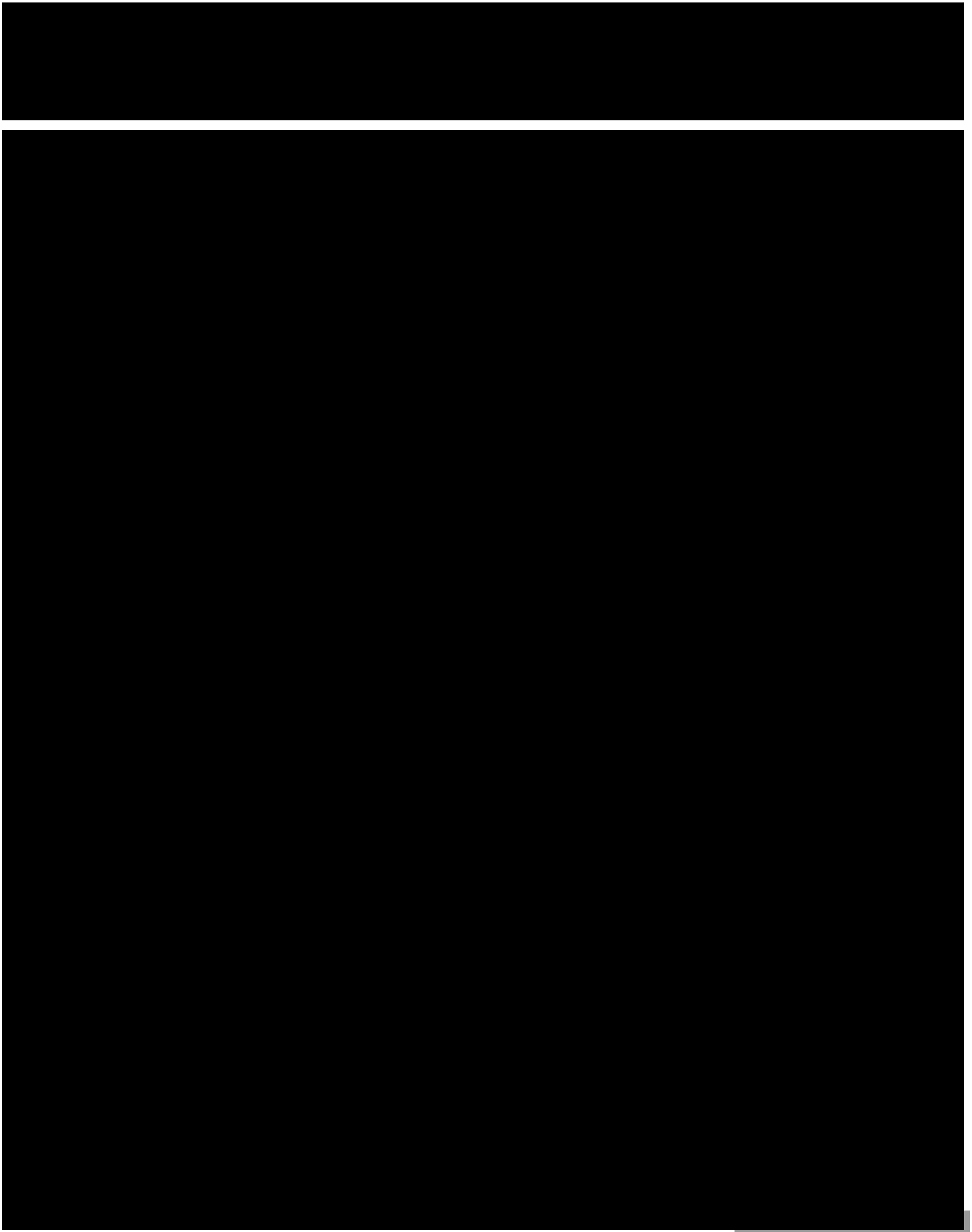

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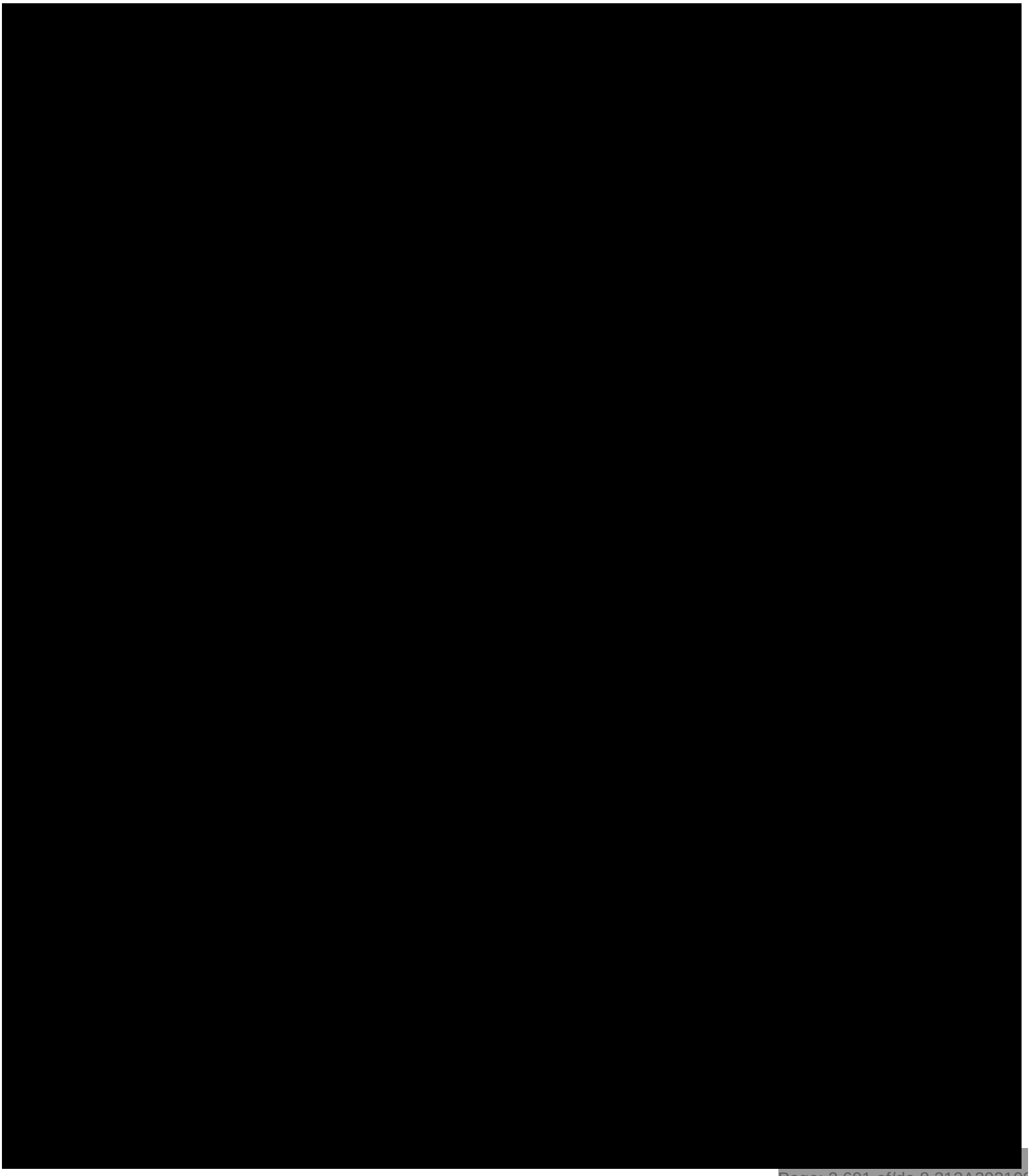

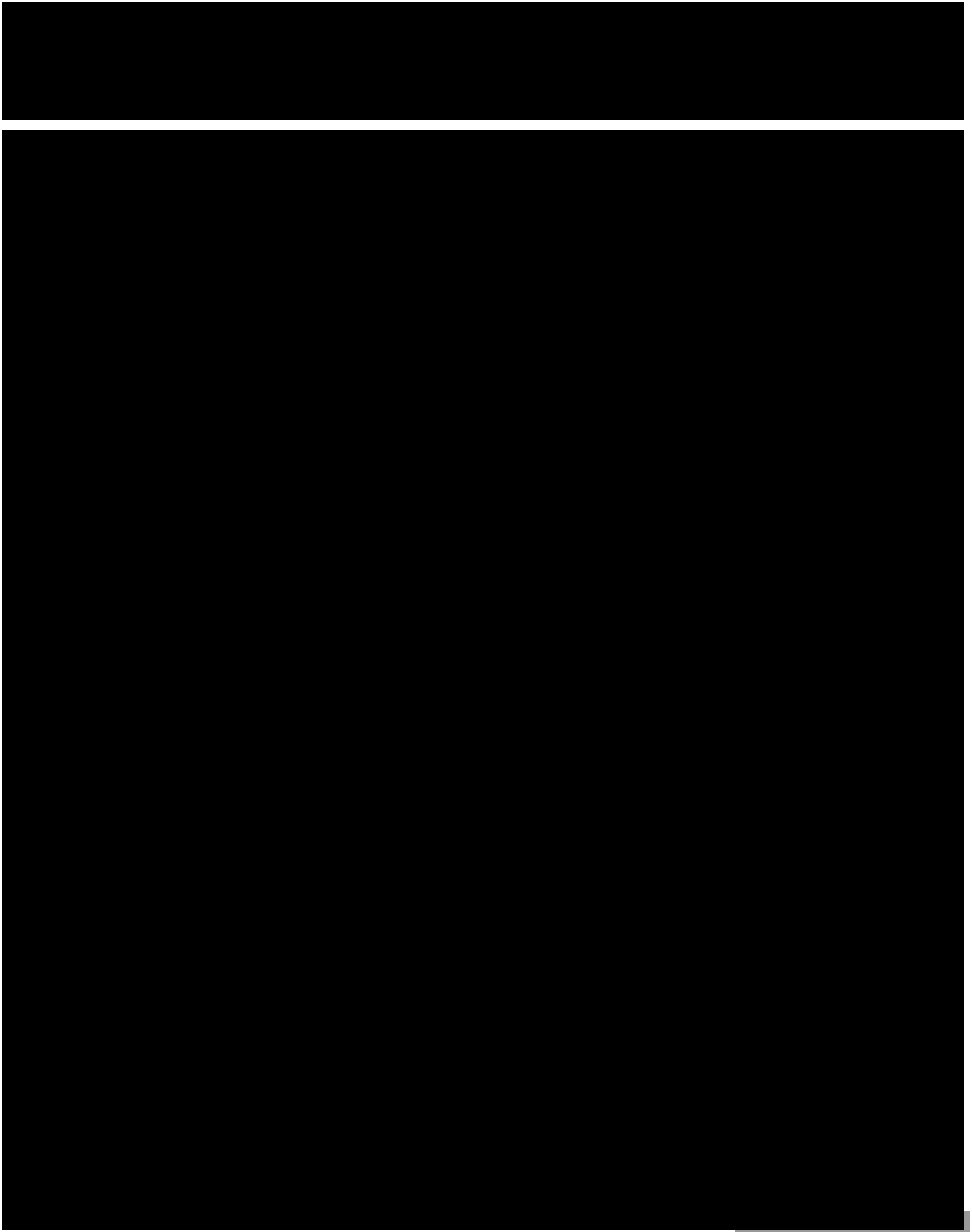

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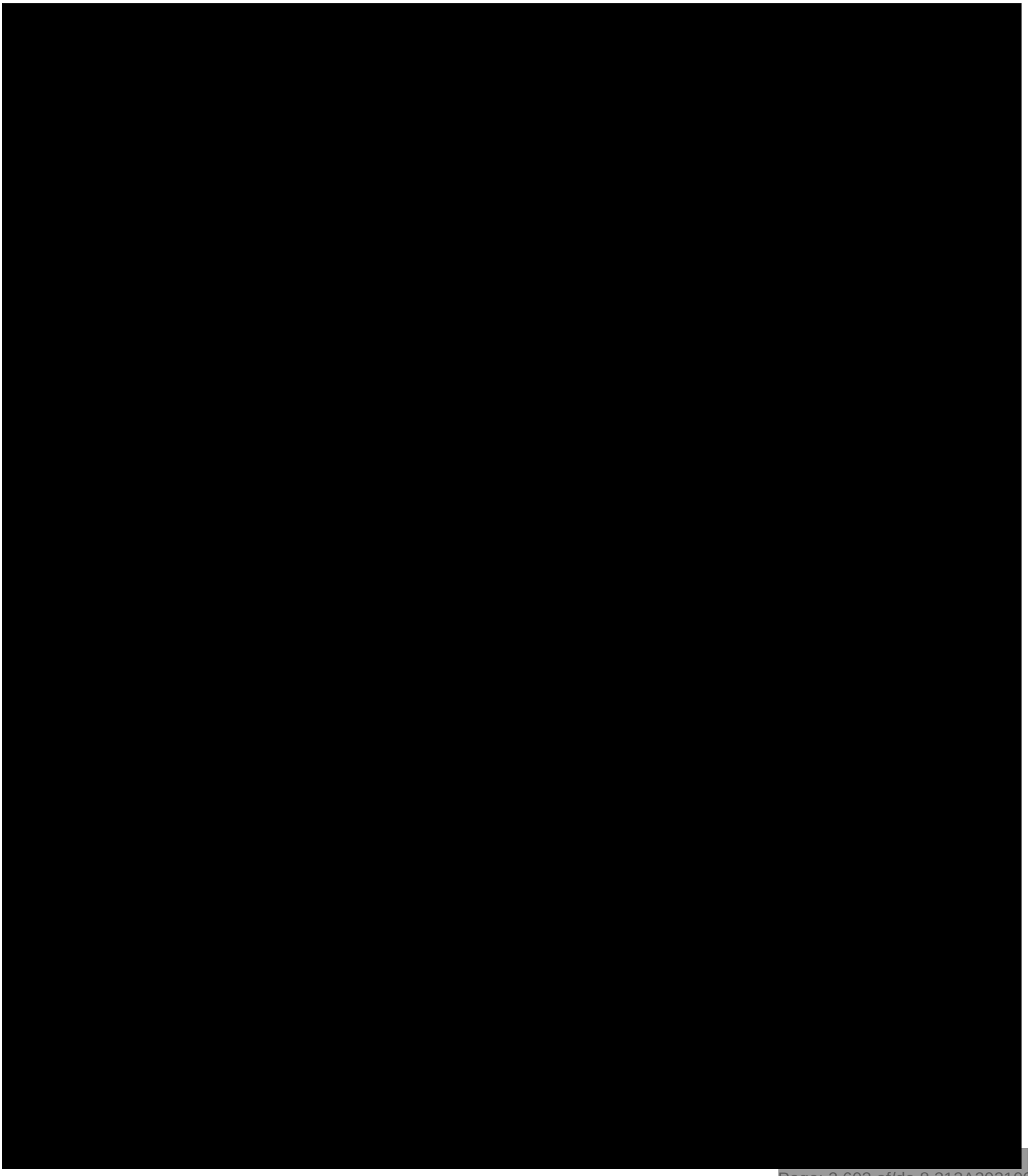

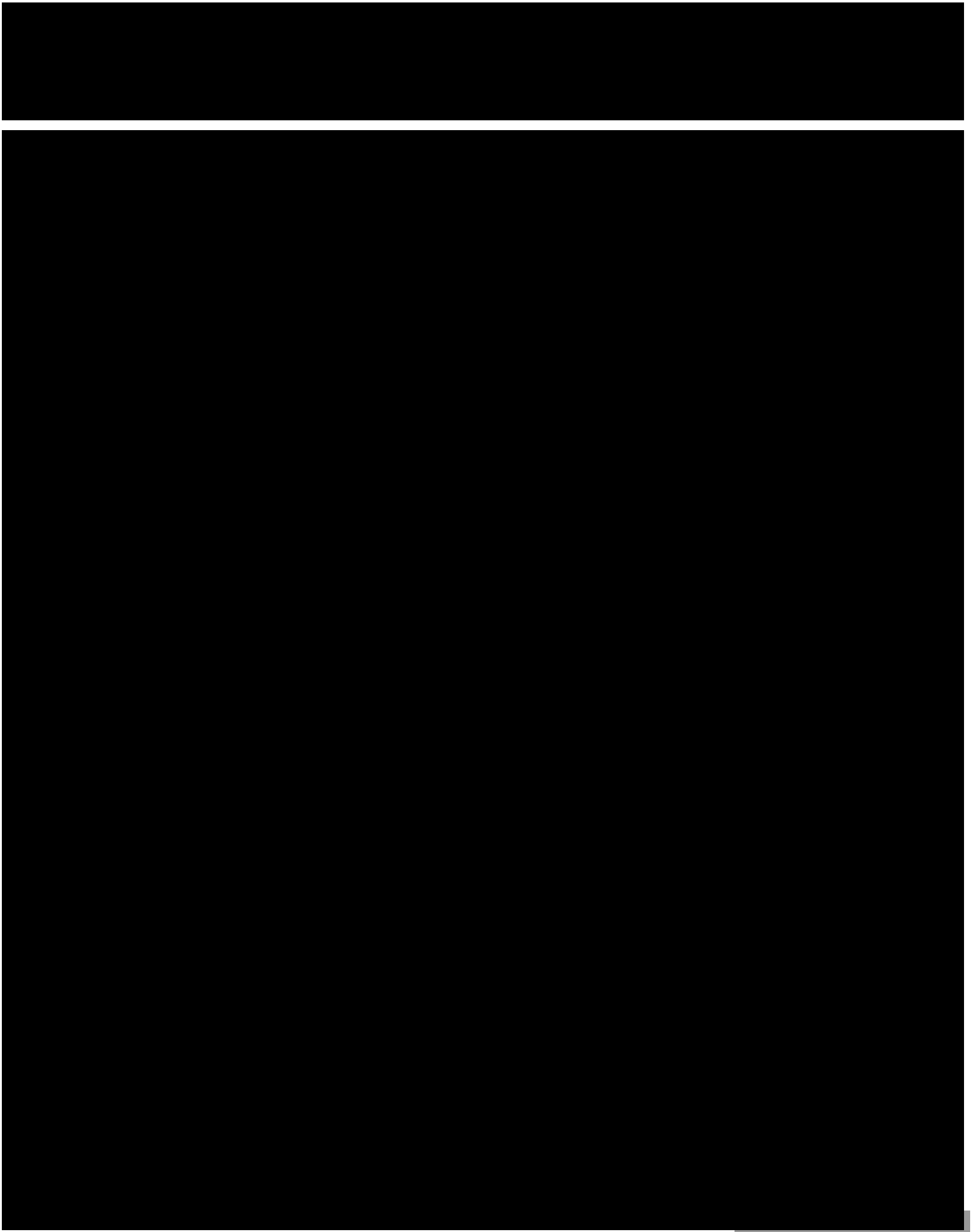

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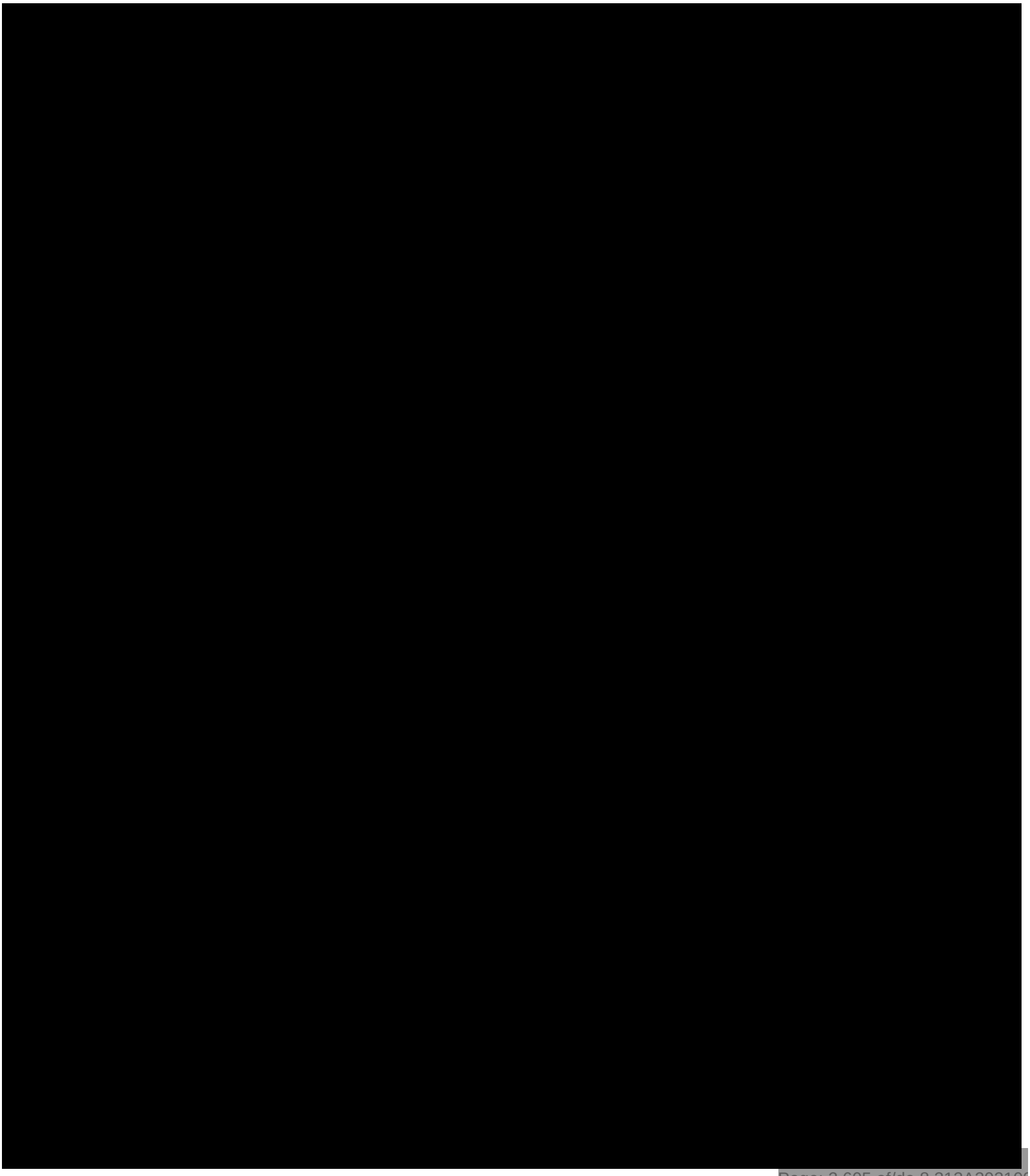

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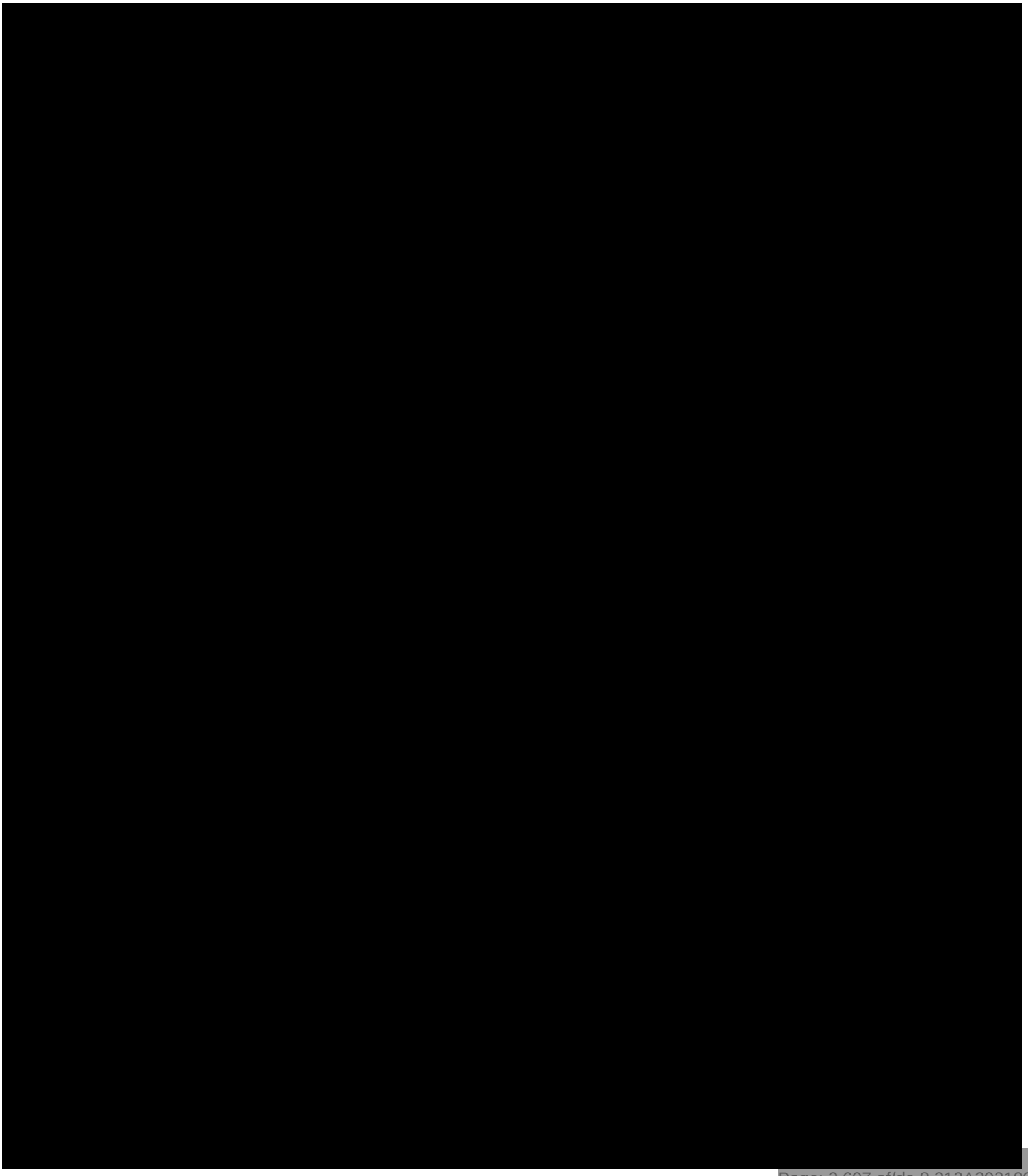

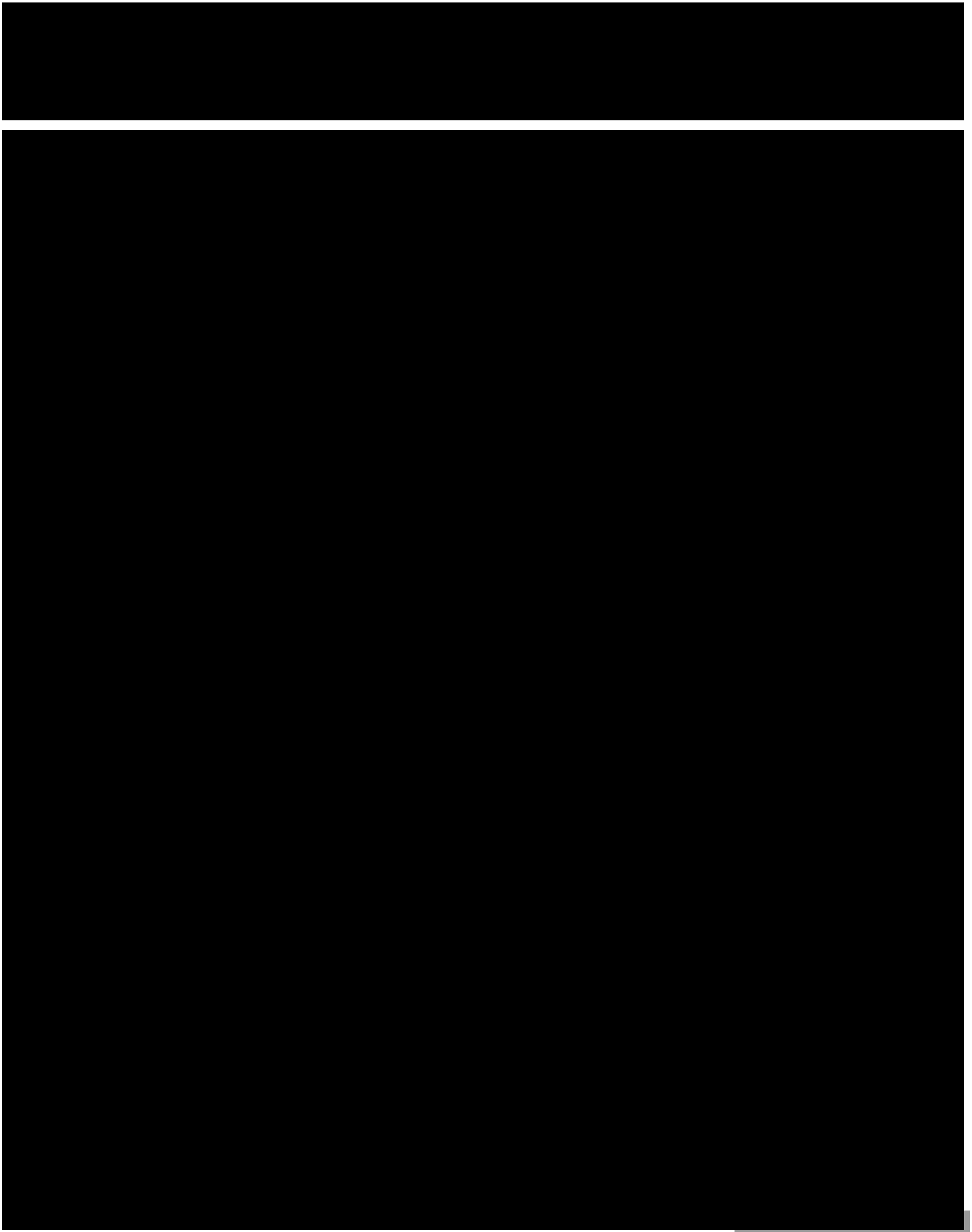

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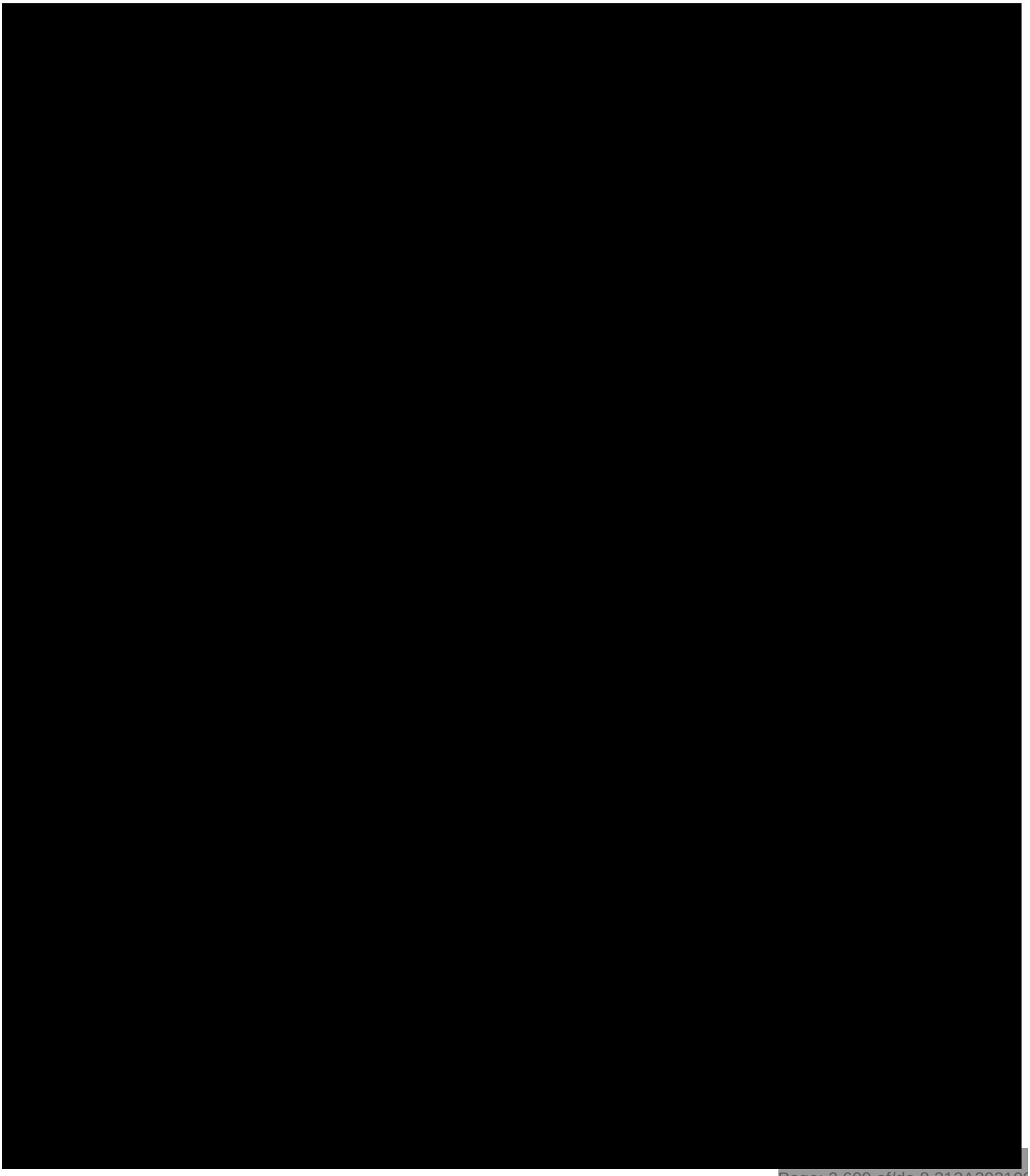

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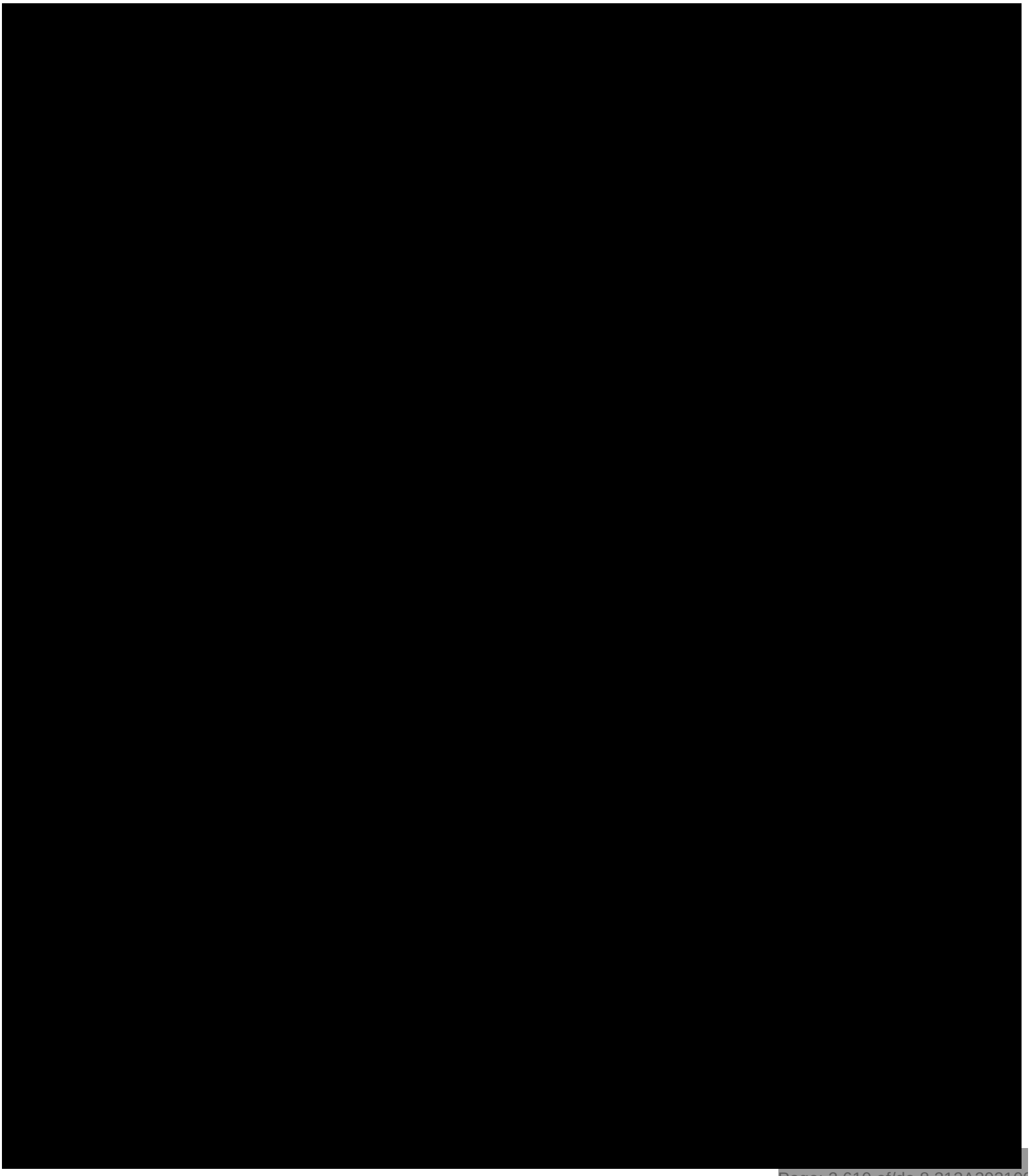

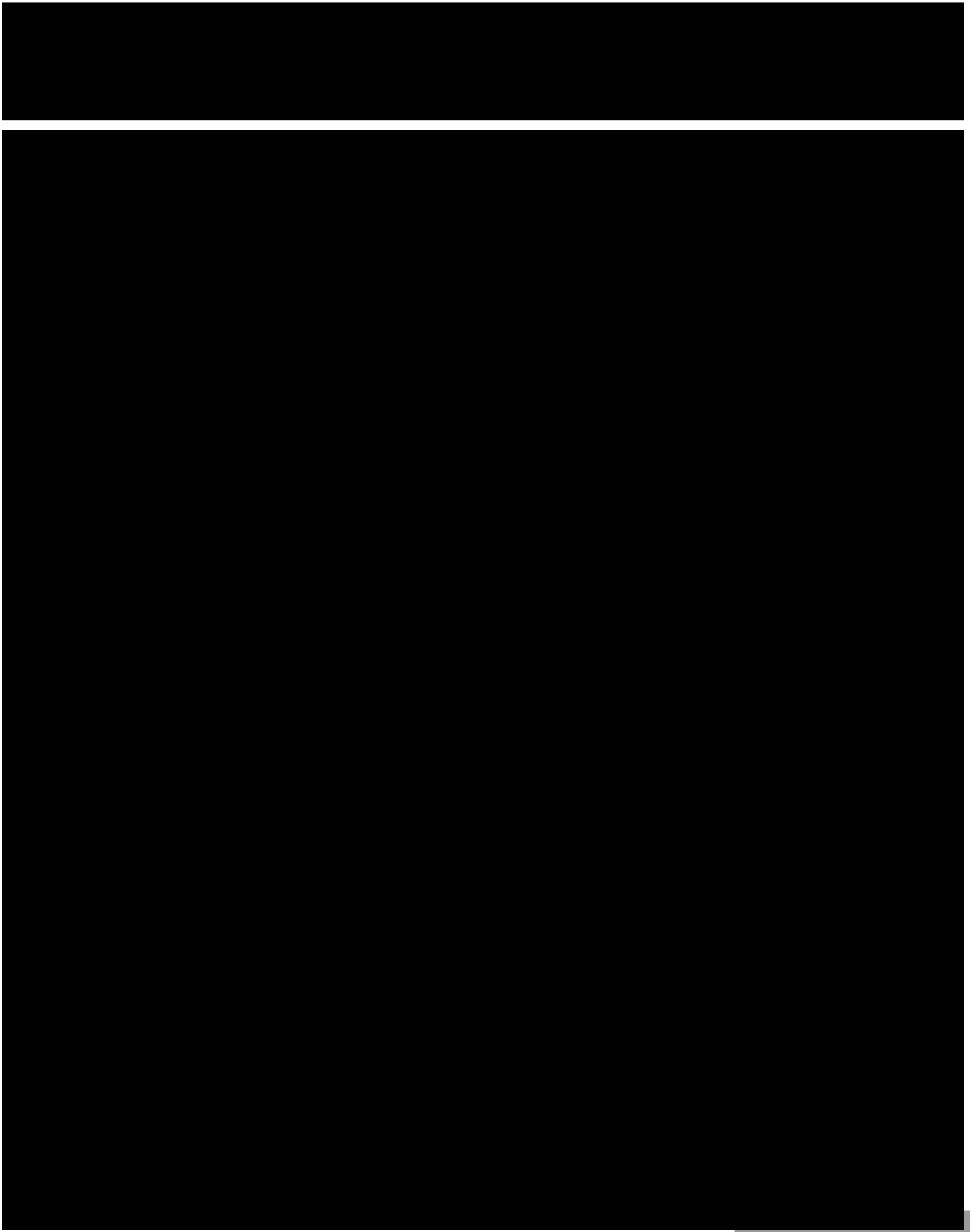

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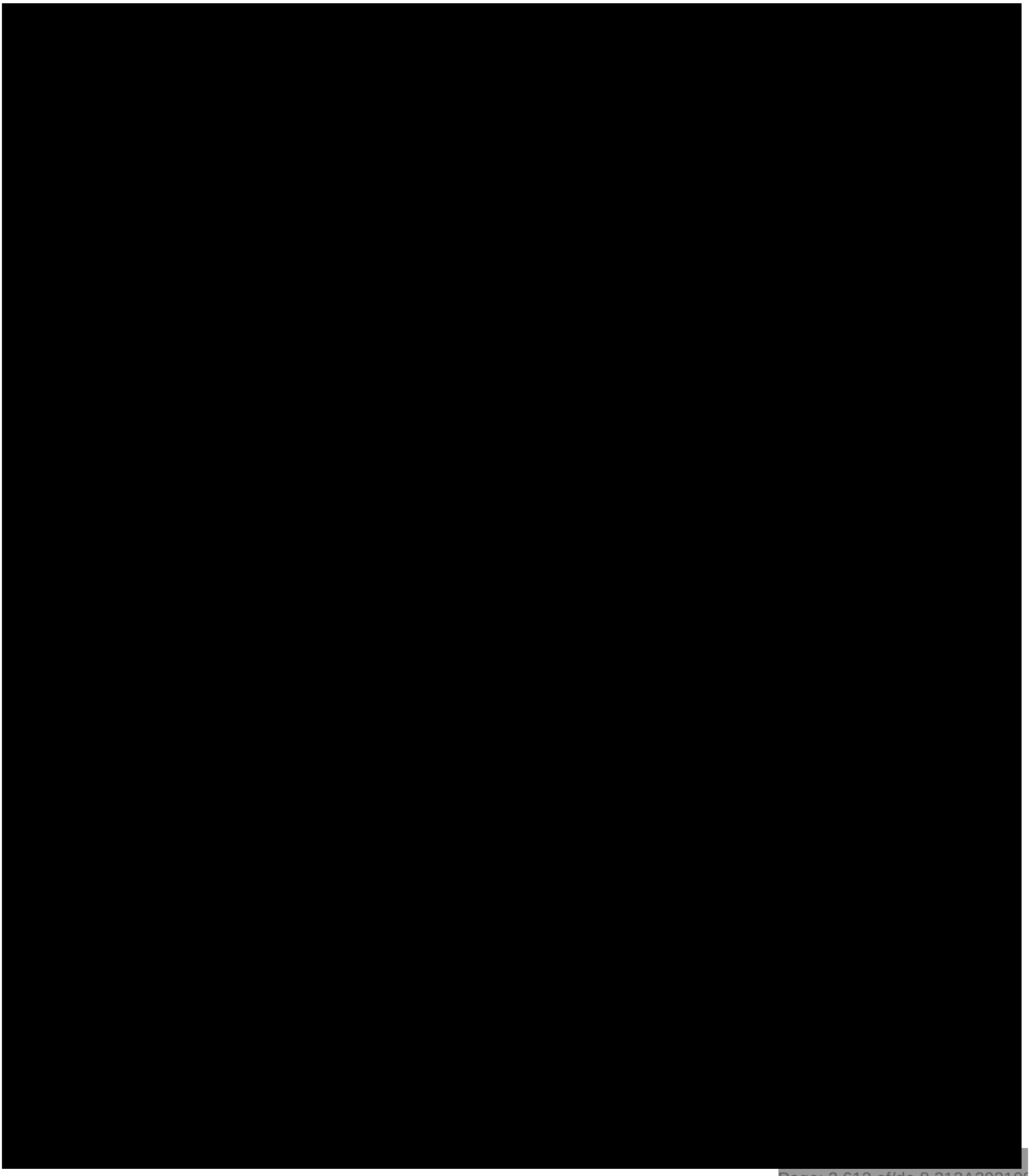

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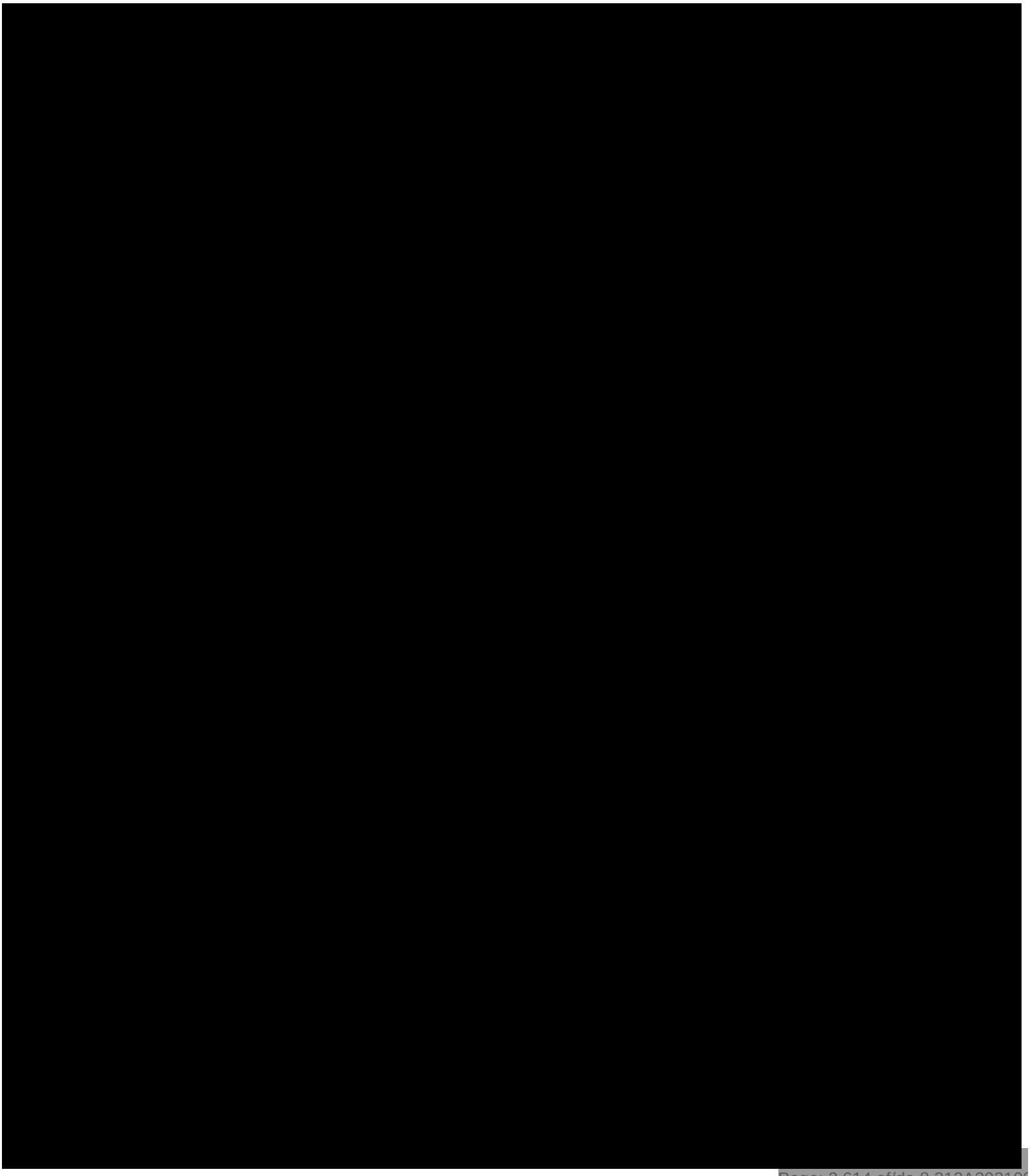

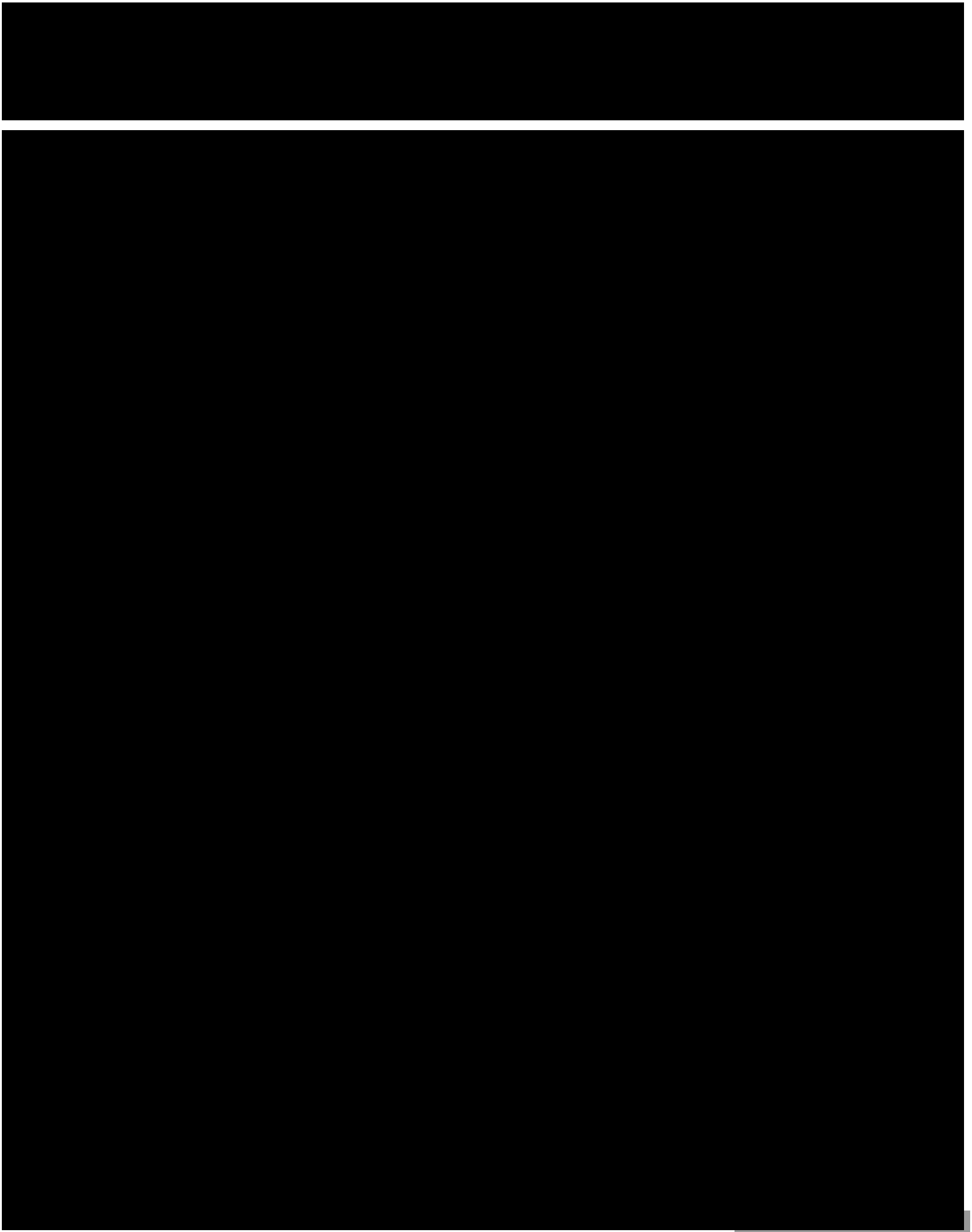

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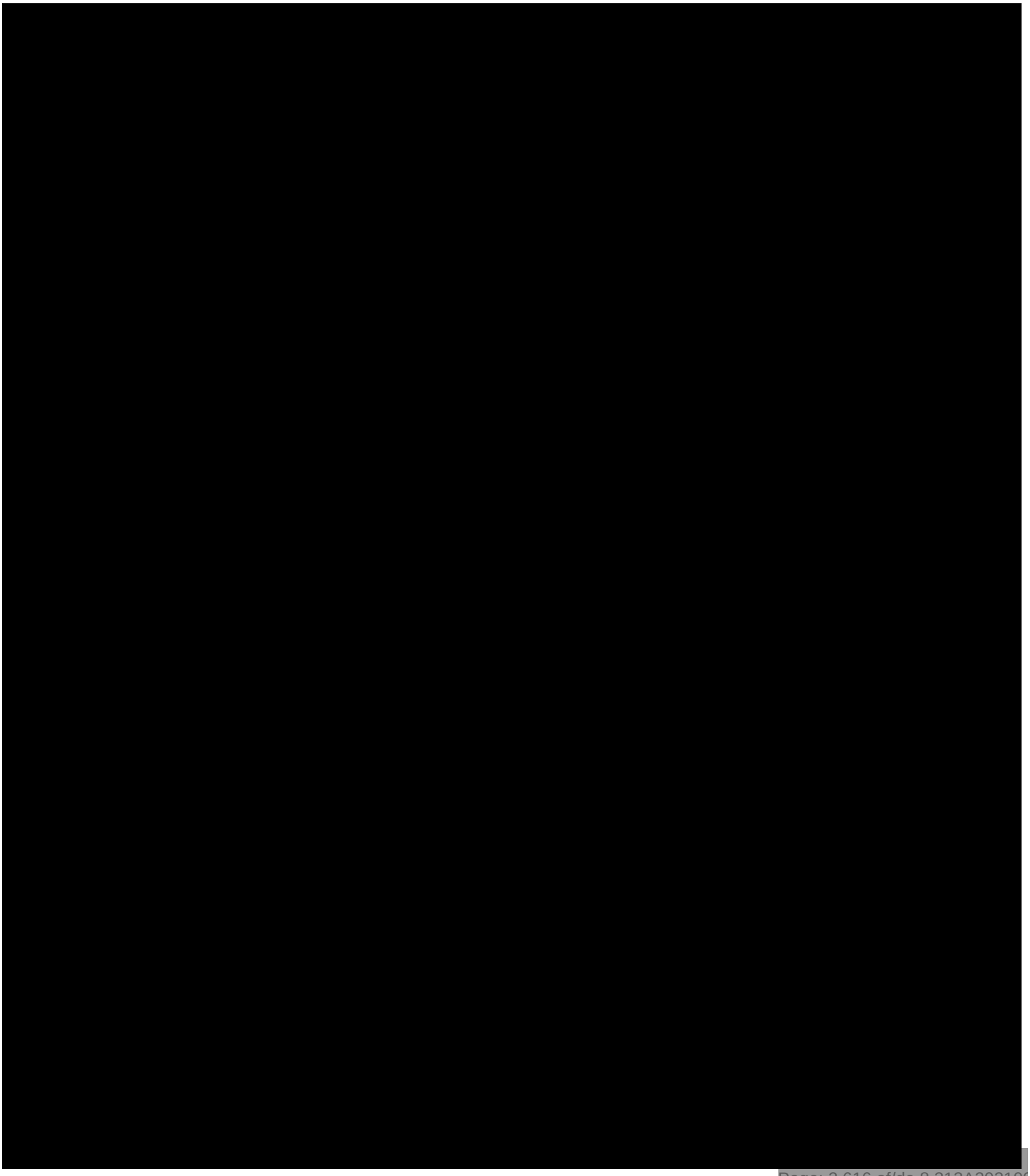

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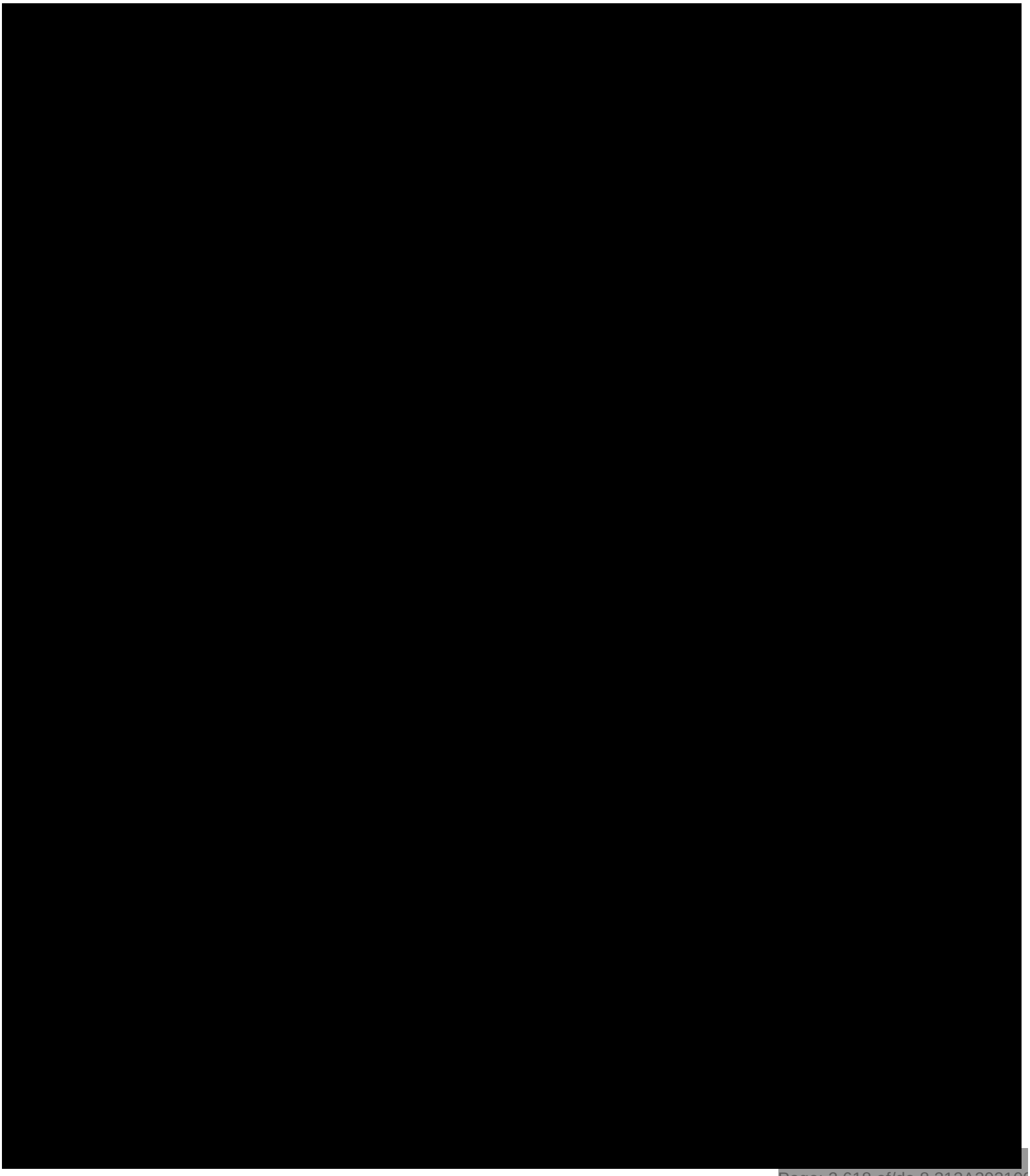

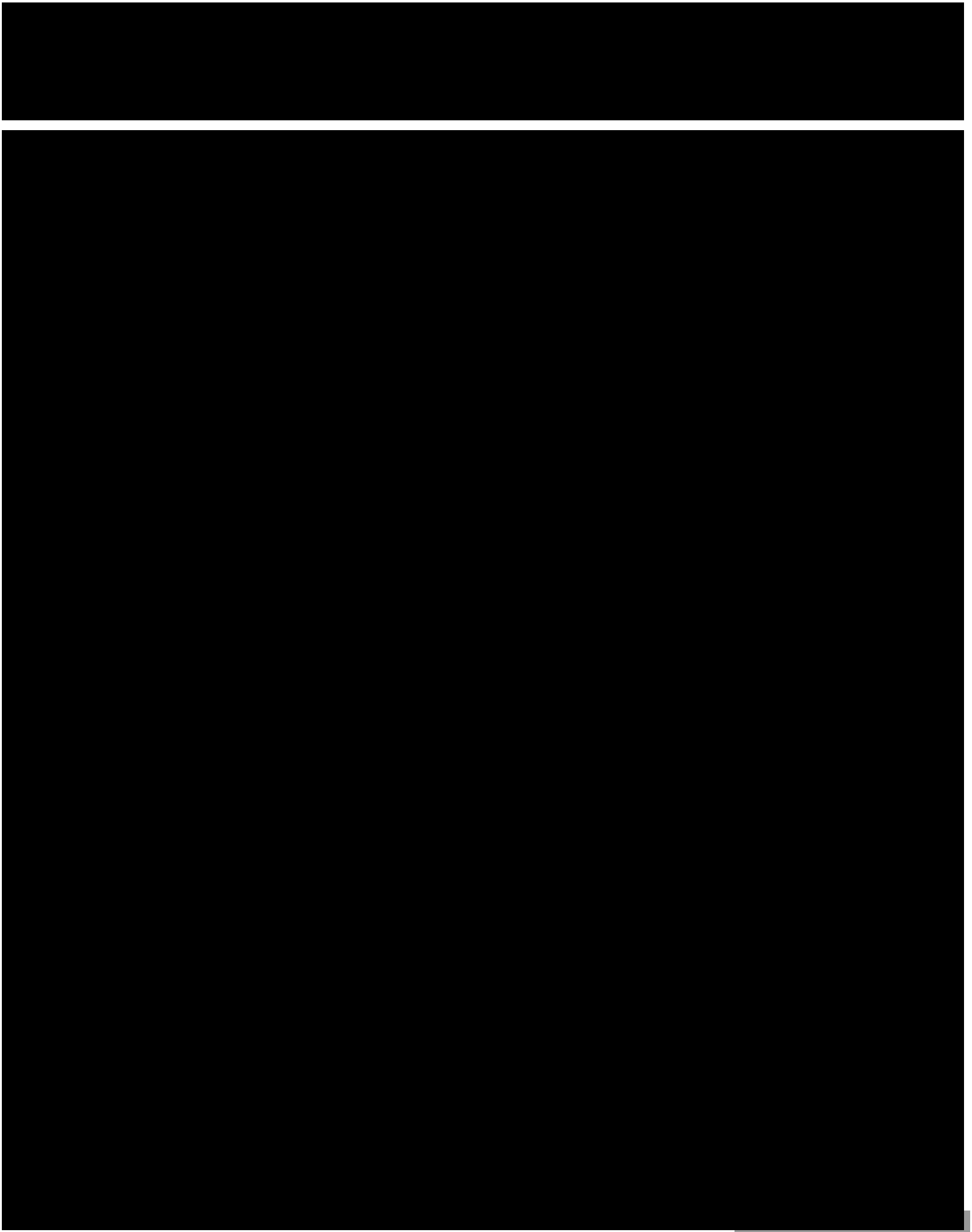

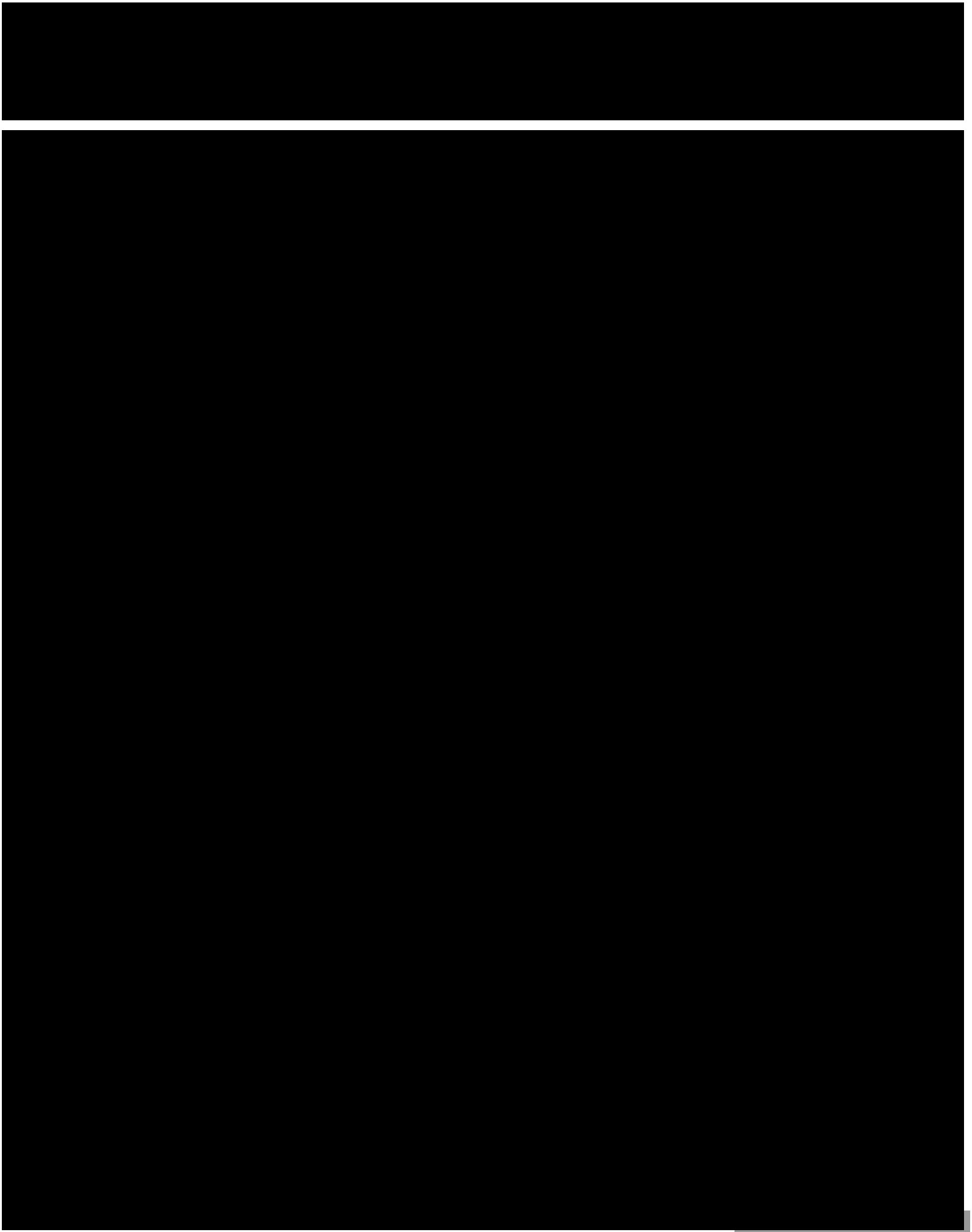

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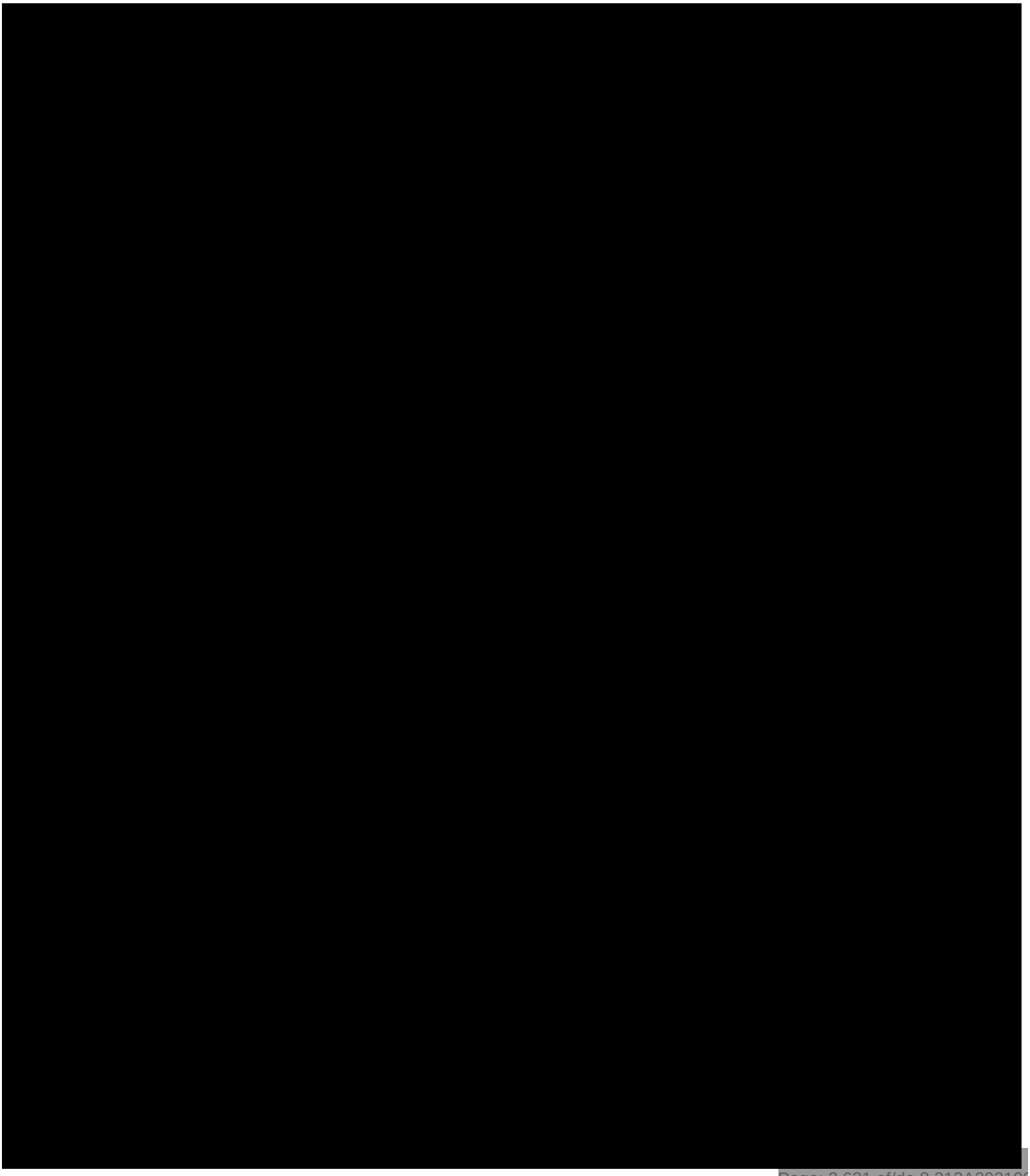

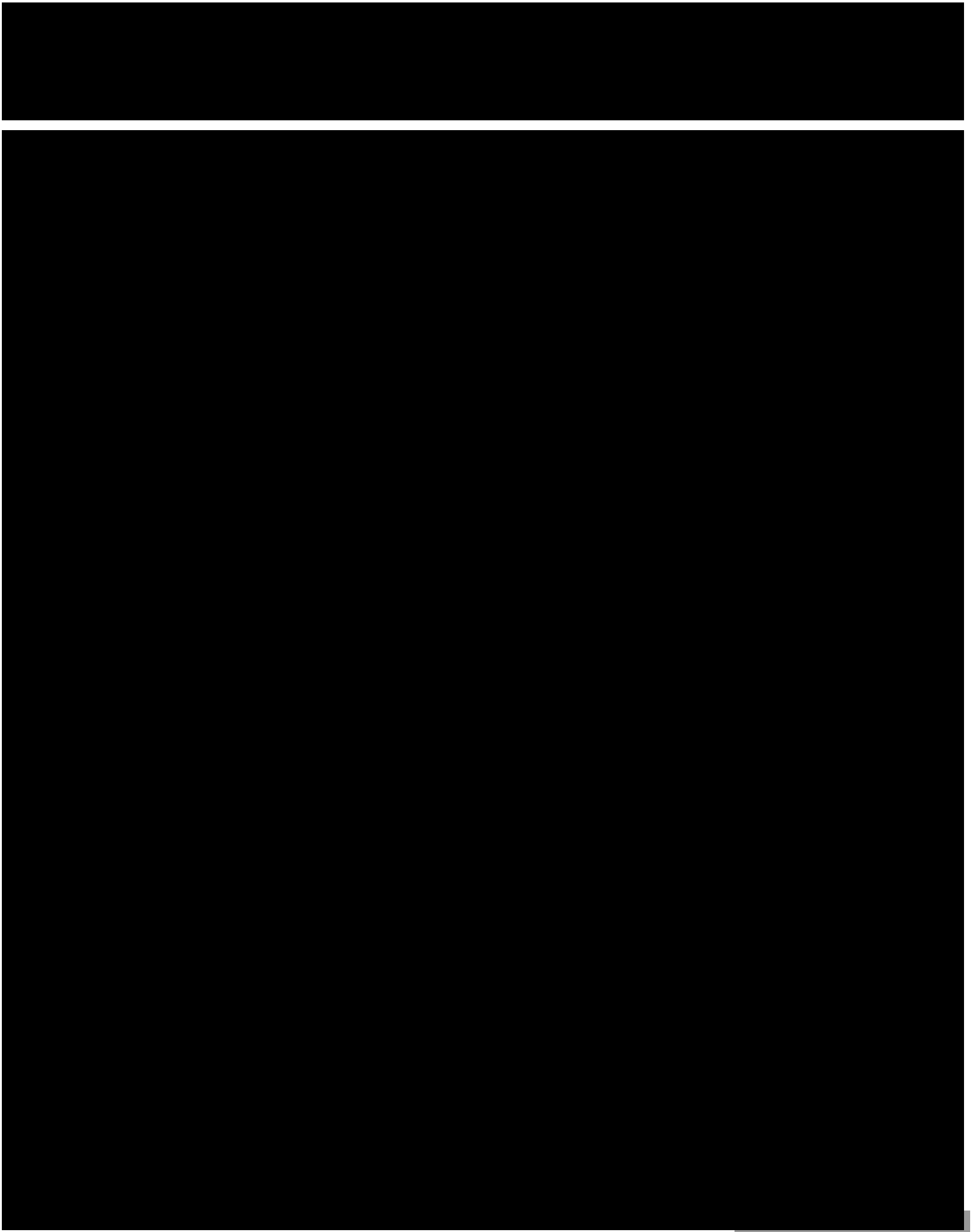

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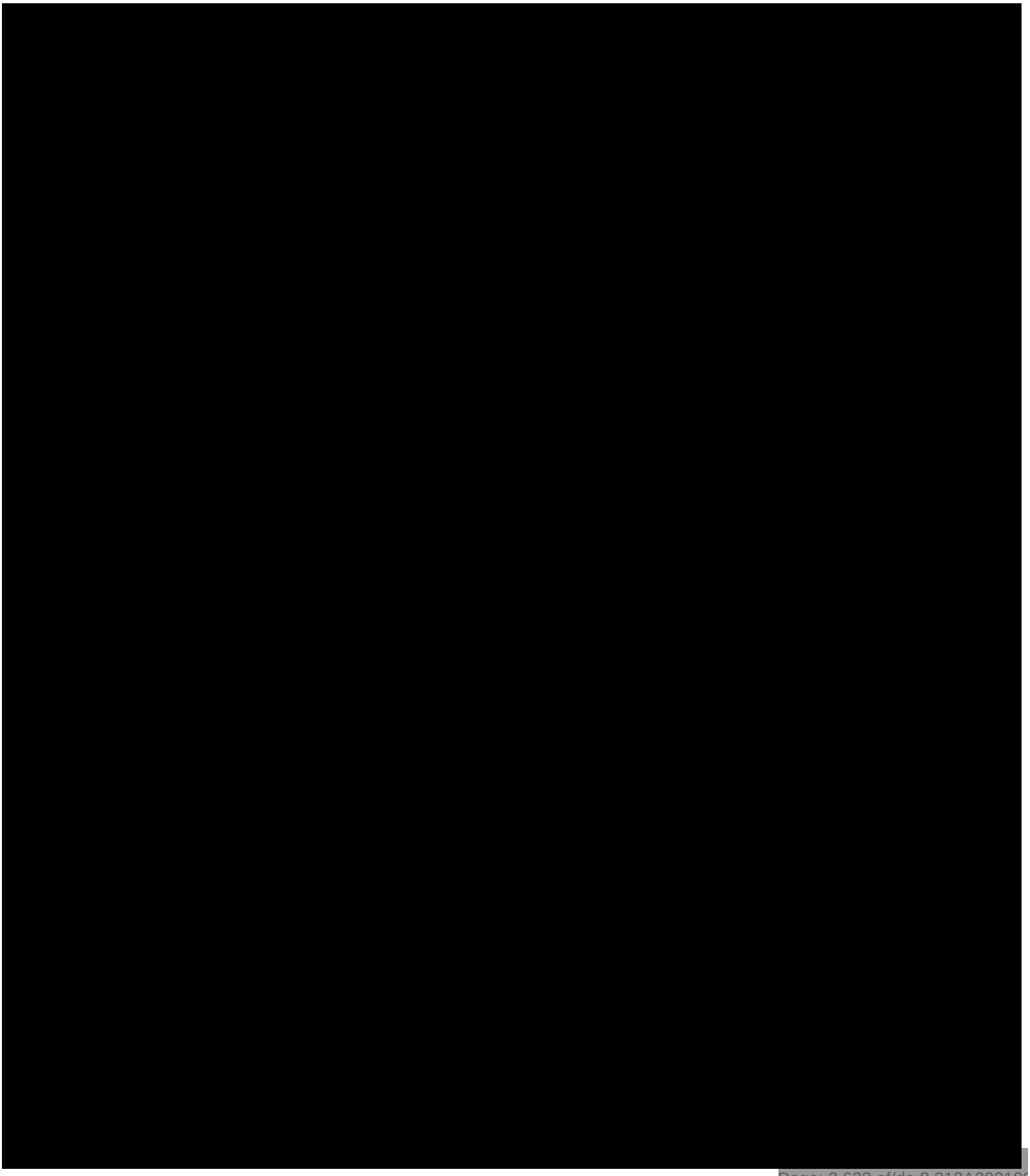

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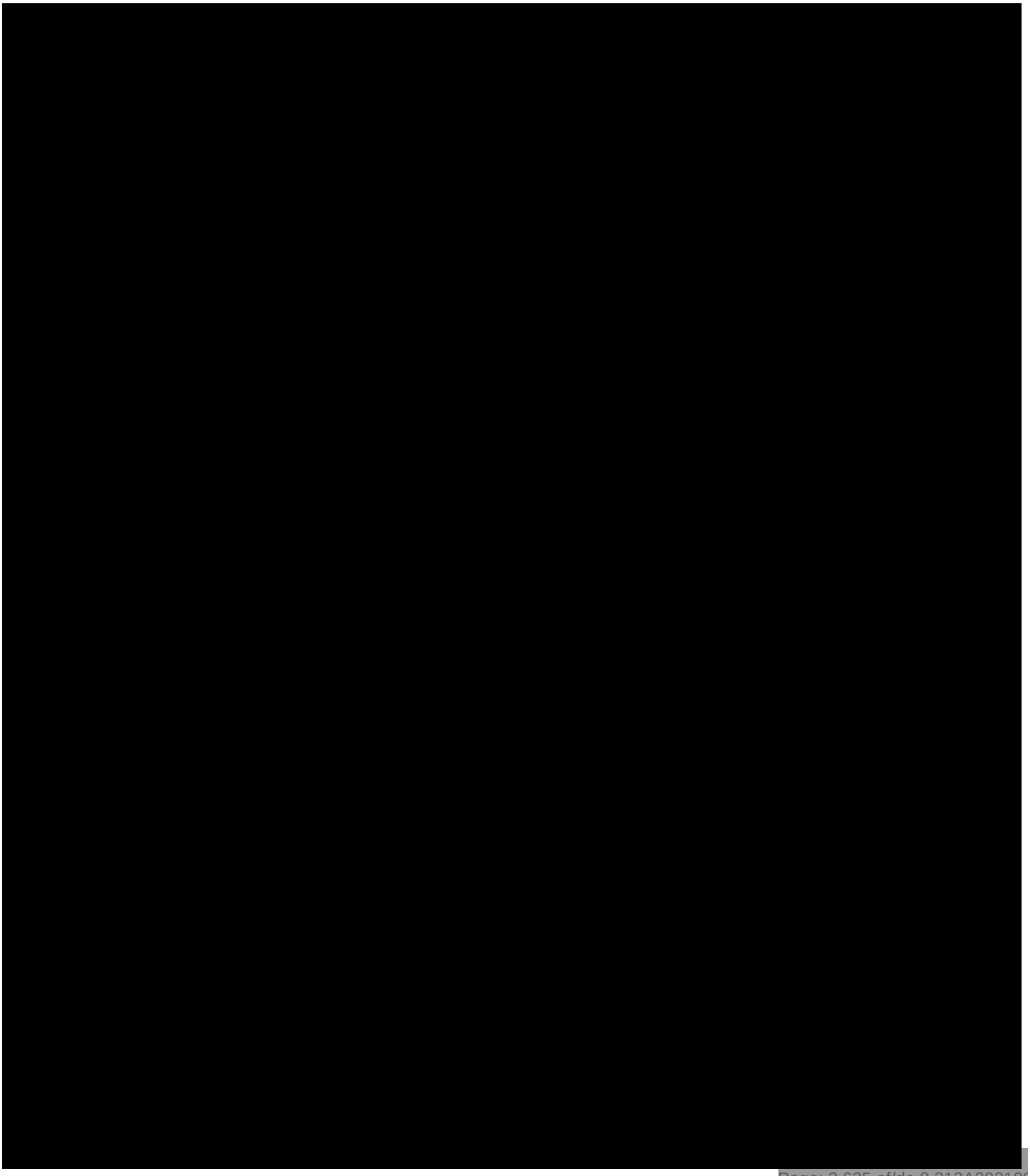

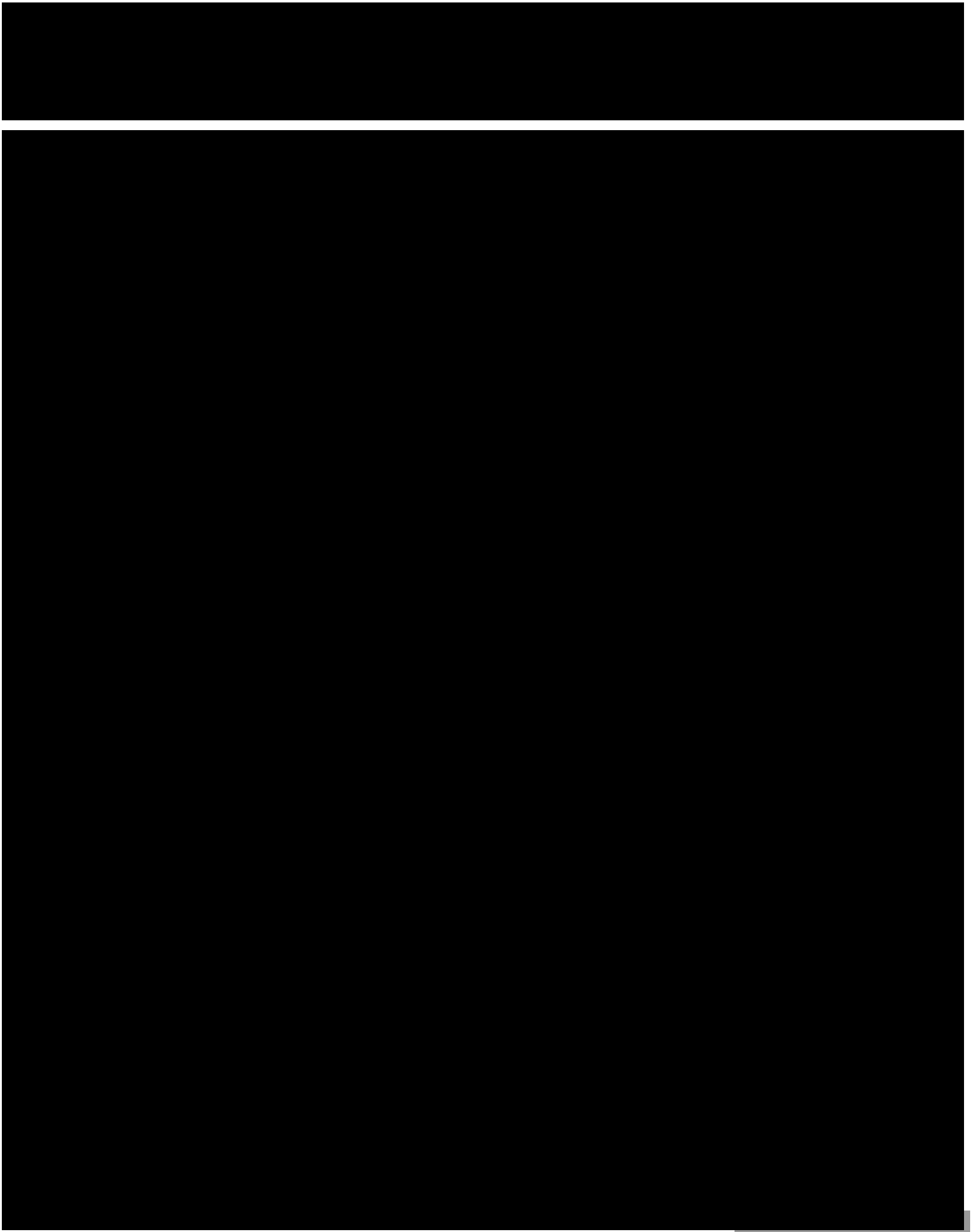

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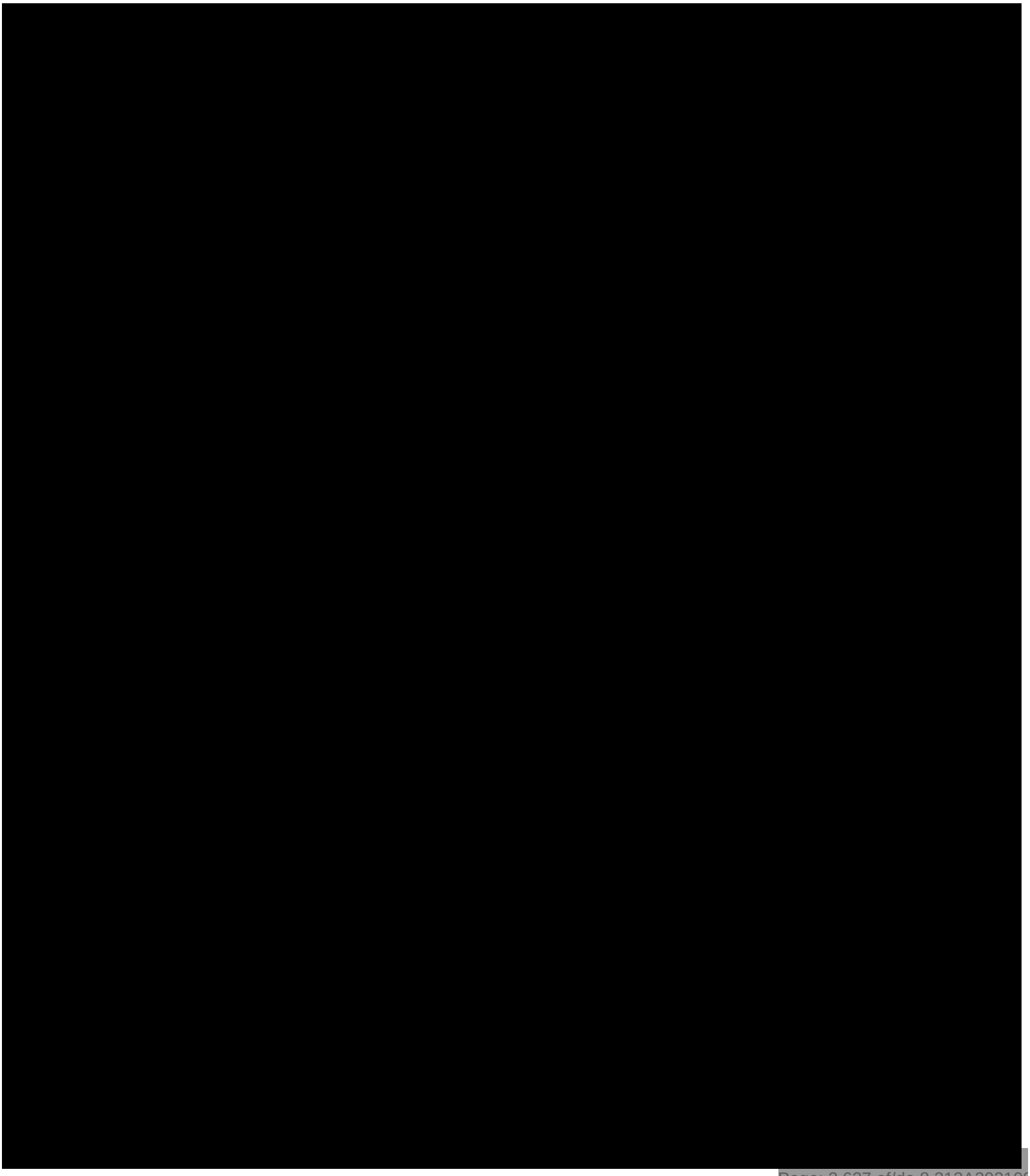

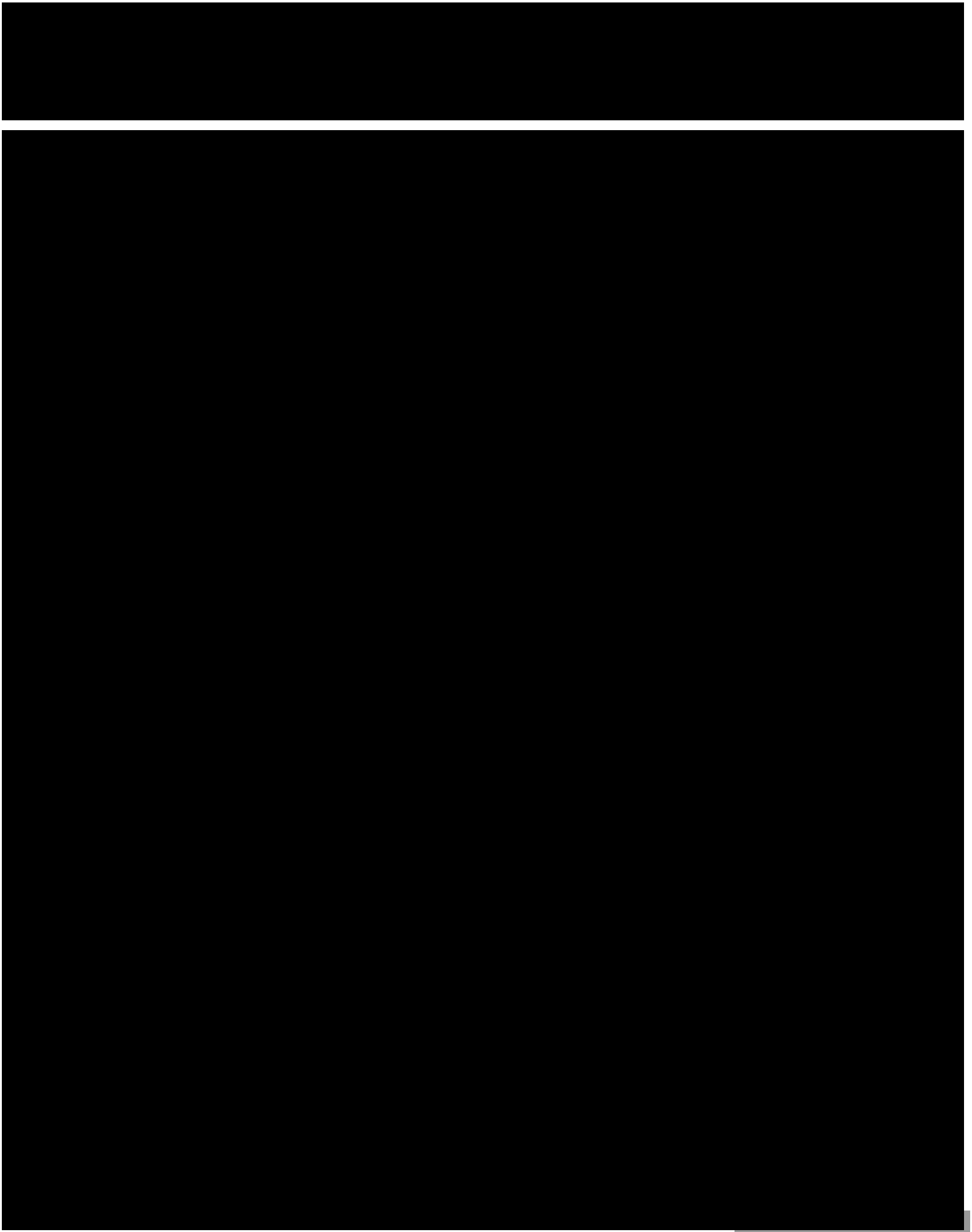

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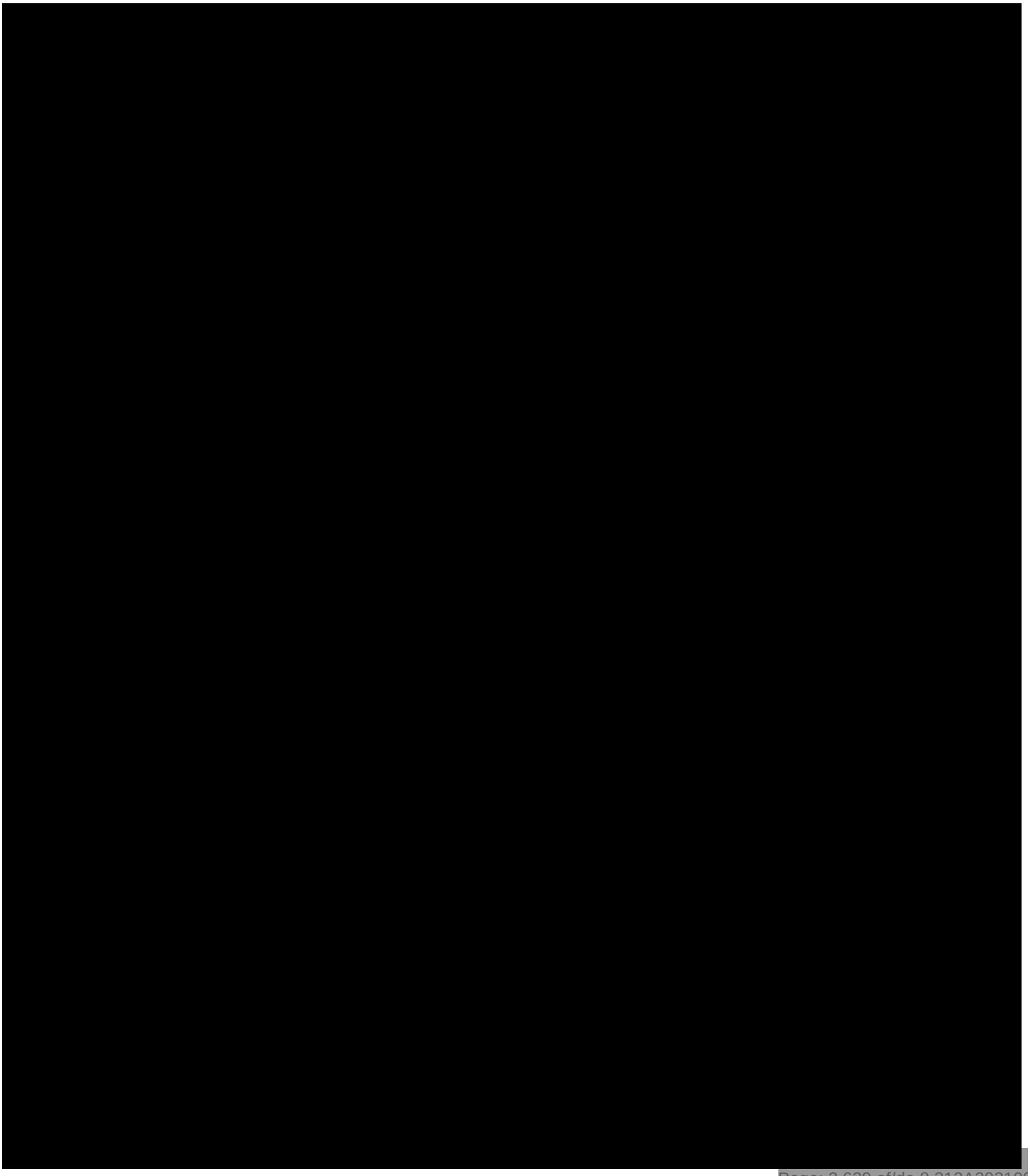

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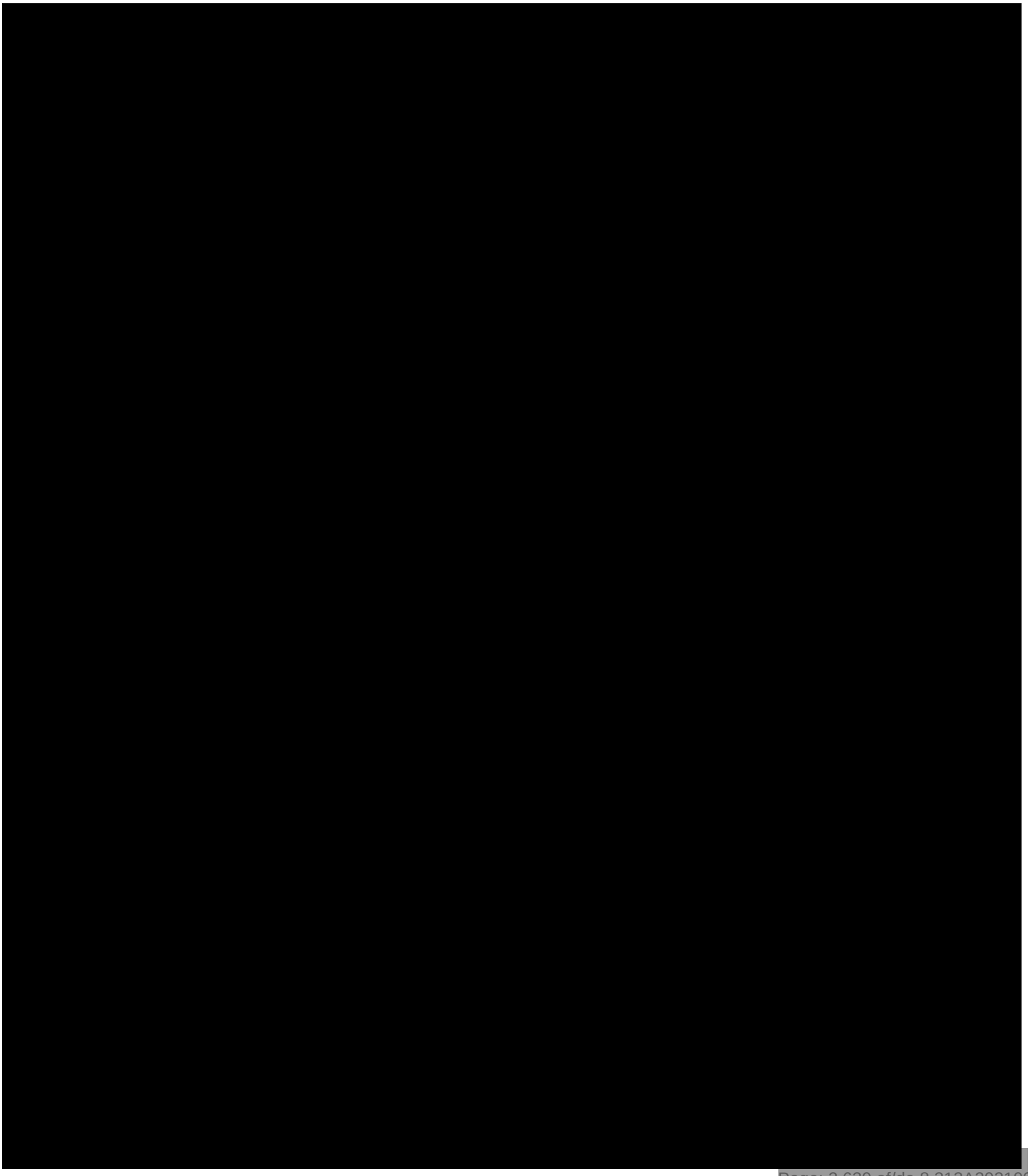

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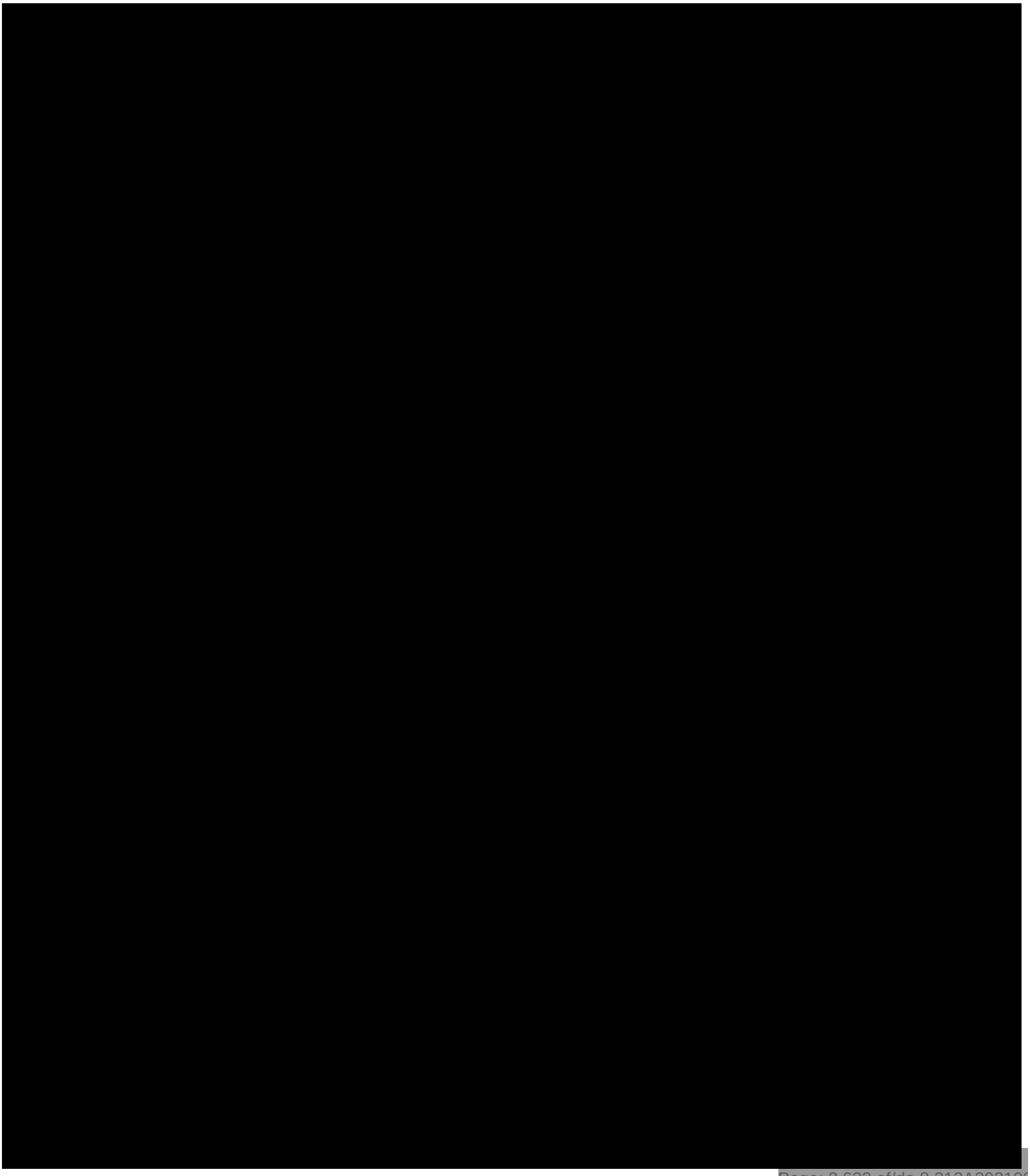

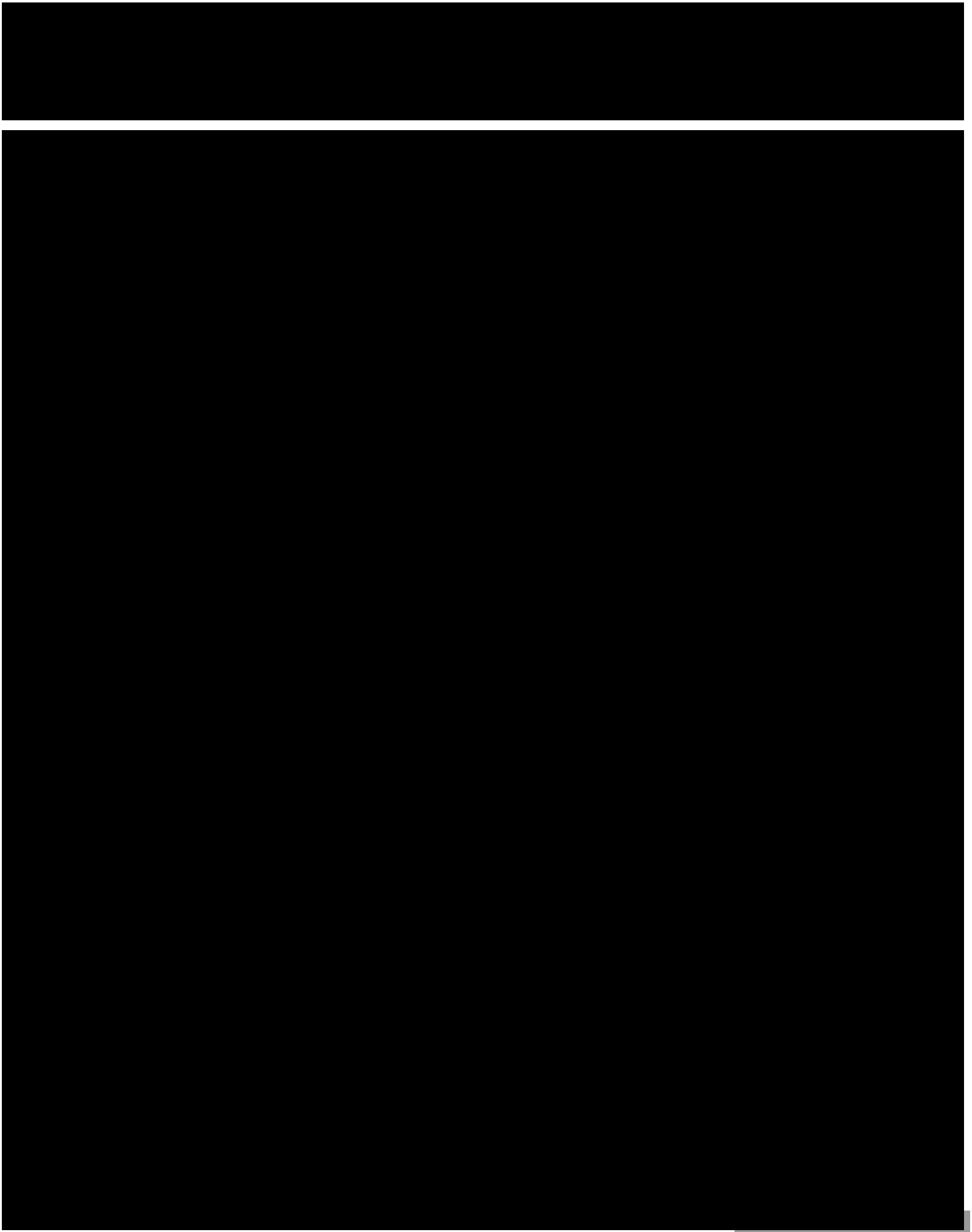

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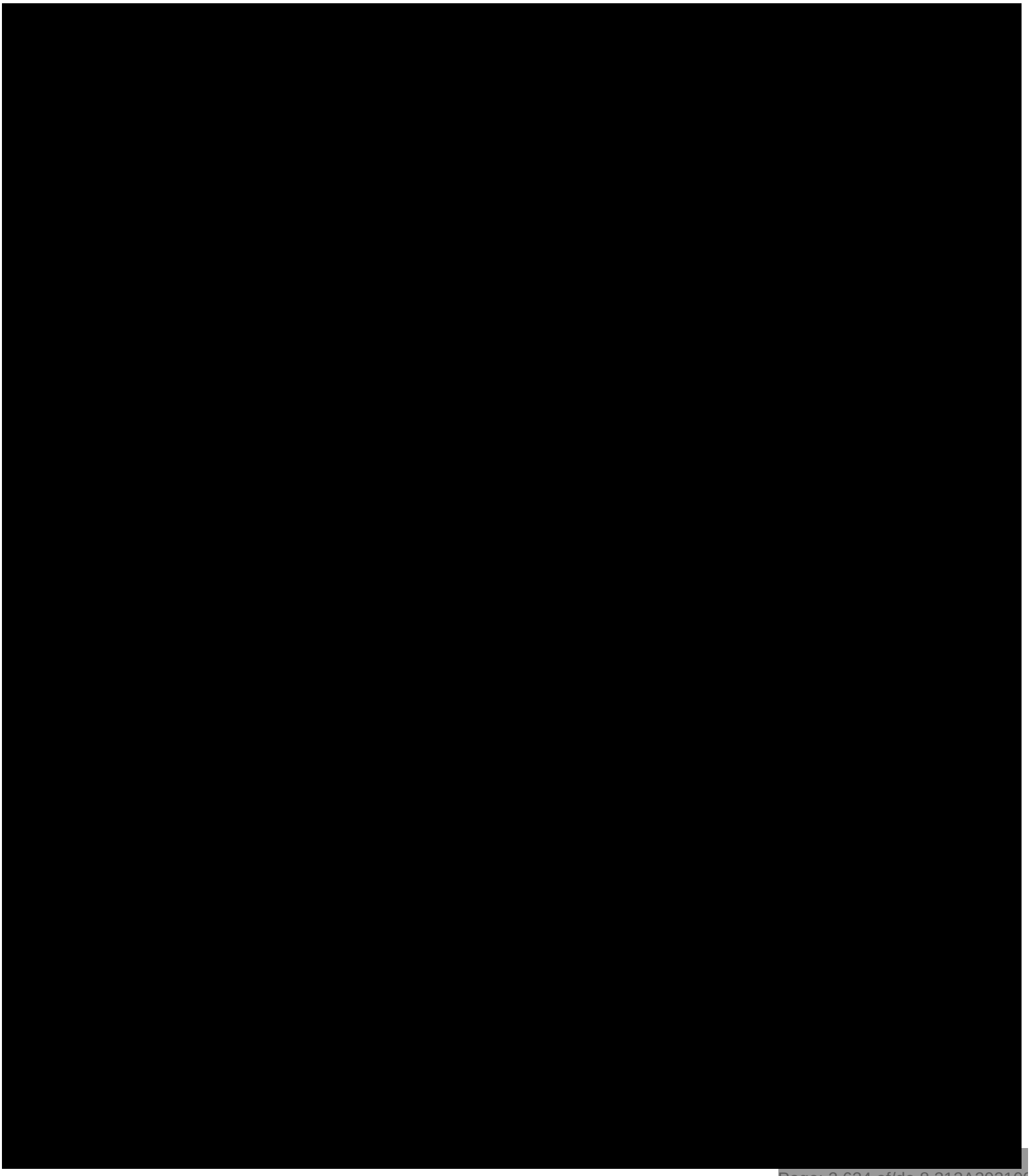

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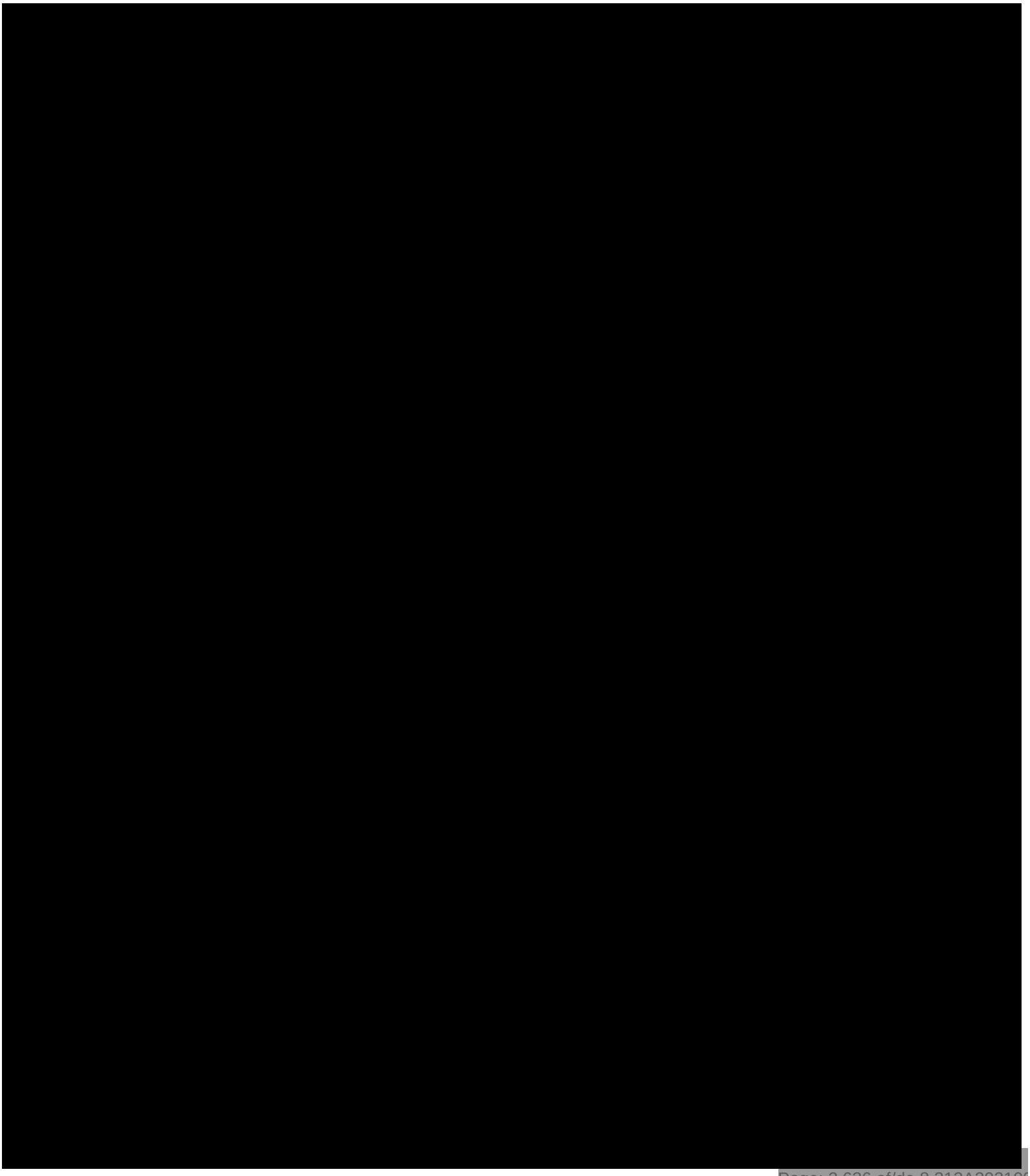

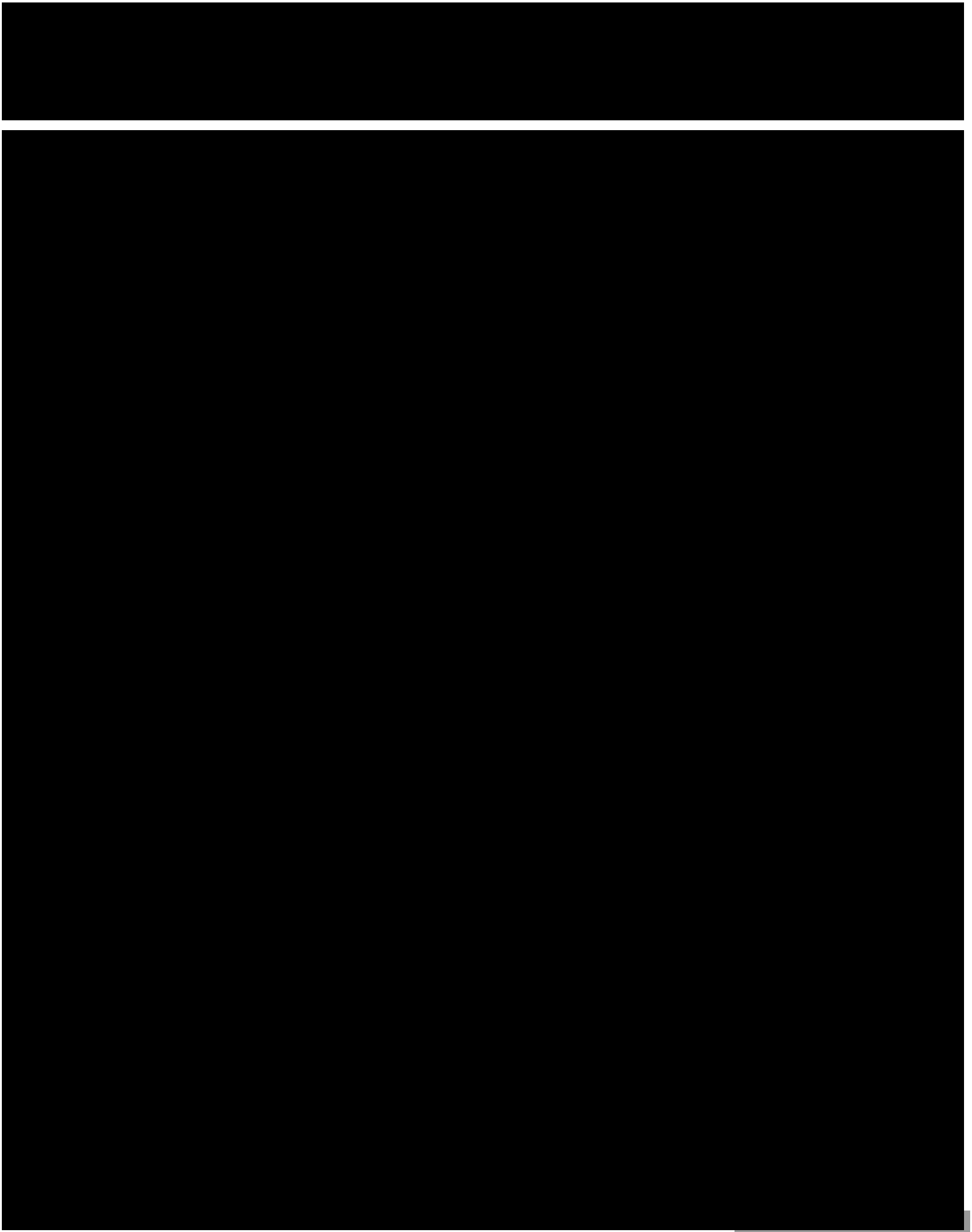

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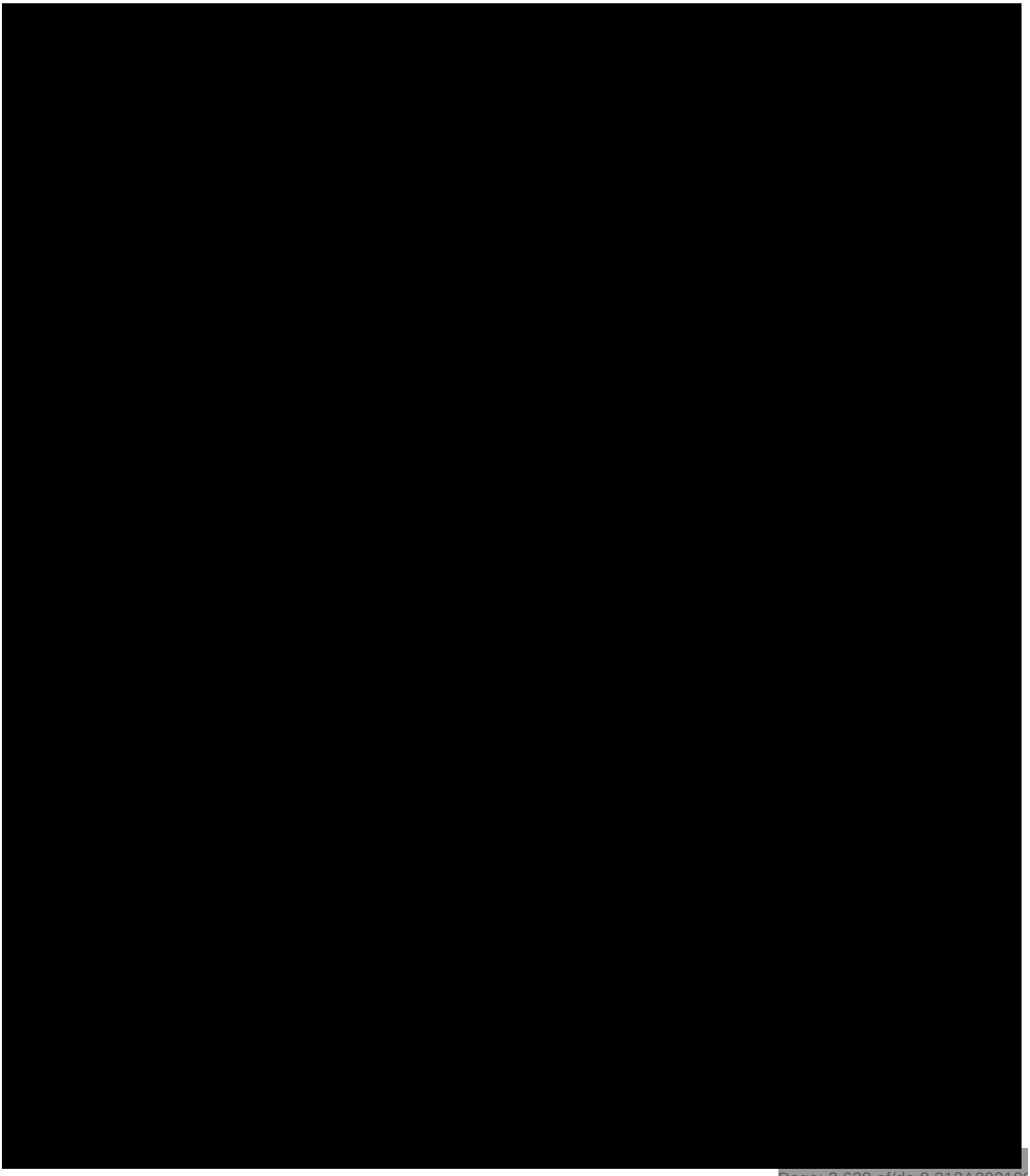

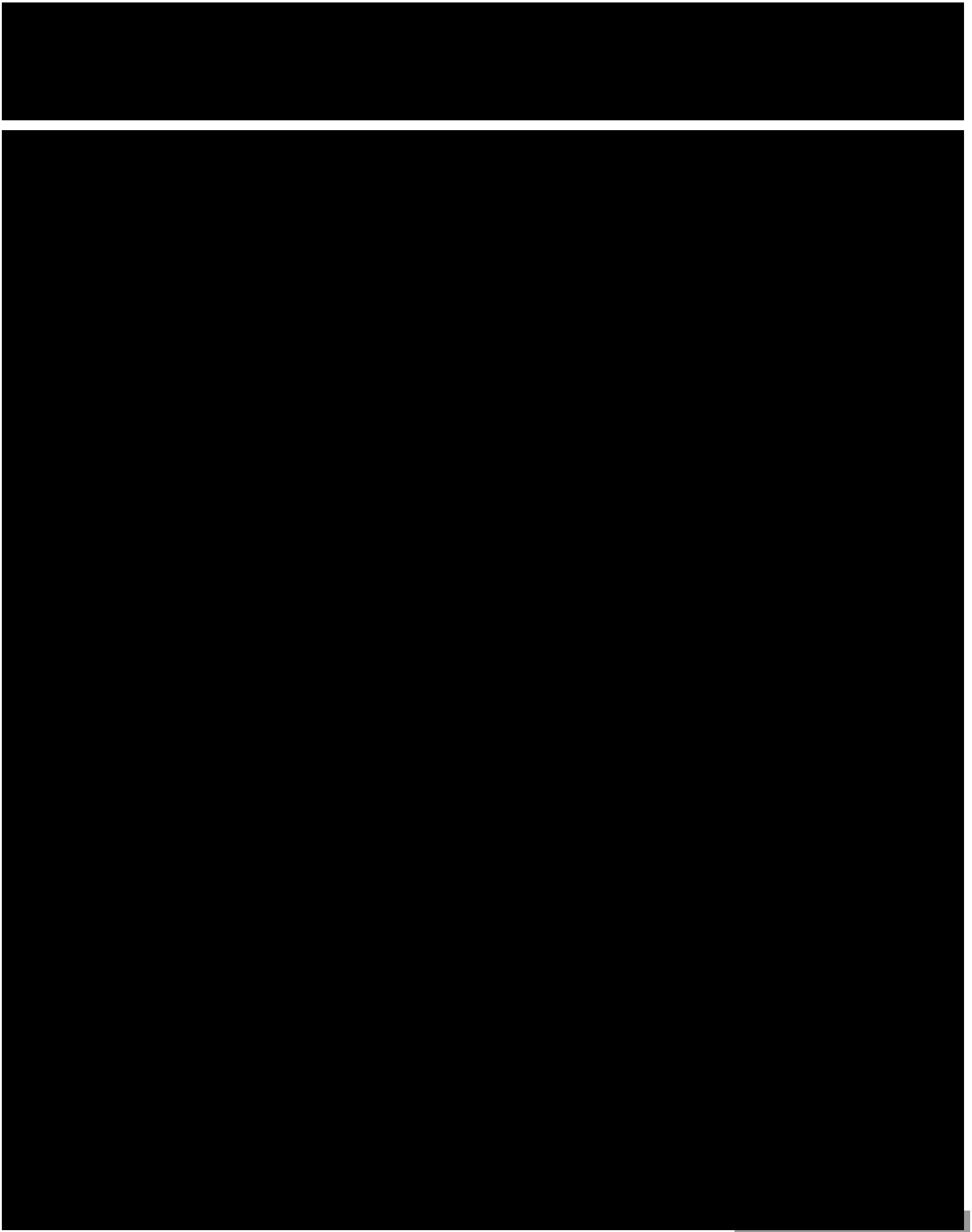

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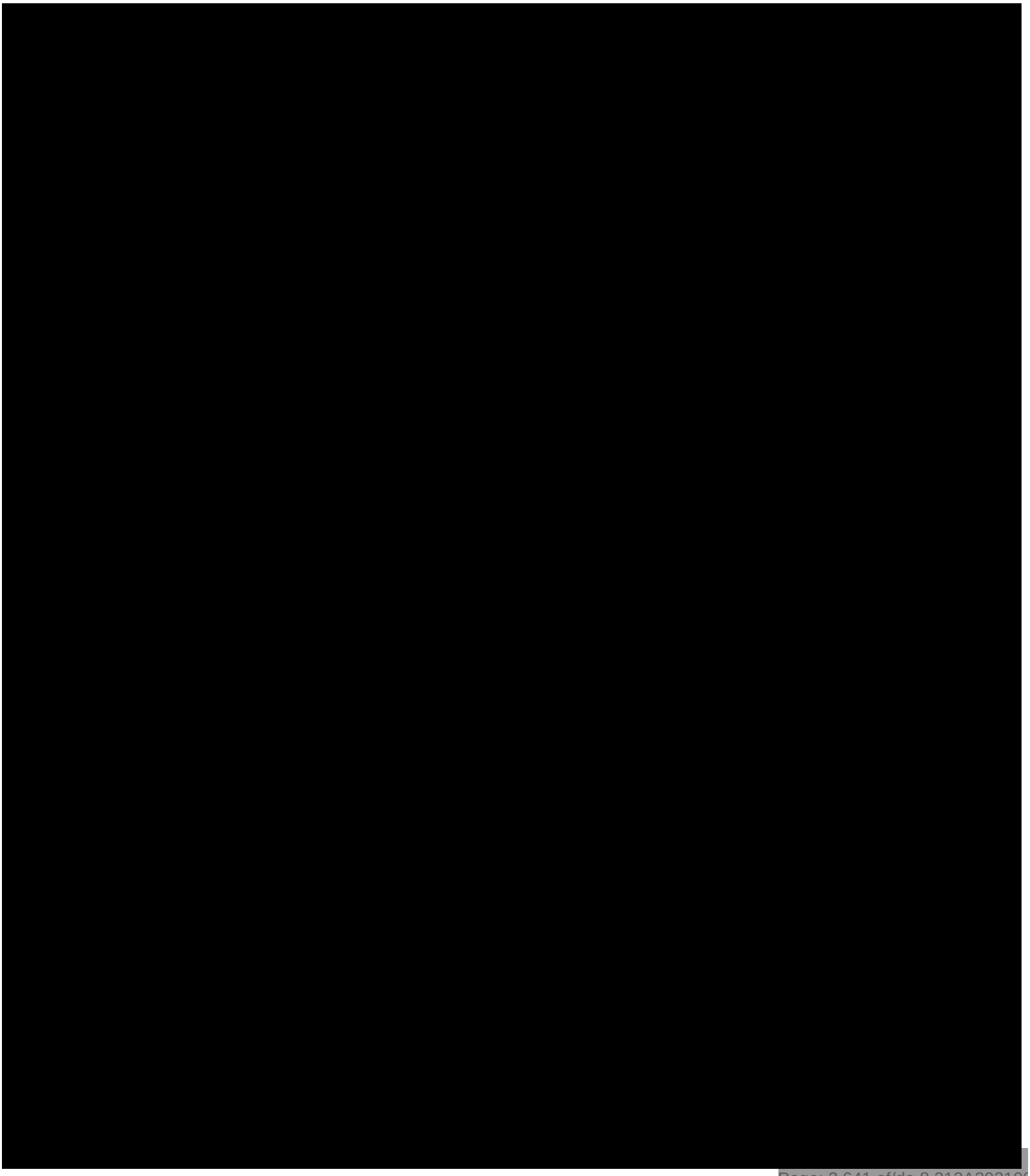

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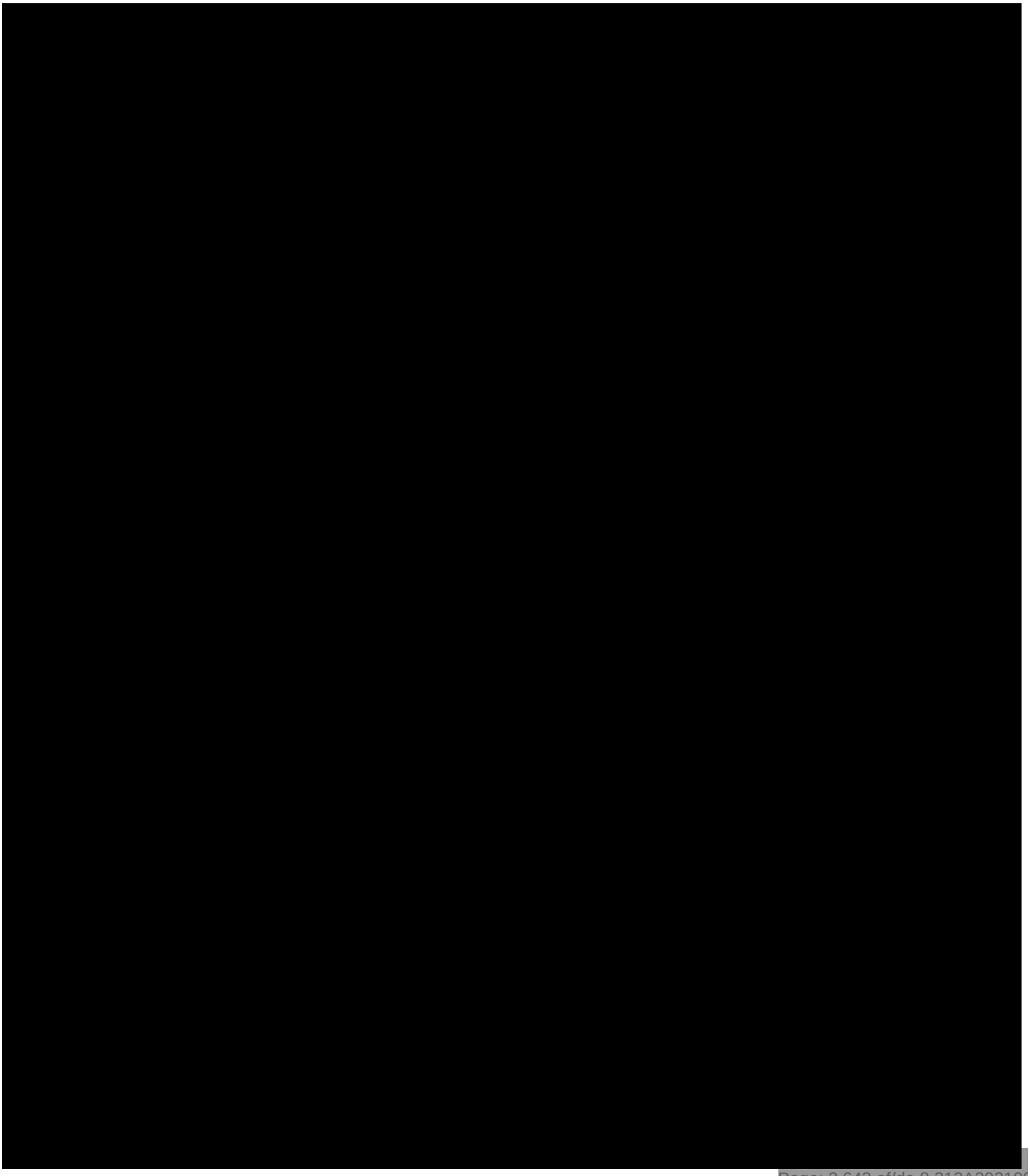

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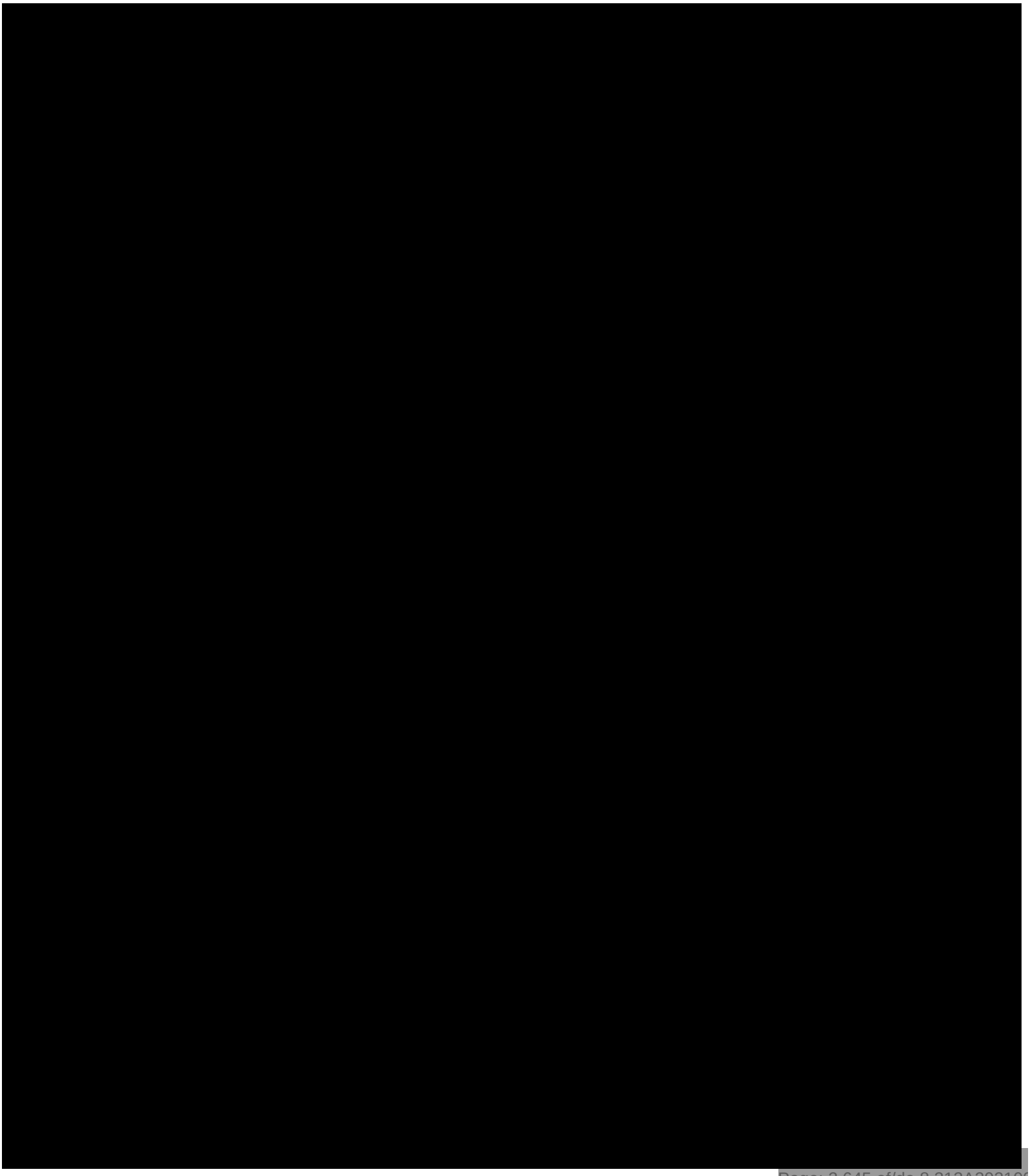

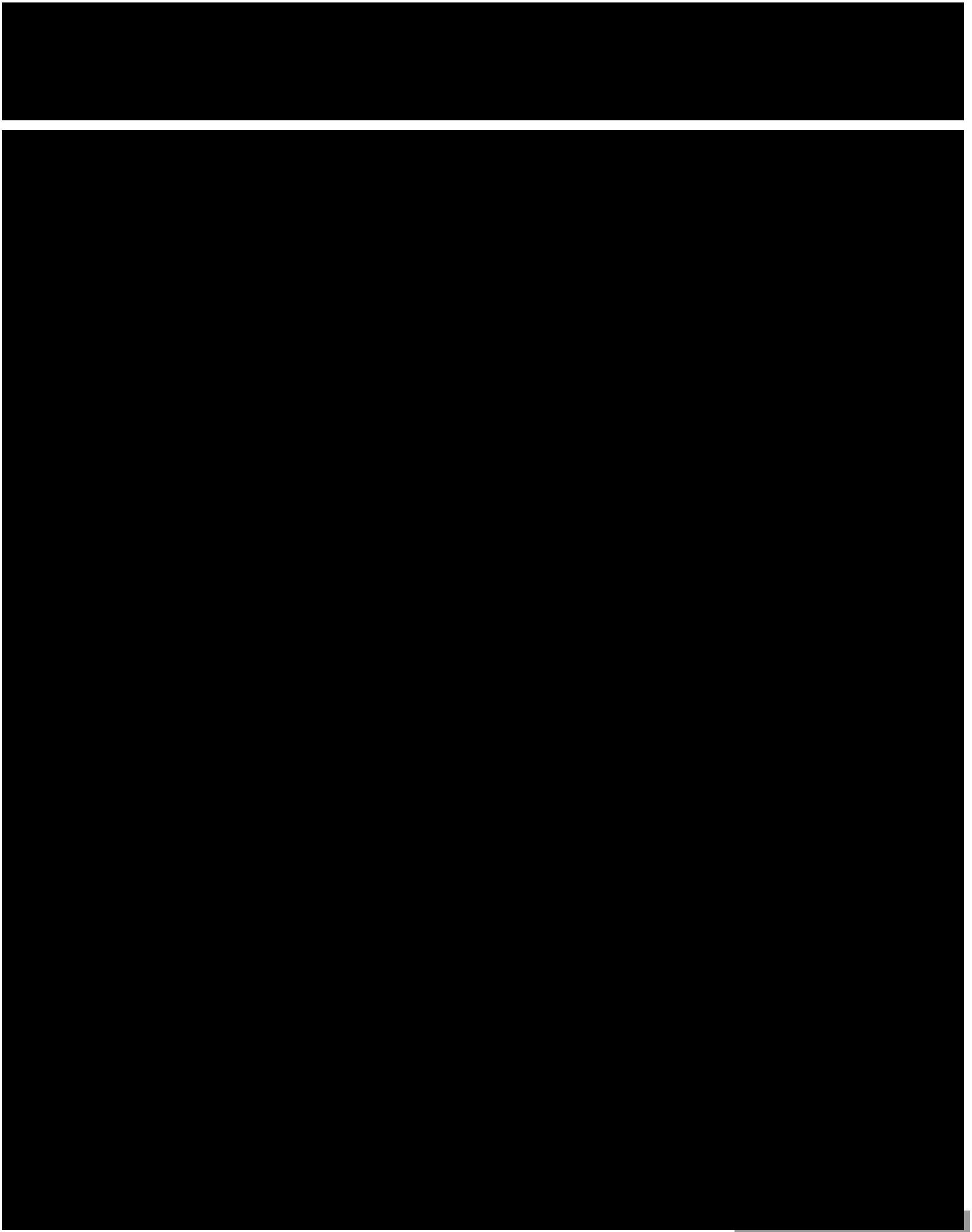

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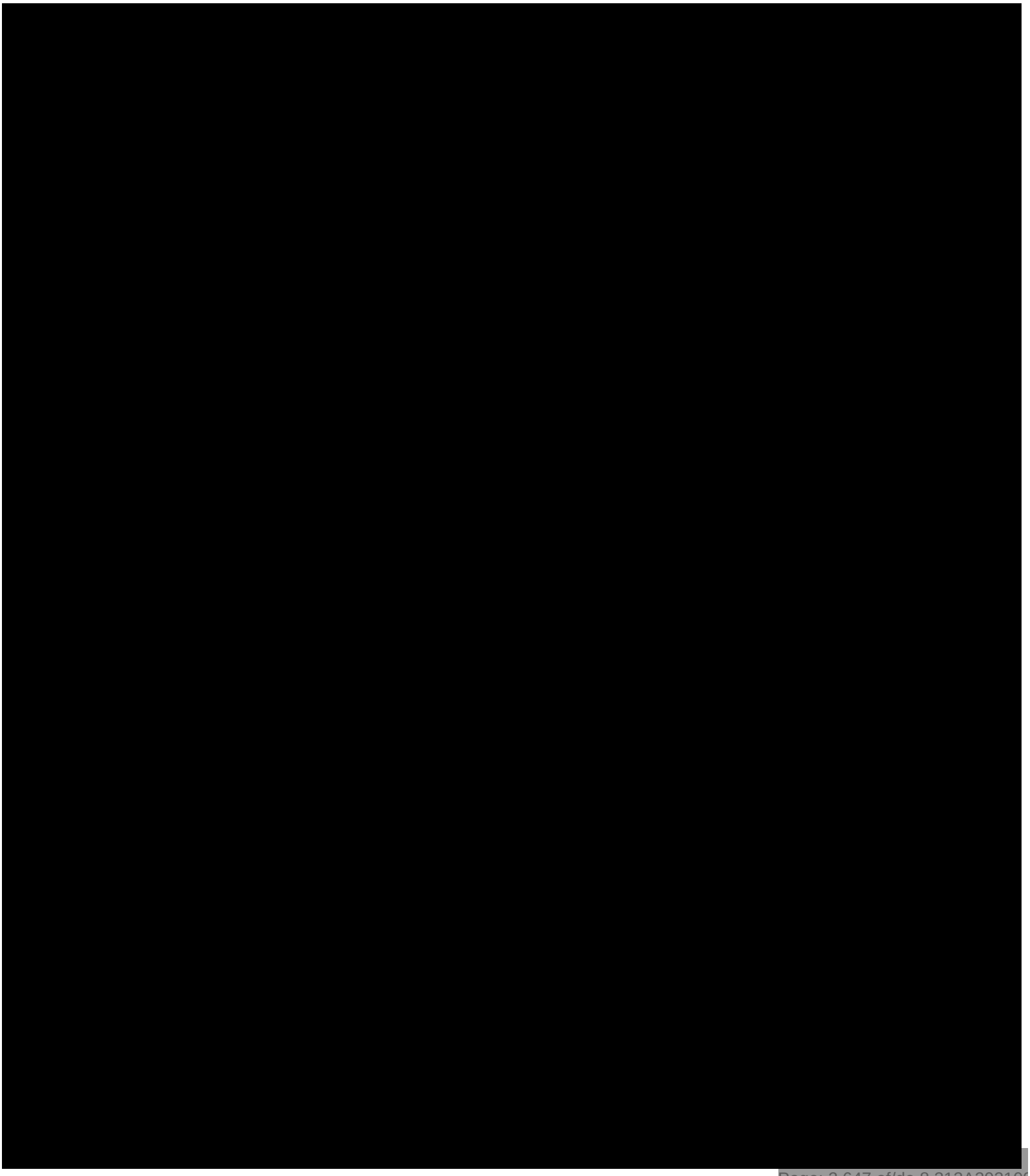

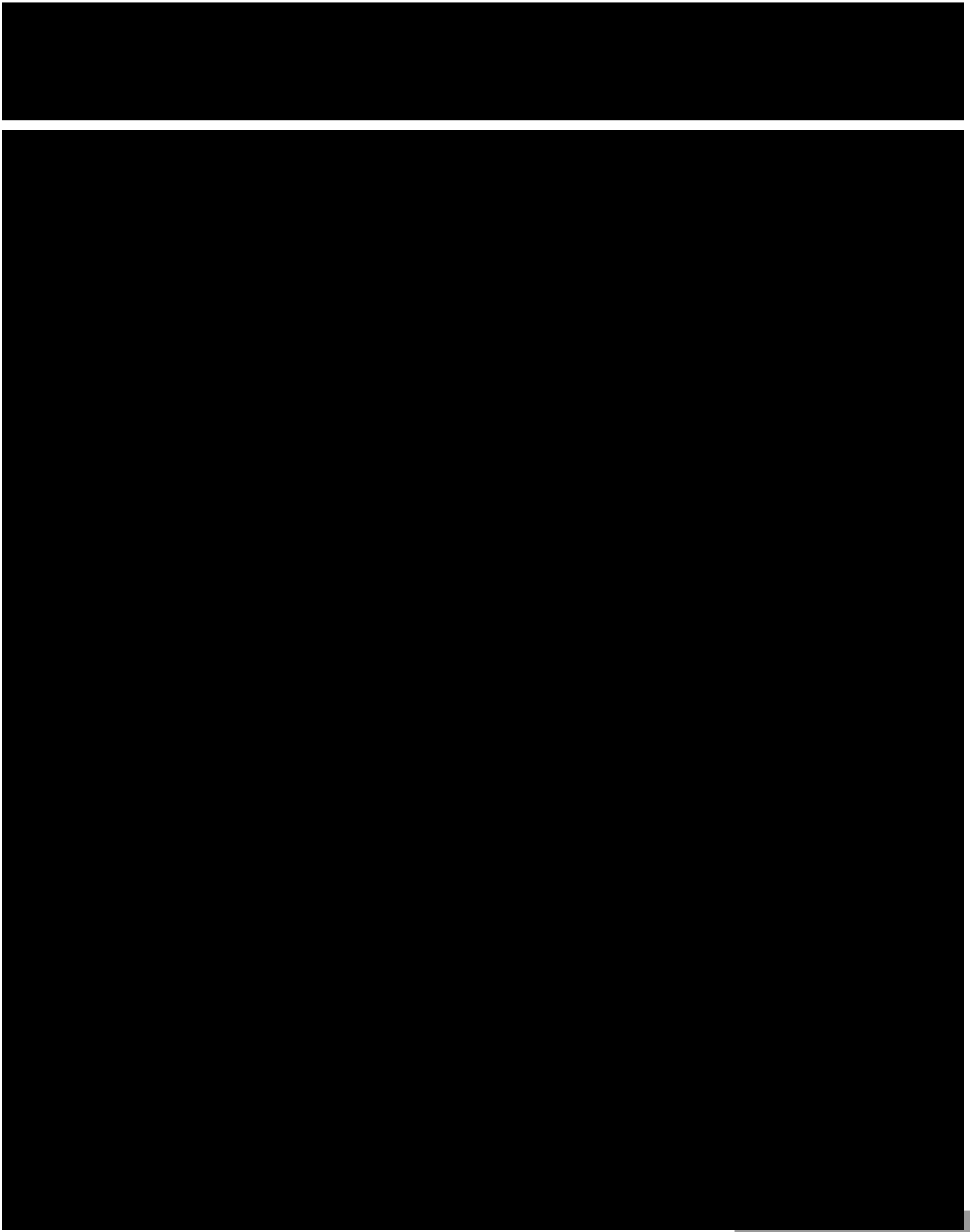

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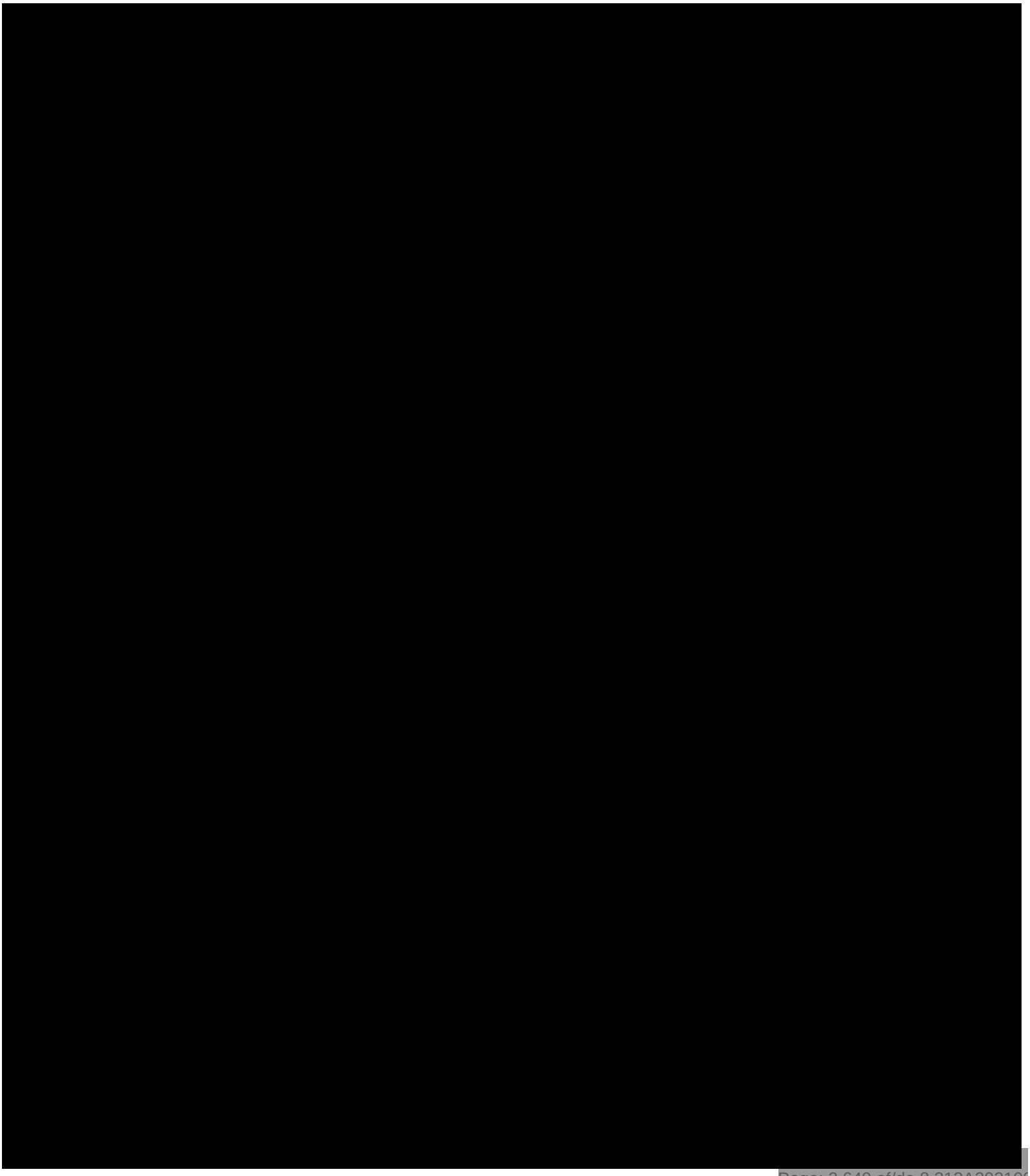

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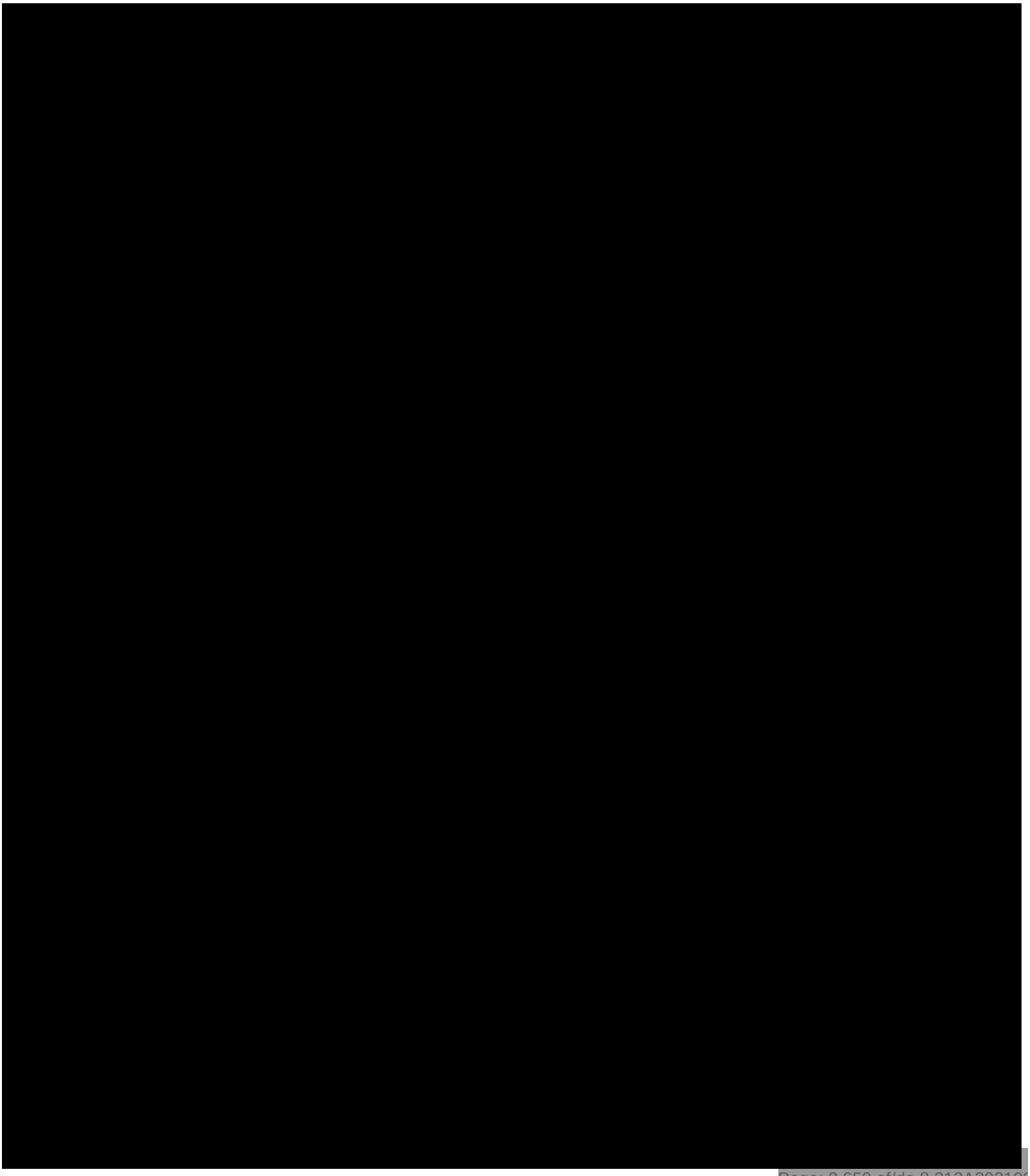

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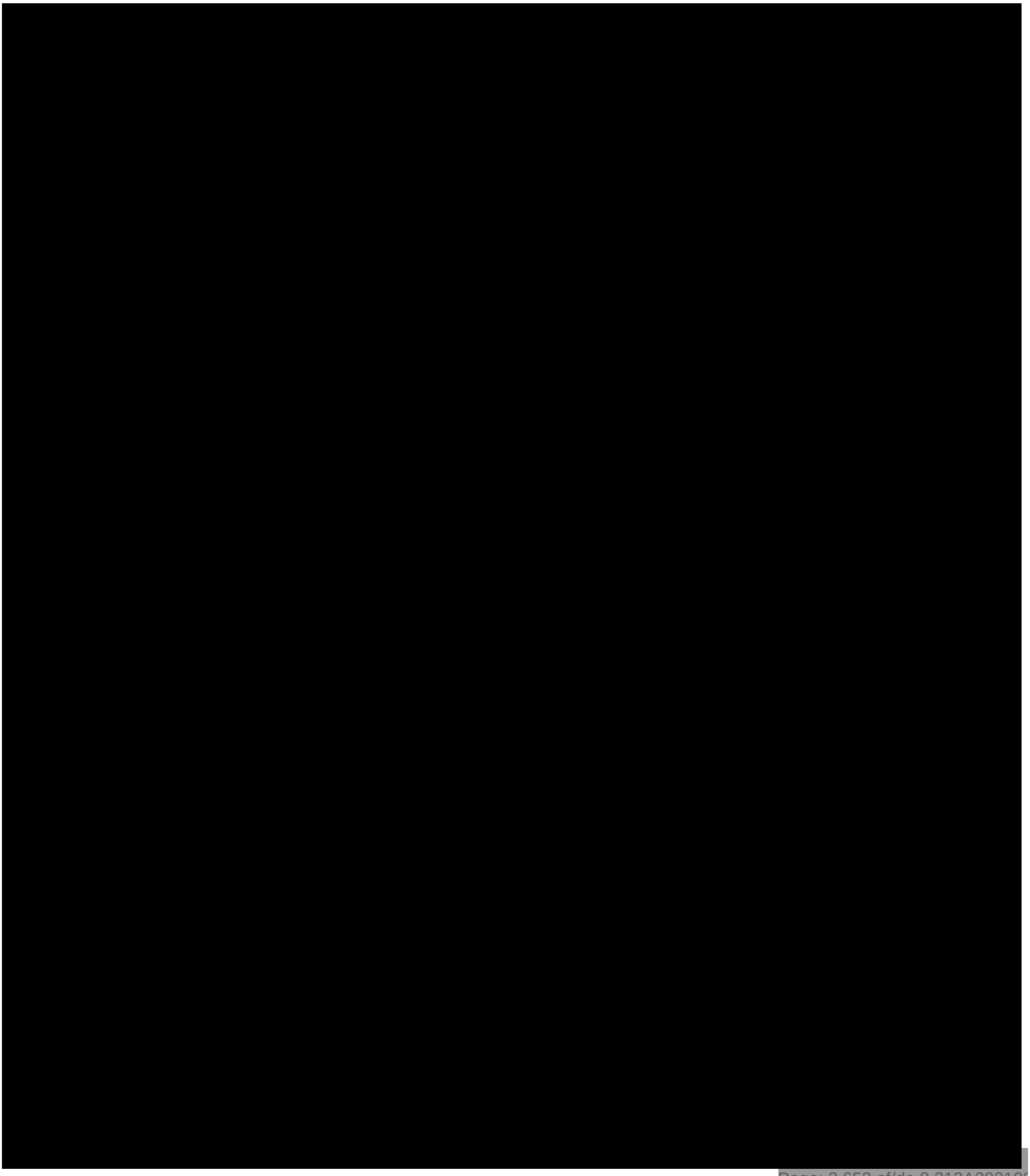

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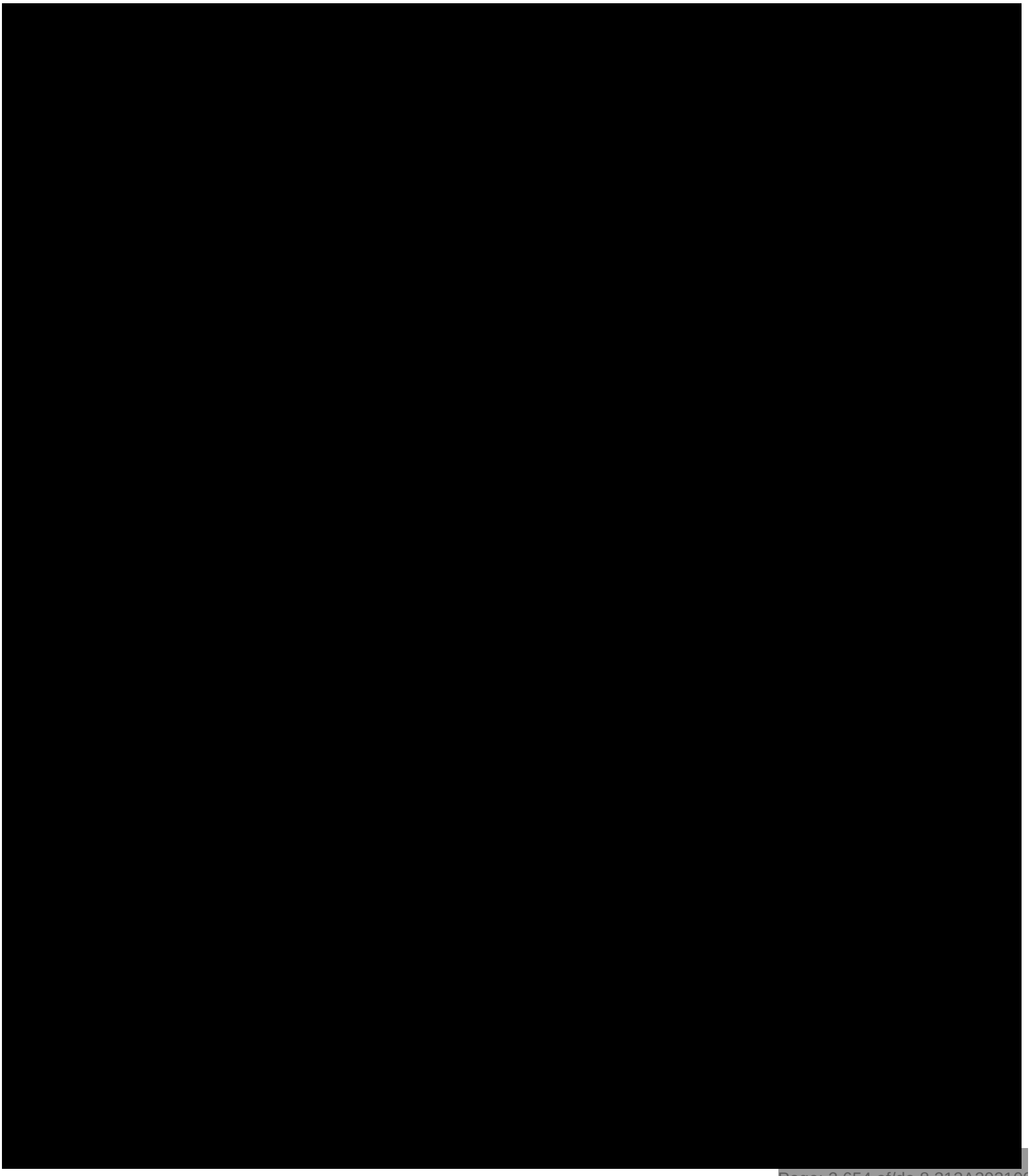

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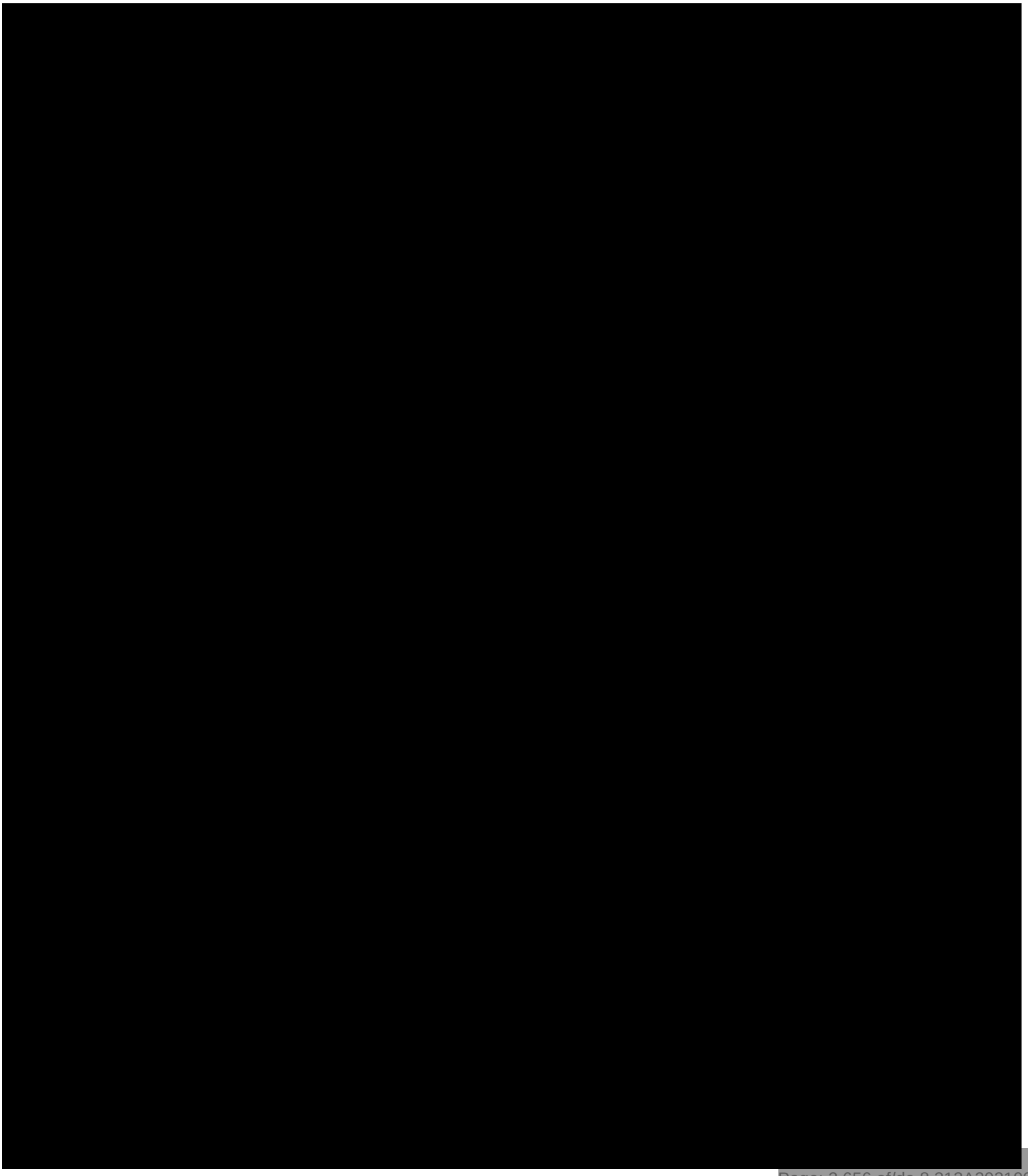

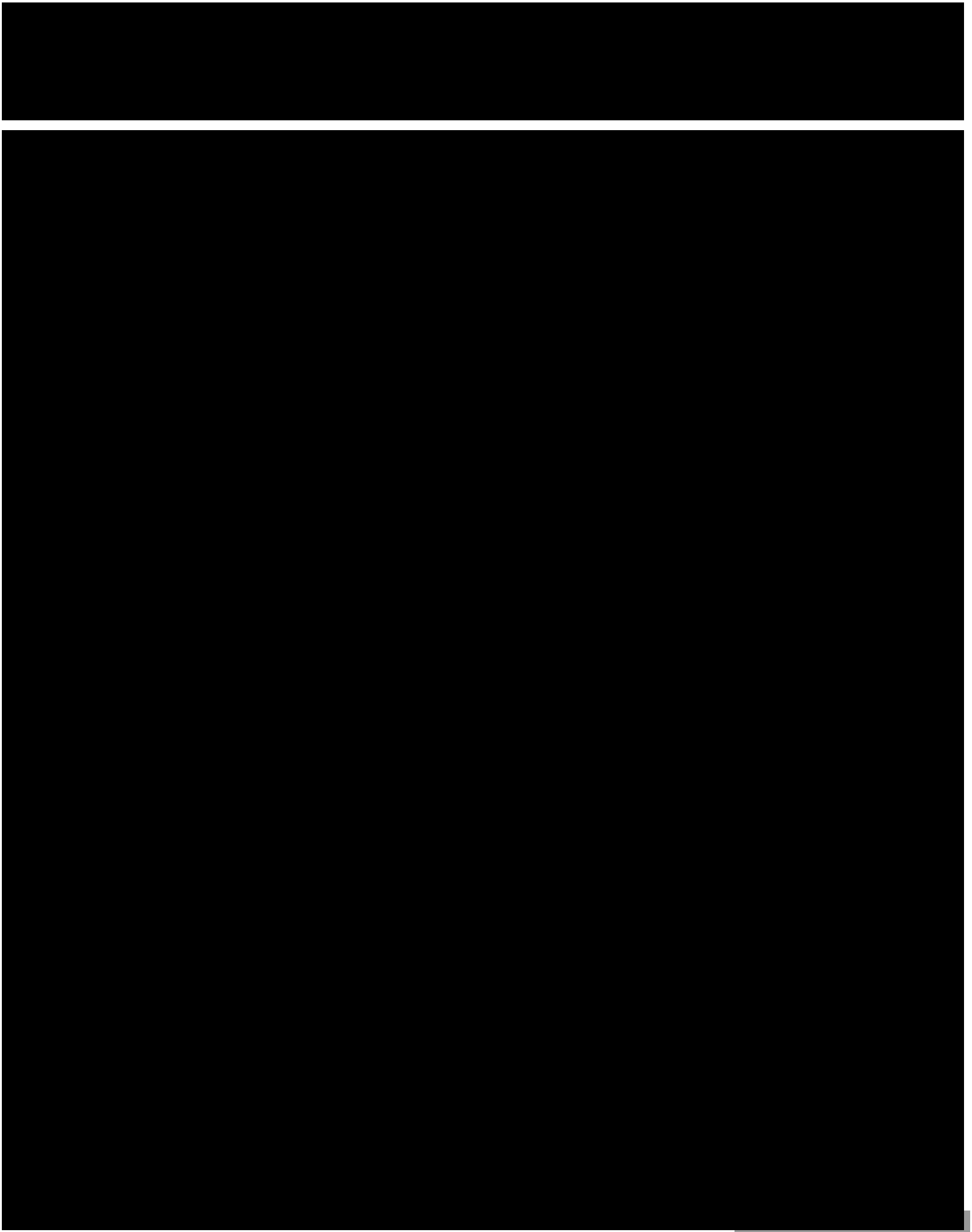

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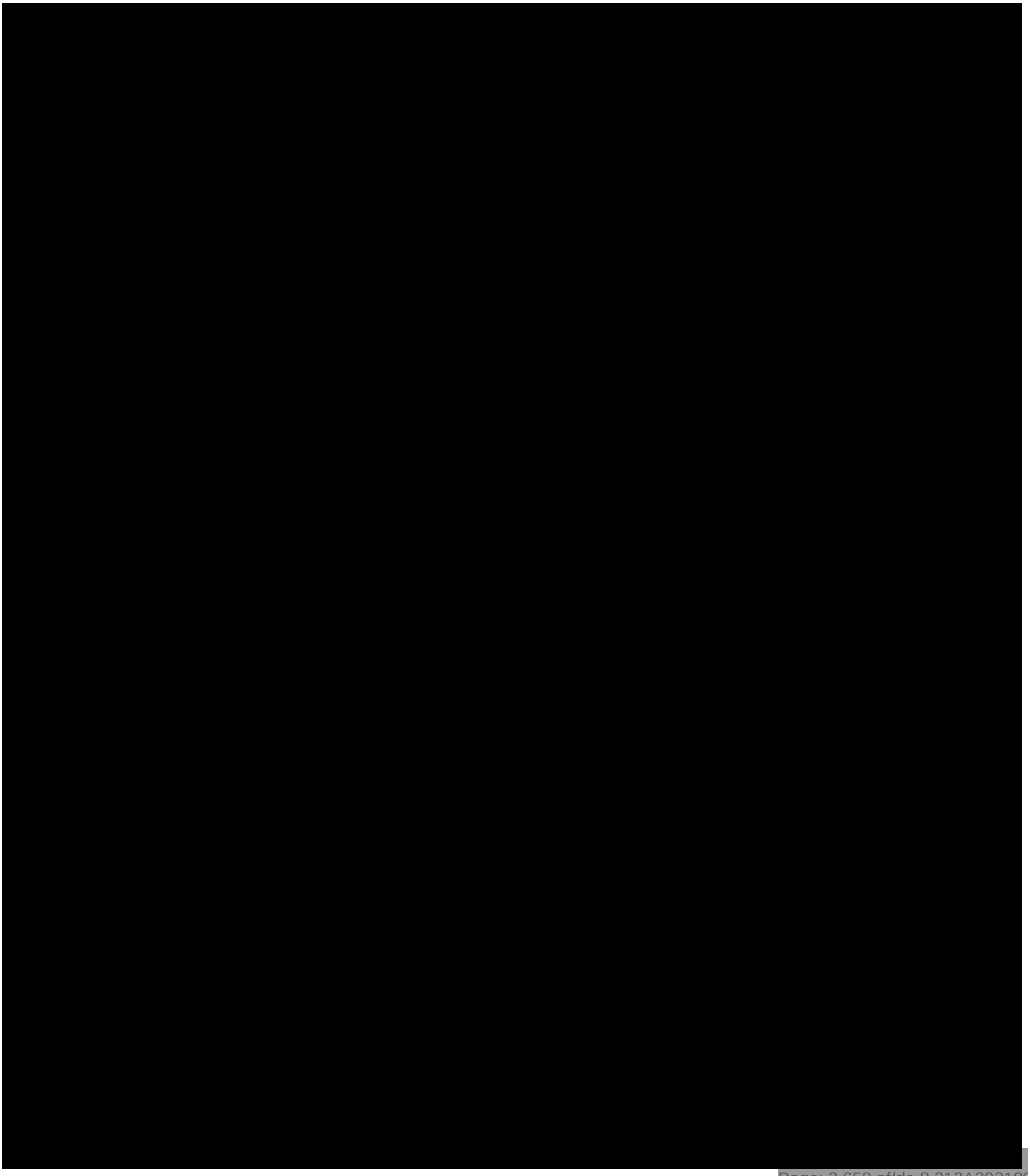

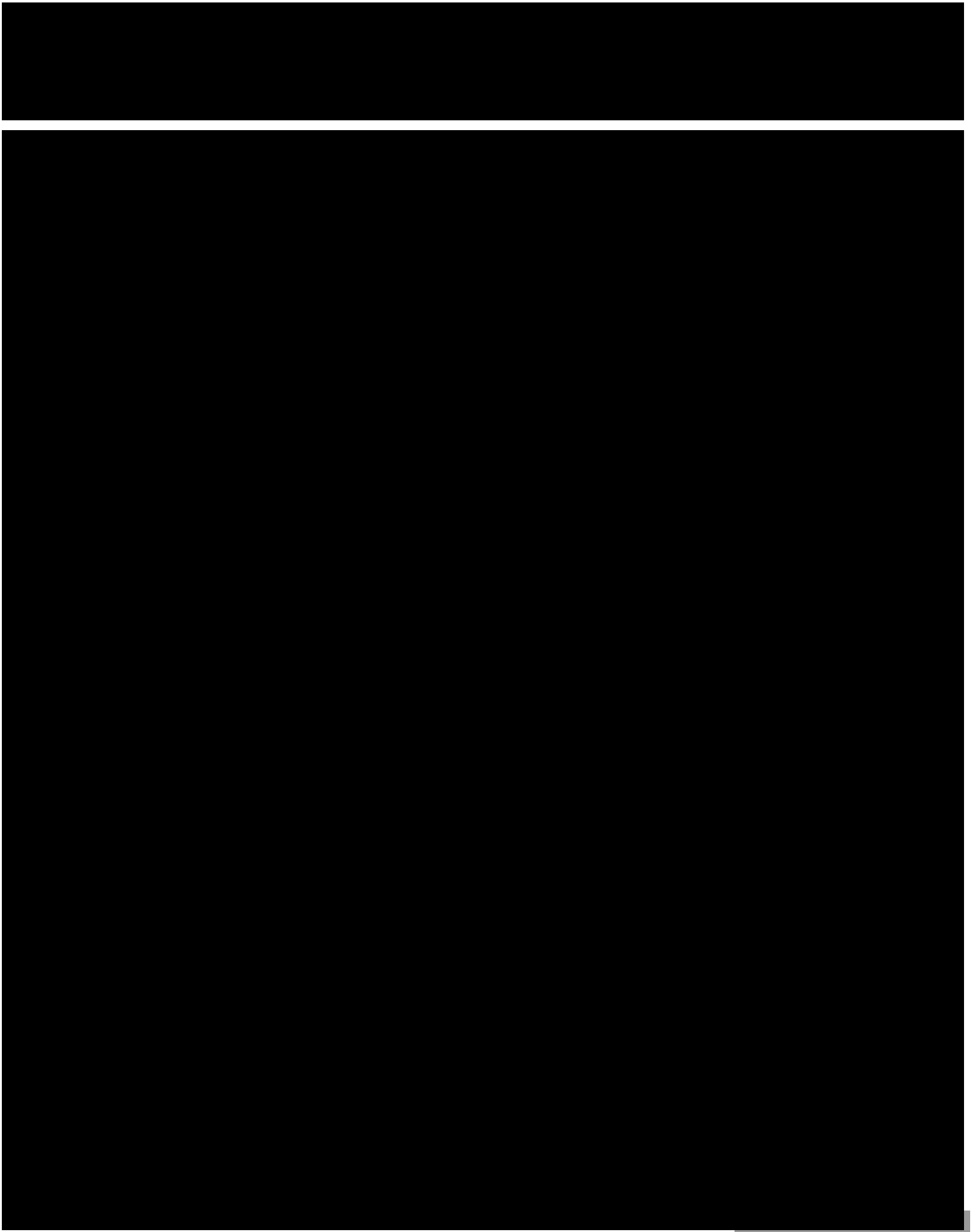

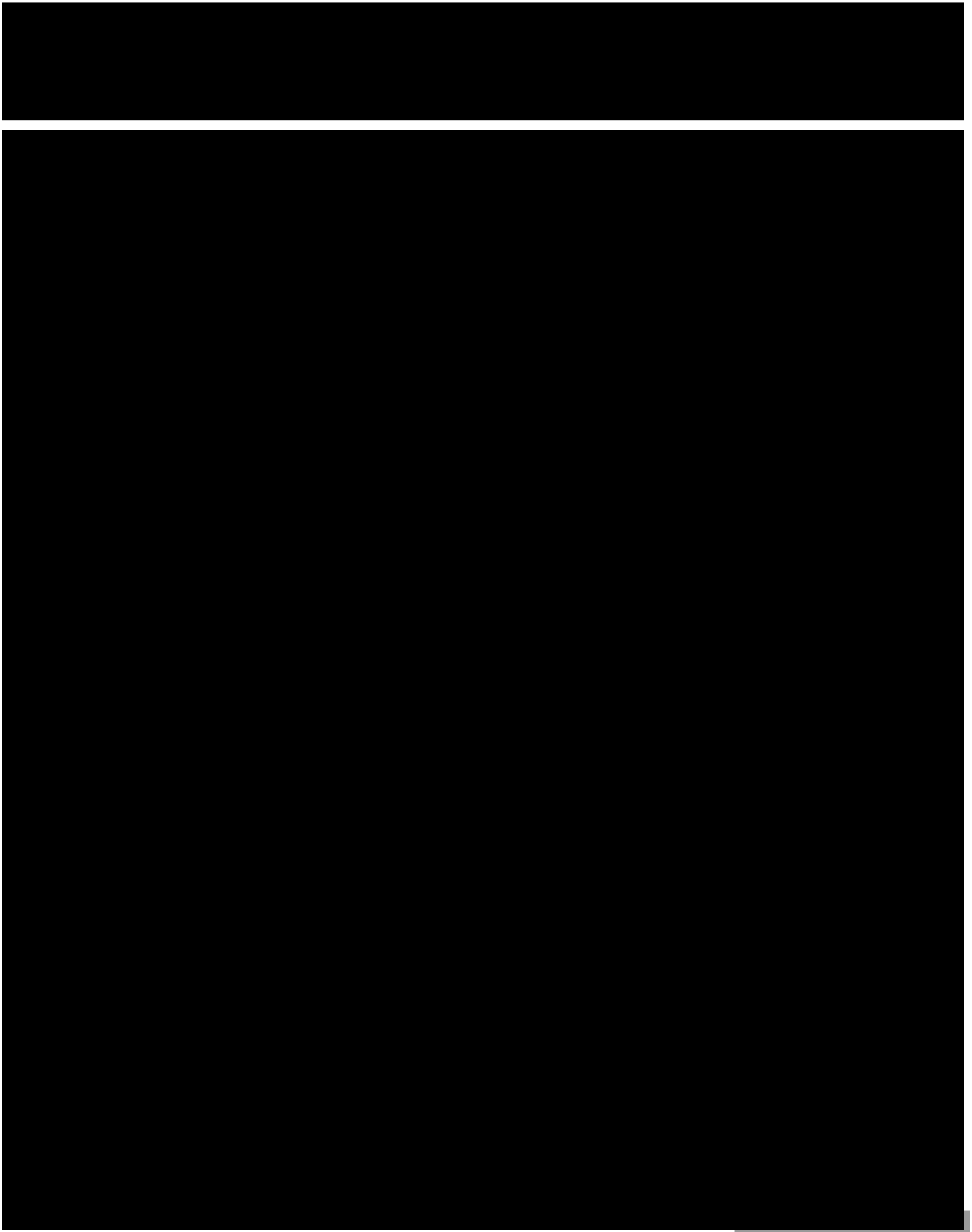

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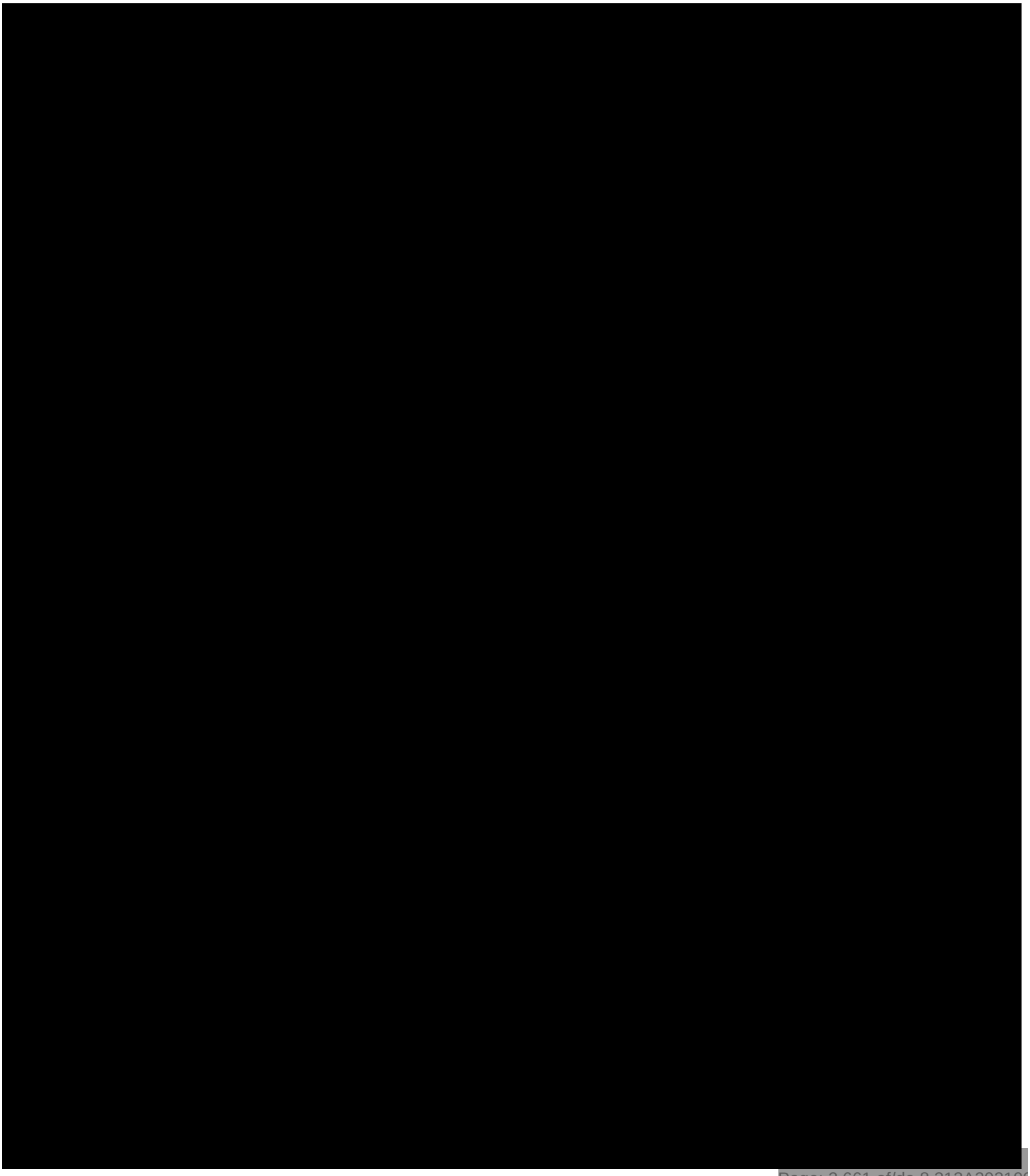

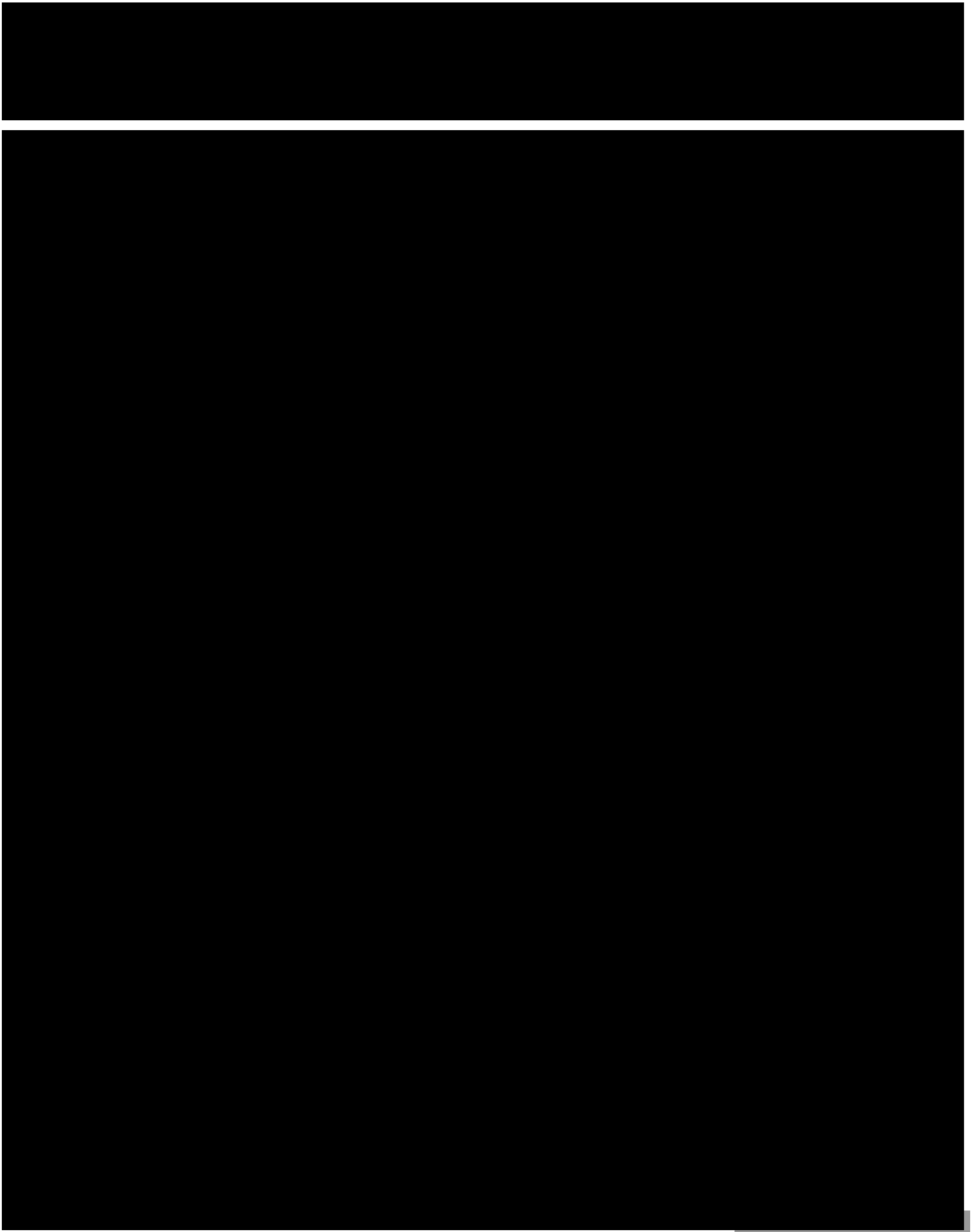

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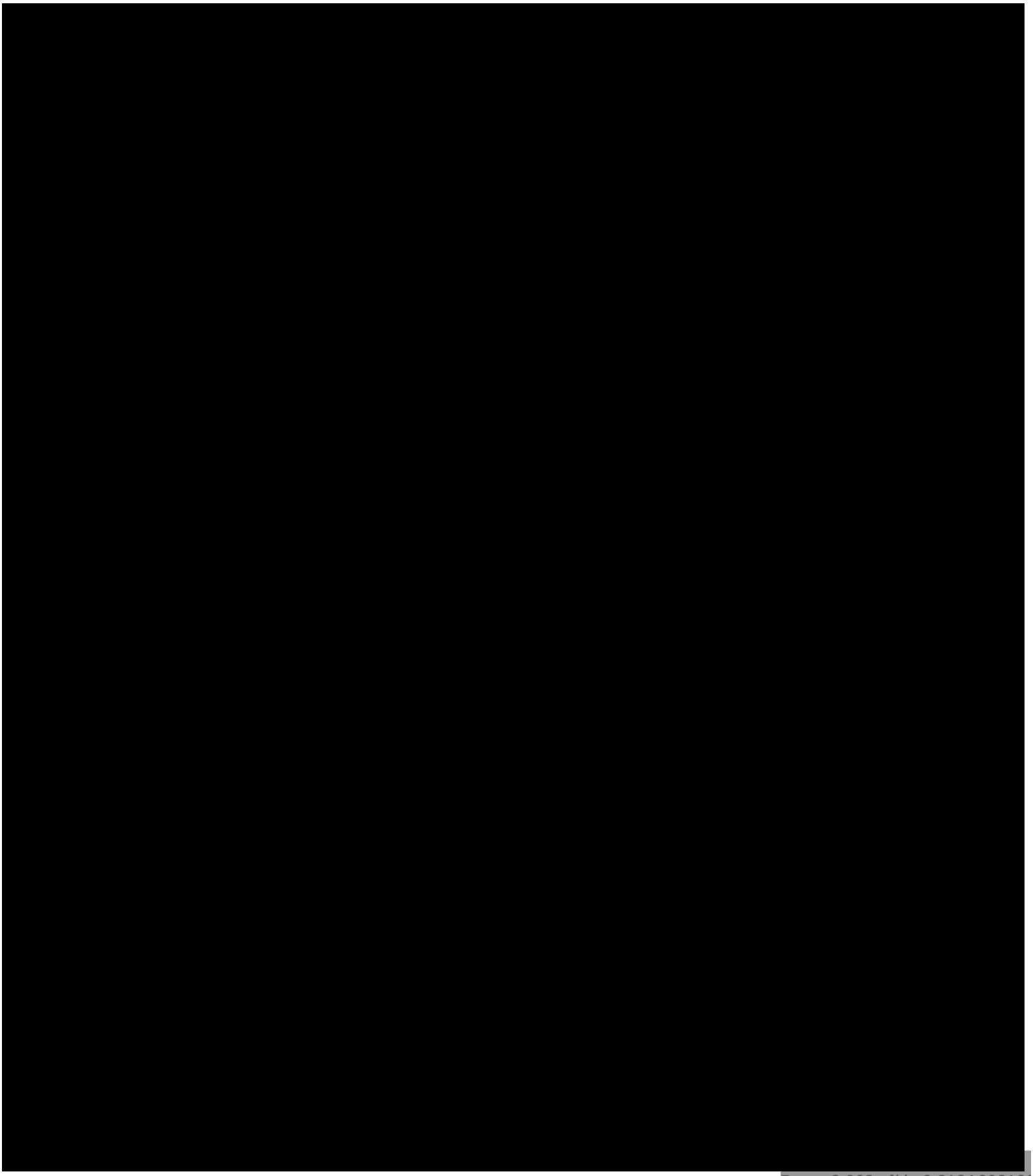

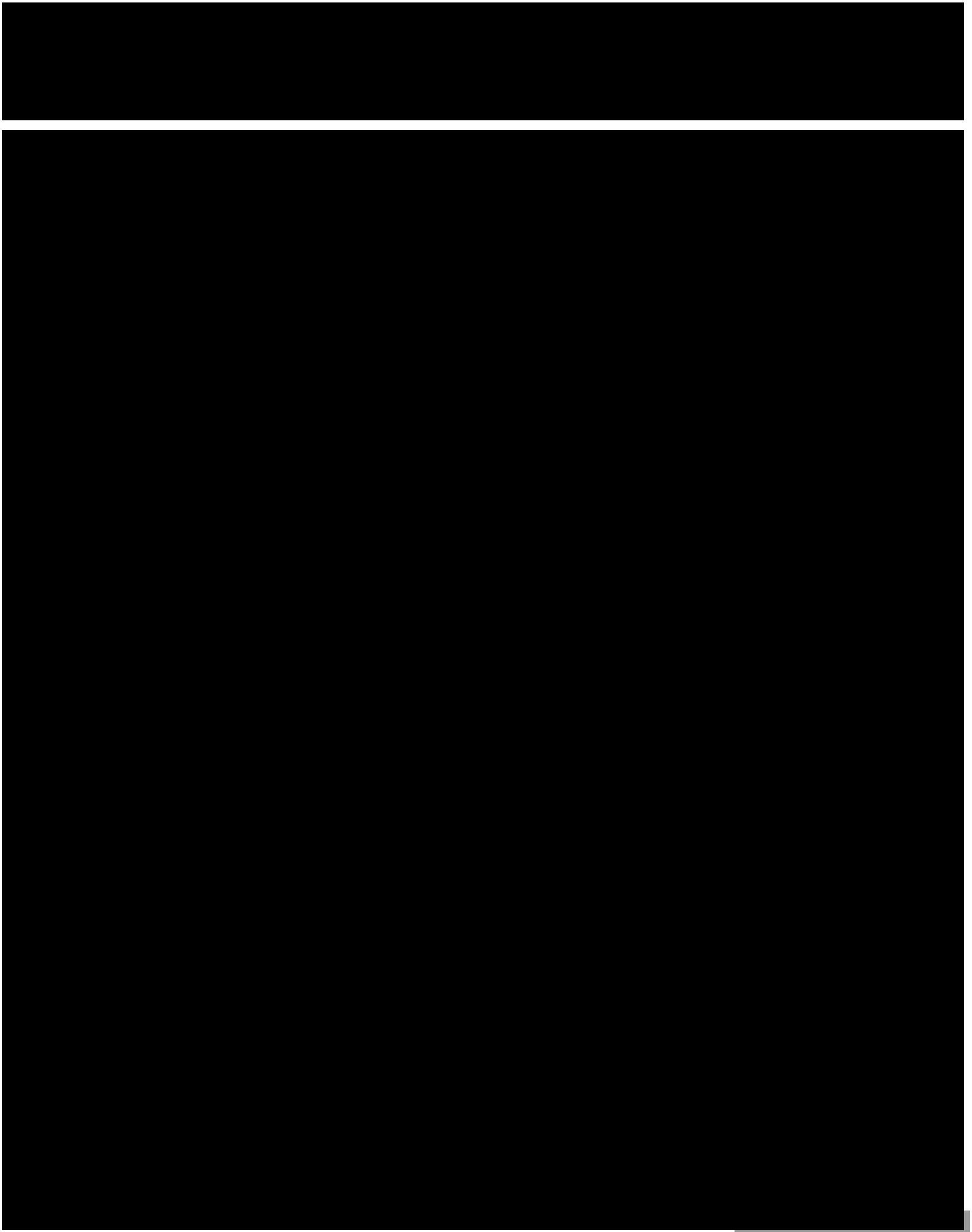

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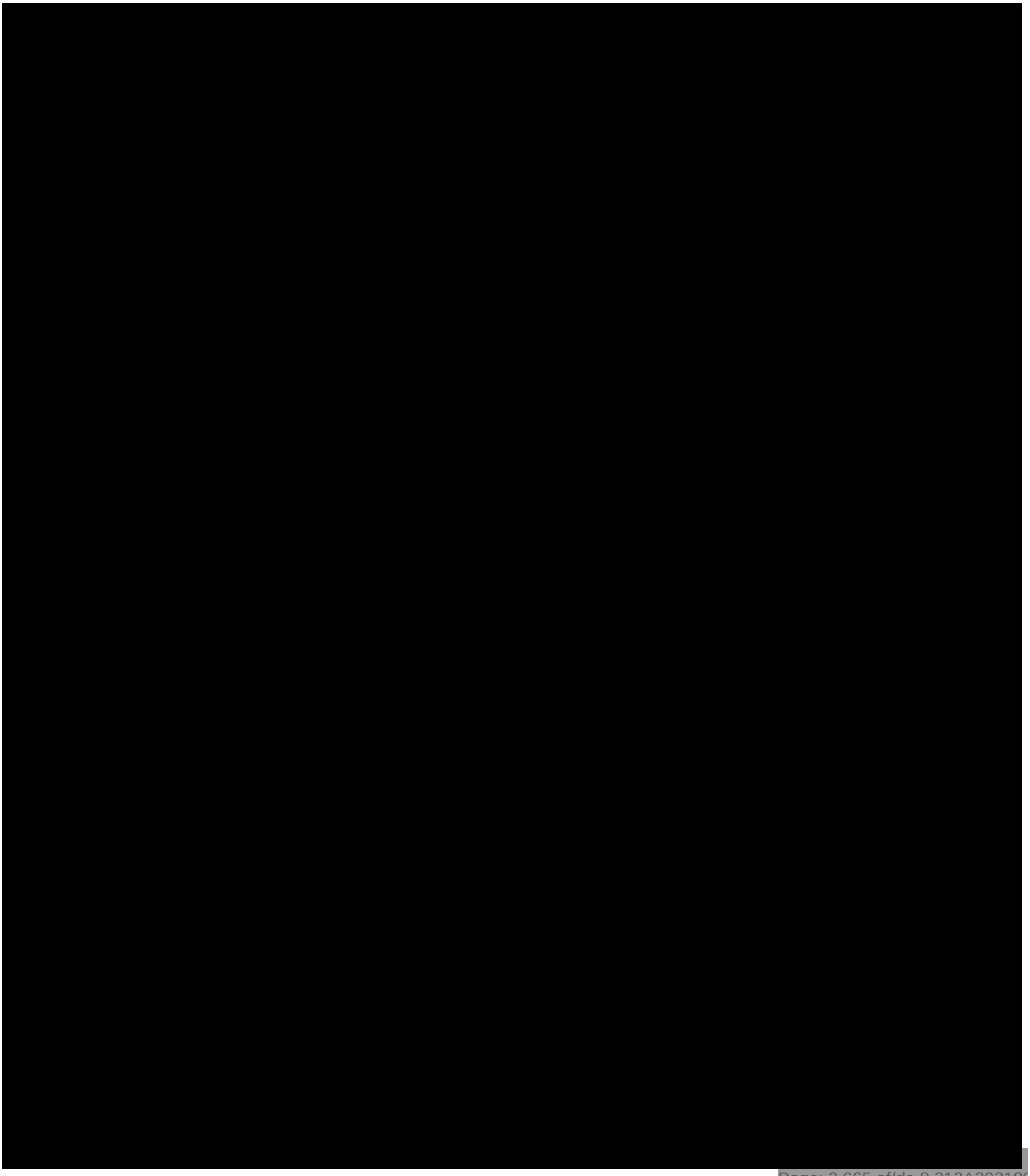

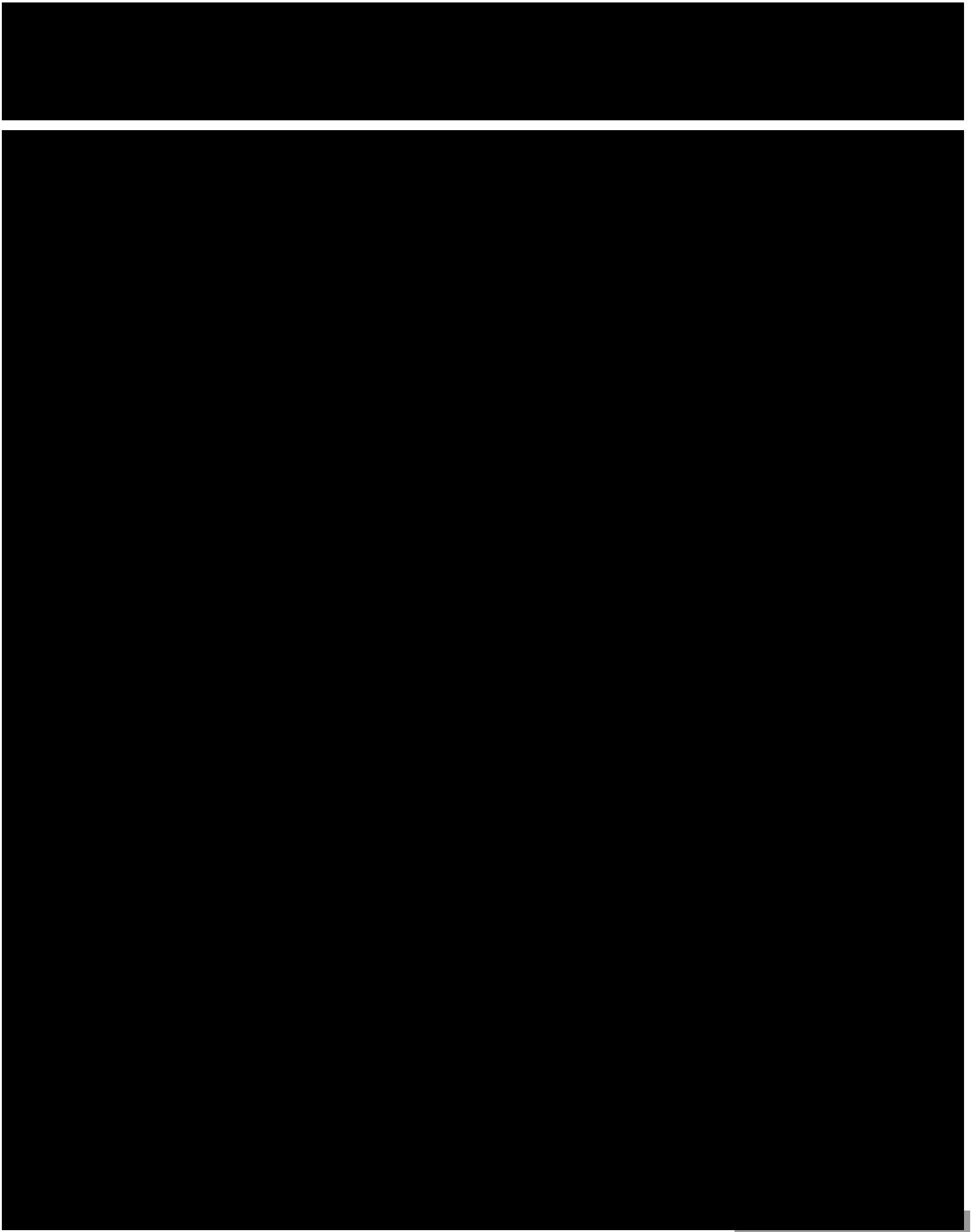

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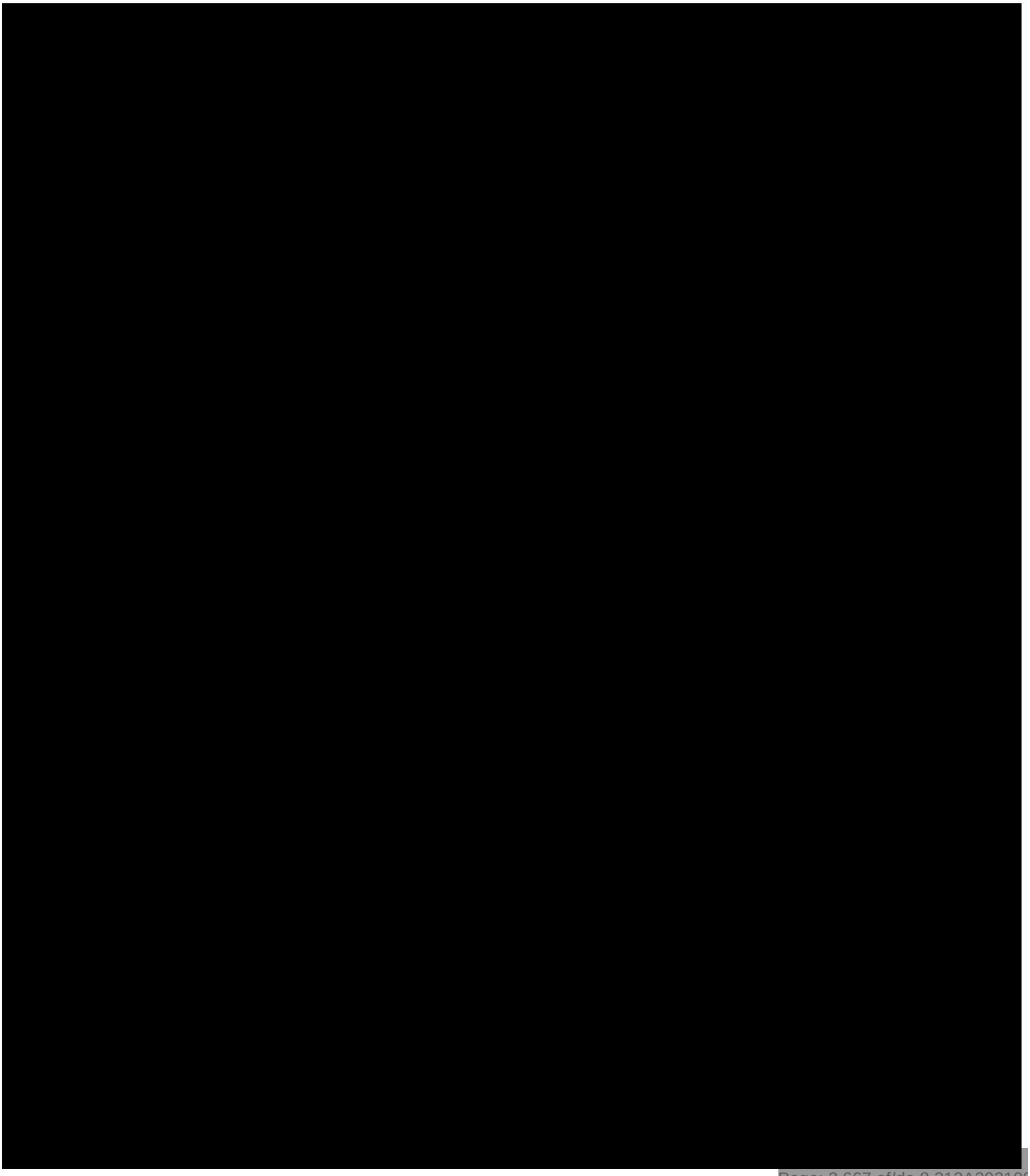

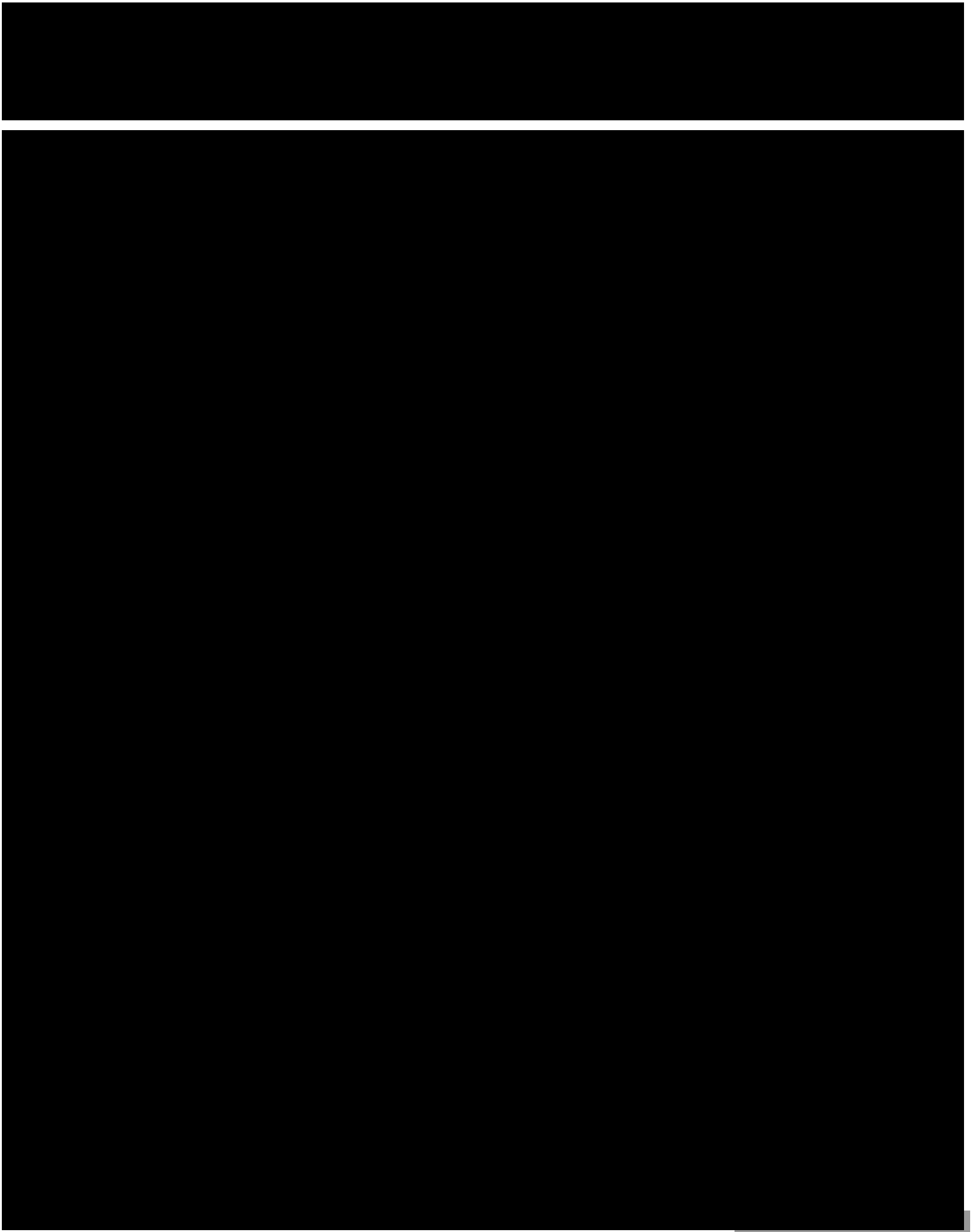

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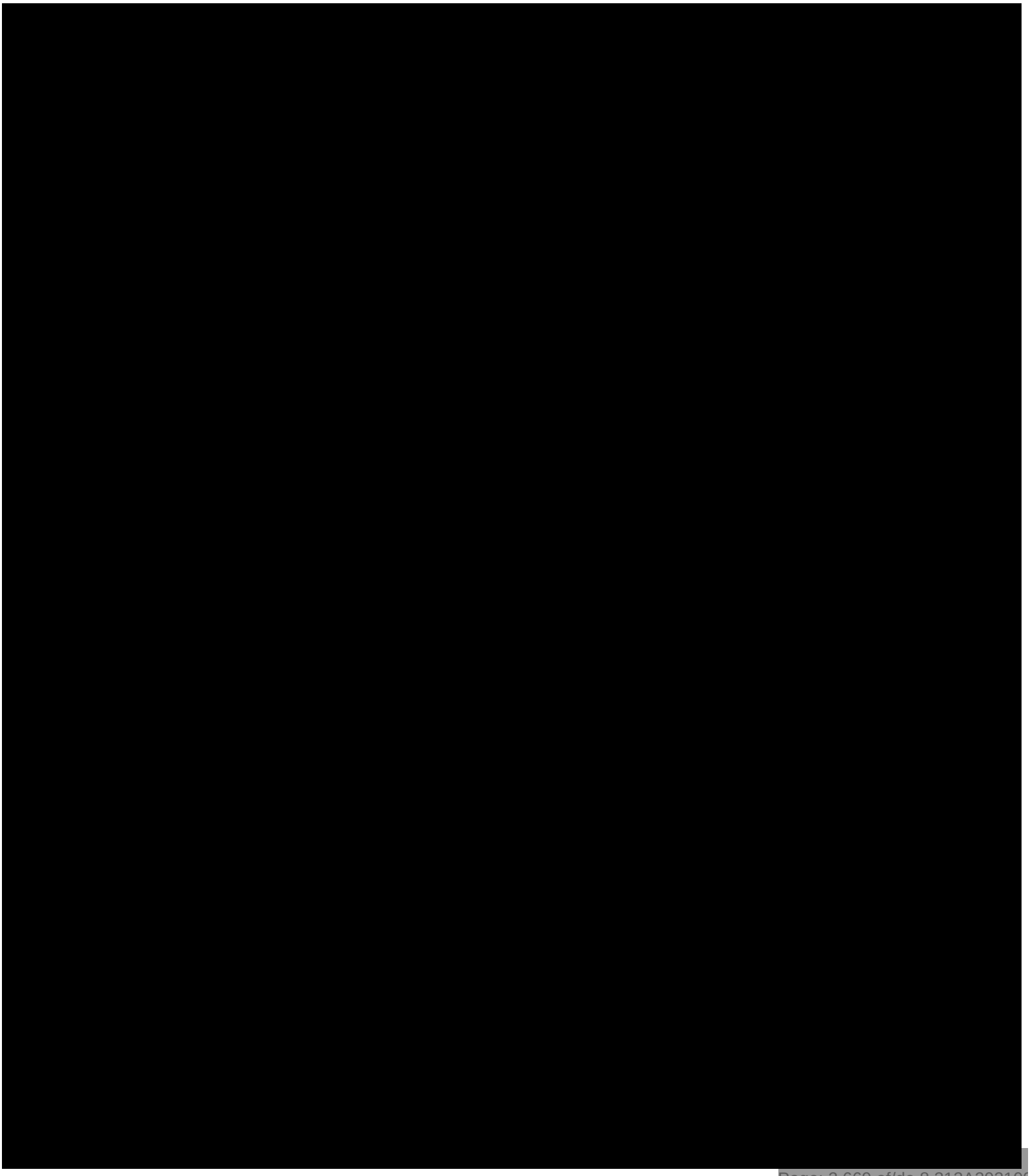

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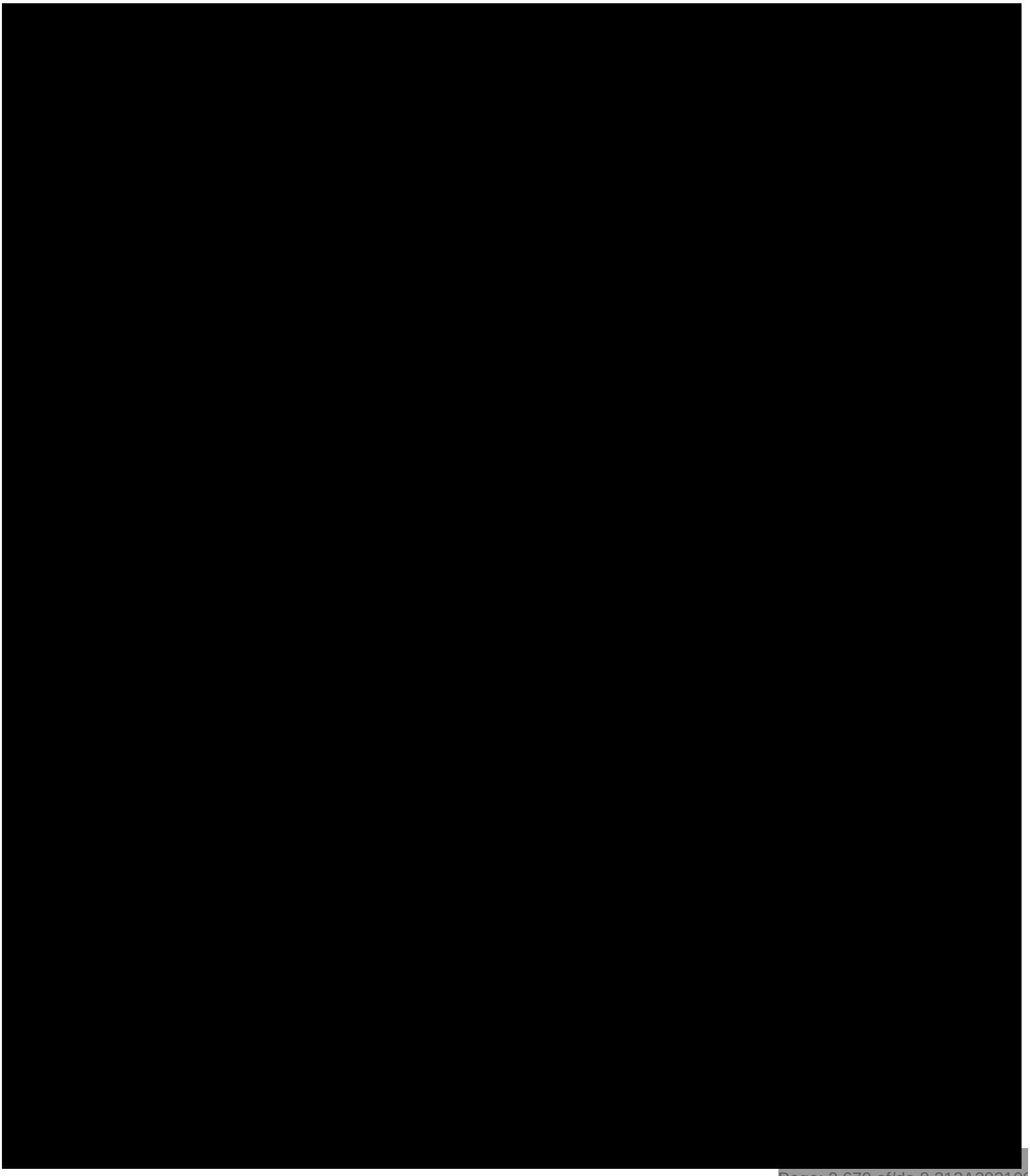

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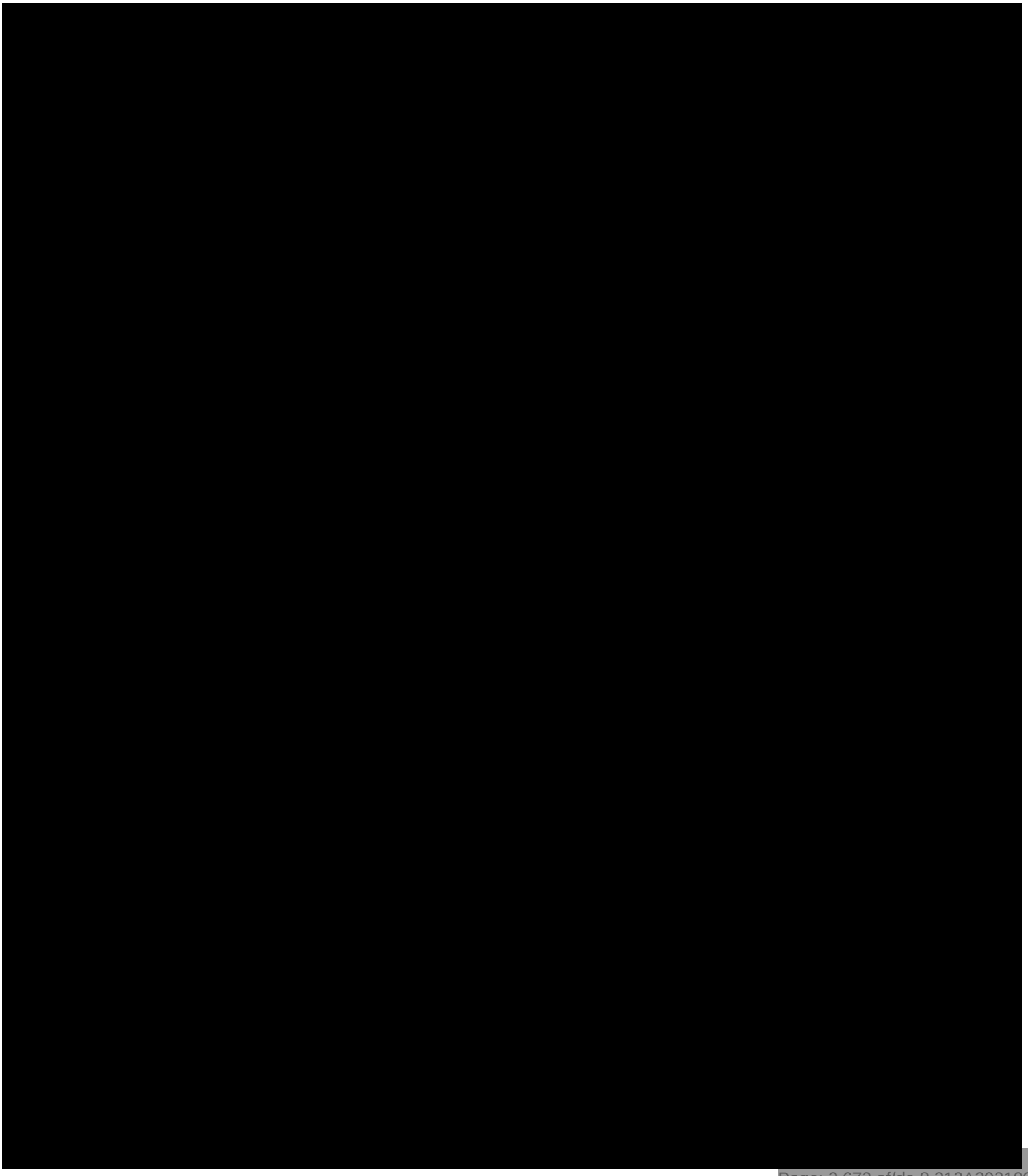

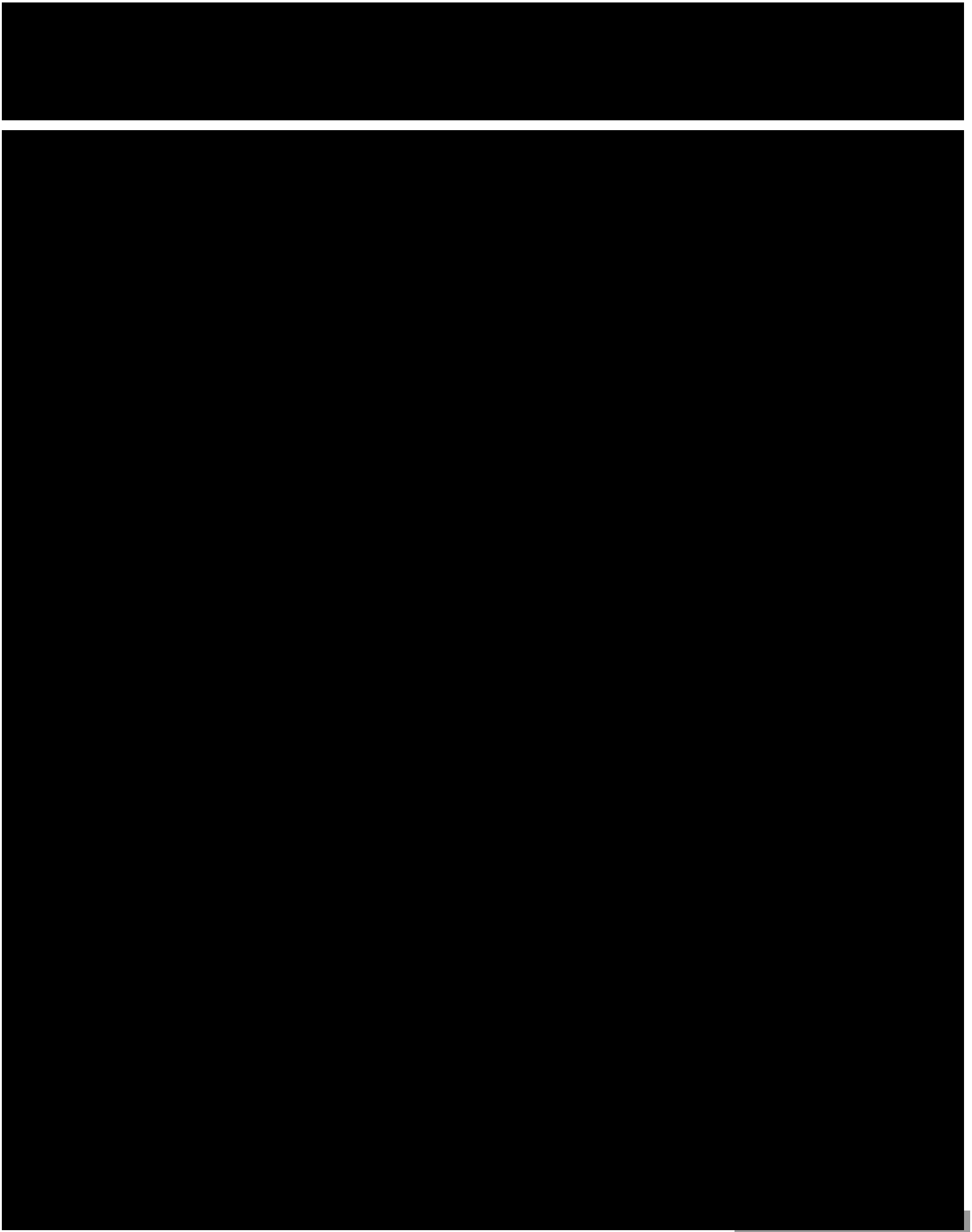

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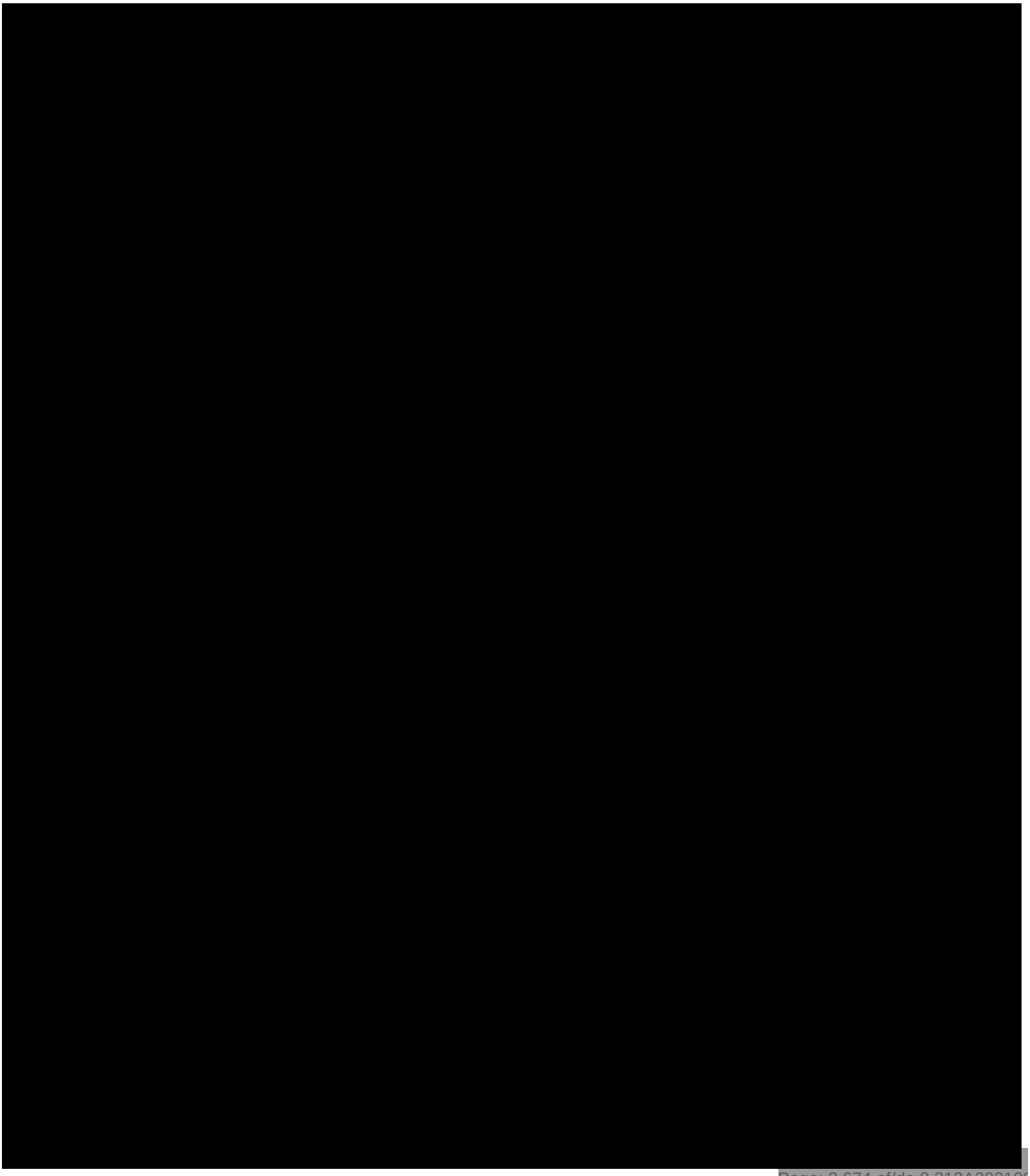

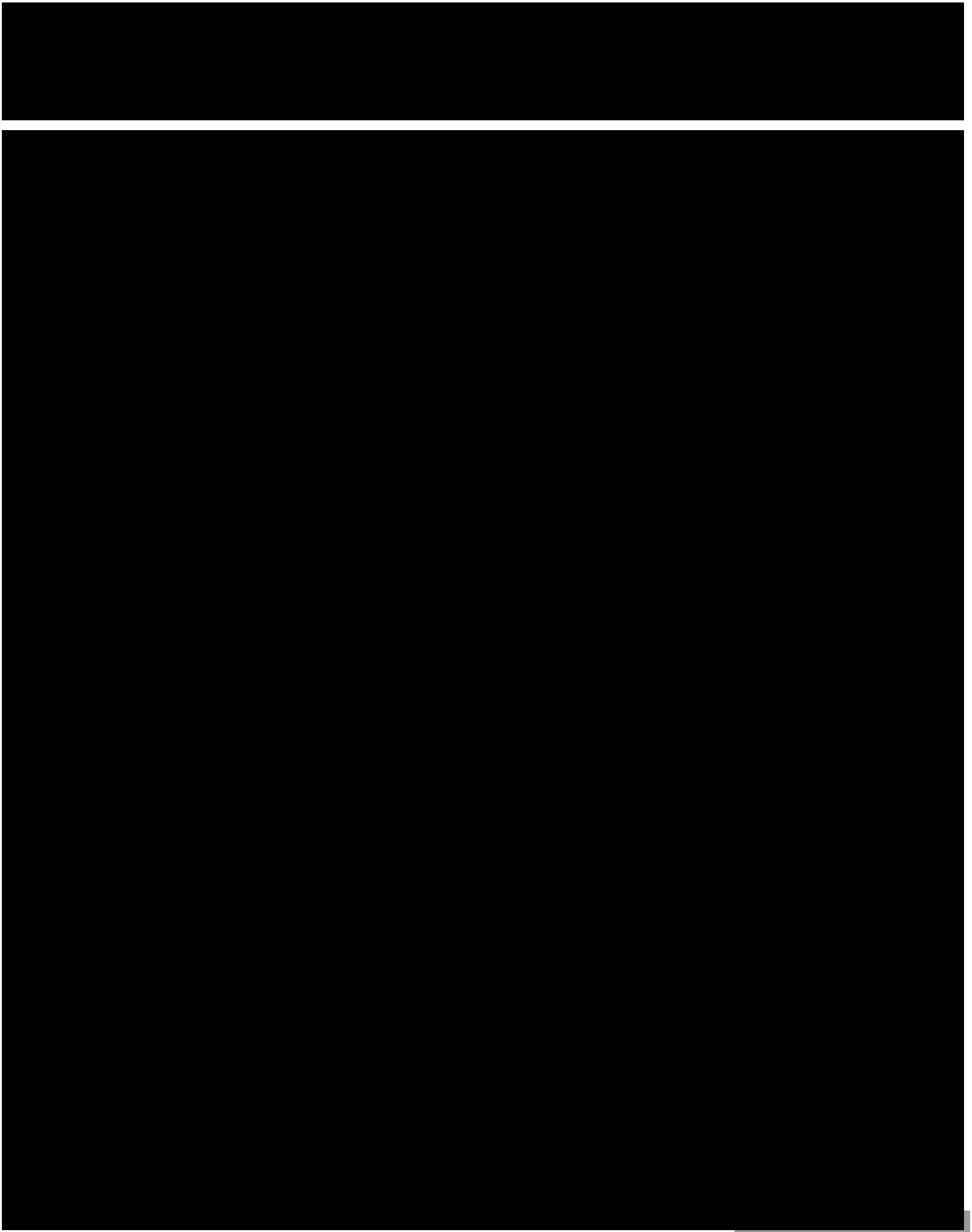

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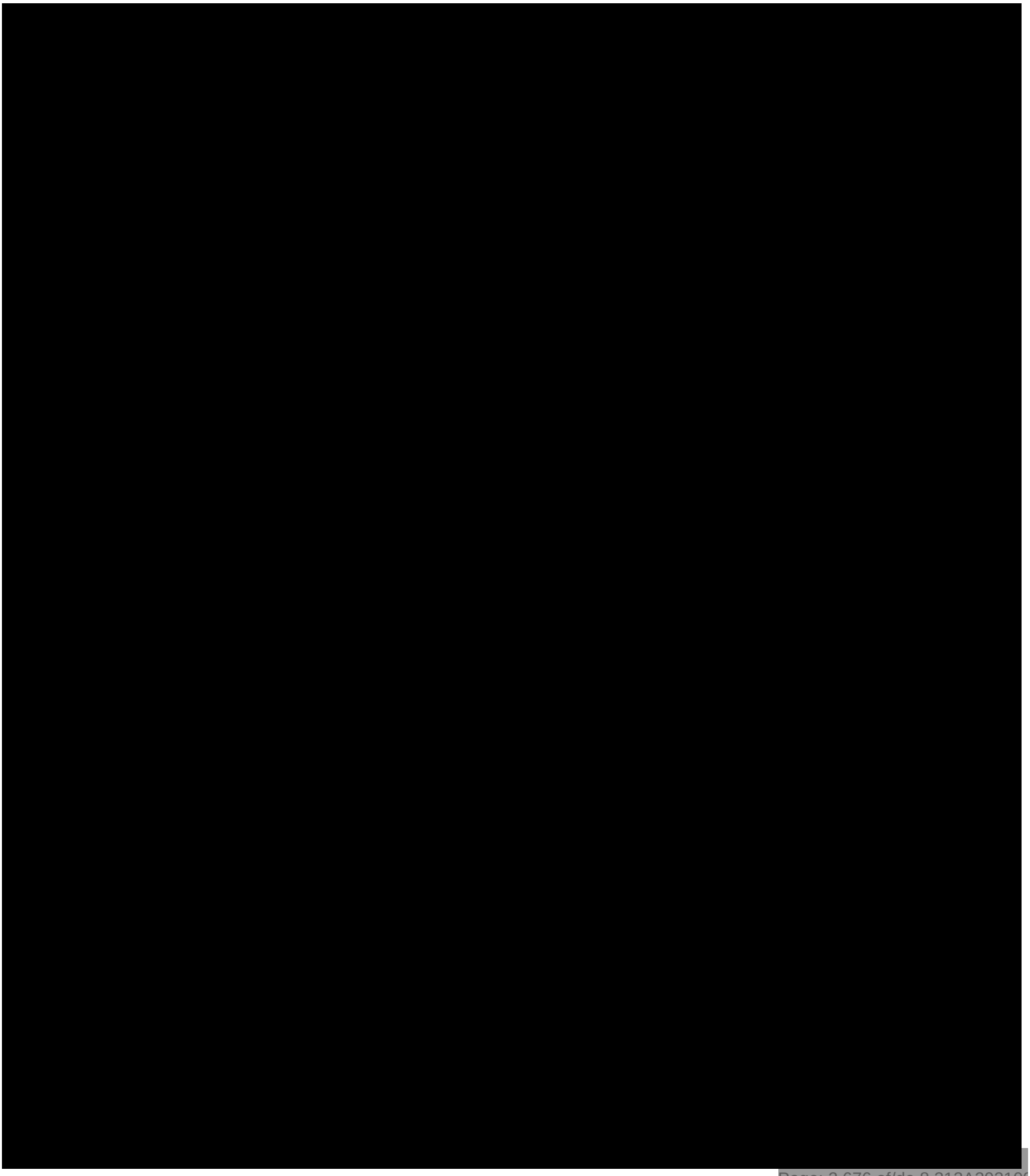

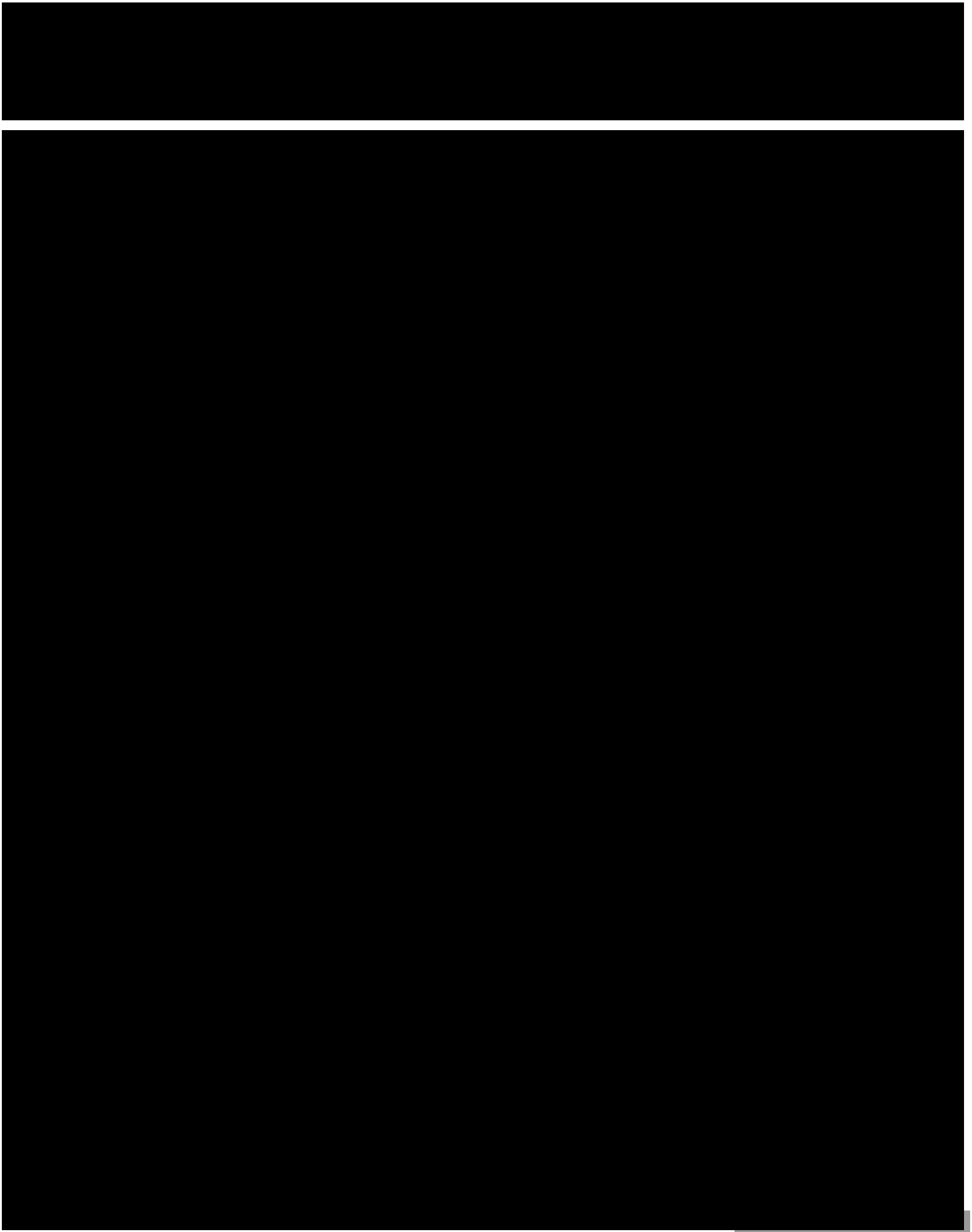

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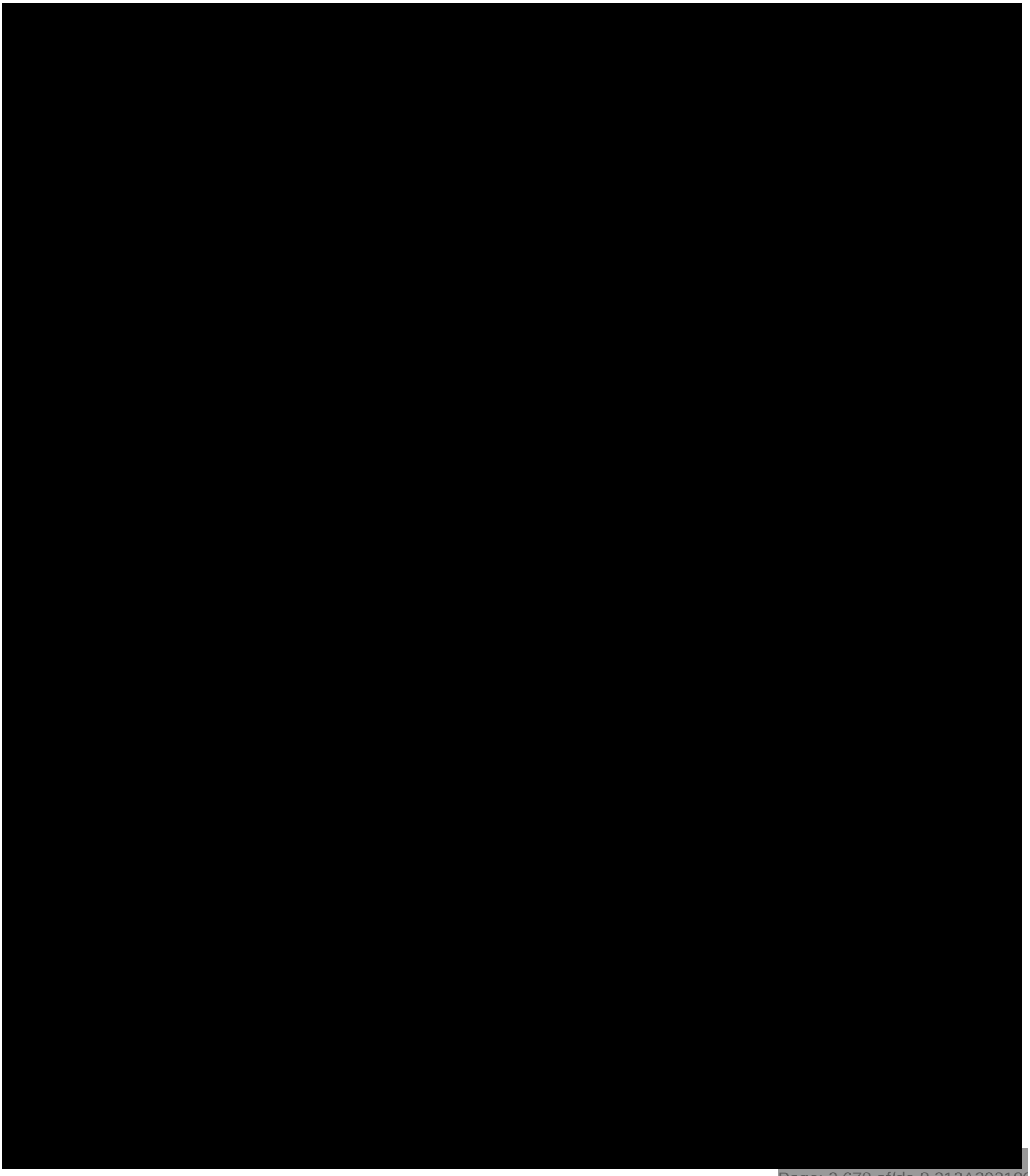

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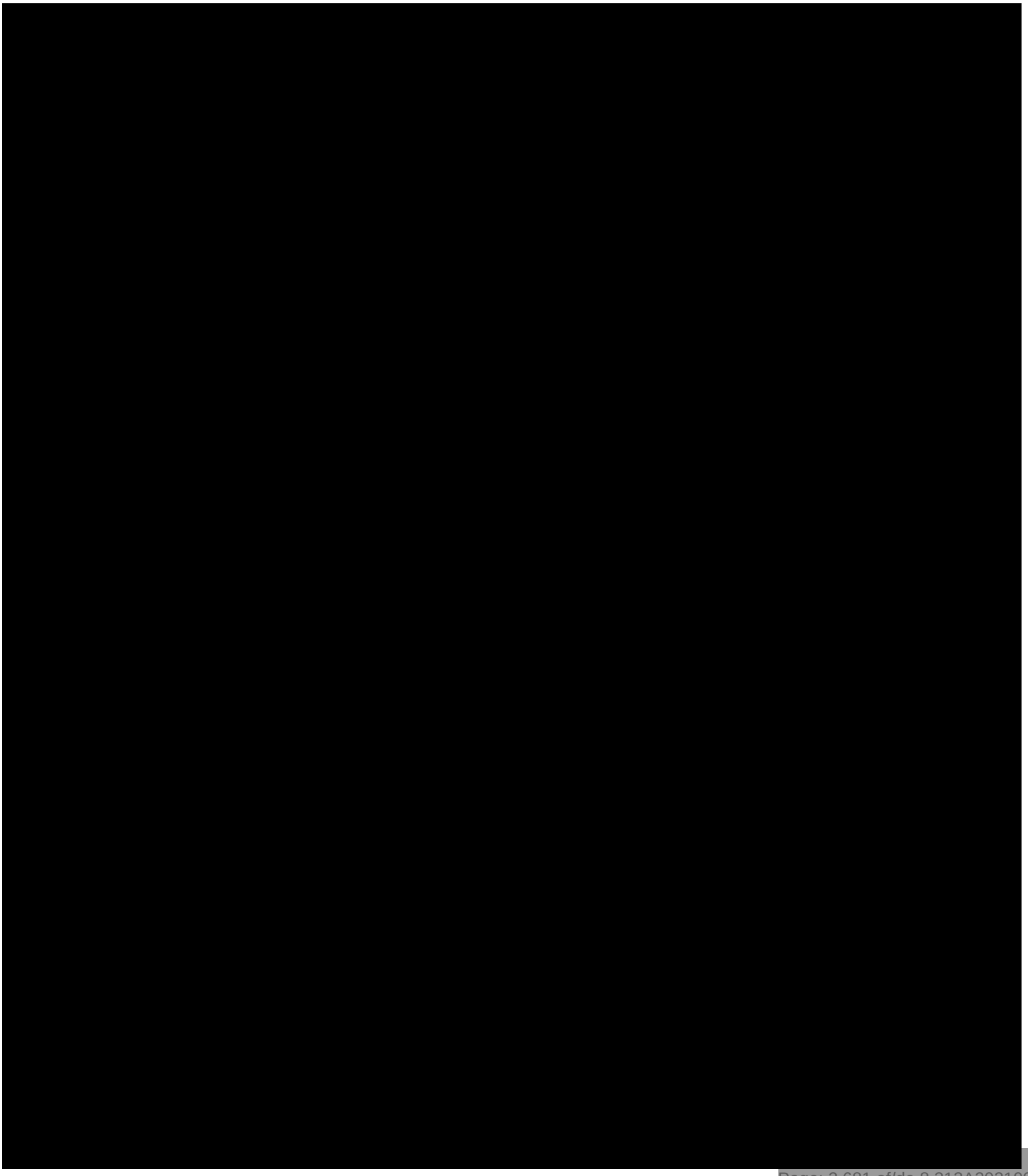

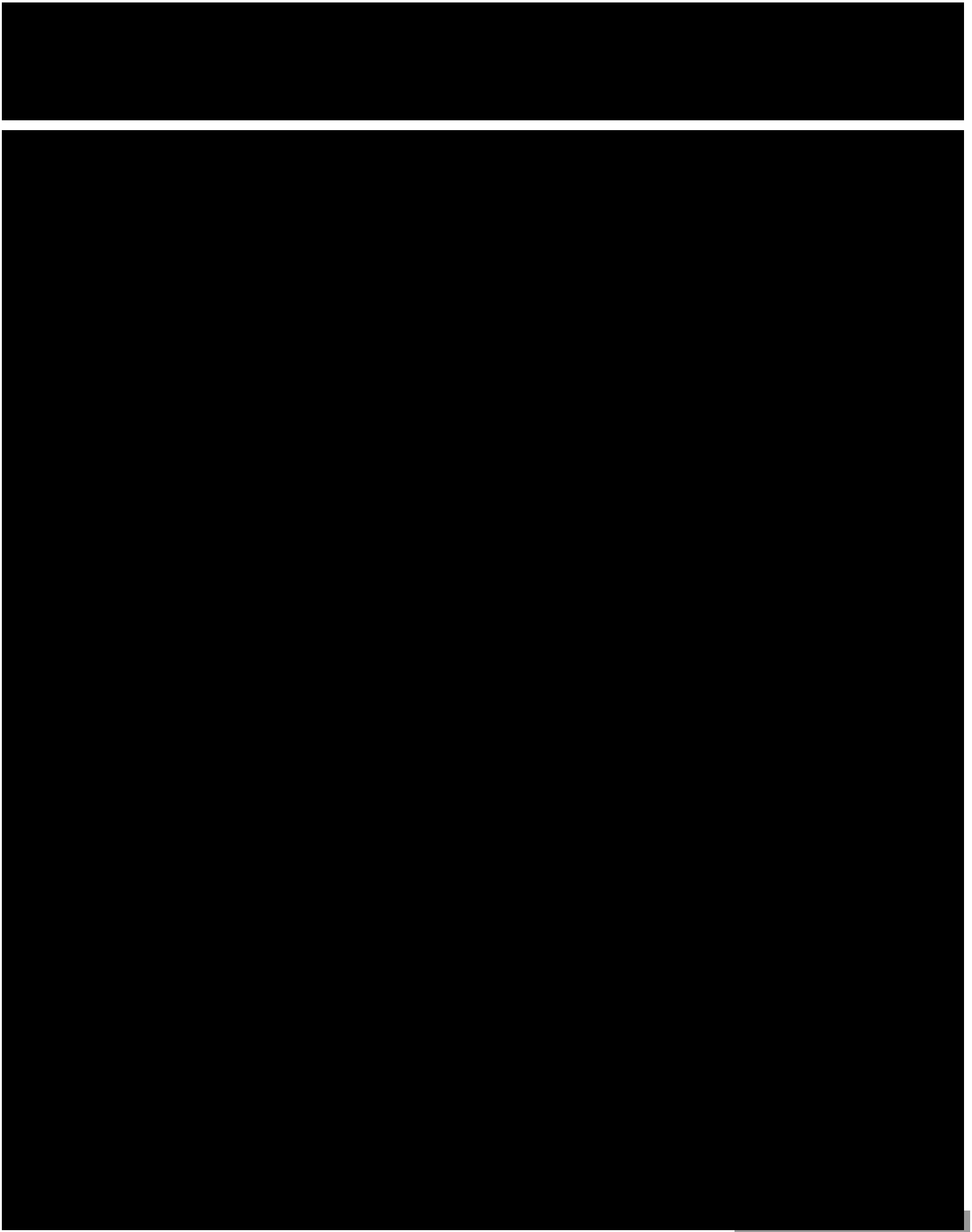

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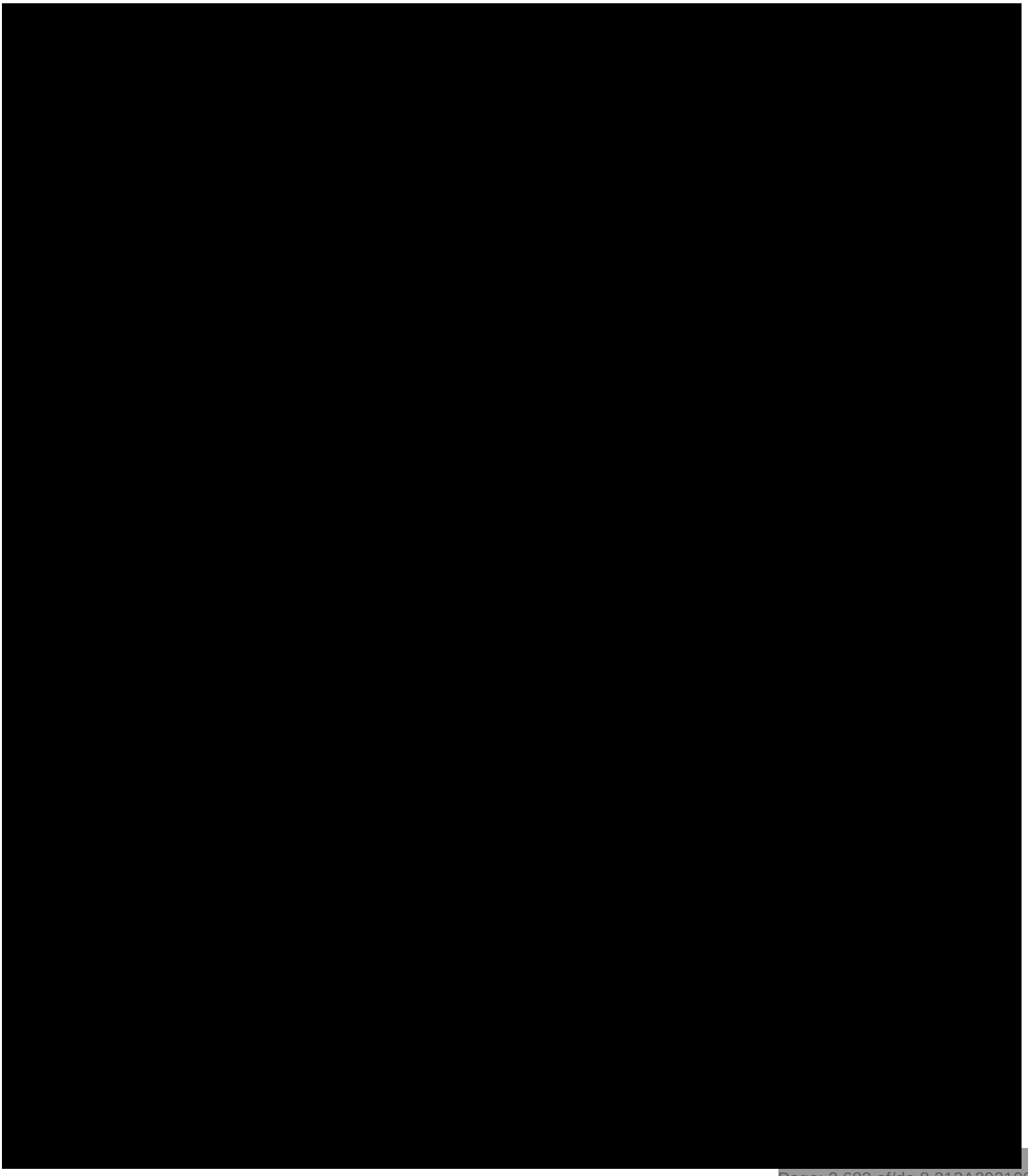

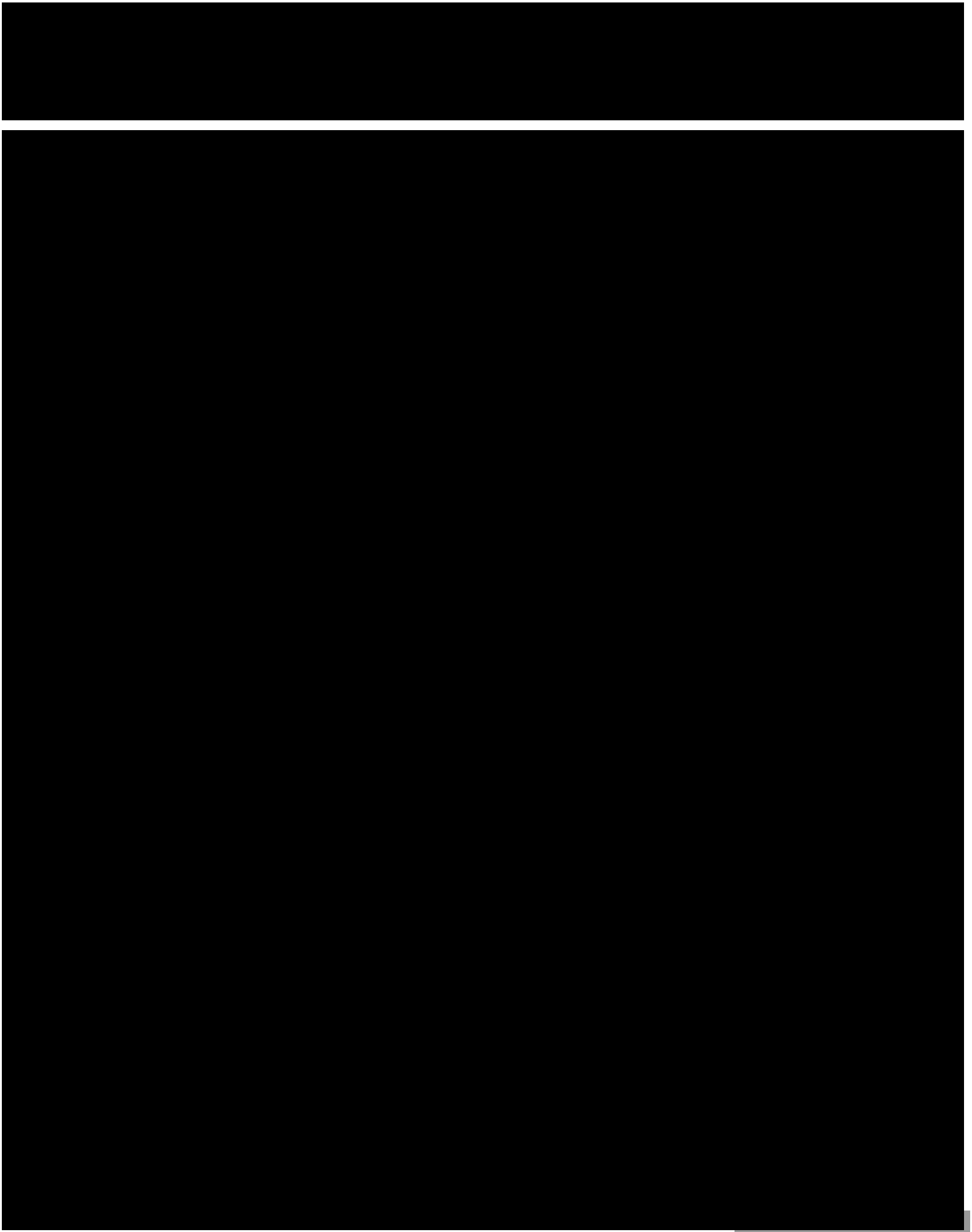

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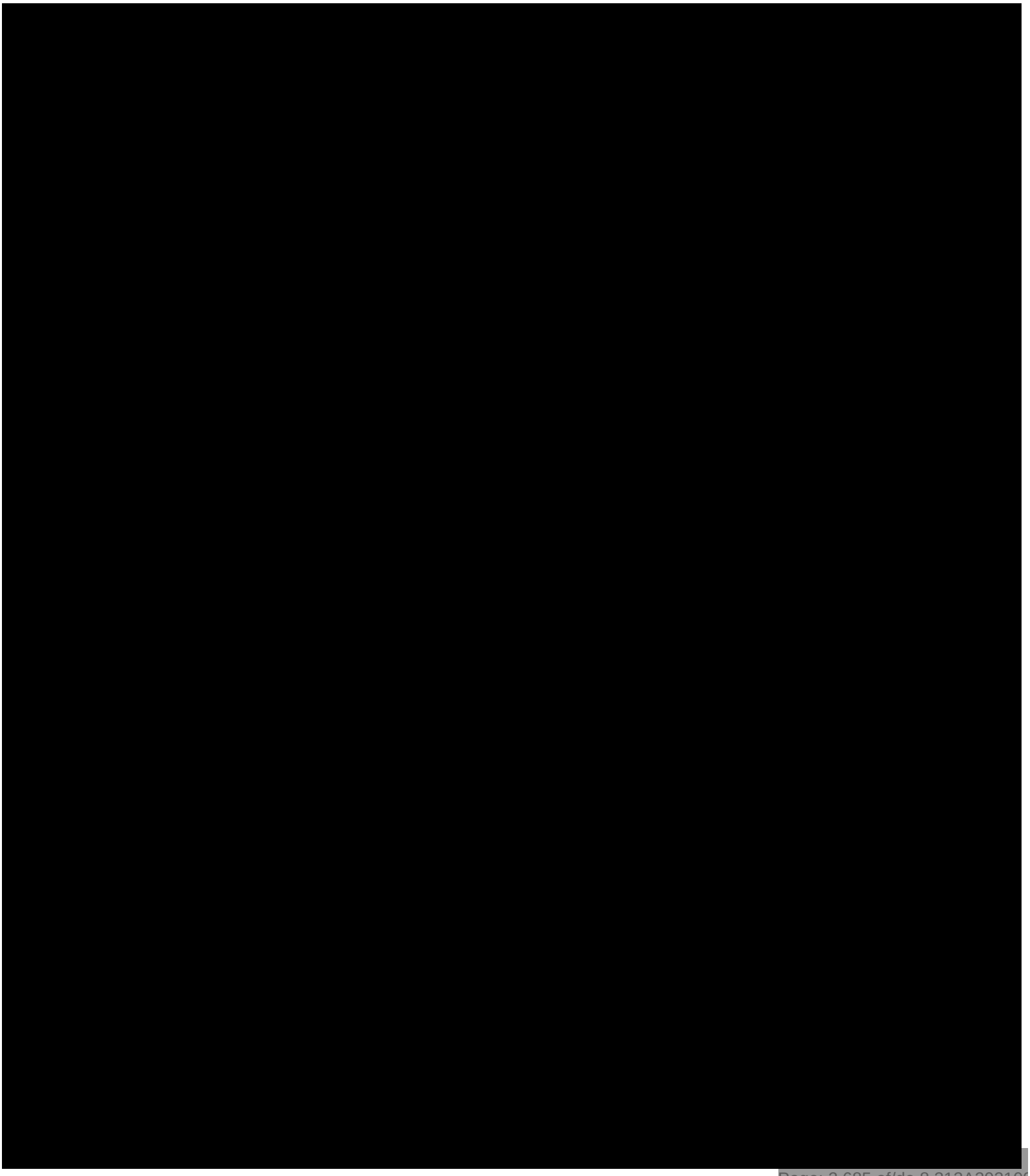

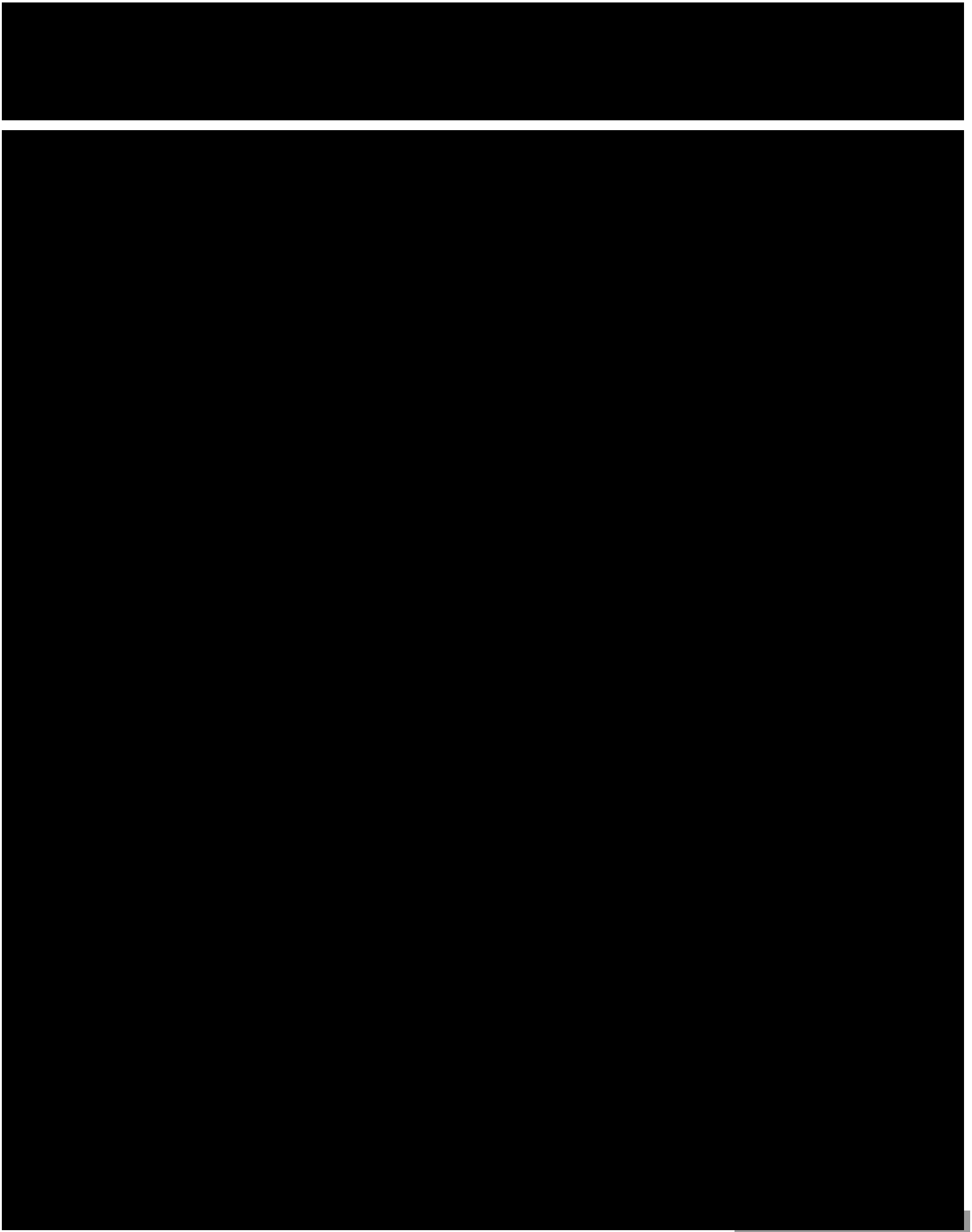

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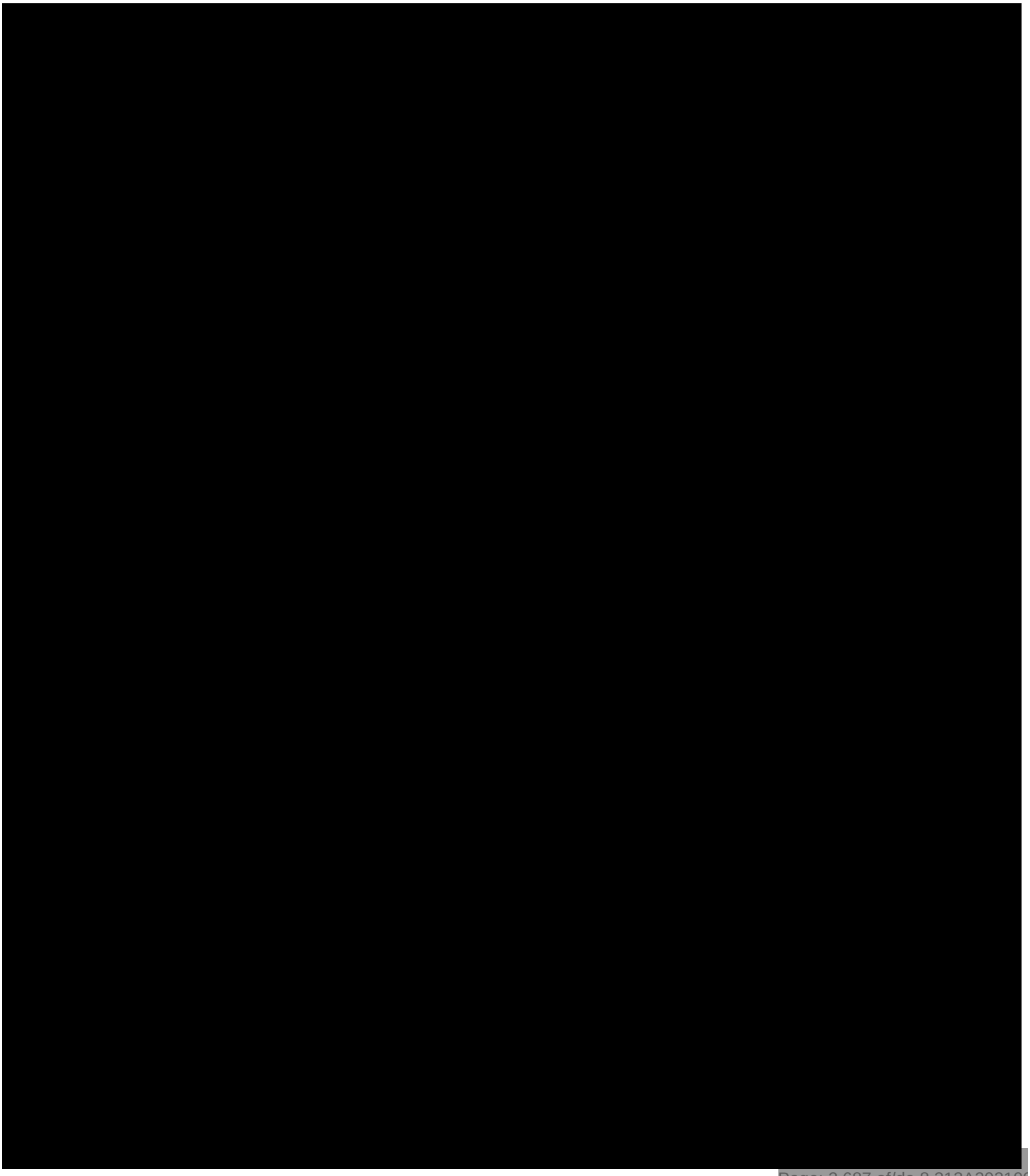

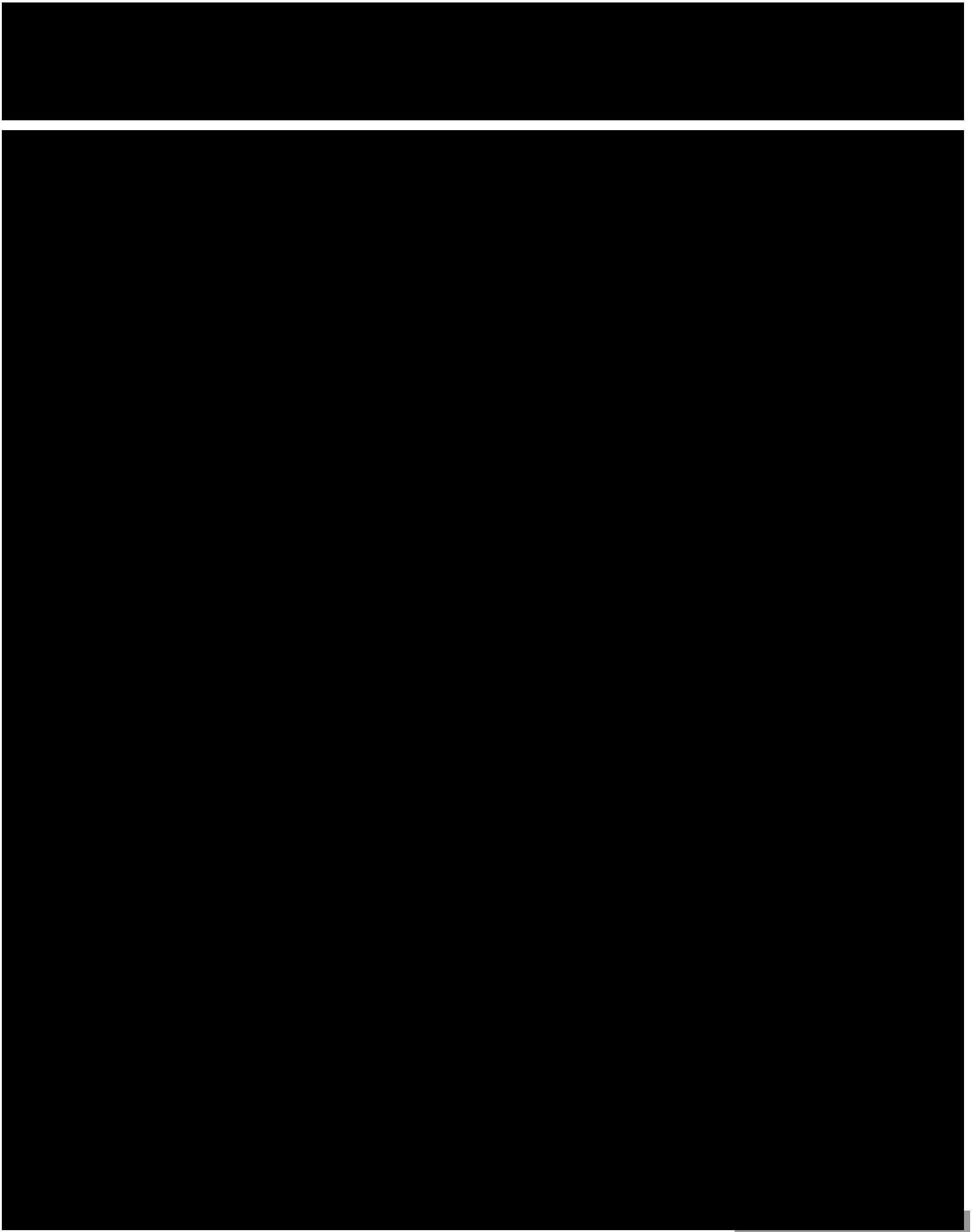

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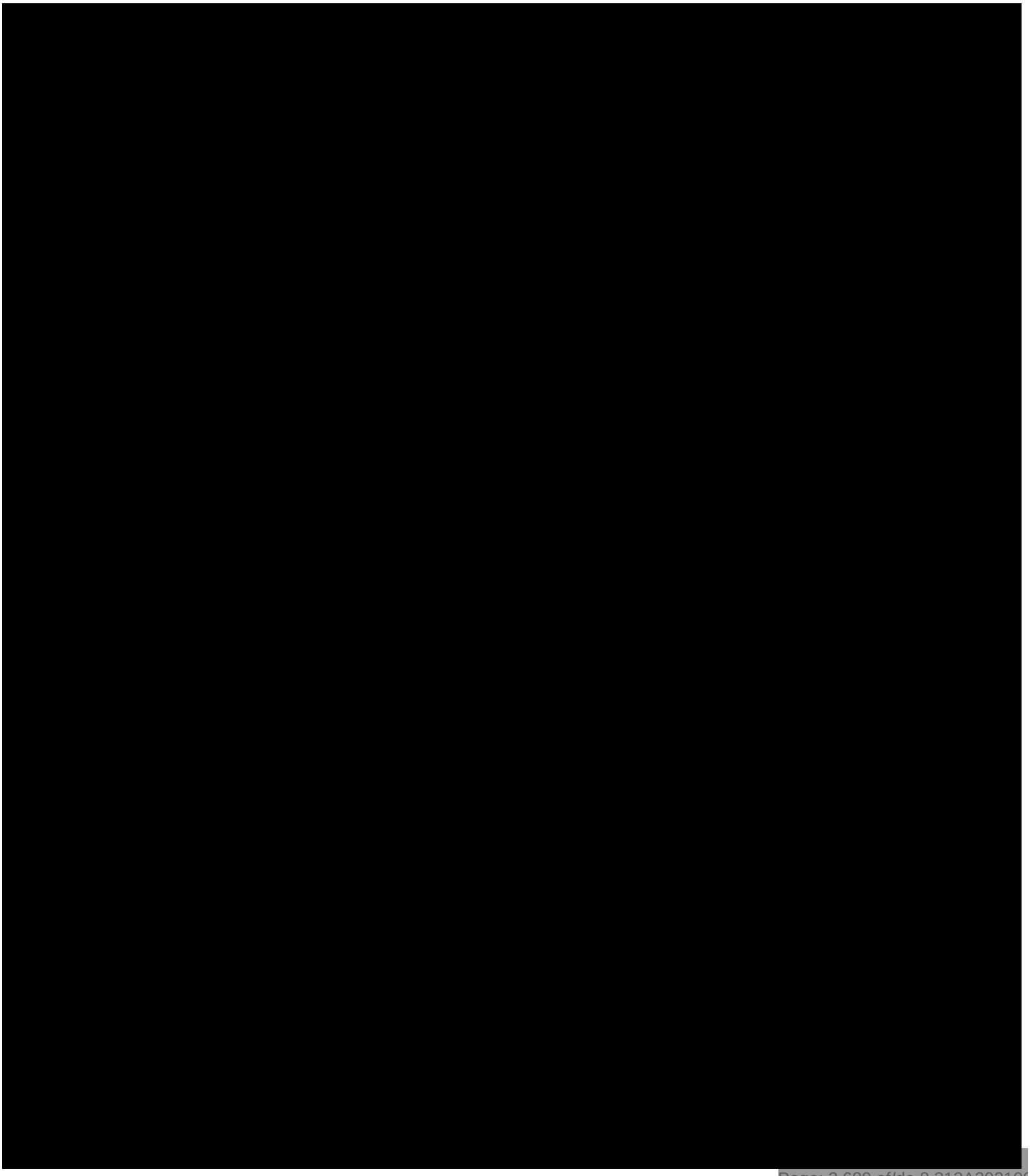

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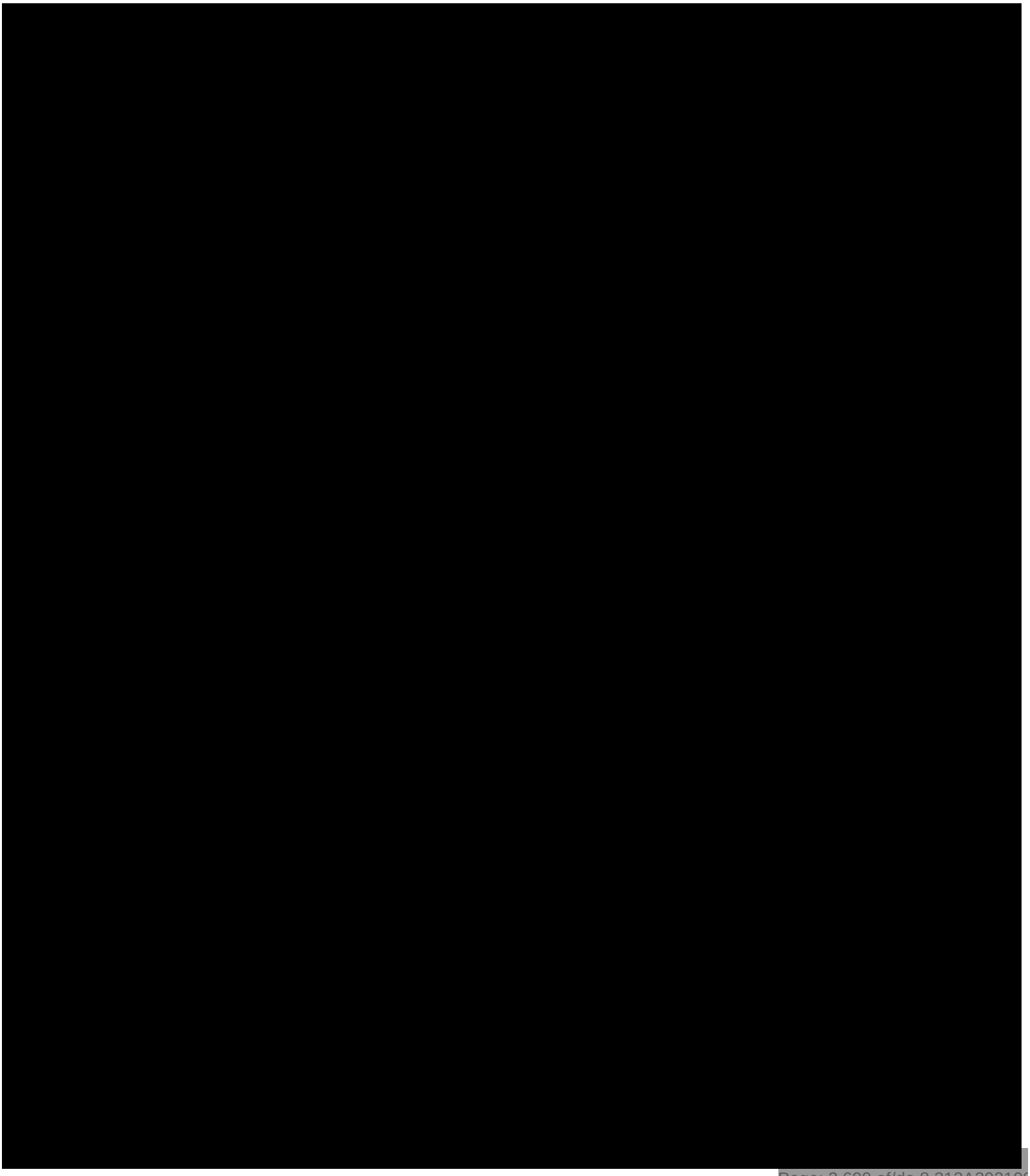

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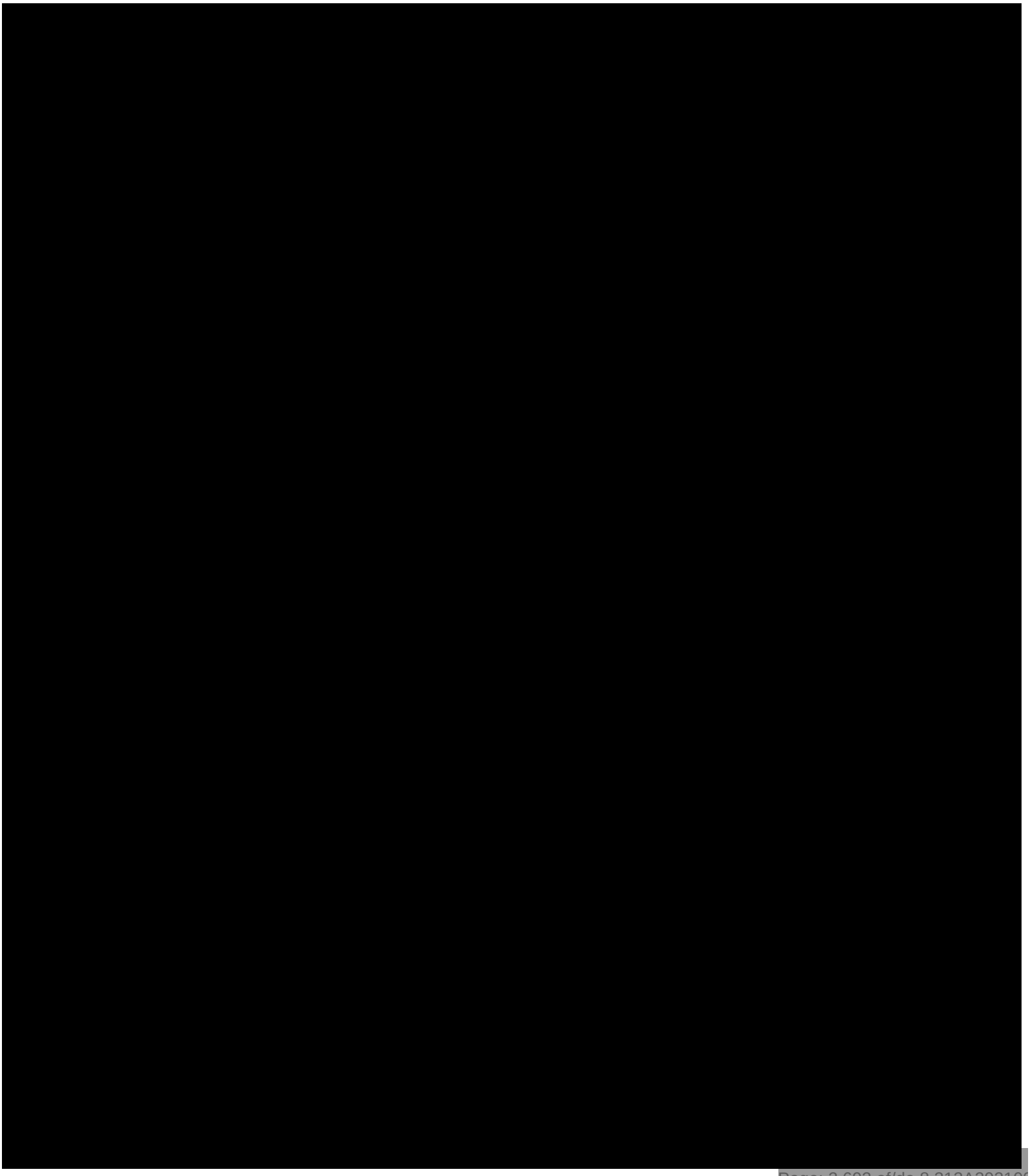

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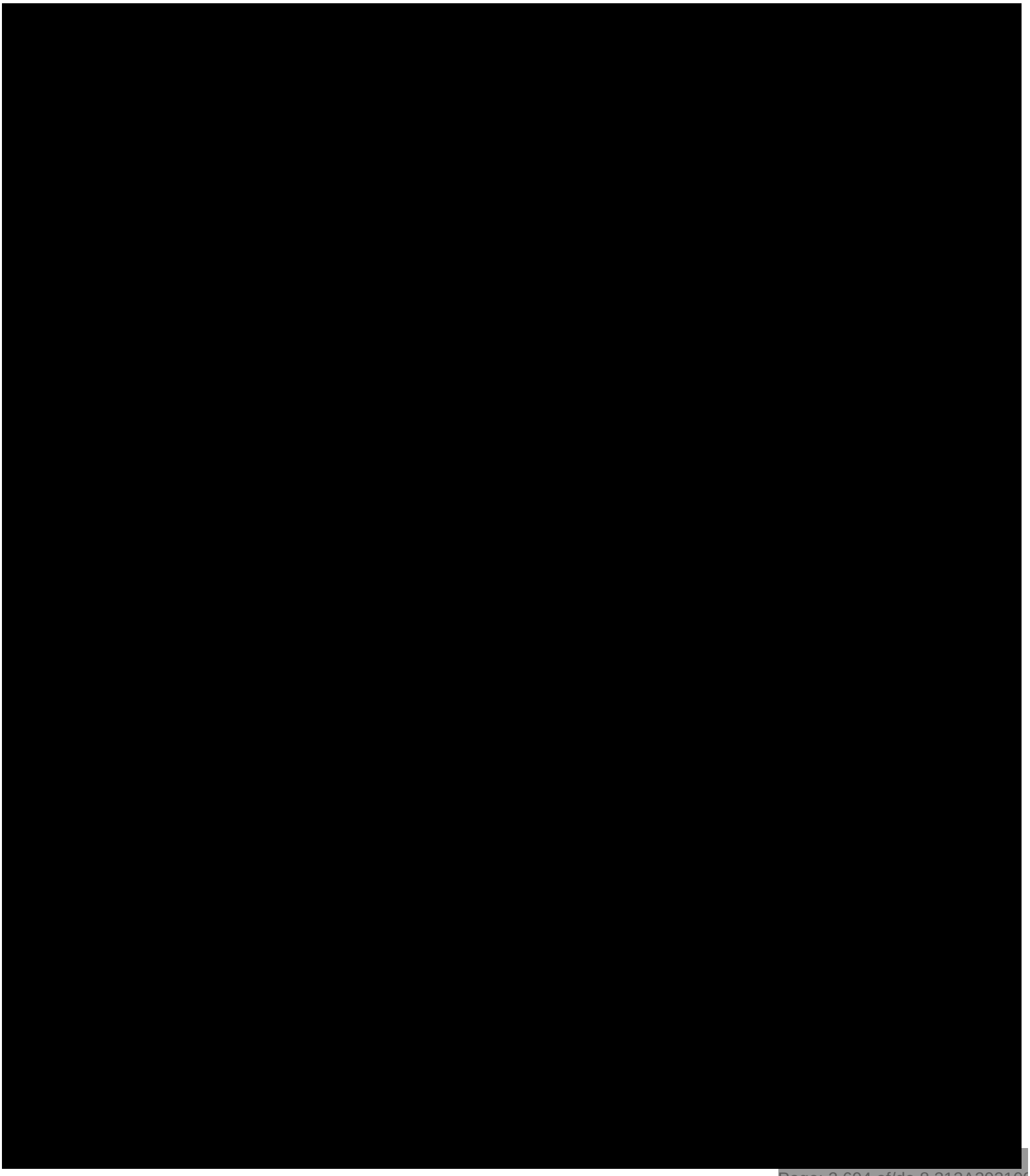

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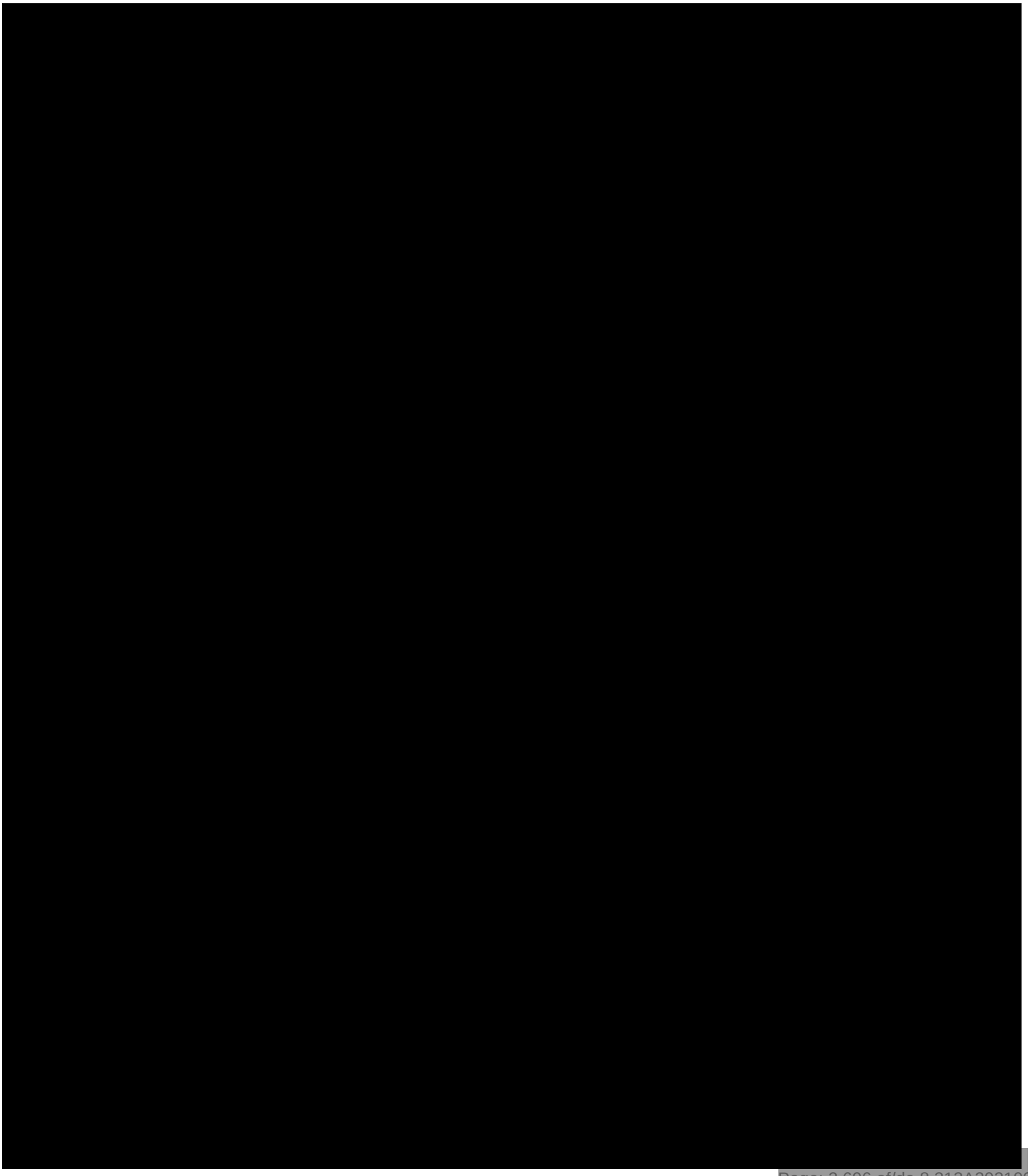

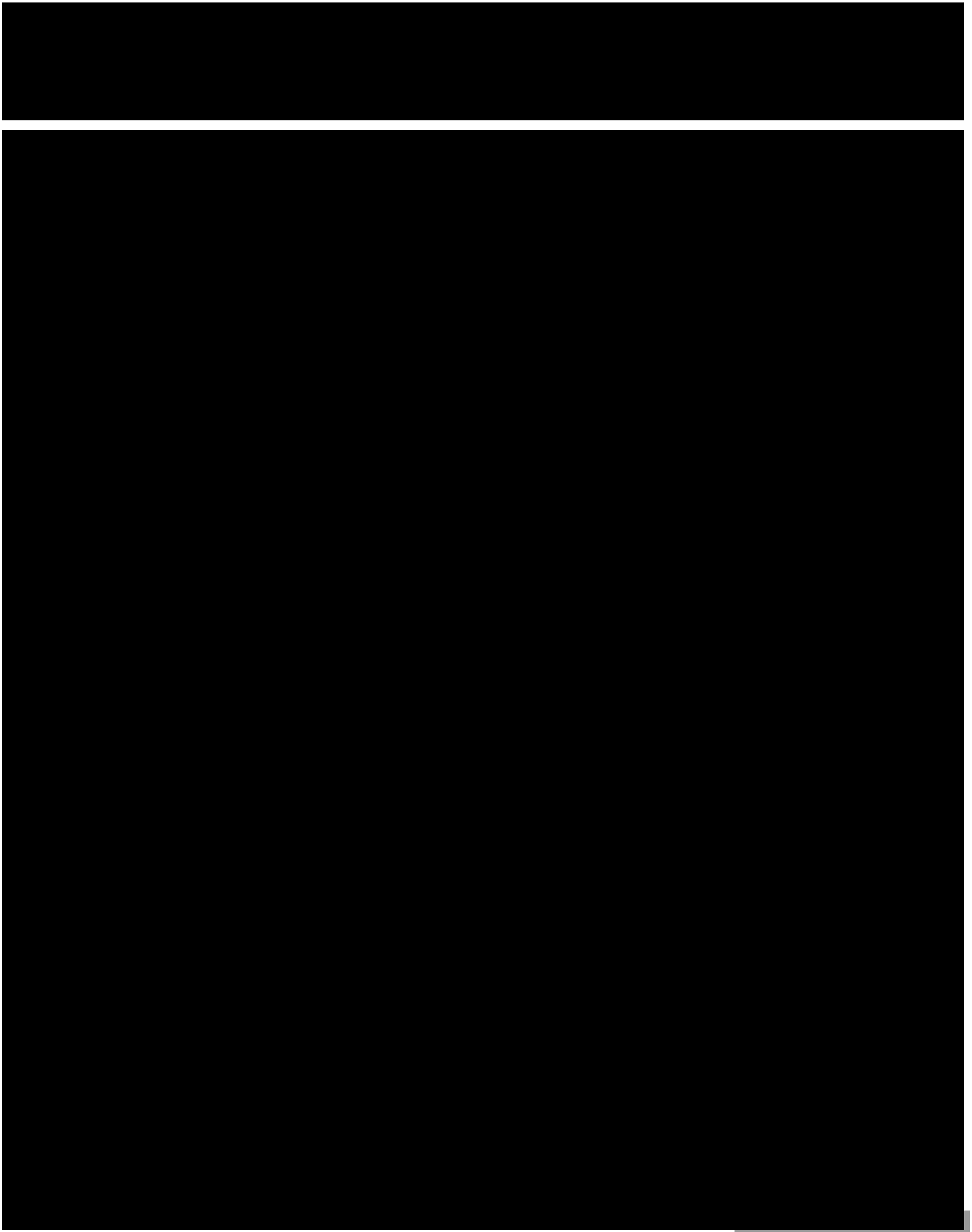

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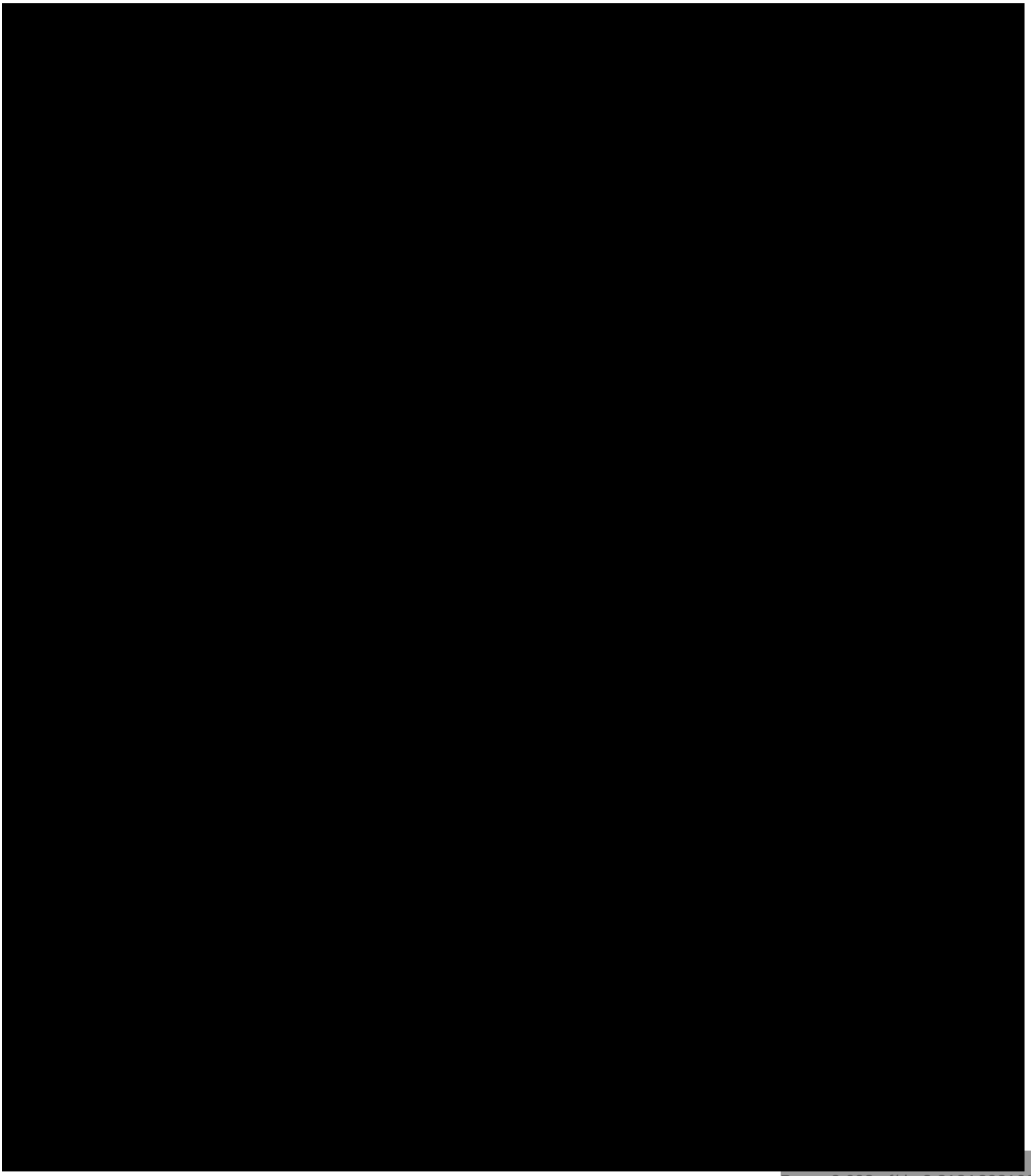

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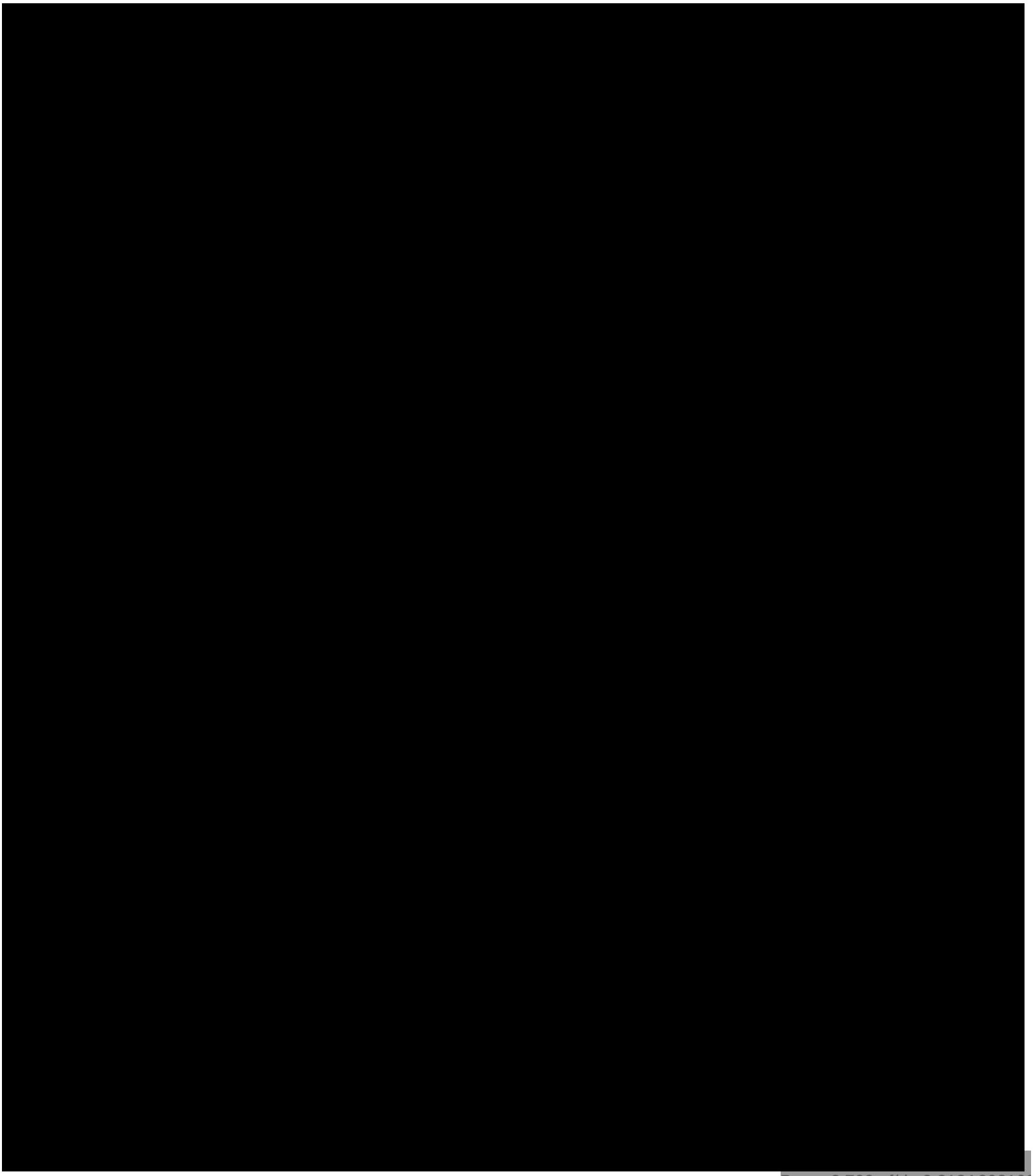

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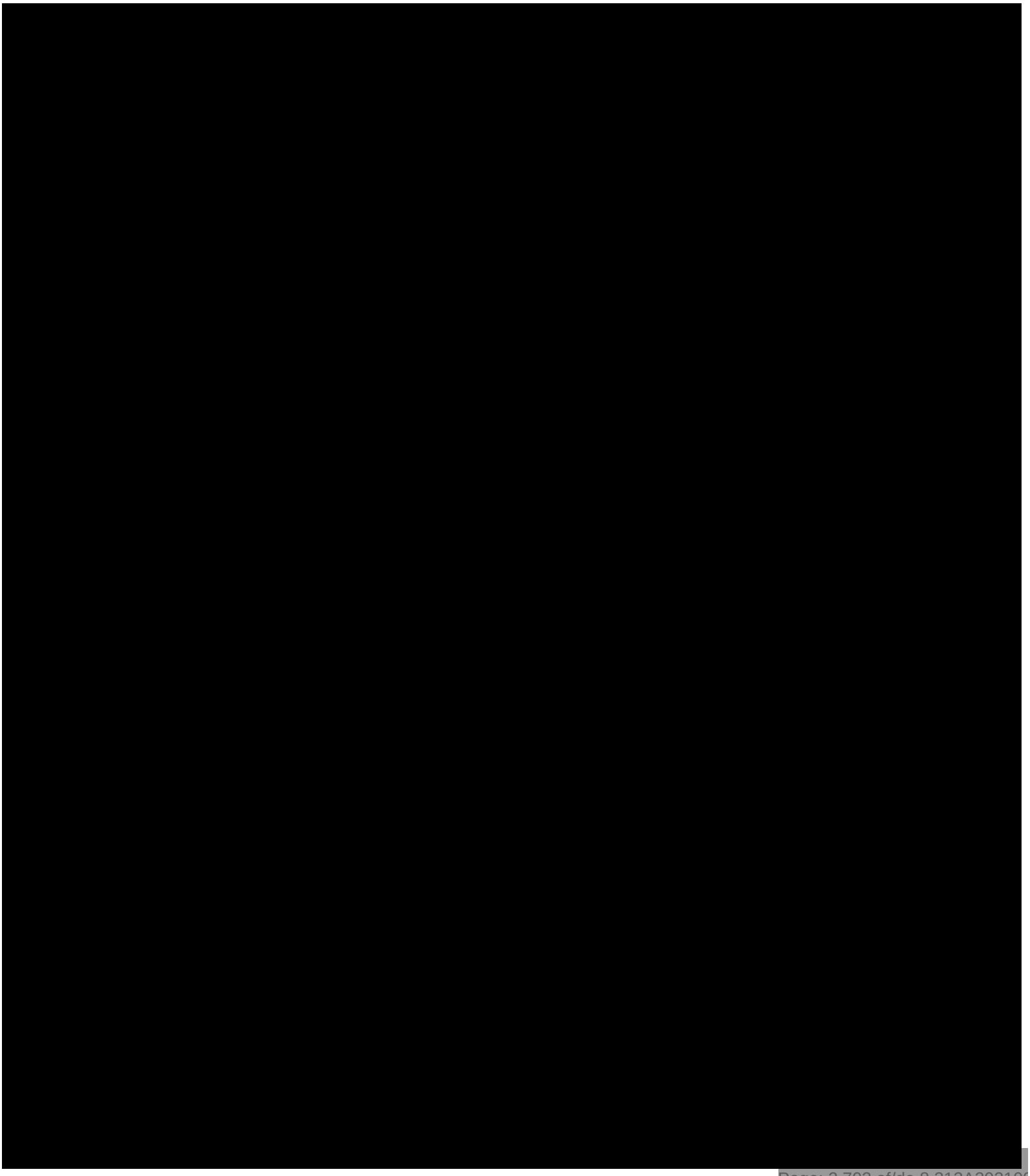

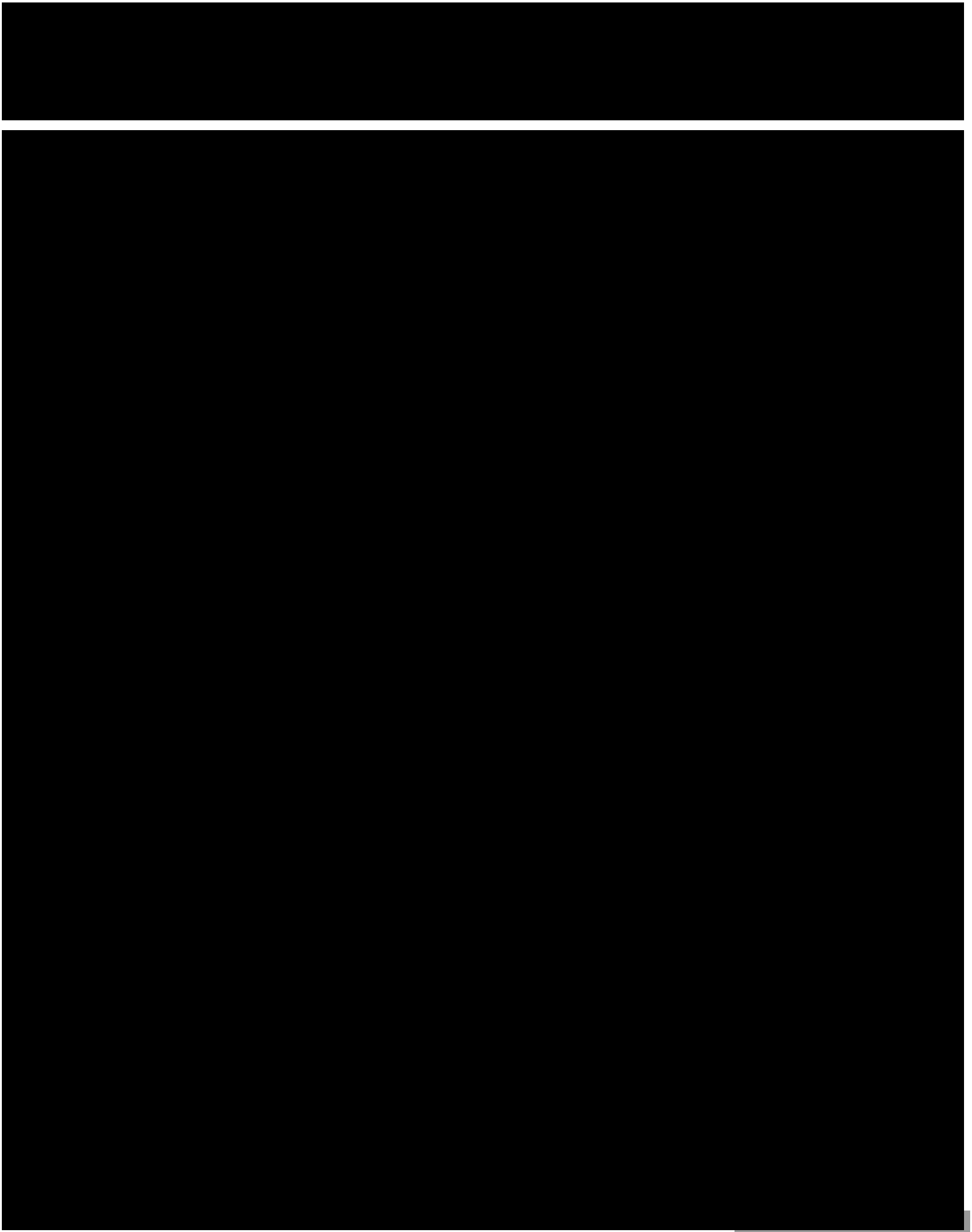

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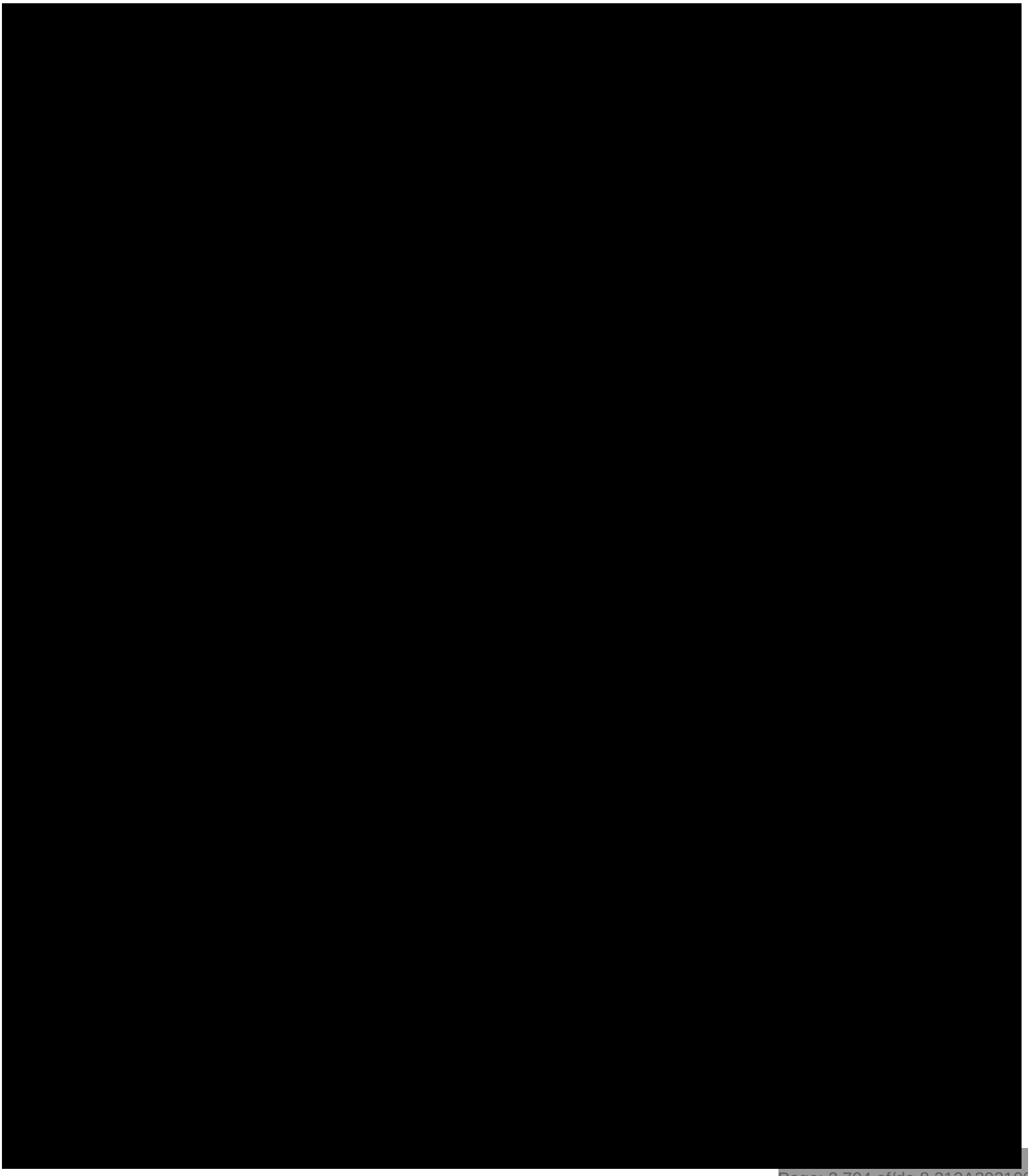

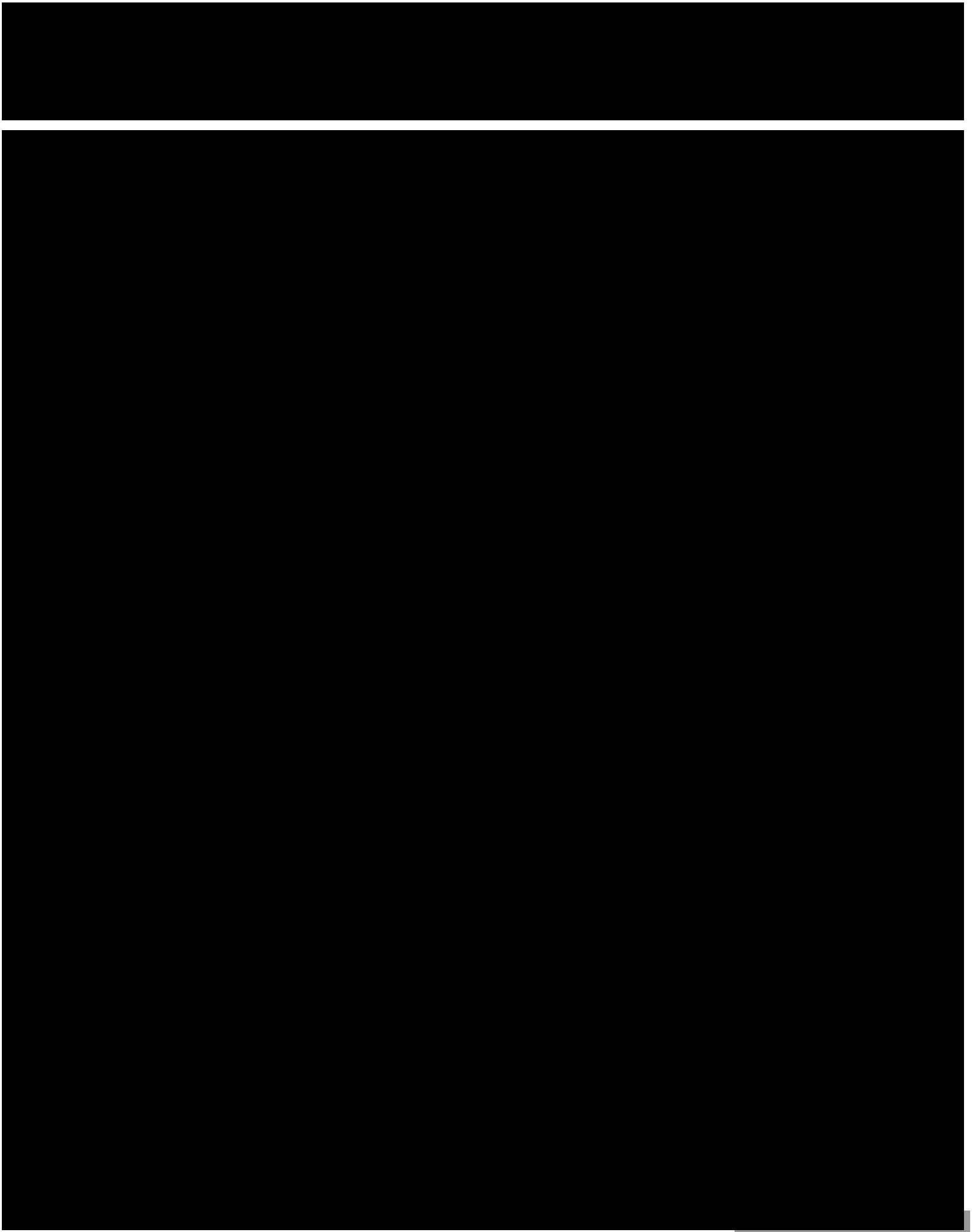

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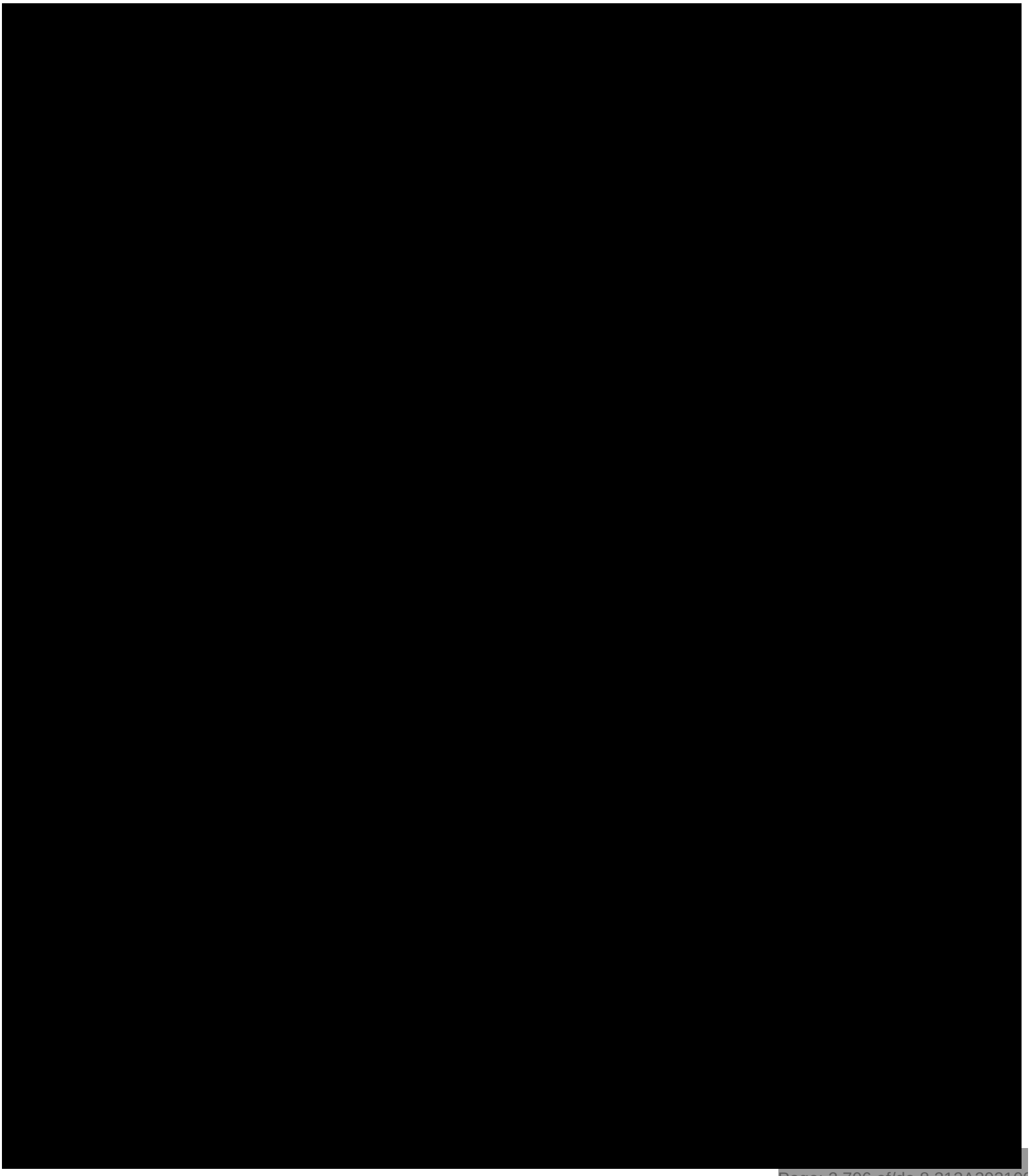

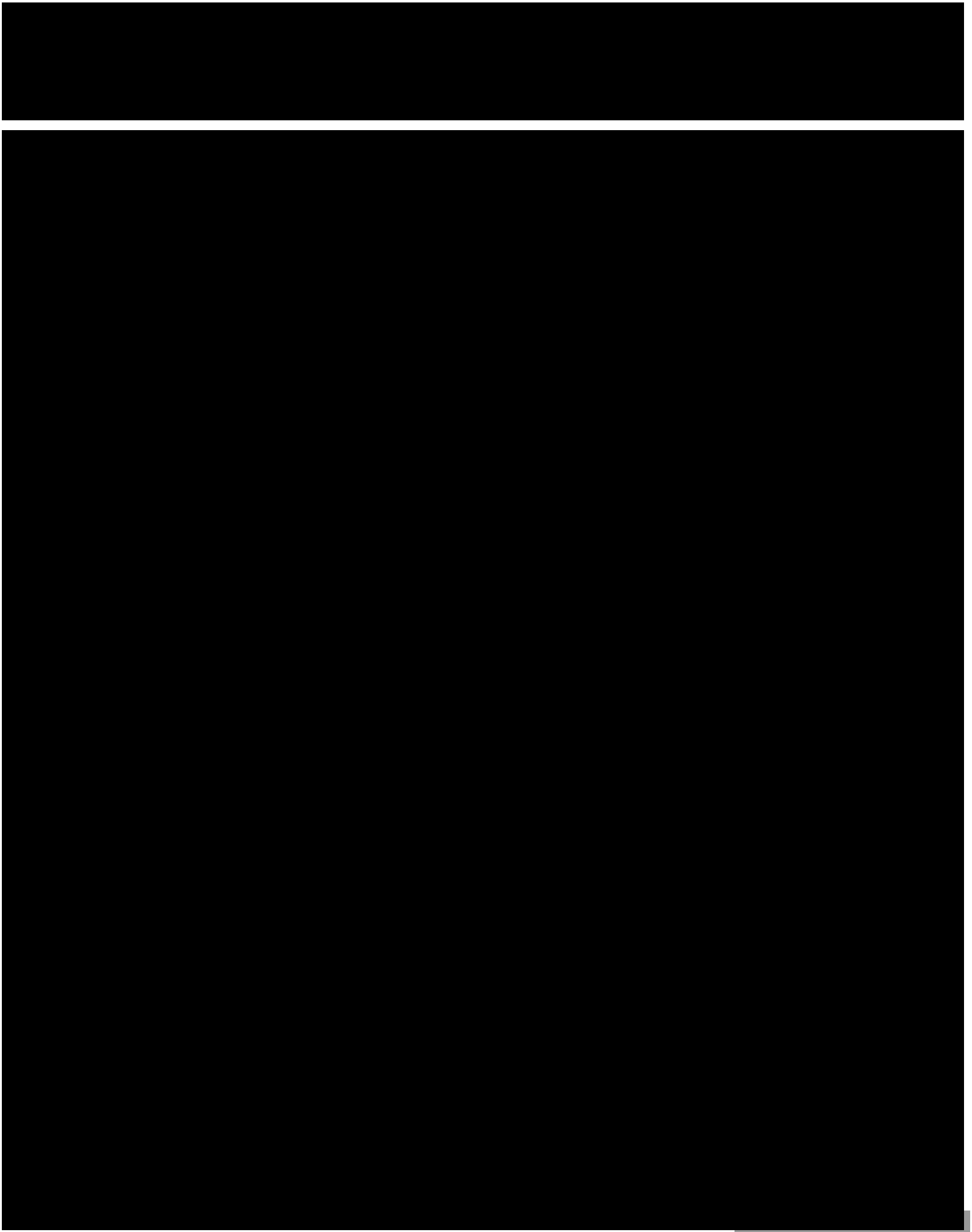

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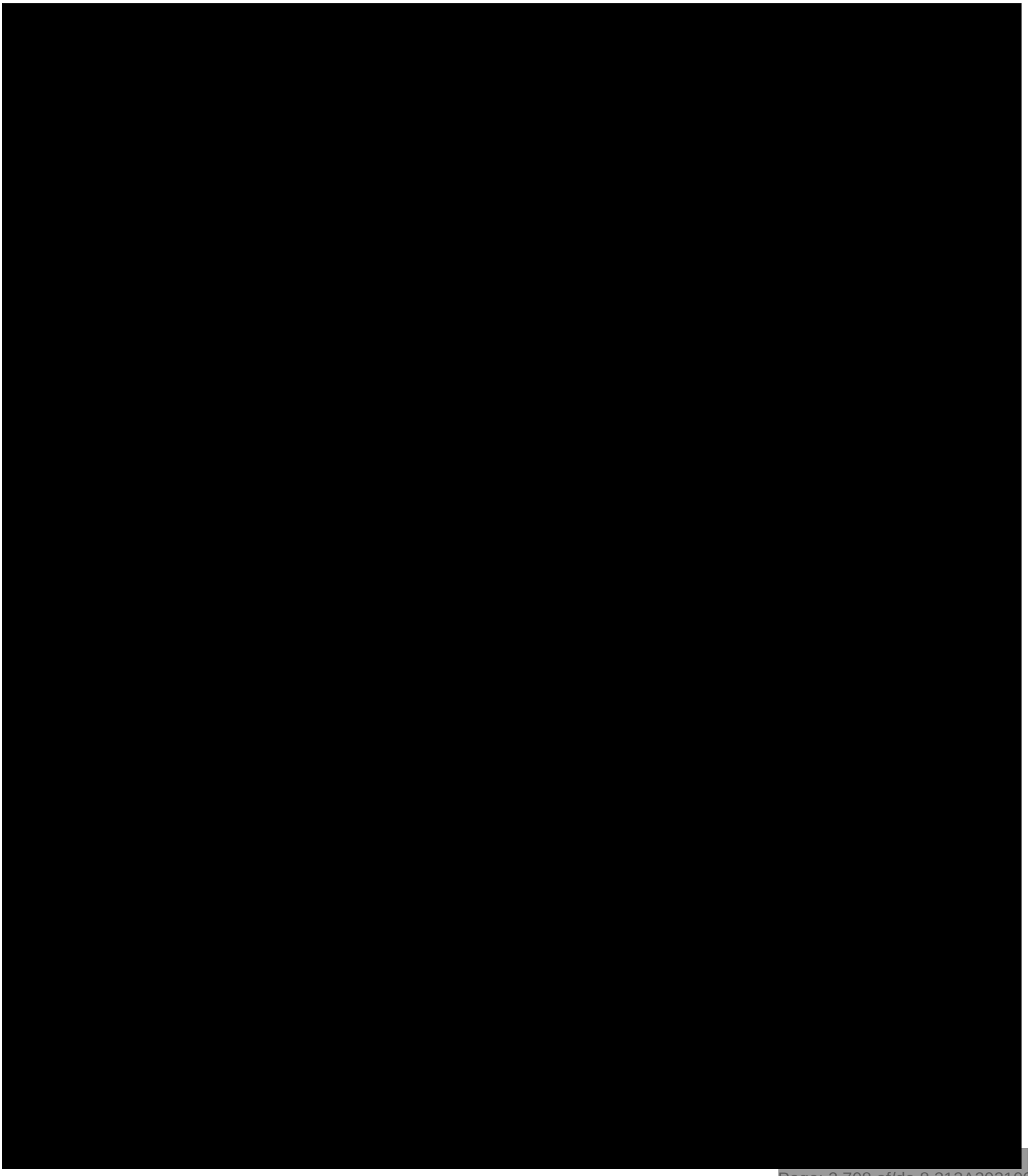

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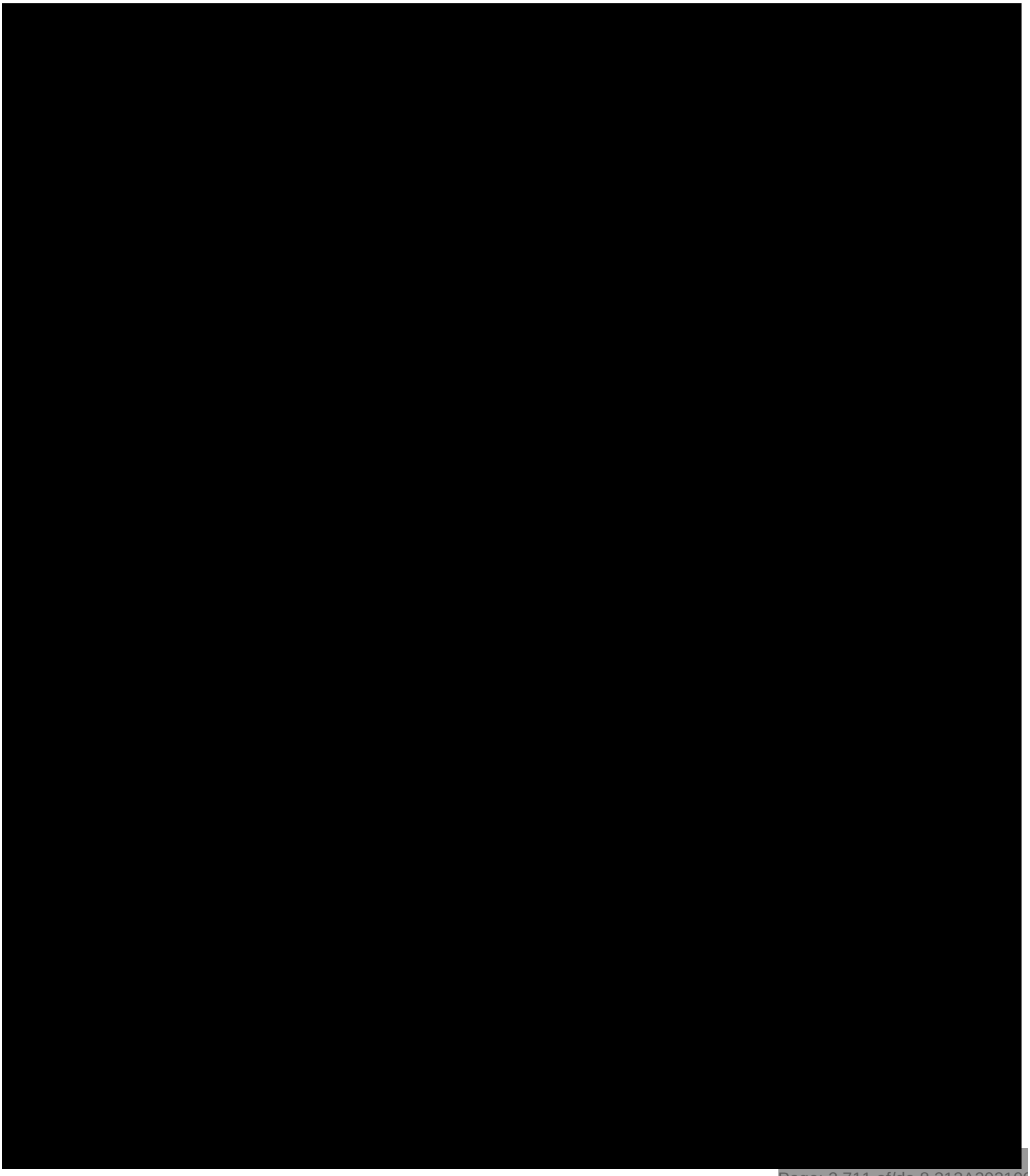

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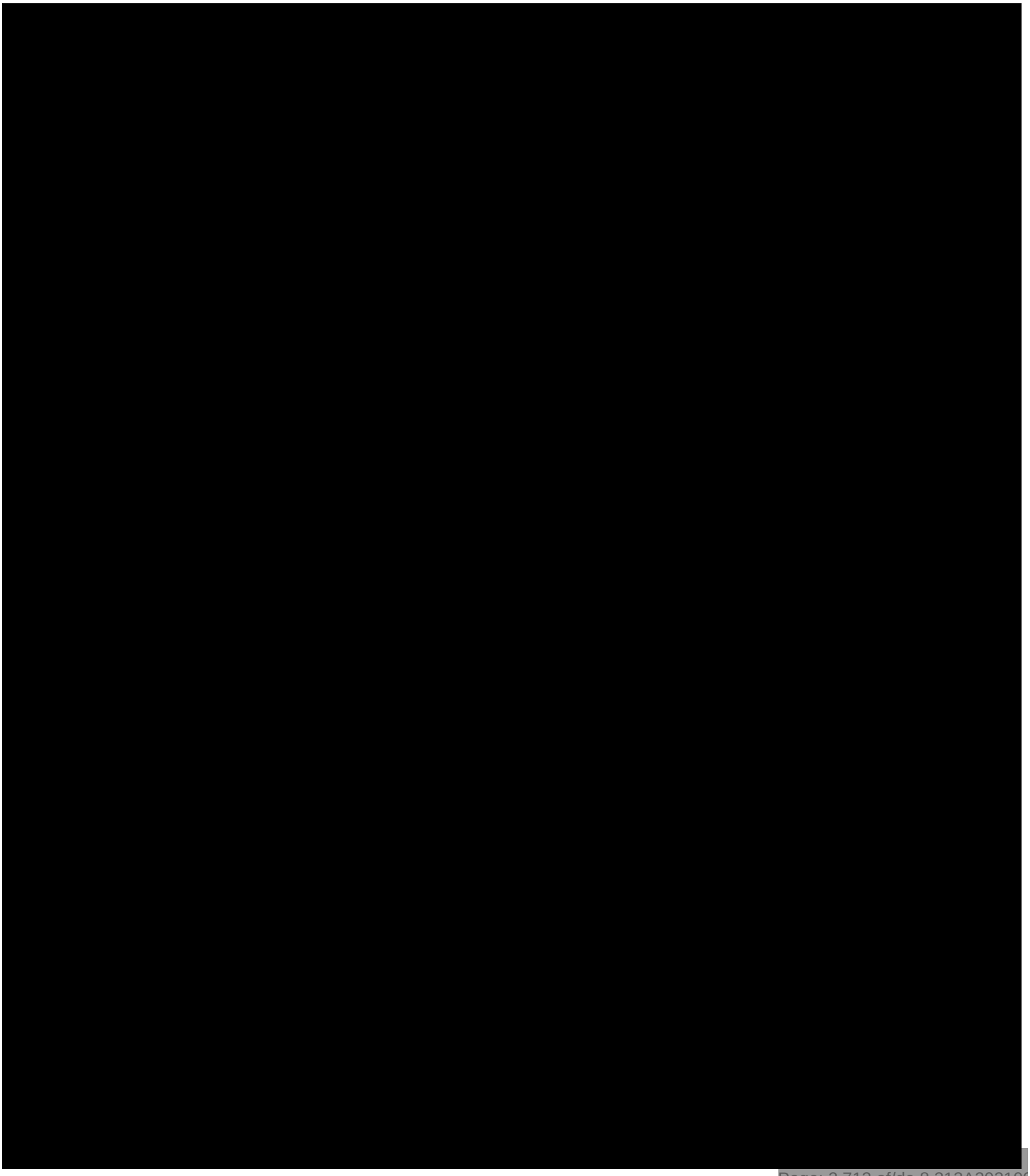

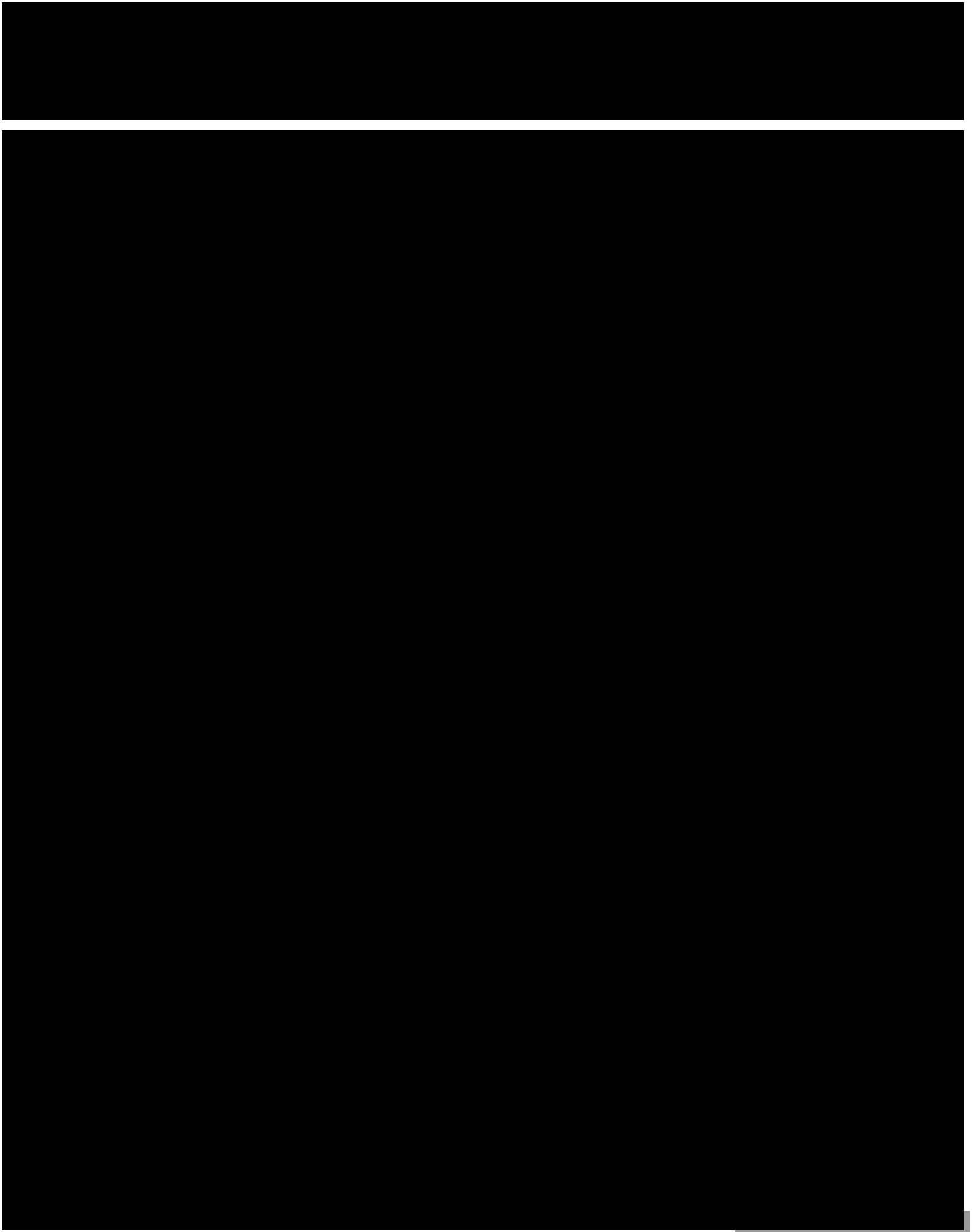

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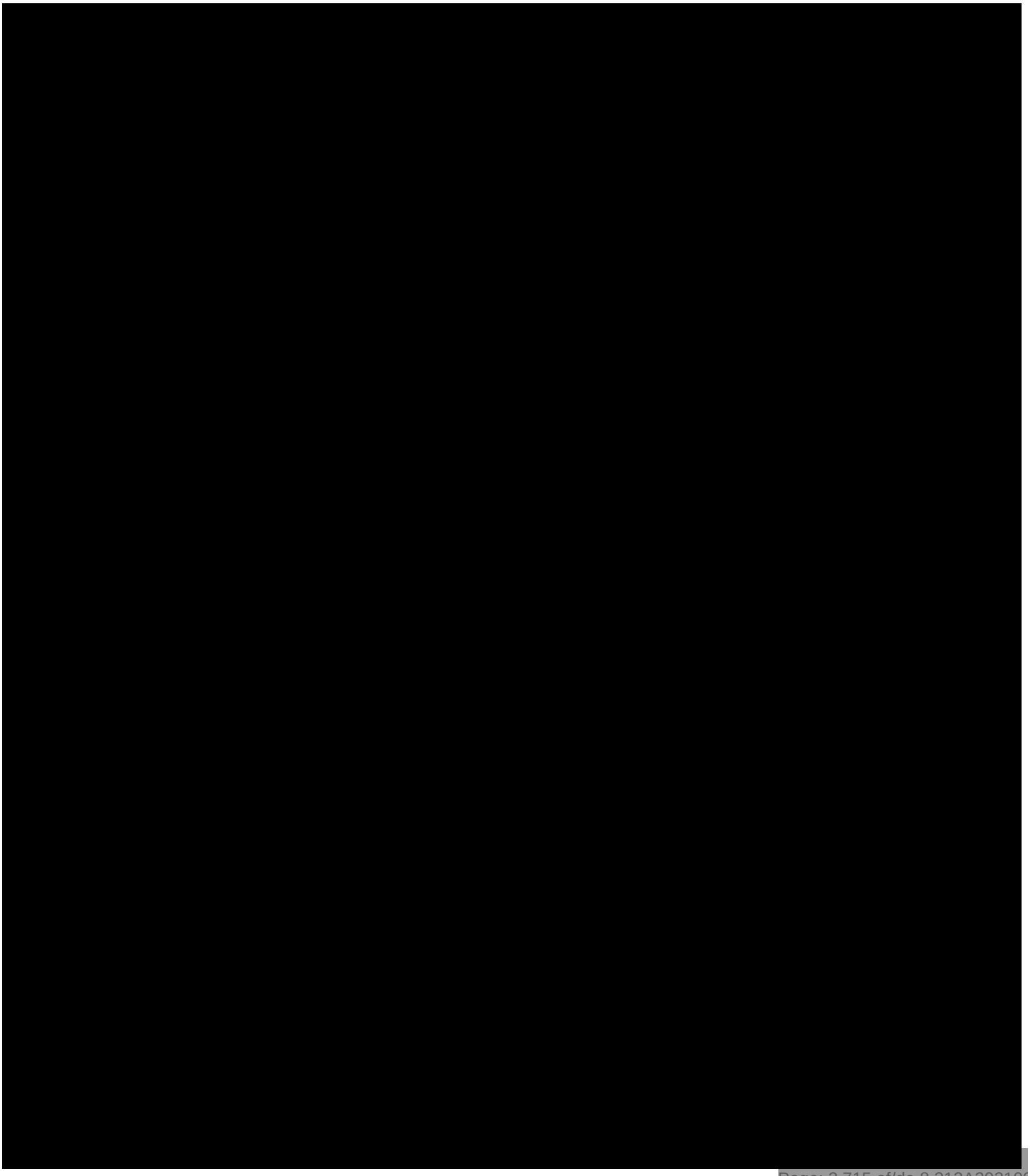

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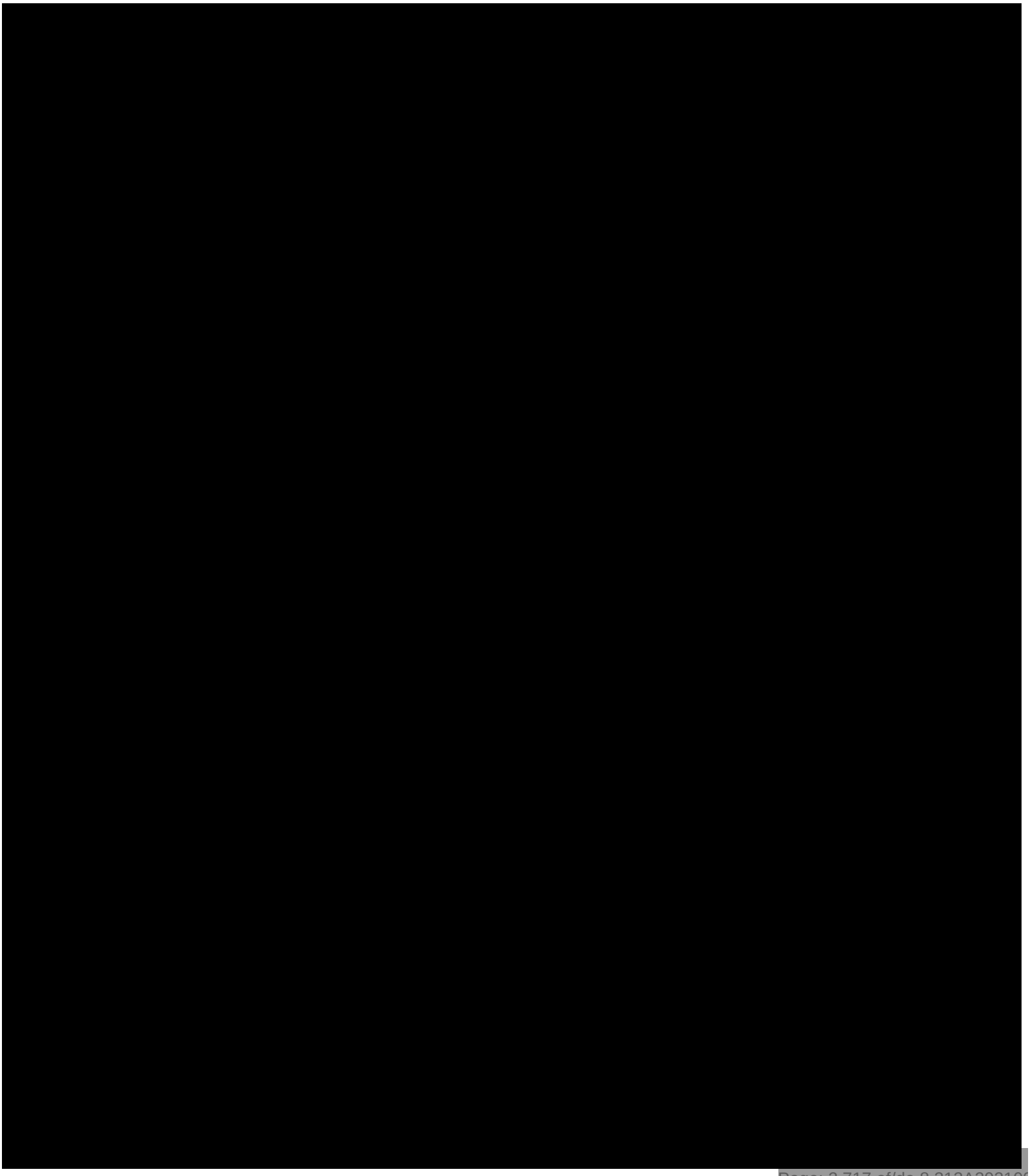

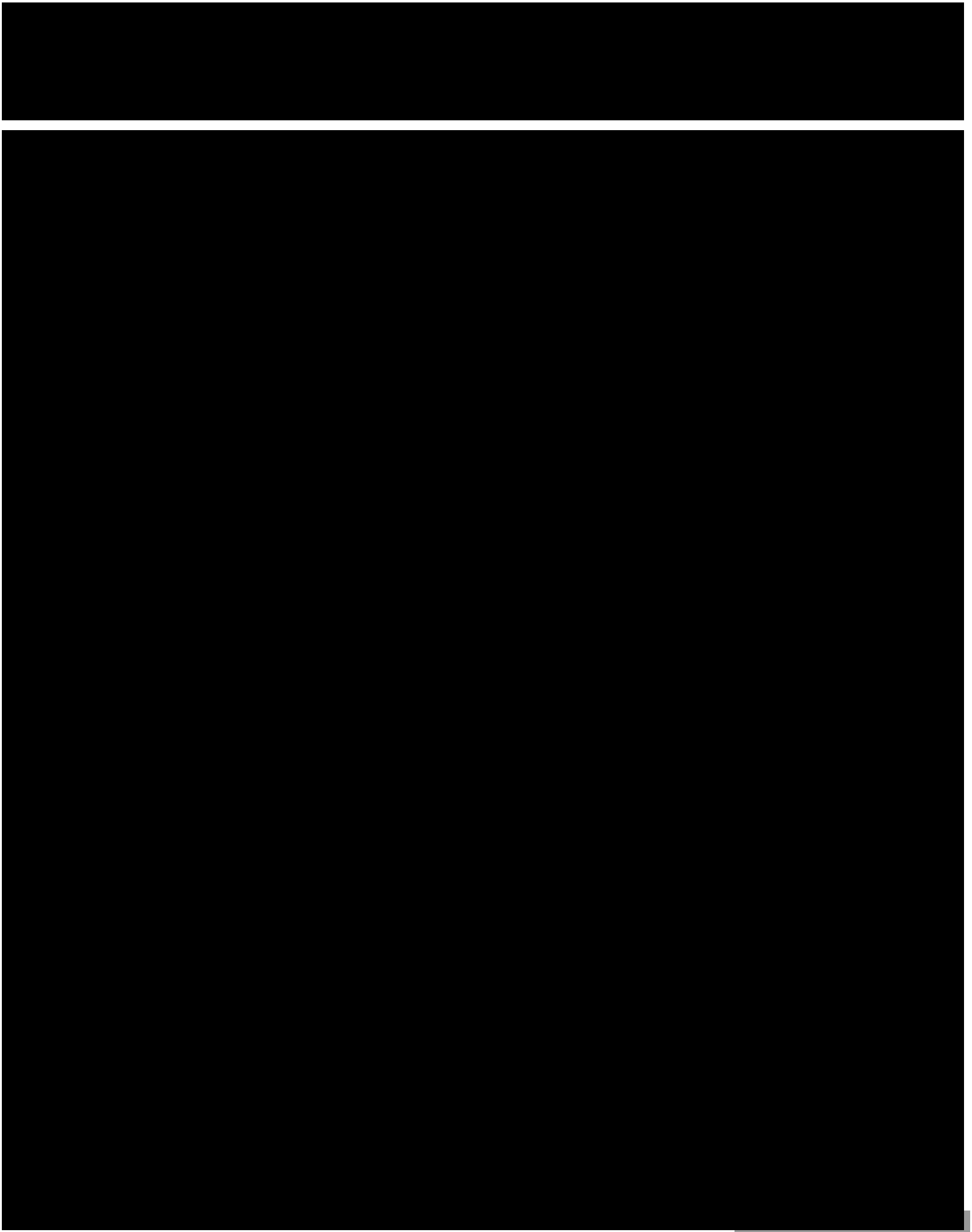

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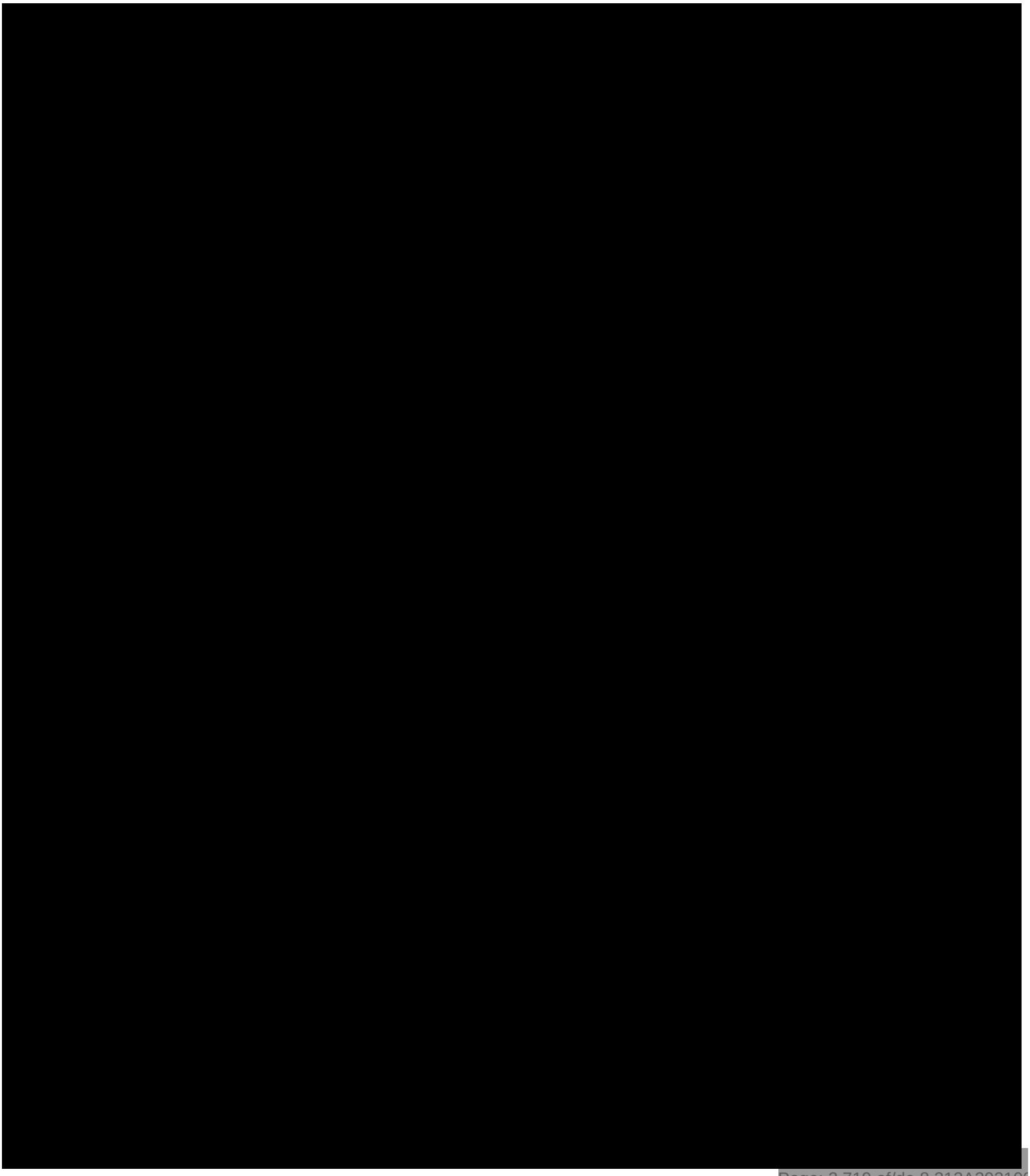

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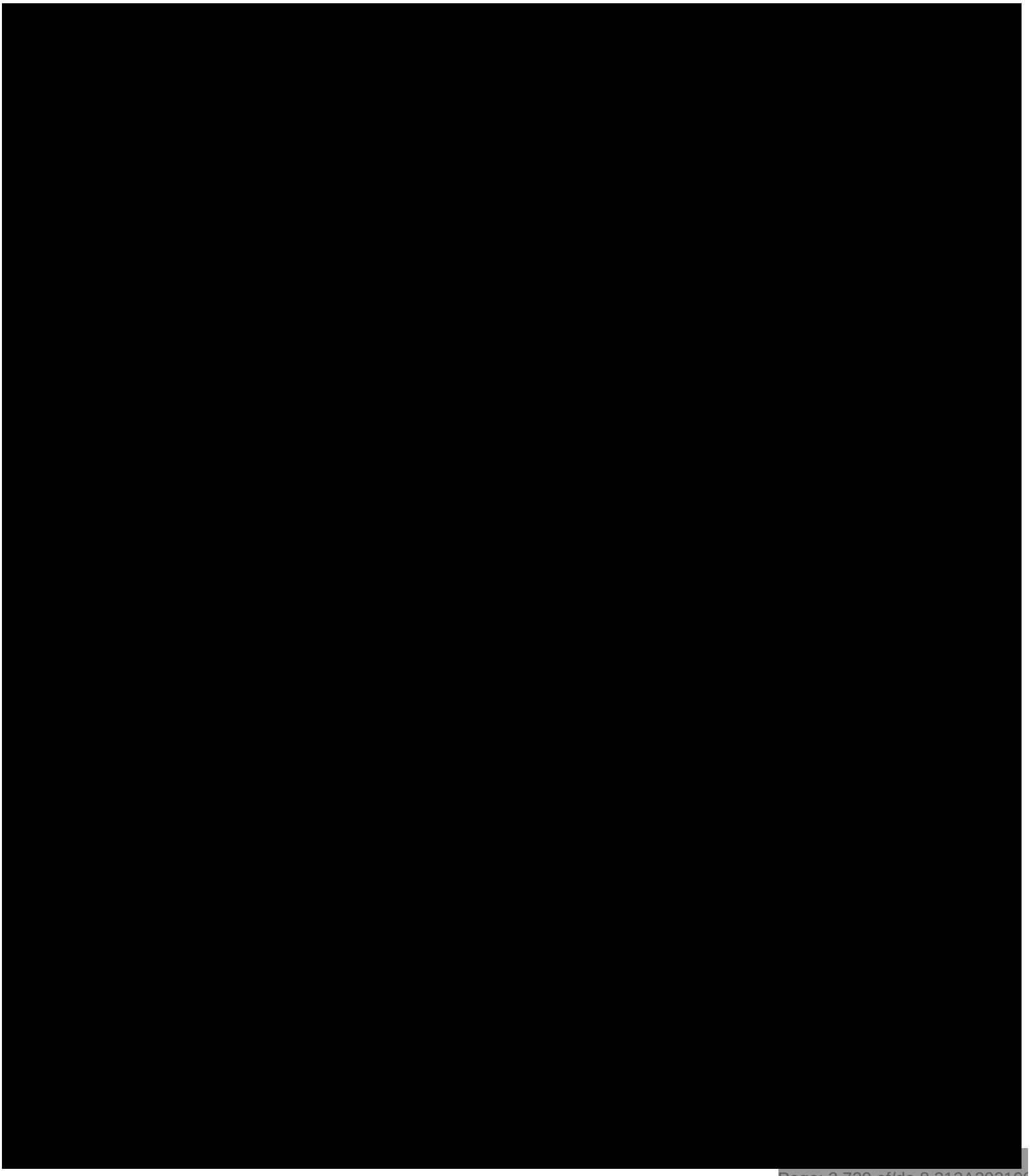

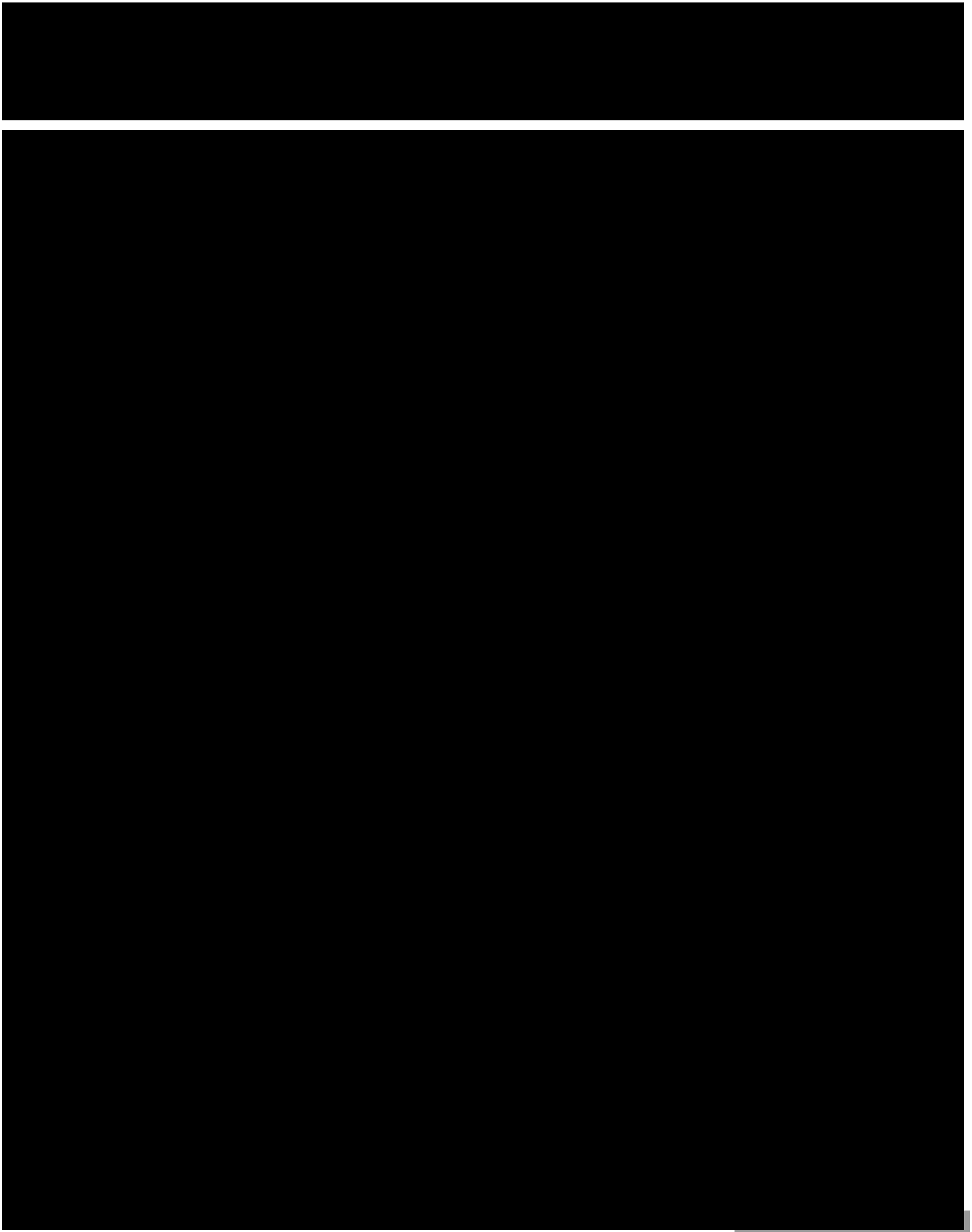

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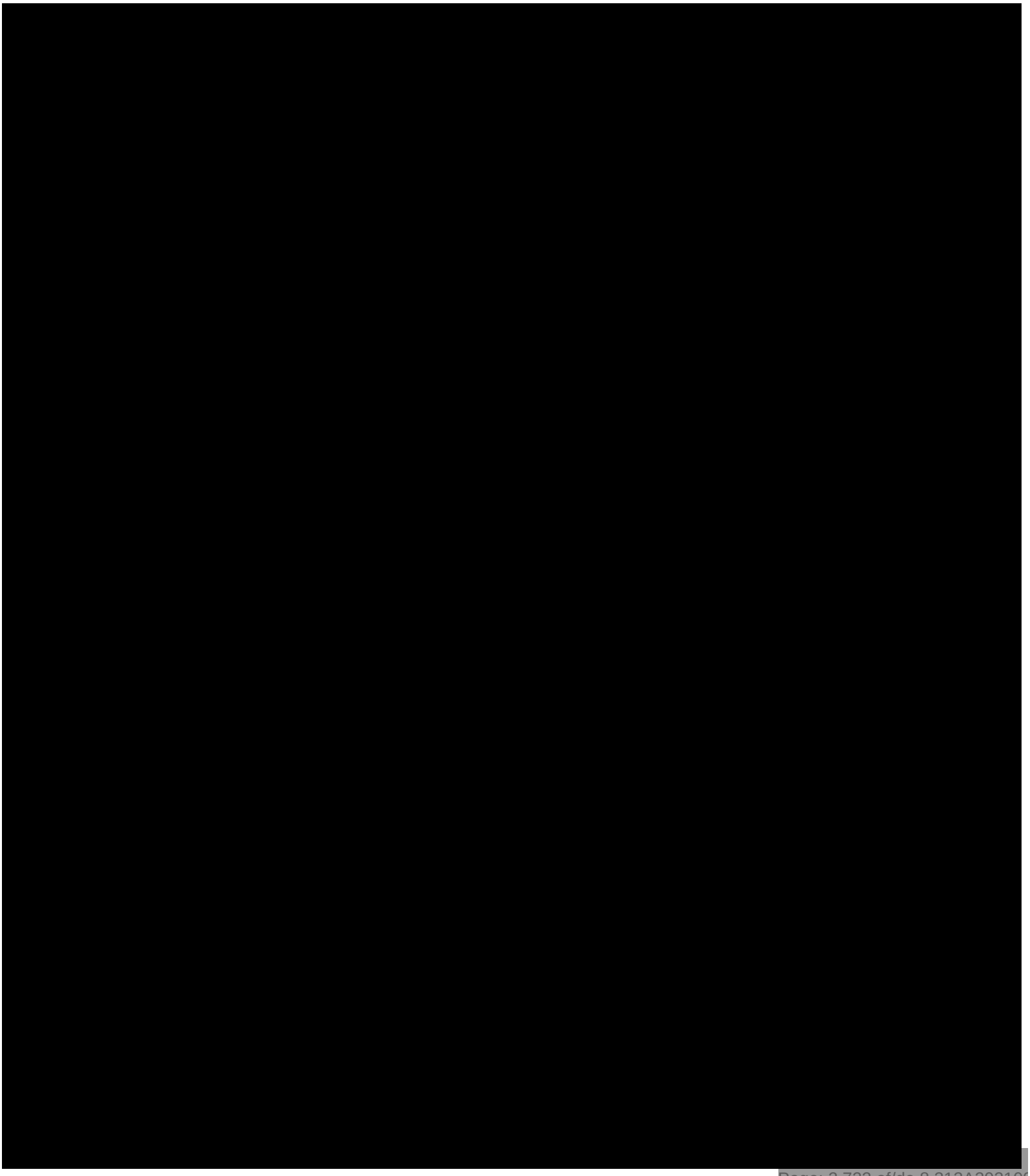

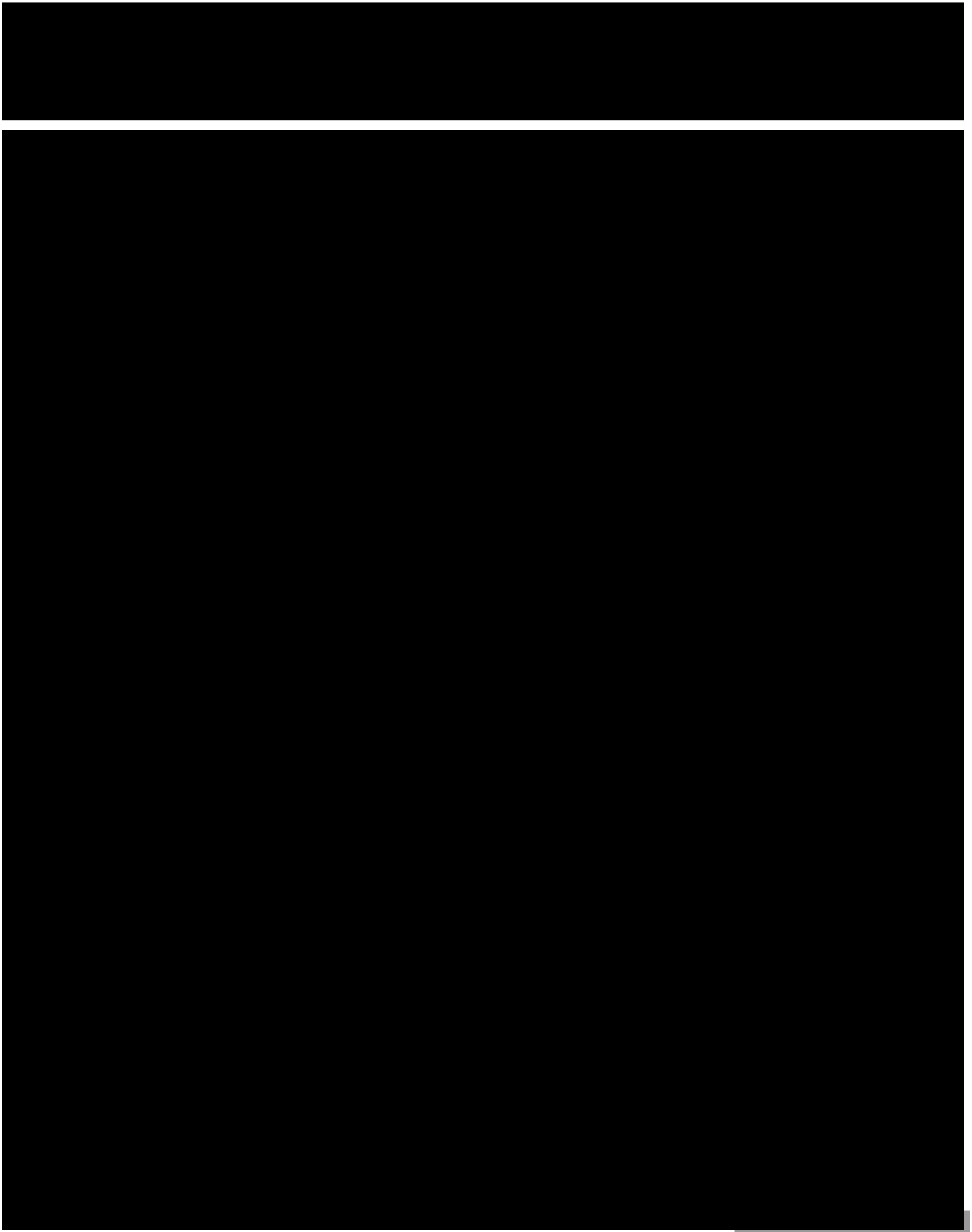

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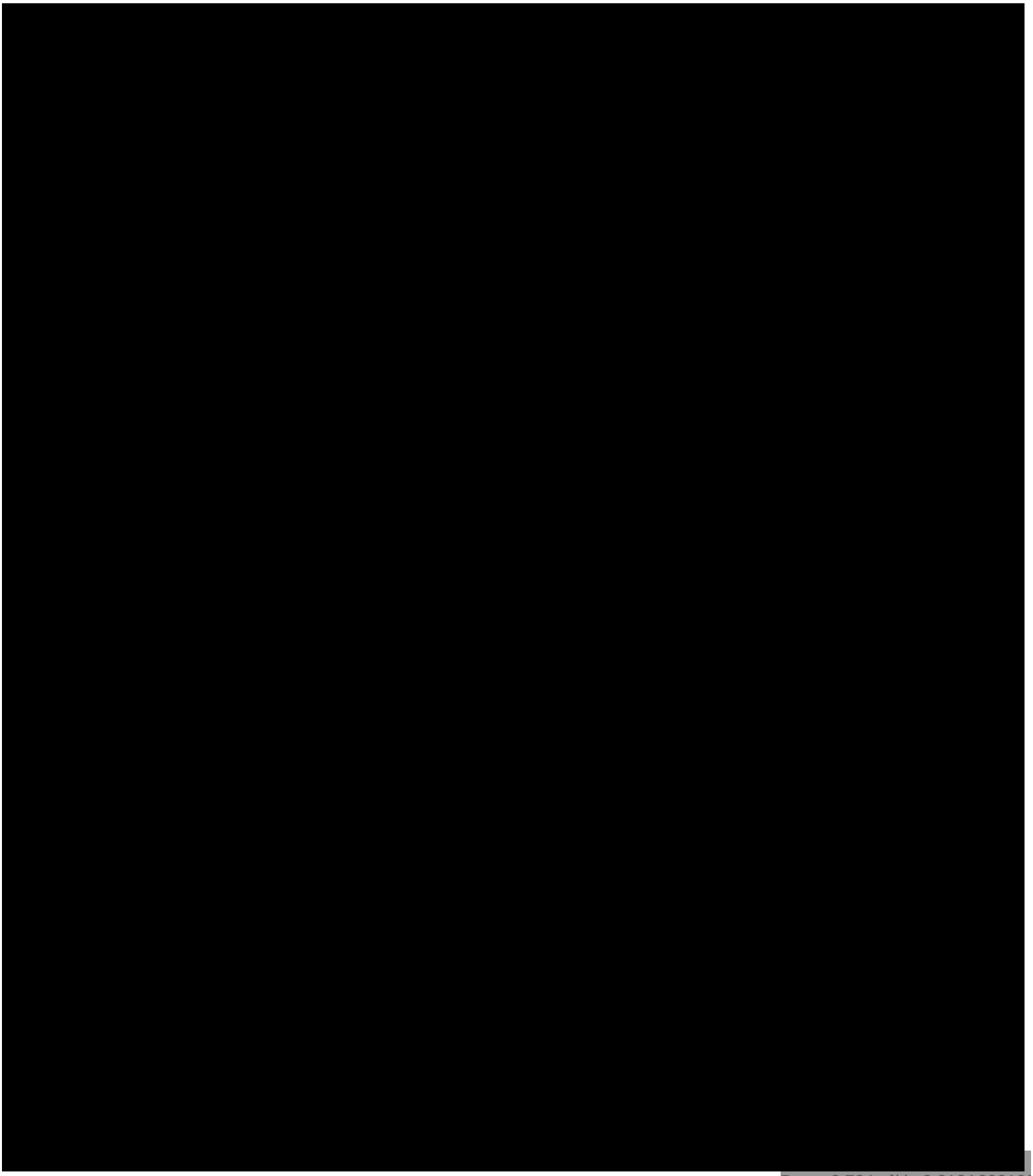

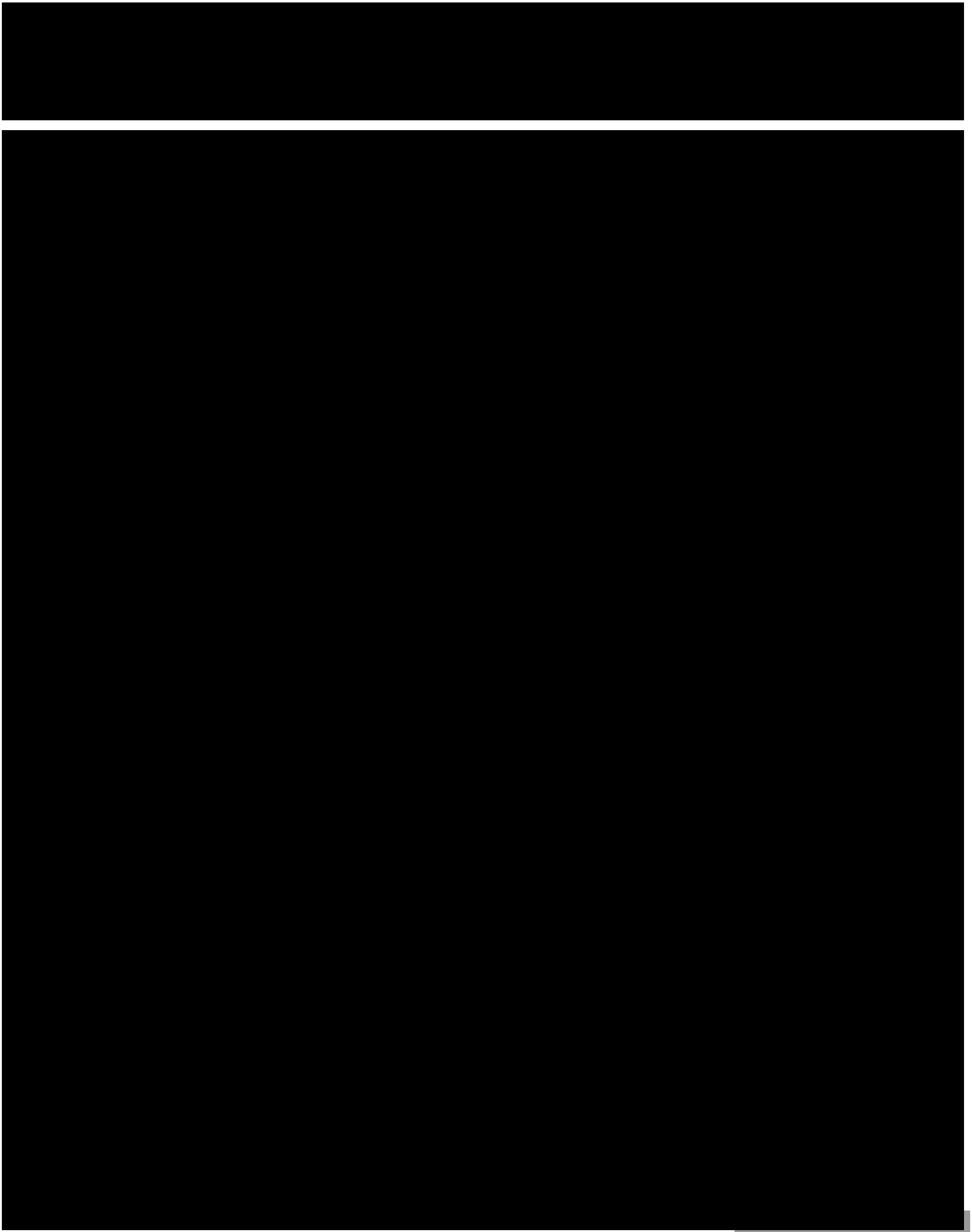

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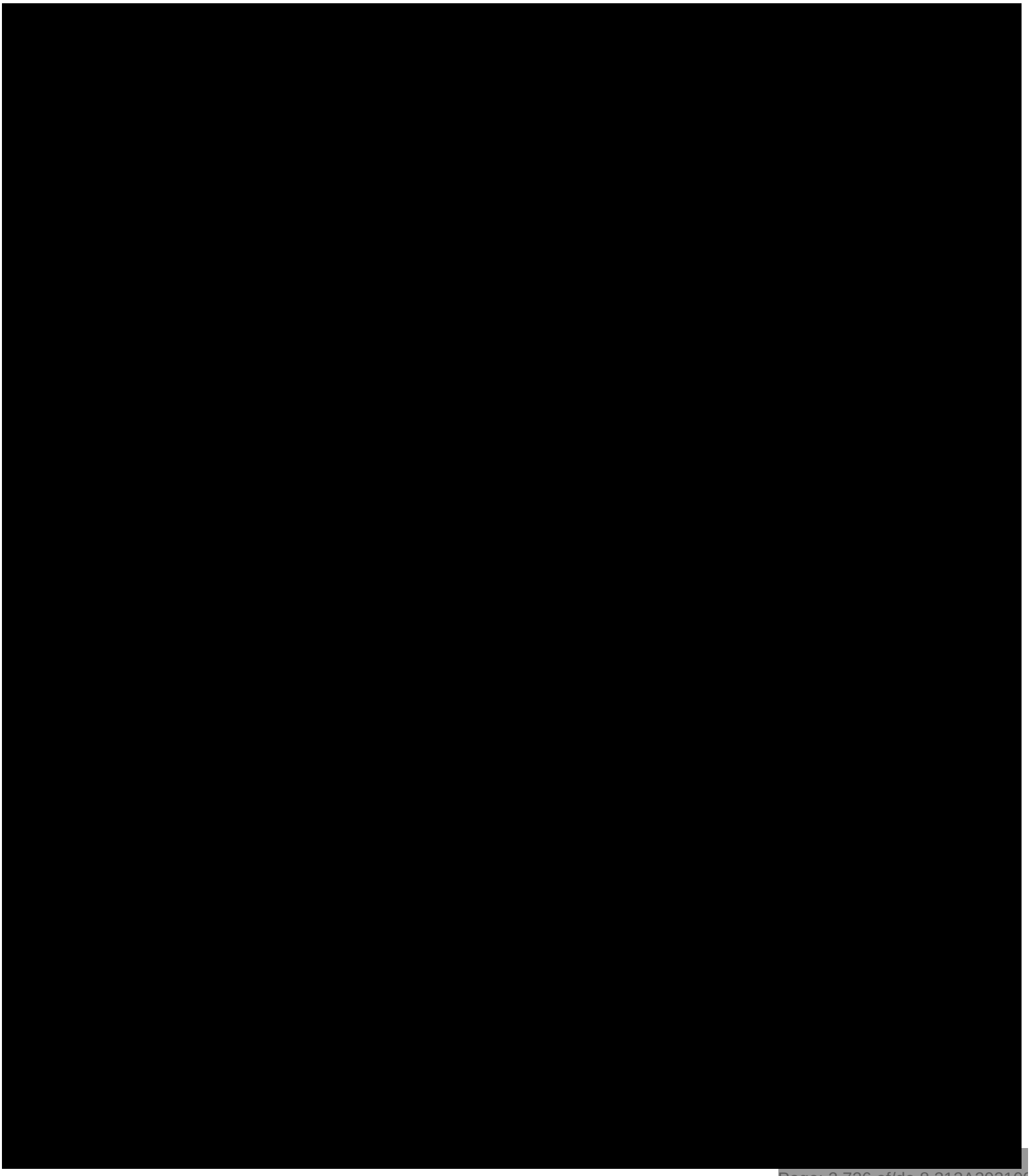

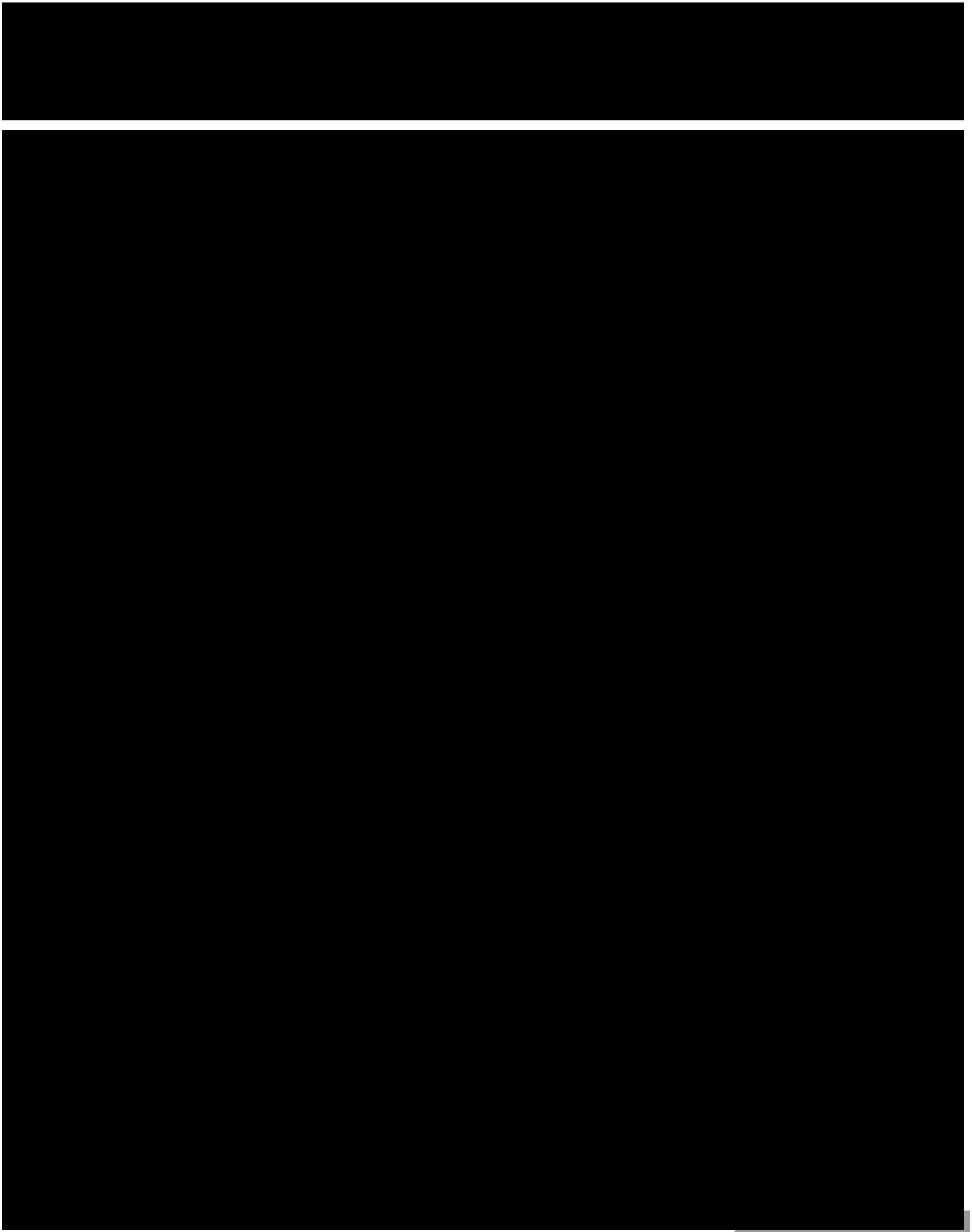

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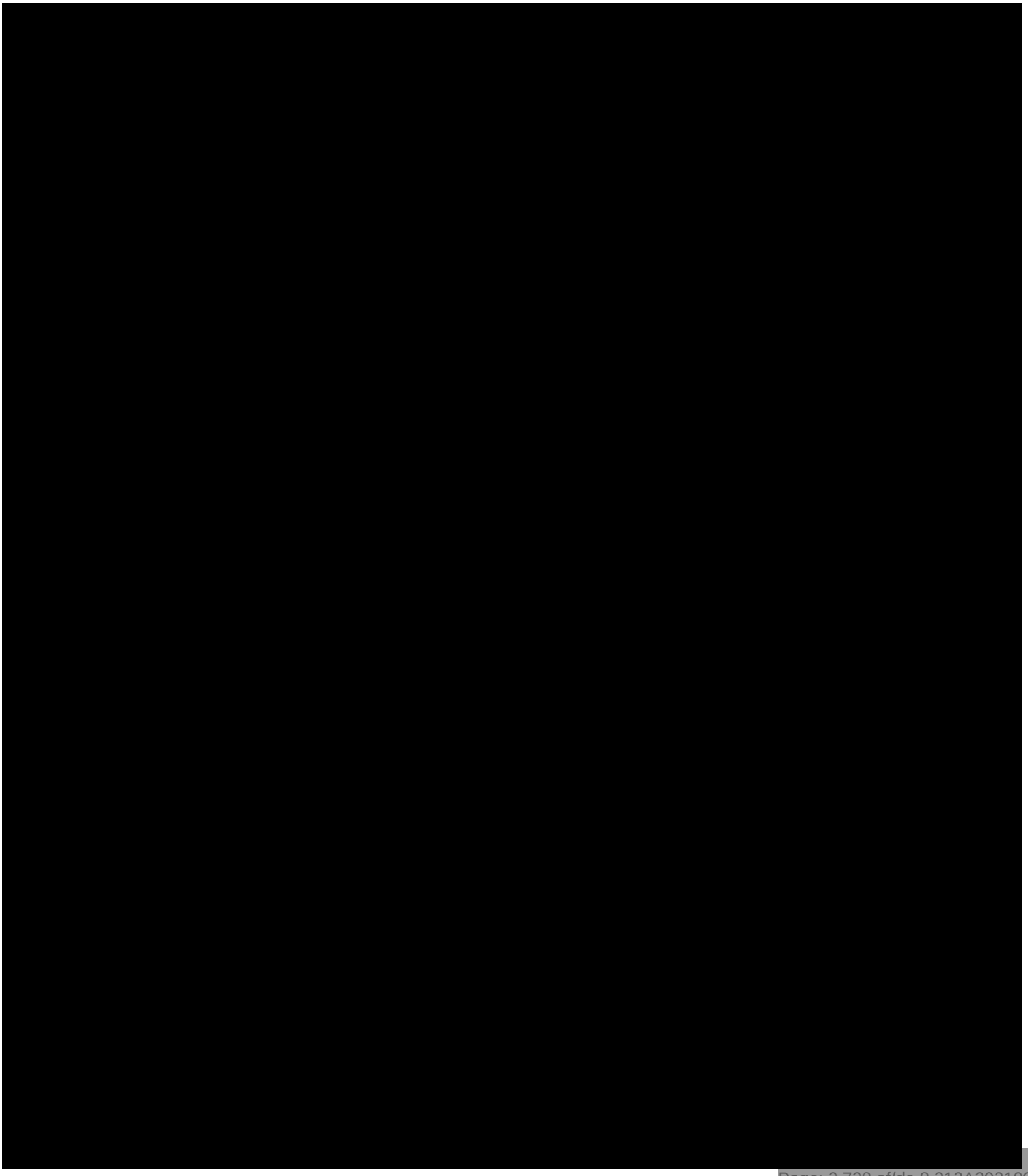

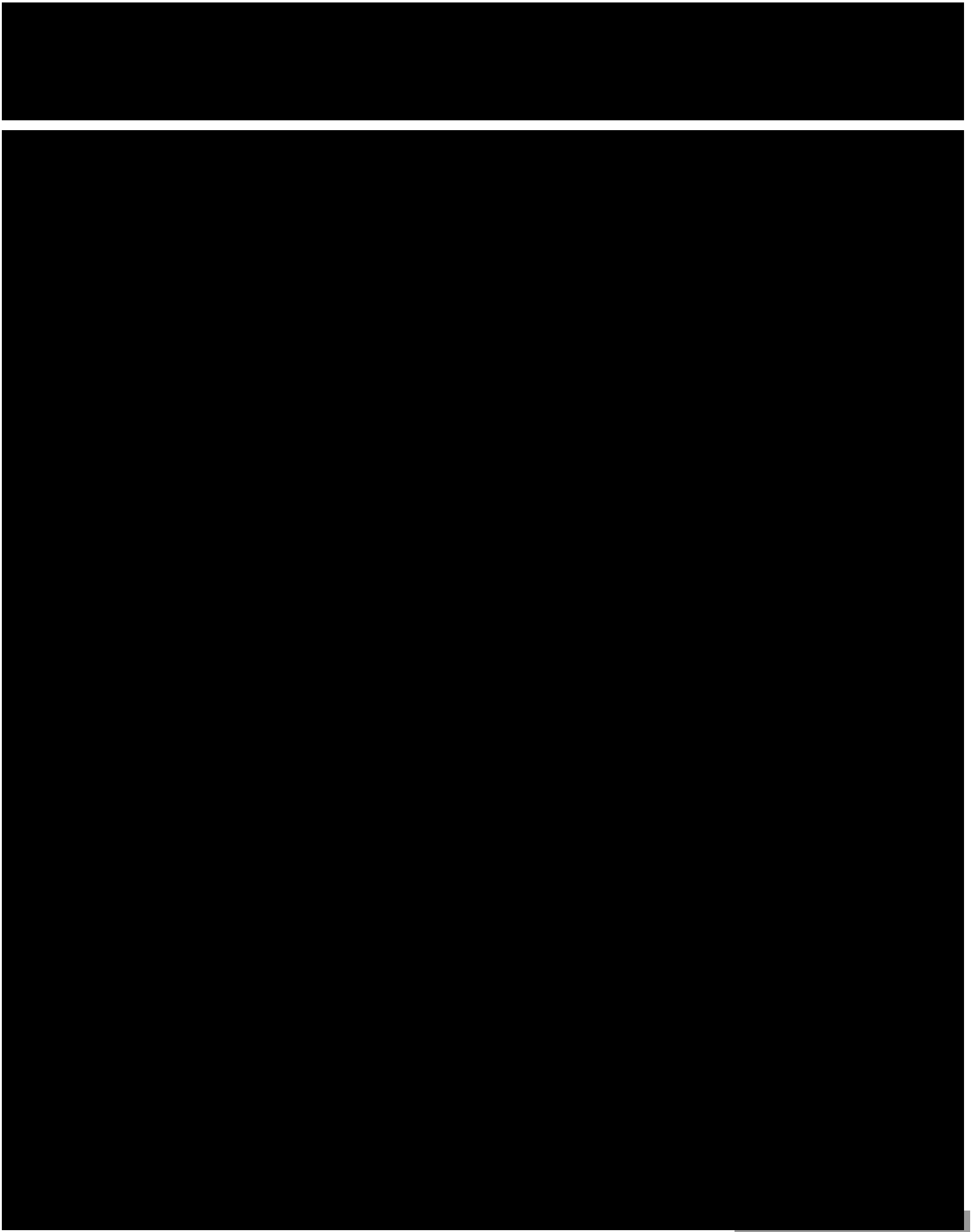

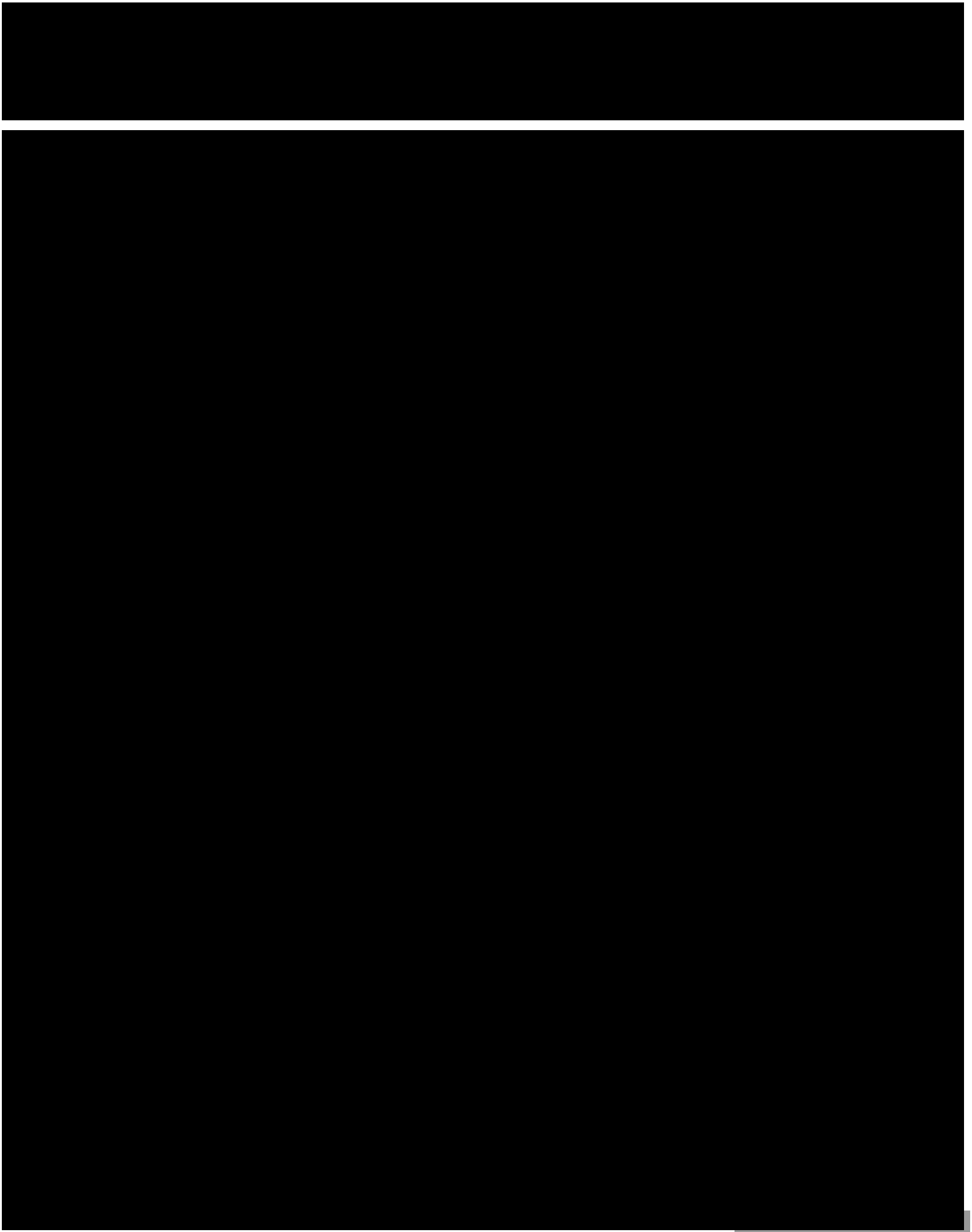

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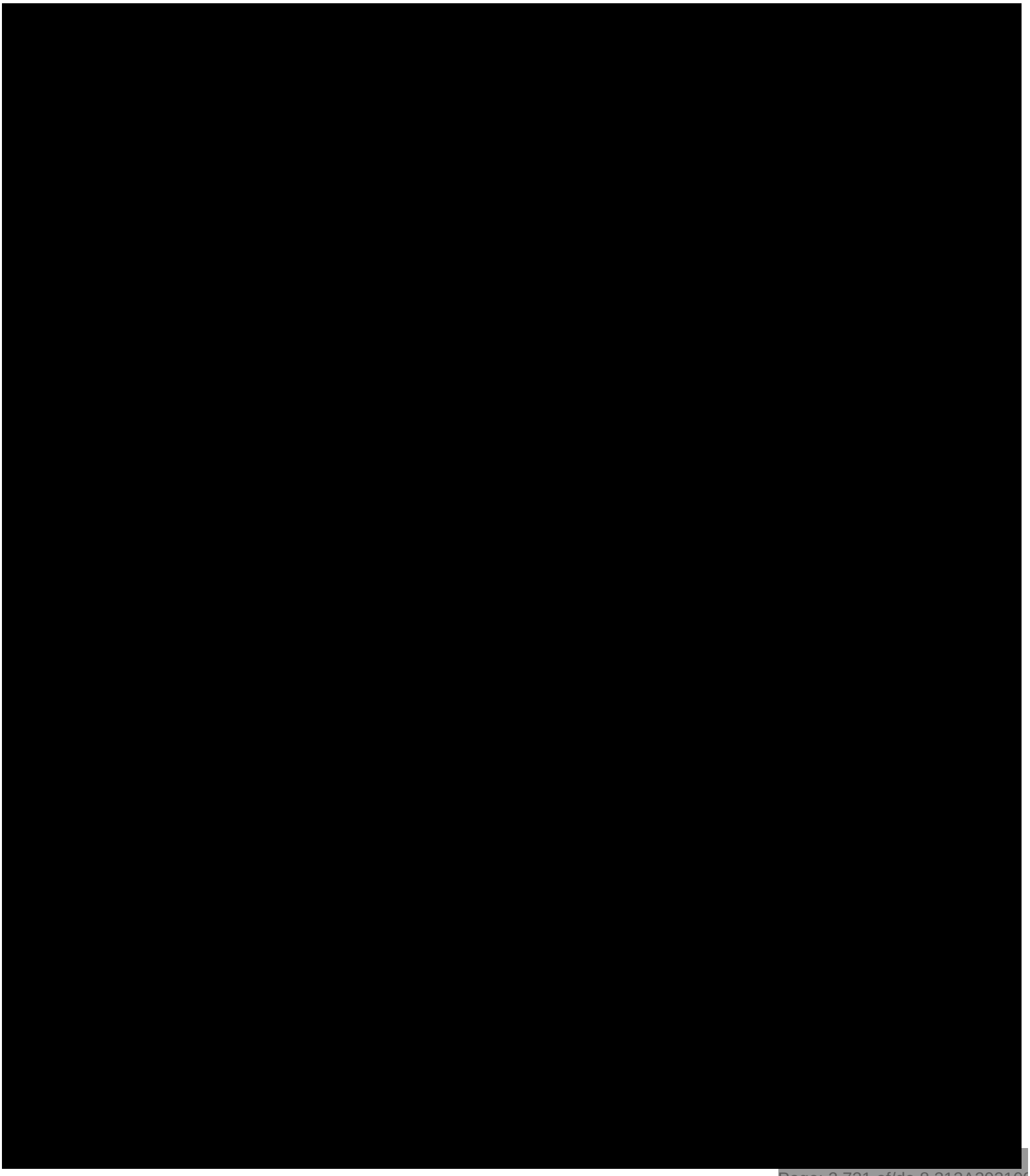

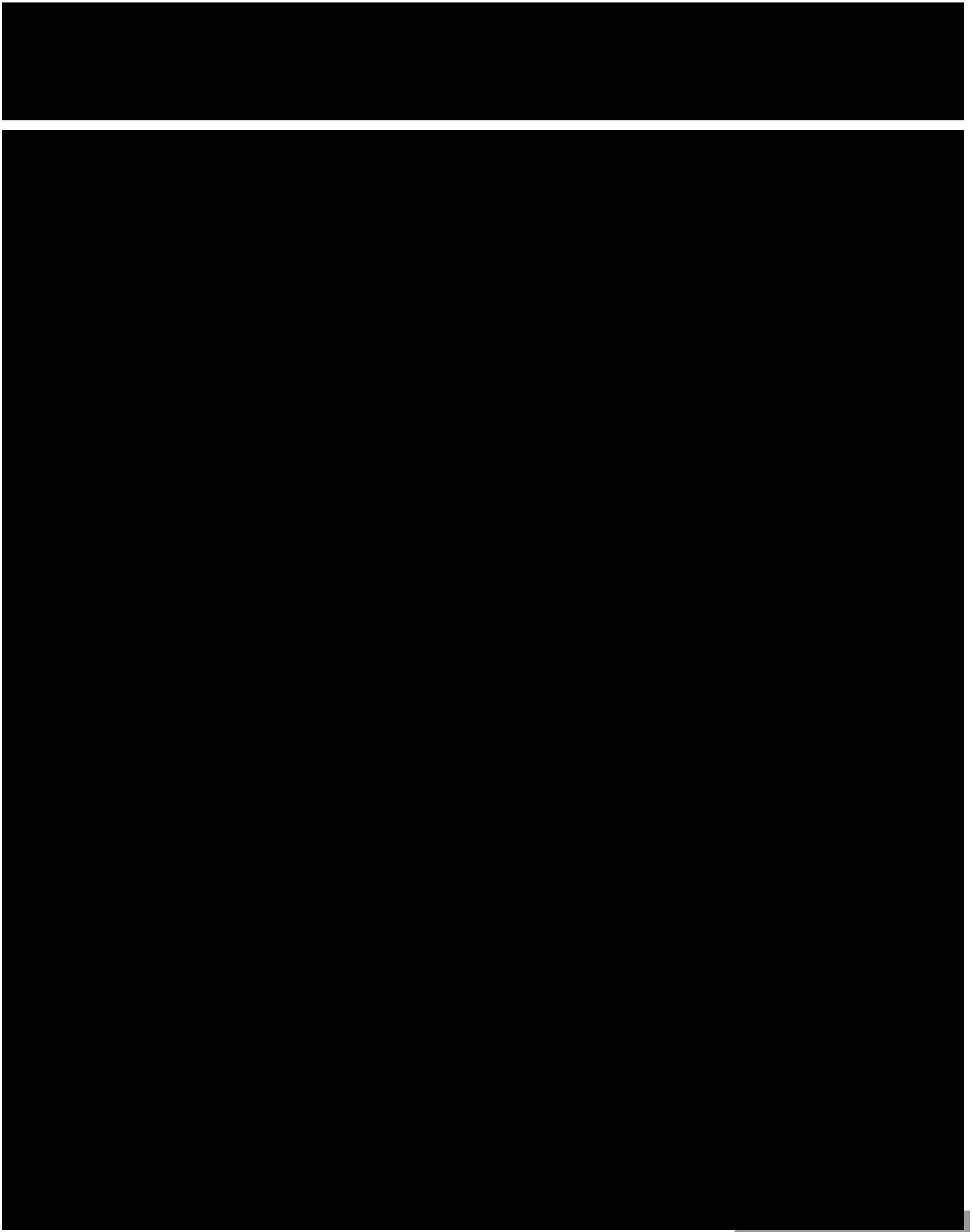

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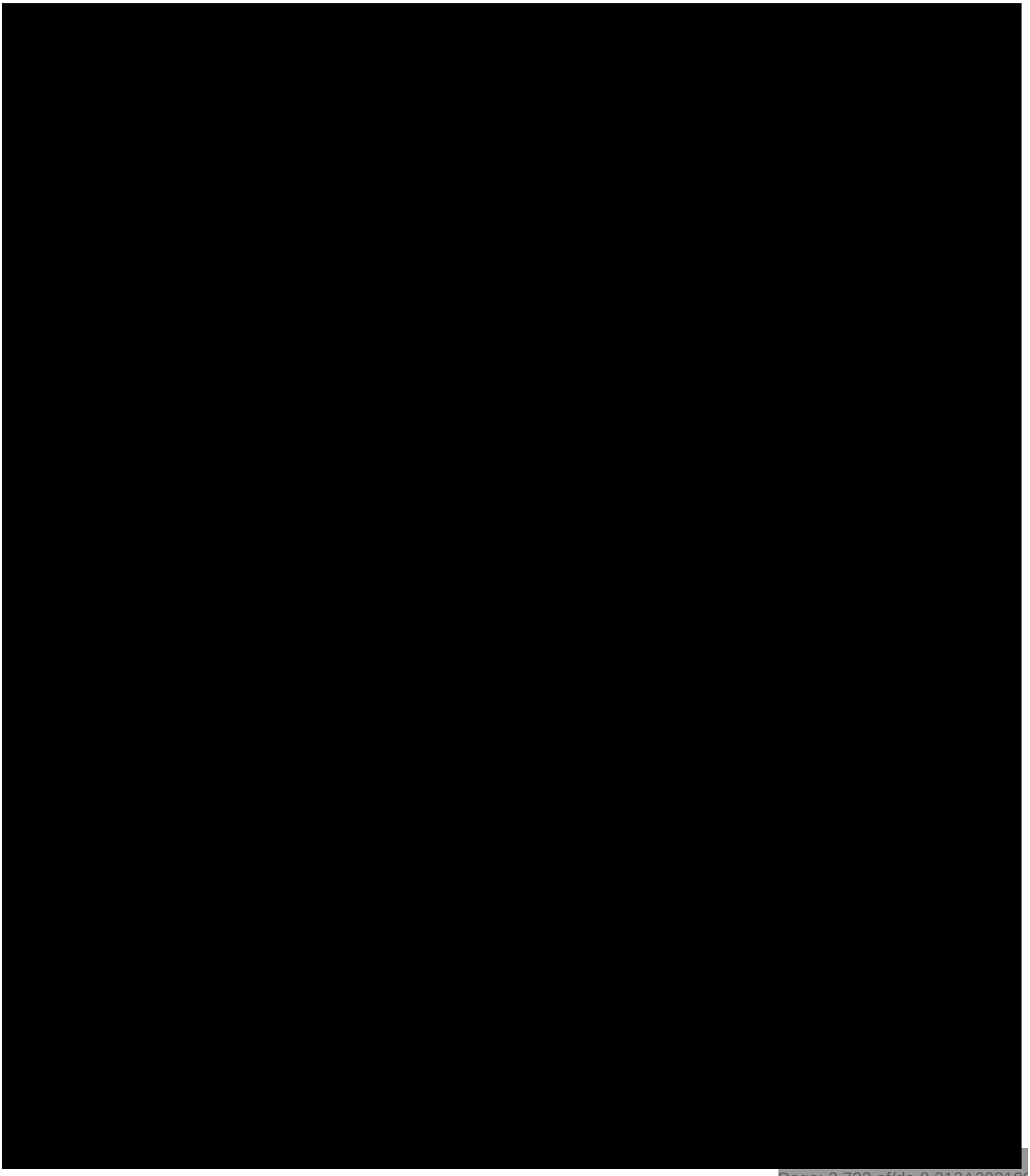

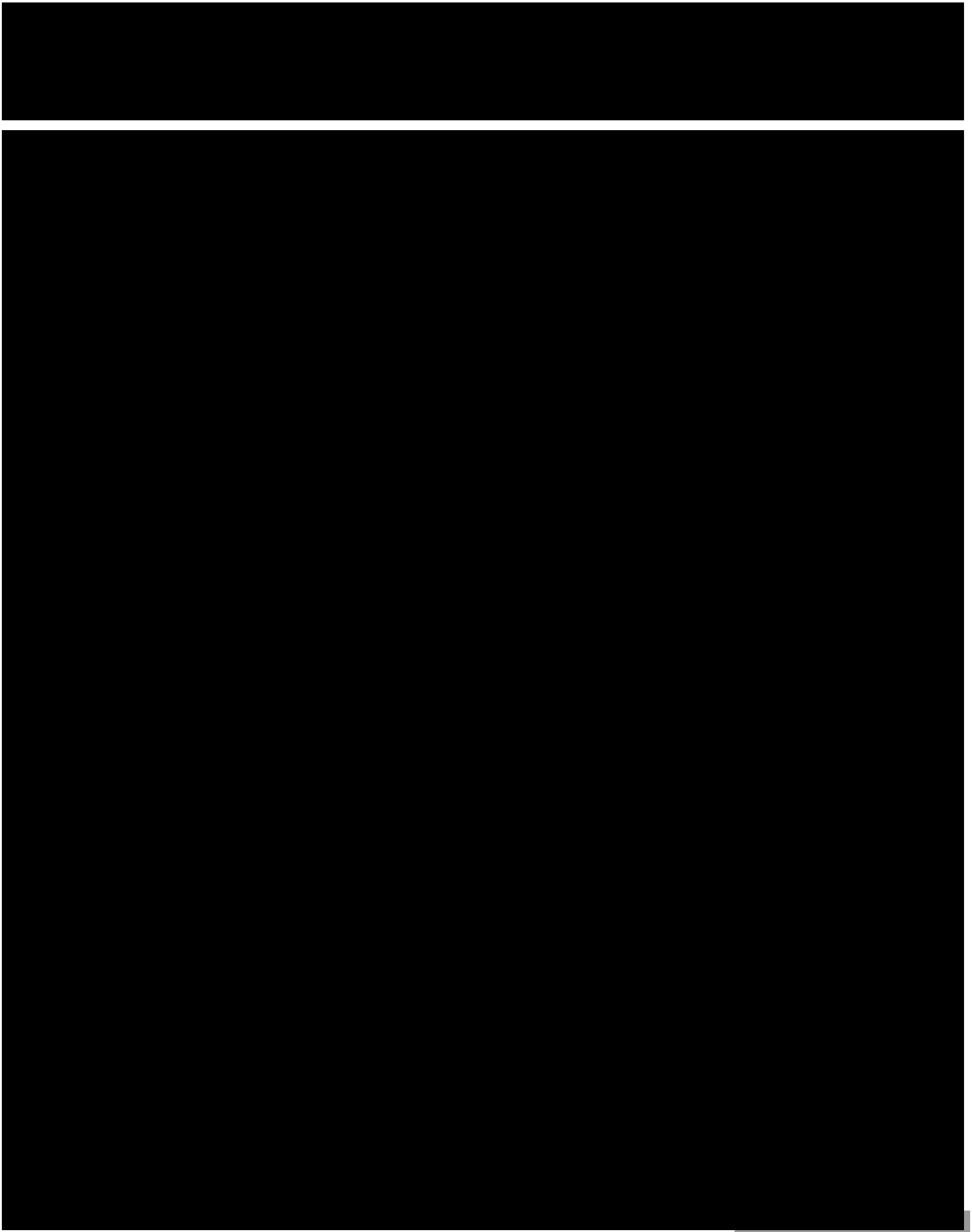

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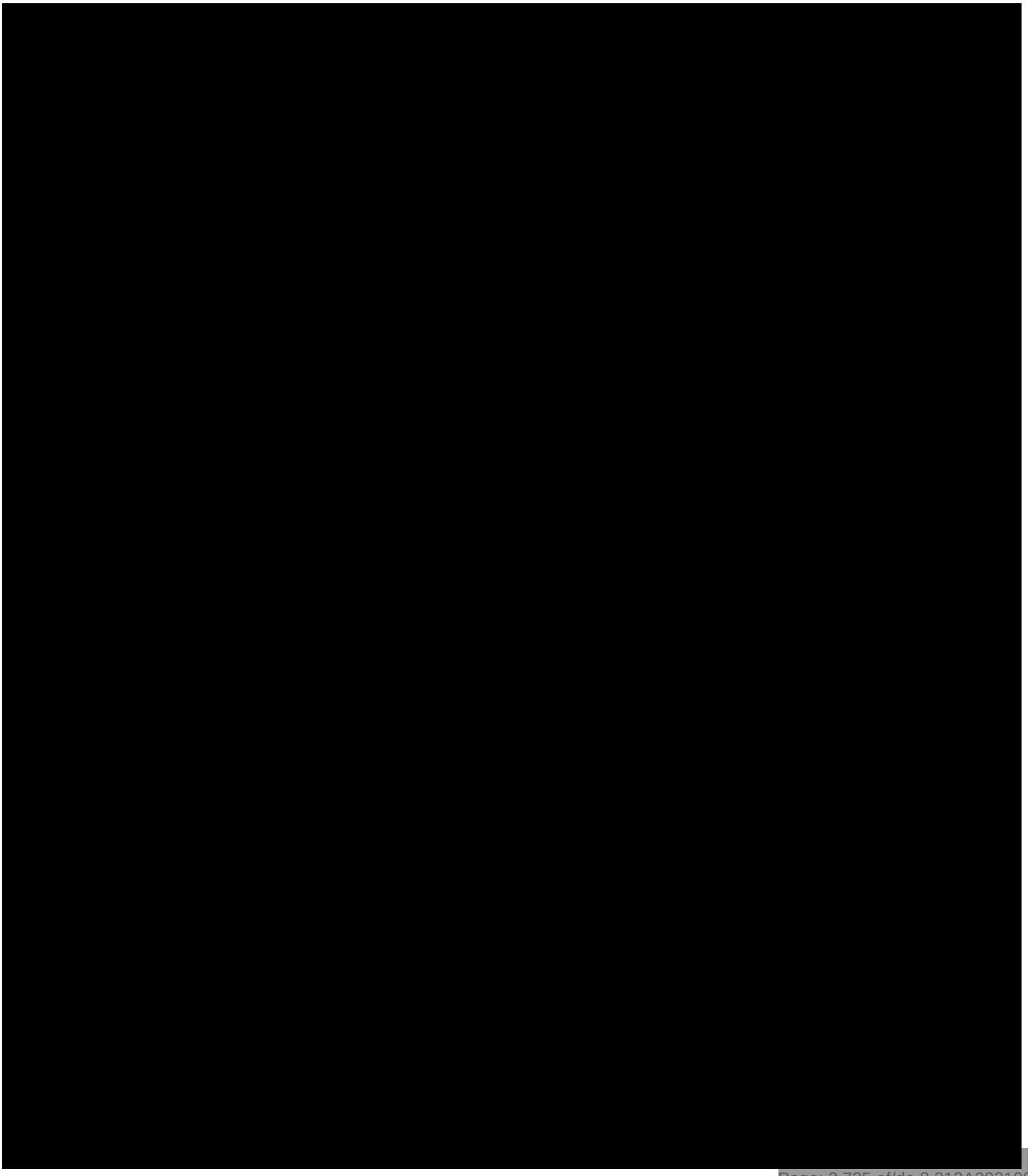

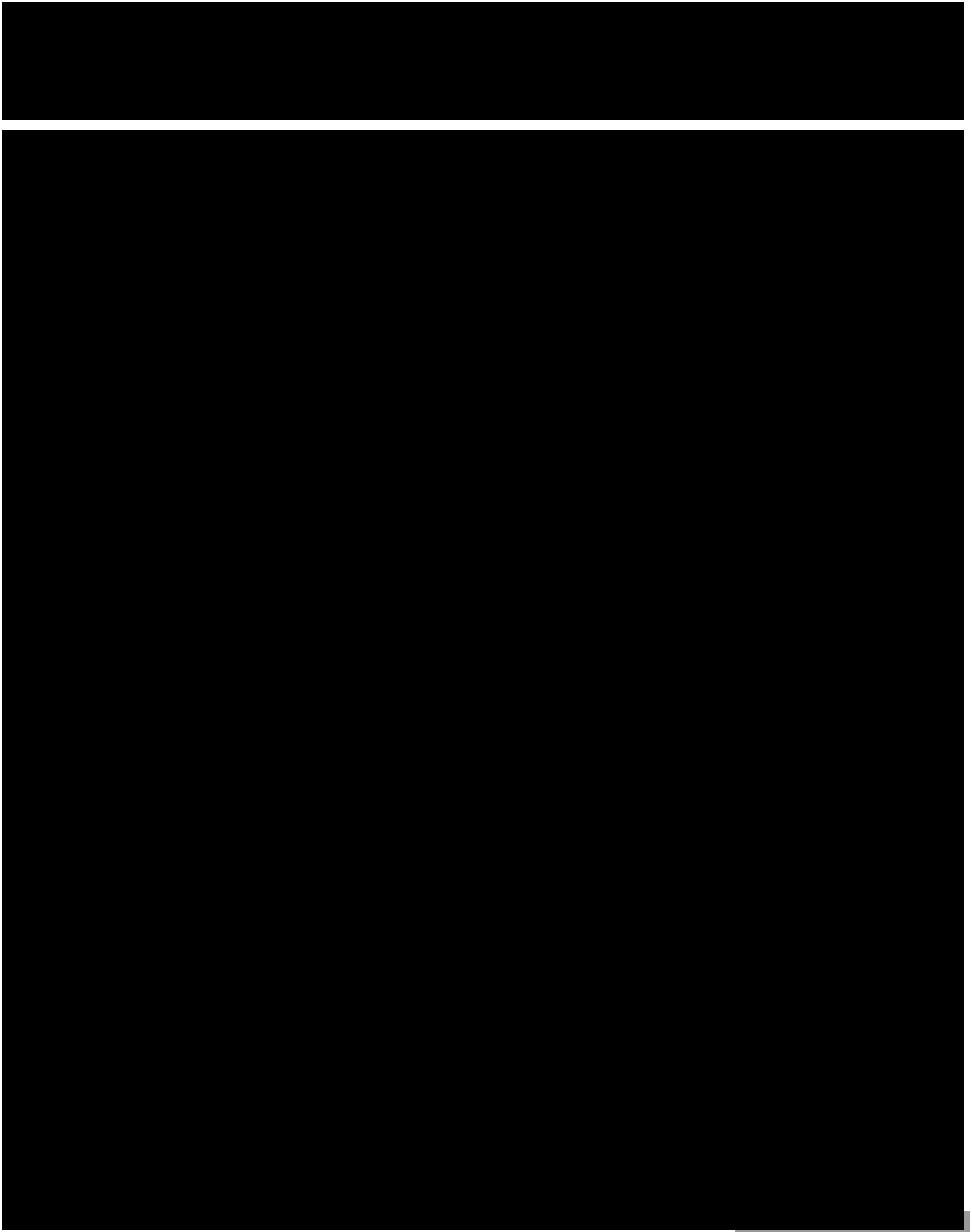

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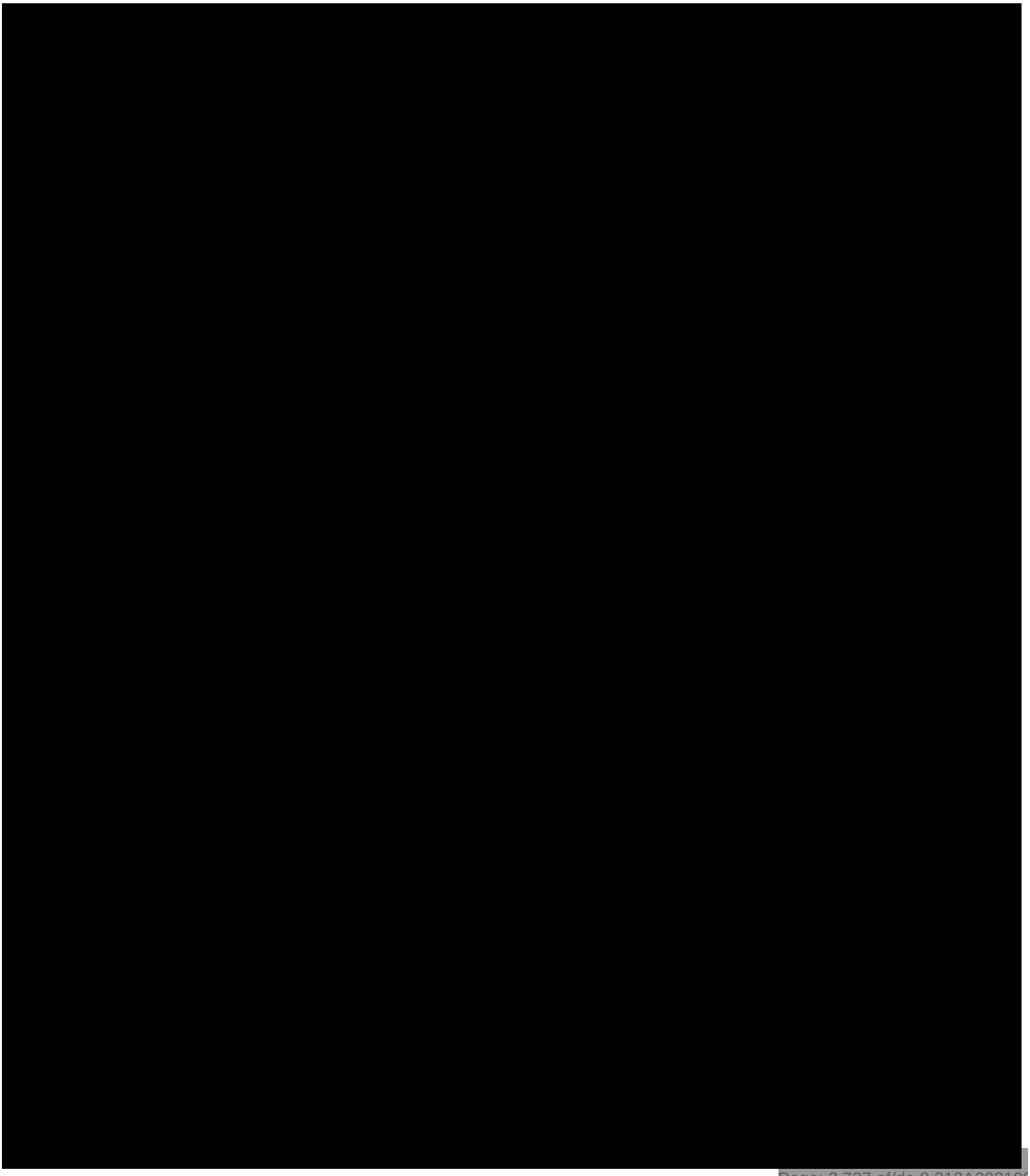

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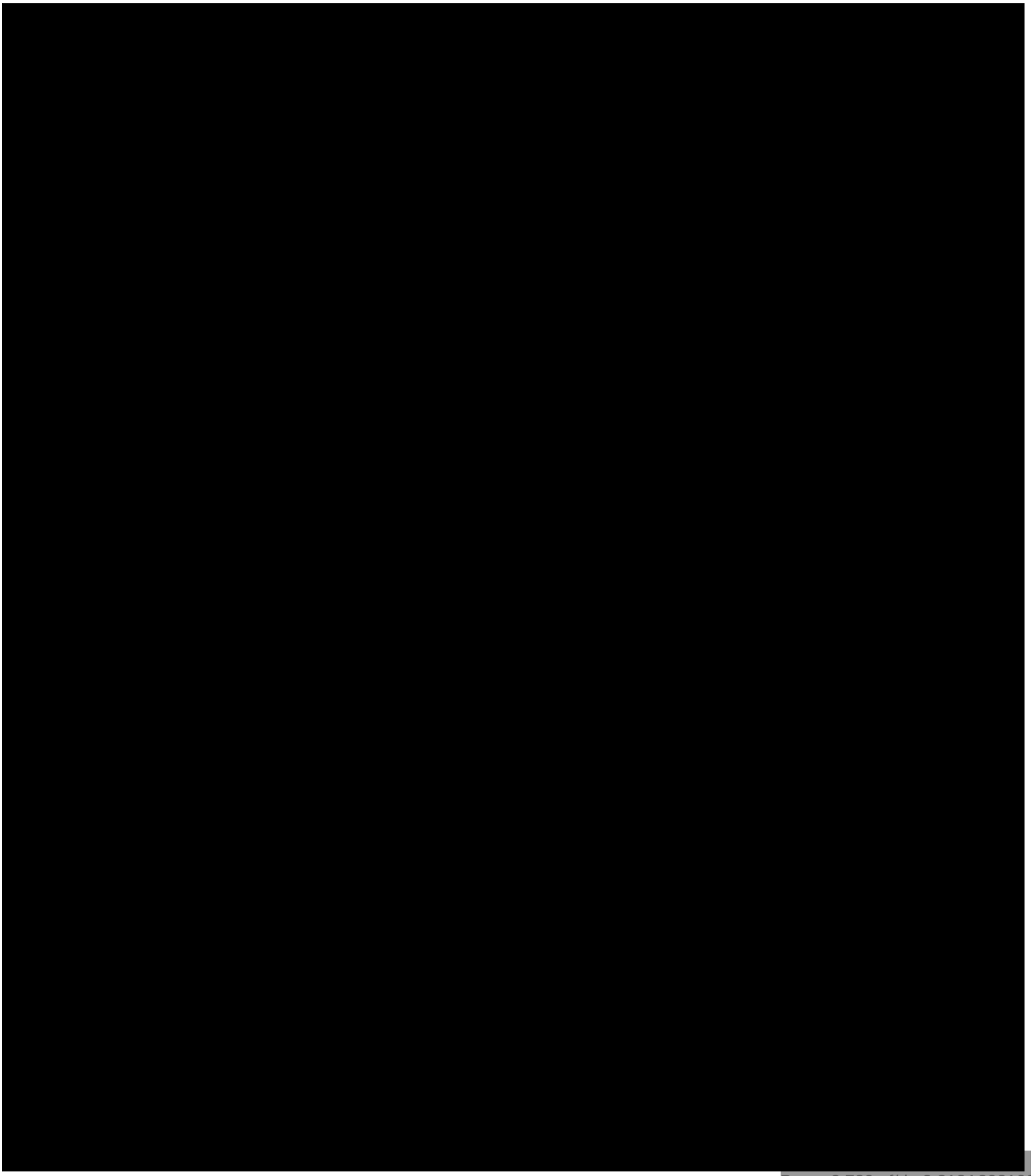

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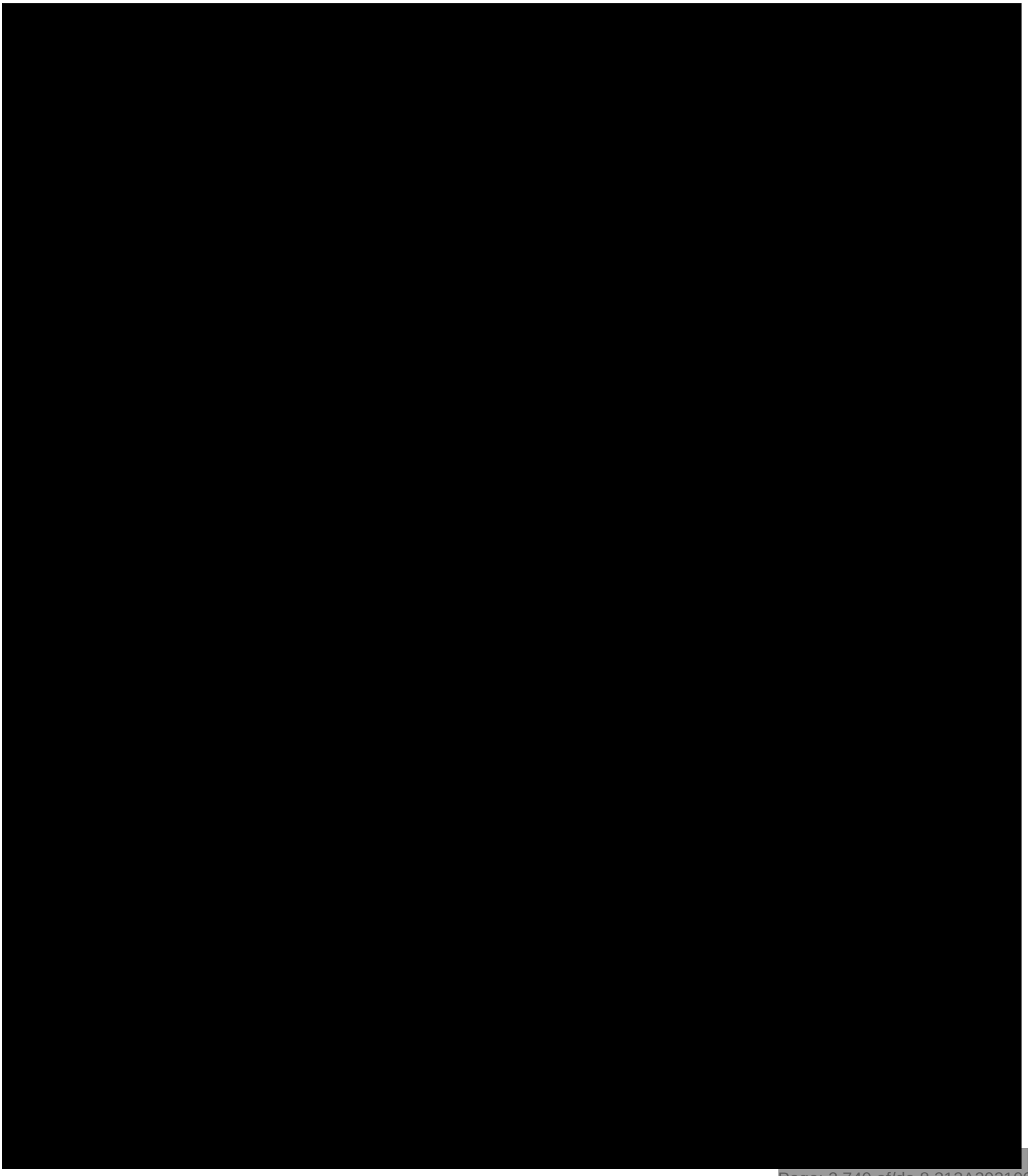

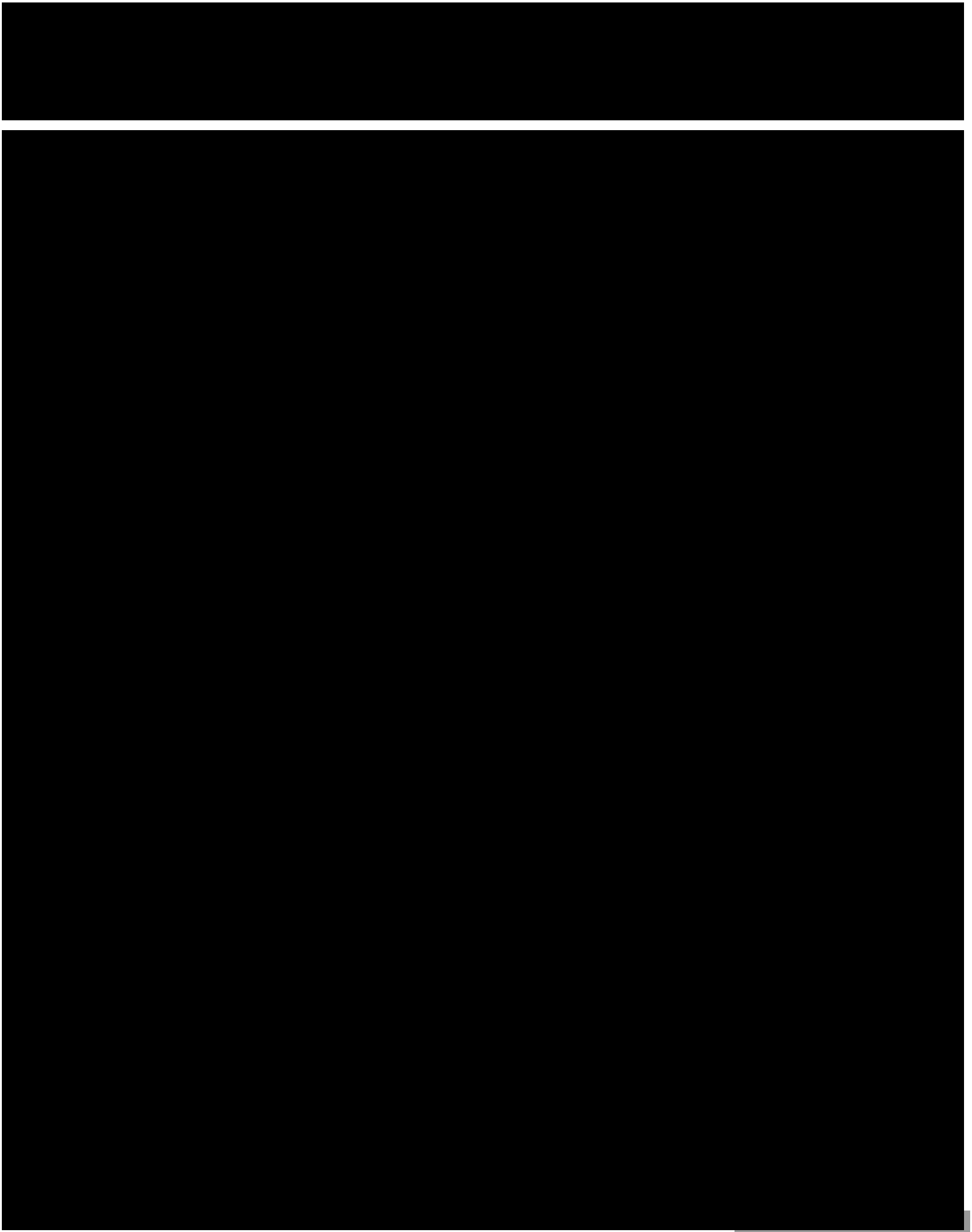

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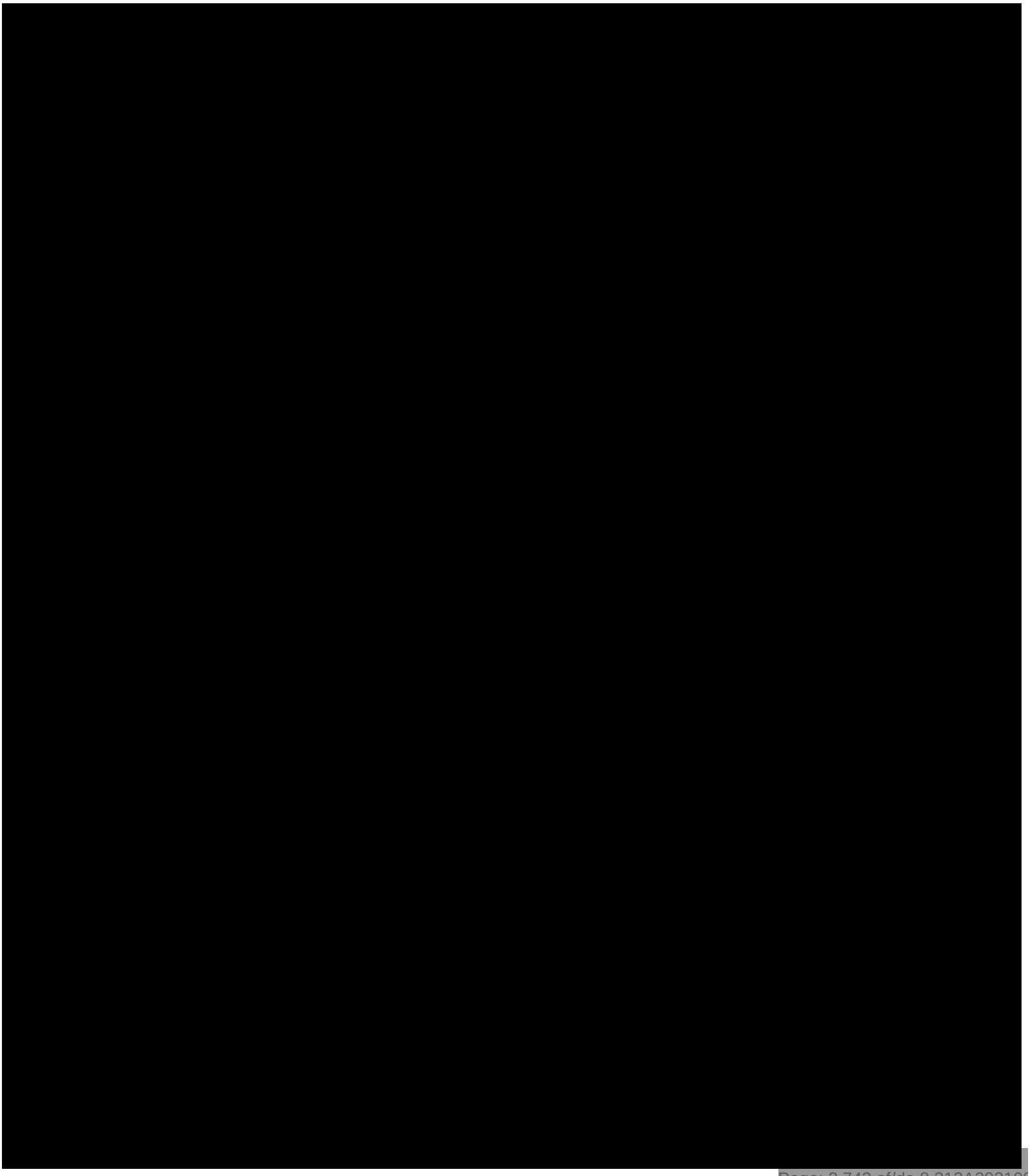

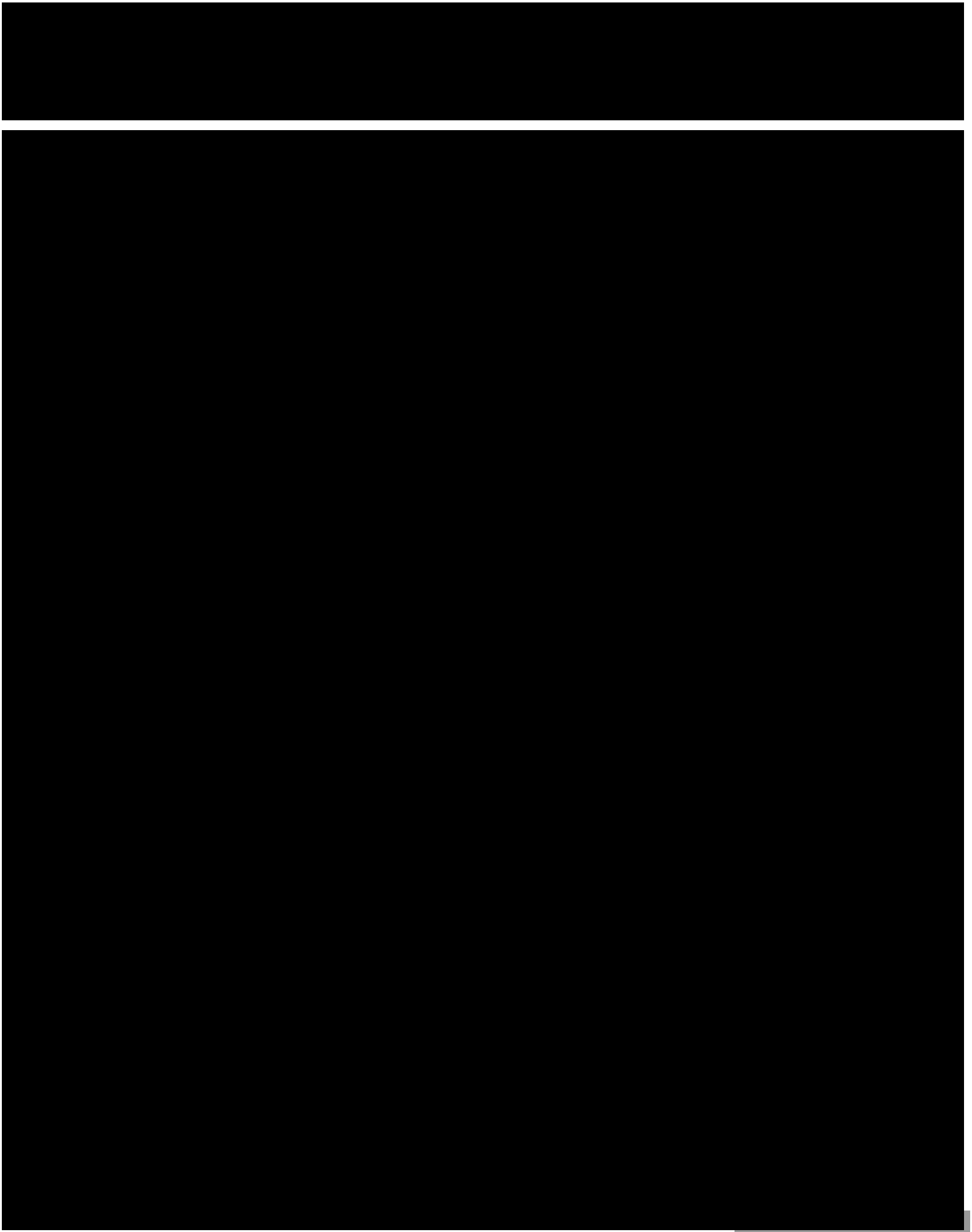

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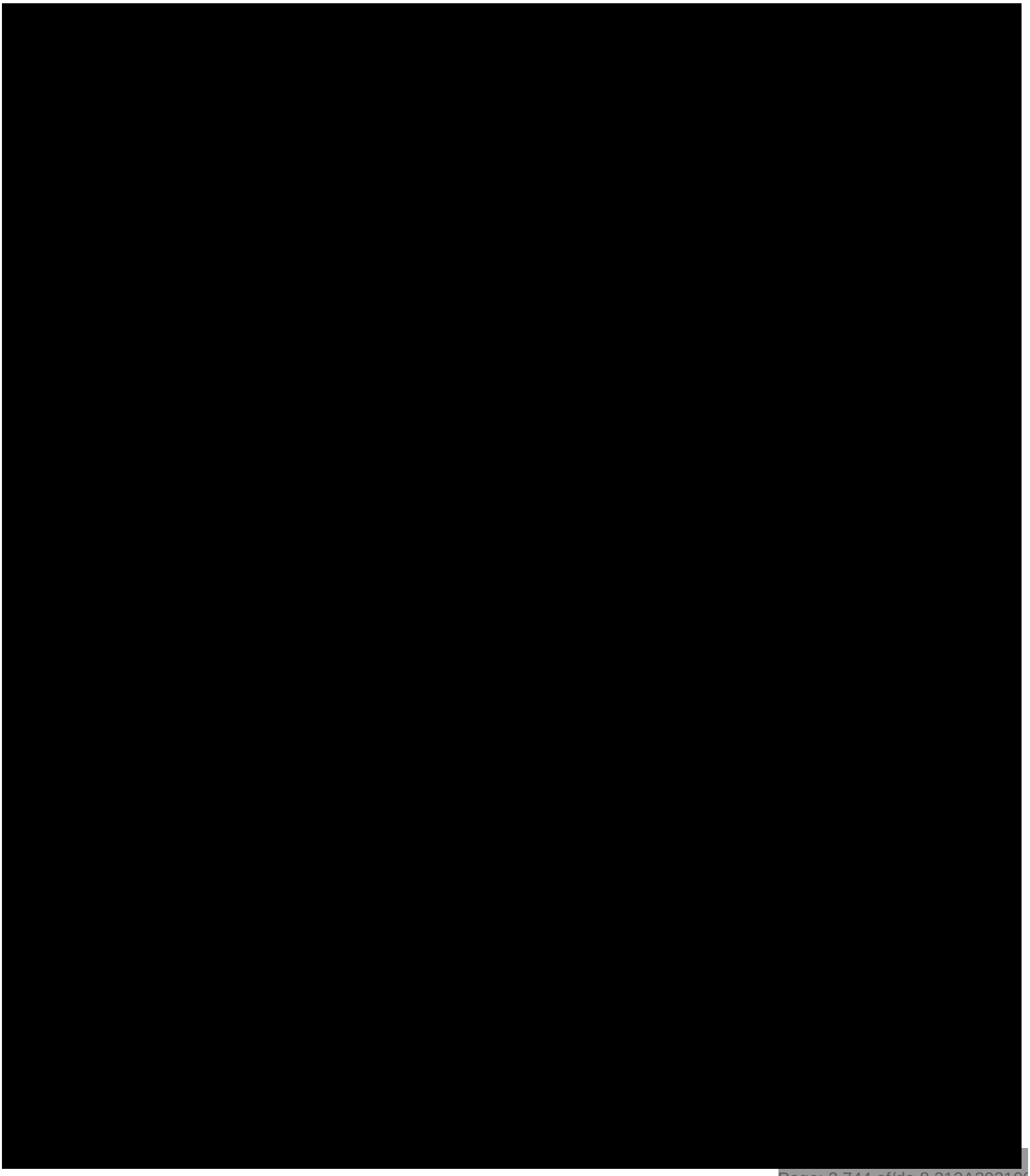

From: Antonio, Christopher (HC/SC)
Sent: 2021-03-25 3:14 PM
Cc: Panetta, Vincent (HC/SC); Akel, Sereen H (HC/SC); Patel, Shalu (HC/SC); Eassa, Samar (HC/SC); Tang, Marianne (HC/SC)
Bcc: [redacted]
Subject: COVID-19 Interim Order Application - Amending the Food and Drug Regulations
Attachments: Draft Guidance on amendments to the Food and Drug Regulations for drugs for use in relation to COVID-19.pdf; Lignes directrices sur les modifications apportées au Règlement sur les aliments et drogues relativement aux drogues utilisées dans le traitement de la COVID-19 .pdf

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Dear Sir or Madam:

Following our email sent to you on March 23rd regarding the *Regulations Amending the Food and Drug Regulations (Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19)* ("amending regulations") and on the accompanying amendments to the *Fees in Respect of Drugs and Medical Devices Order* ("fees order"), please see attached the advanced release of the *Guidance on amendments to the Food and Drug Regulations for drugs for use in relation to COVID-19* to aid you in the planning process of your future submissions.

As mentioned in our earlier correspondence, both regulatory packages will be published in the March 31, 2021 issue of the Canada Gazette II. At that time, we will also be launching a 30-day consultation period on the Guidance Document.

We would like to draw your attention to page 10 of the Guidance Document, which outlines the requirements under Section 19 of the amending regulations. Specifically, that an ISAD interim order authorization issued before March 18, 2021 for a COVID-19 drug will be revoked unless the manufacturer files a submission for the drug within the prescribed timeline. The manufacturer **must file the submission by close of business on Wednesday, June 16, 2021** in order to maintain its ability sell the drug after June 16, 2021 and before the submission receives a Notice of Compliance.

In addition, new updated Regulatory Enrolment Process (REP) Regulatory Transaction forms will be published to Health Canada's REP information page on April 1, 2021. The new REP forms will allow manufacturers to file a submission relying on modified requirements introduced through the amending regulations and to claim the fee remission introduced in section 14.1 of the fees order. Additional information detailing the steps required to complete these forms will be sent to you on March 31, 2021. If you intend to prepare such a submission before the updated REP forms have been published, please contact hc.eReview.sc@canada.ca.

We look forward to discussing your submission at your earliest convenience. Please contact the Office of Regulatory Affairs as soon as possible to schedule your pre-submission meeting.

Madame ou Monsieur :

À la suite de notre courriel qui vous a été envoyé le 23 mars concernant le *Règlement modifiant le règlement sur les aliments et drogues (Arrêté provisoire concernant l'importation, la vente et la publicité de médicaments à utiliser en relation avec le COVID-19)* (« l'article modificatif ») ainsi que les modifications à *l'Arrêté sur les prix à payer à l'égard des drogues et instruments médicaux* (« l'arrêté sur les prix »), veuillez trouver ci-joint une publication anticipée du document d'orientation intitulé *Lignes directrices sur les modifications apportées au Règlement sur les aliments et drogues relativement aux drogues utilisées dans le traitement de la COVID-19* pour vous aider dans le processus de planification de vos futures soumissions.

Comme nous l'avons mentionné dans notre correspondance précédente, les deux ensembles de règlements seront publiés dans le numéro du 31 mars 2021 de la Gazette du Canada II. À ce moment-là, nous lancerons également une période de consultation de 30 jours sur le document d'orientation.

Nous attirons votre attention à la page 10 du document d'orientation, qui décrit les exigences de l'article 19 du règlement modificatif. Plus précisément, une autorisation de commande provisoire de l'ISAD qui a été délivrée avant le 18 mars 2021 à l'égard d'une drogue contre la COVID-19 sera révoquée à moins que le fabricant ne dépose une soumission à l'égard de la drogue dans le délais prescrit. Le fabricant **doit déposer la soumission avant la fermeture des bureaux le mercredi 16 juin 2021** pour pouvoir continuer à vendre la drogue après le 16 juin 2021 et avant qu'un avis de conformité ne soit émit à l'égard de la soumission.

De plus, de nouveaux modèles de transactions réglementaires du processus d'inscription réglementaire (PIR) ont été mis à jour et seront publiés le 1 avril 2021 au site web de Santé Canada traitant sur le PIR. Les nouveaux modèles permettront aux fabricants de déposer une soumission qui se fie aux exigences modifiées introduites à travers l'article modificatif. Les nouveaux modèles permettront aussi aux fabricants à être remboursé selon l'article 14.1 de l'arrêté sur les prix. De plus amples détails concernant les démarches à prendre pour remplir les nouveaux modèles vous seront communiqués le 31 mars 2021. Si vous souhaitez préparer une telle soumission avant que les nouveaux modèles ne soient publiés, veuillez contacter hc.eReview.sc@canada.ca.

Nous sommes impatients de discuter de votre soumission dans les meilleurs délais. Veuillez contacter le bureau des affaires réglementaires dès que possible pour planifier votre réunion de pré-soumission.

Thank you / Merci,

Christopher Antonio
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Biologic and Radiopharmaceutical Drugs Directorate (new name)
Health Products and Food Branch / Health Canada
christopher.antonio@canada.ca / Tel: 613-864-9579 / Fax: 613-946-9520

Gestionnaire
Bureau des affaires réglementaires
Direction des médicaments biologiques et radiopharmaceutiques (nouveau nom)
Direction générale des produits de santé et des aliments / Santé Canada
christopher.antonio@canada.ca / Tel: 613-864-9579 / Fax: 613-946-9520

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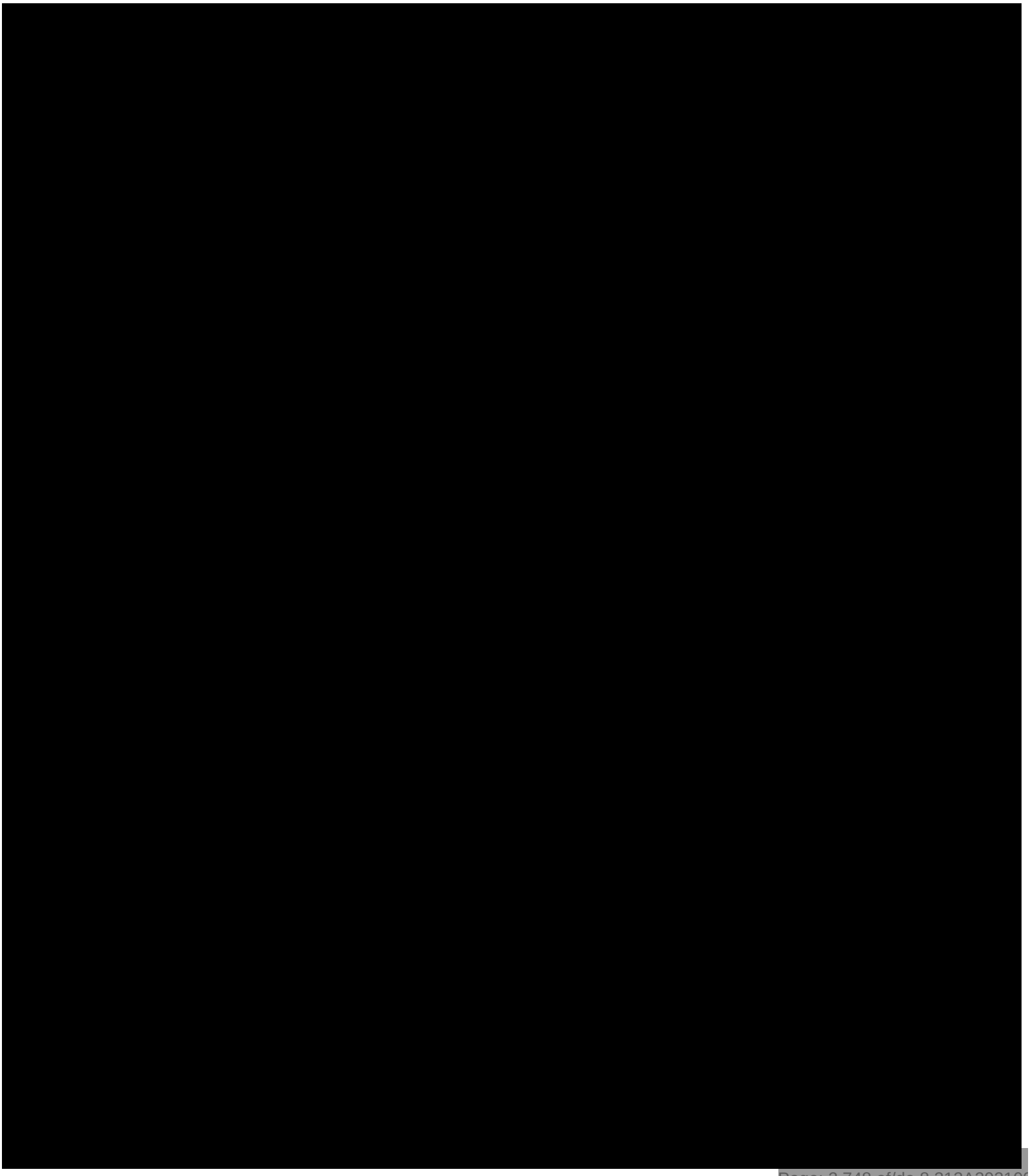

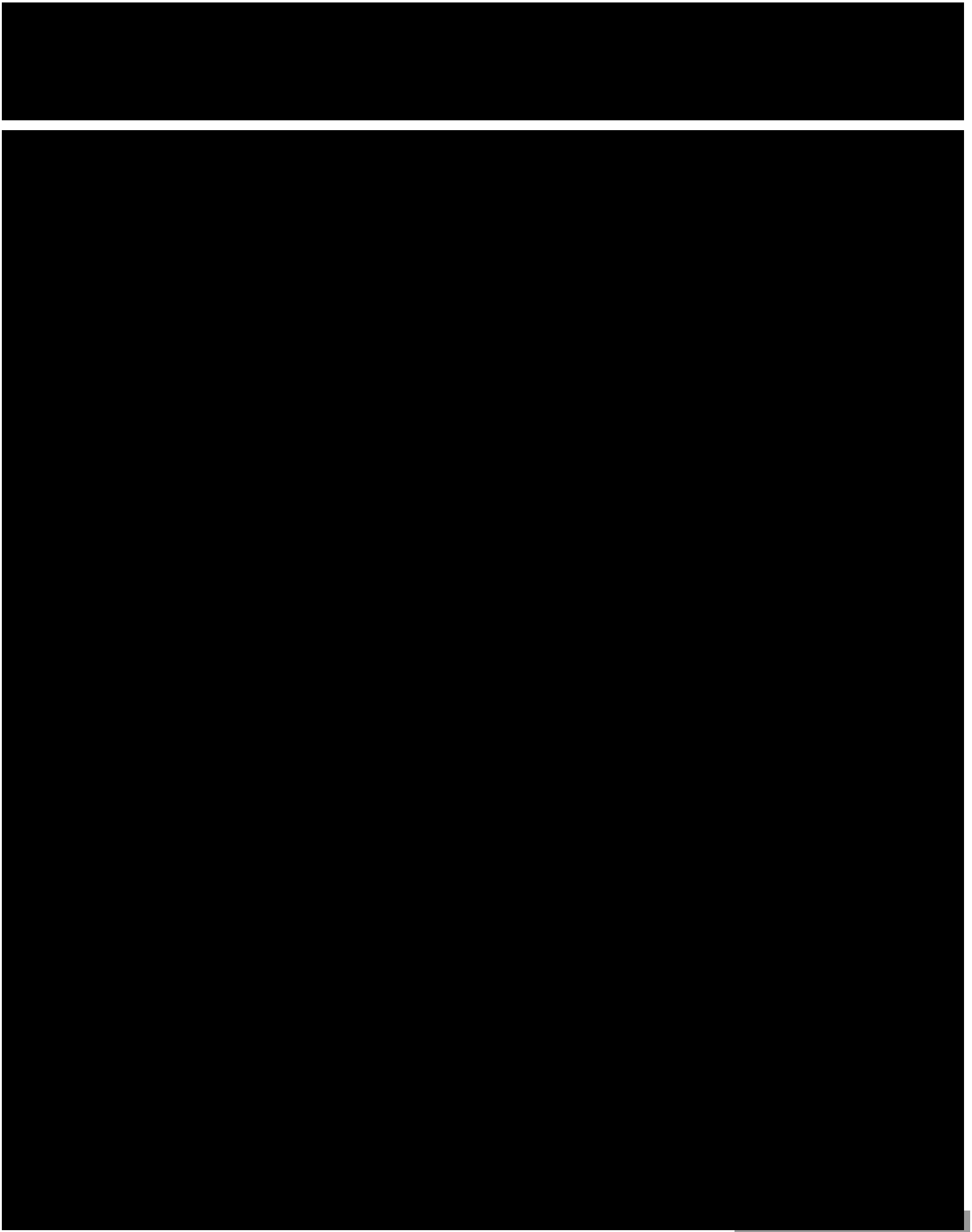

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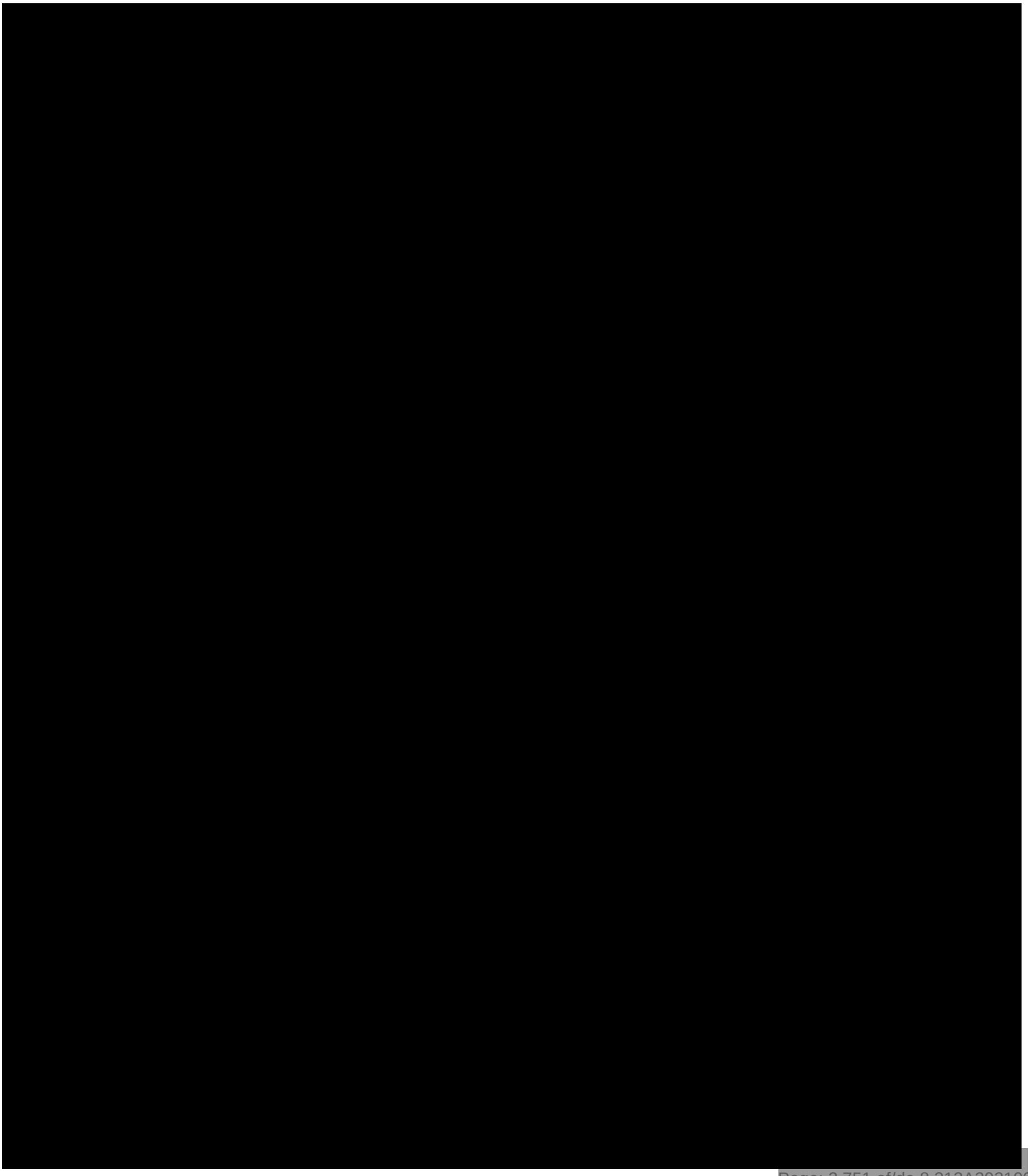

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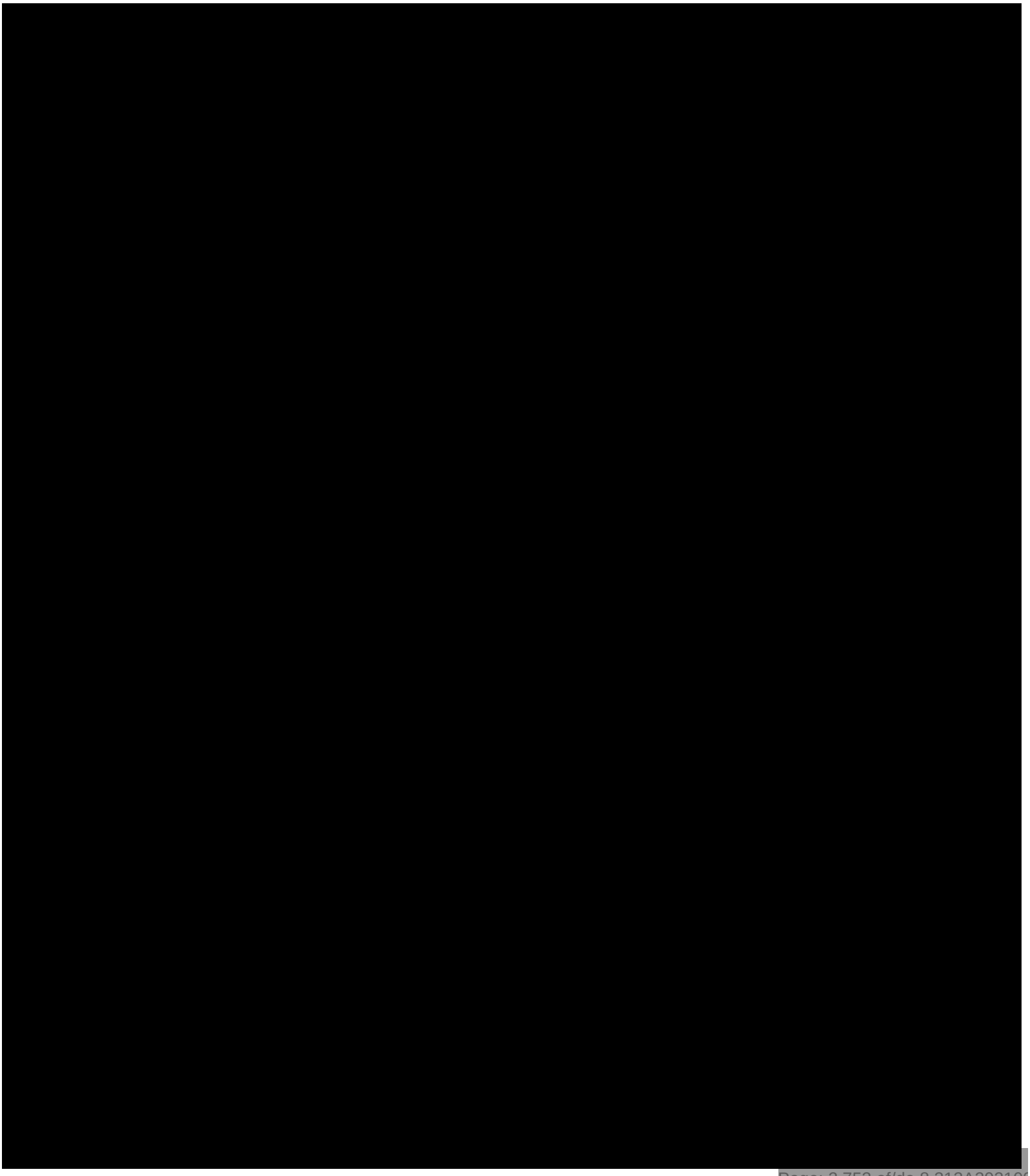

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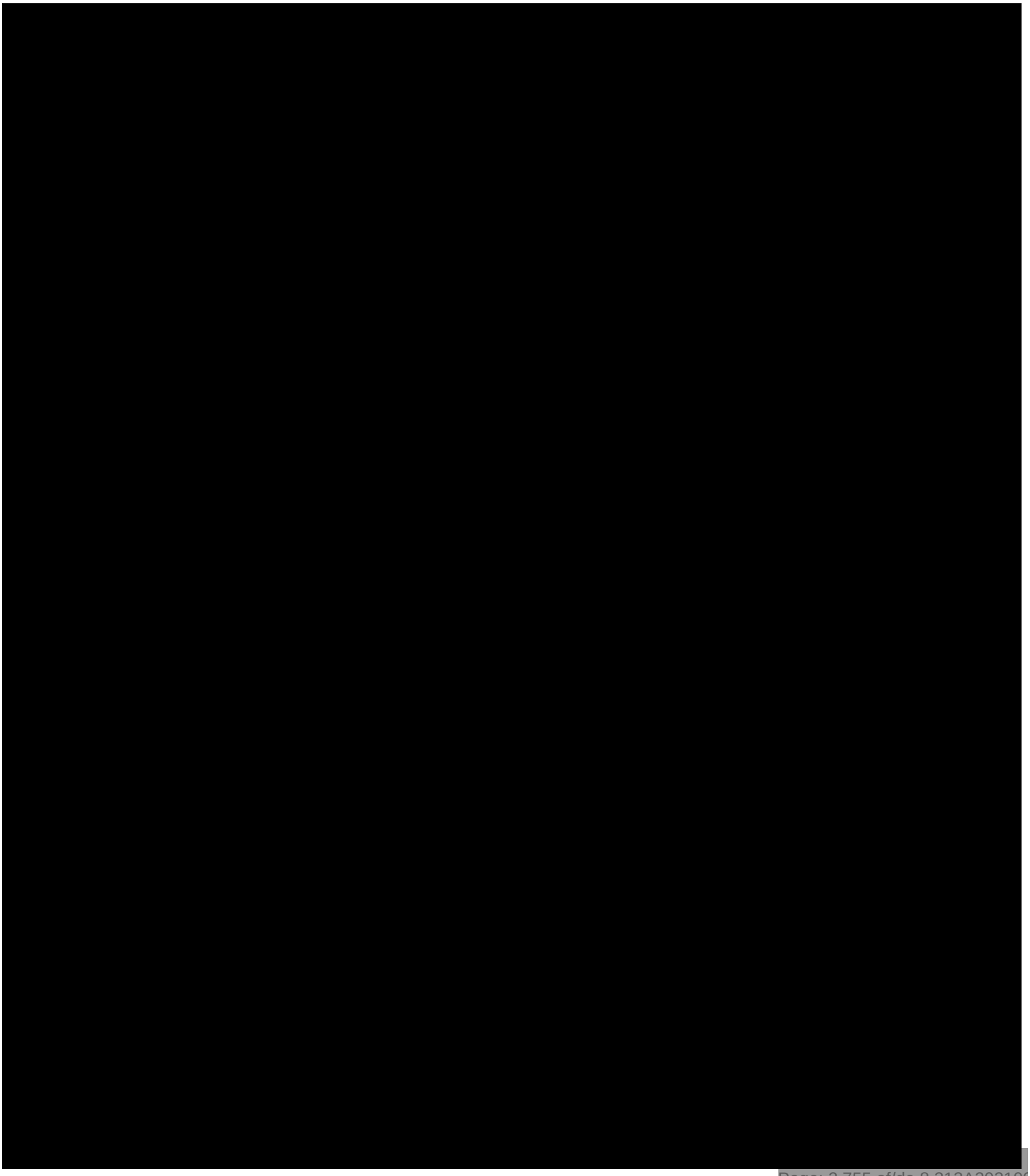

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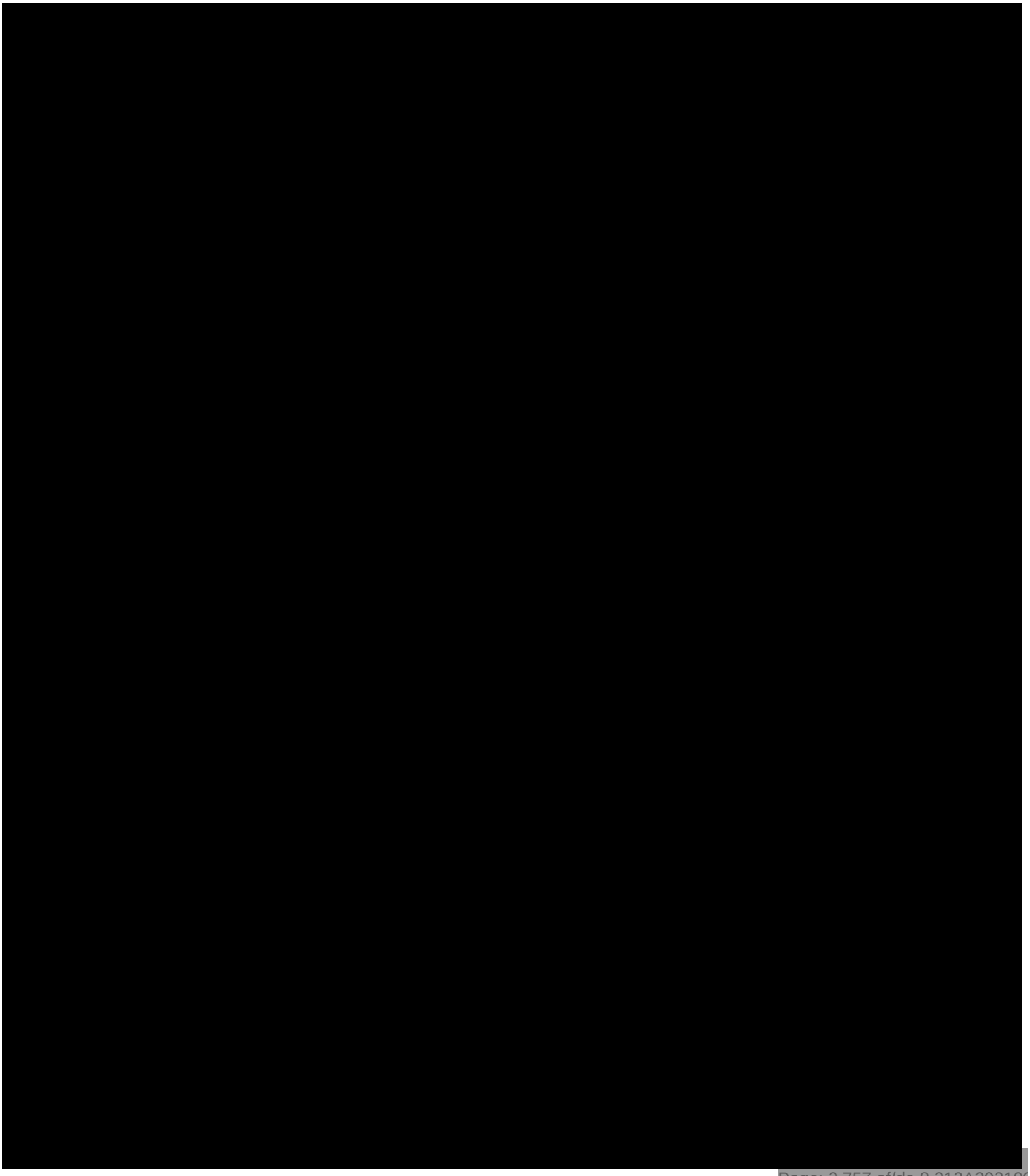

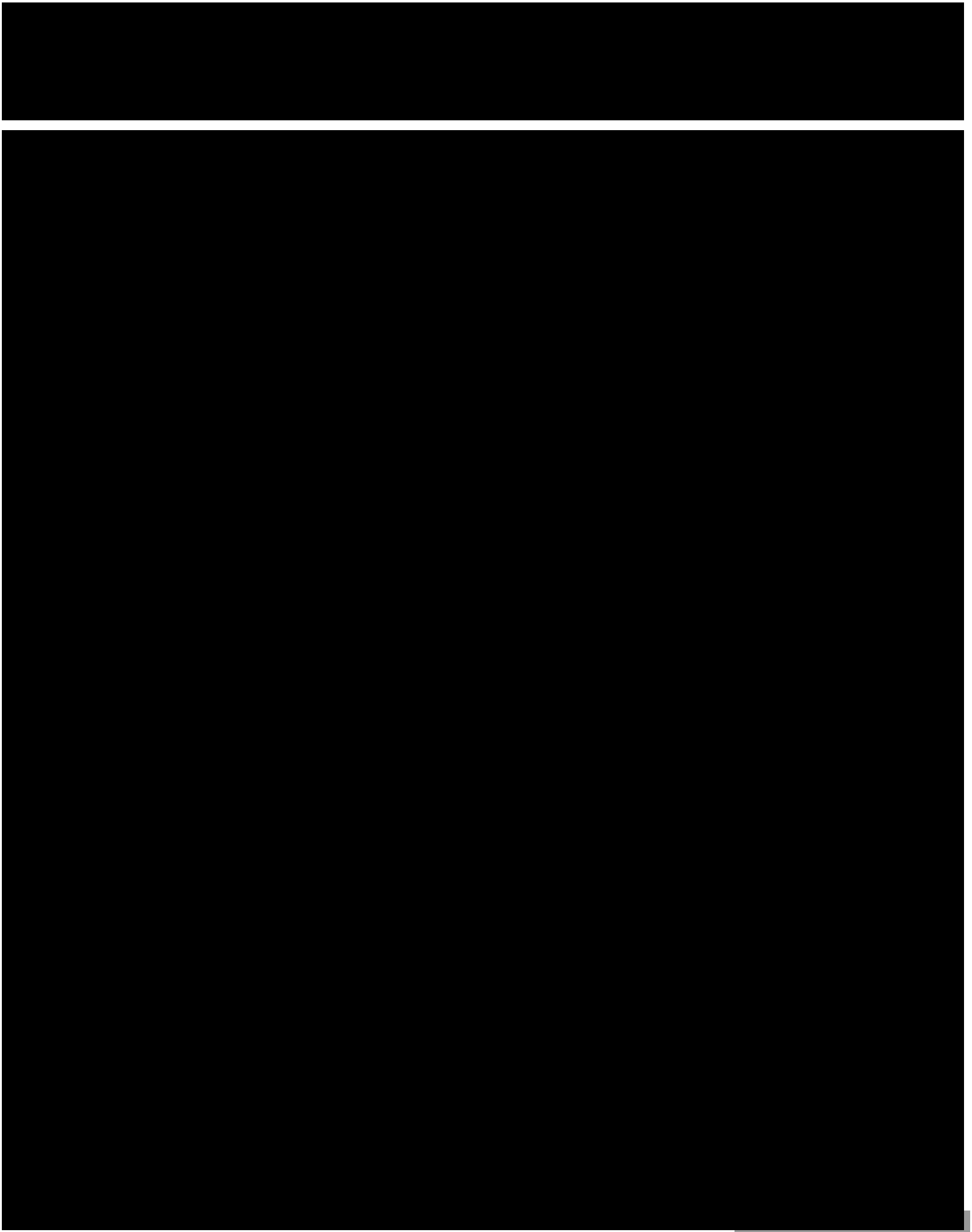

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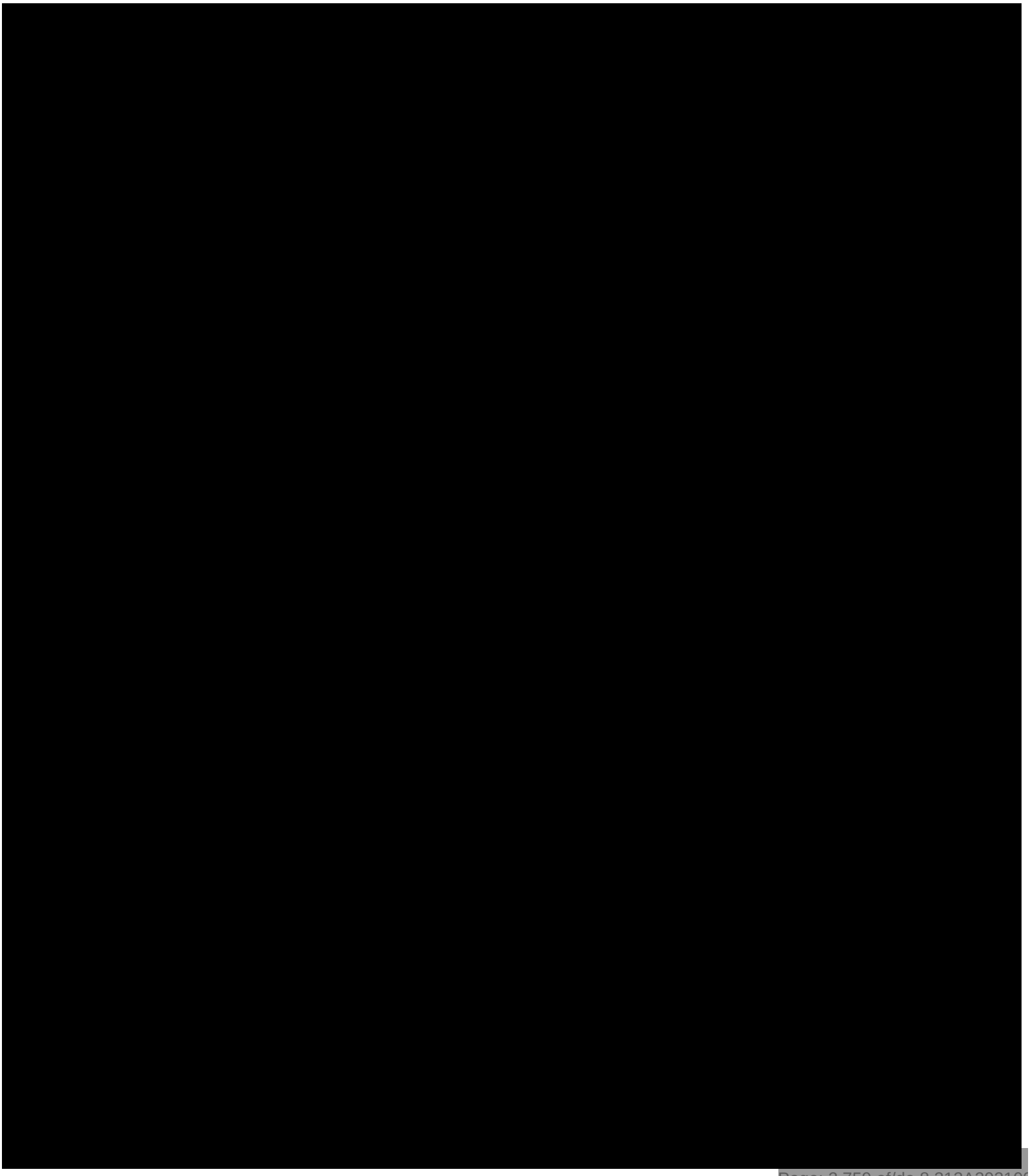

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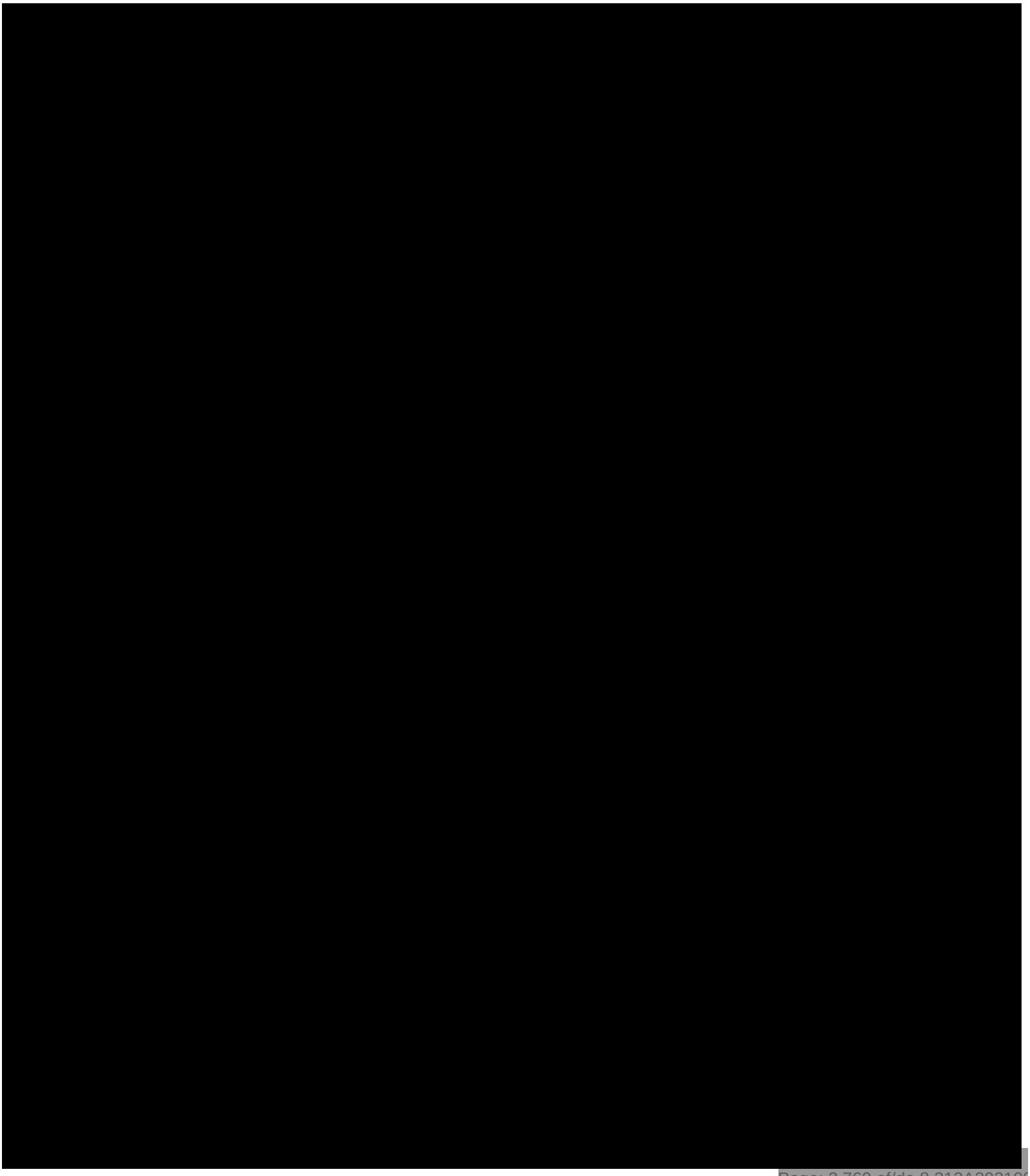

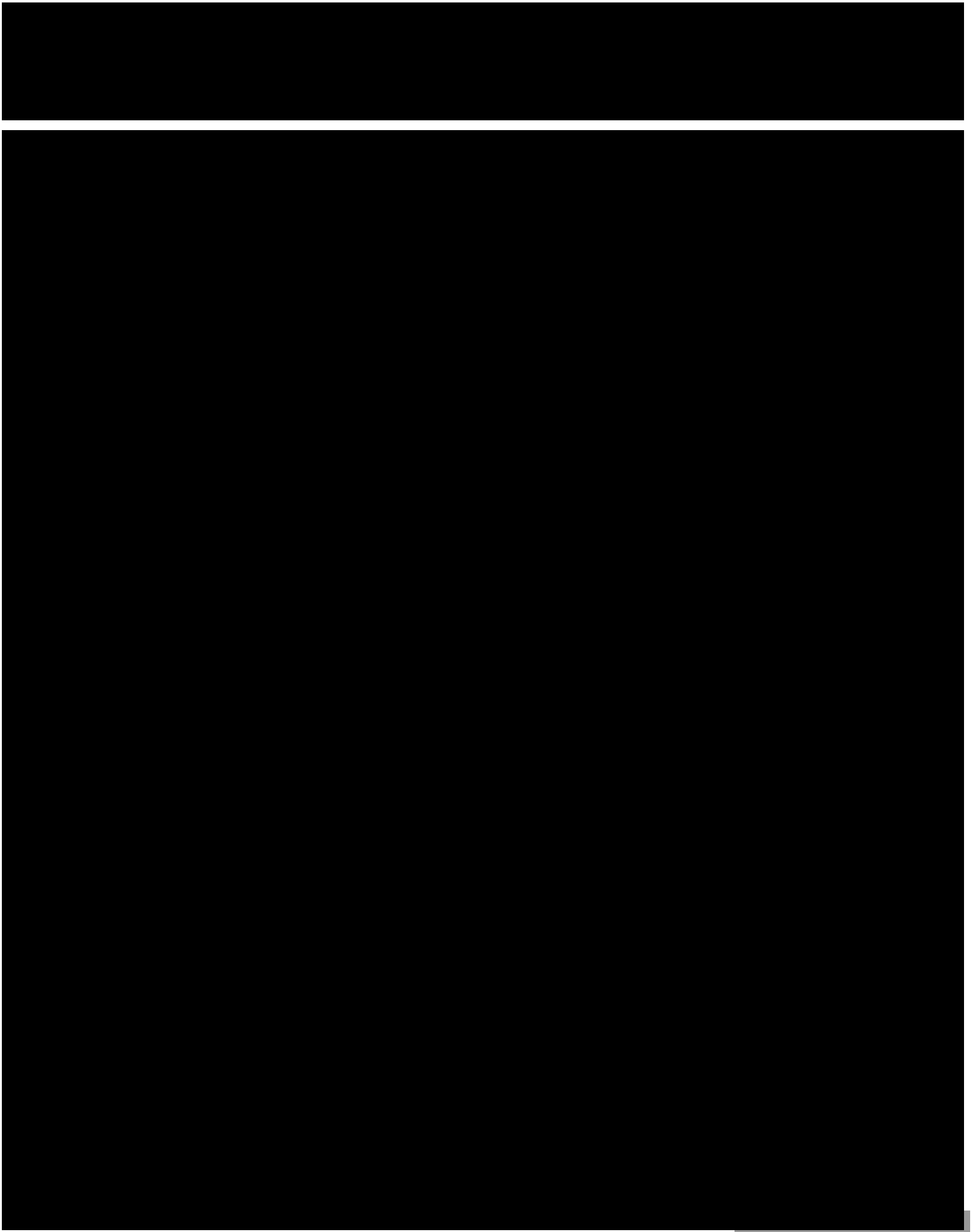

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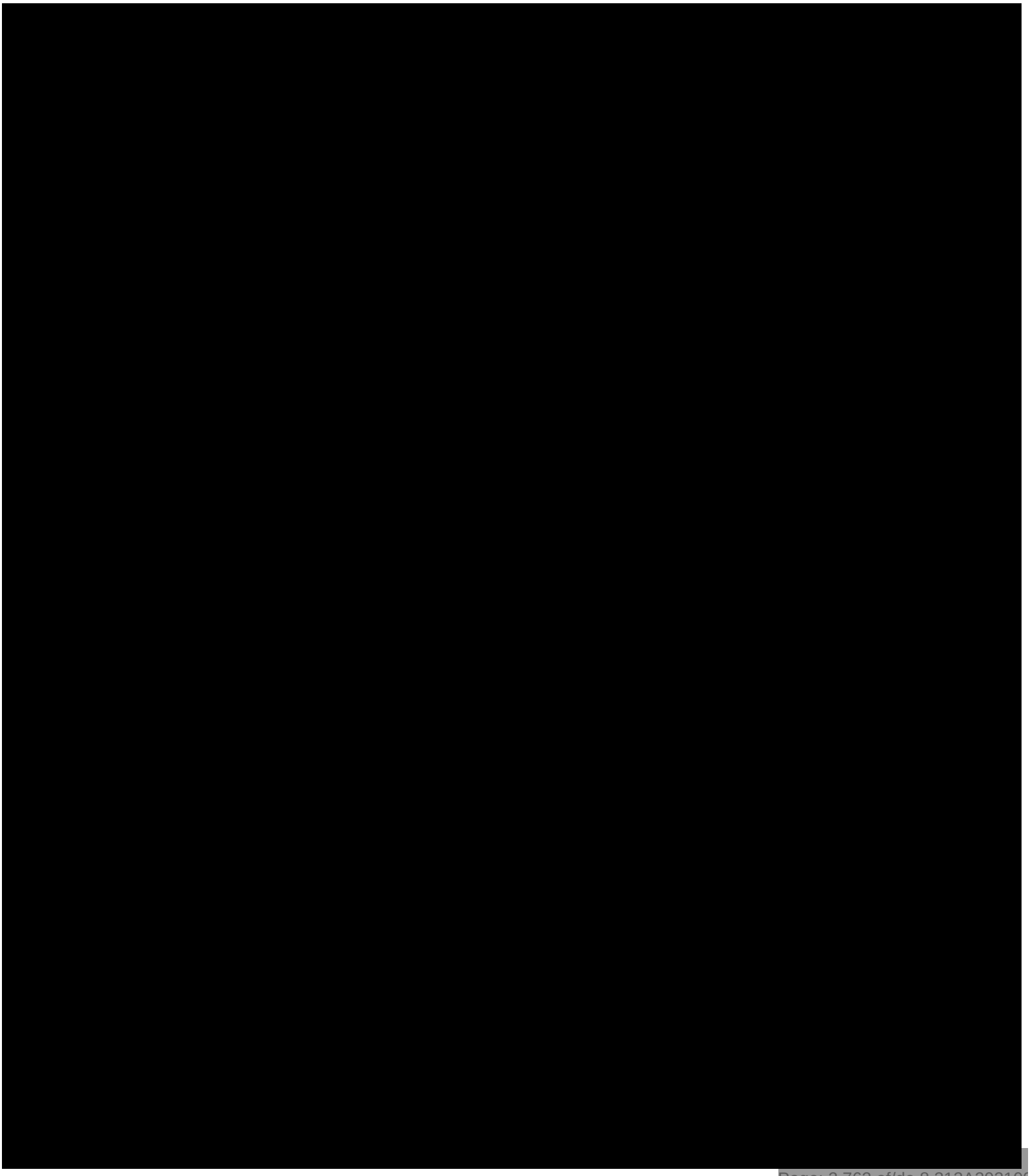

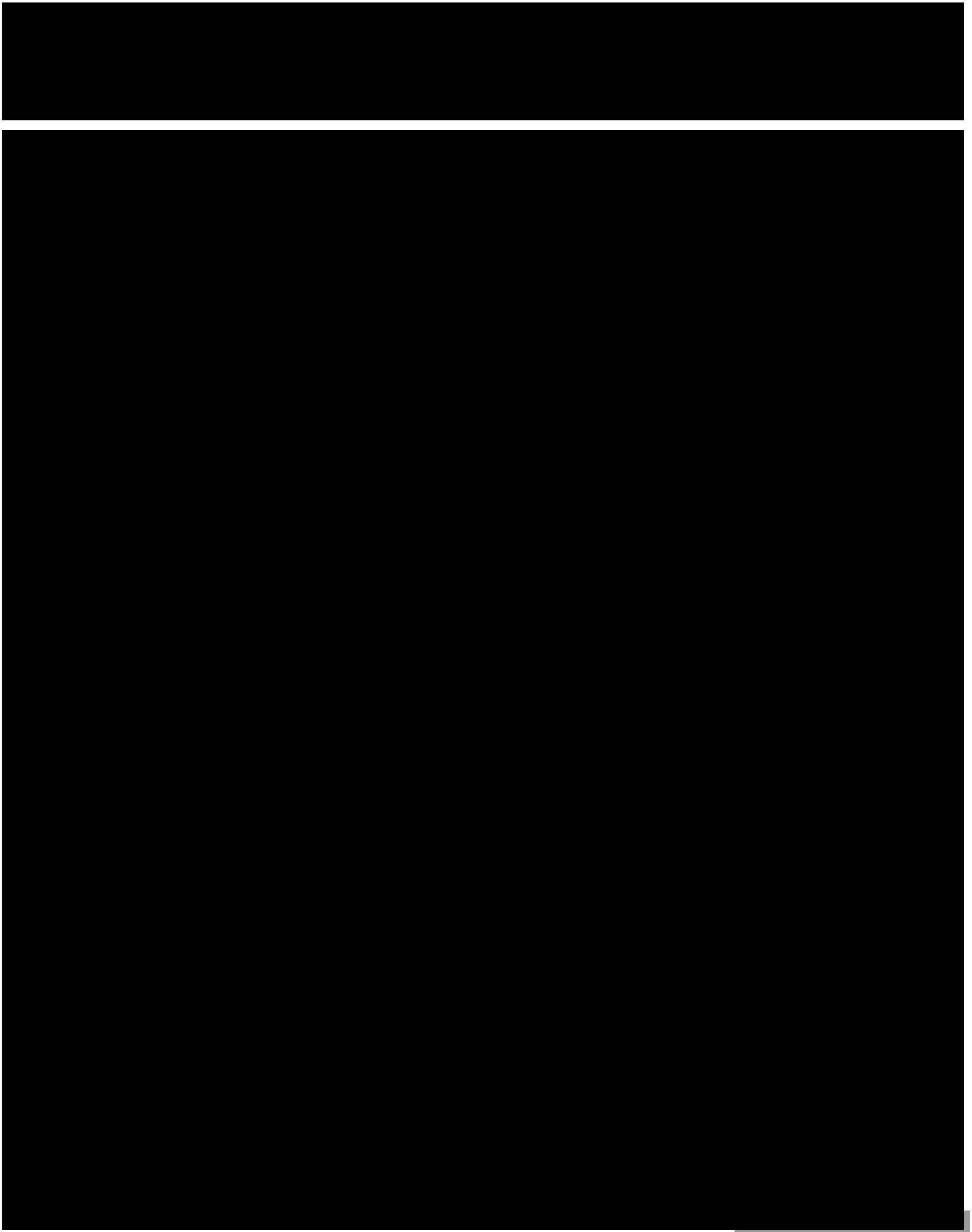

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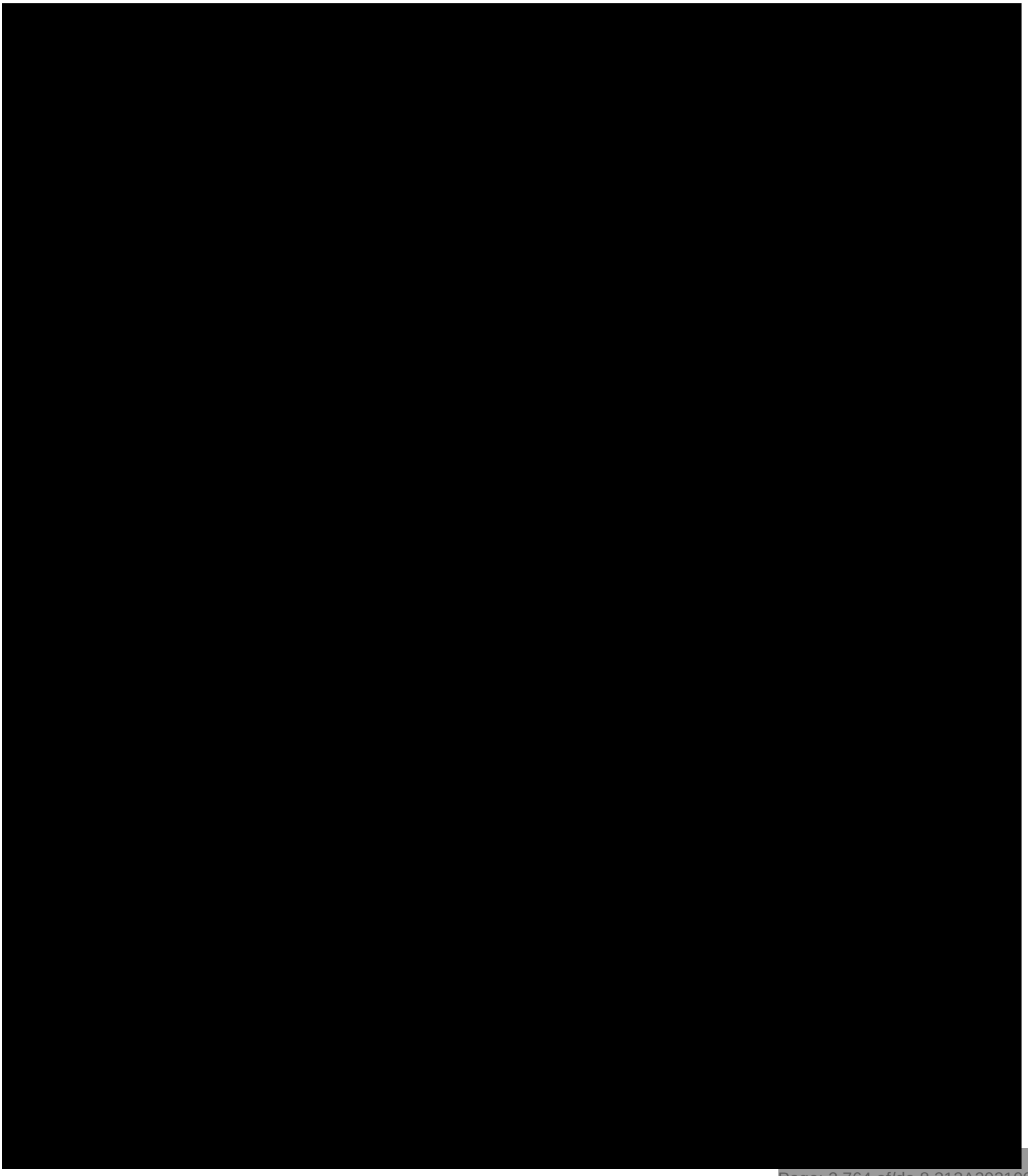

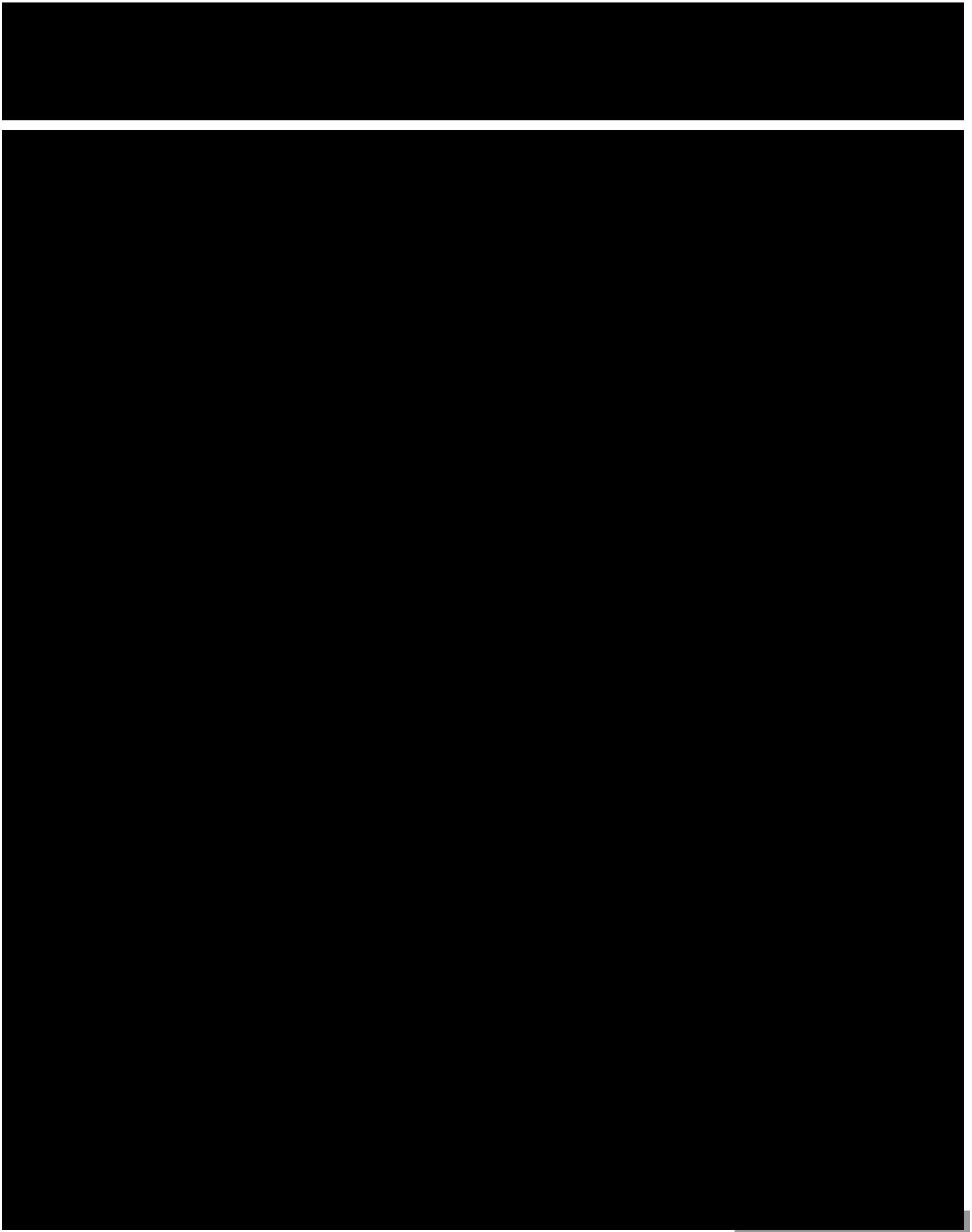

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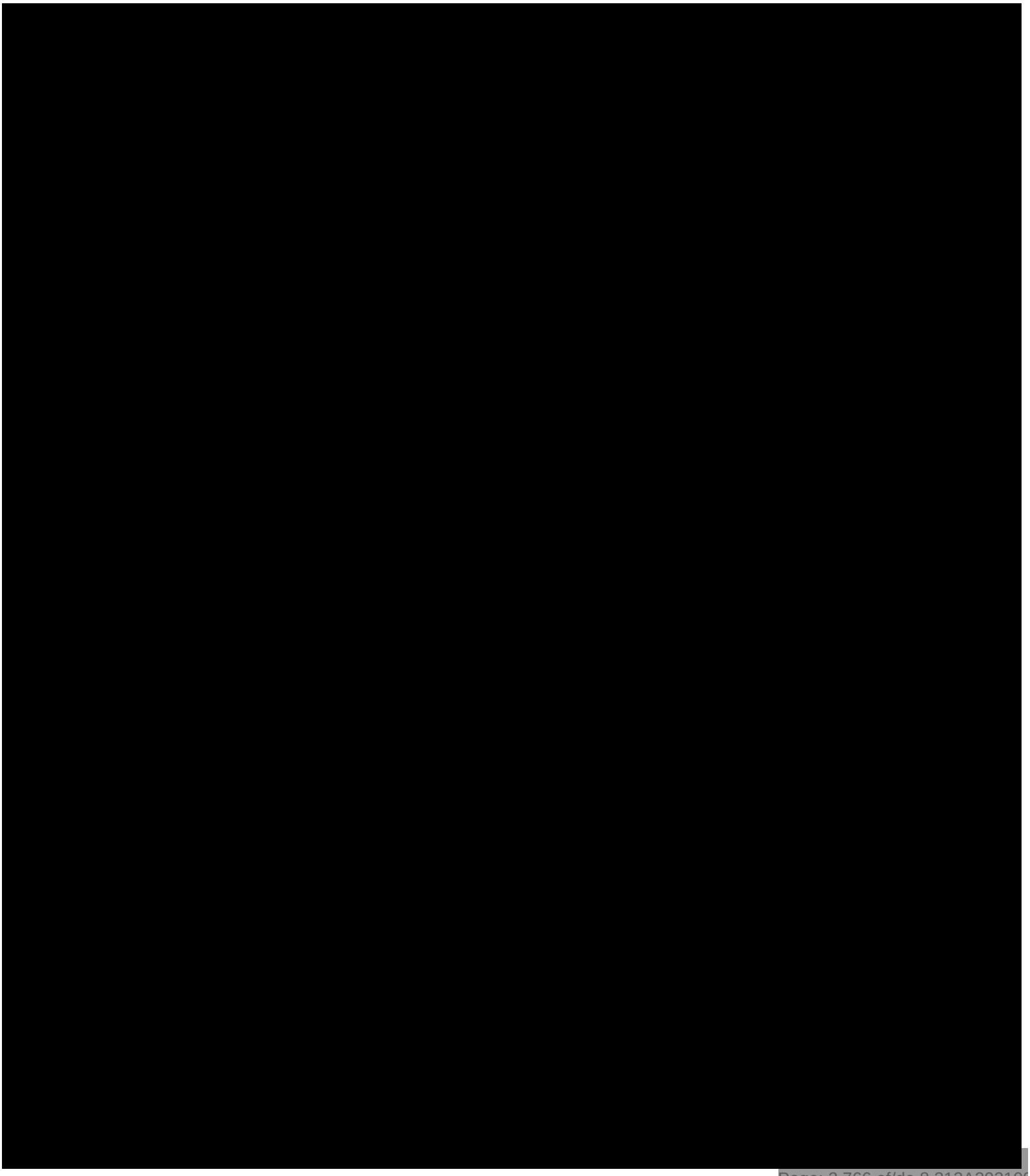

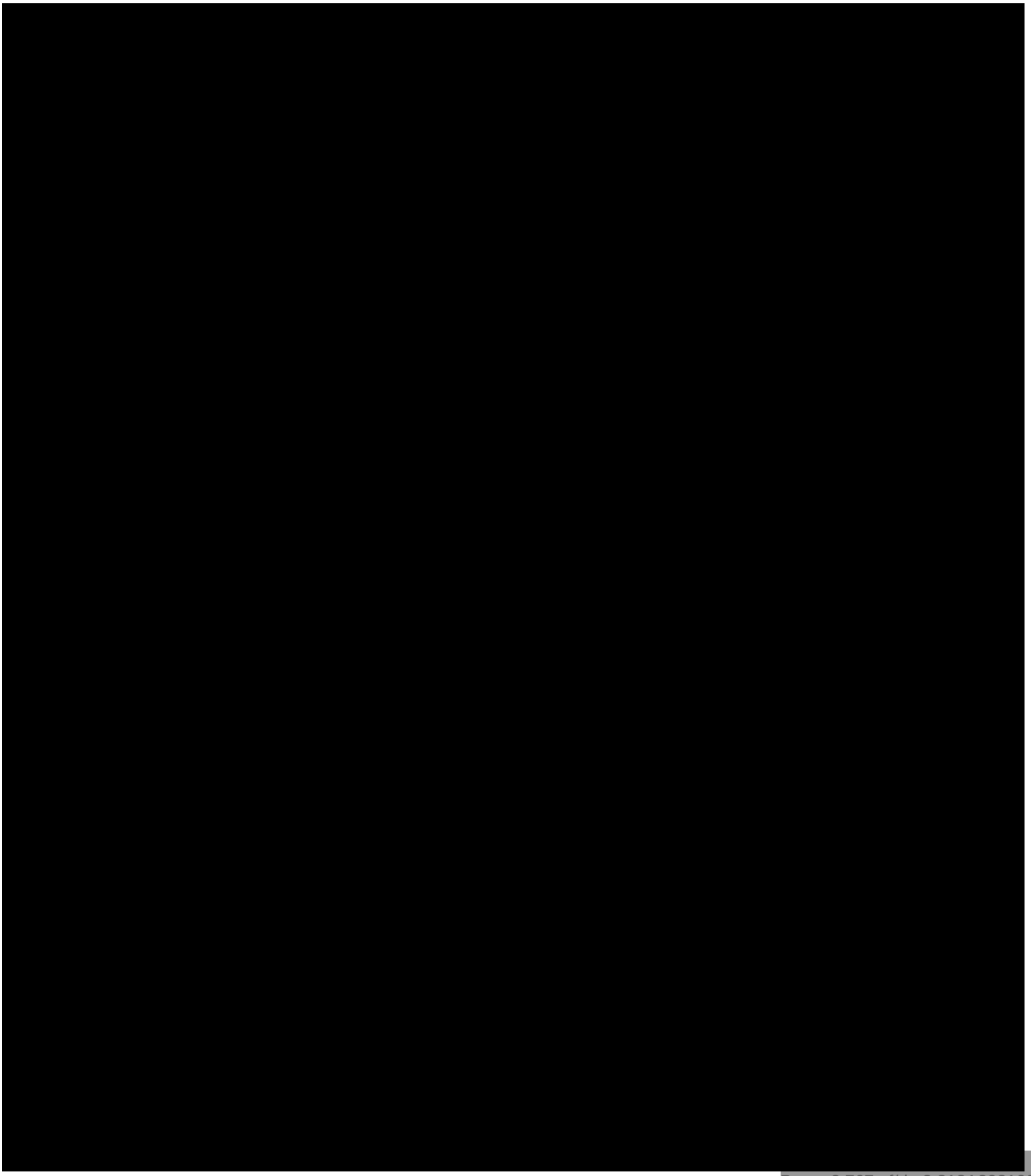

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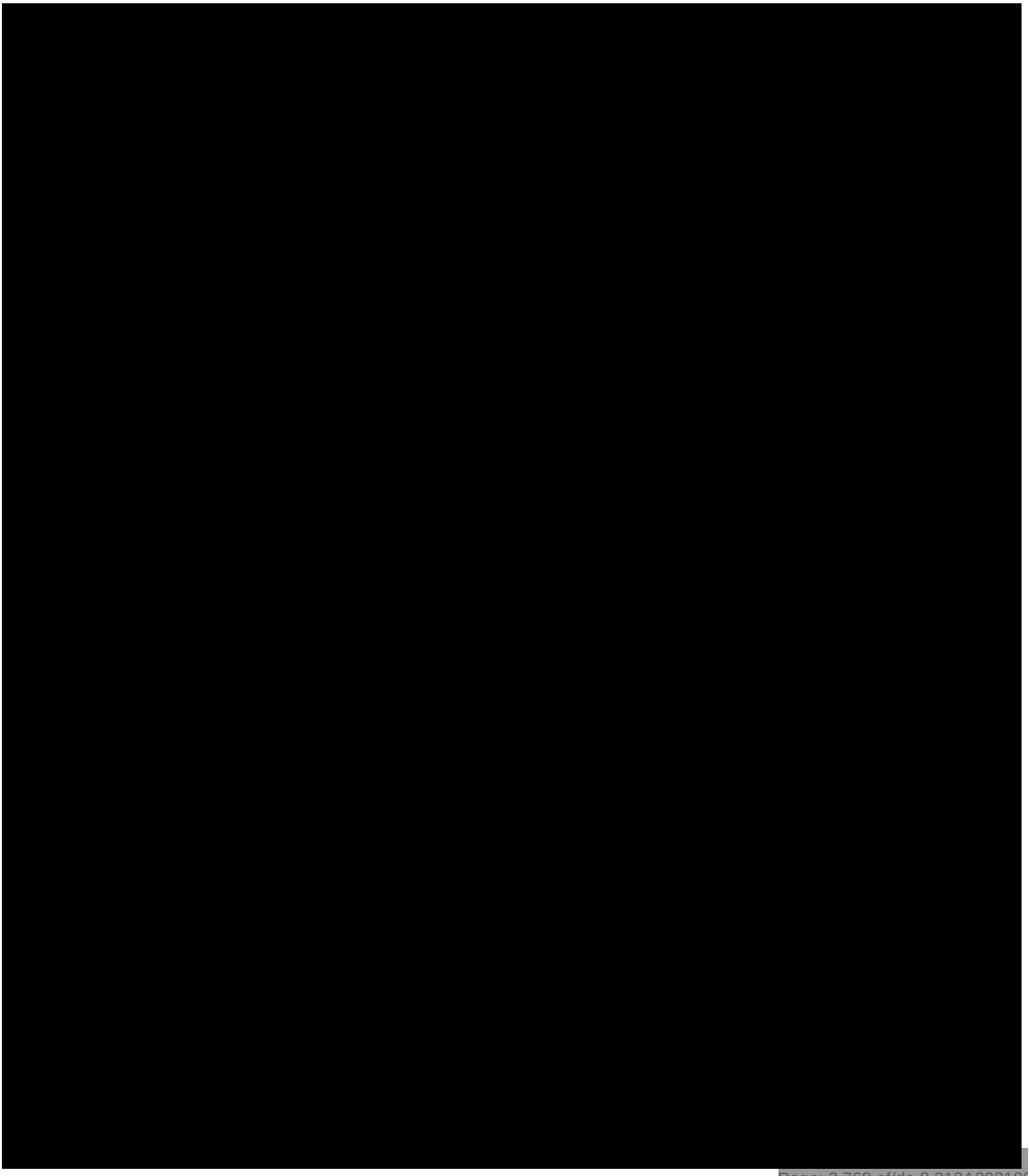

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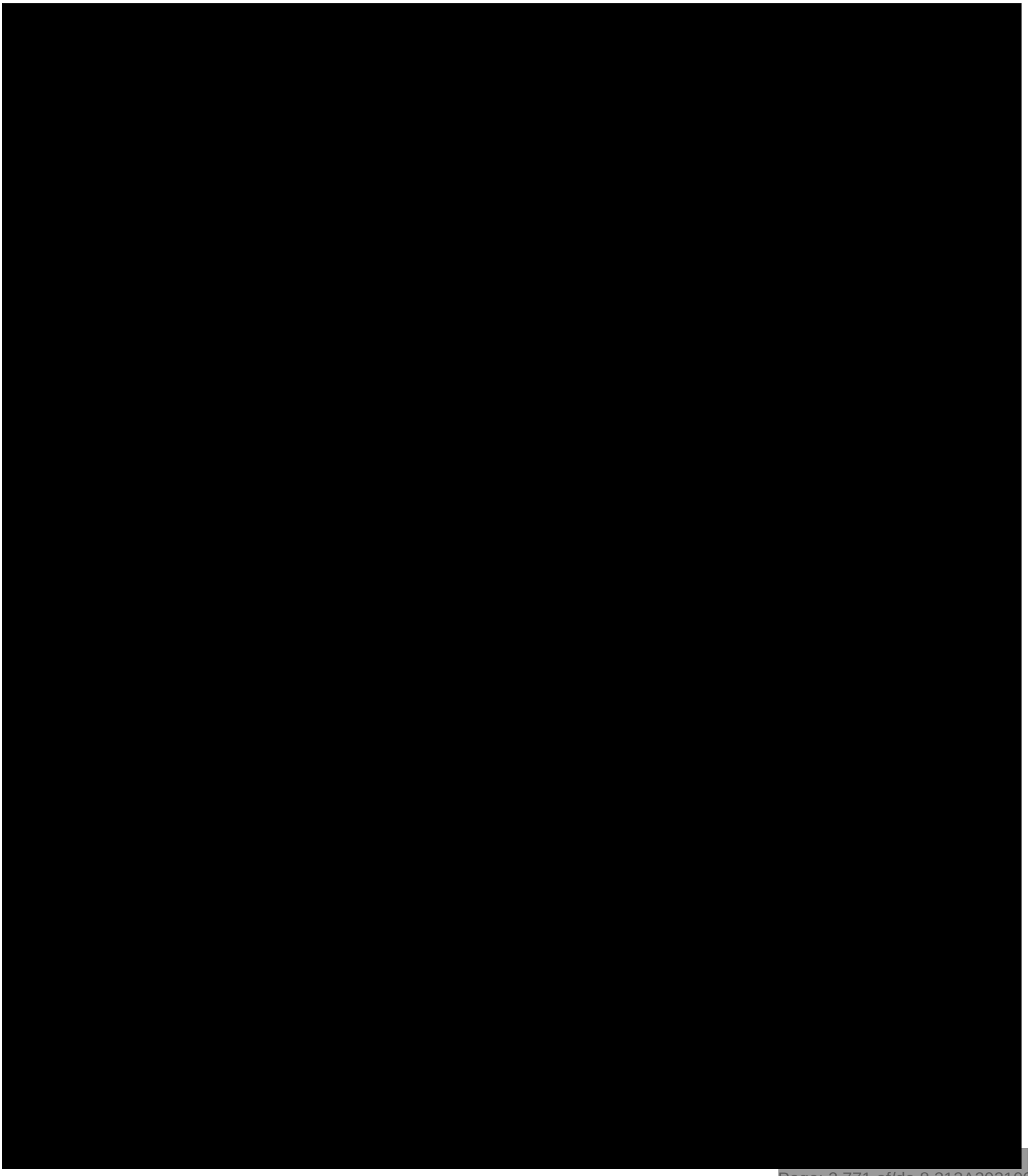

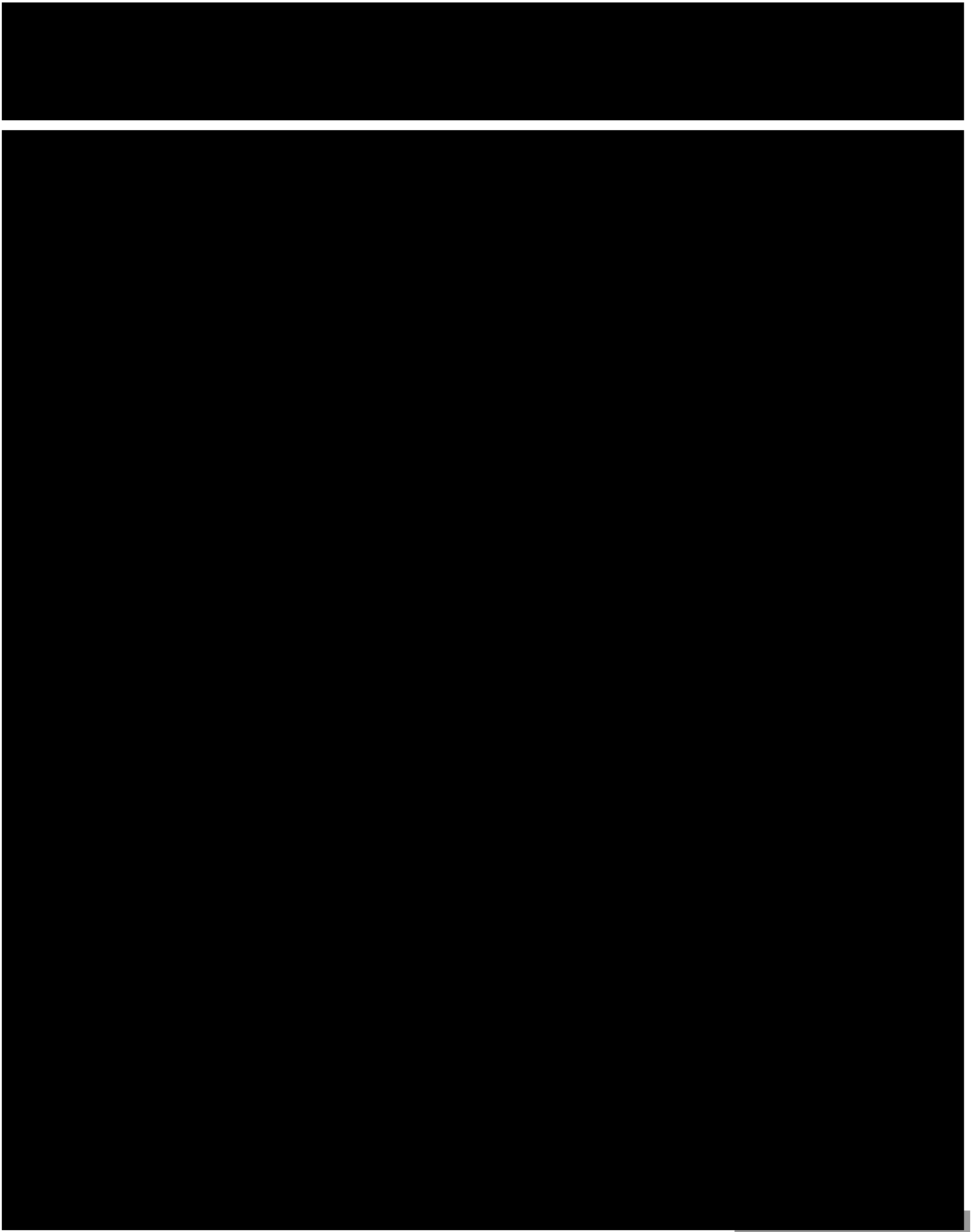

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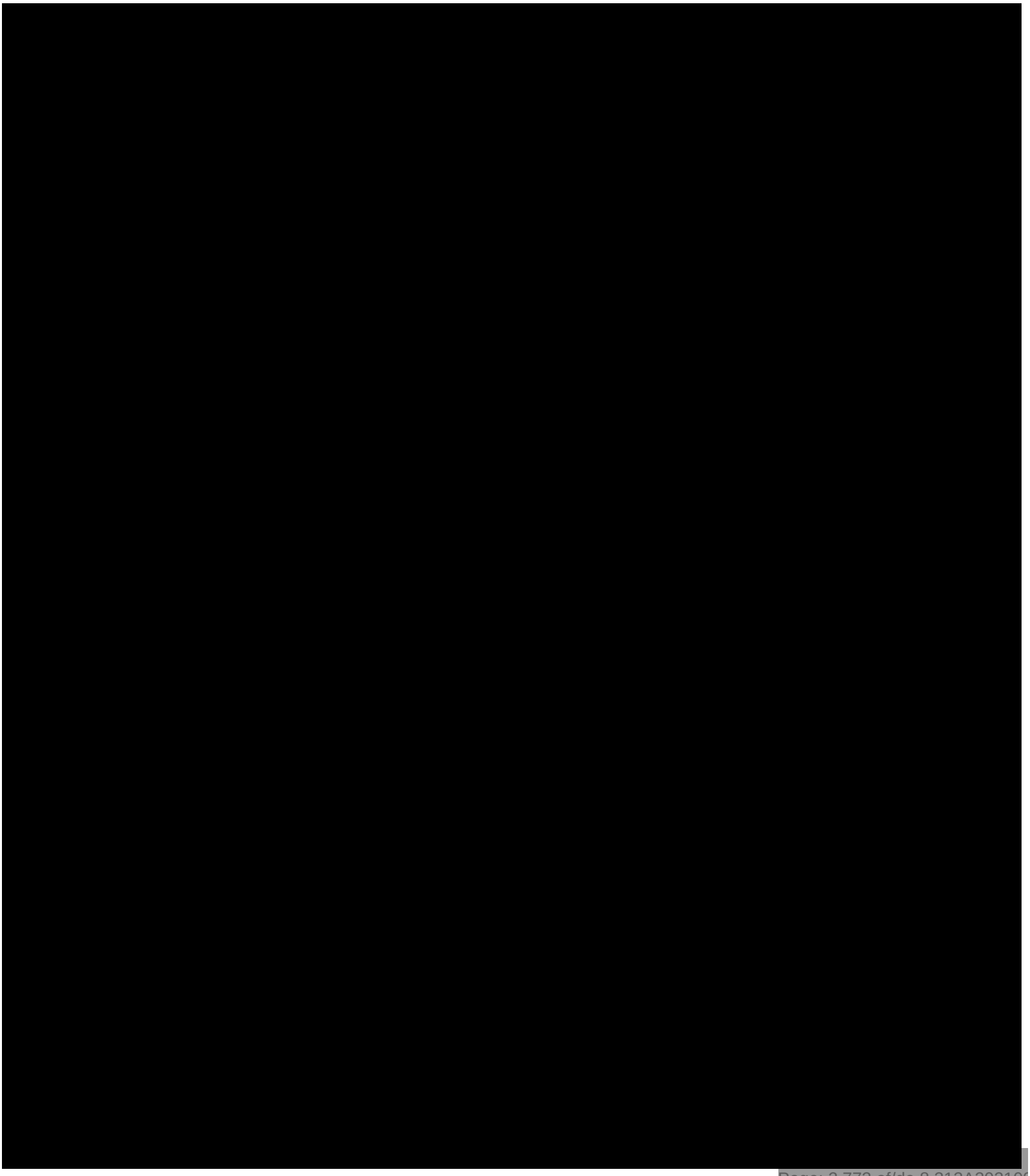

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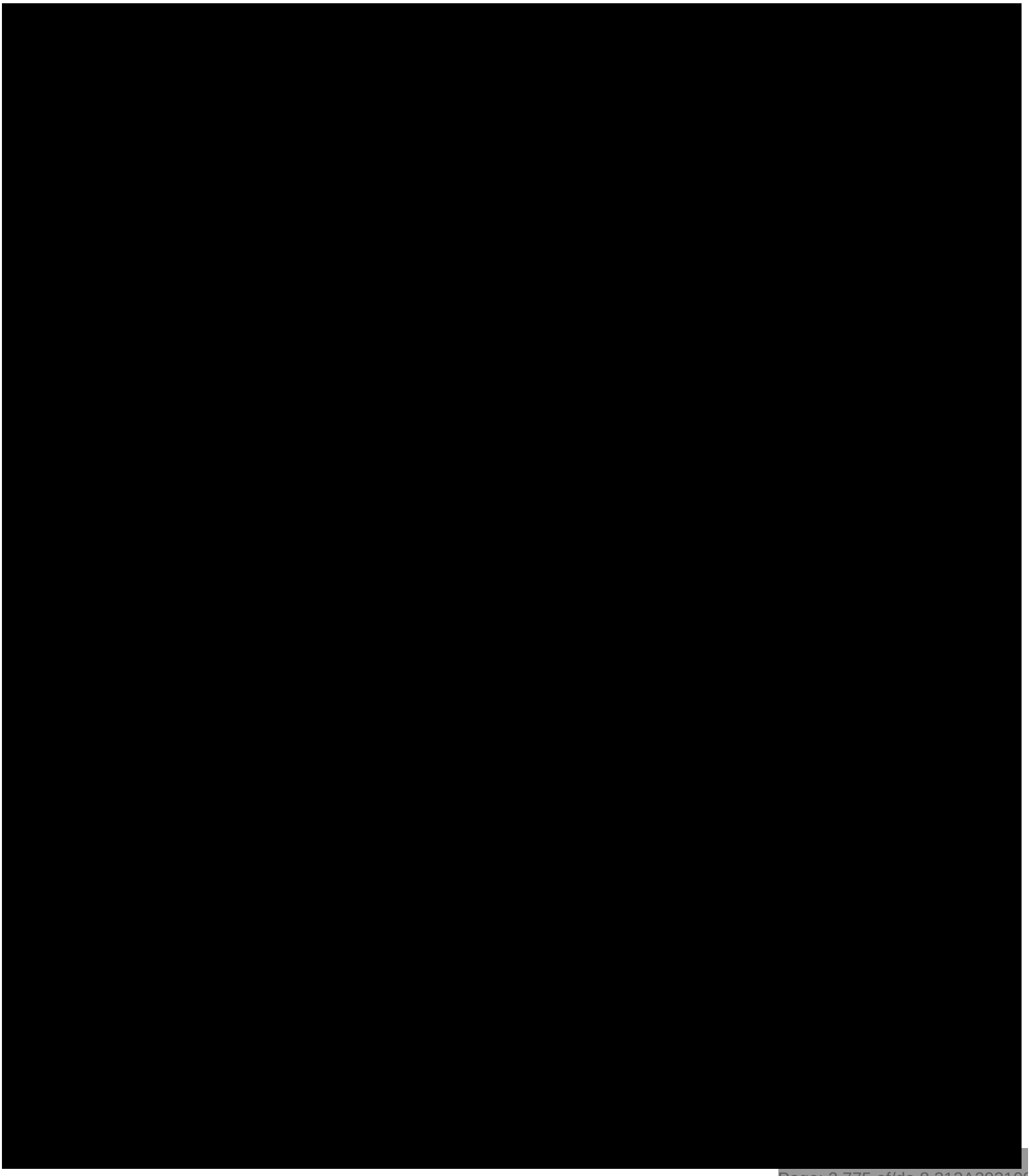

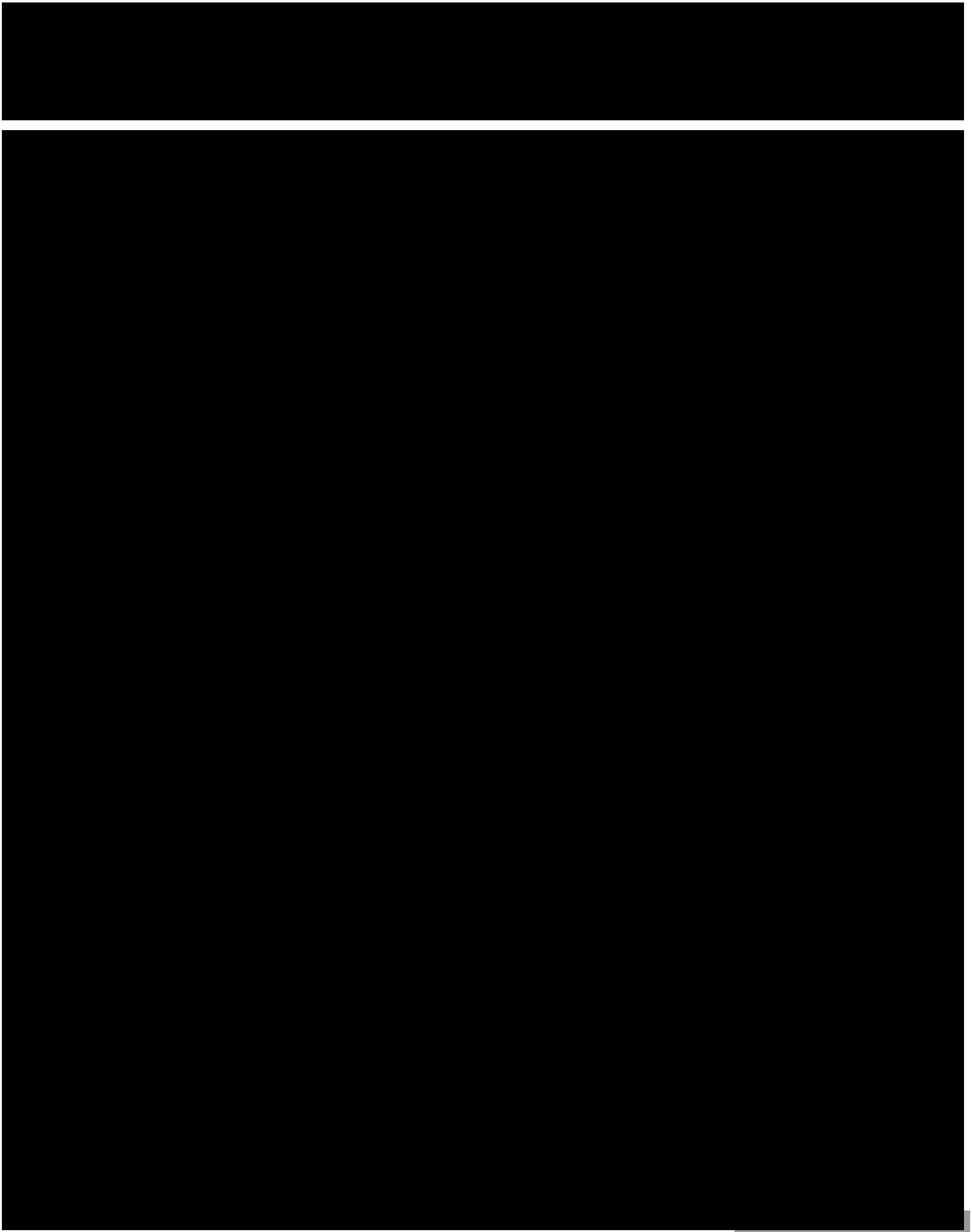

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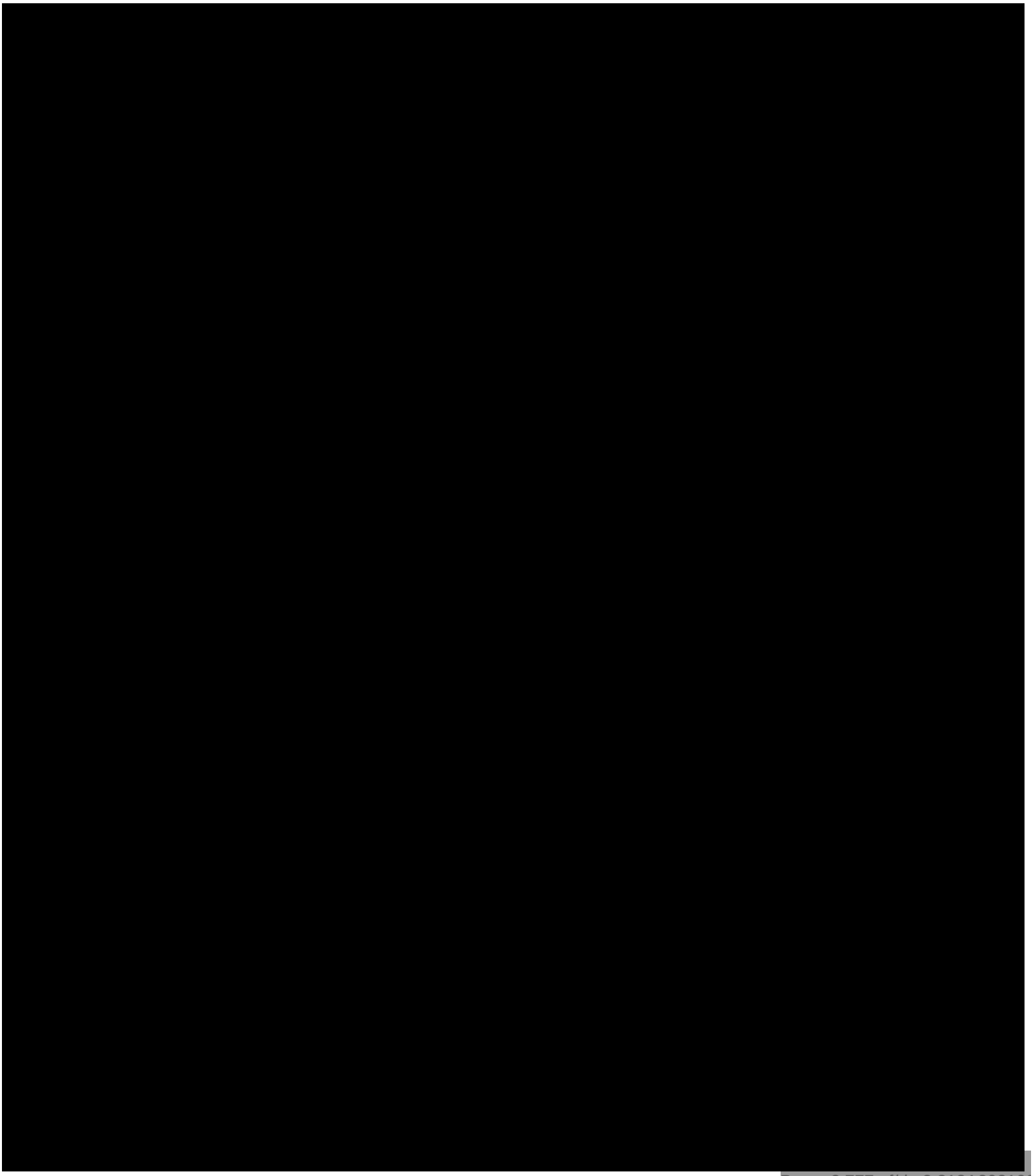

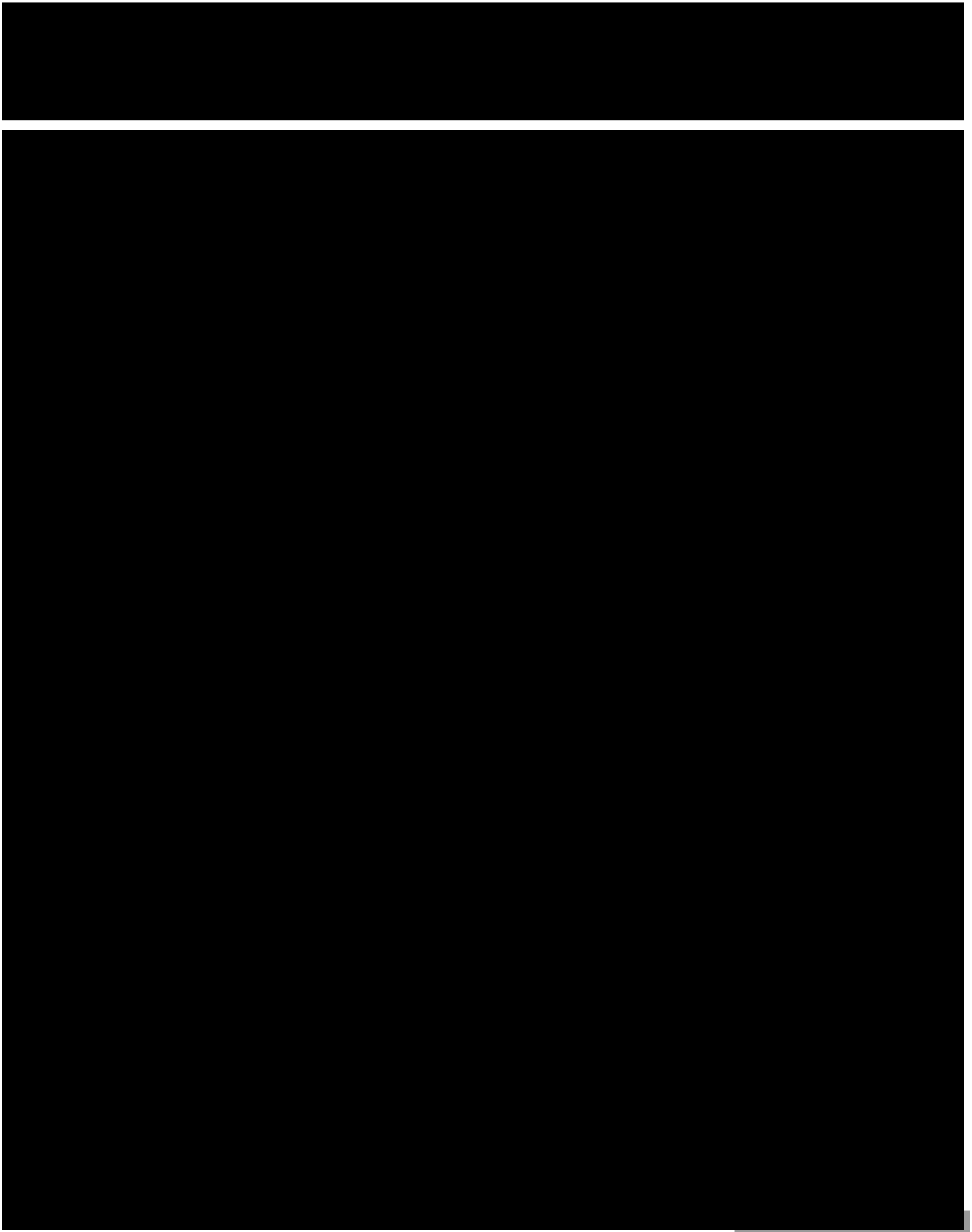

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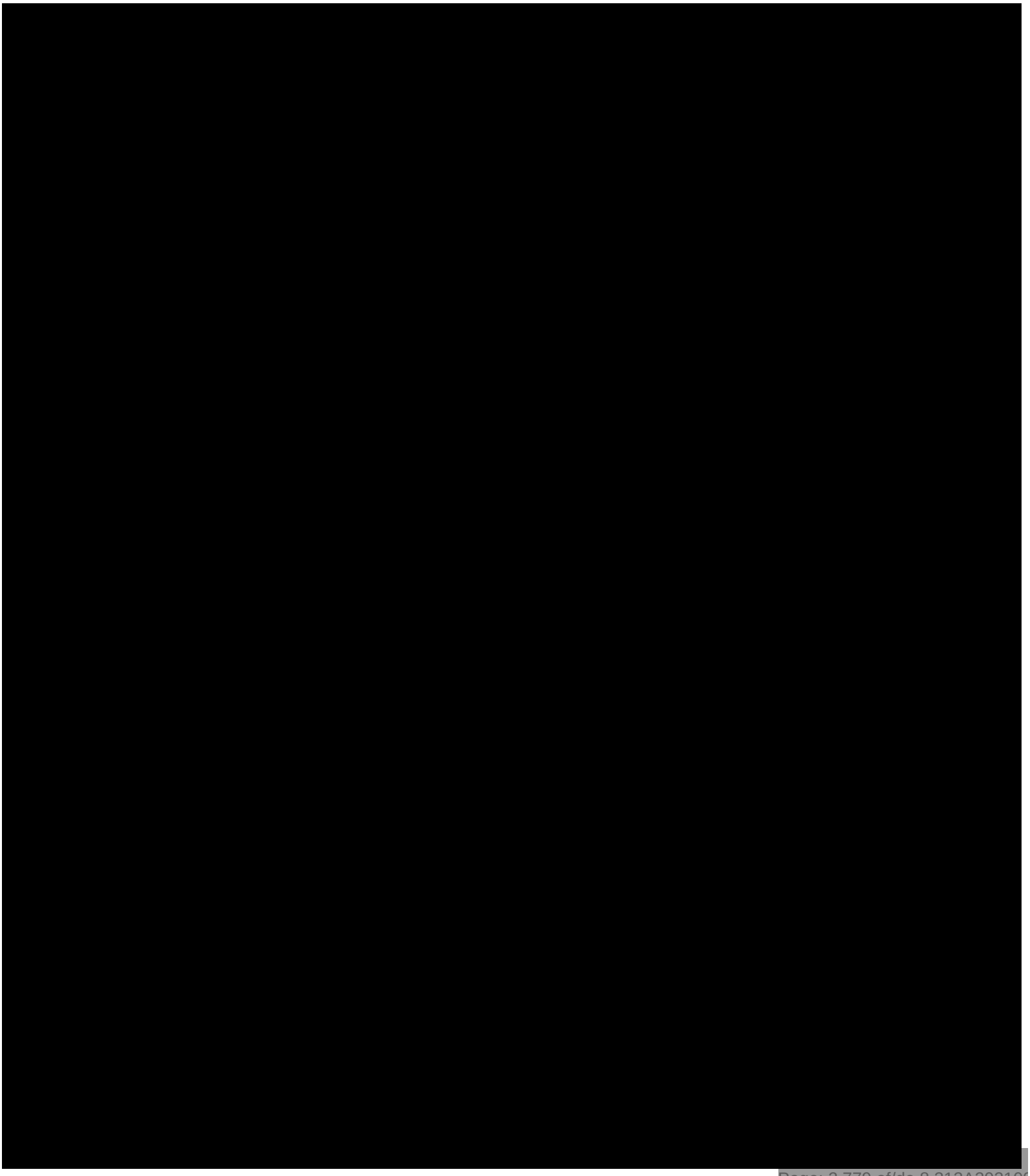

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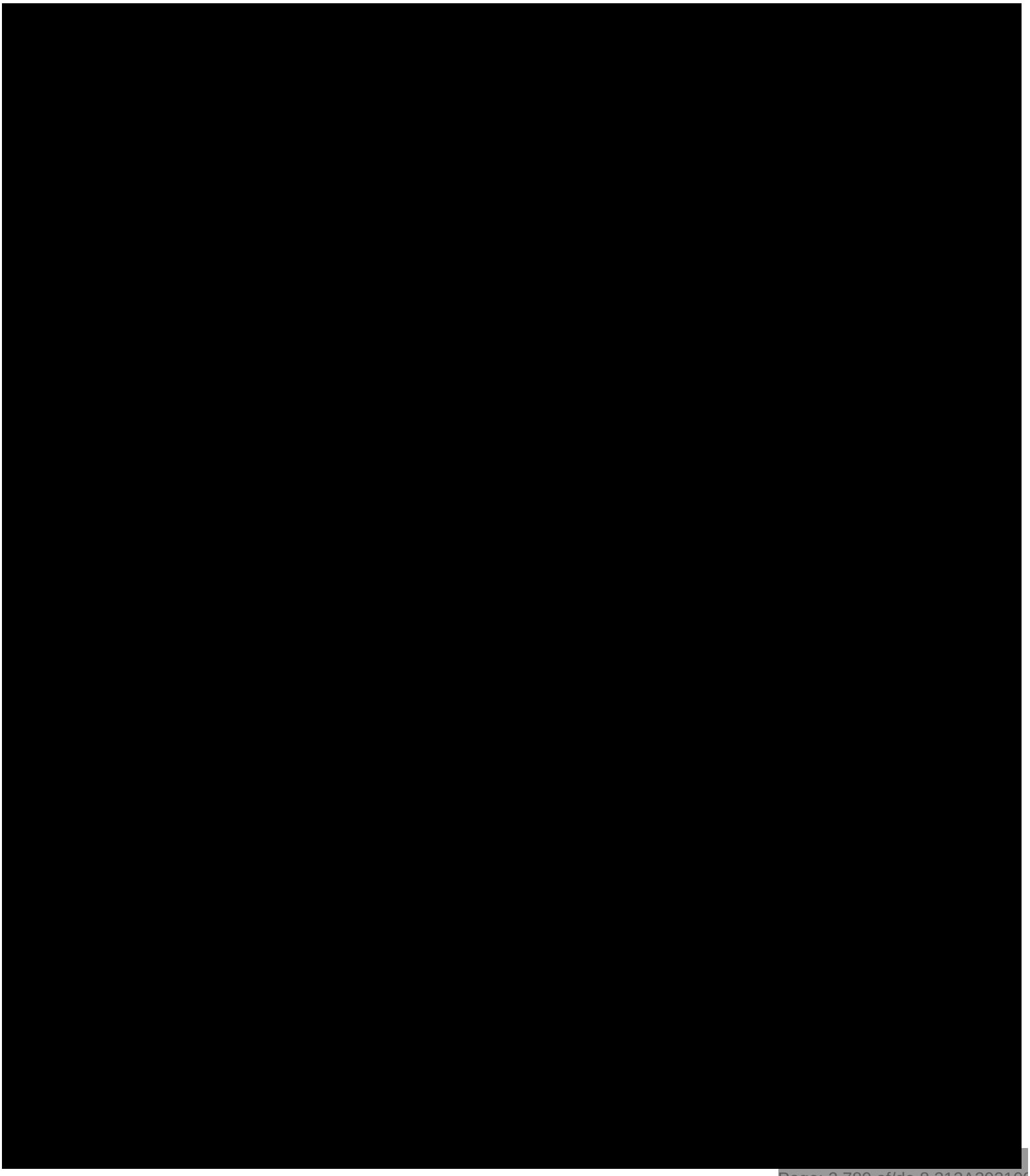

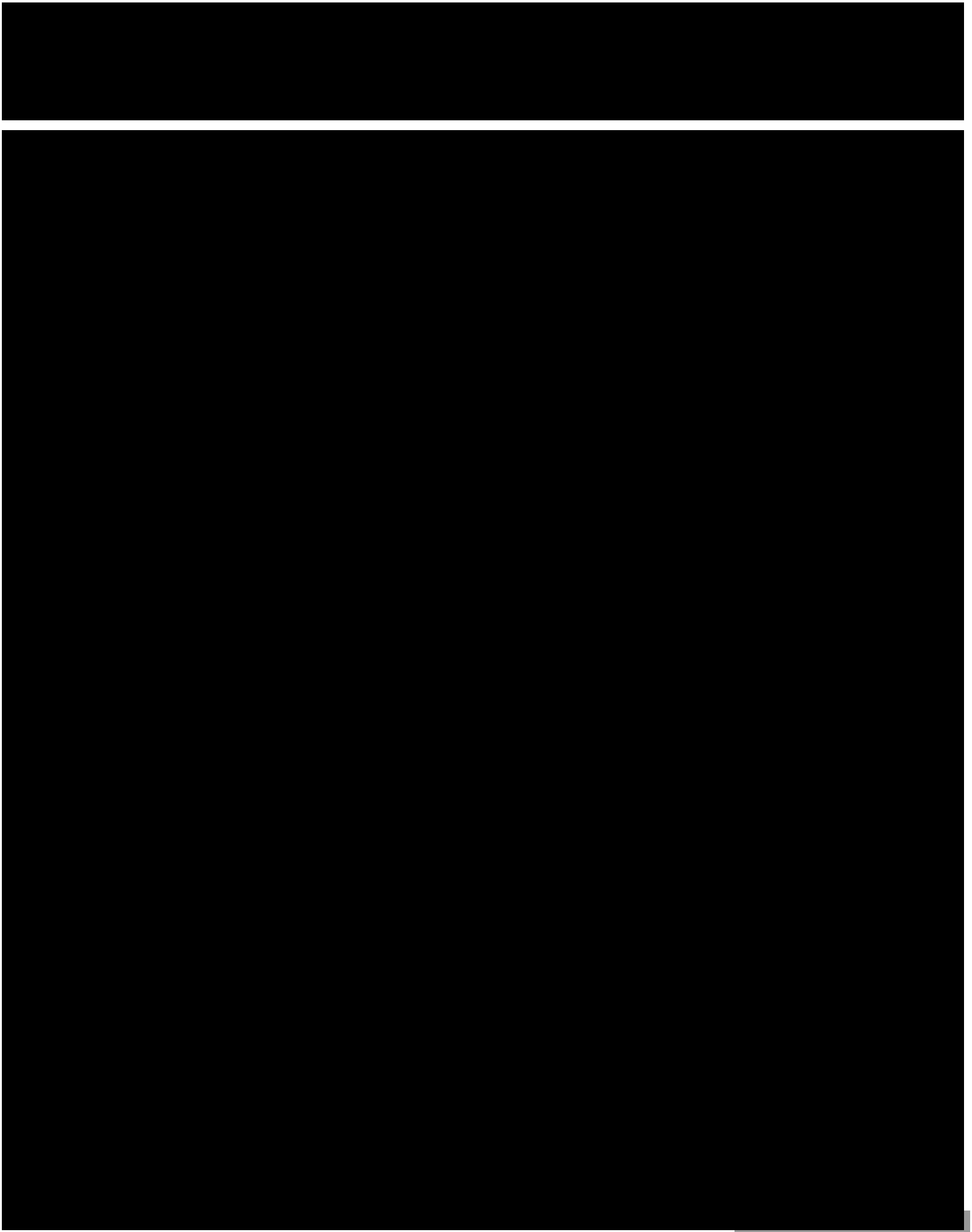

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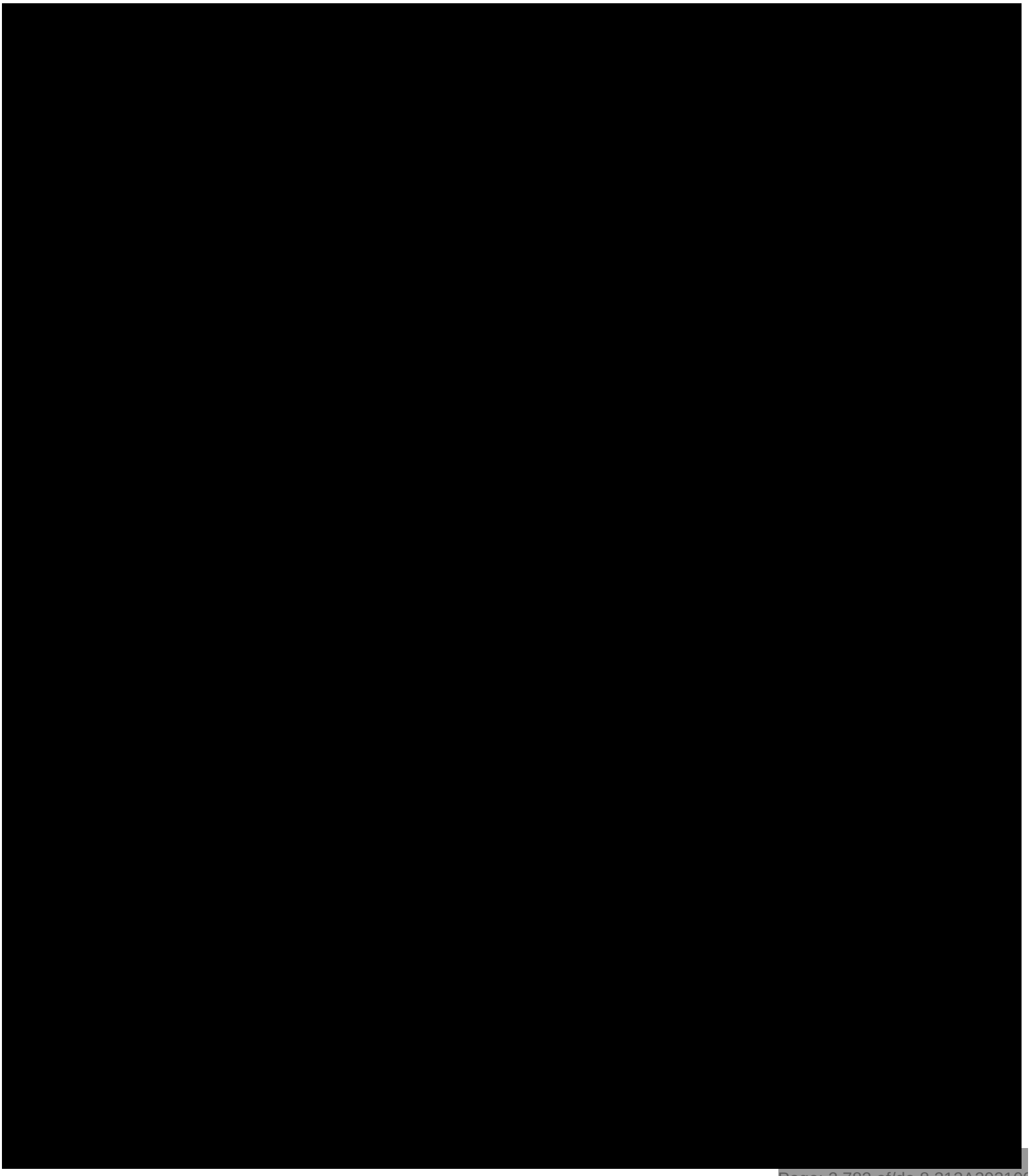

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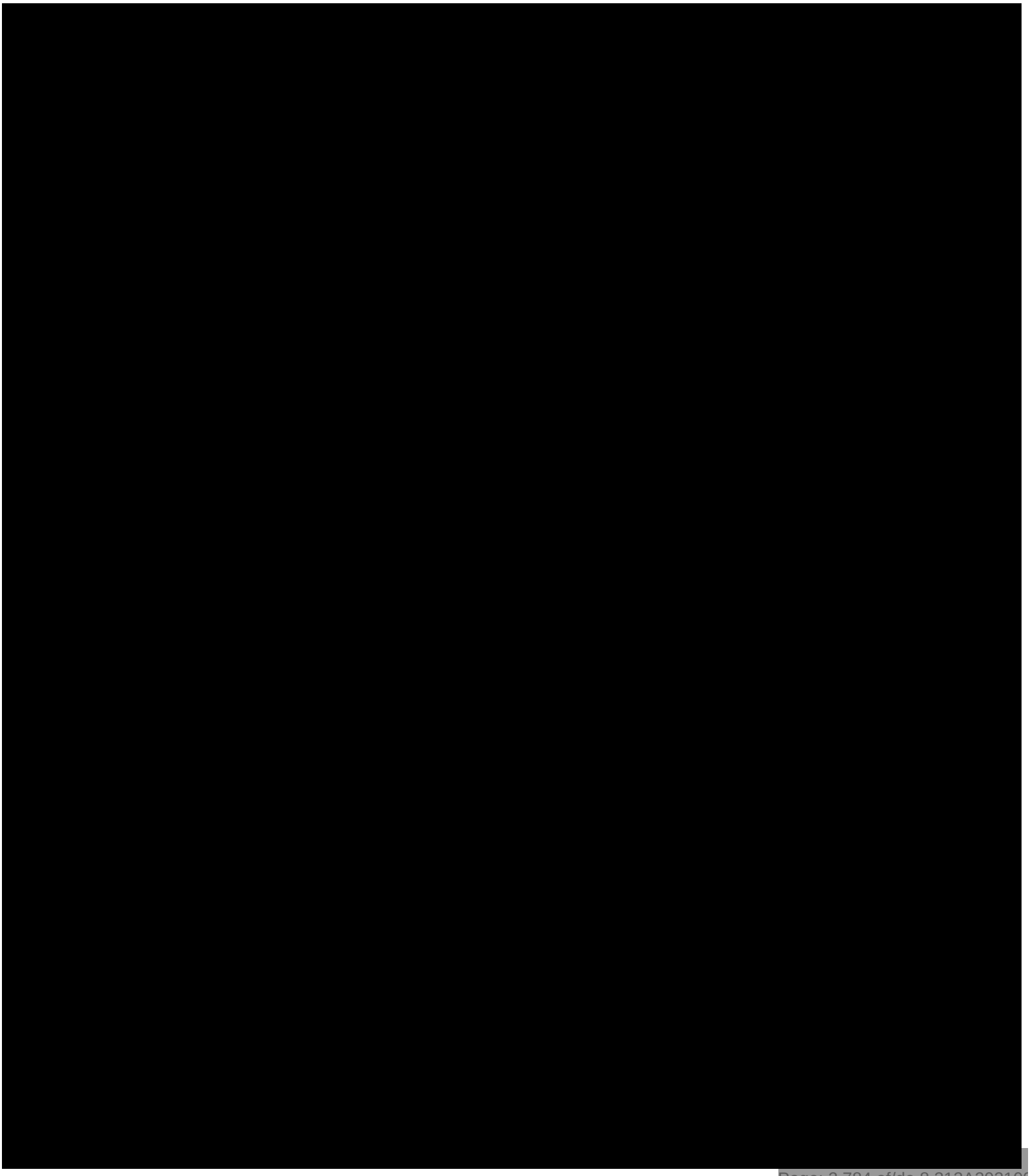

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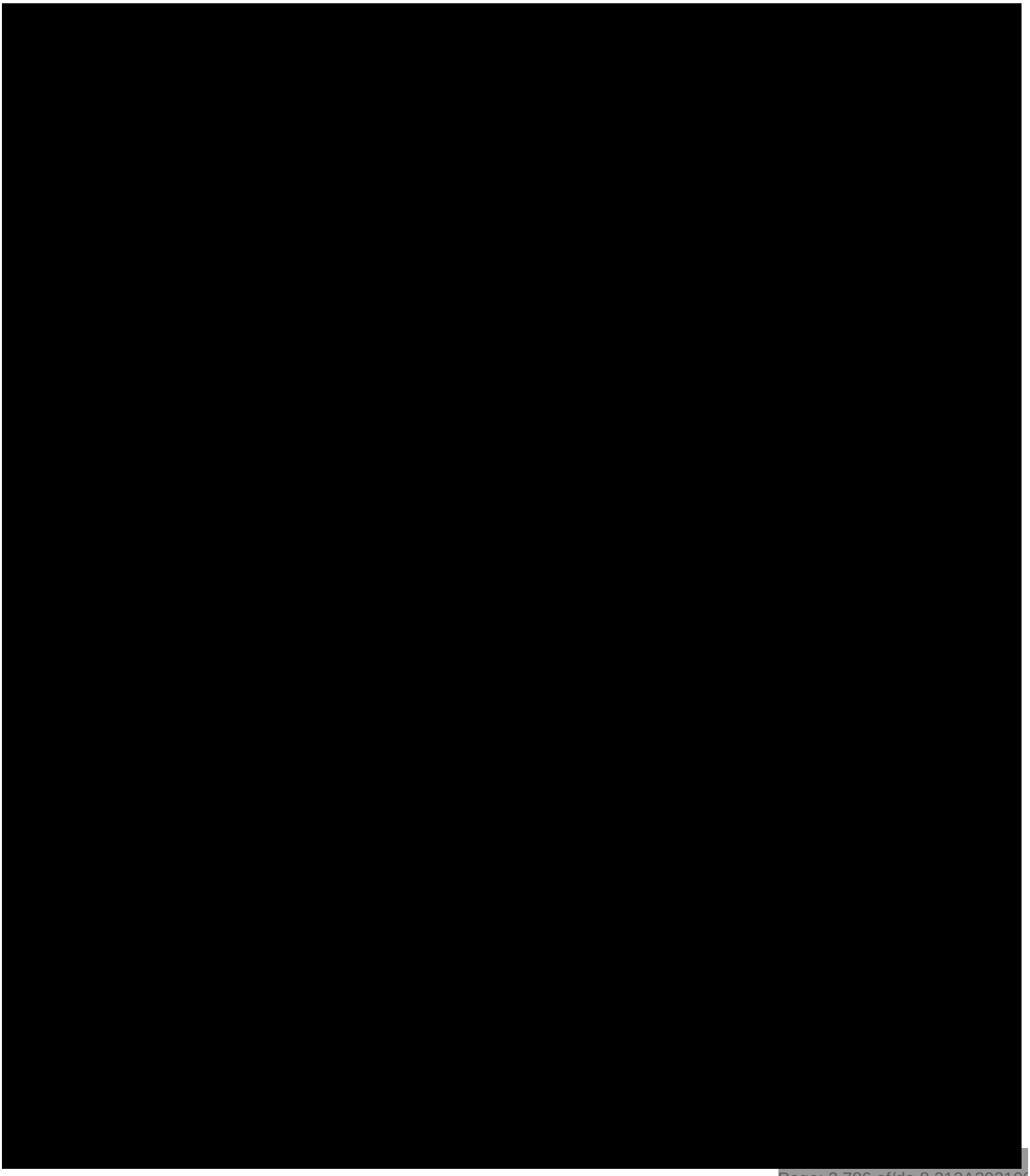

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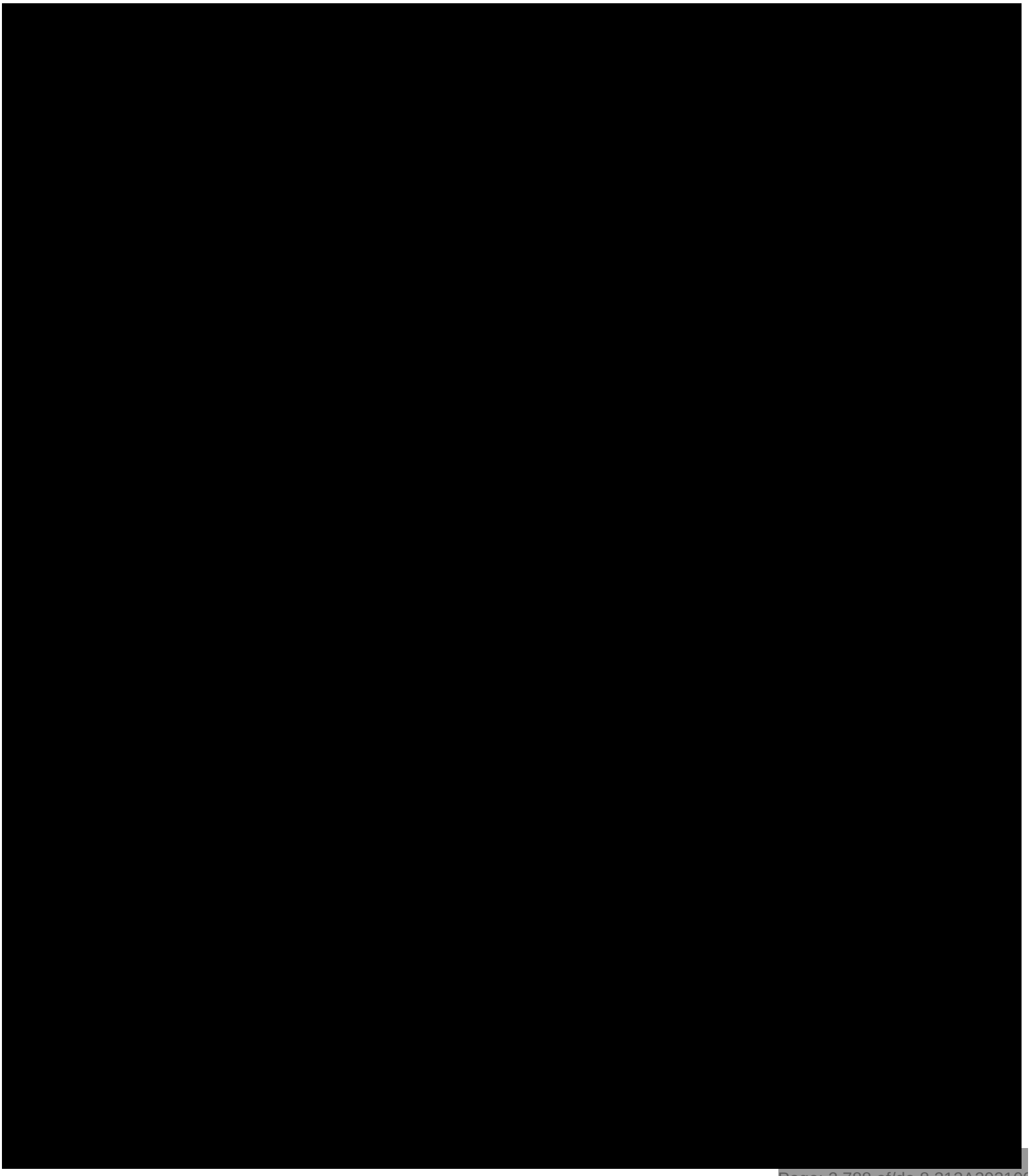

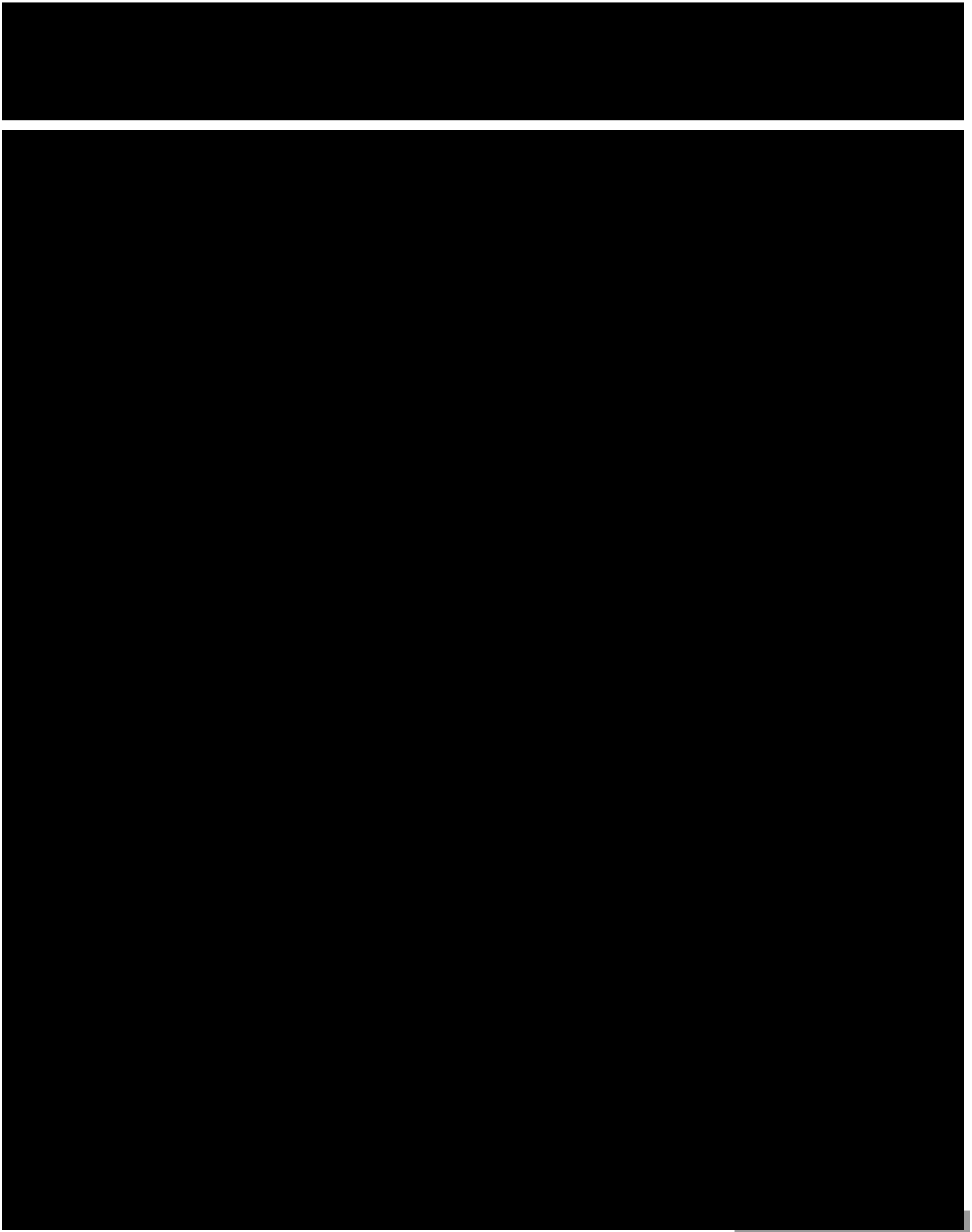

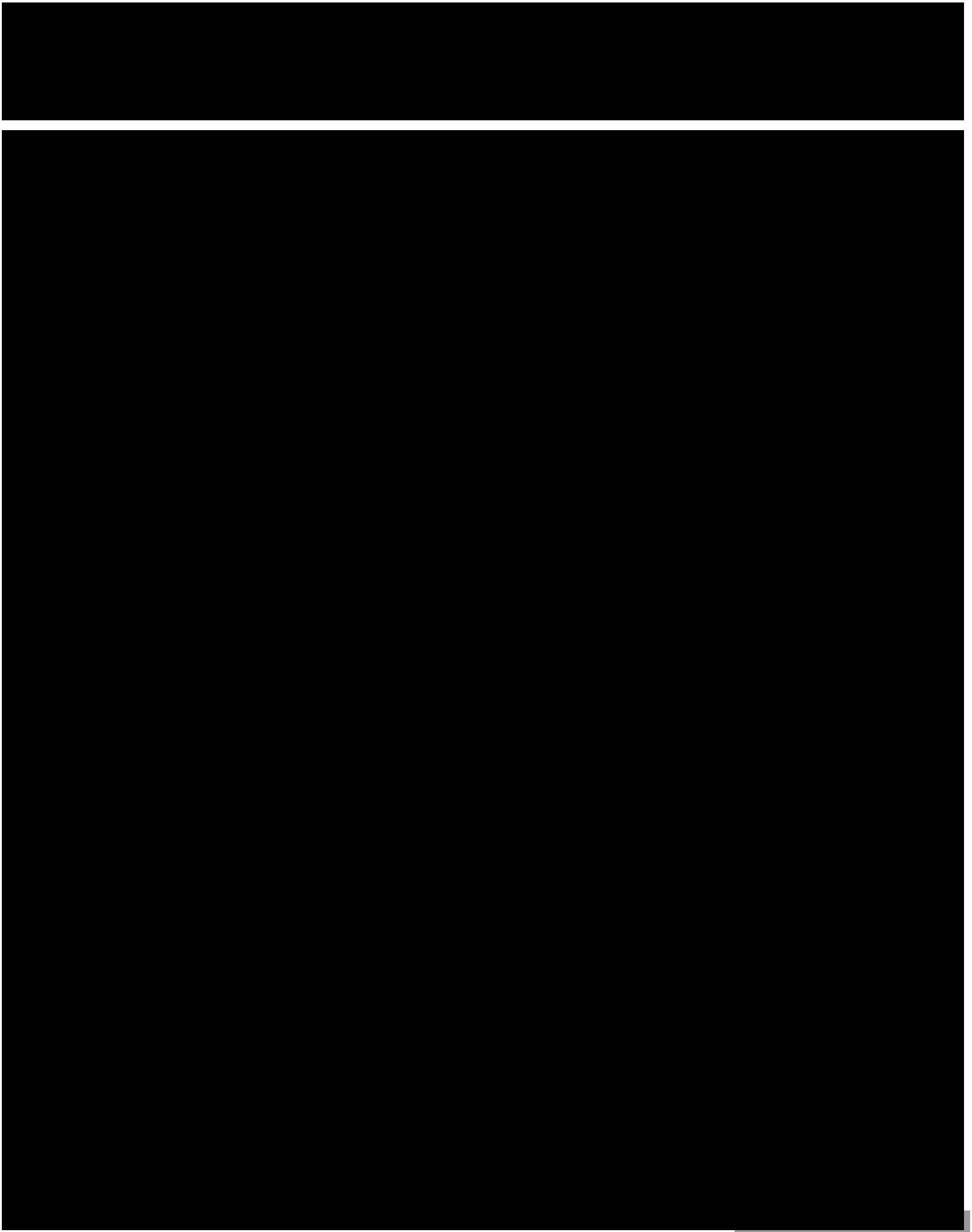

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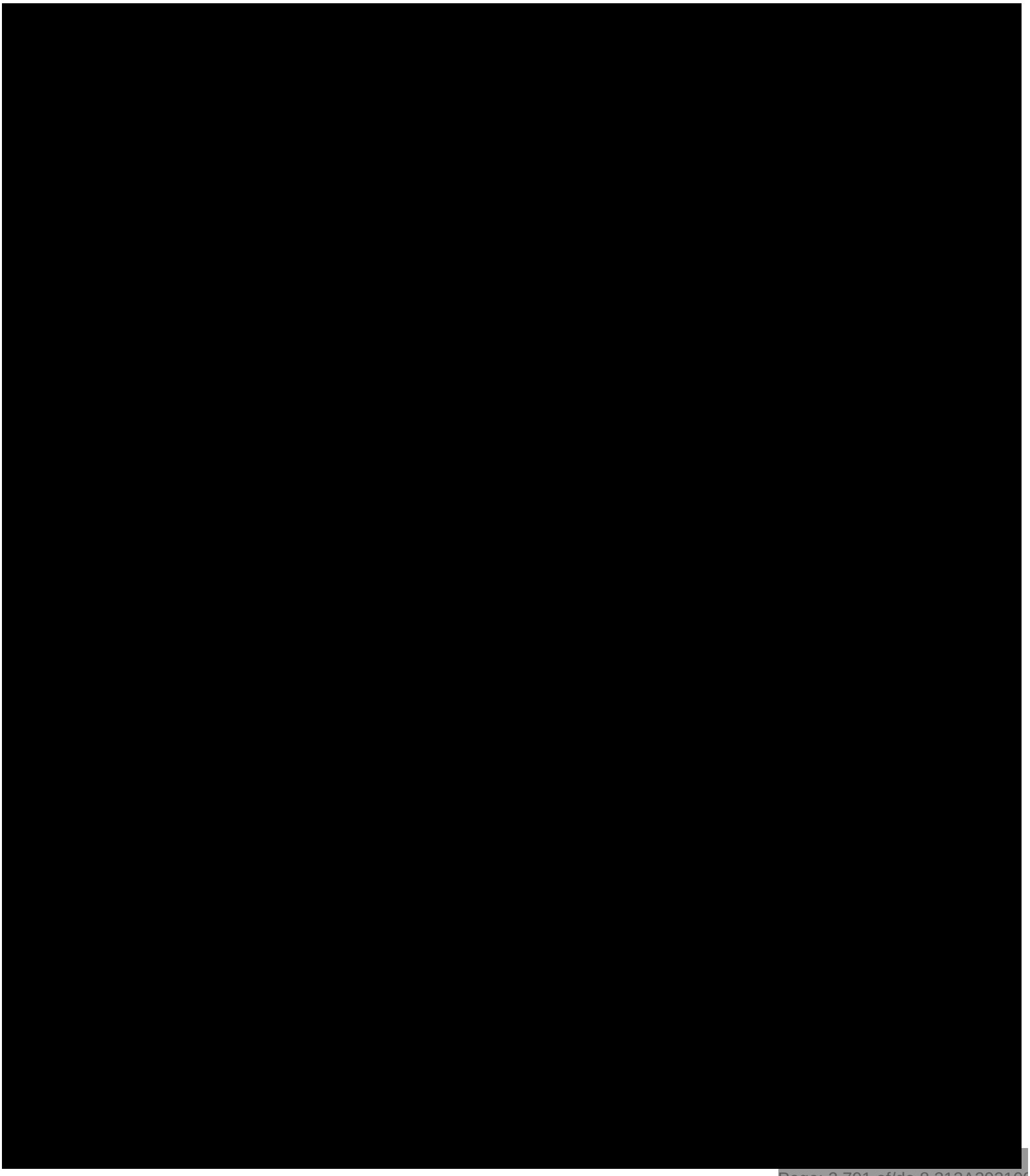

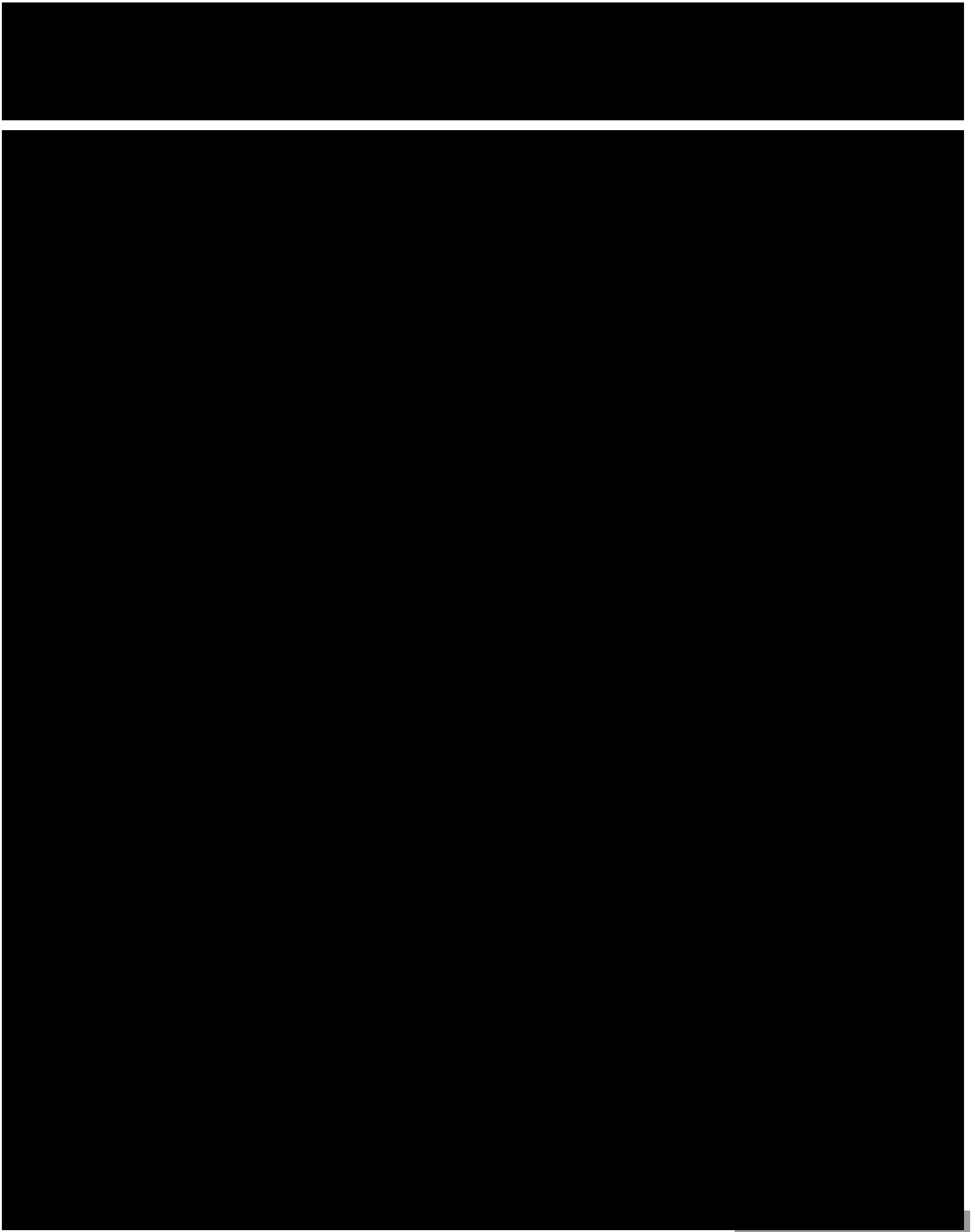

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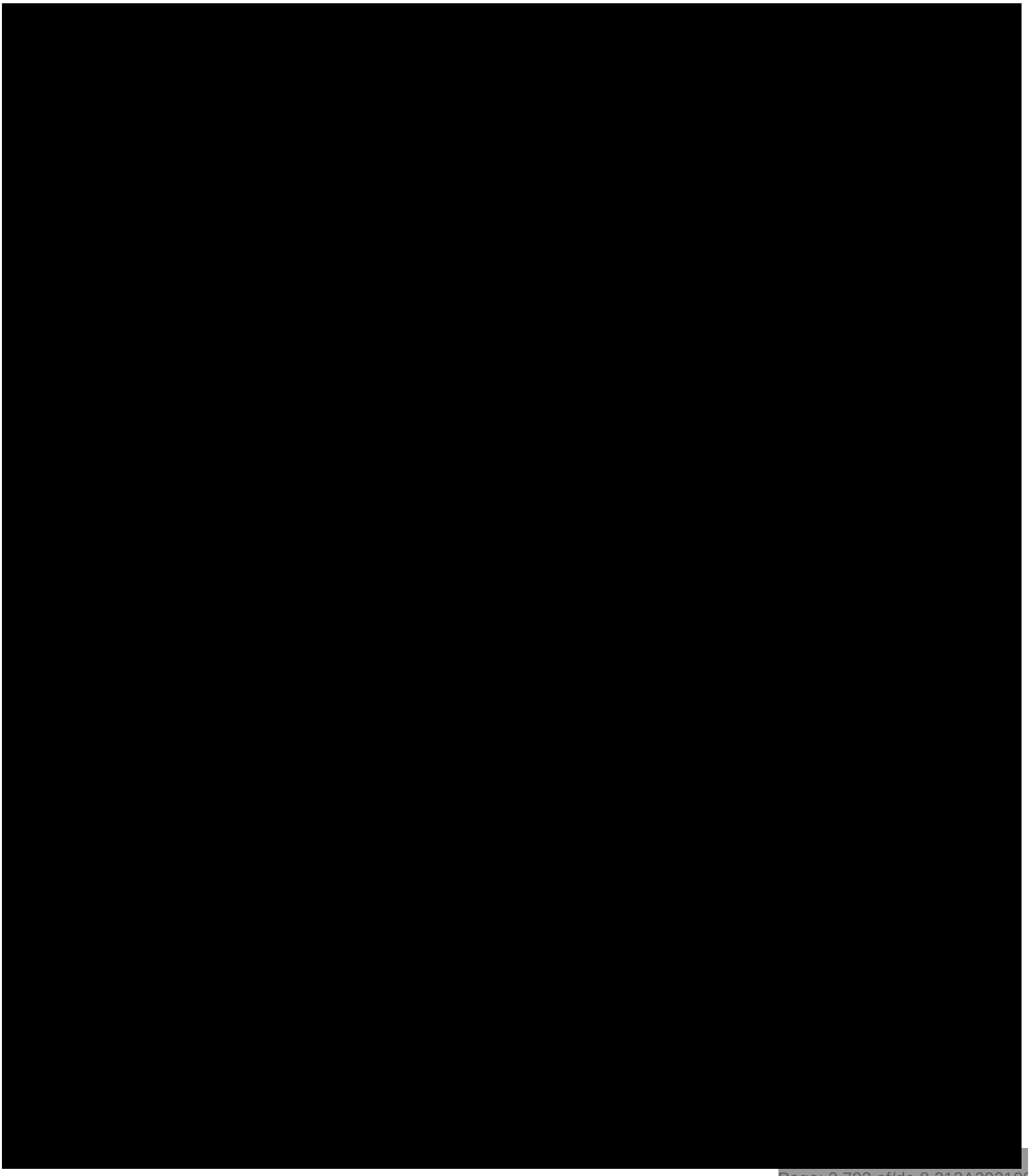

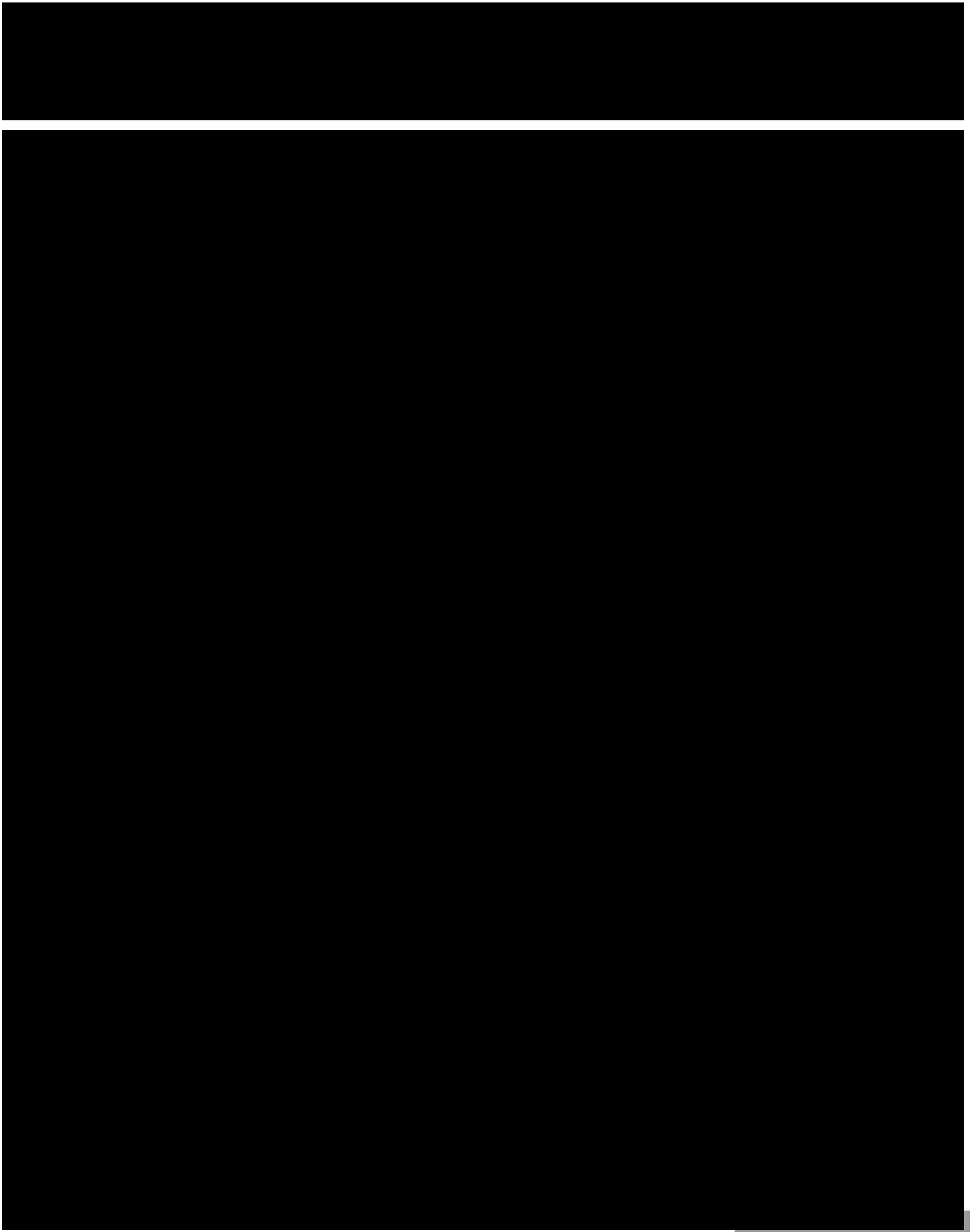

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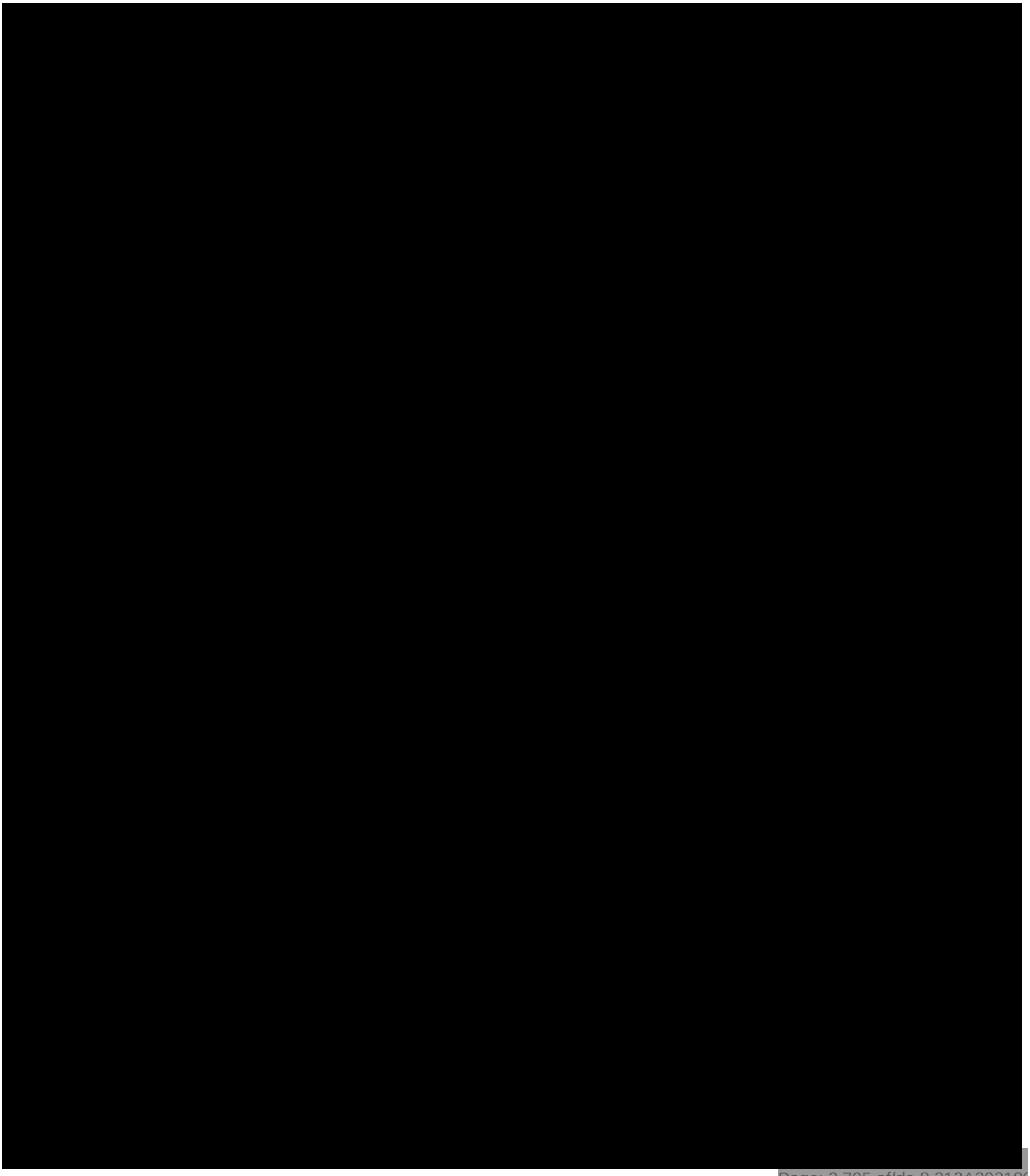

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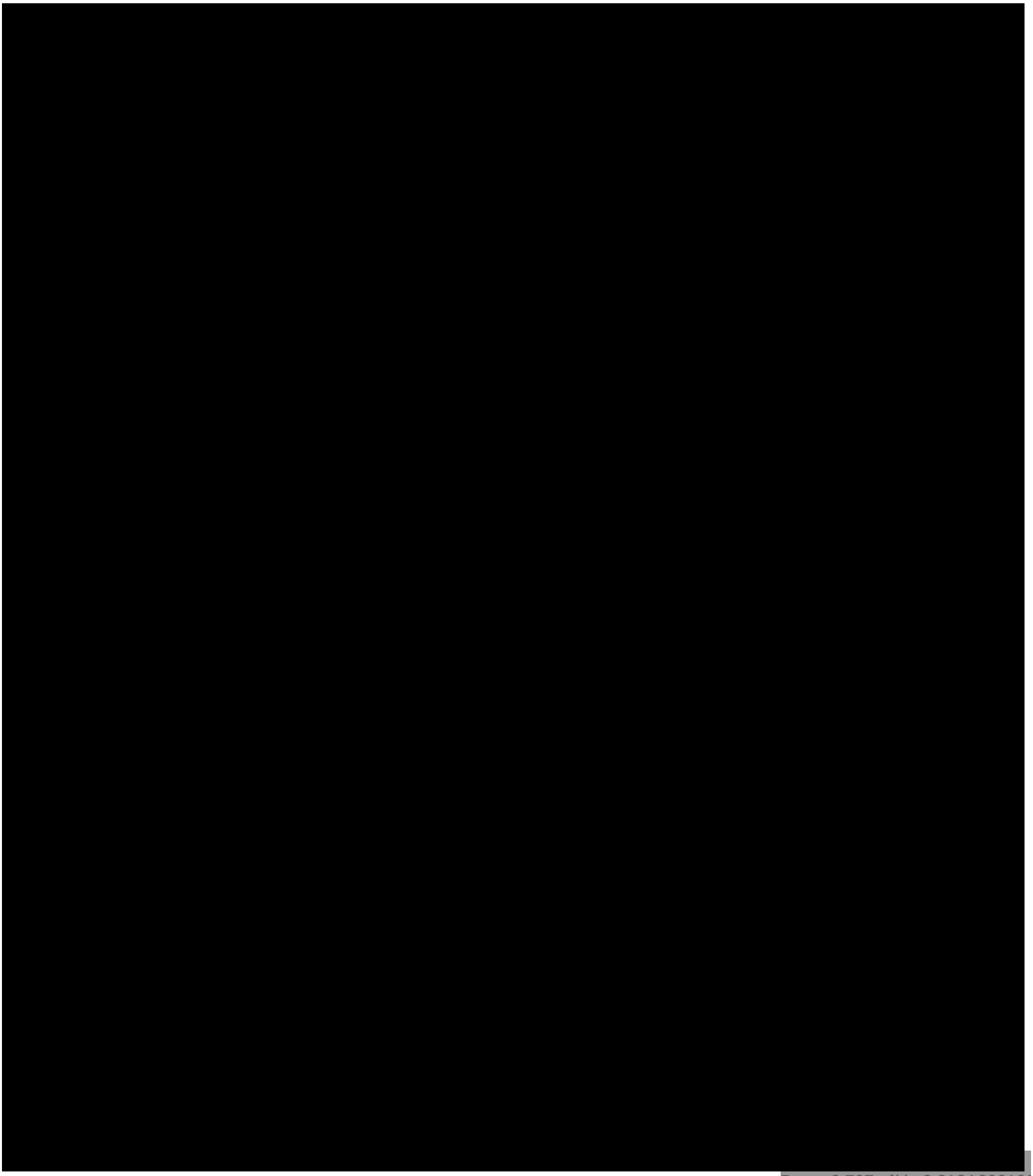

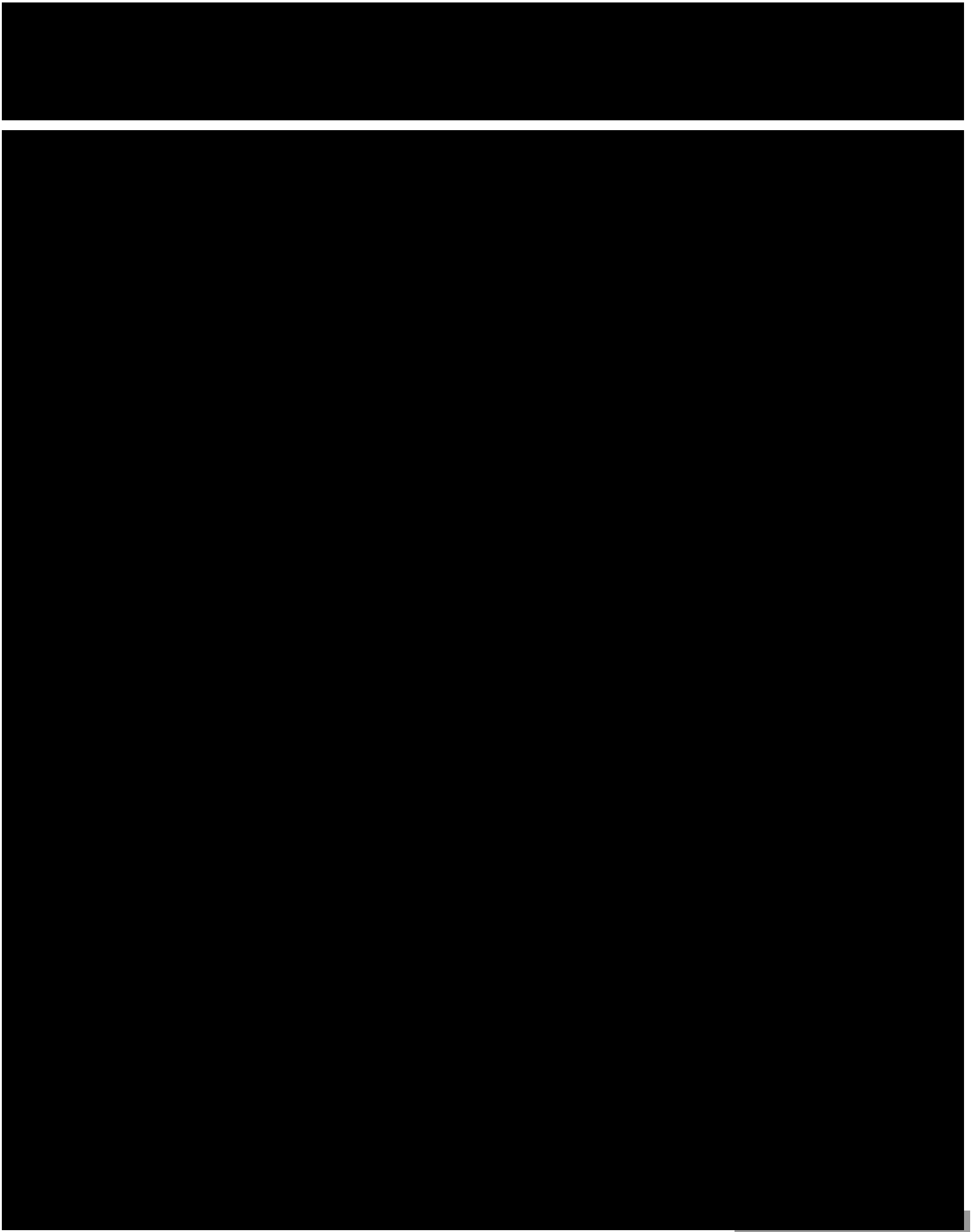

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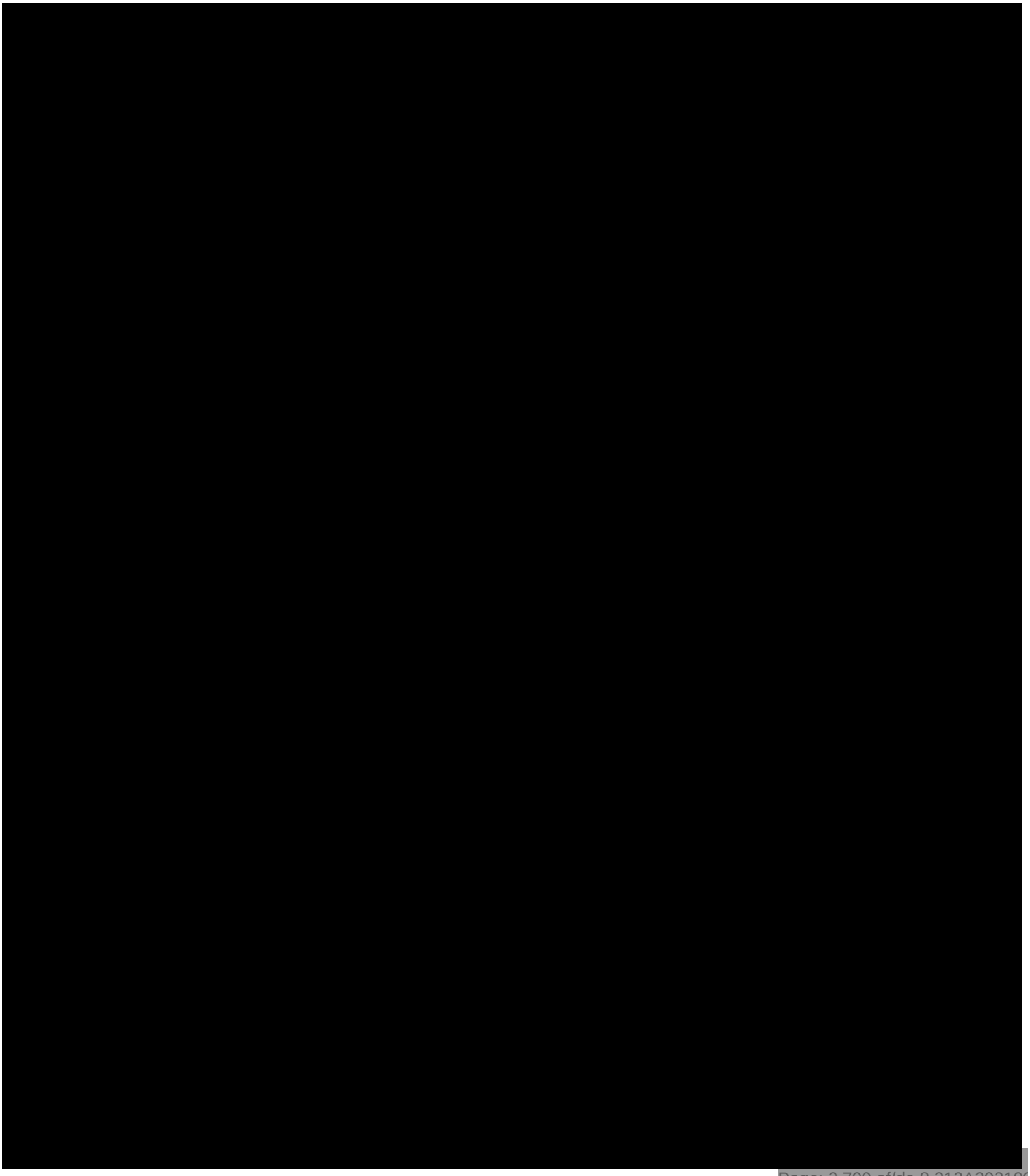

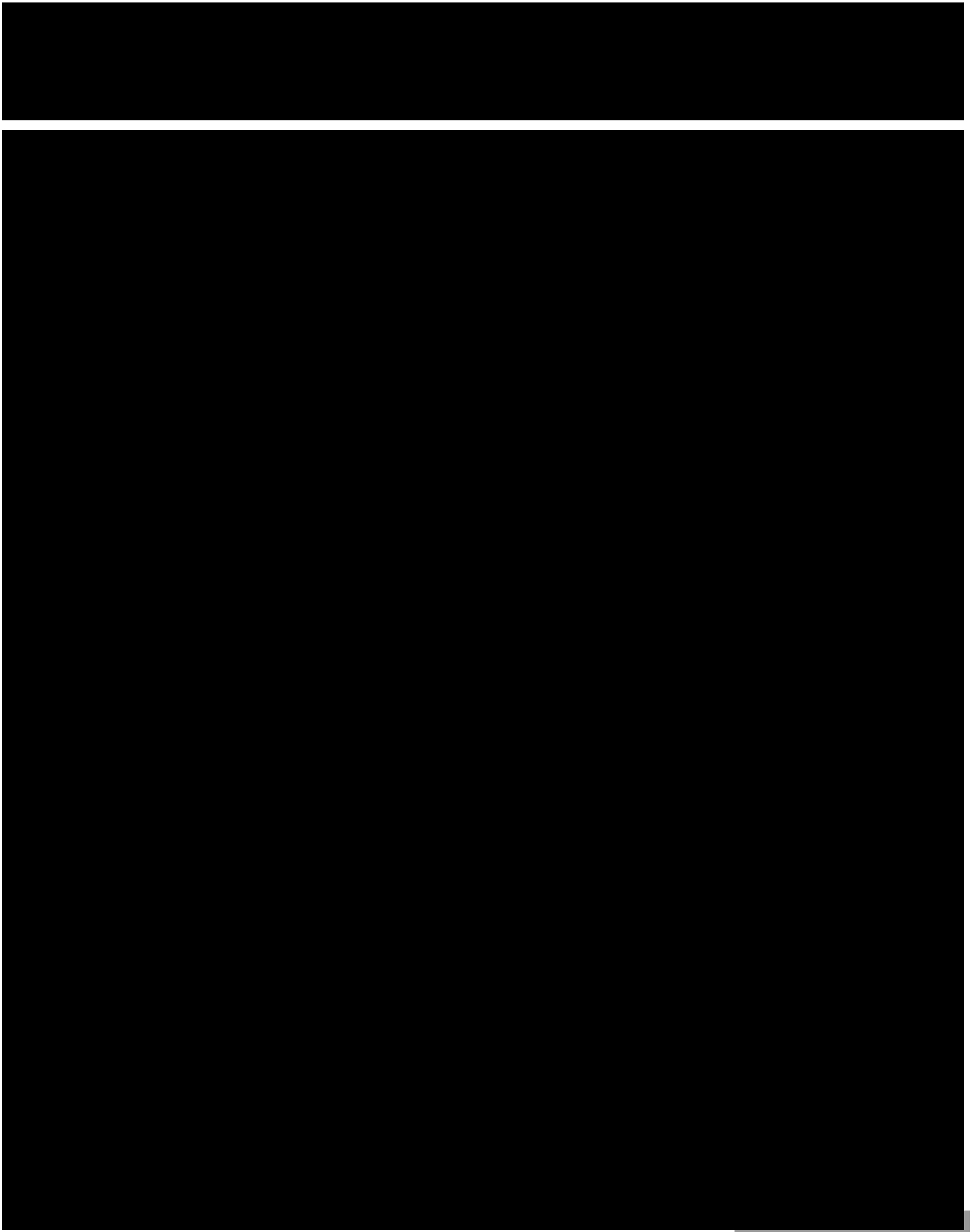

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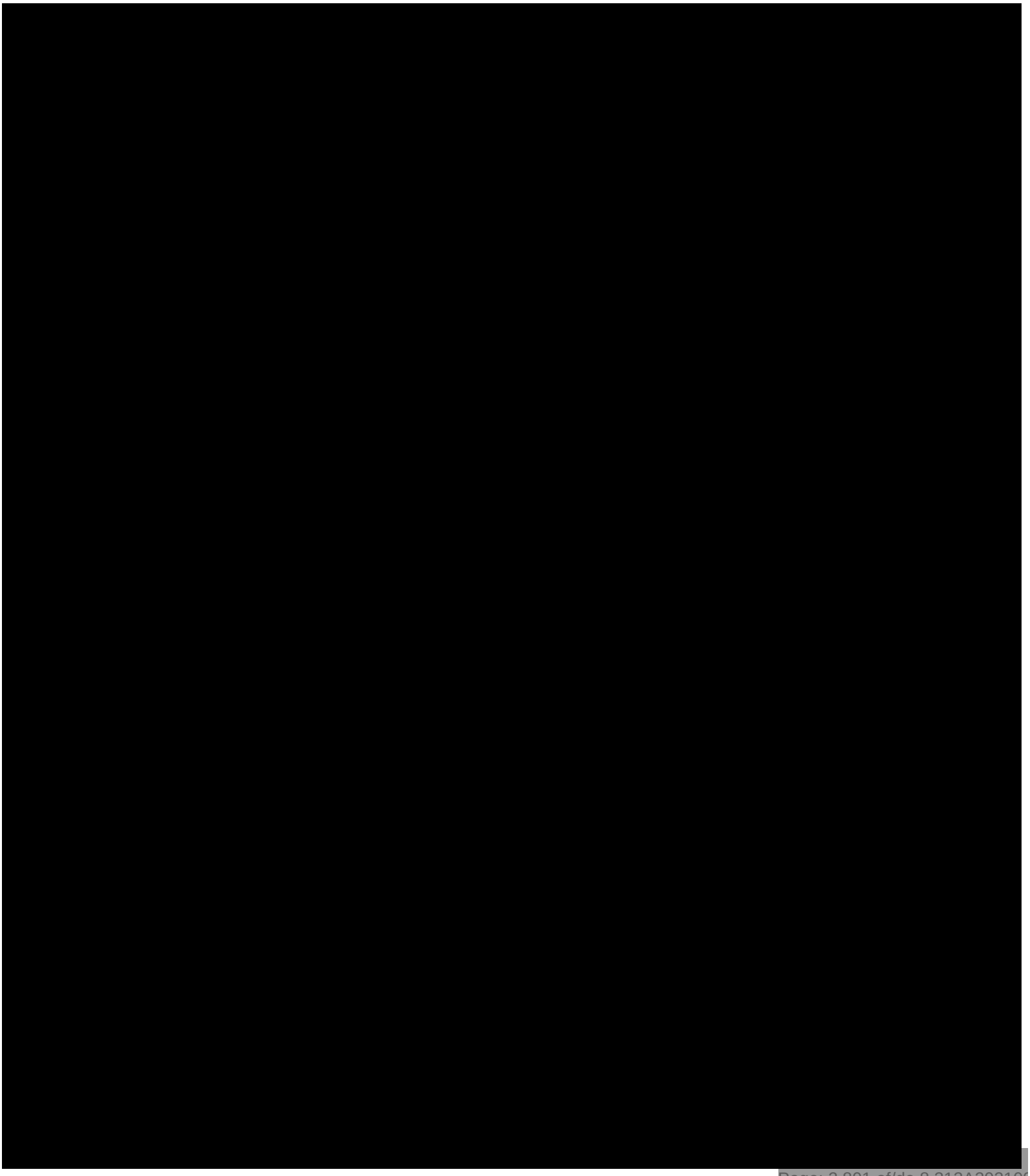

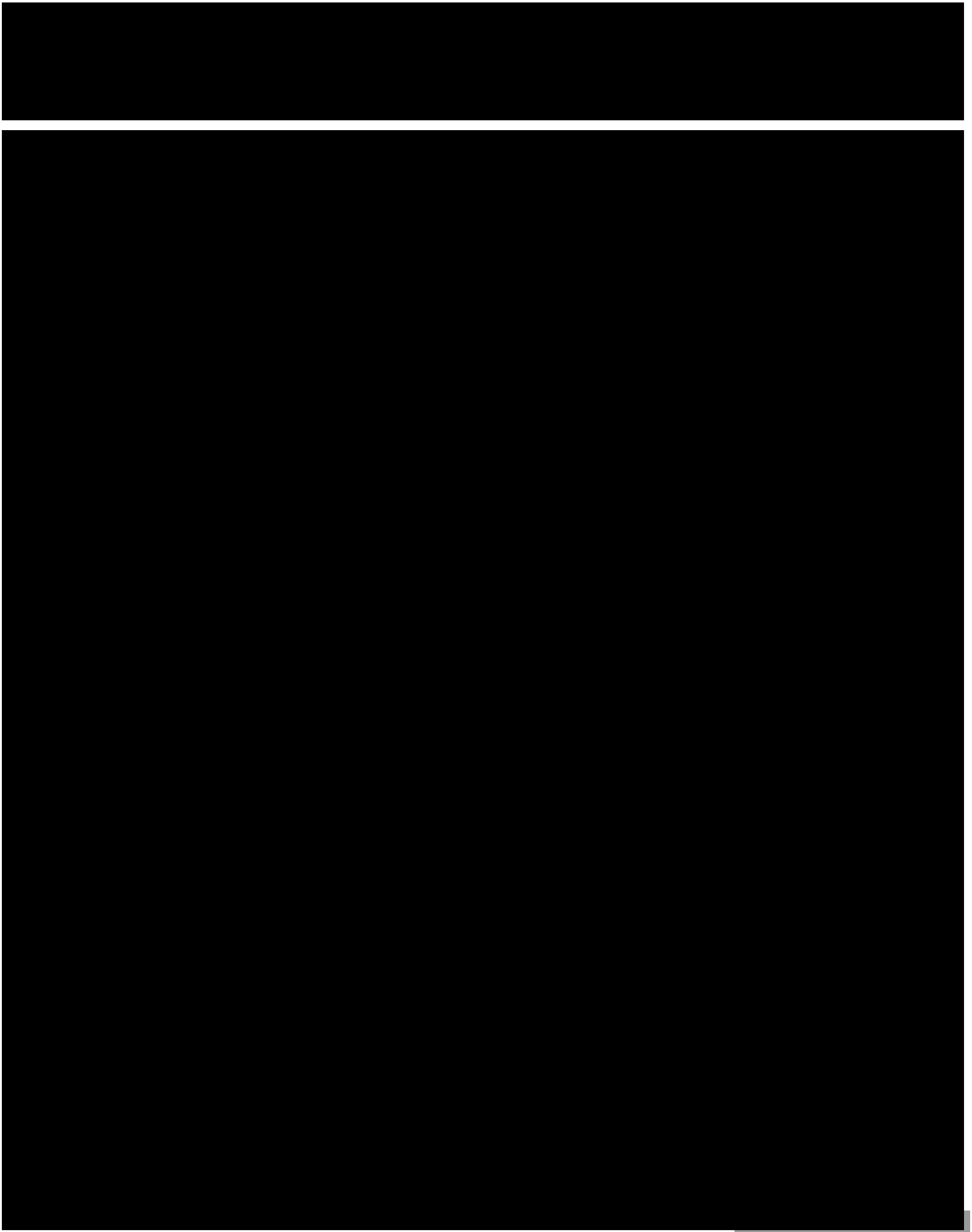

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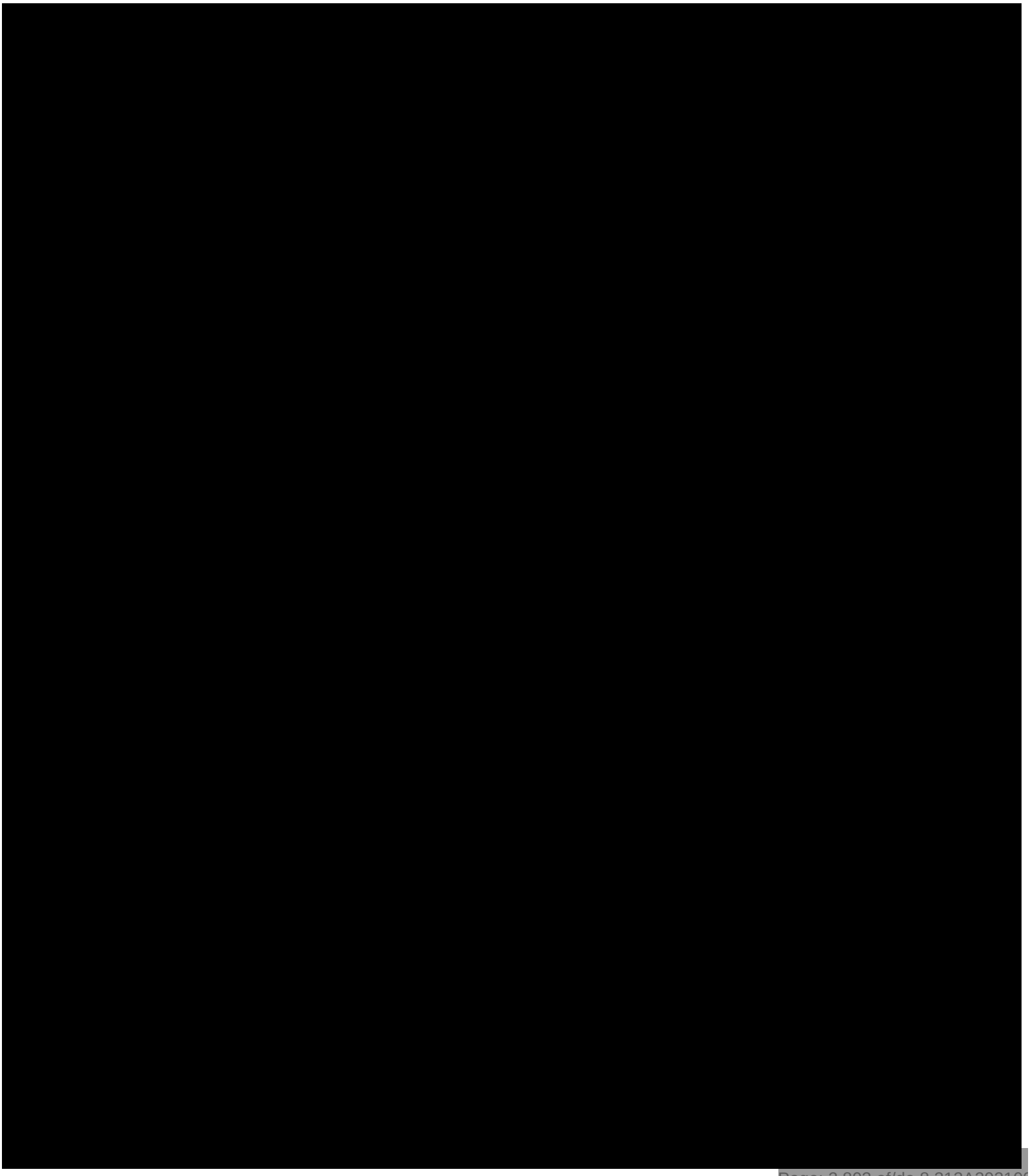

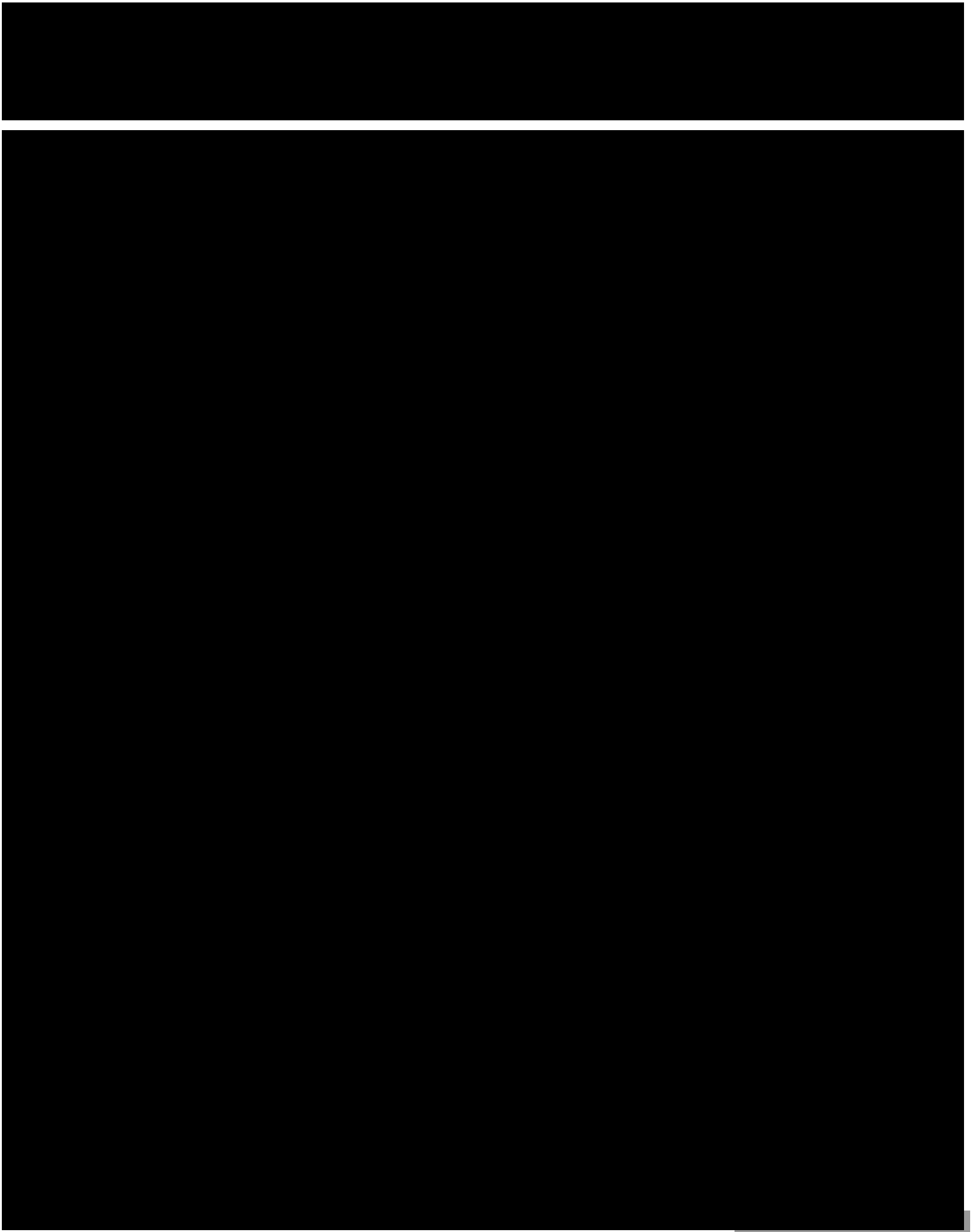

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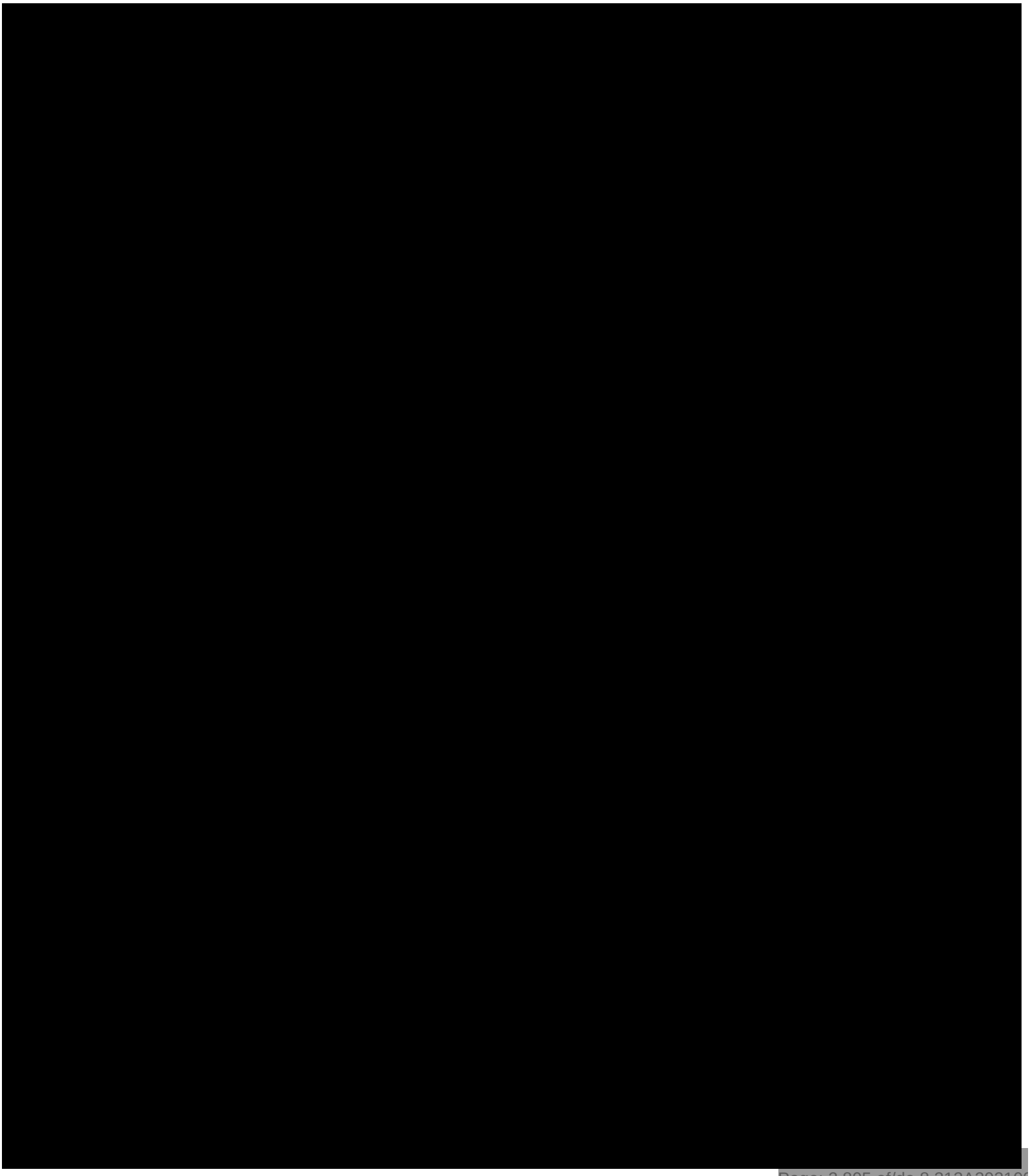

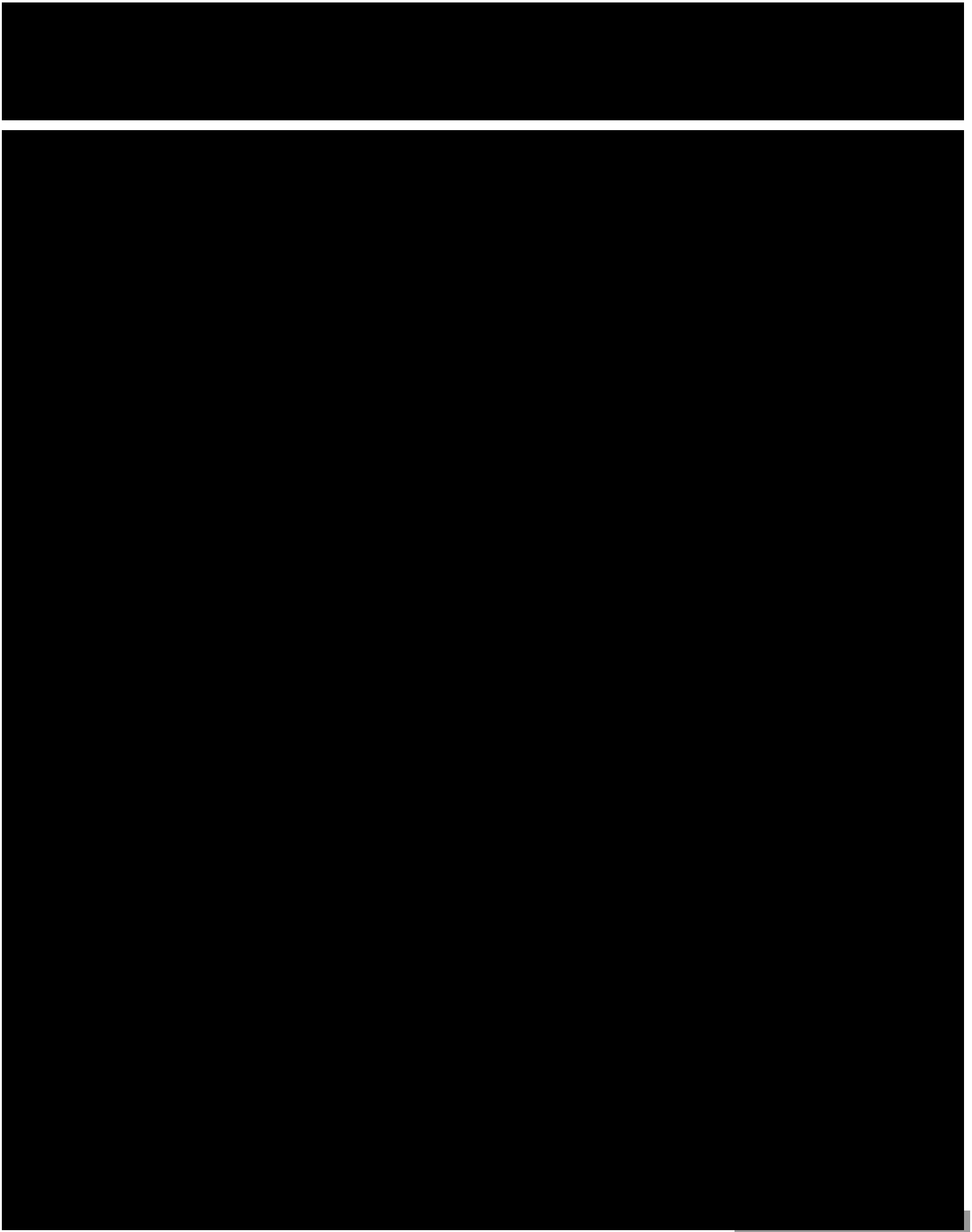

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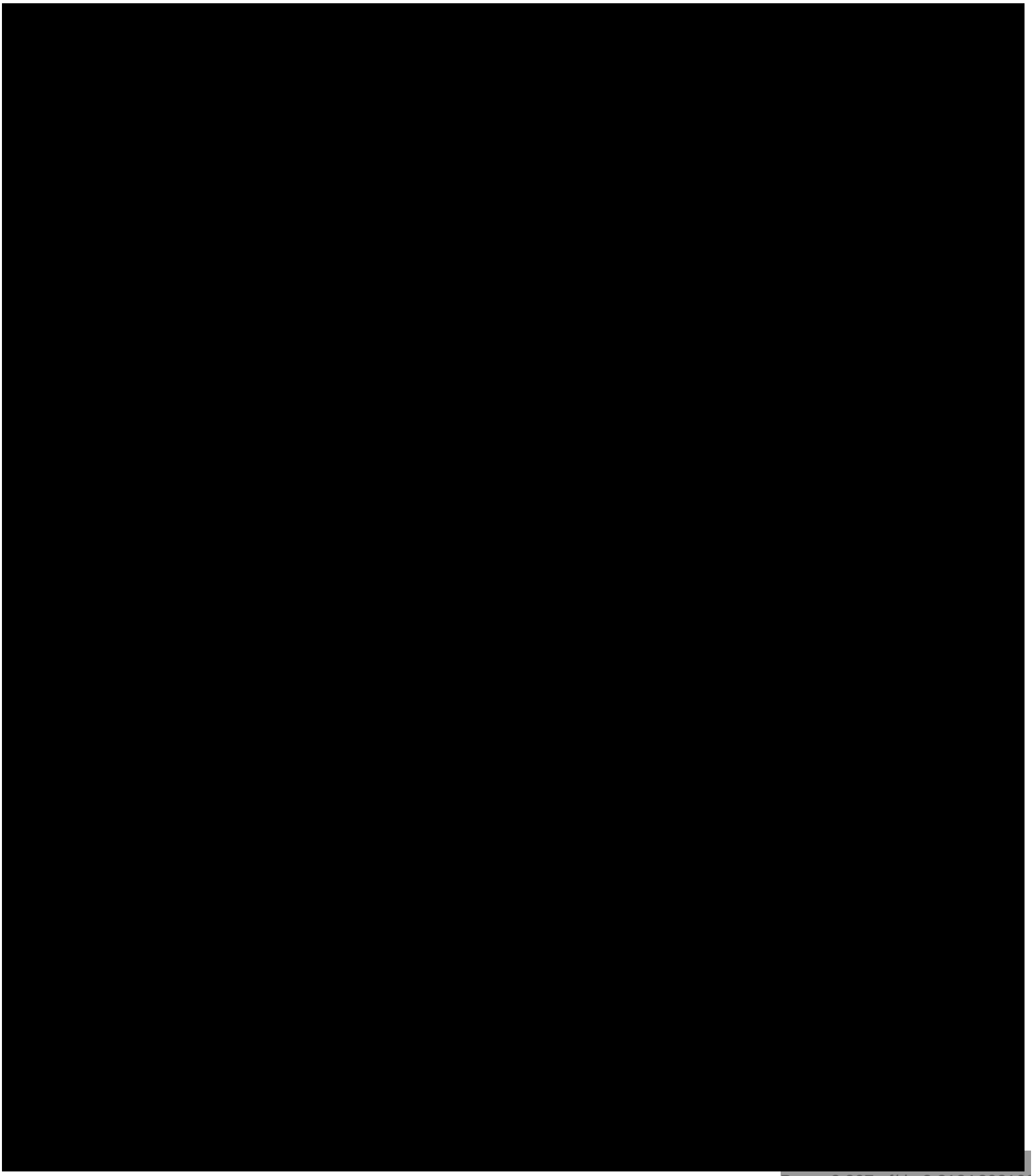

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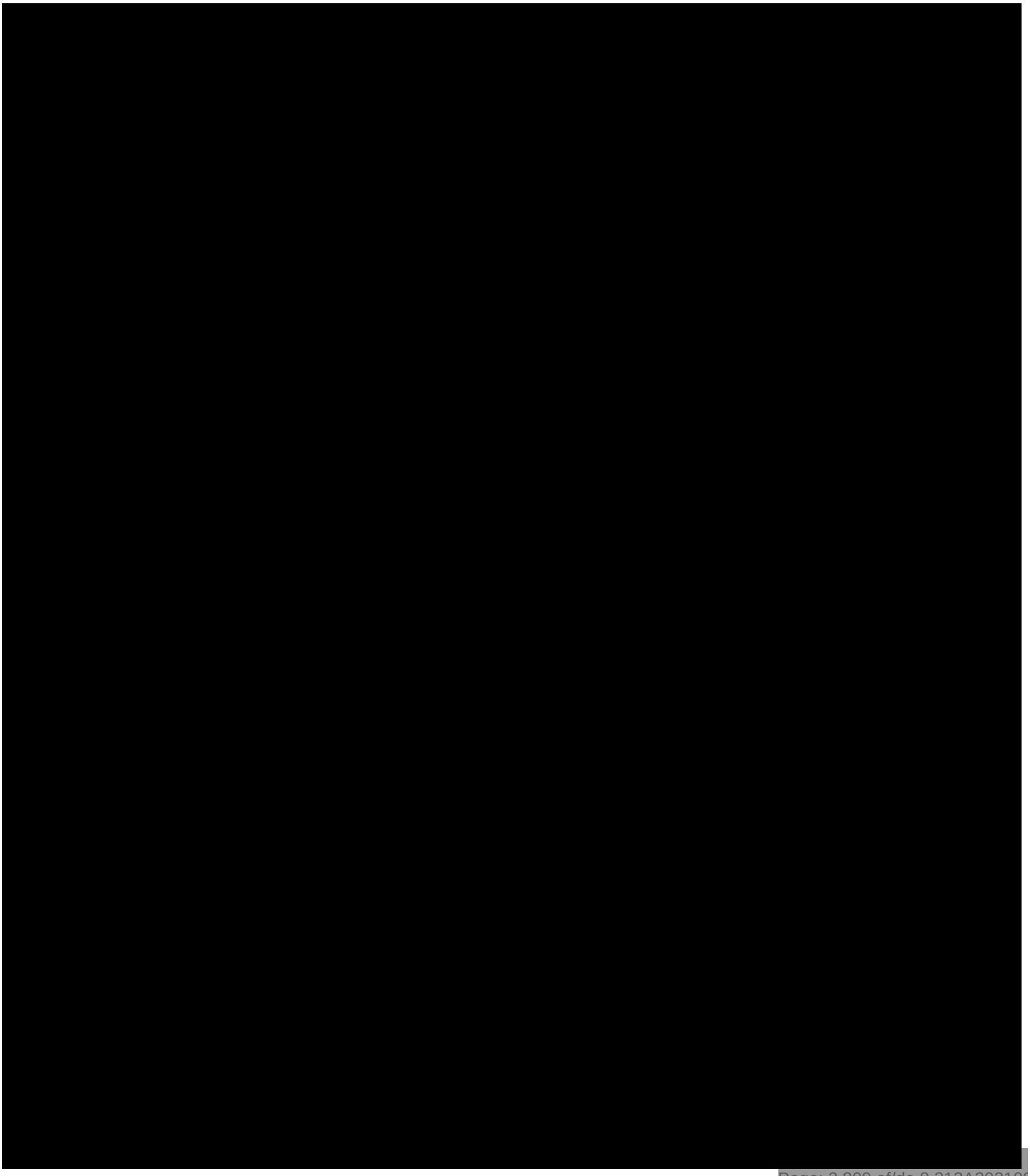

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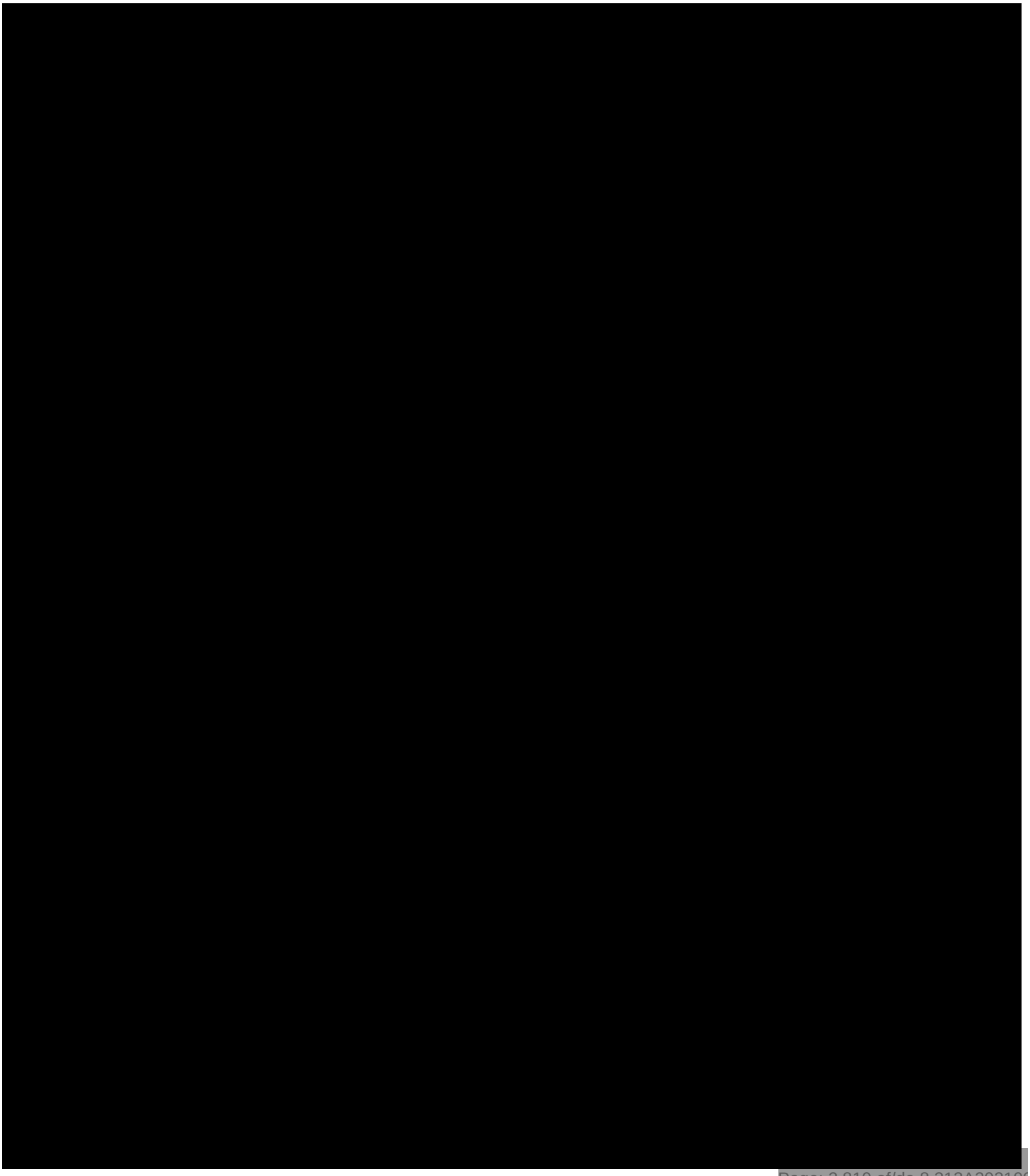

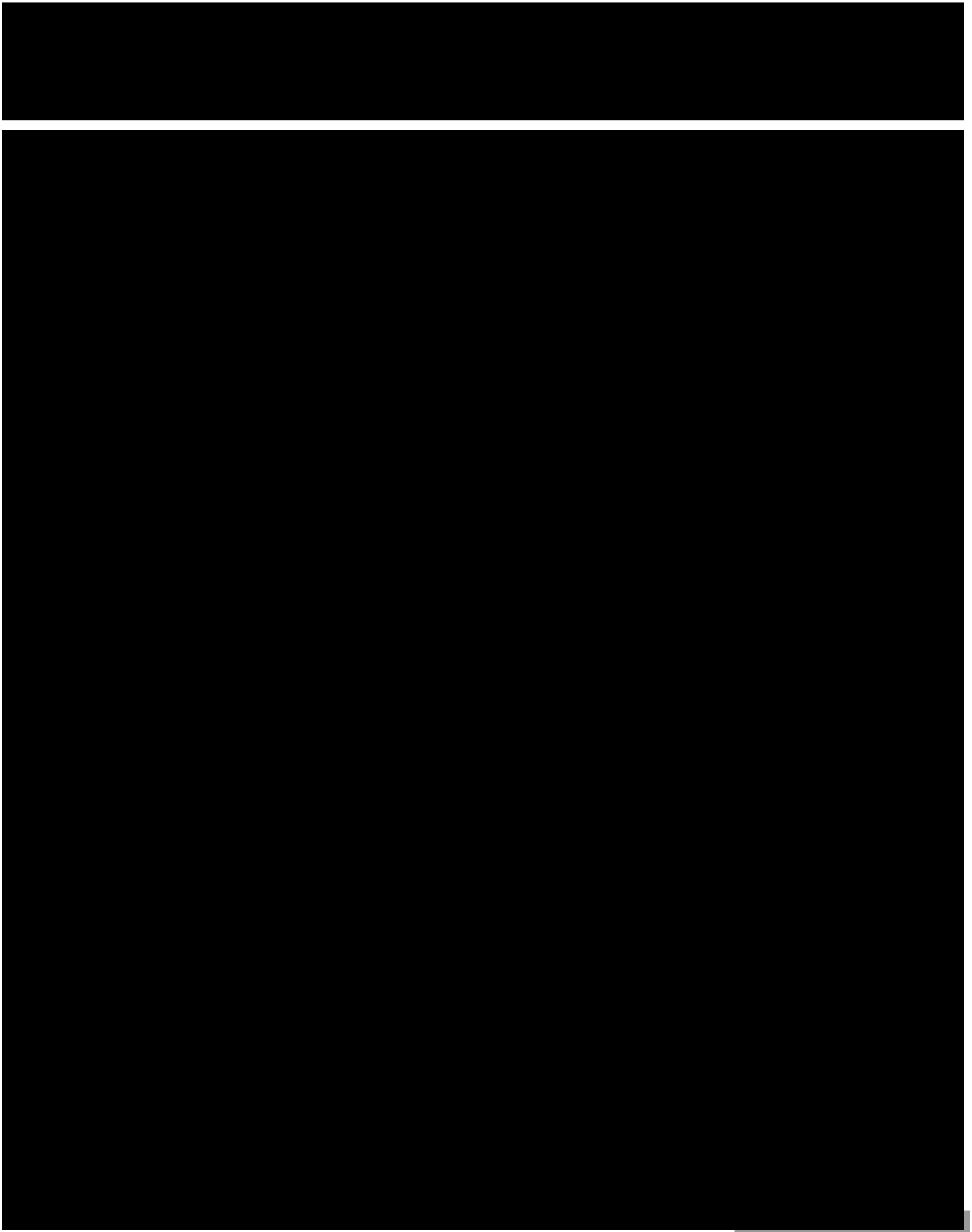

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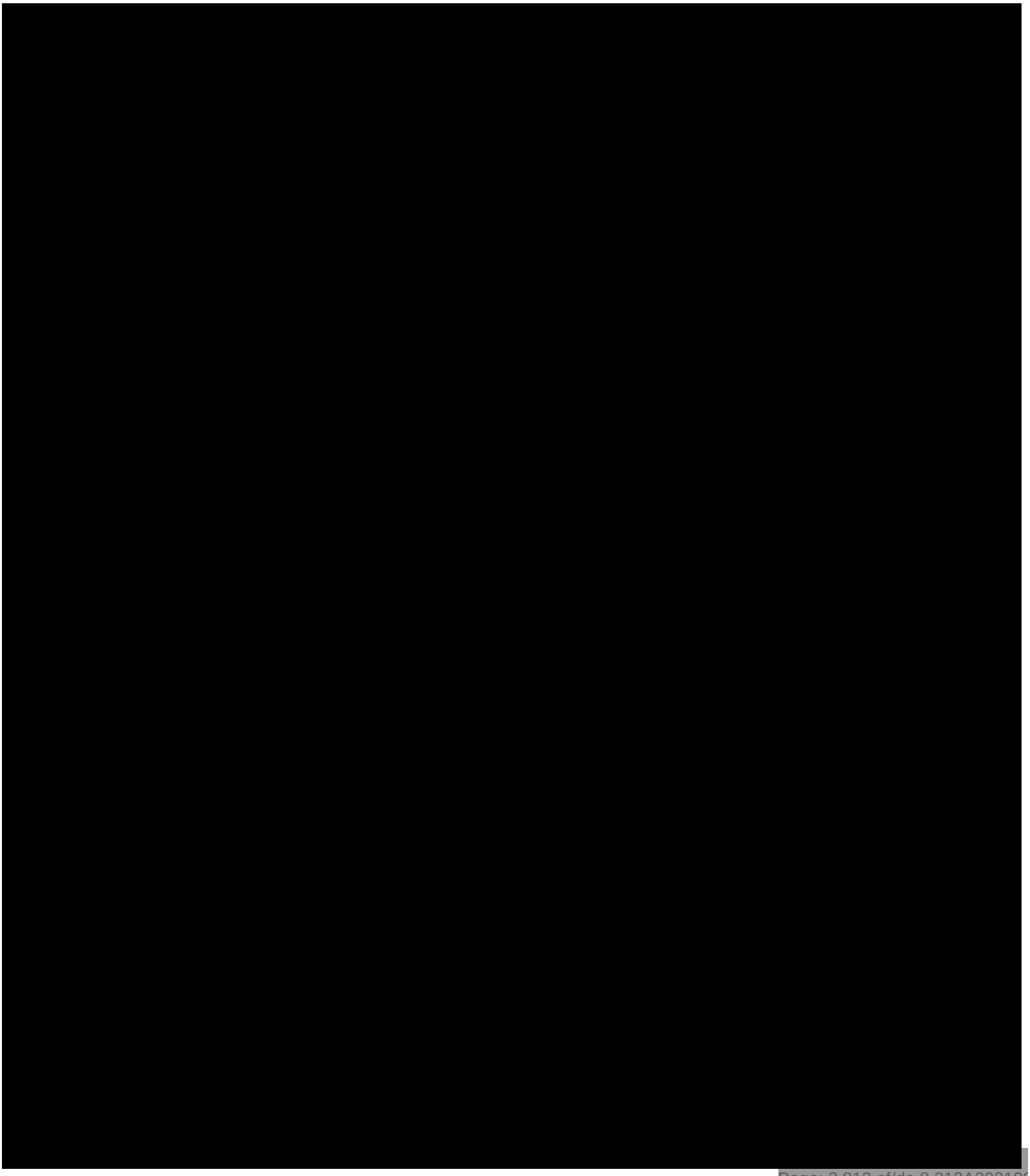

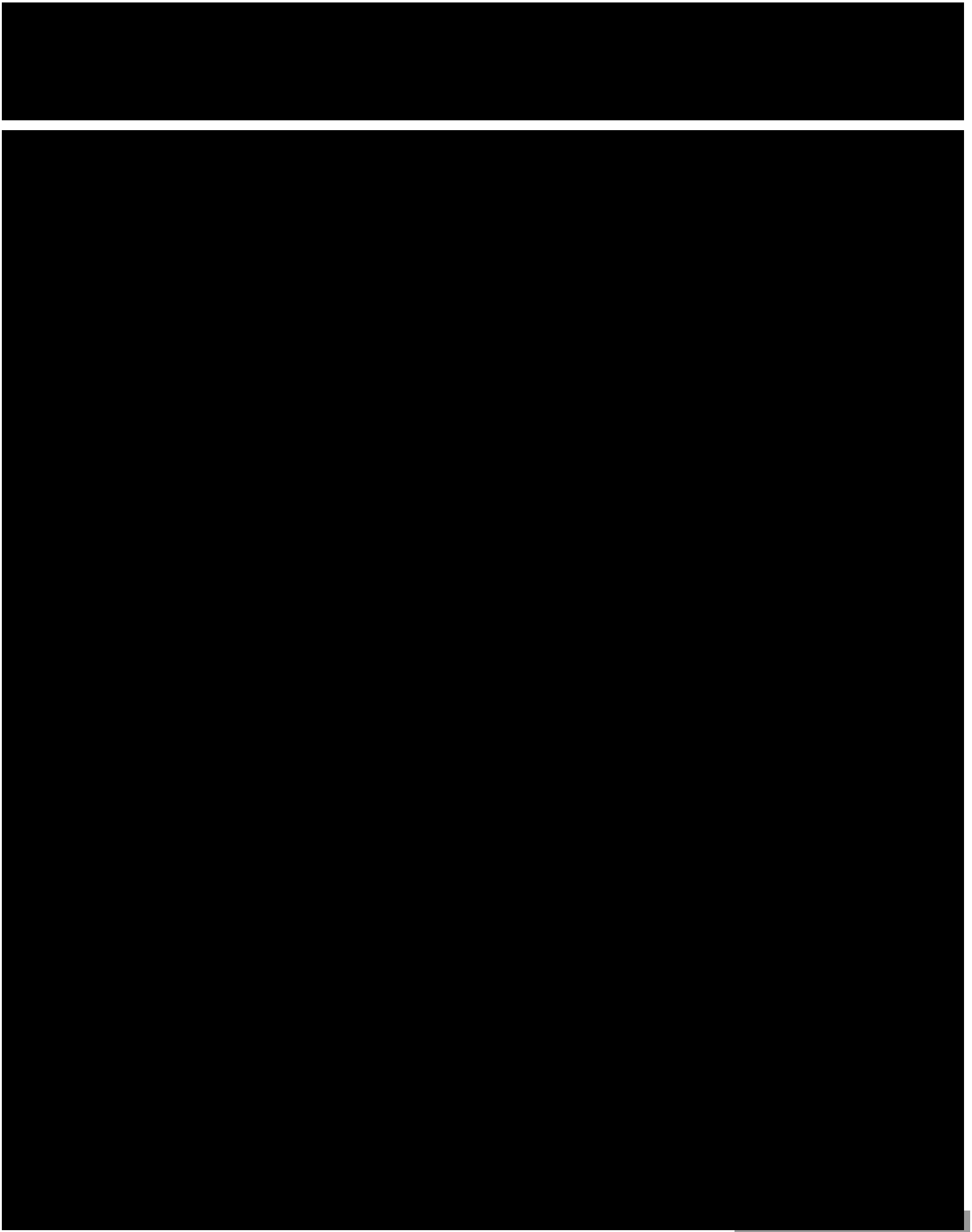

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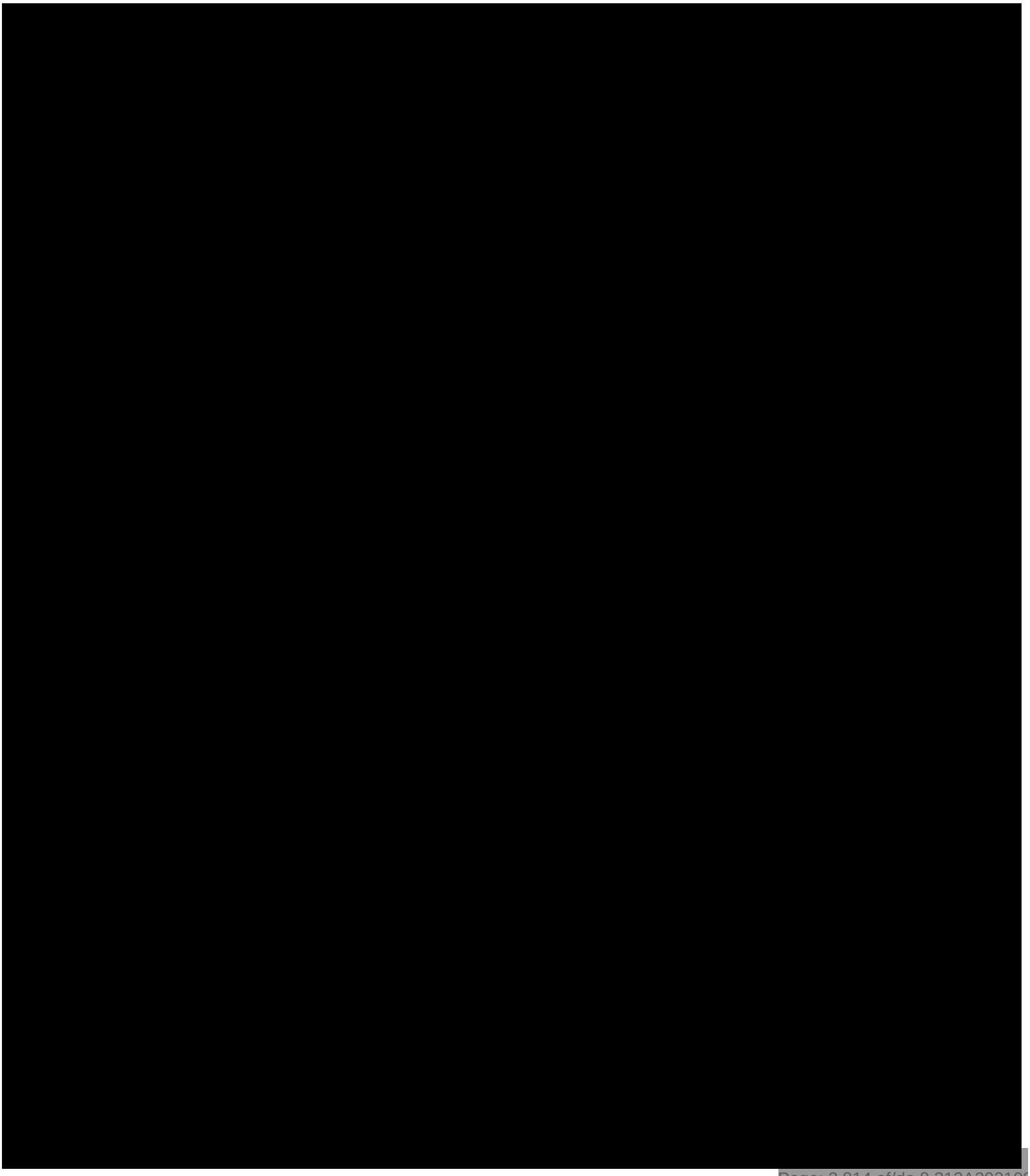

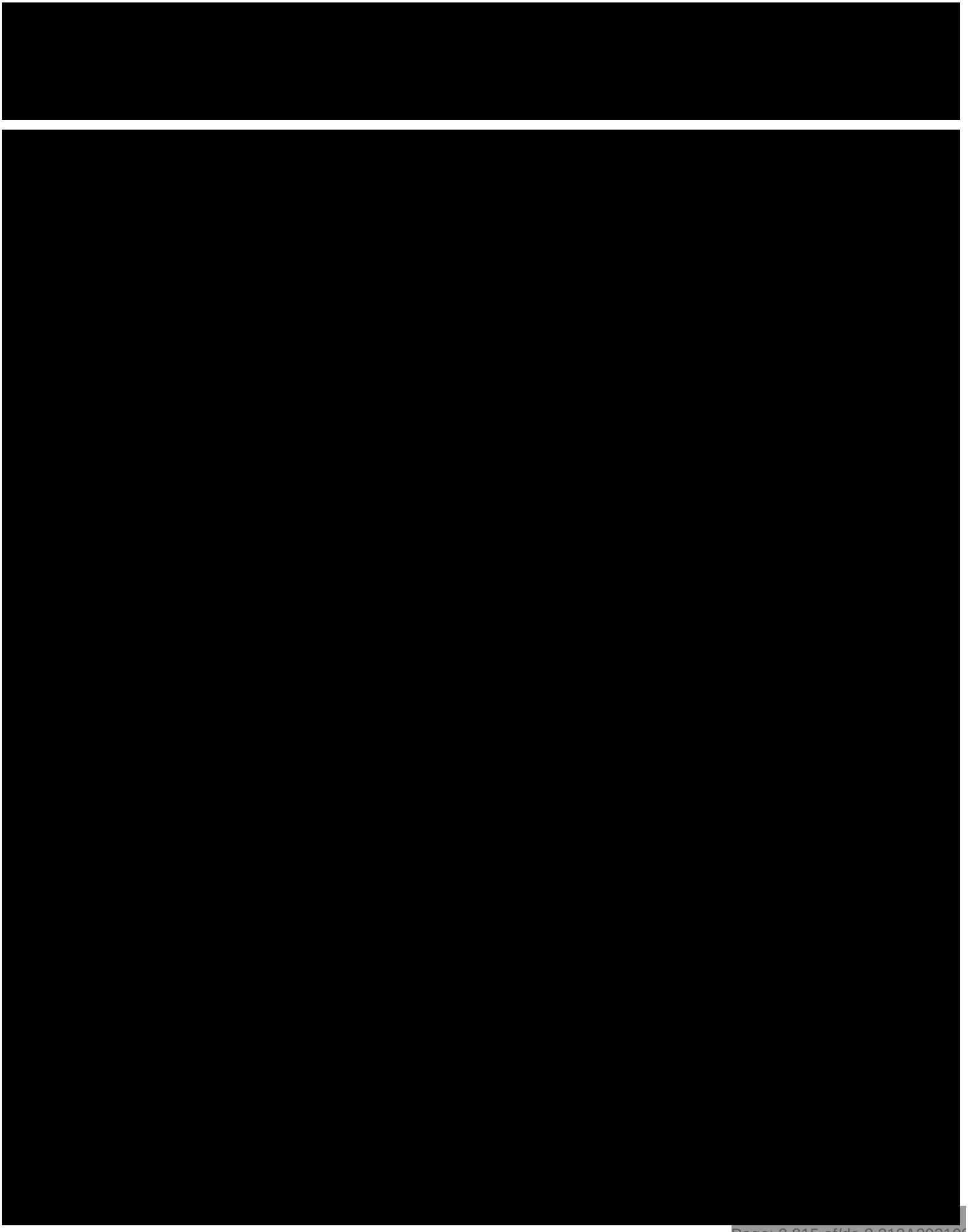

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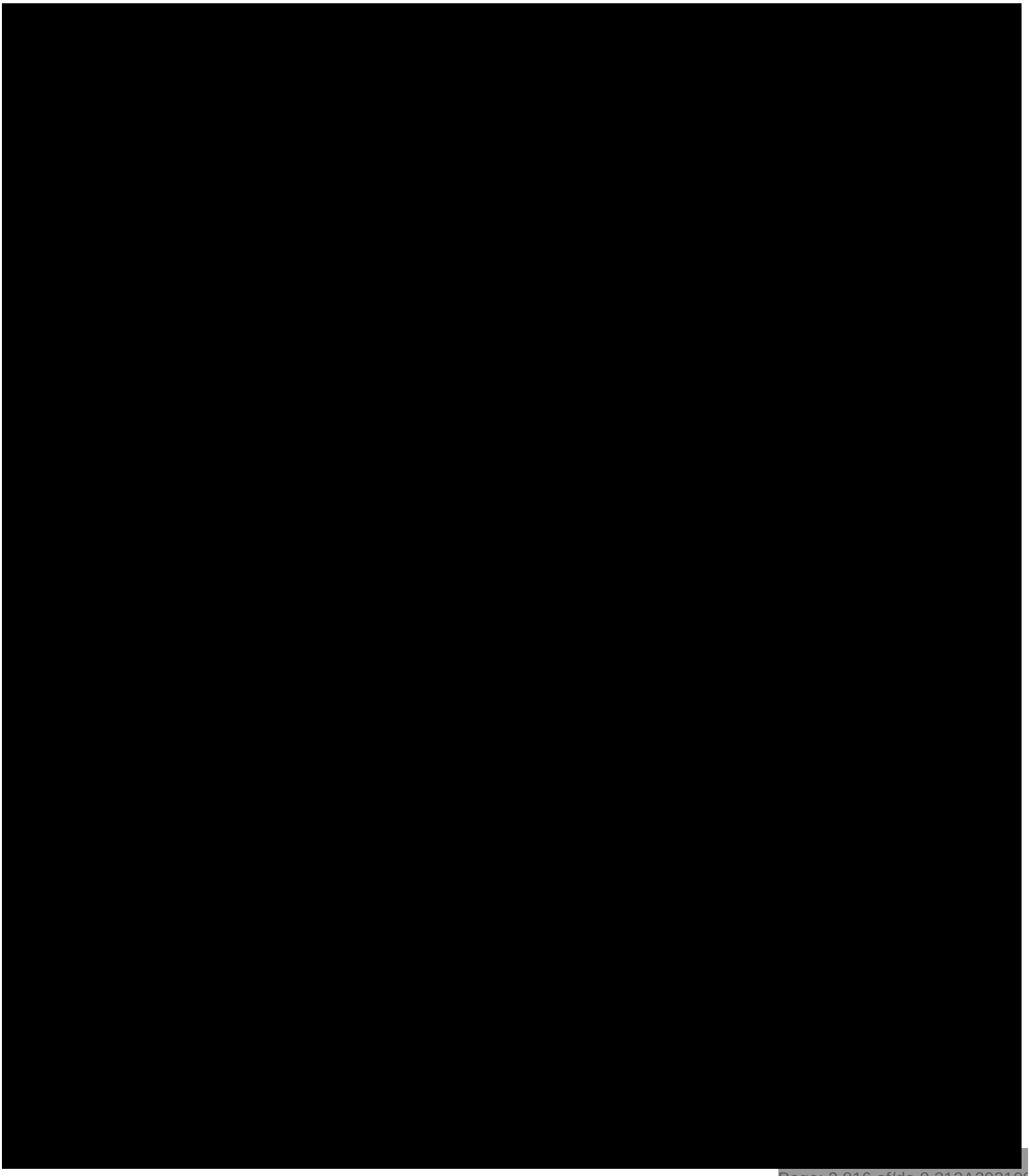

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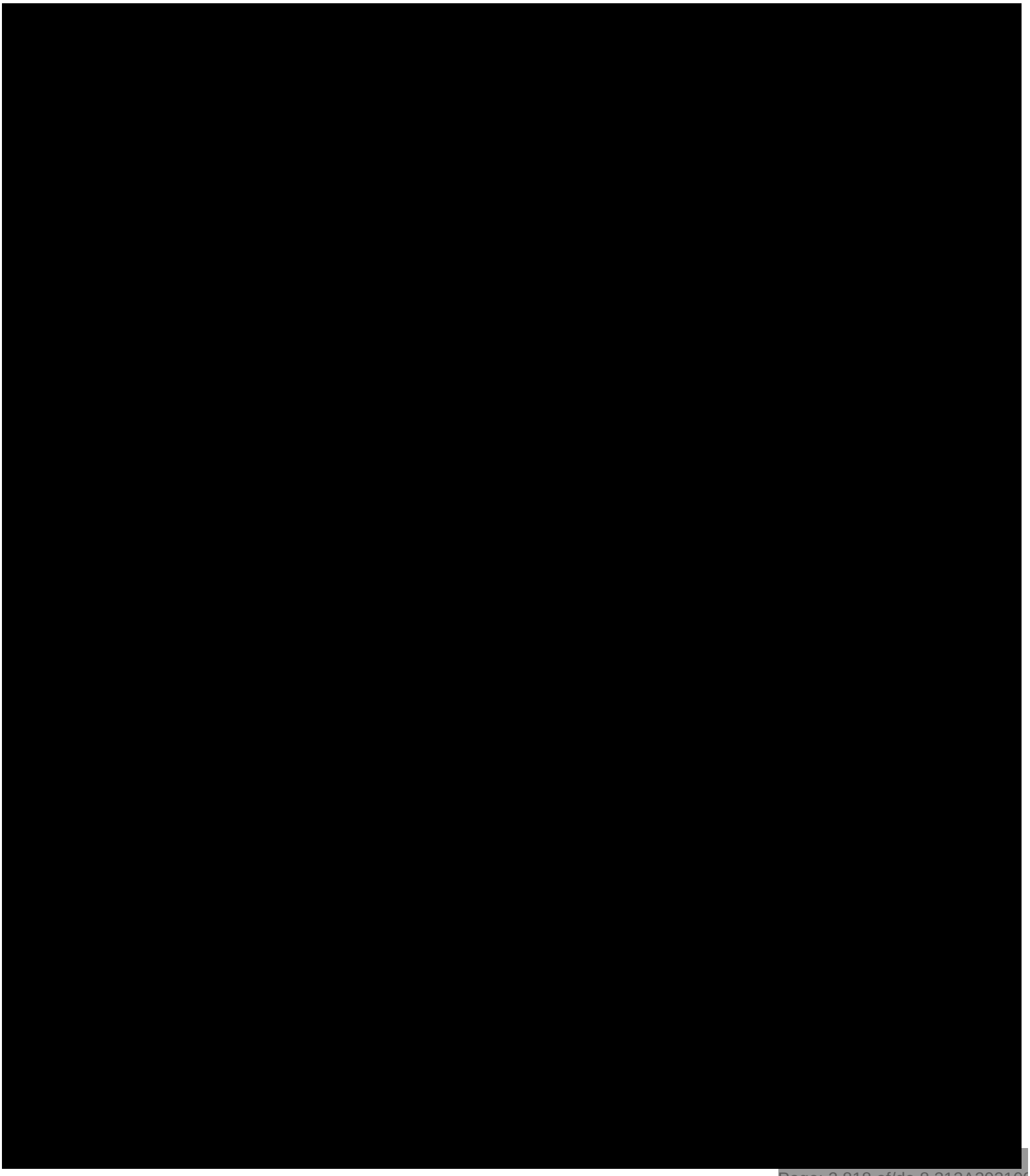

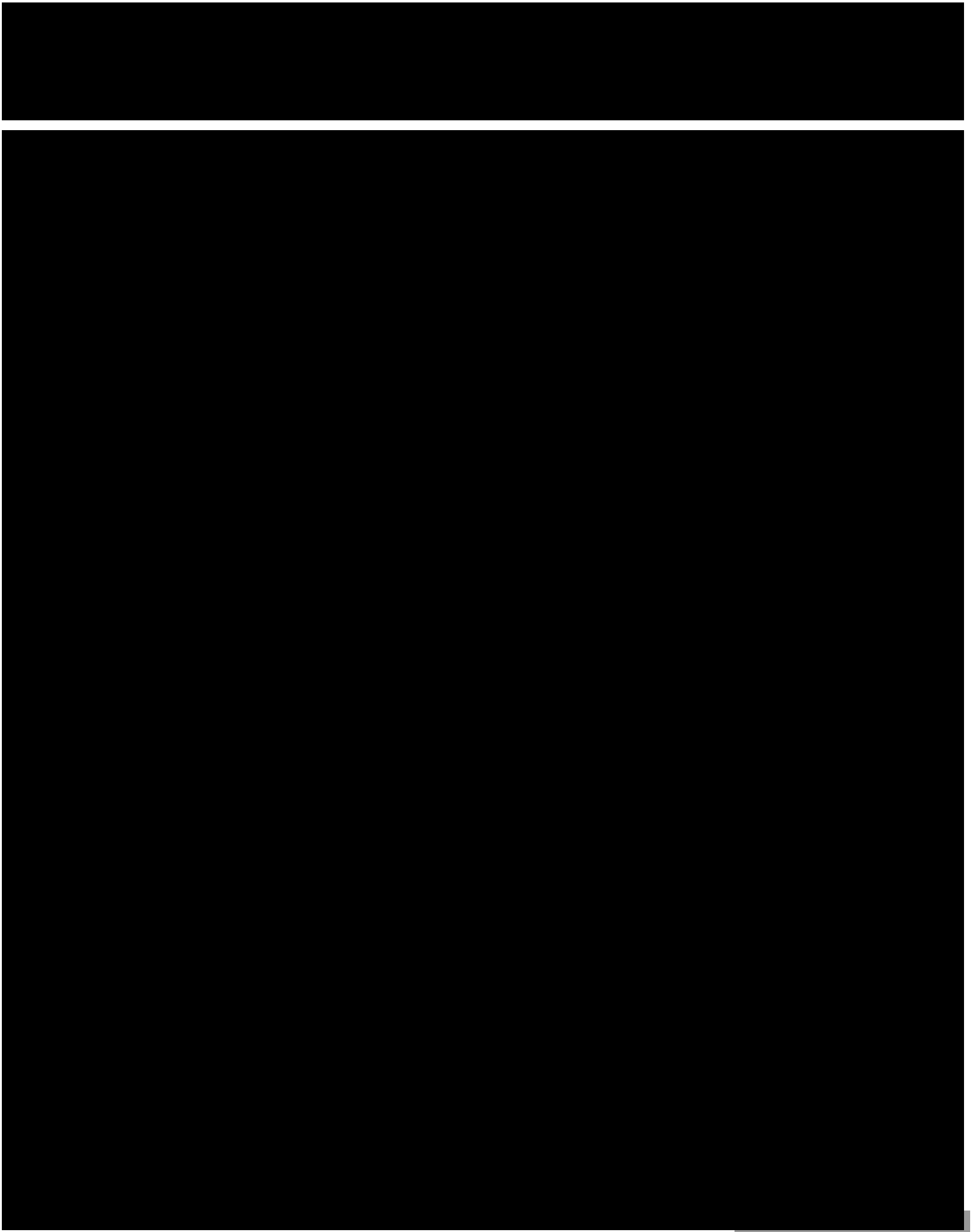

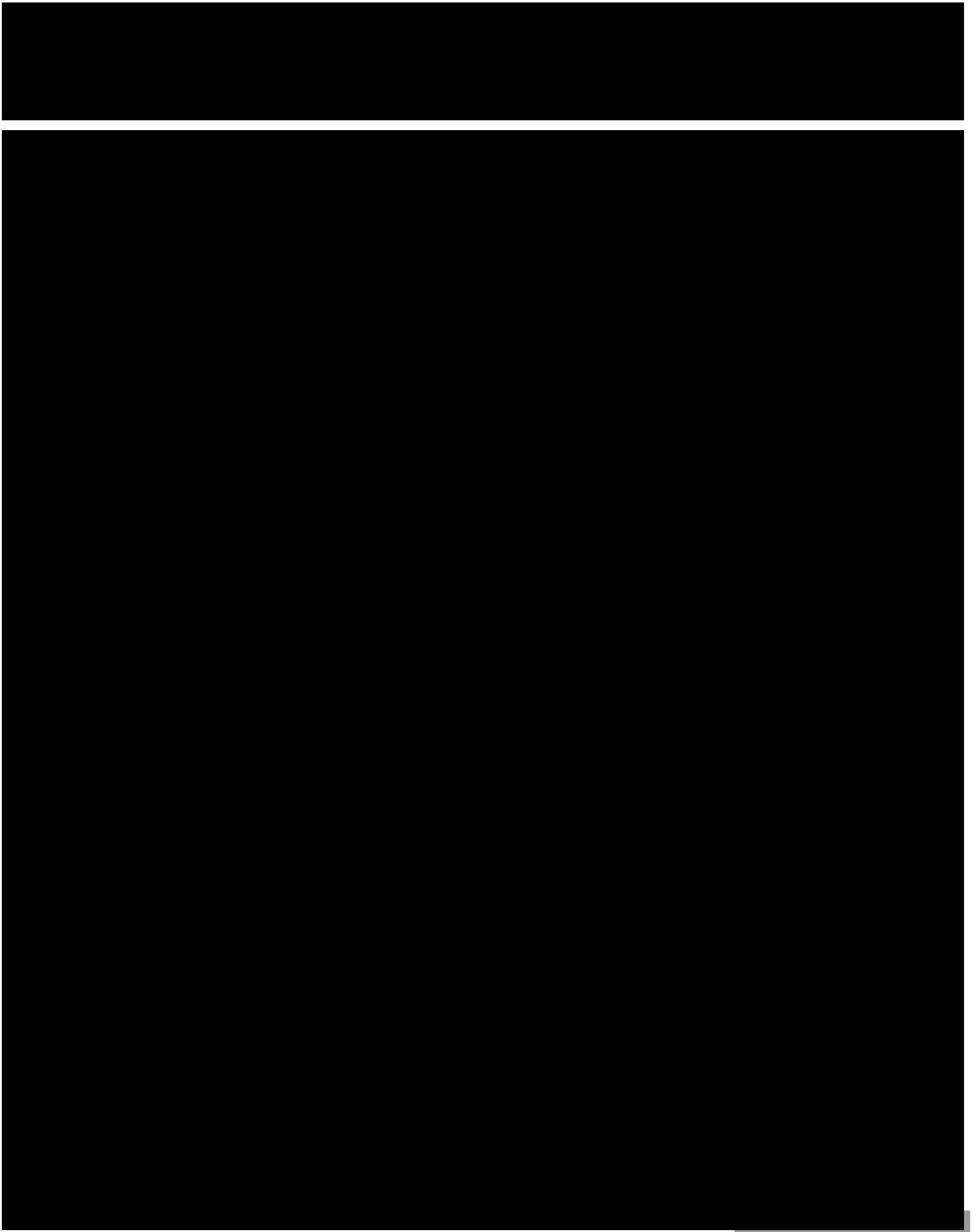

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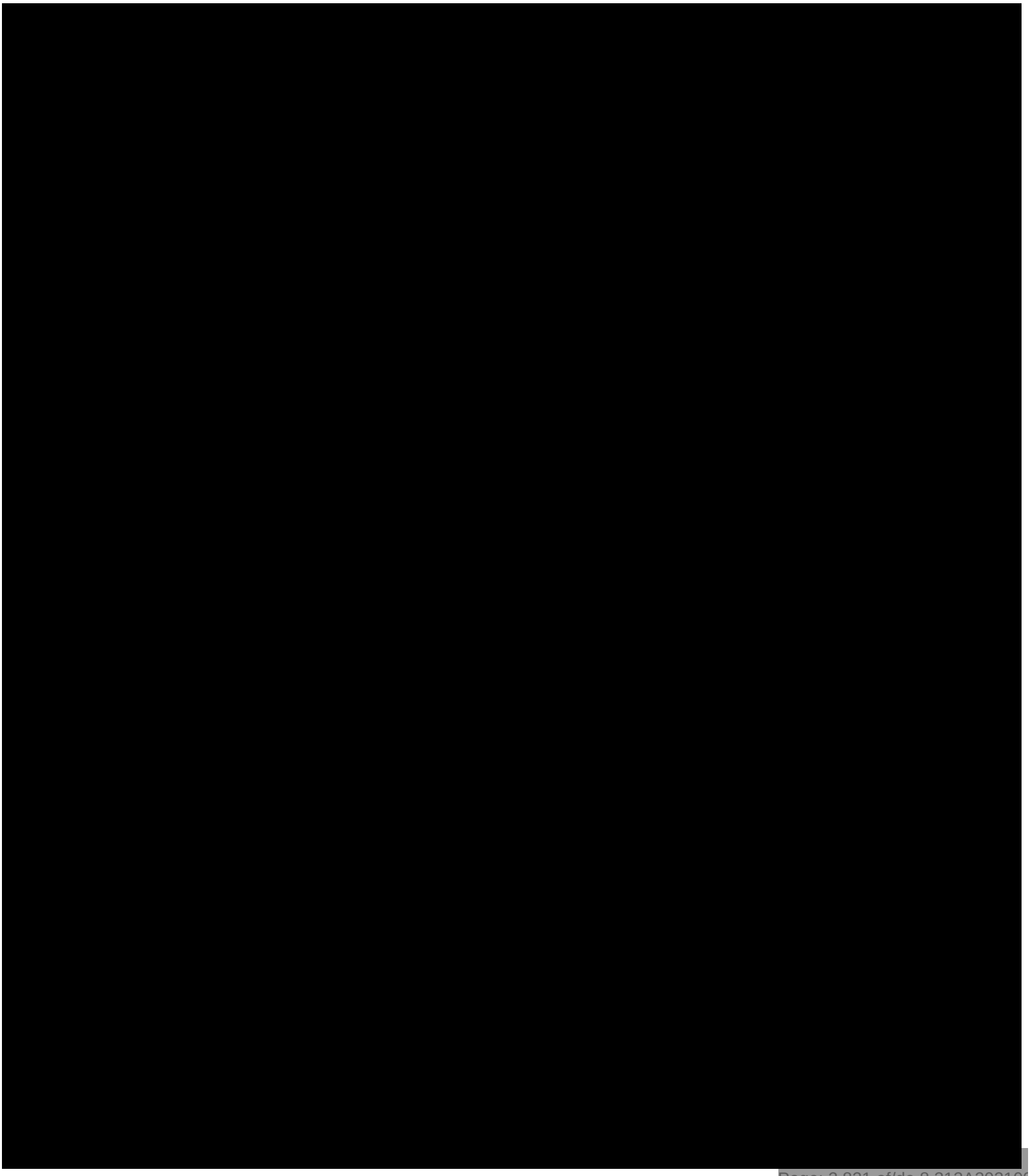

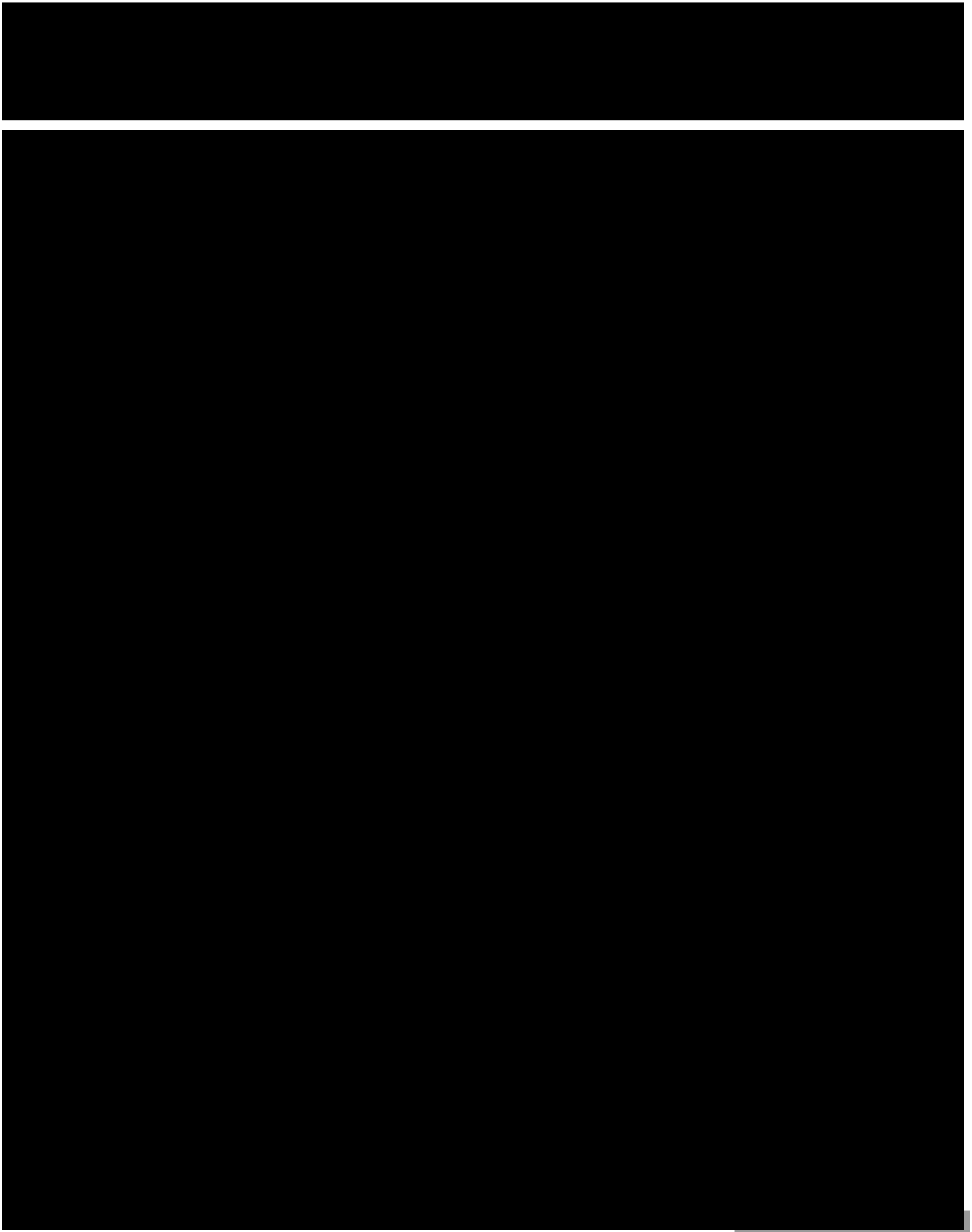

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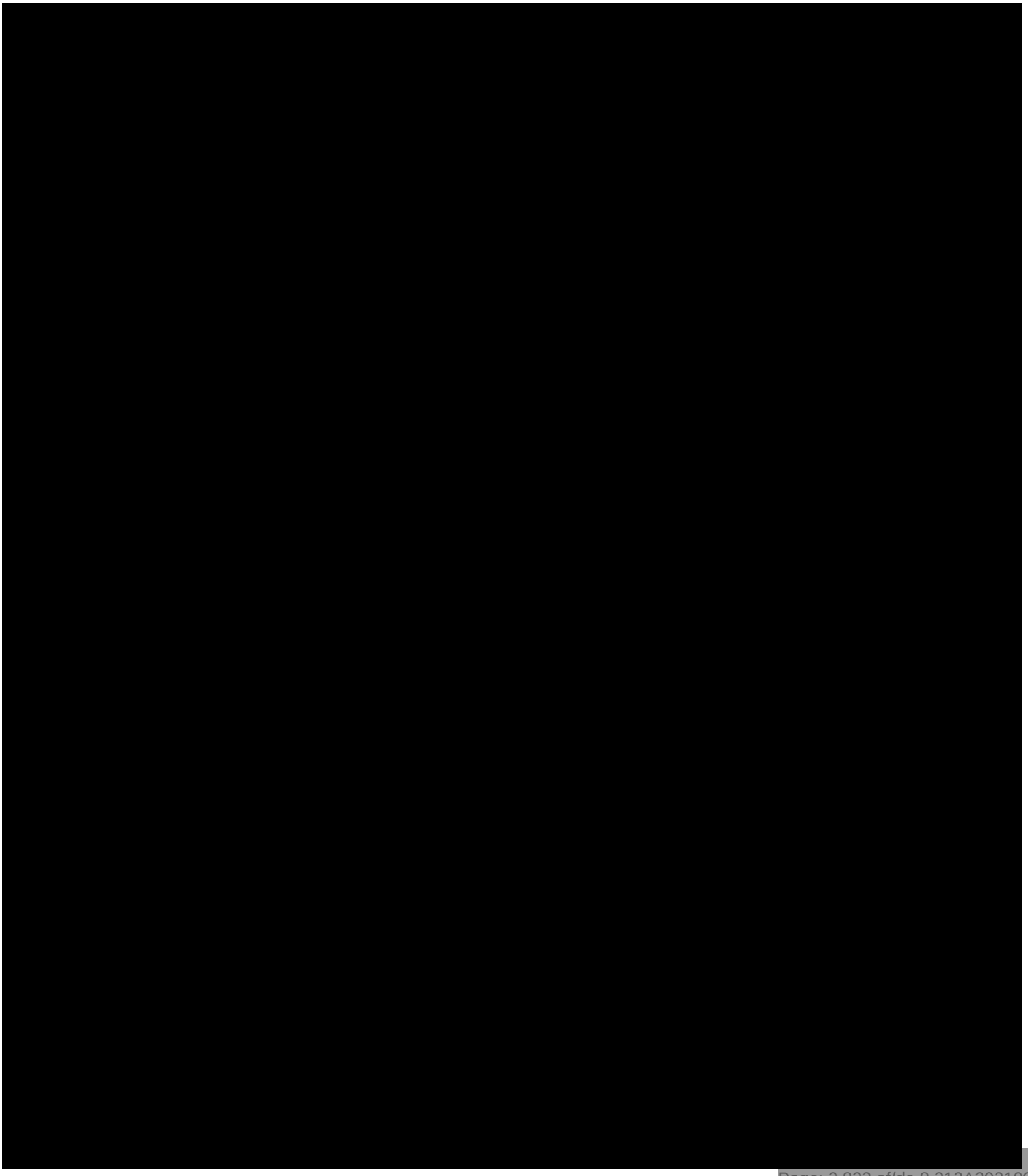

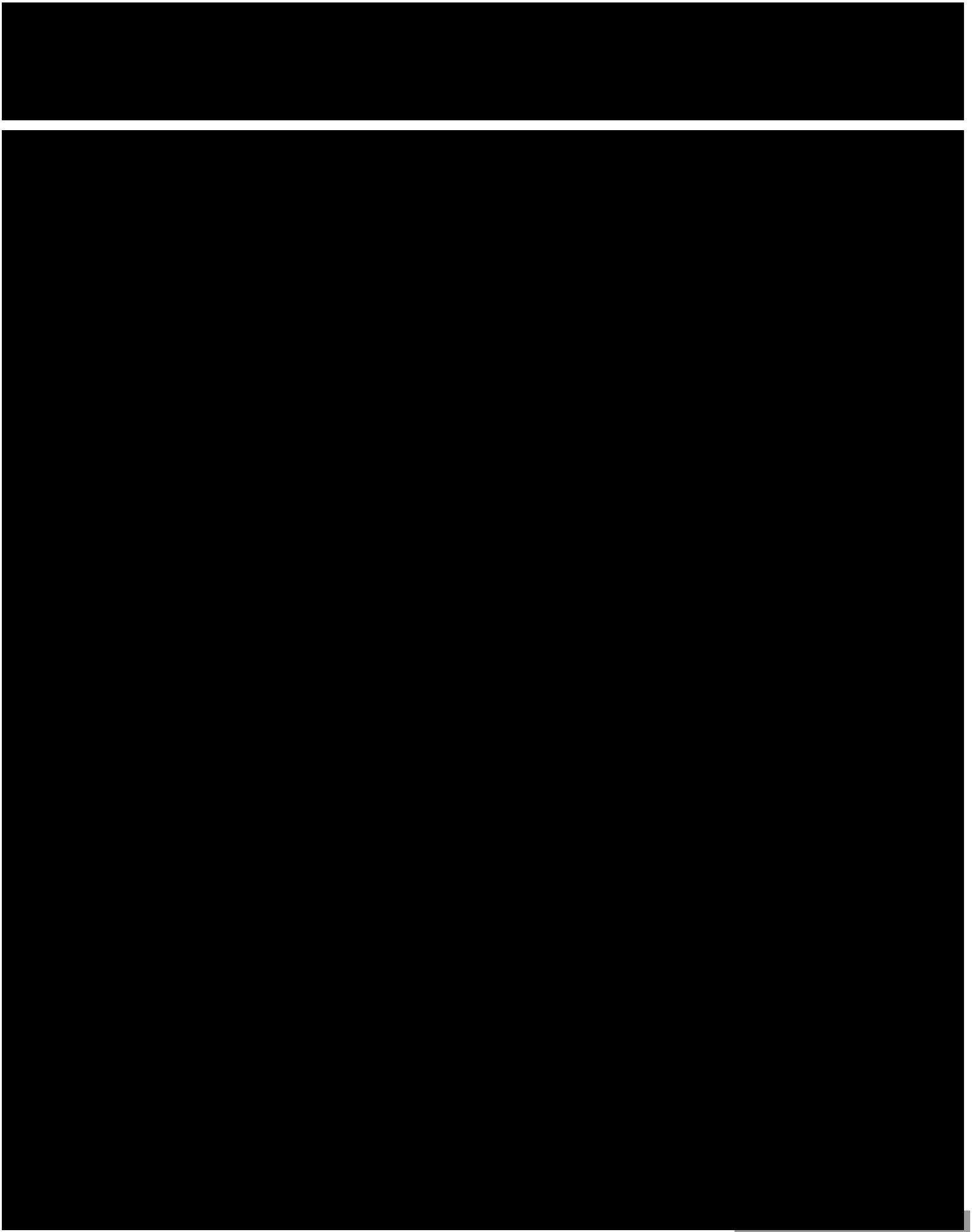

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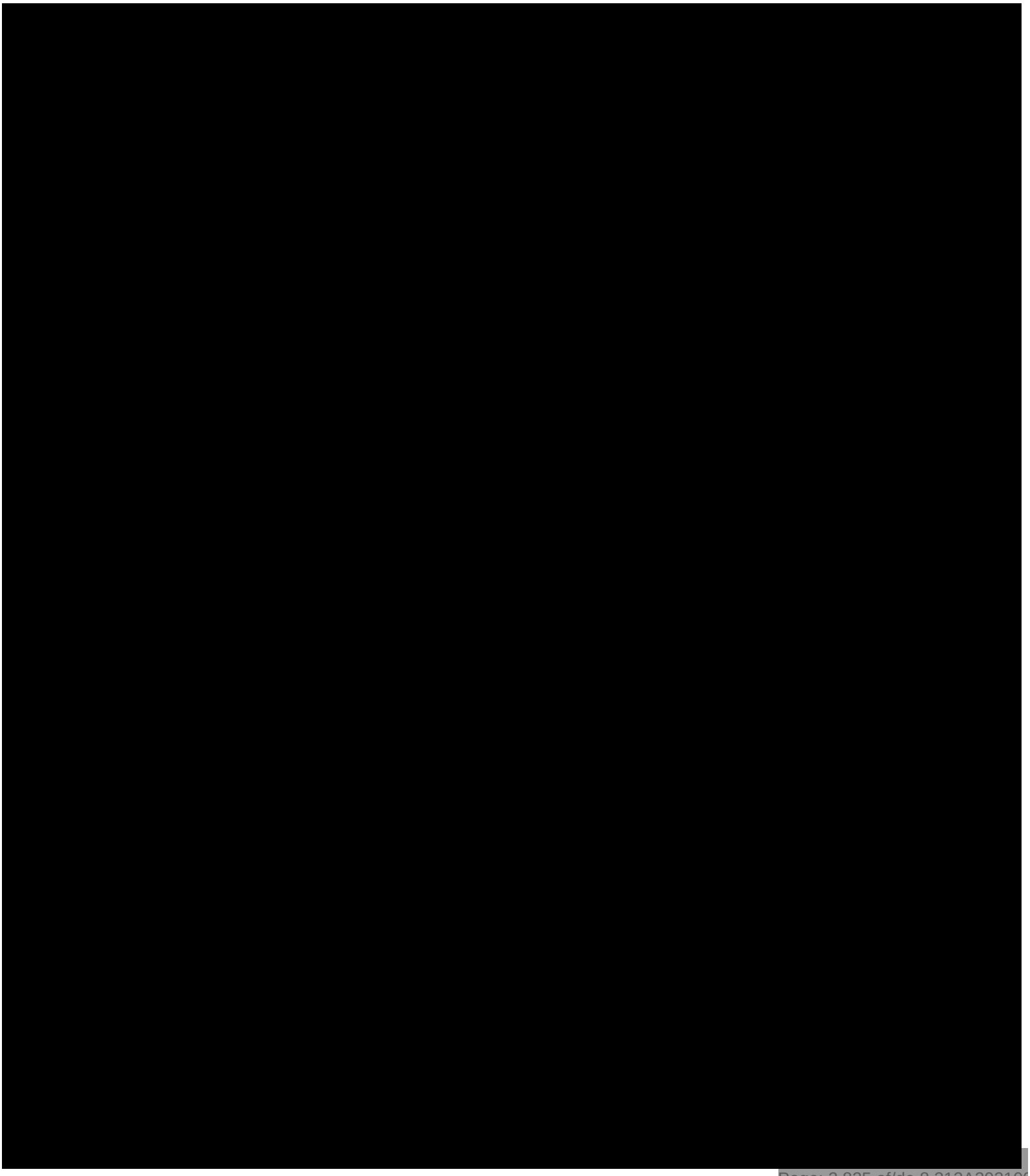

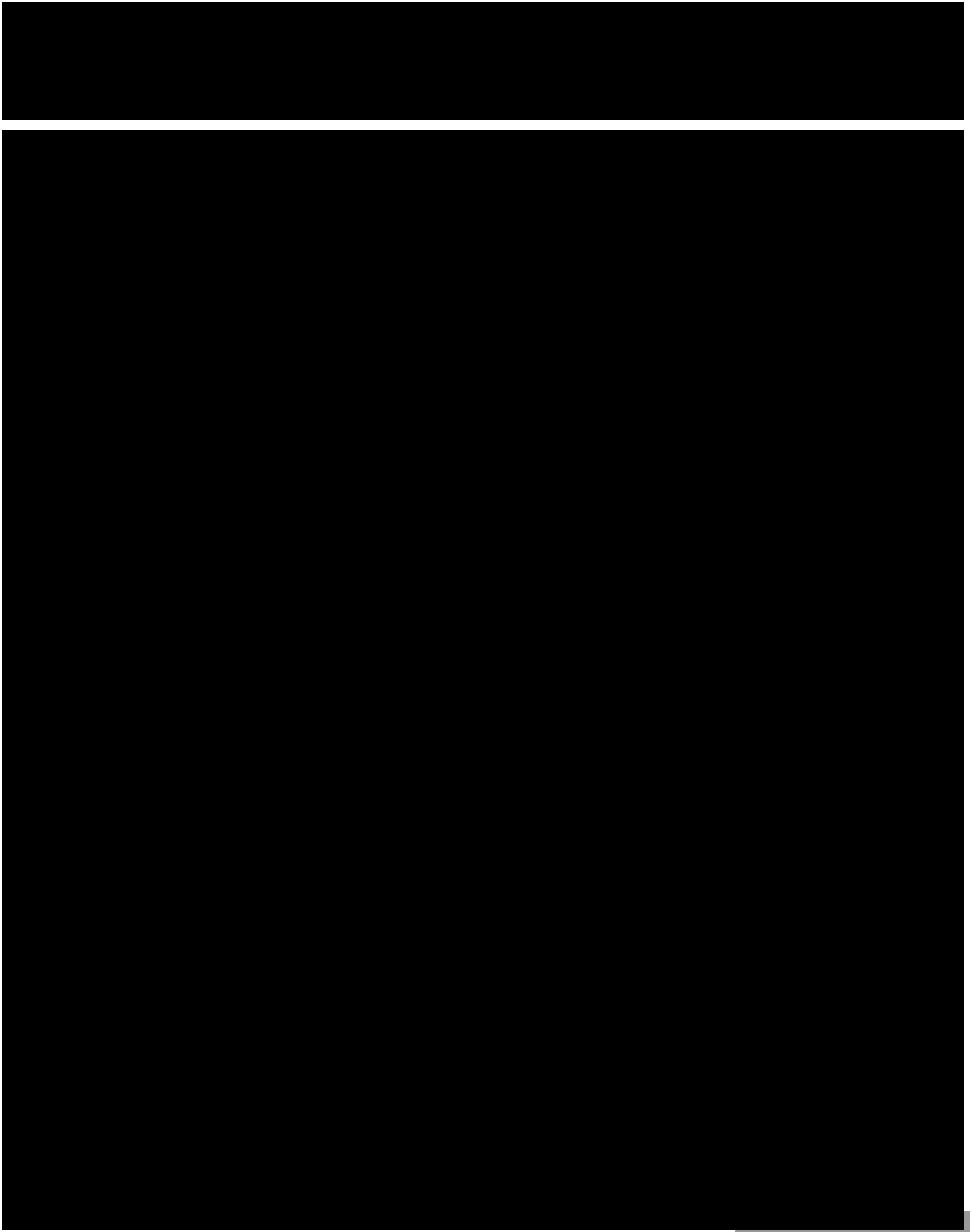

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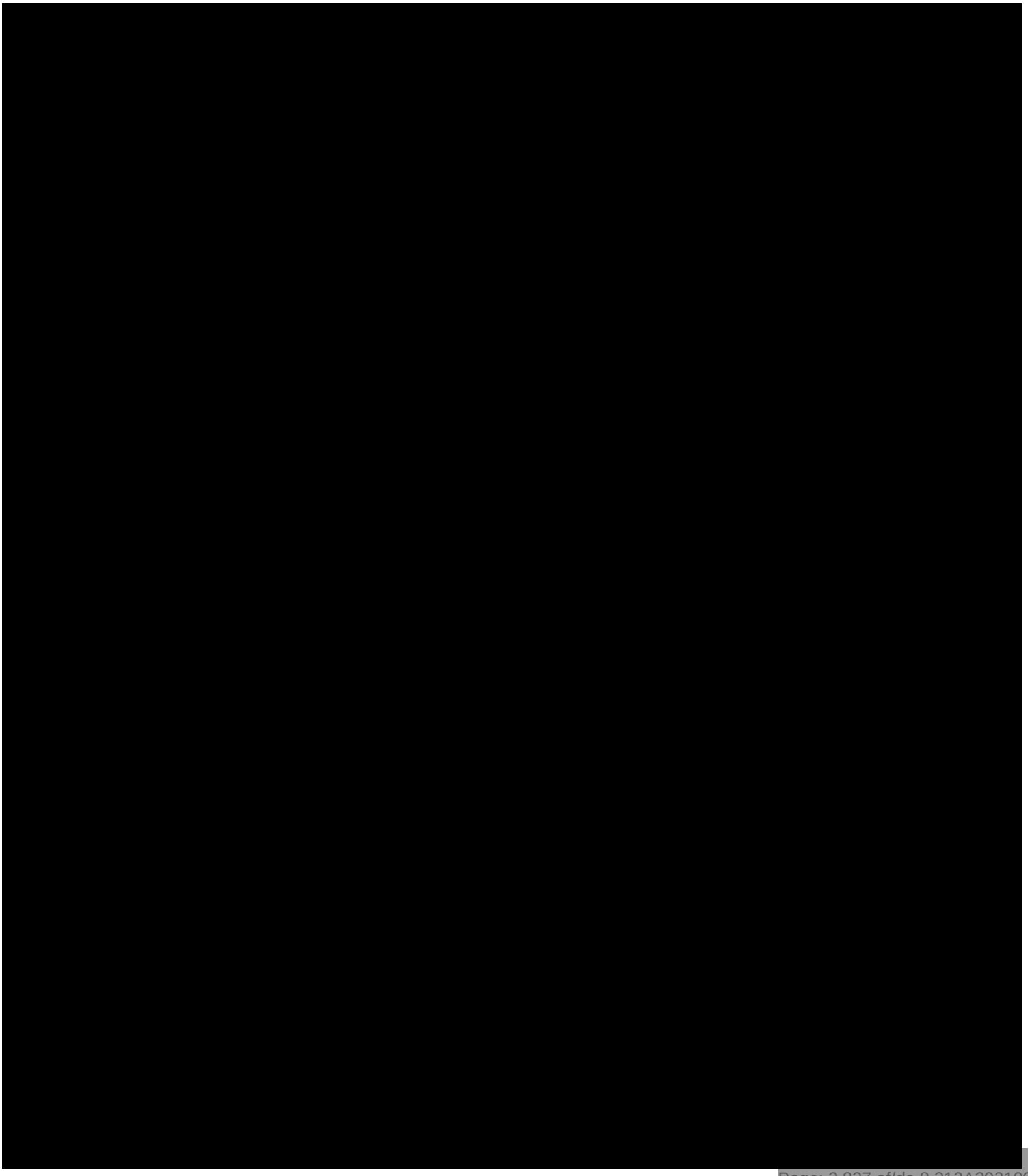

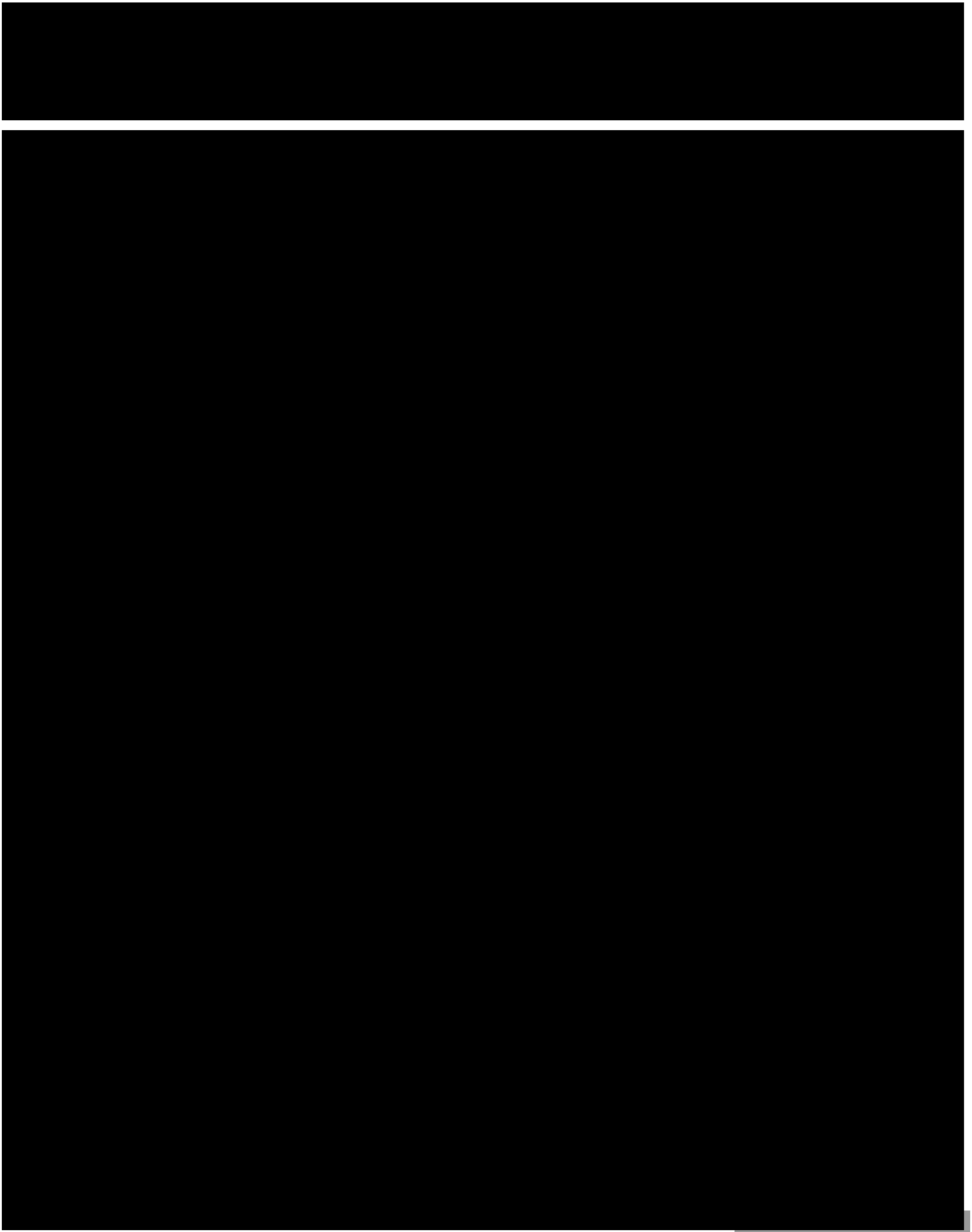

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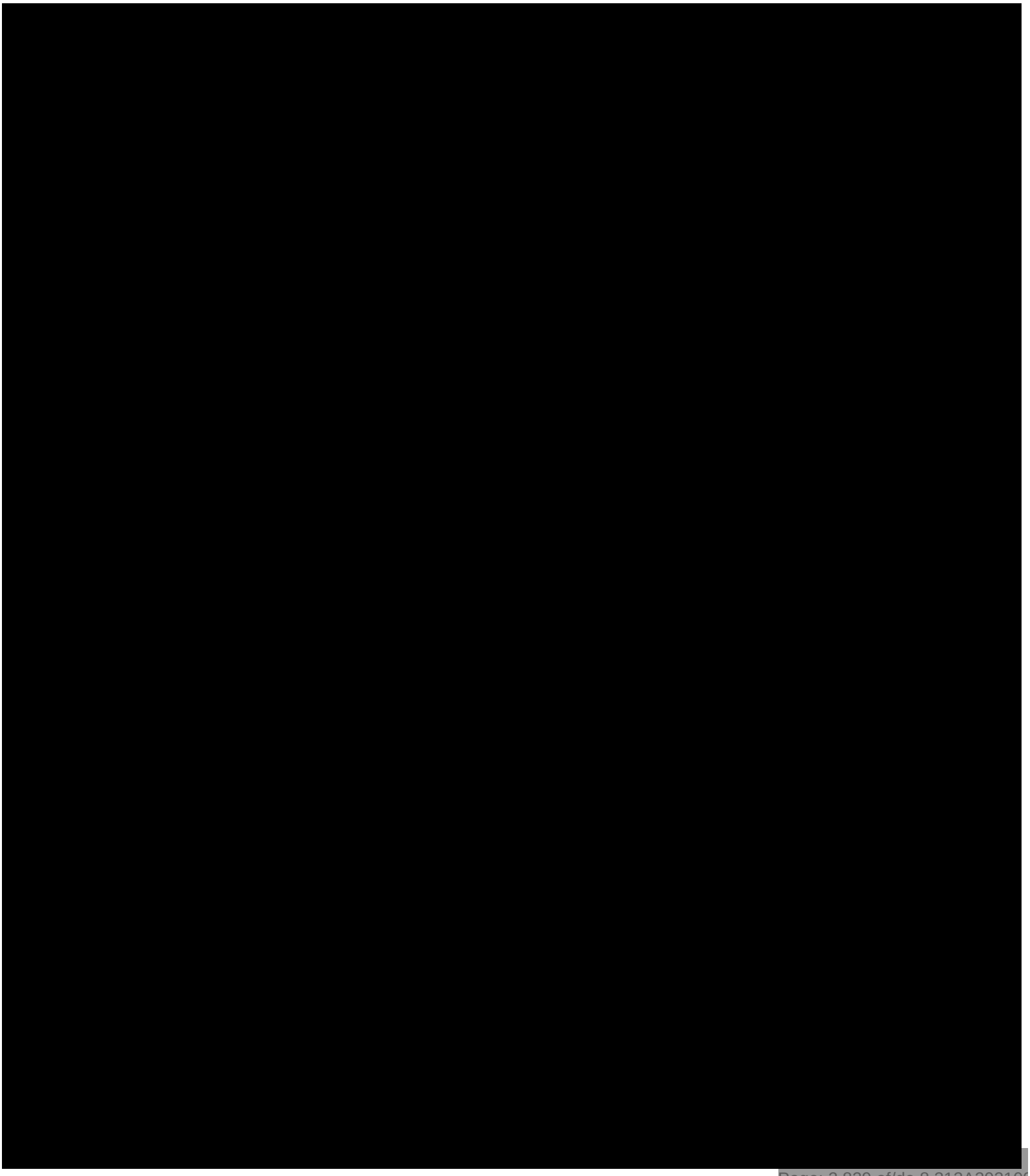

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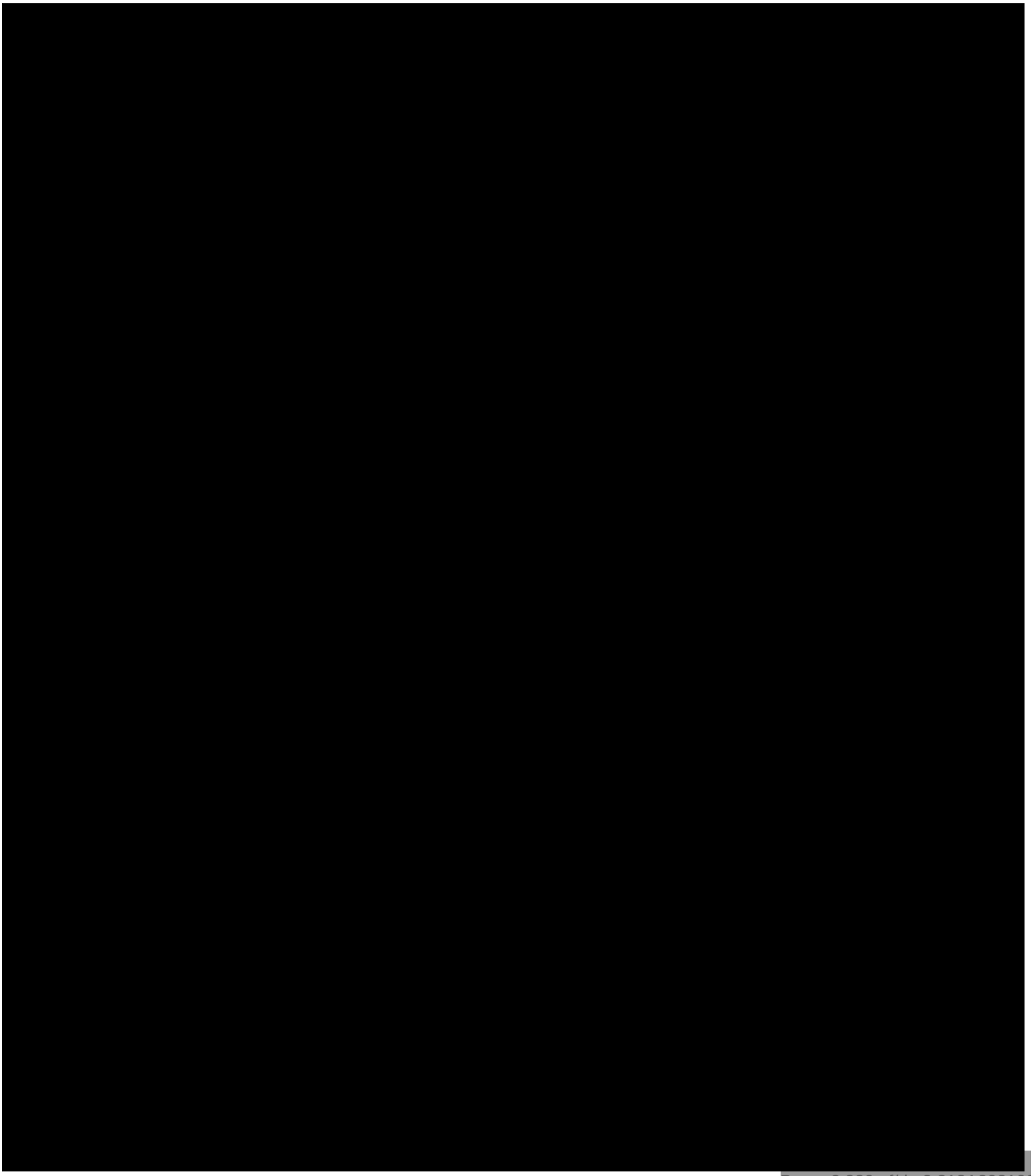

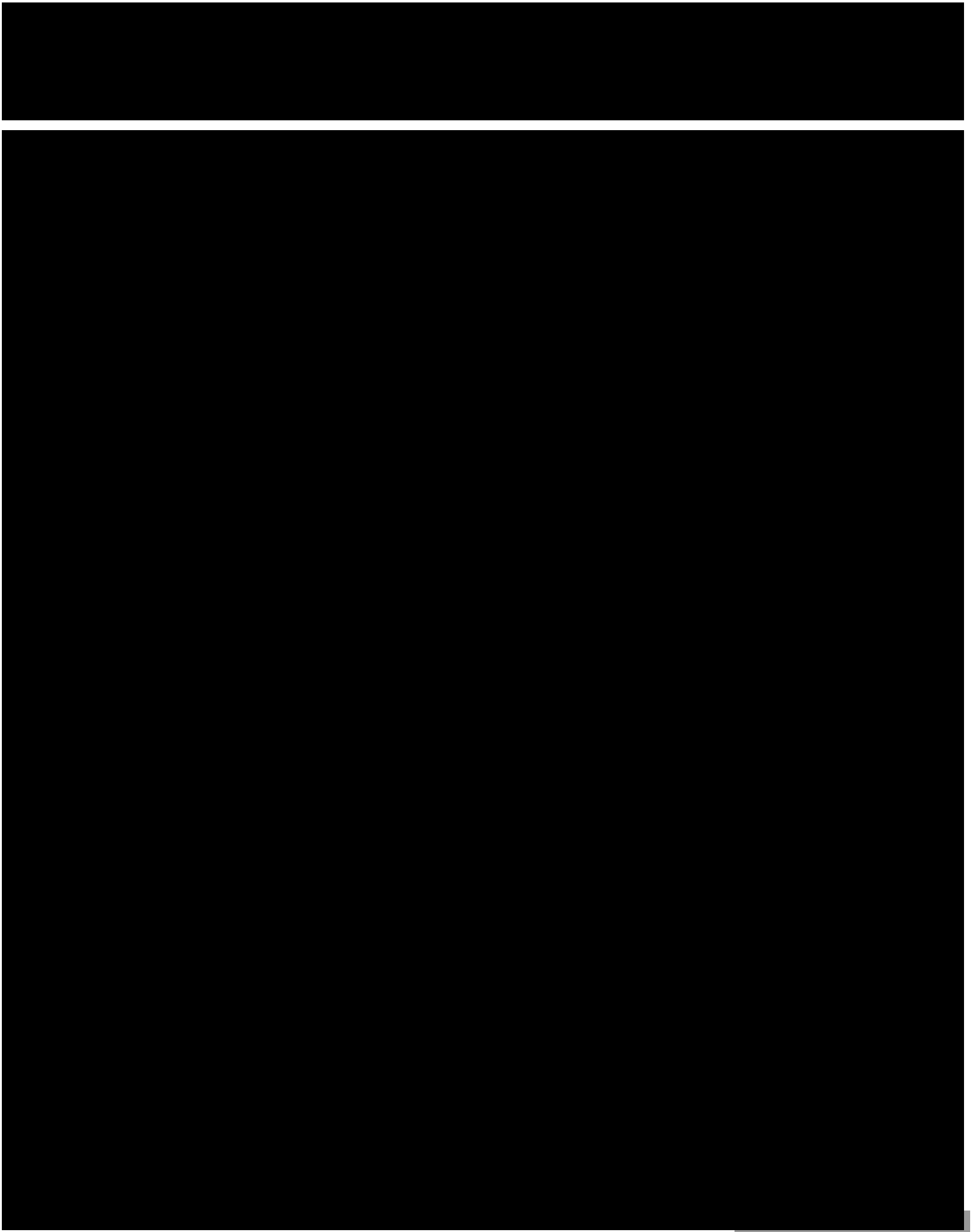

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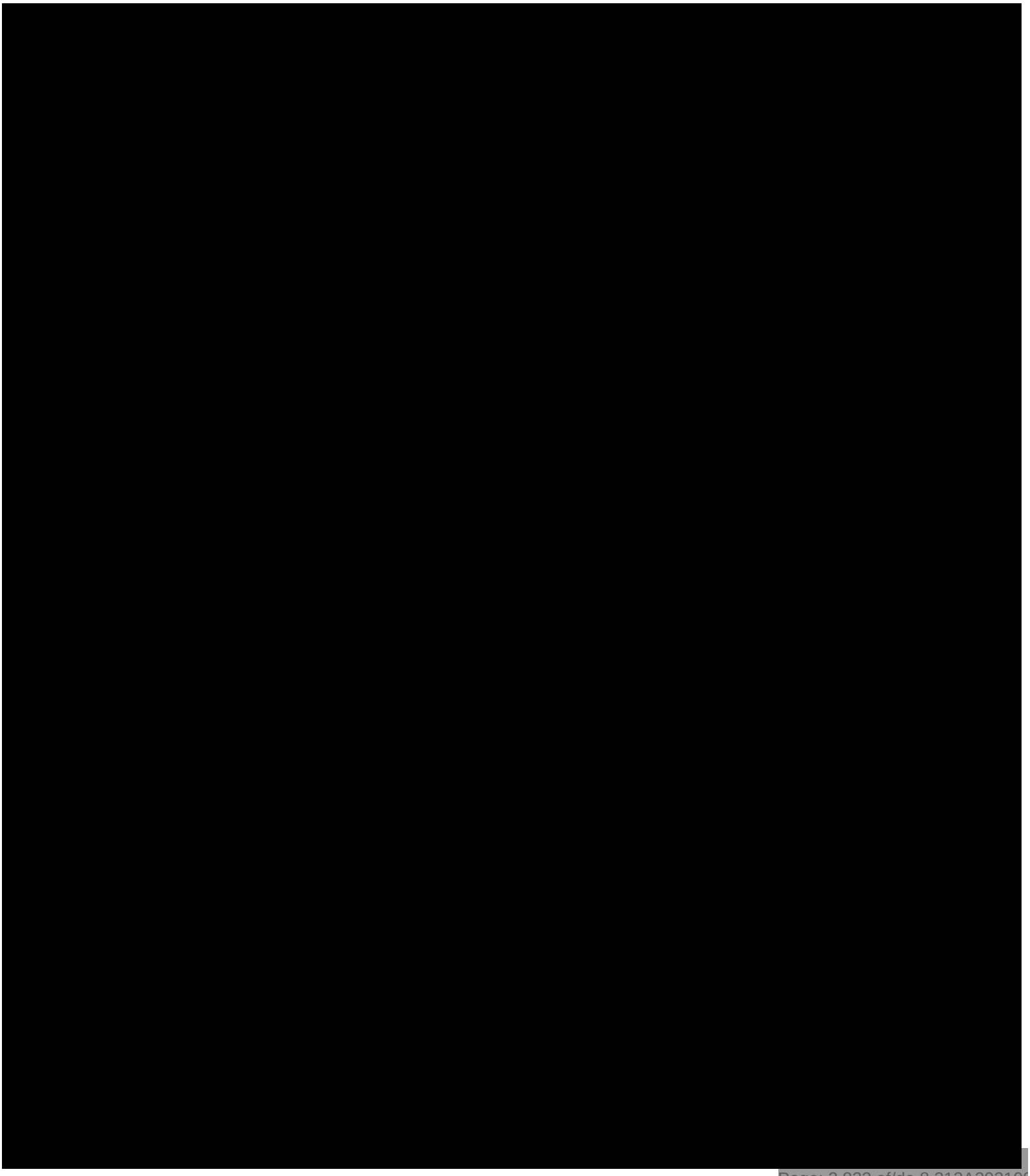

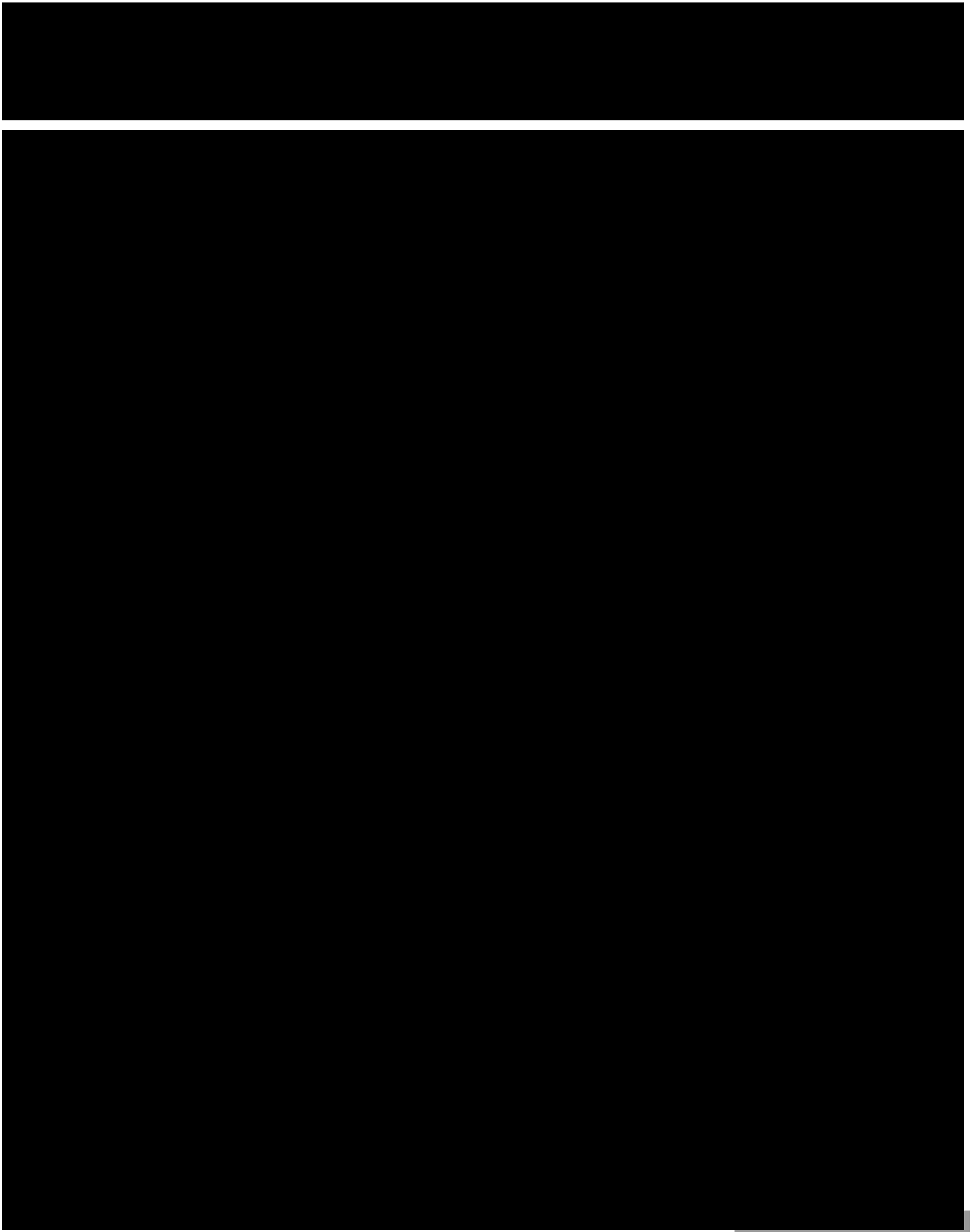

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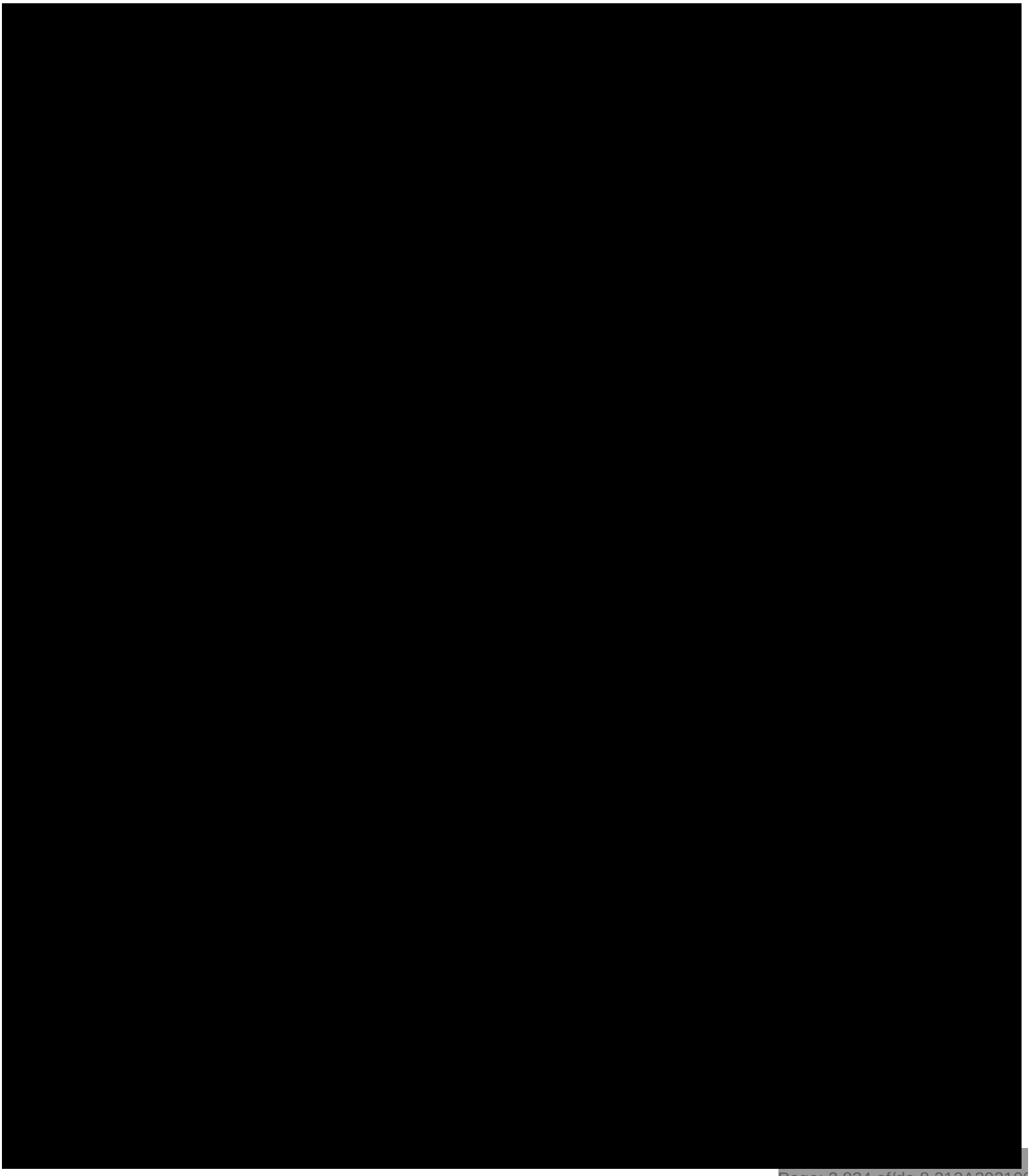

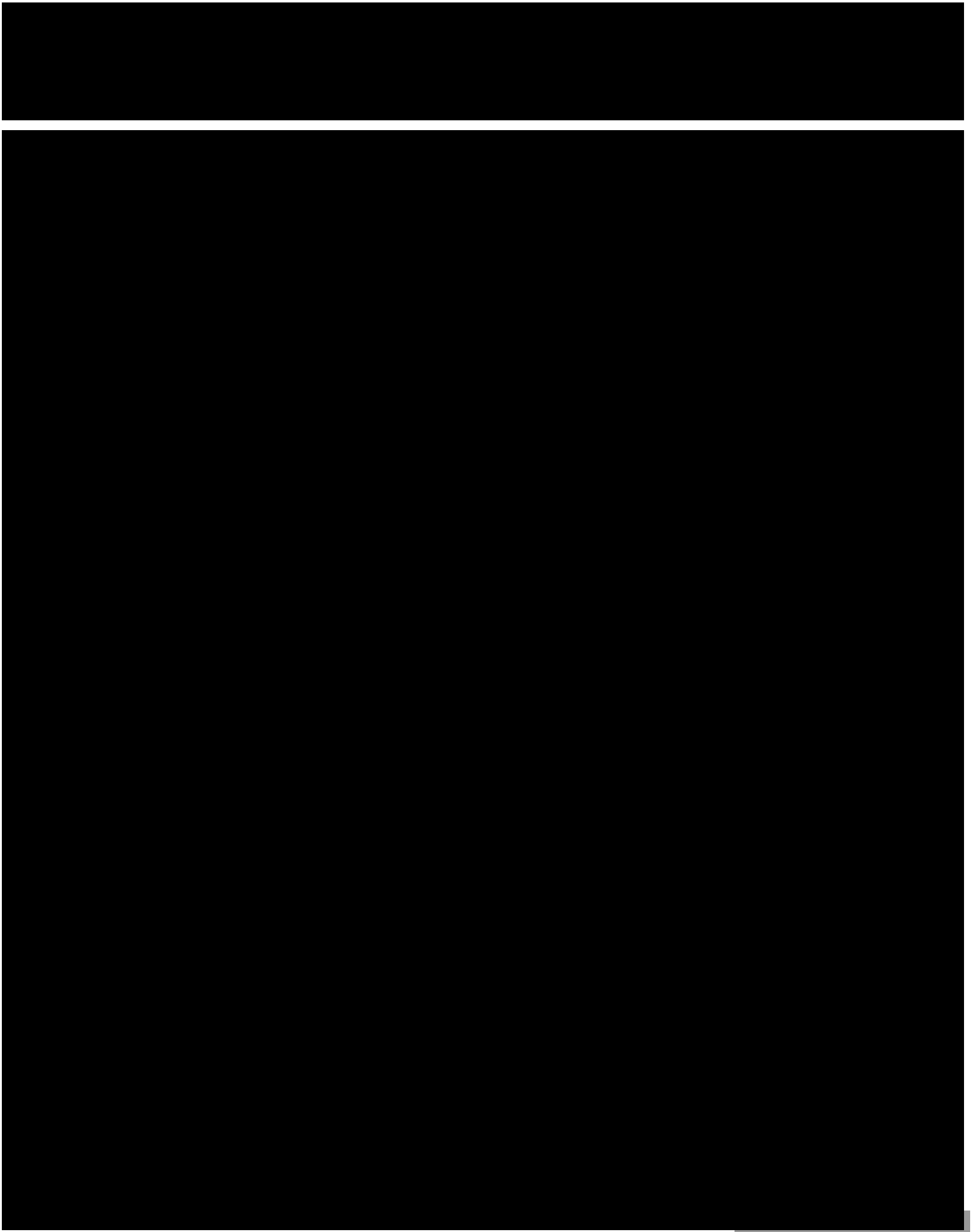

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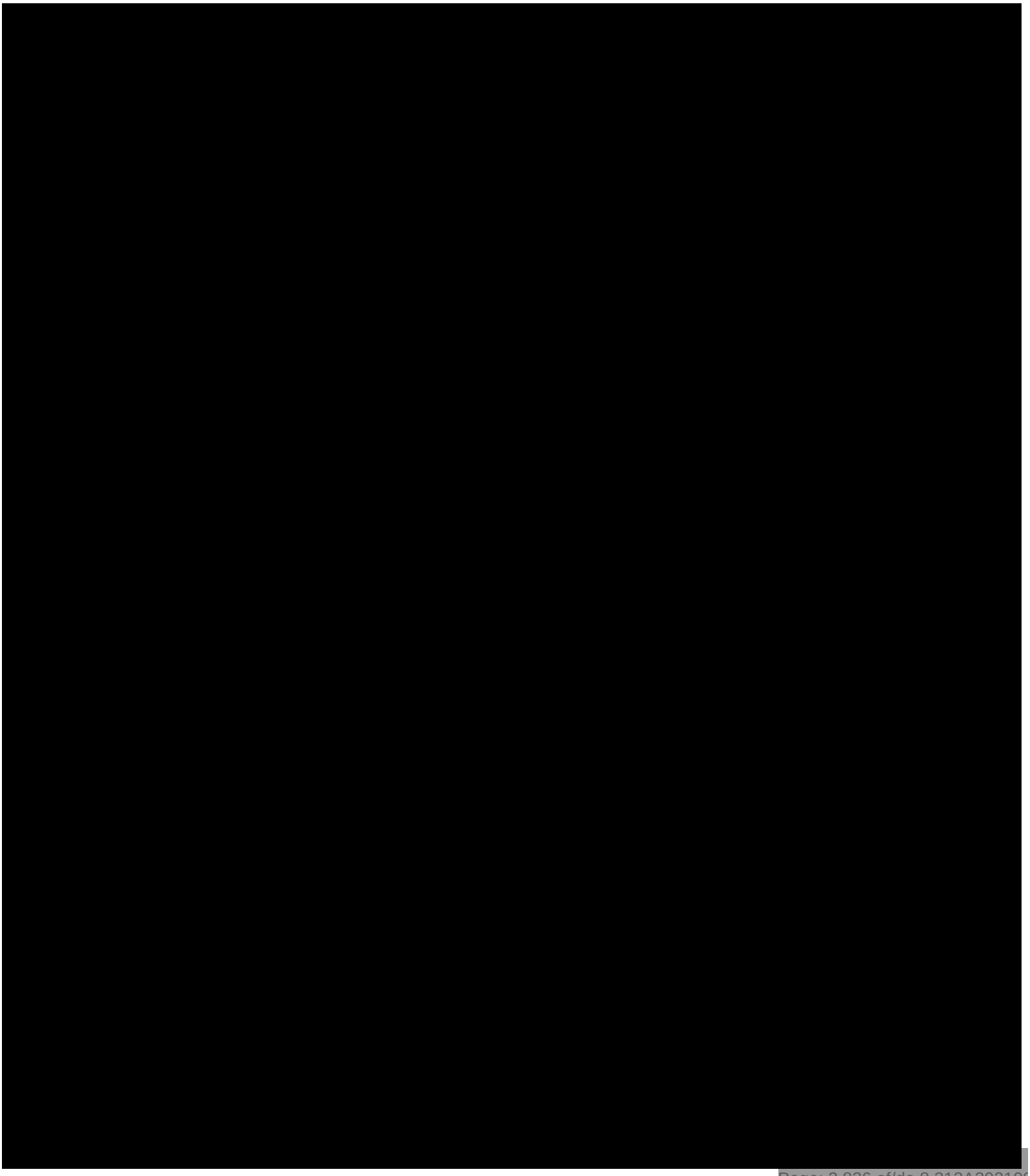

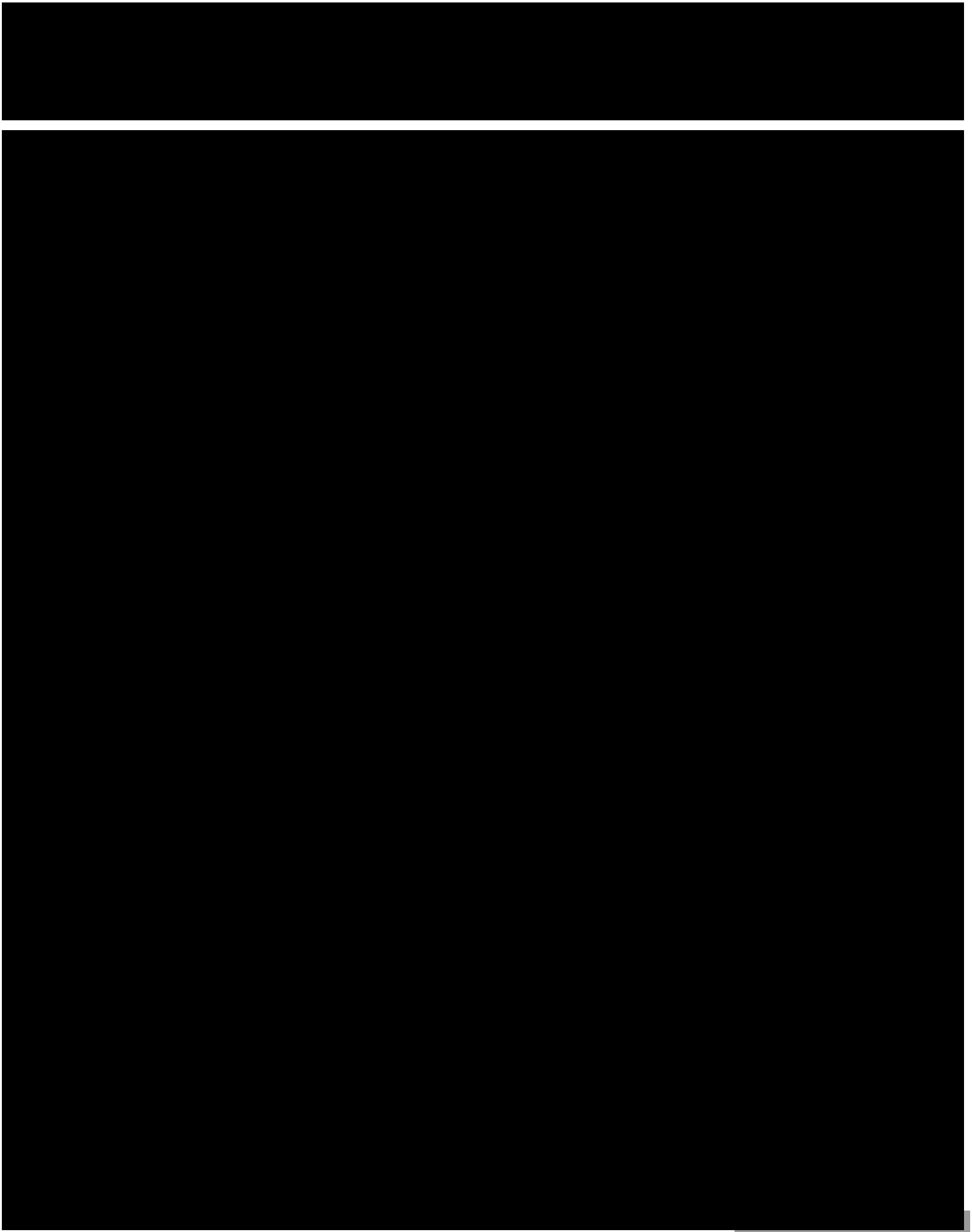

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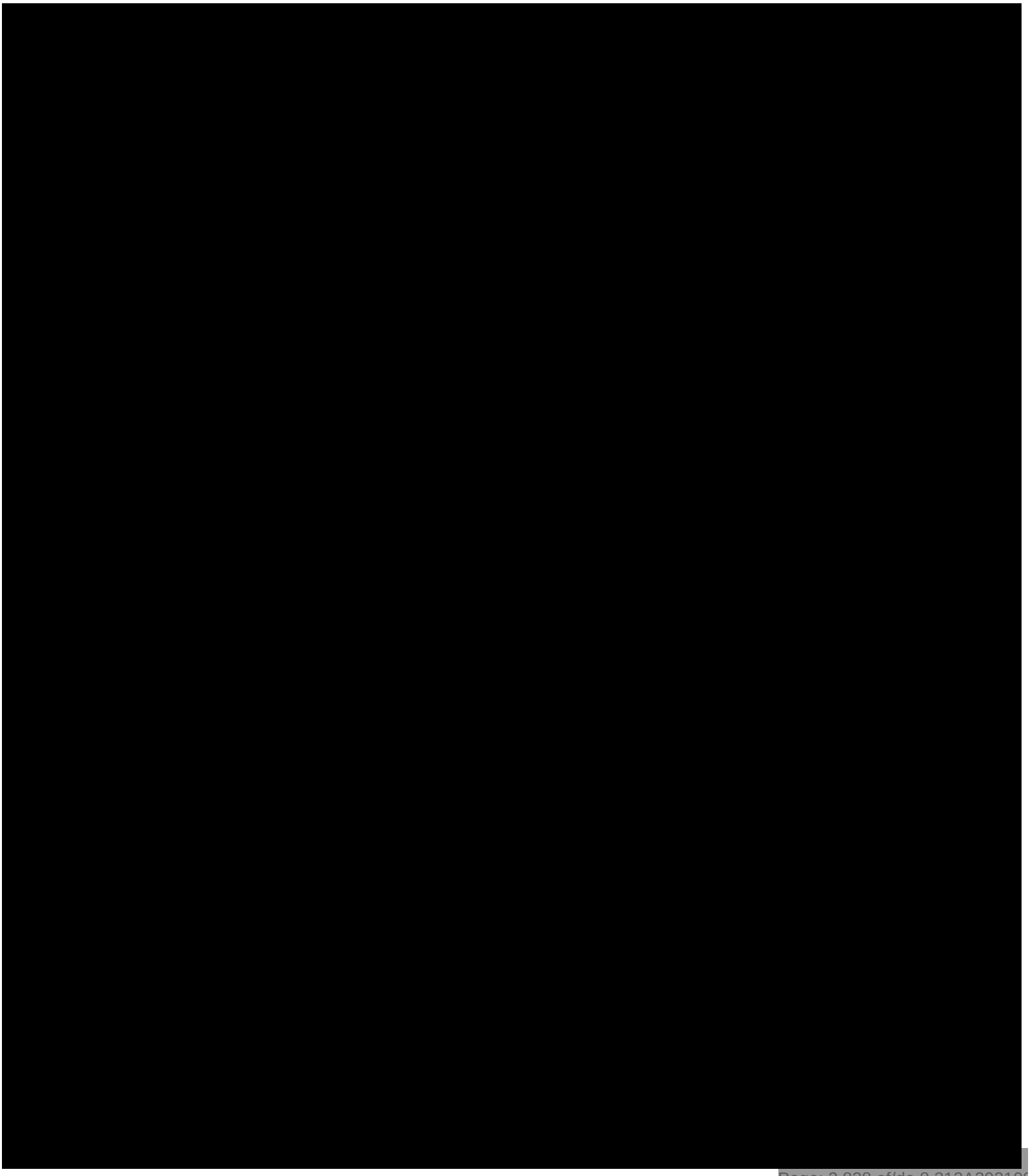

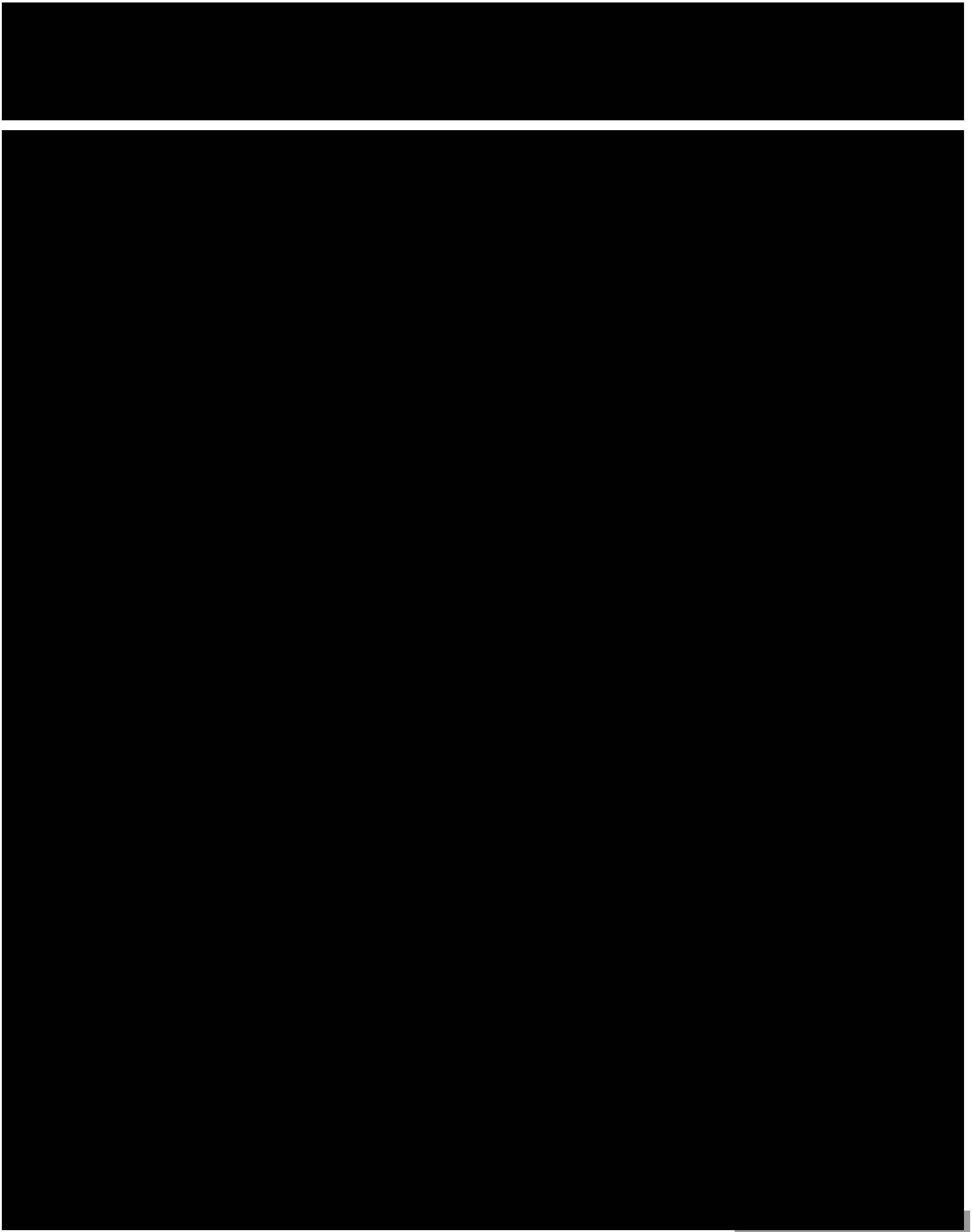

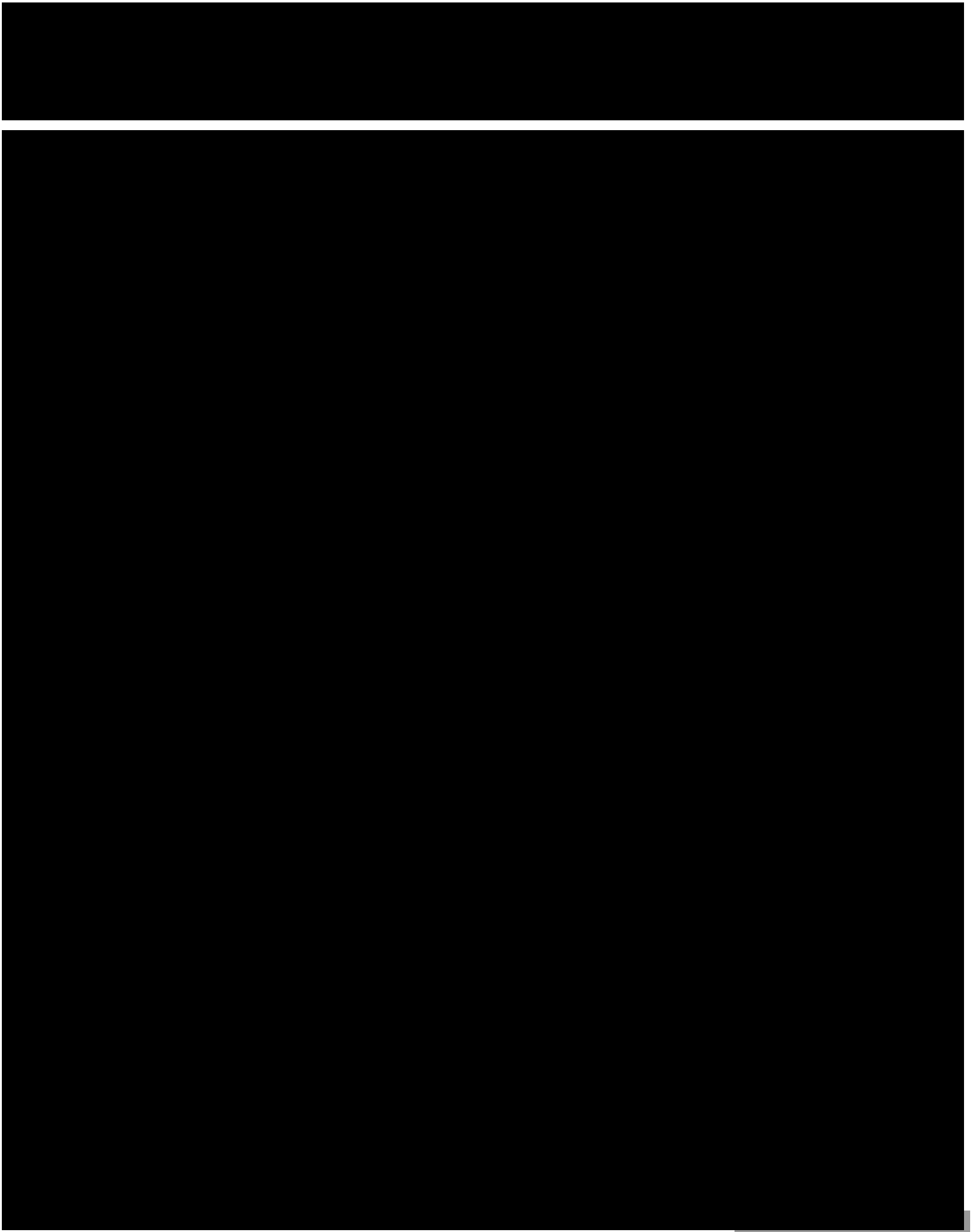

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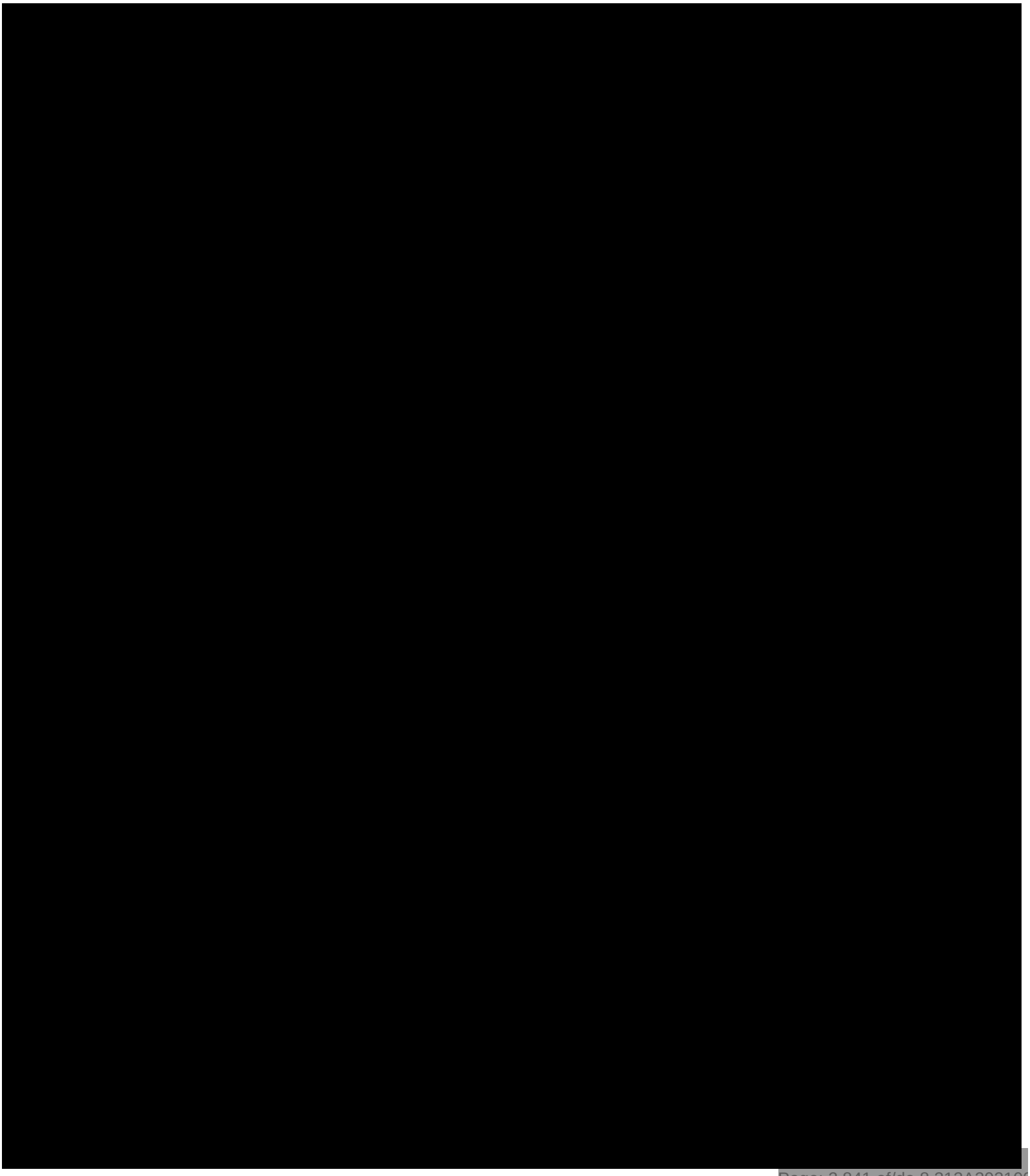

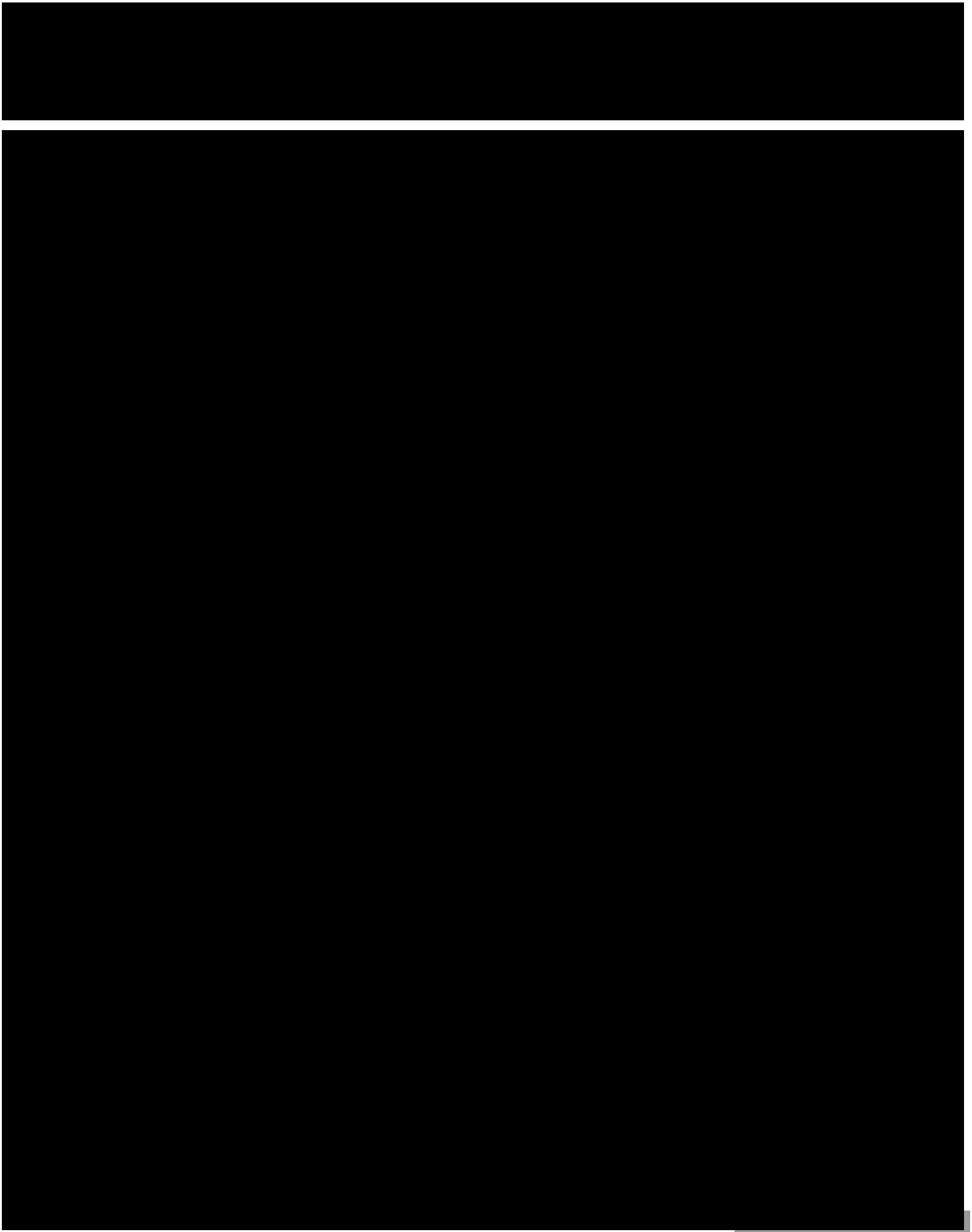

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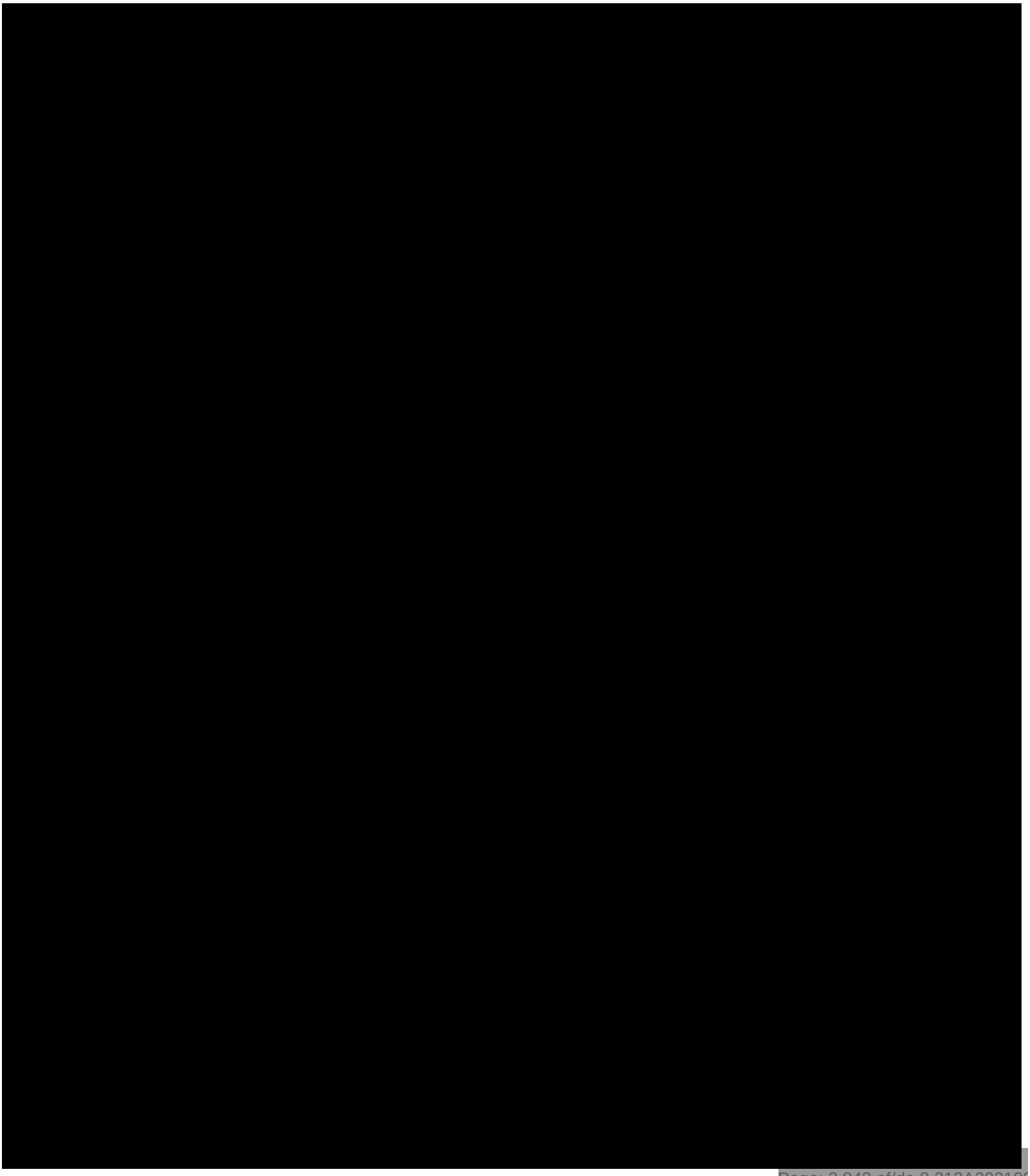

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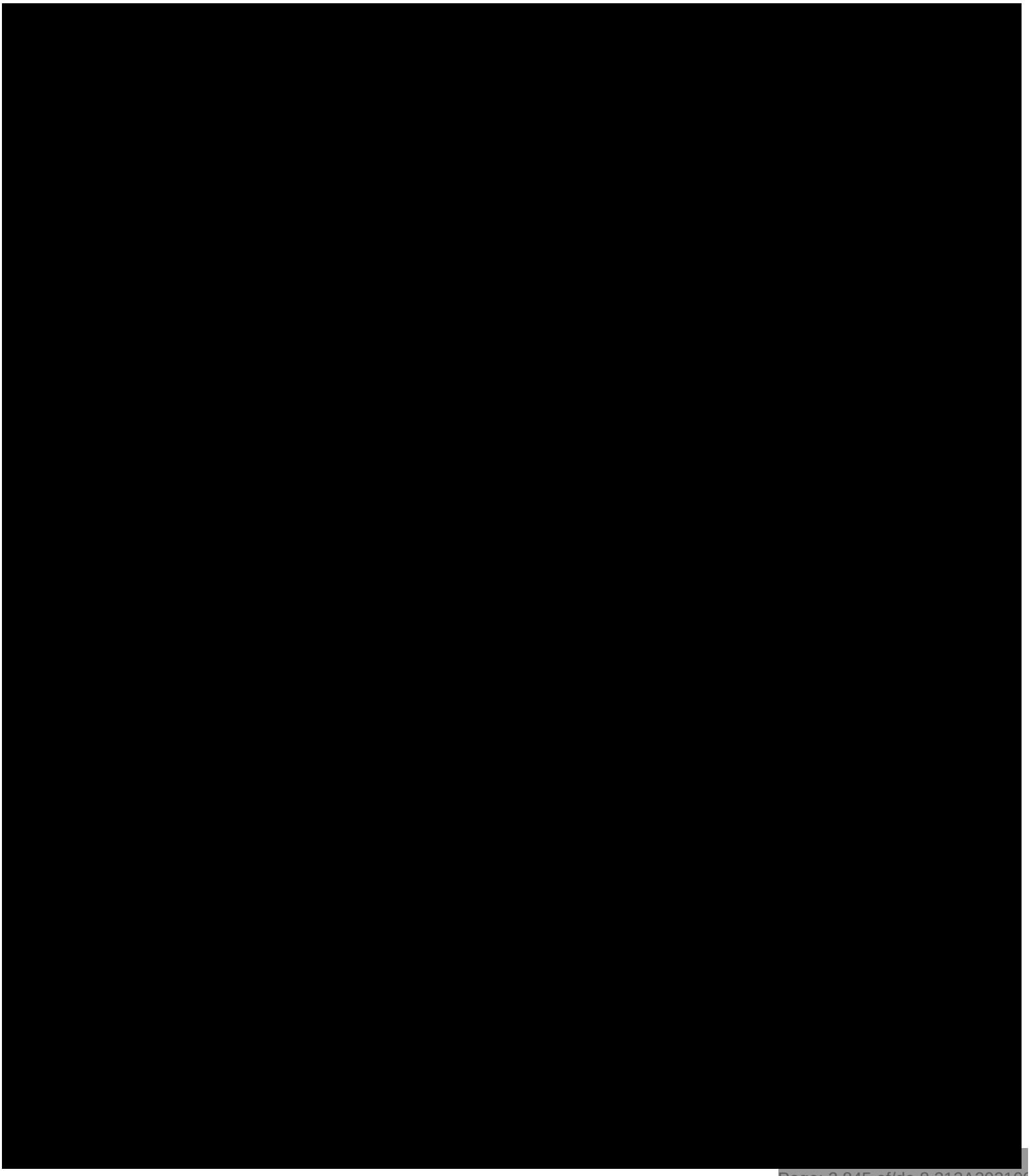

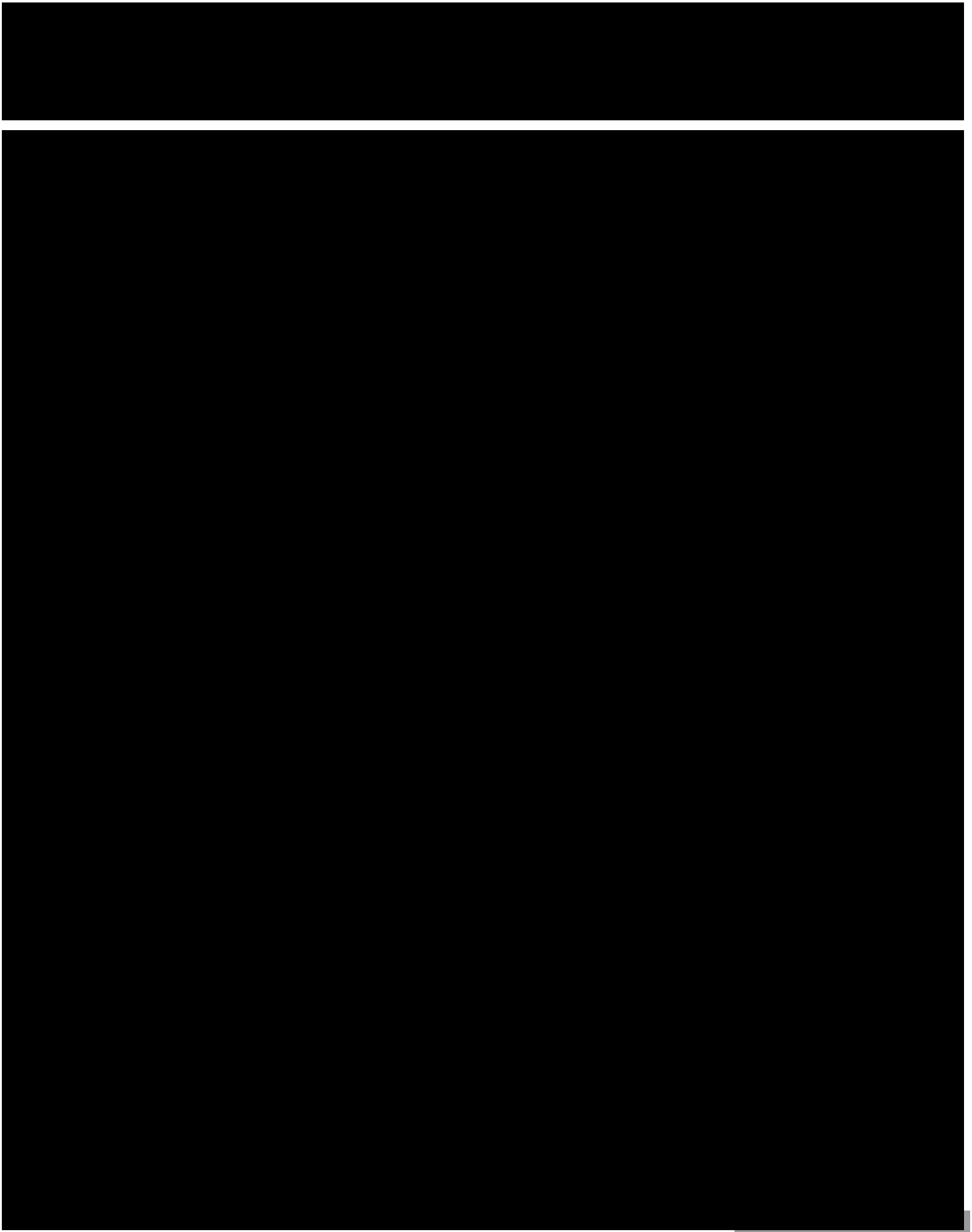

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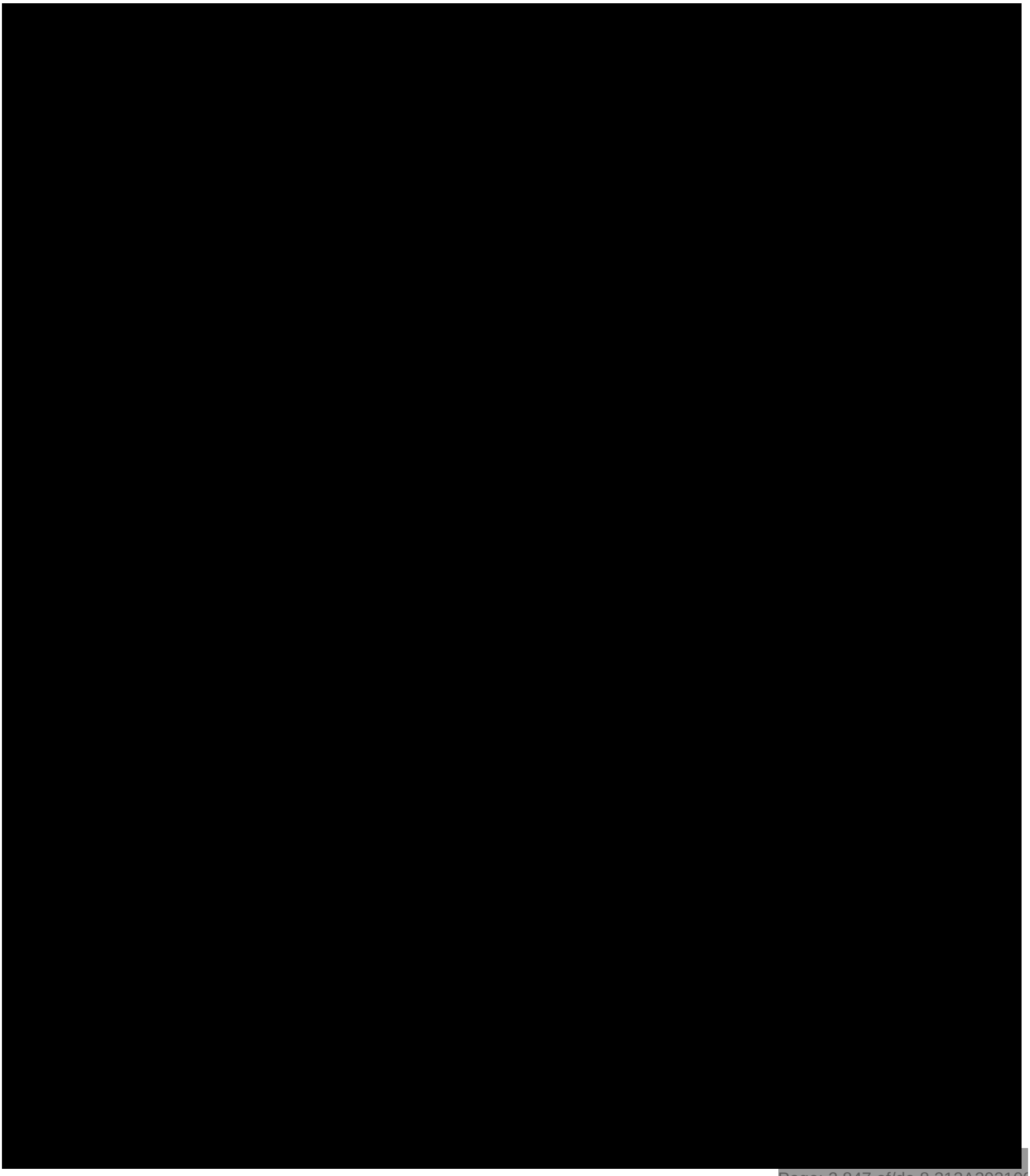

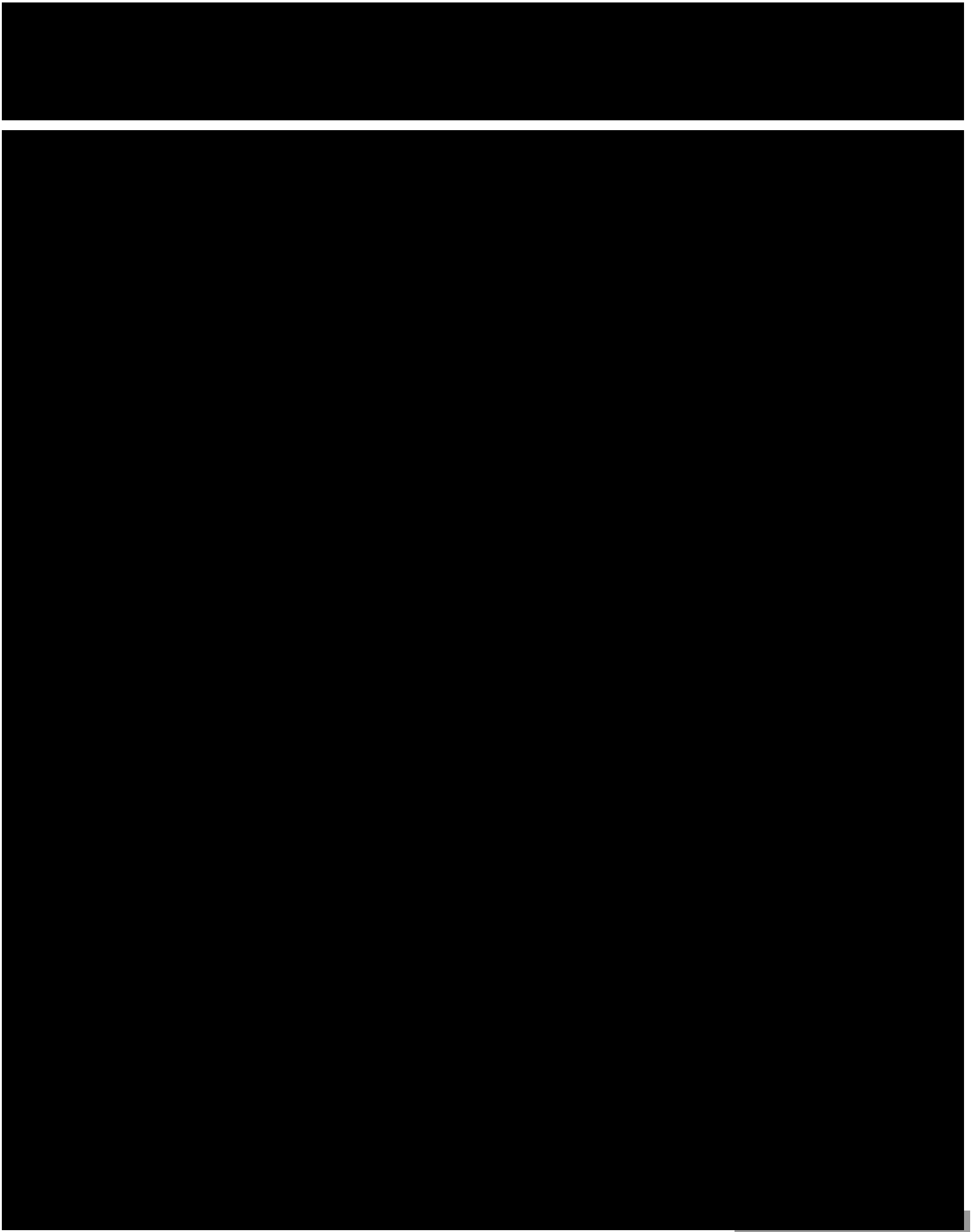

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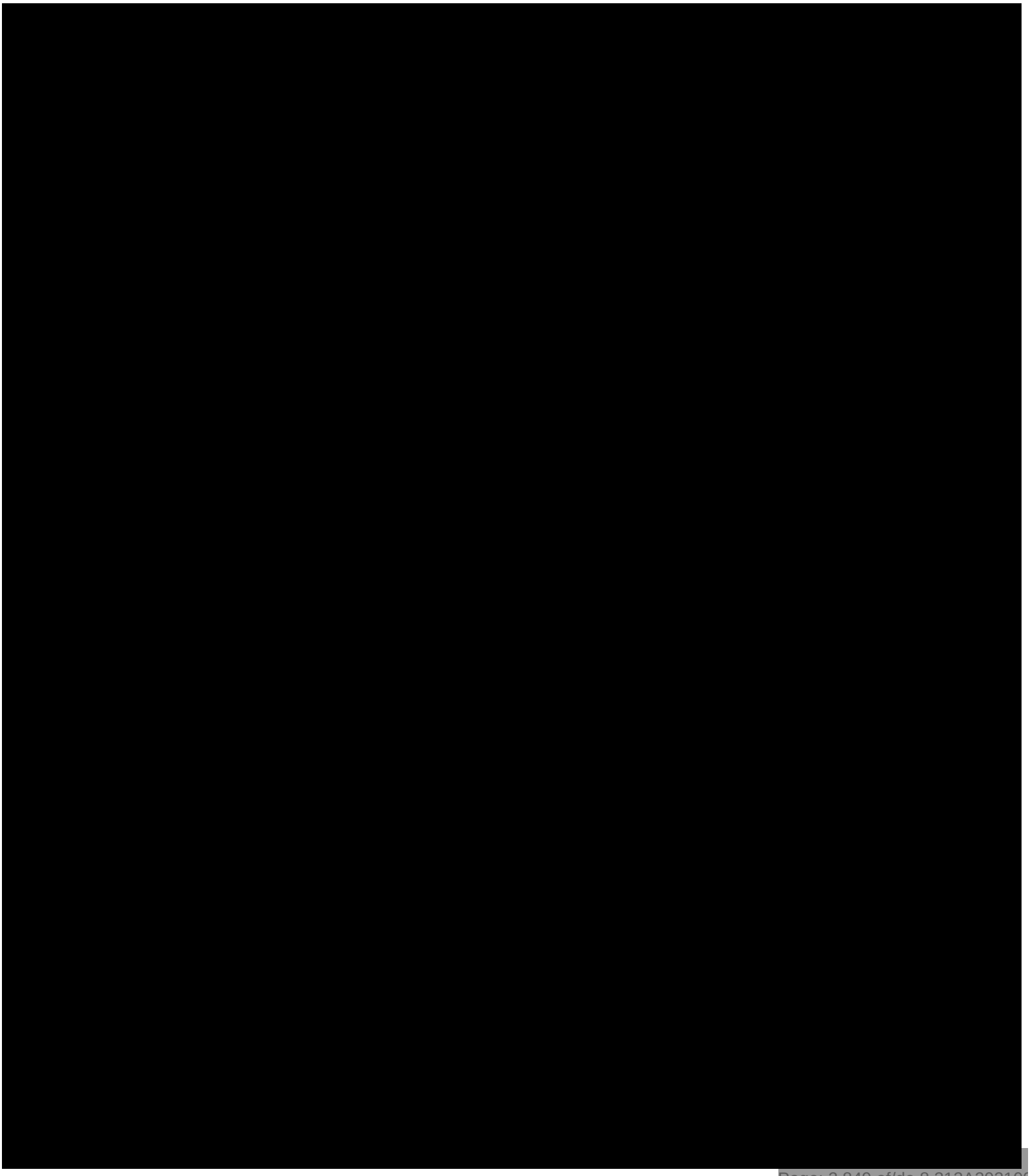

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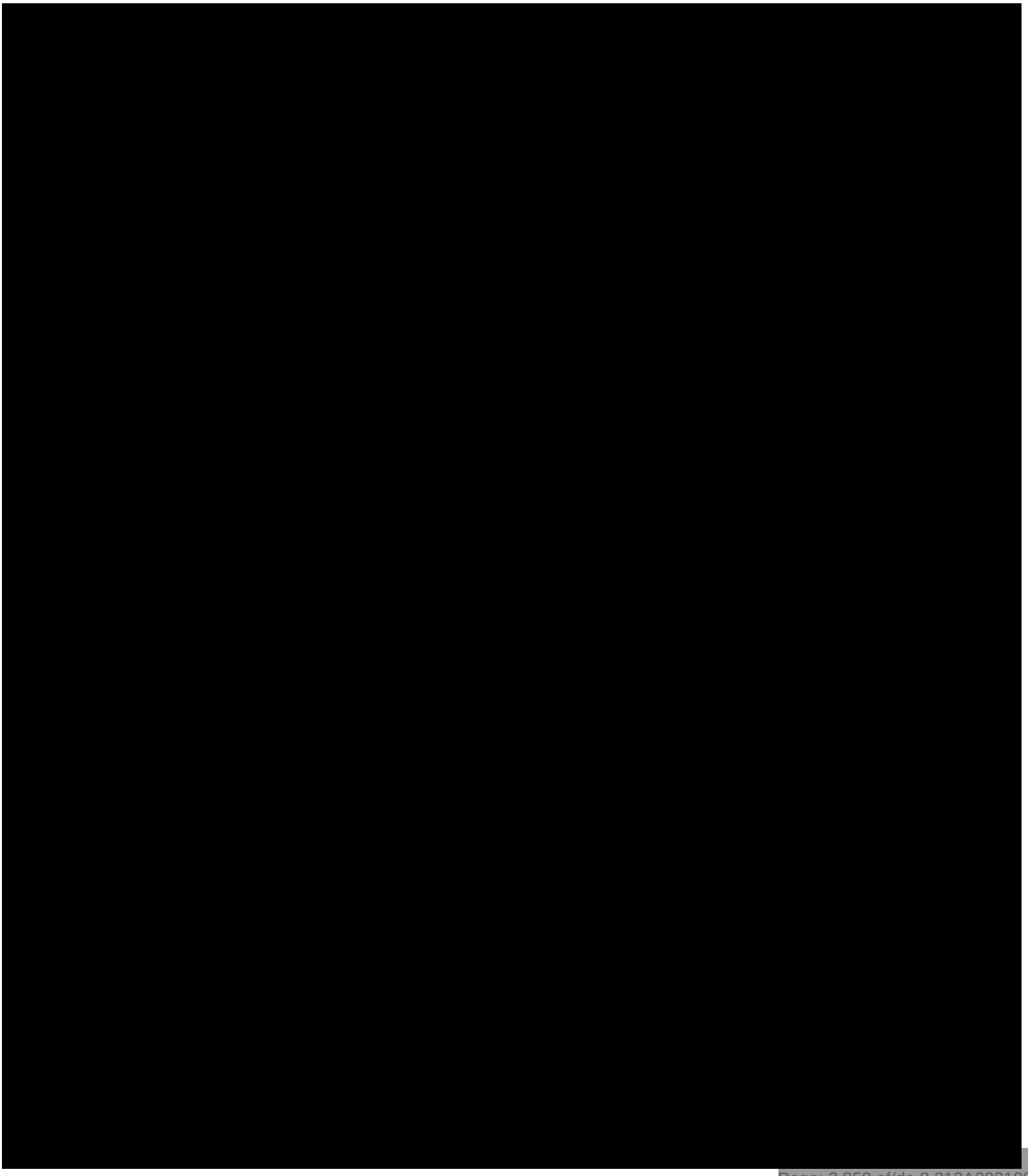

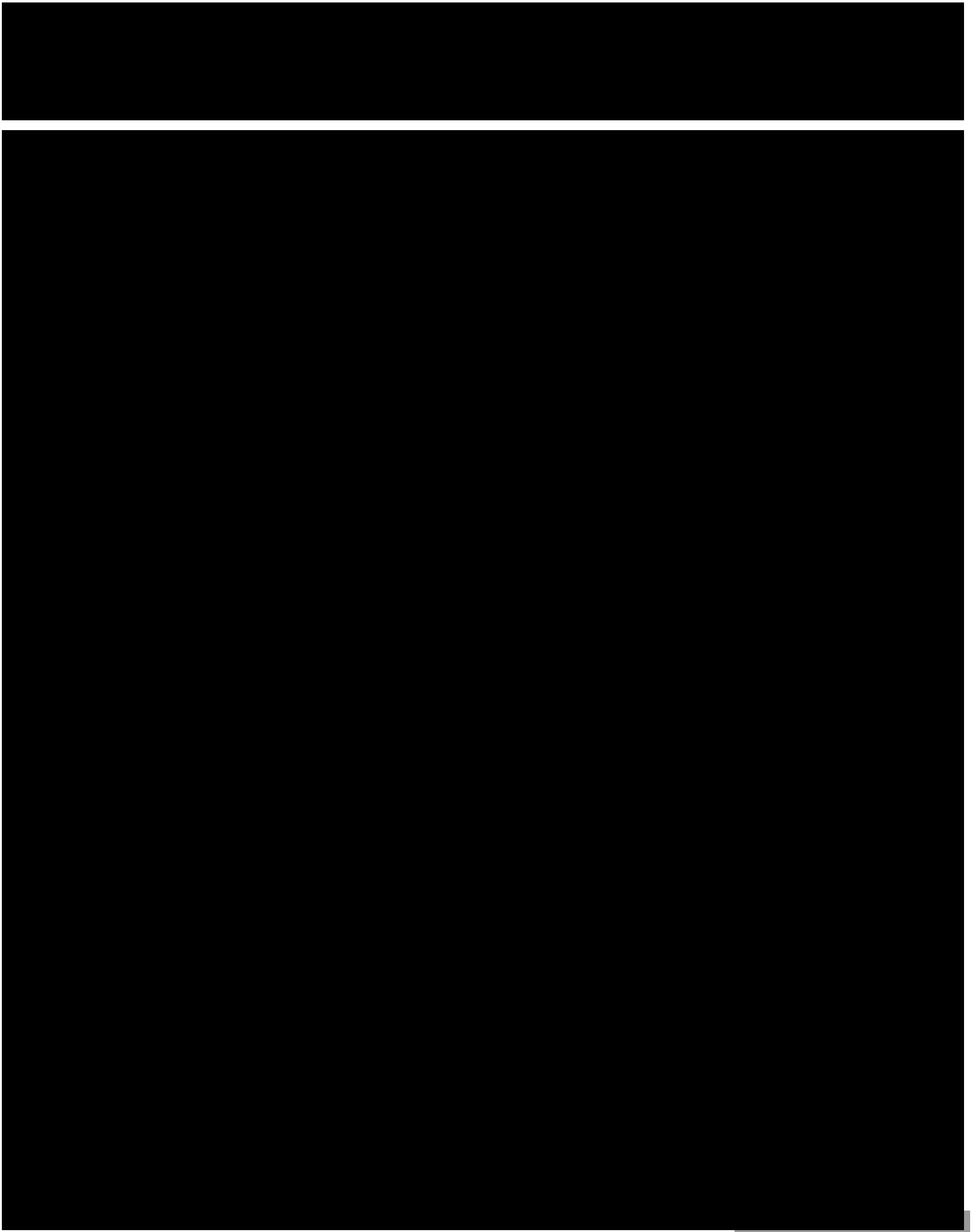

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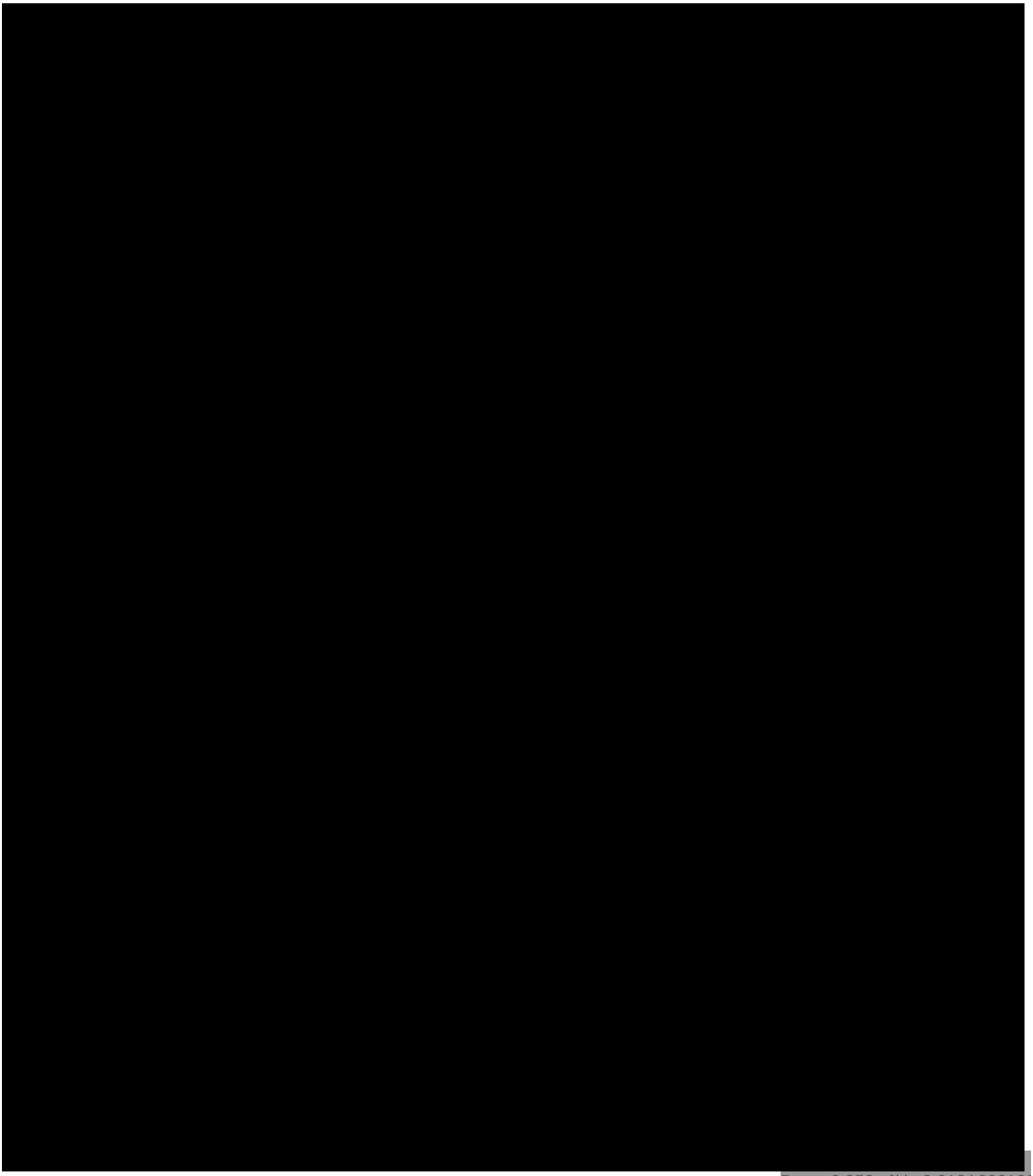

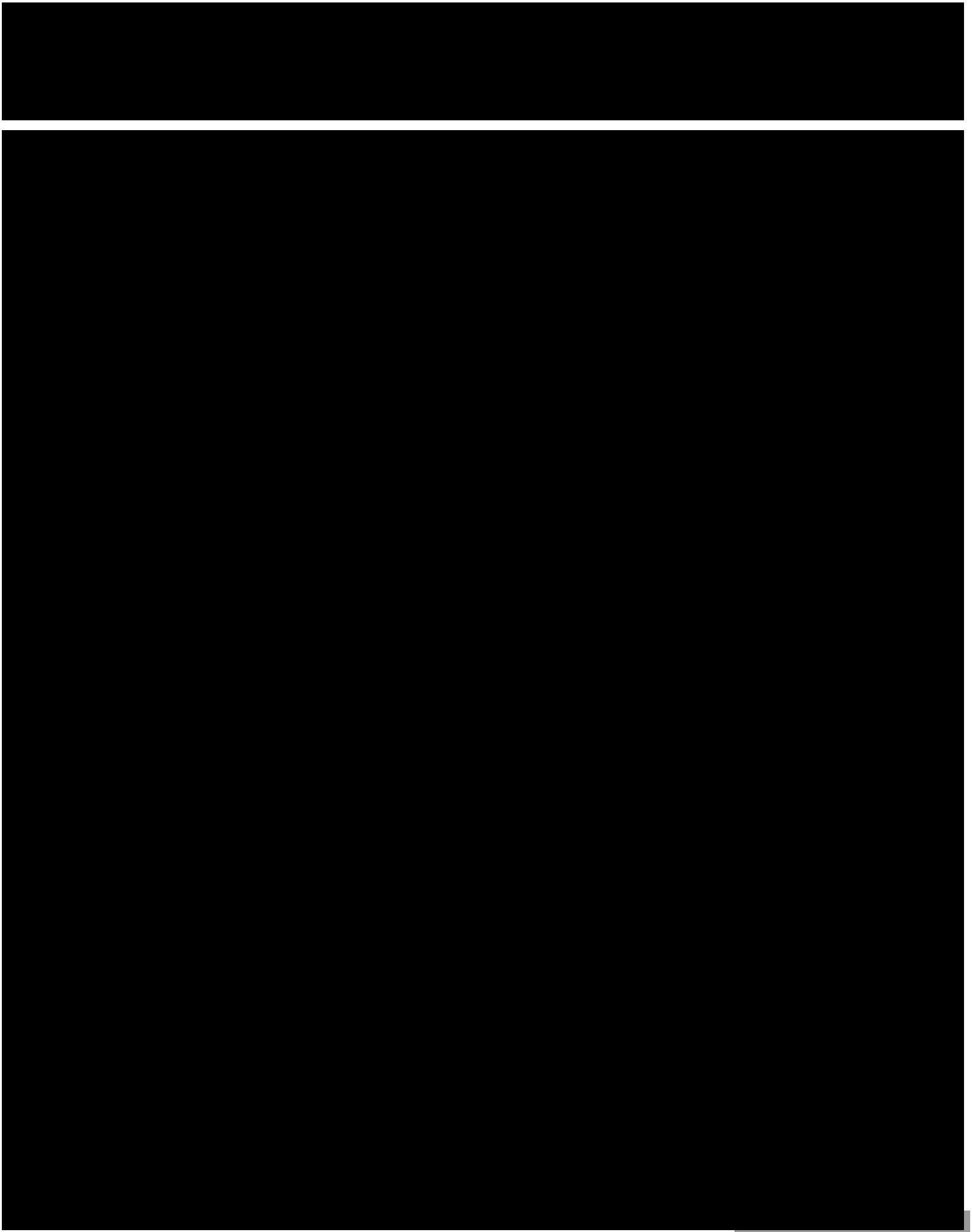

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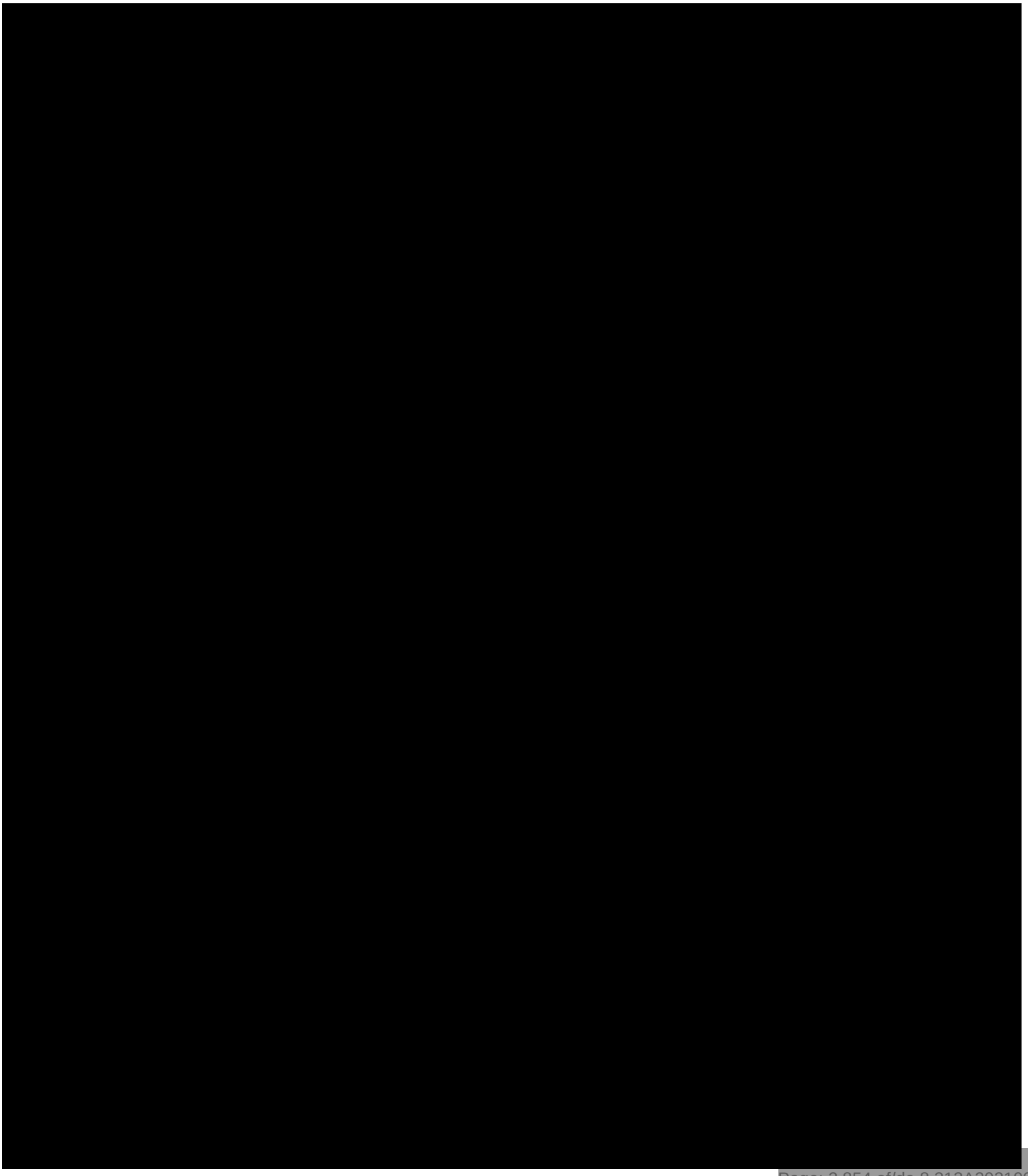

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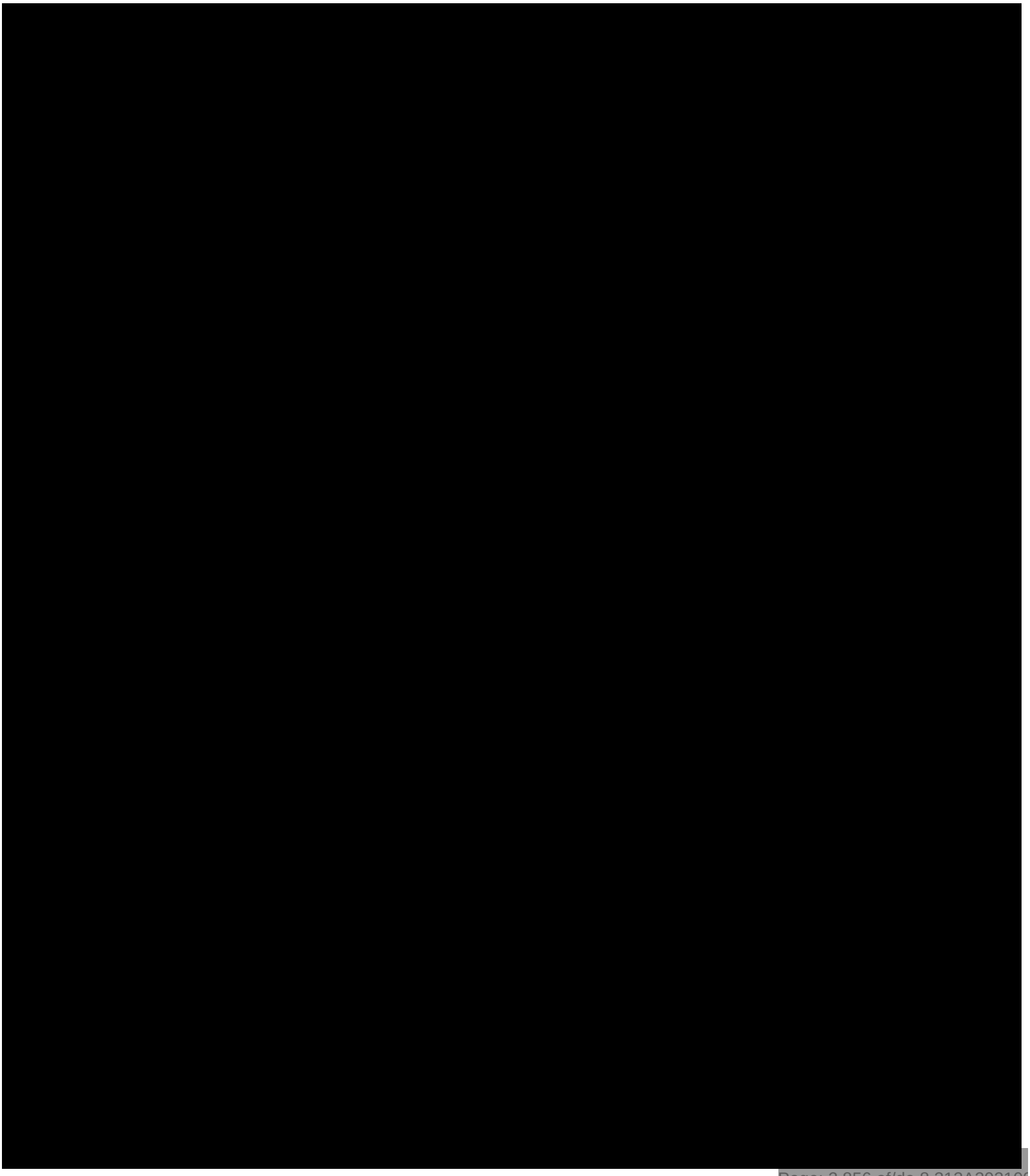

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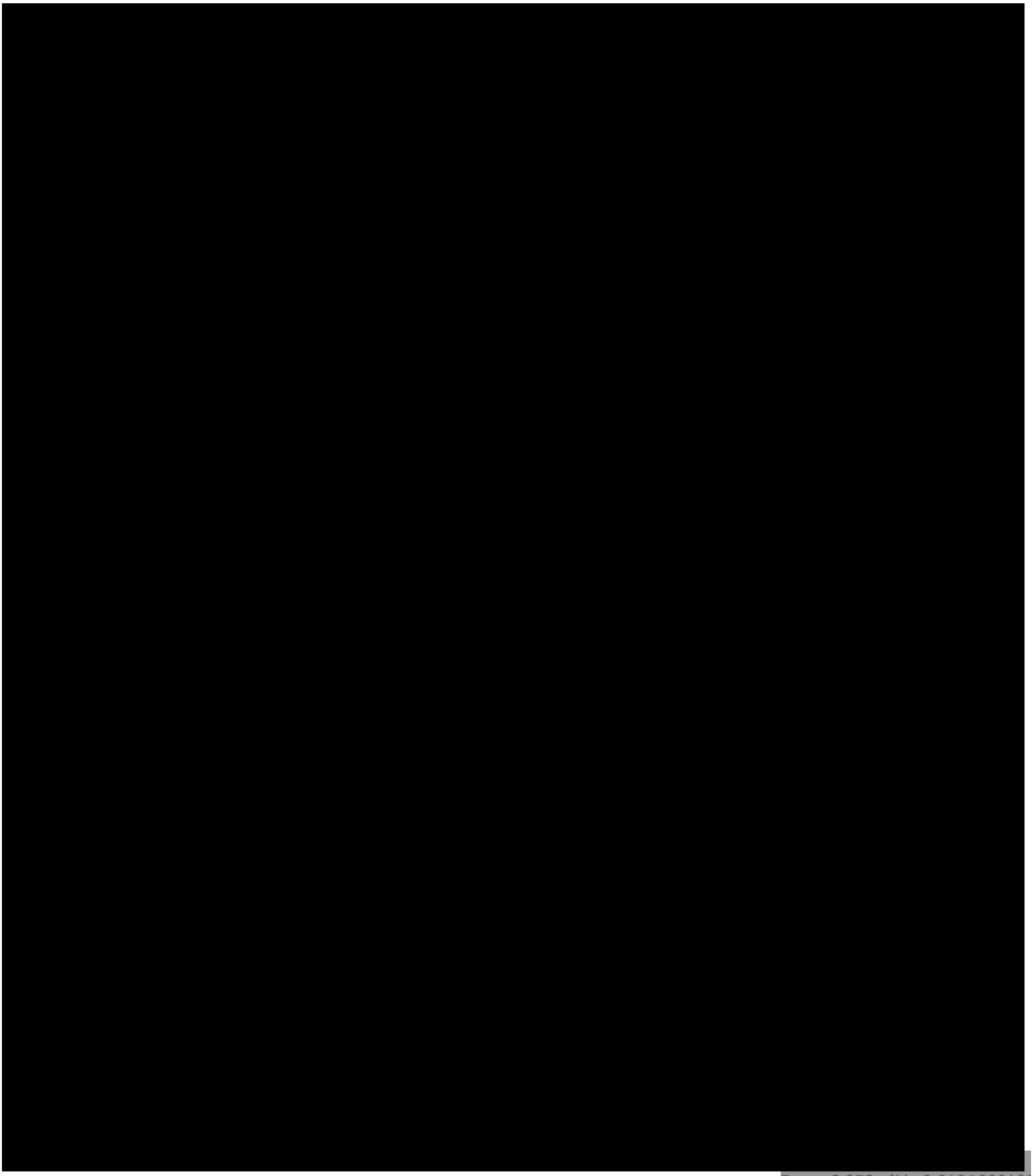

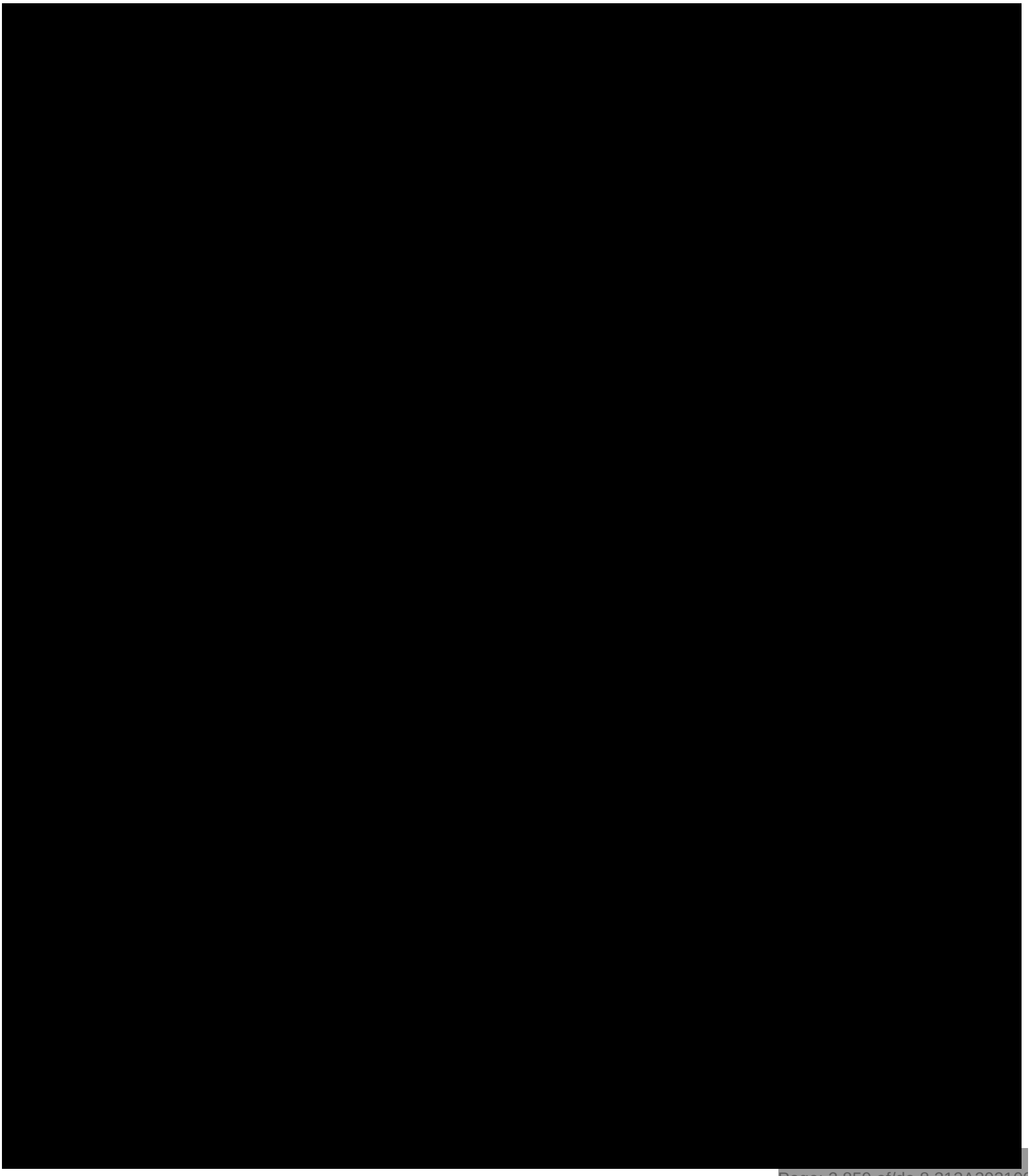

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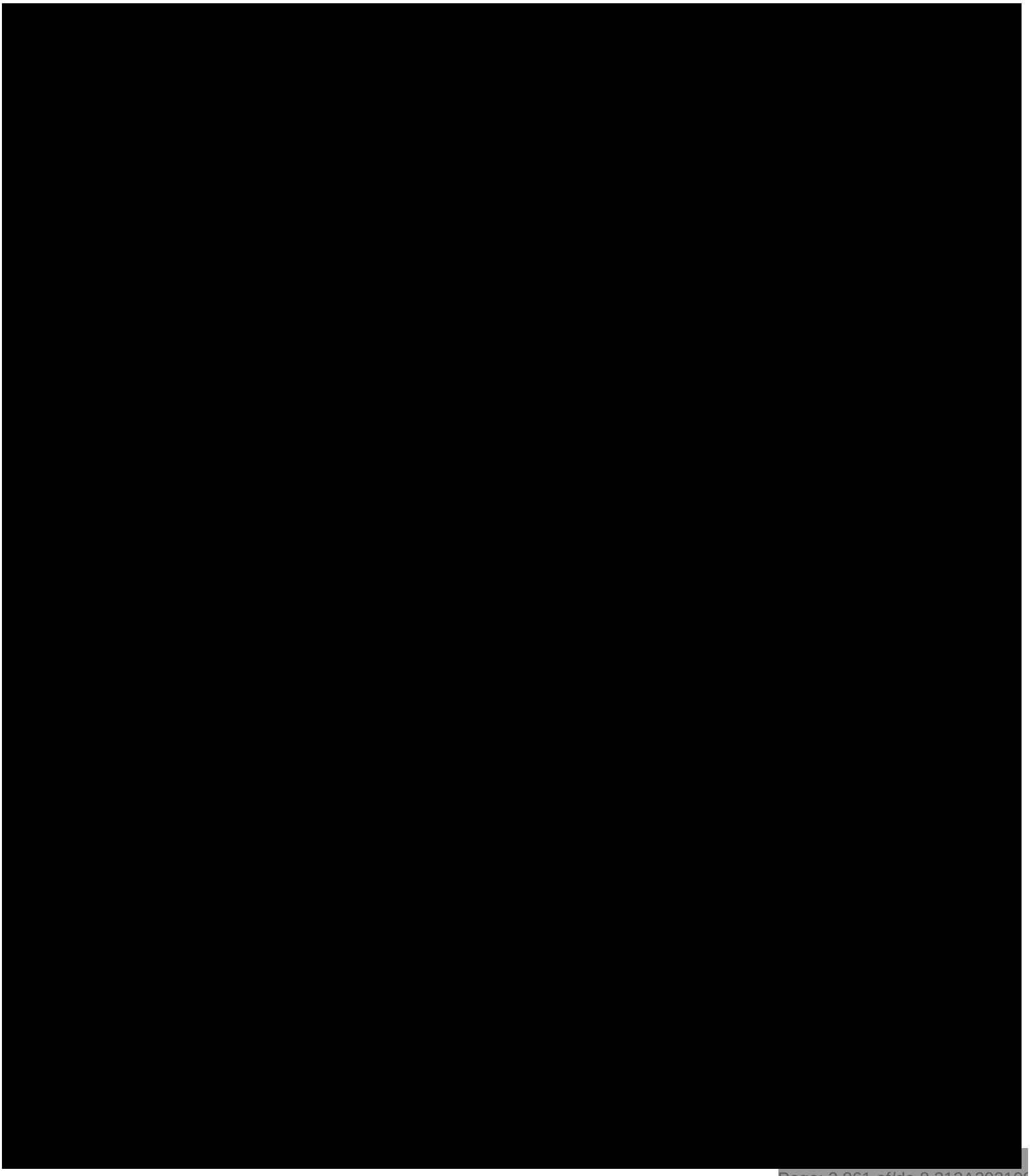

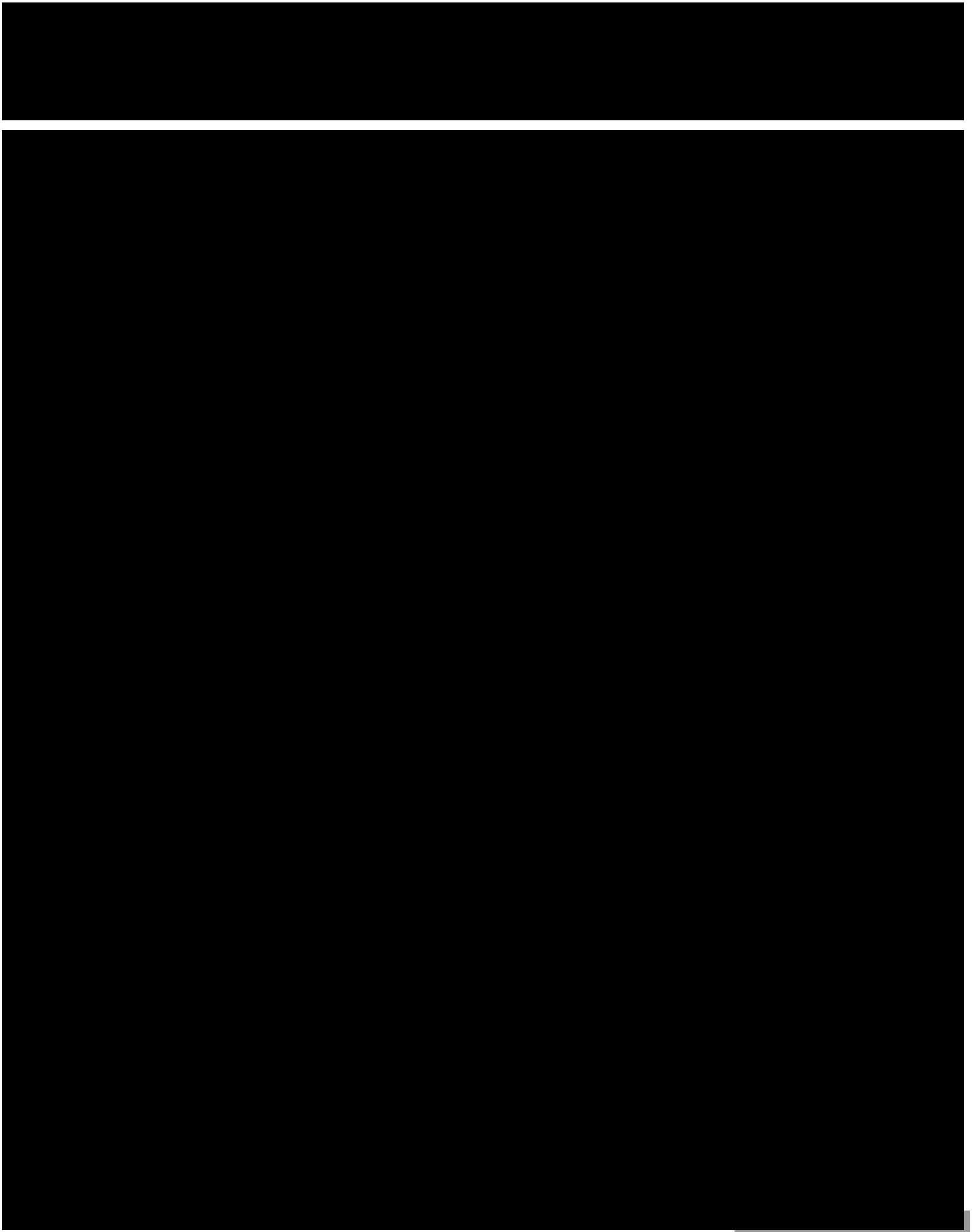

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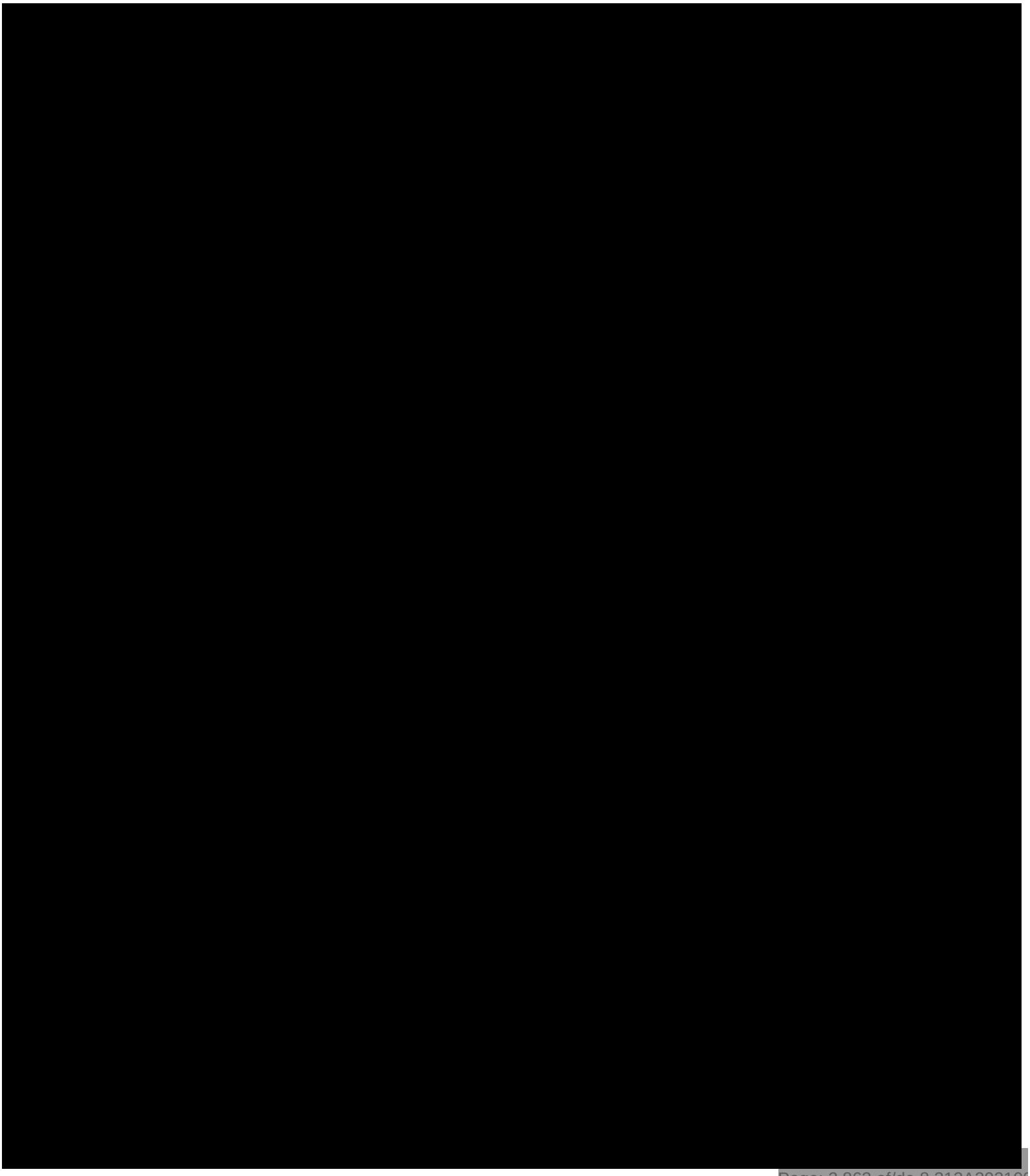

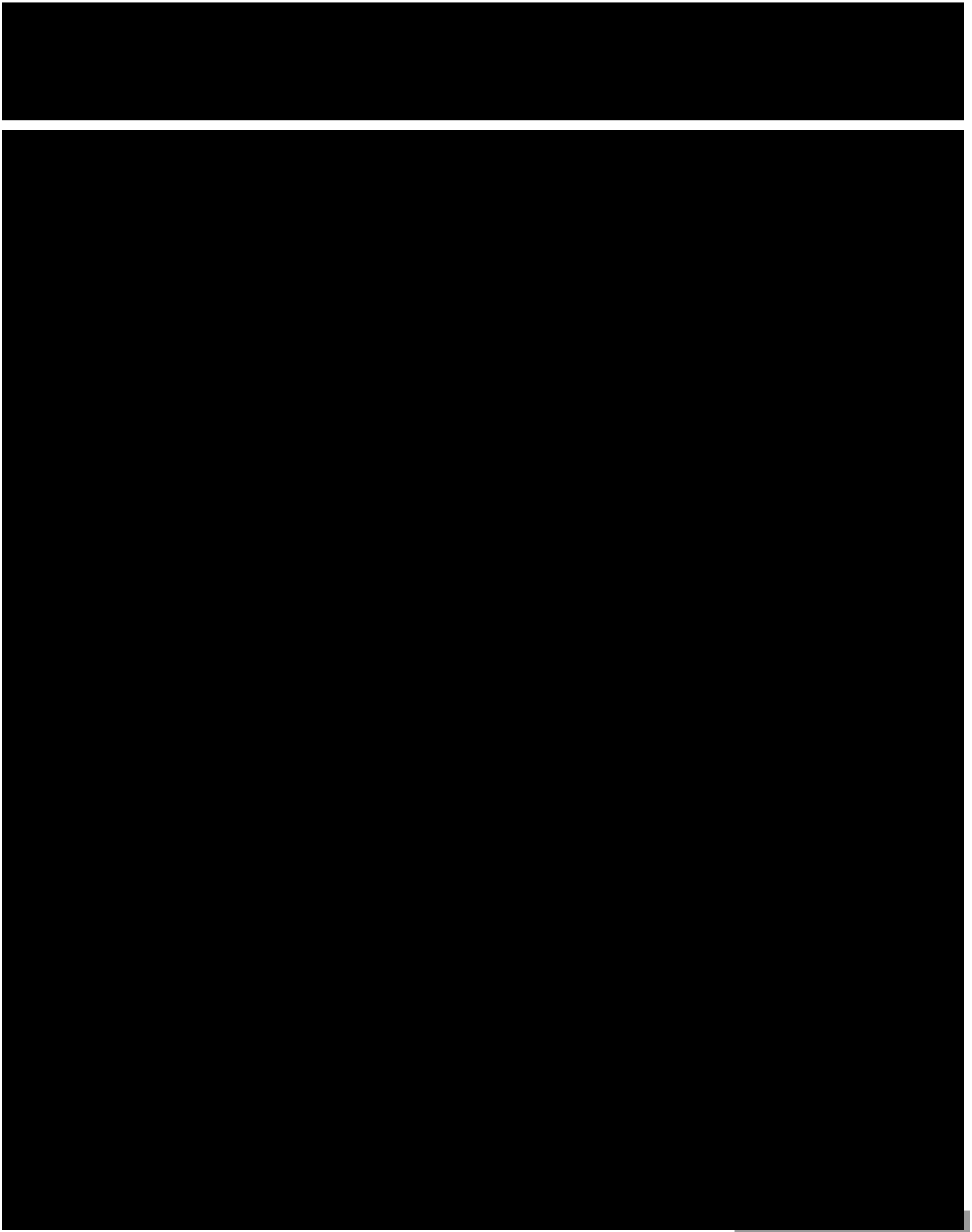

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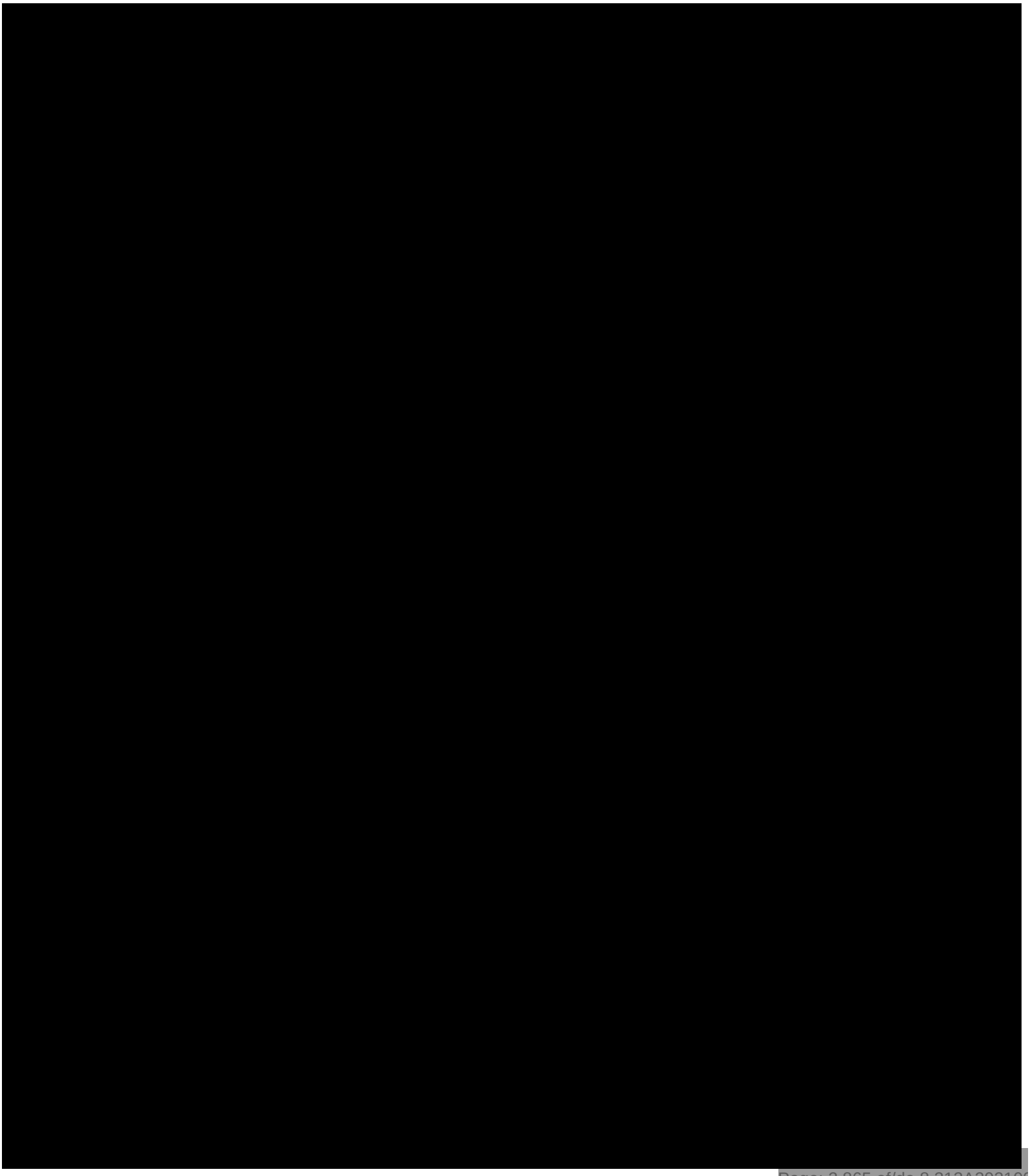

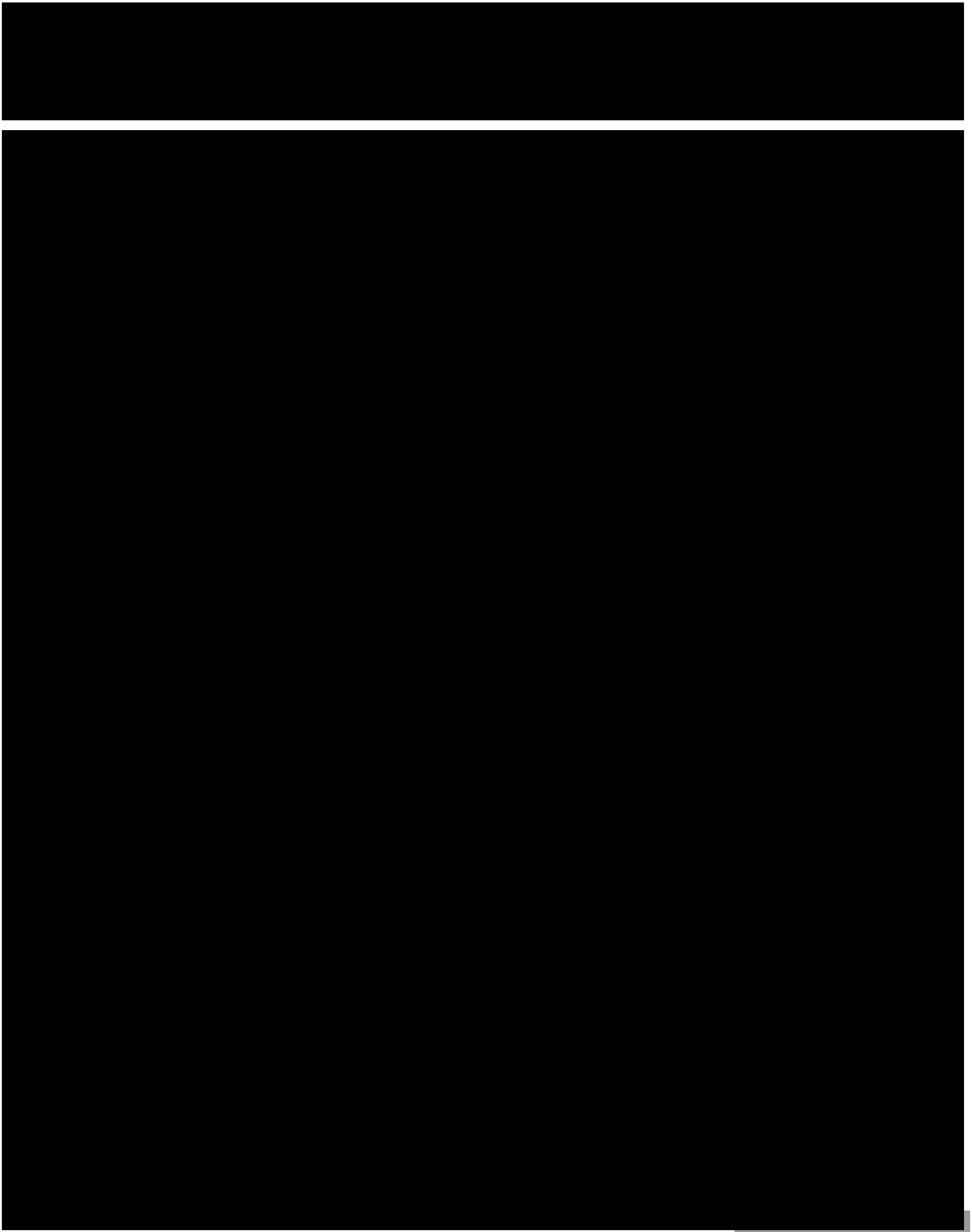

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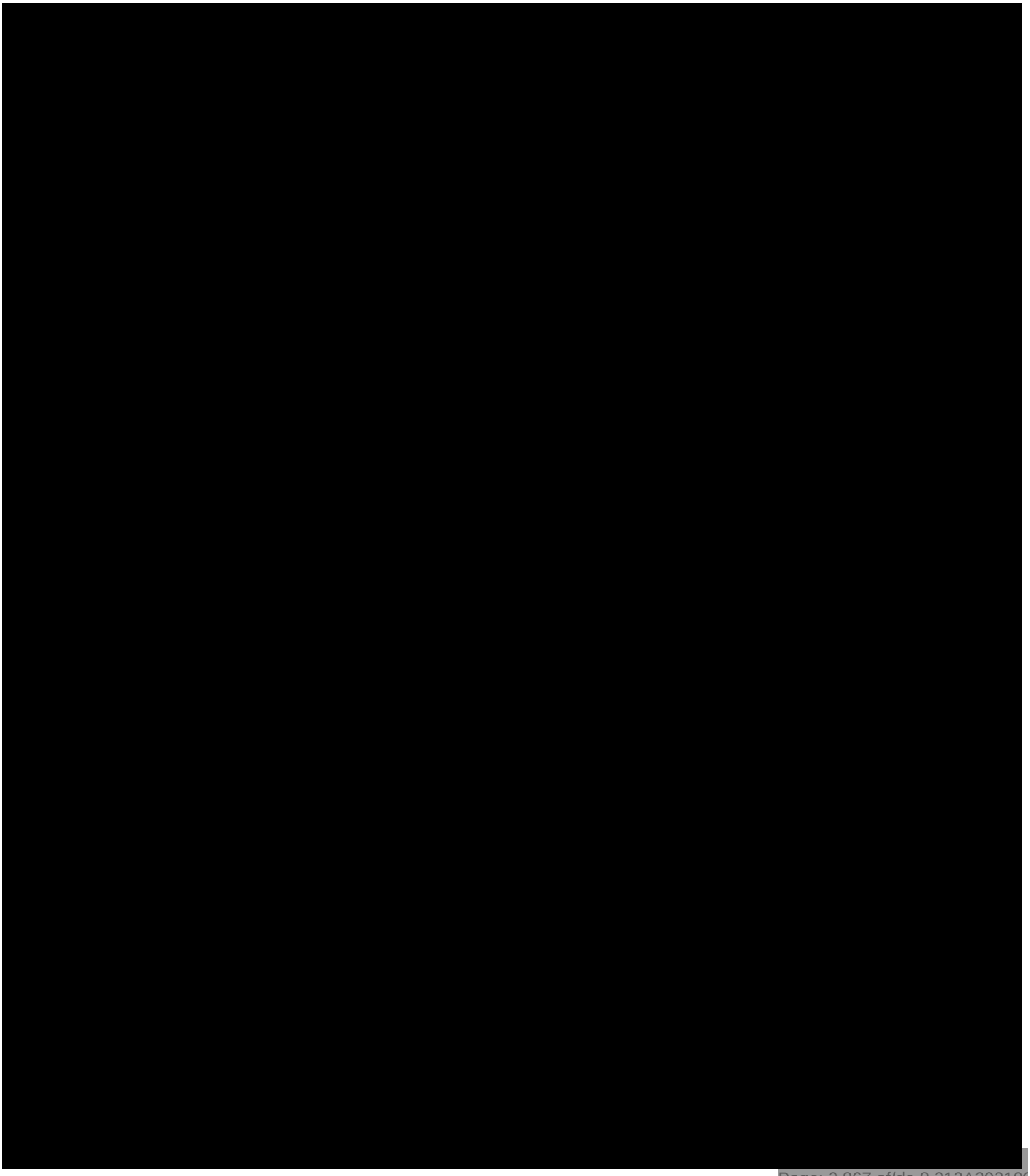

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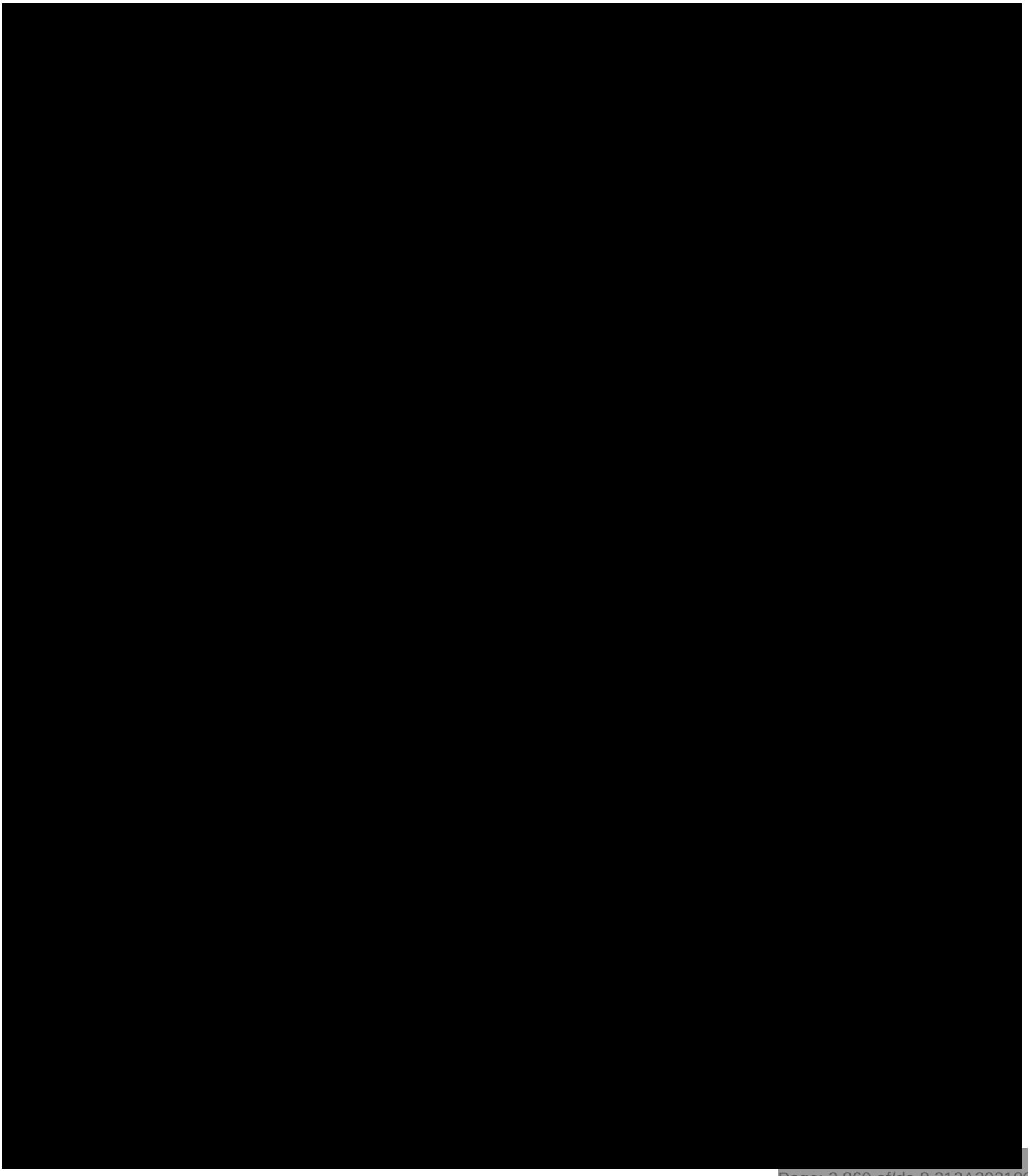

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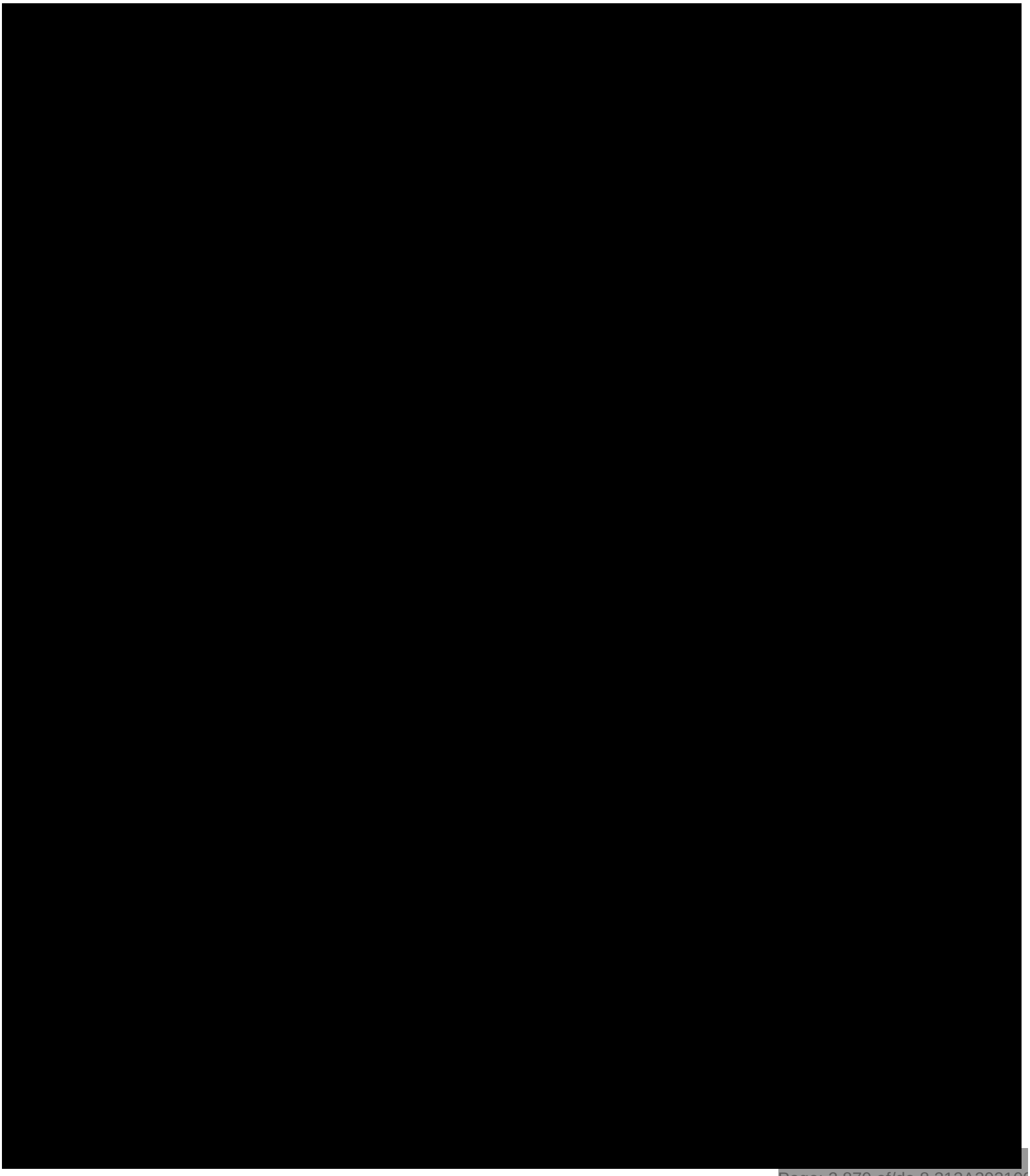

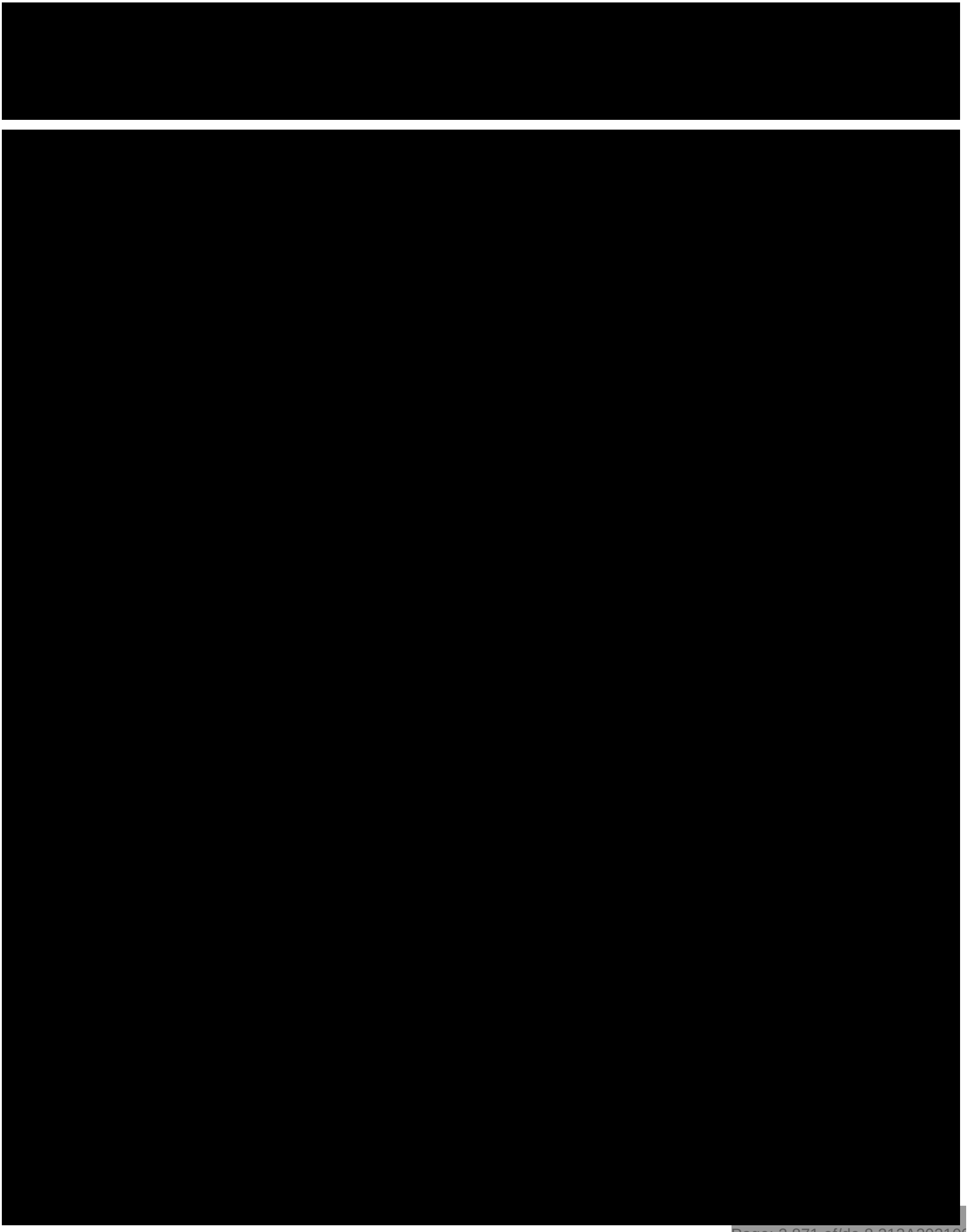

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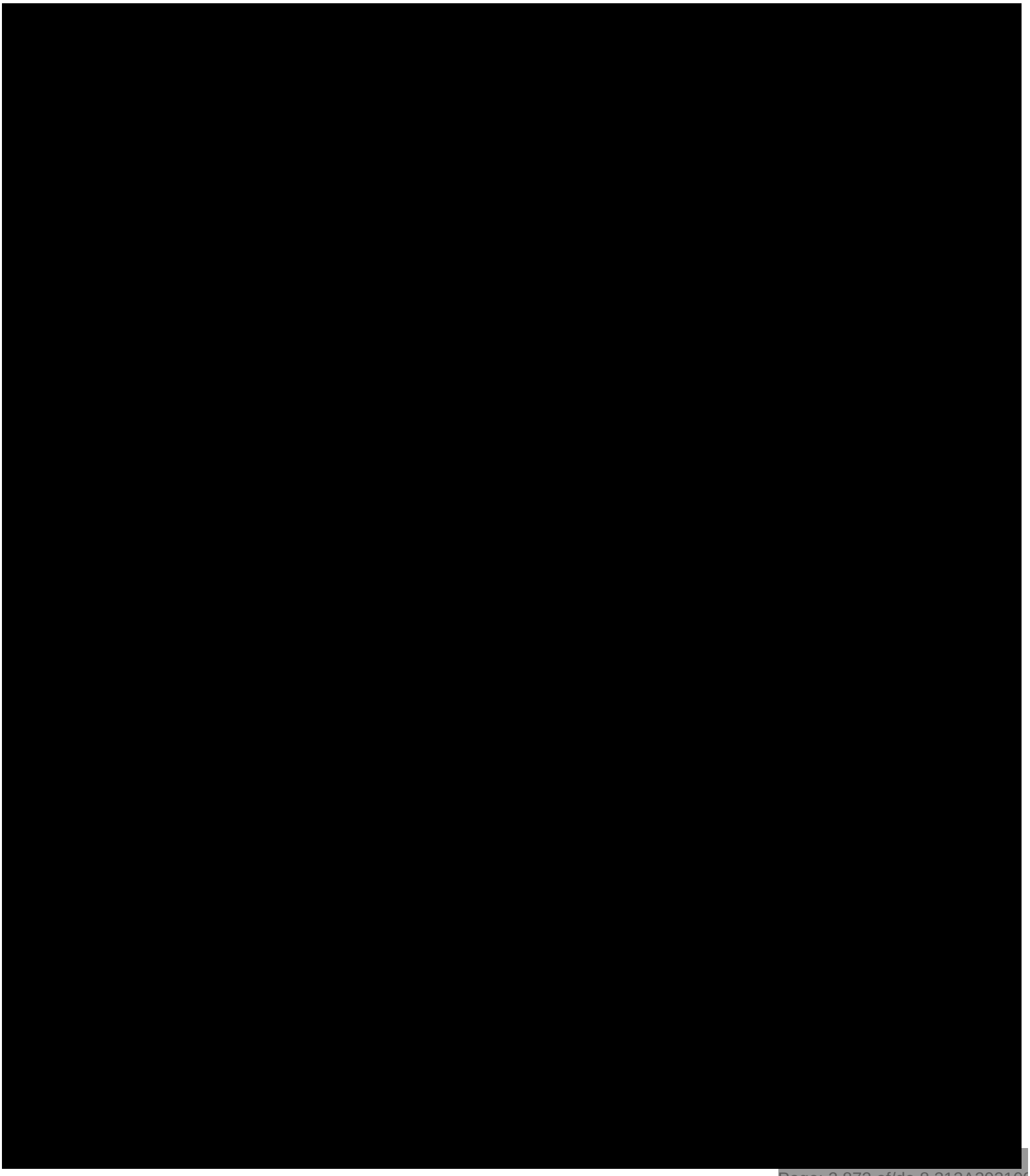

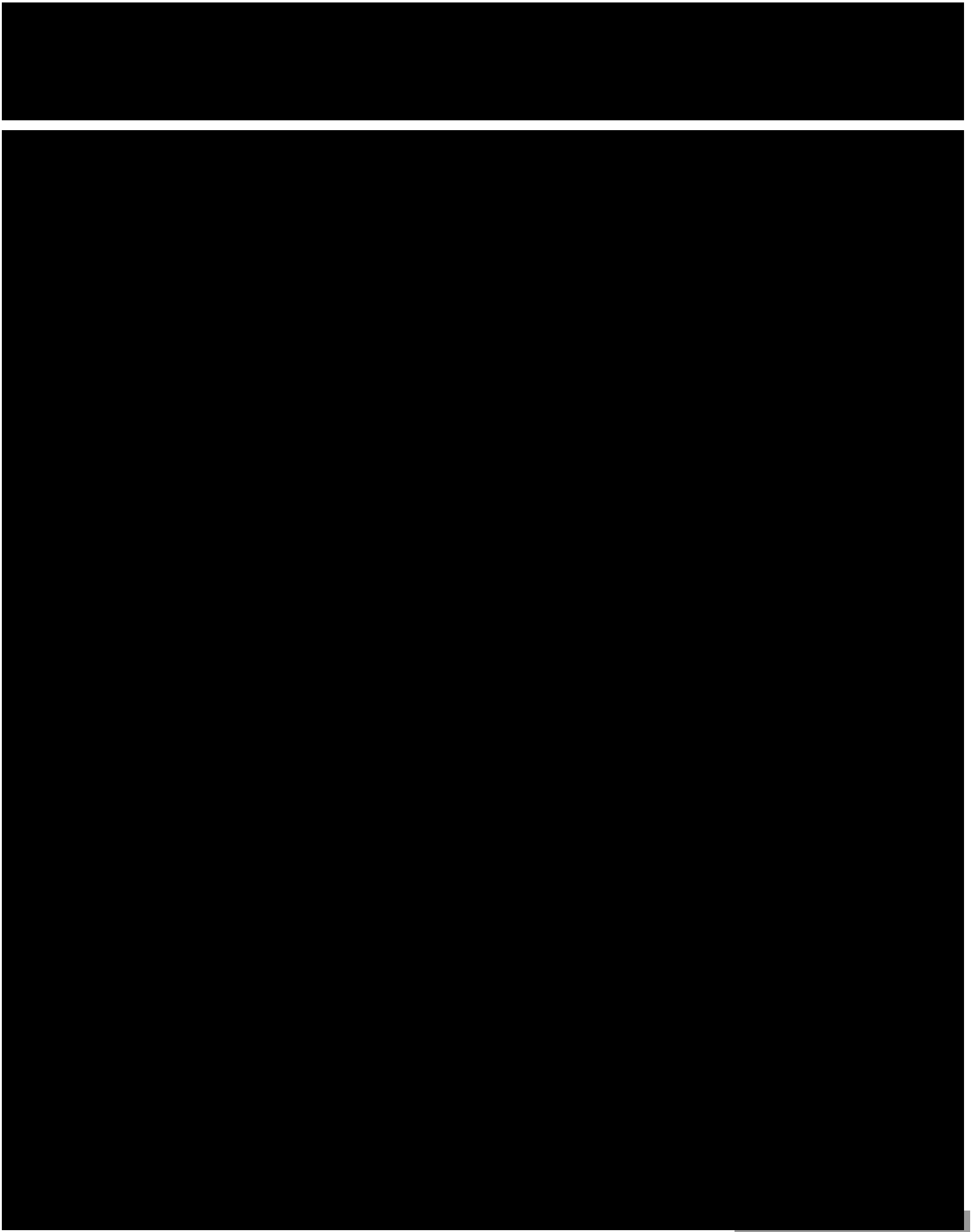

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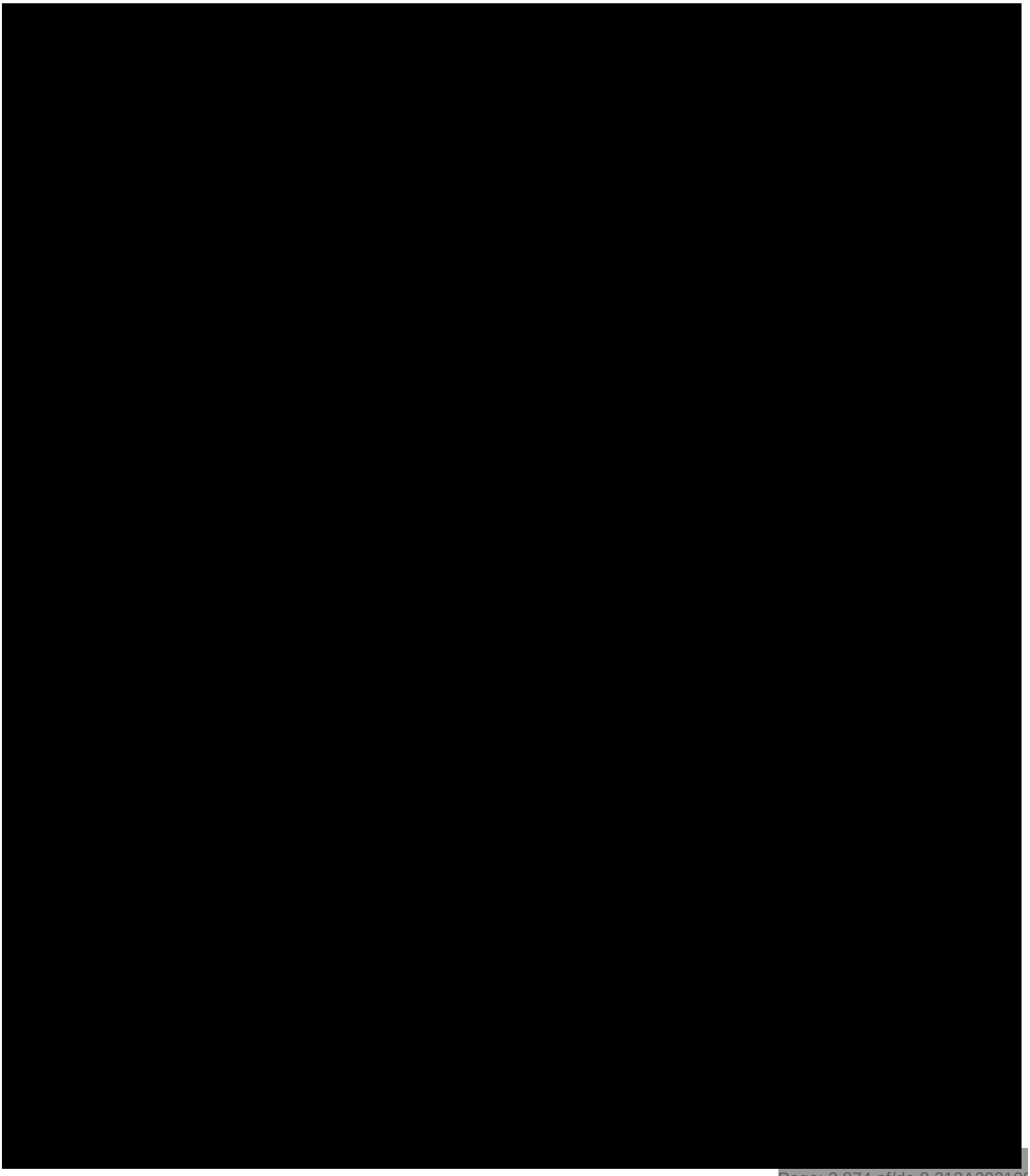

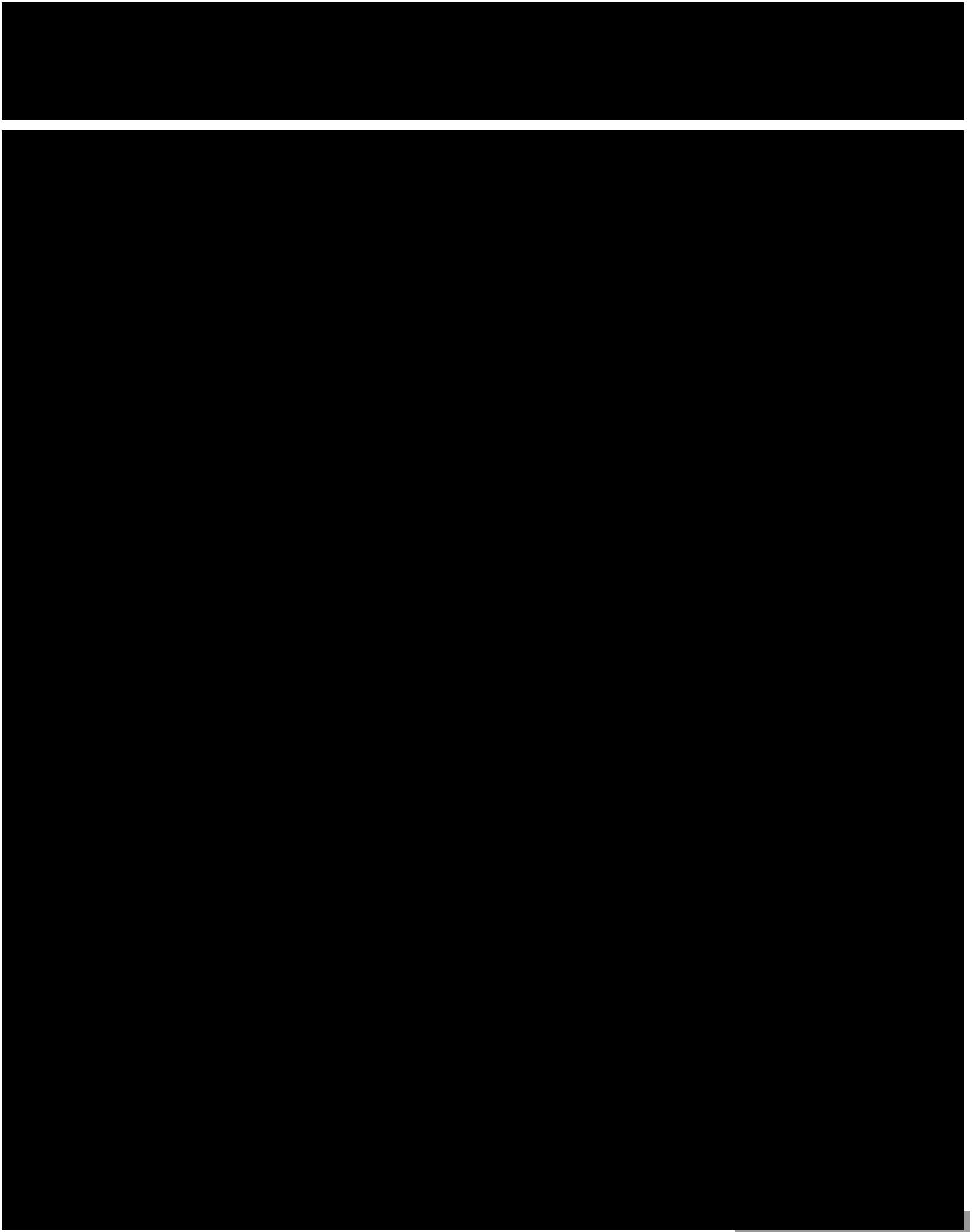

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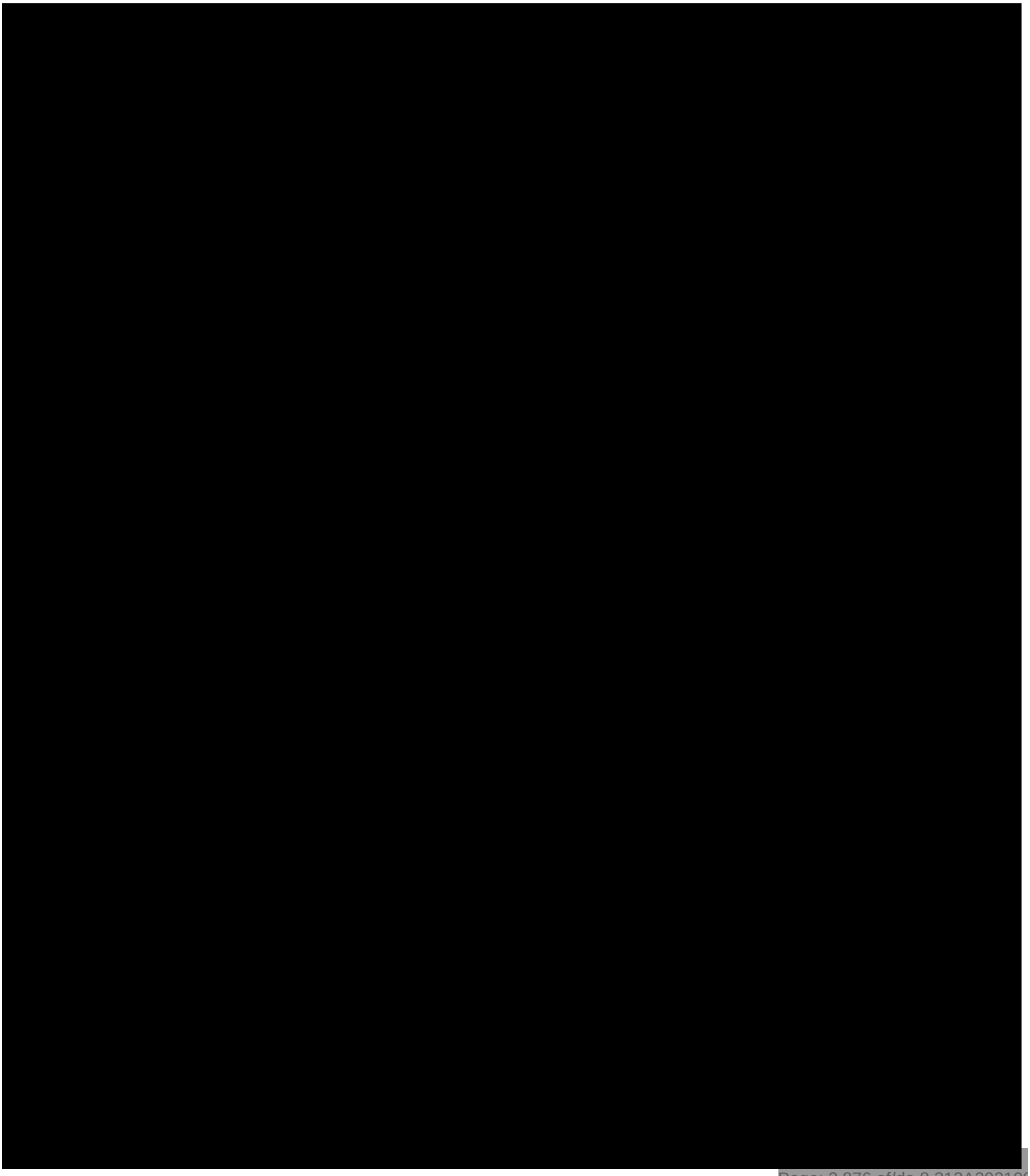

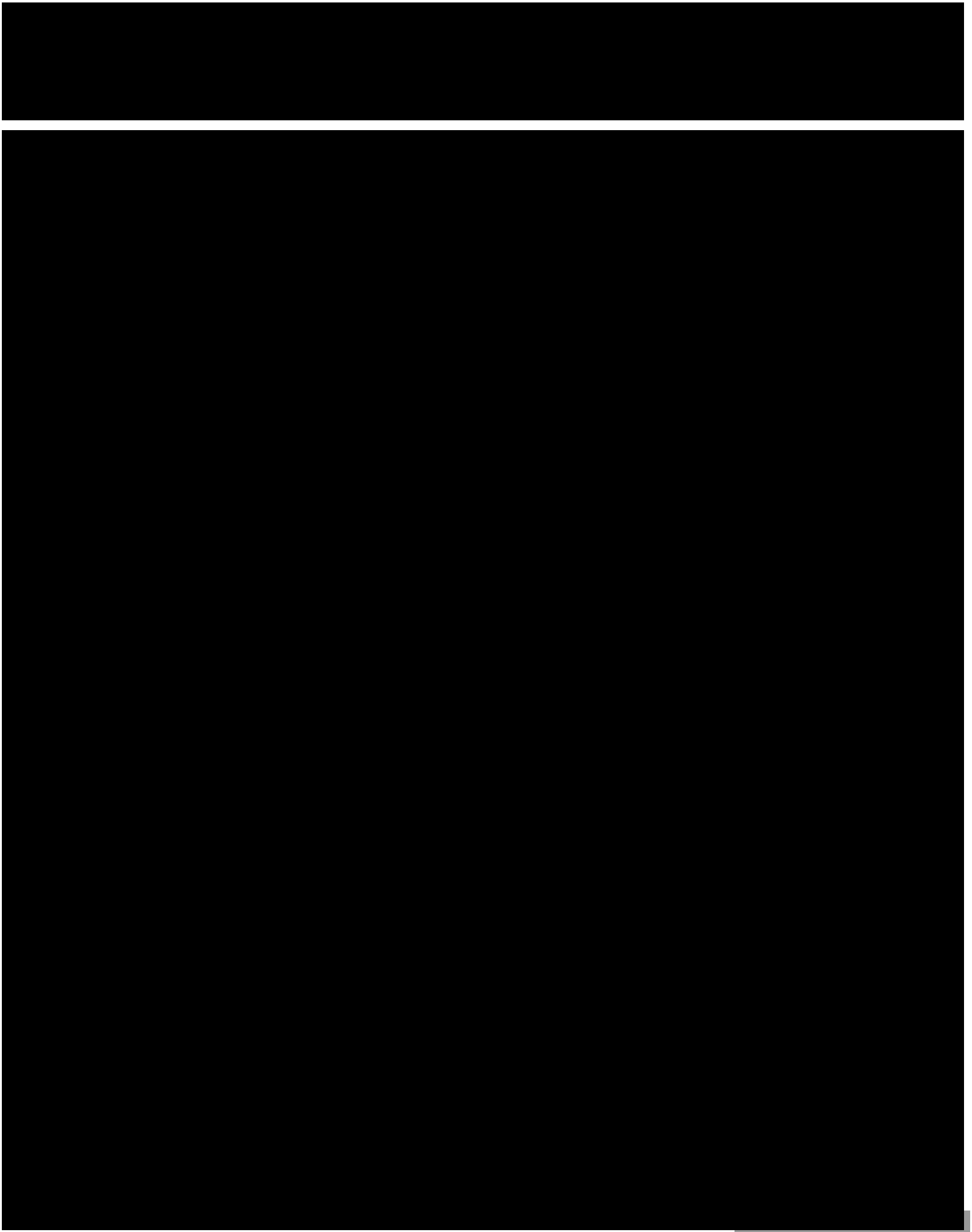

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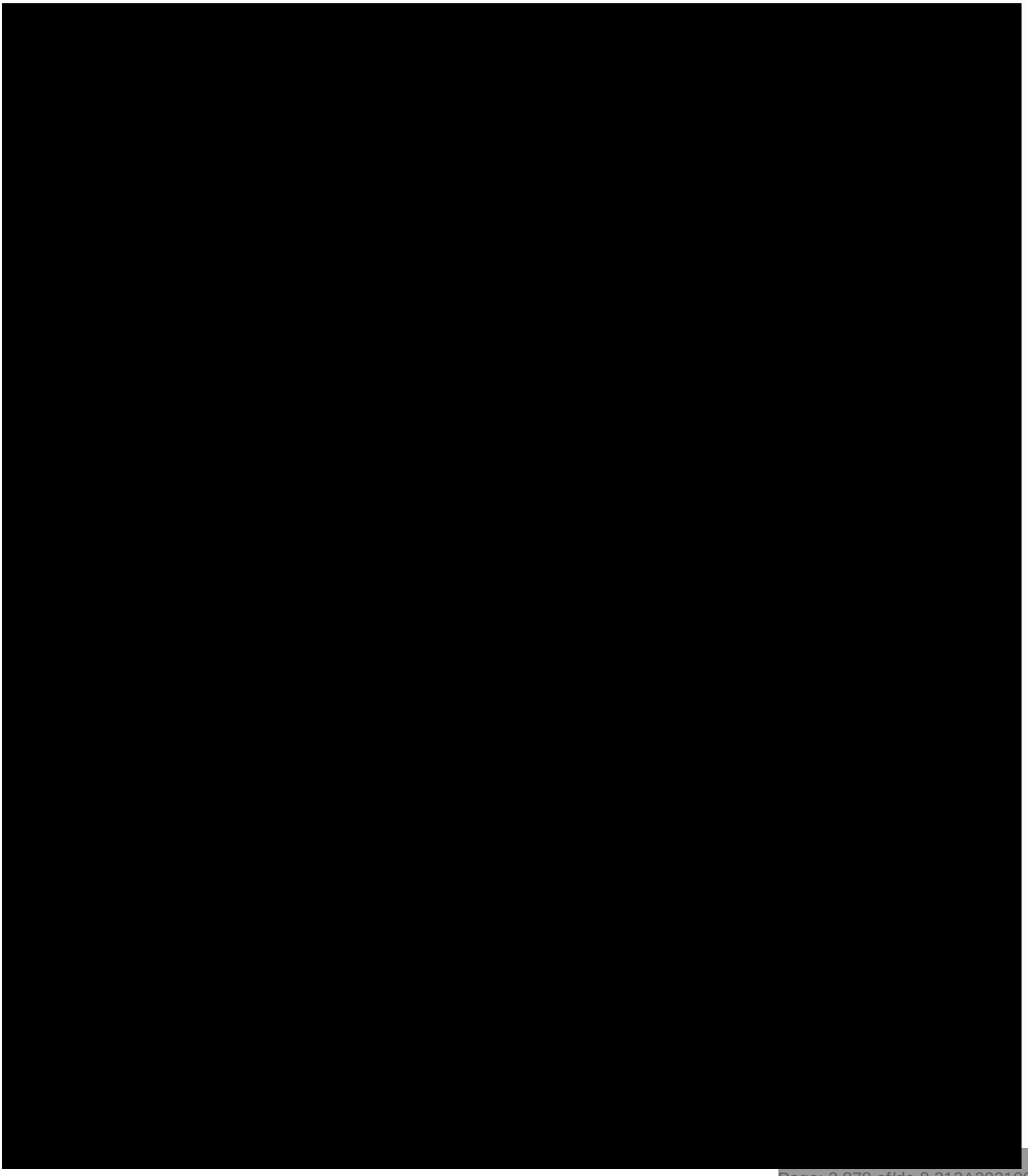

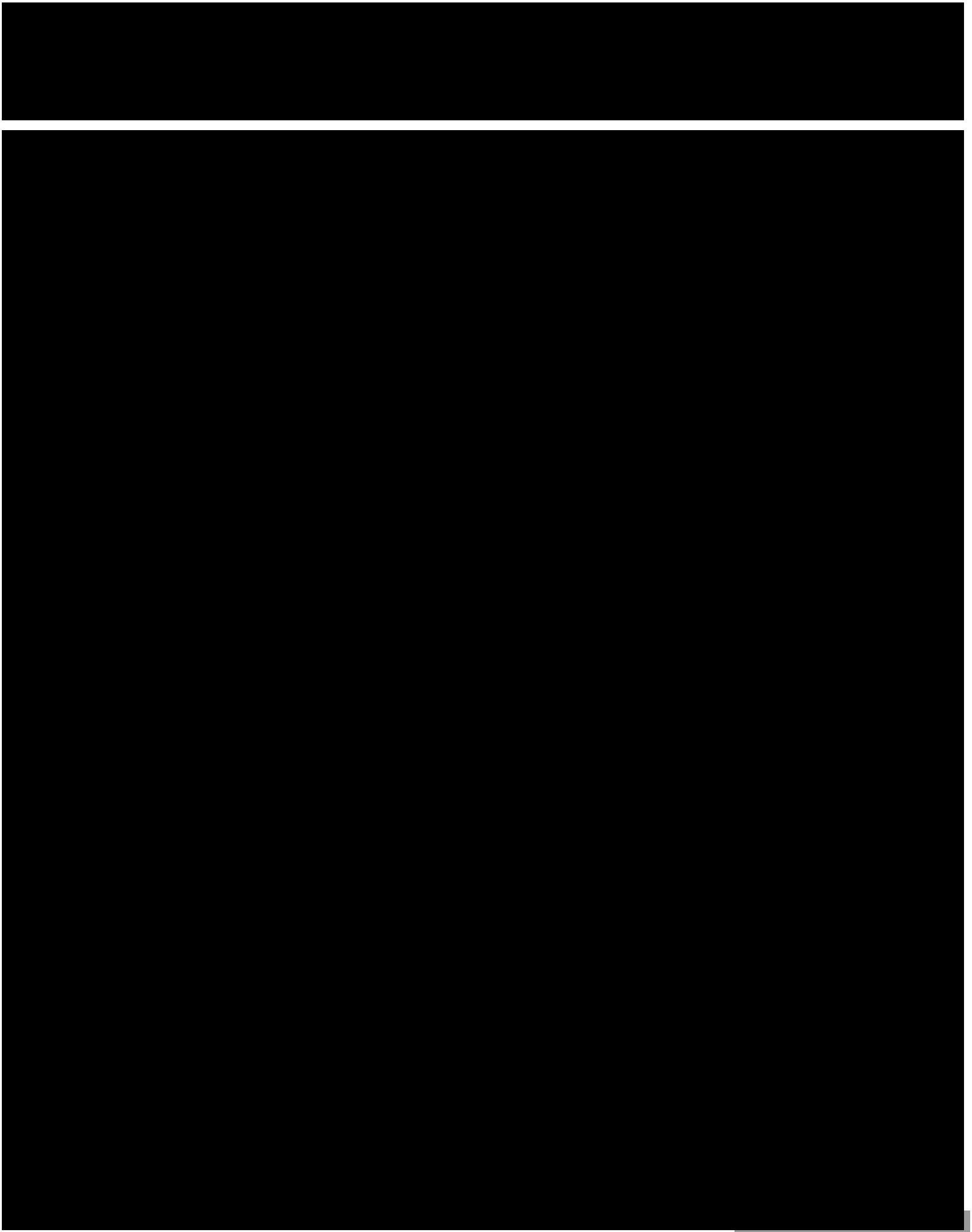

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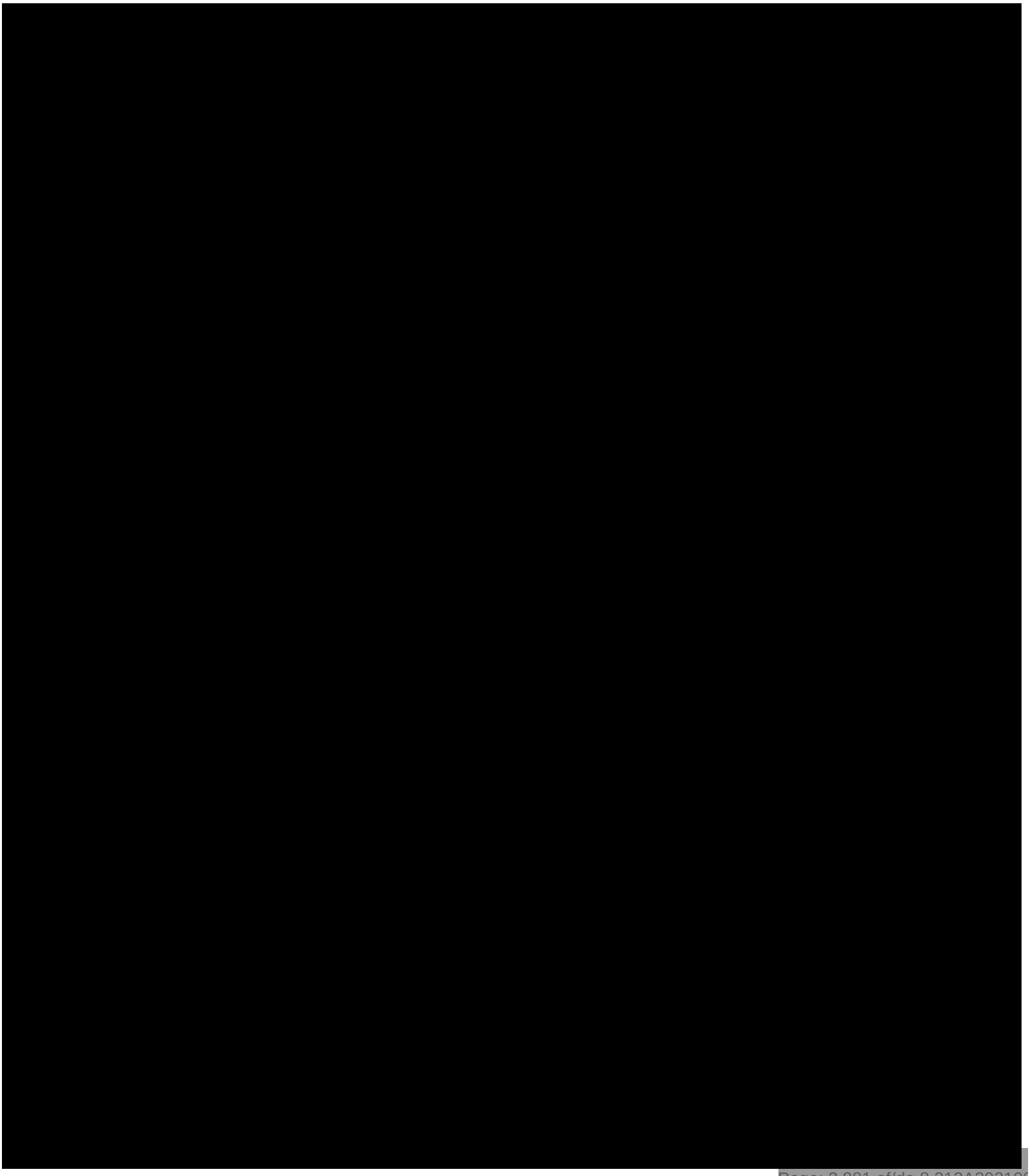

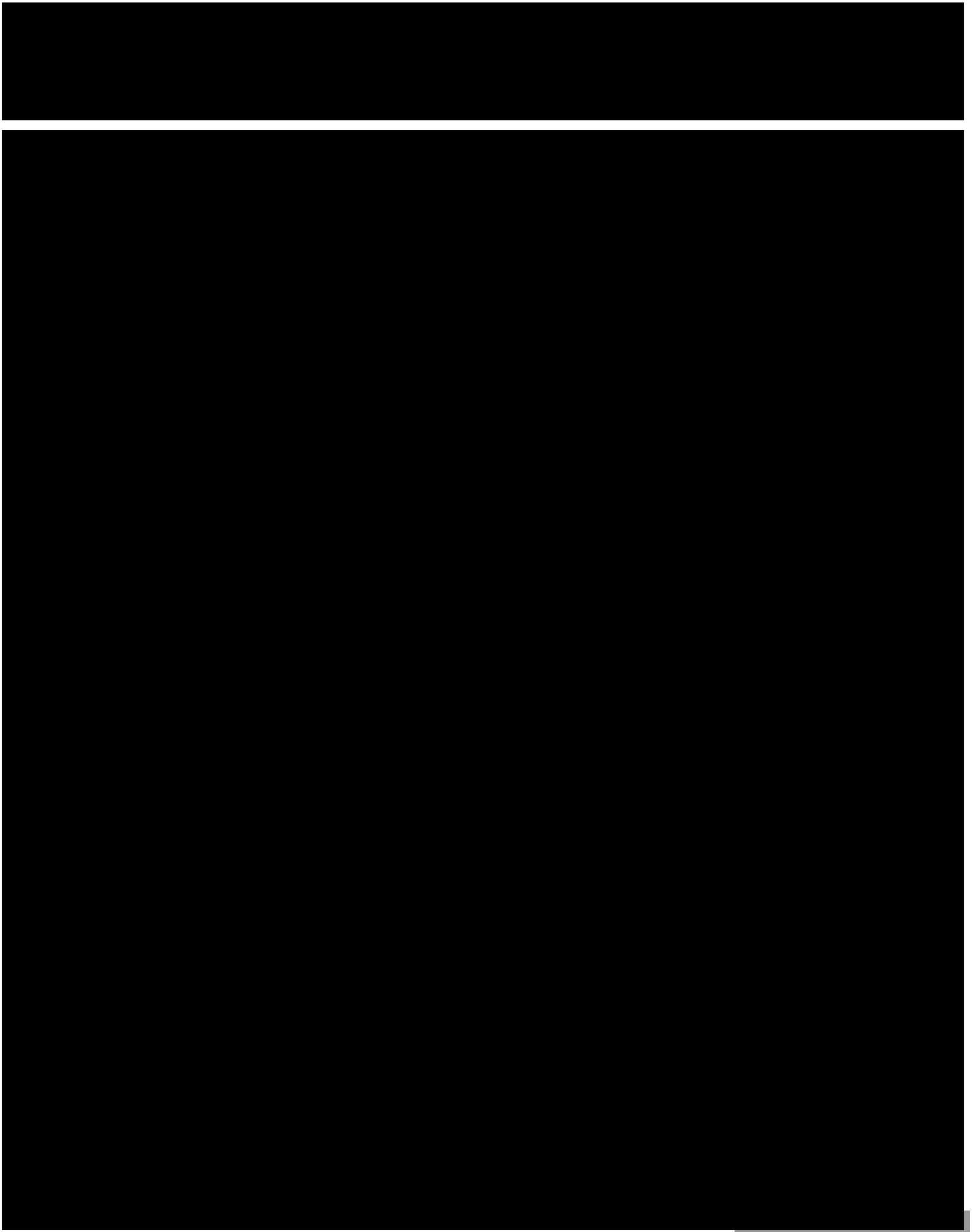

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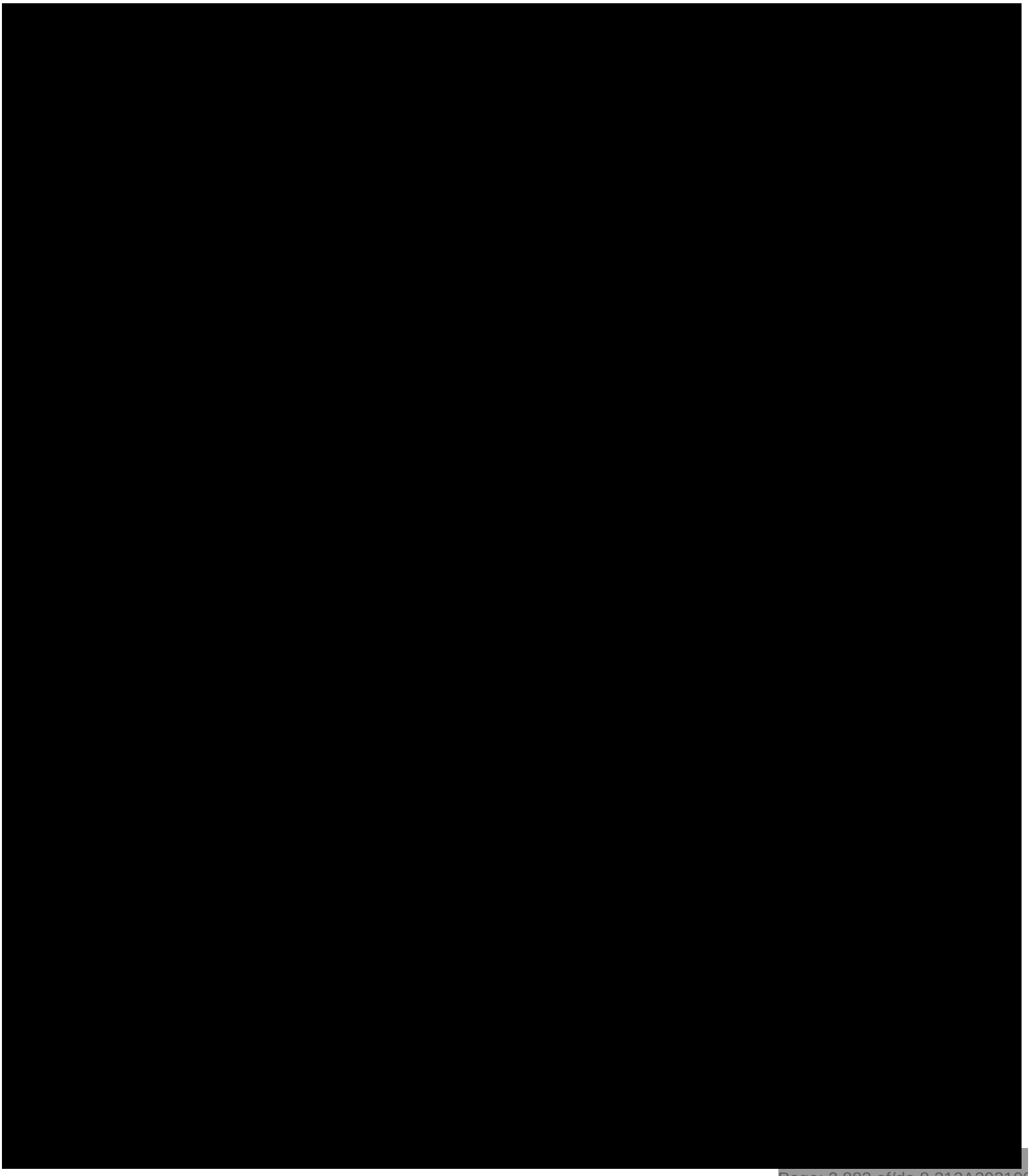

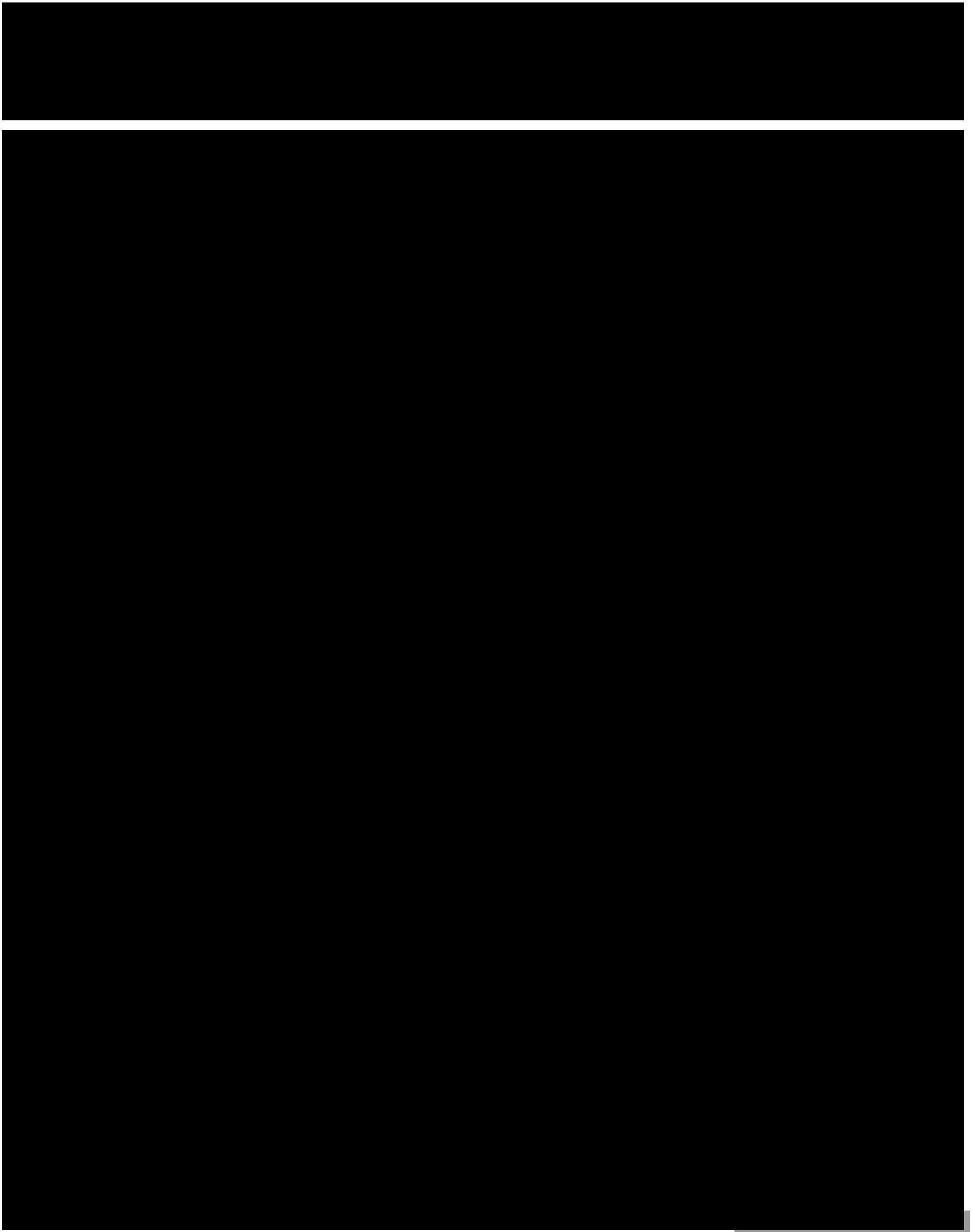

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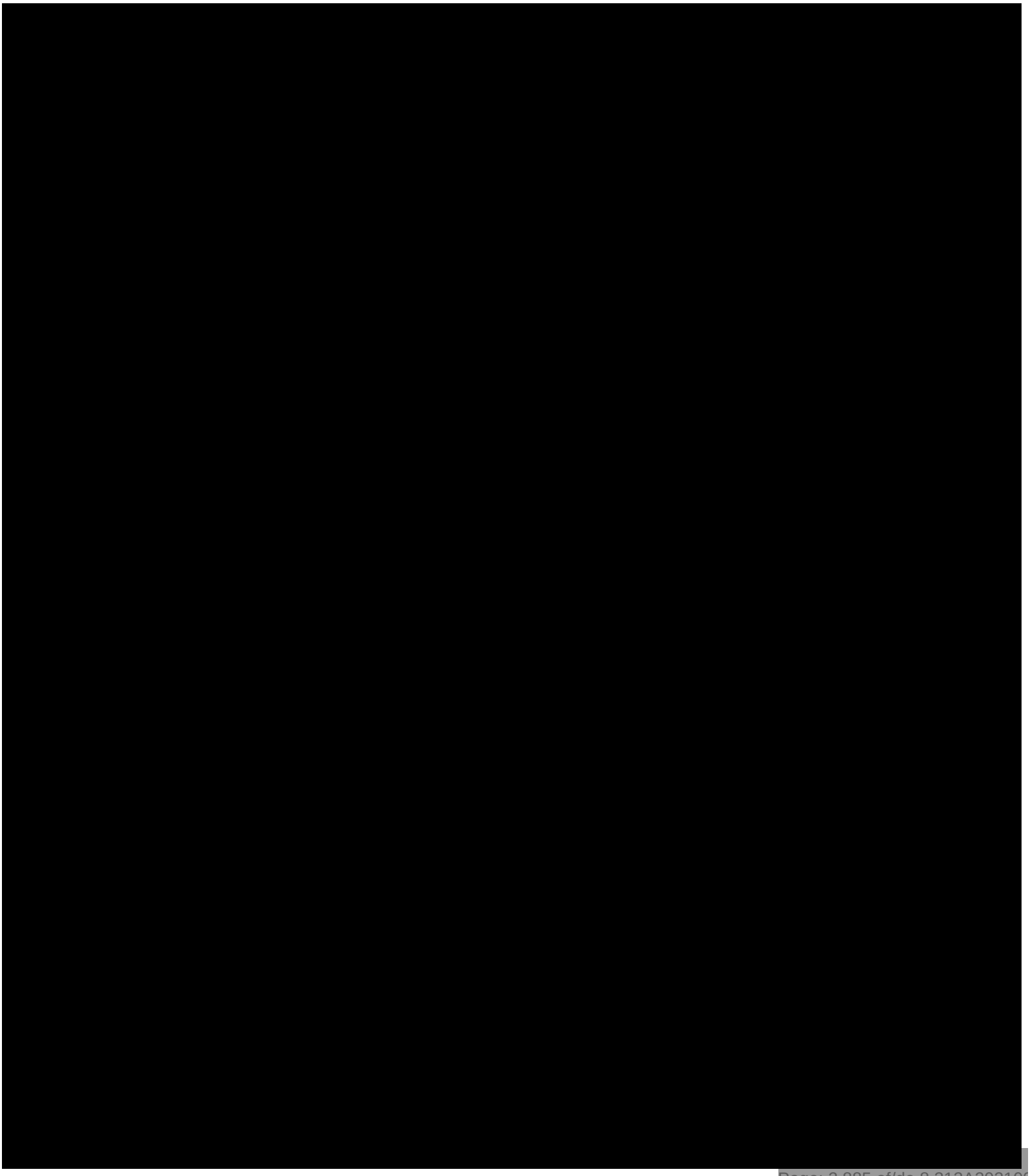

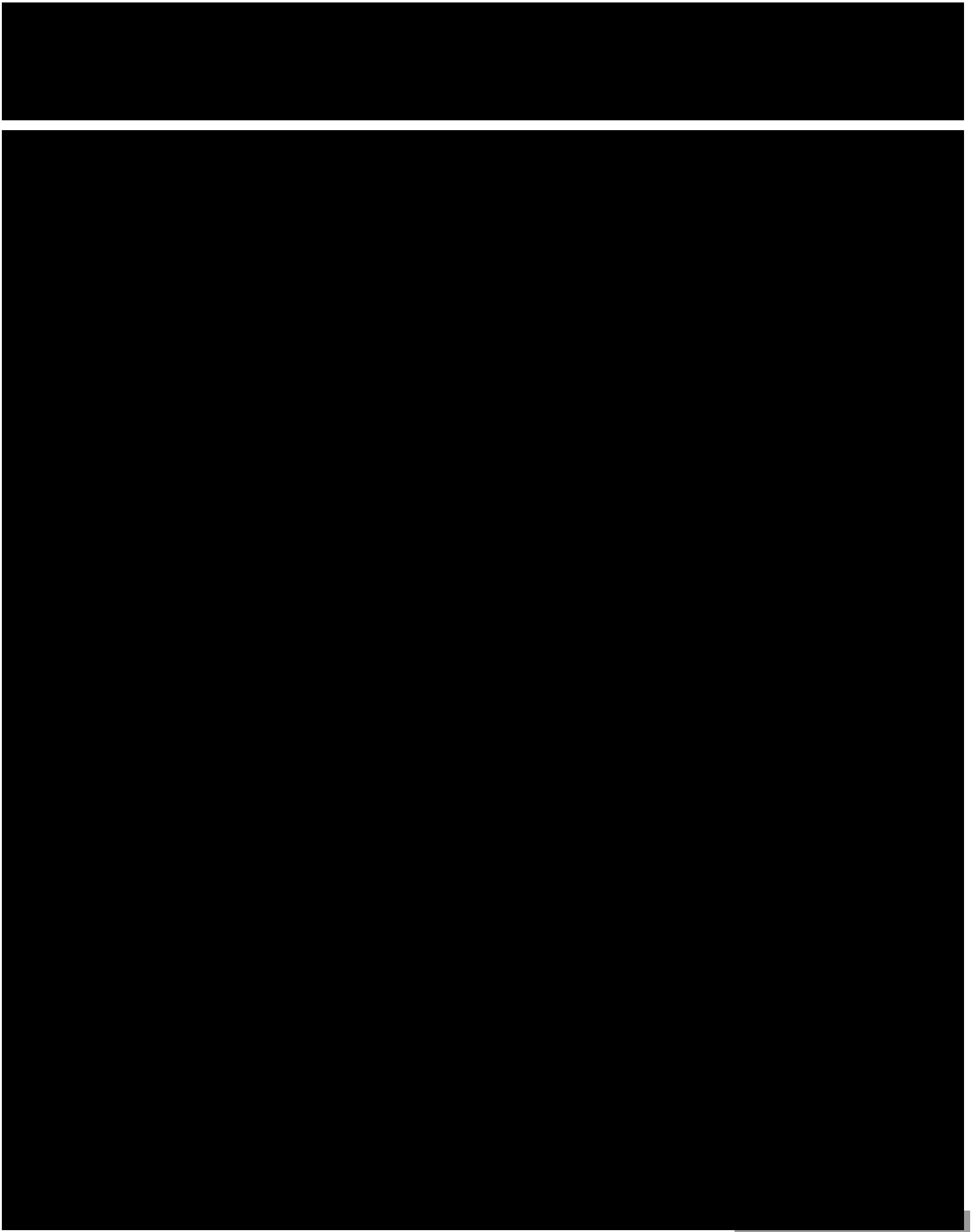

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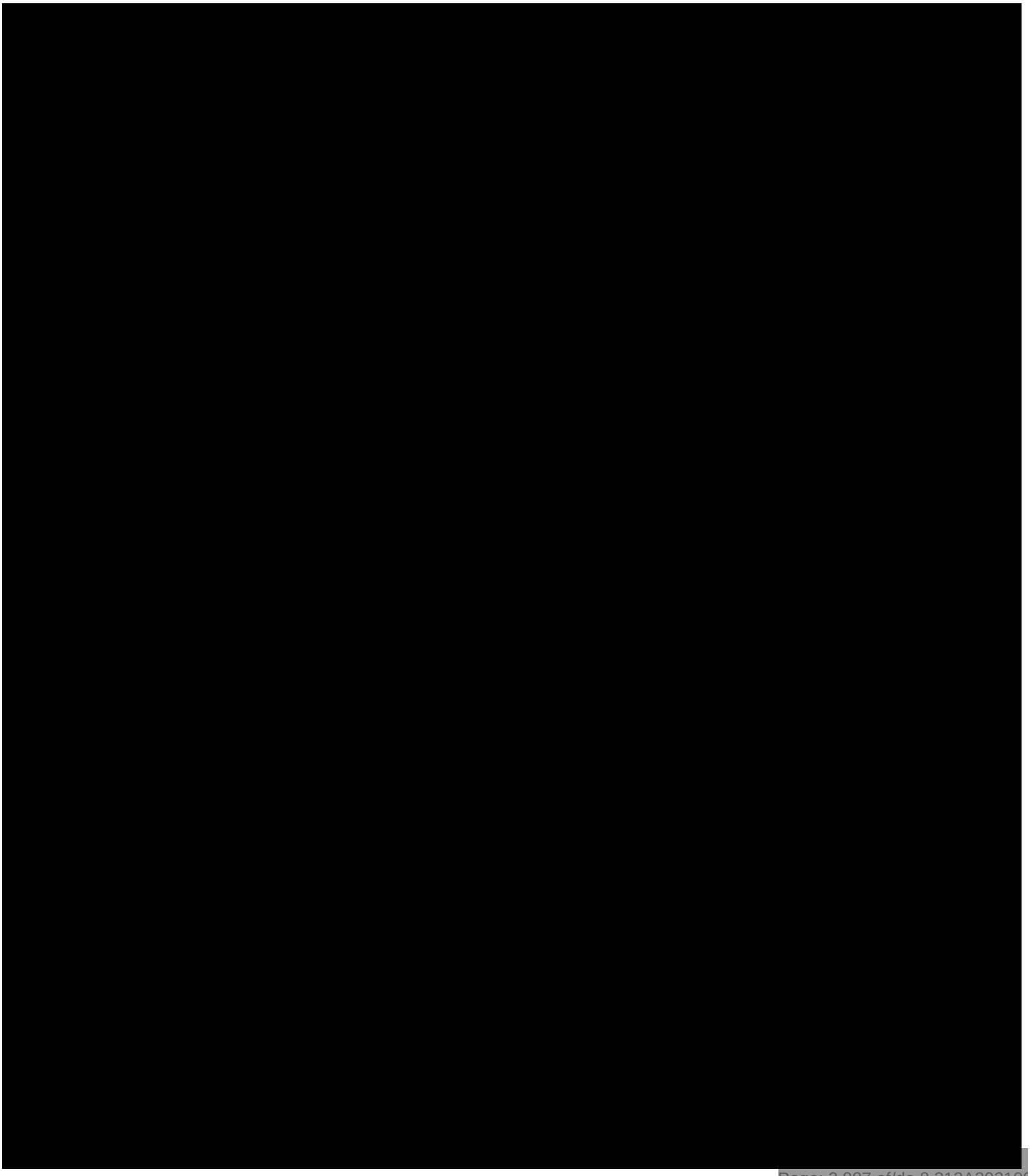

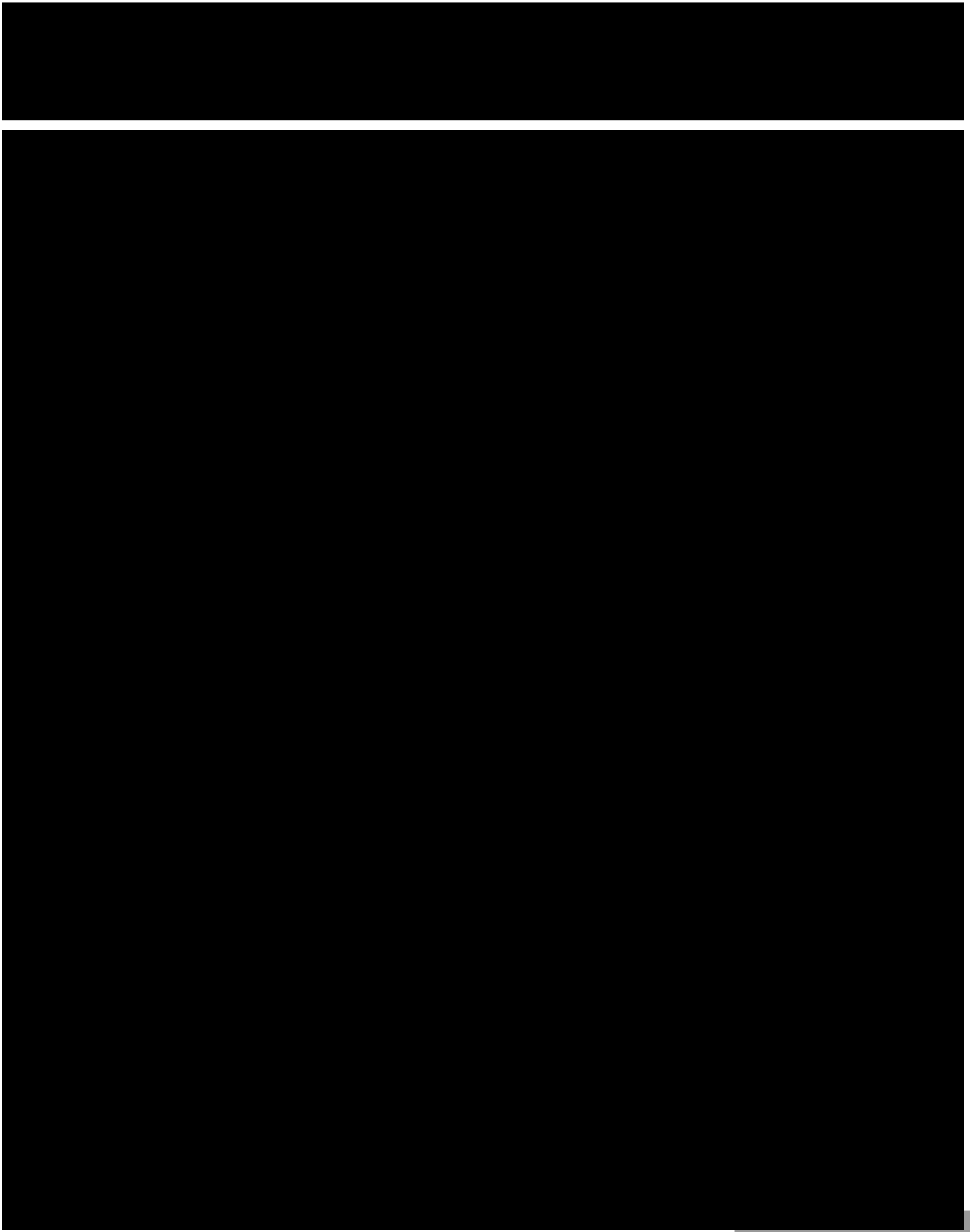

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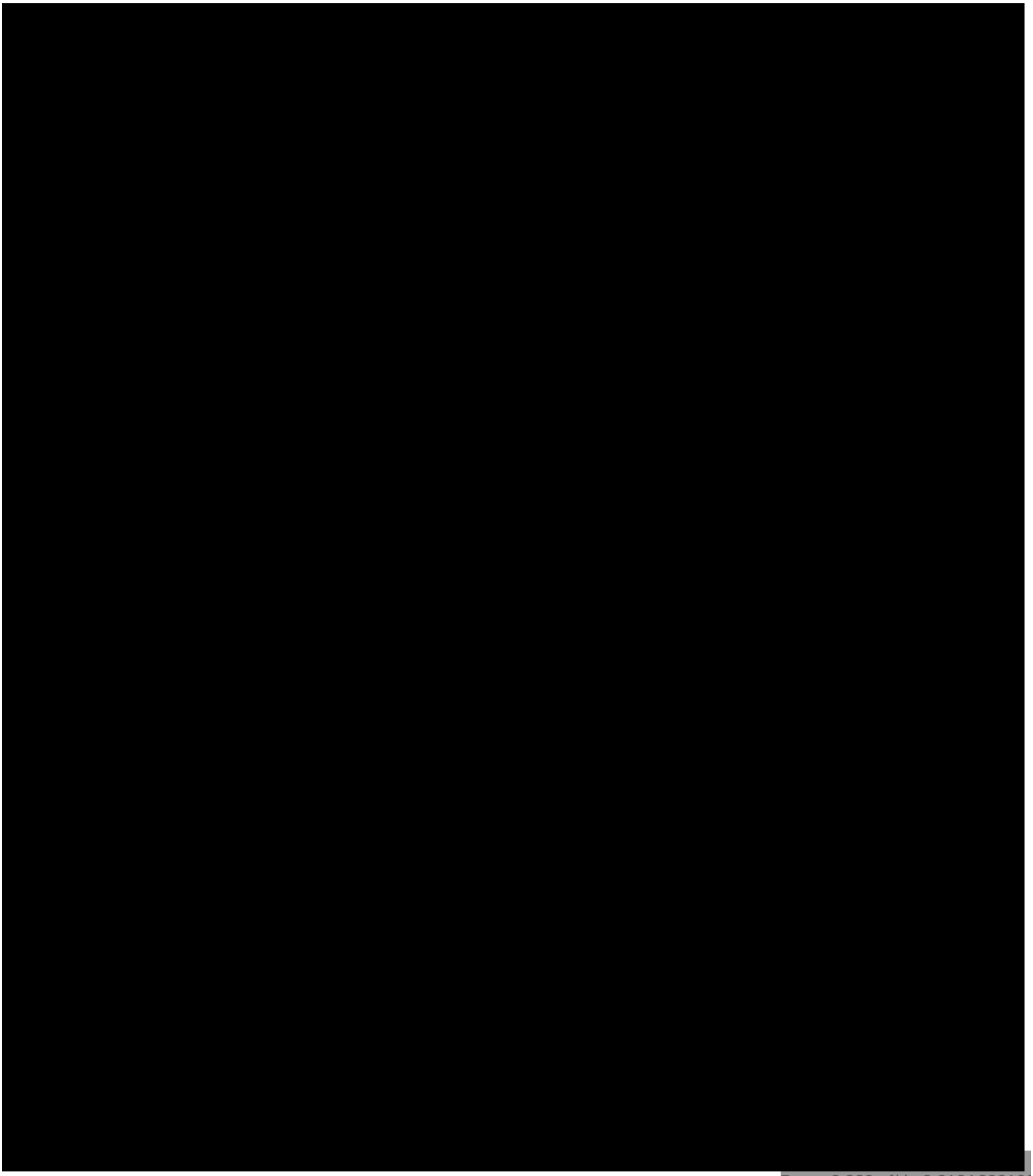

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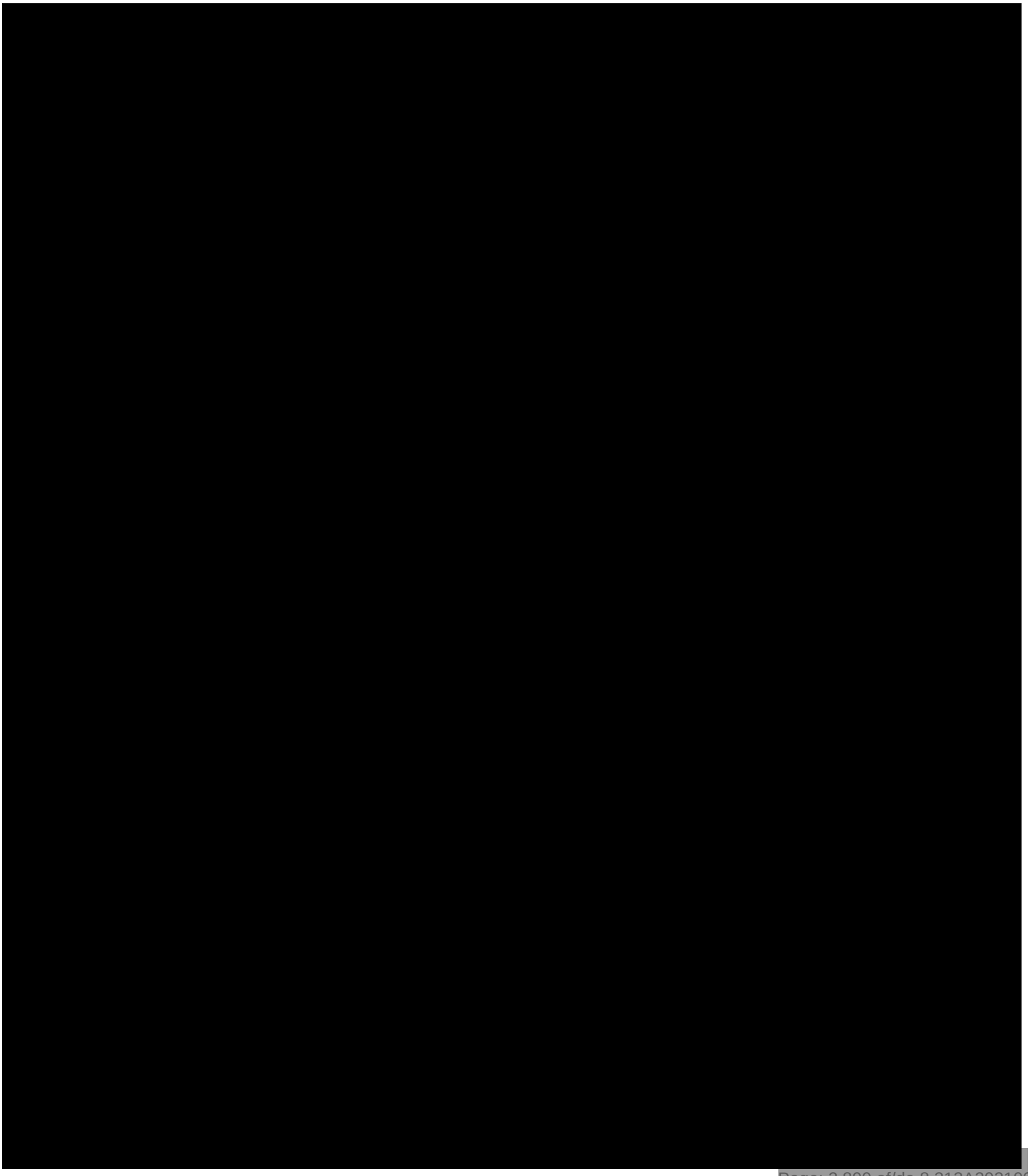

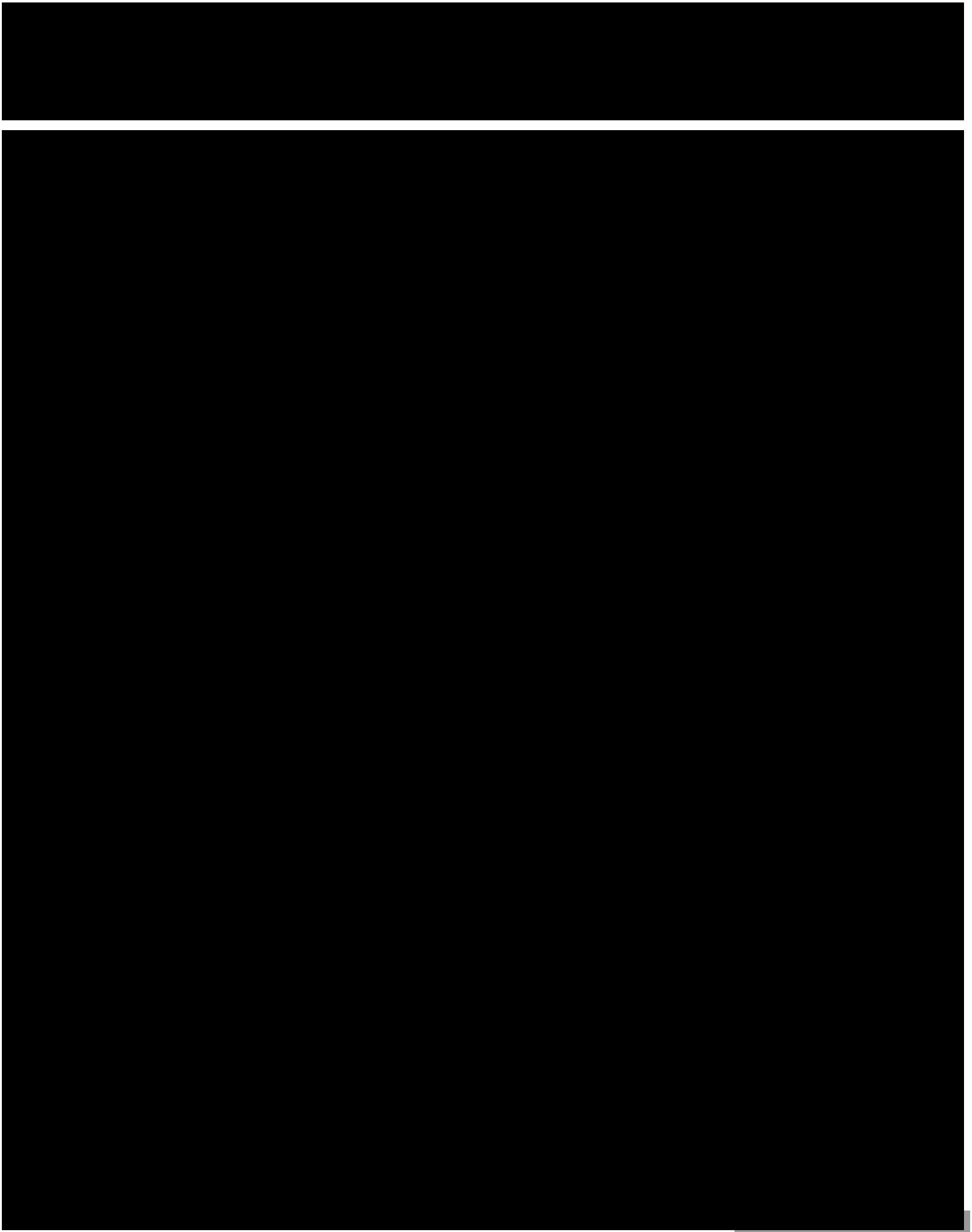

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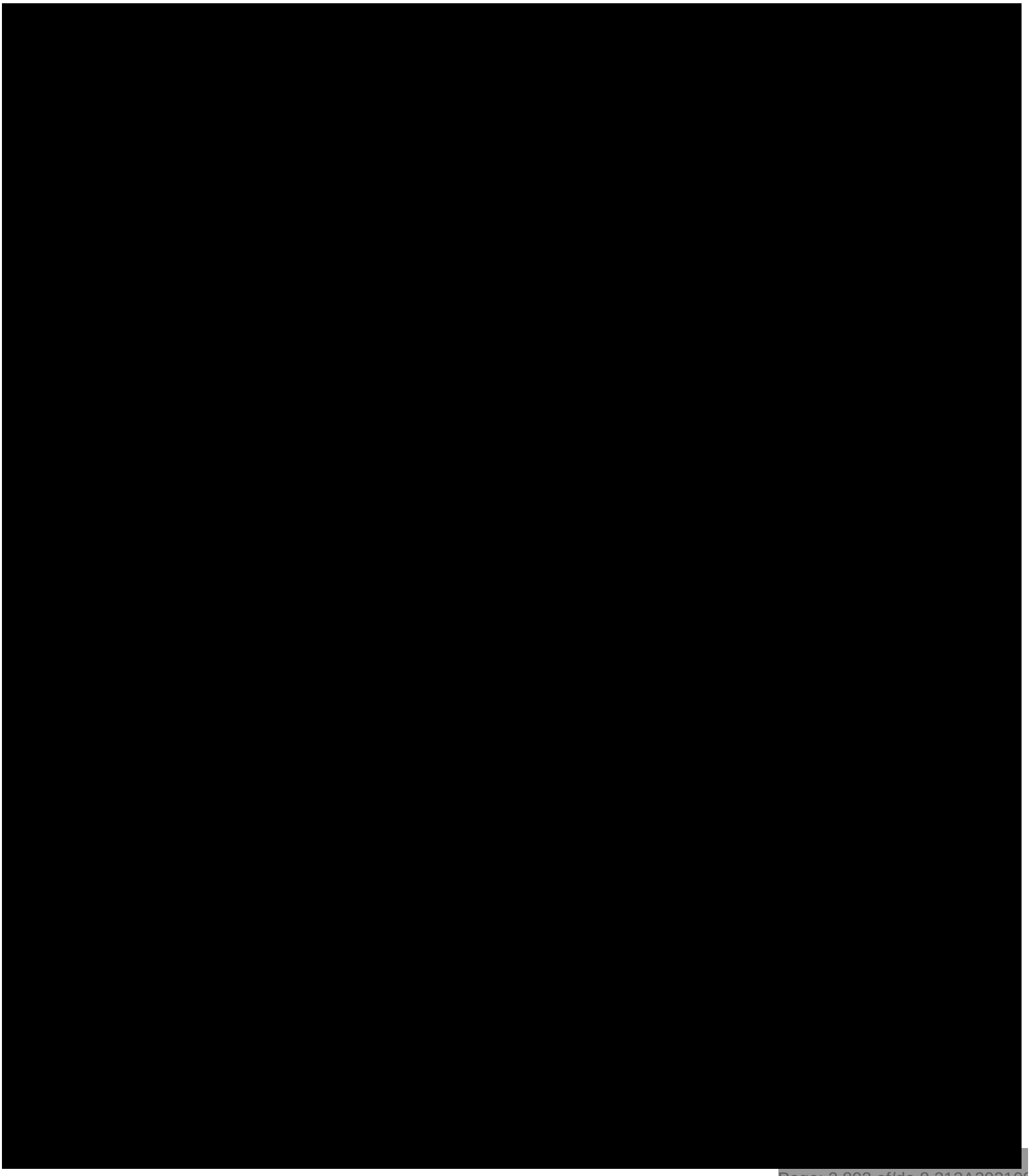

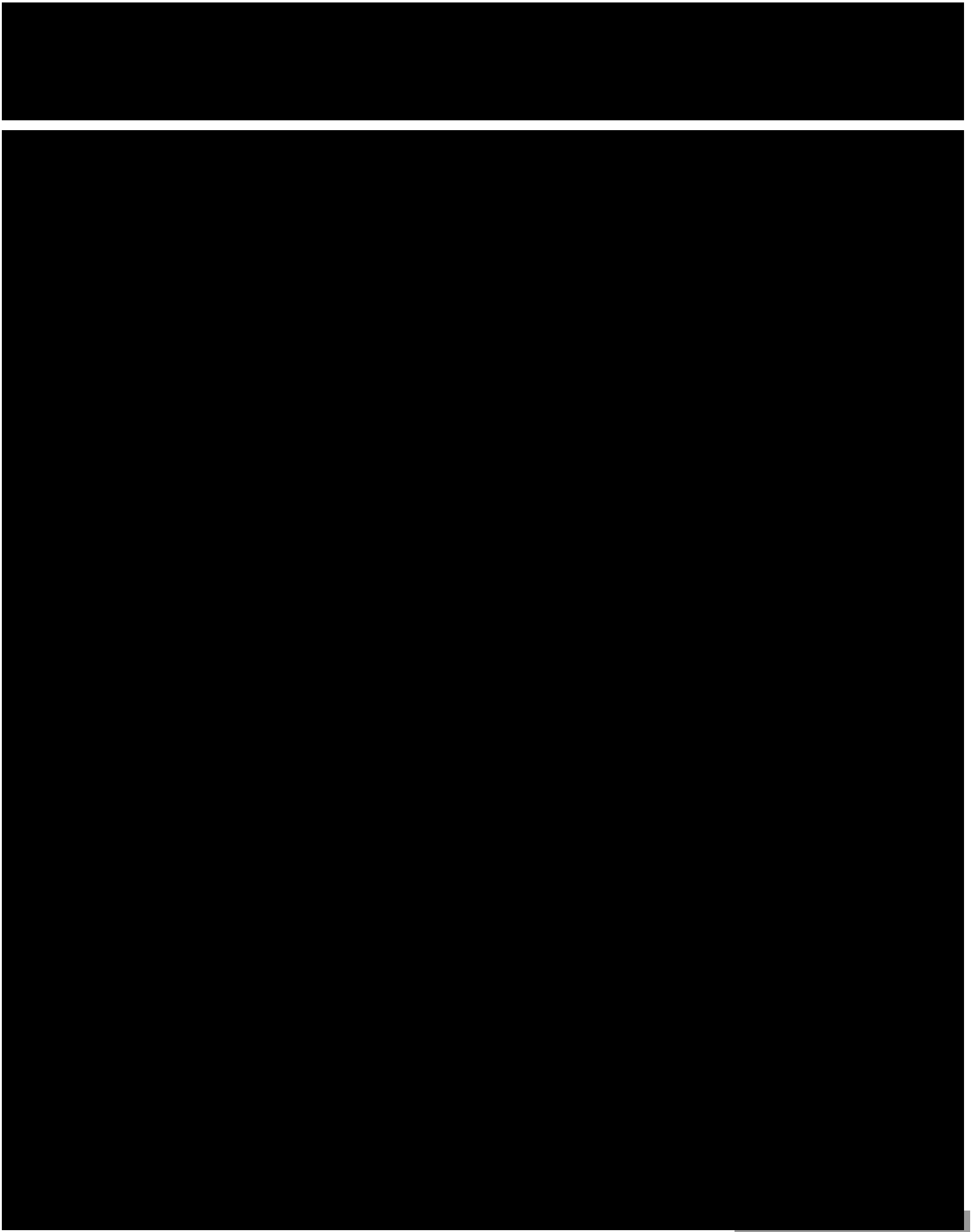

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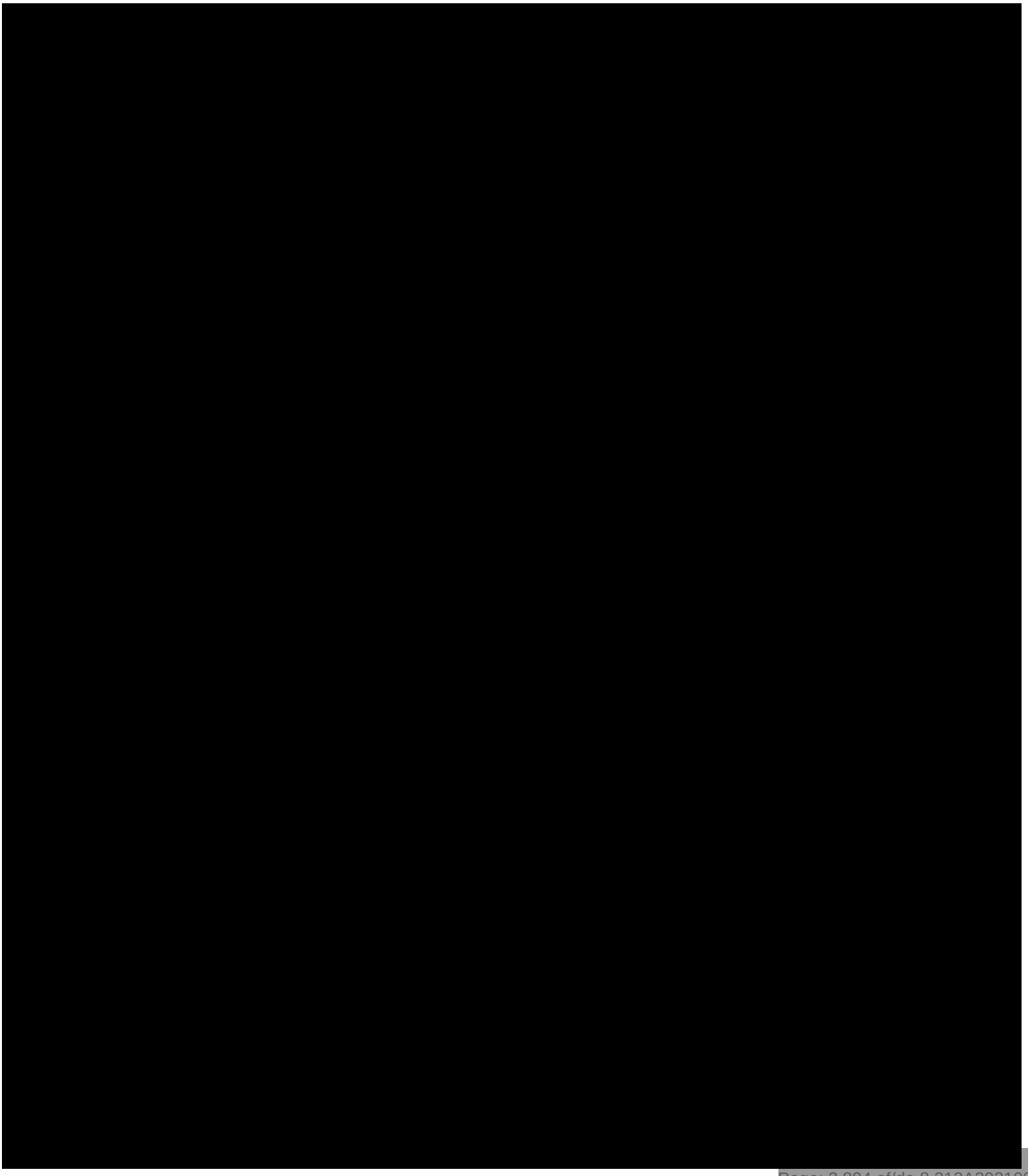

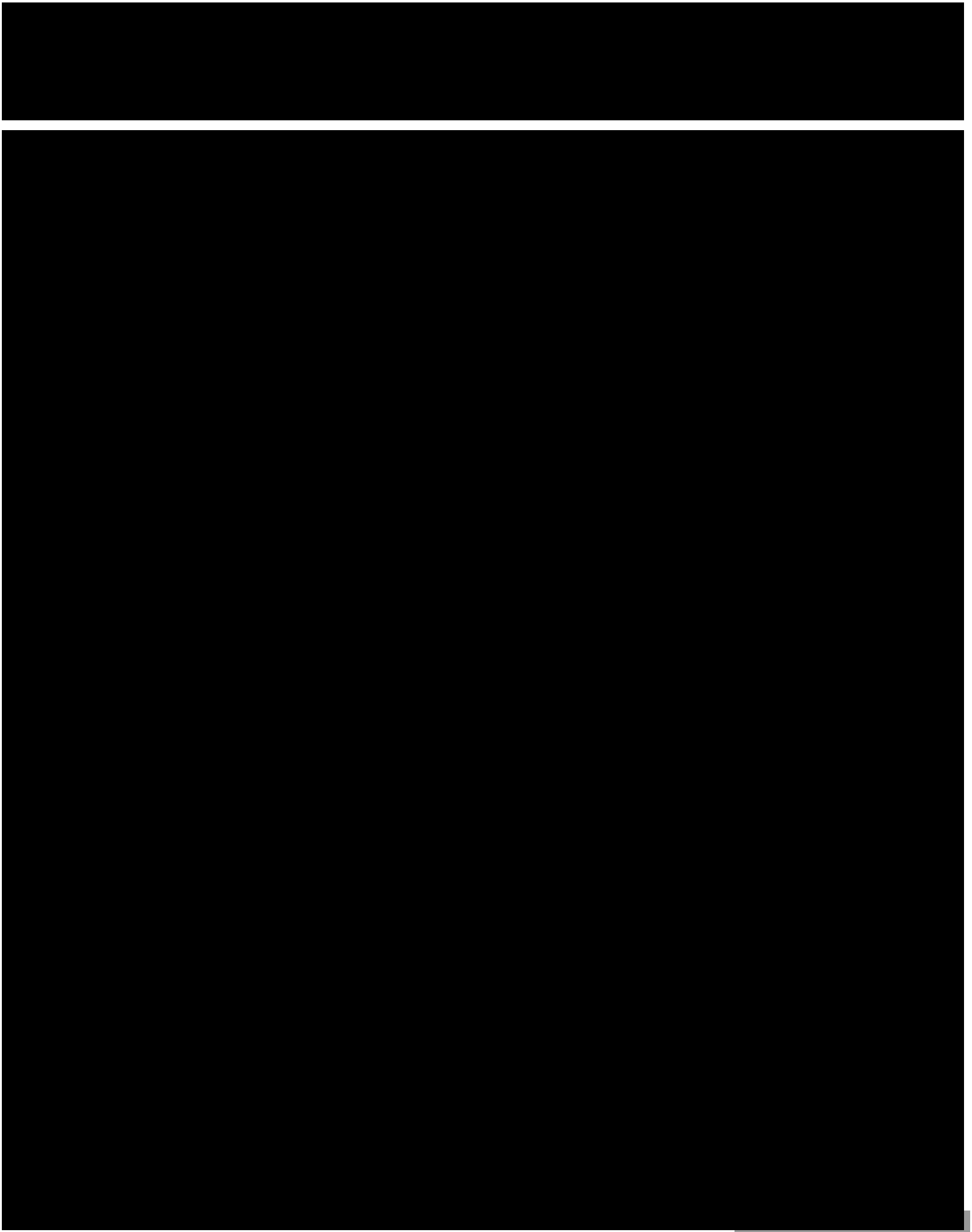

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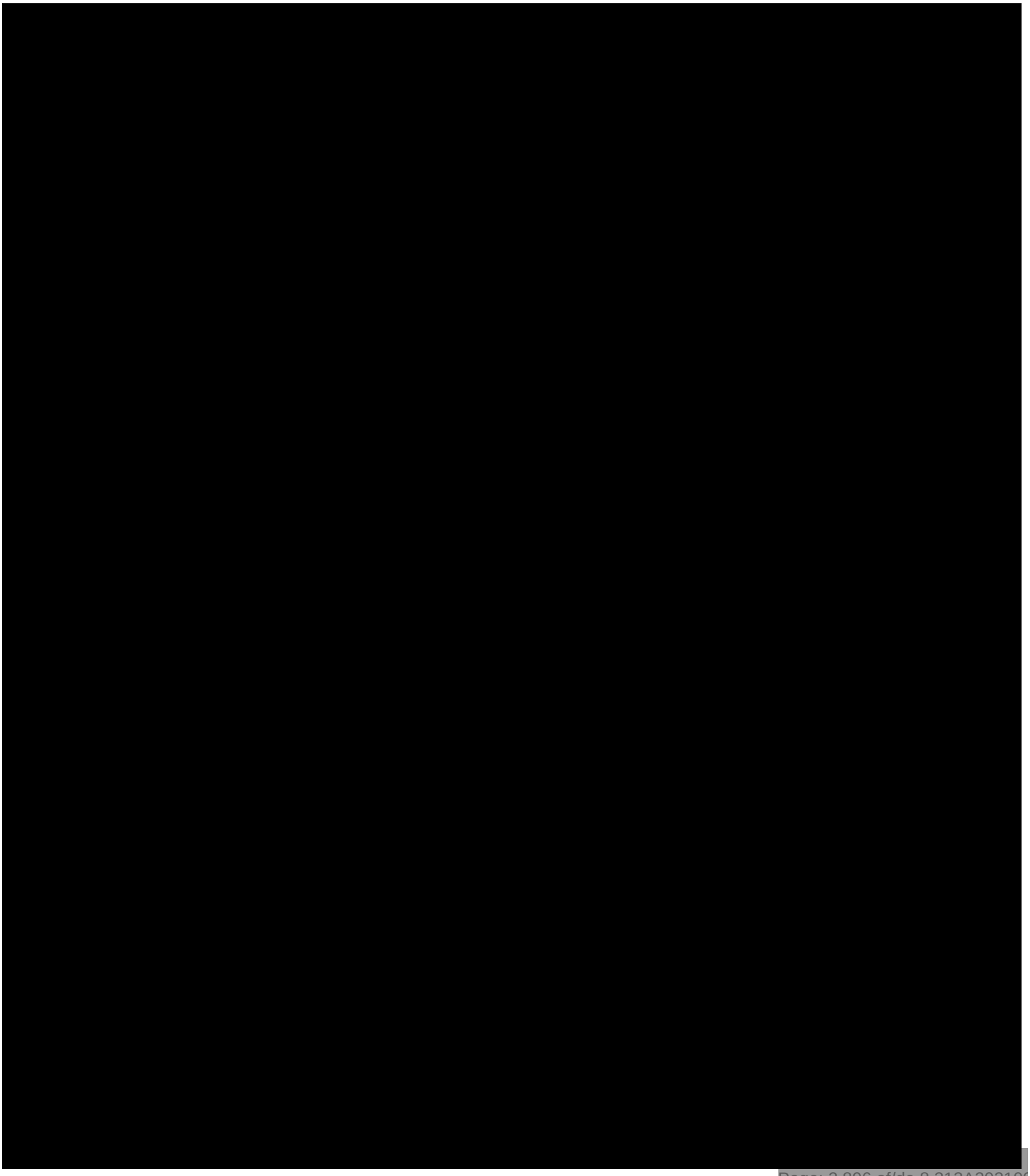

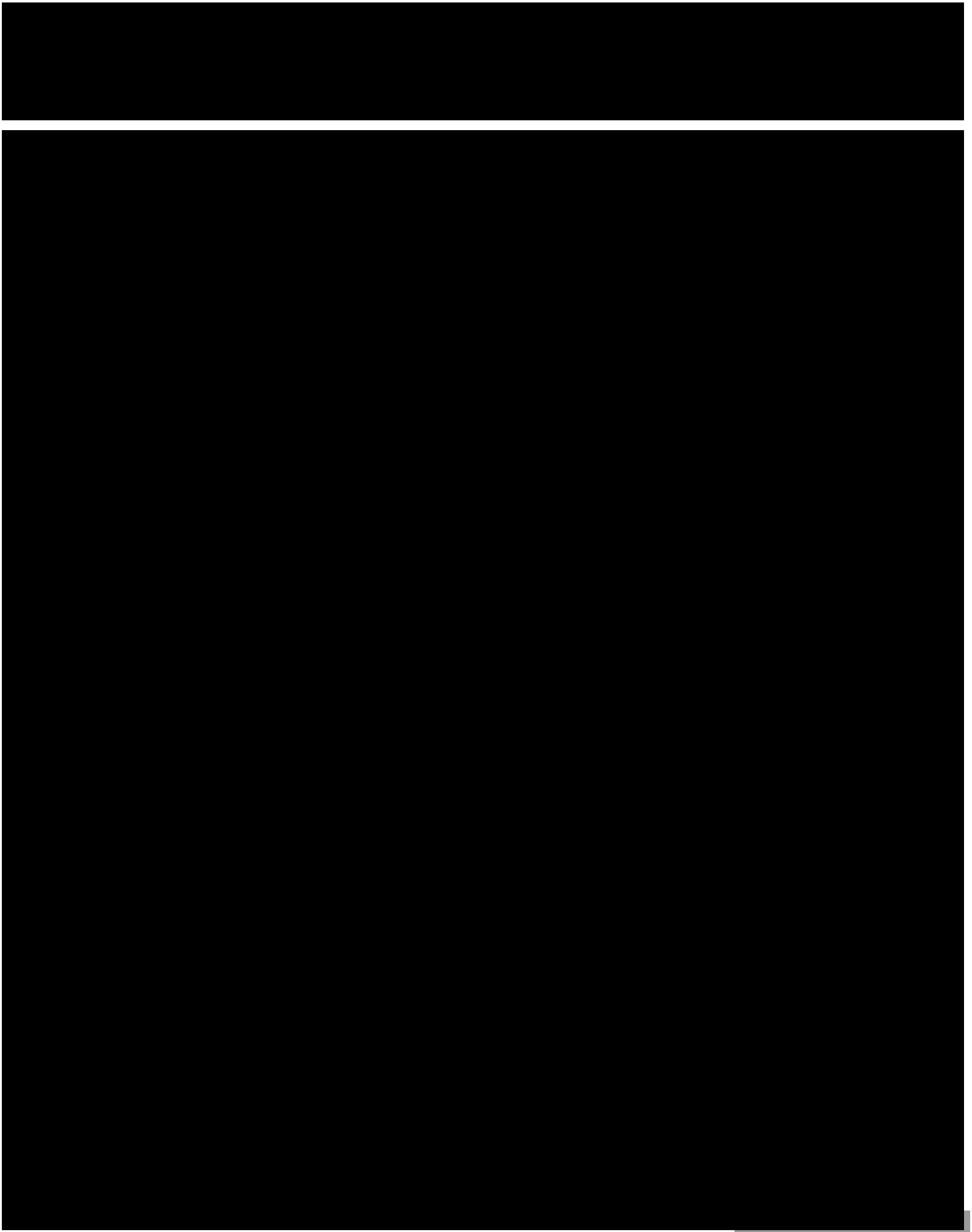

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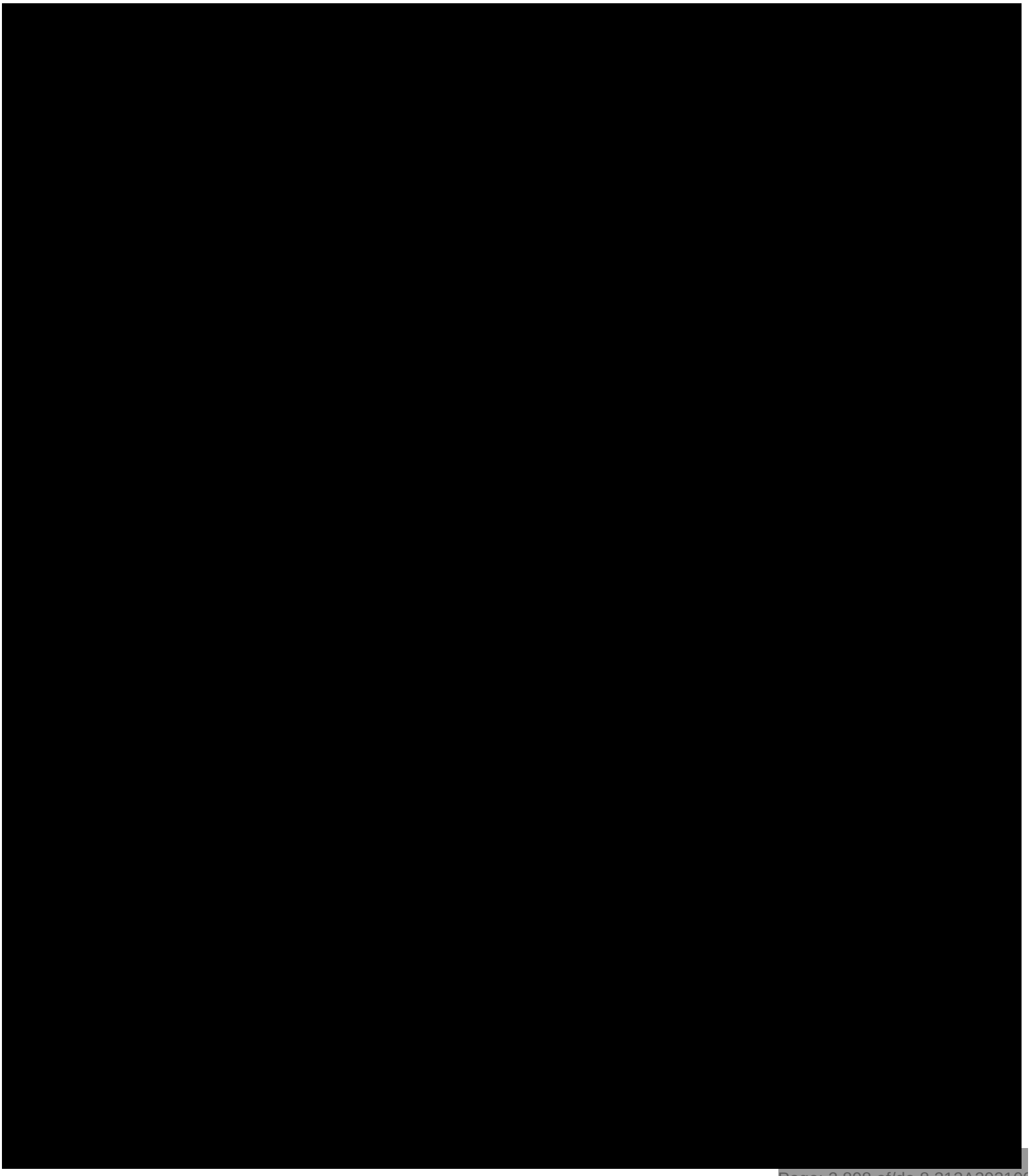

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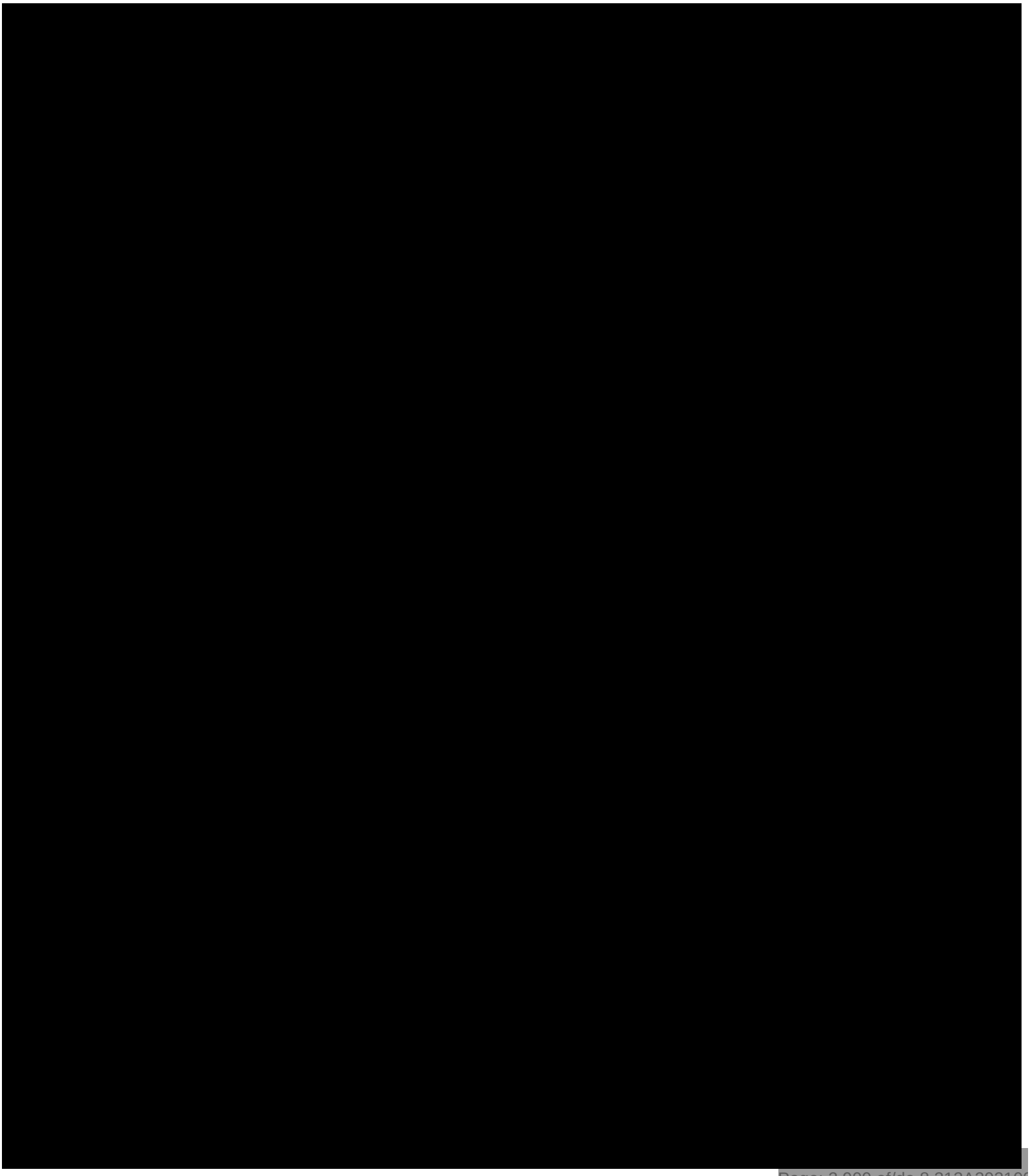

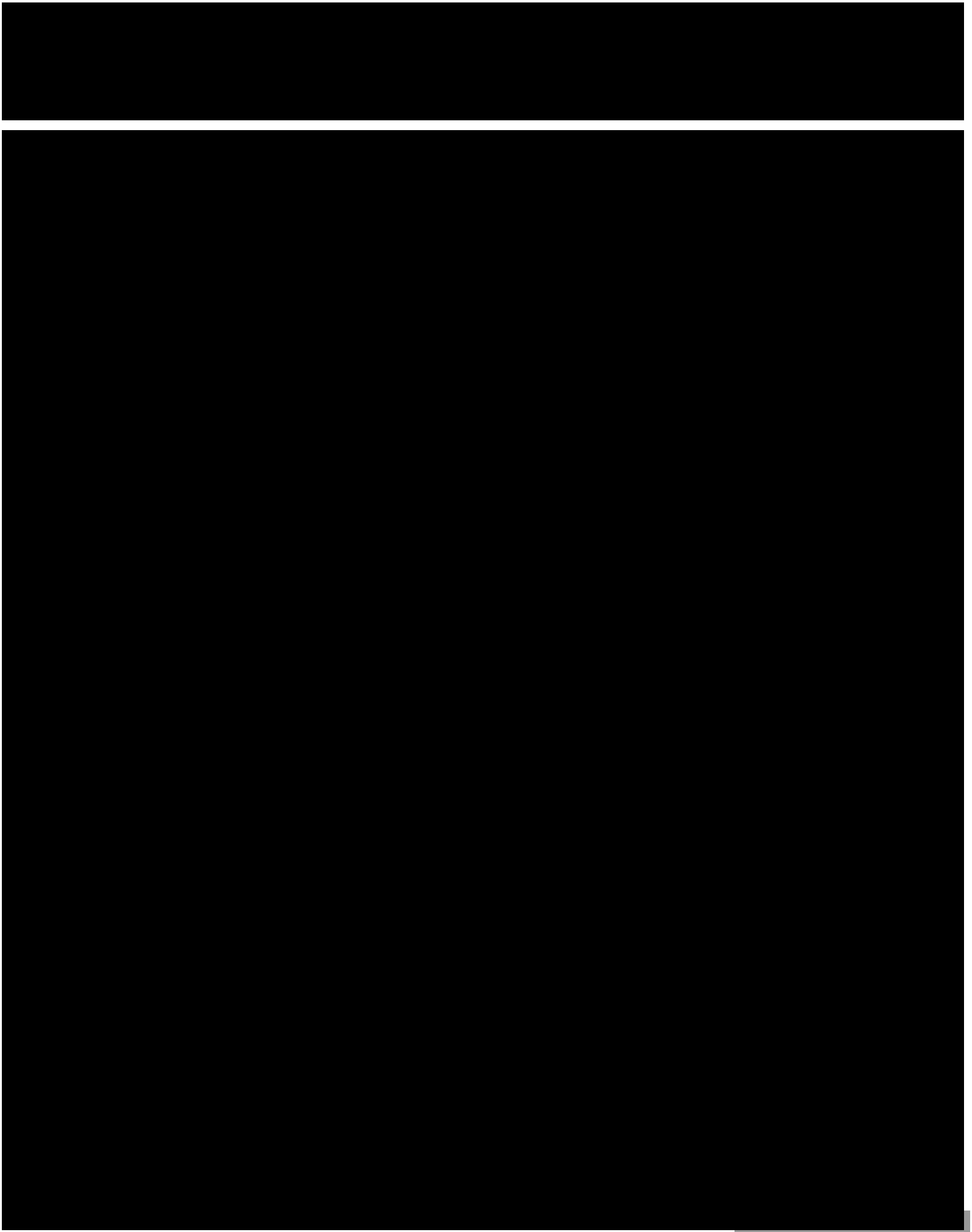

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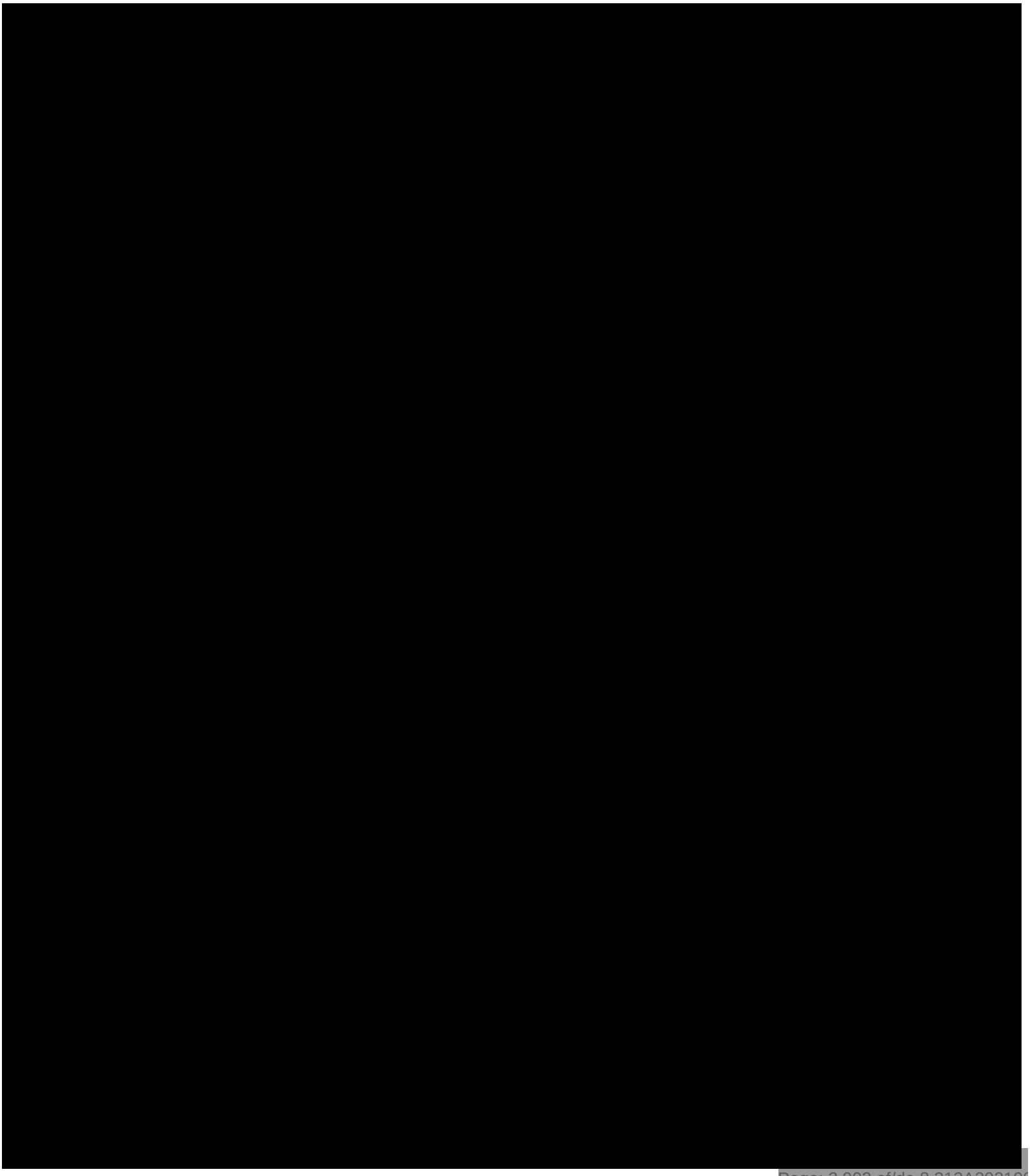

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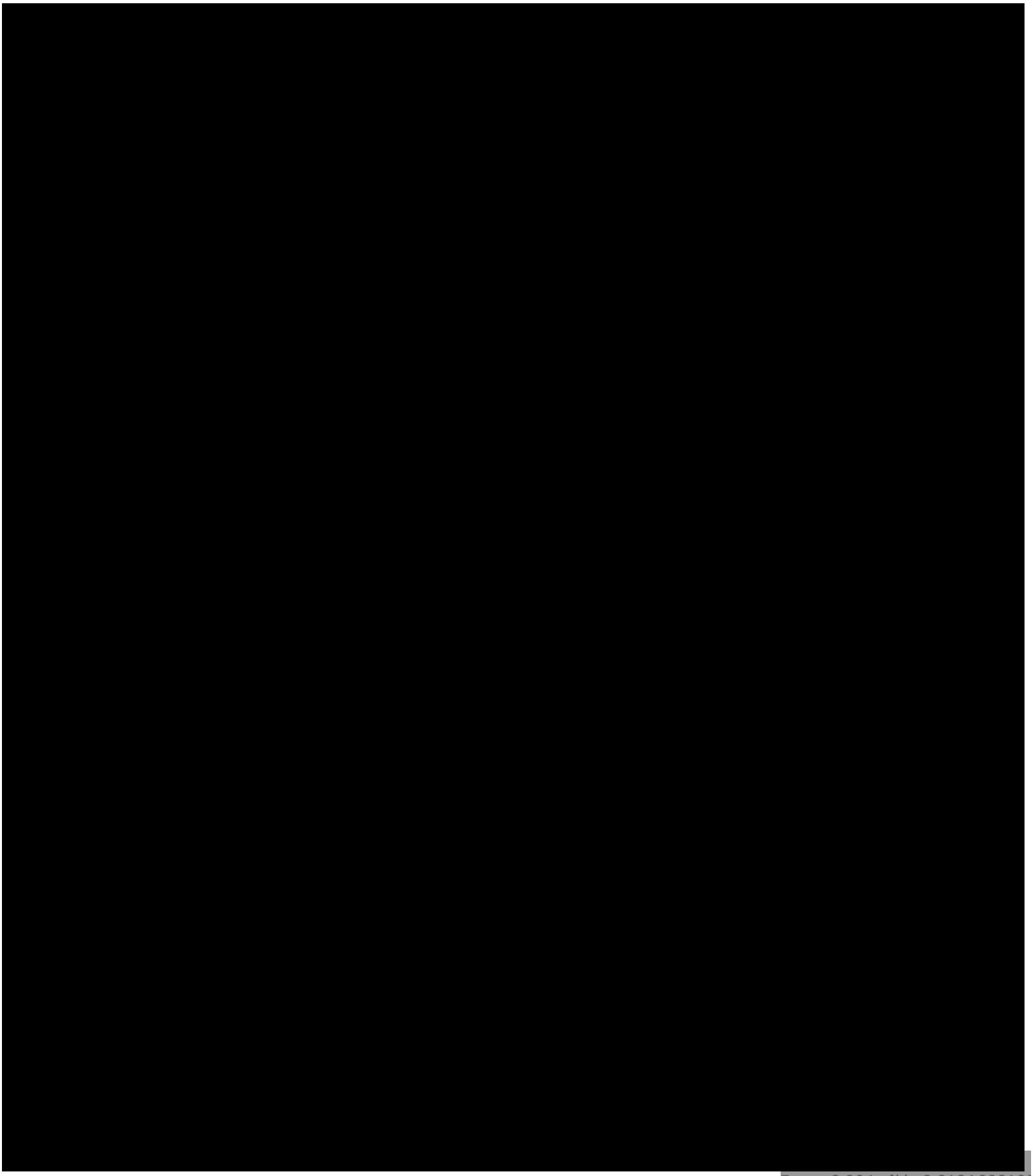

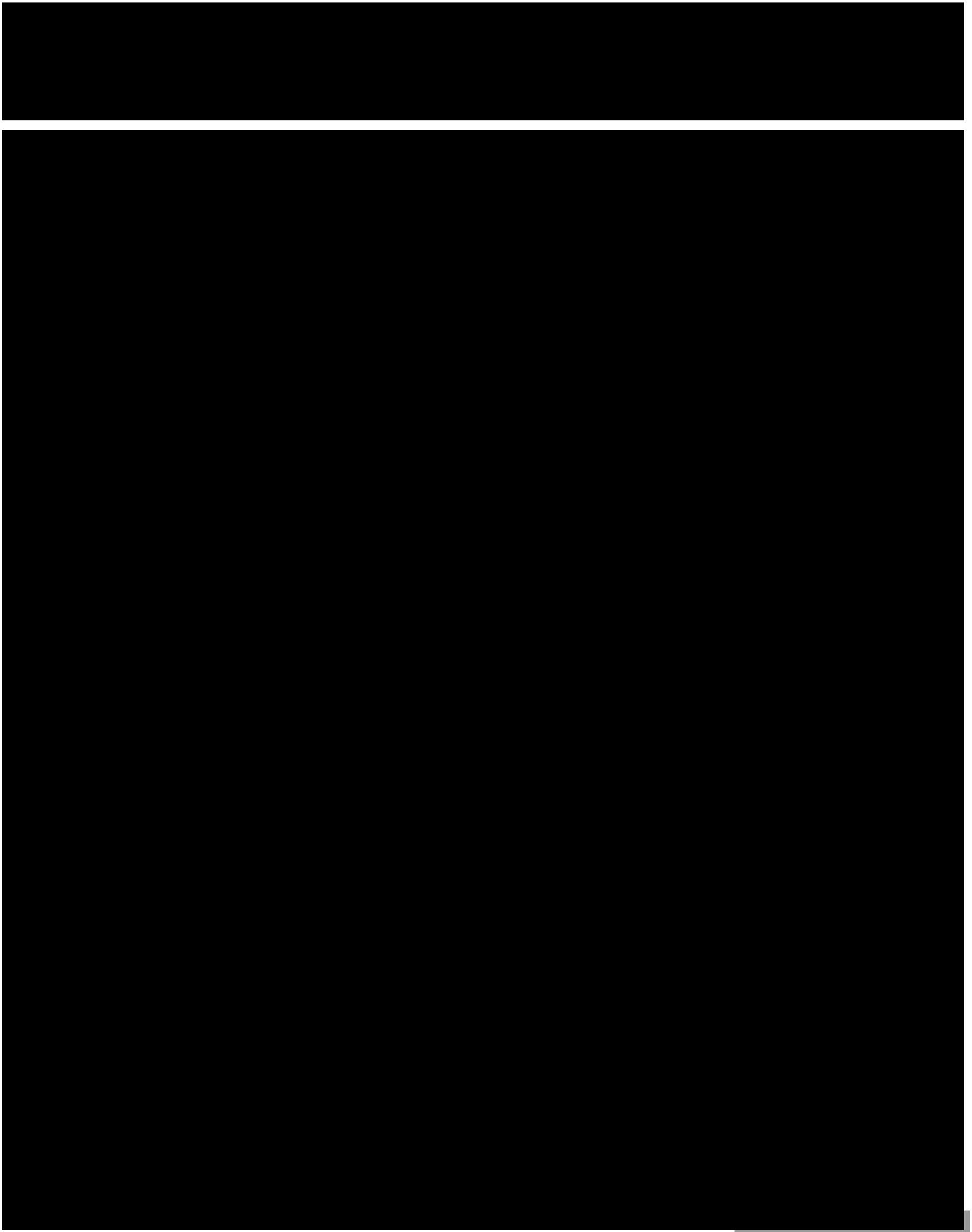

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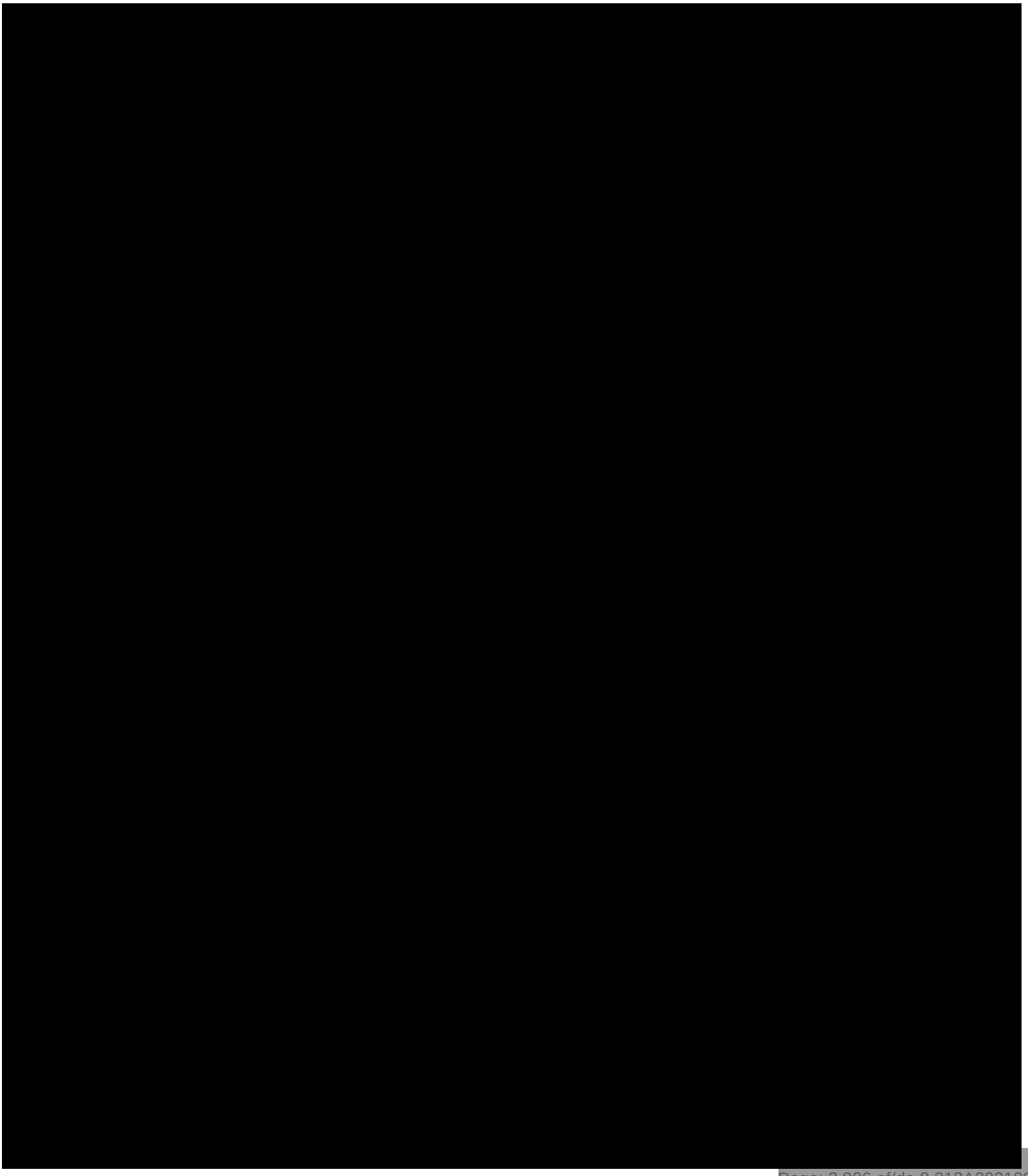

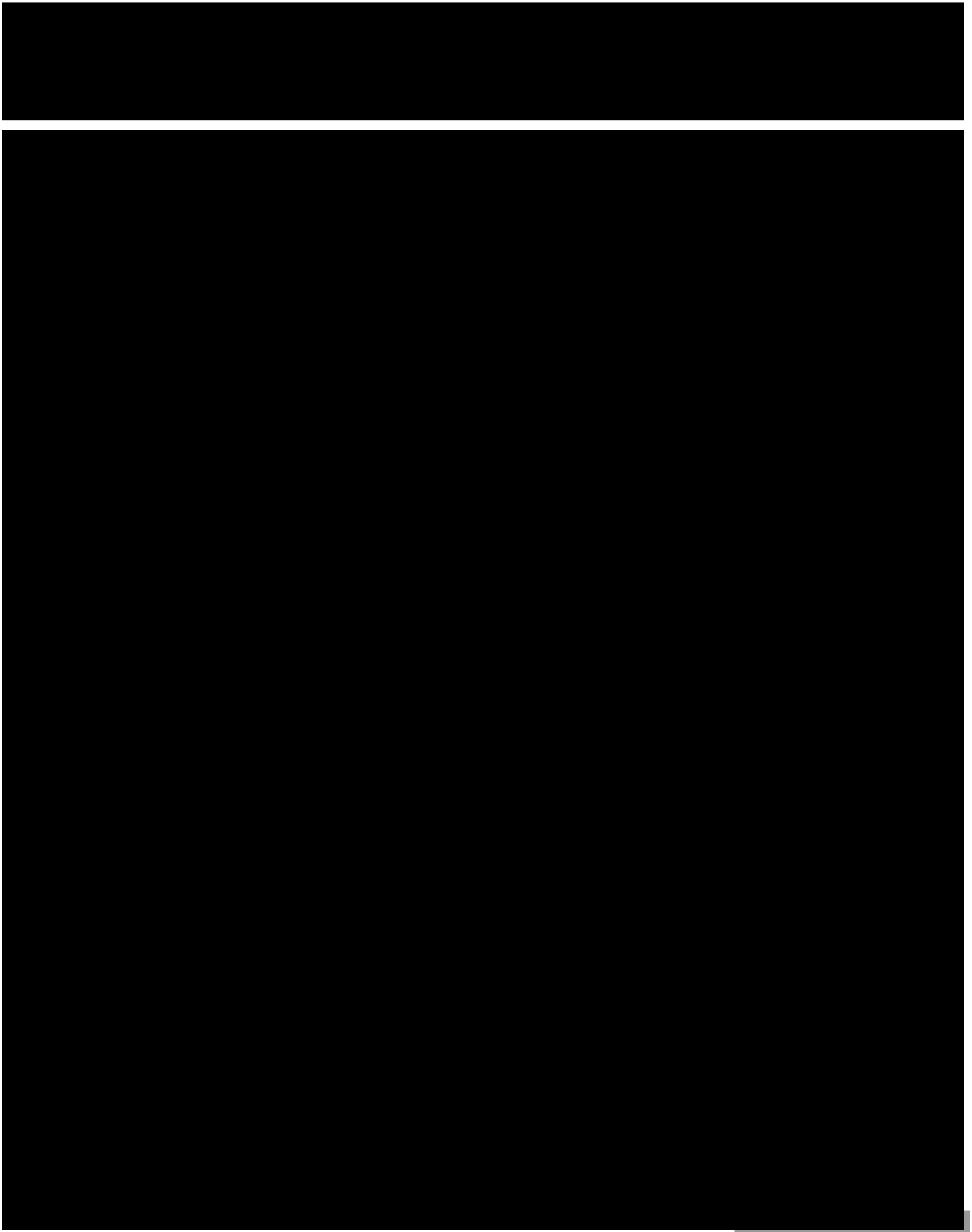

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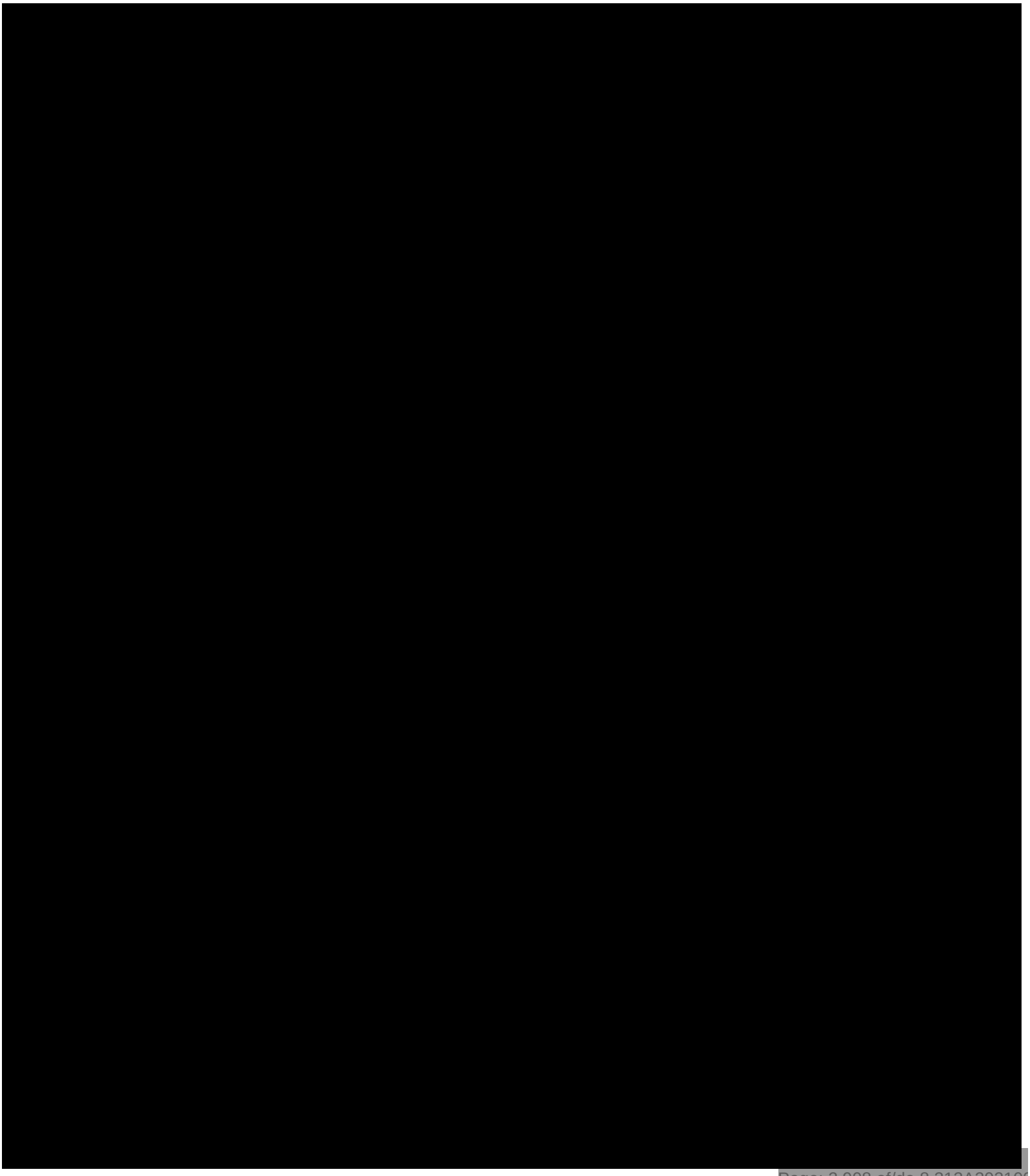

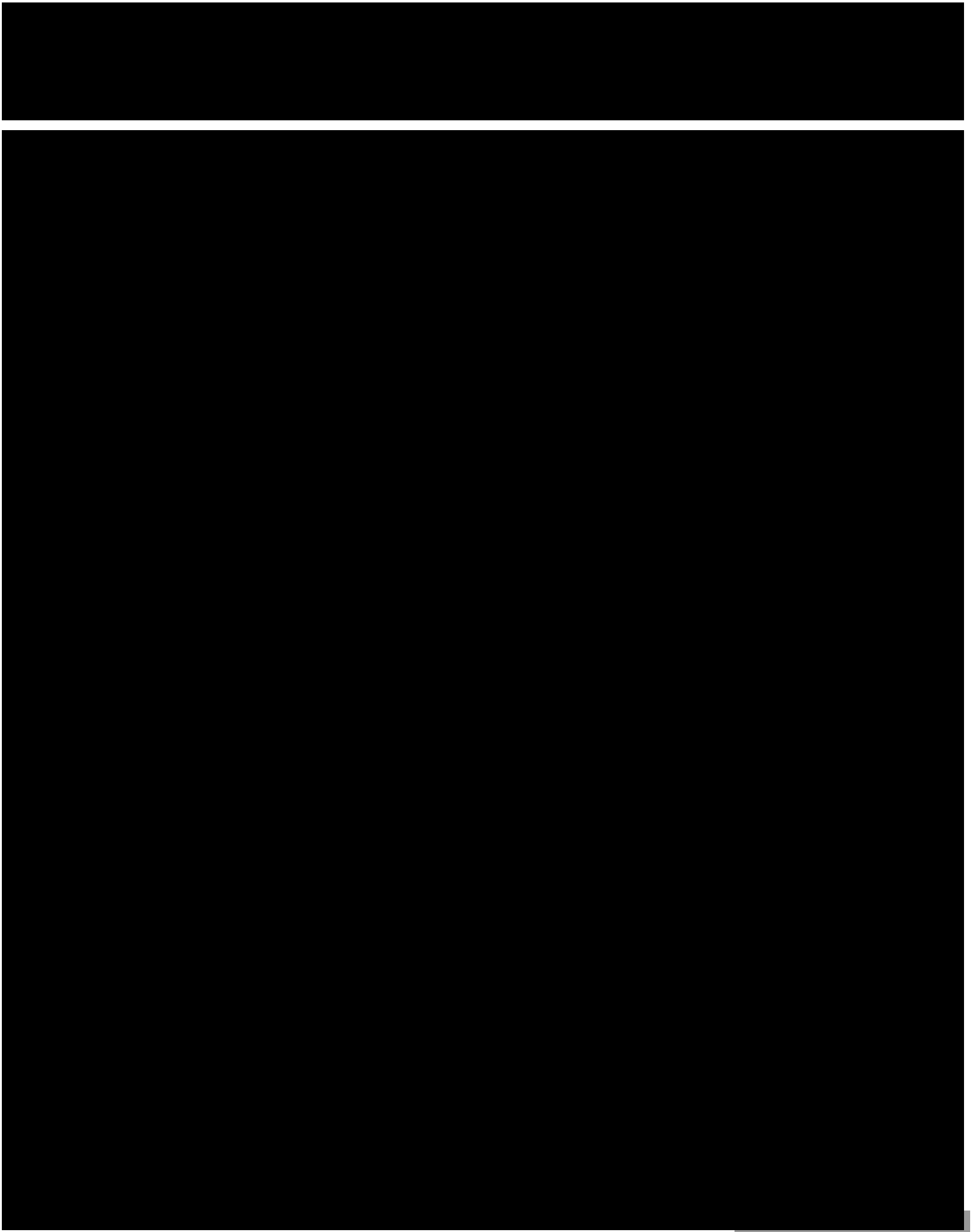

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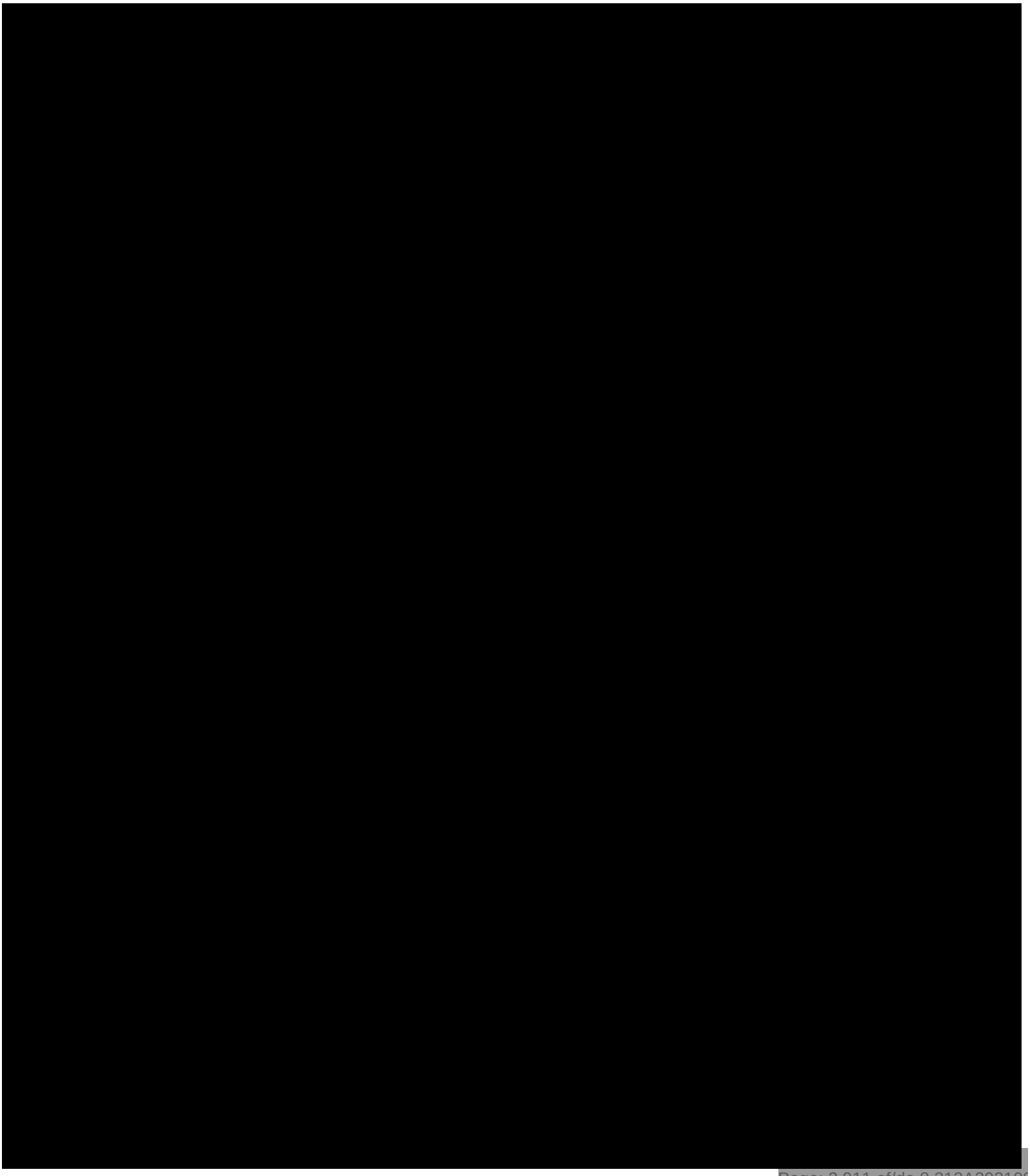

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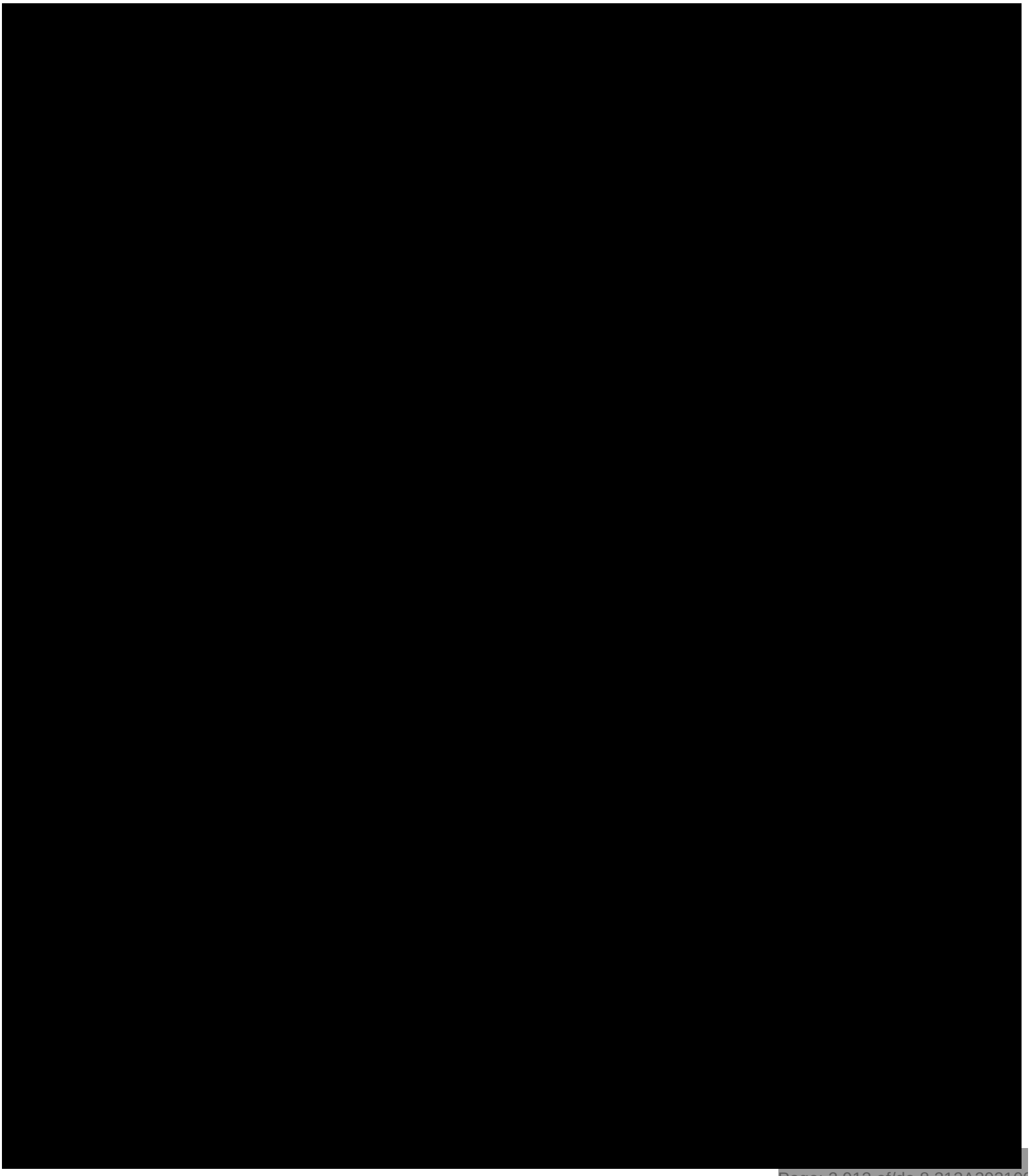

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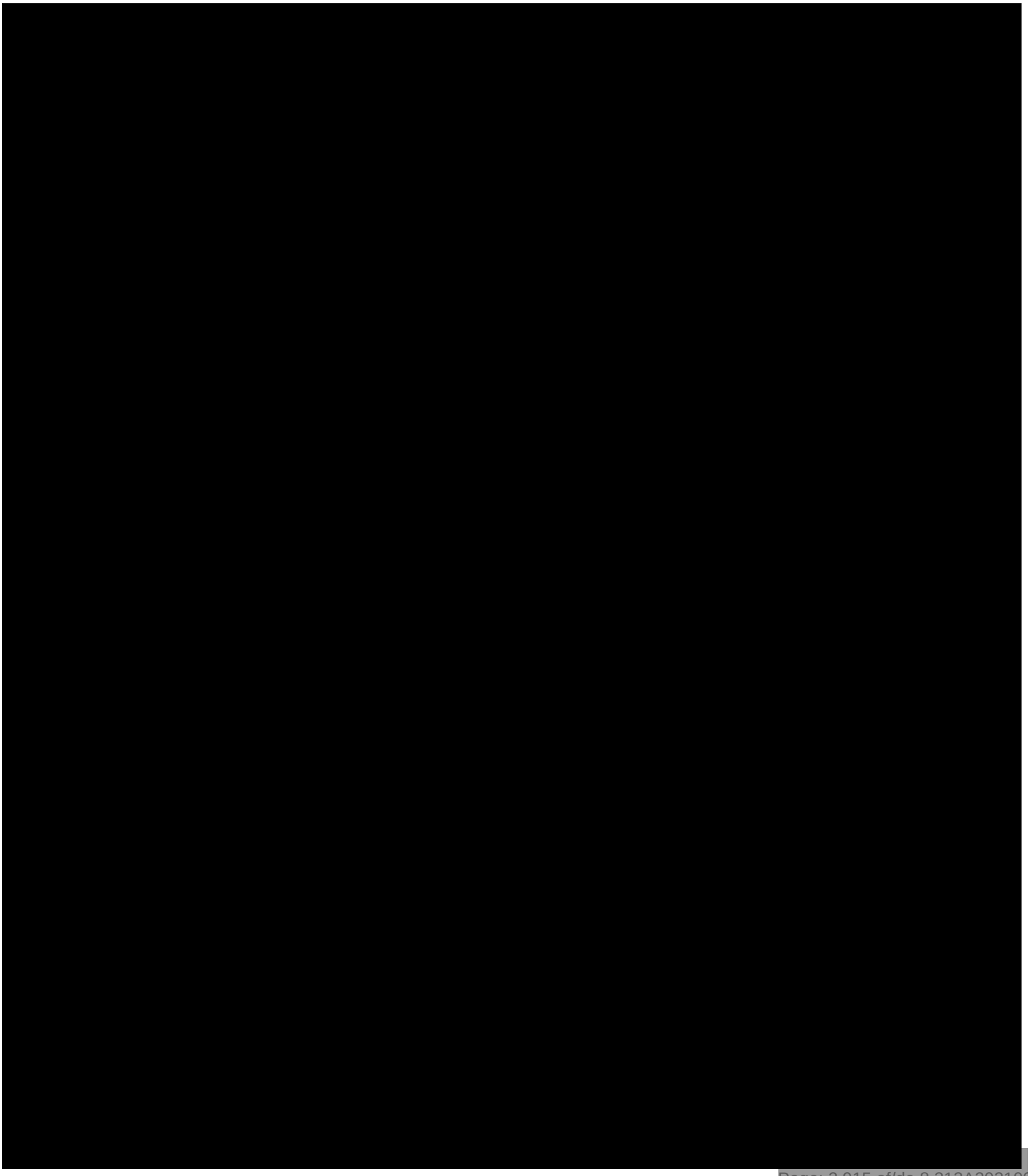

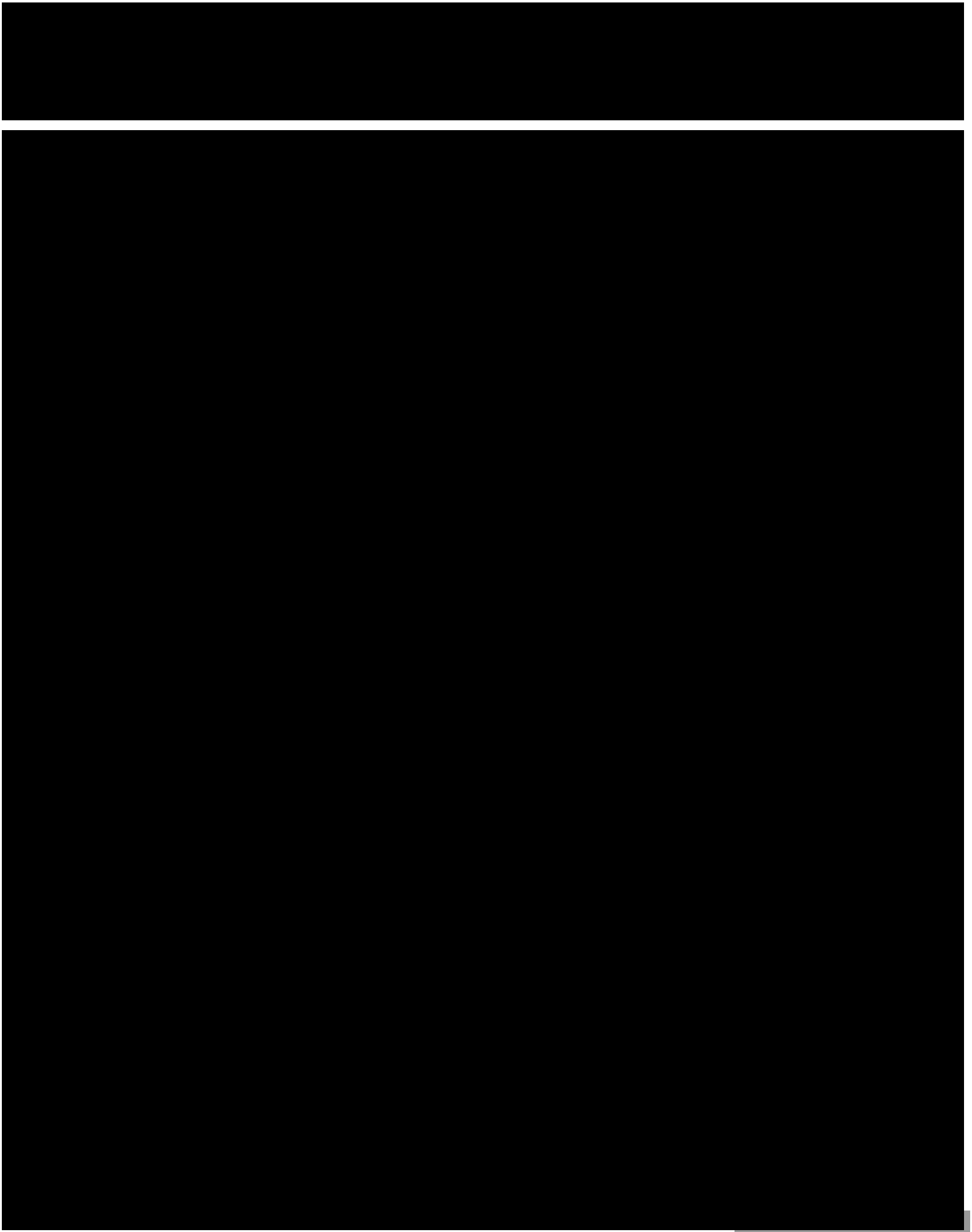

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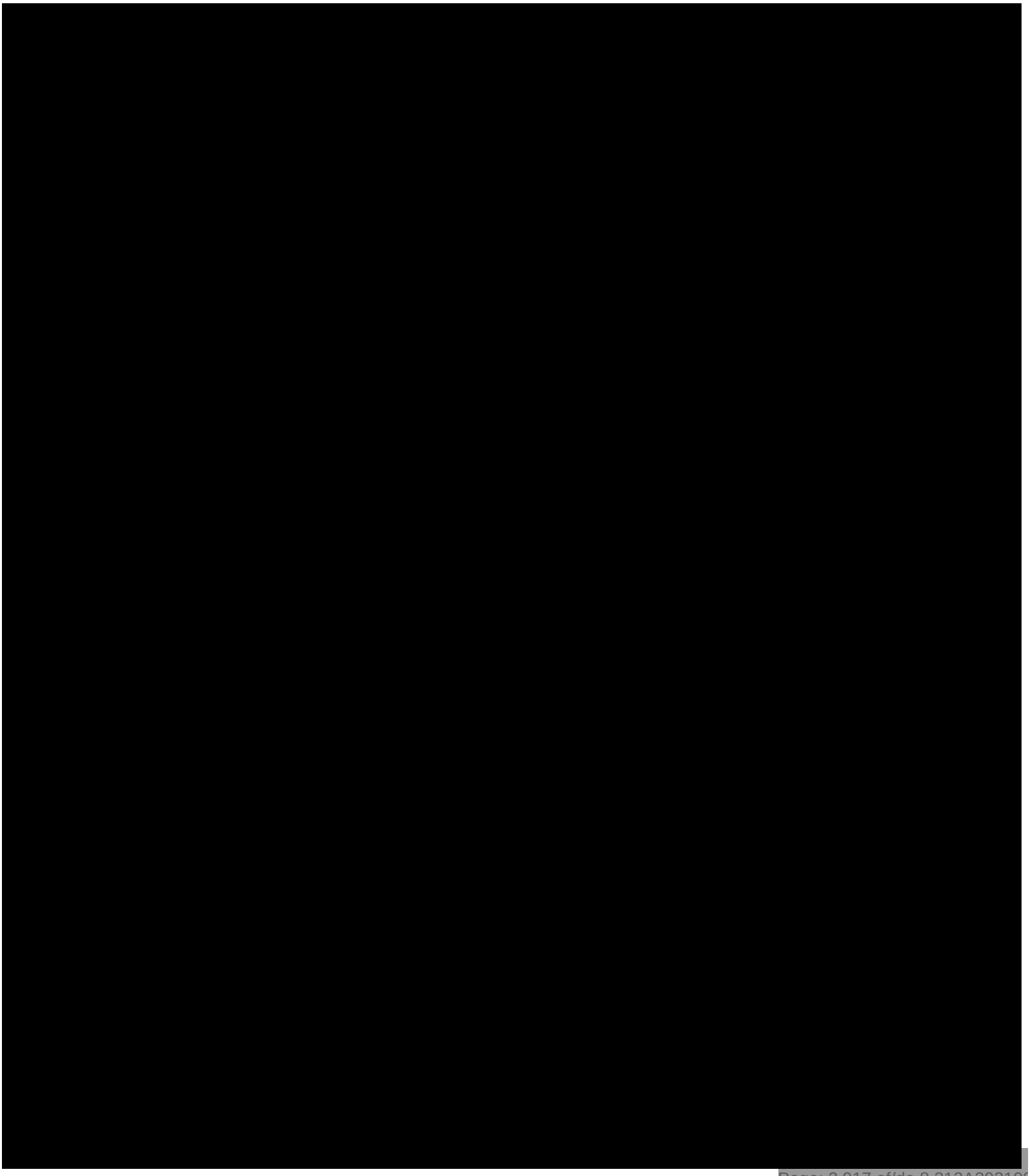

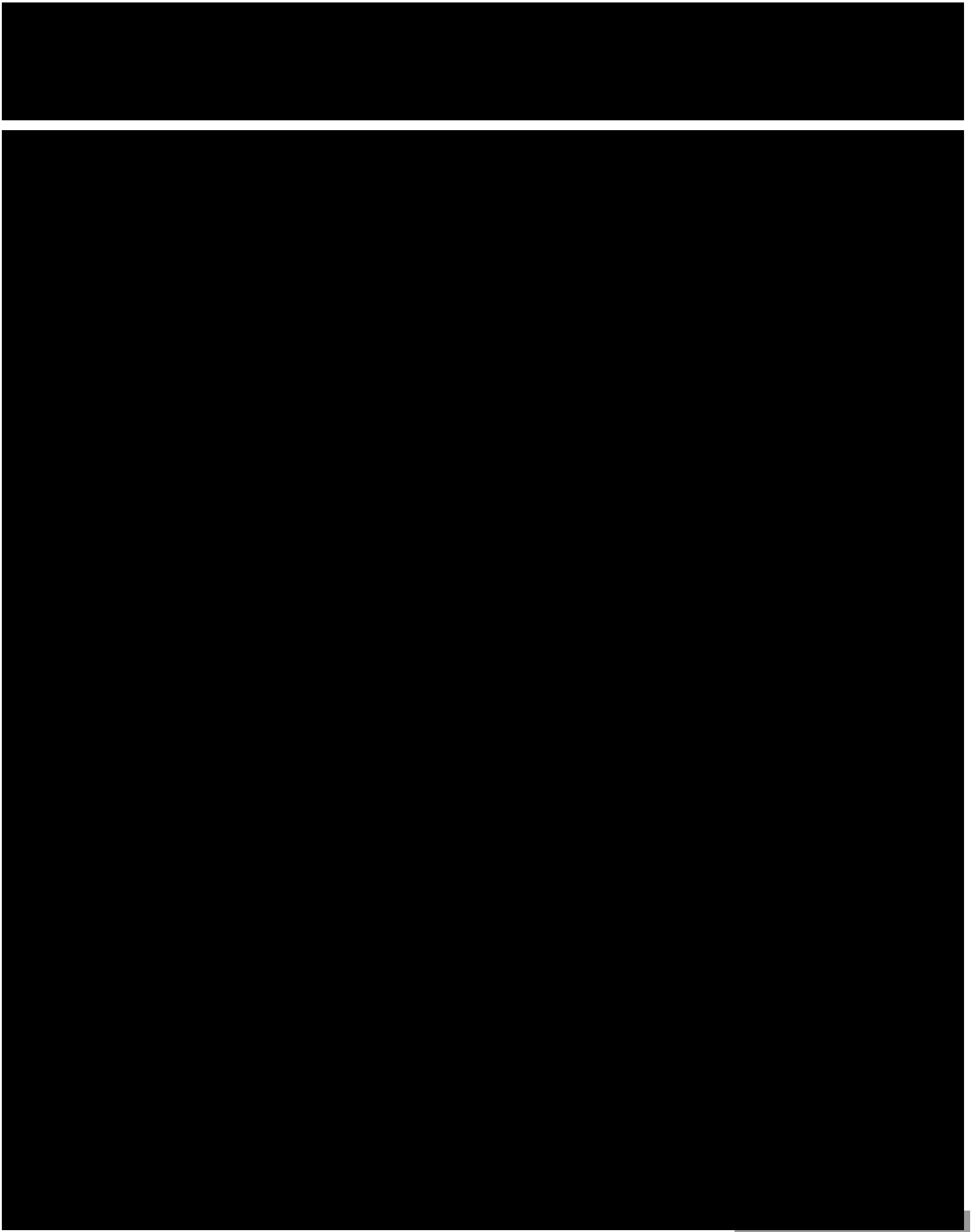

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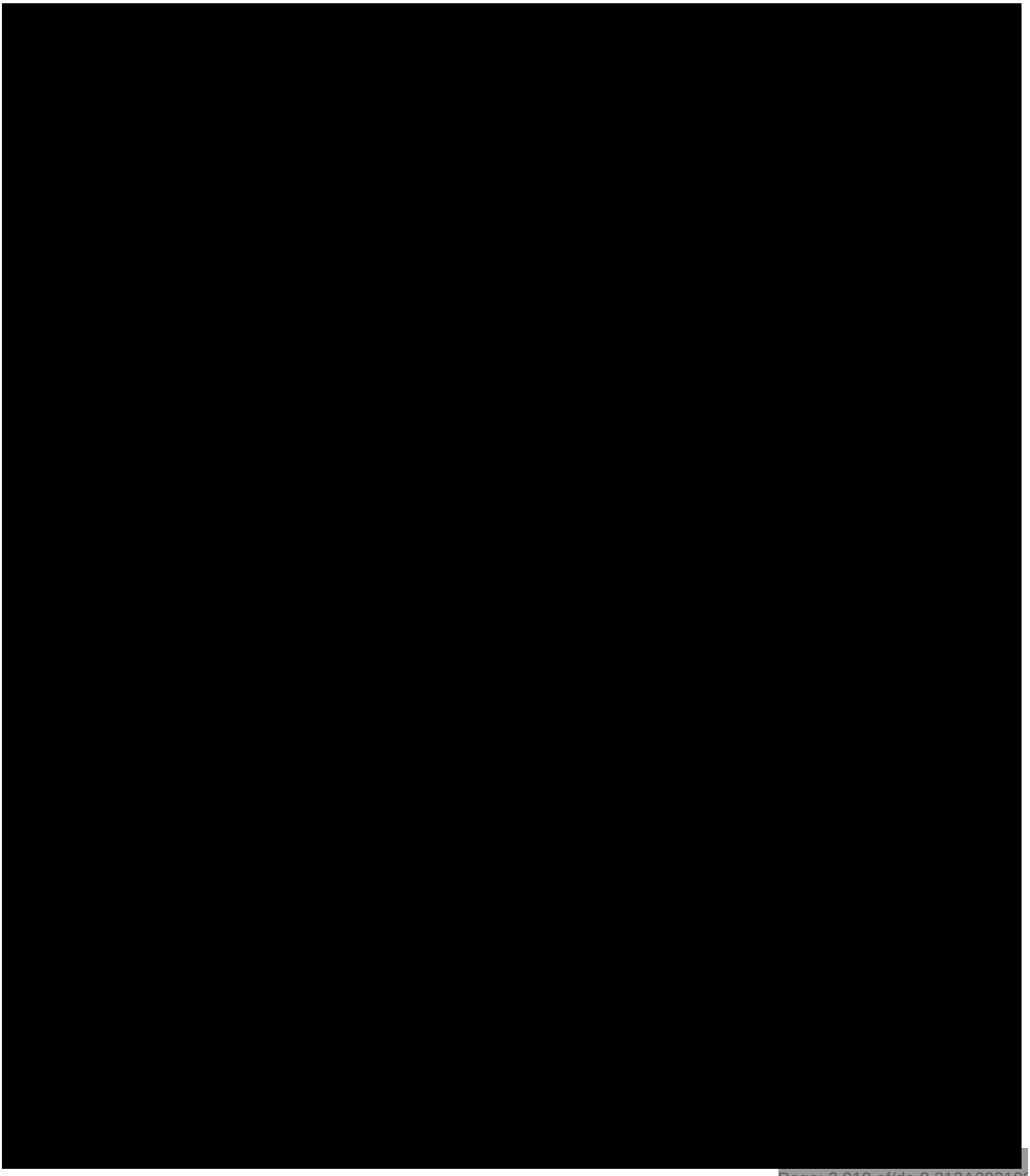

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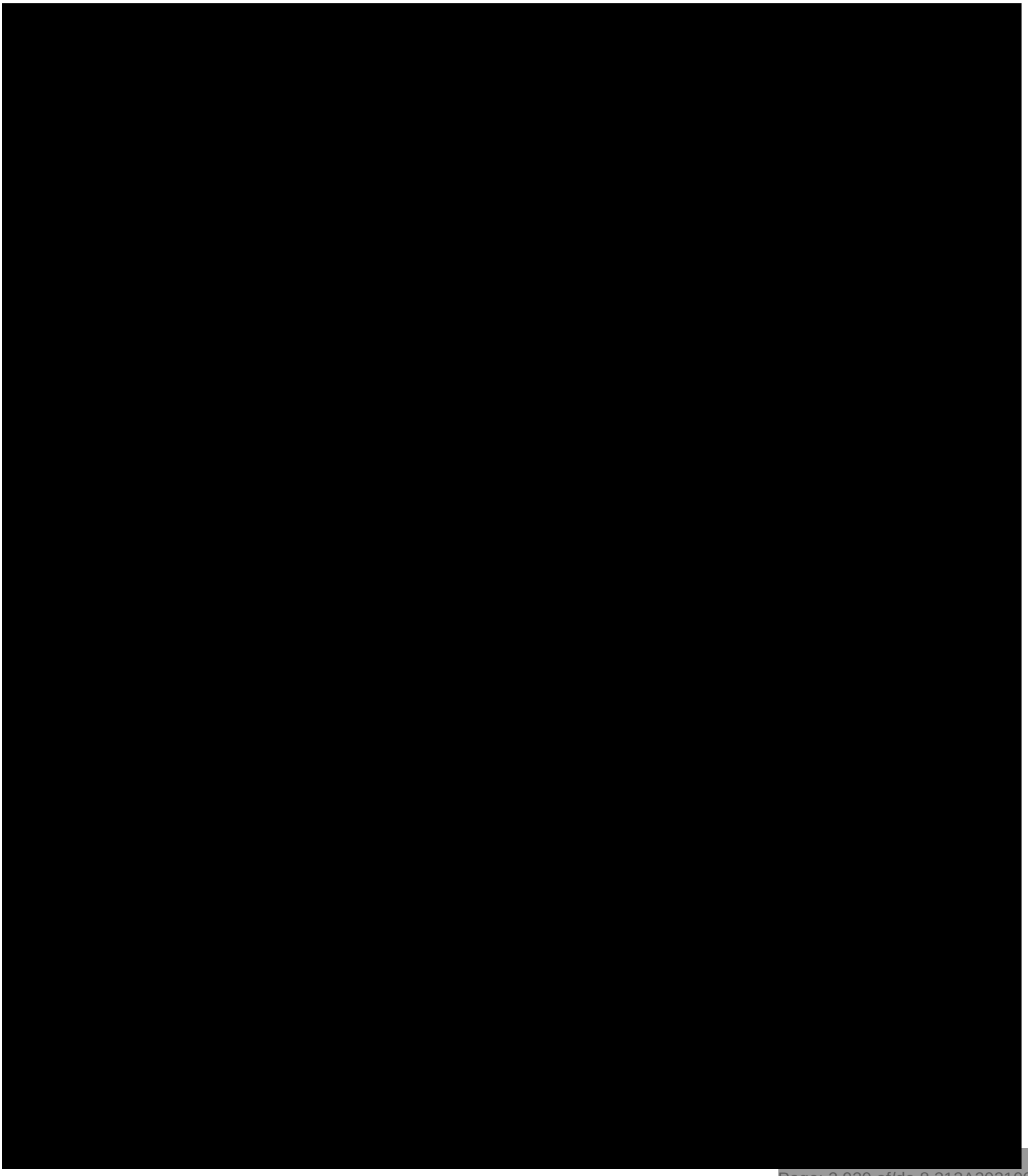

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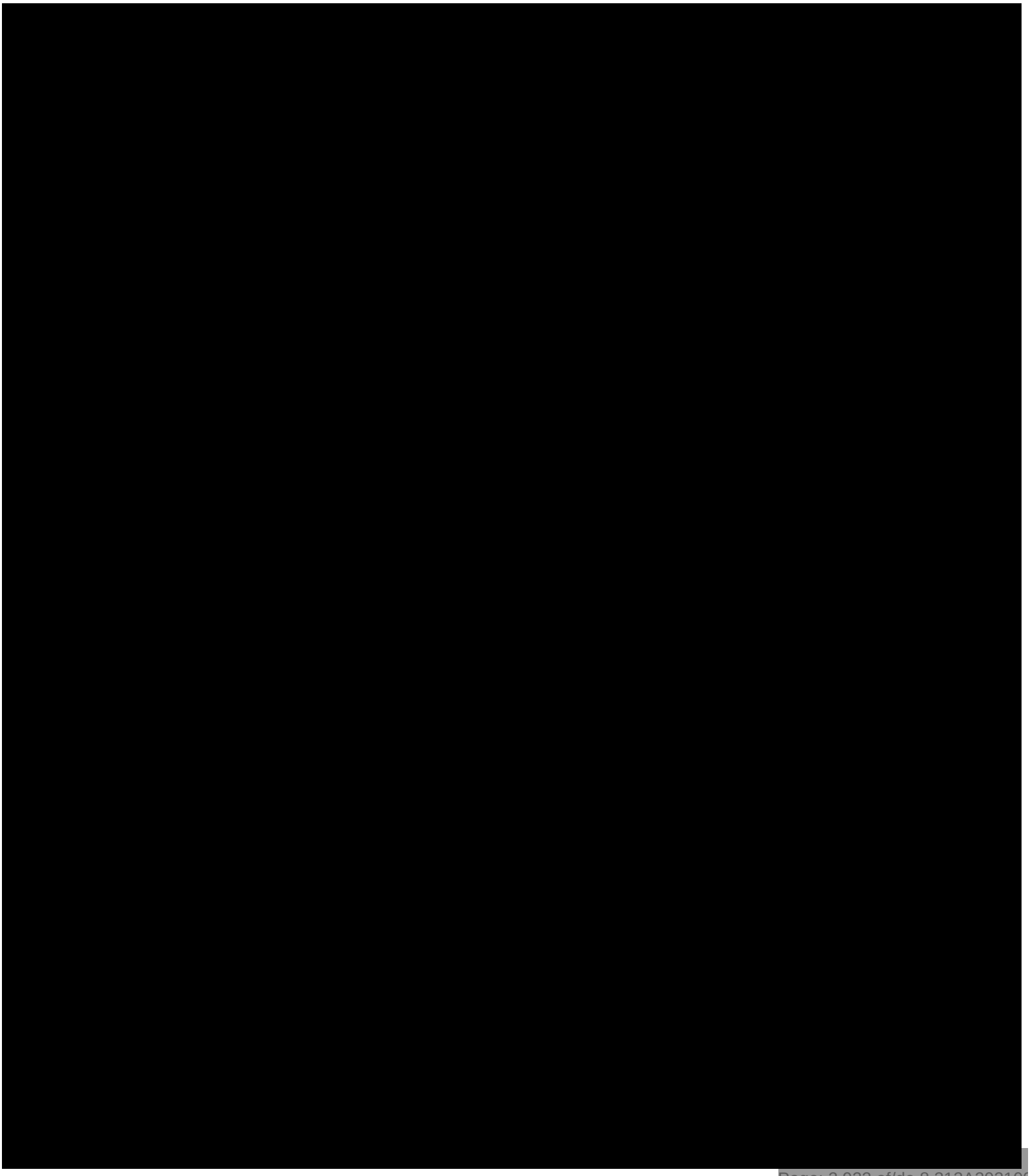

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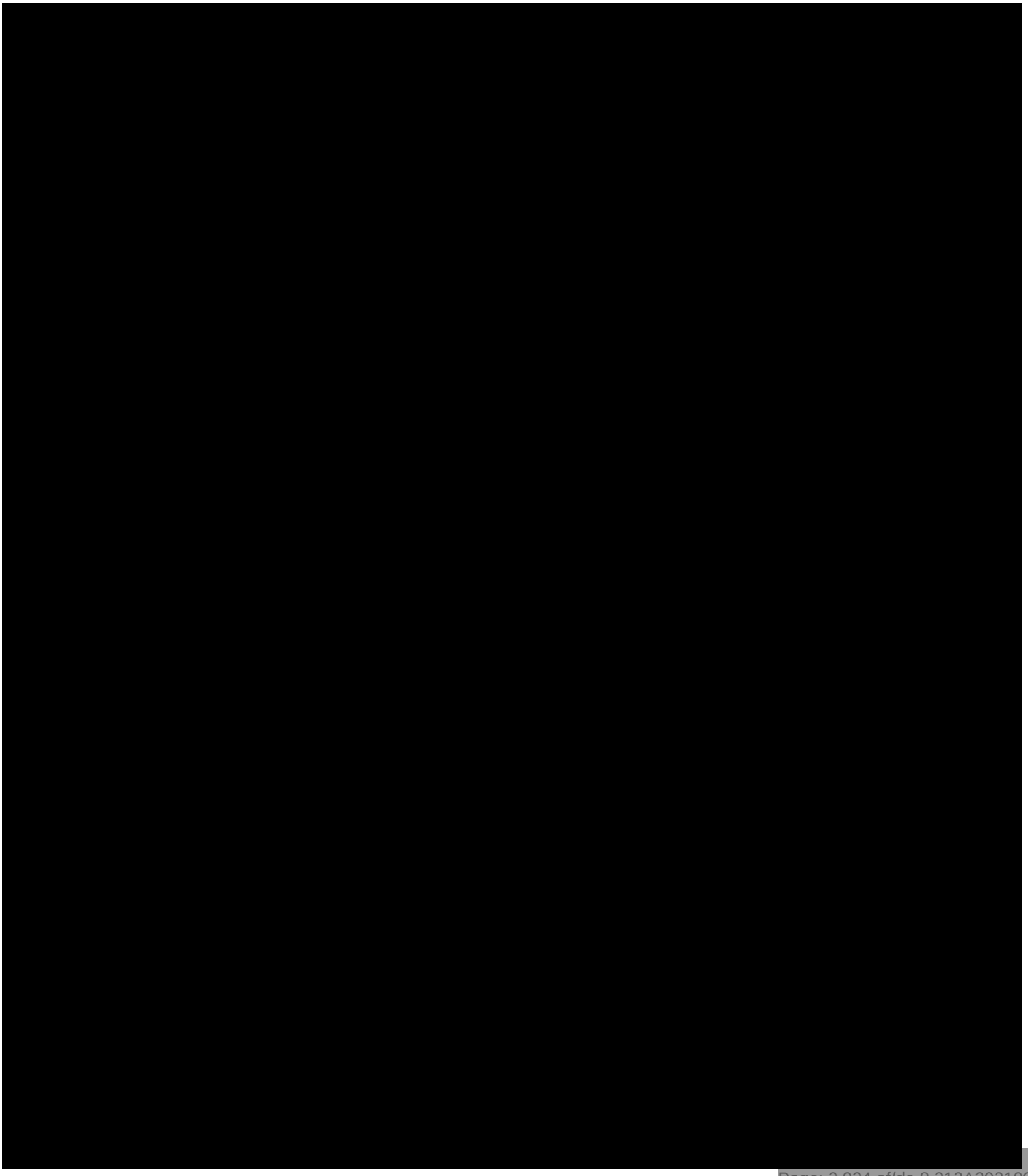

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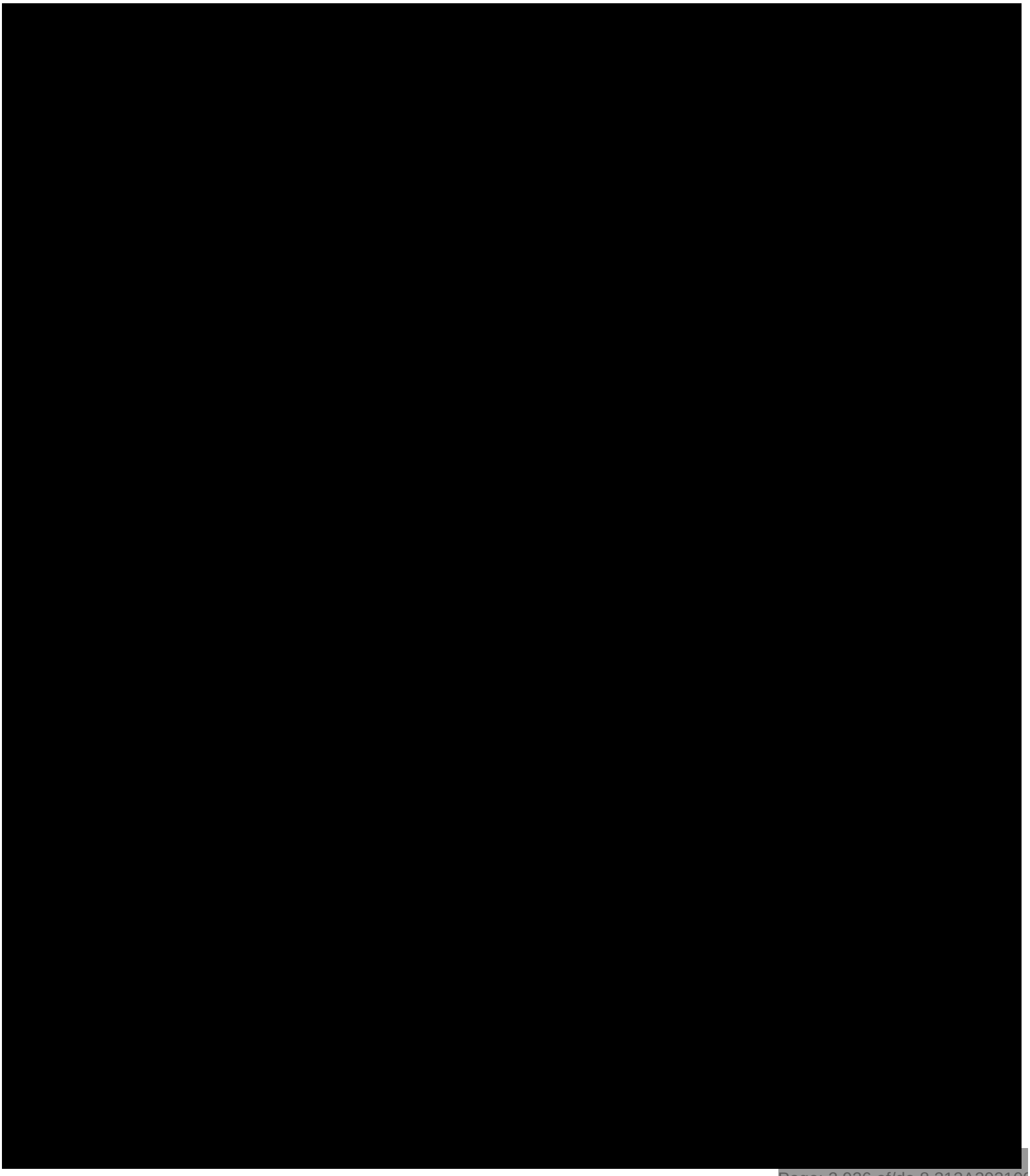

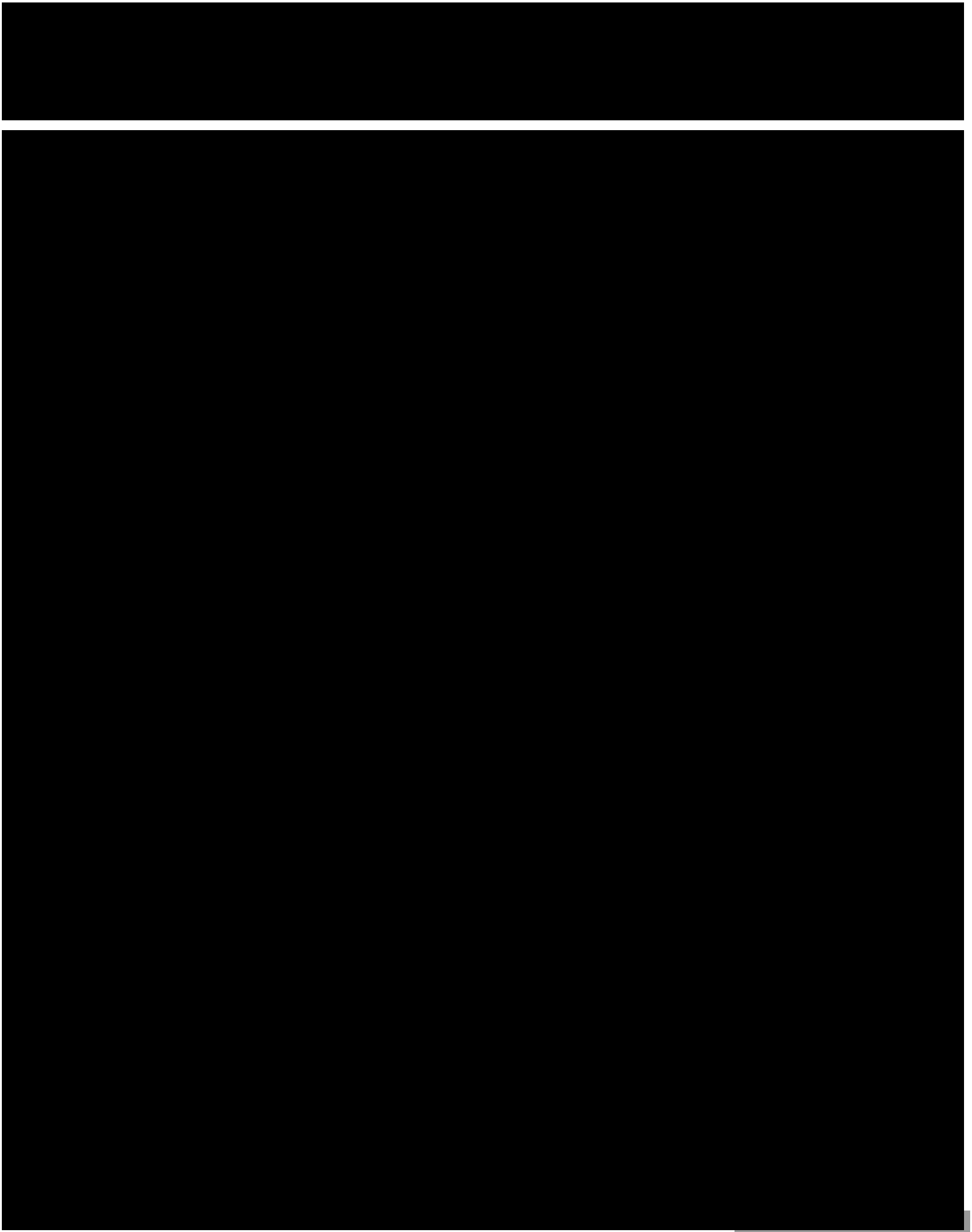

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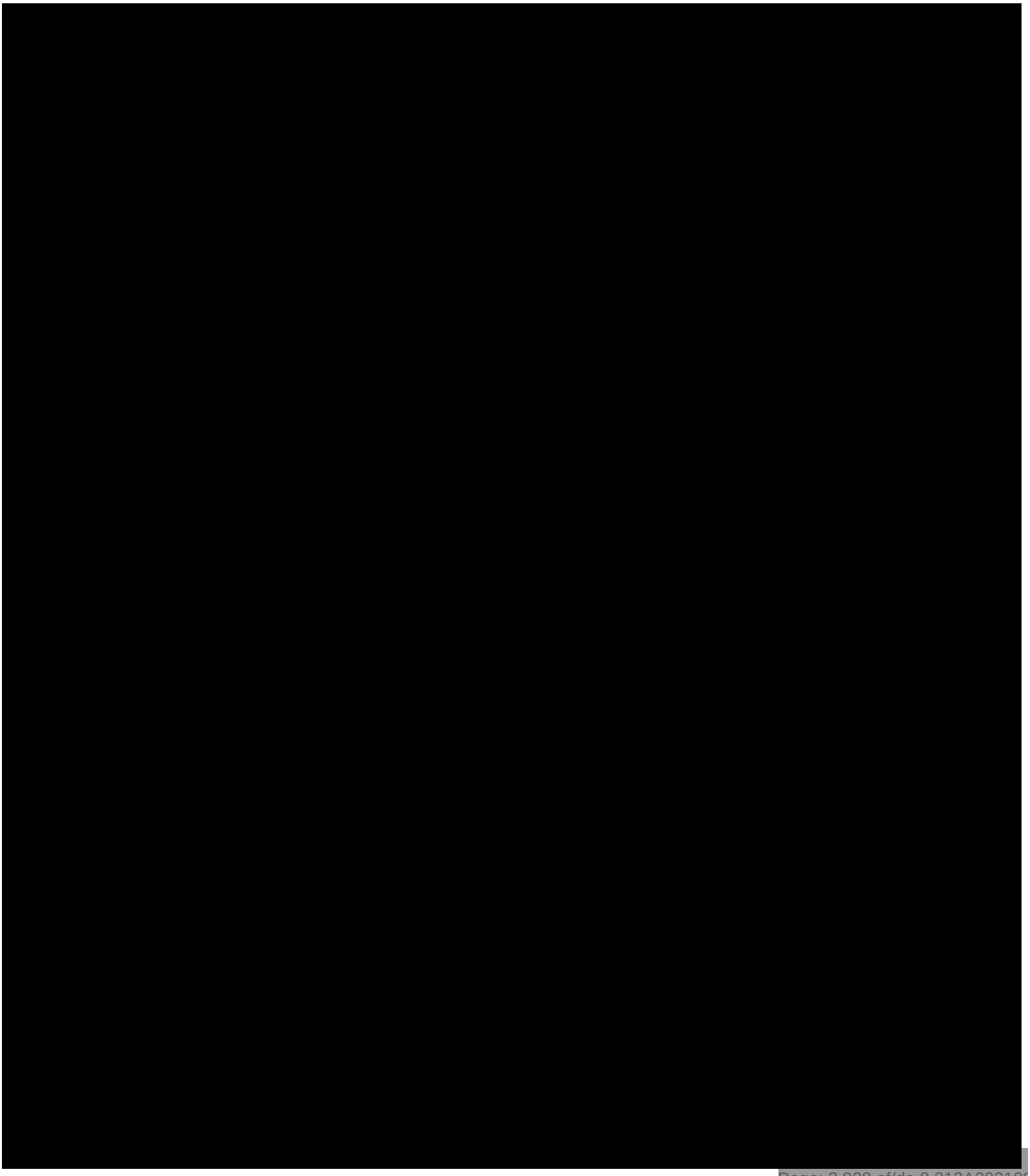

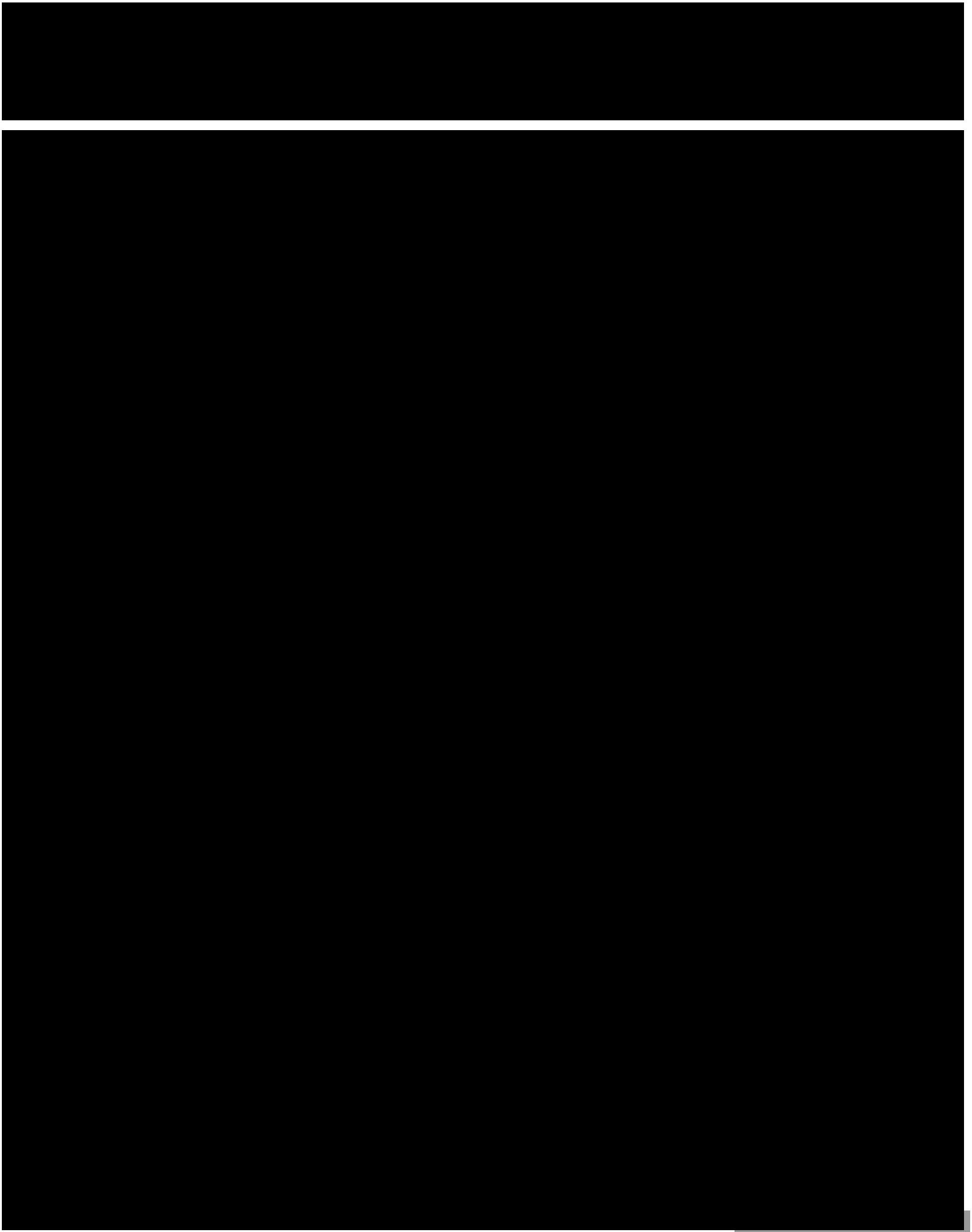

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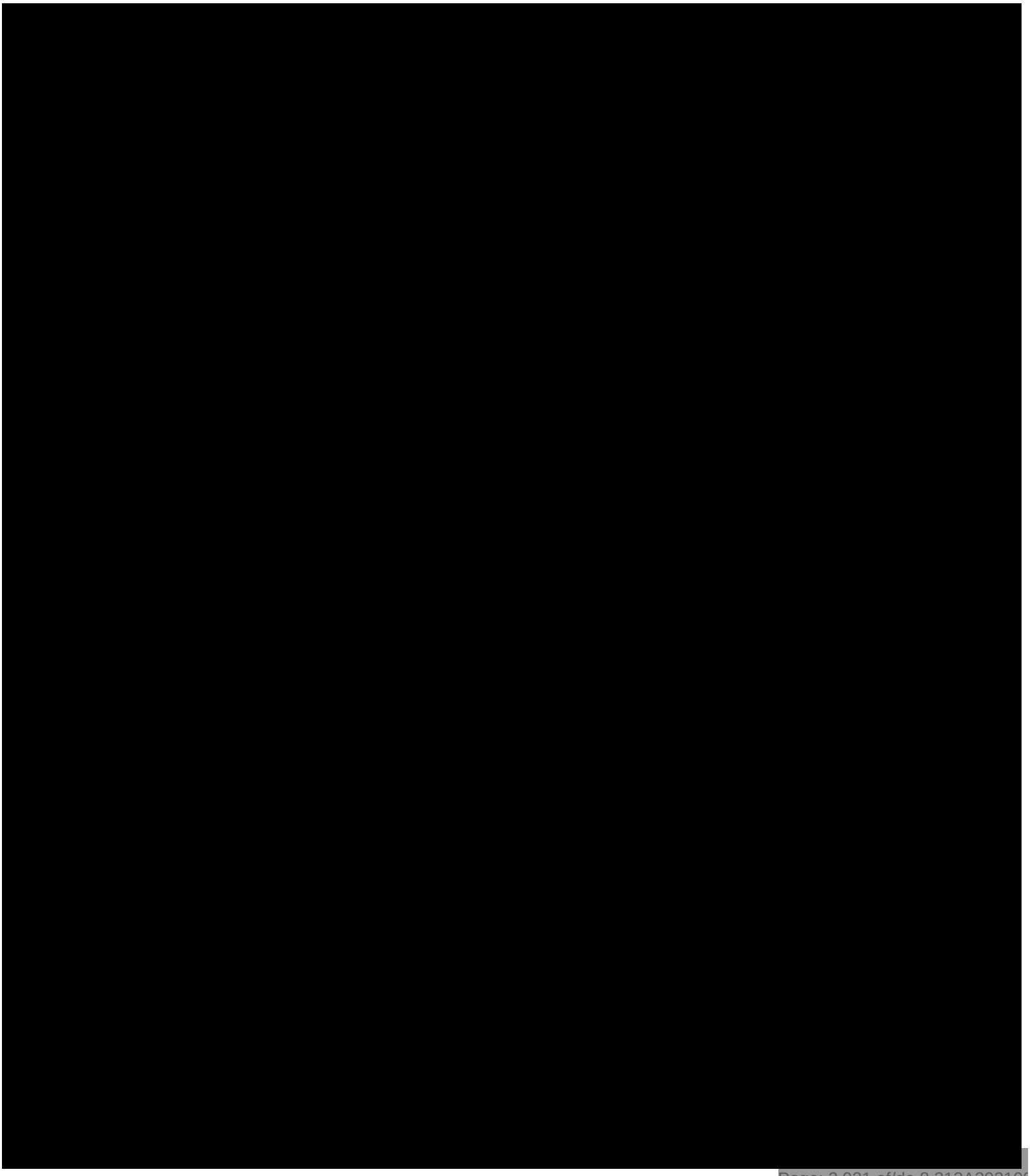

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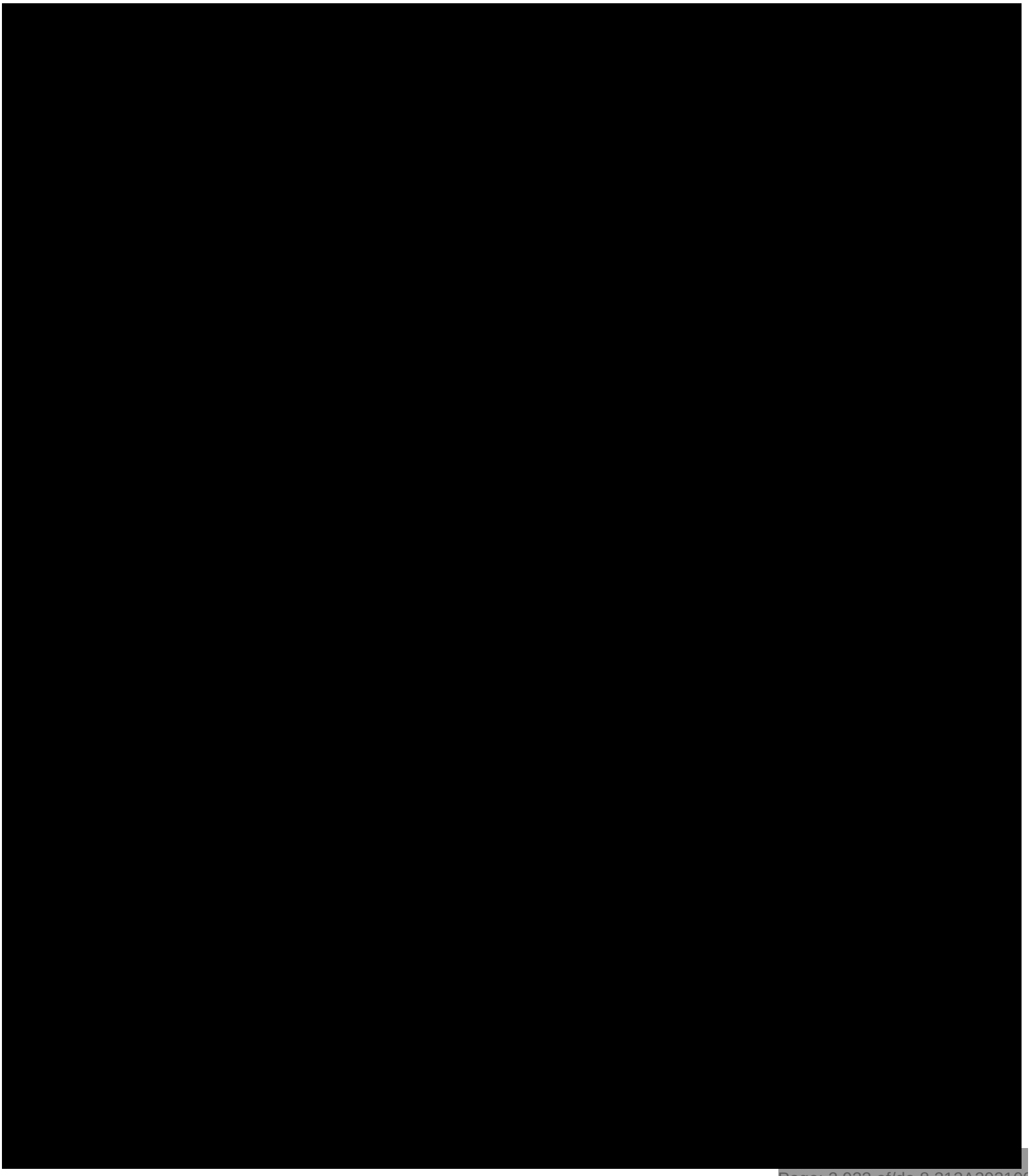

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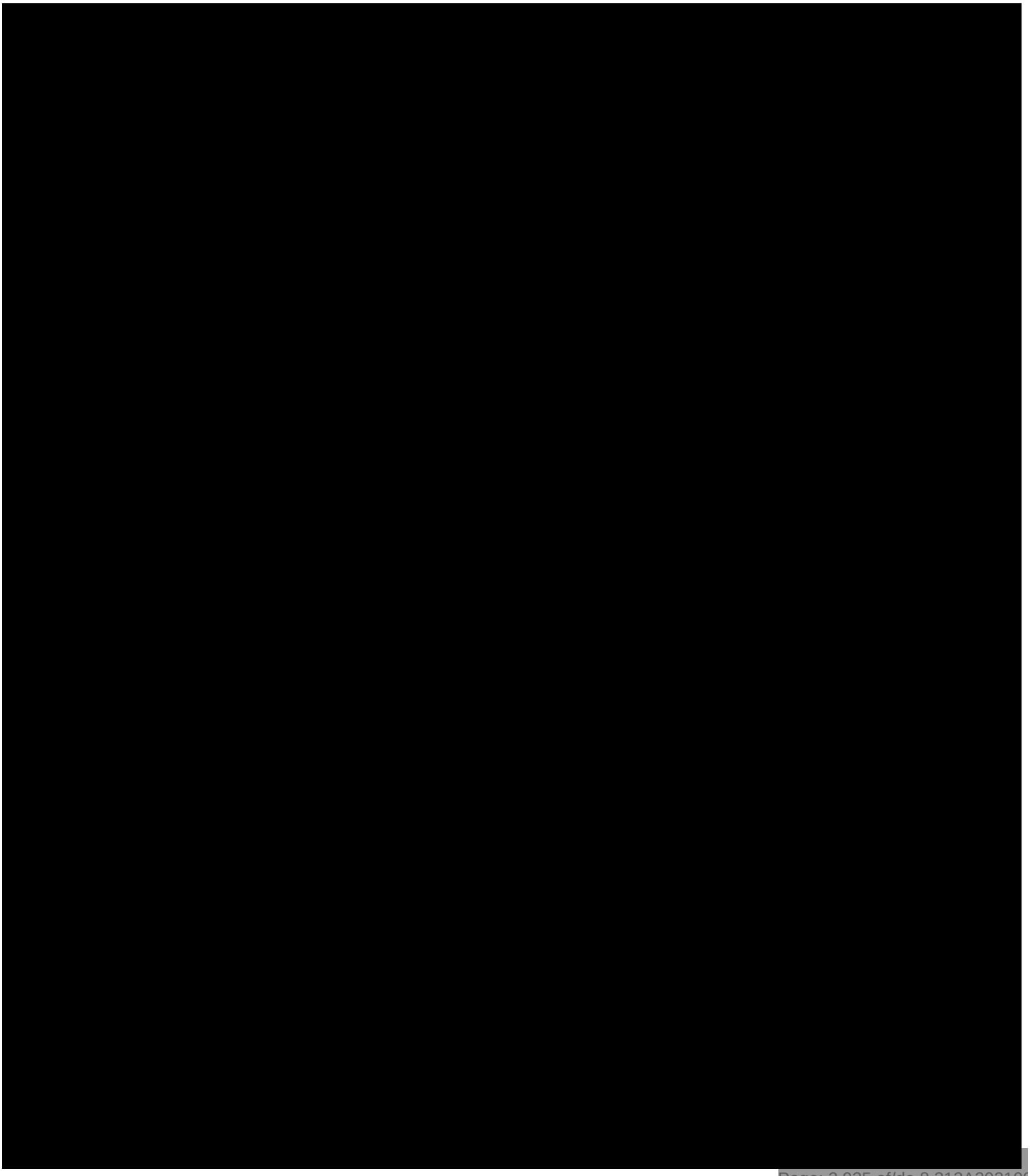

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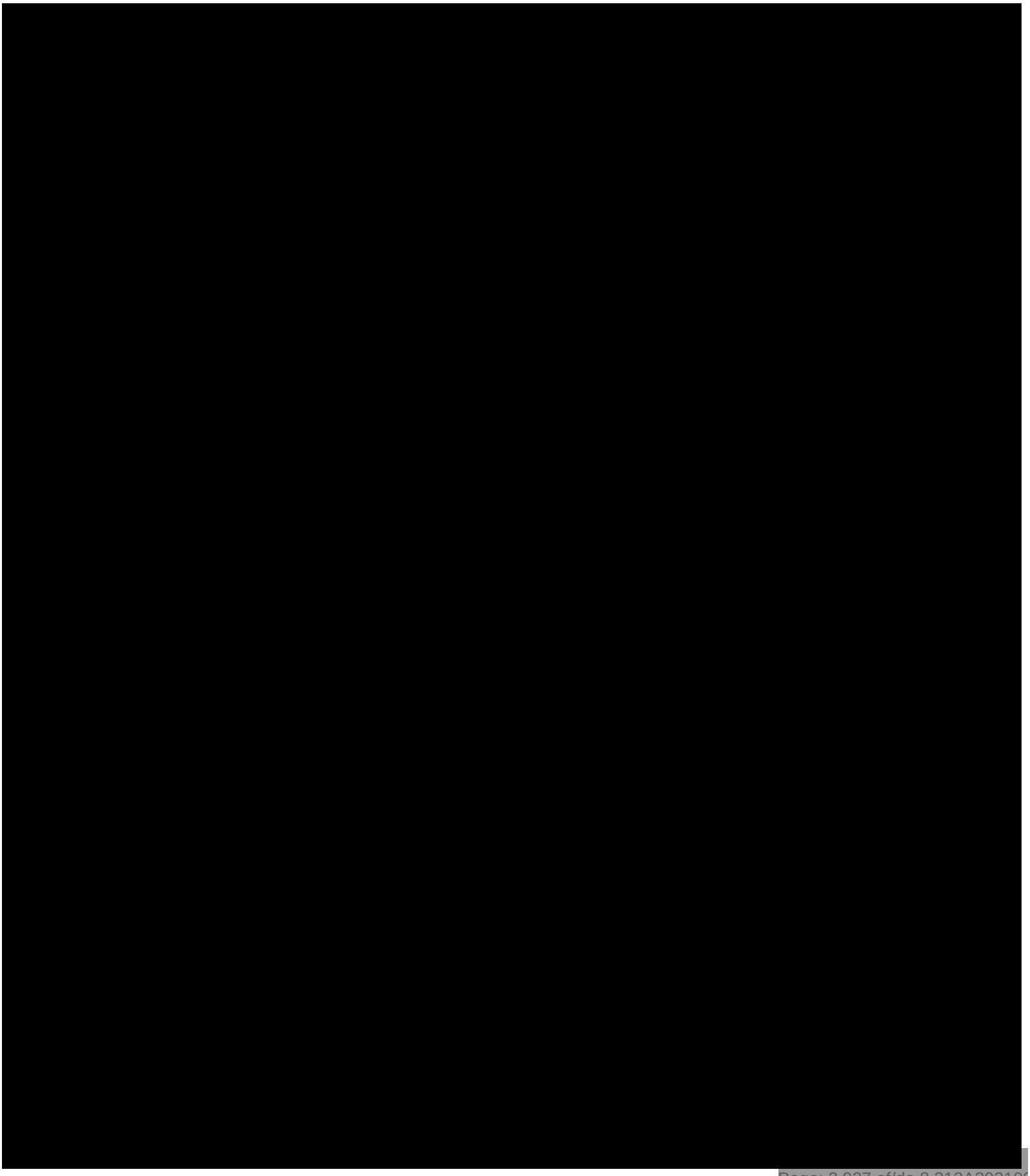

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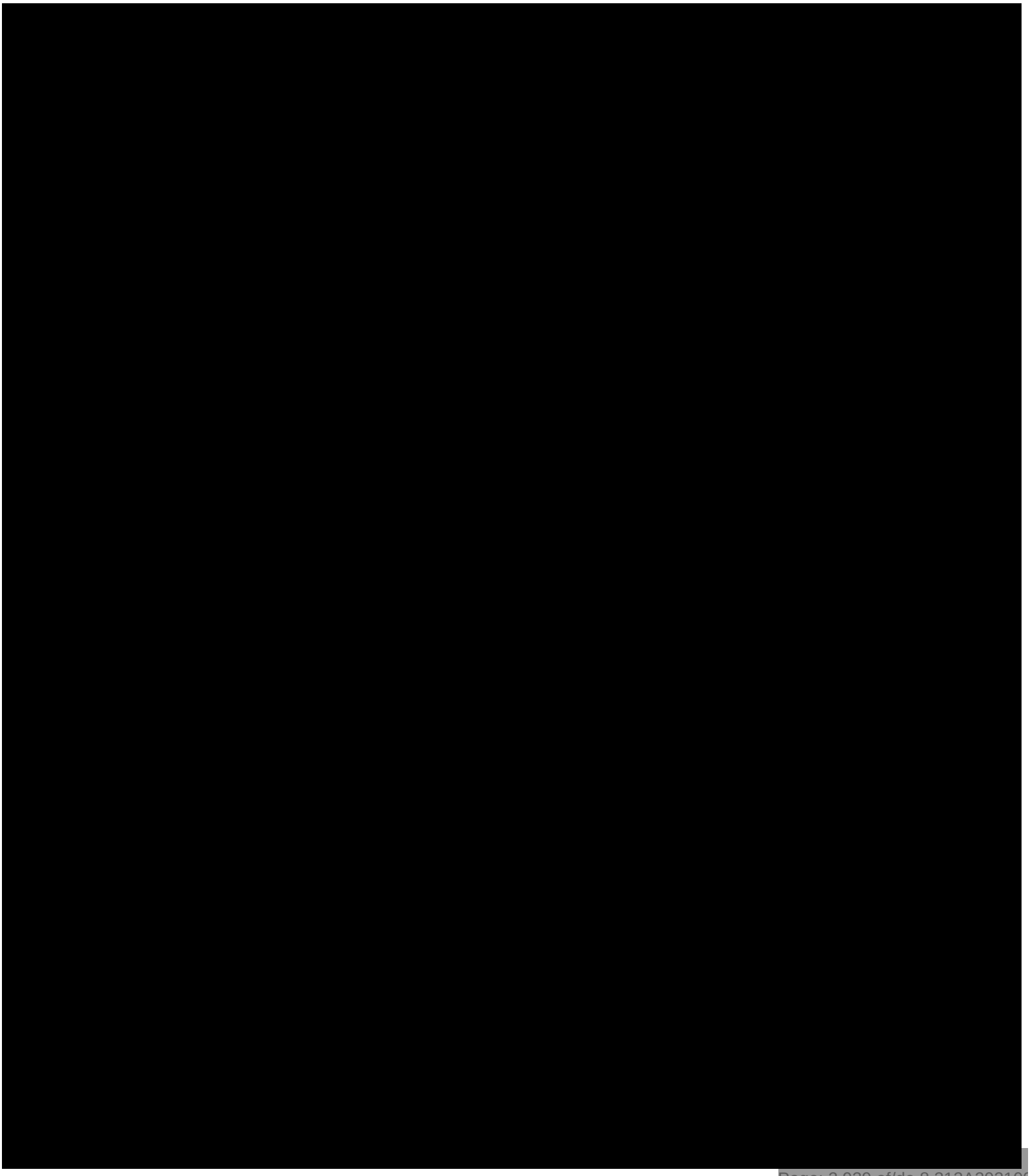

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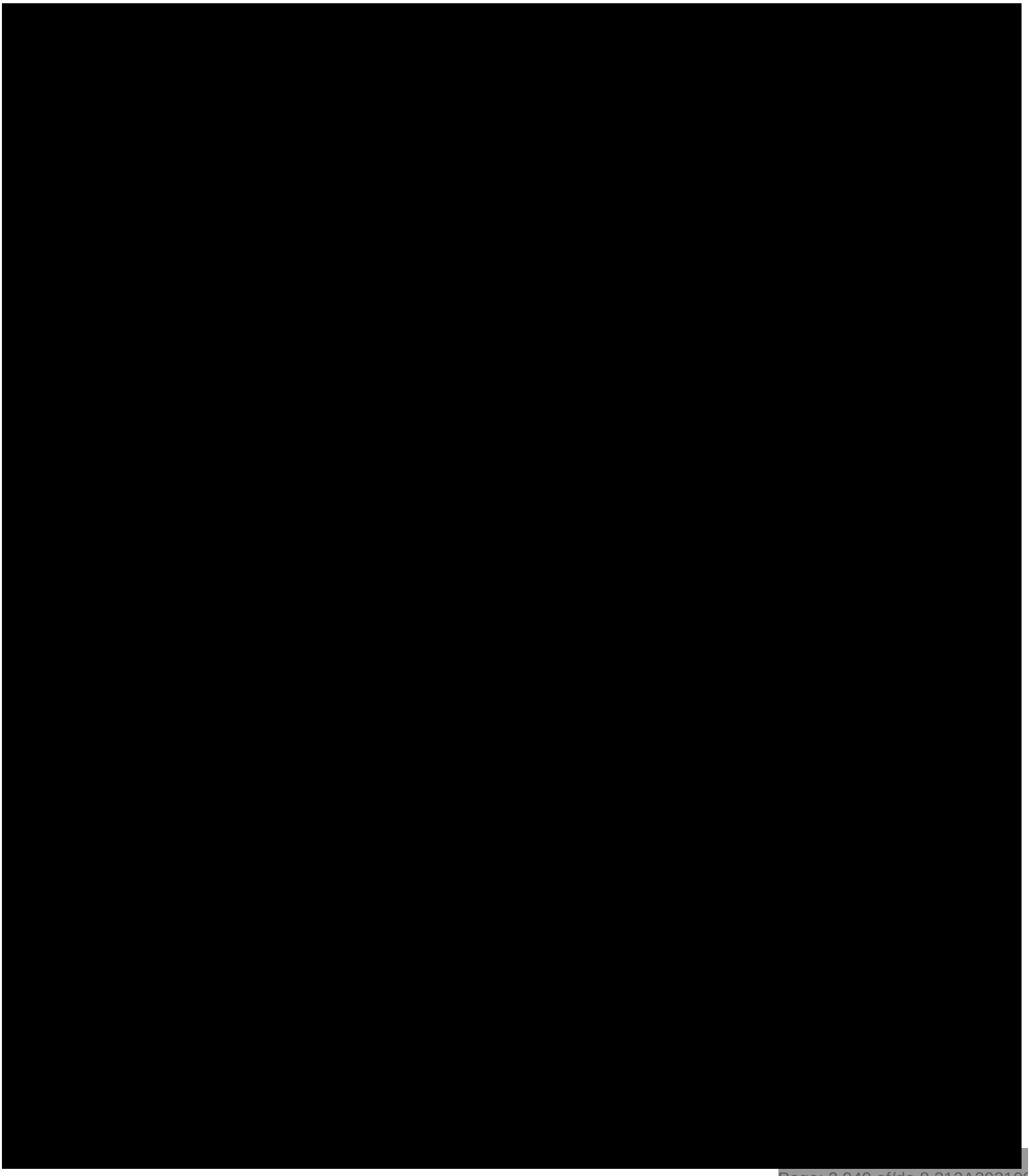

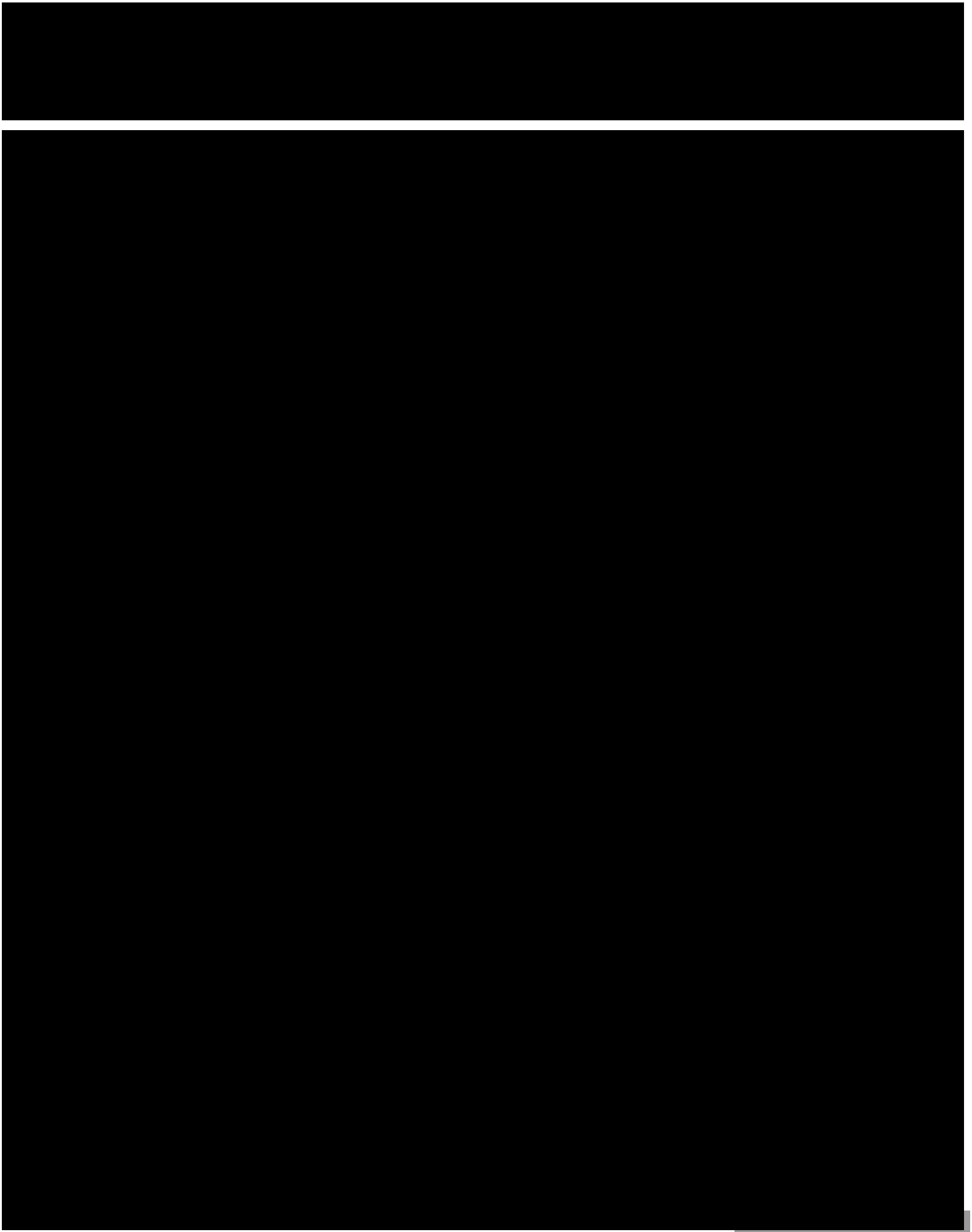

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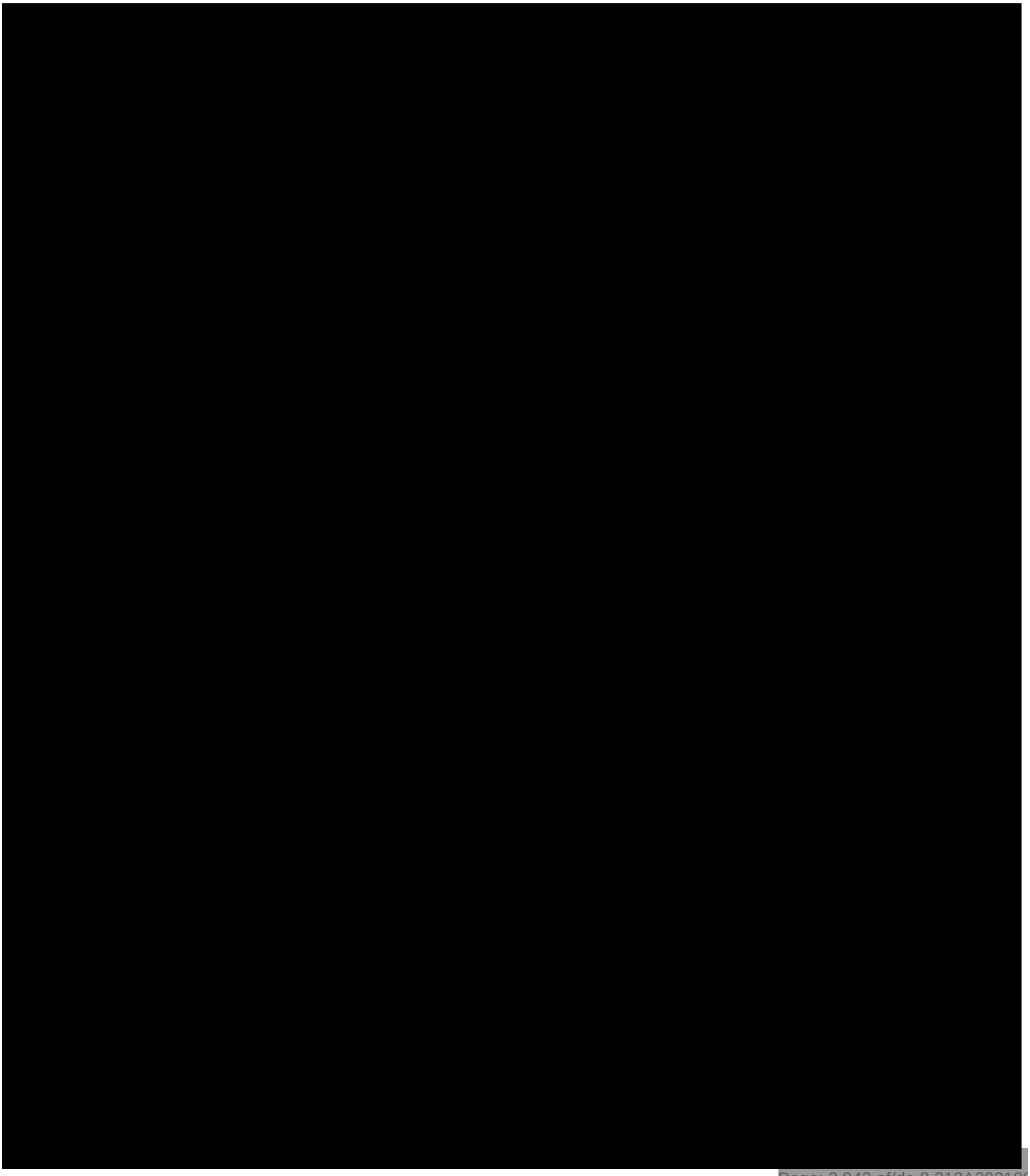

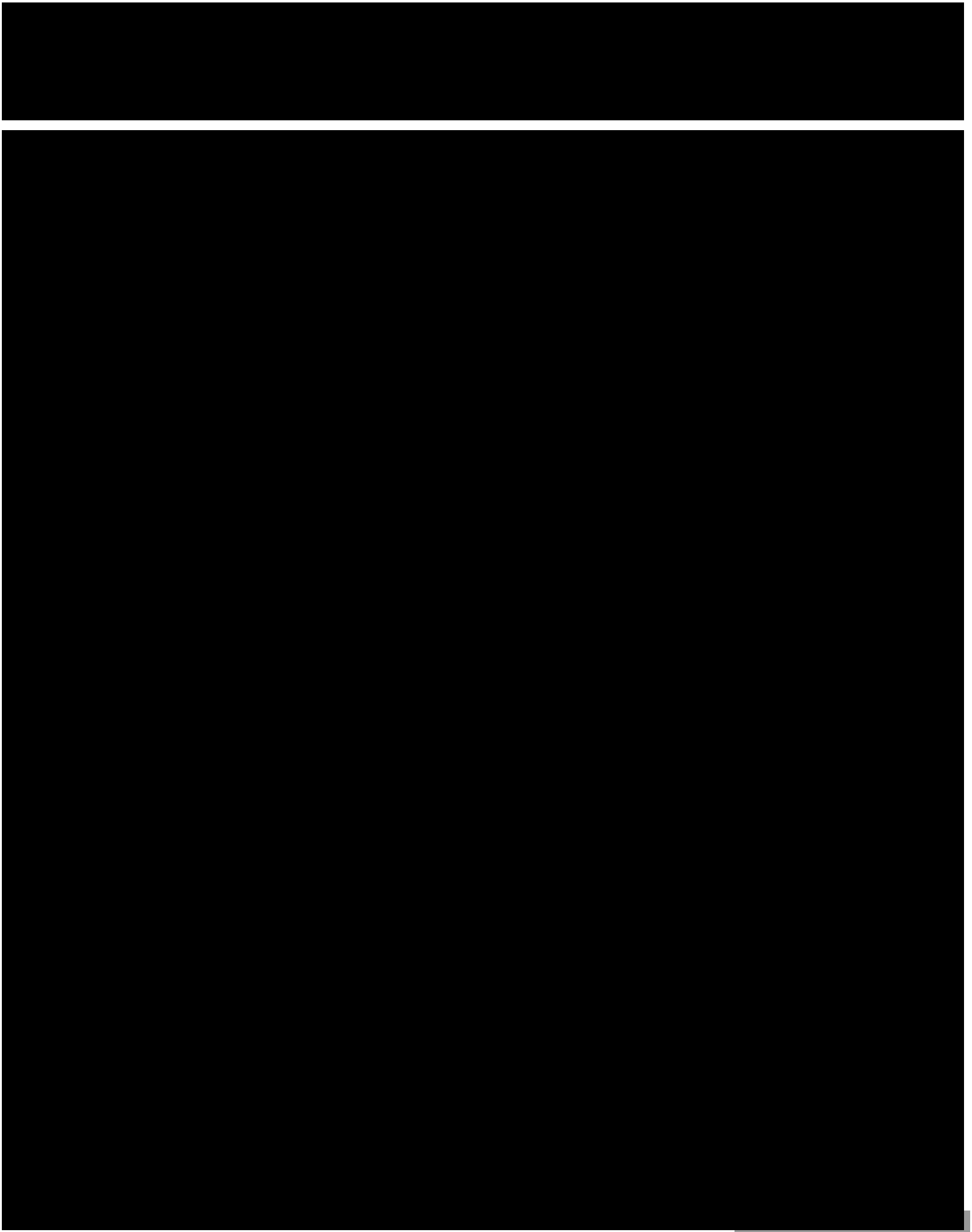

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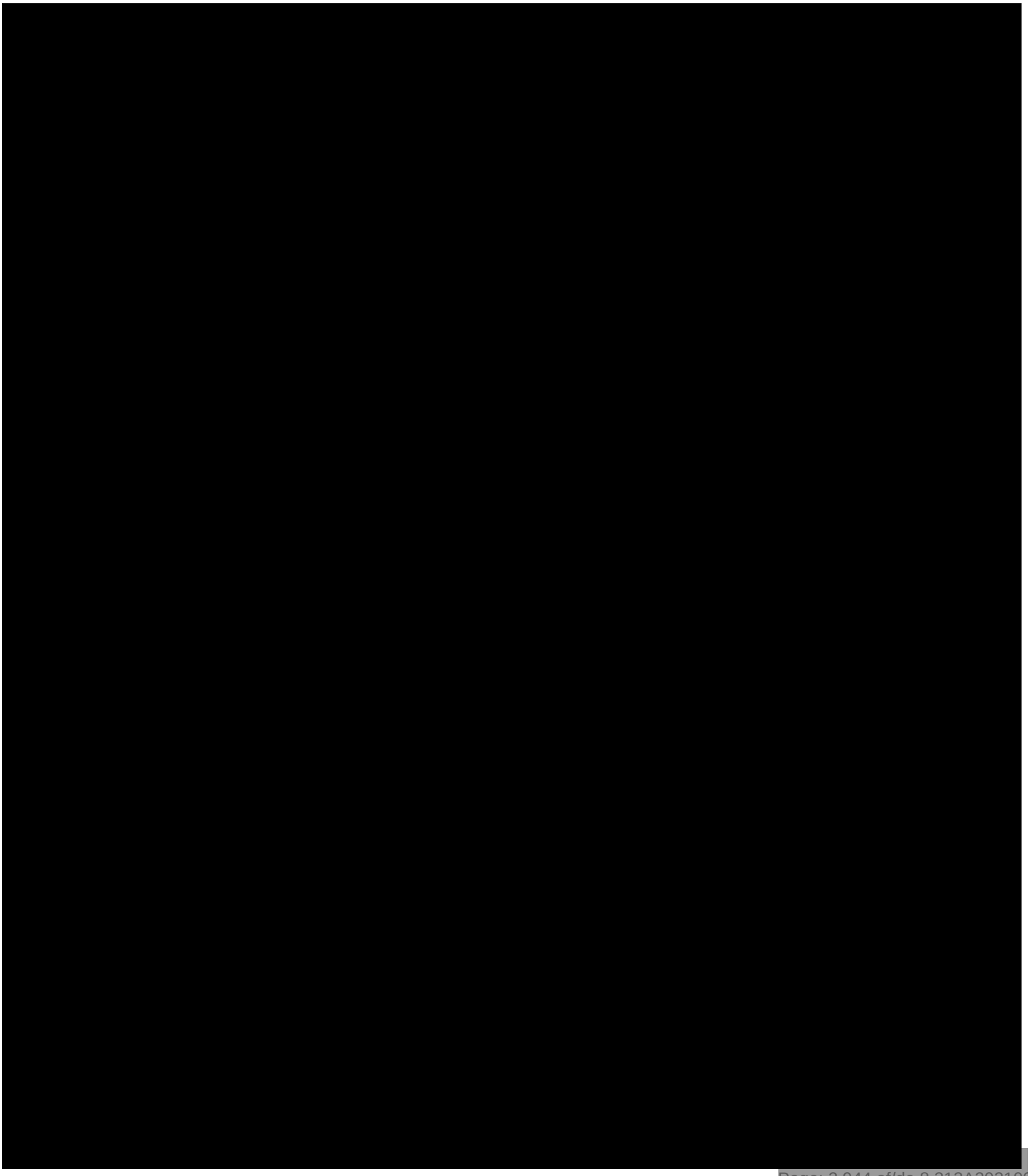

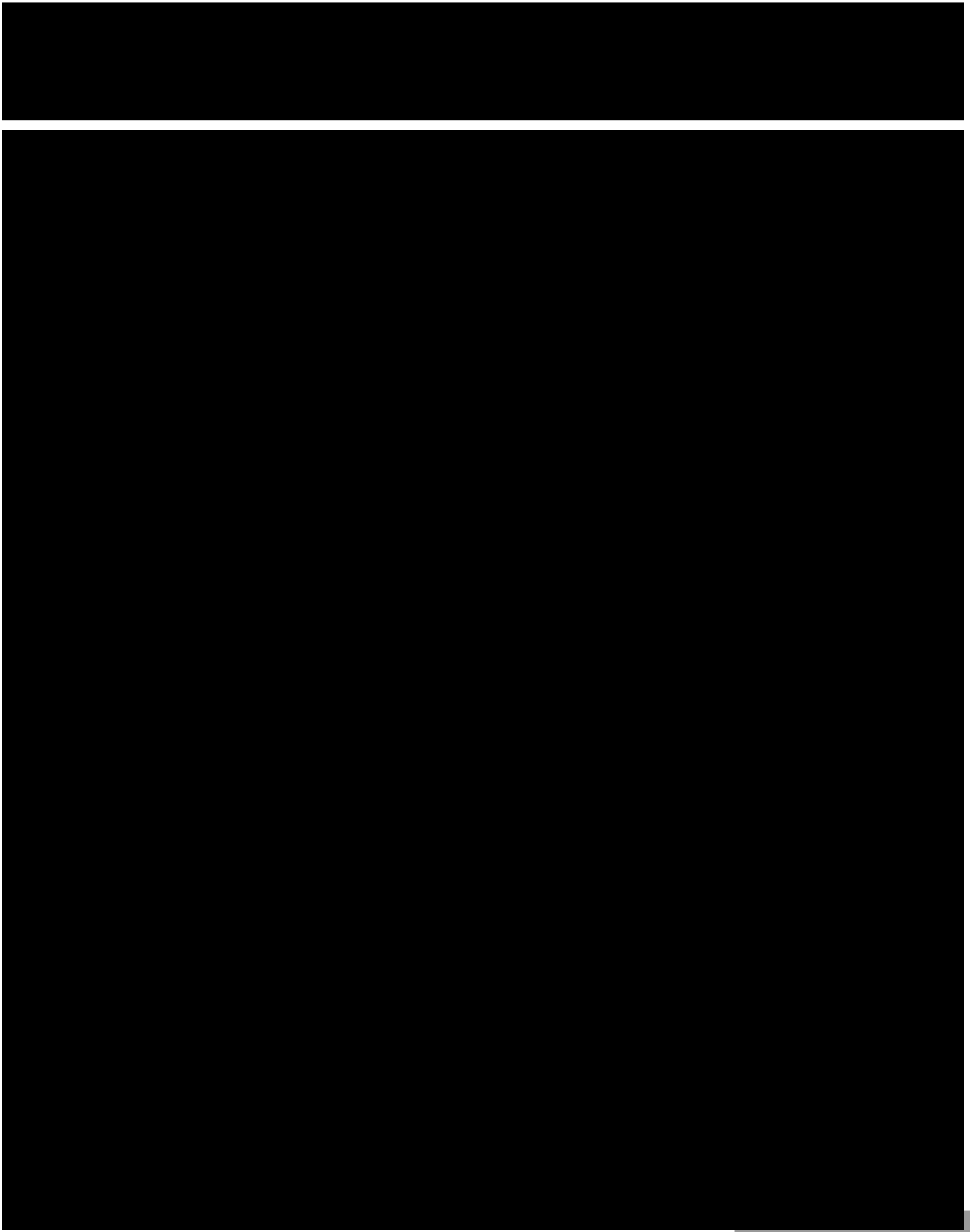

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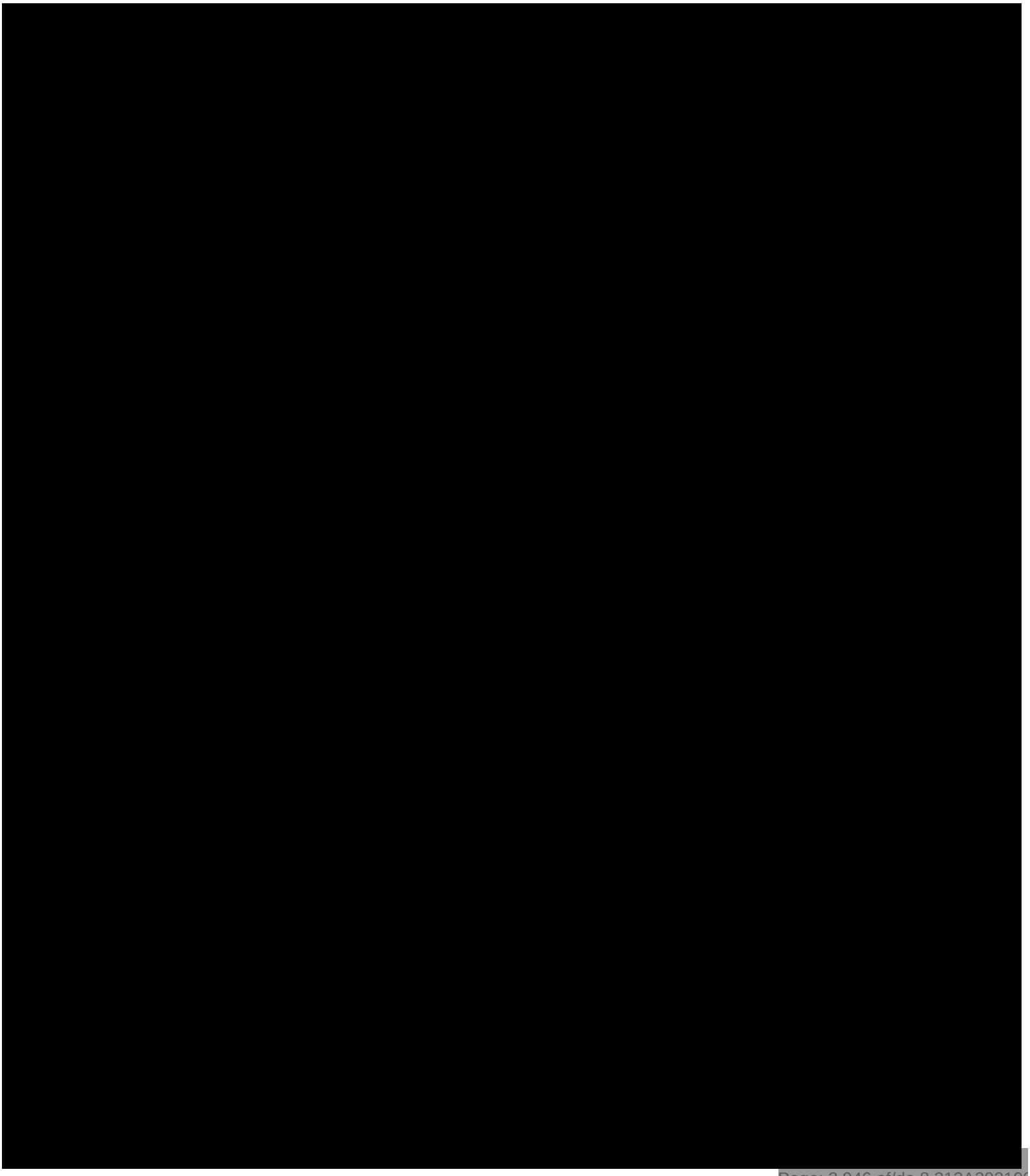

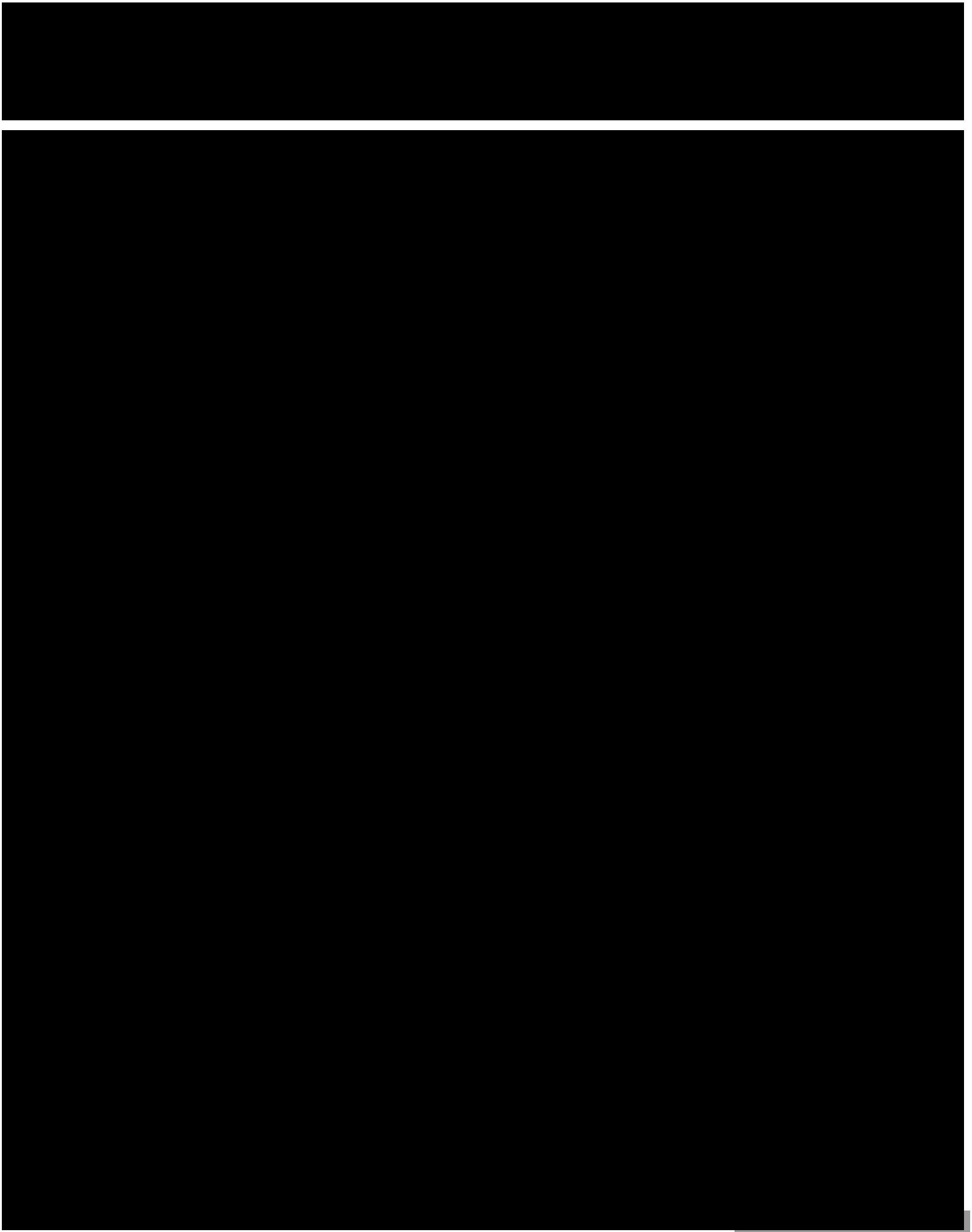

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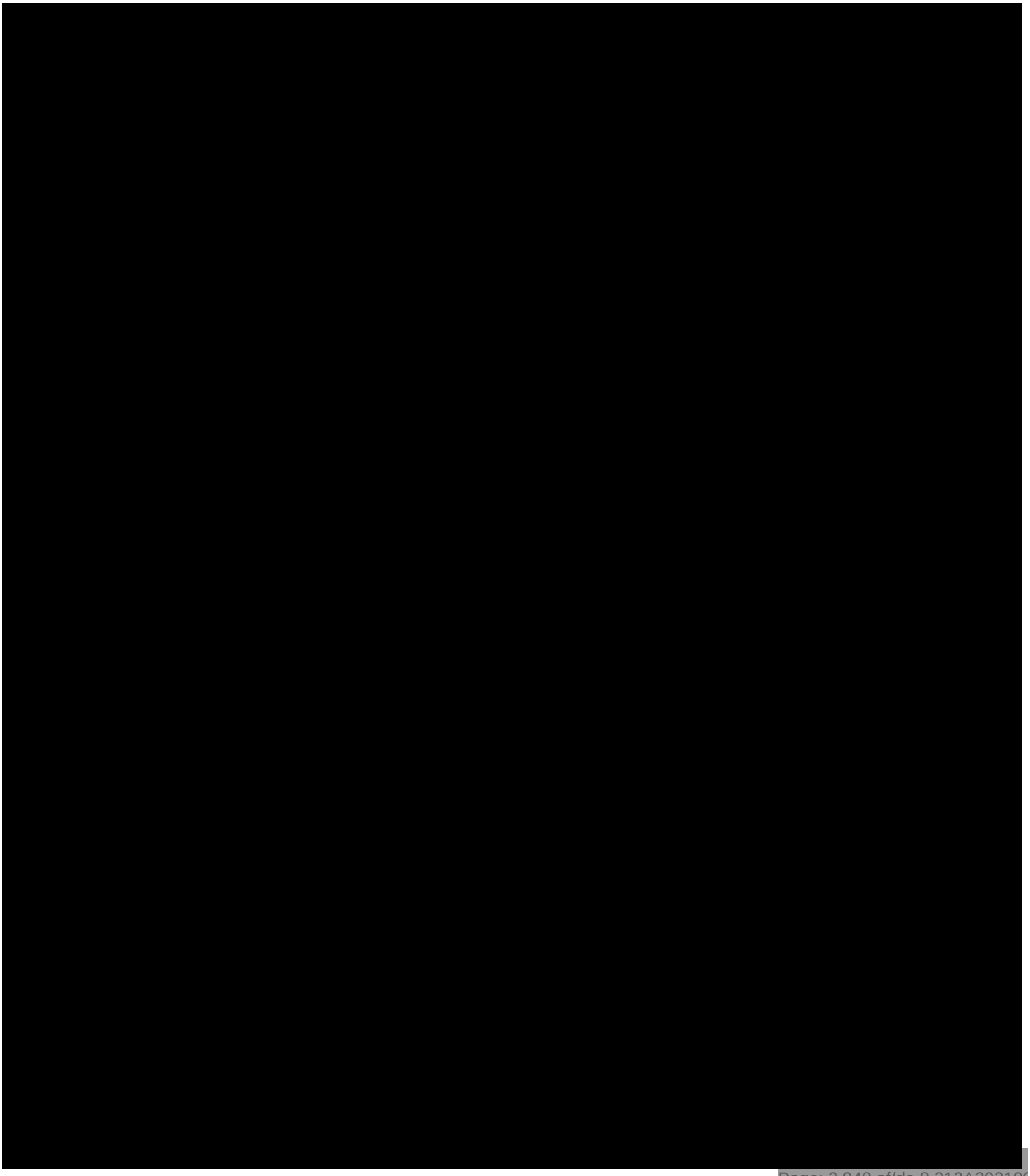

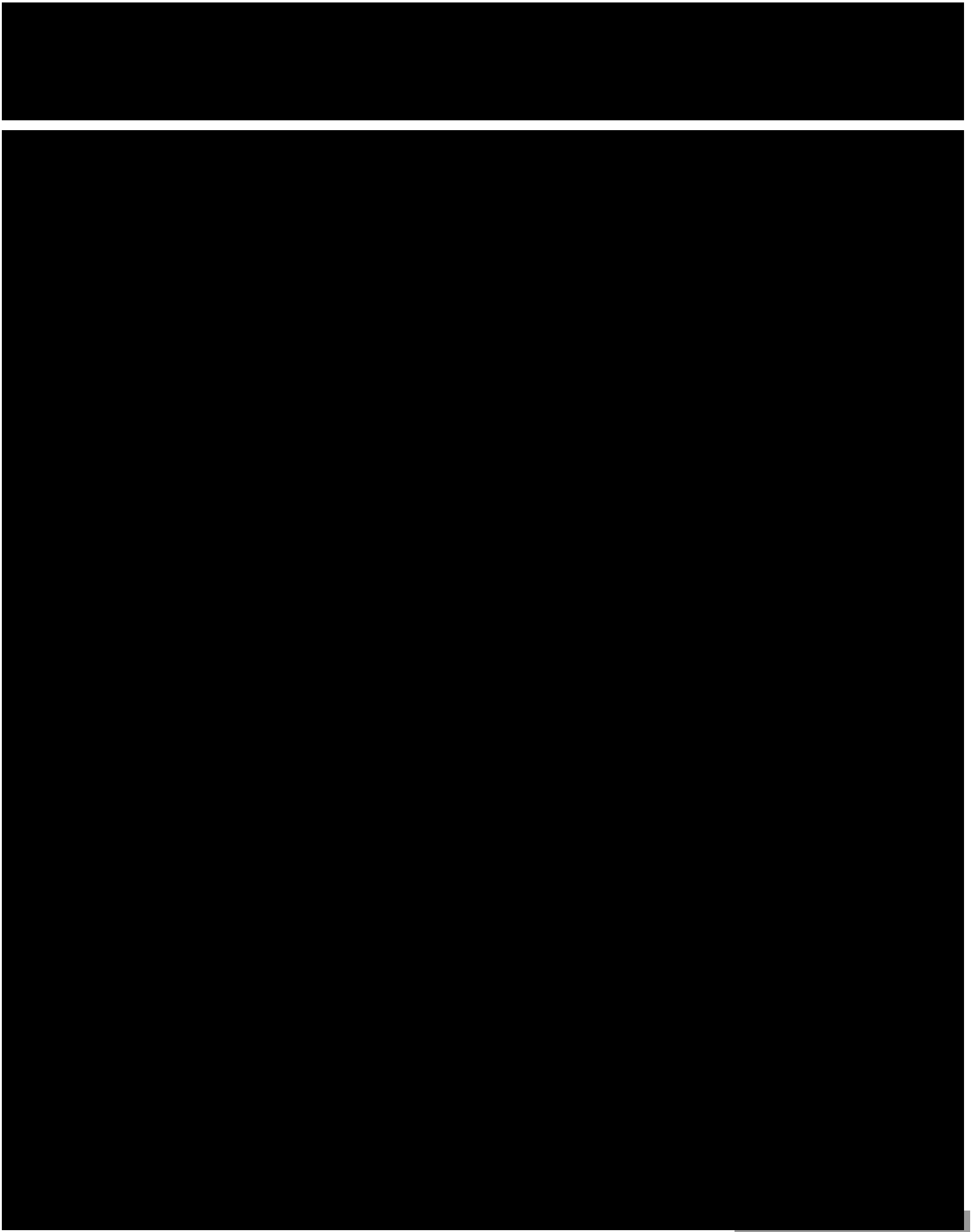

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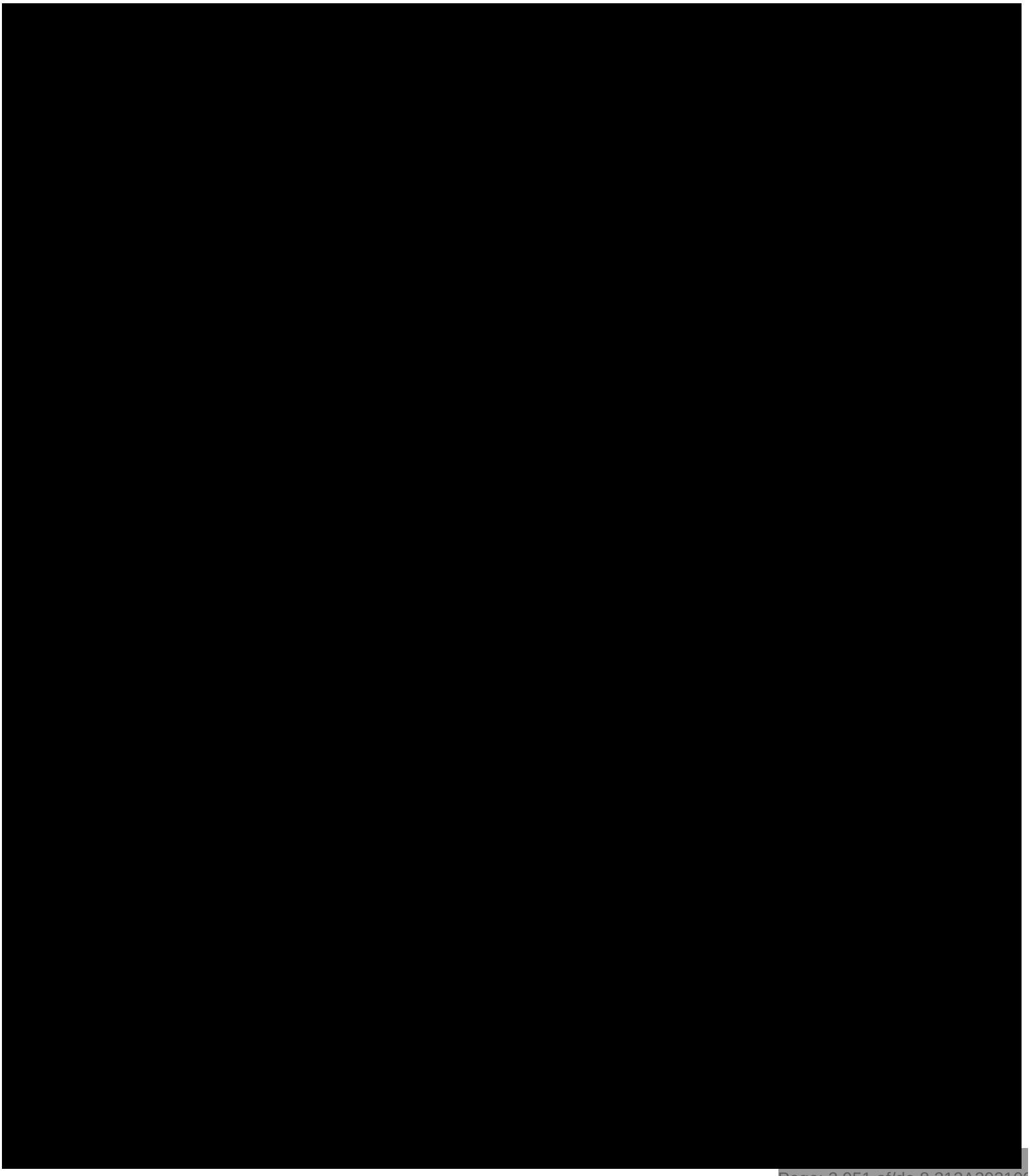

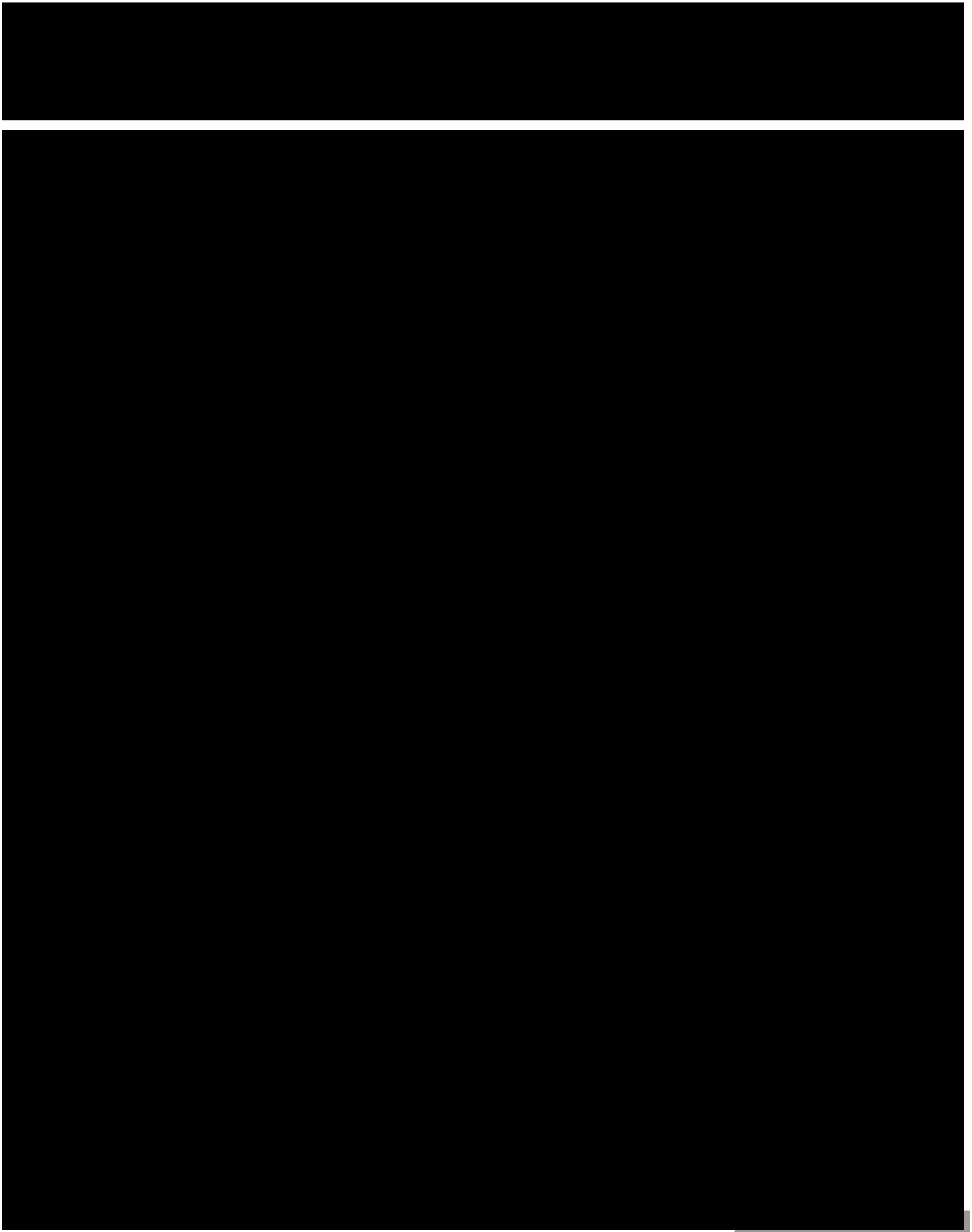

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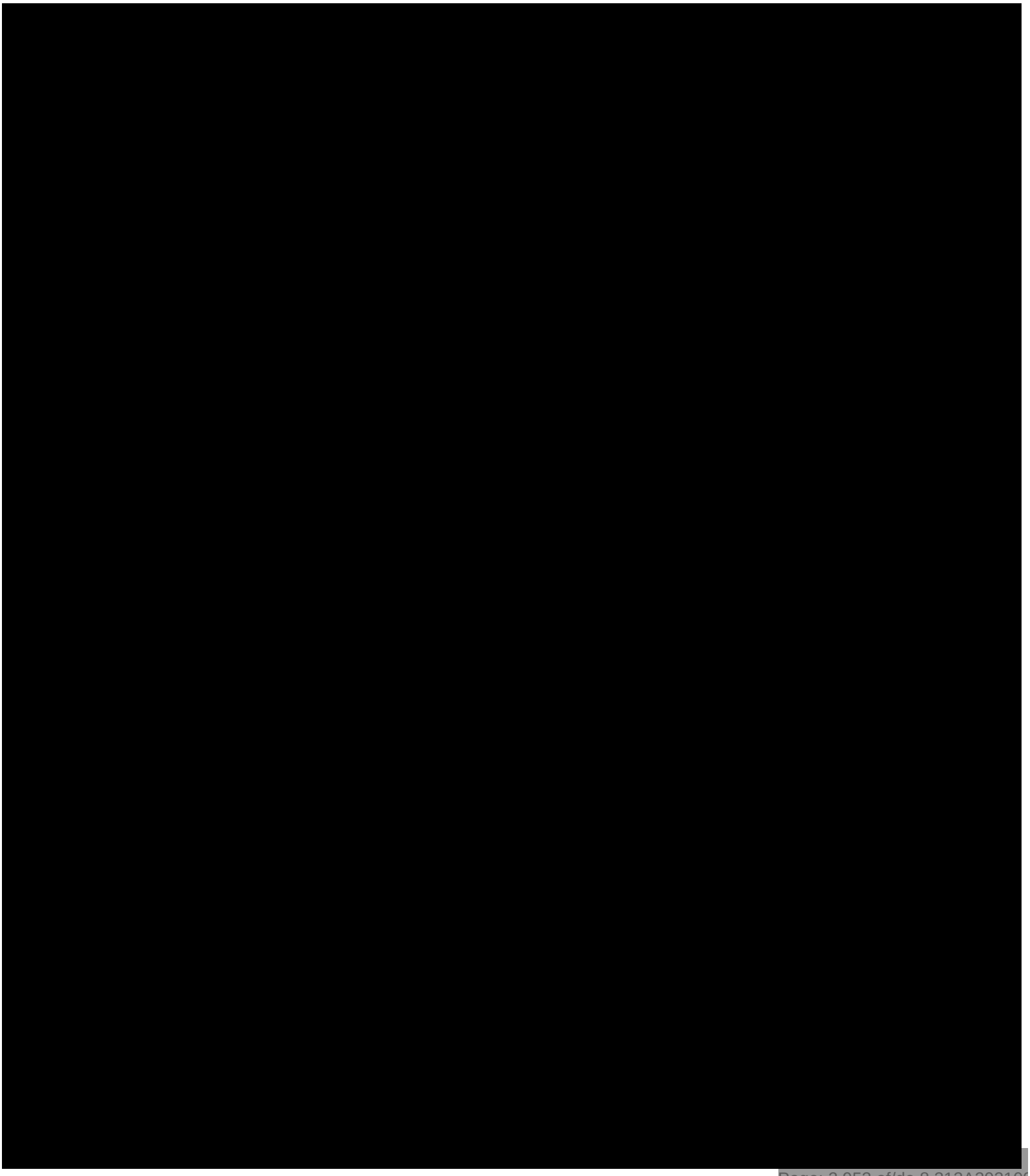

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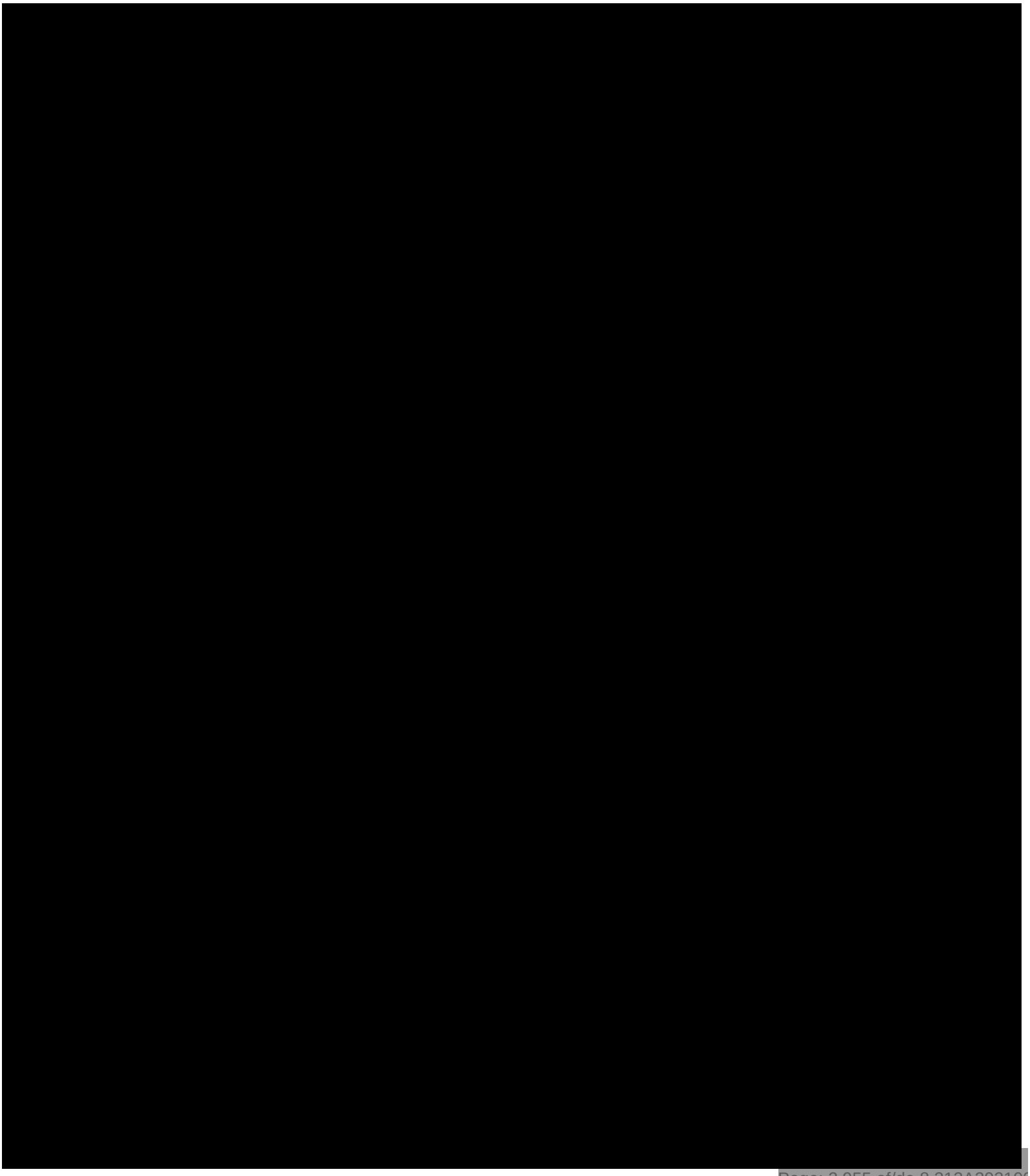

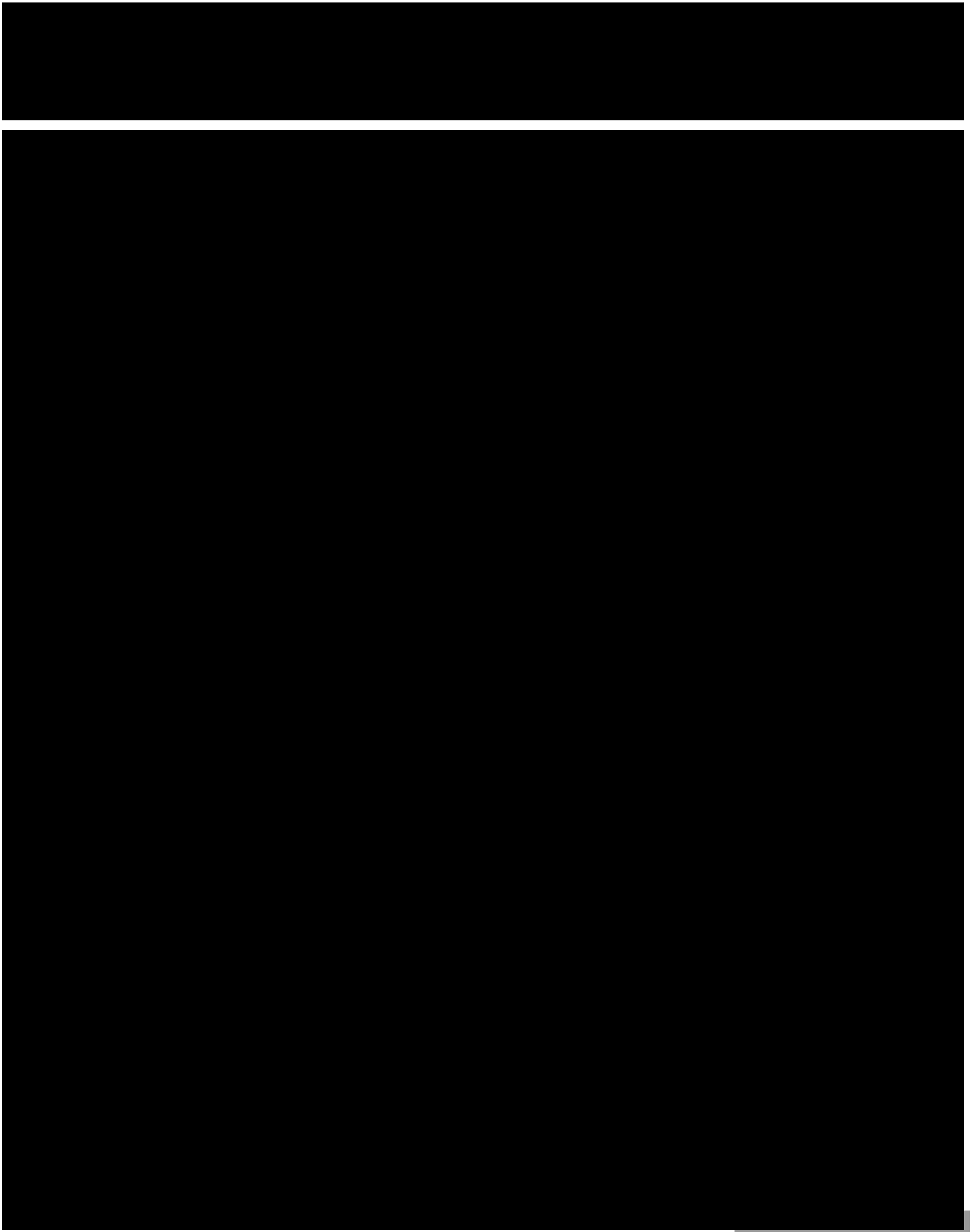

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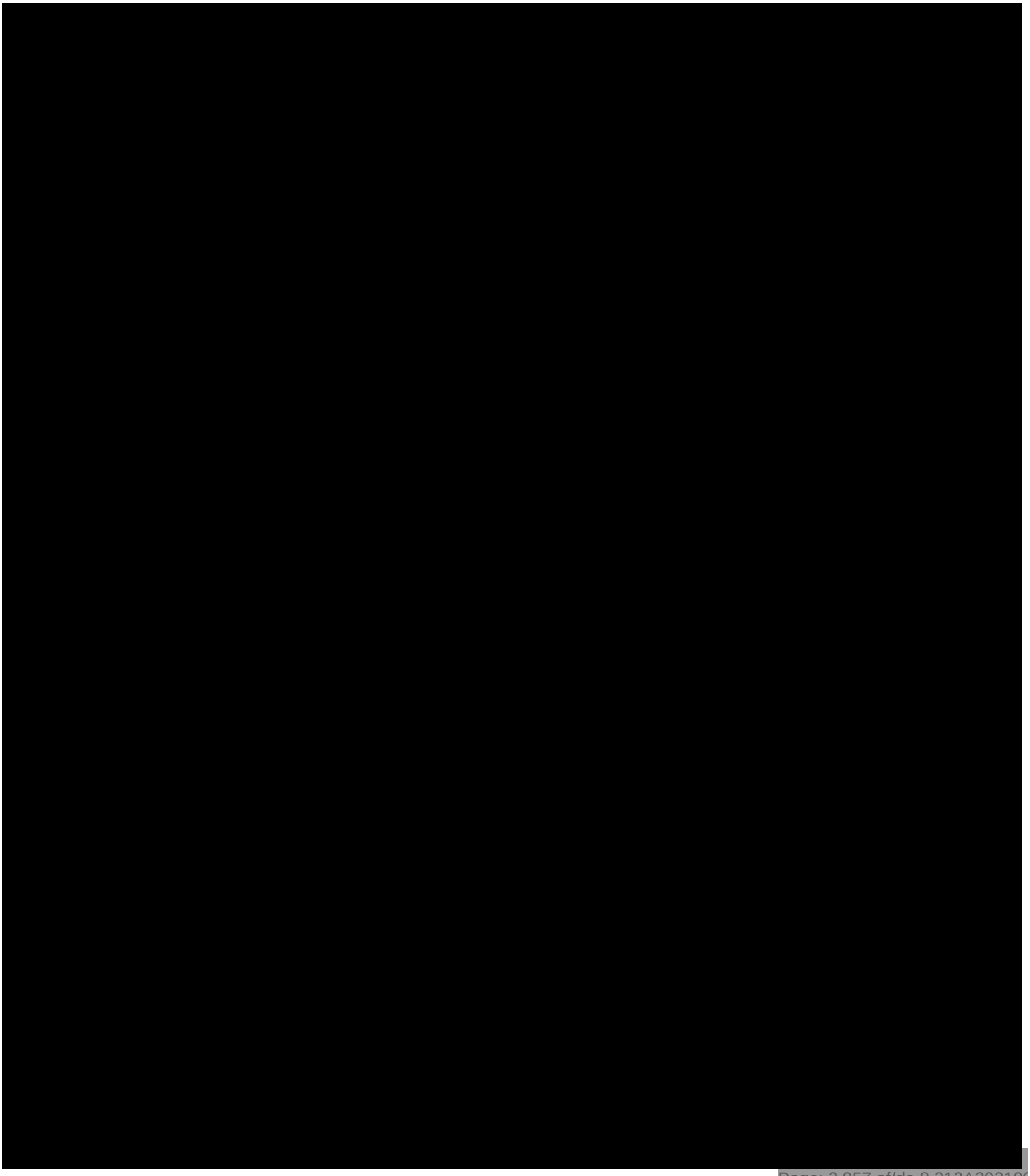

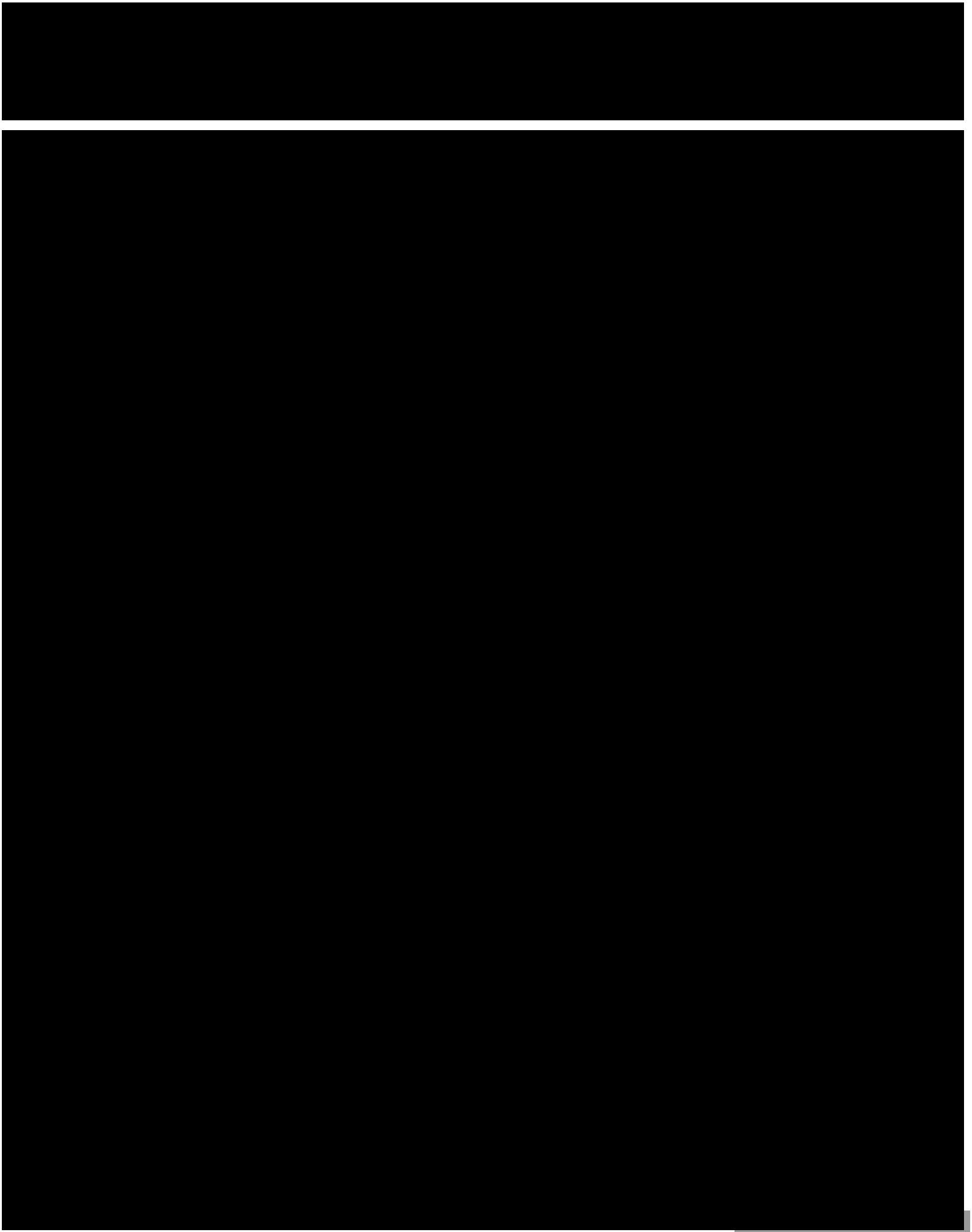

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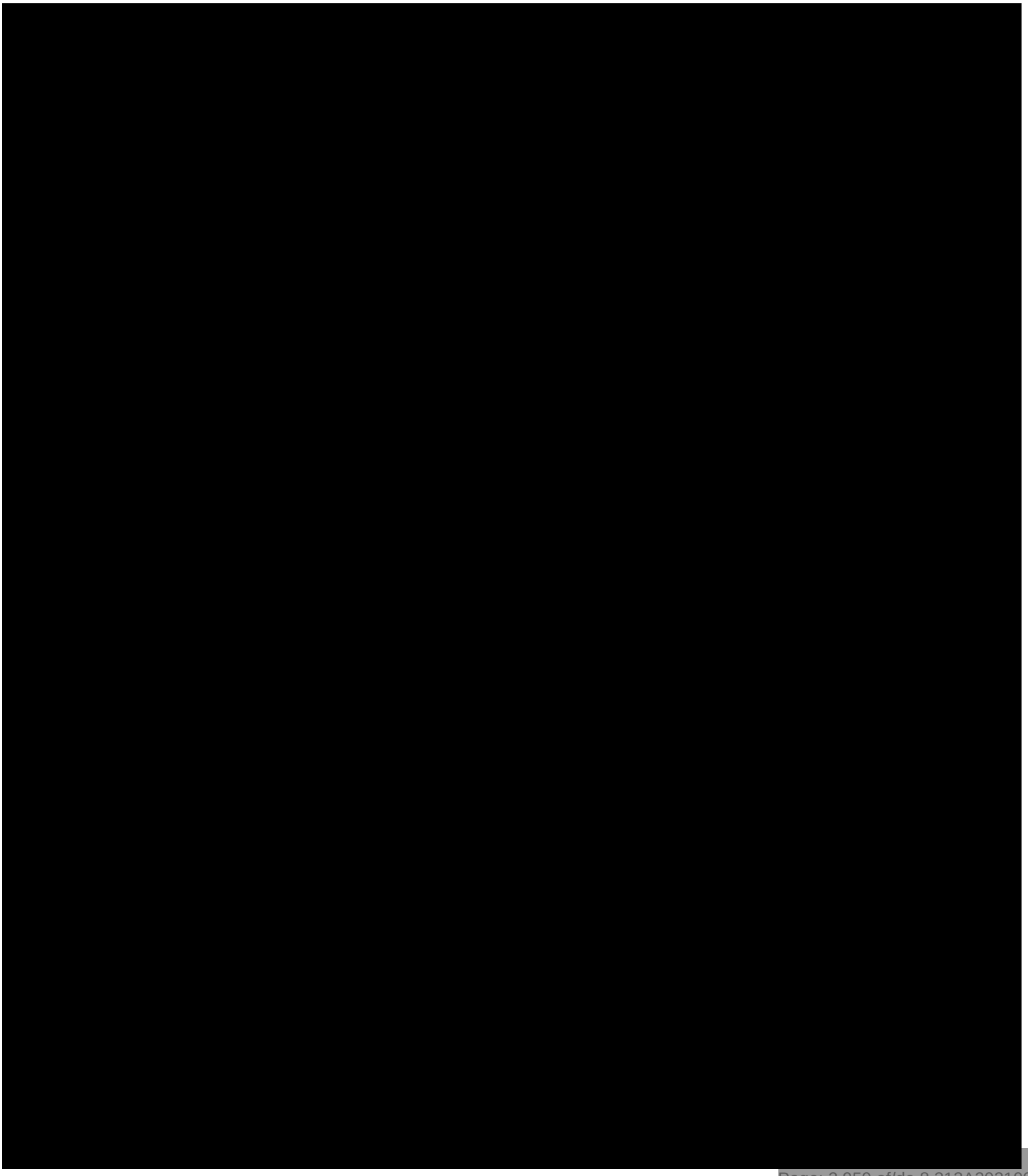

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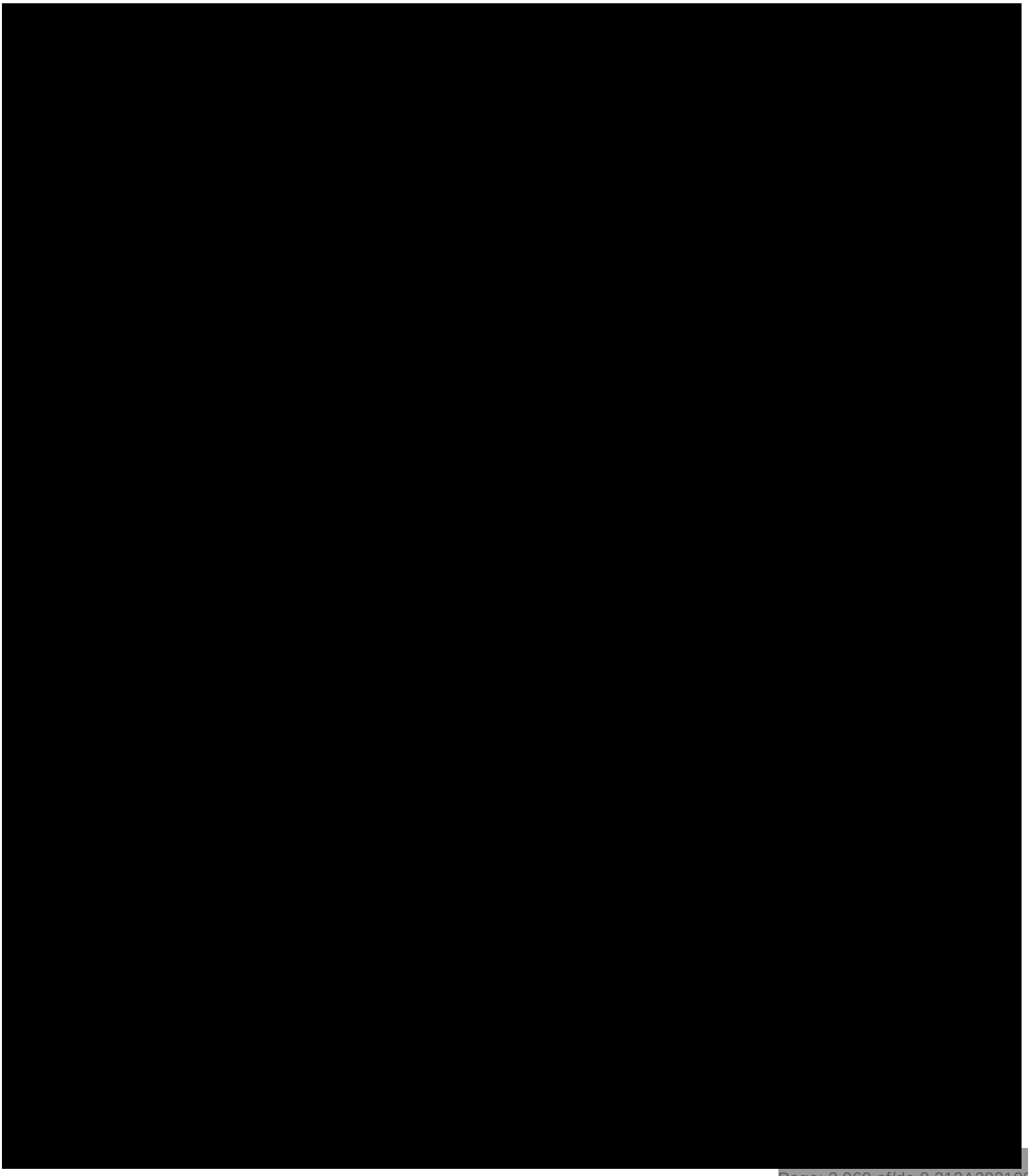

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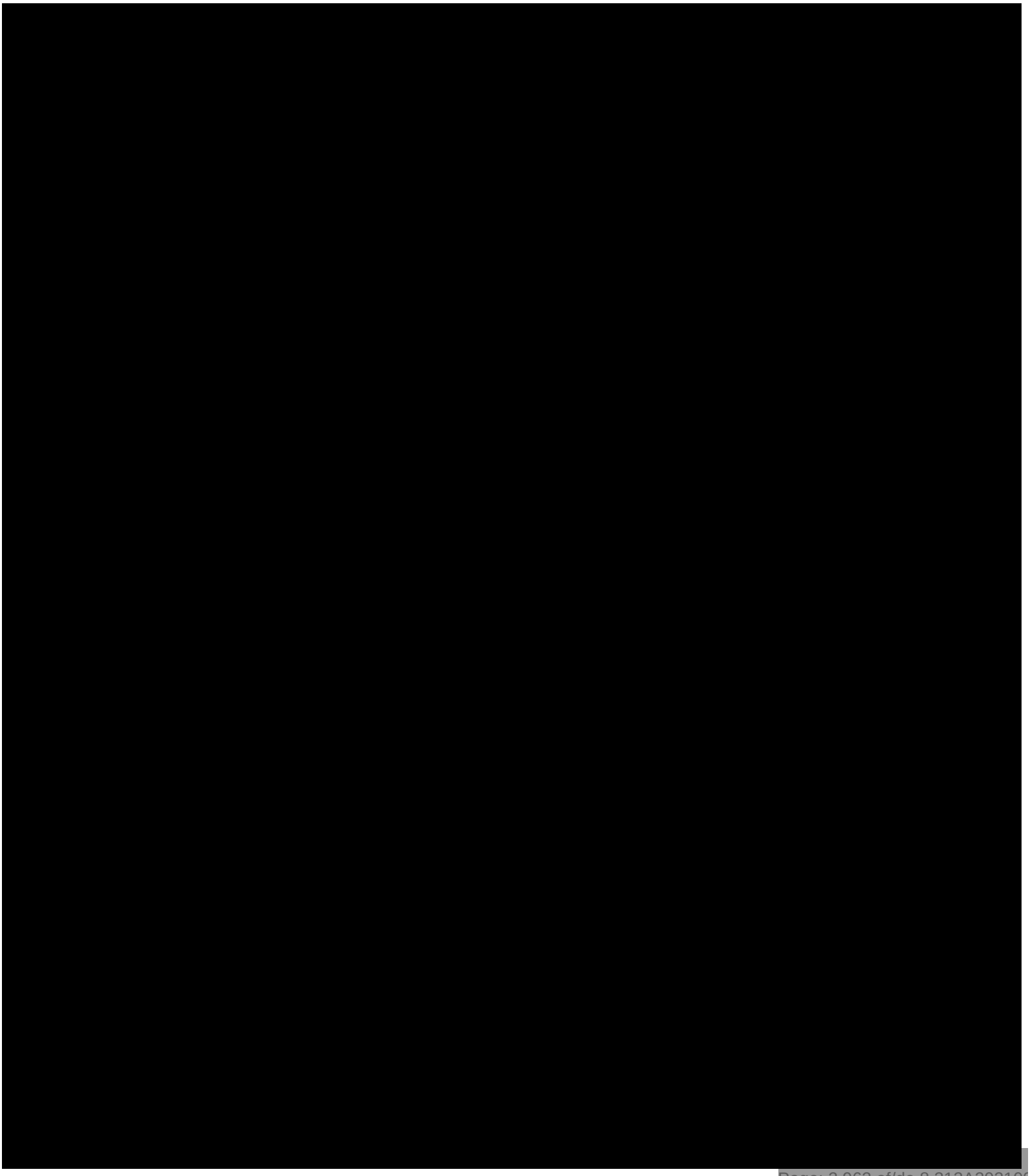

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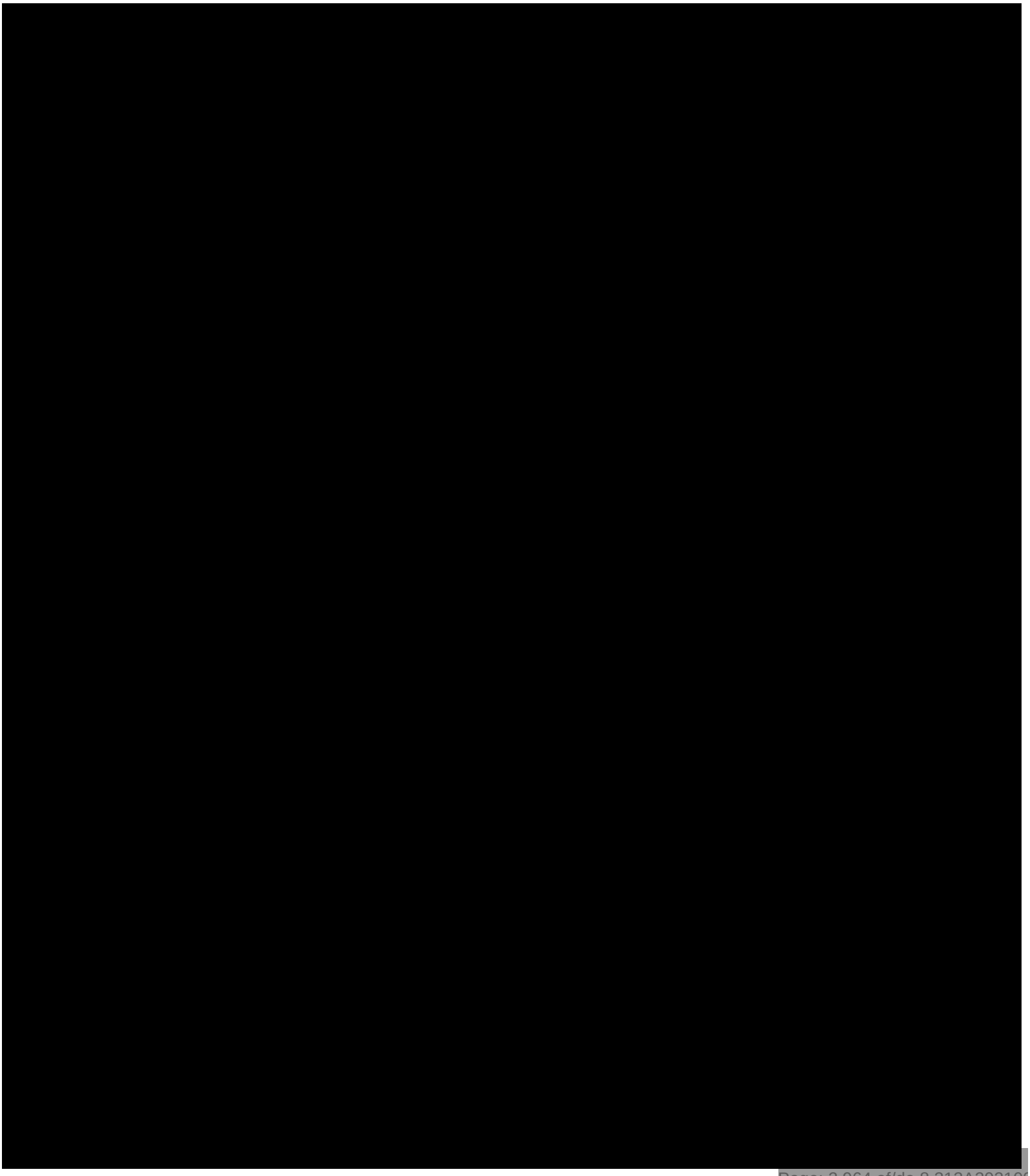

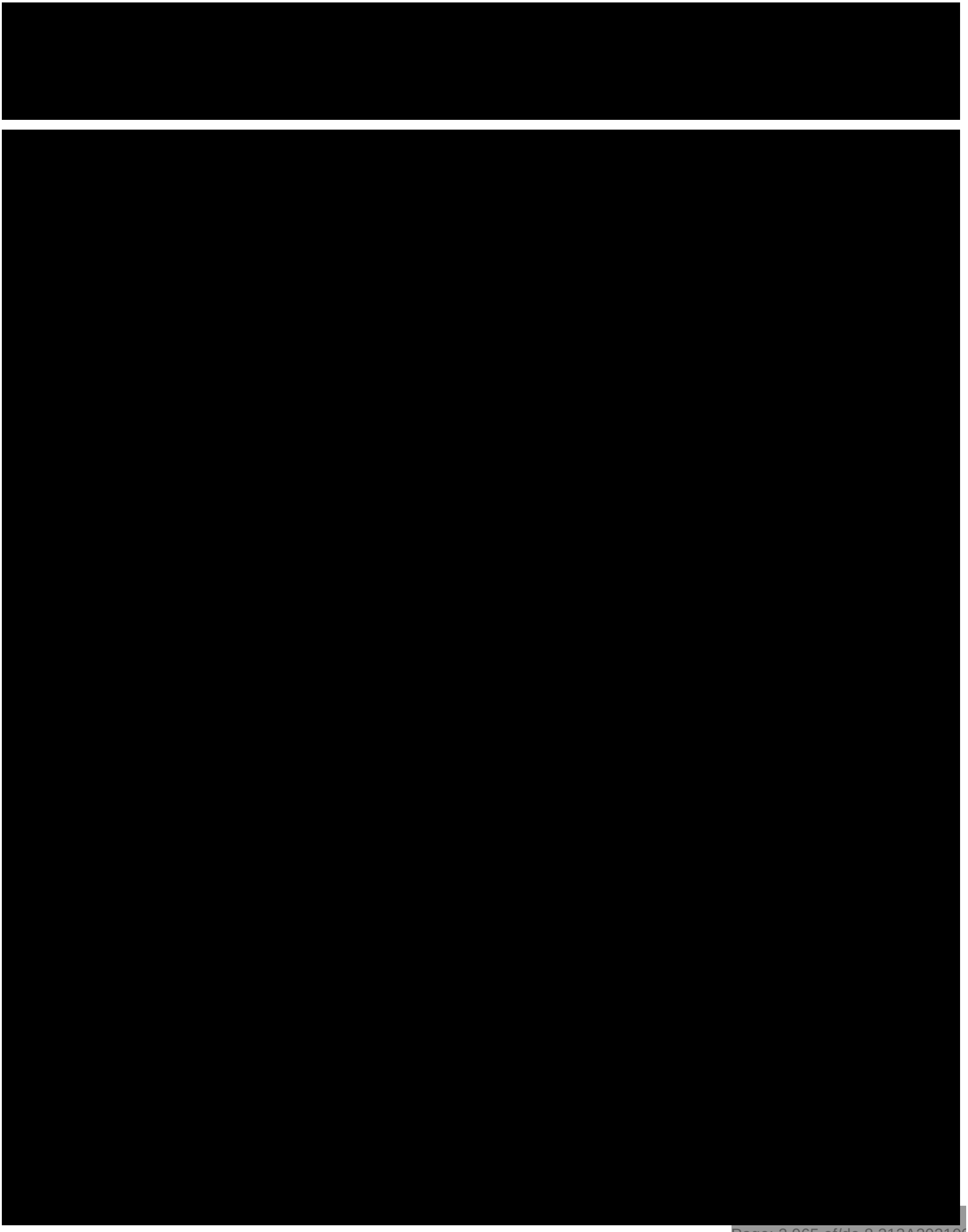

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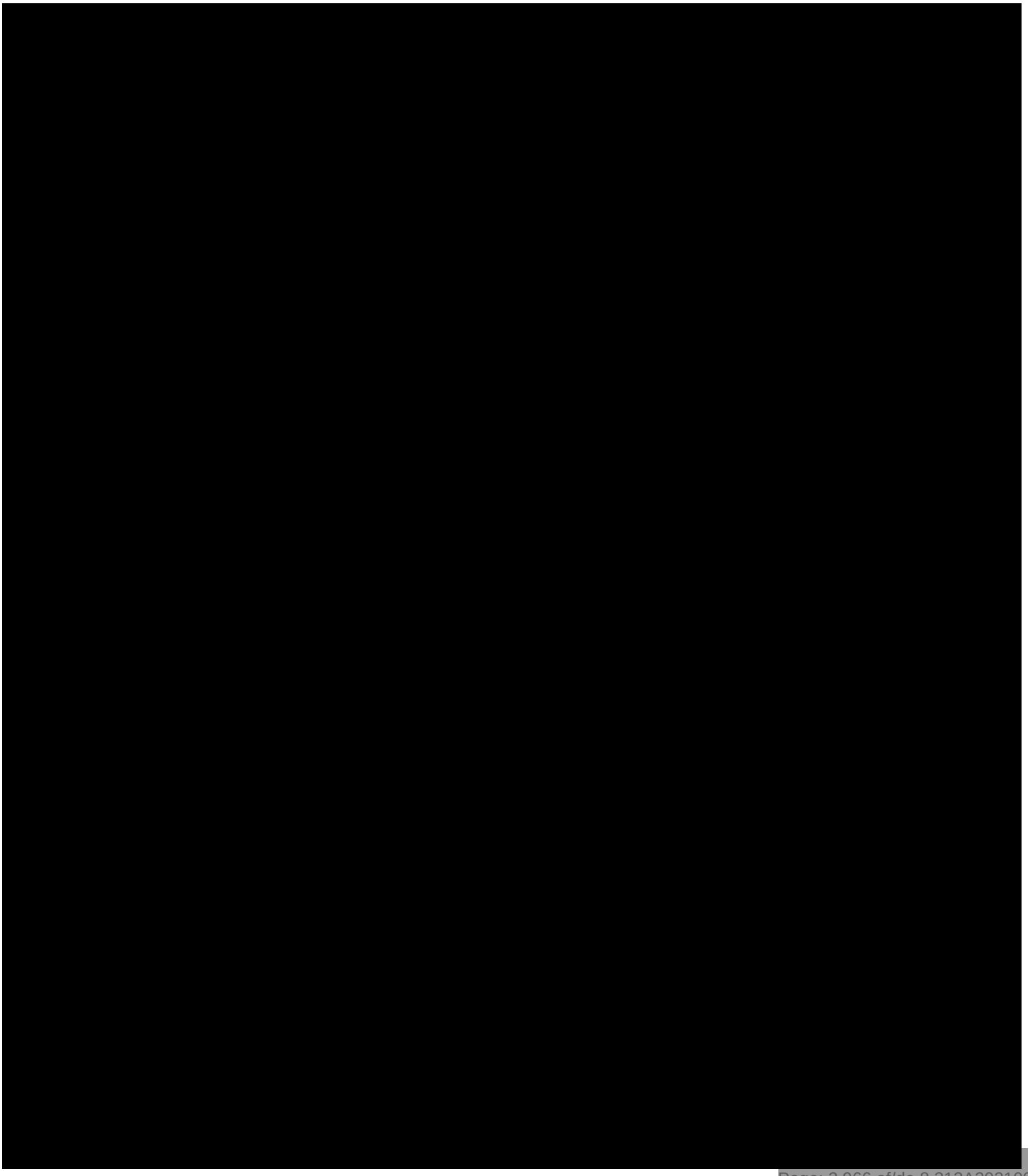

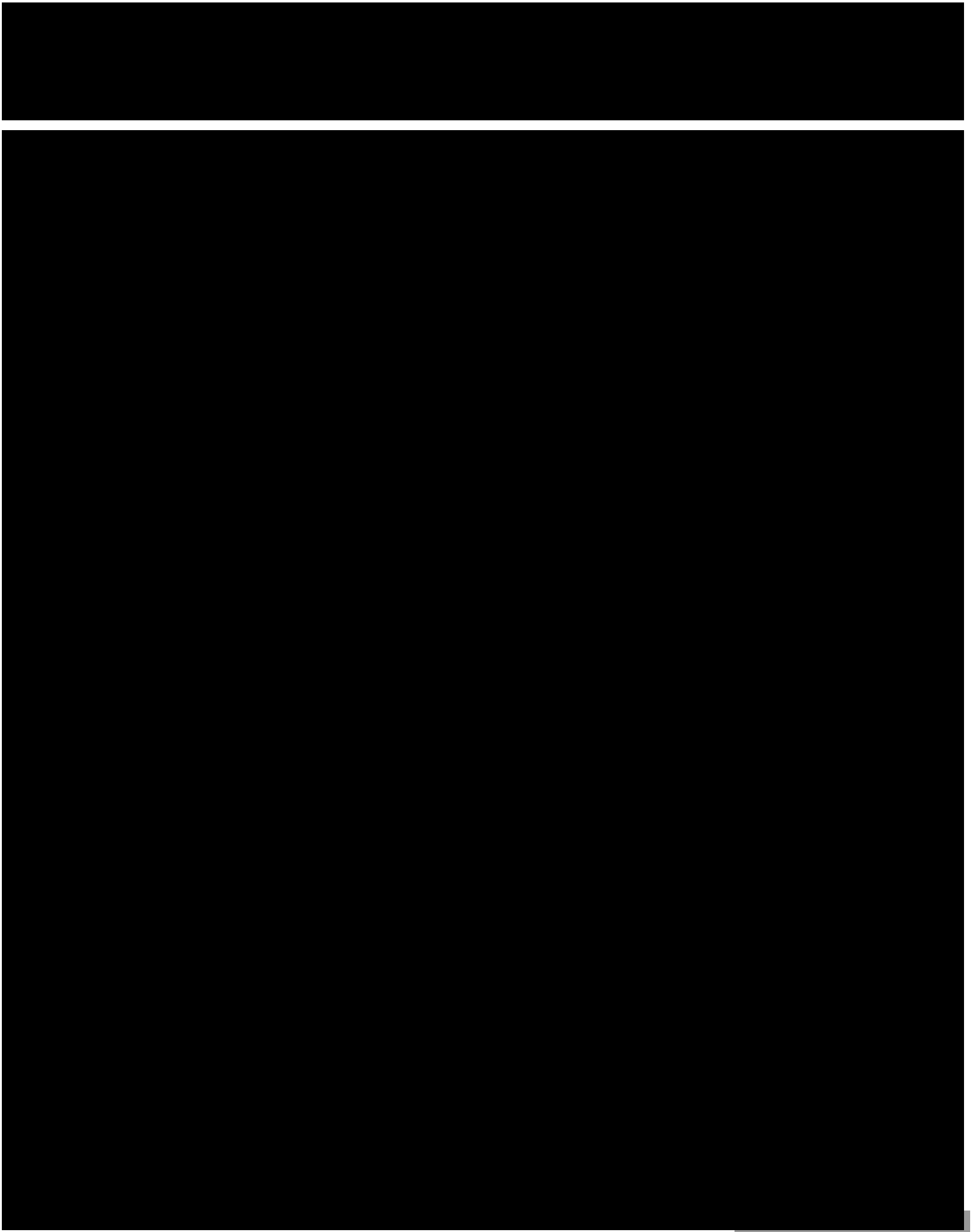

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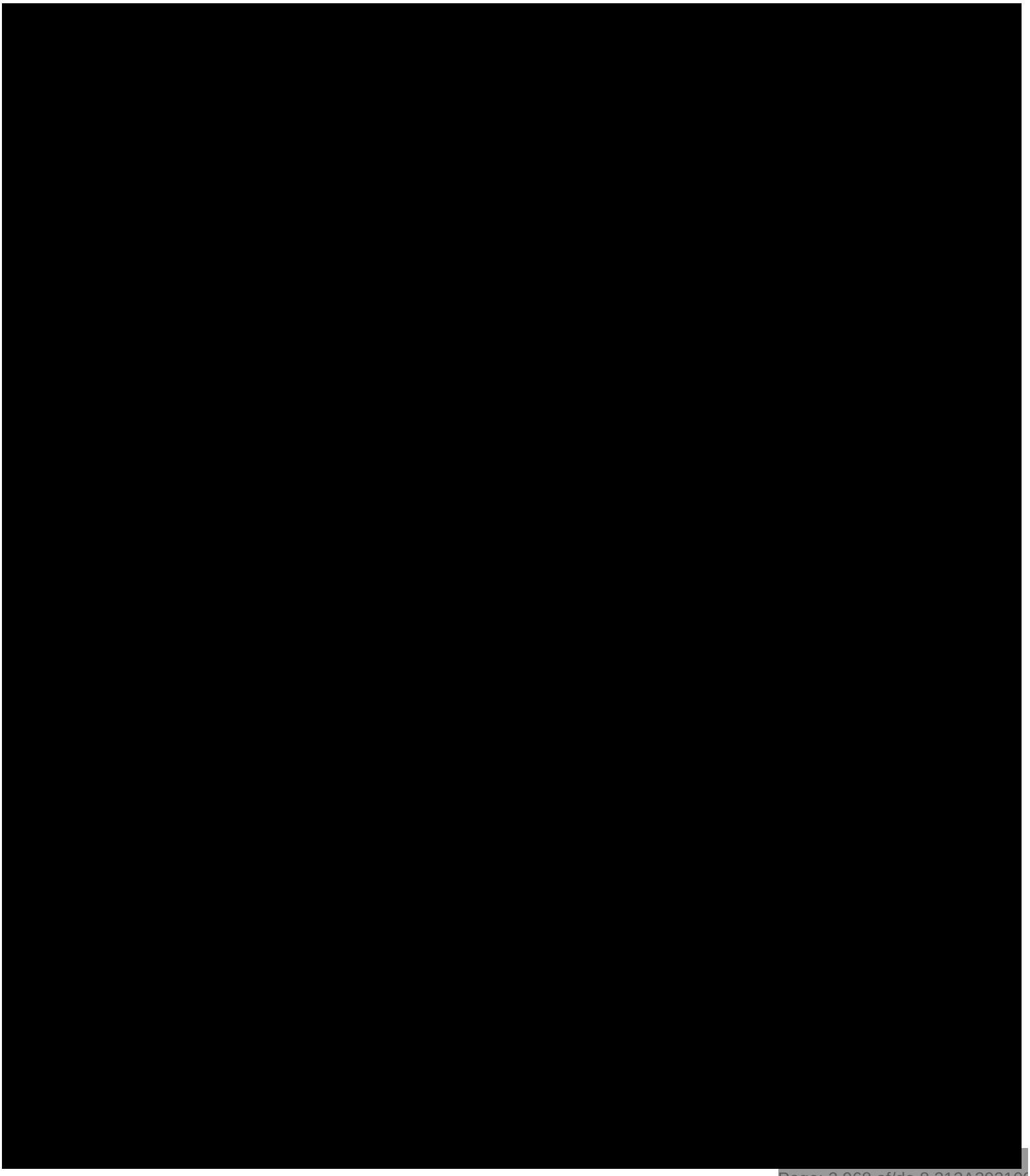

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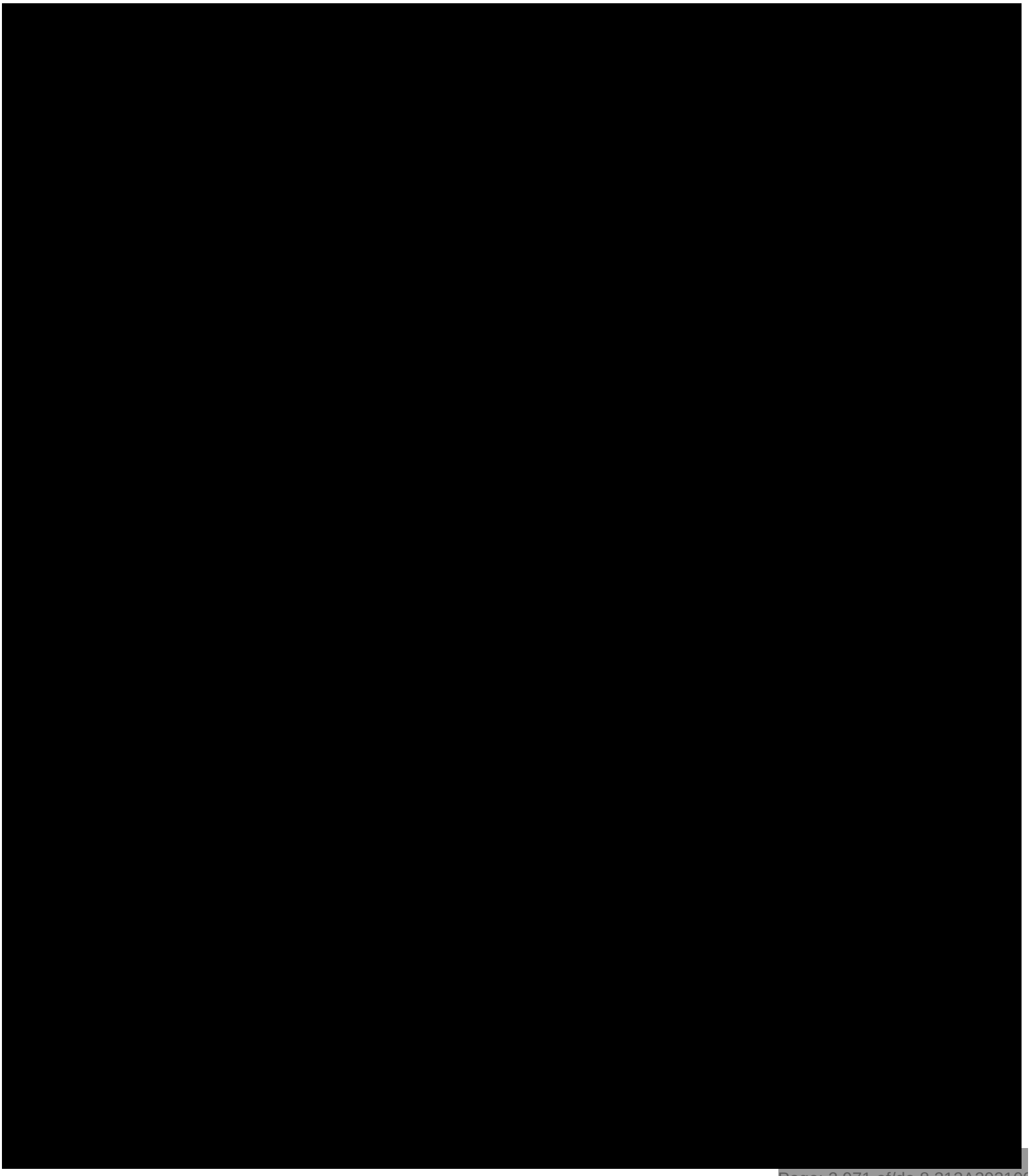

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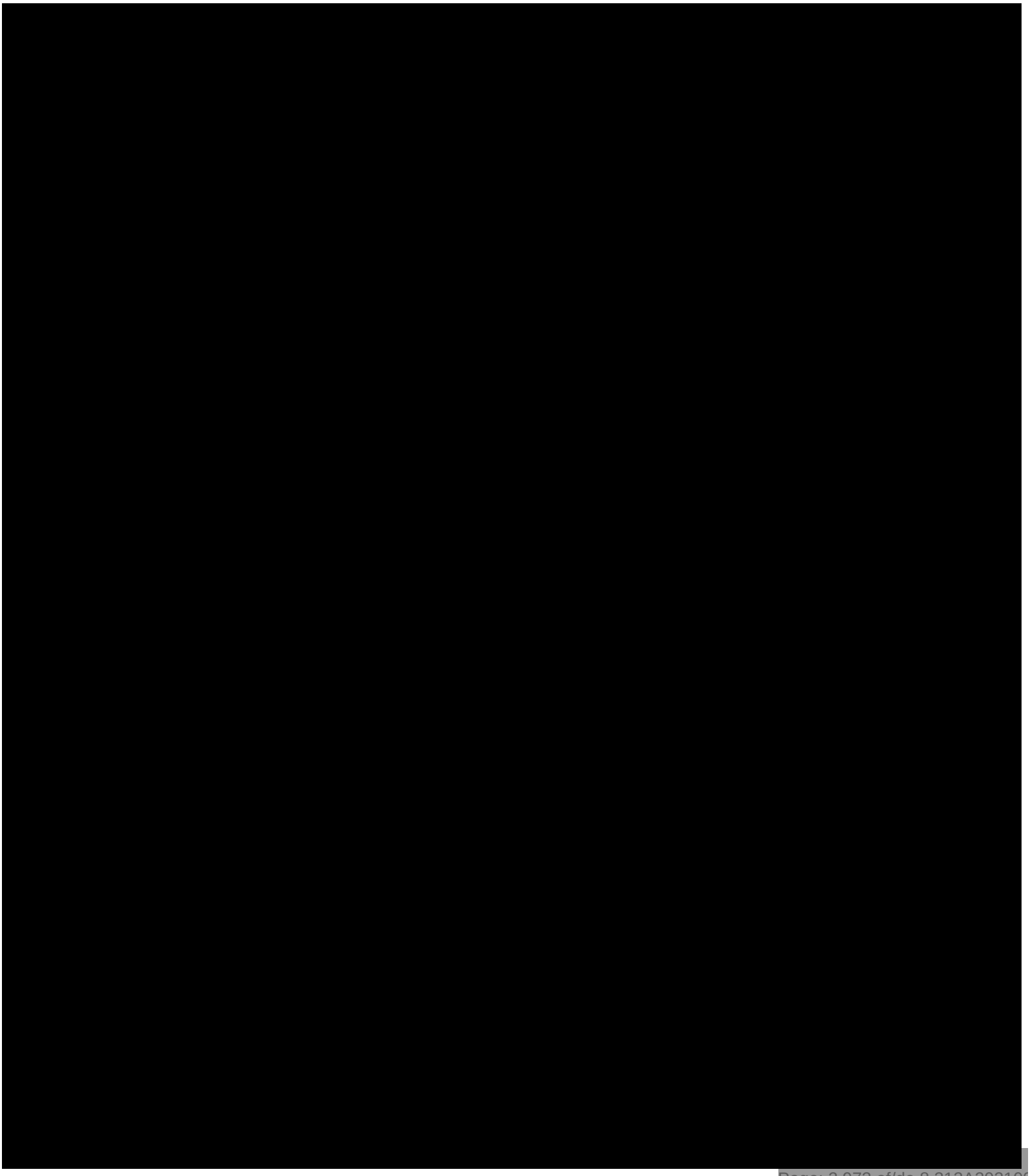

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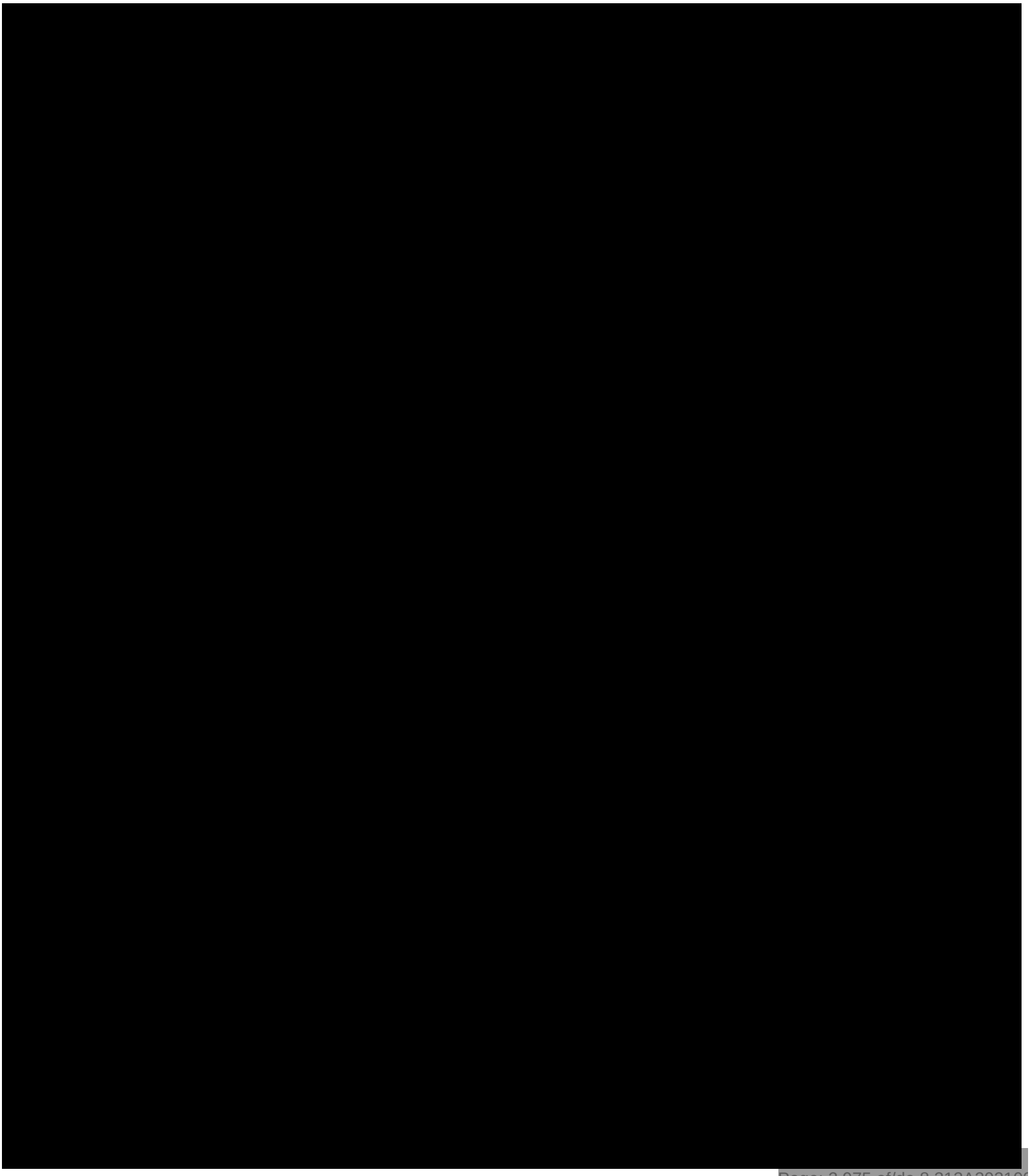

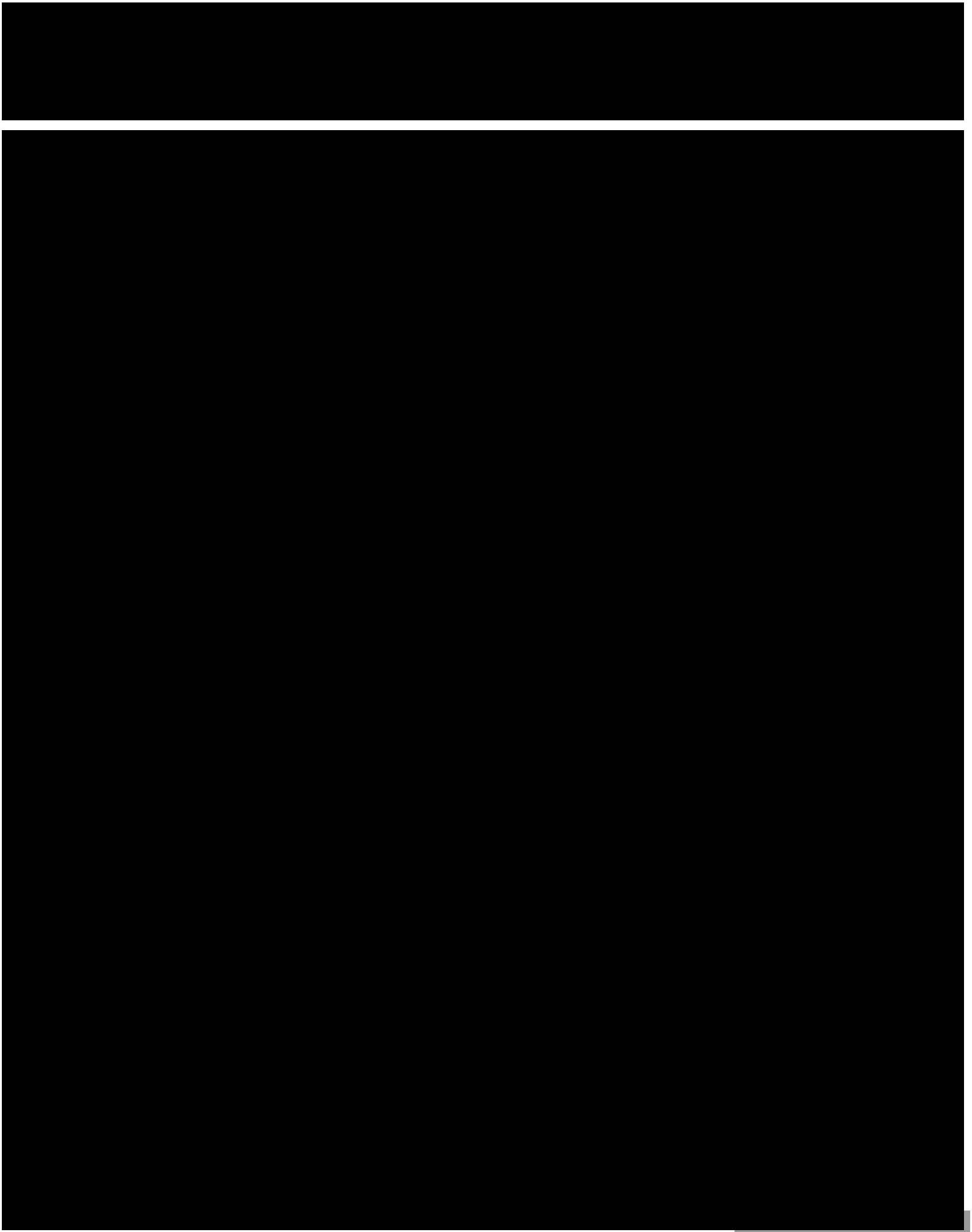

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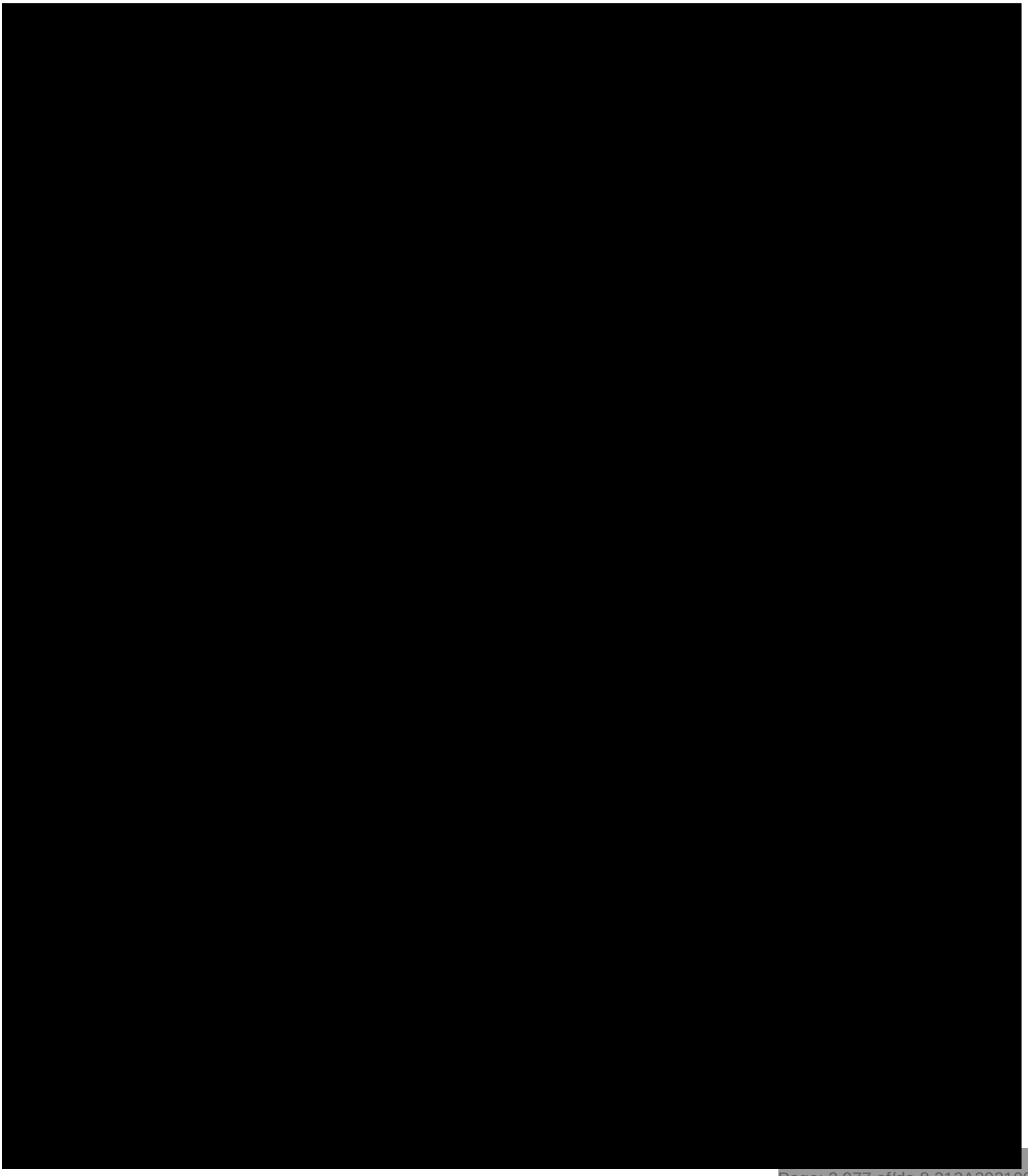

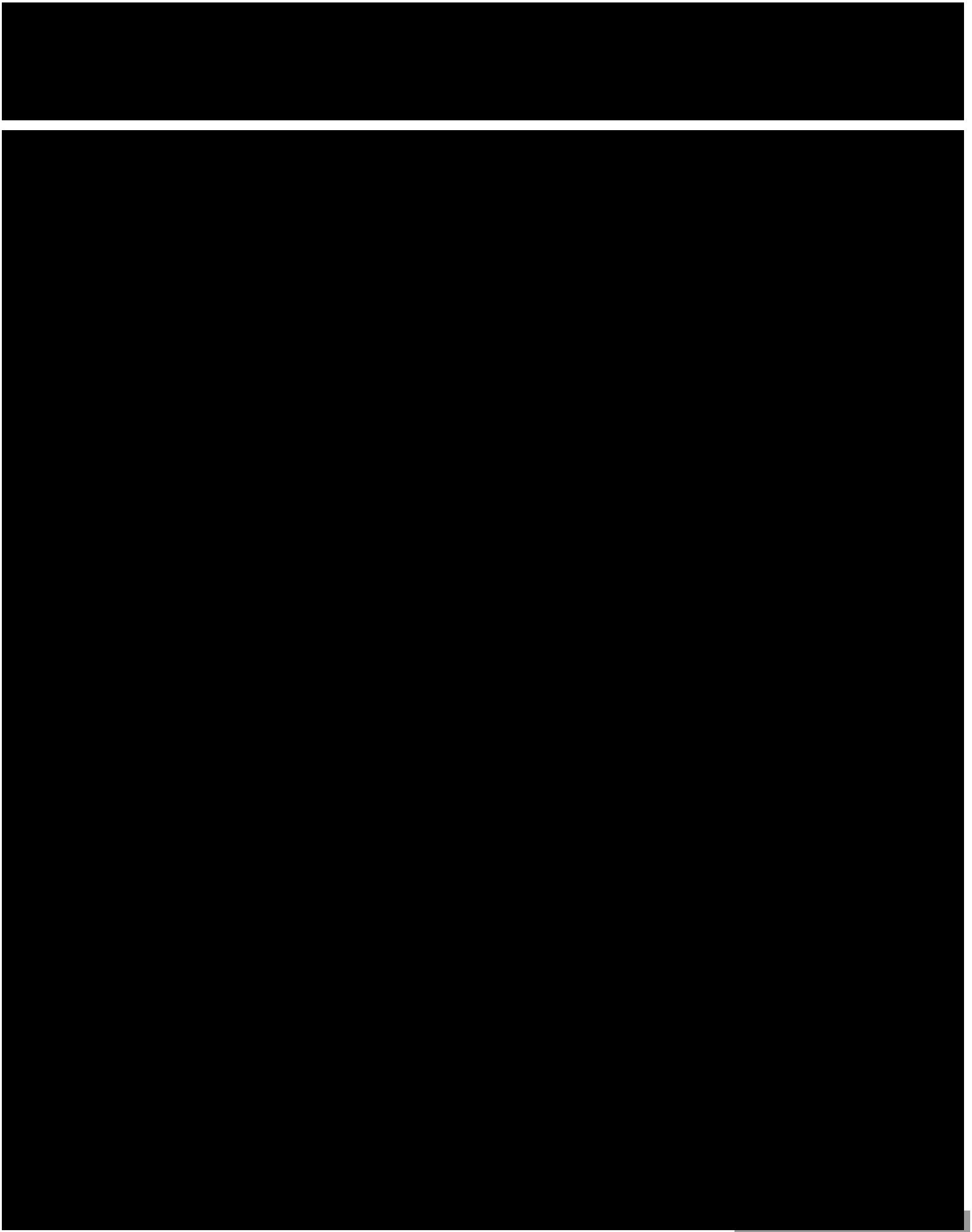

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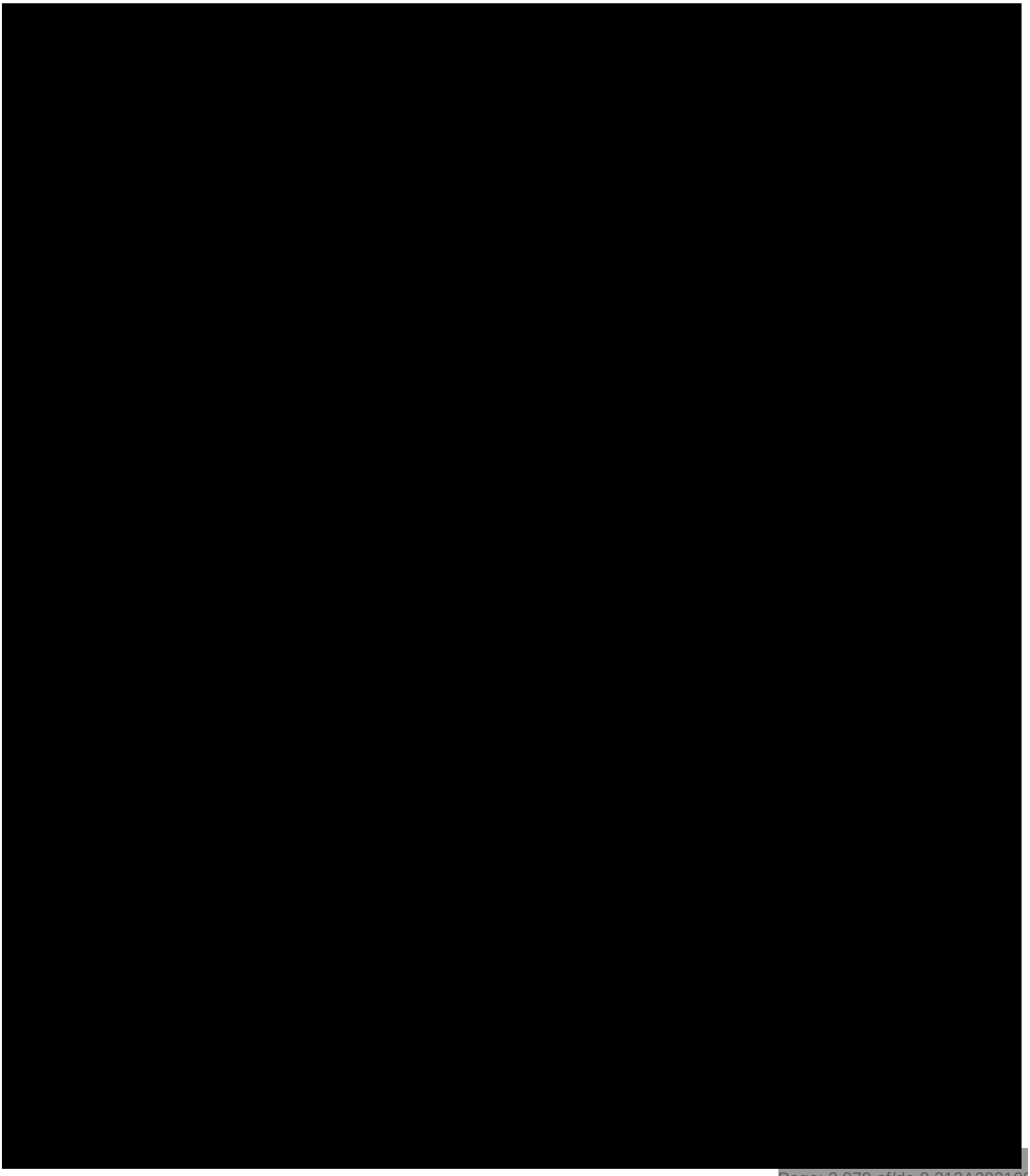

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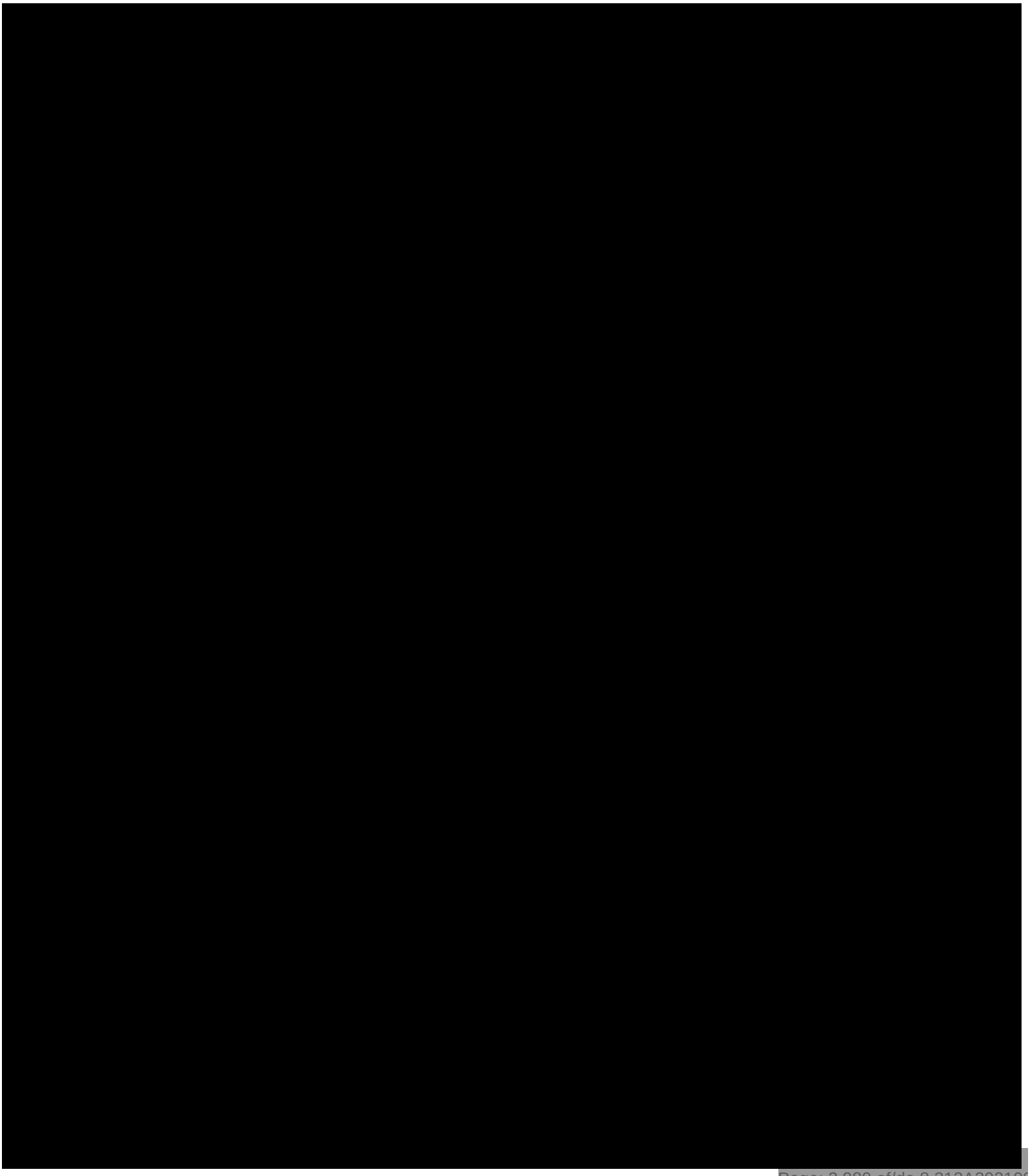

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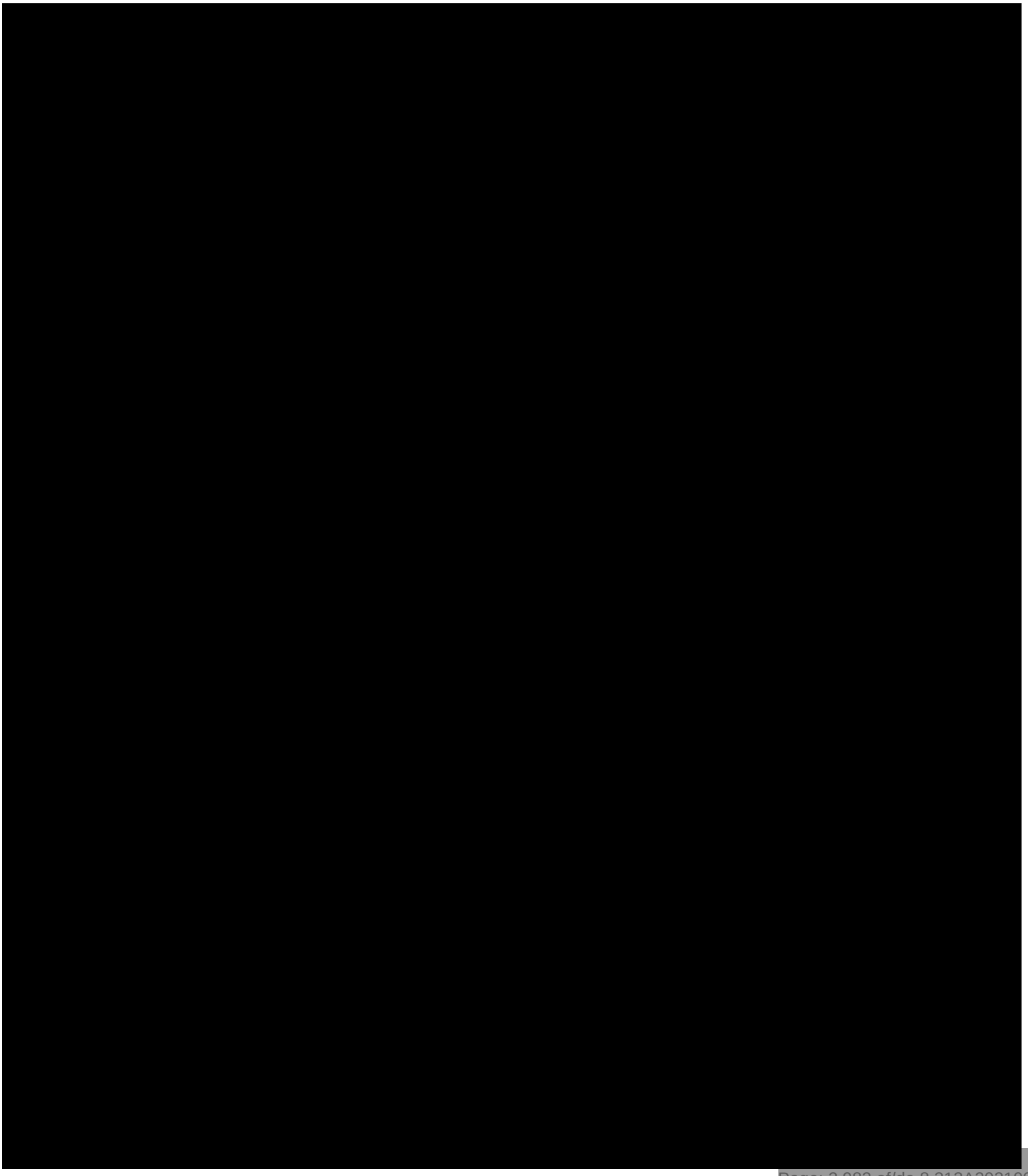

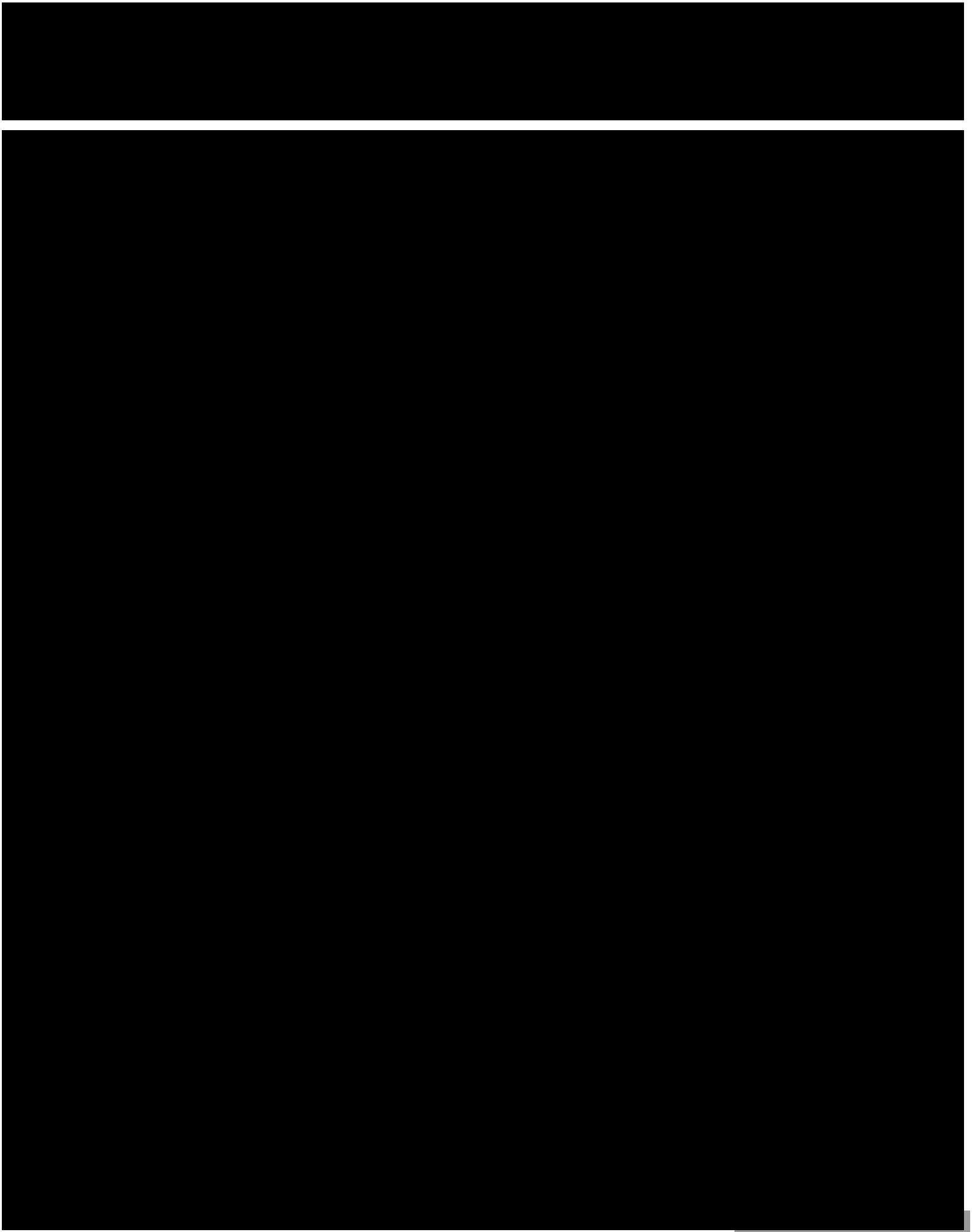

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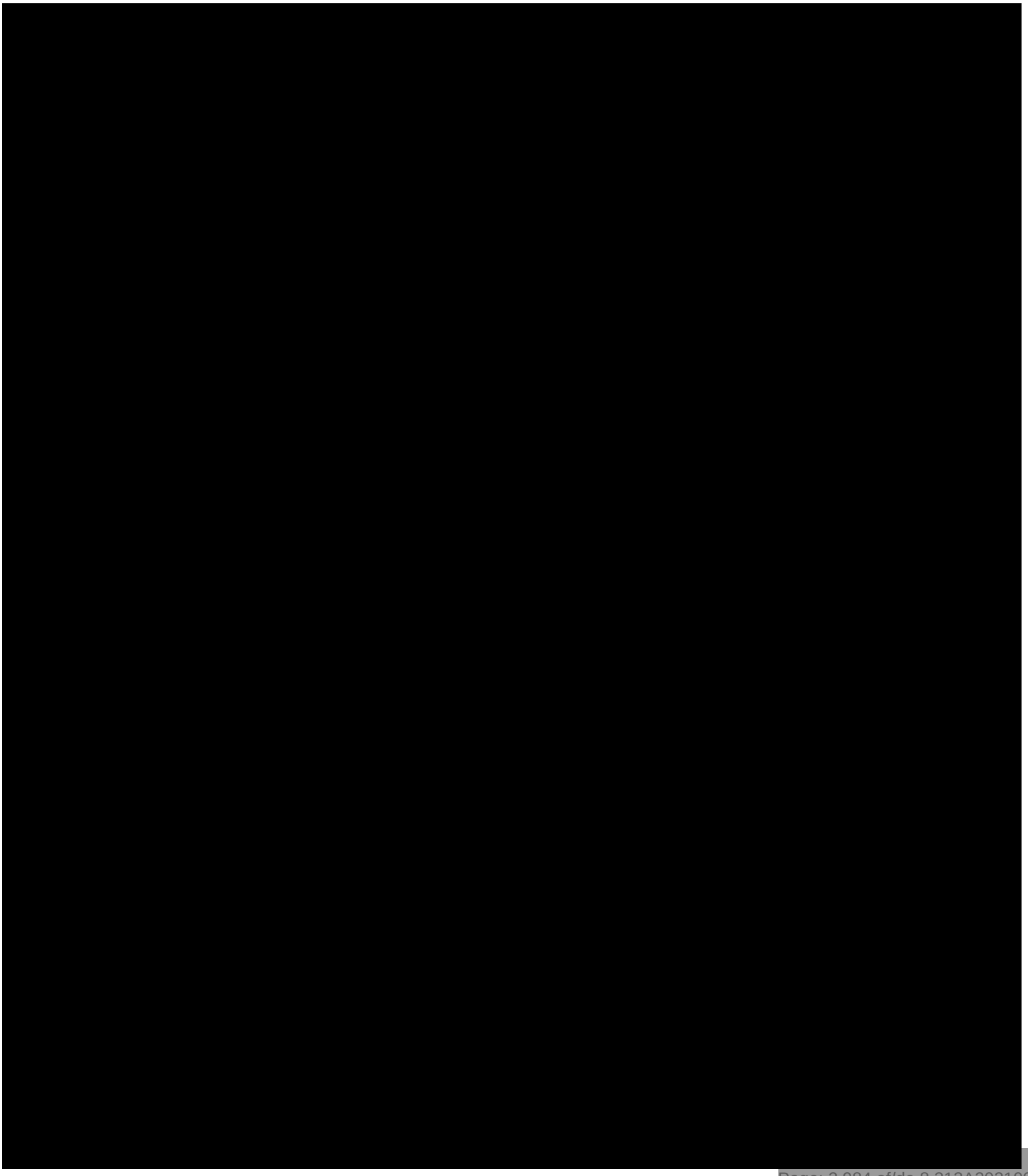

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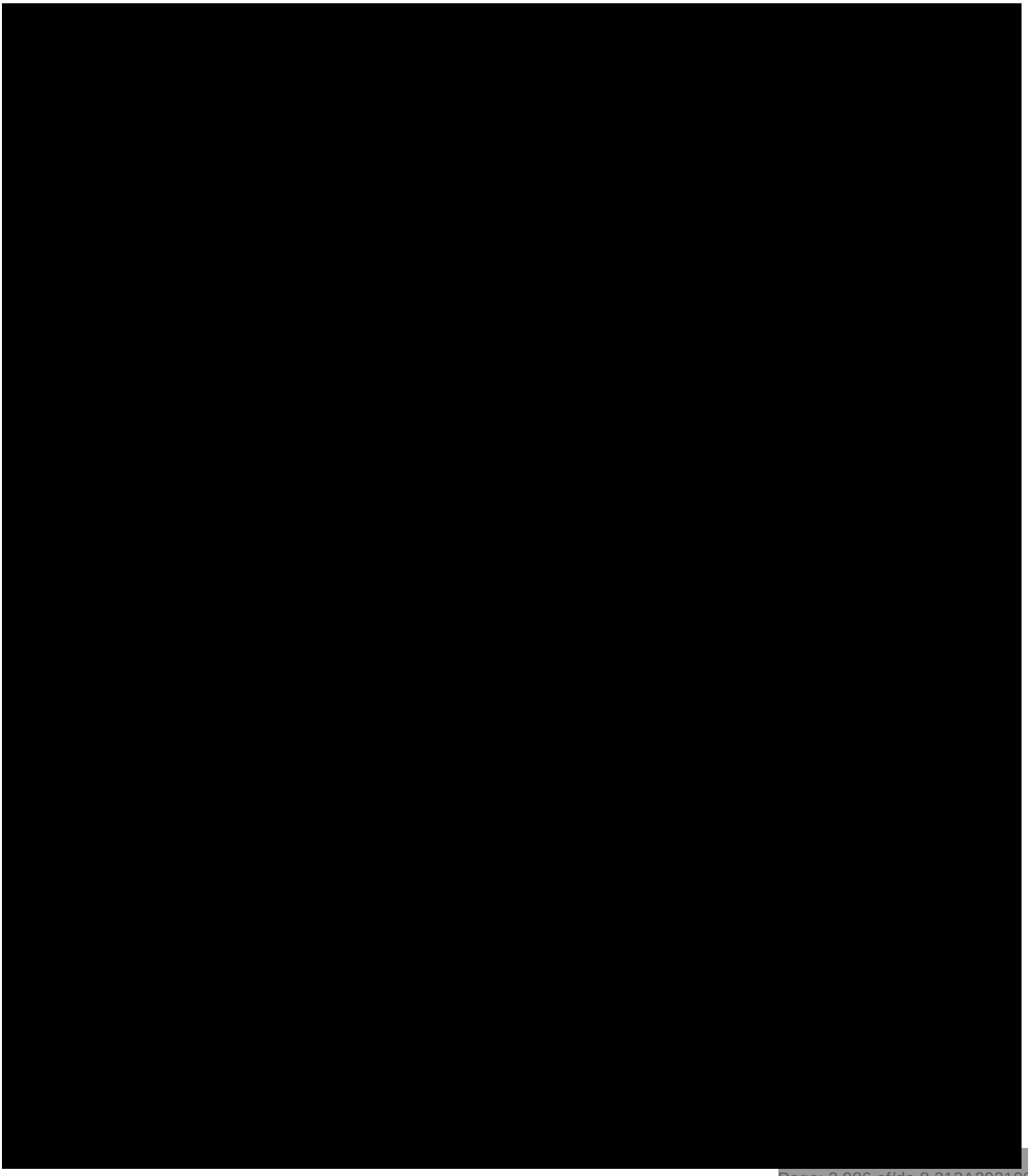

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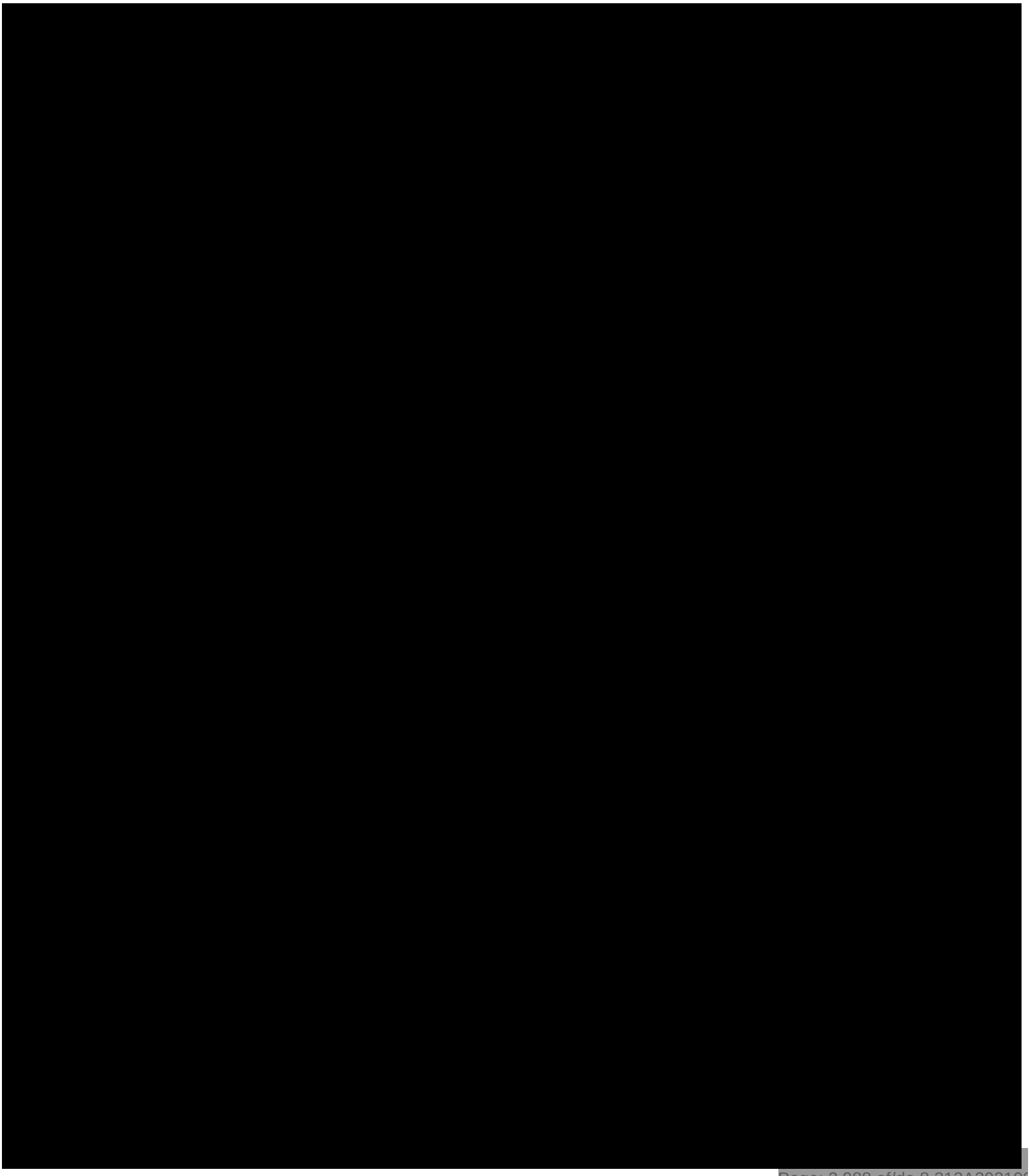

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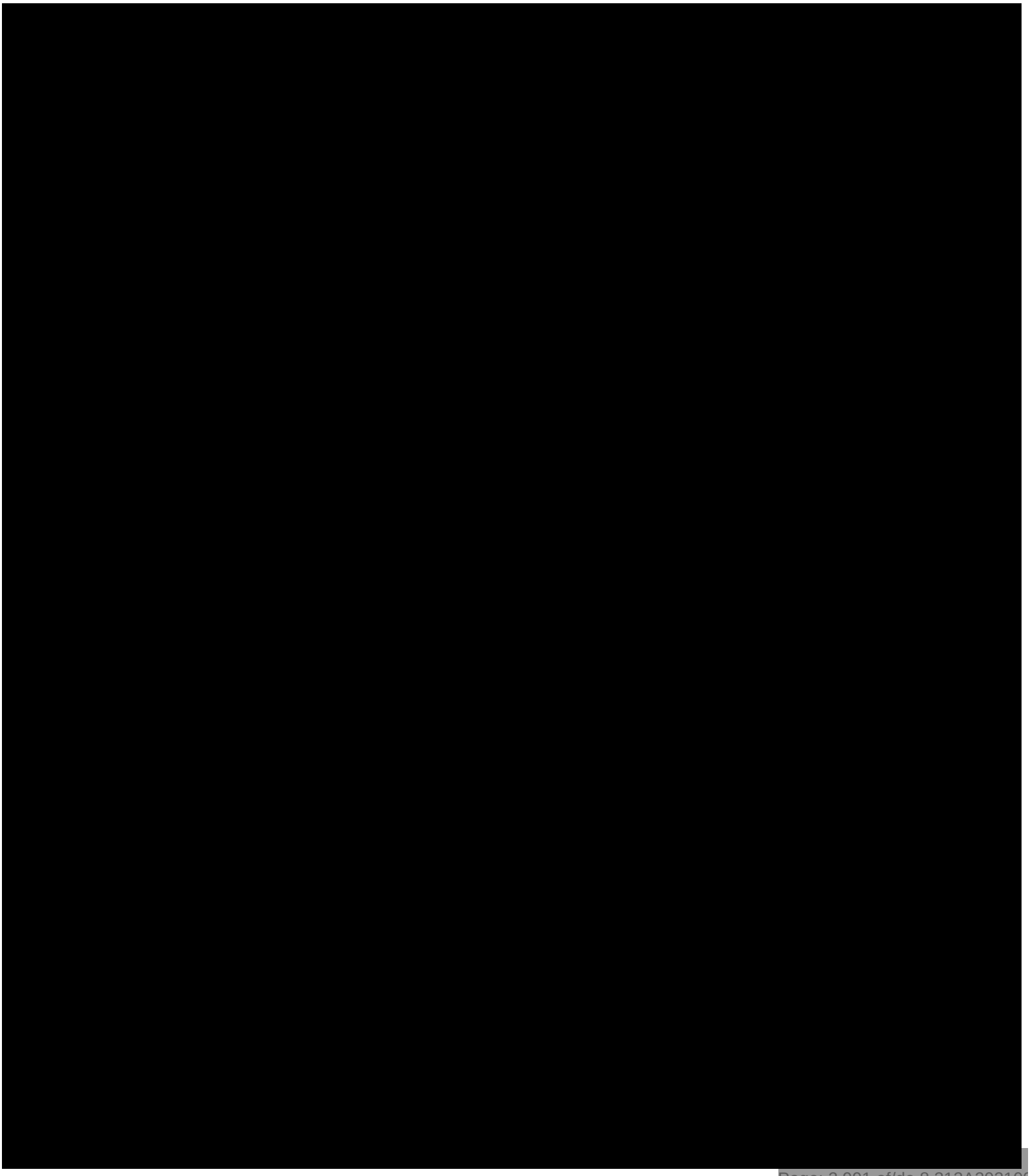

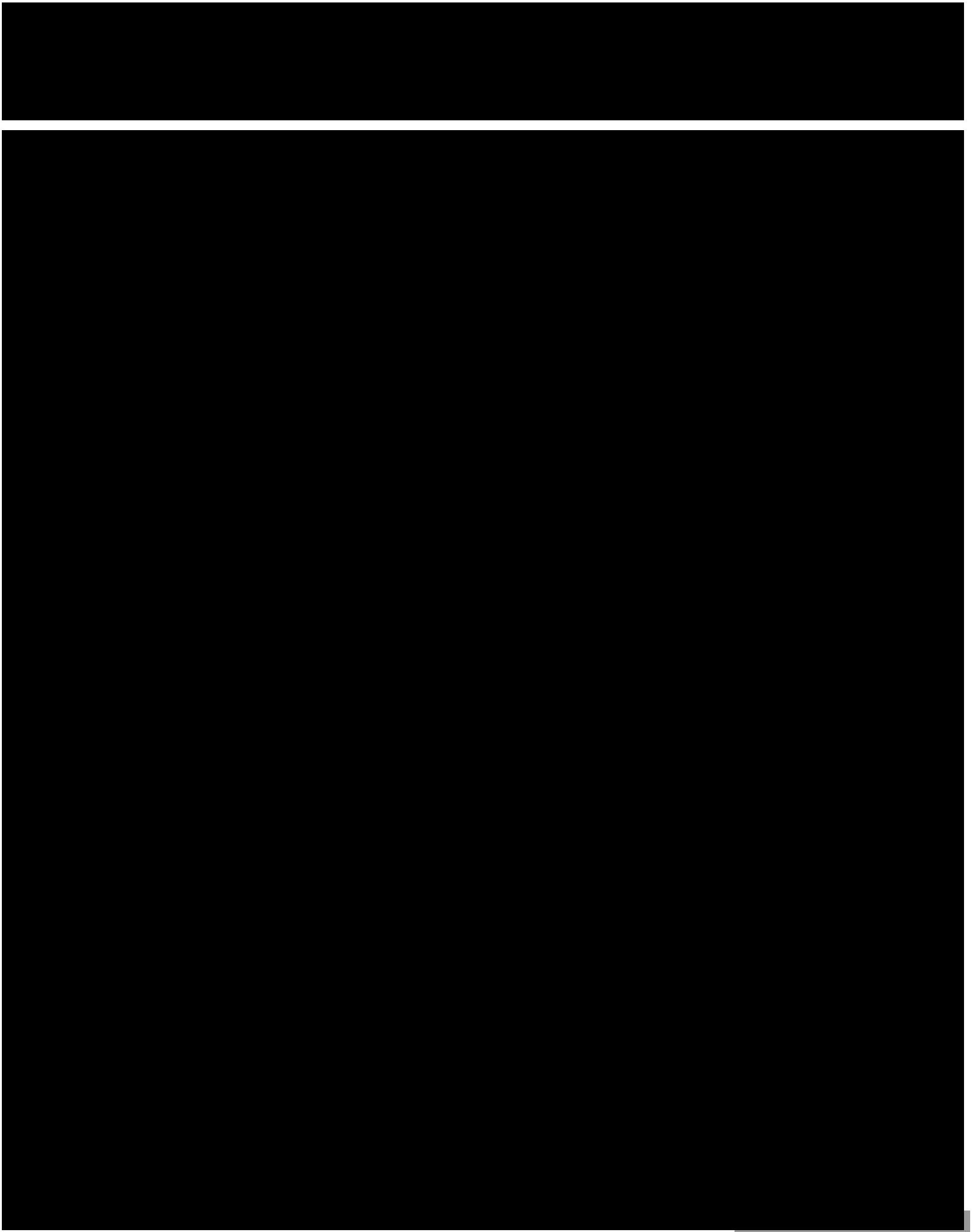

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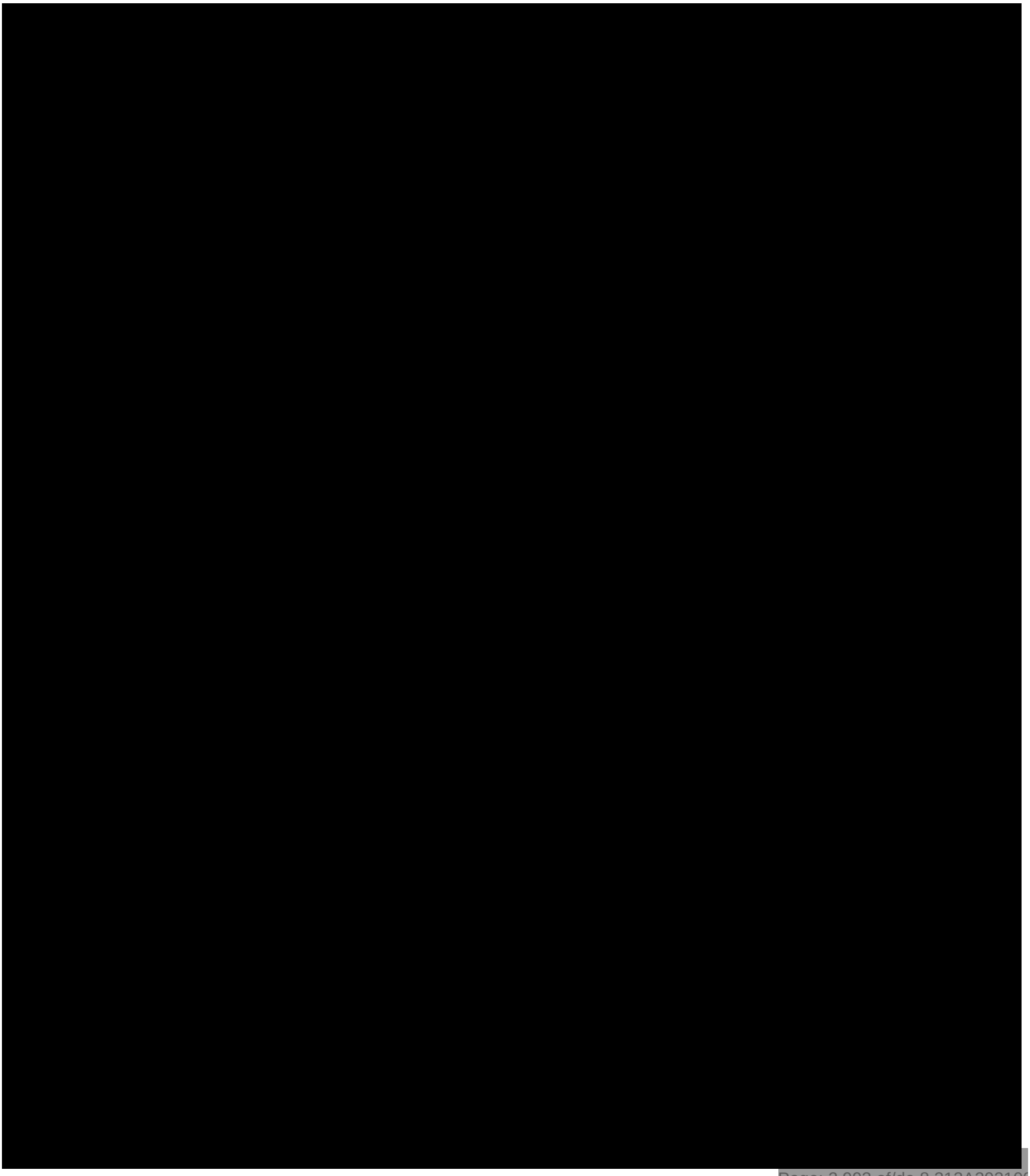

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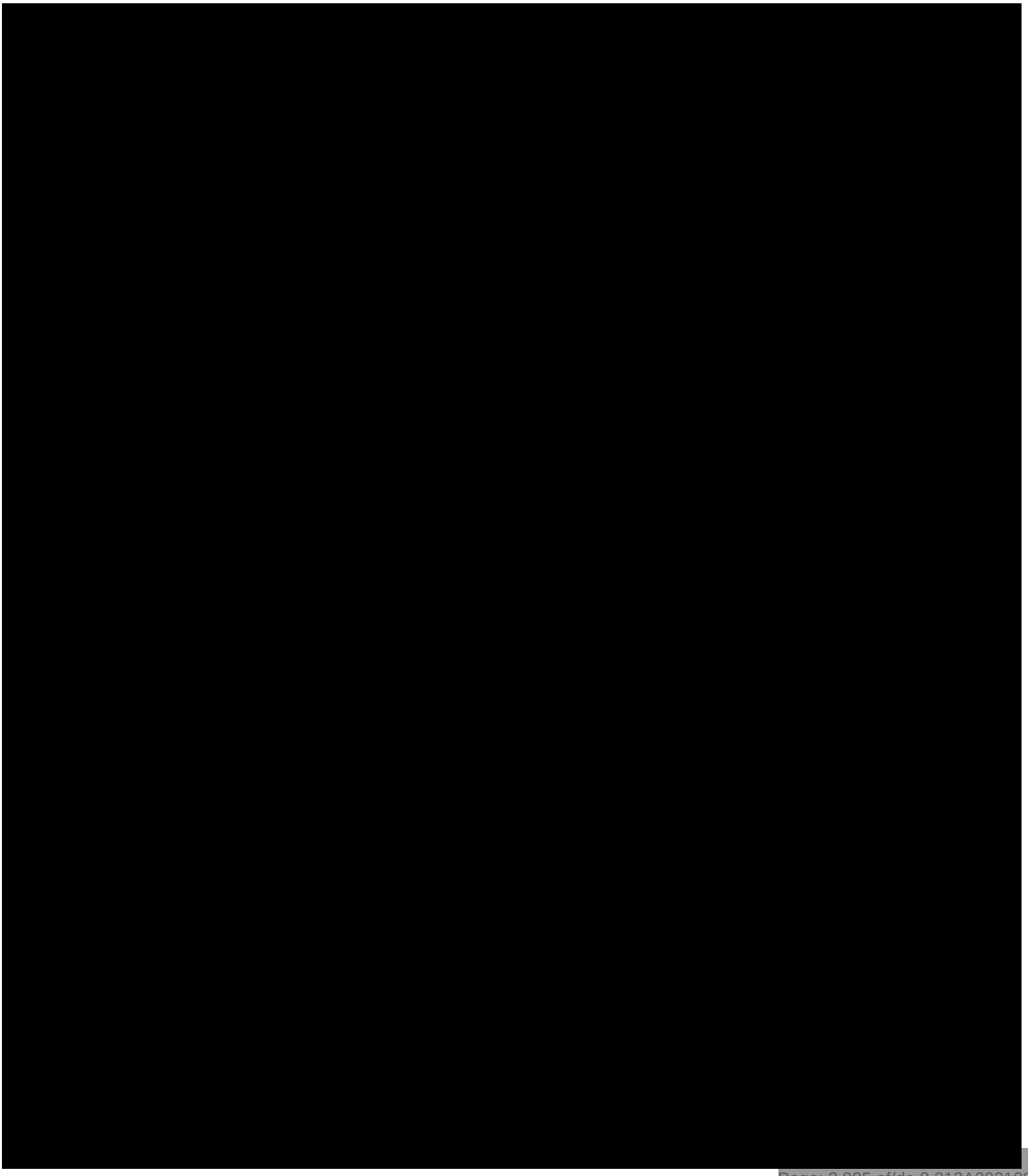

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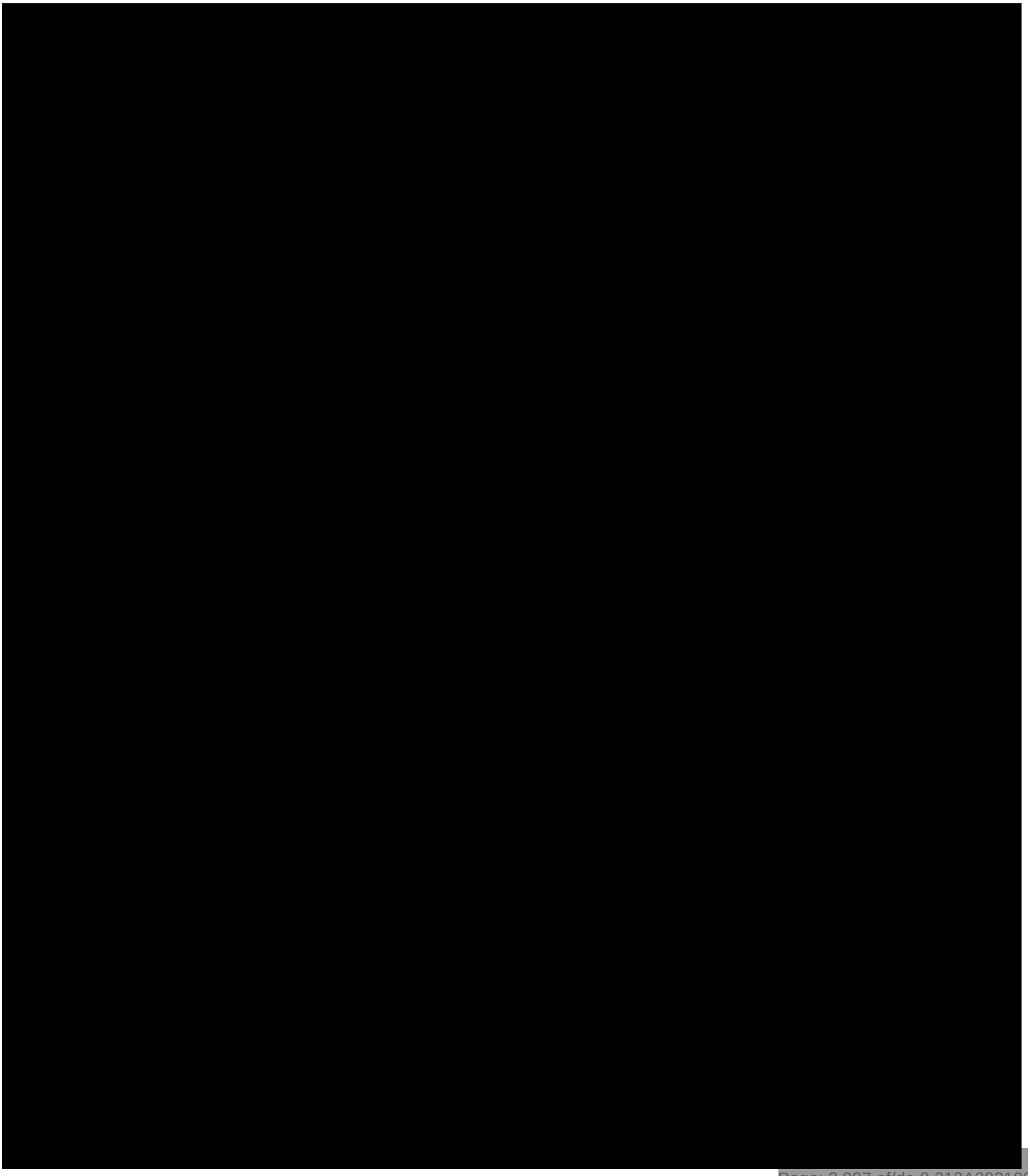

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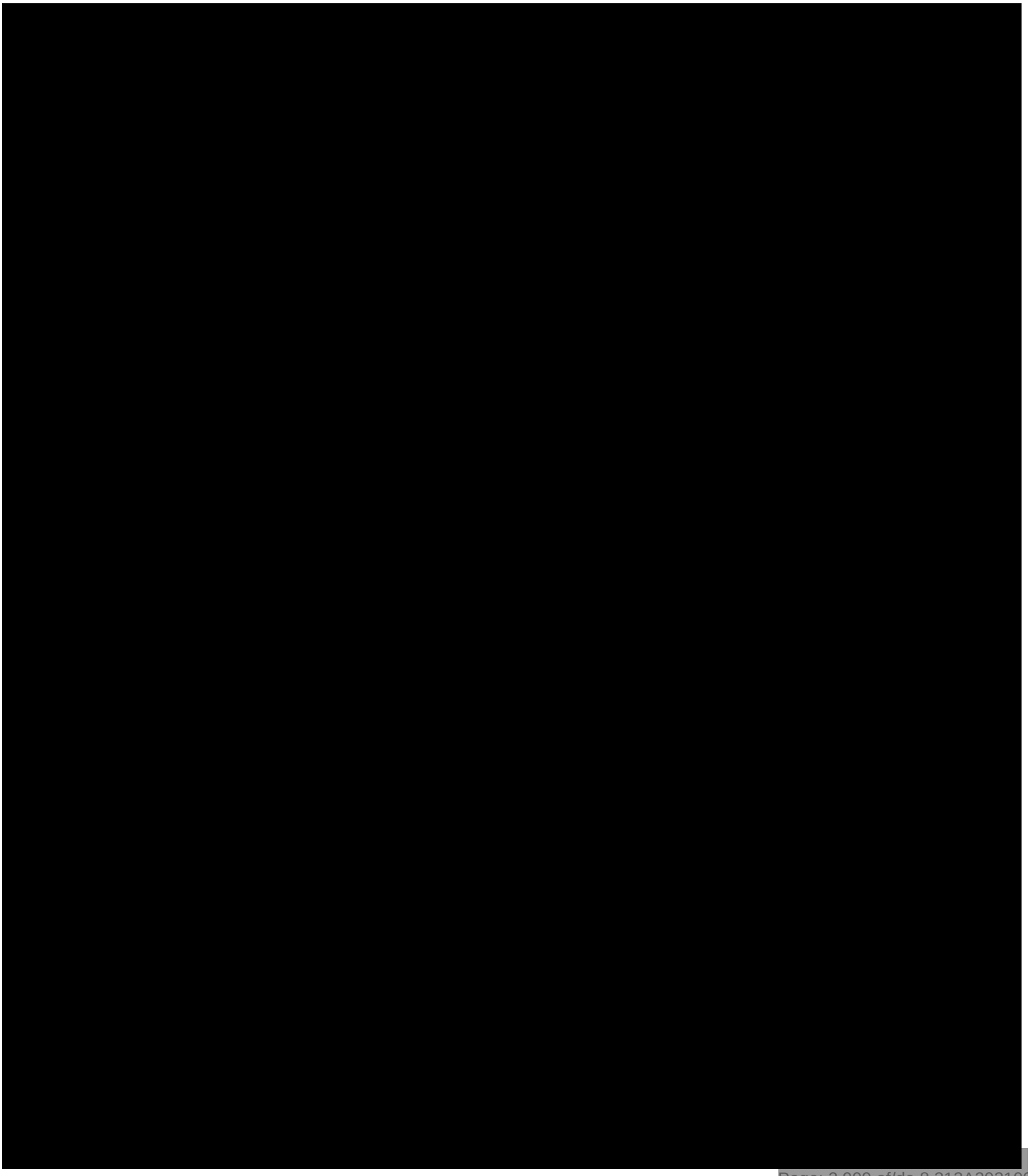

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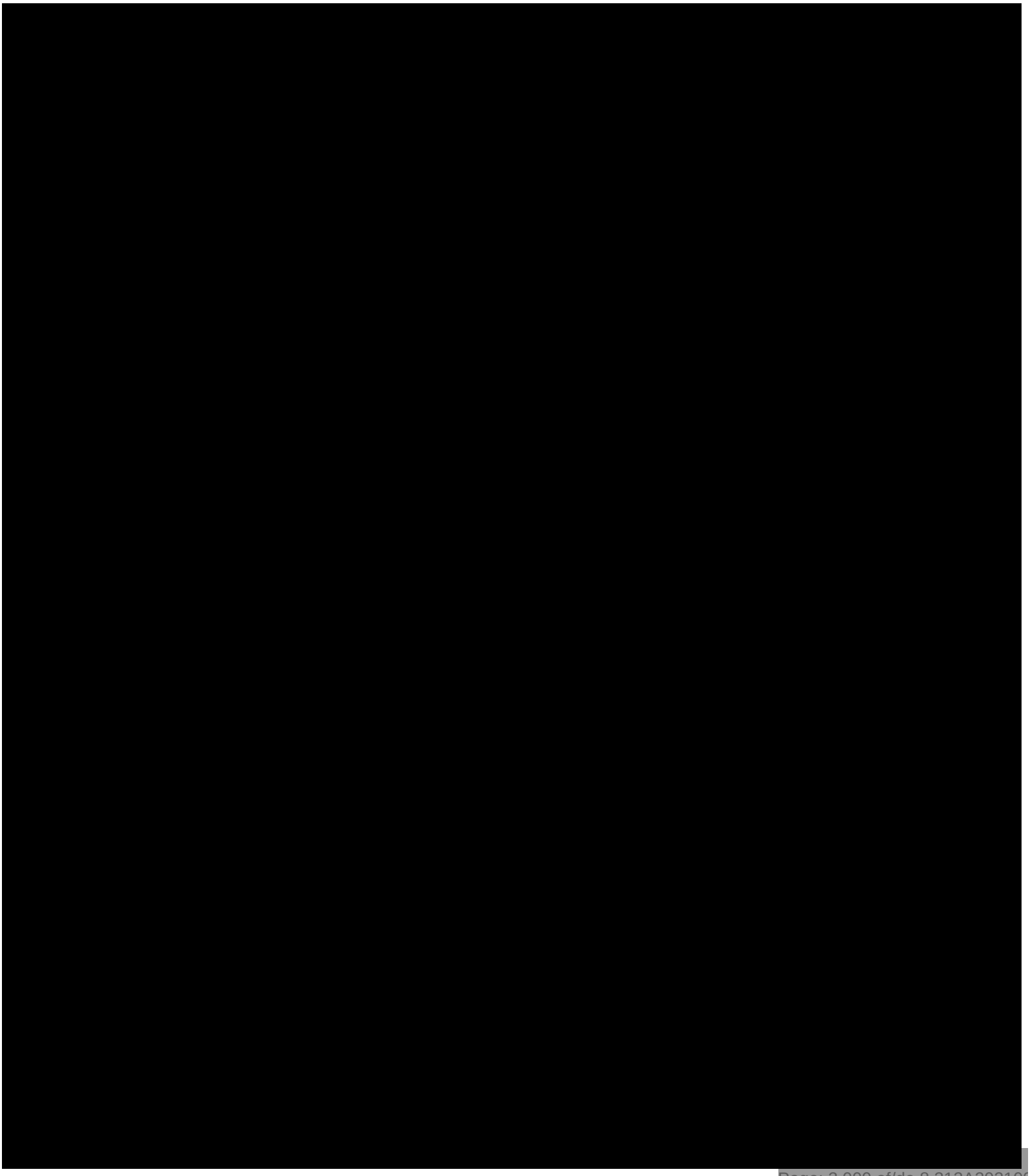

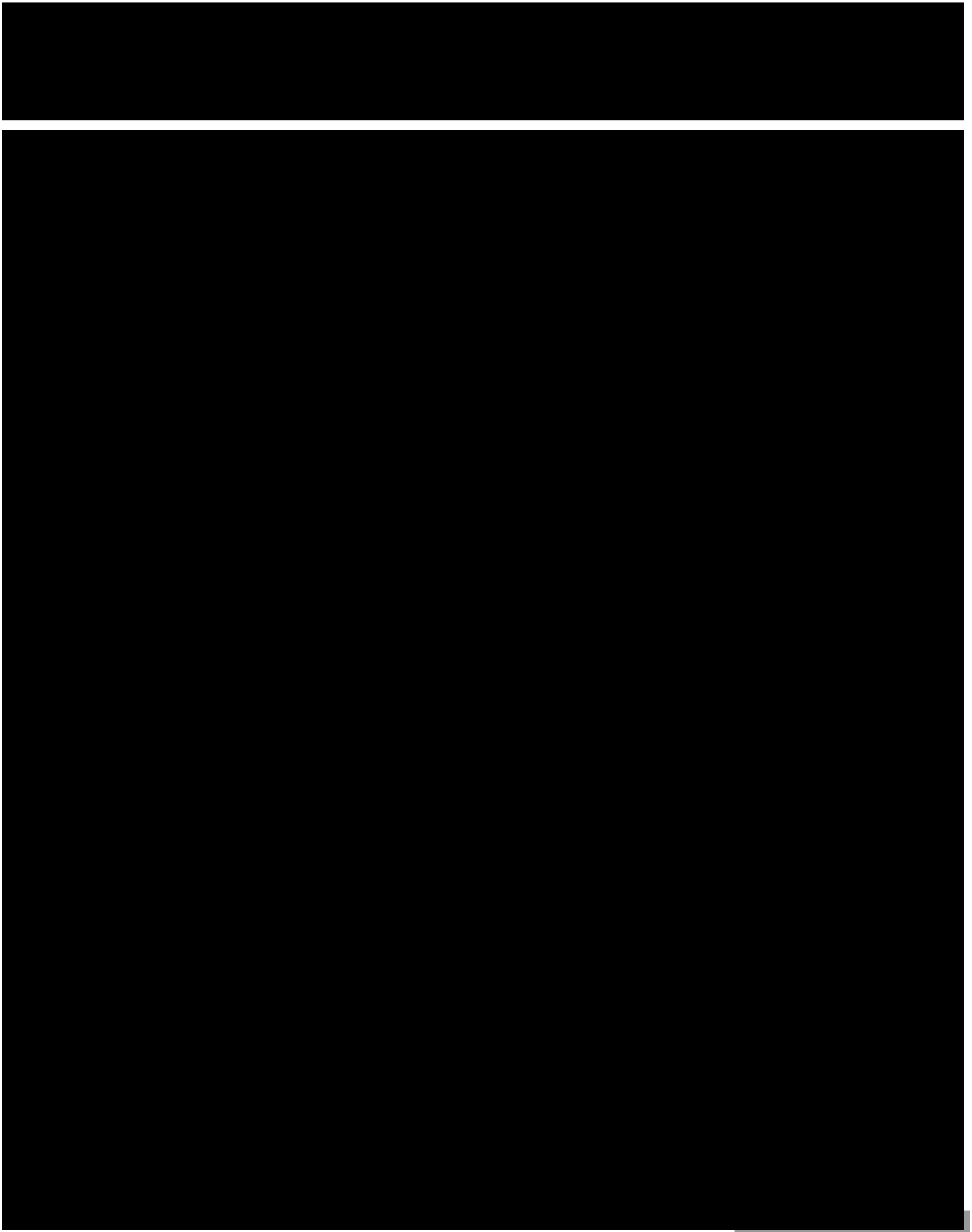

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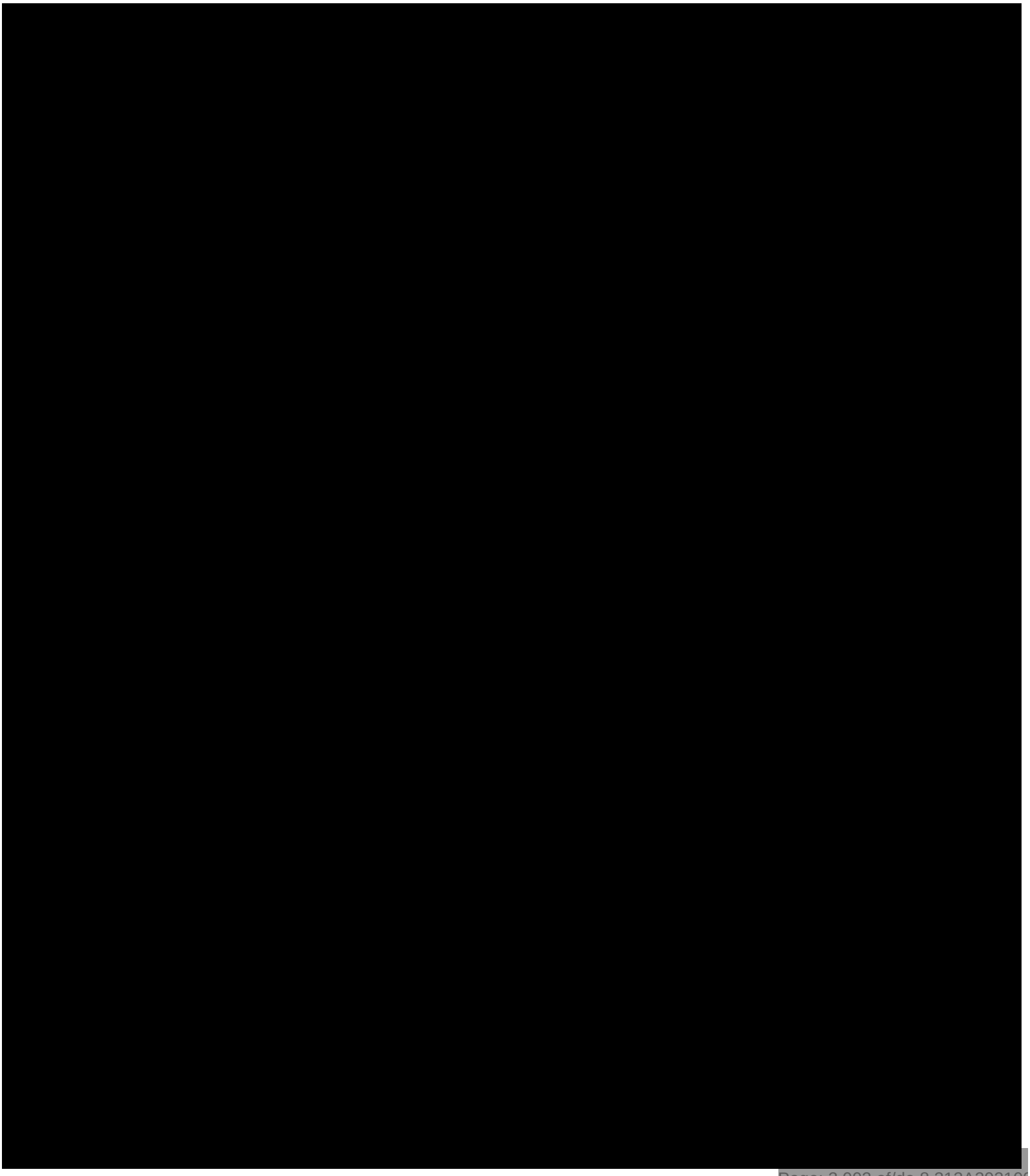

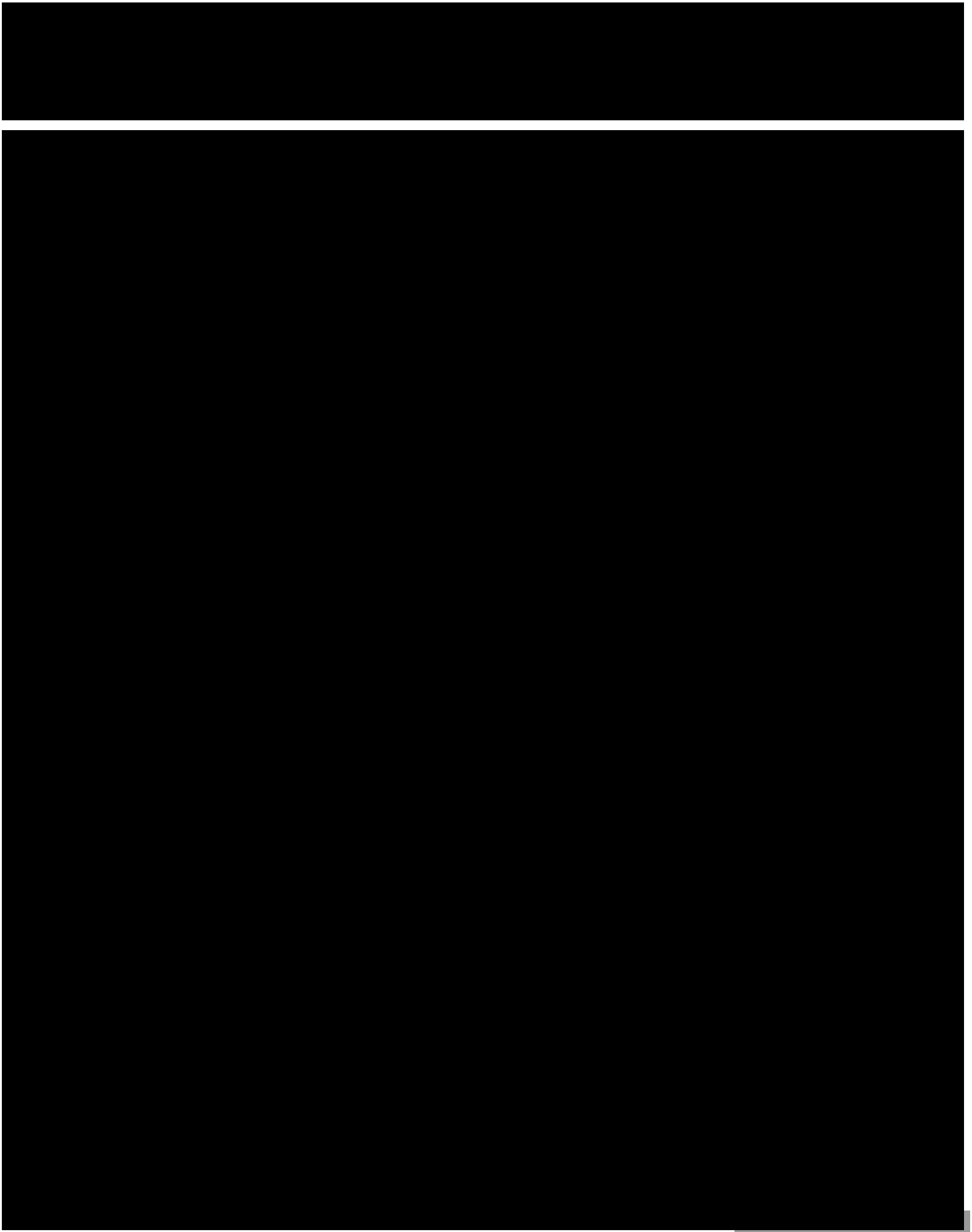

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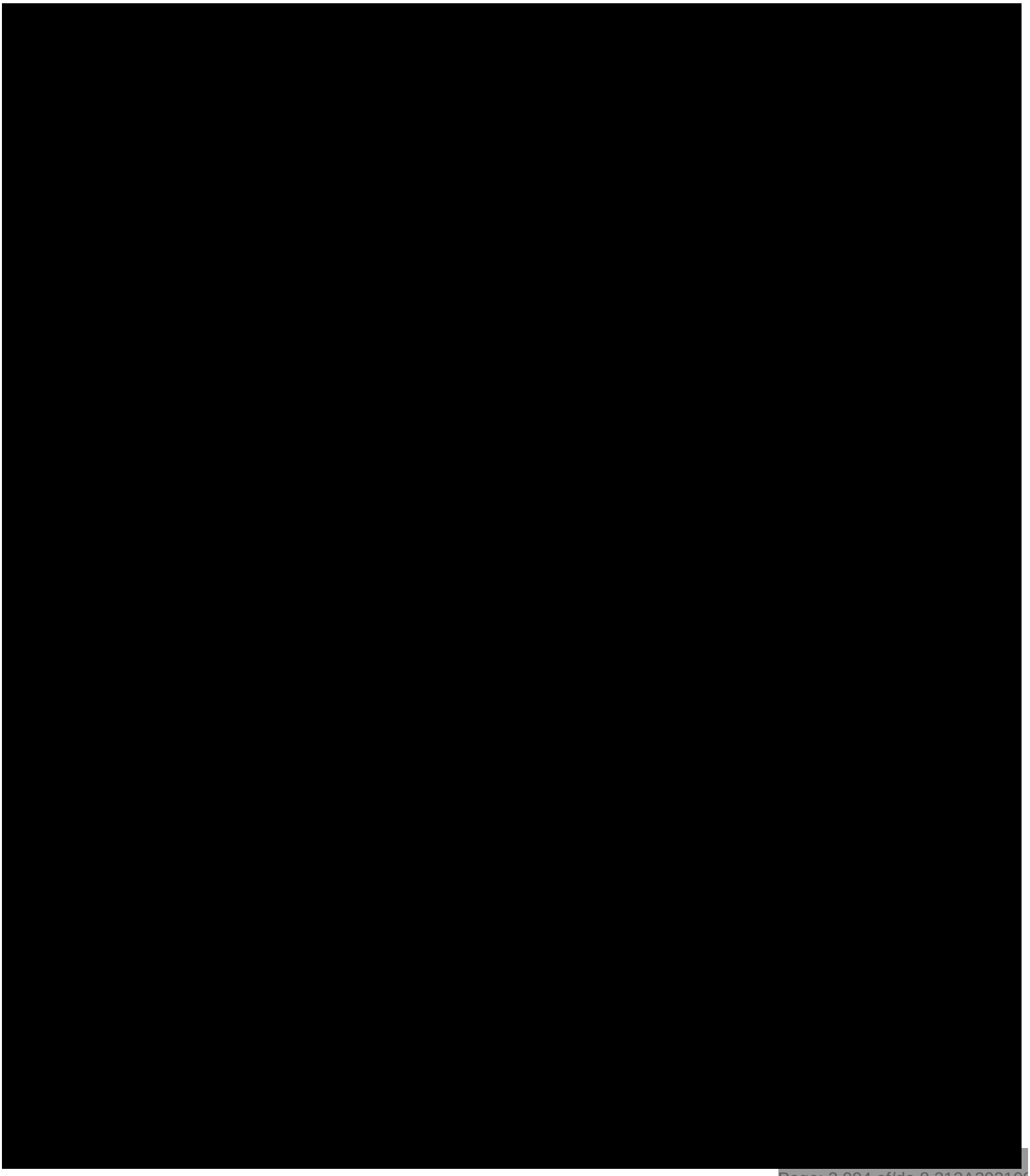

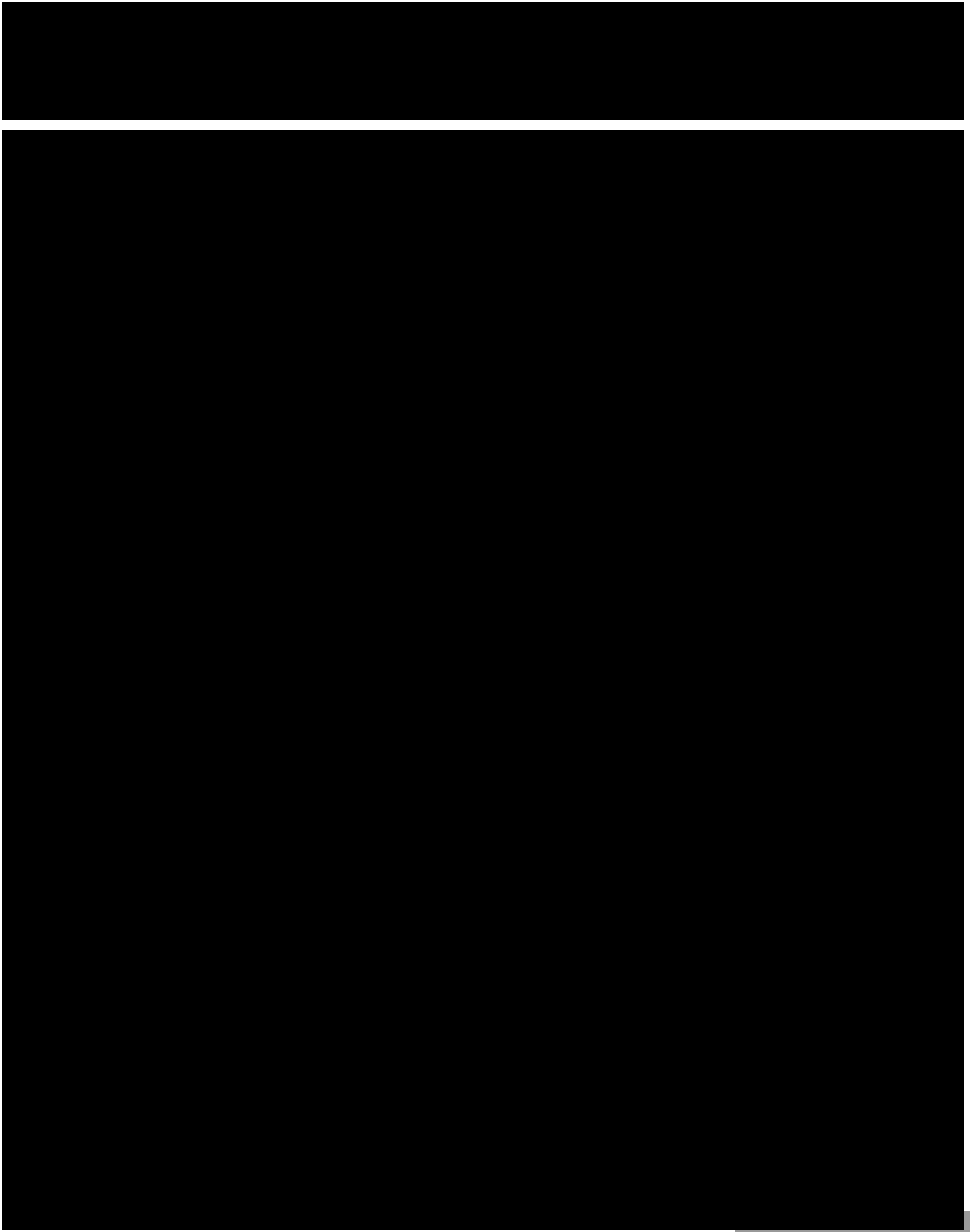

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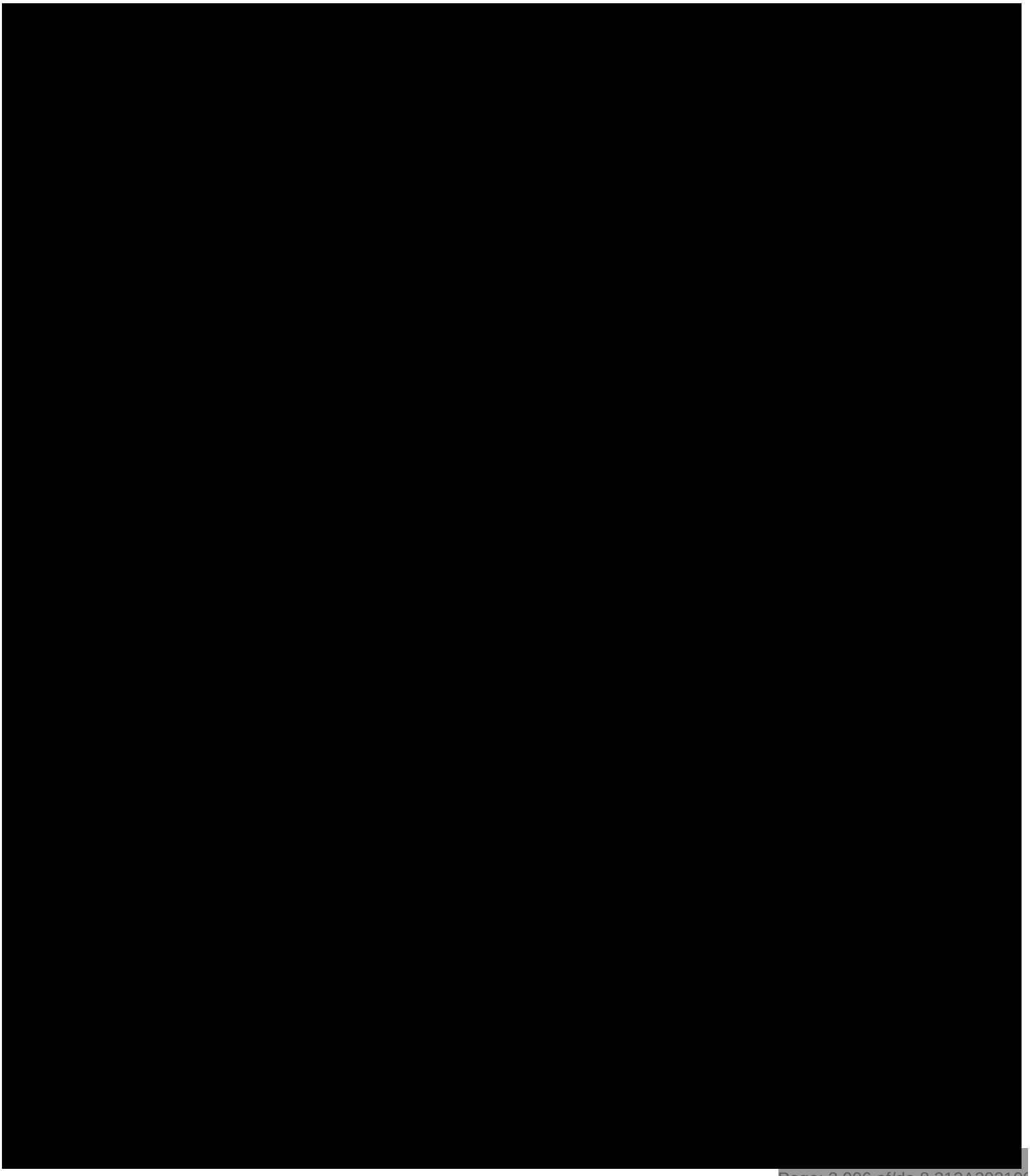

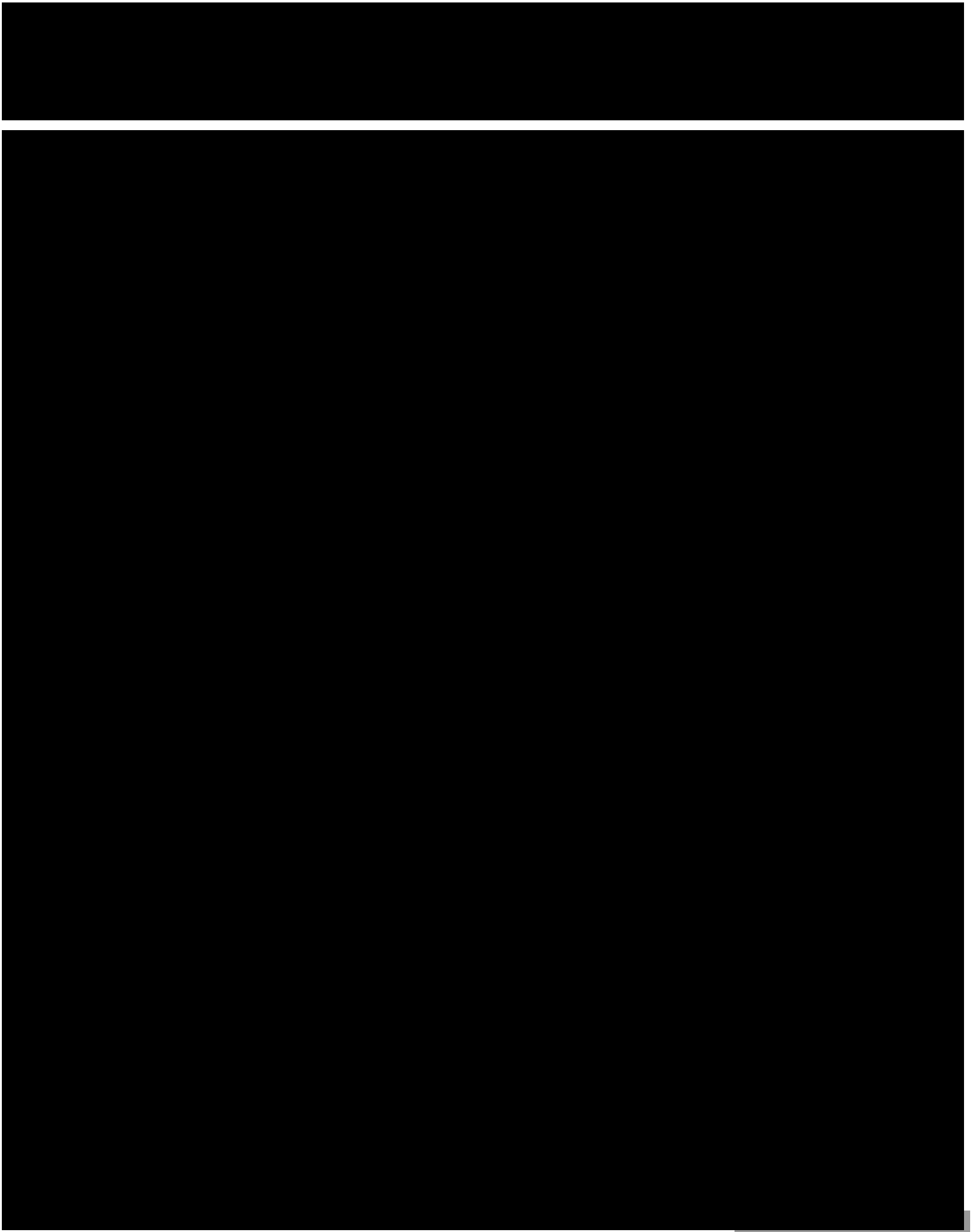

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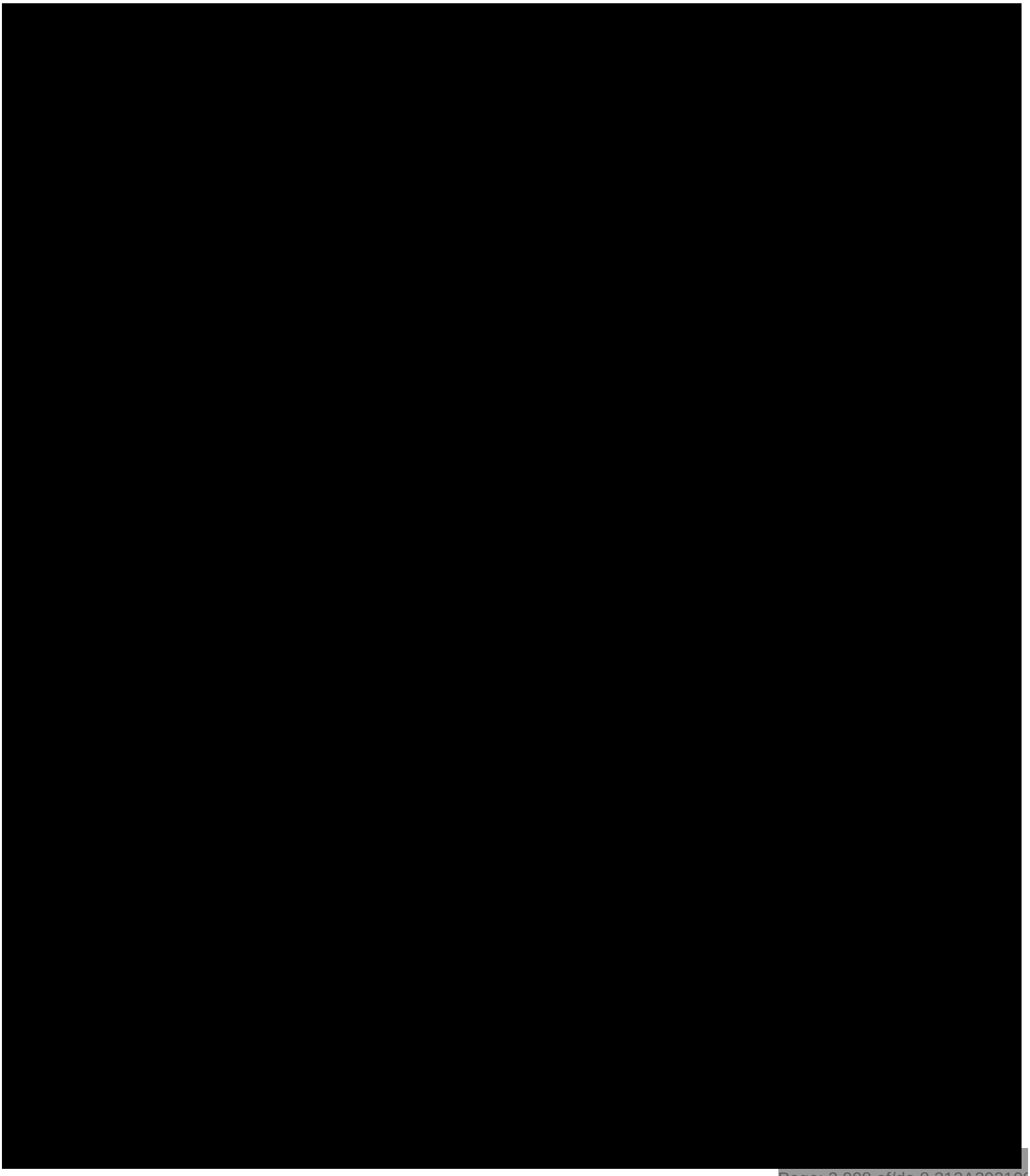

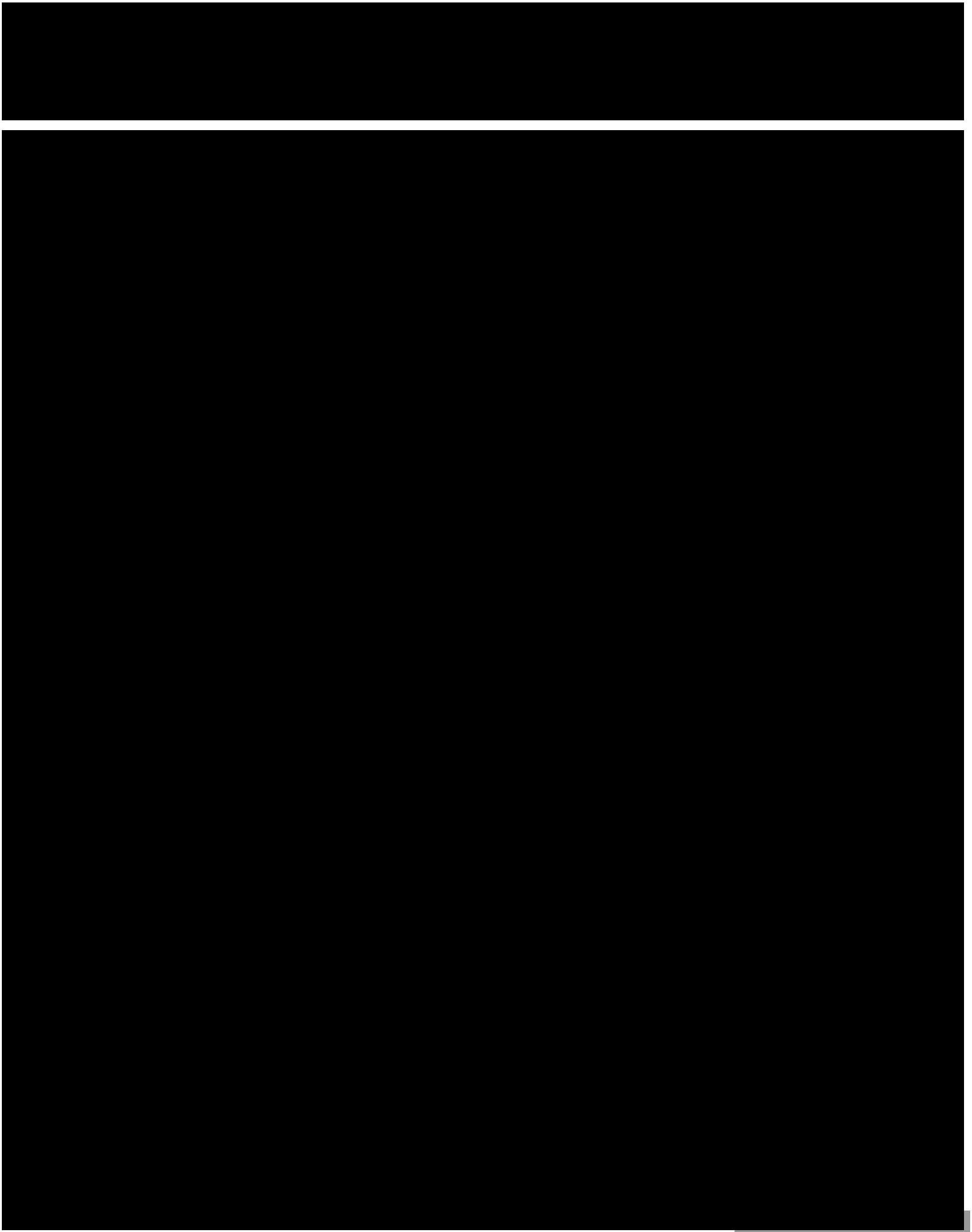

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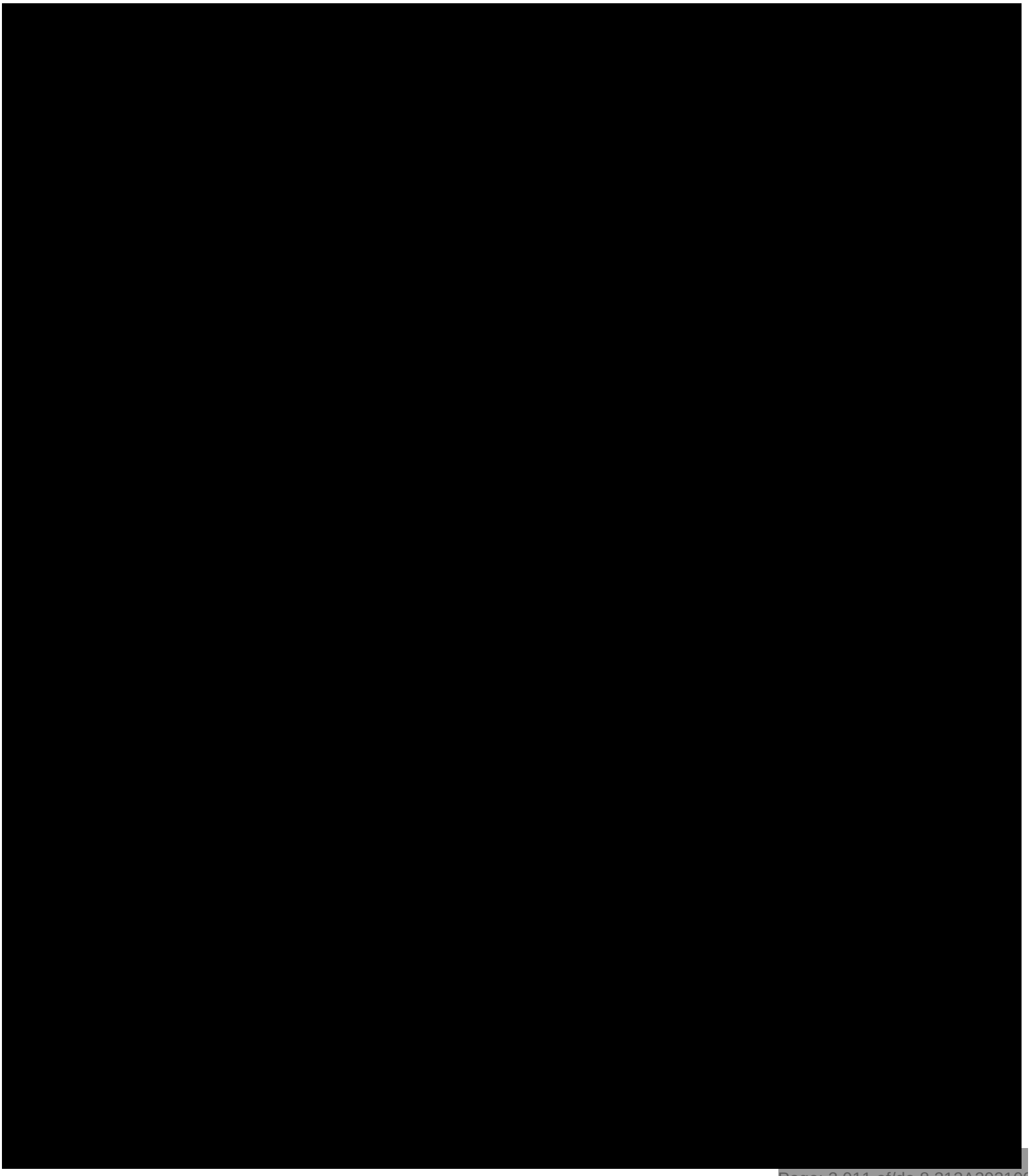

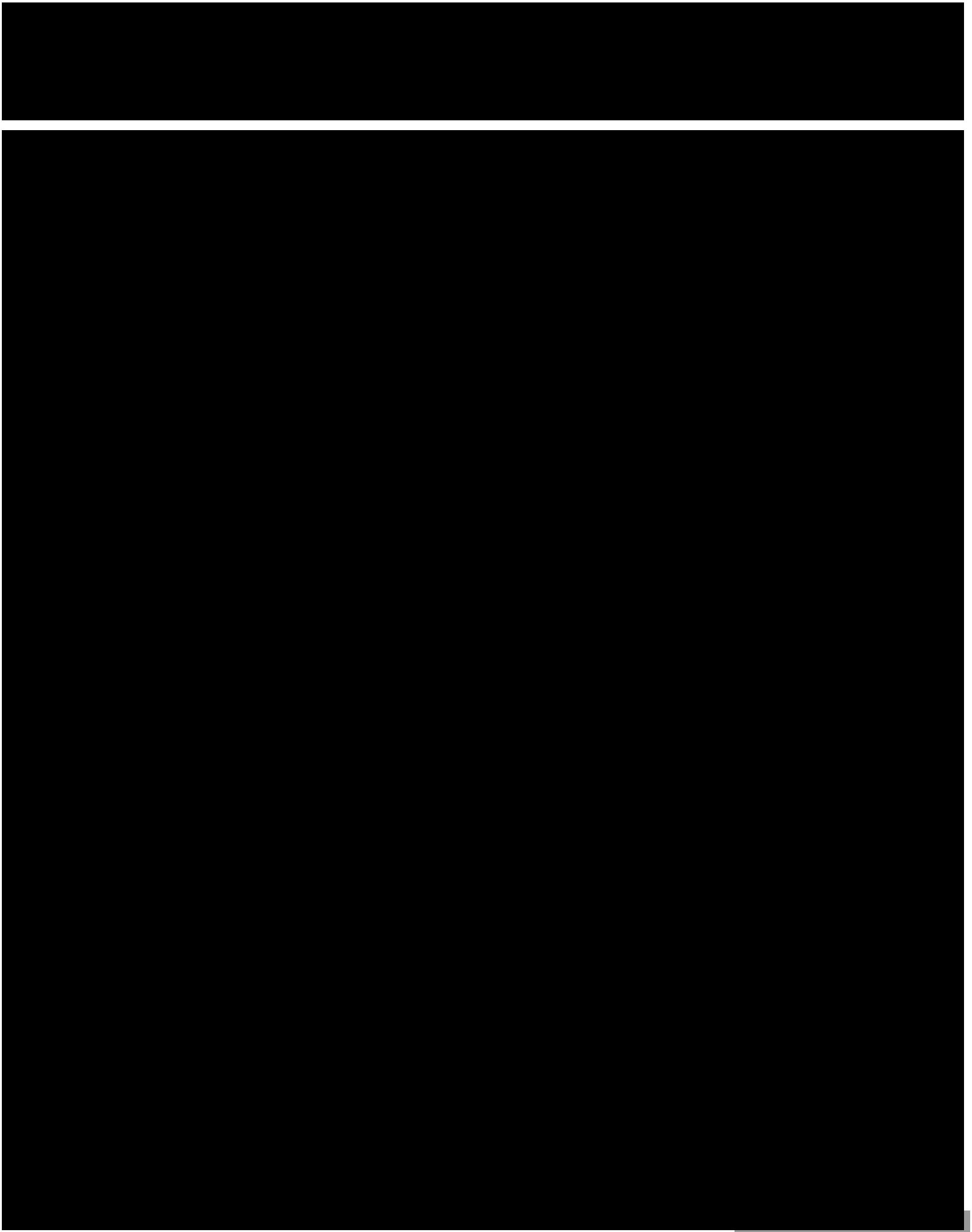

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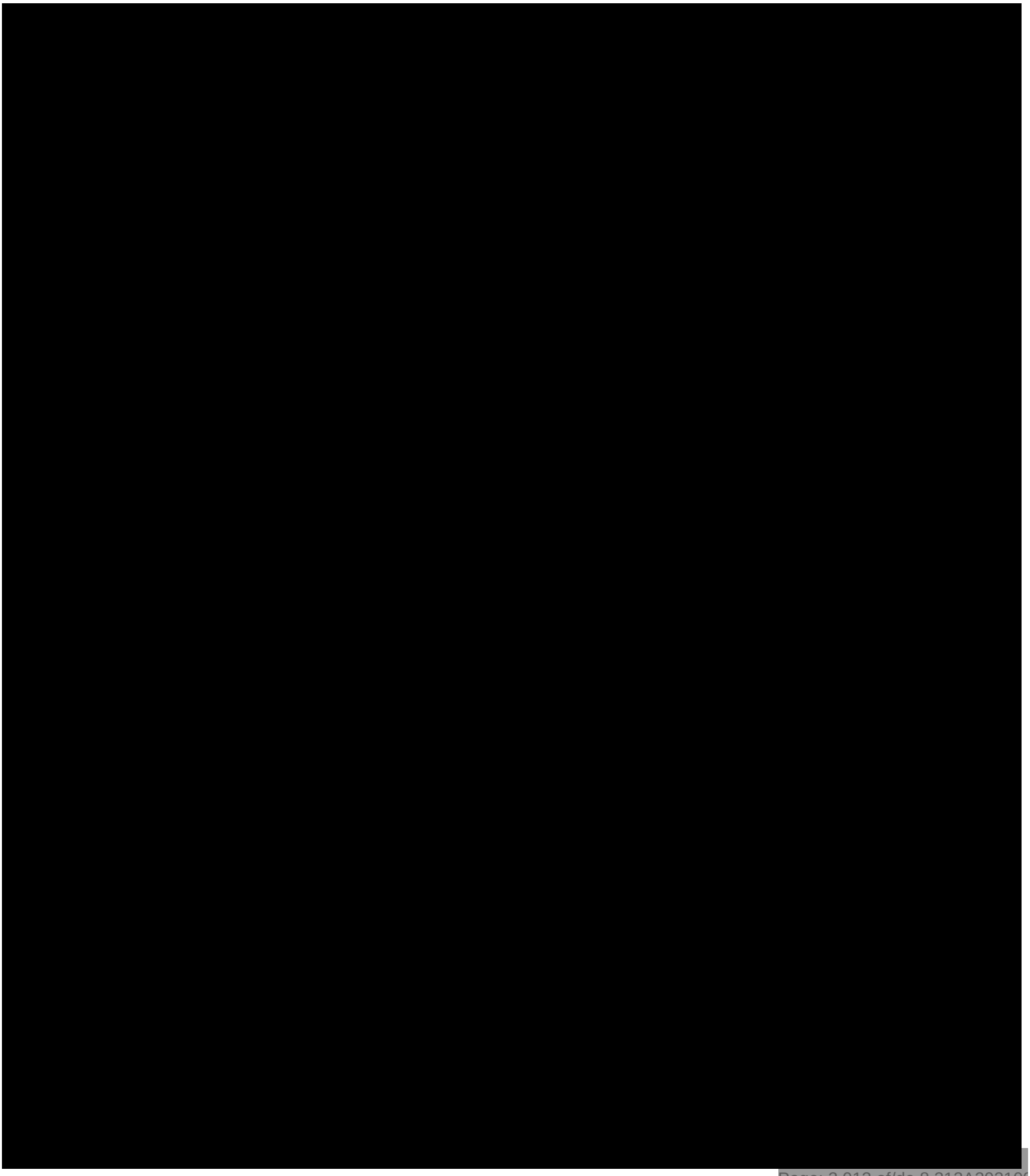

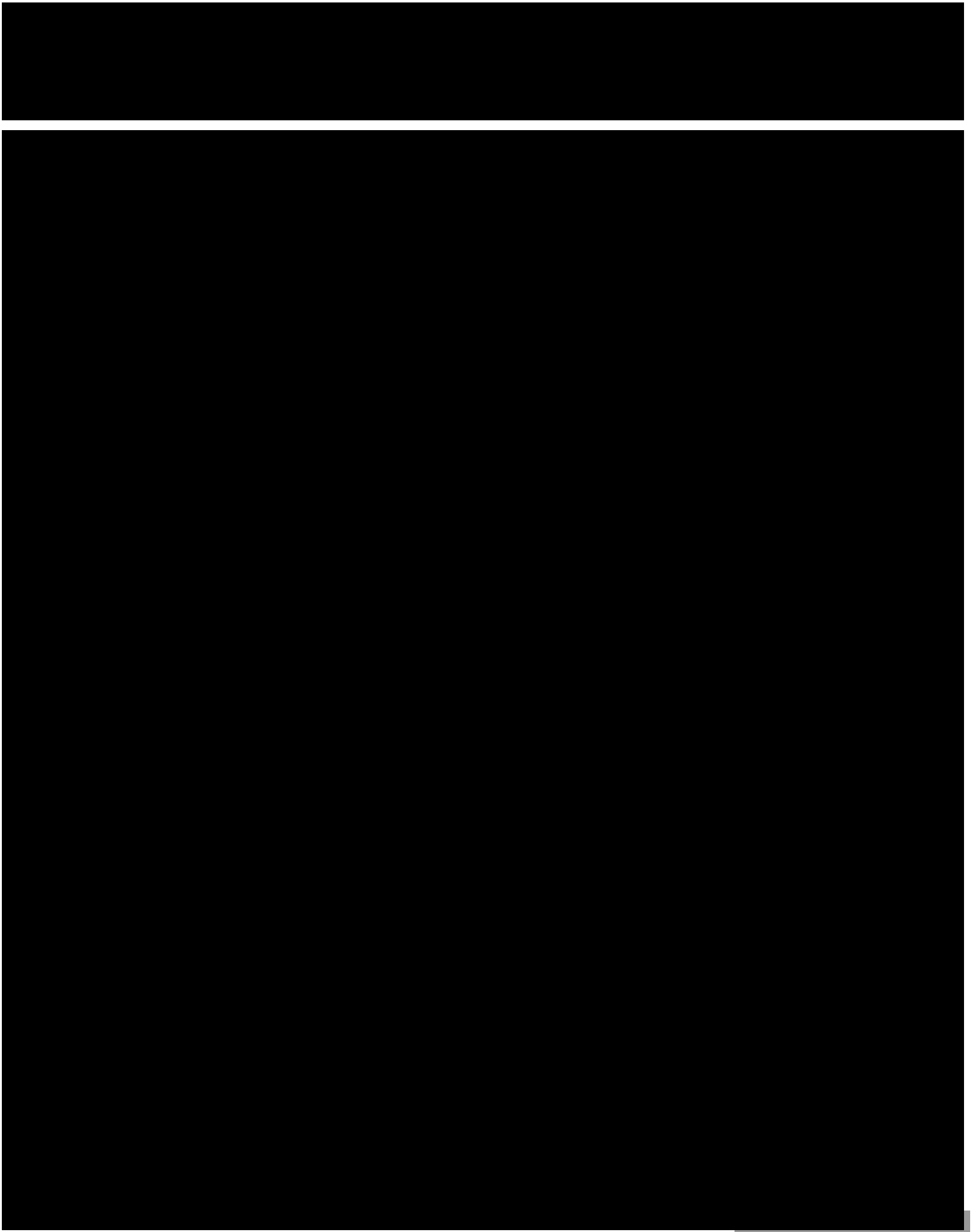

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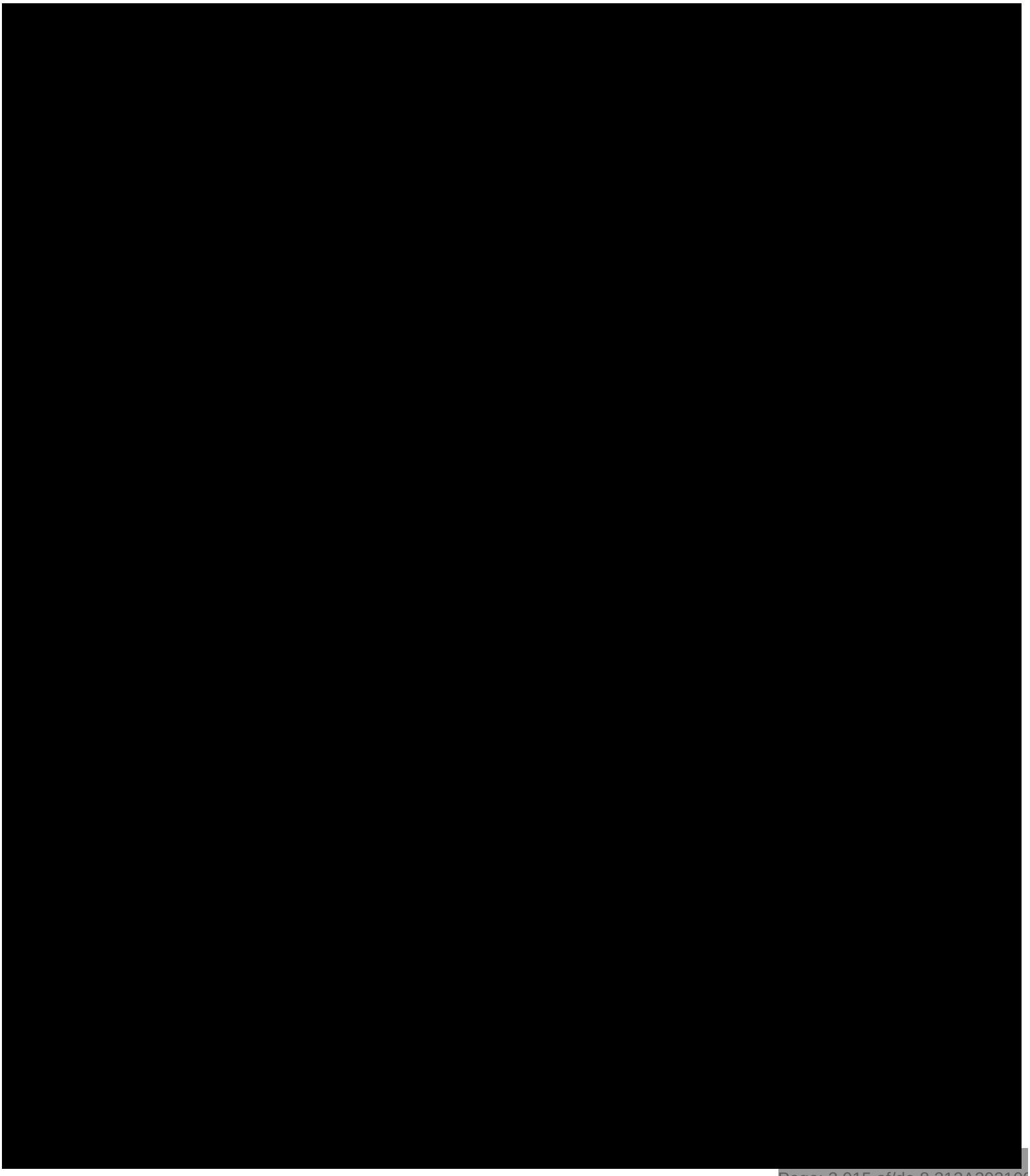

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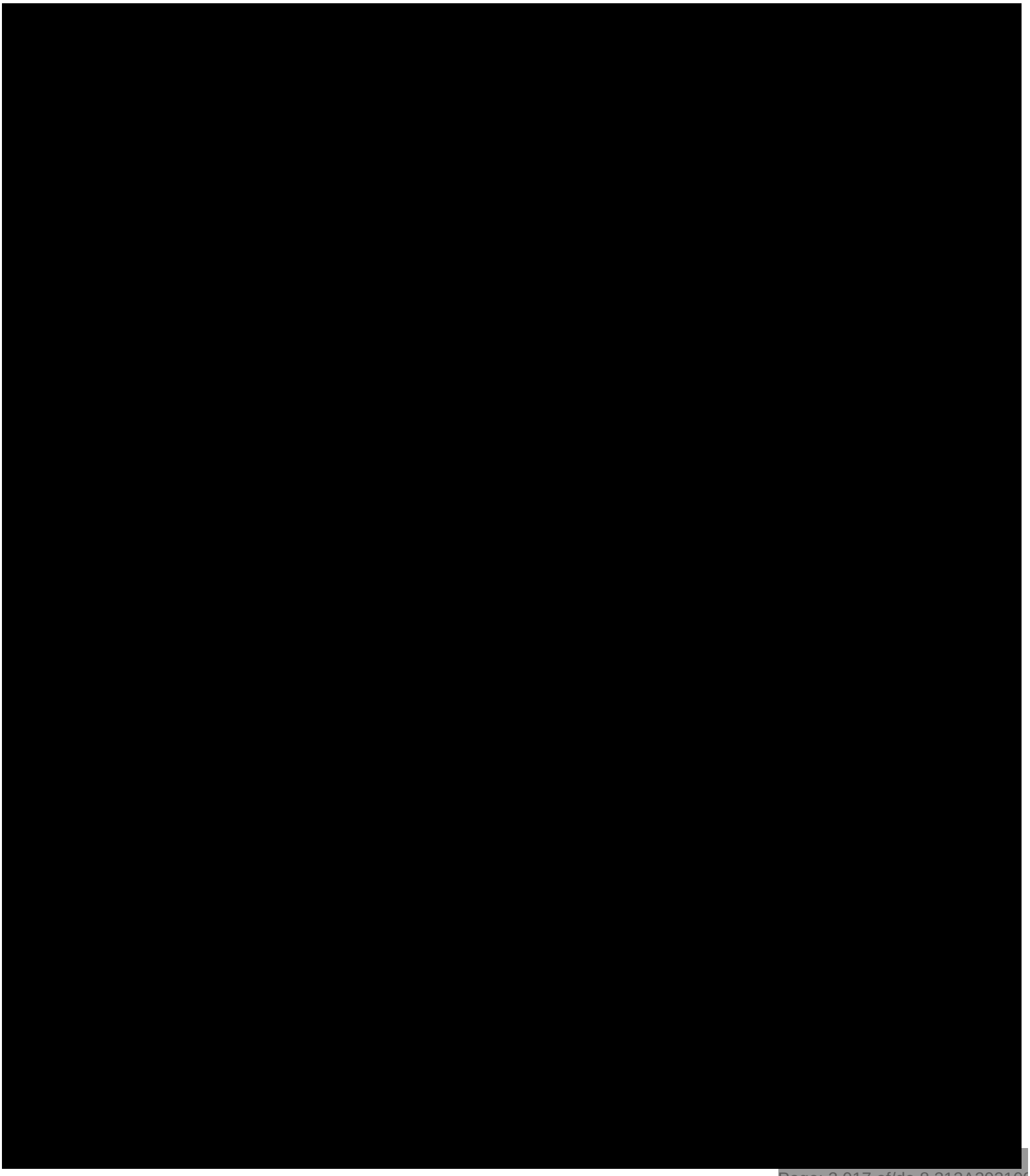

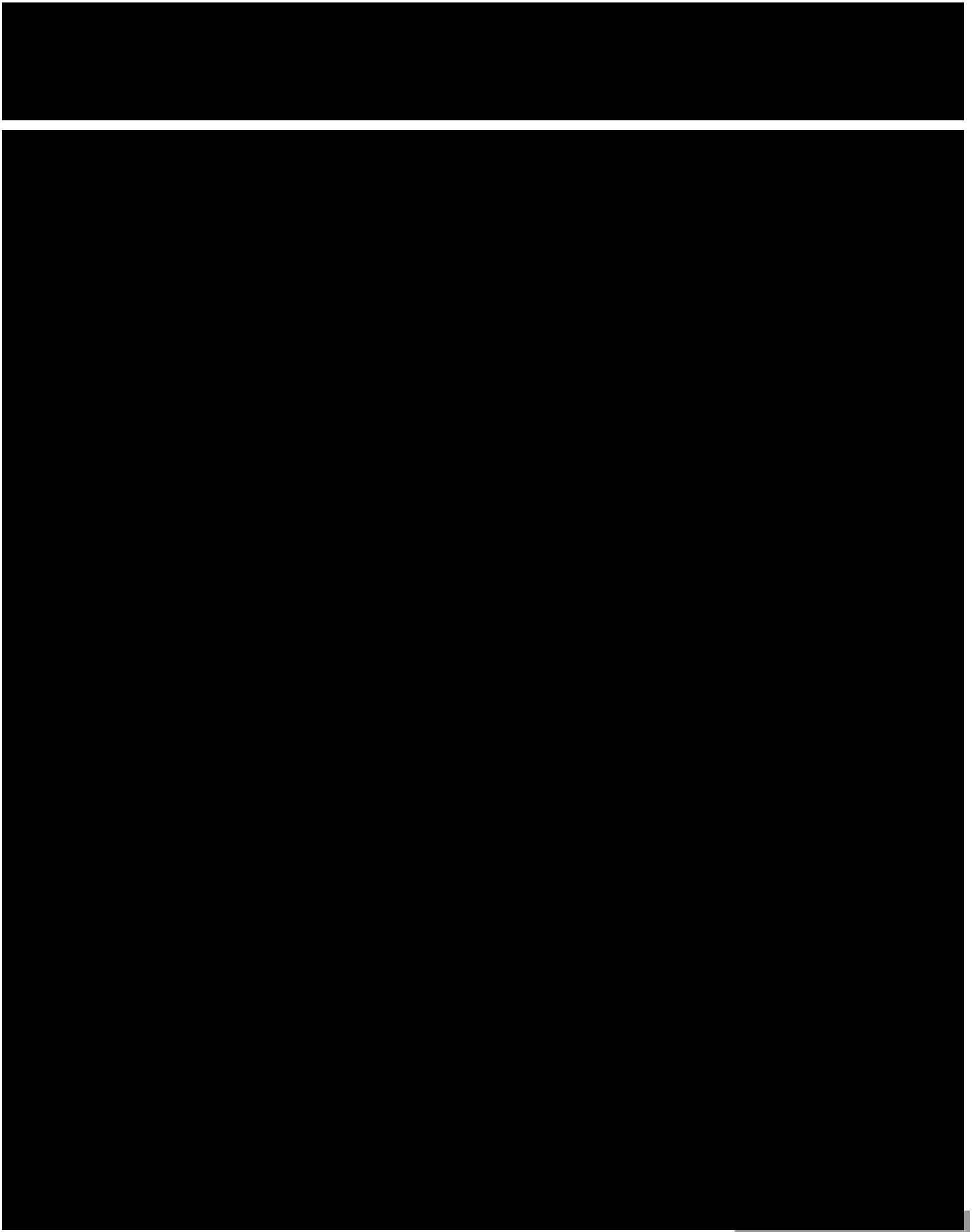

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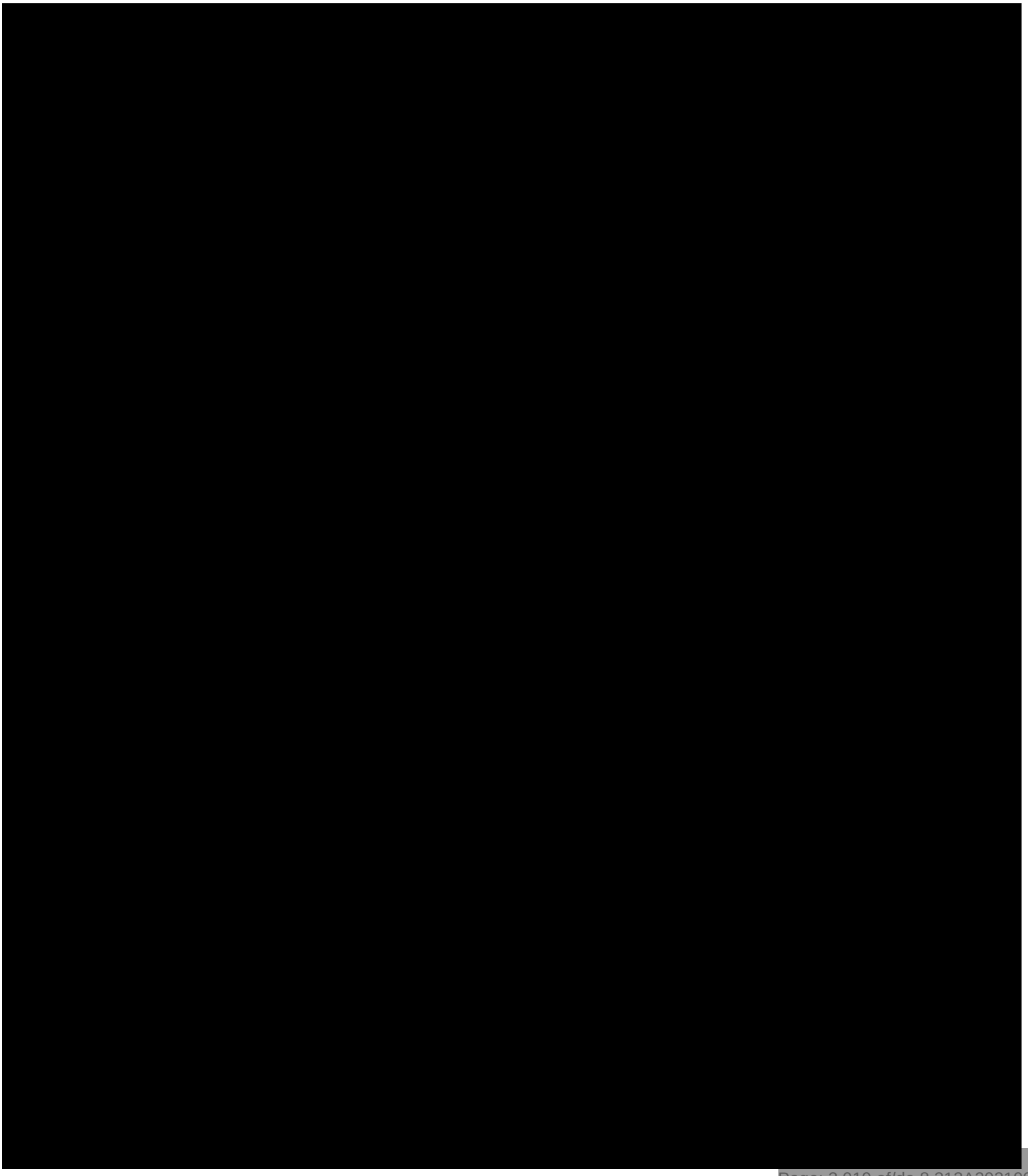

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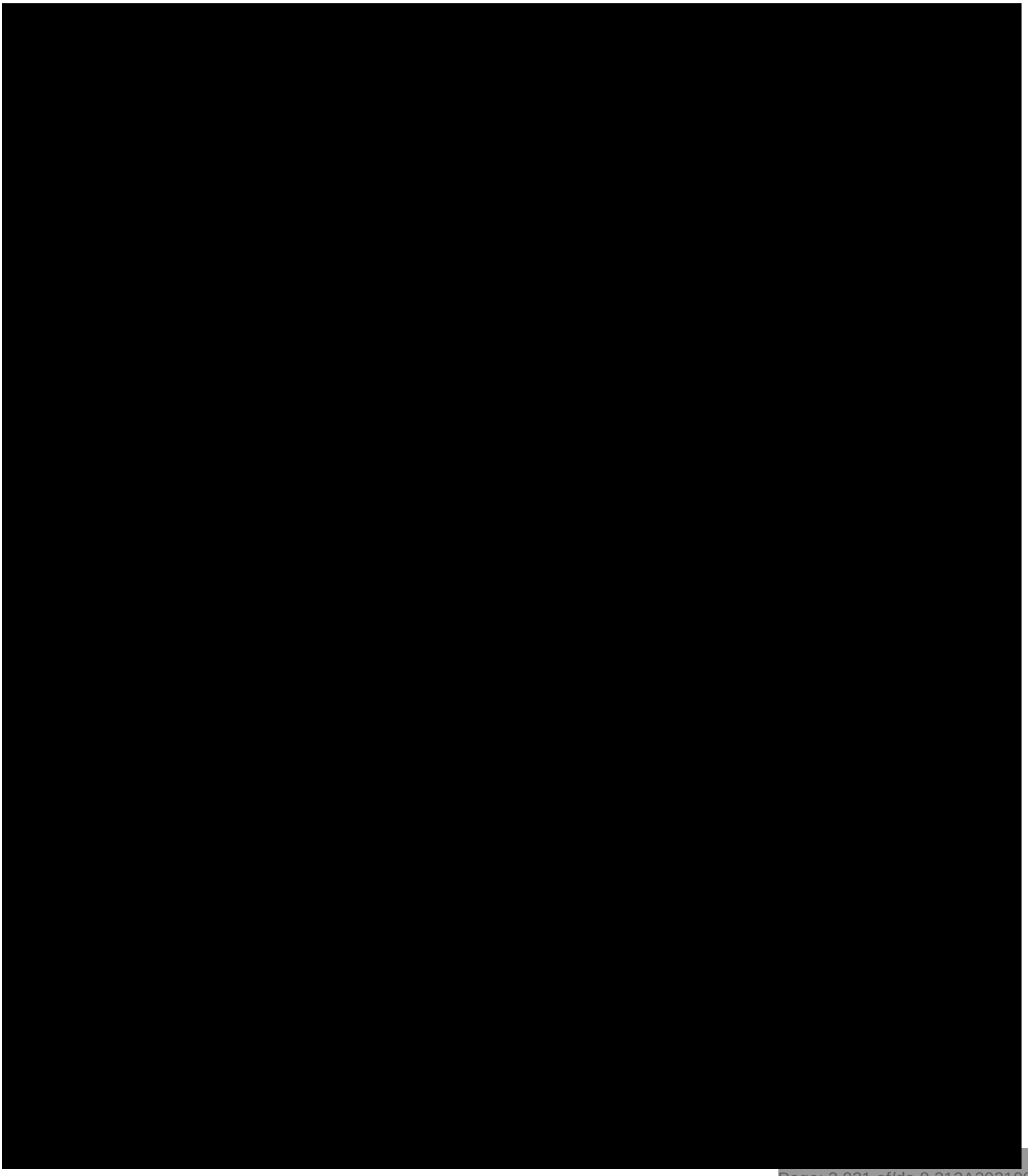

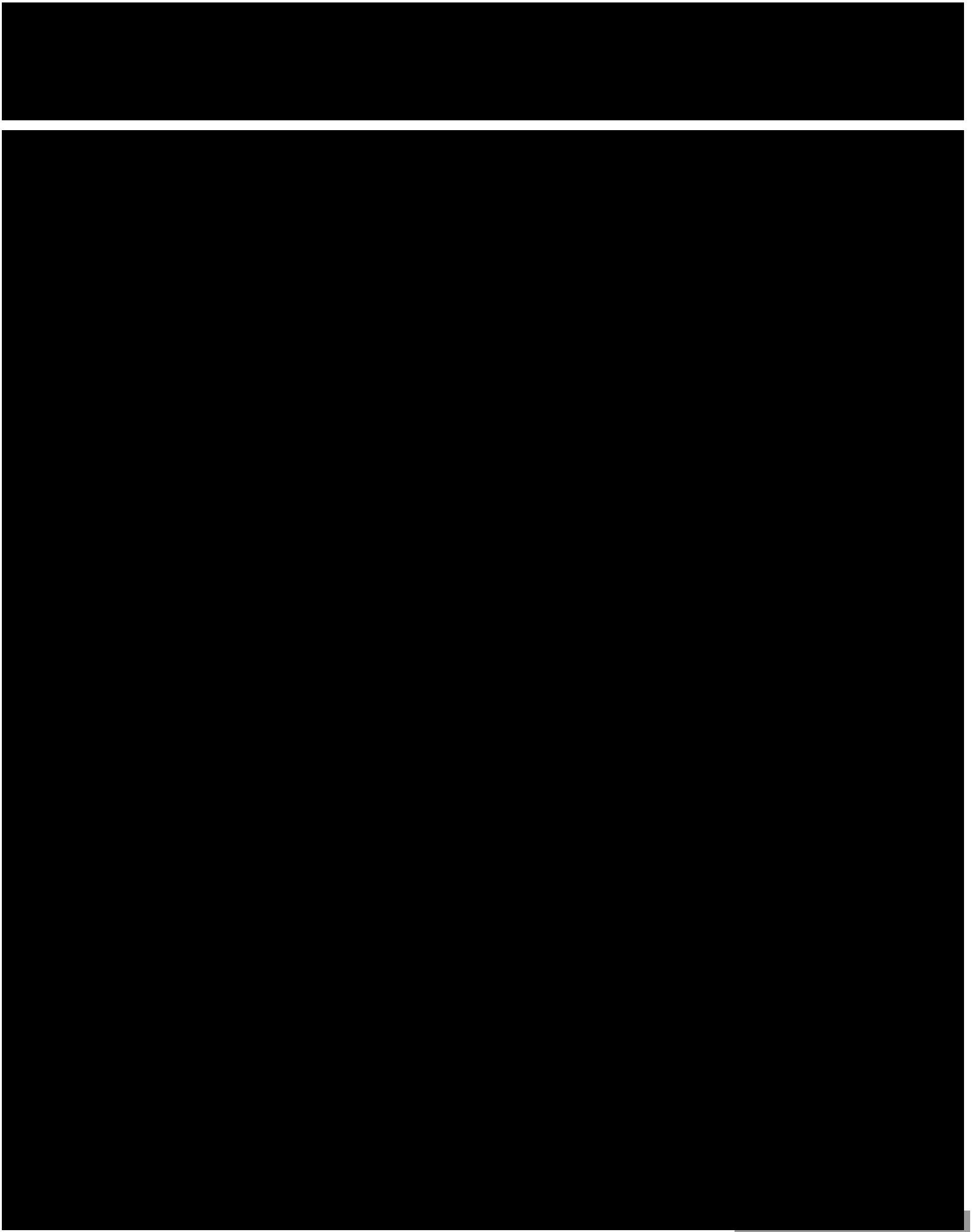

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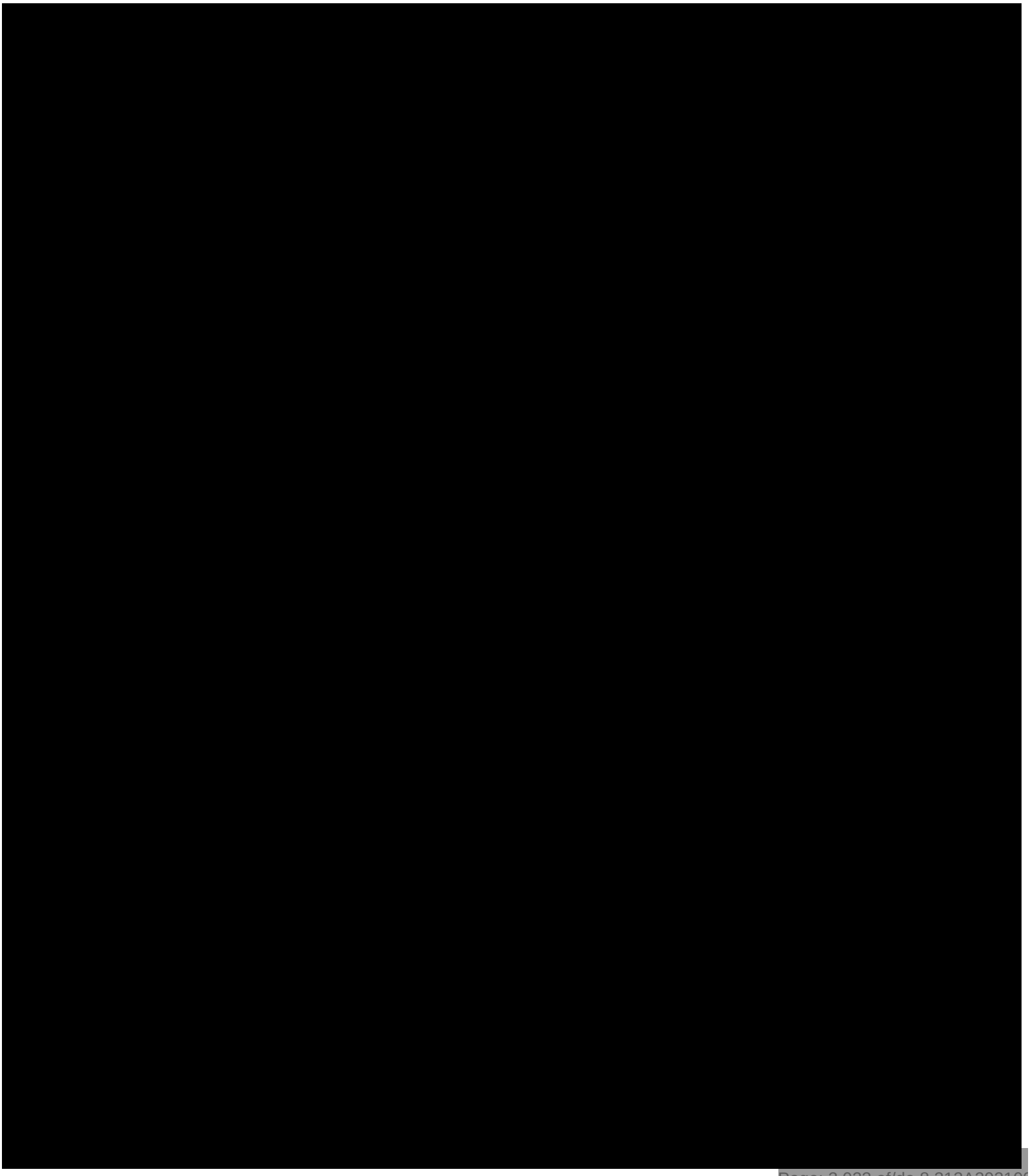

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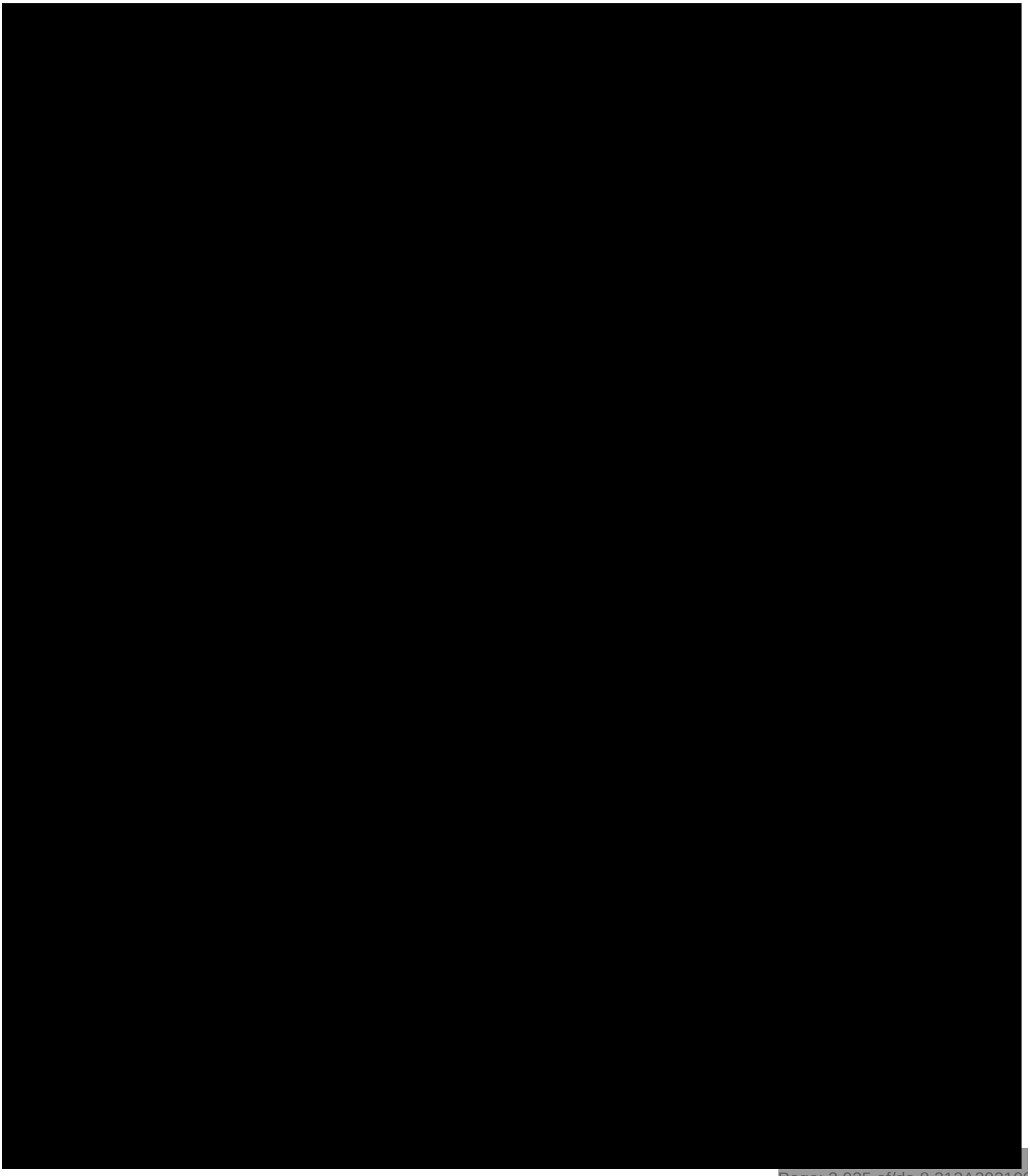

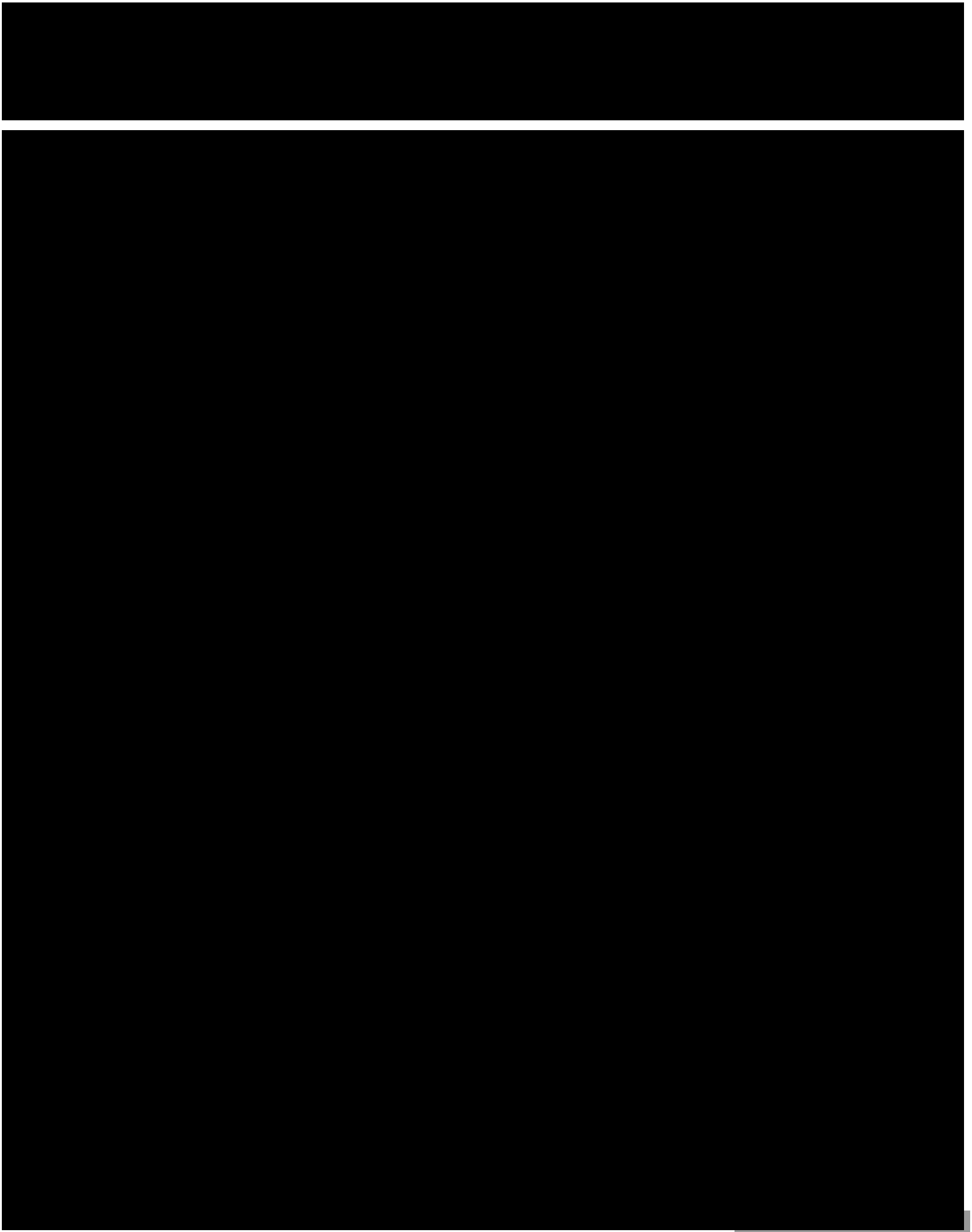

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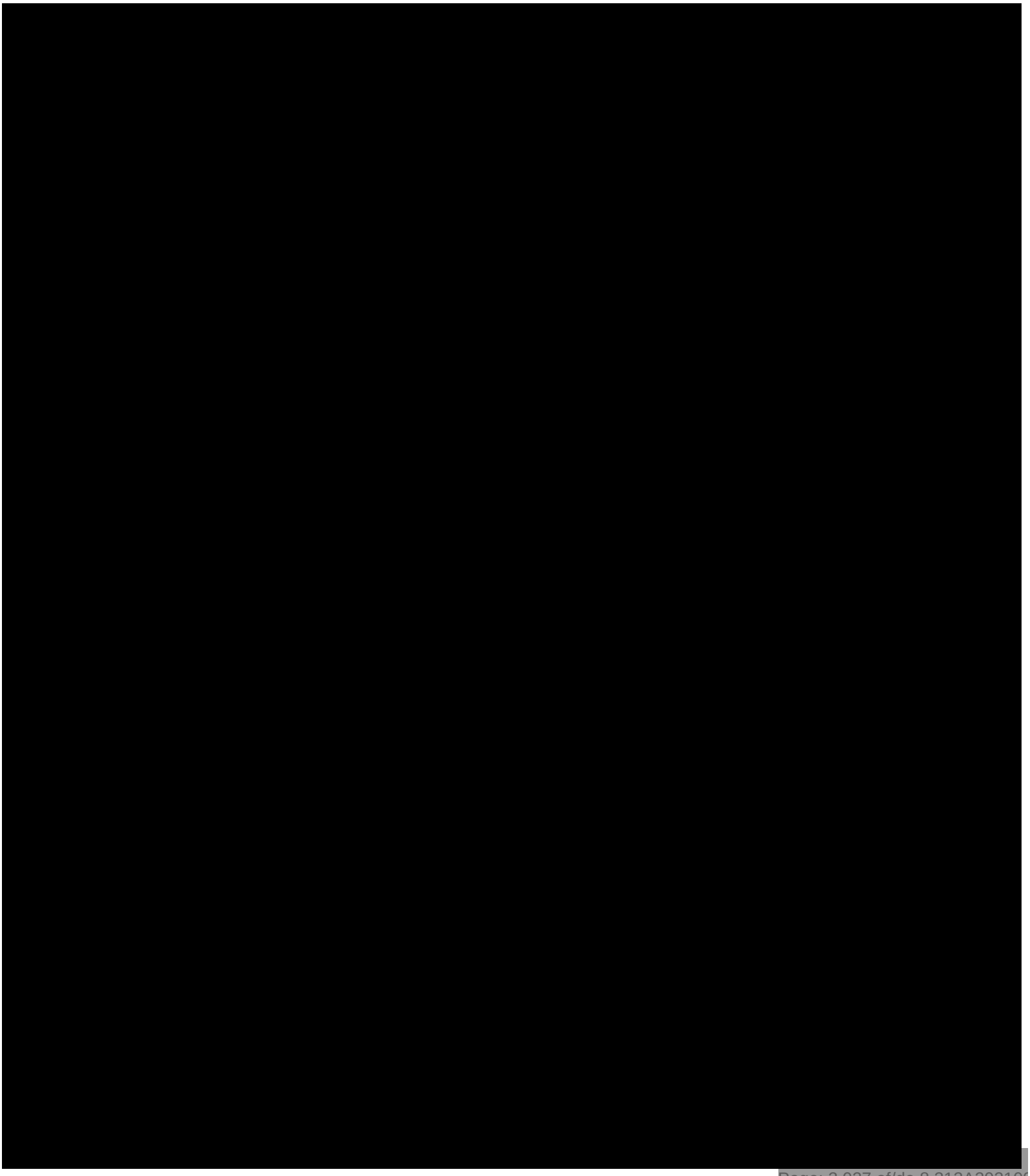

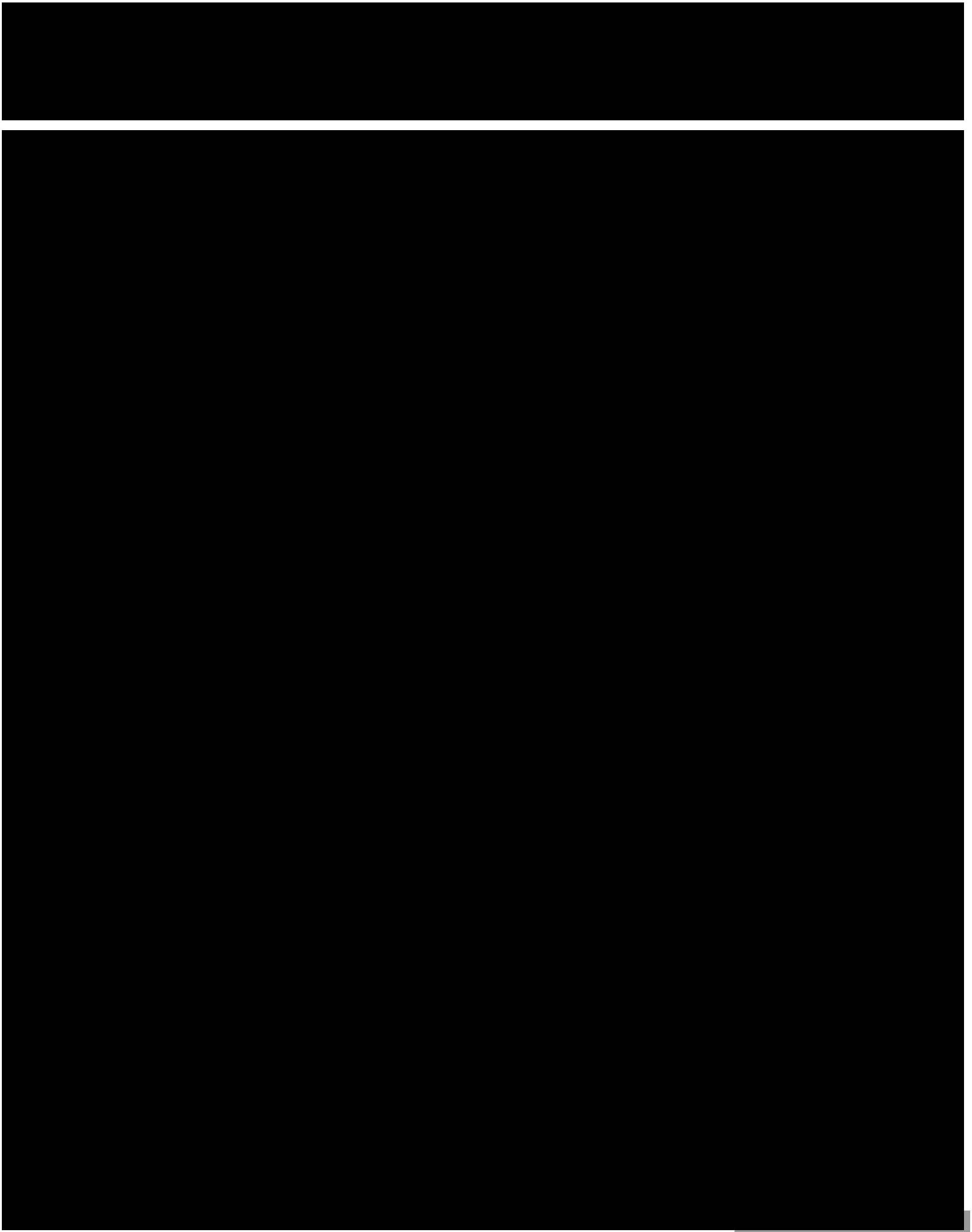

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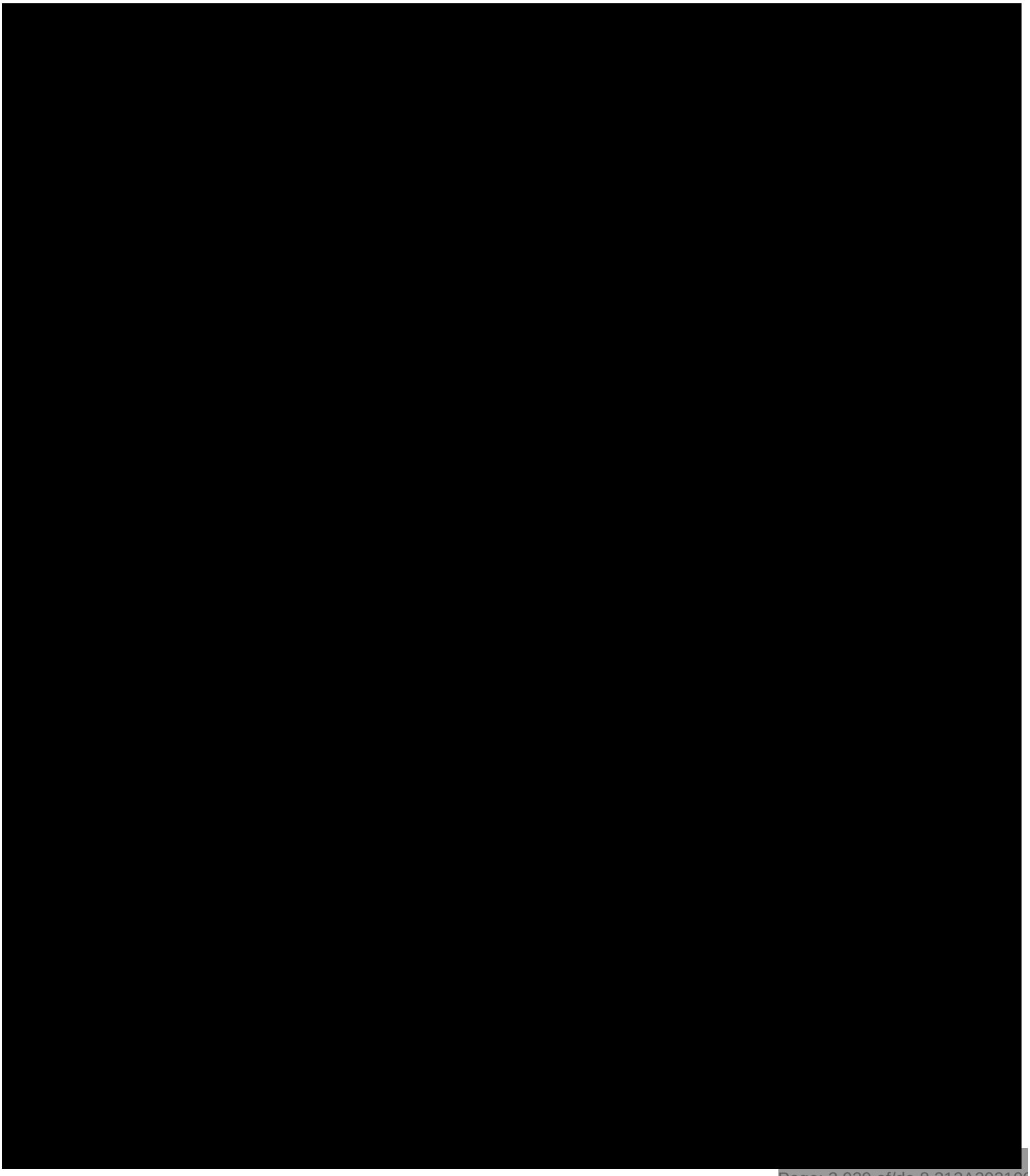

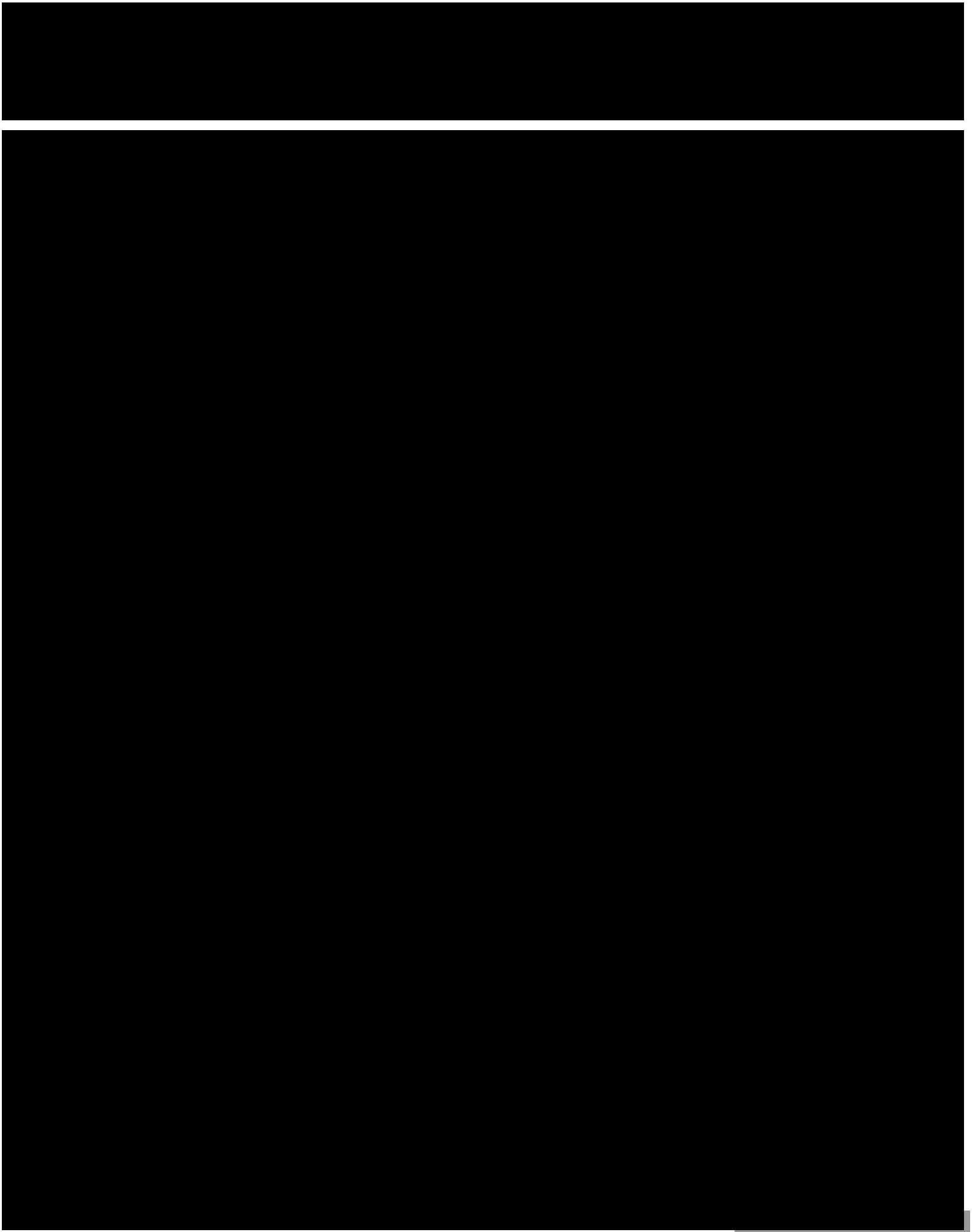

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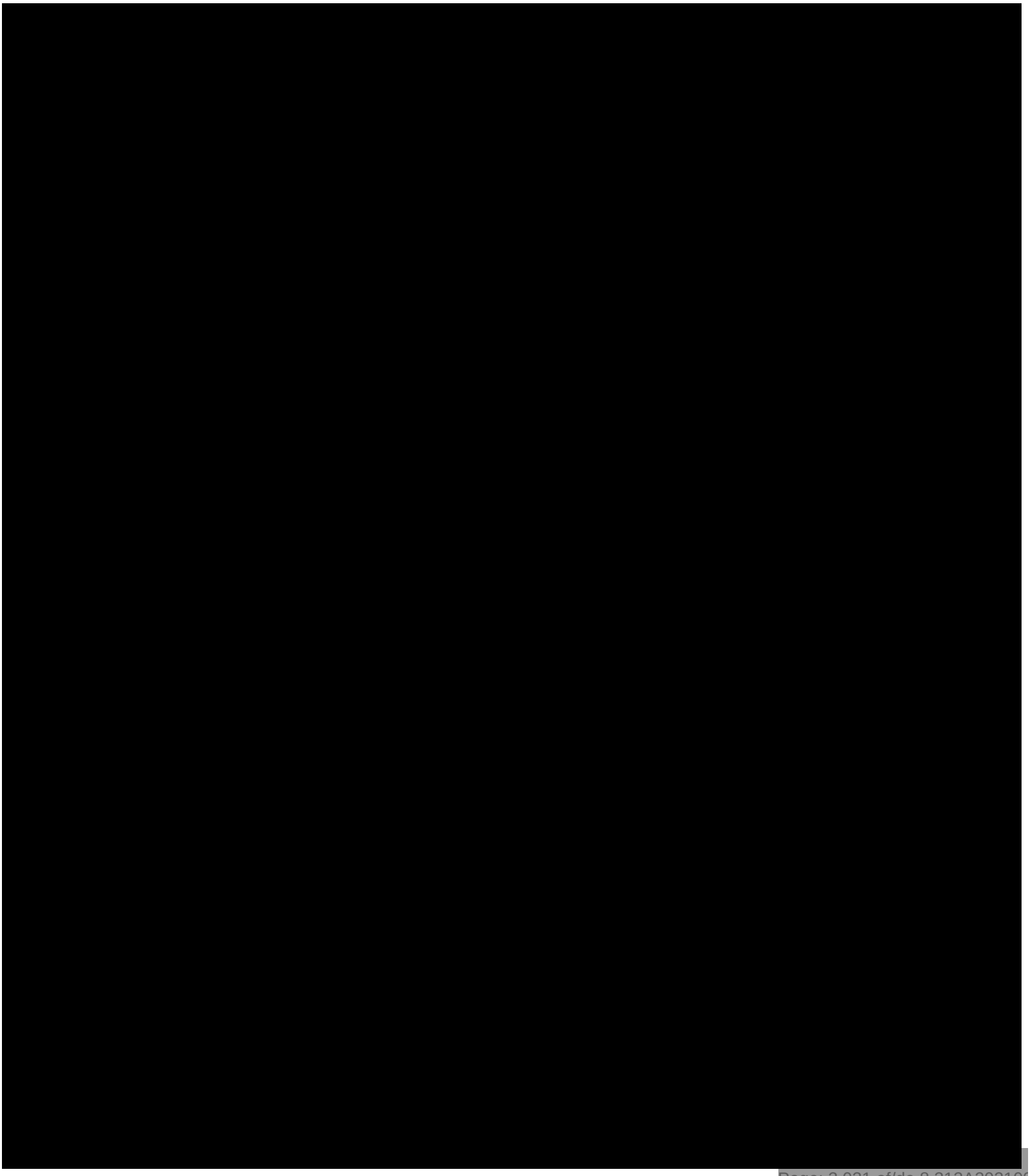

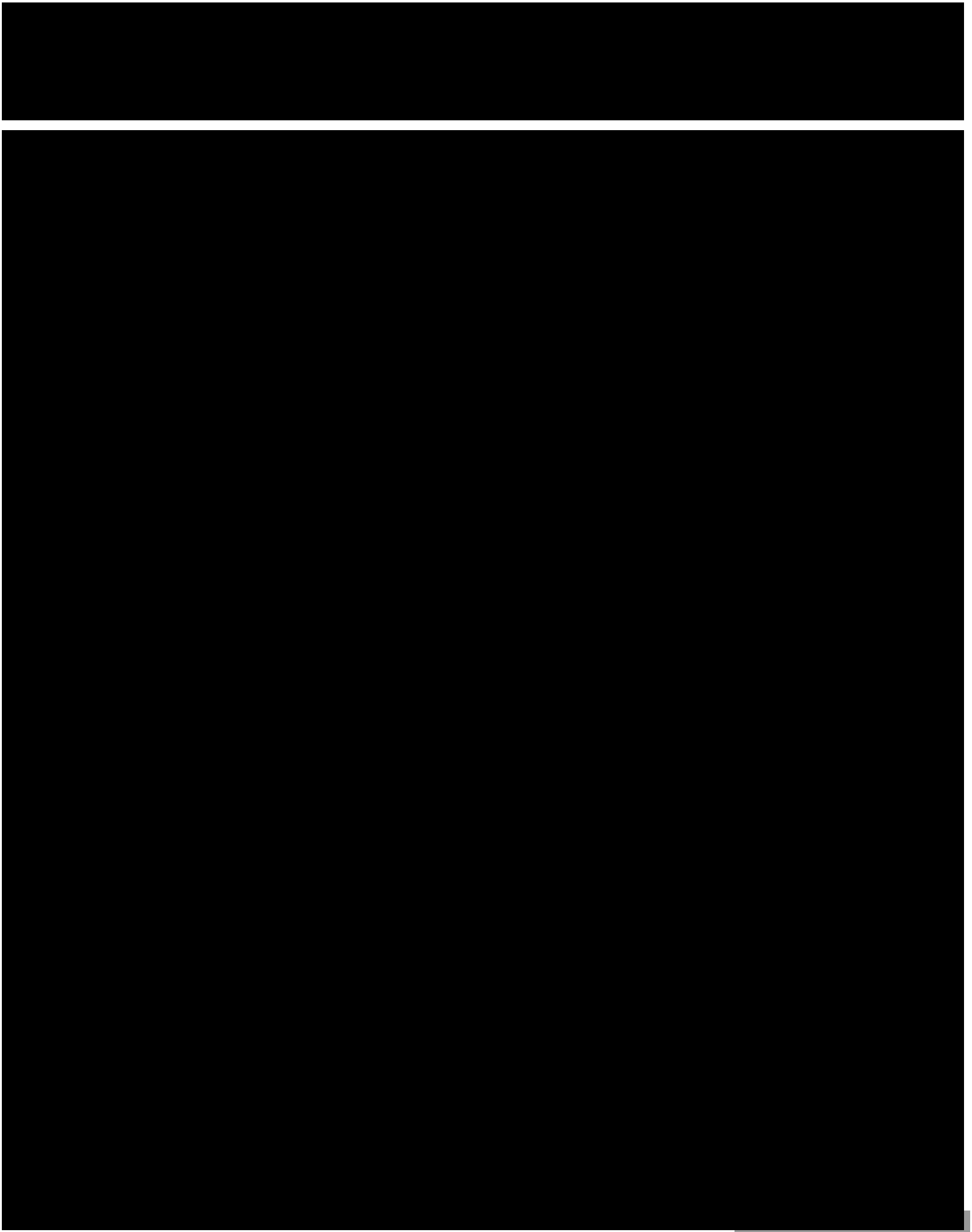

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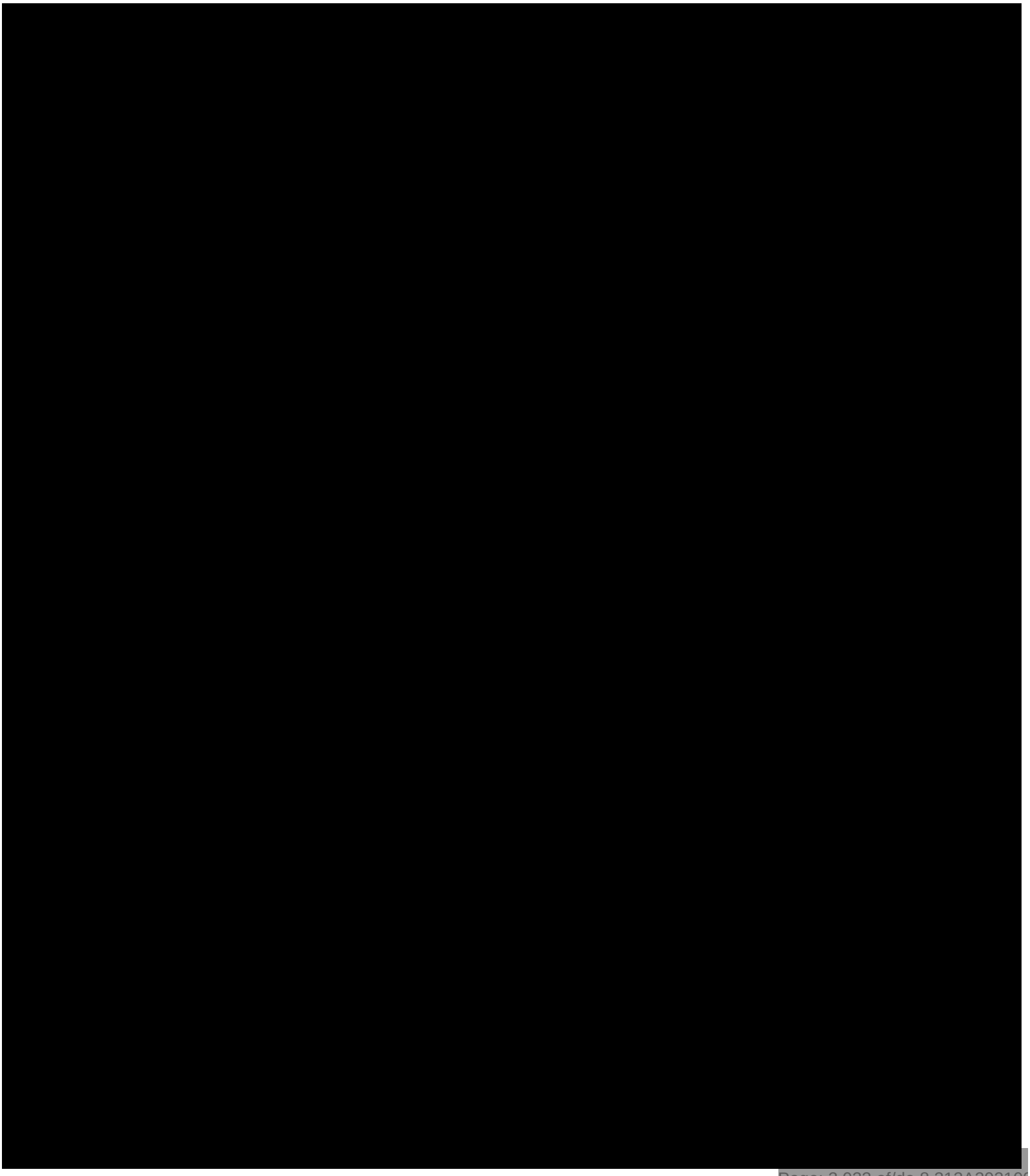

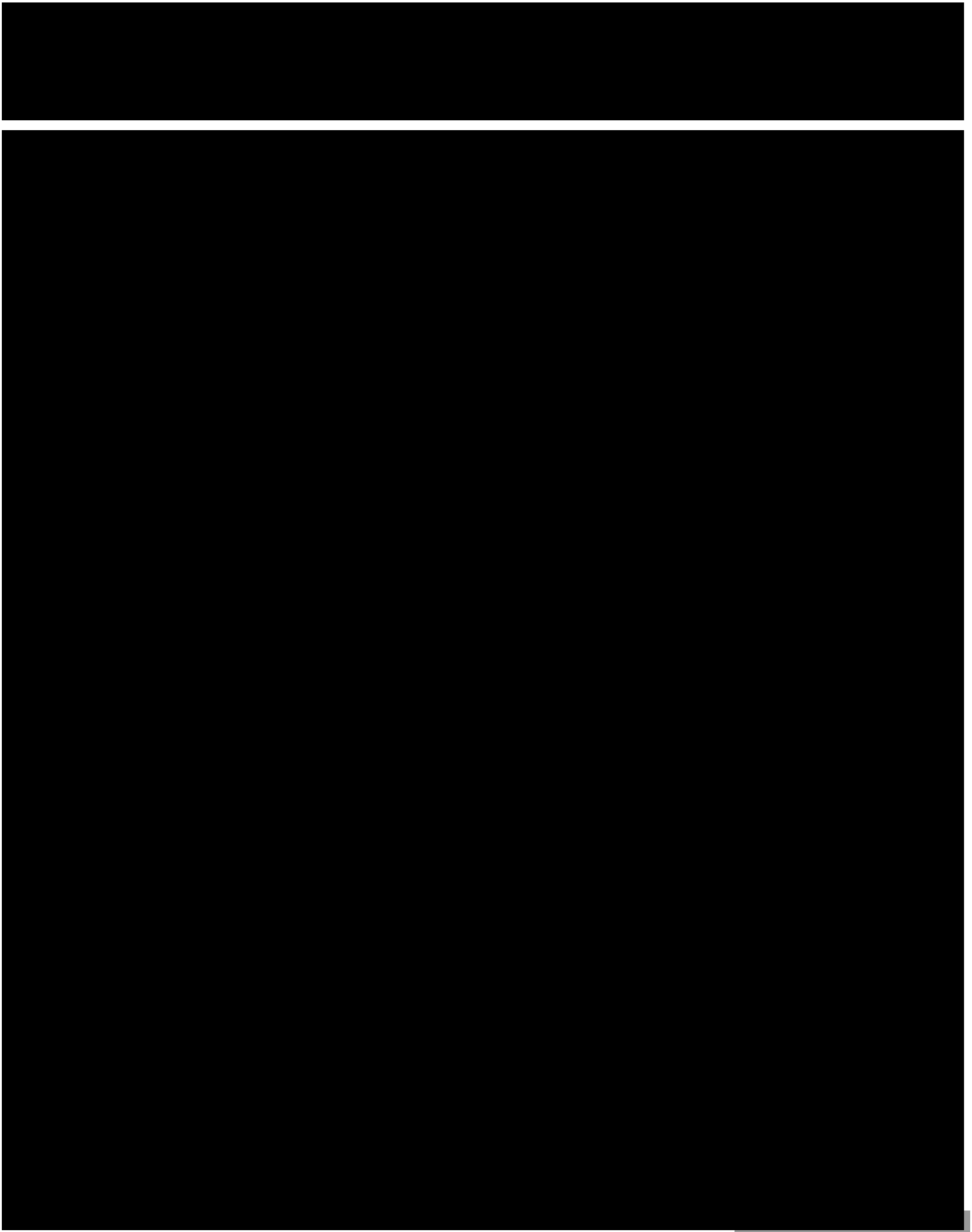

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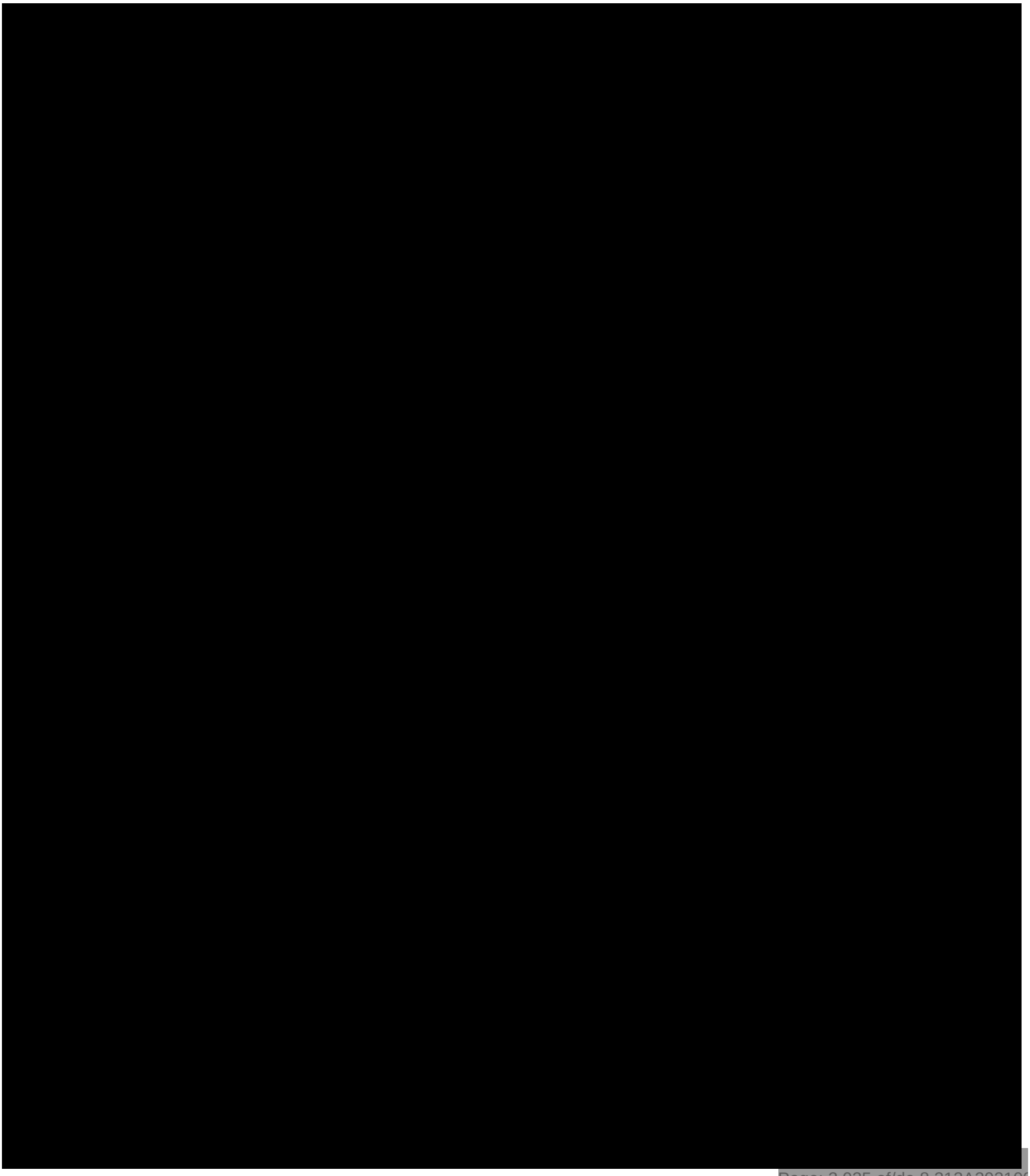

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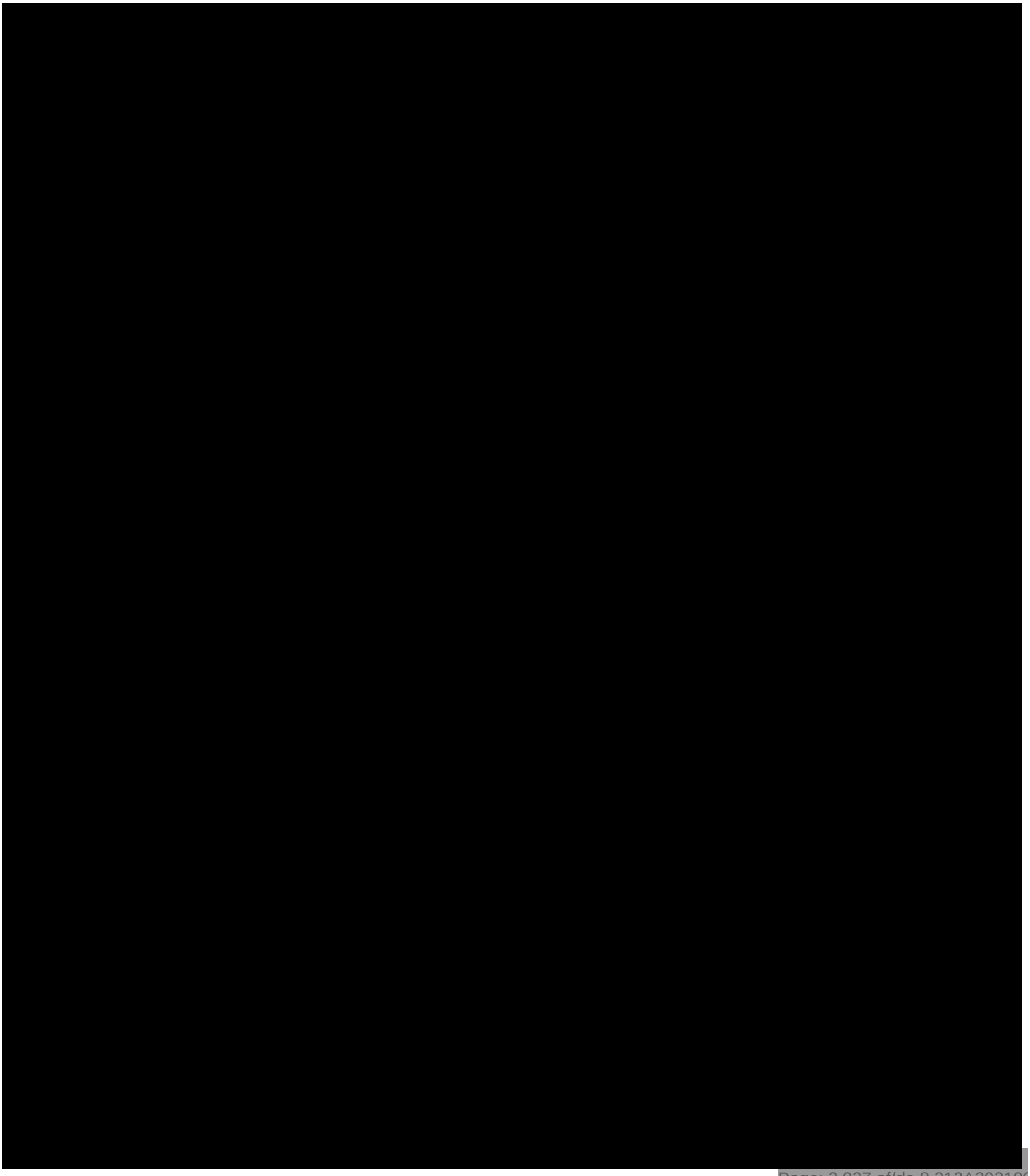

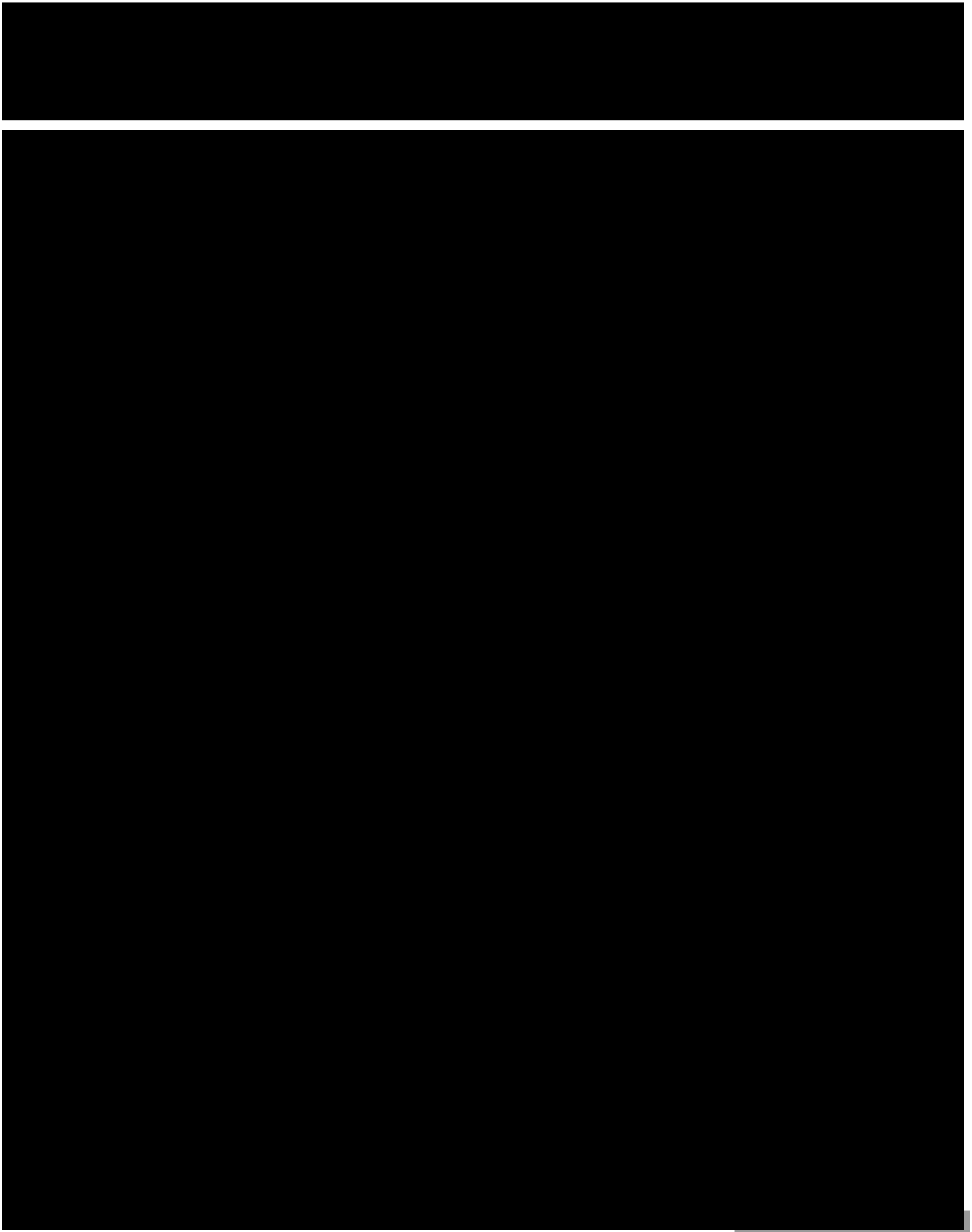

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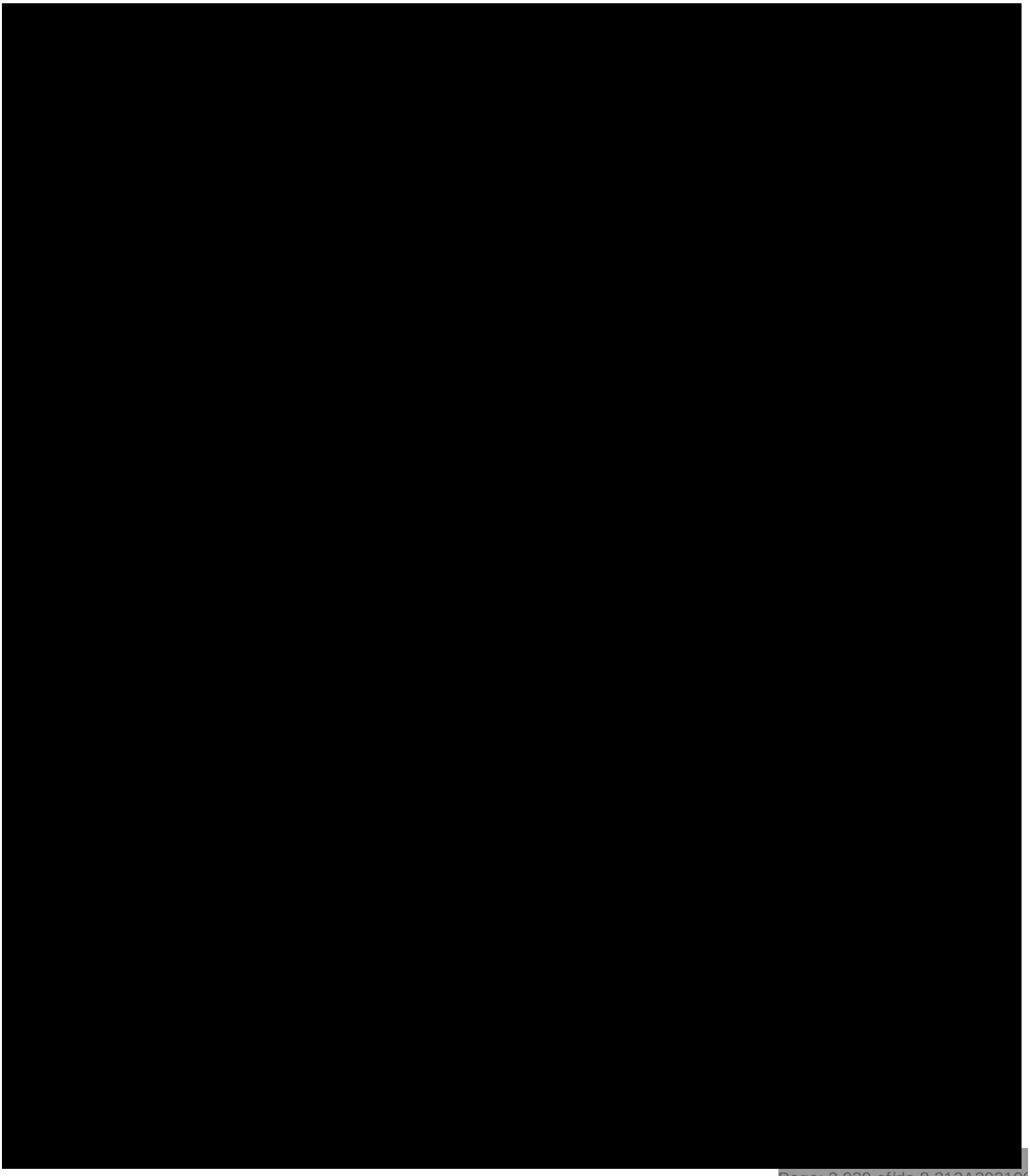

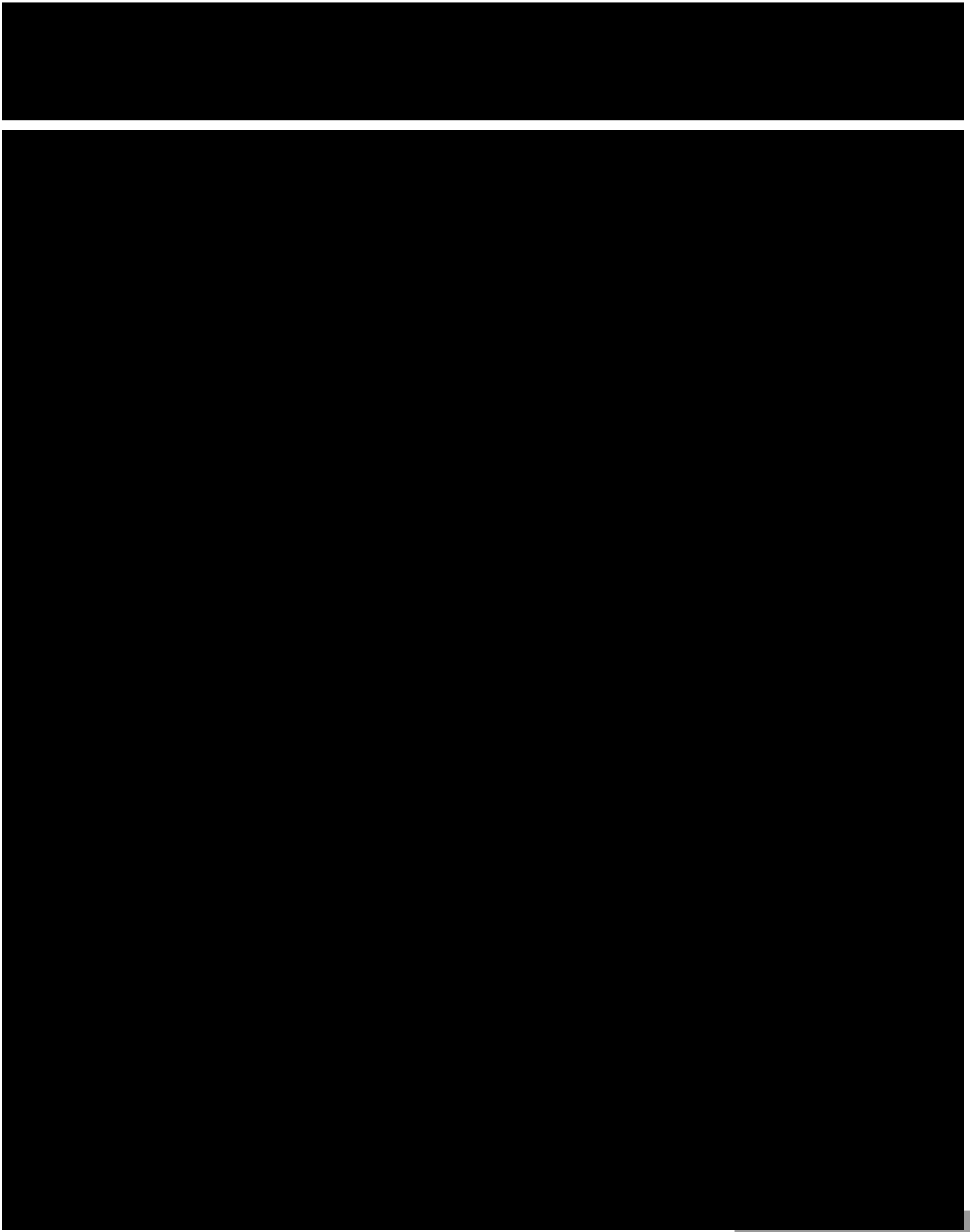

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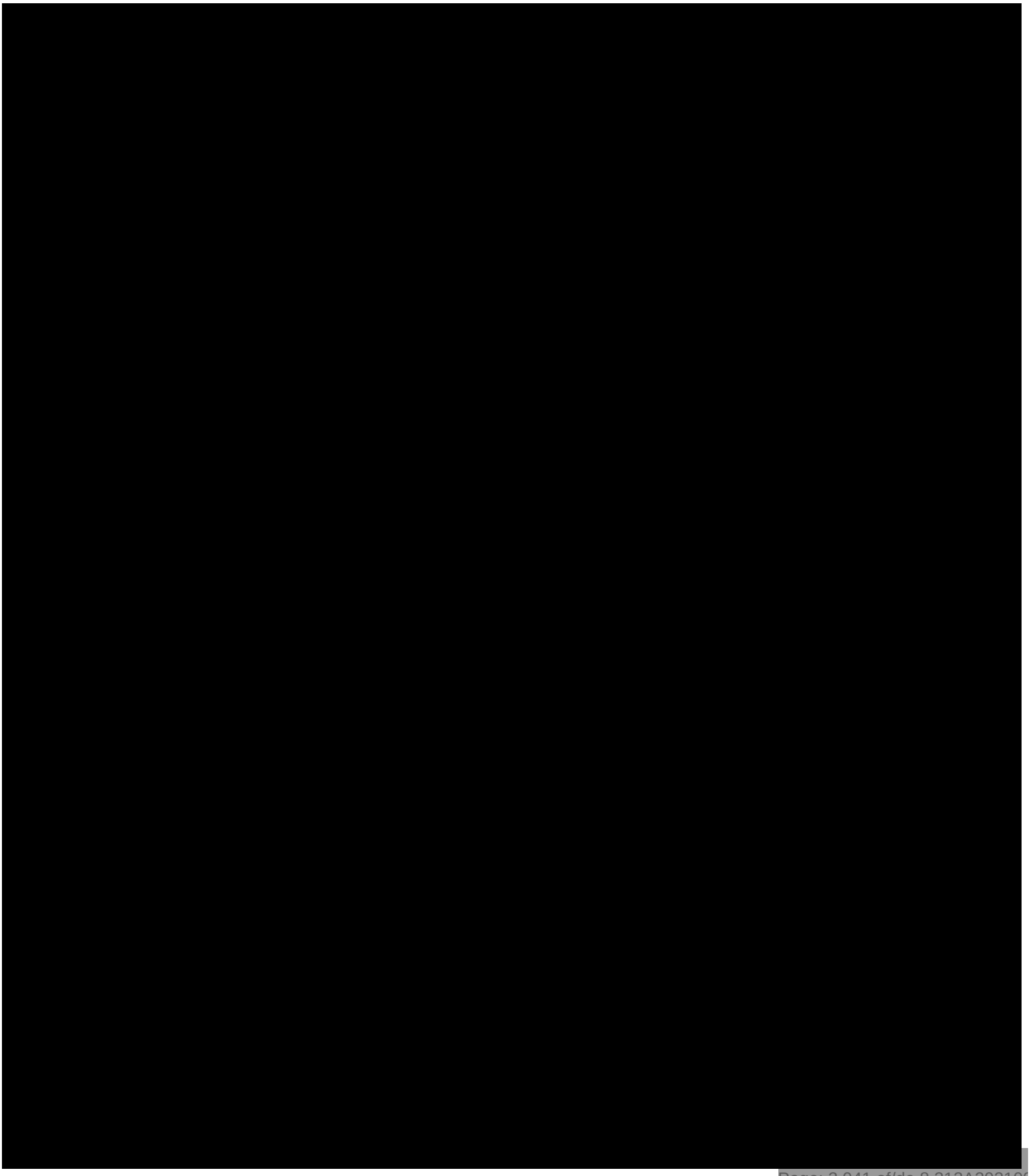

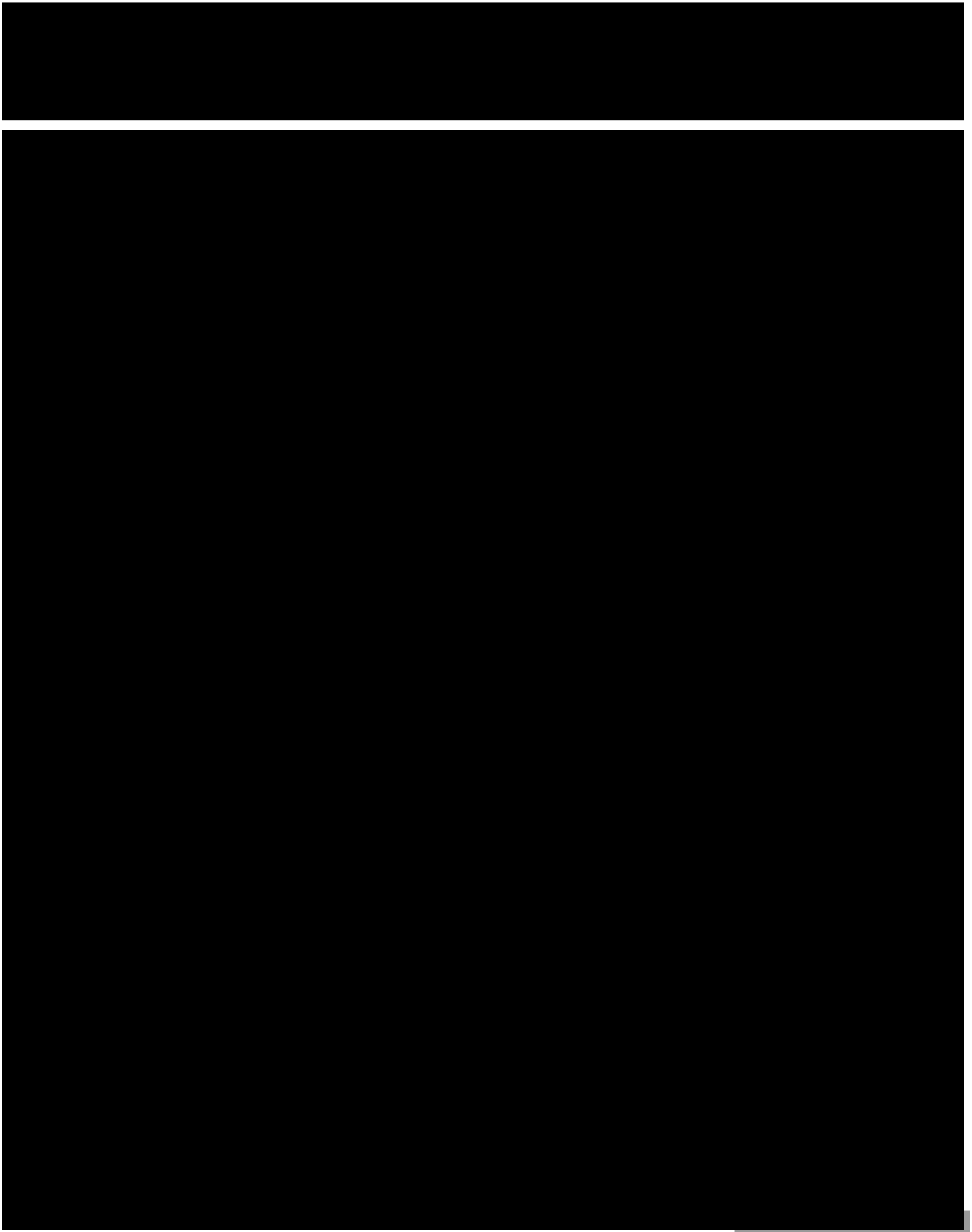

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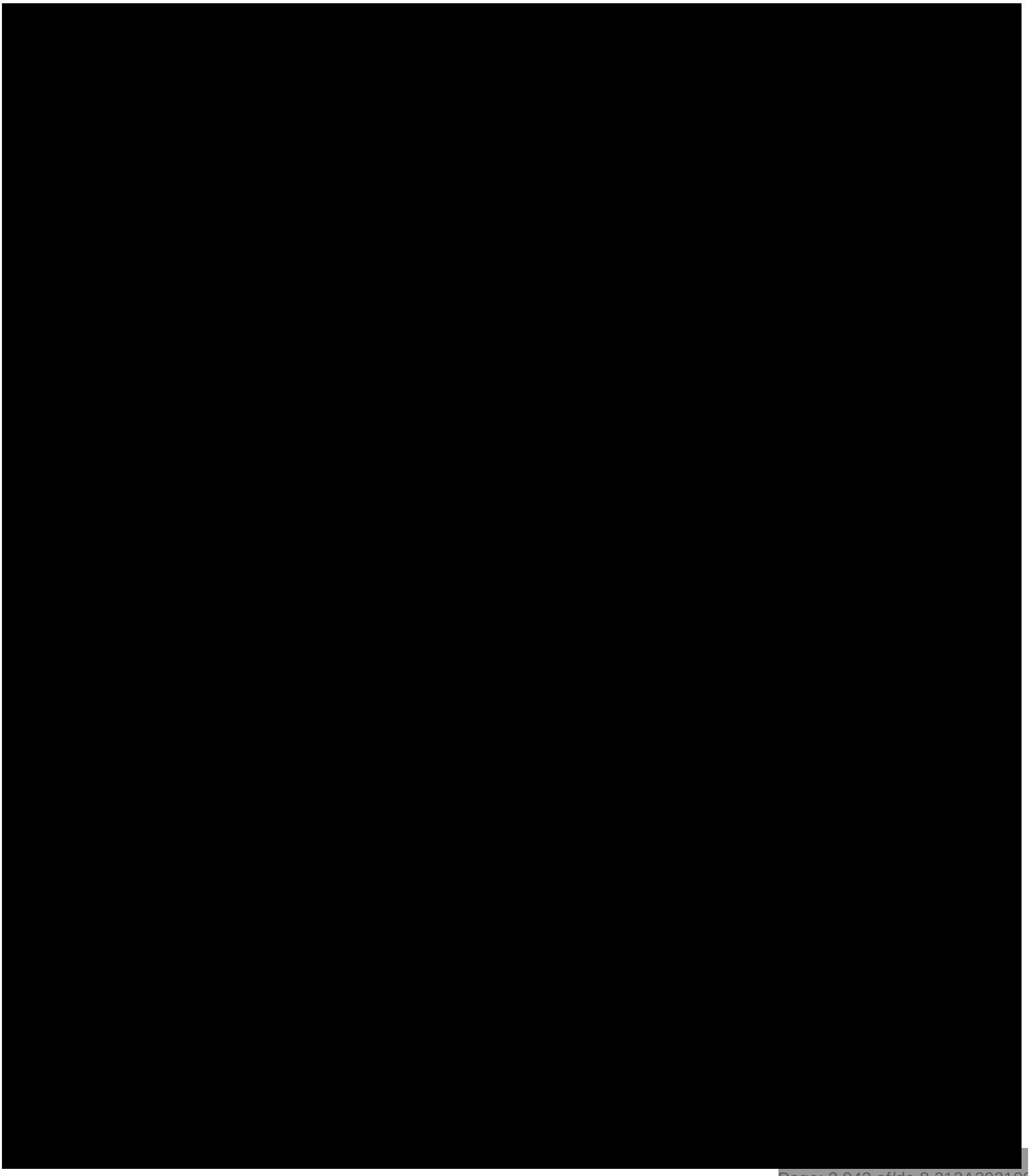

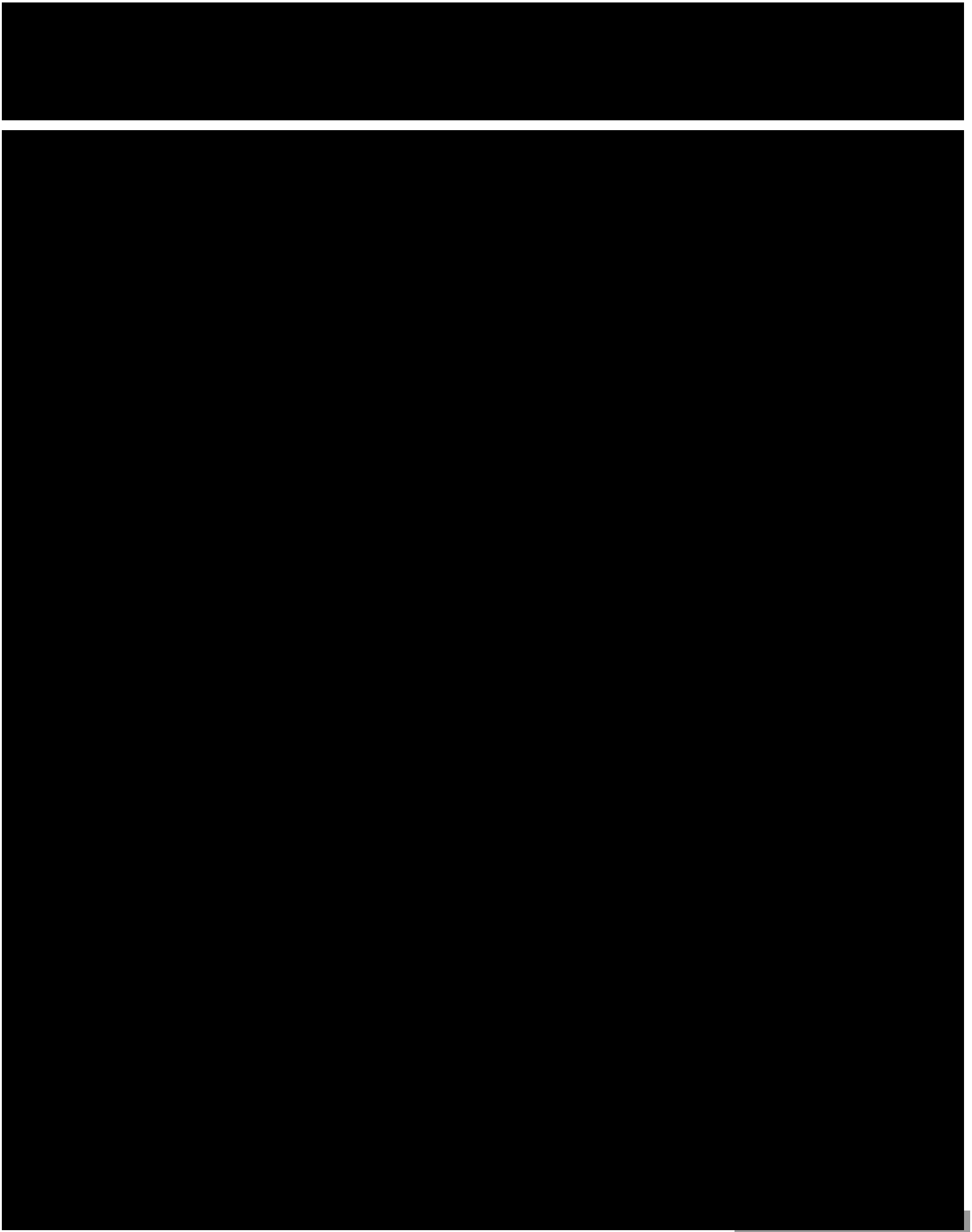

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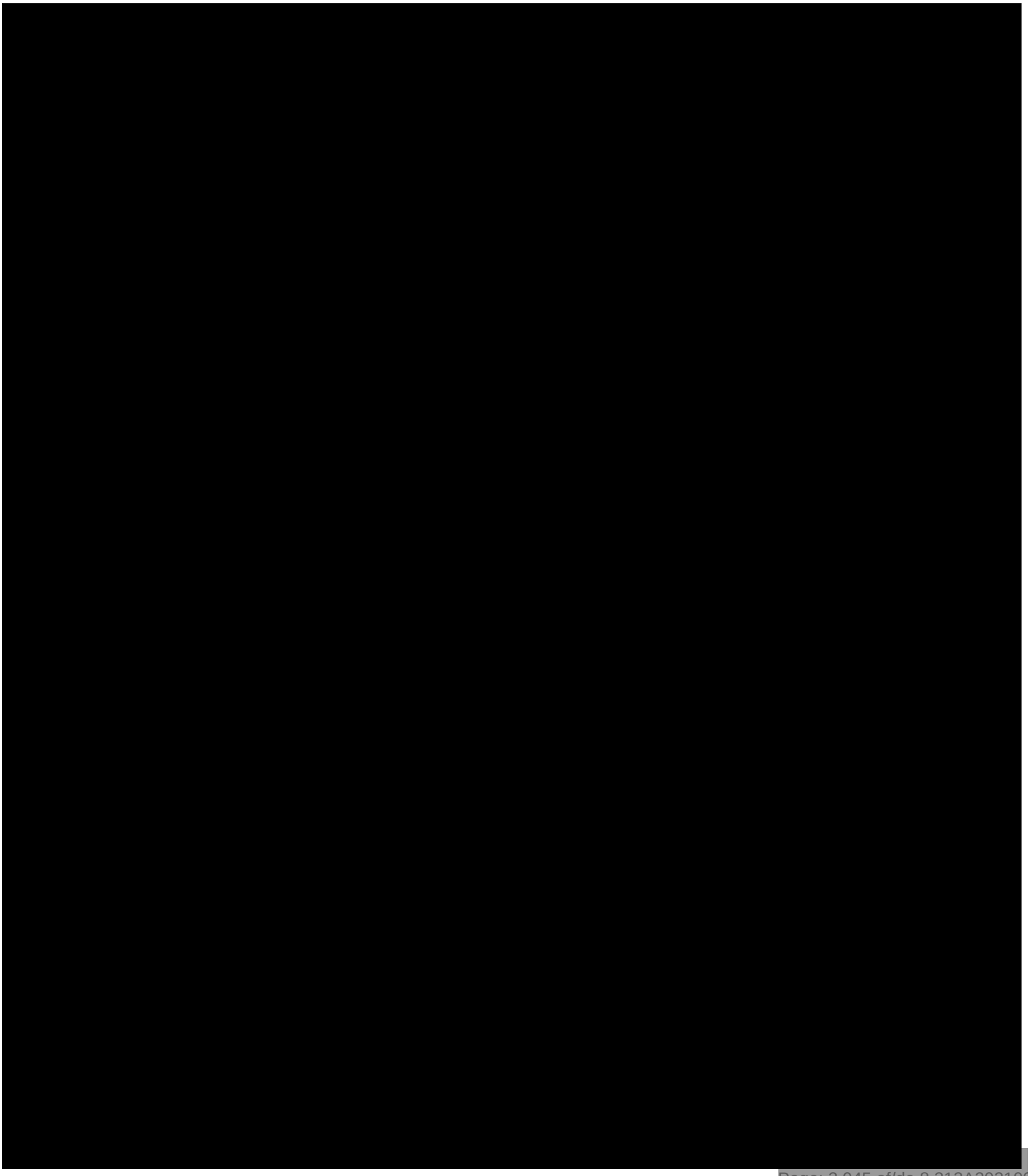

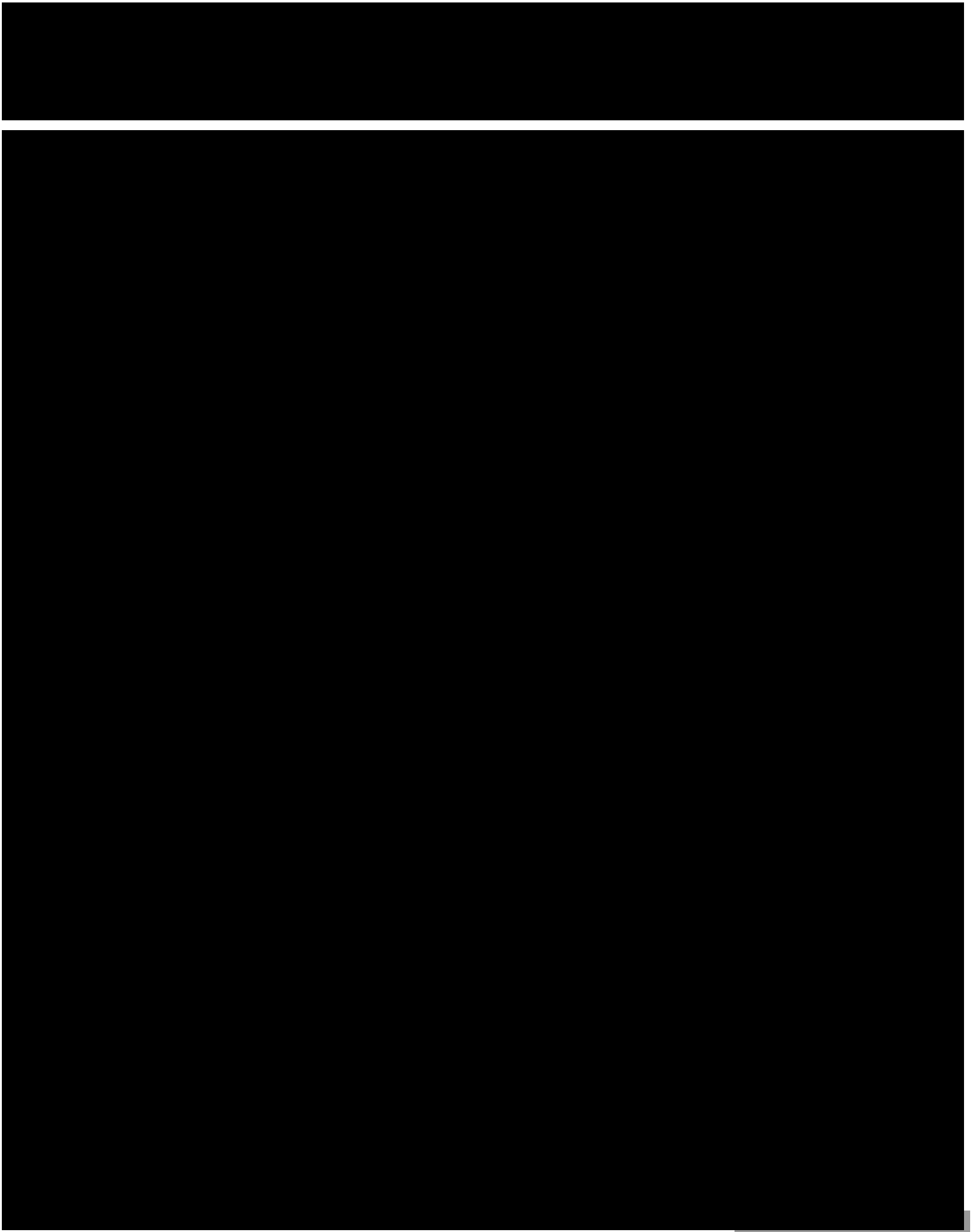

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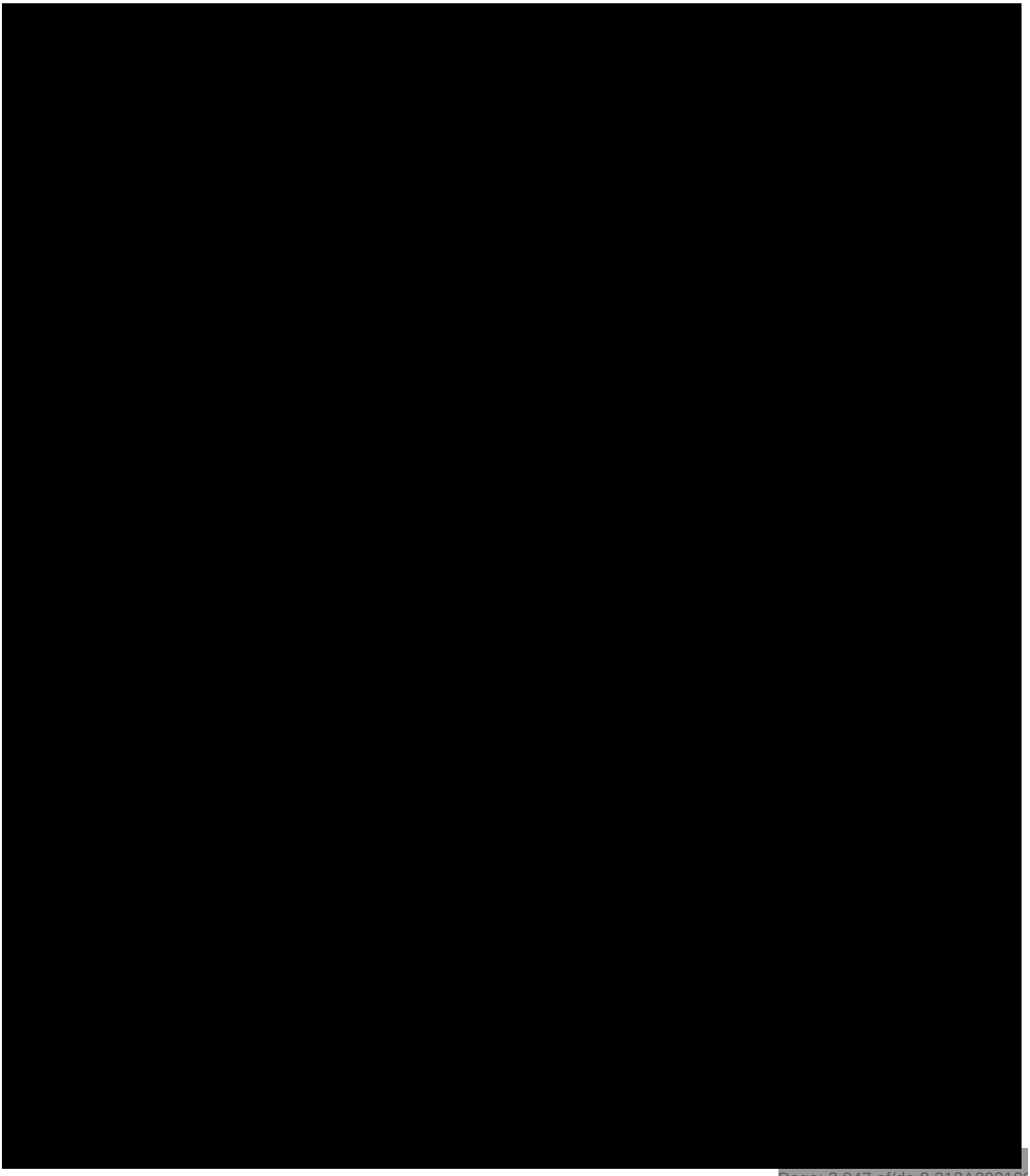

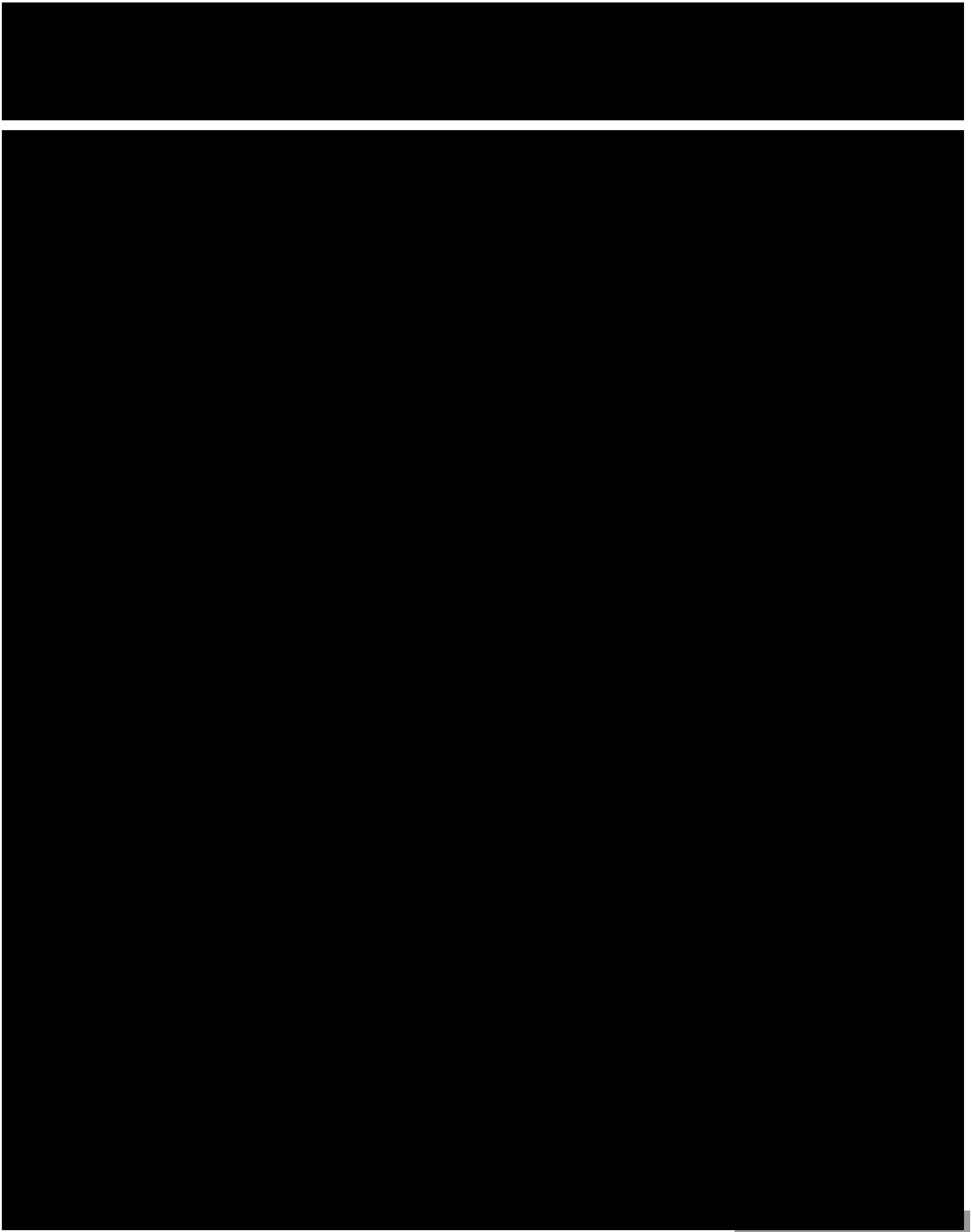

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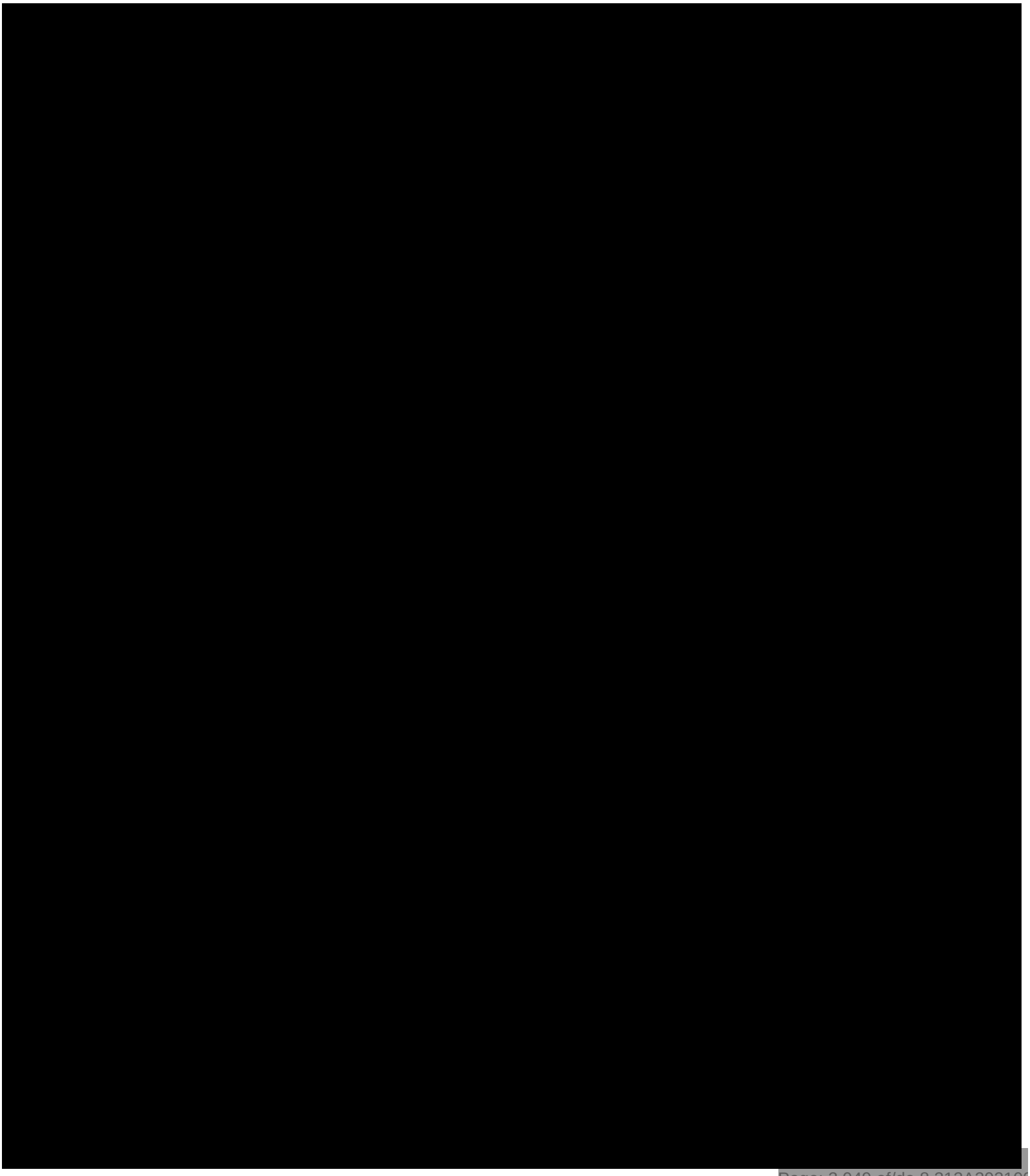

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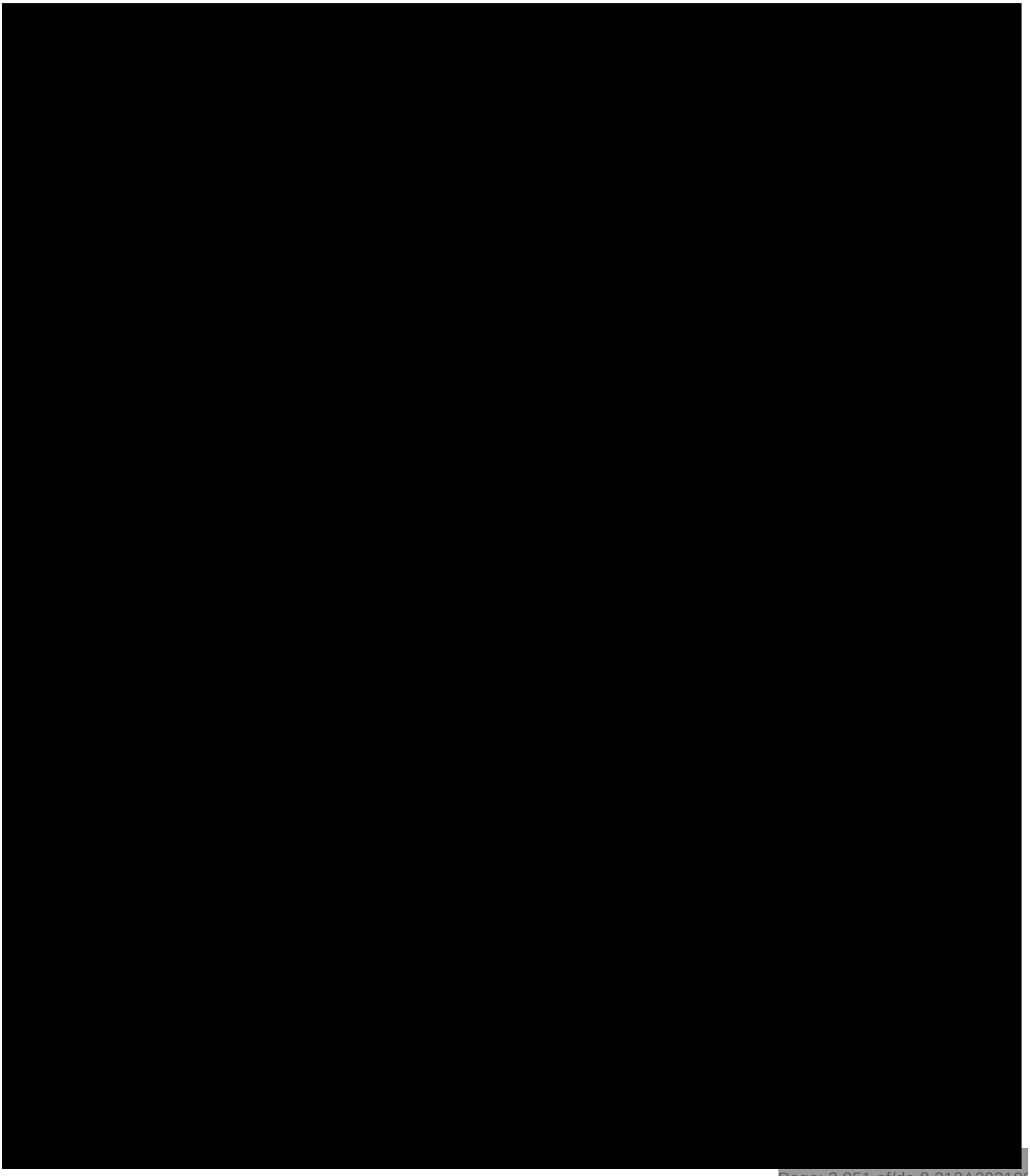

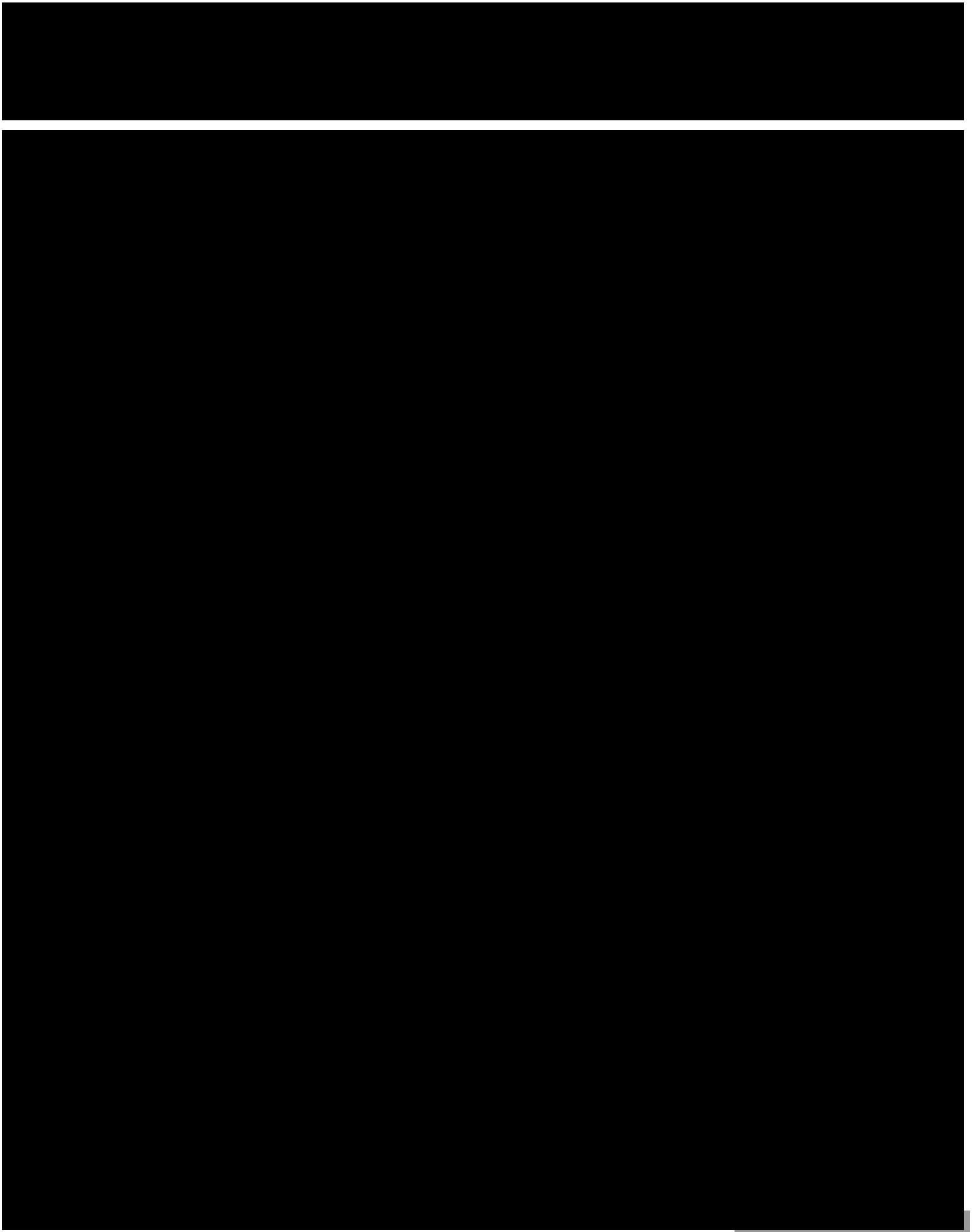

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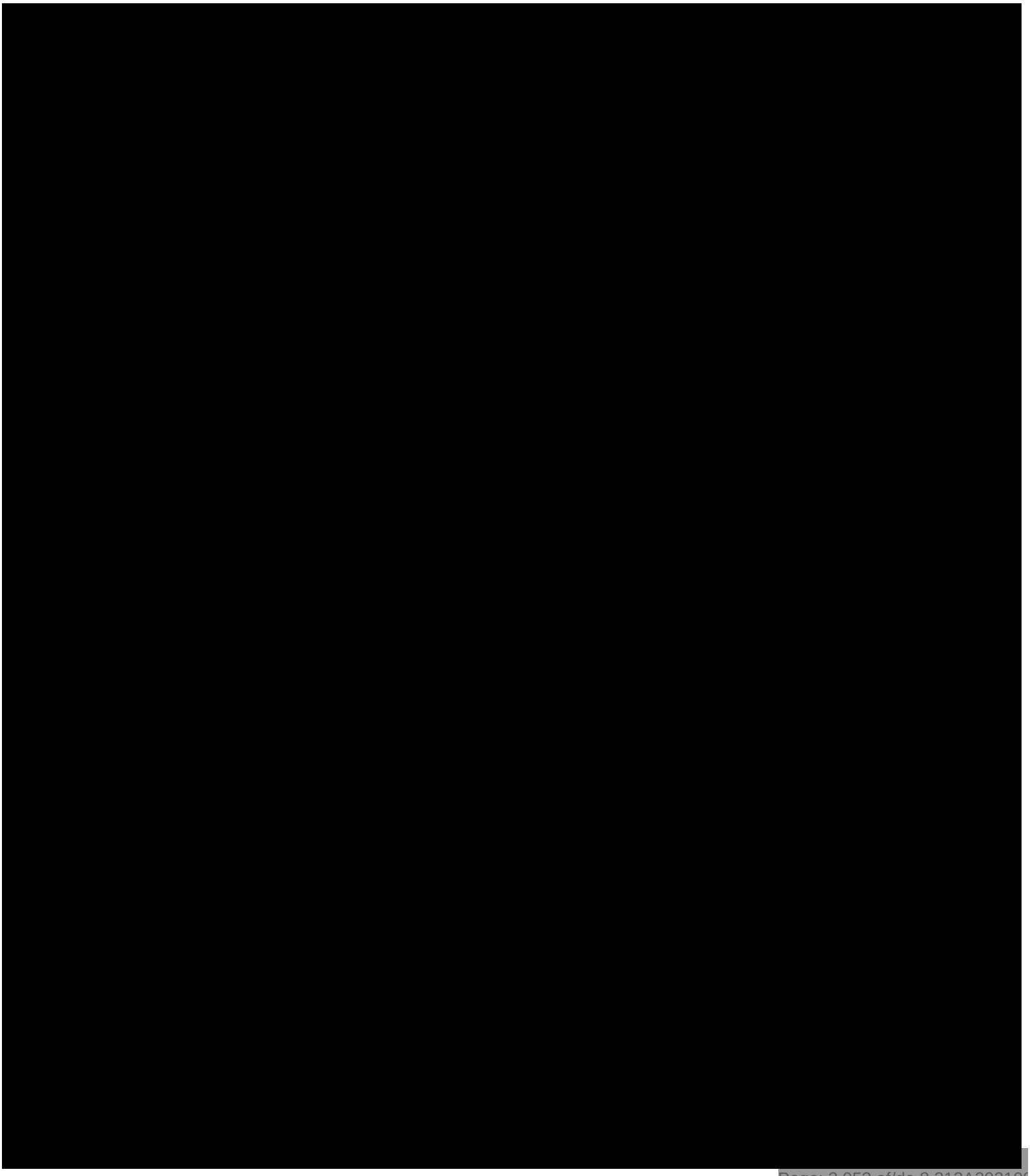

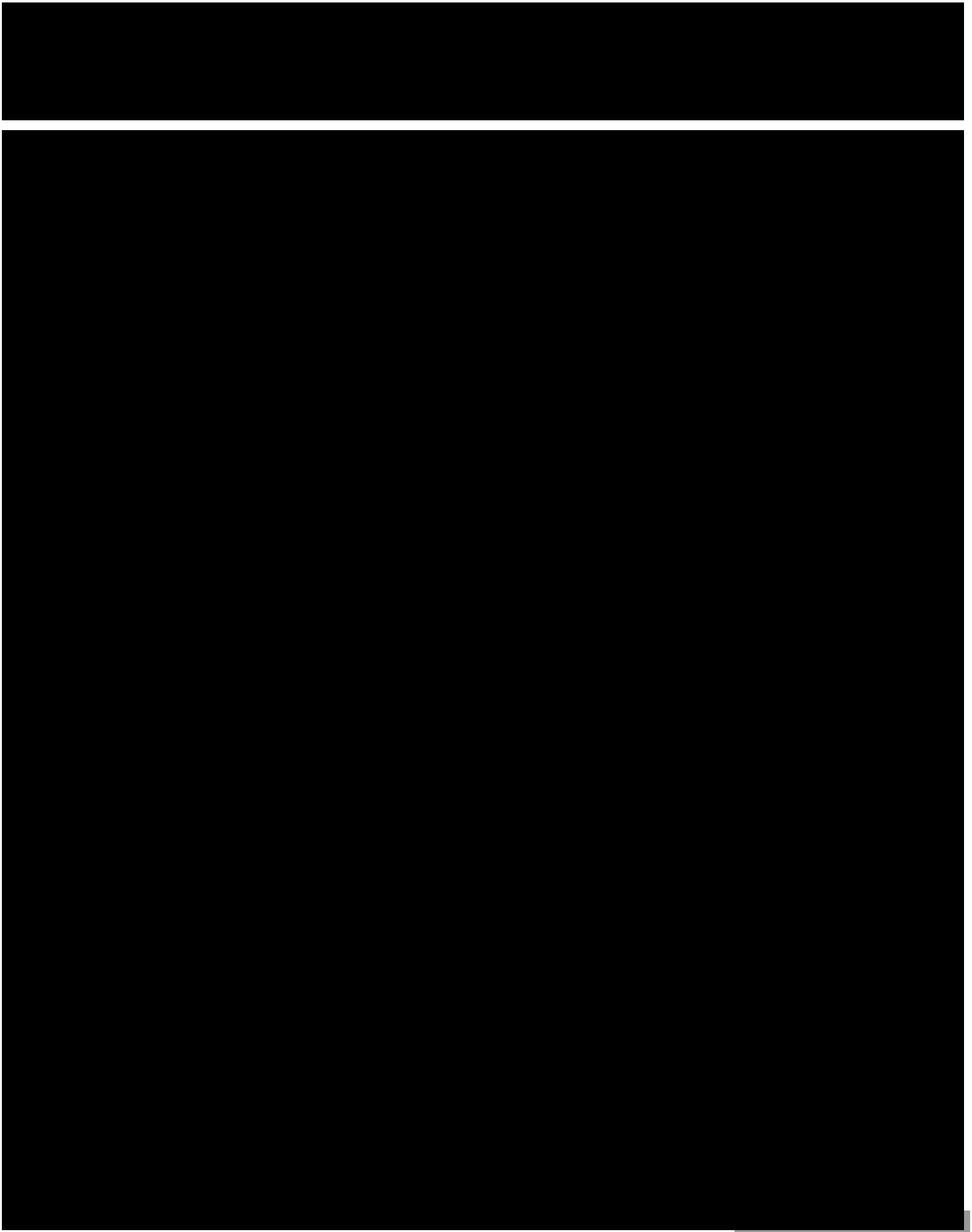

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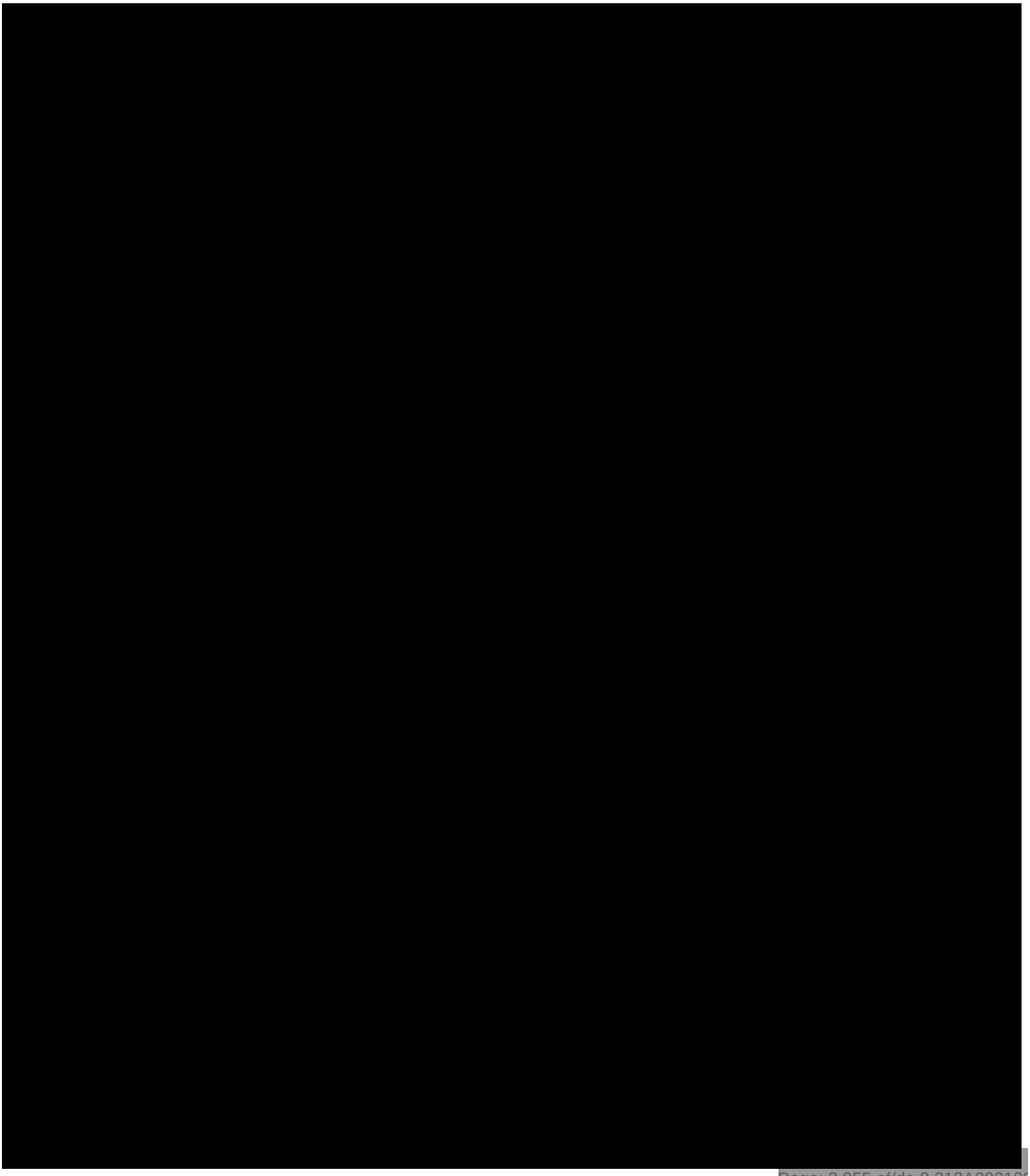

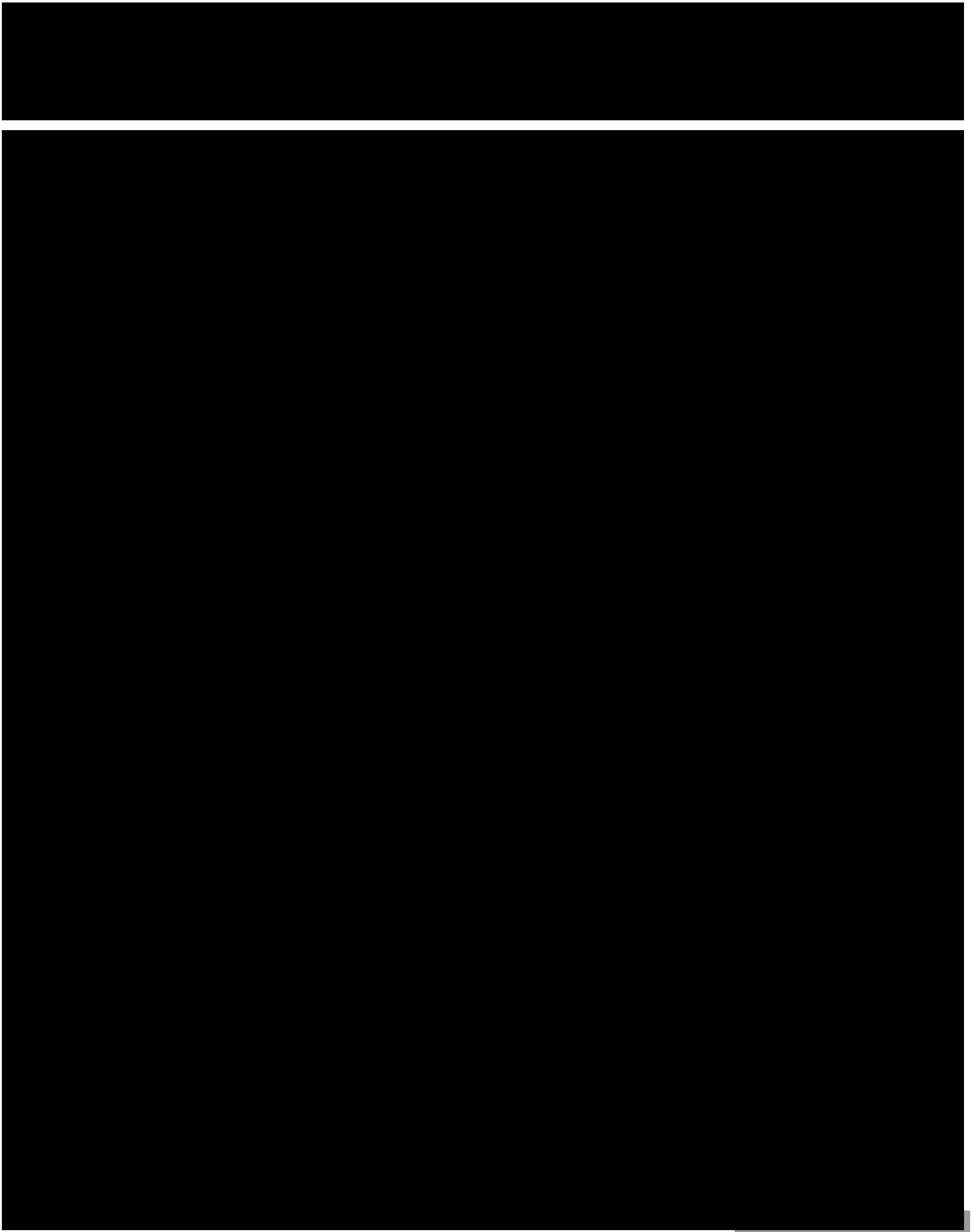

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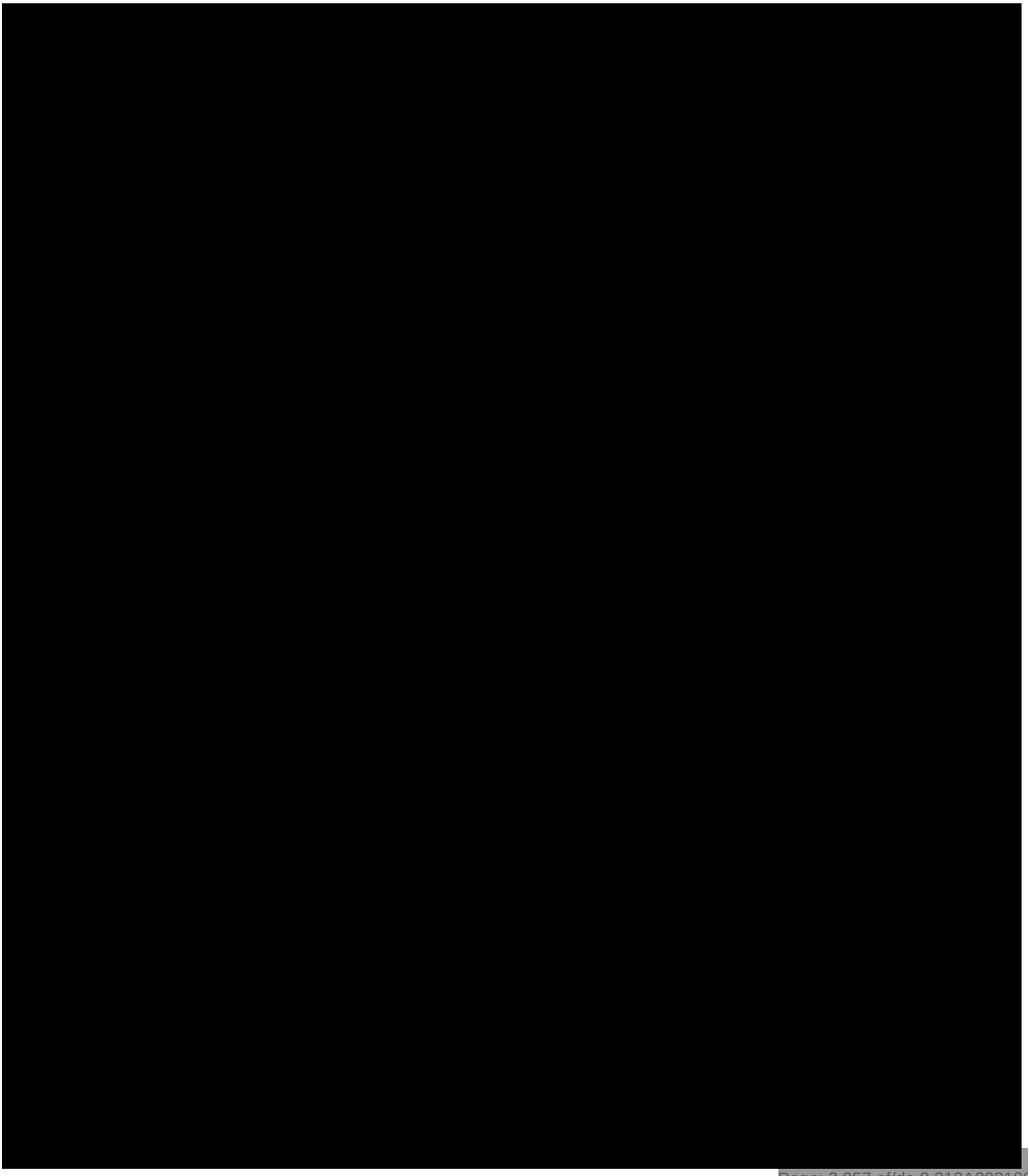

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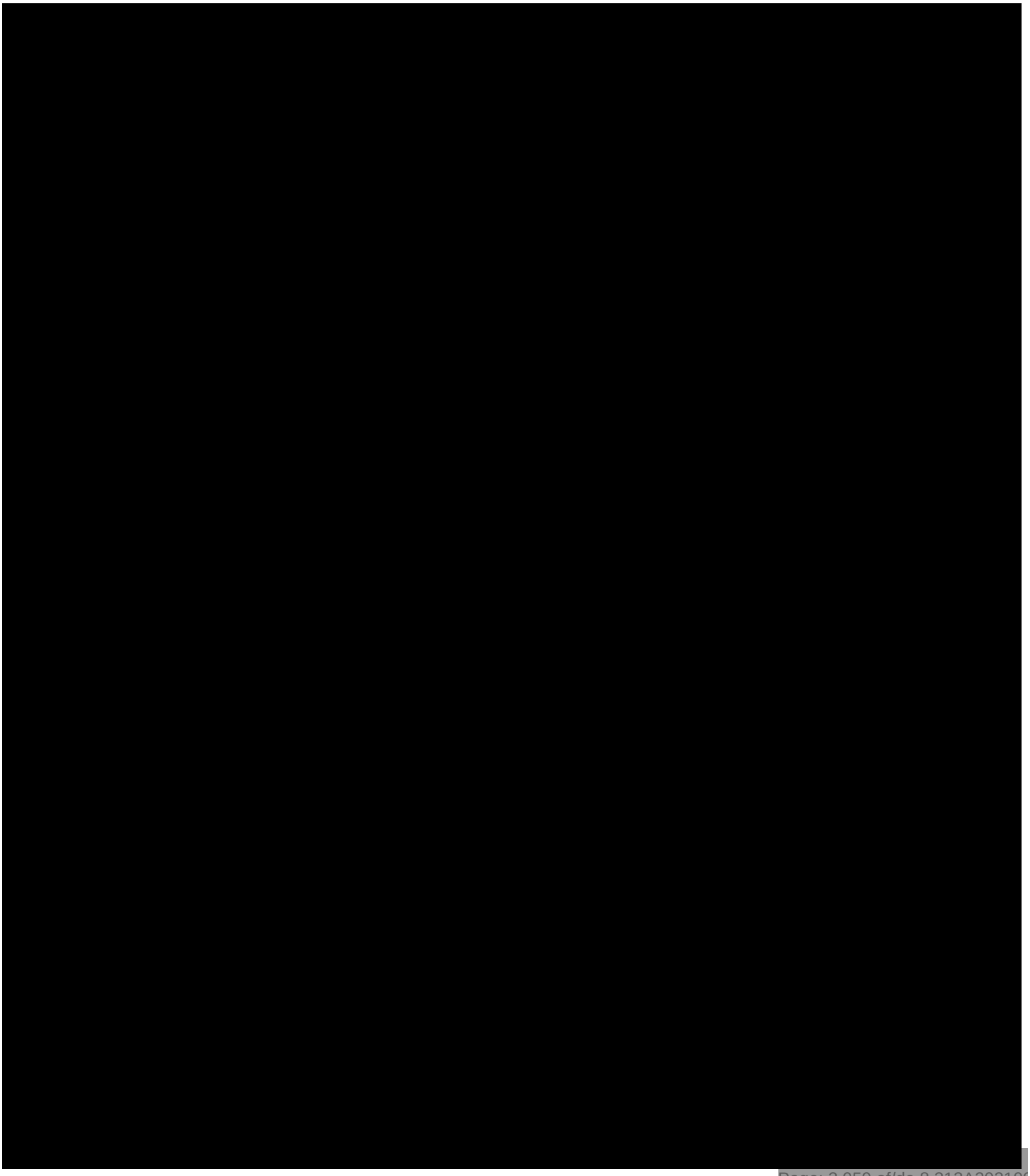

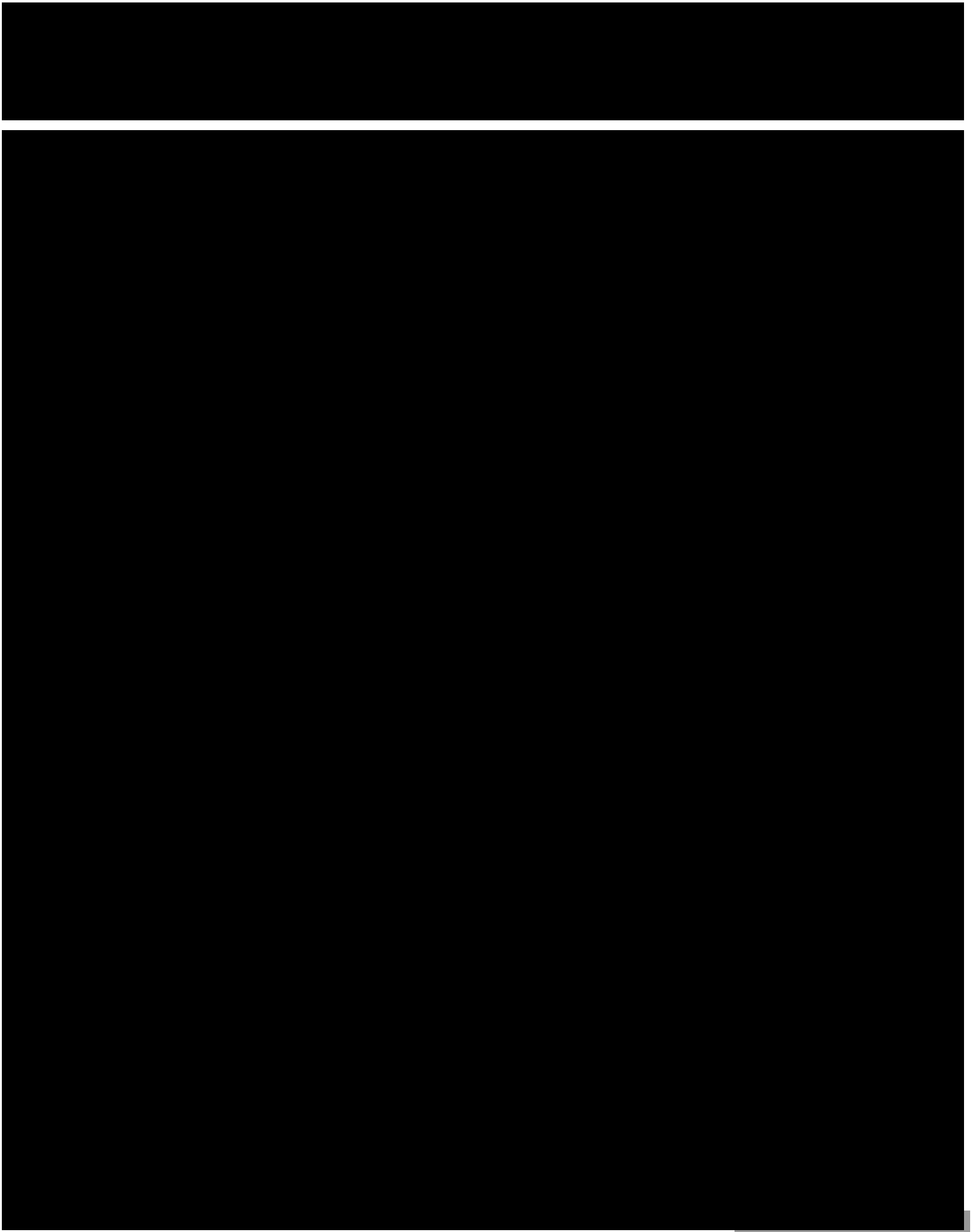

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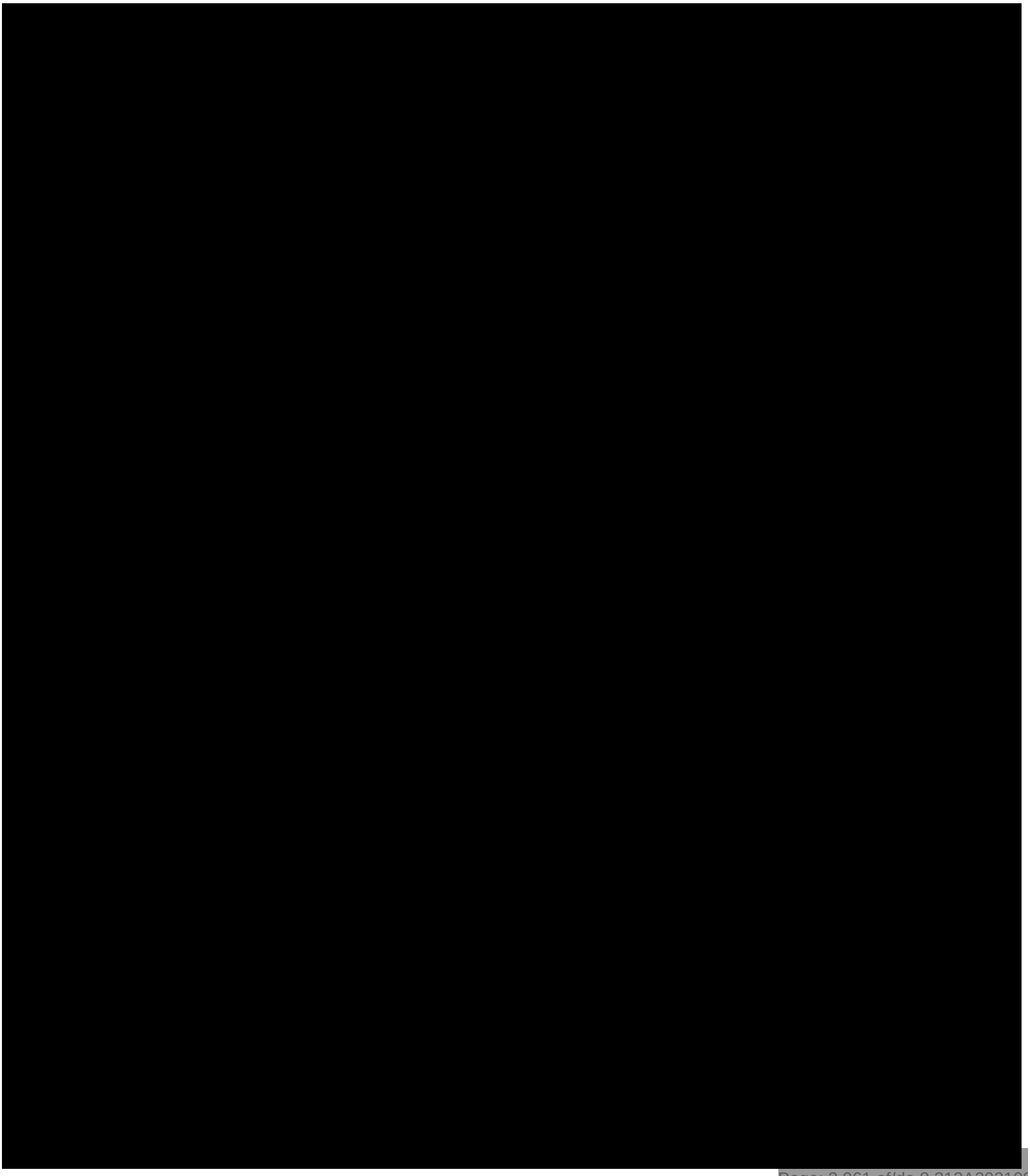

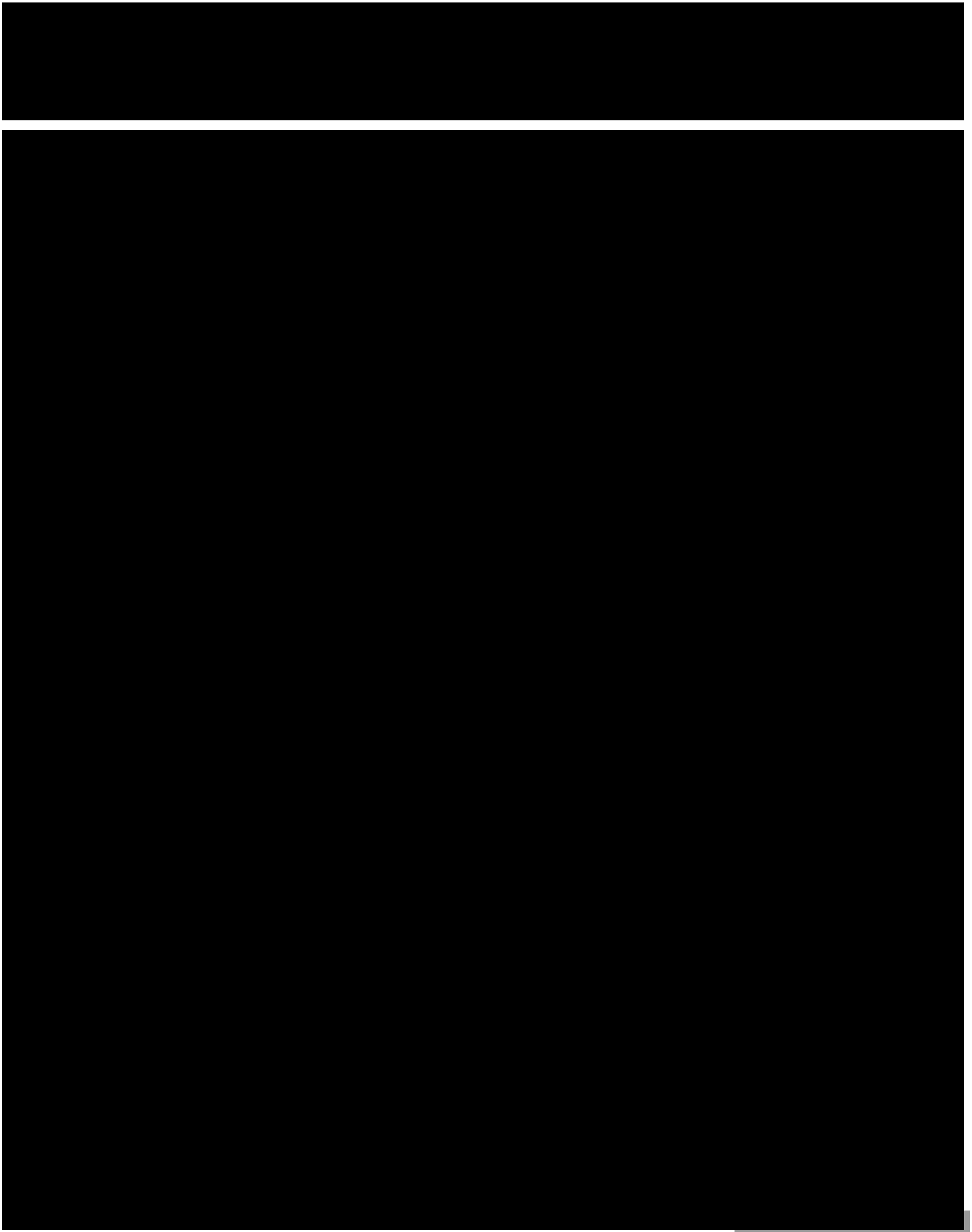

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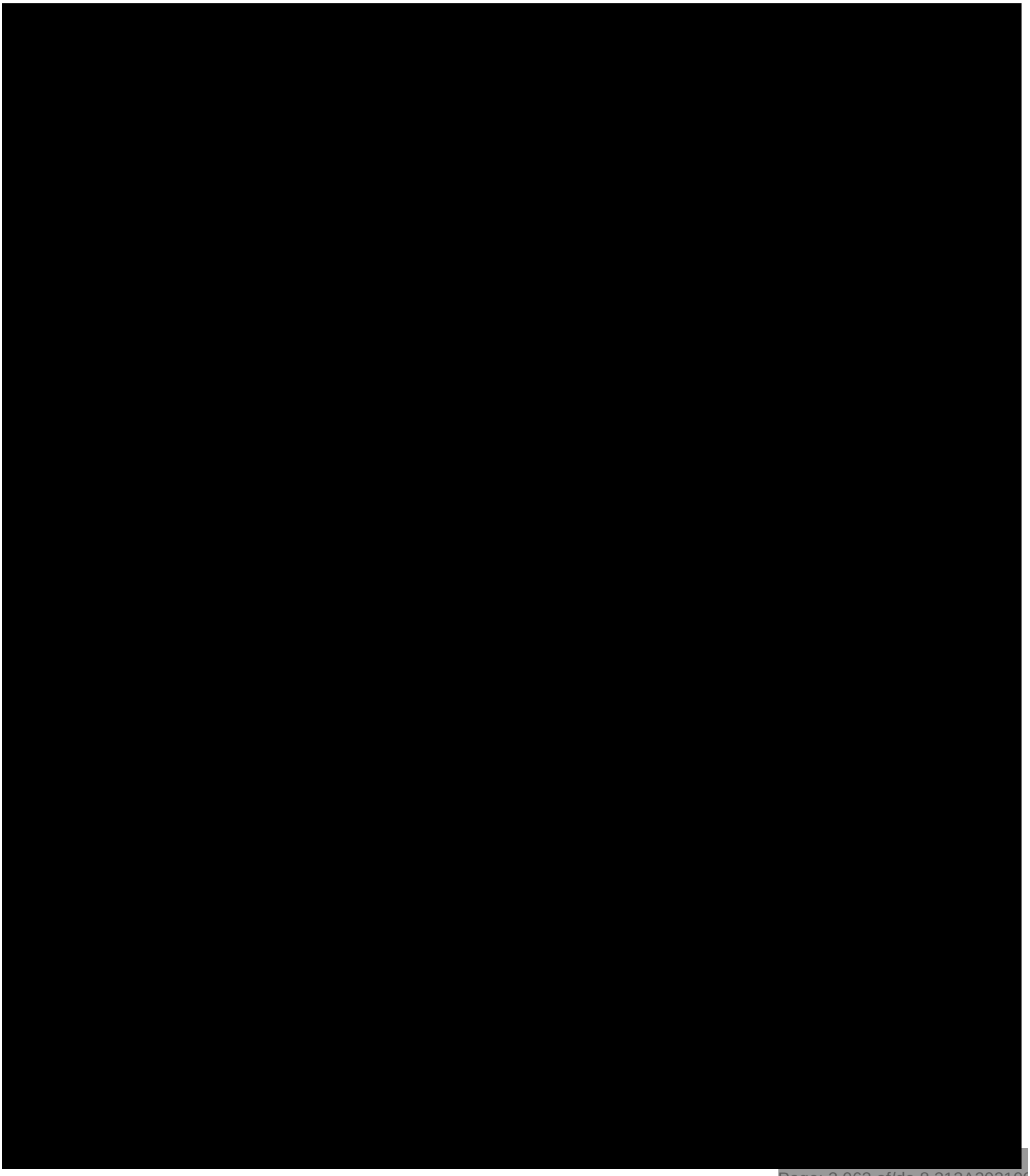

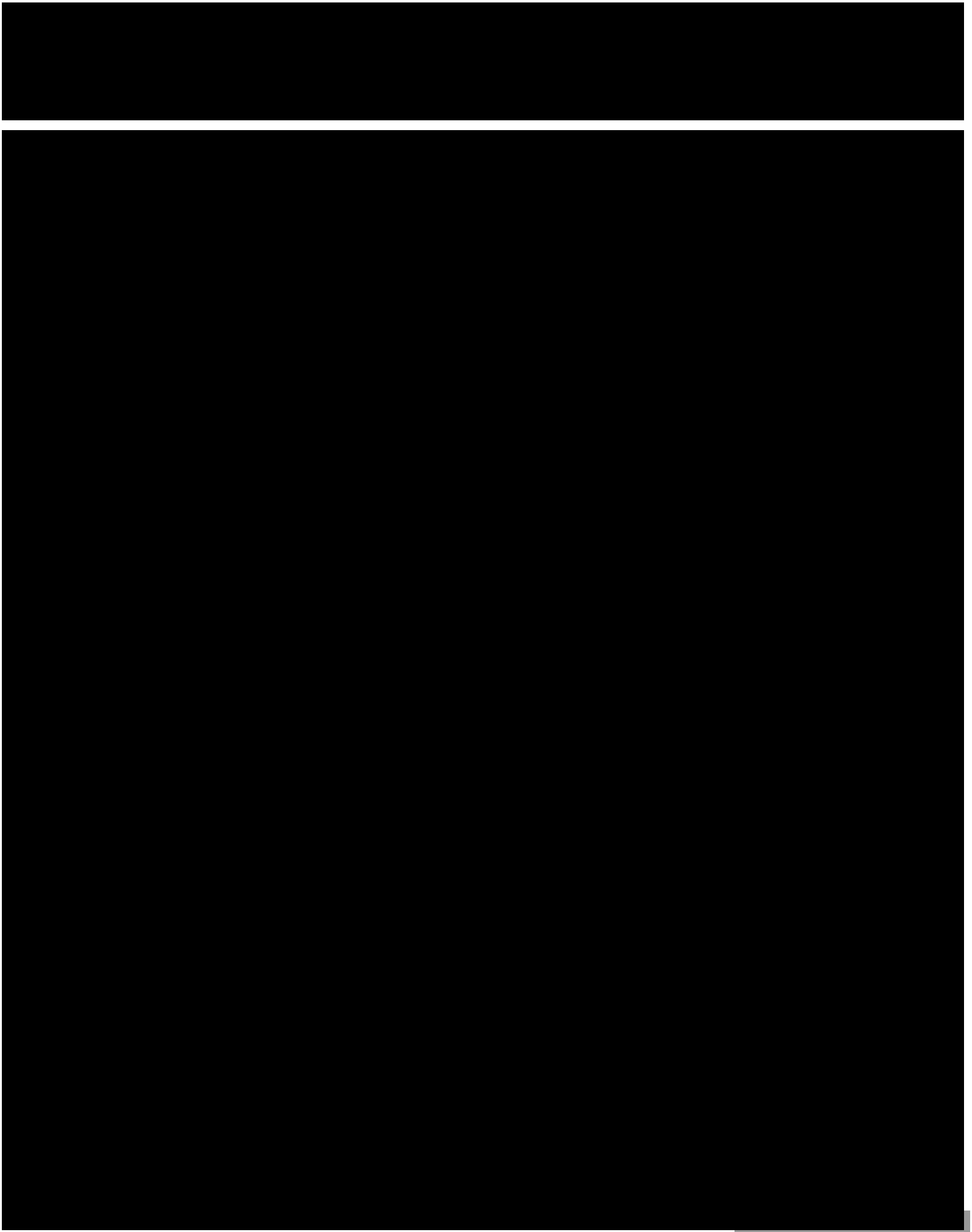

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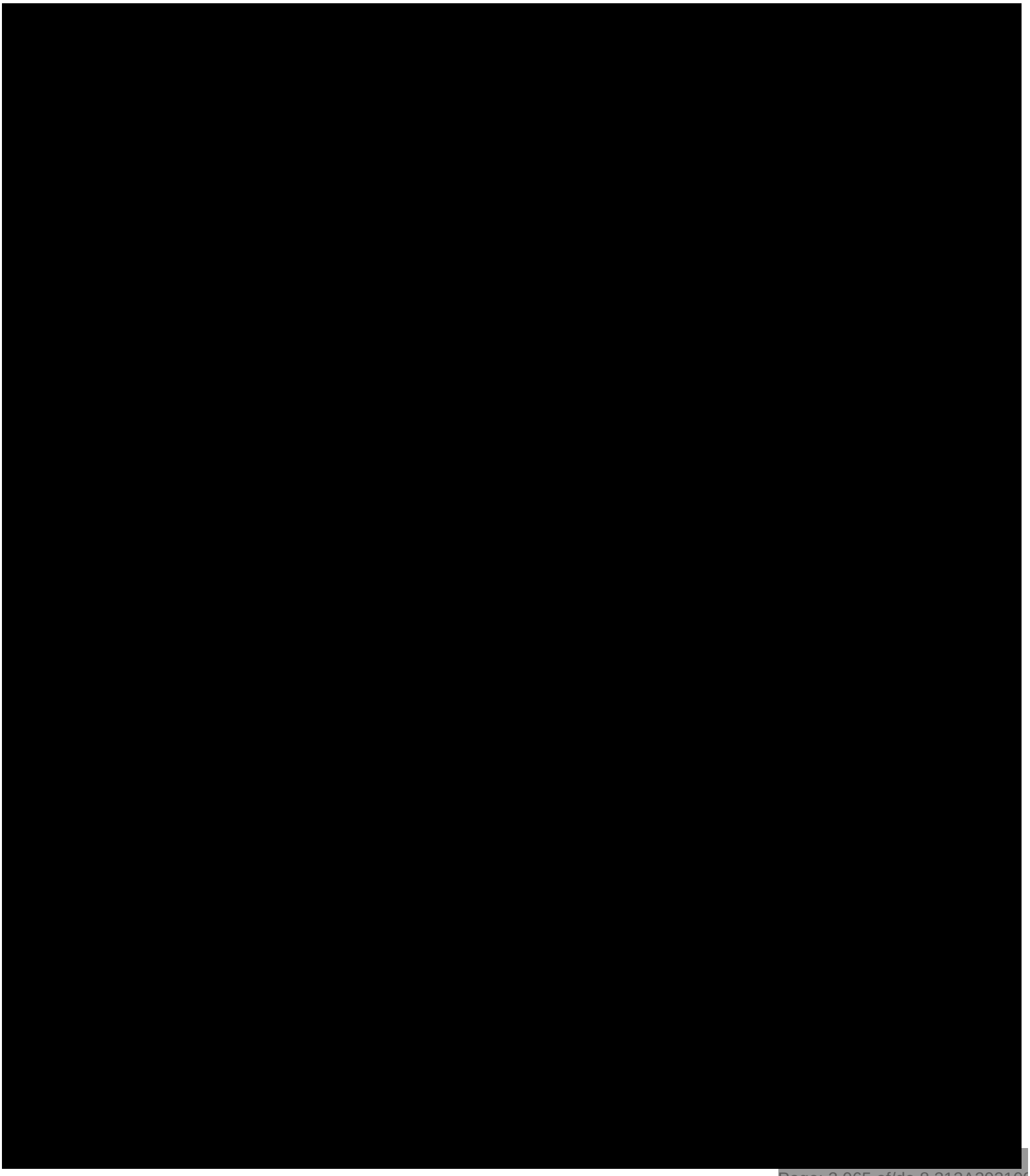

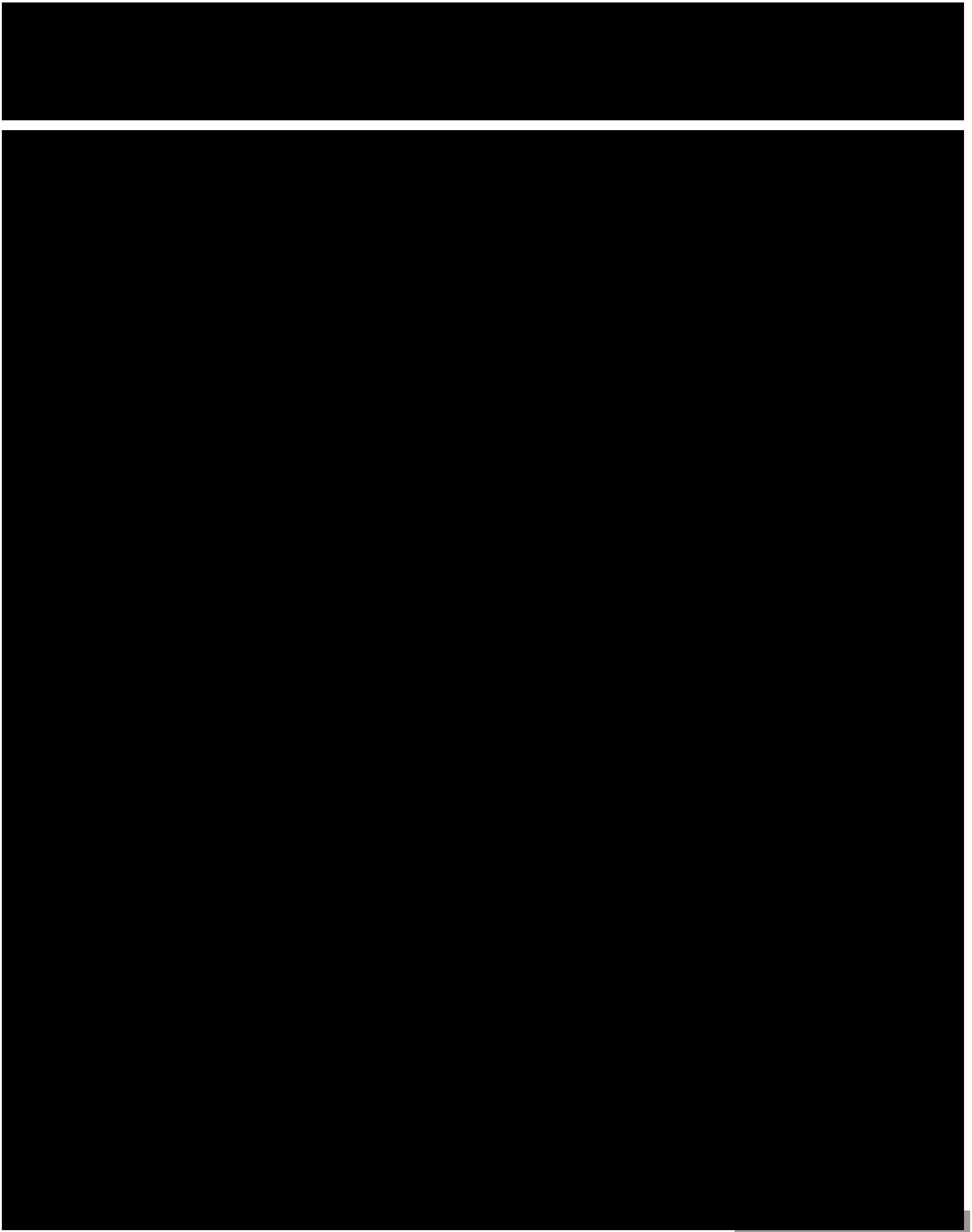

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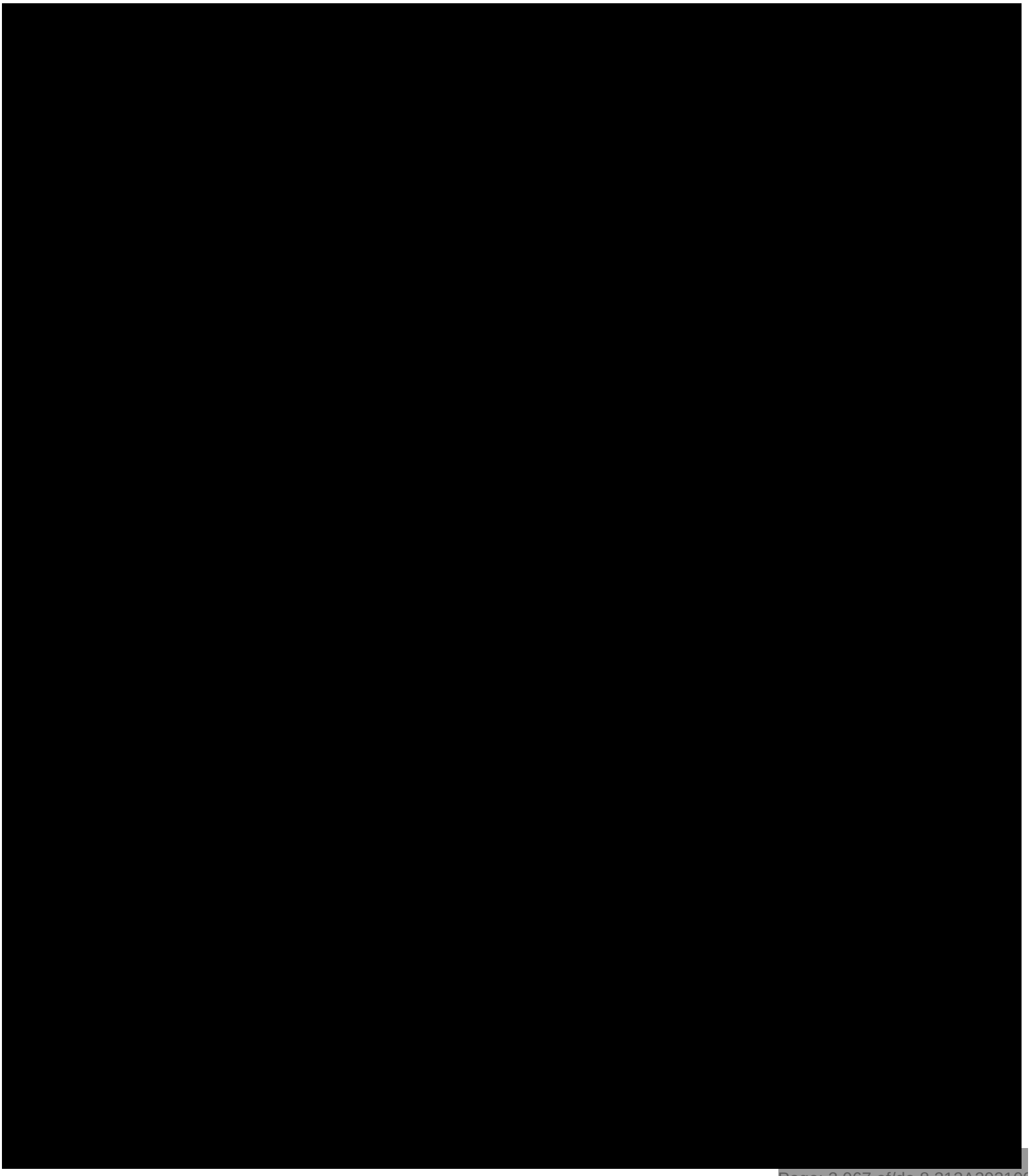

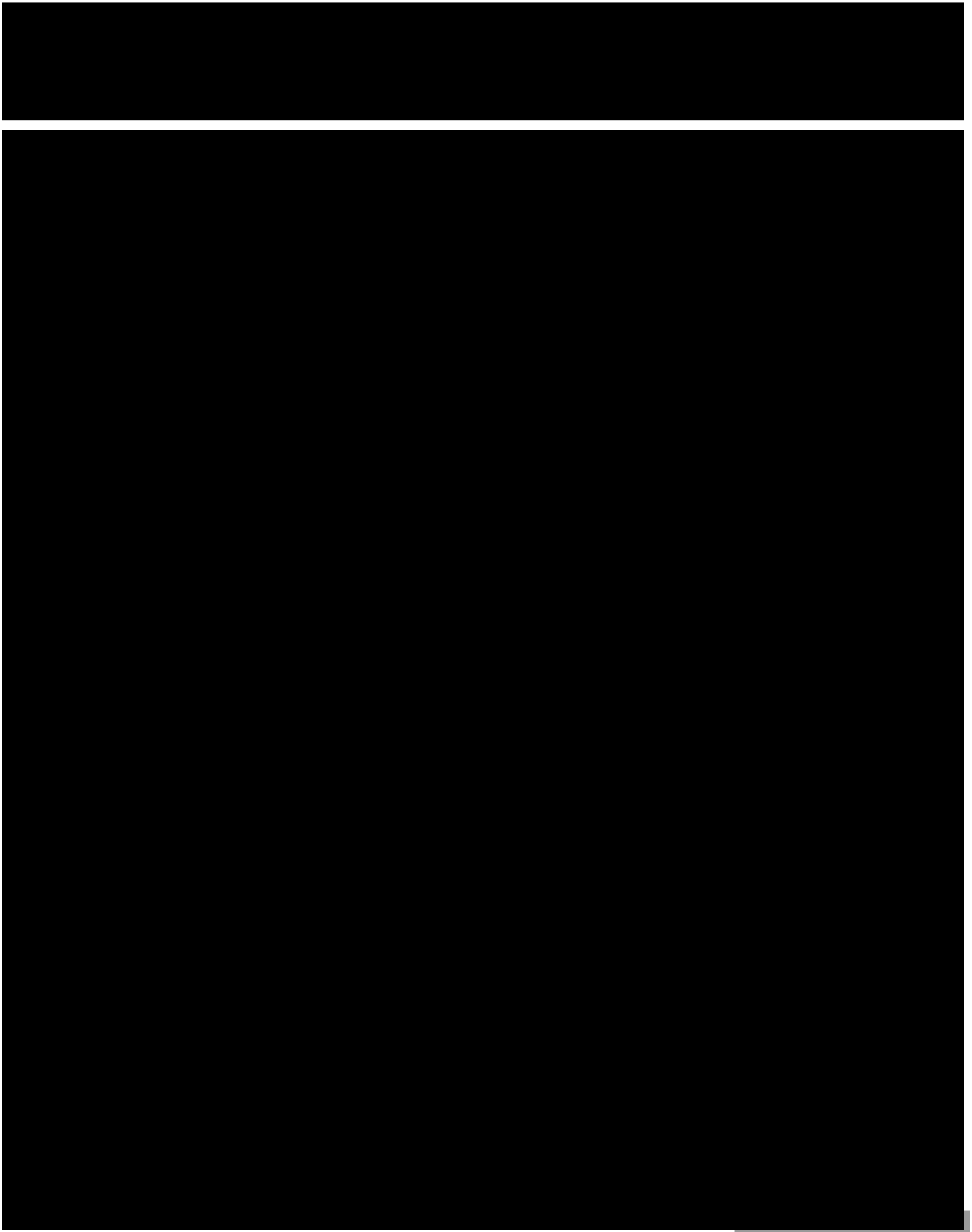

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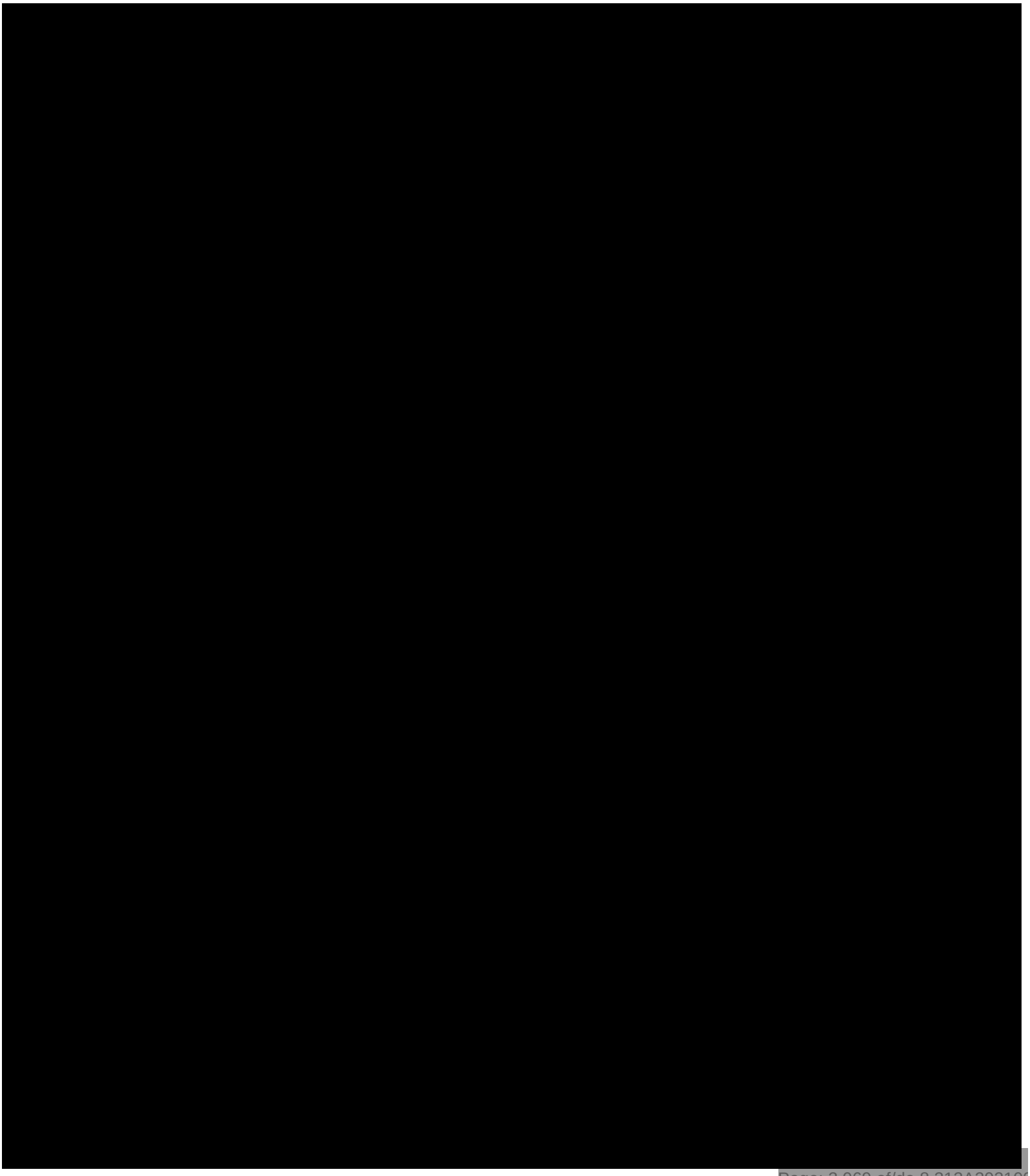

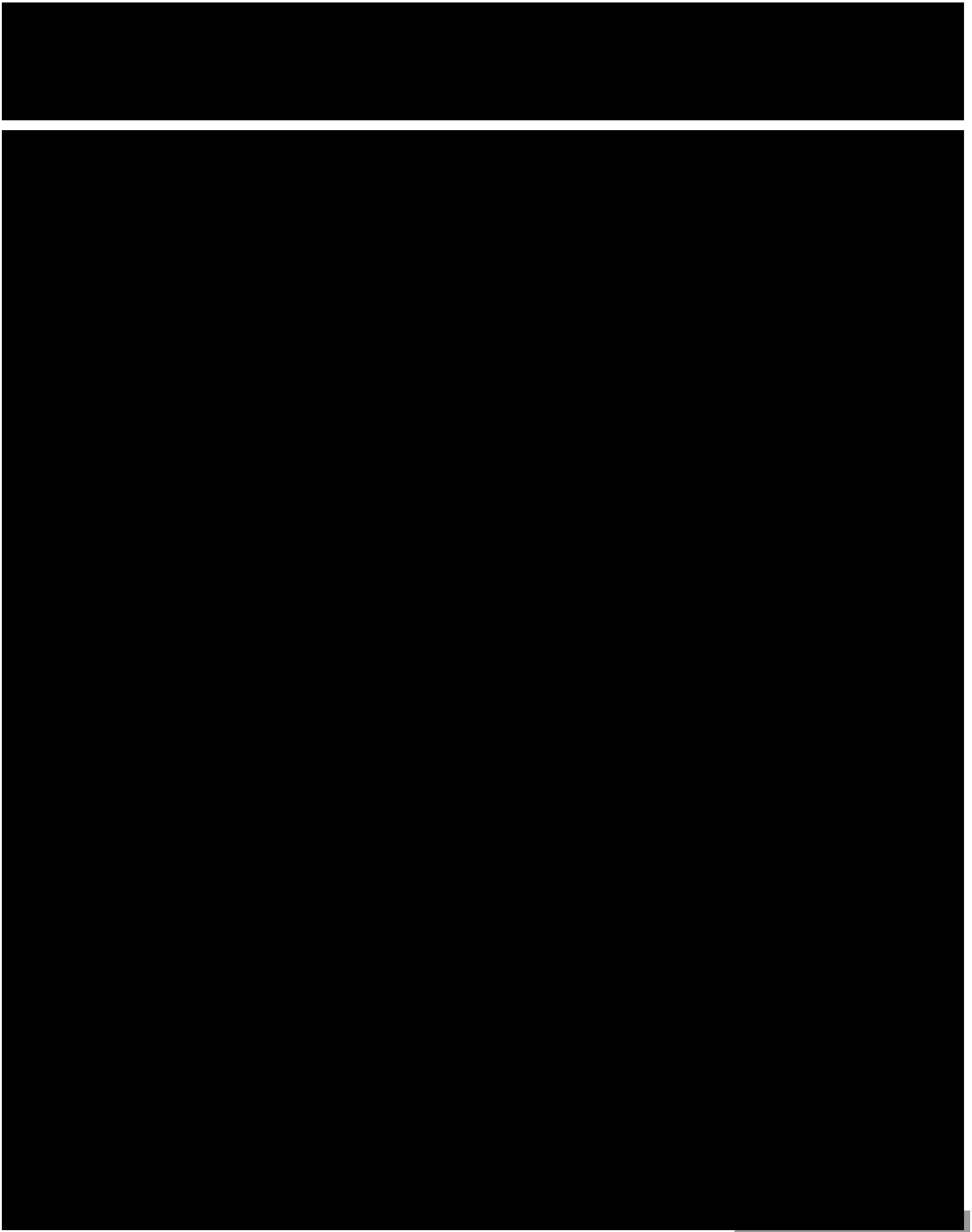

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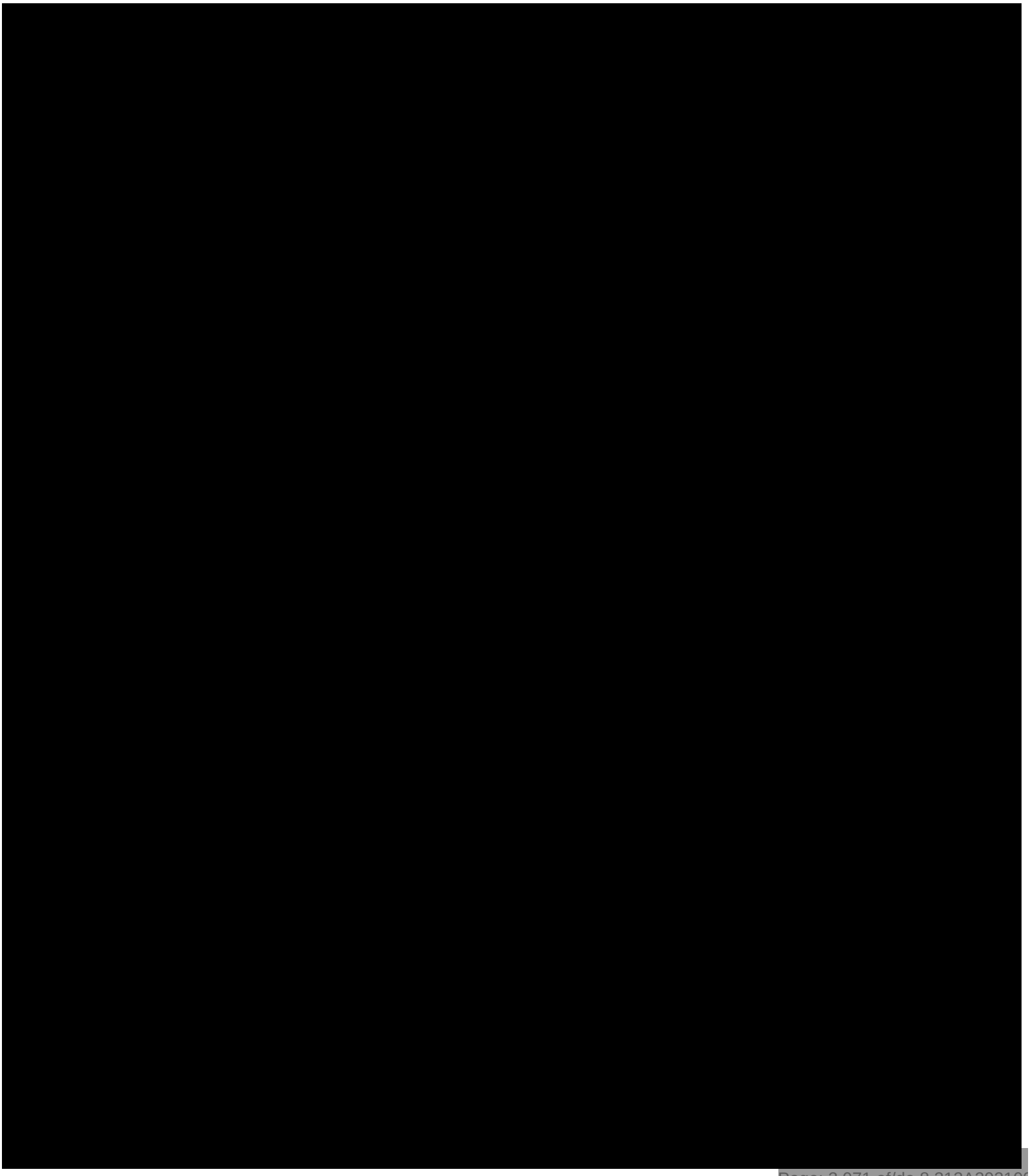

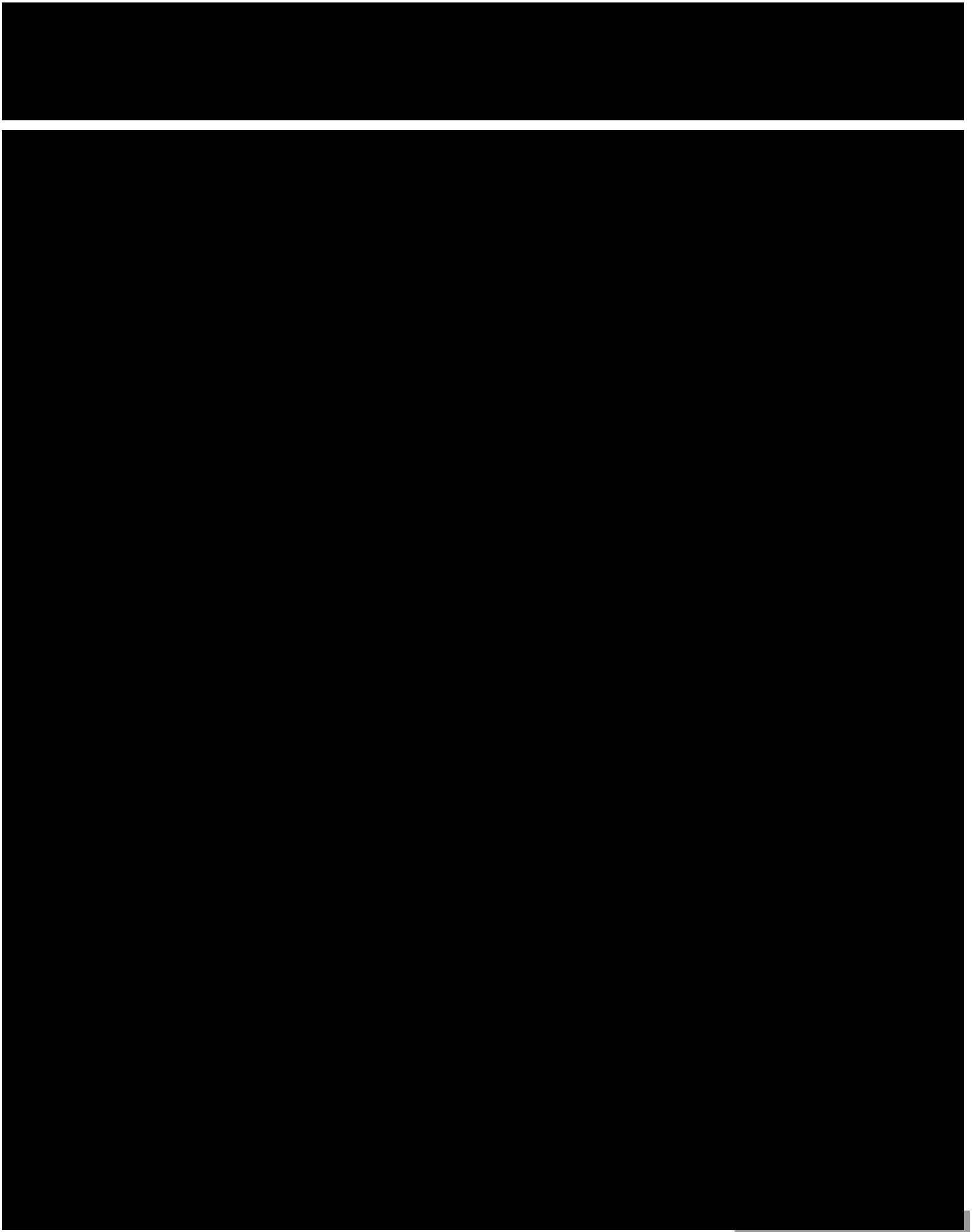

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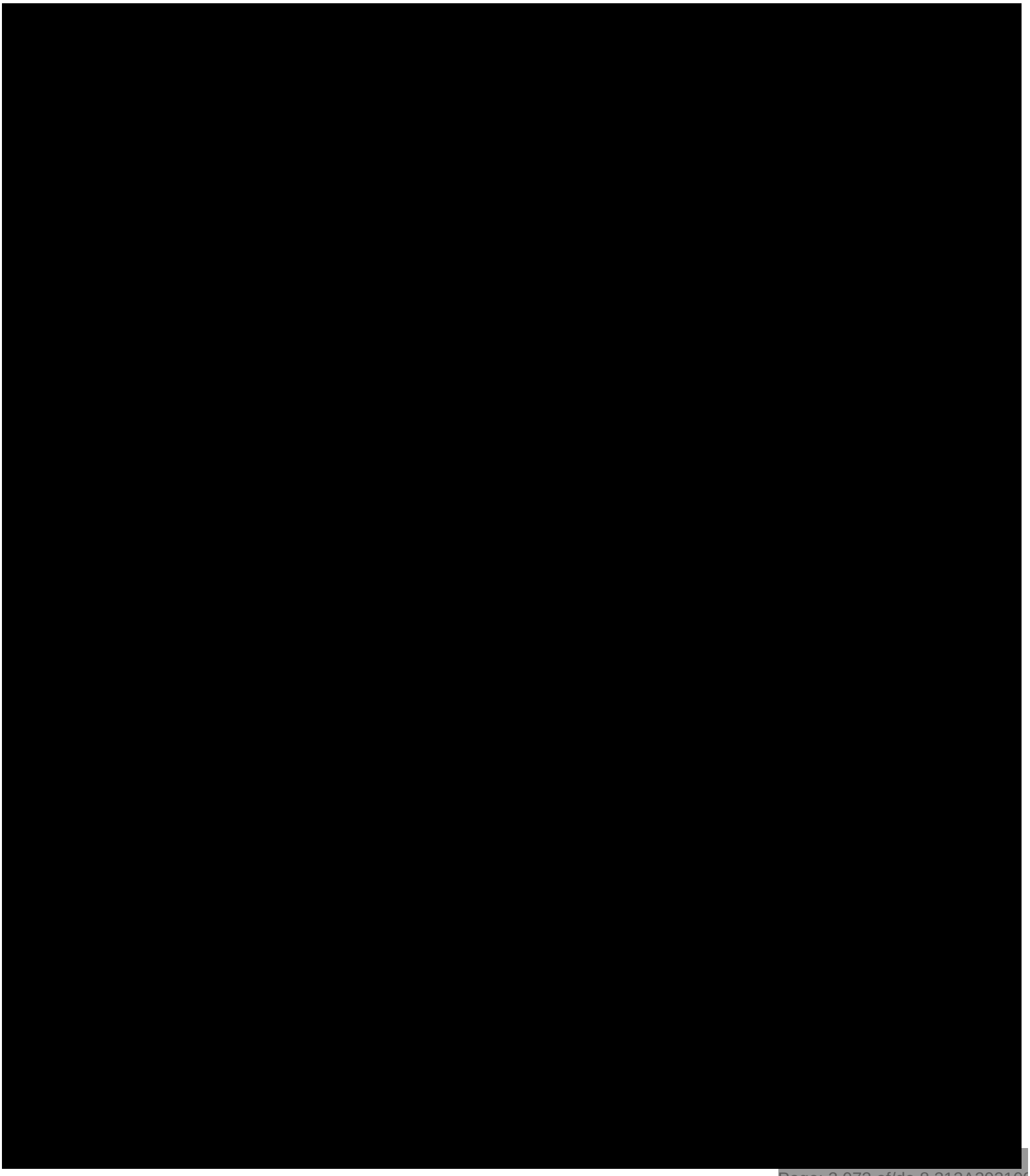

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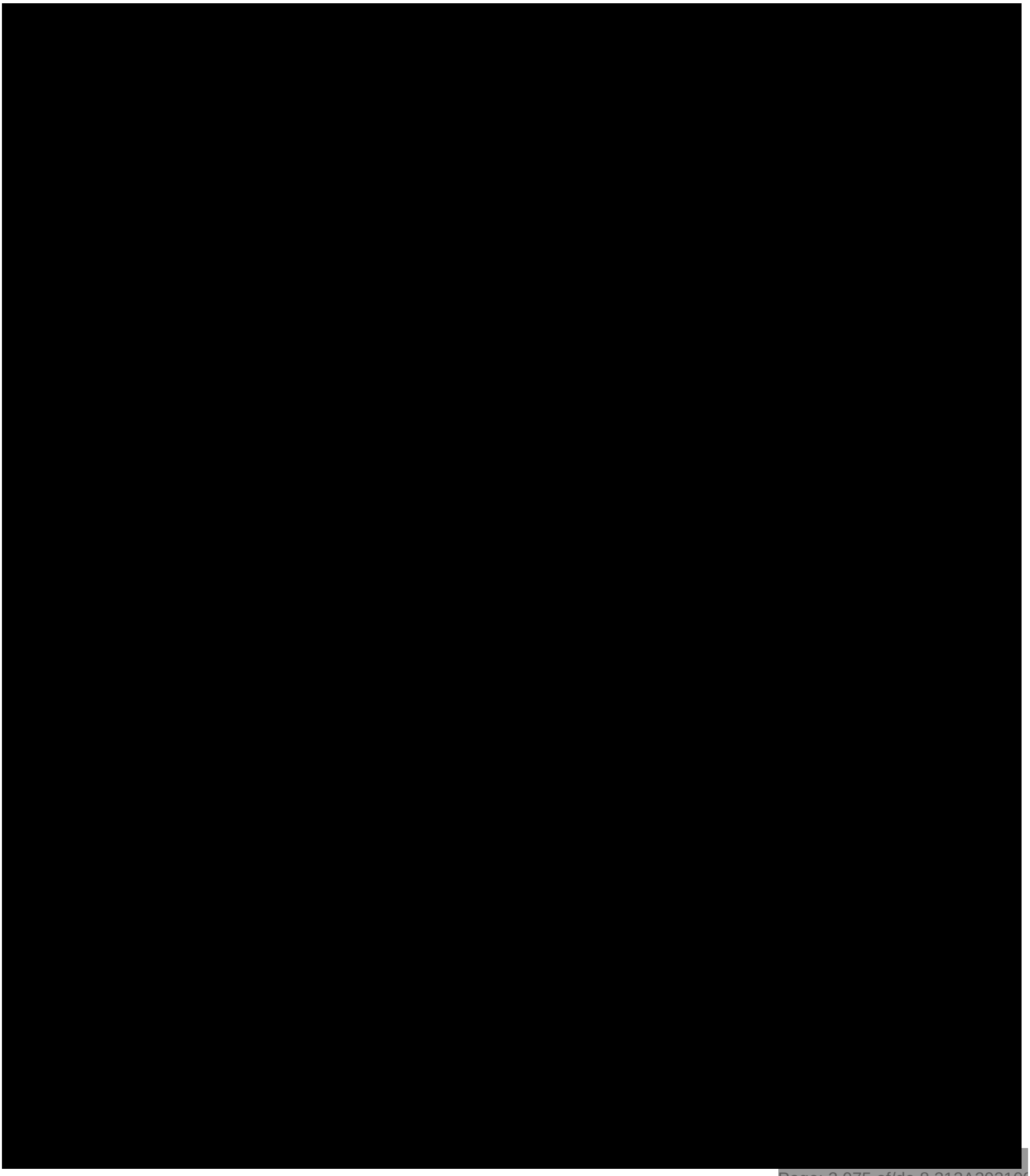

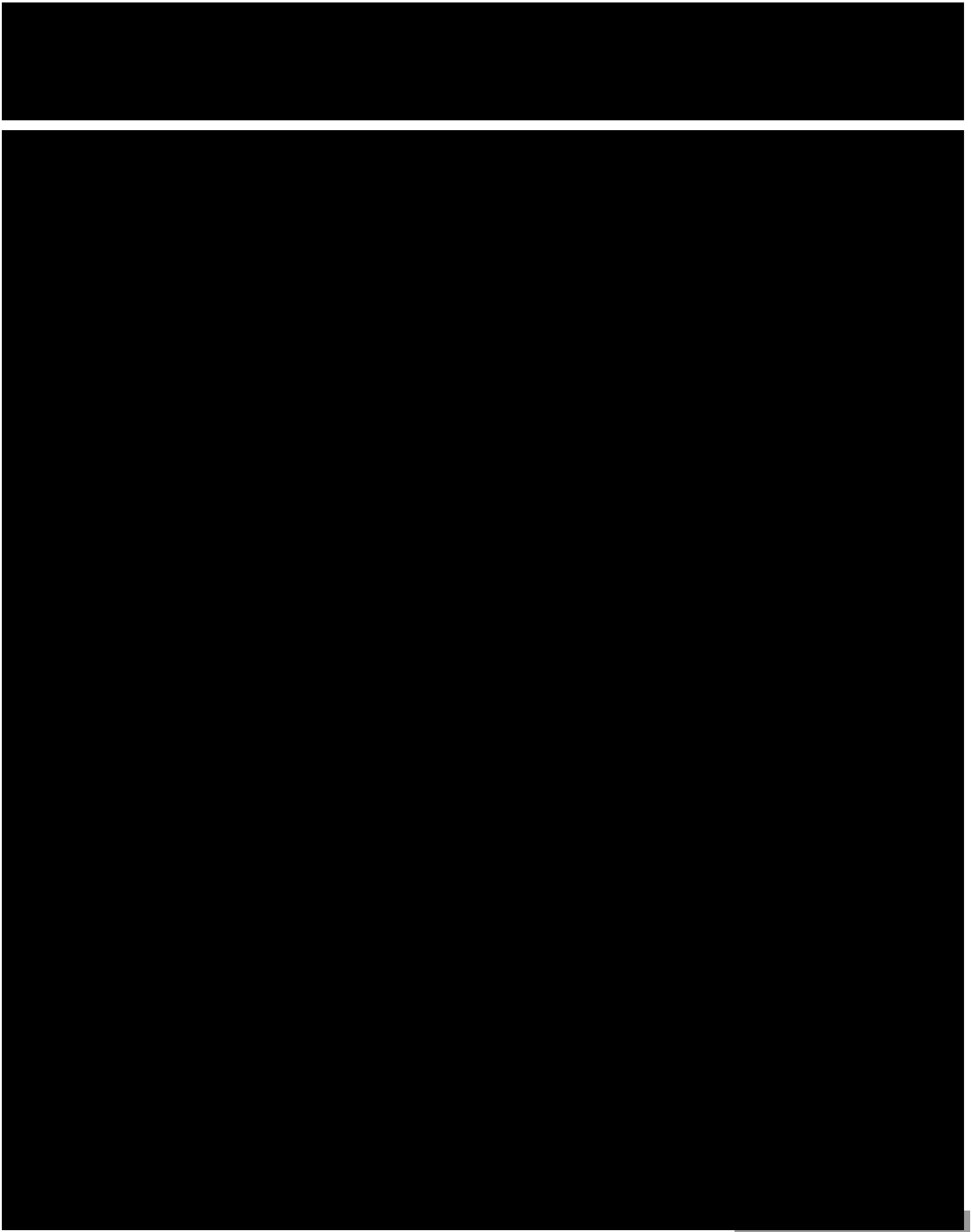

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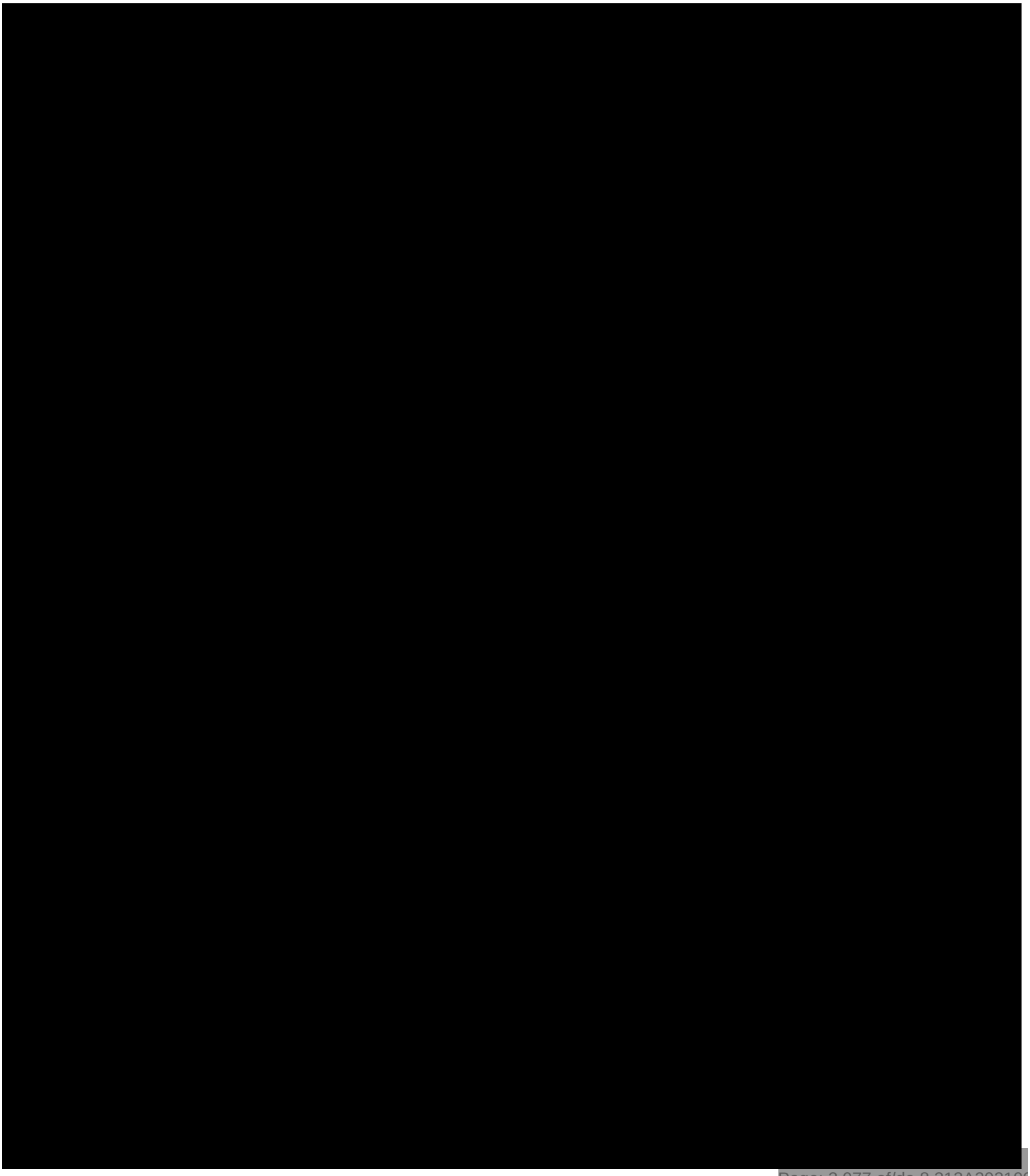

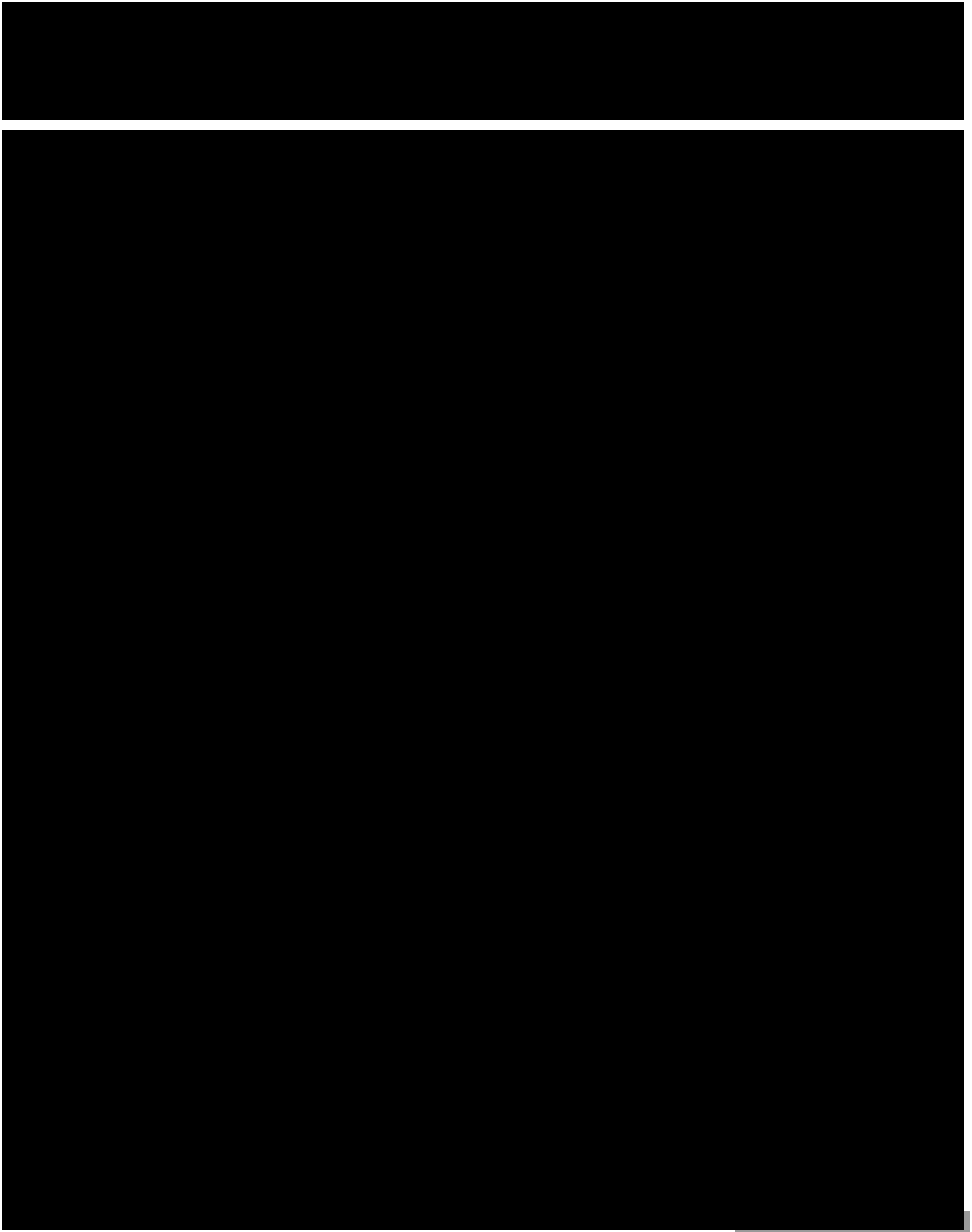

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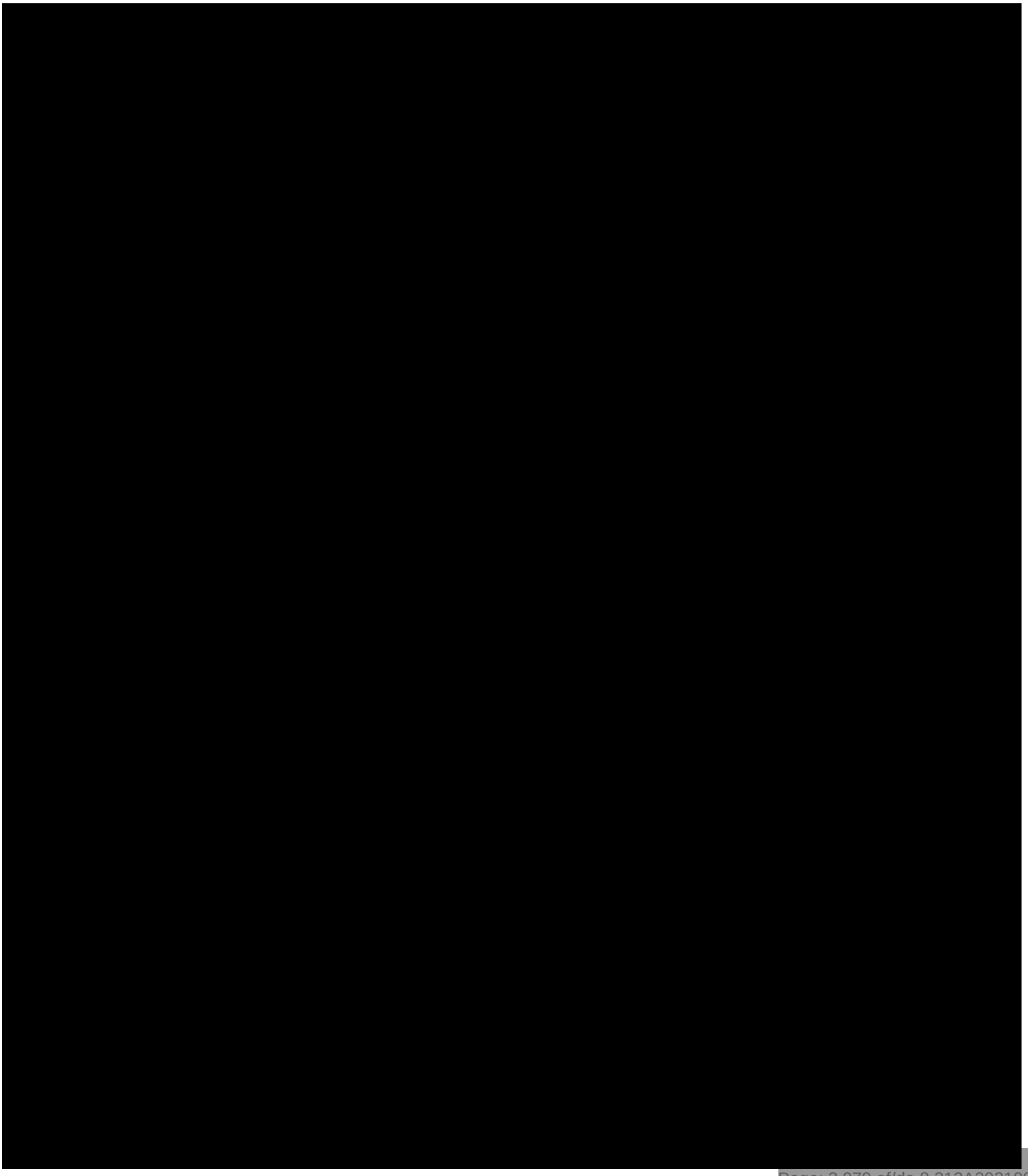

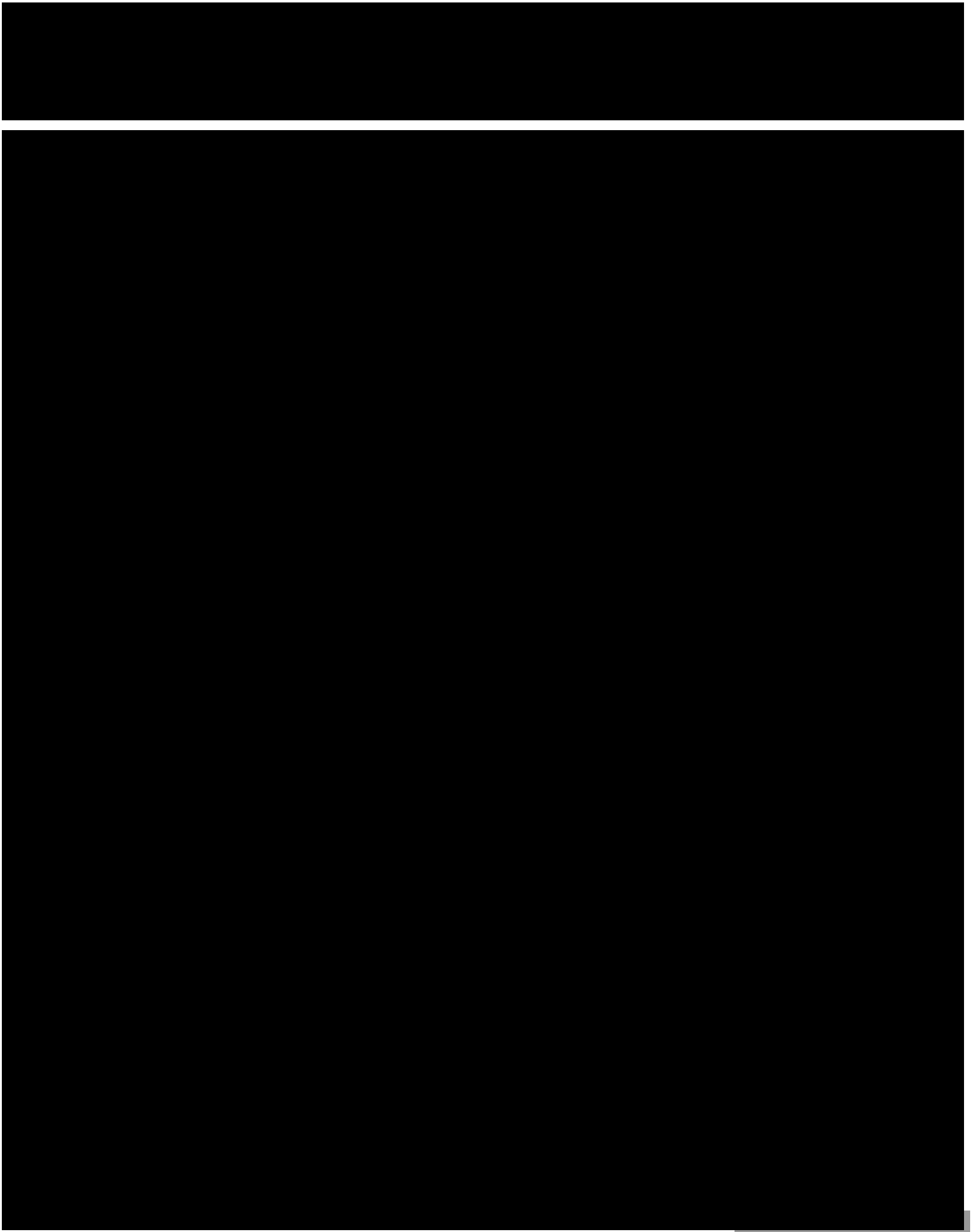

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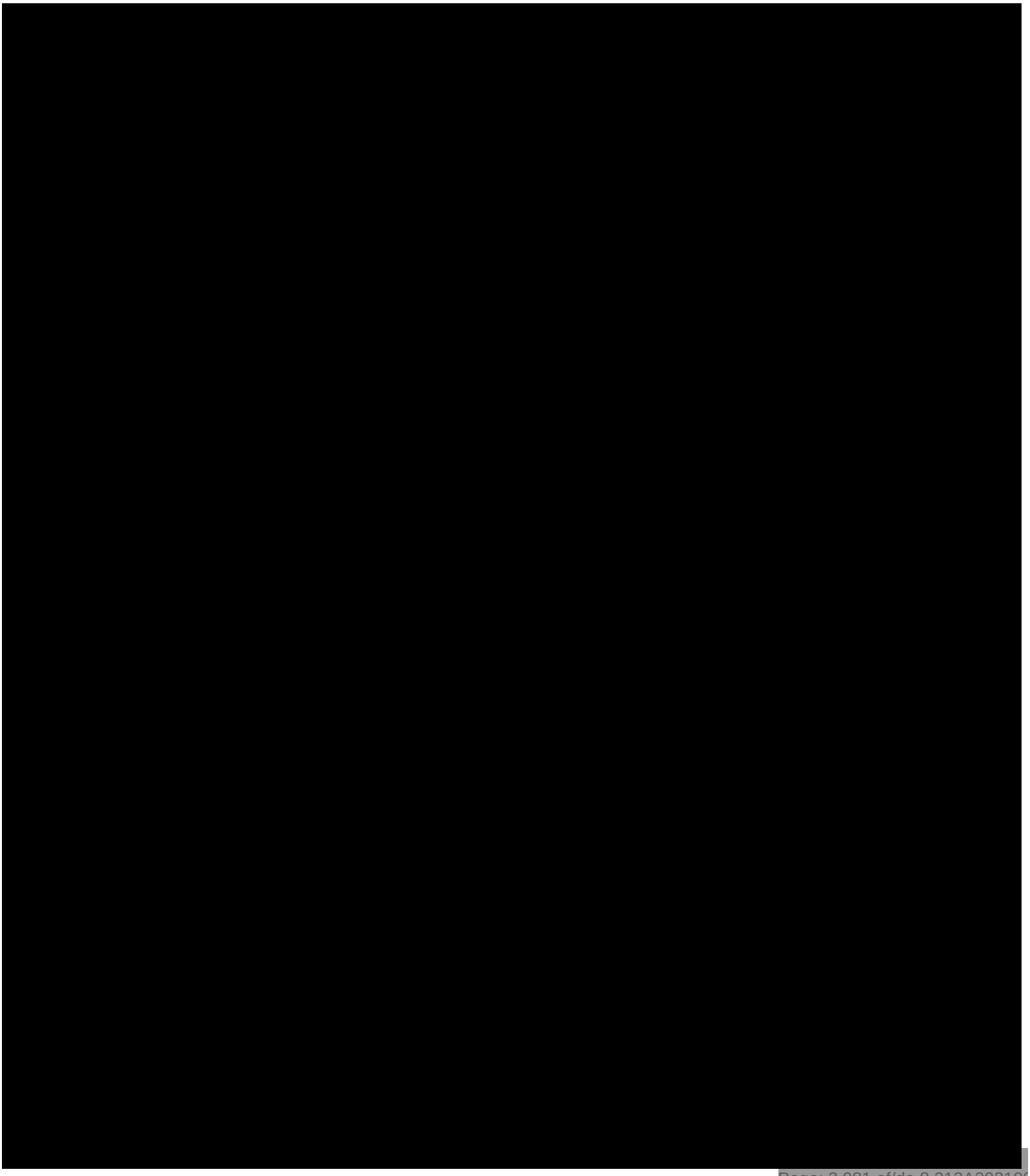

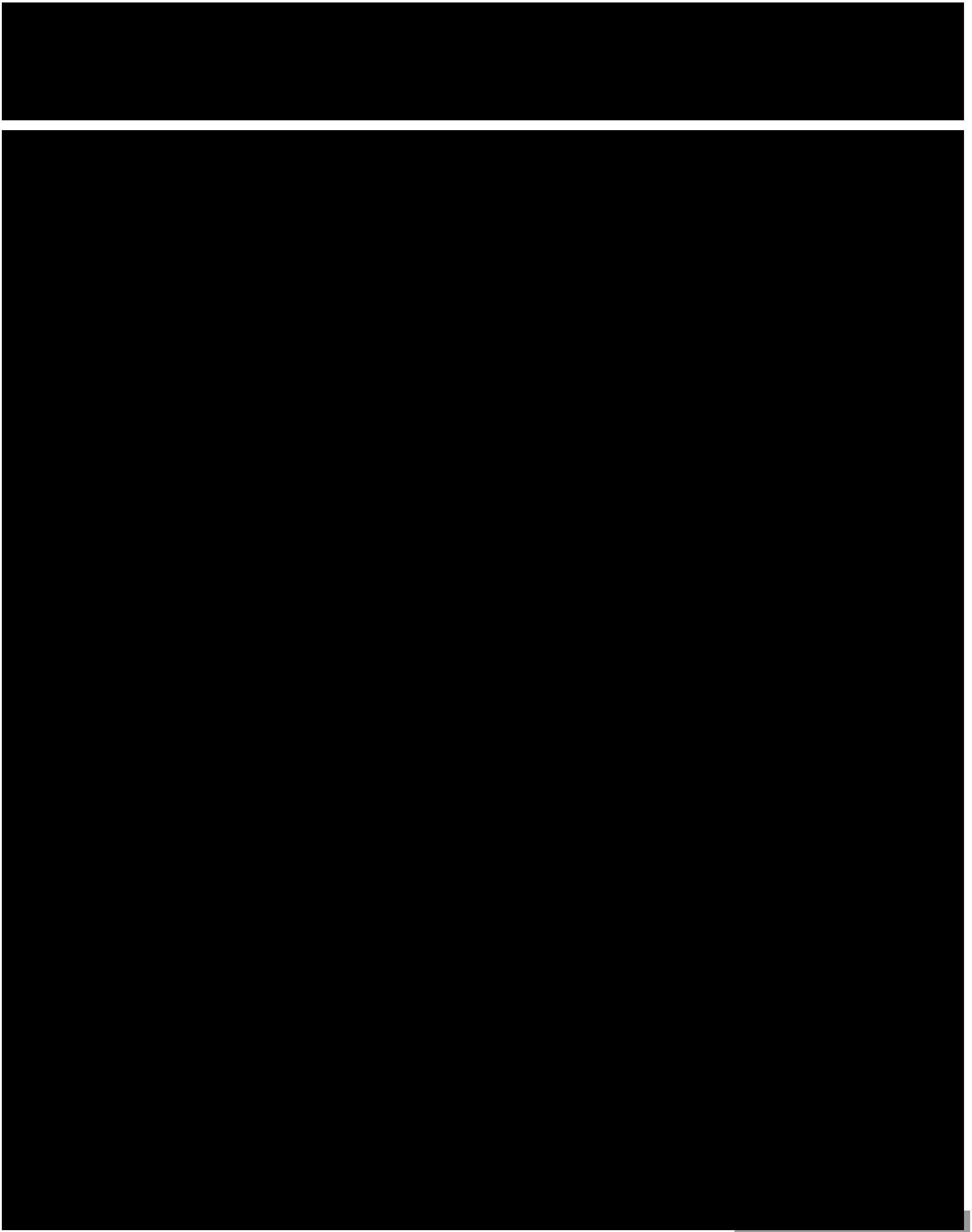

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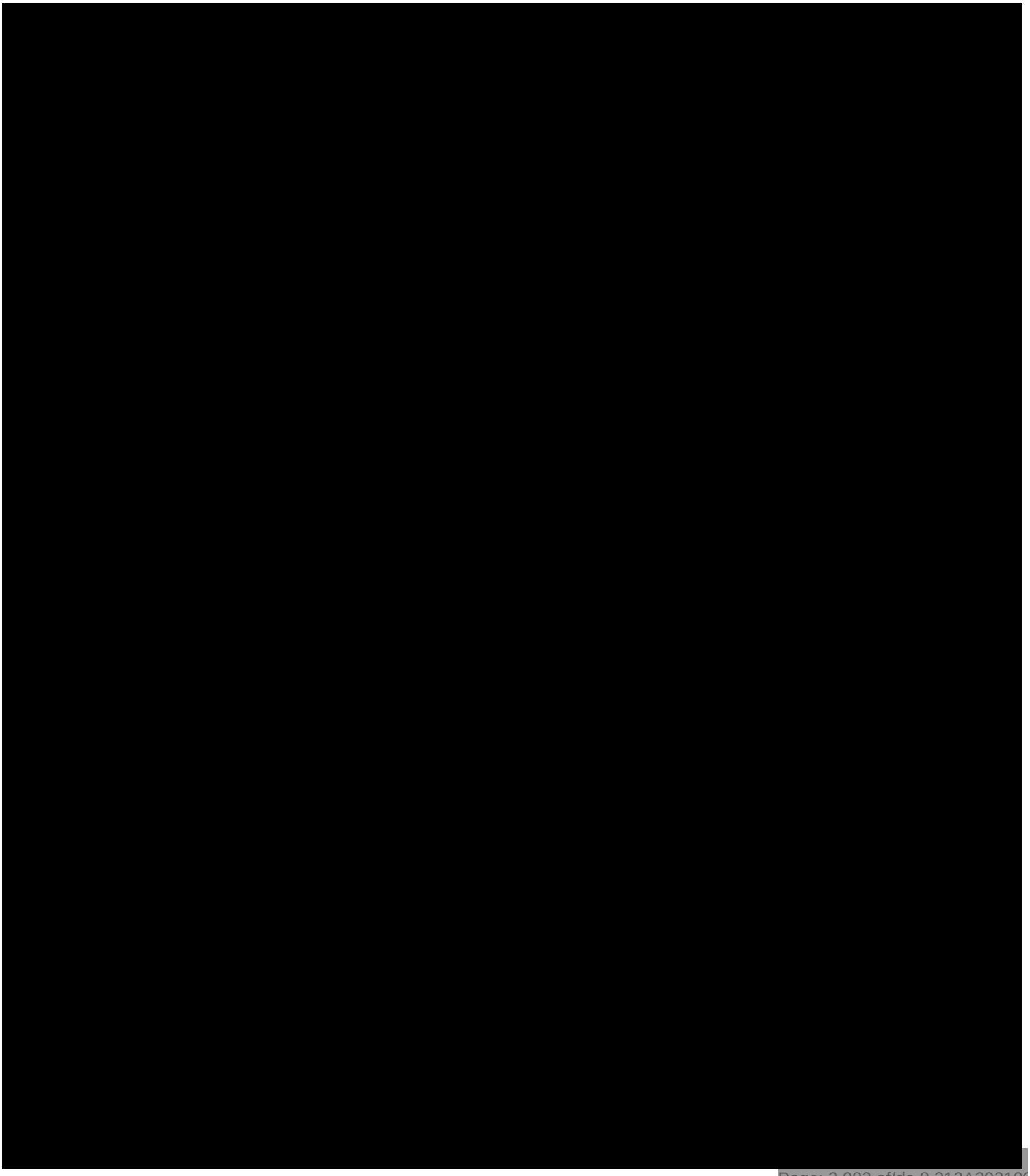

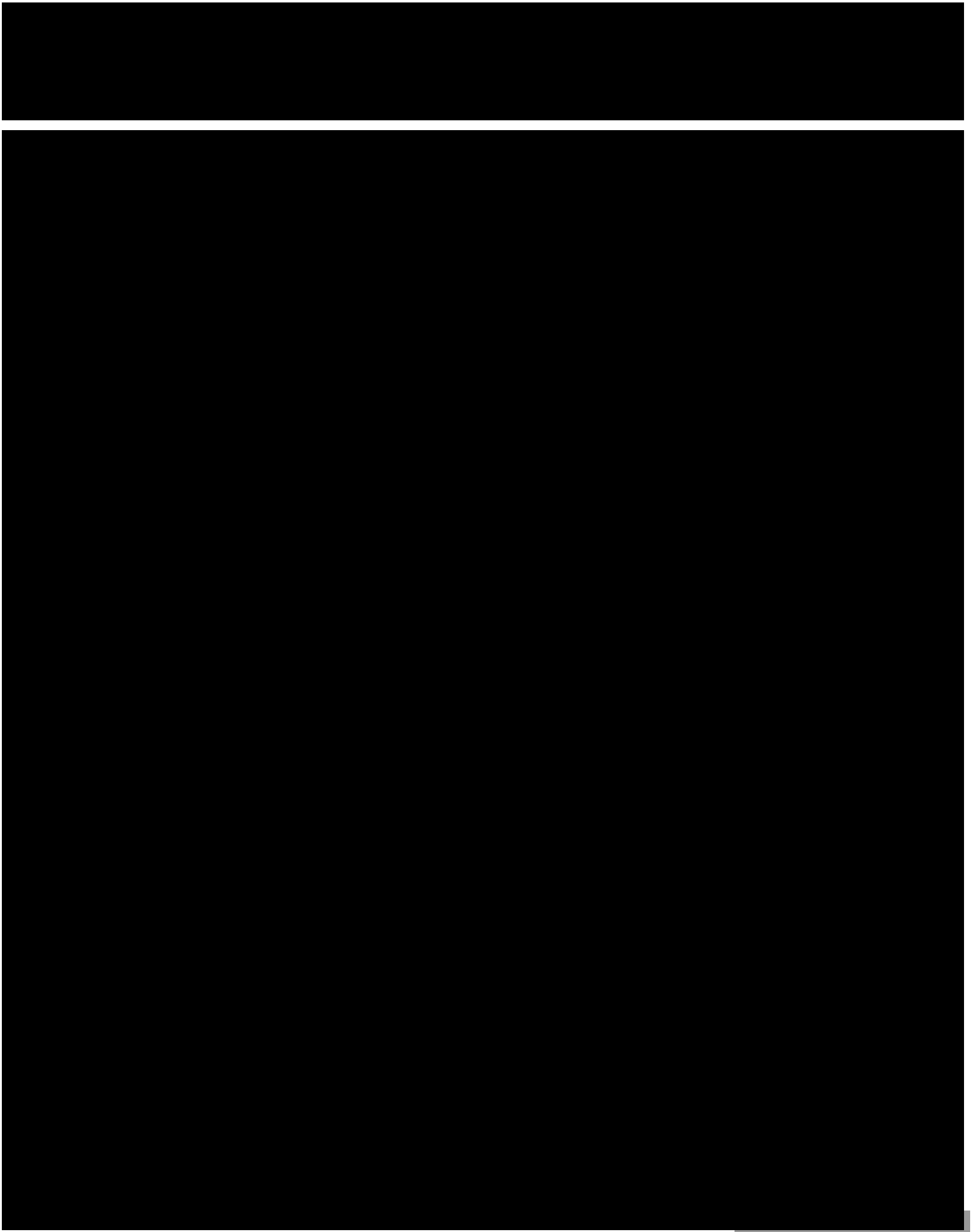

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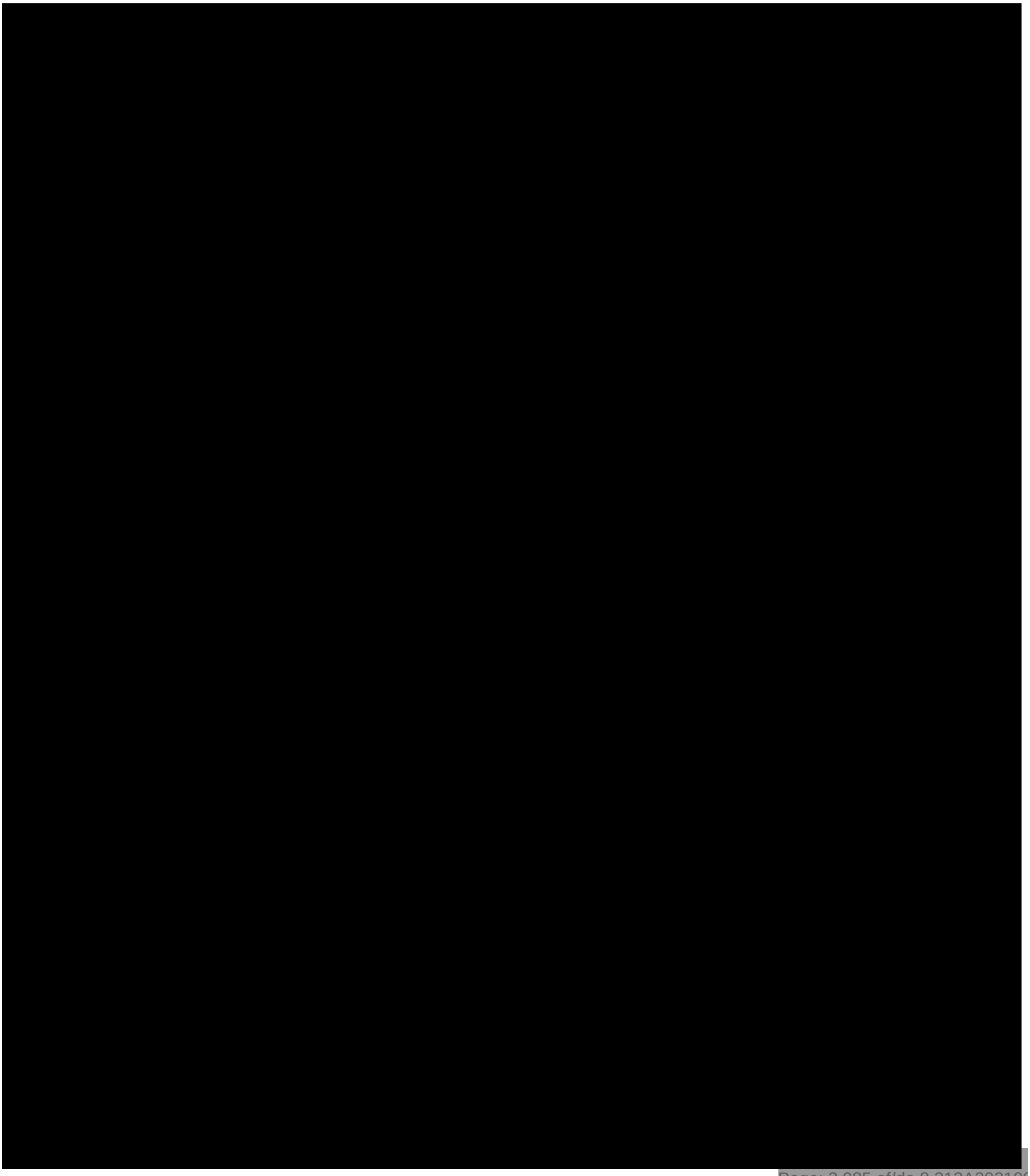

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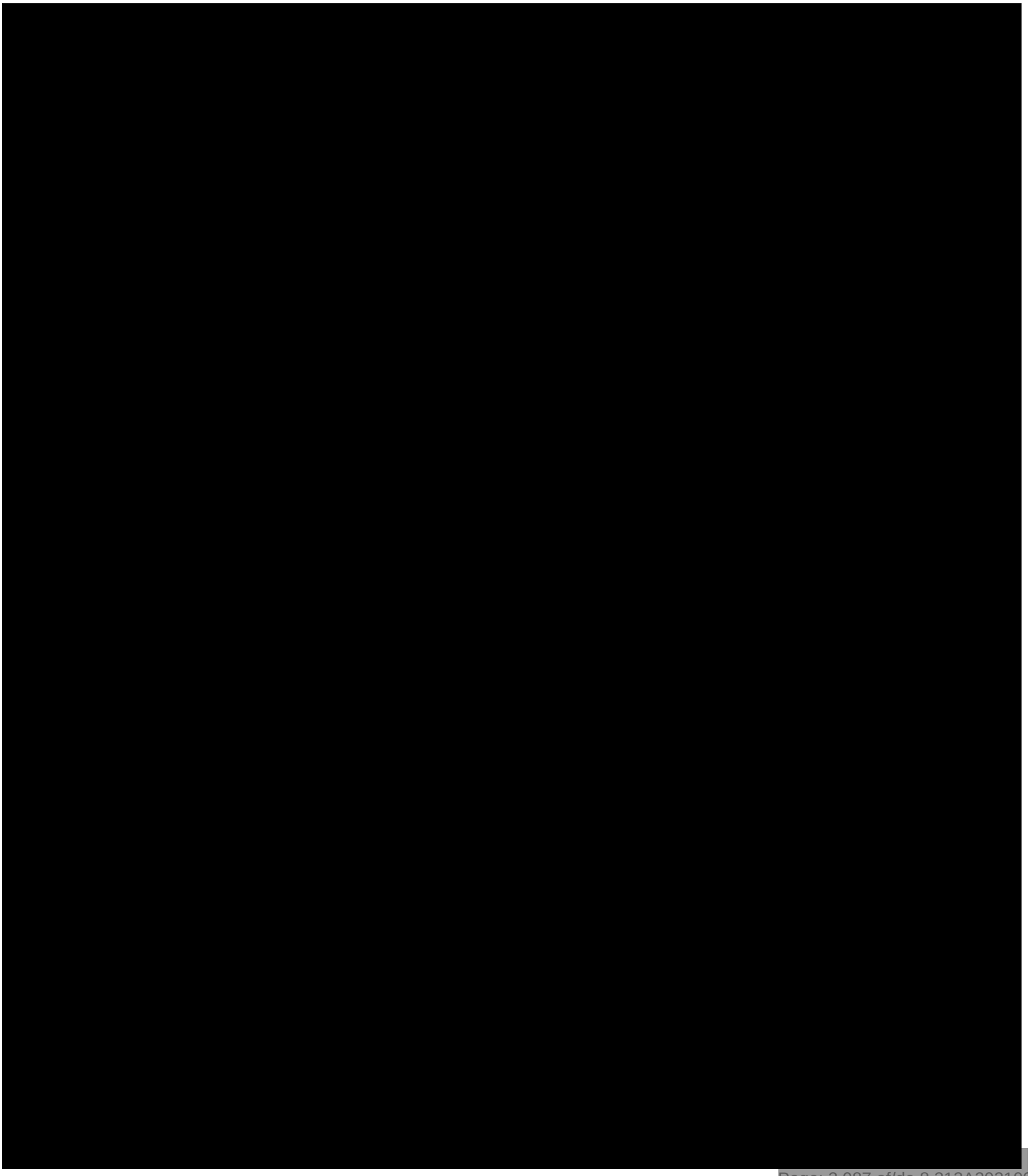

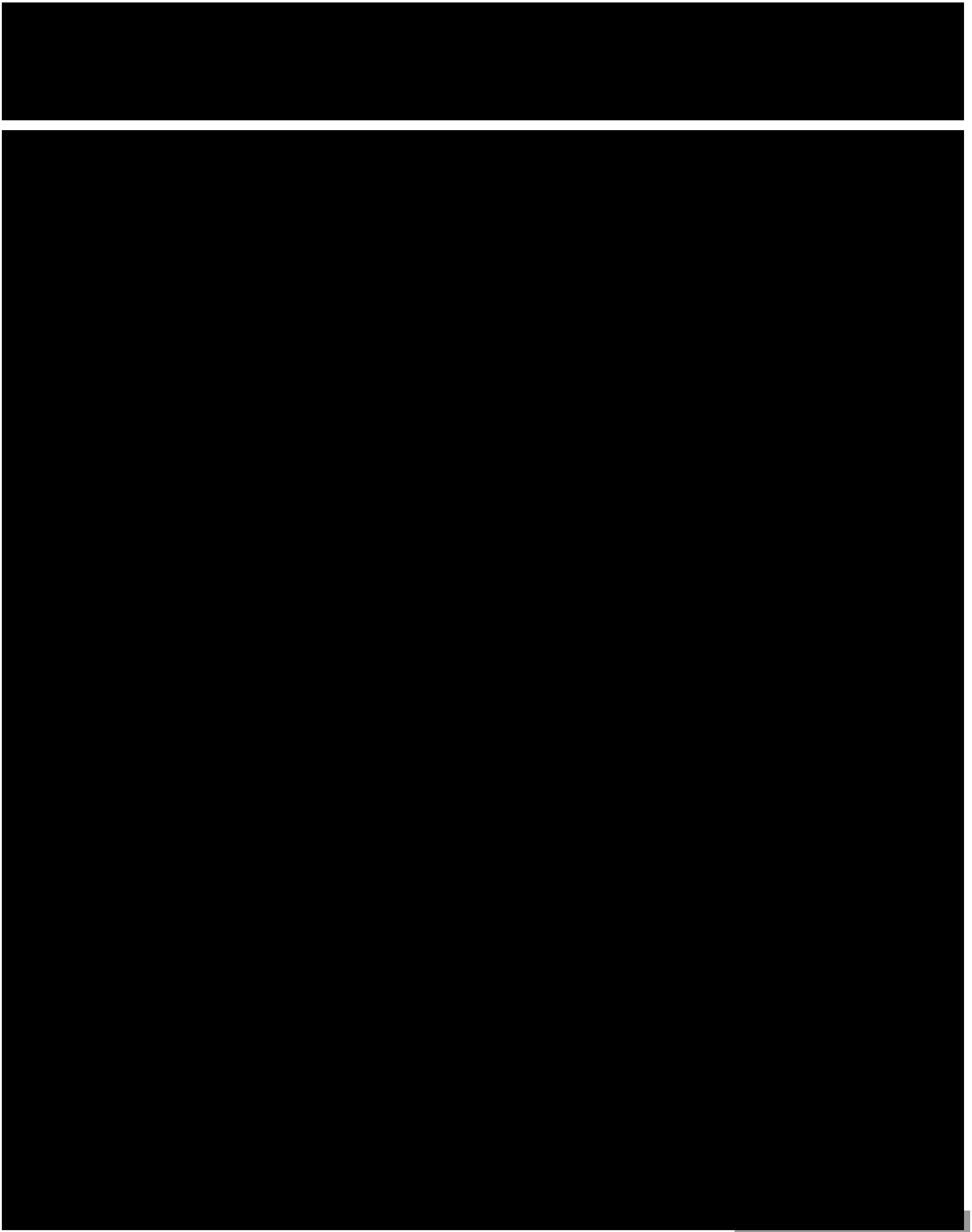

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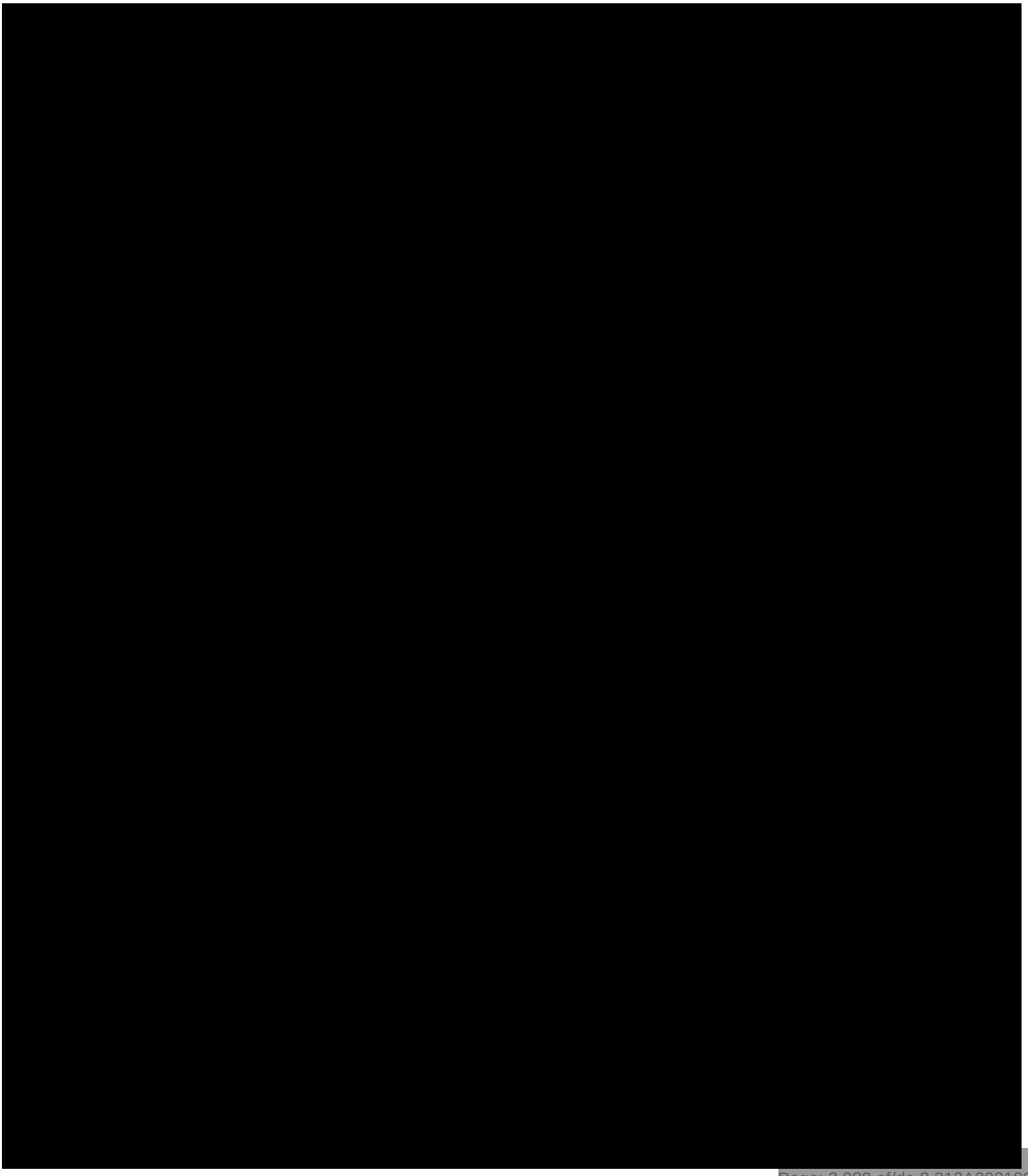

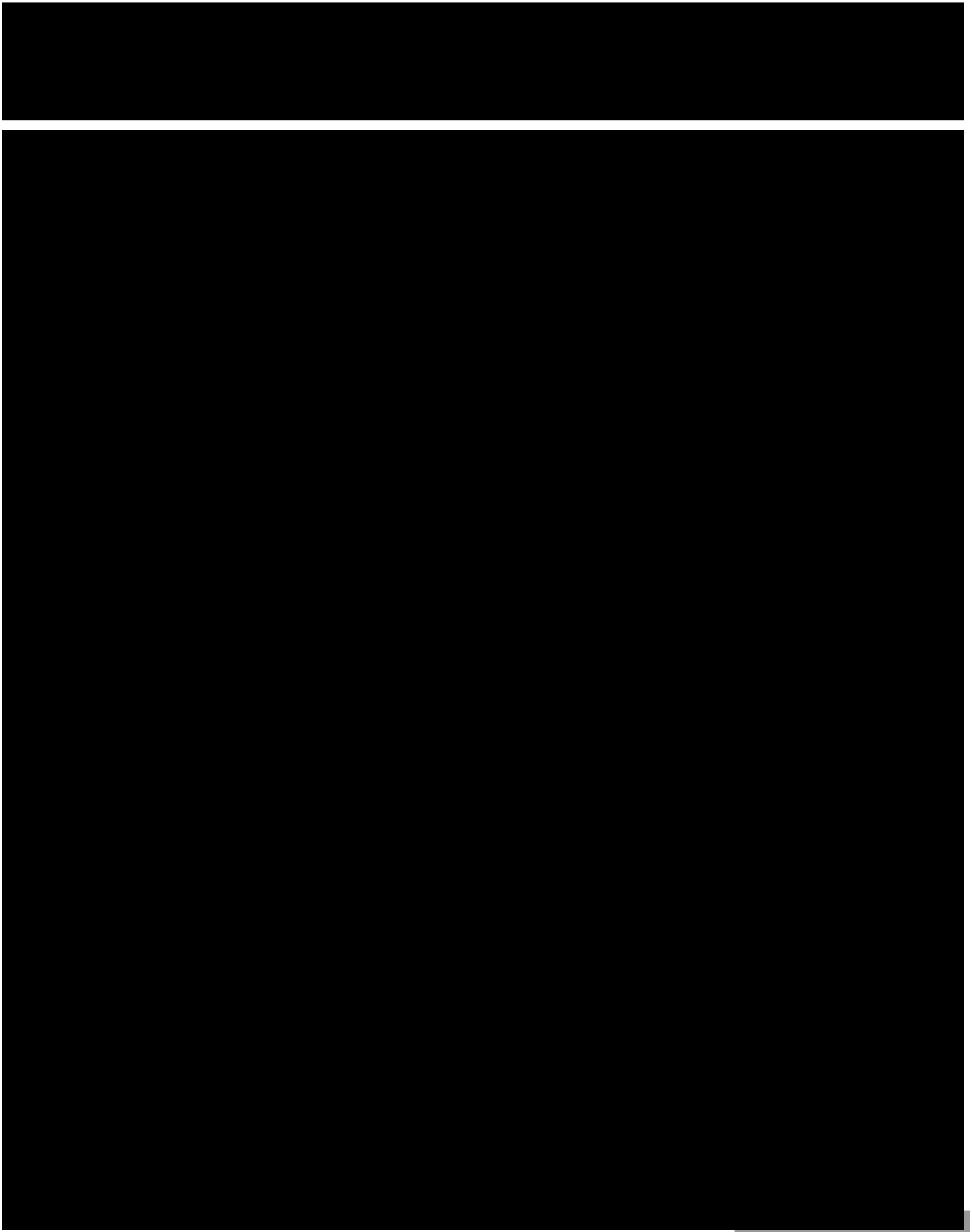

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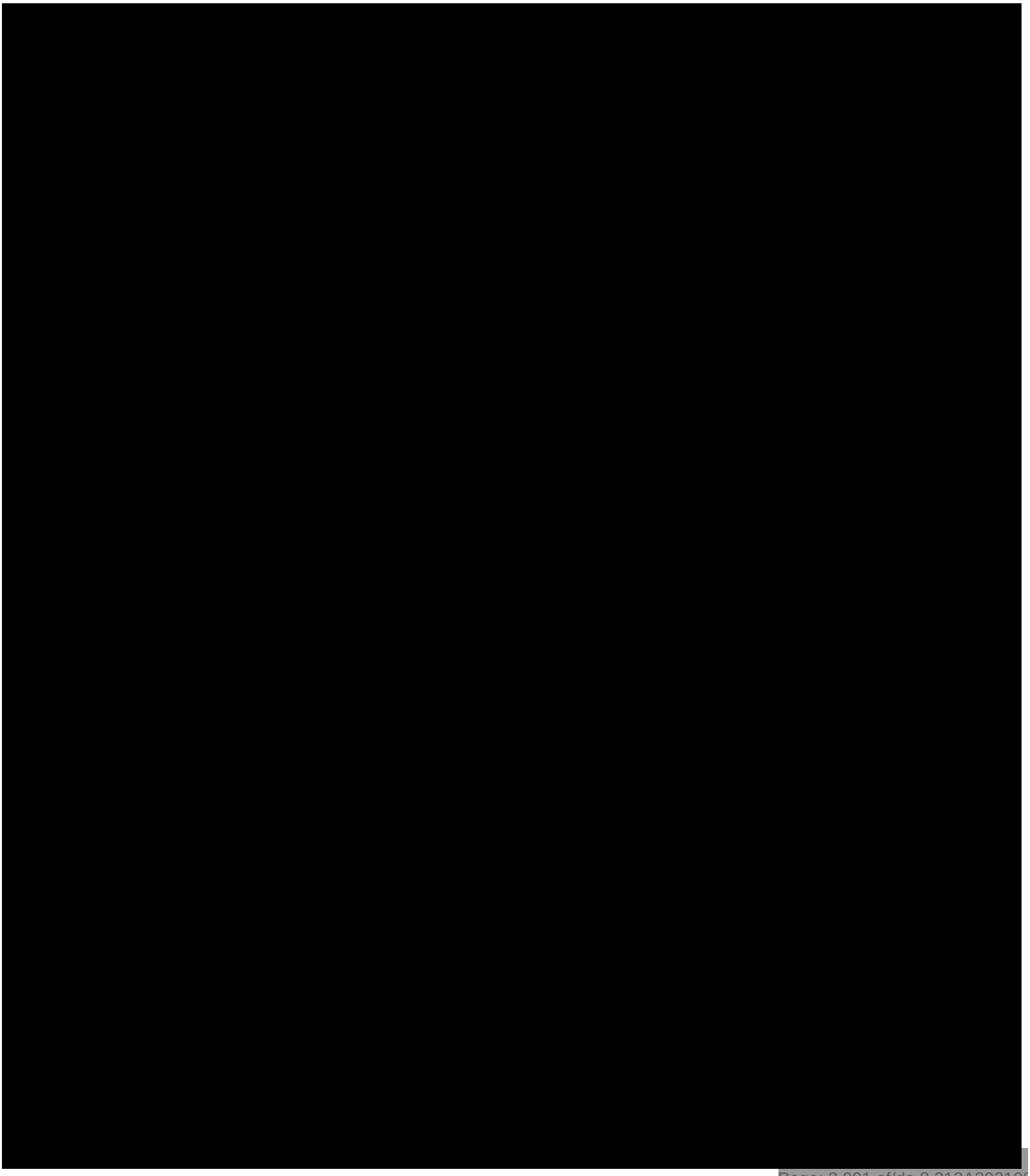

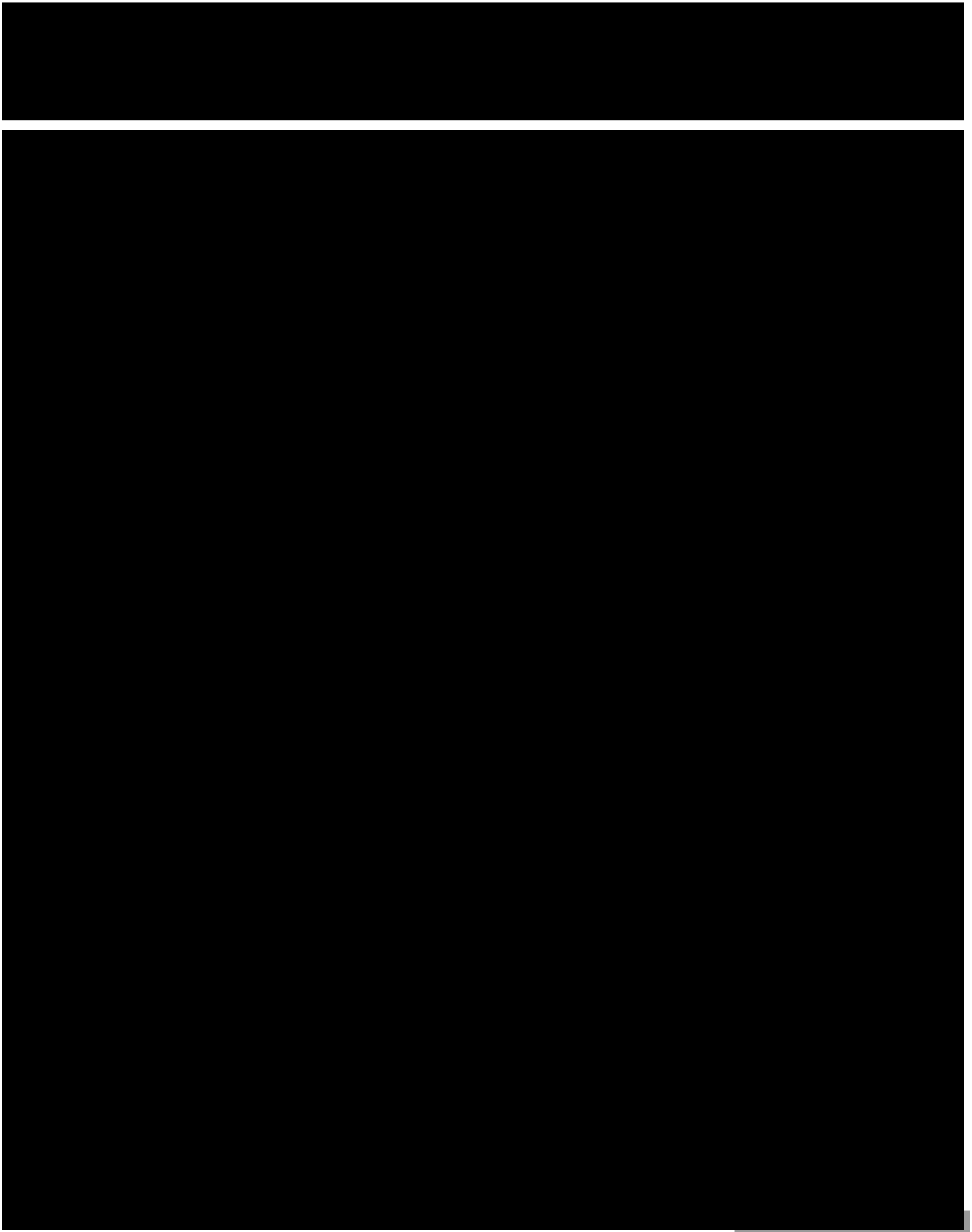

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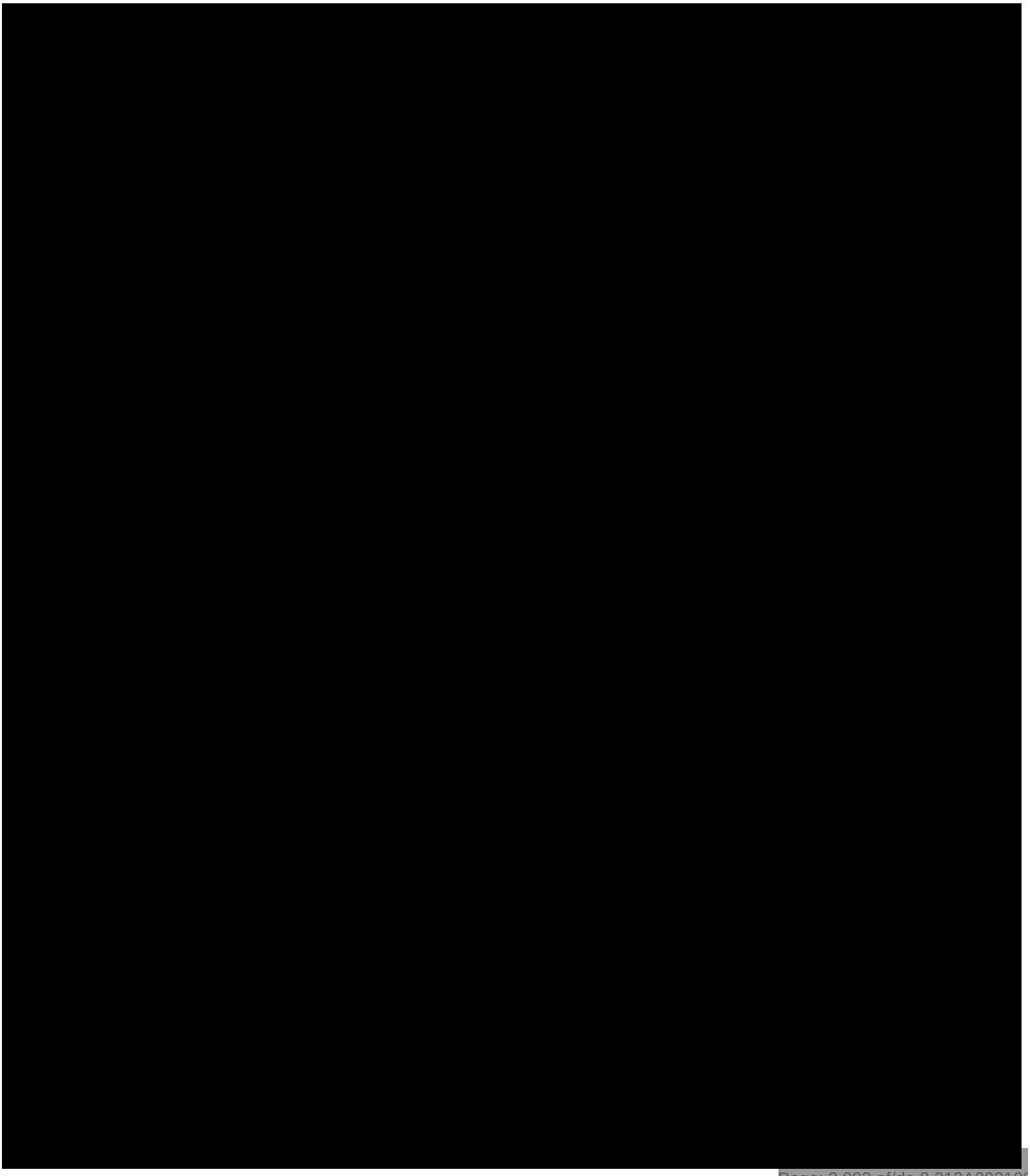

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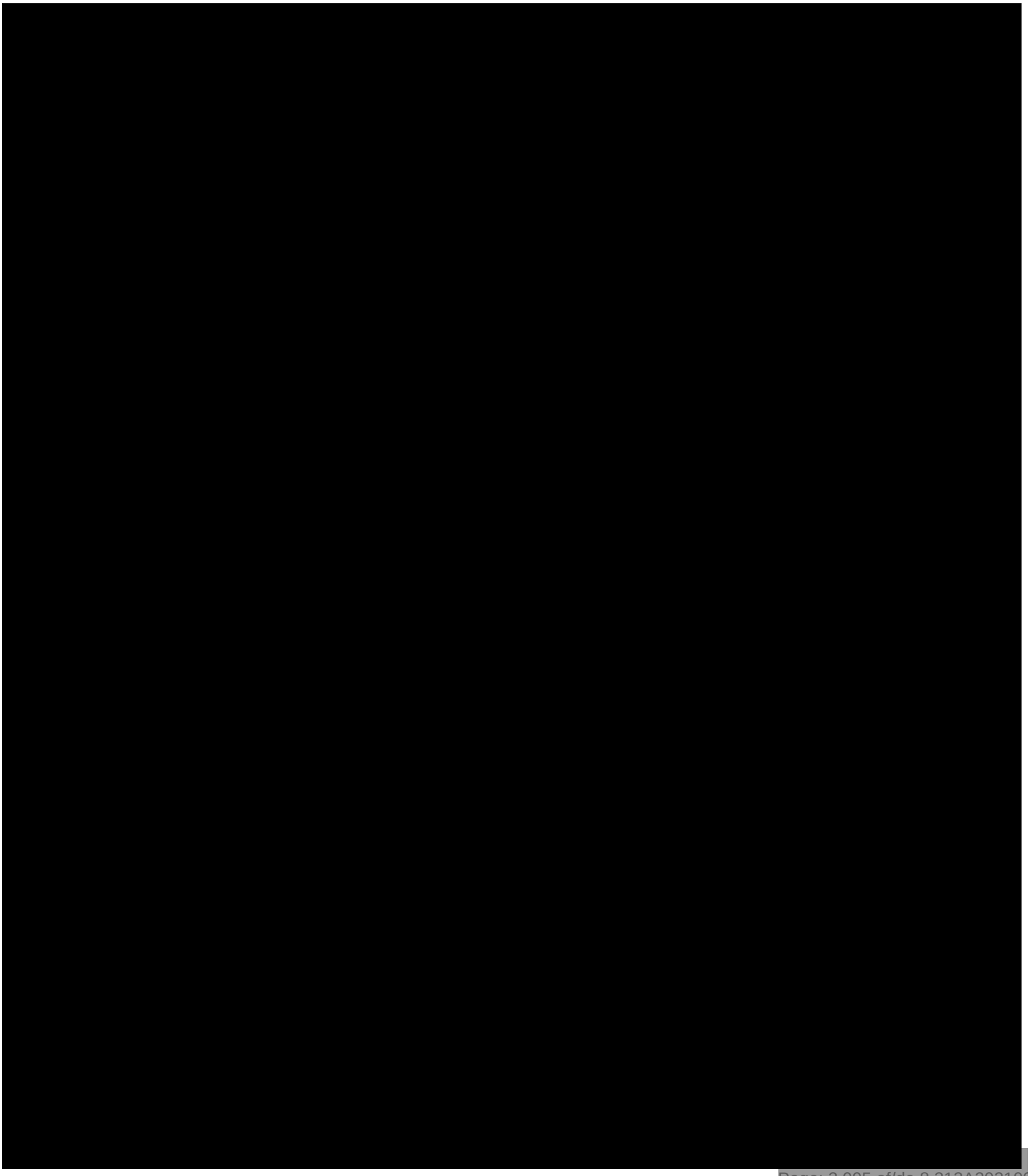

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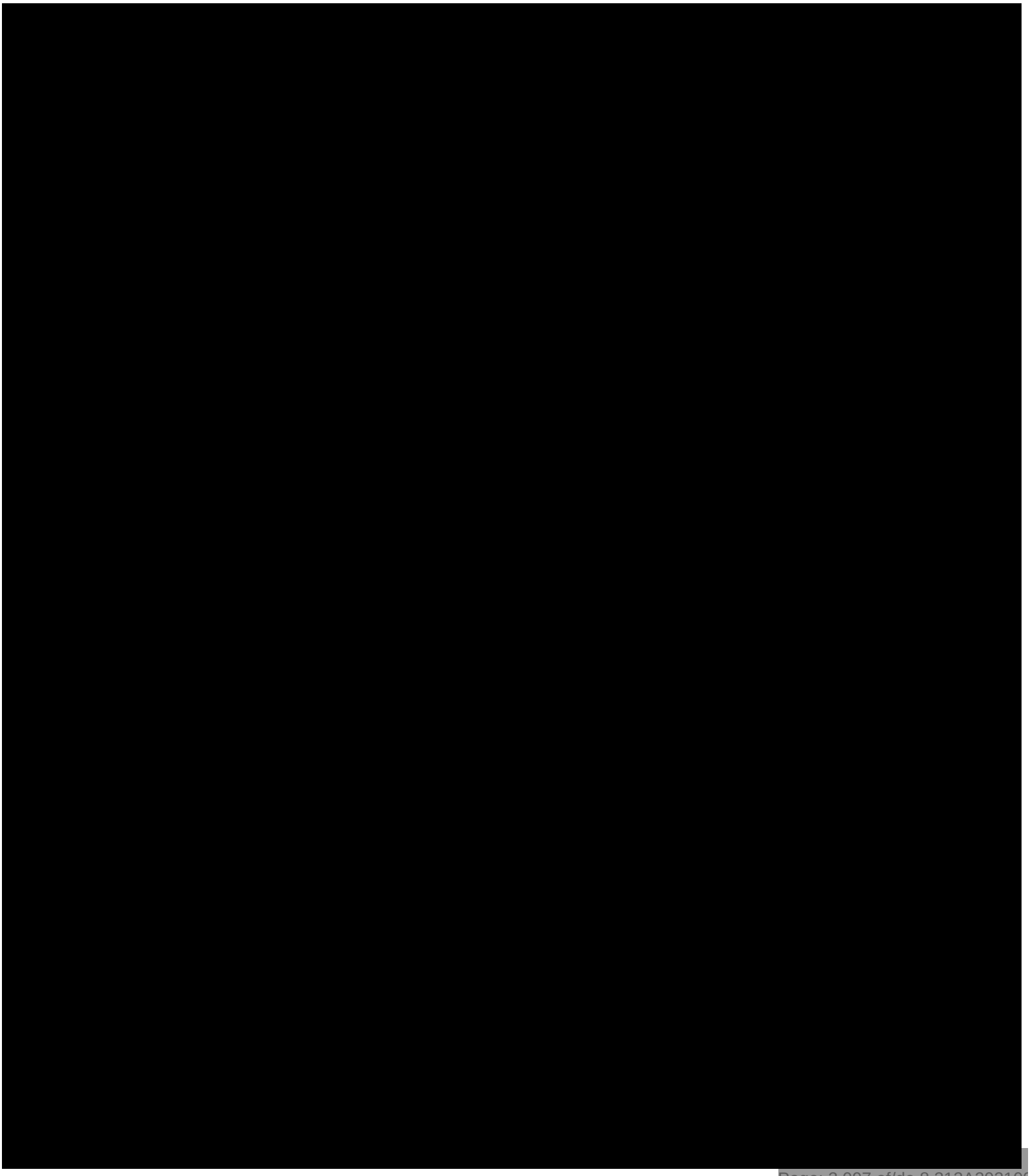

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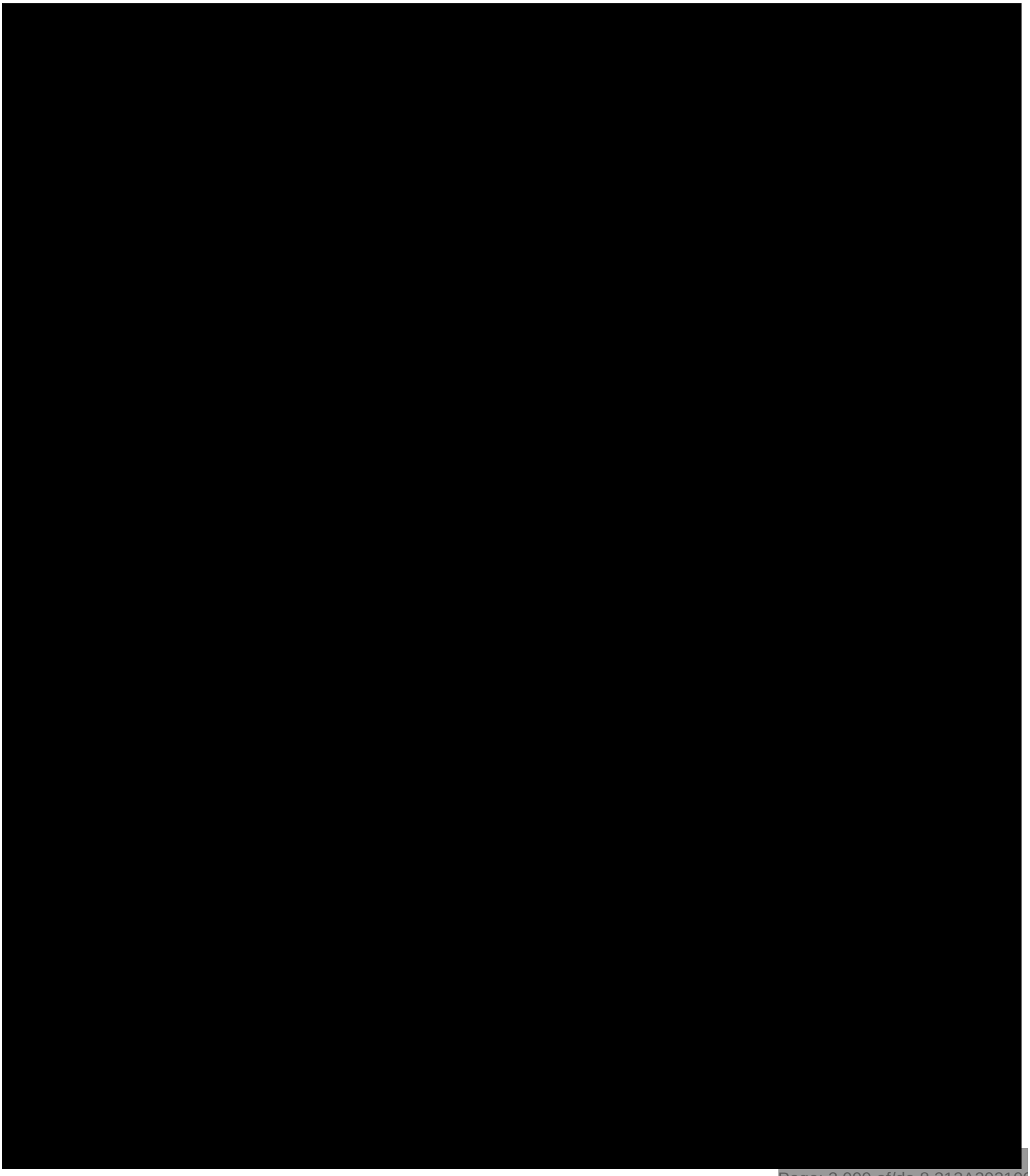

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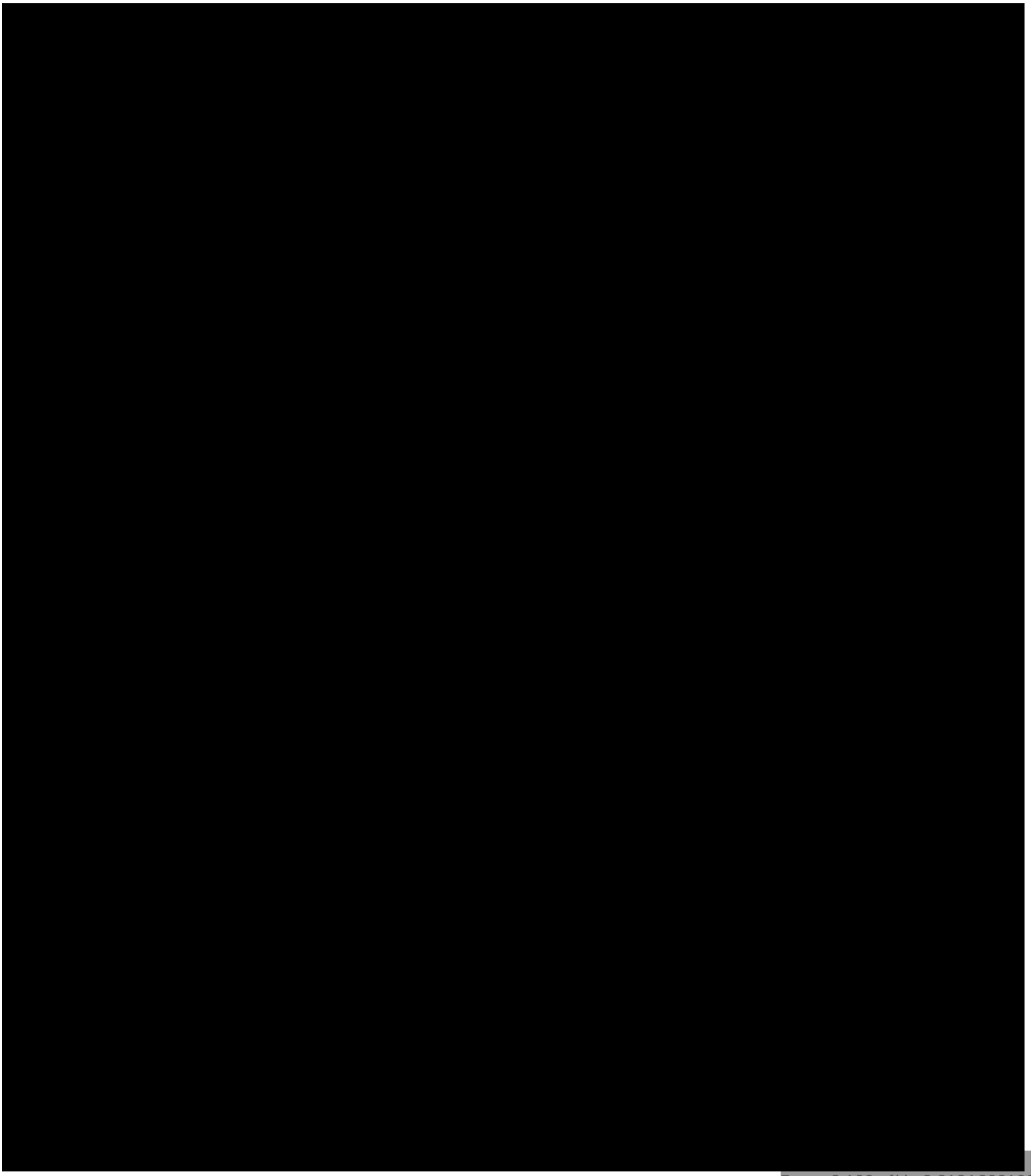

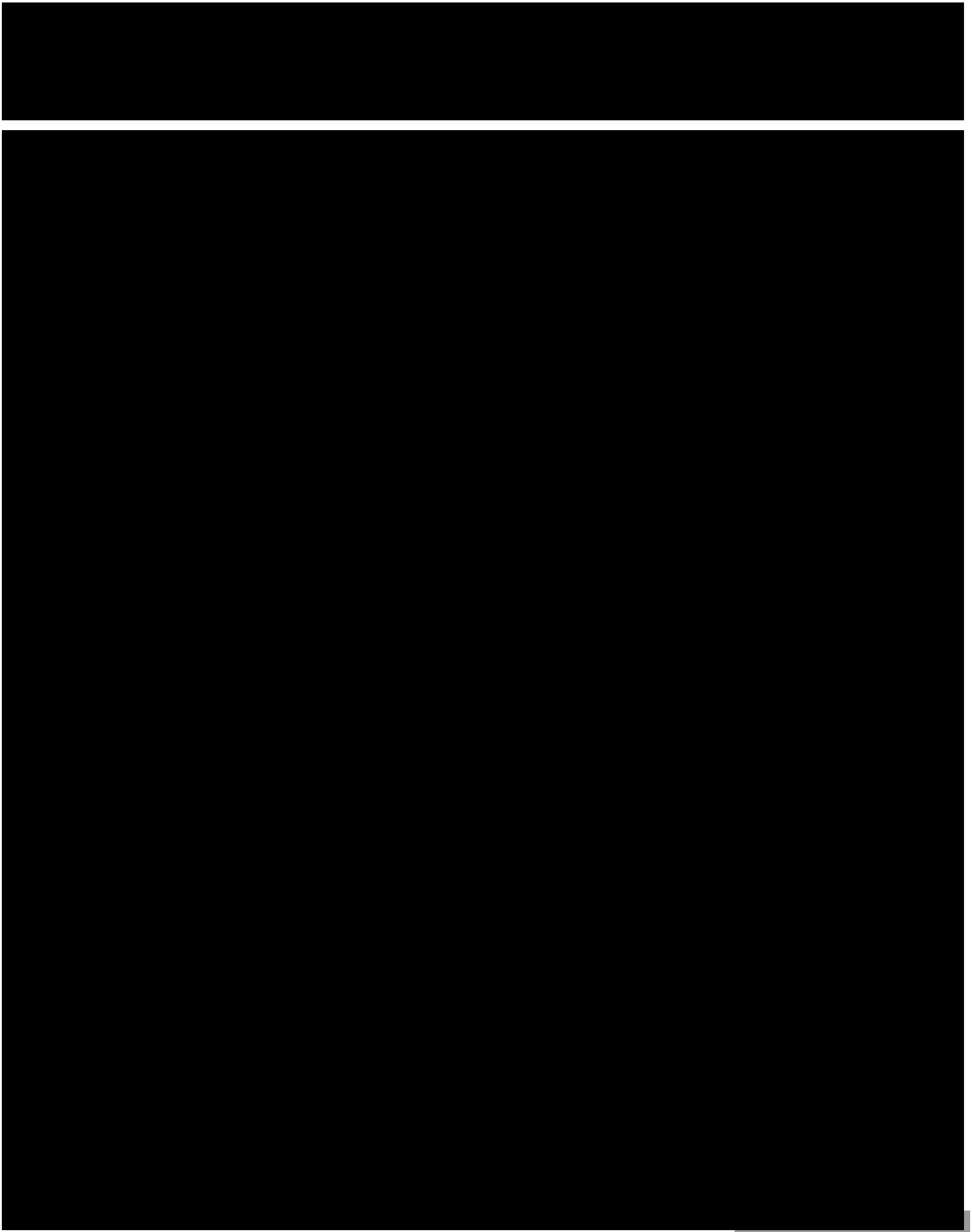

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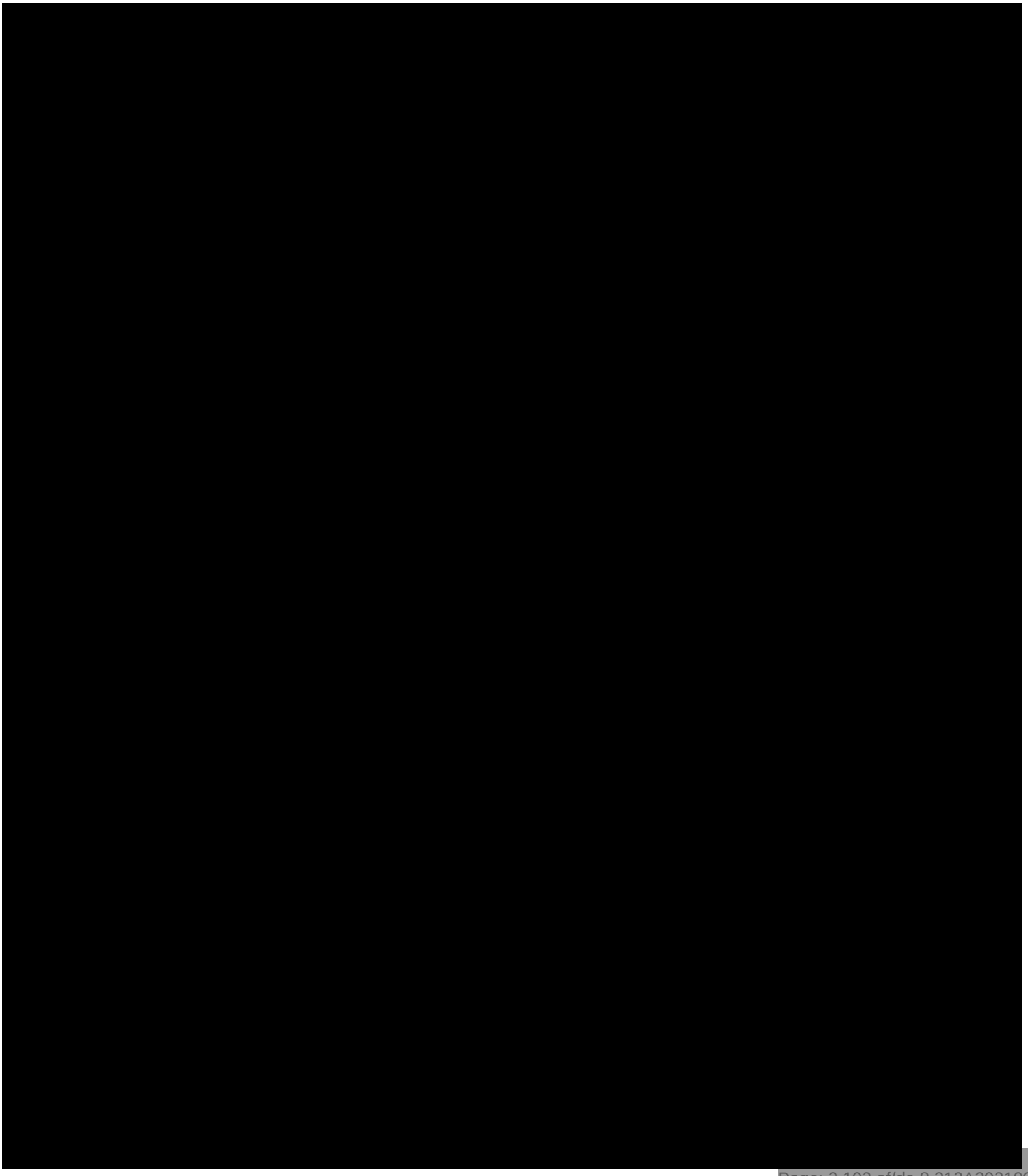

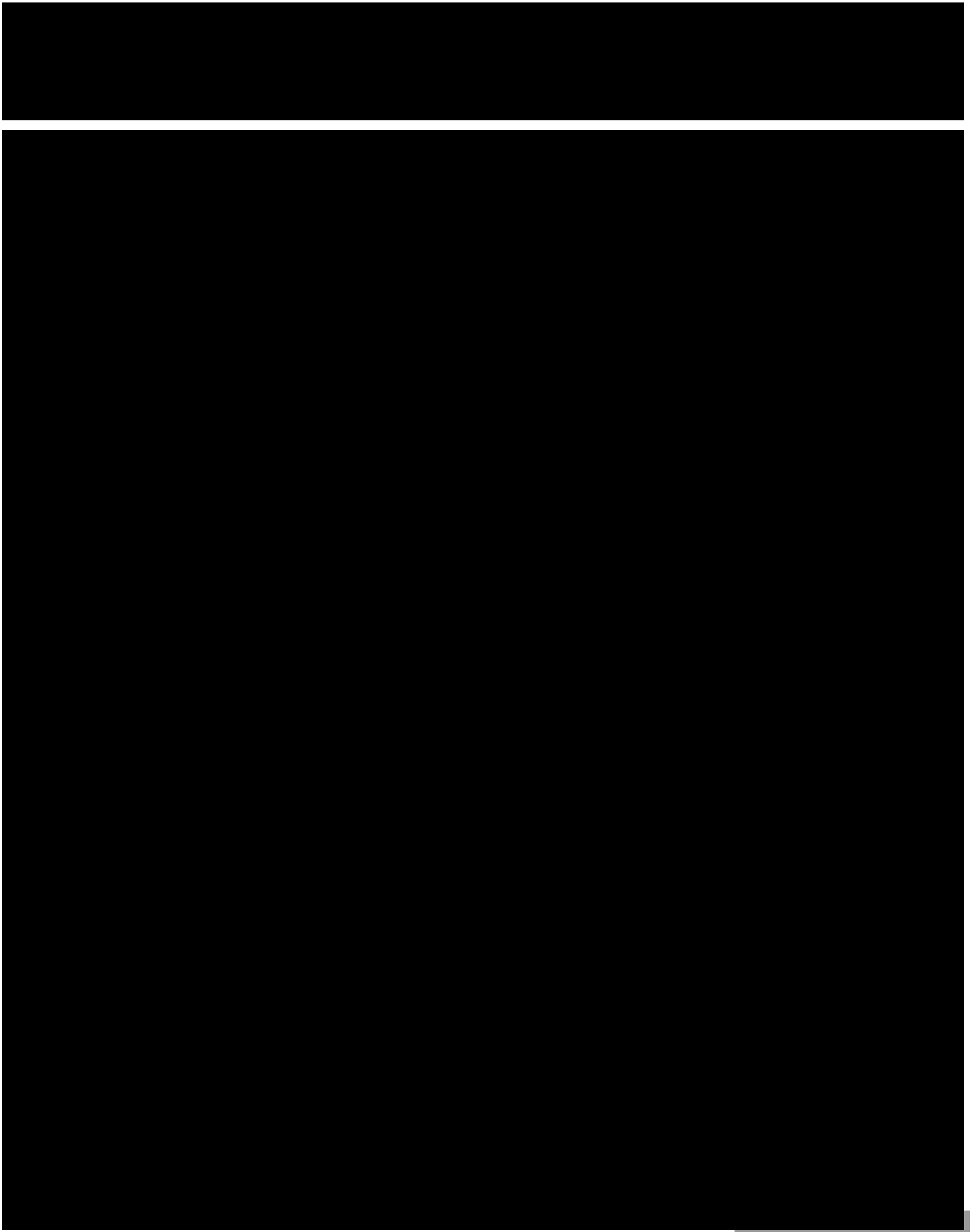

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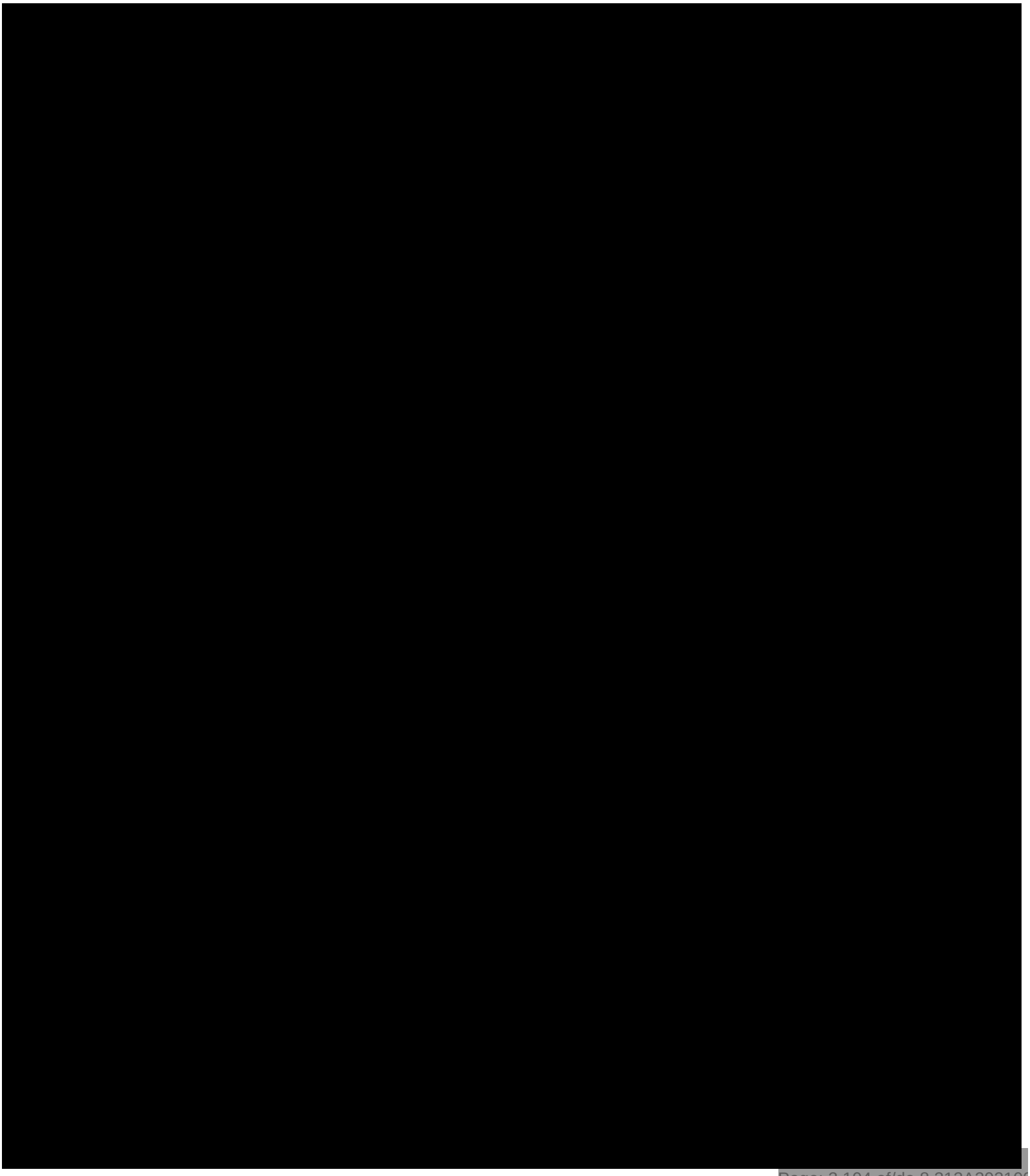

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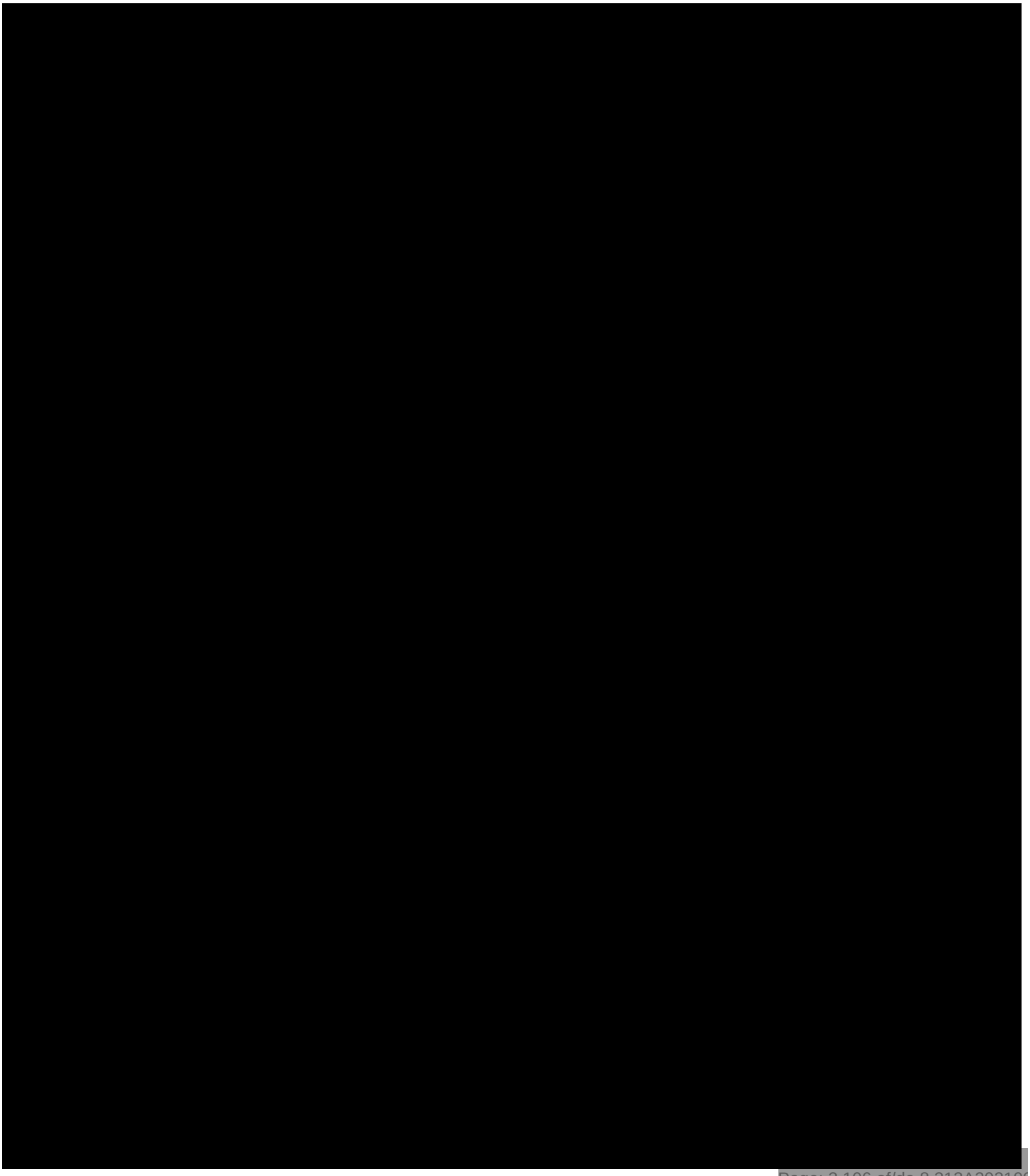

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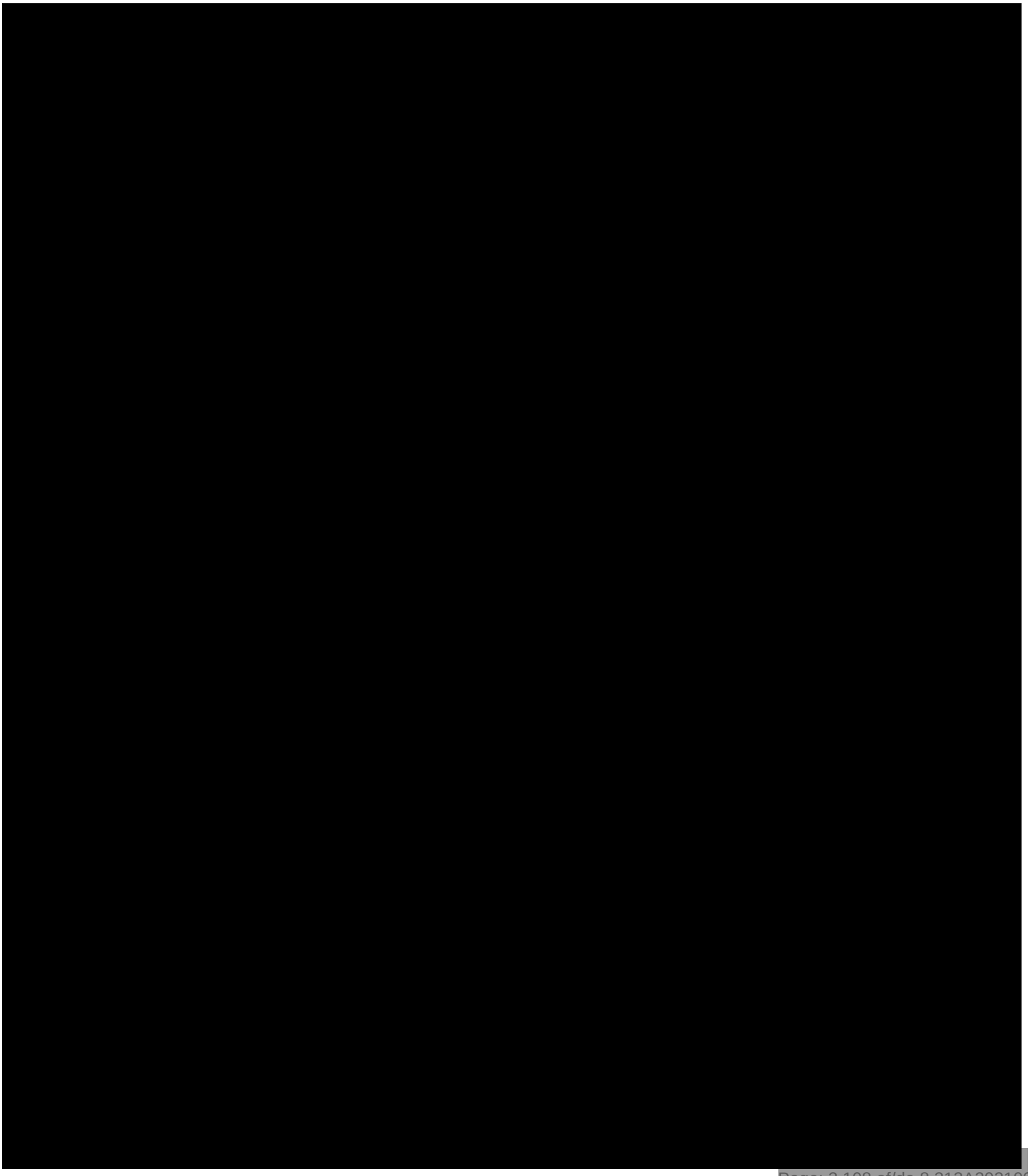

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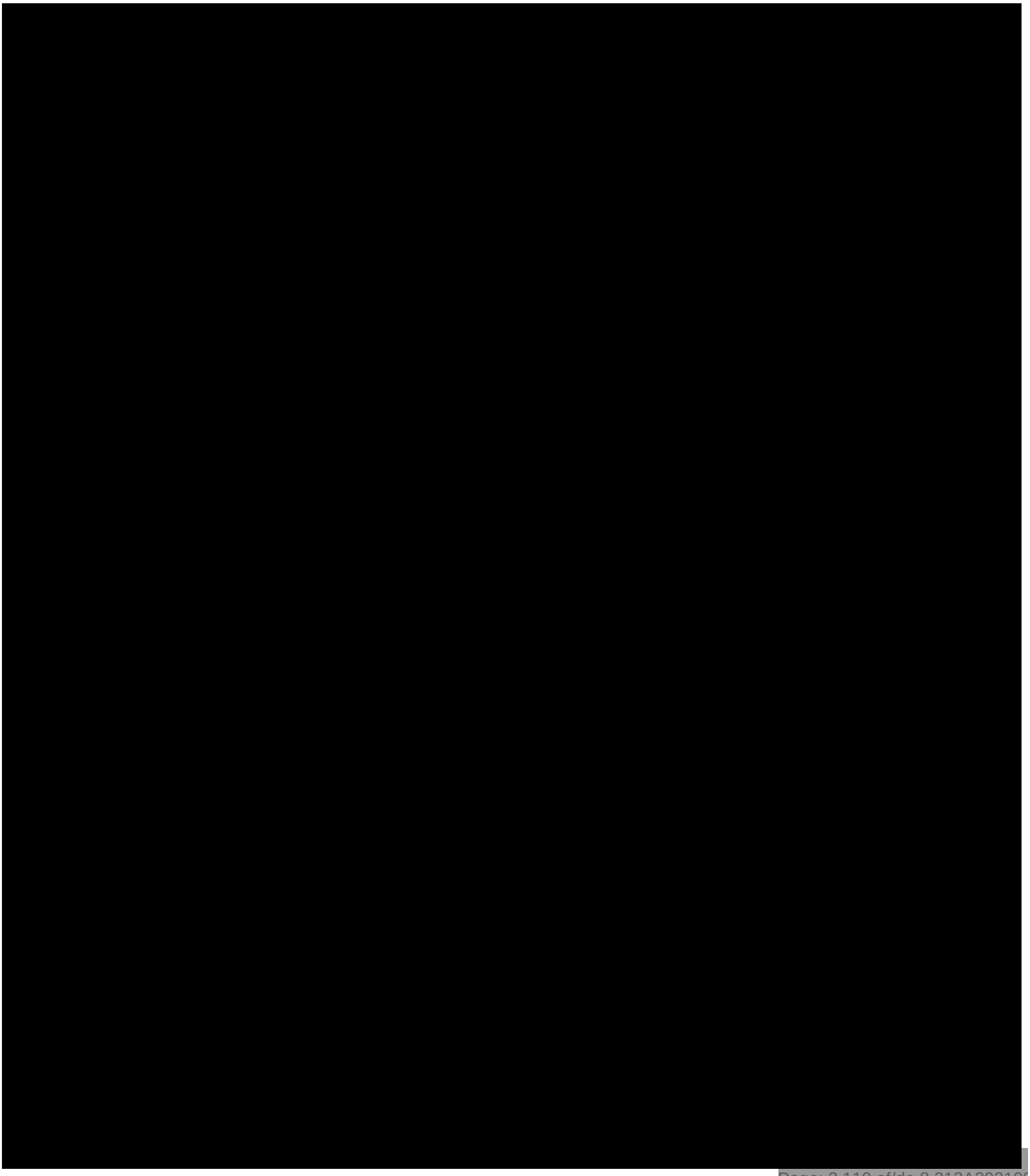

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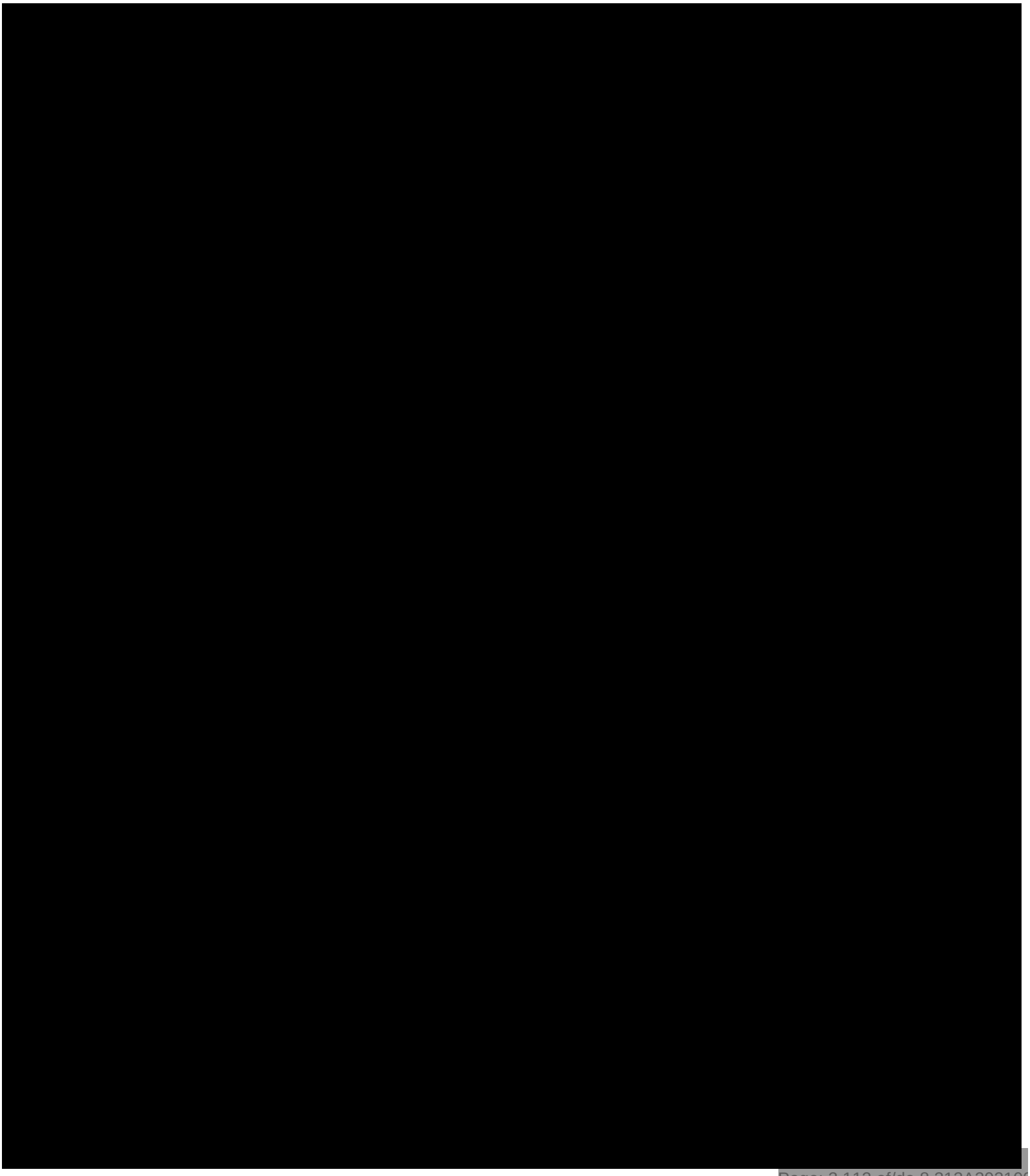

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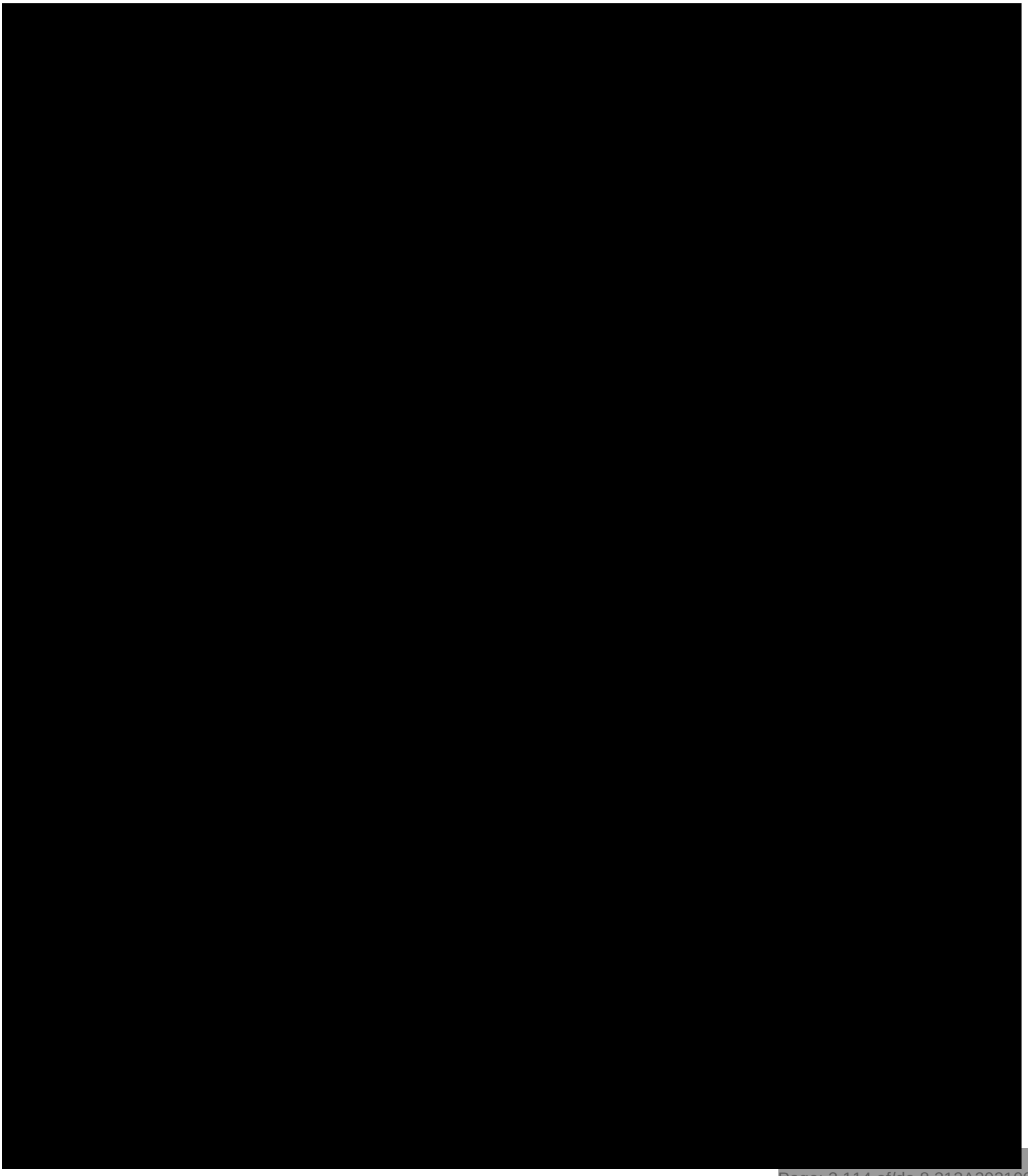

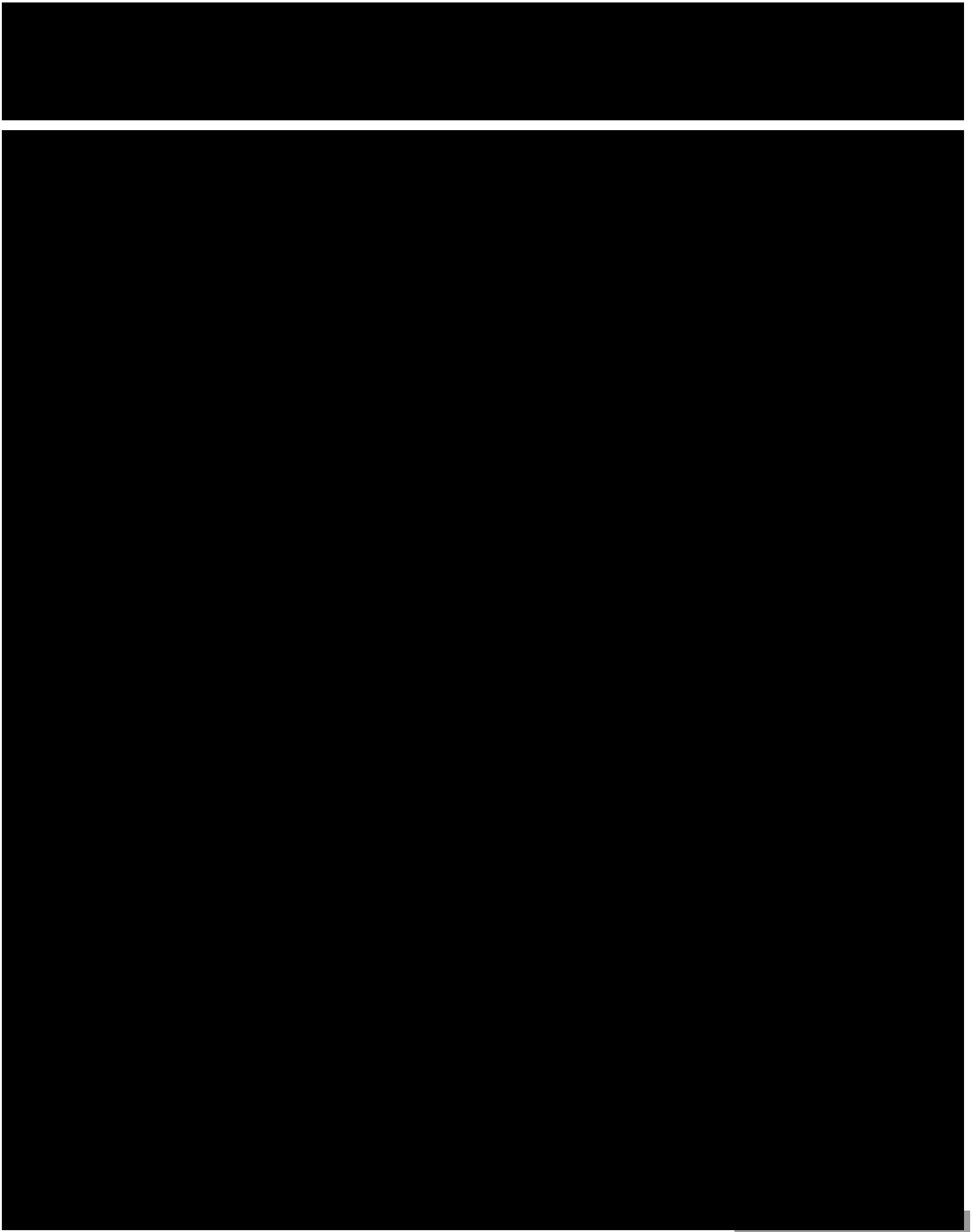

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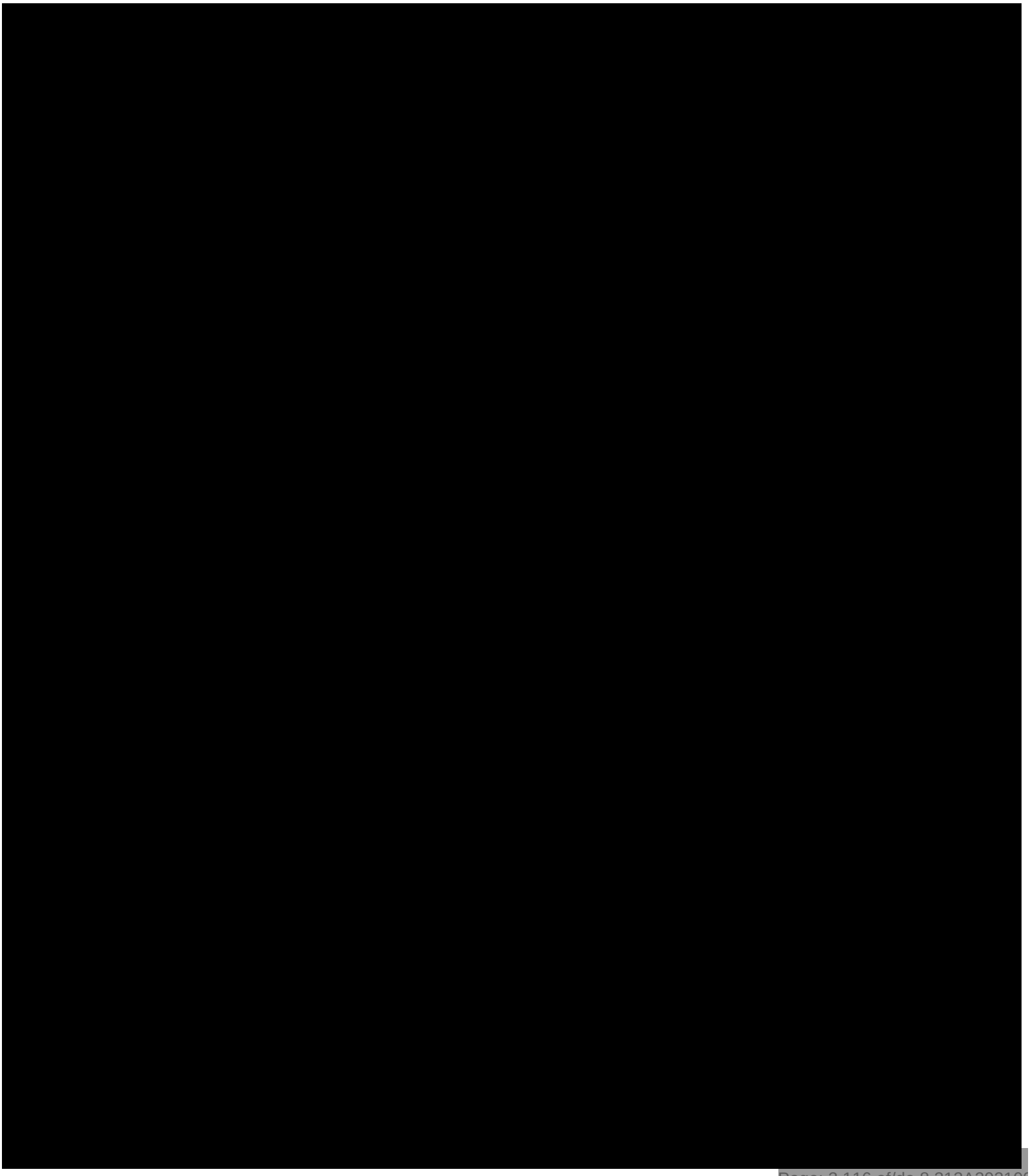

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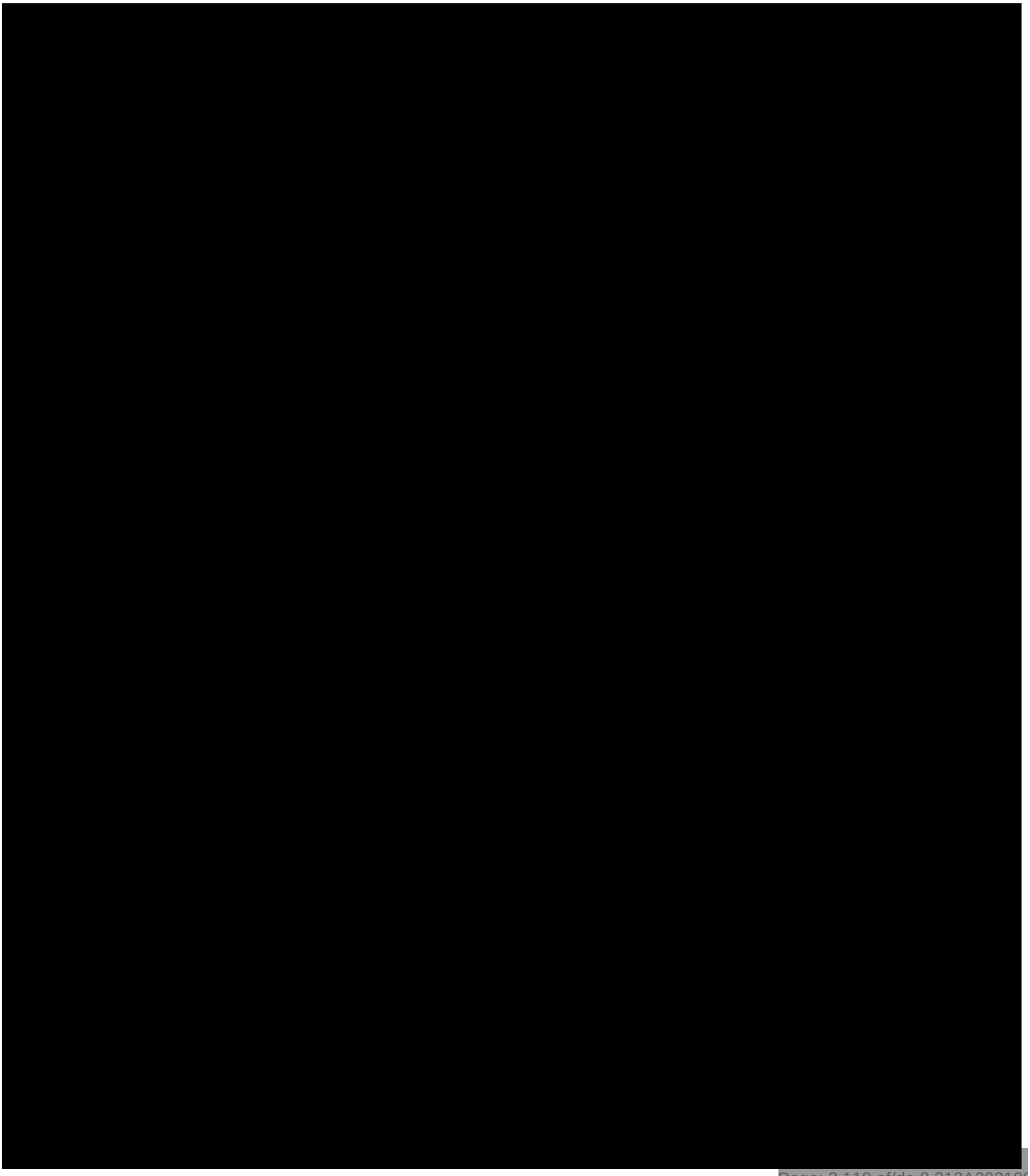

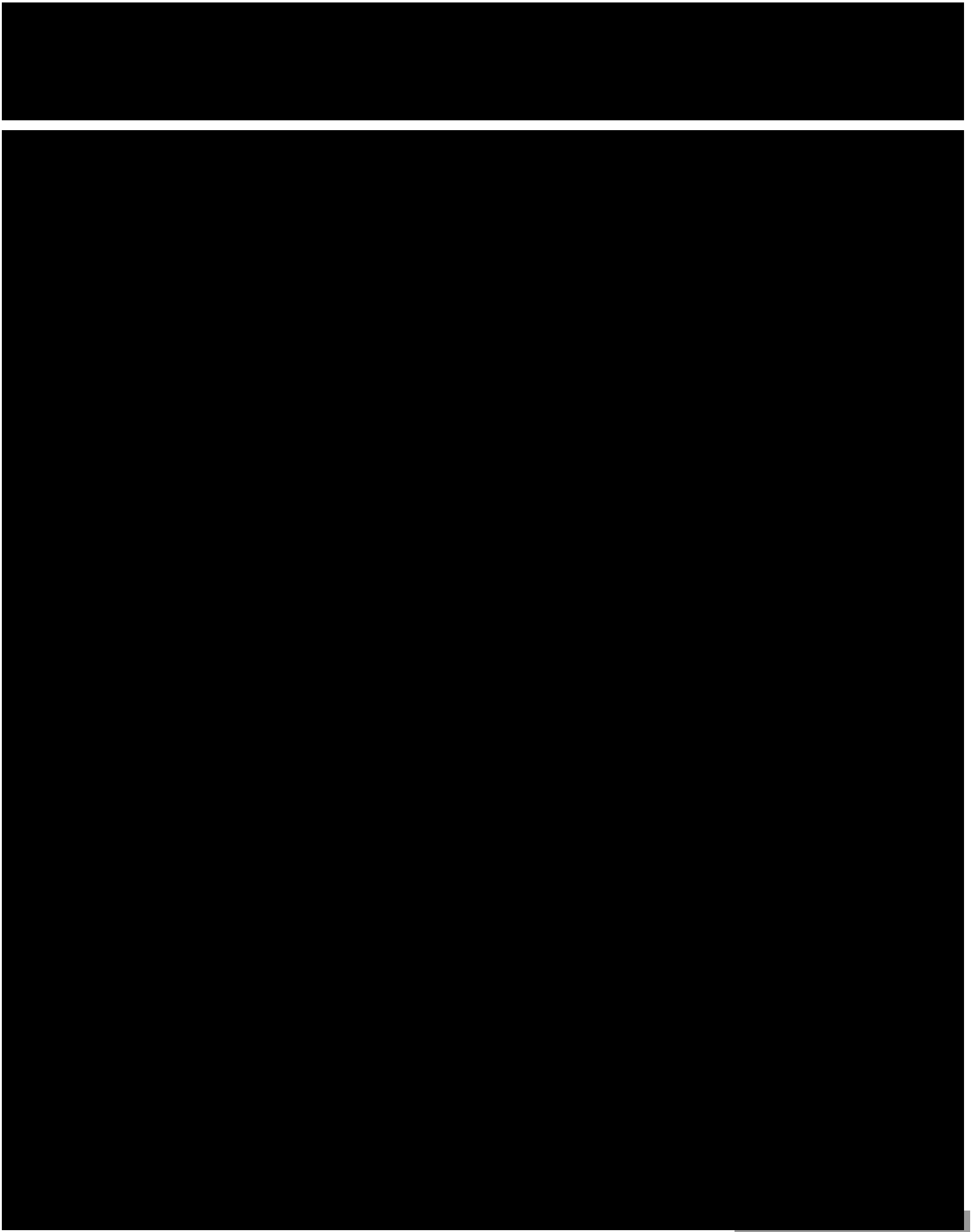

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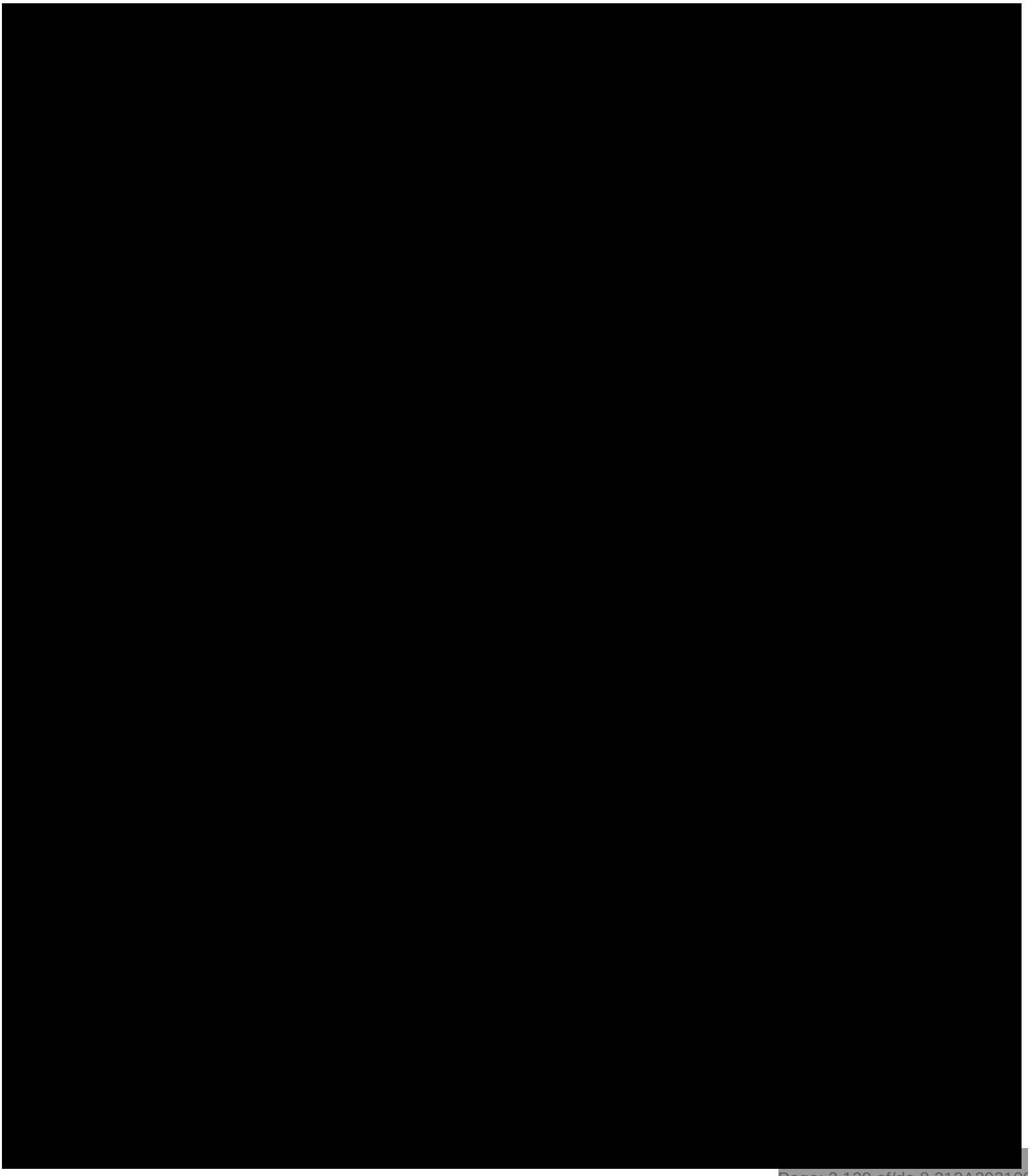

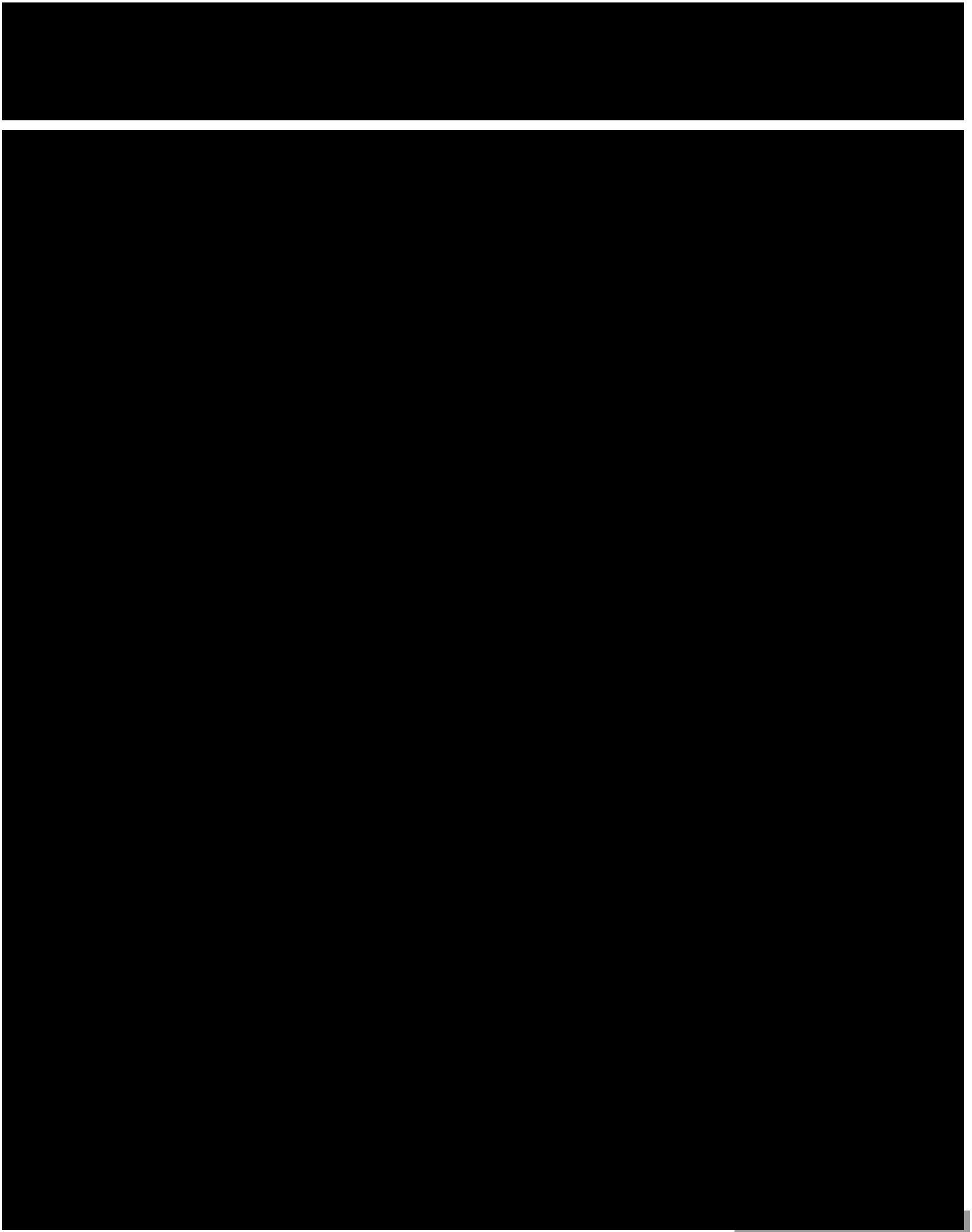

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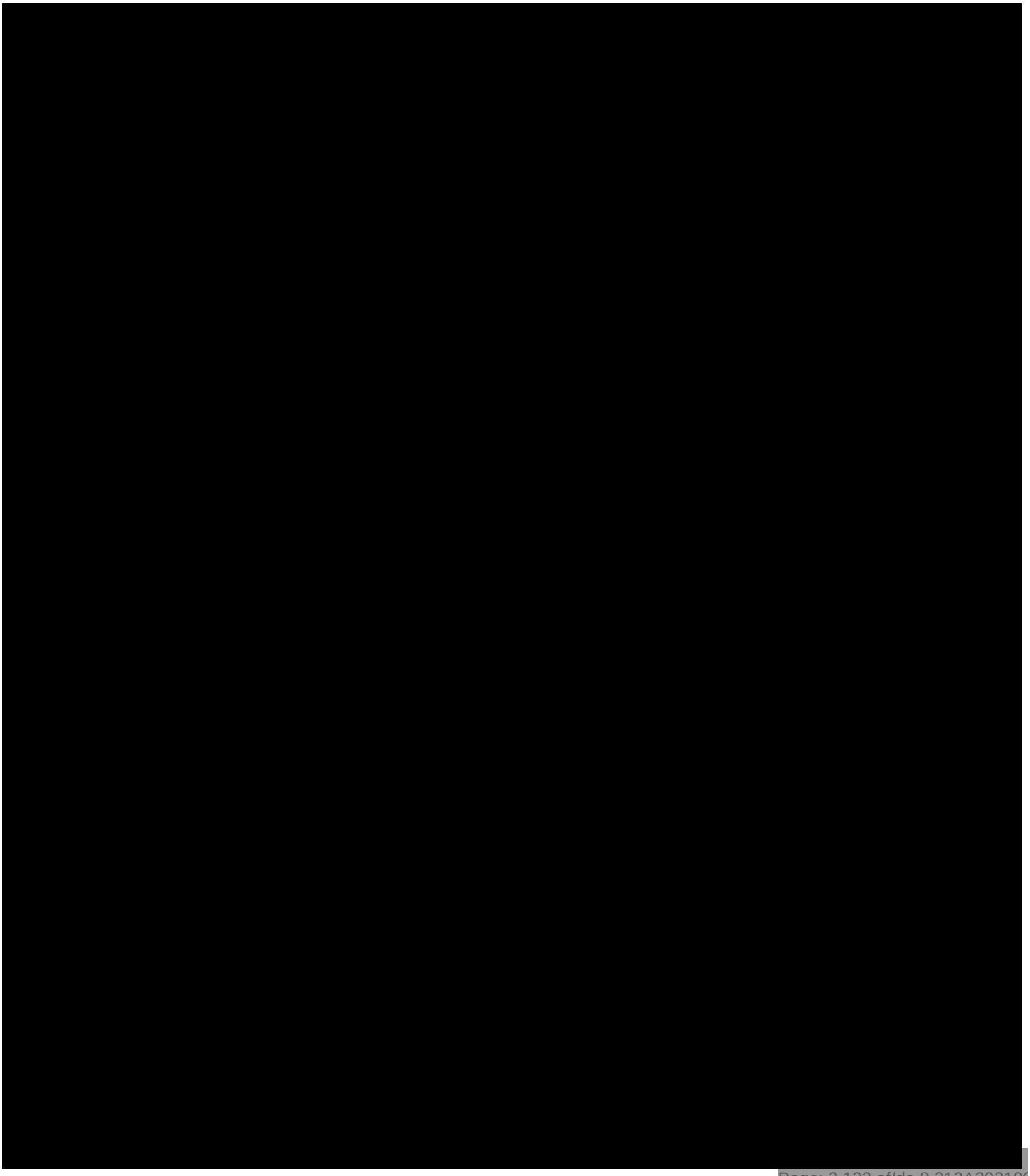

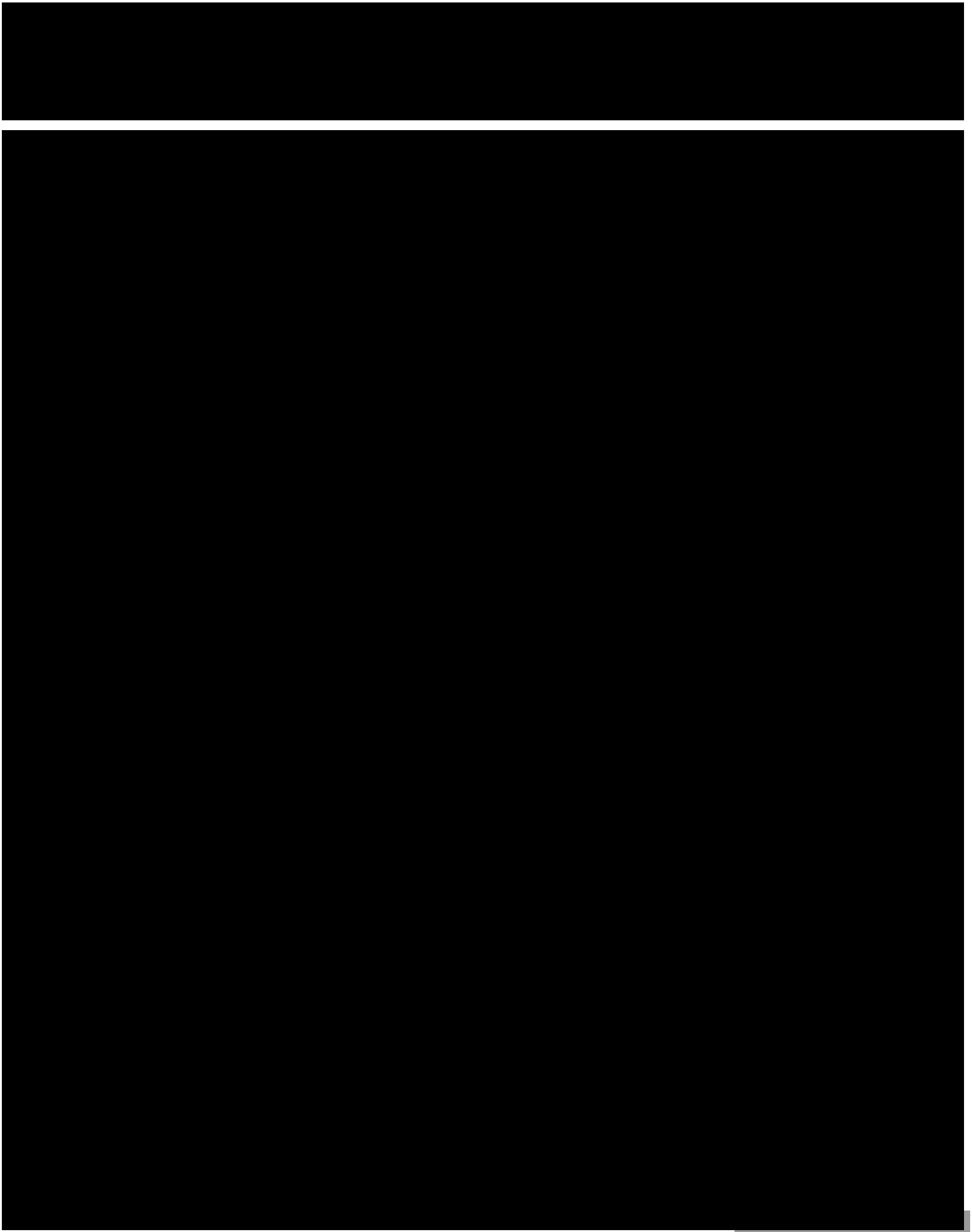

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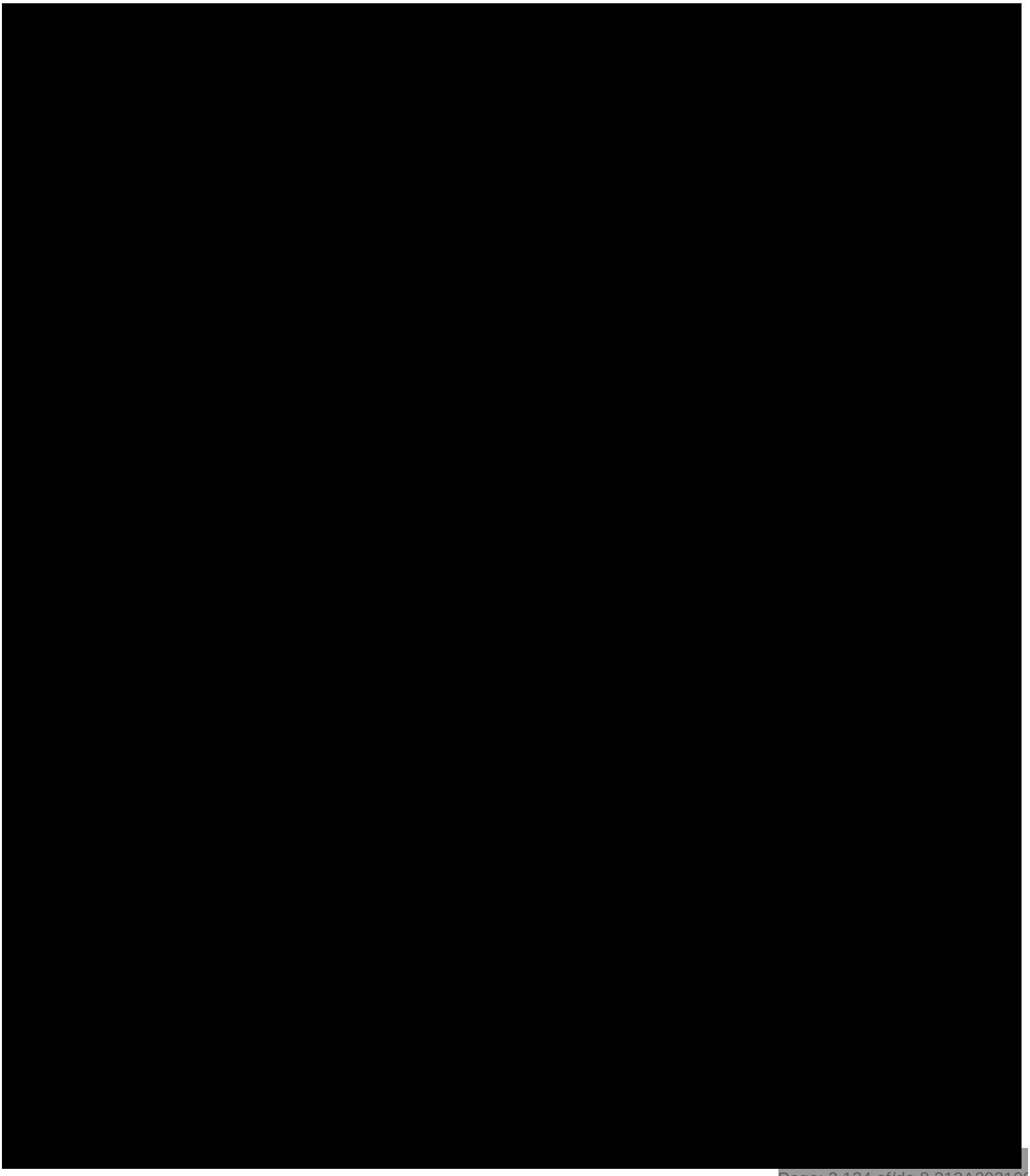

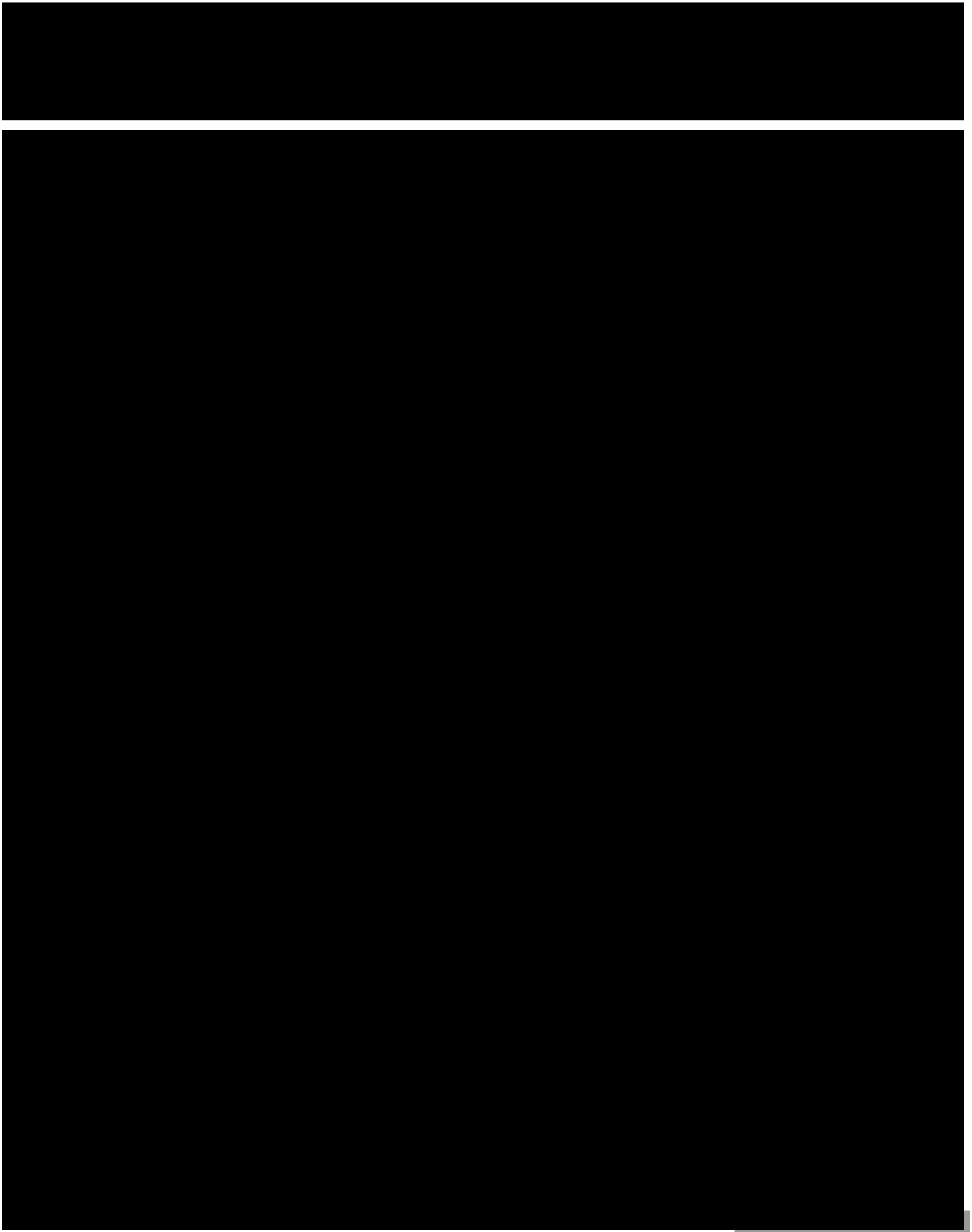

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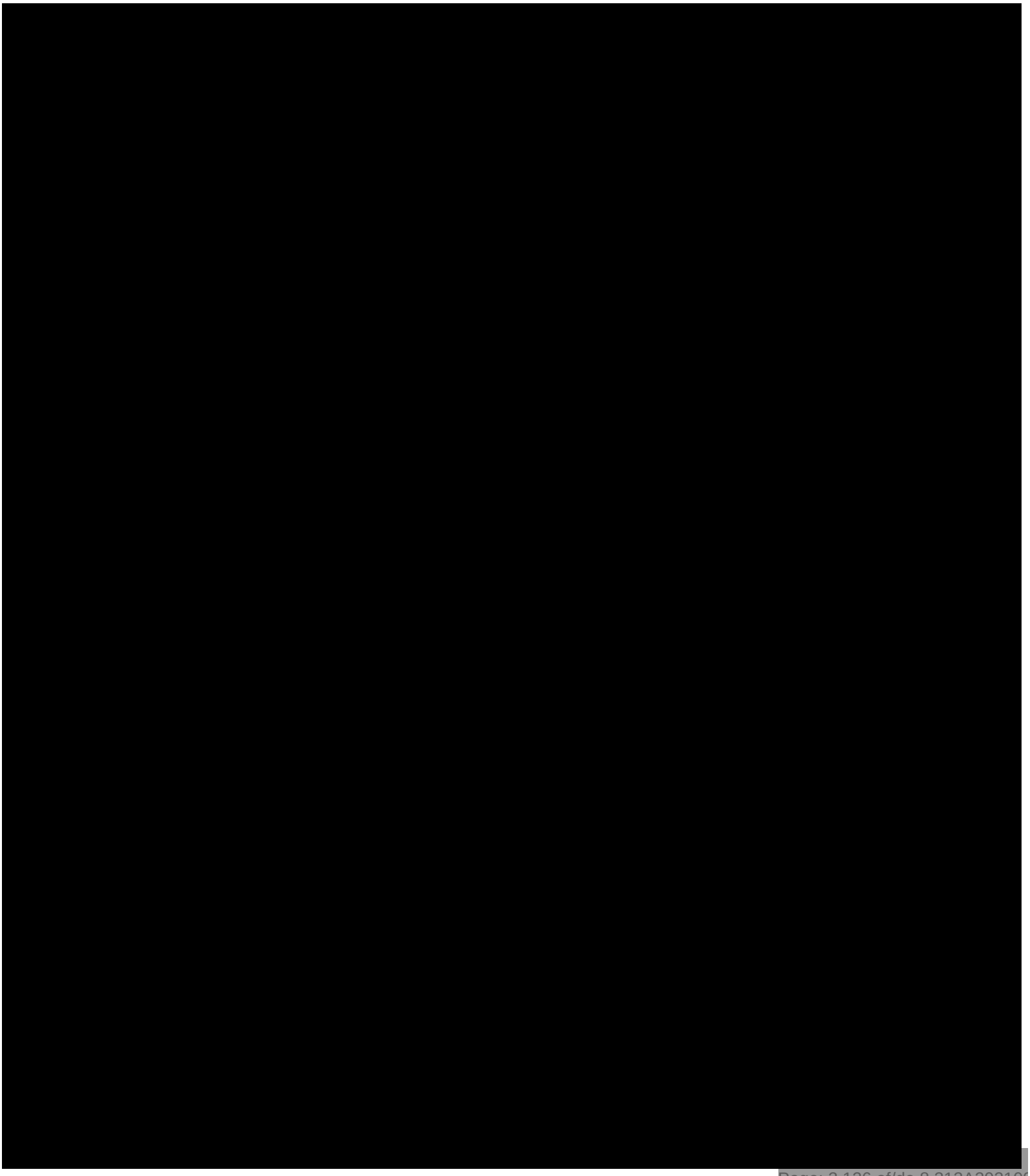

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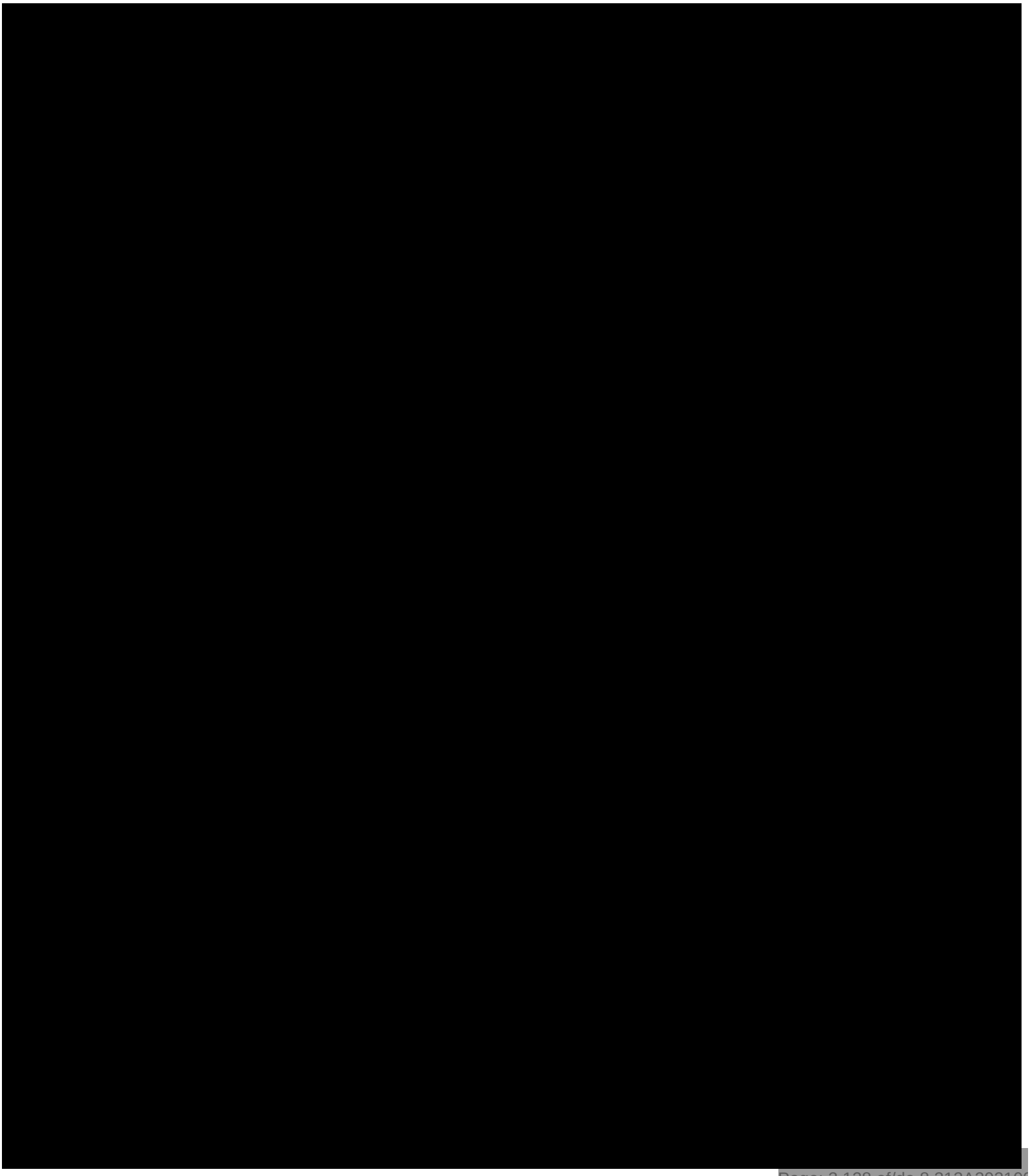

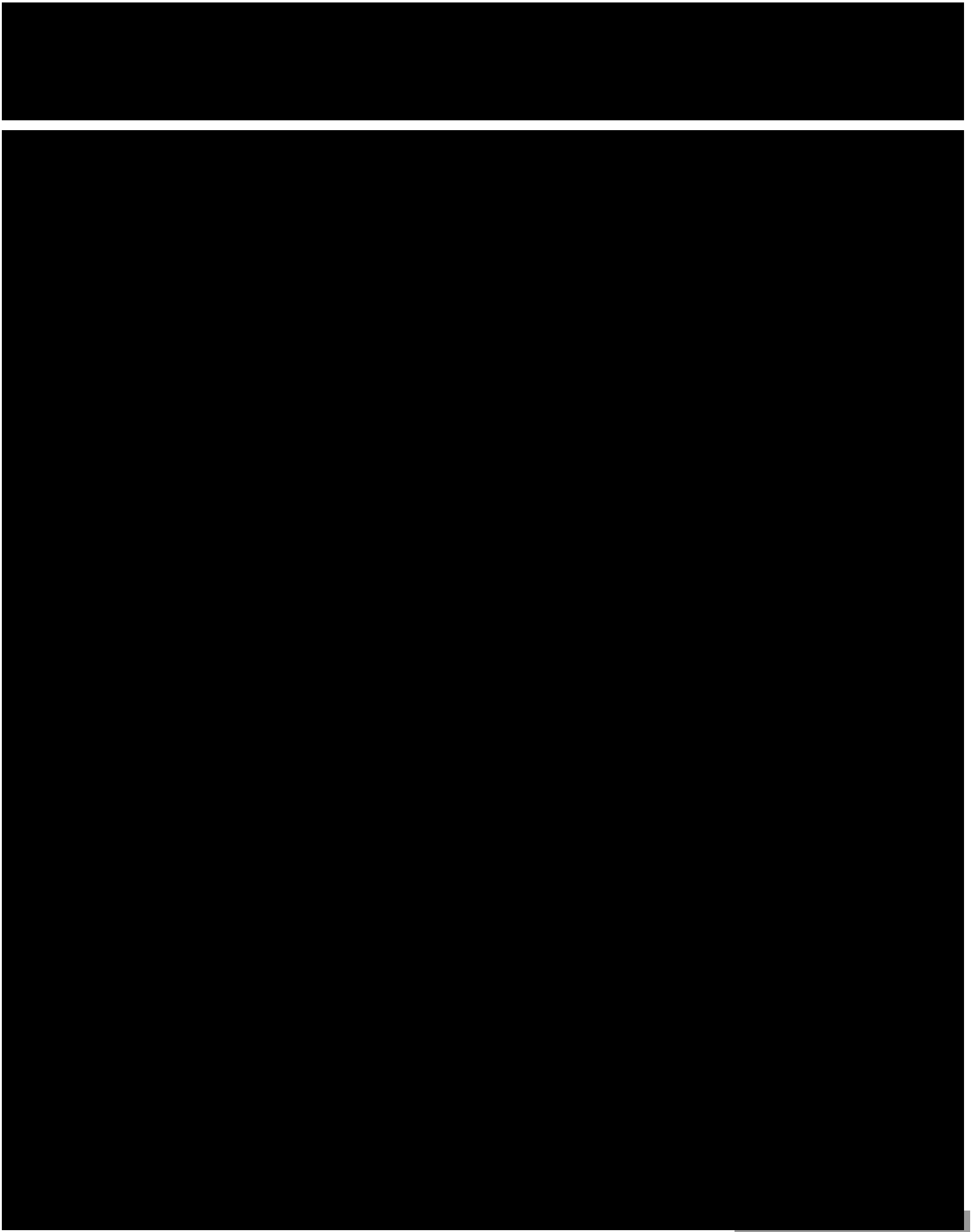

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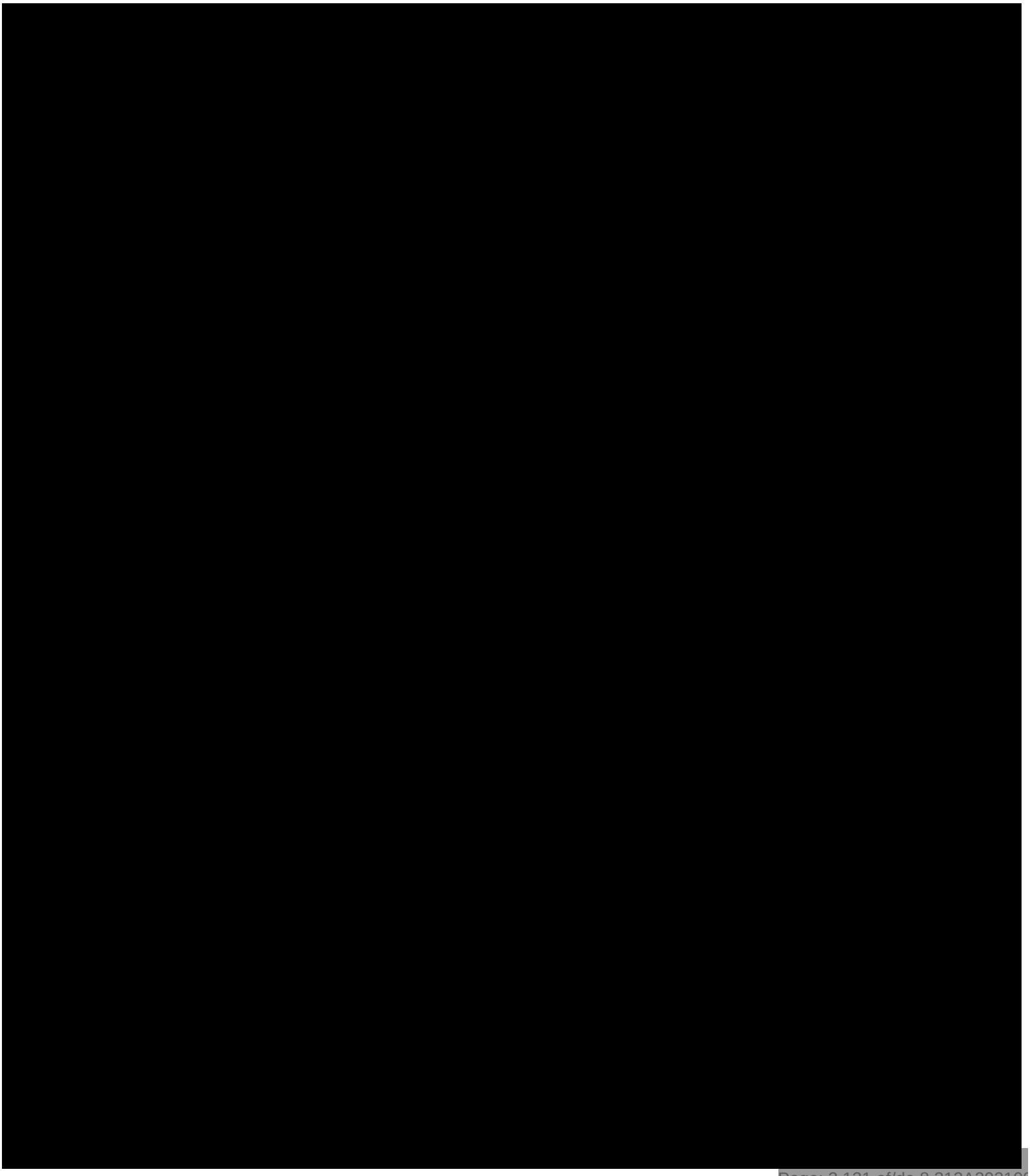

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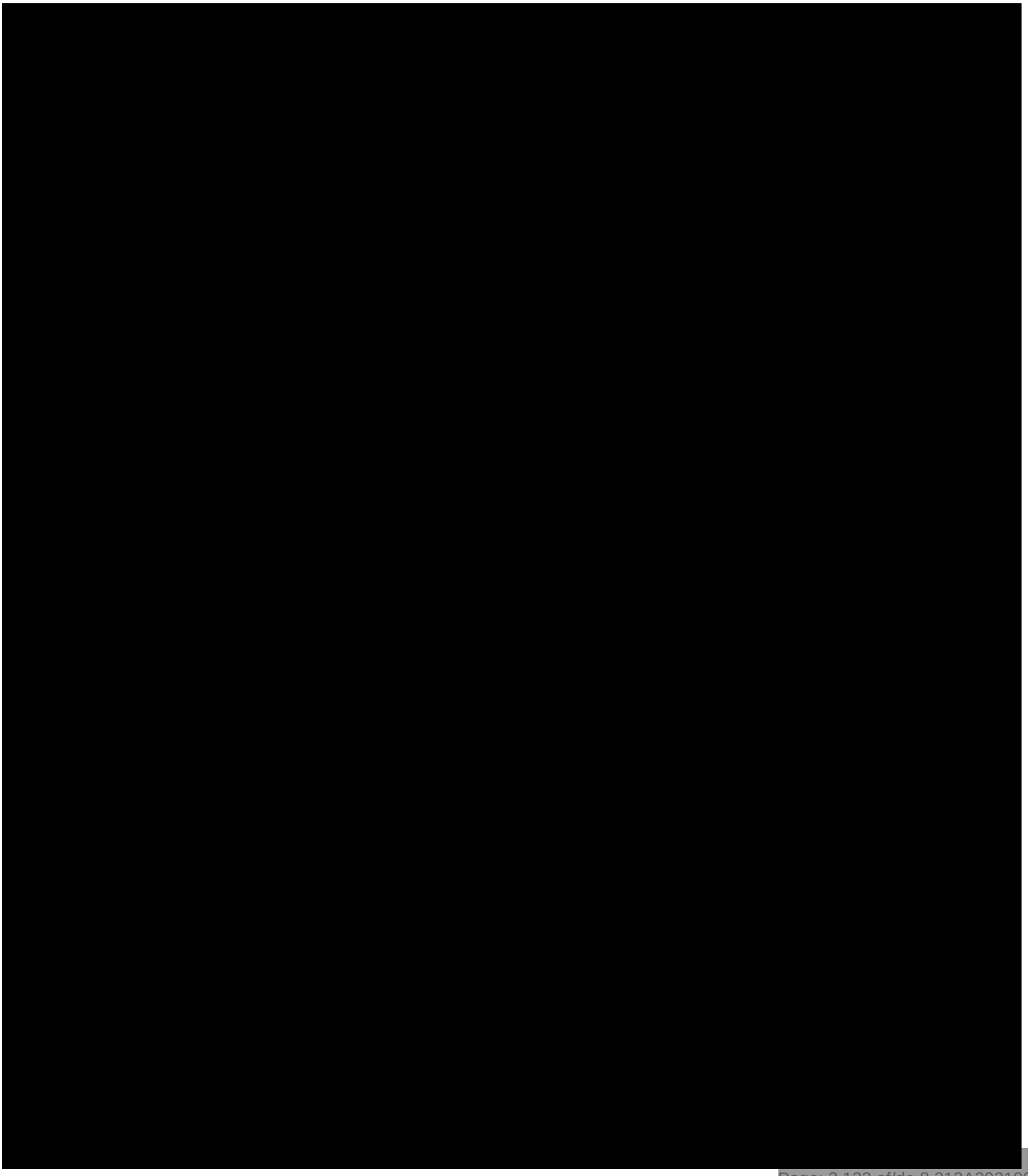

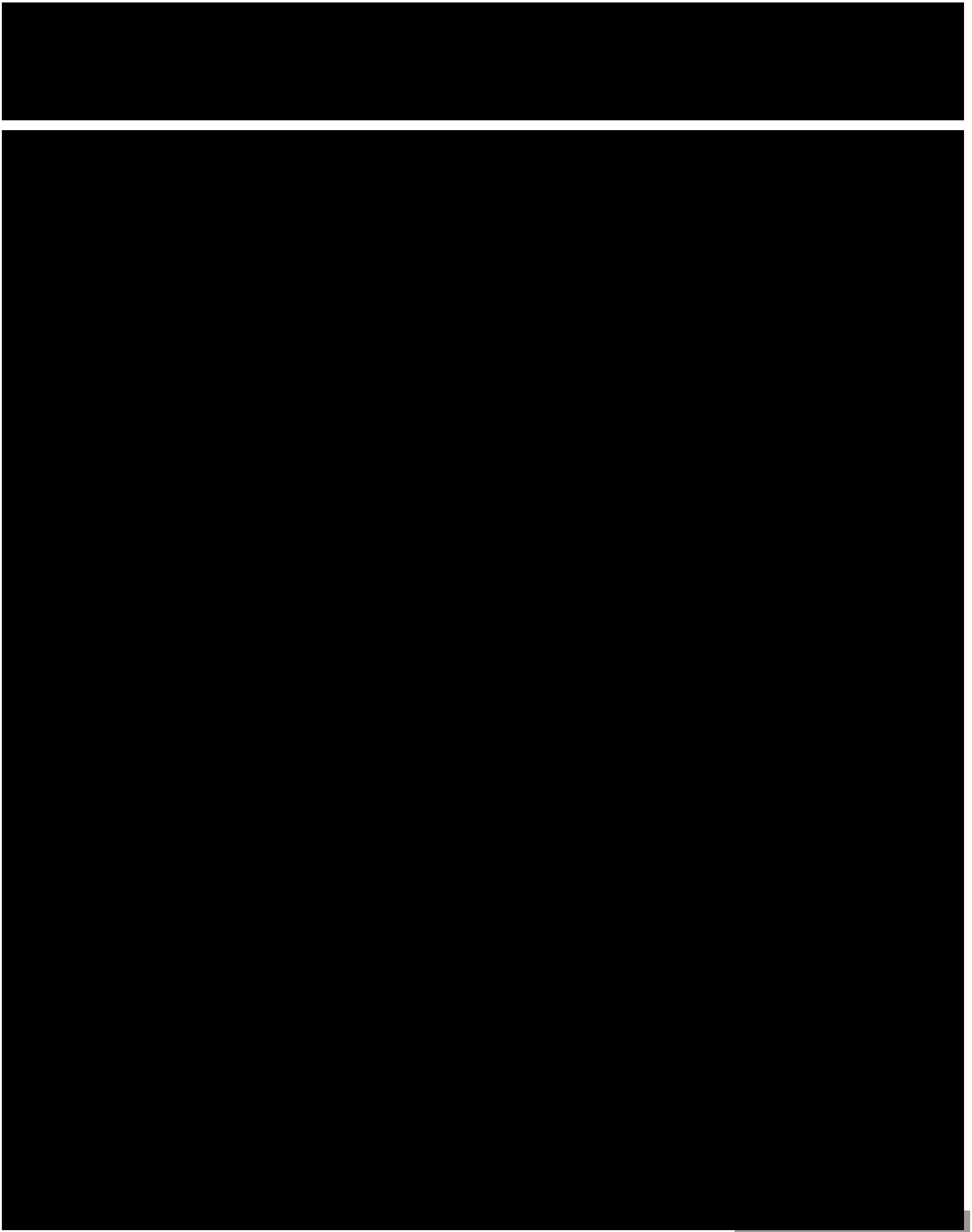

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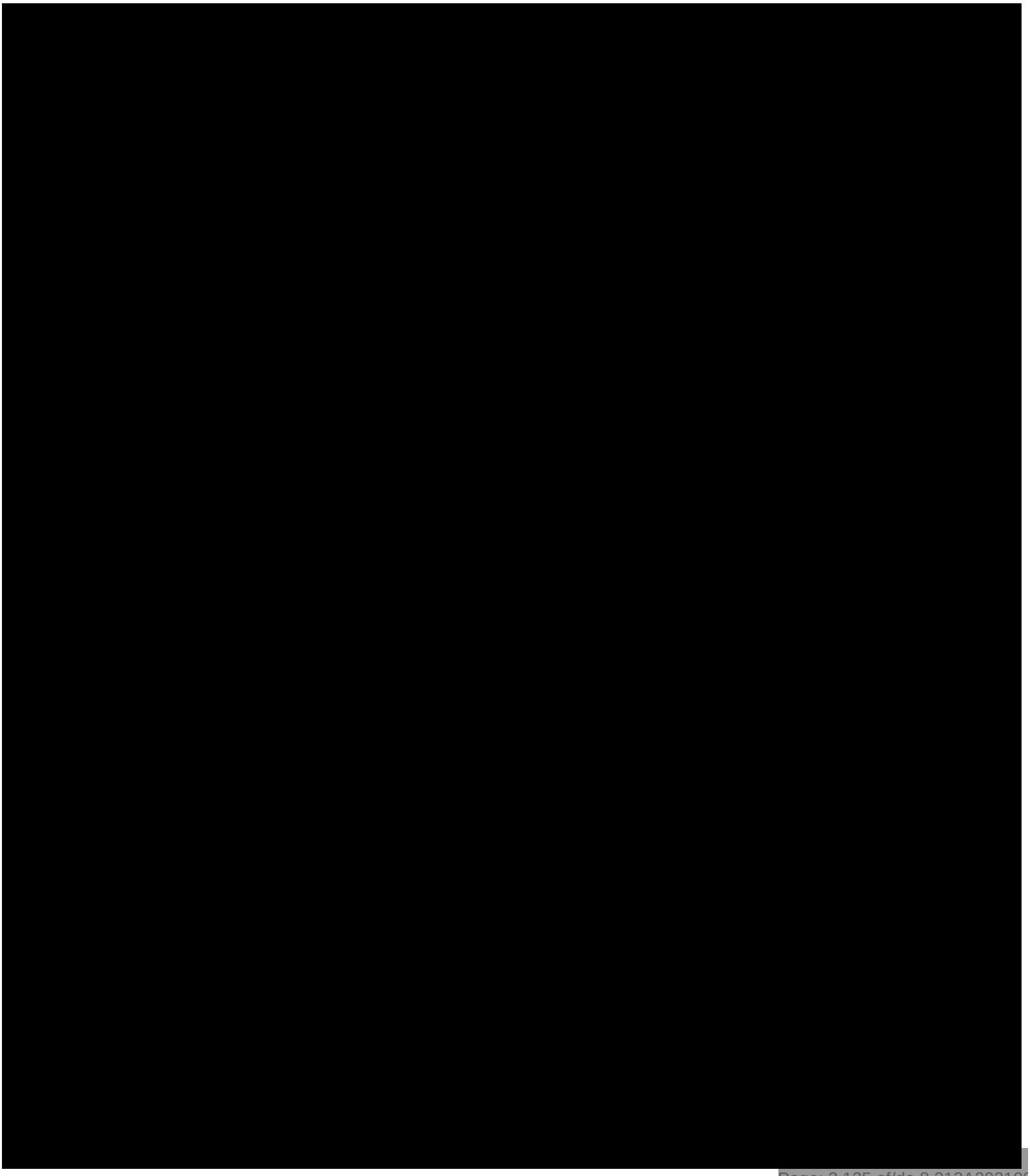

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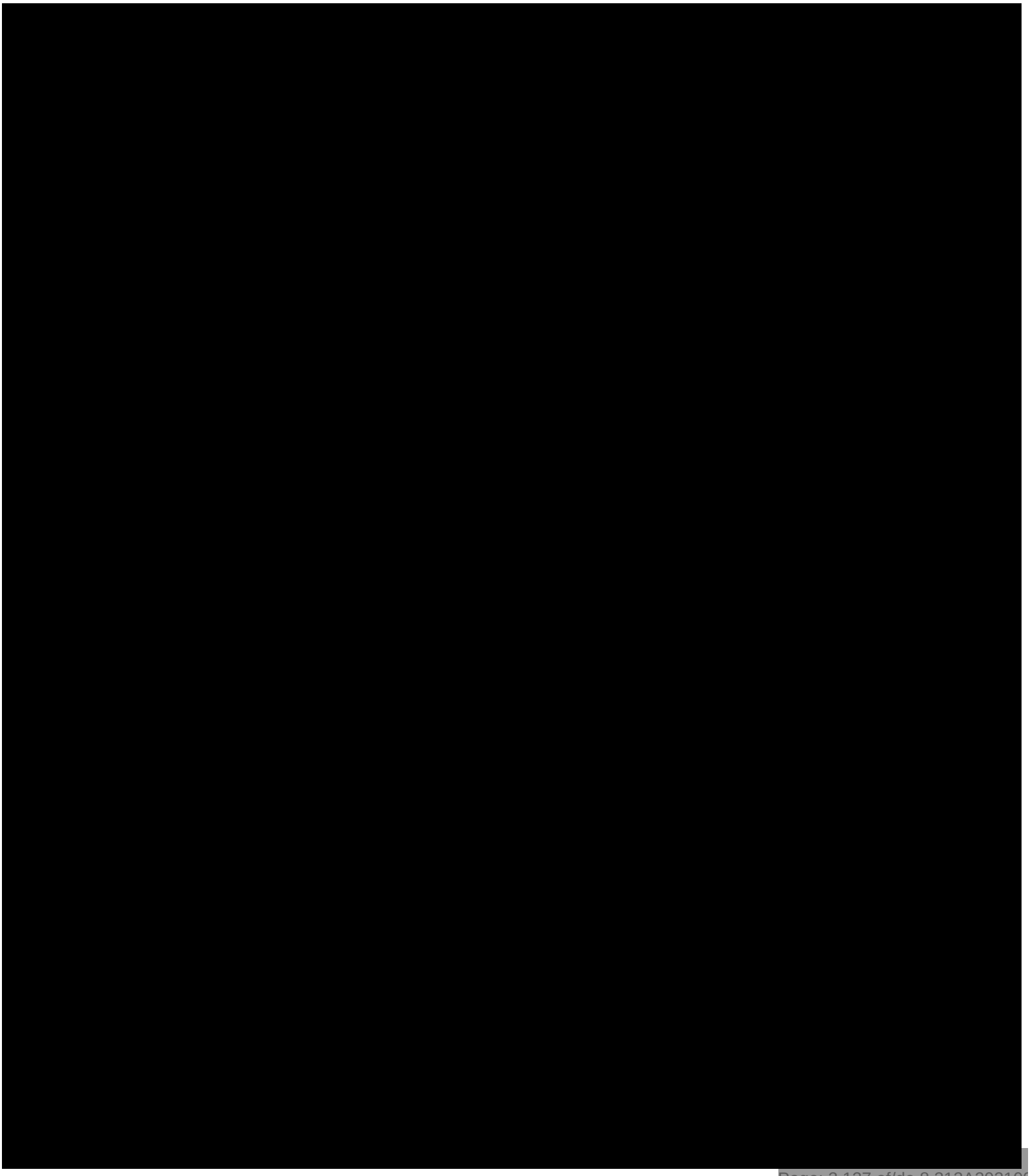

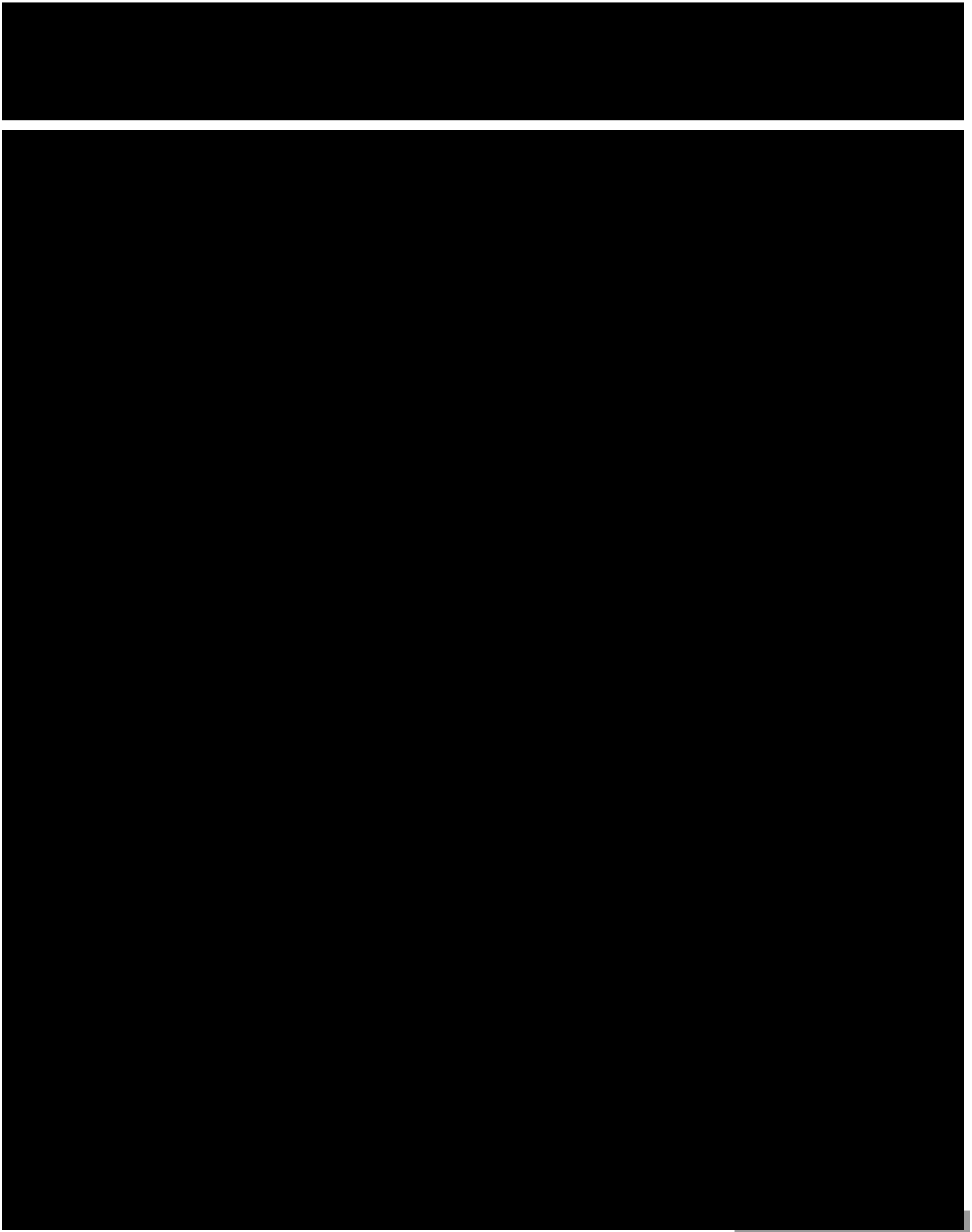

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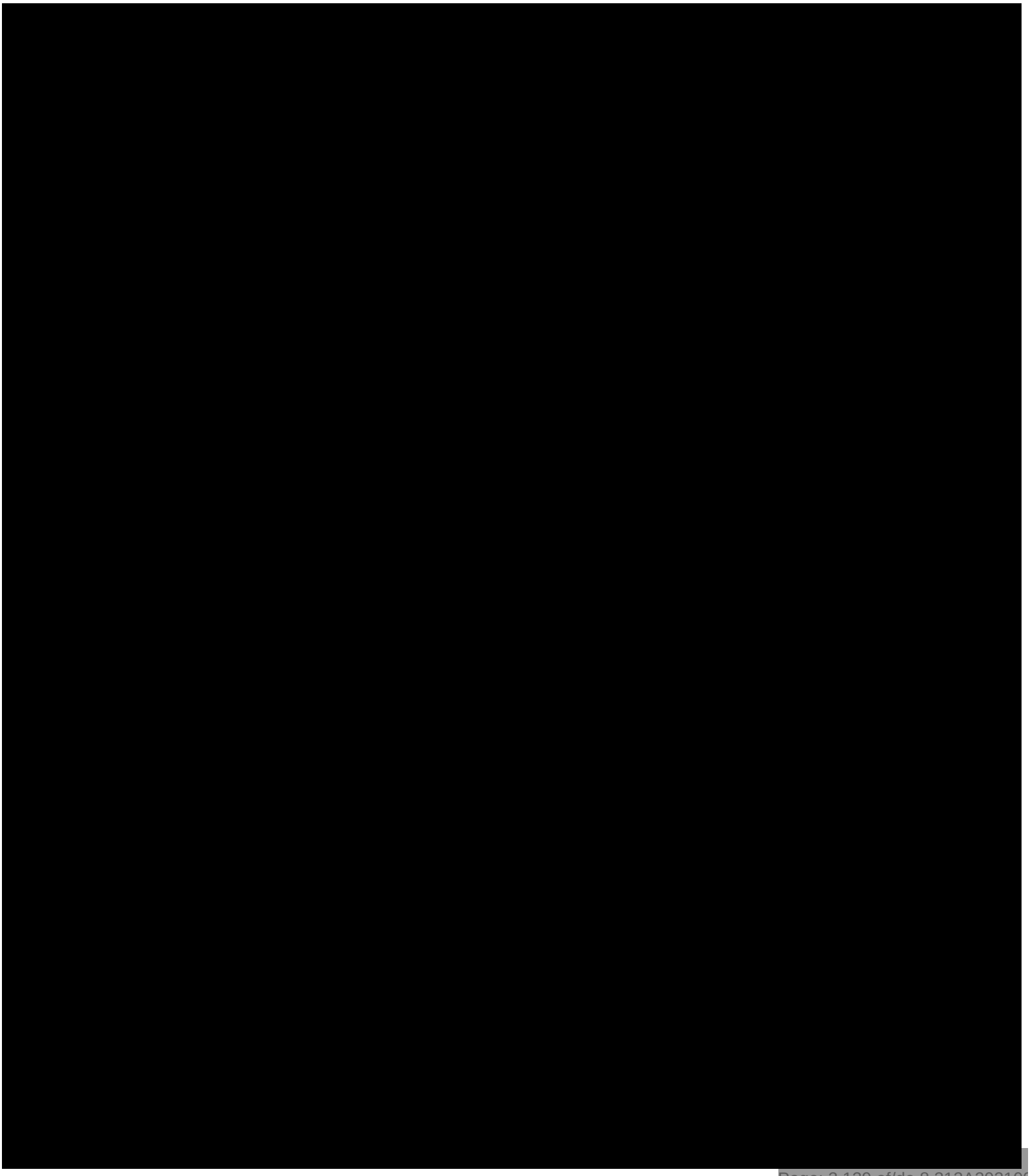

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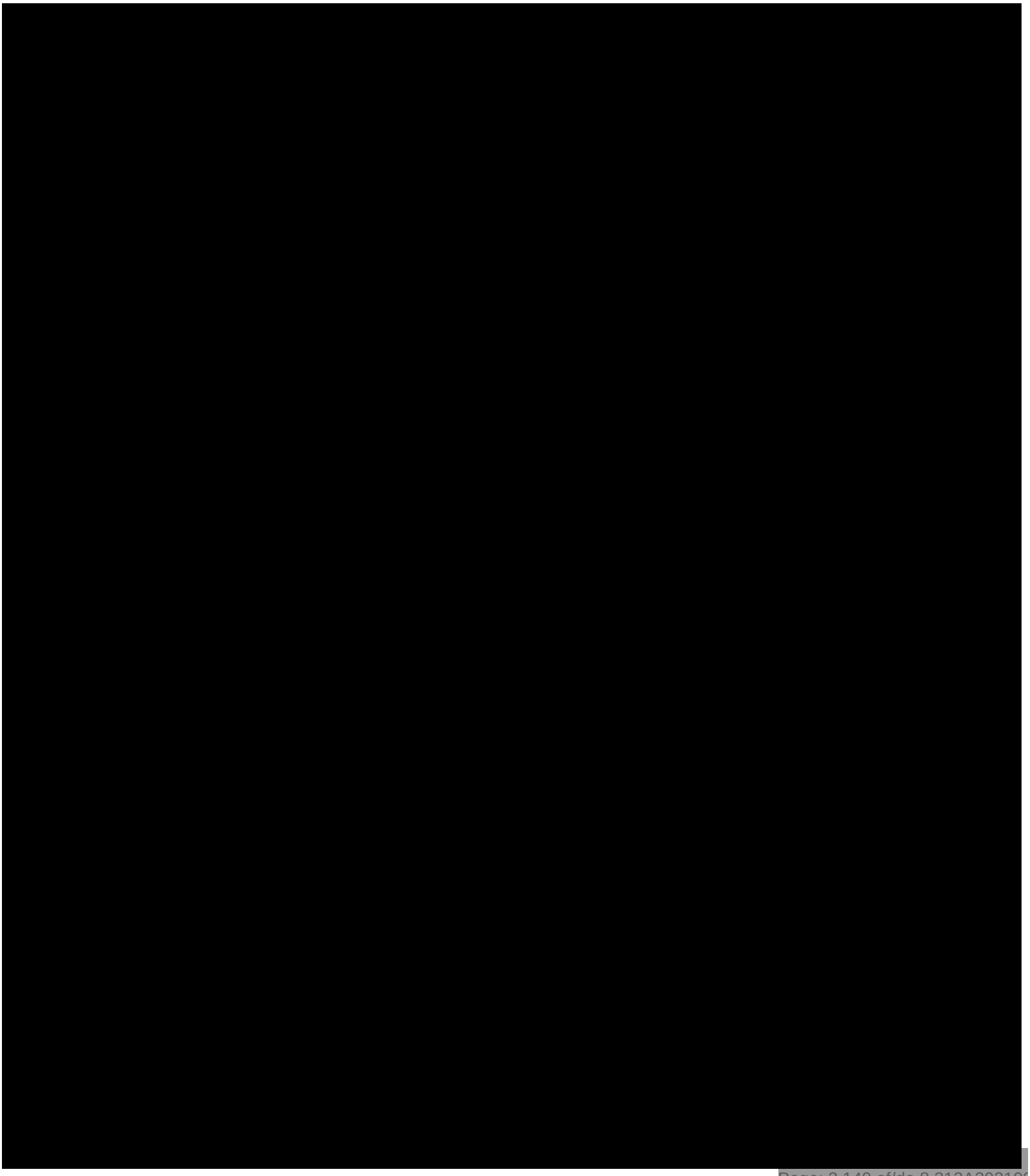

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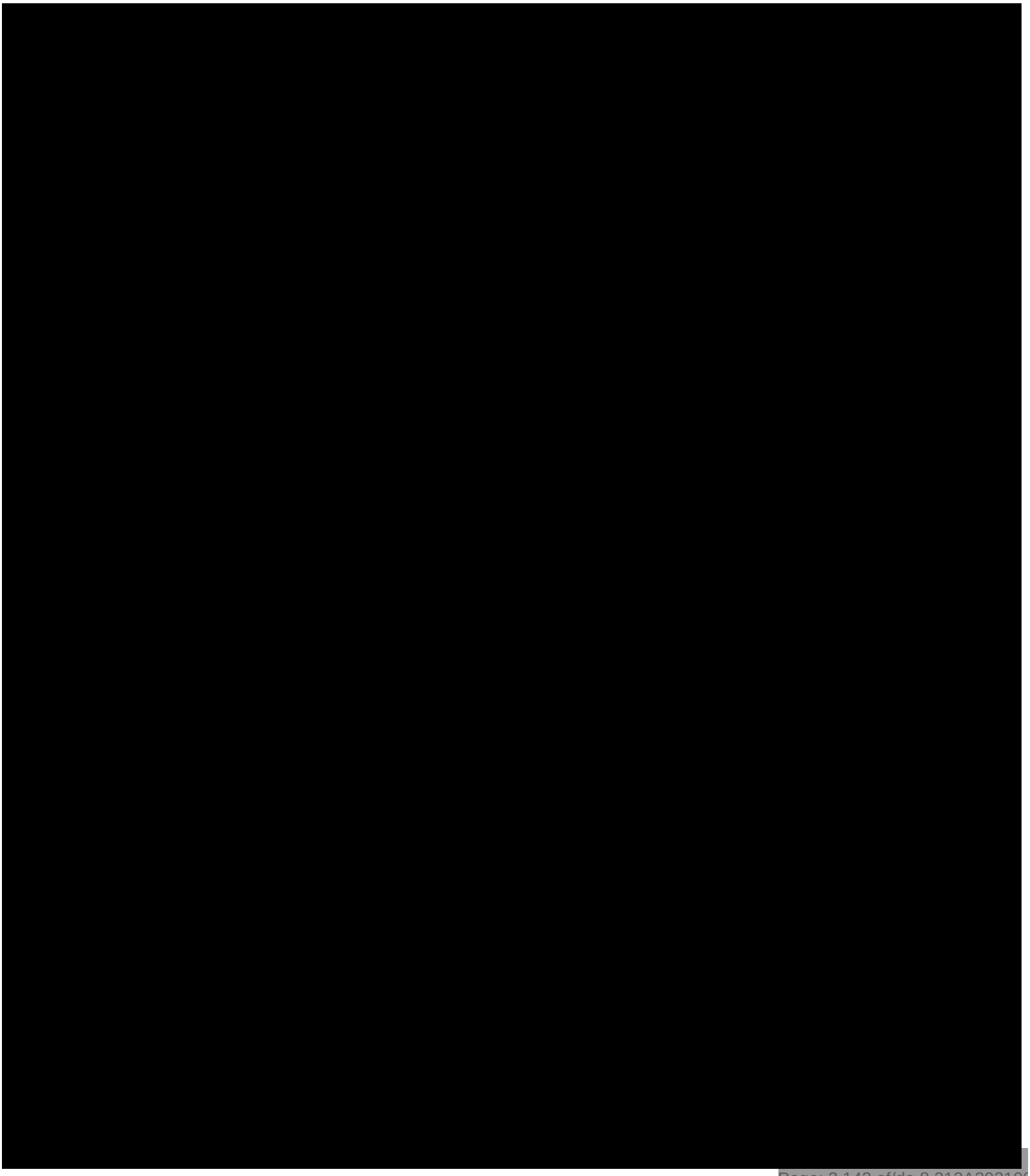

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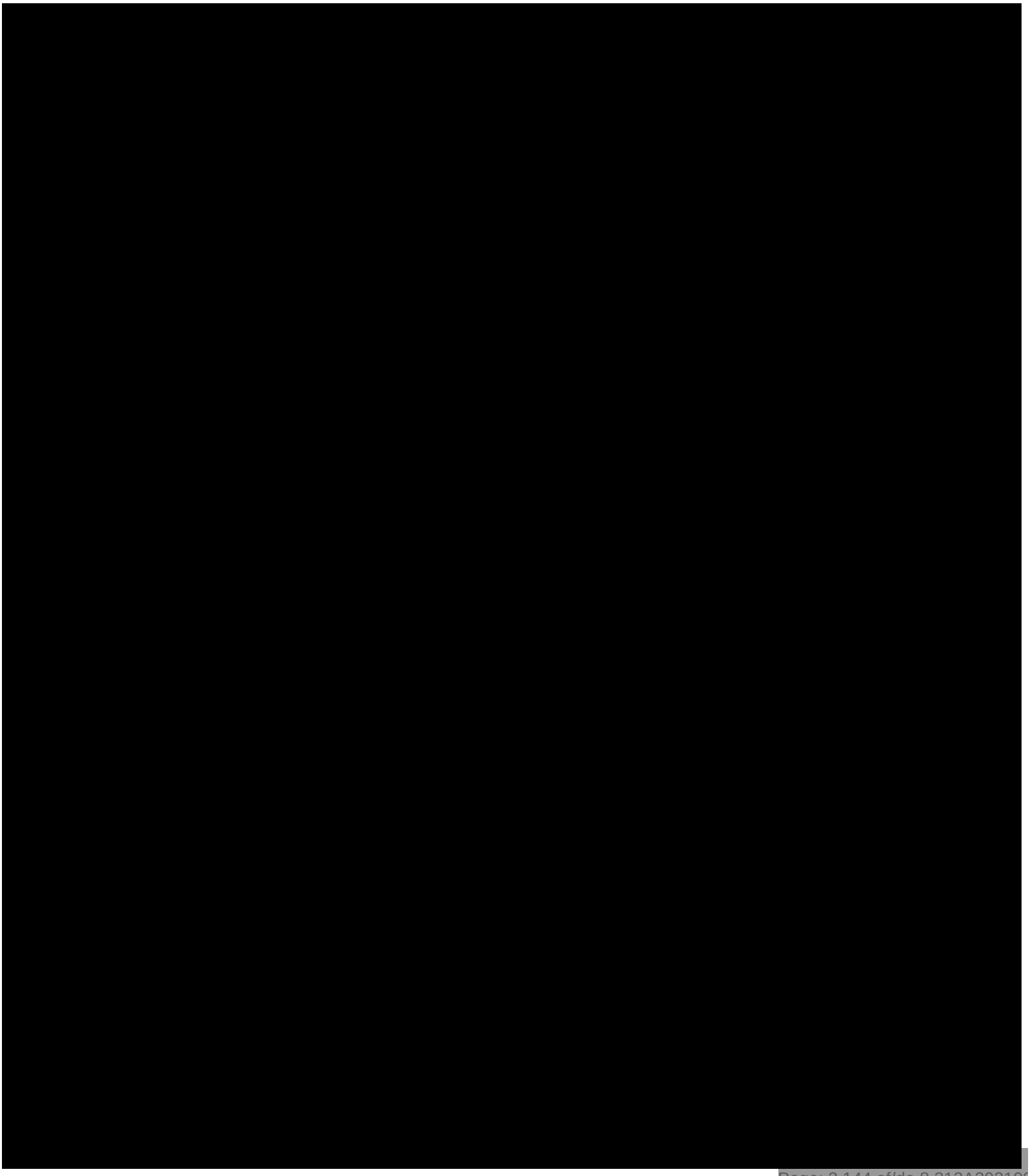

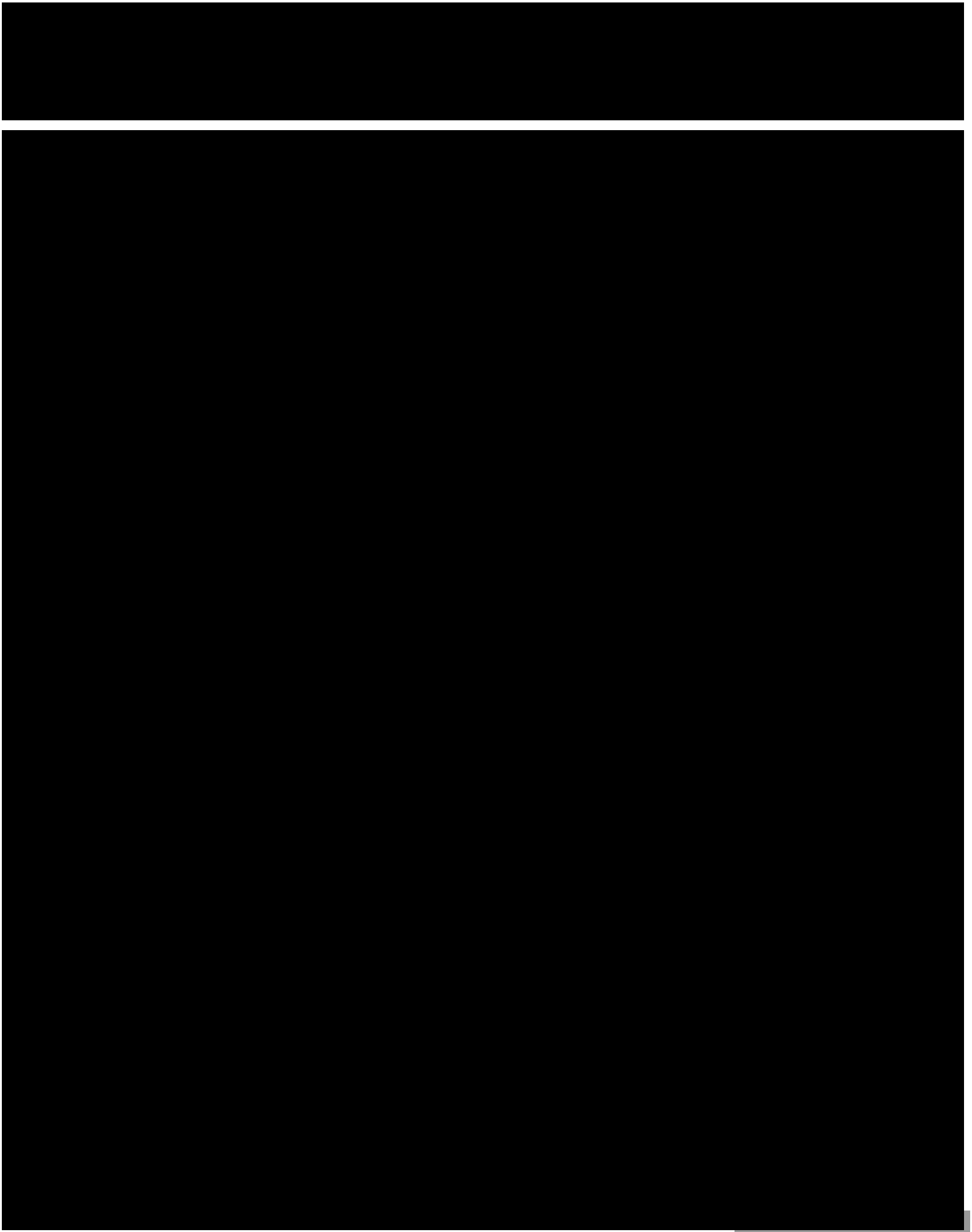

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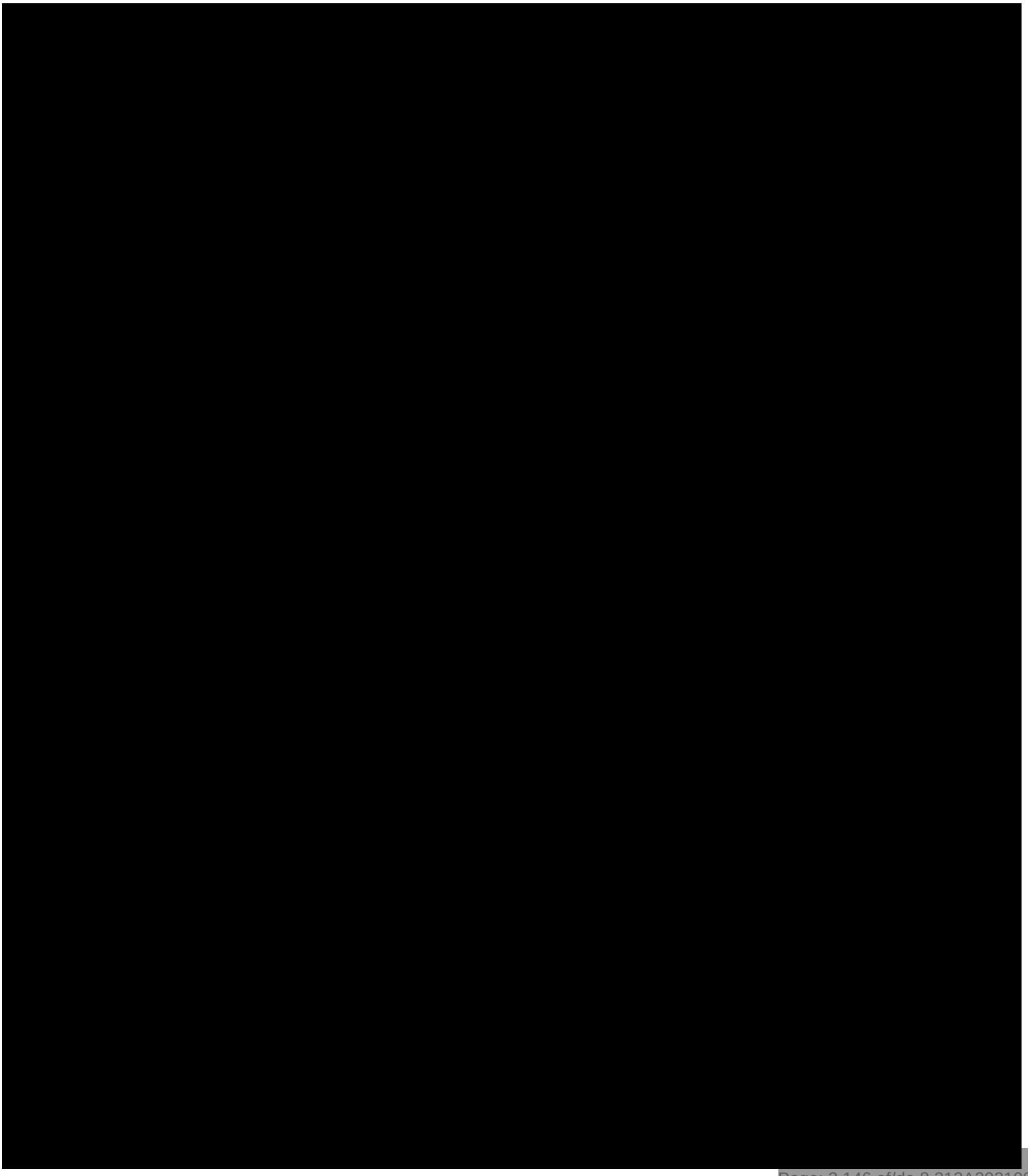

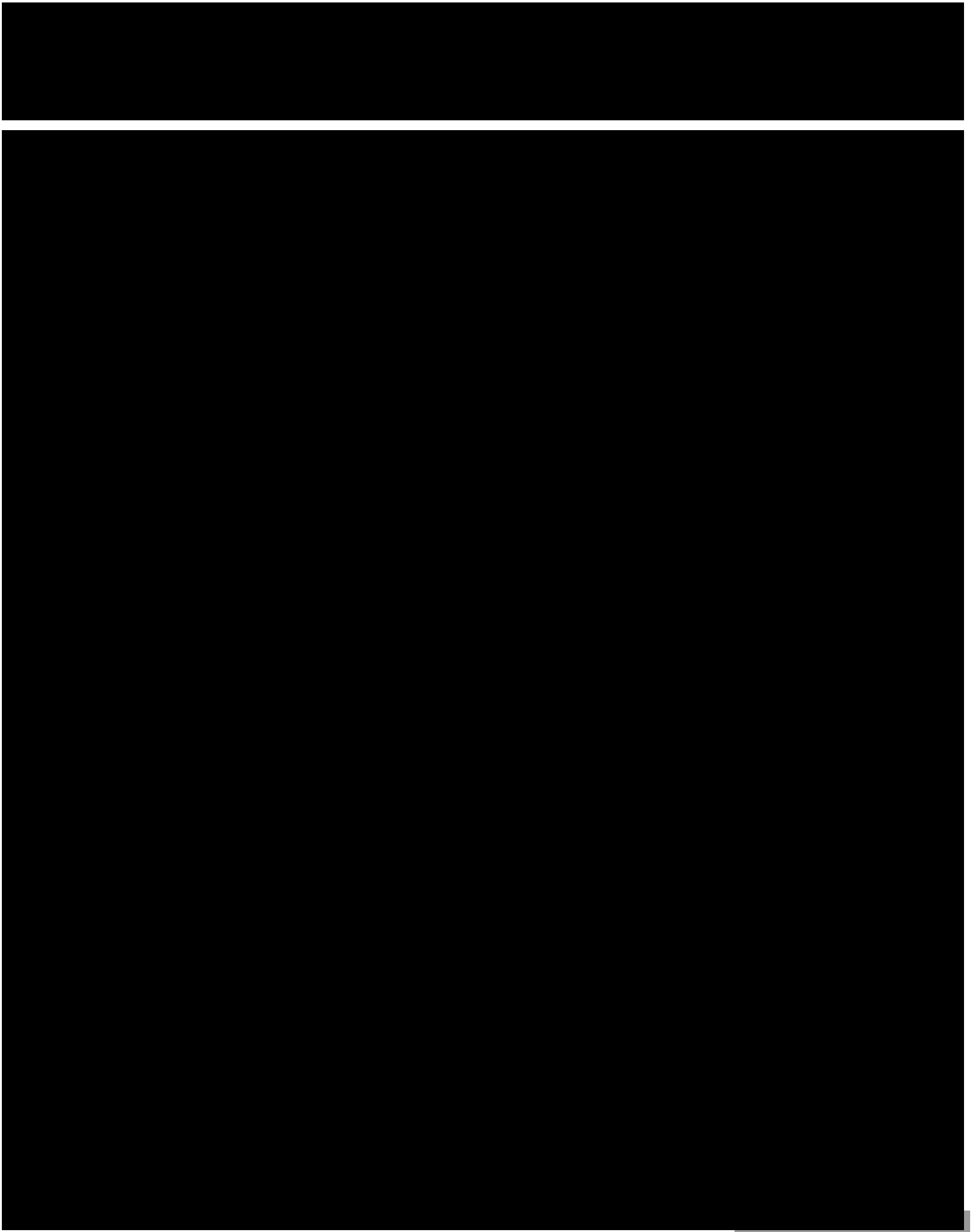

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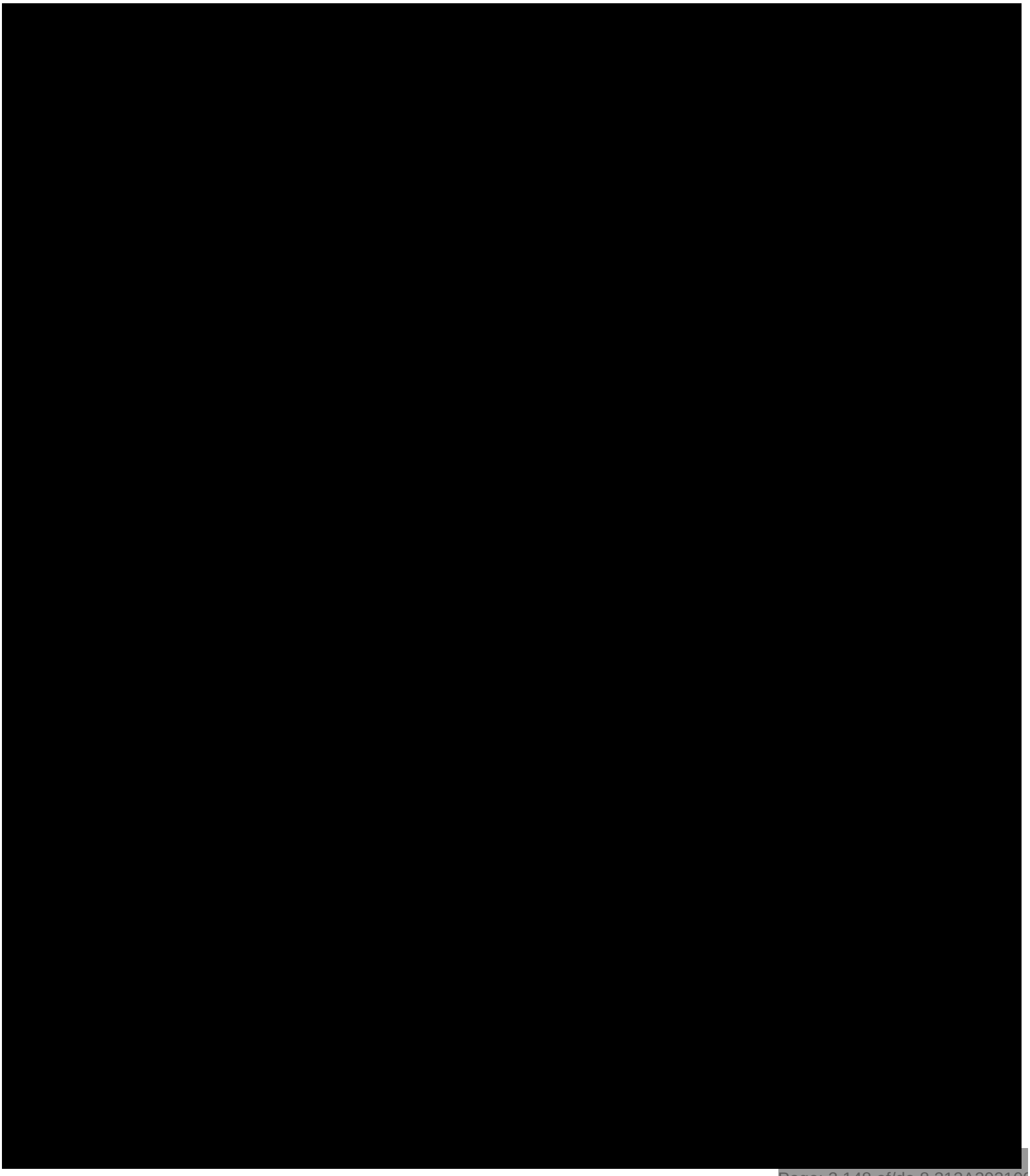

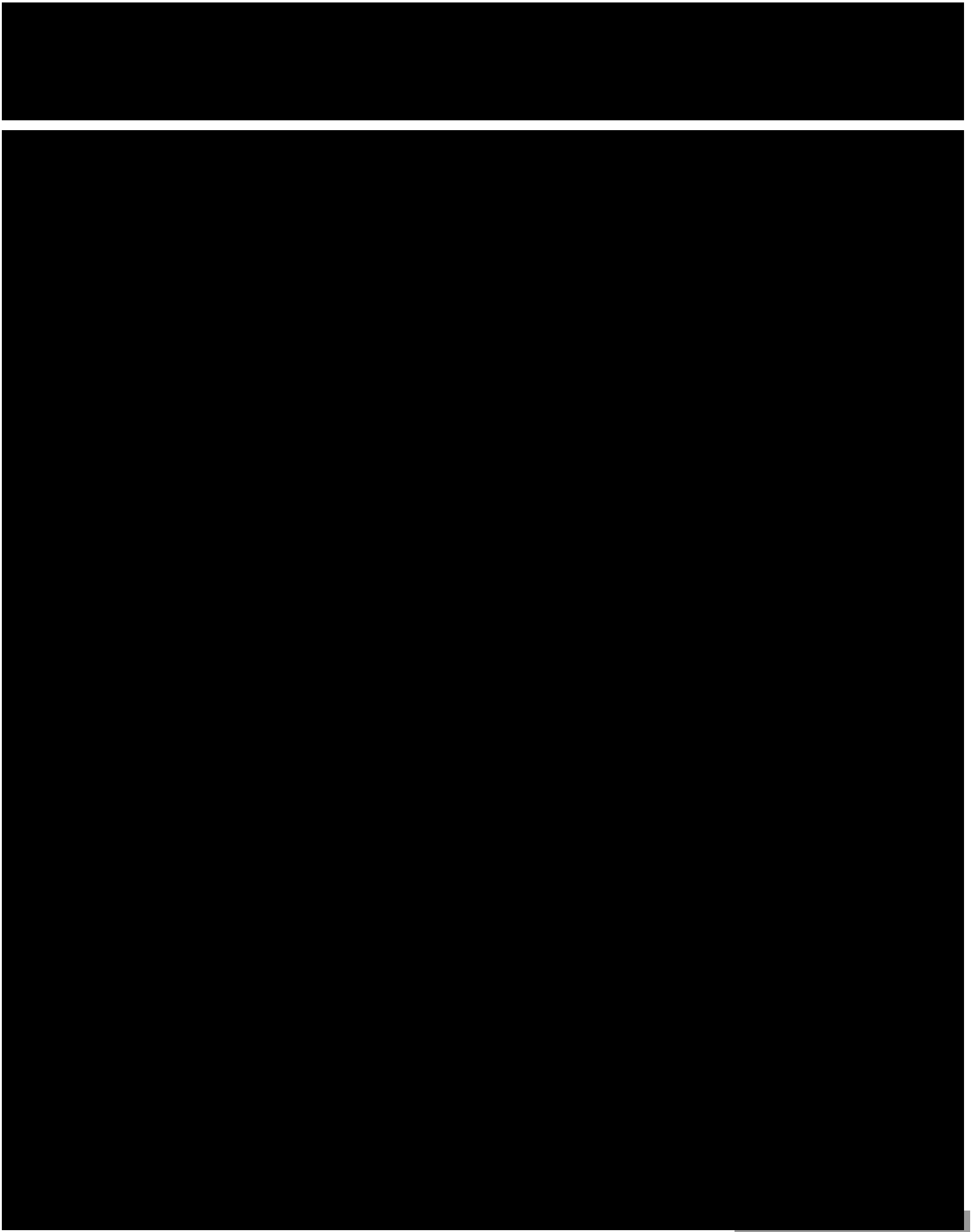

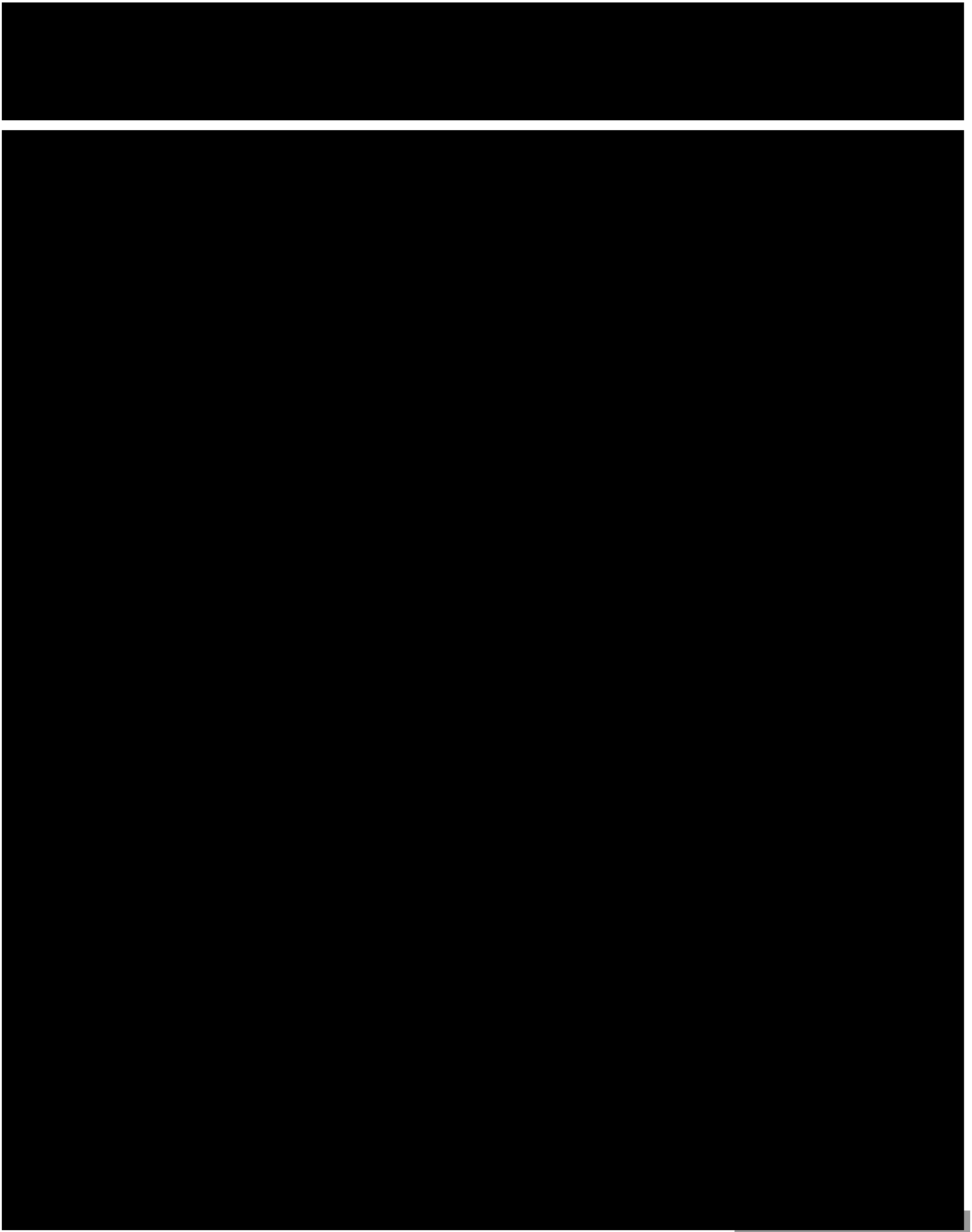

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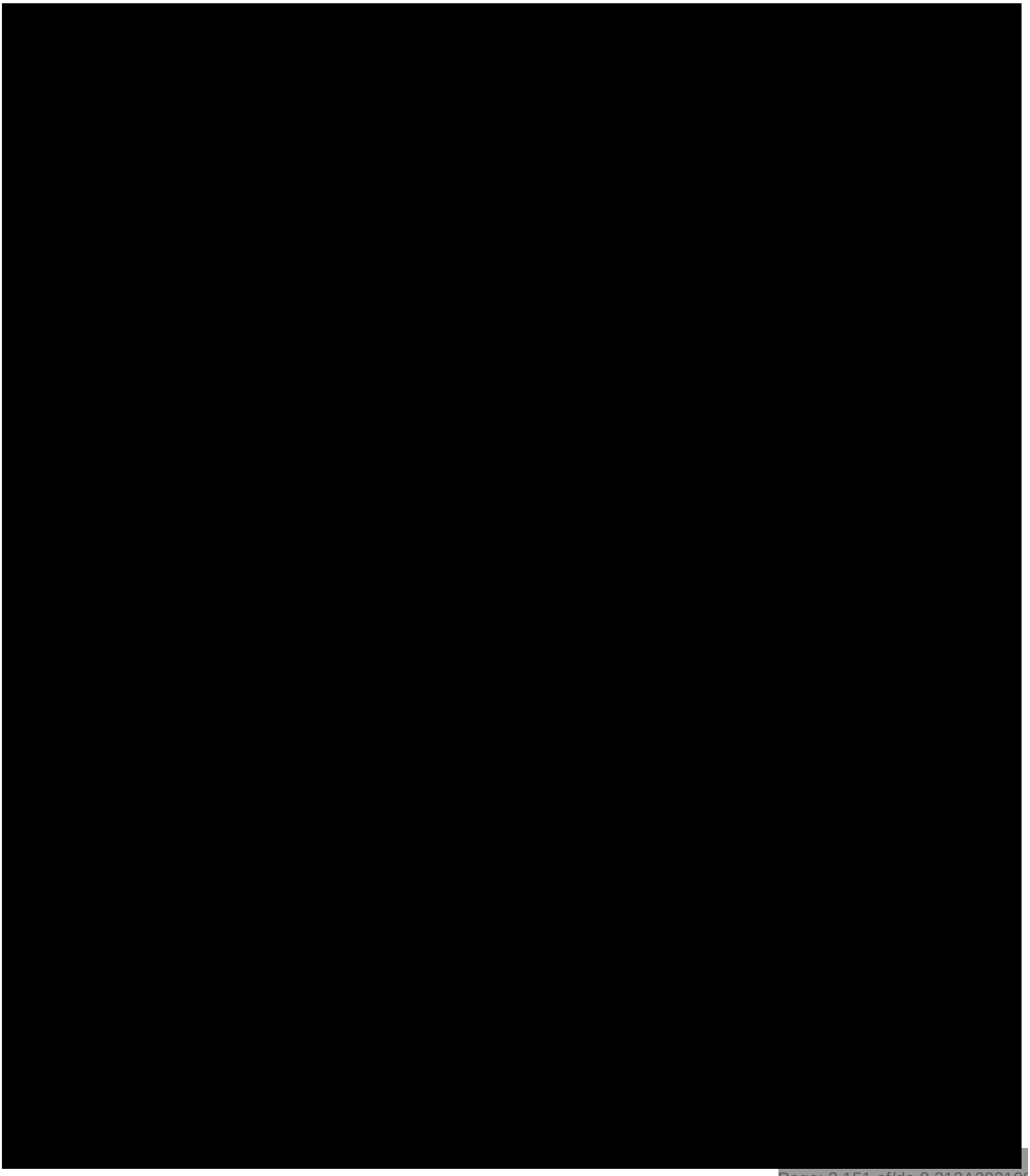

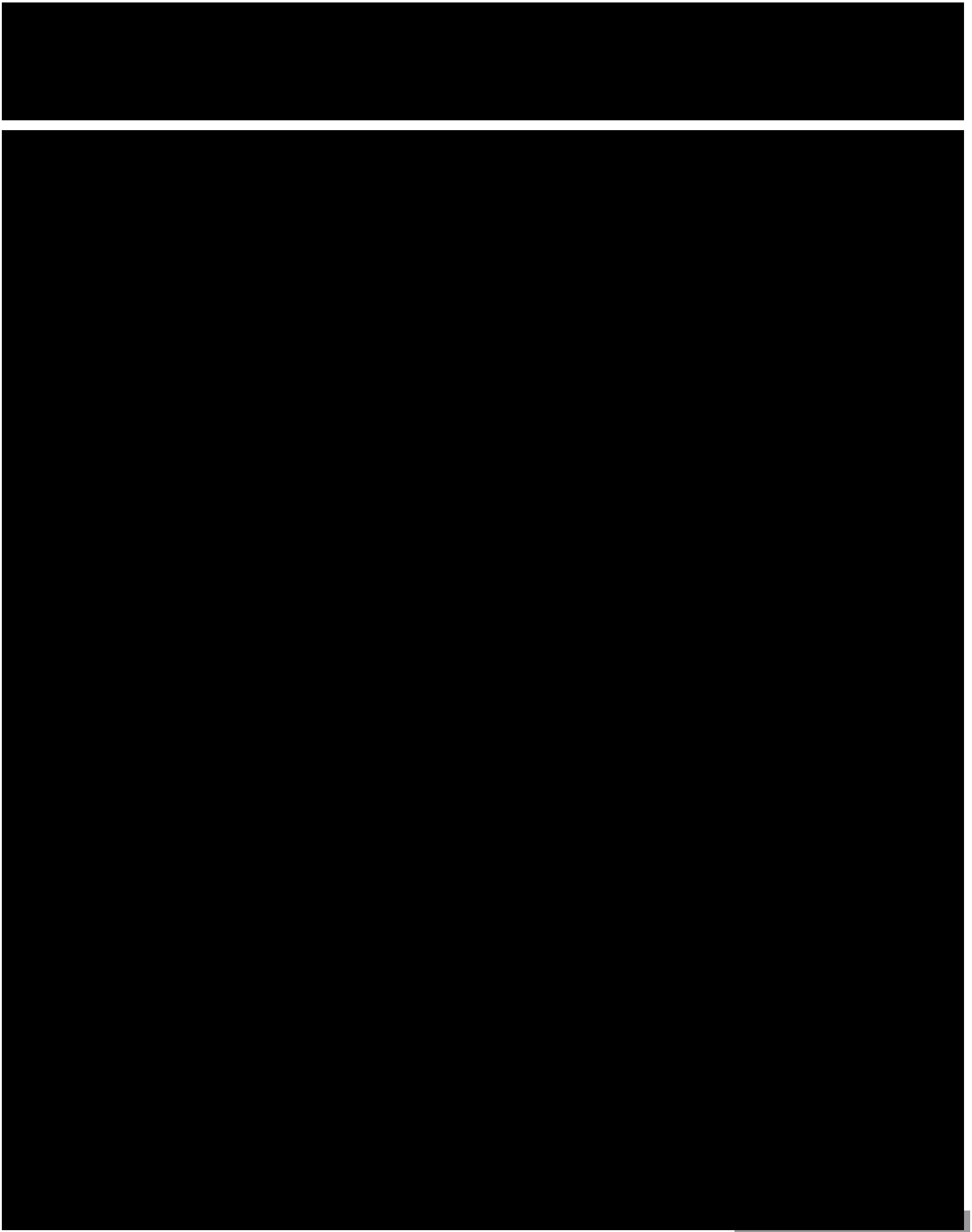

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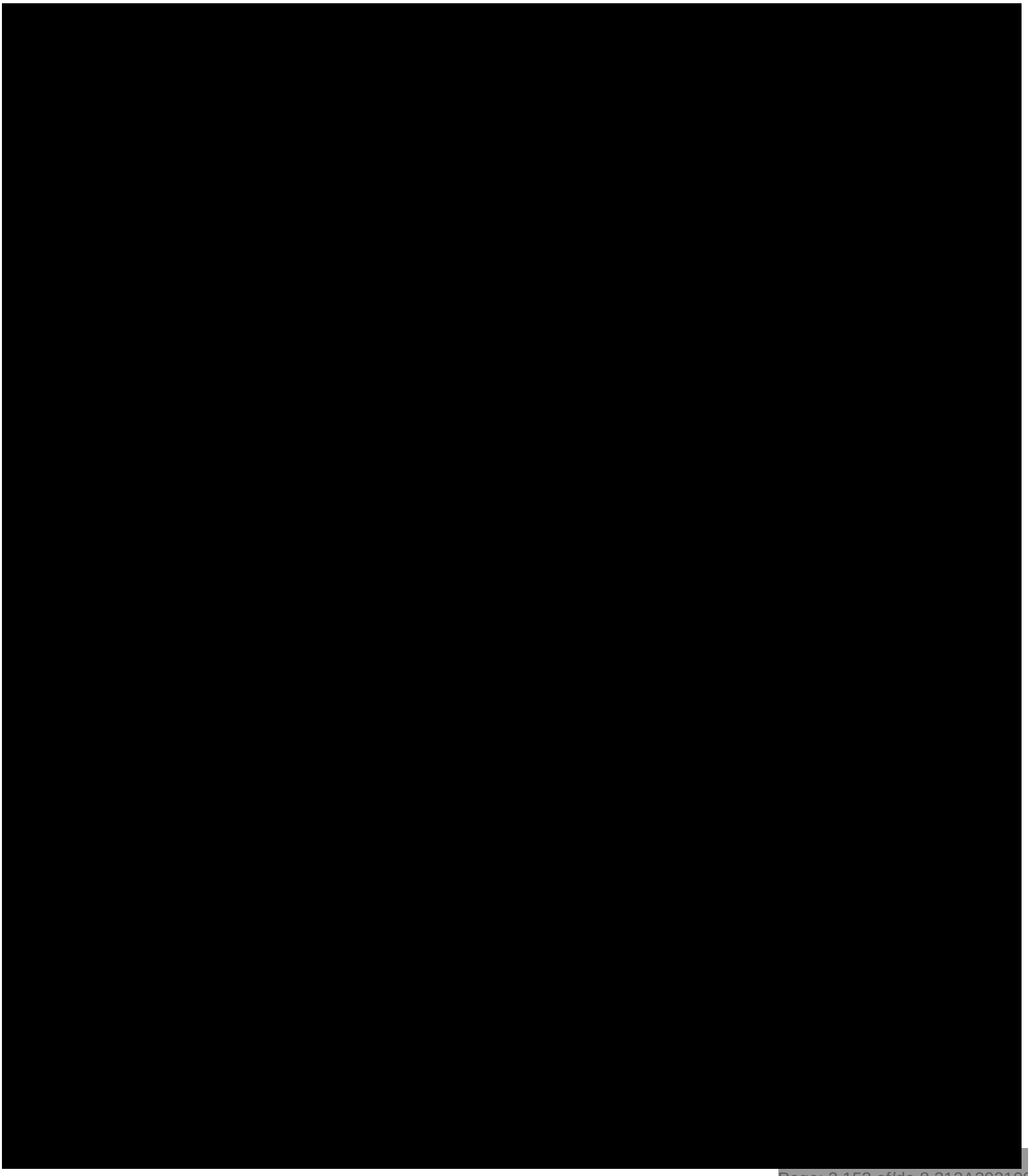

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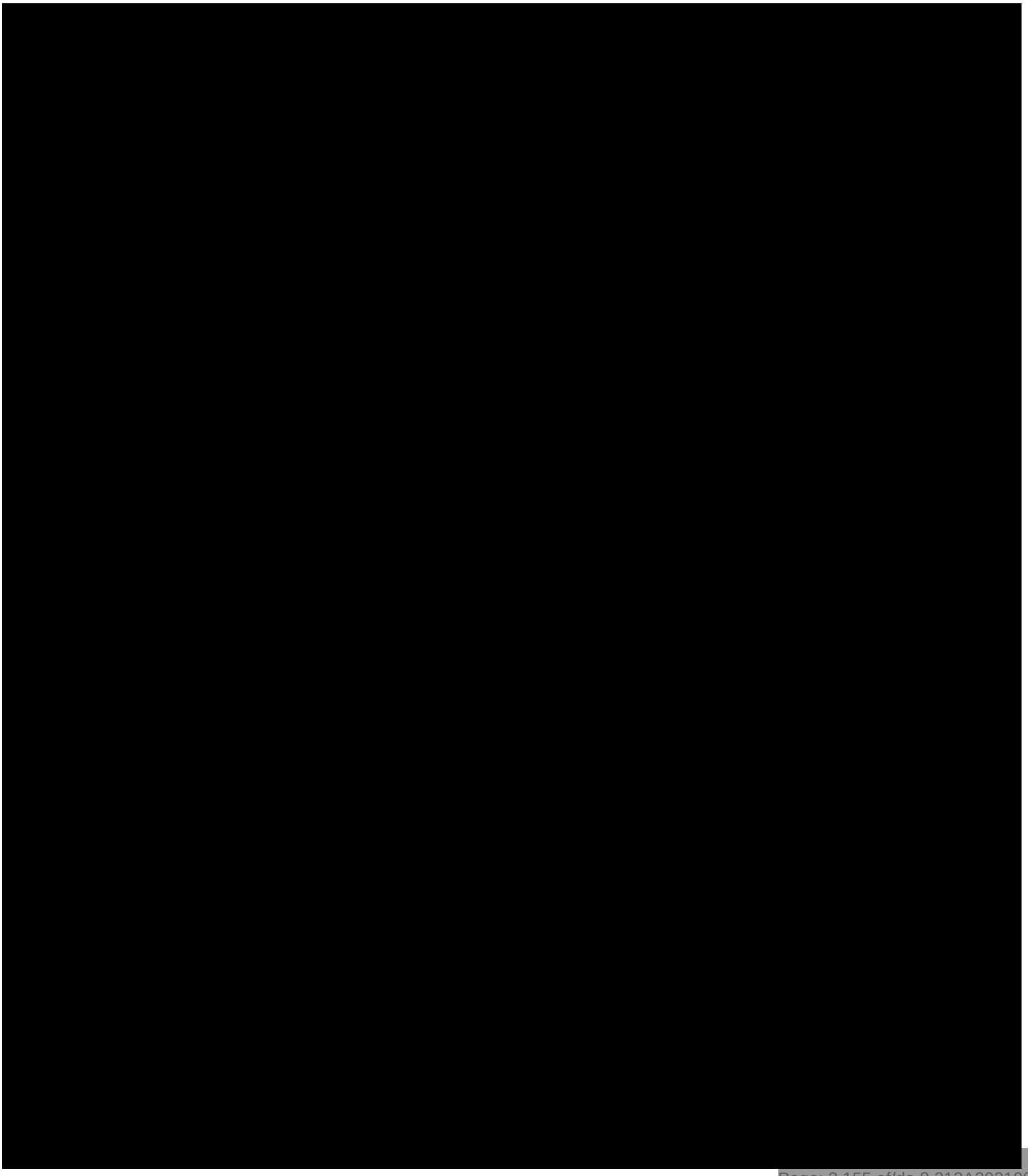

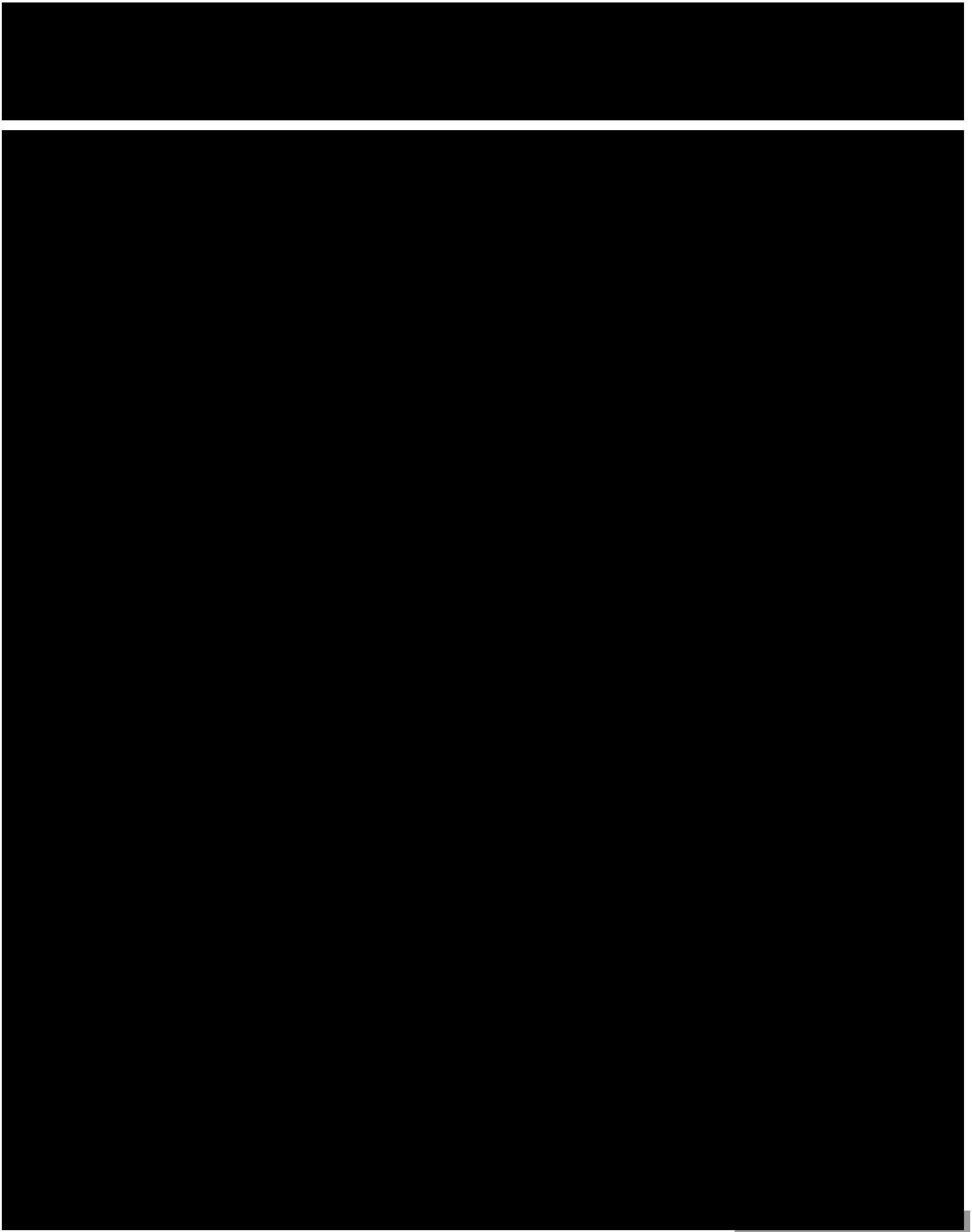

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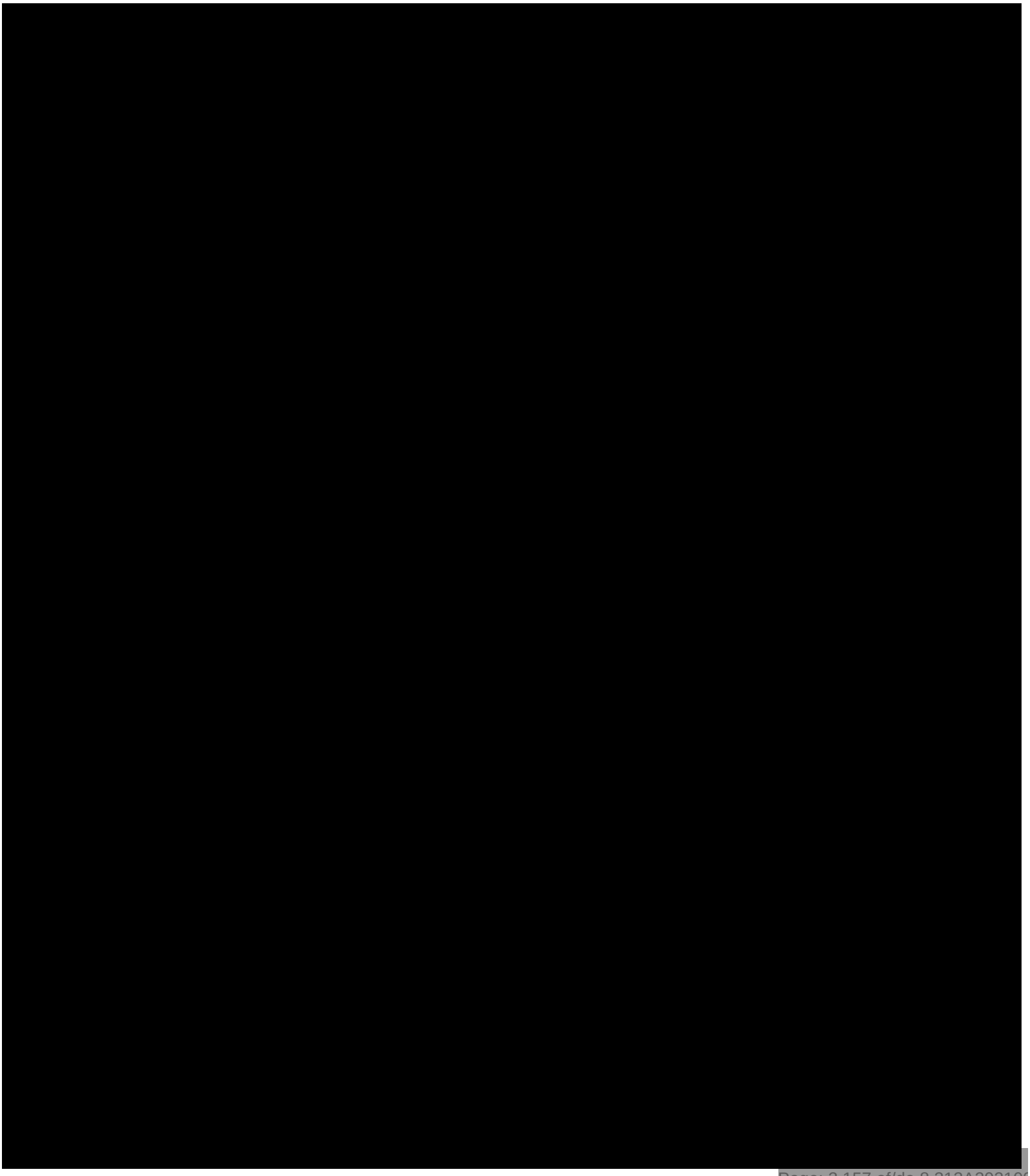

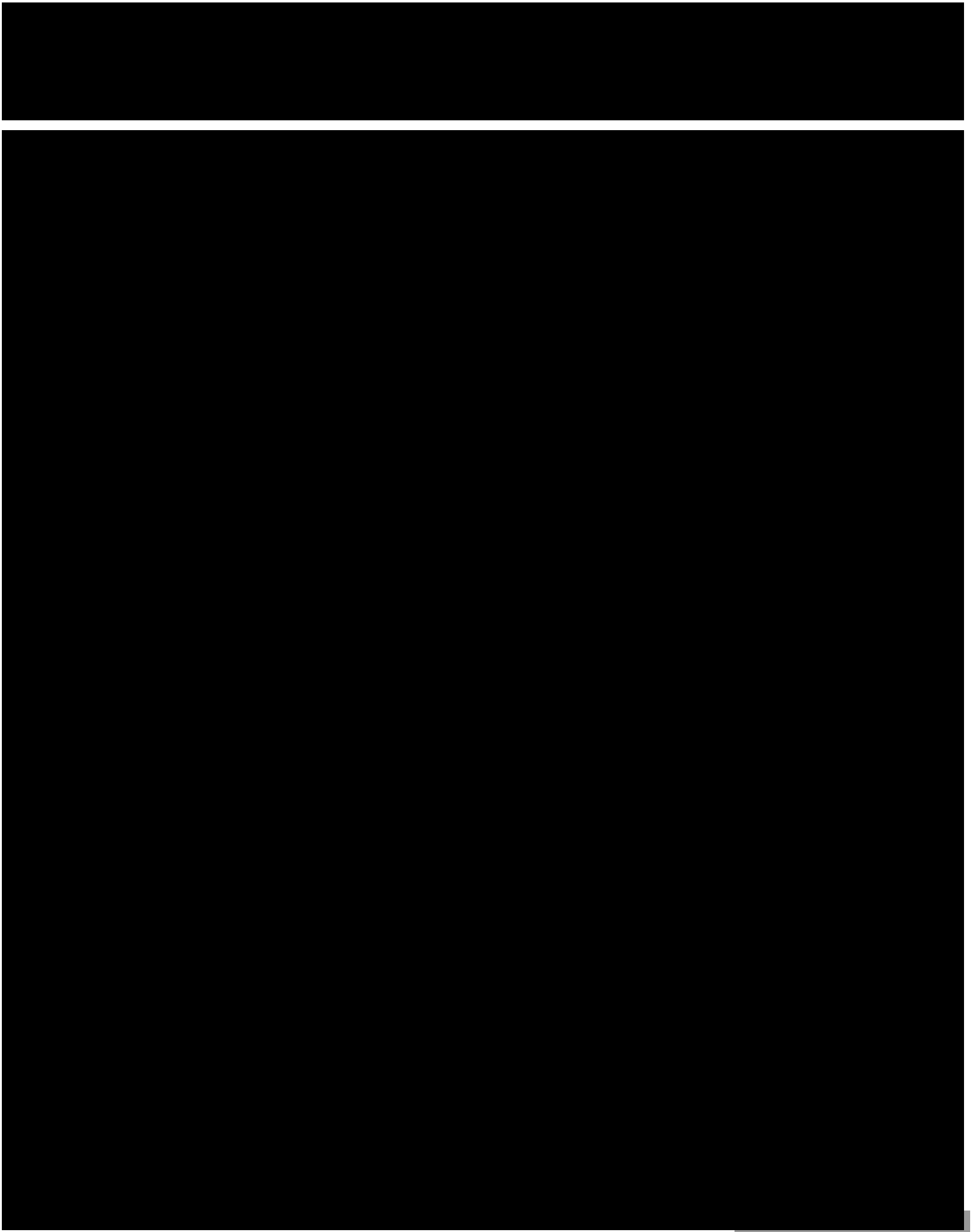

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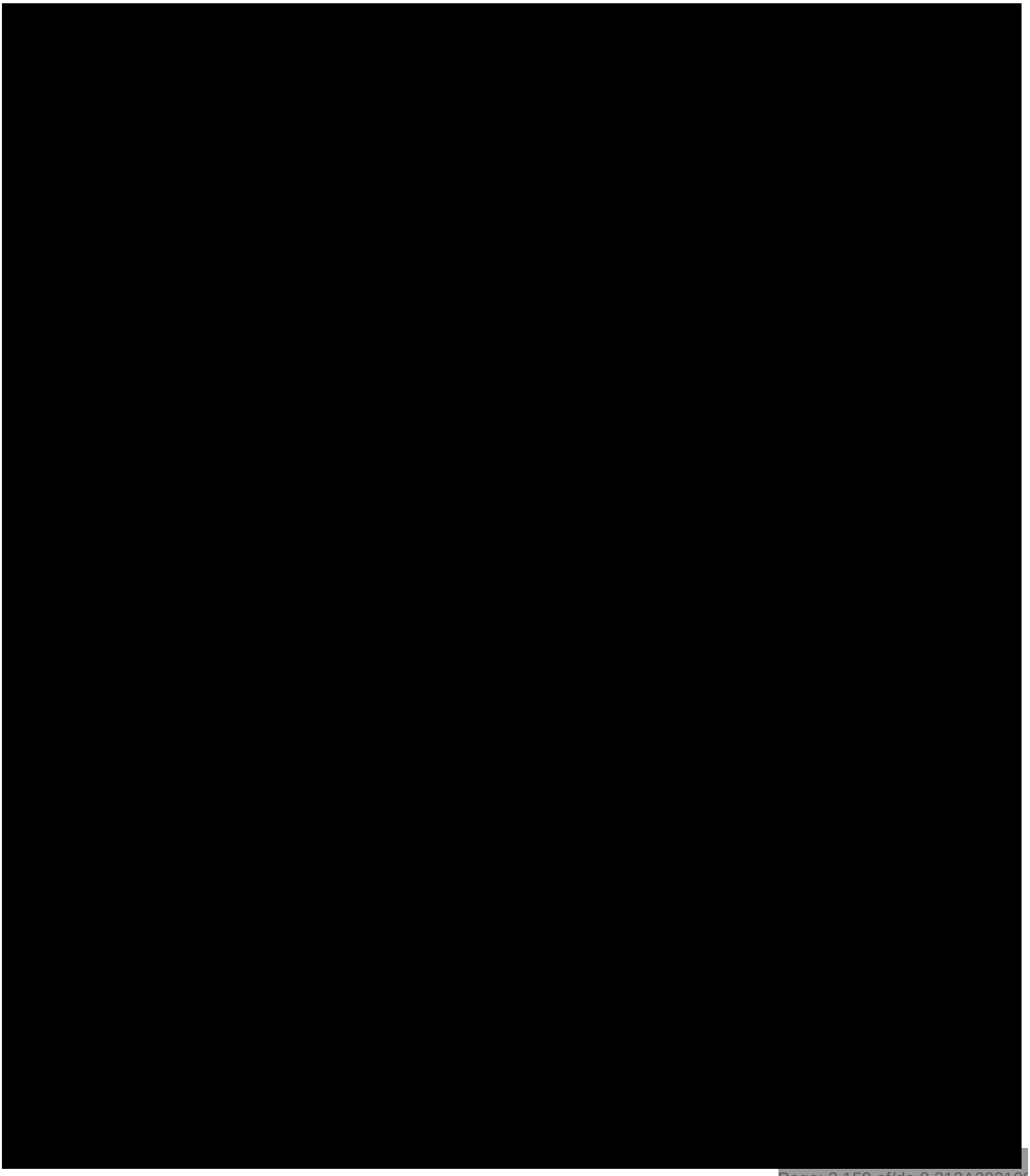

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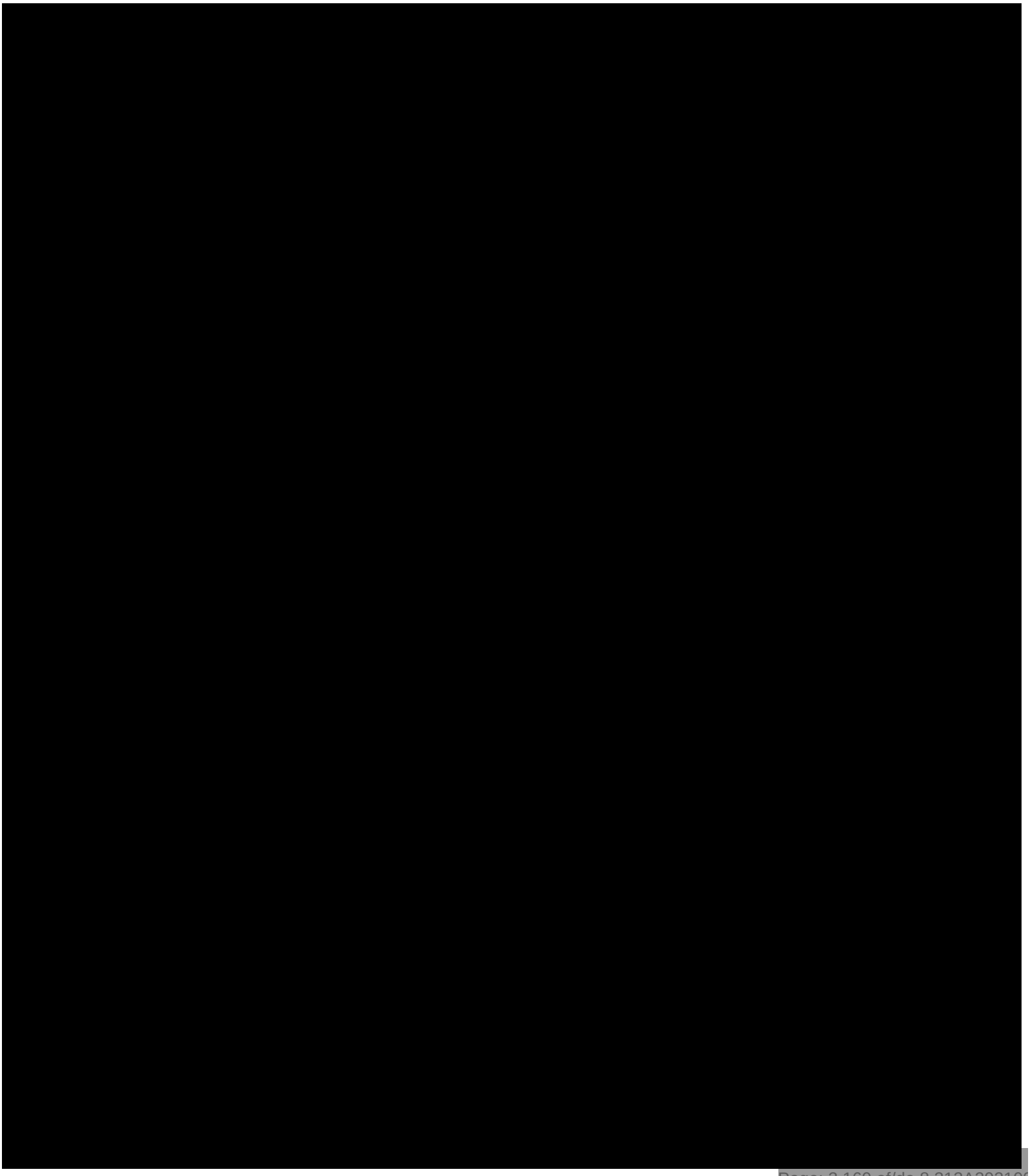

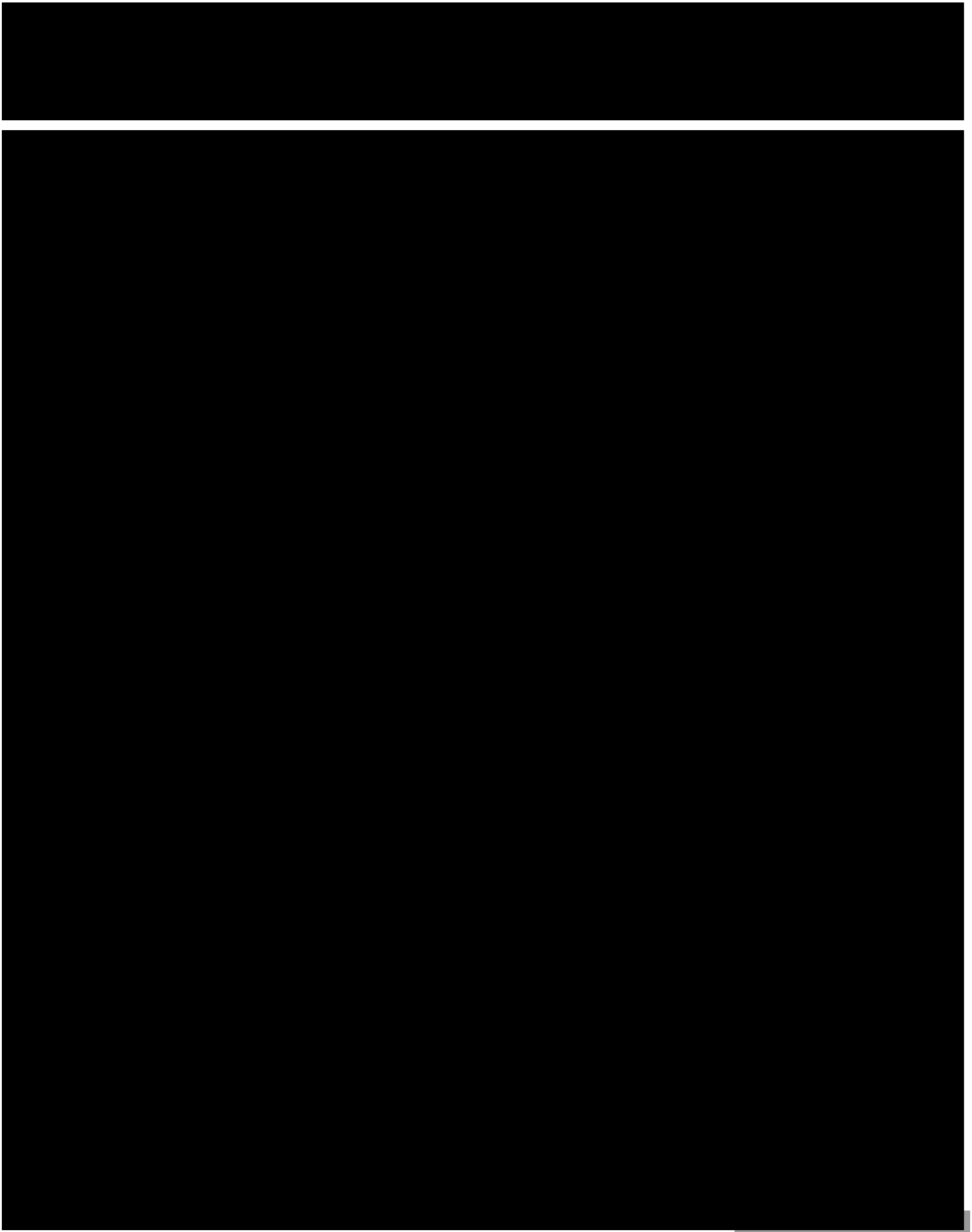

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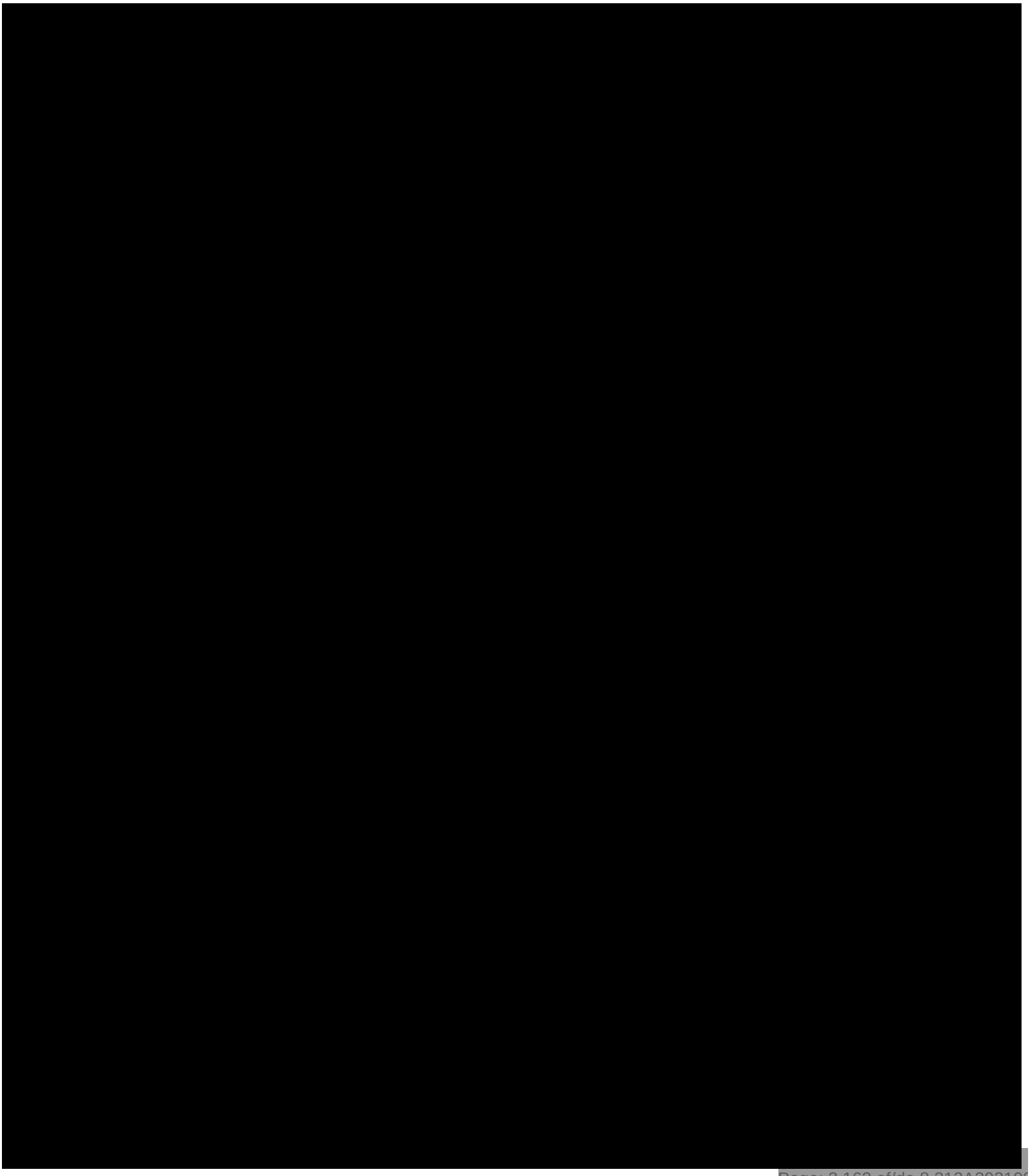

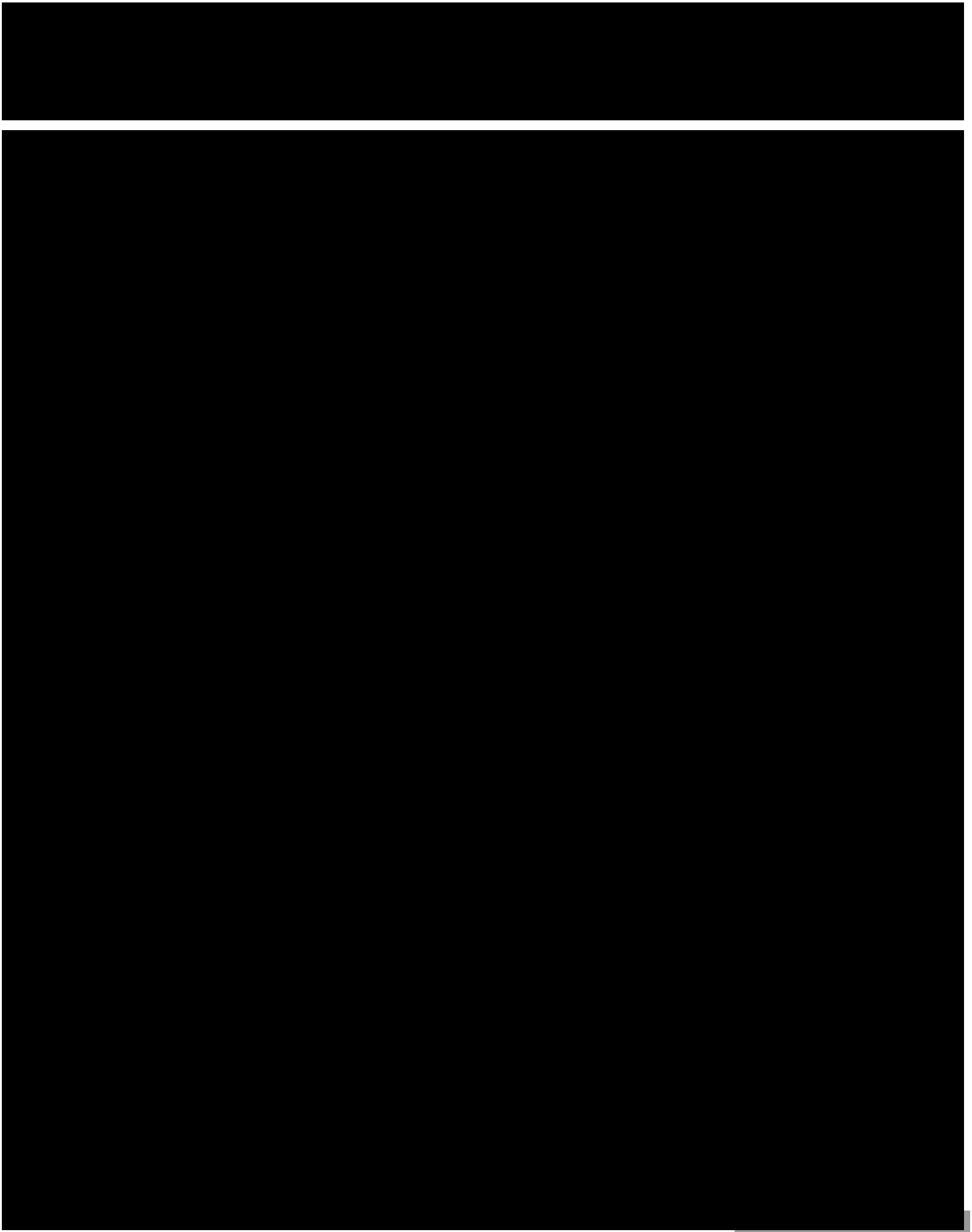

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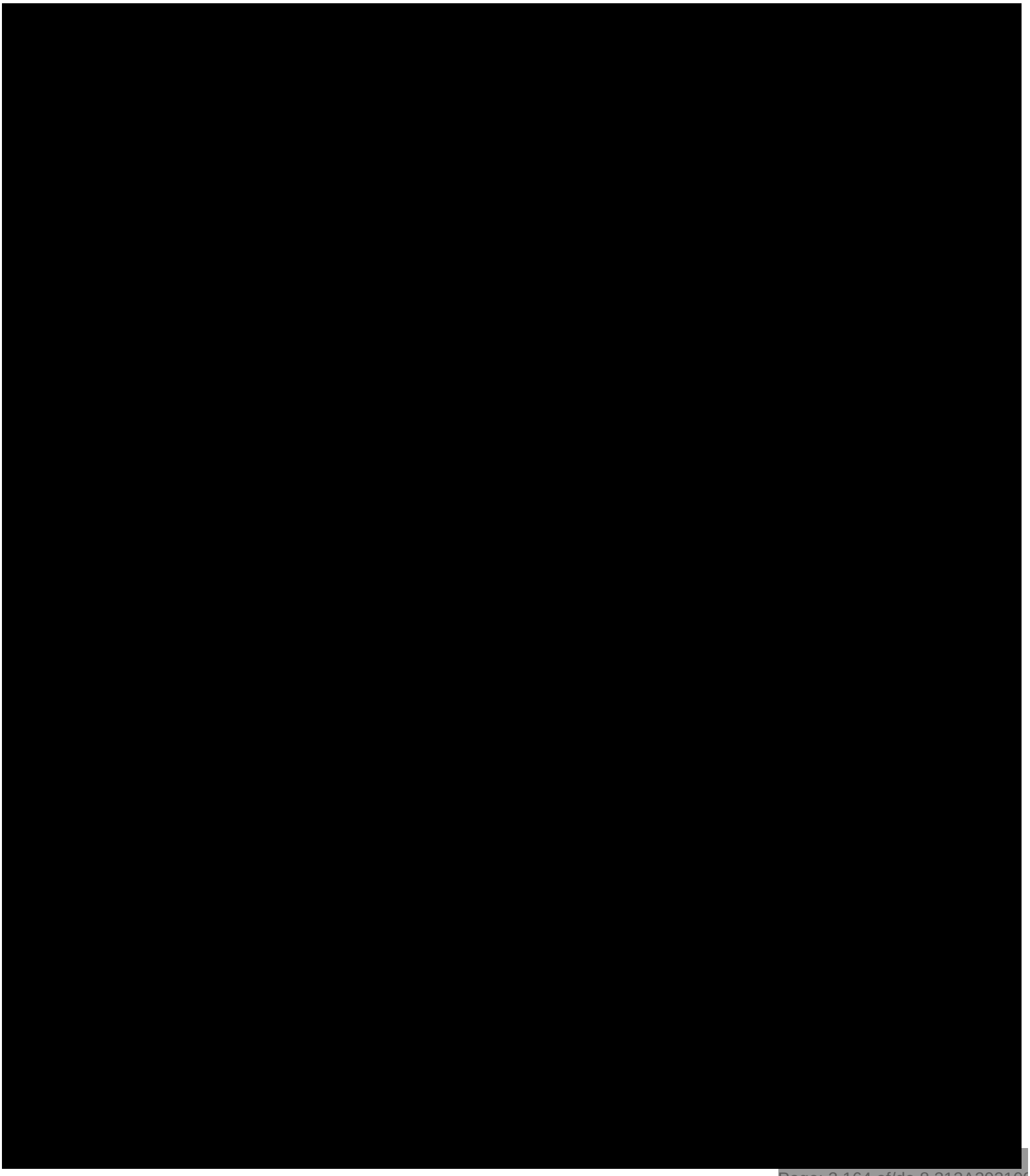

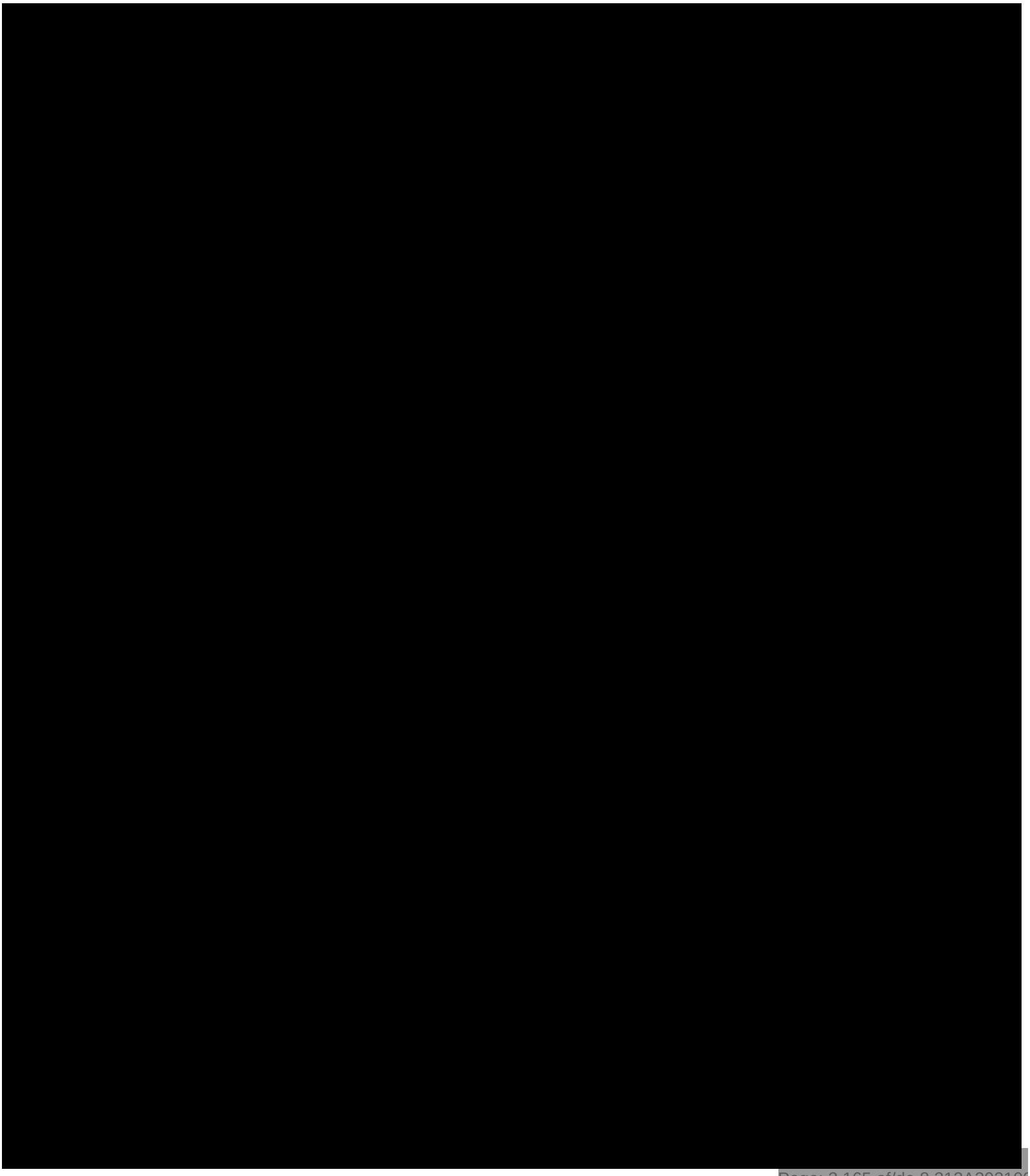

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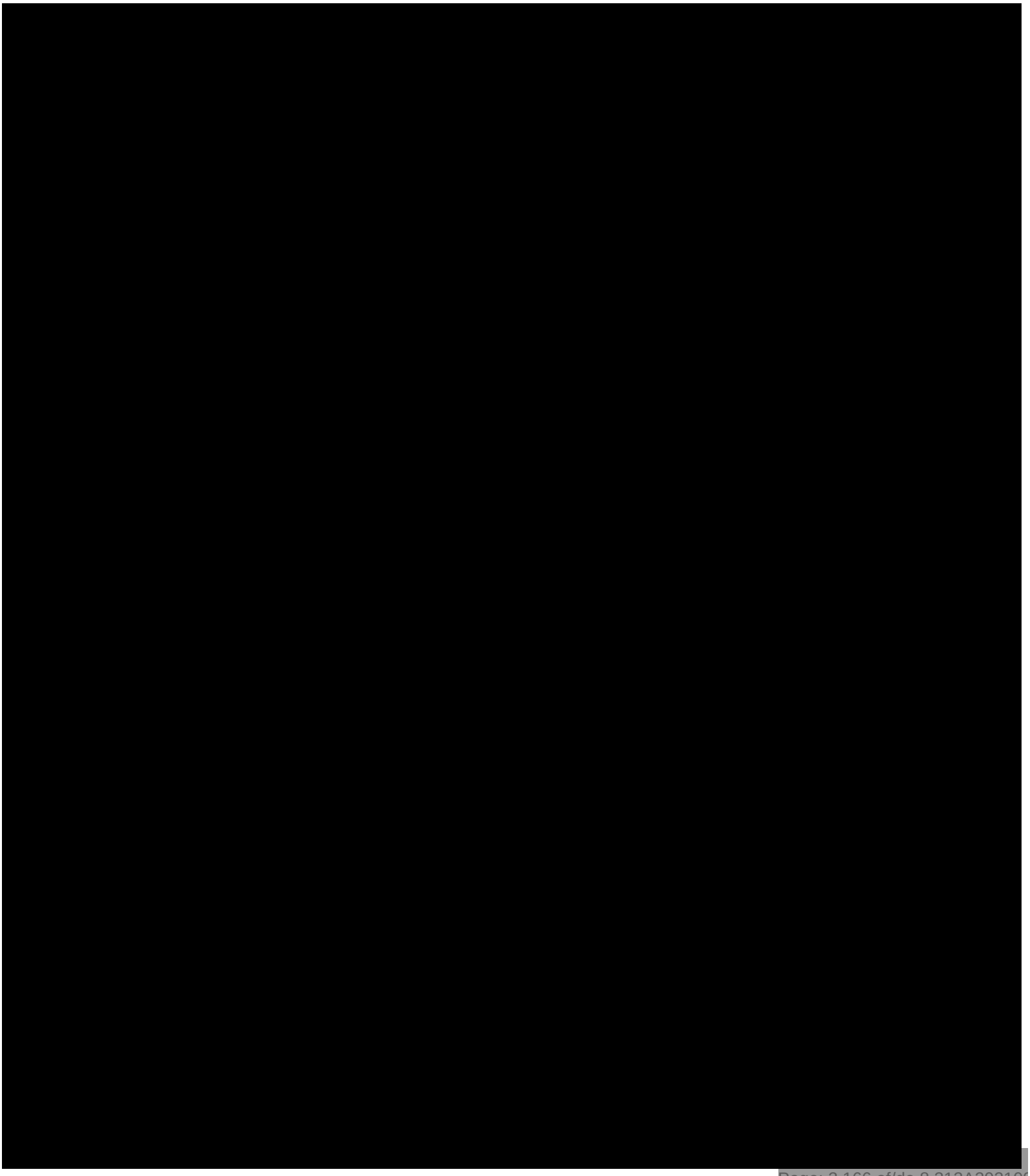

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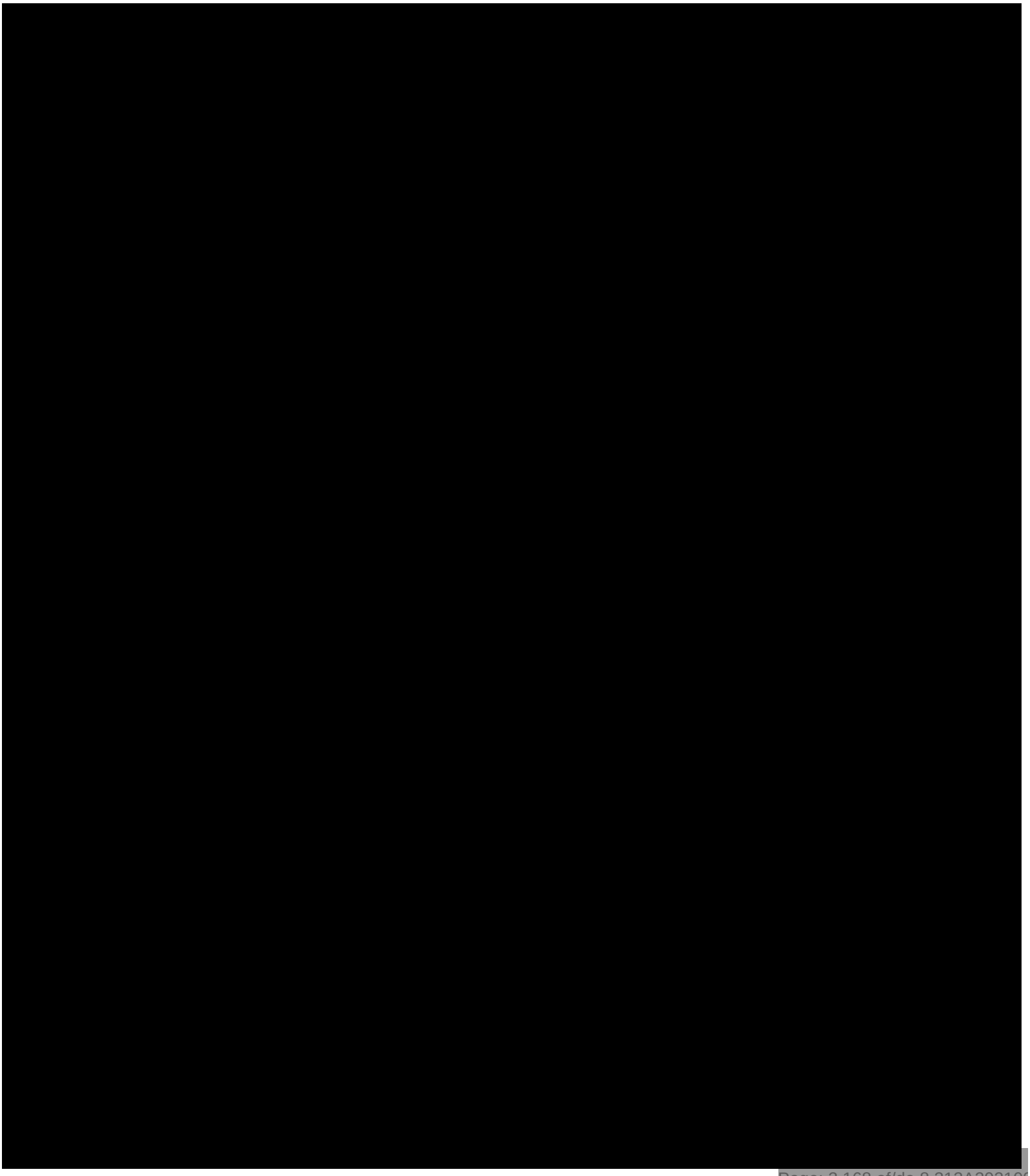

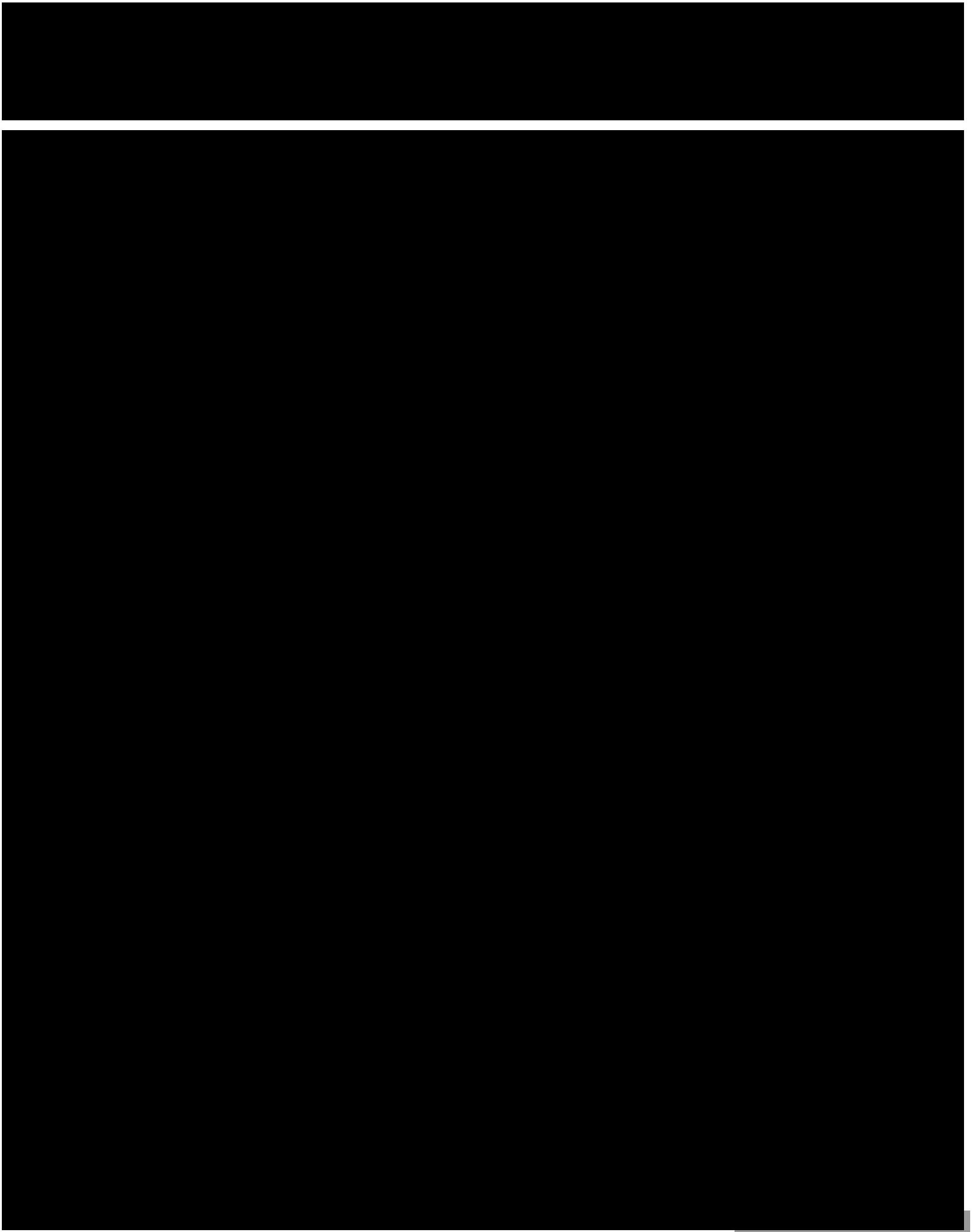

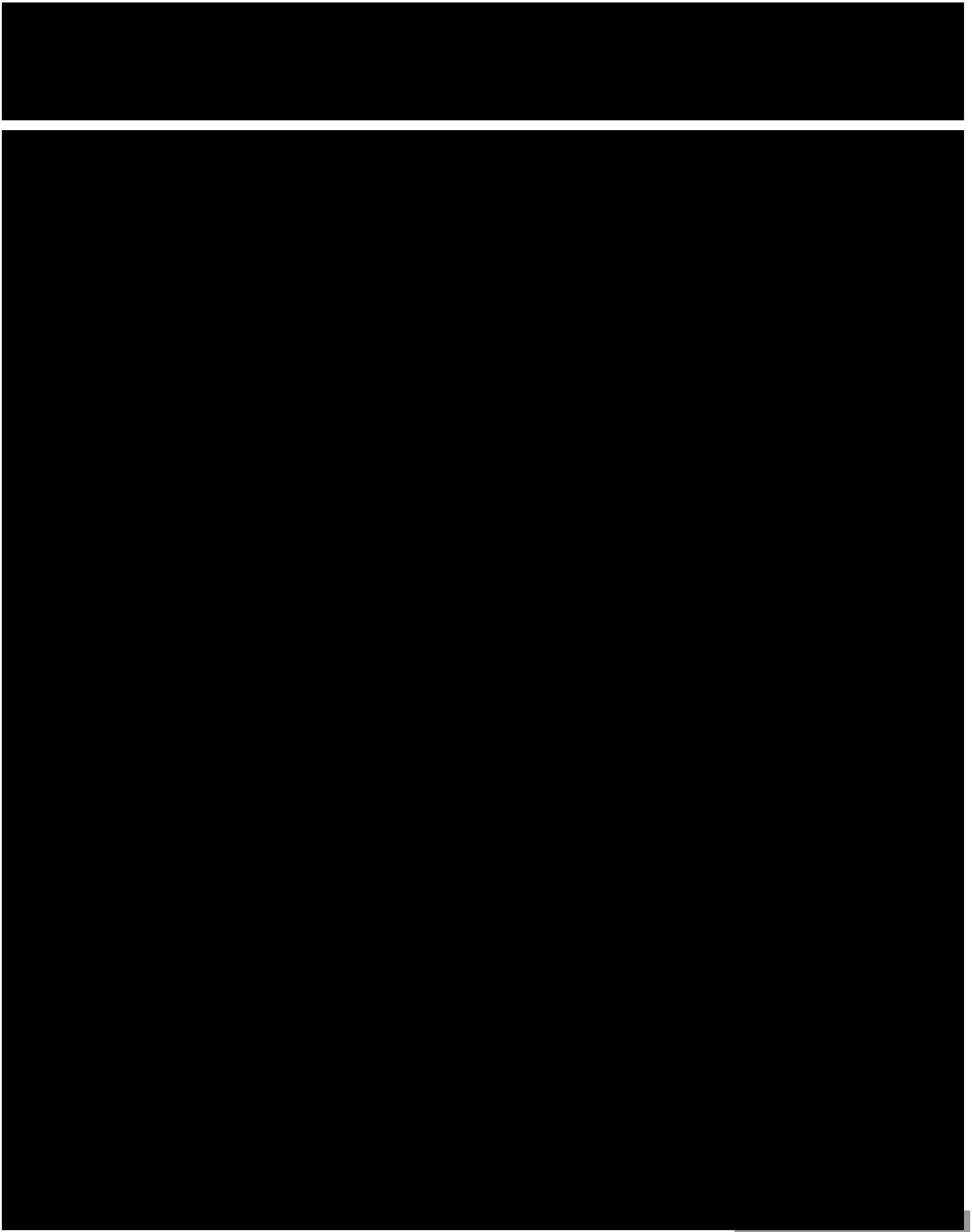

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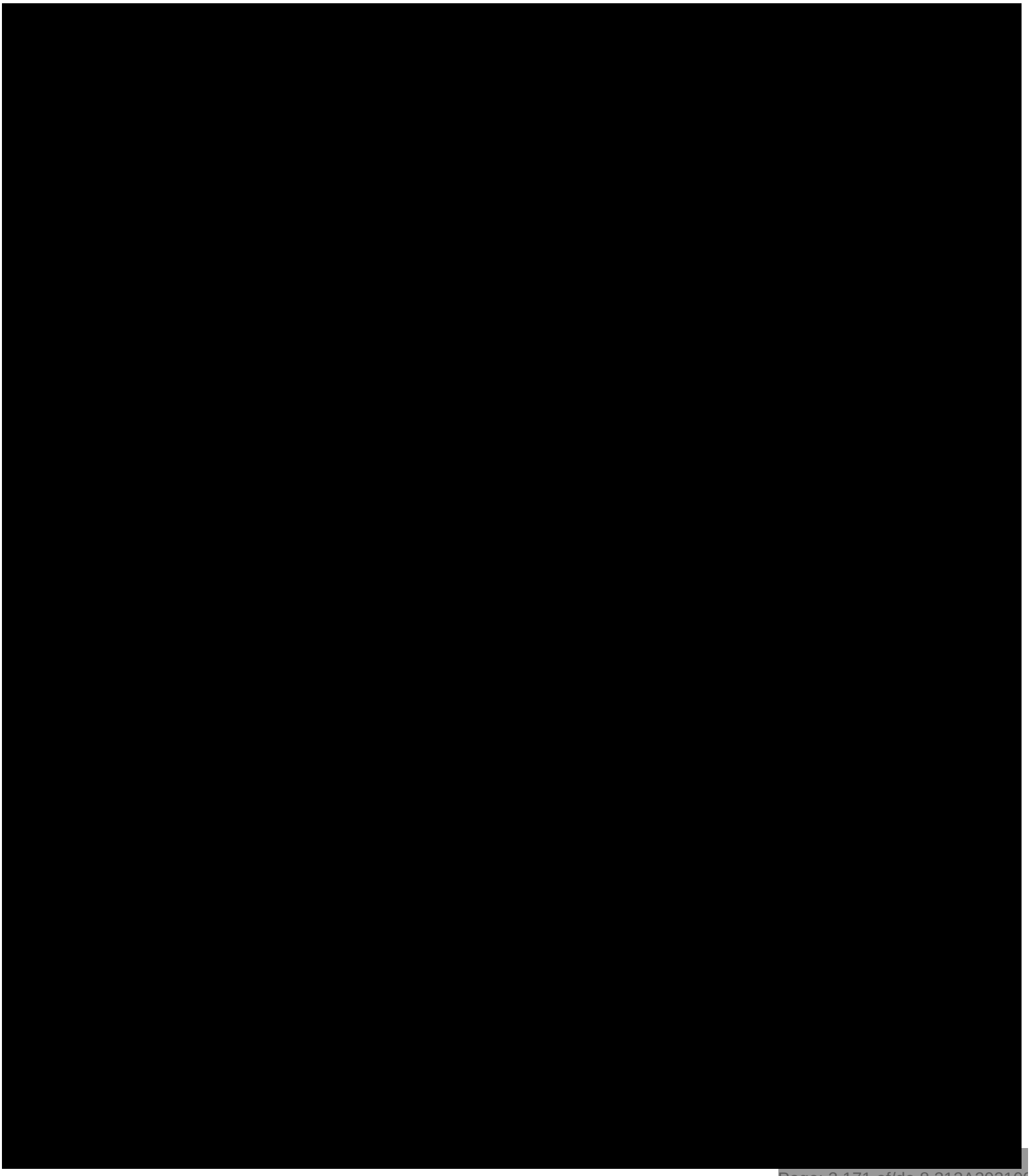

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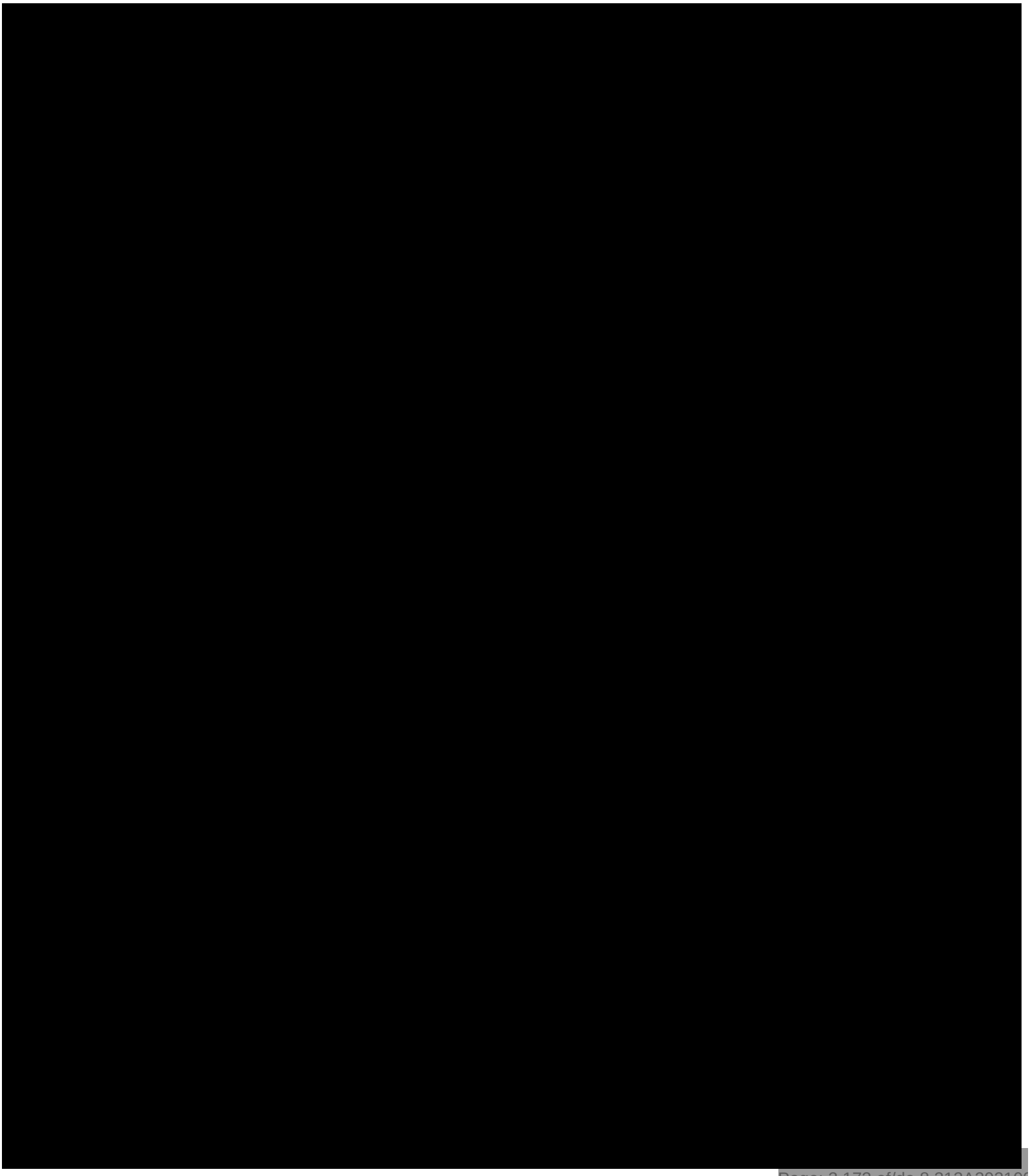

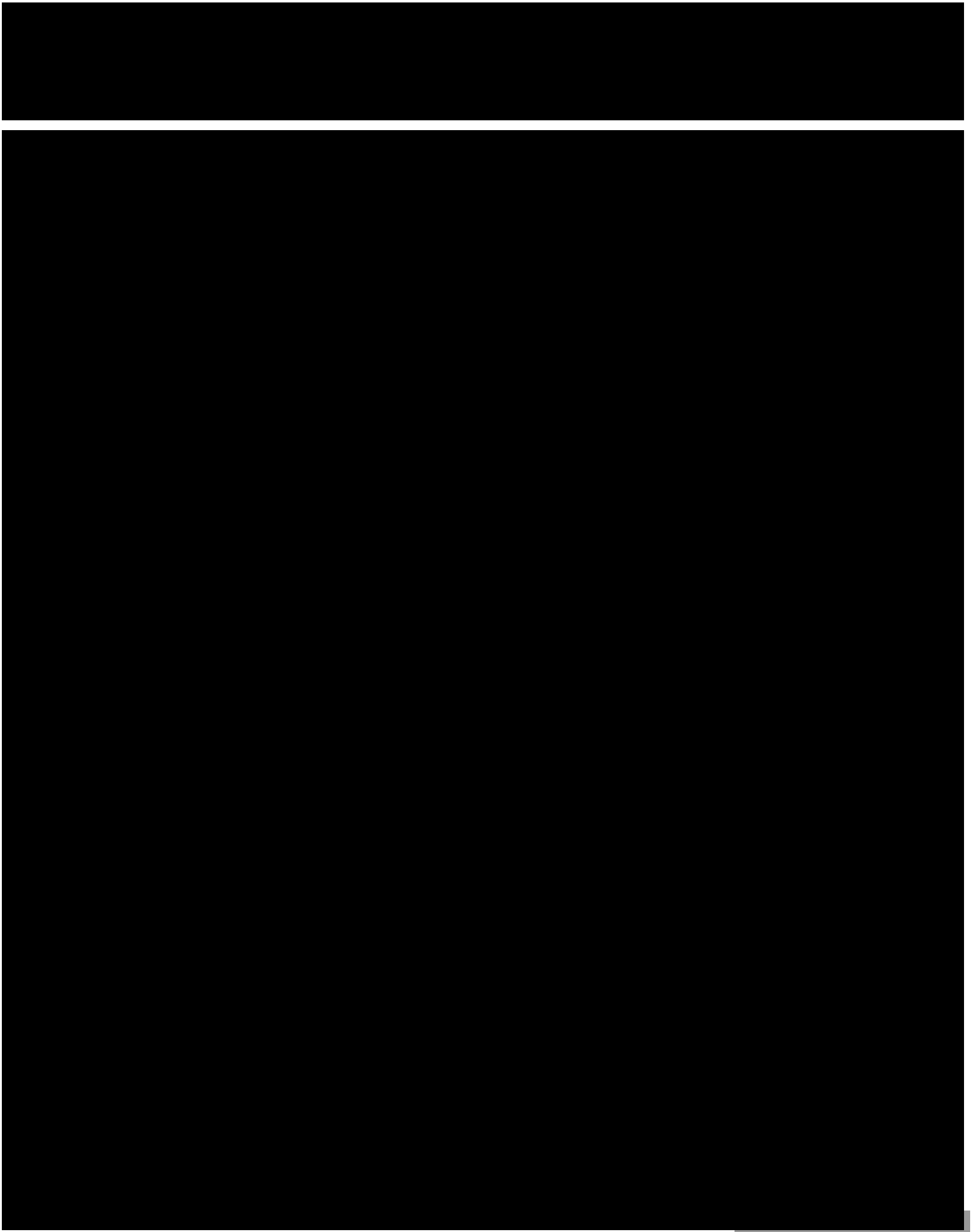

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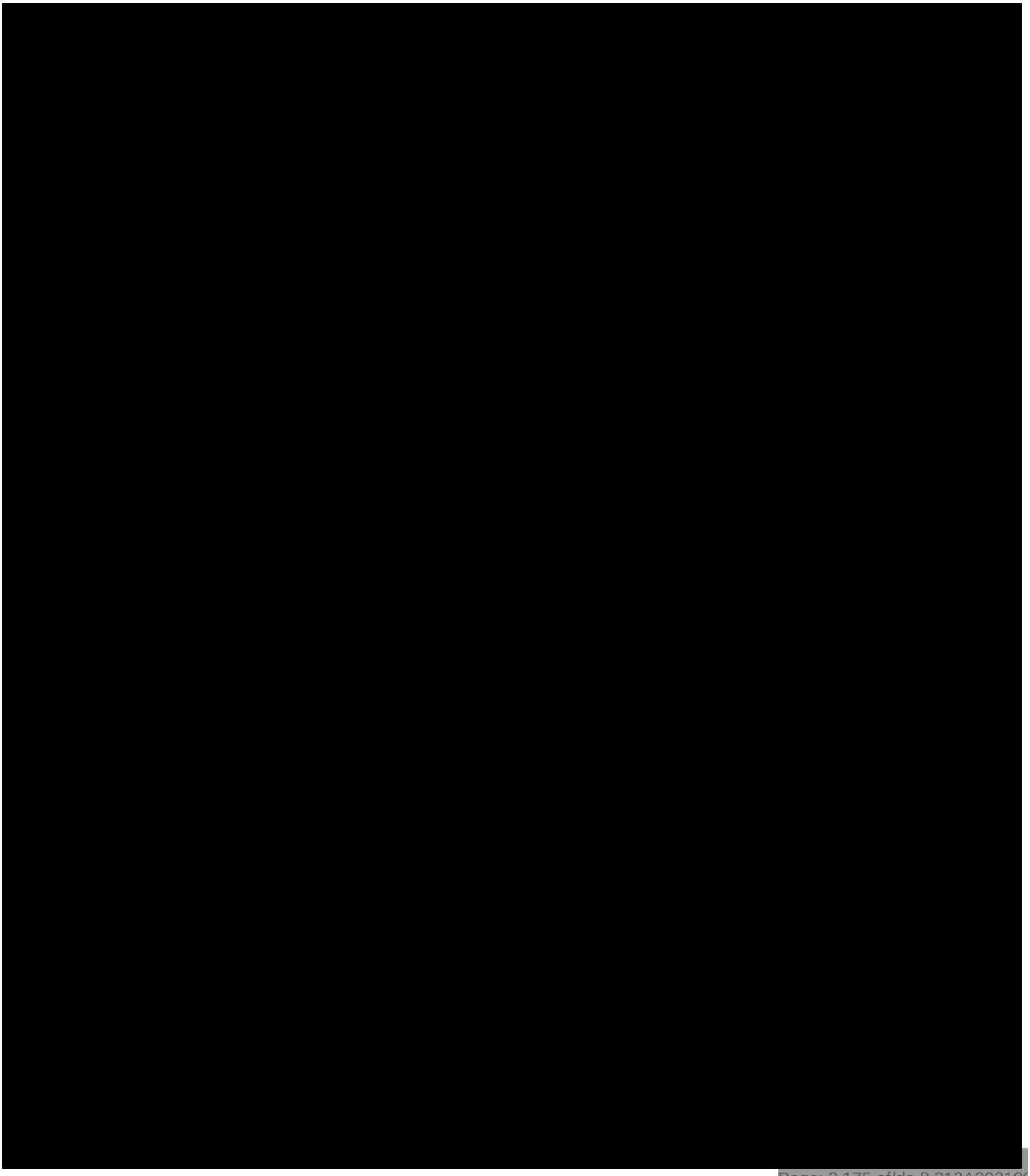

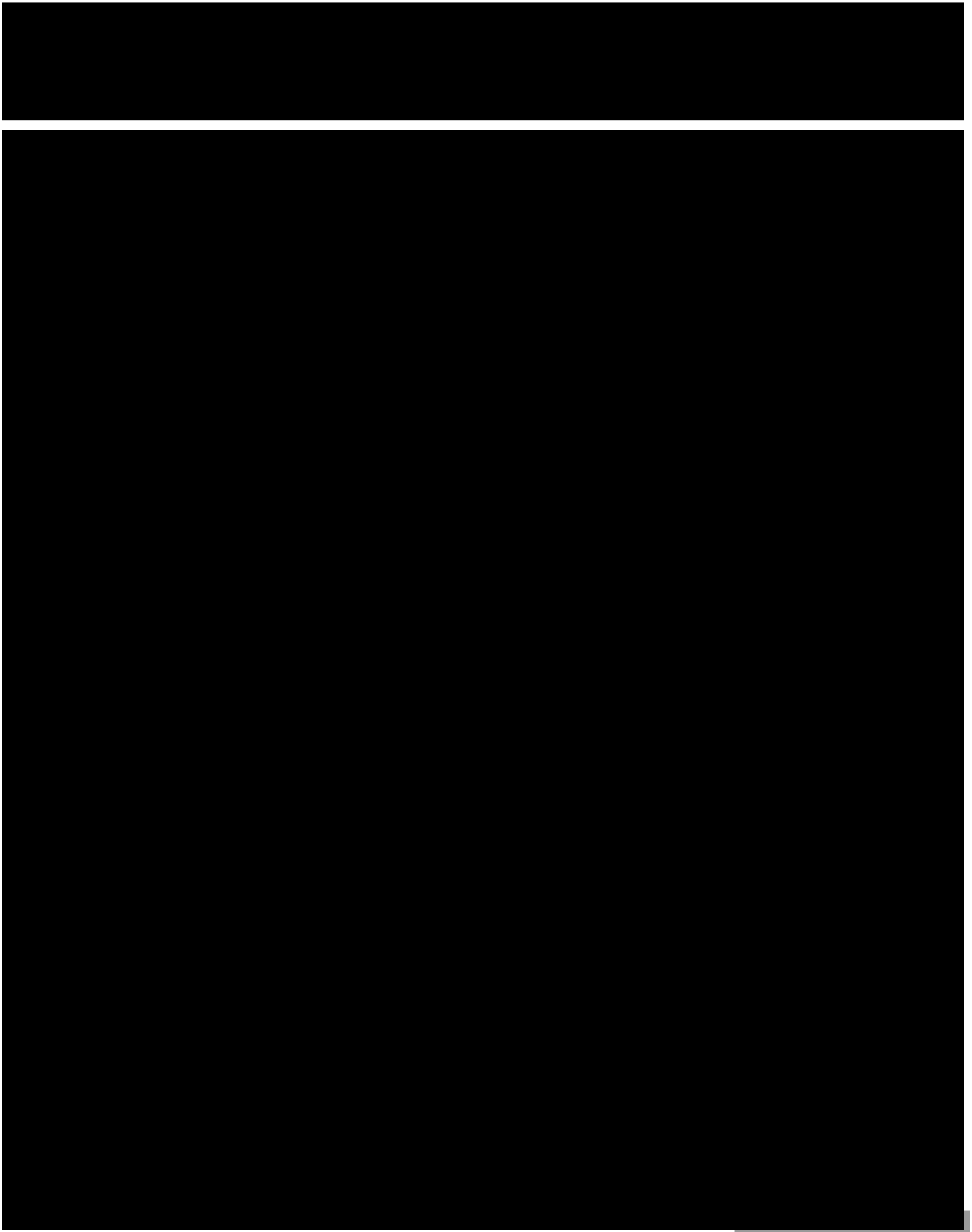

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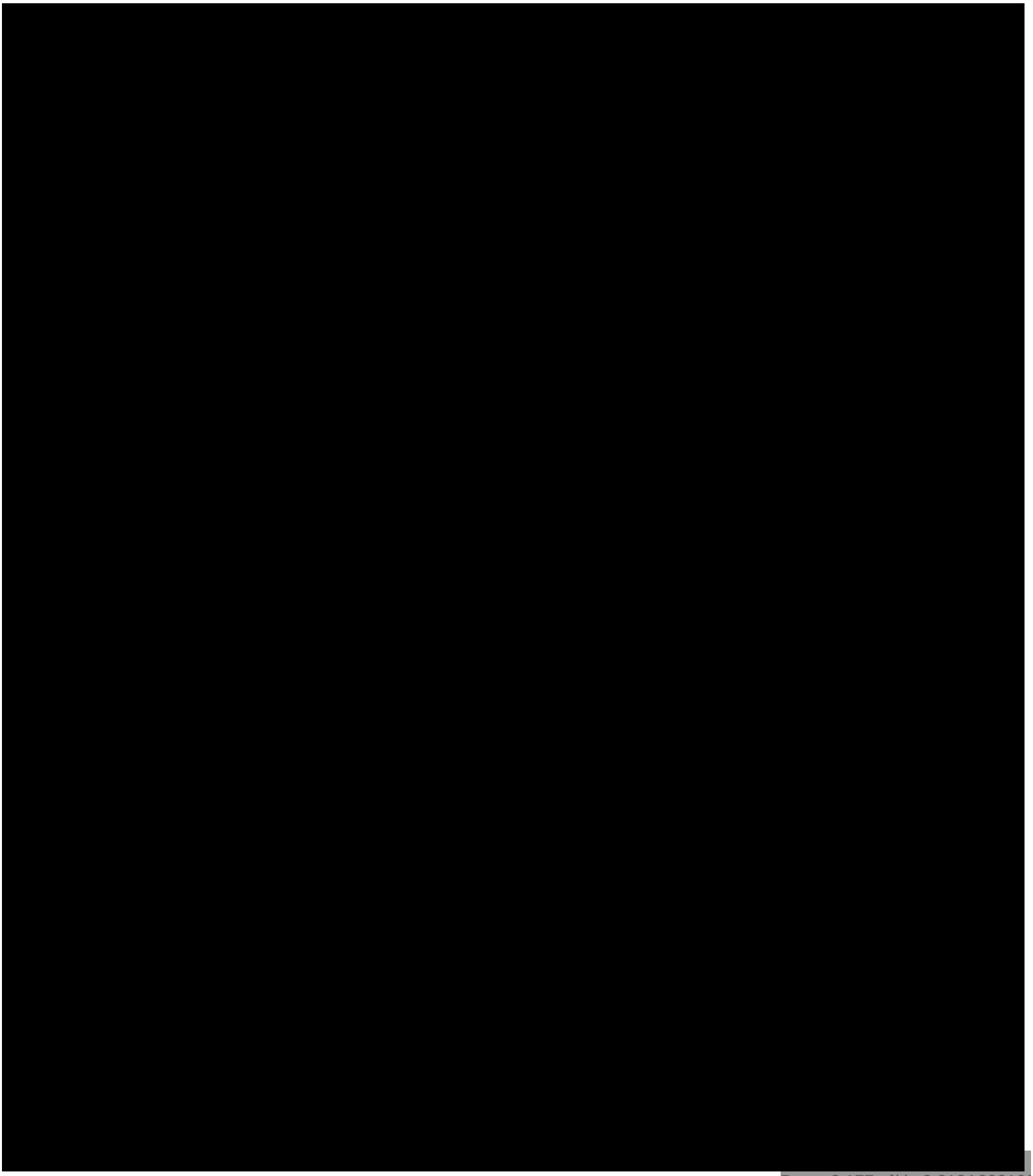

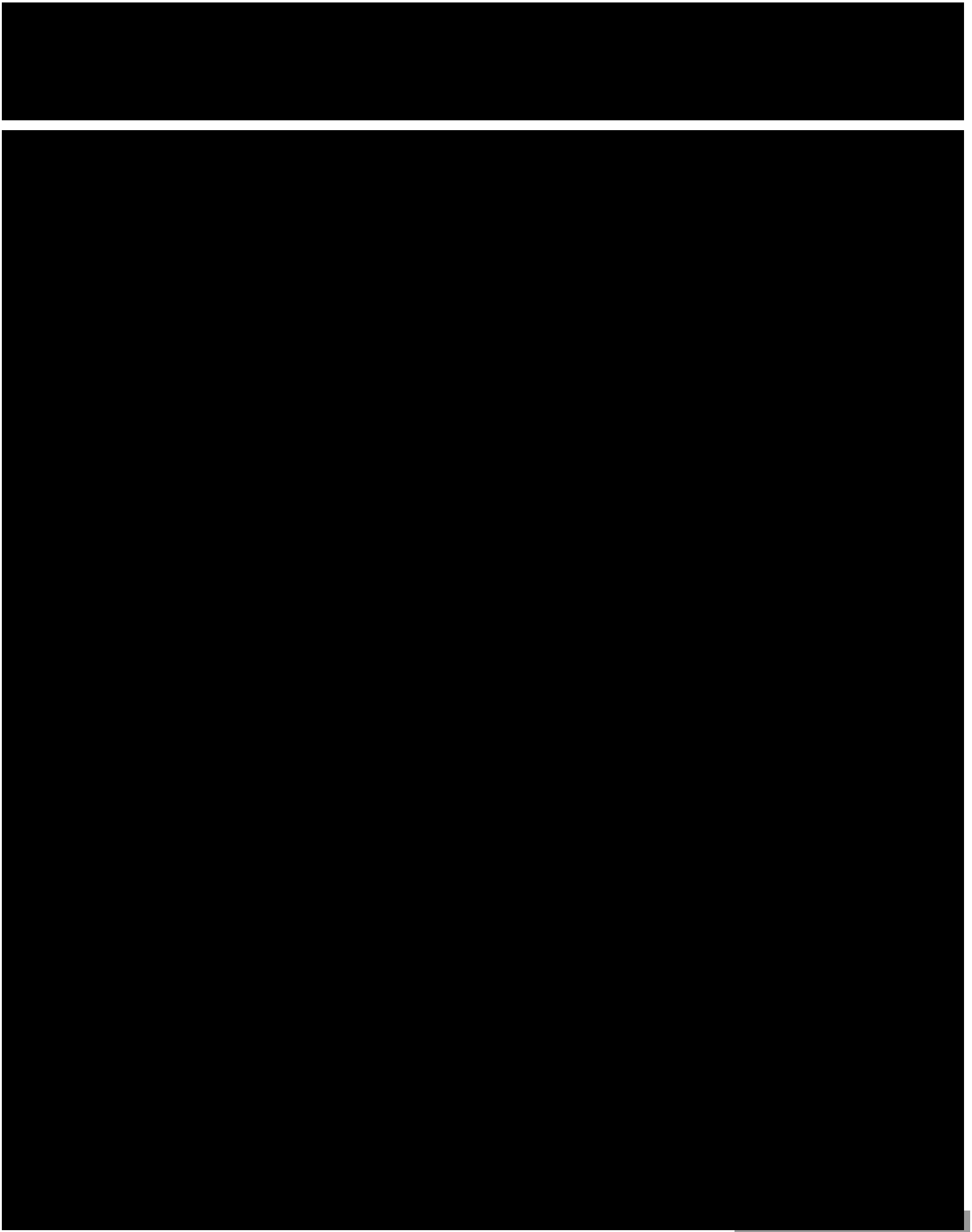

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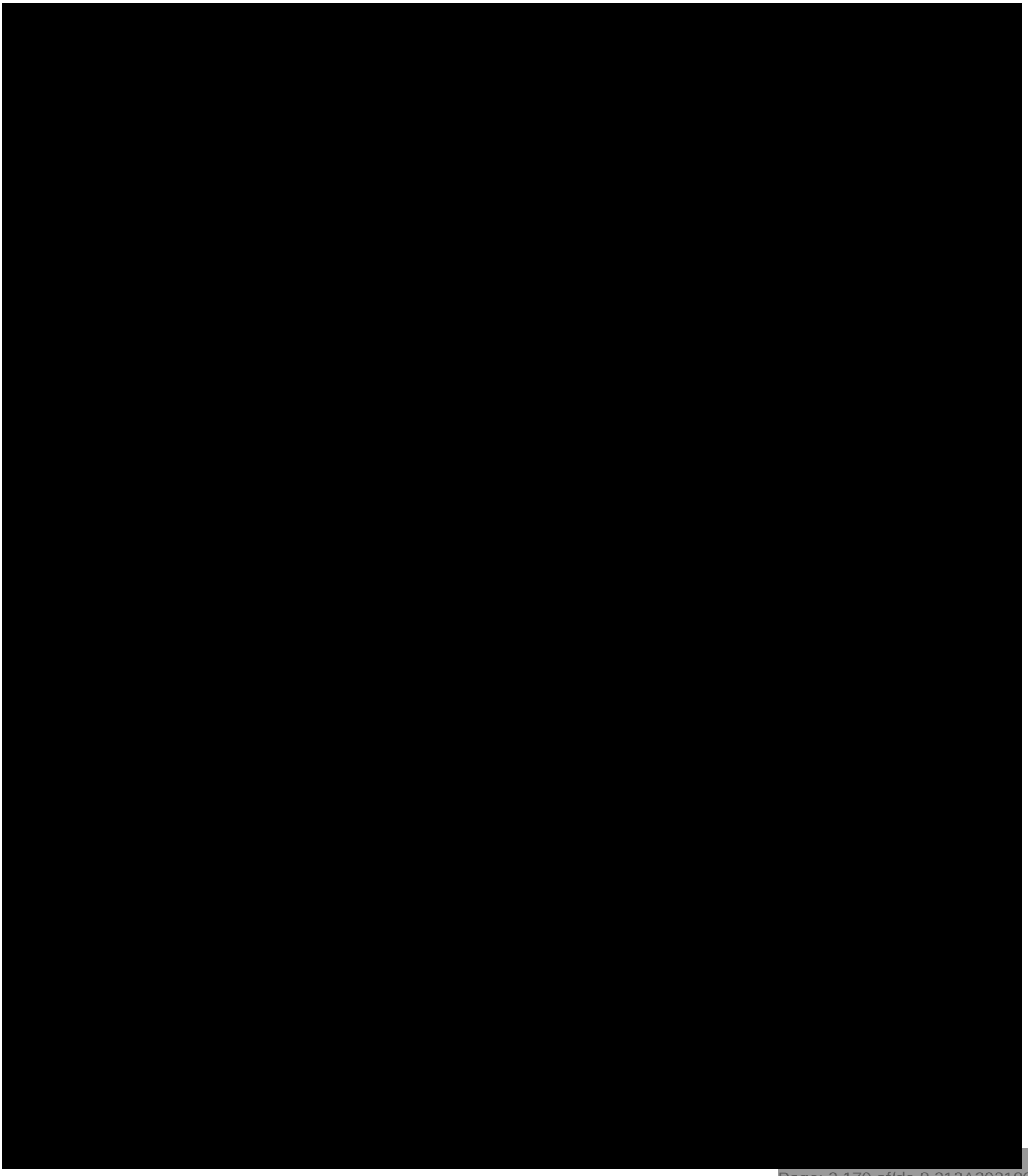

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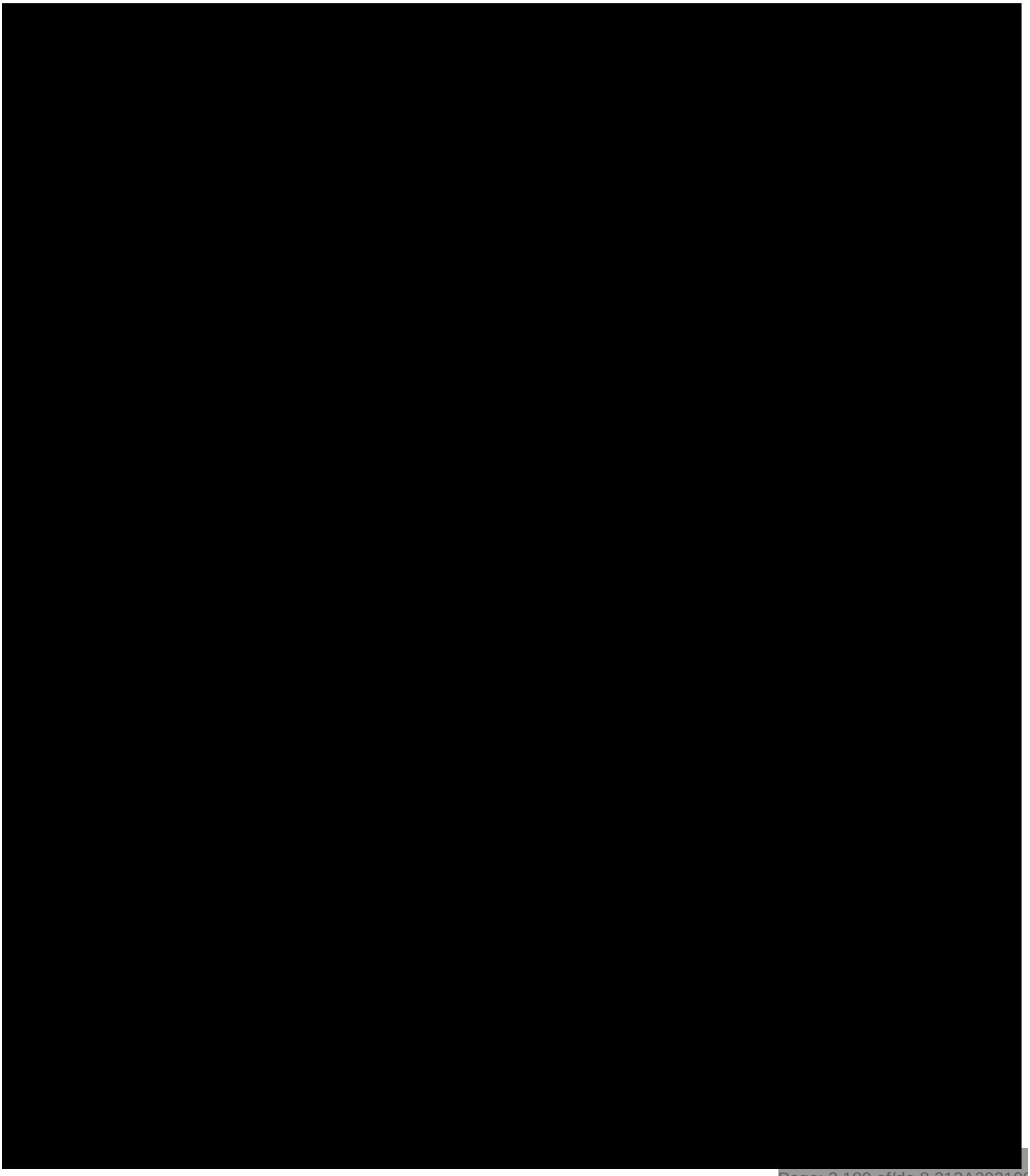

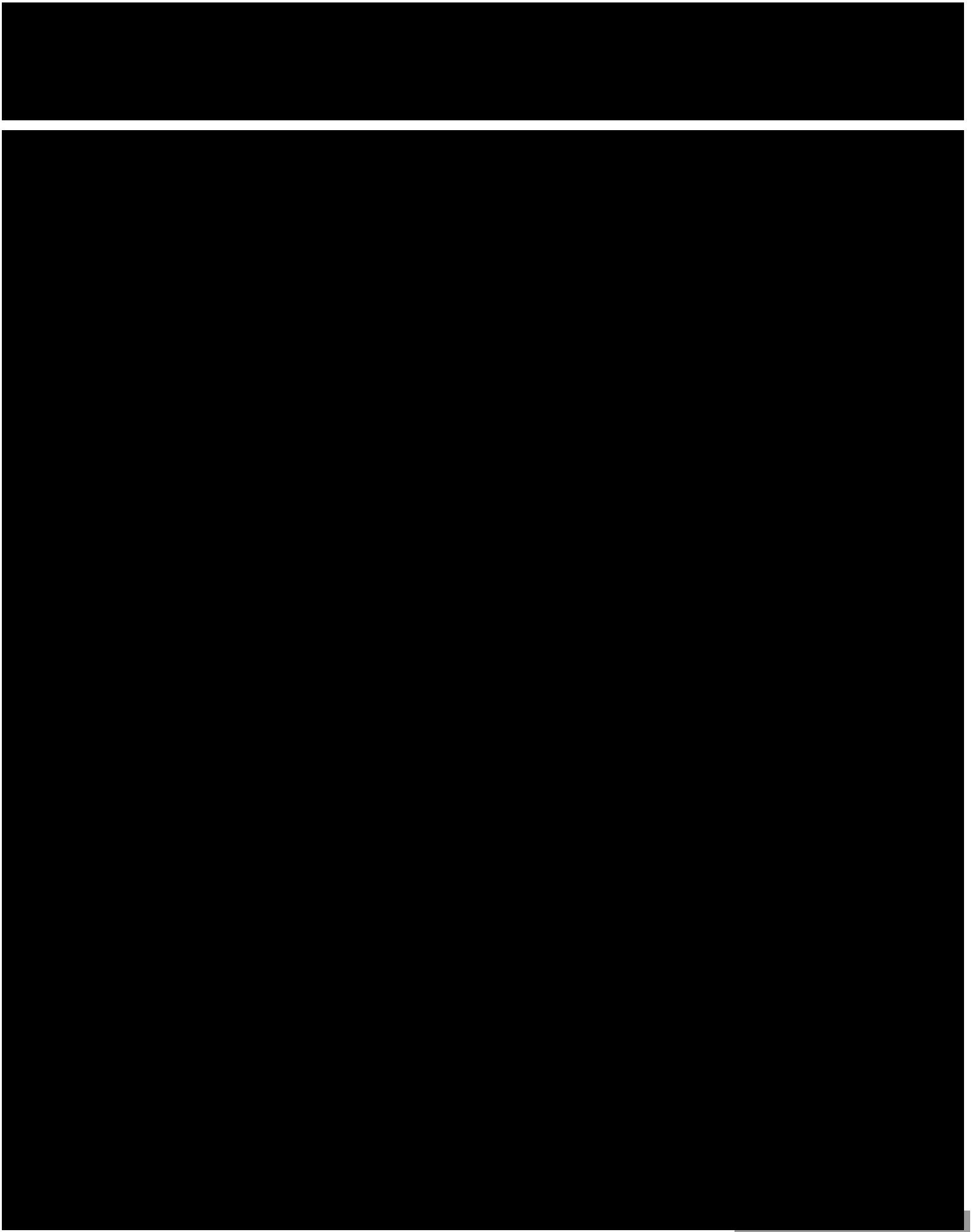

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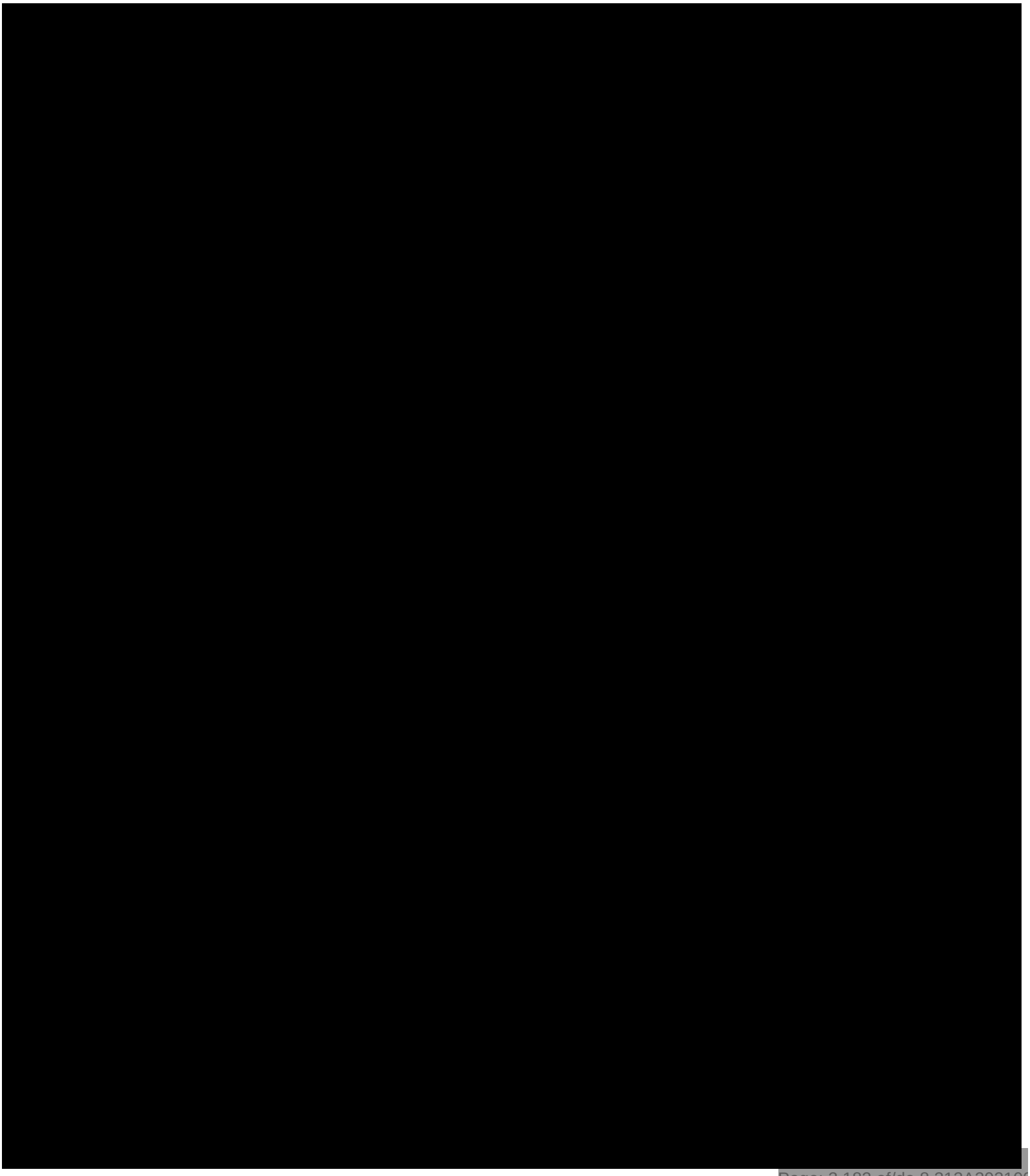

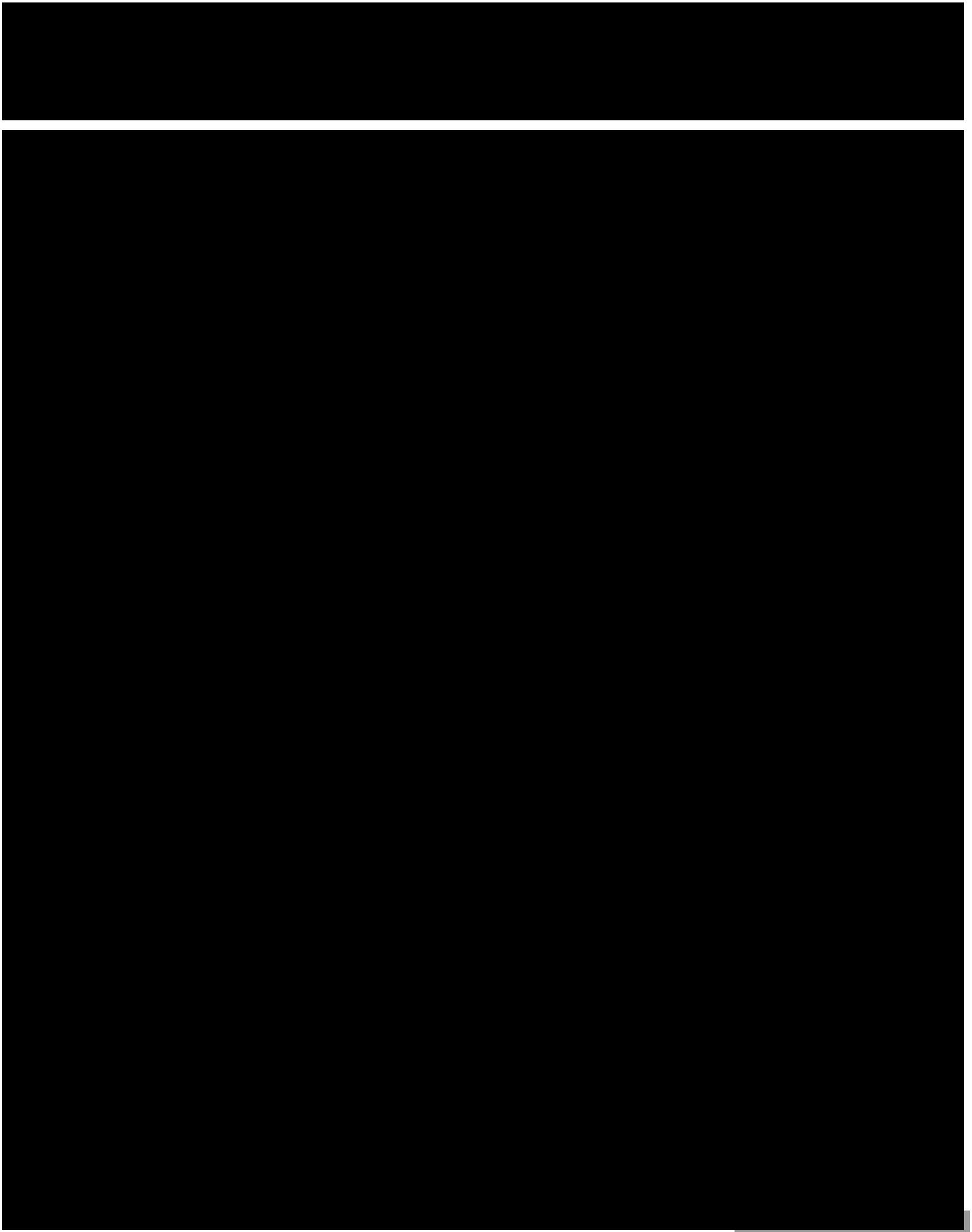

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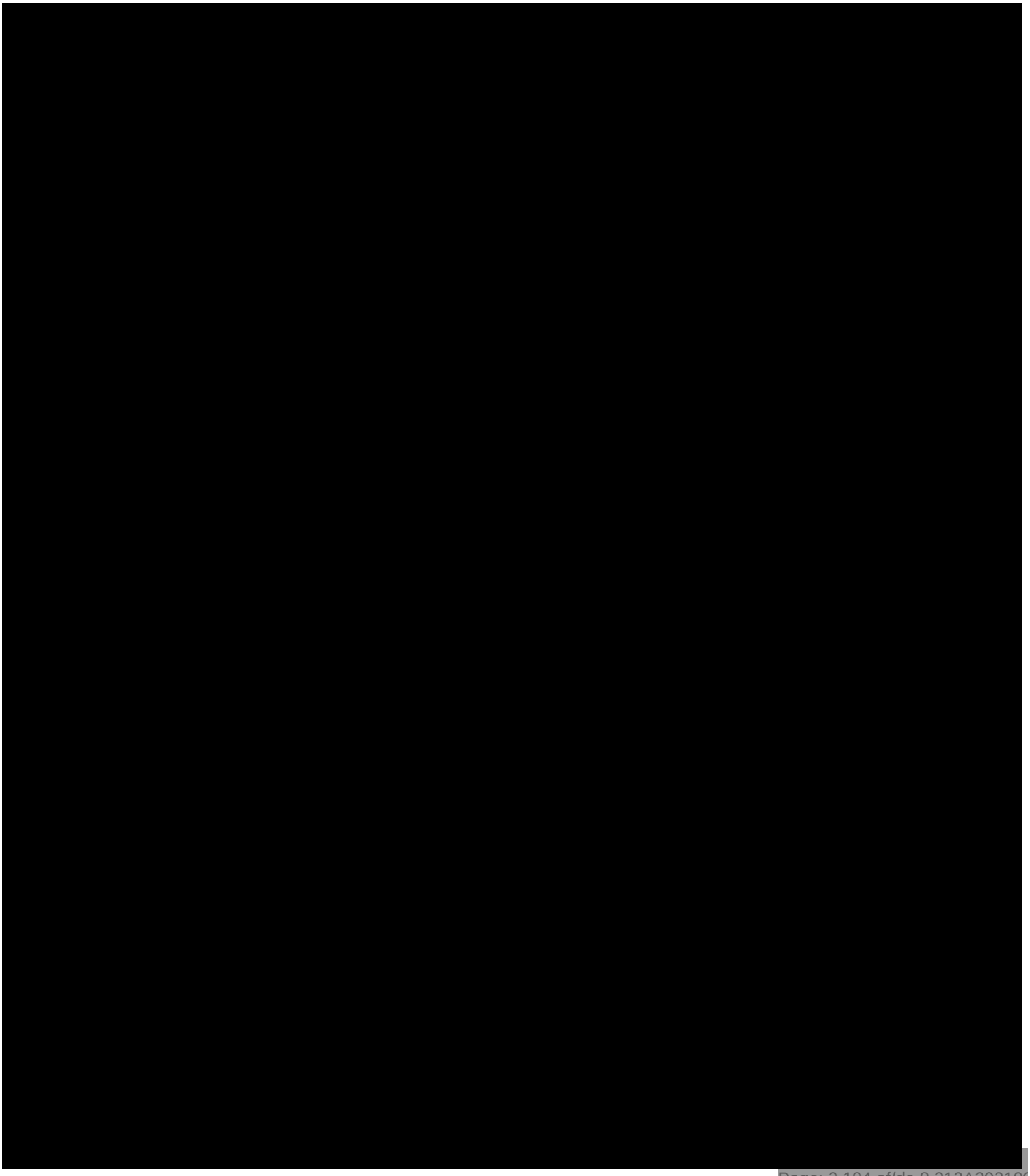

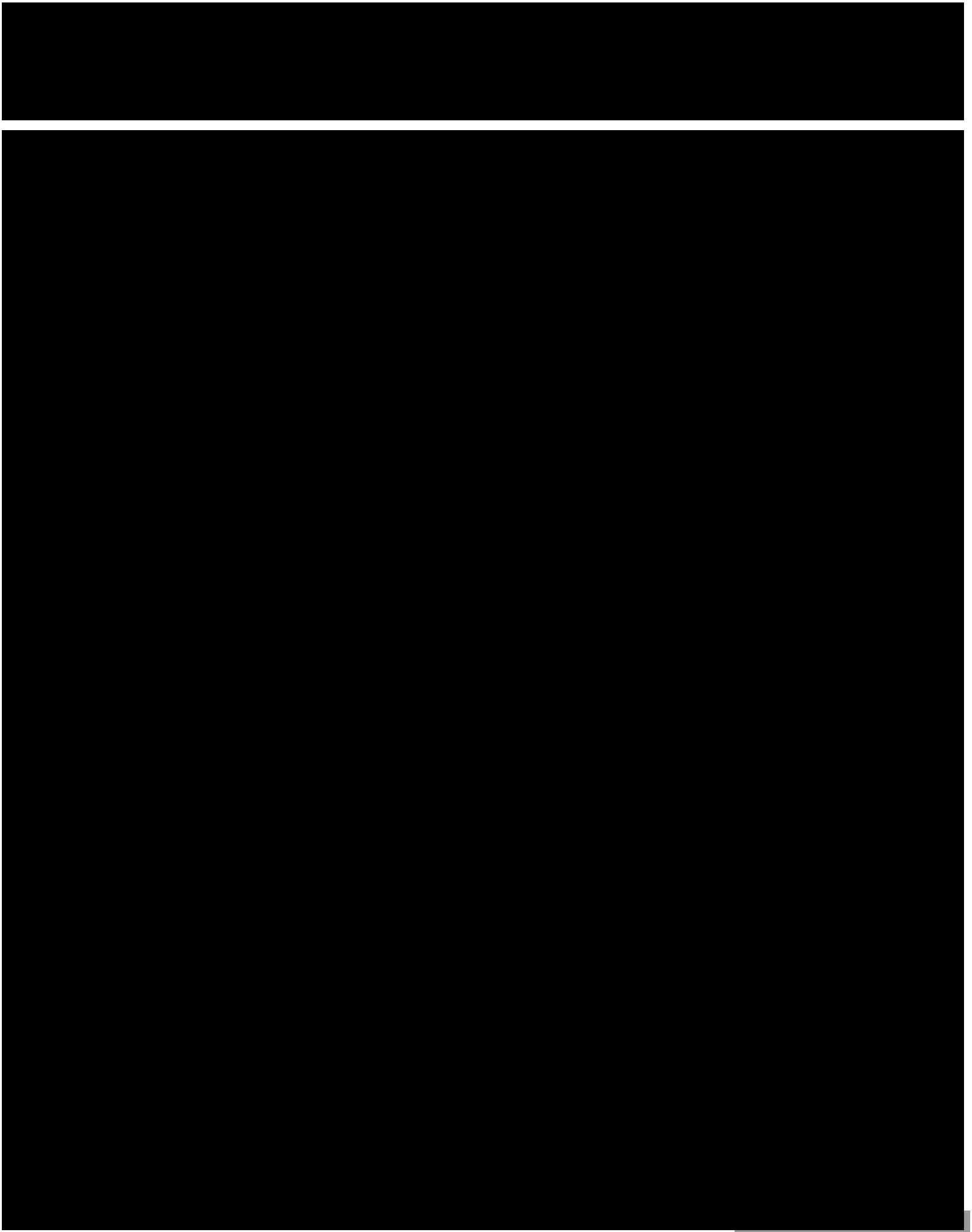

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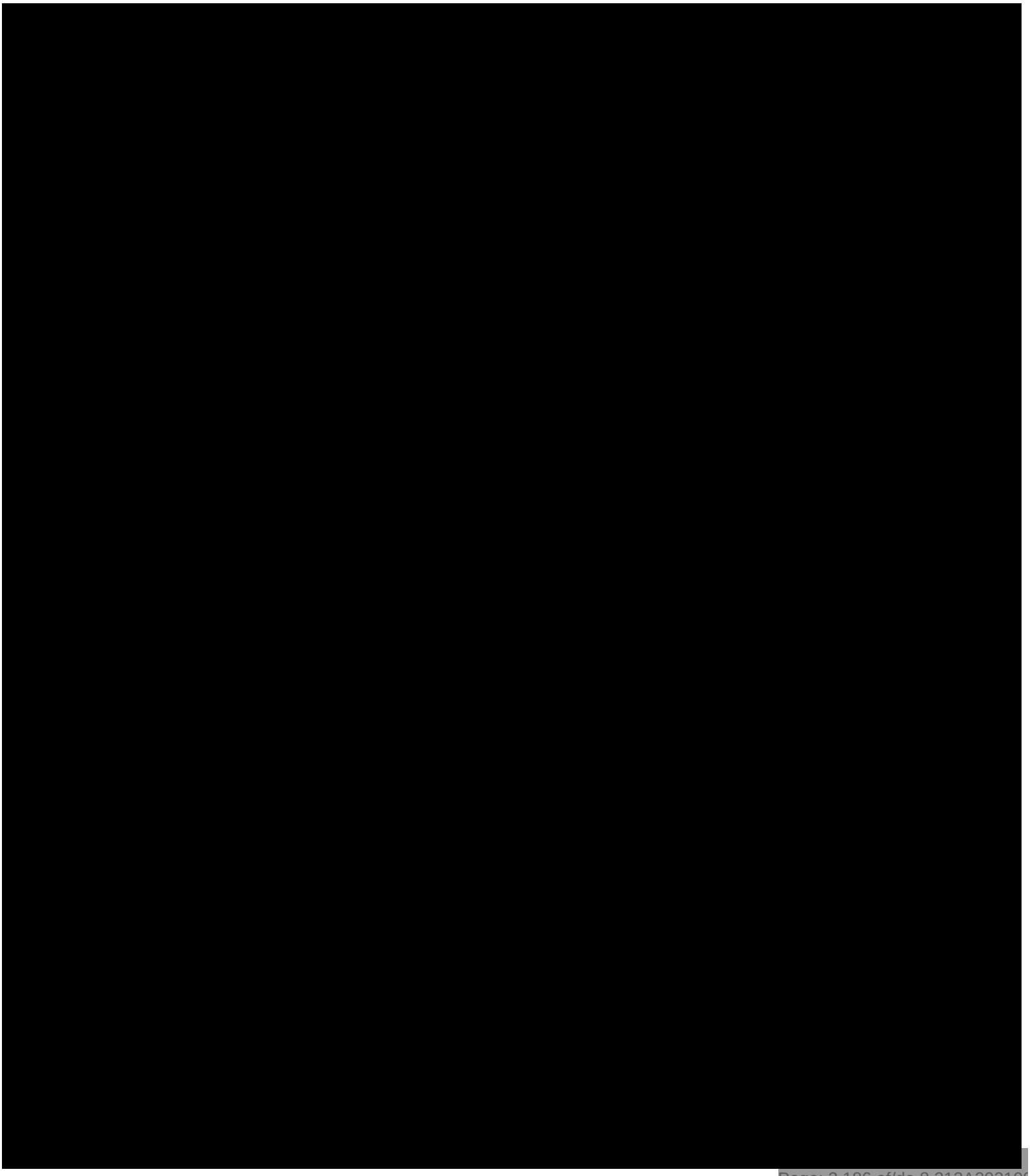

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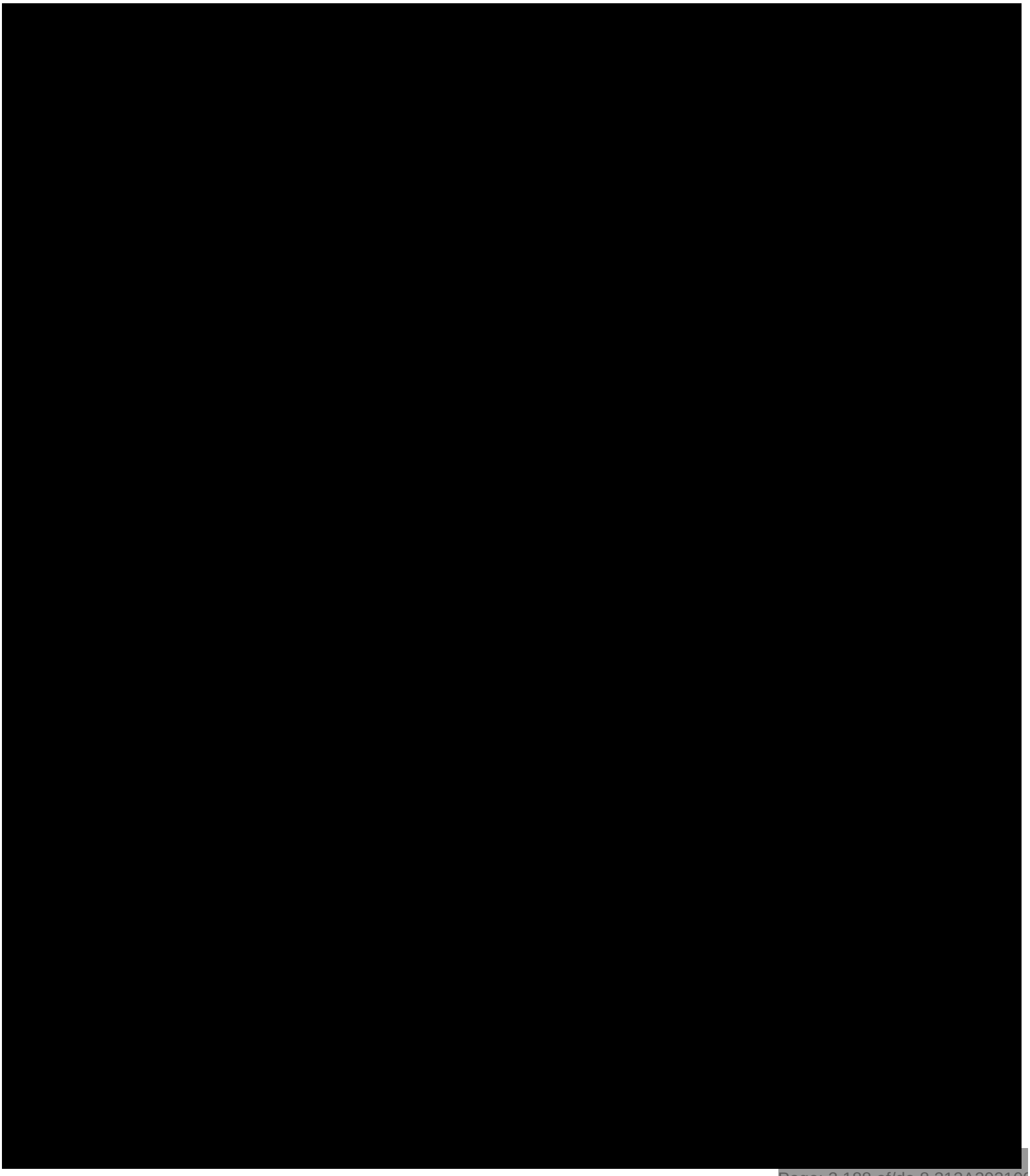

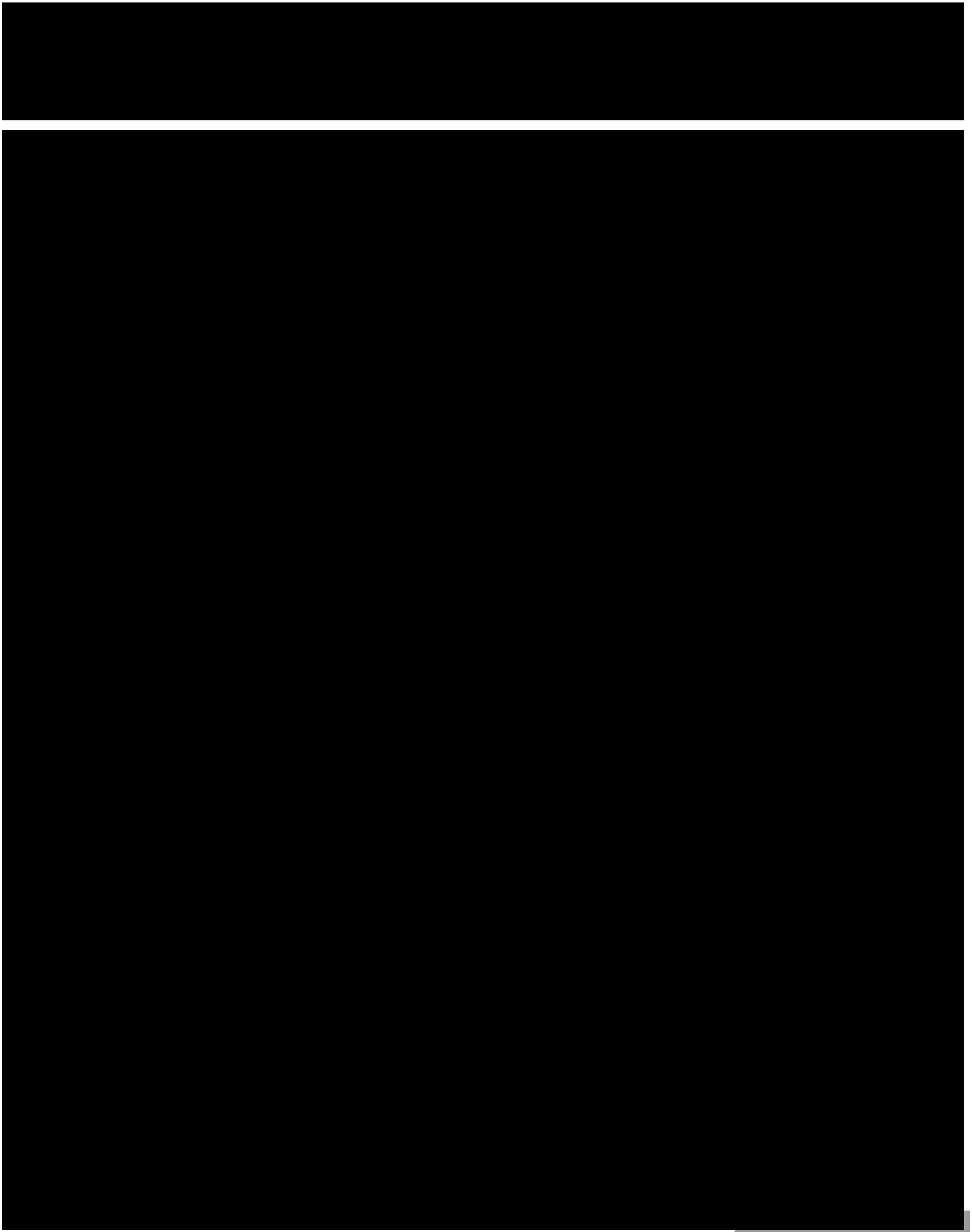

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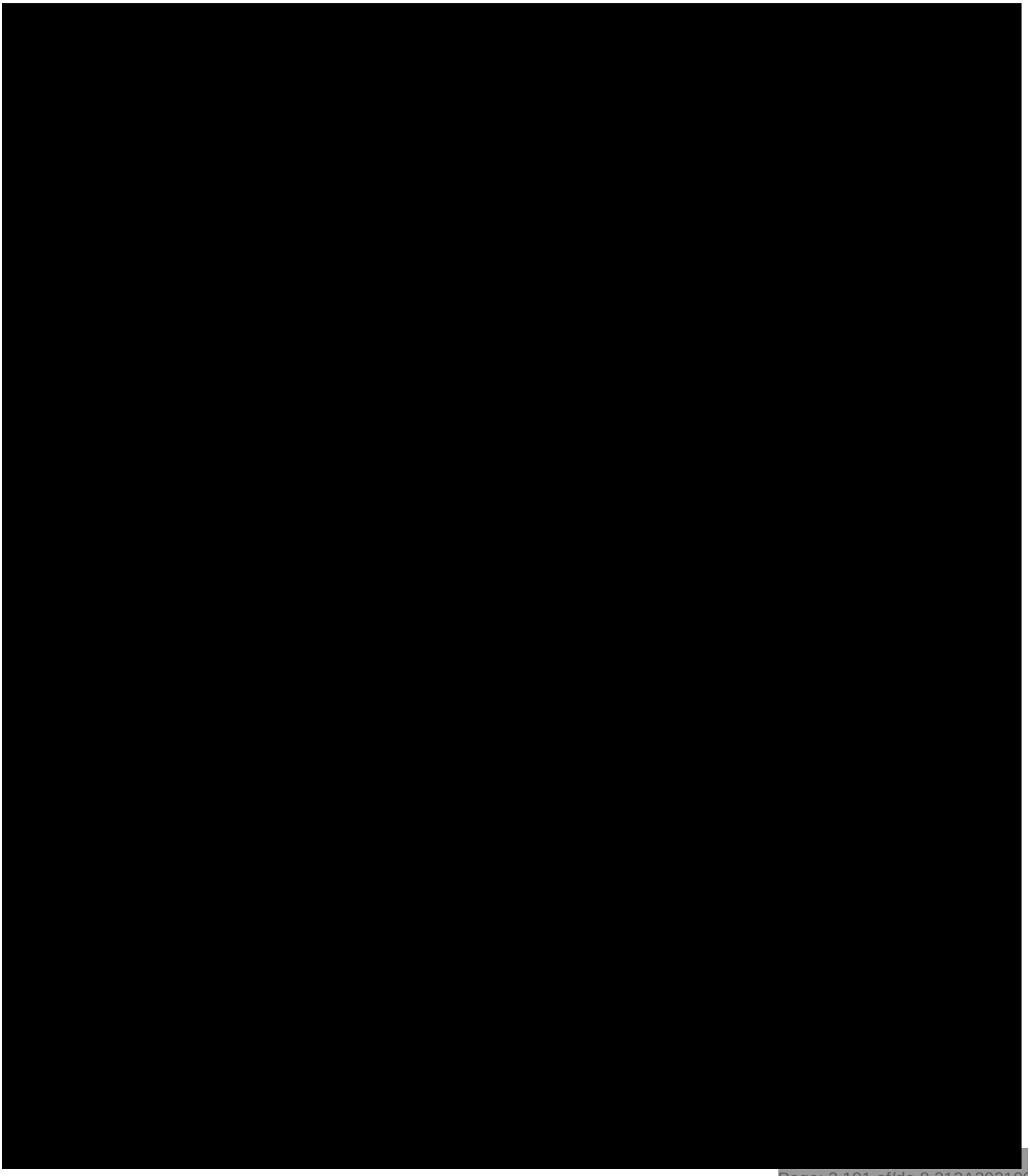

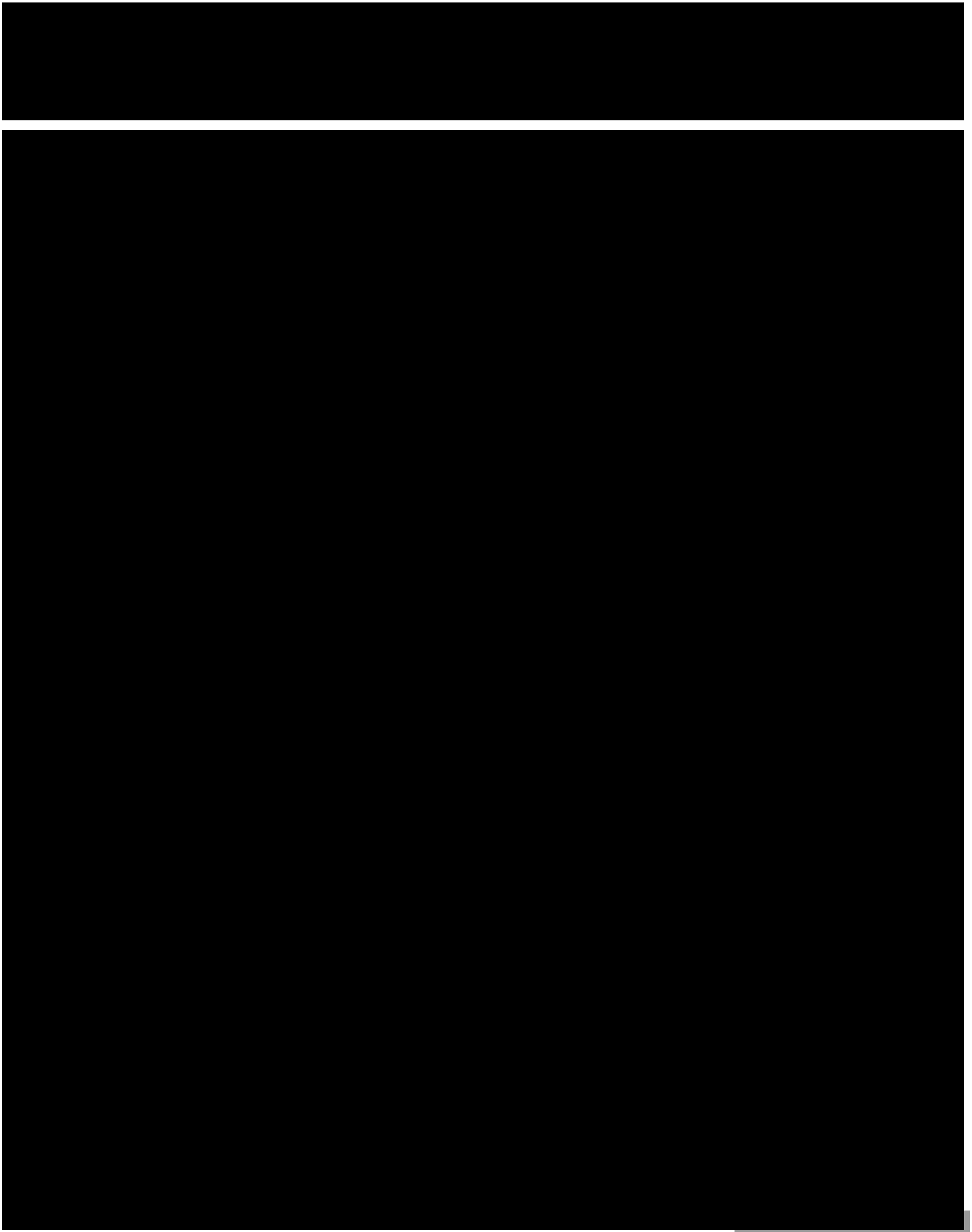

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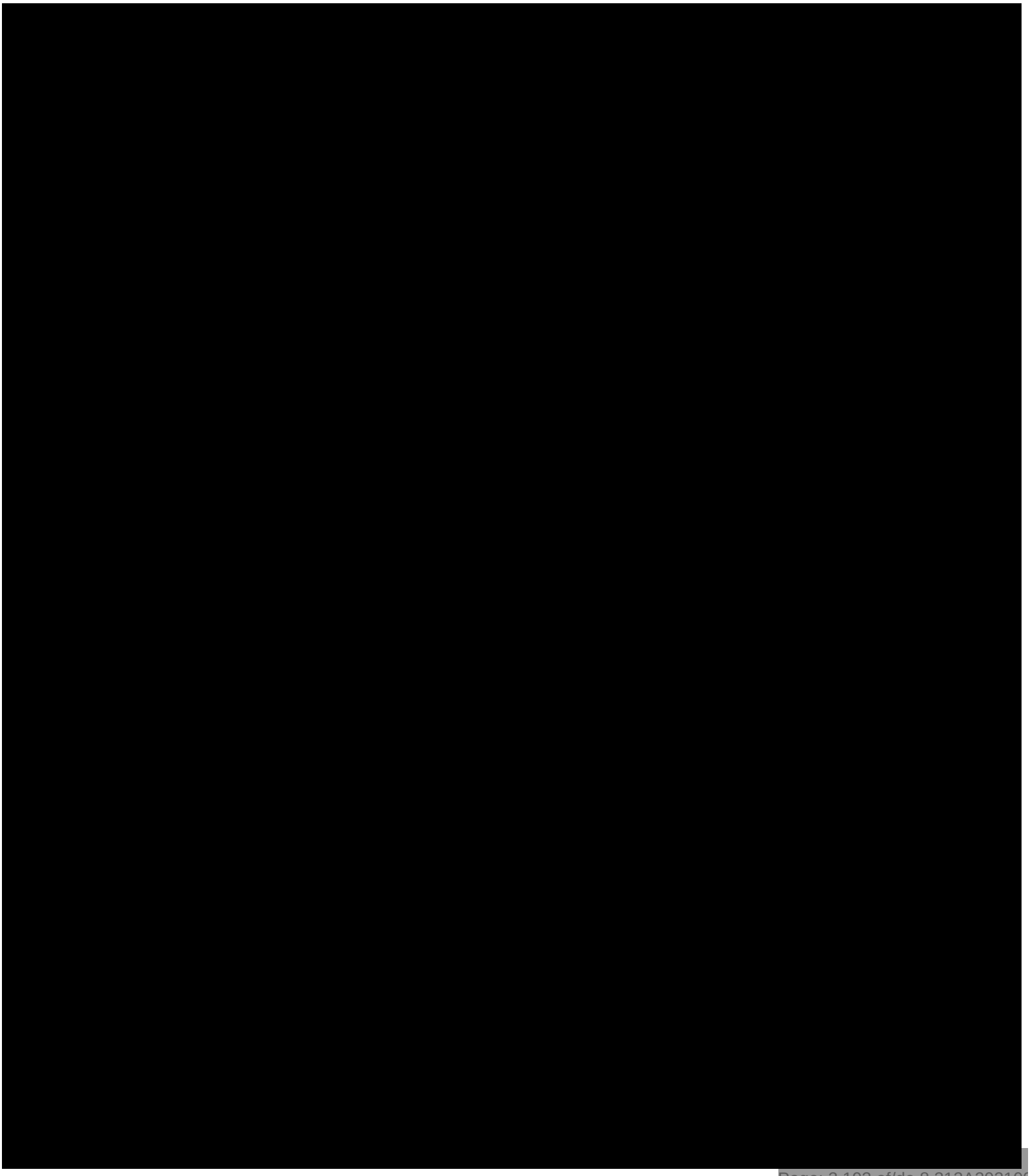

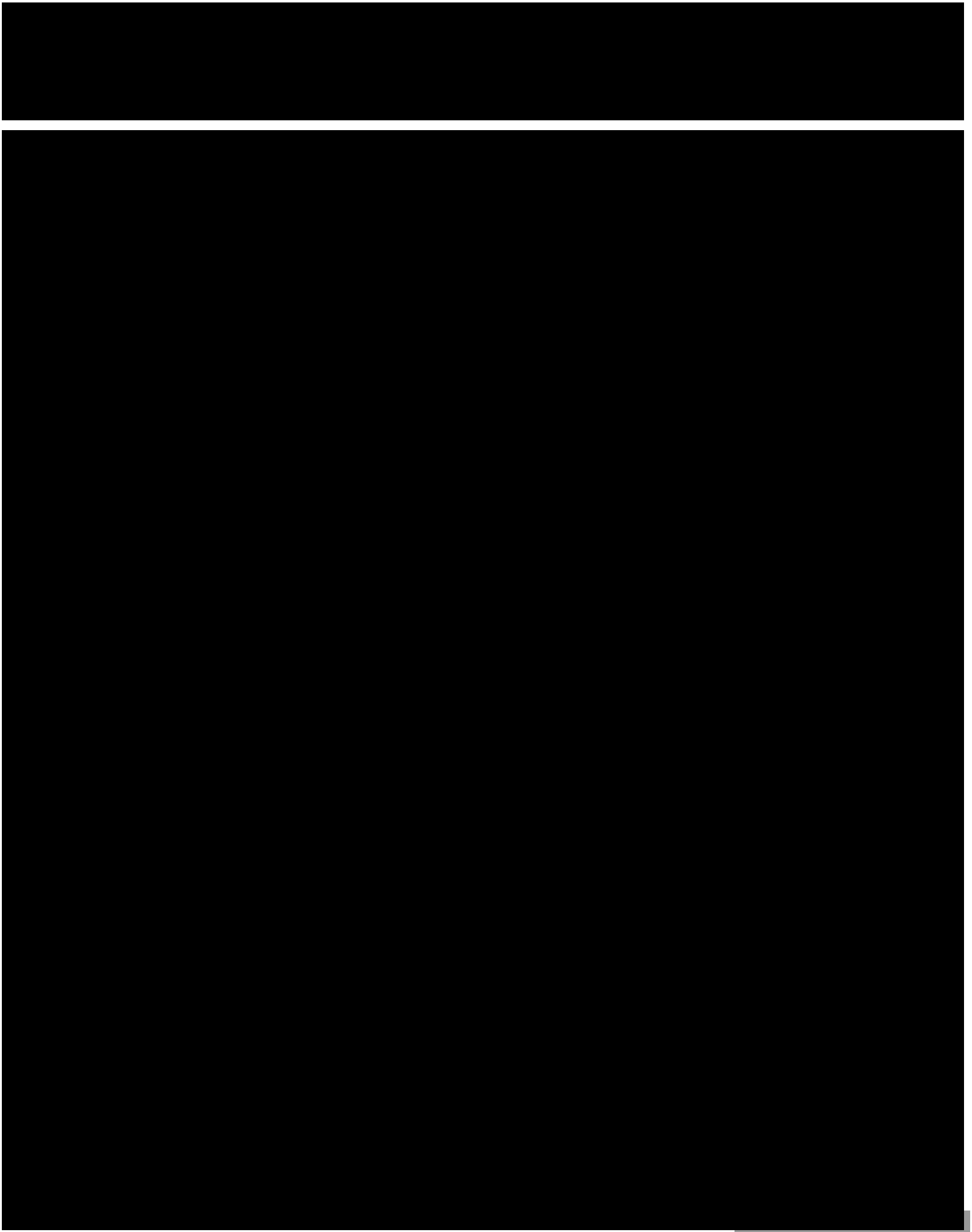

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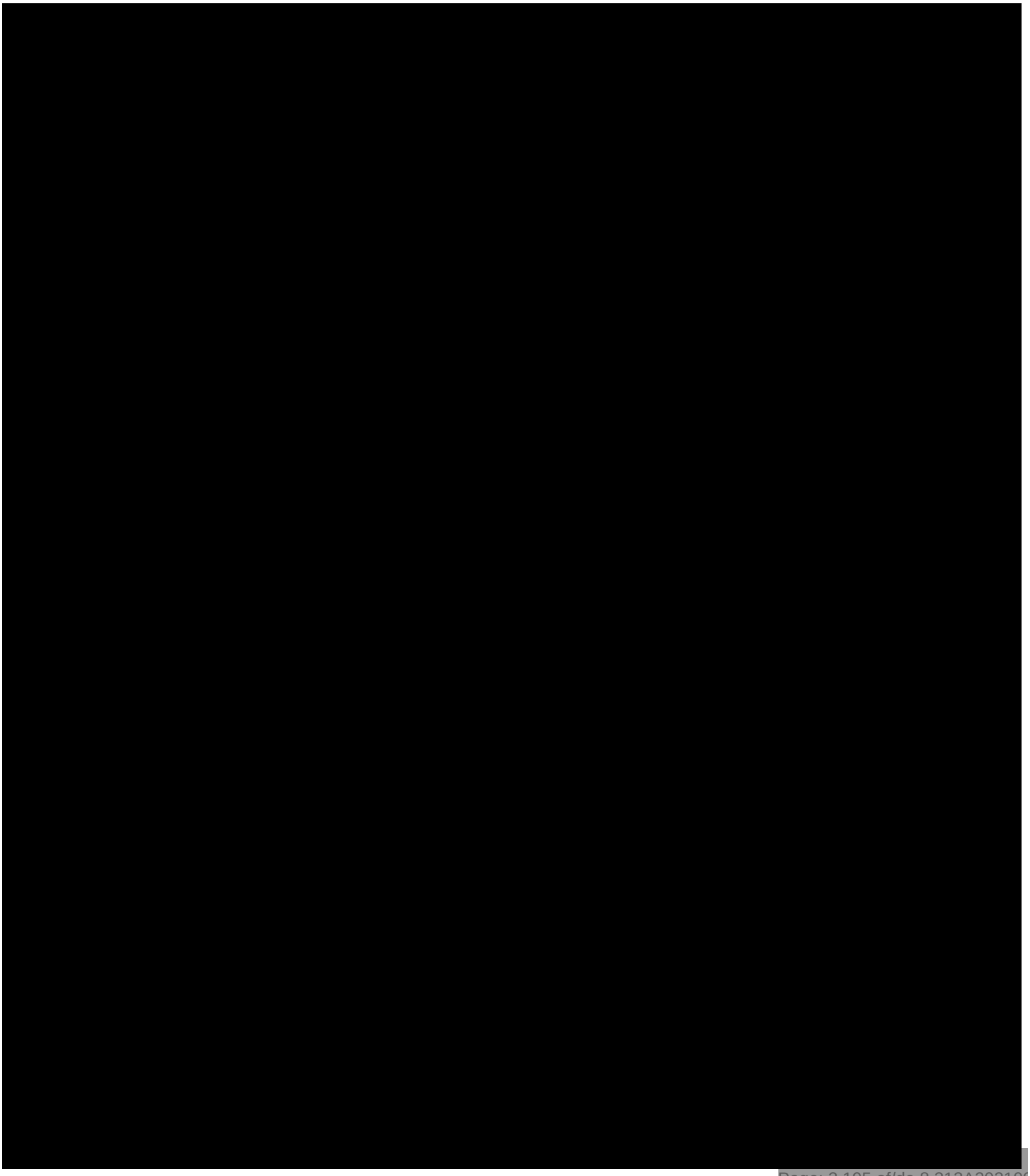

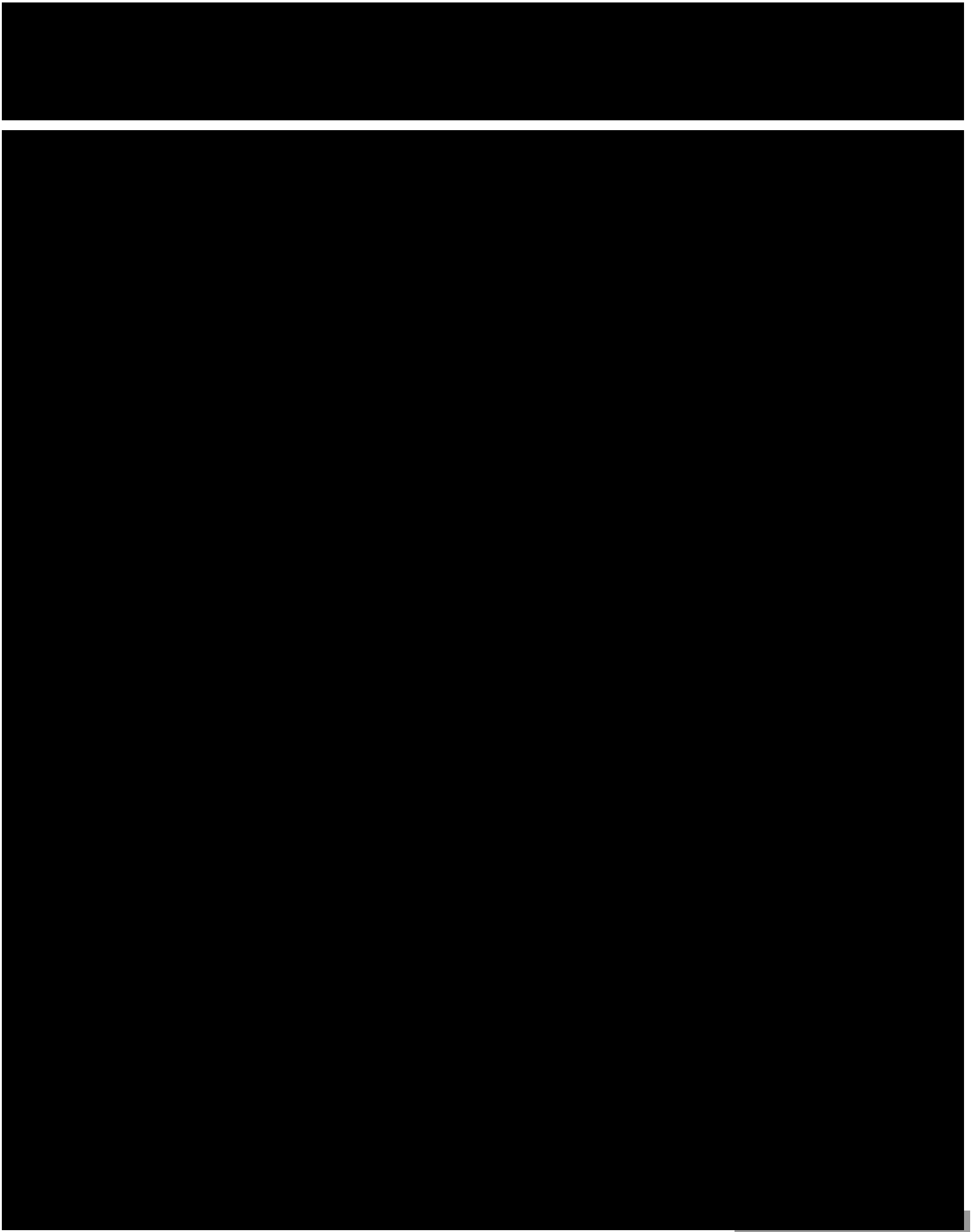

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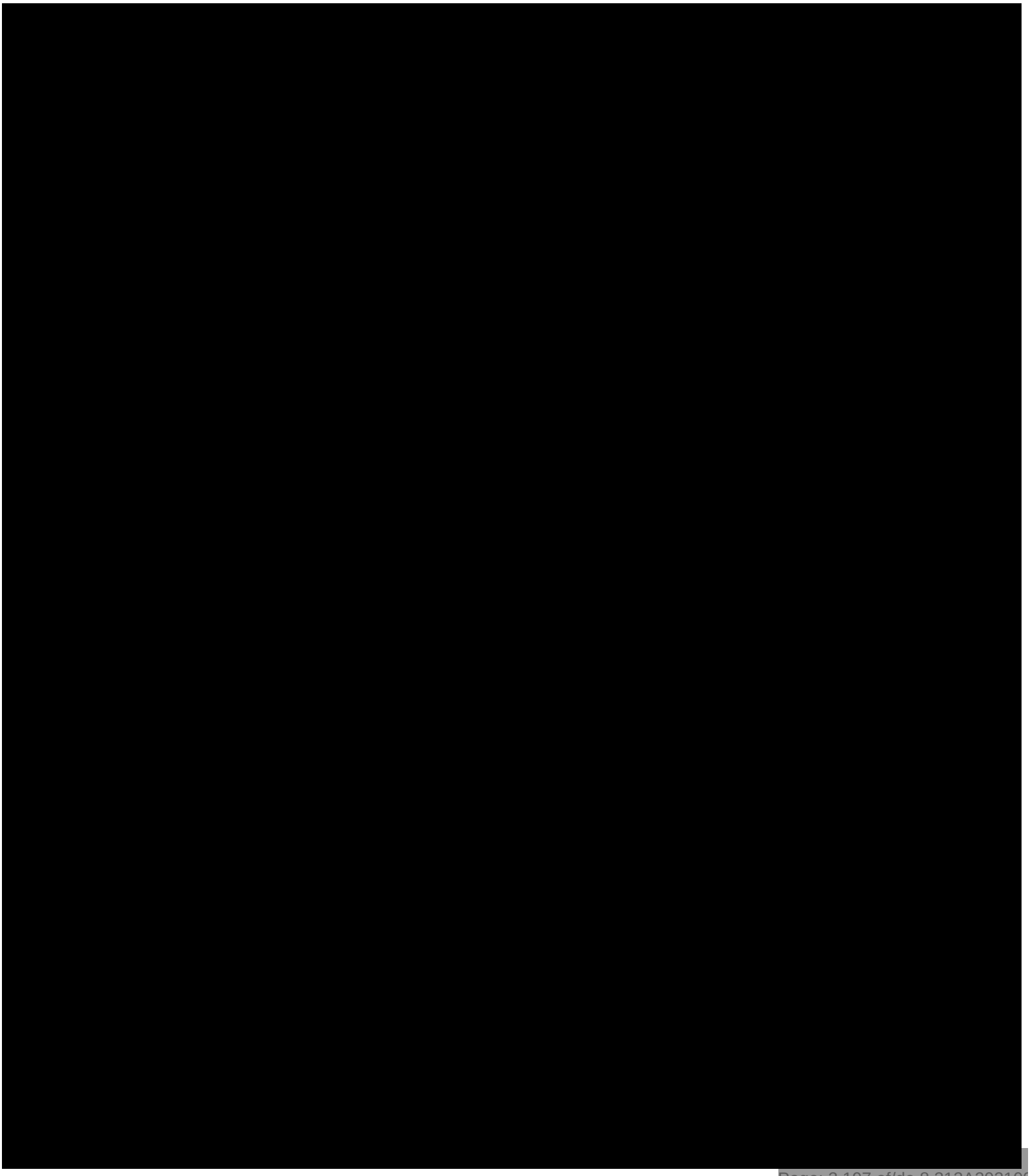

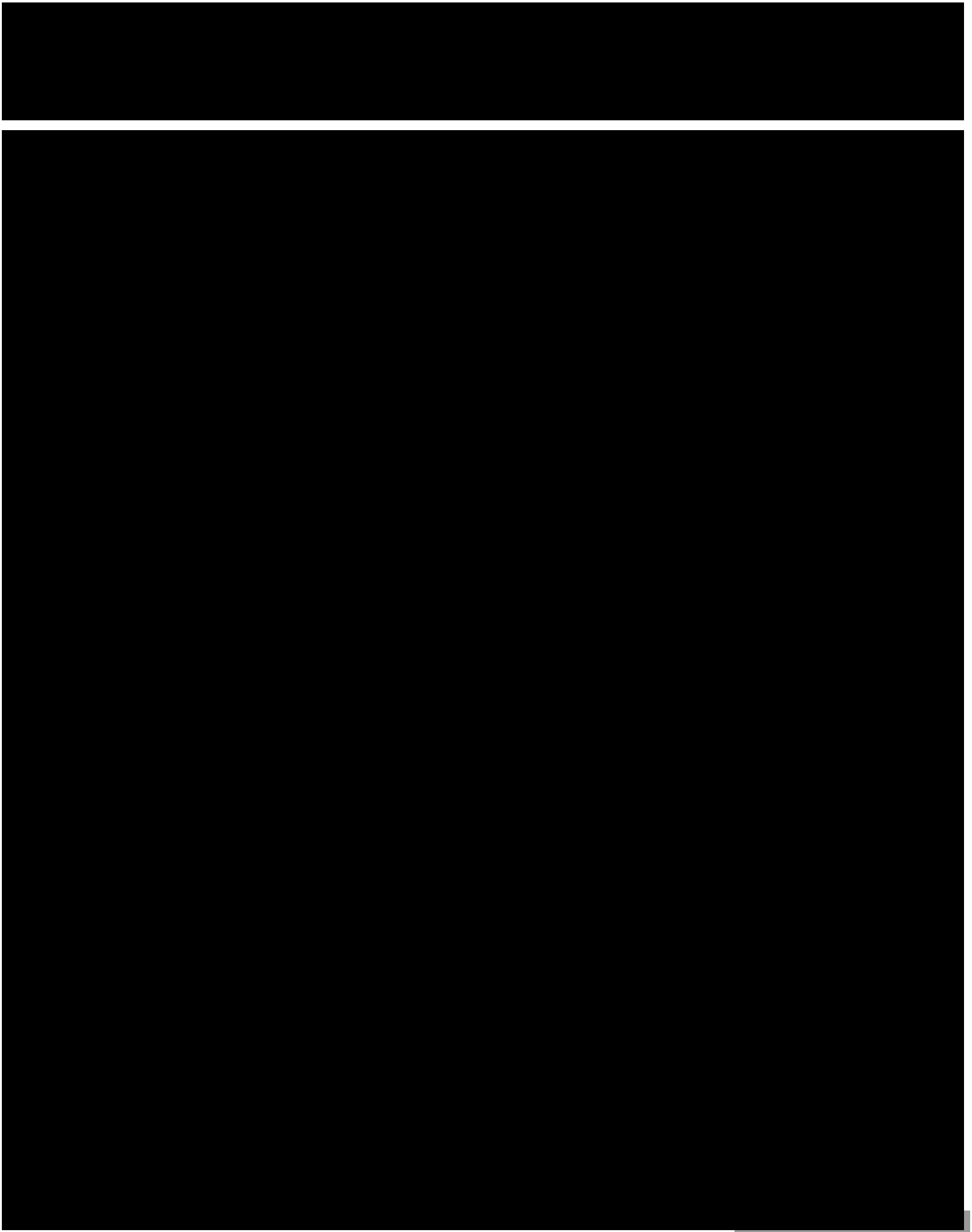

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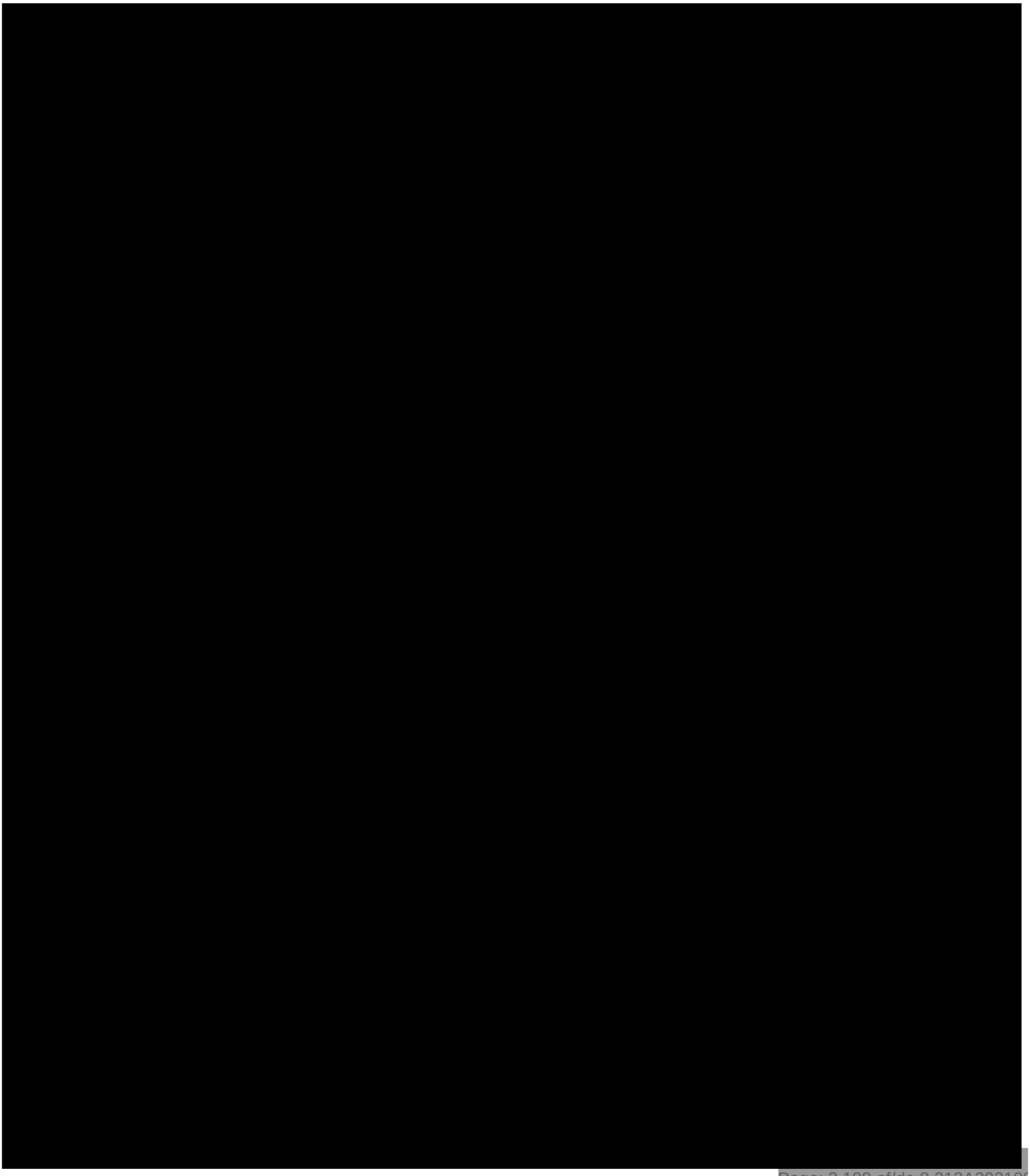

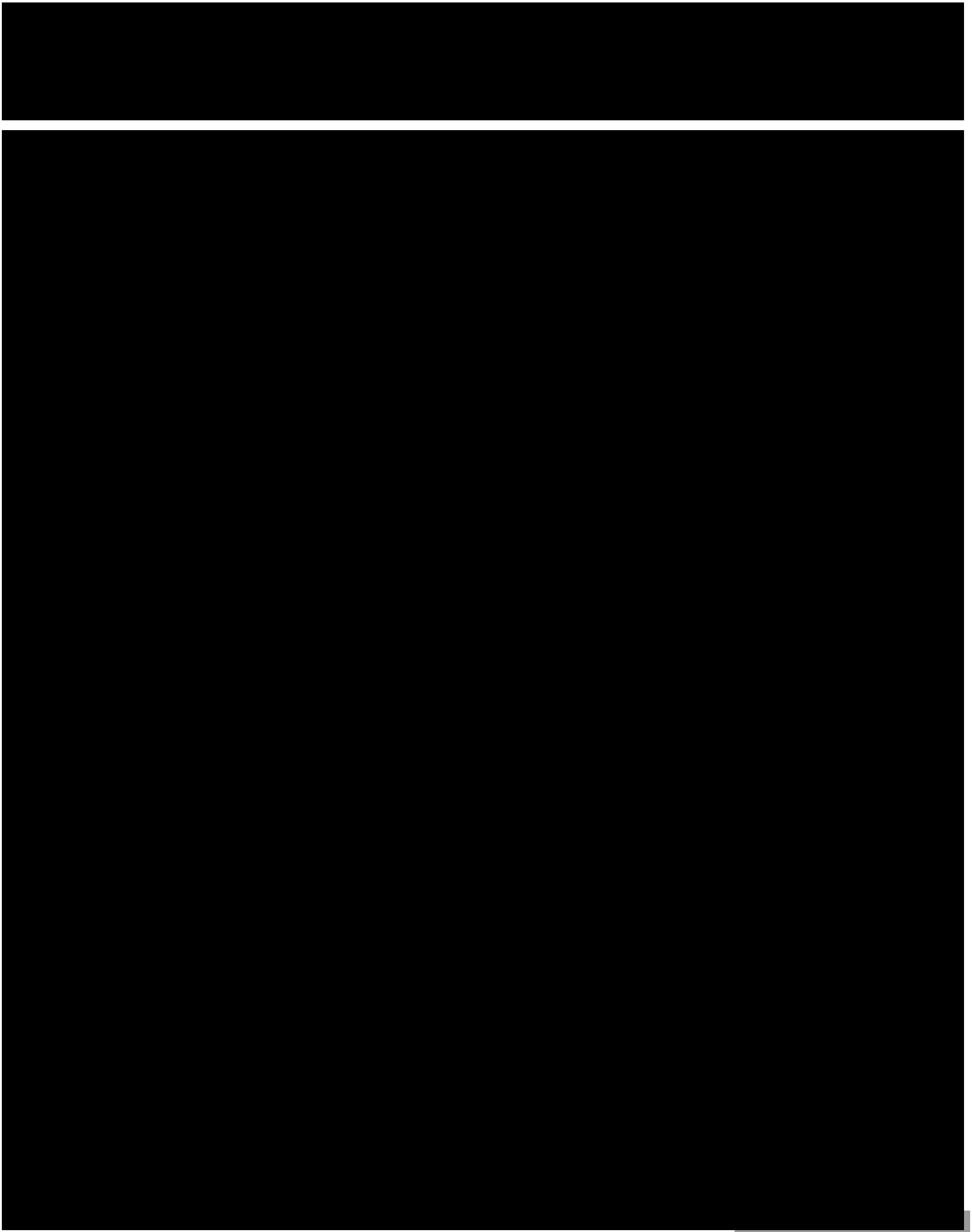

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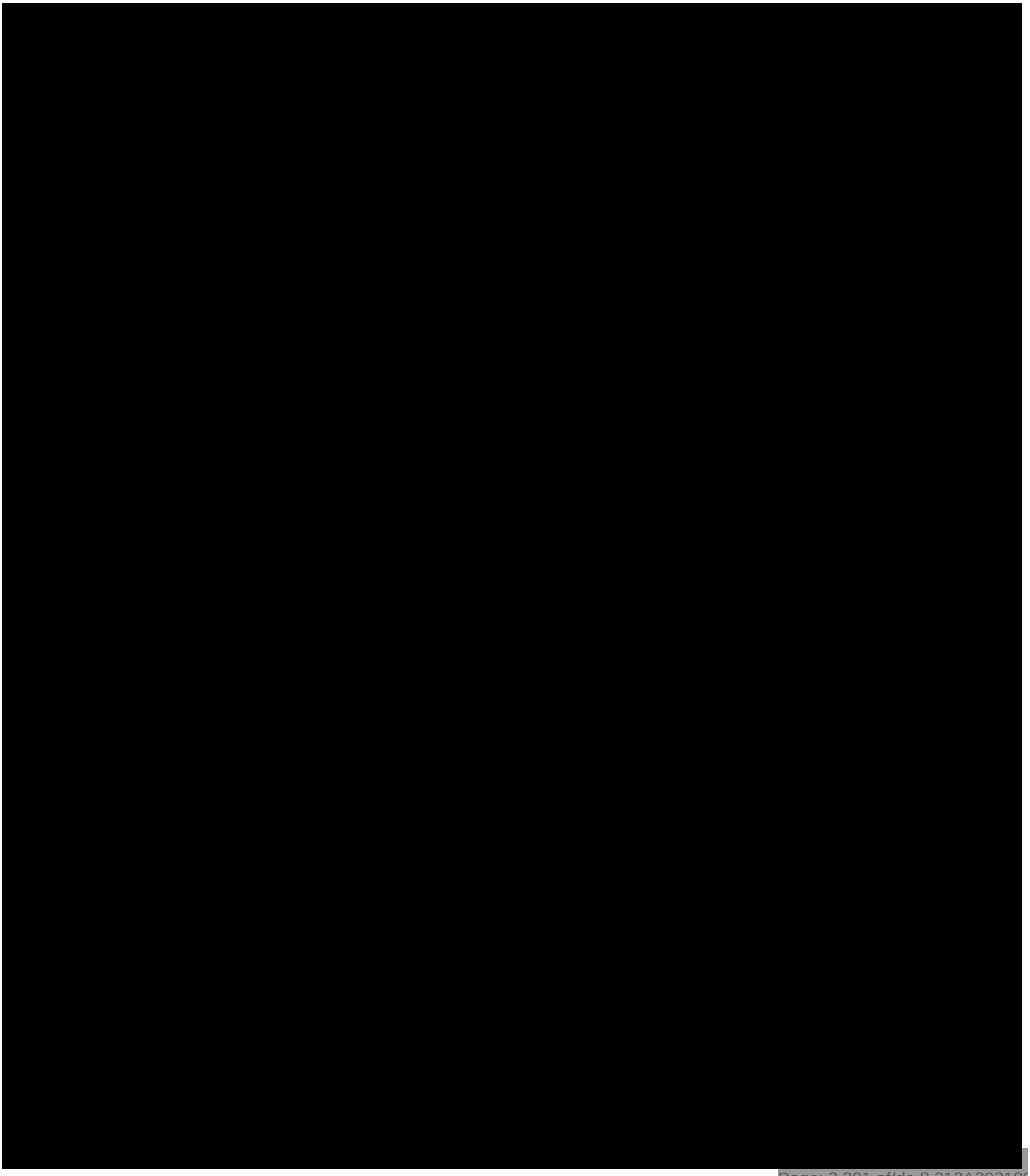

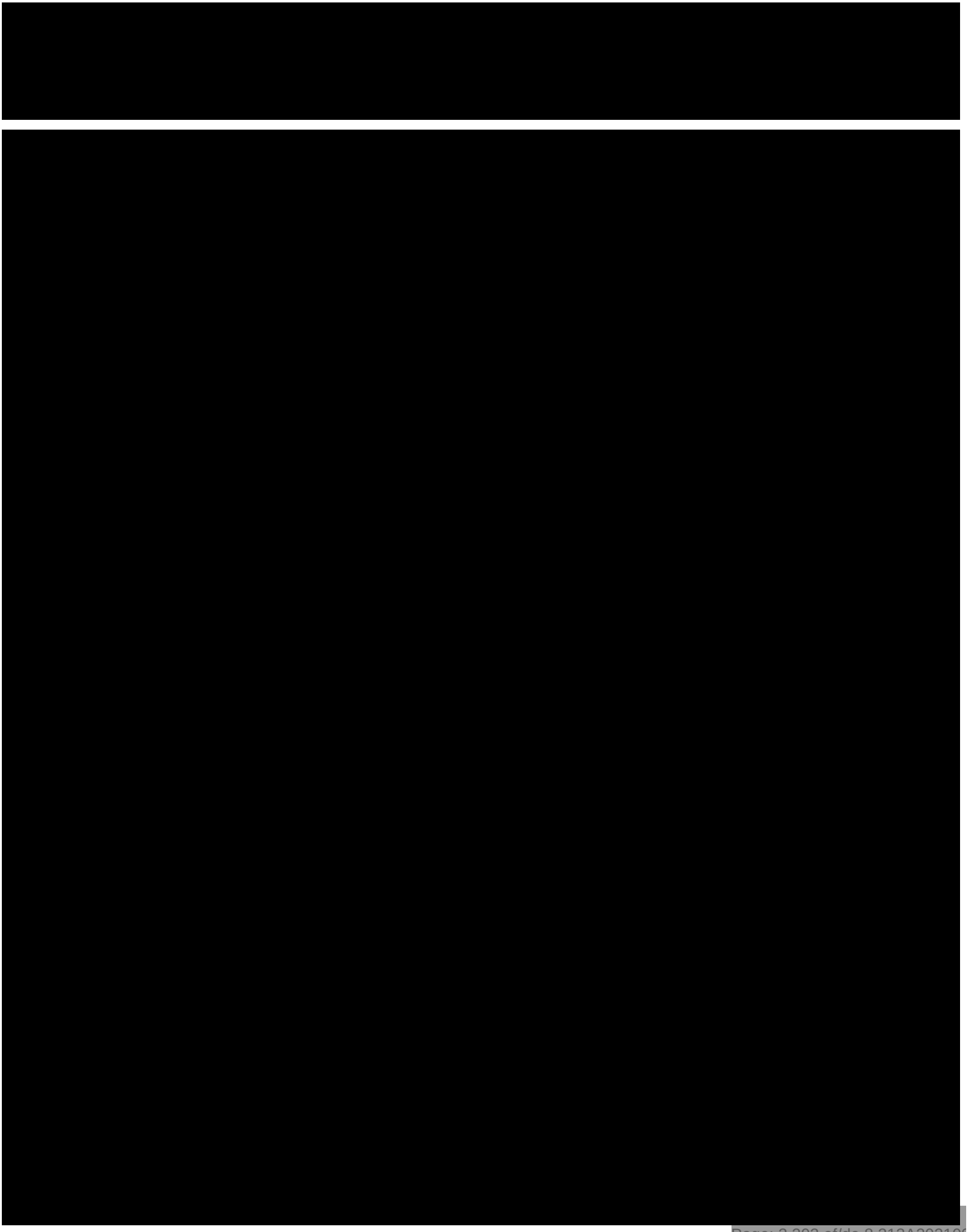

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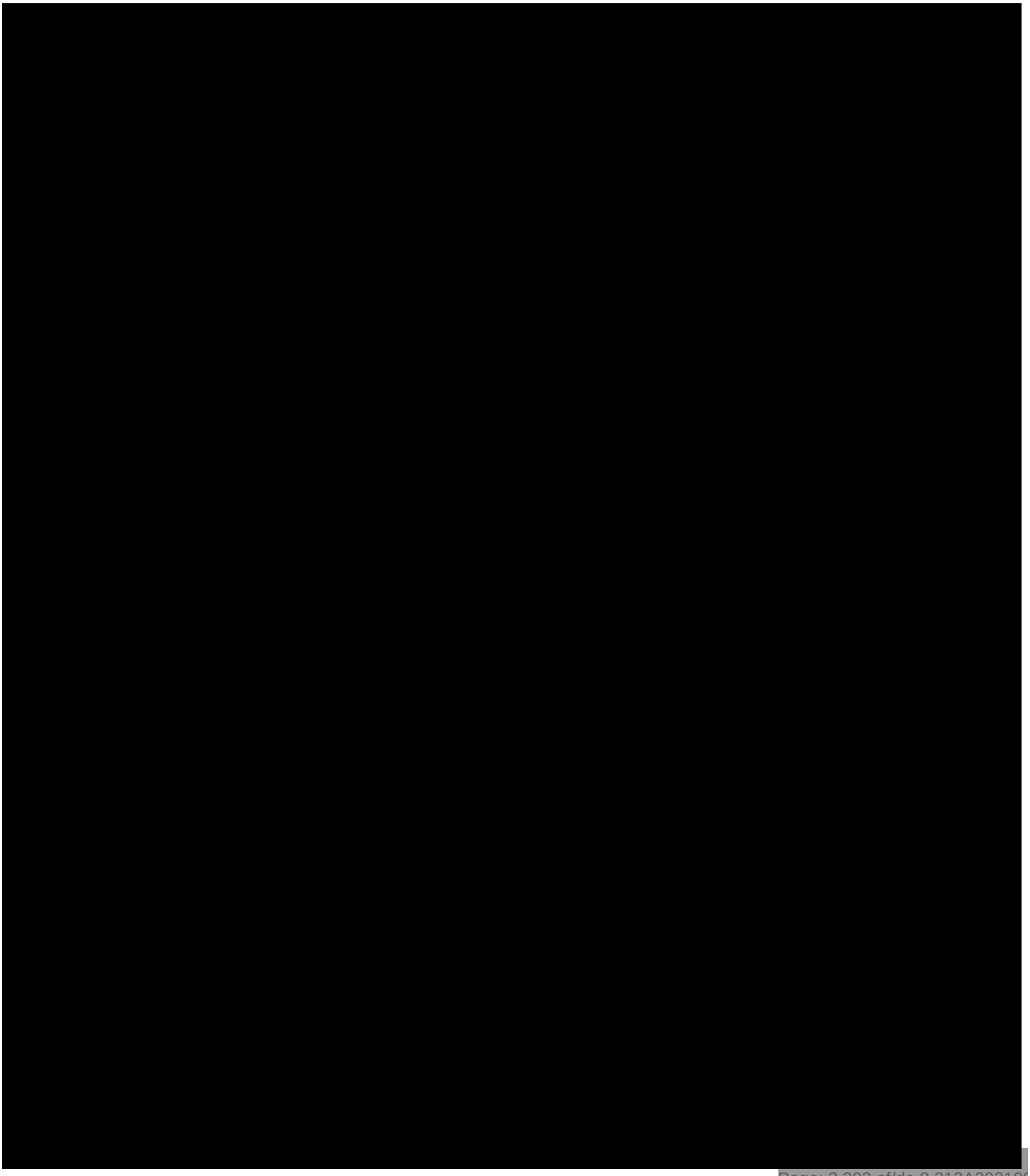

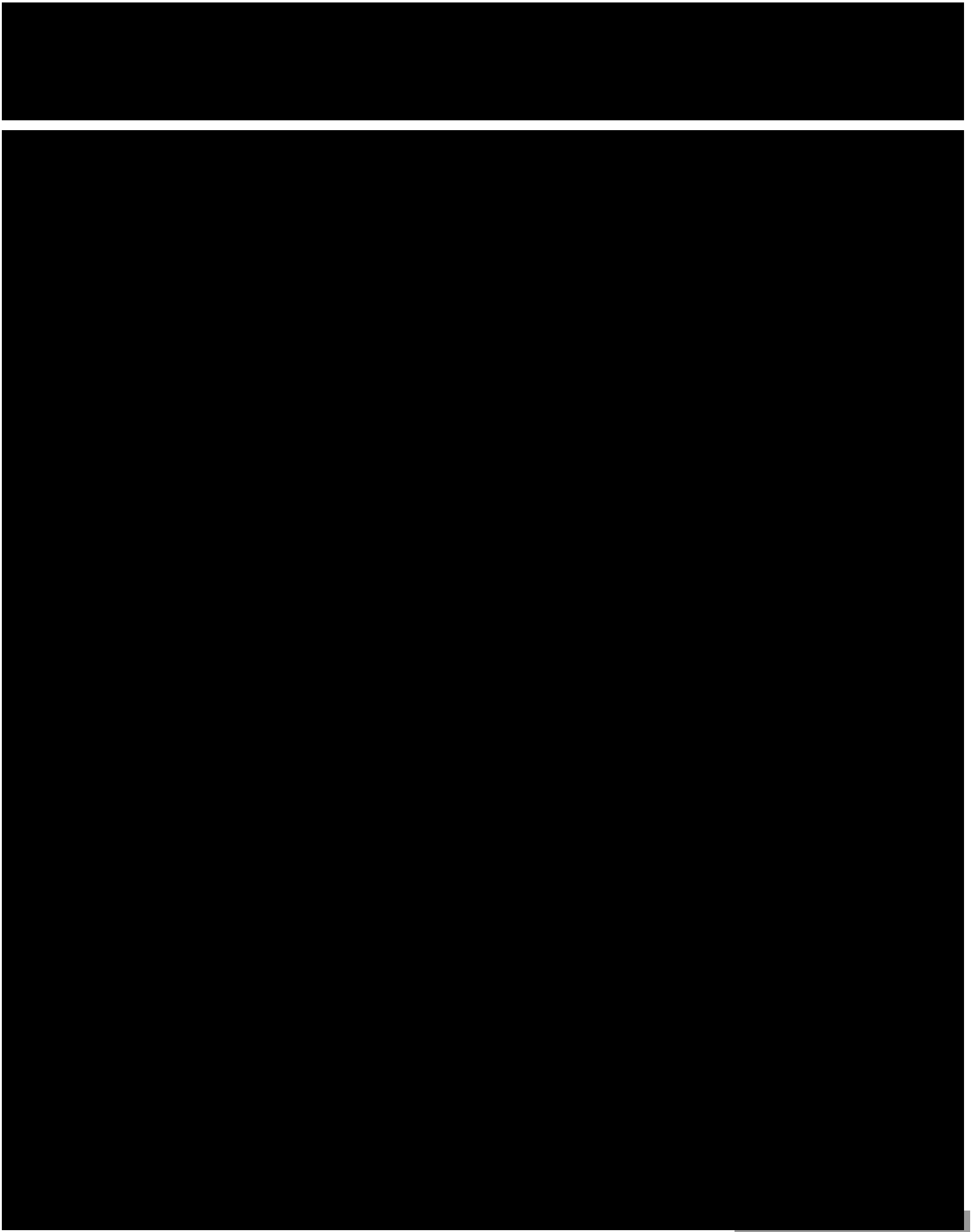

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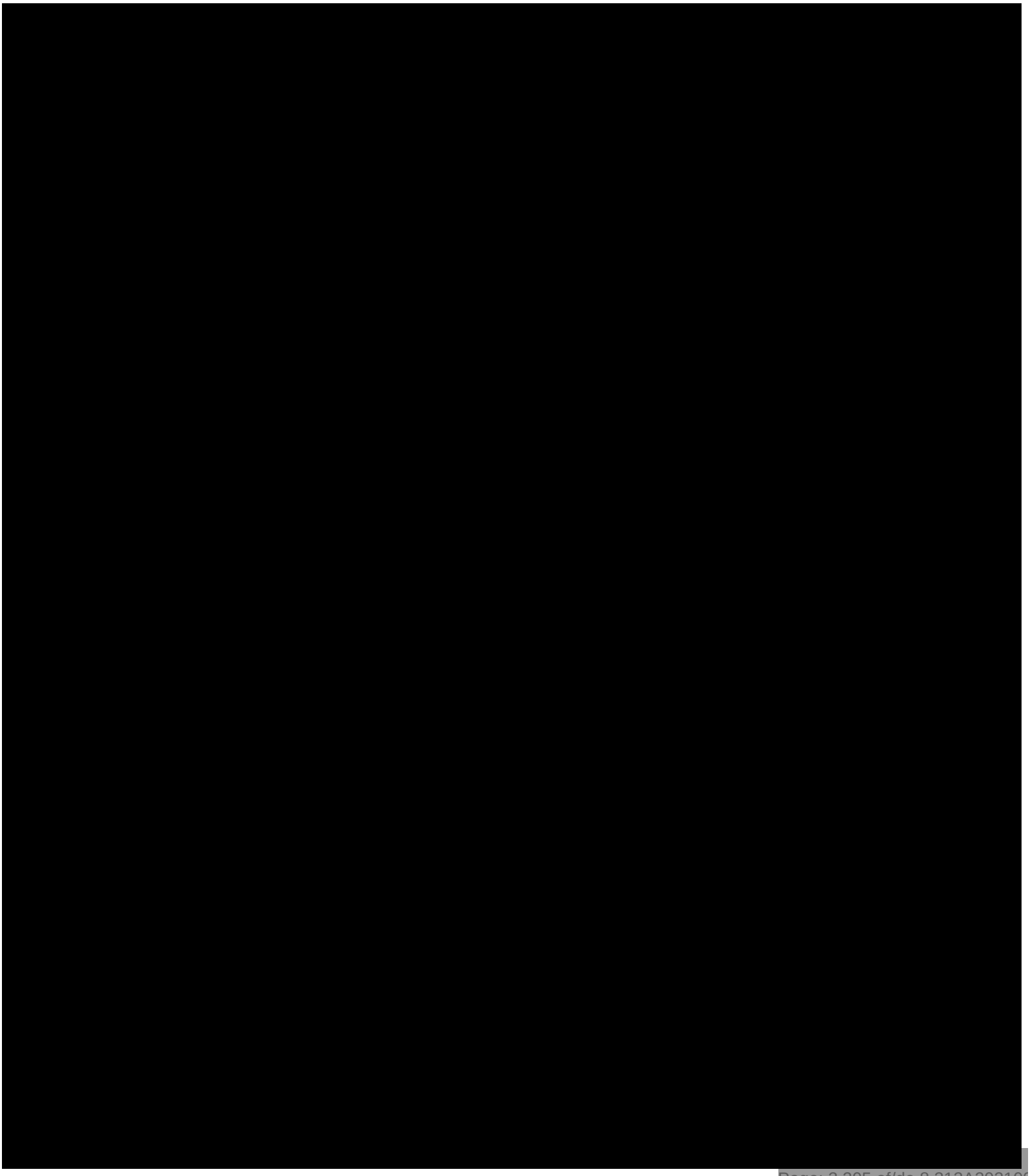

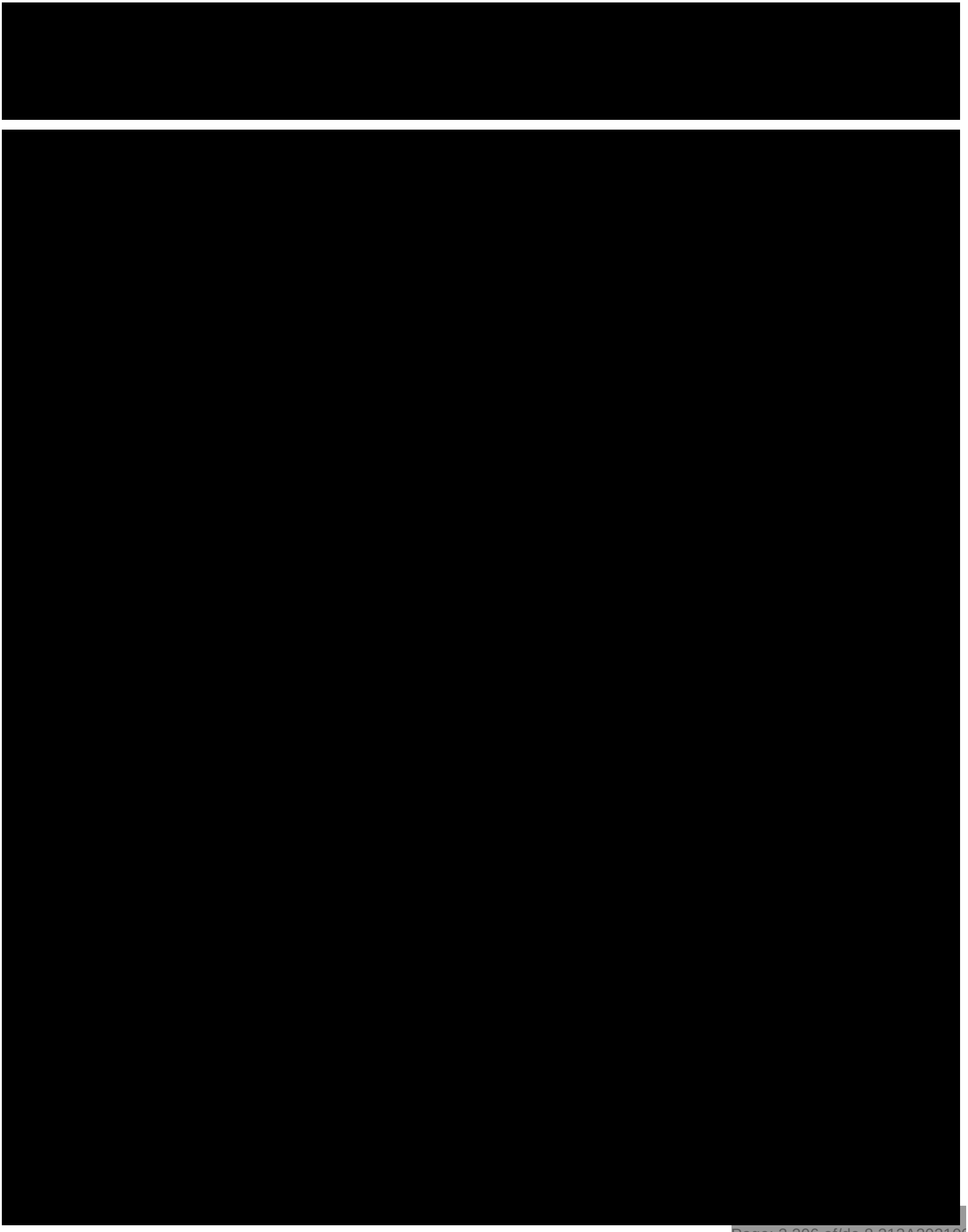

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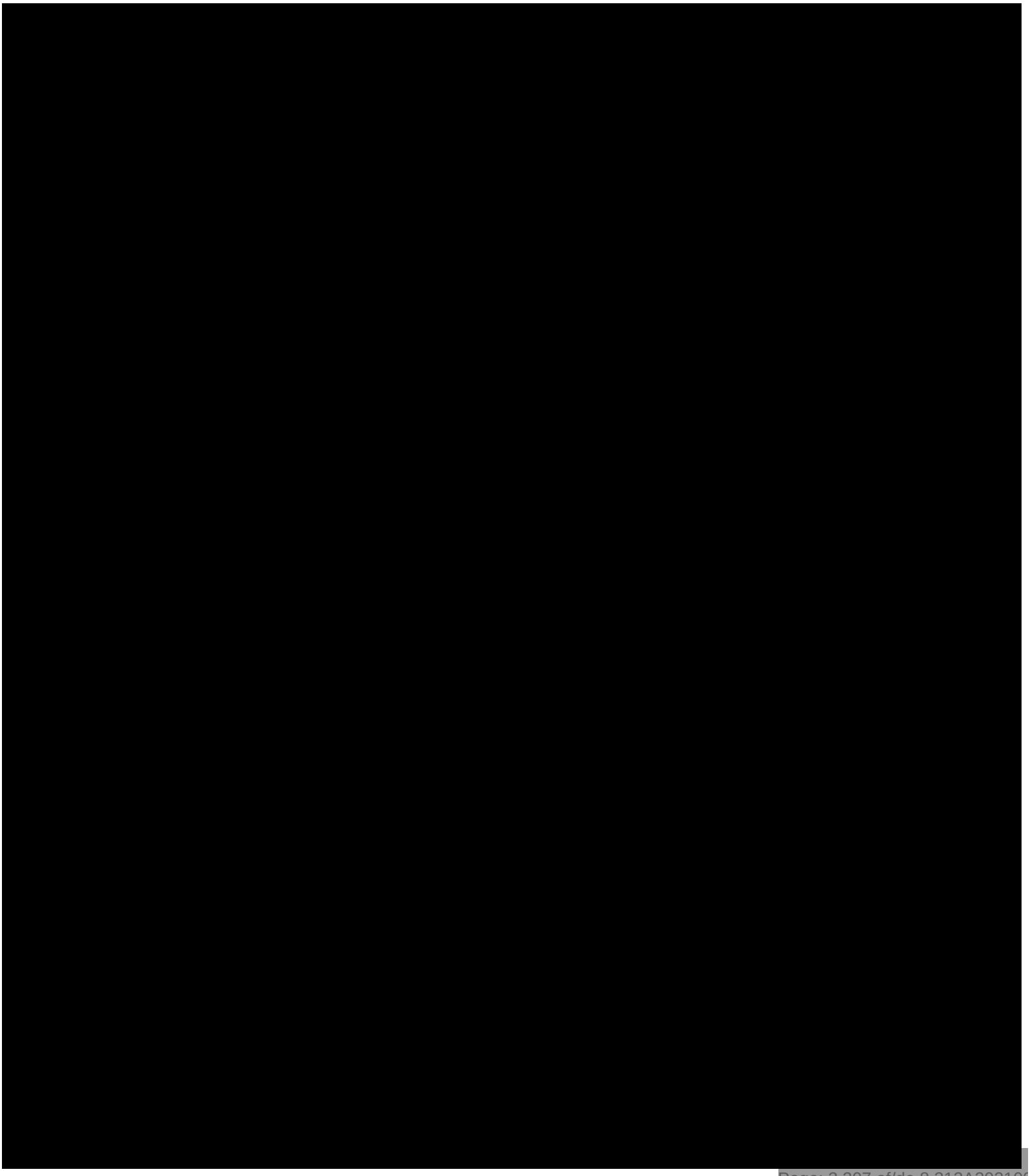

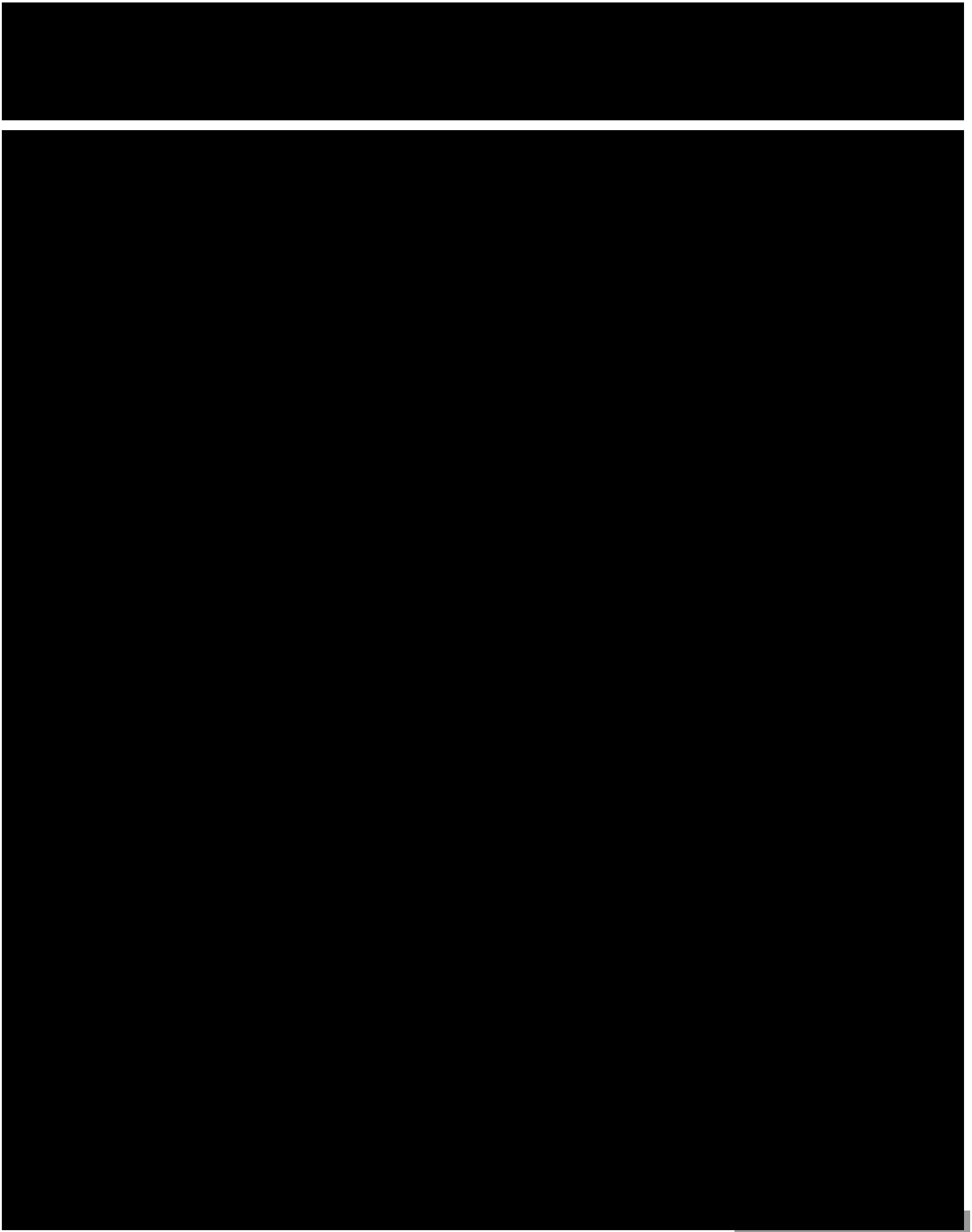

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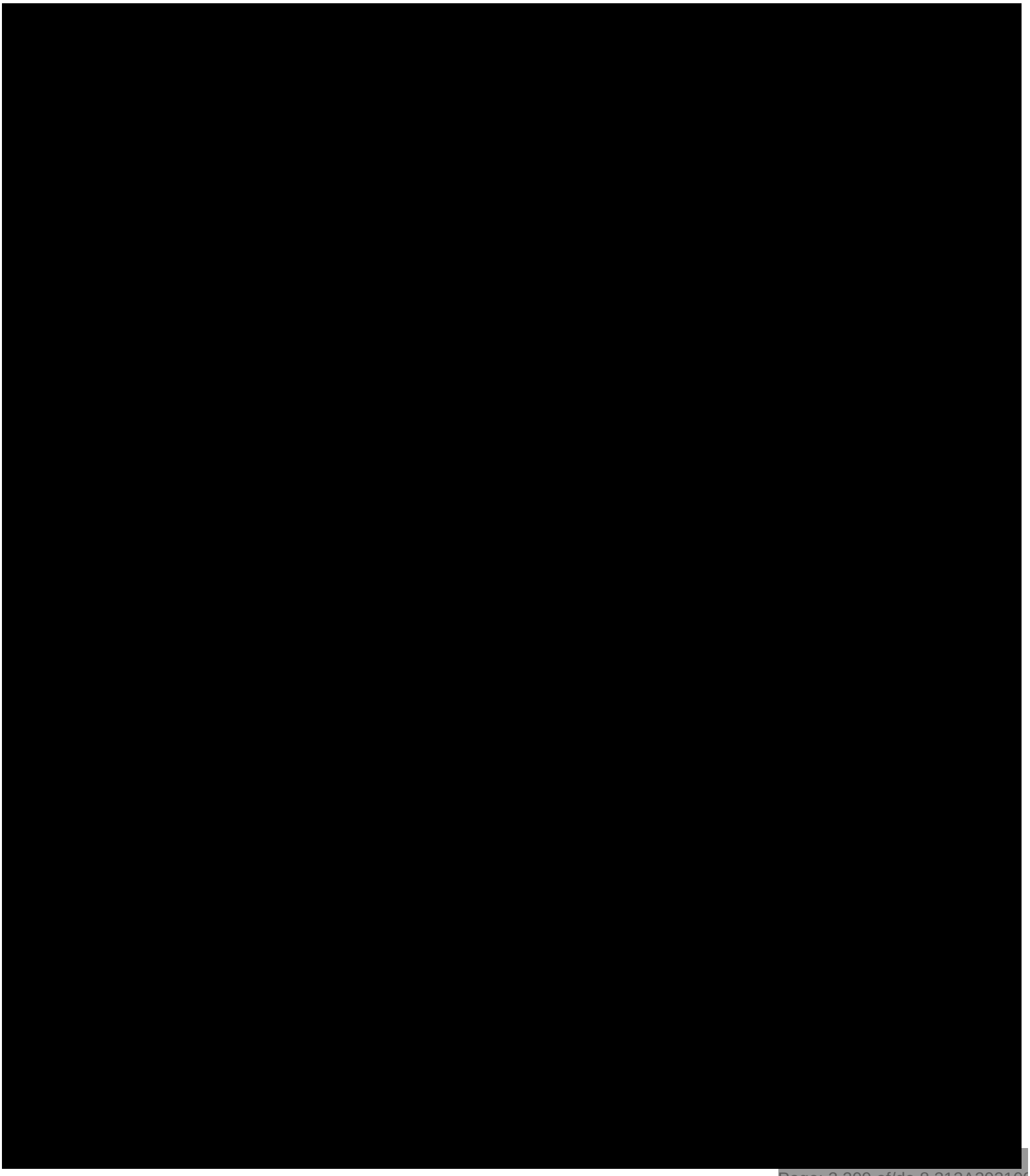

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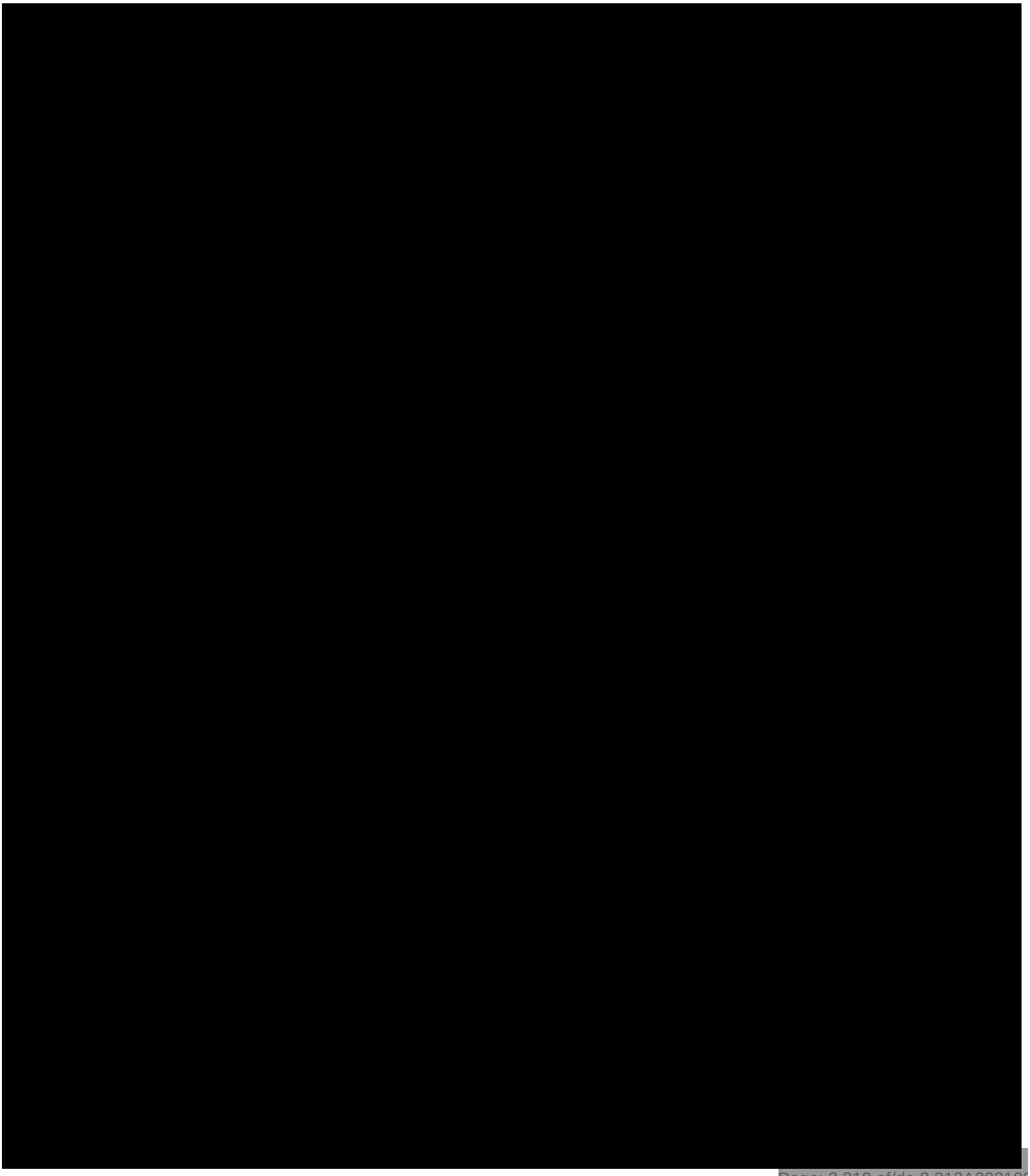

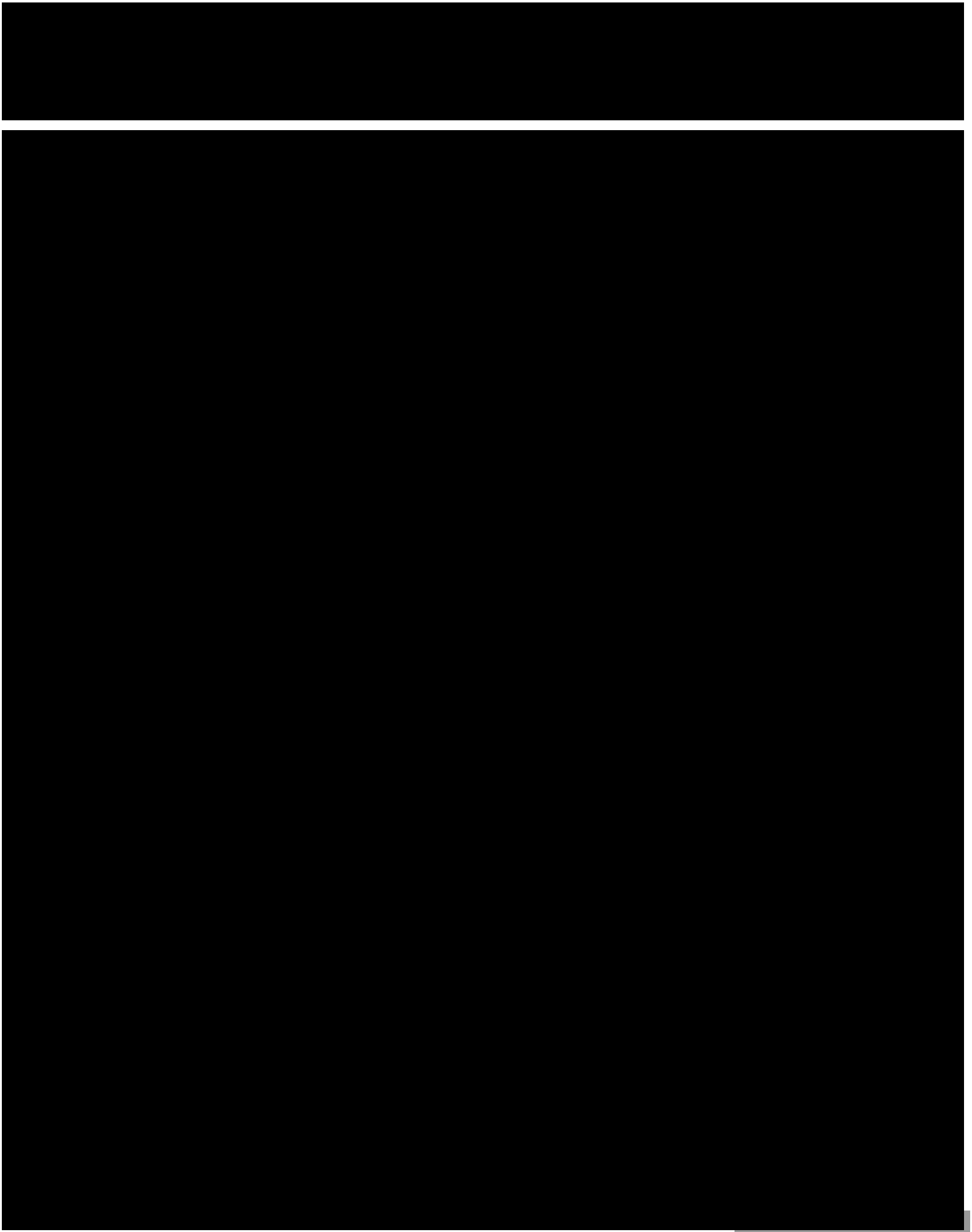

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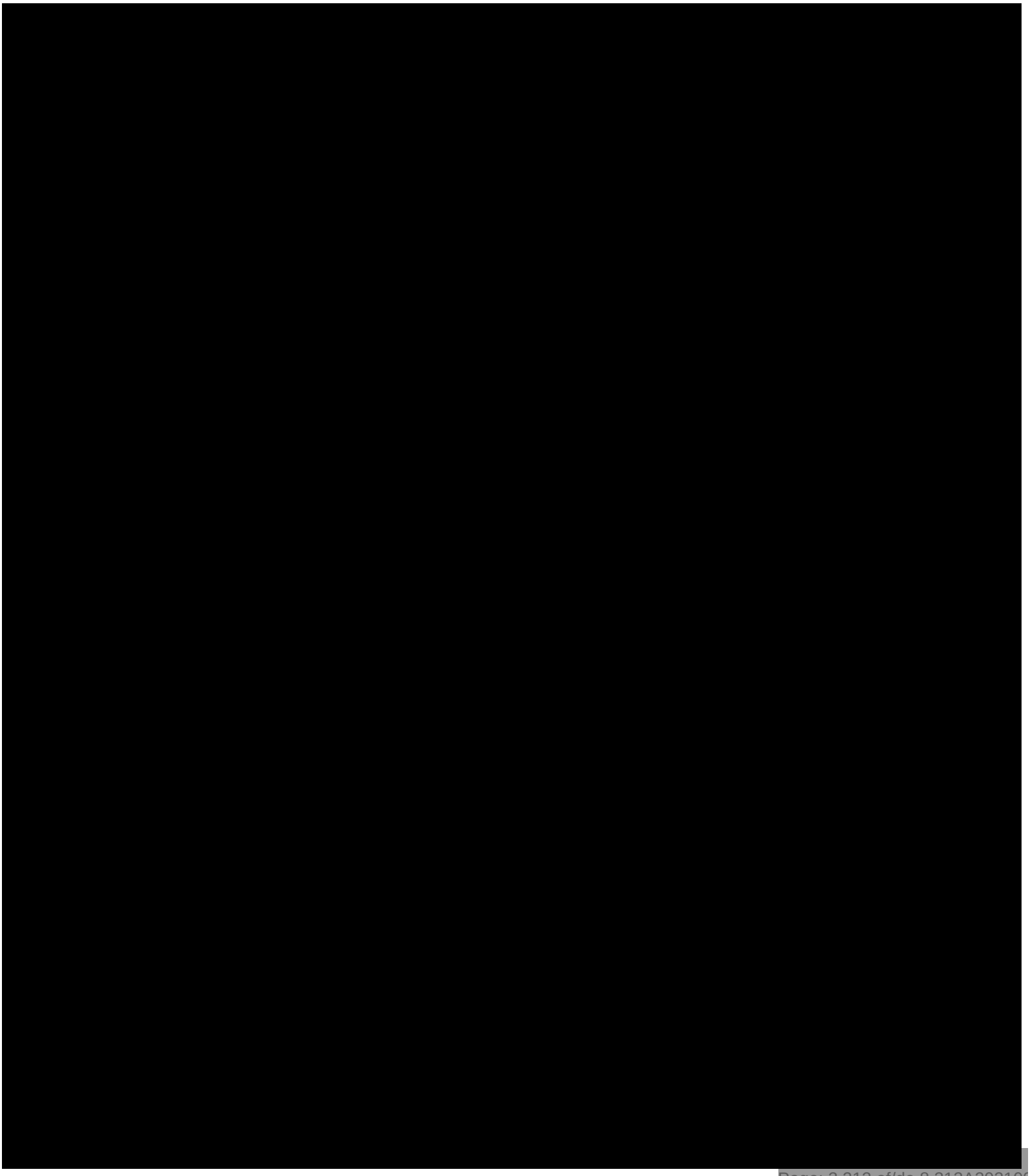

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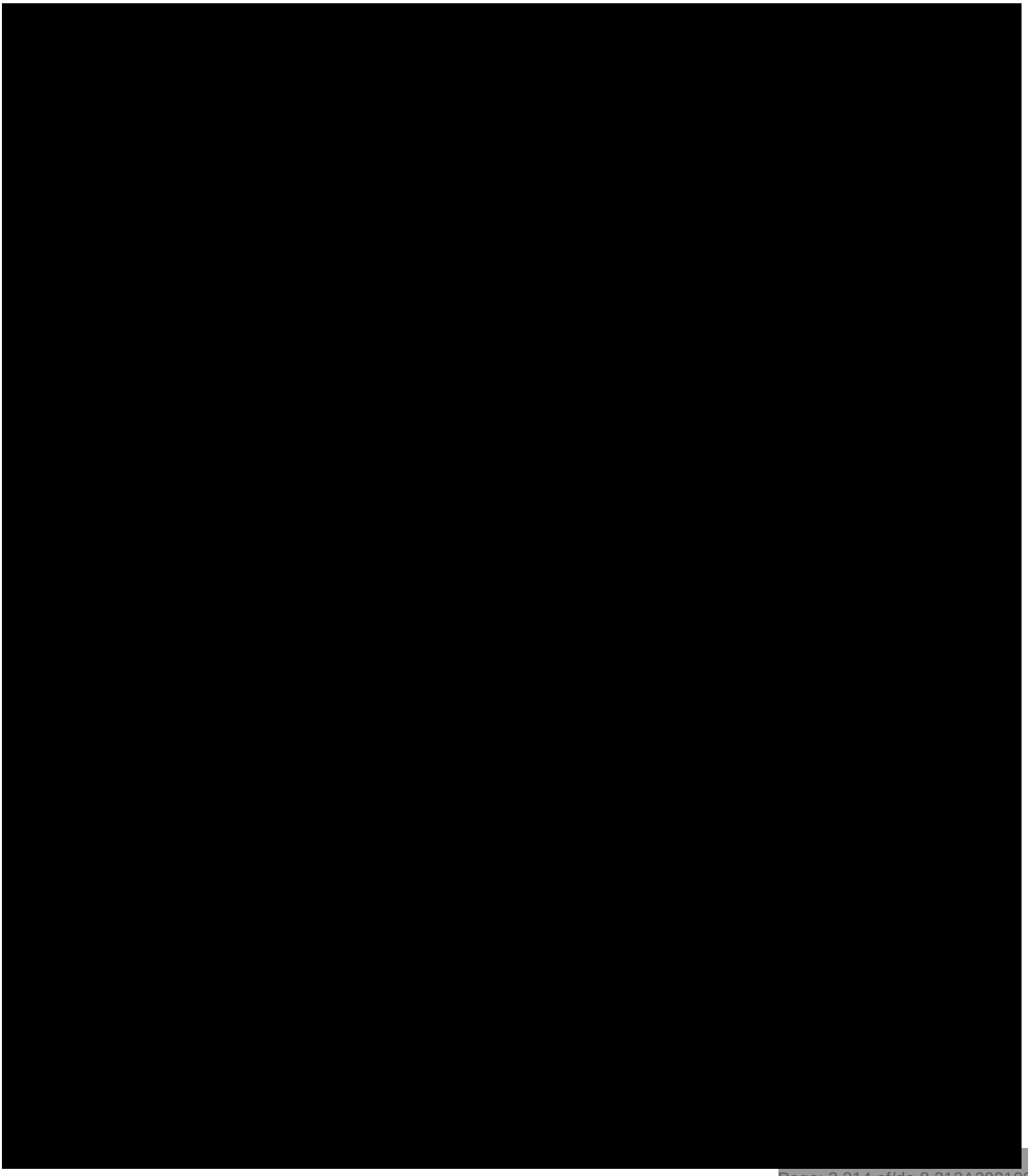

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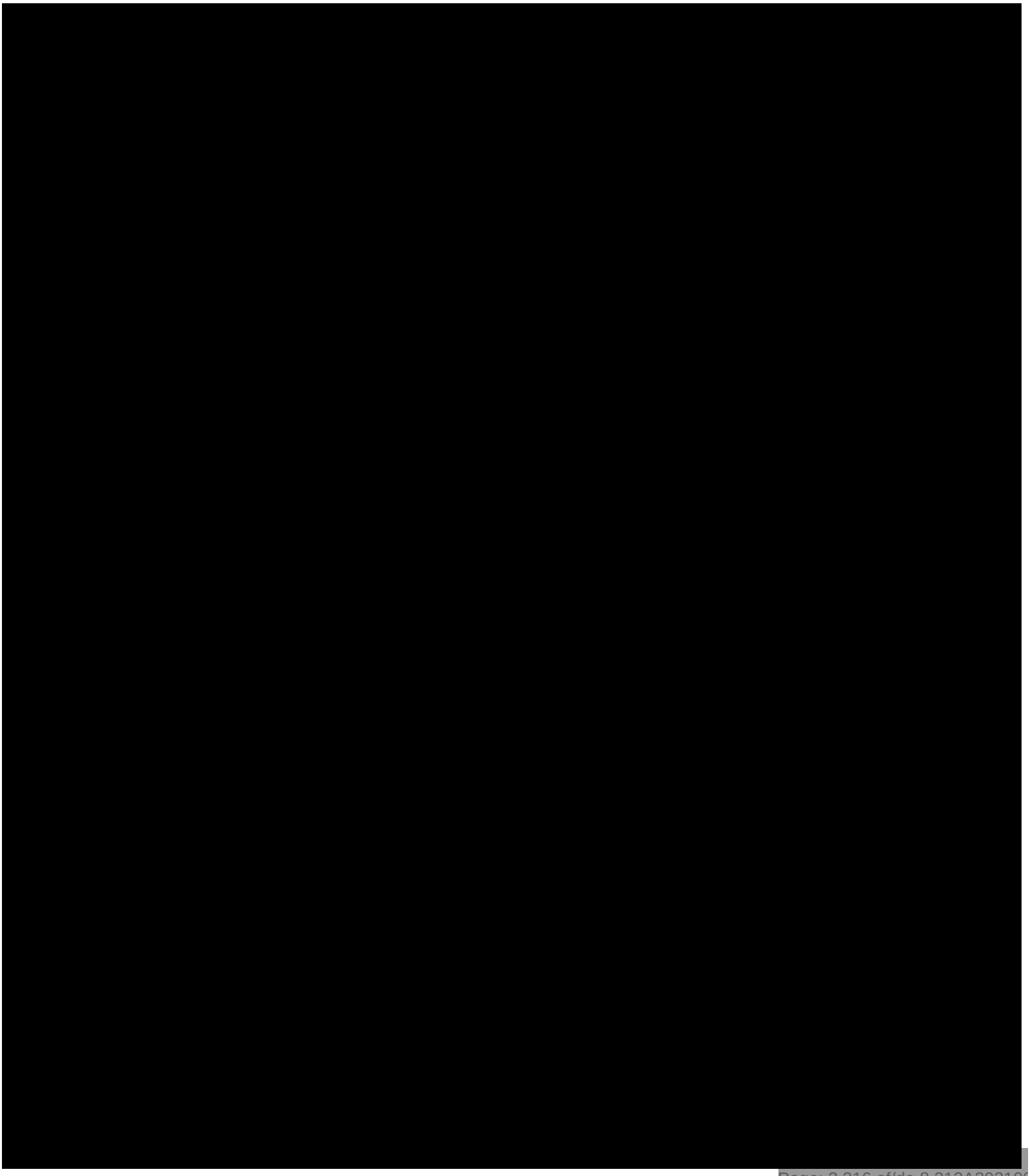

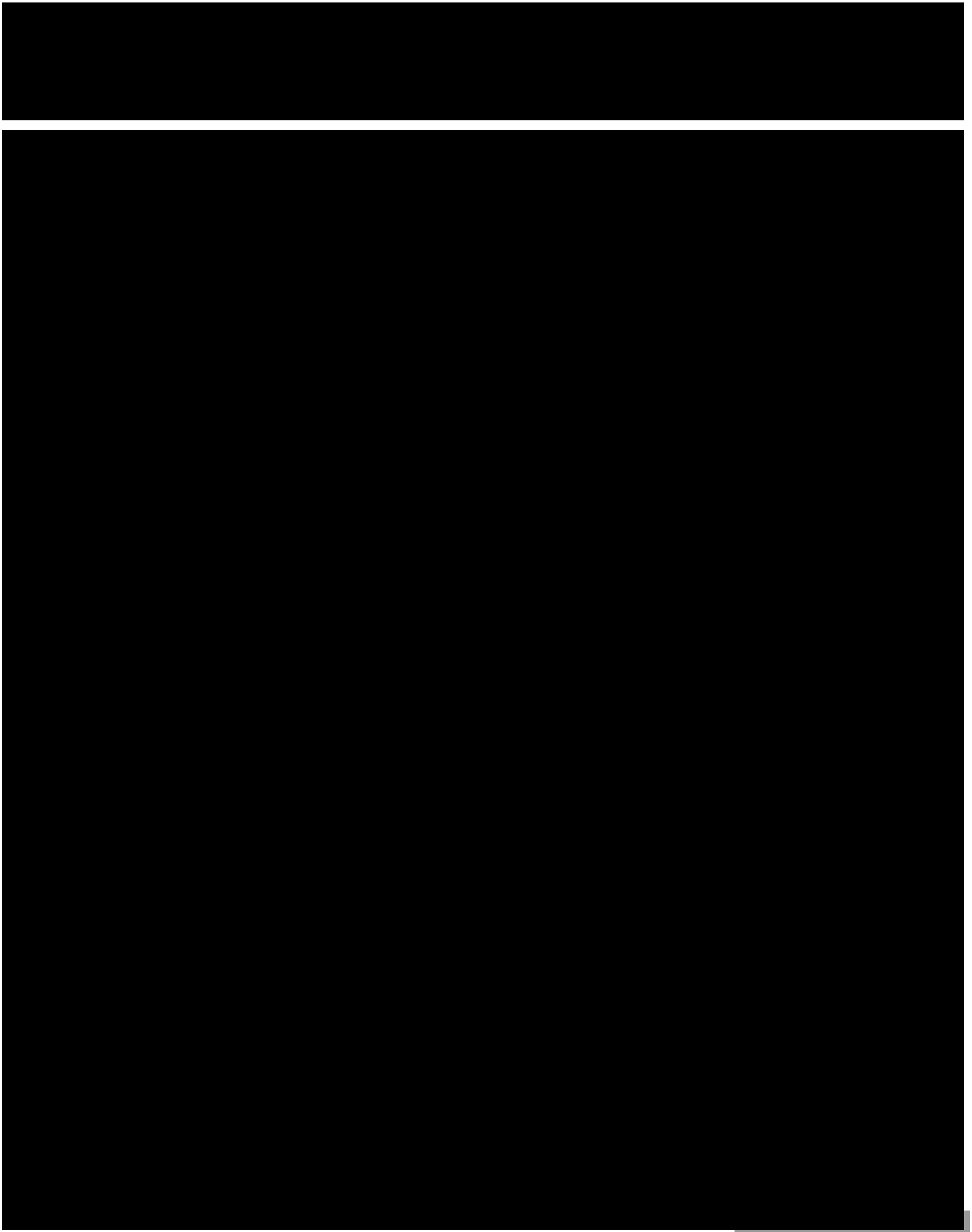

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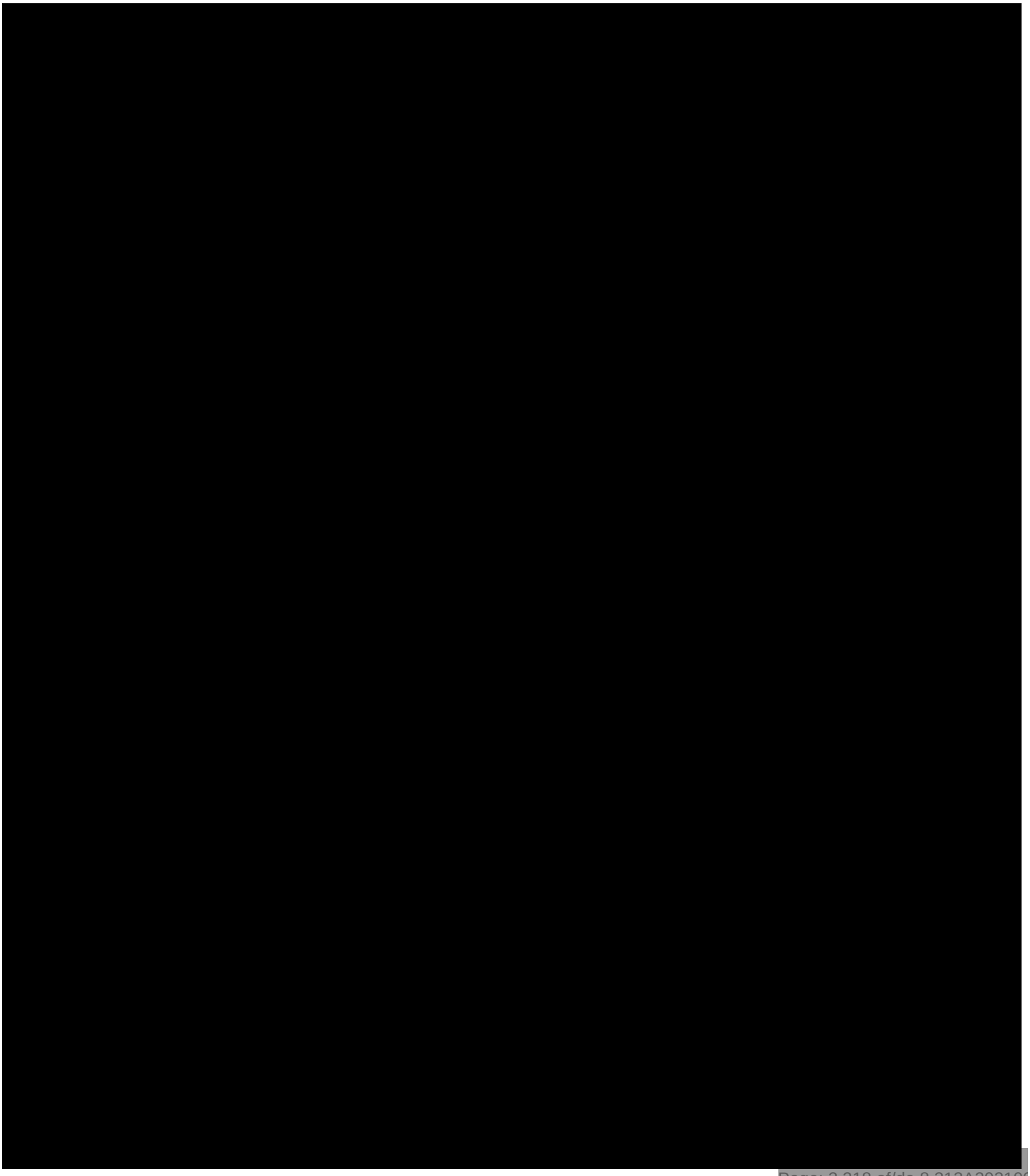

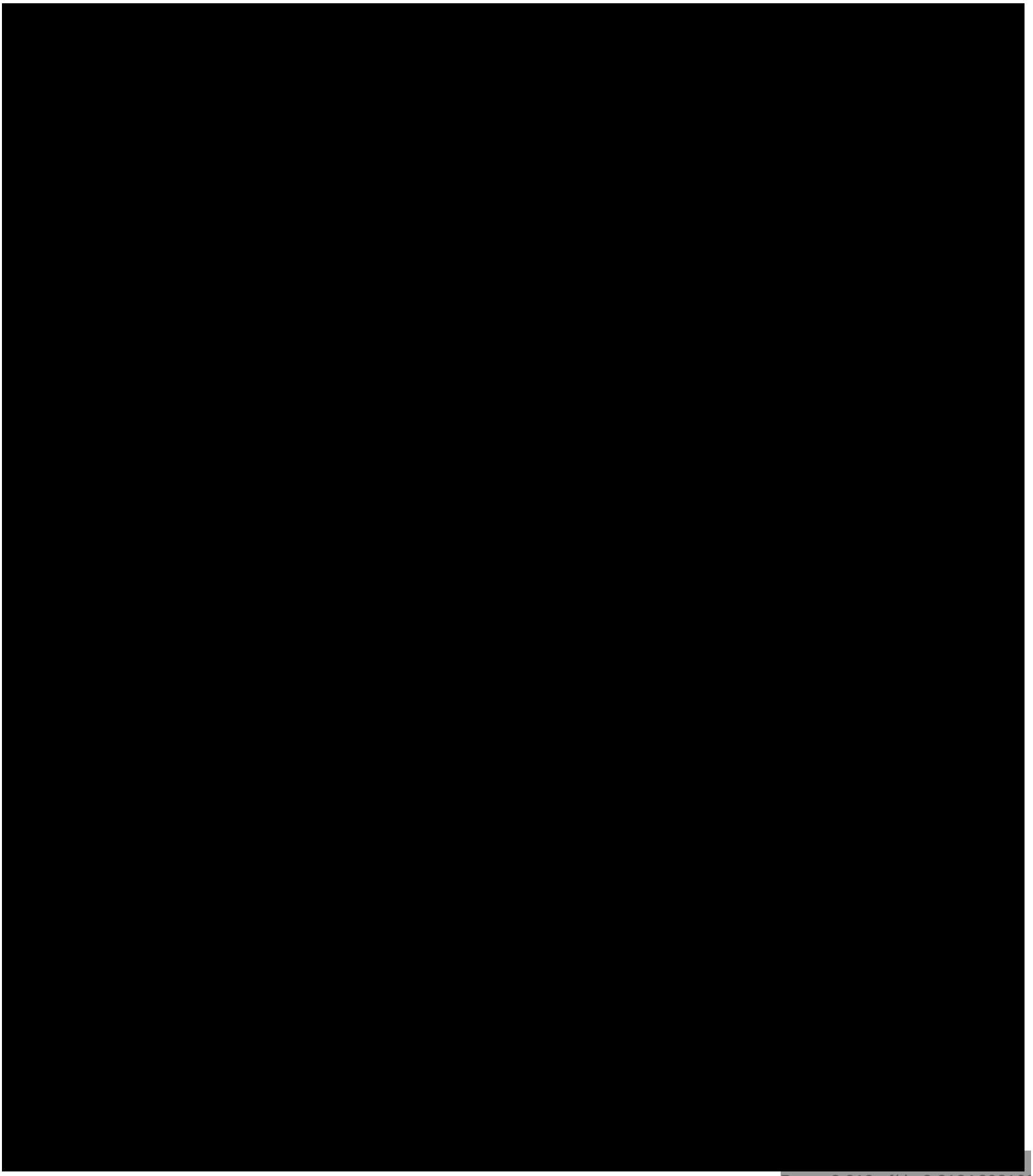

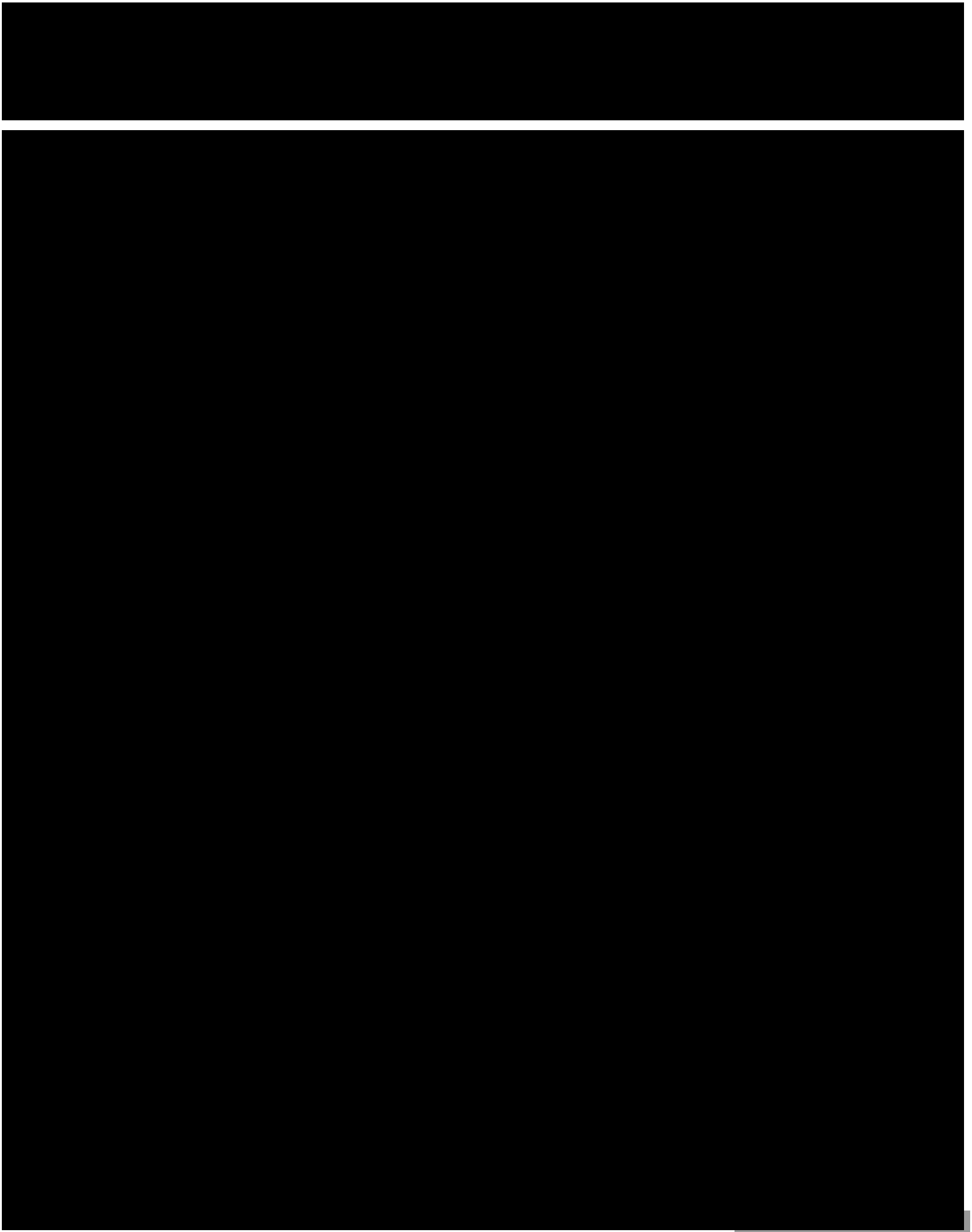

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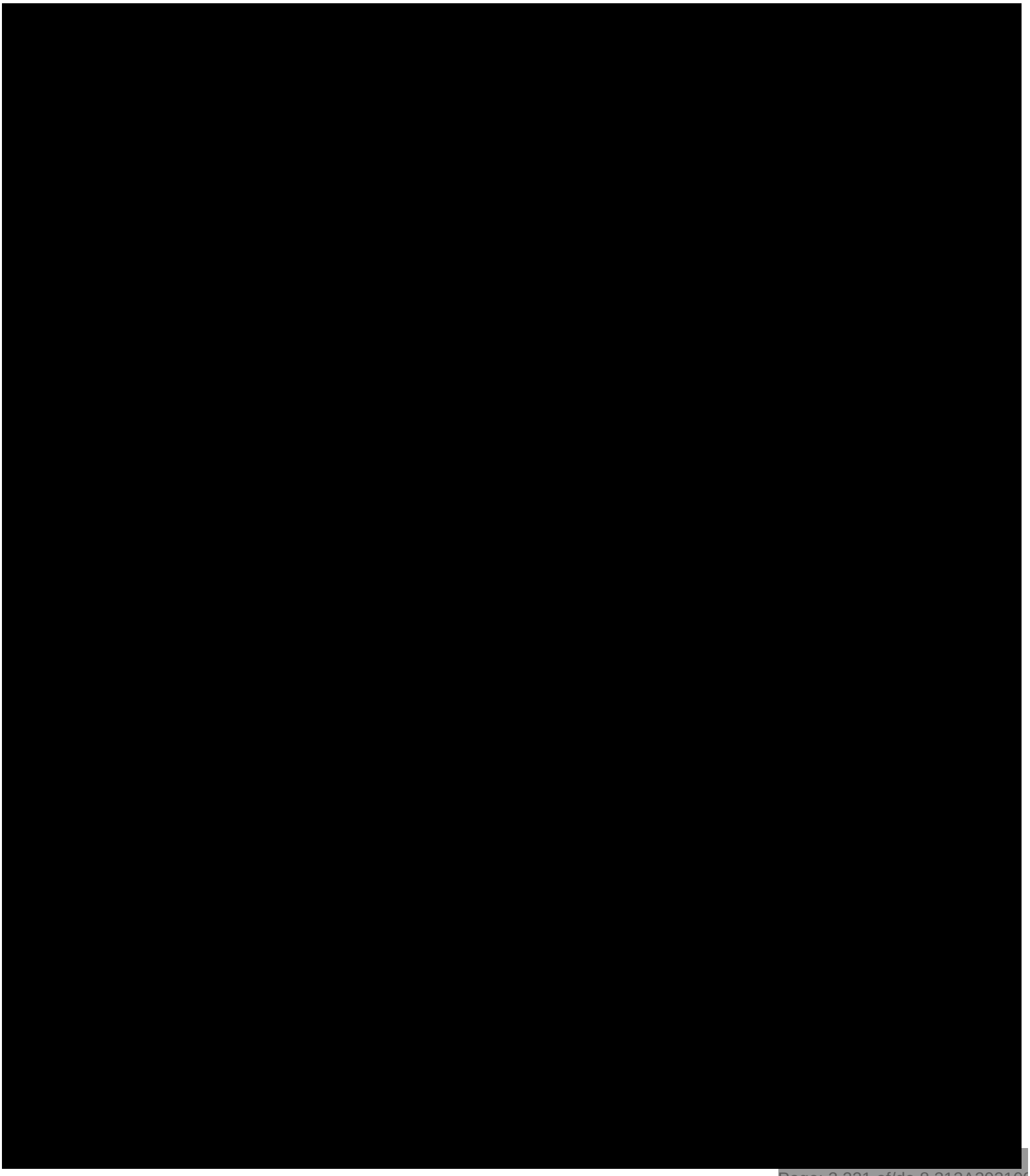

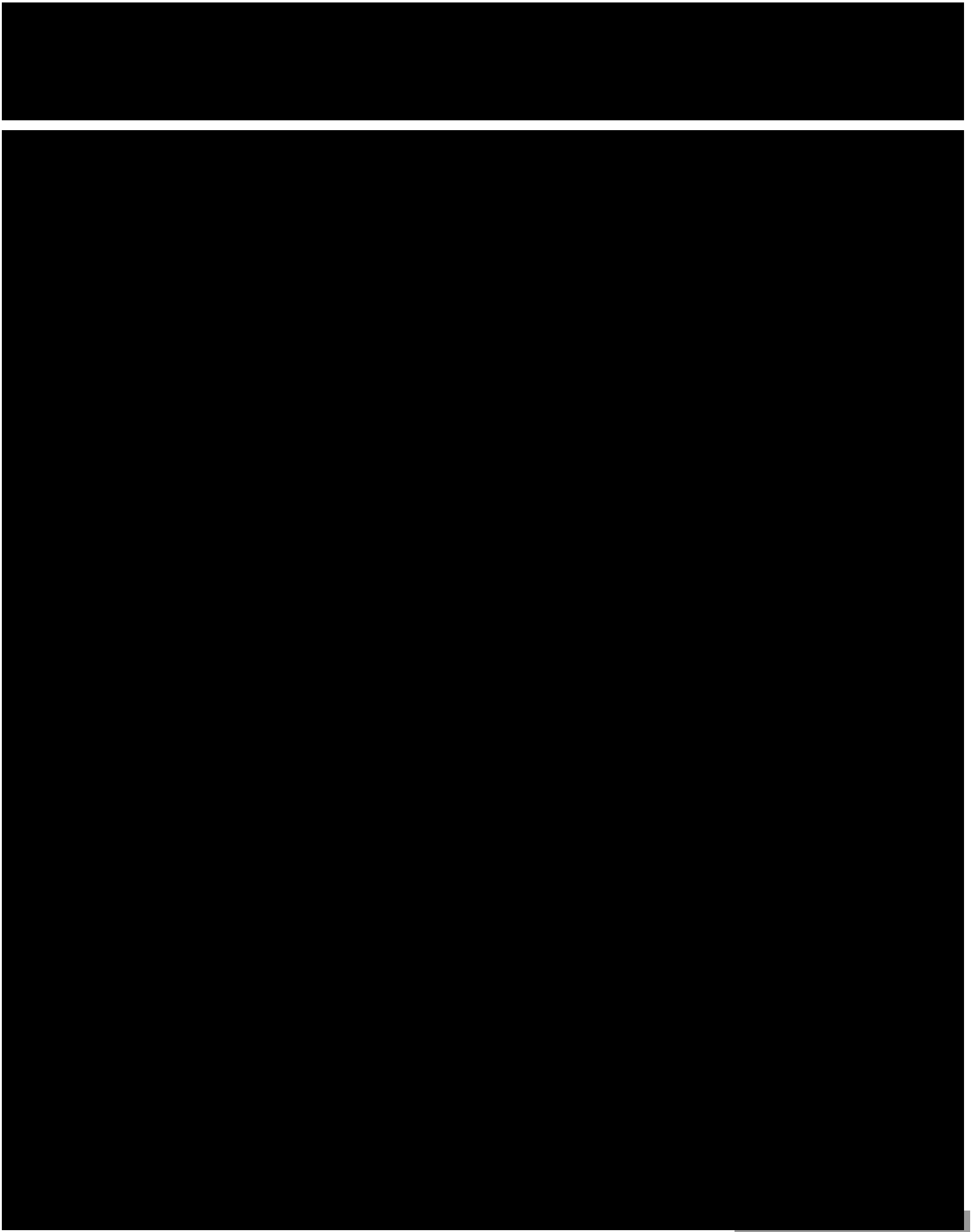

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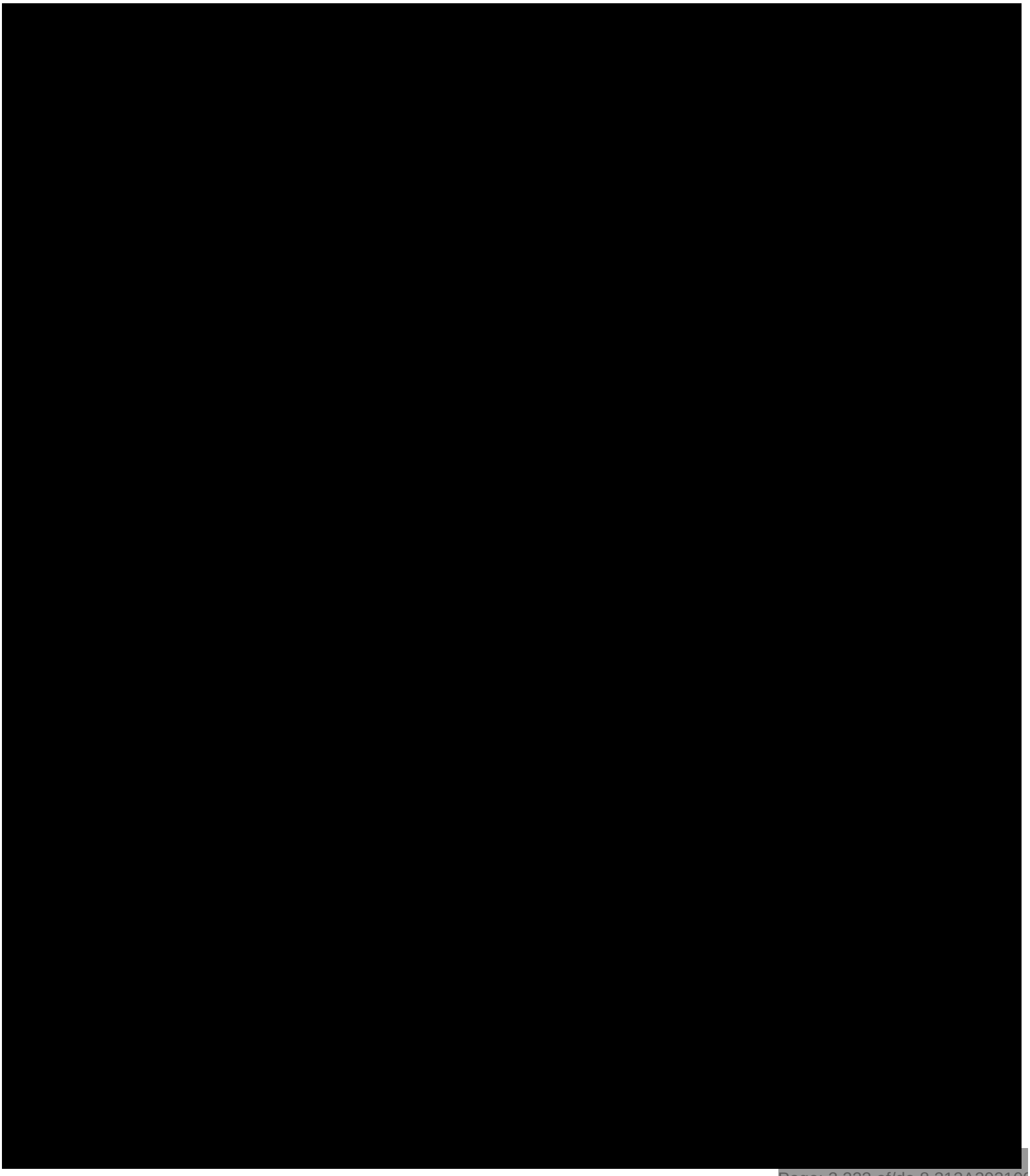

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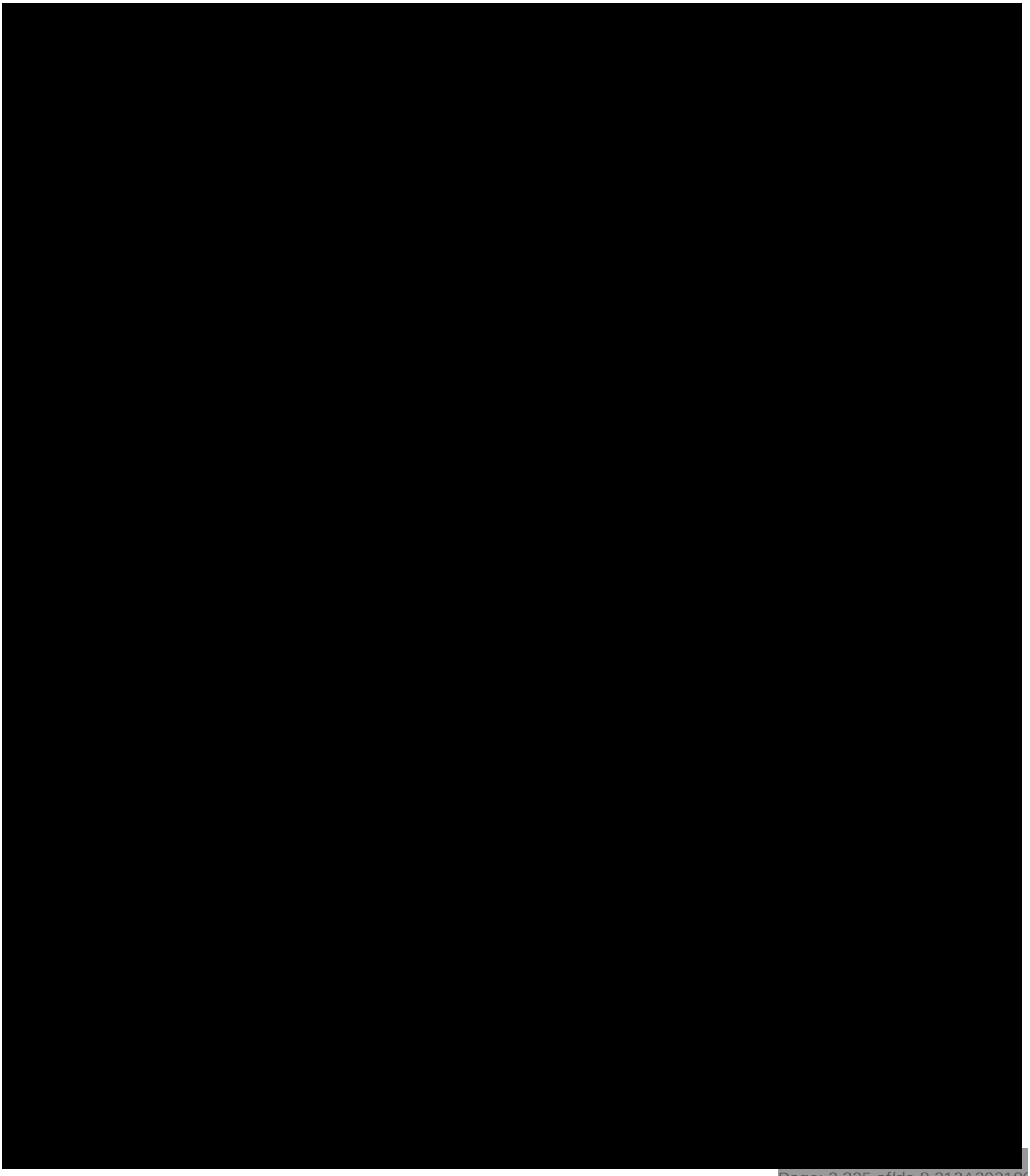

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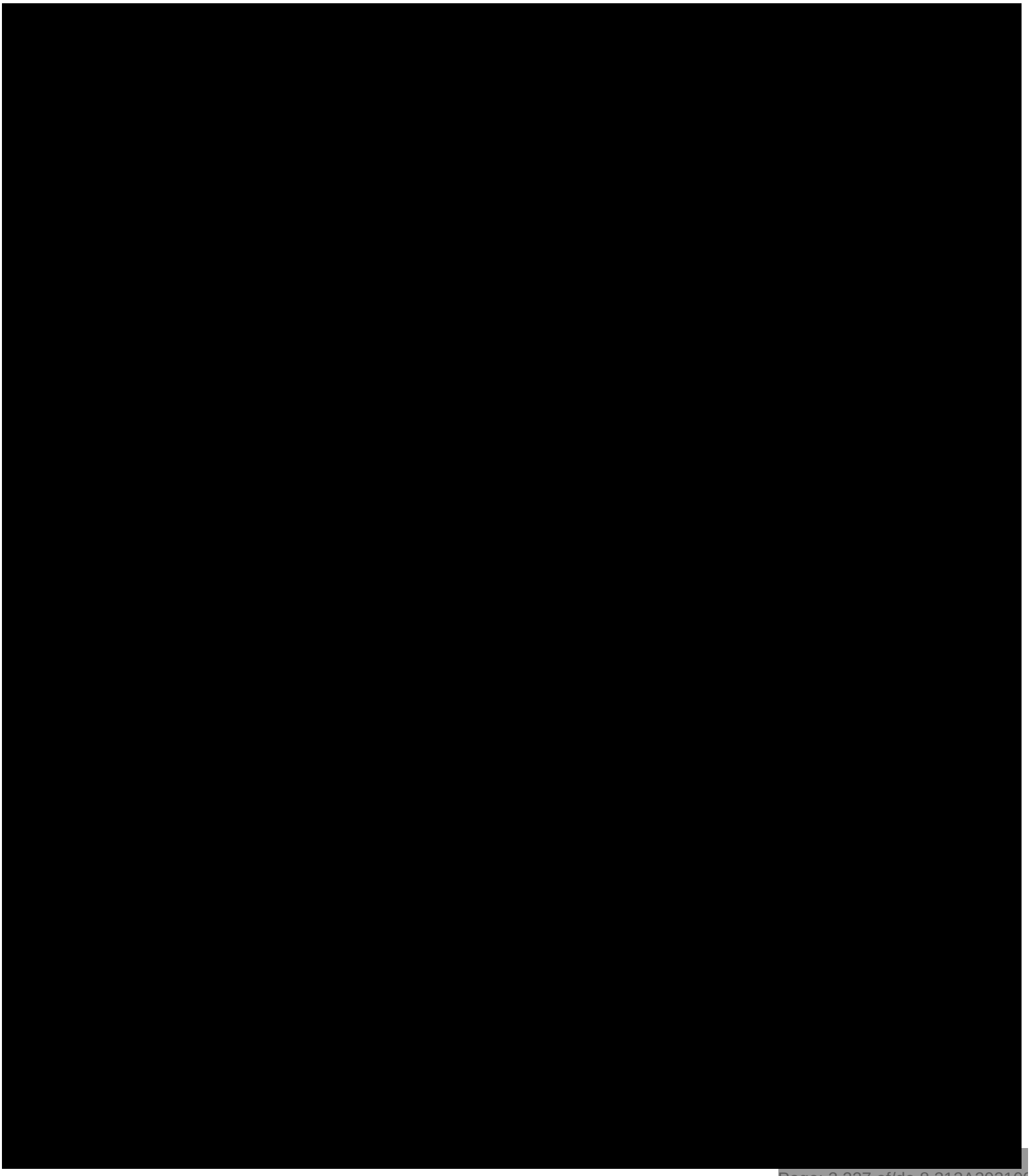

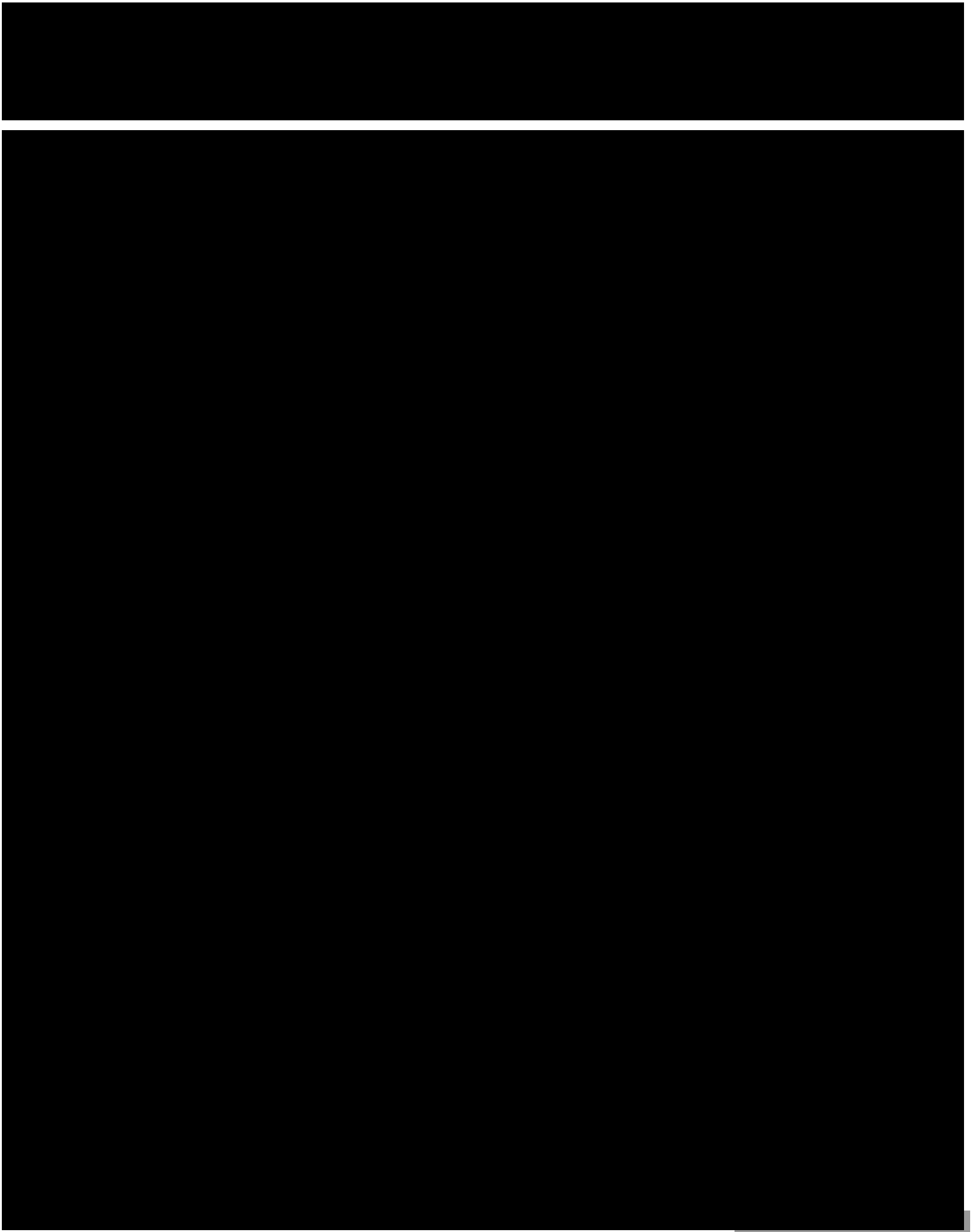

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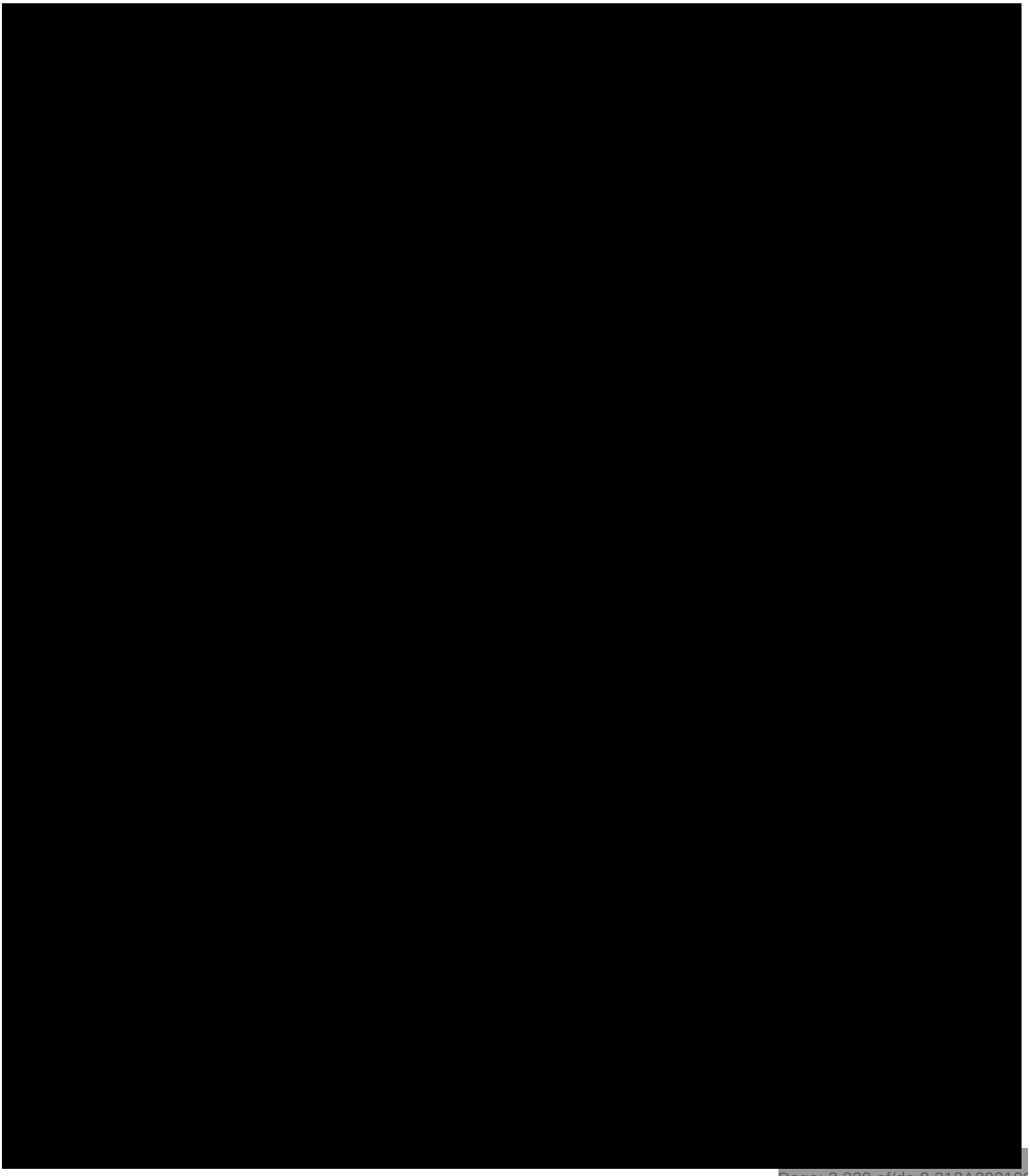

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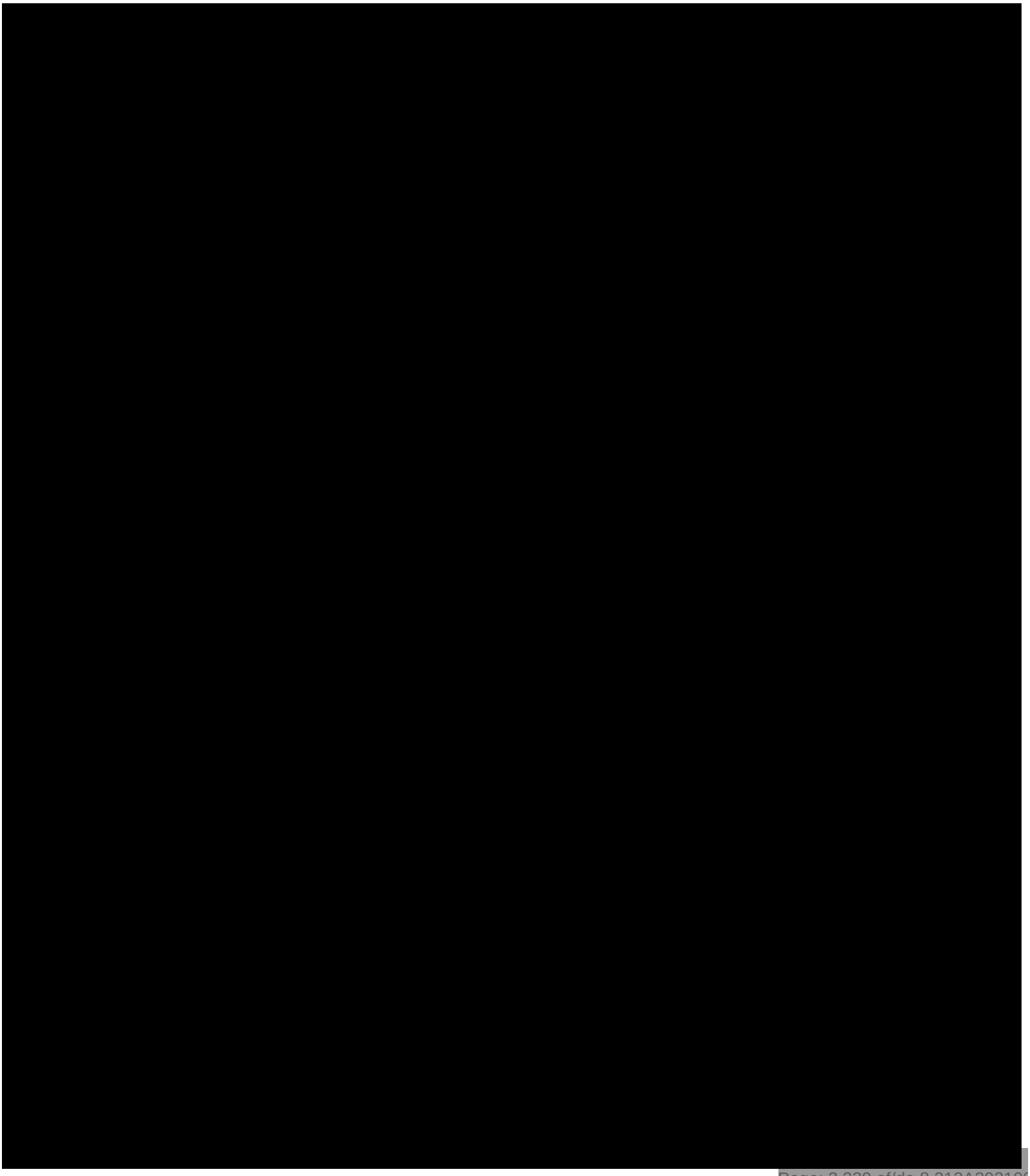

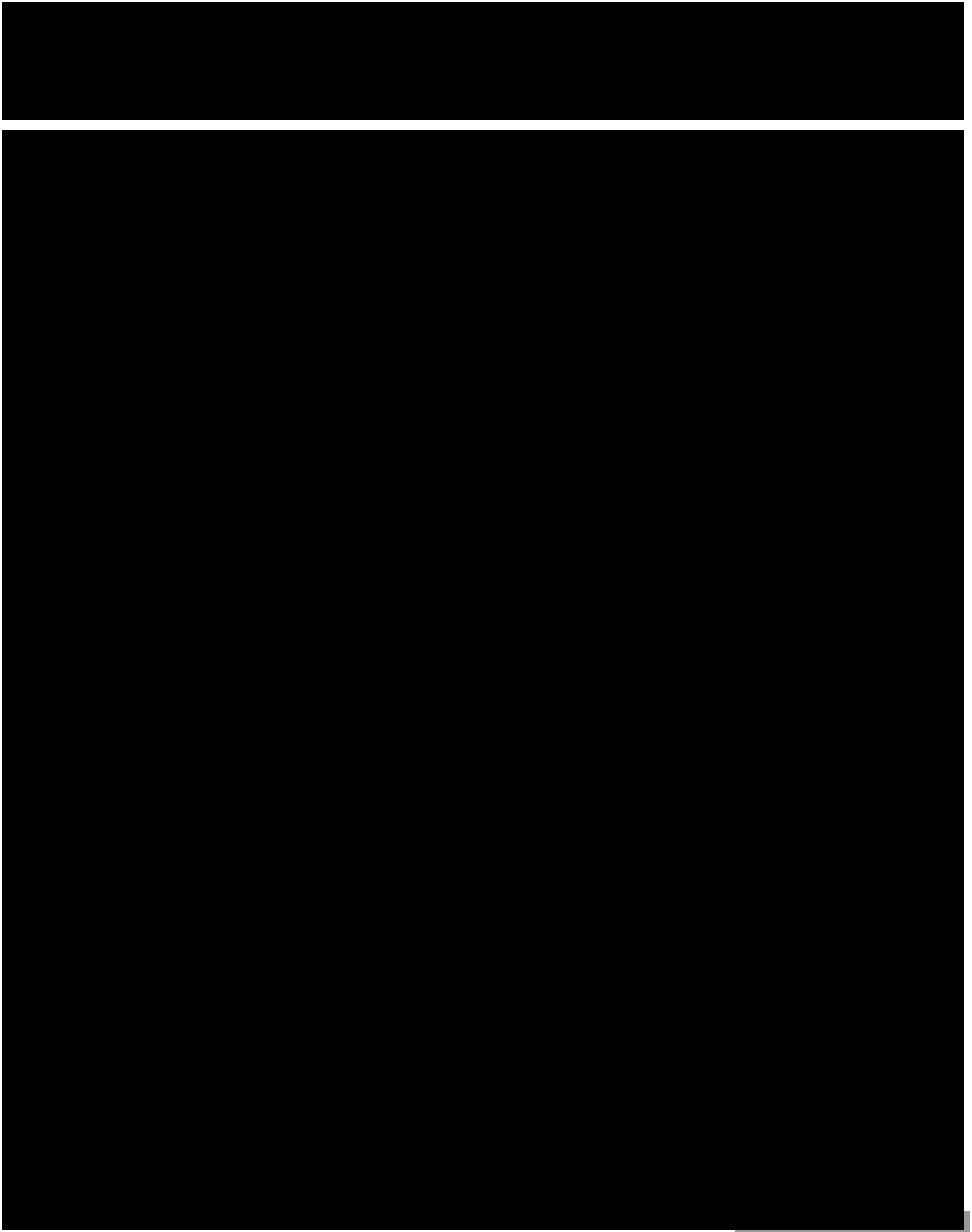

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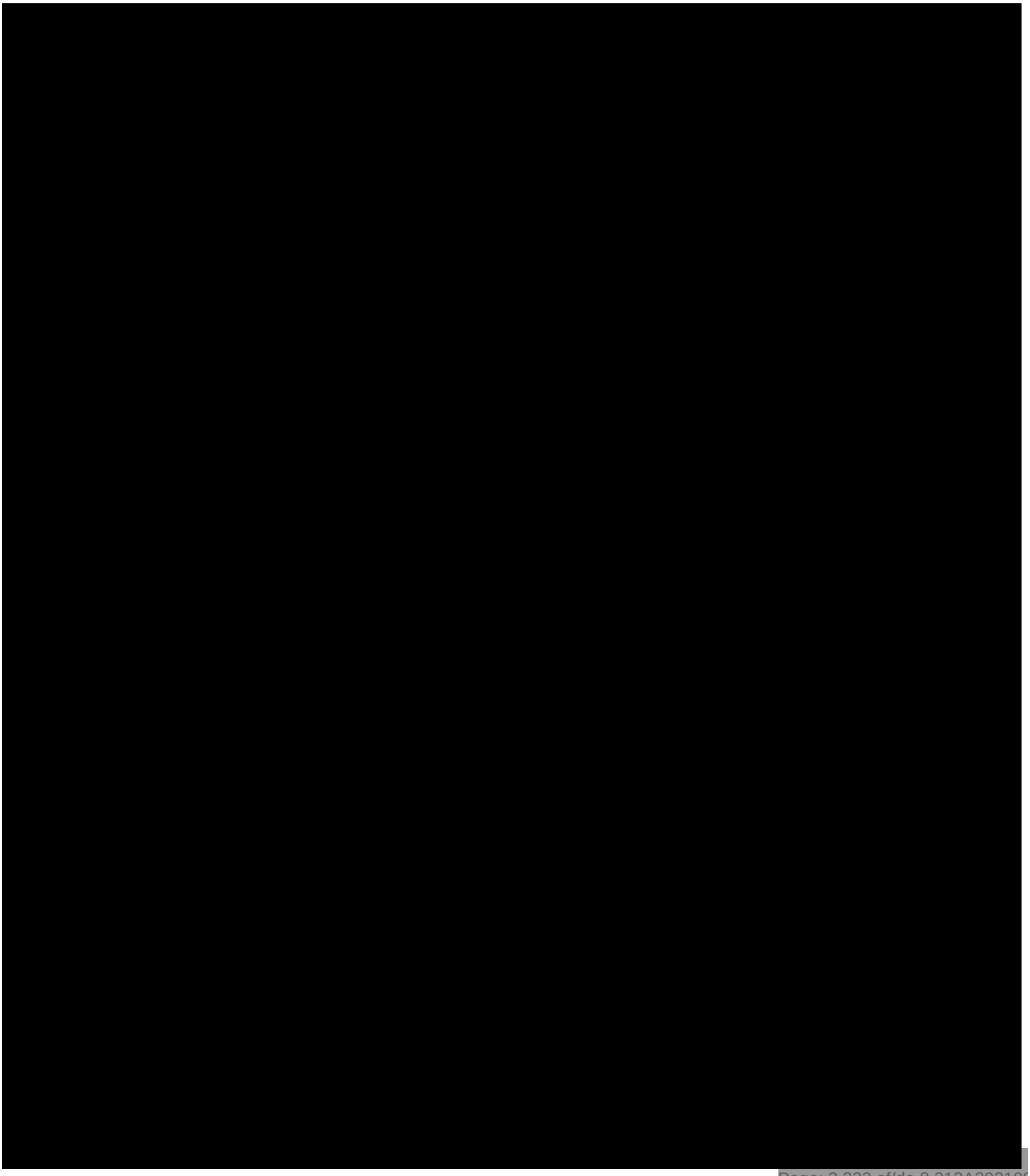

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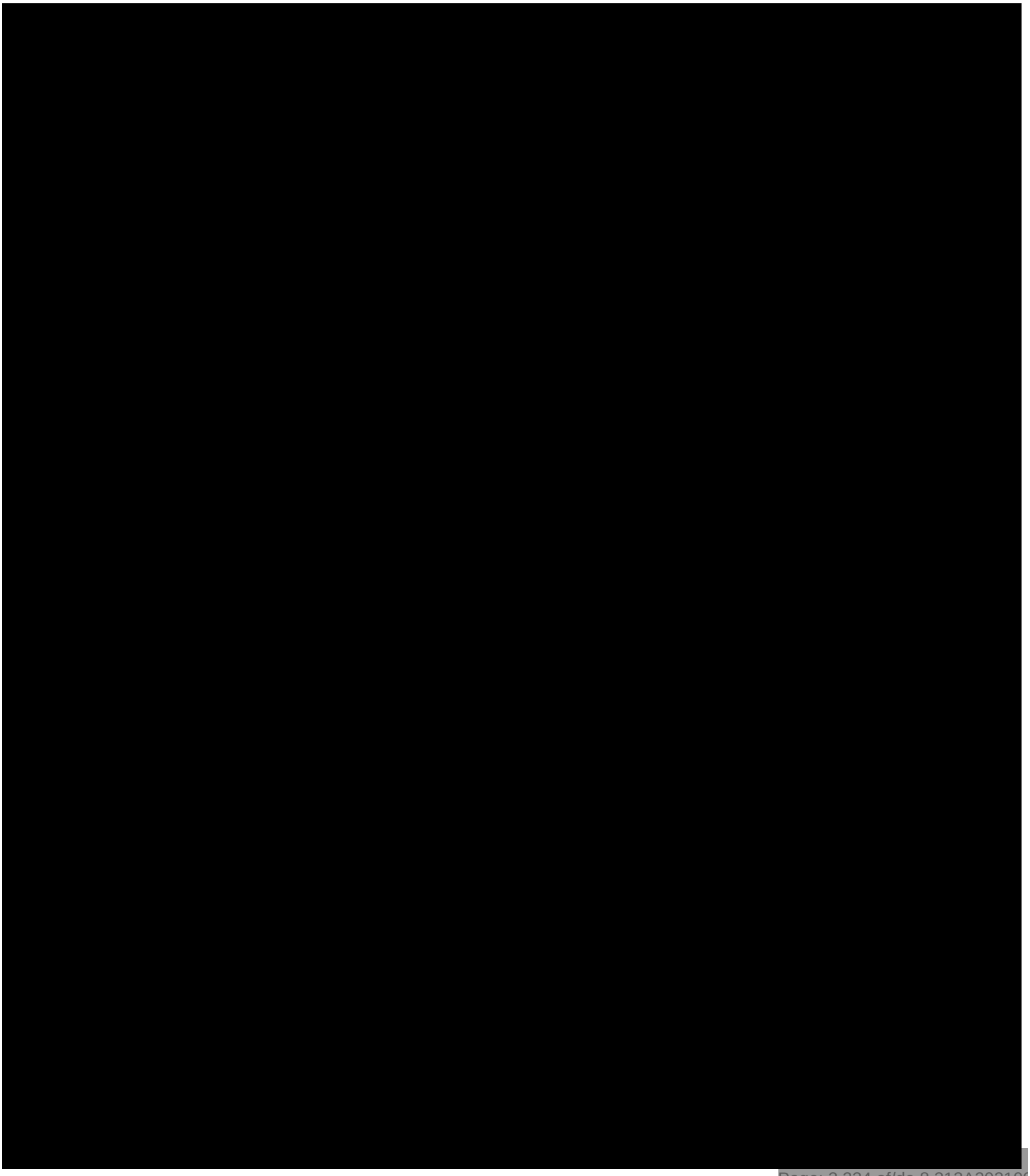

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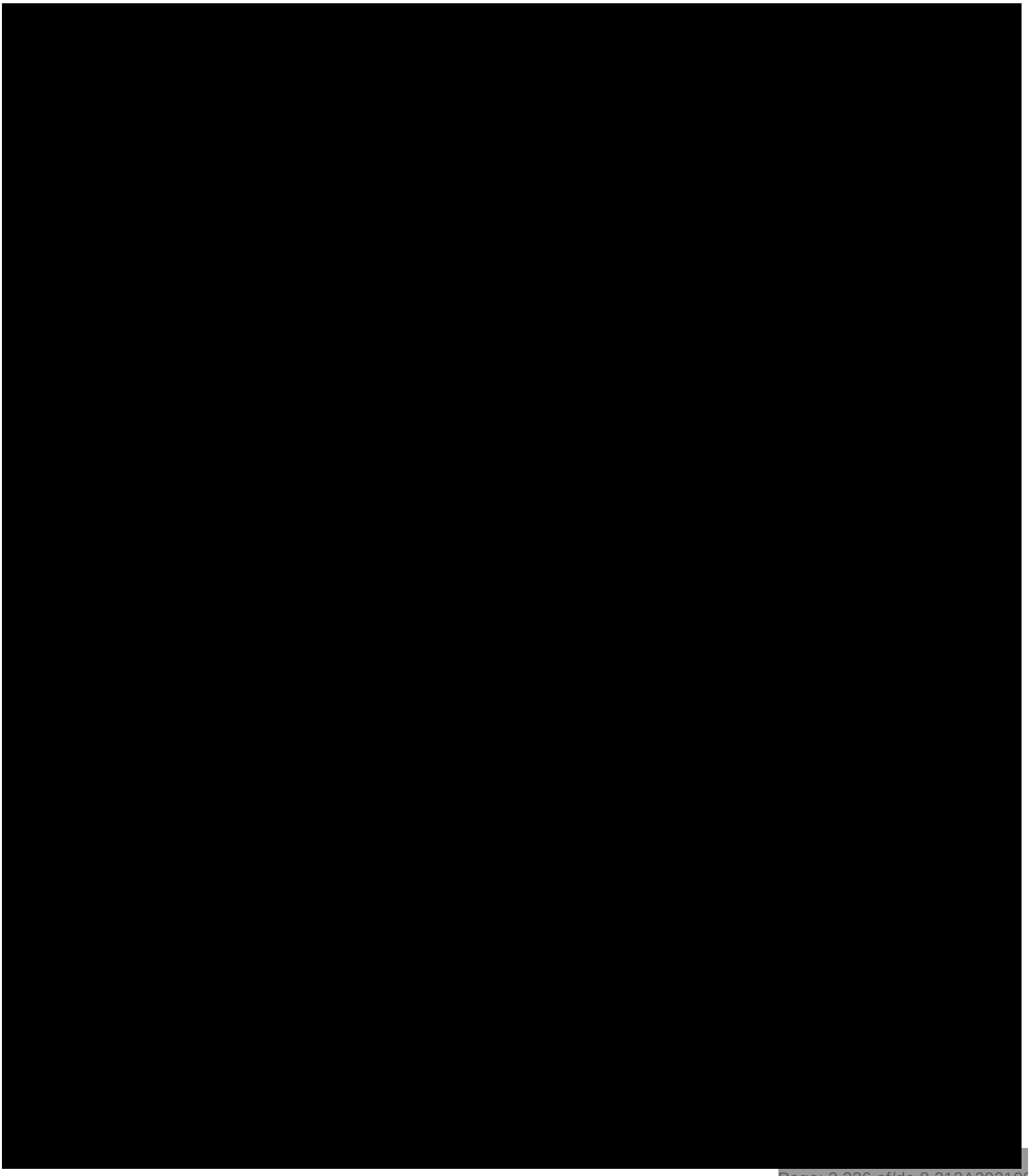

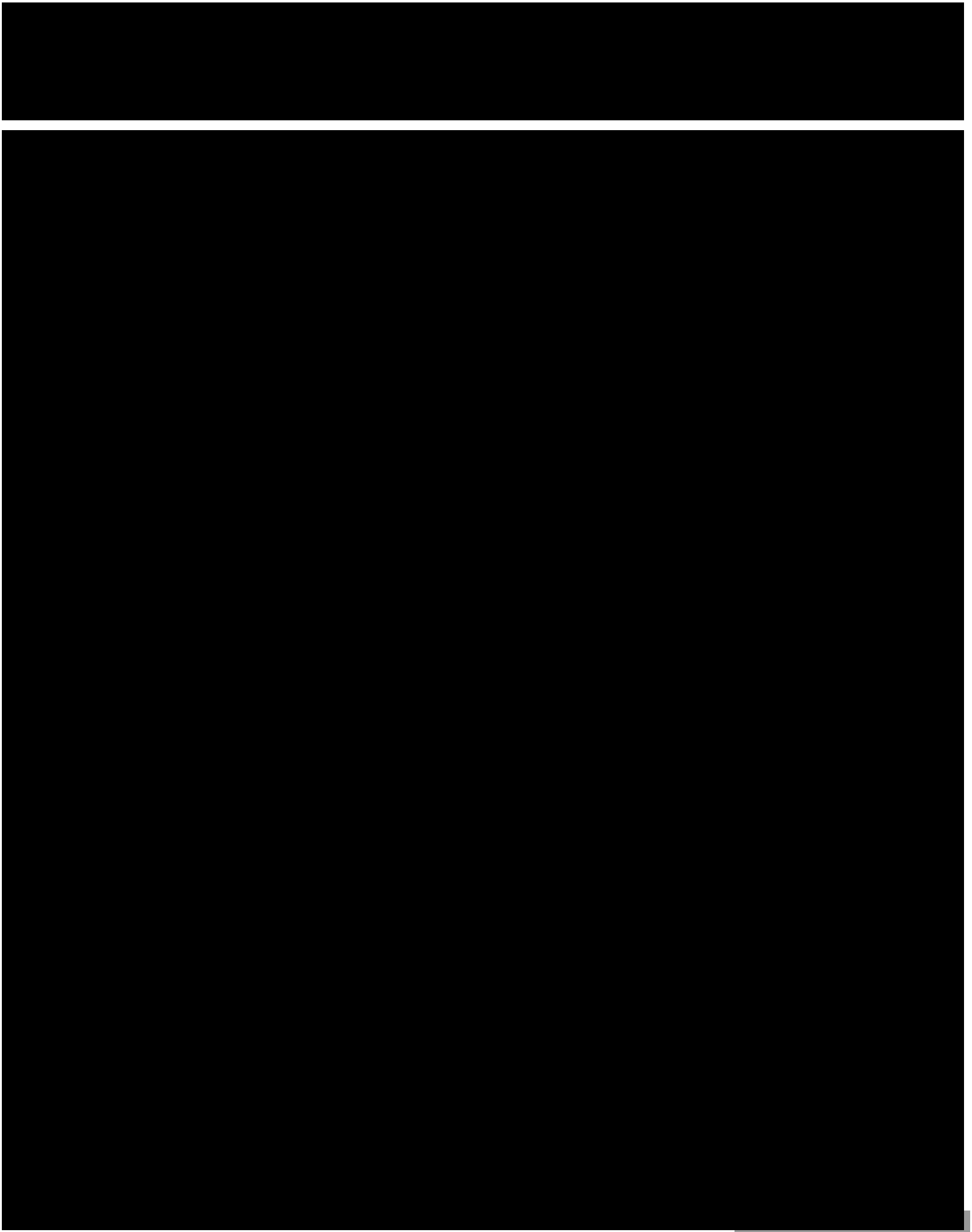

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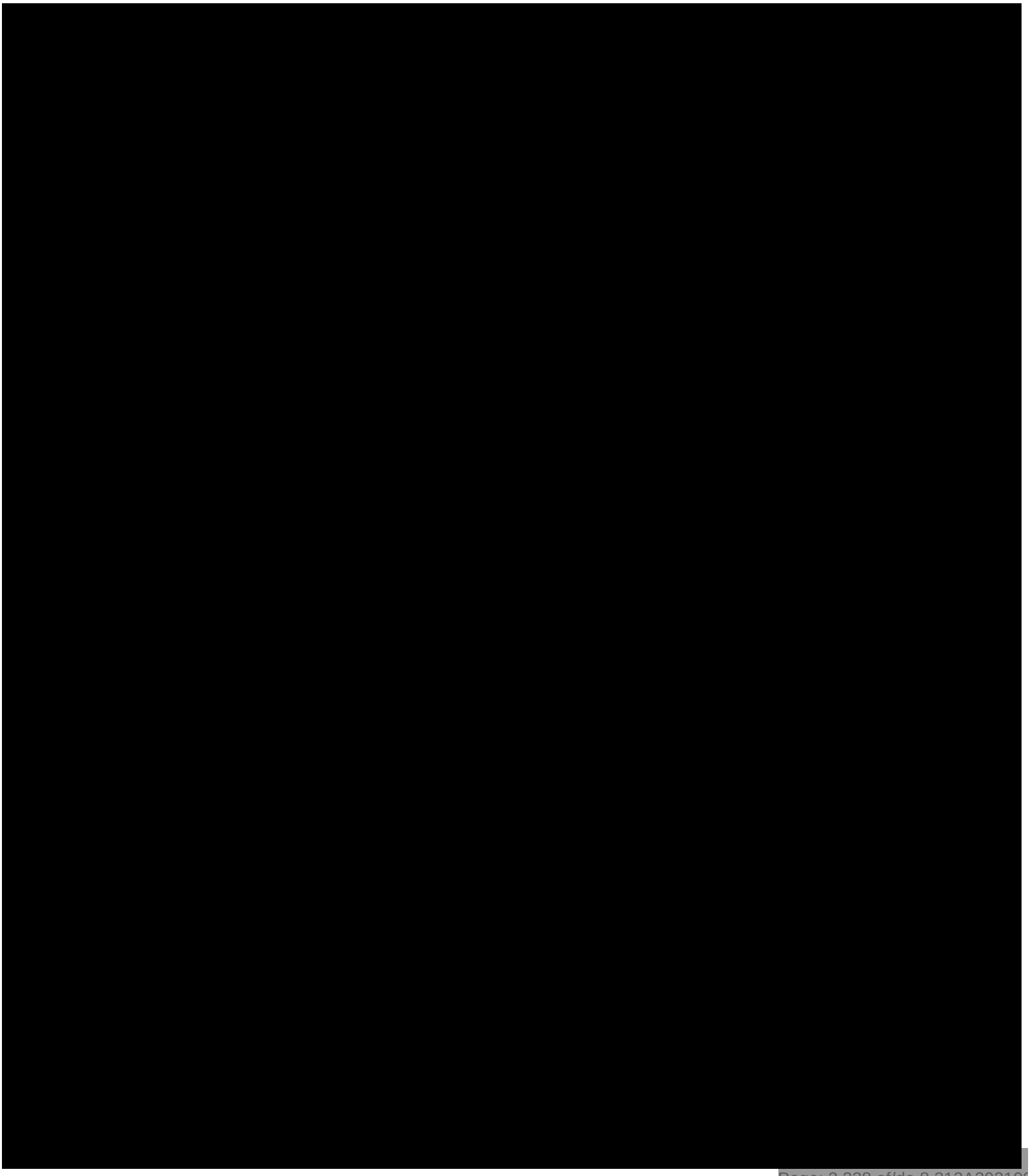

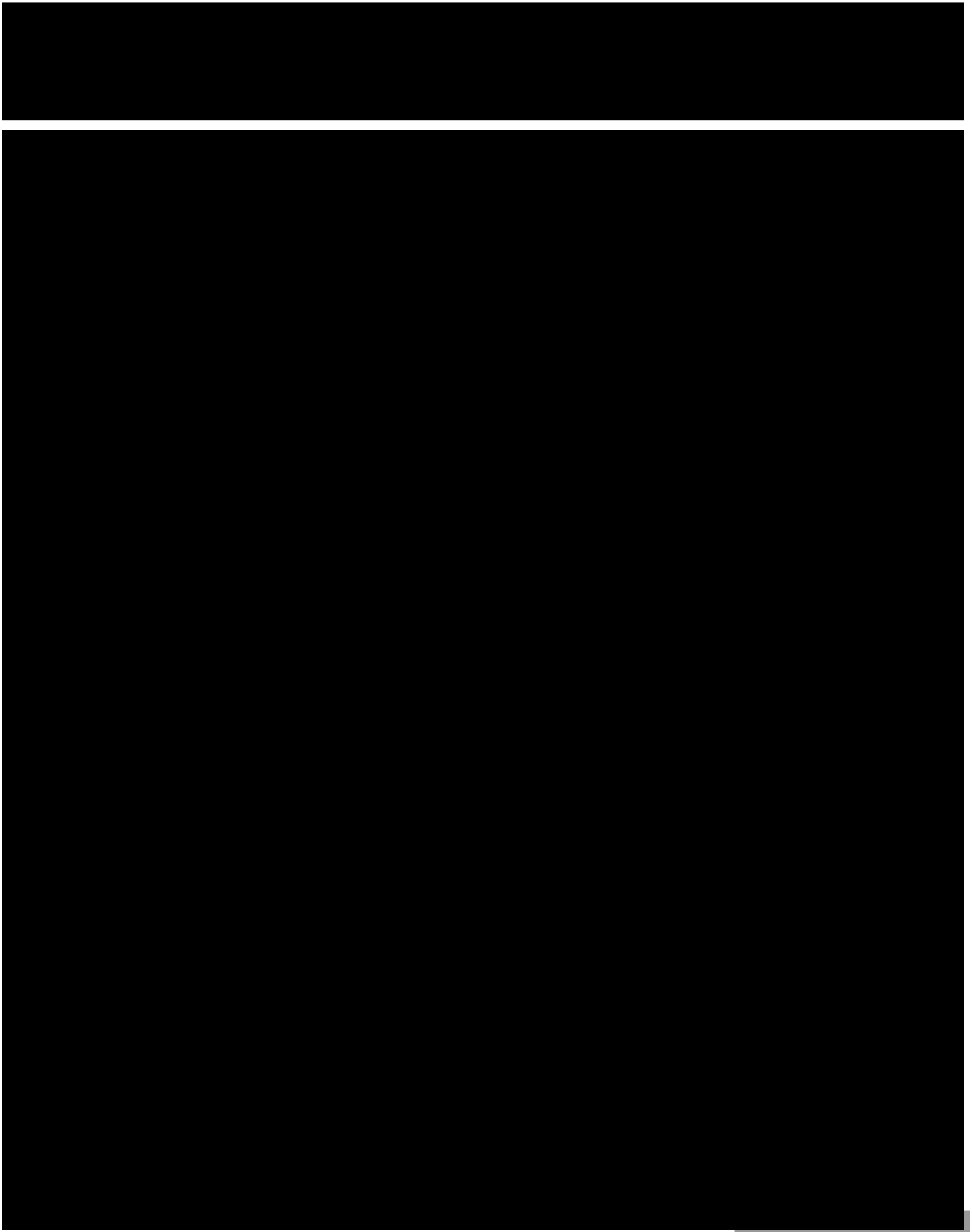

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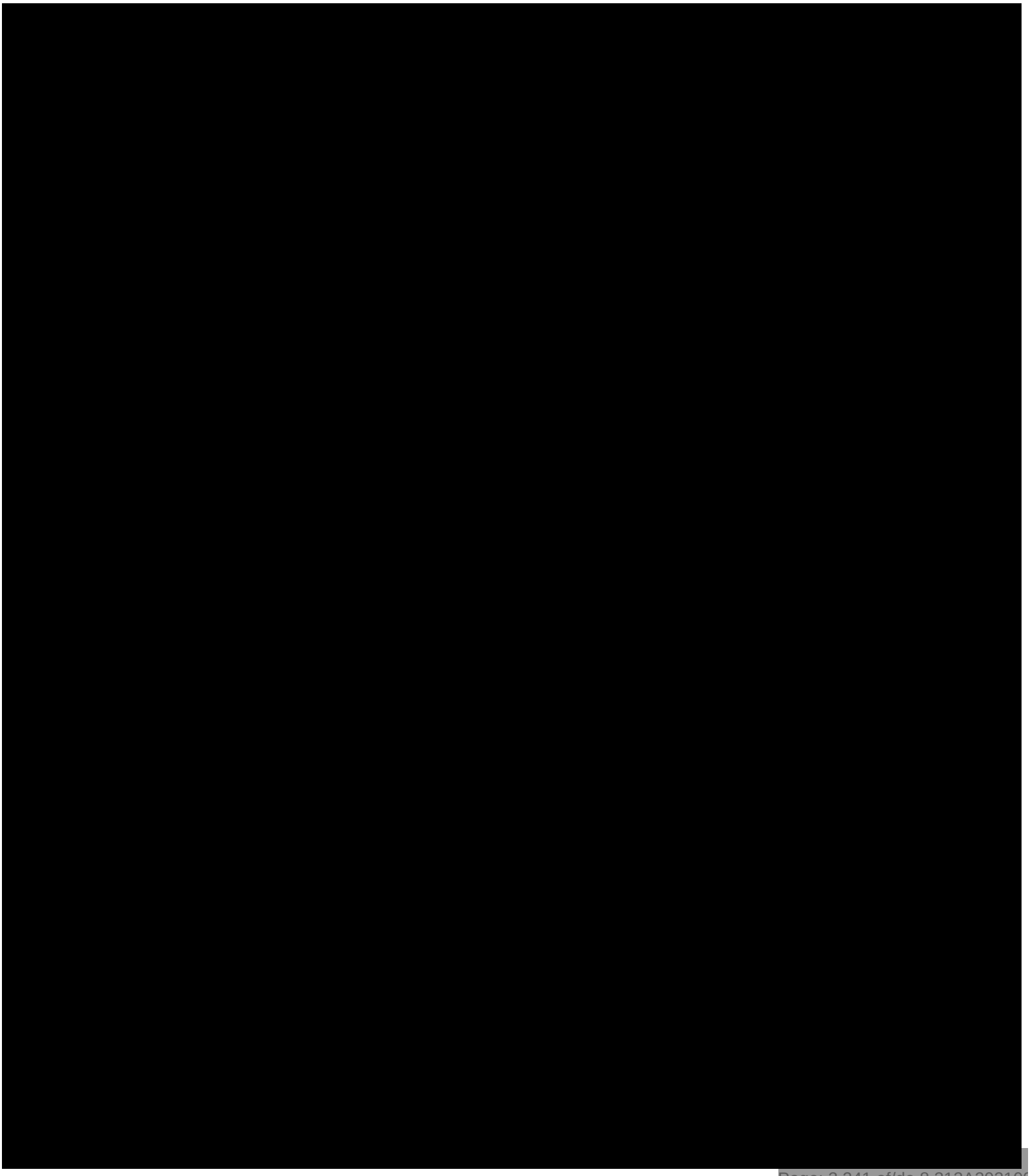

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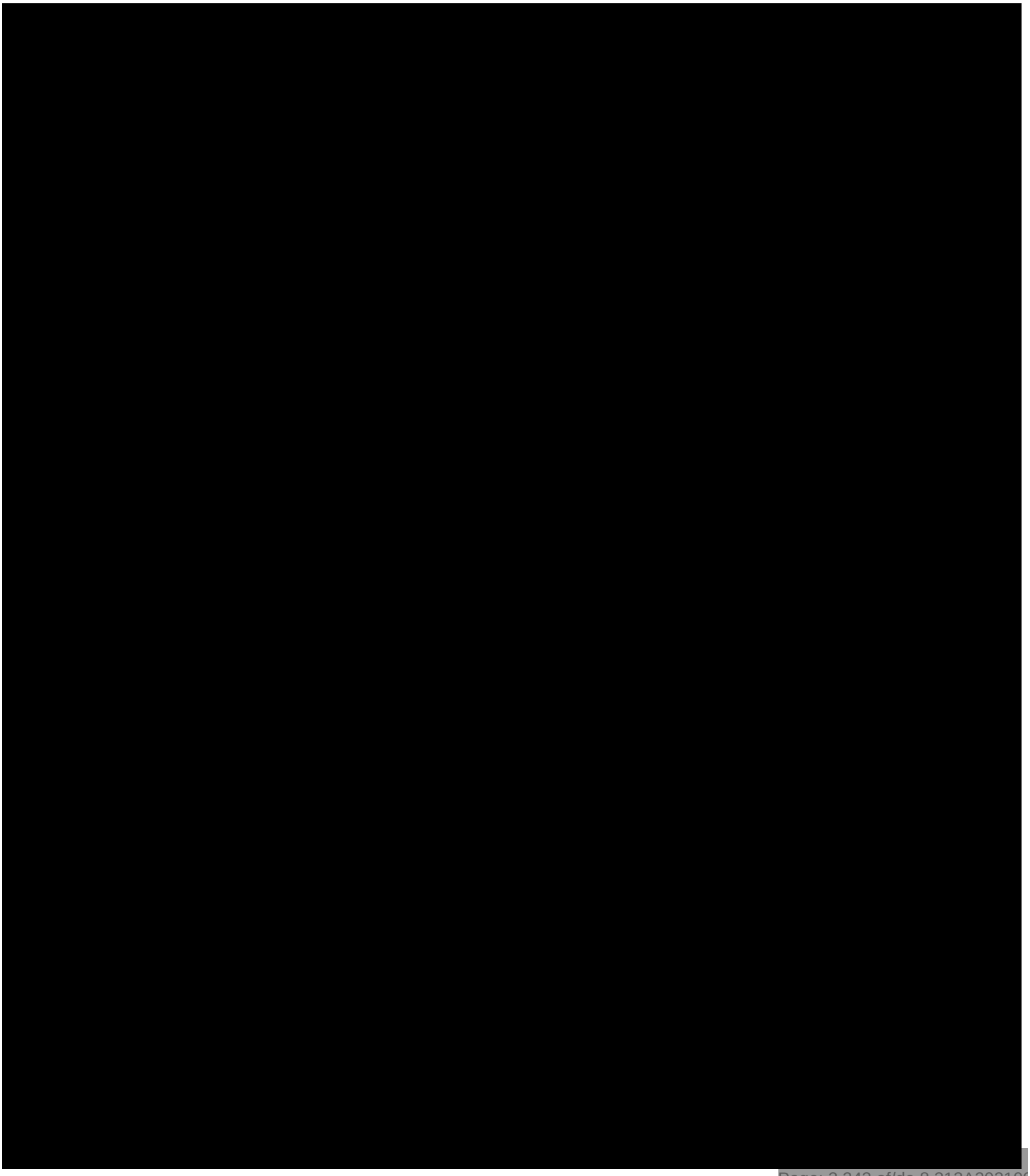

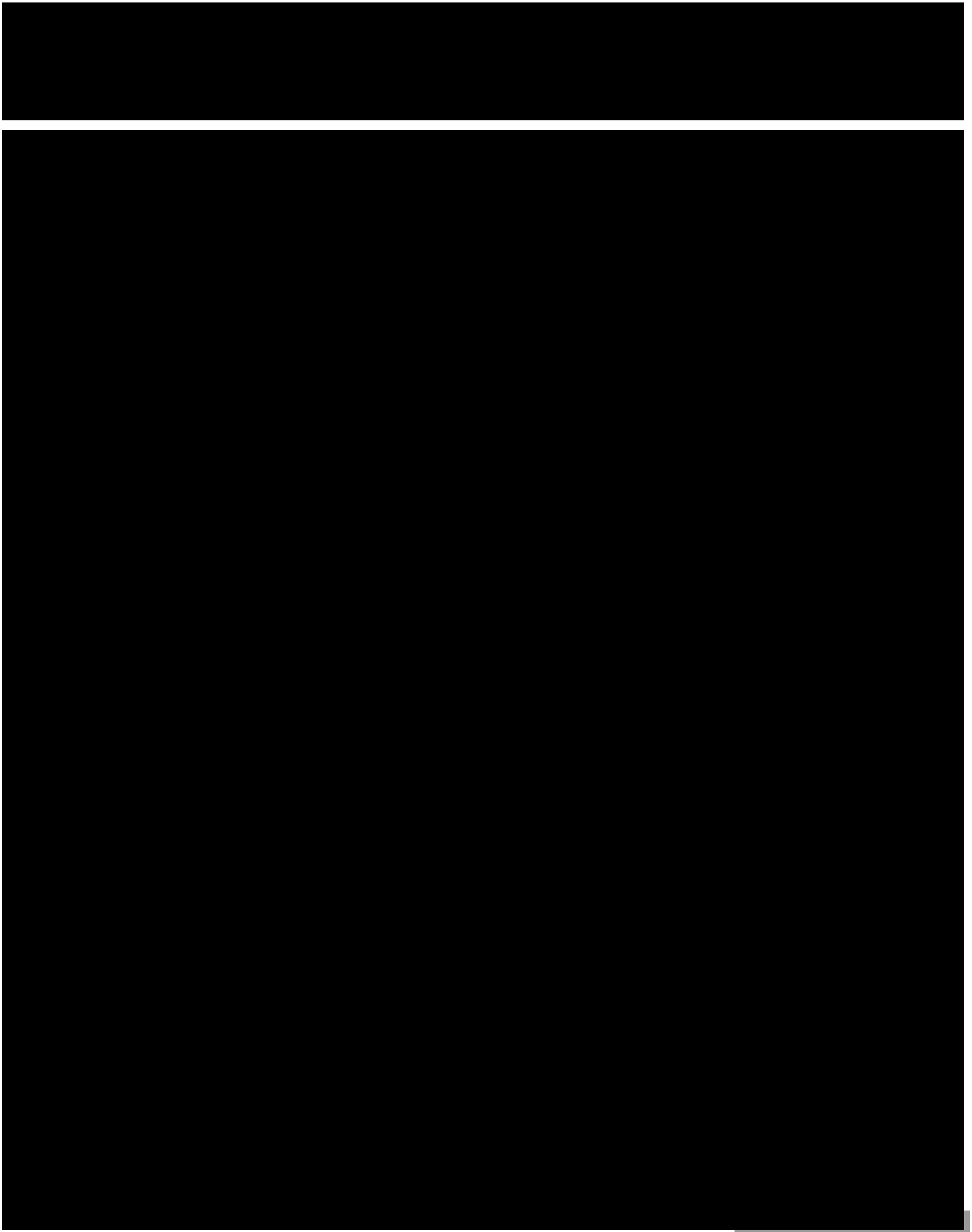

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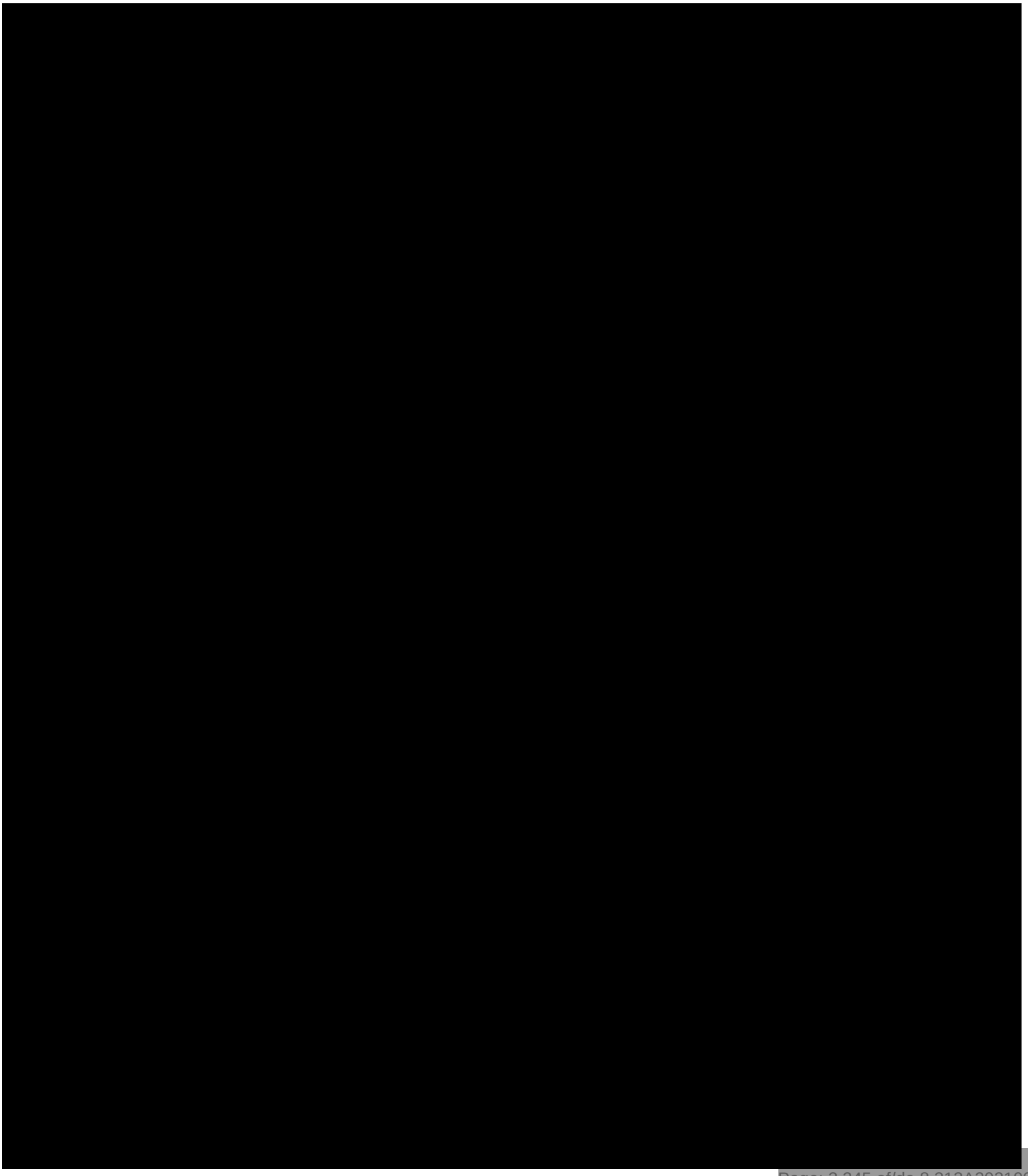

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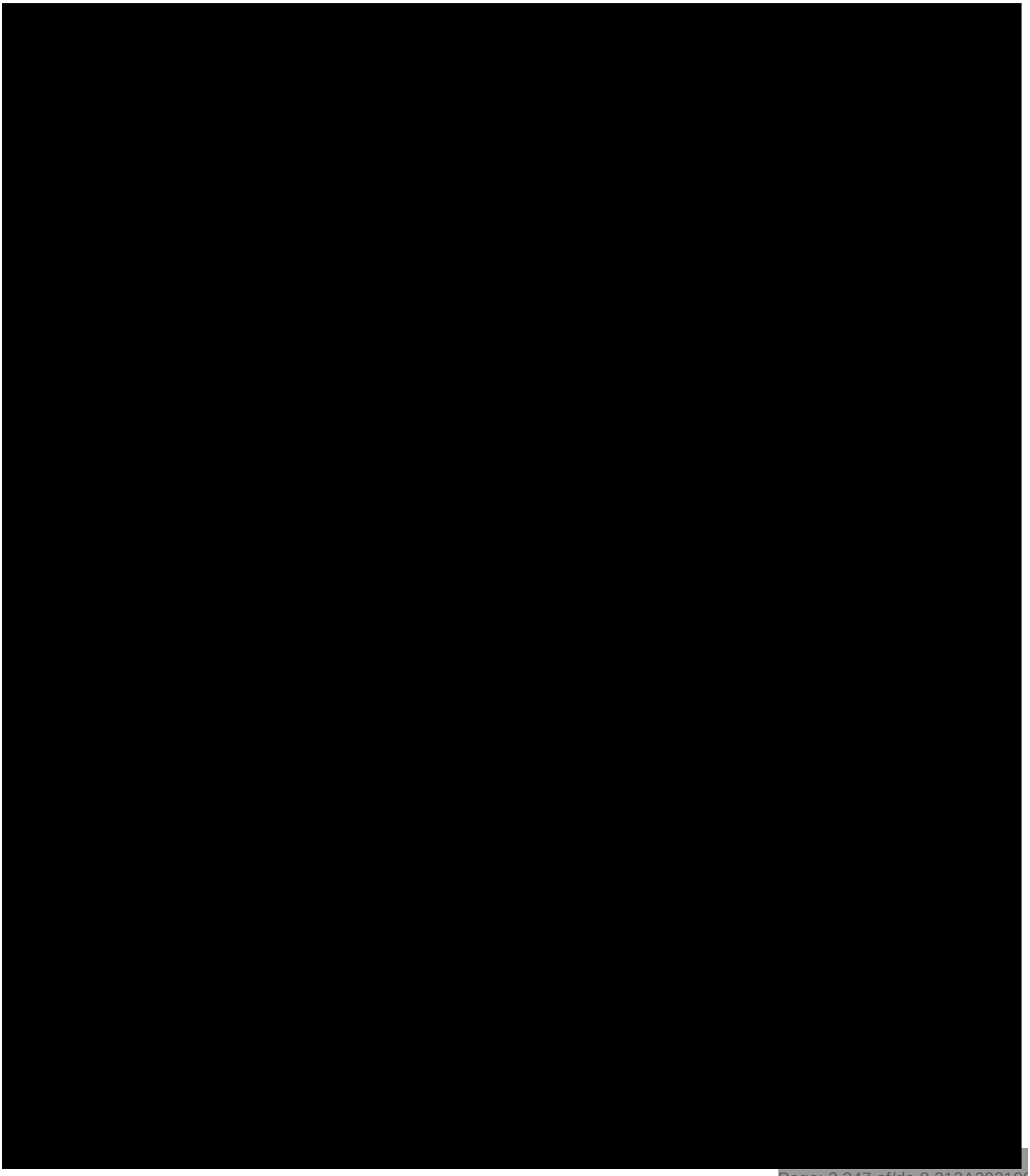

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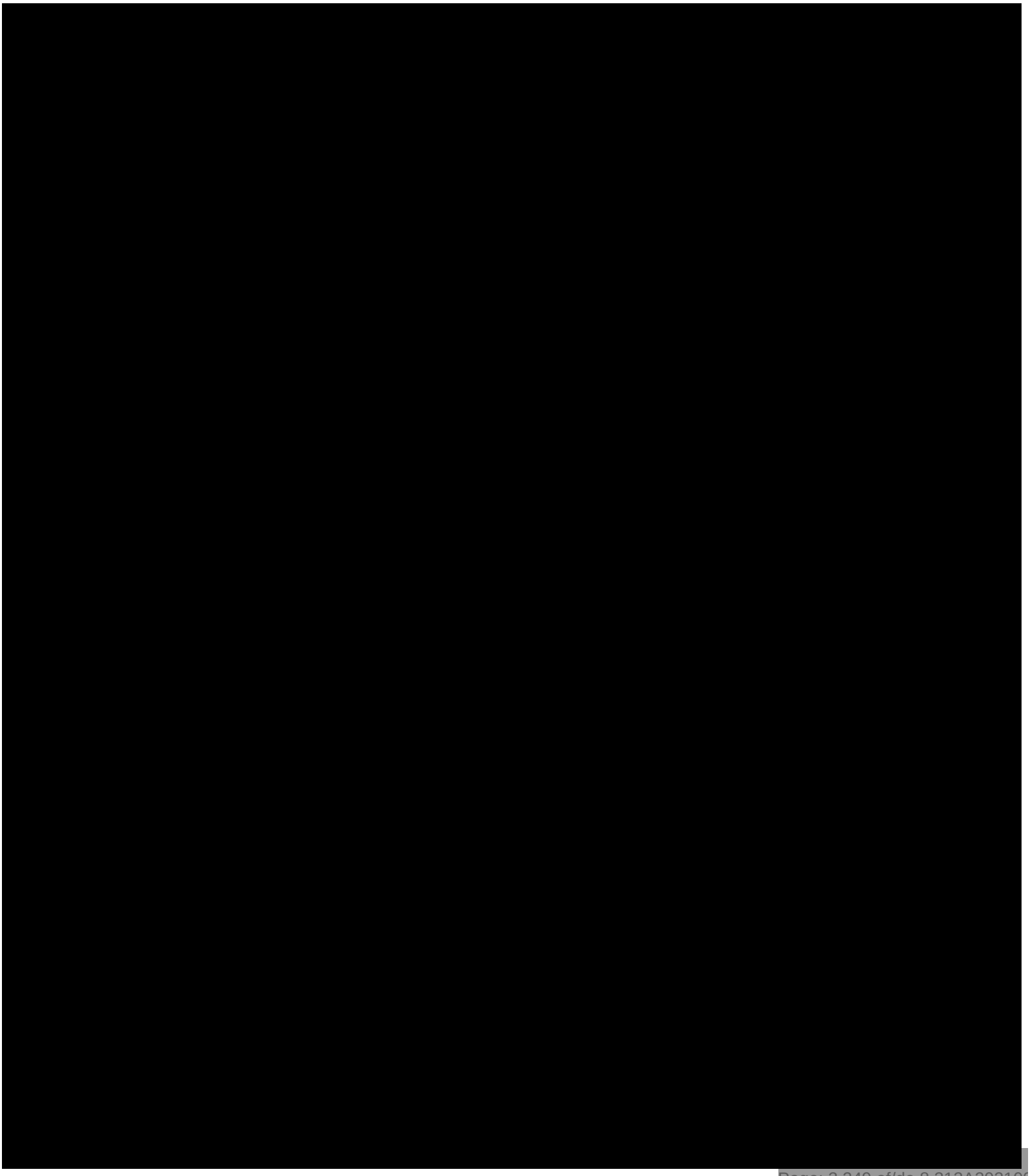

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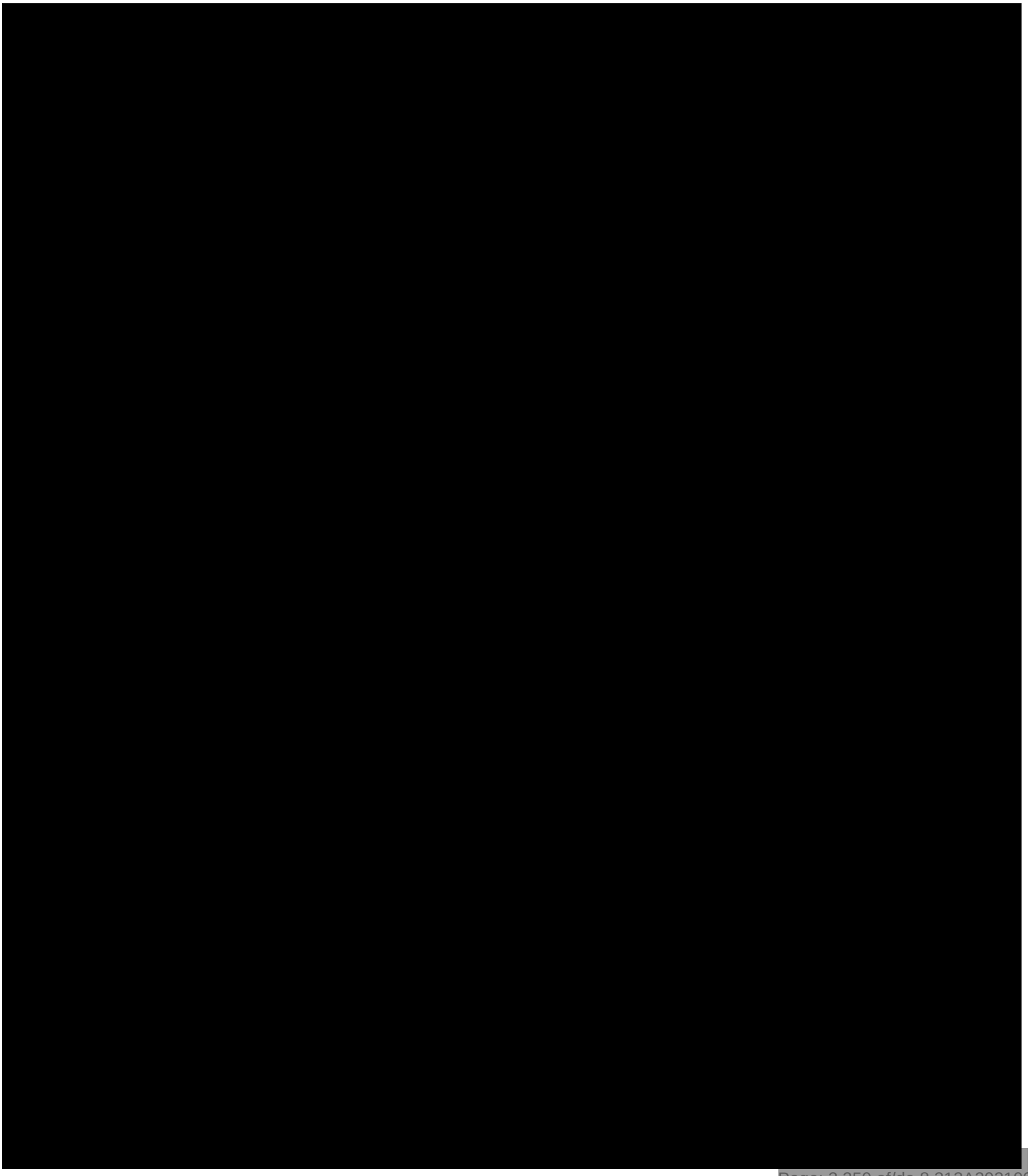

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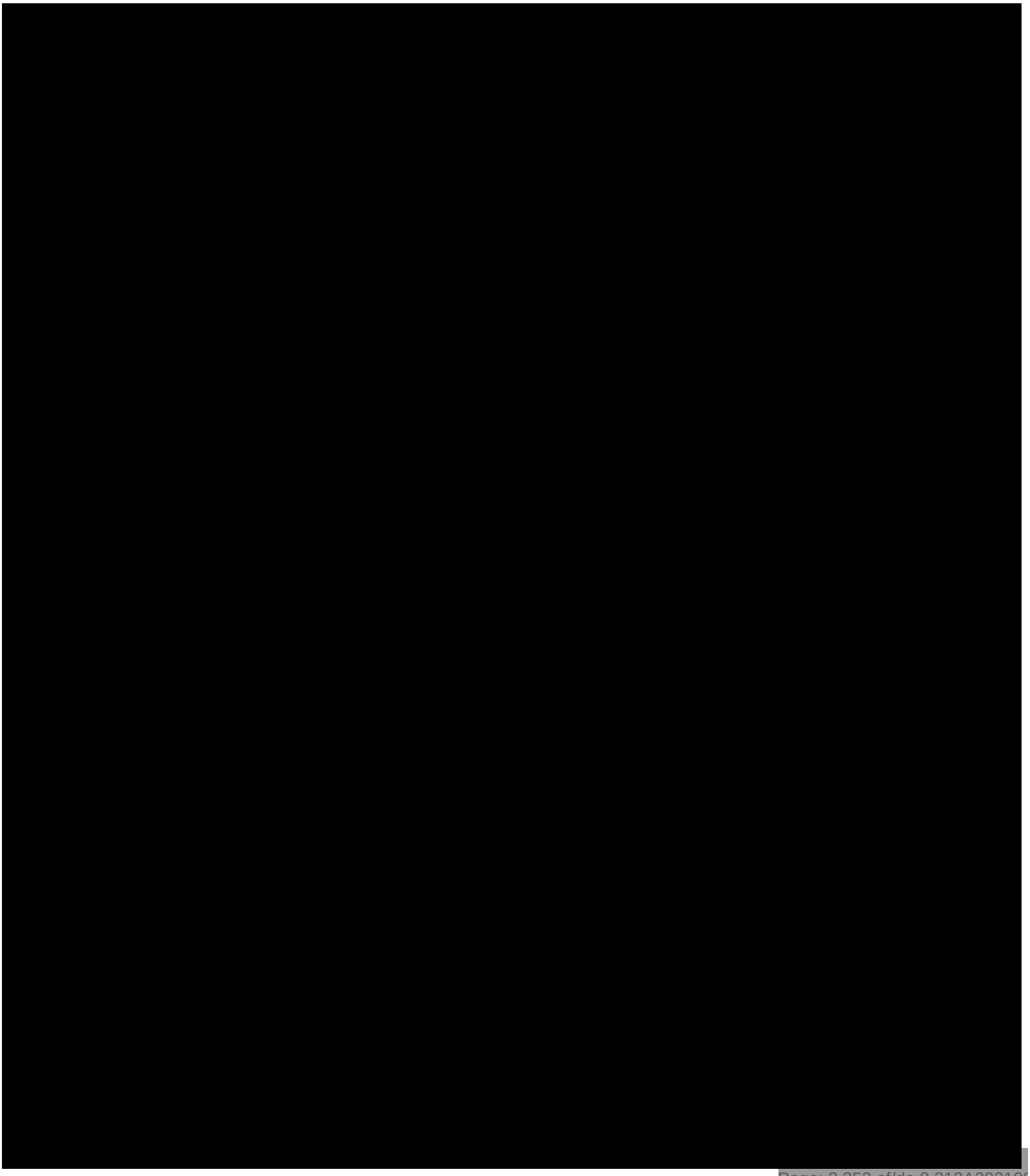

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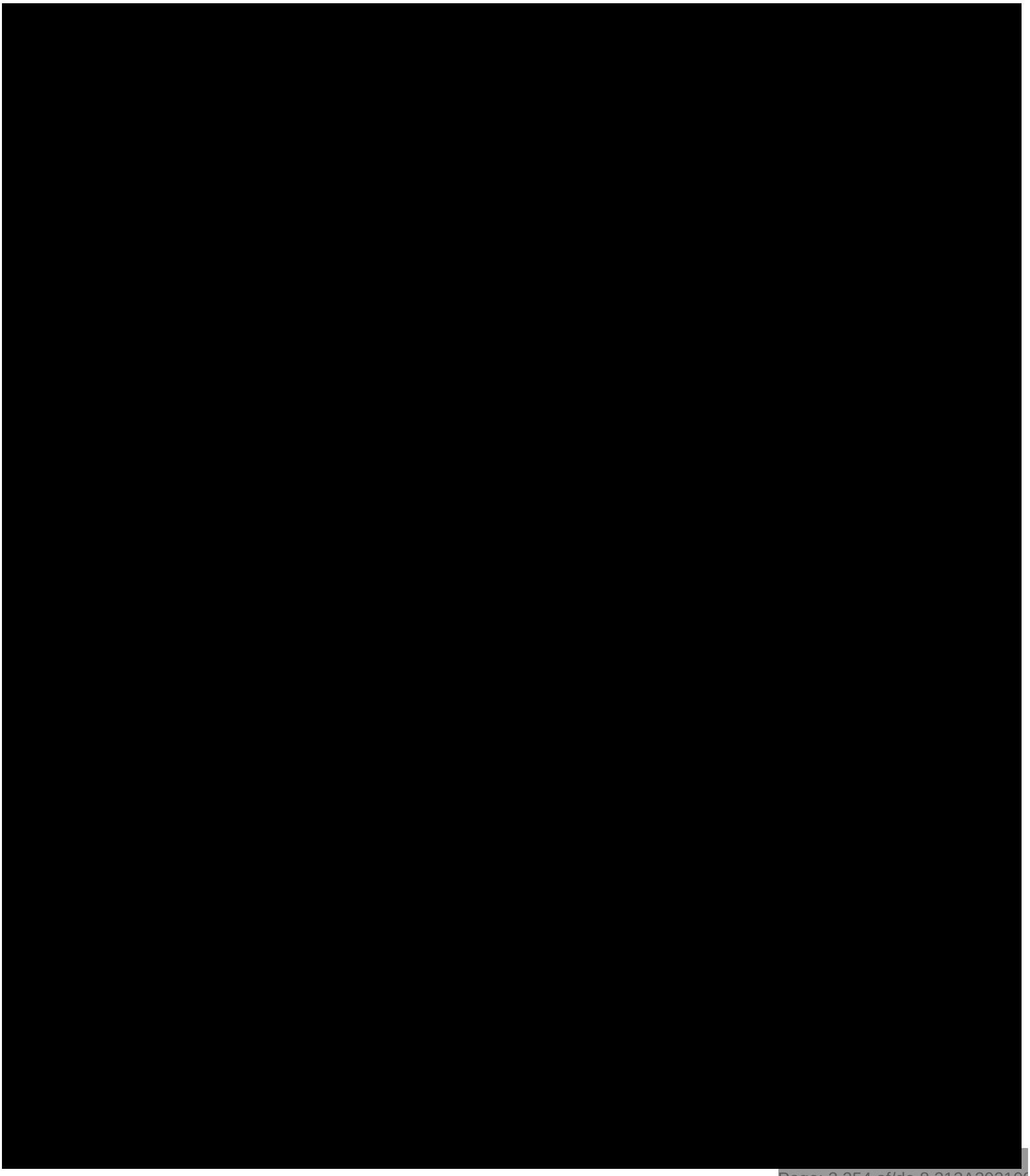

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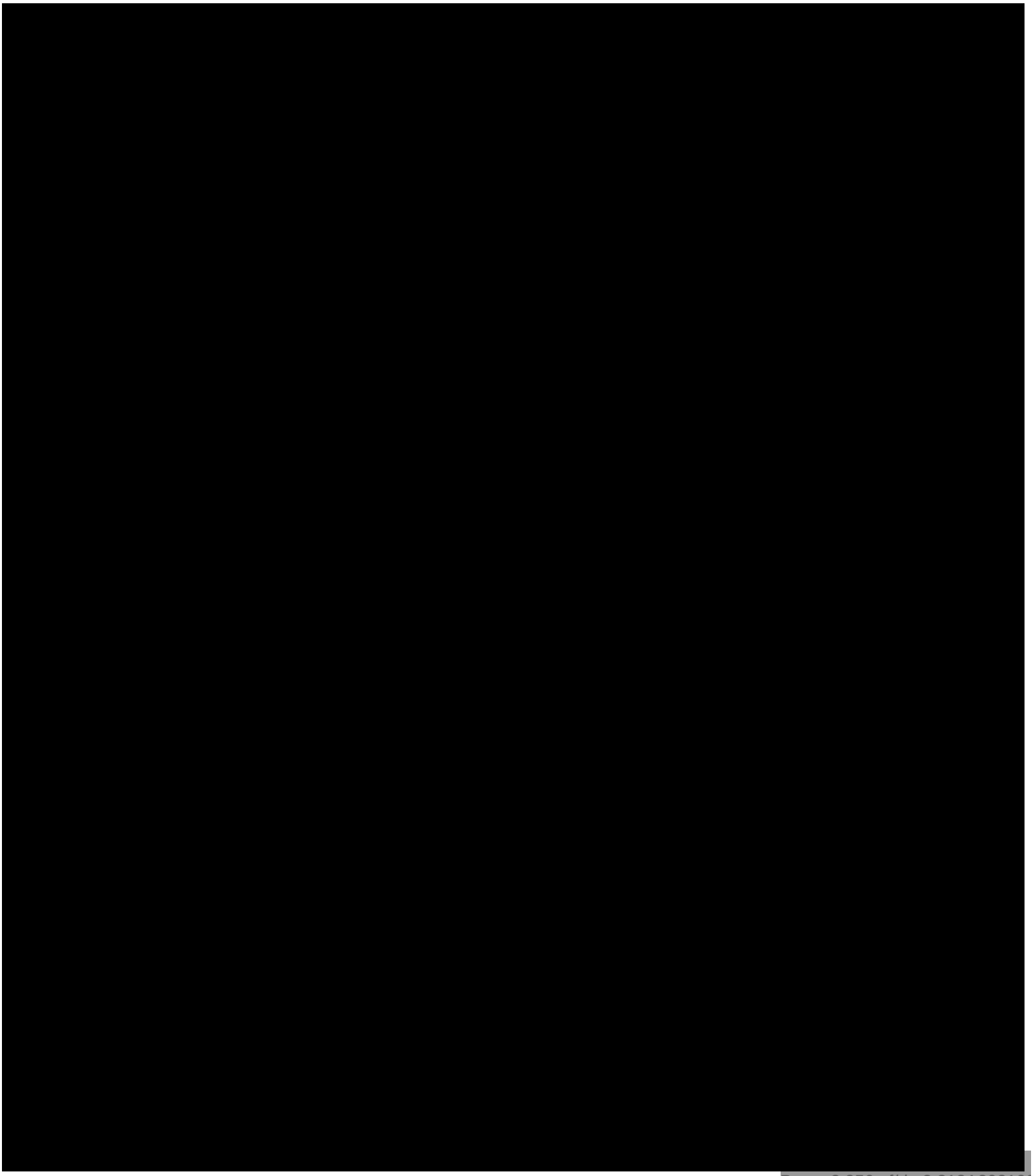

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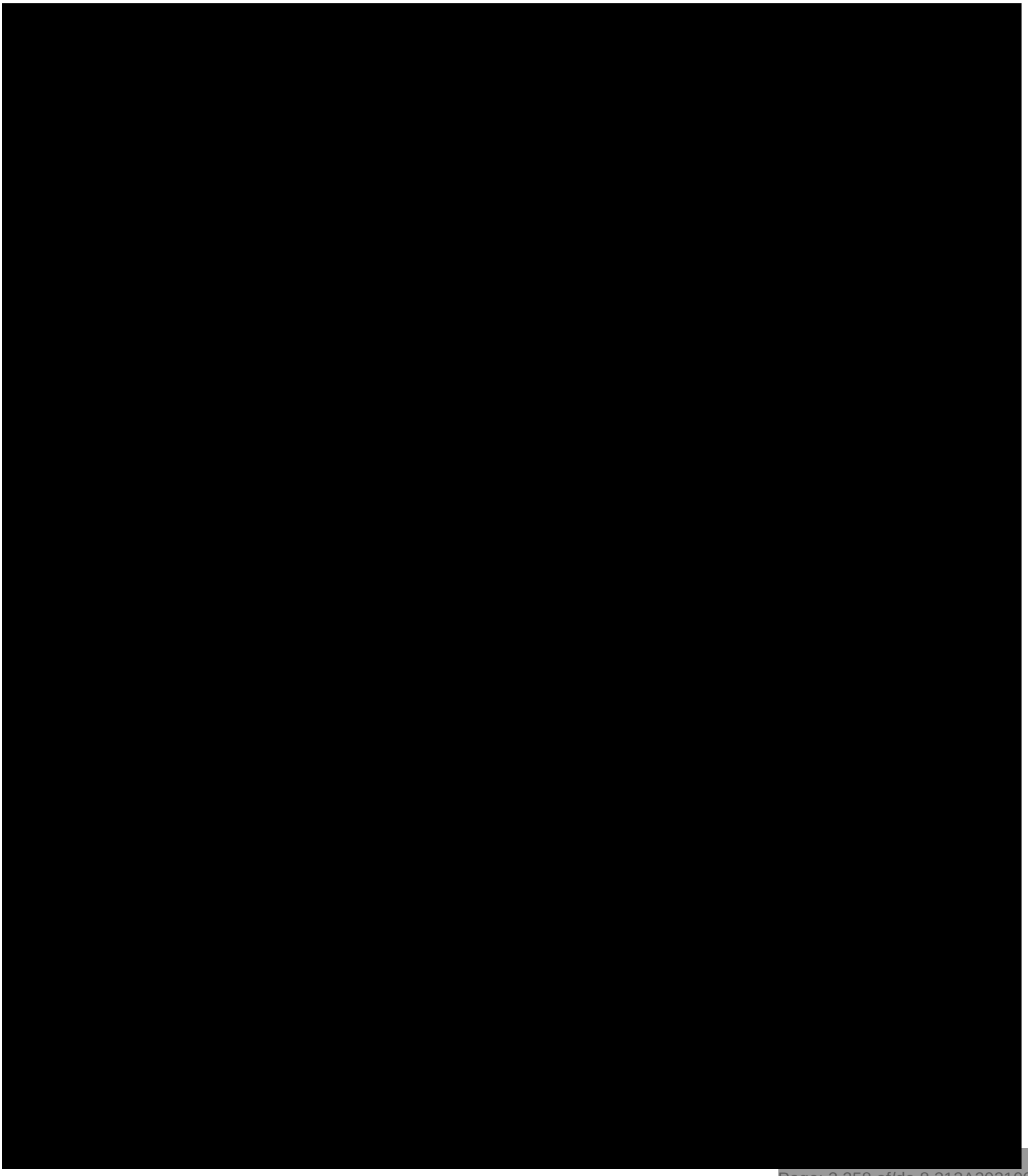

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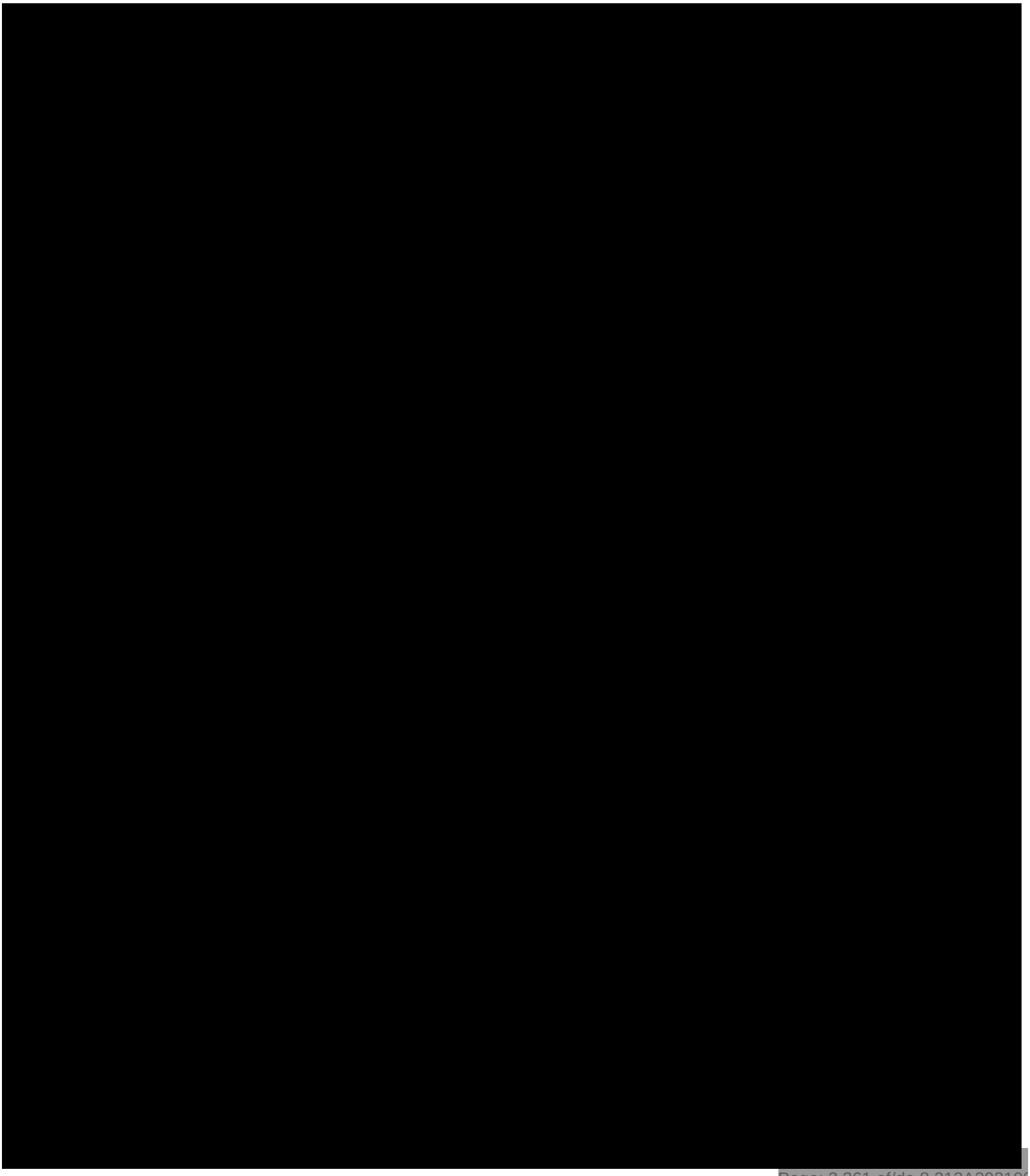

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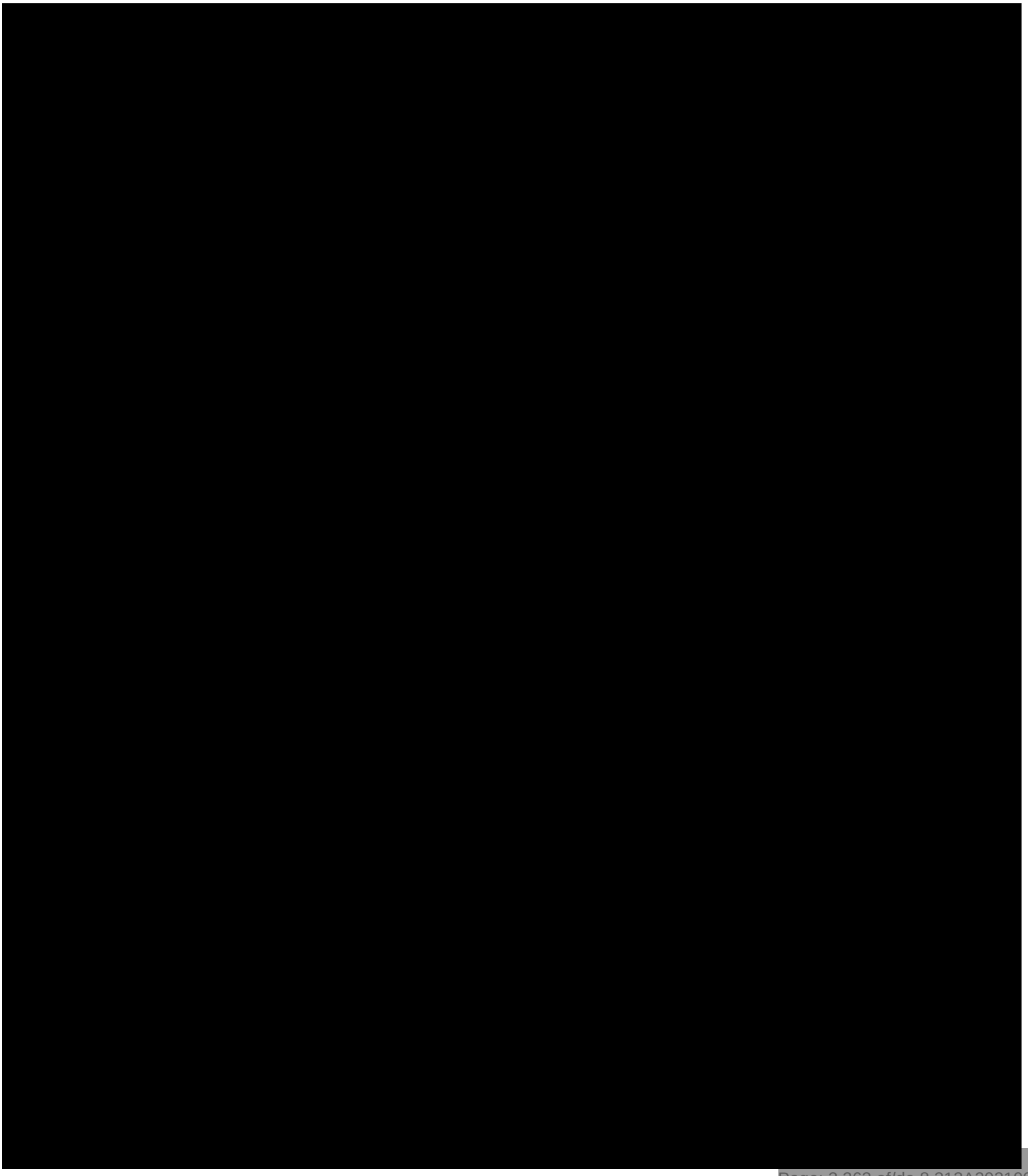

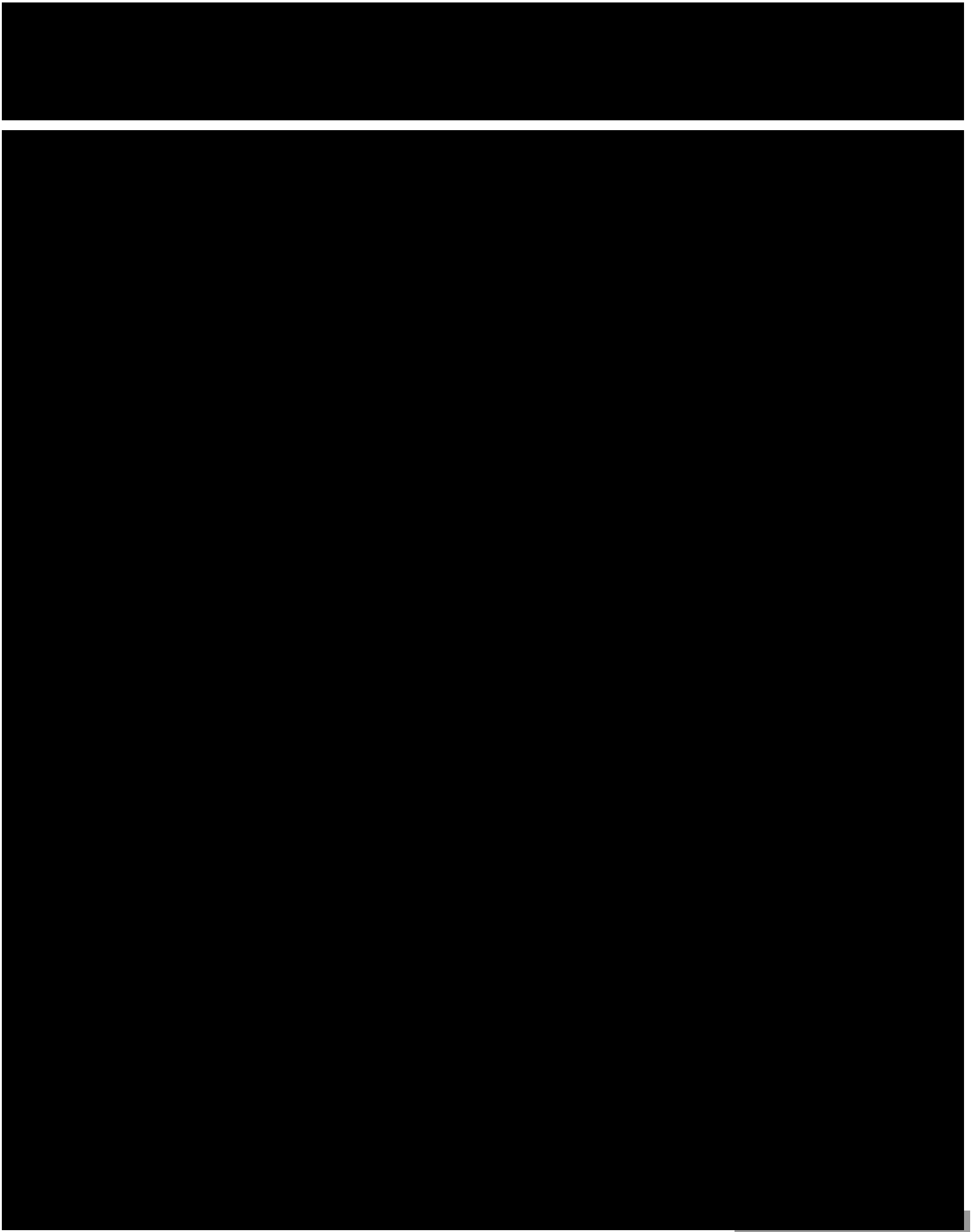

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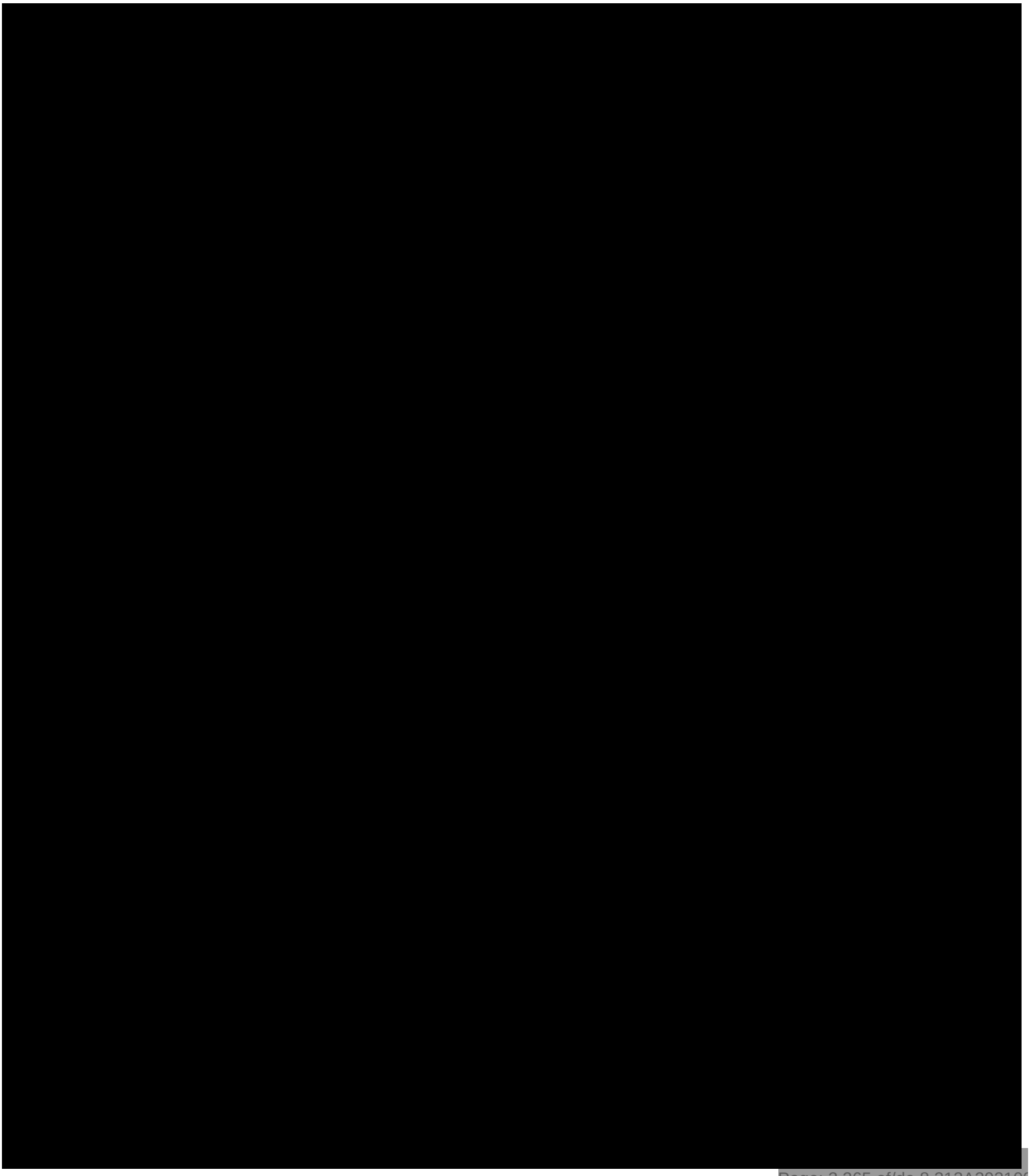

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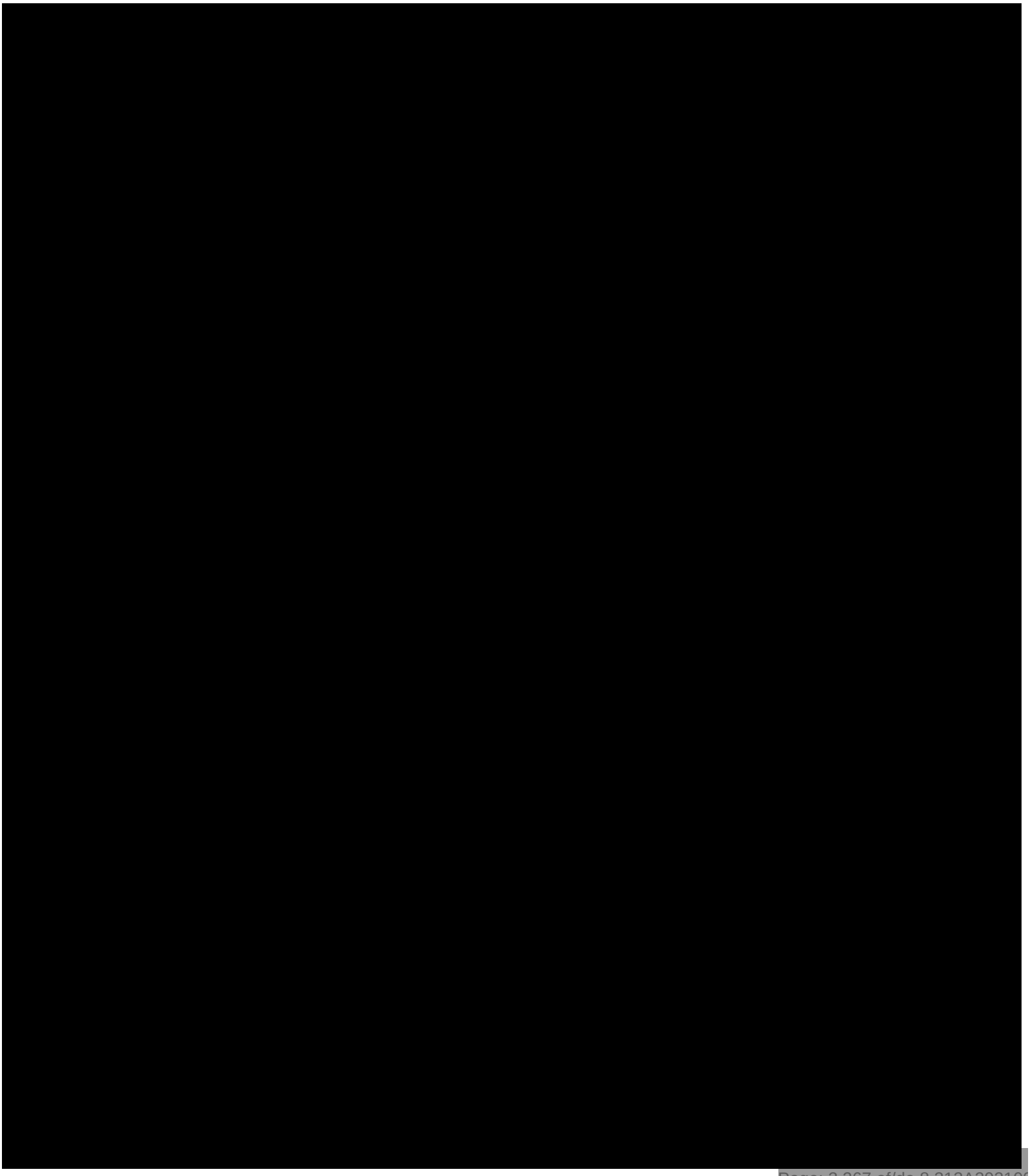

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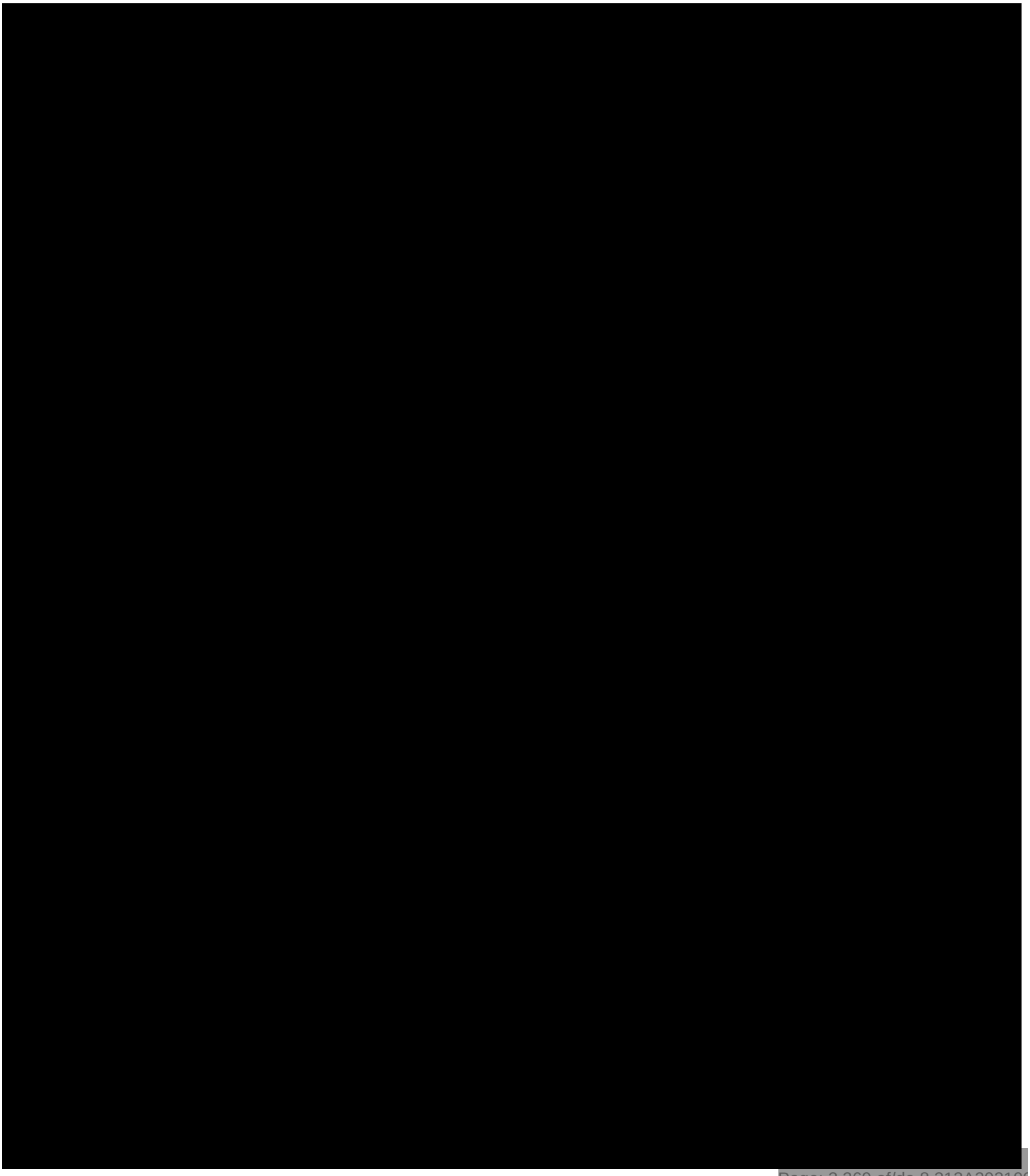

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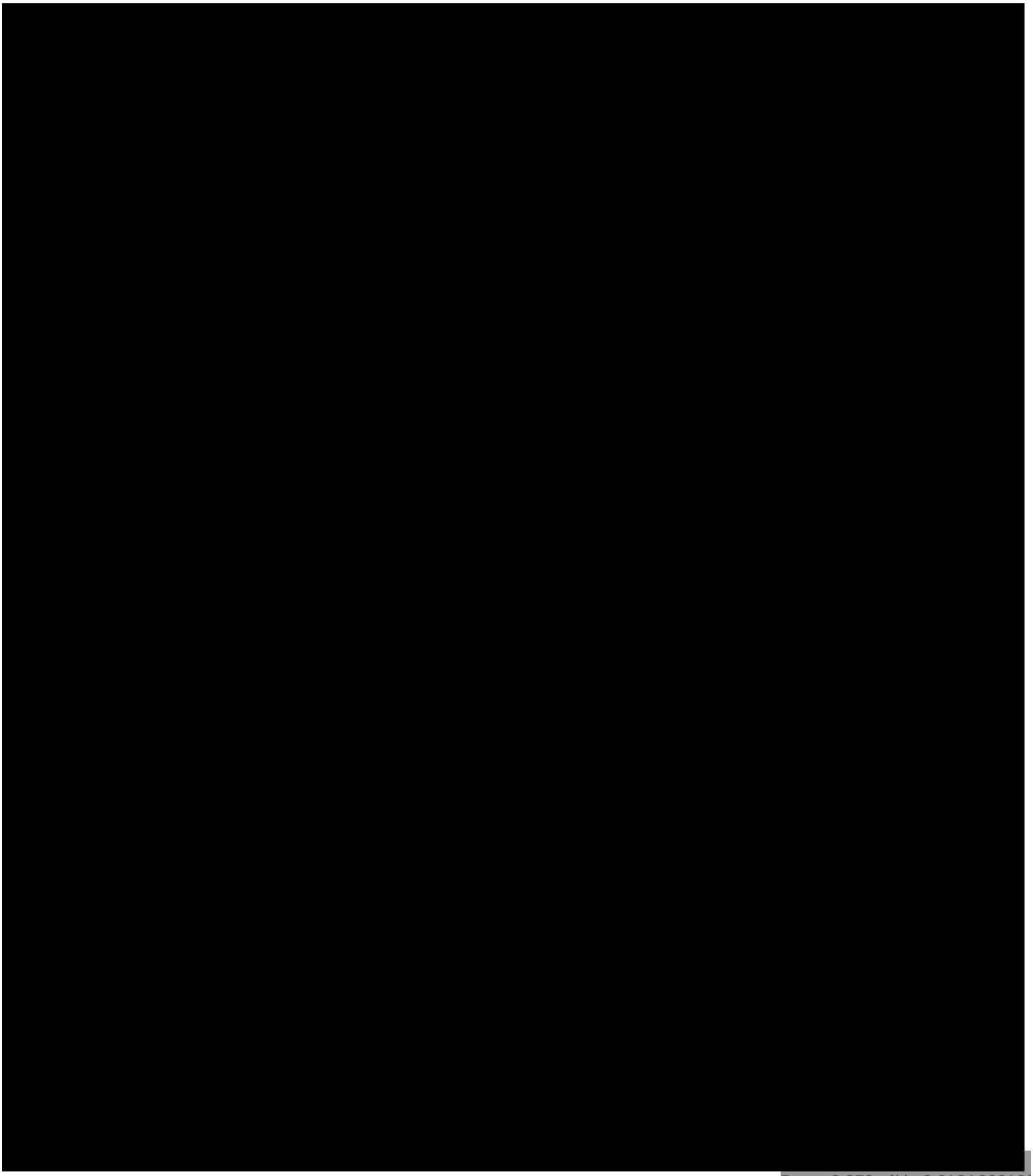

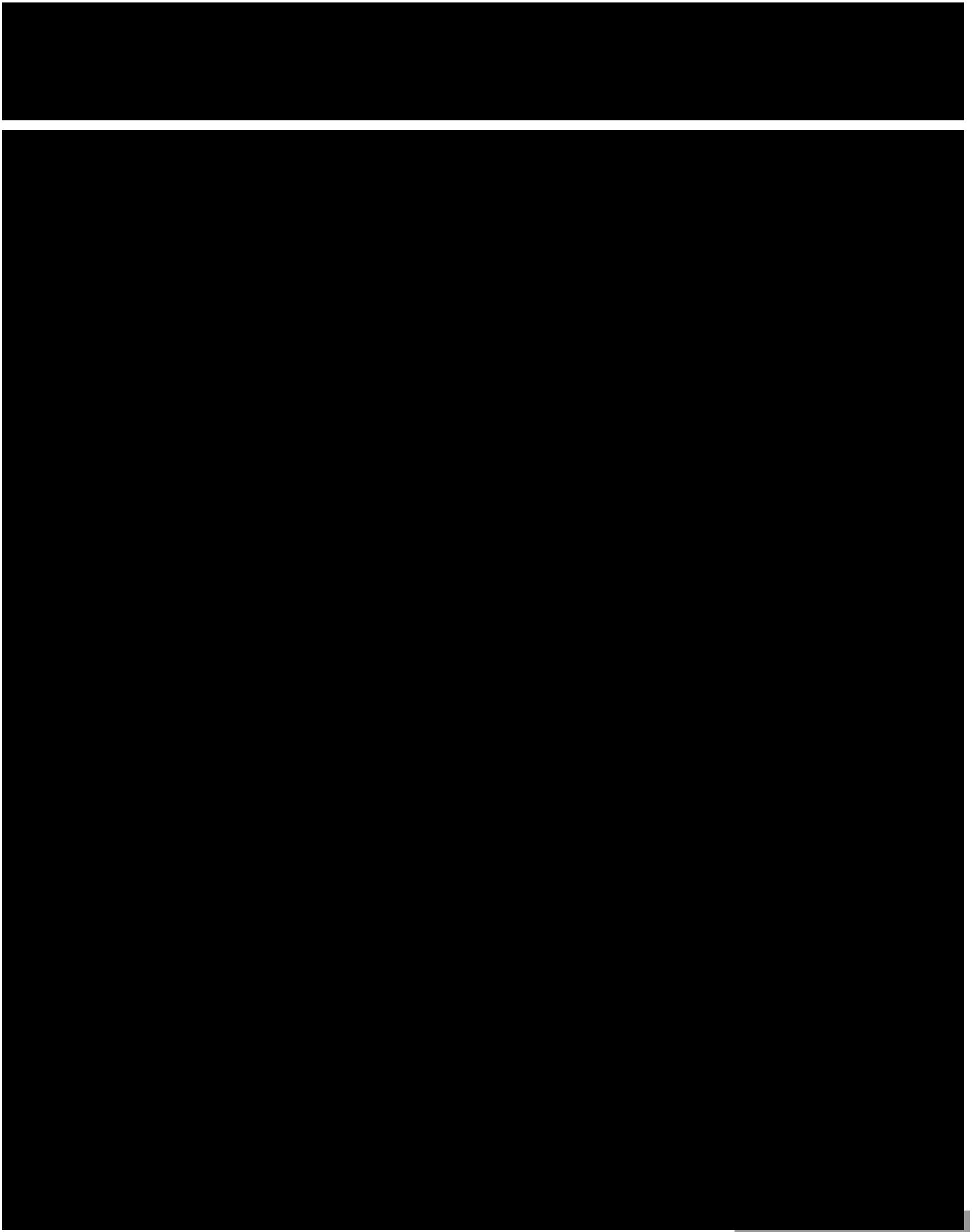

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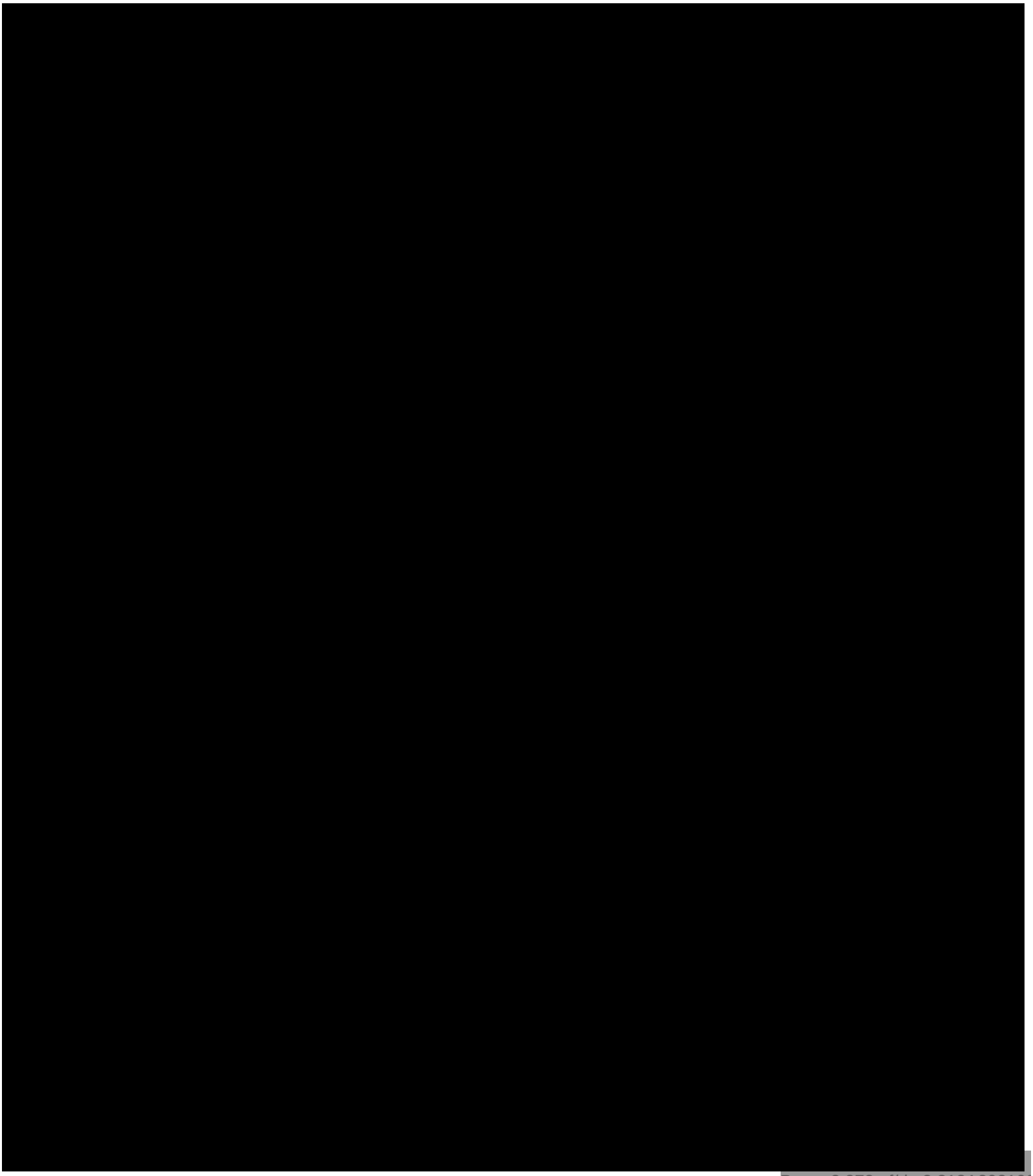

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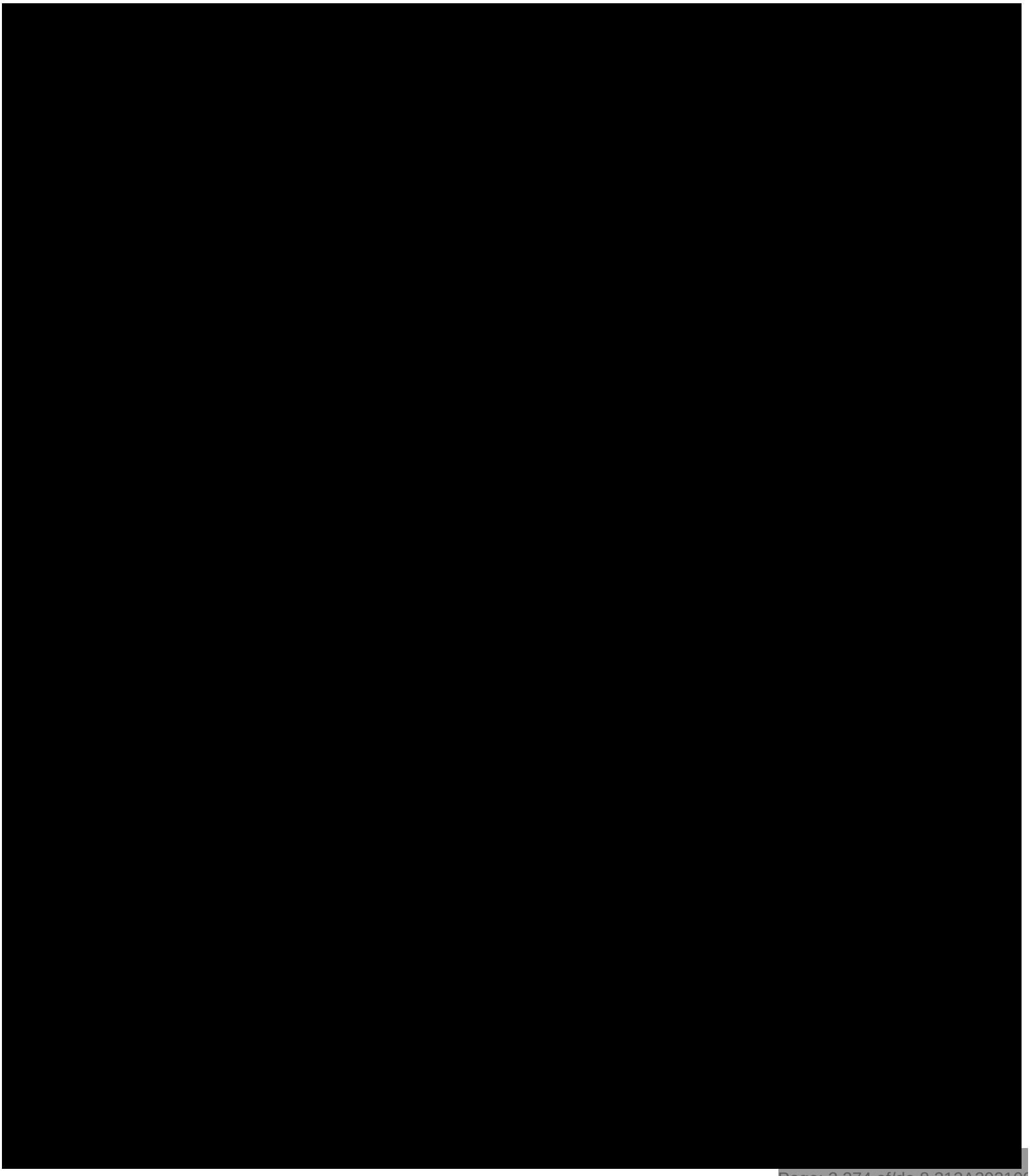

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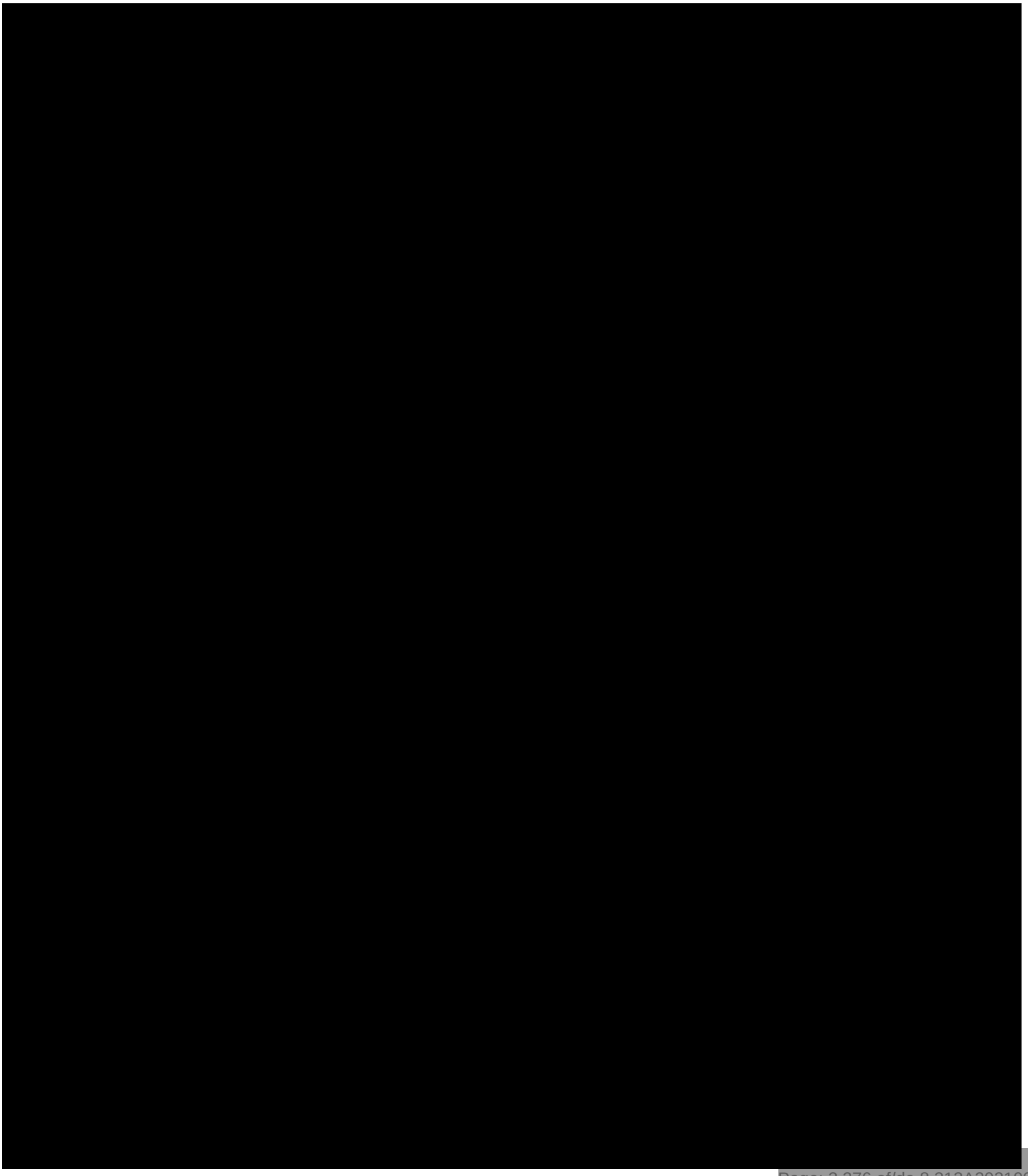

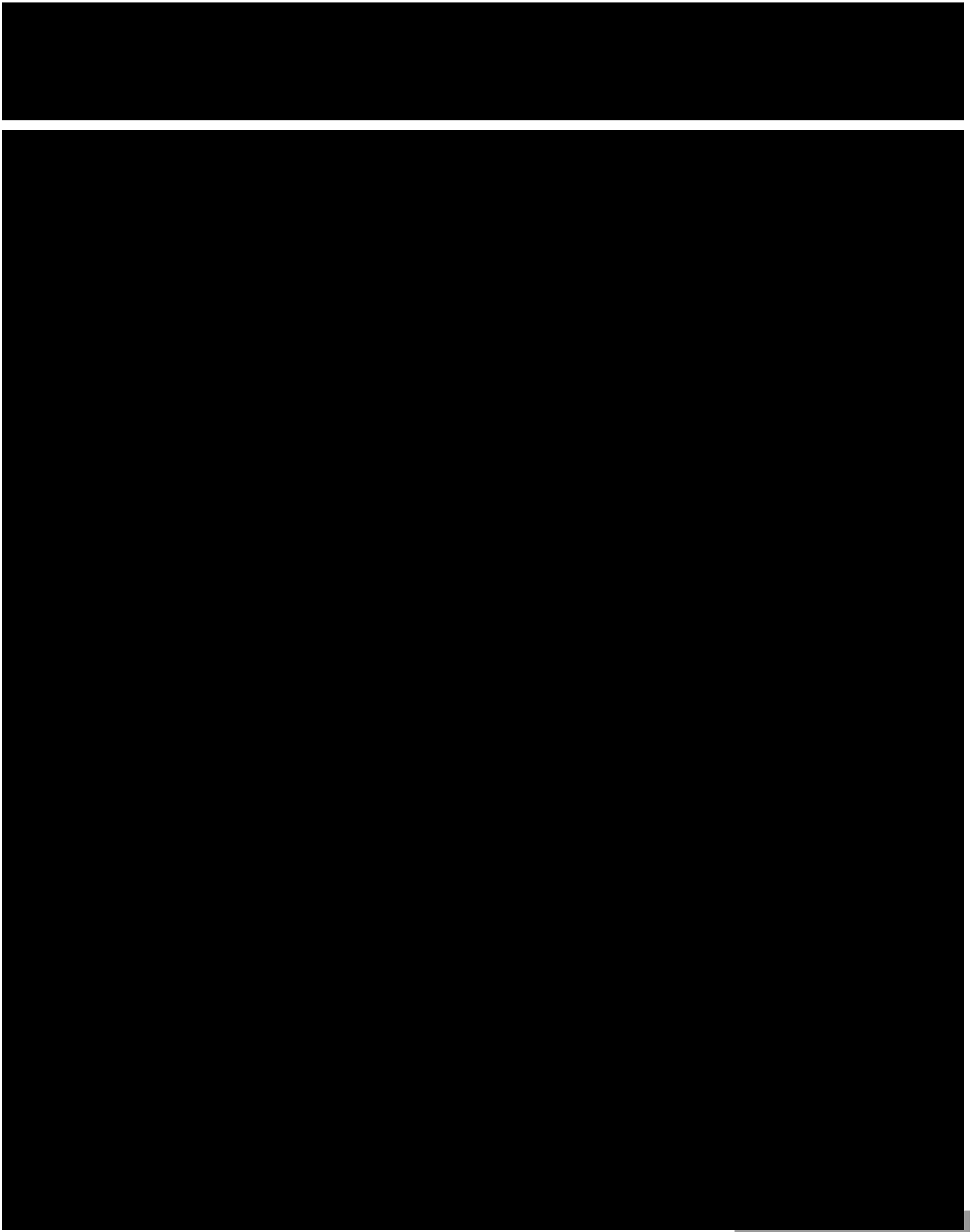

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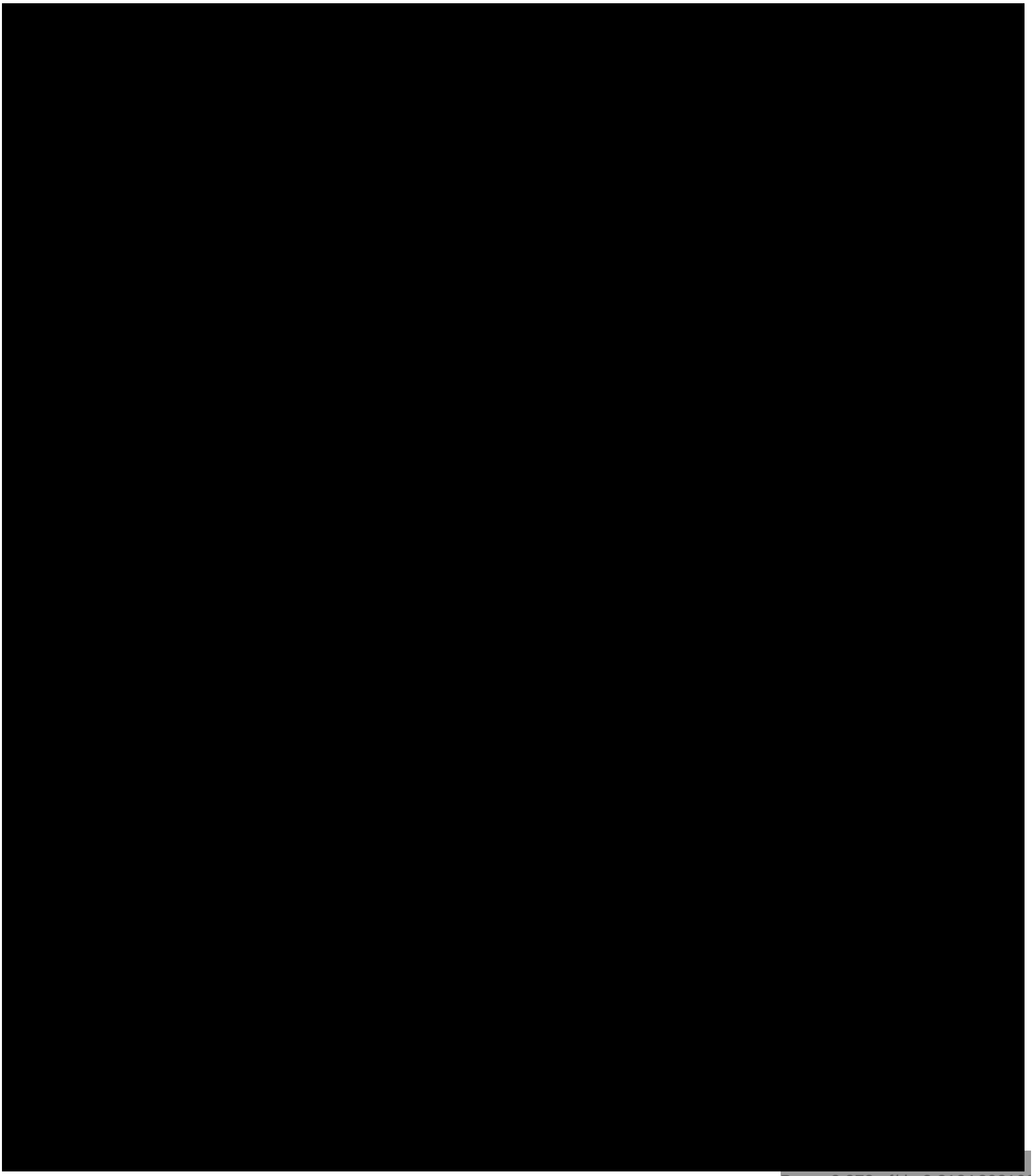

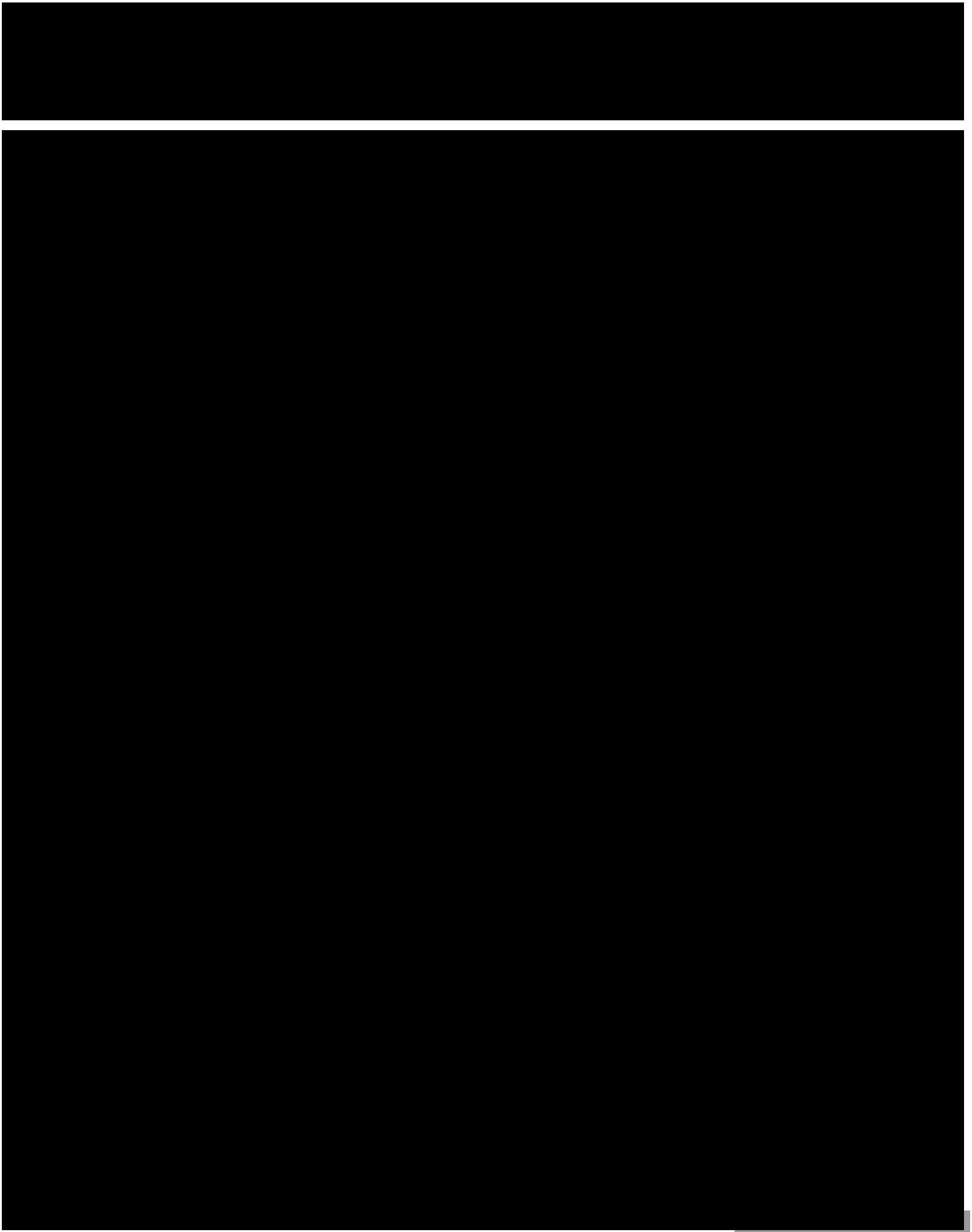

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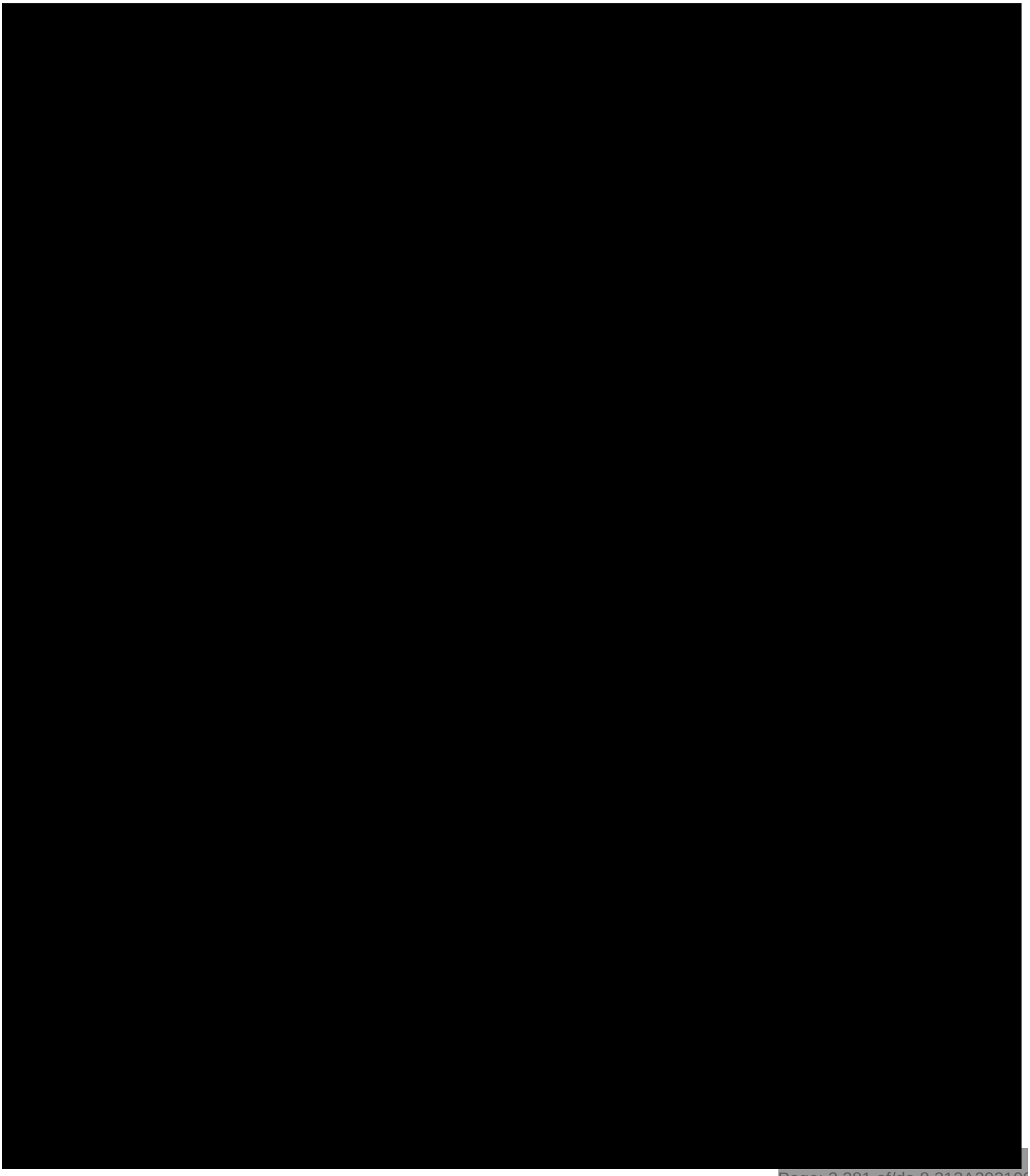

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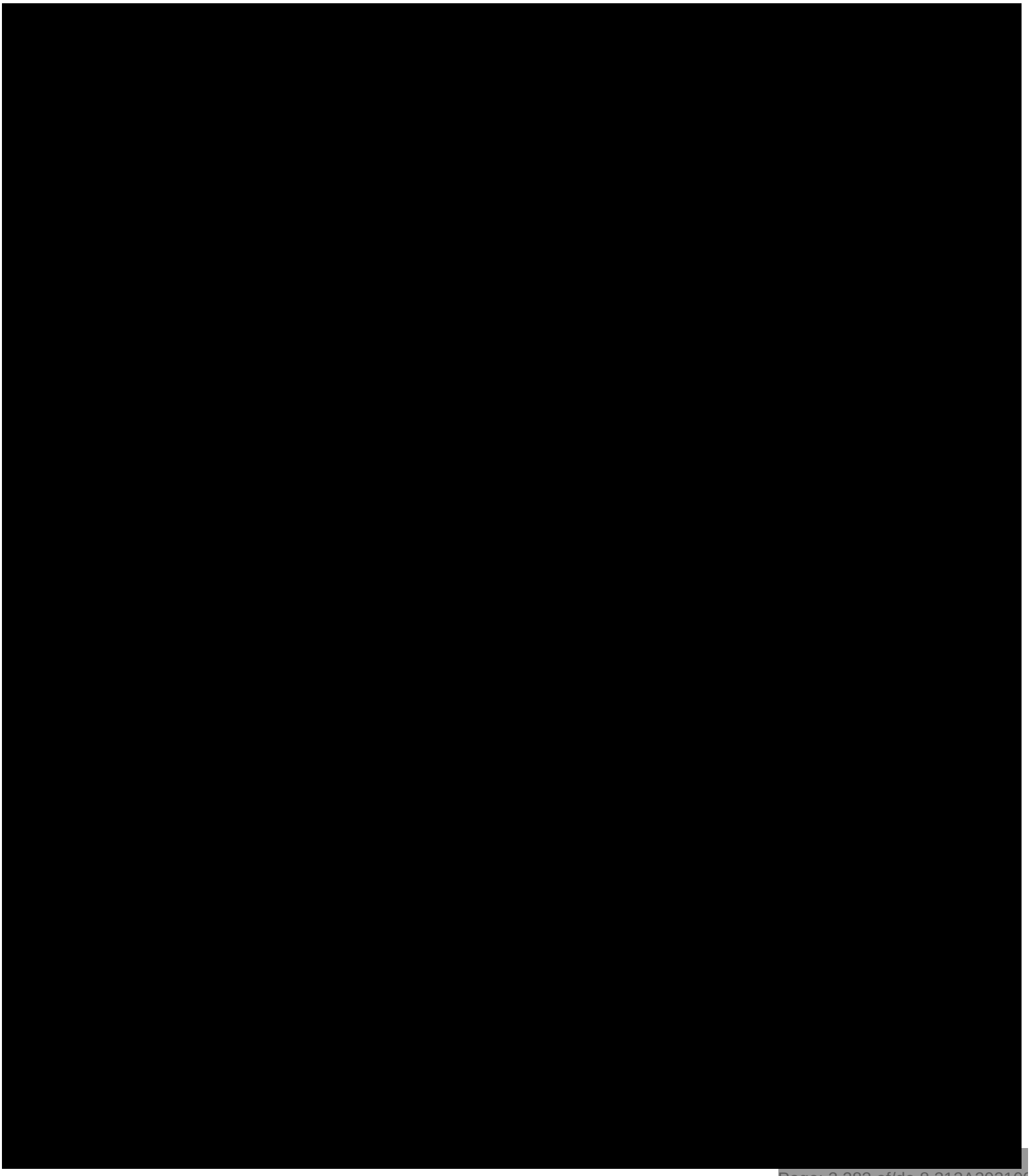

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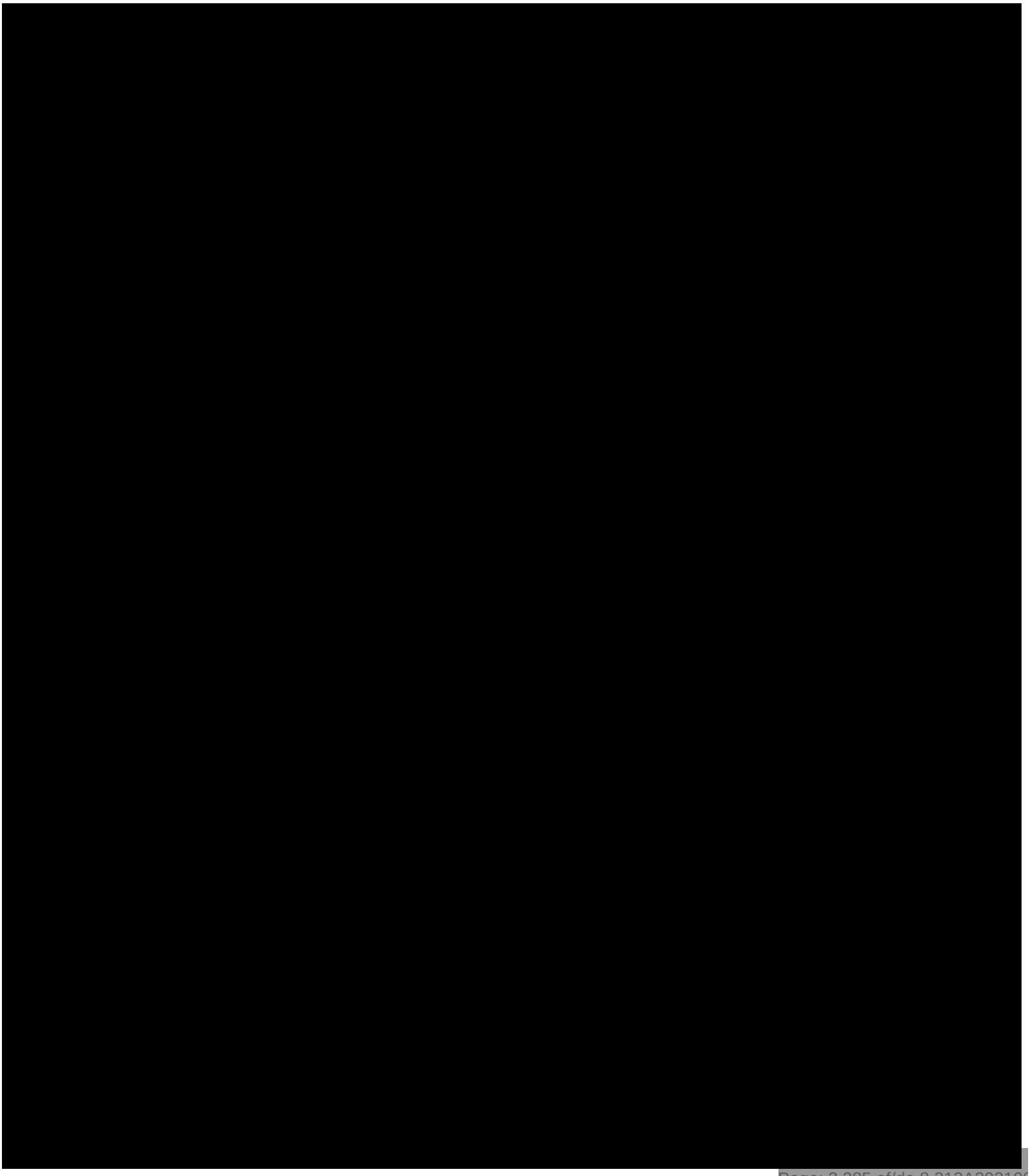

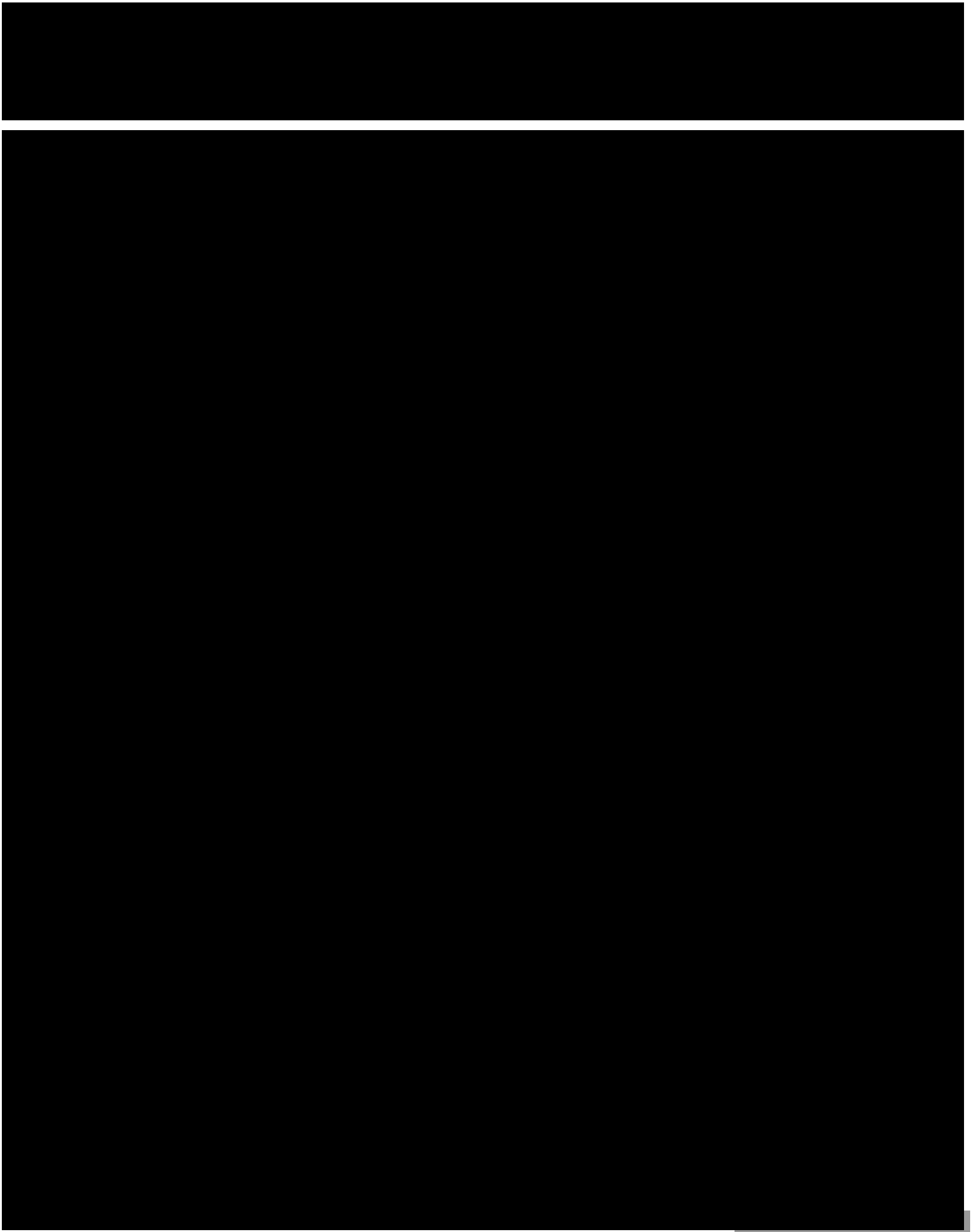

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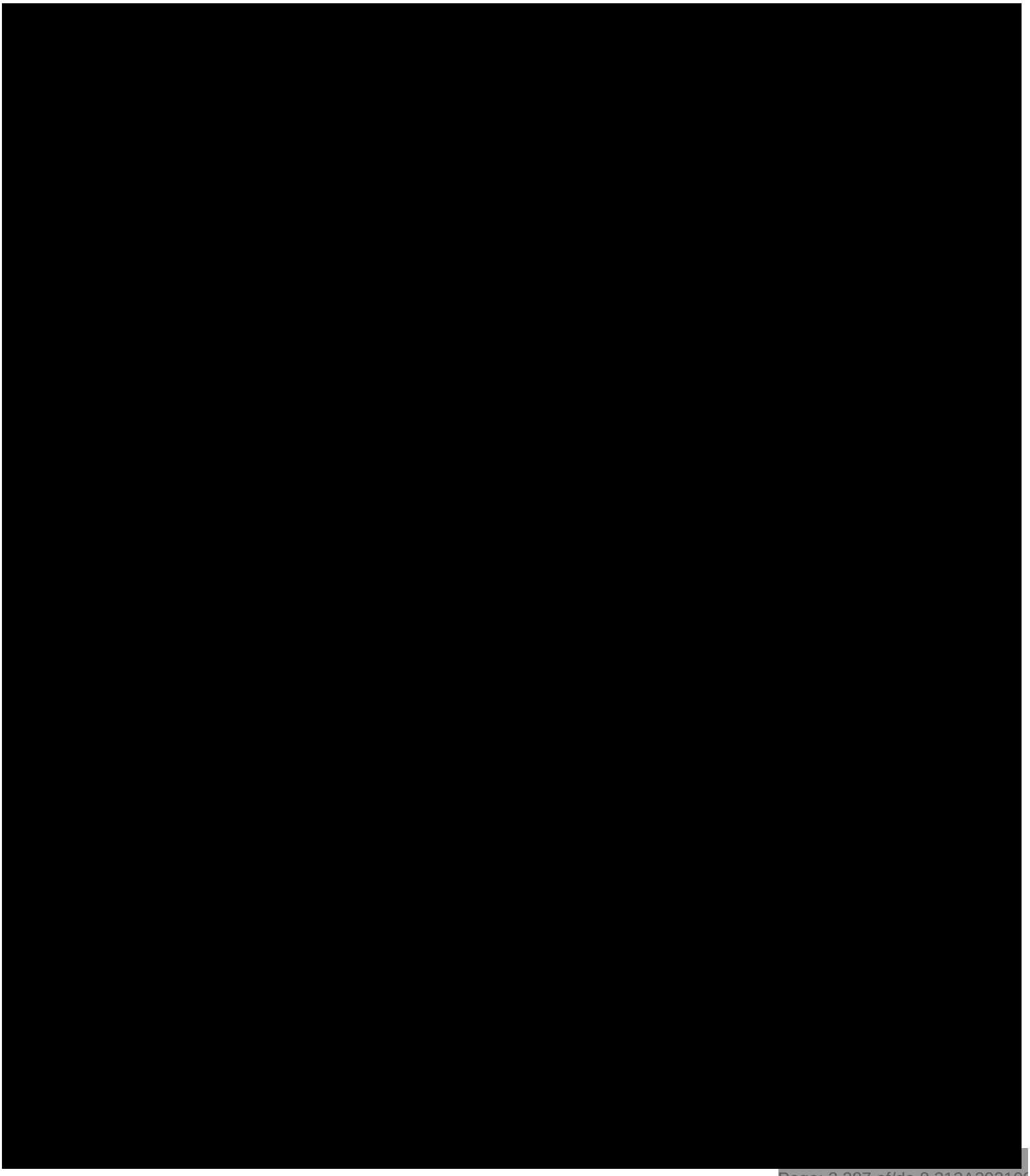

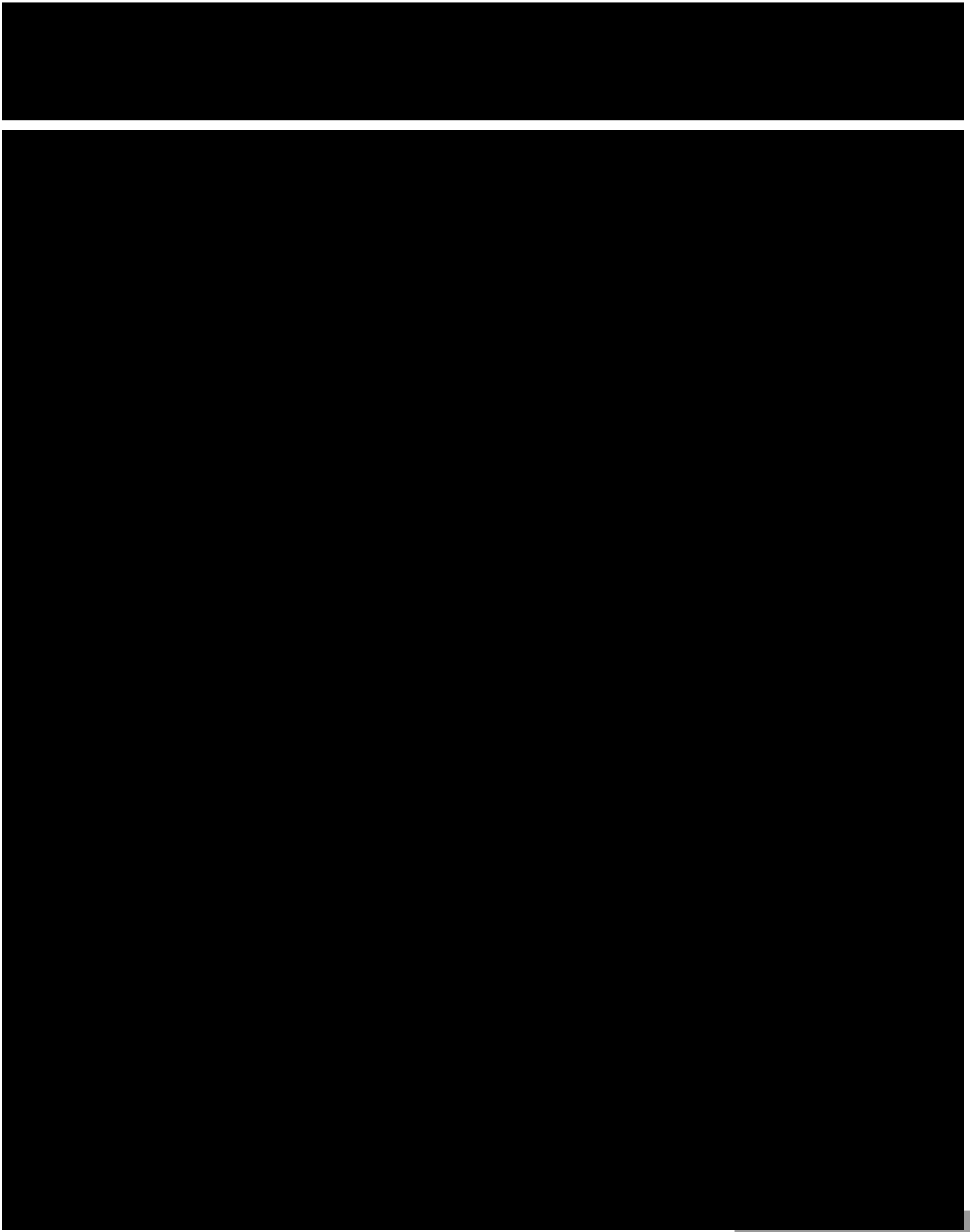

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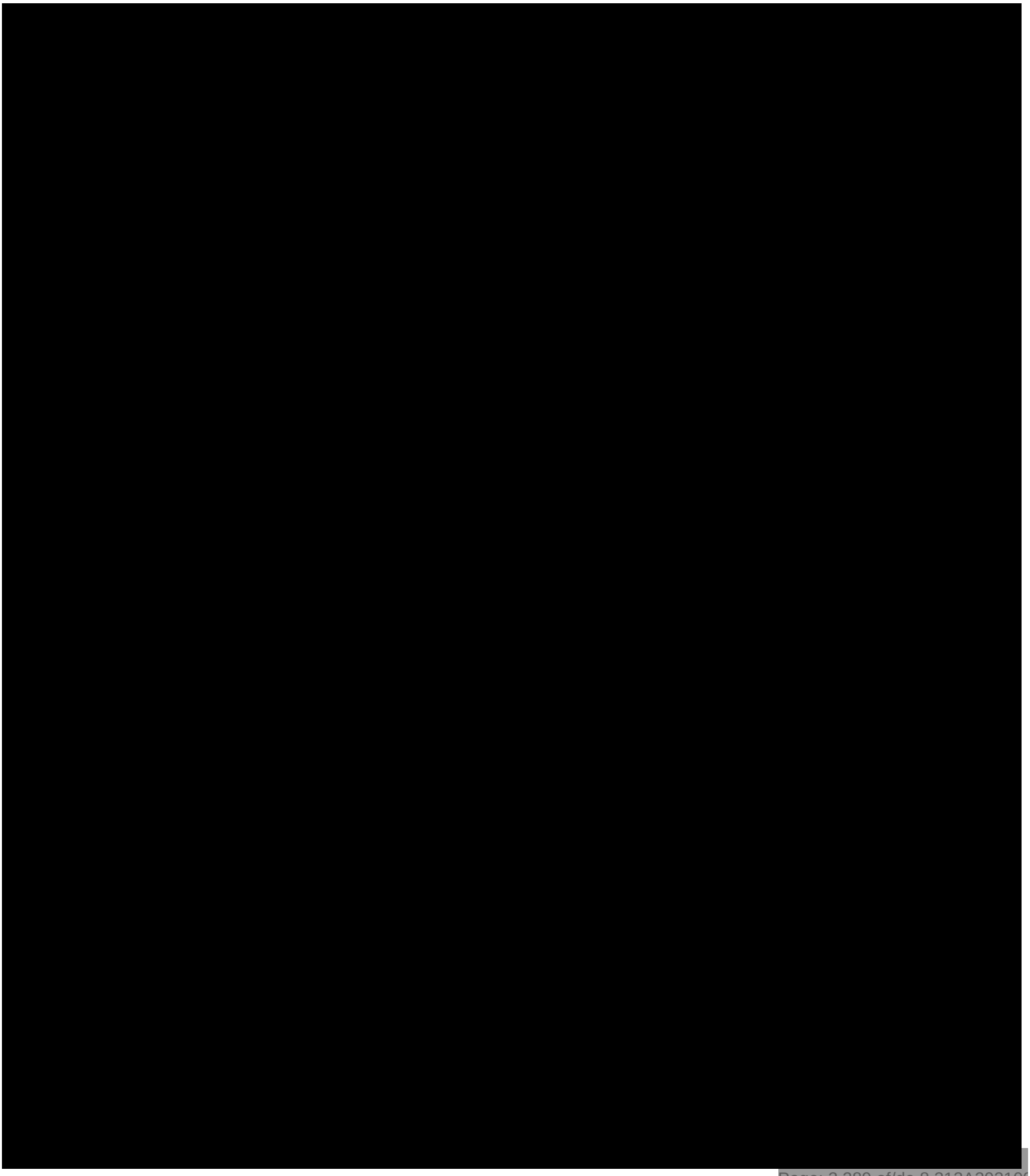

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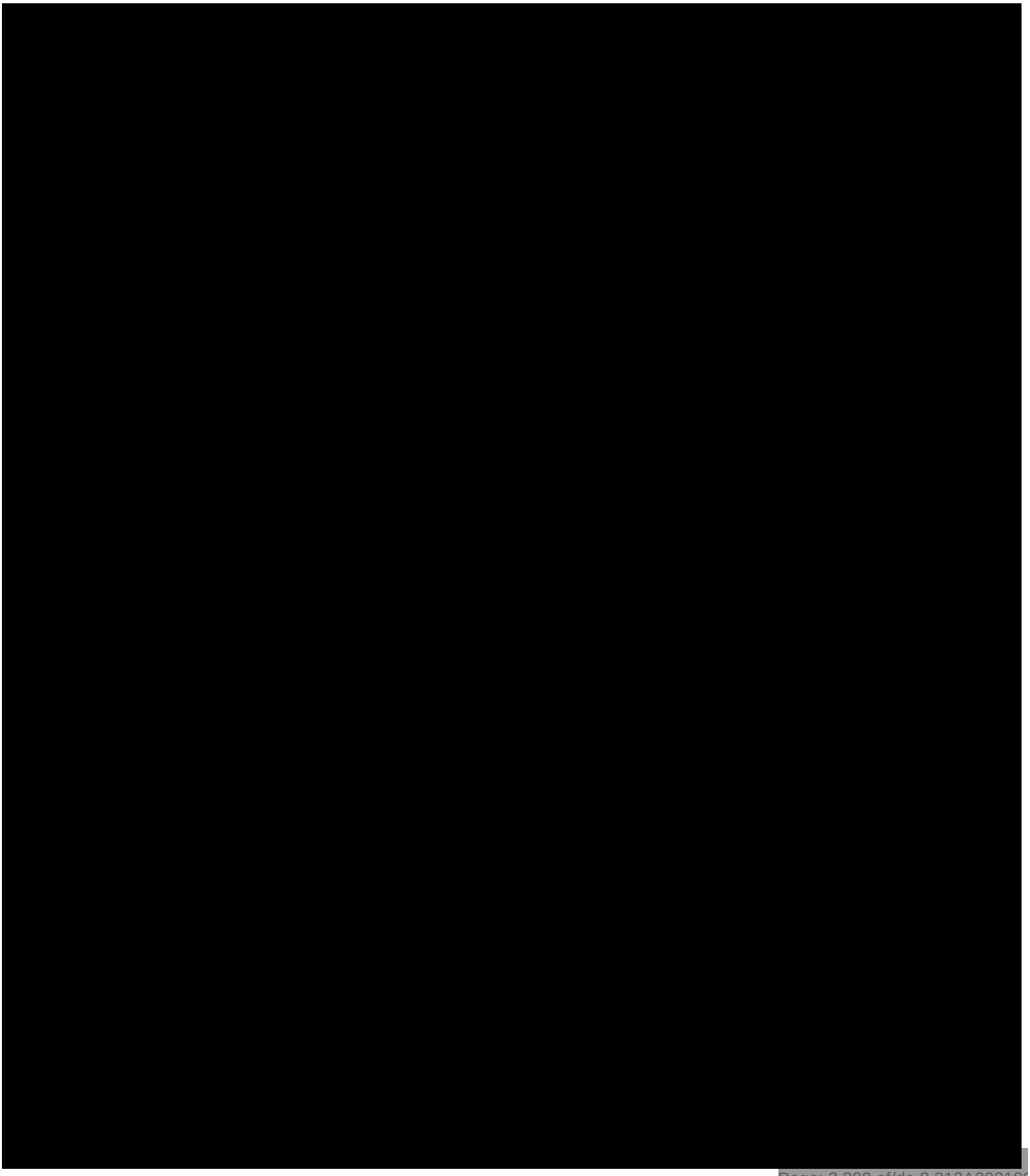

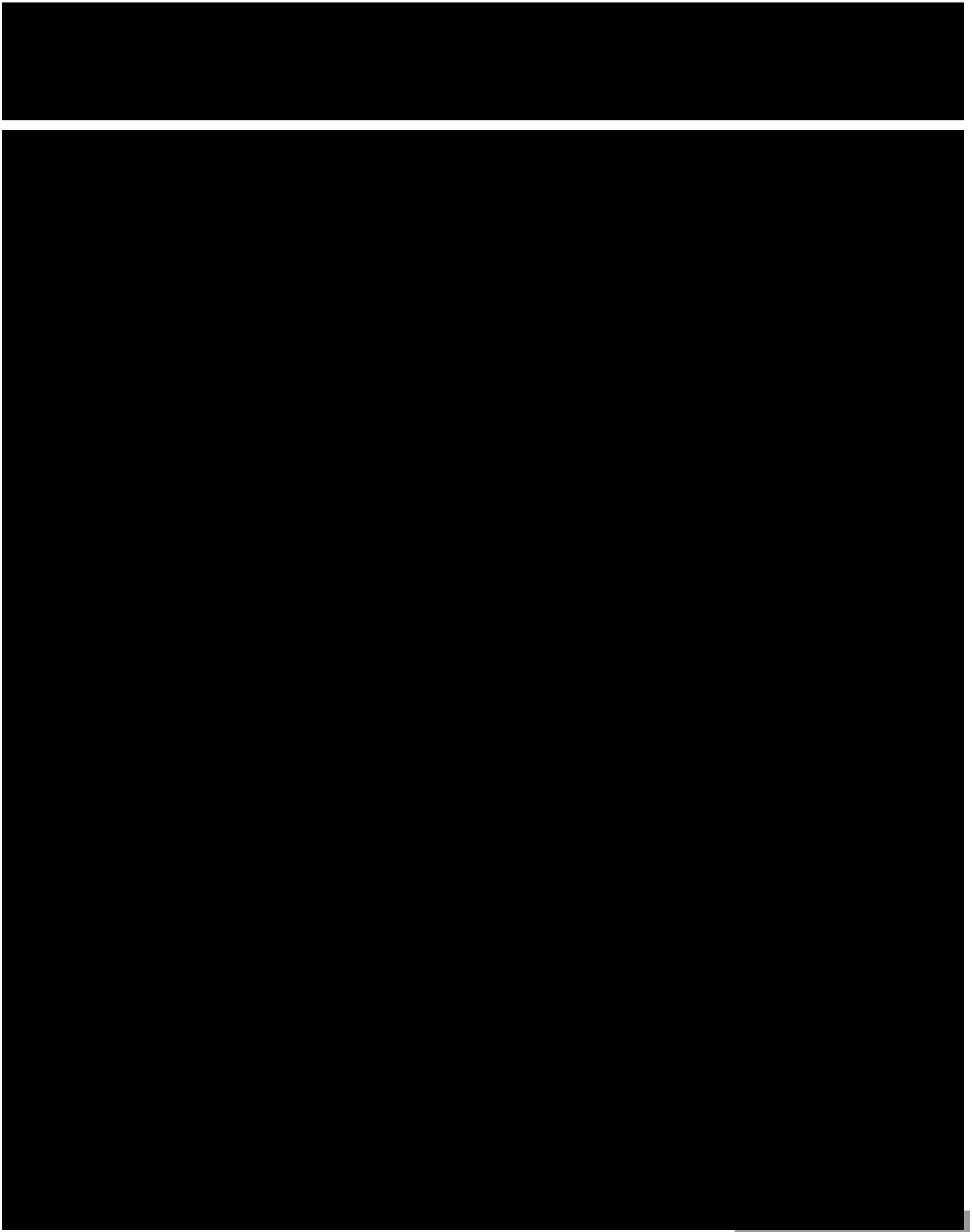

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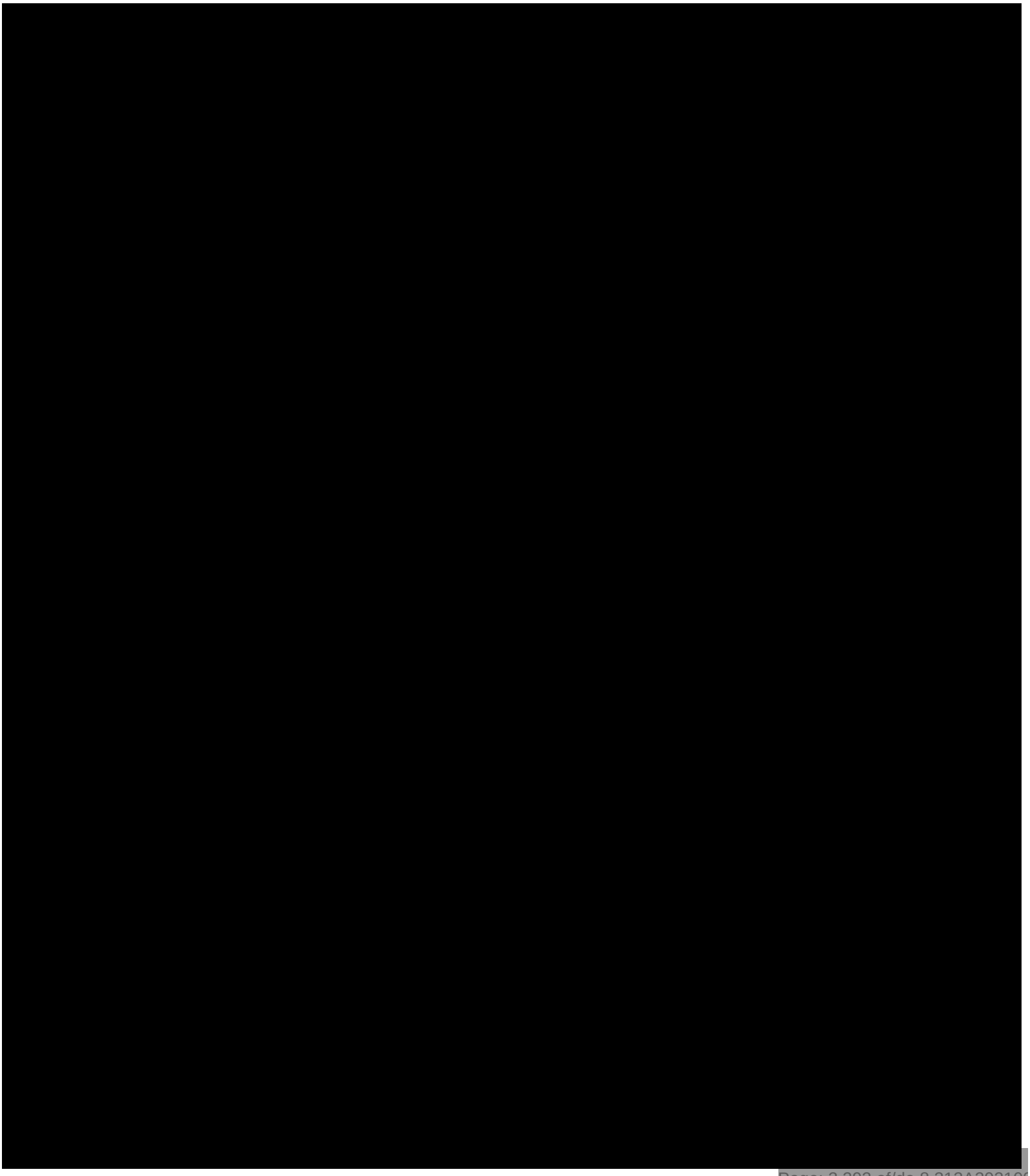

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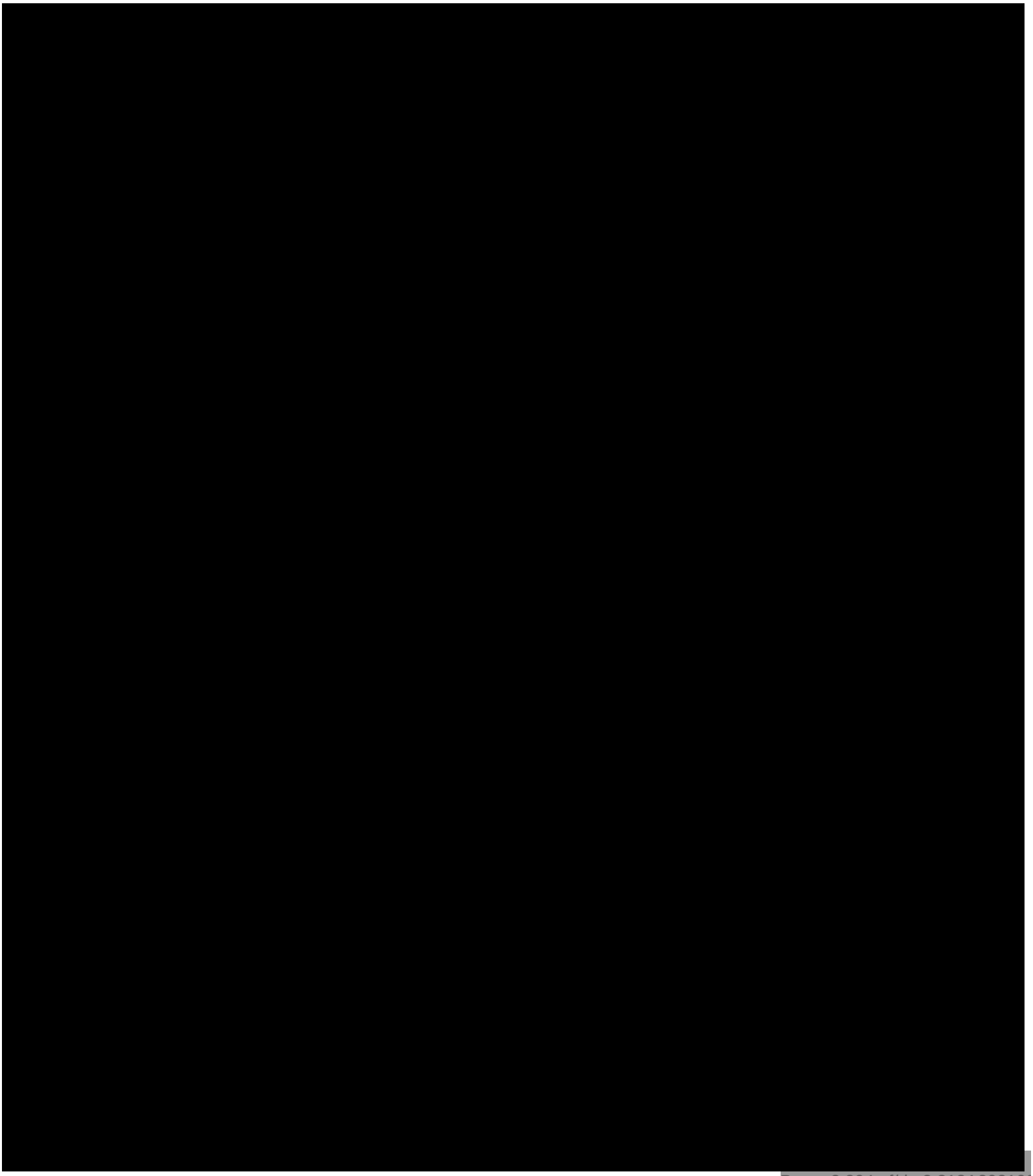

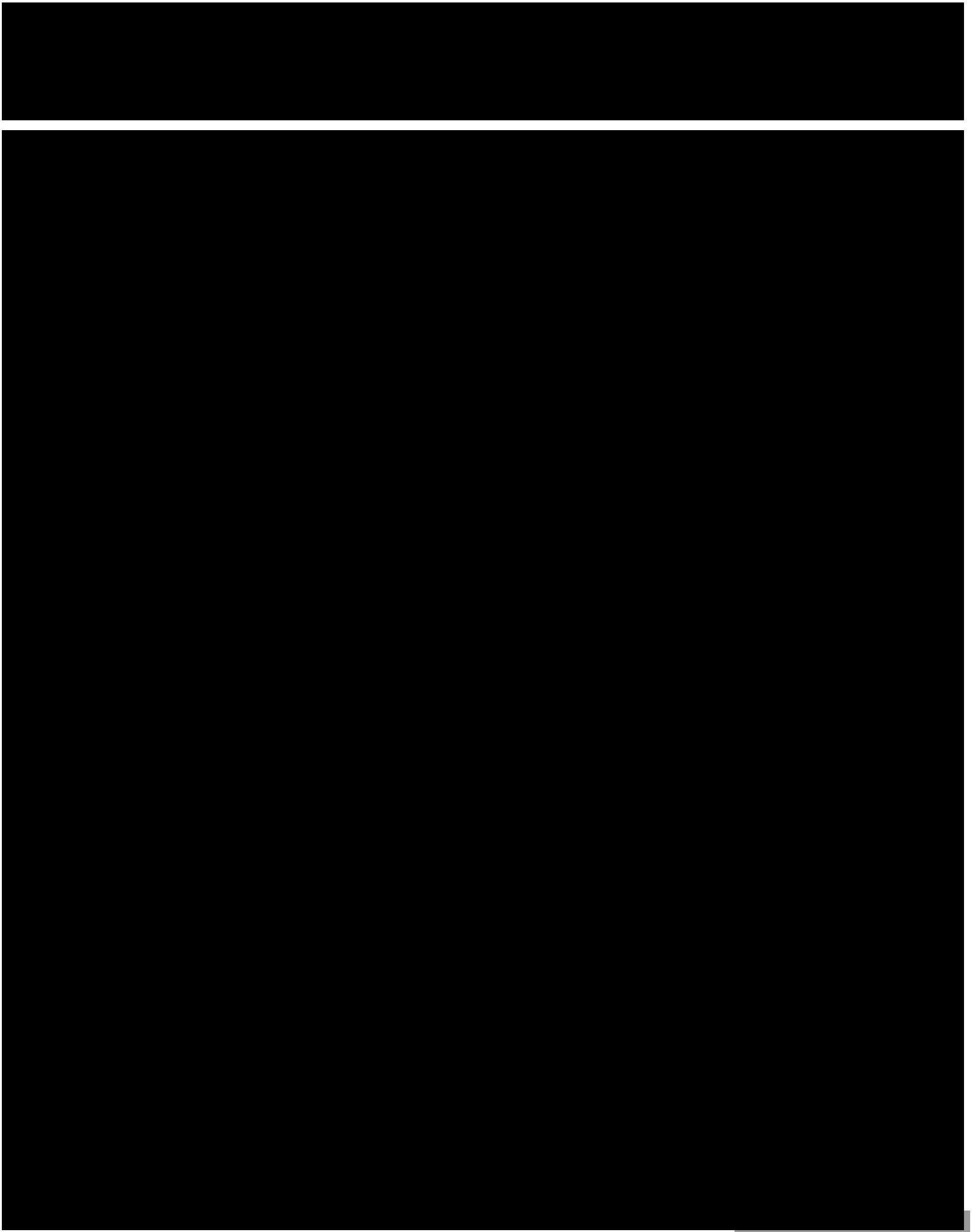

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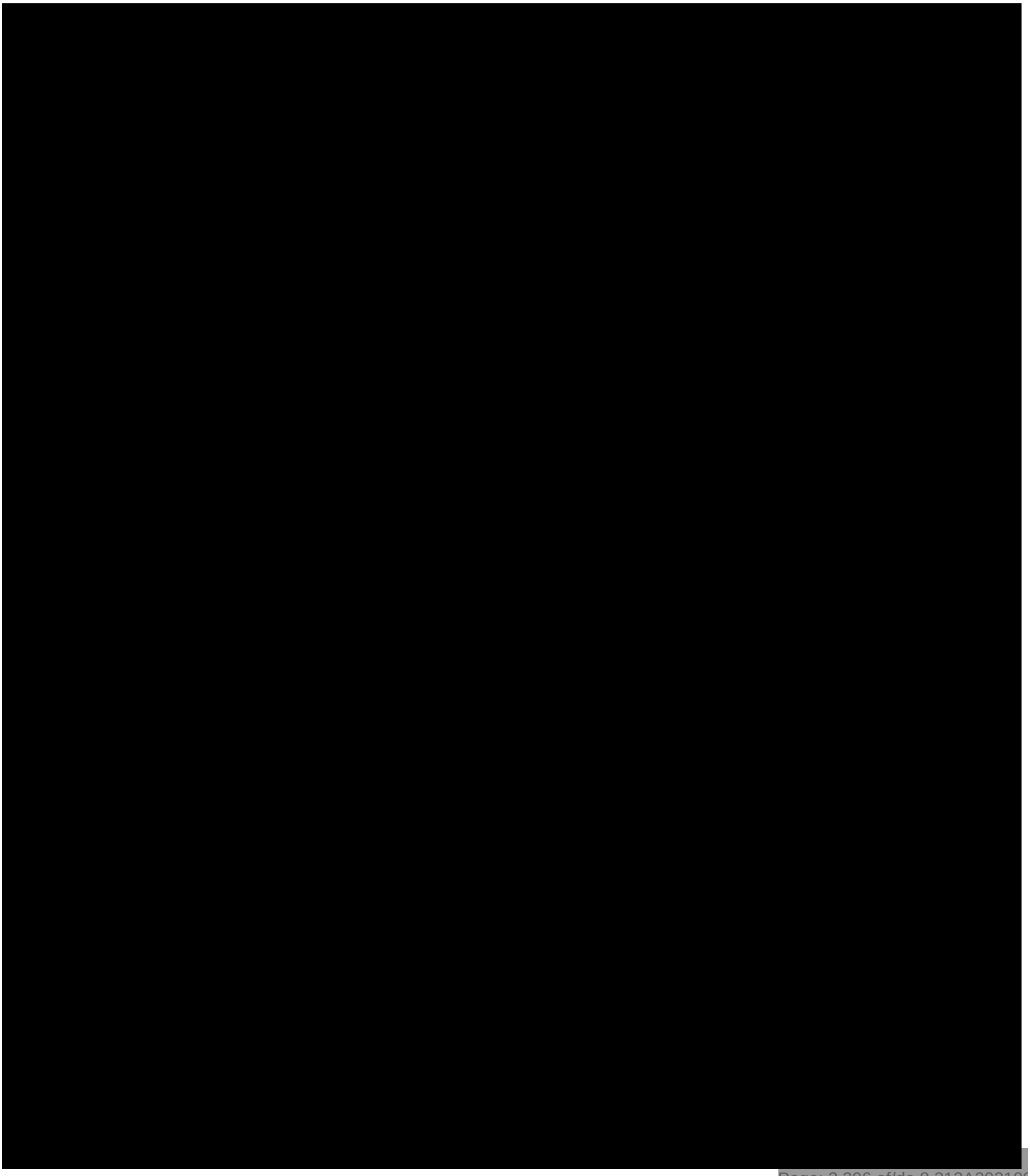

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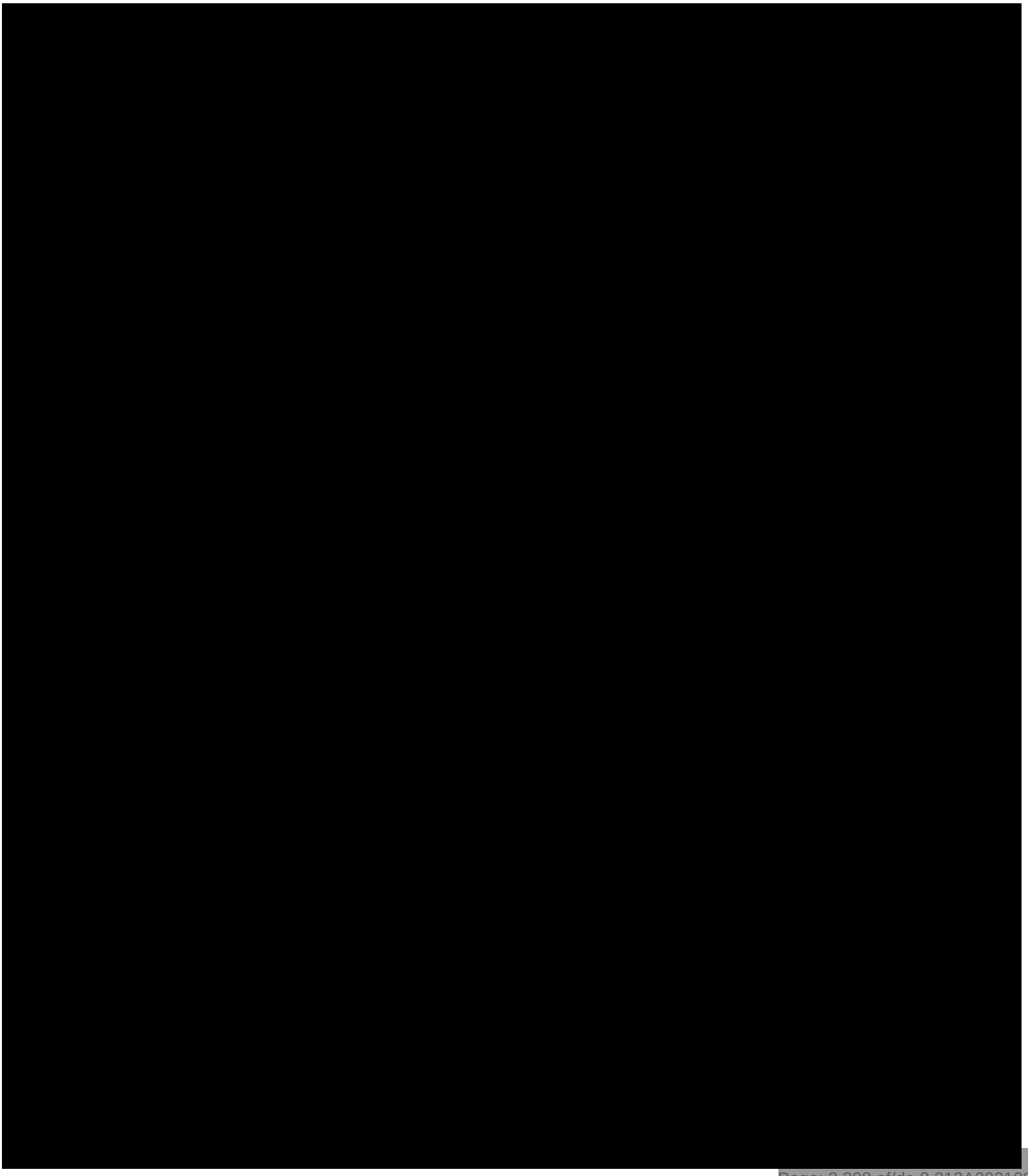

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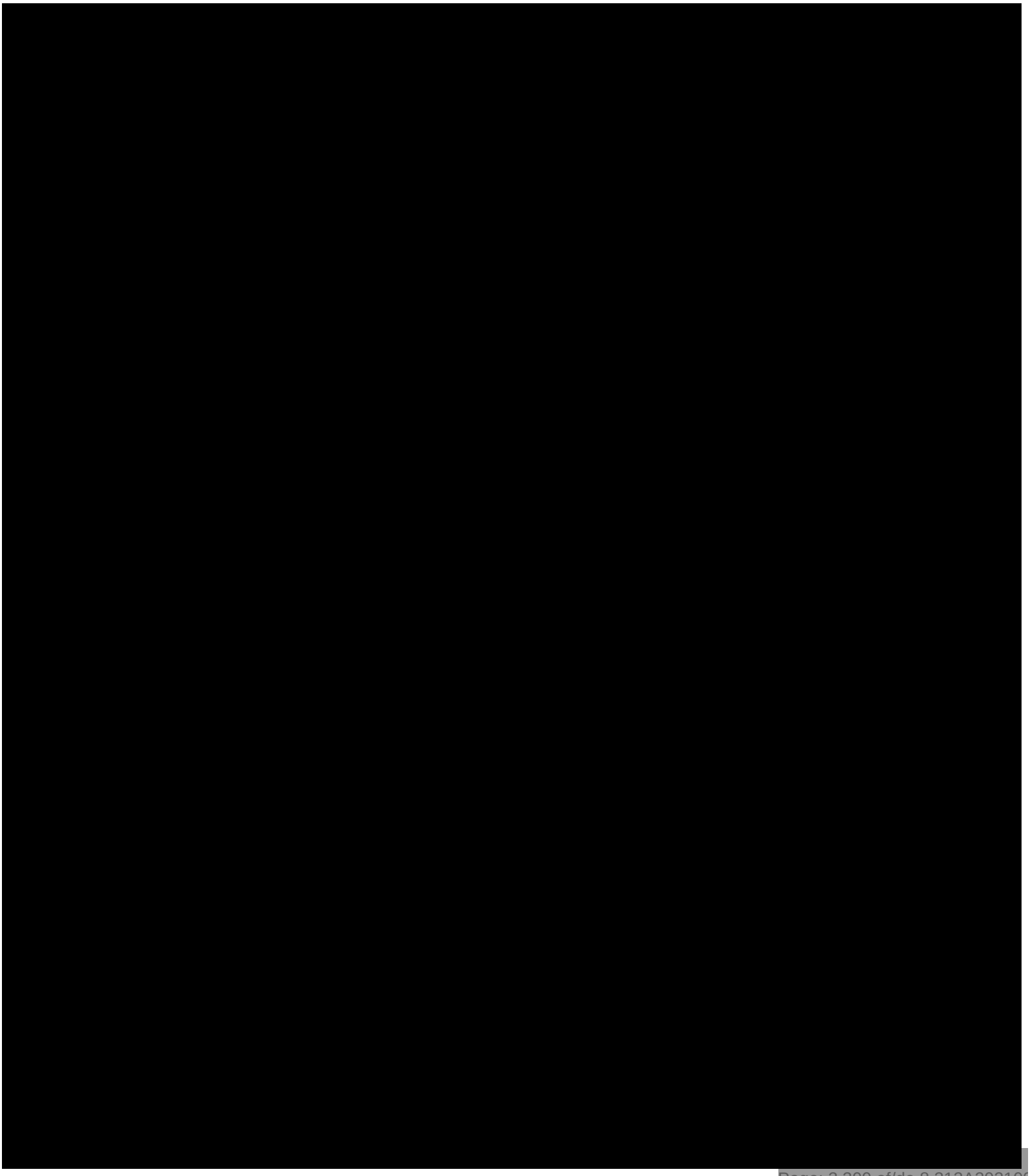

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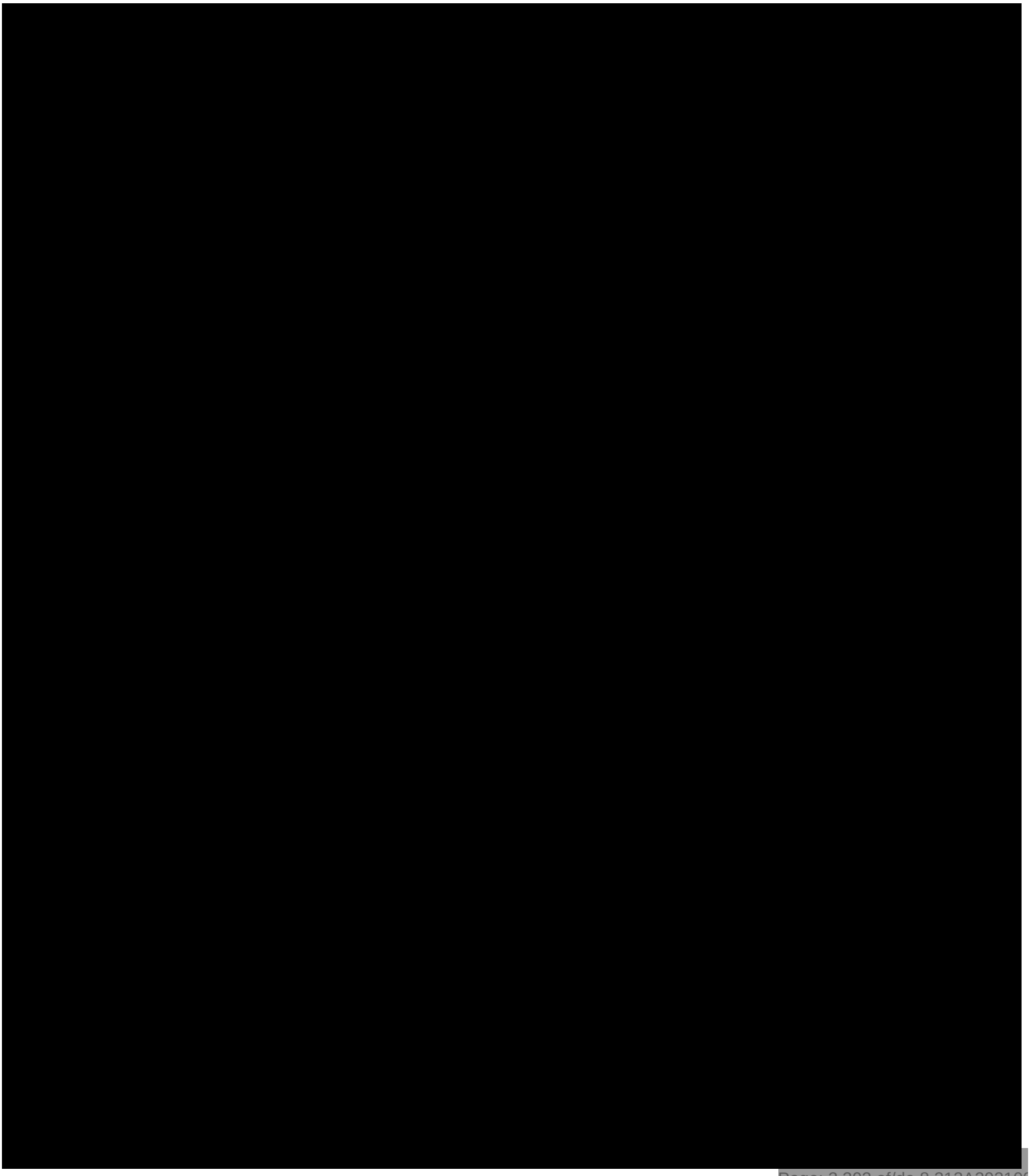

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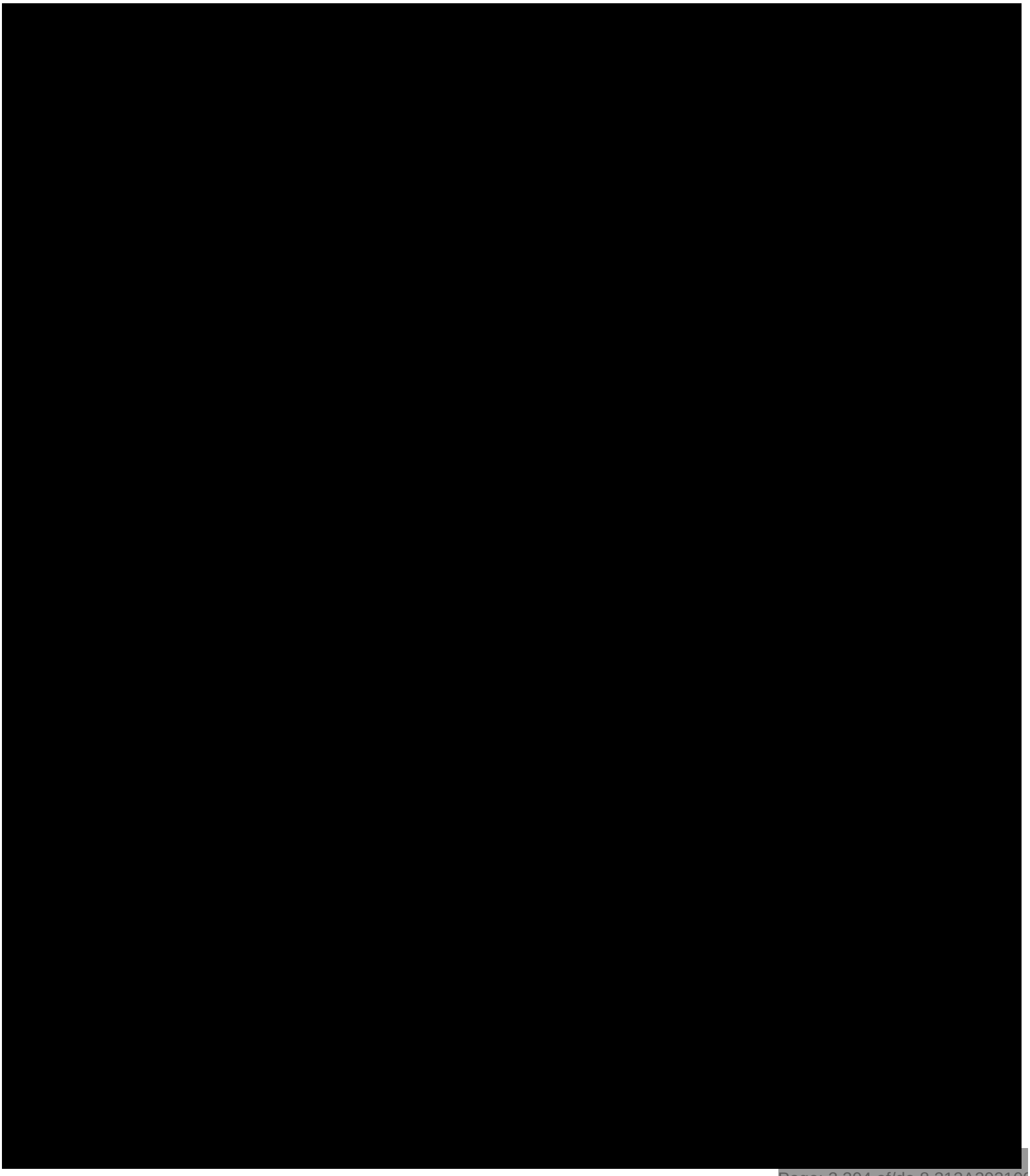

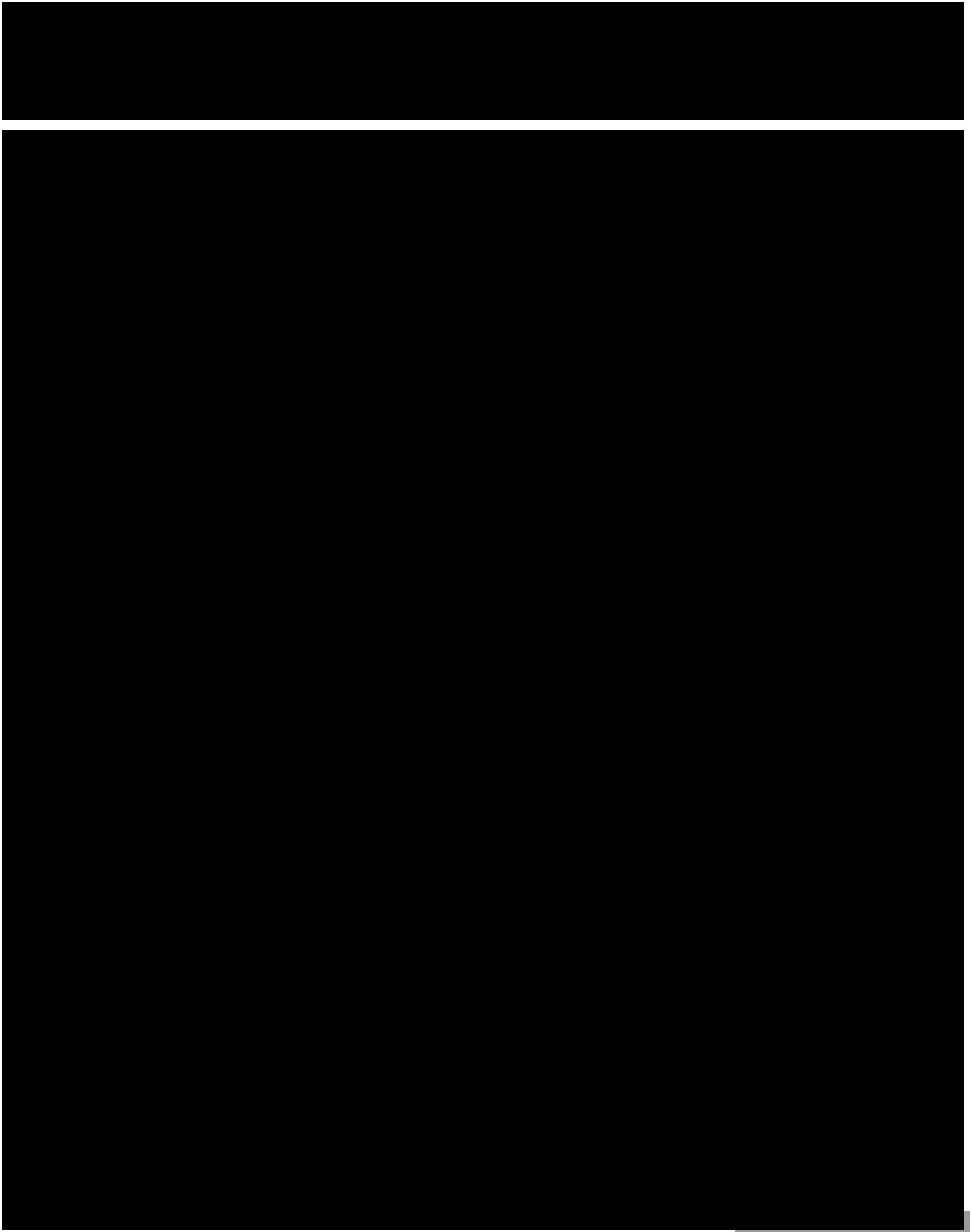

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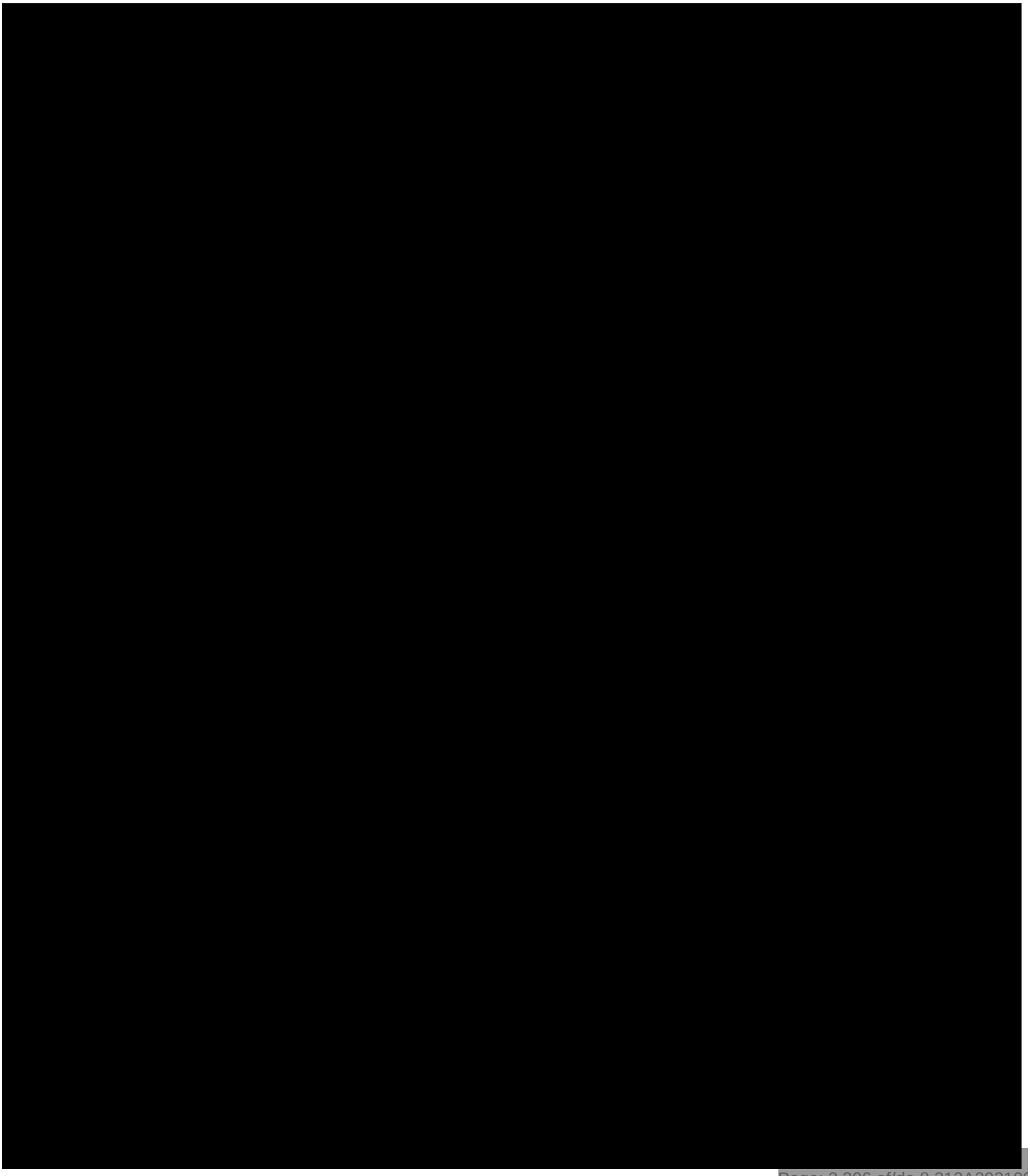

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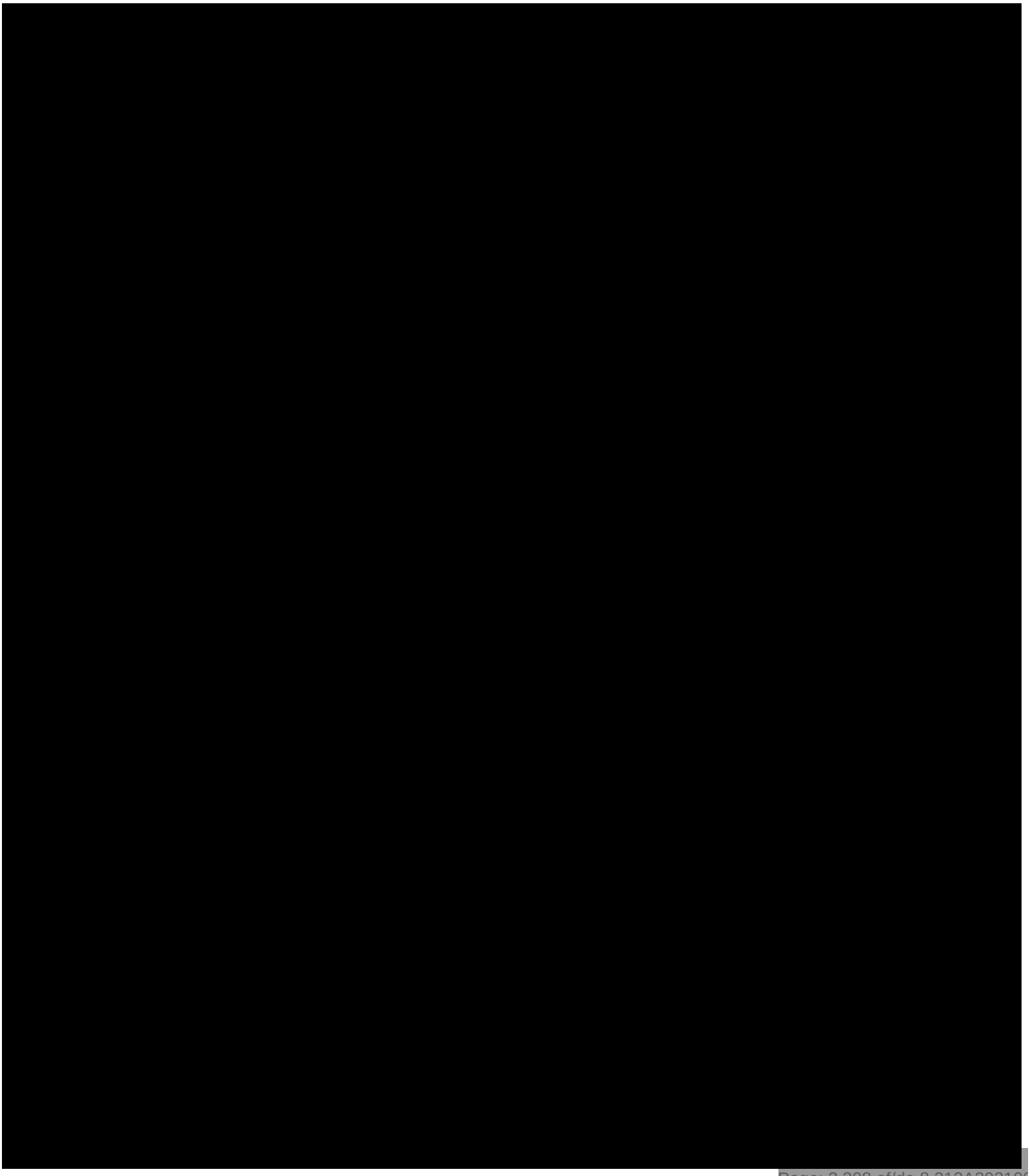

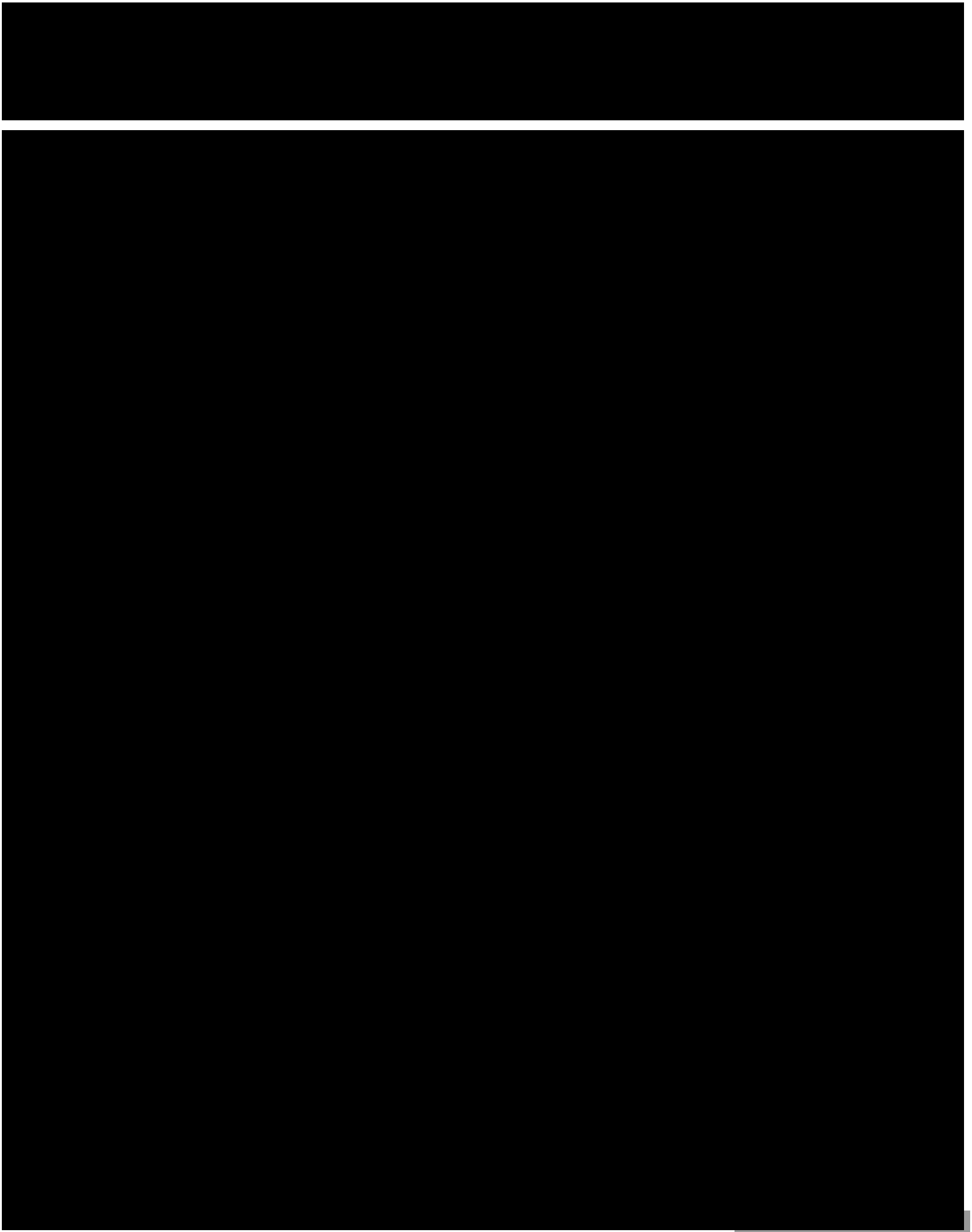

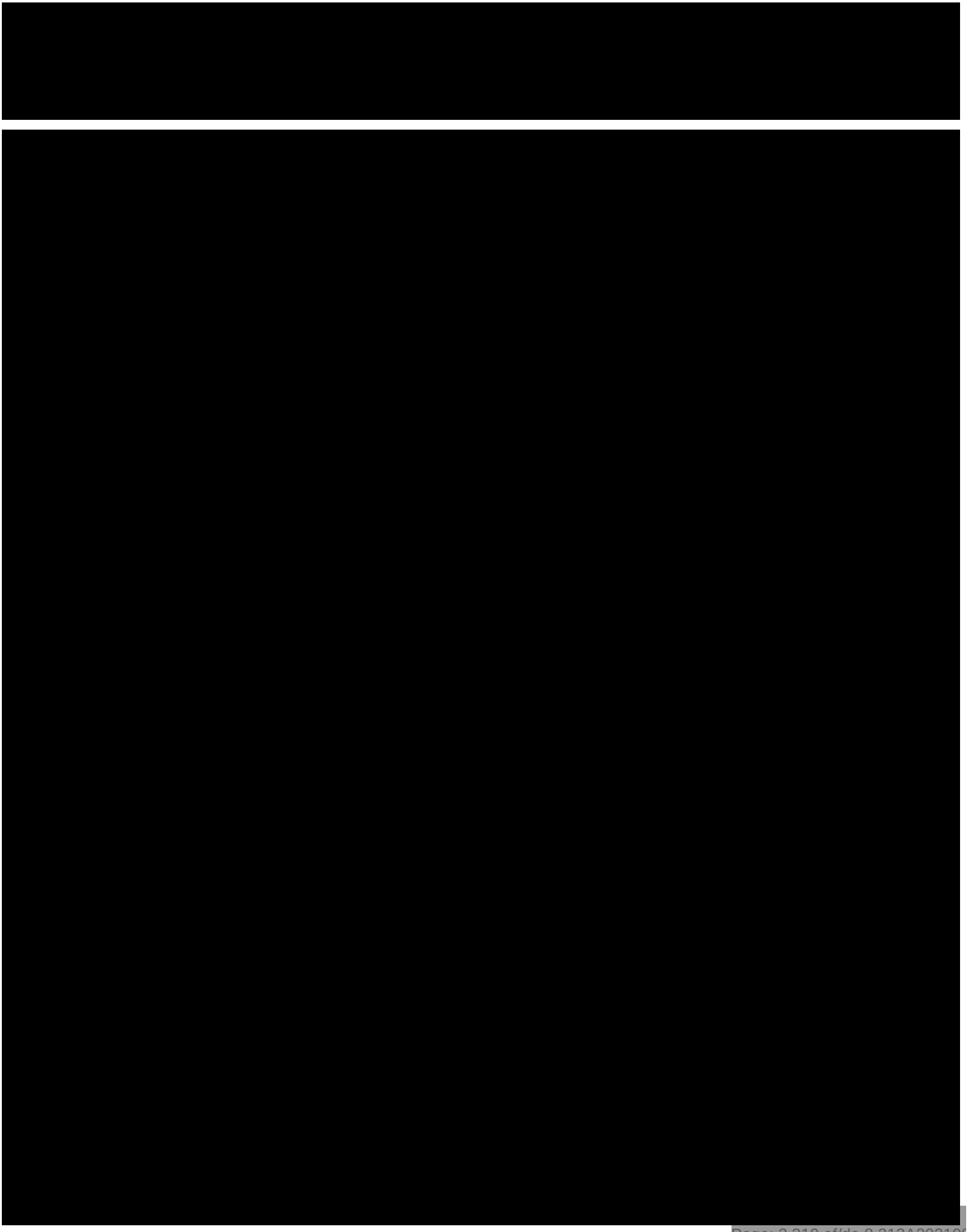

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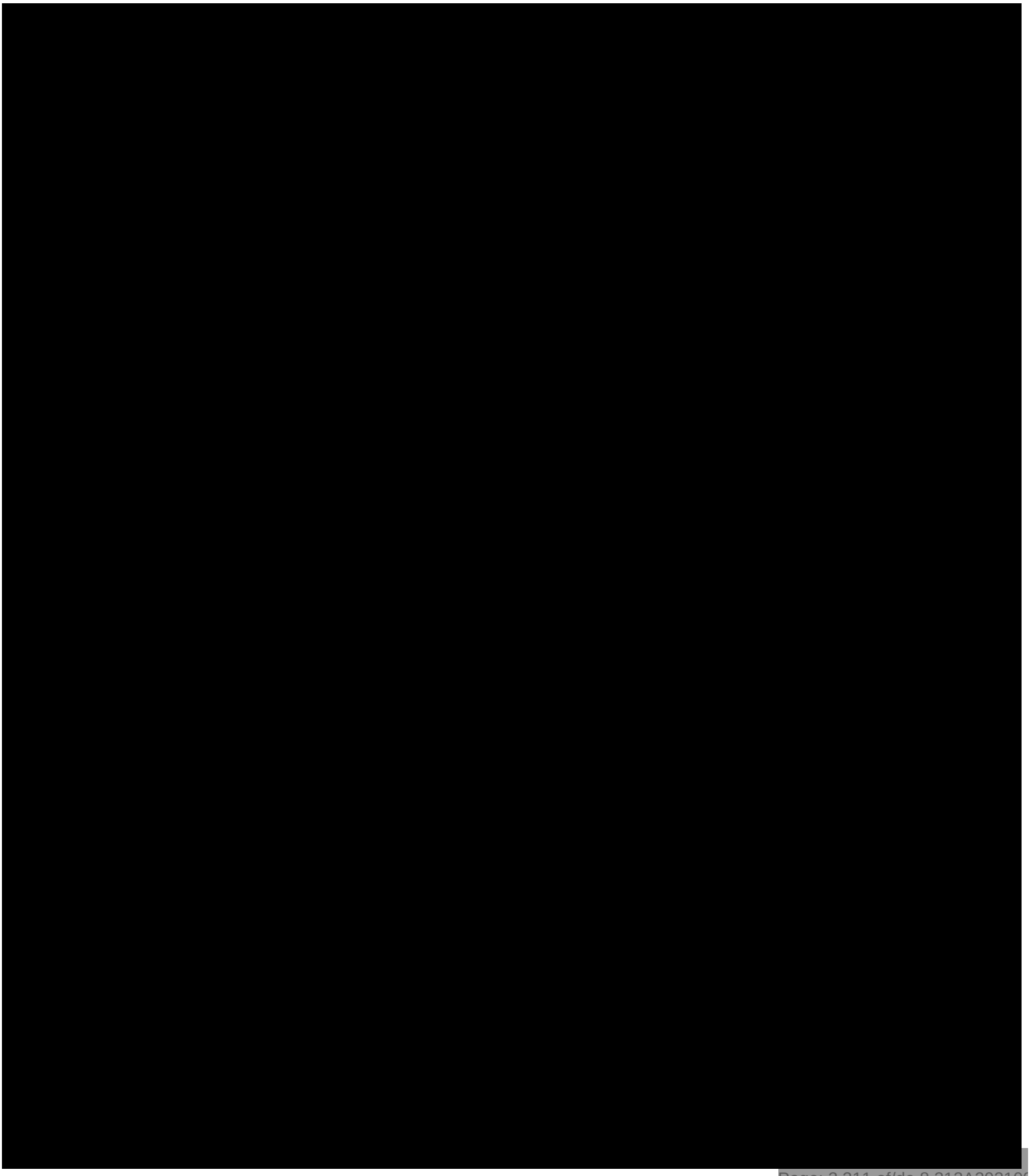

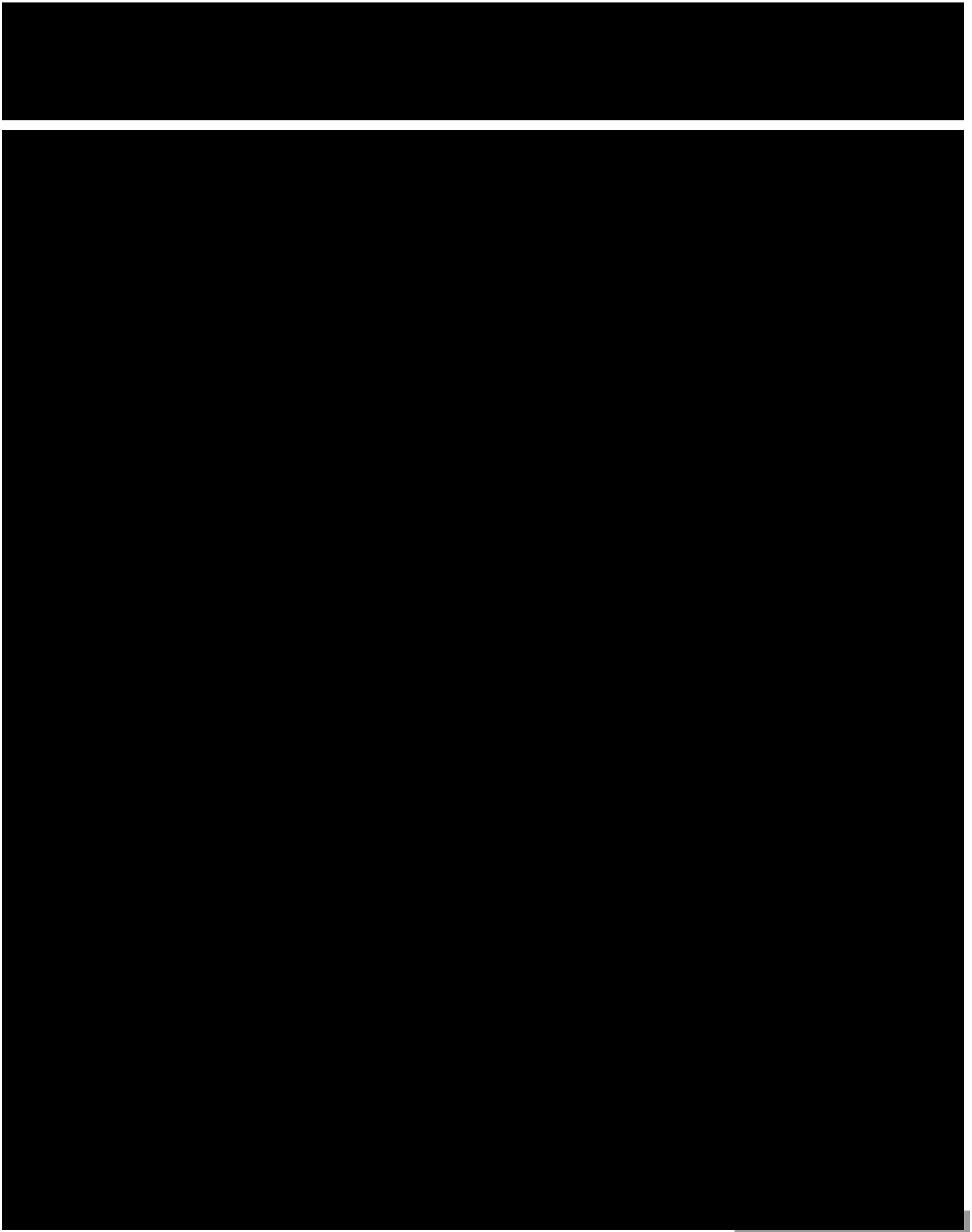

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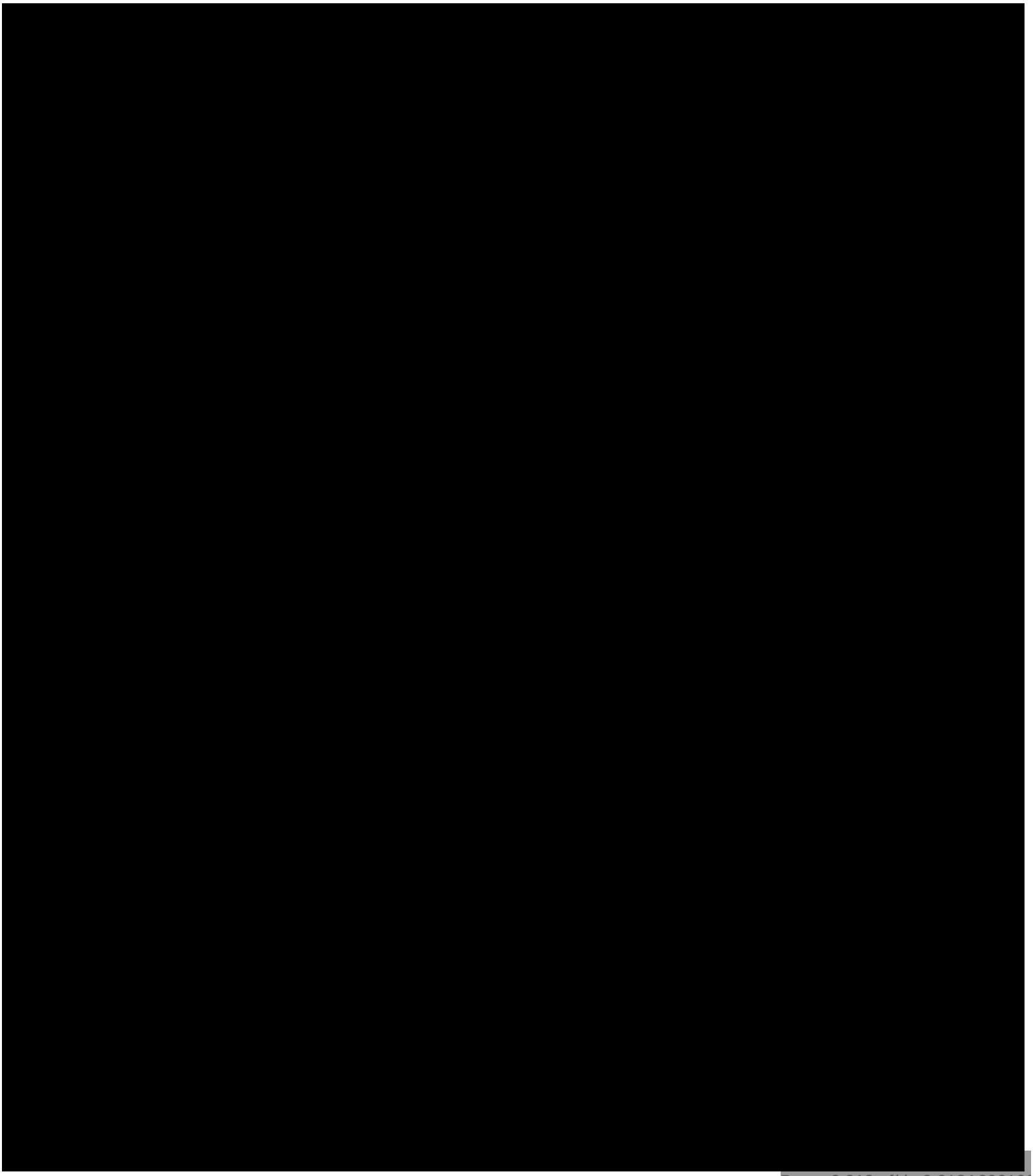

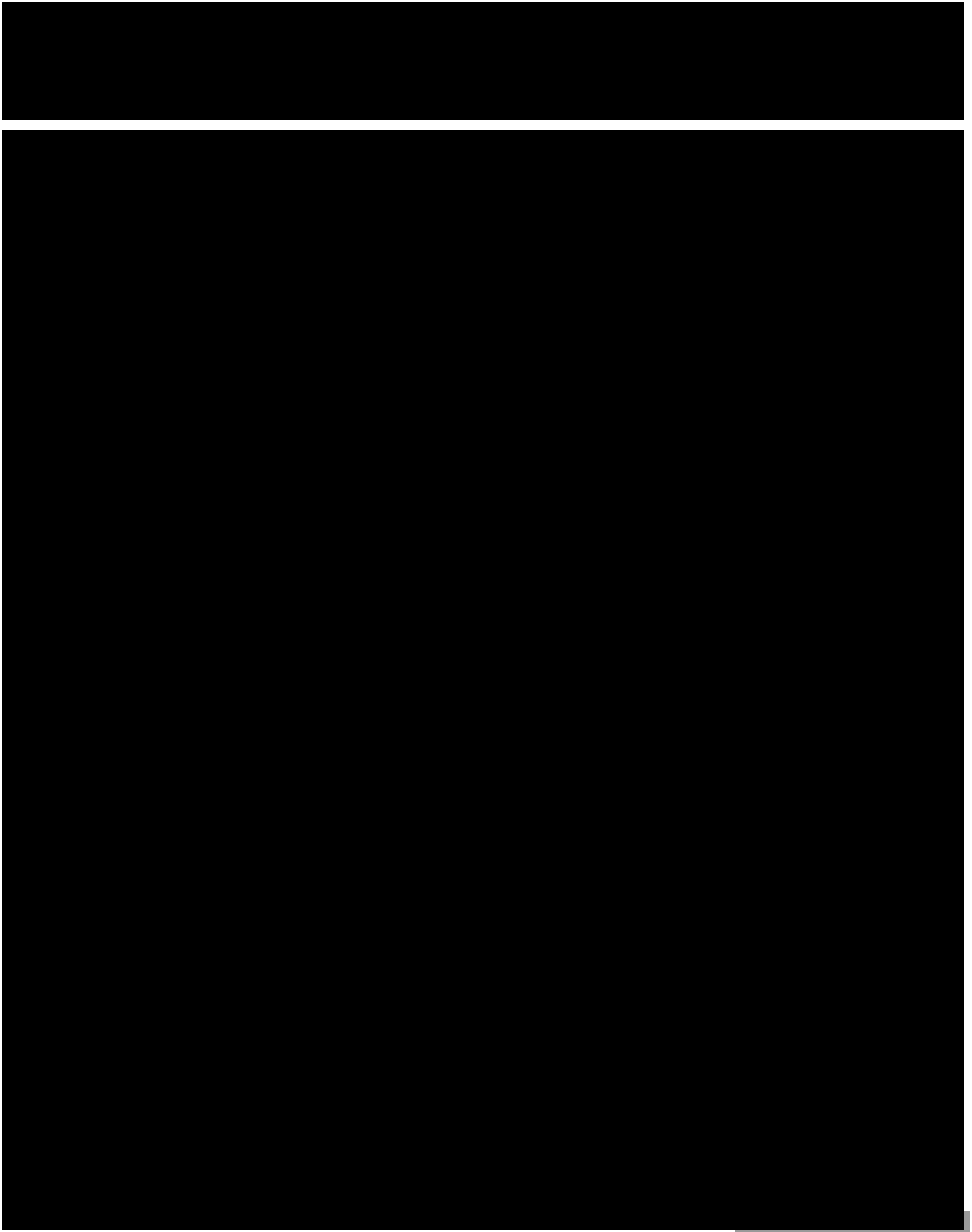

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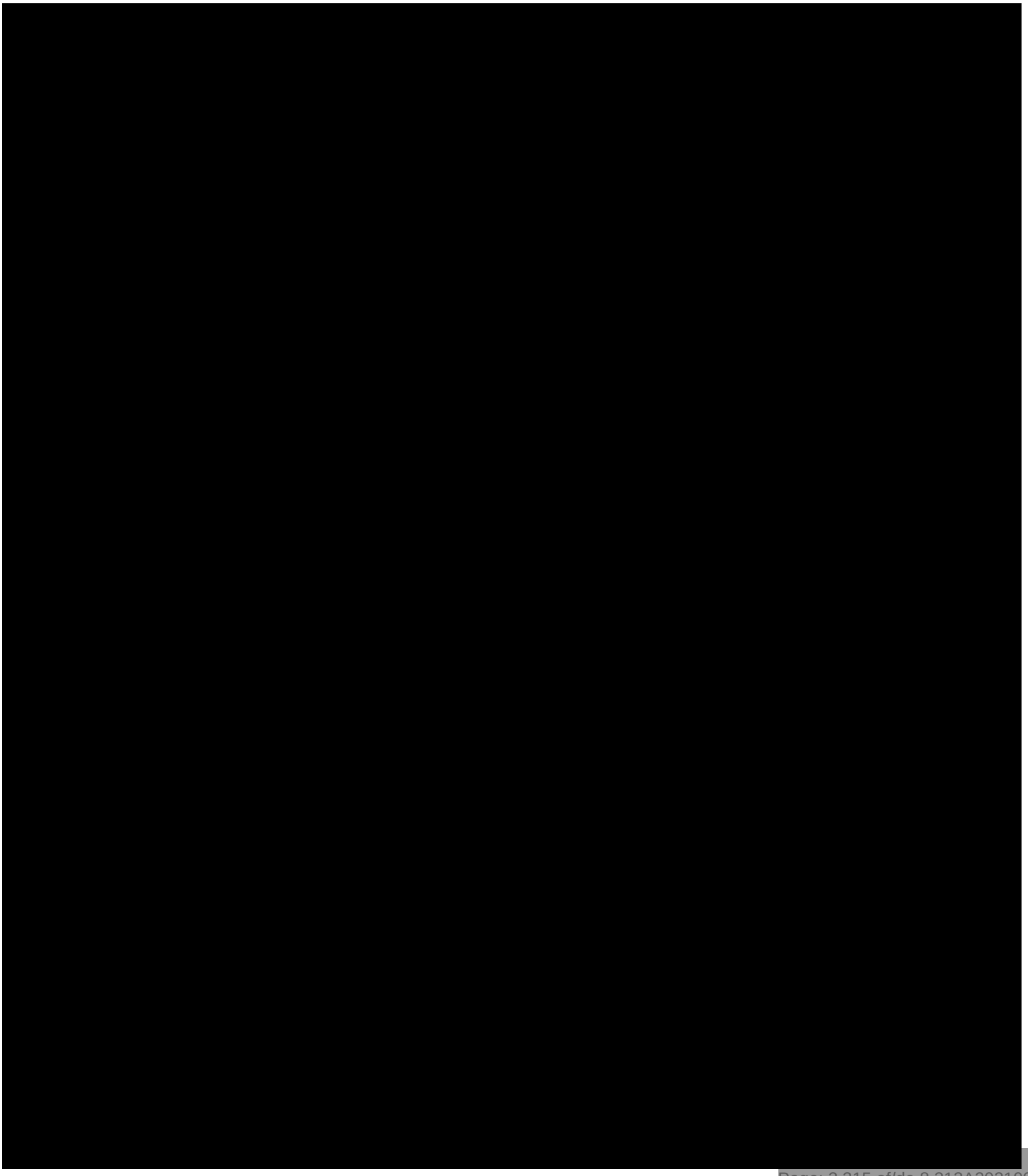

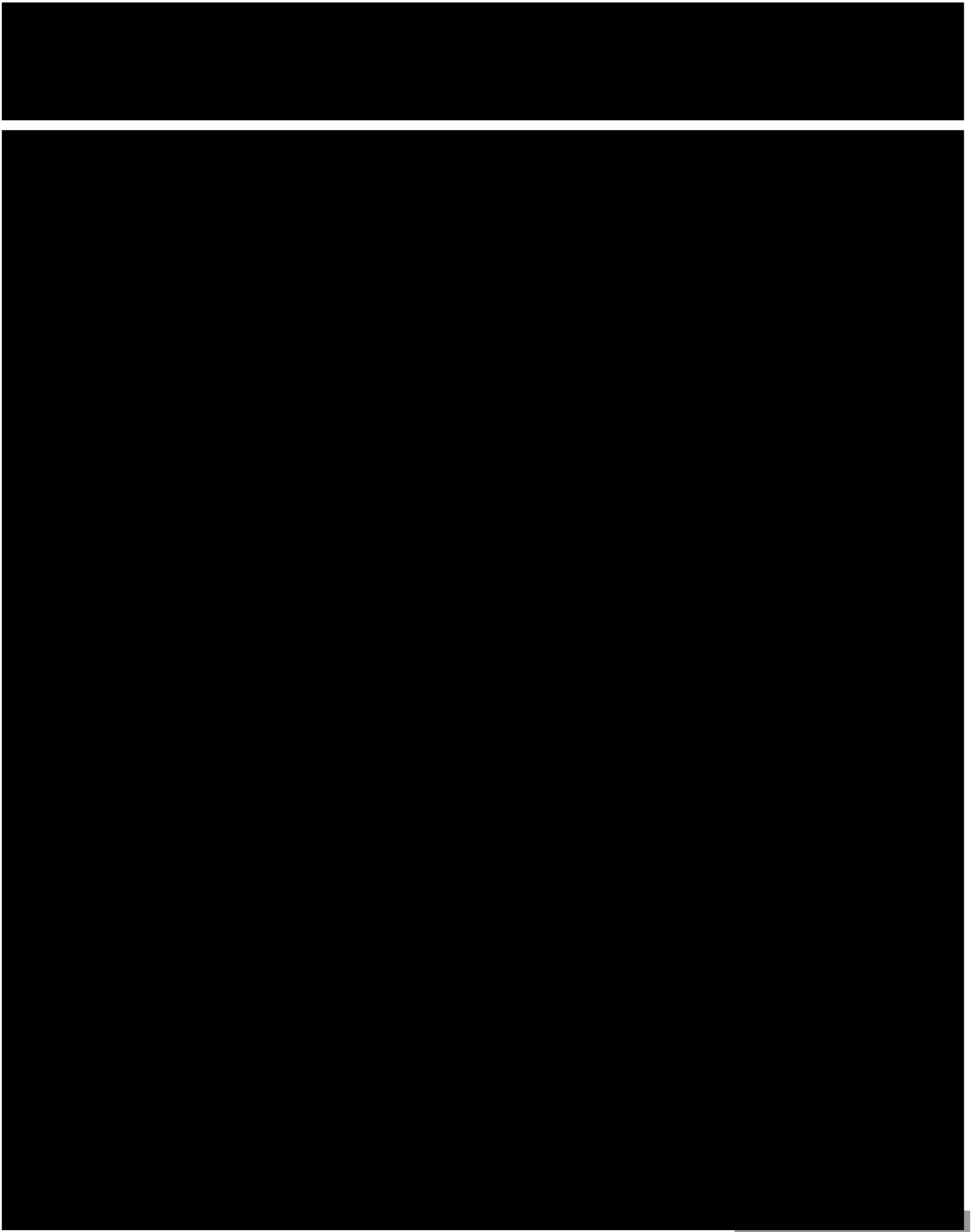

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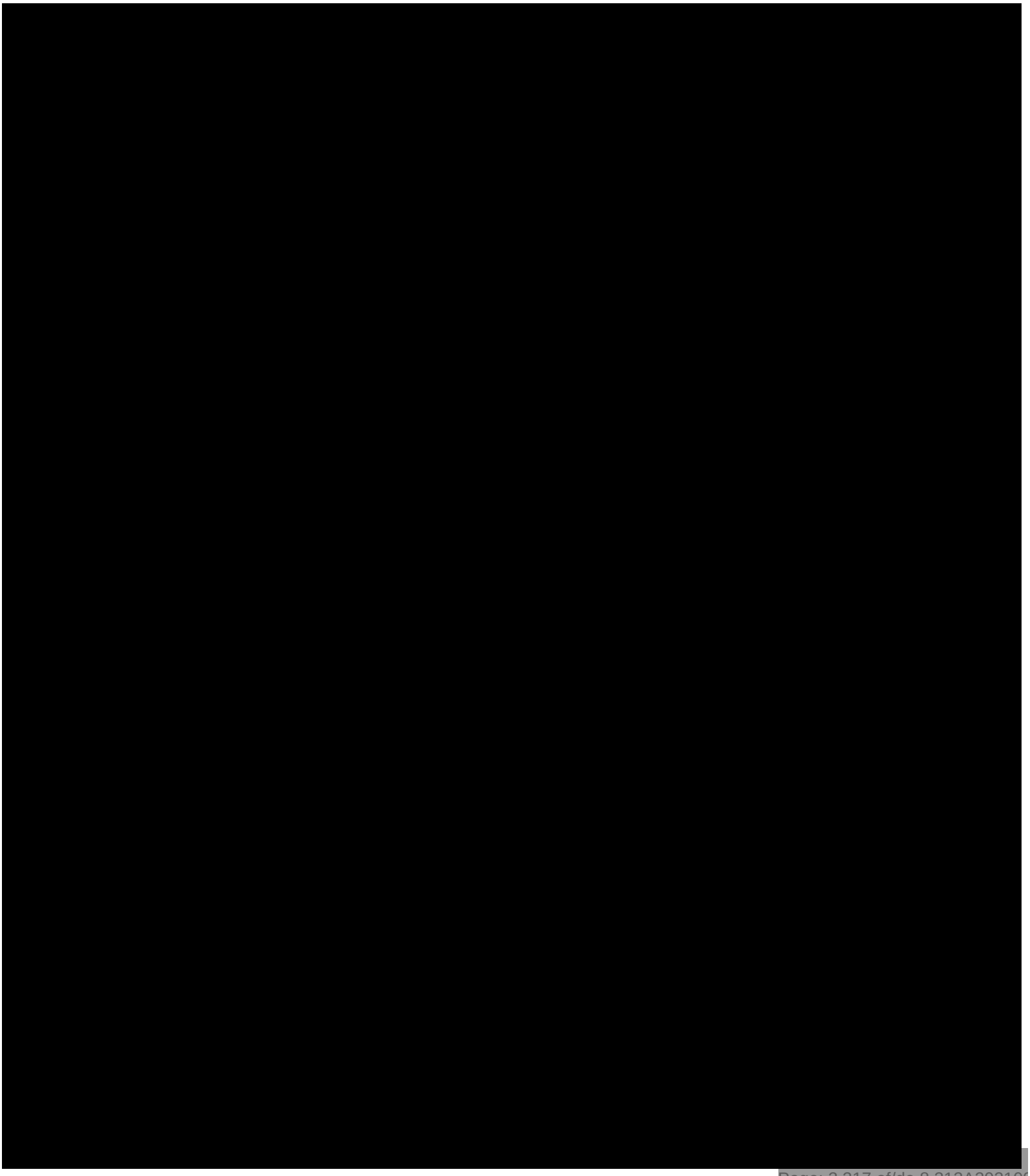

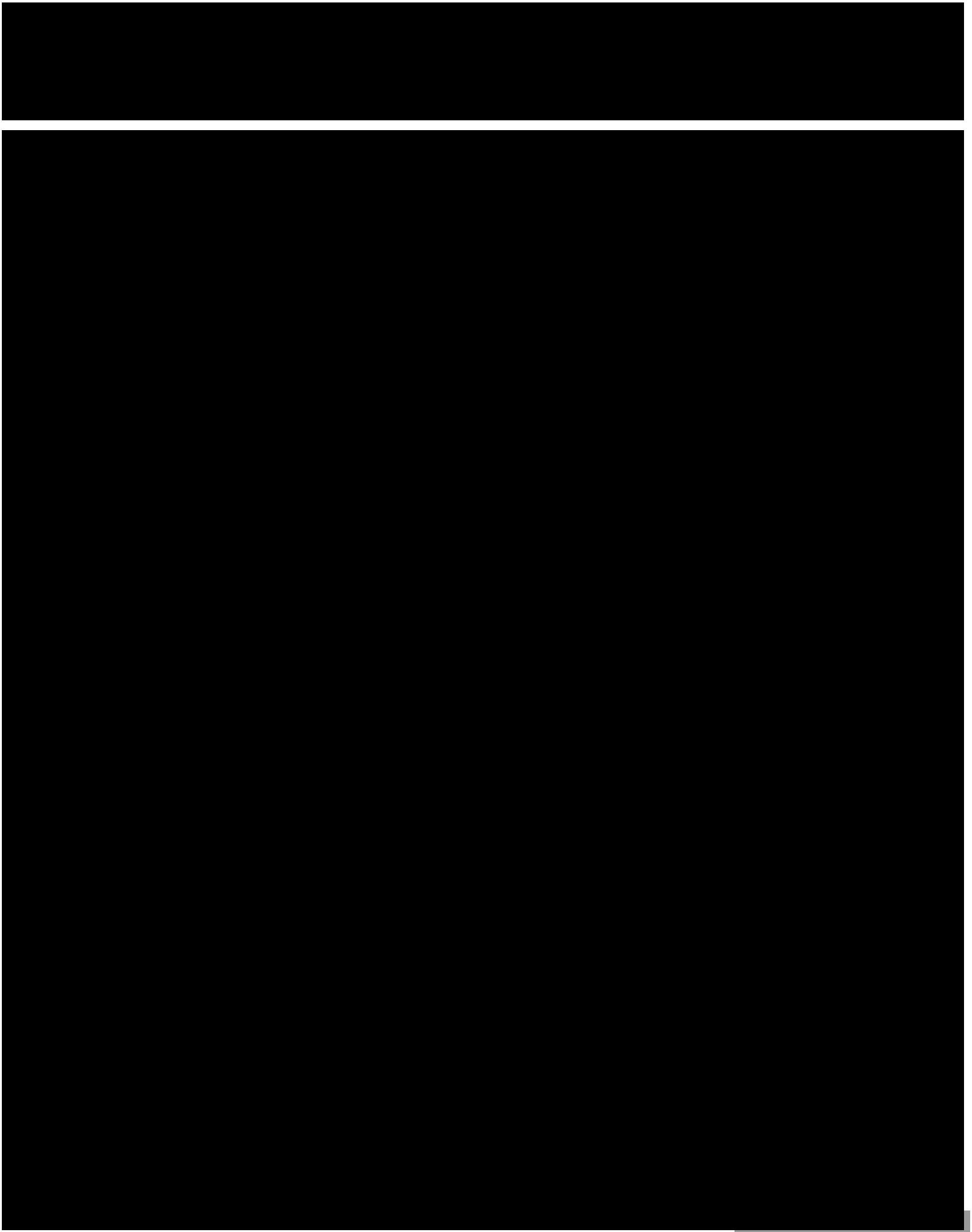

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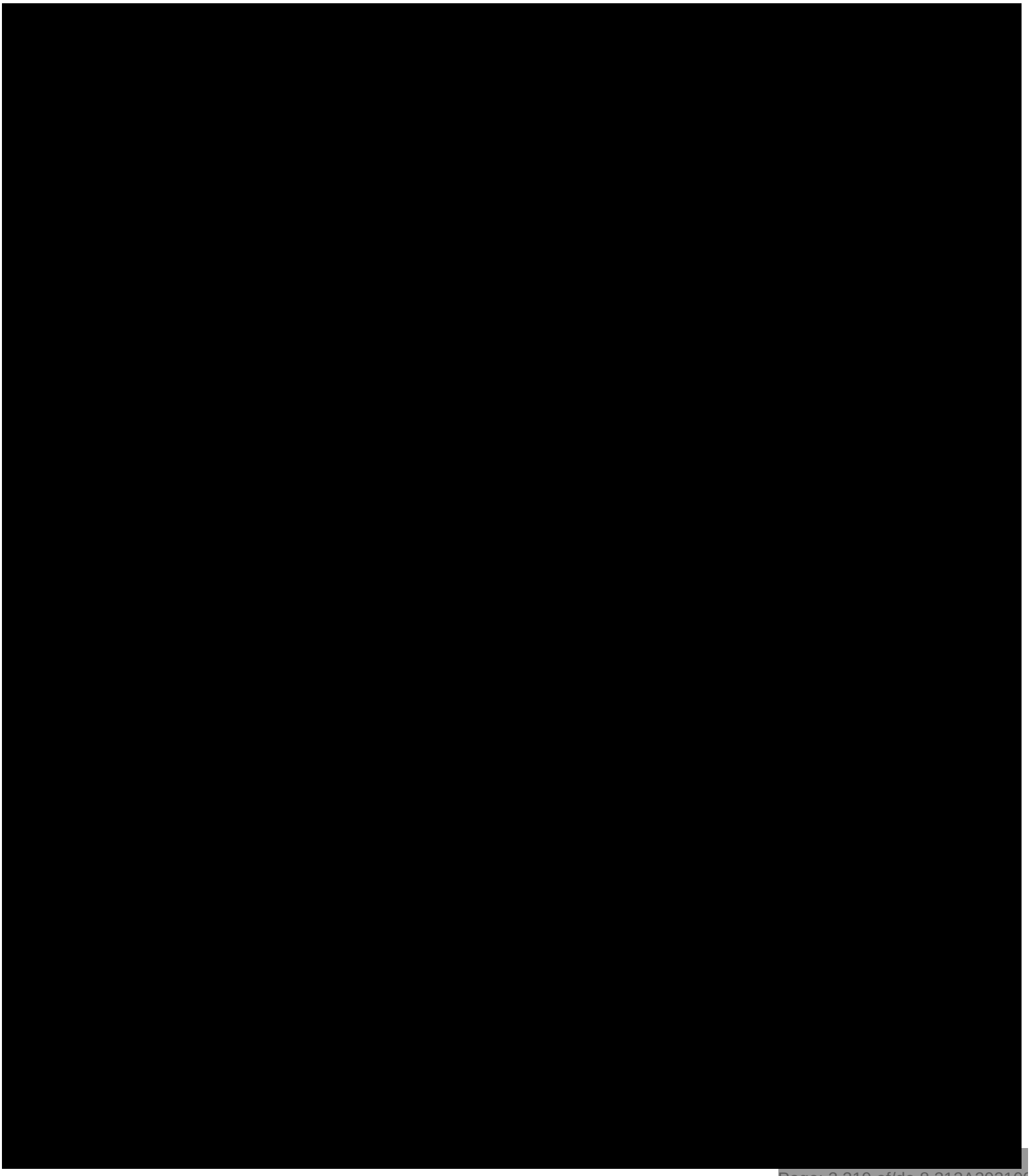

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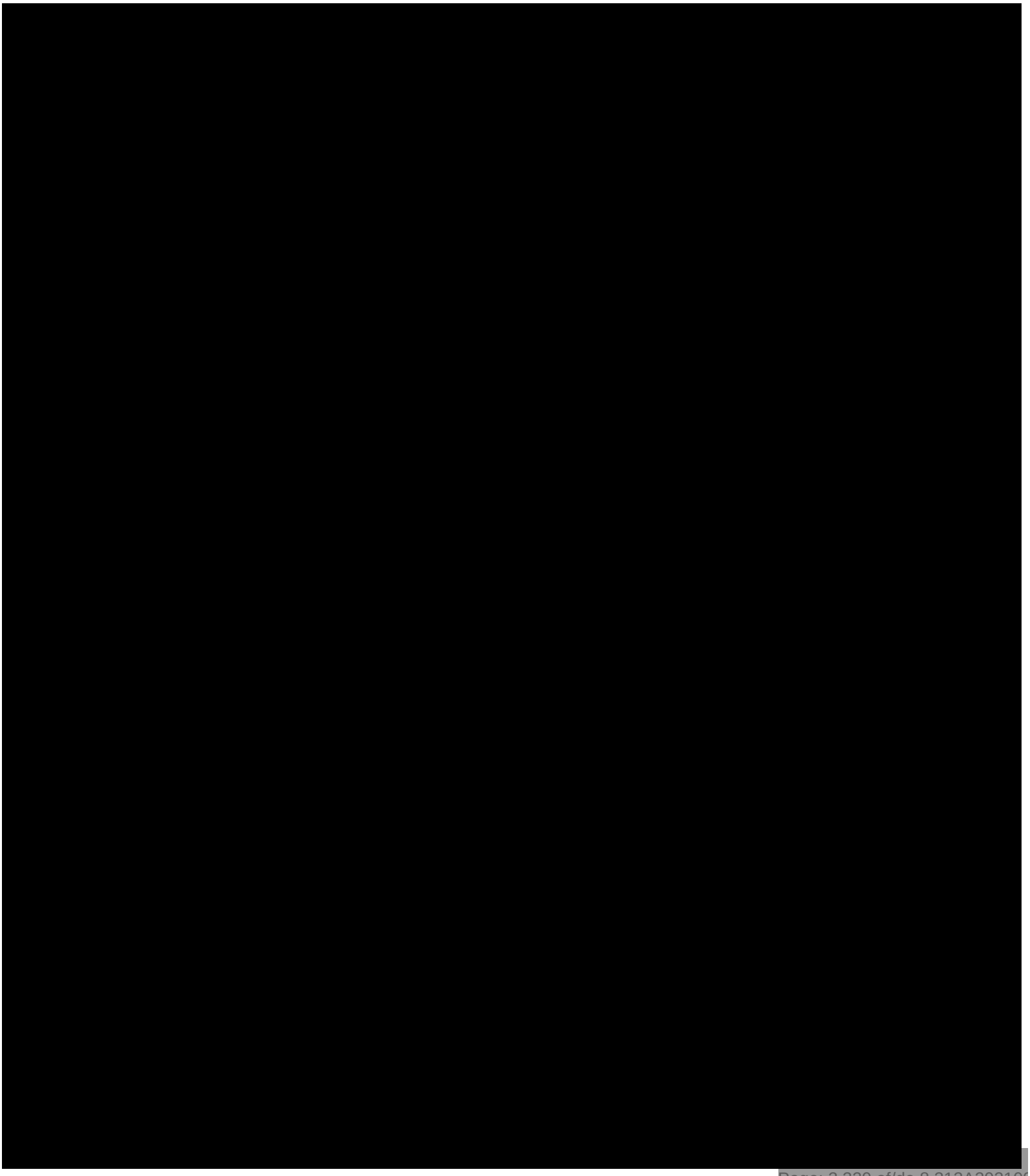

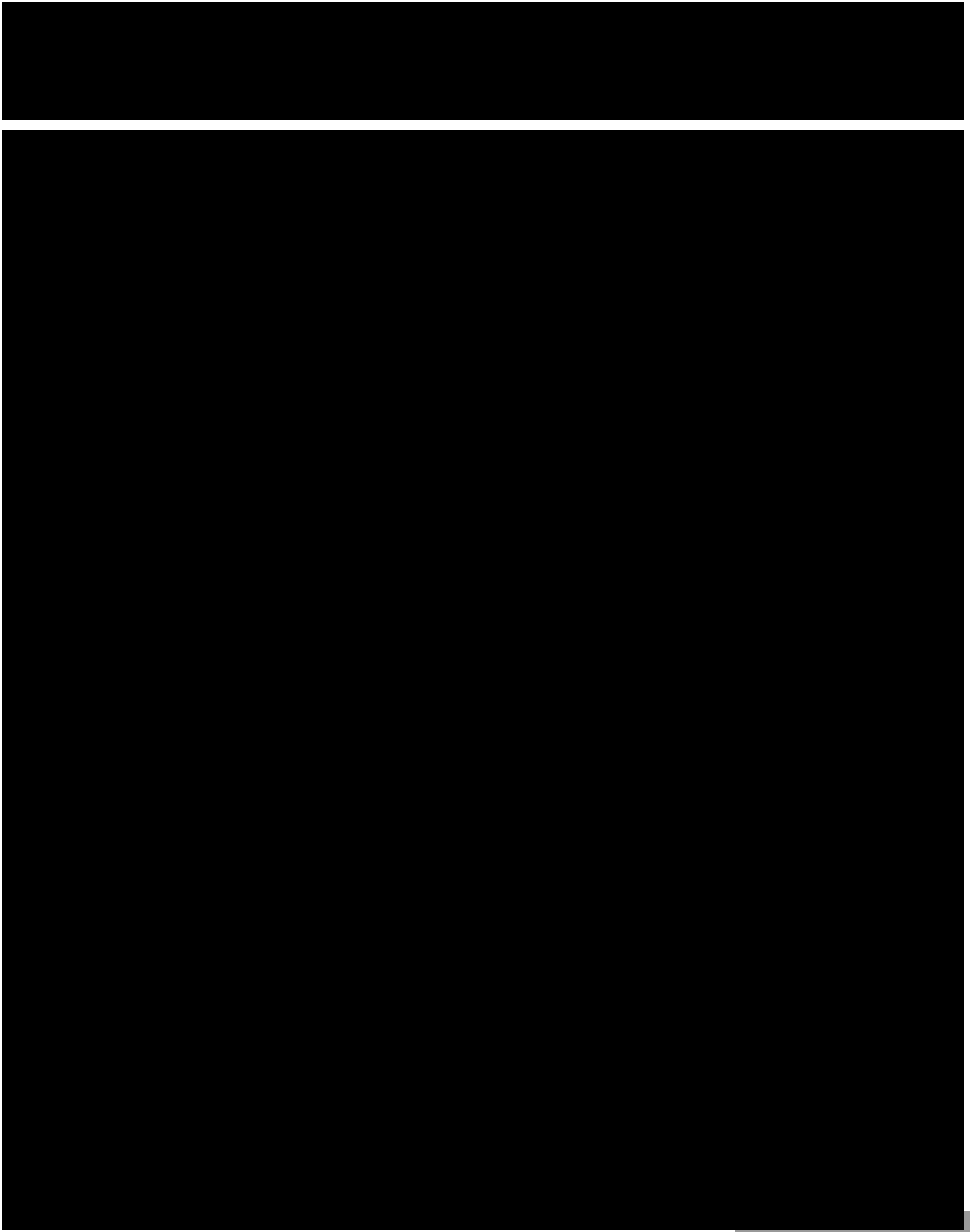

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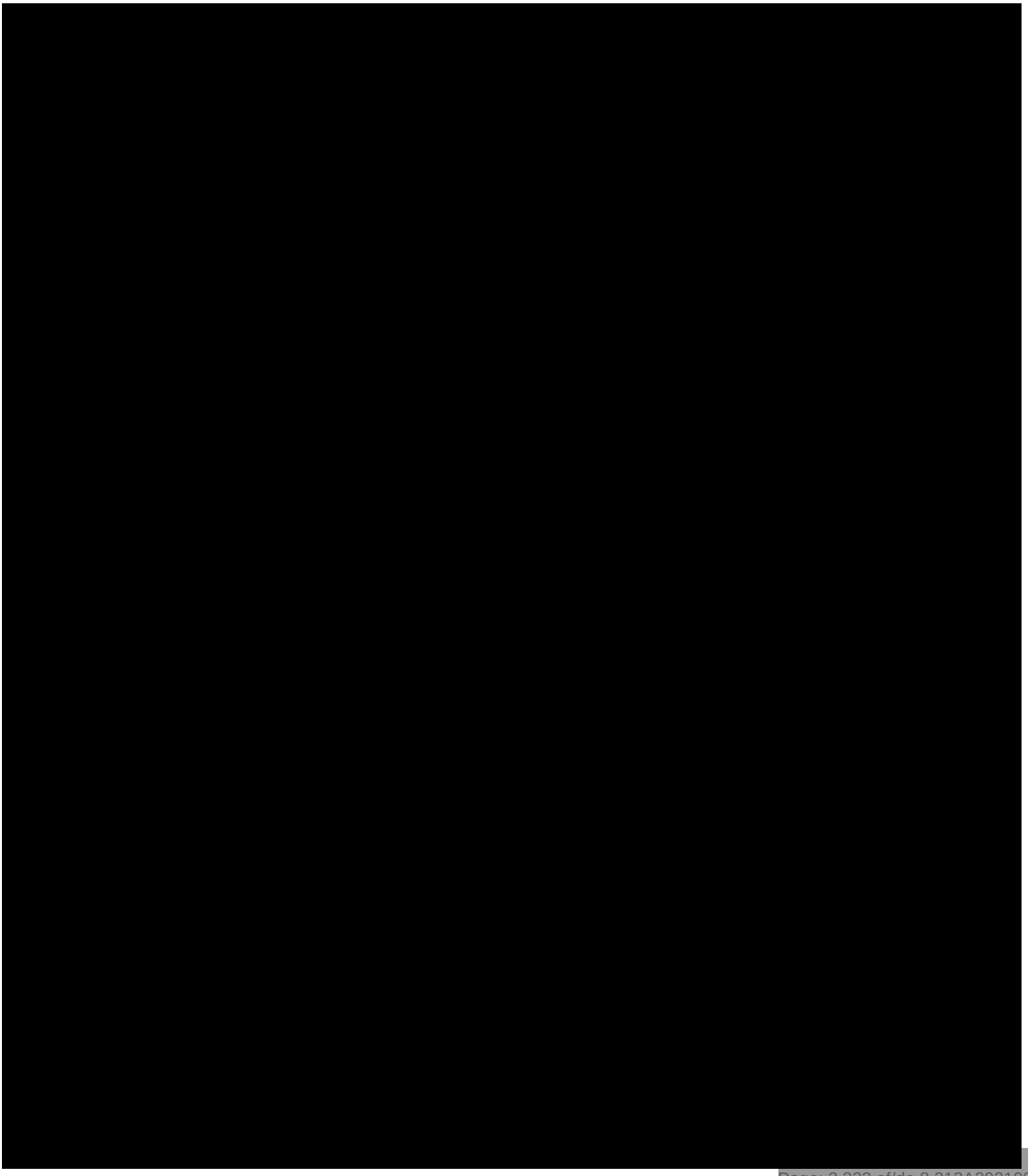

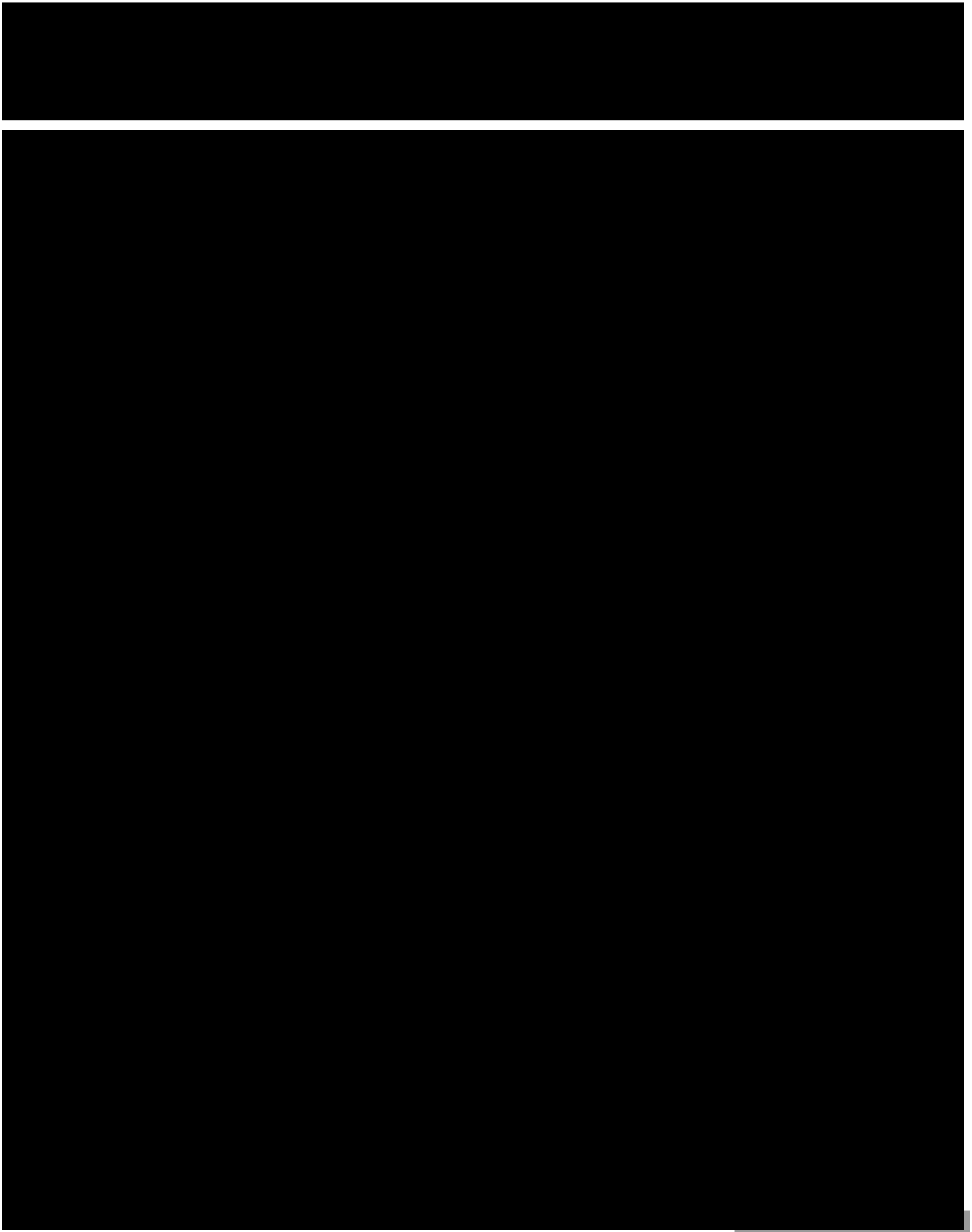

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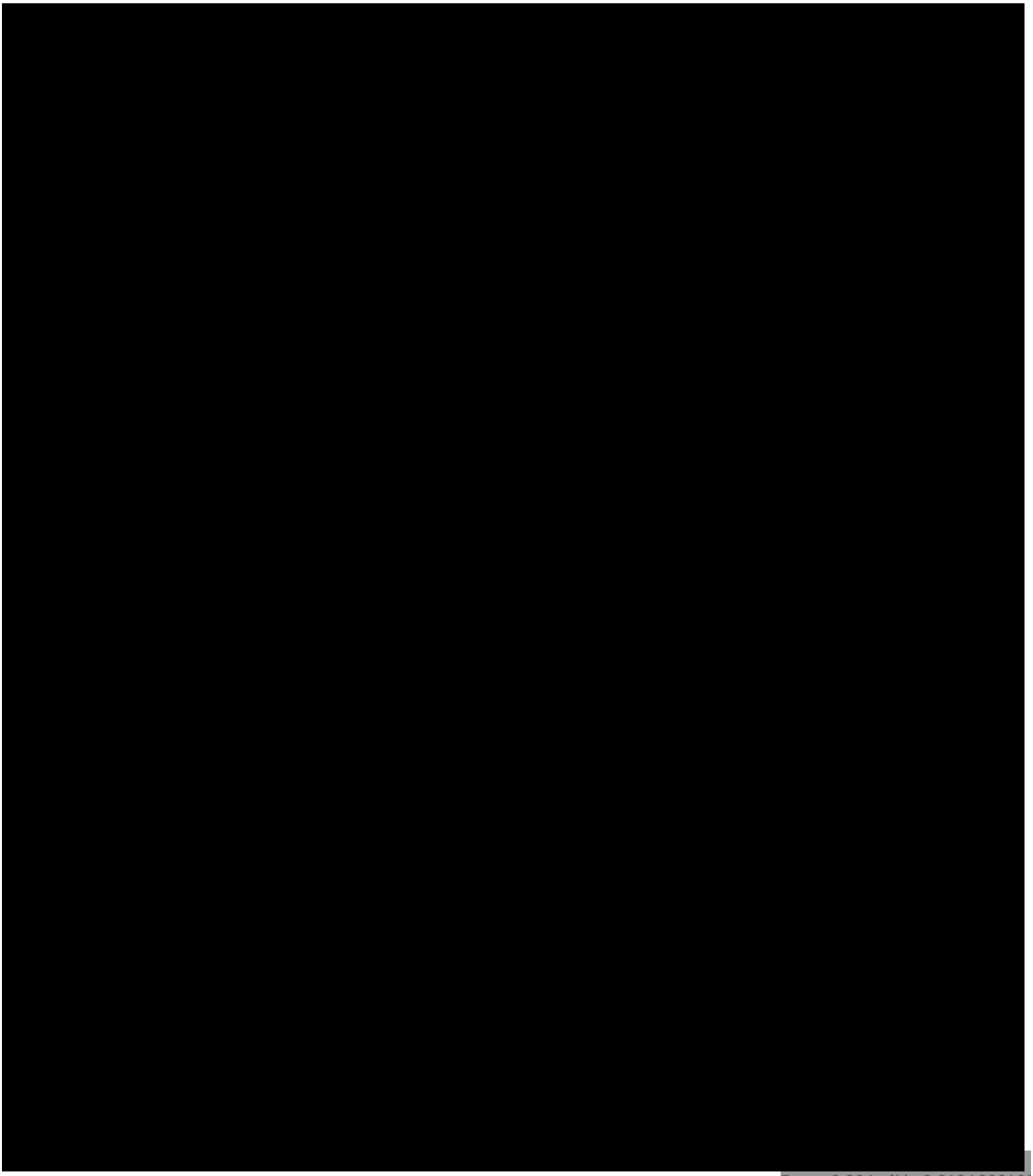

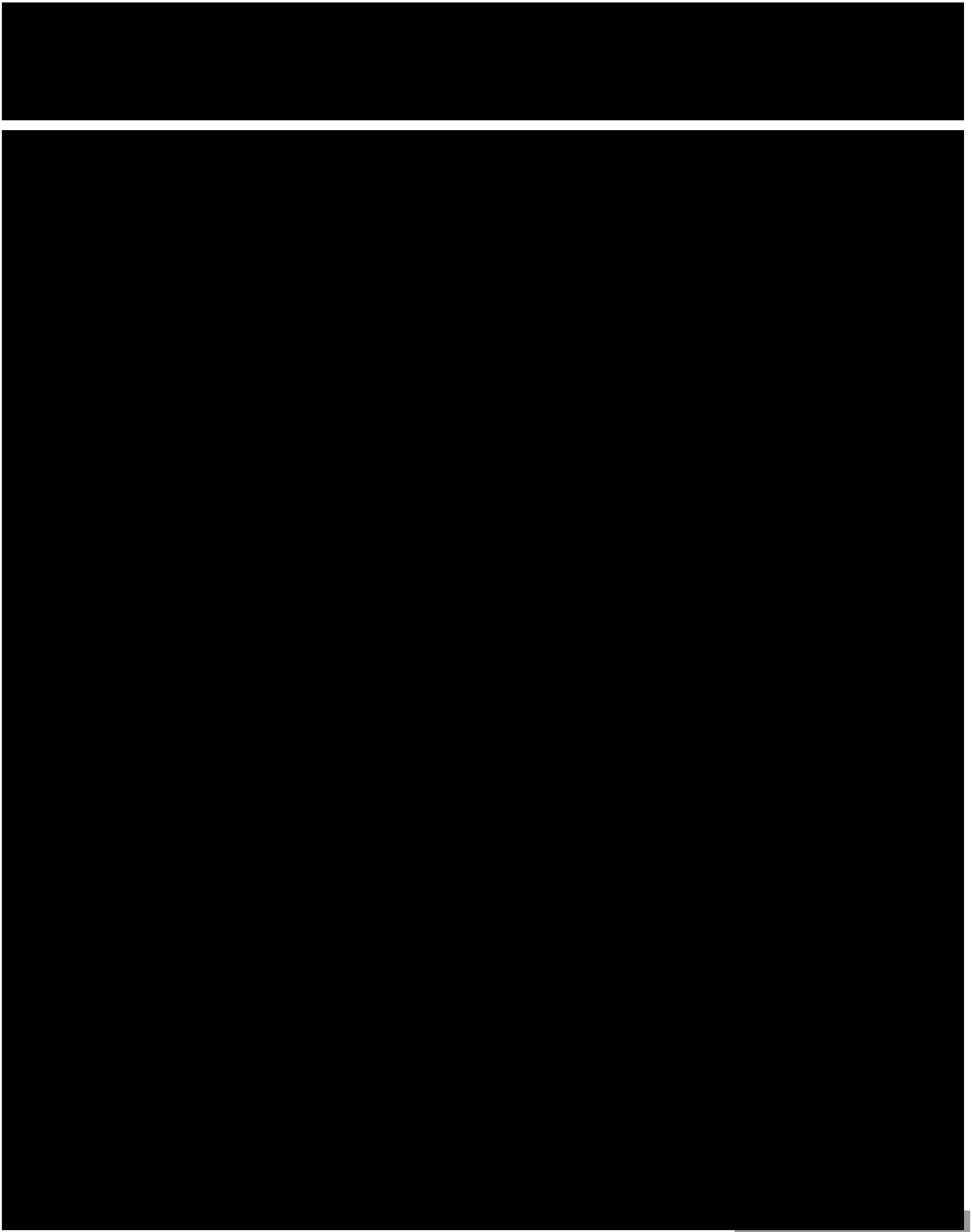

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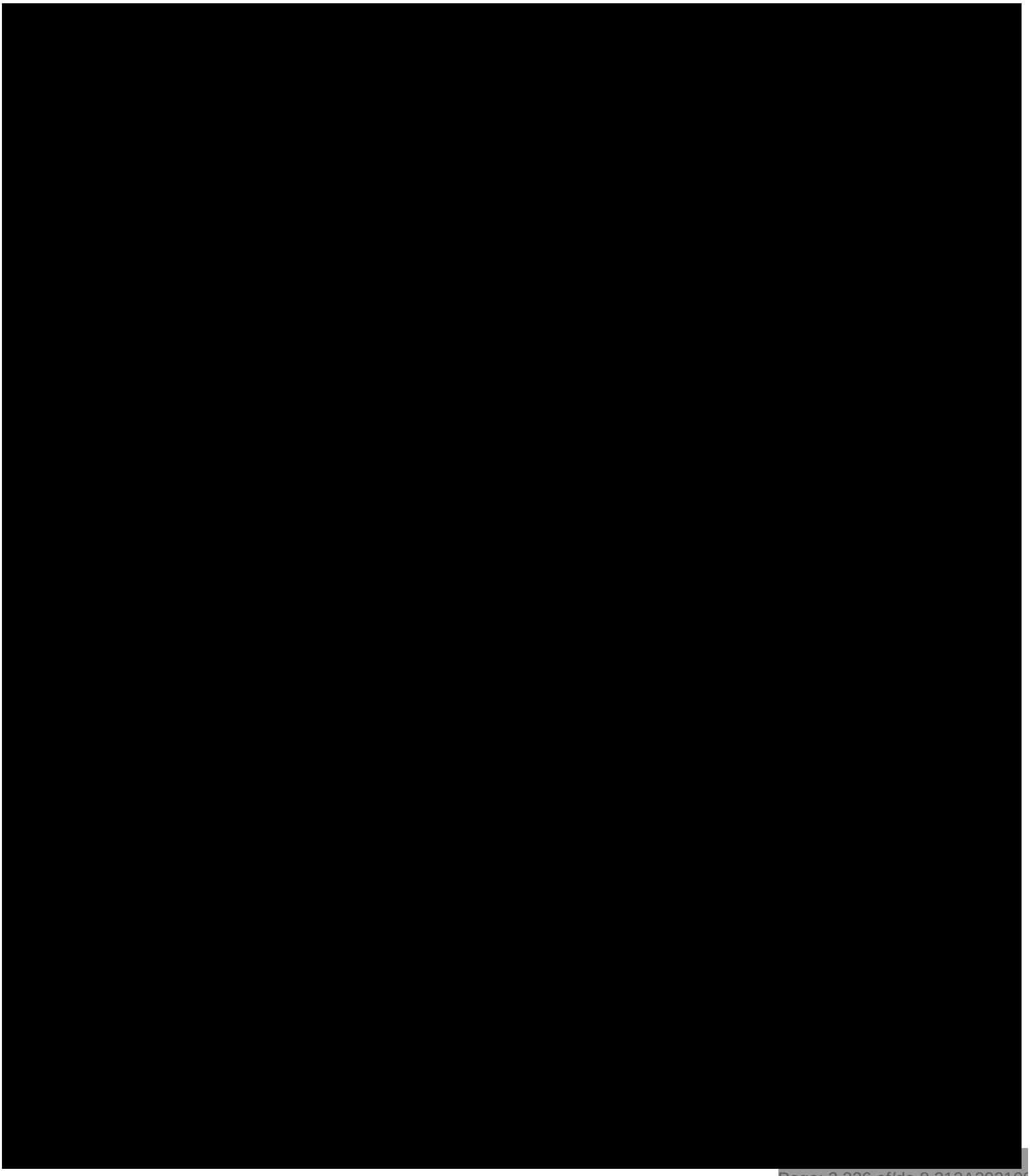

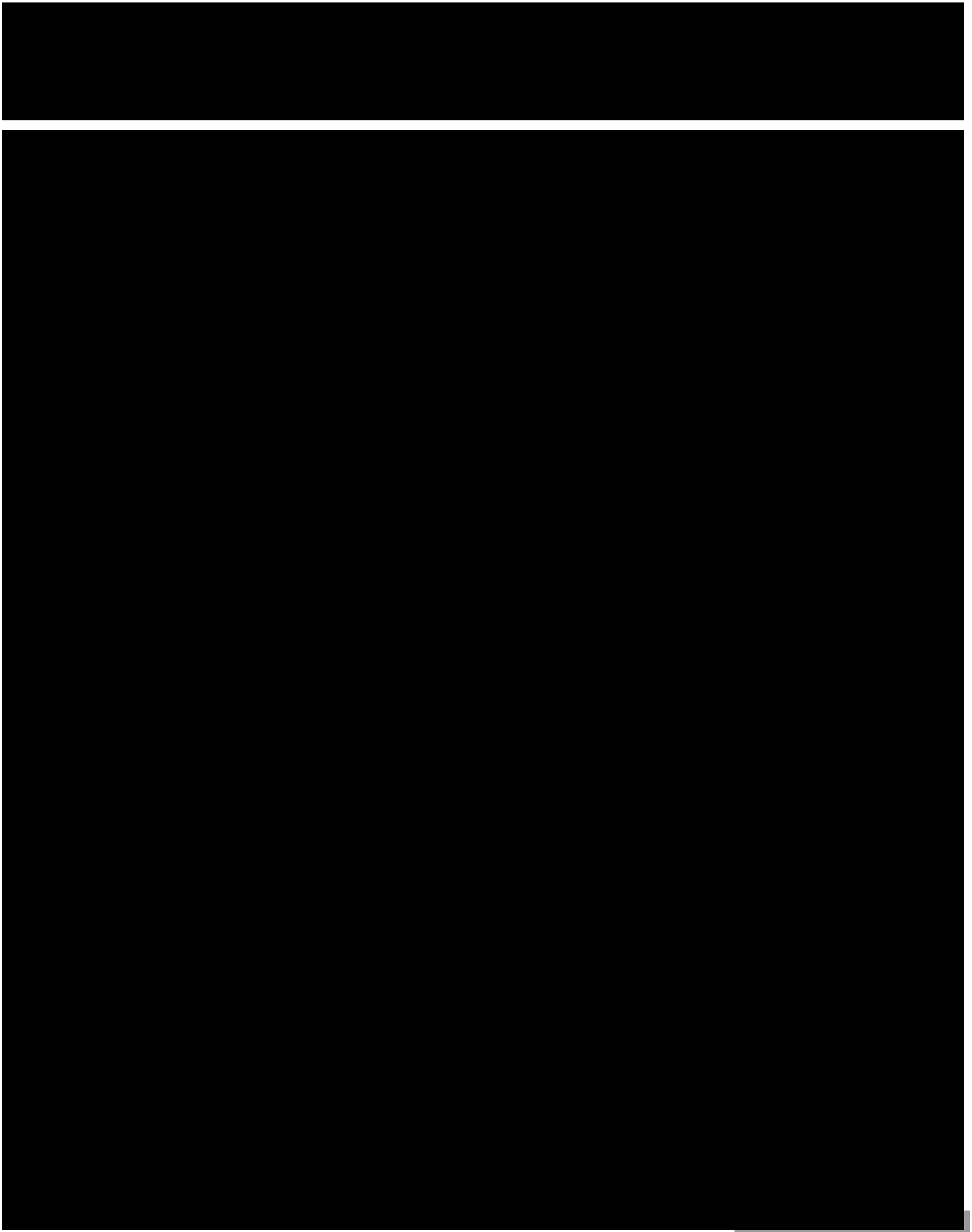

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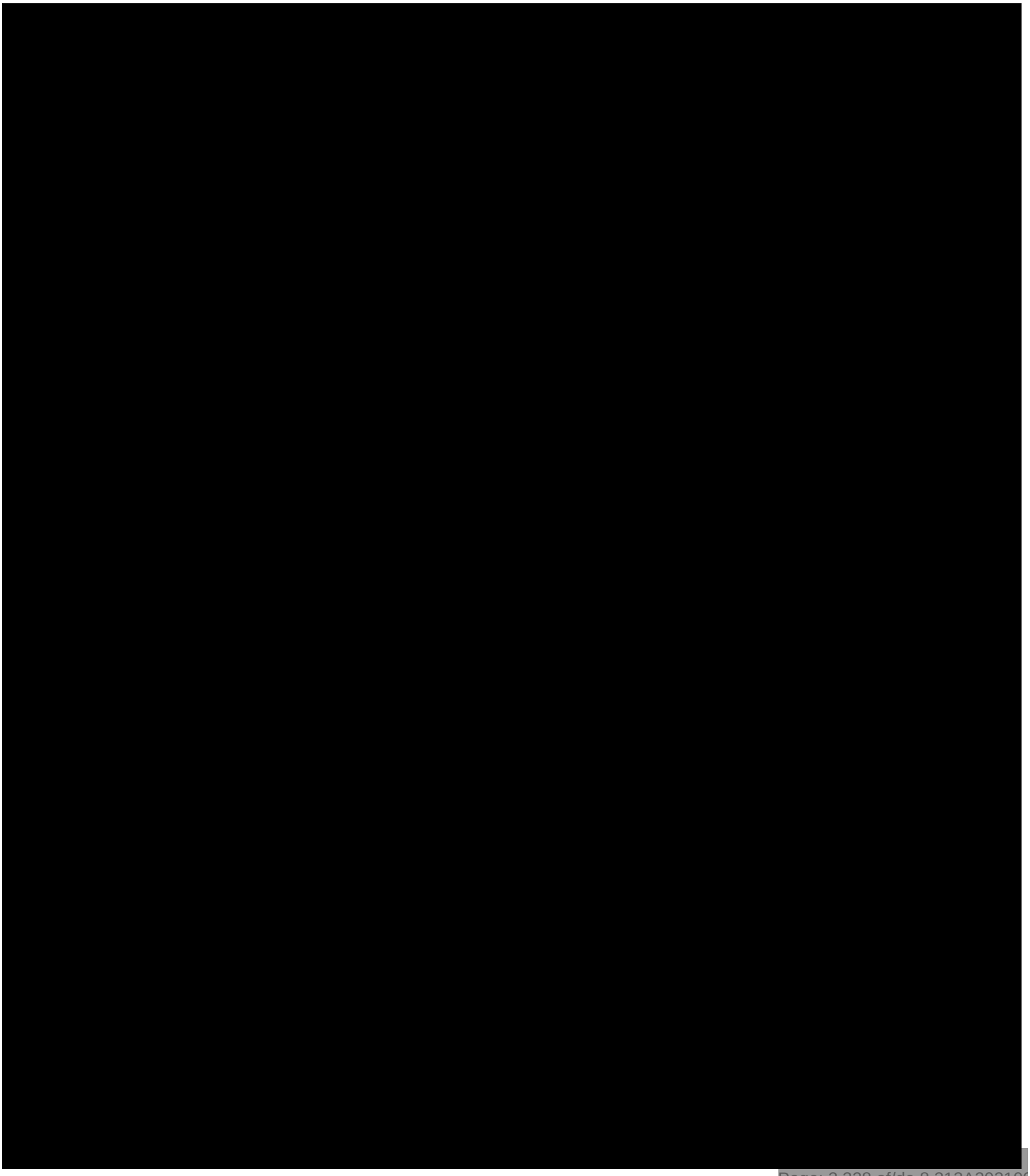

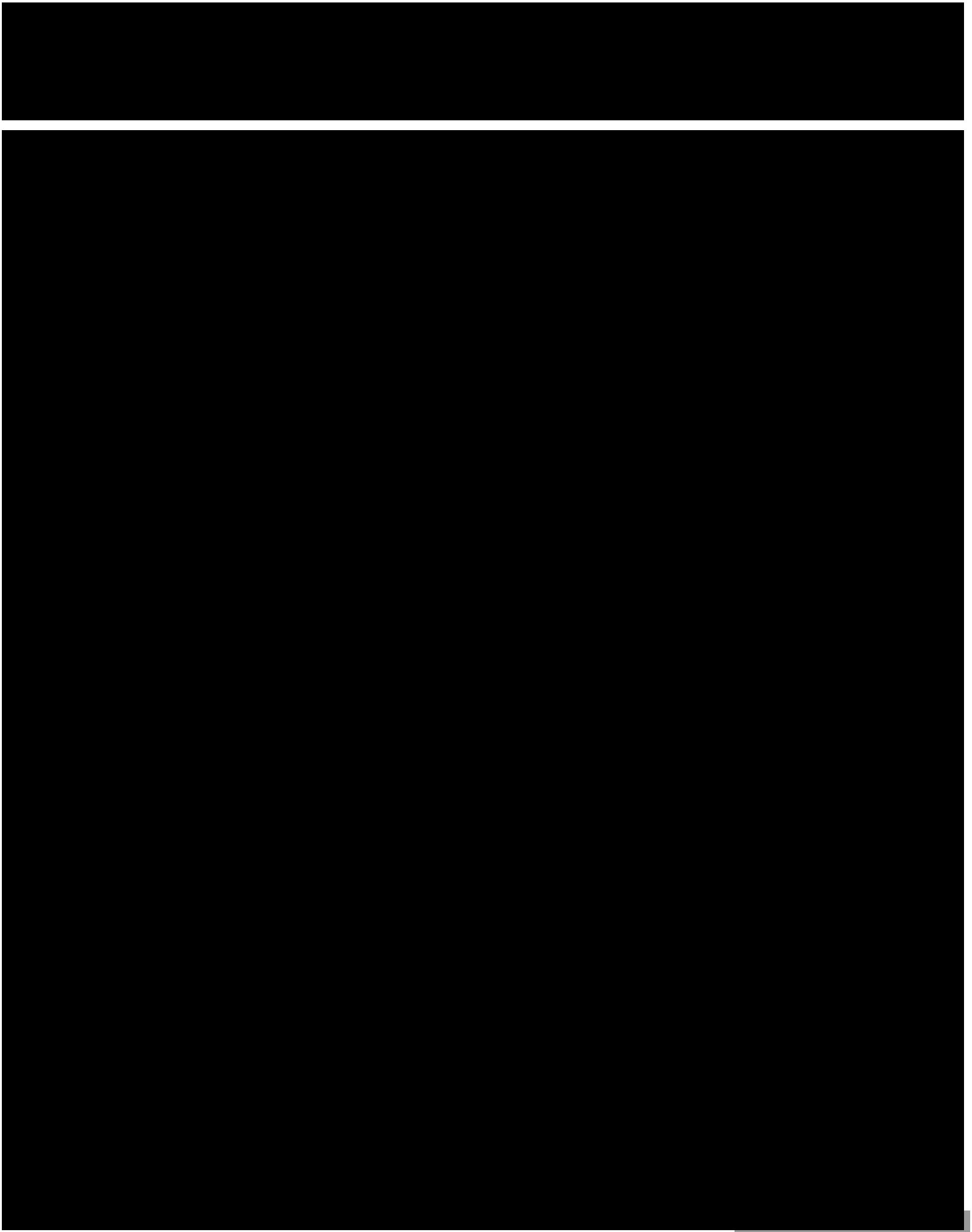

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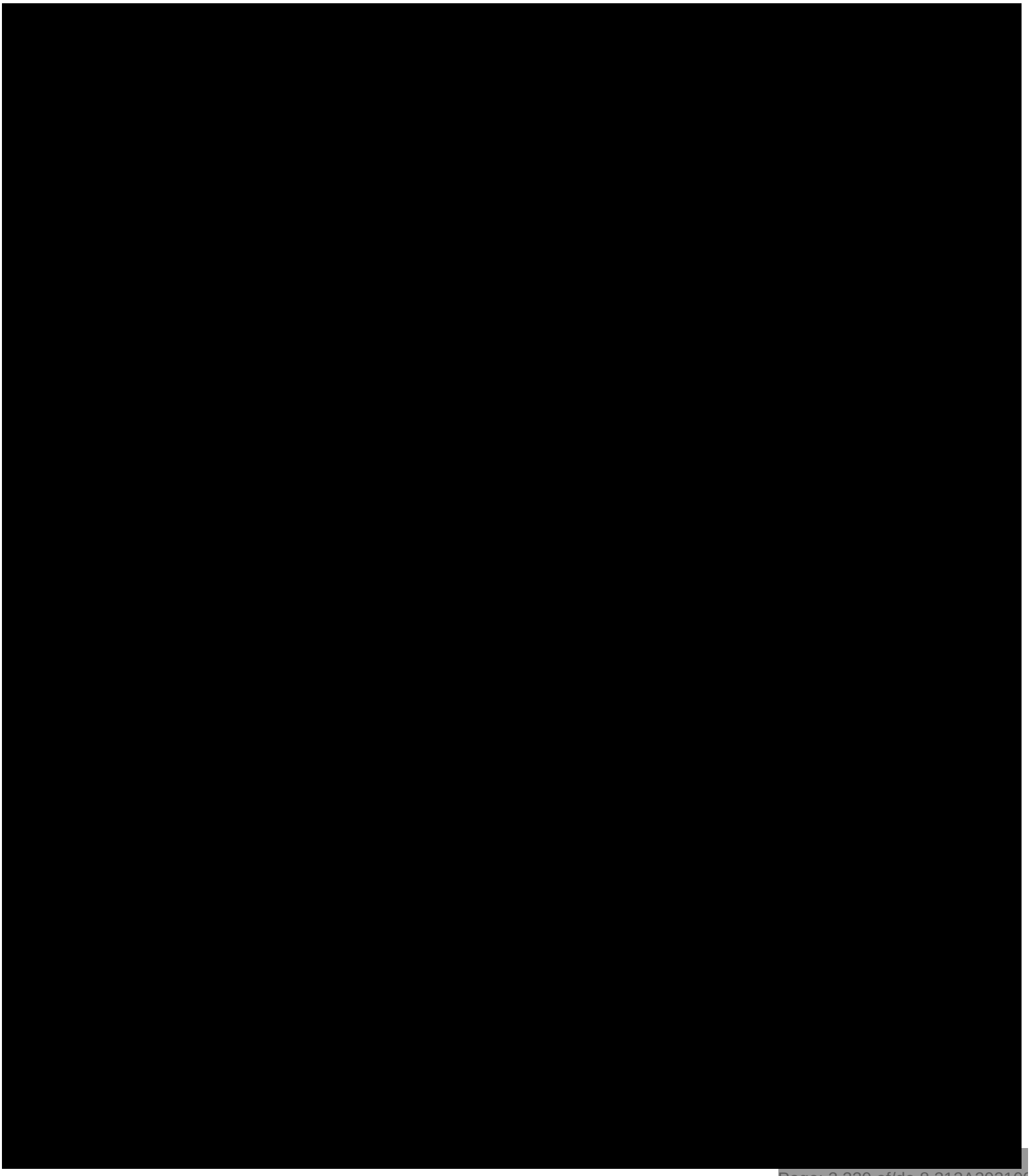

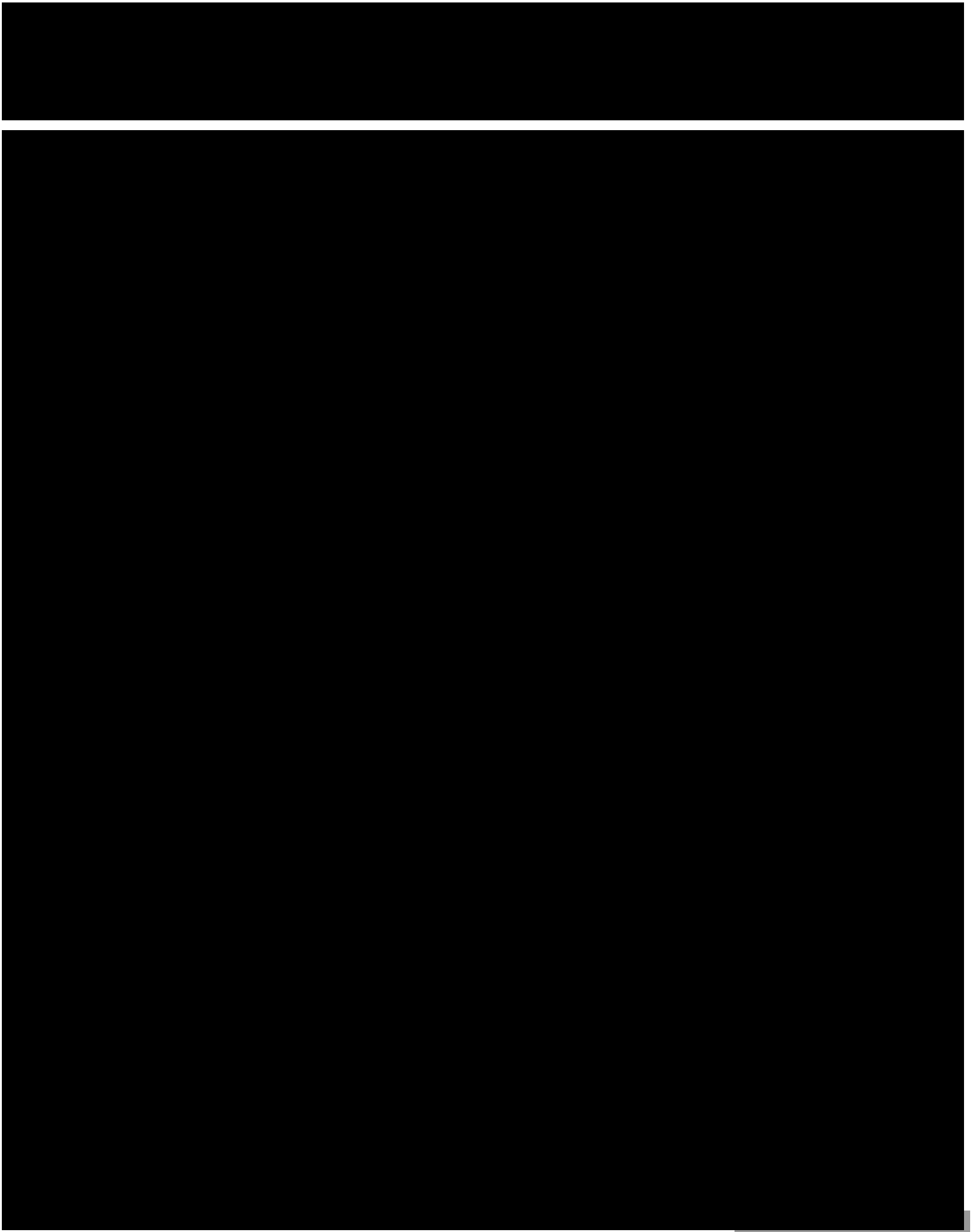

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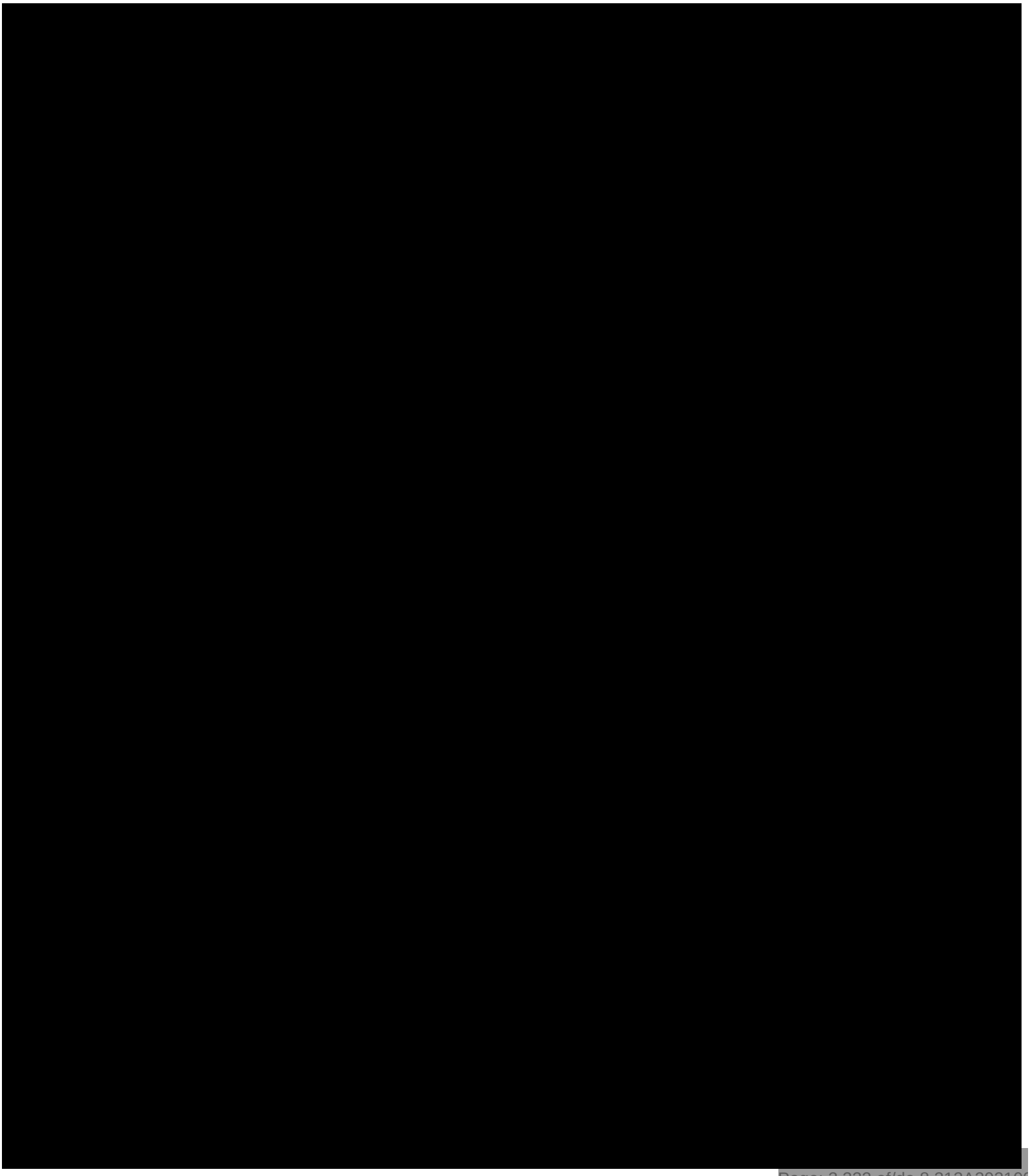

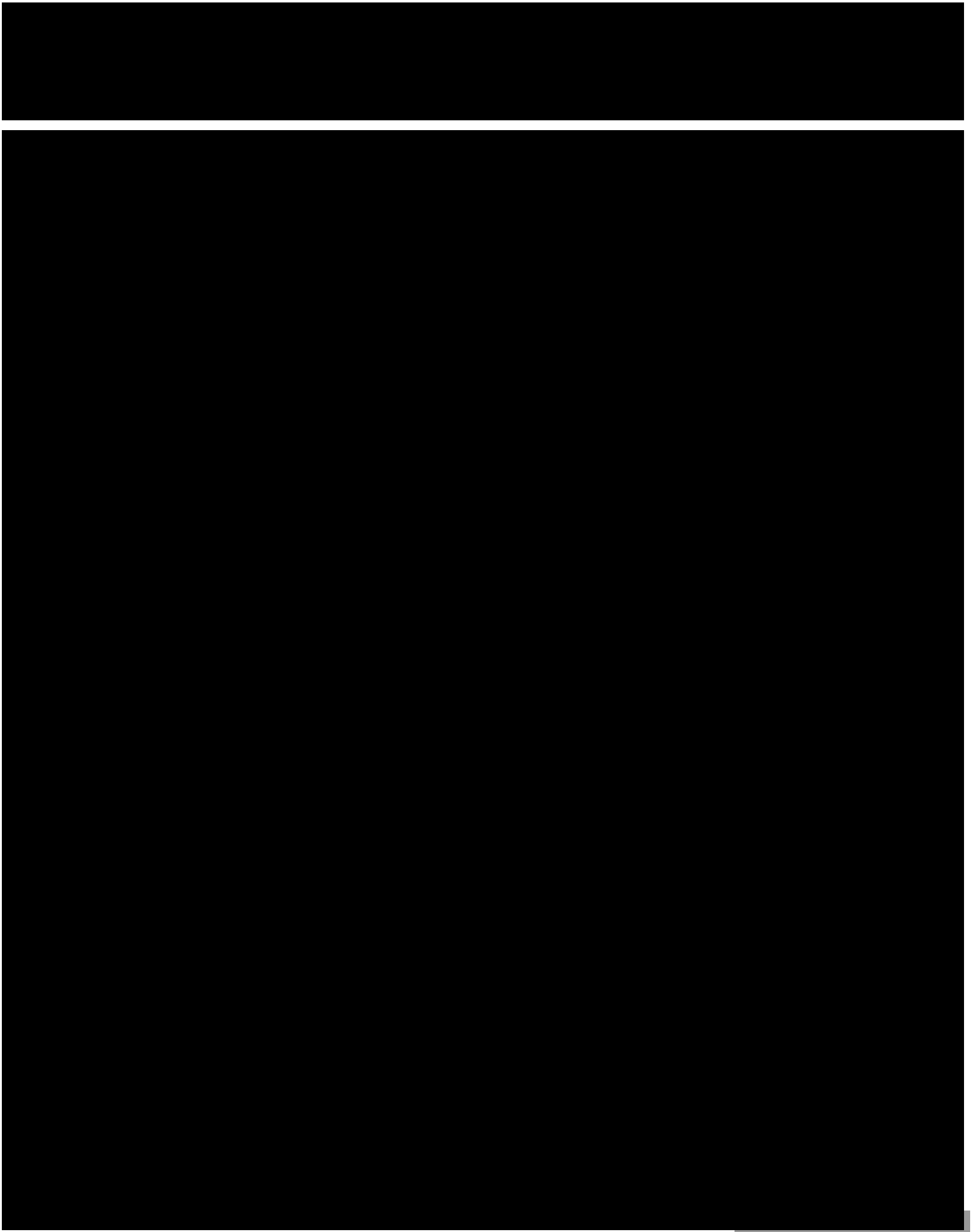

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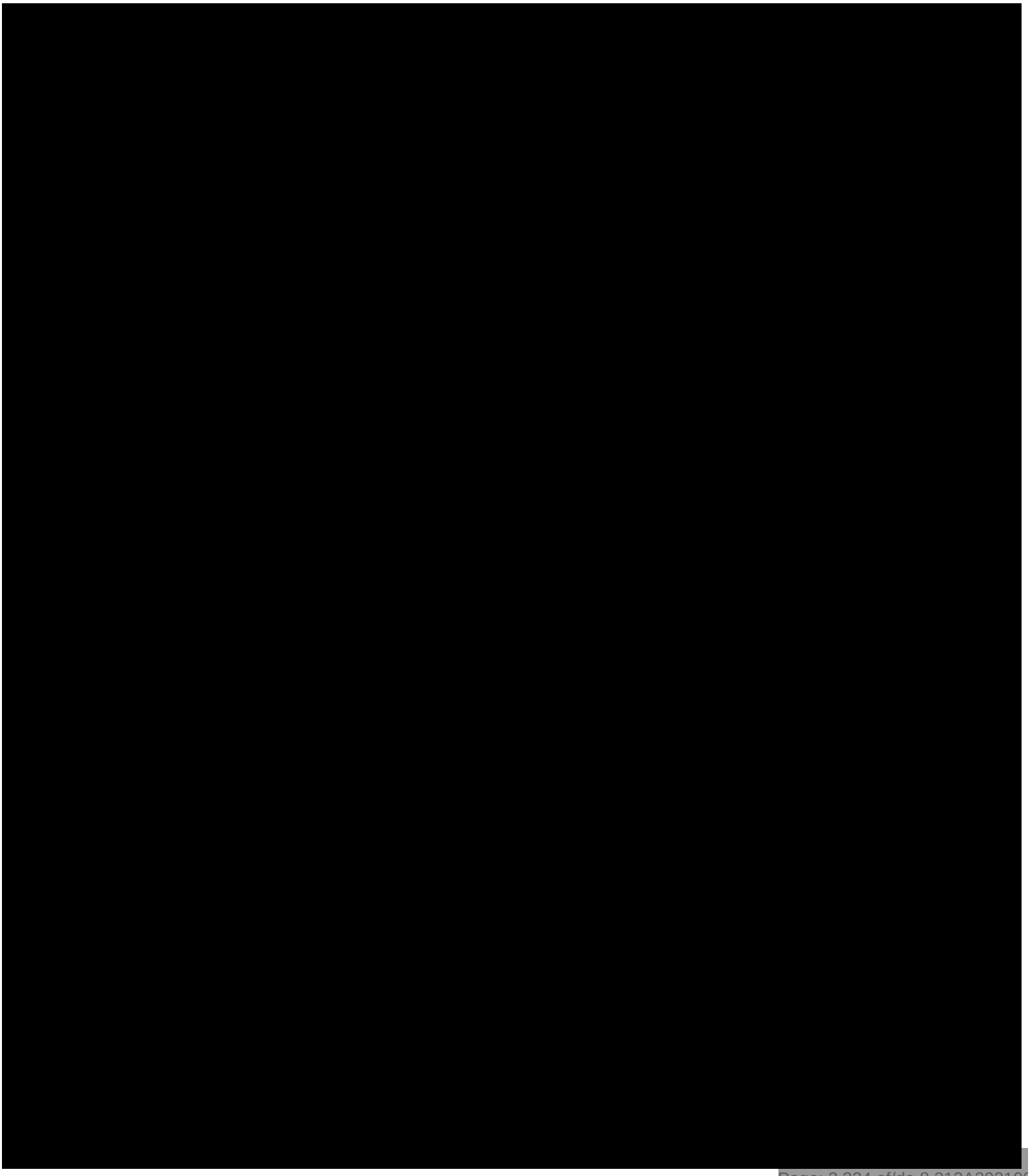

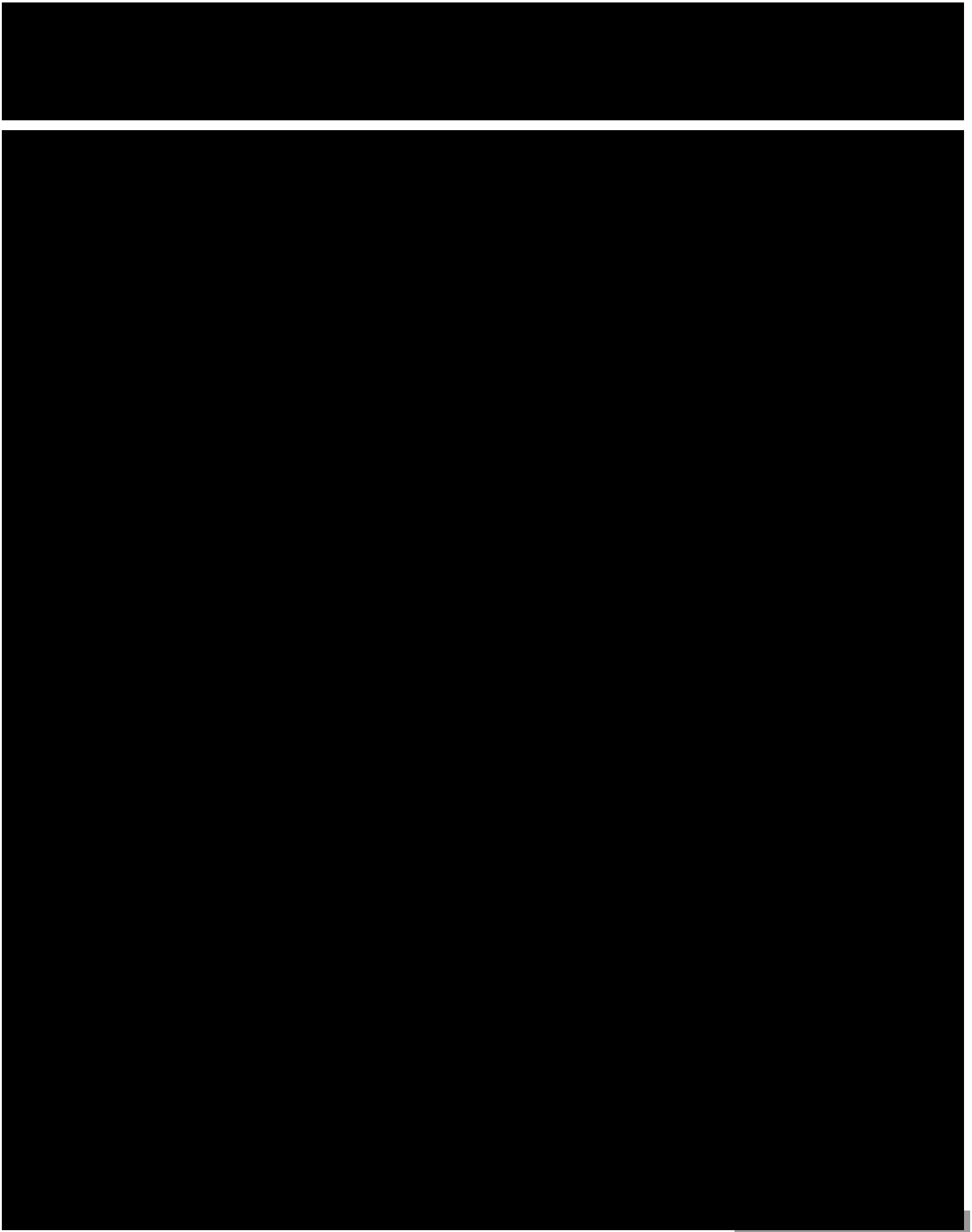

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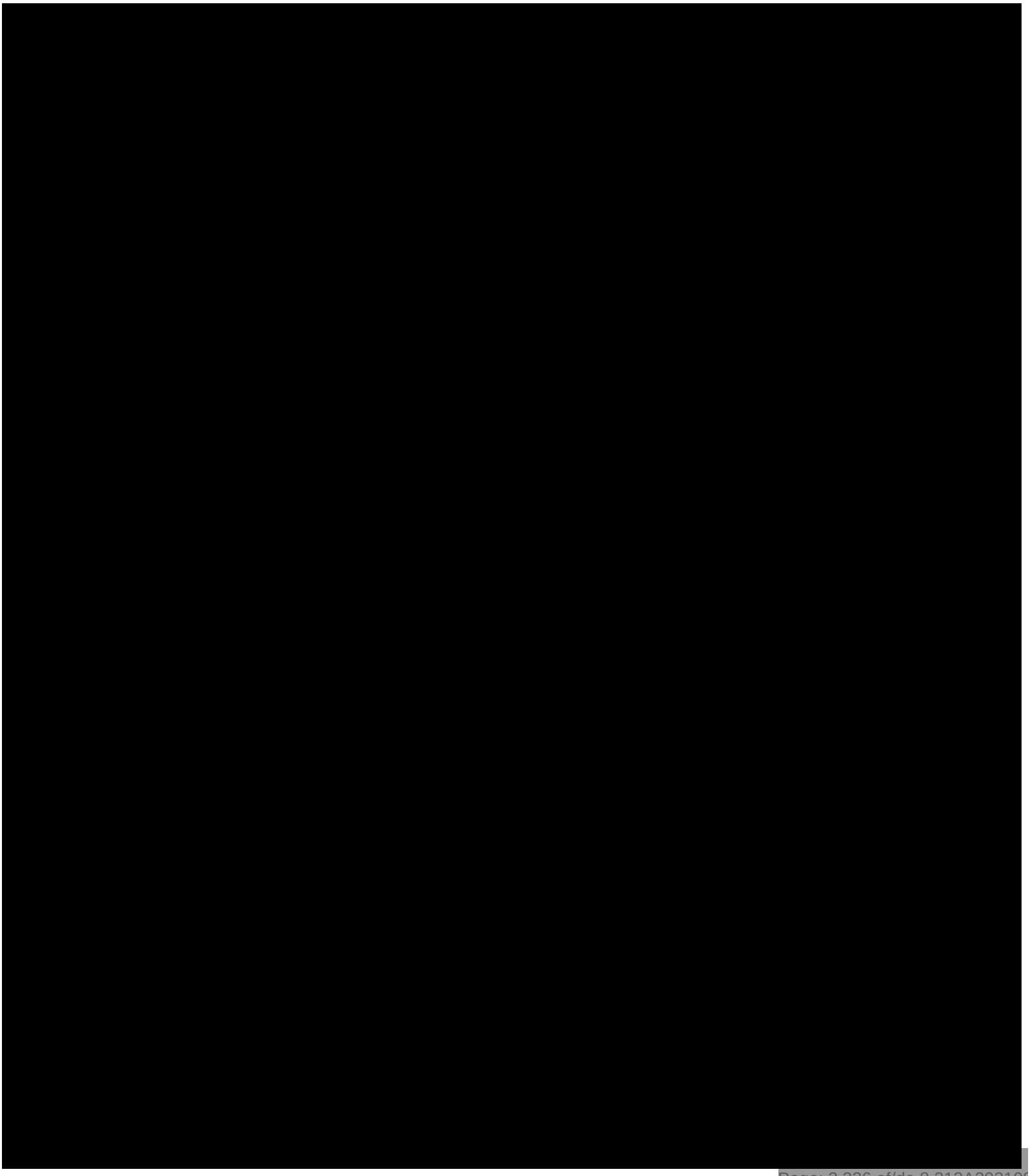

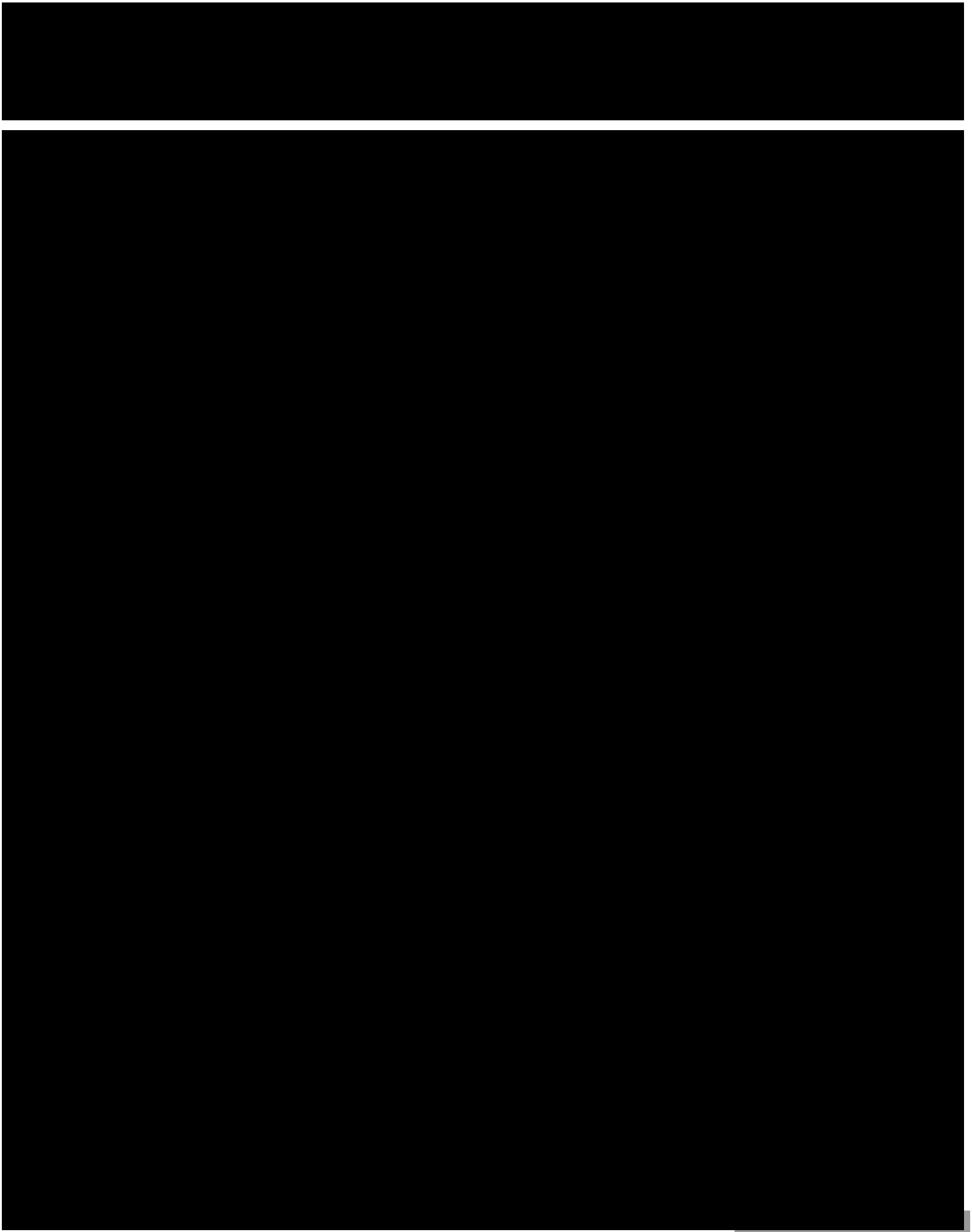

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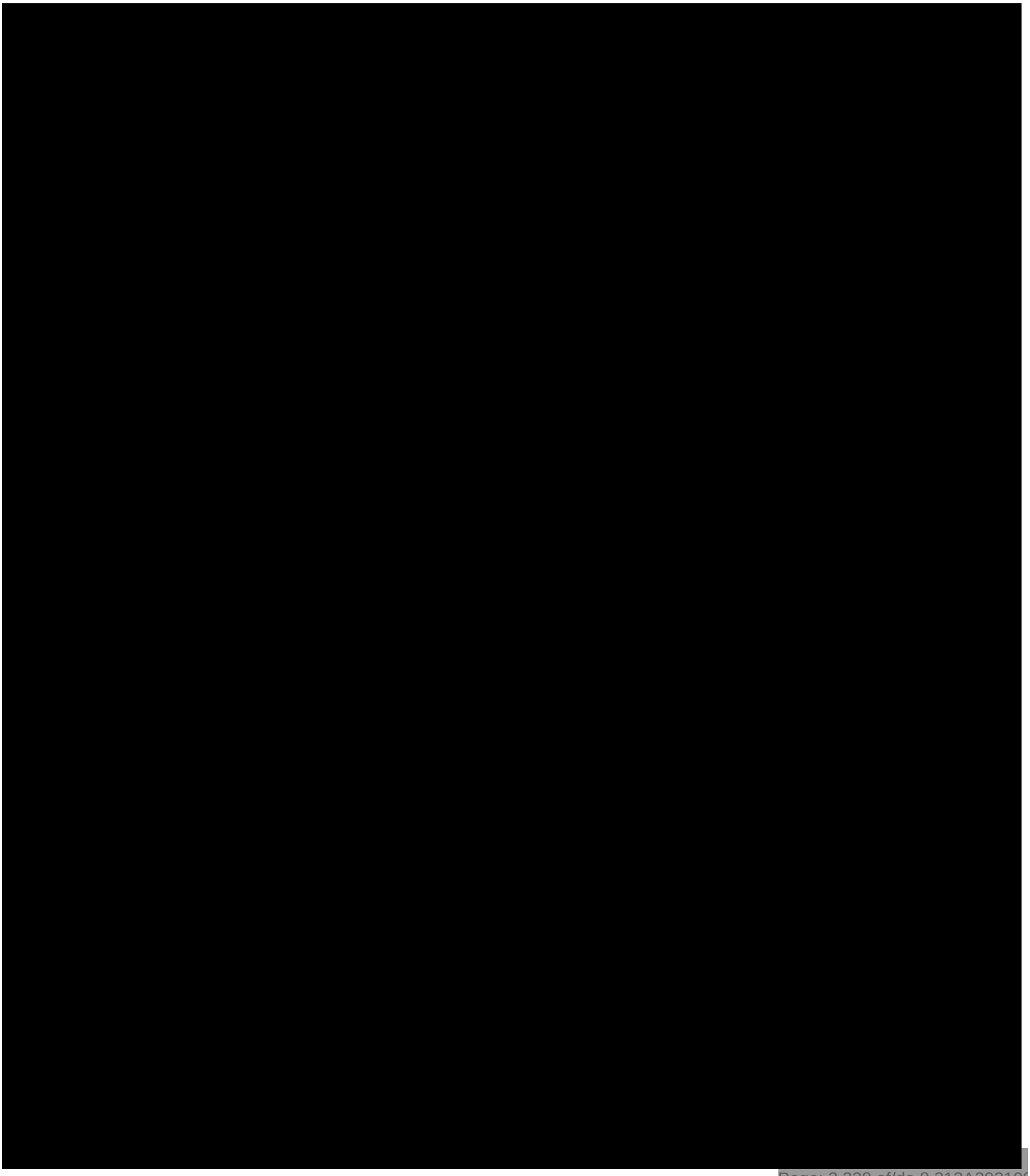

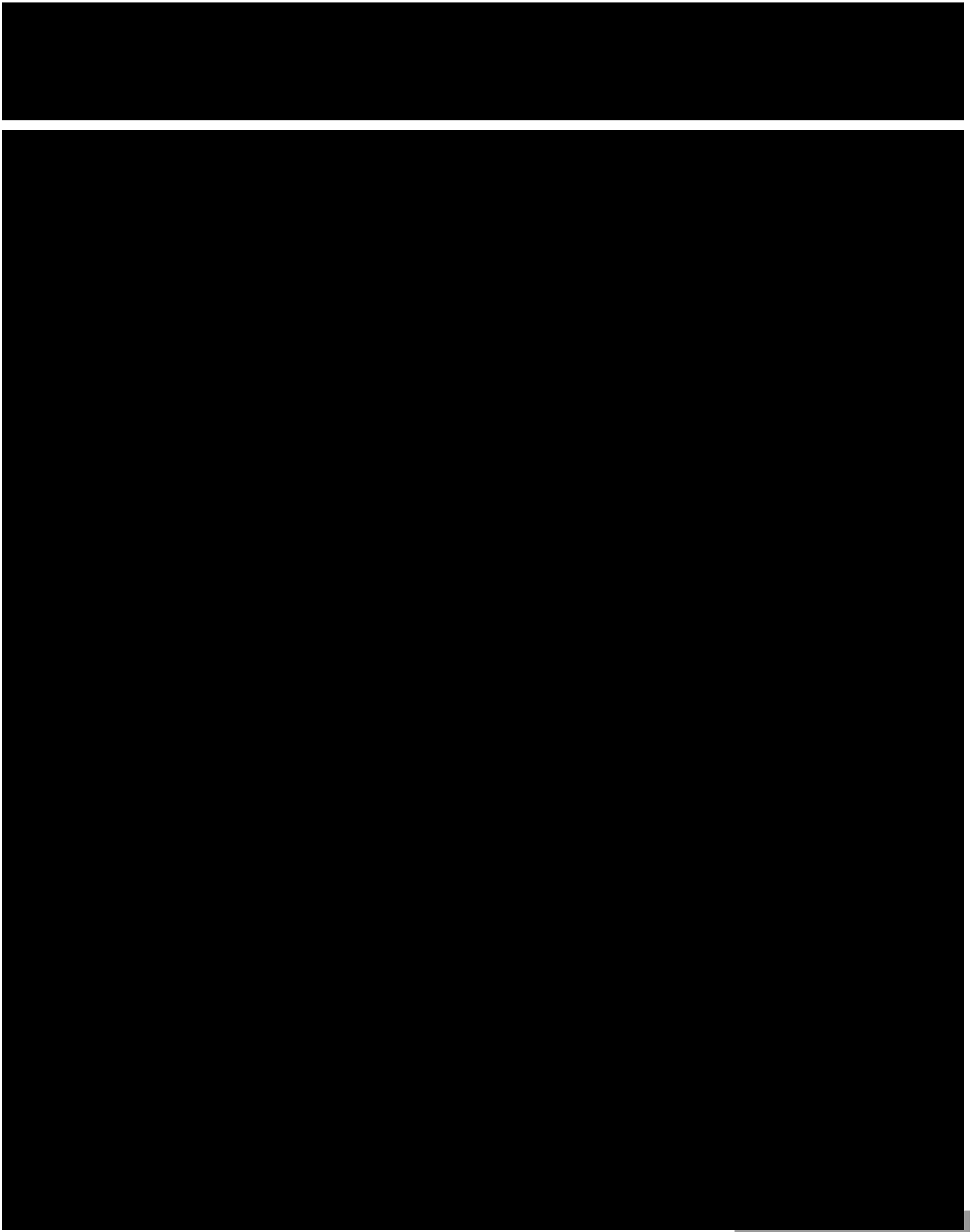

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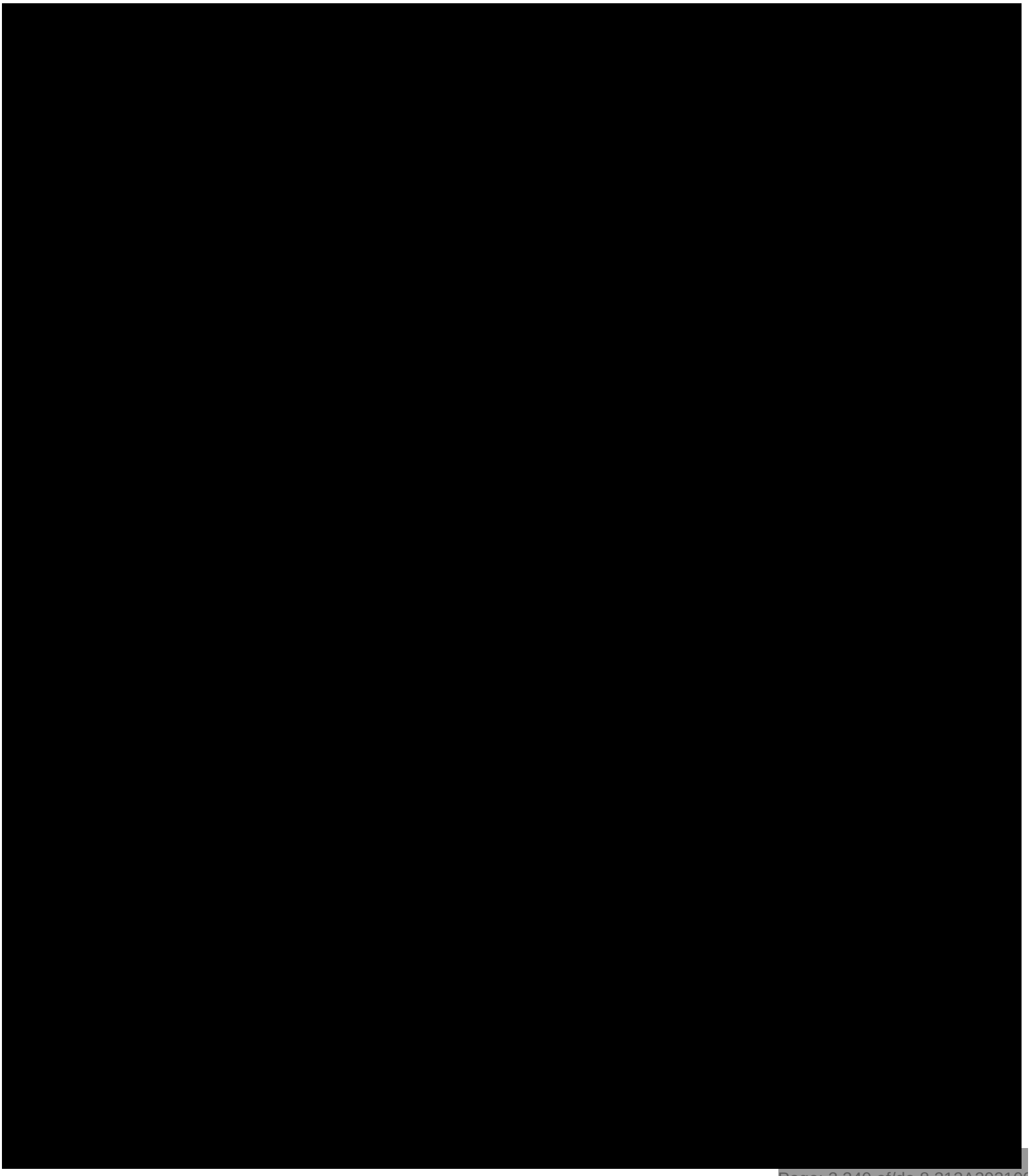

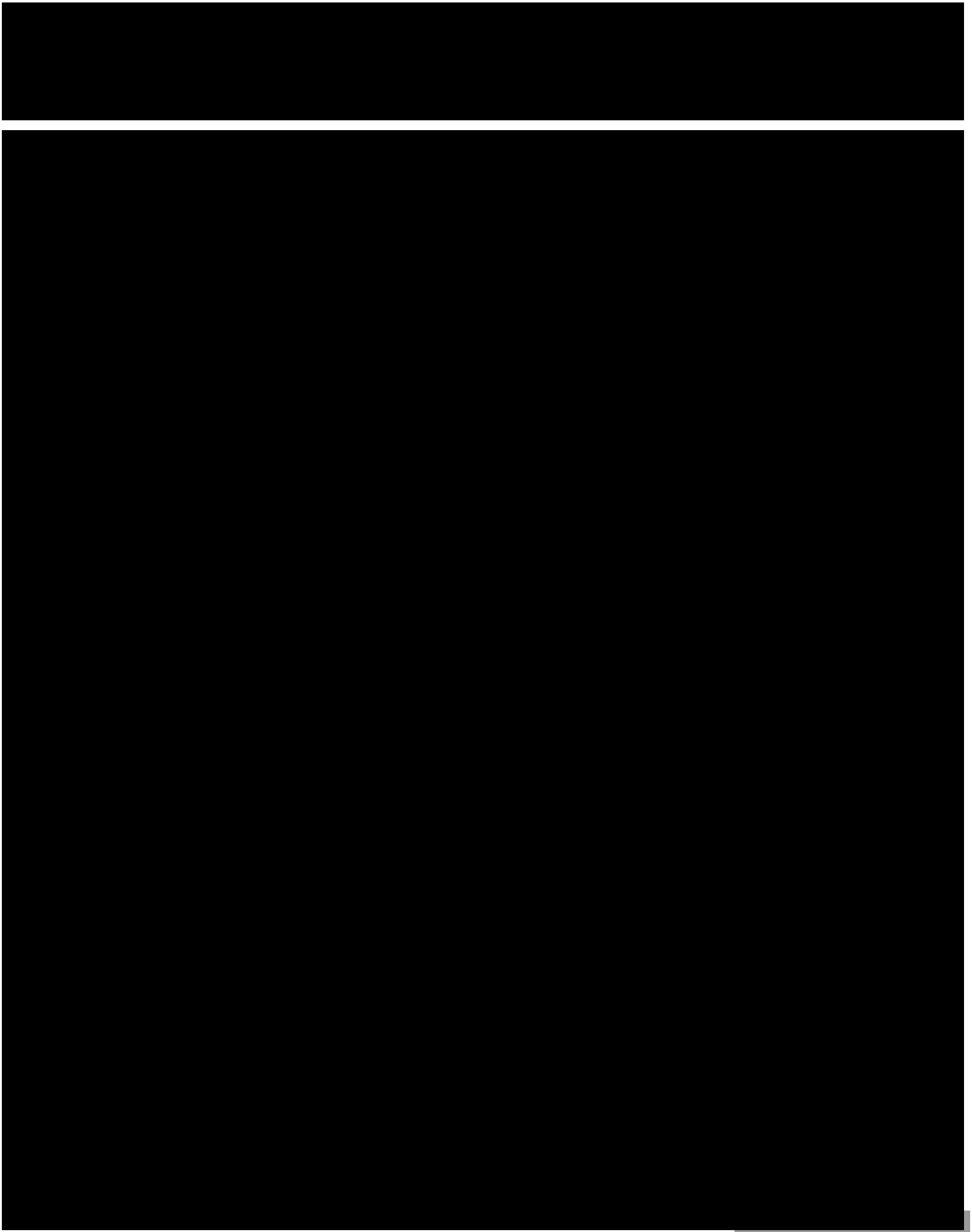

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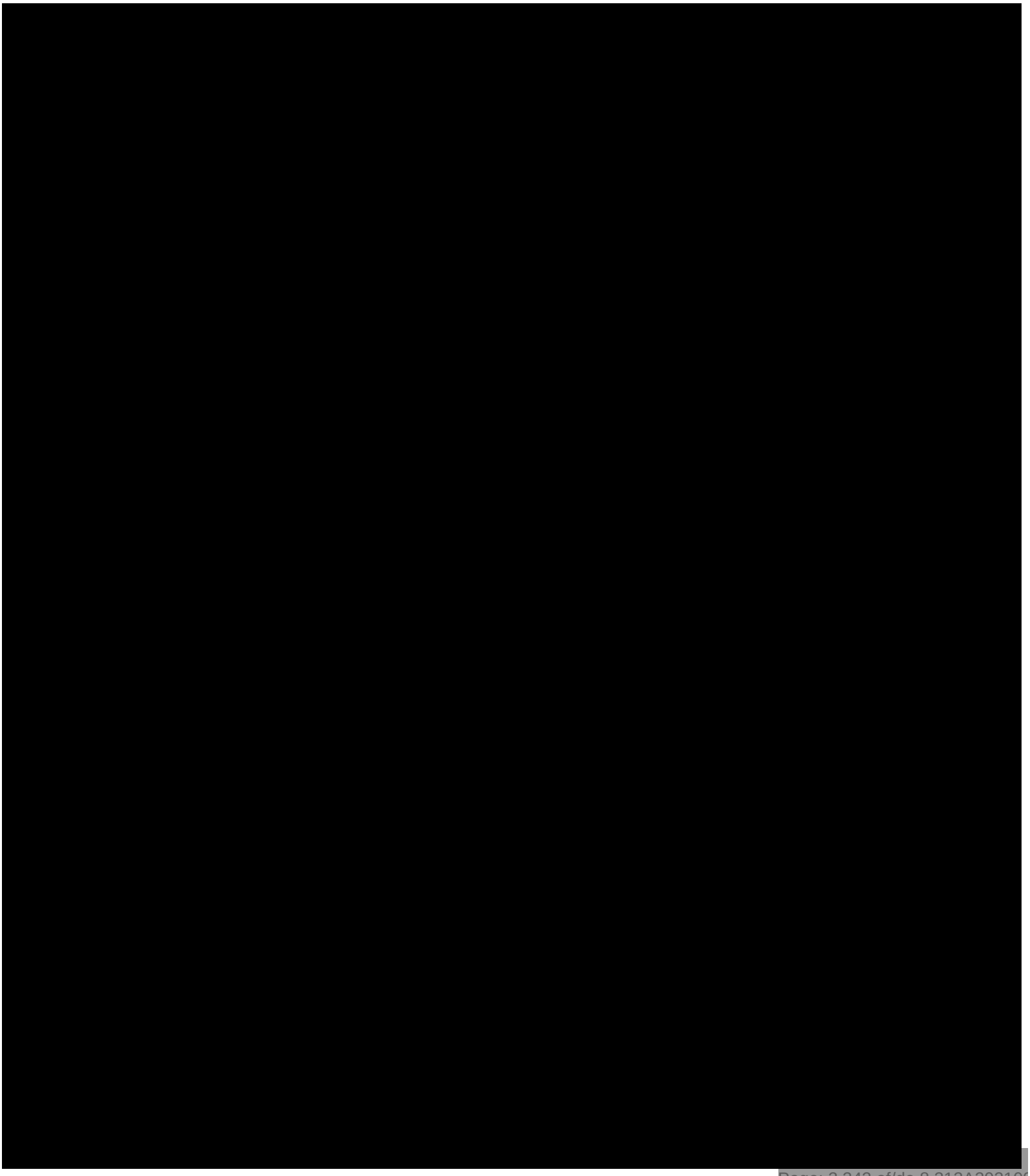

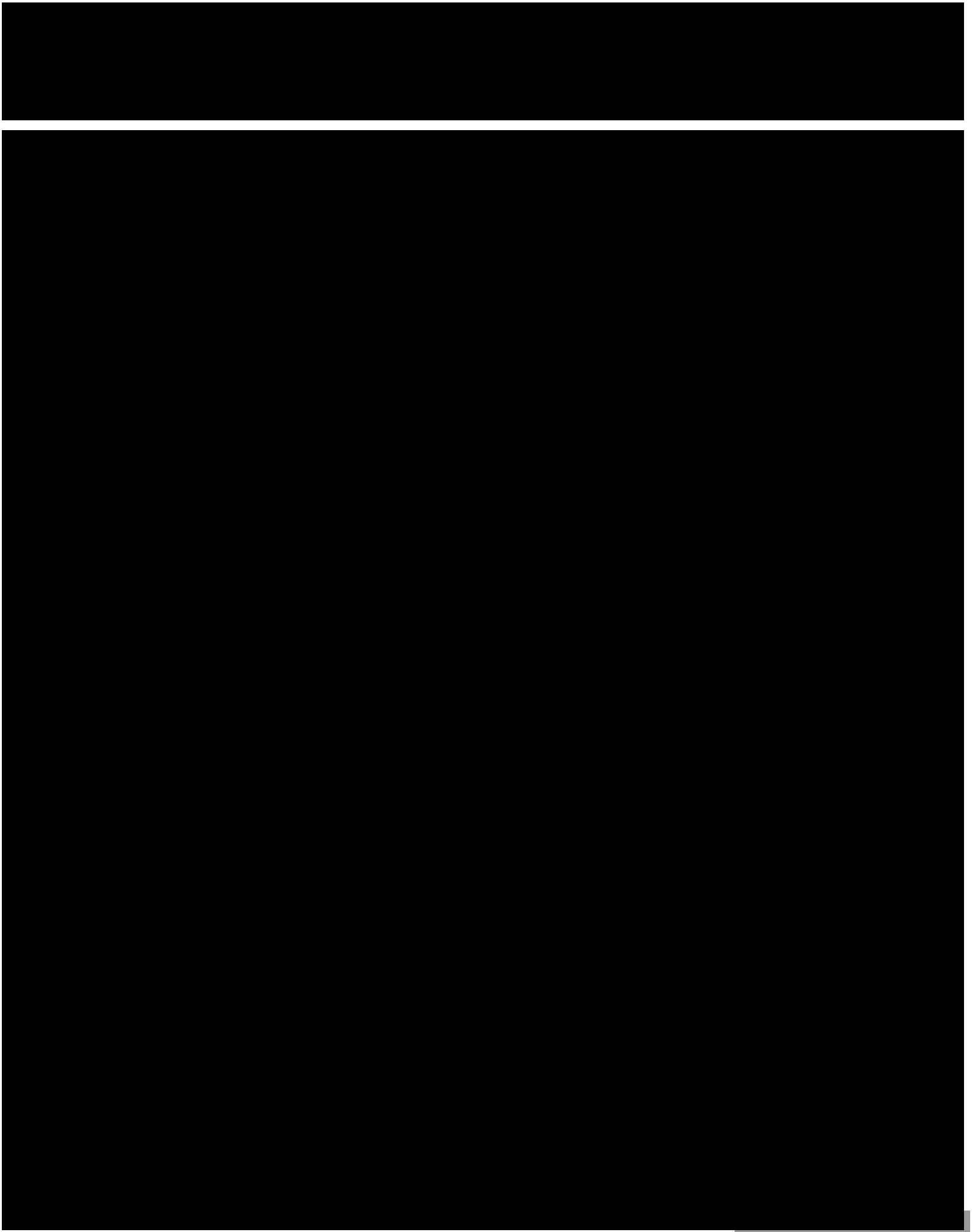

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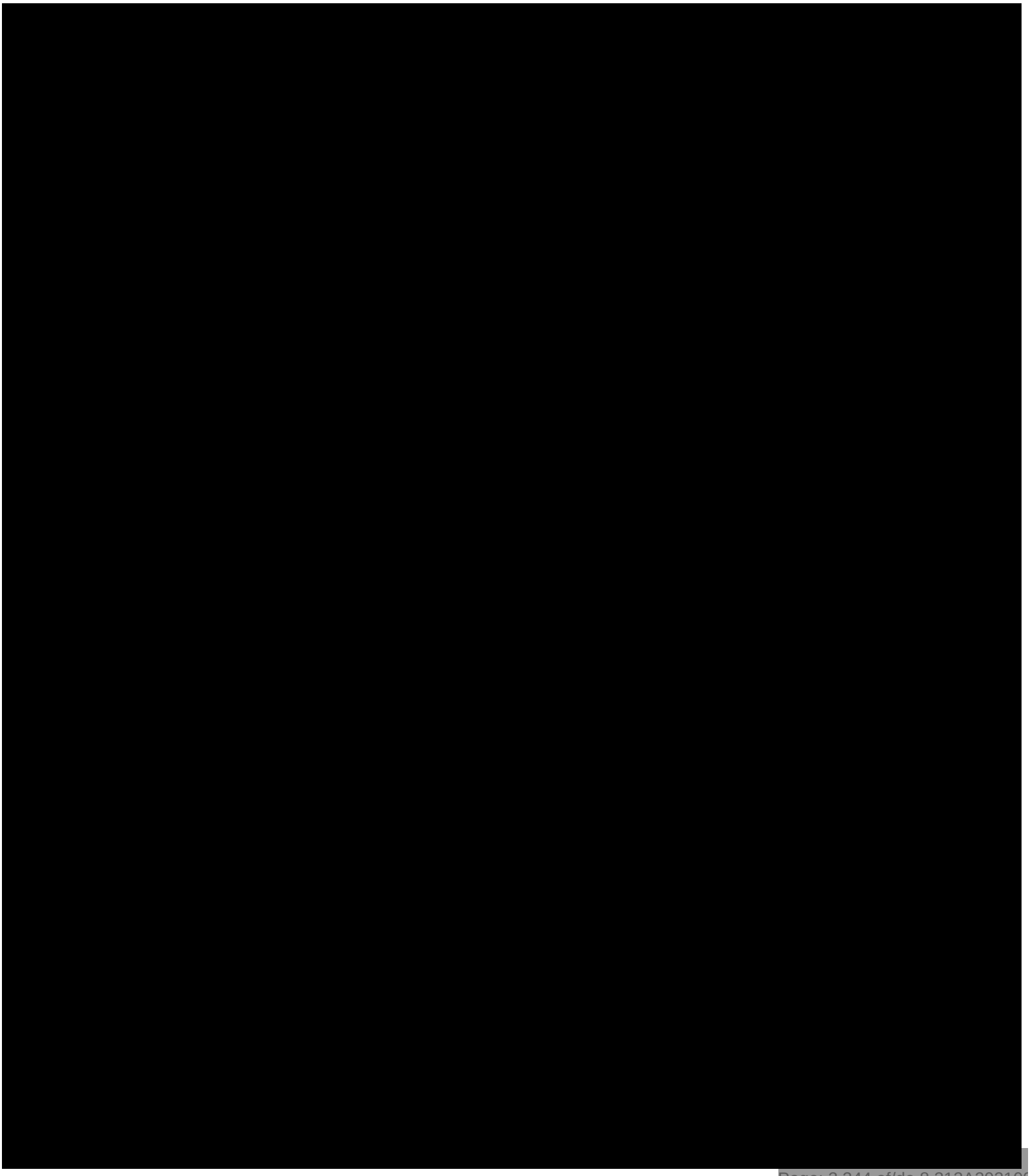

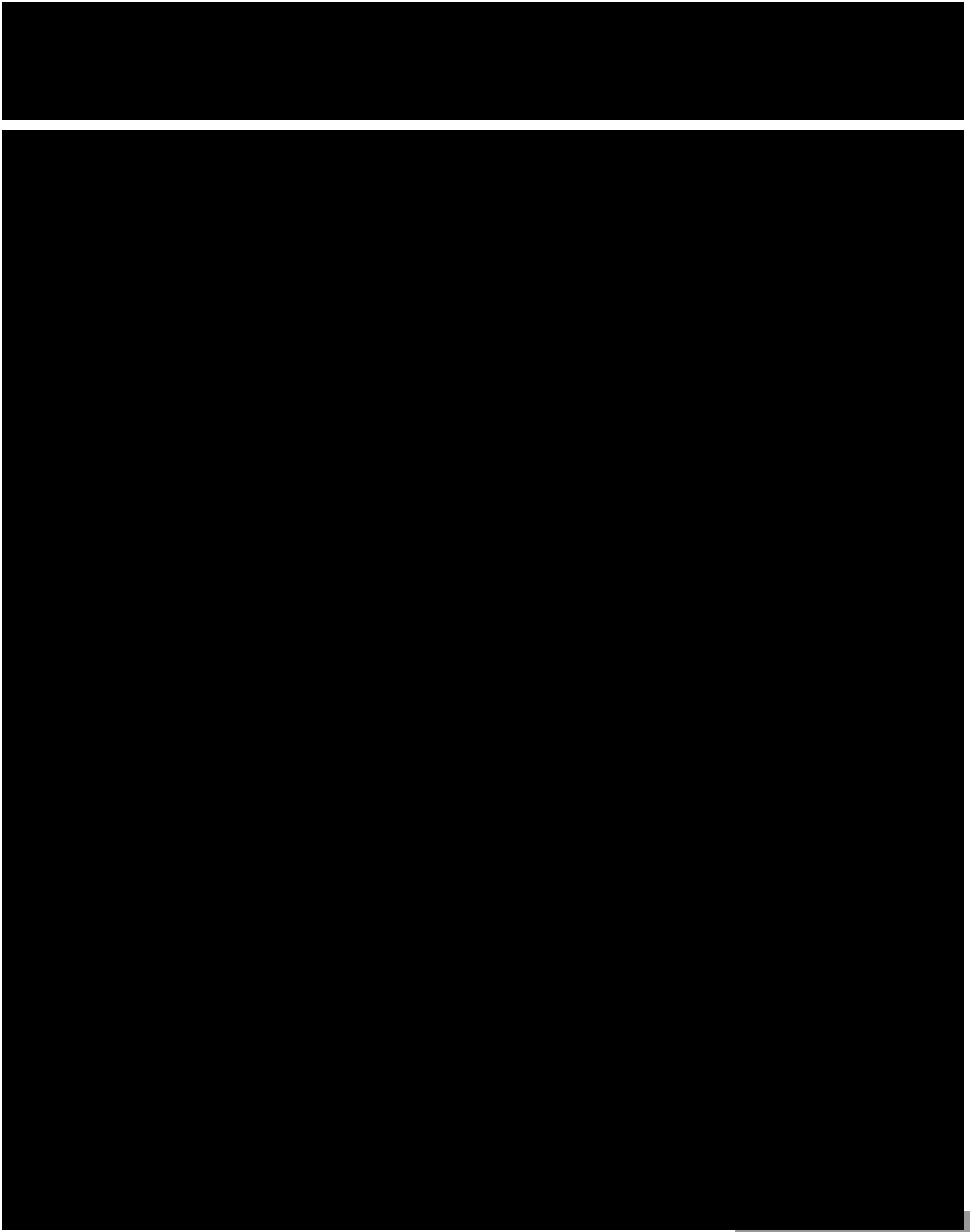

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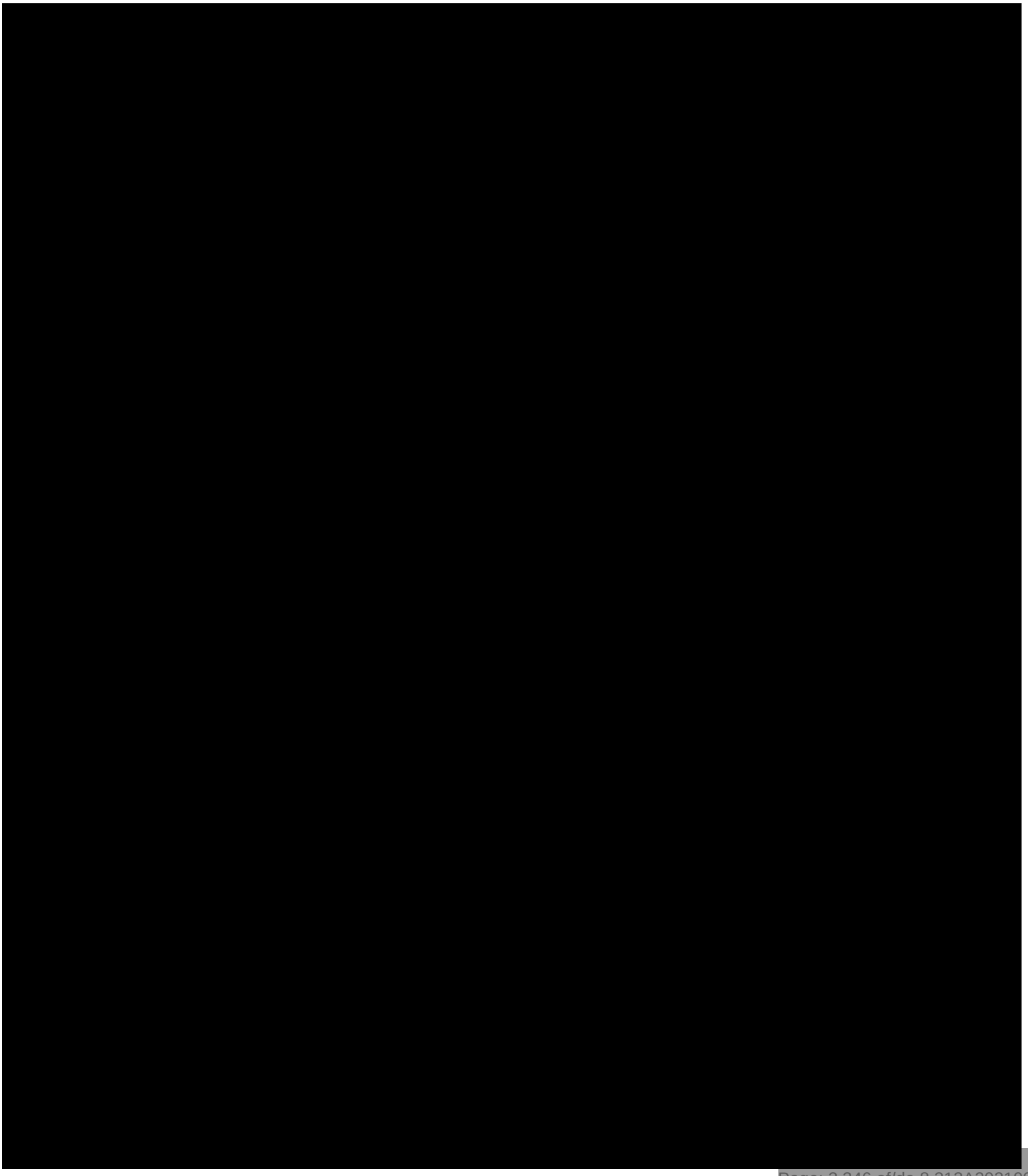

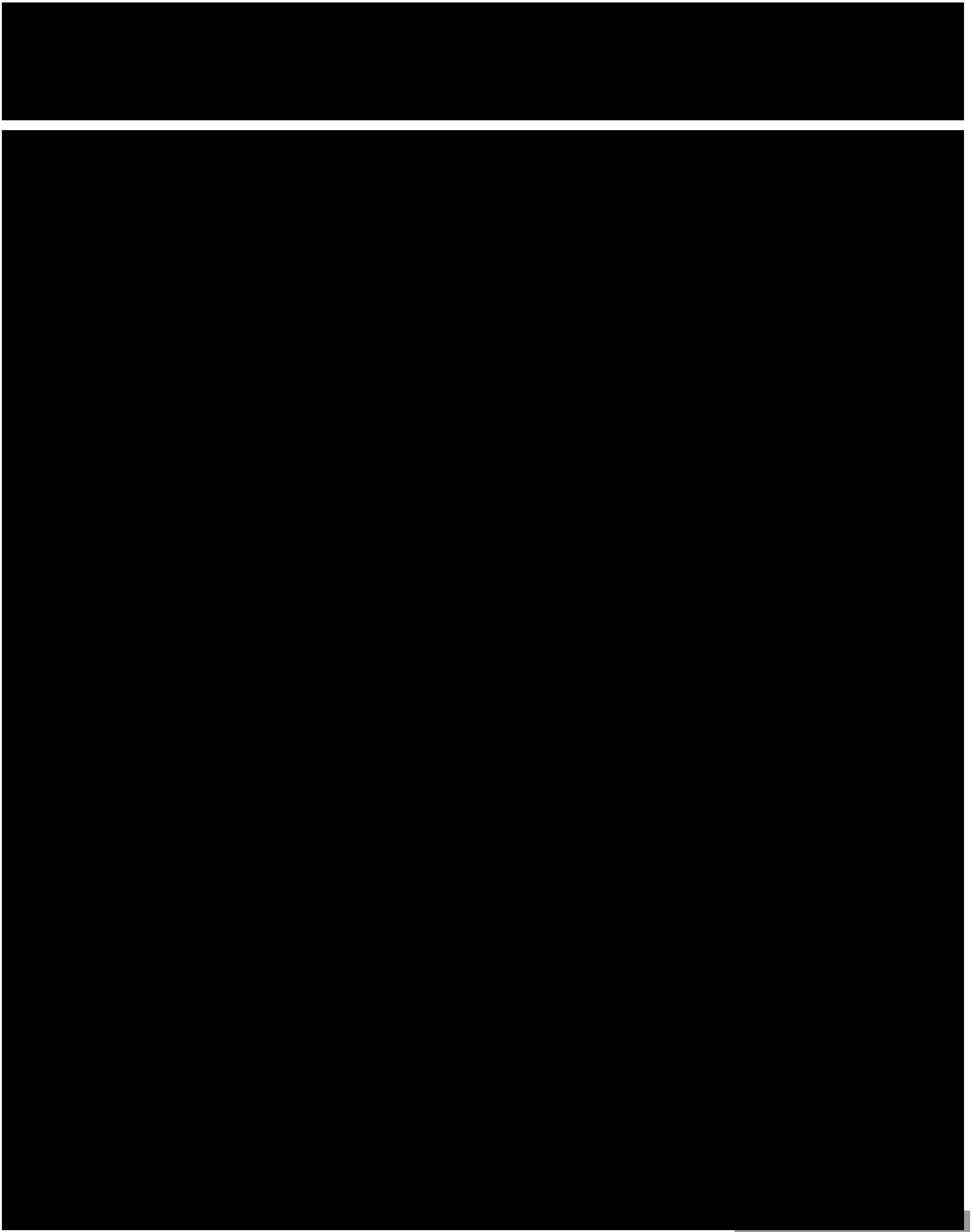

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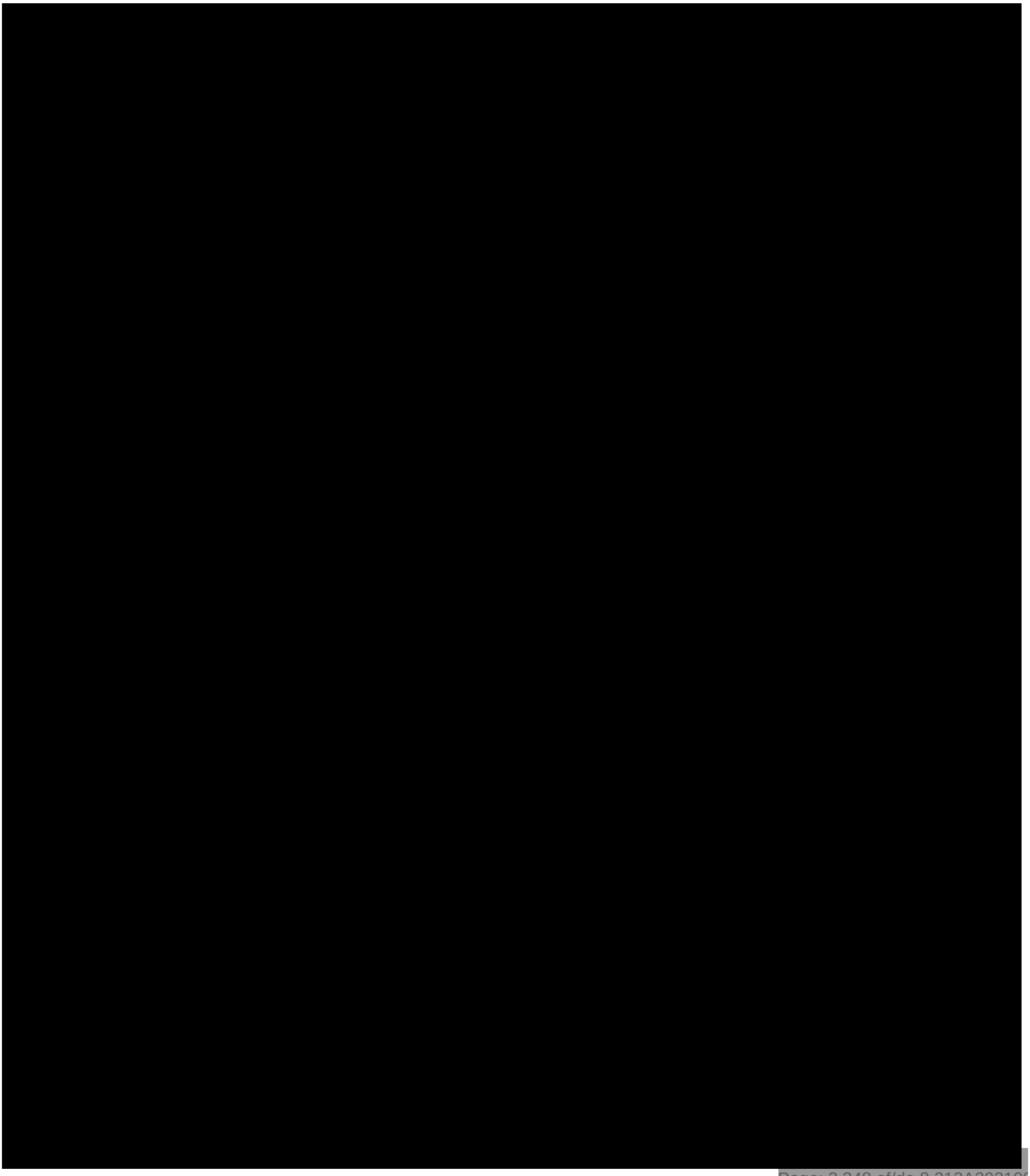

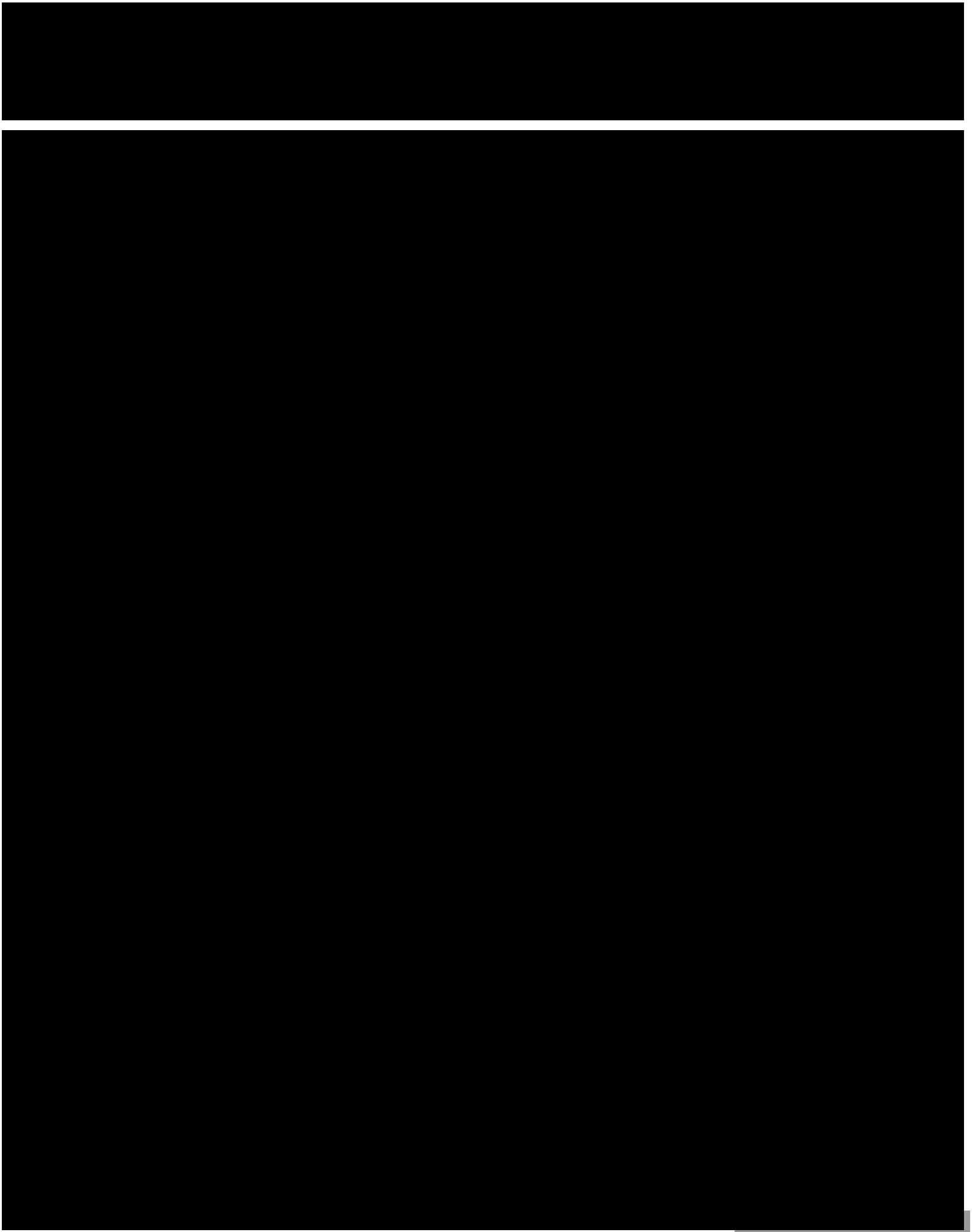

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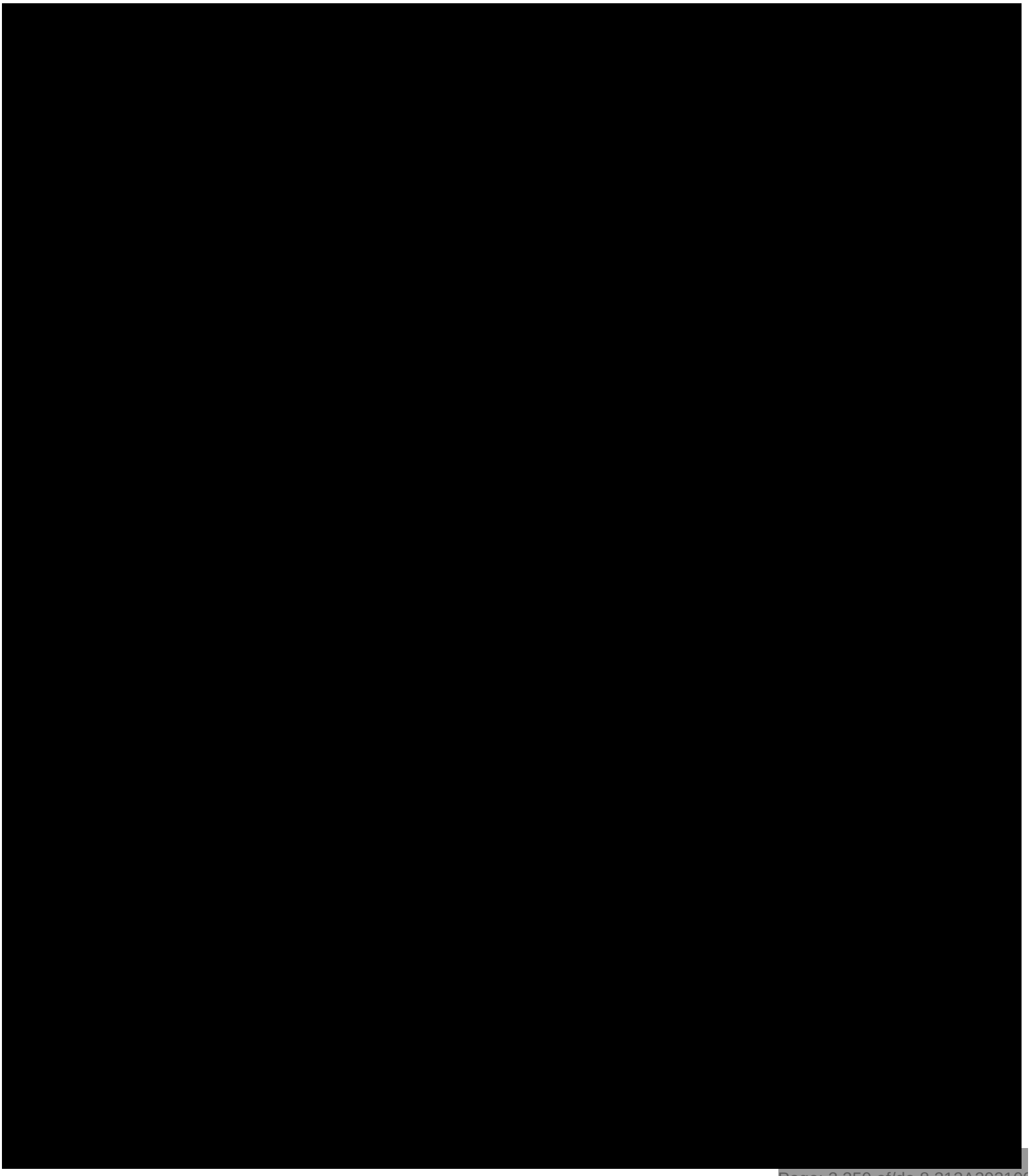

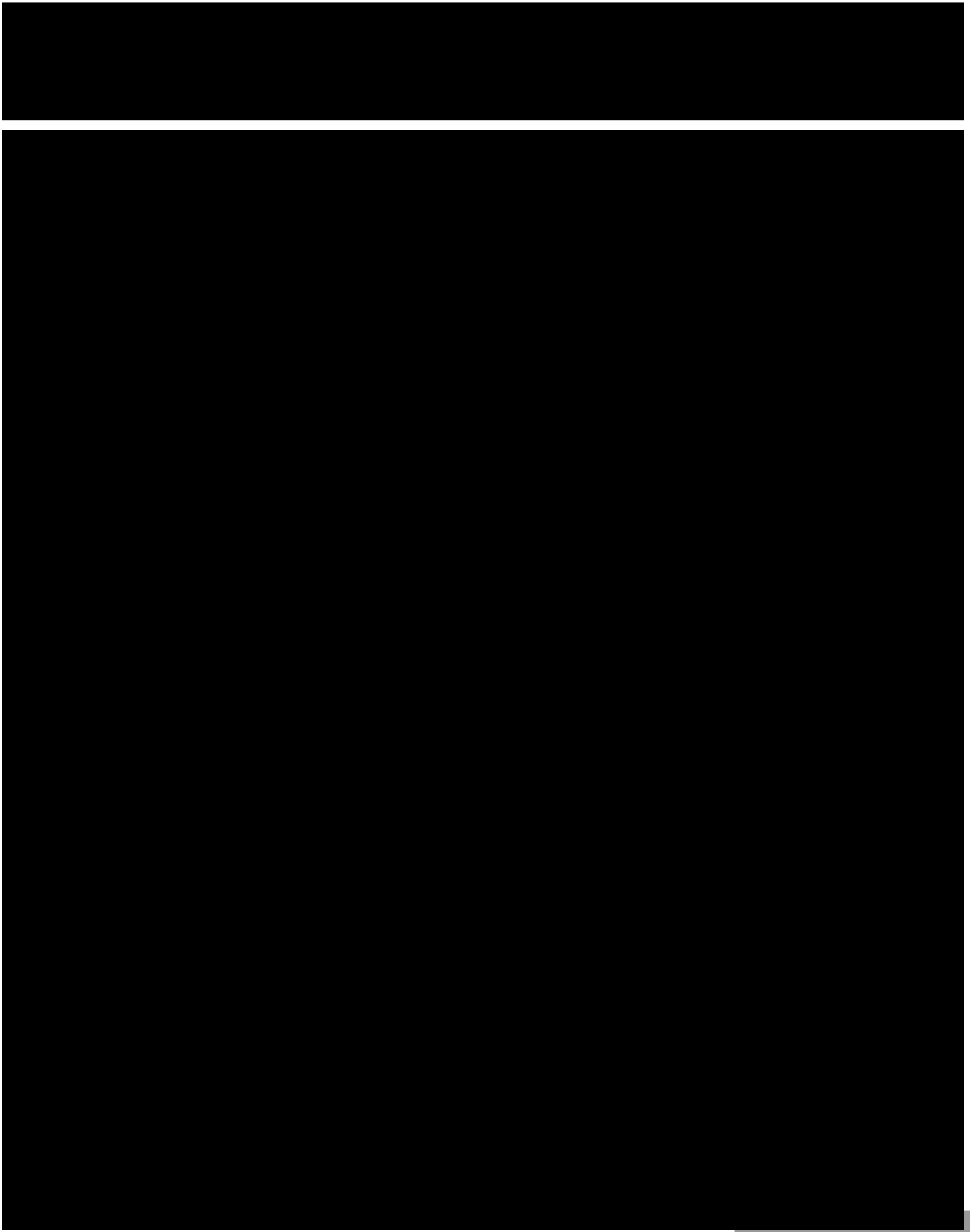

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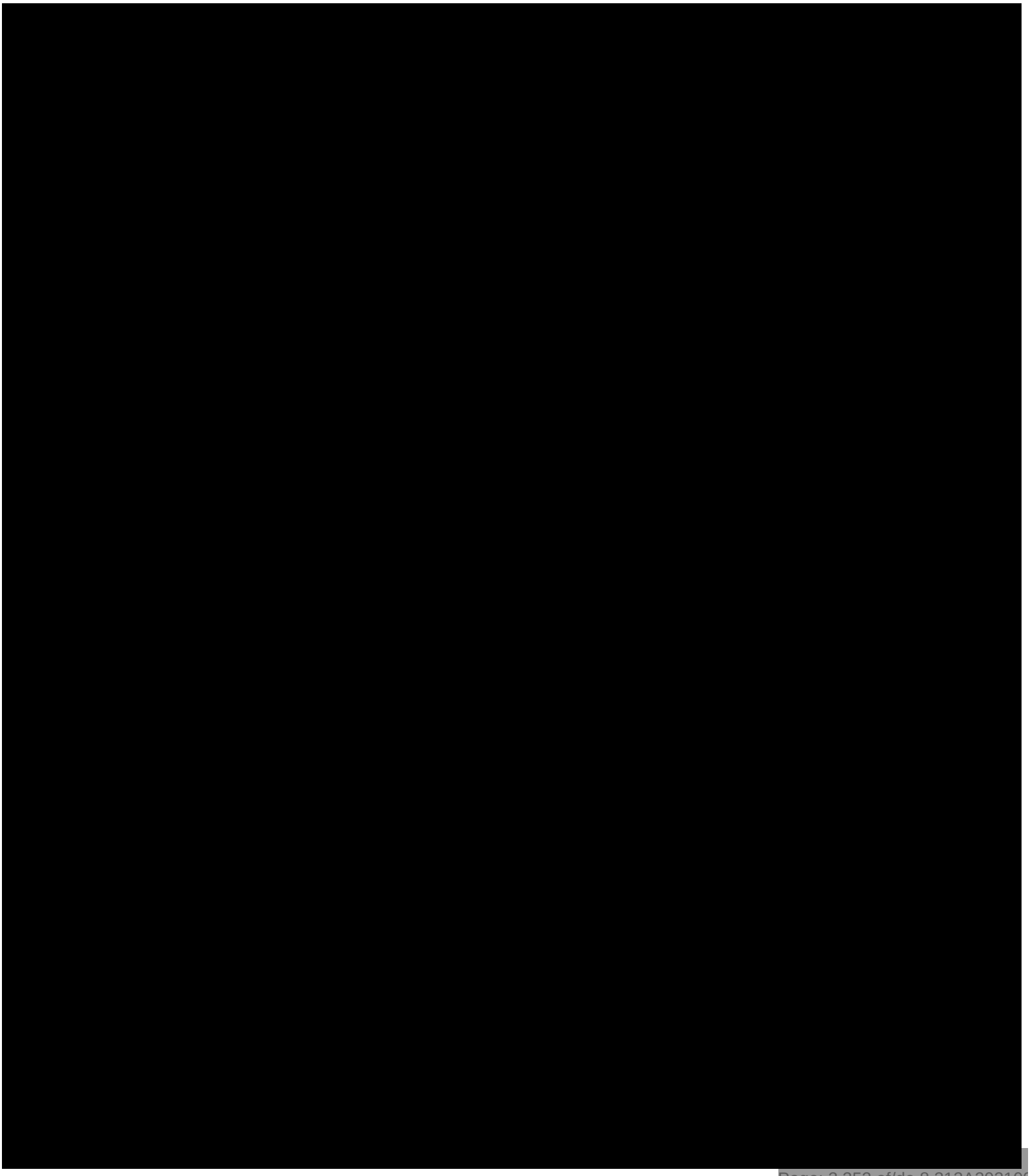

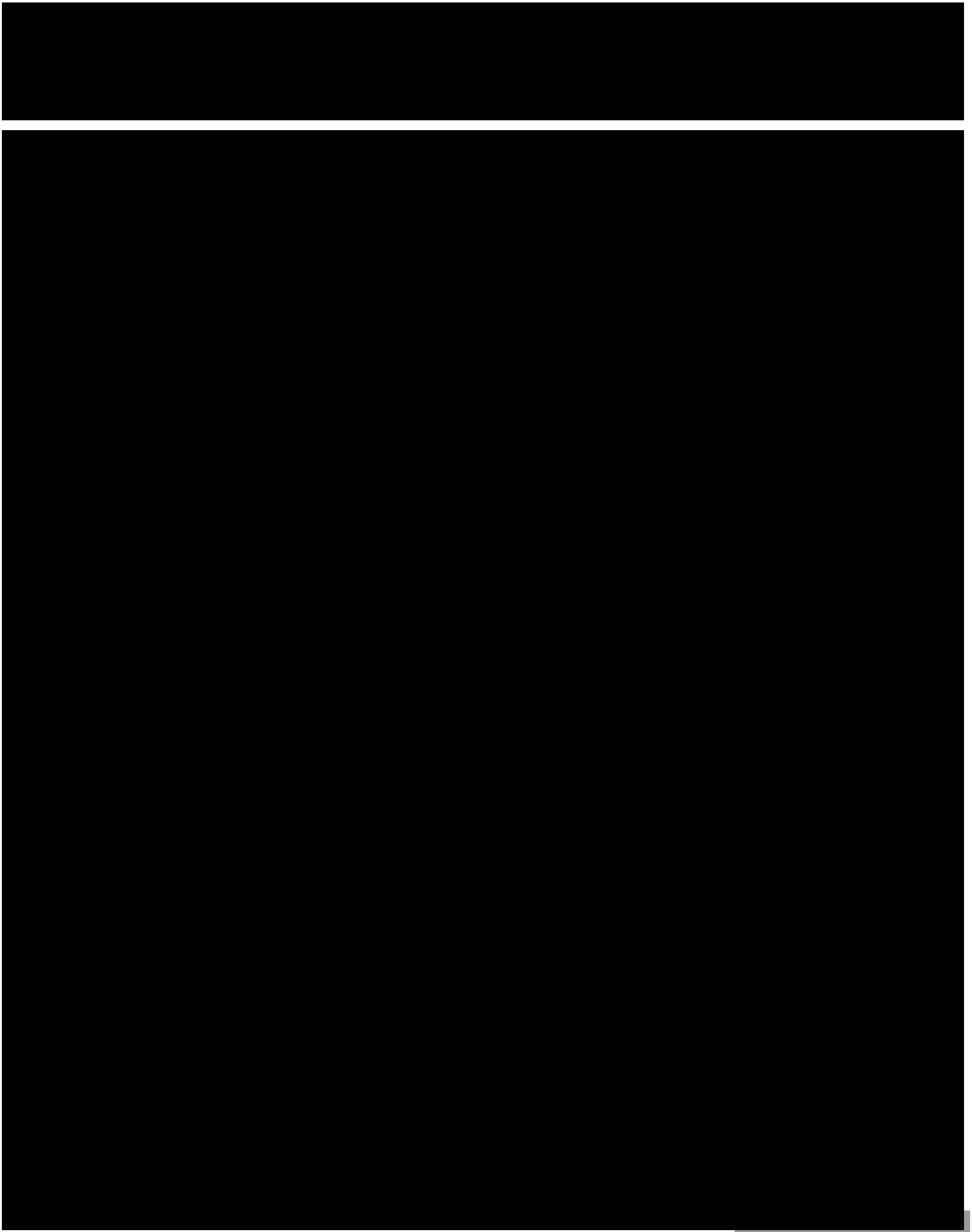

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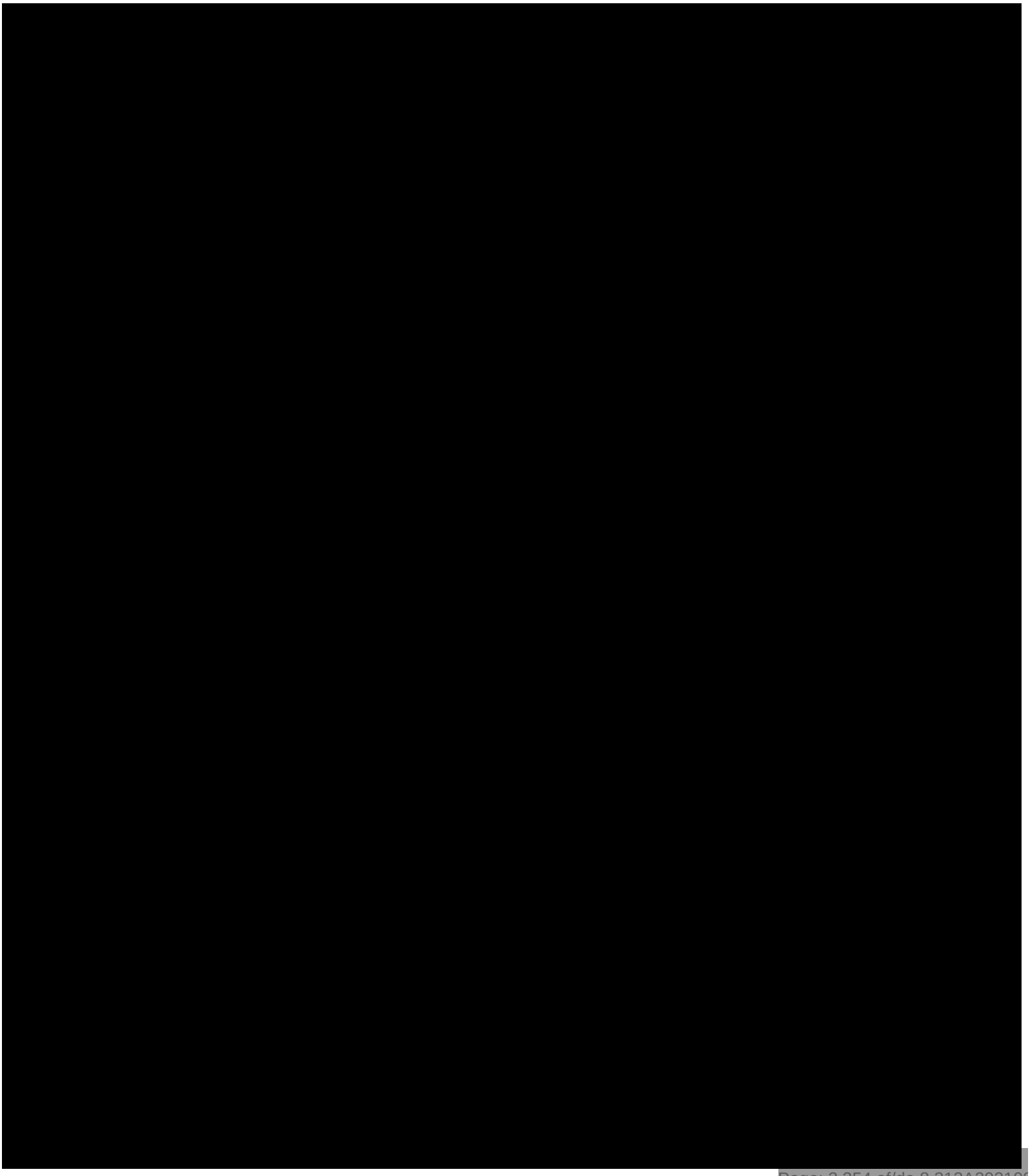

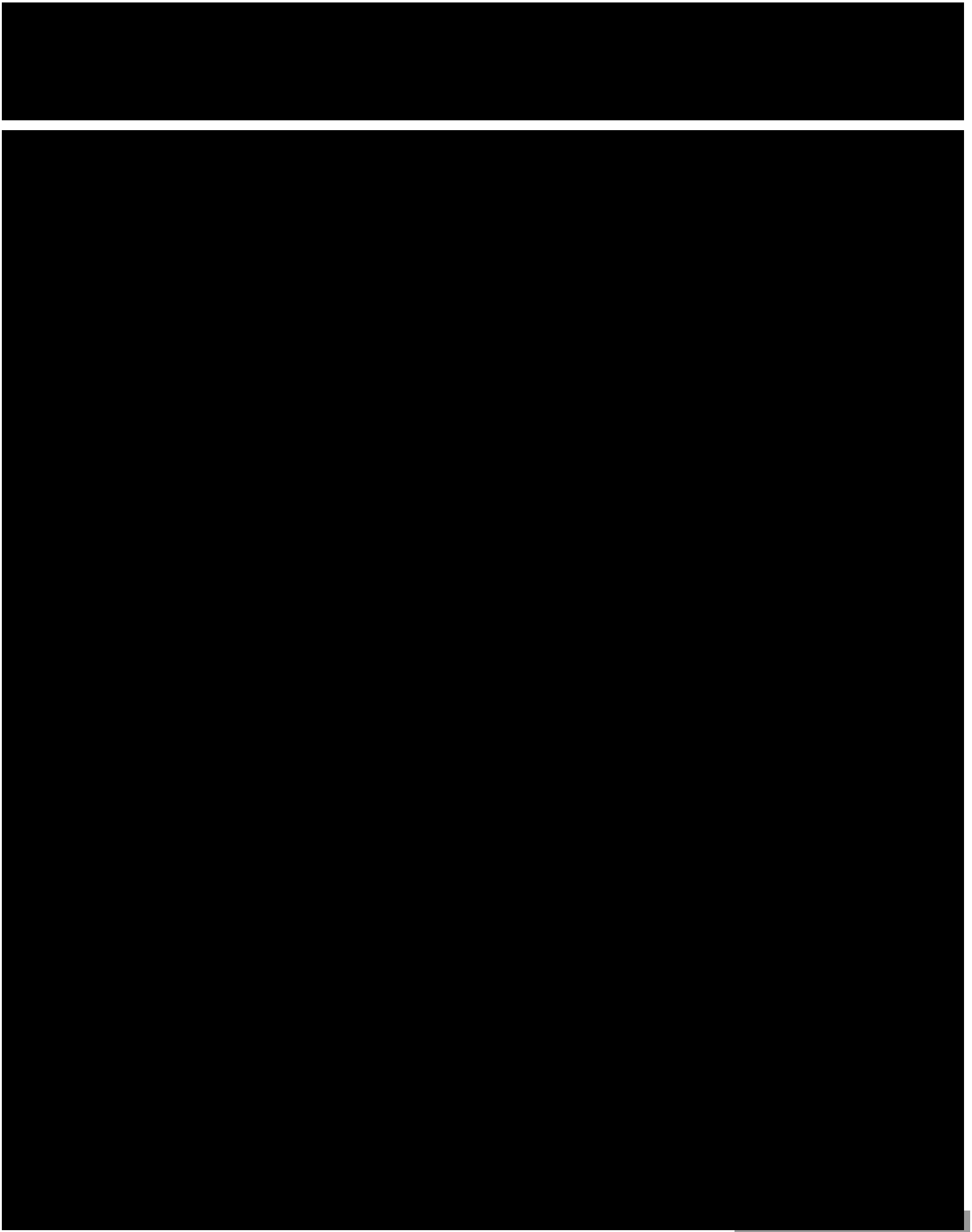

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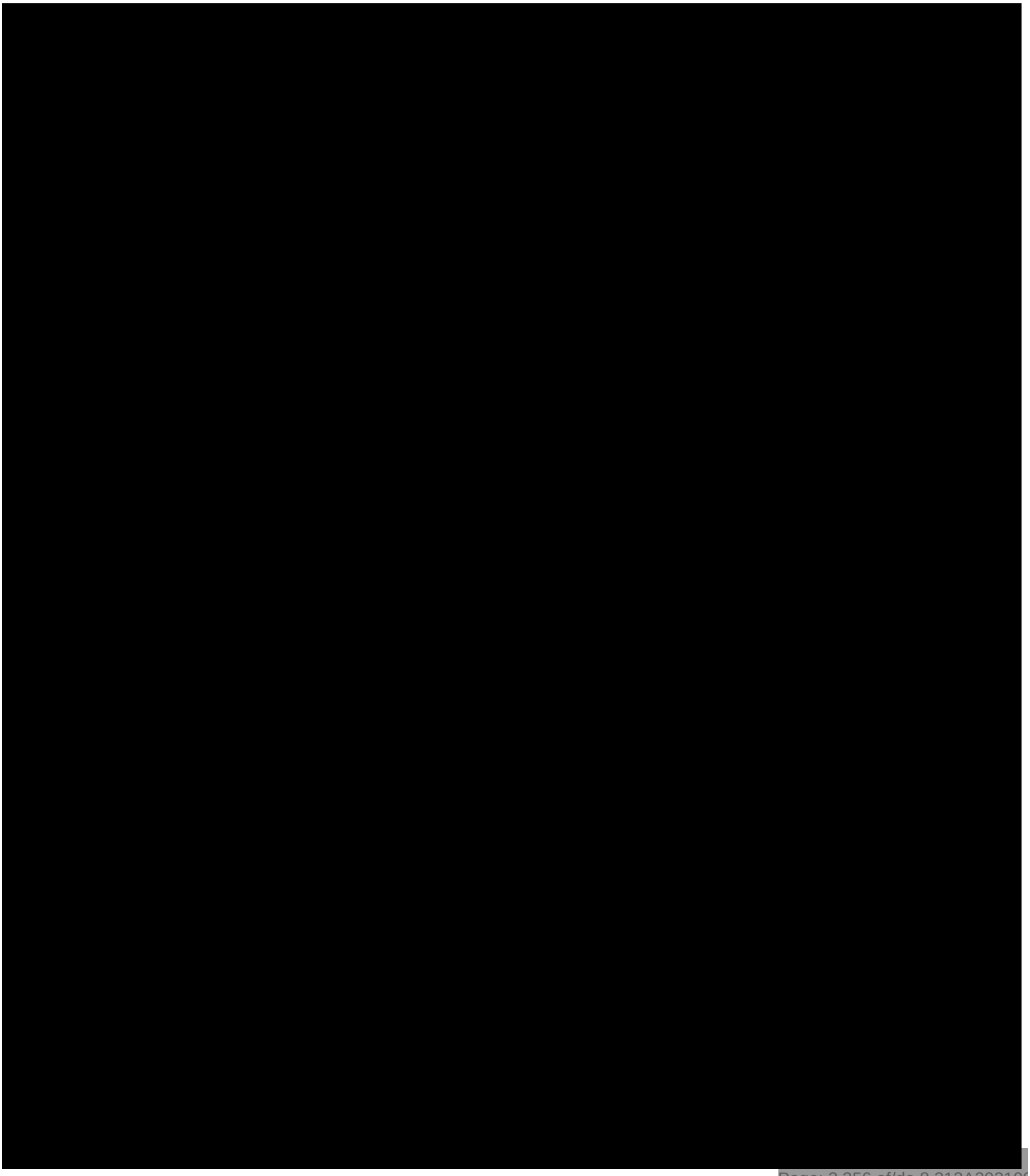

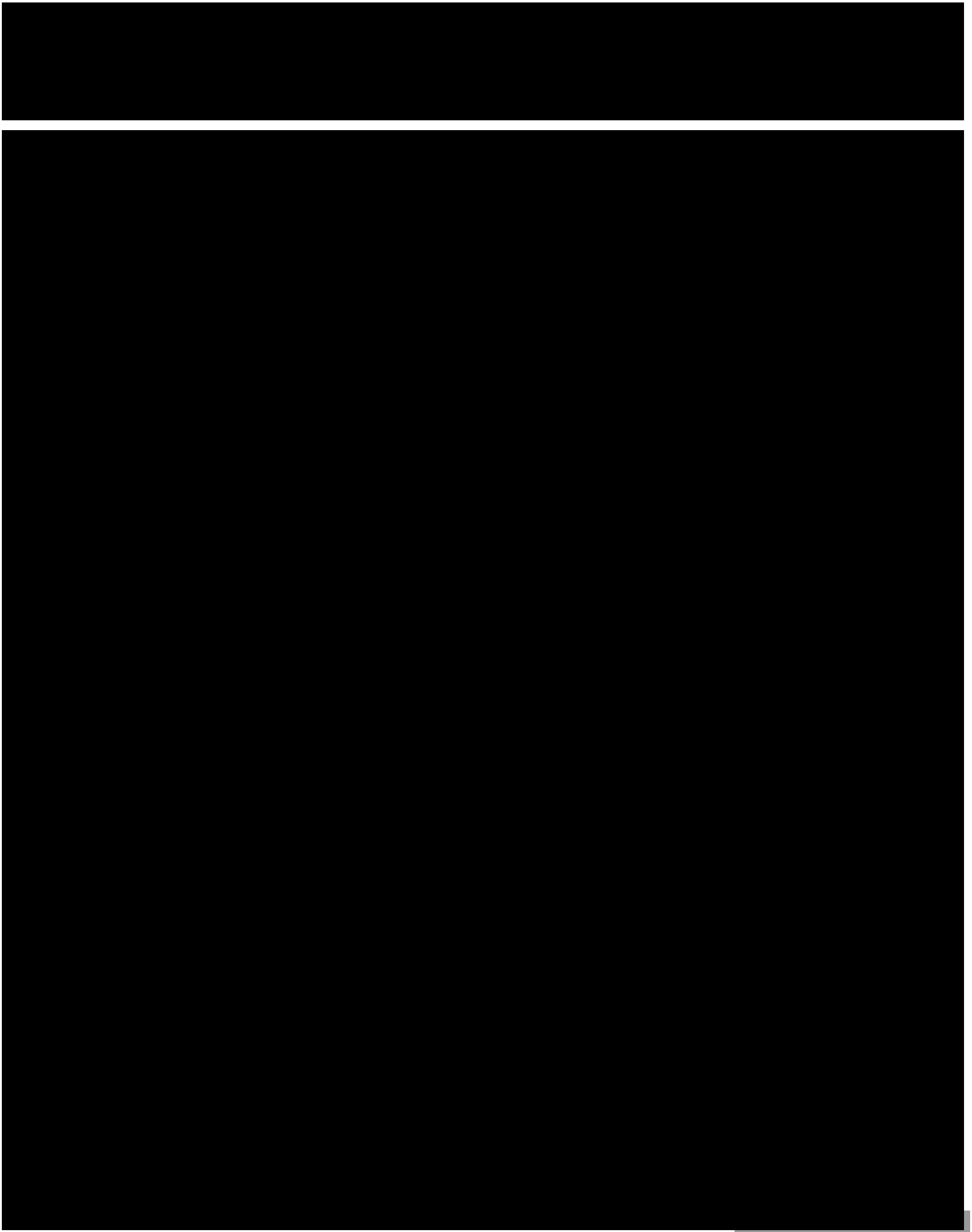

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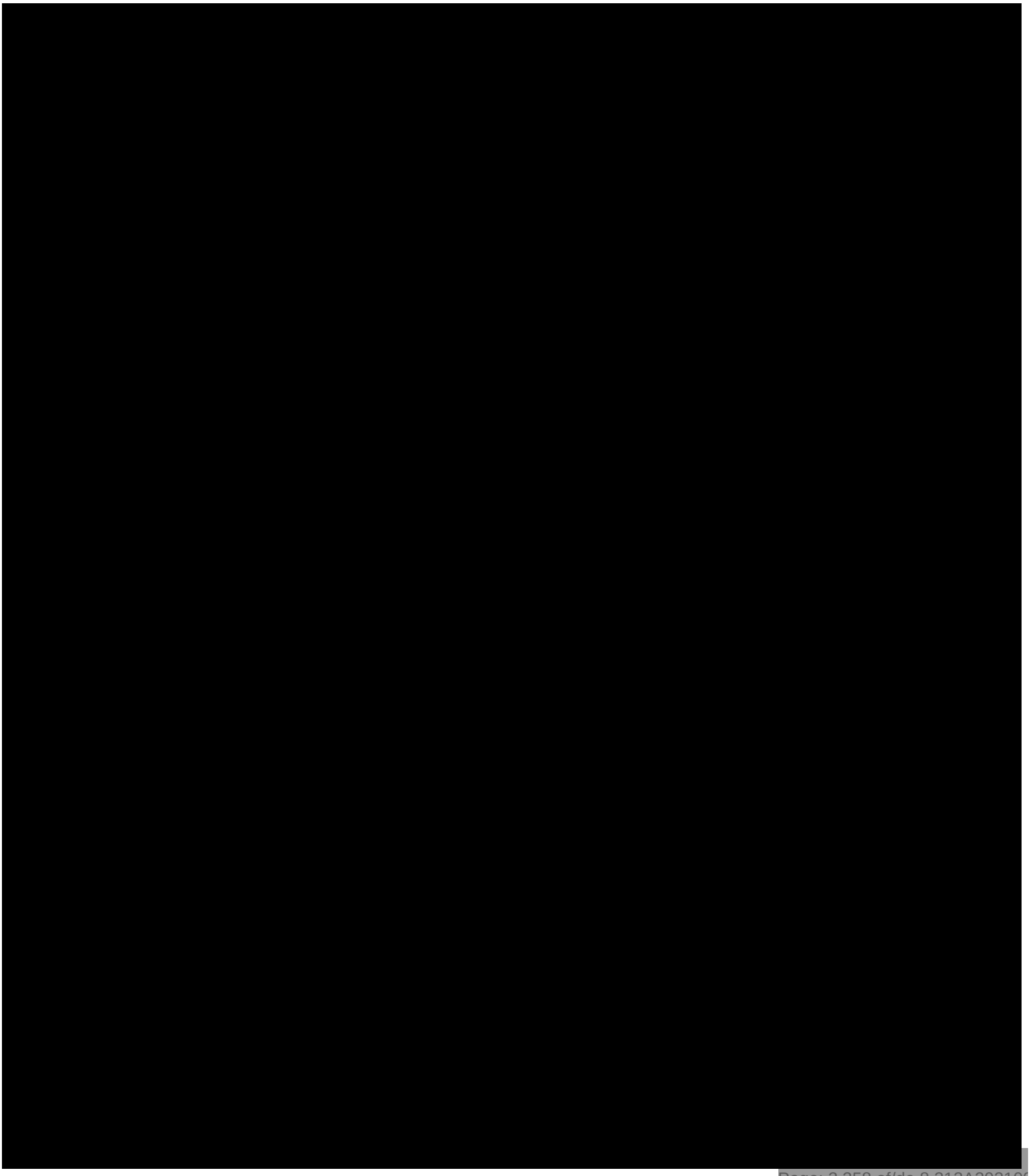

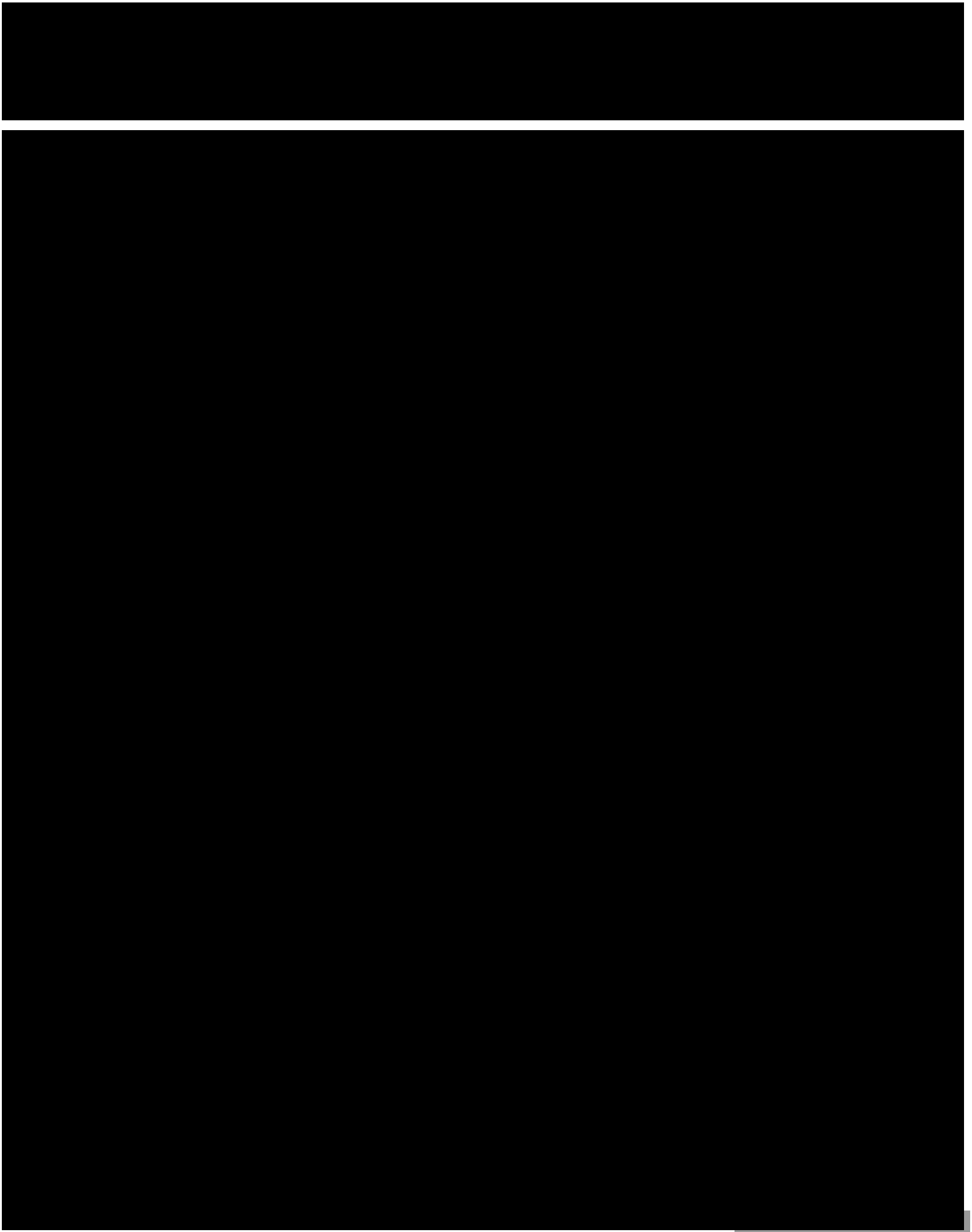

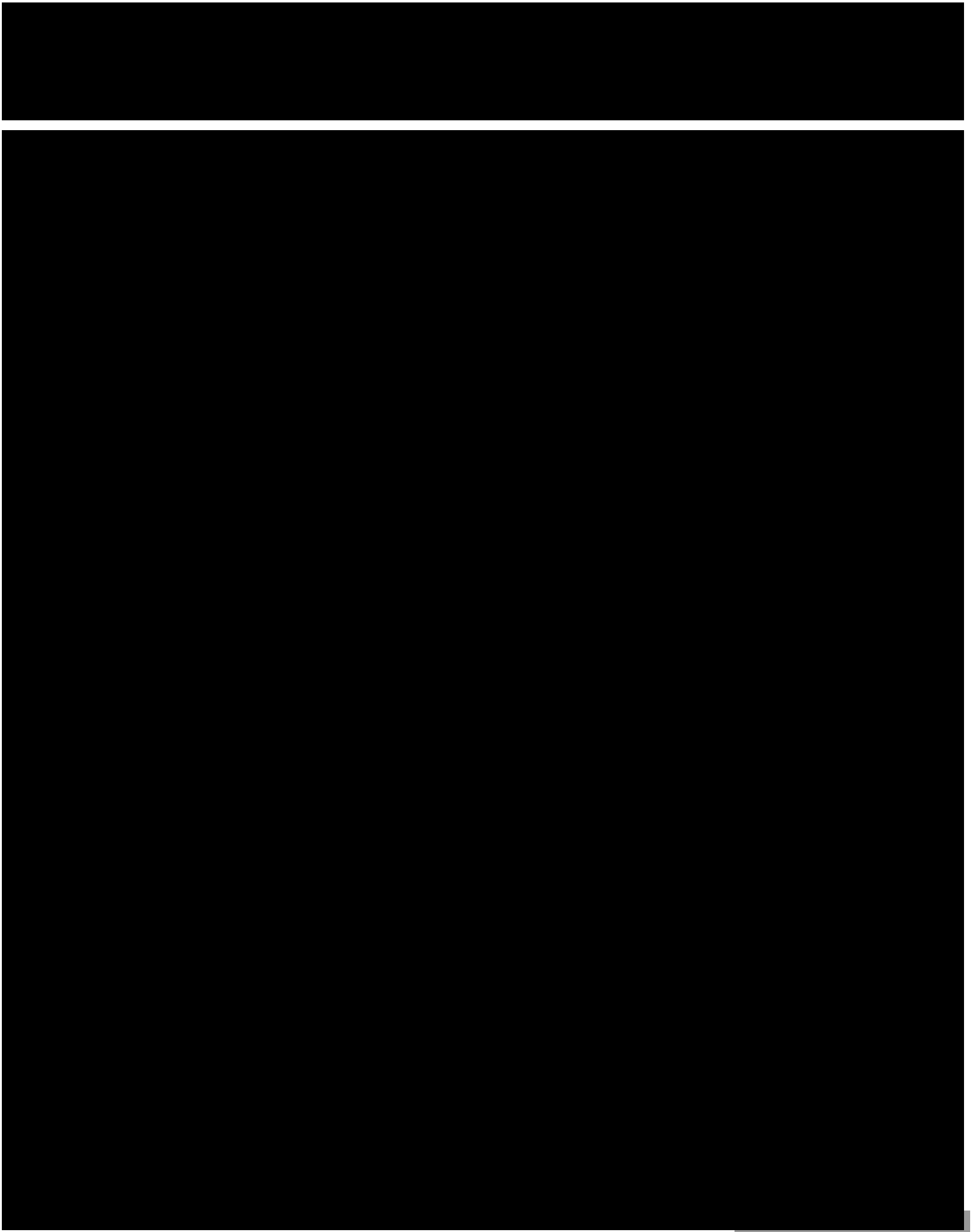

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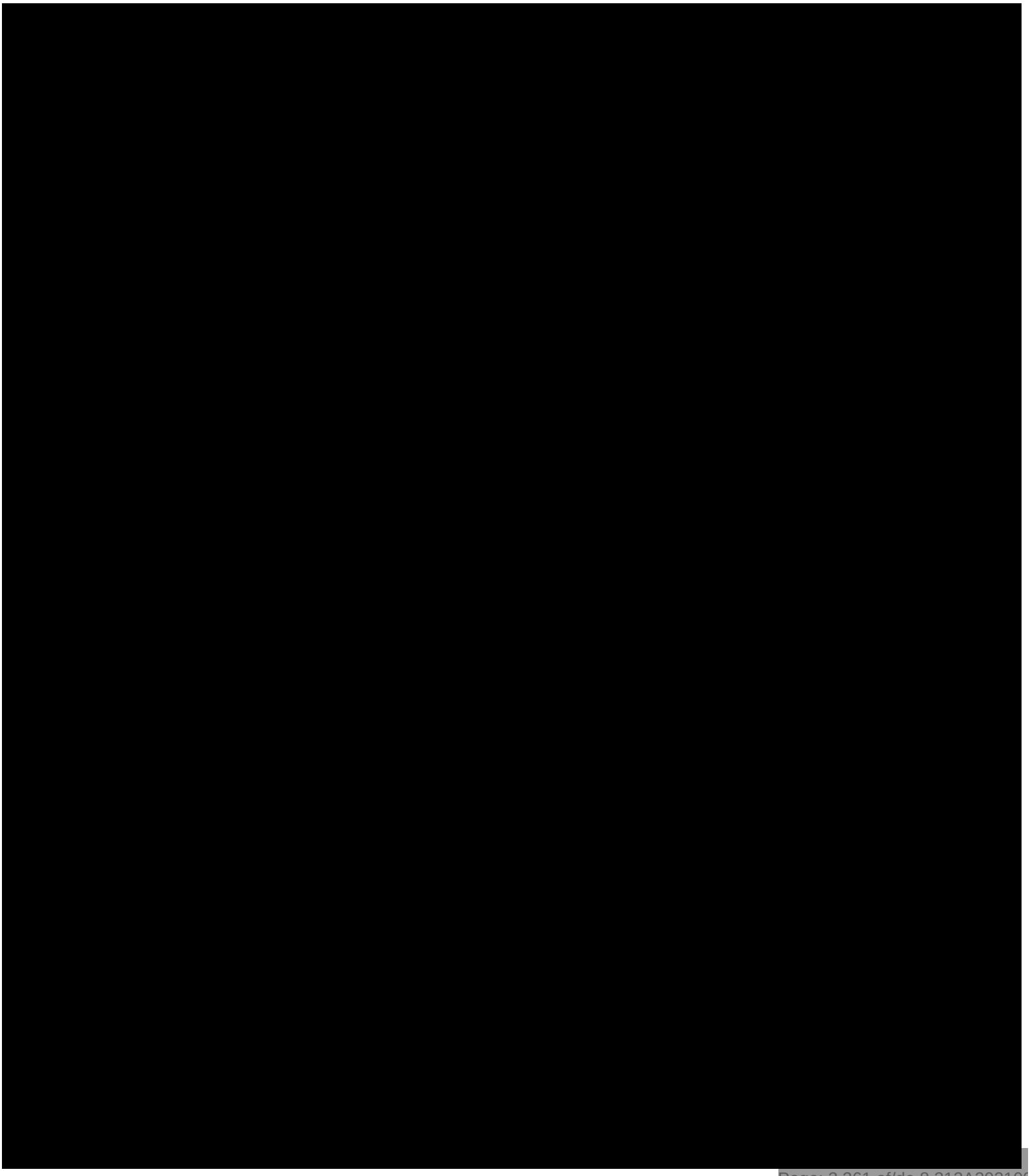

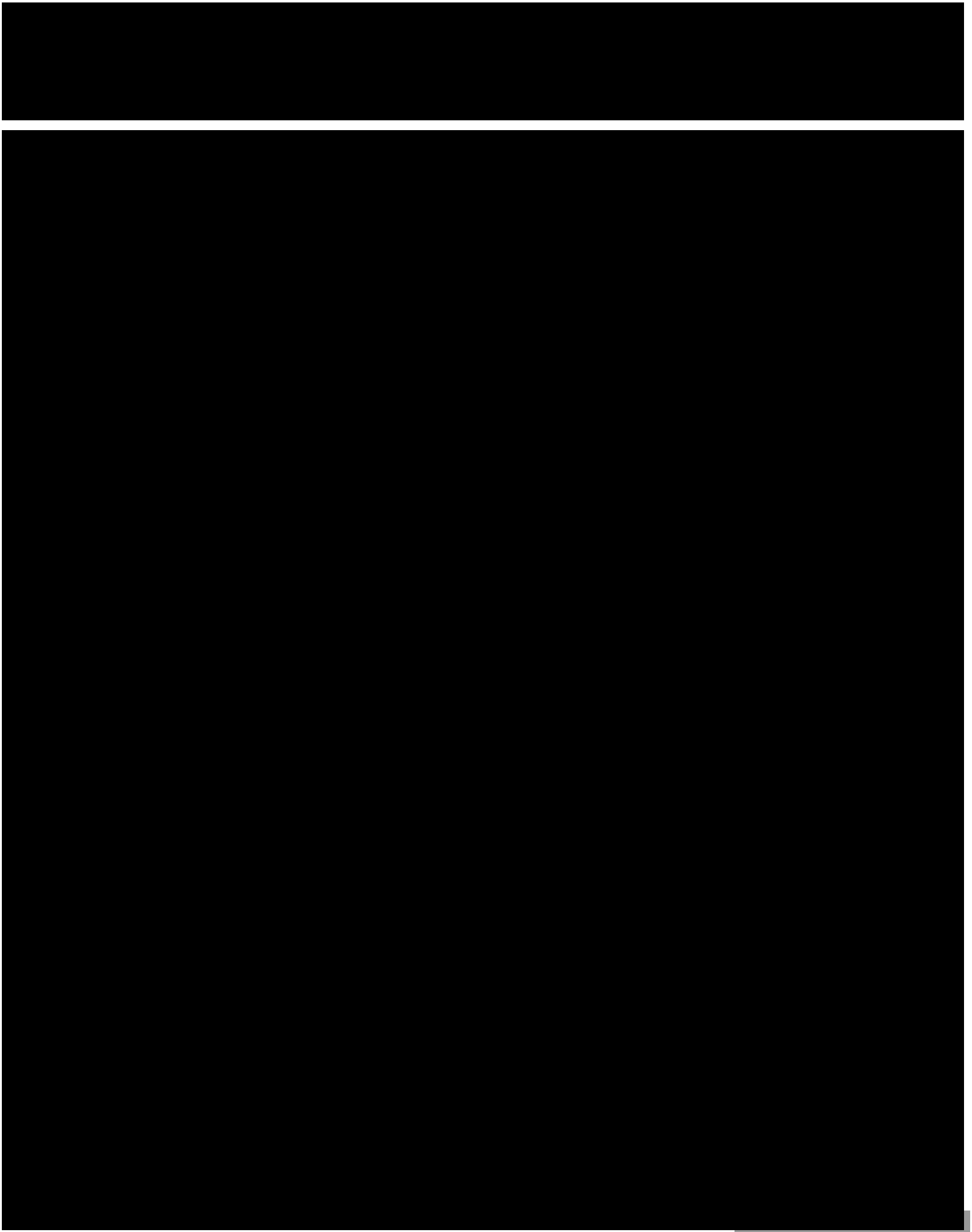

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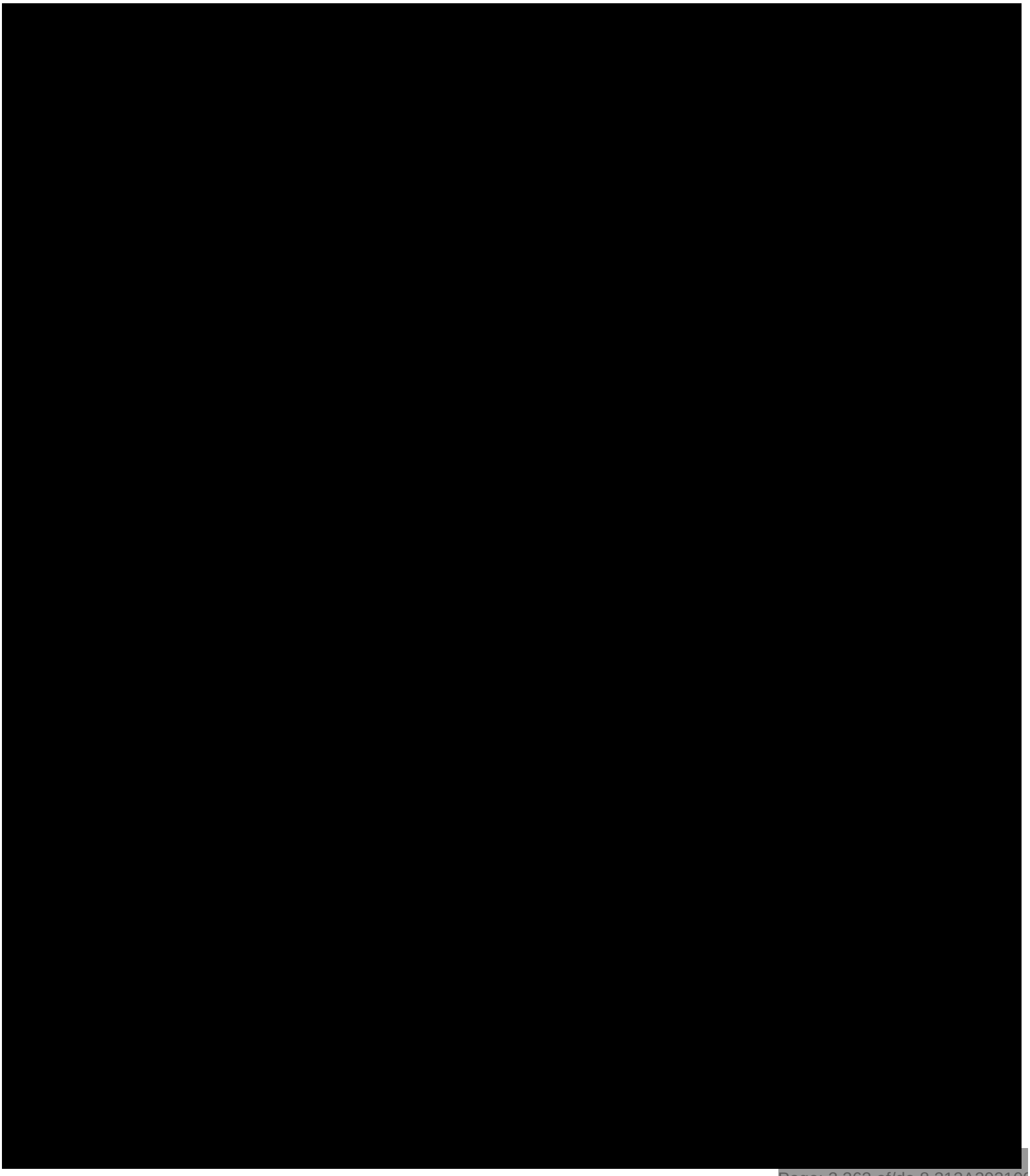

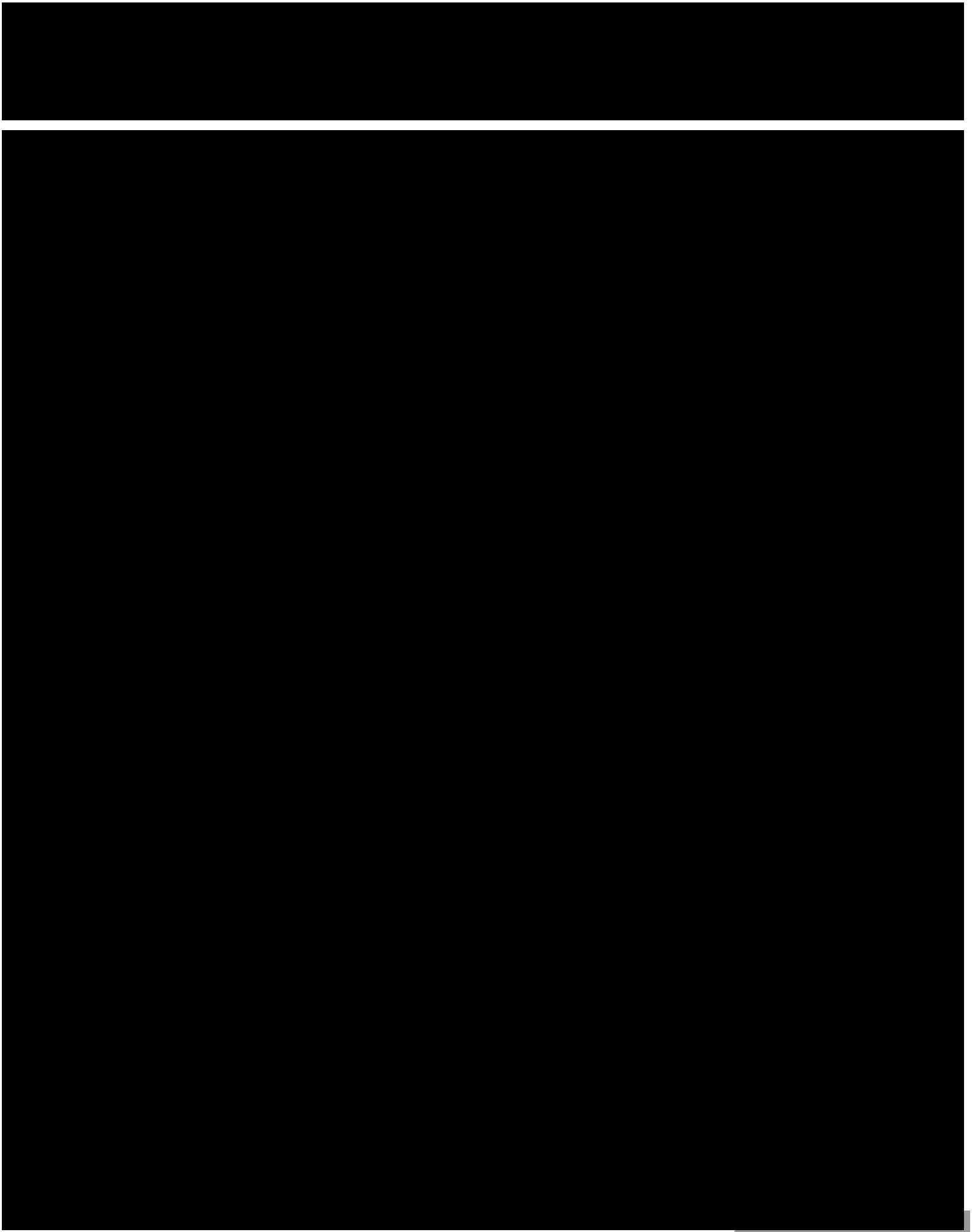

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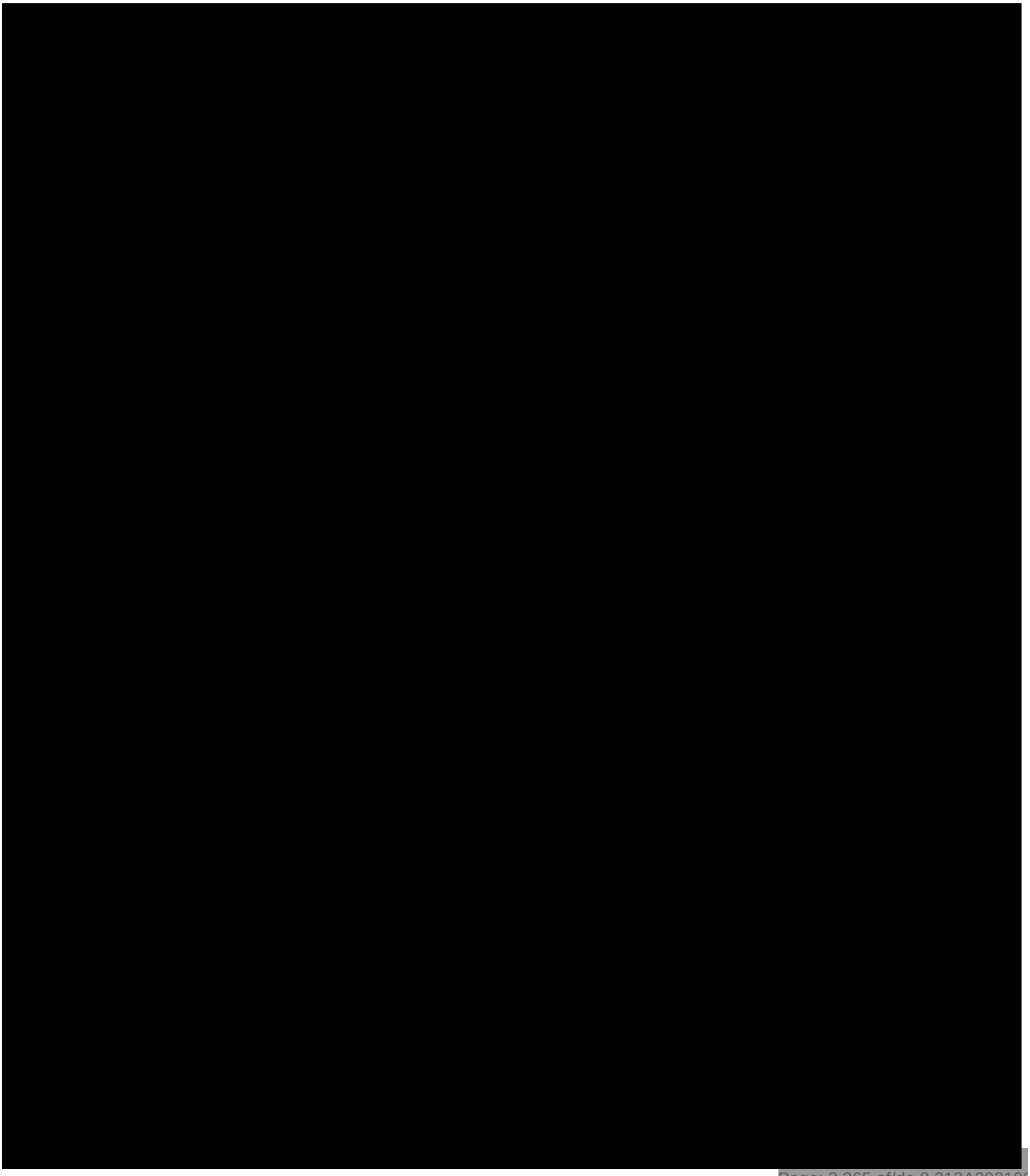

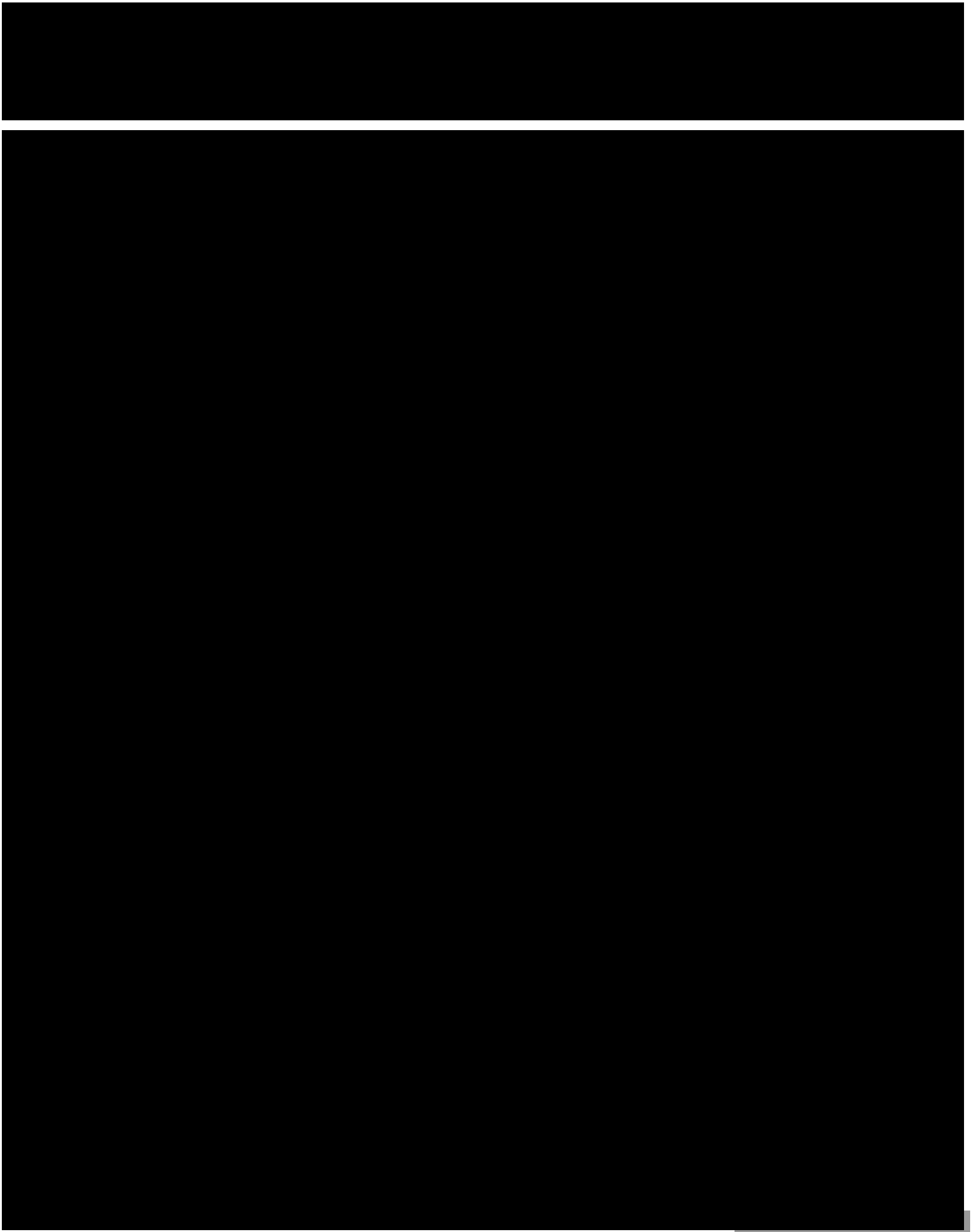

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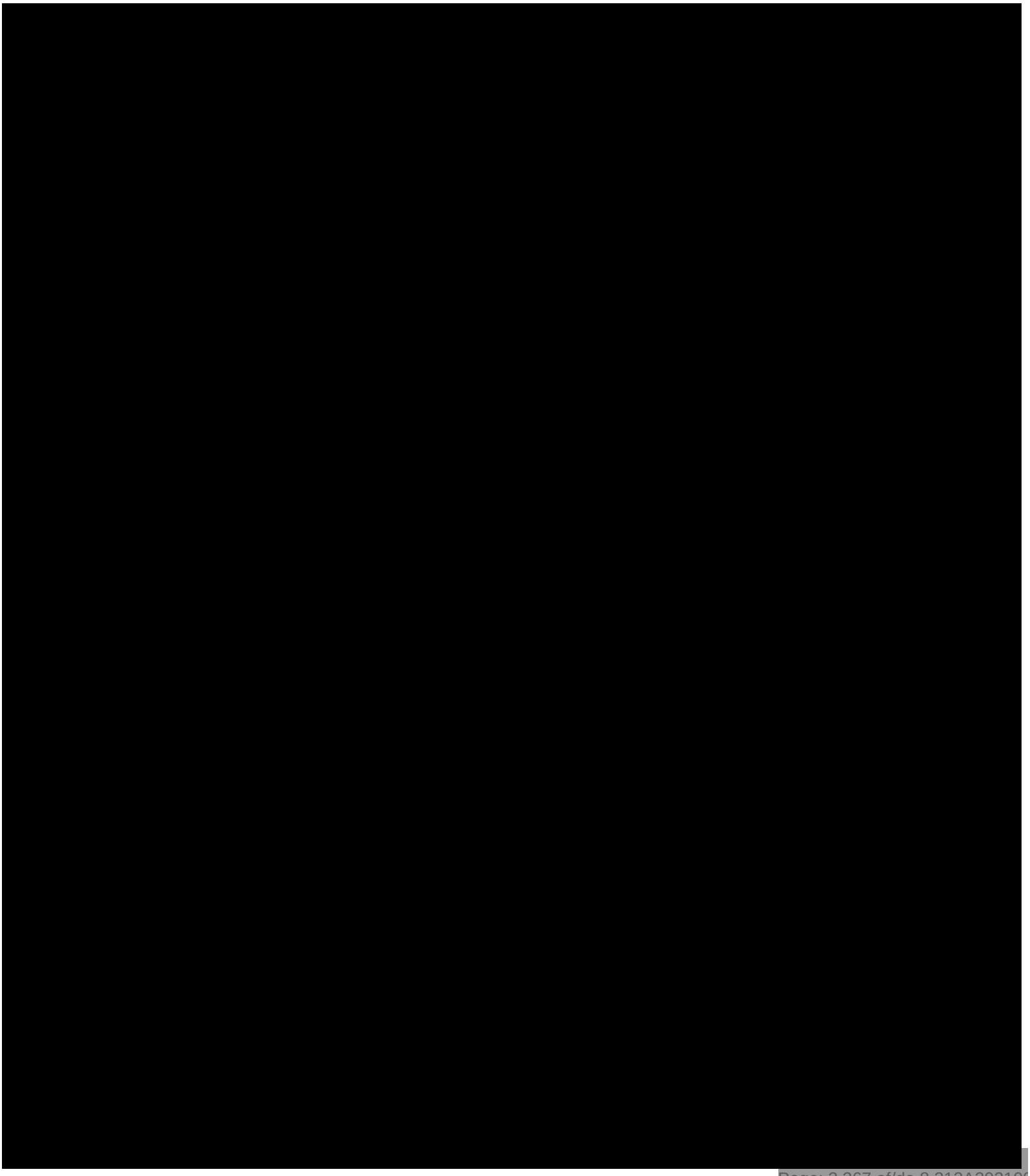

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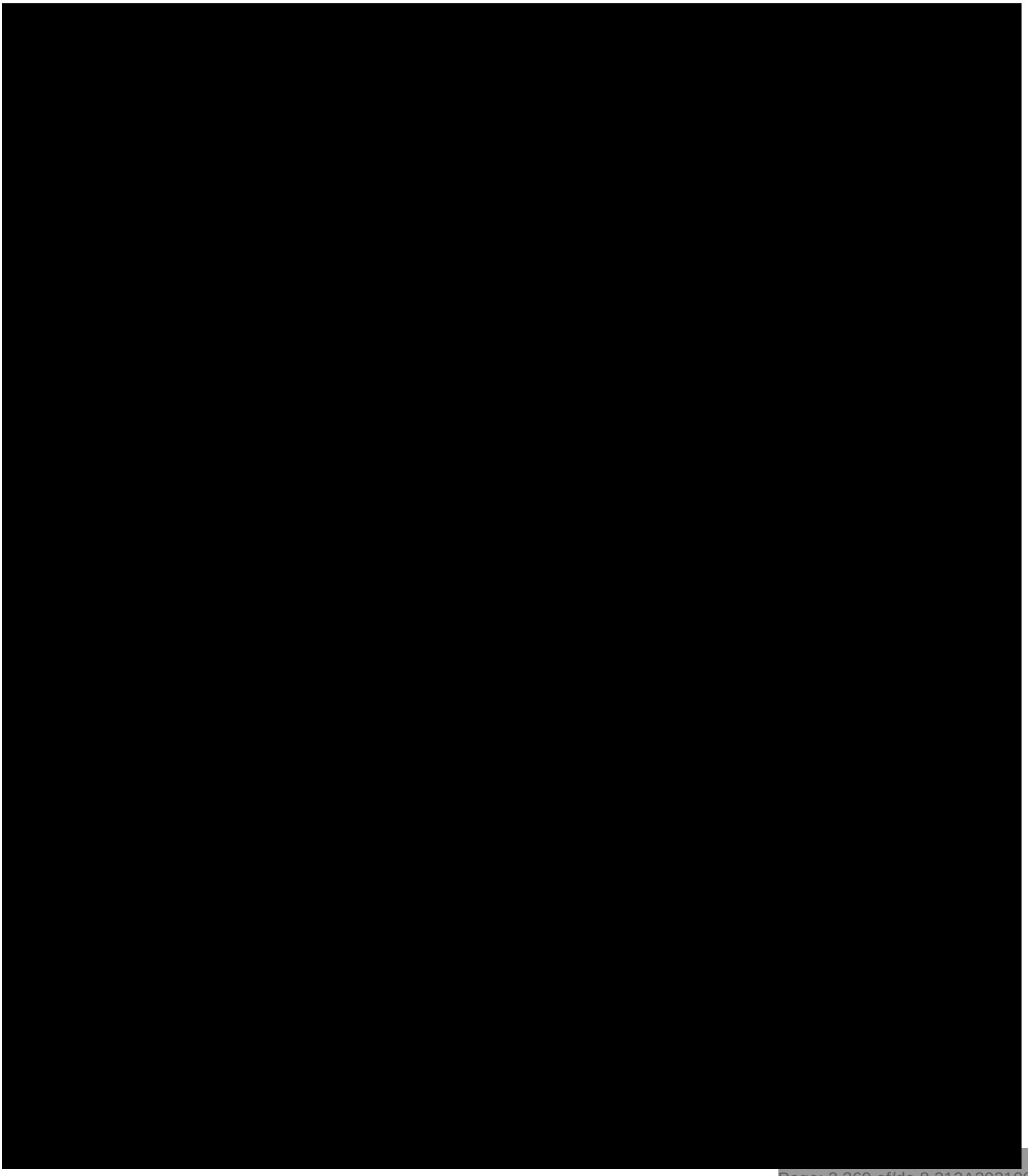

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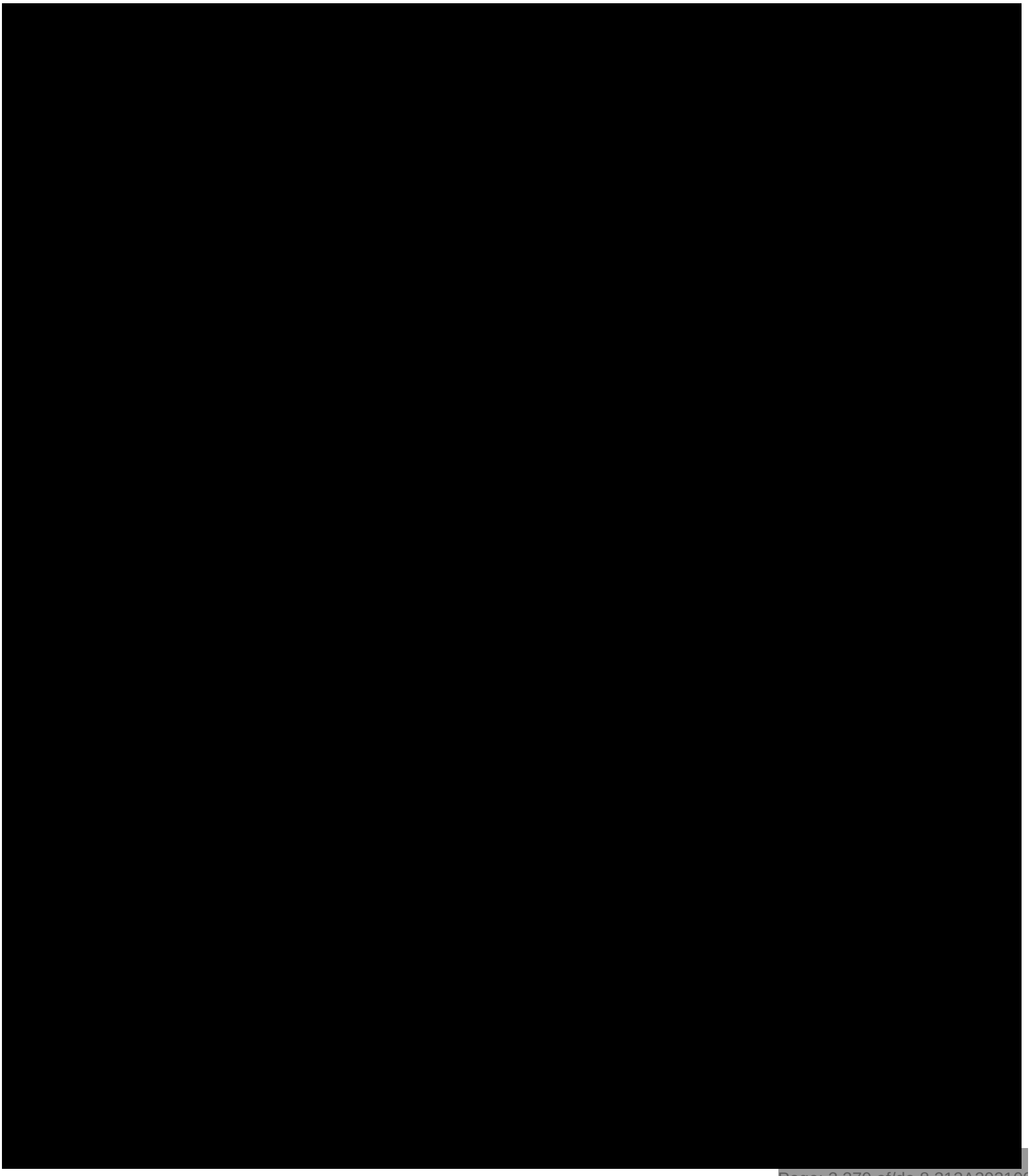

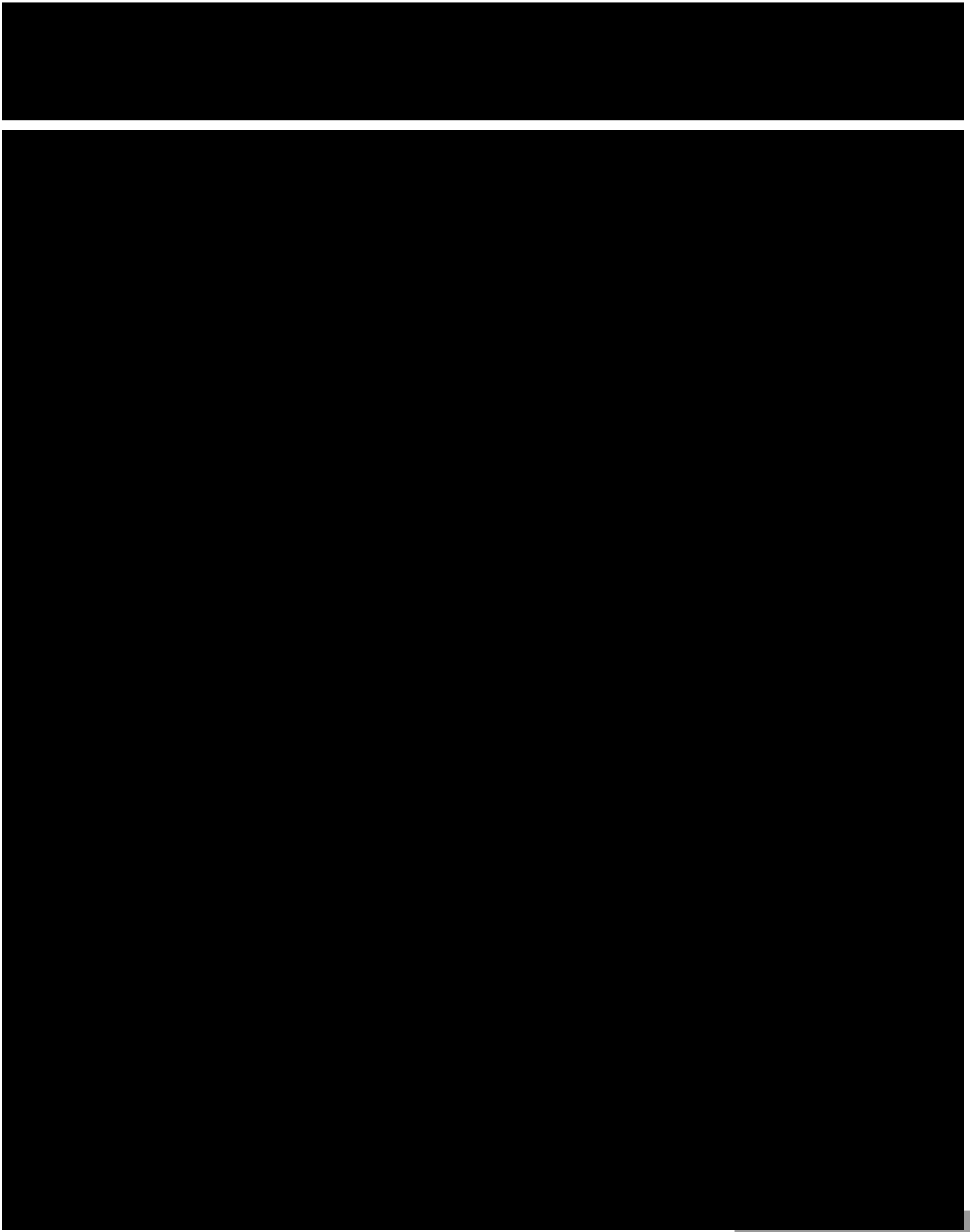

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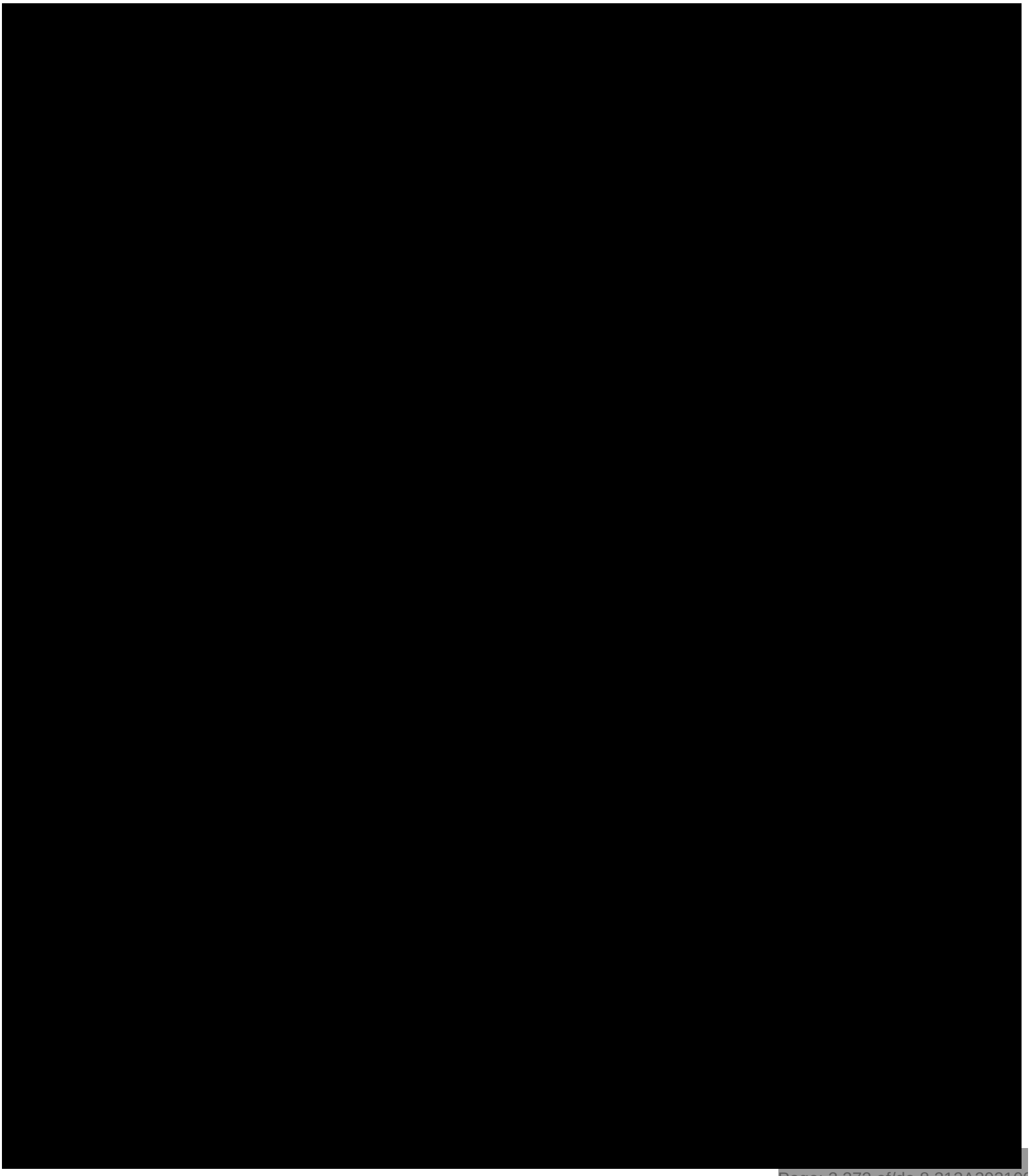

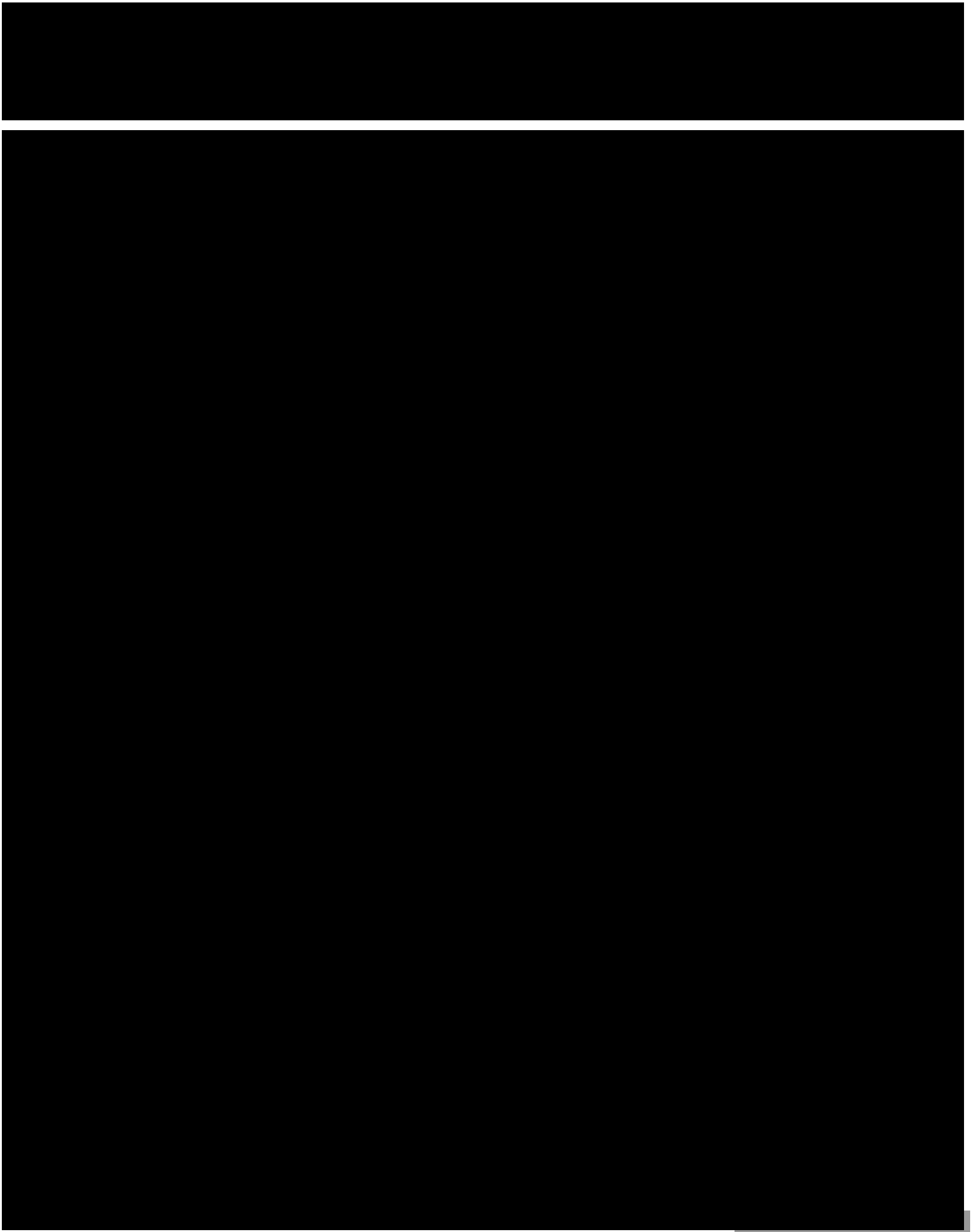

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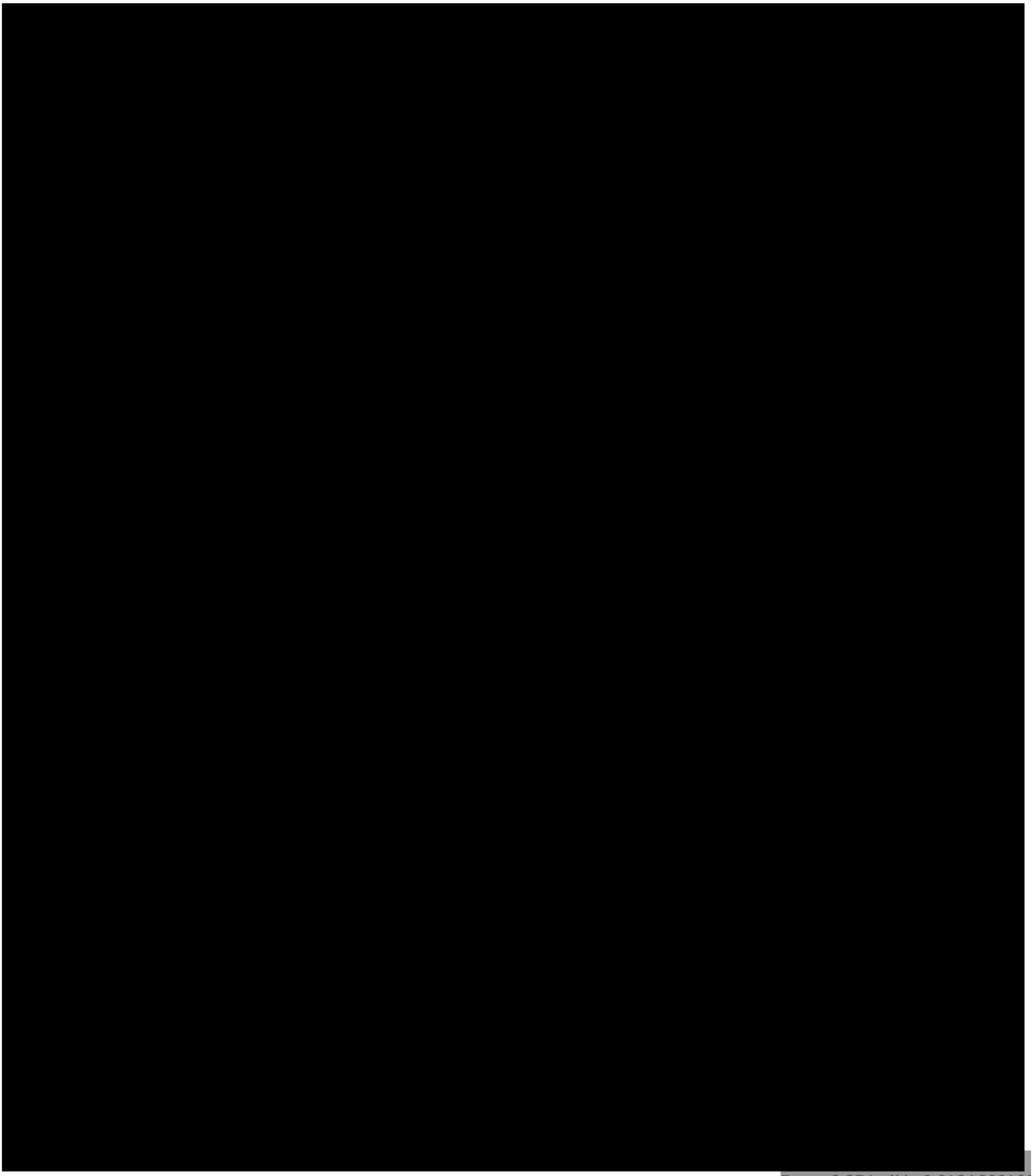

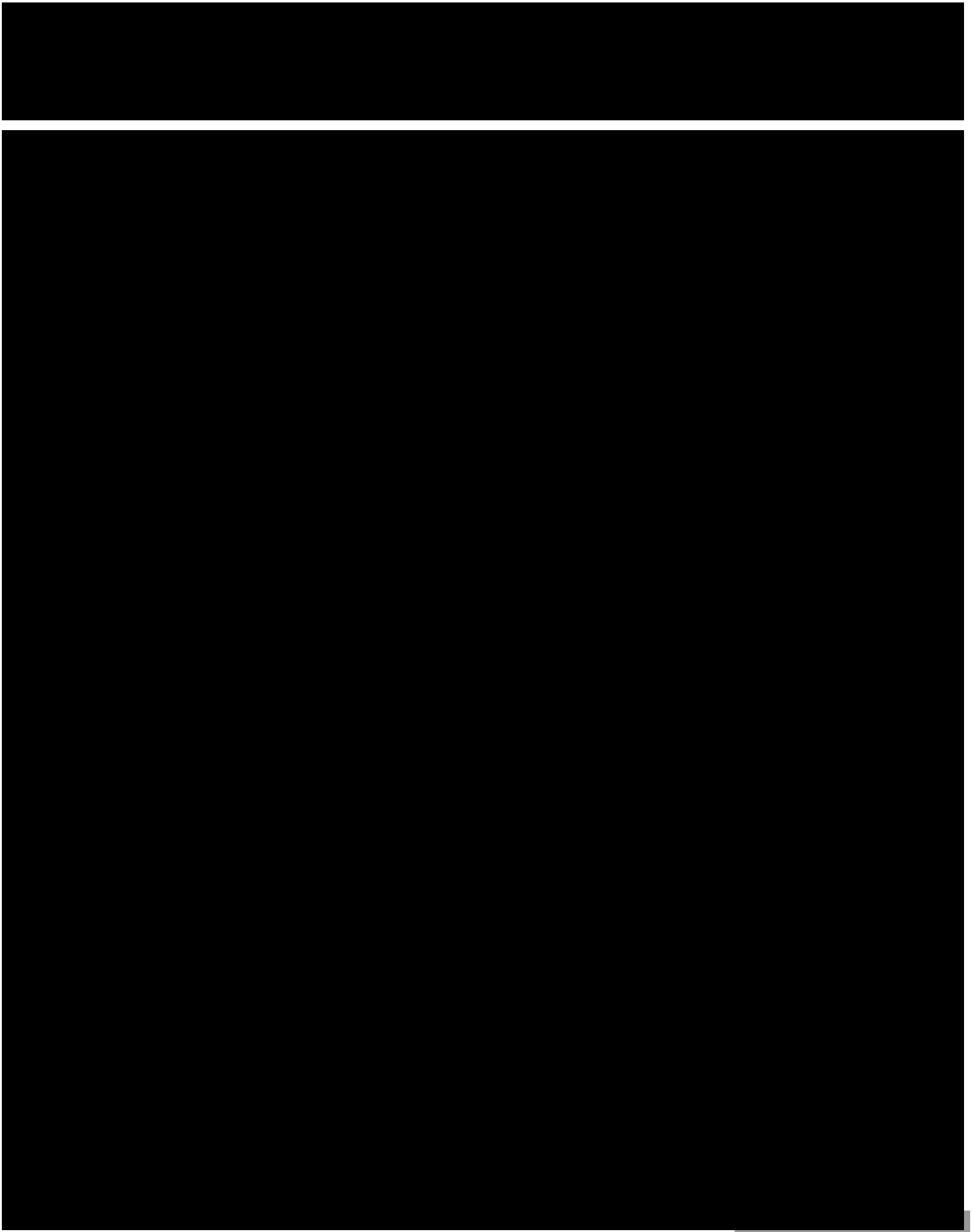

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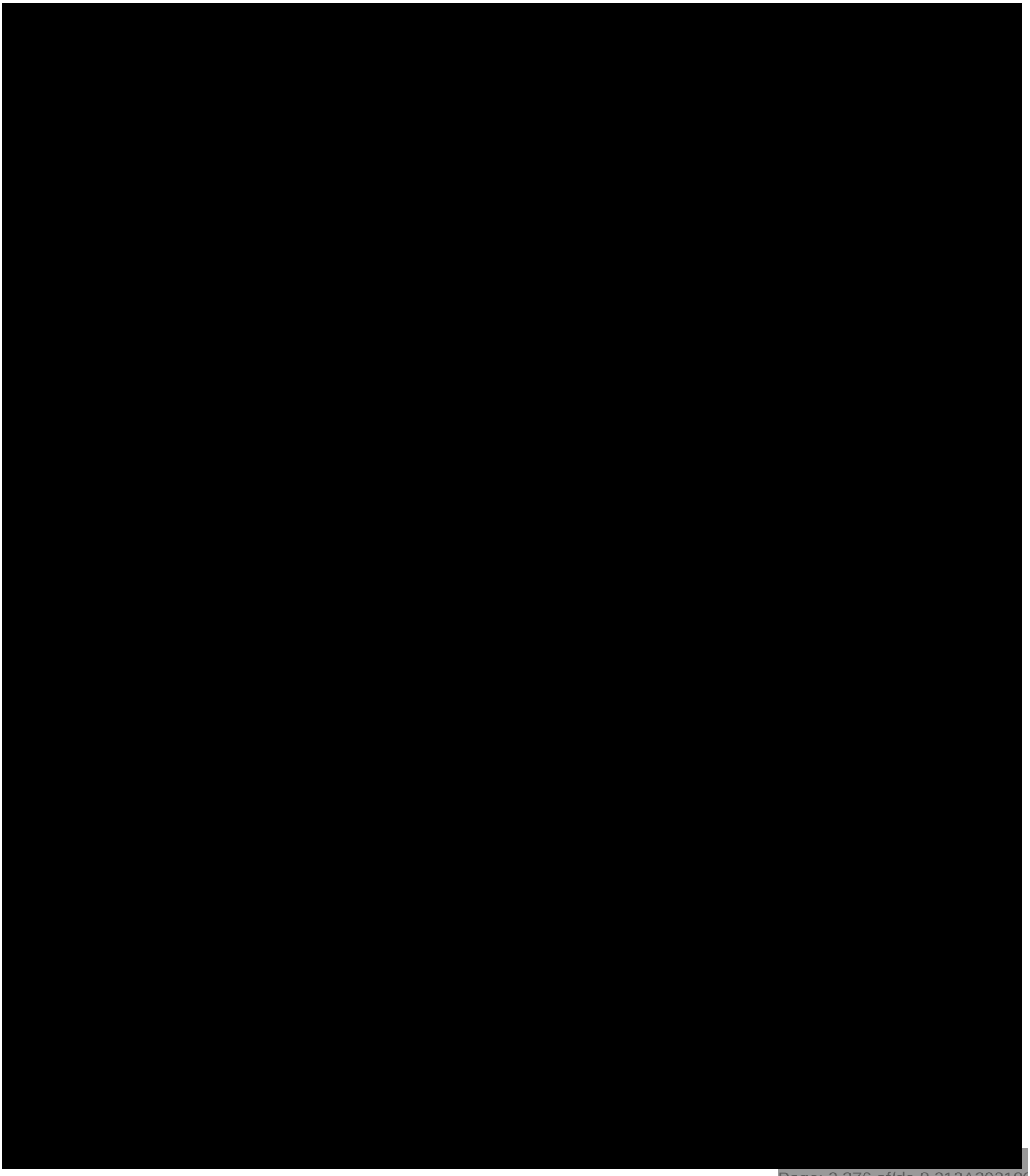

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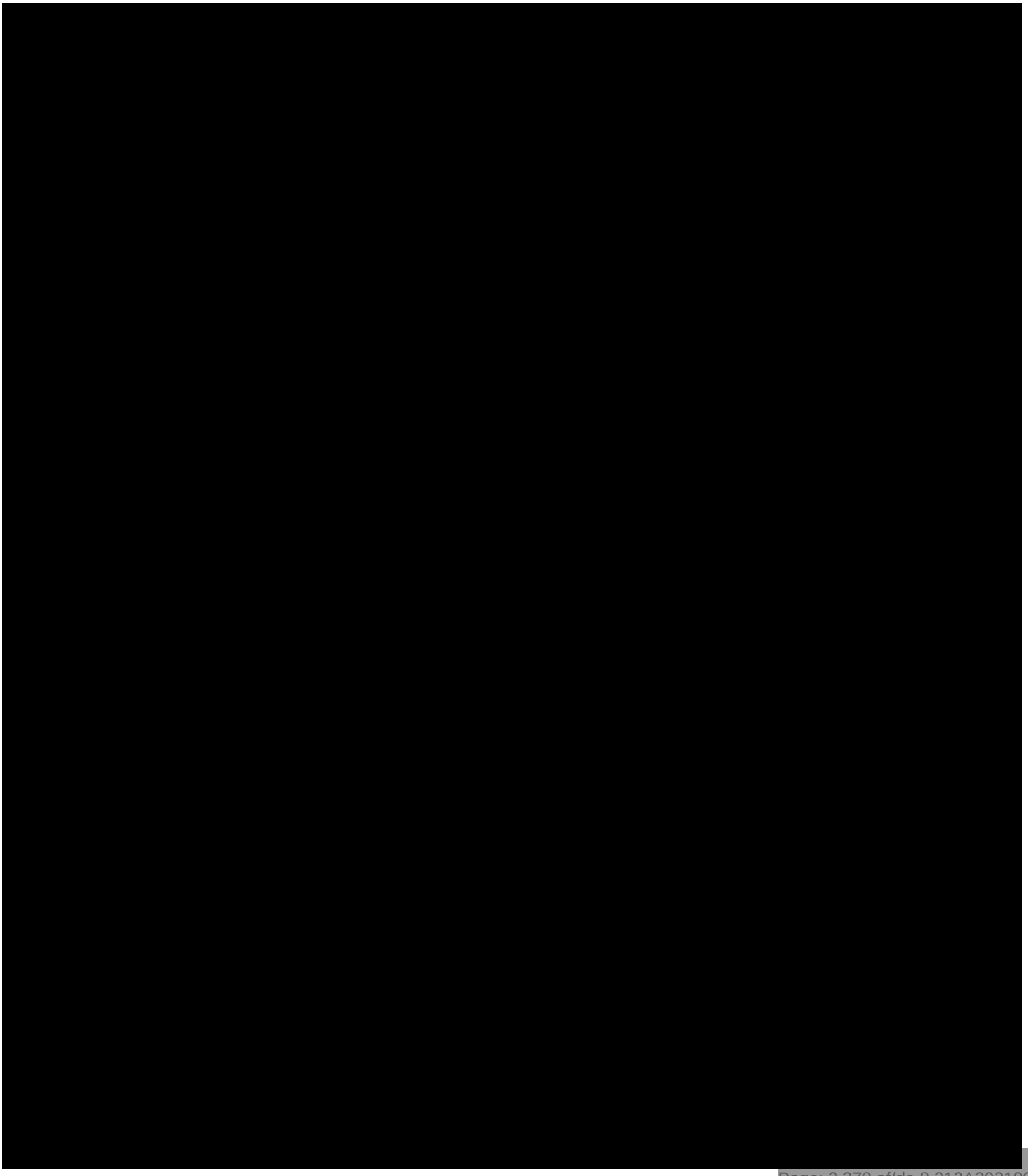

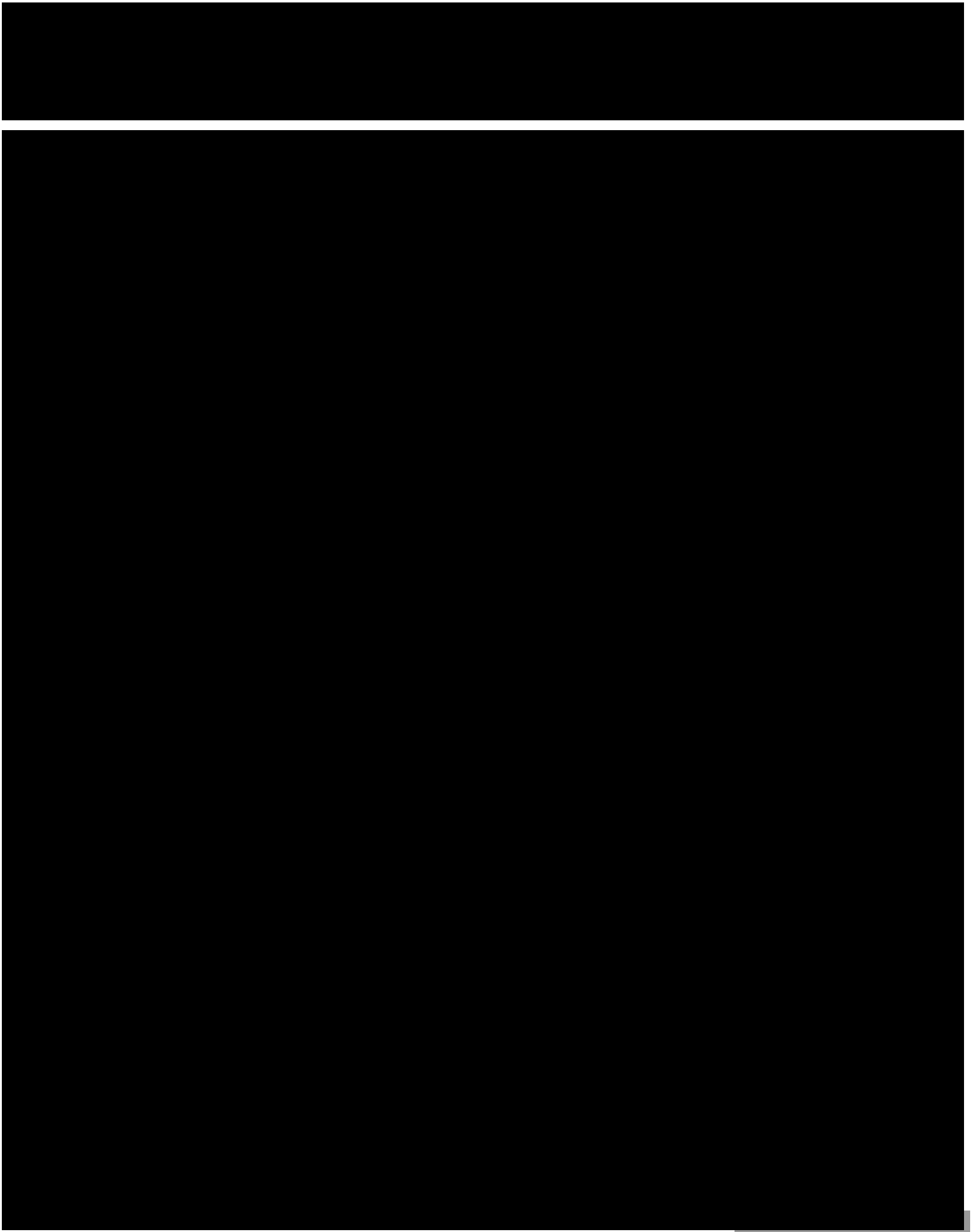

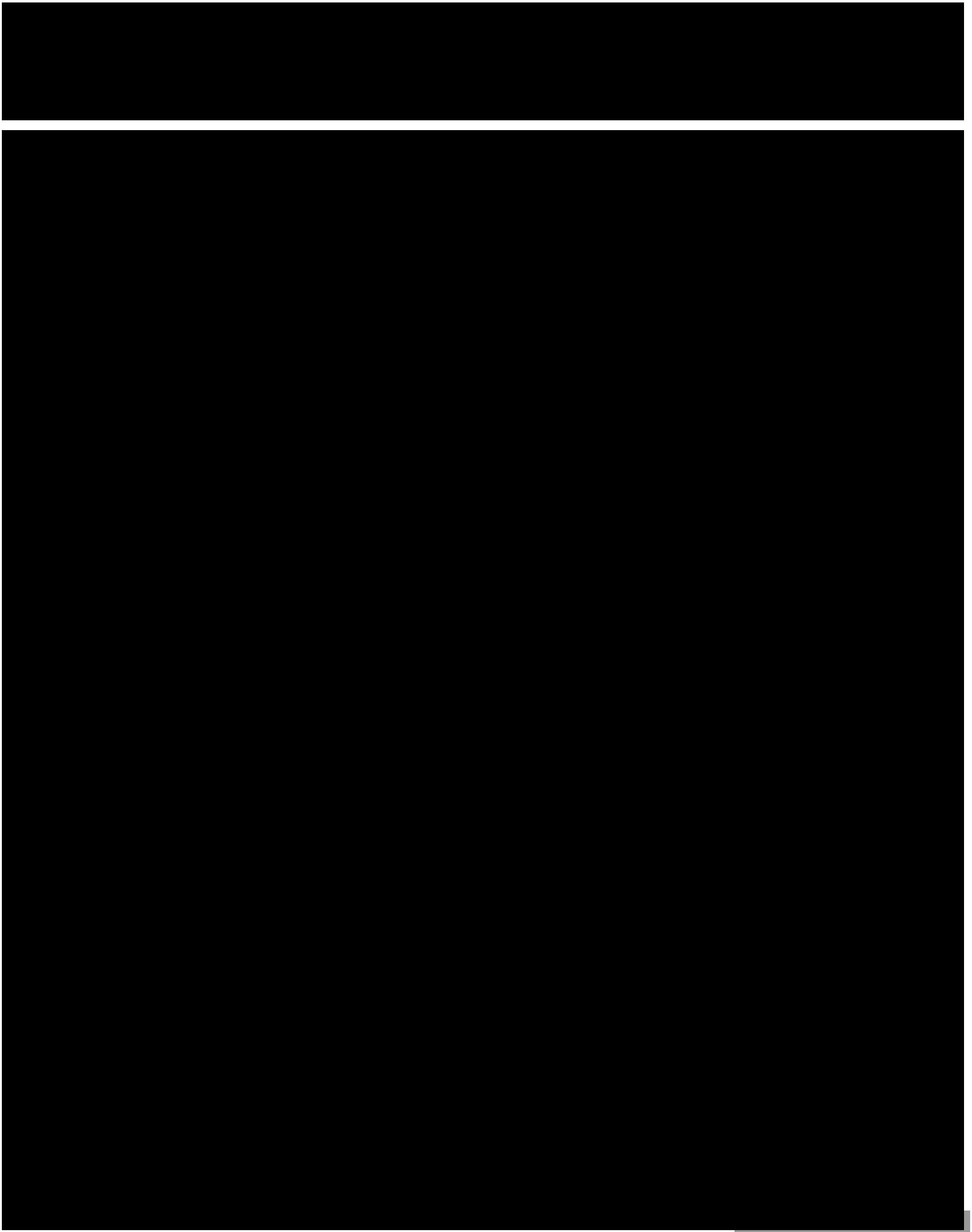

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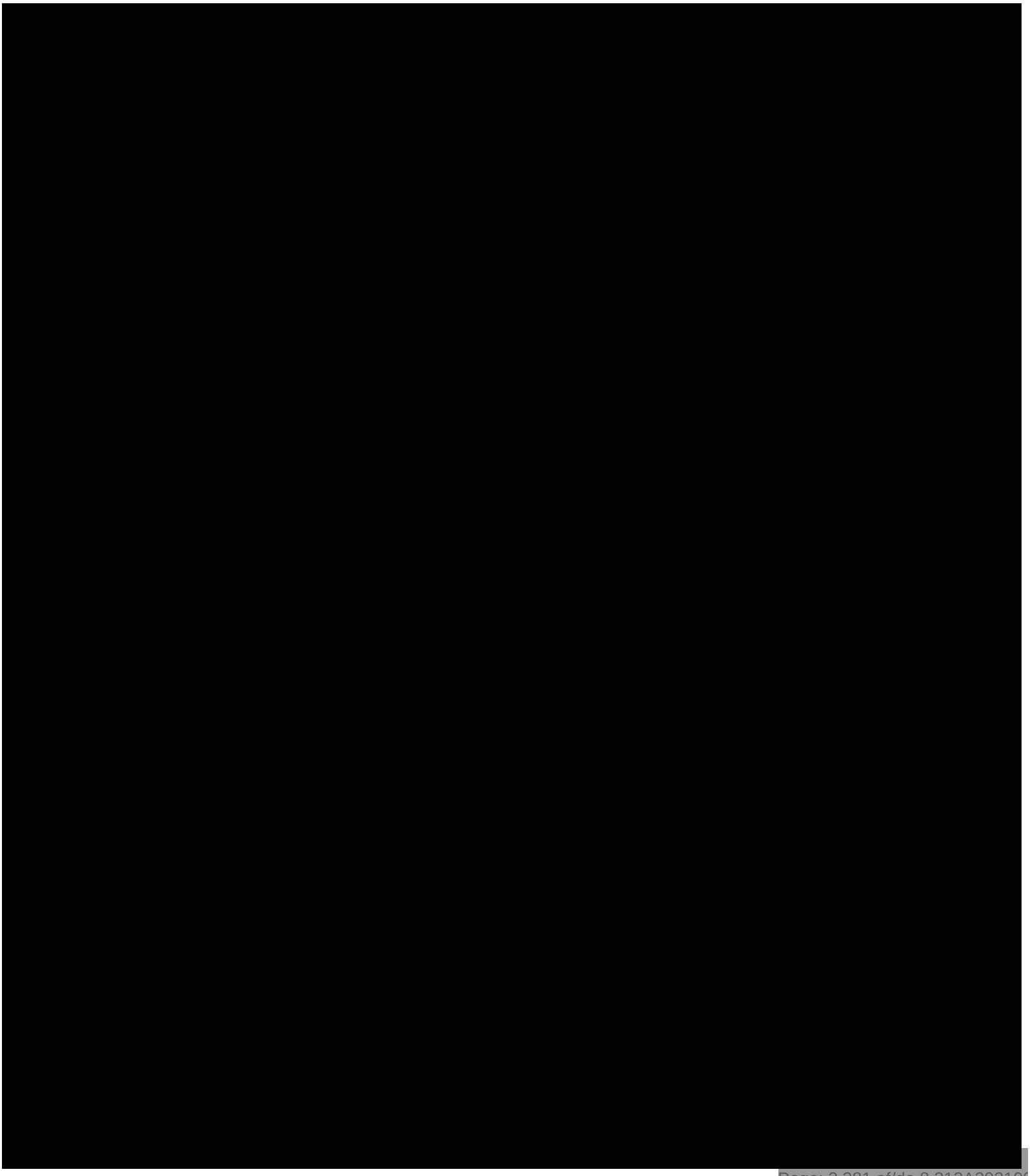

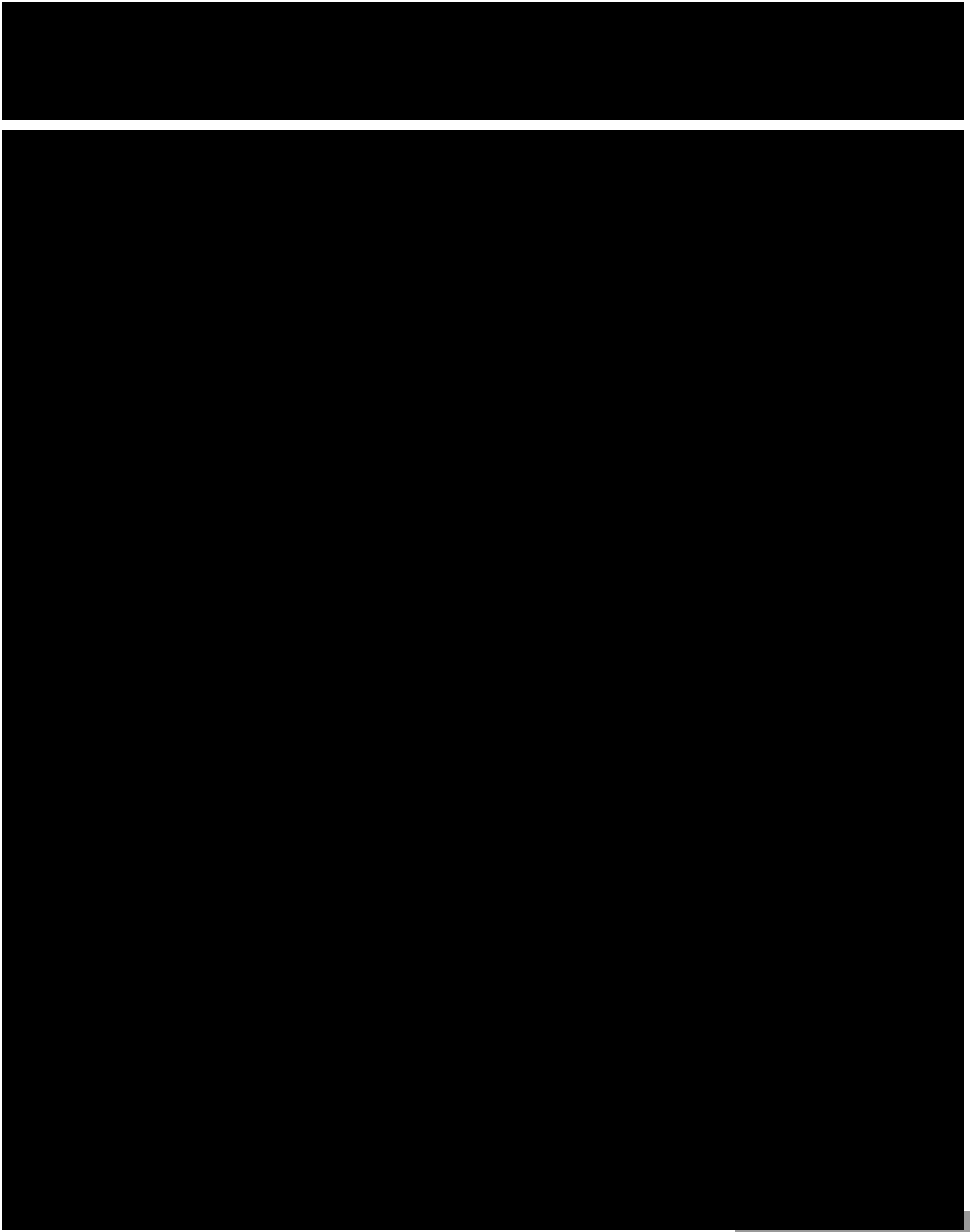

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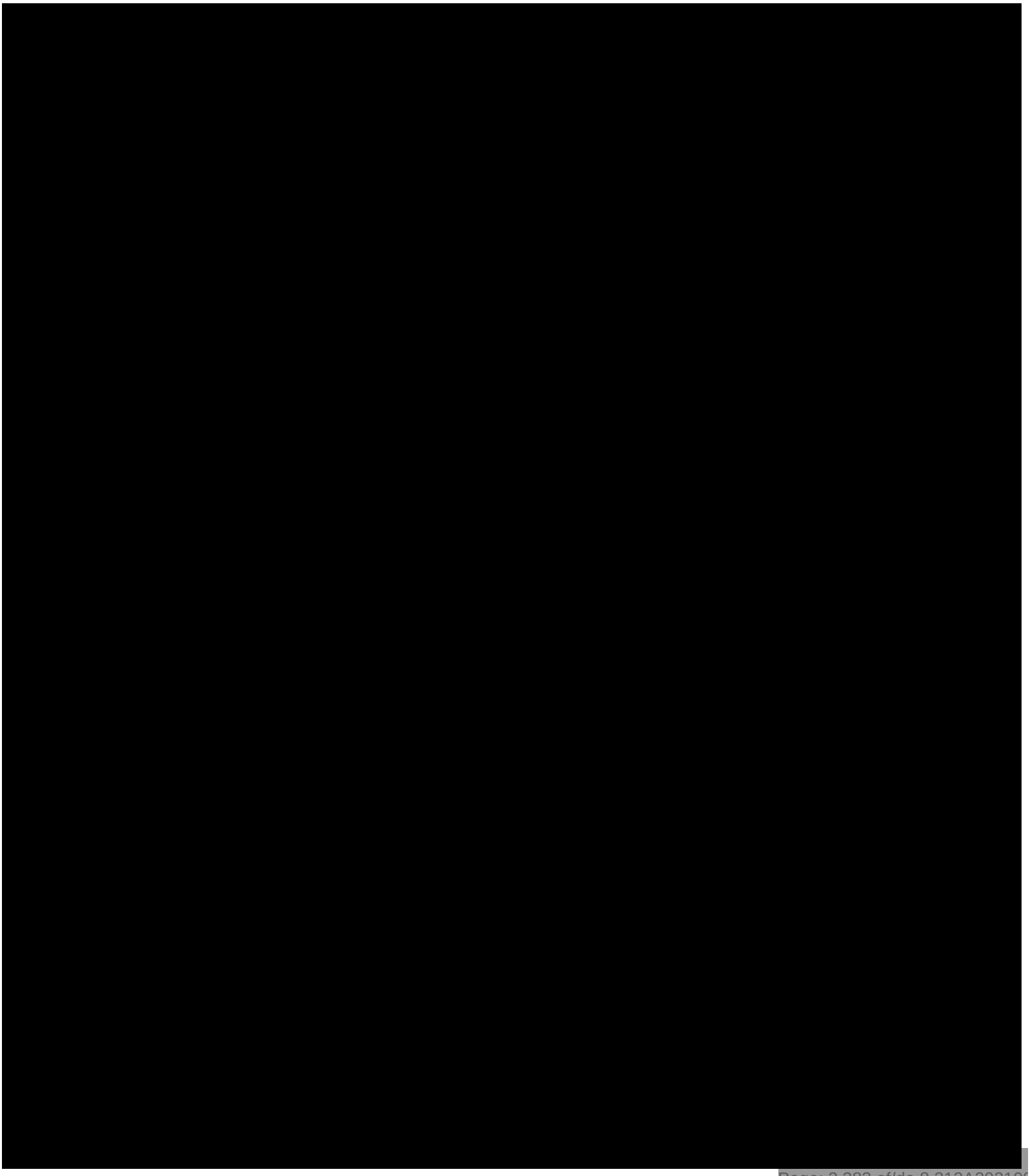

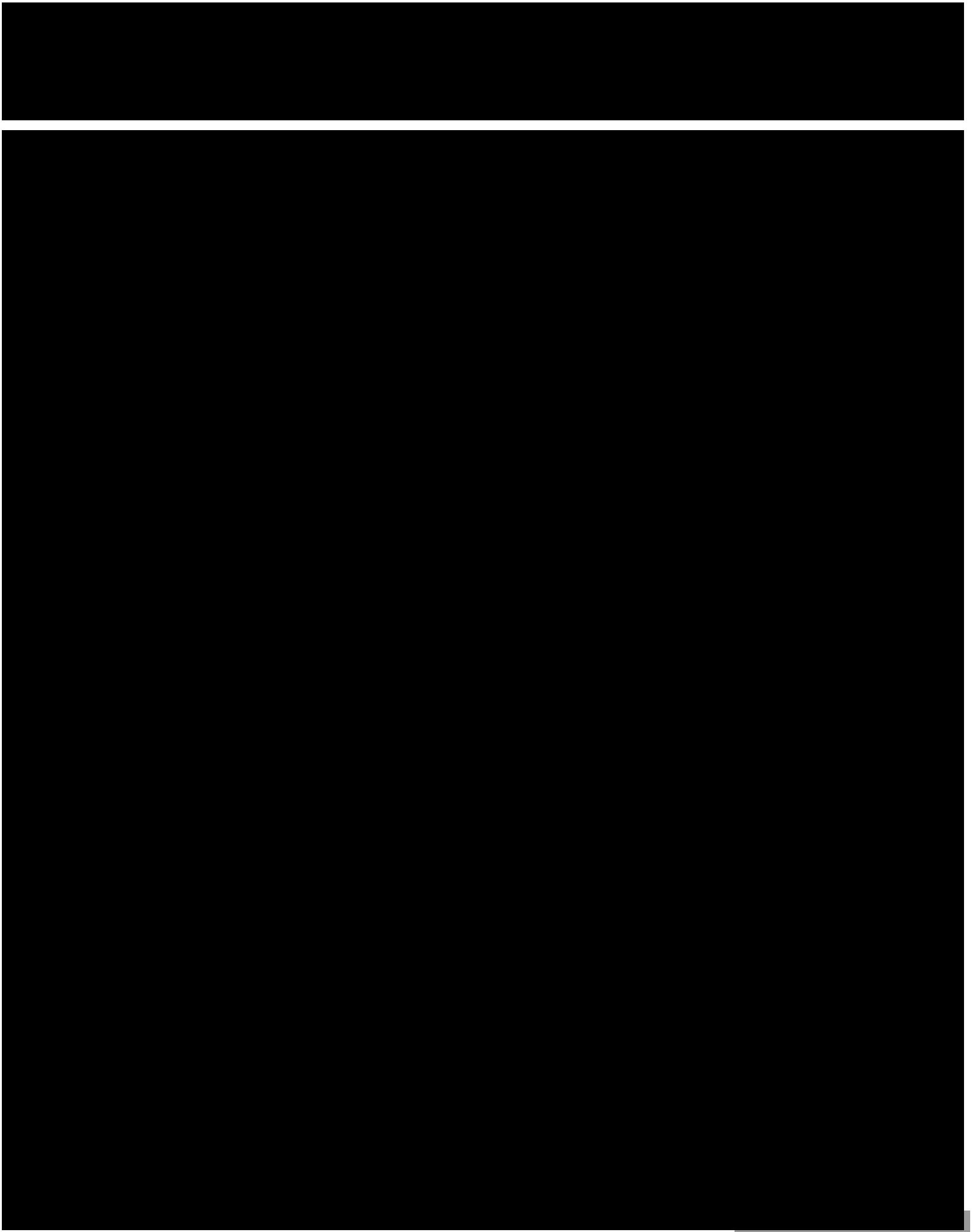

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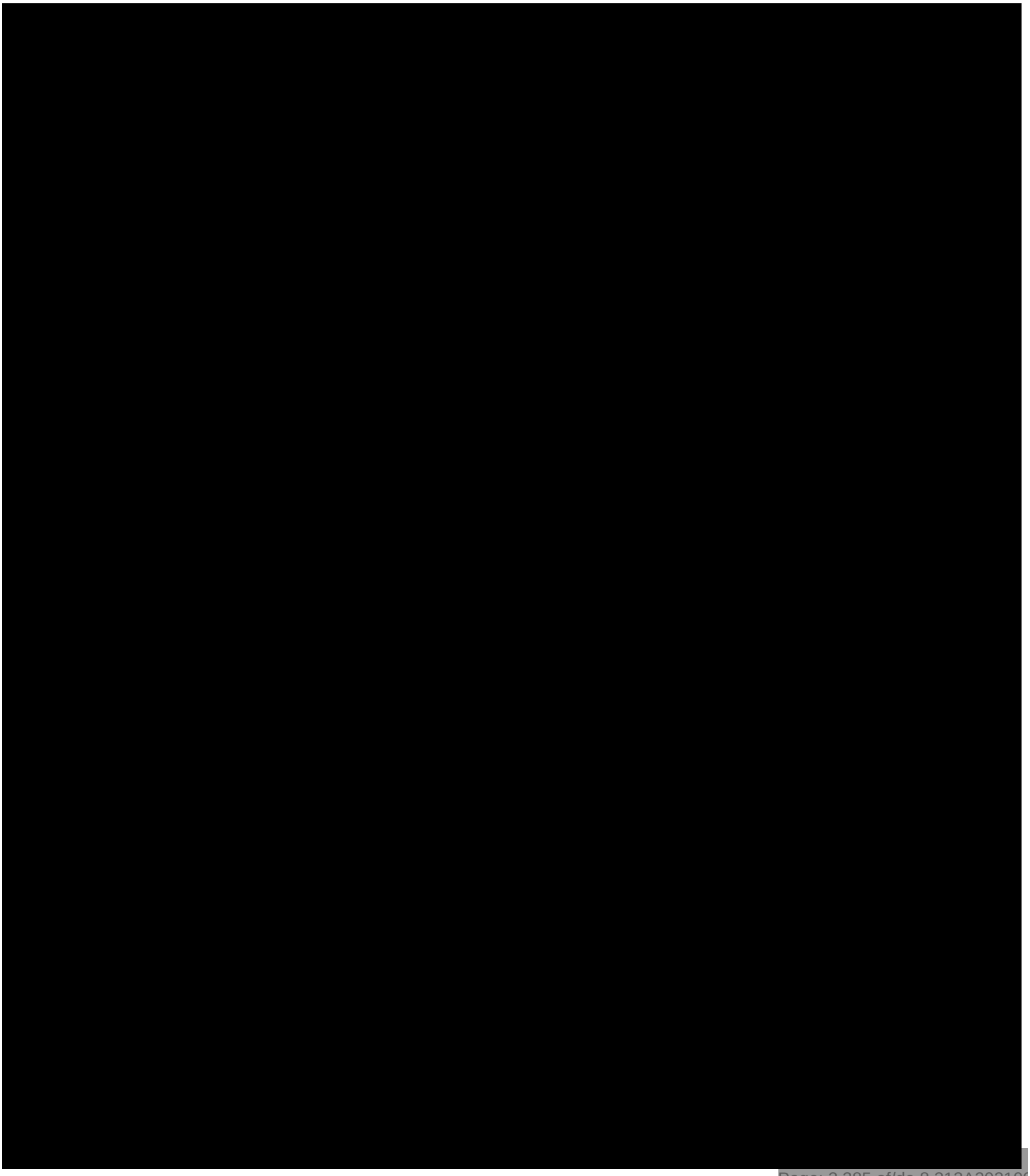

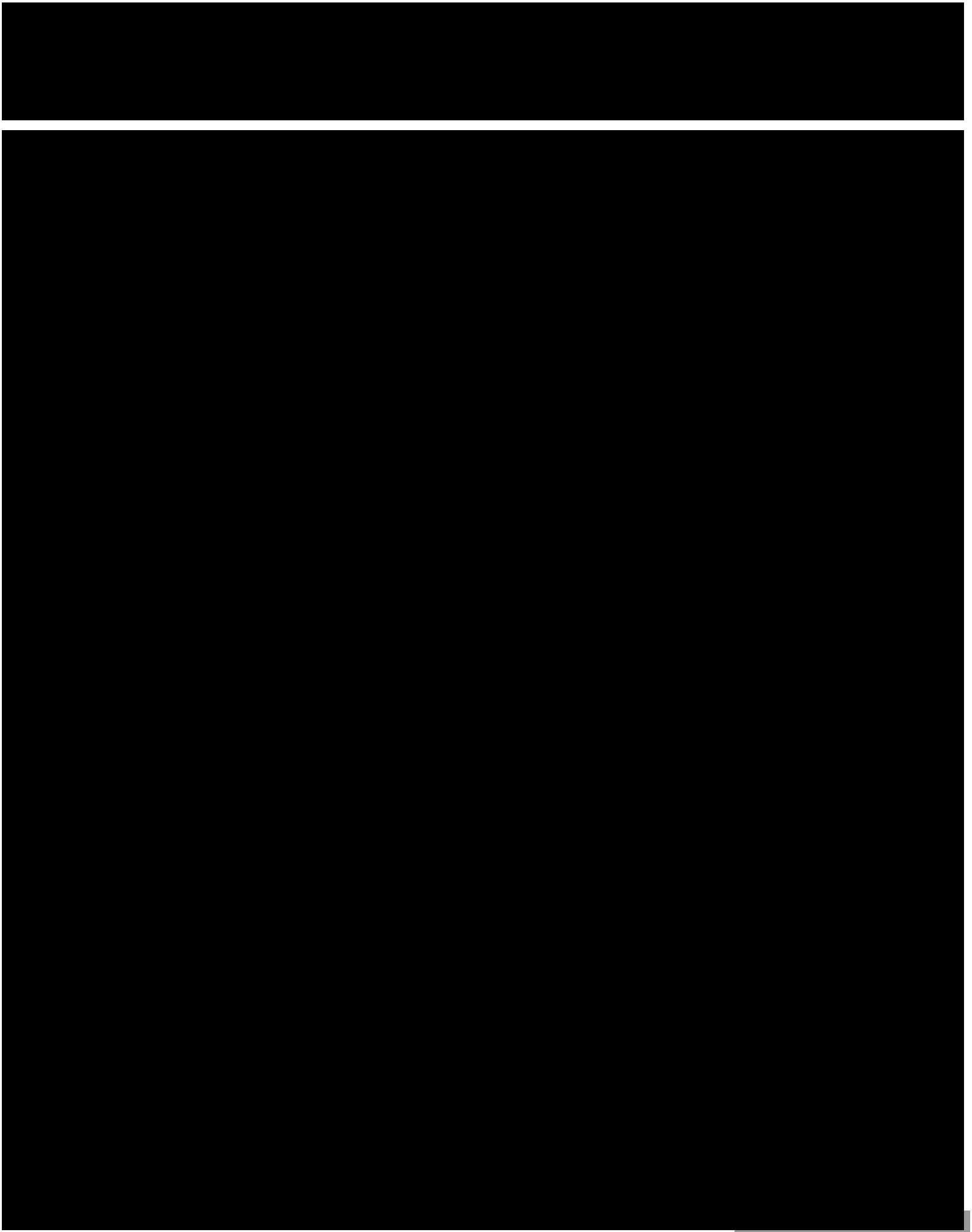

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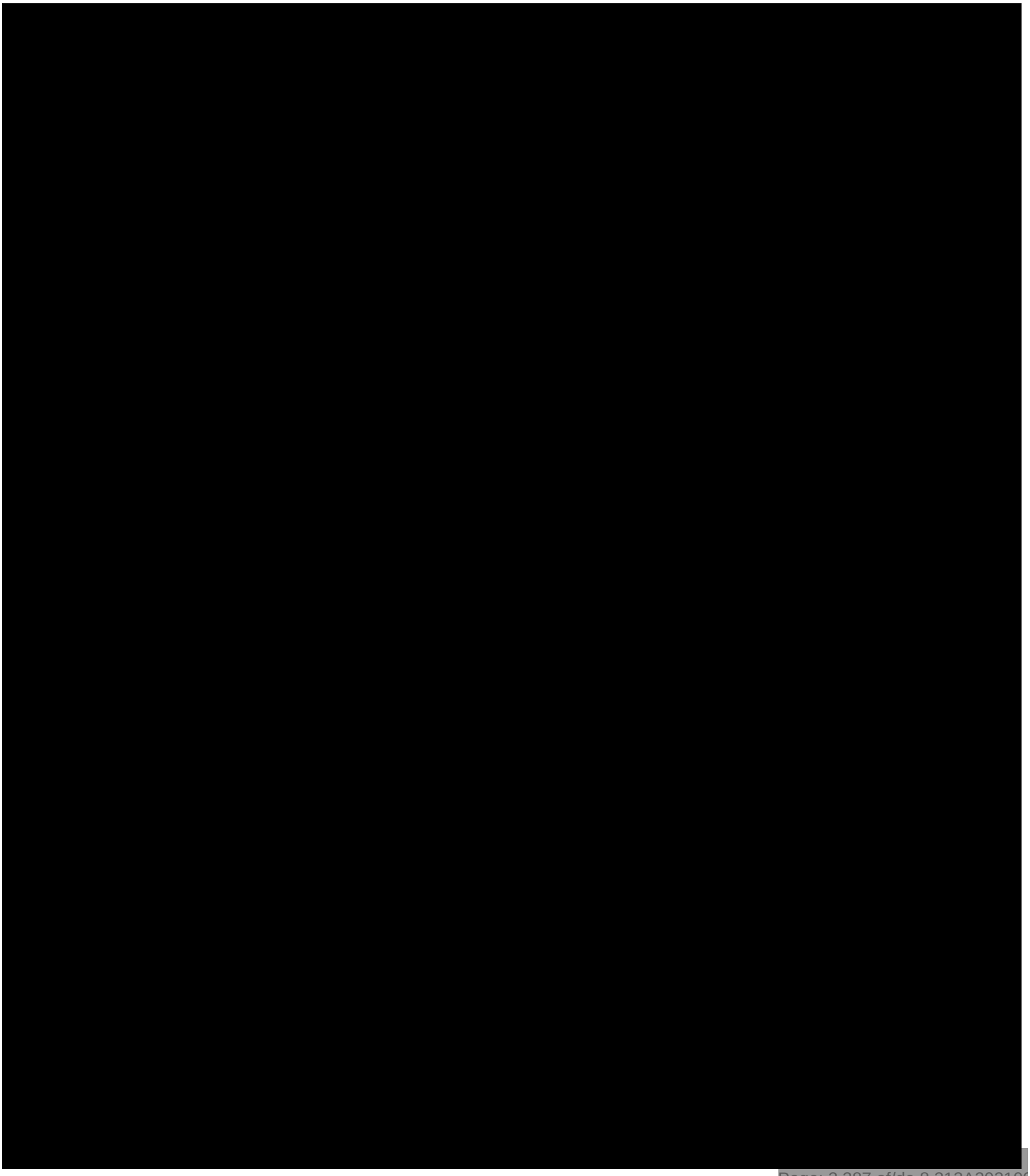

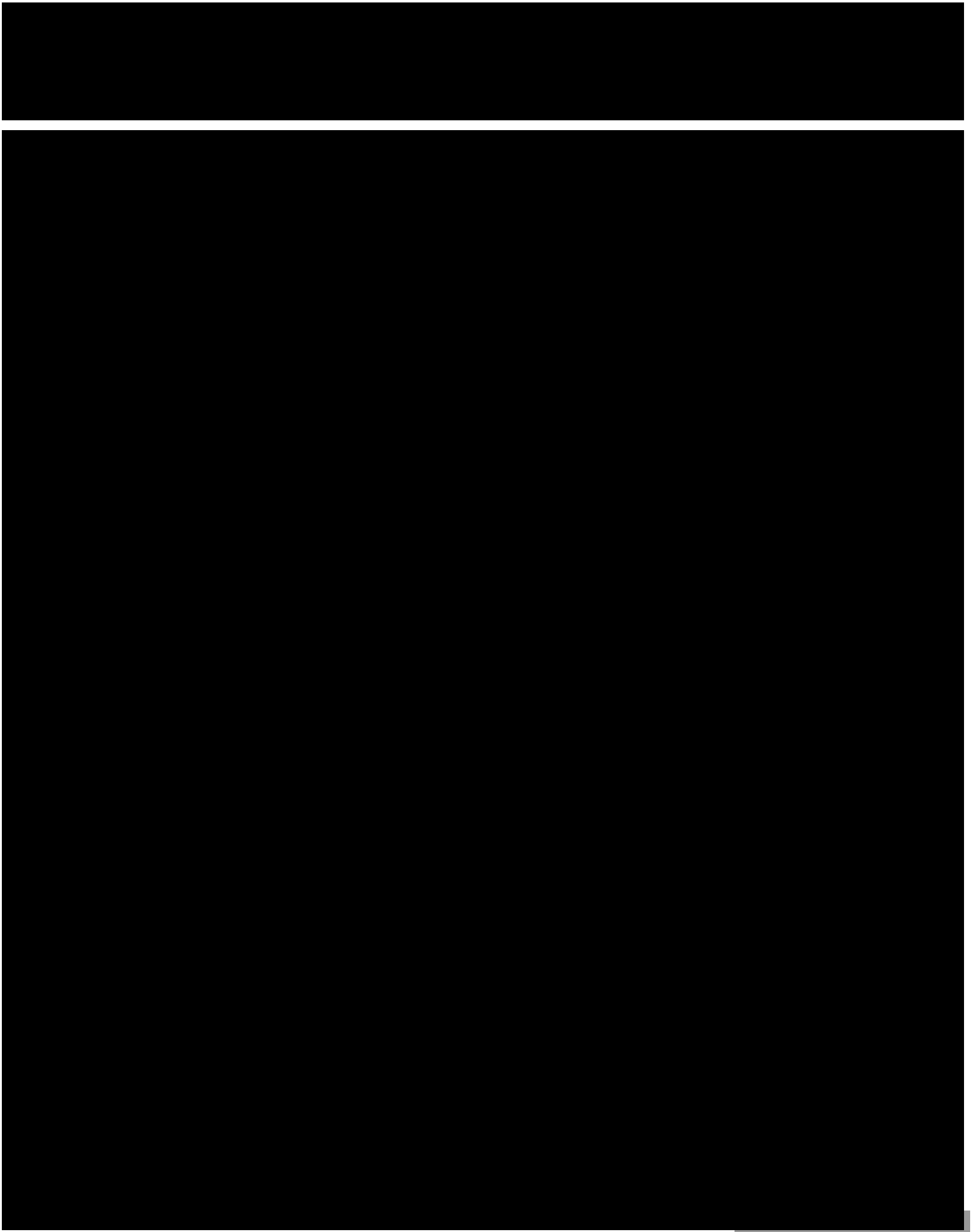

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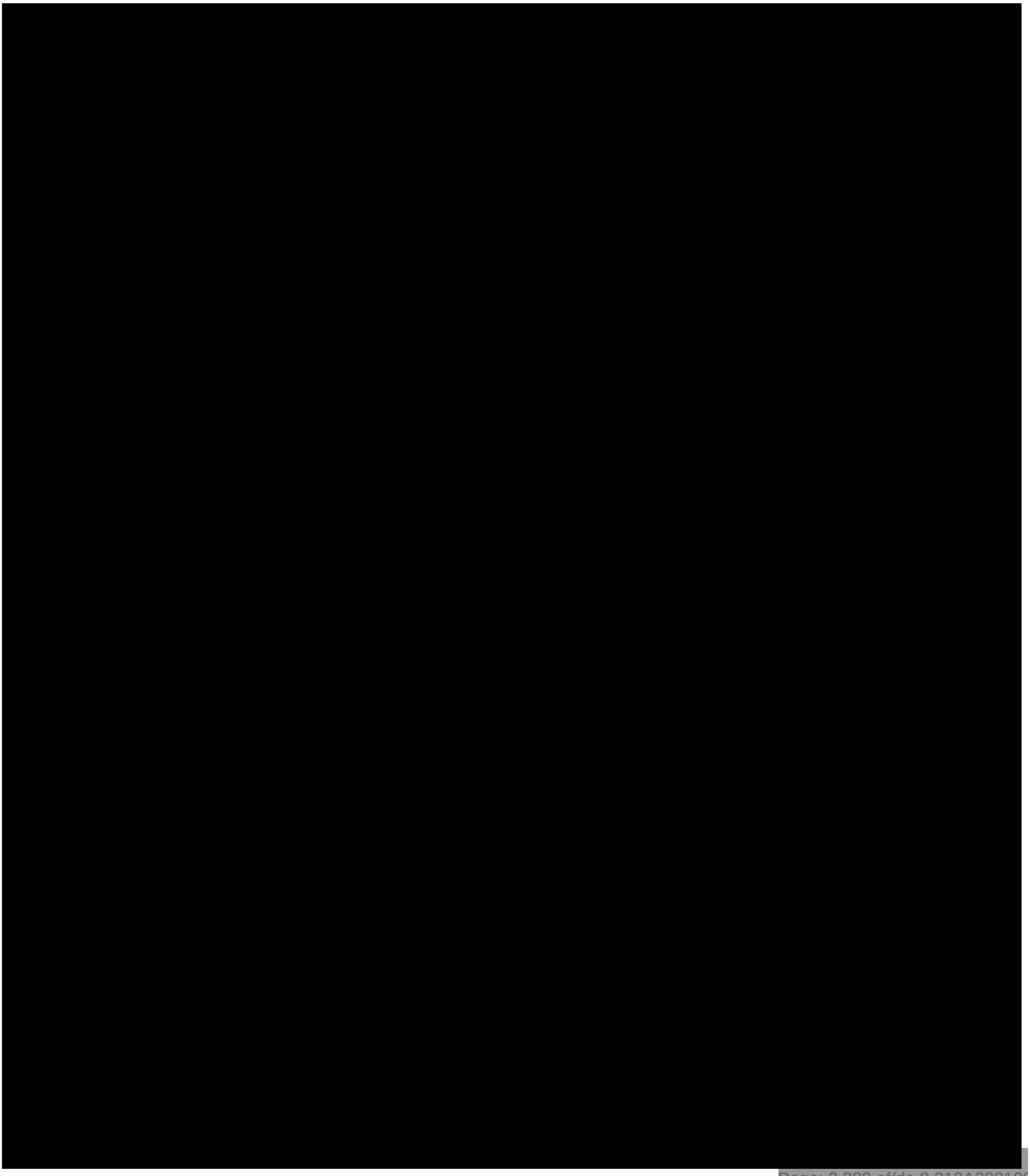

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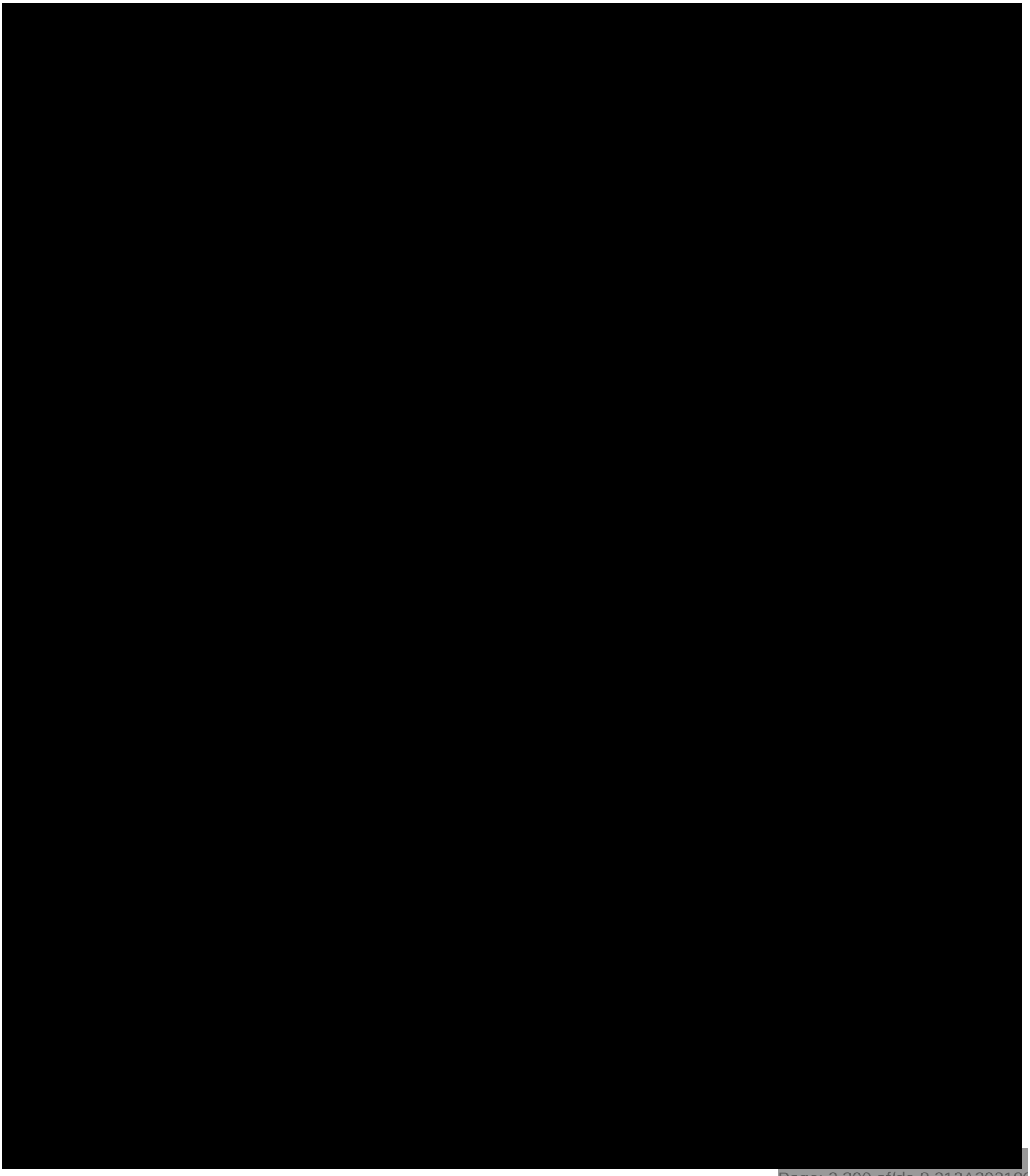

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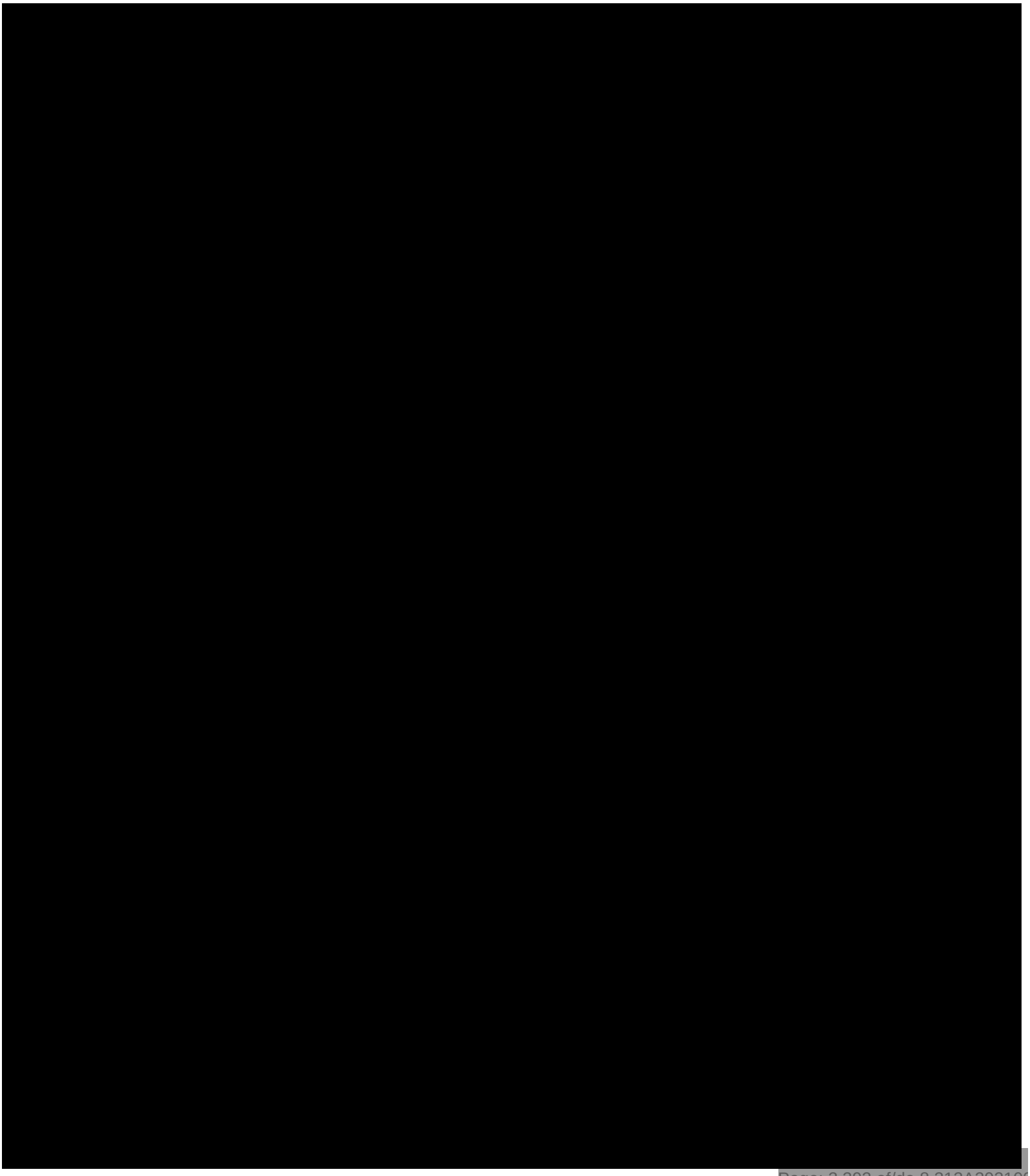

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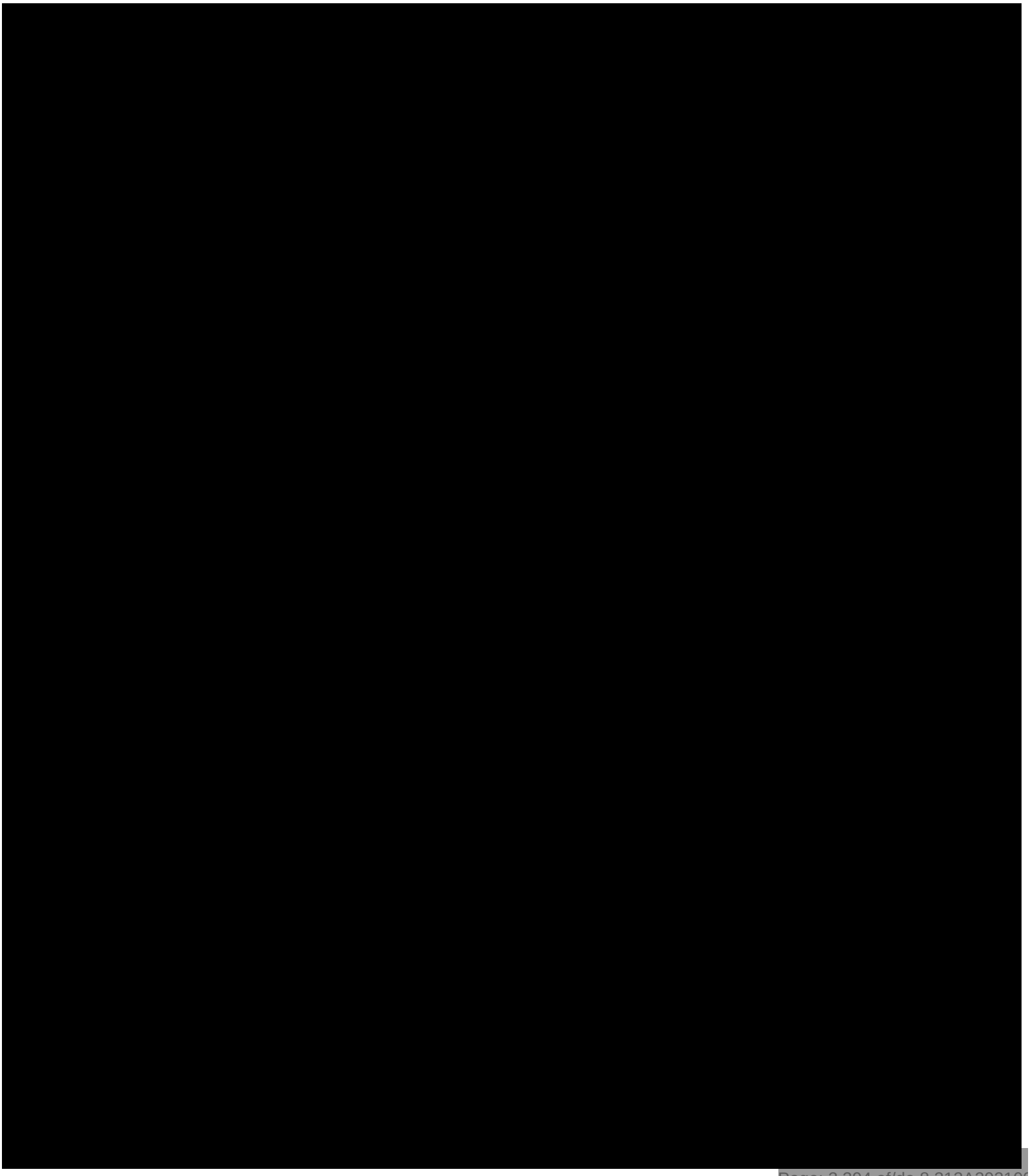

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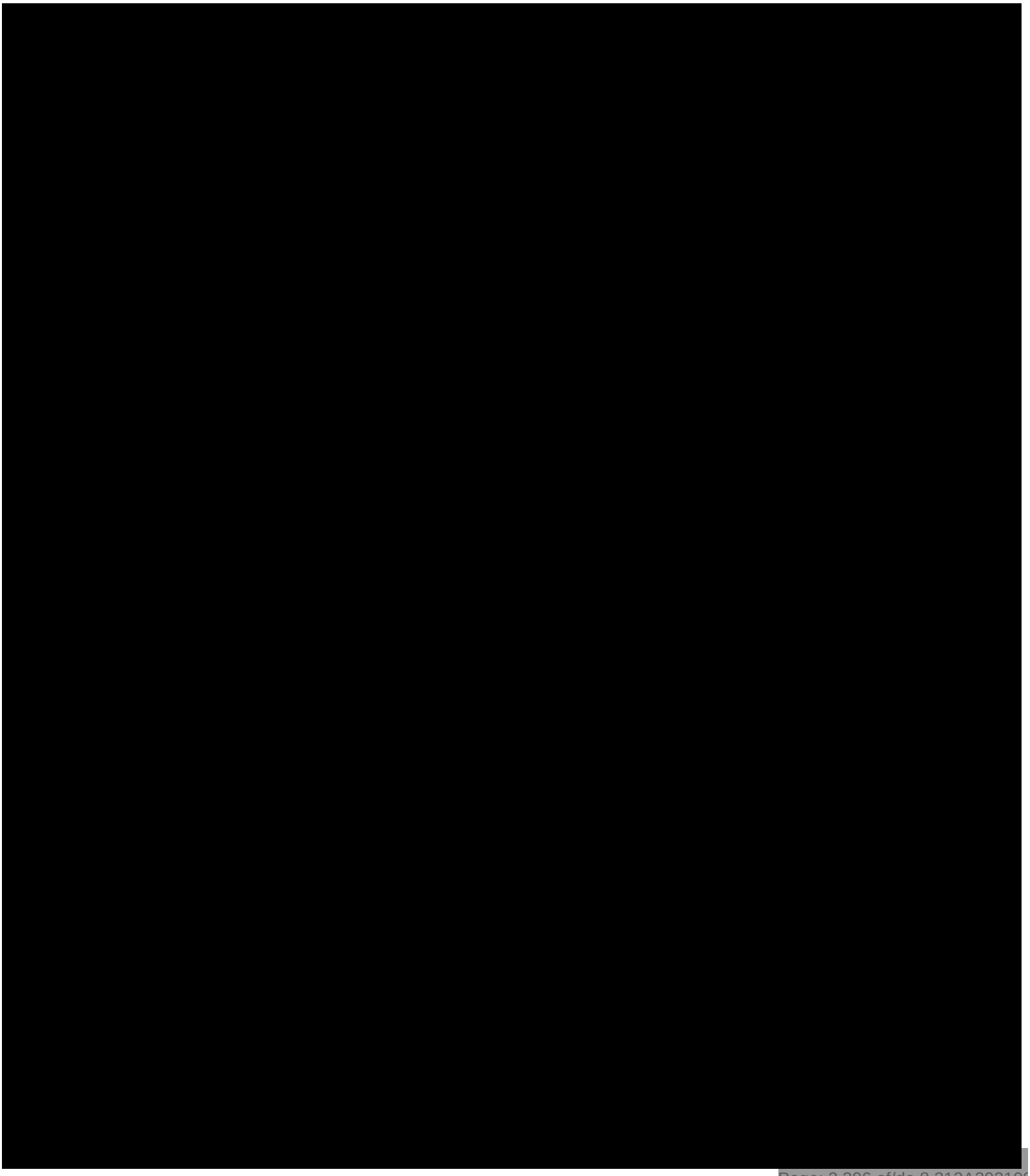

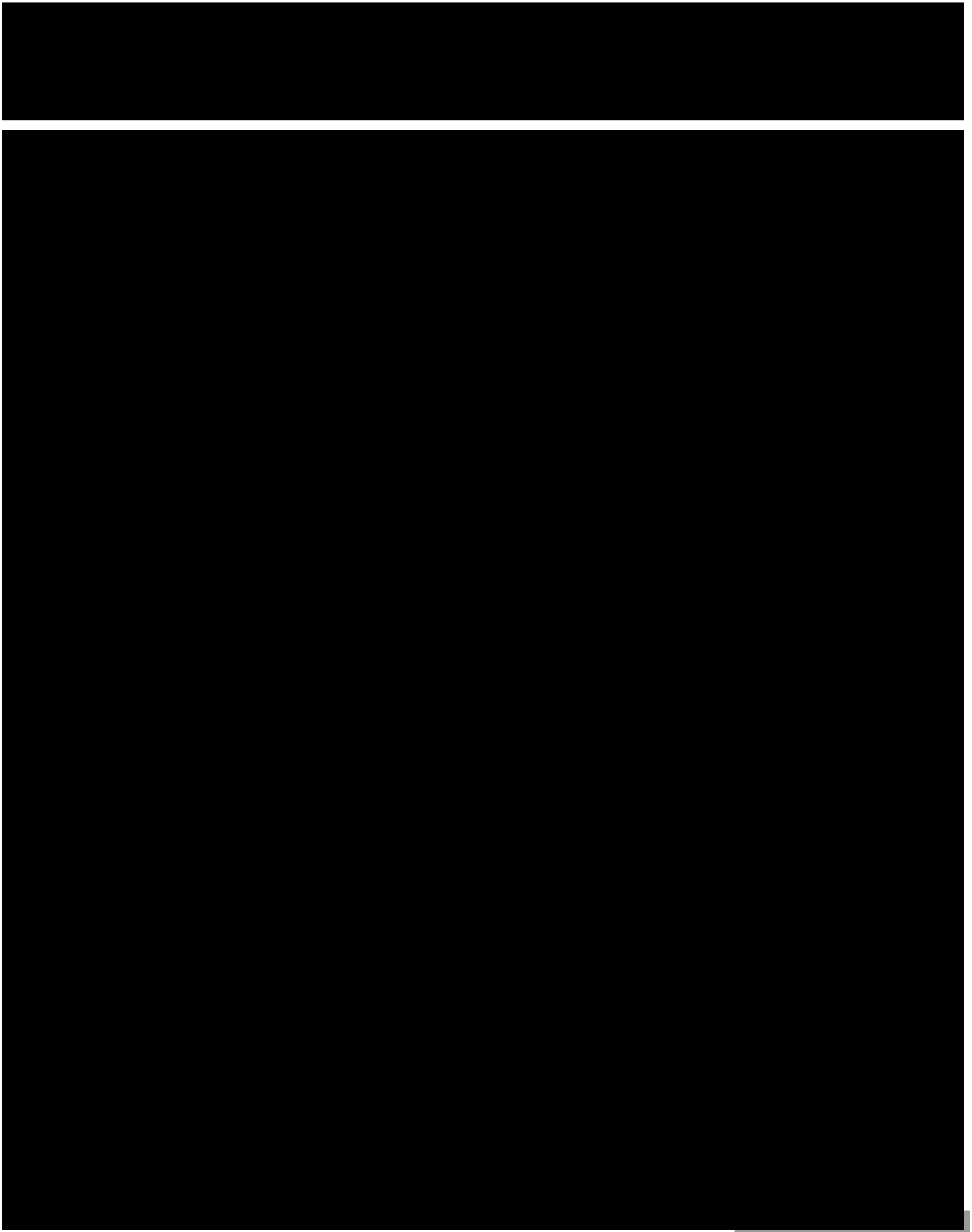

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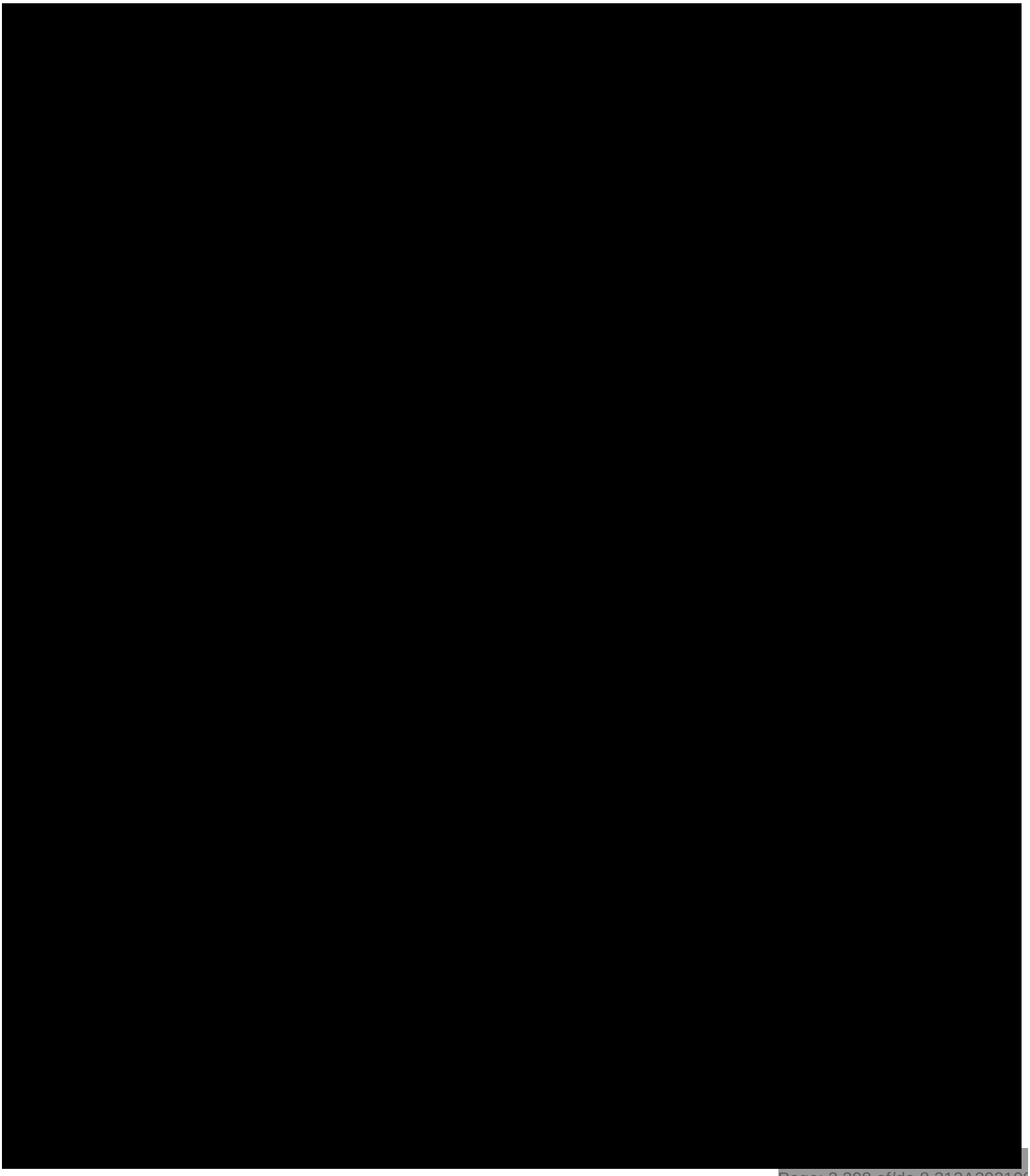

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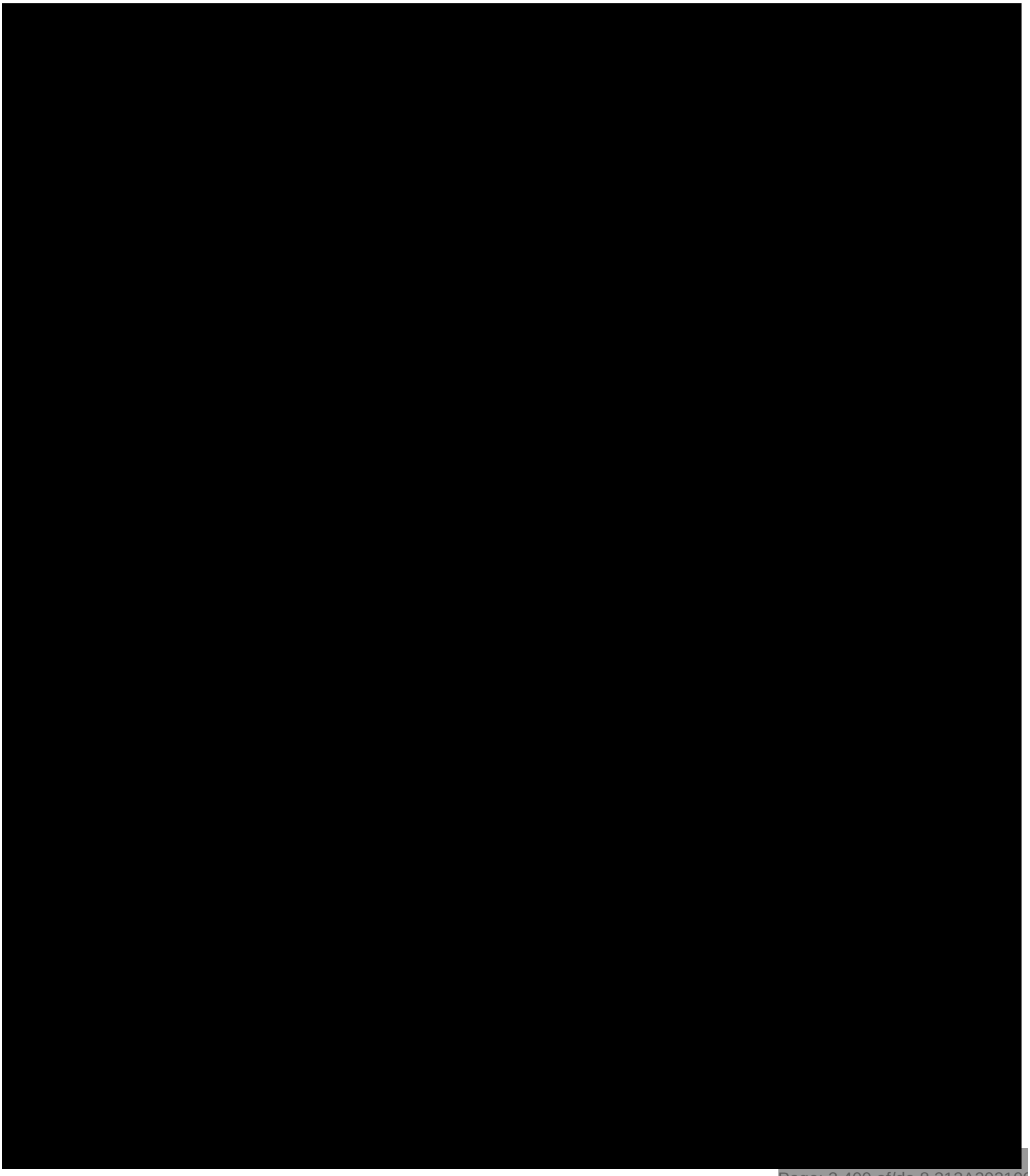

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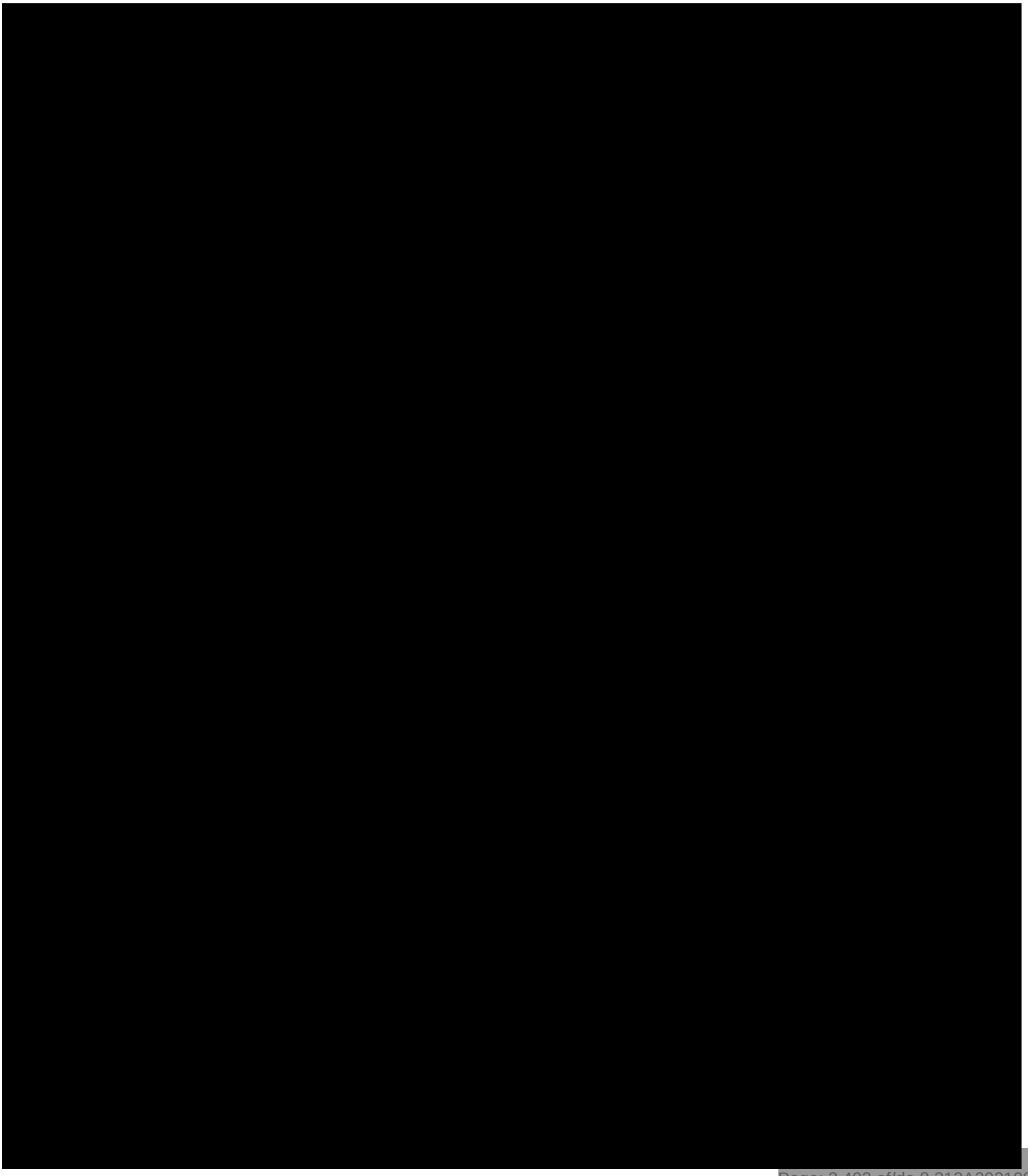

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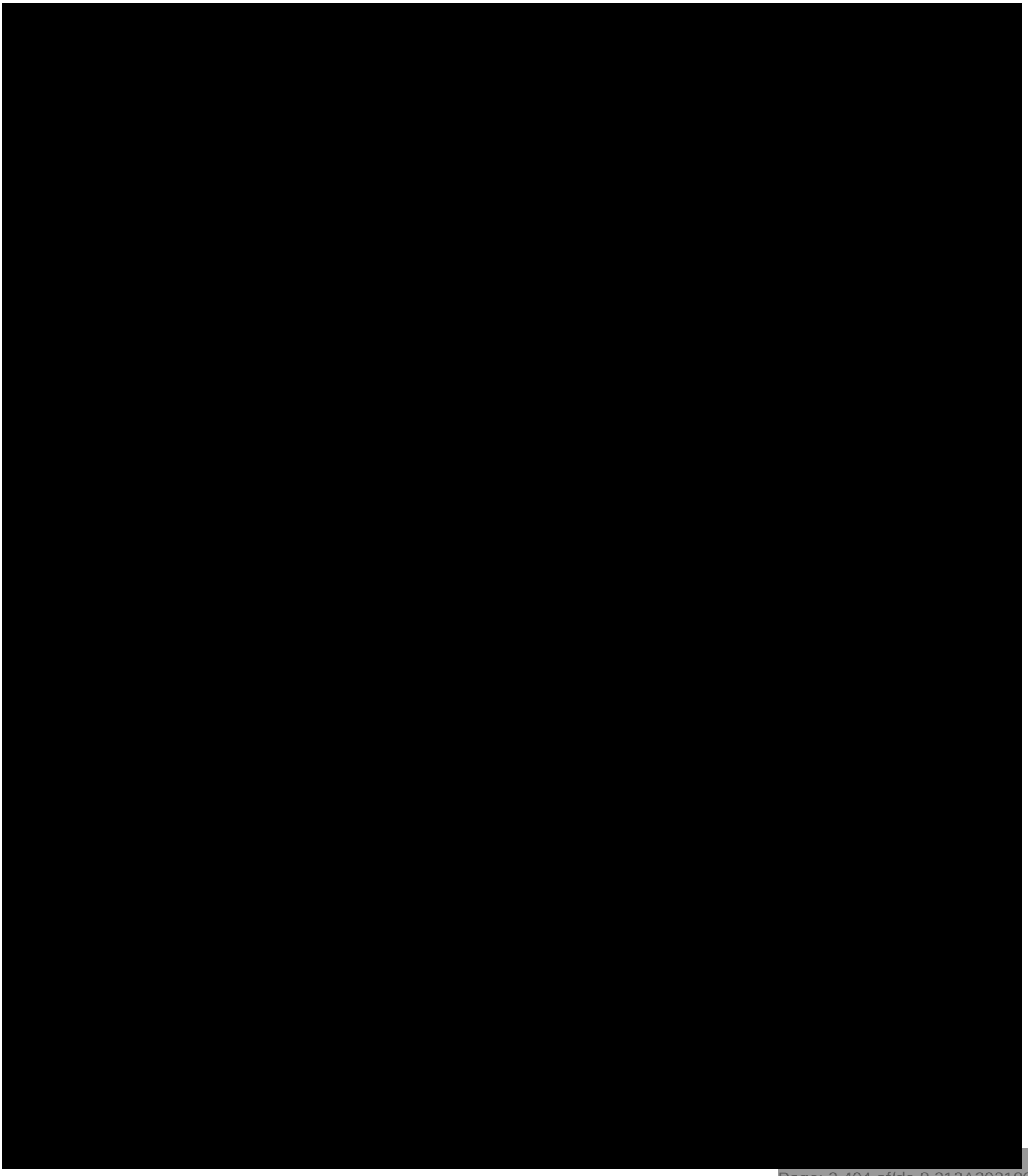

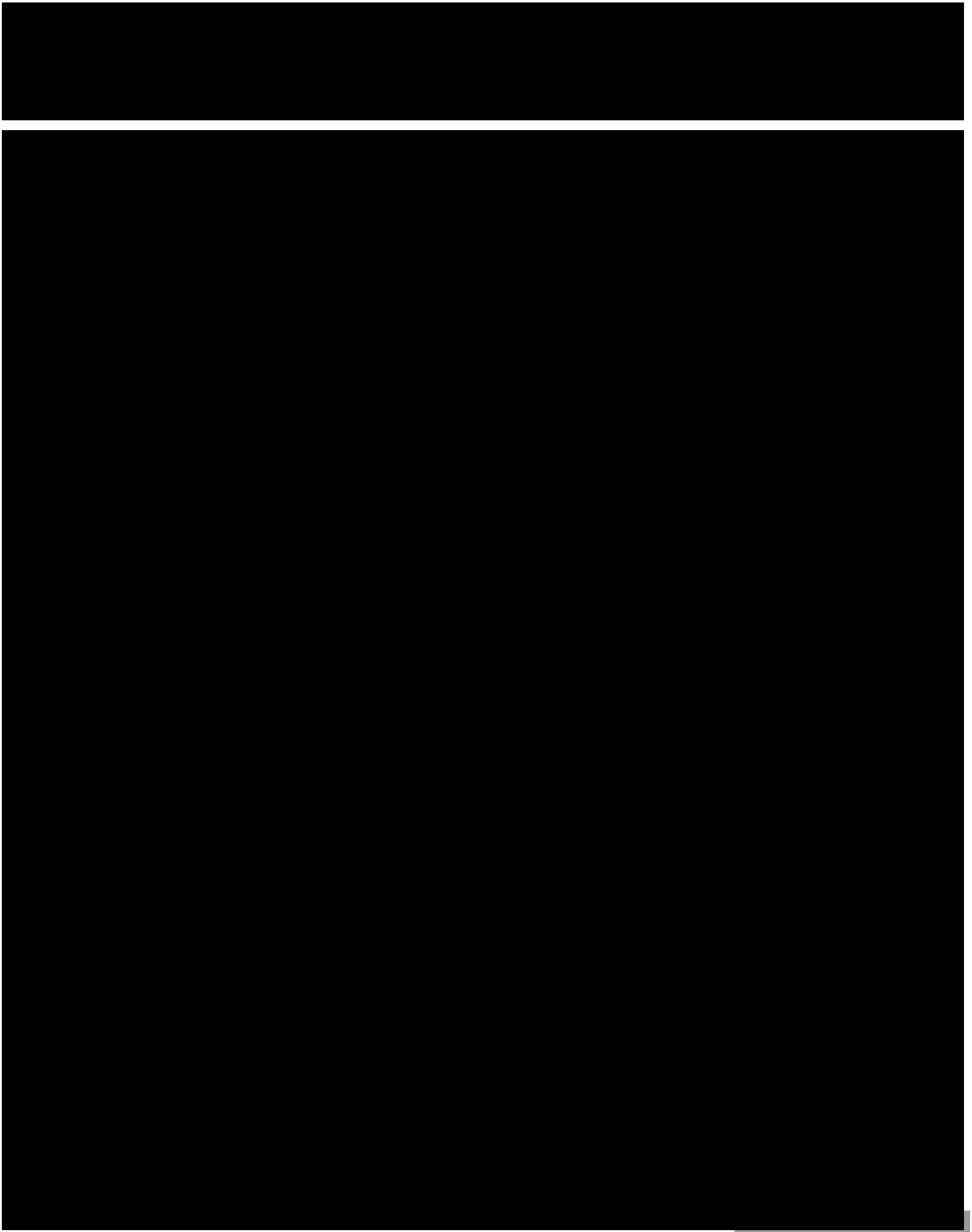

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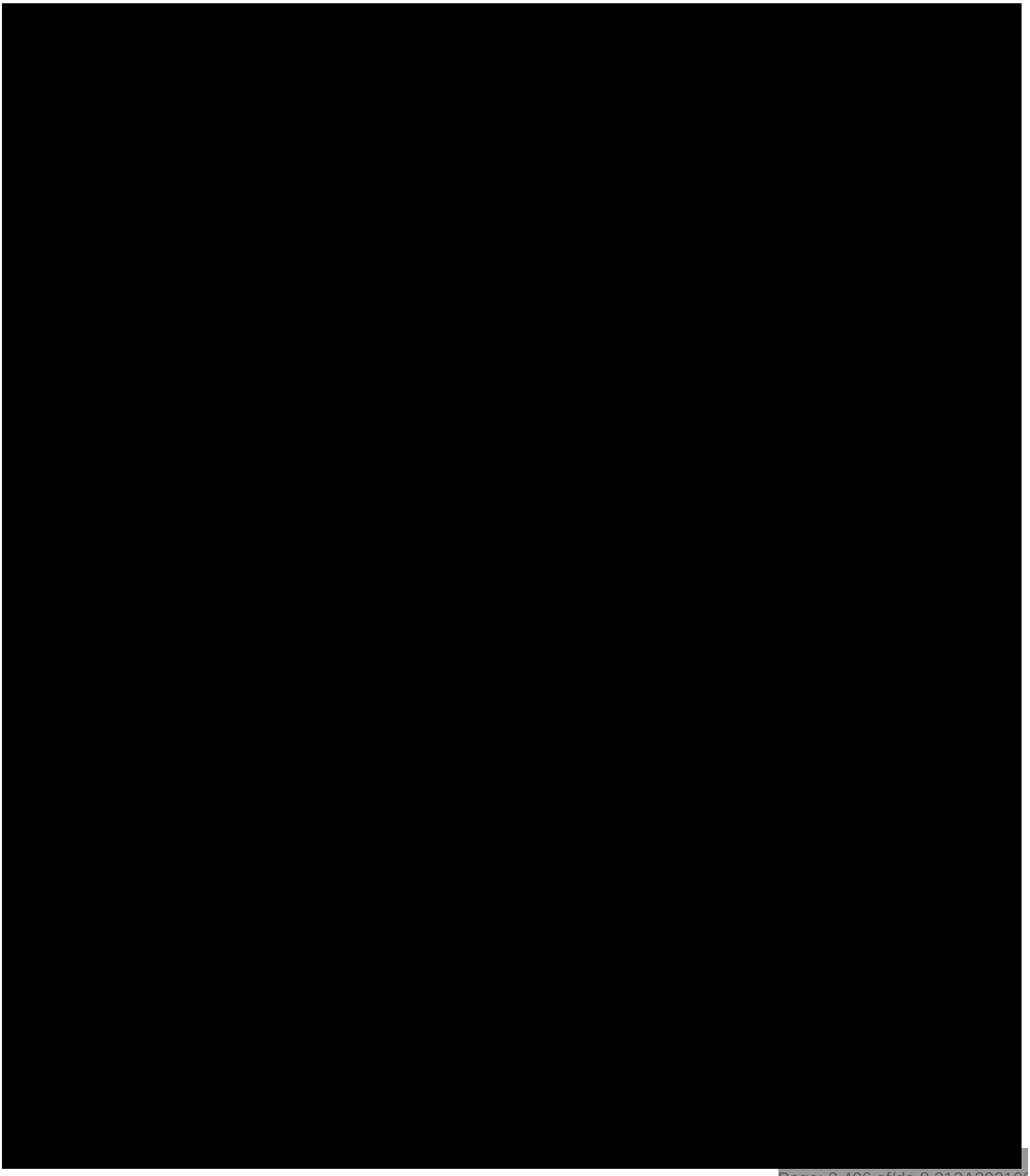

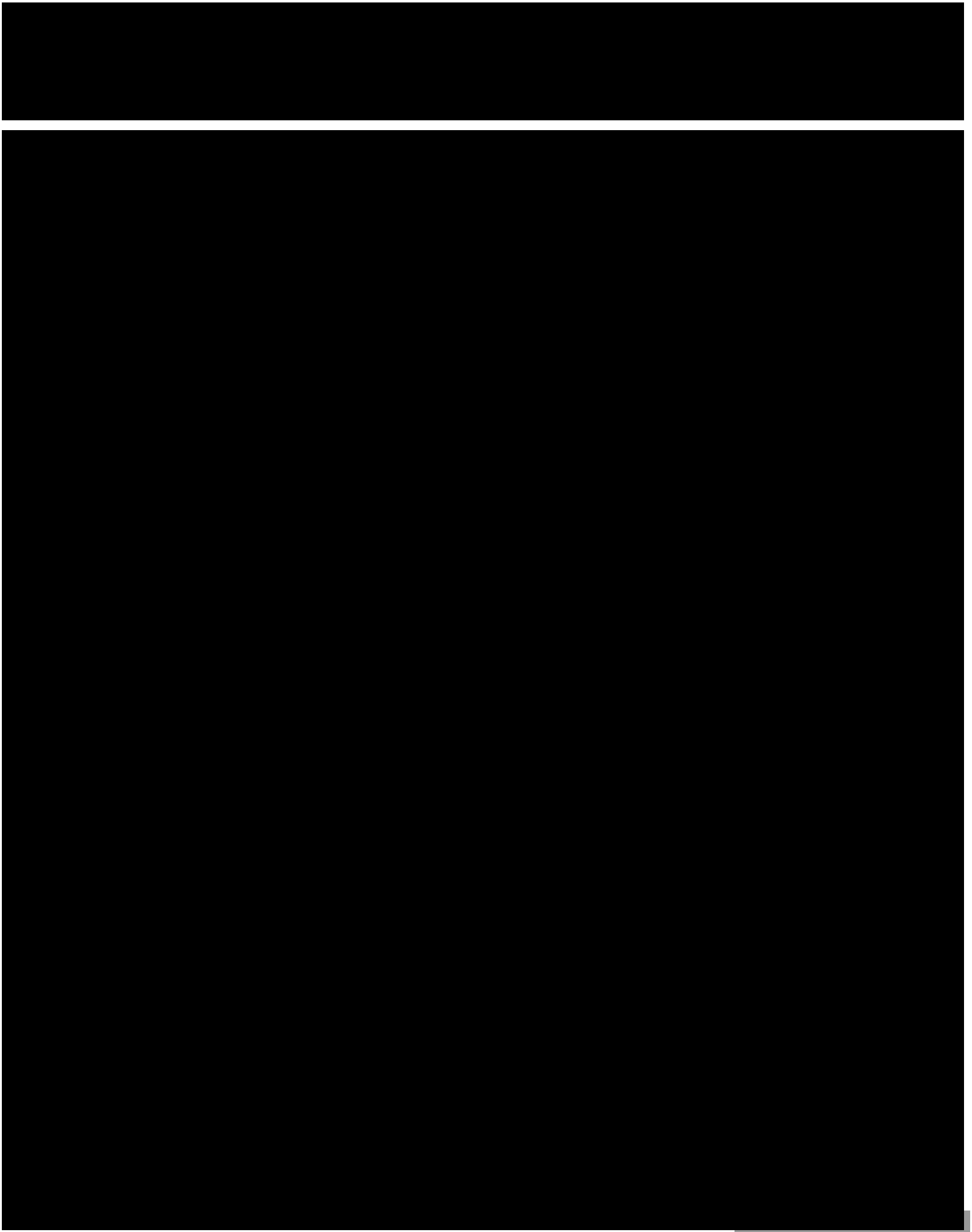

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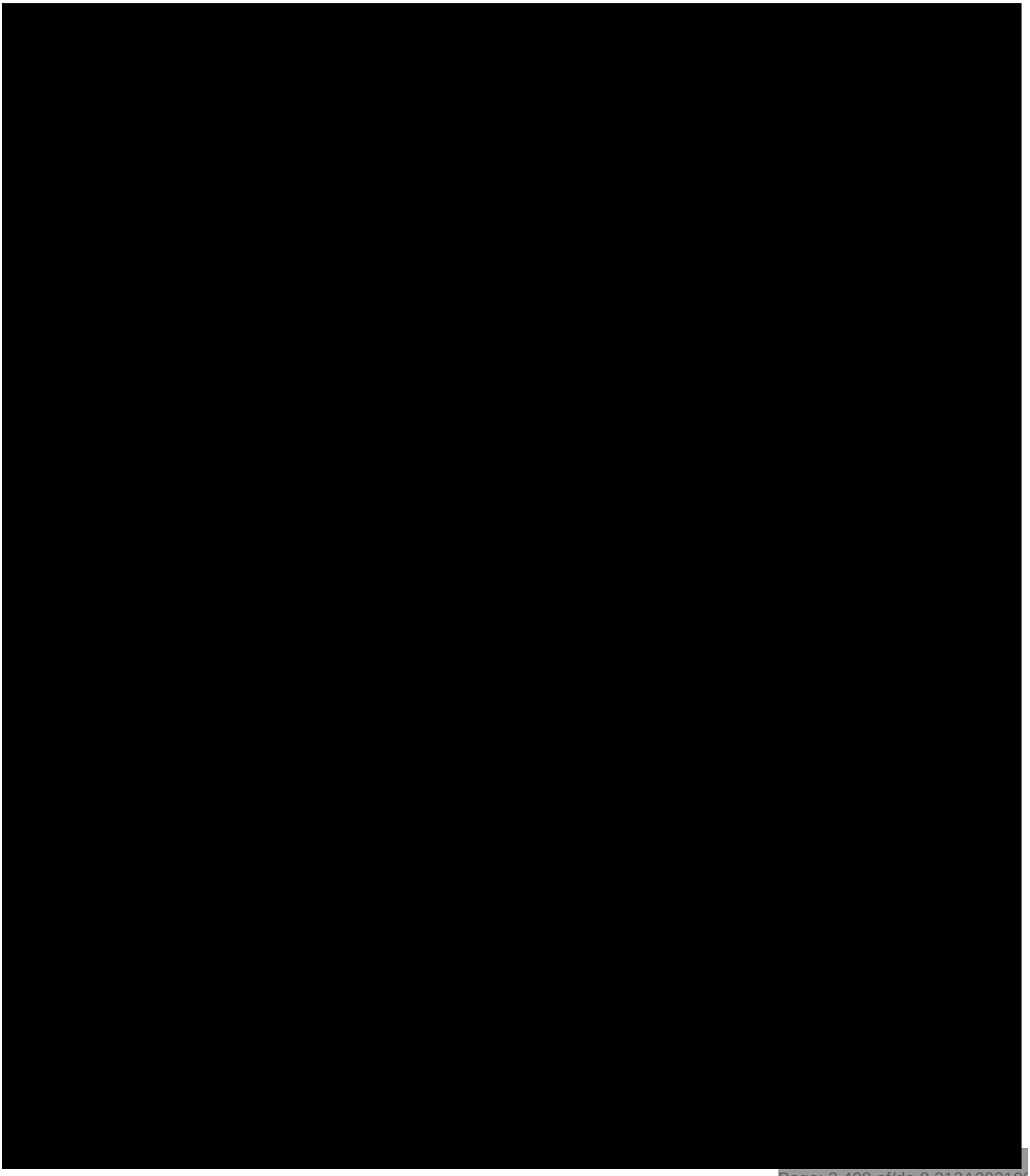

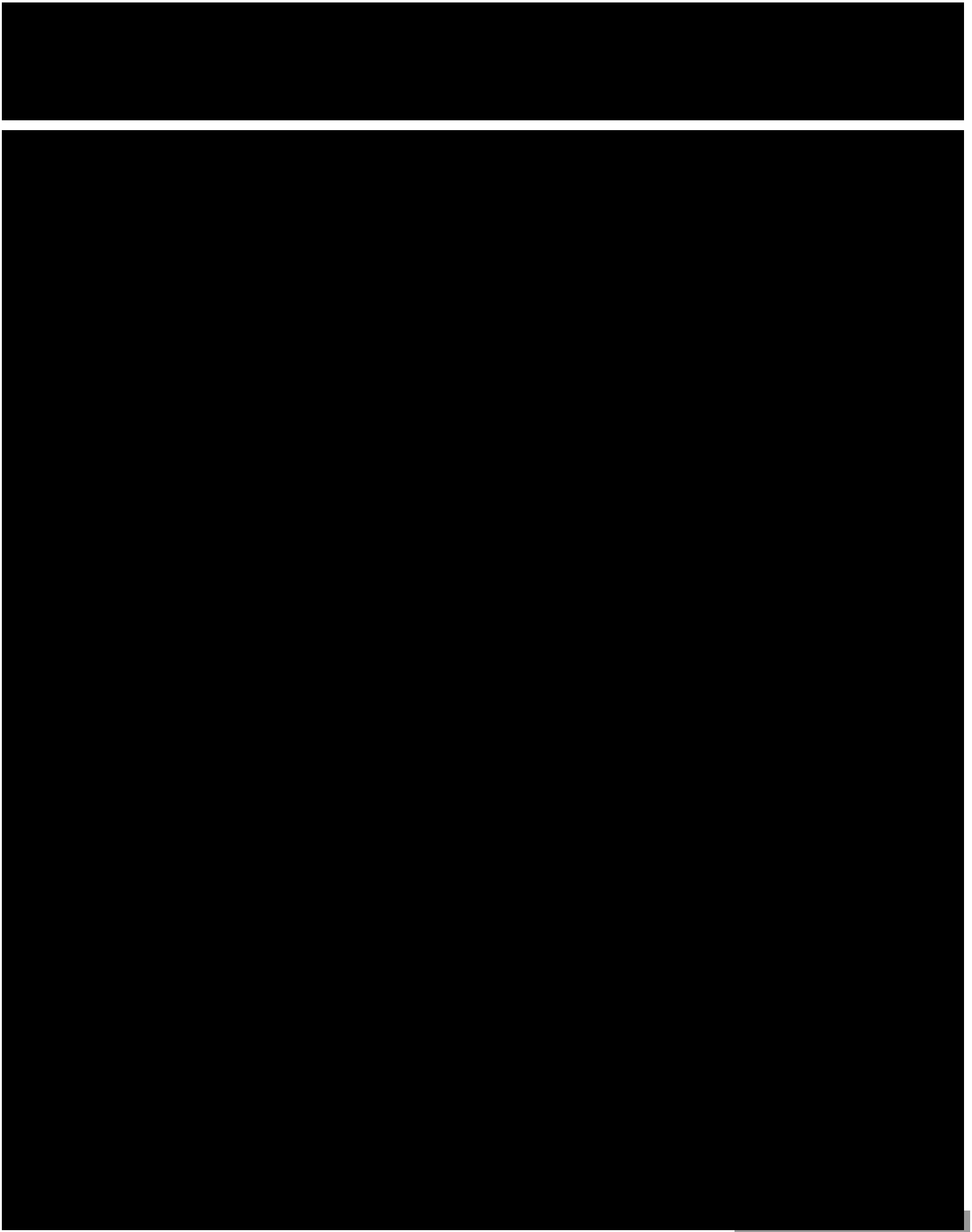

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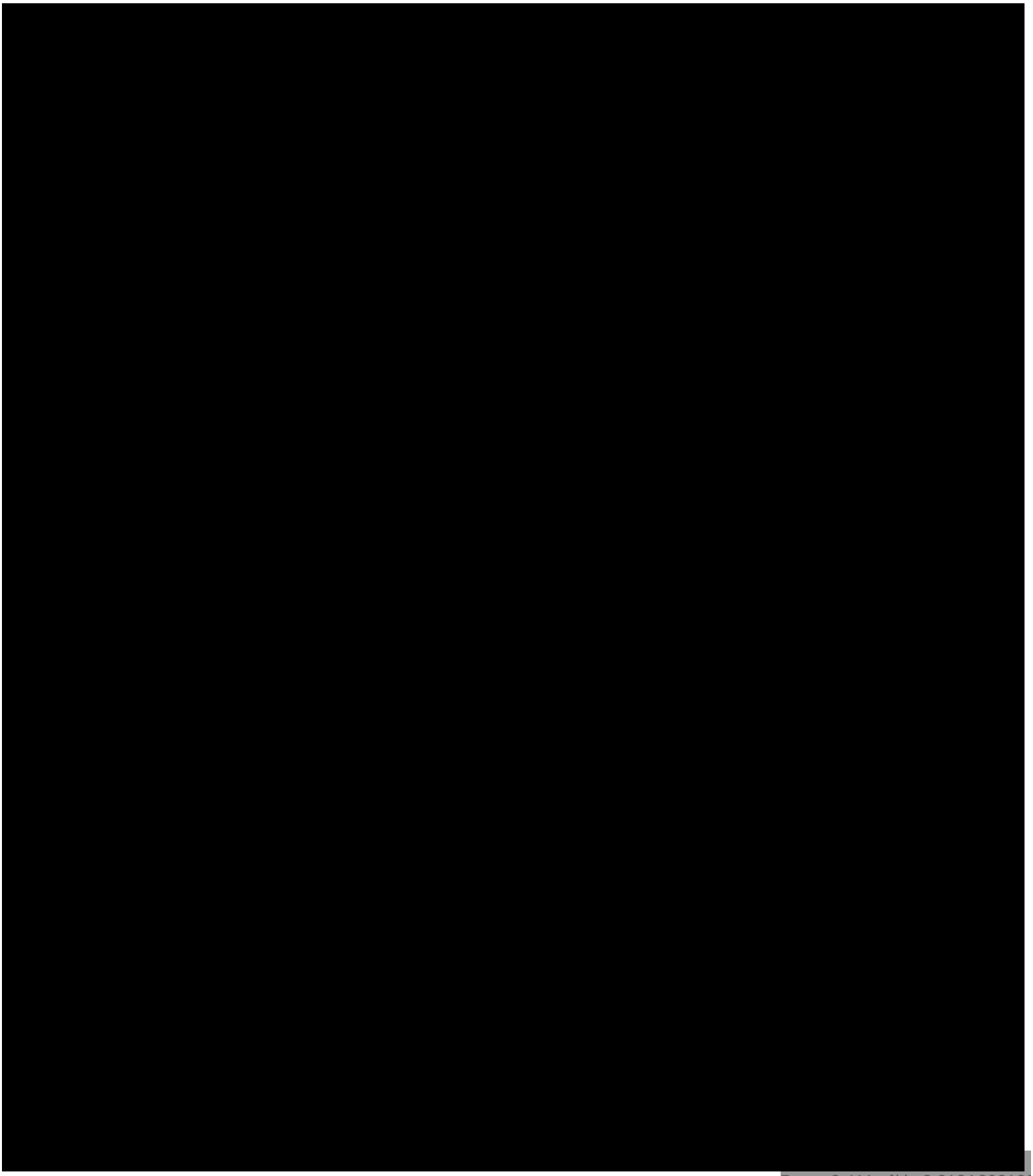

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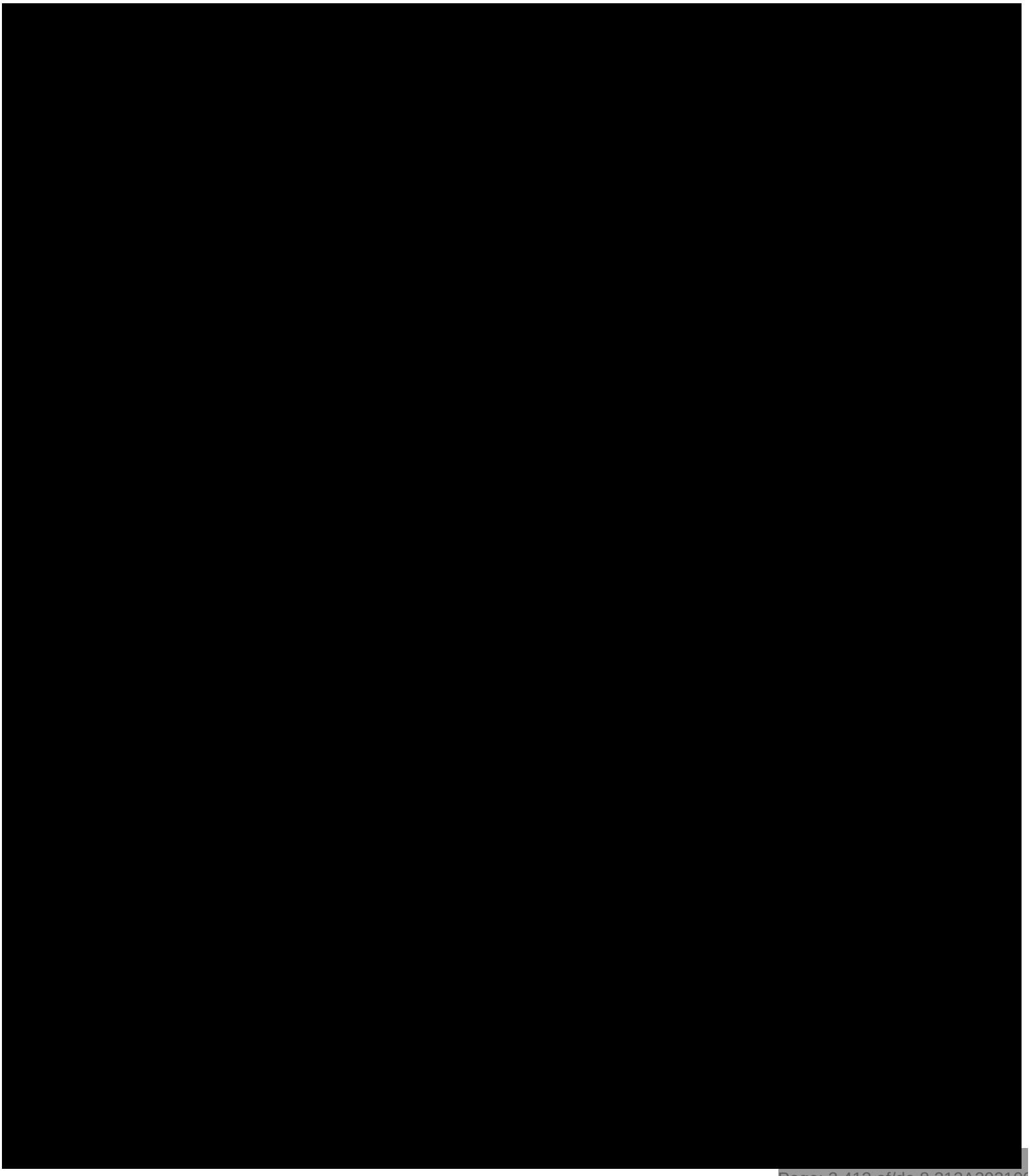

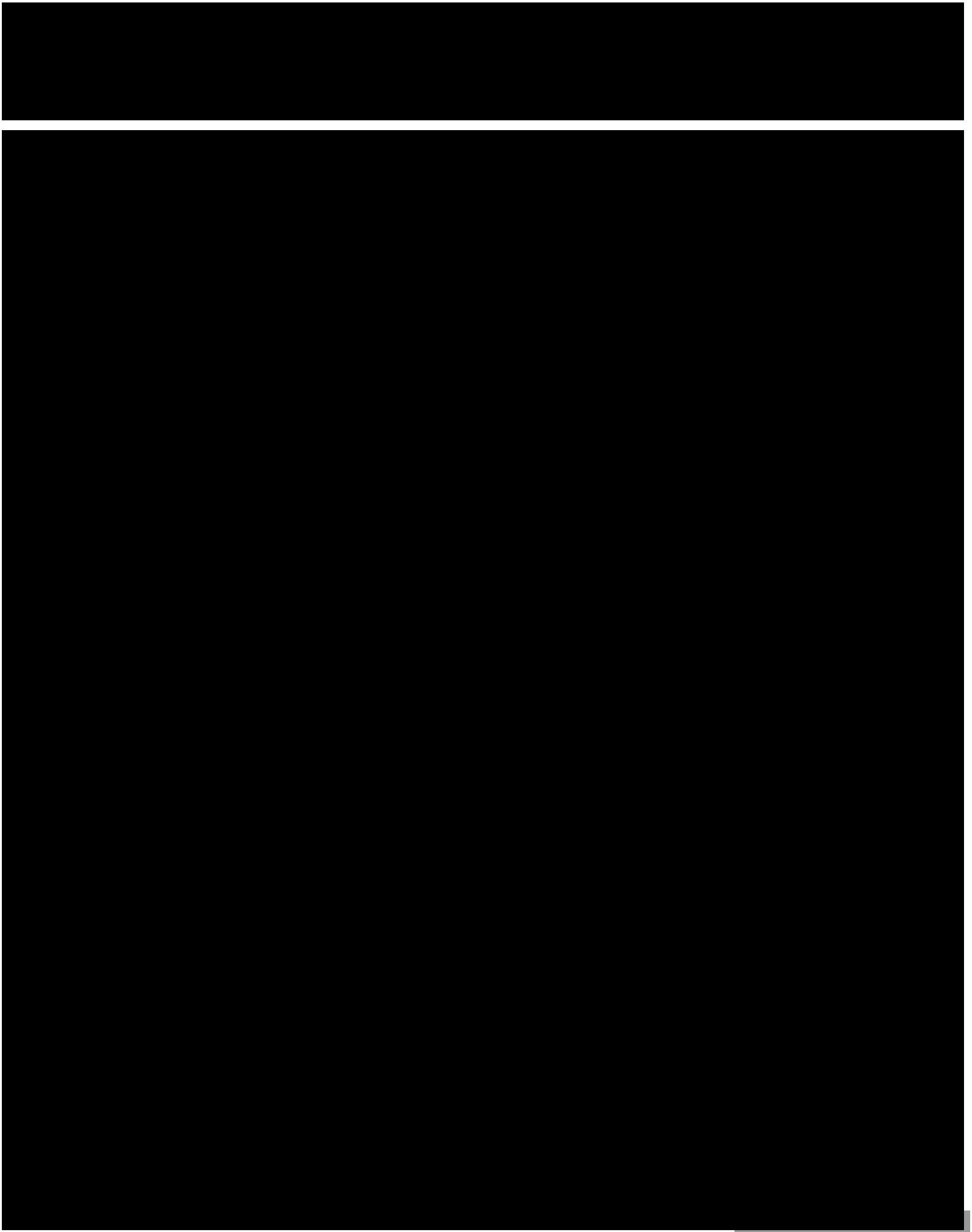

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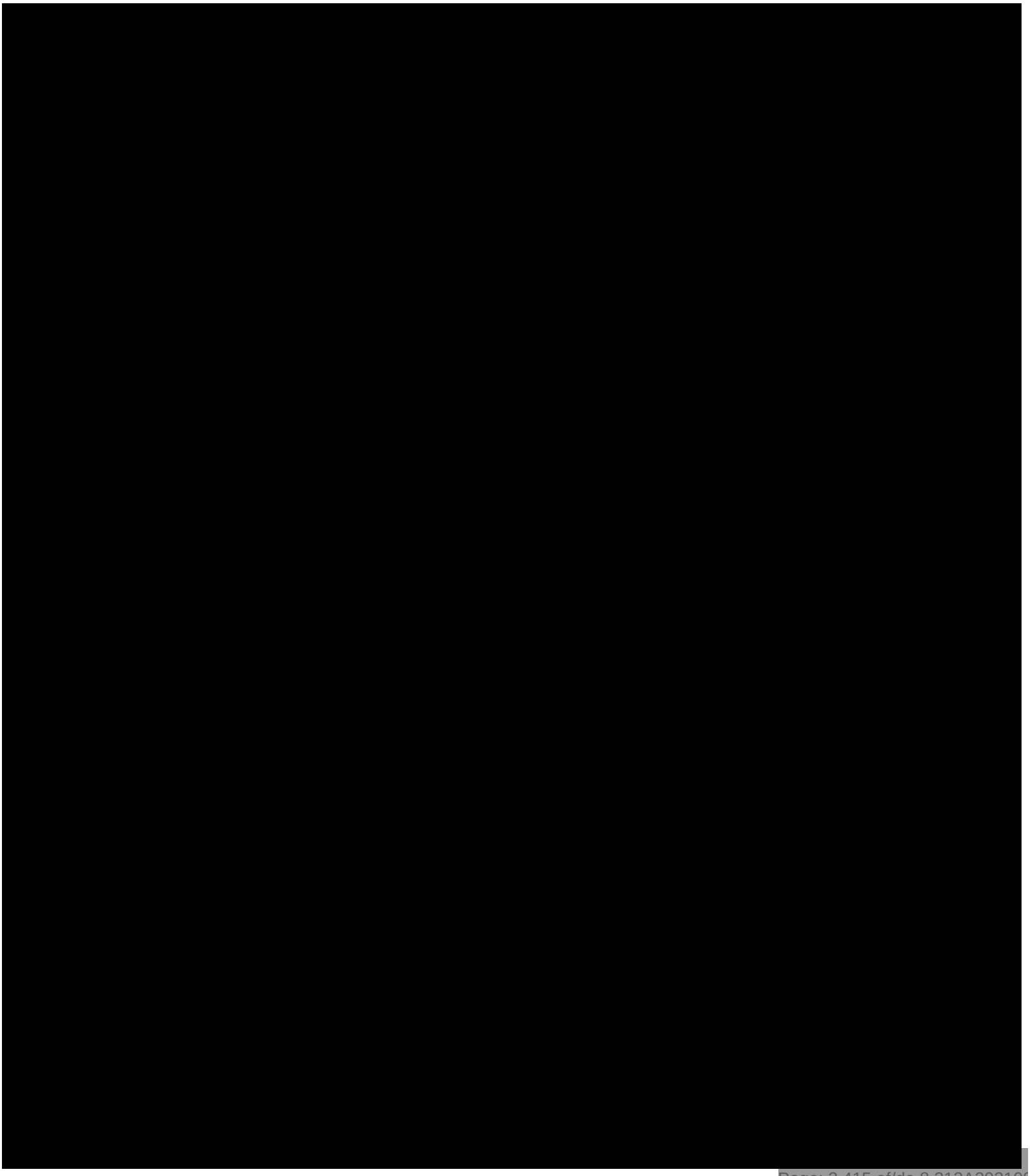

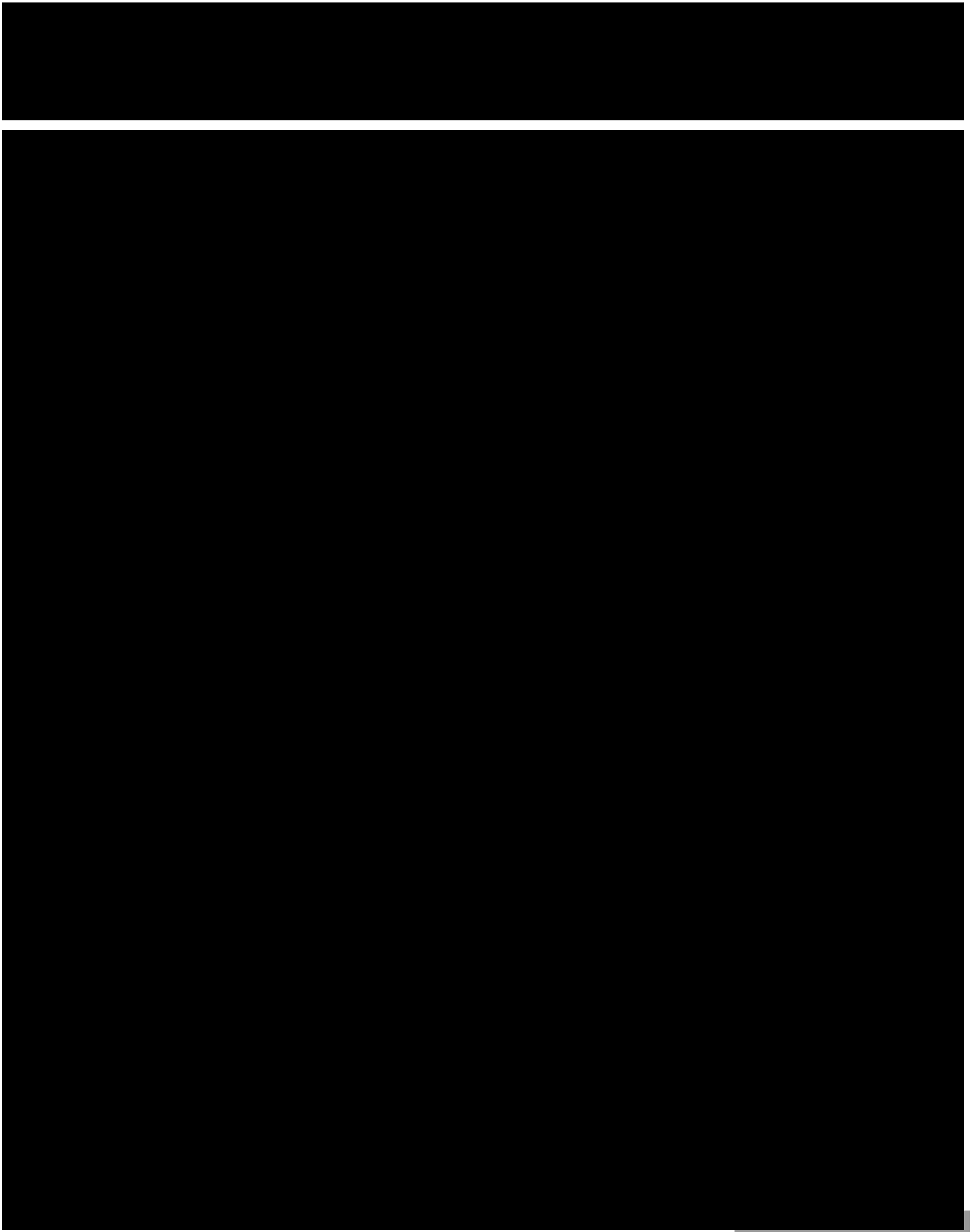

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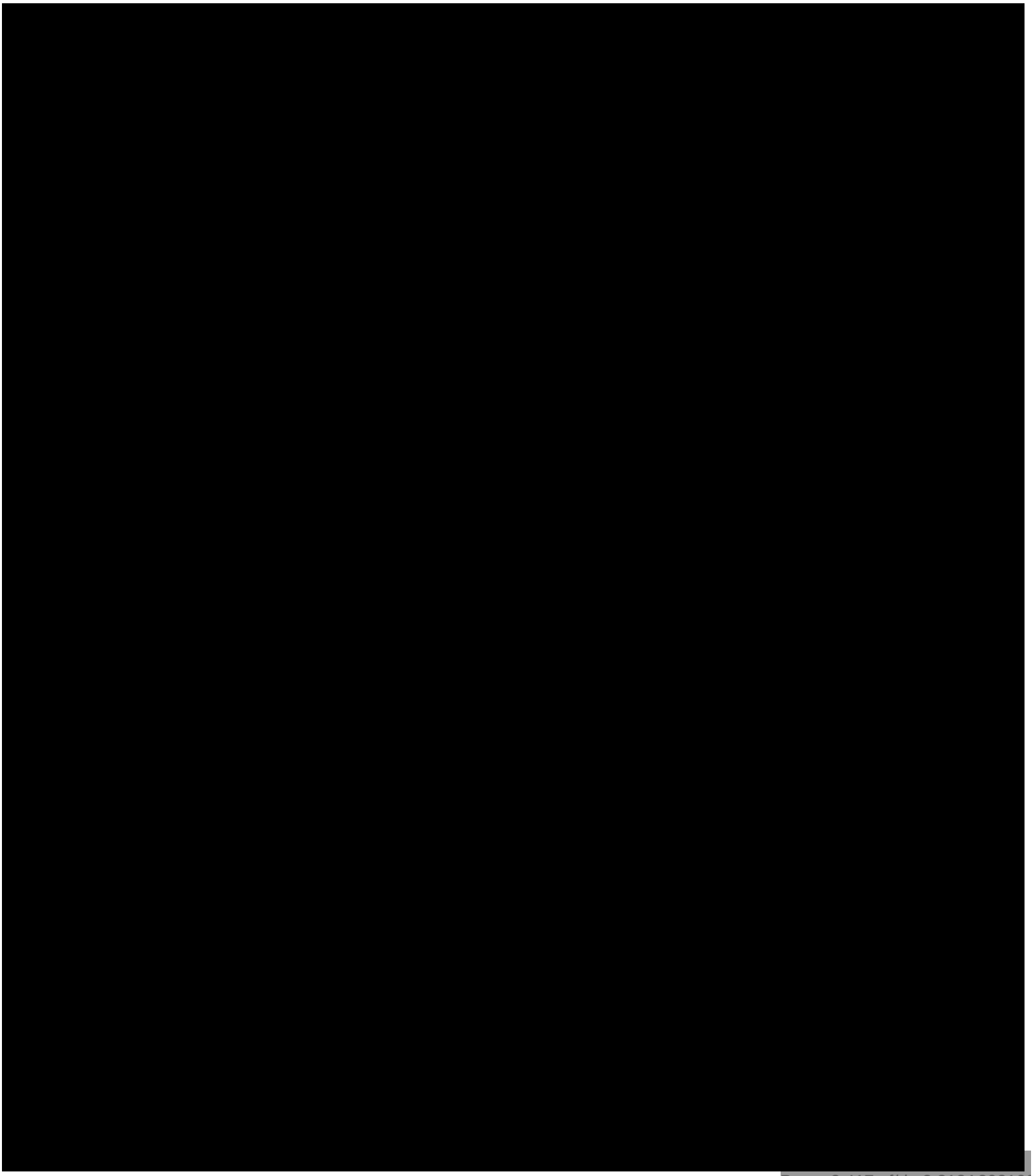

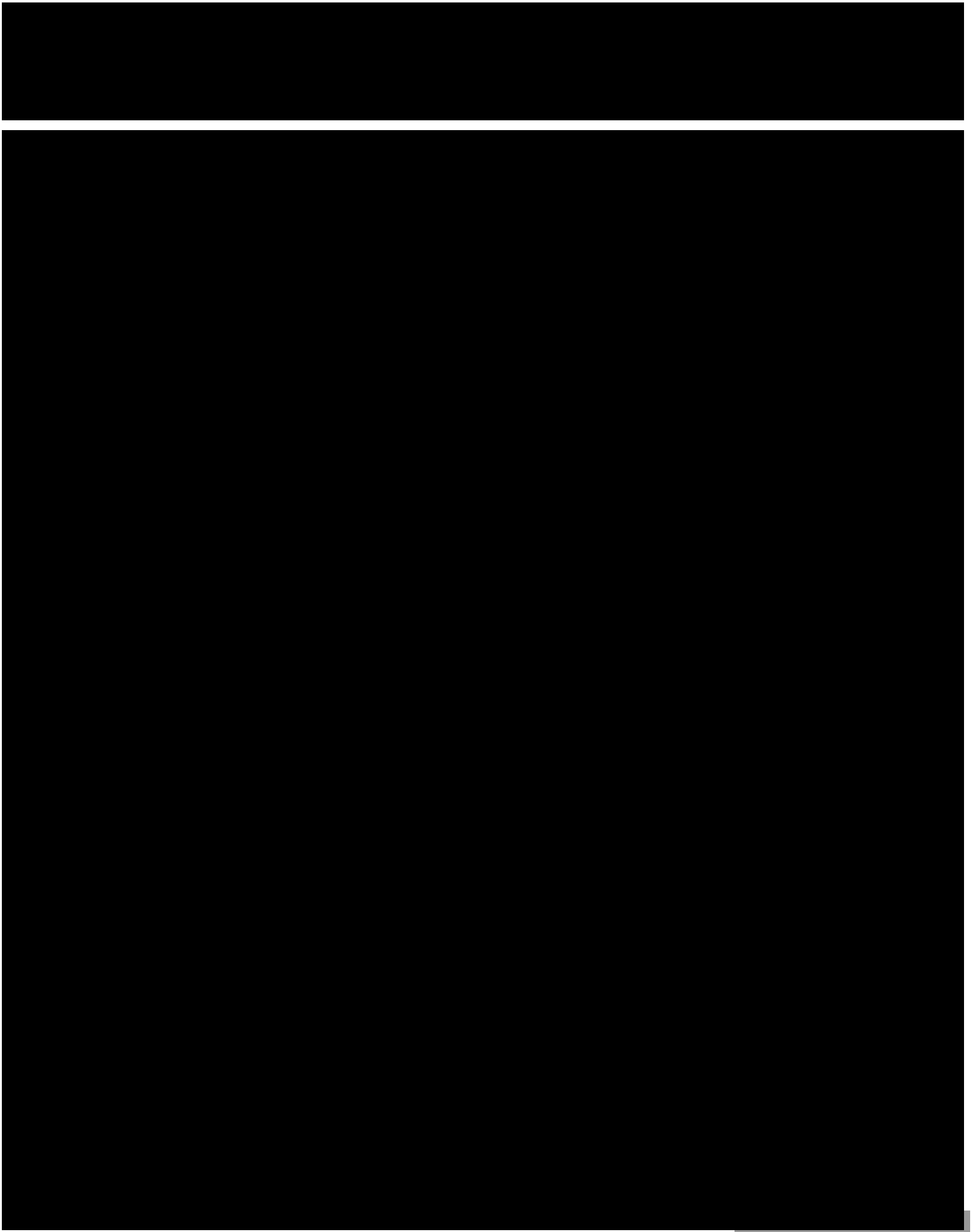

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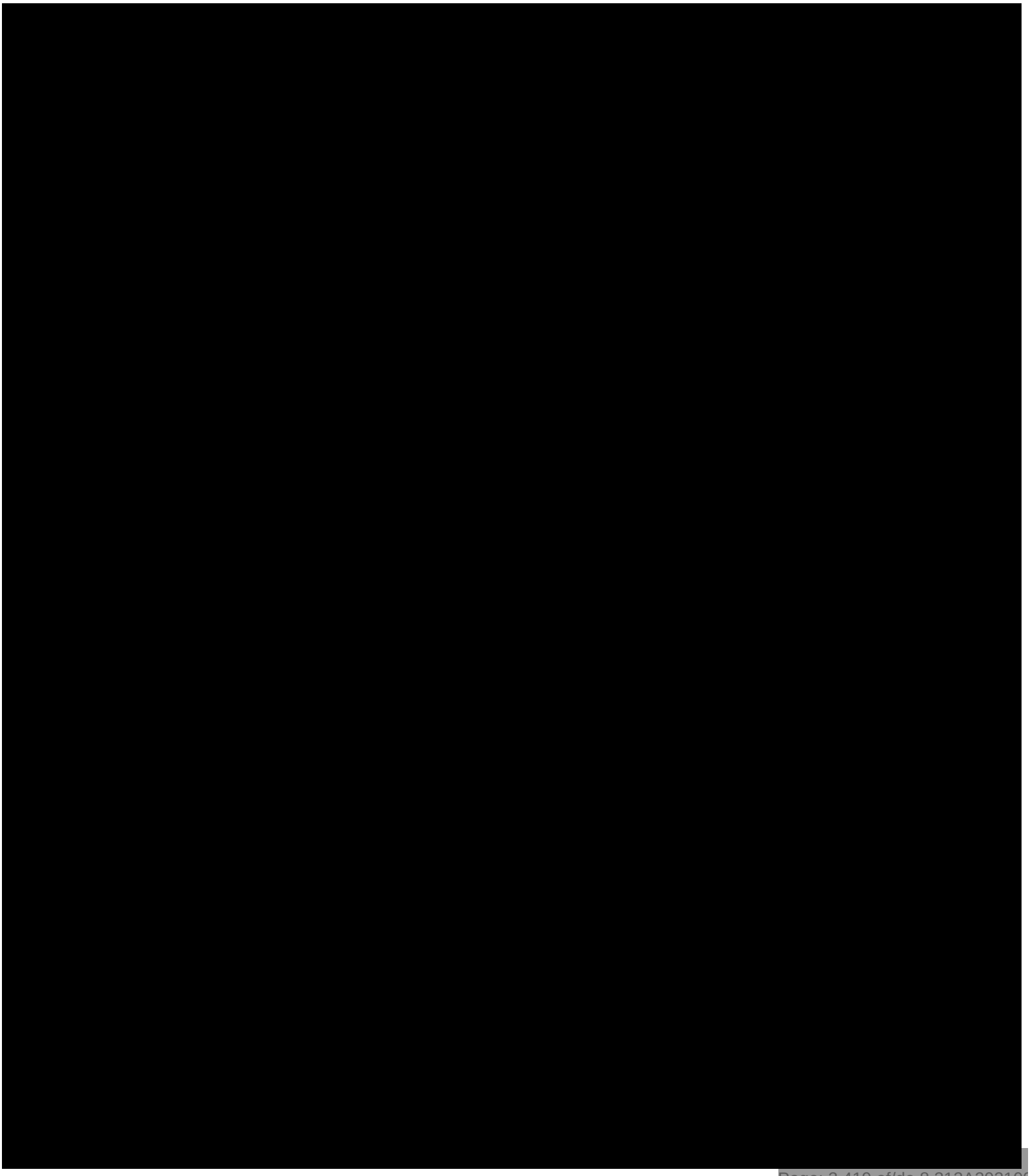

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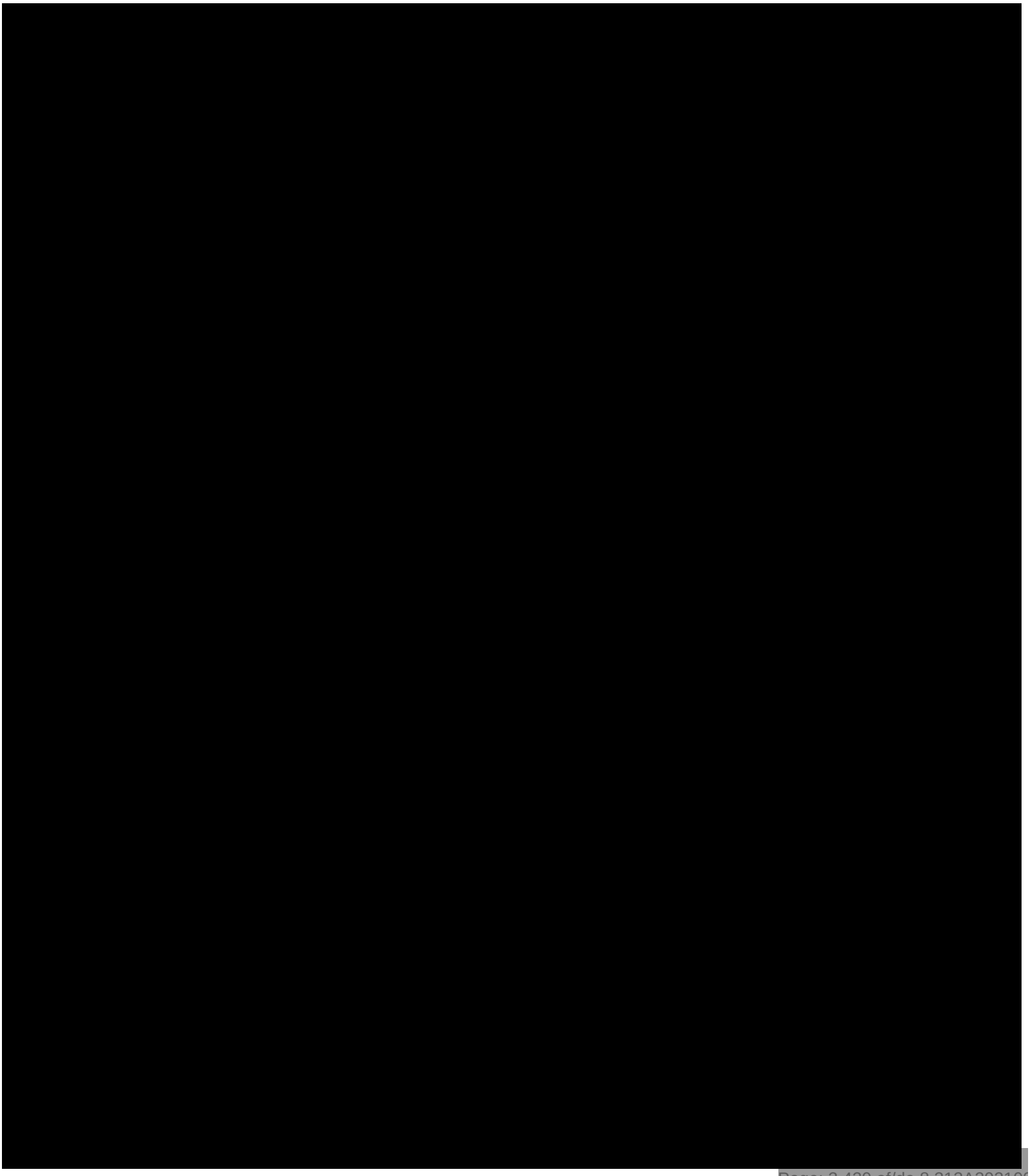

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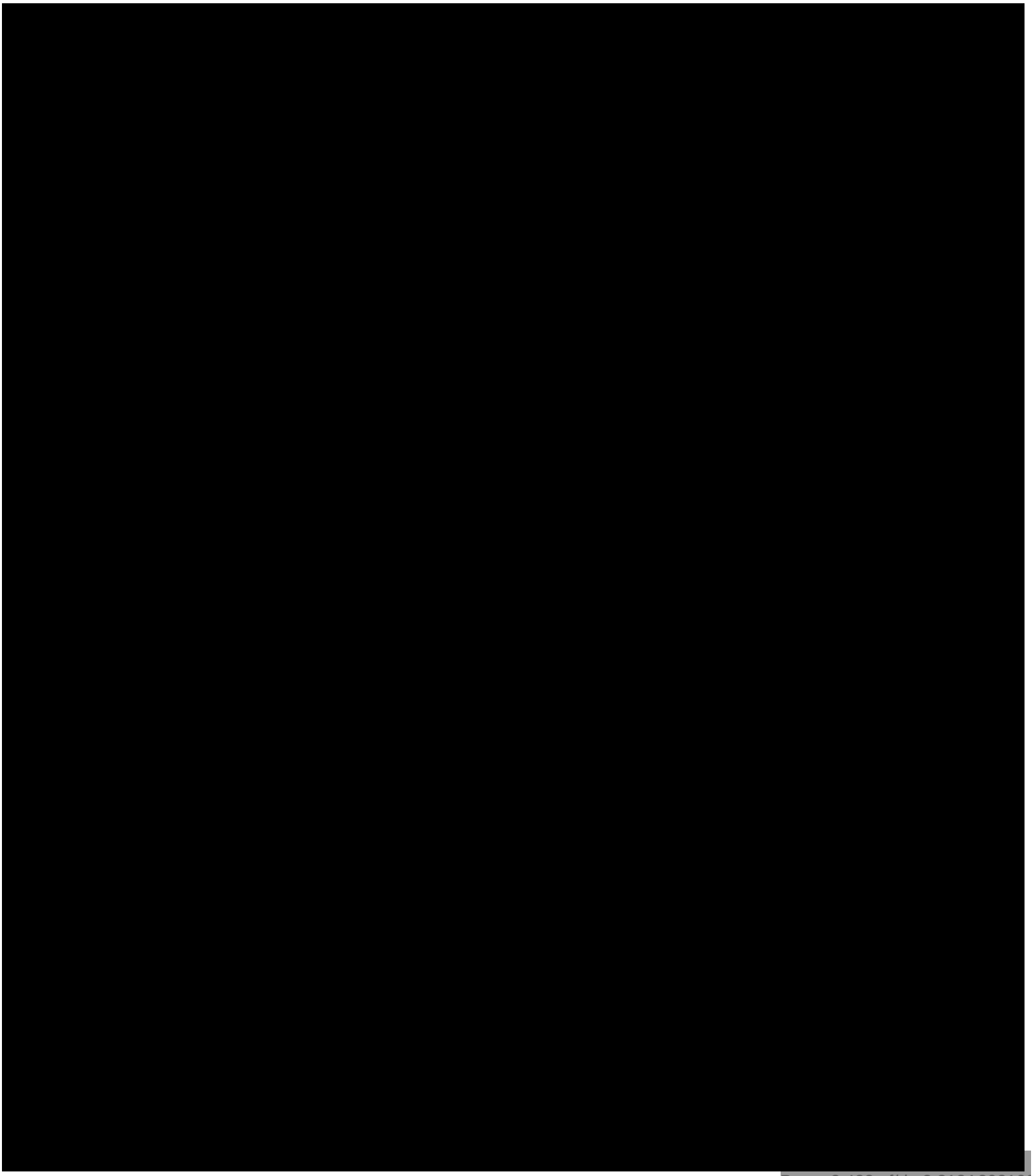

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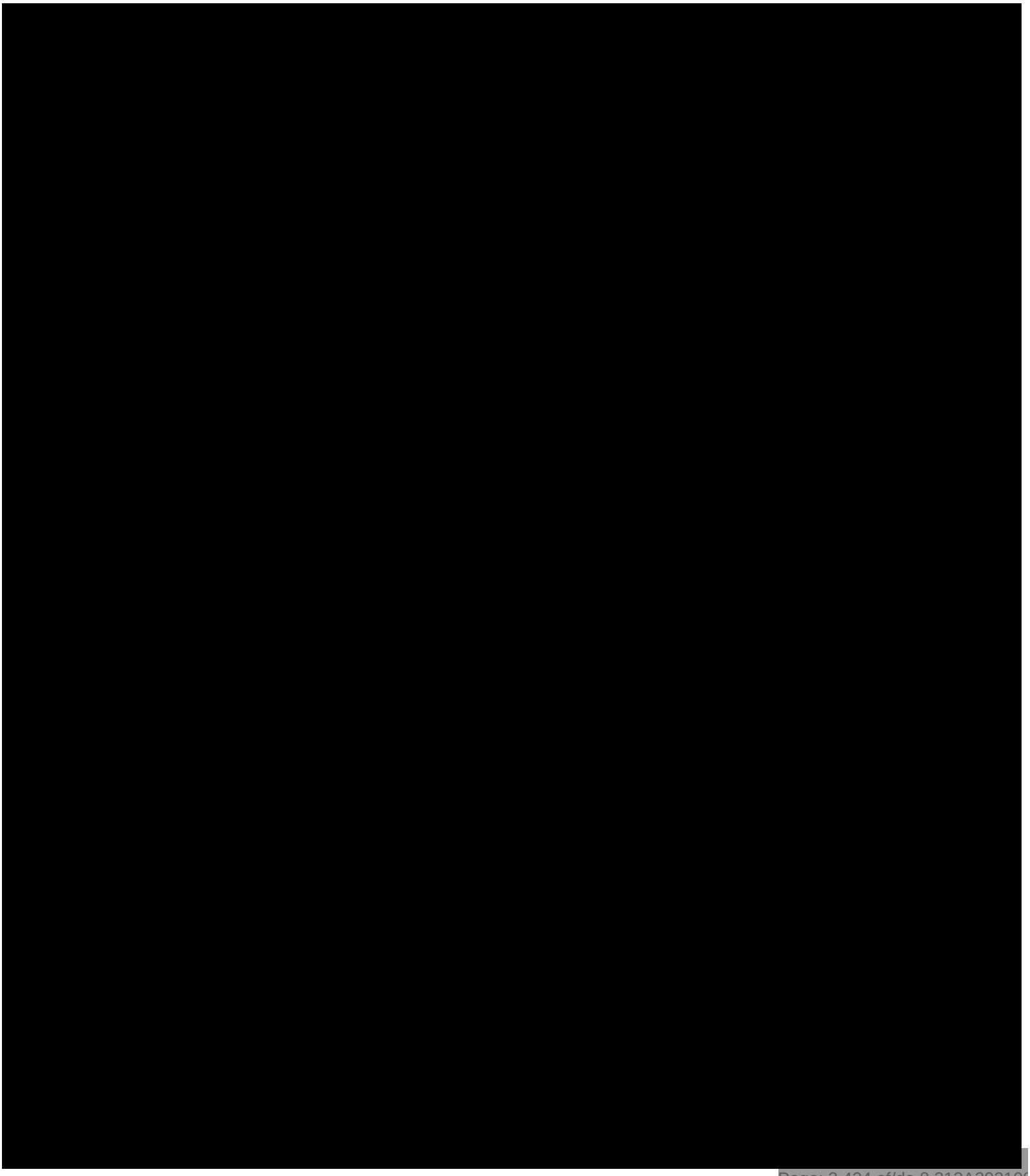

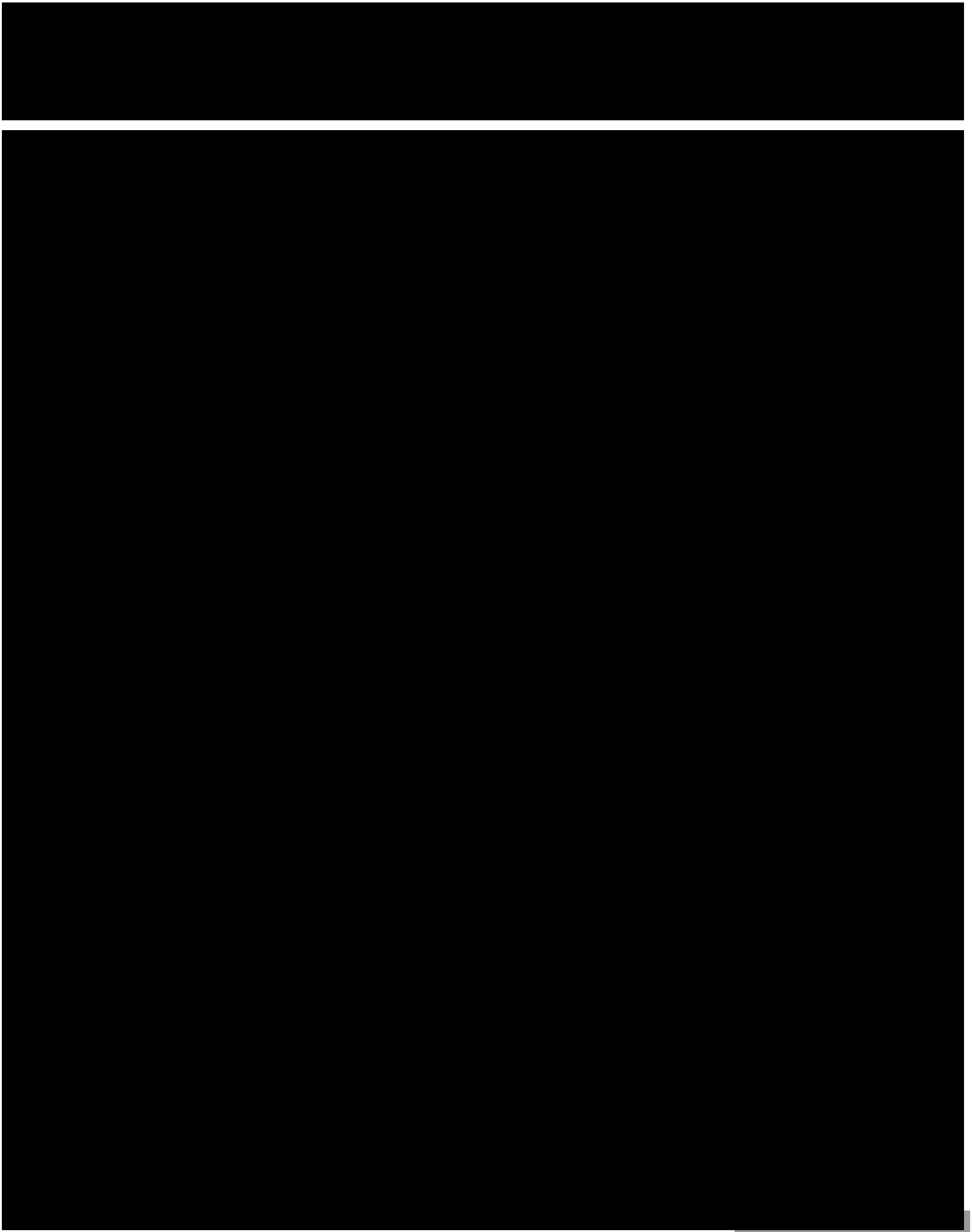

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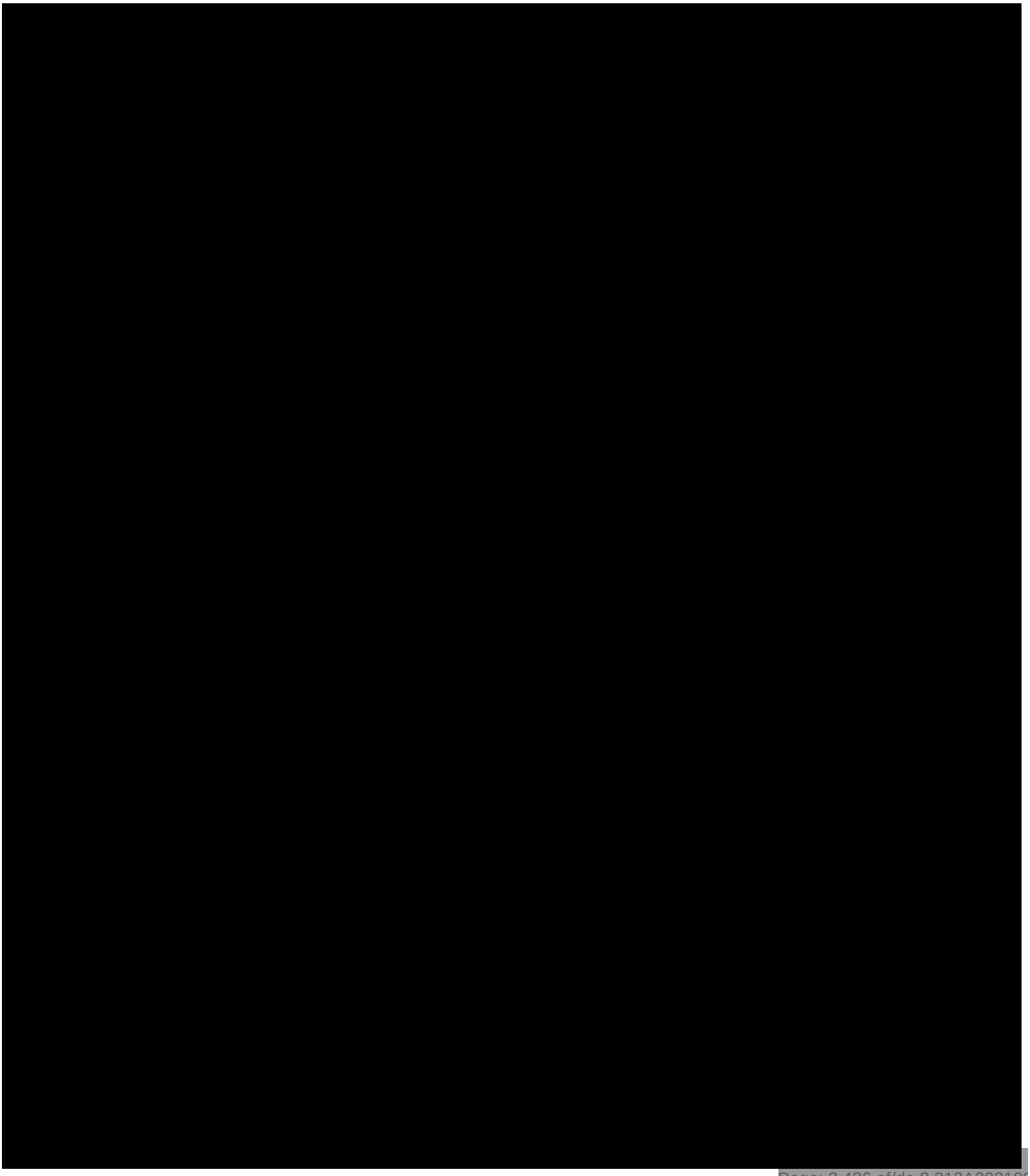

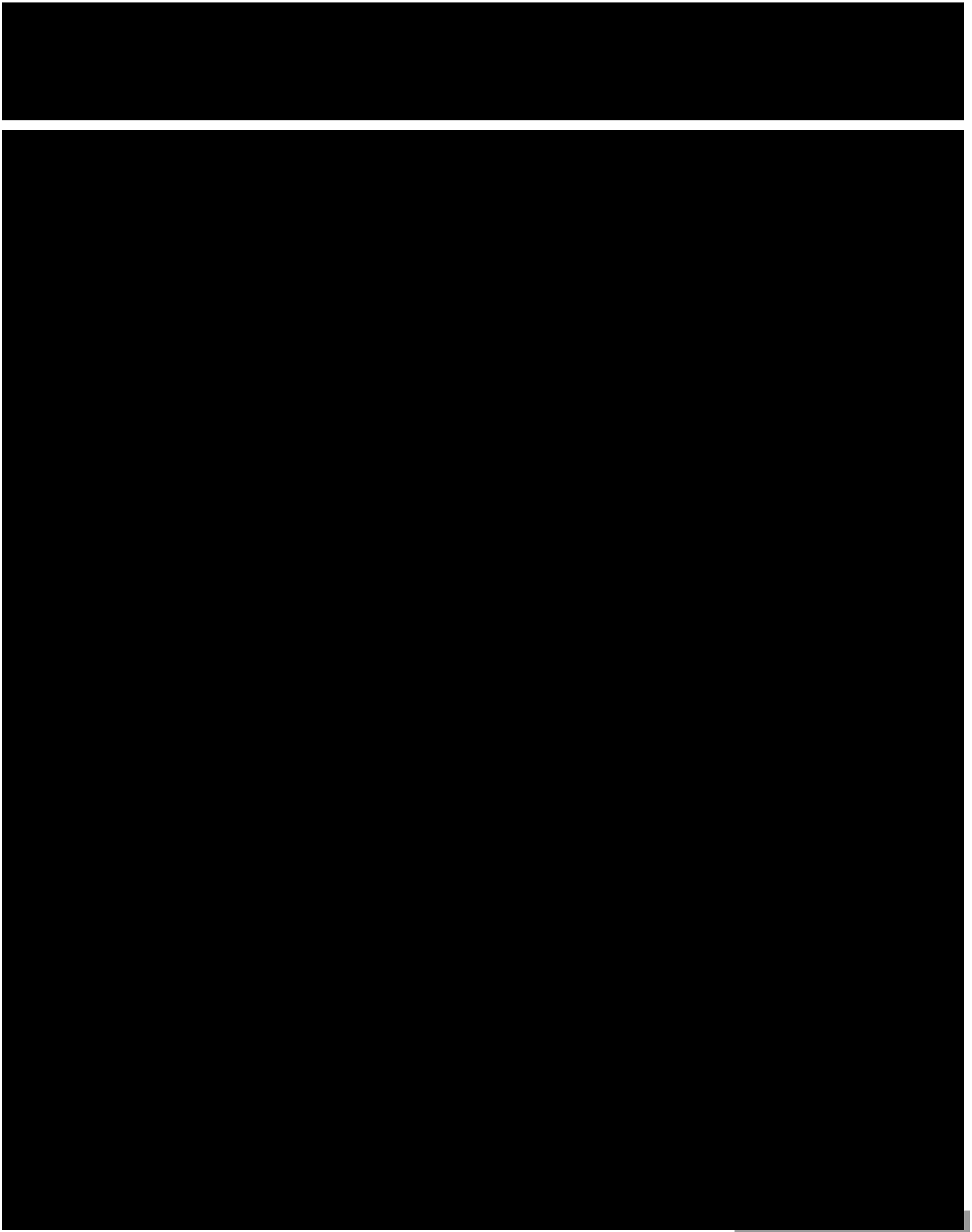

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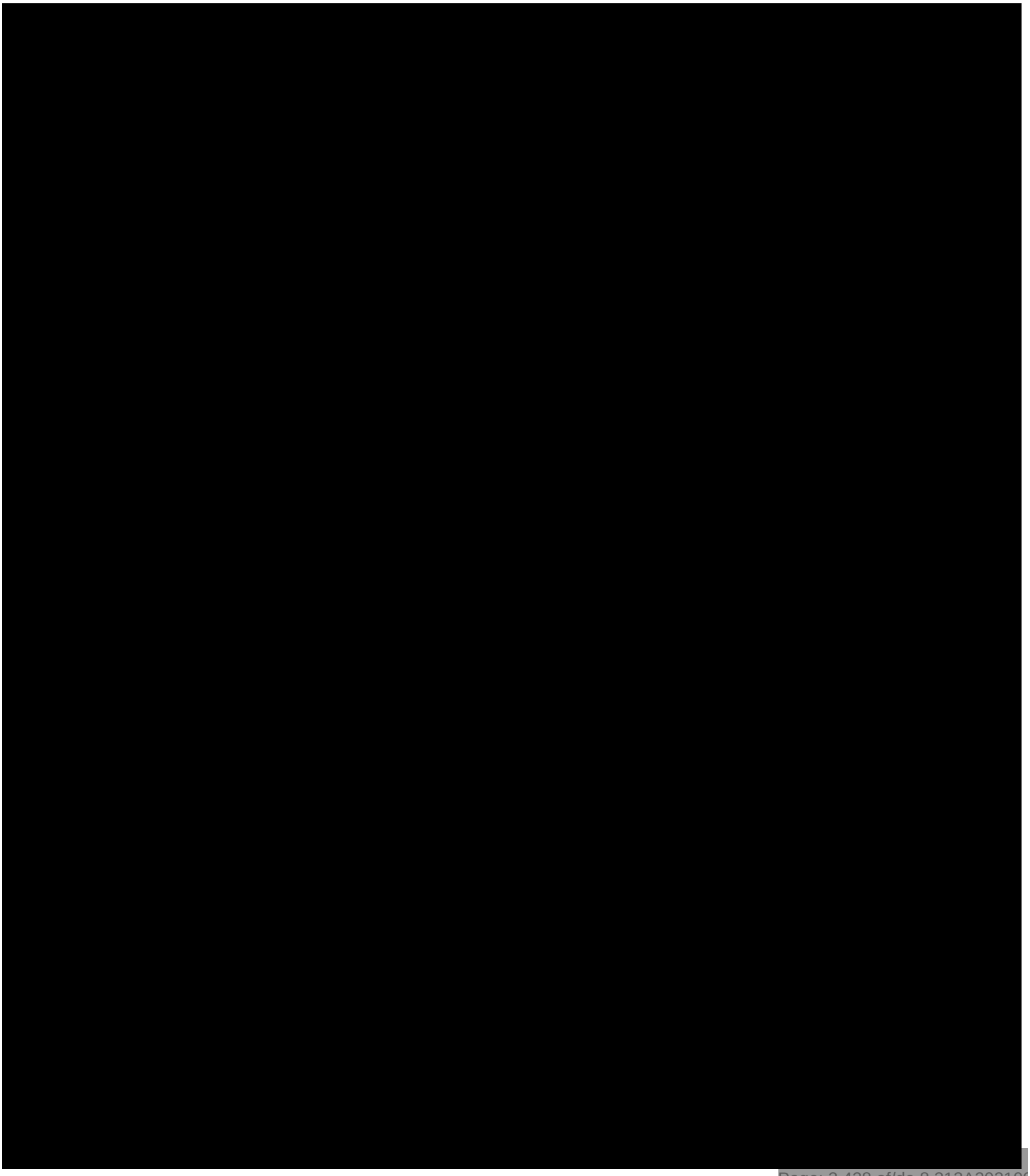

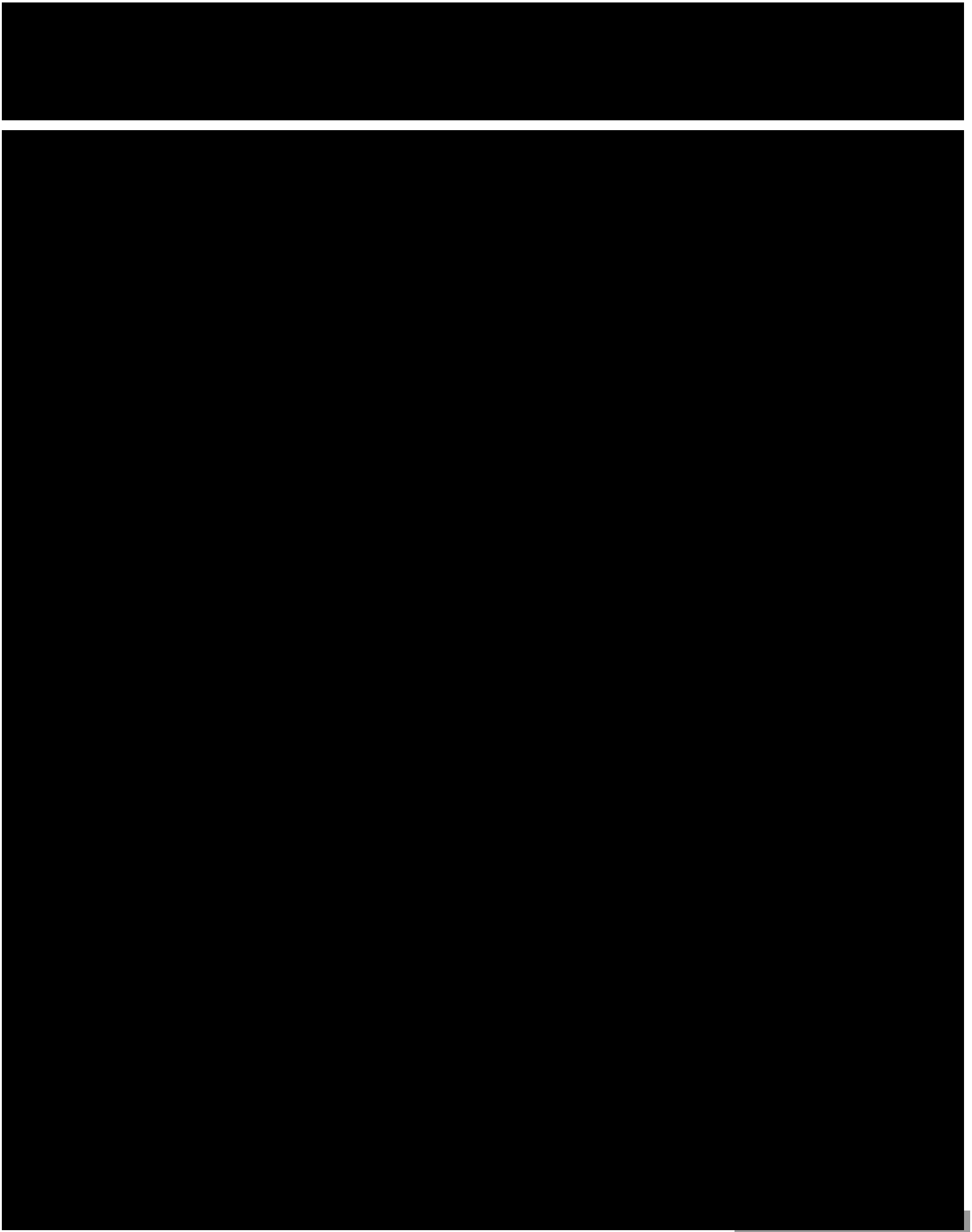

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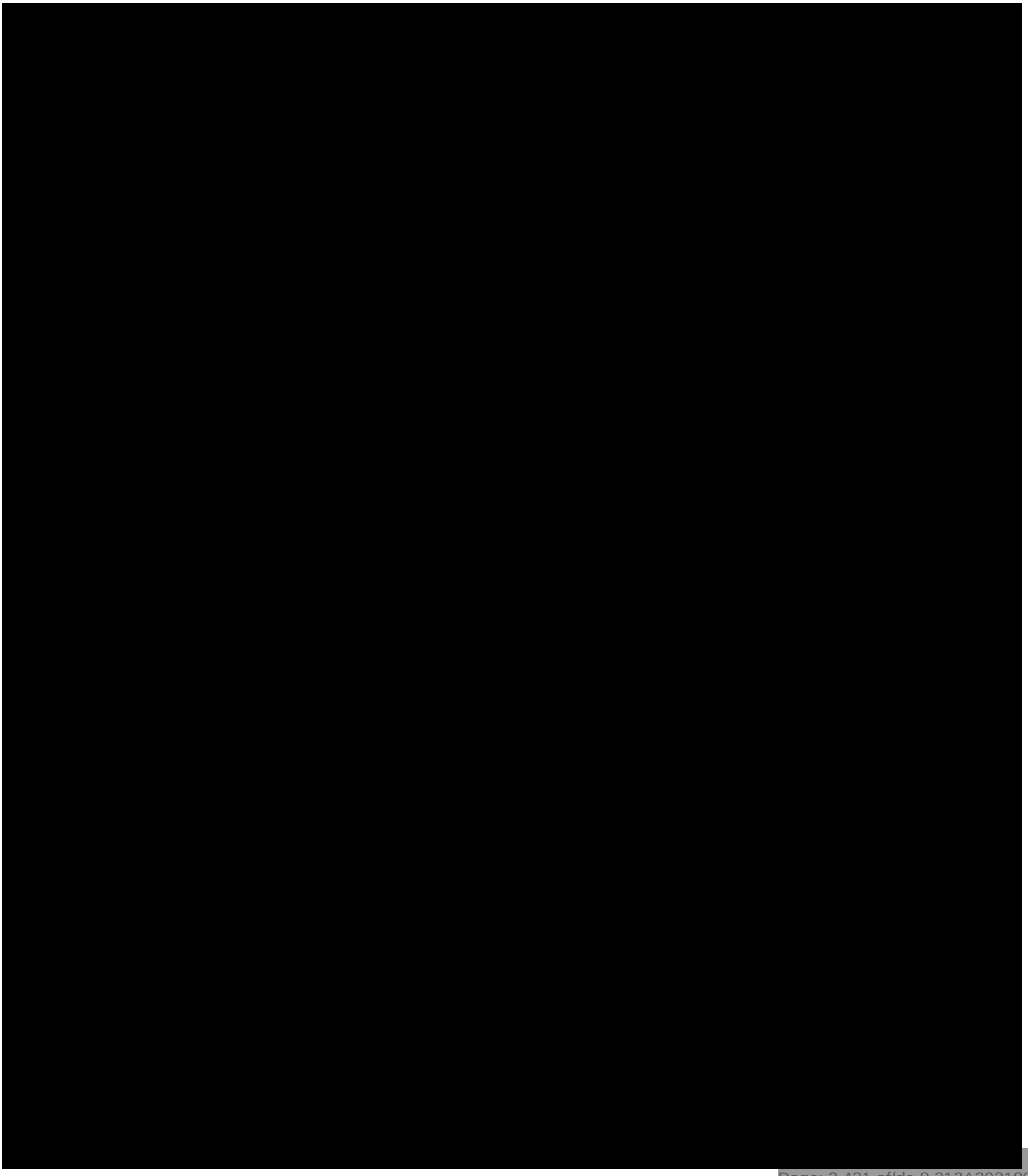

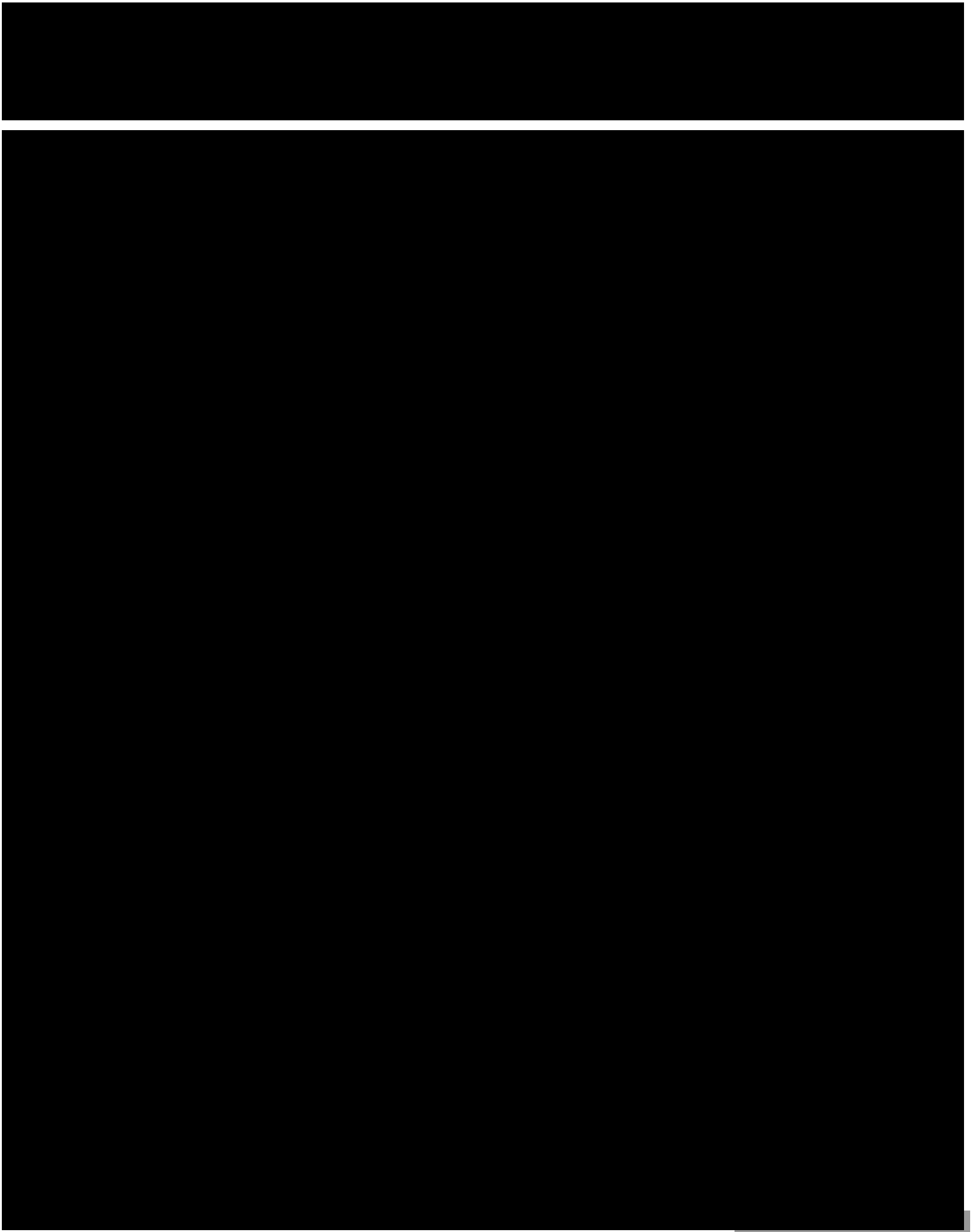

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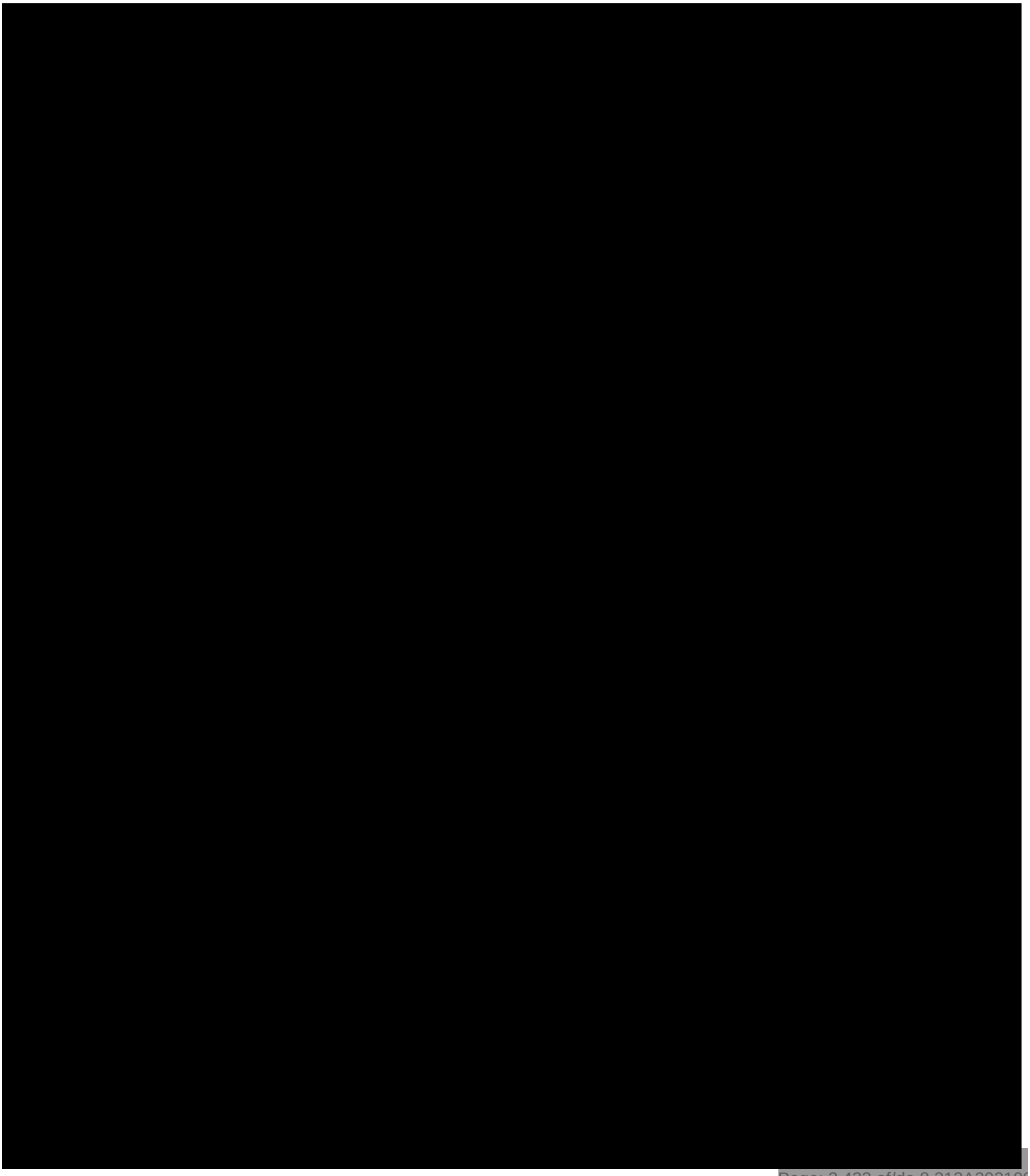

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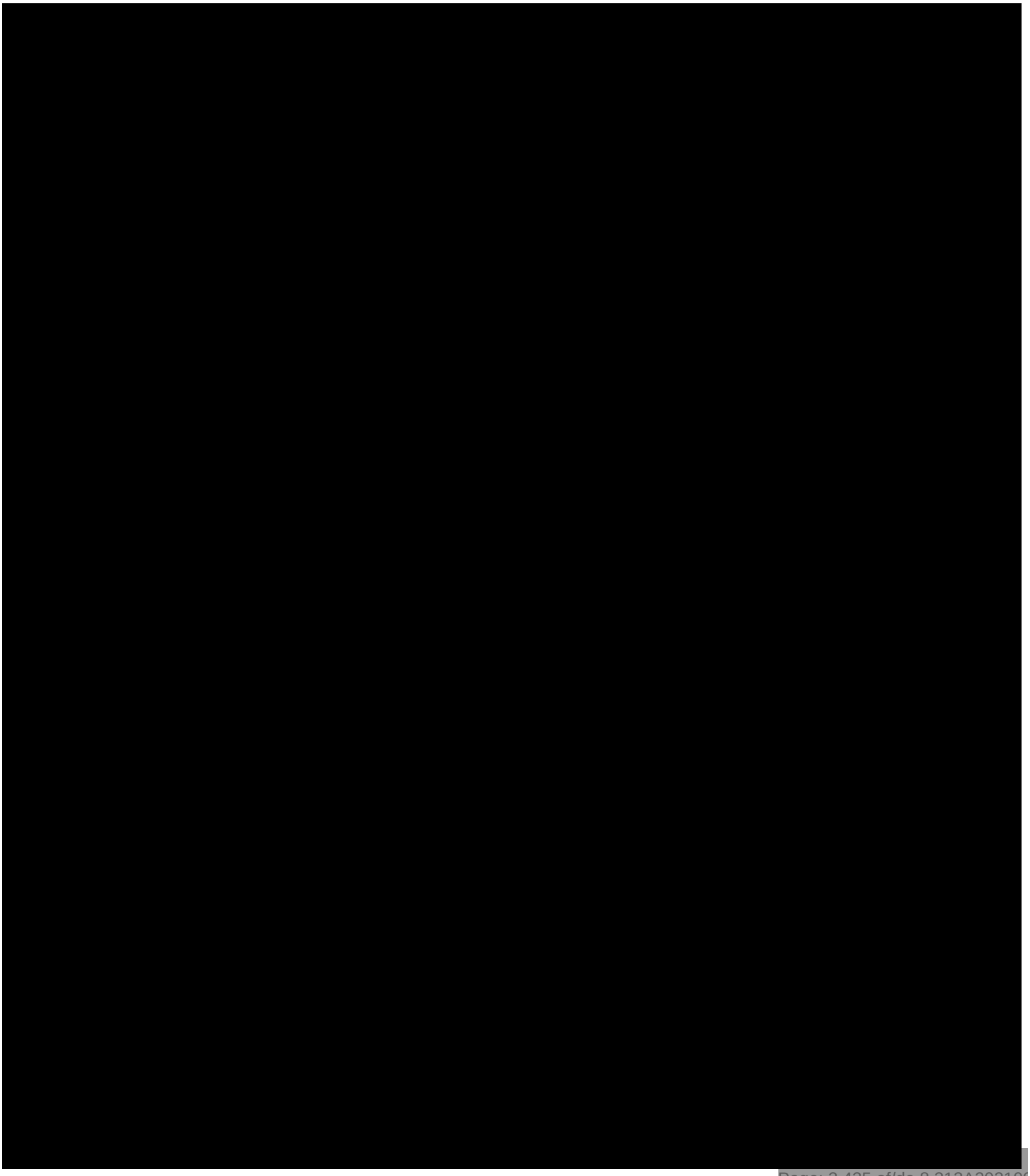

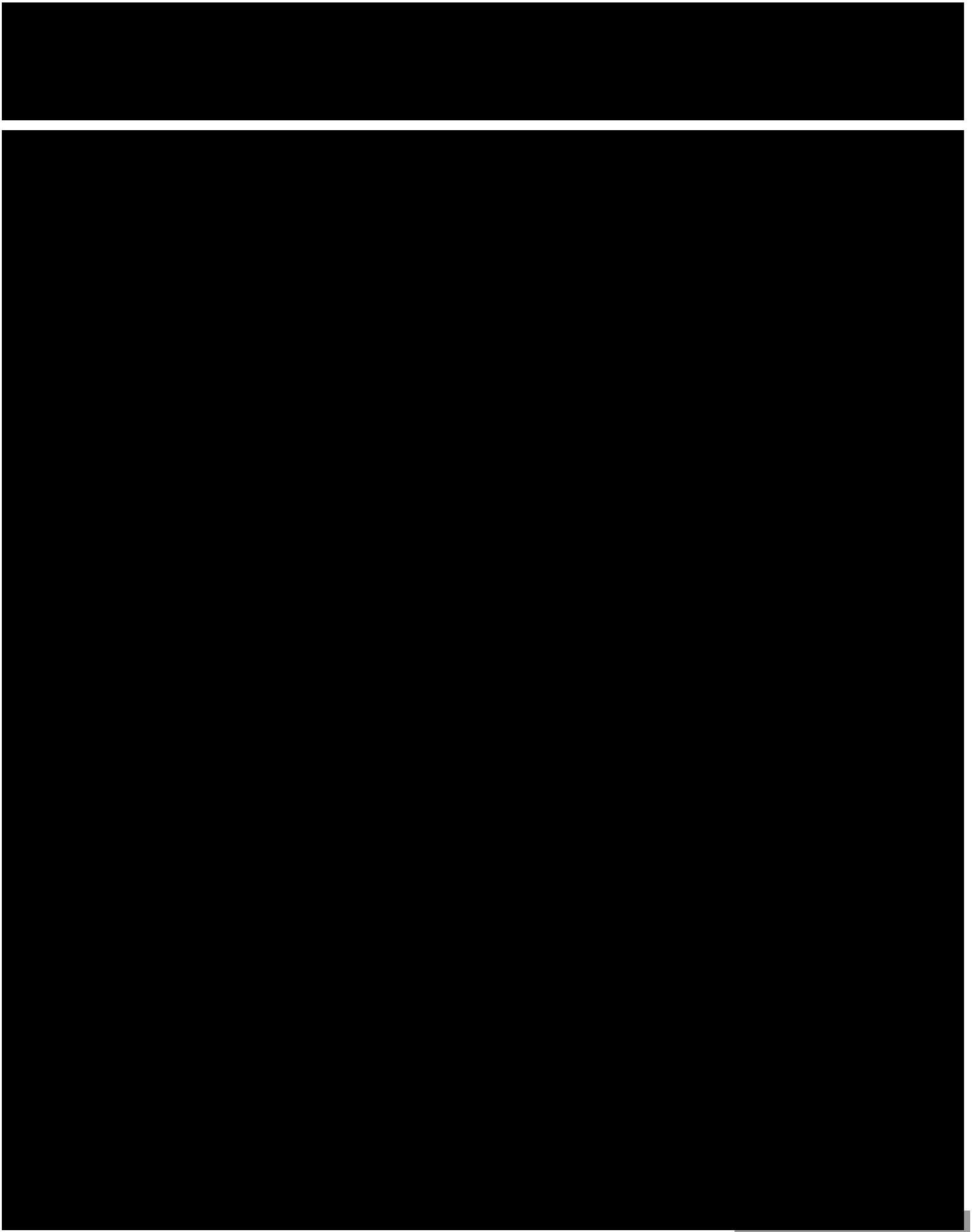

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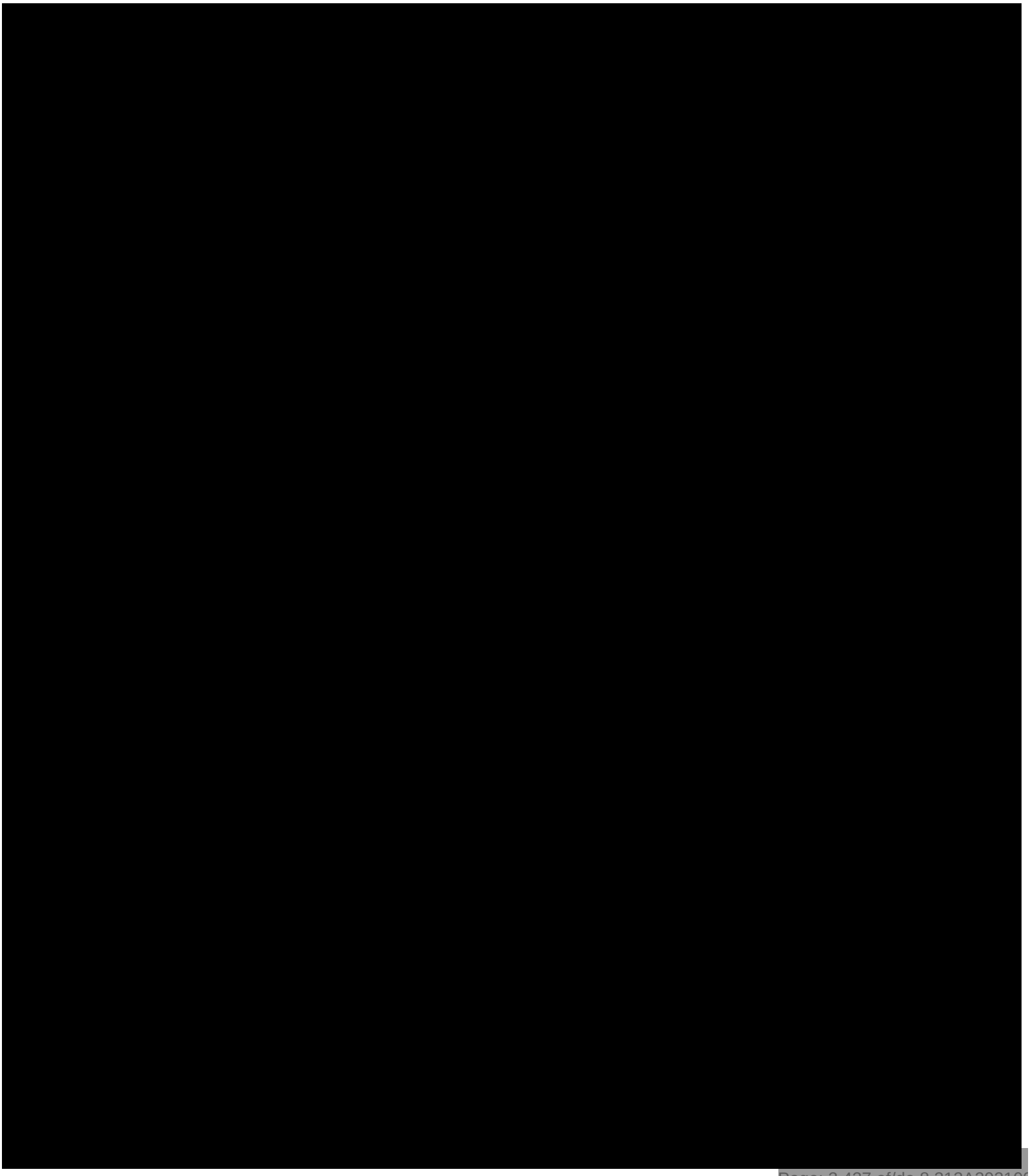

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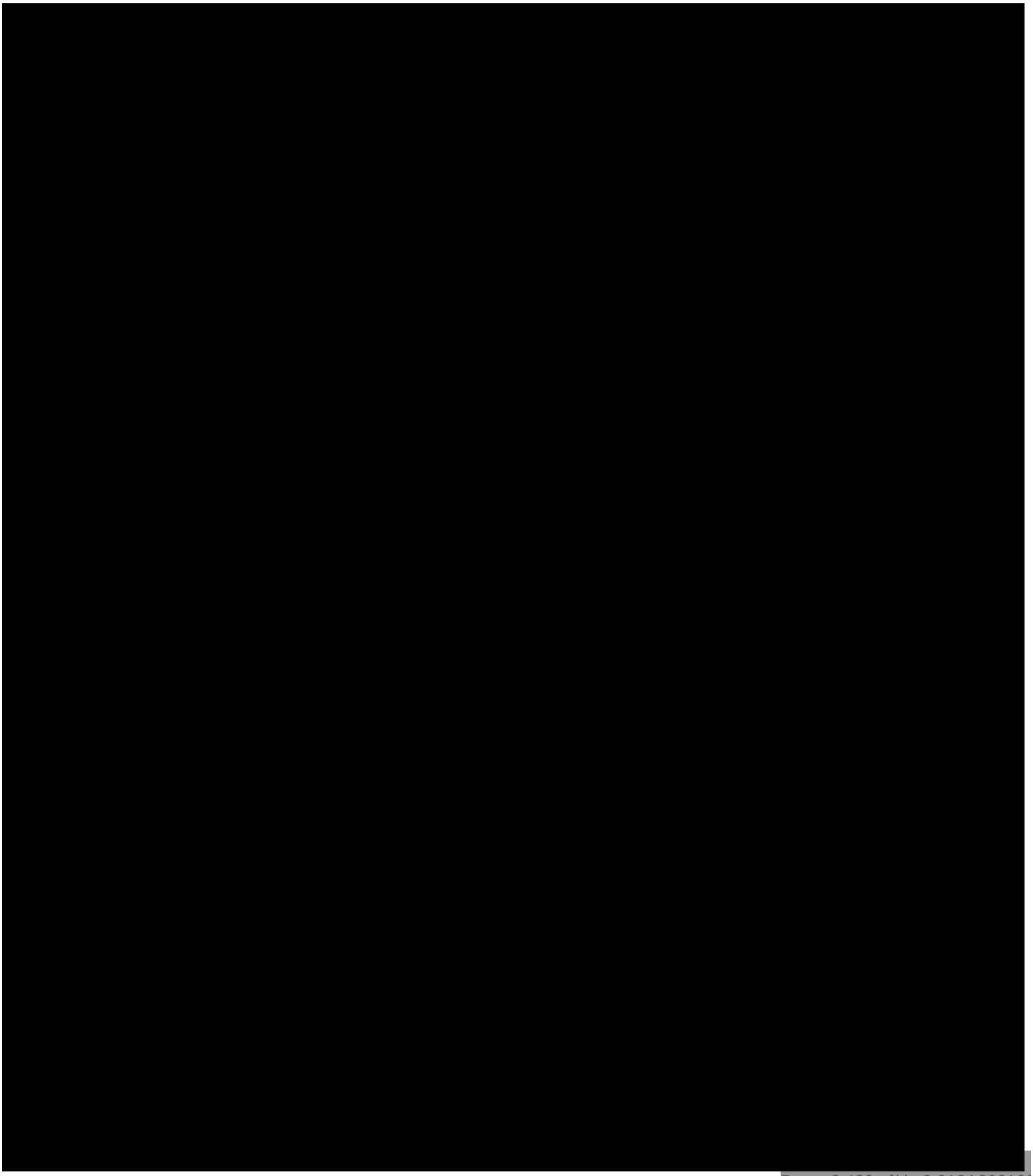

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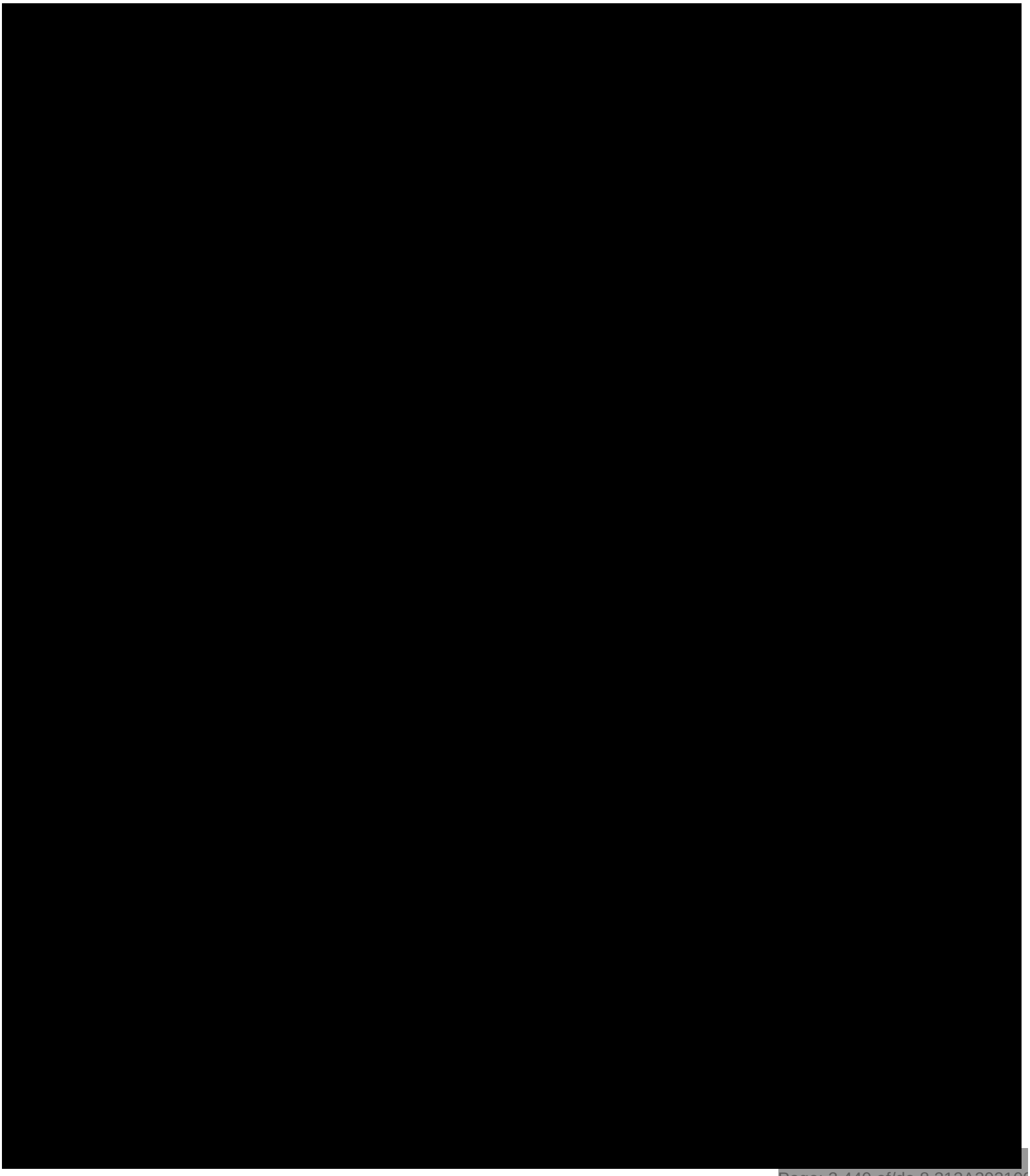

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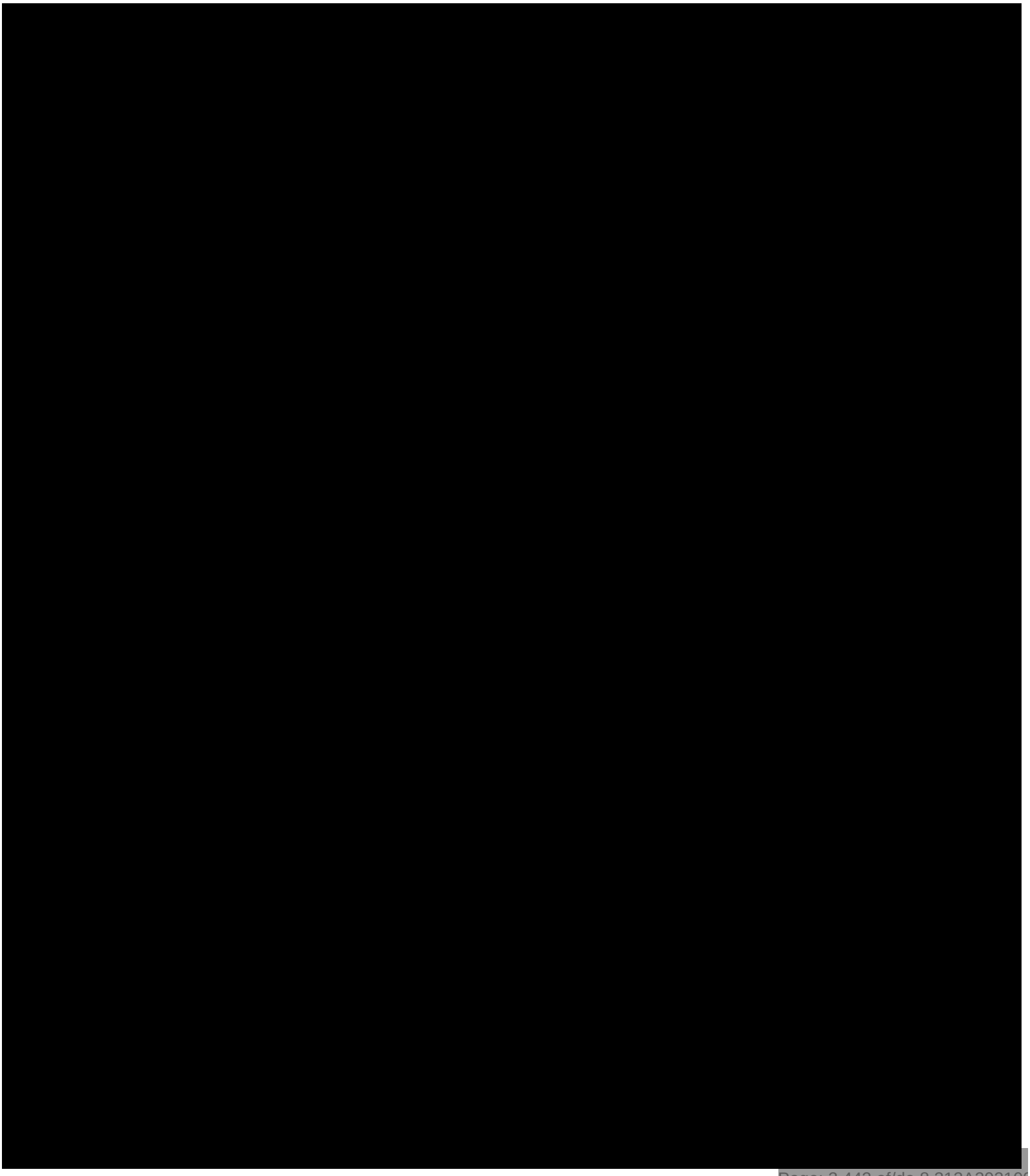

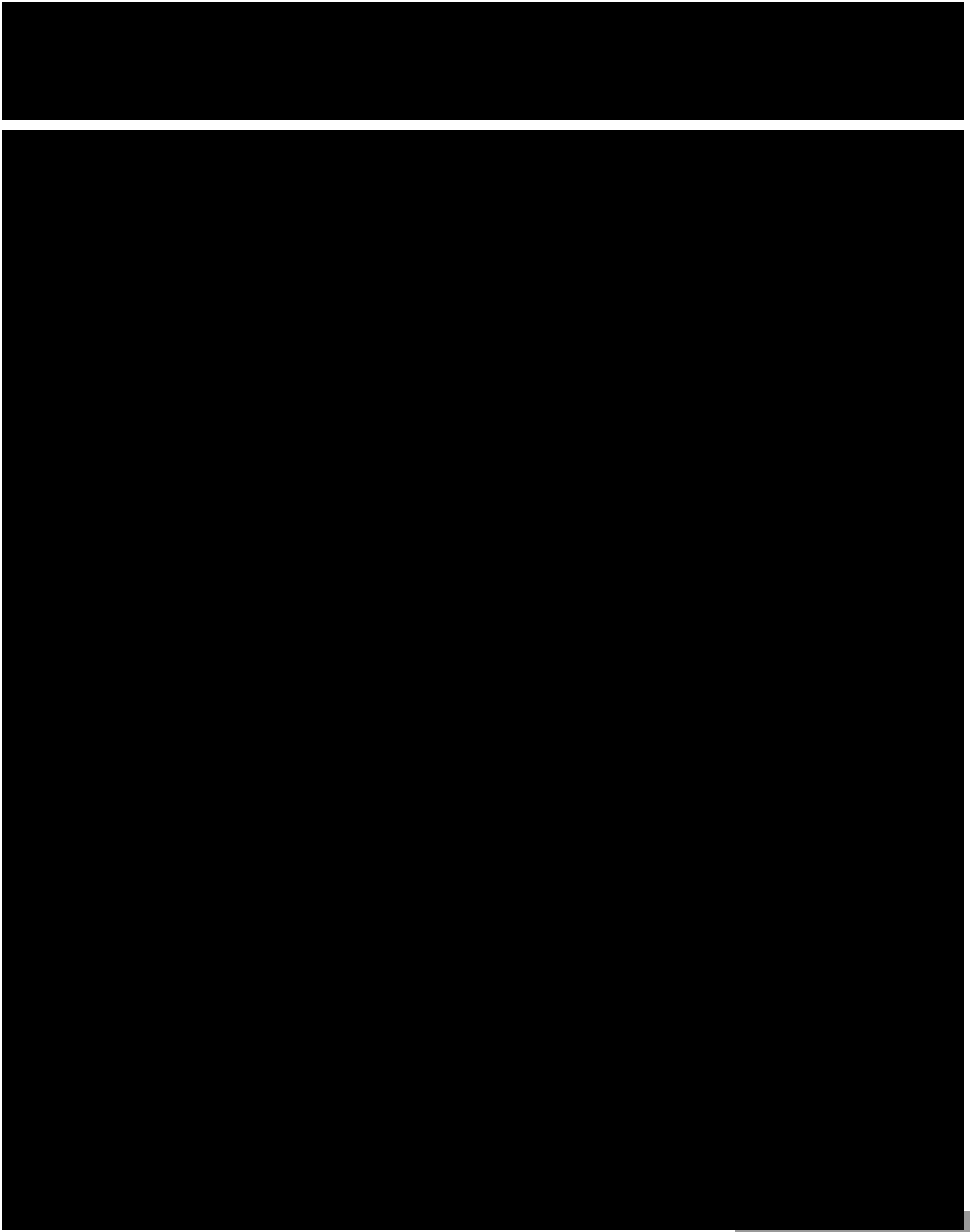

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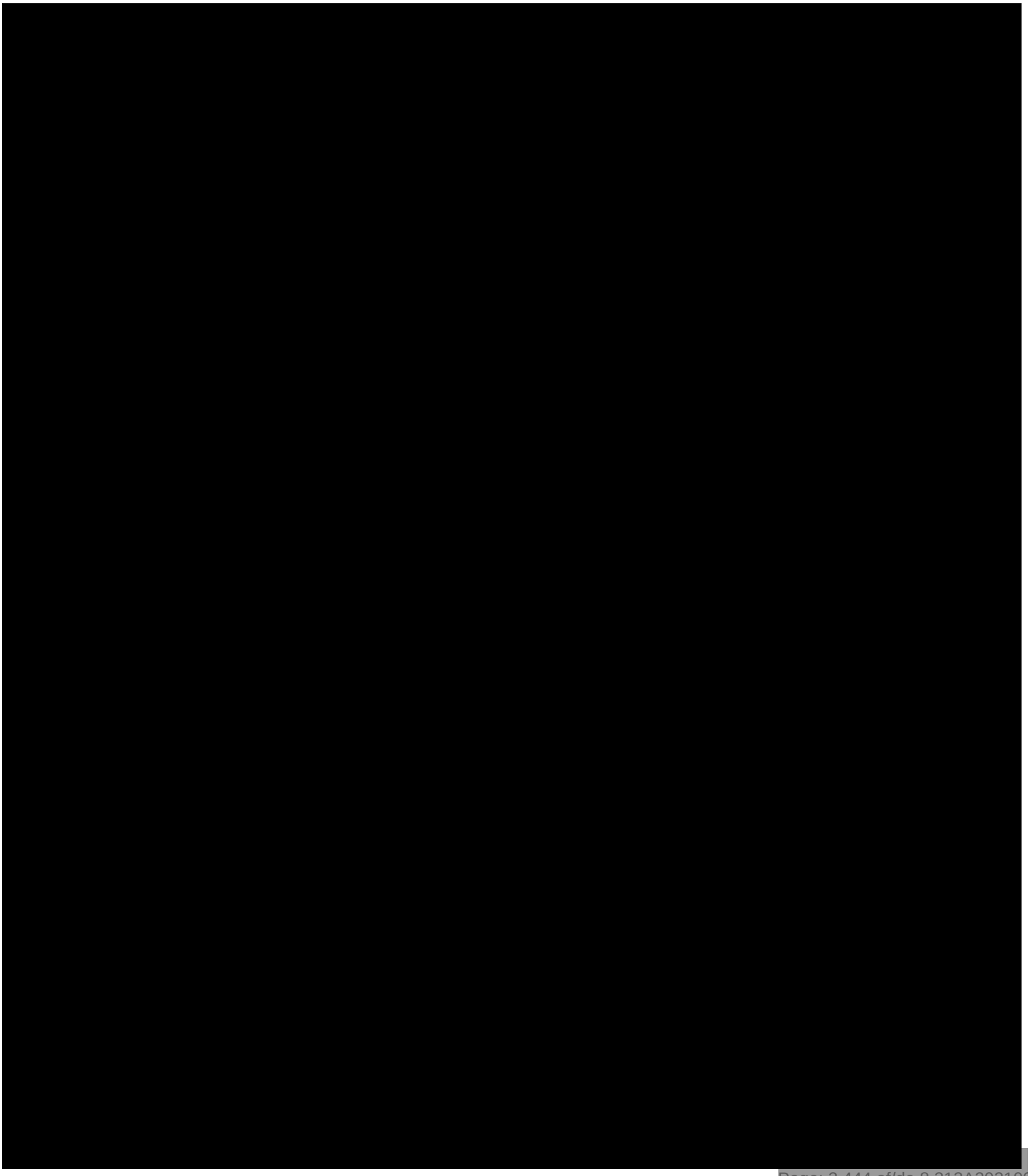

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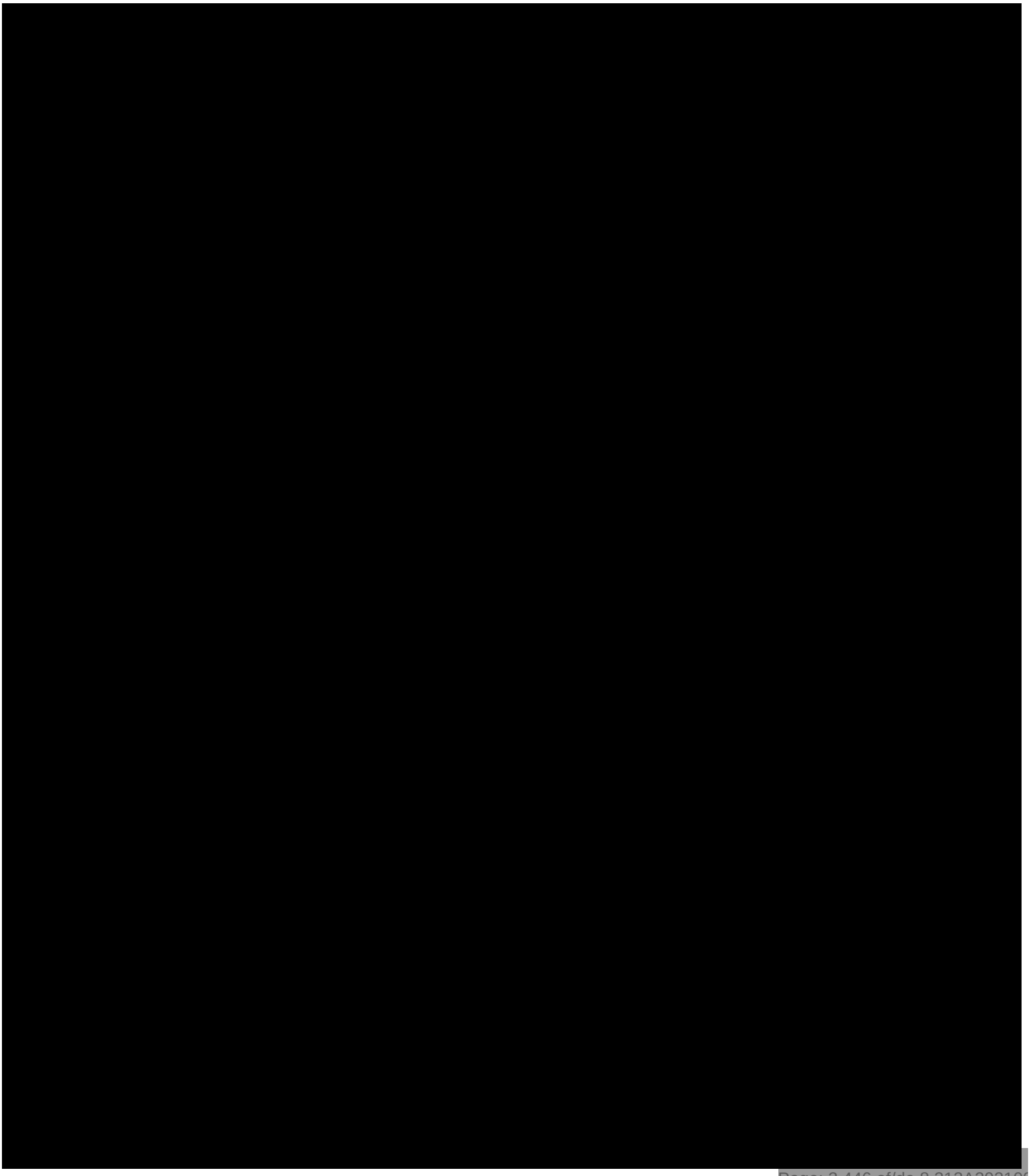

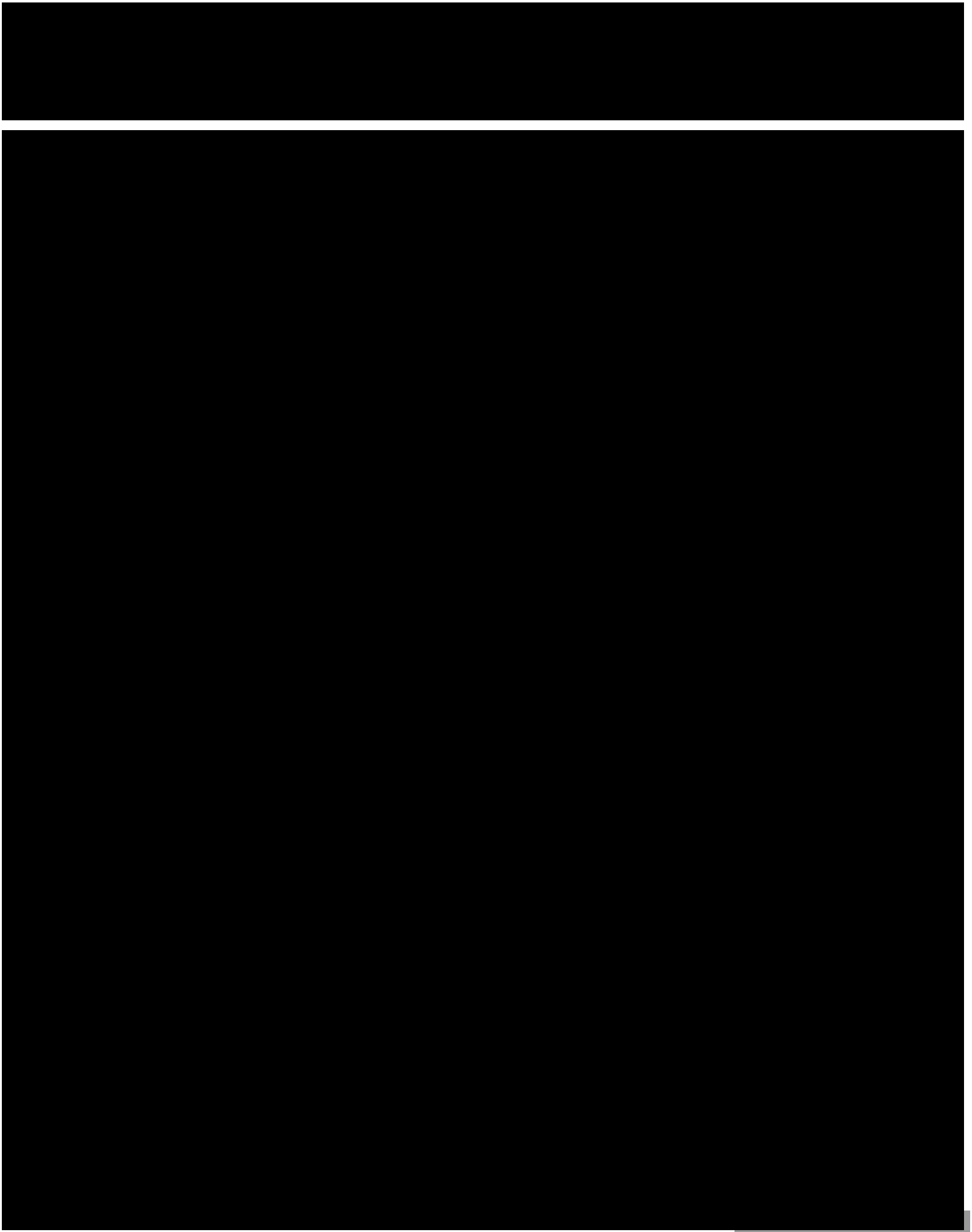

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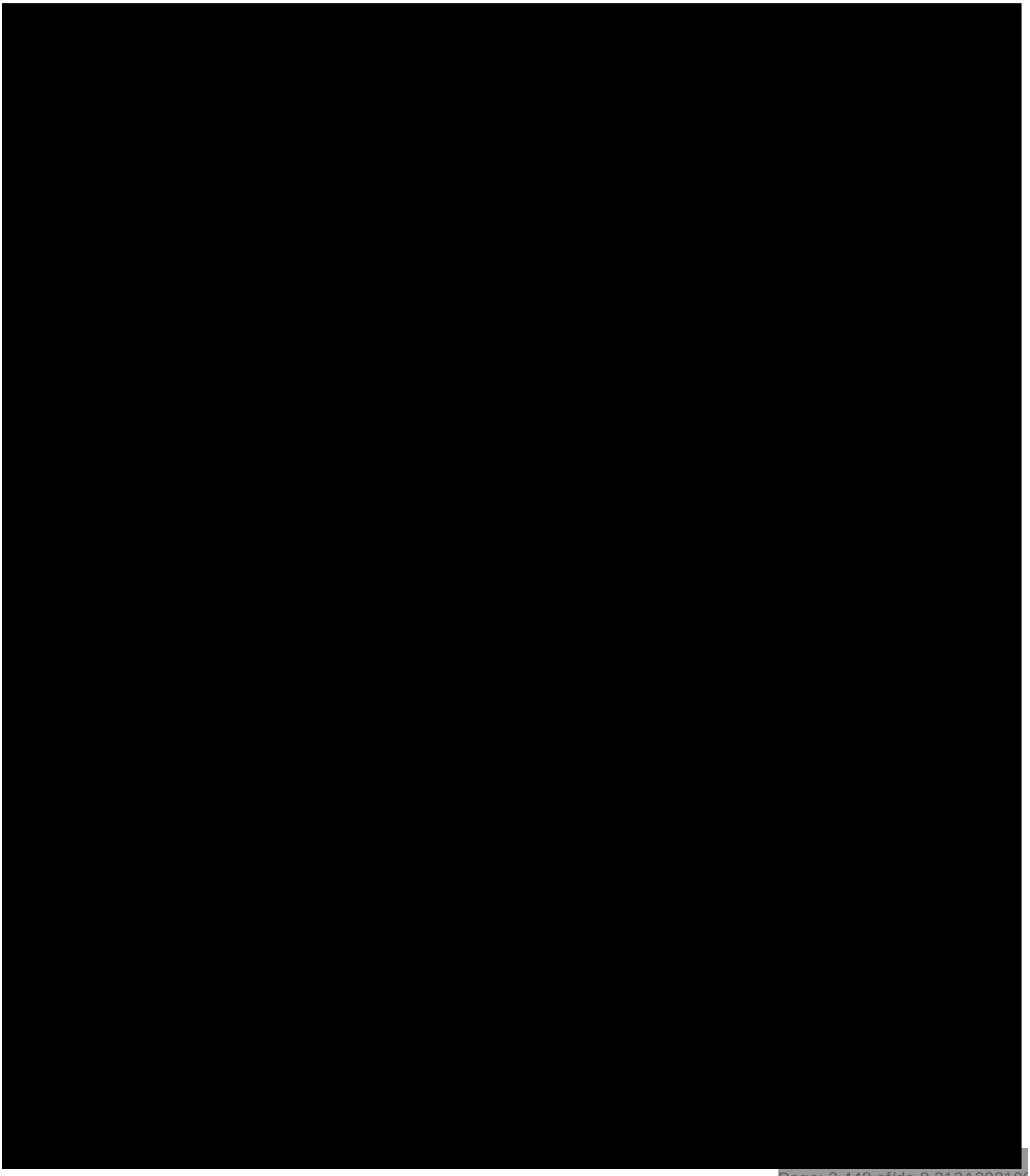

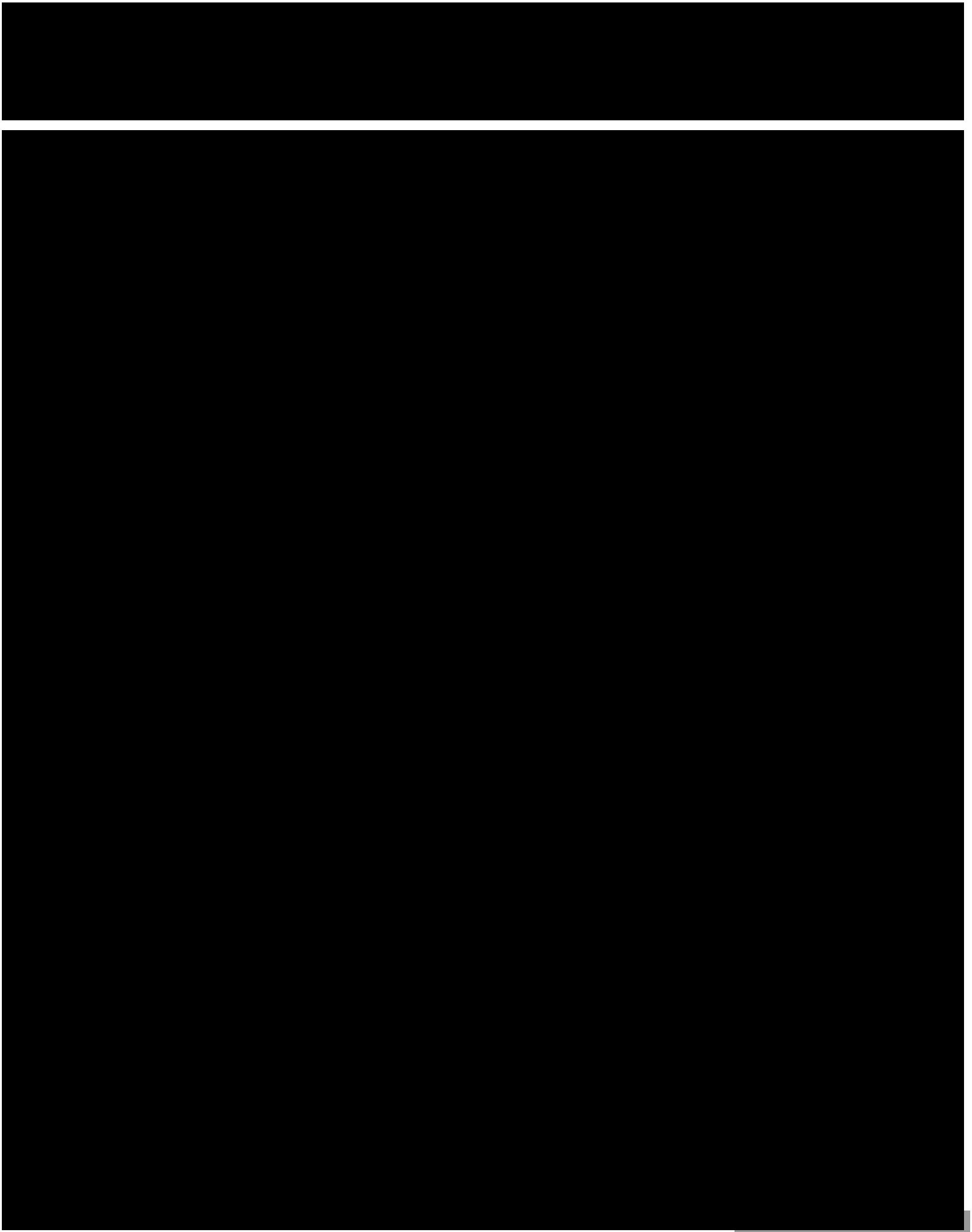

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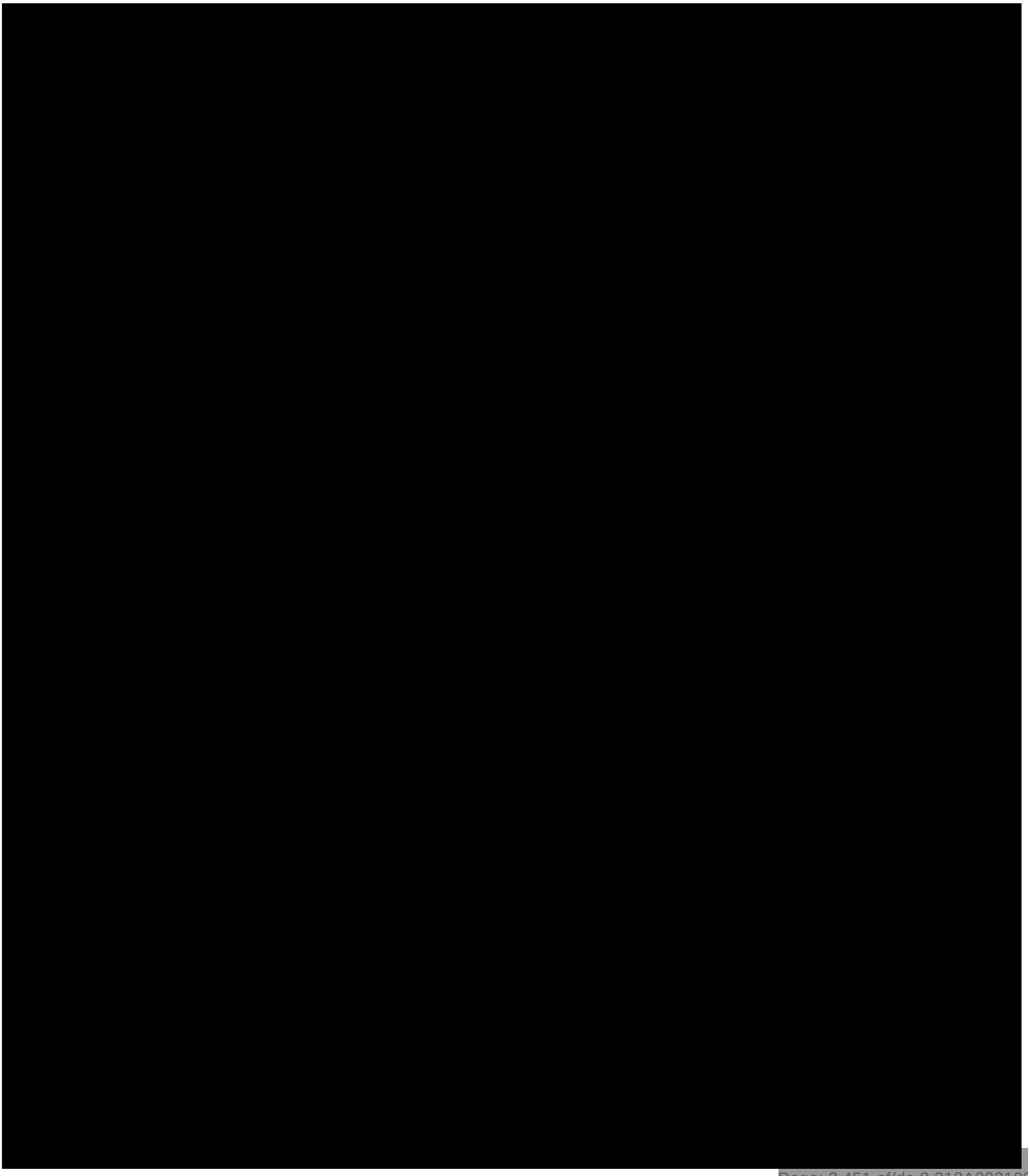

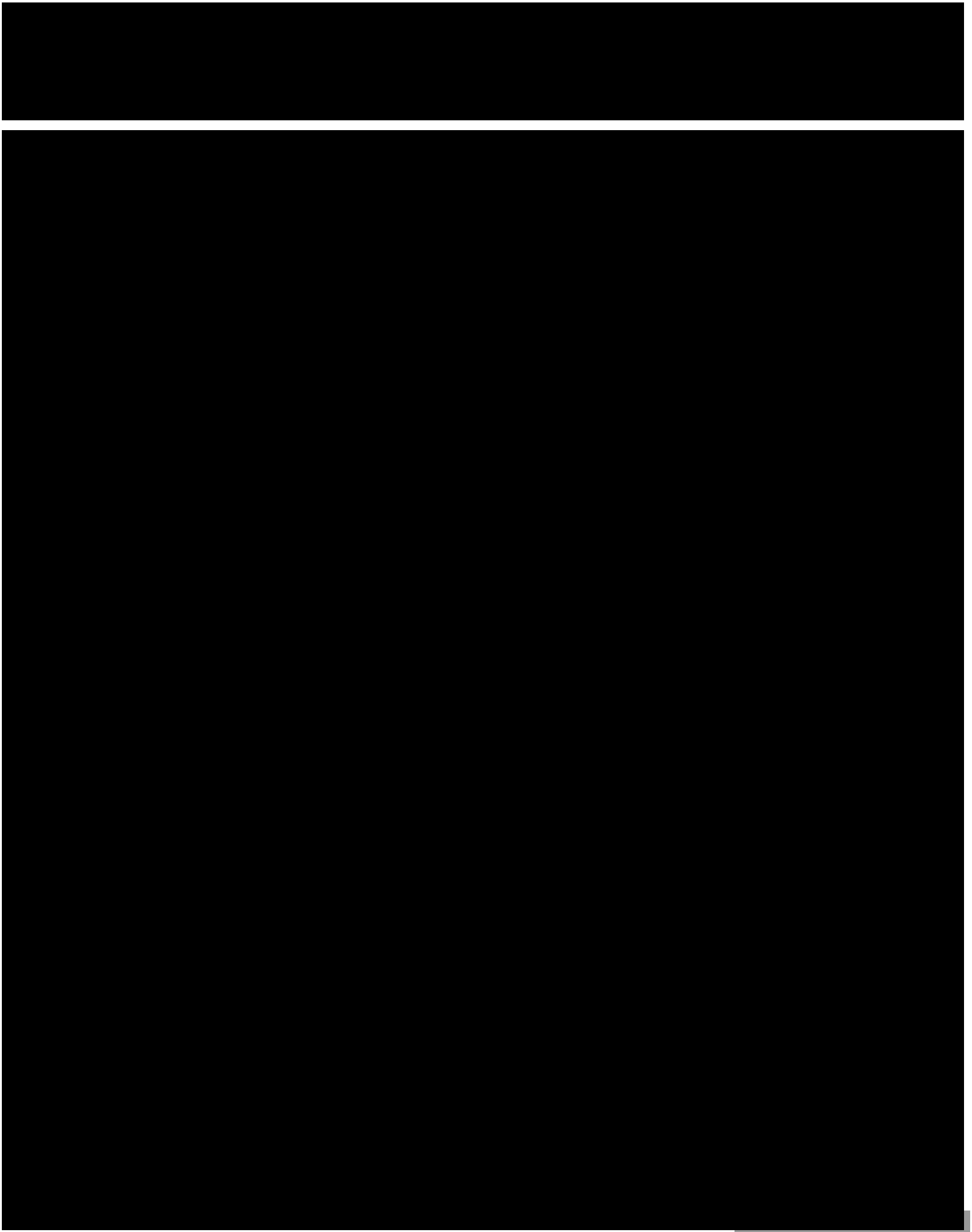

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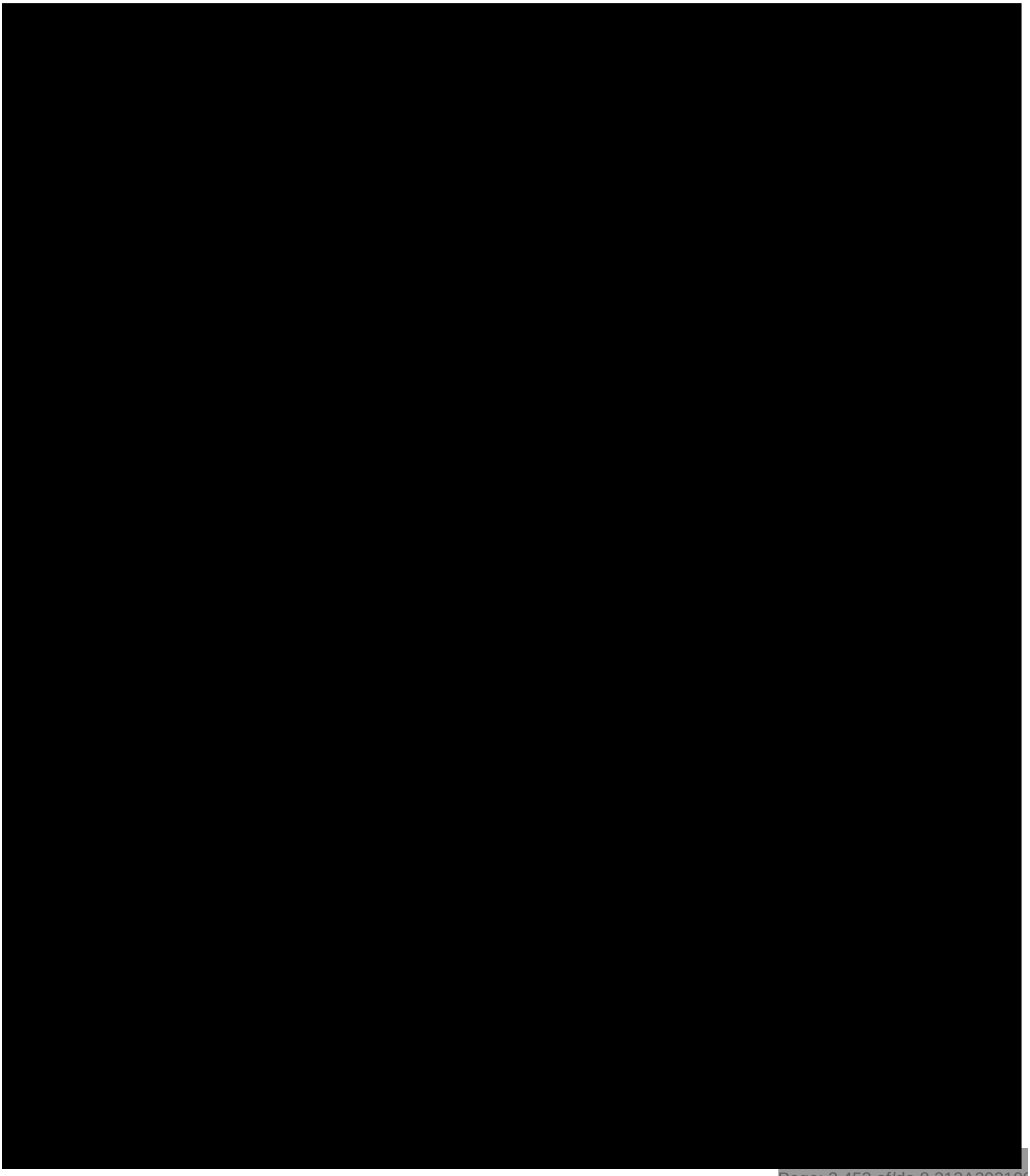

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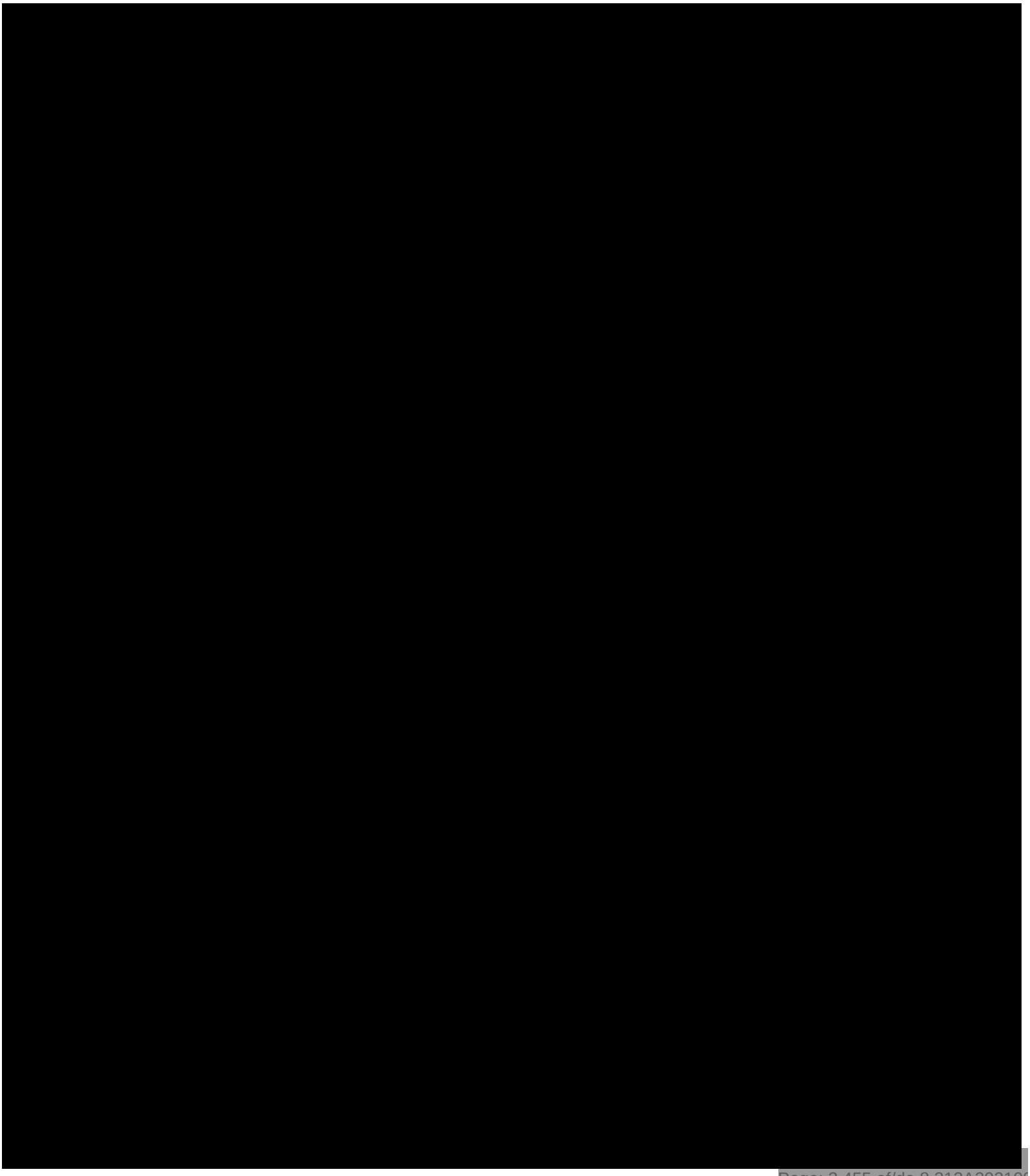

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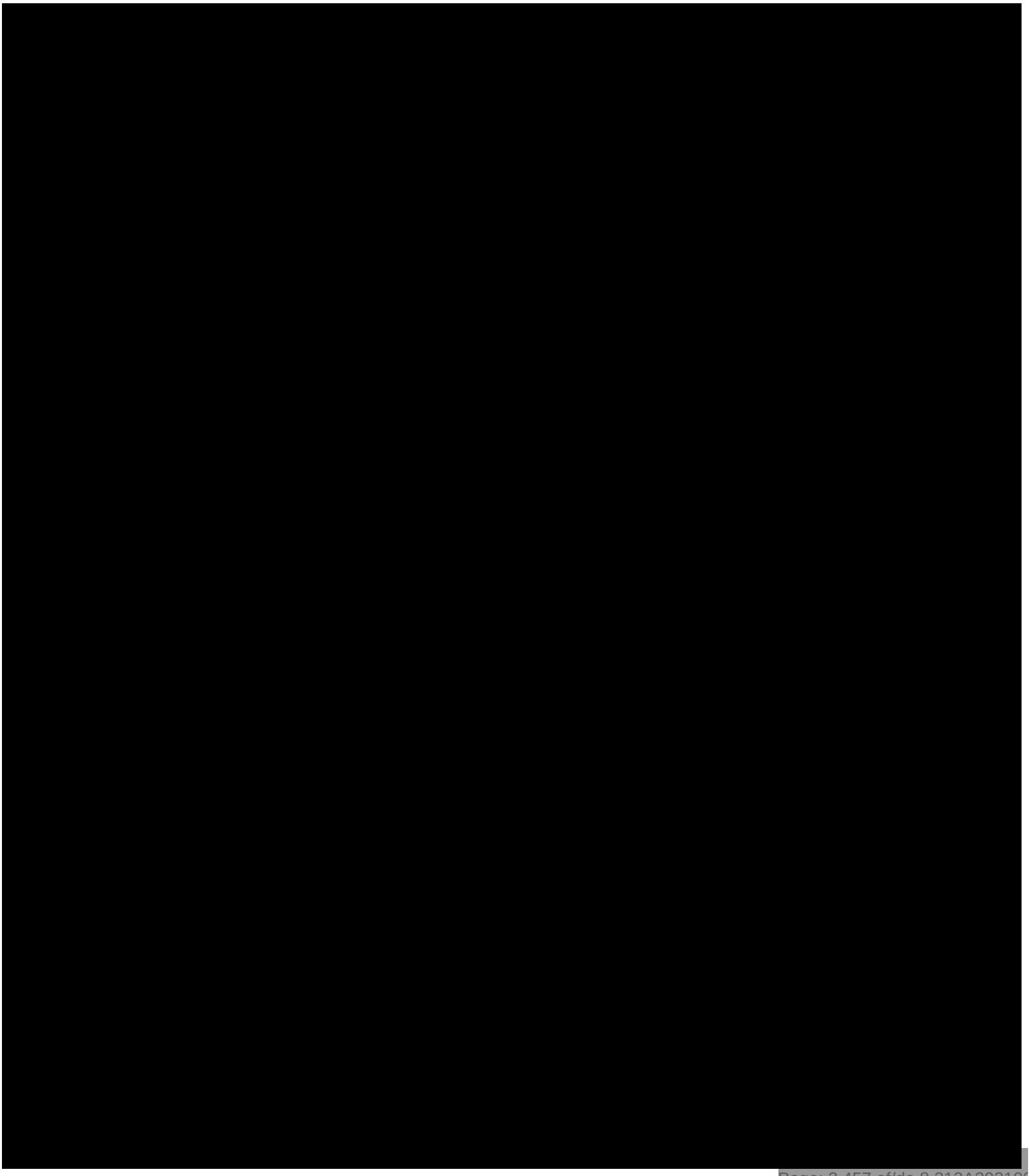

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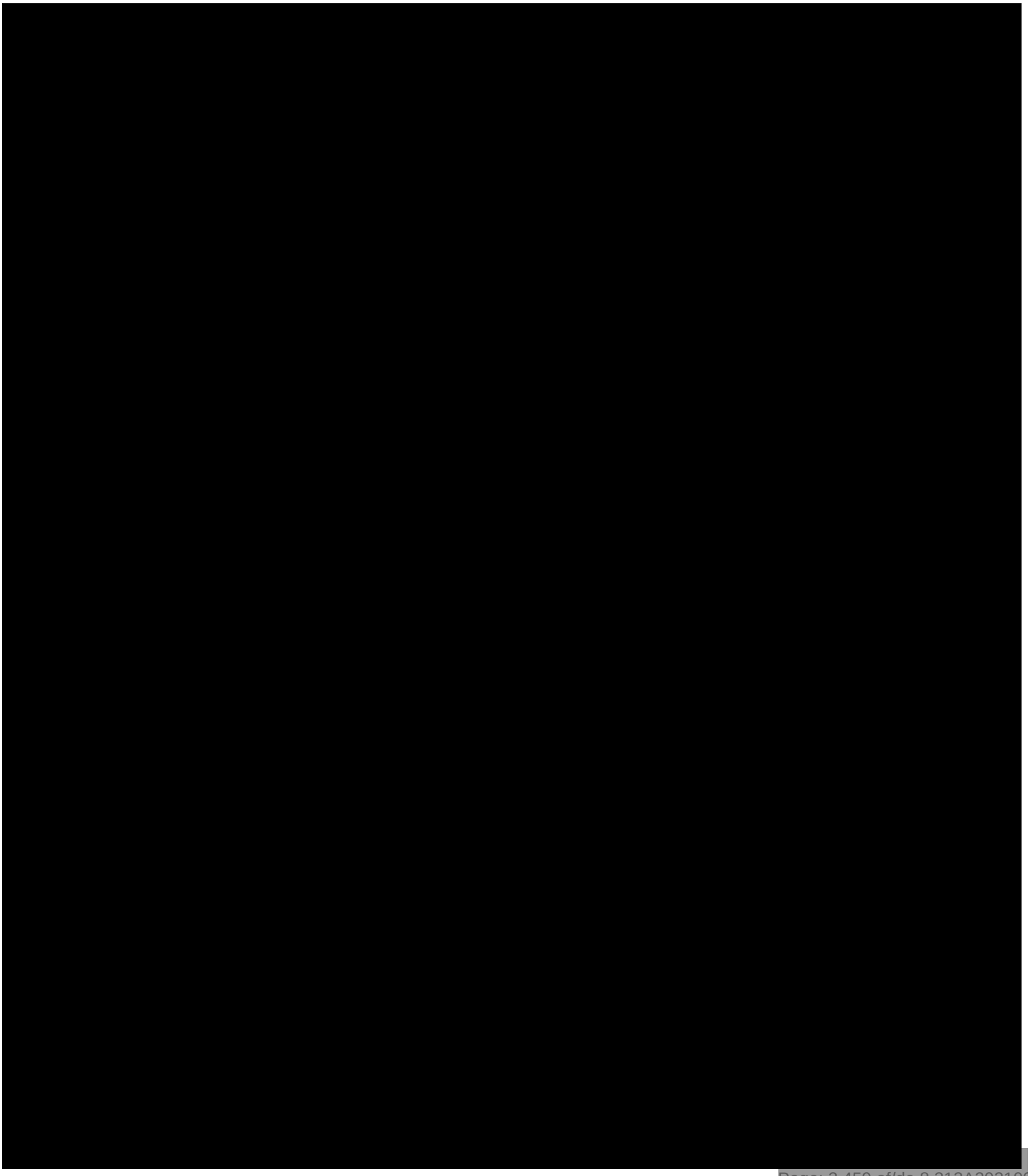

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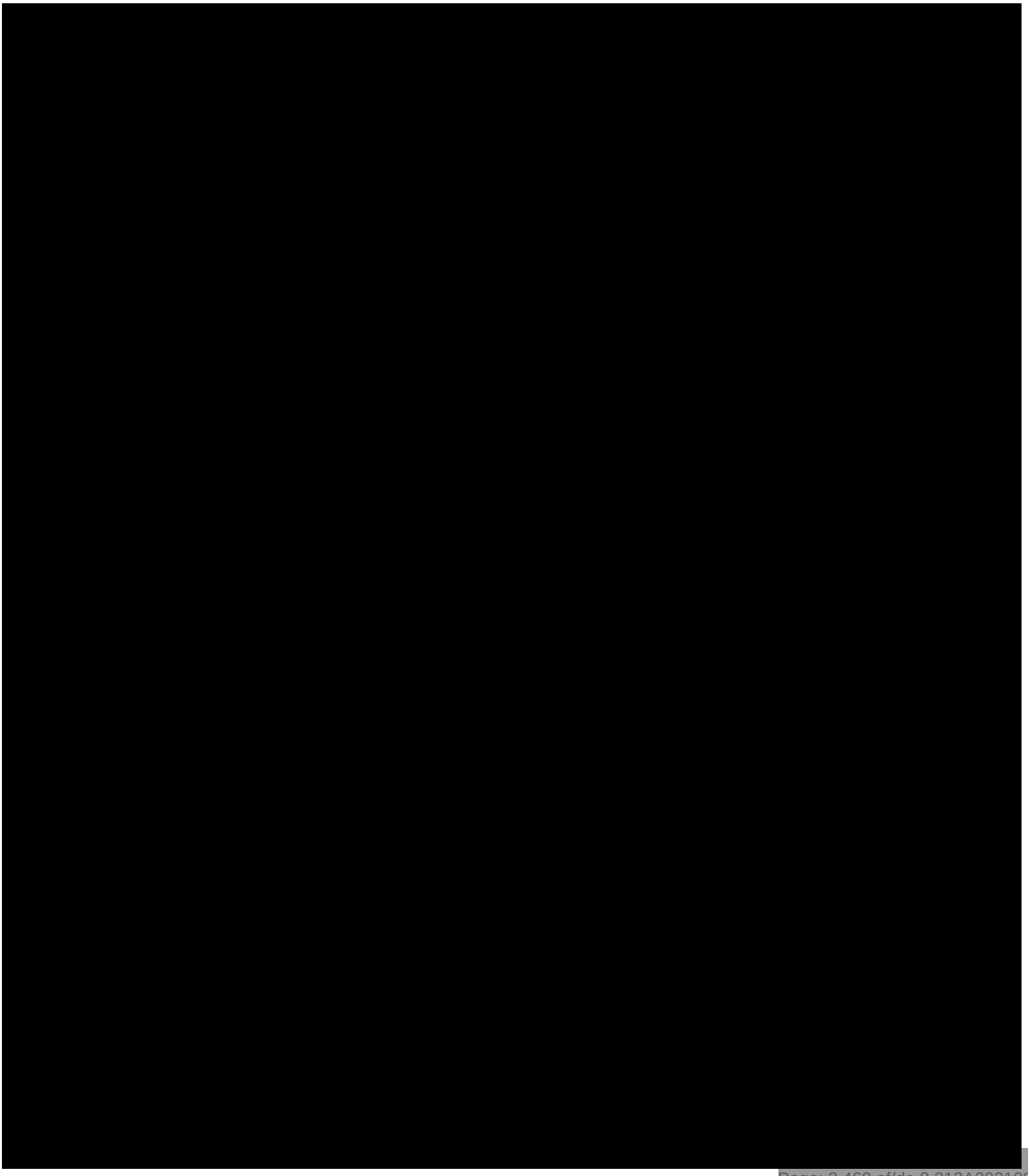

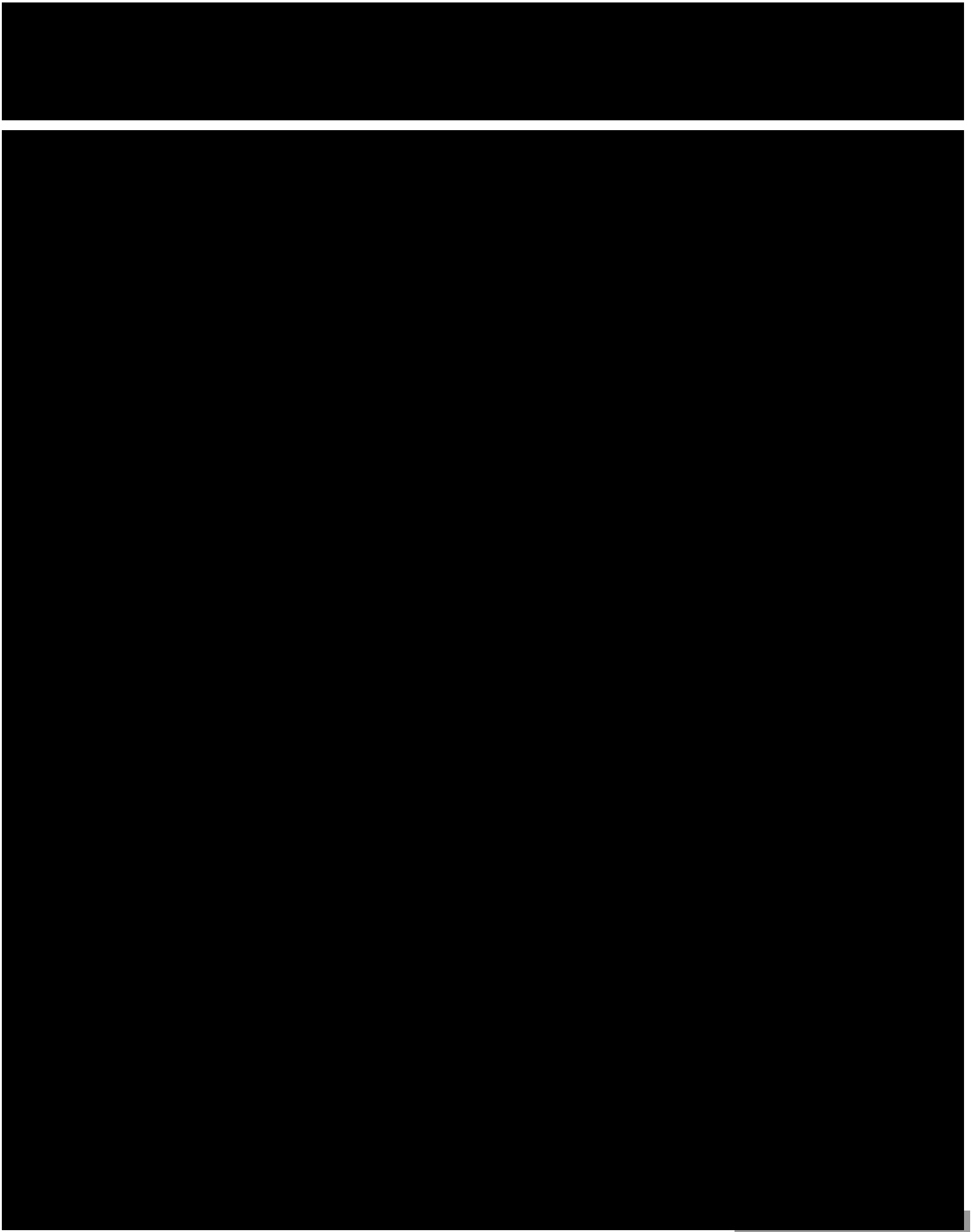

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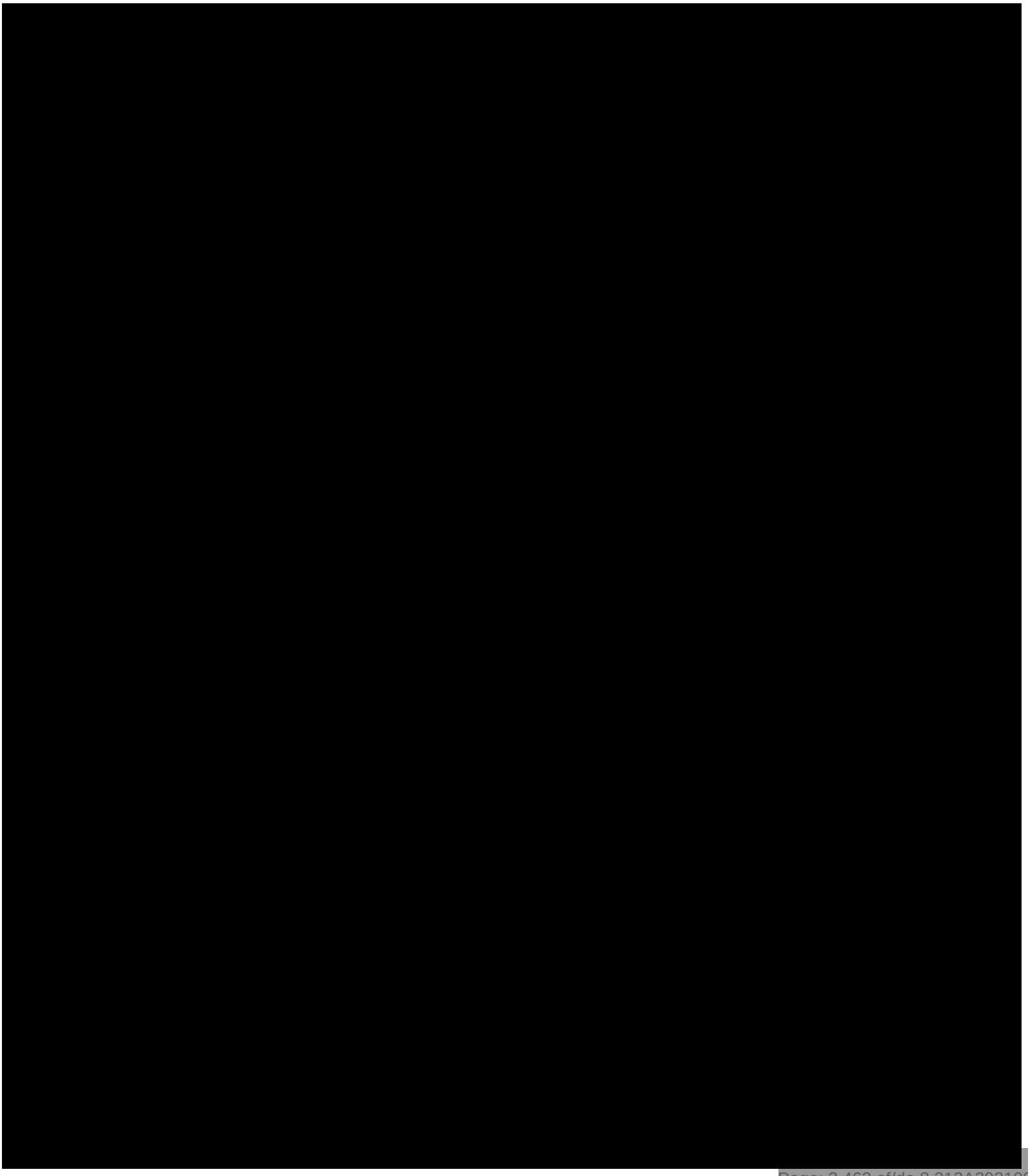

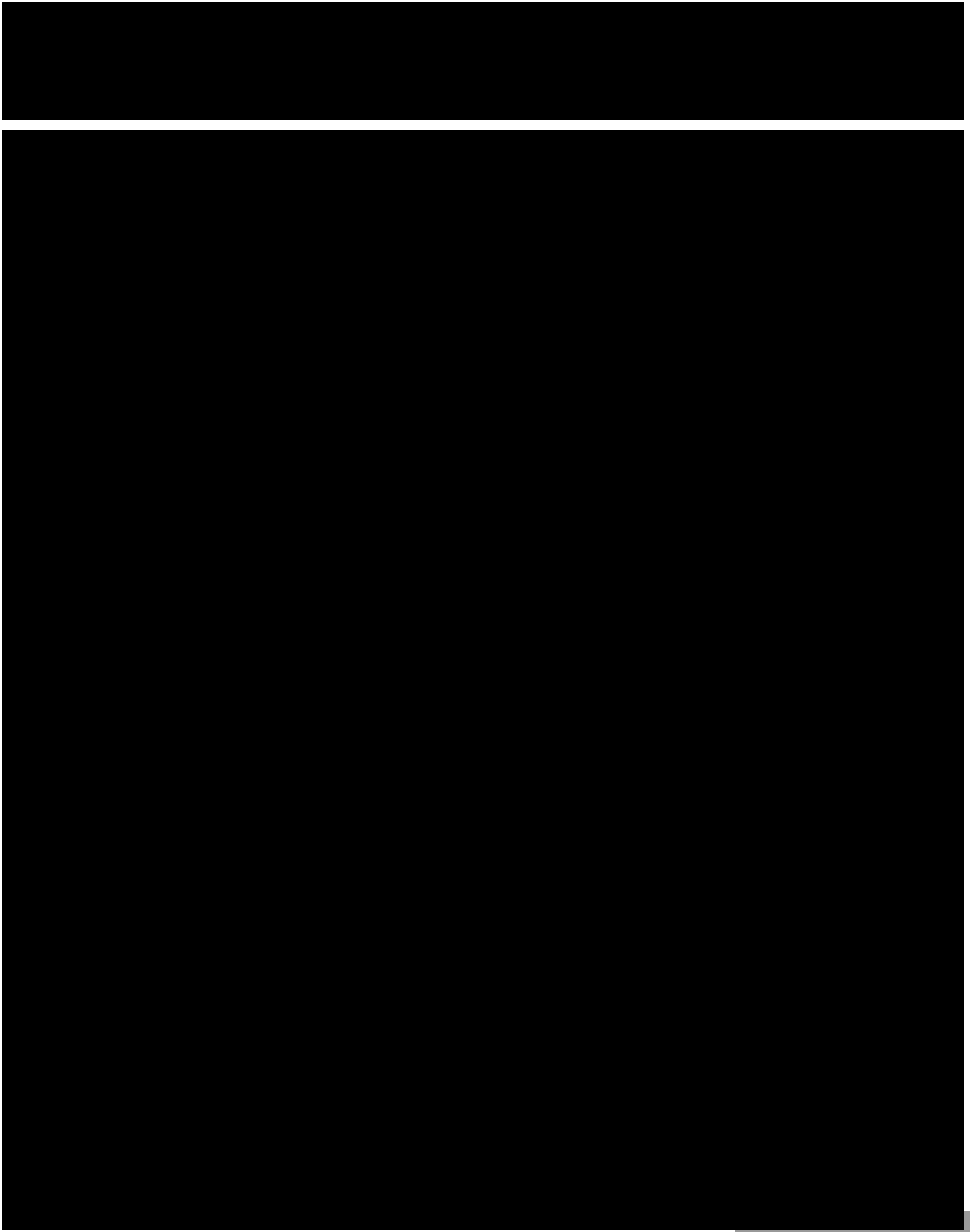

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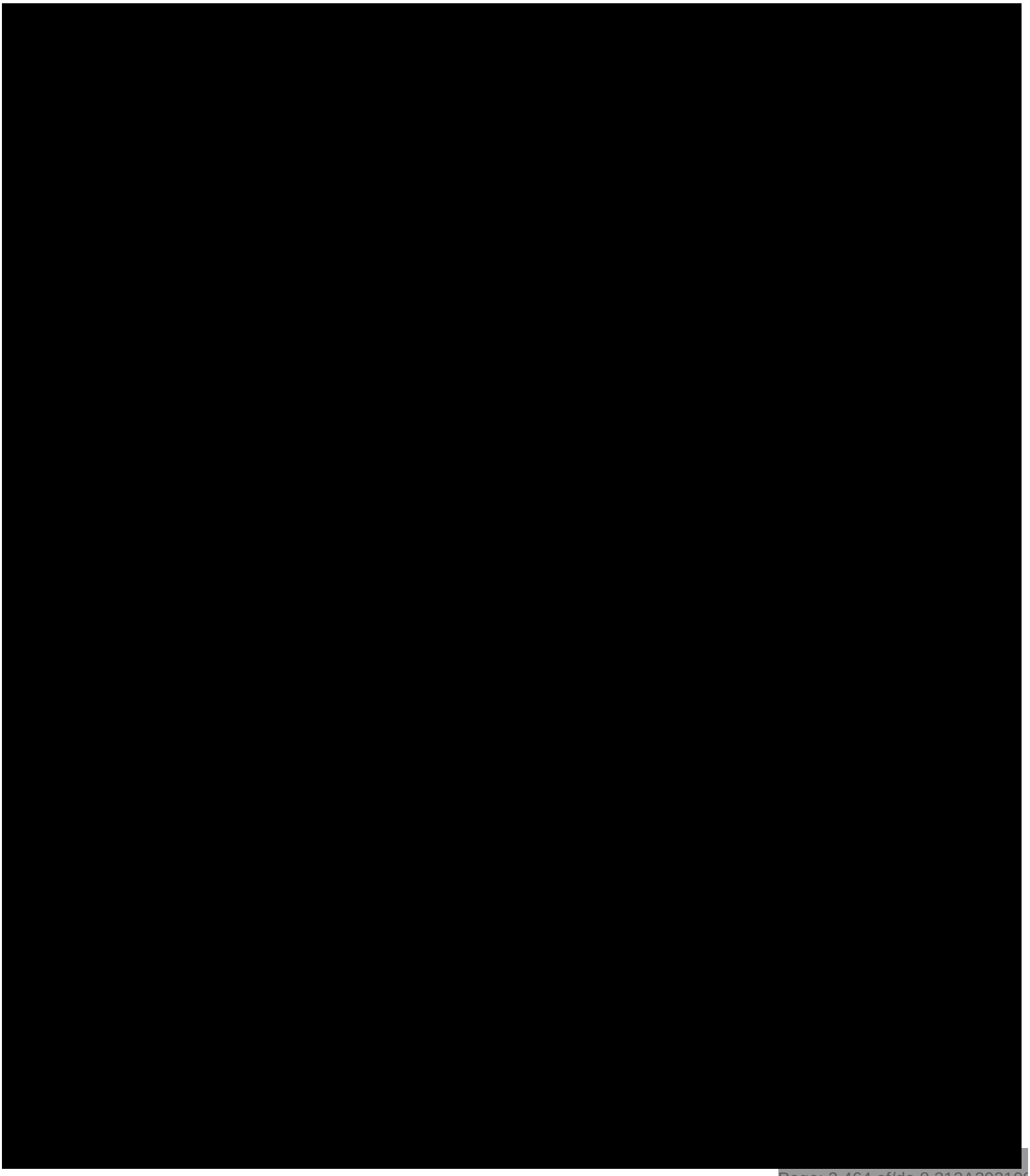

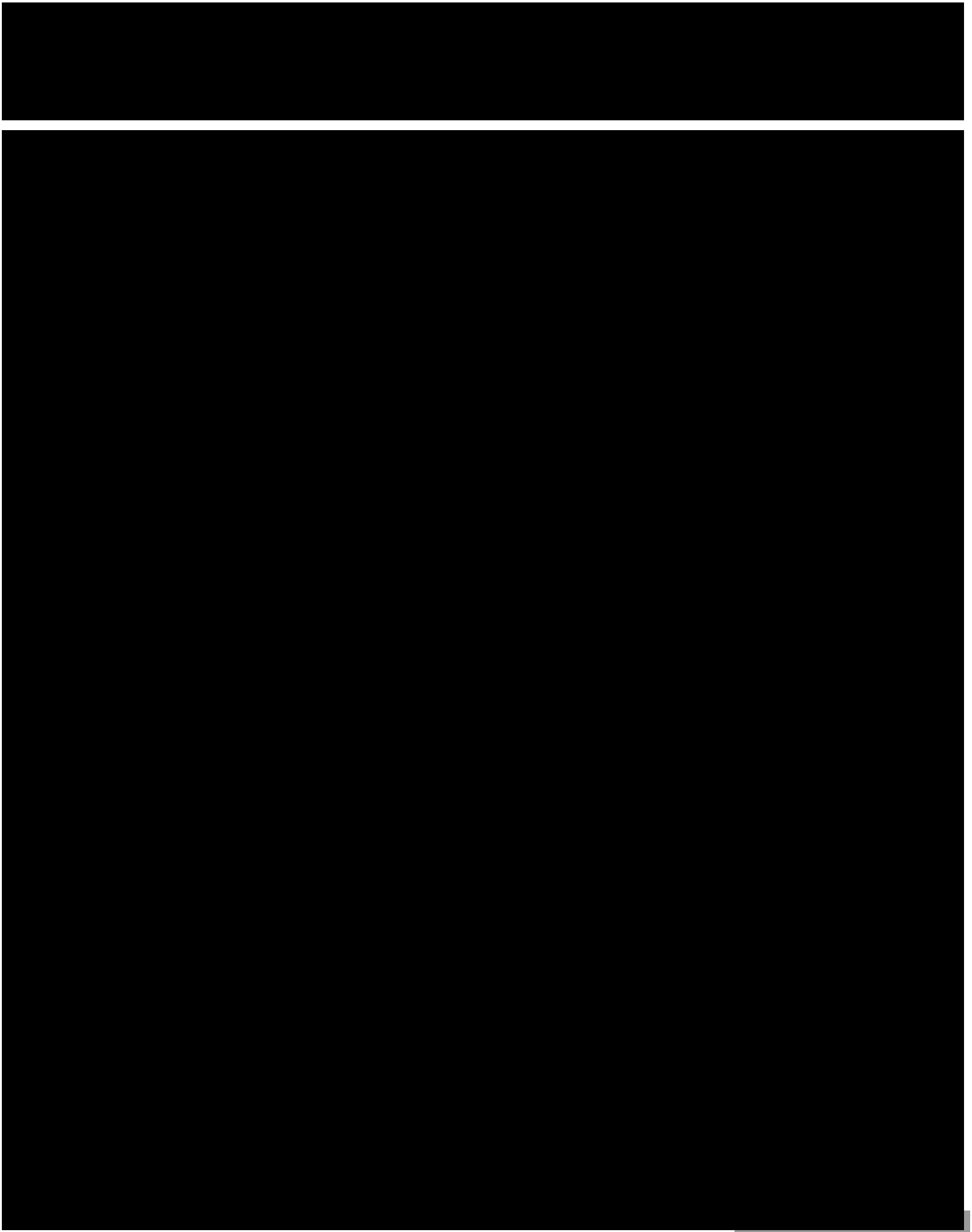

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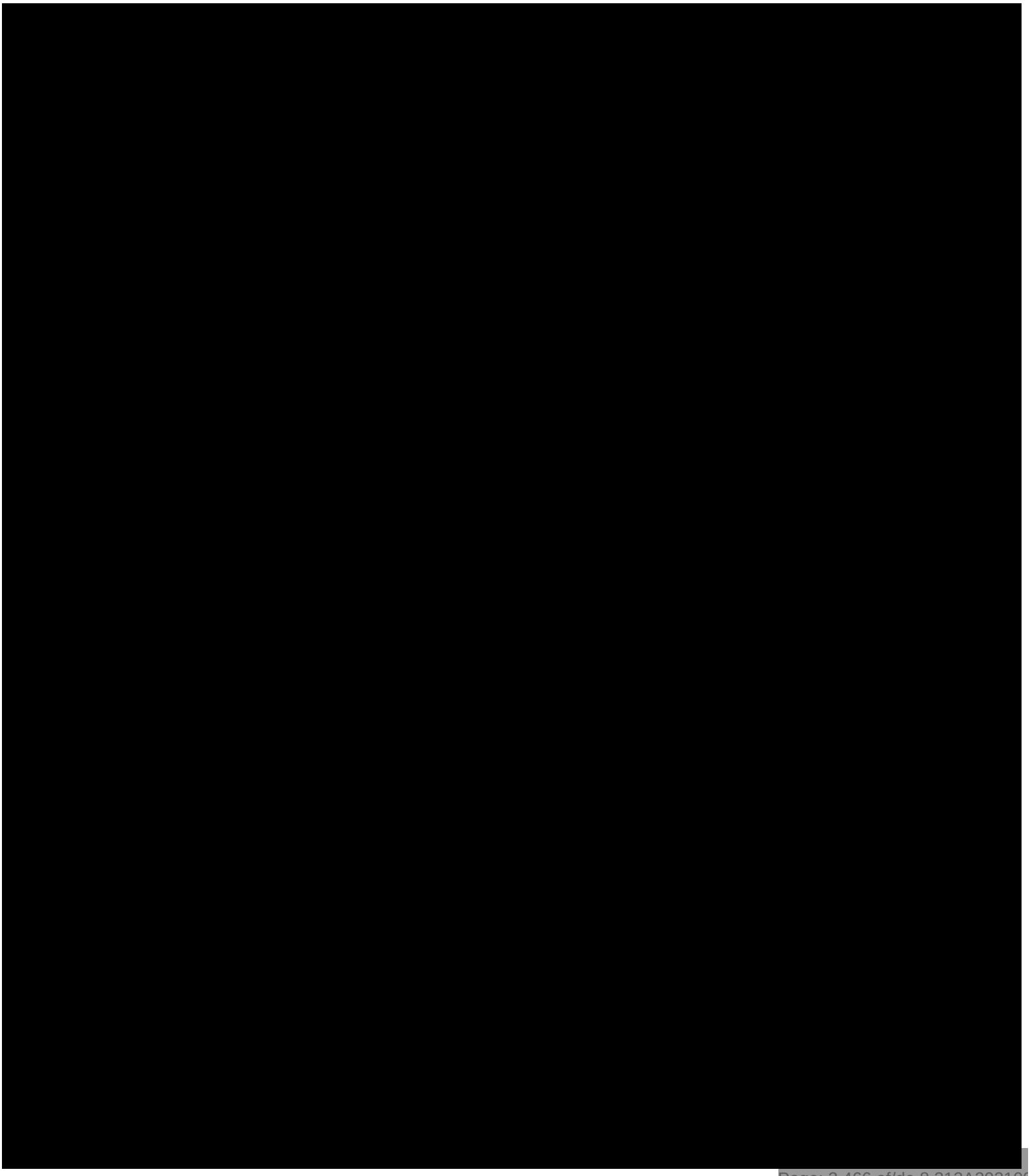

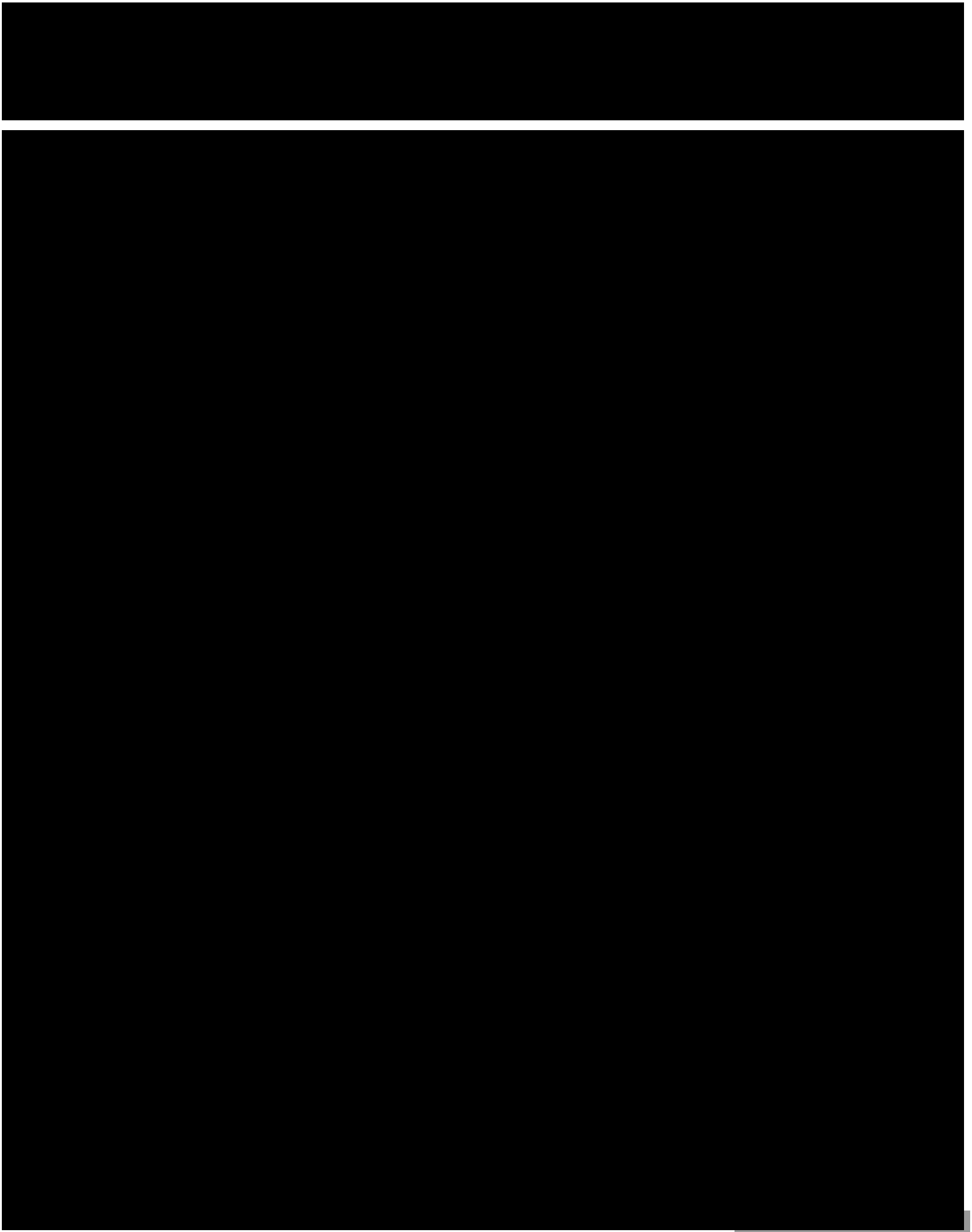

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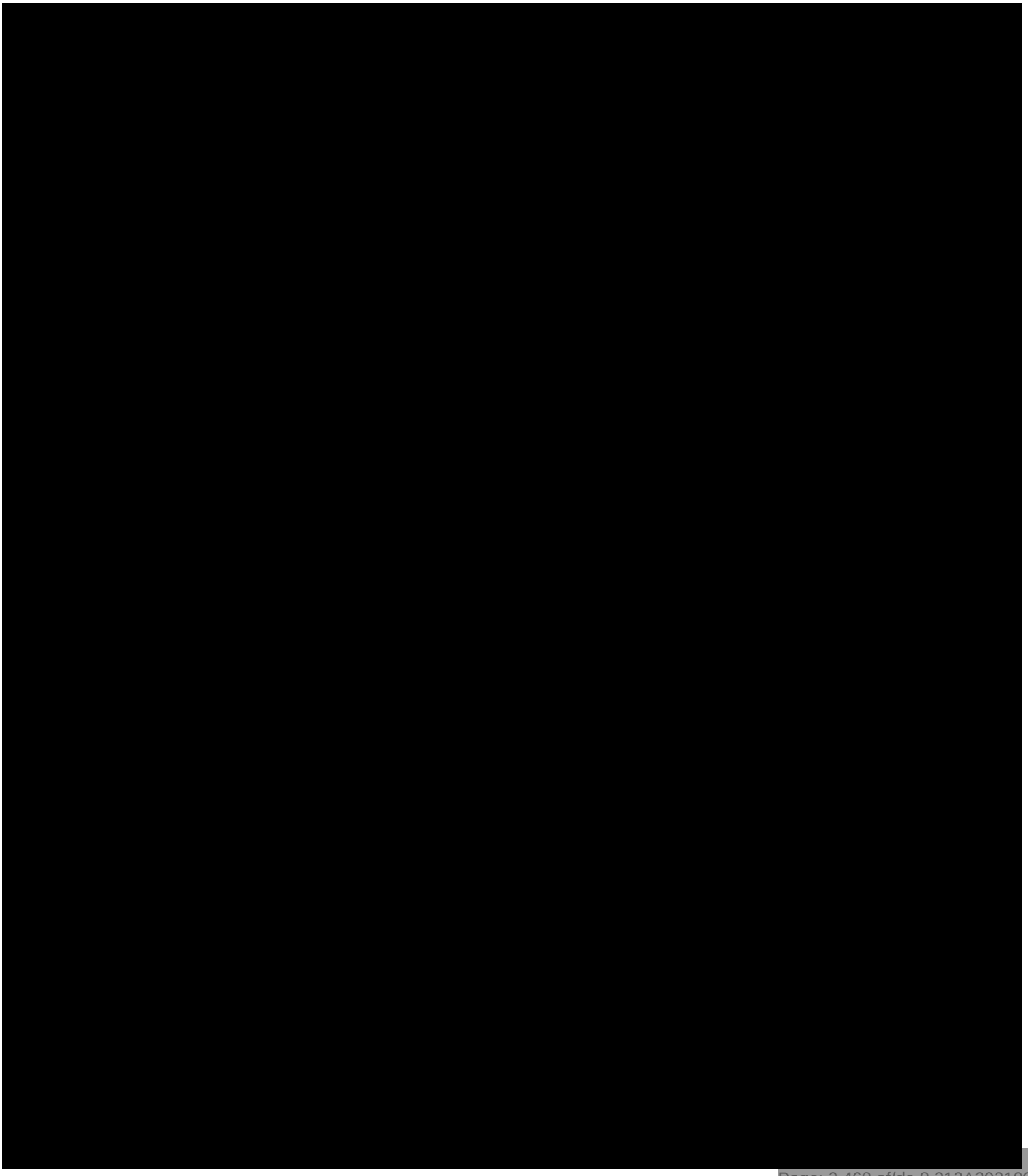

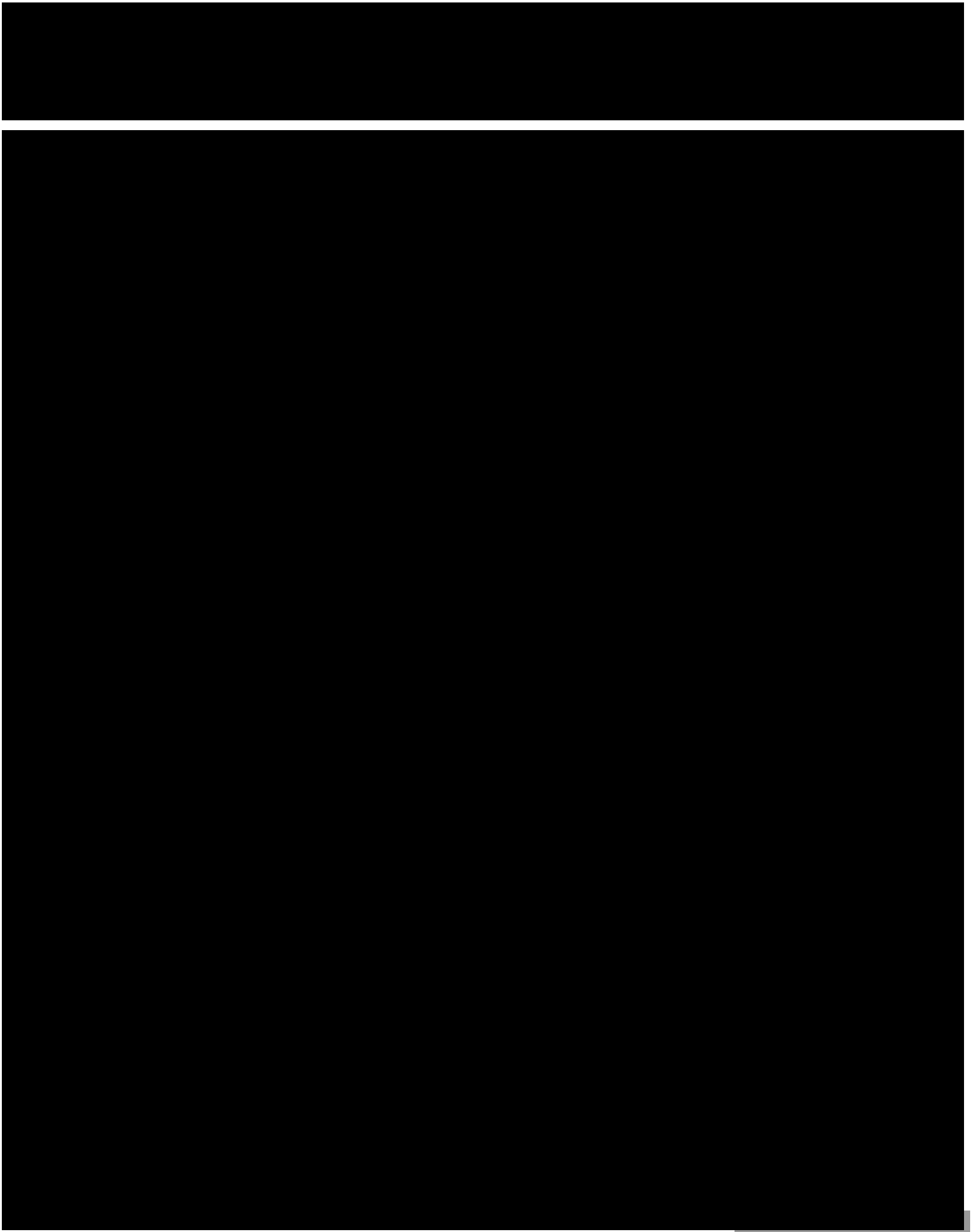

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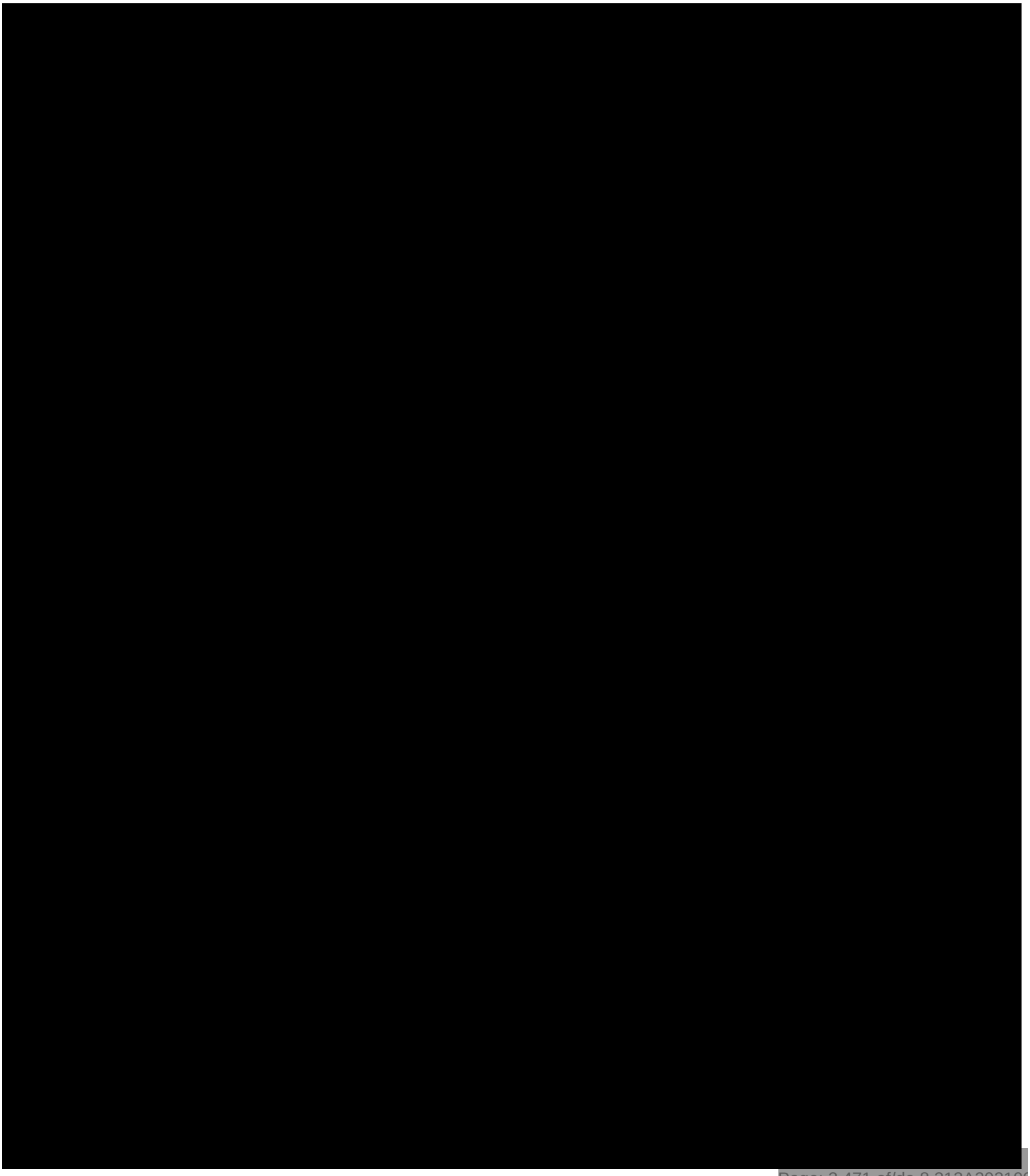

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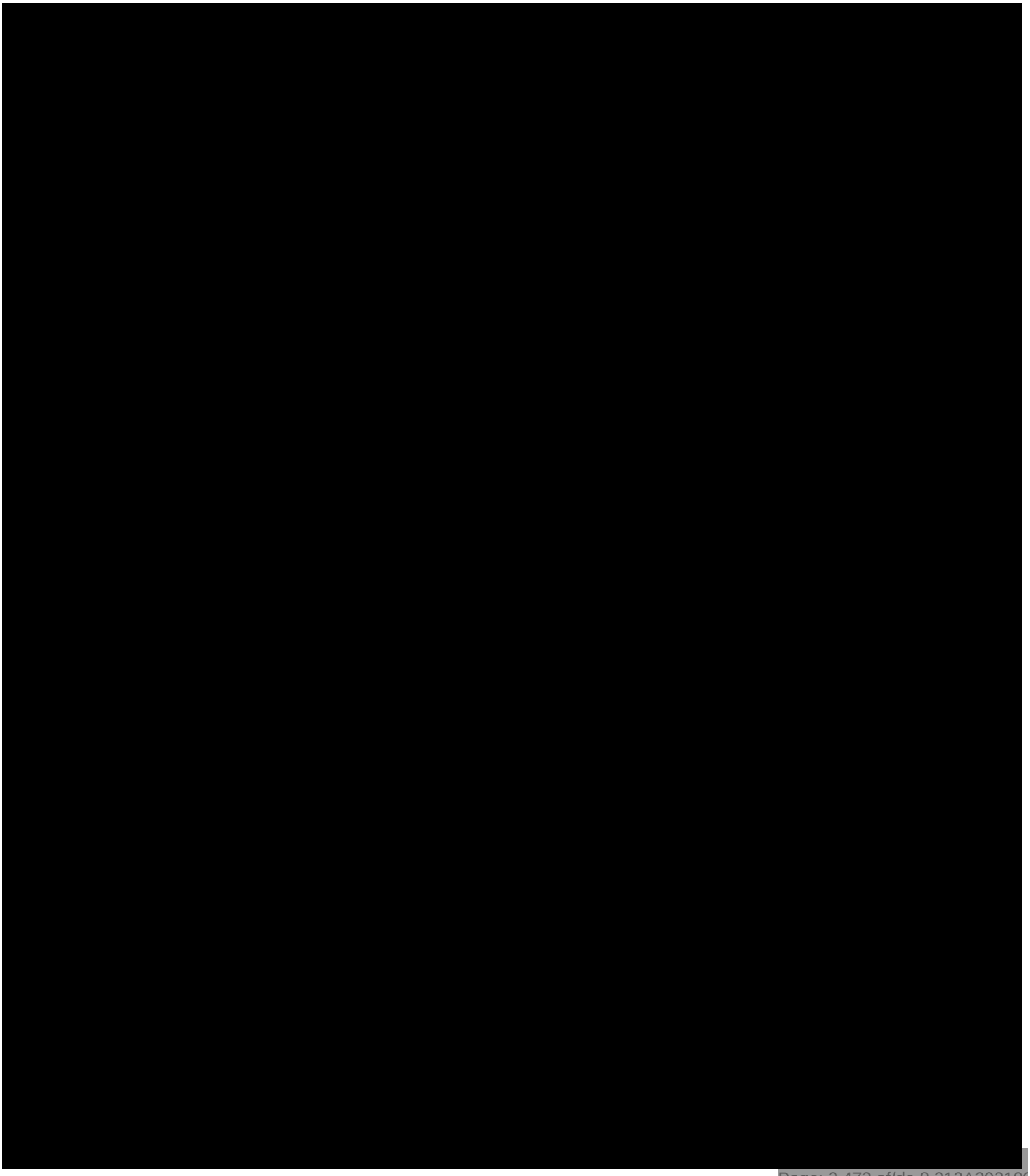

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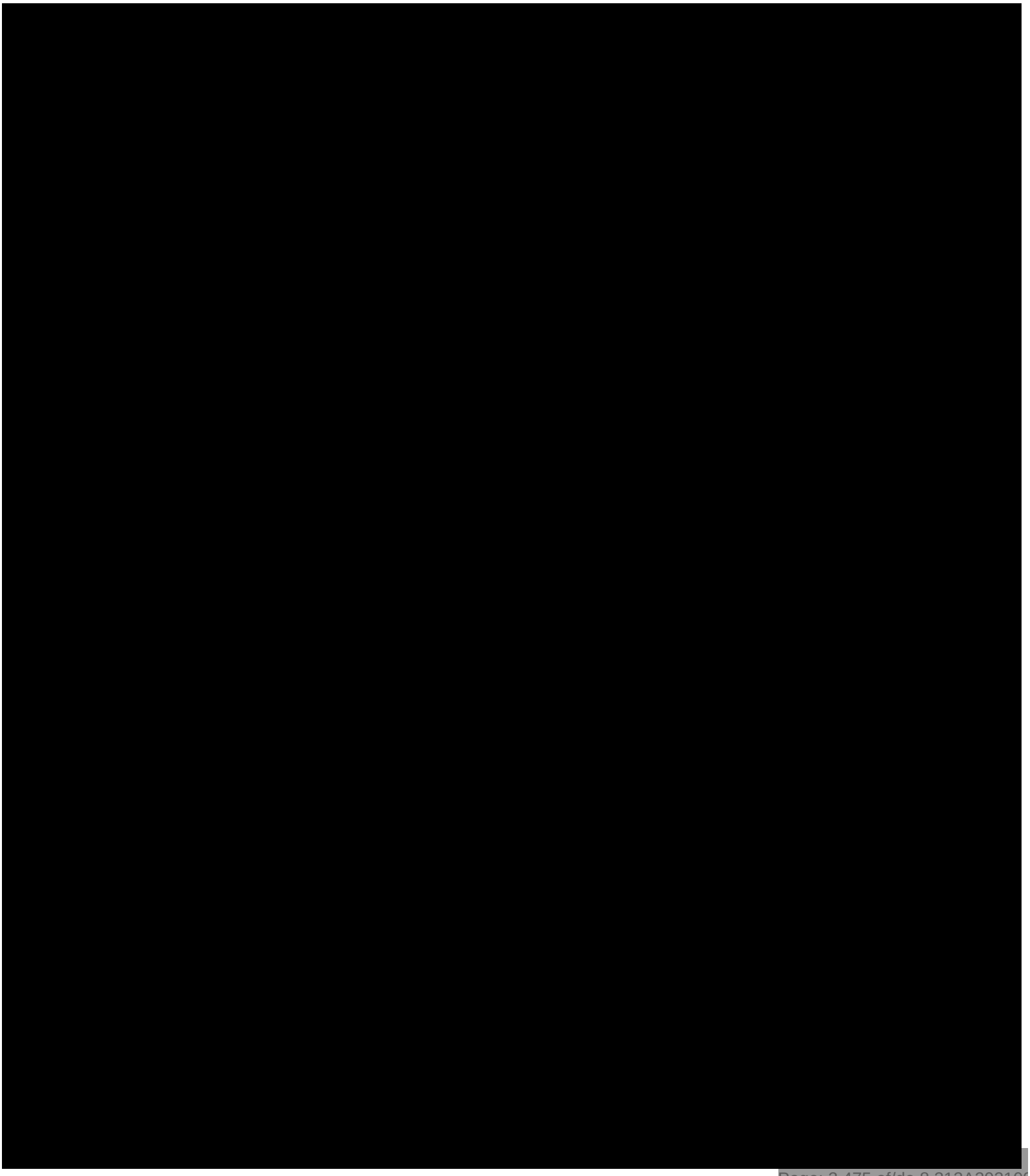

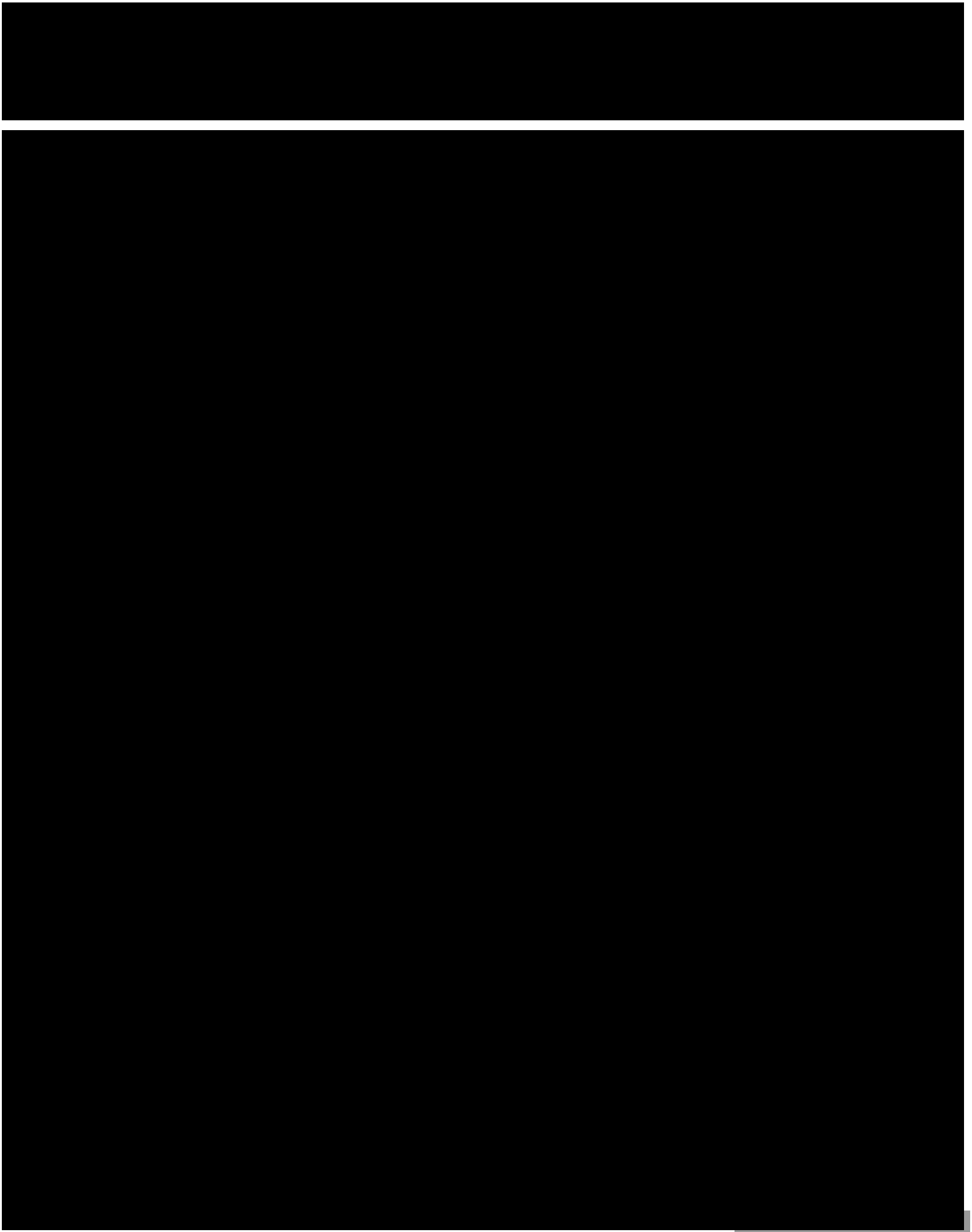

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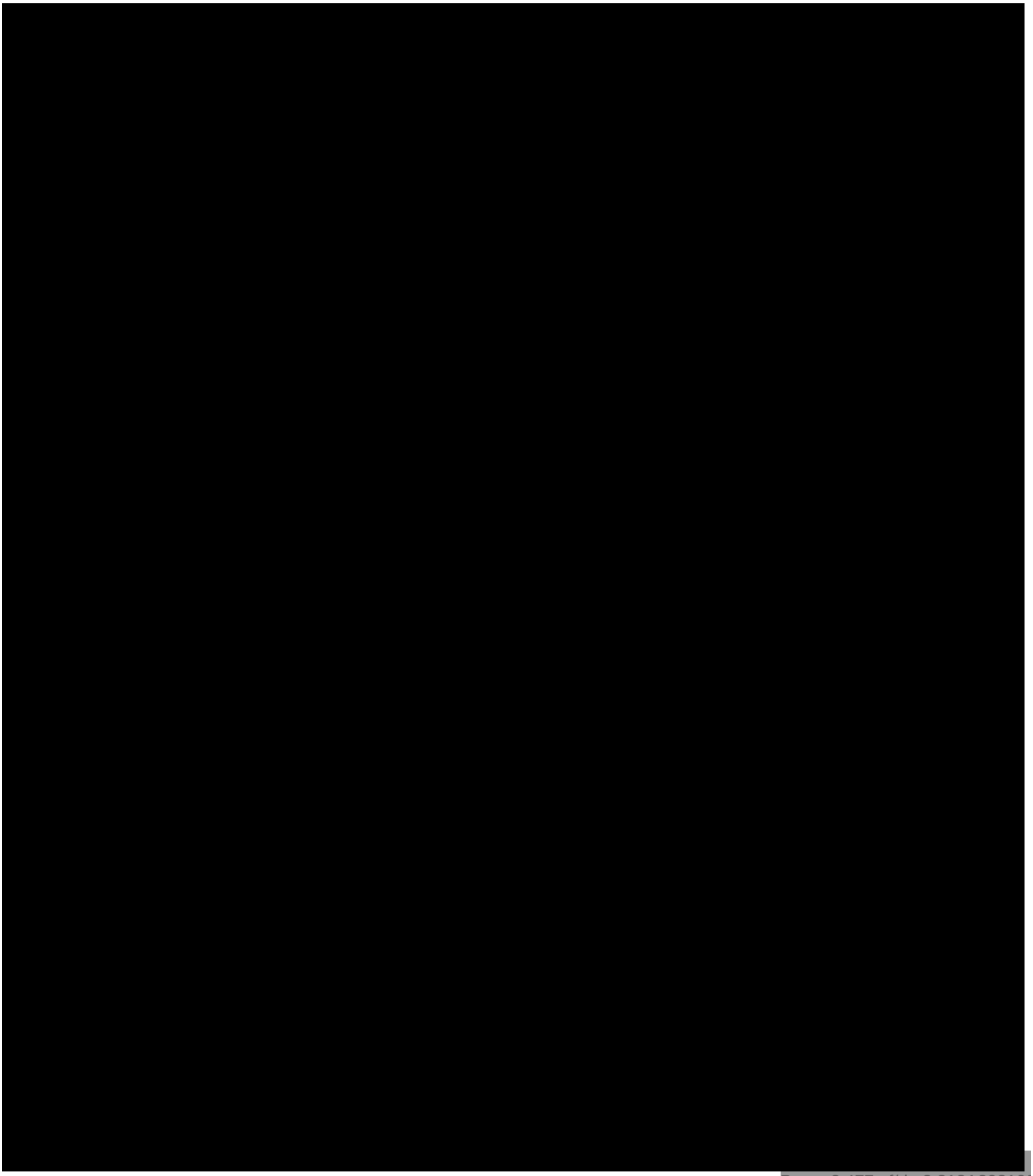

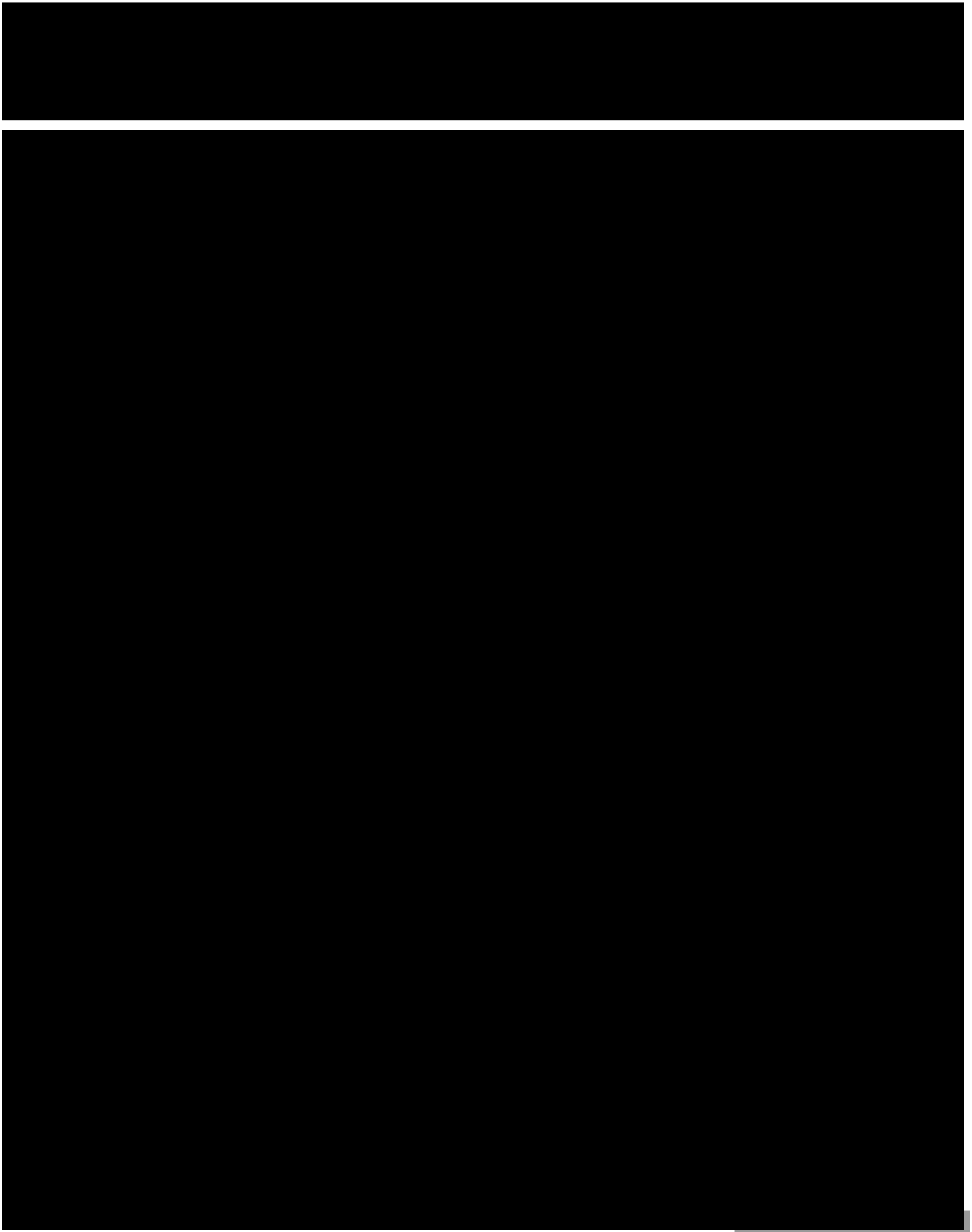

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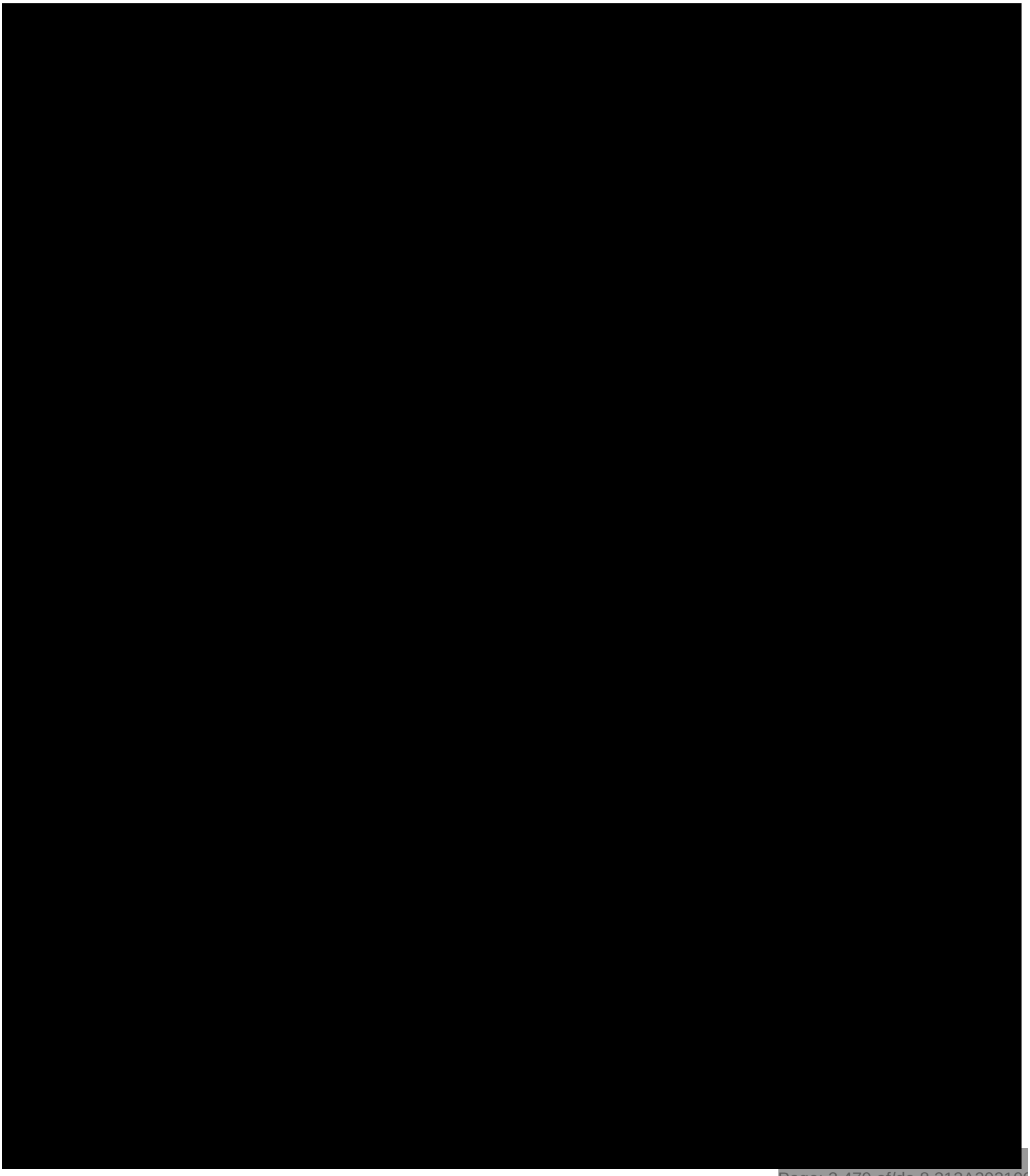

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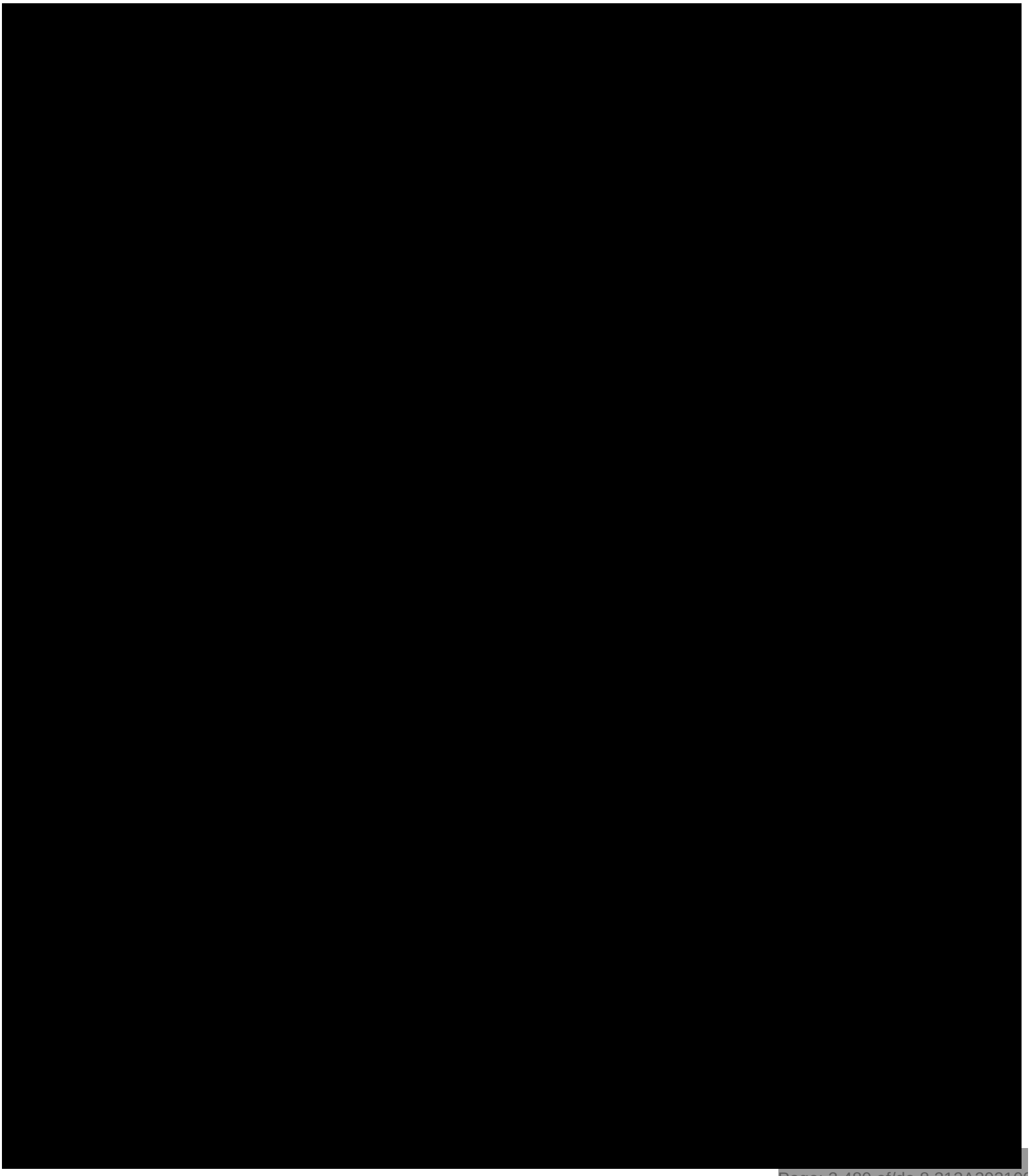

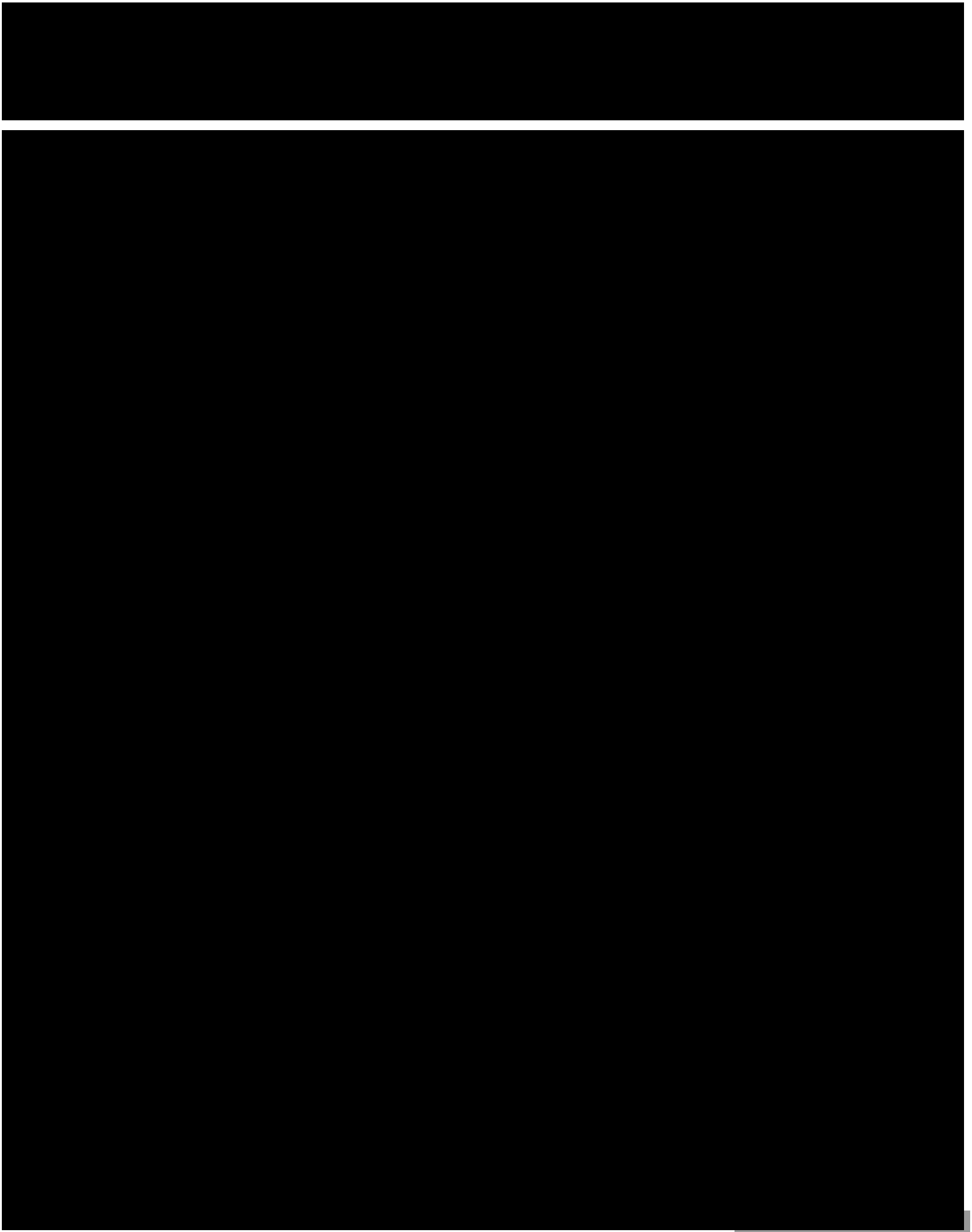

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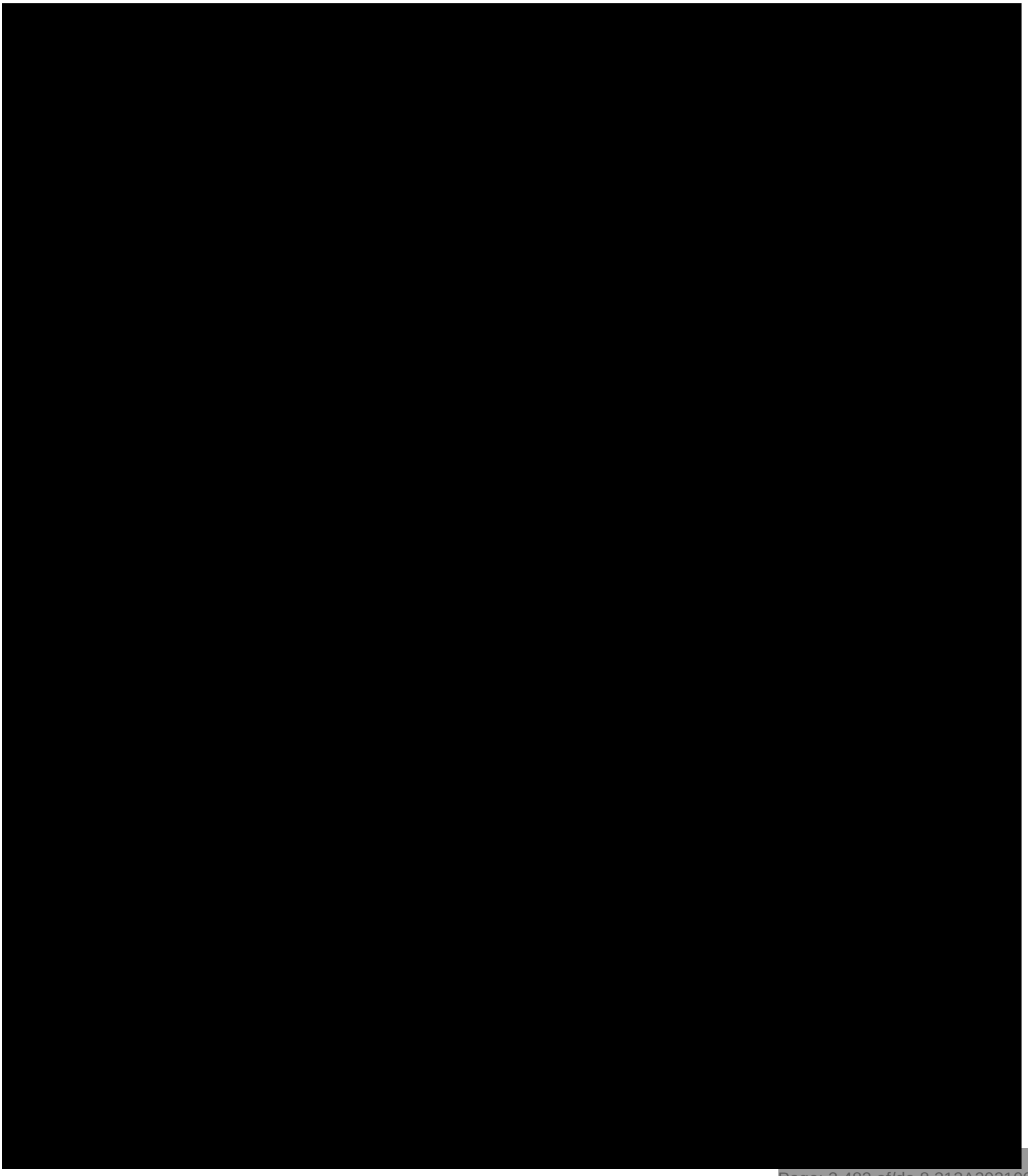

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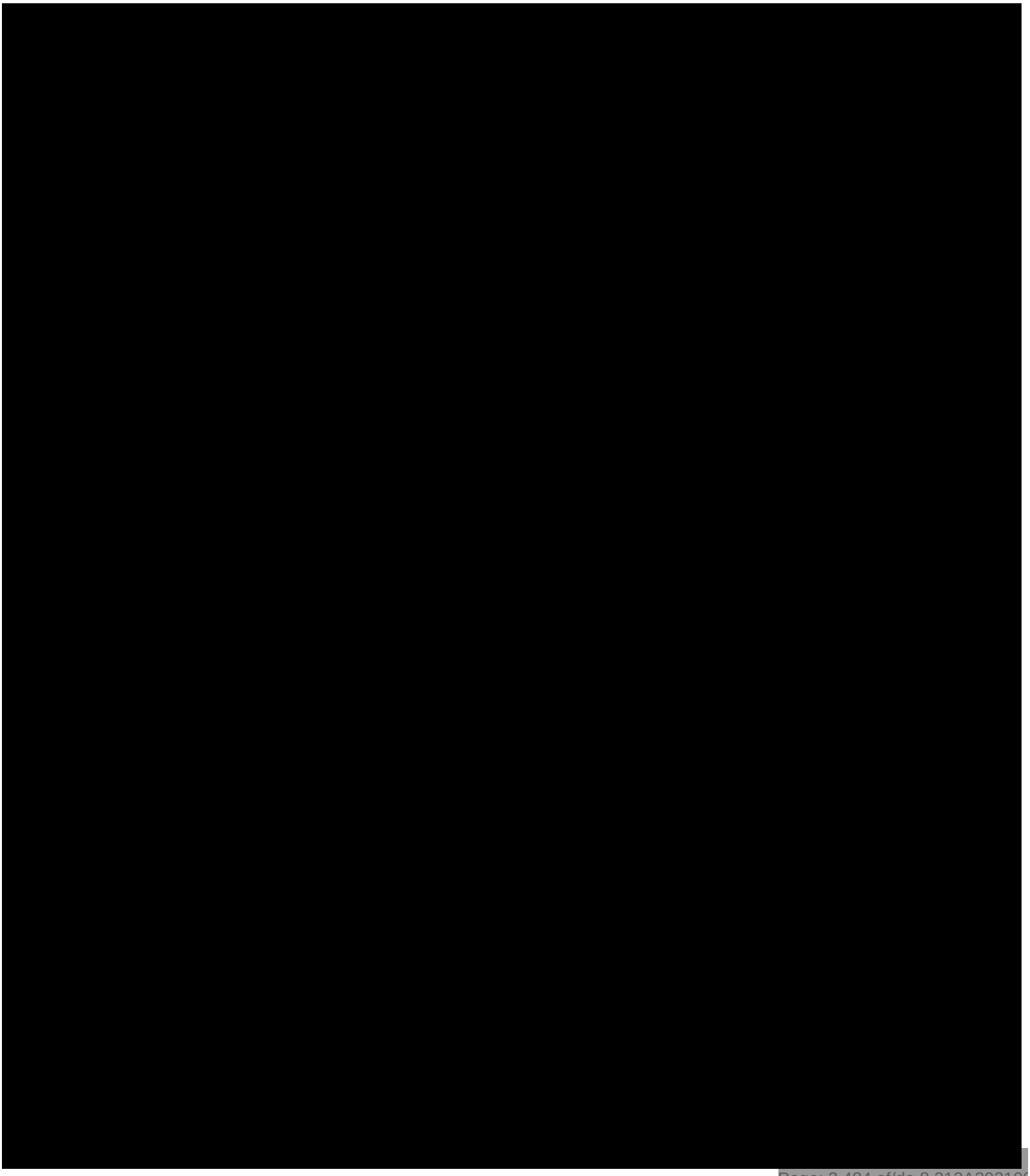

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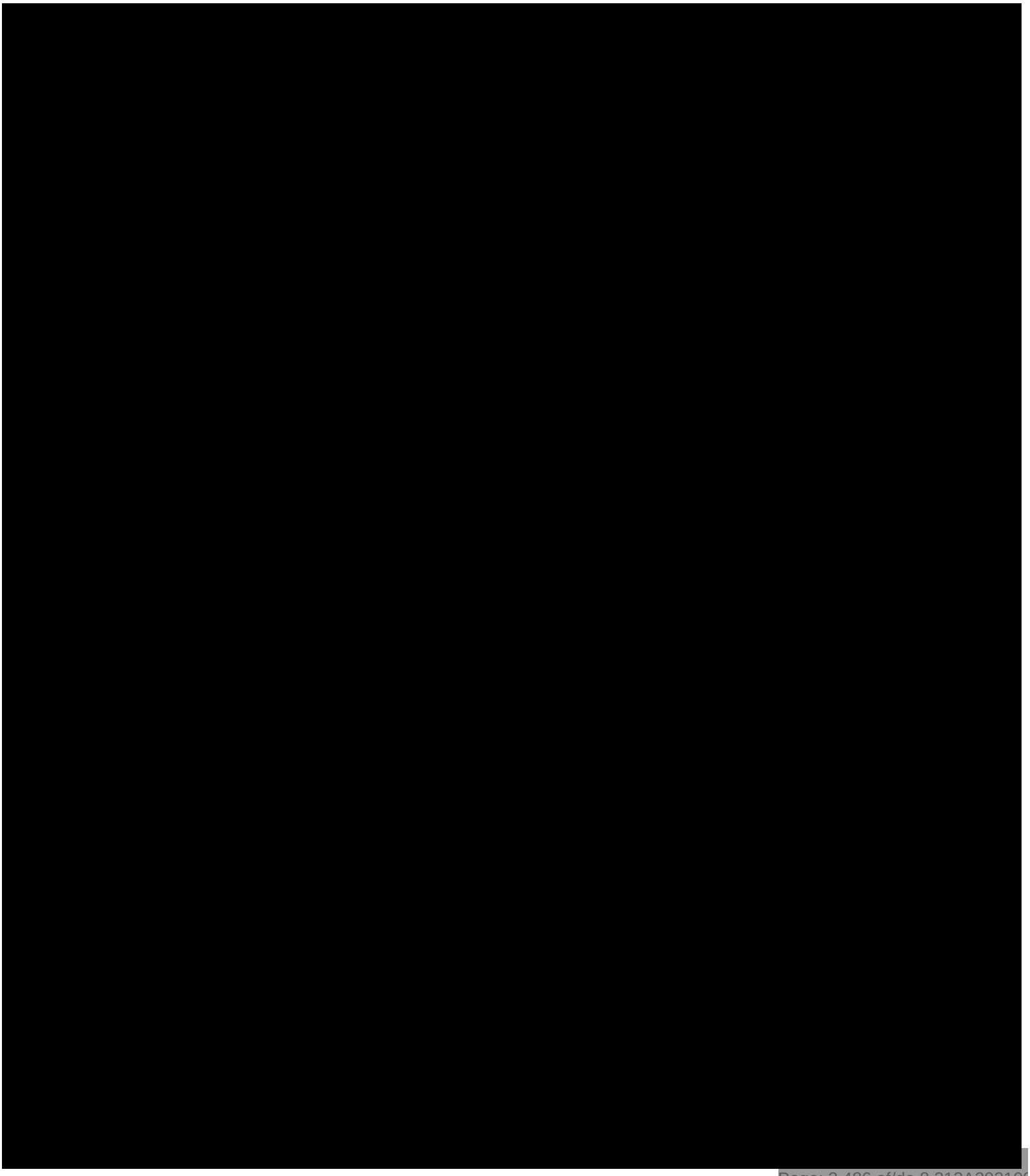

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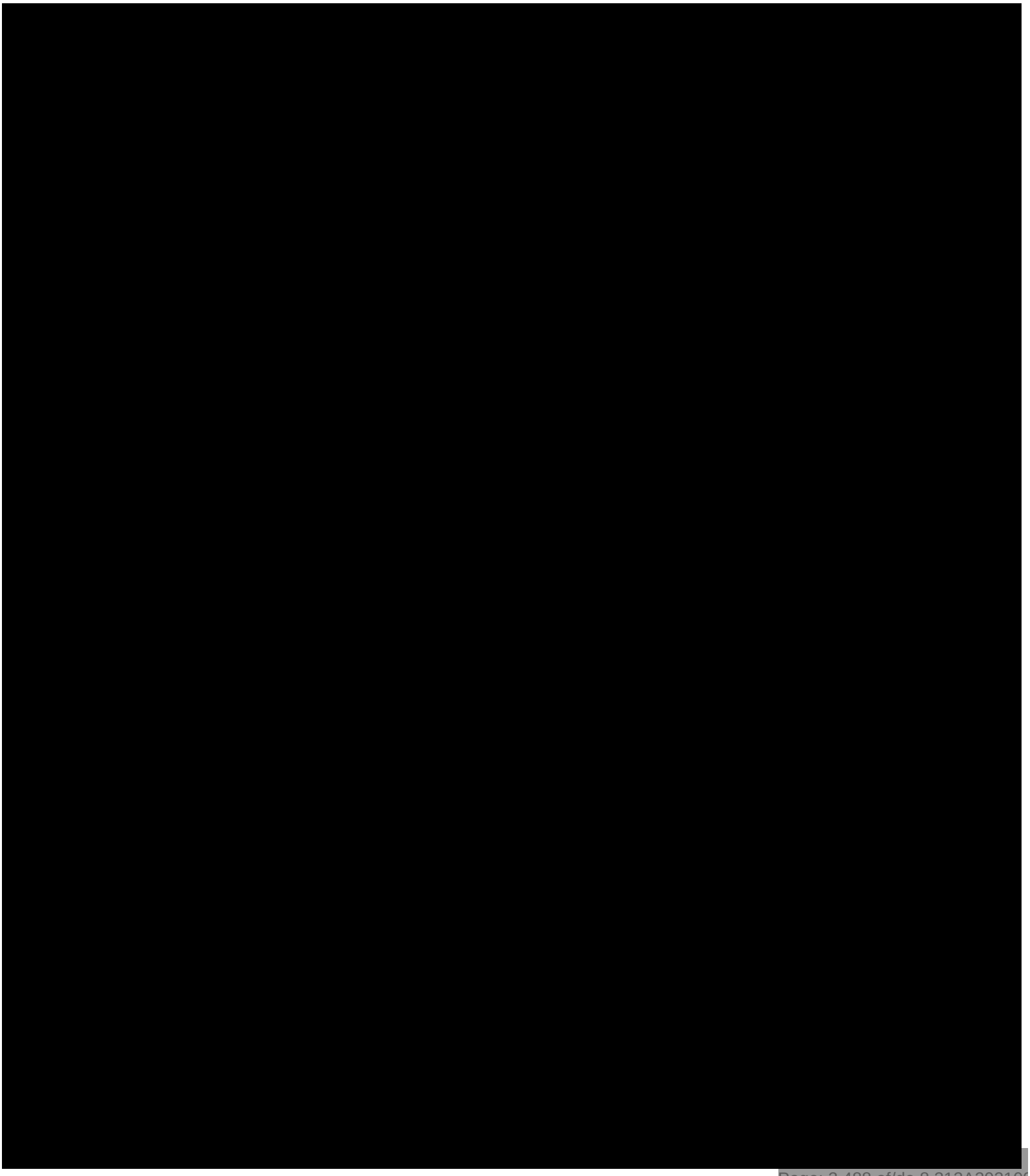

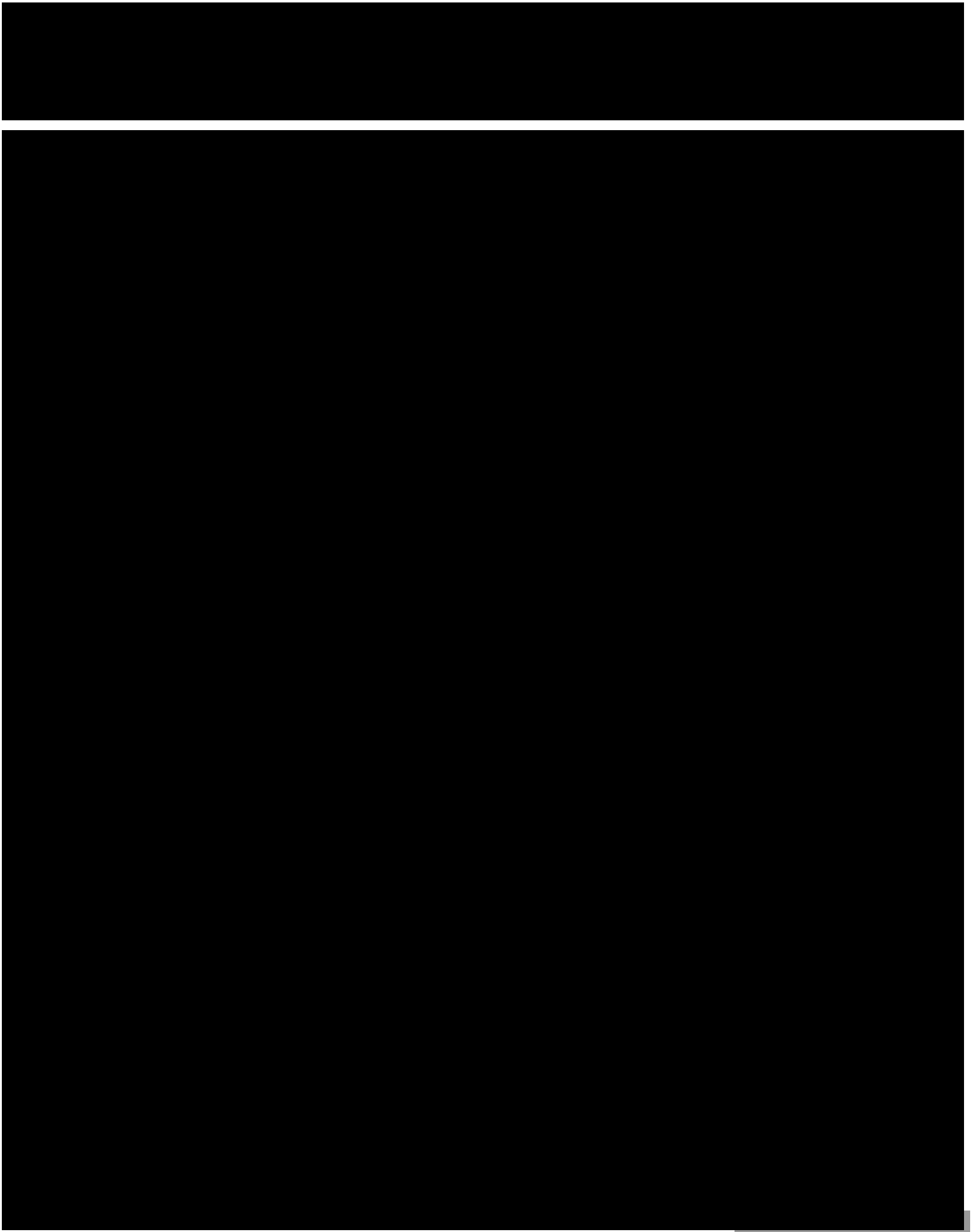

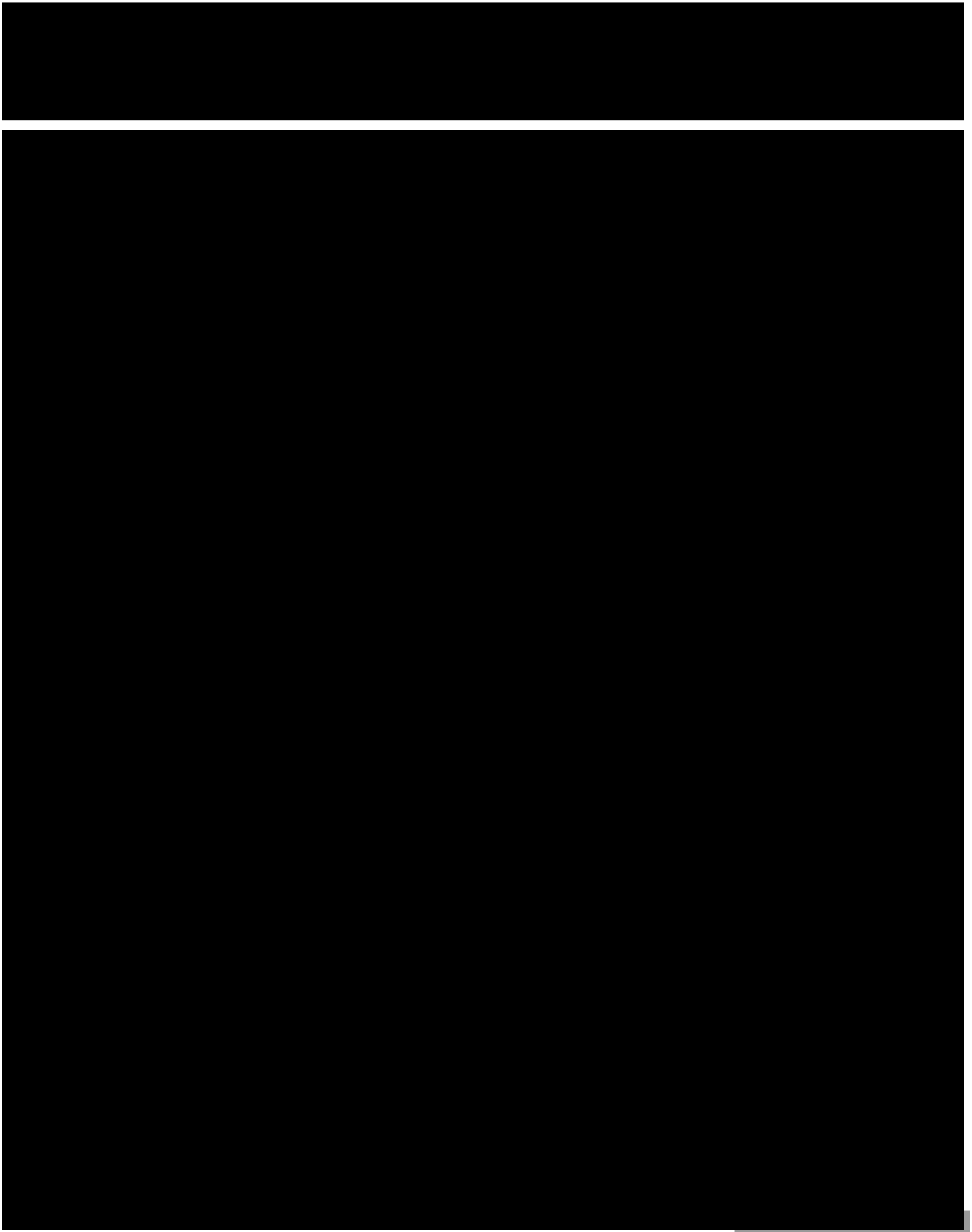

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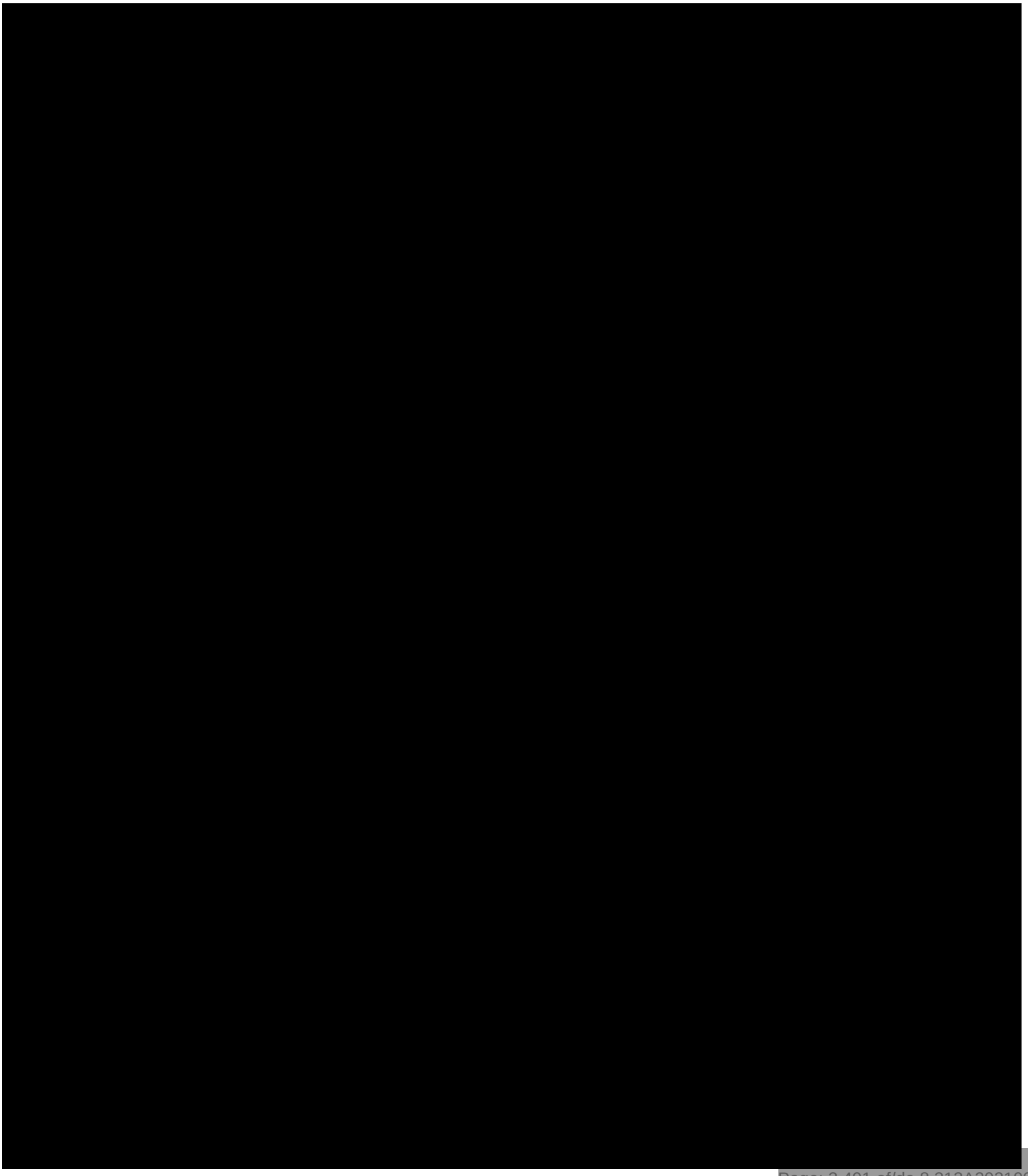

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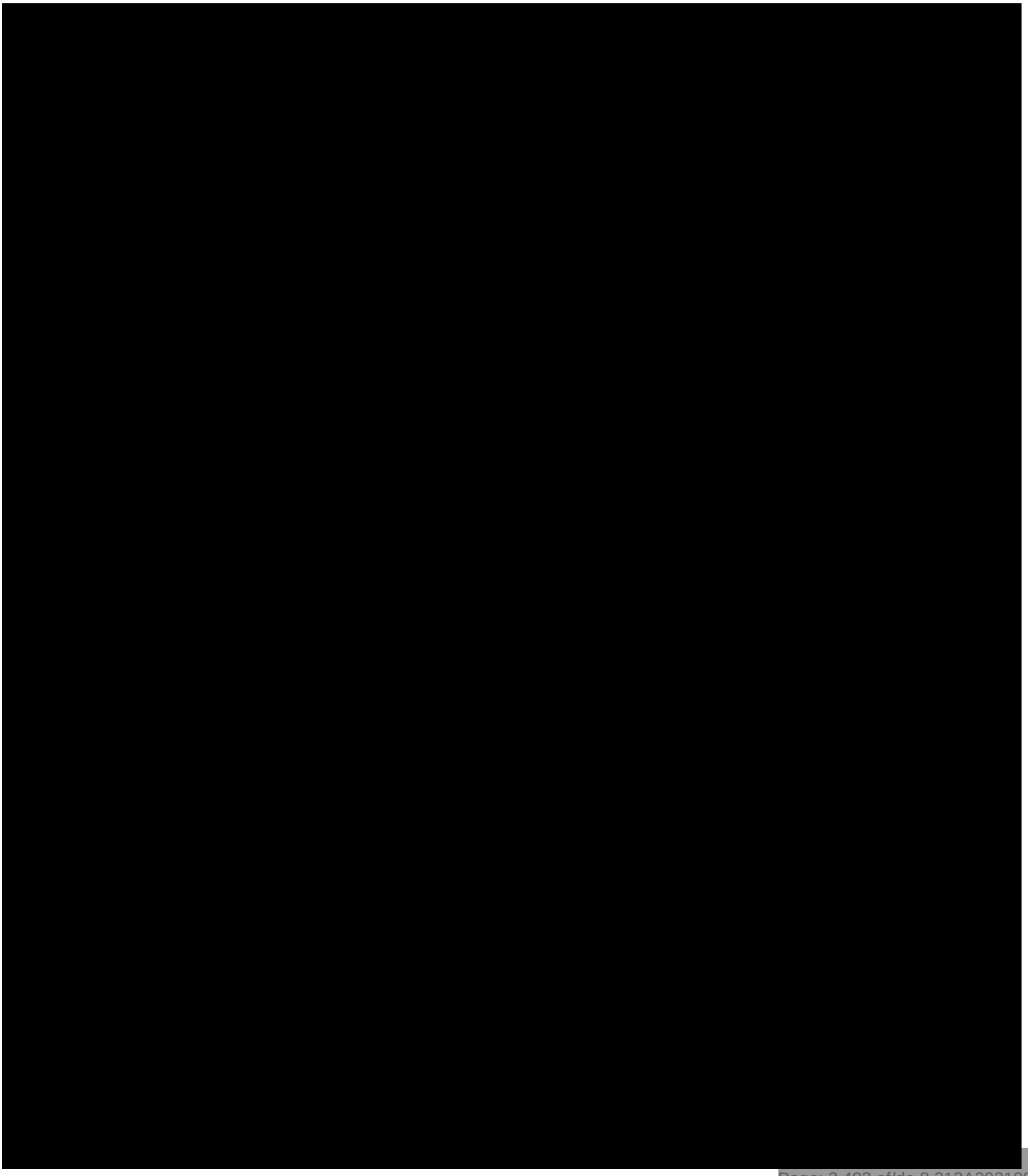

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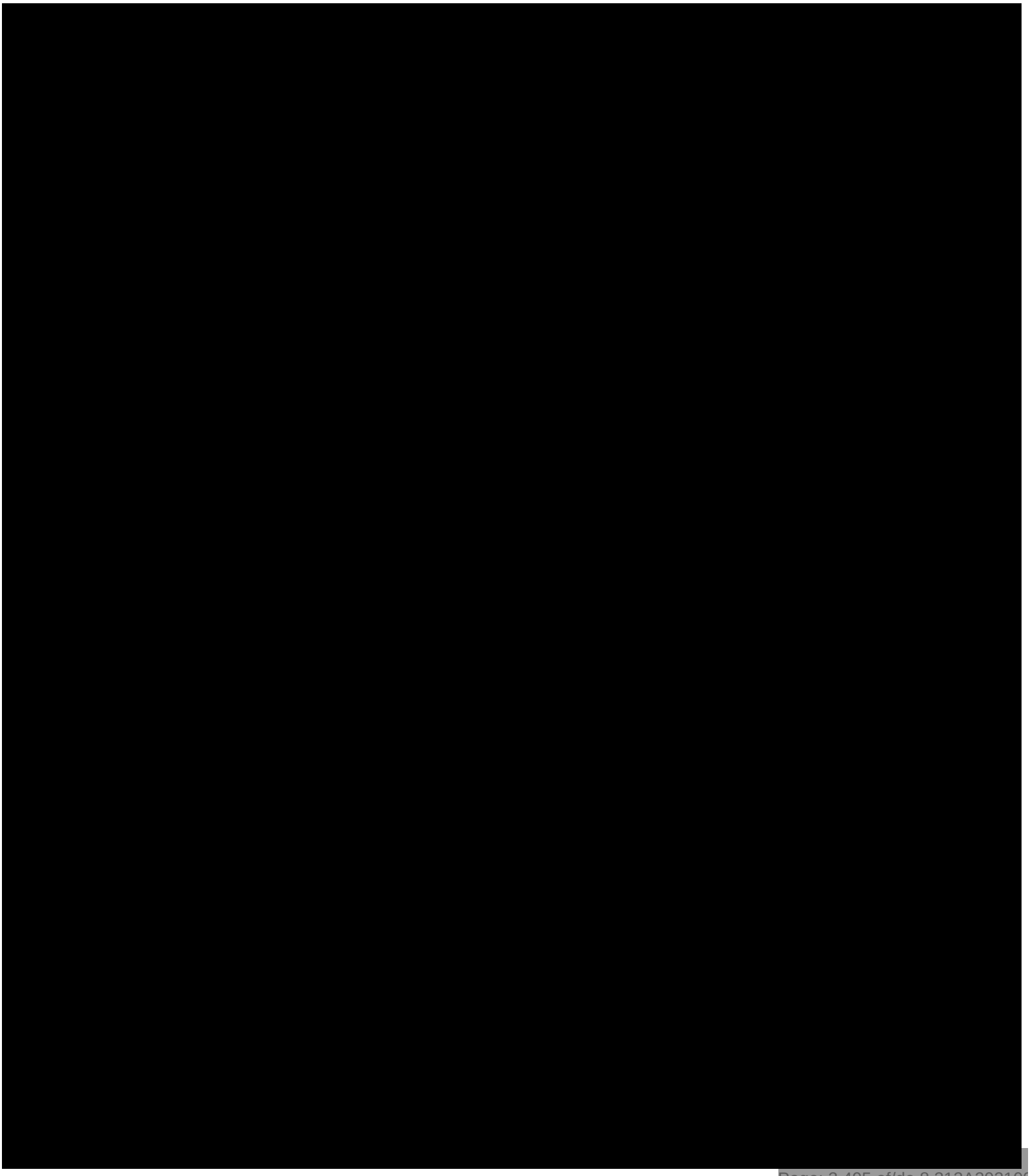

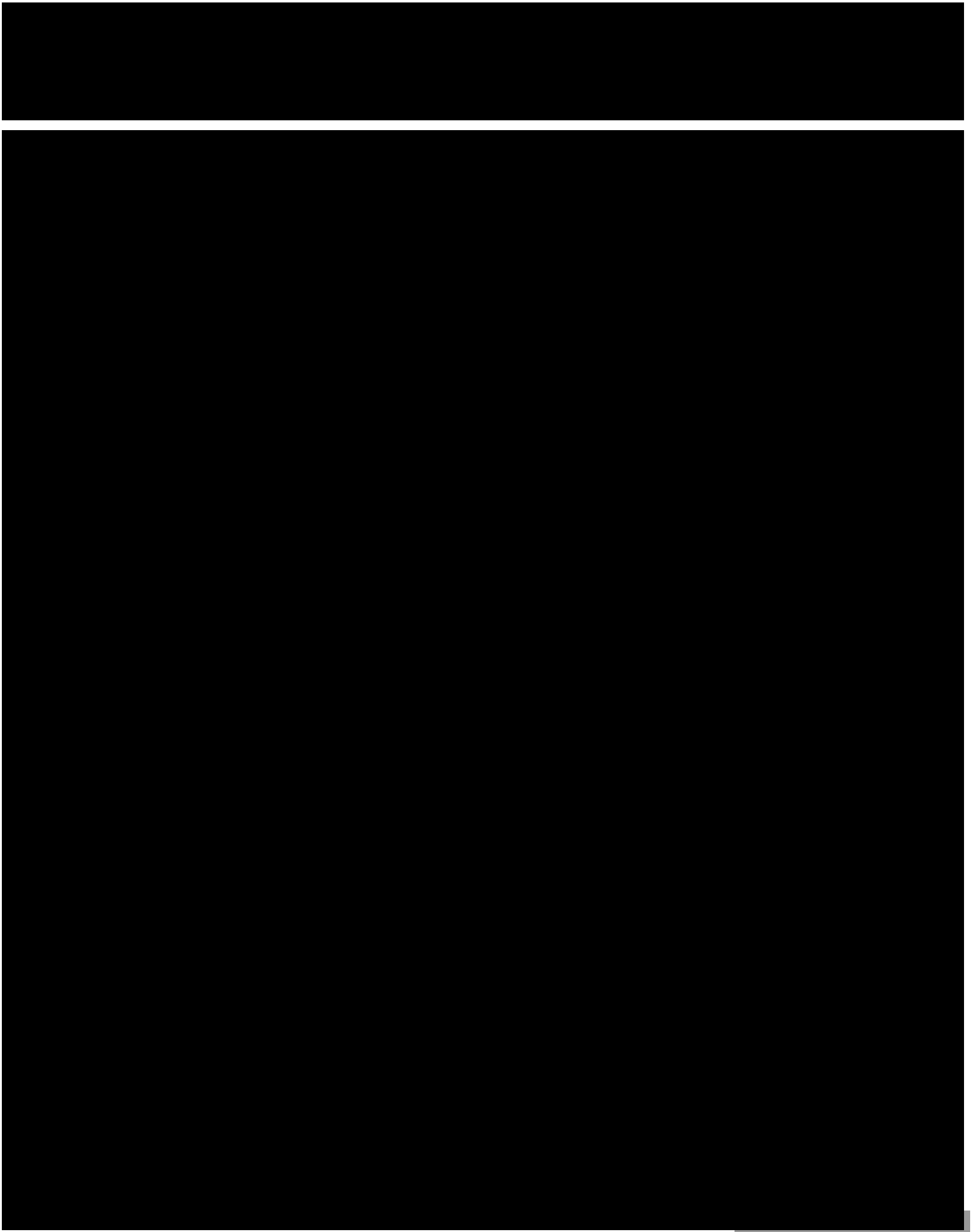

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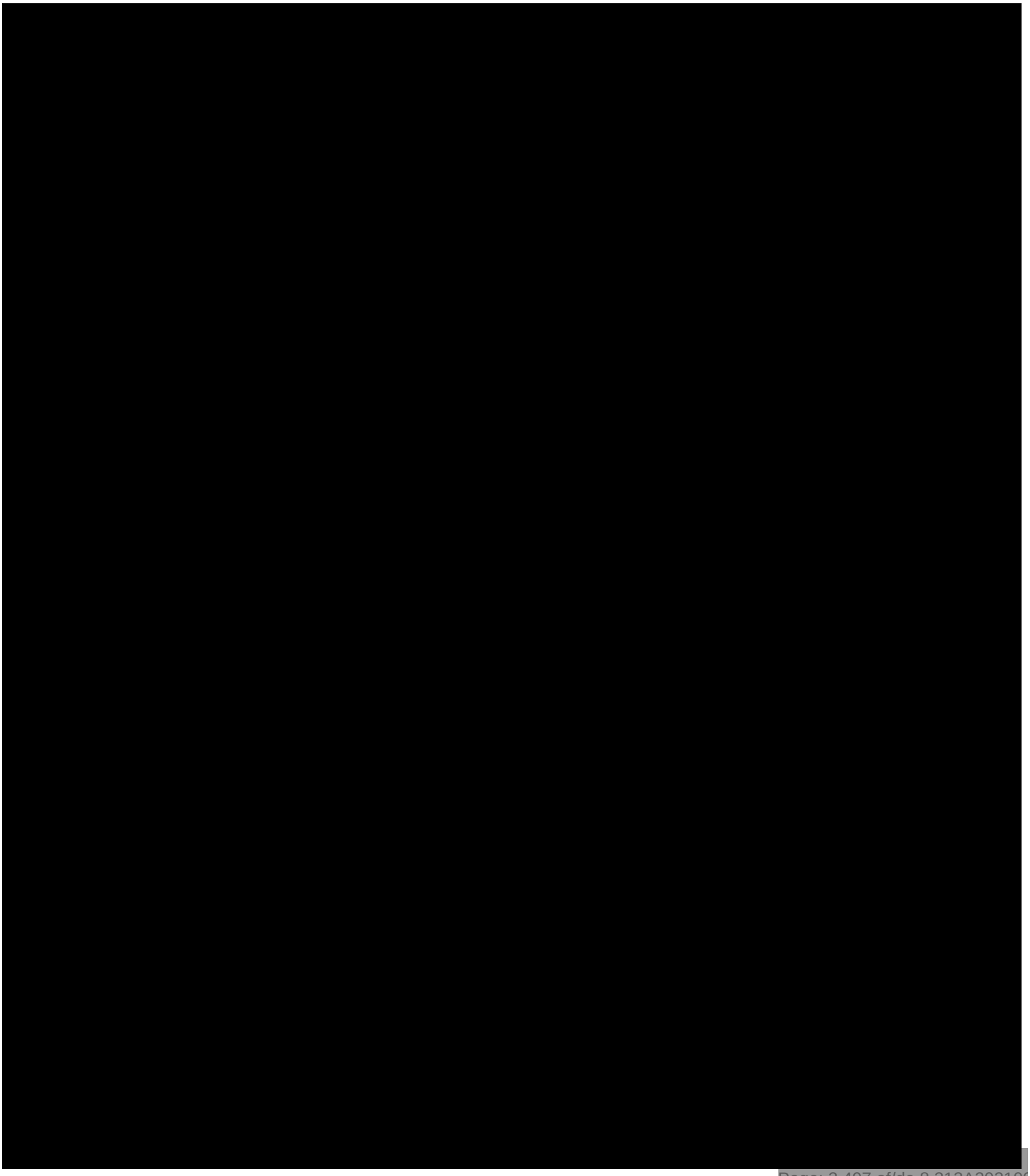

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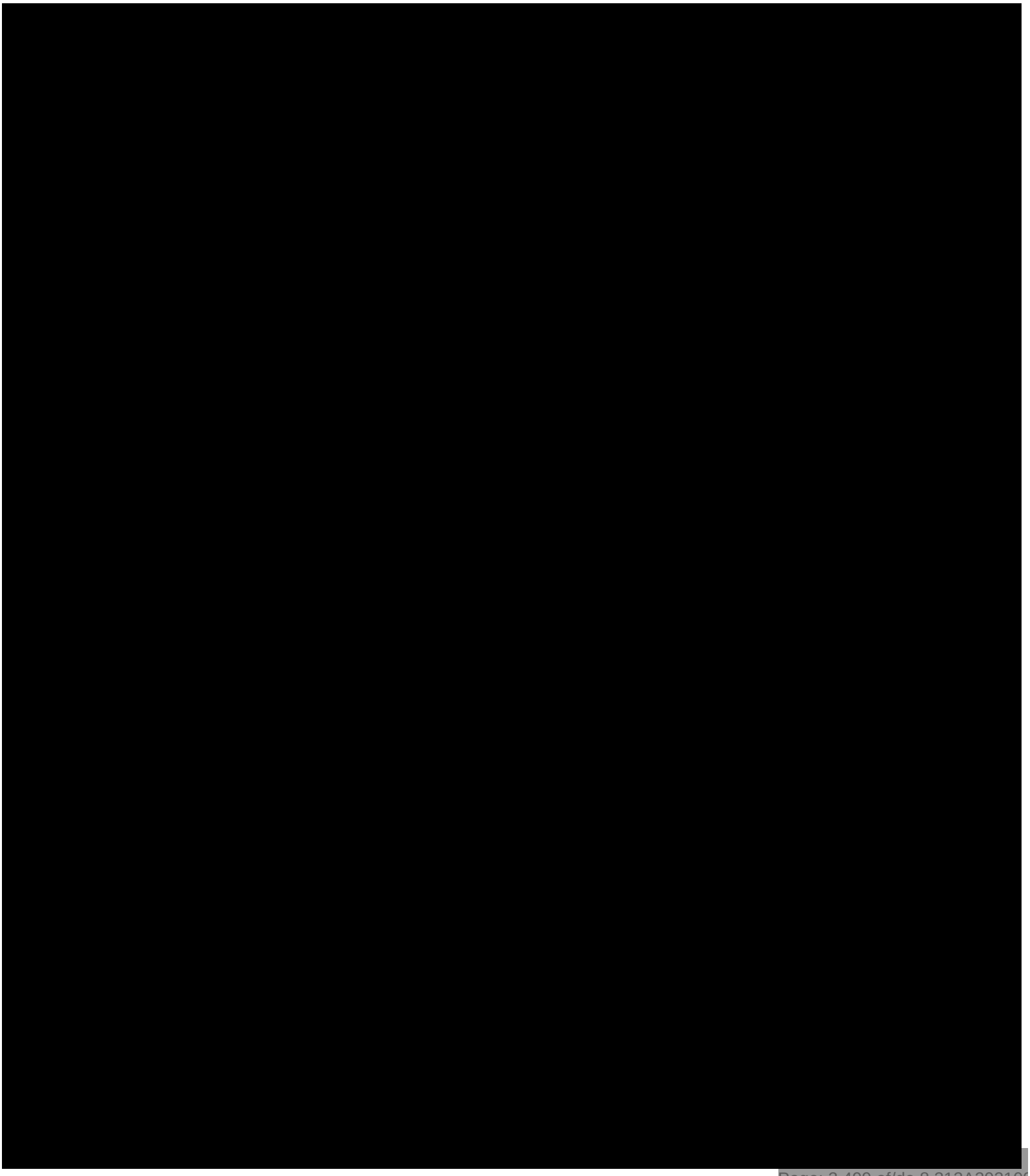

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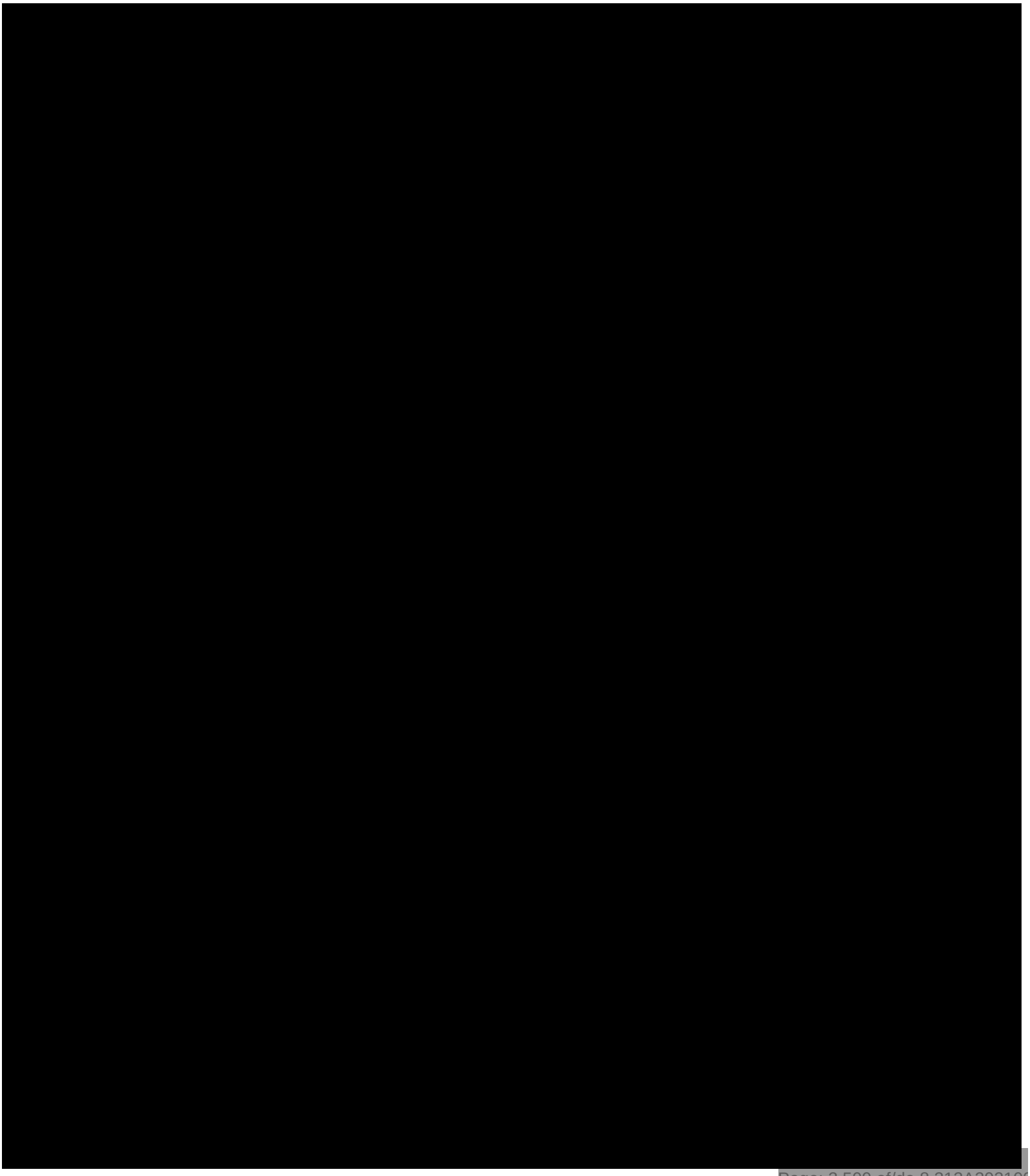

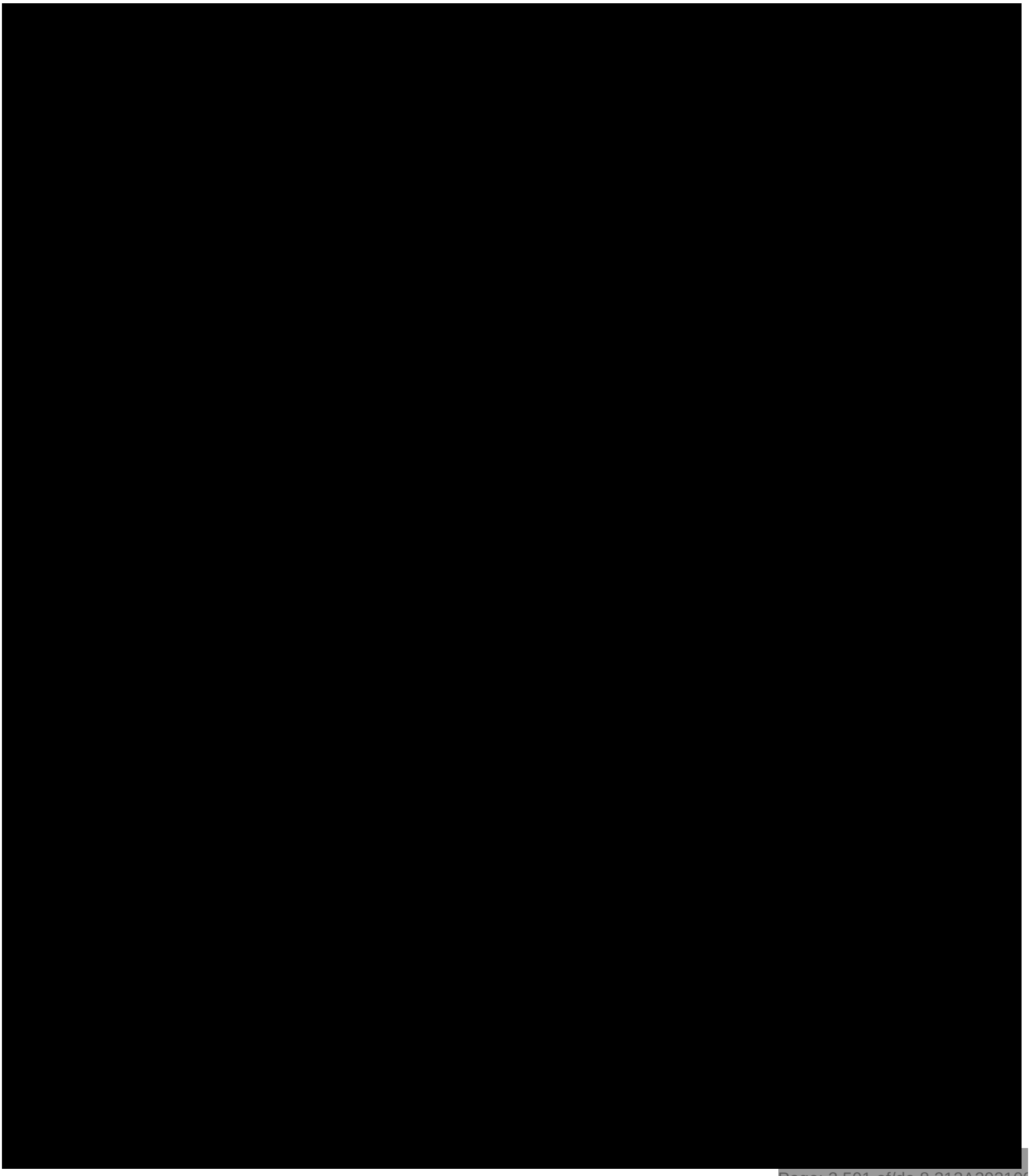

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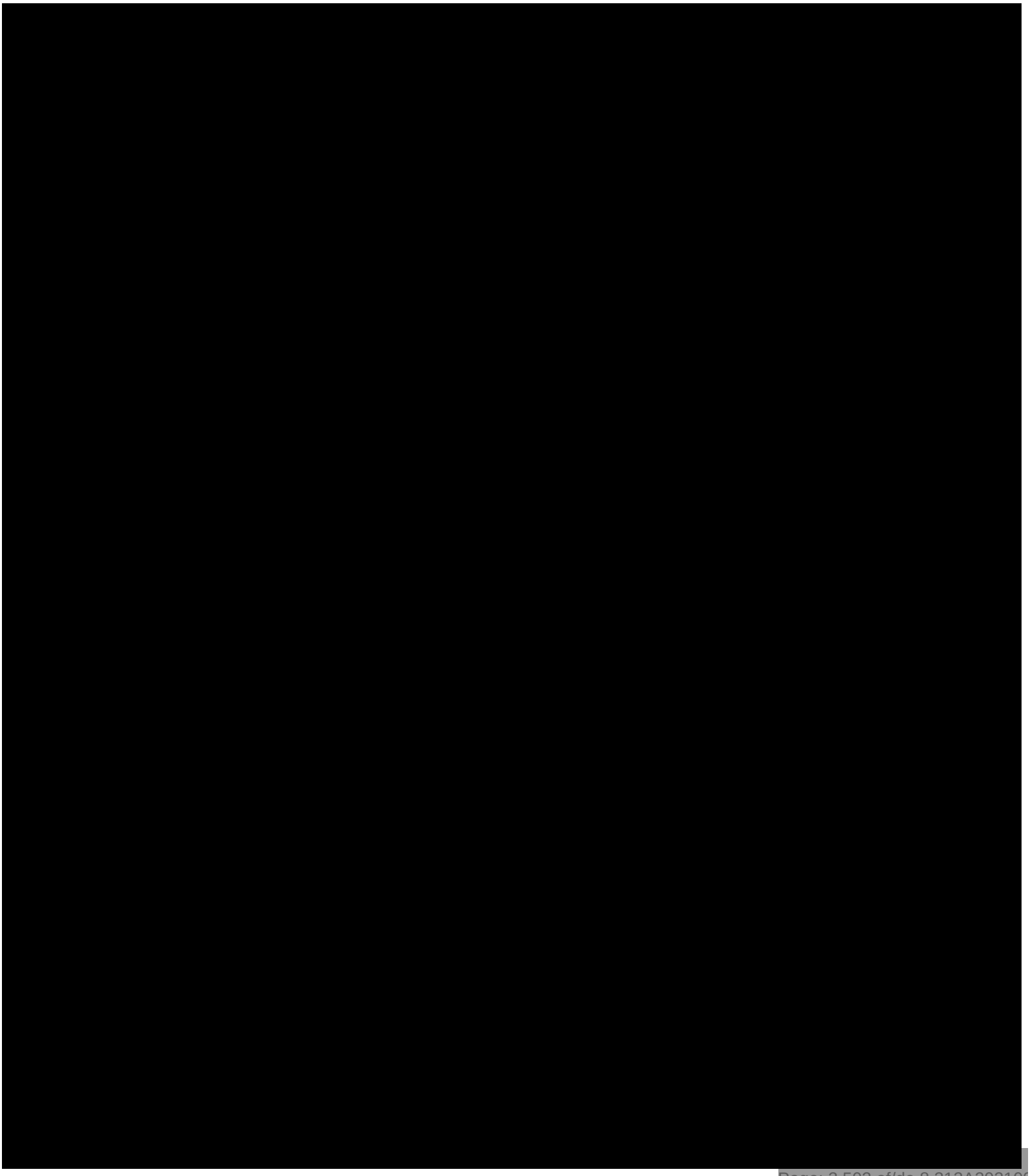

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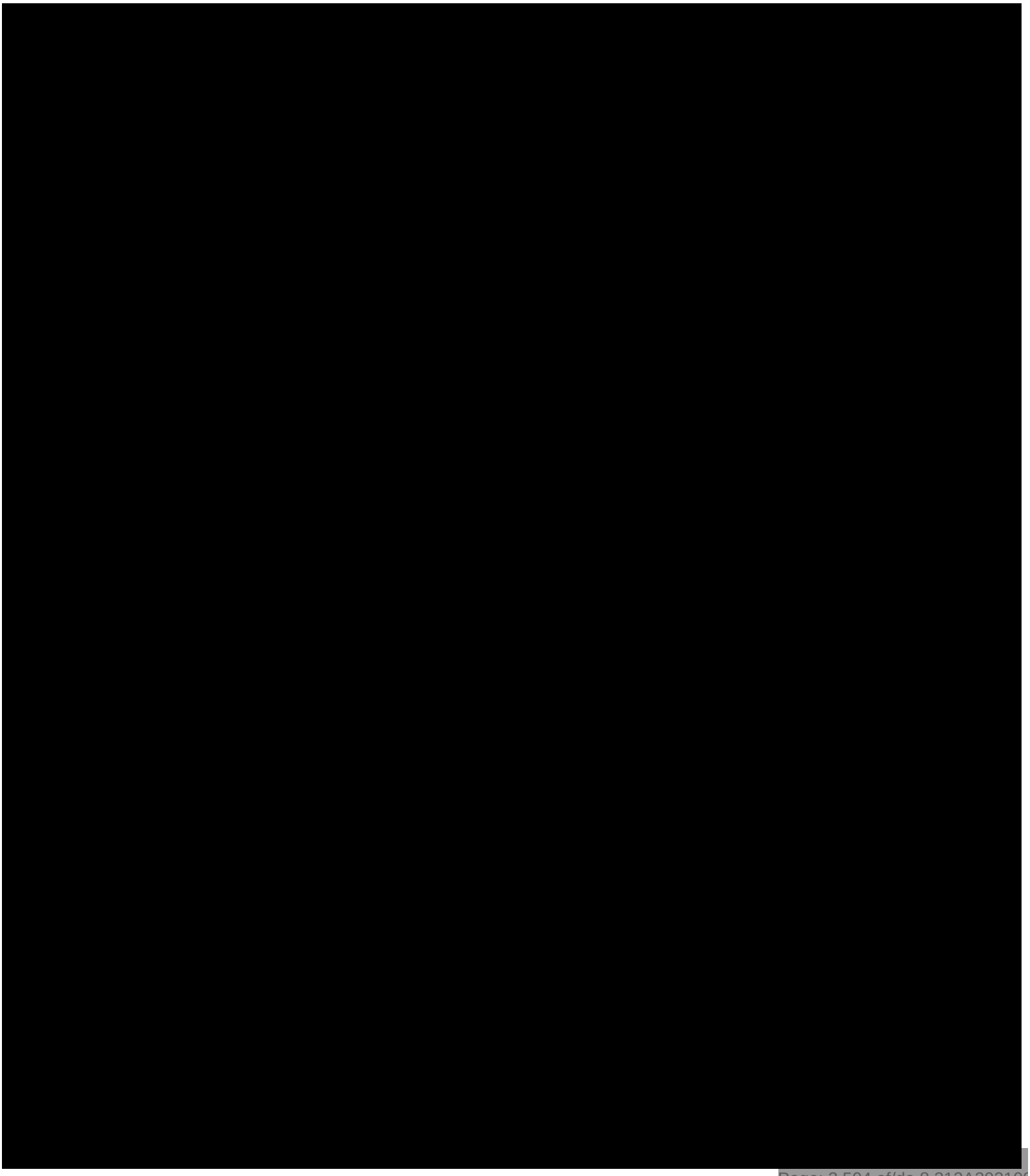

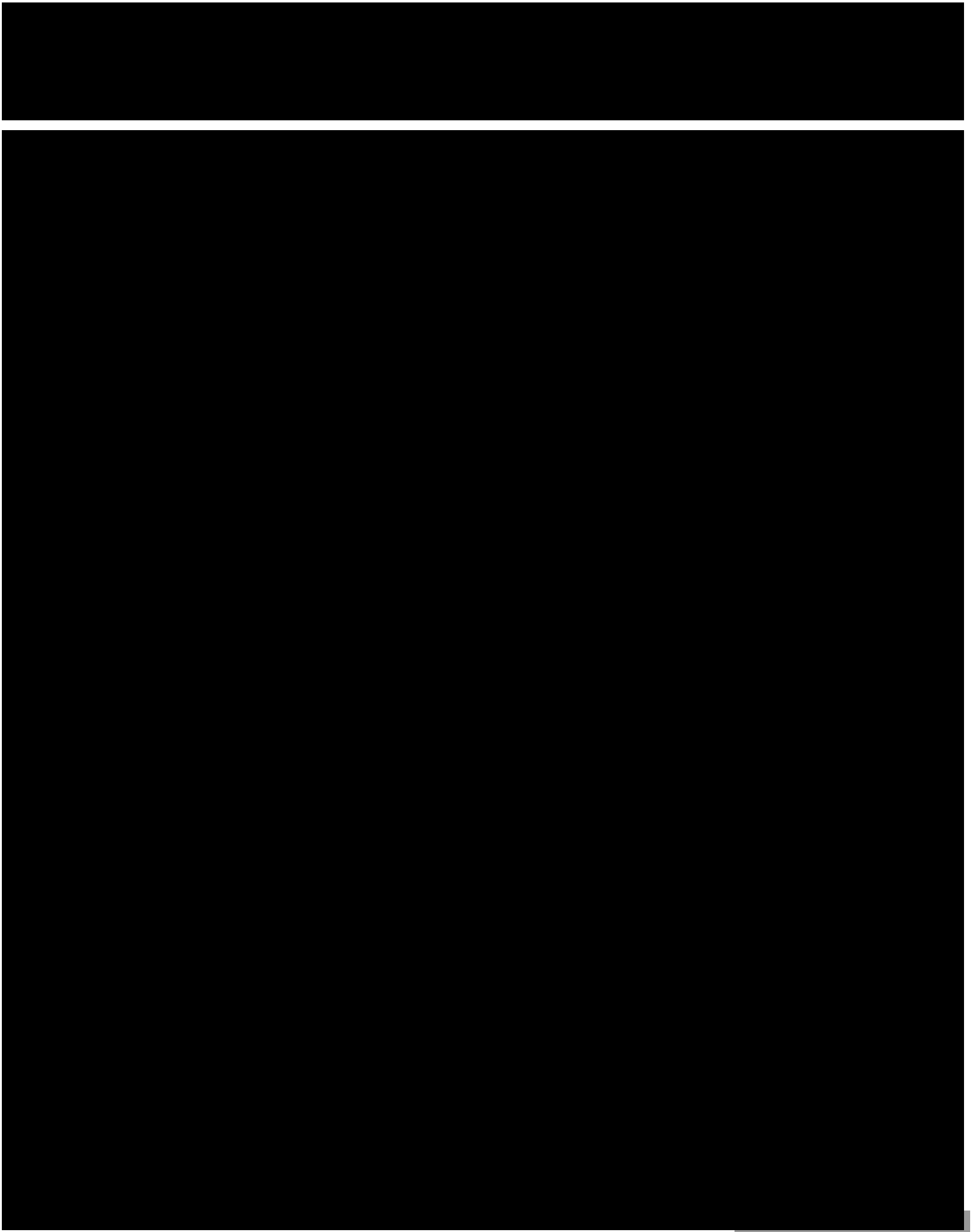

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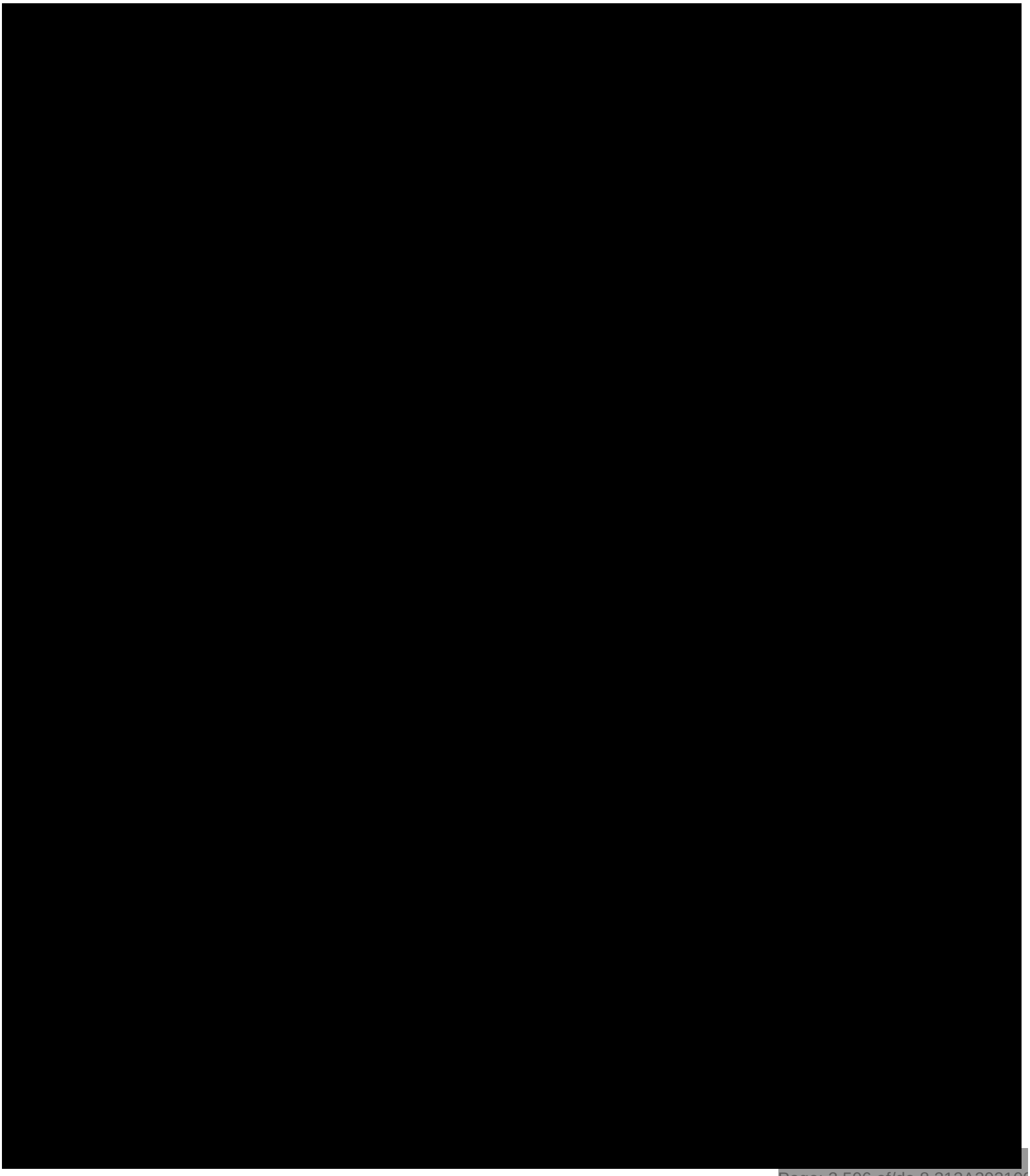

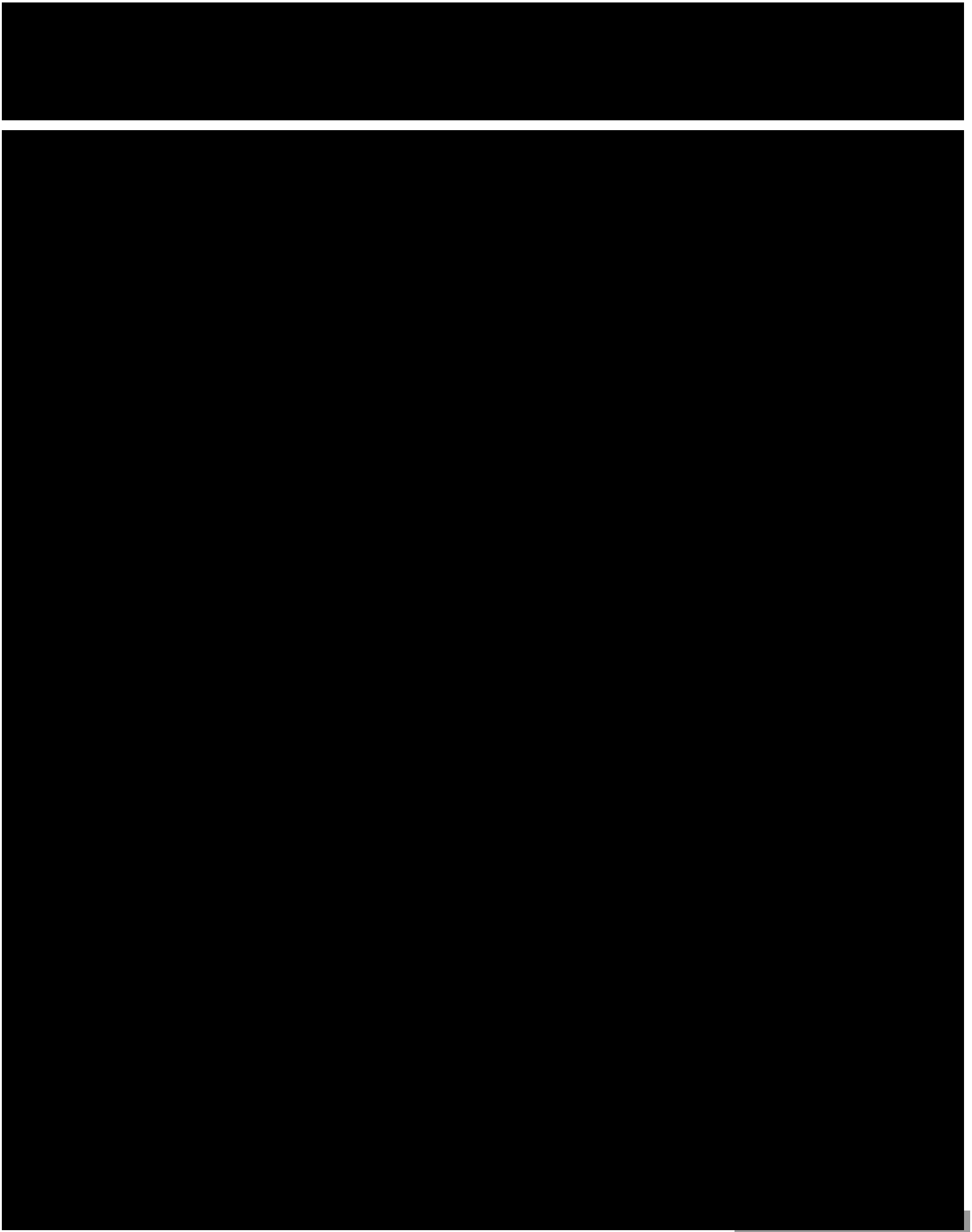

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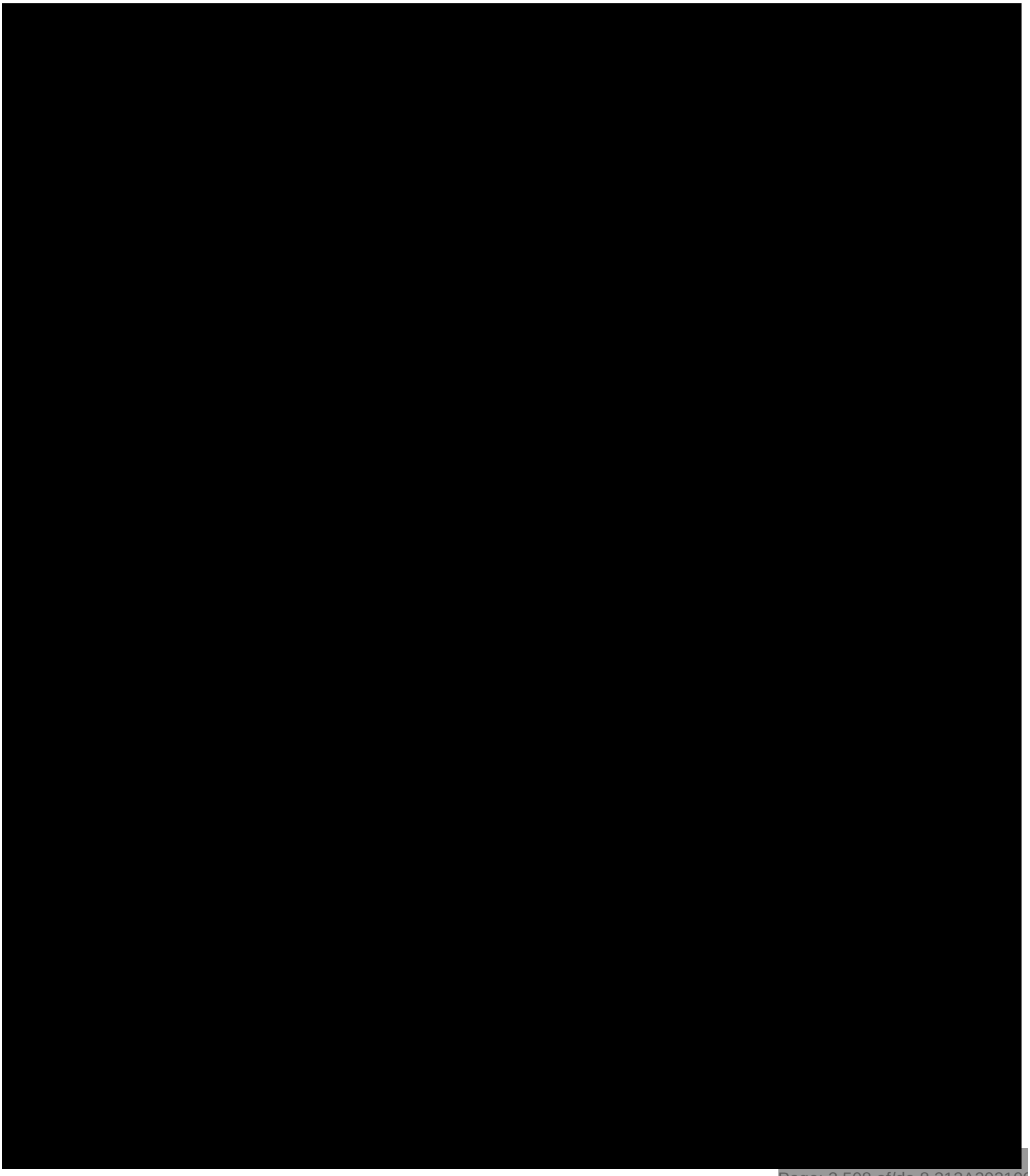

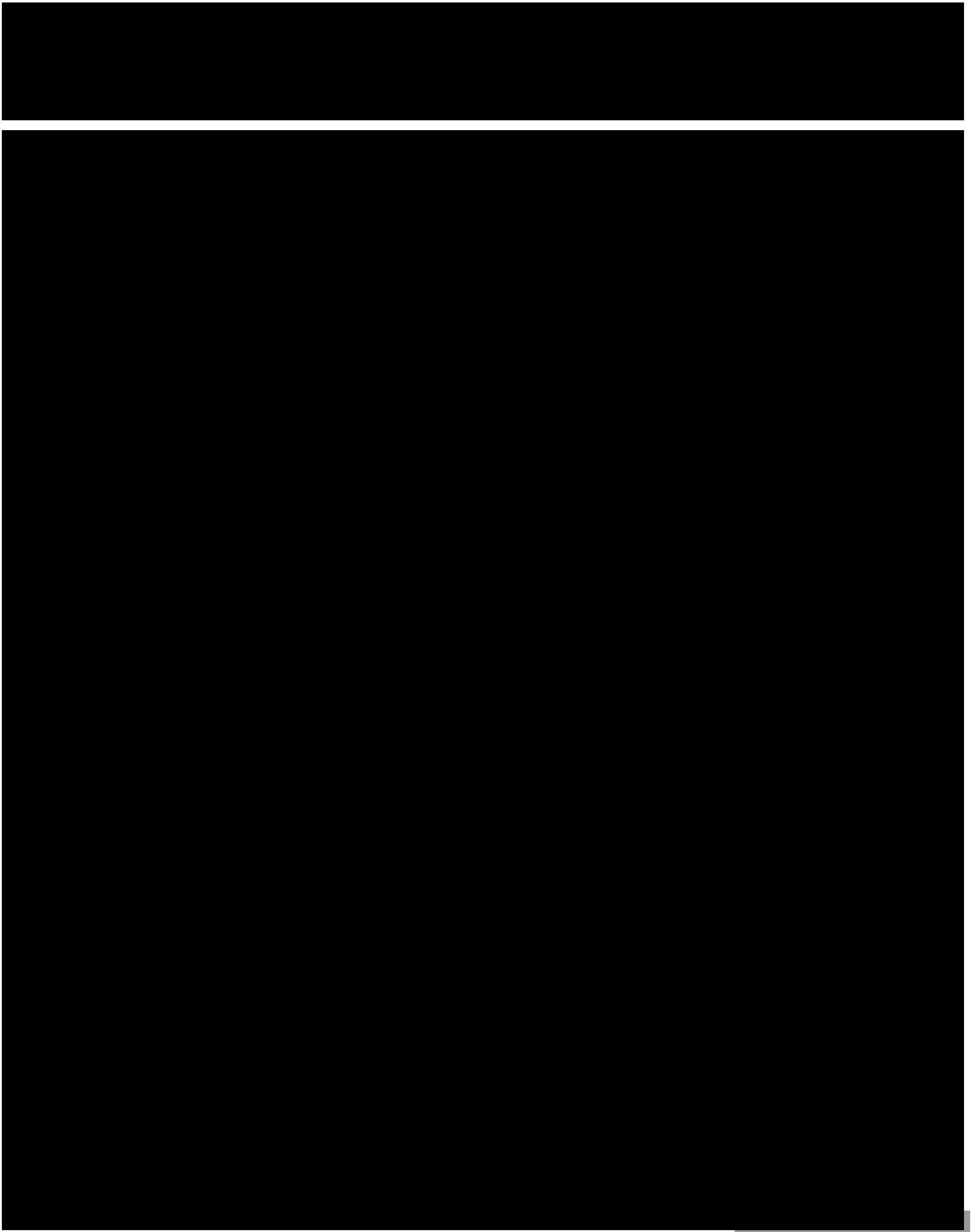

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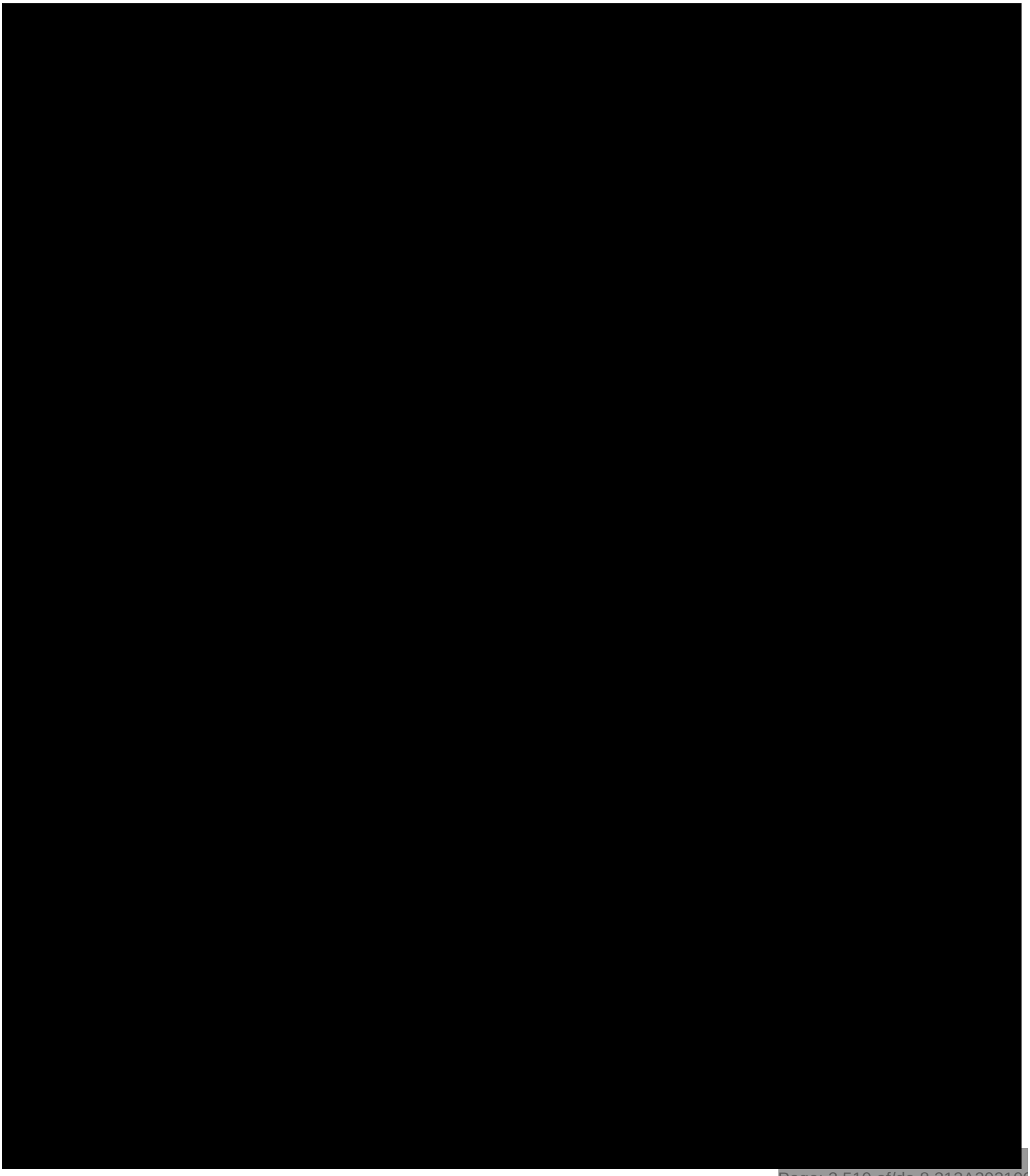

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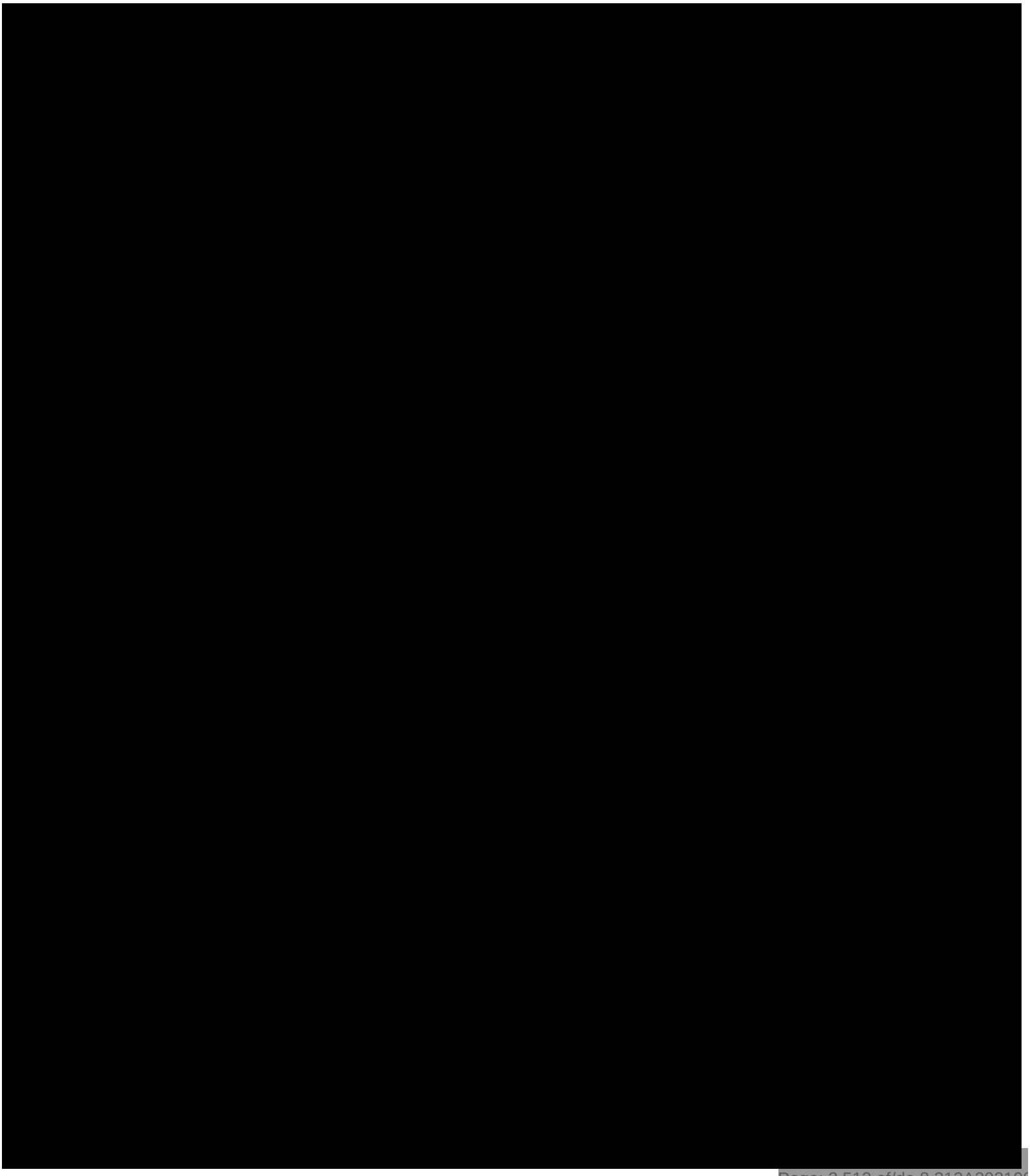

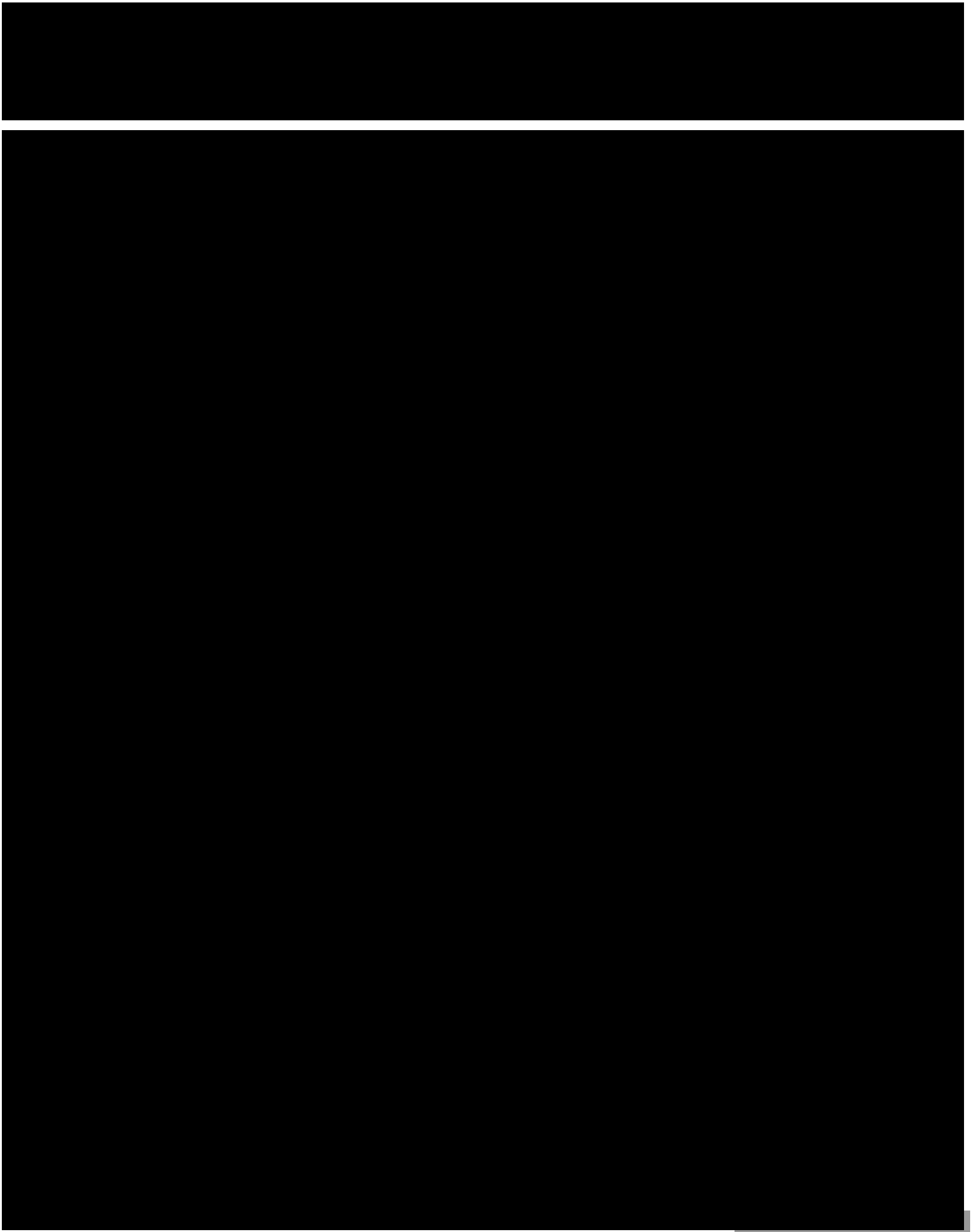

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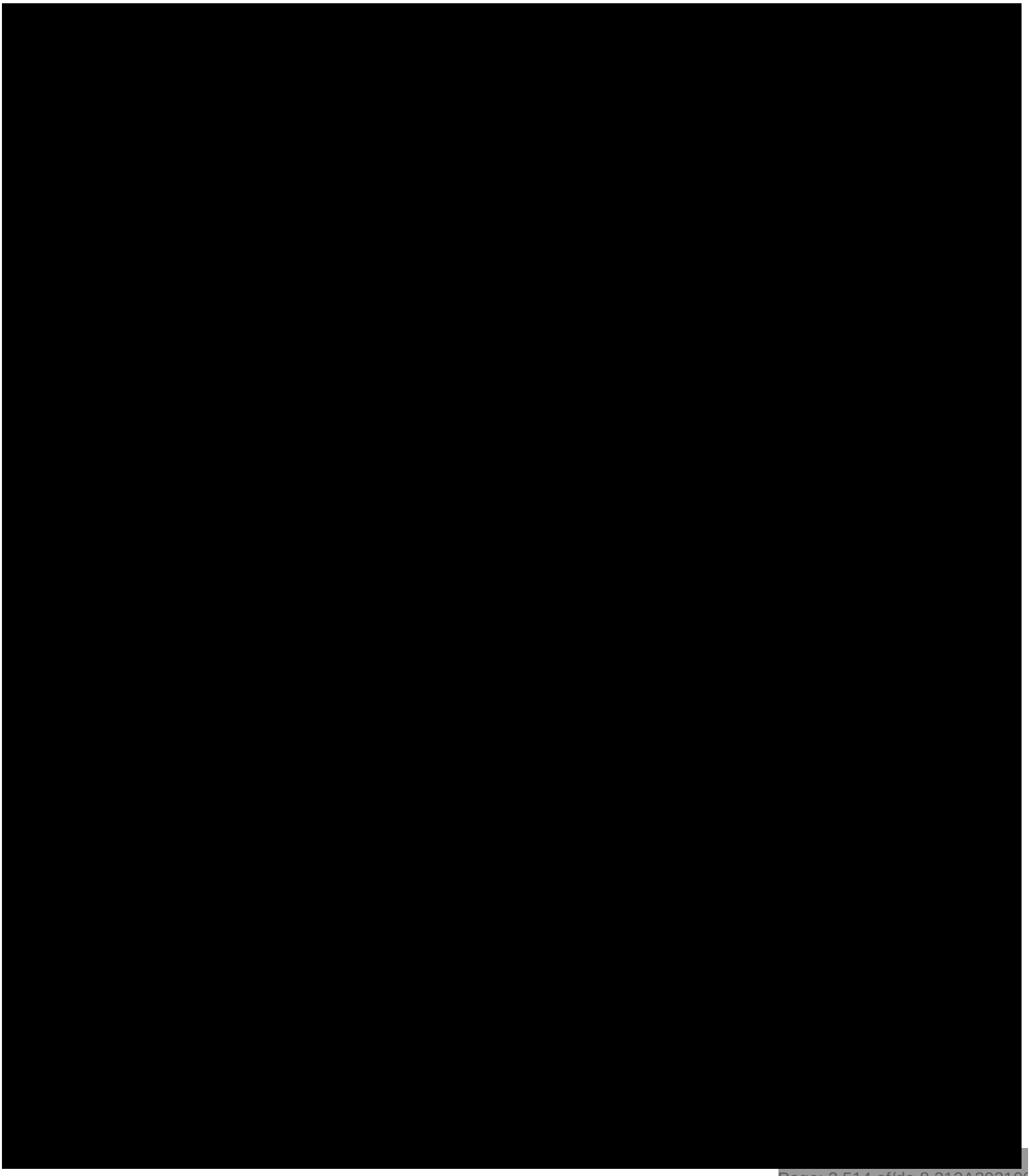

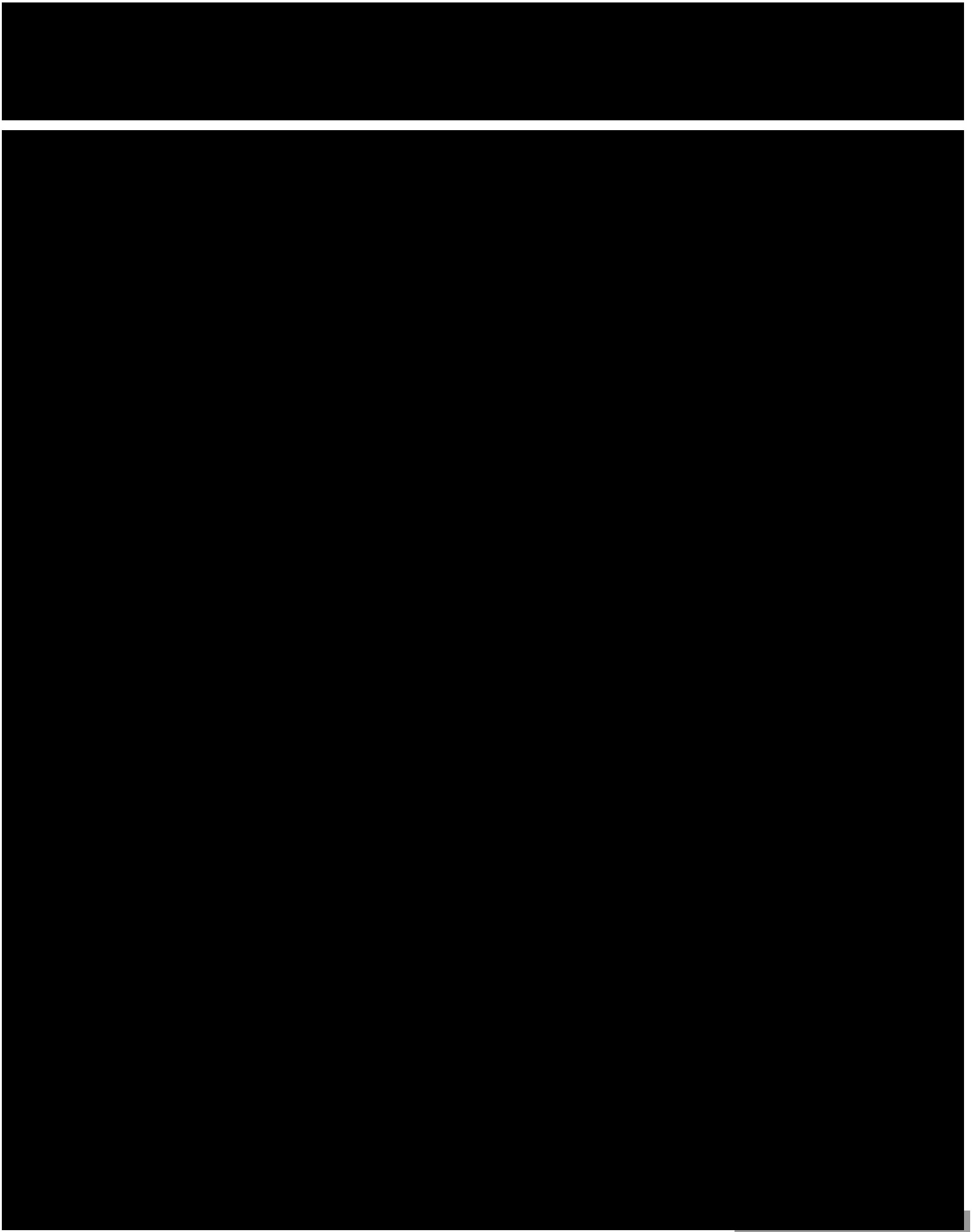

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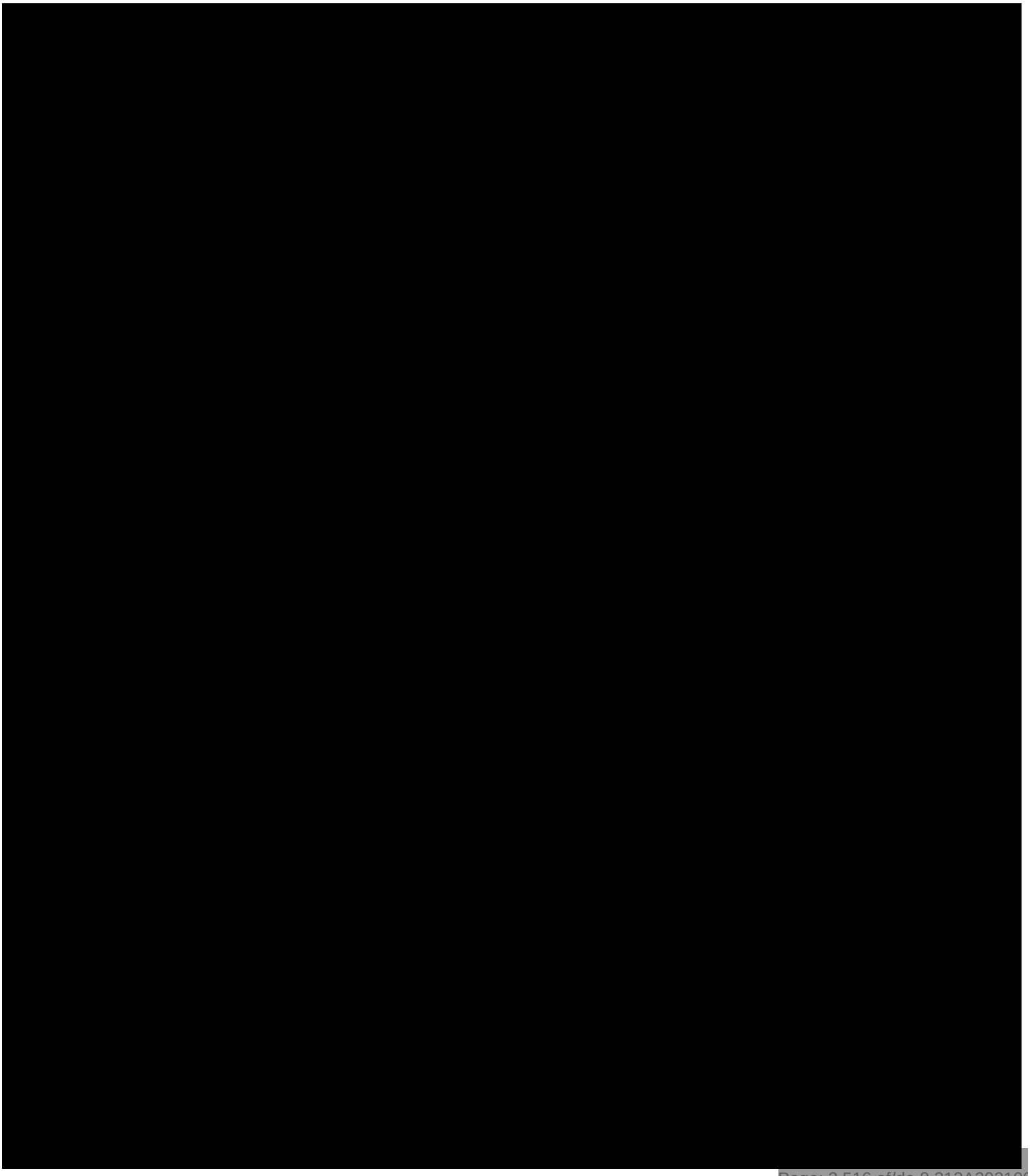

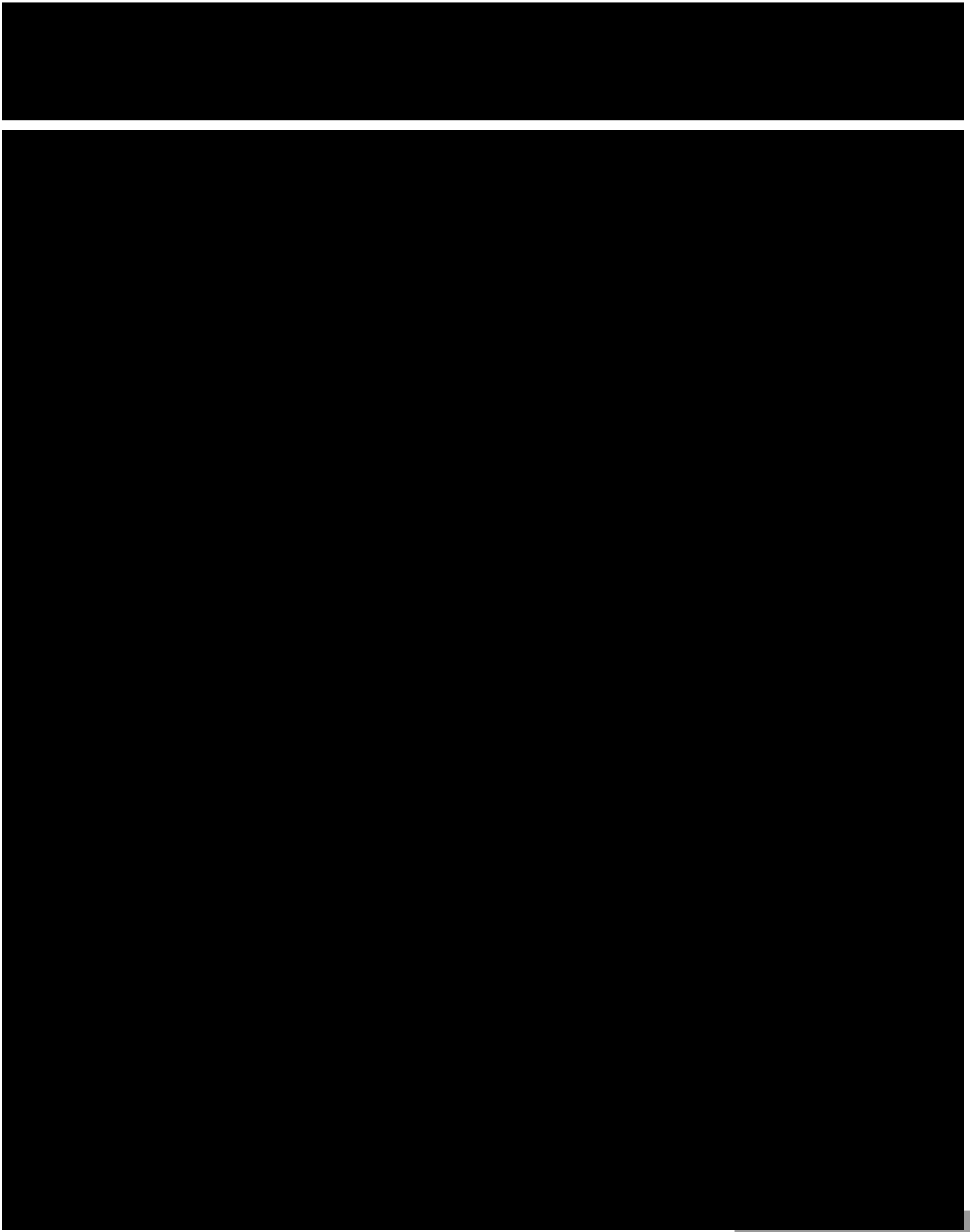

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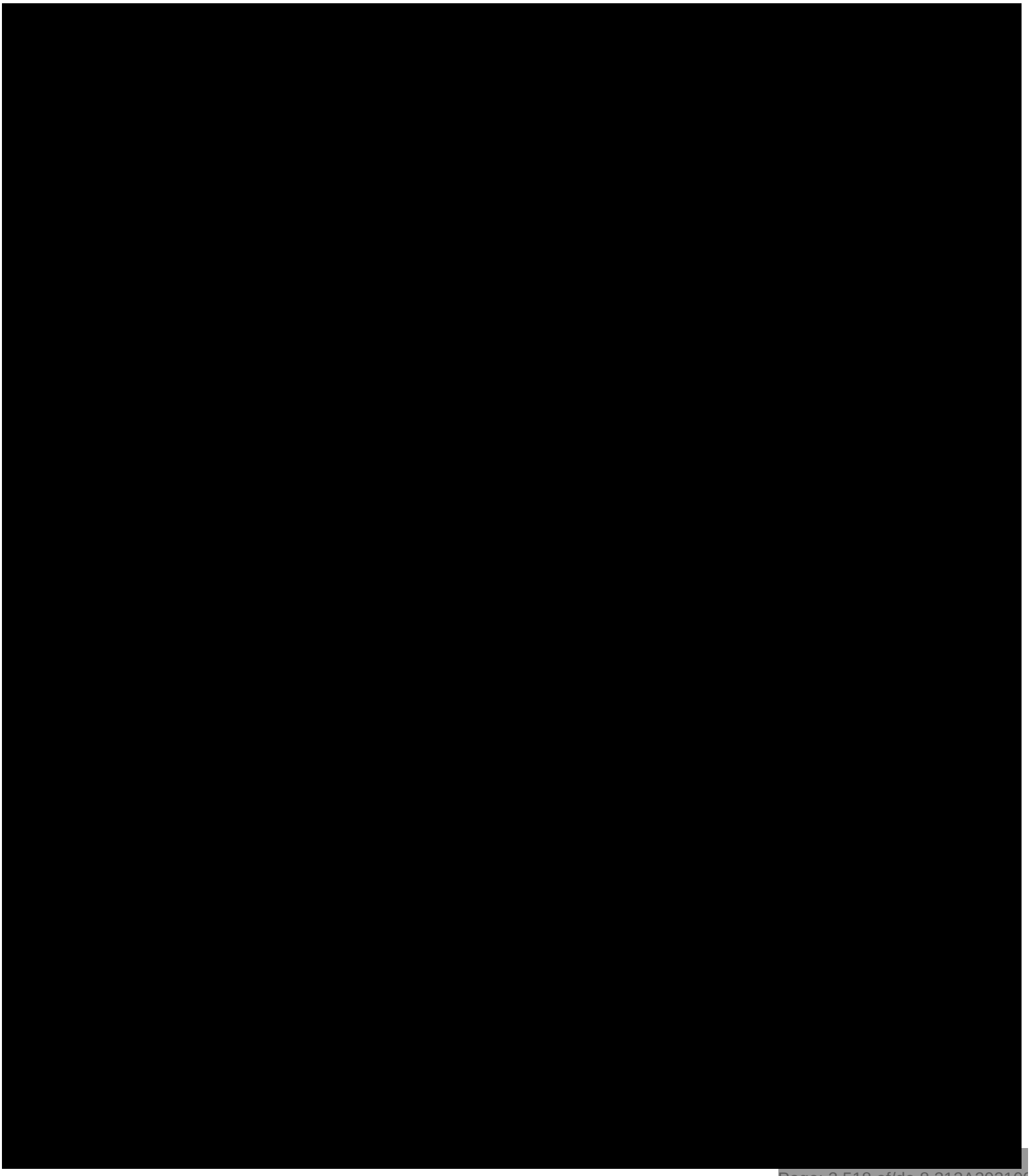

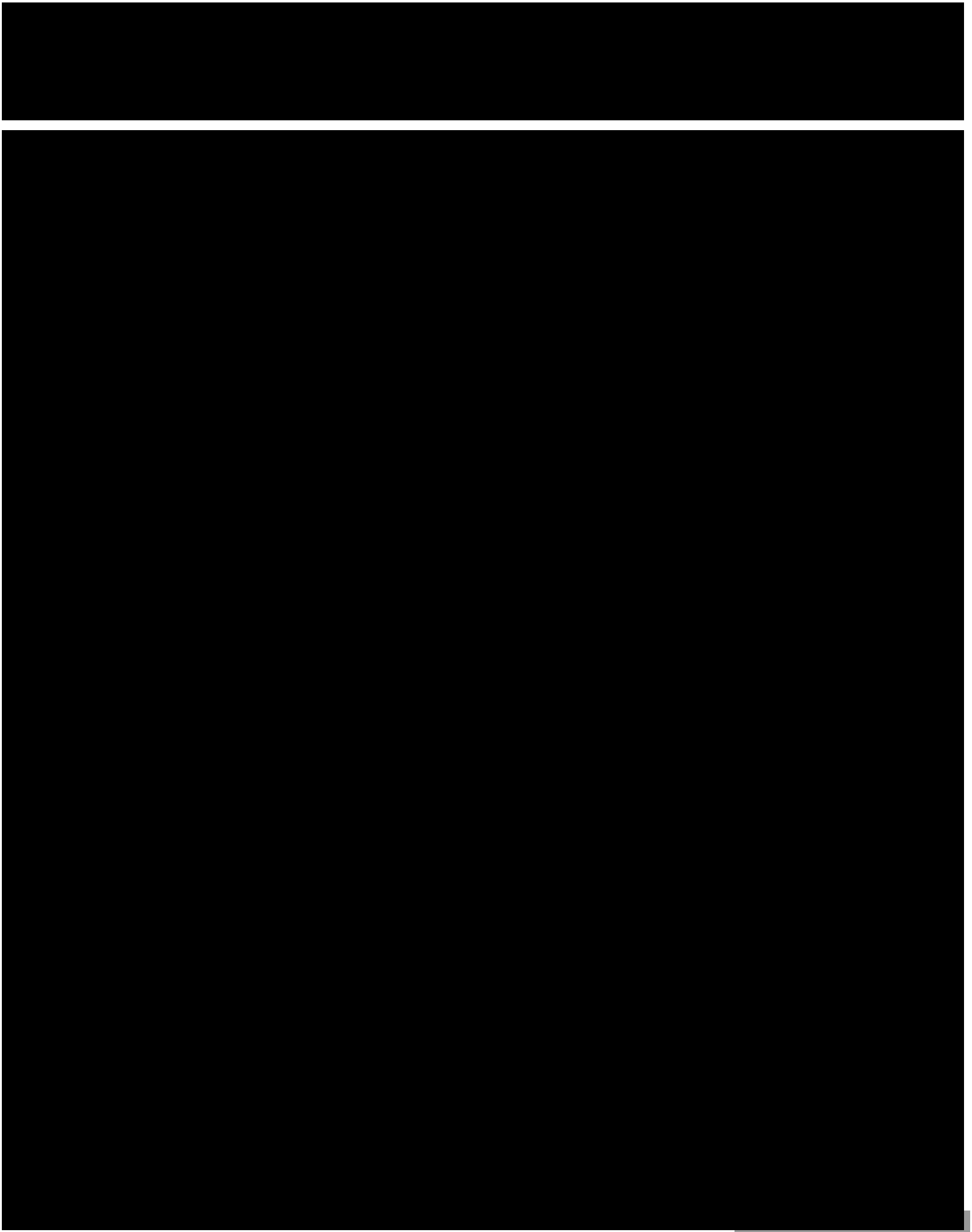

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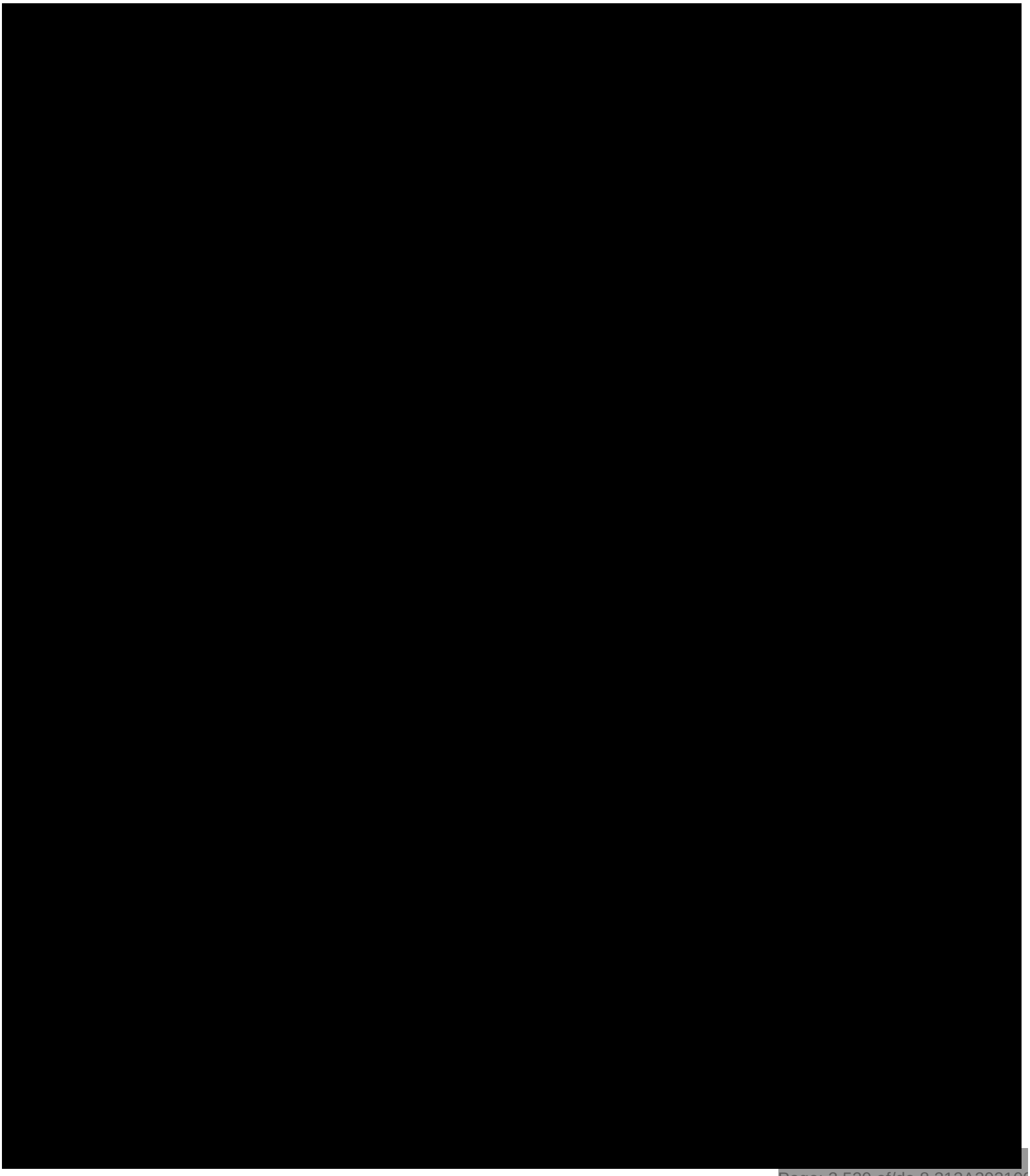

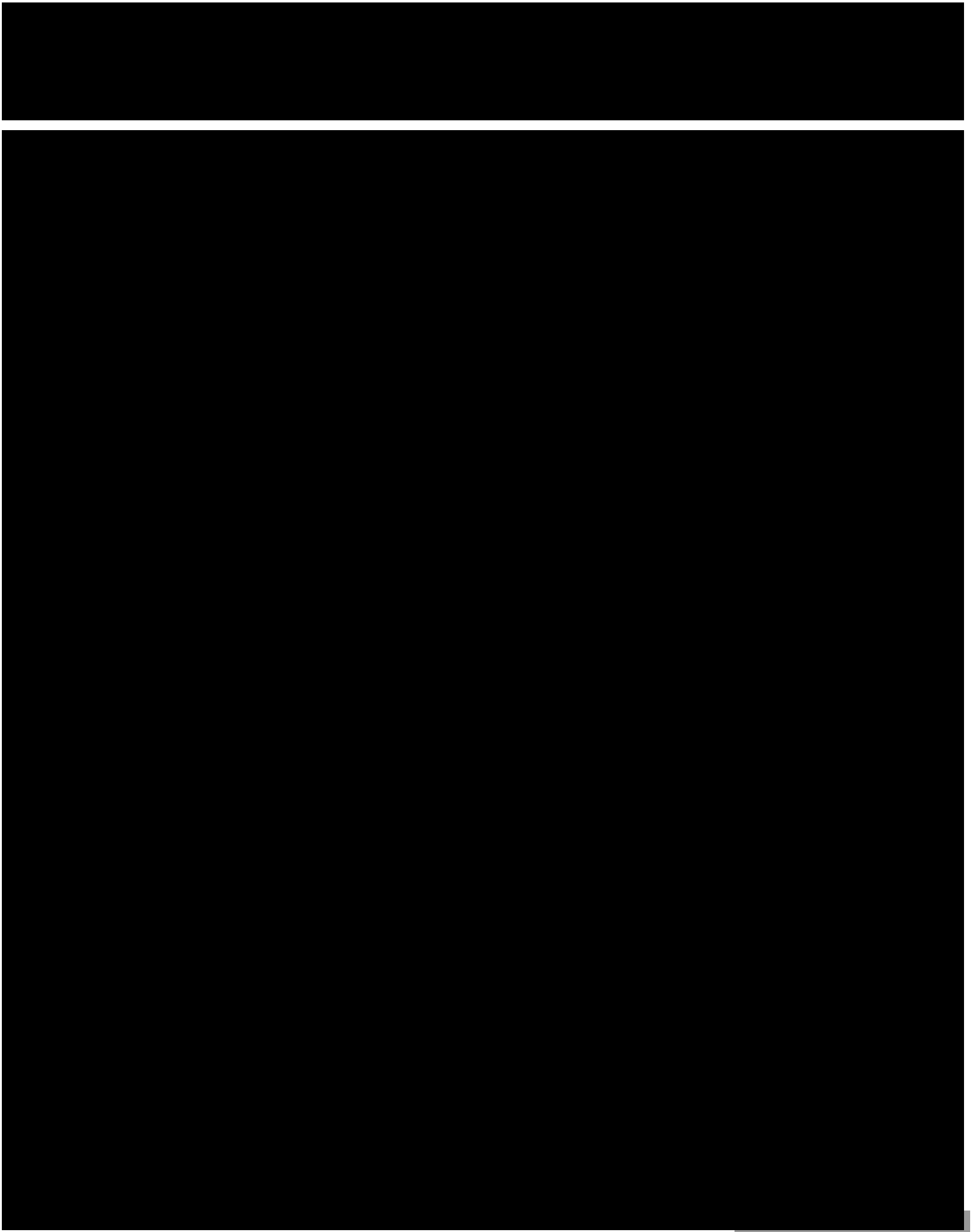

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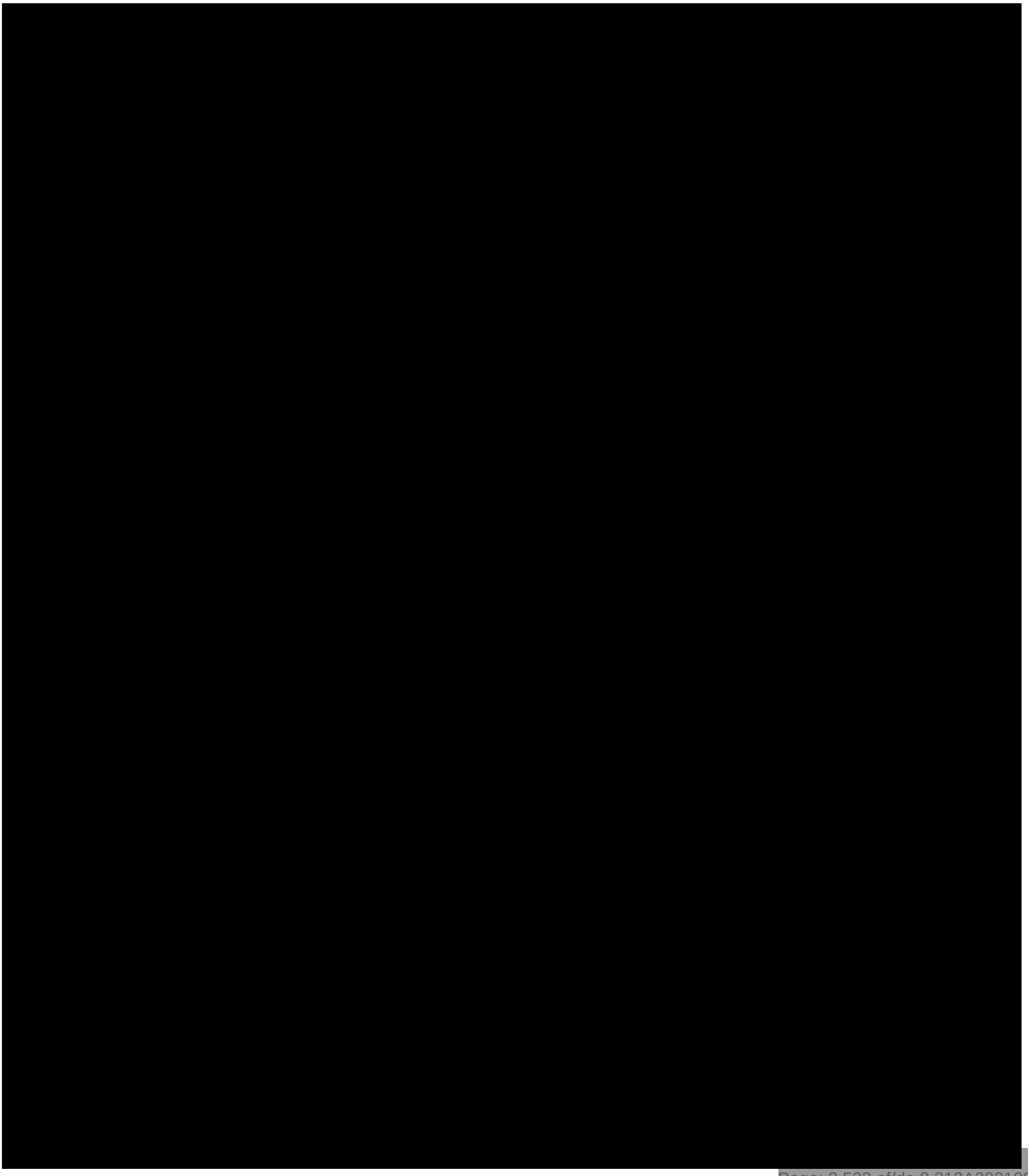

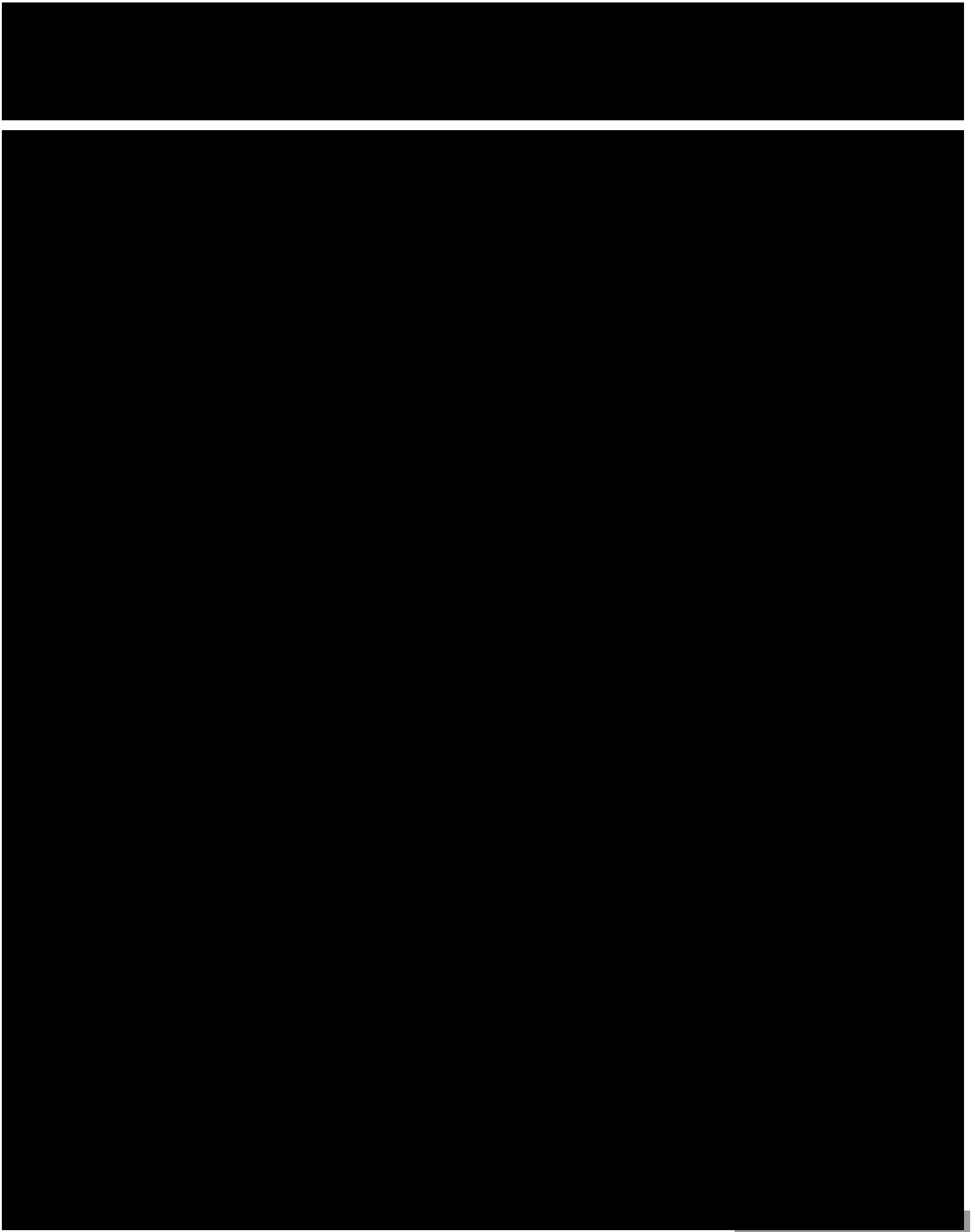

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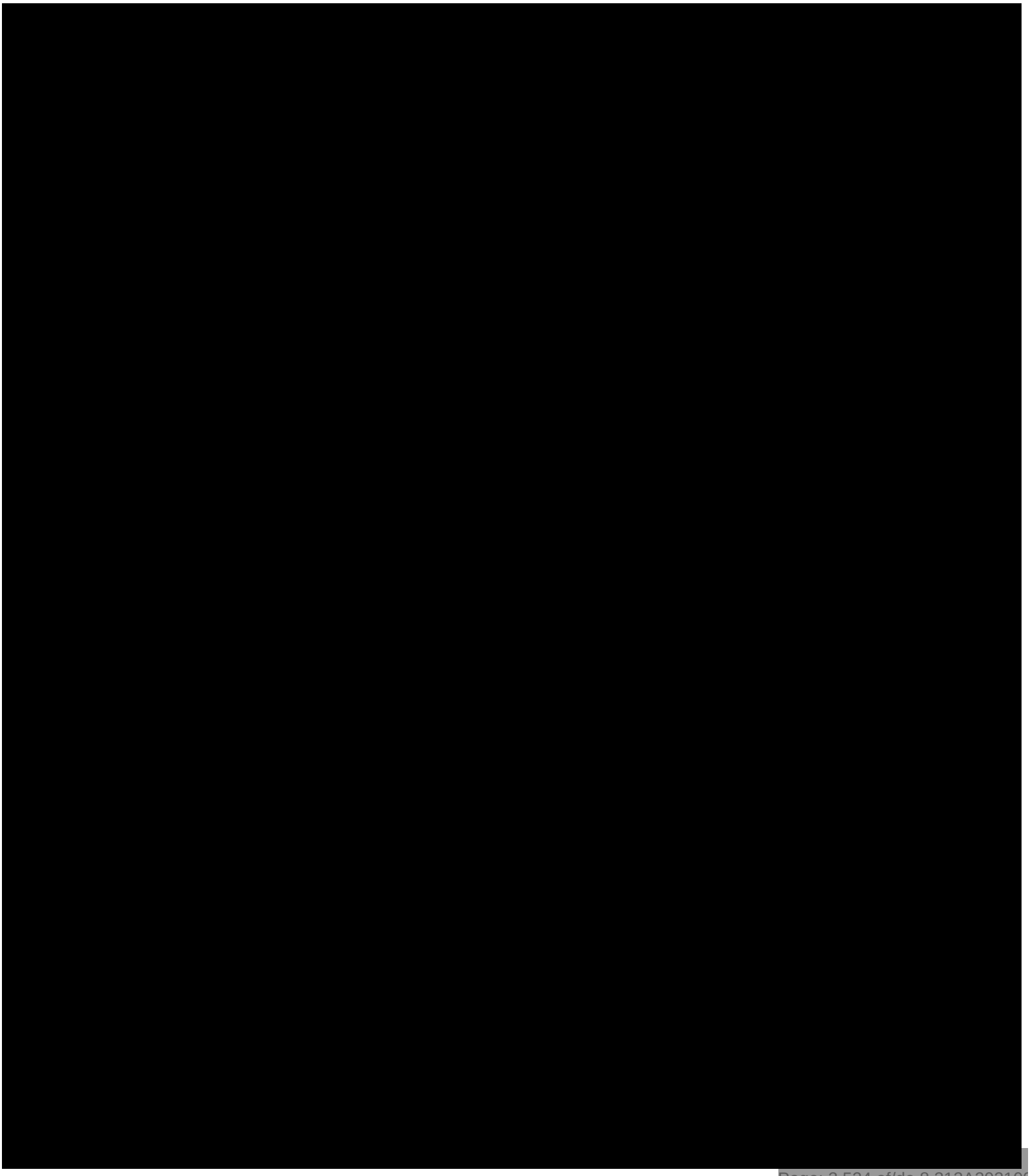

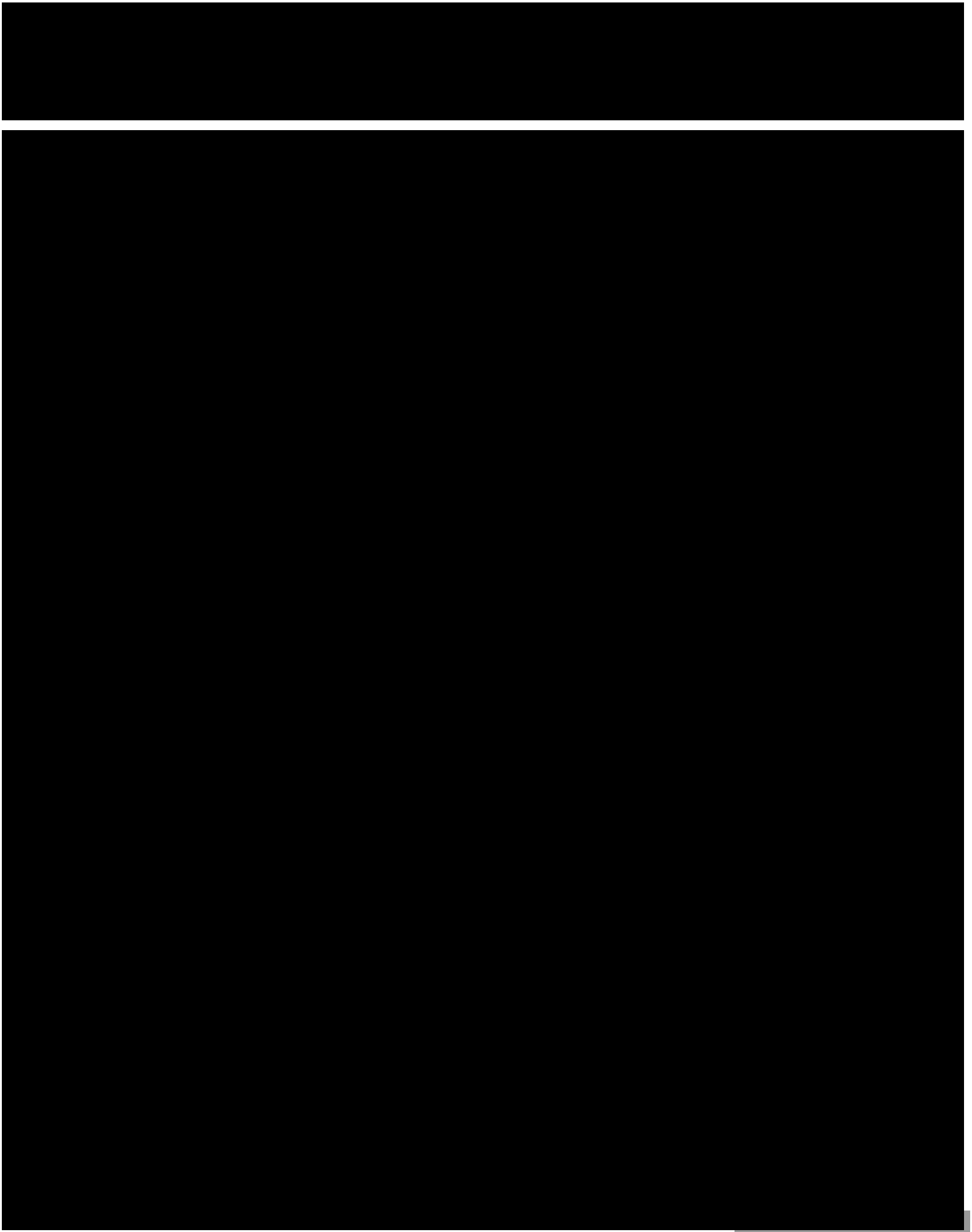

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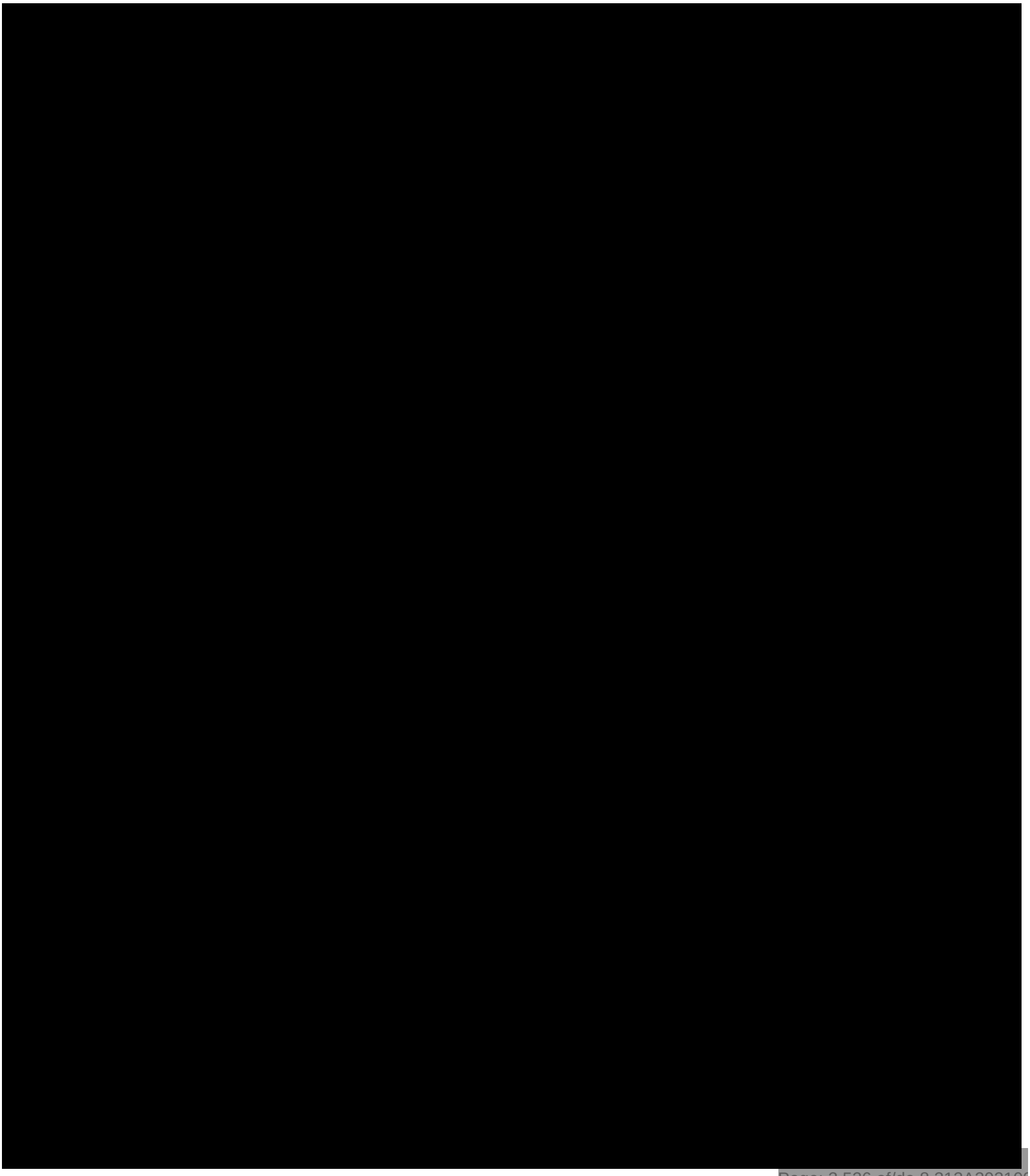

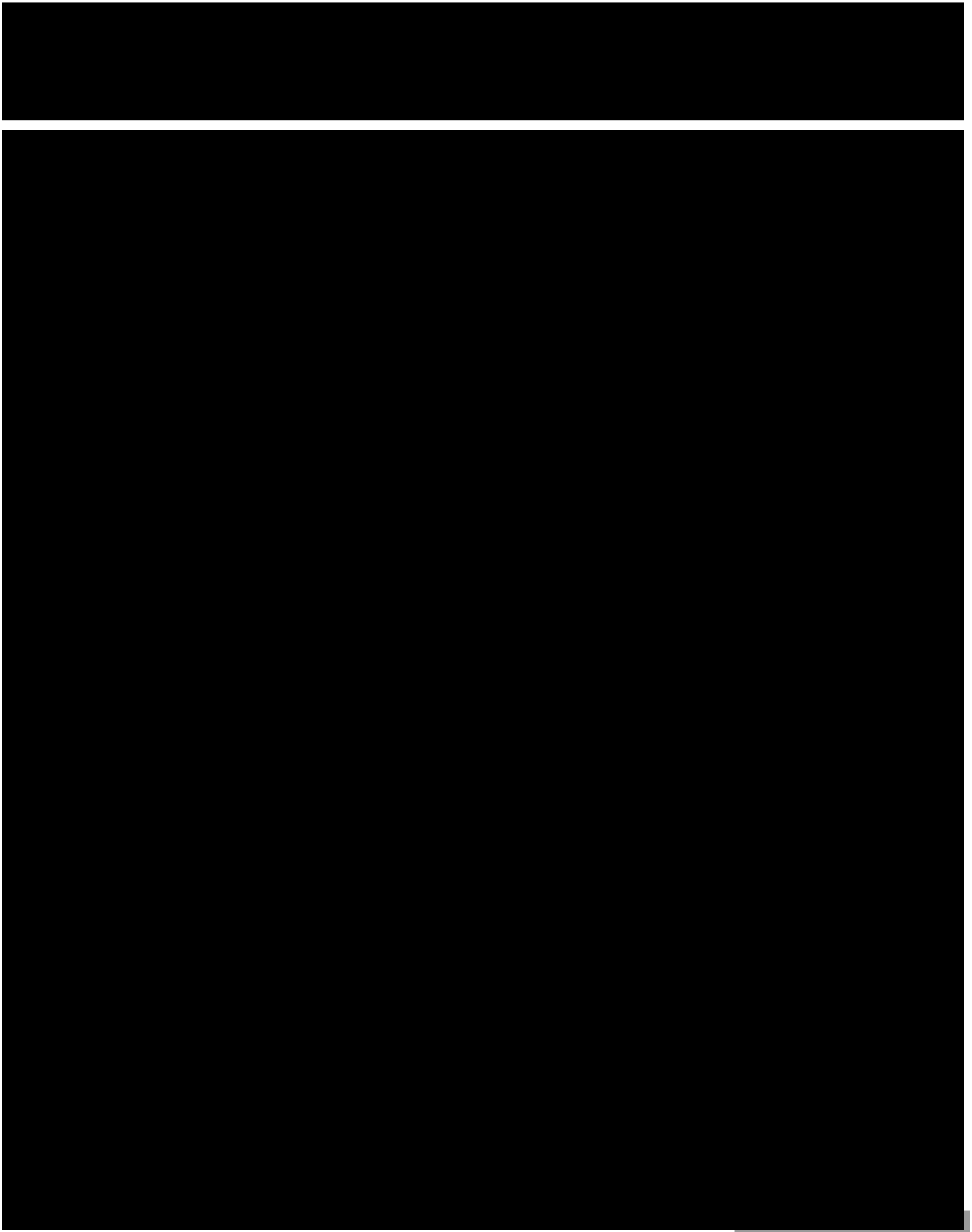

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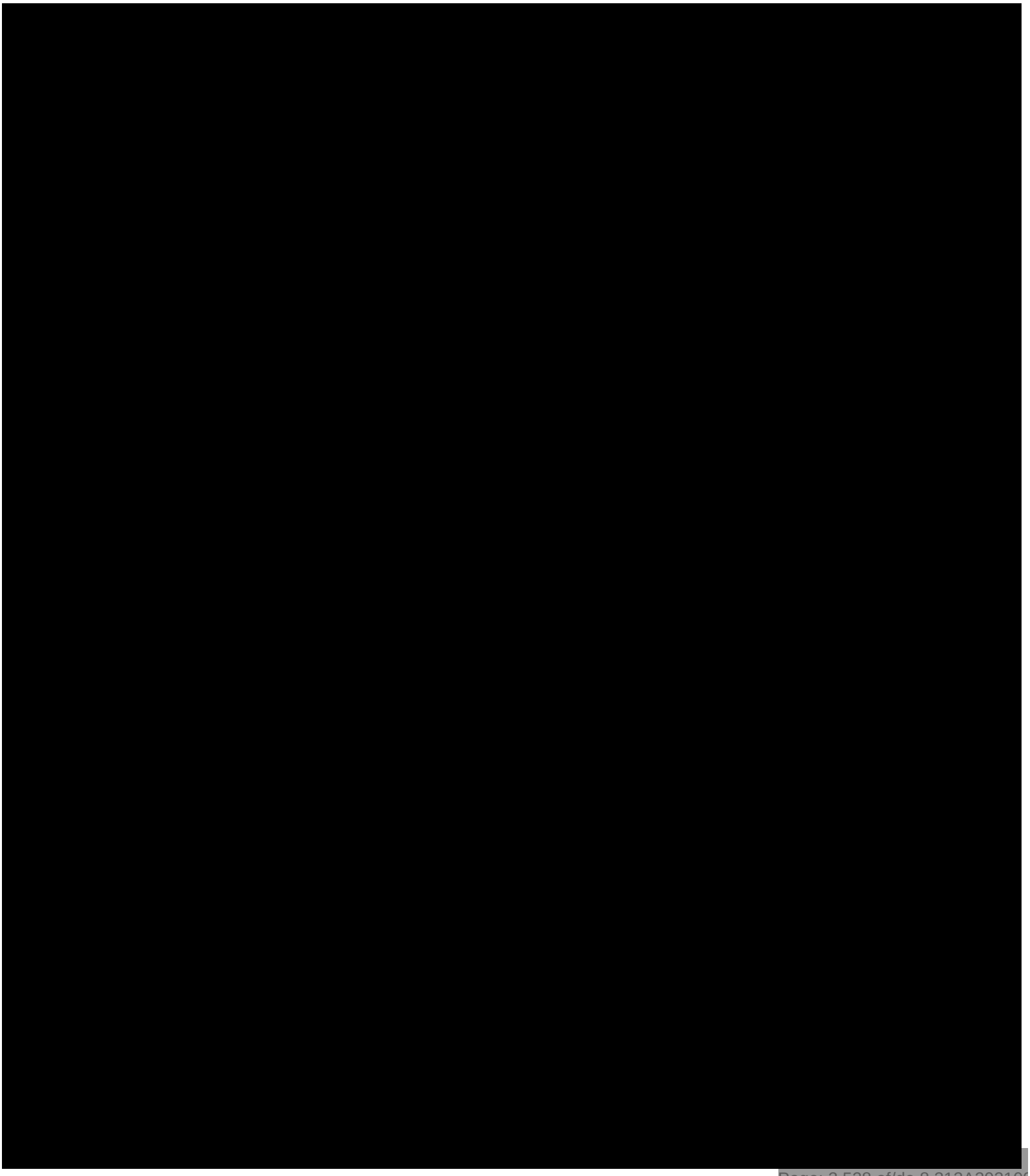

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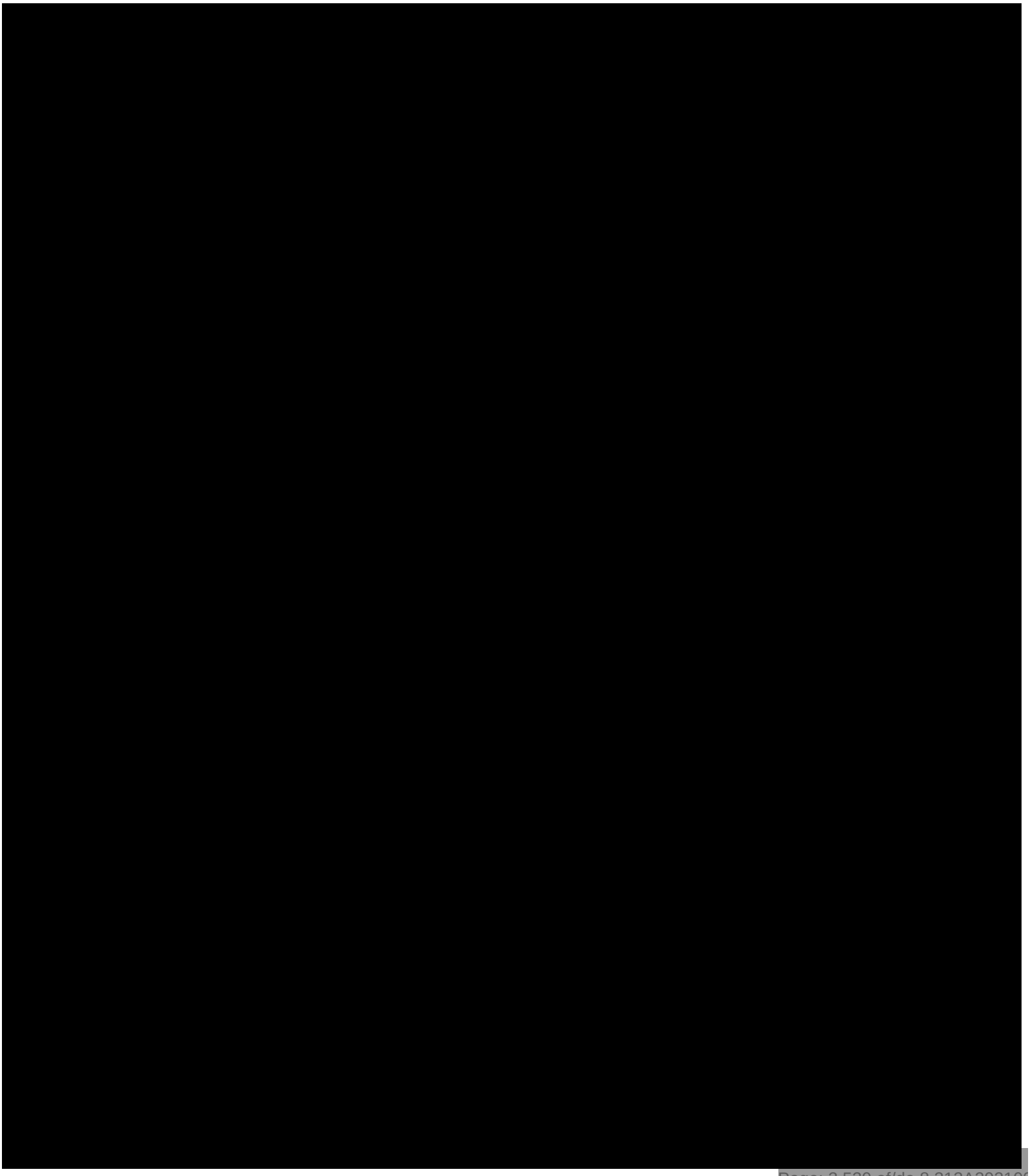

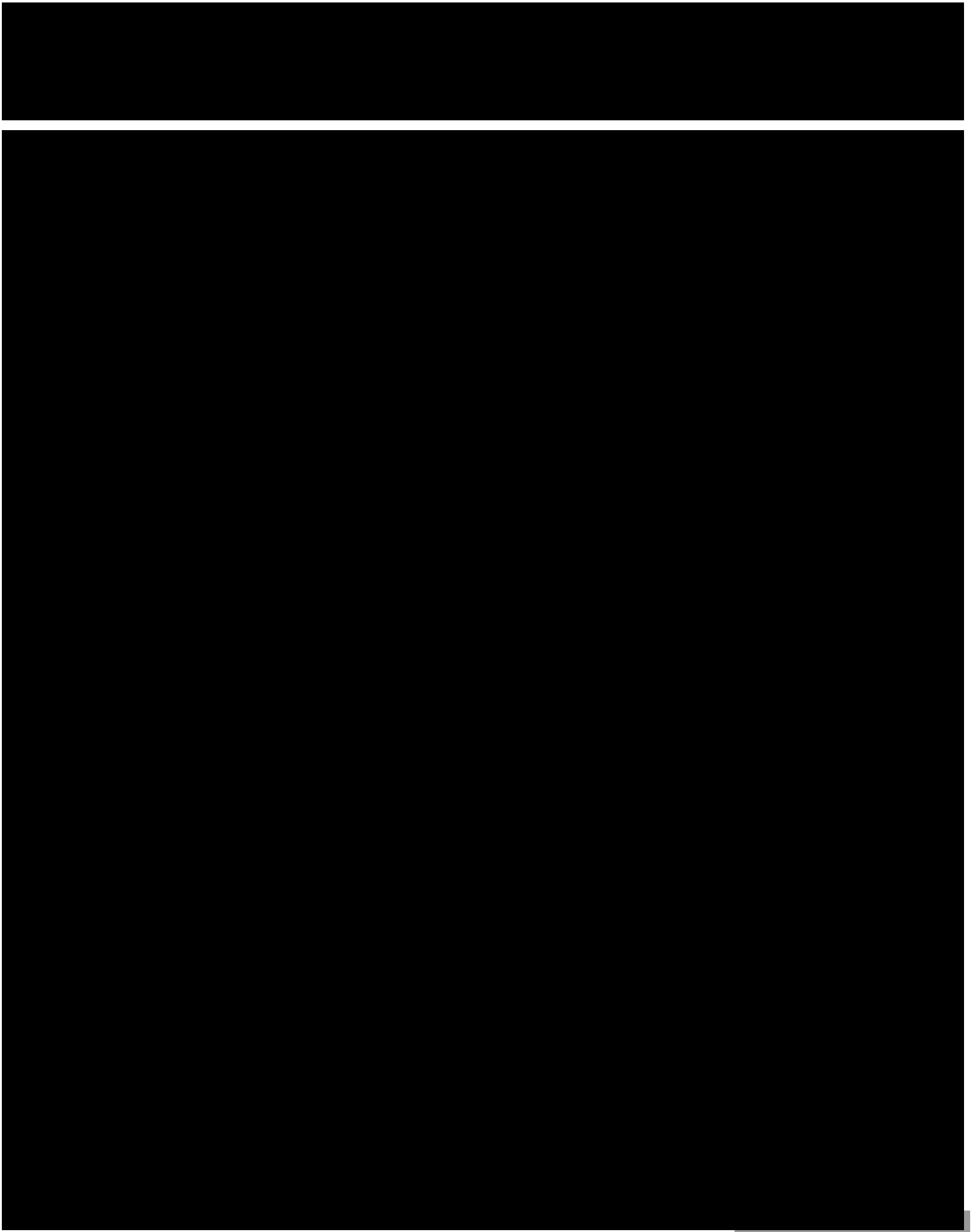

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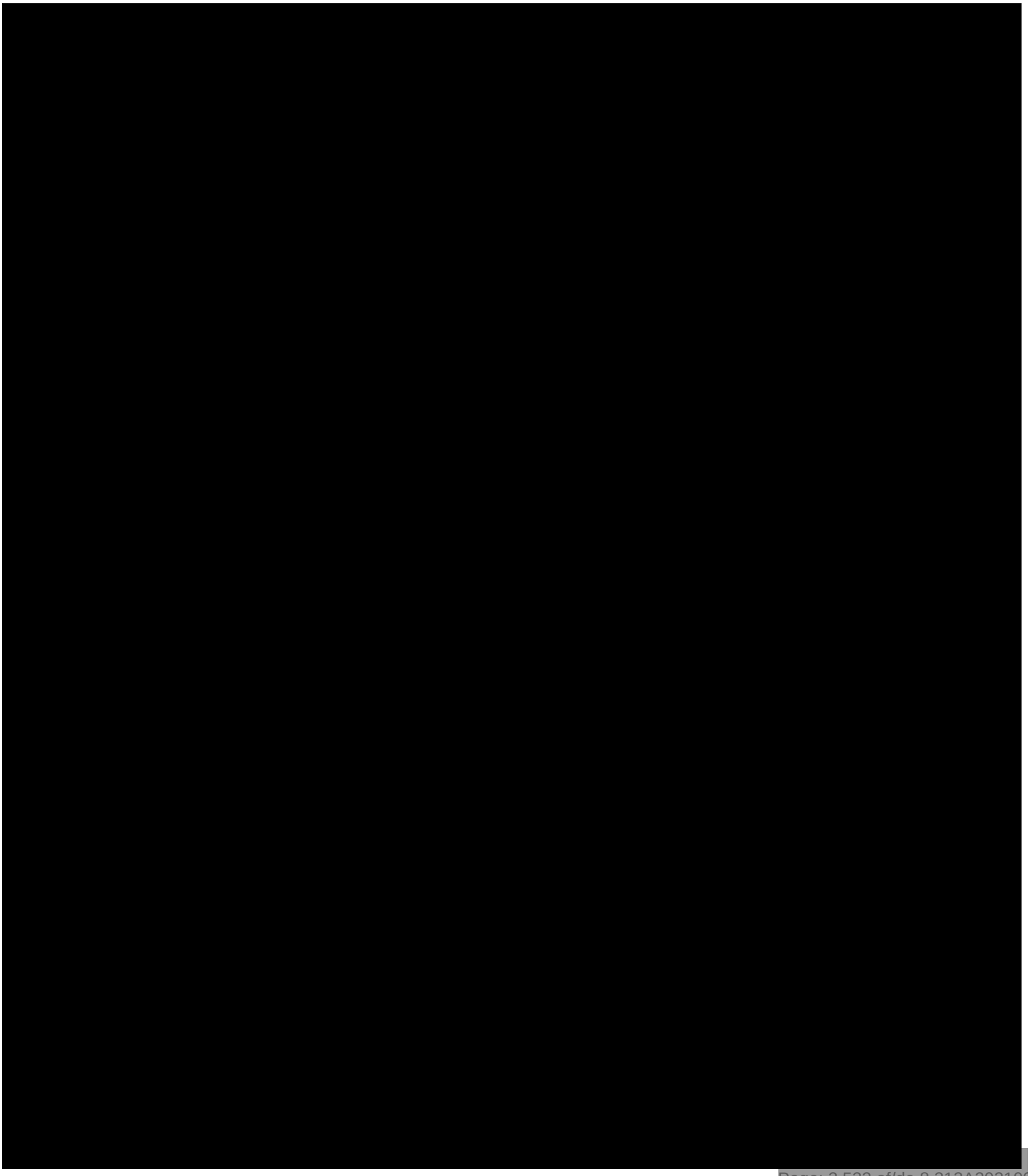

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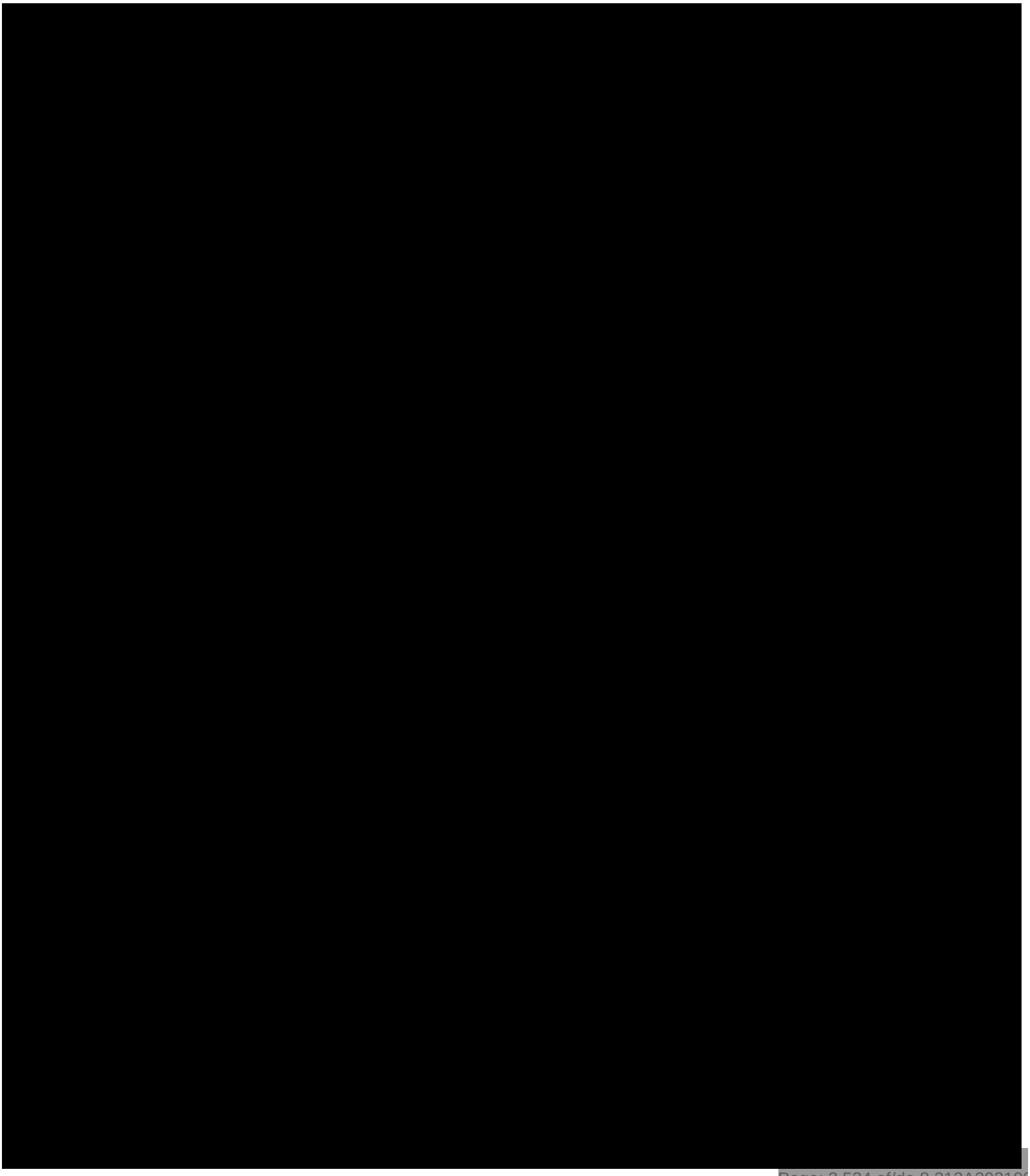

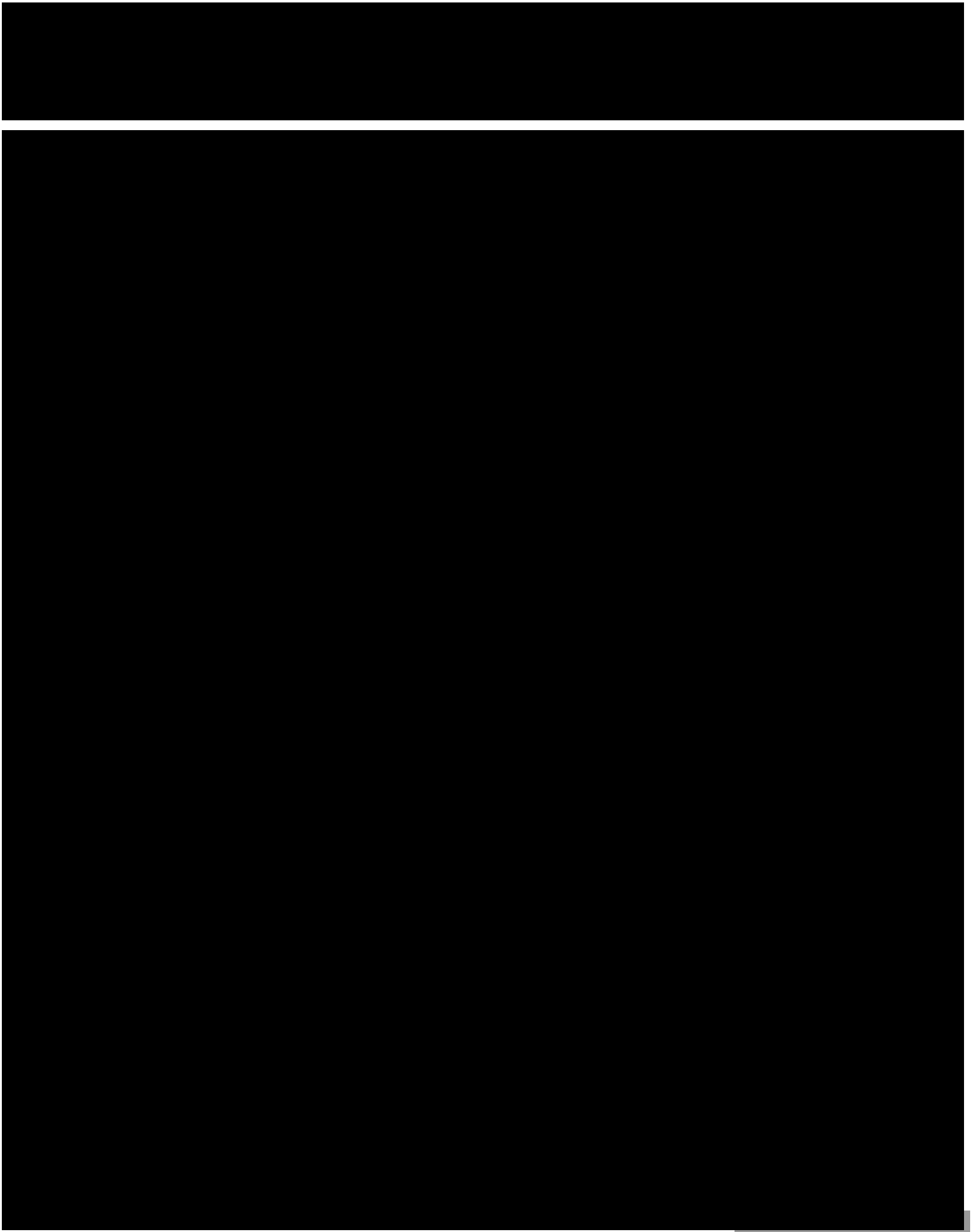

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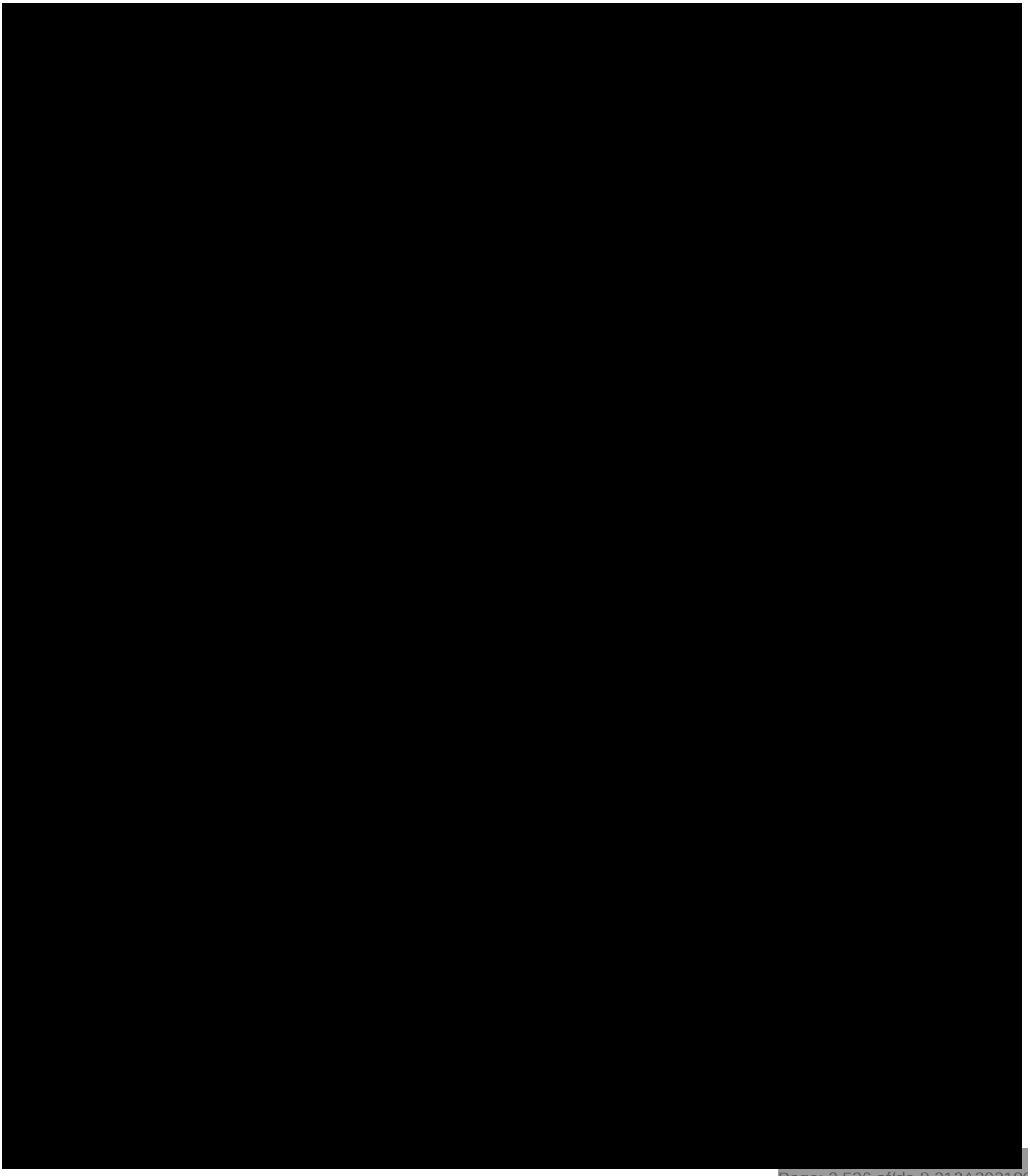

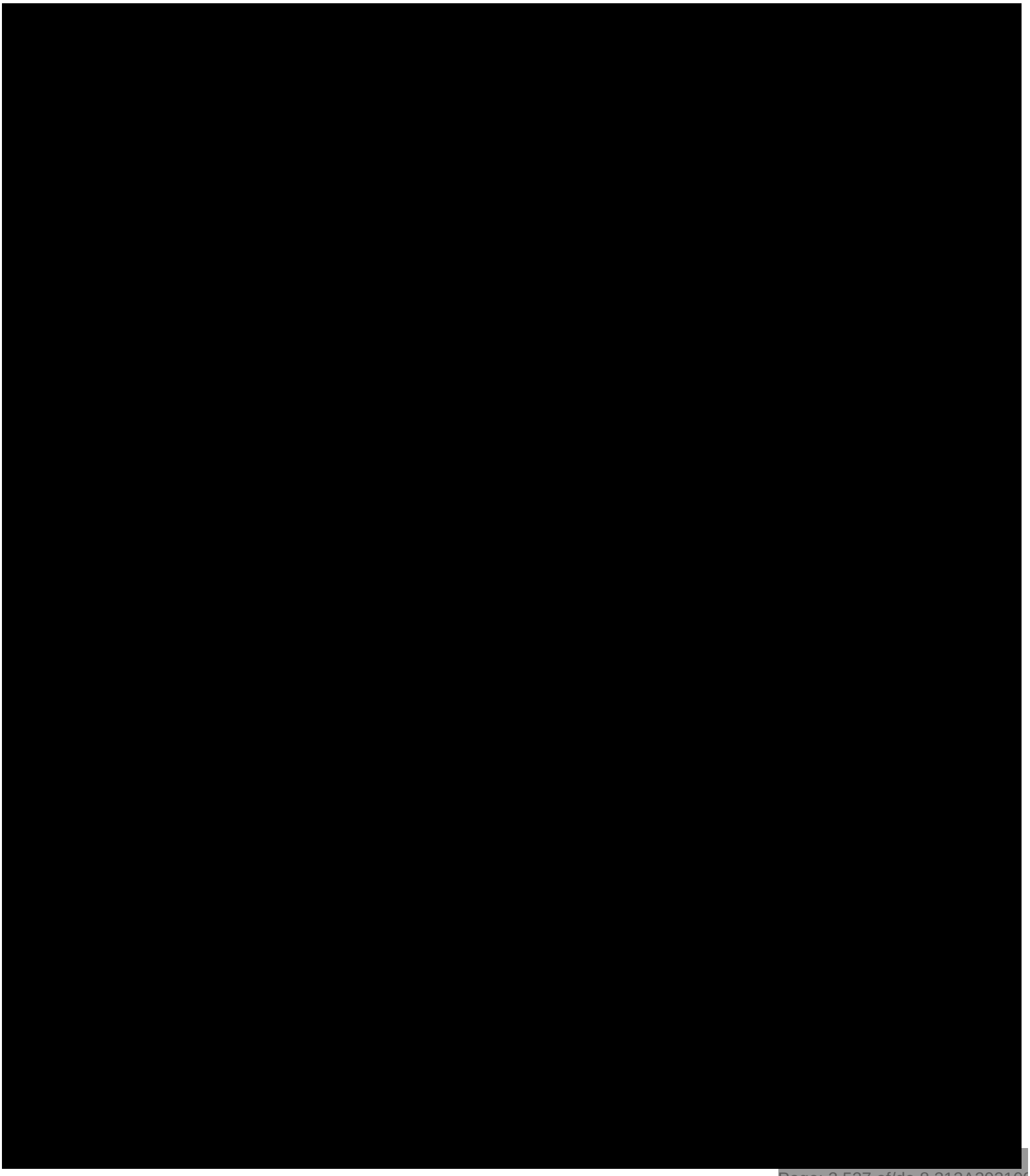

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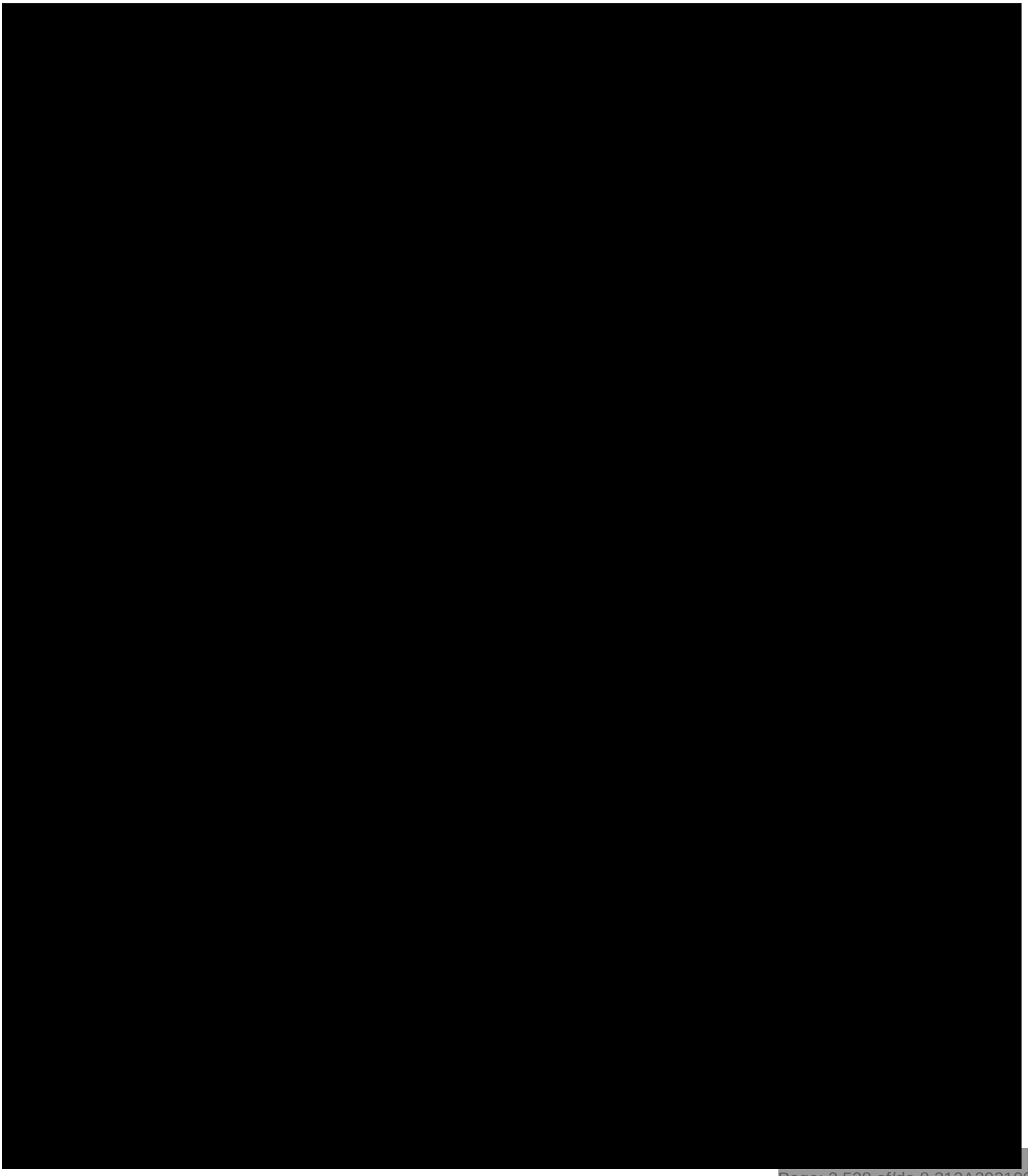

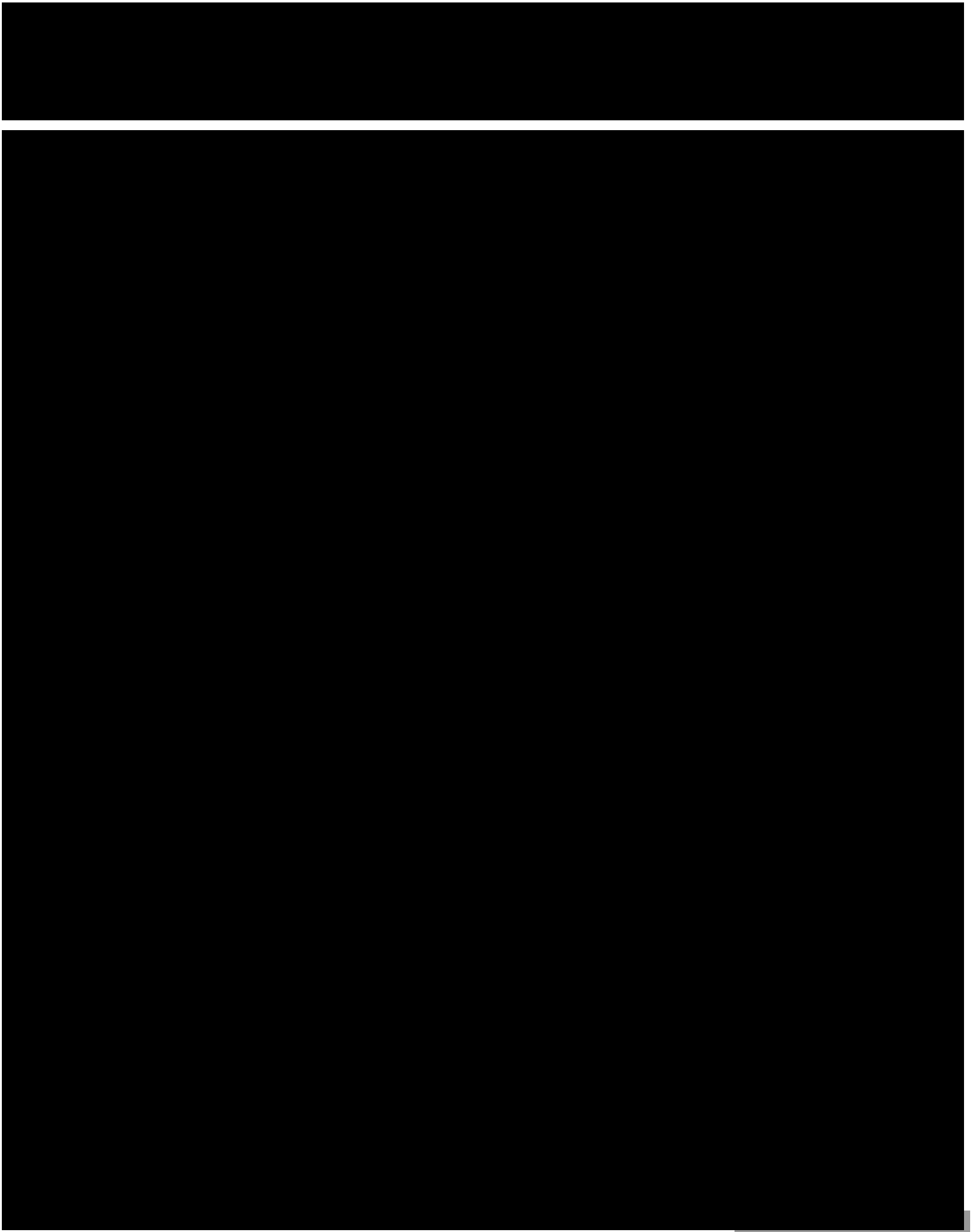

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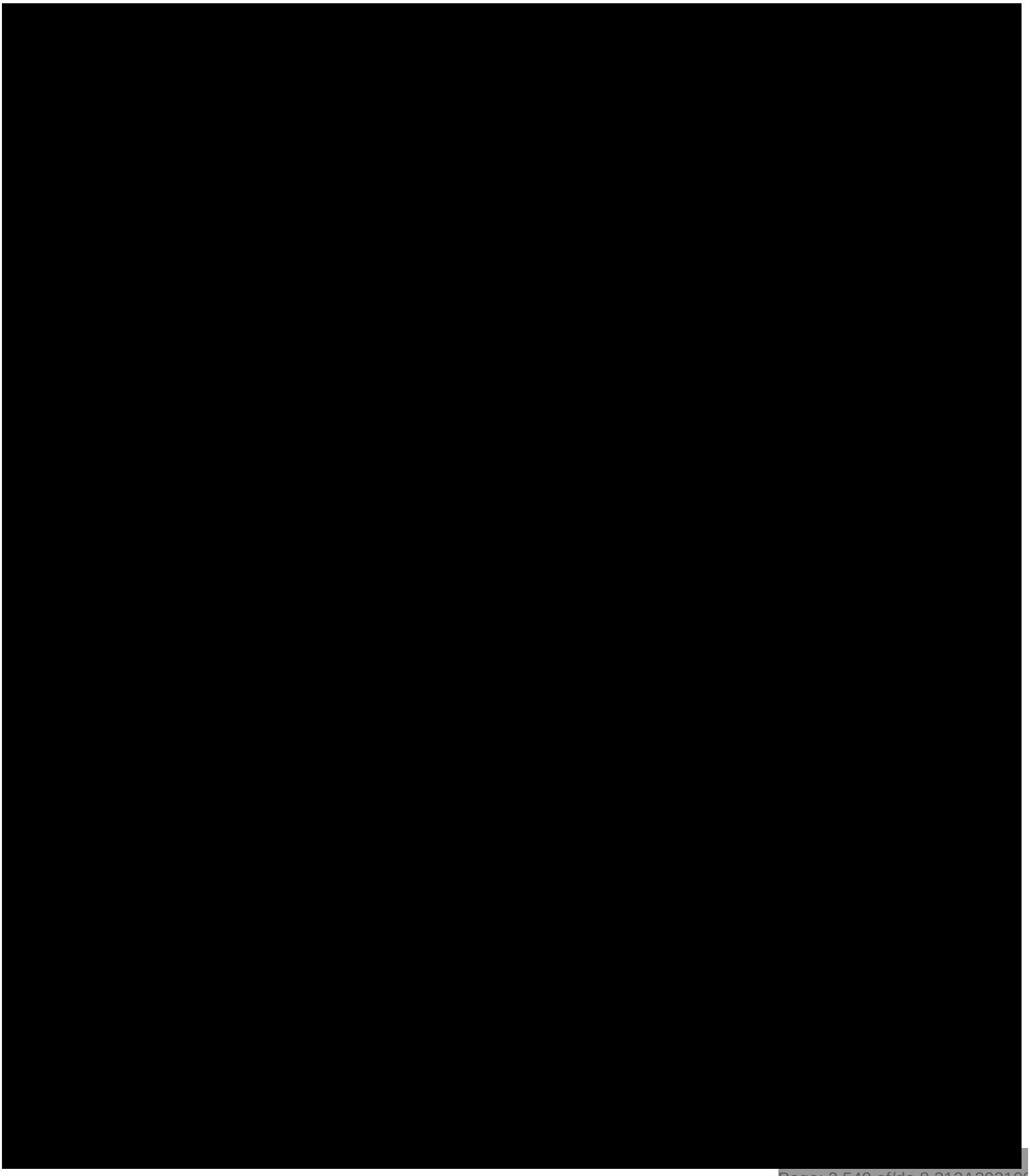

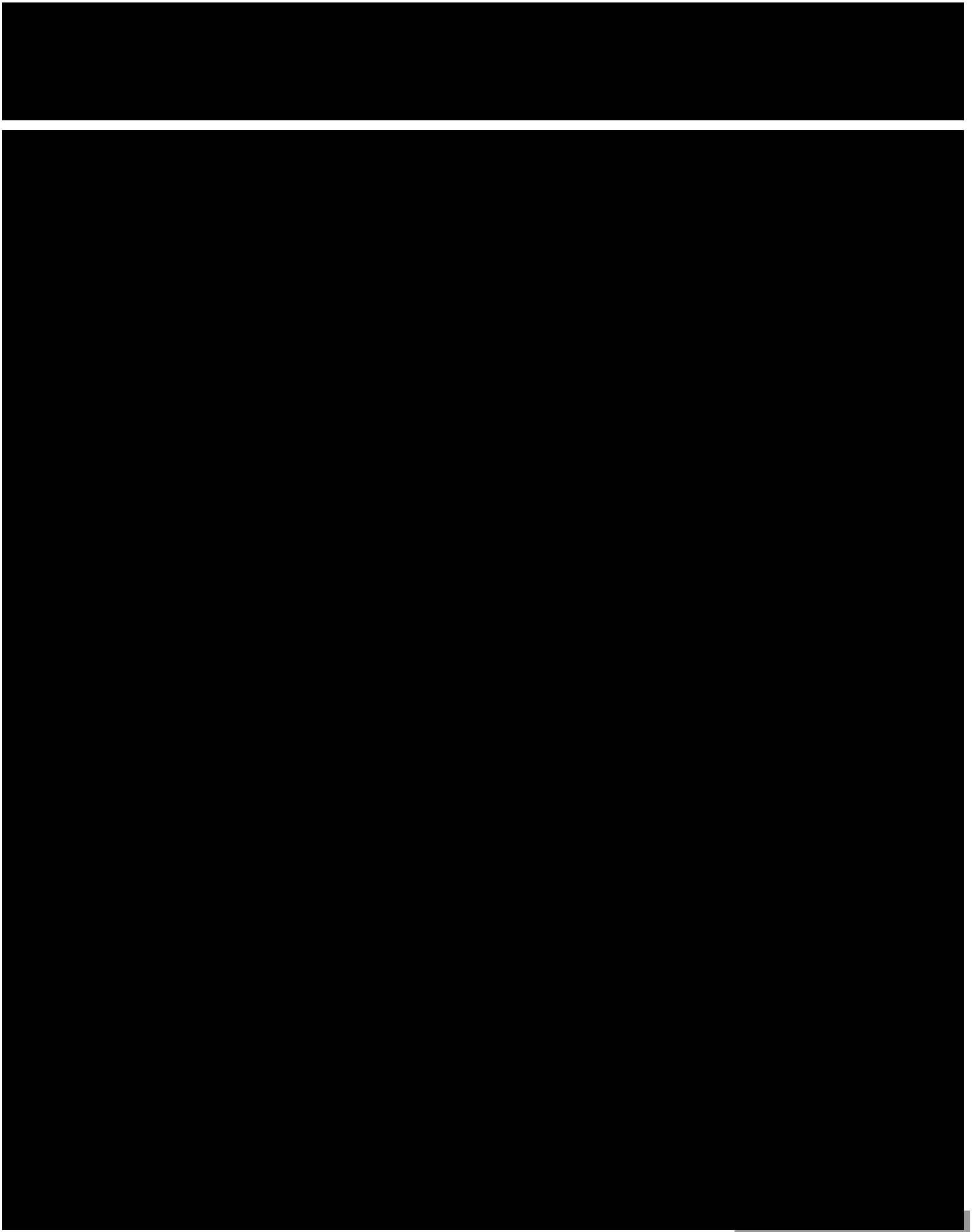

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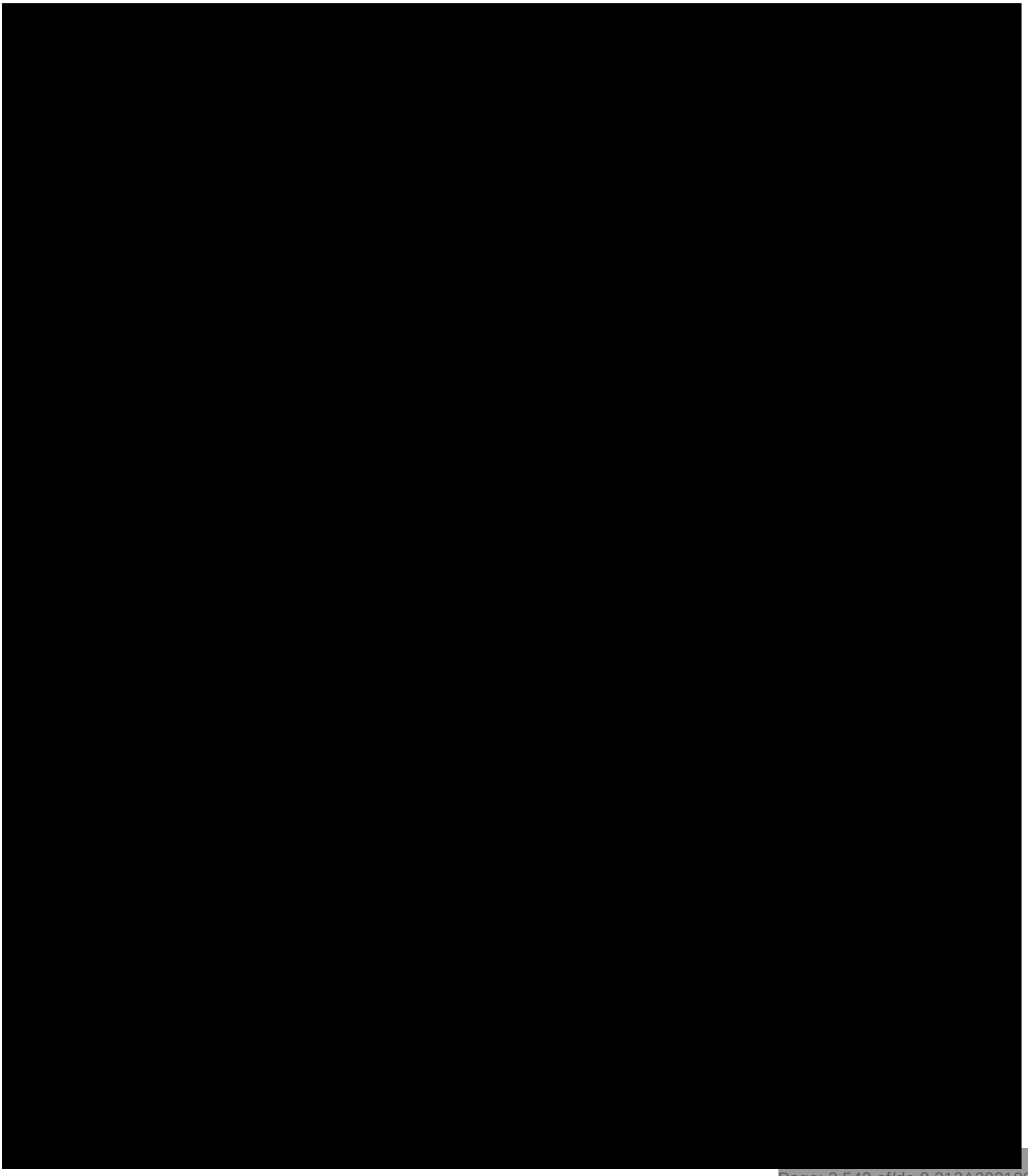

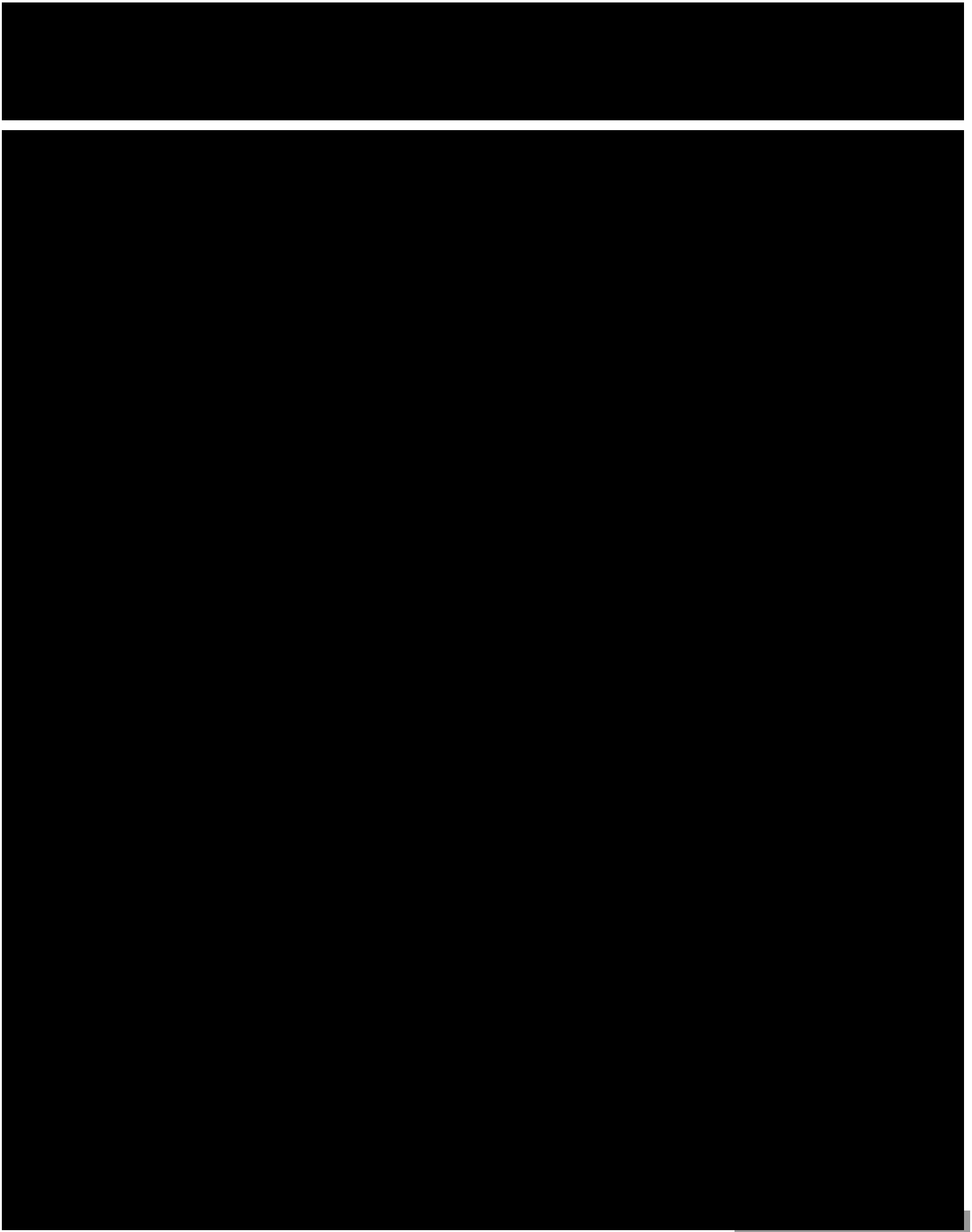

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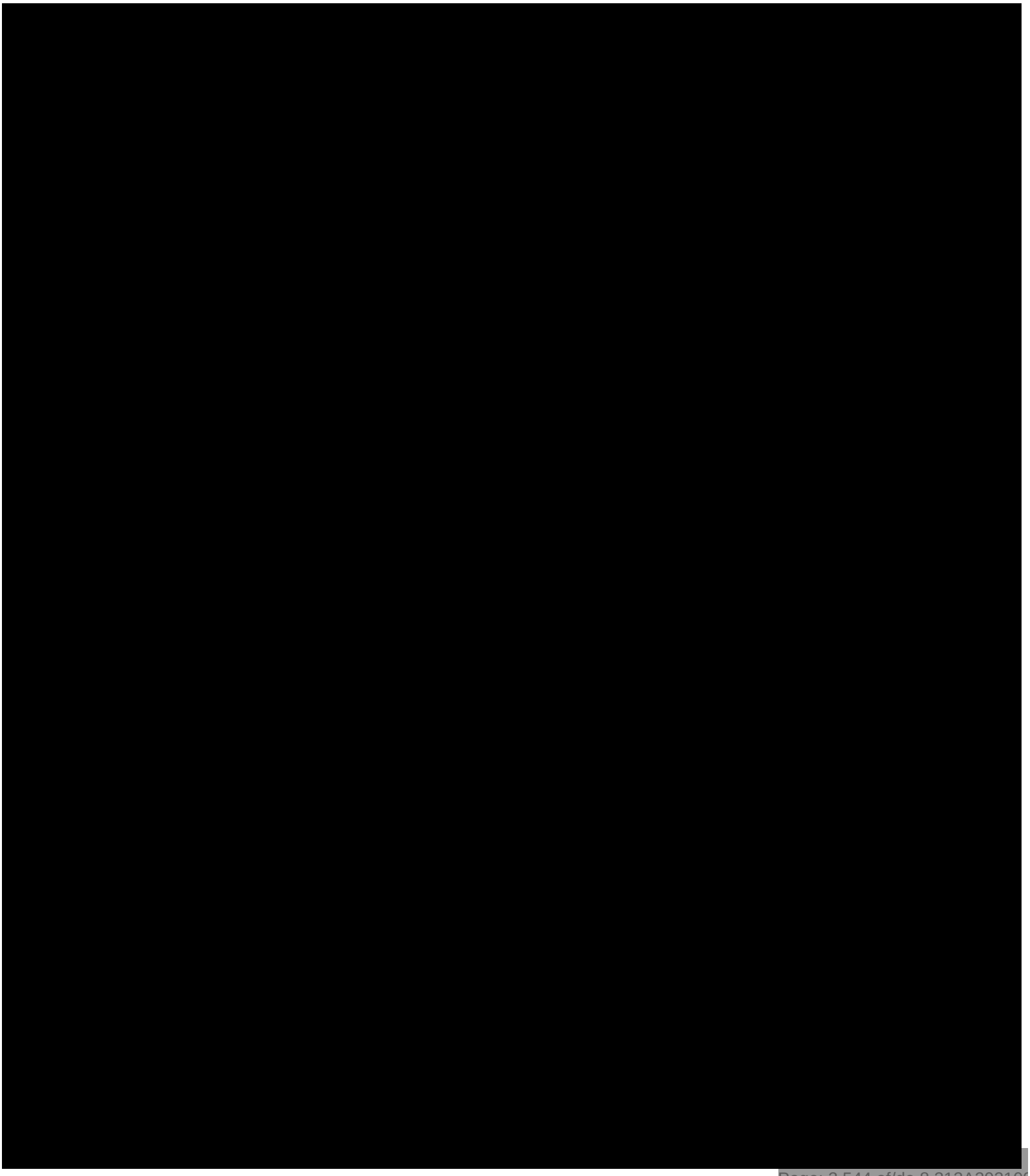

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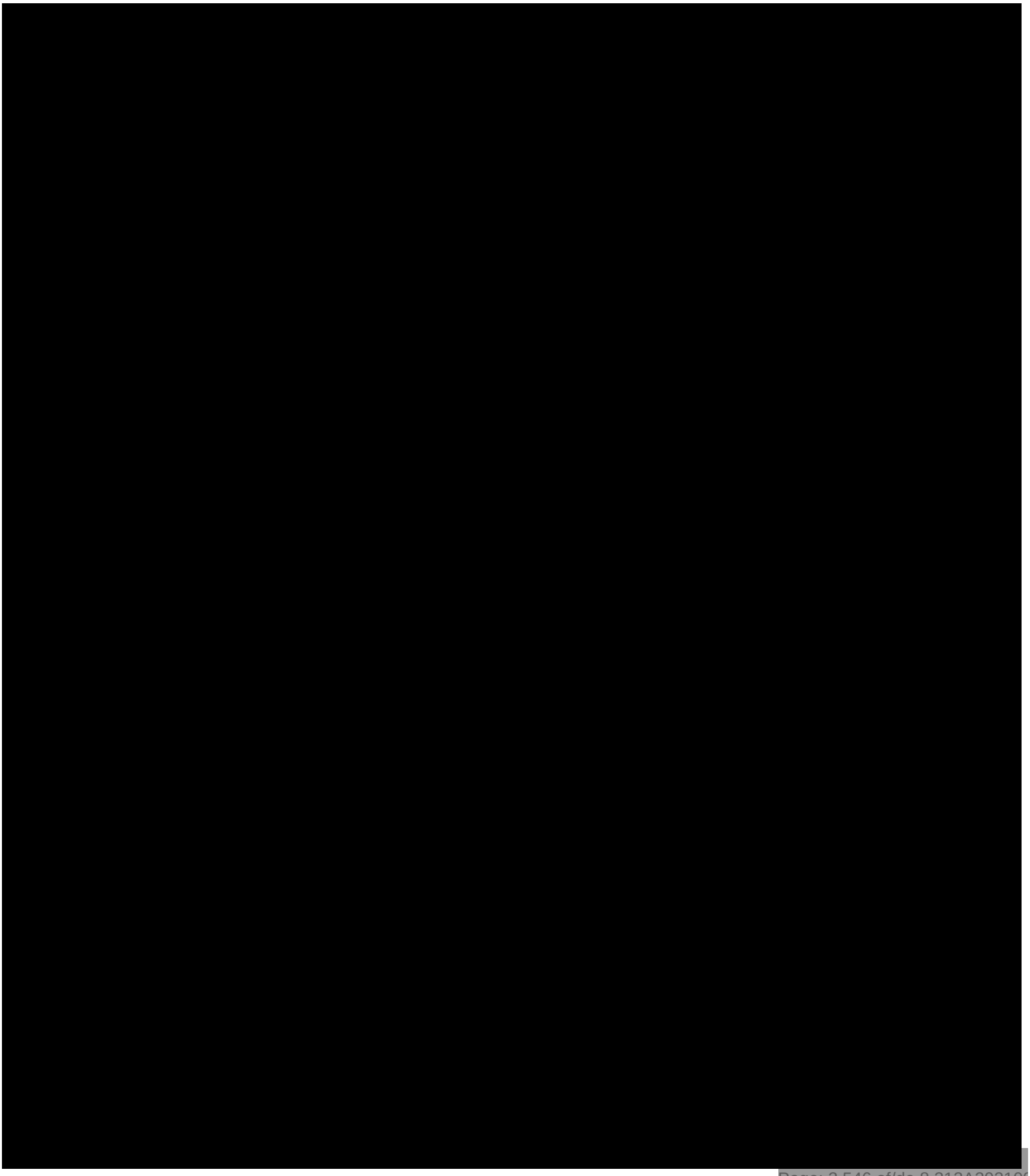

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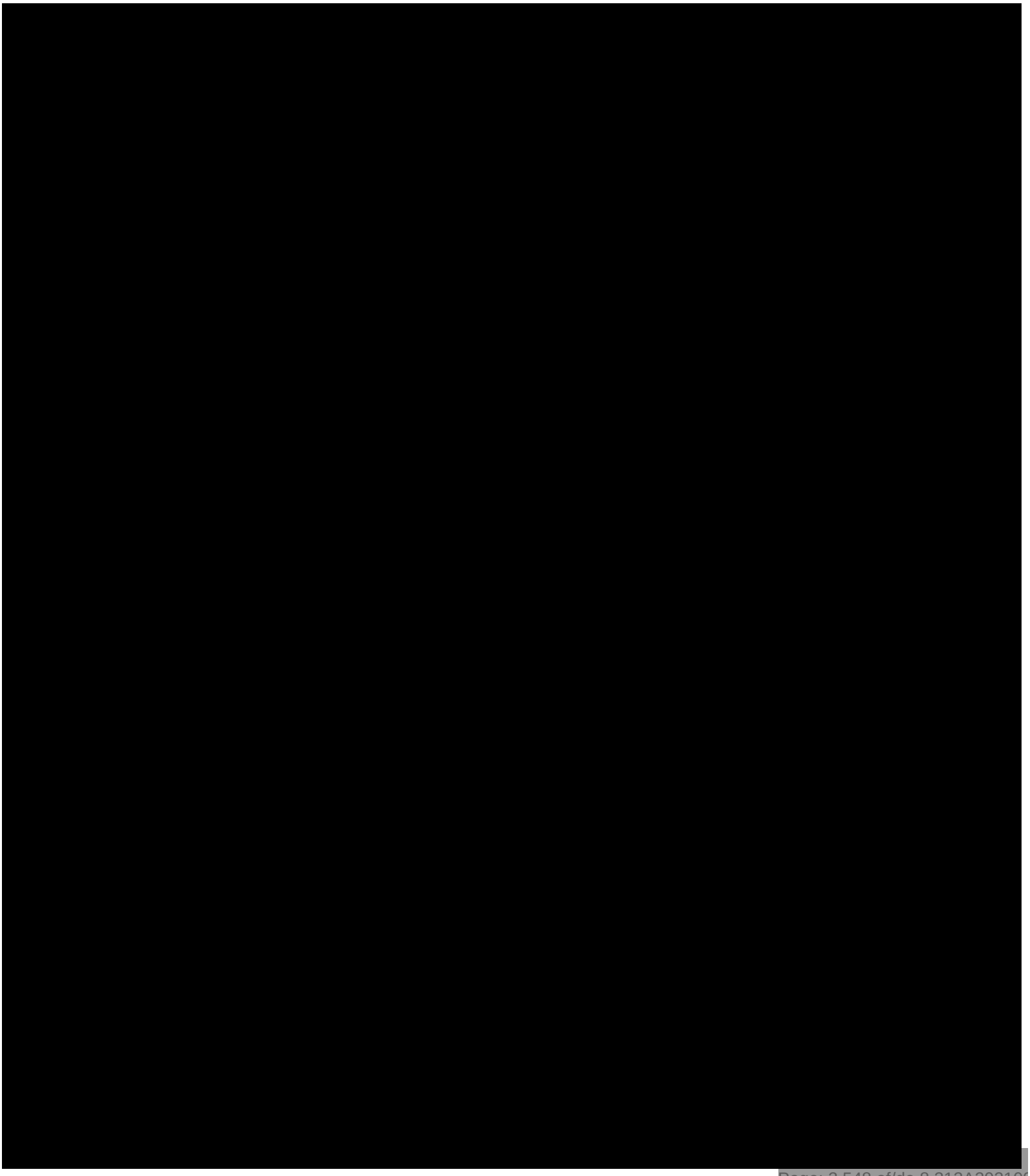

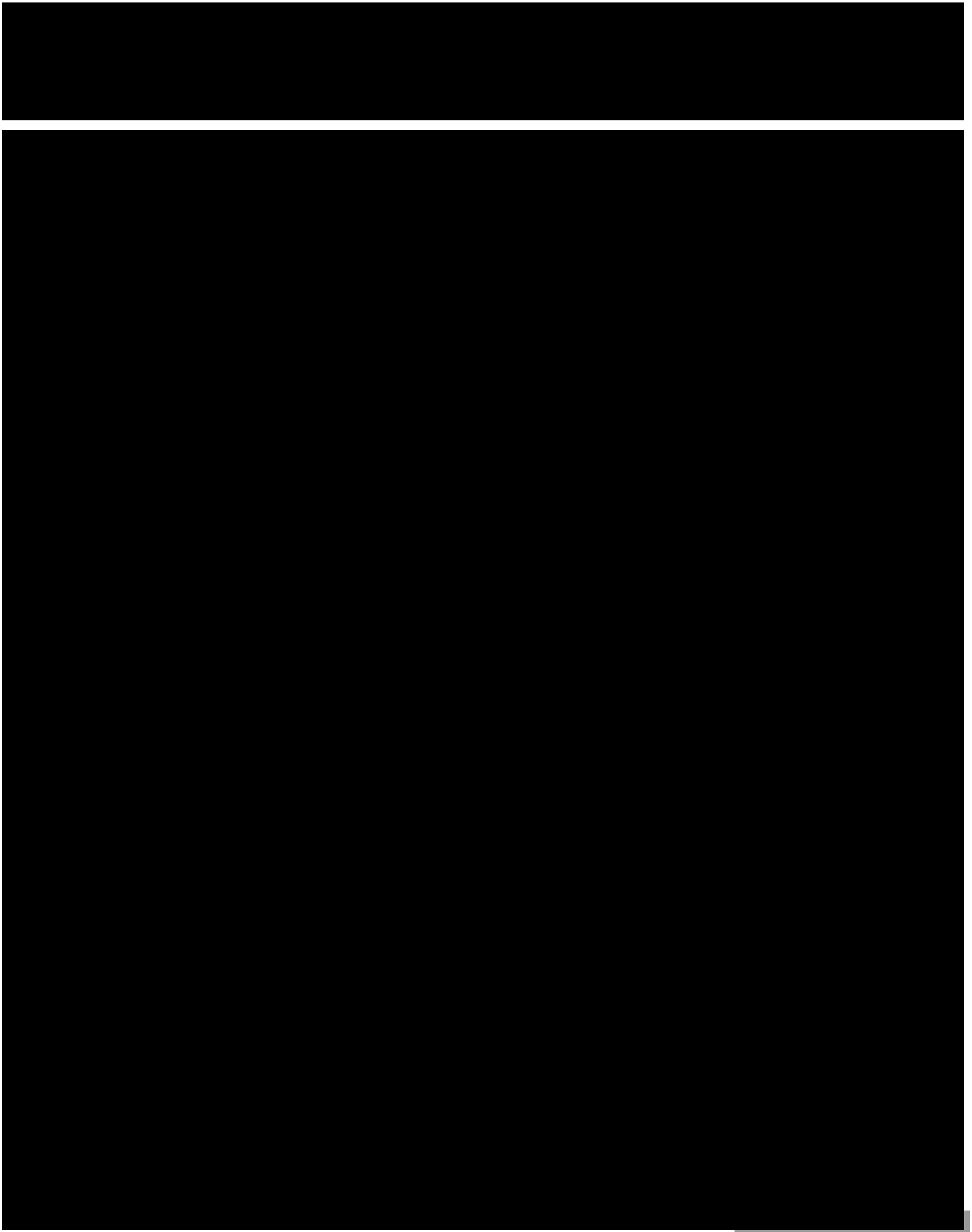

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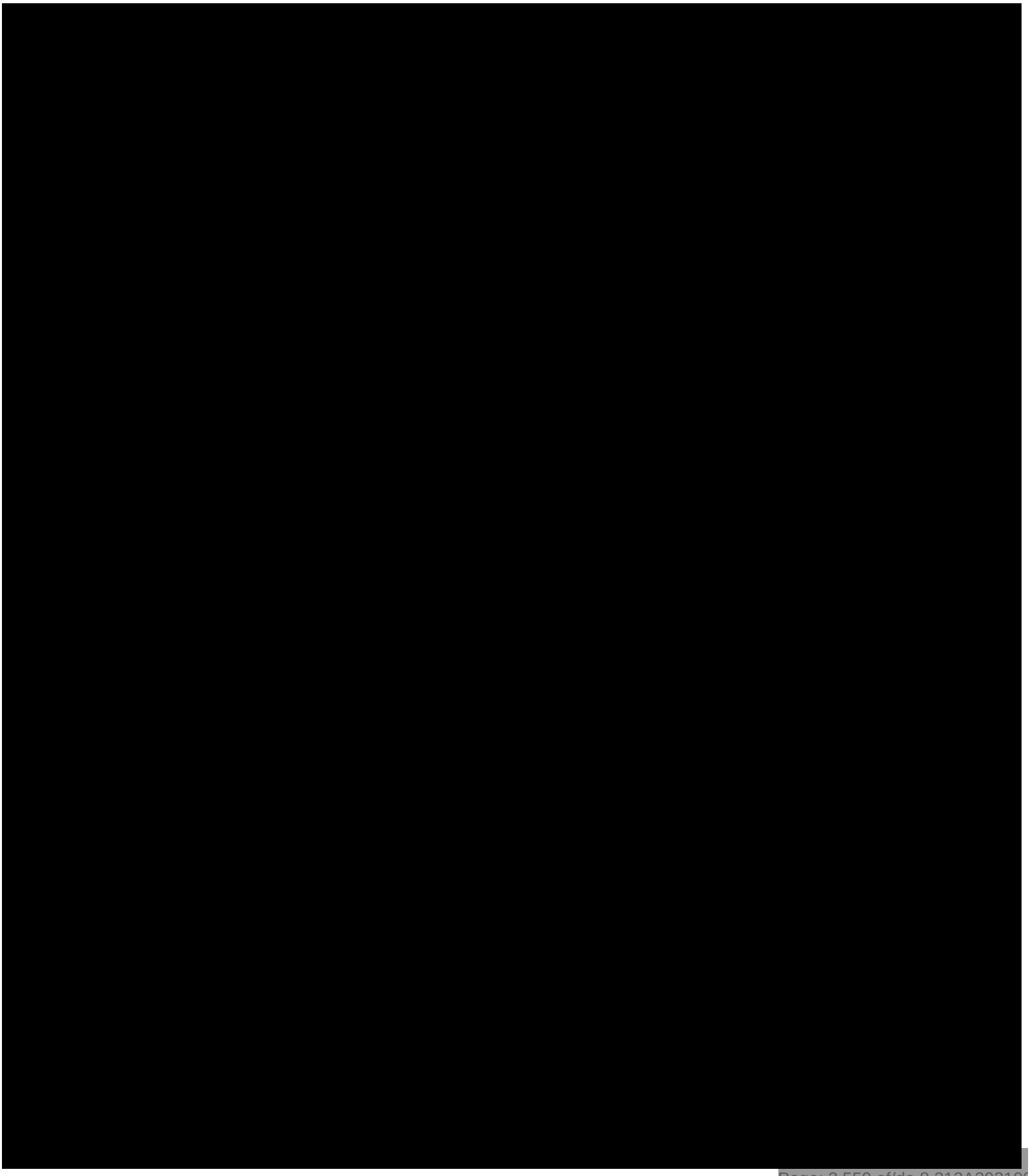

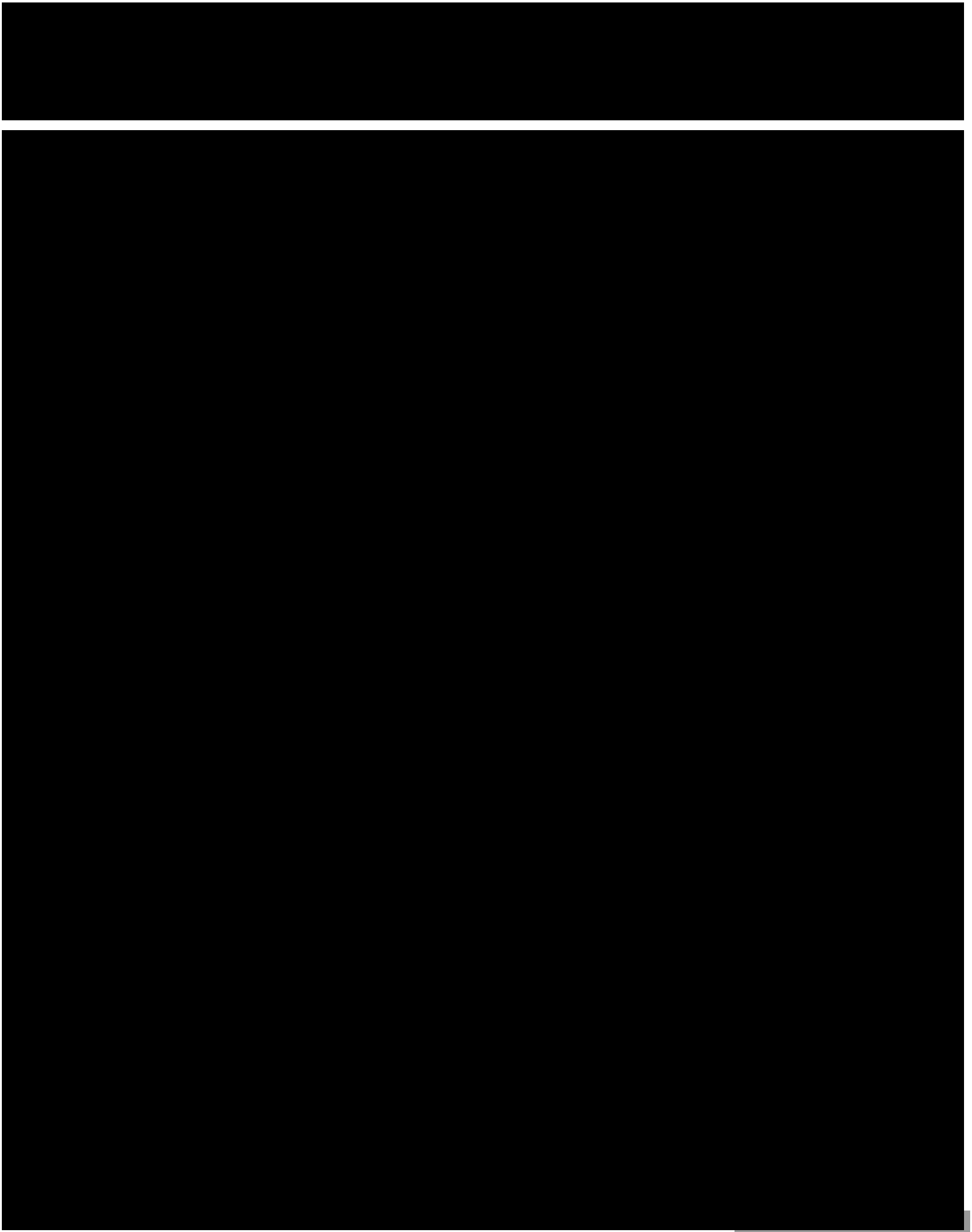

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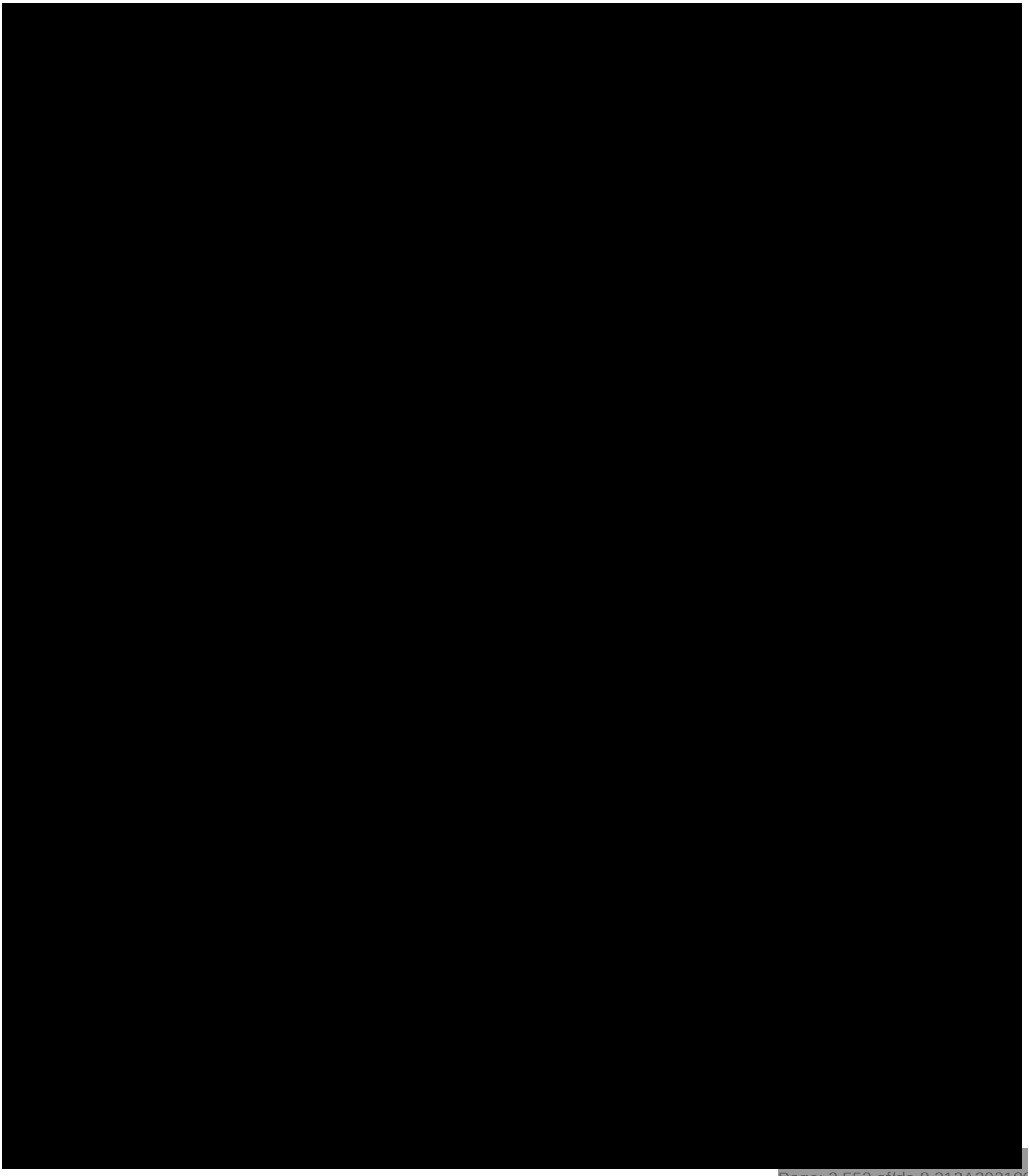

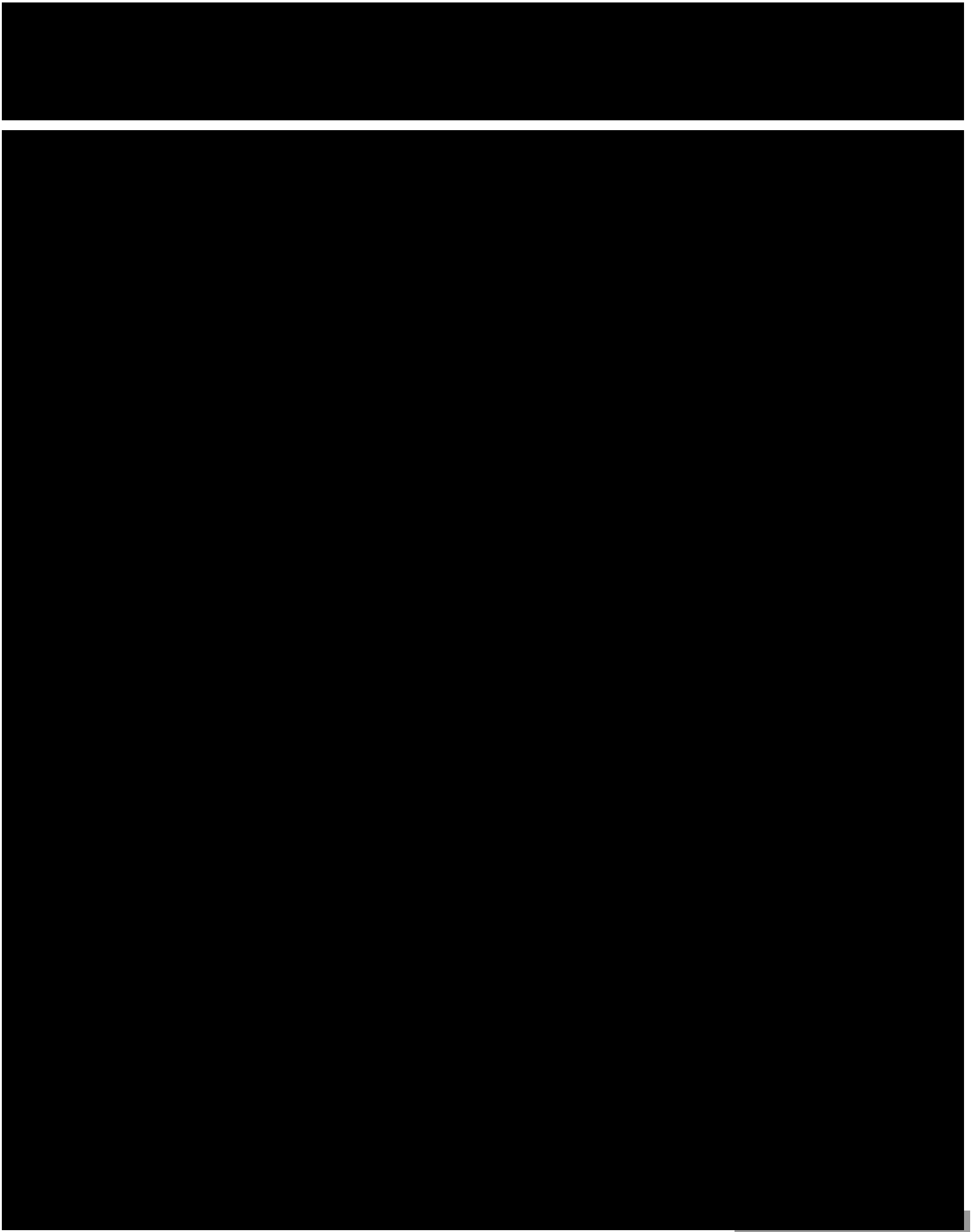

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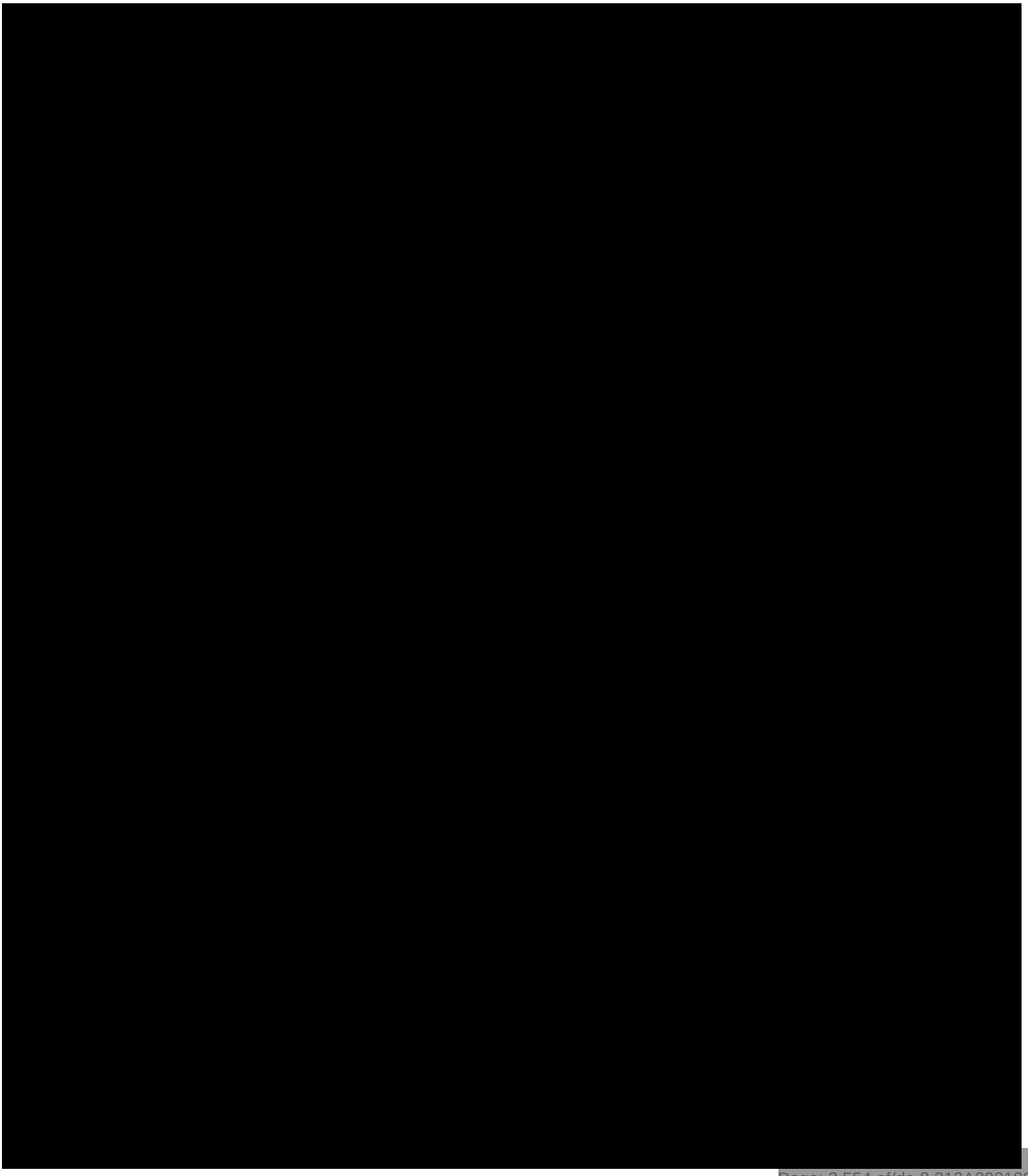

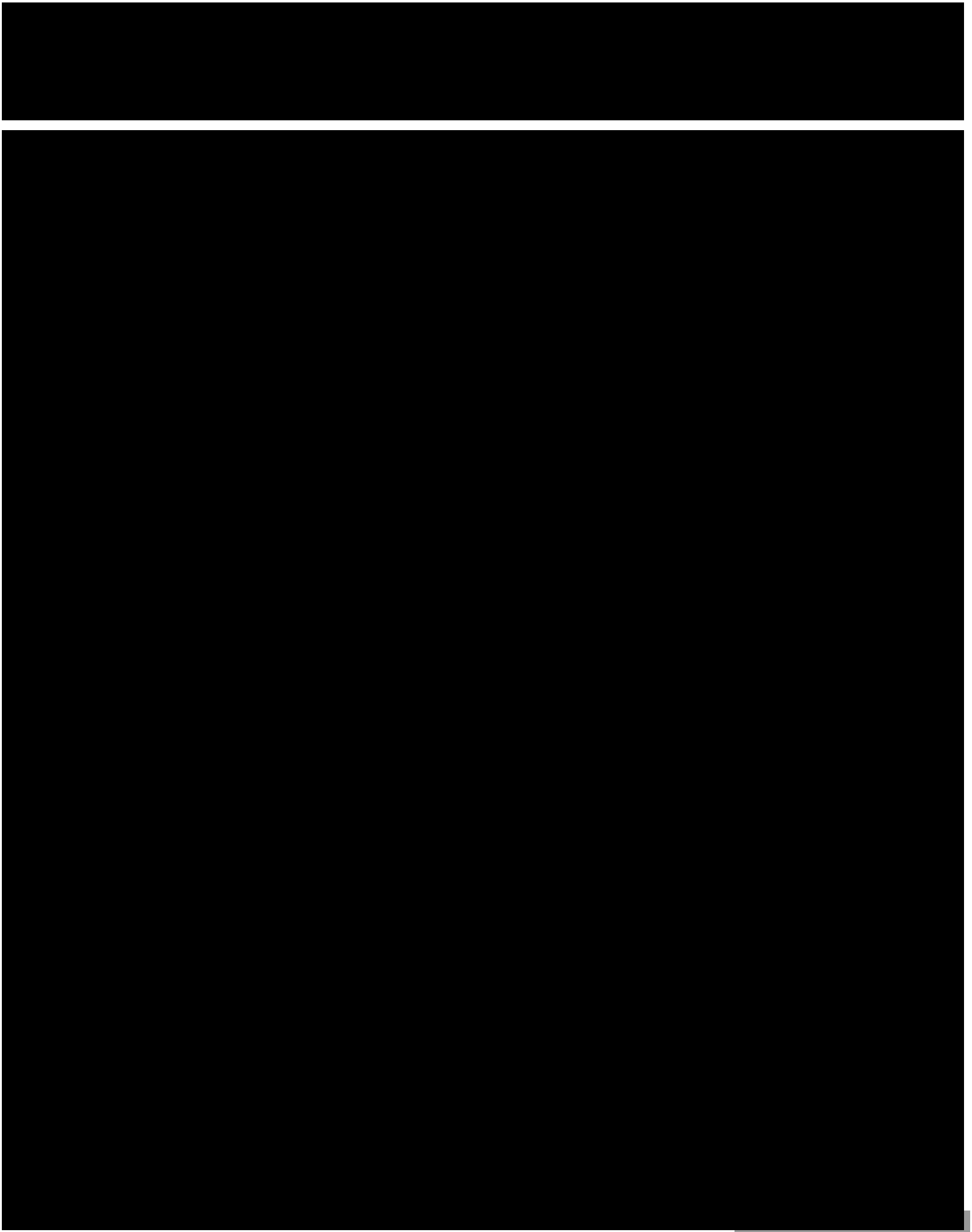

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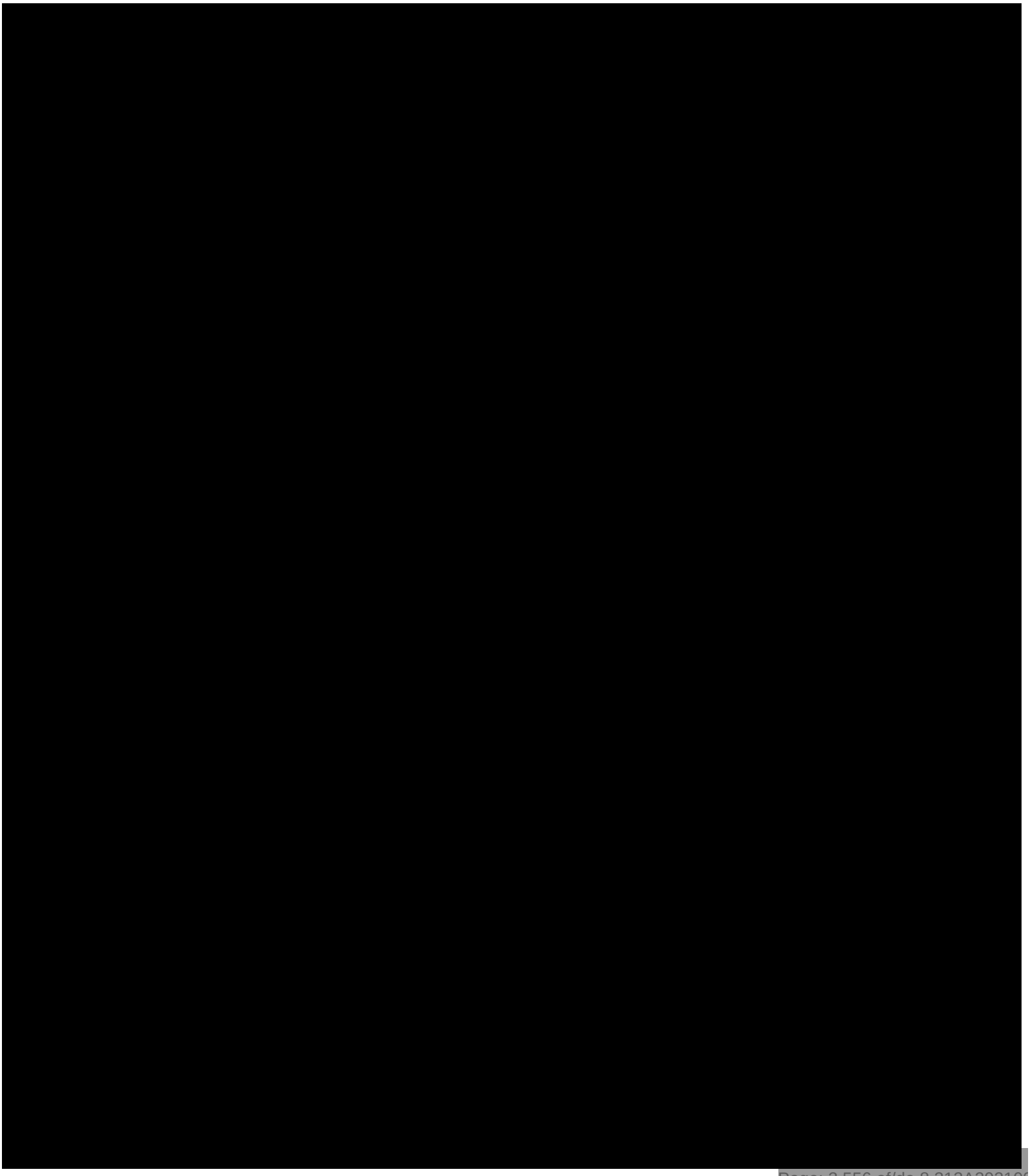

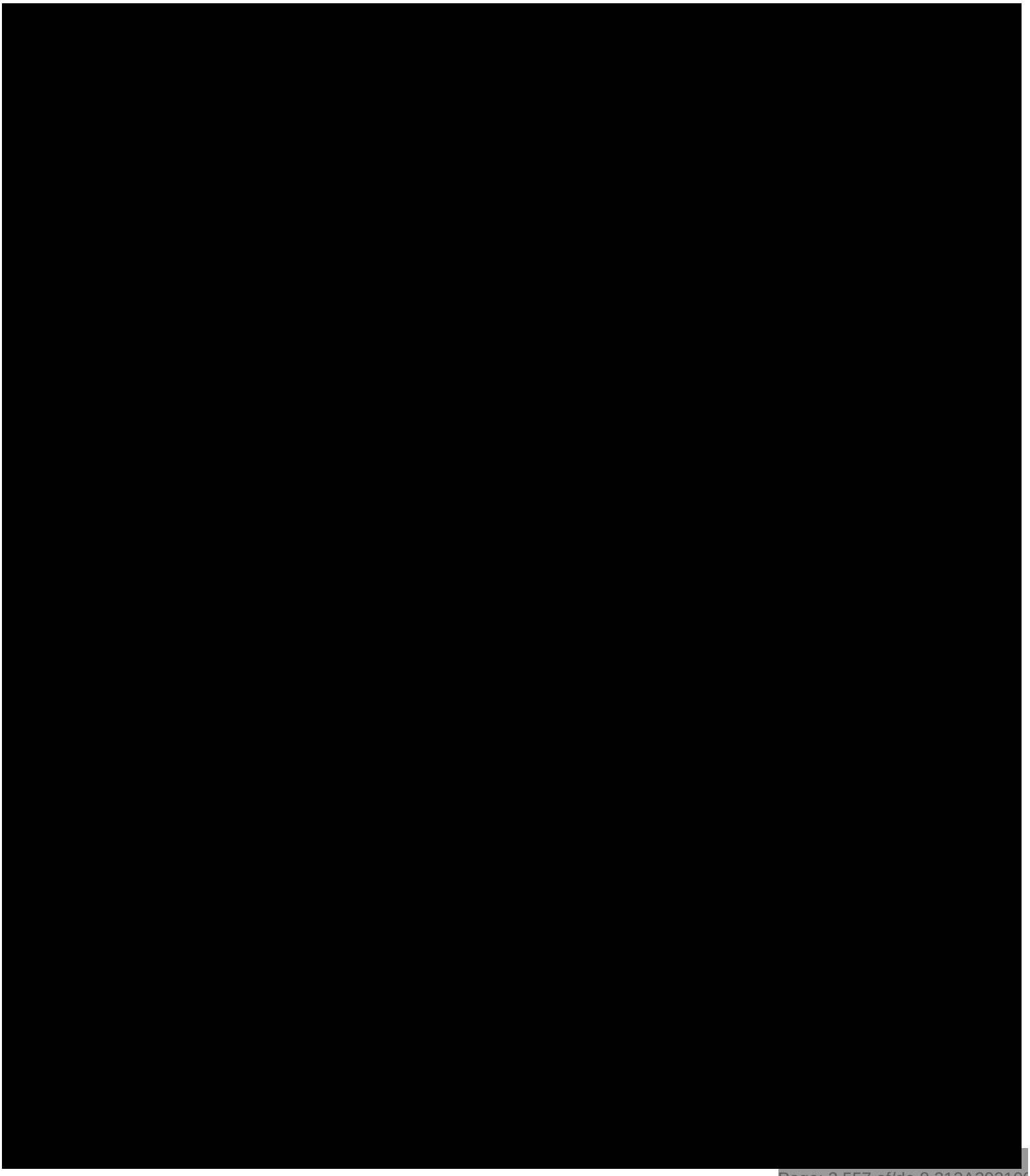

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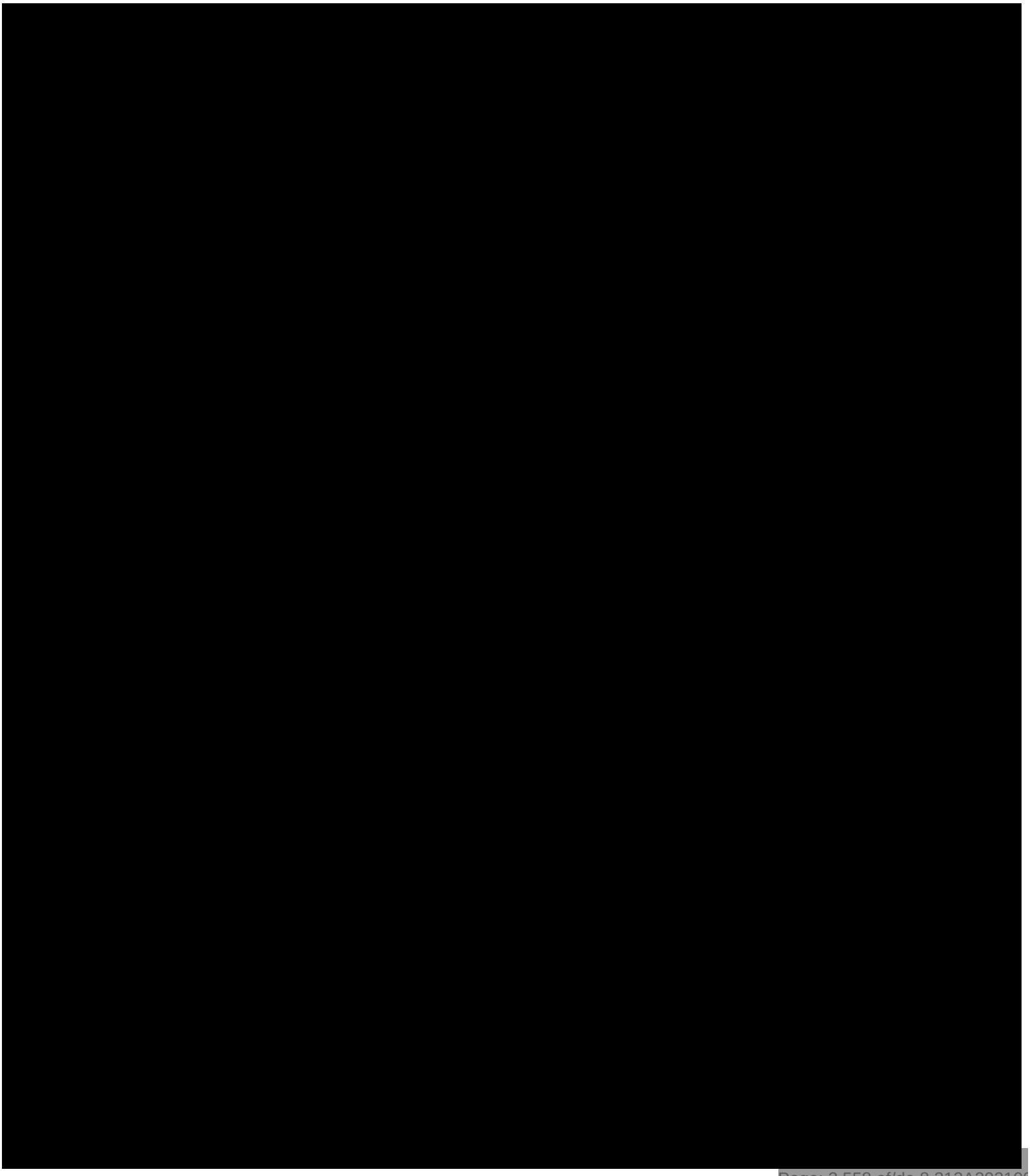

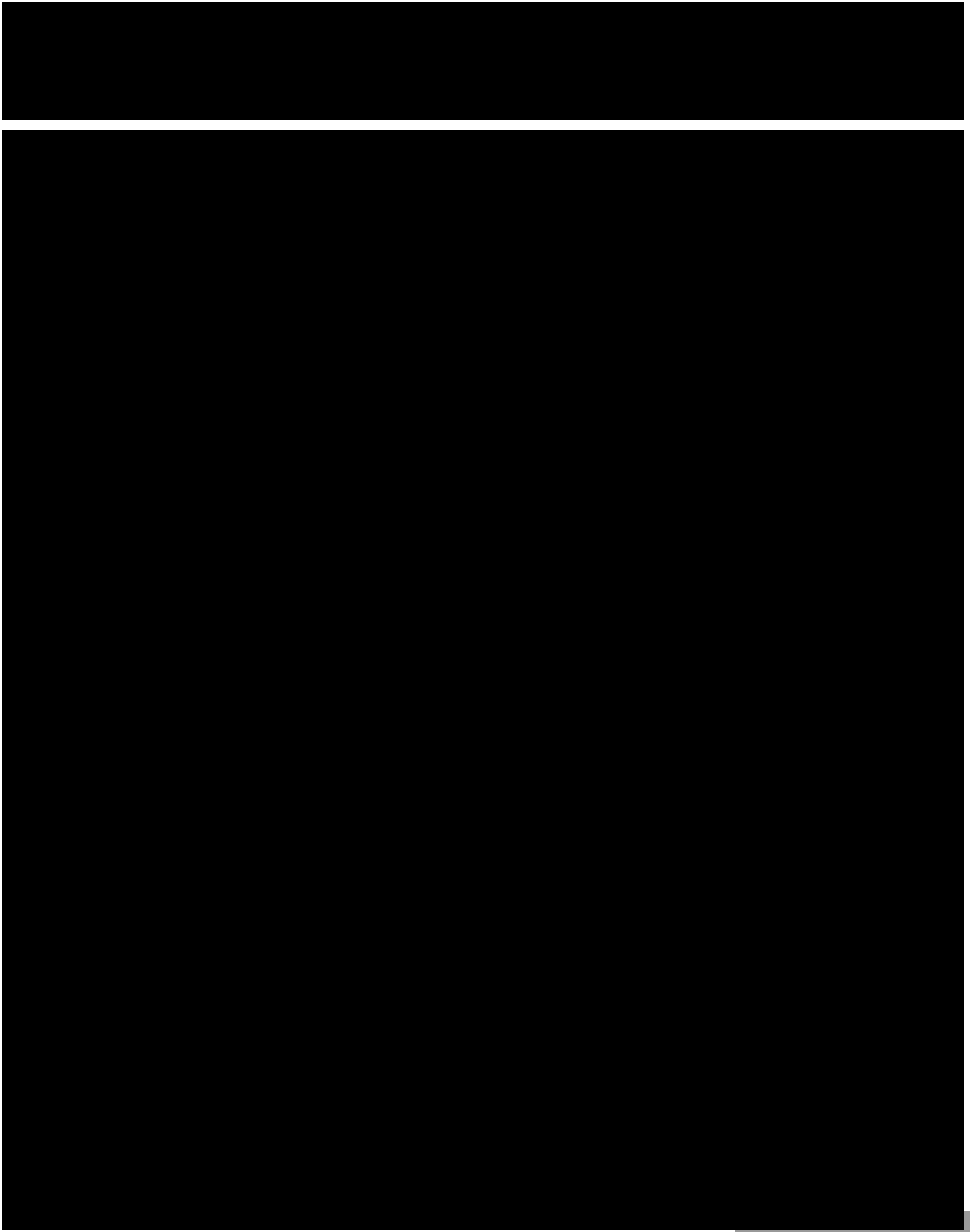

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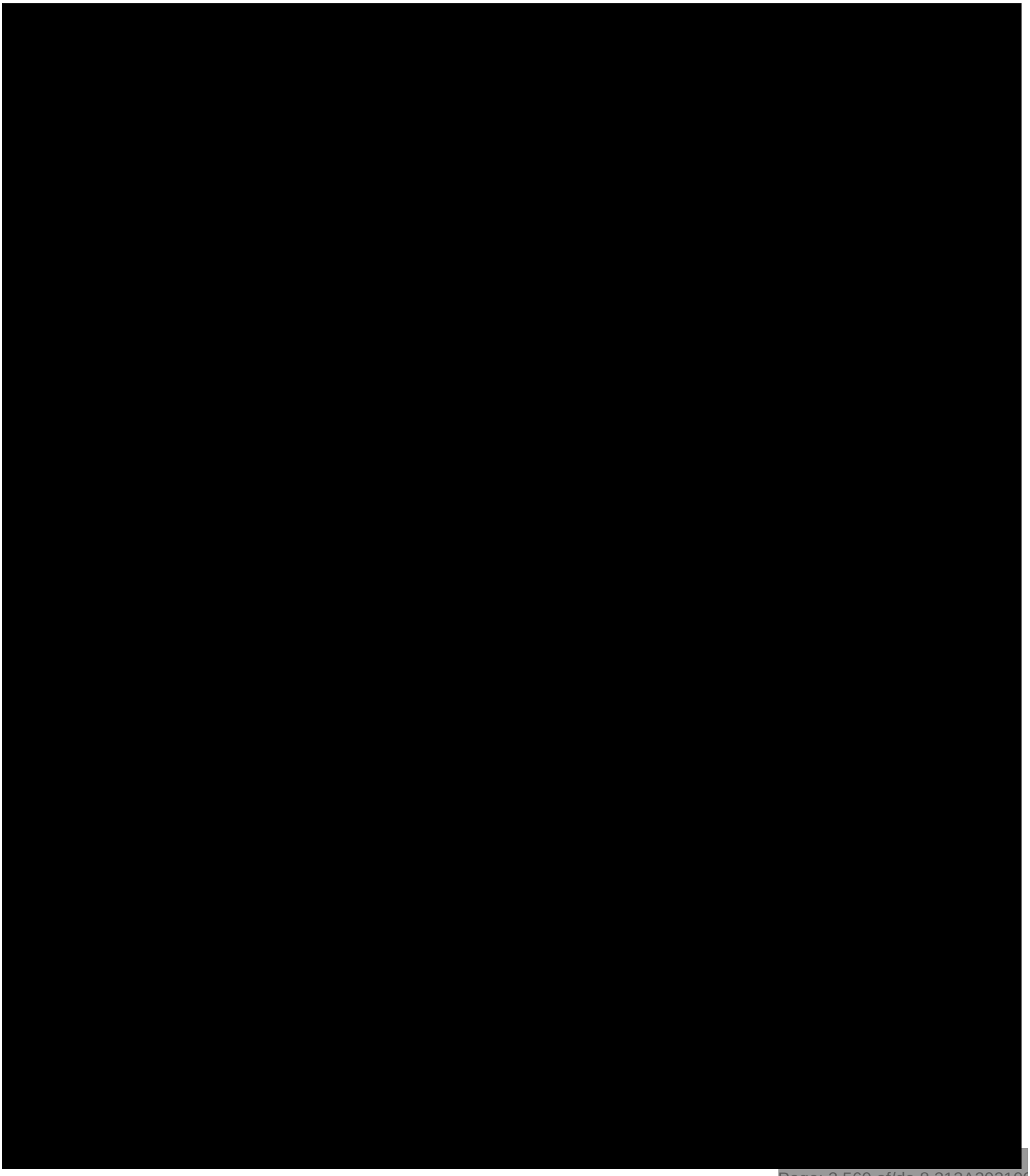

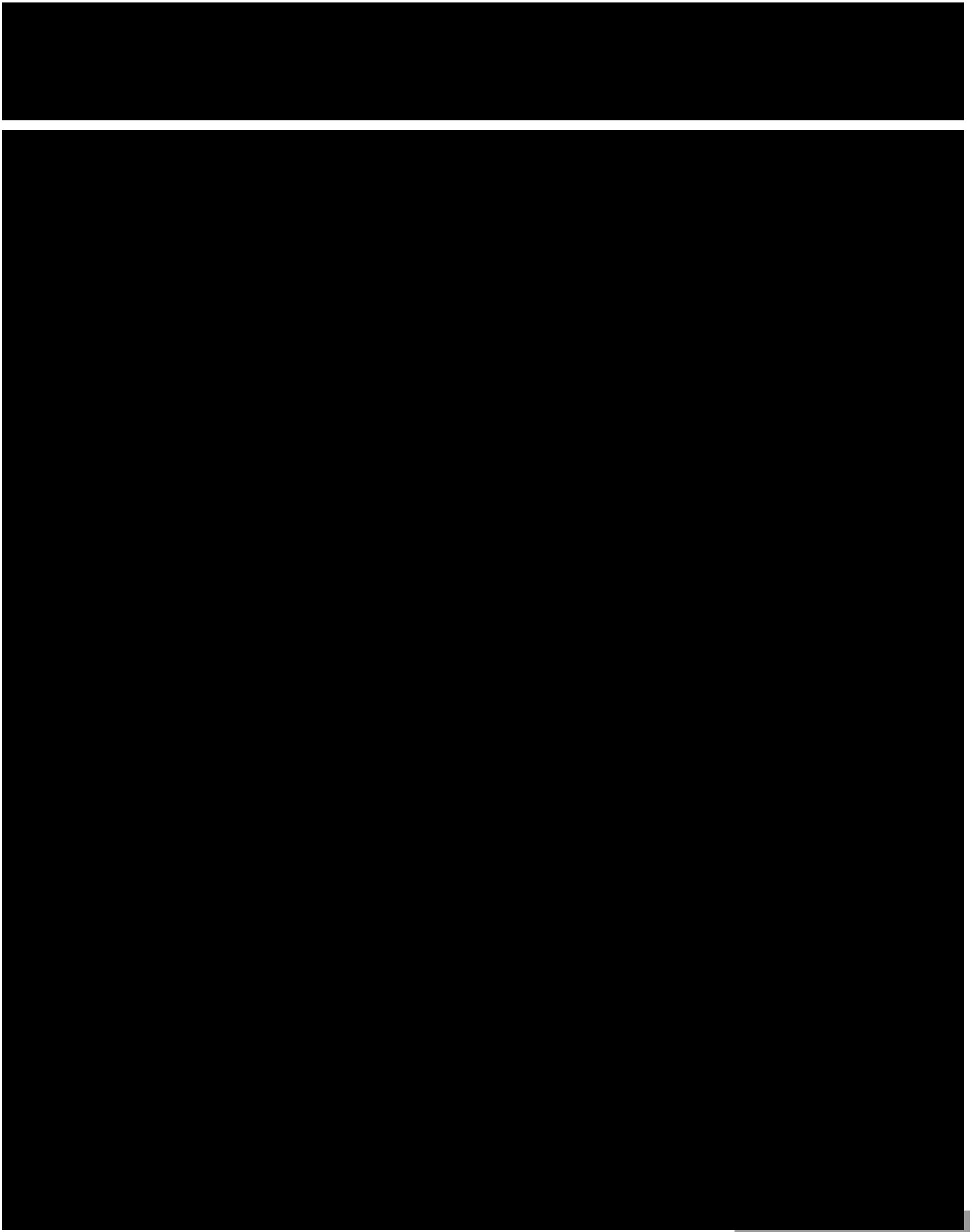

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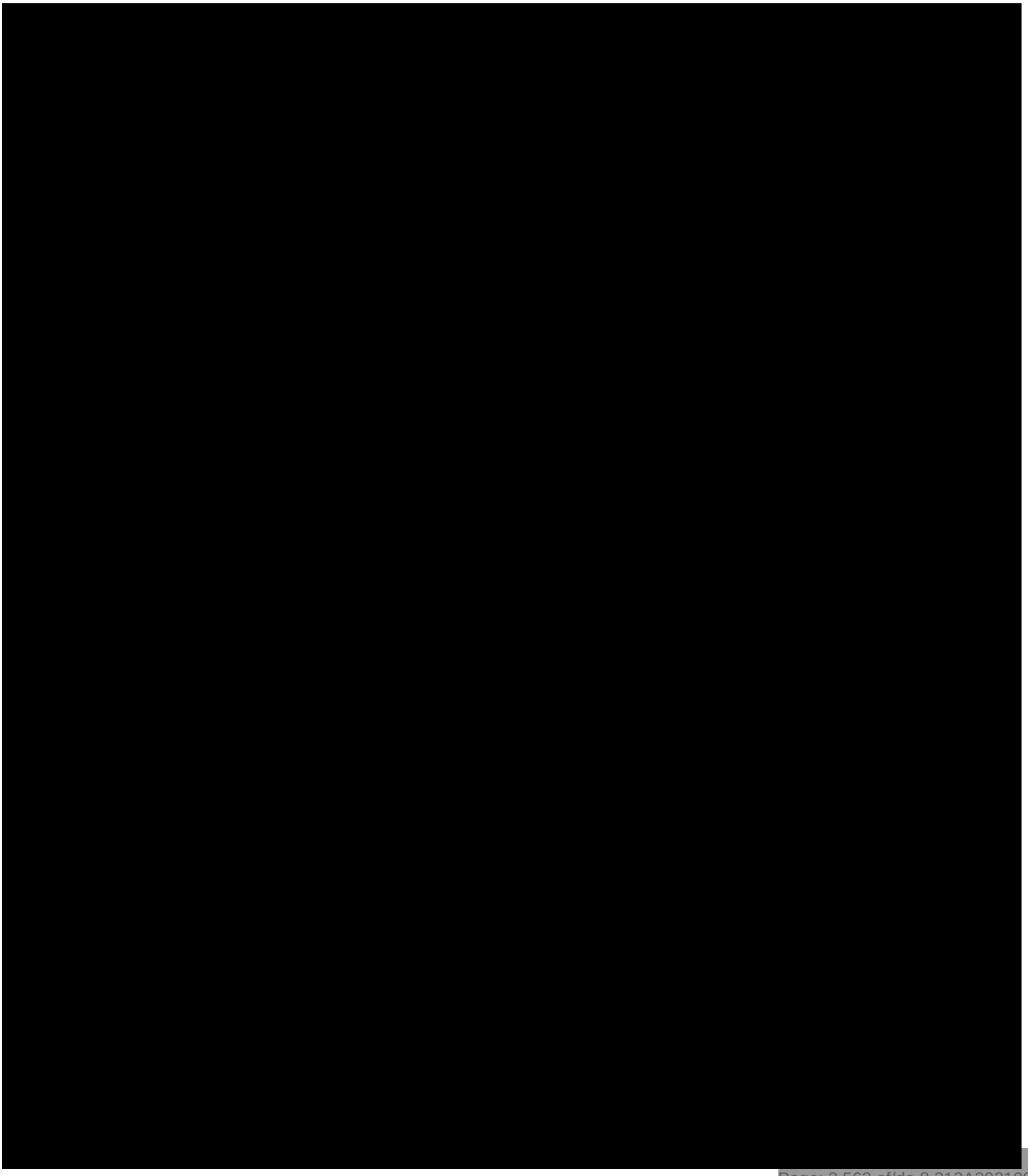

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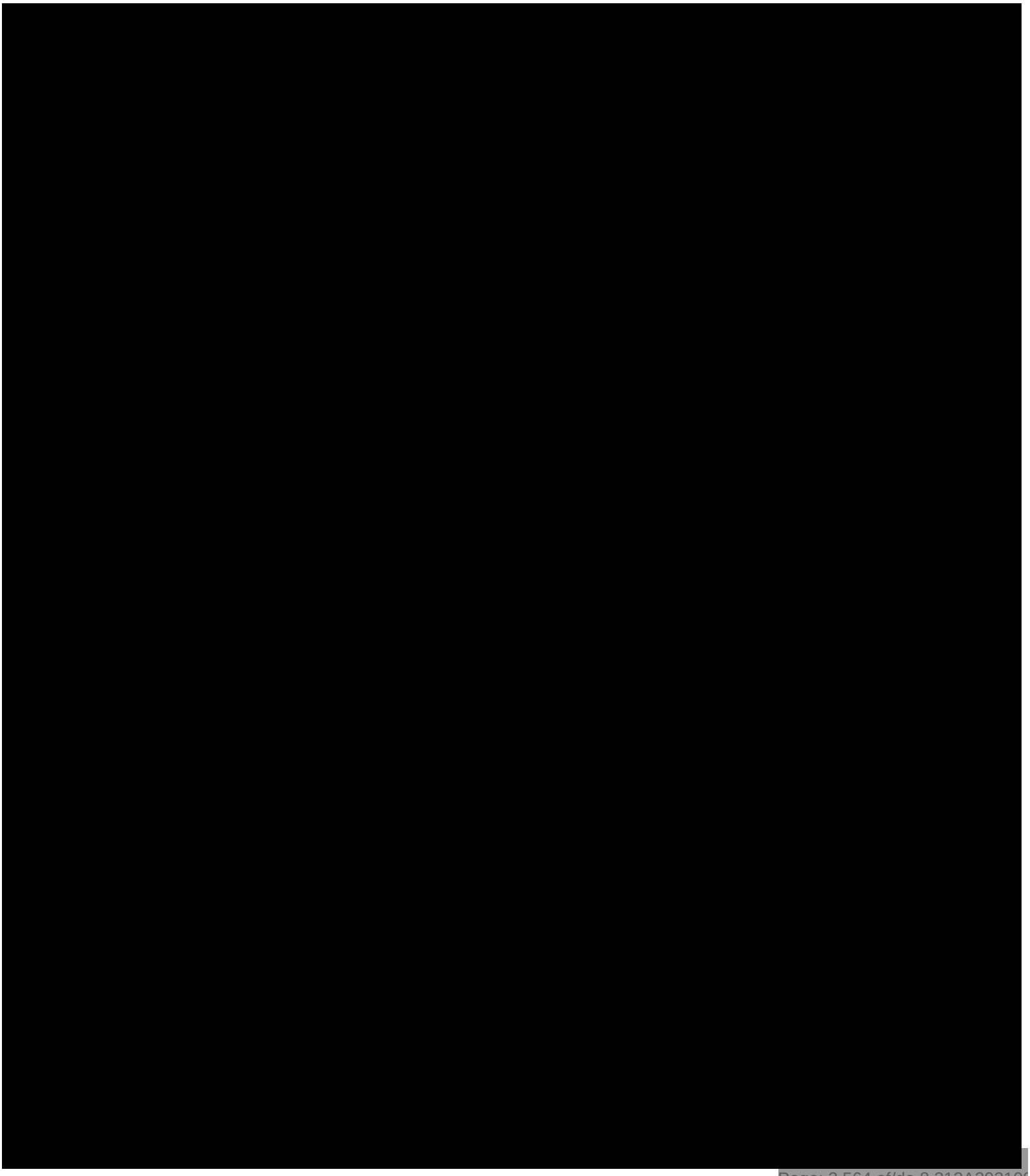

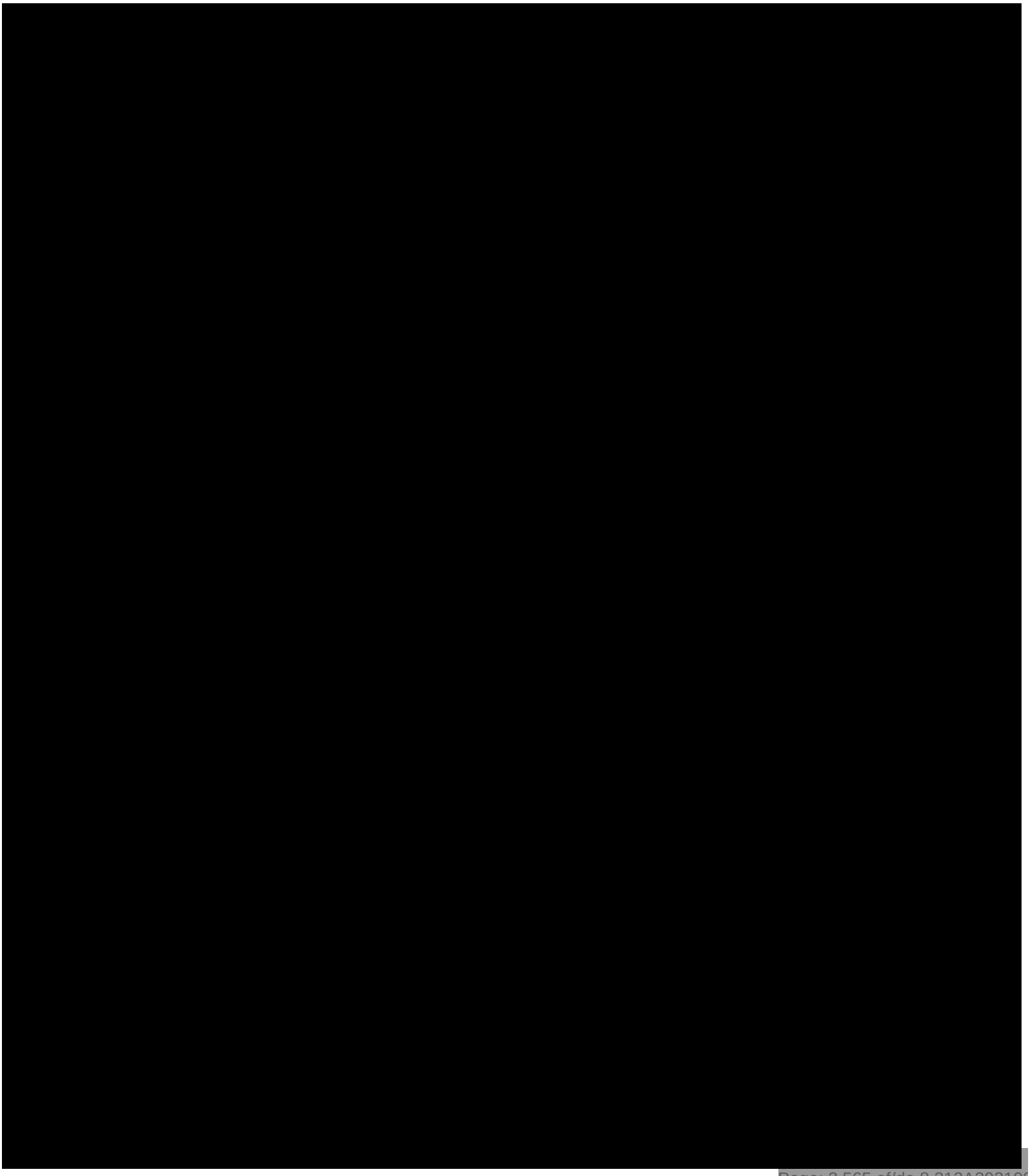

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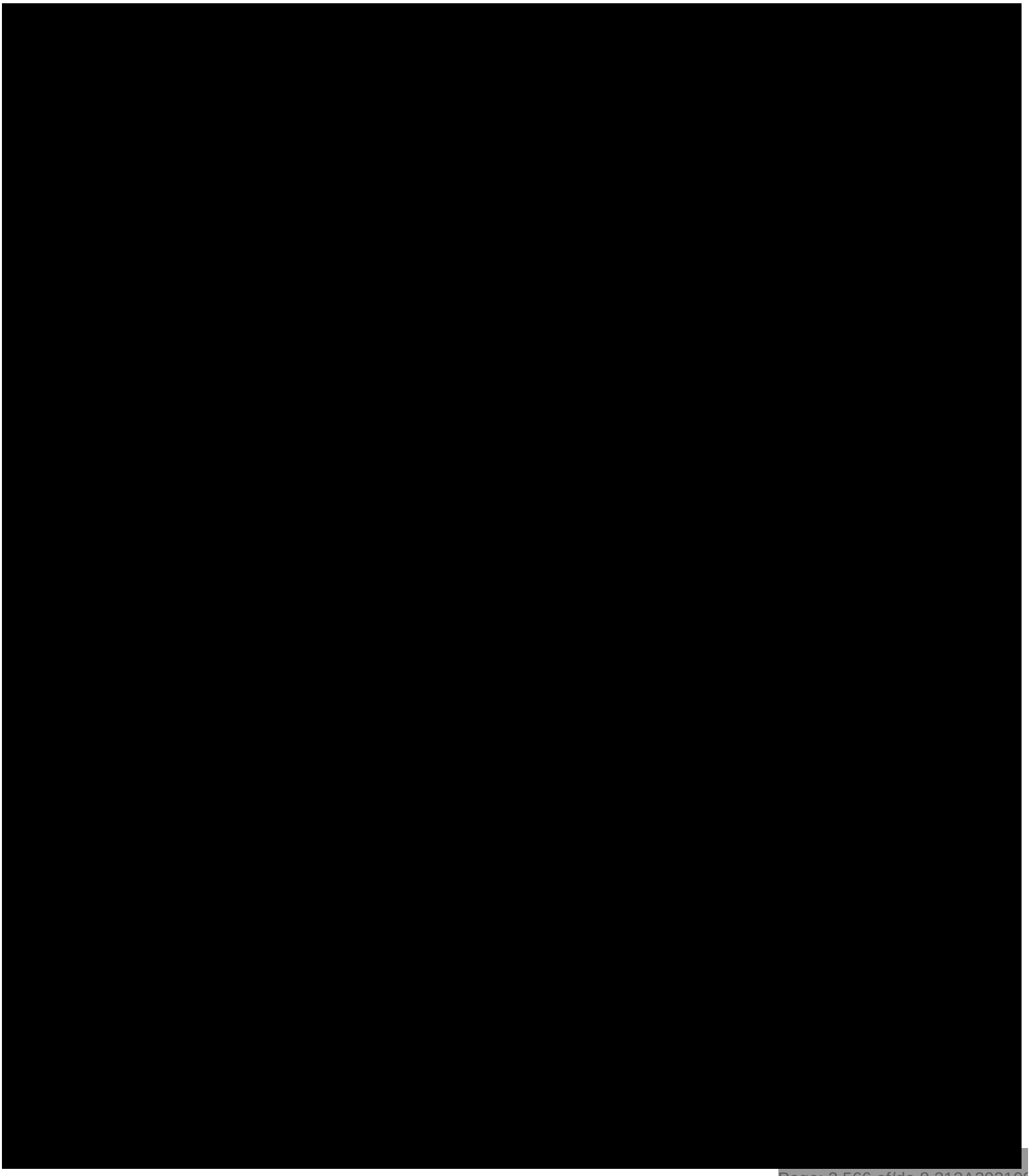

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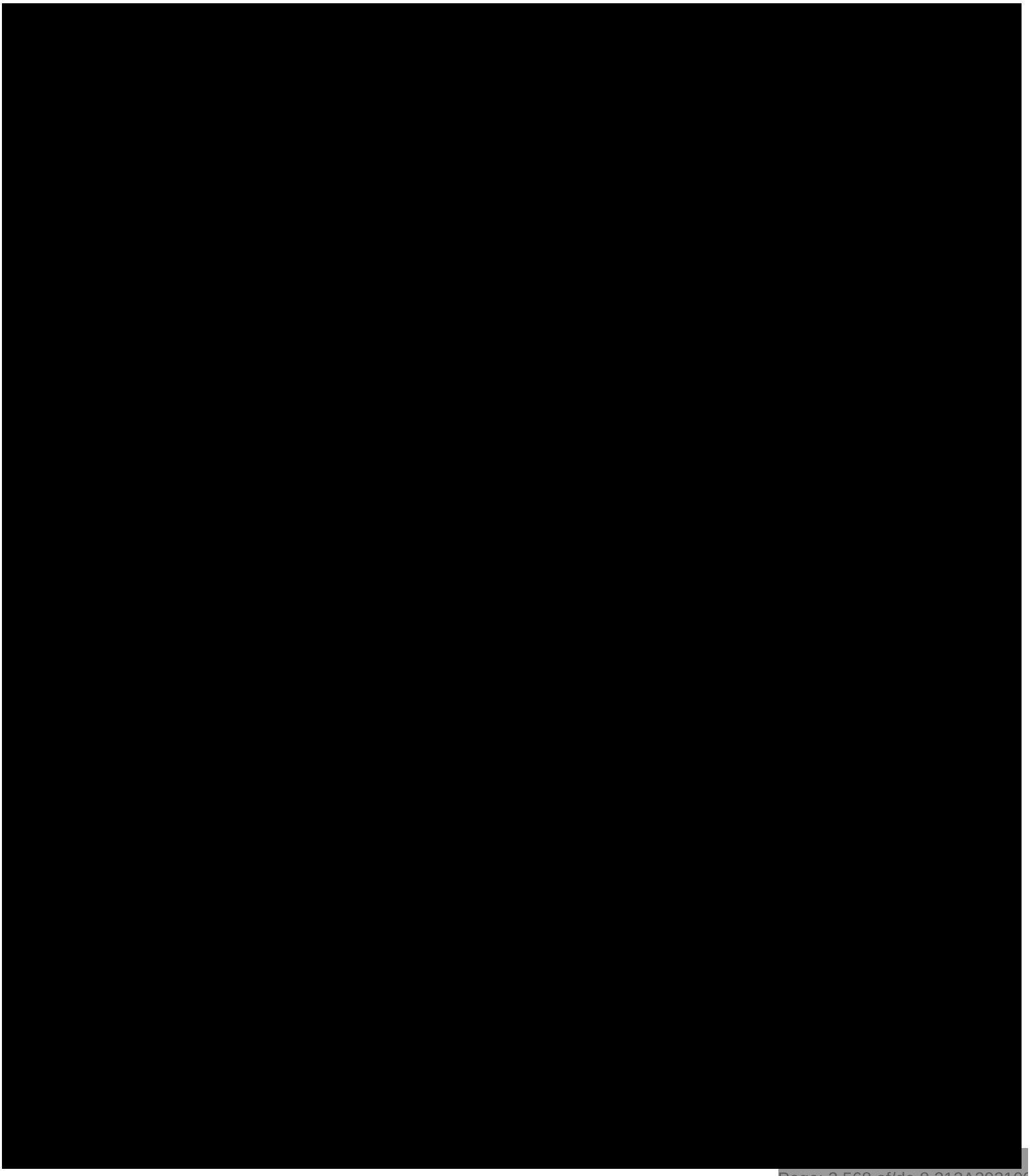

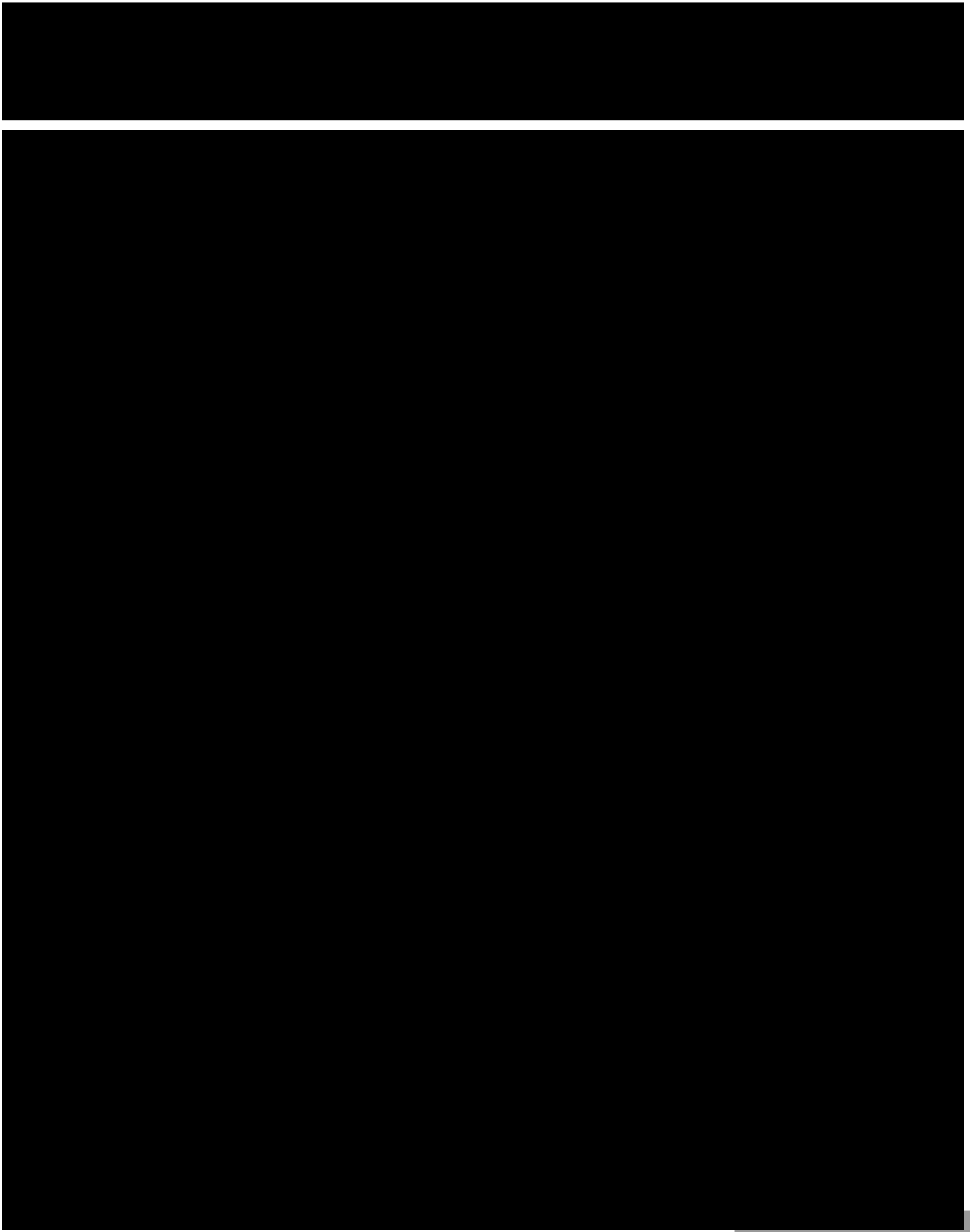

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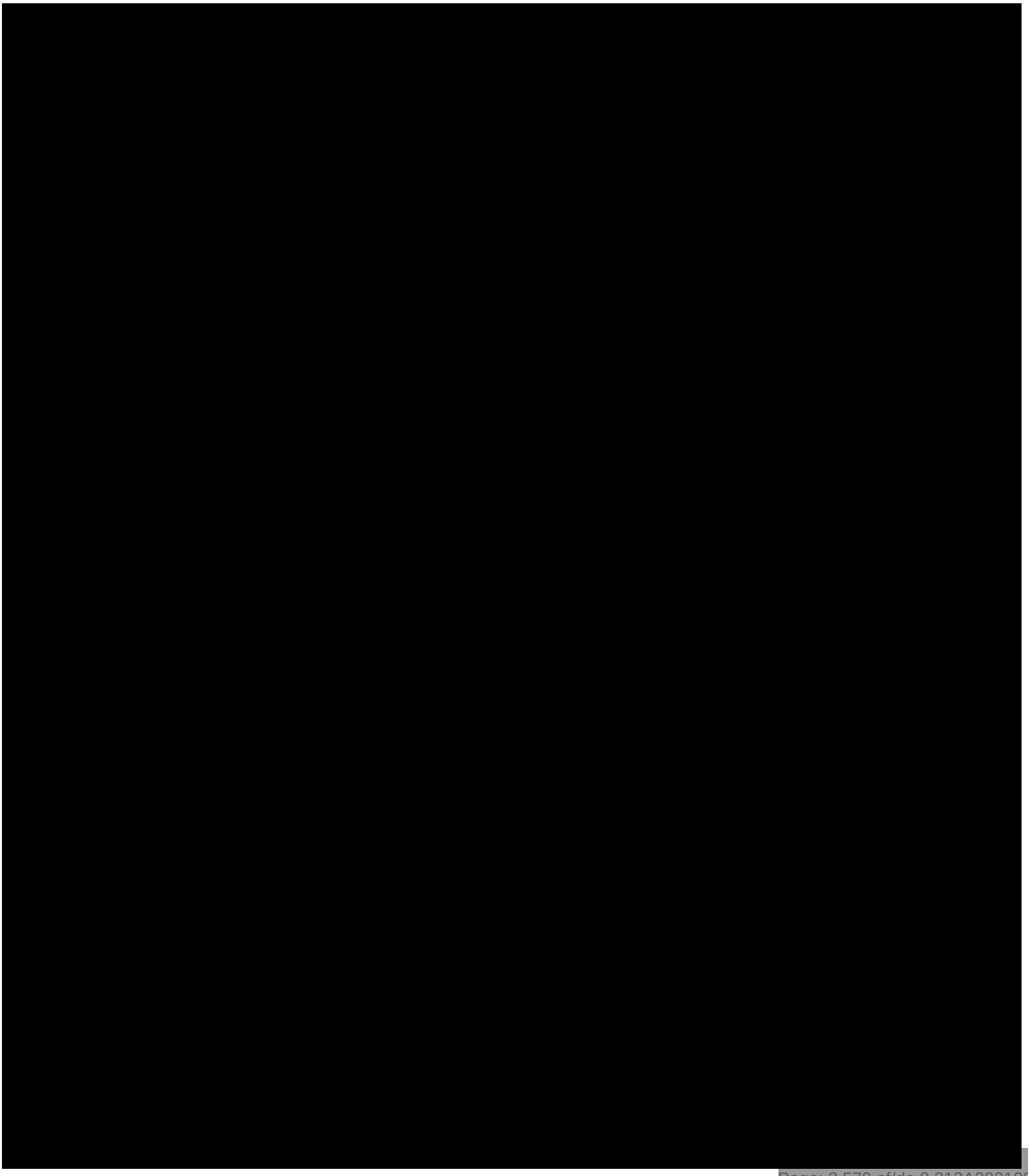

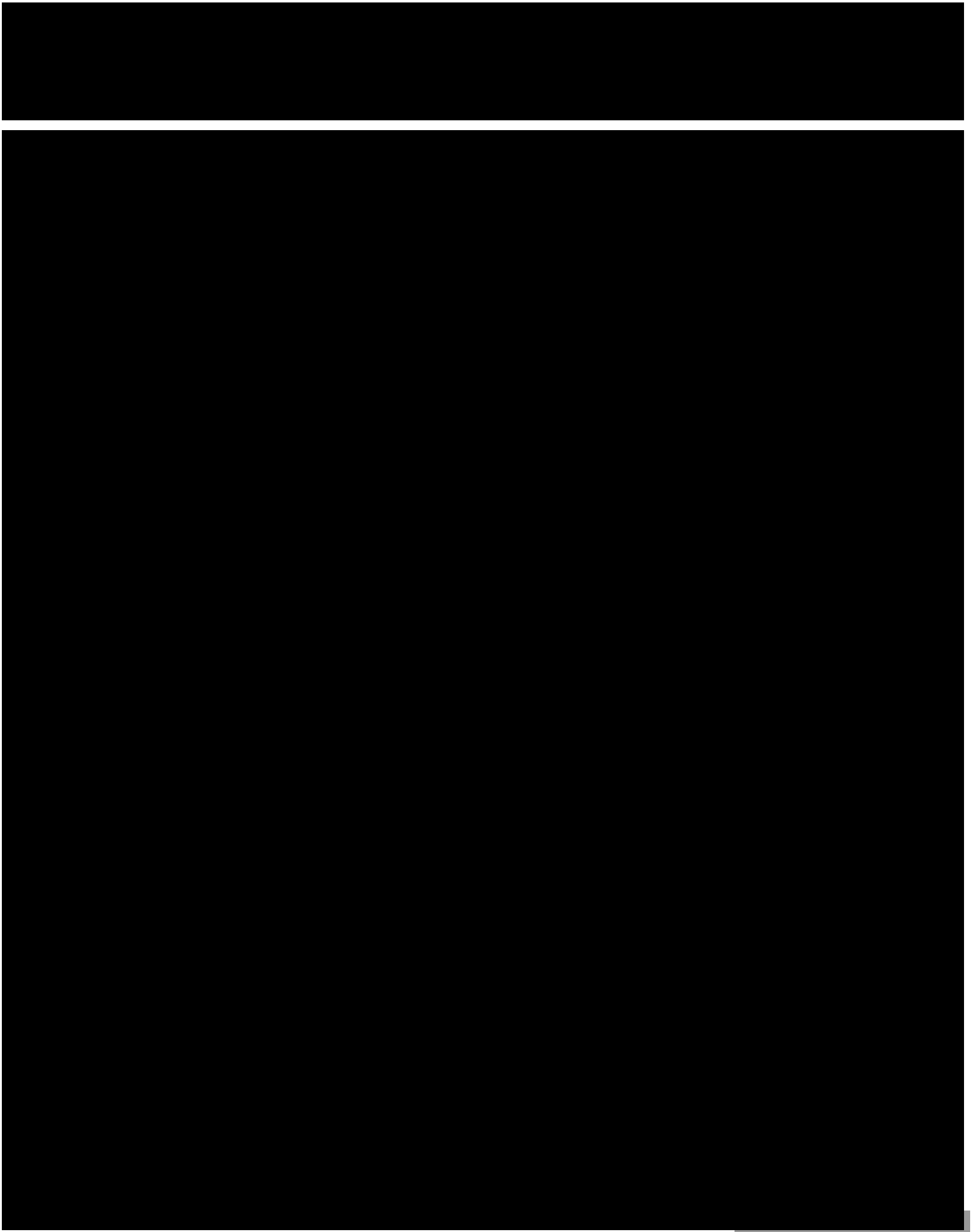

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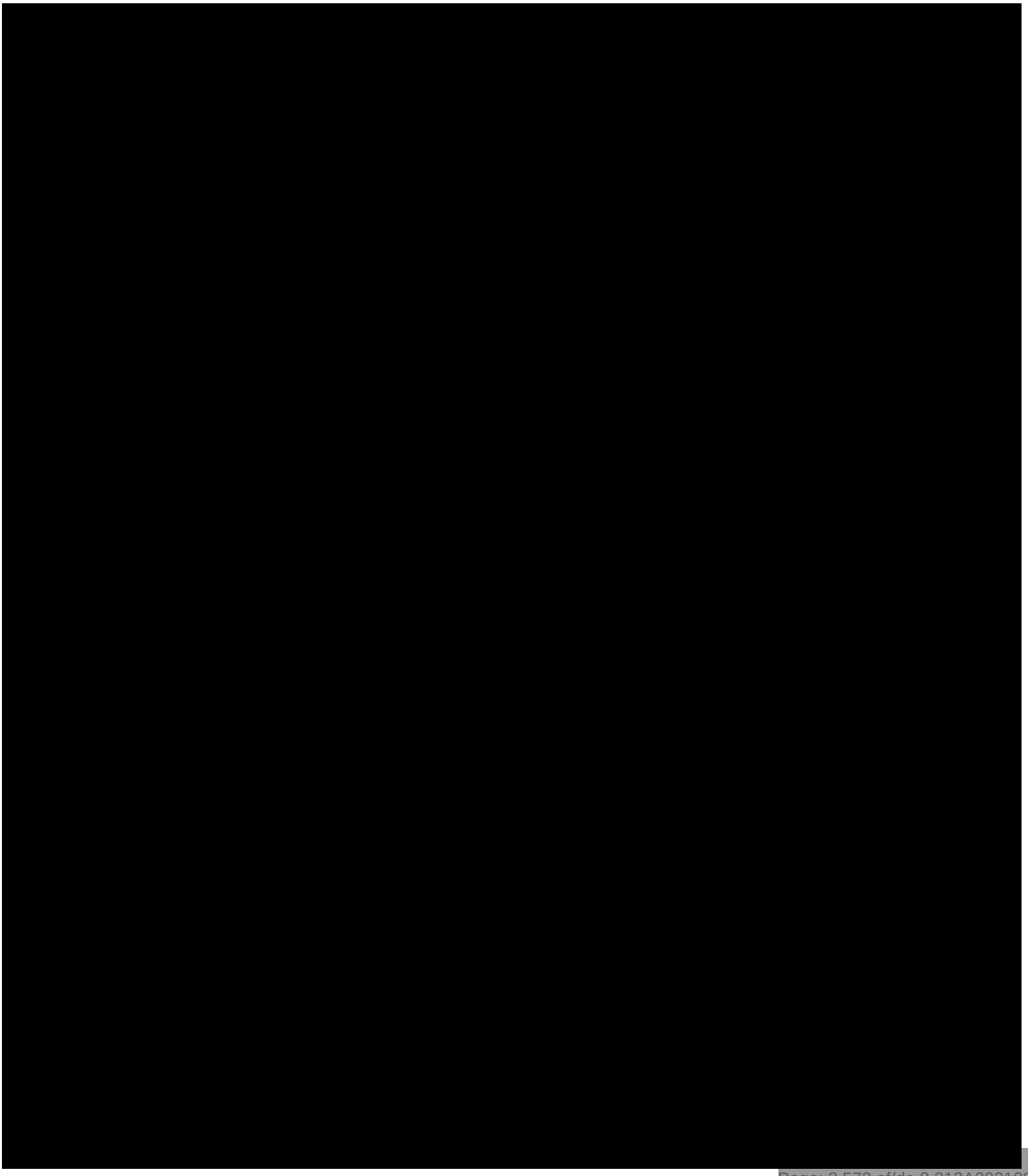

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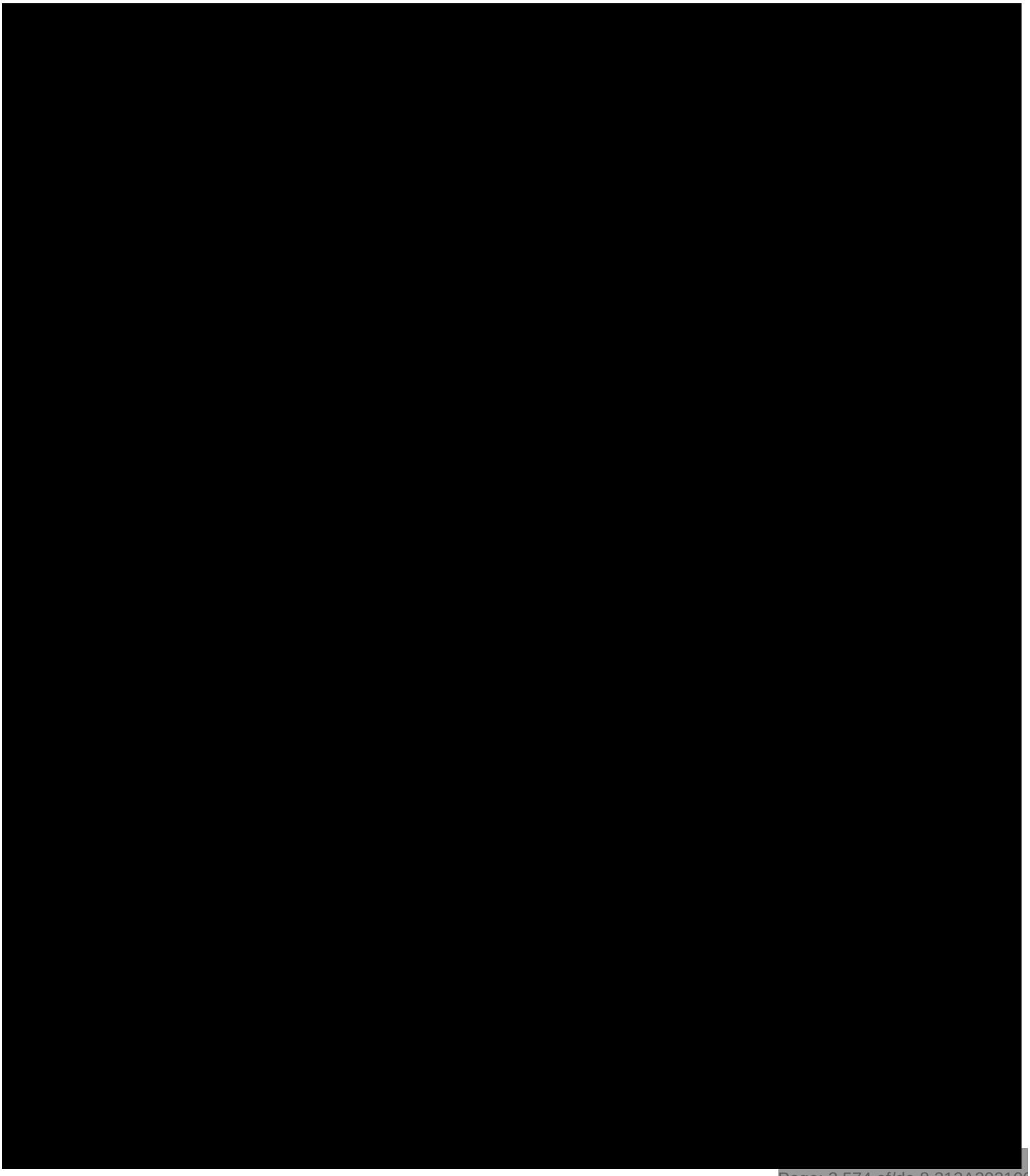

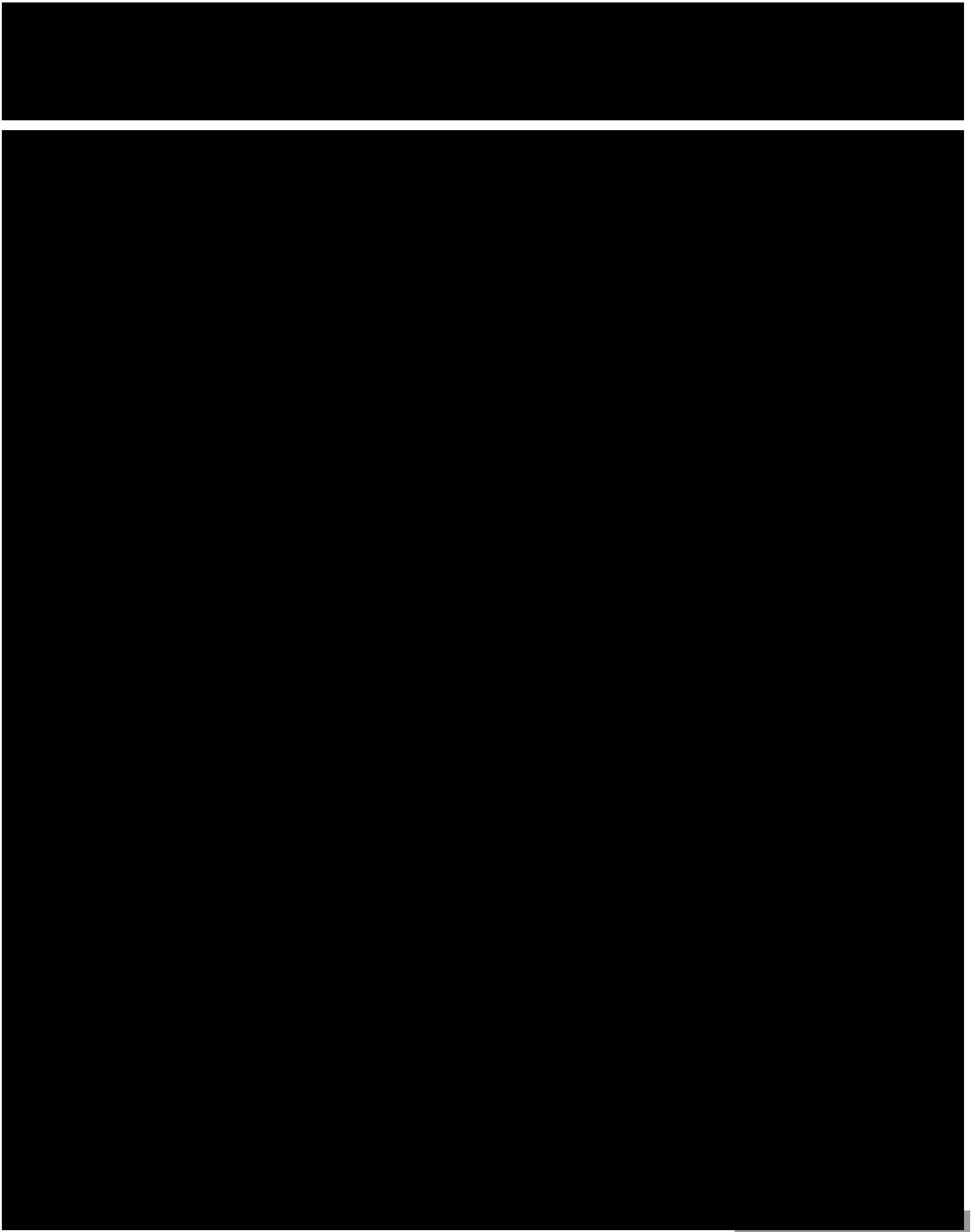

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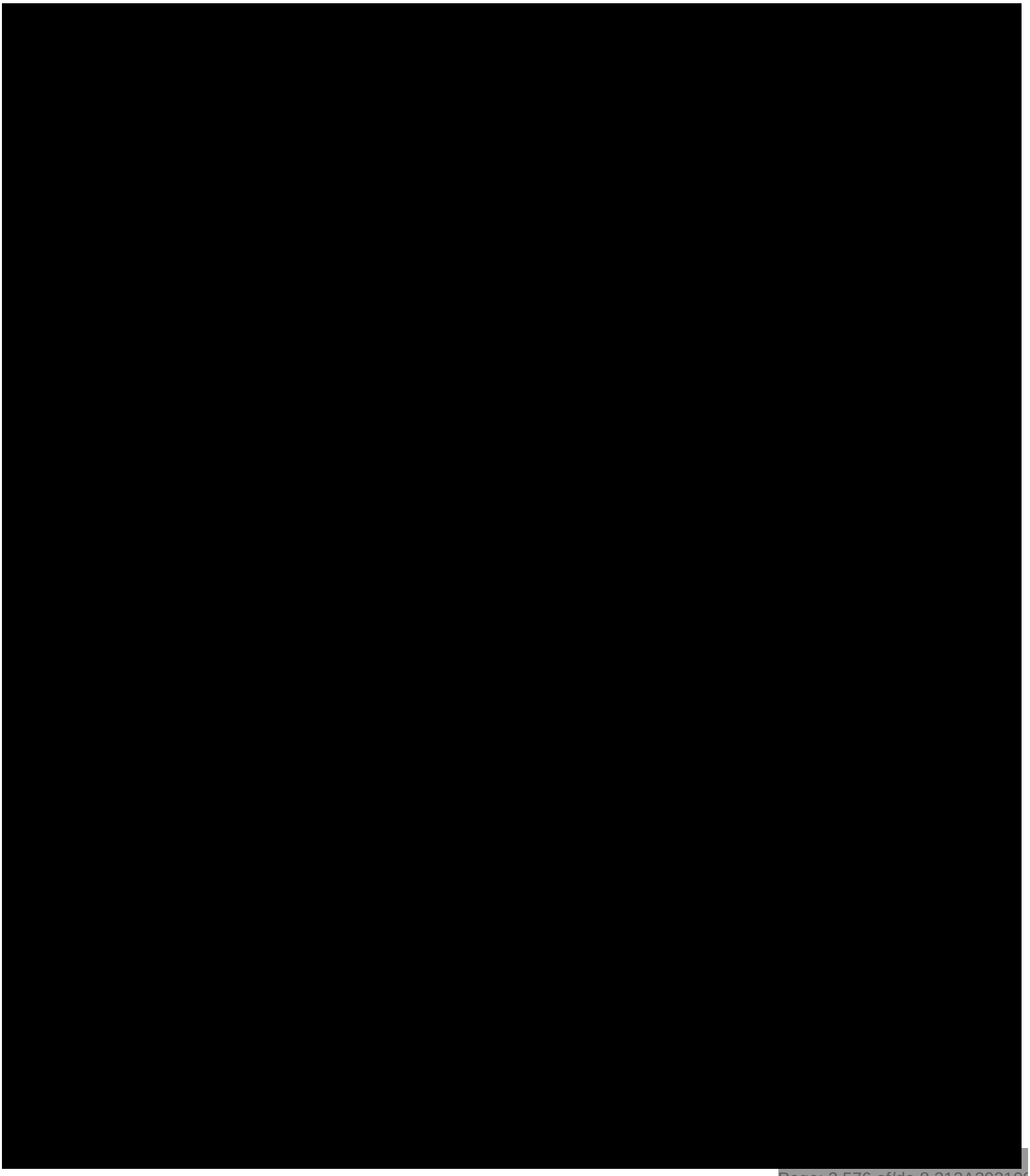

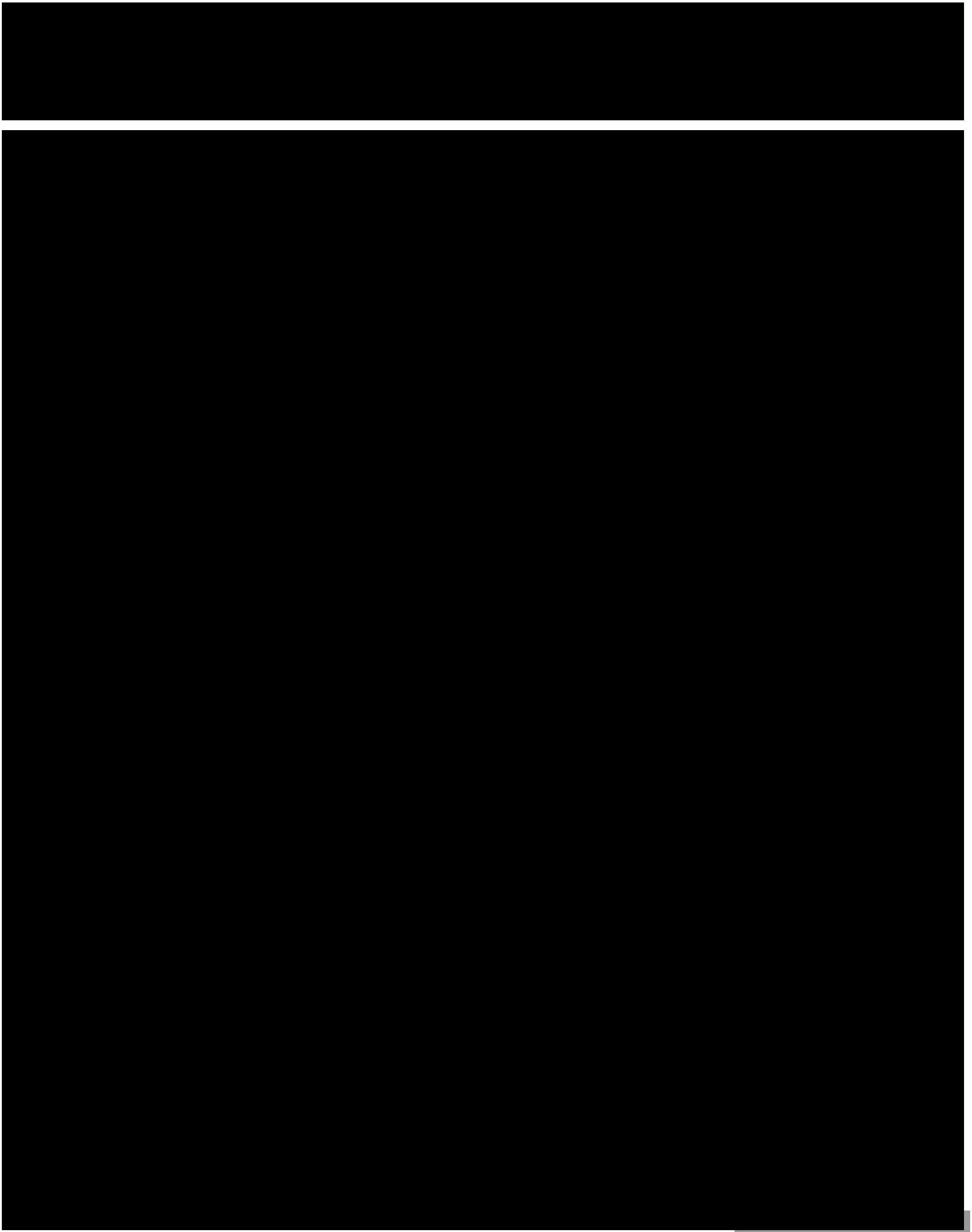

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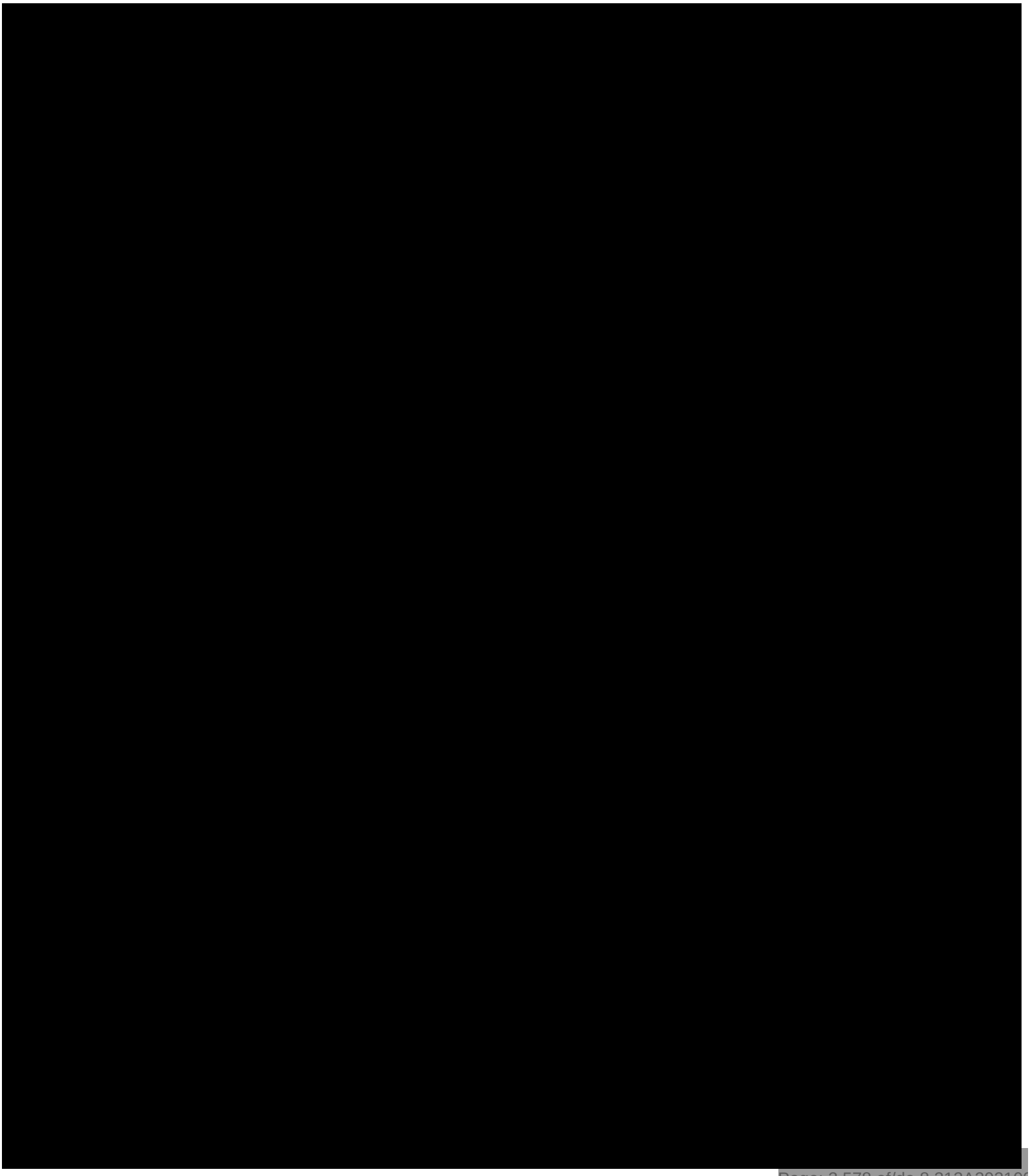

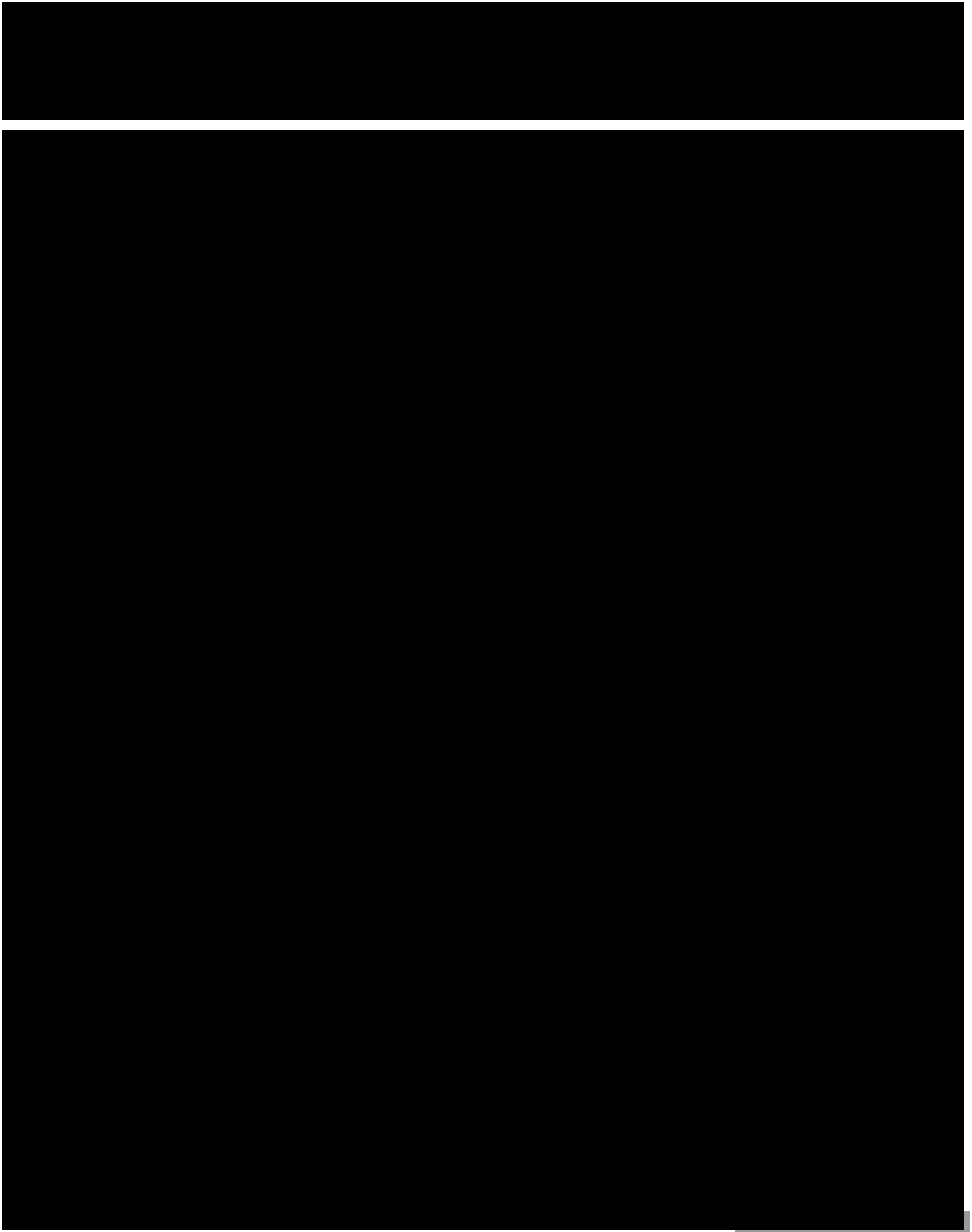

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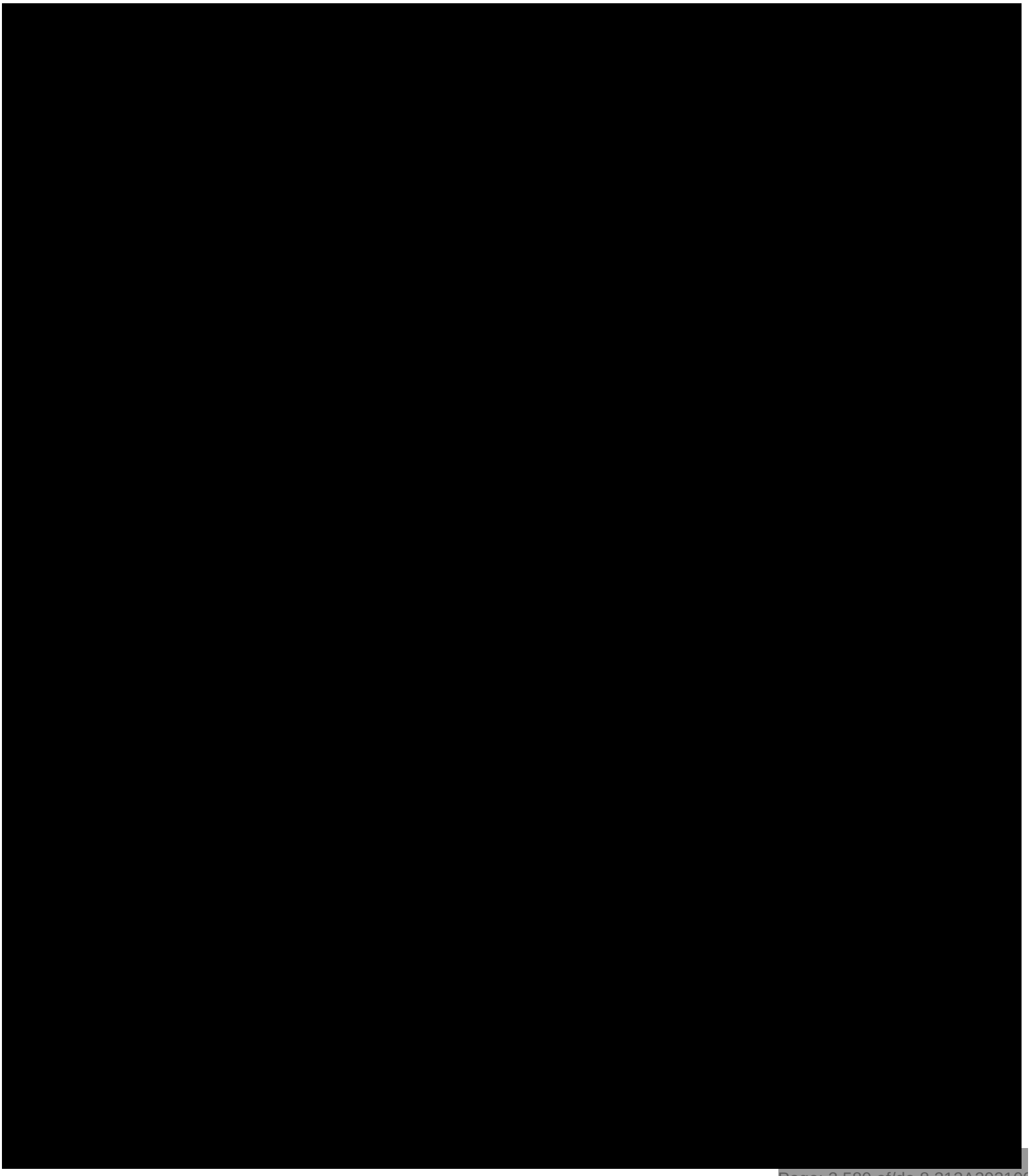

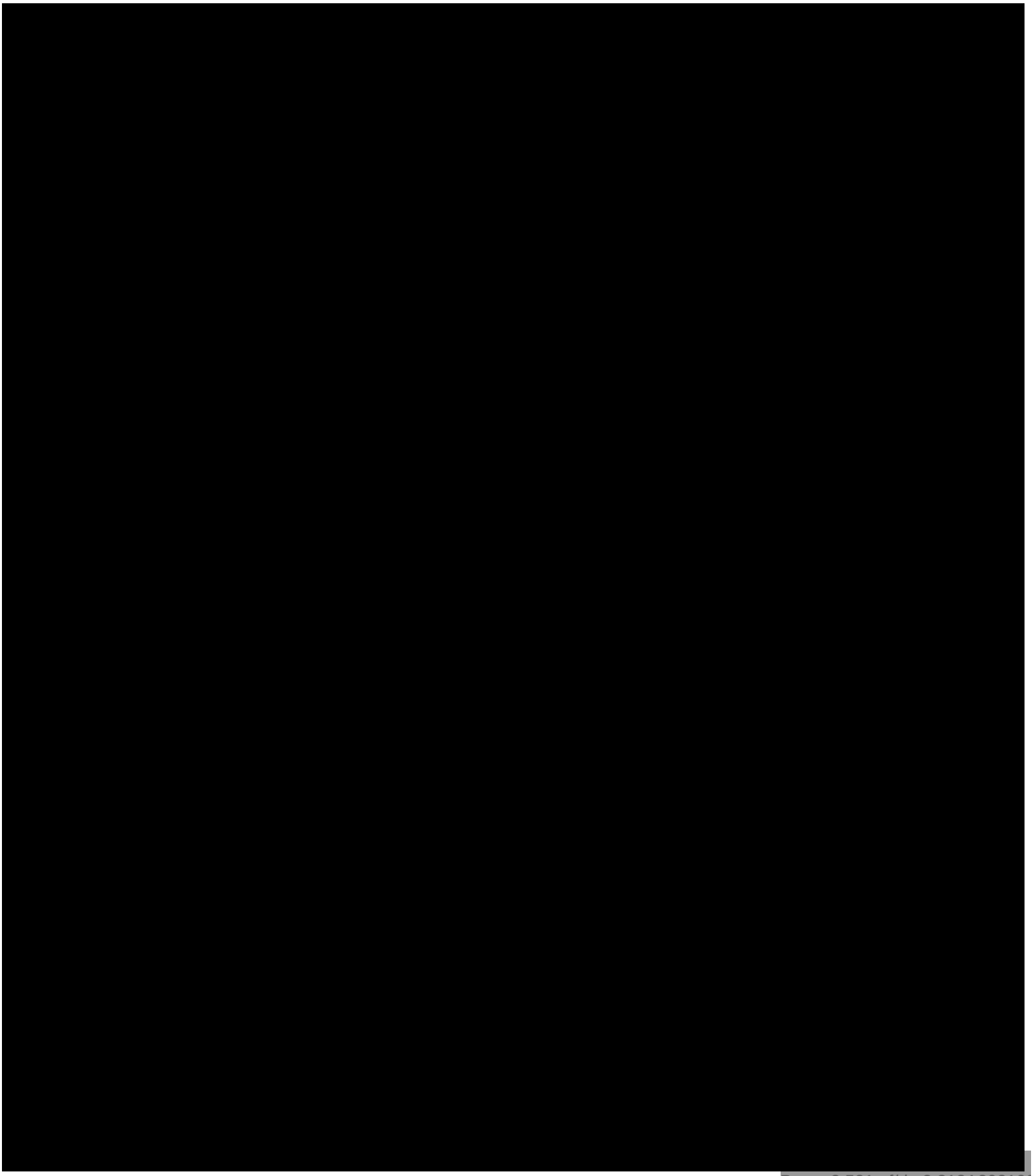

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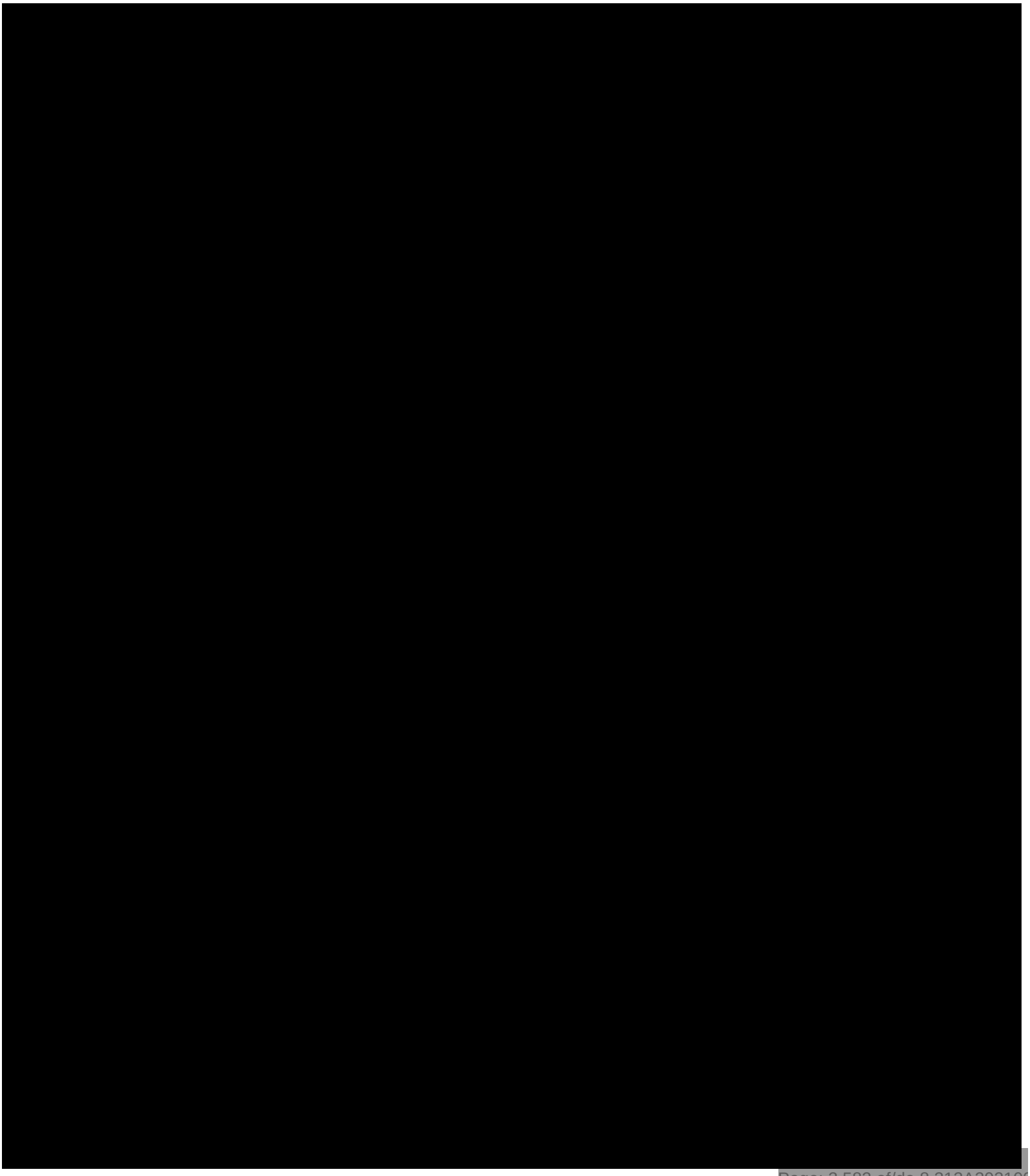

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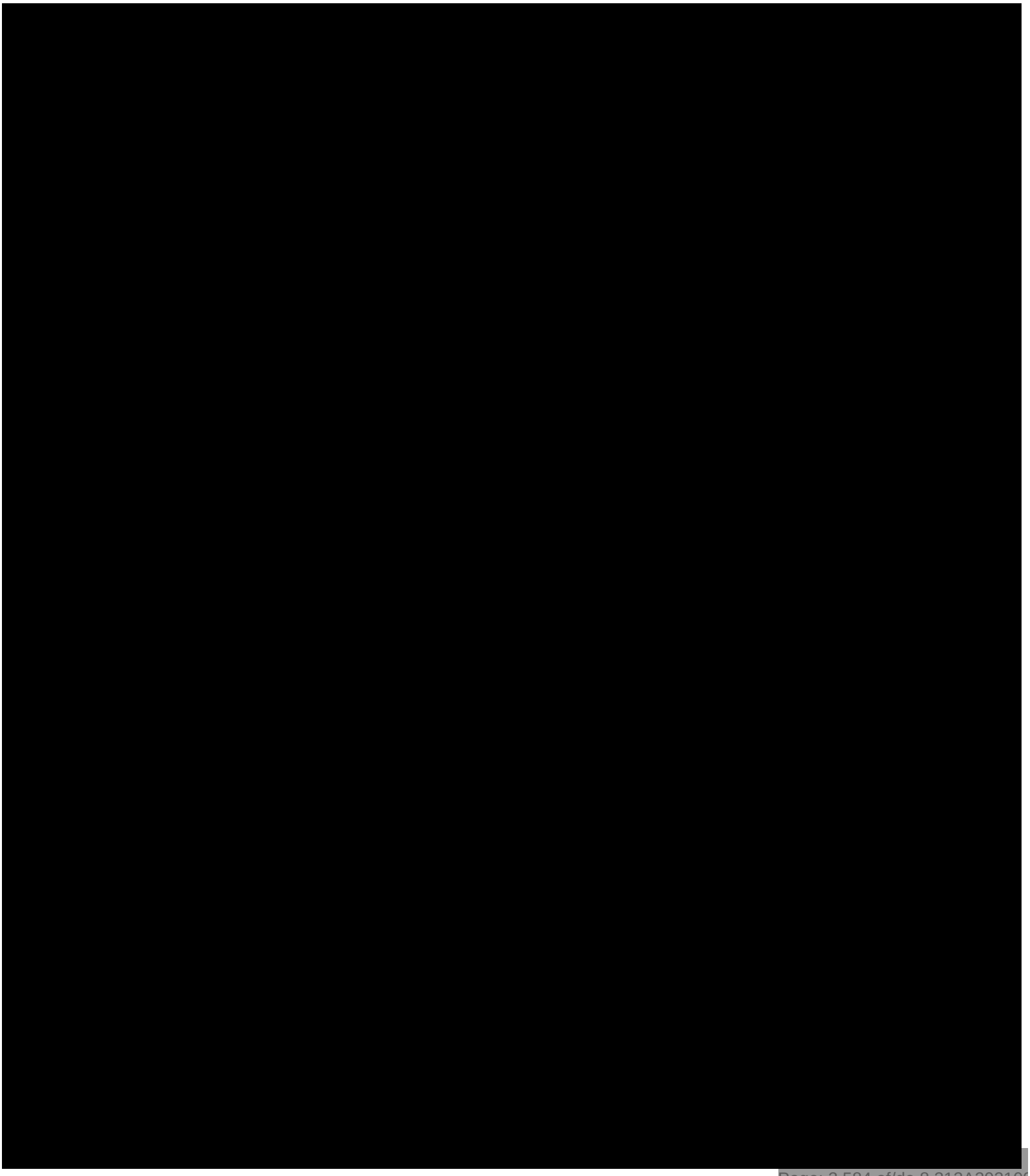

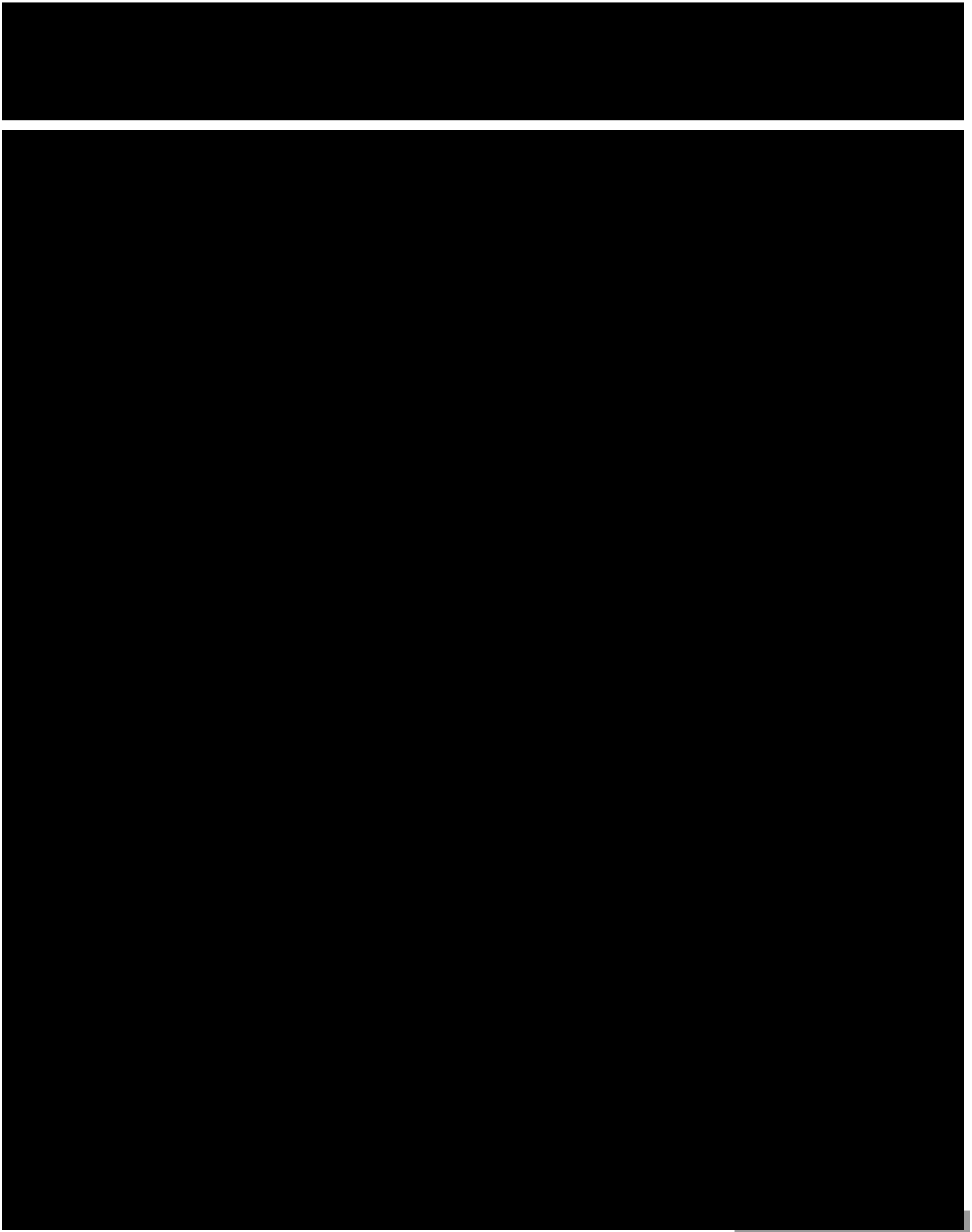

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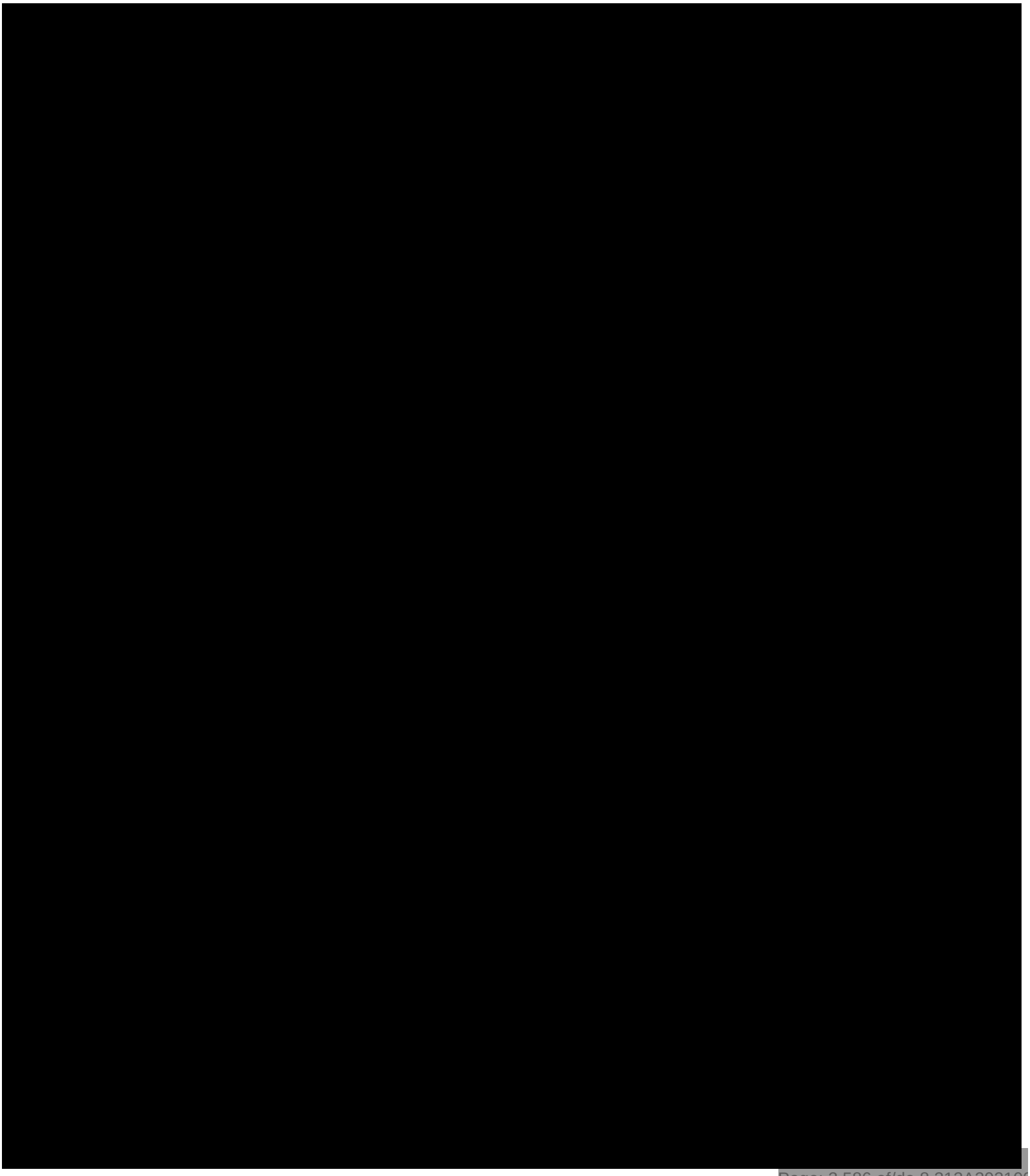

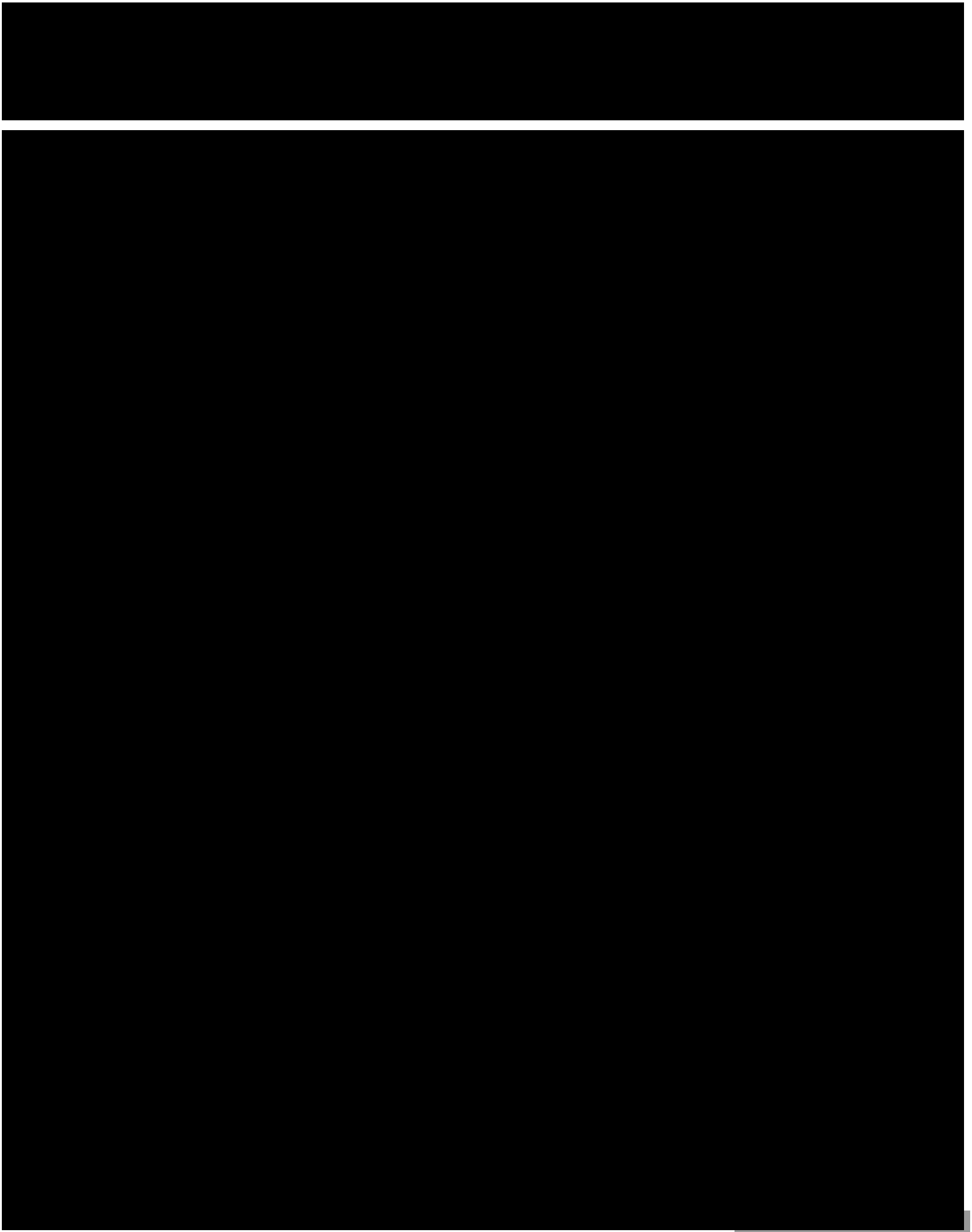

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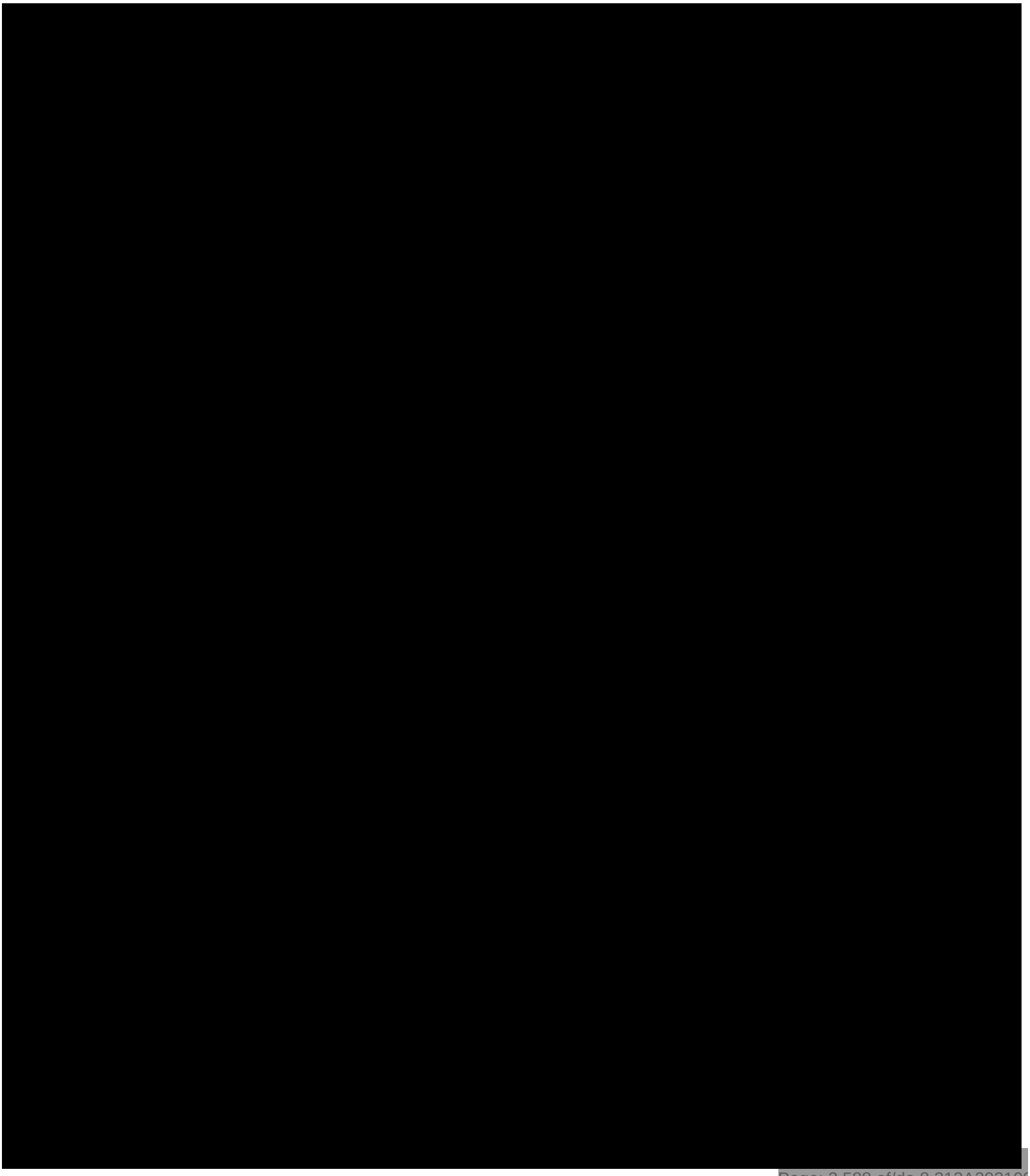

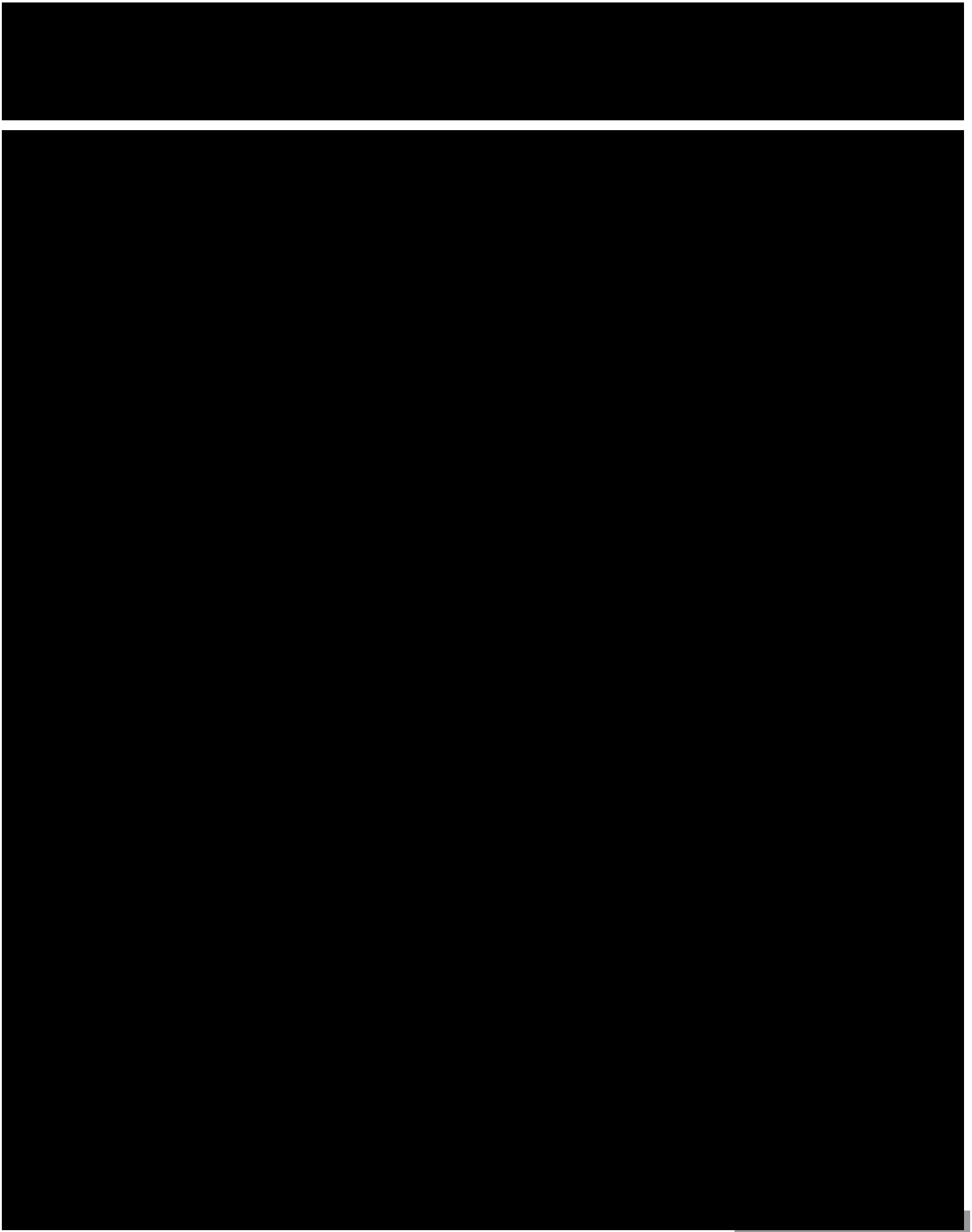

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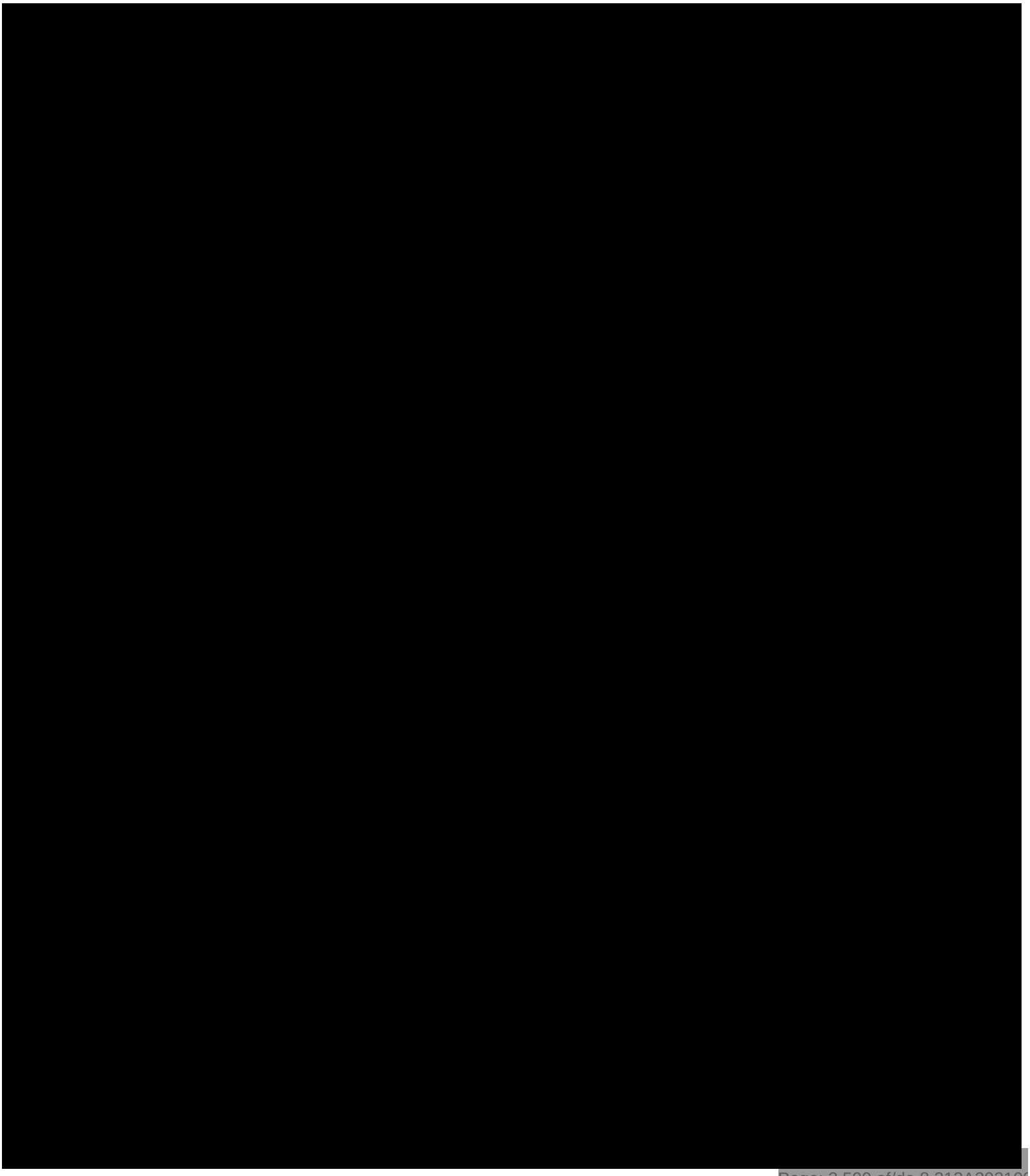

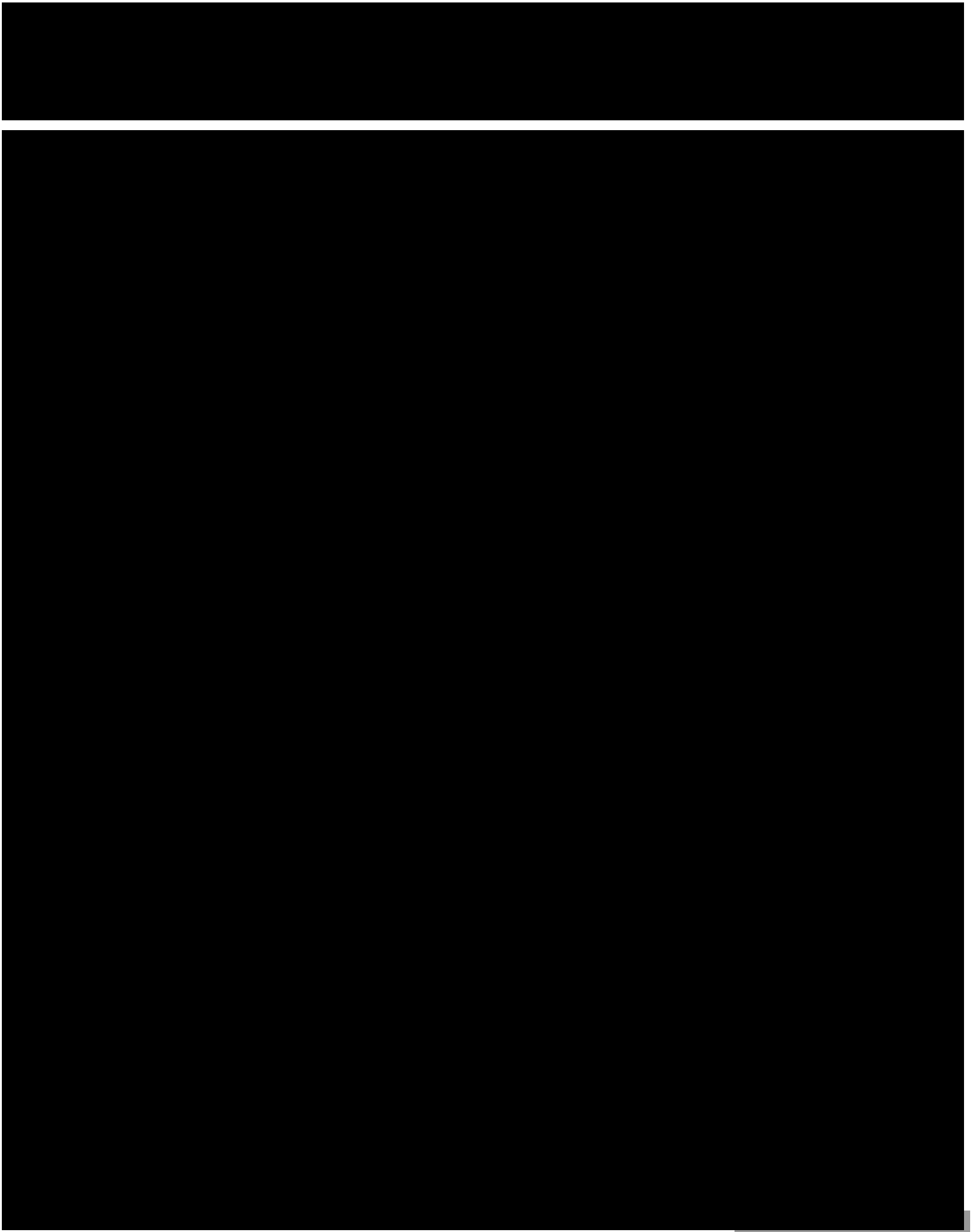

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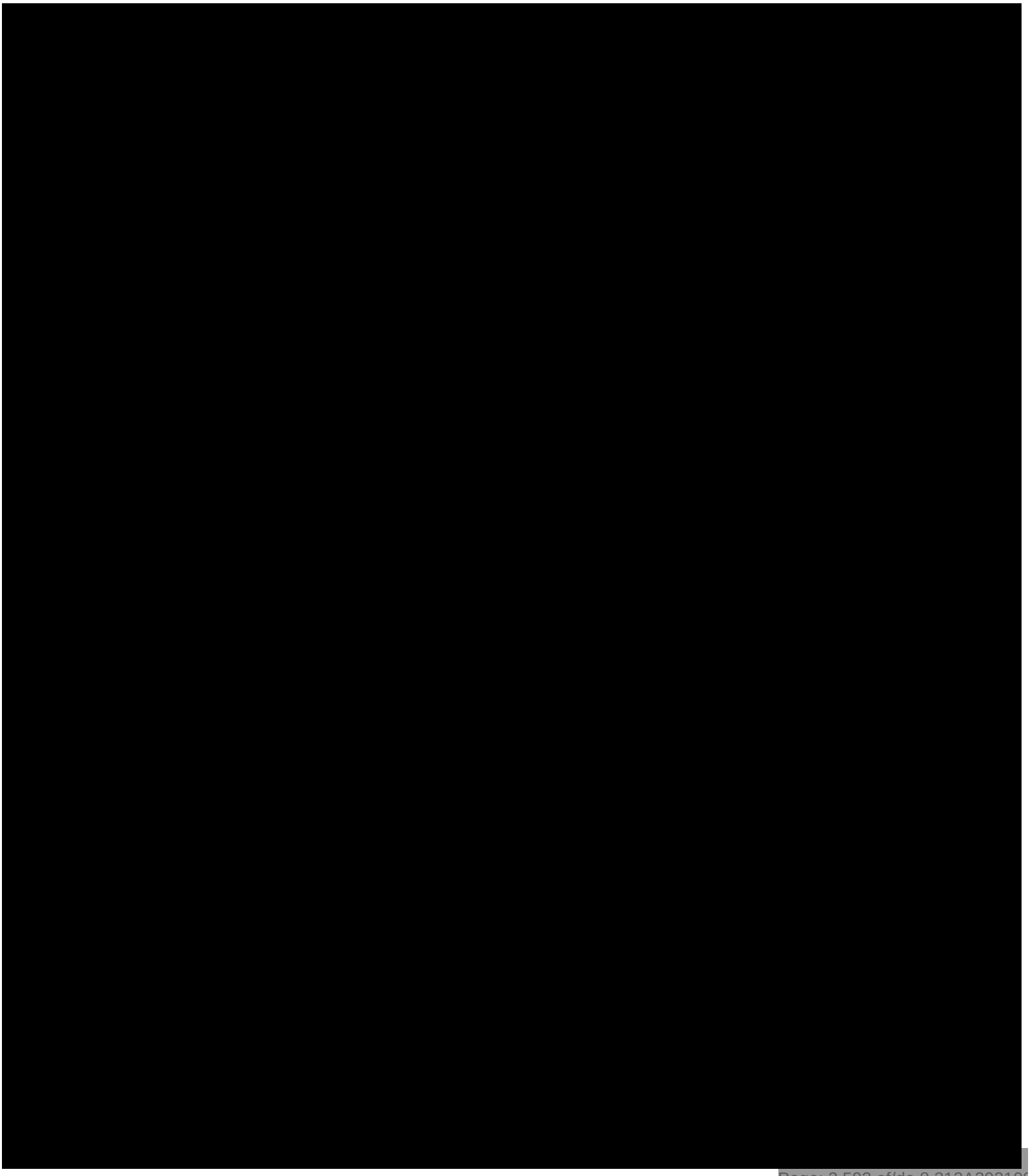

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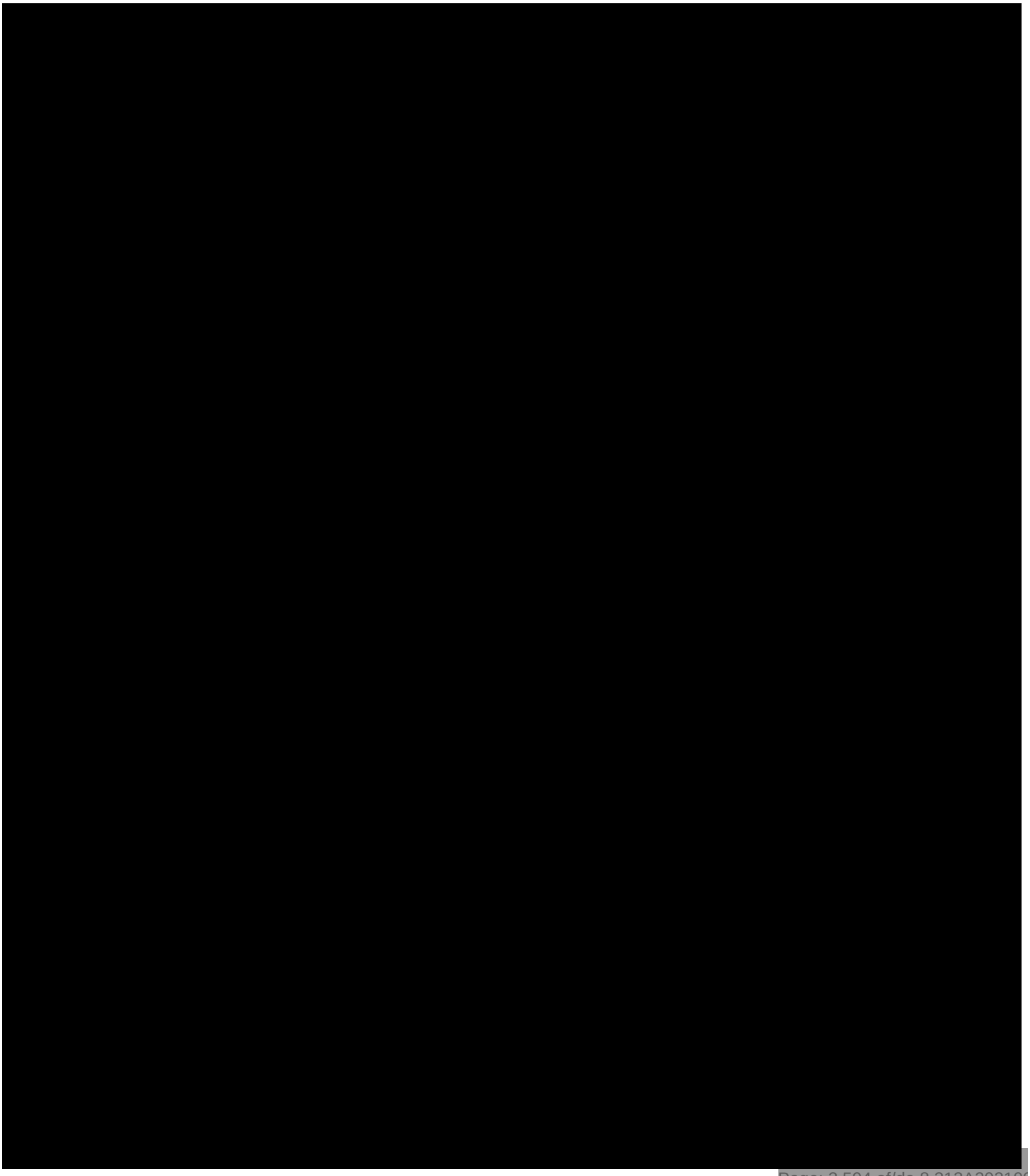

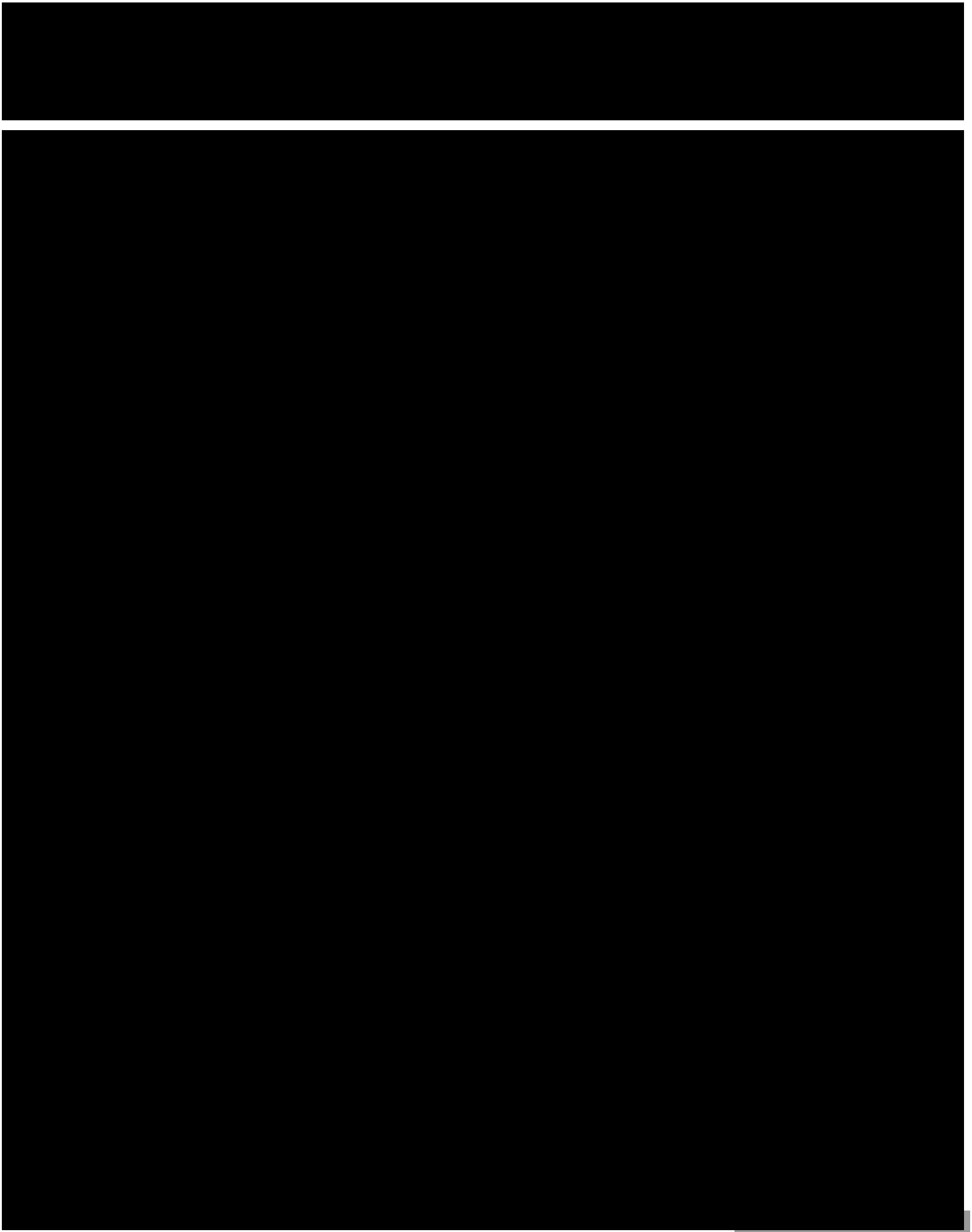

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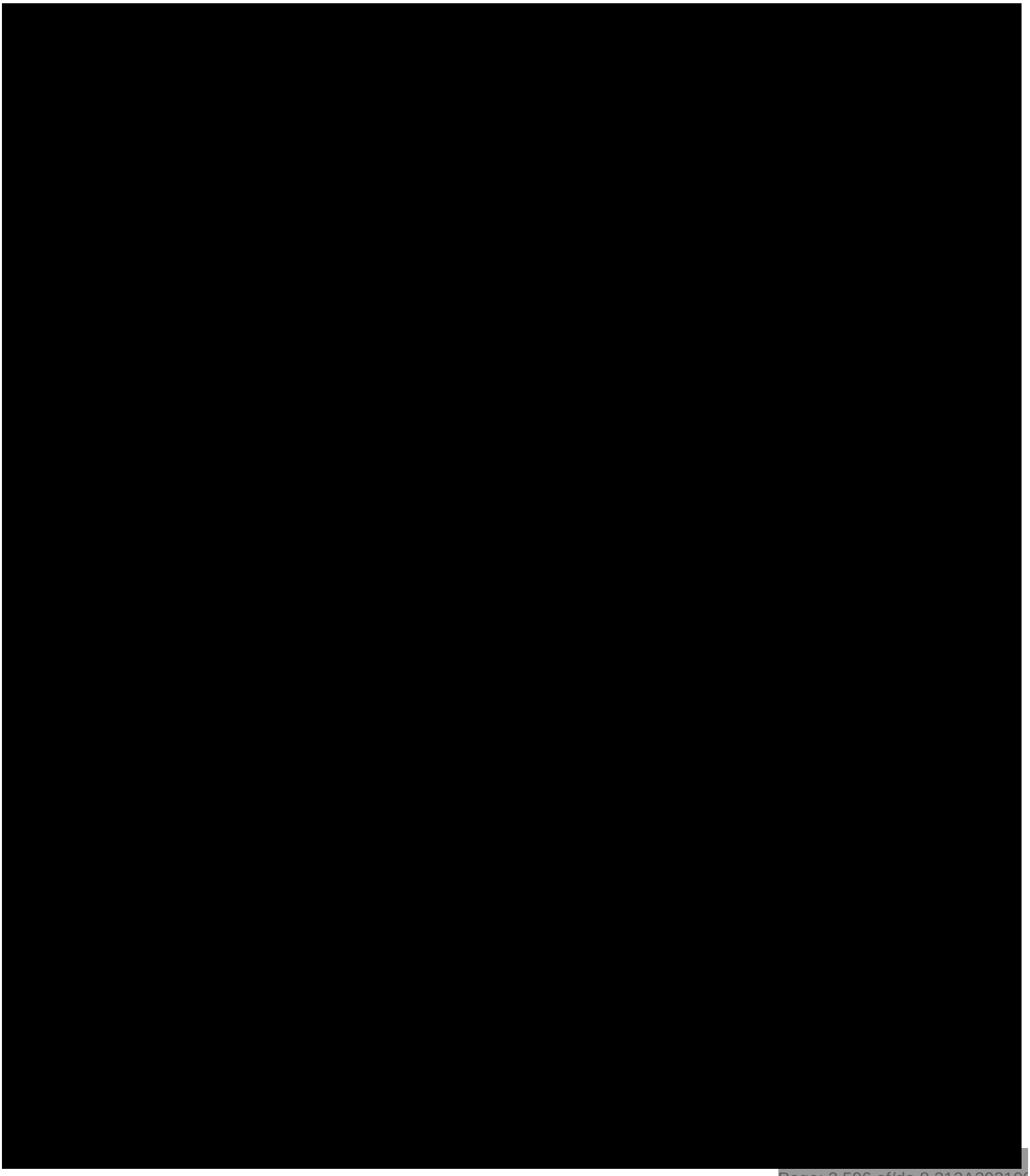

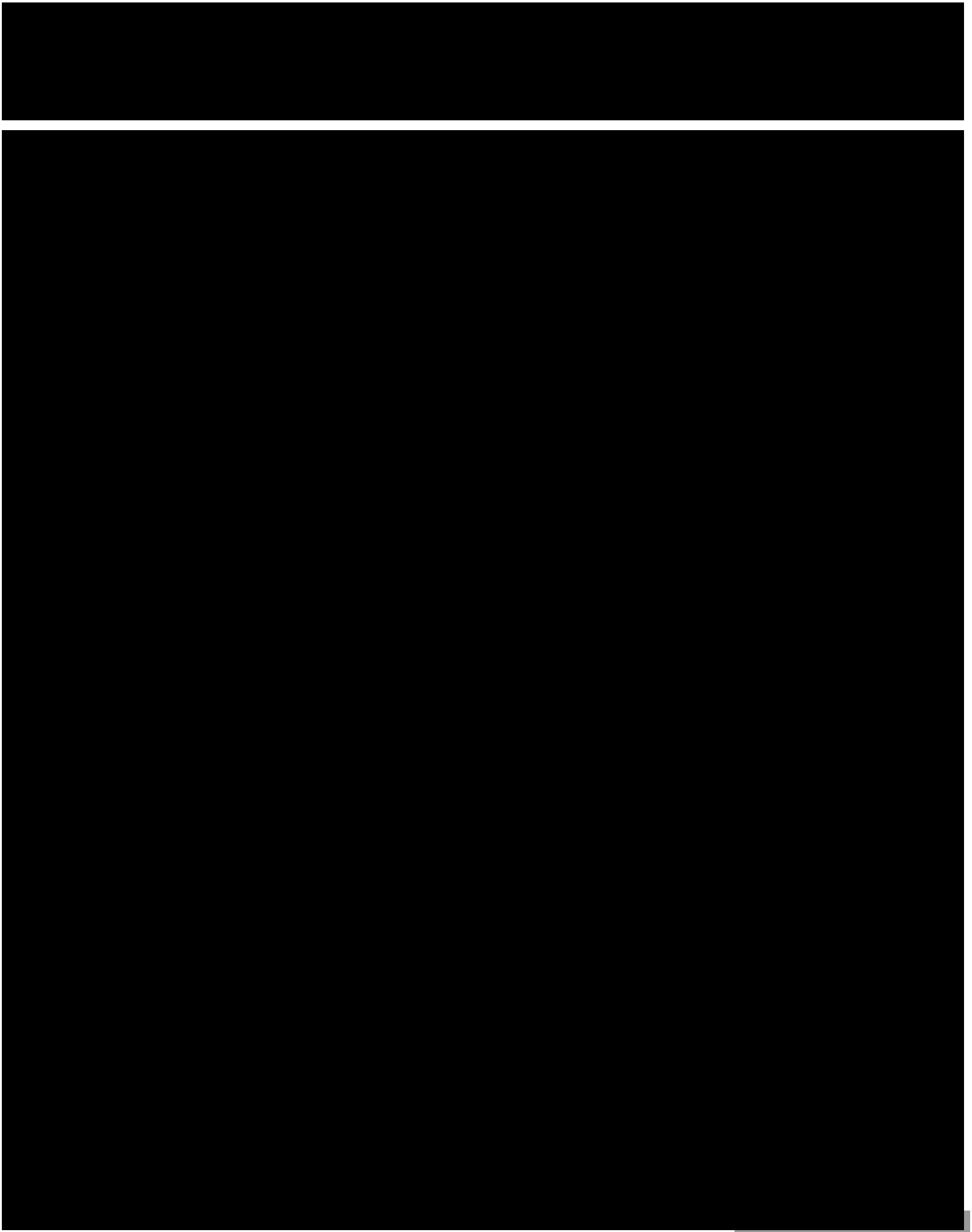

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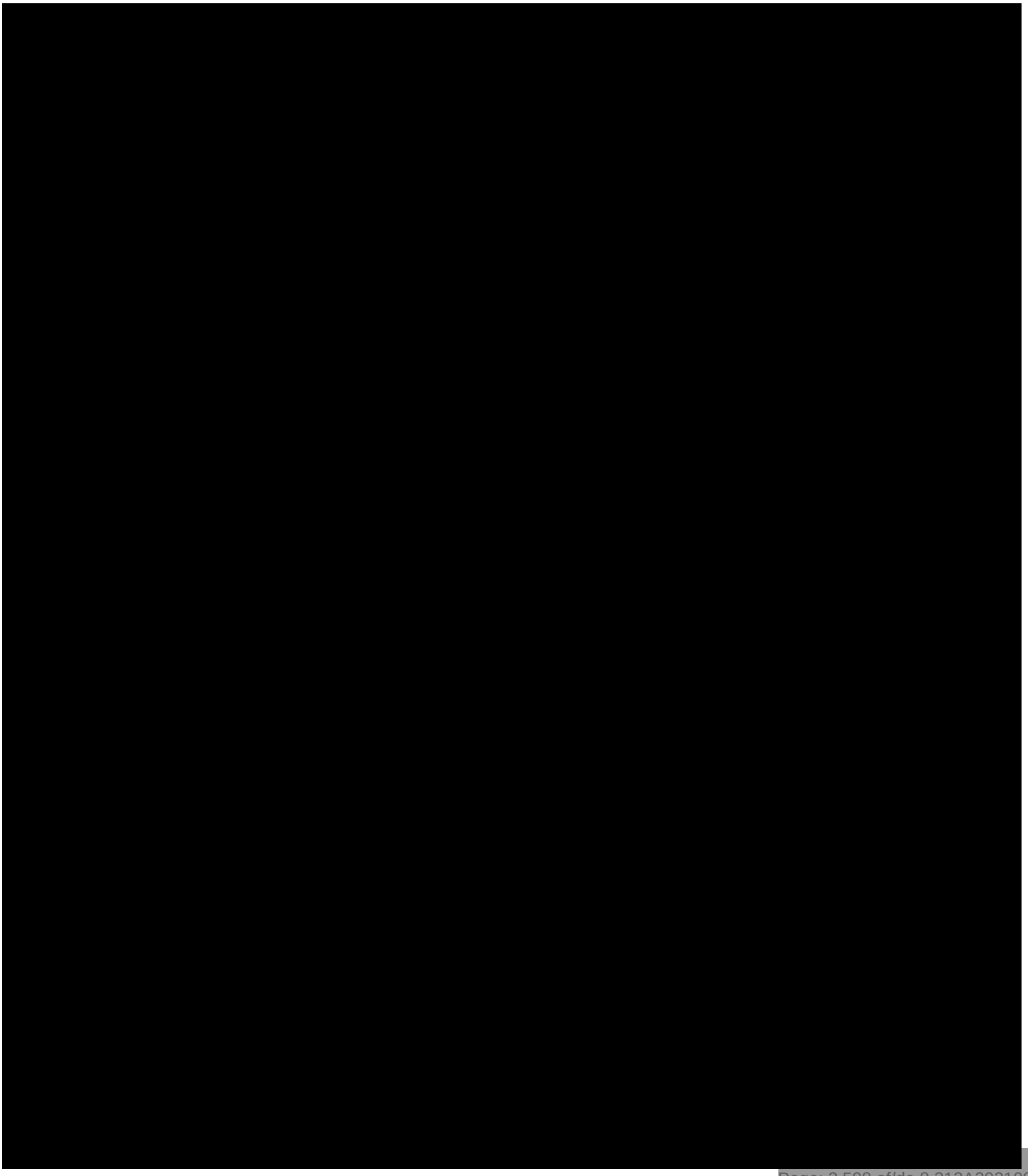

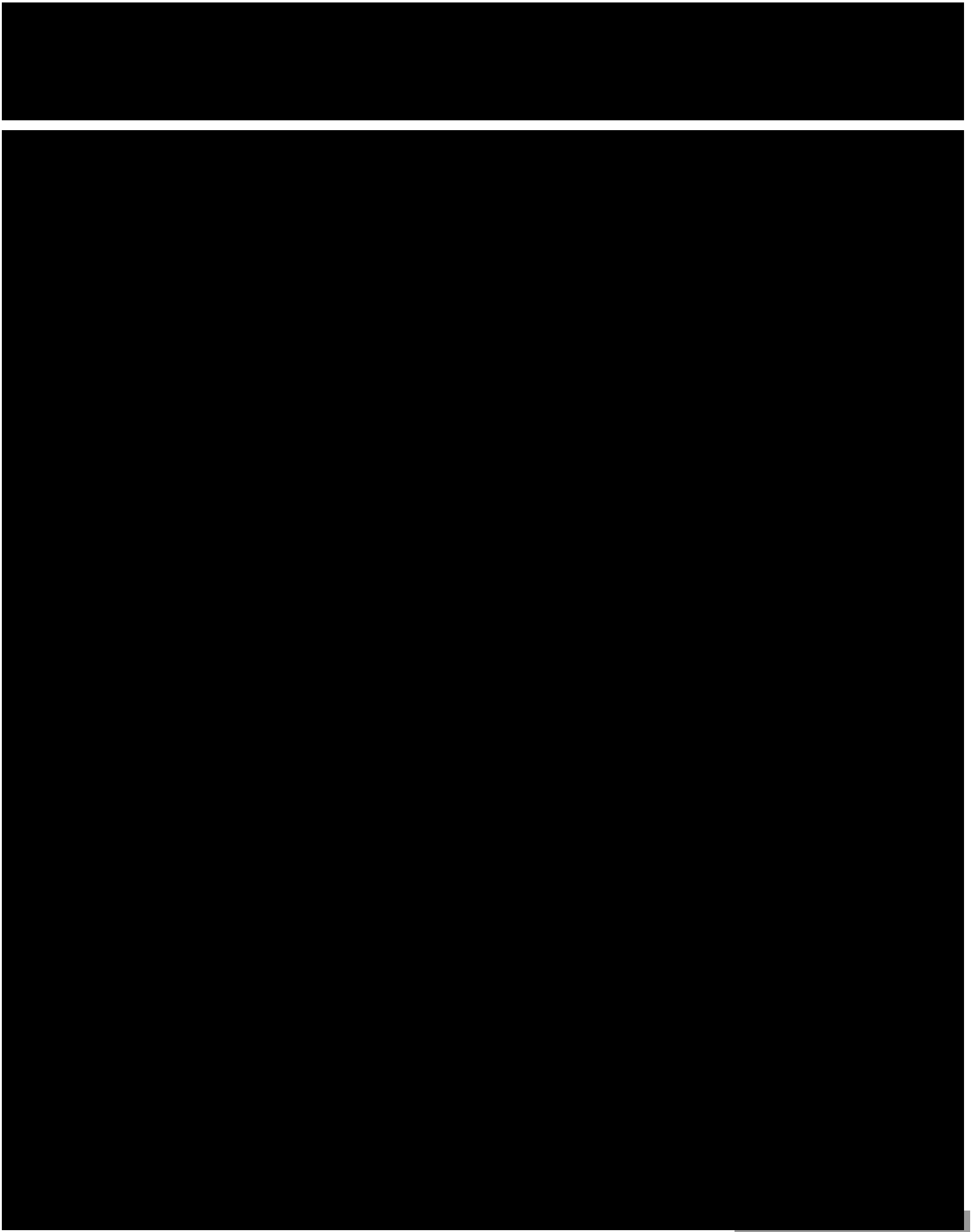

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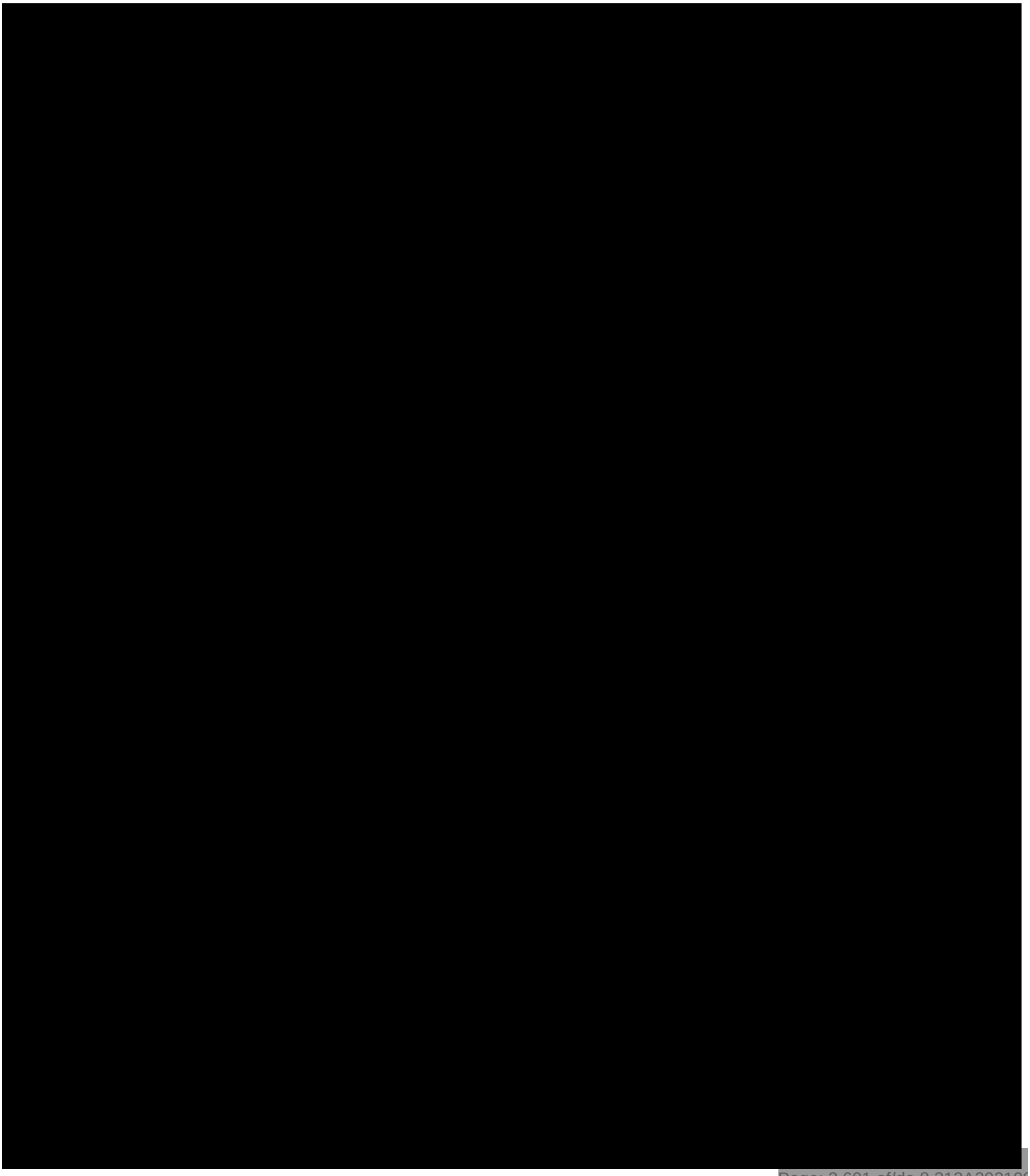

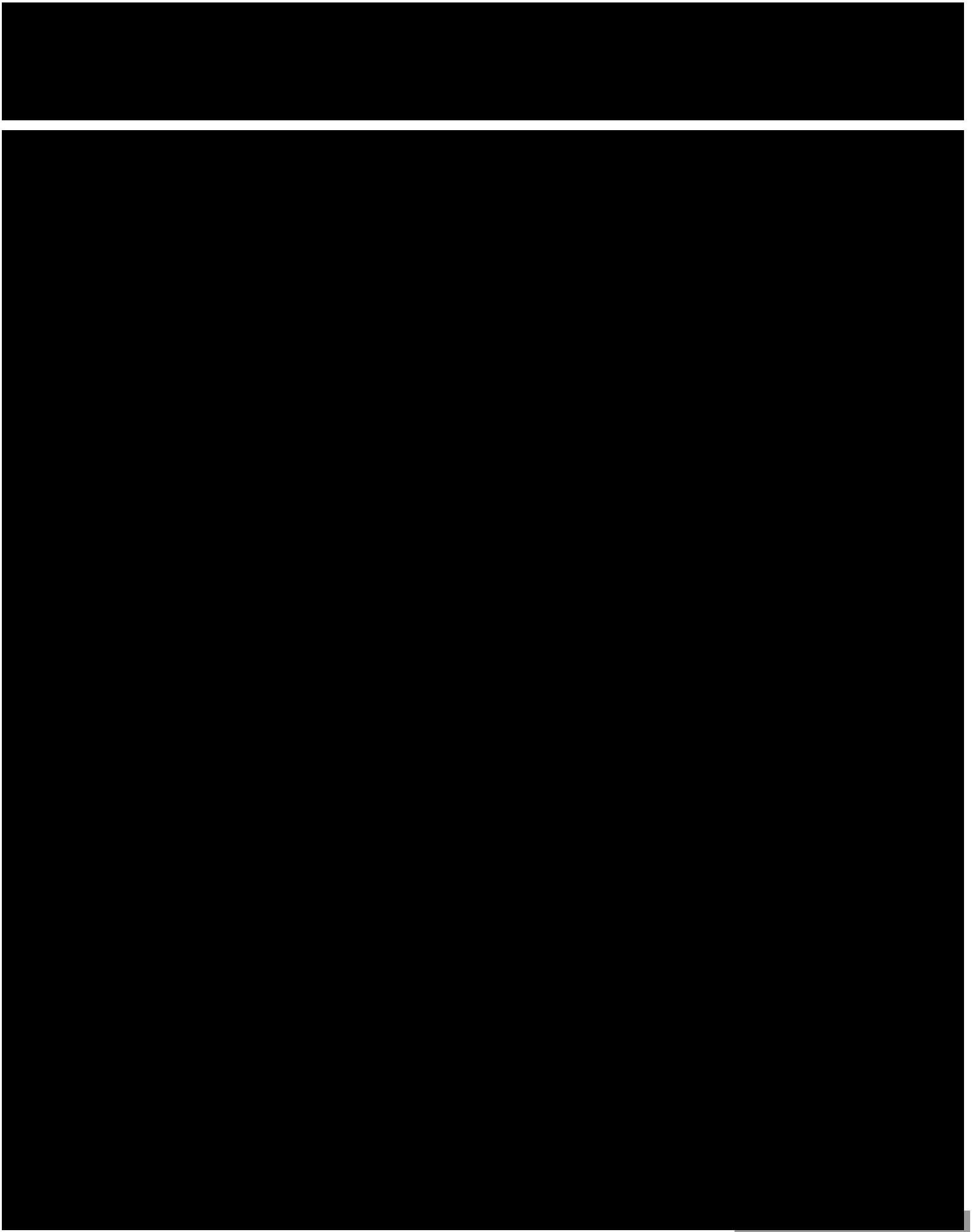

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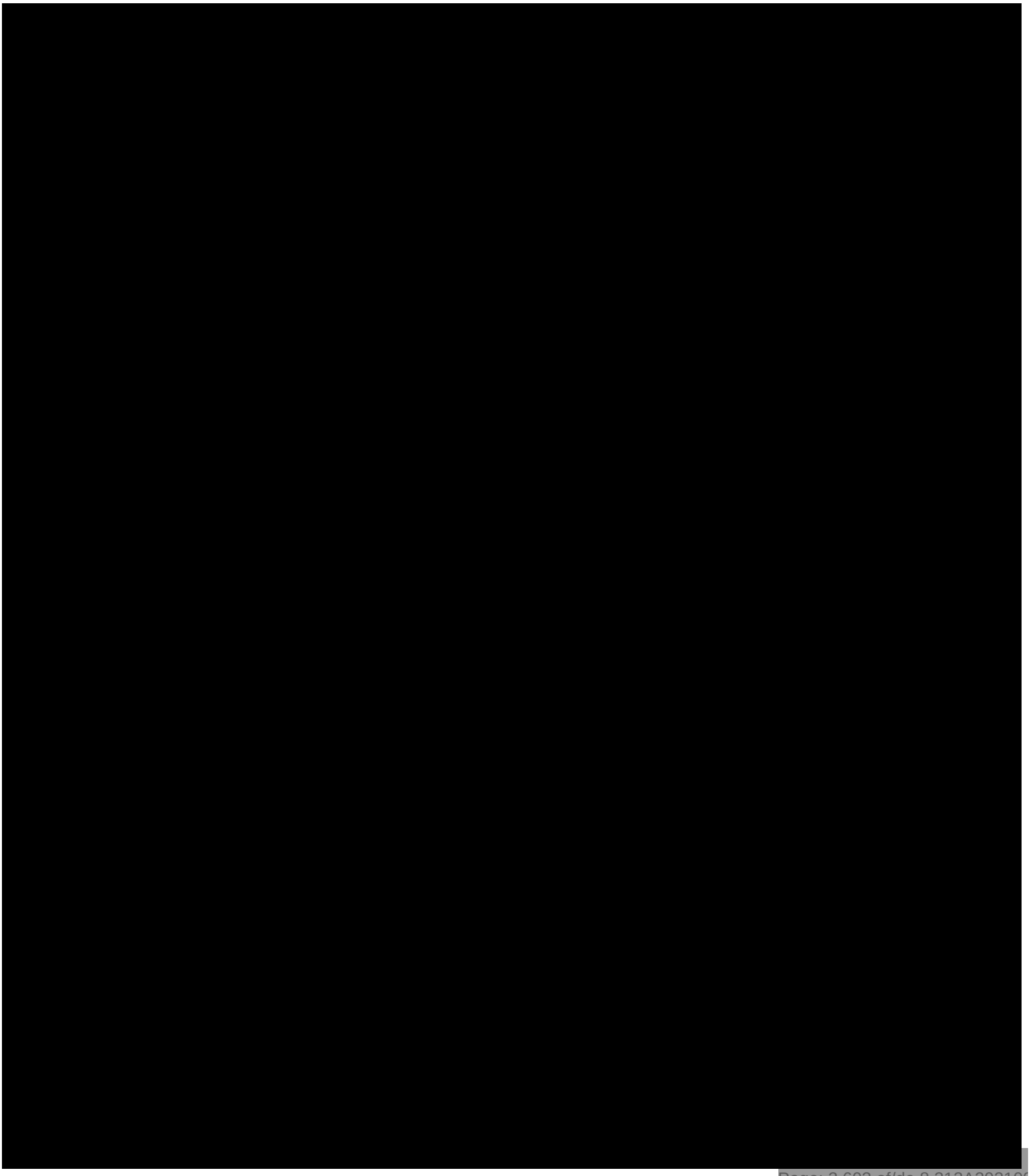

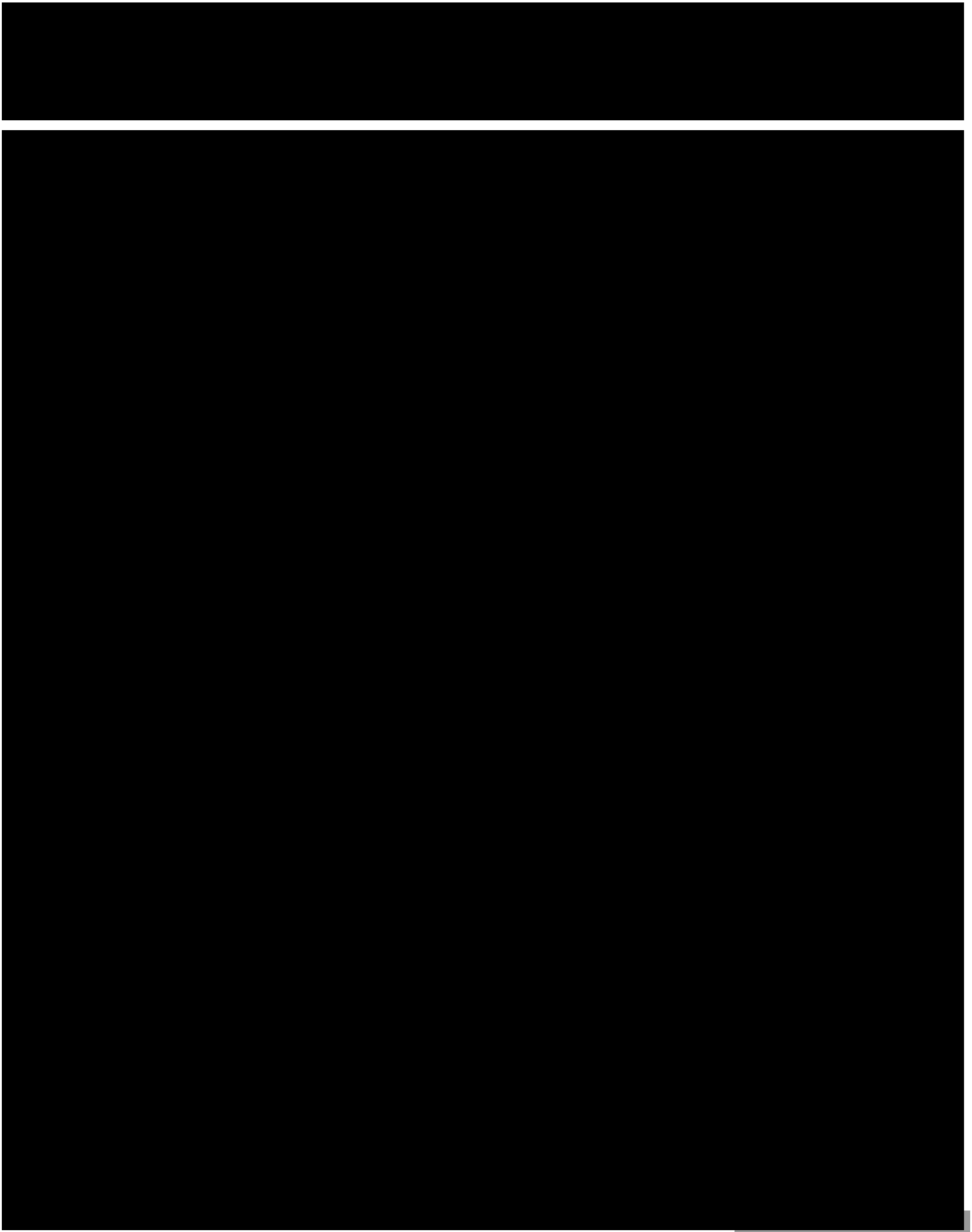

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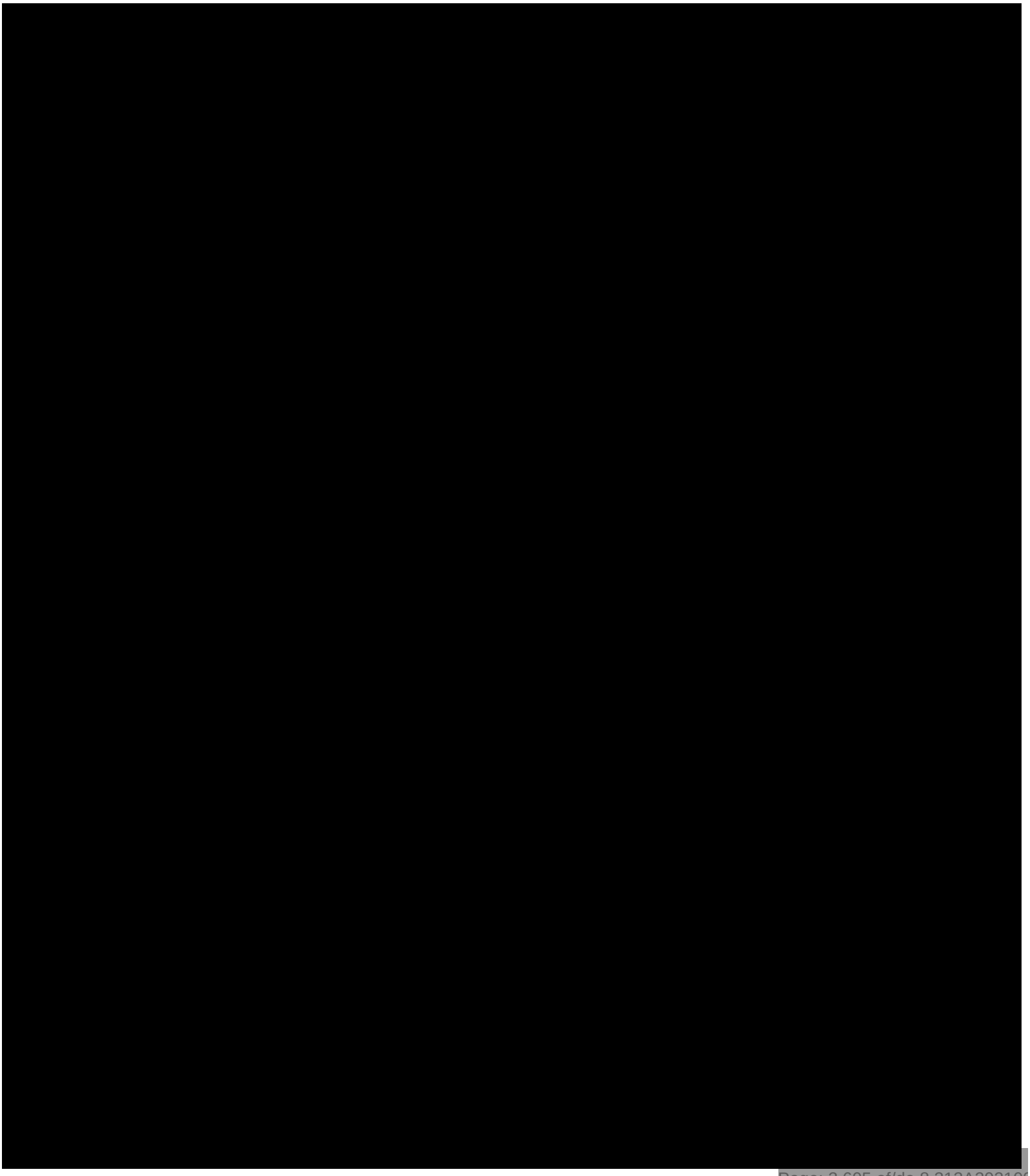

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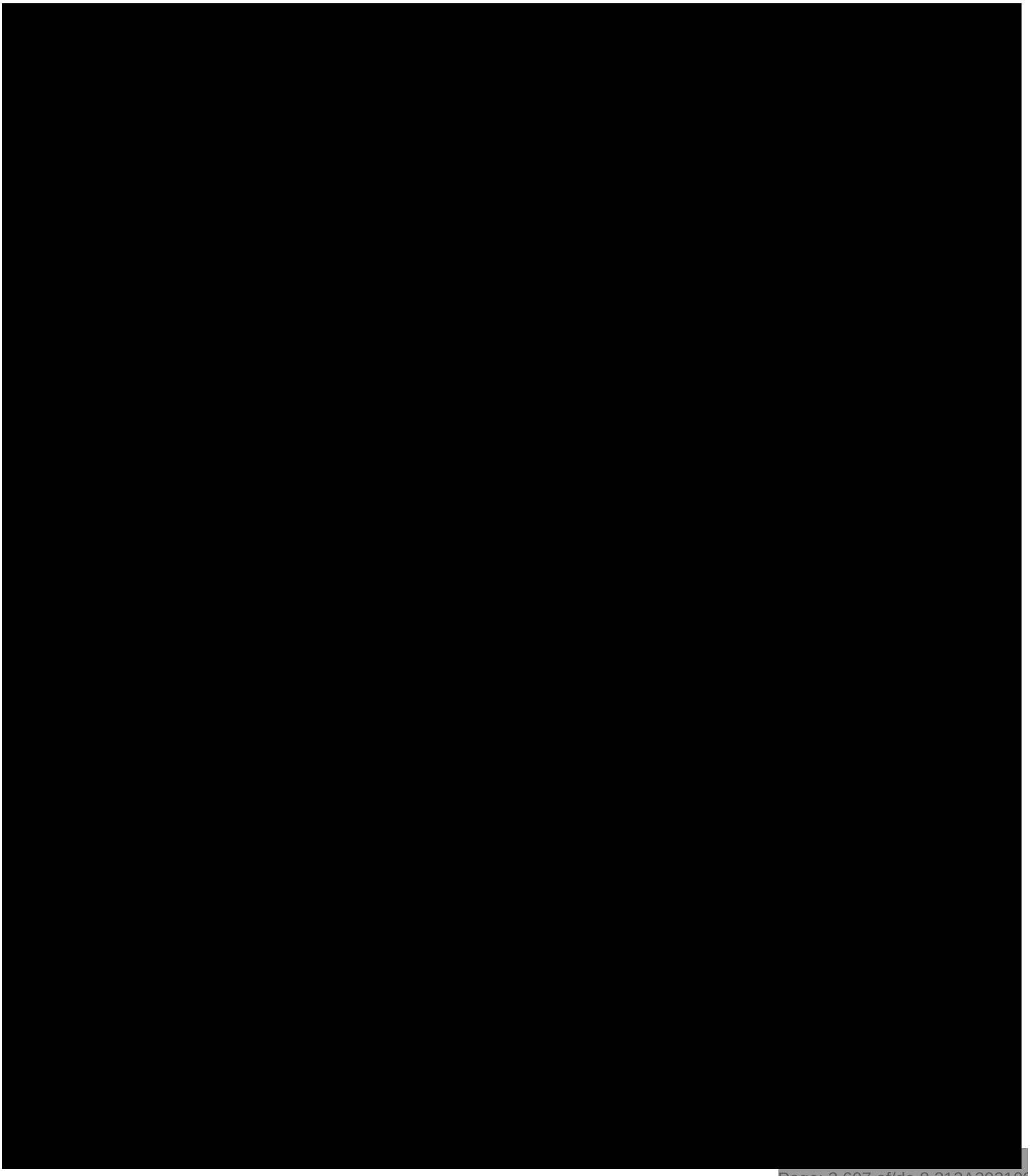

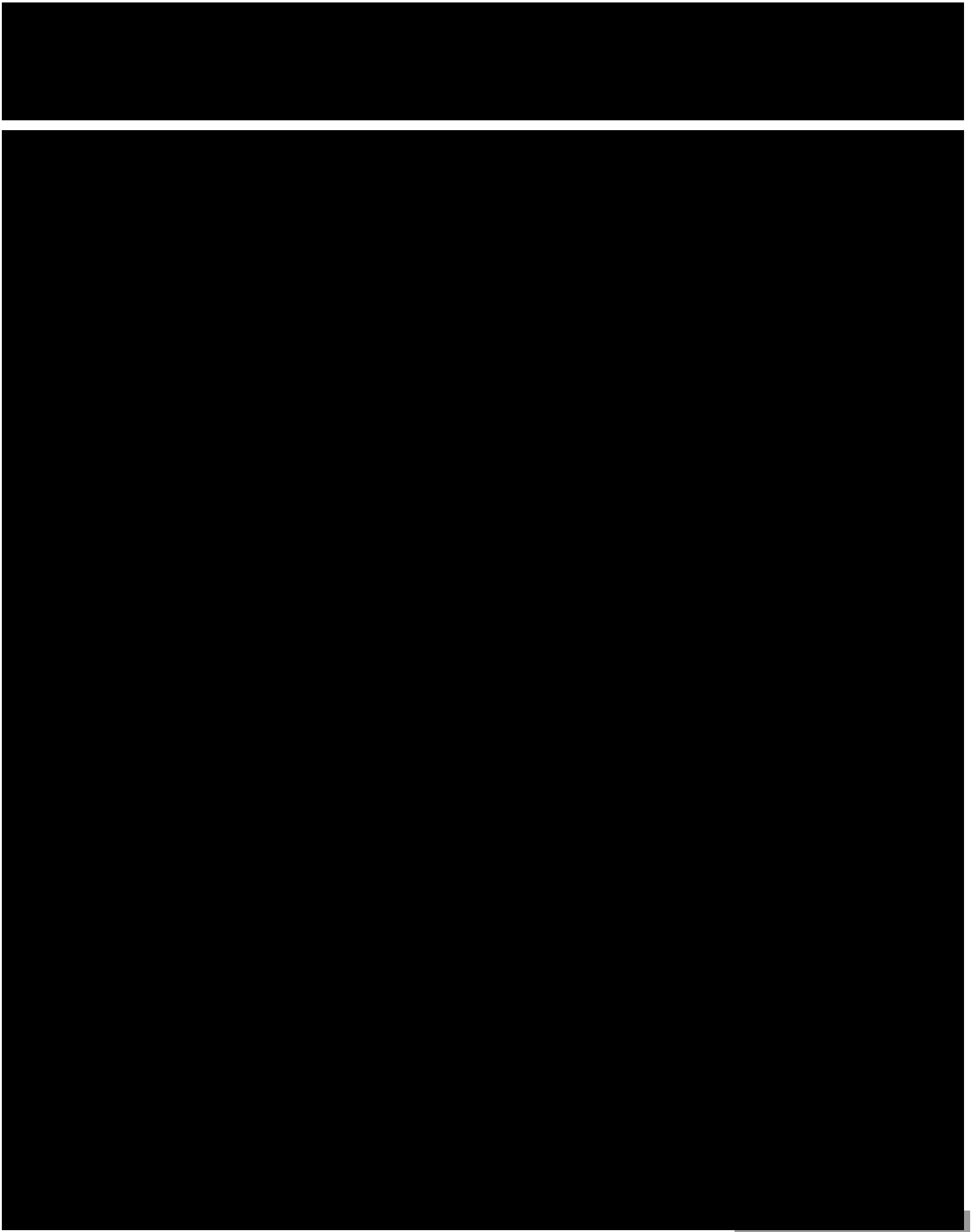

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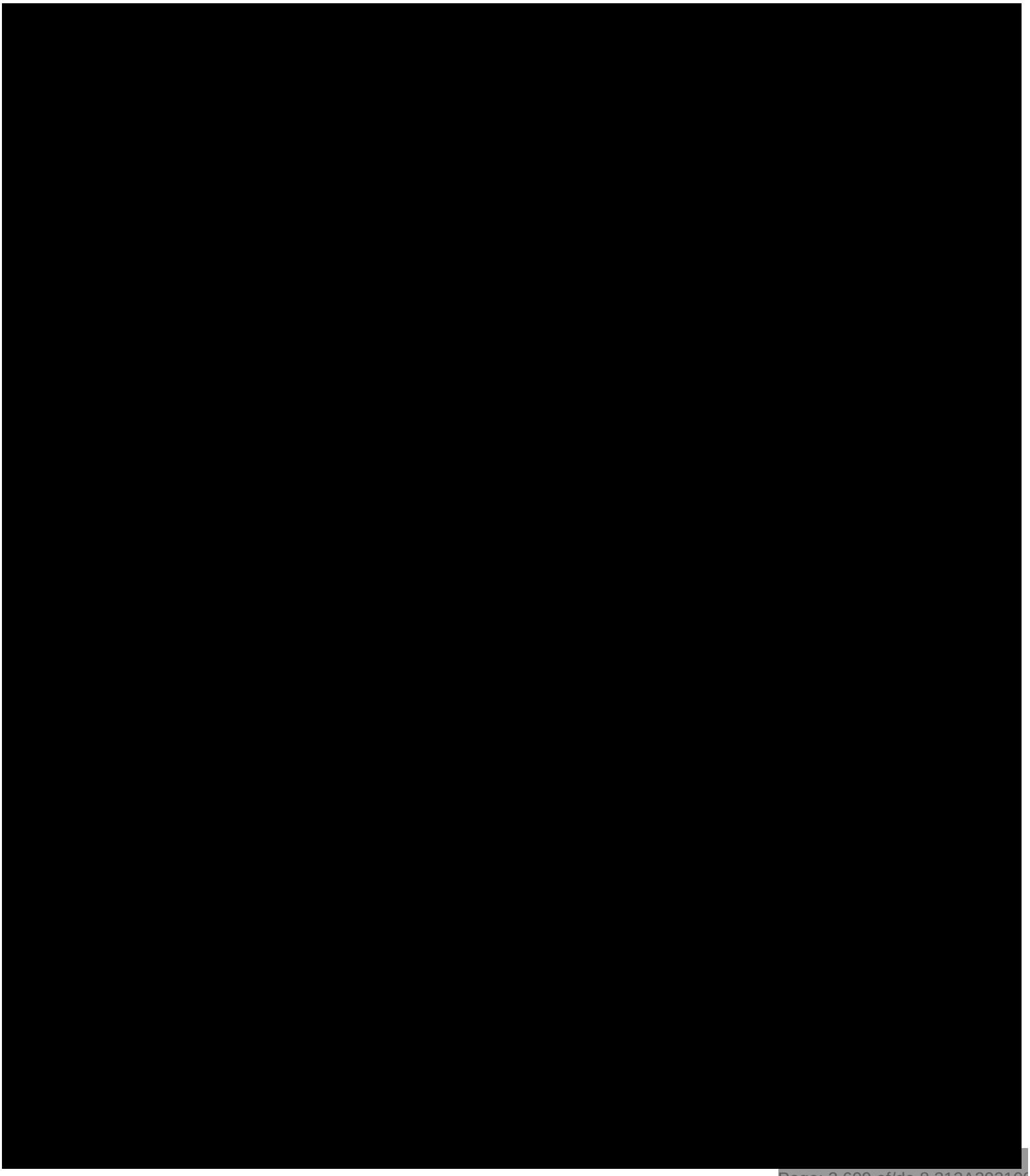

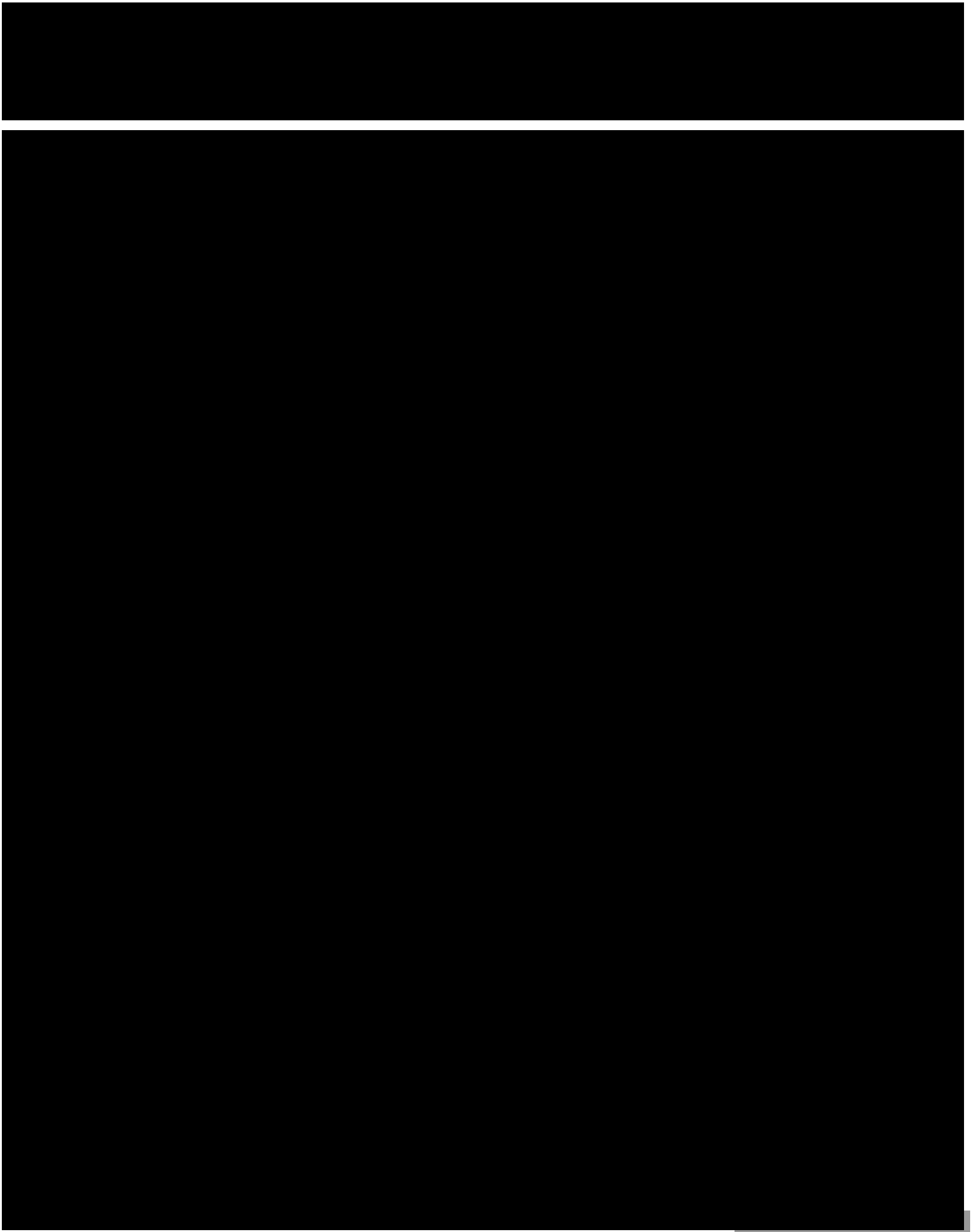

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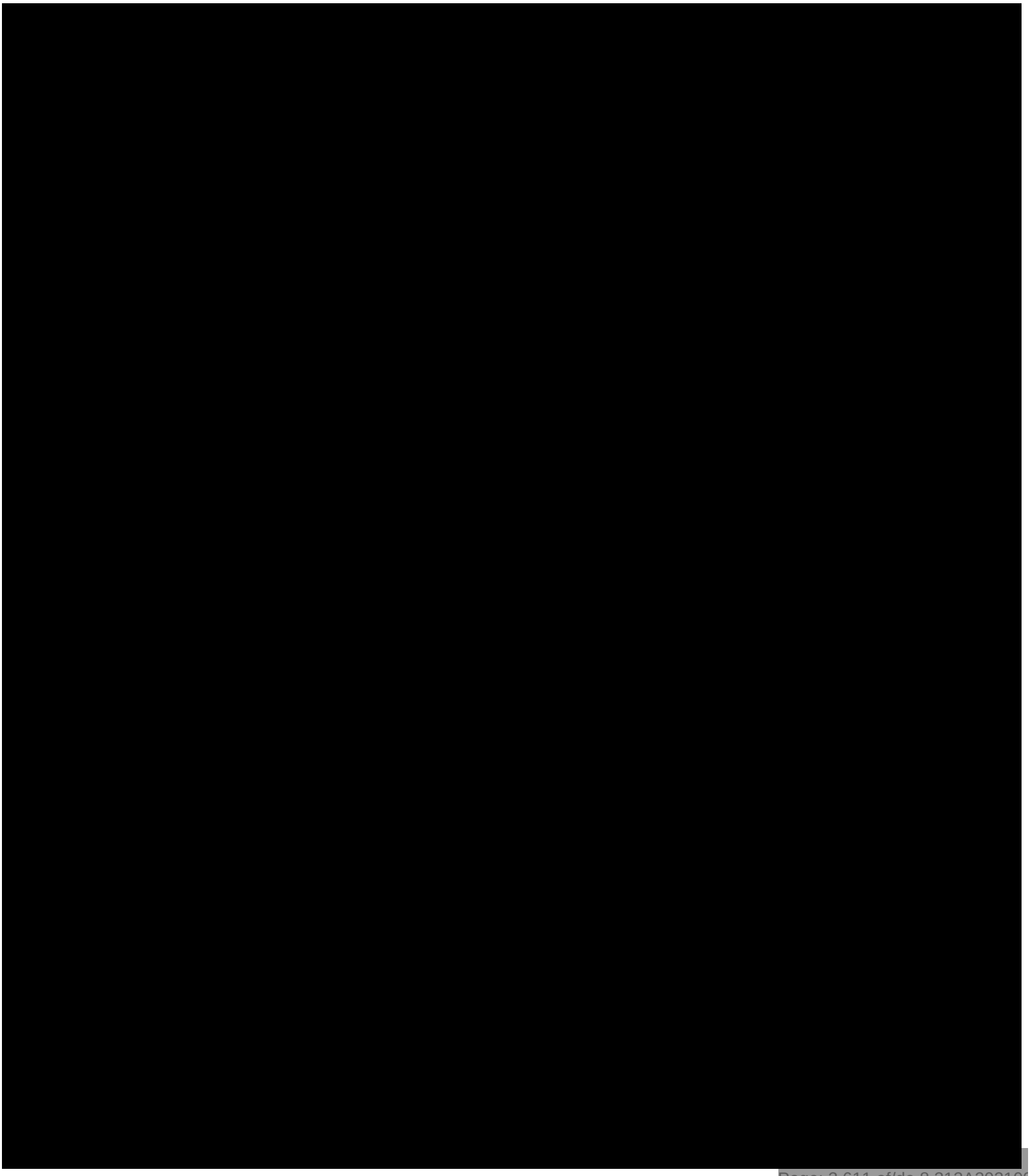

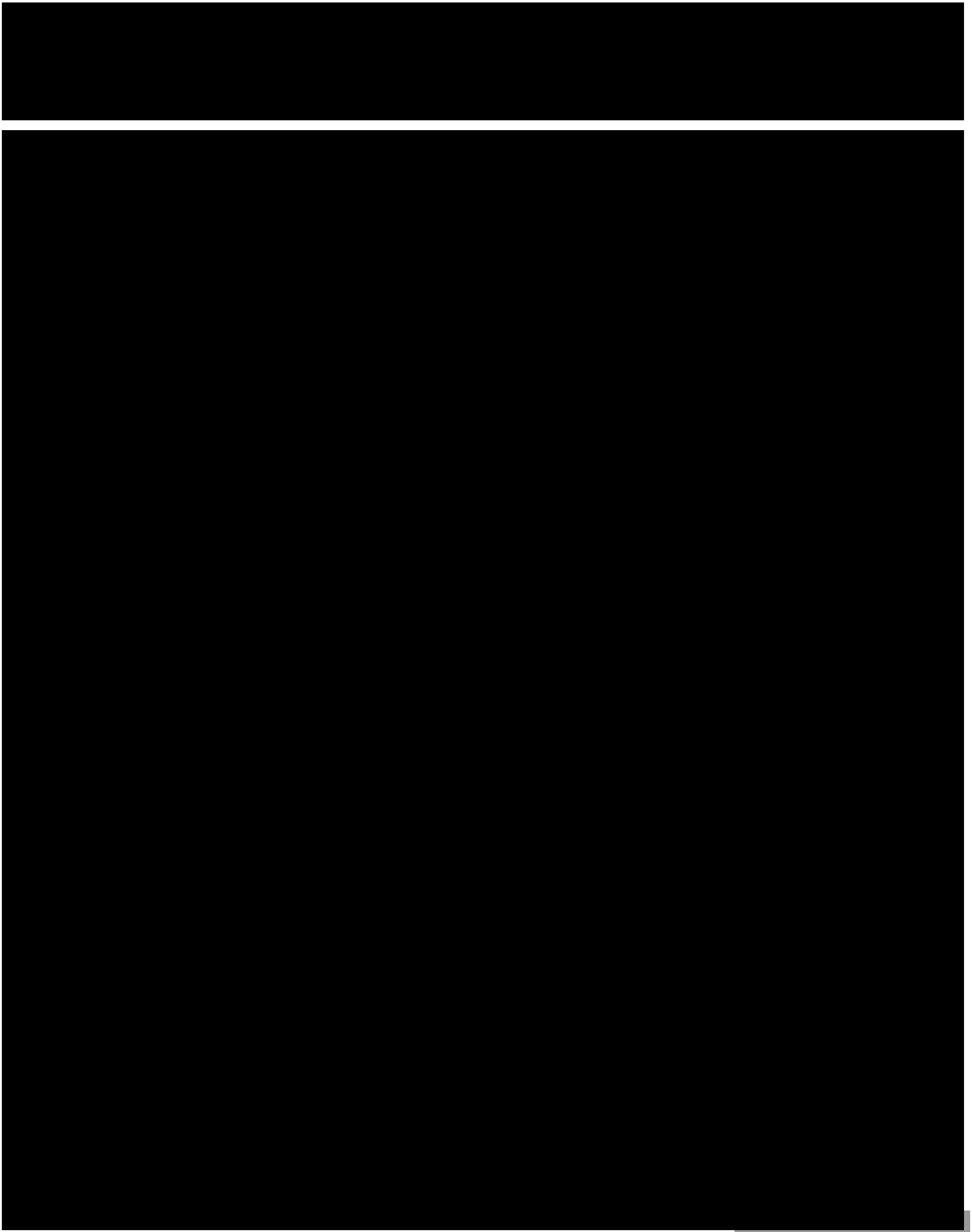

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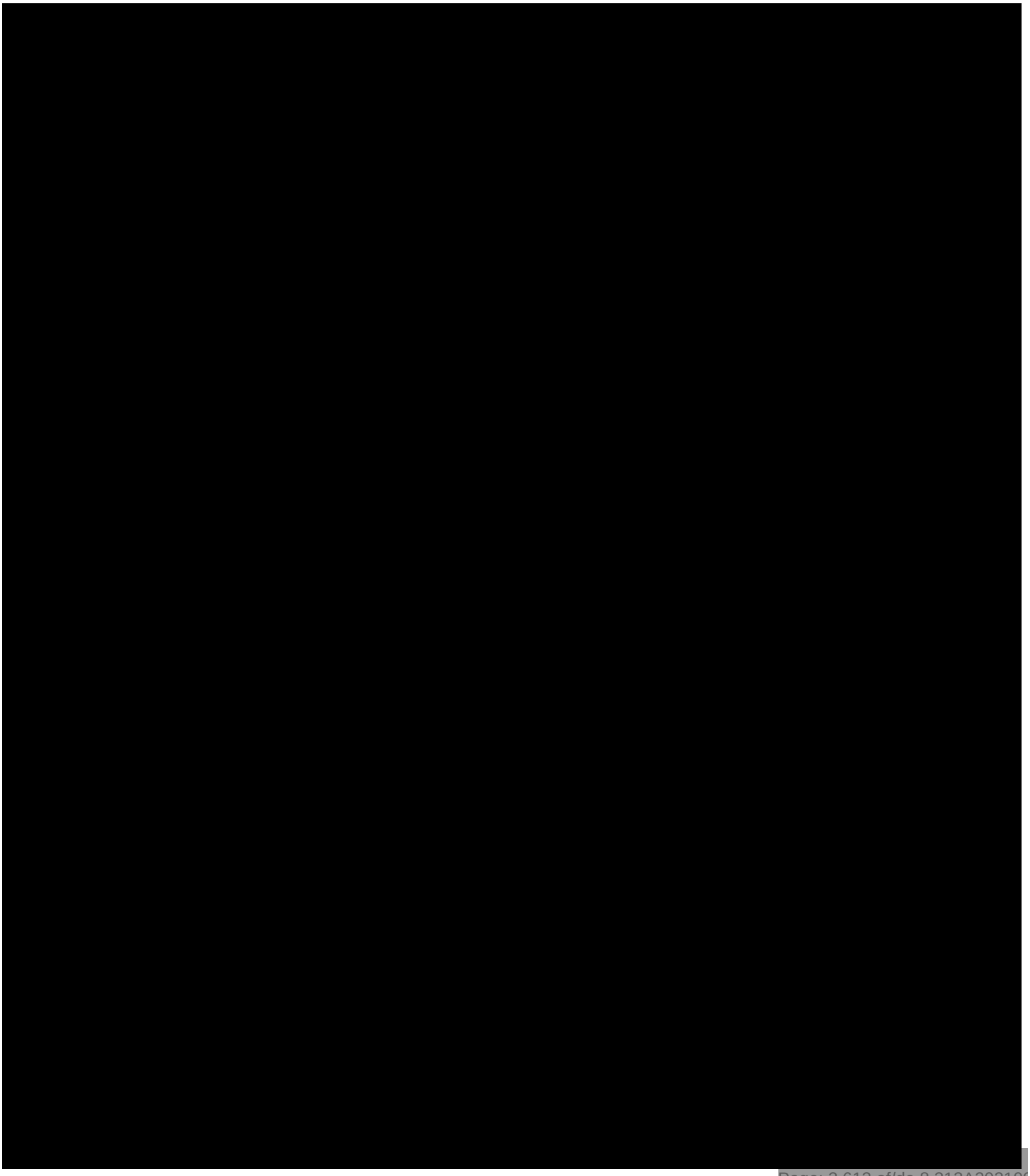

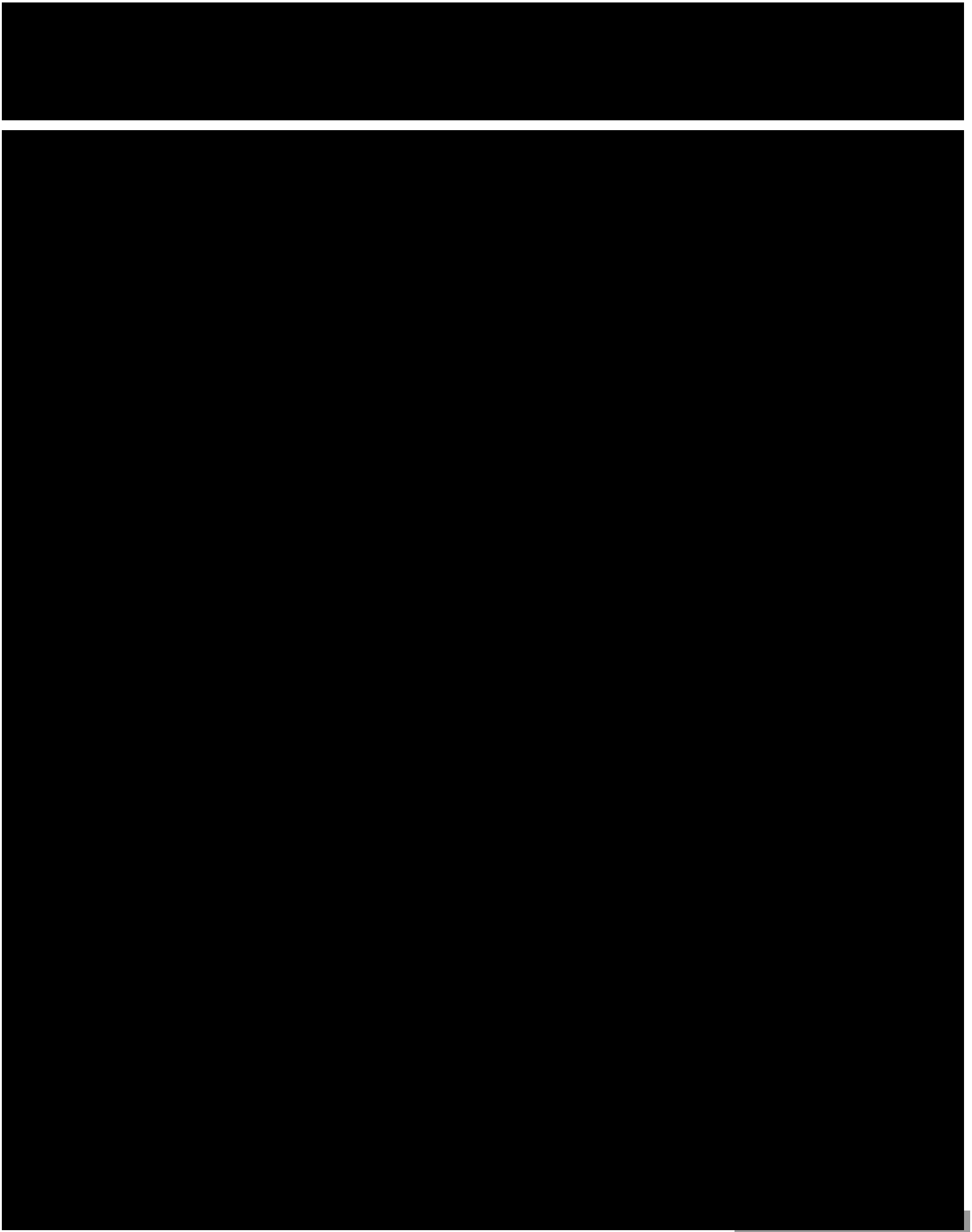

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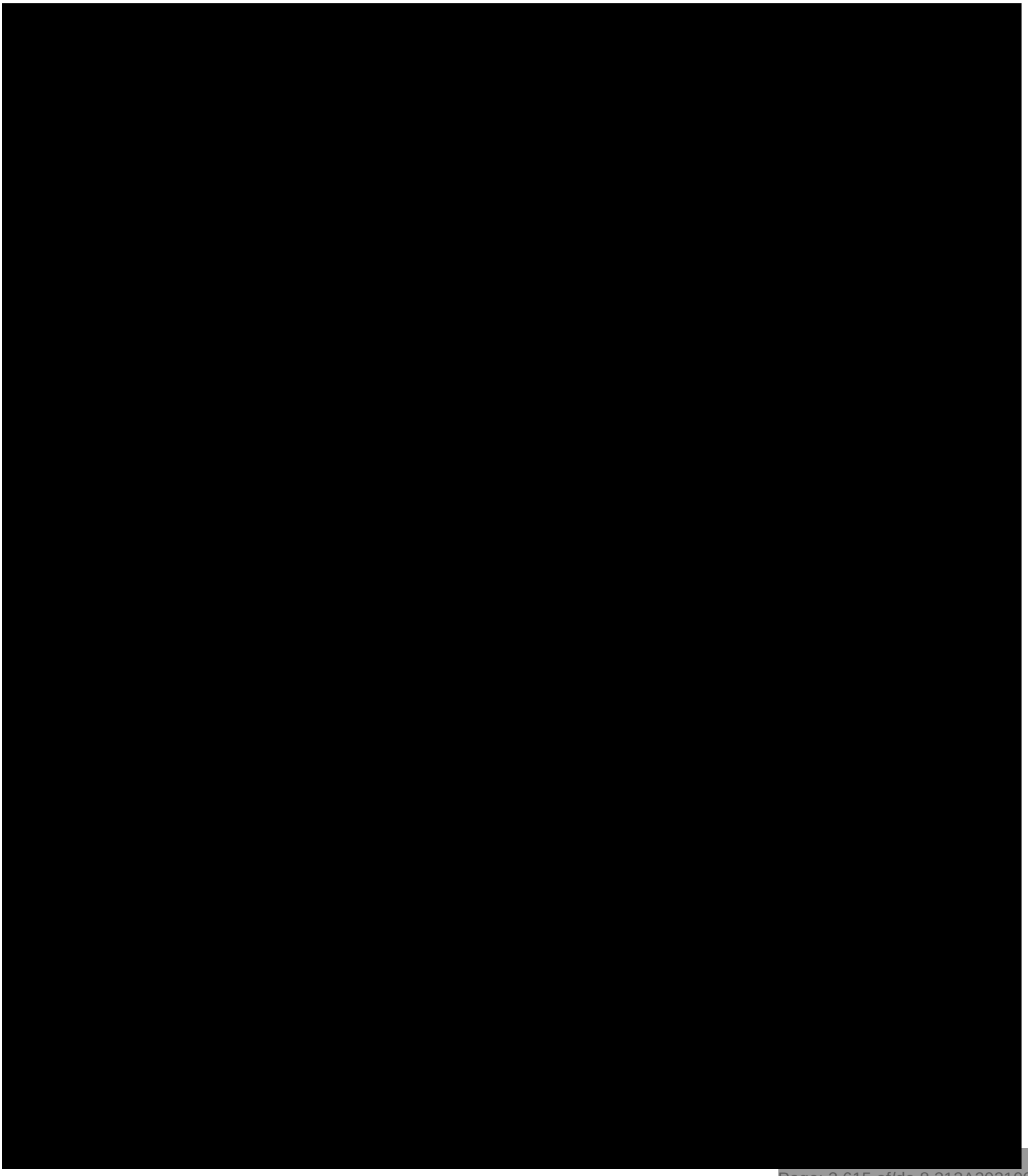

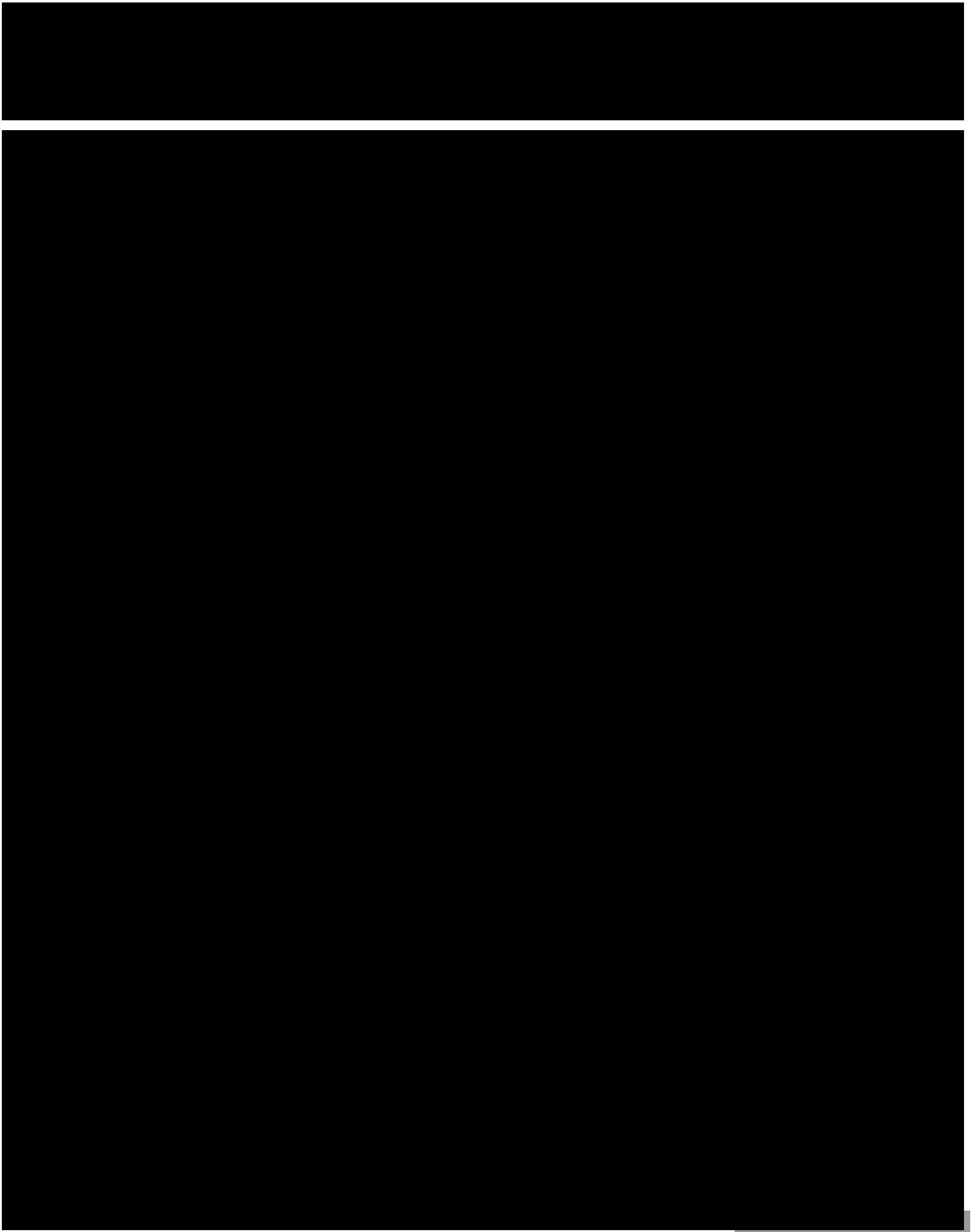

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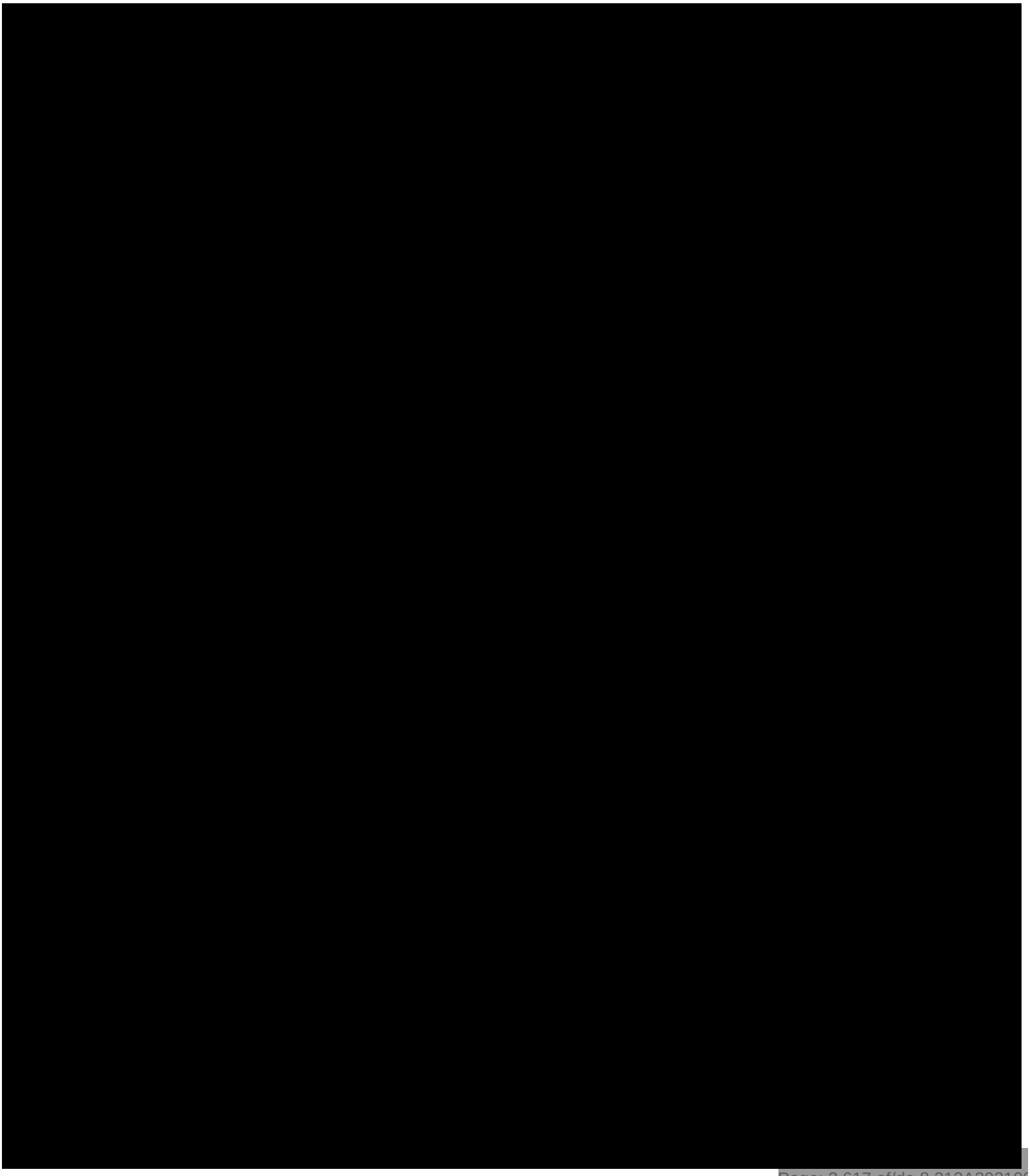

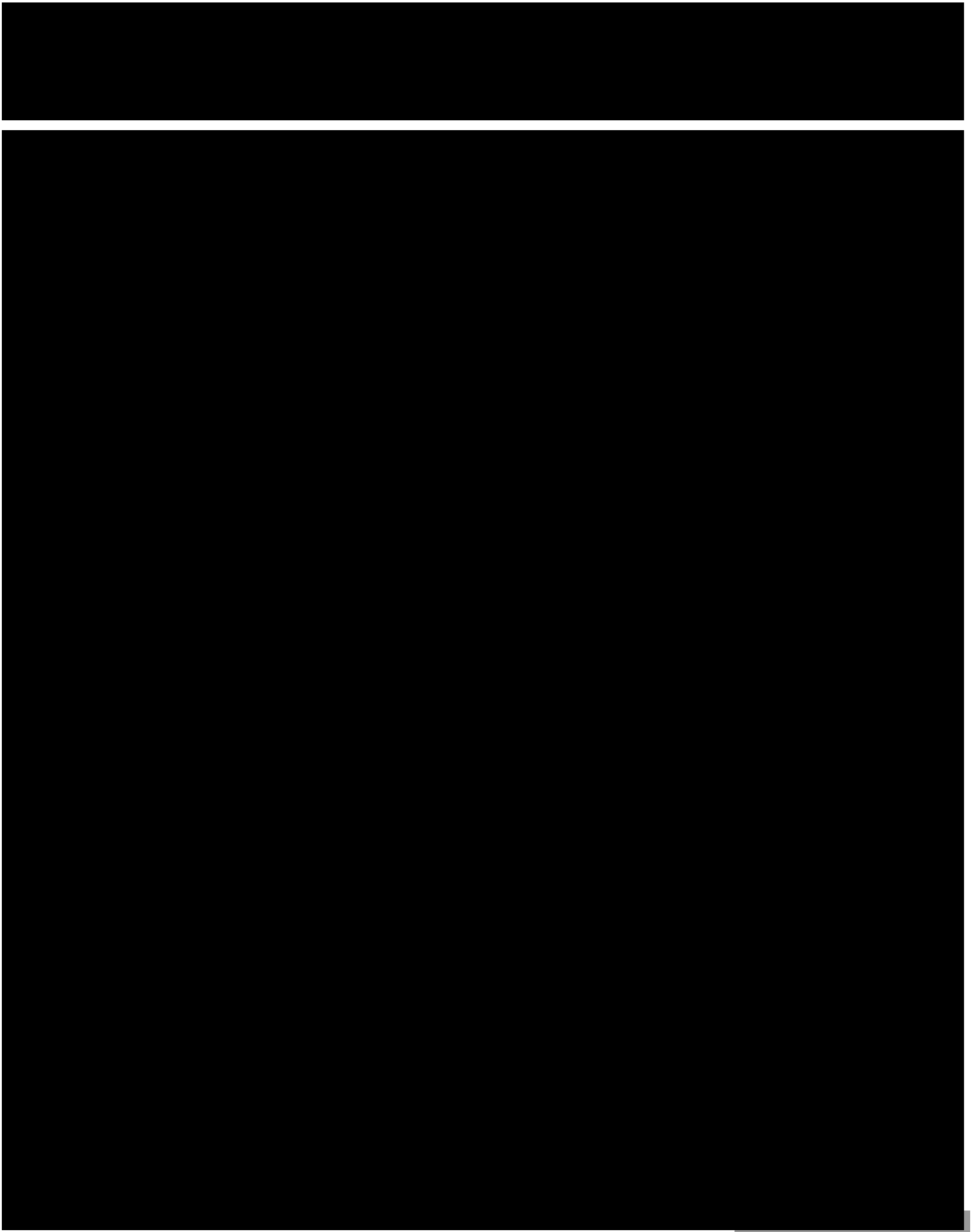

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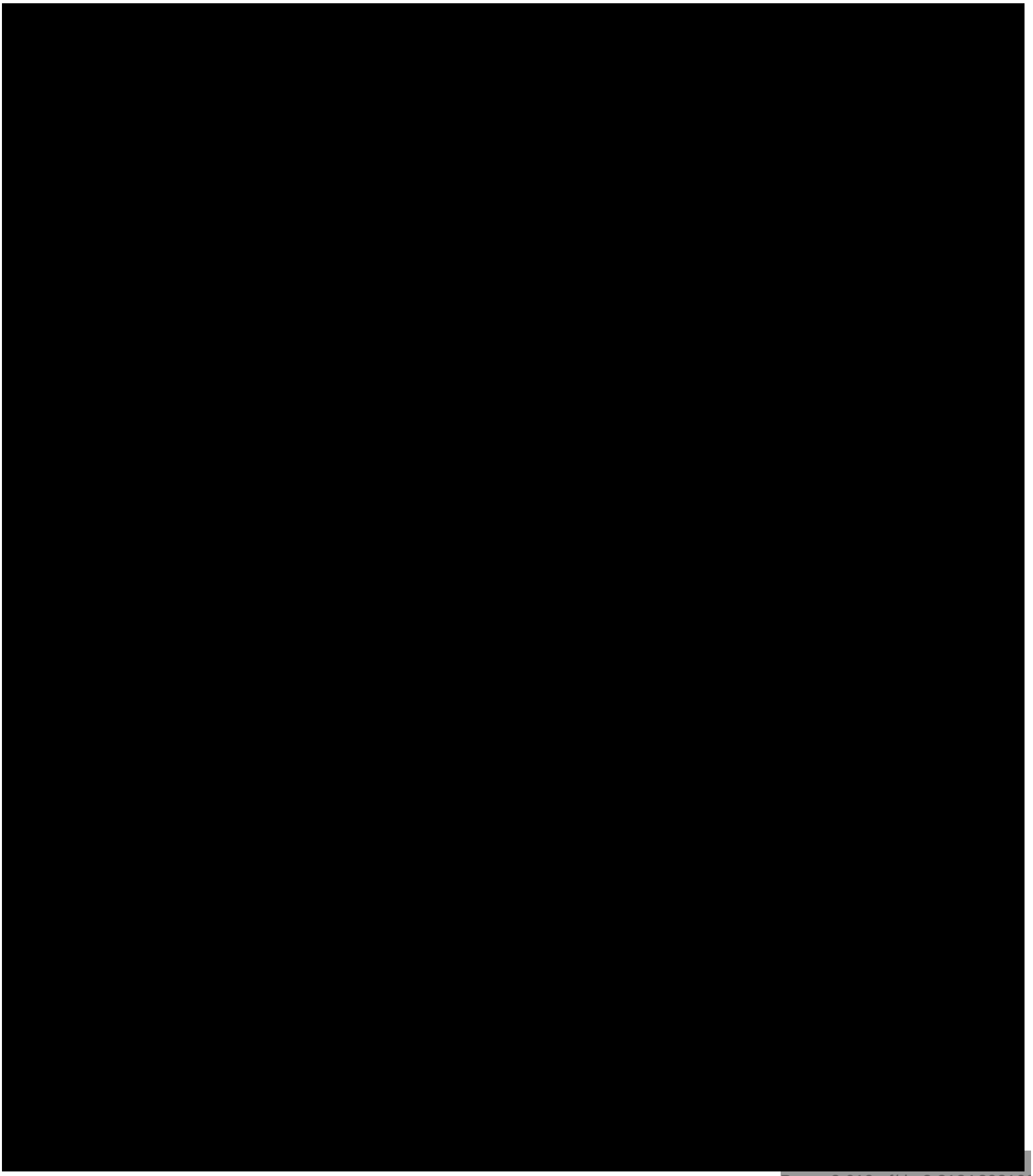

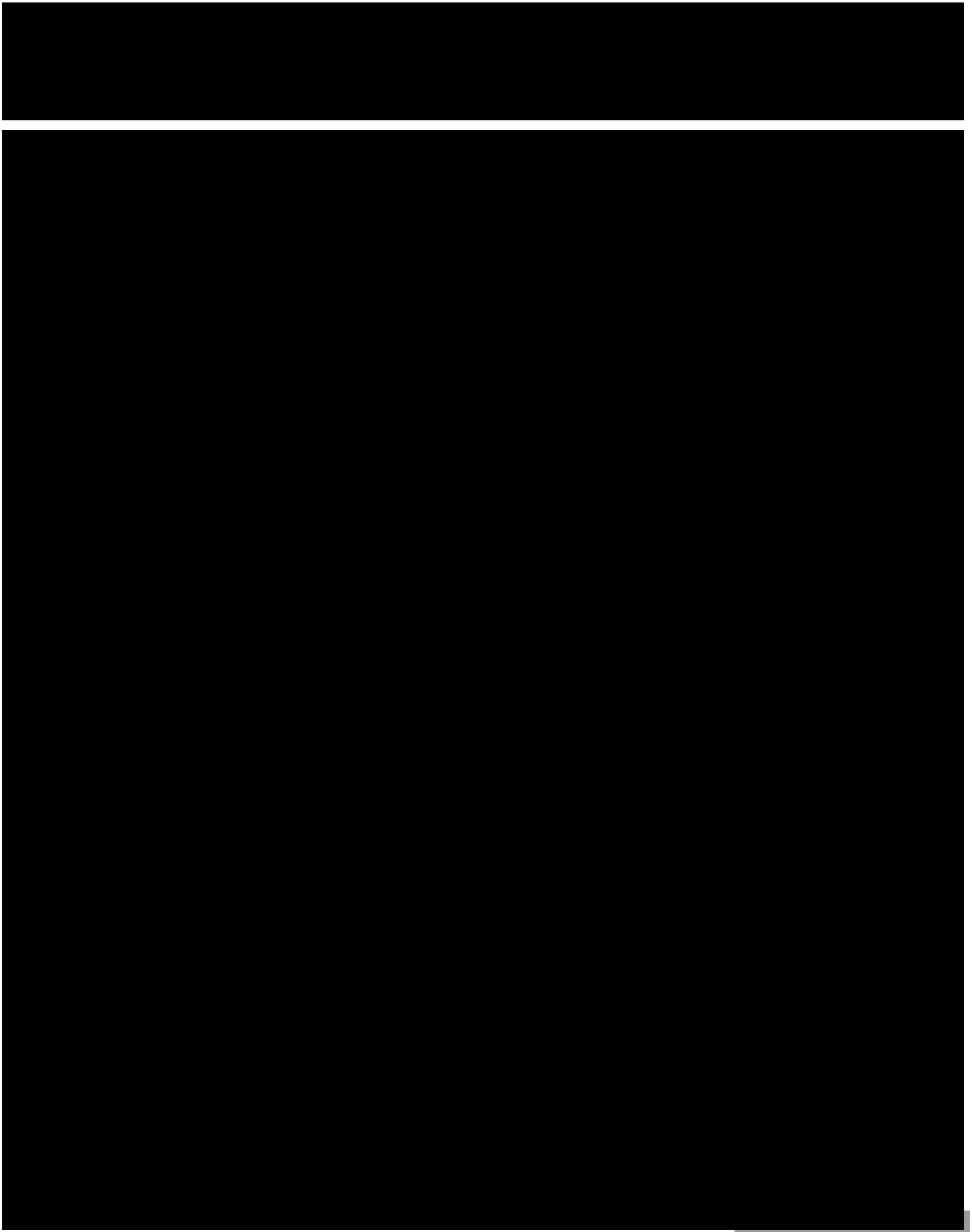

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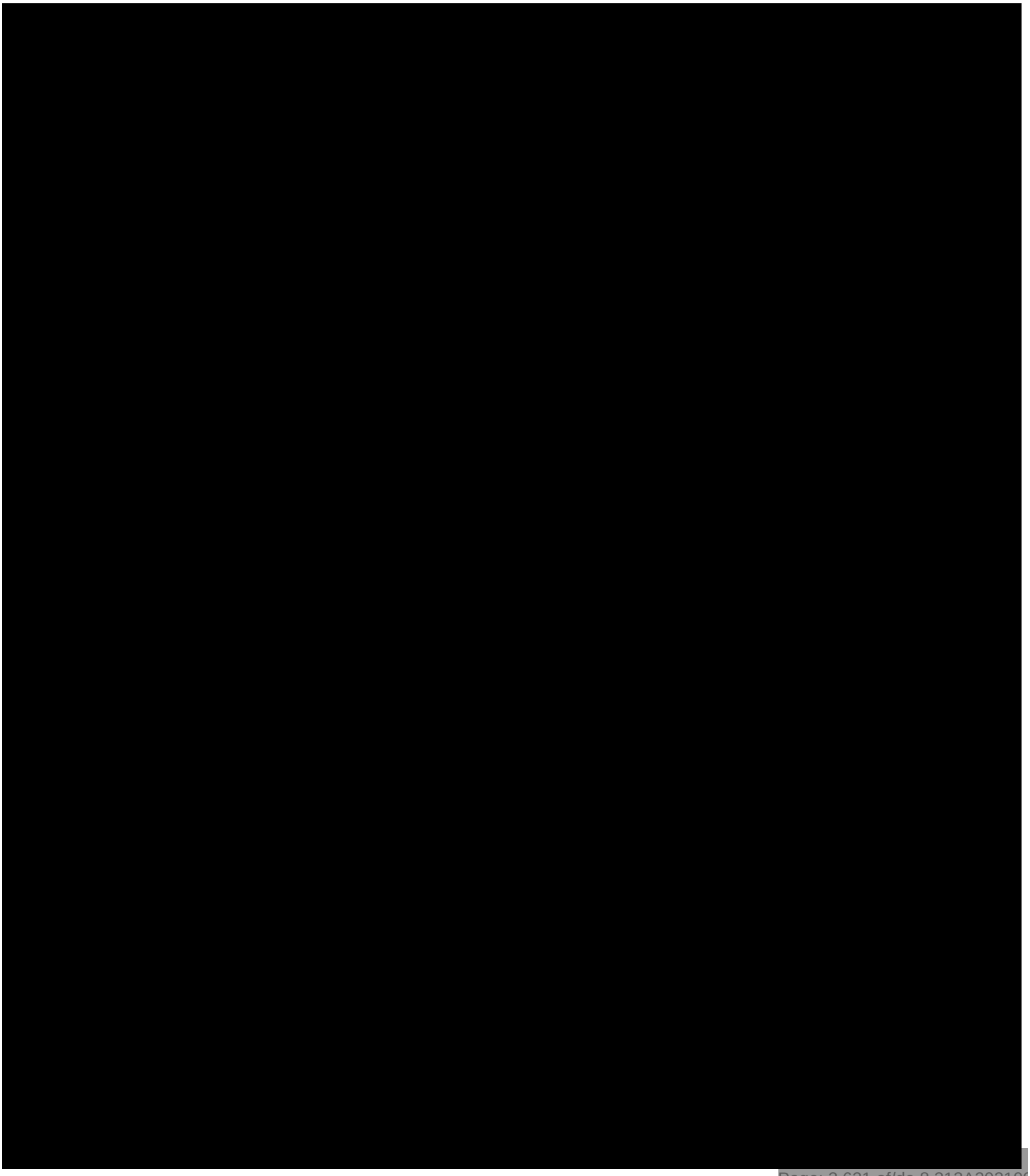

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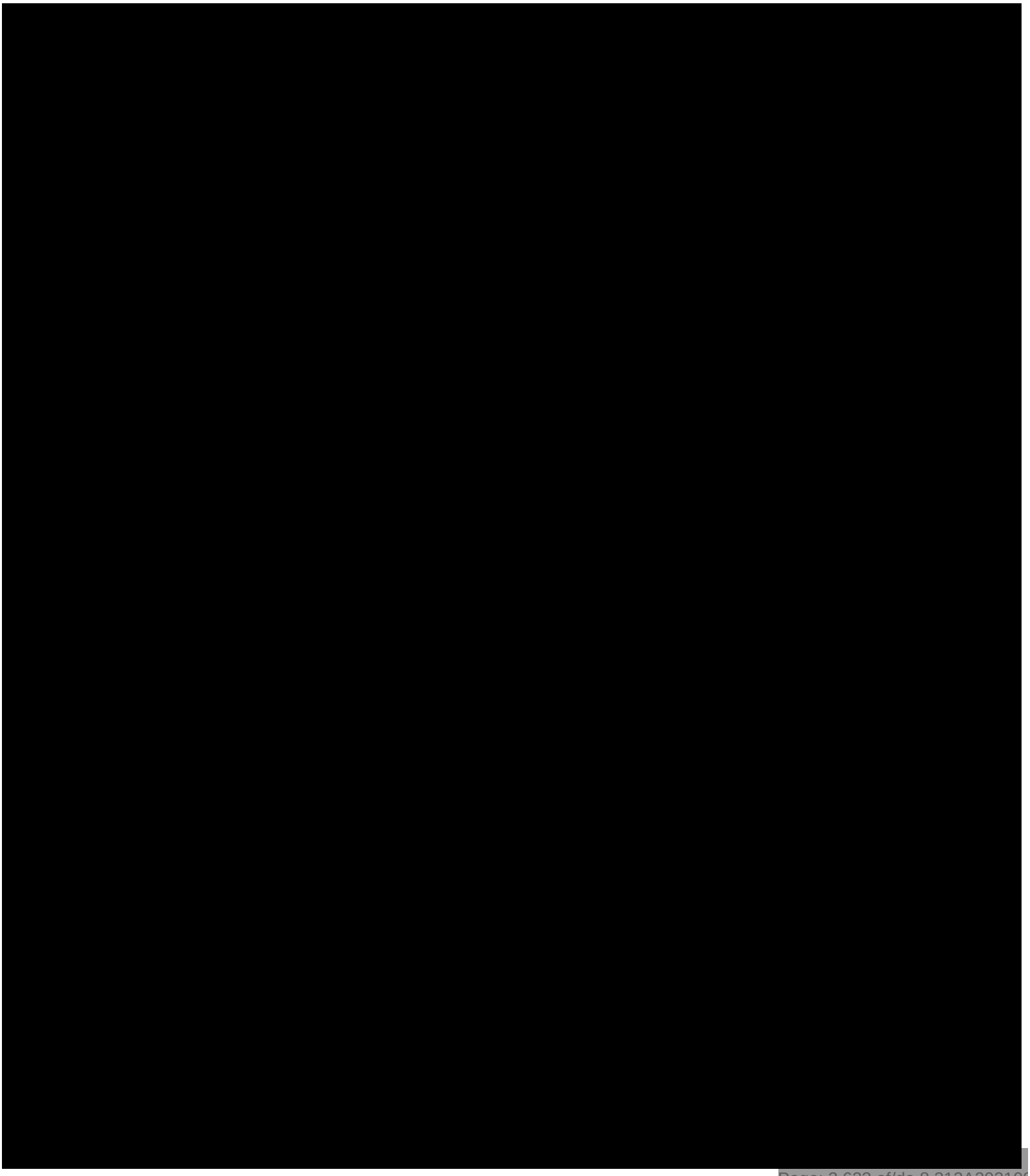

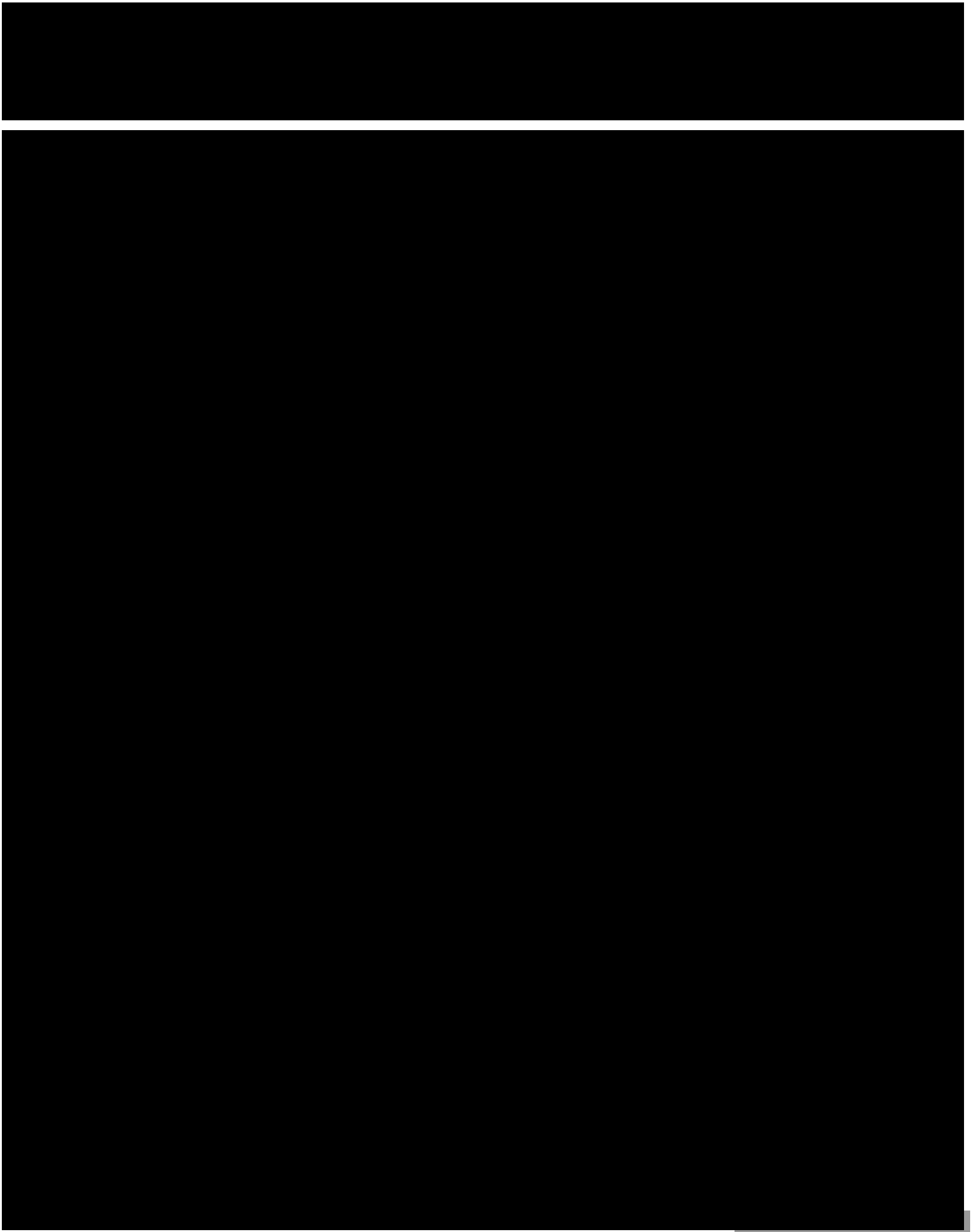

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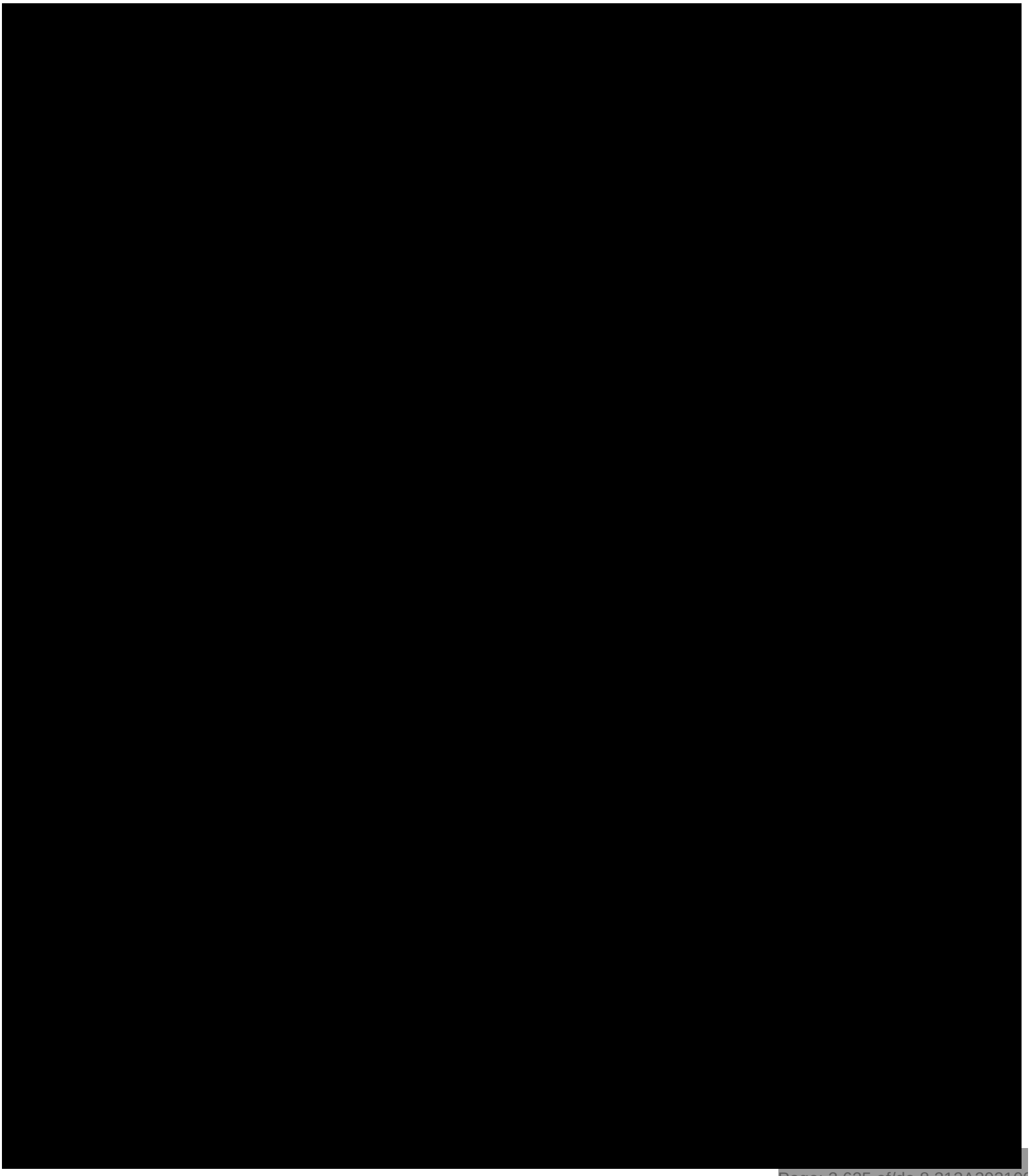

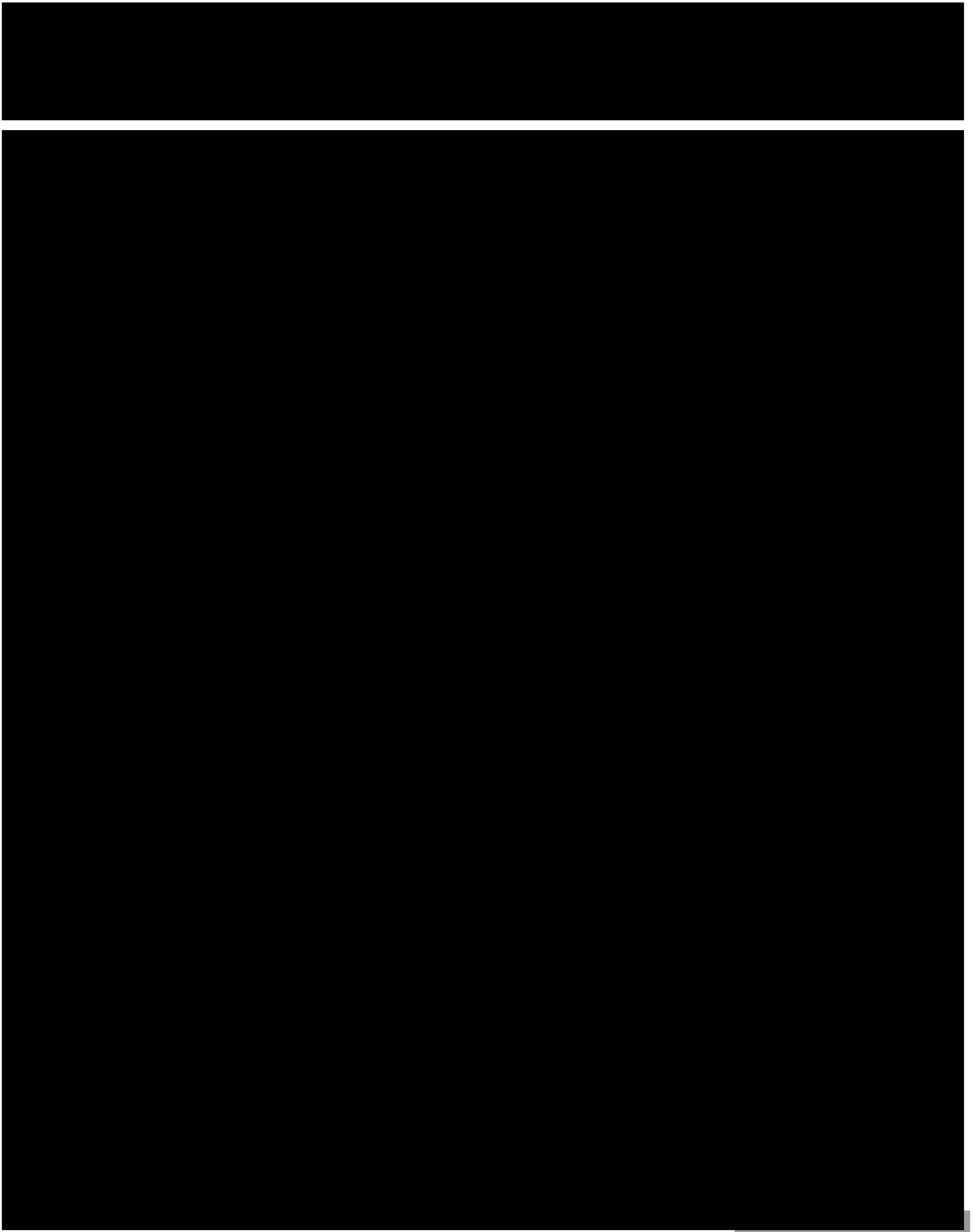

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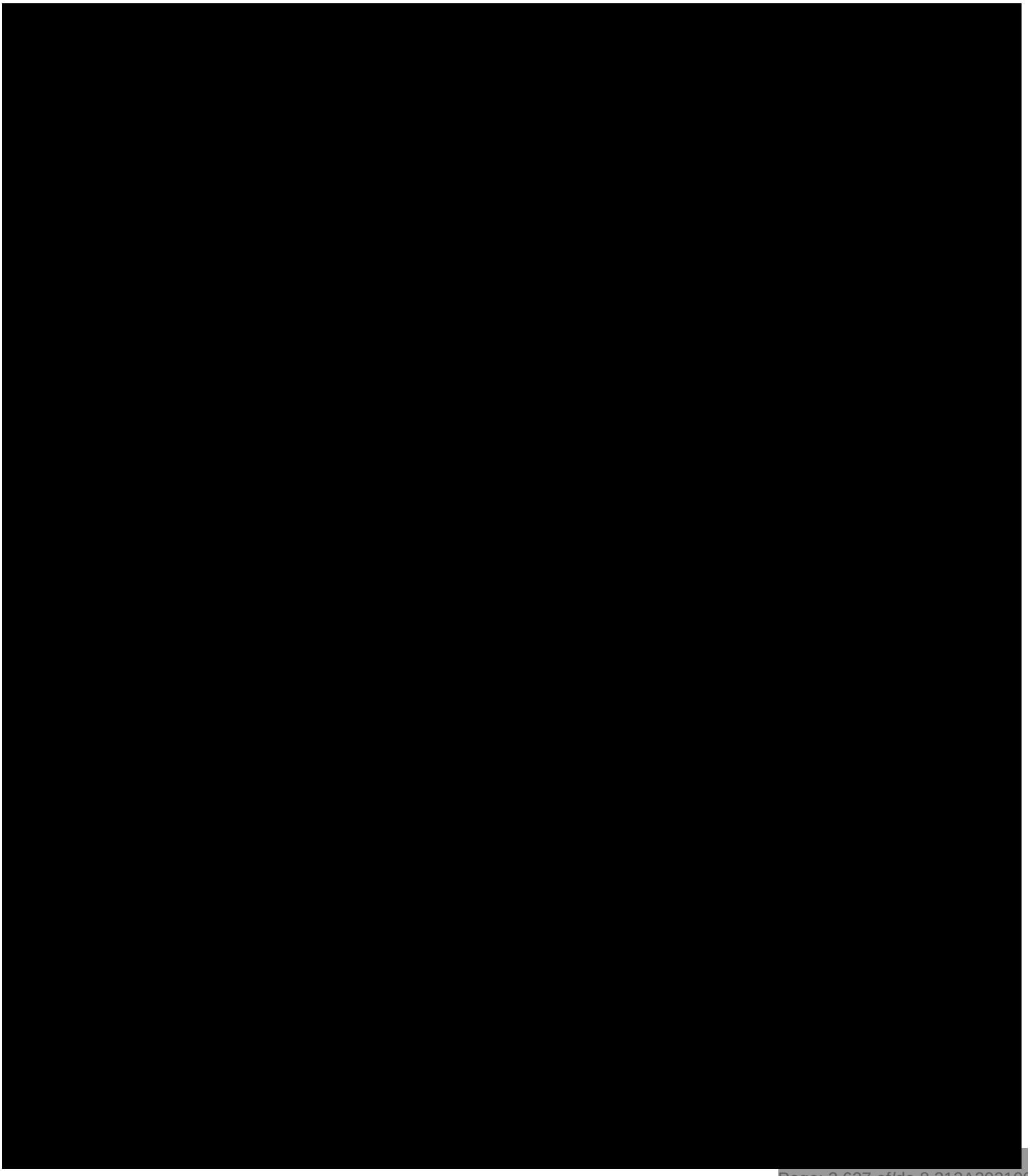

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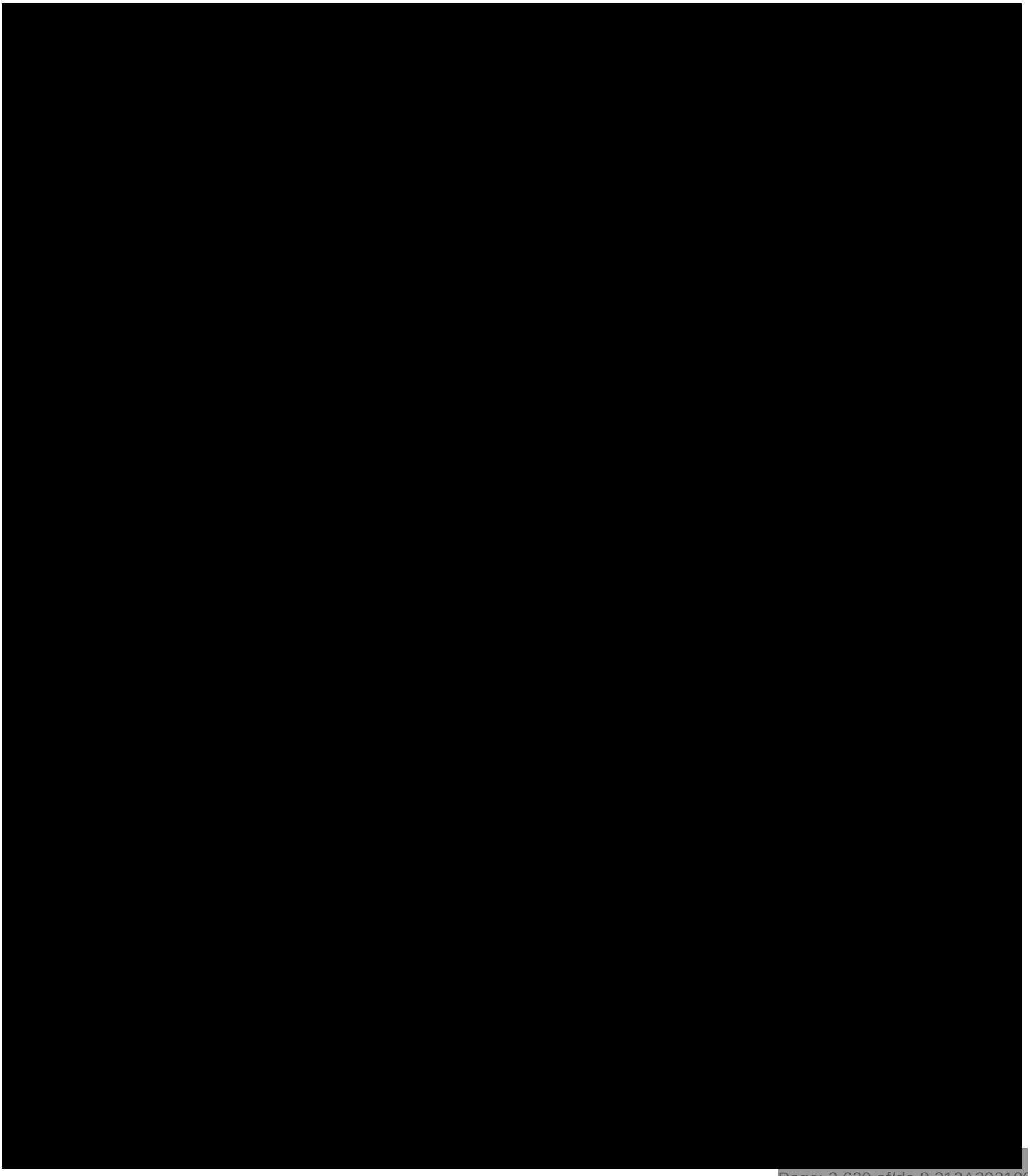

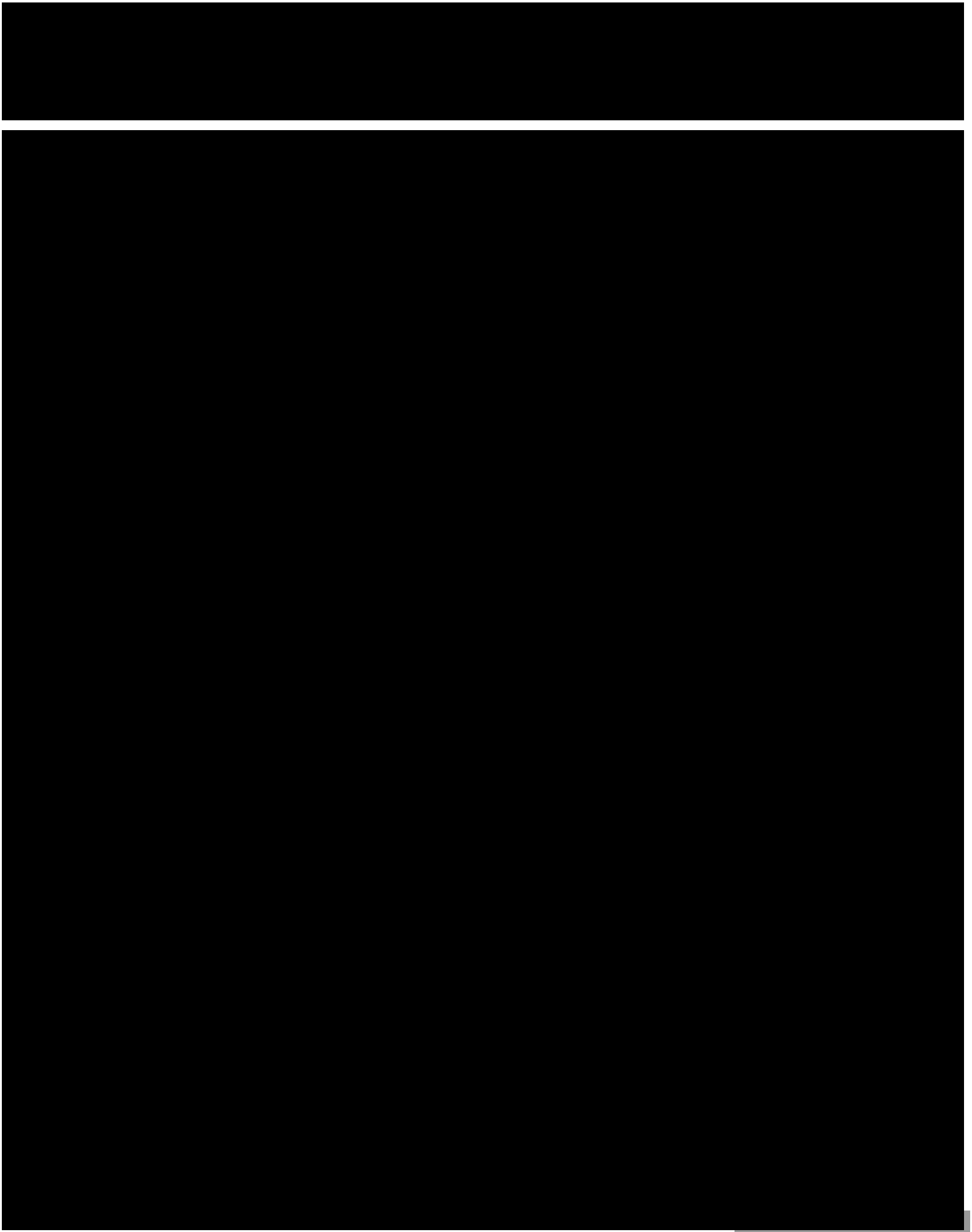

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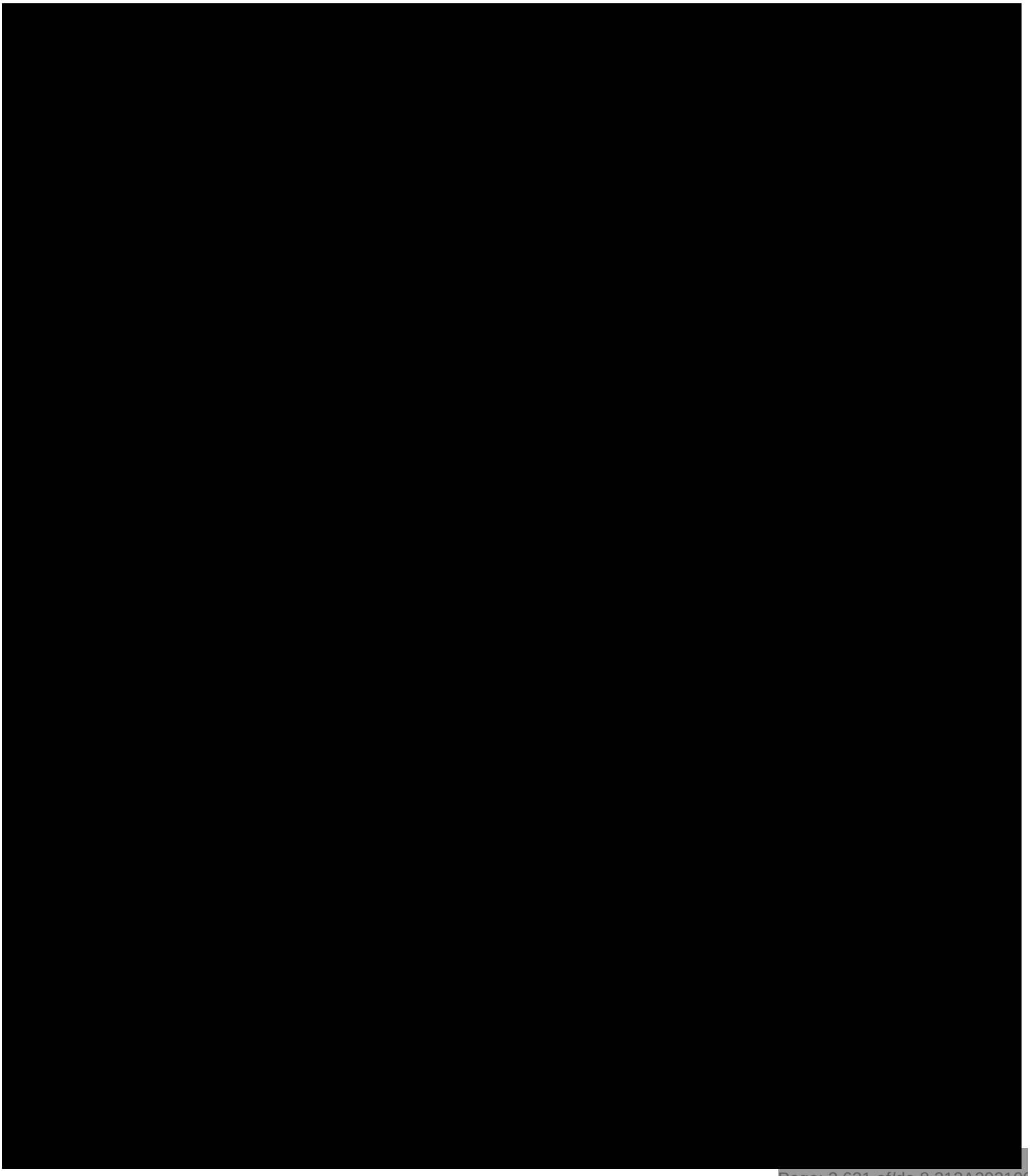

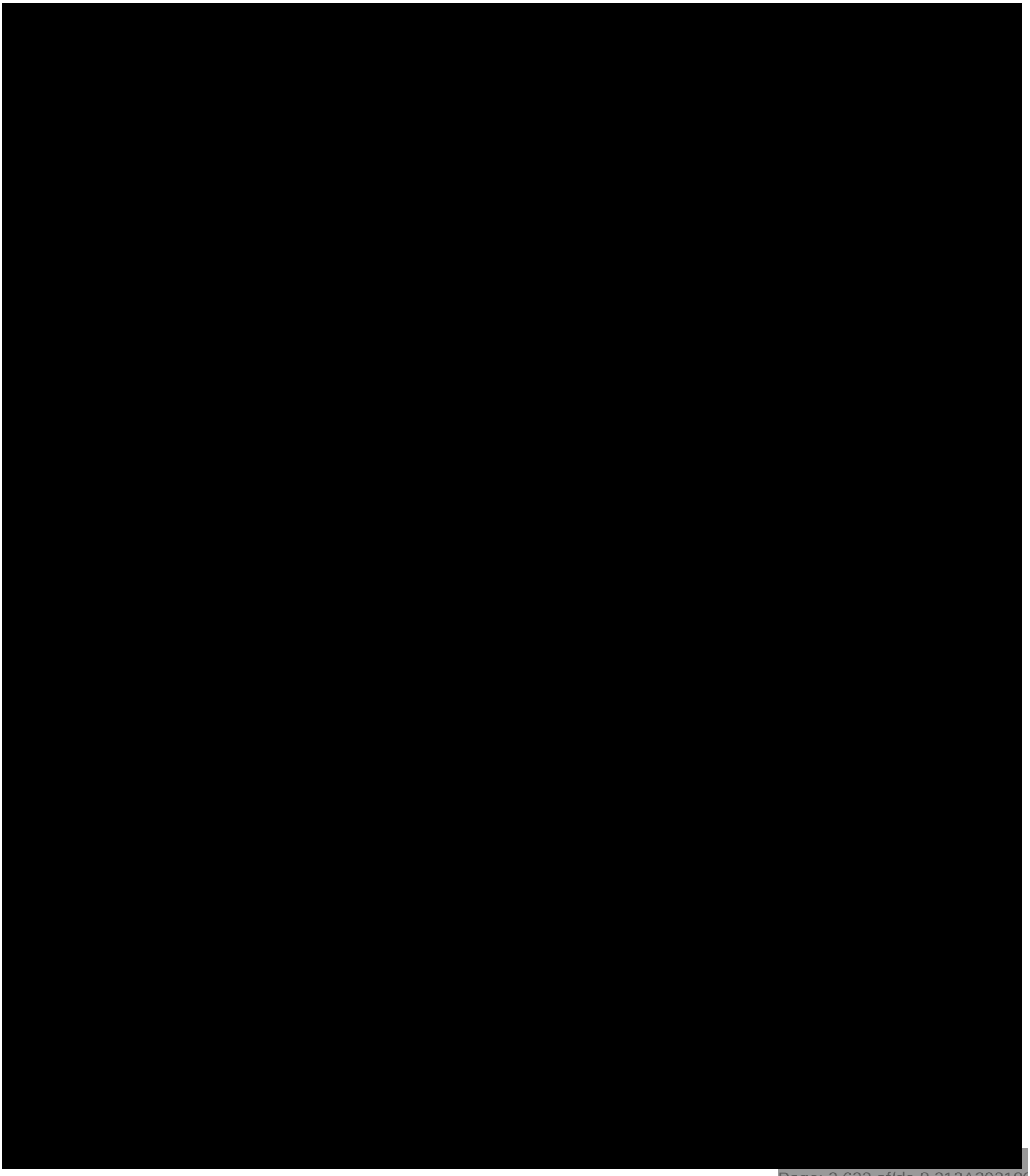

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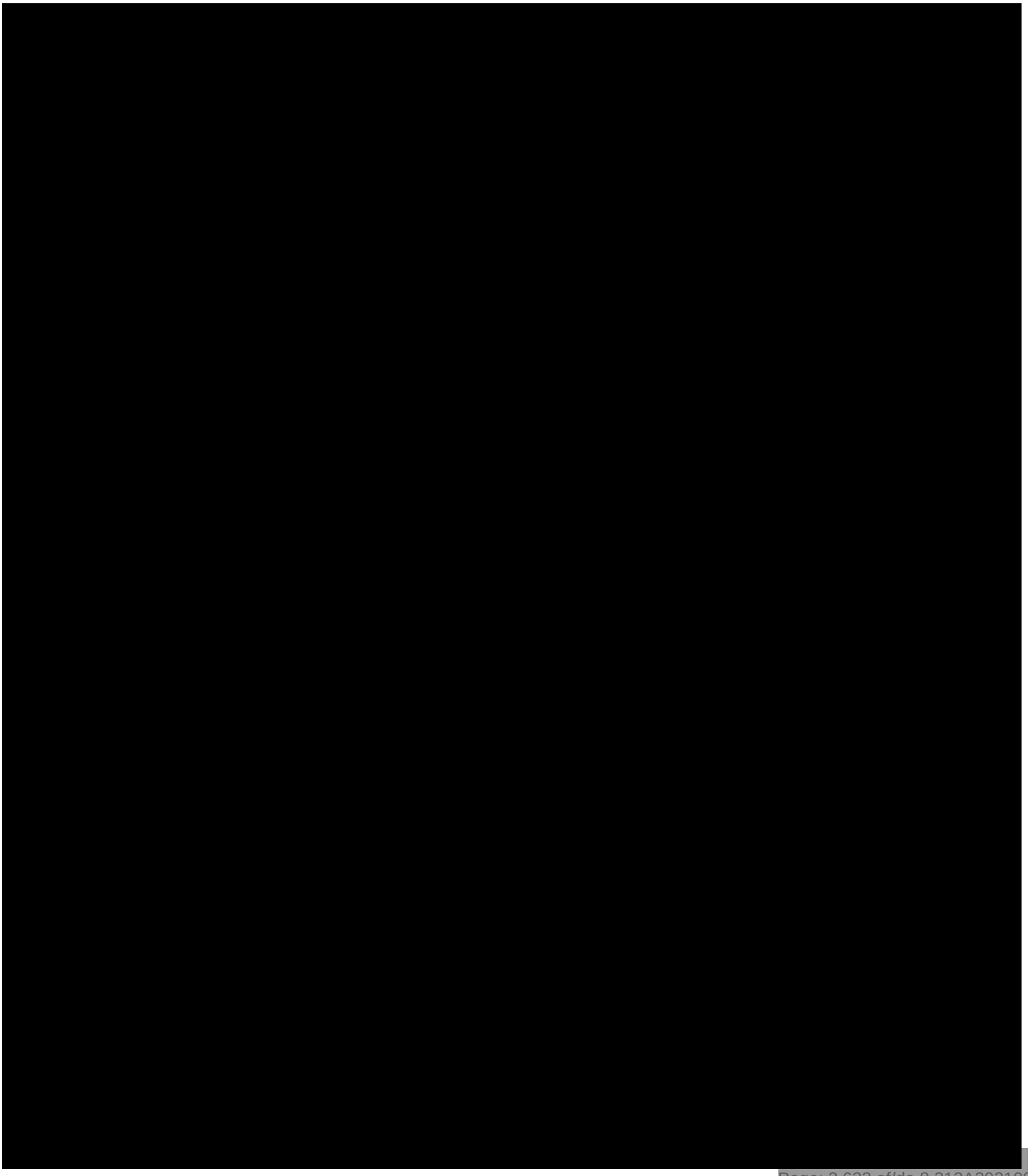

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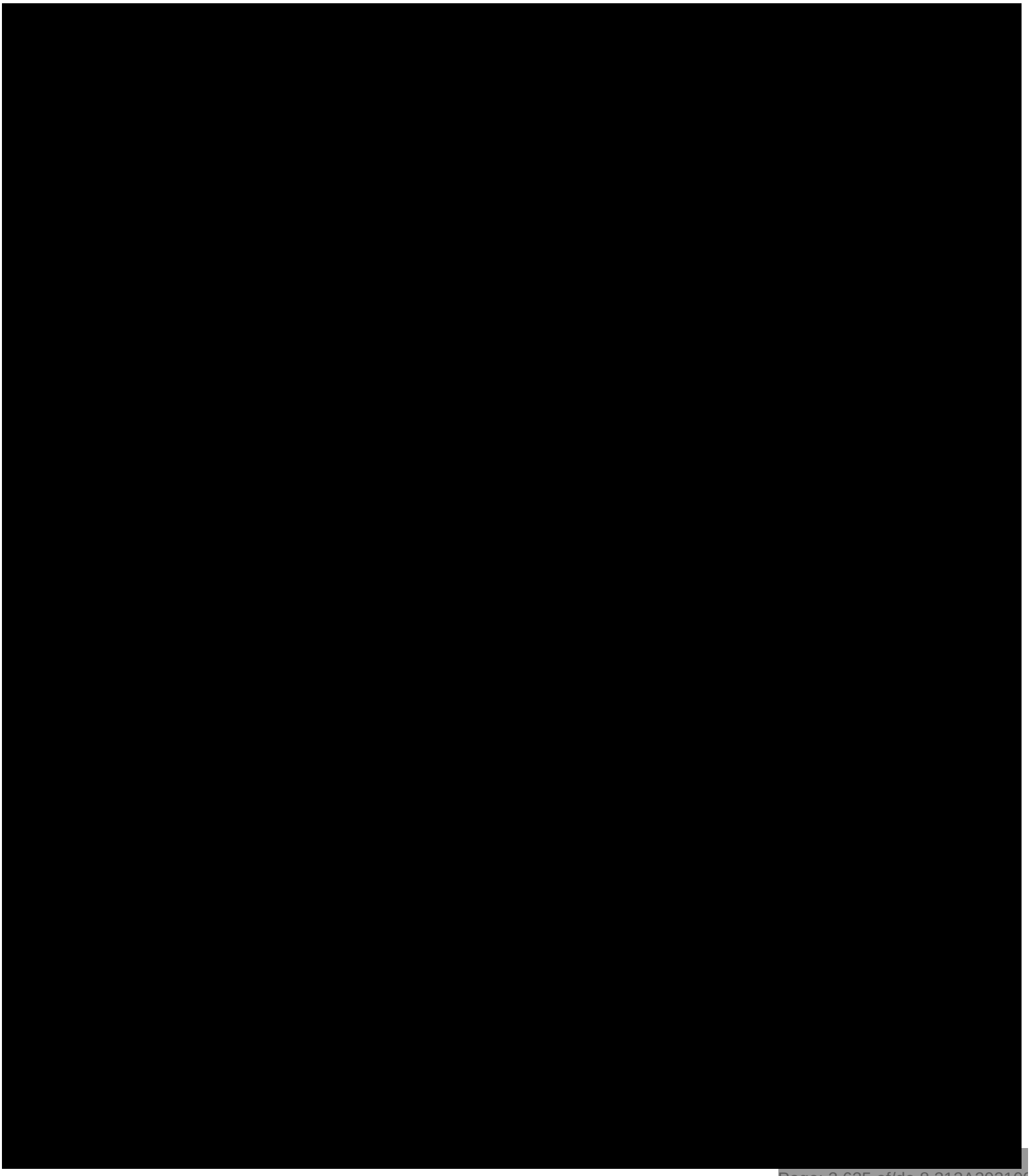

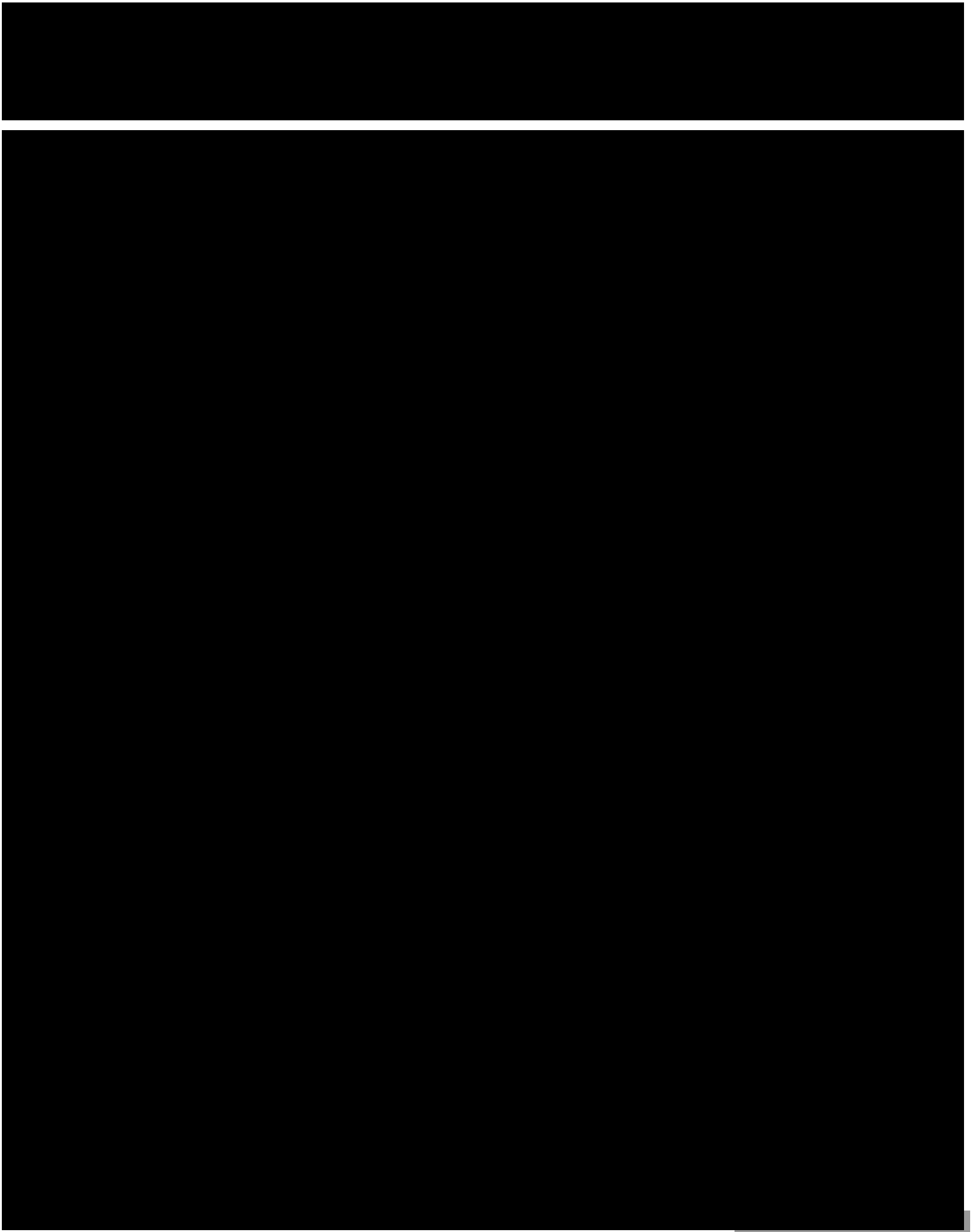

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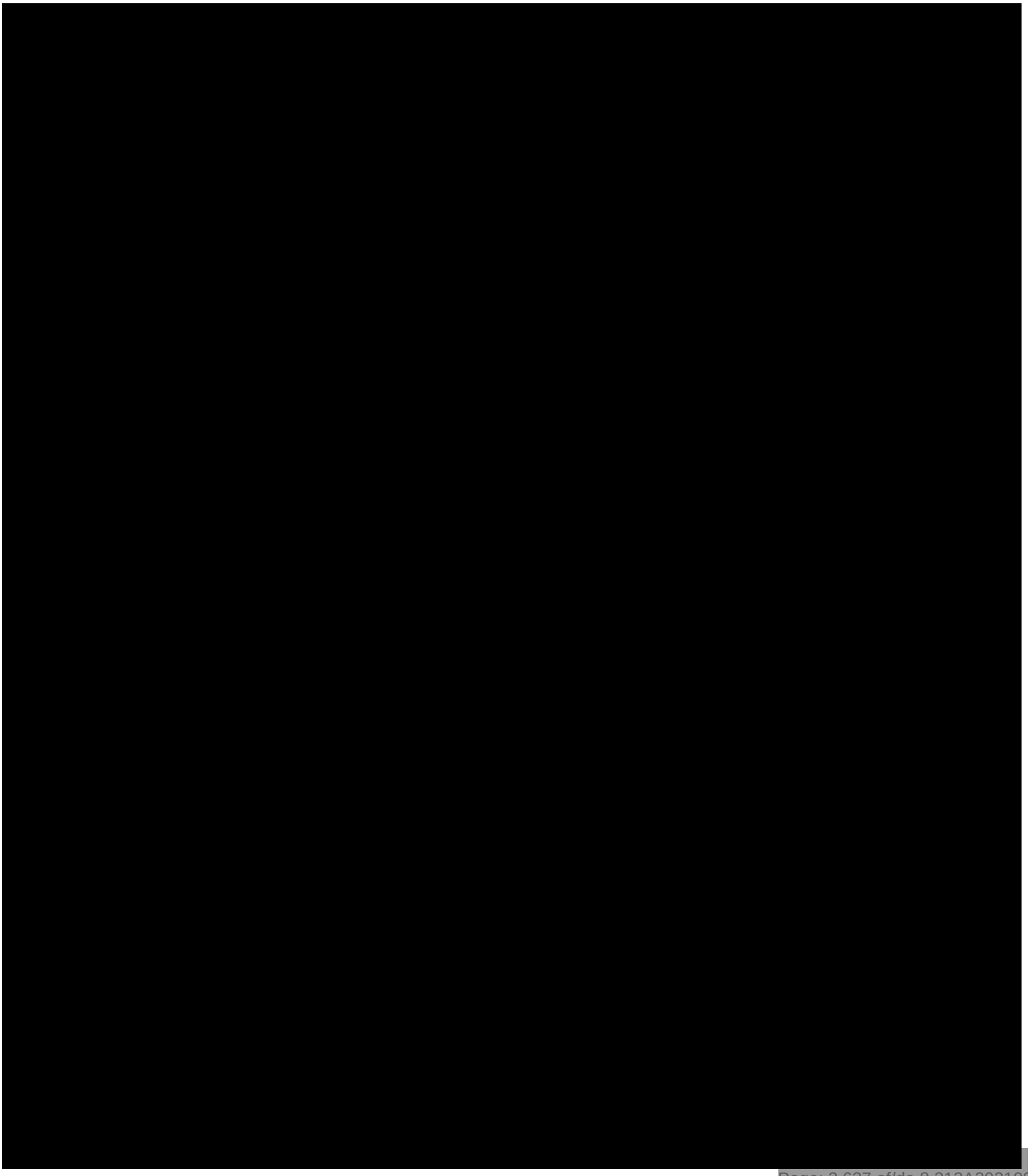

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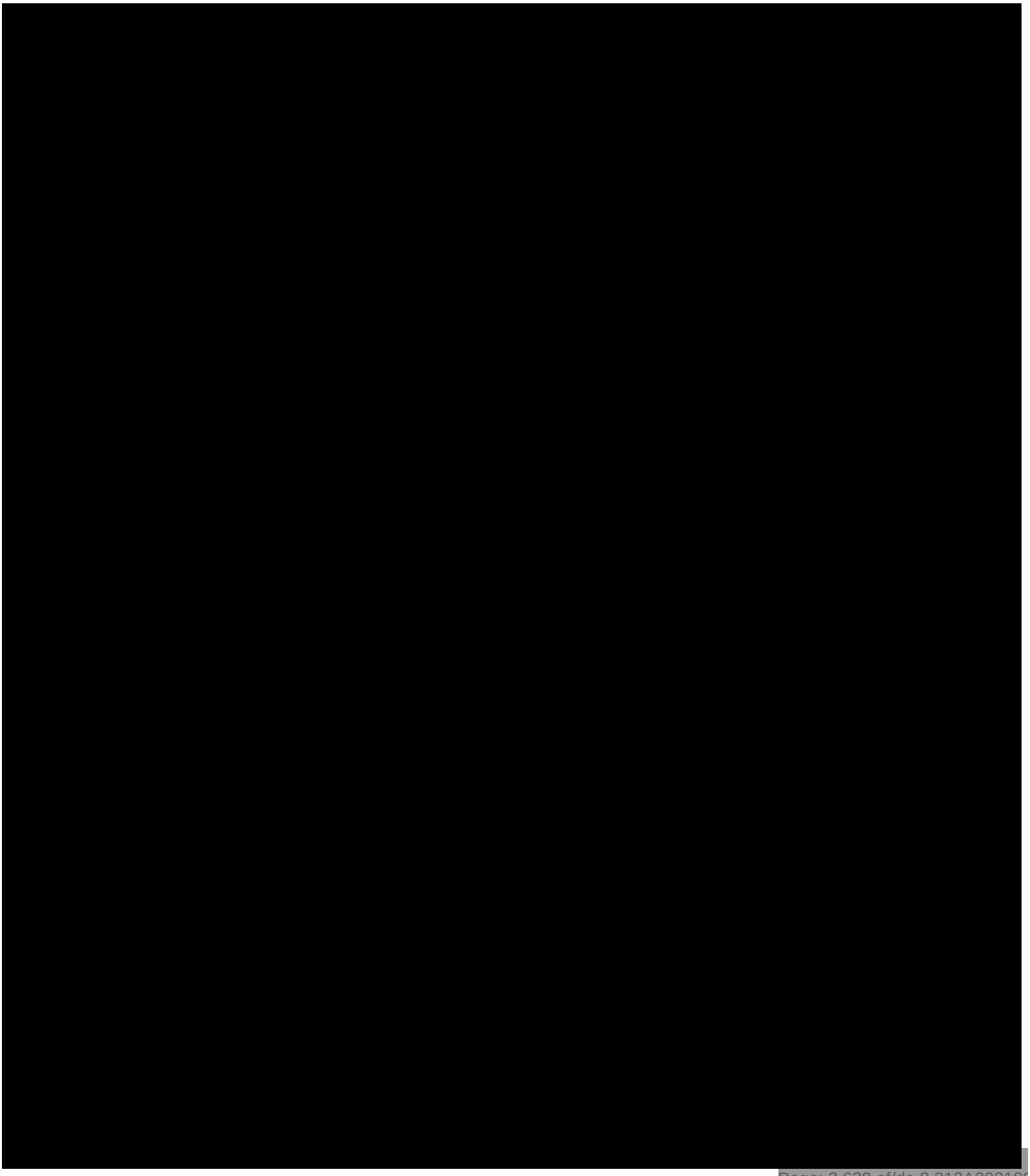

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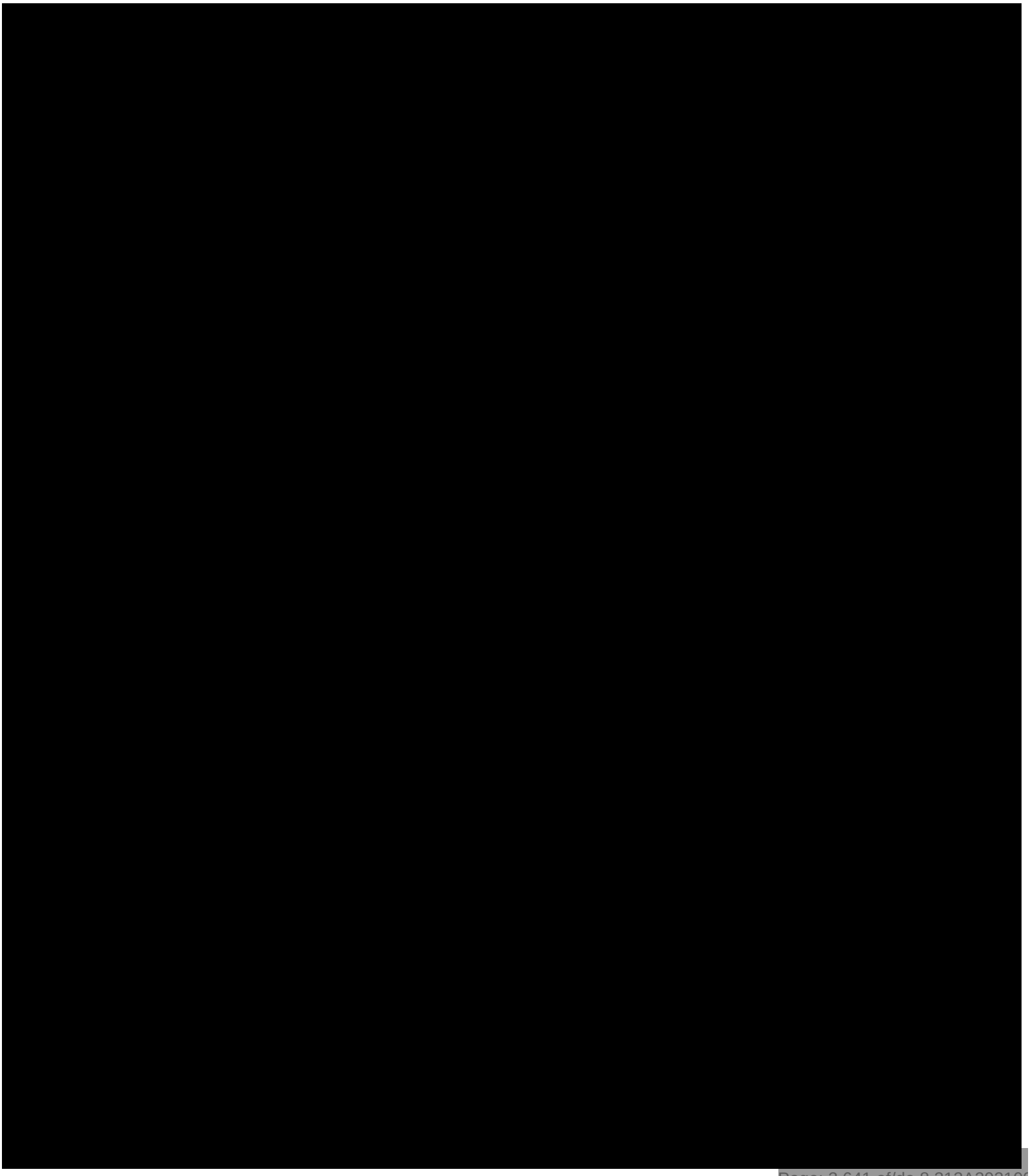

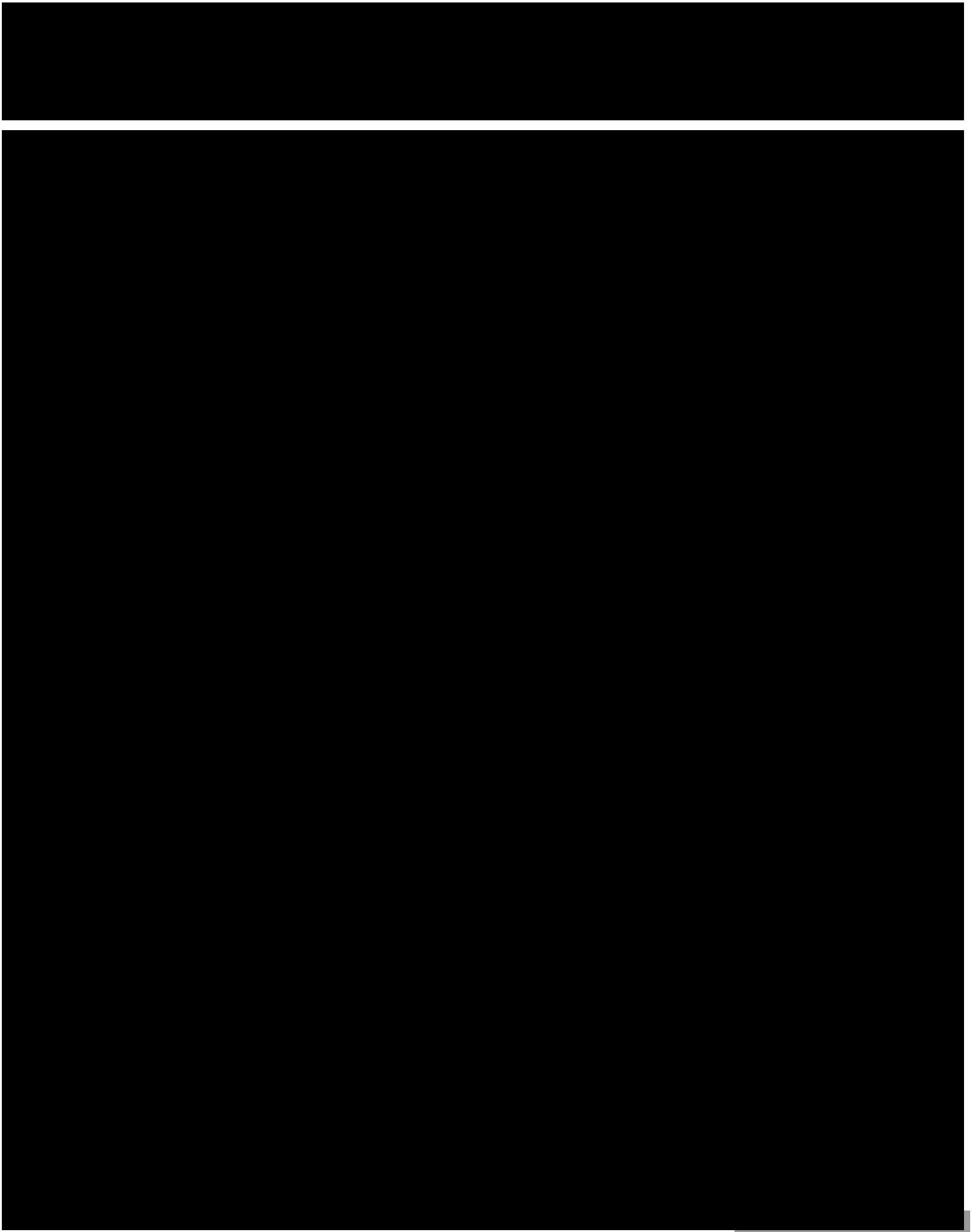

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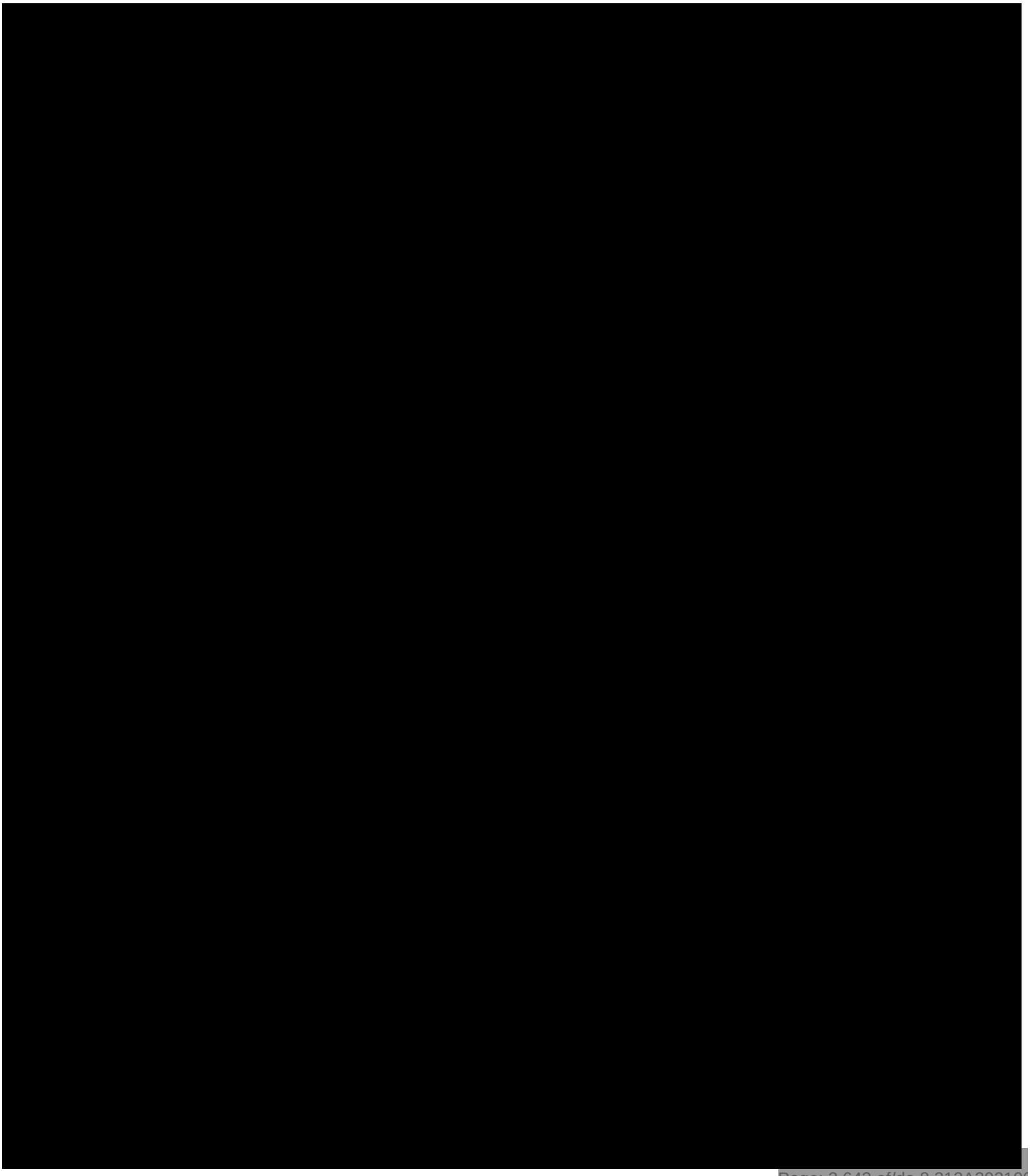

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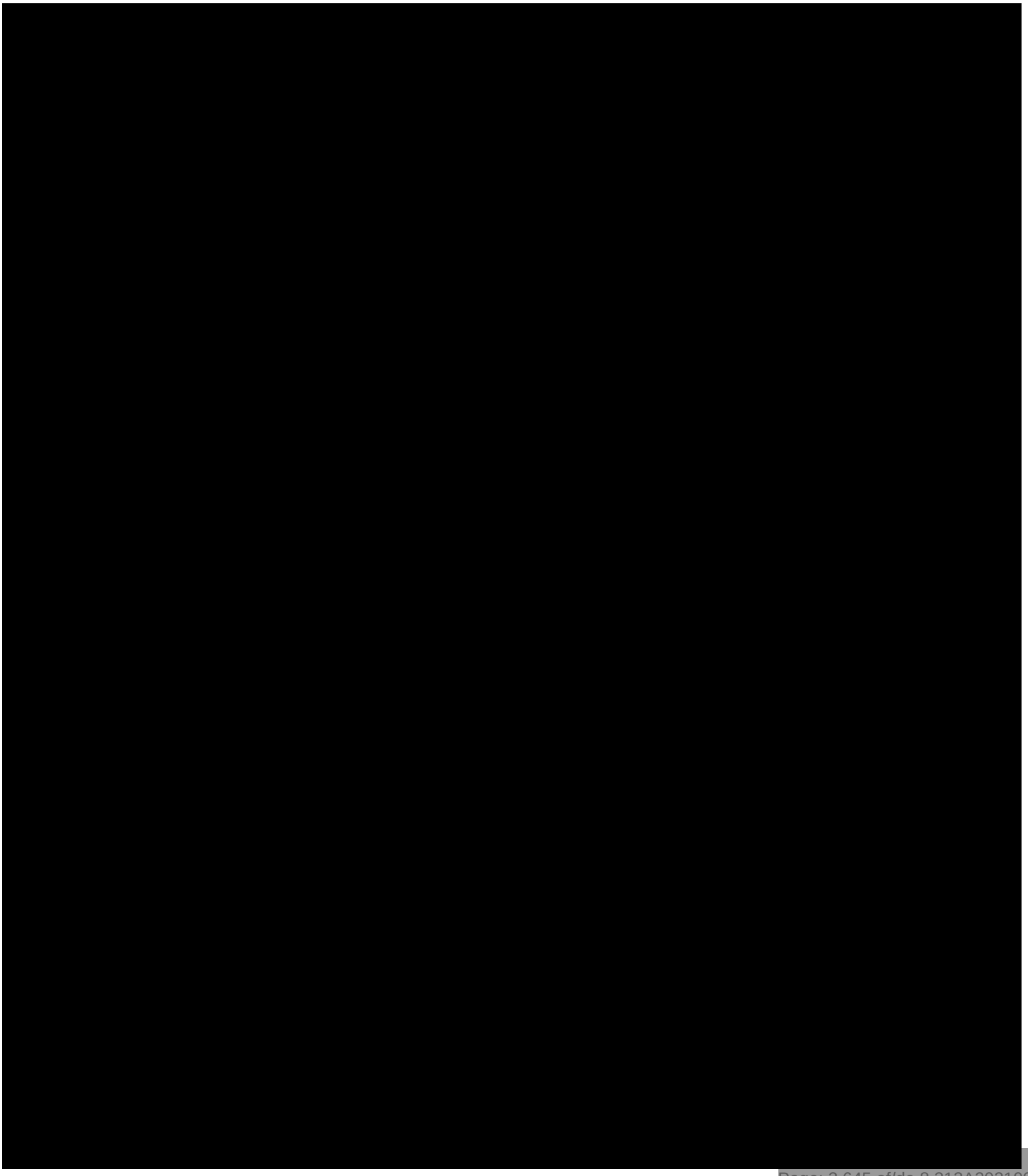

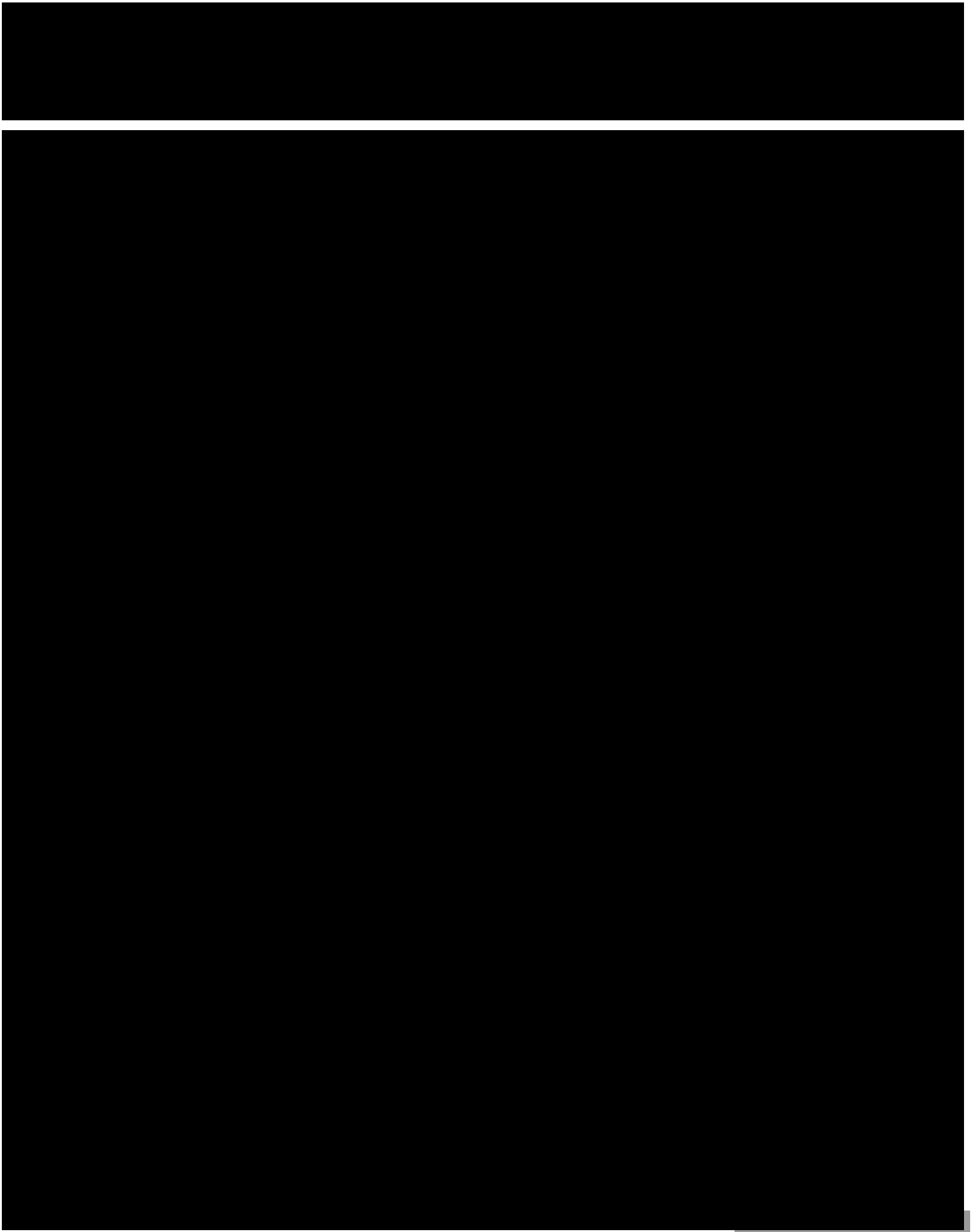

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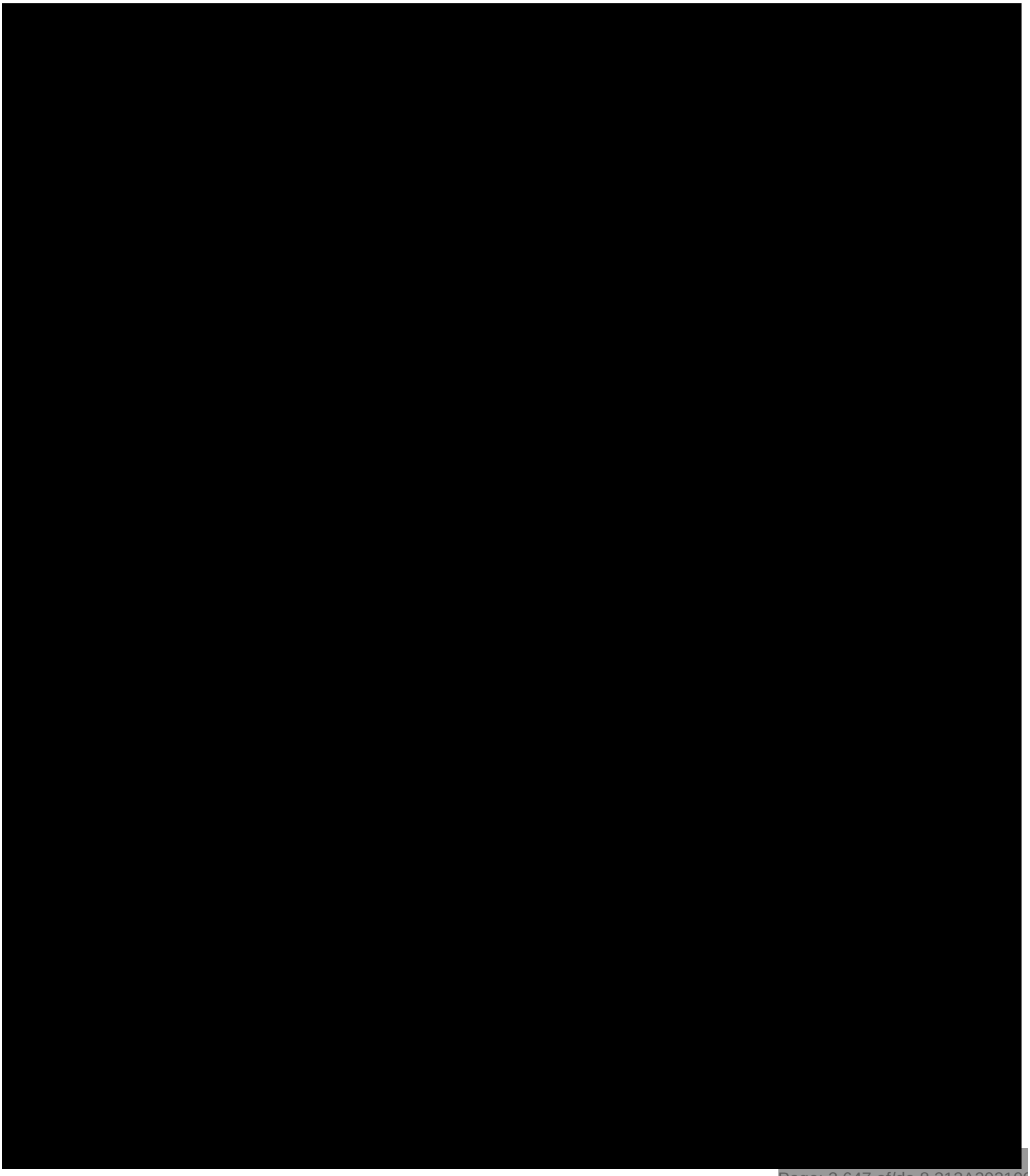

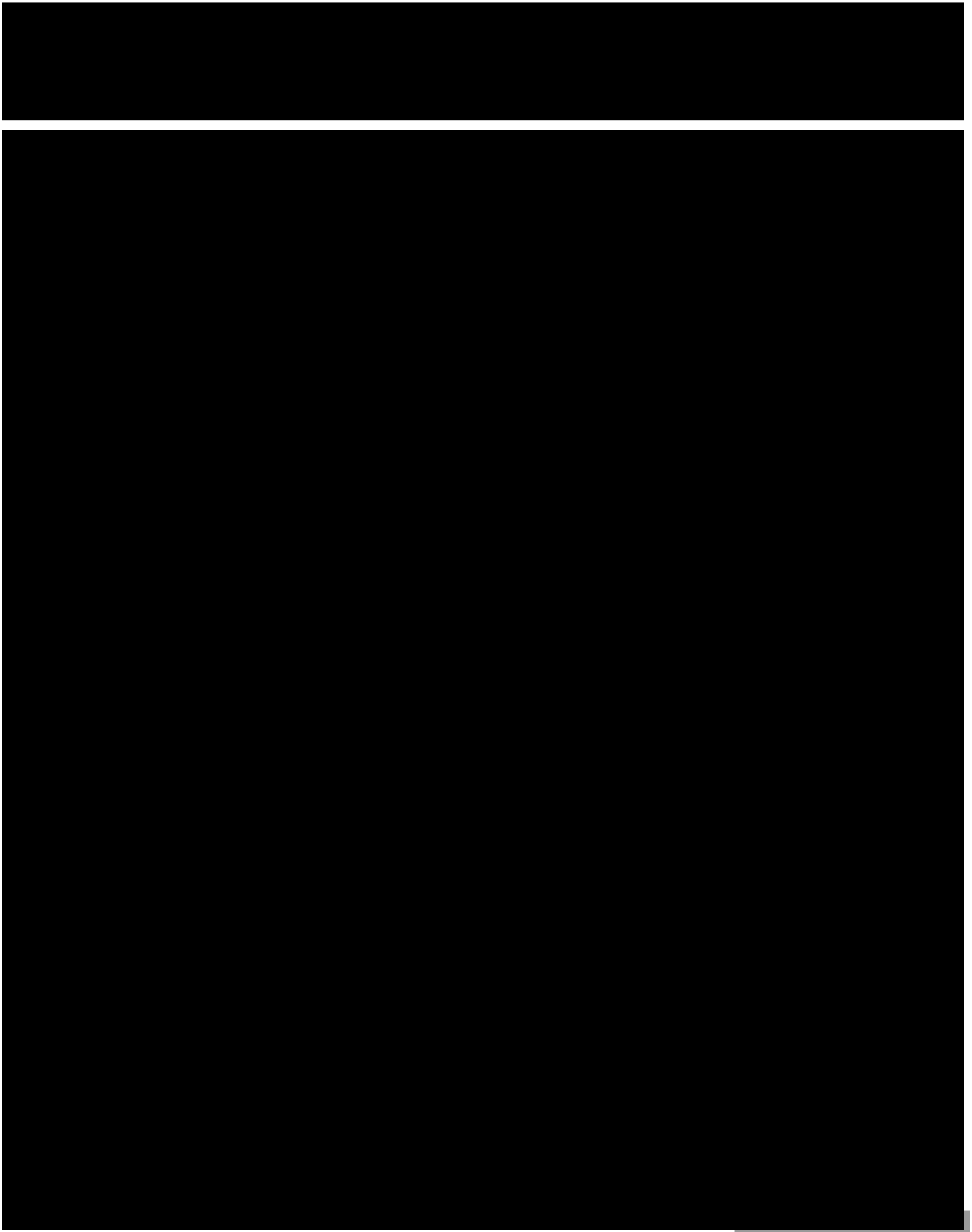

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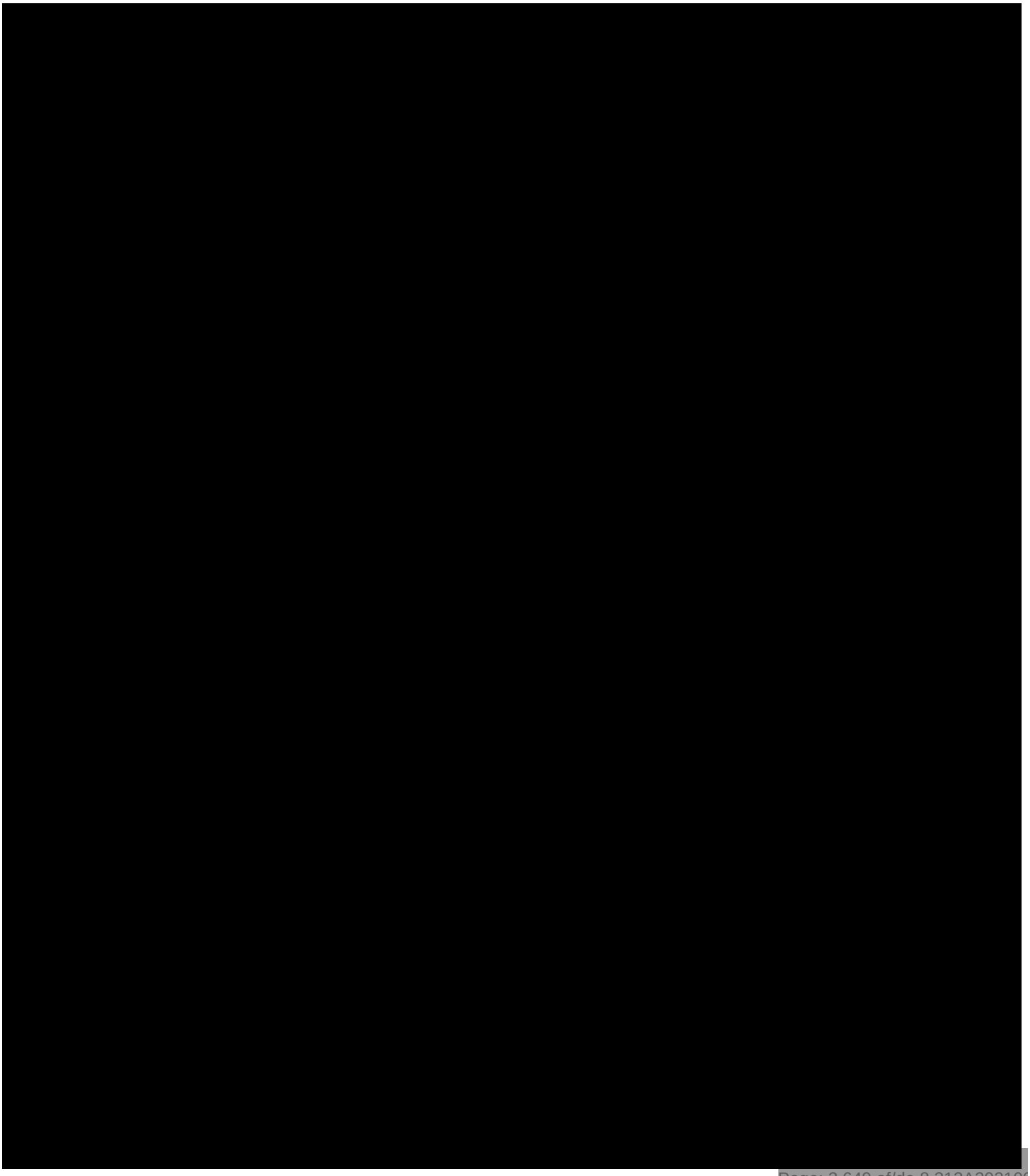

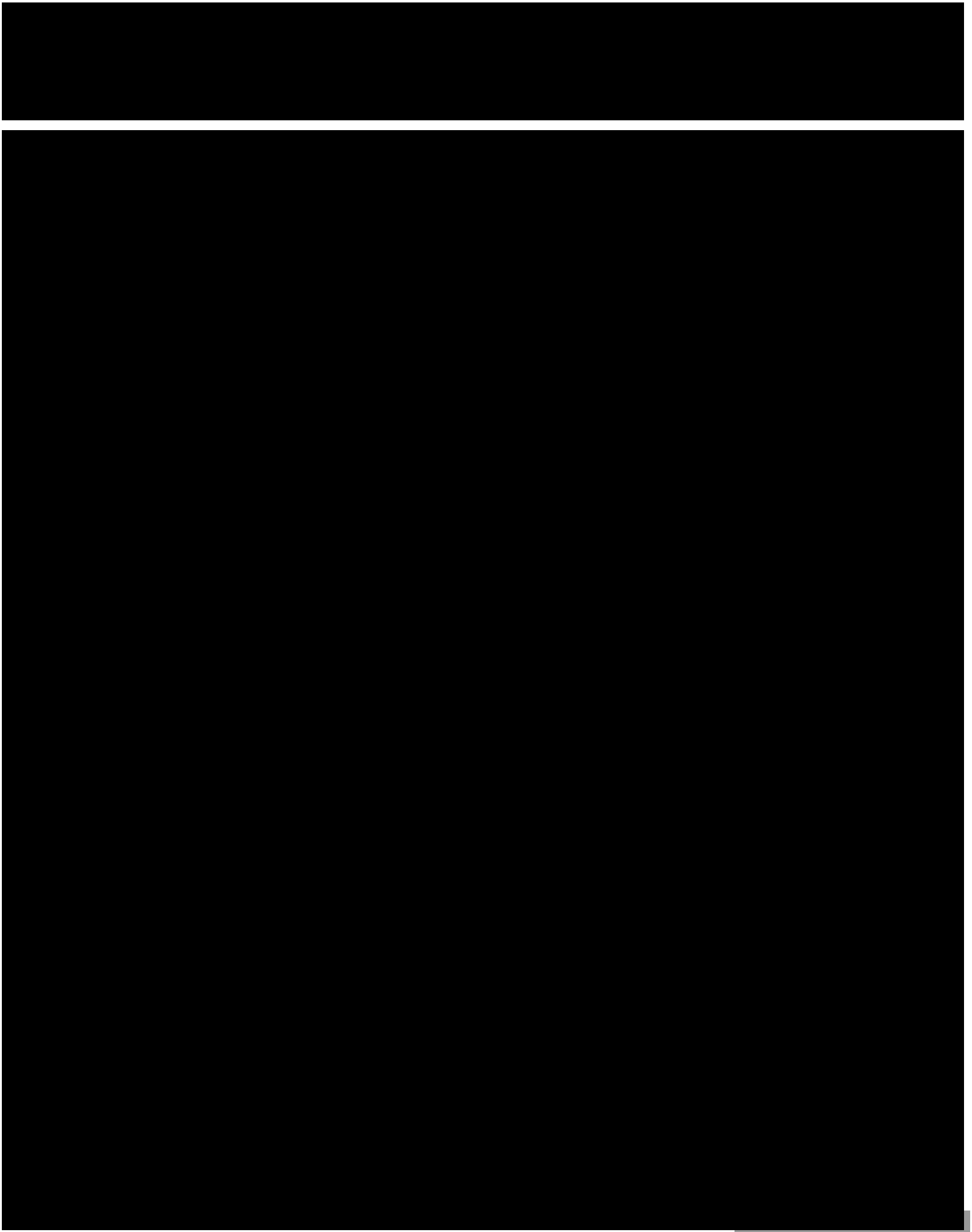

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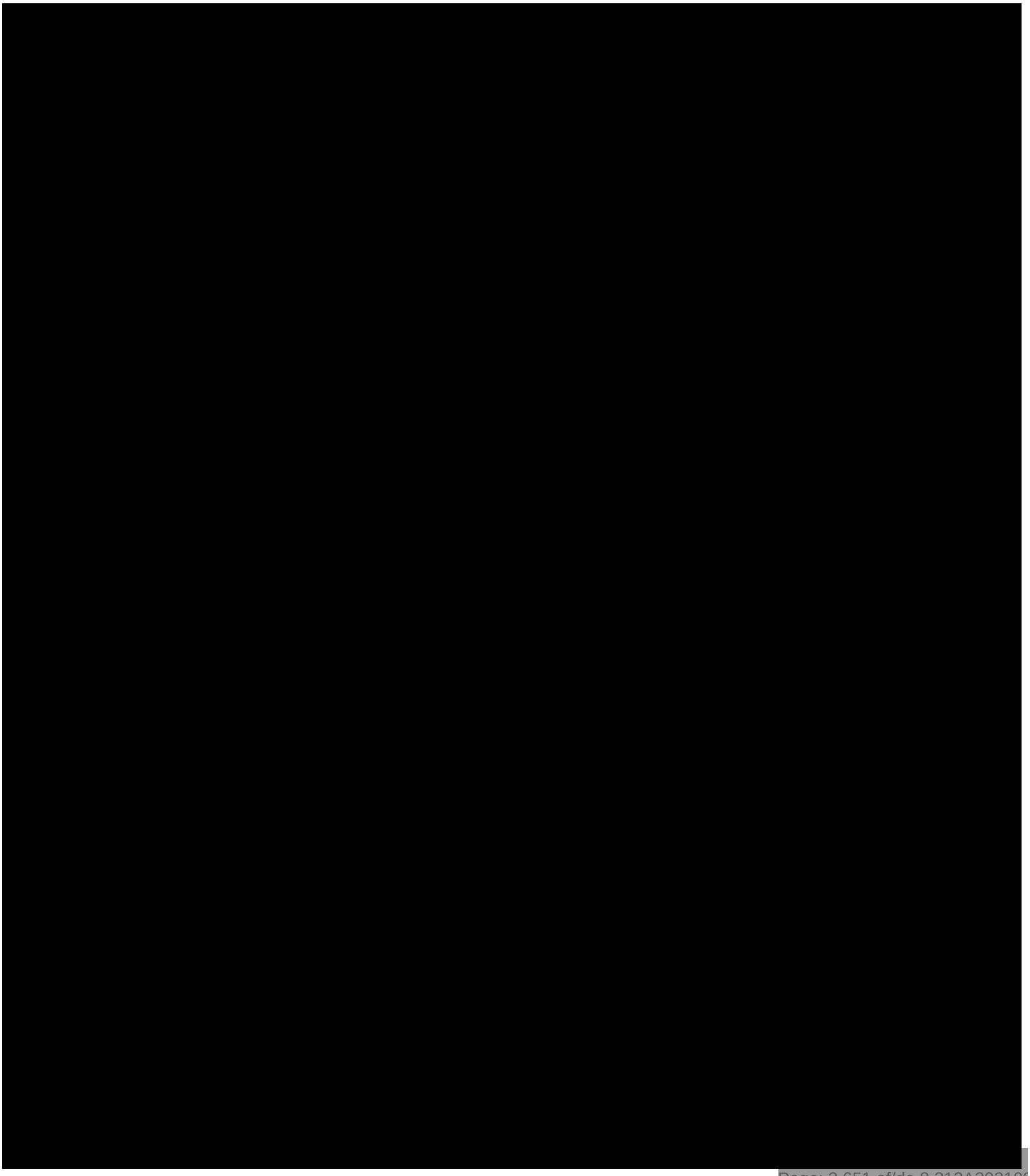

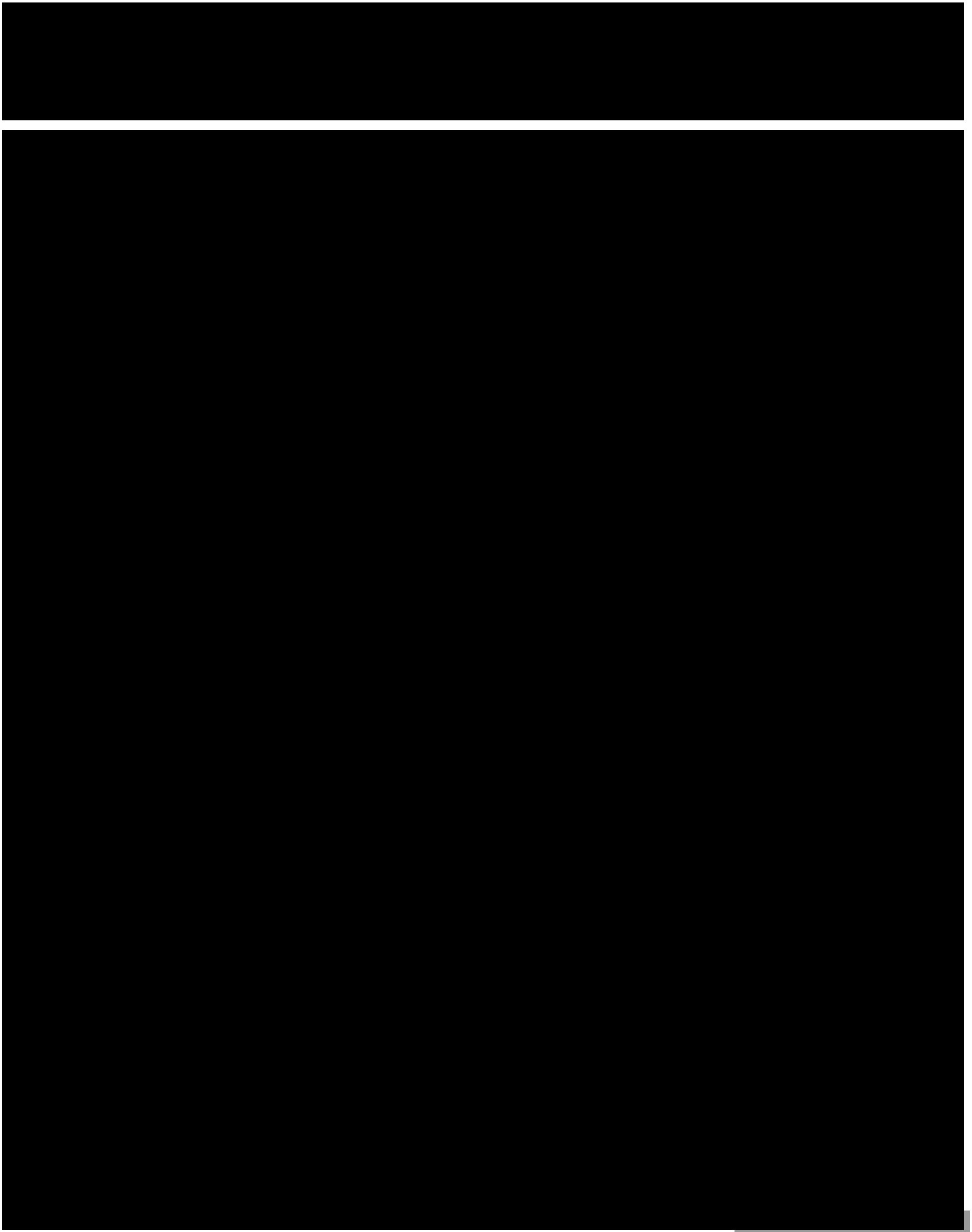

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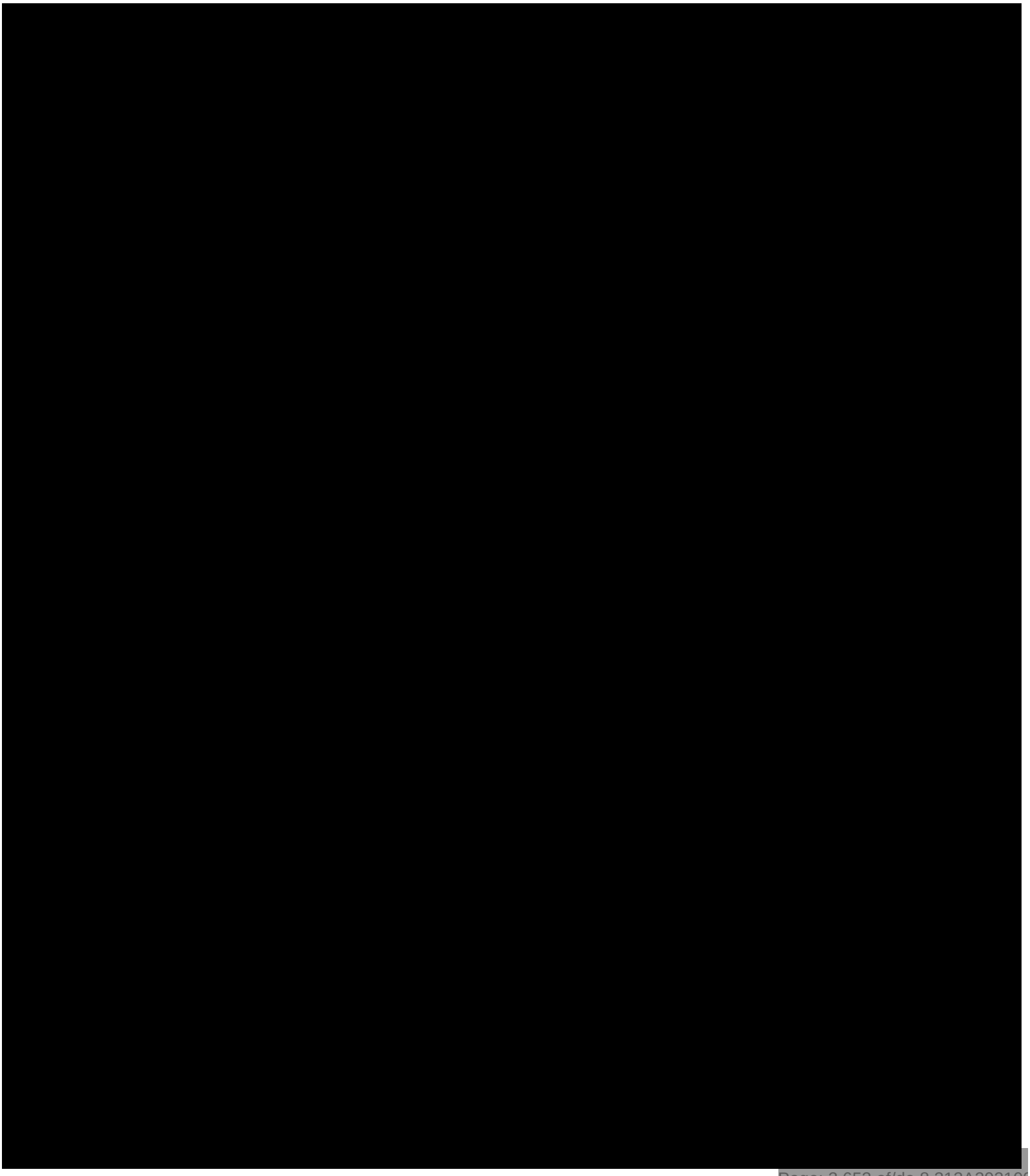

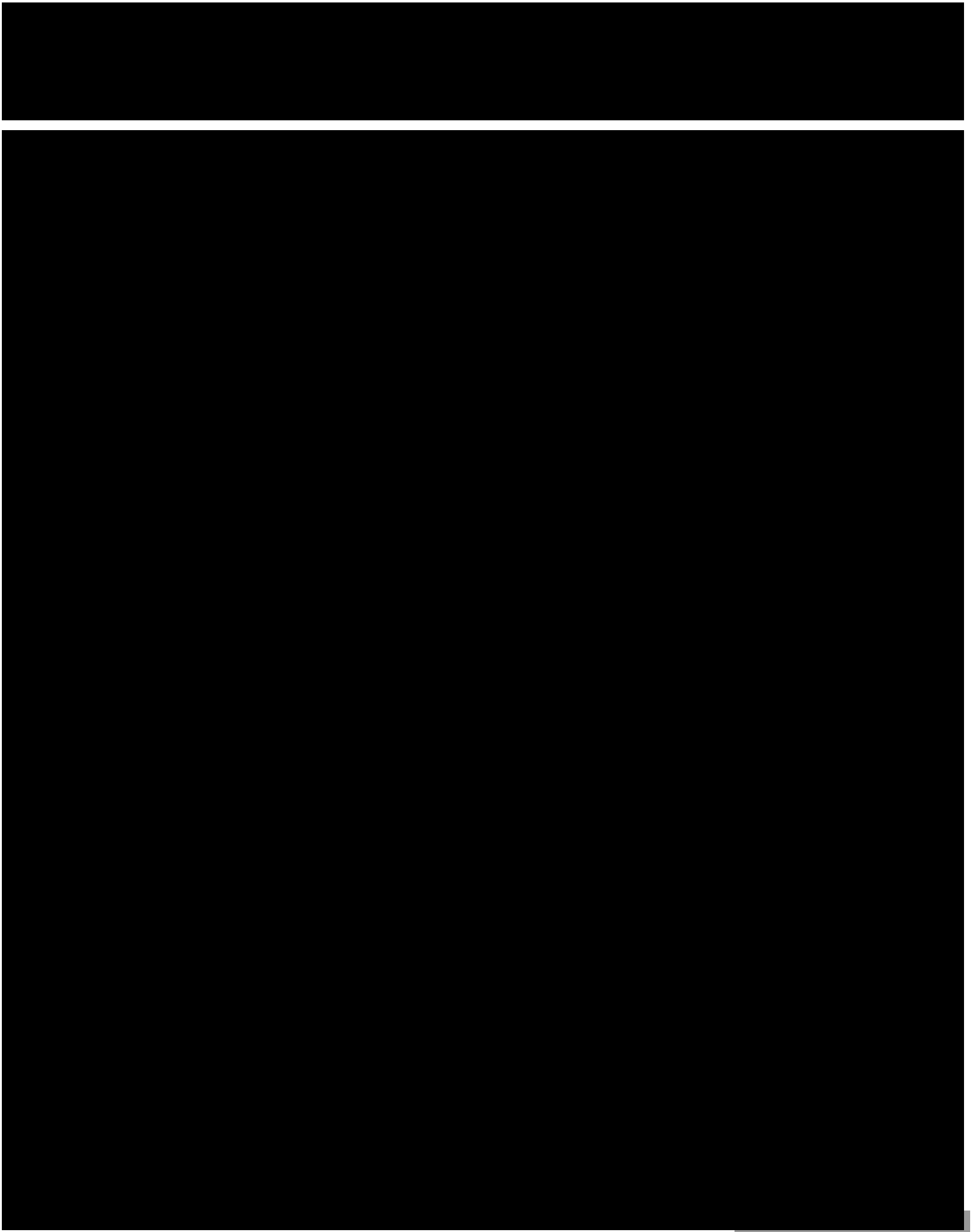

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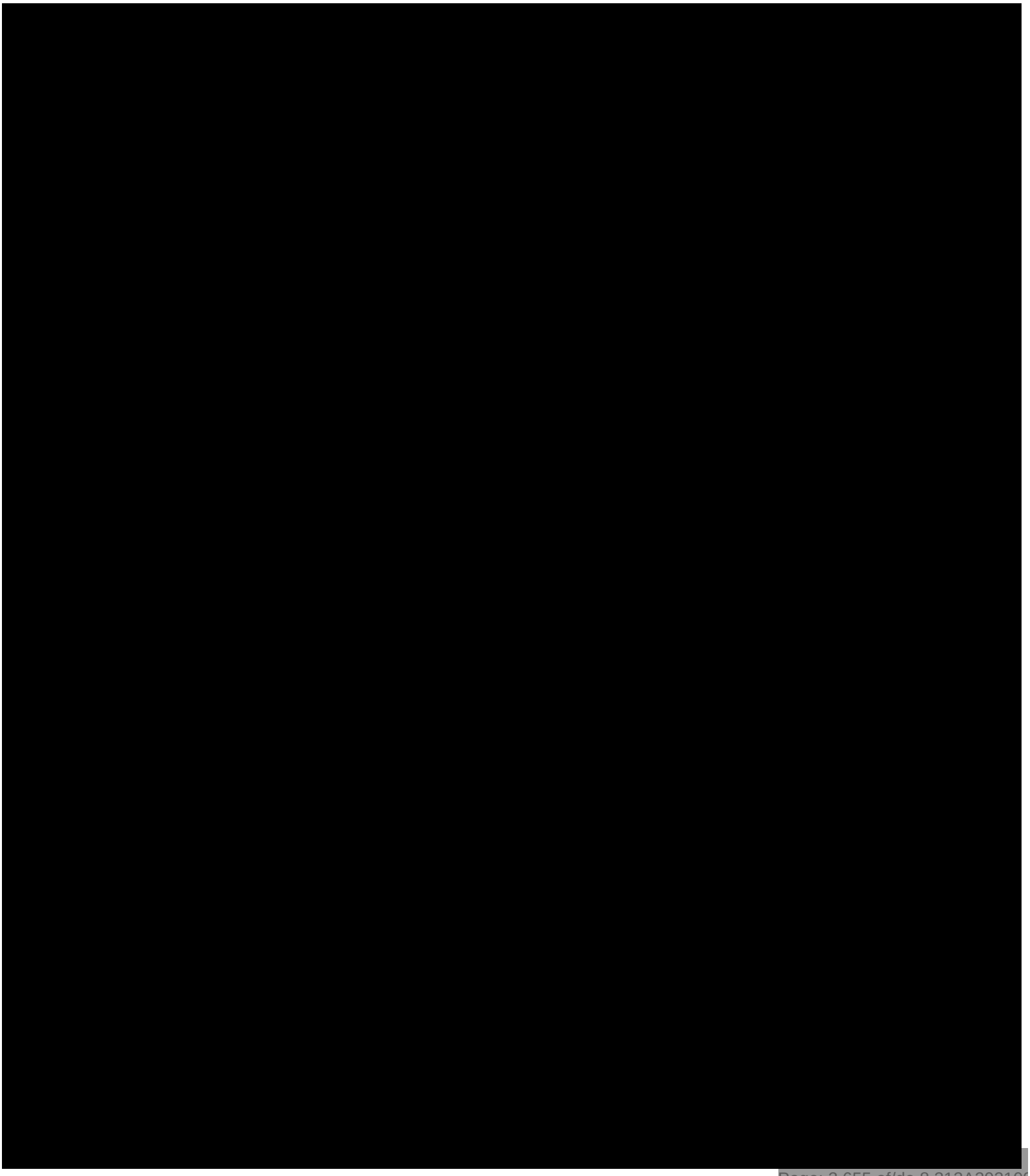

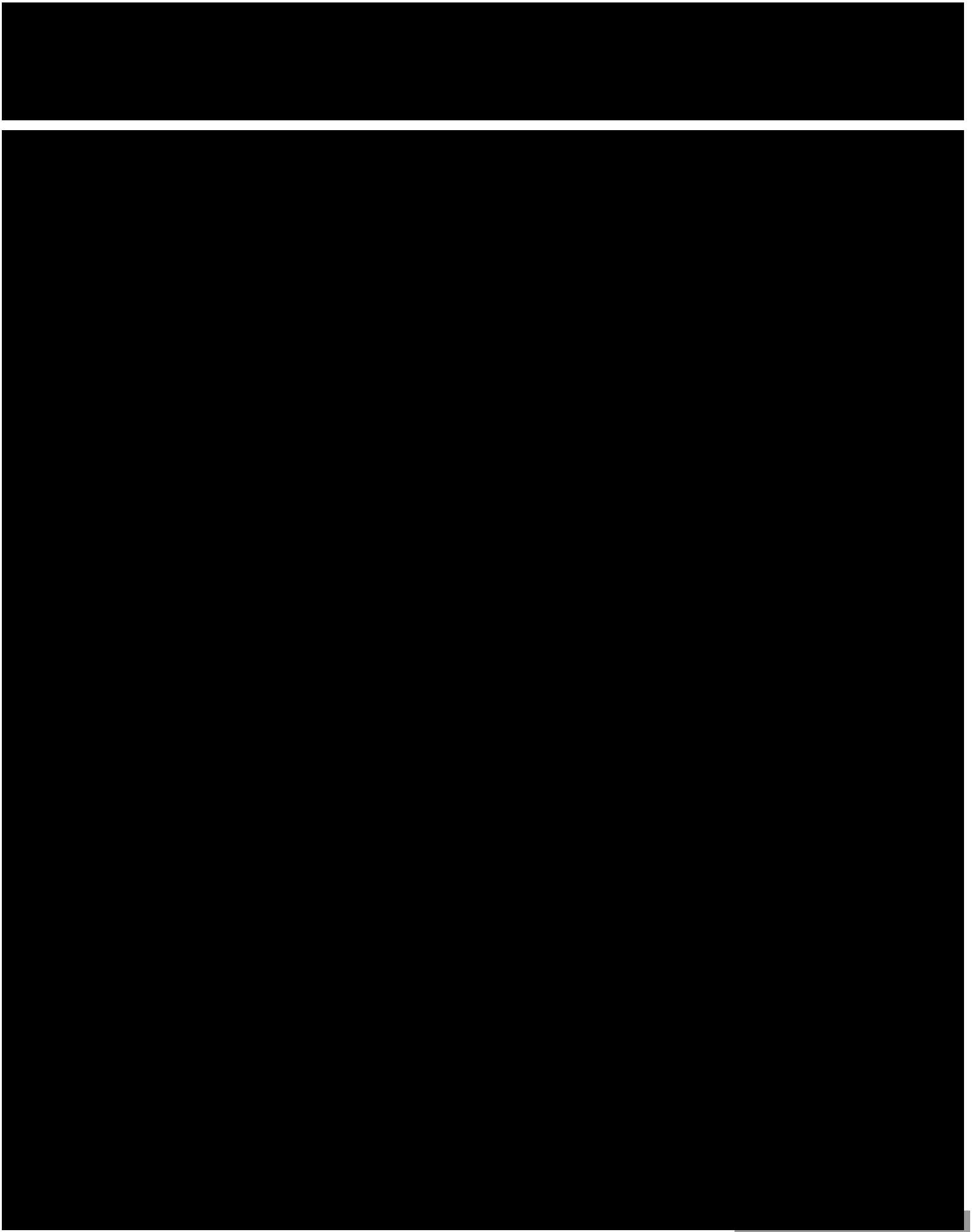

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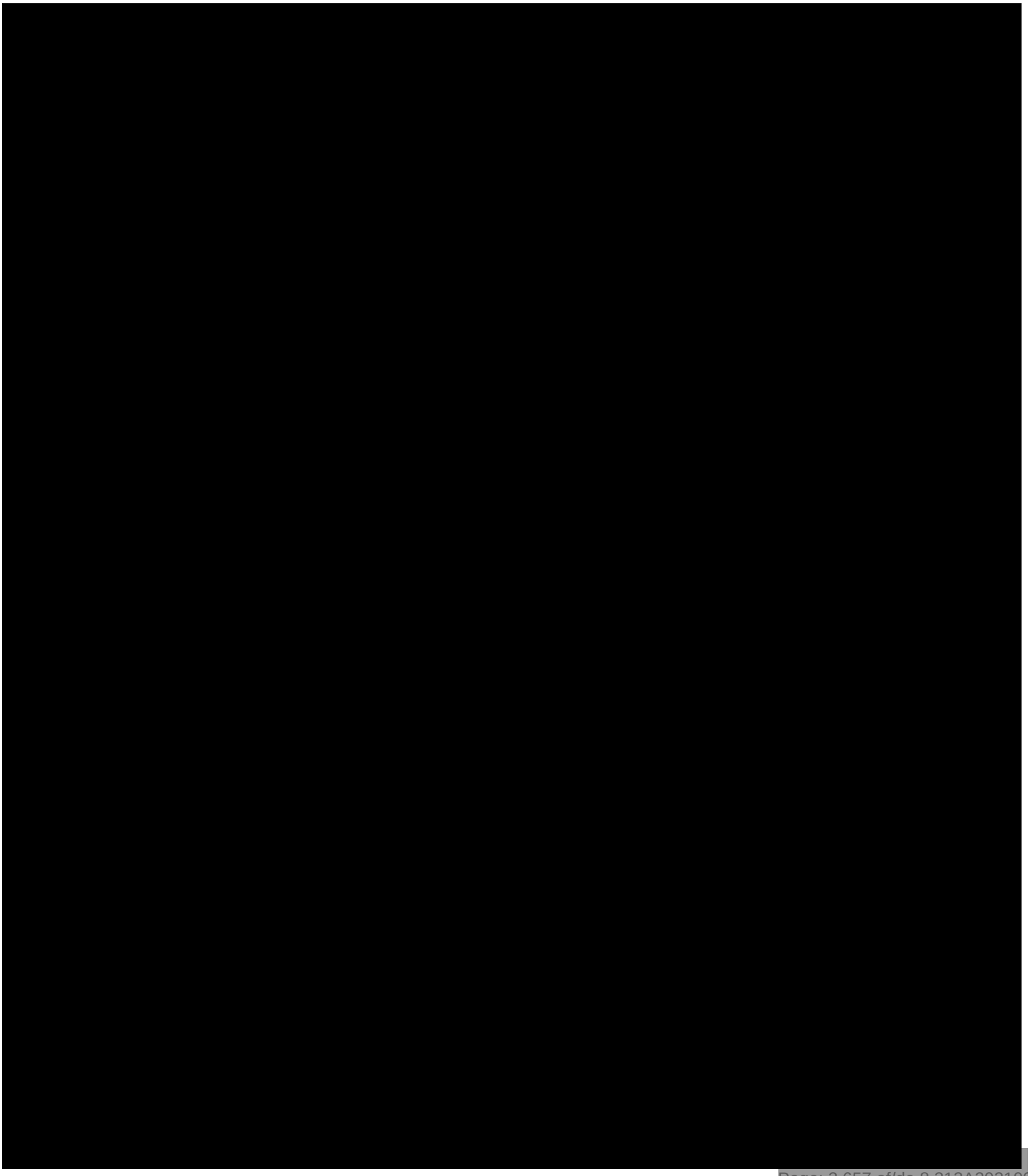

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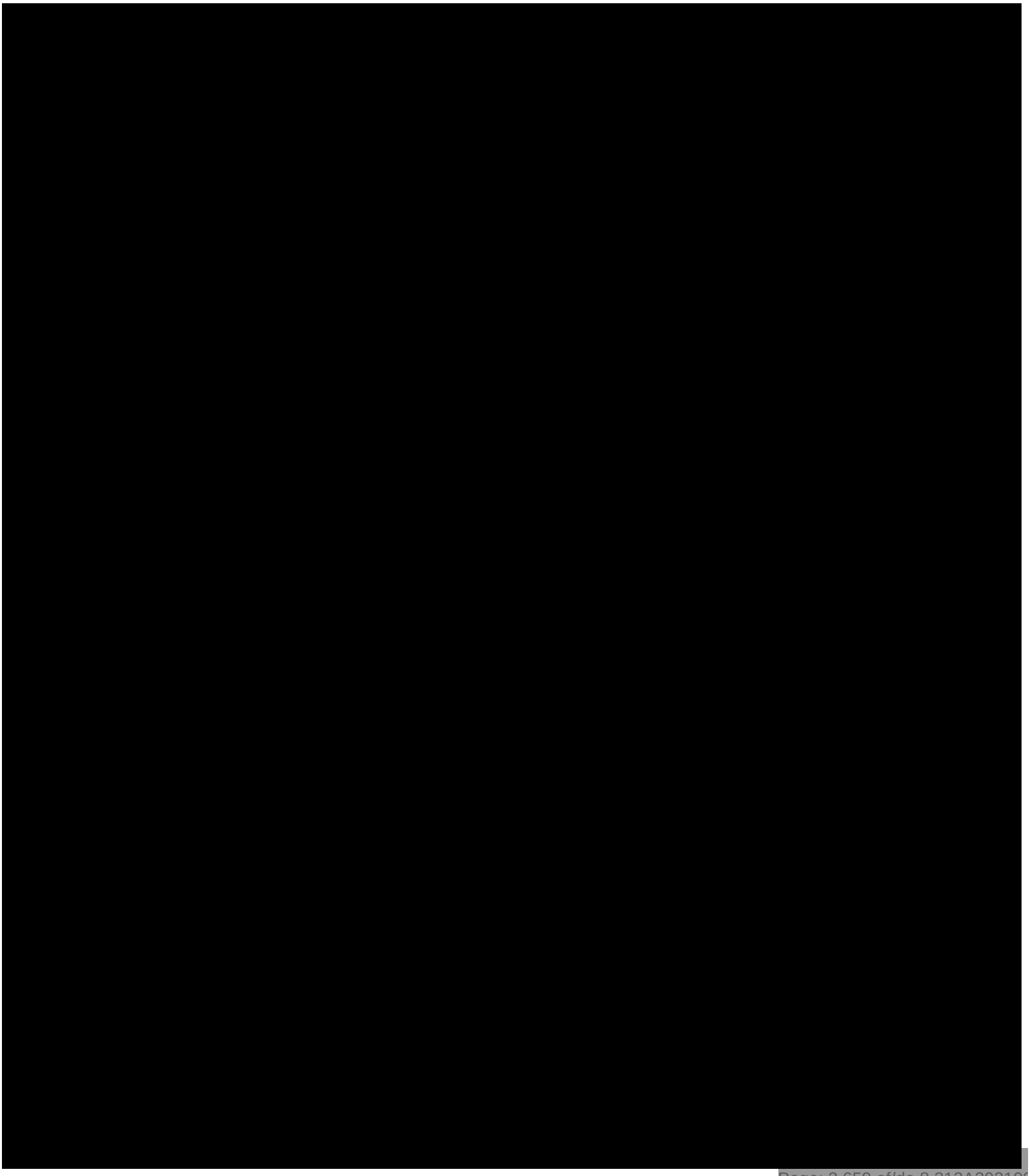

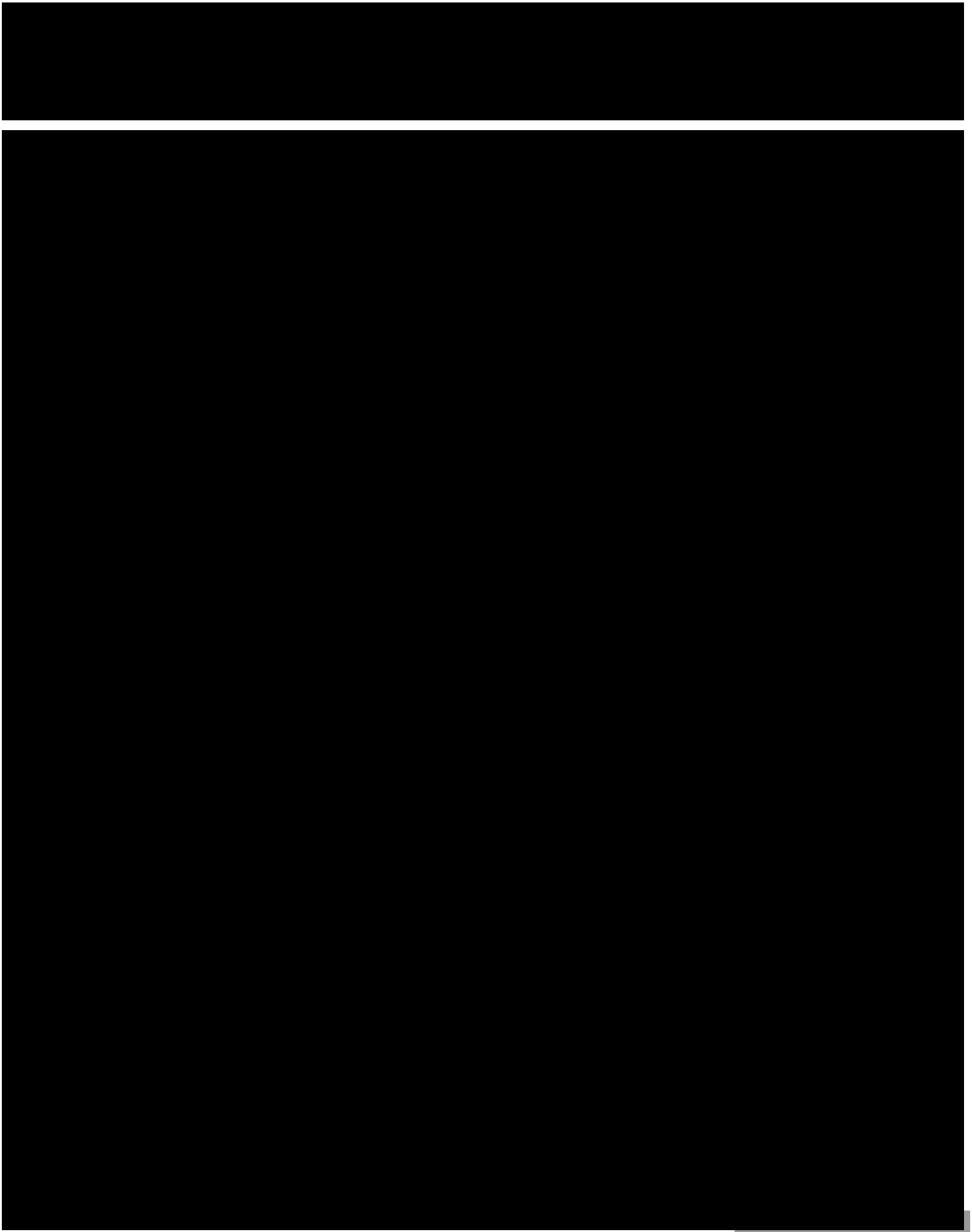

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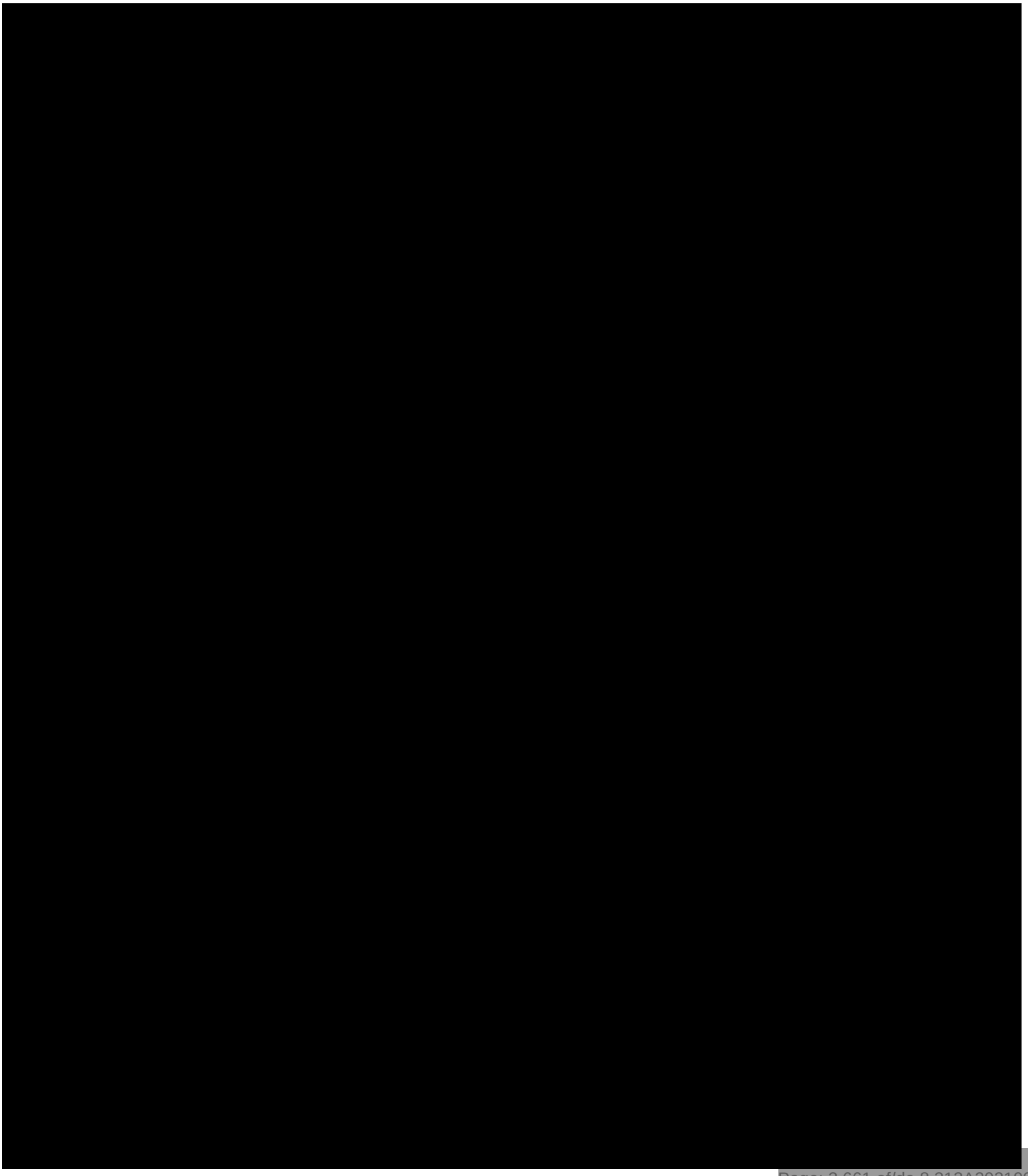

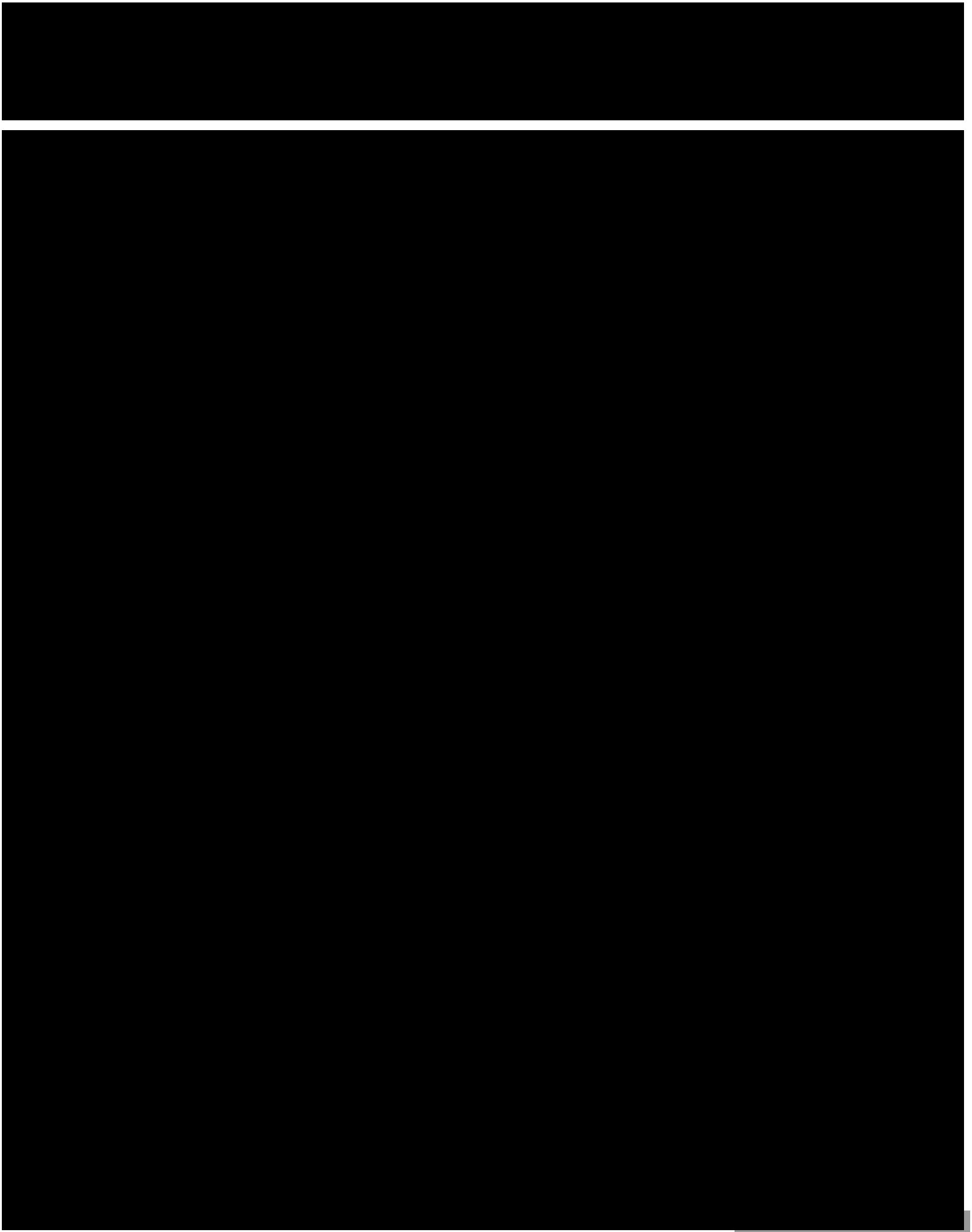

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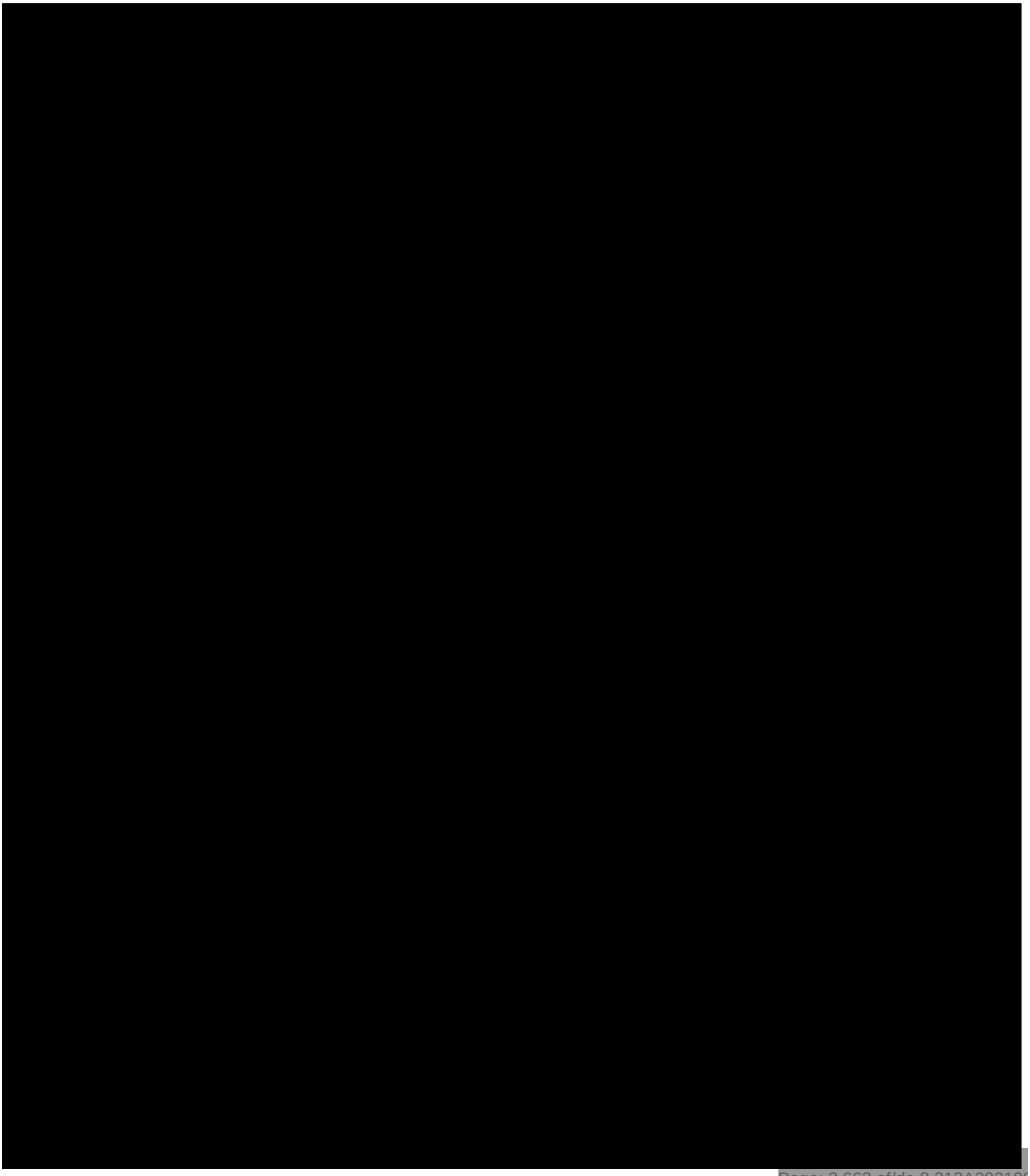

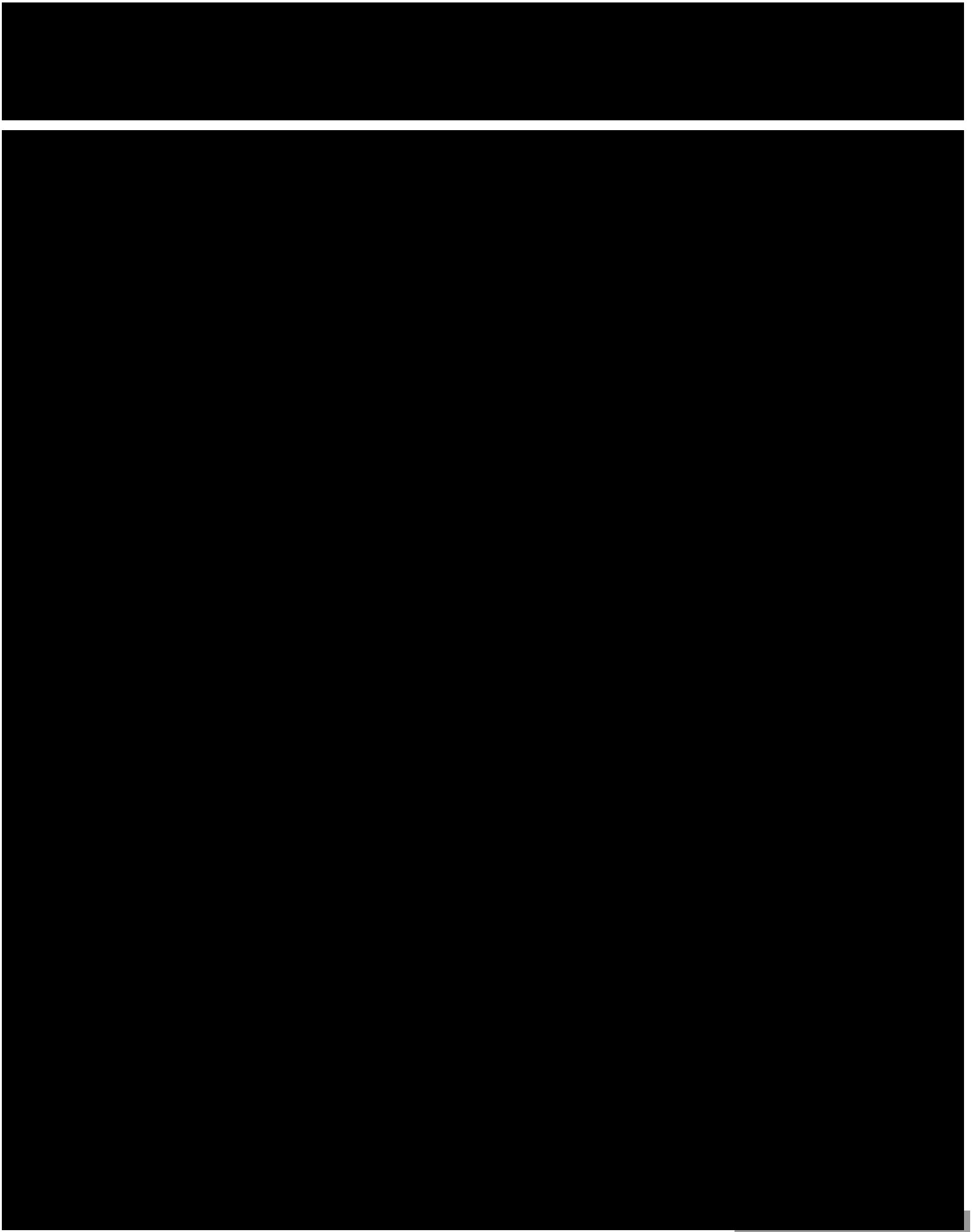

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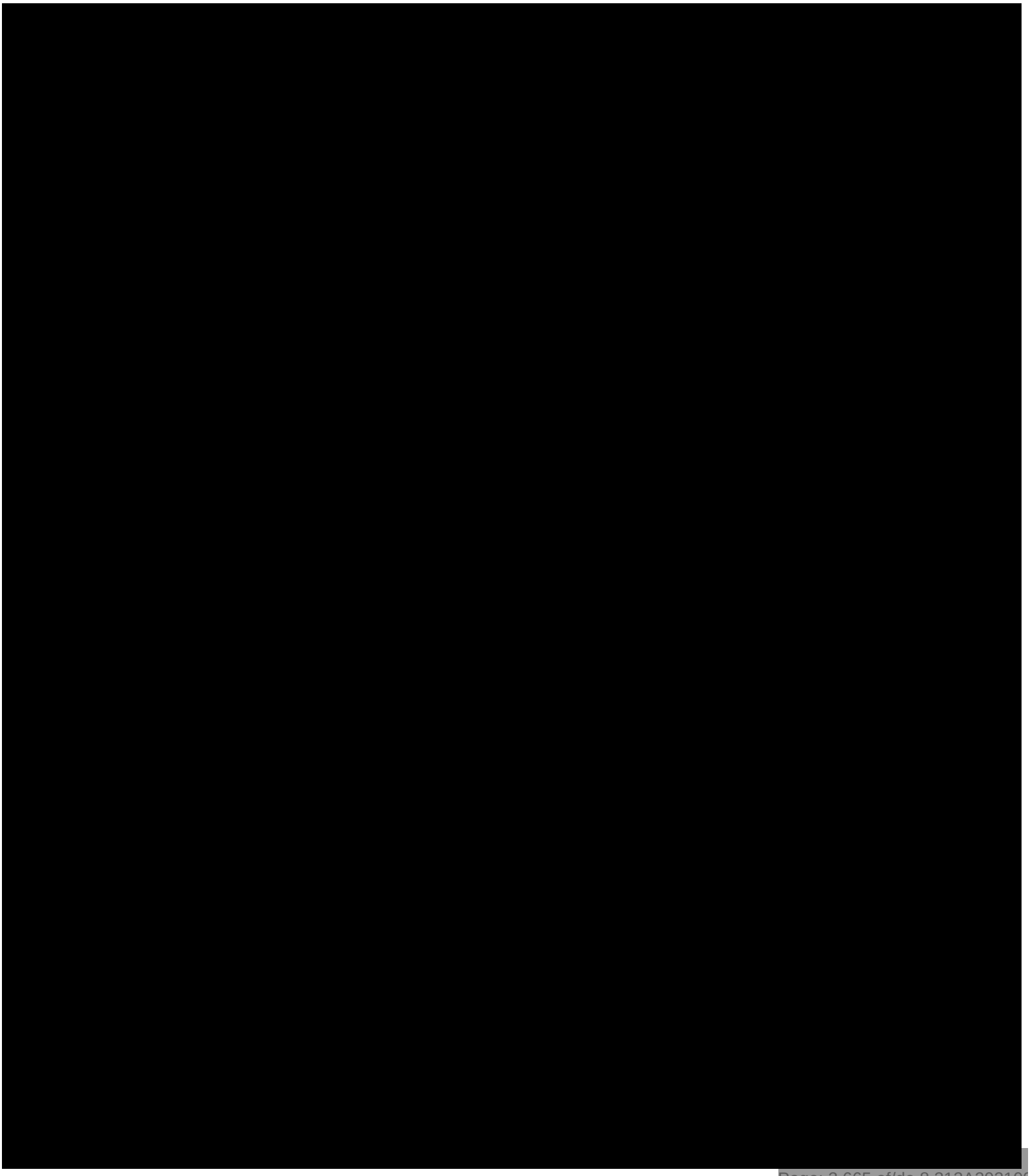

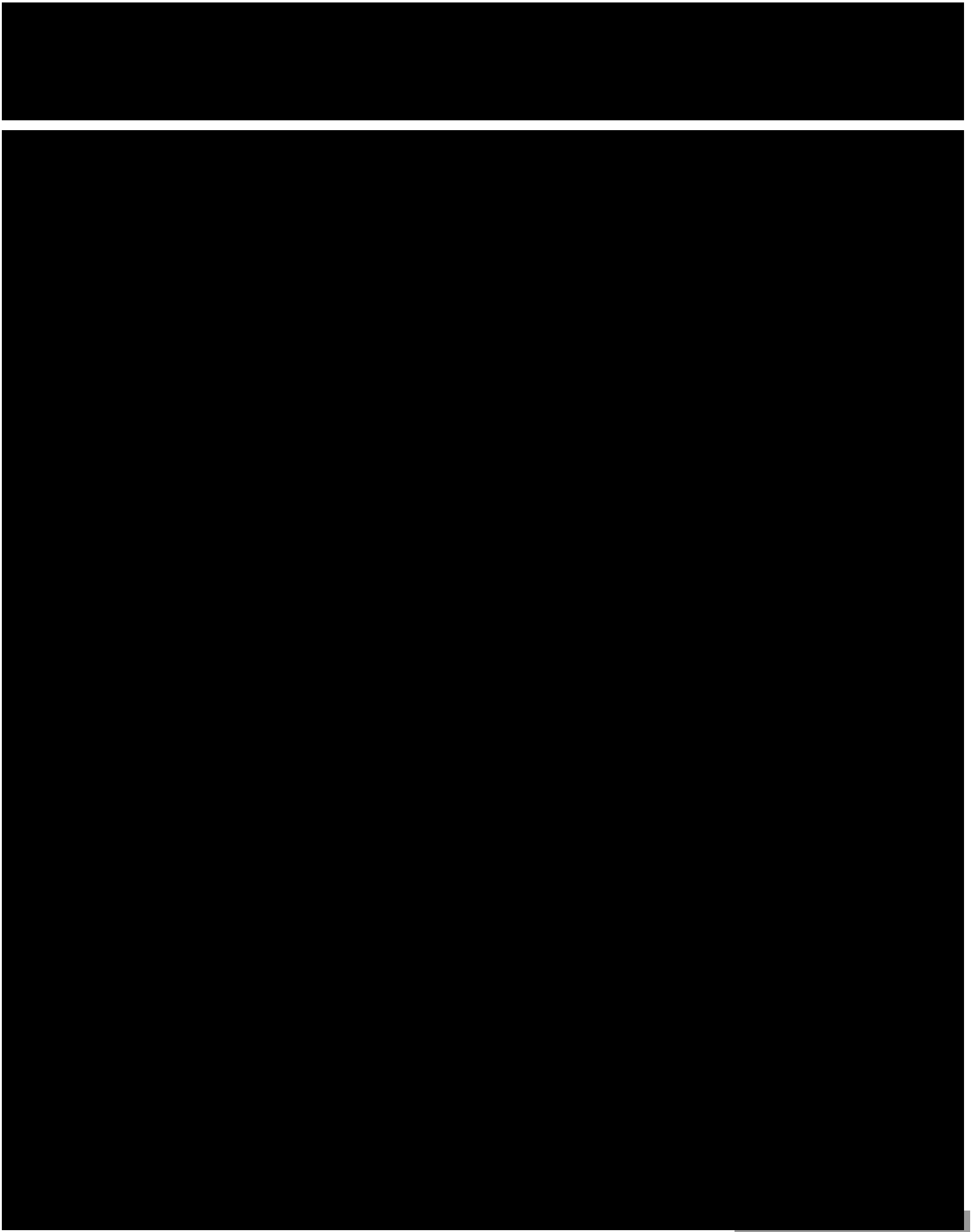

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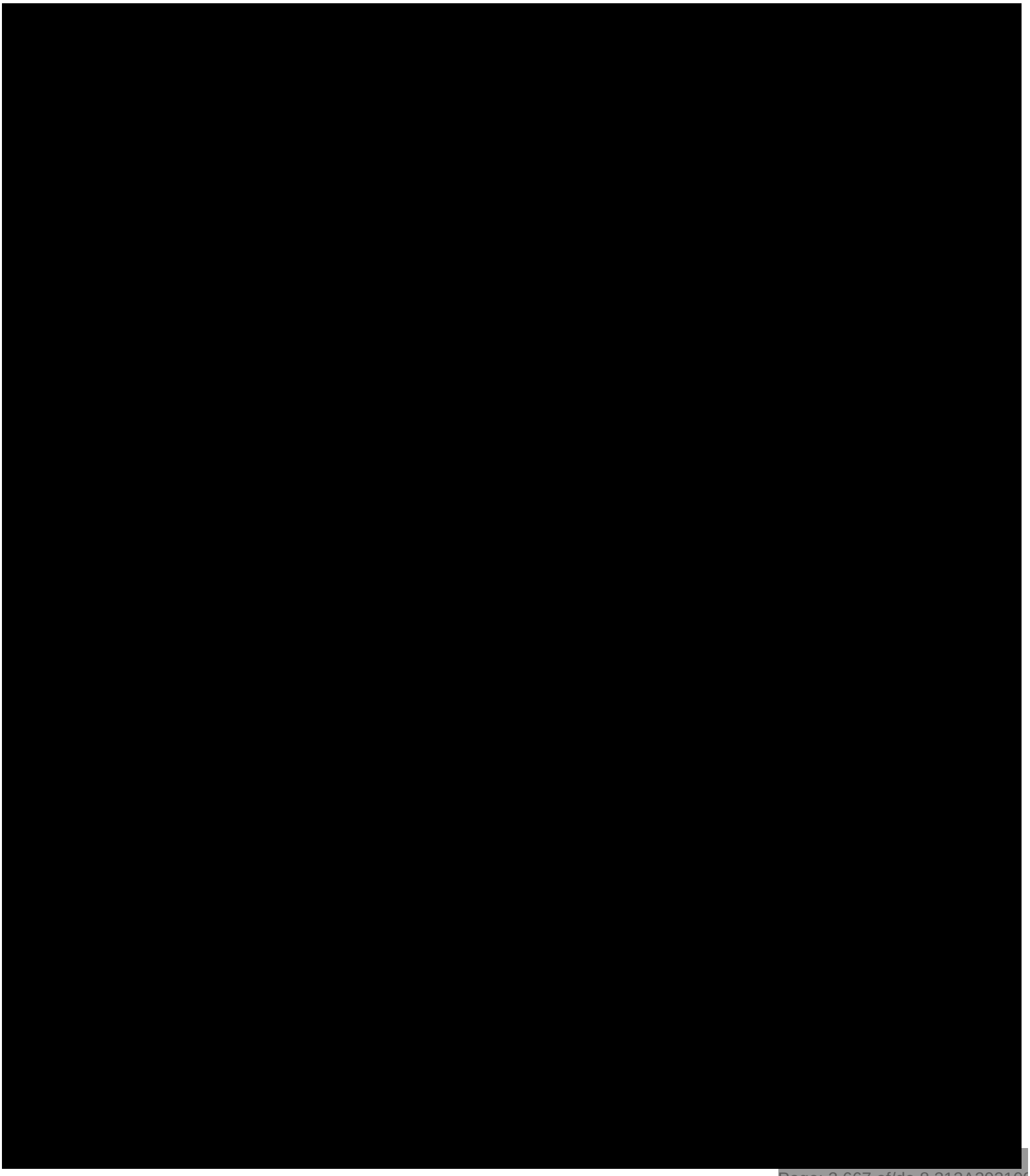

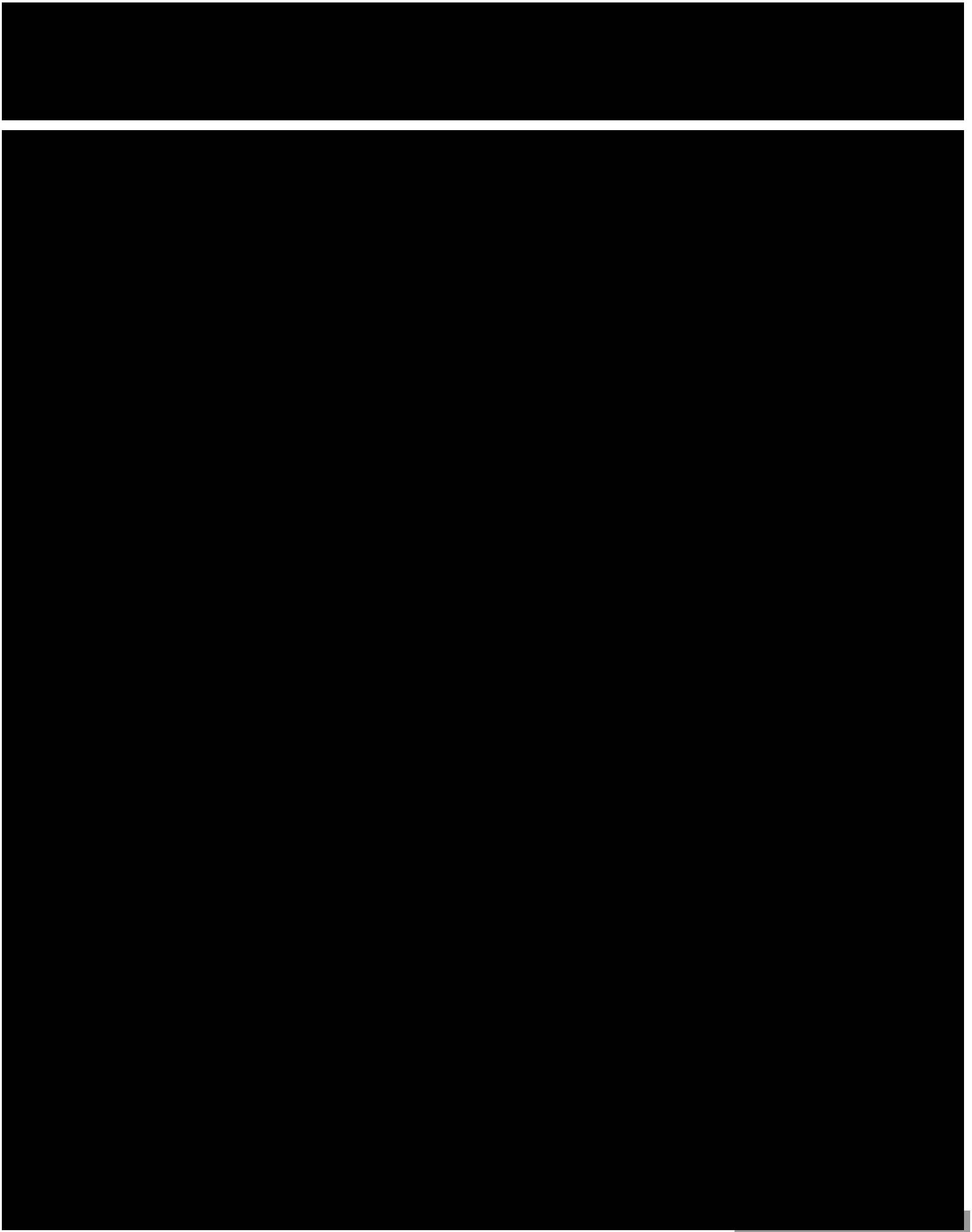

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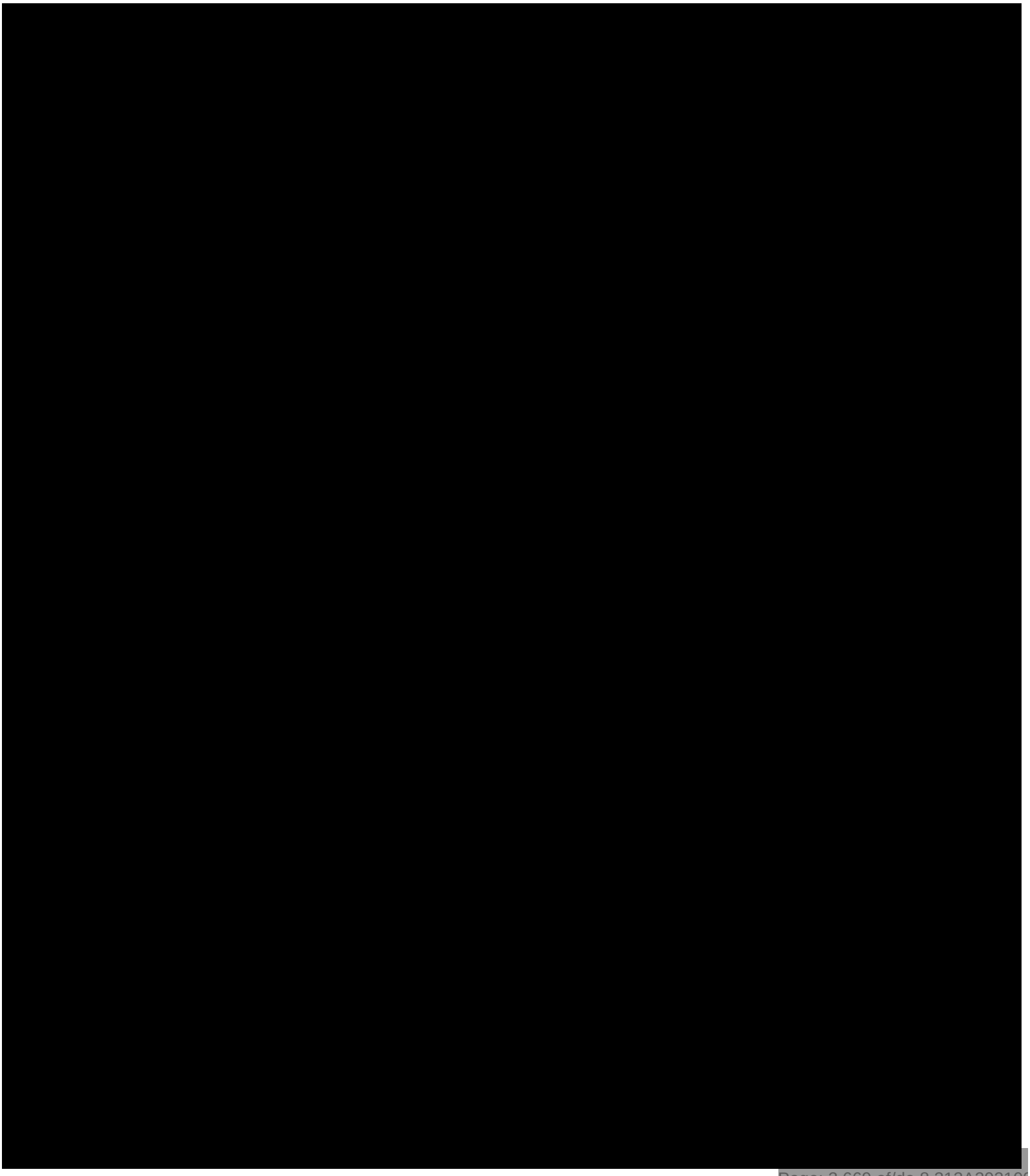

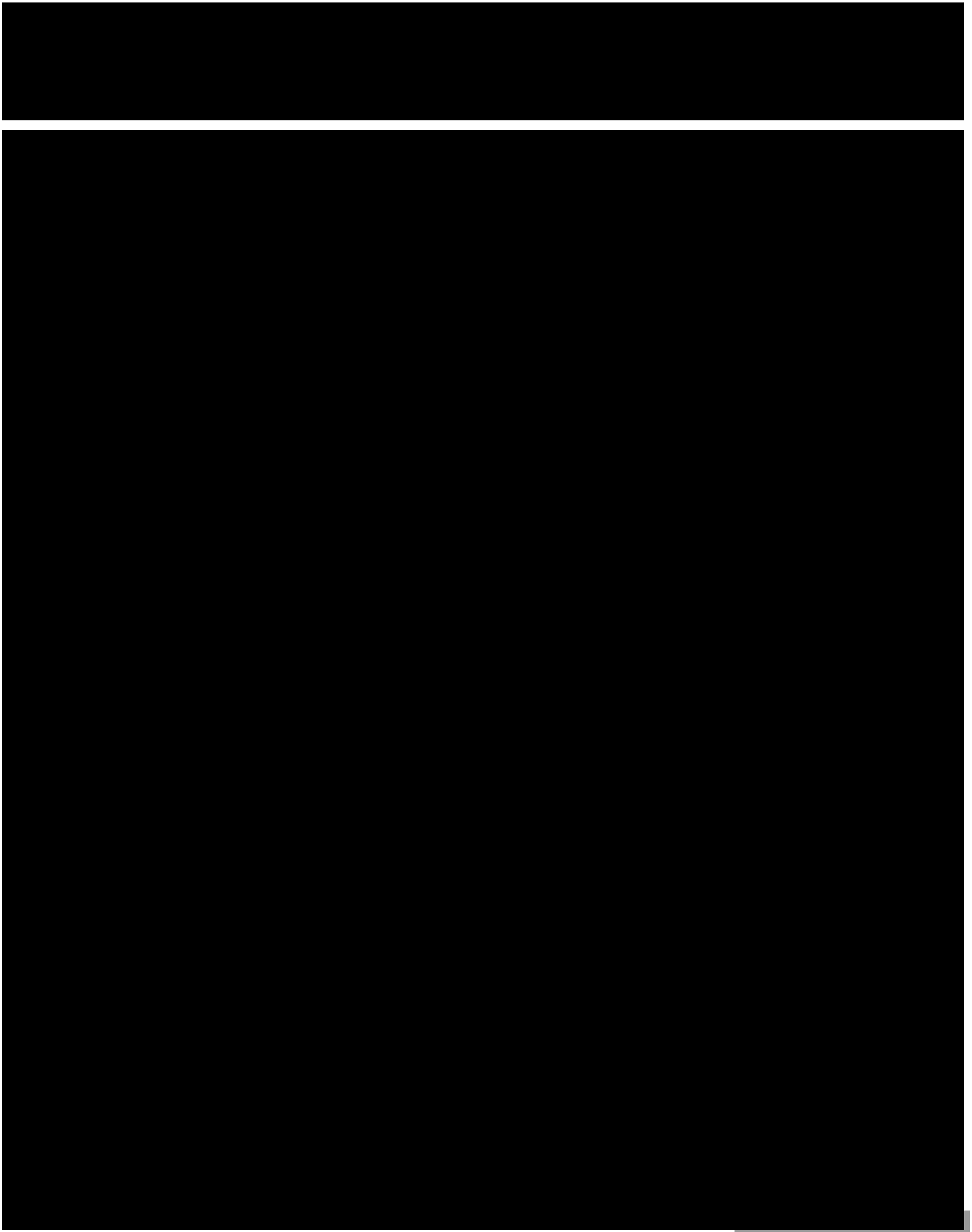

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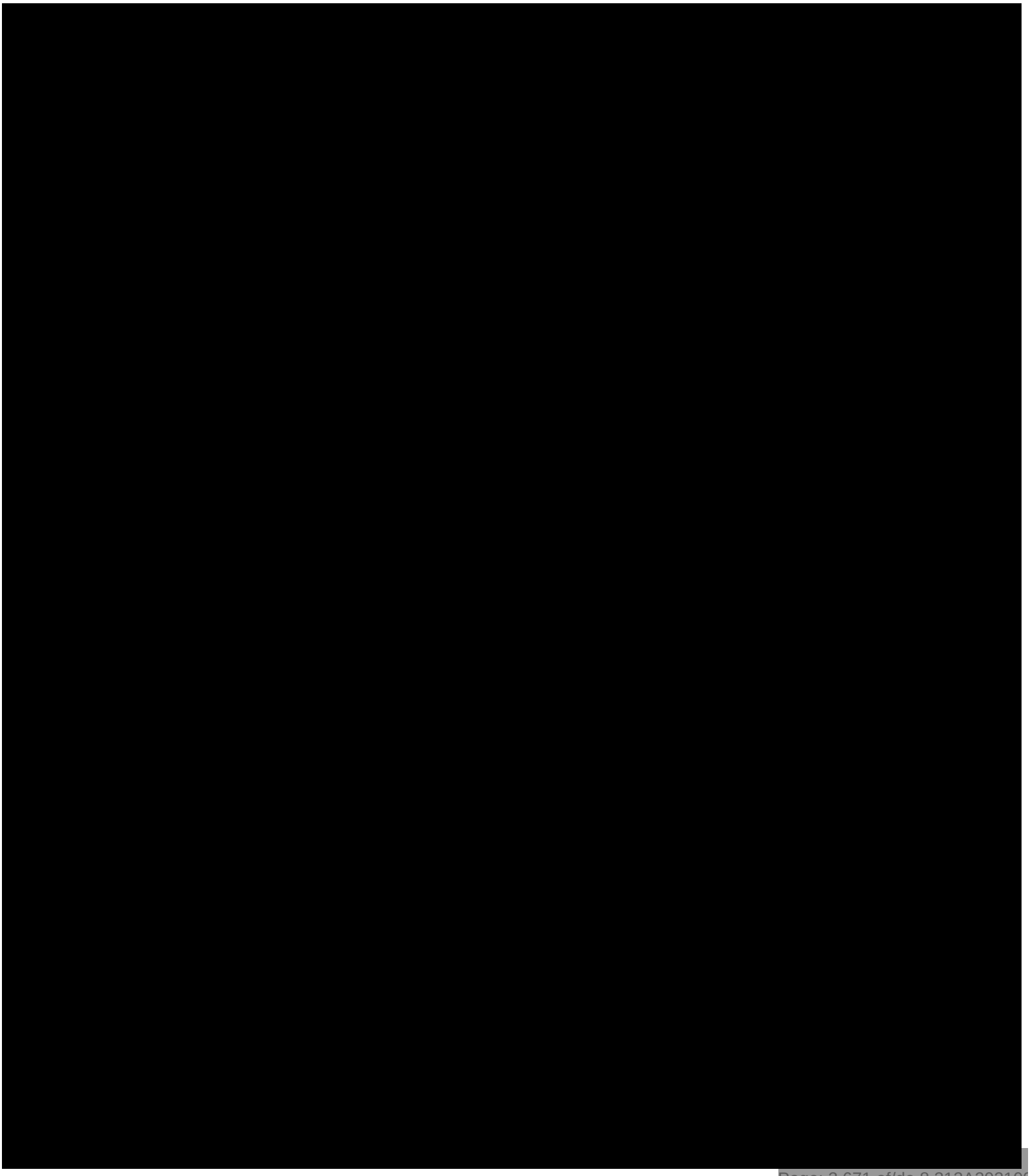

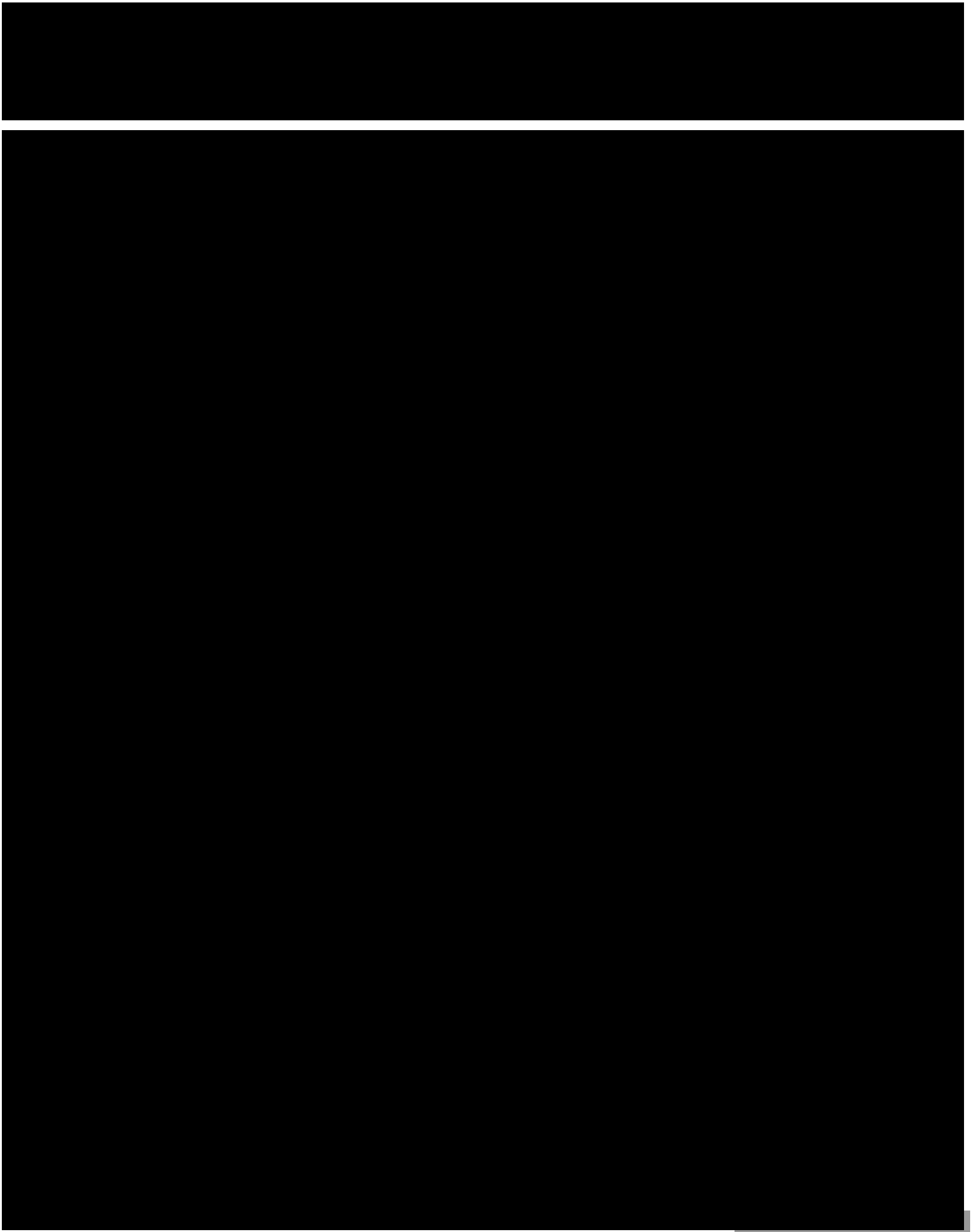

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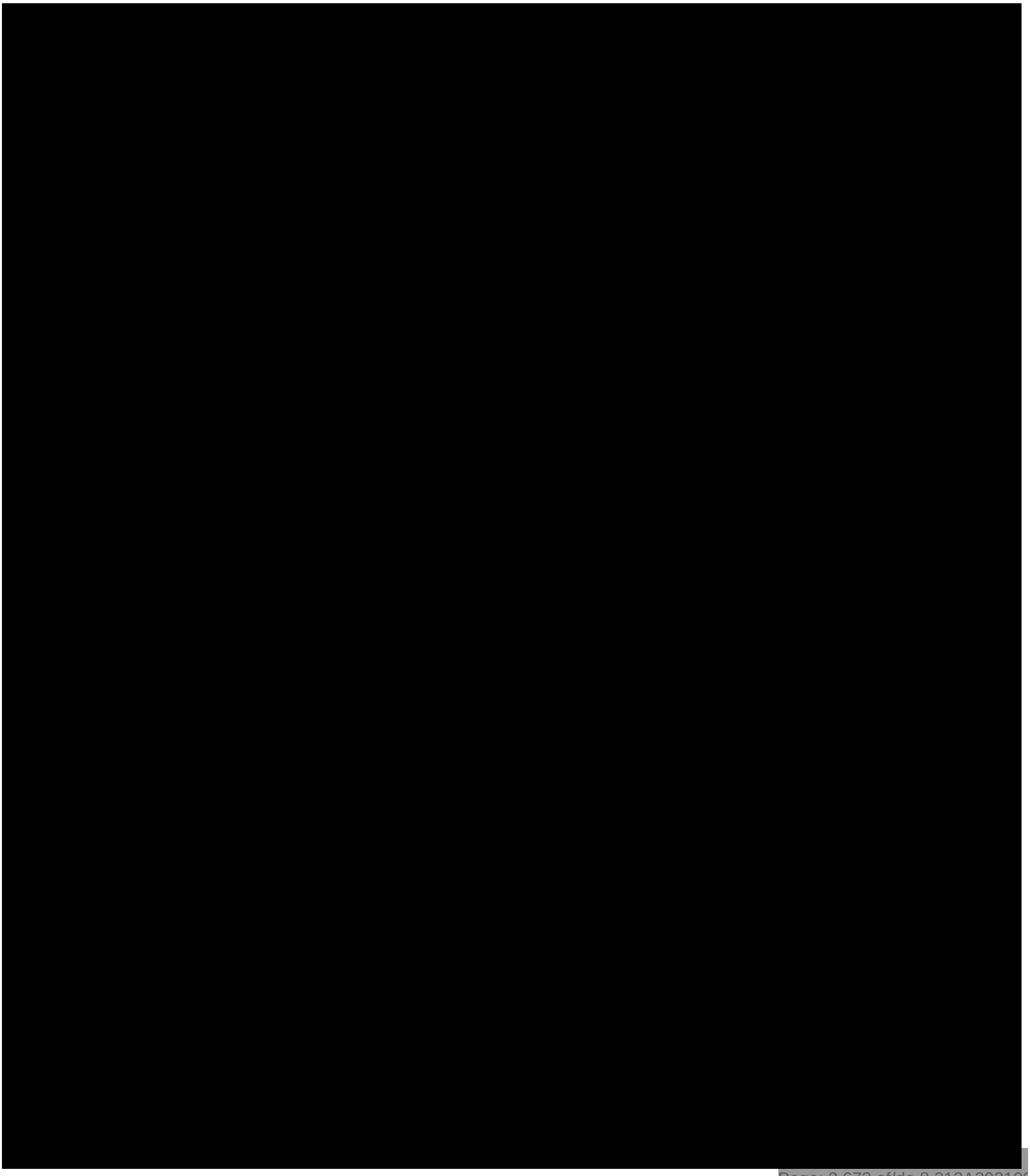

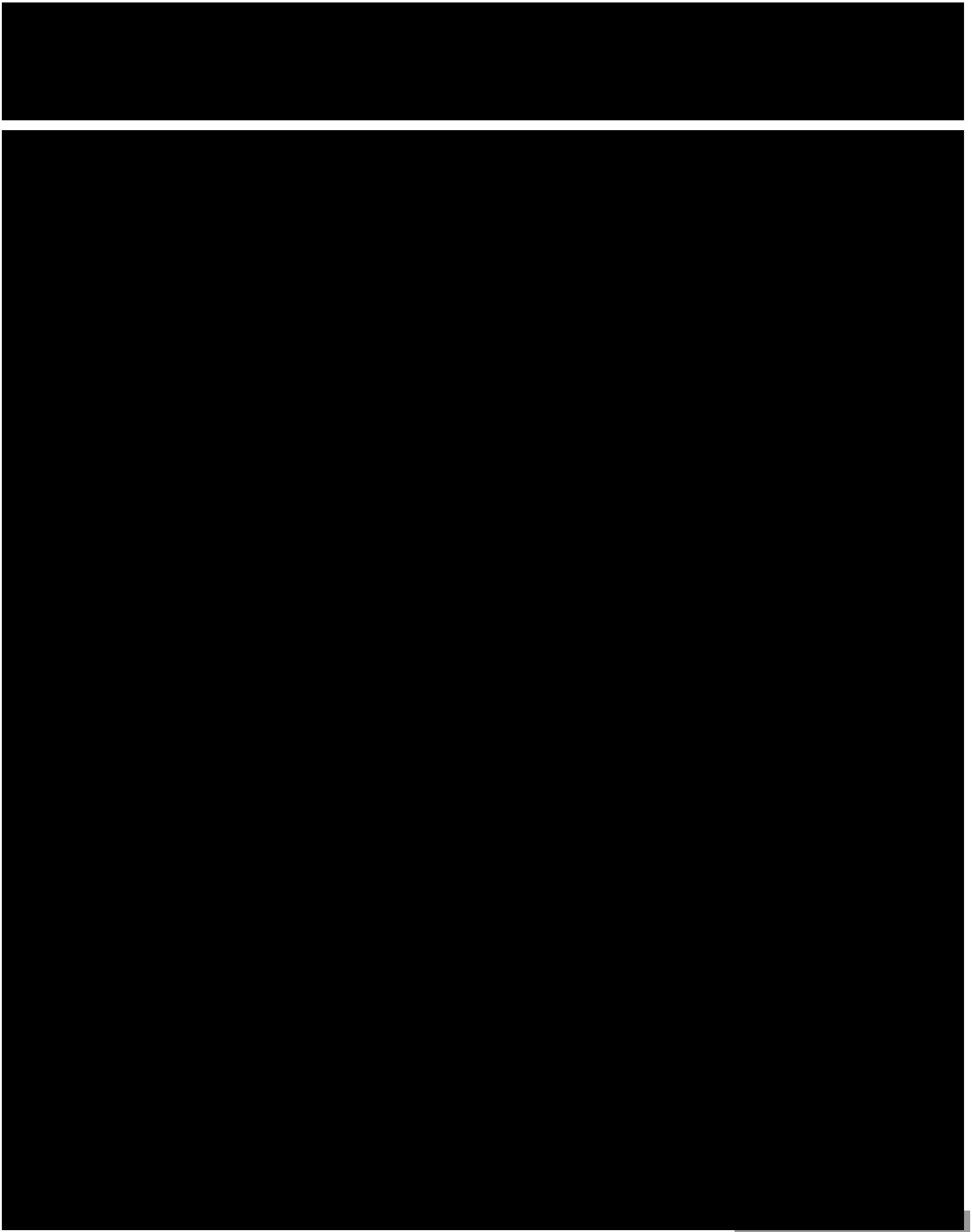

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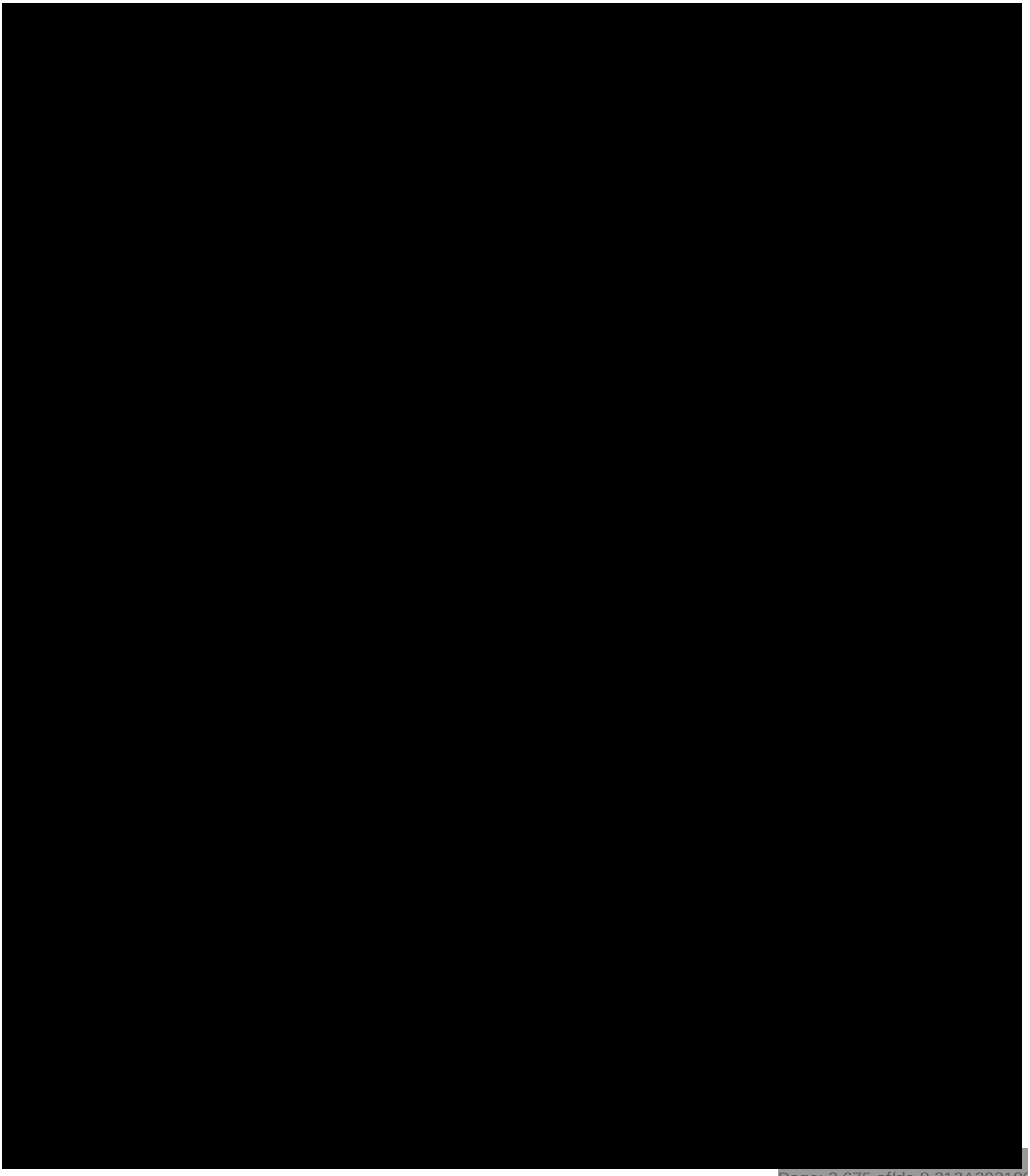

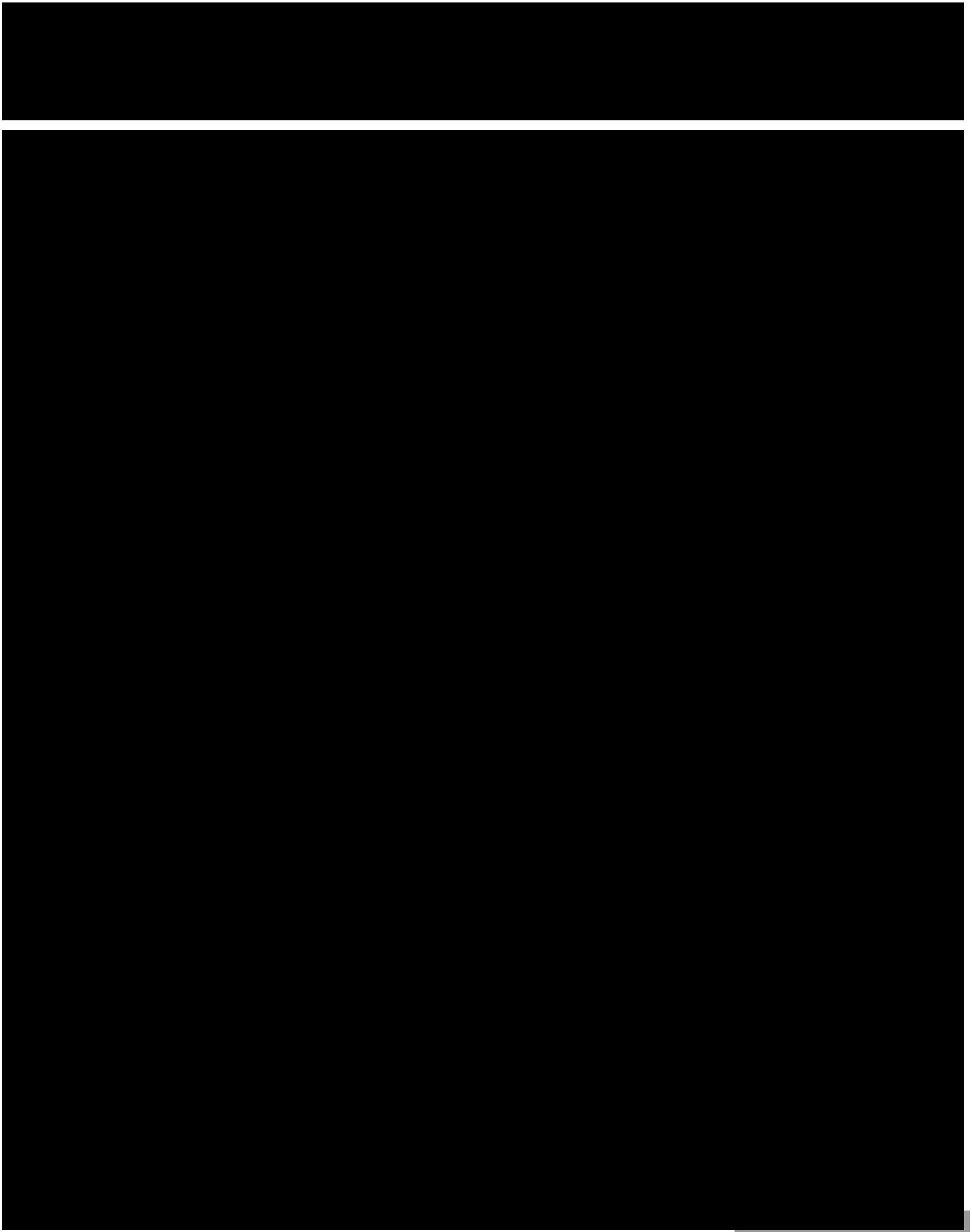

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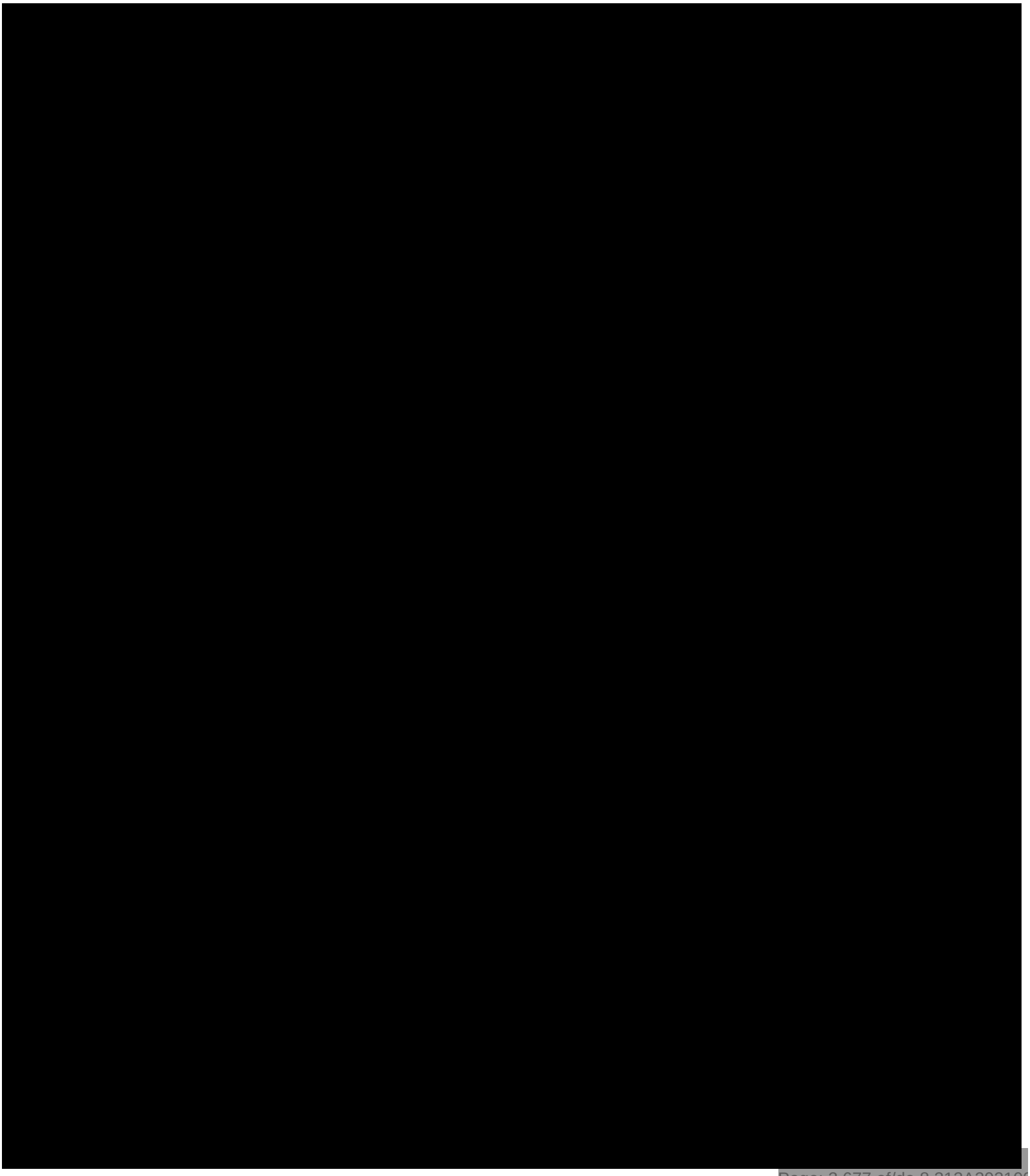

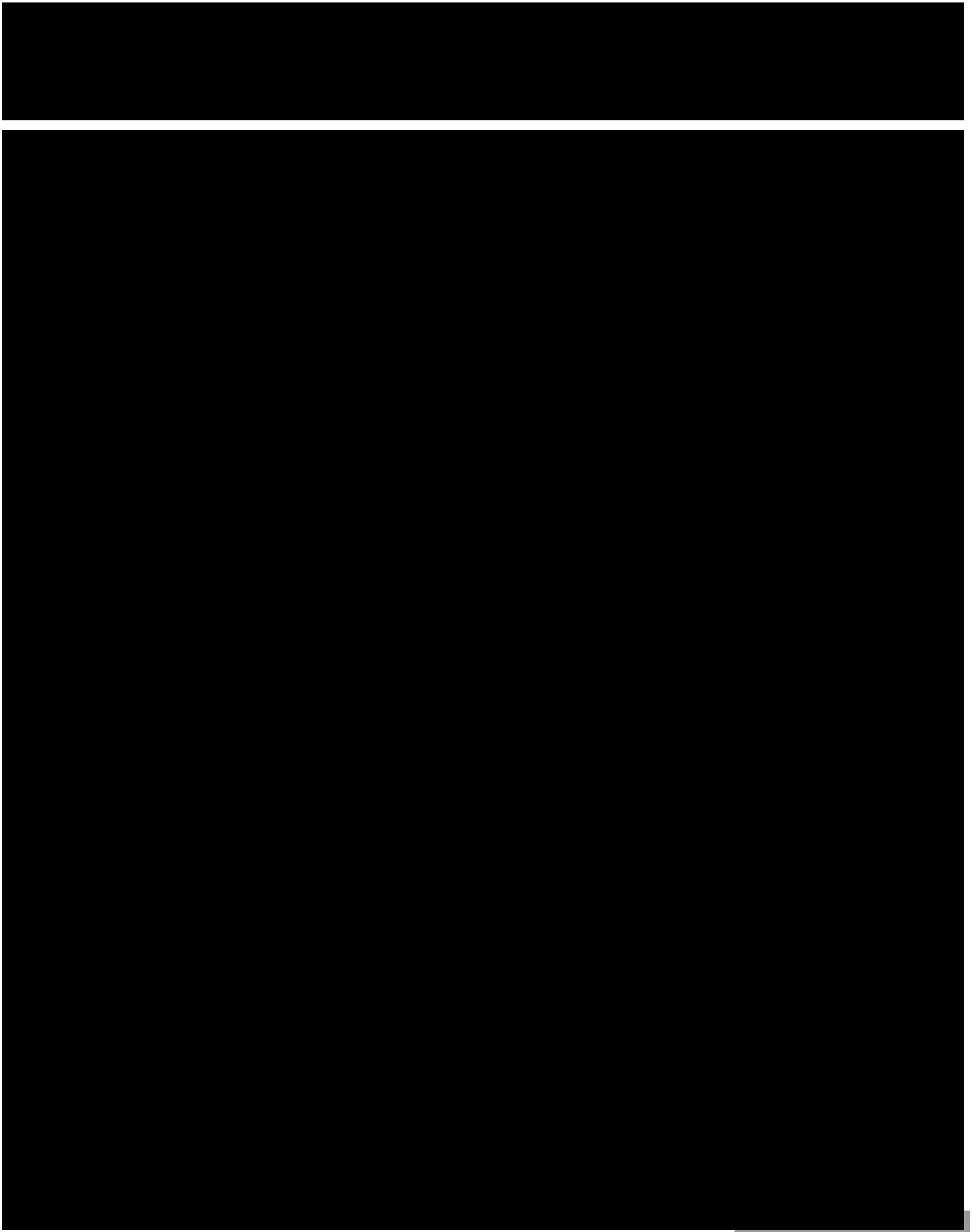

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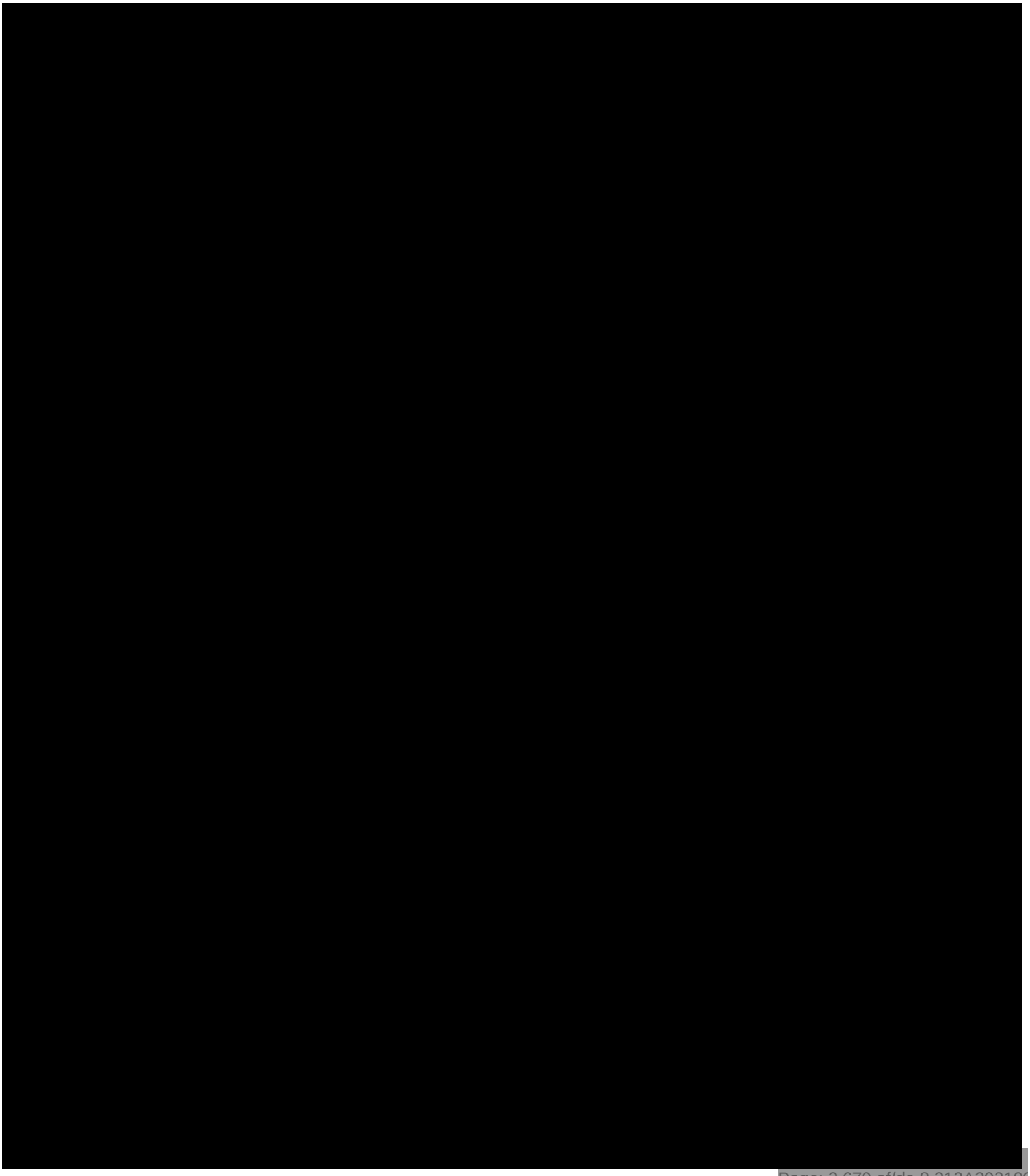

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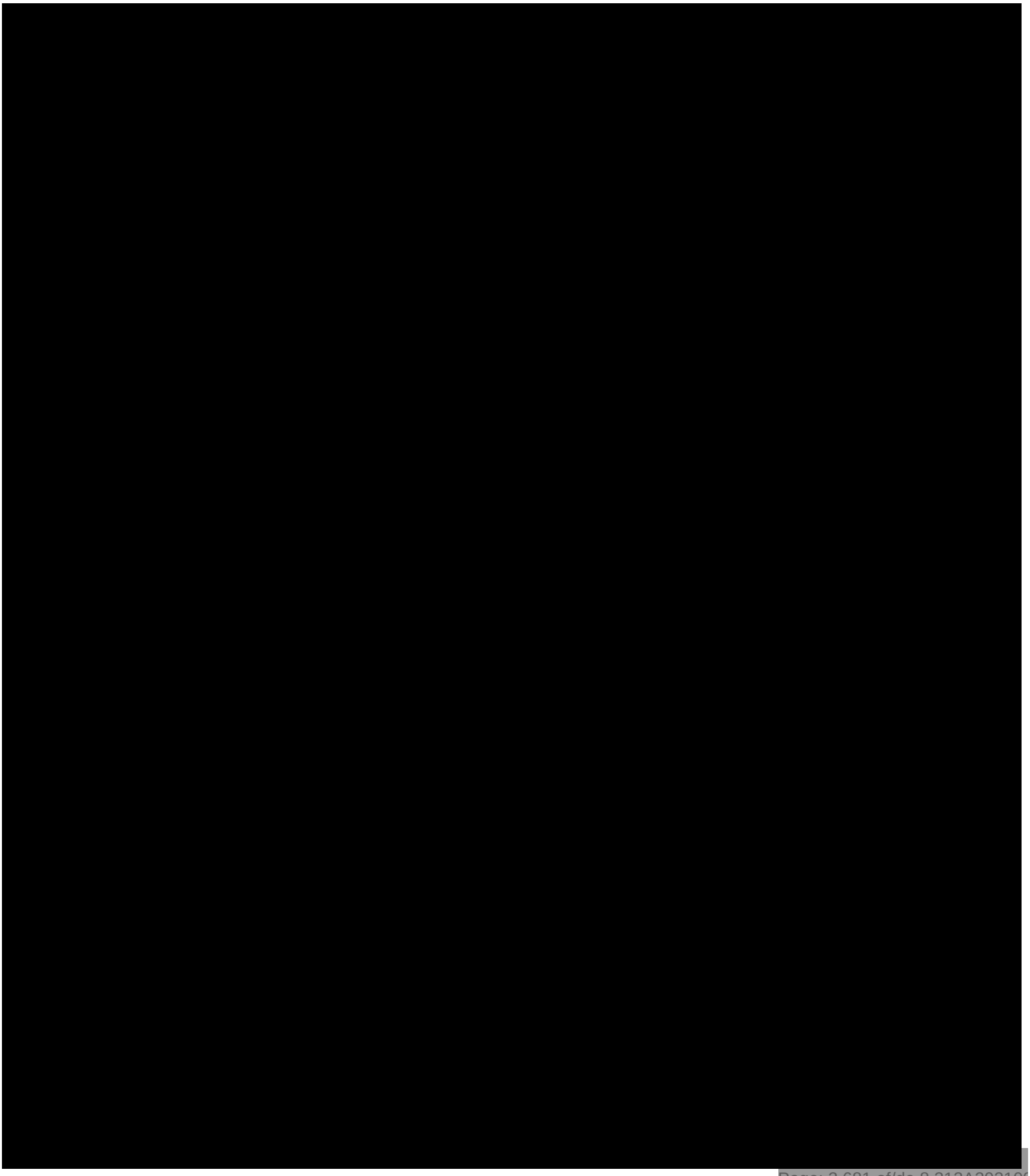

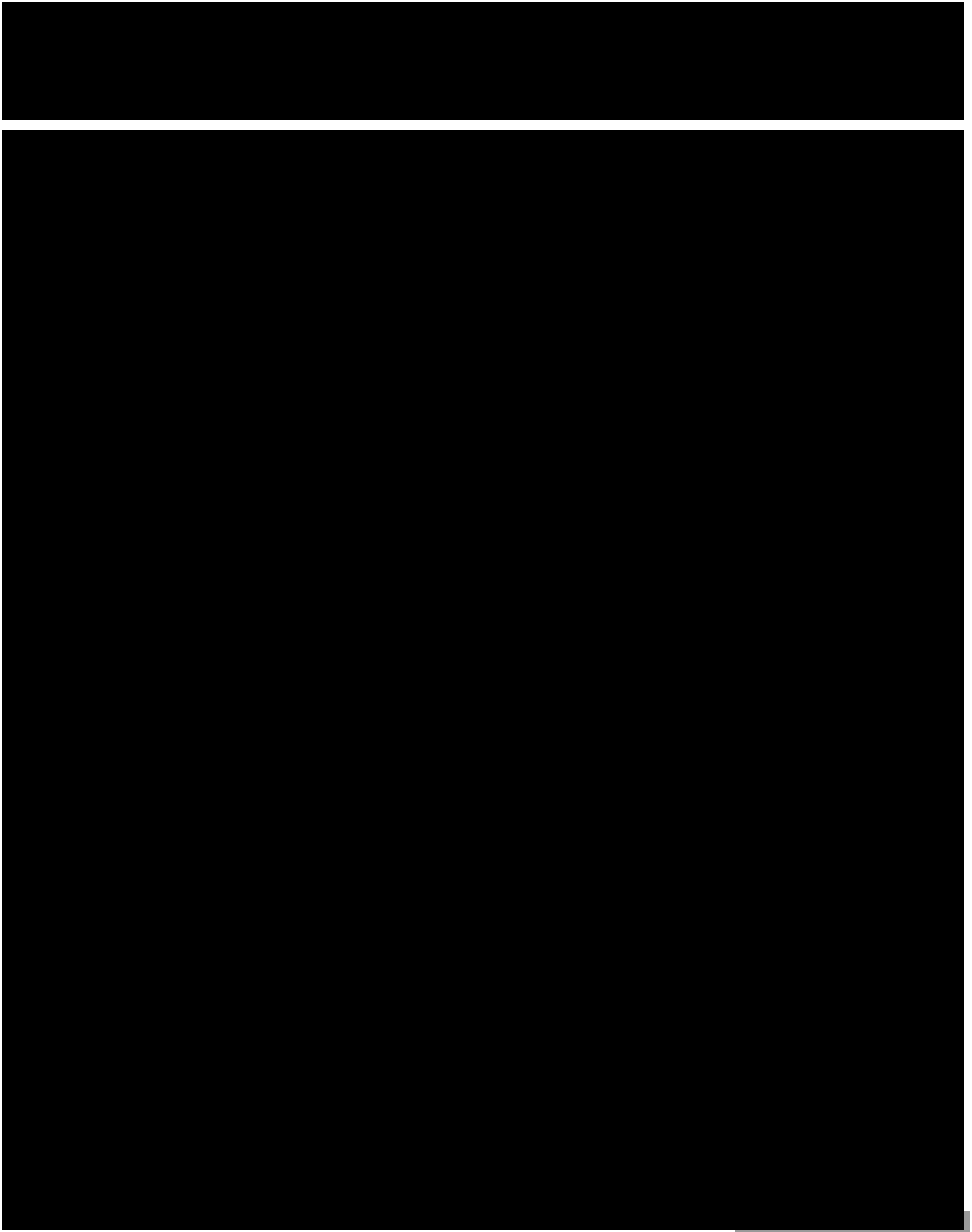

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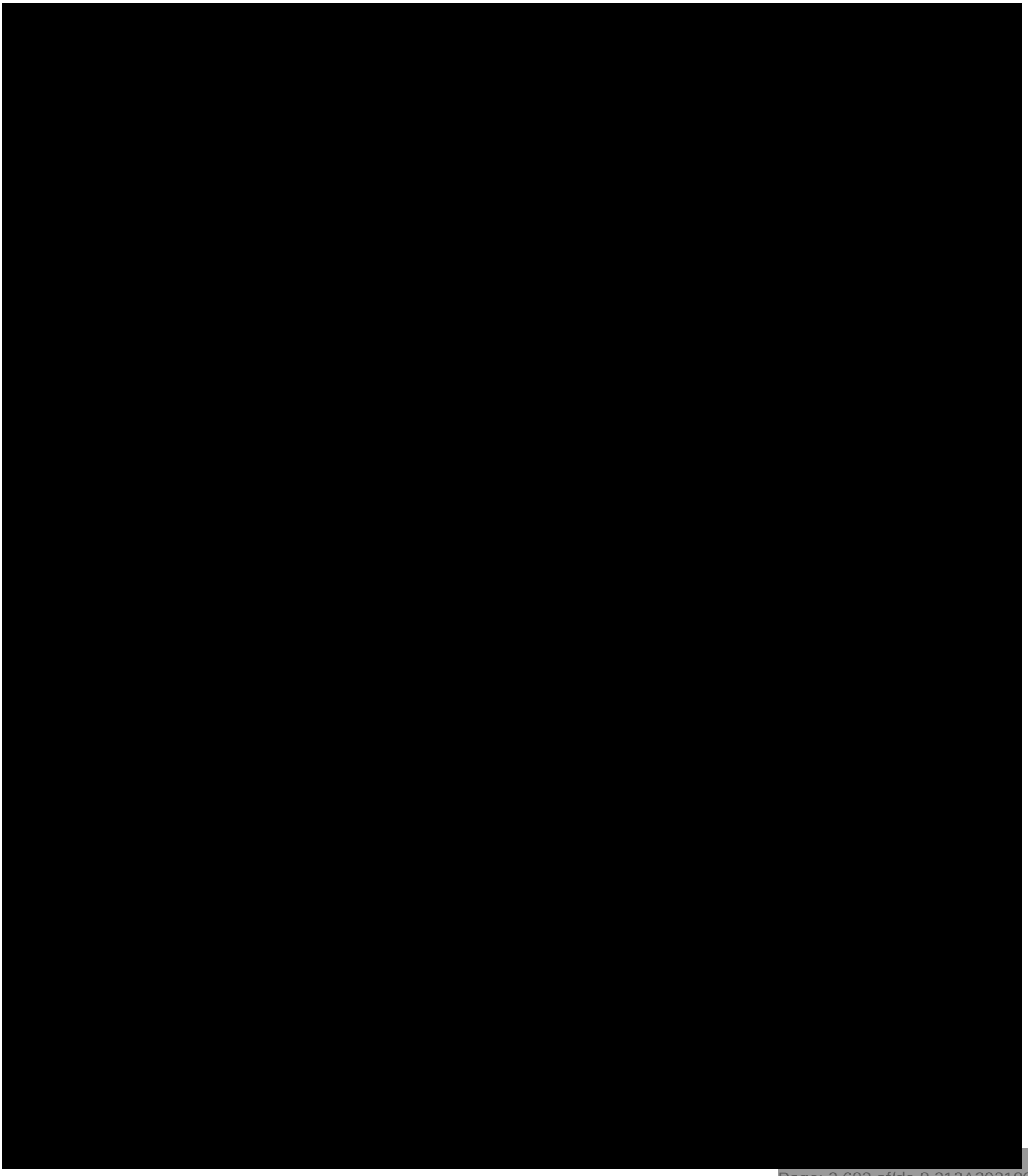

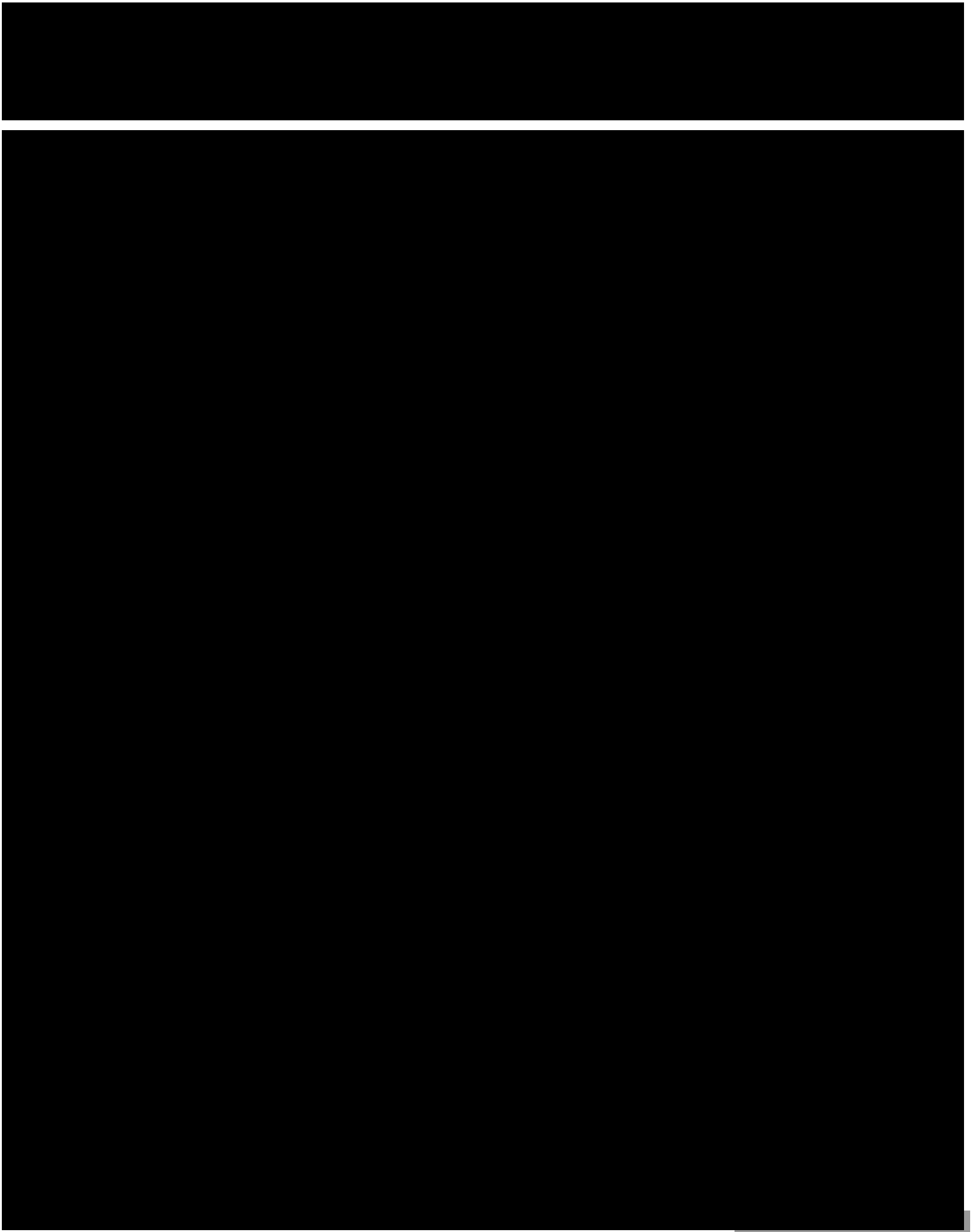

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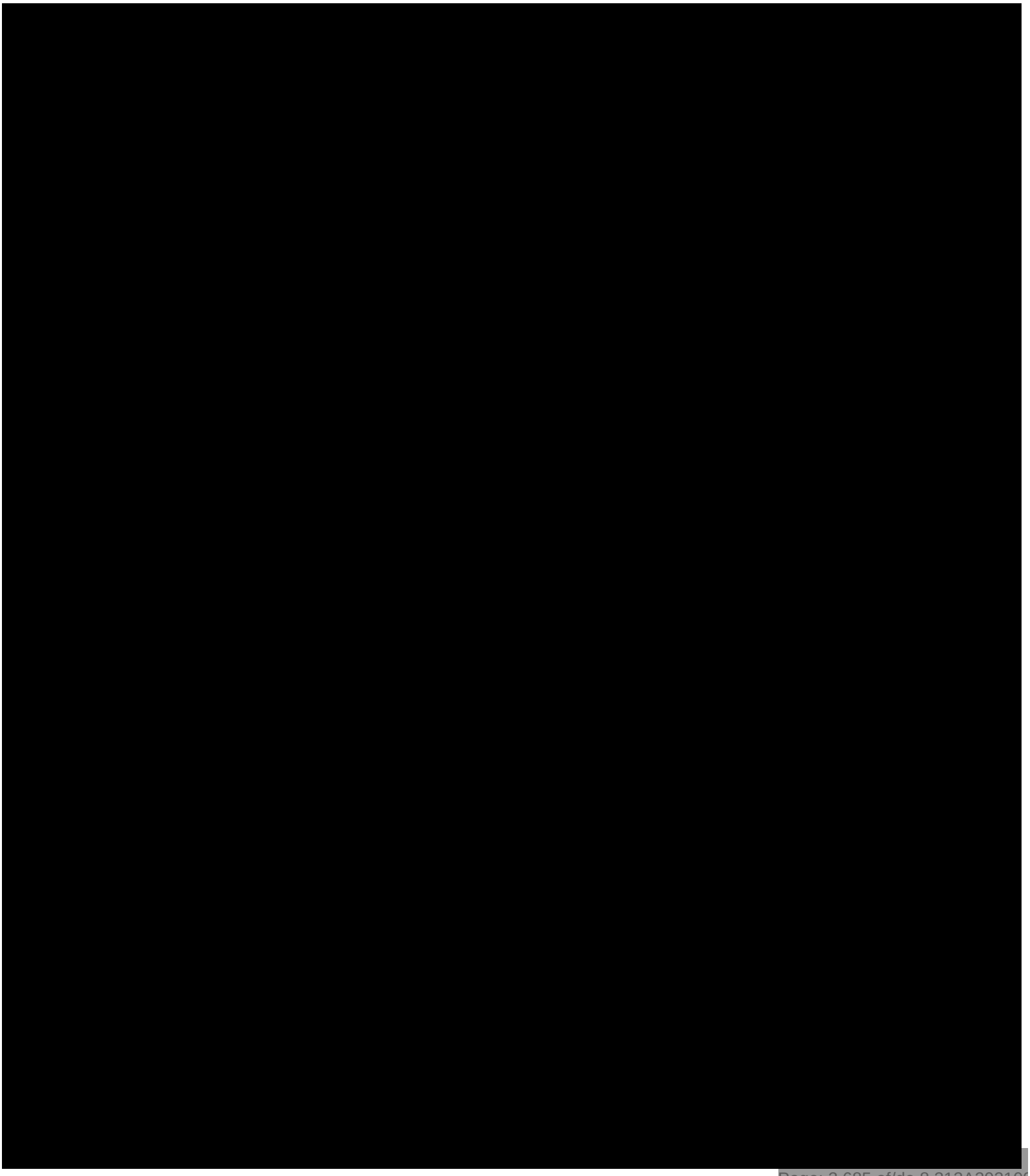

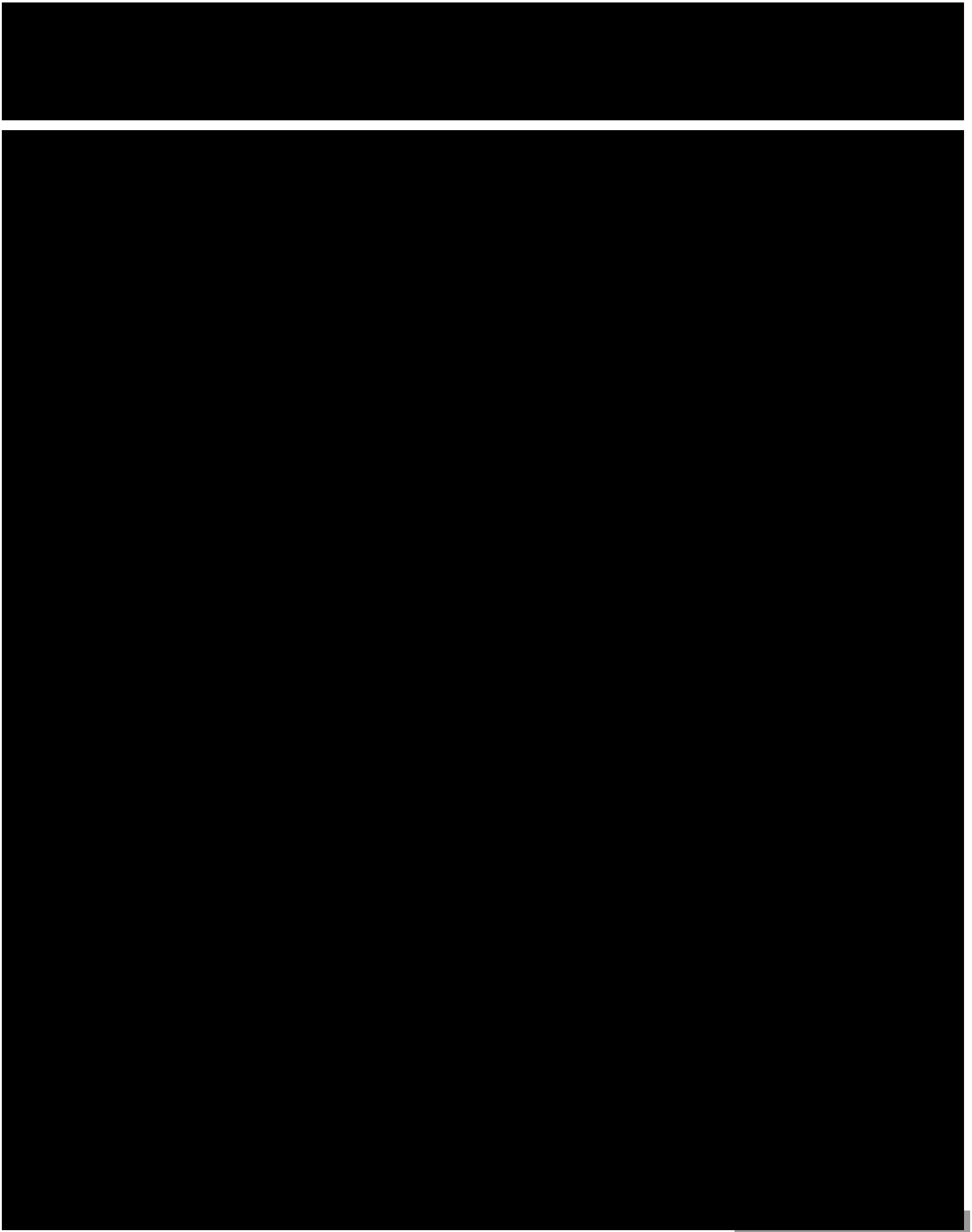

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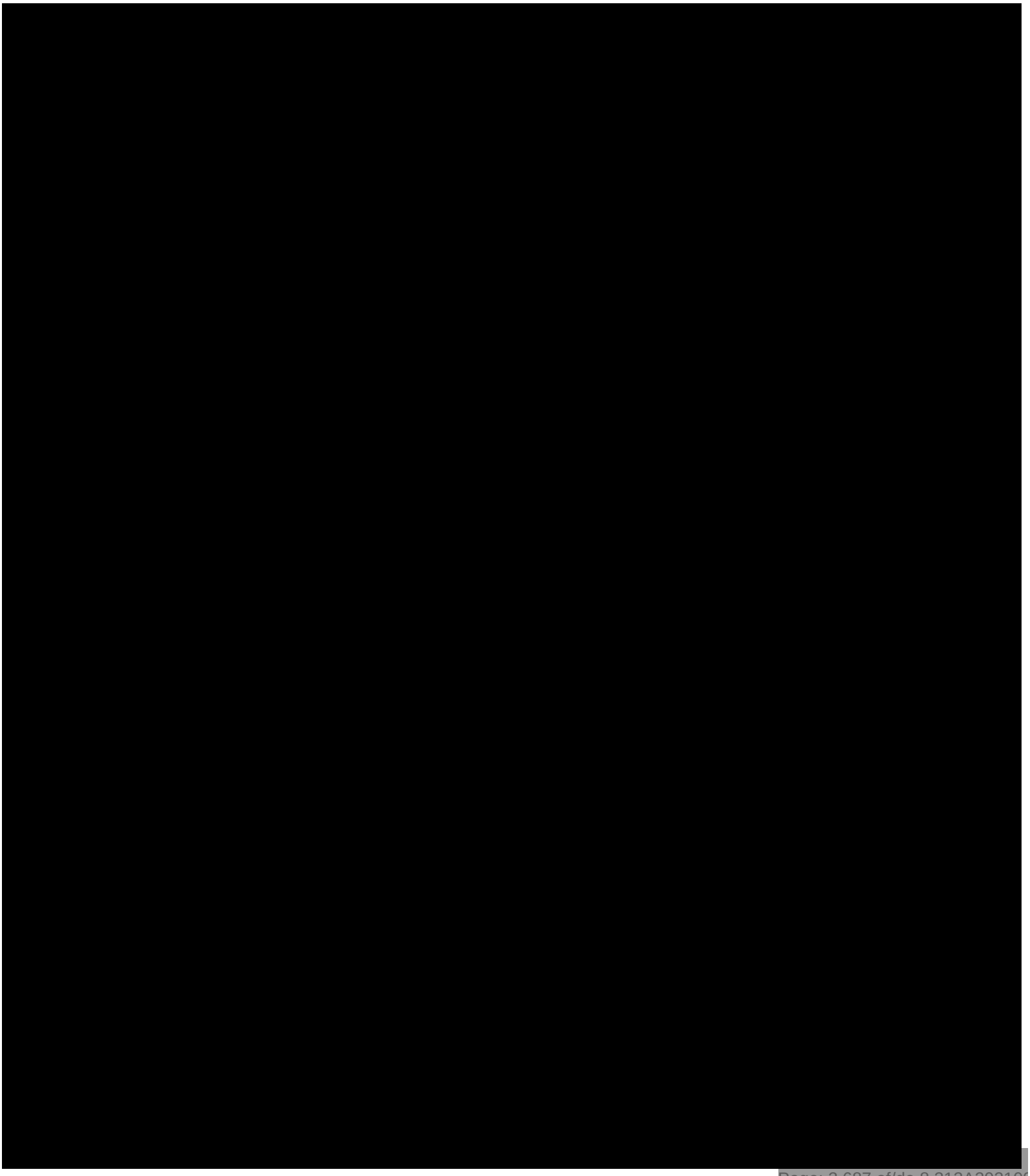

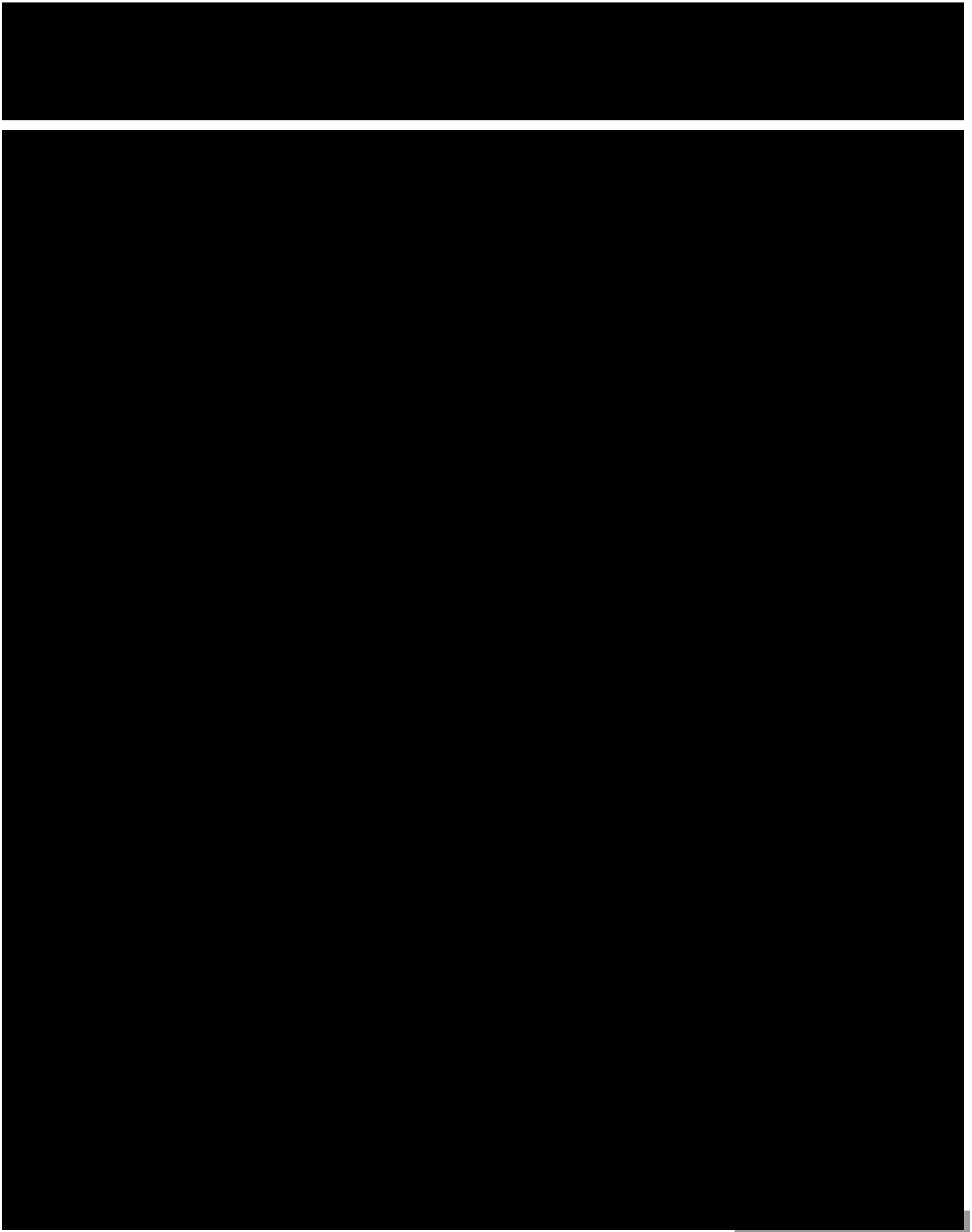

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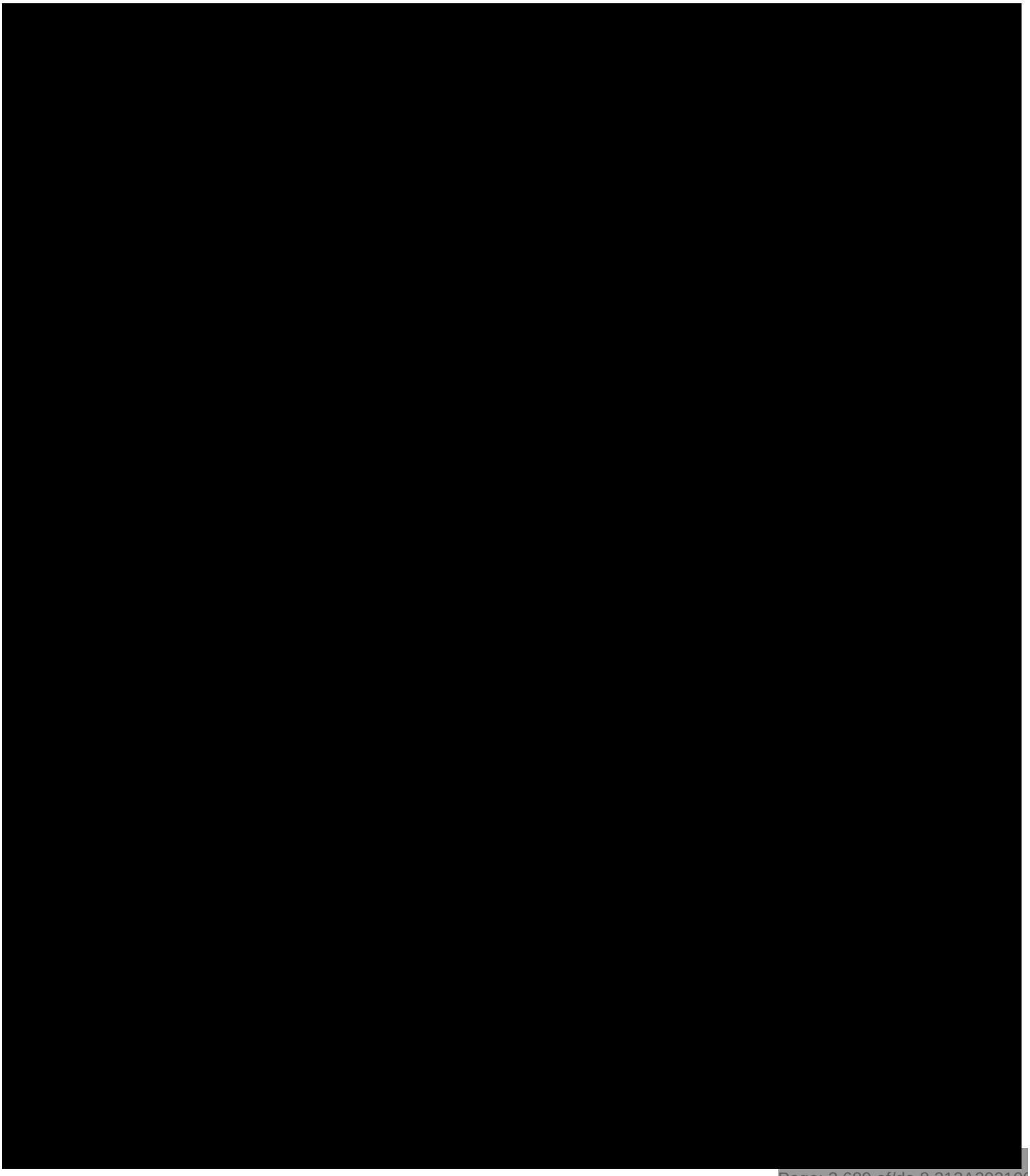

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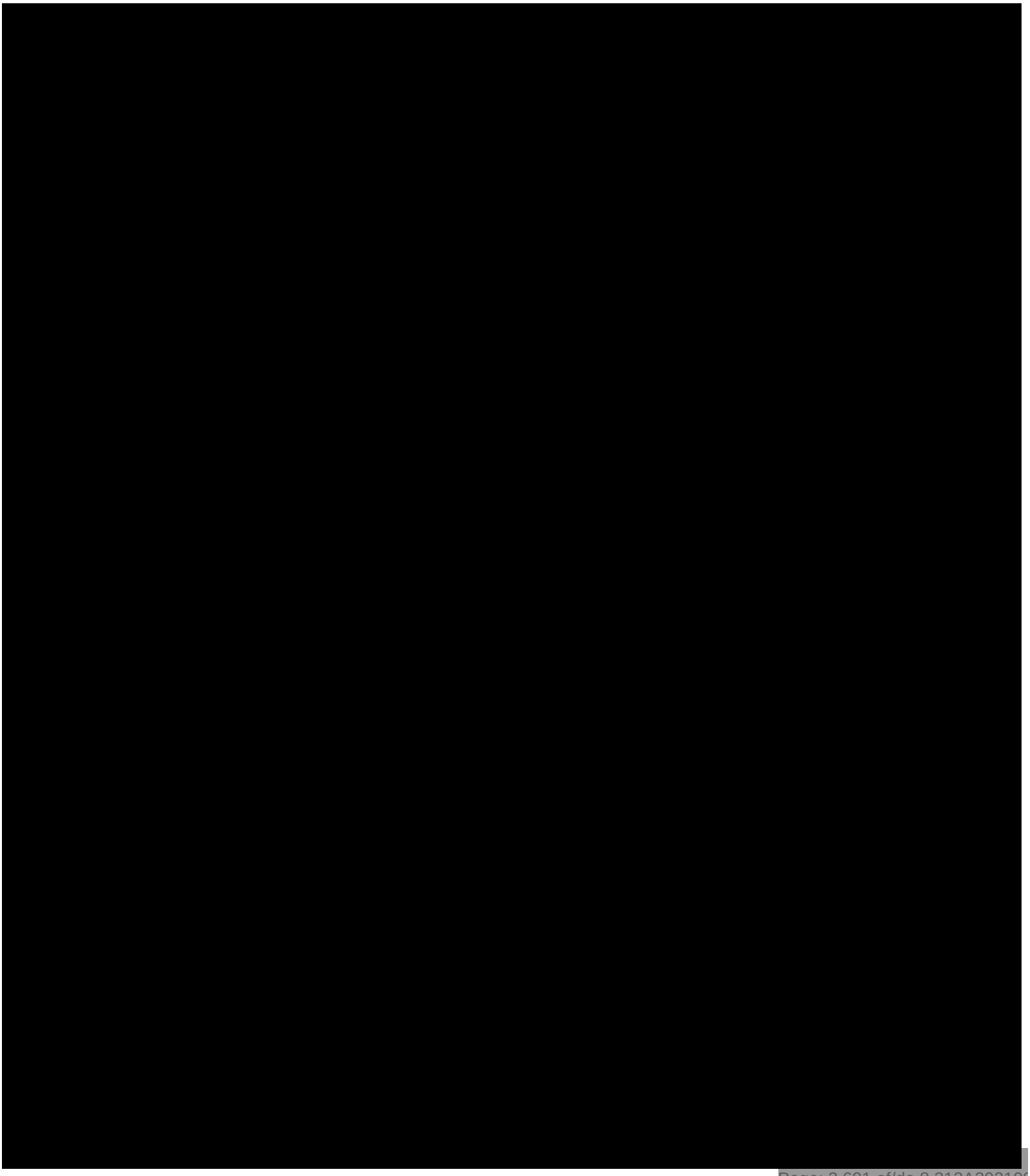

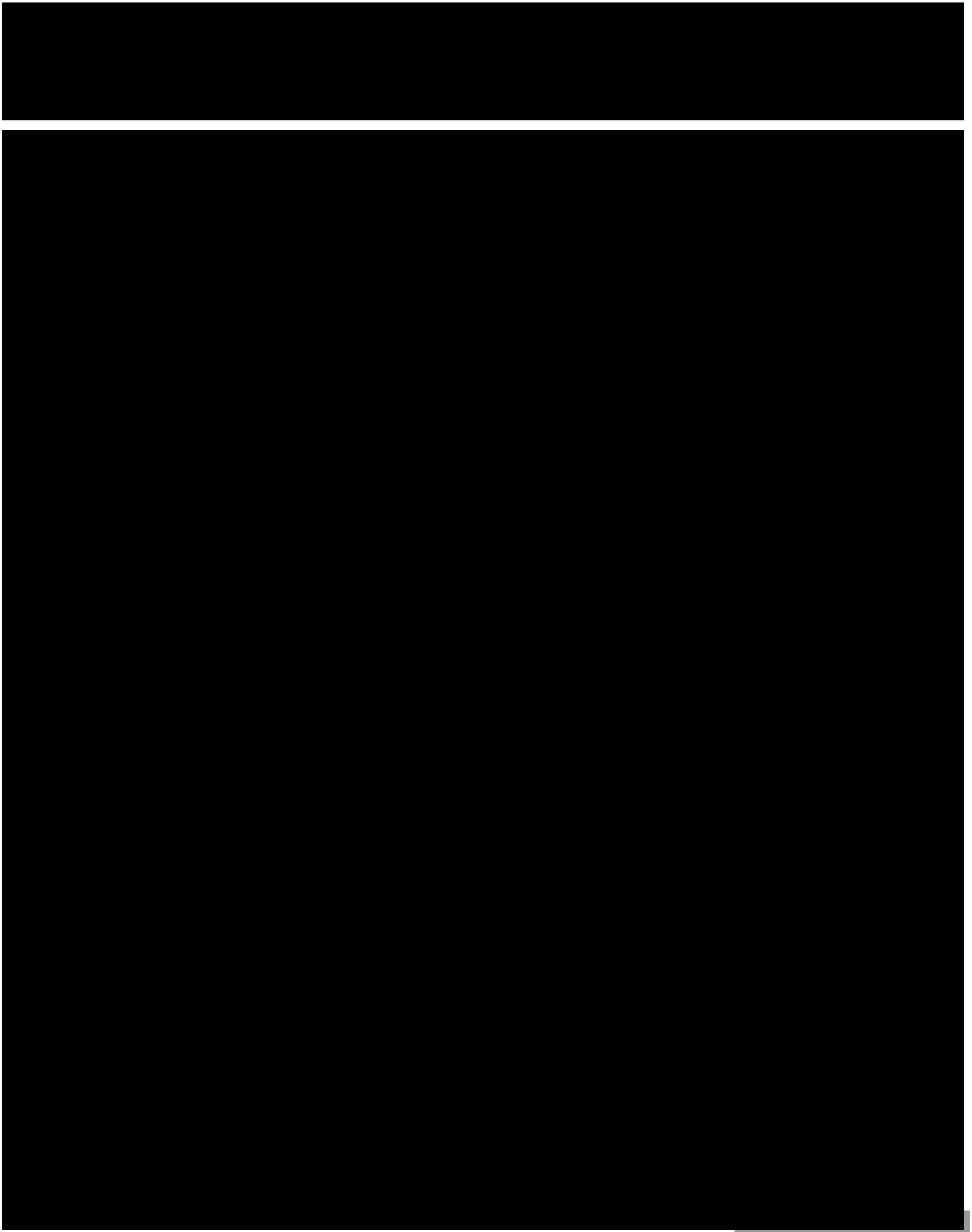

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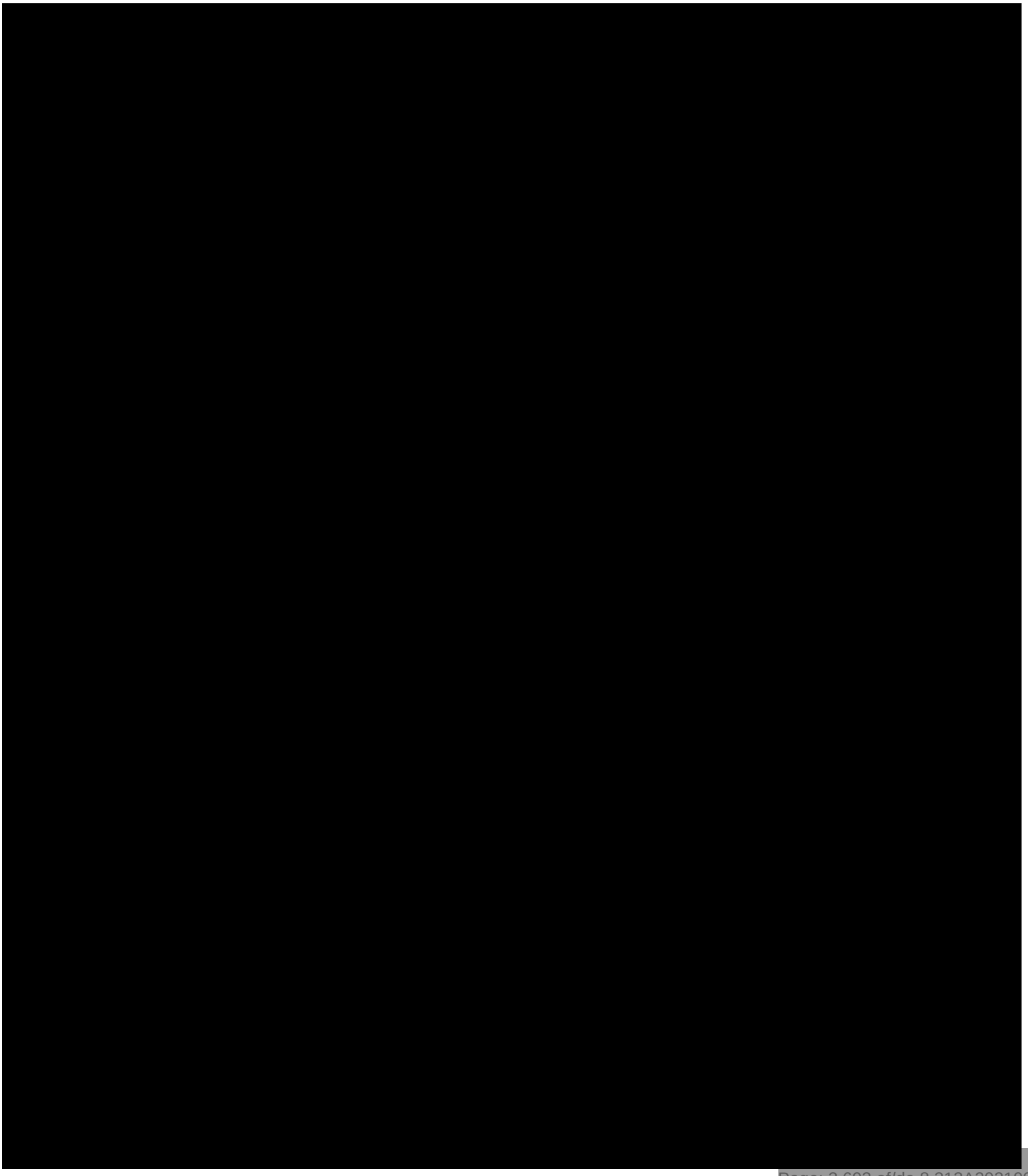

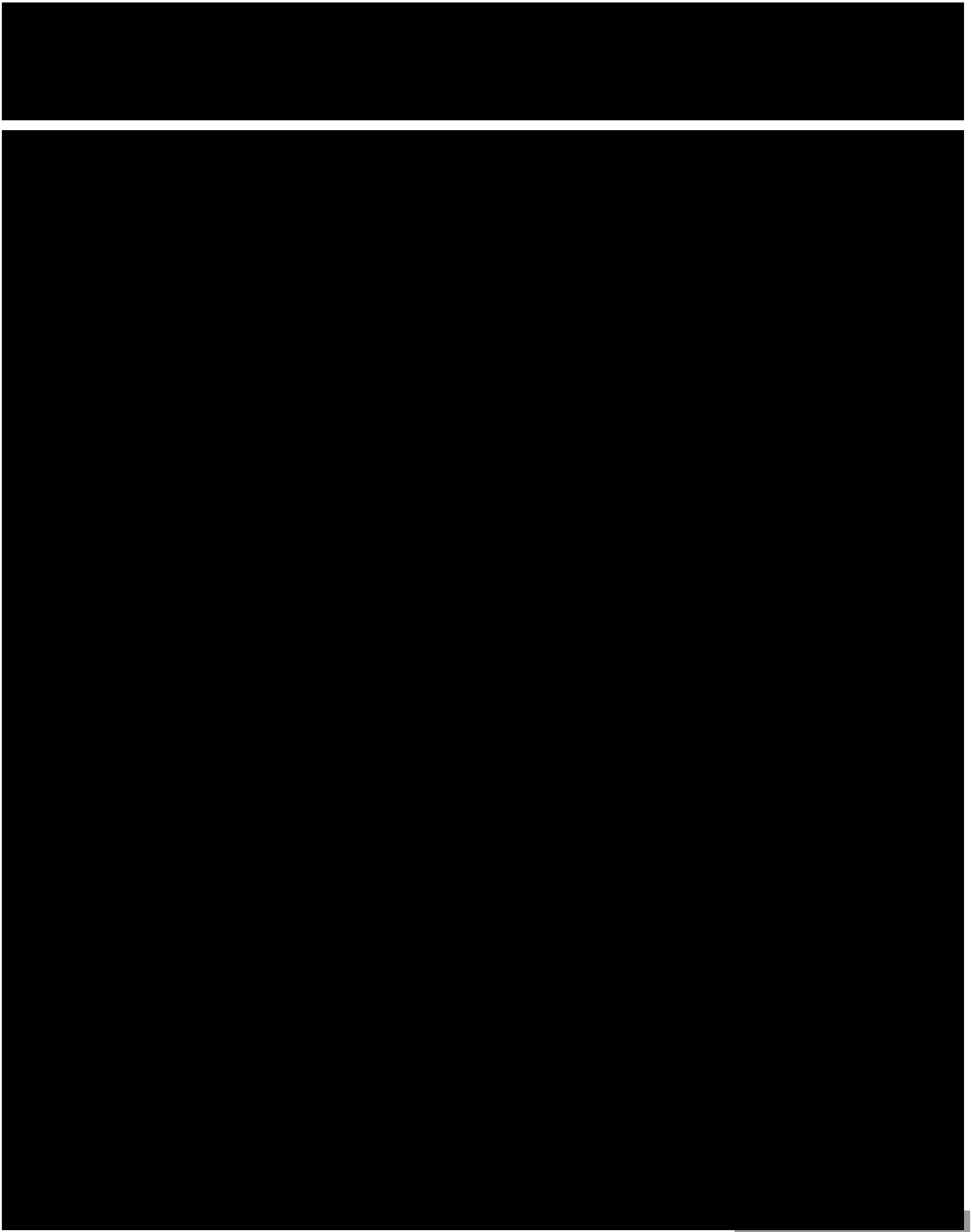

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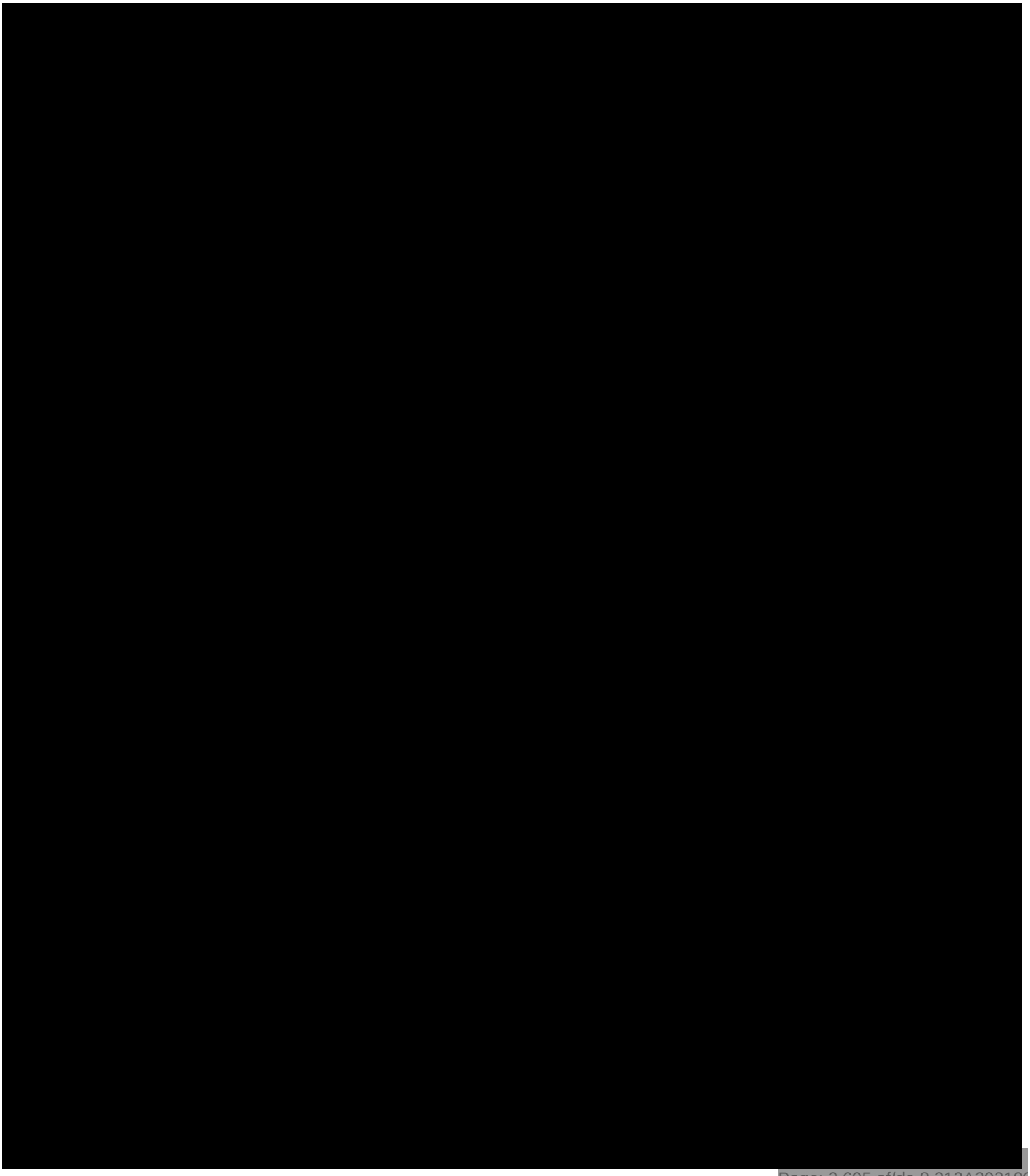

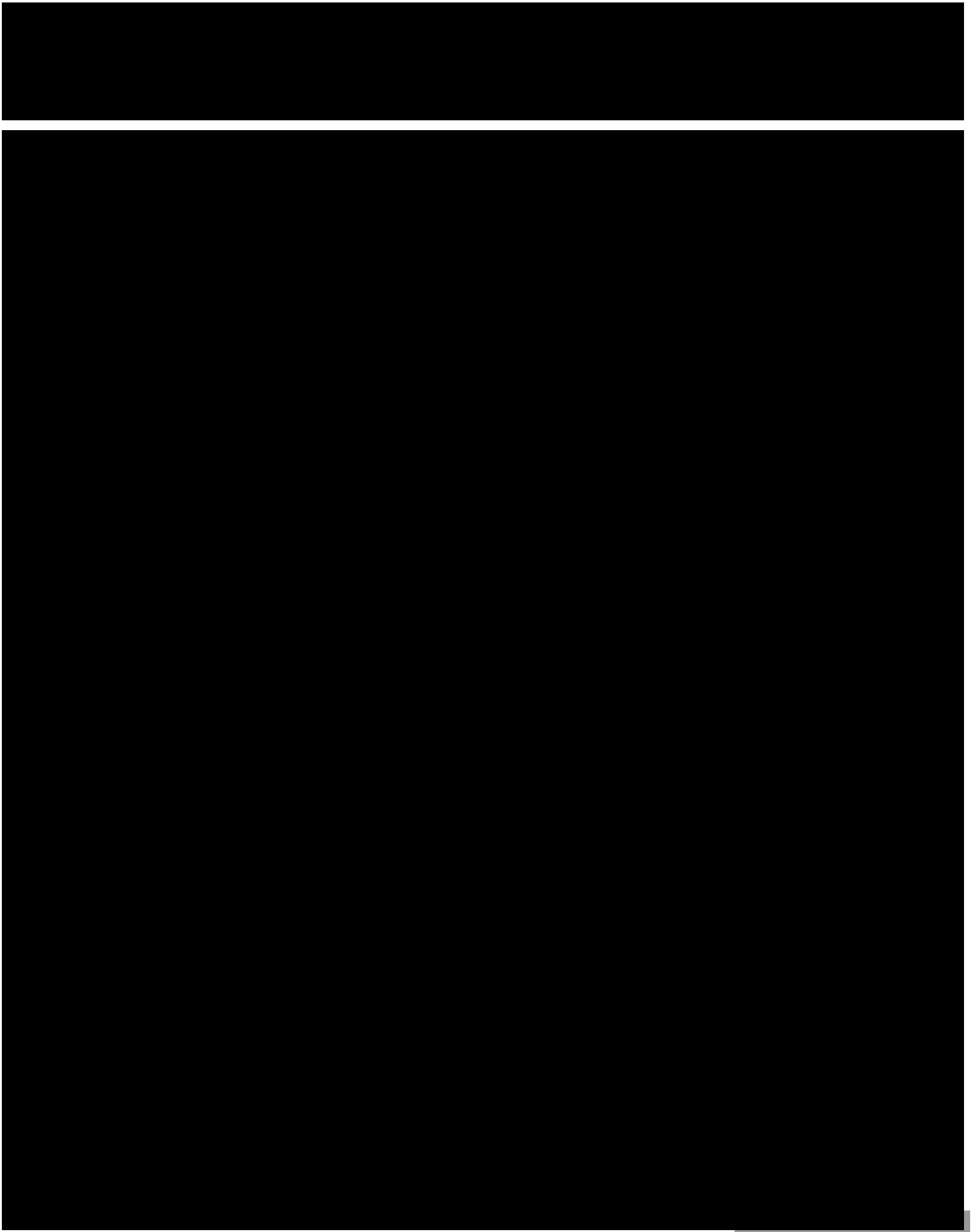

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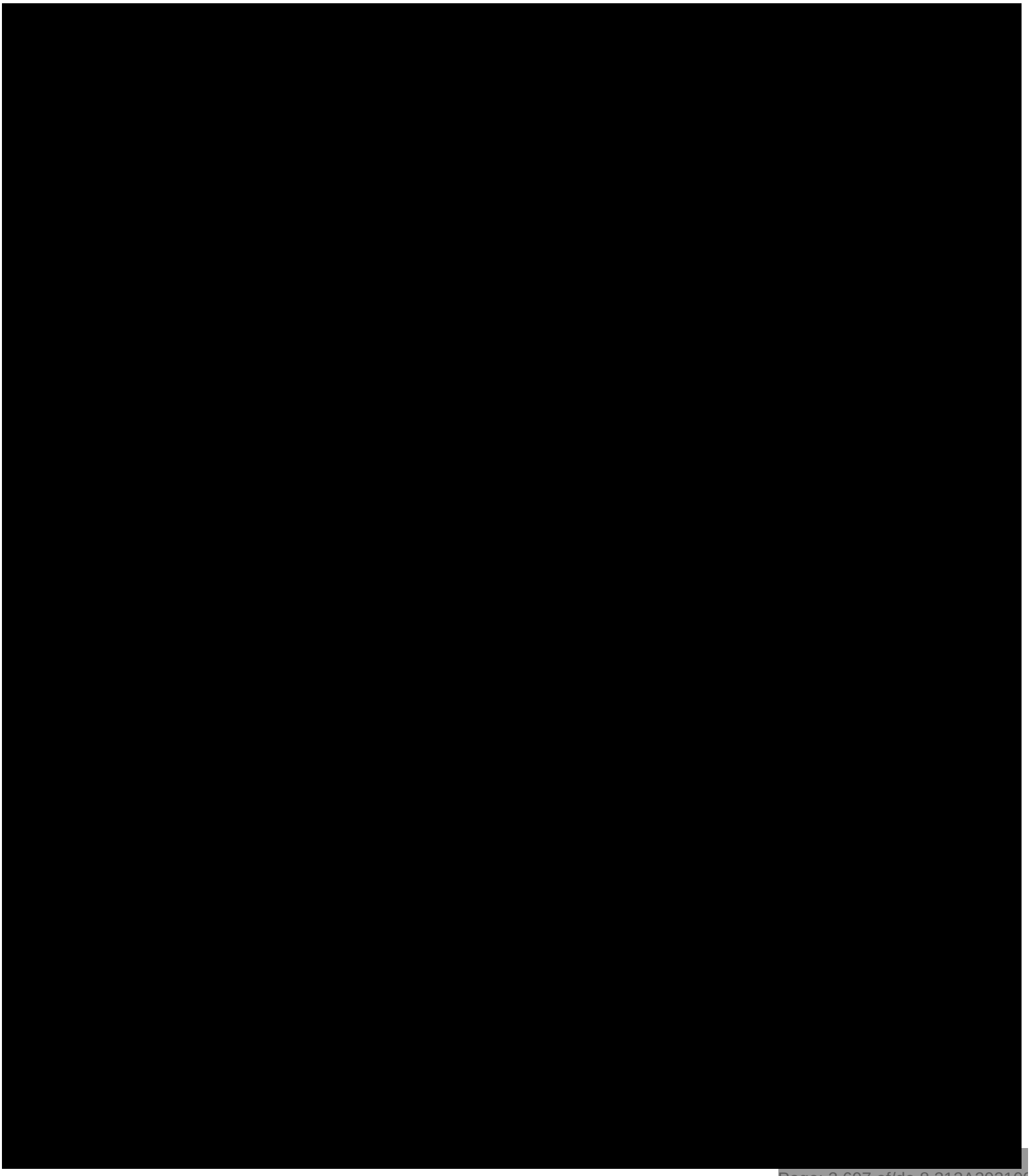

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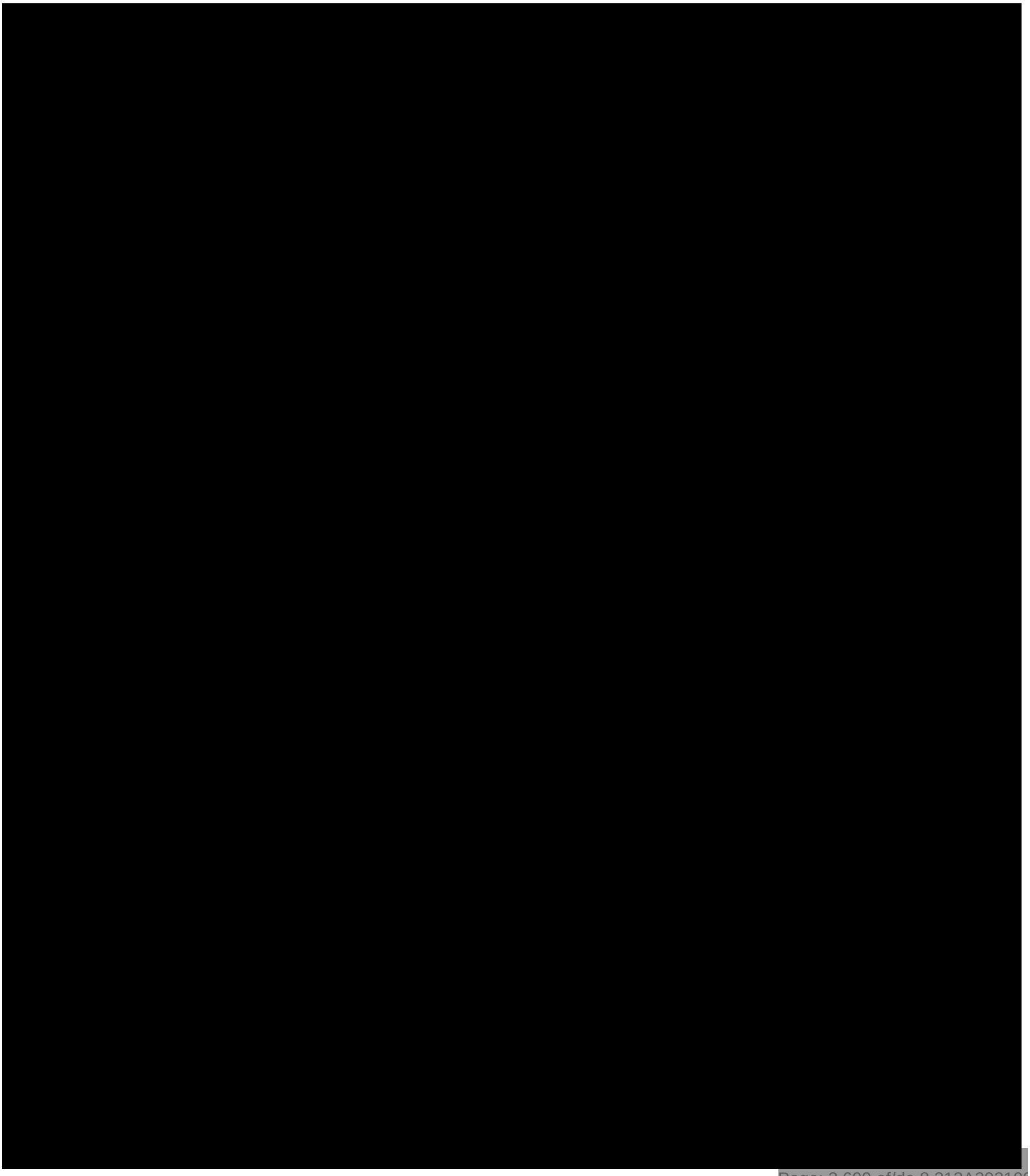

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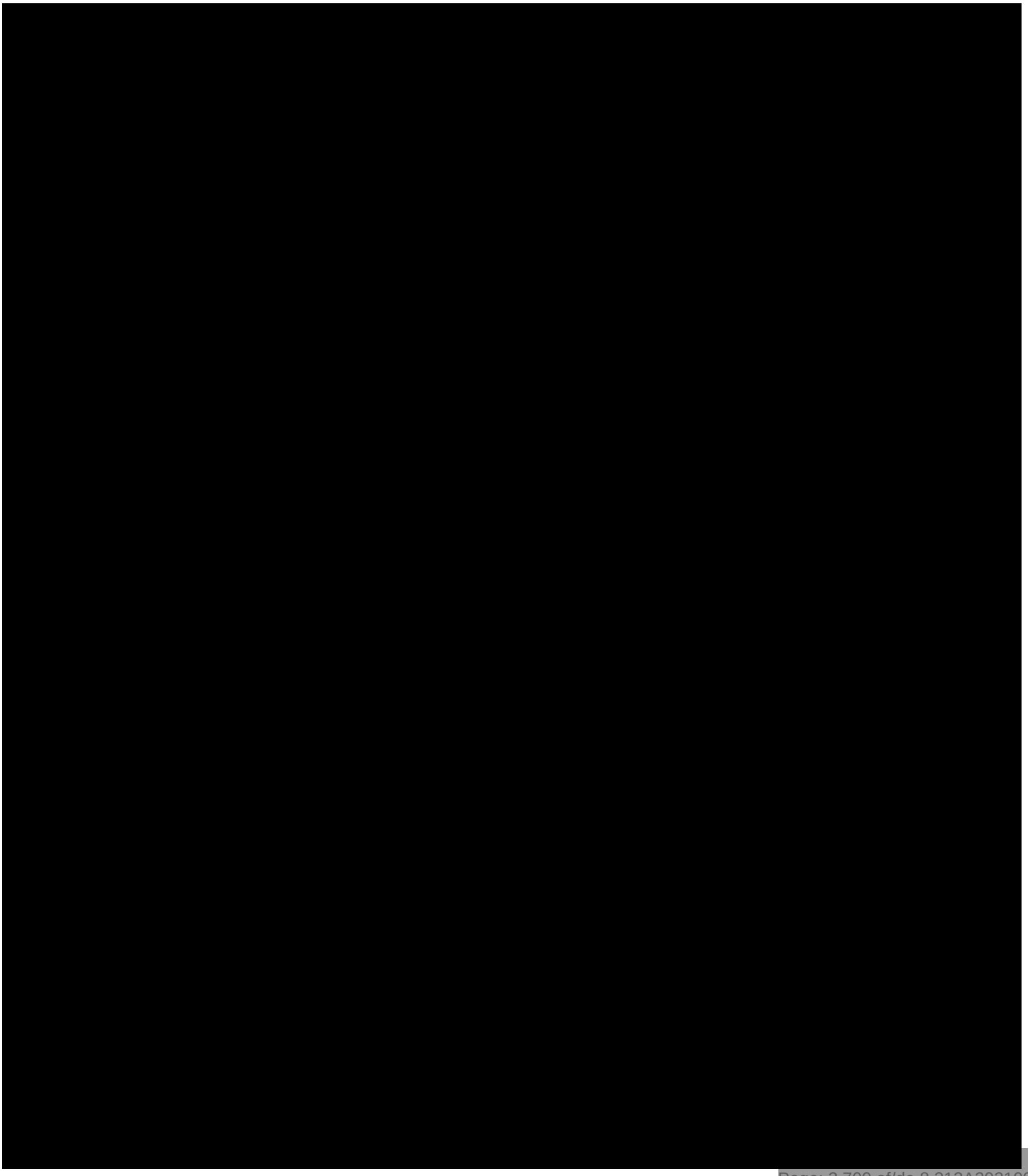

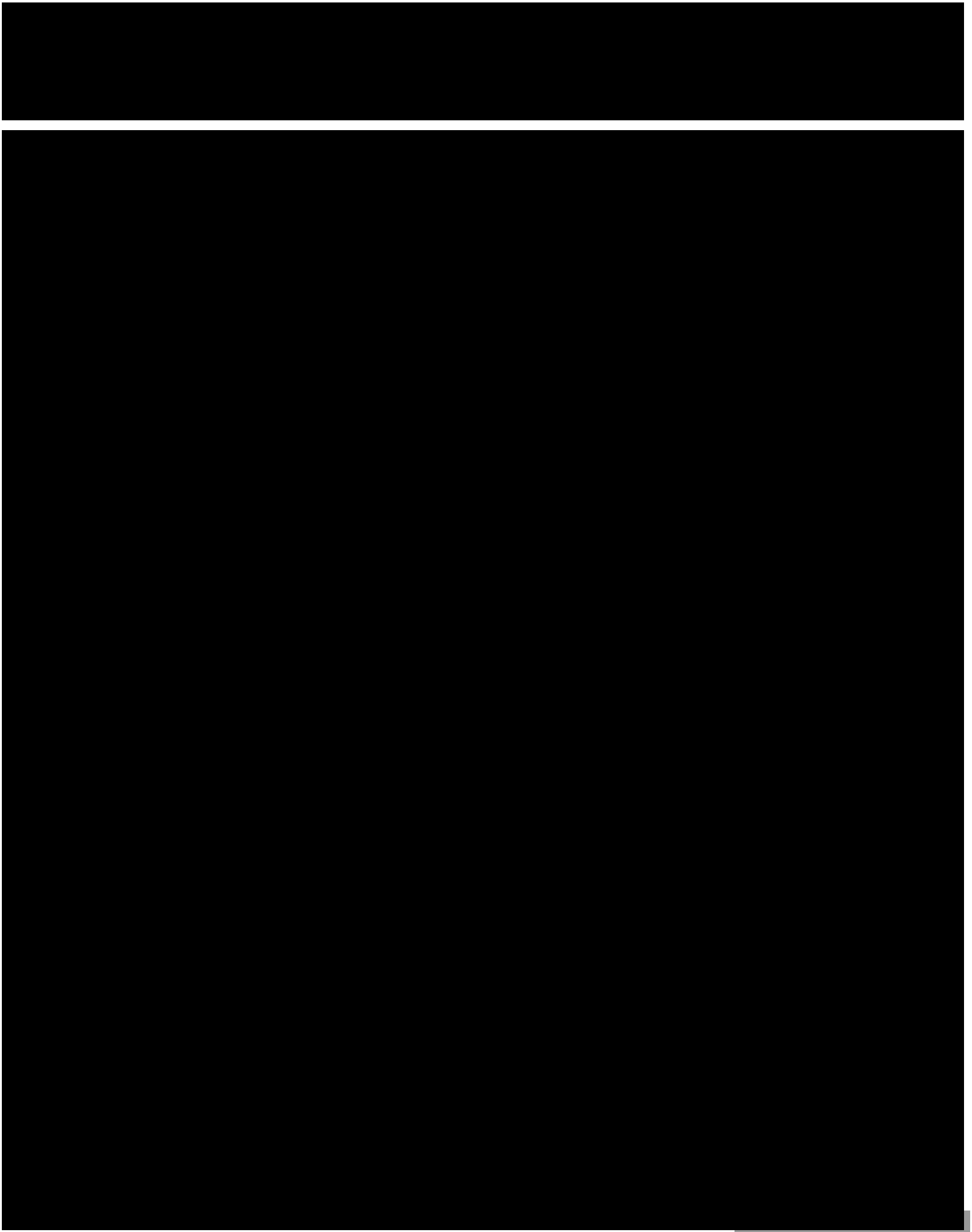

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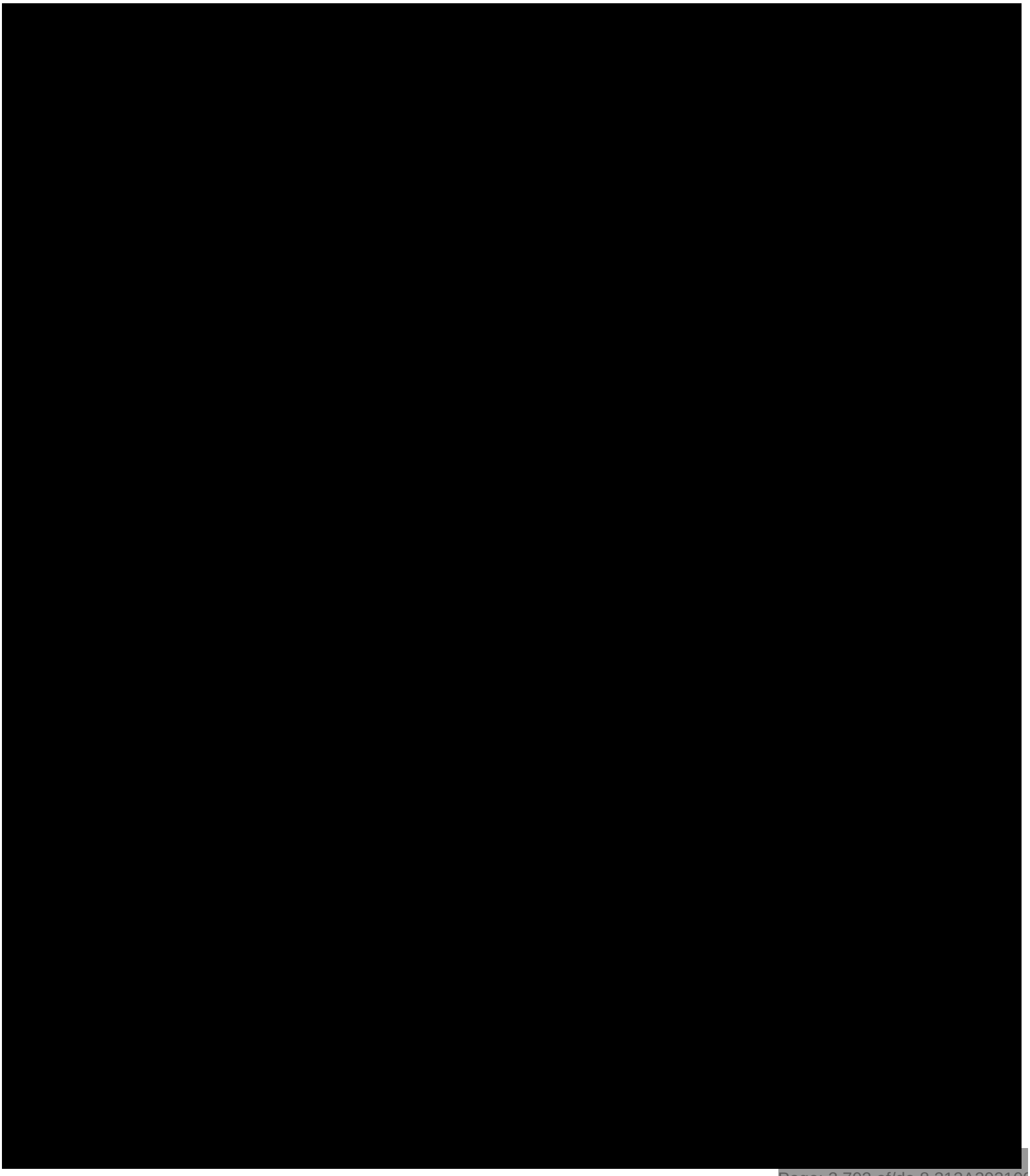

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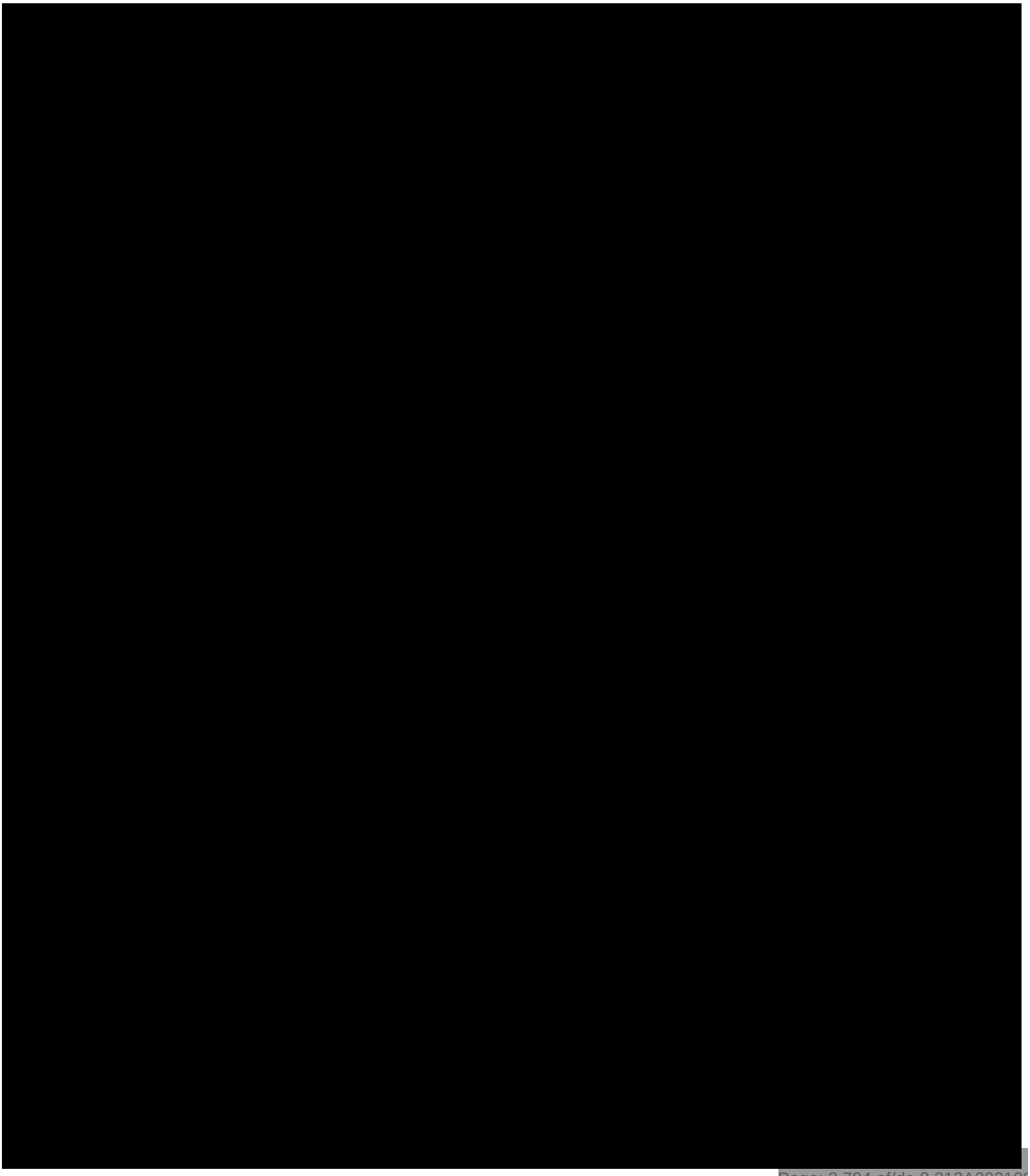

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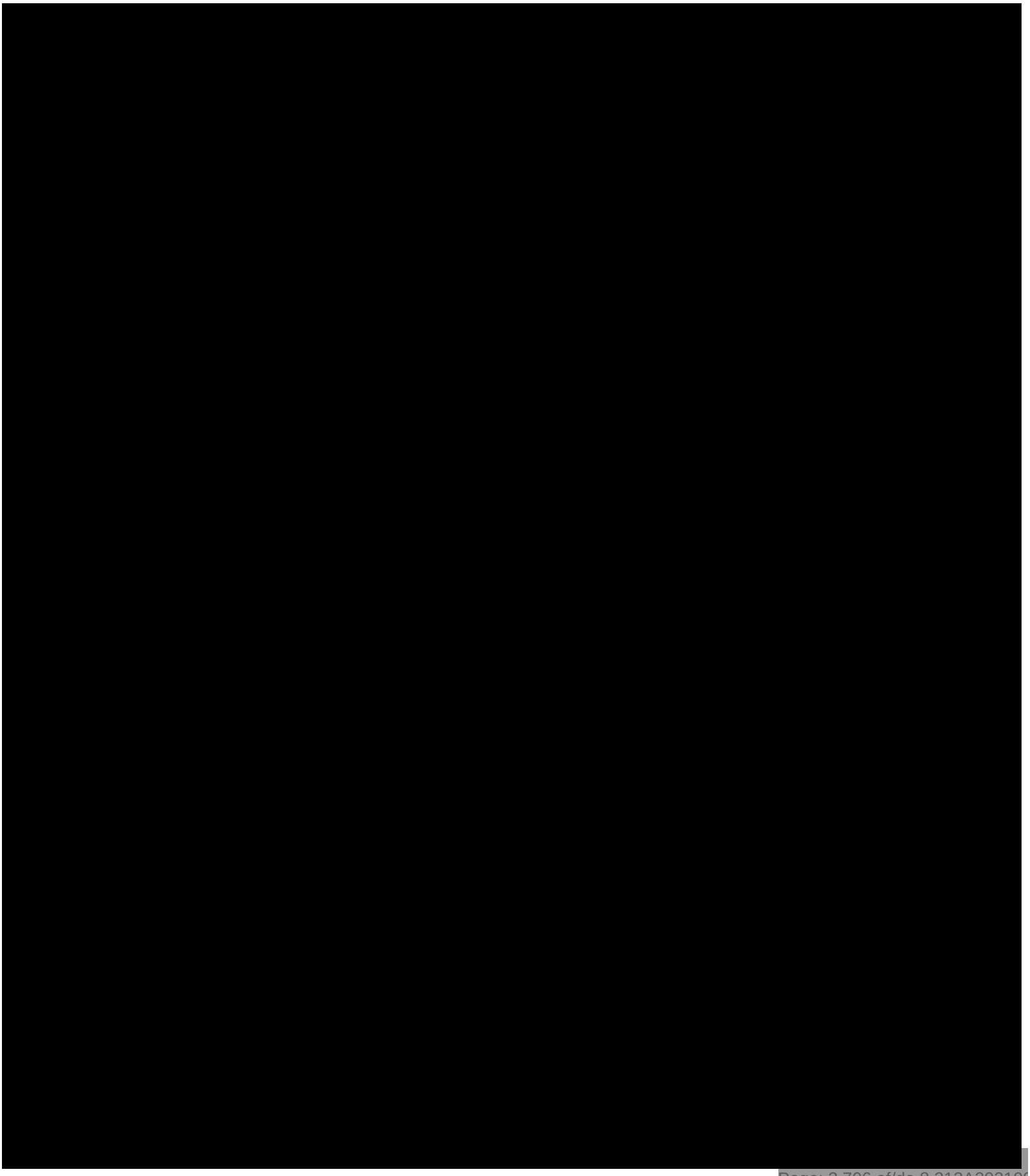

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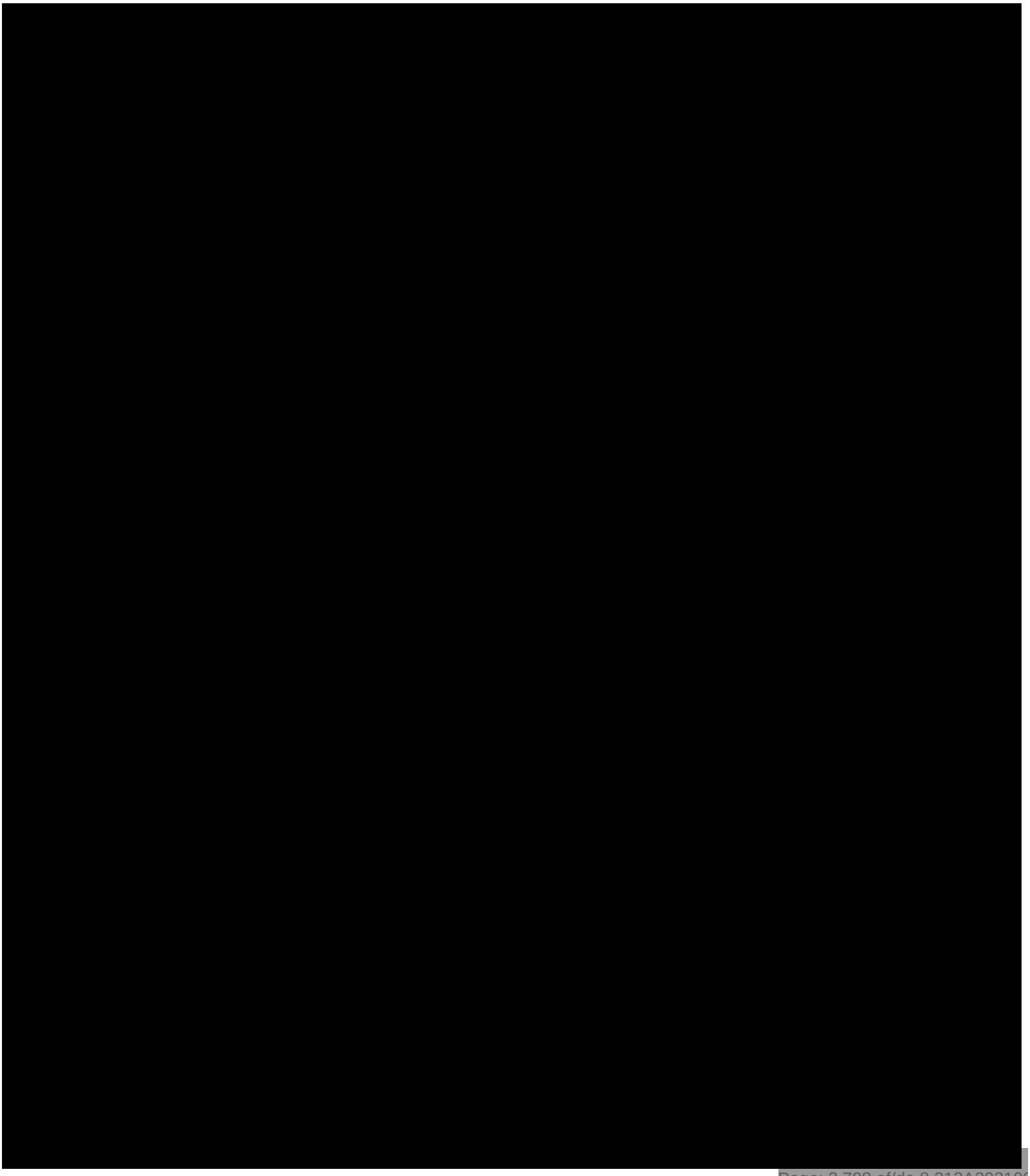

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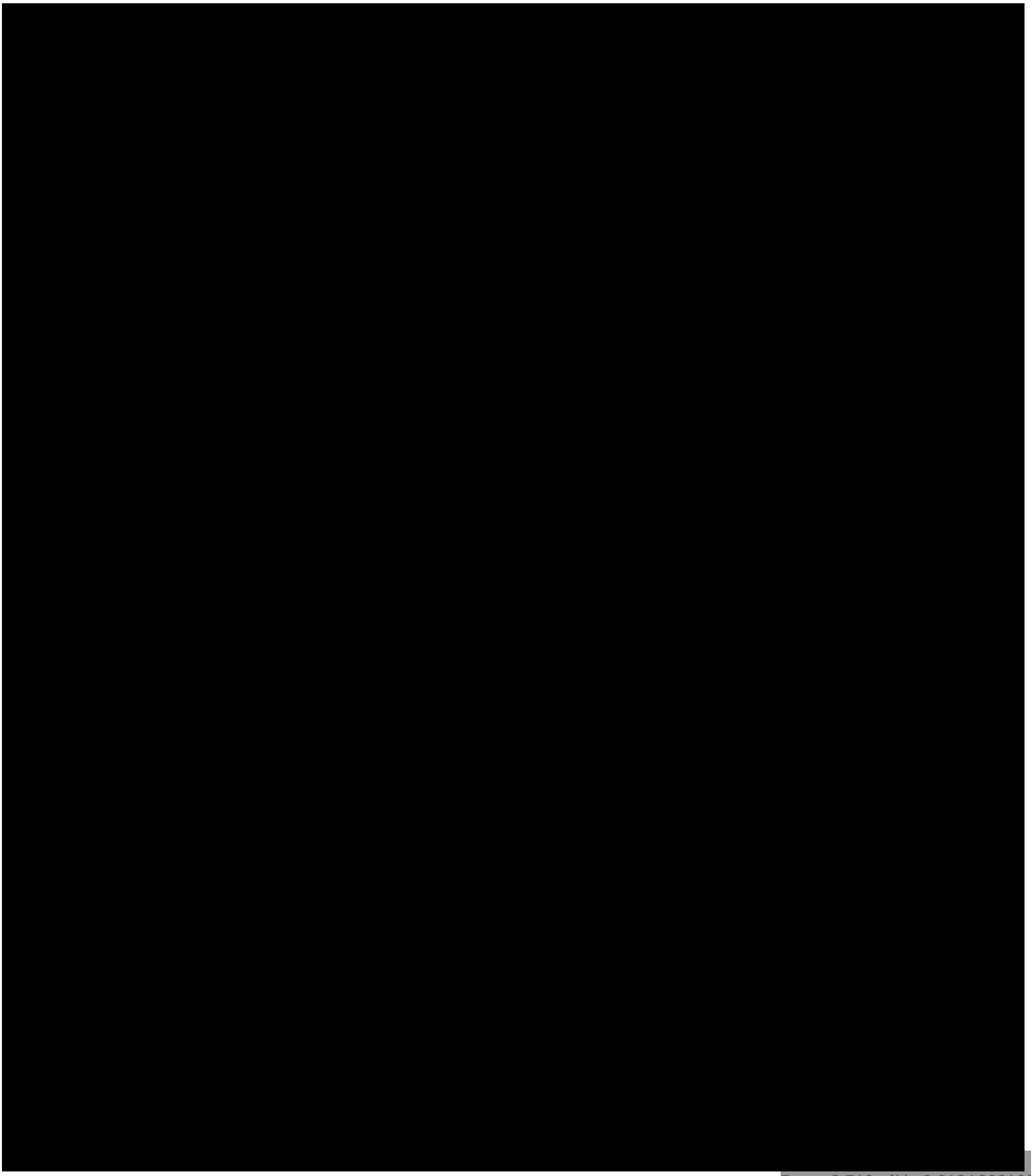

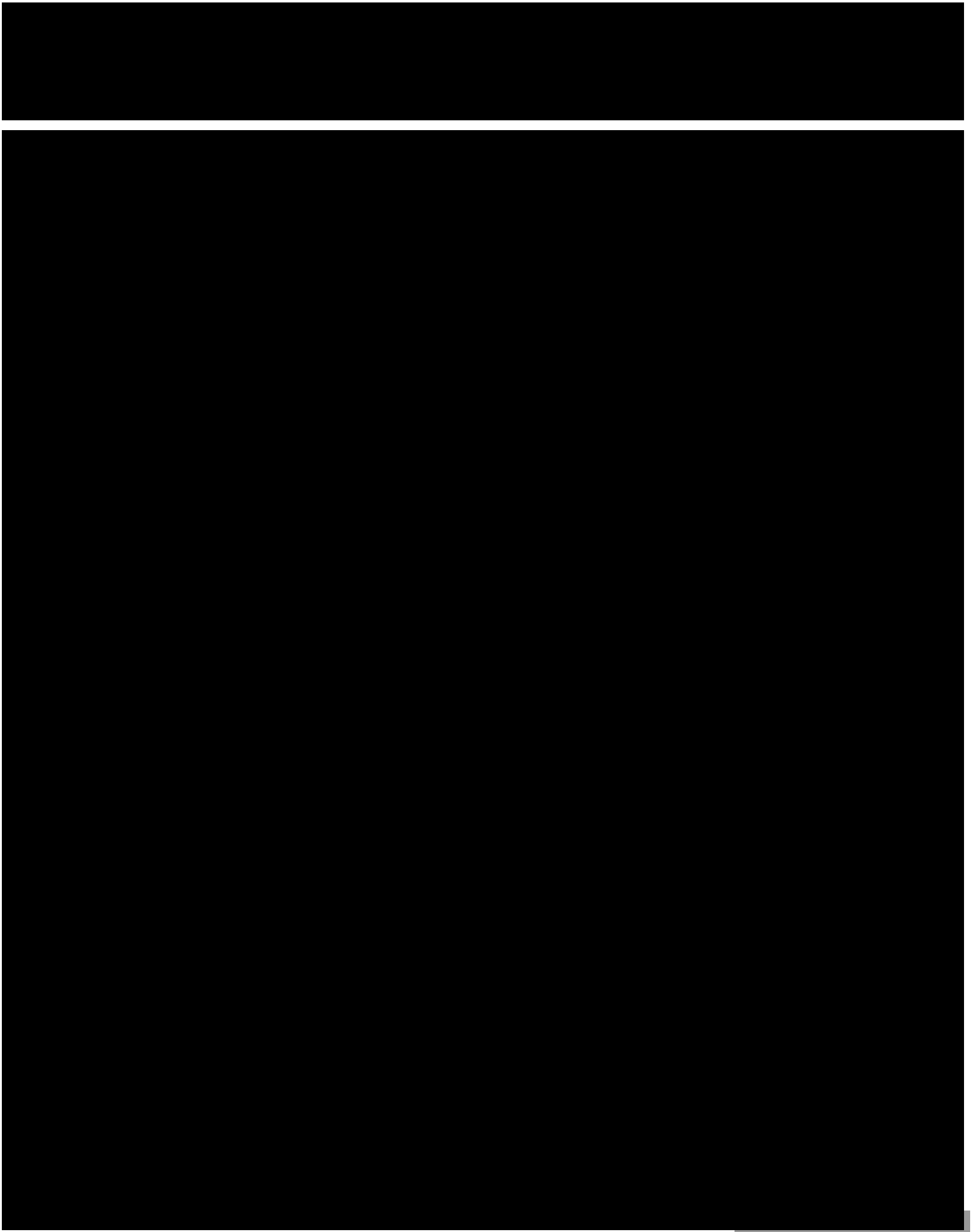

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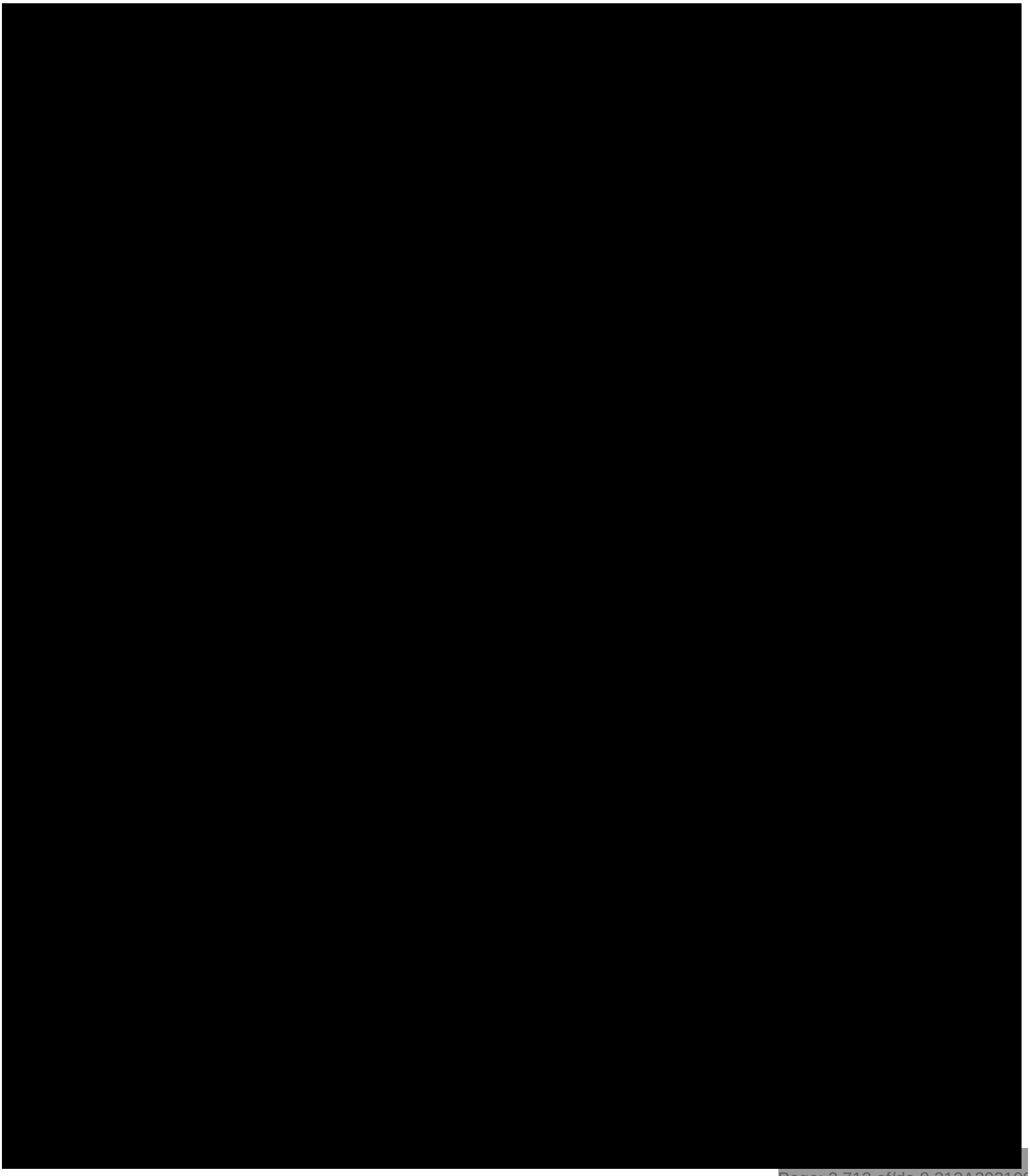

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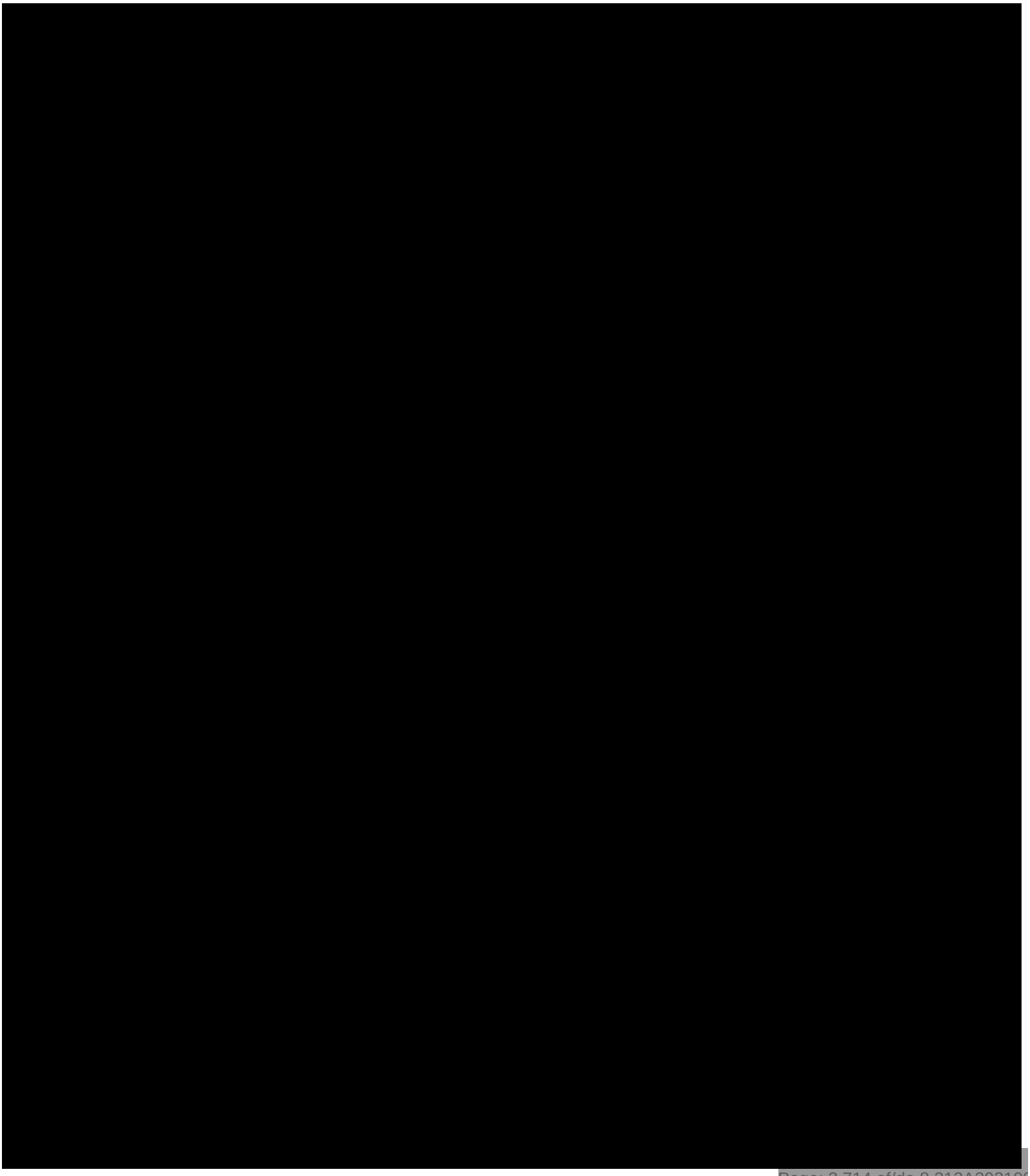

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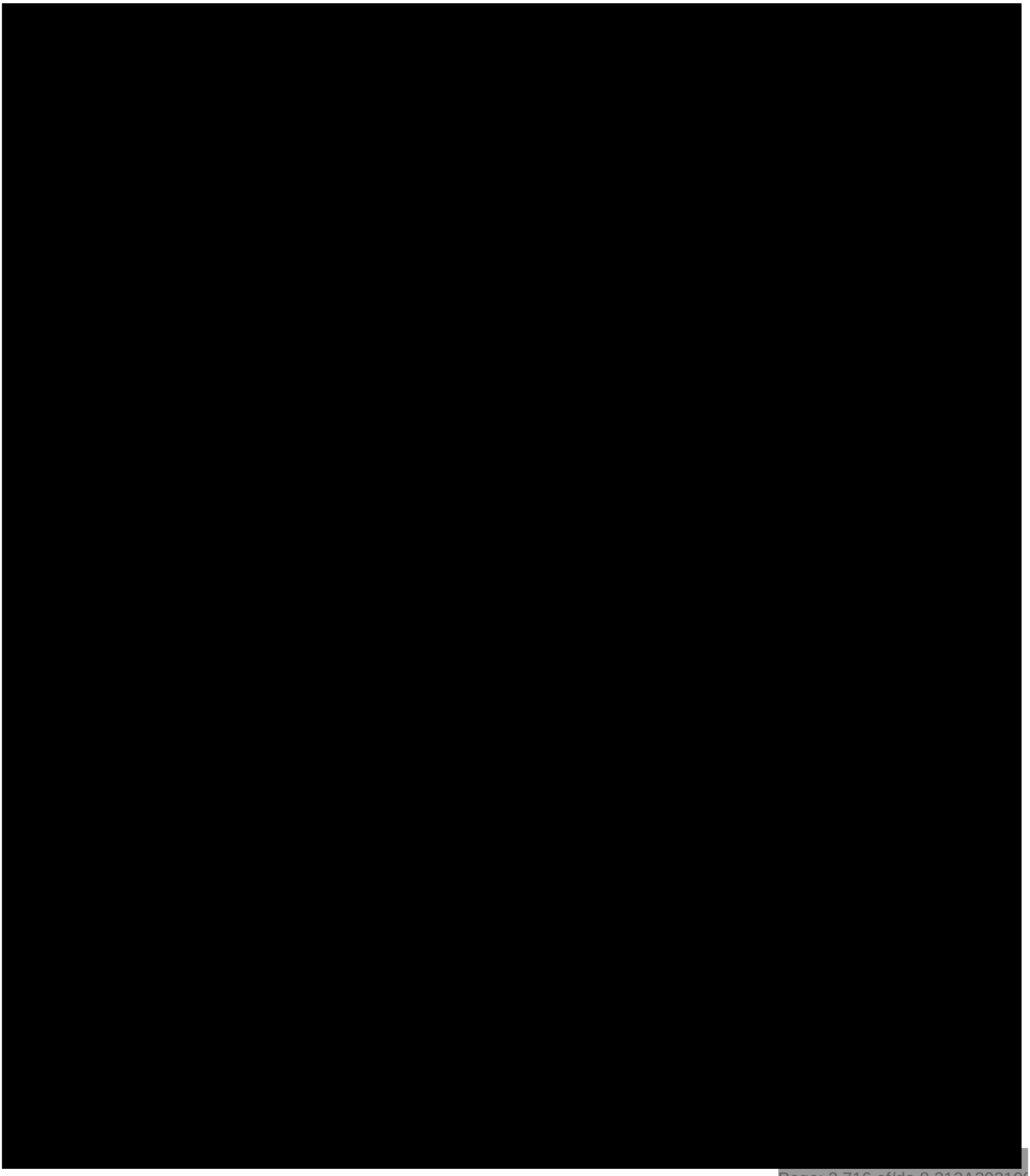

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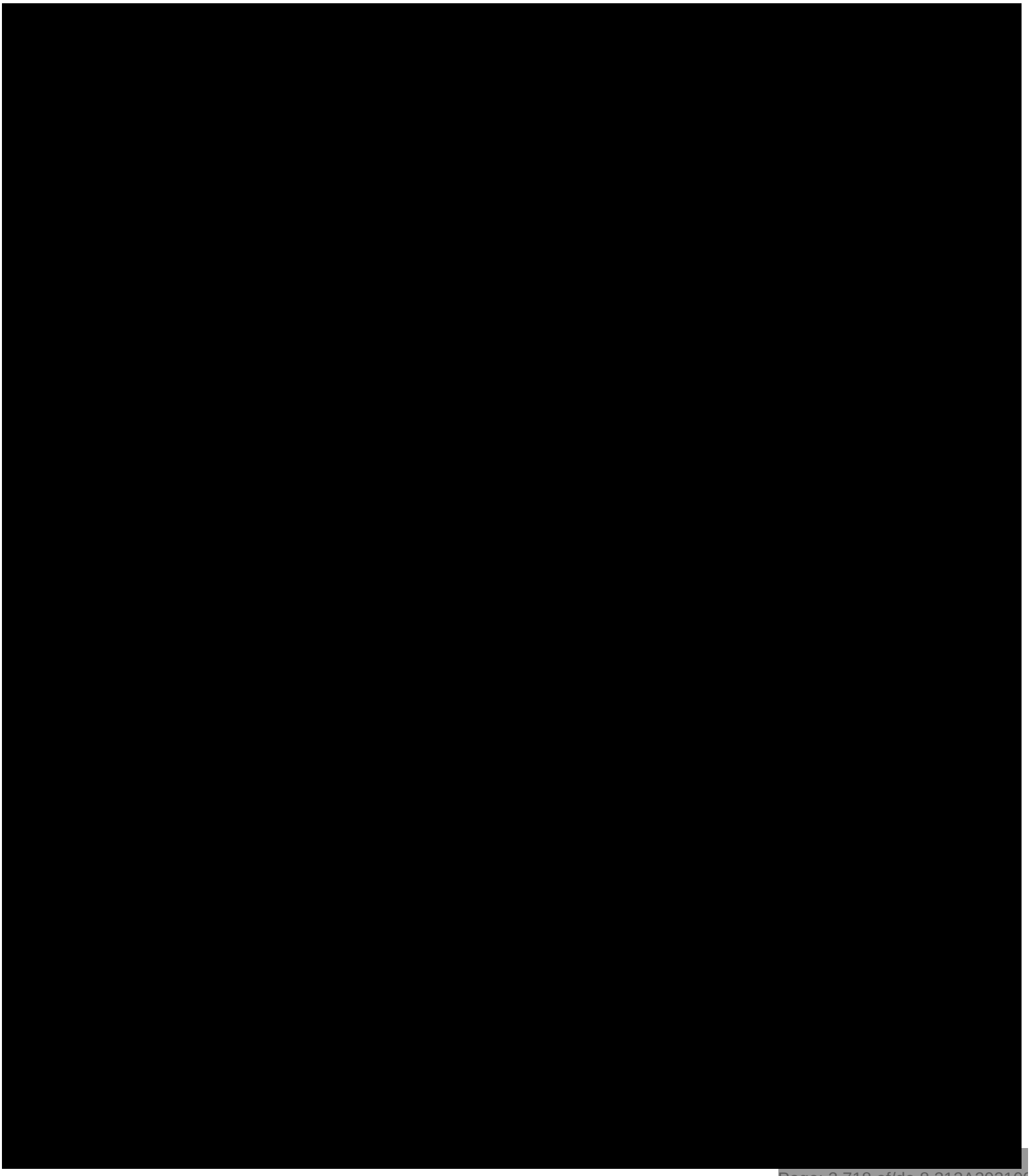

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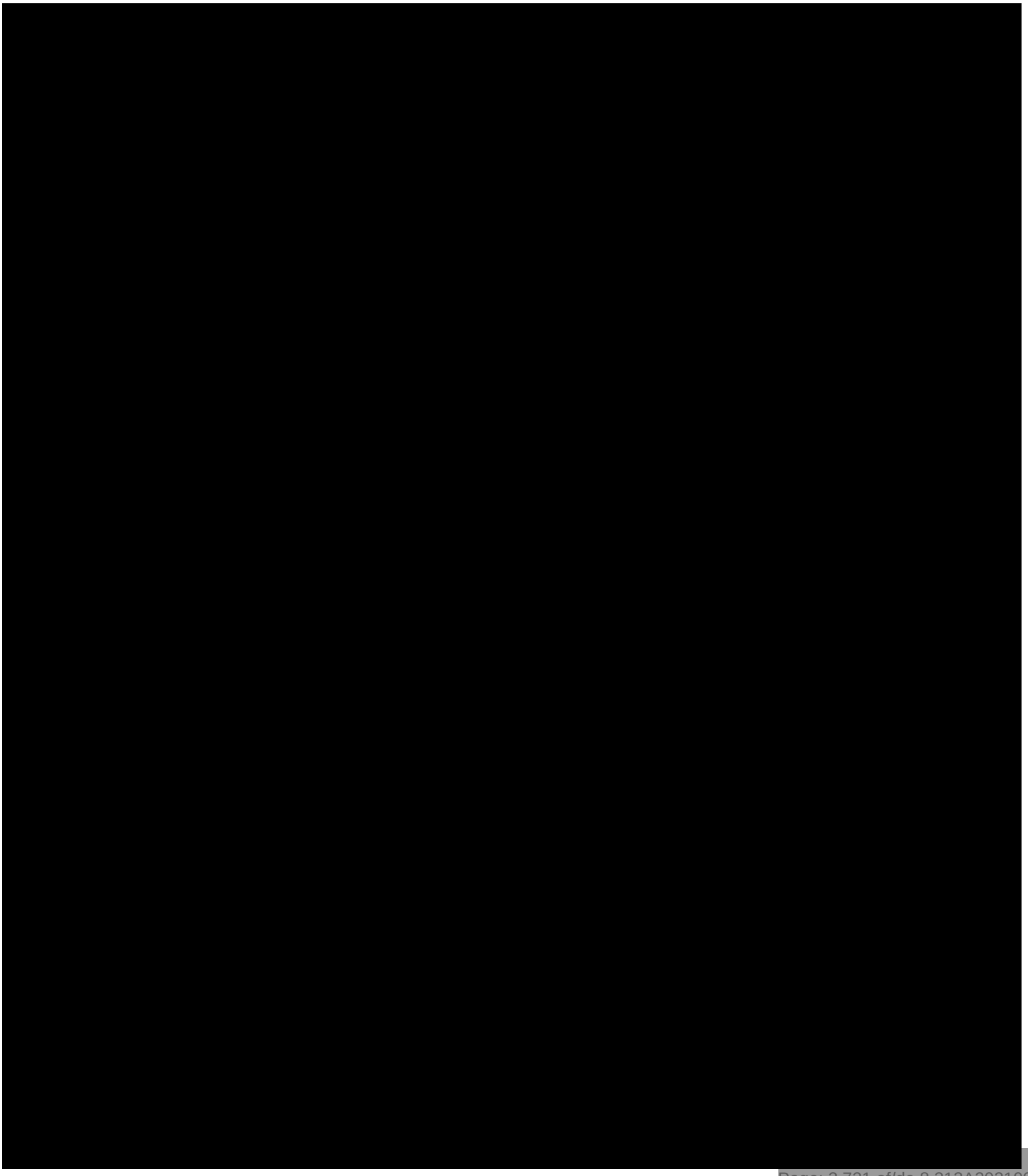

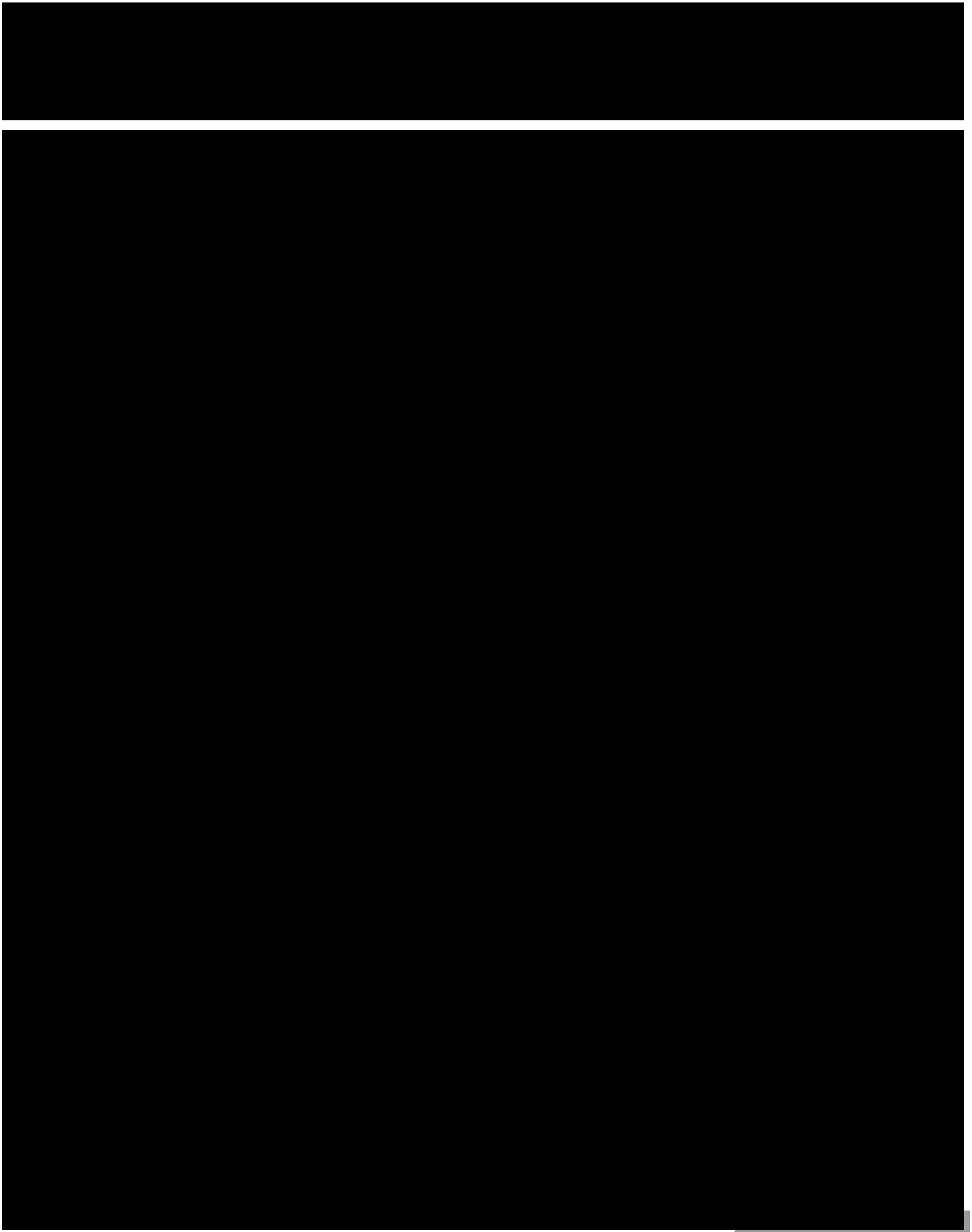

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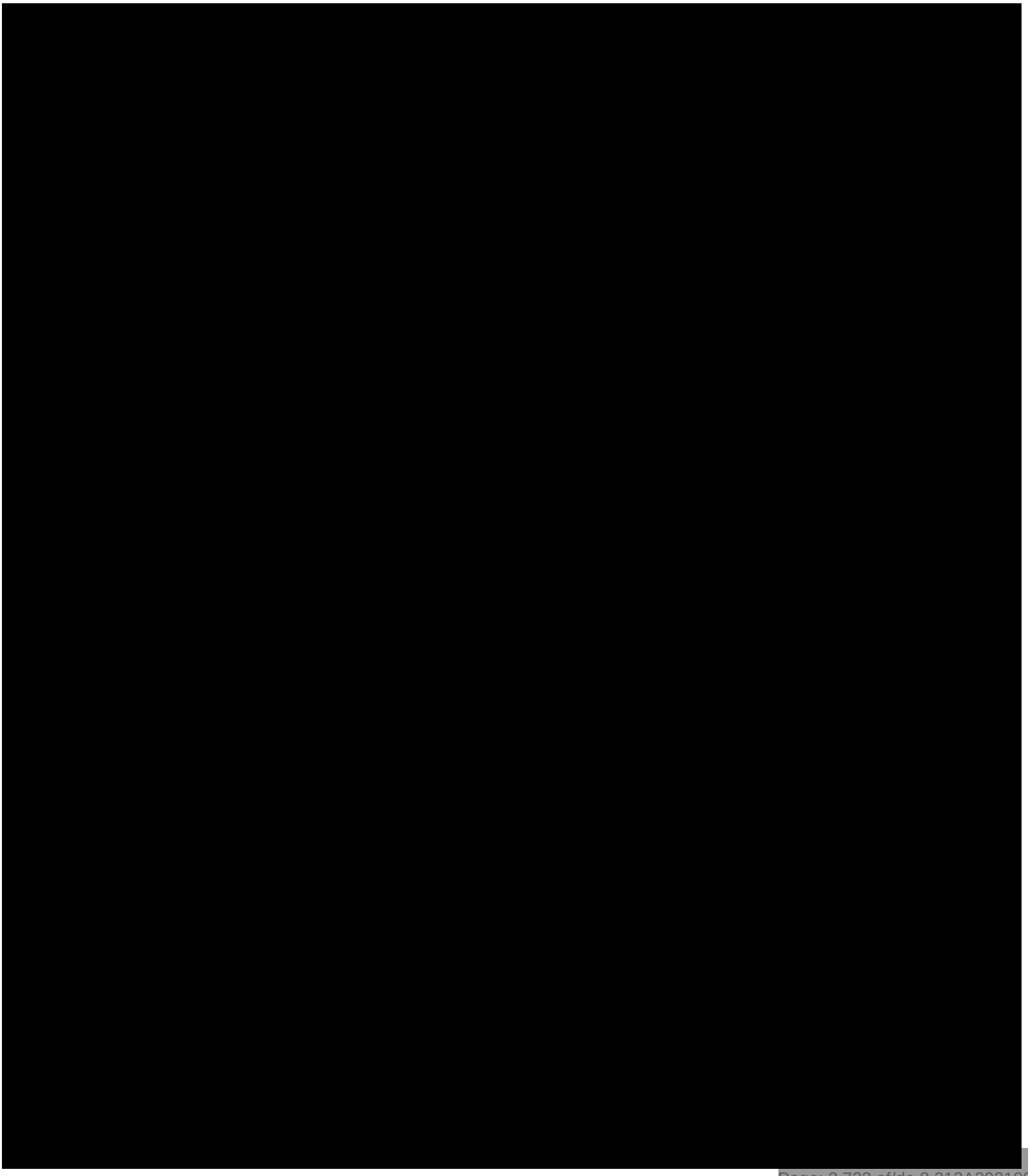

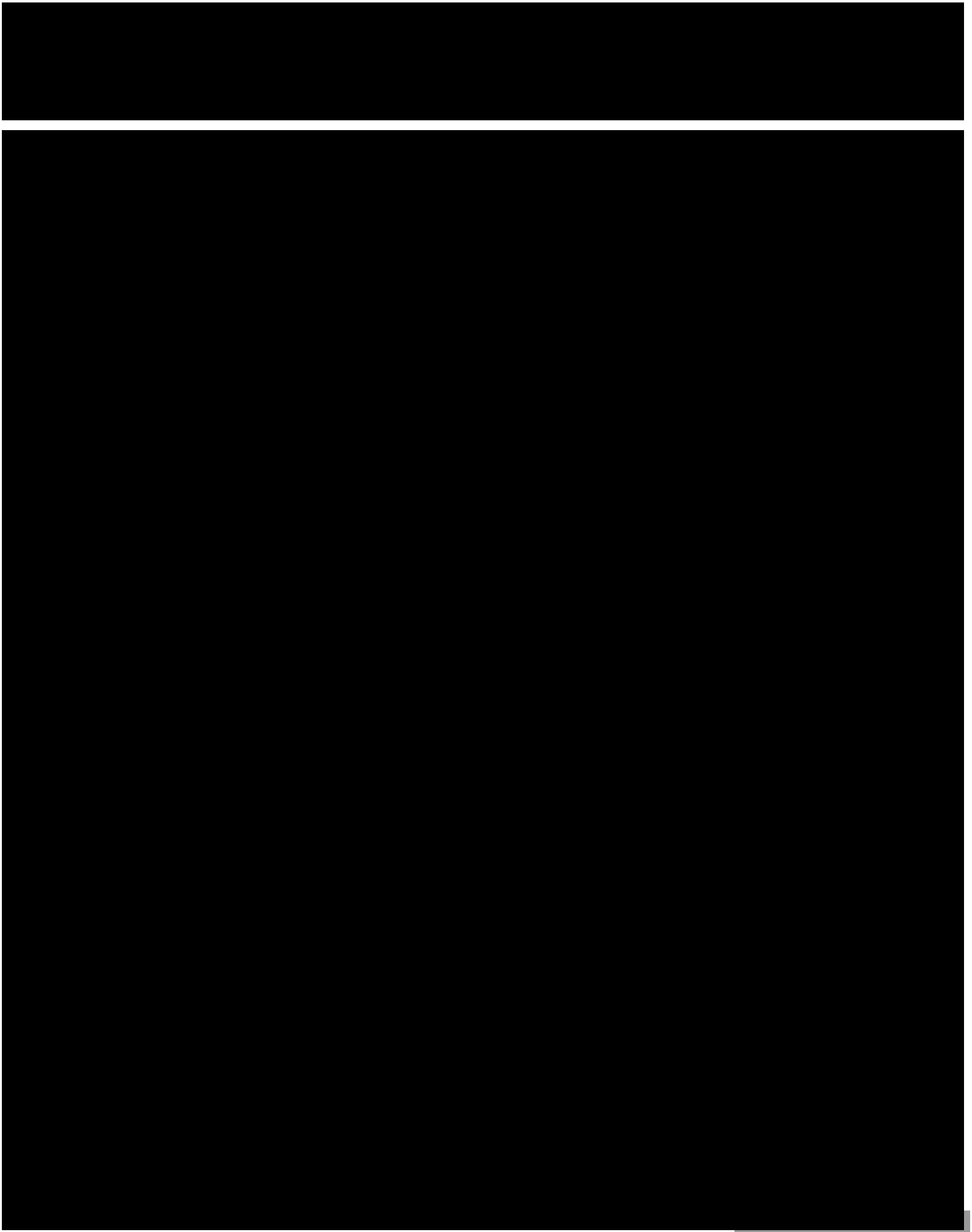

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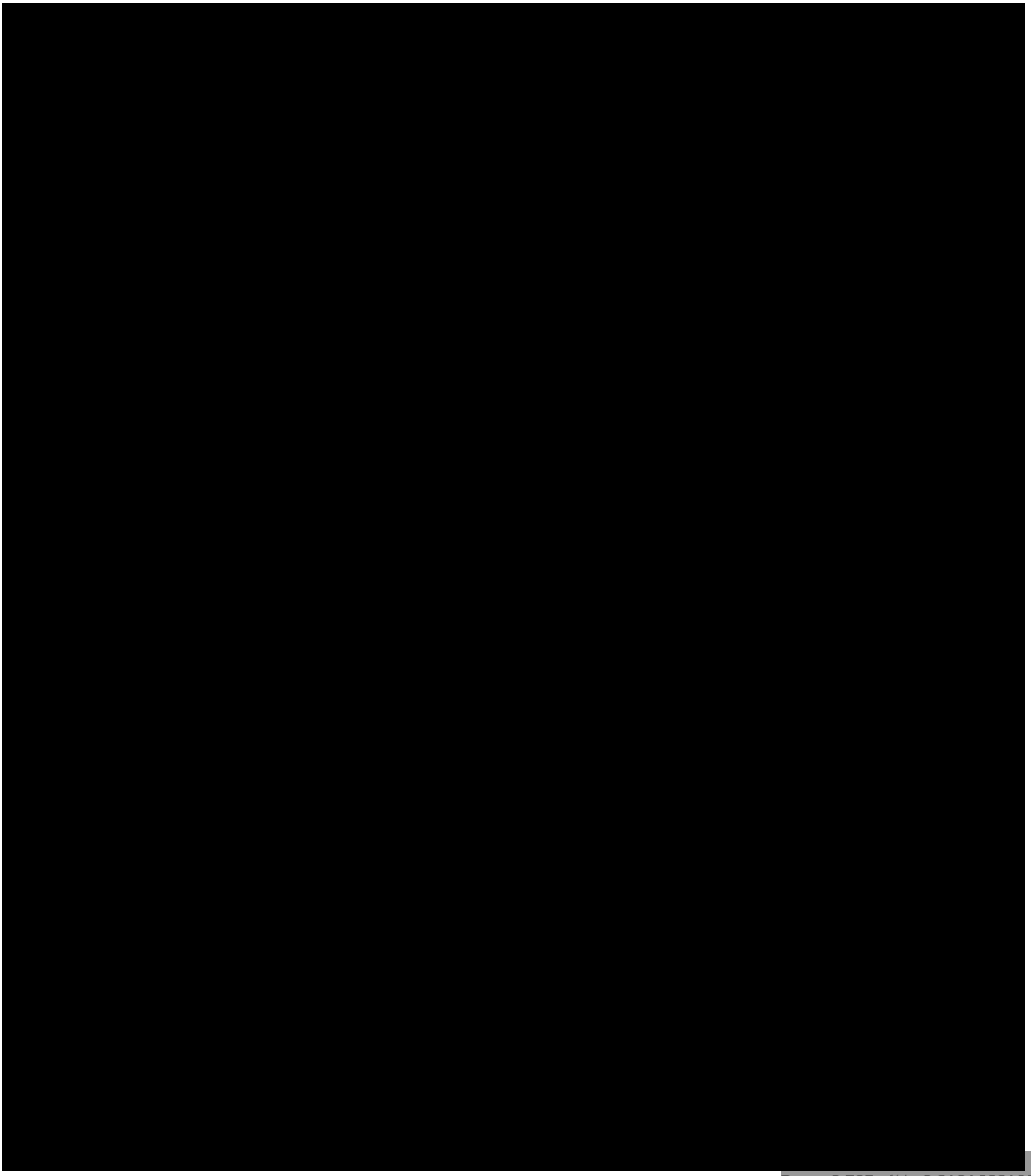

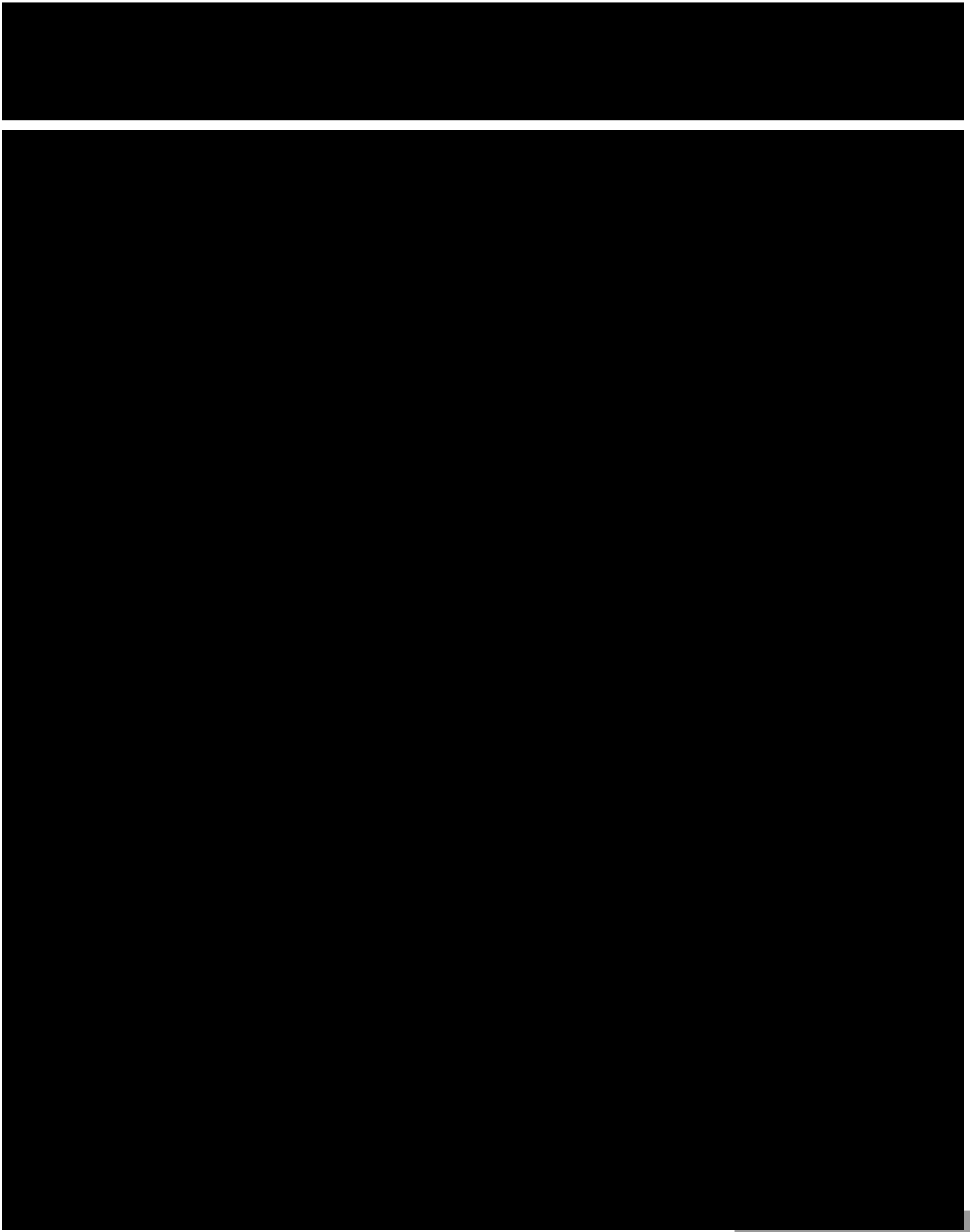

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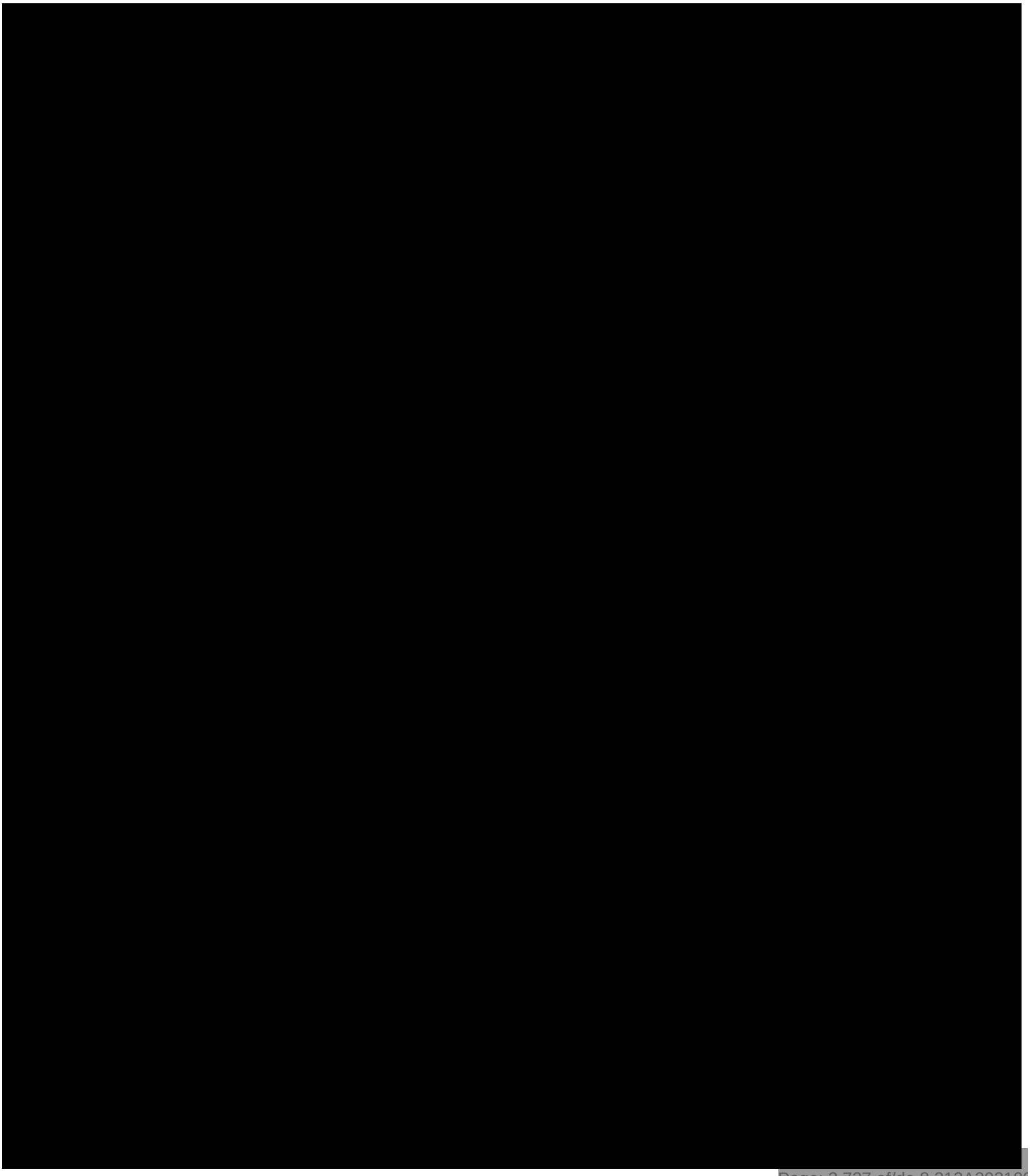

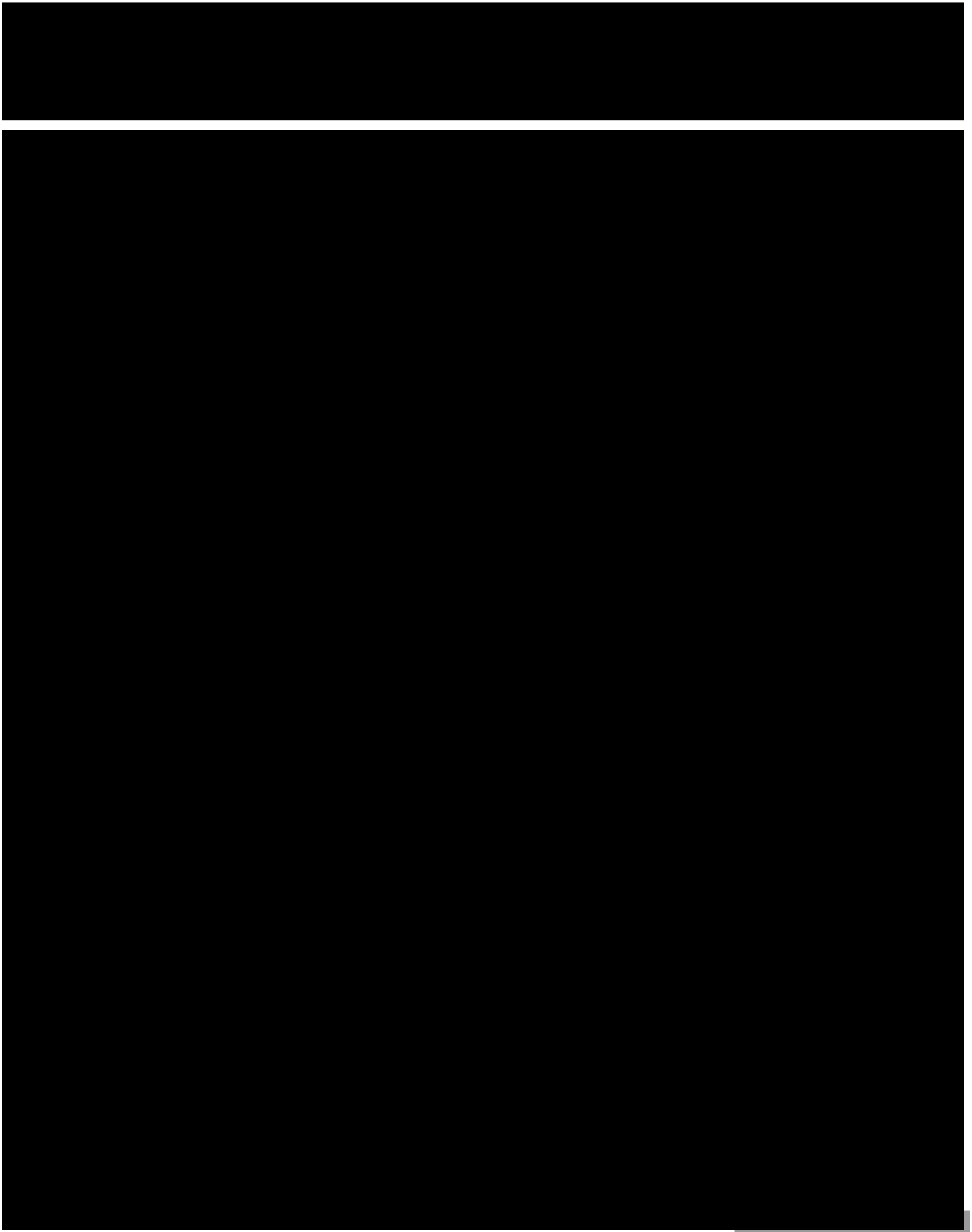

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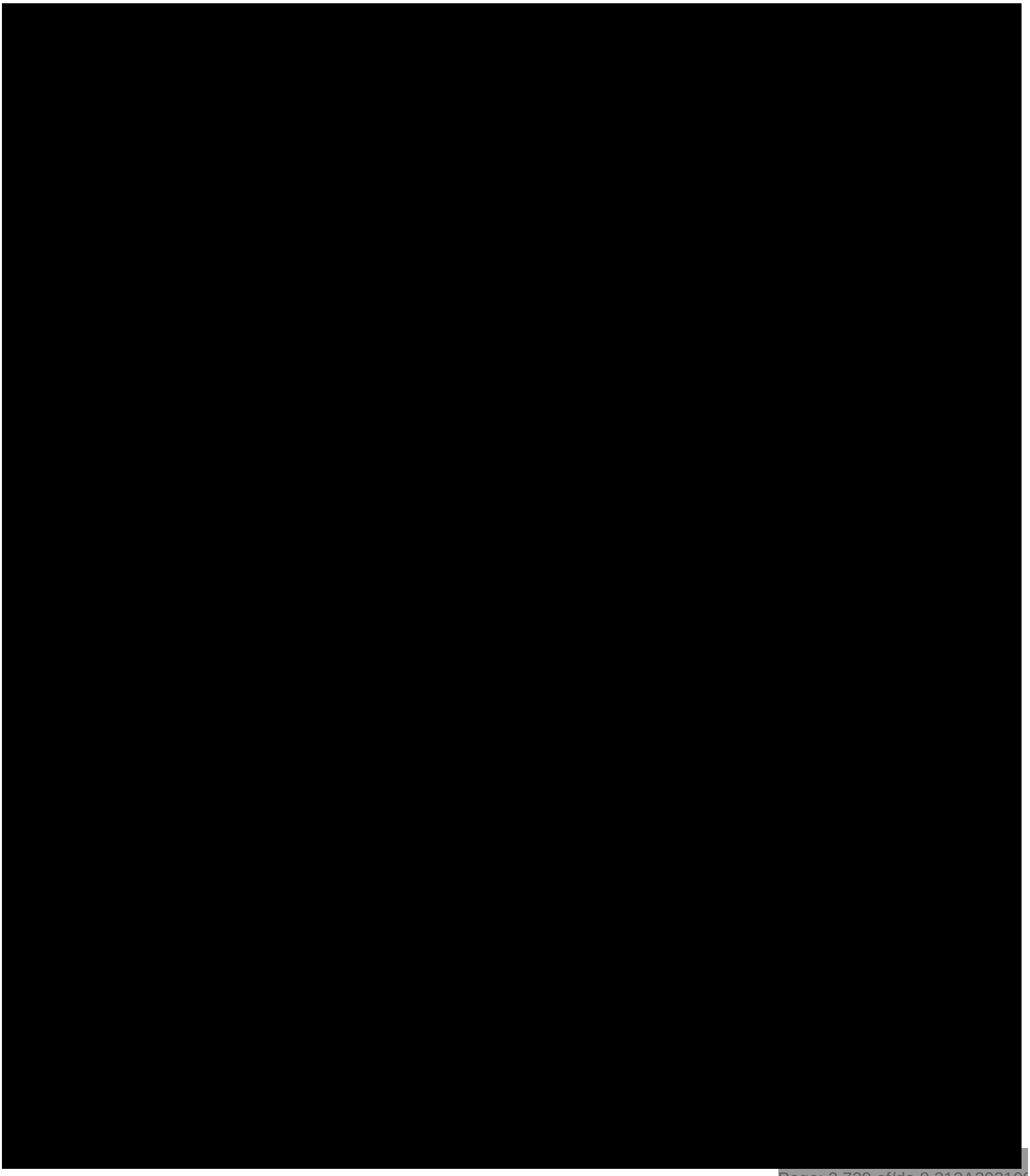

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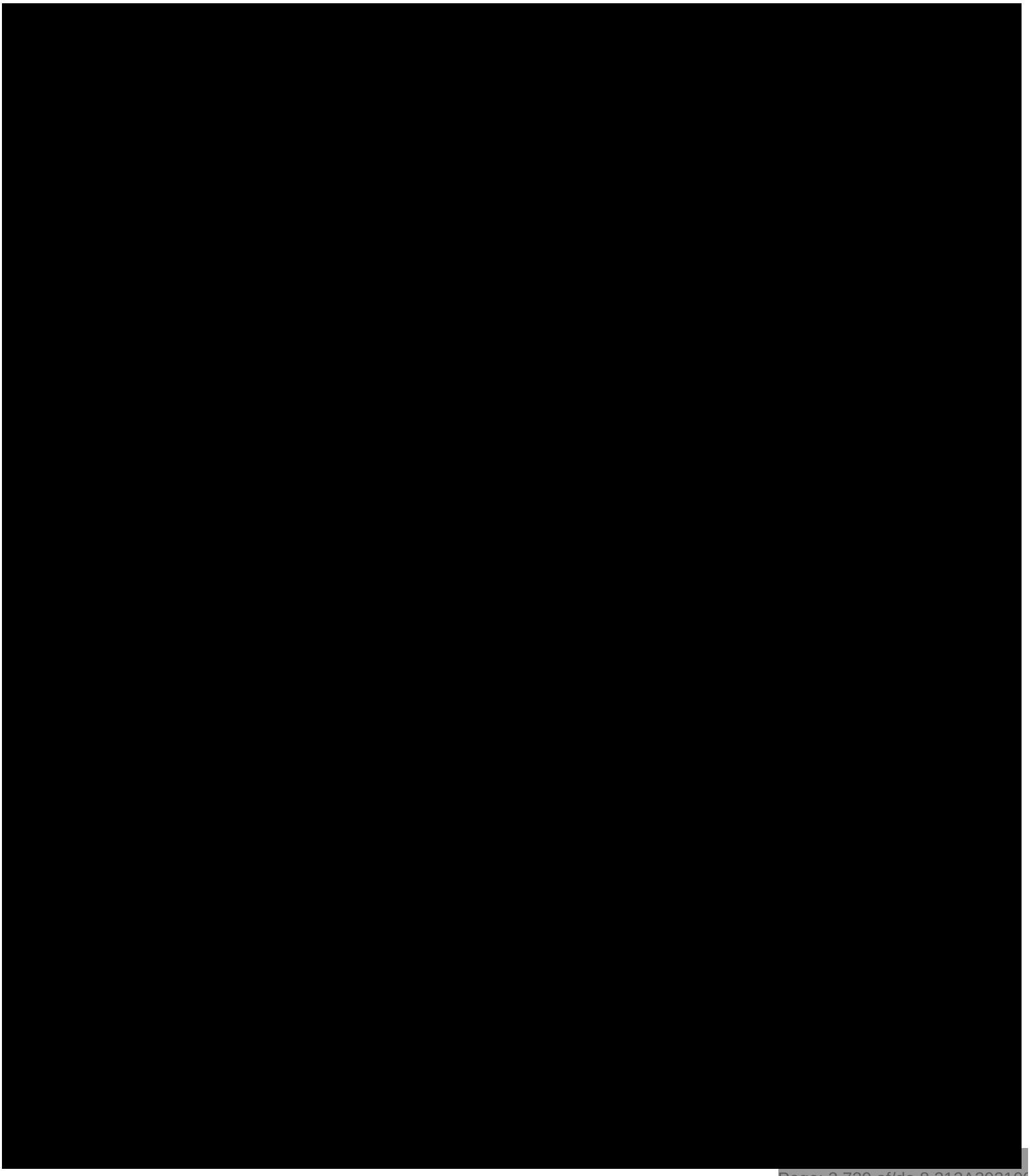

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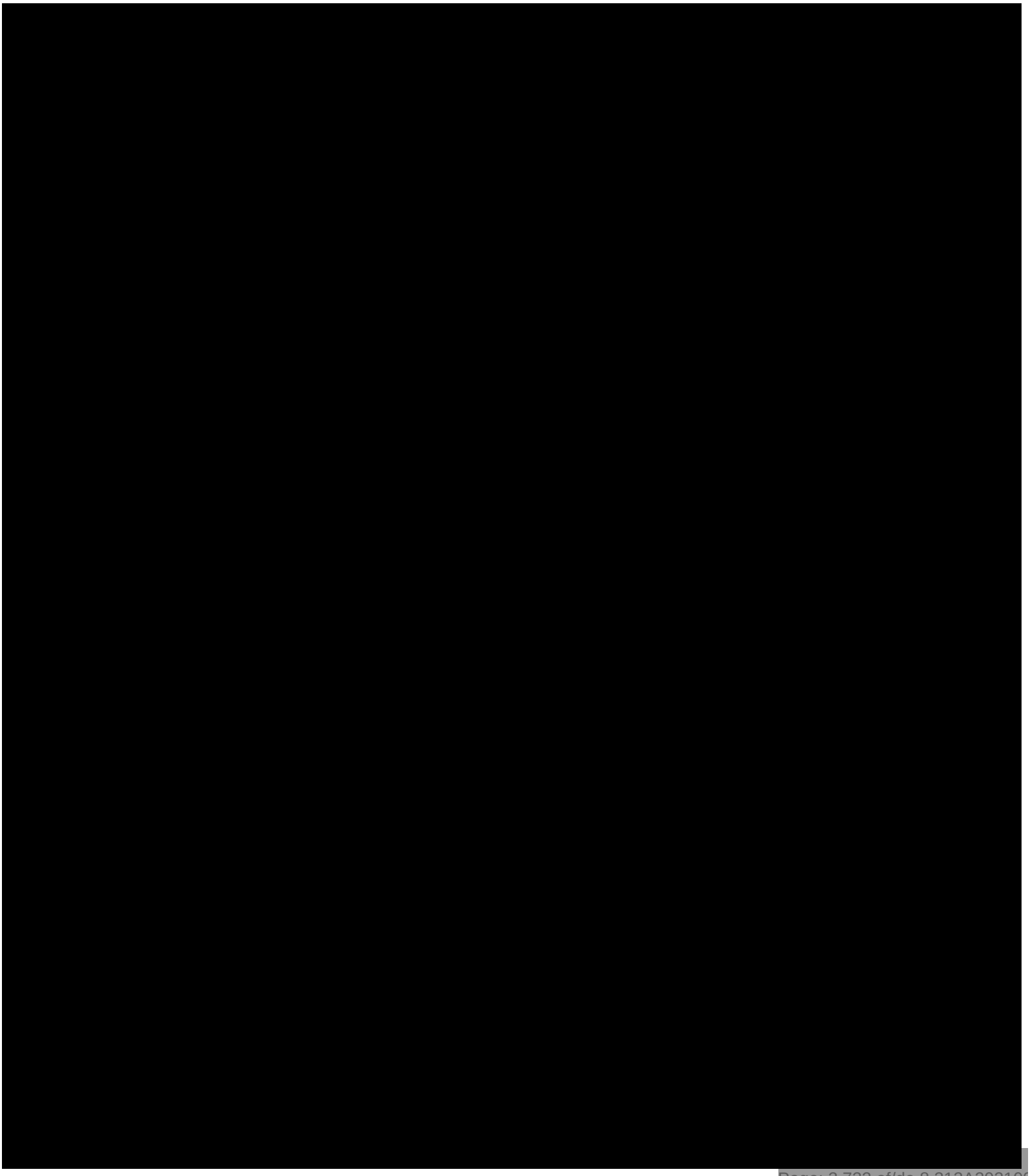

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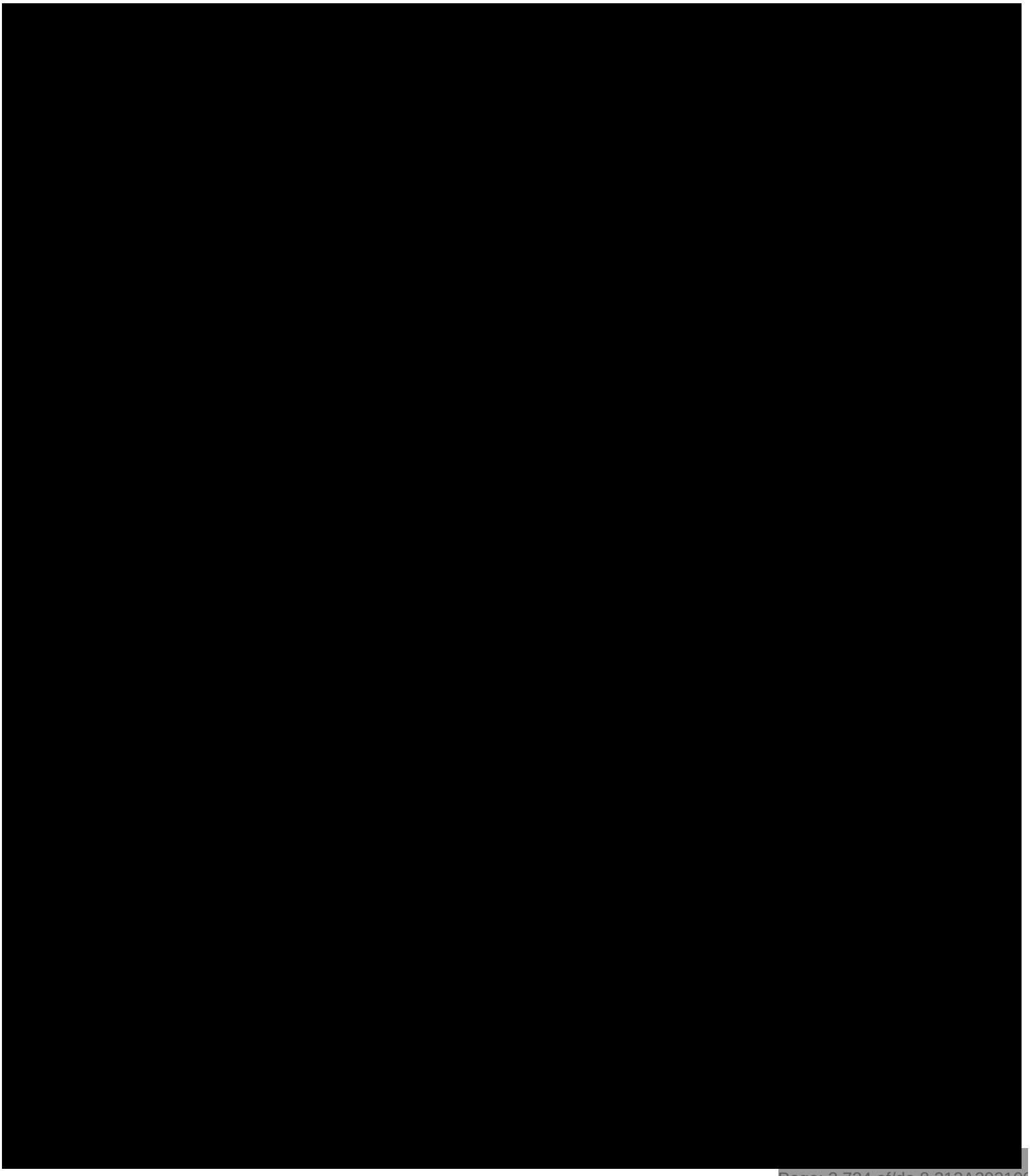

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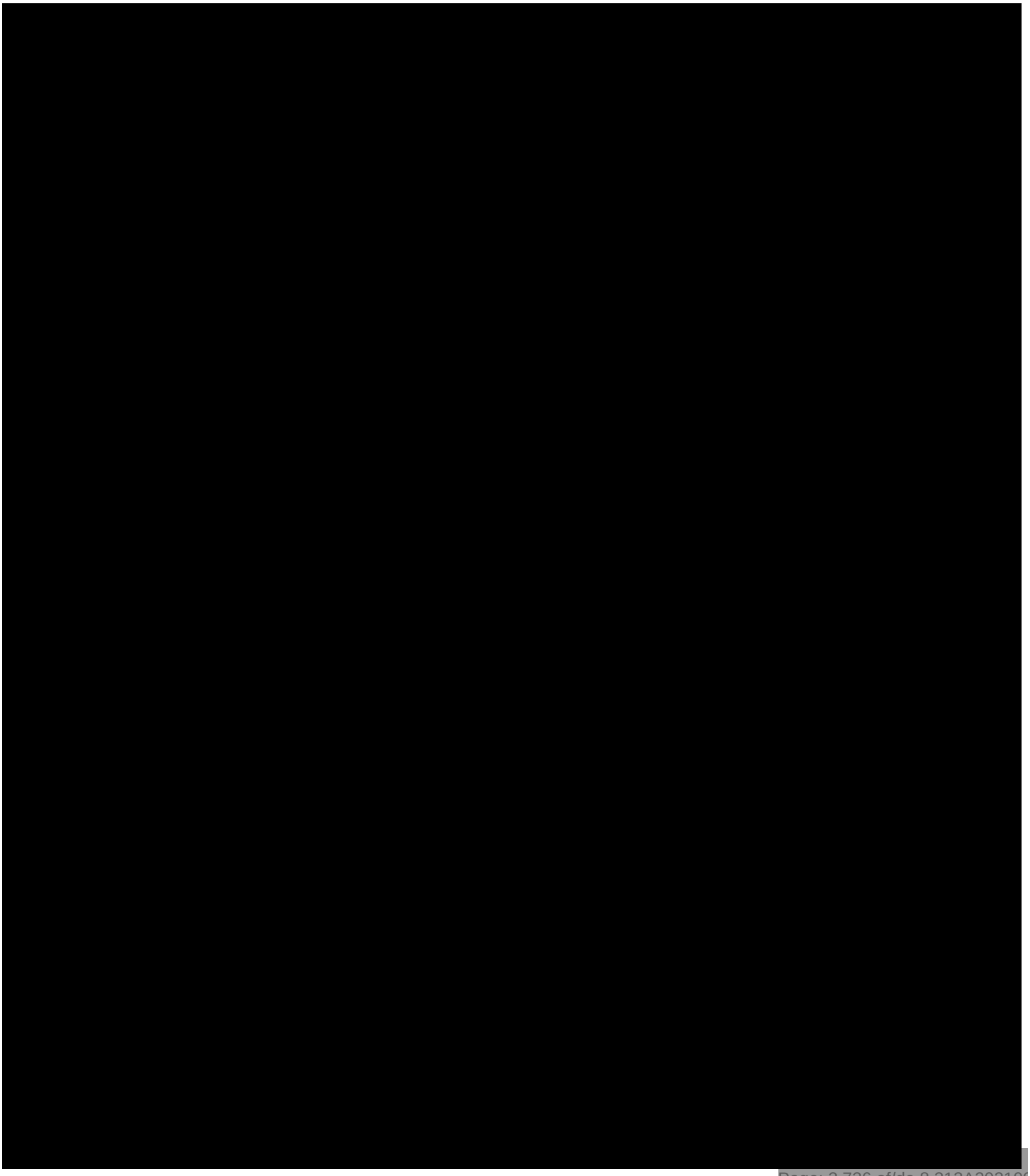

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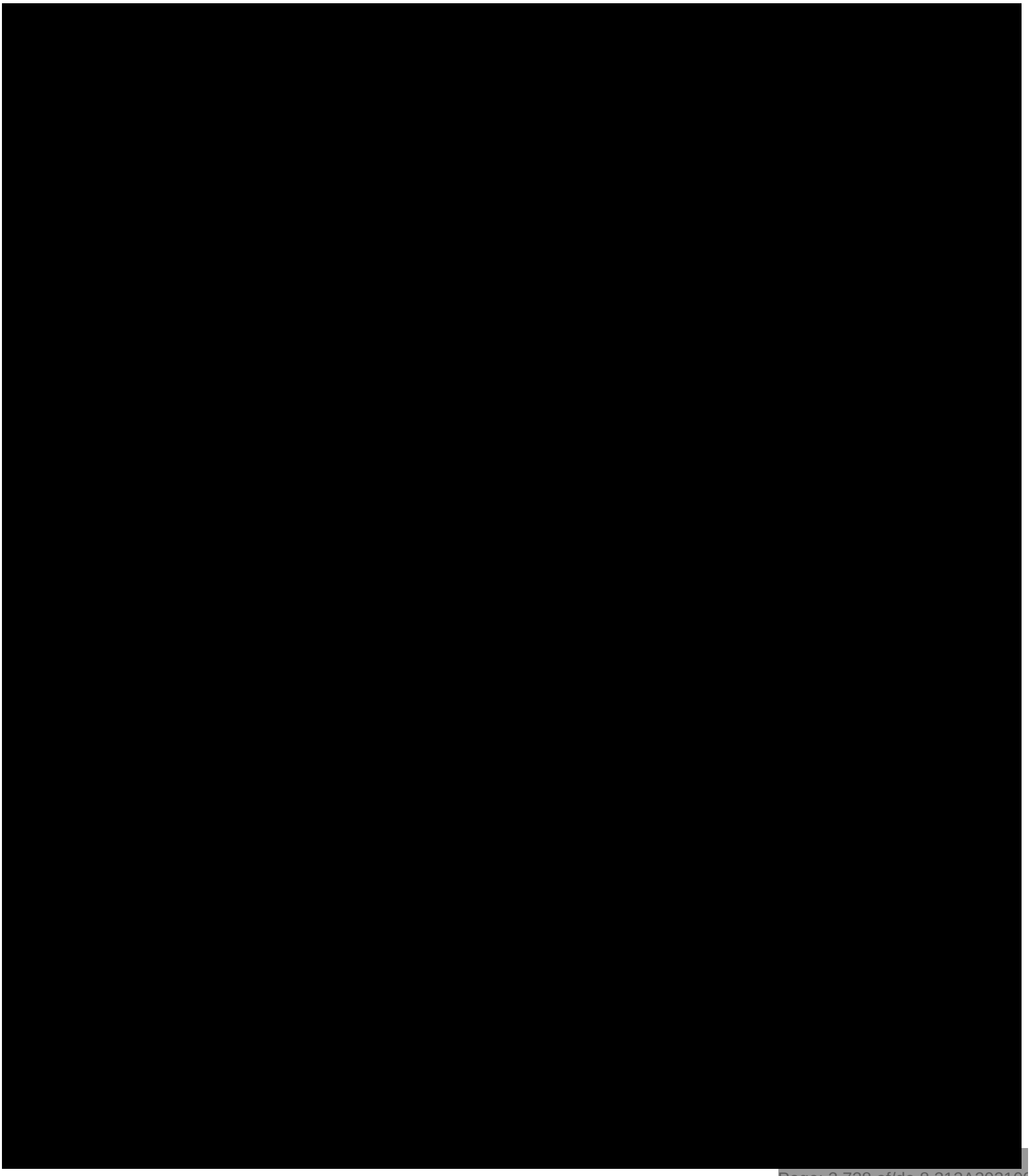

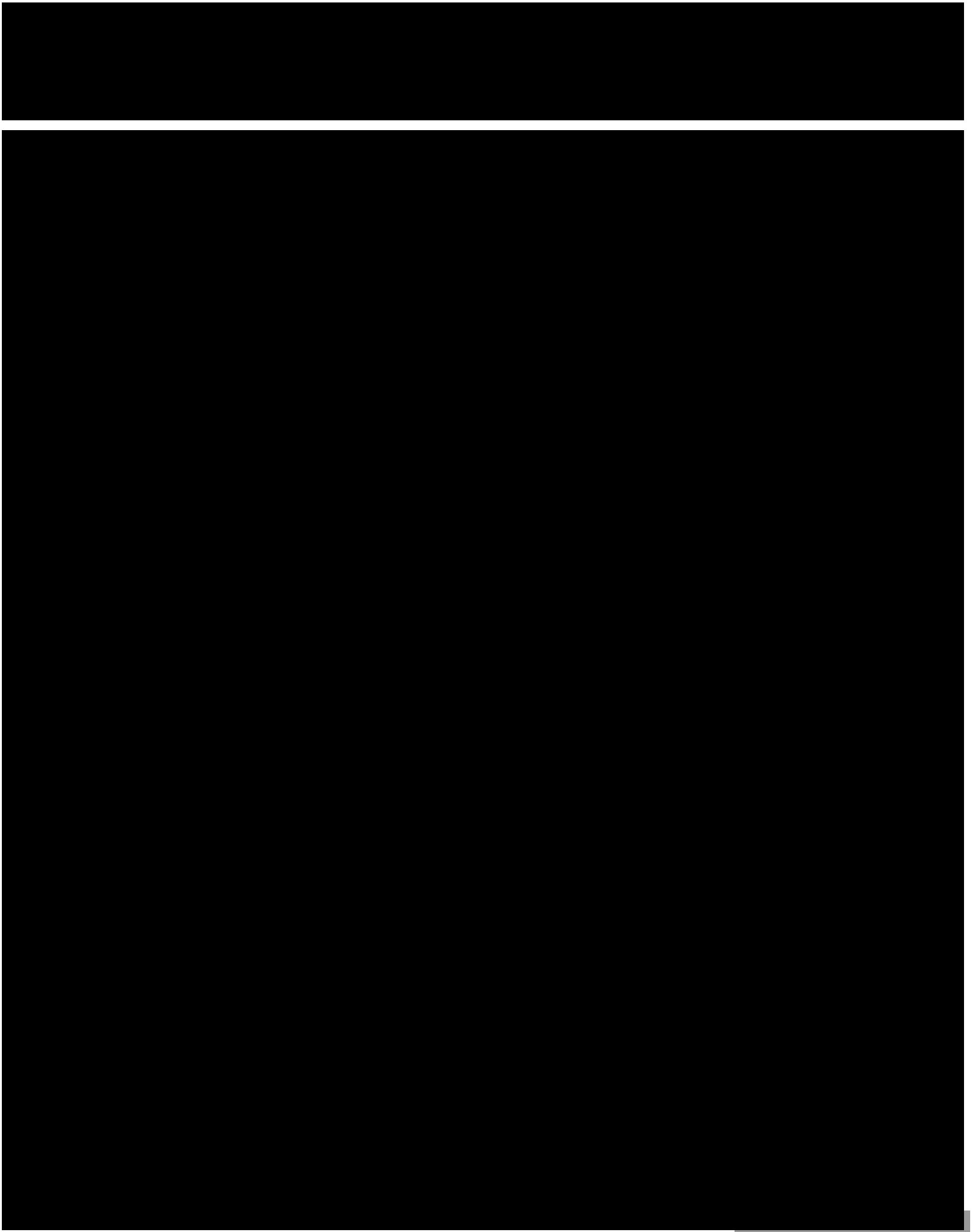

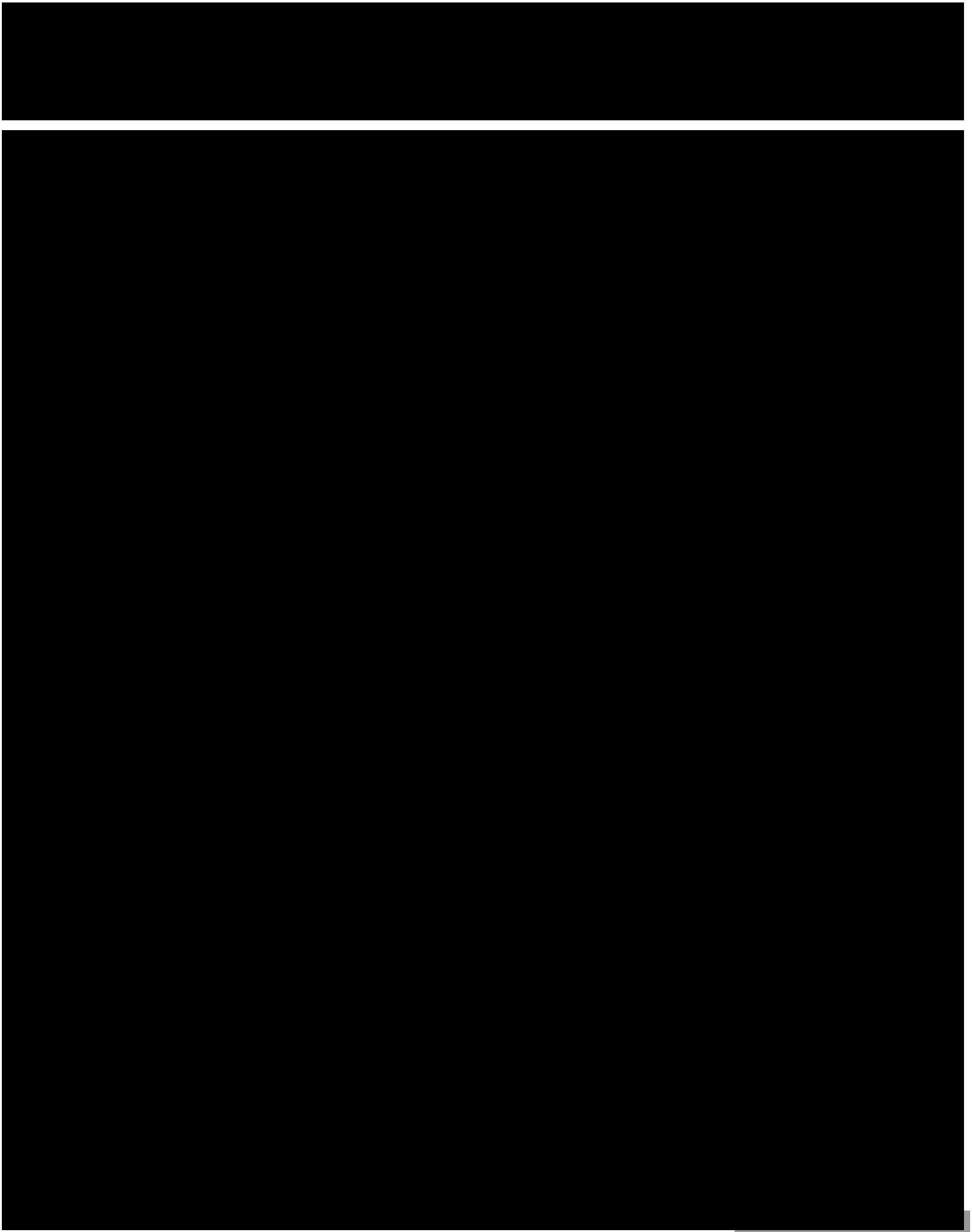

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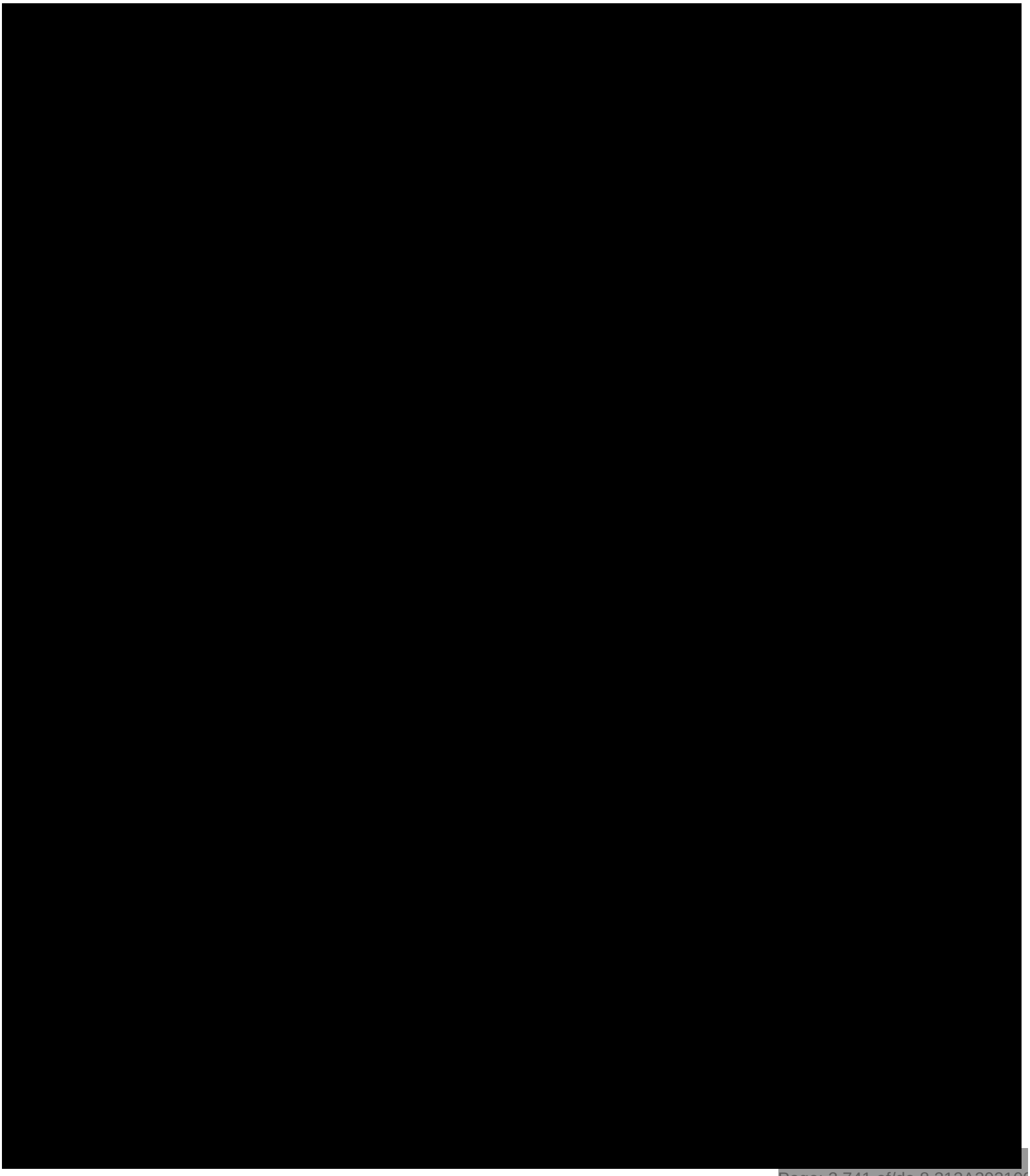

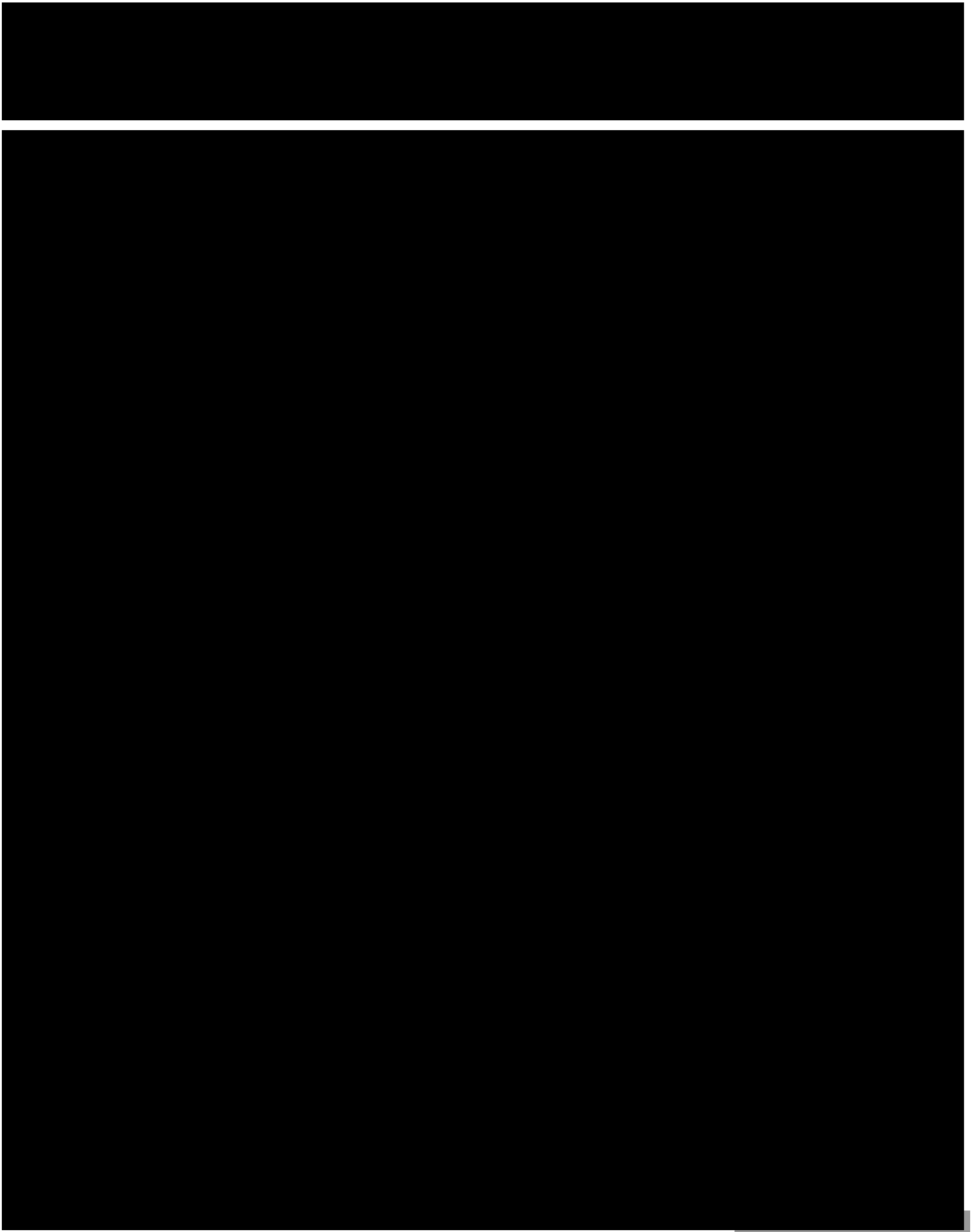

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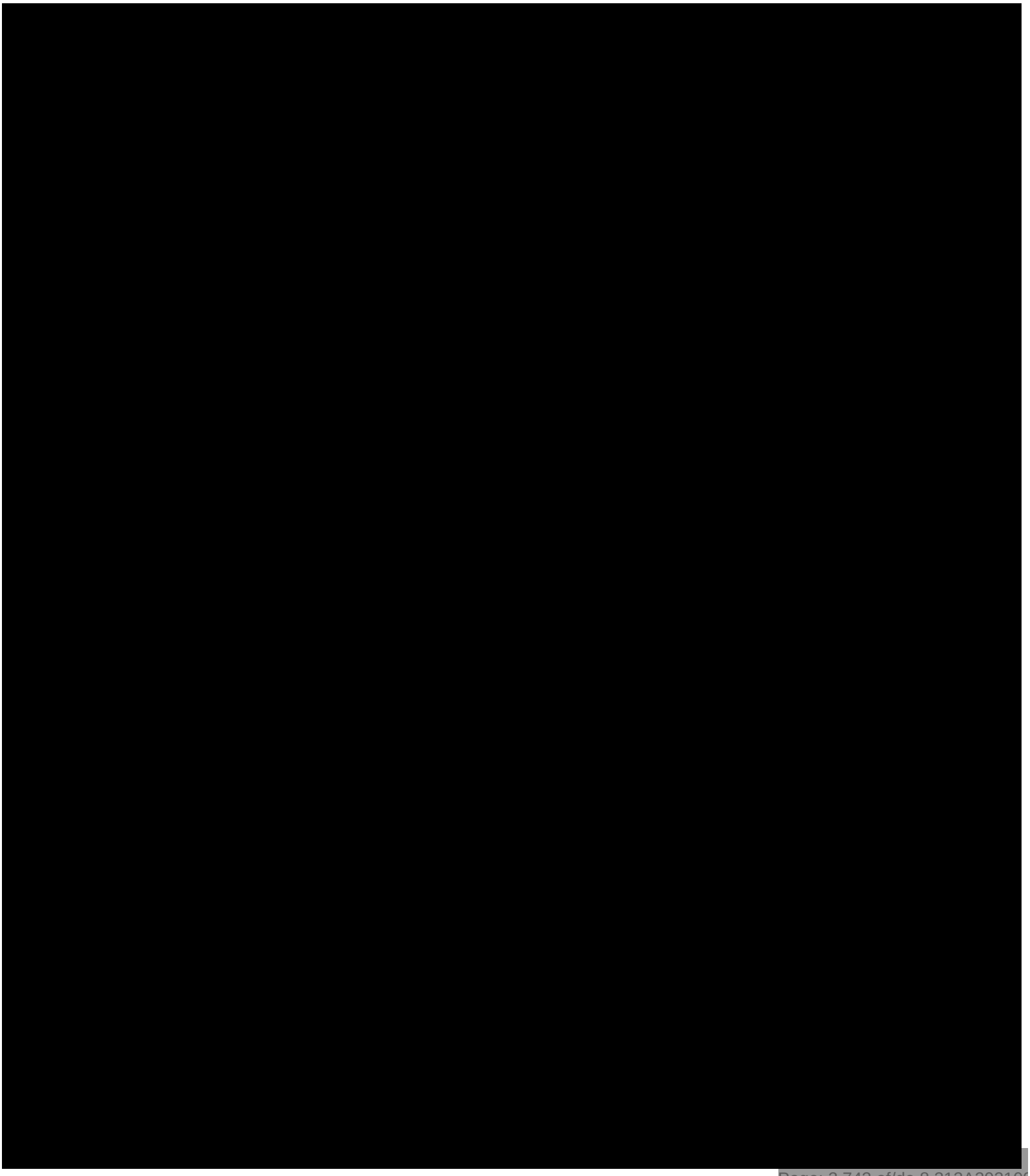

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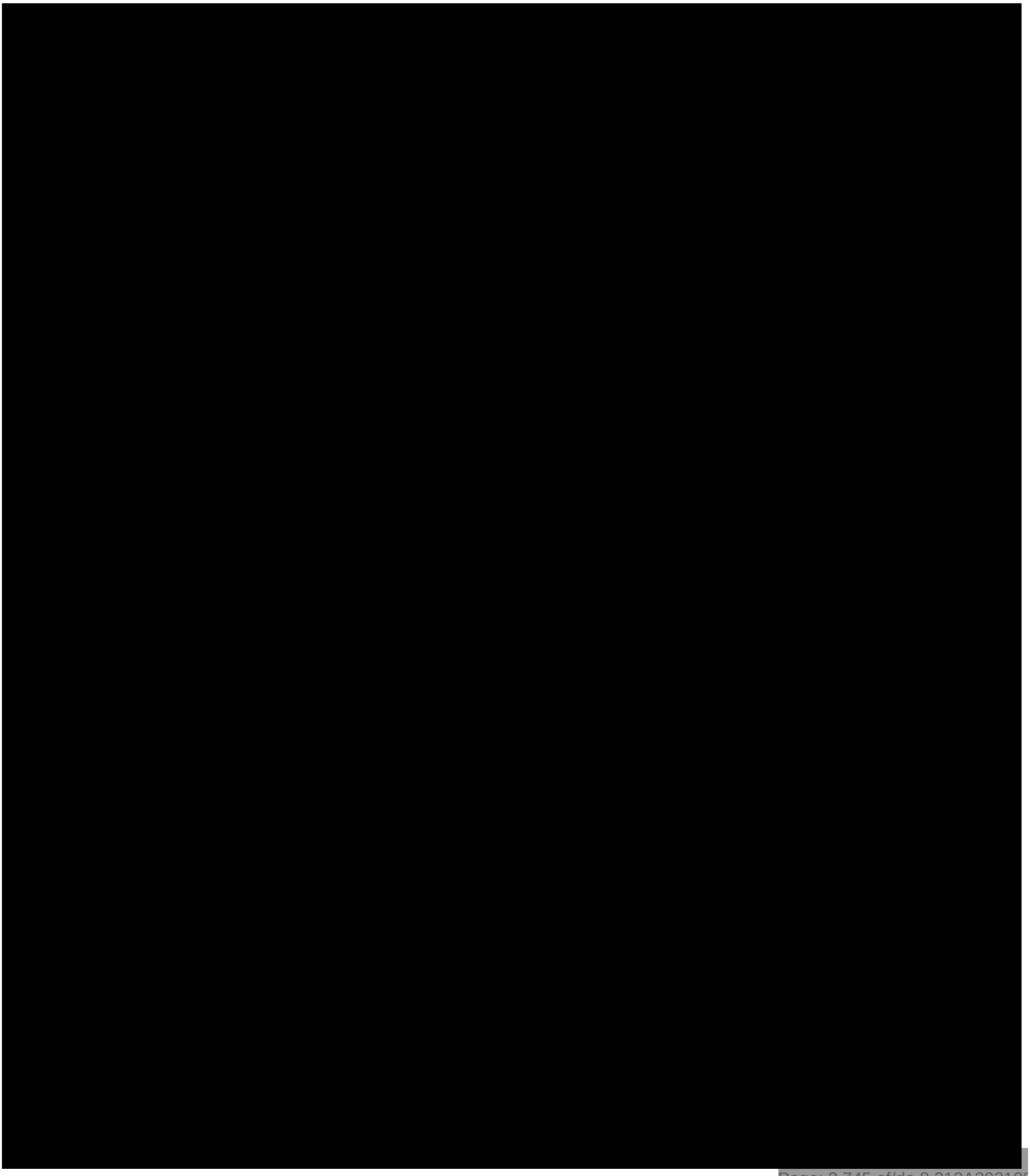

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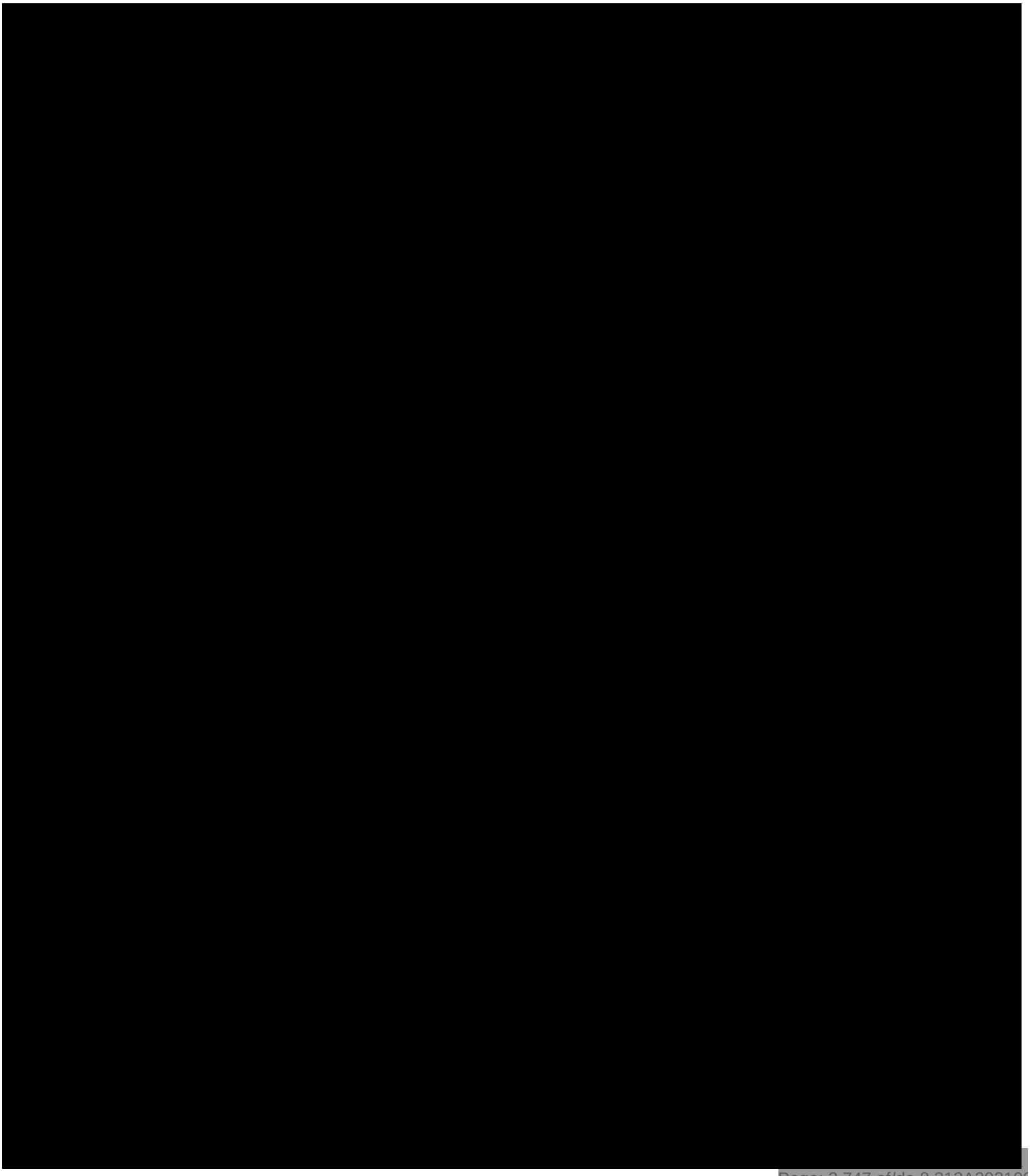

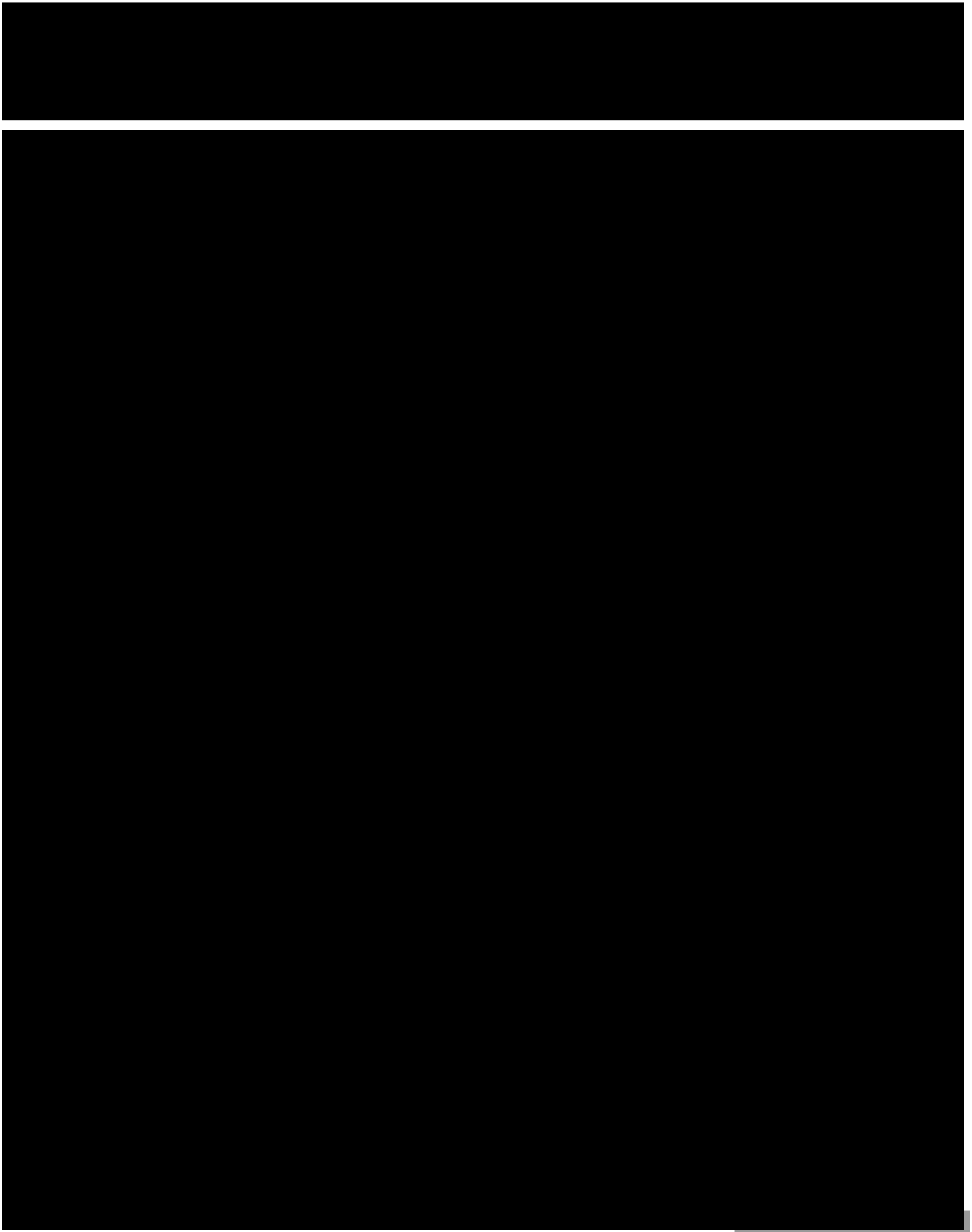

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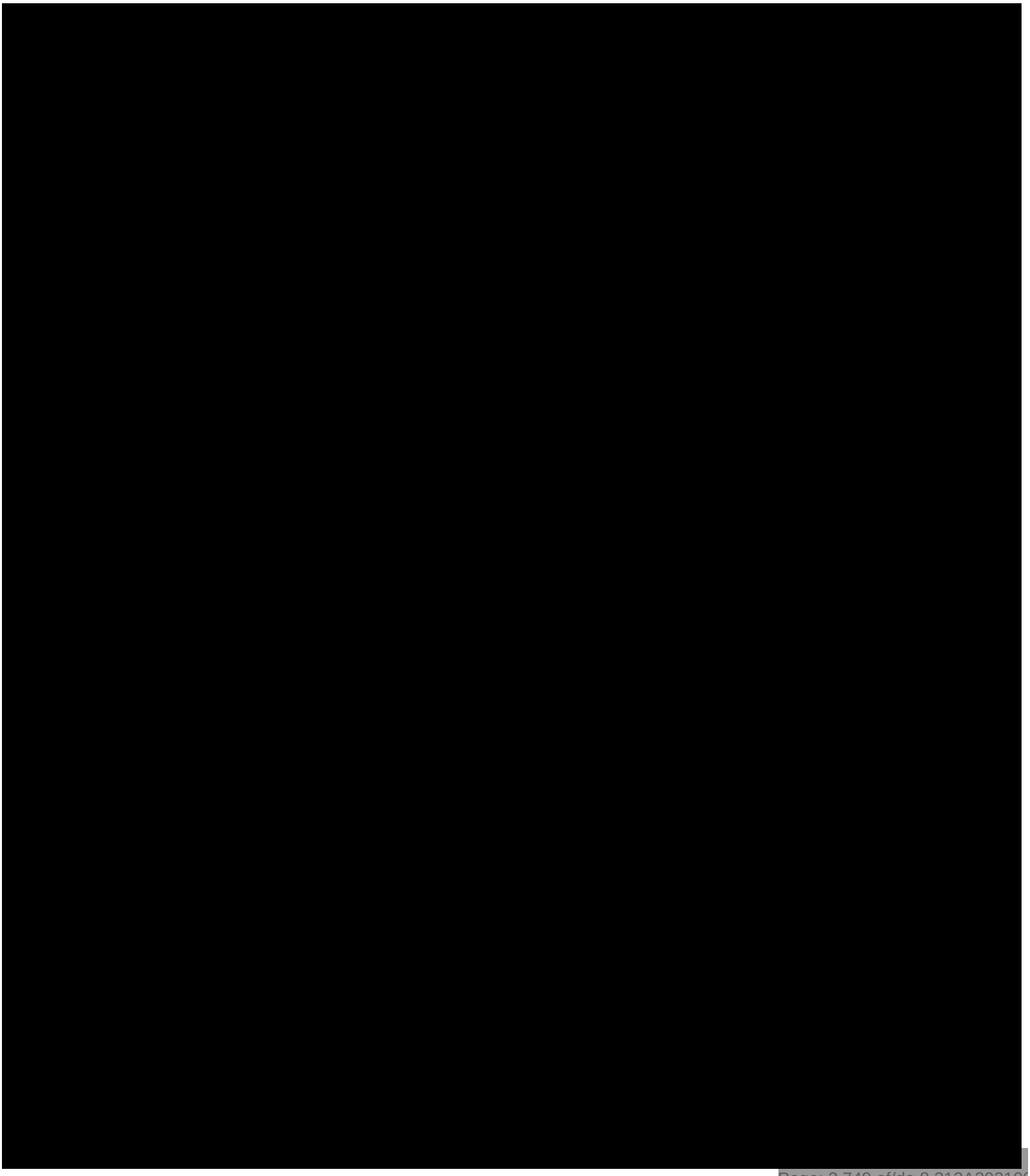

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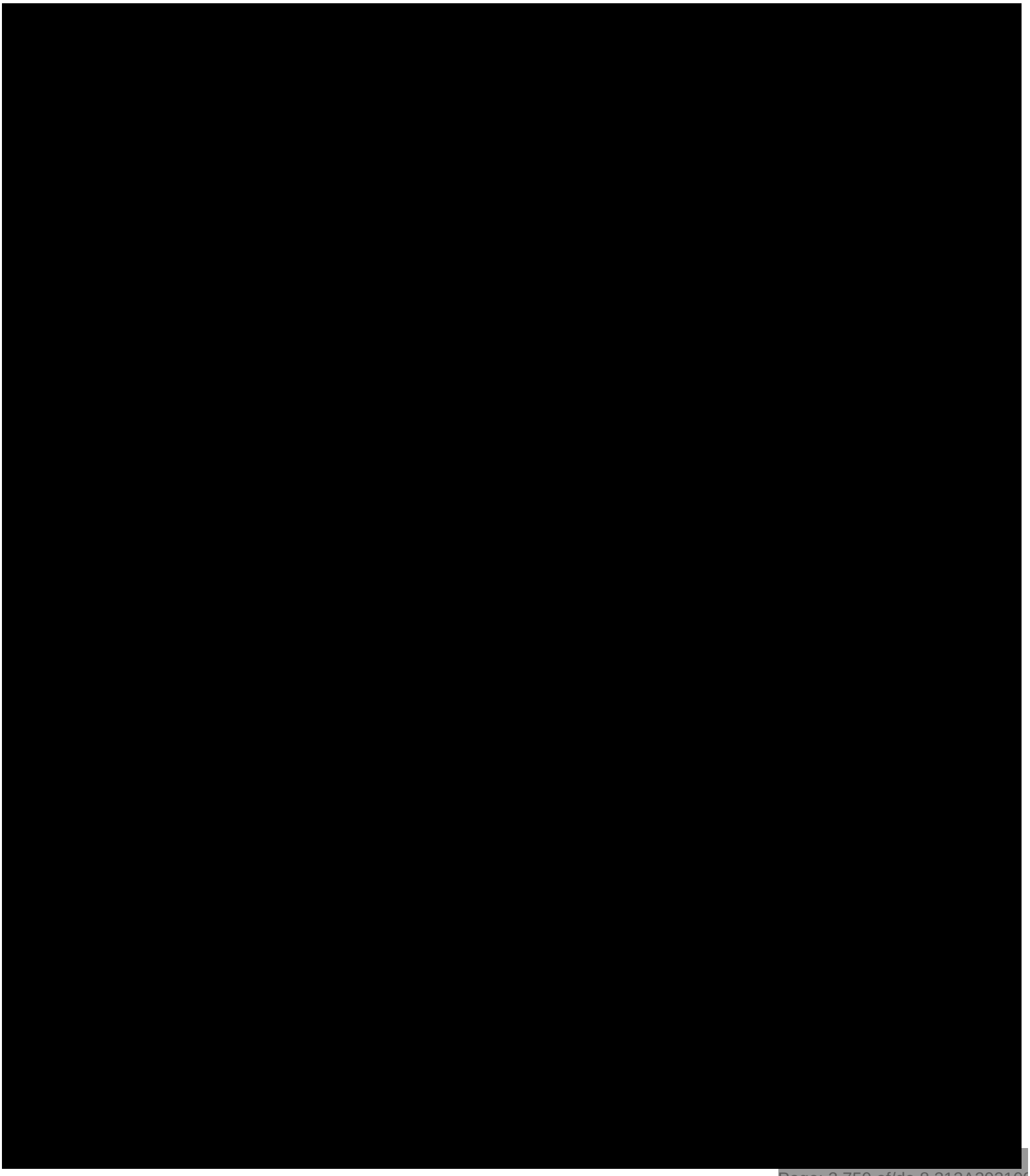

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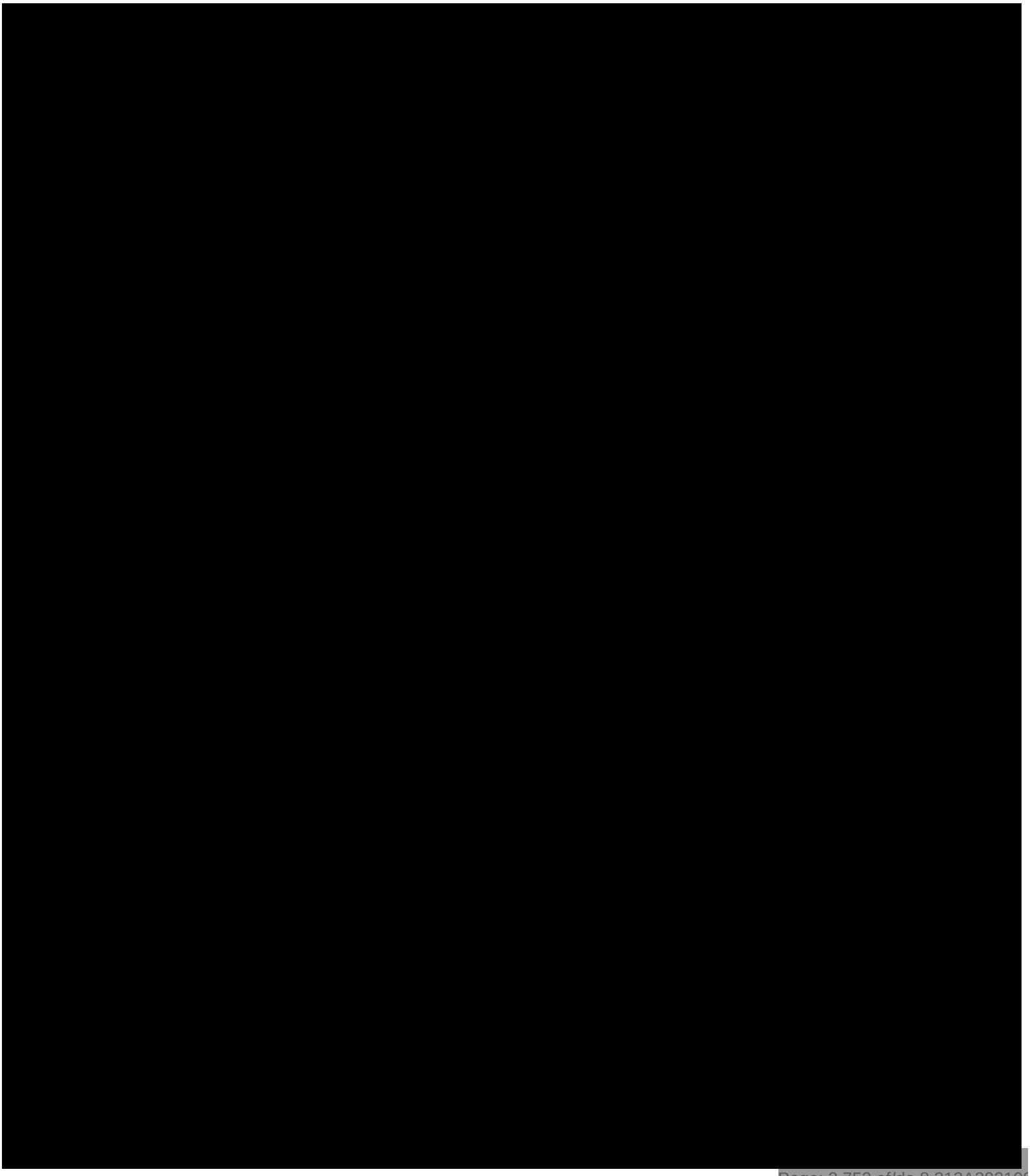

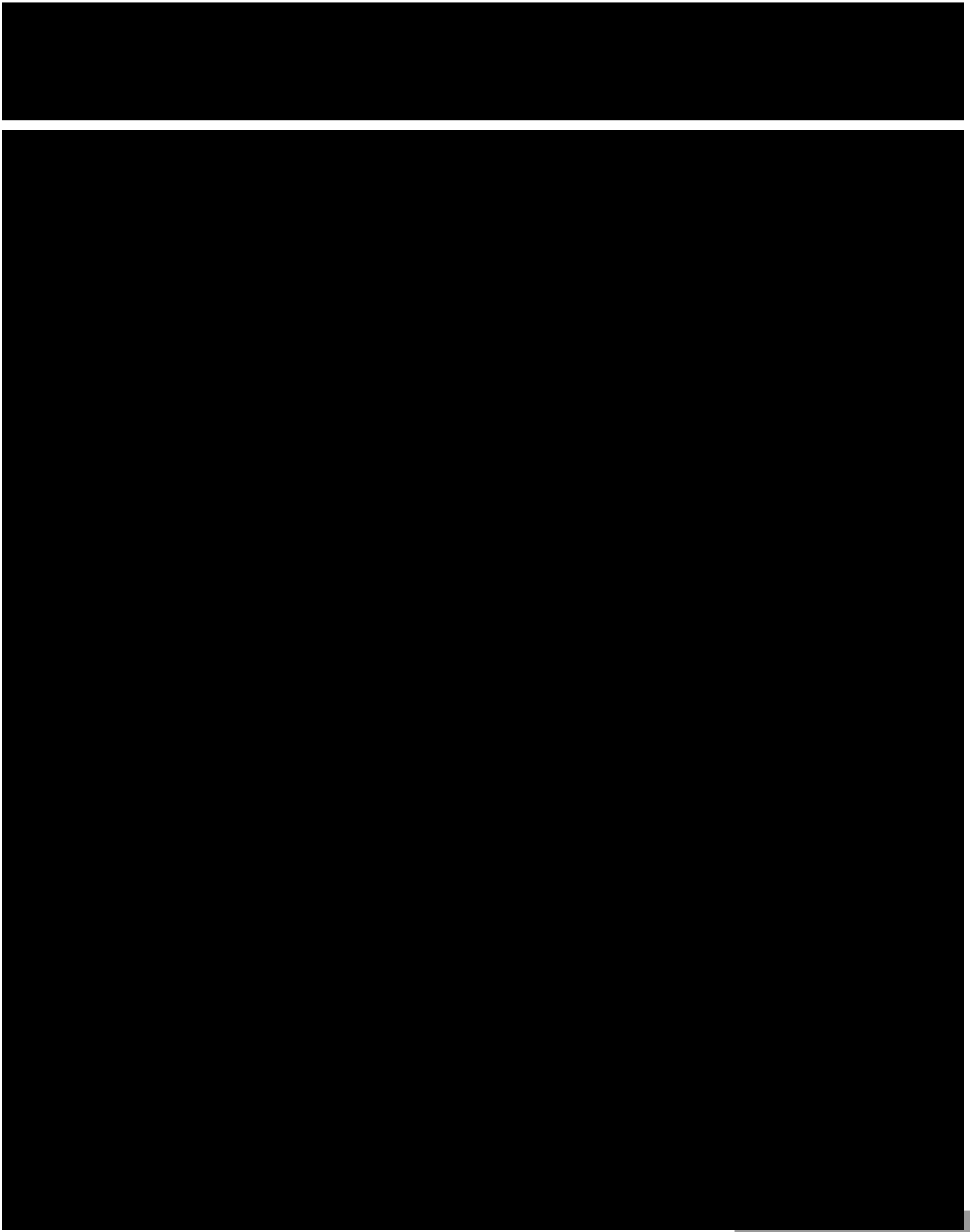

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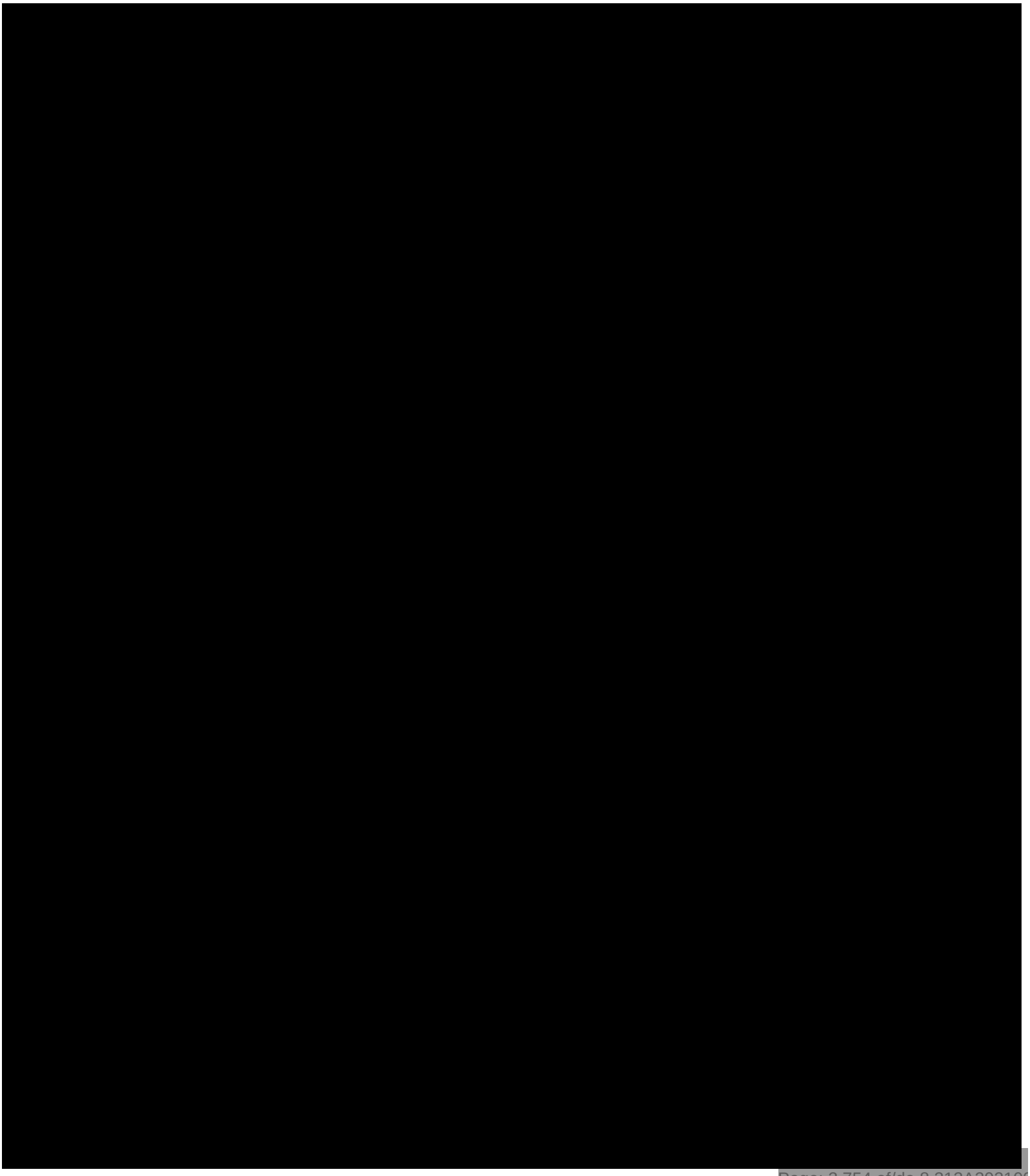

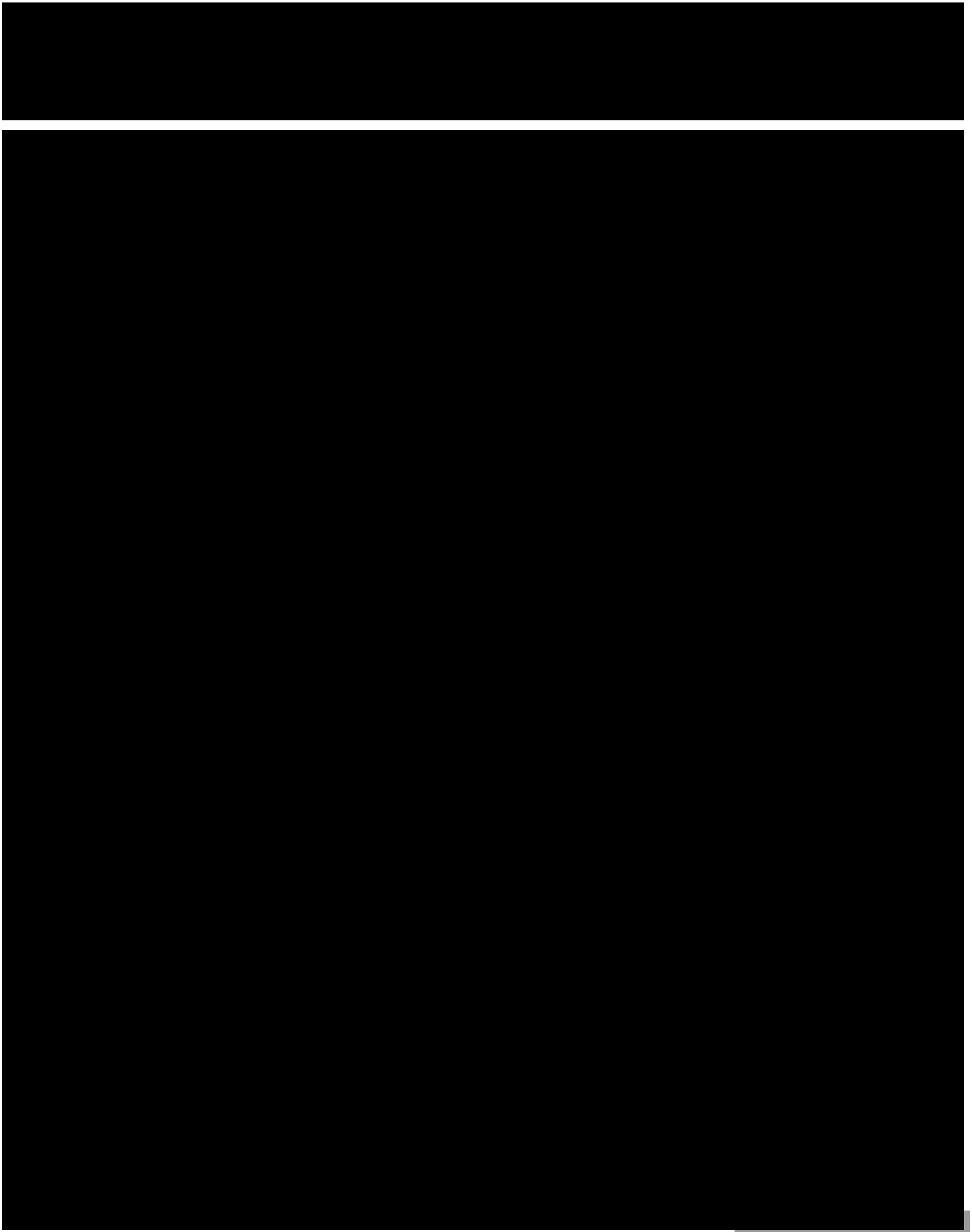

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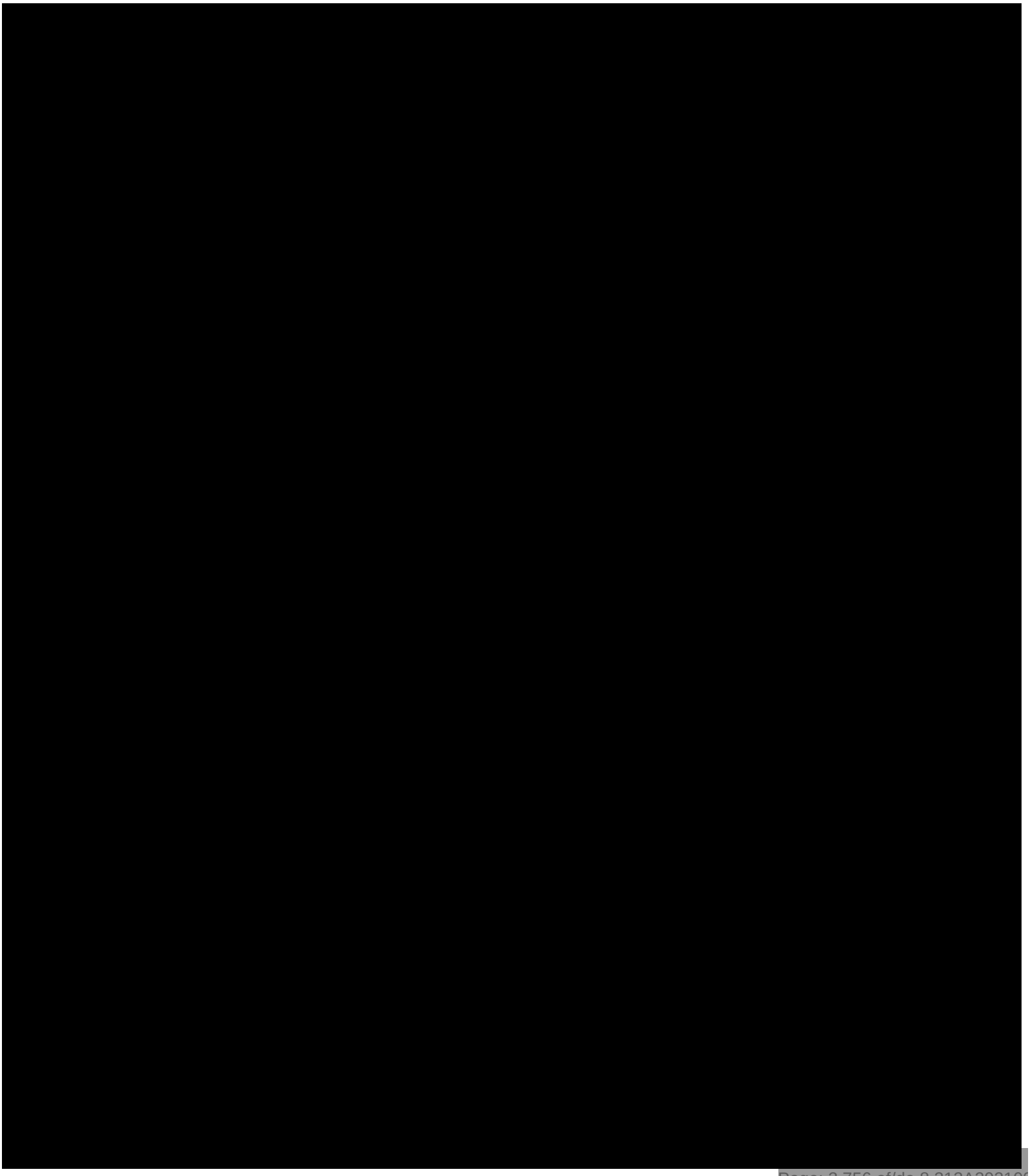

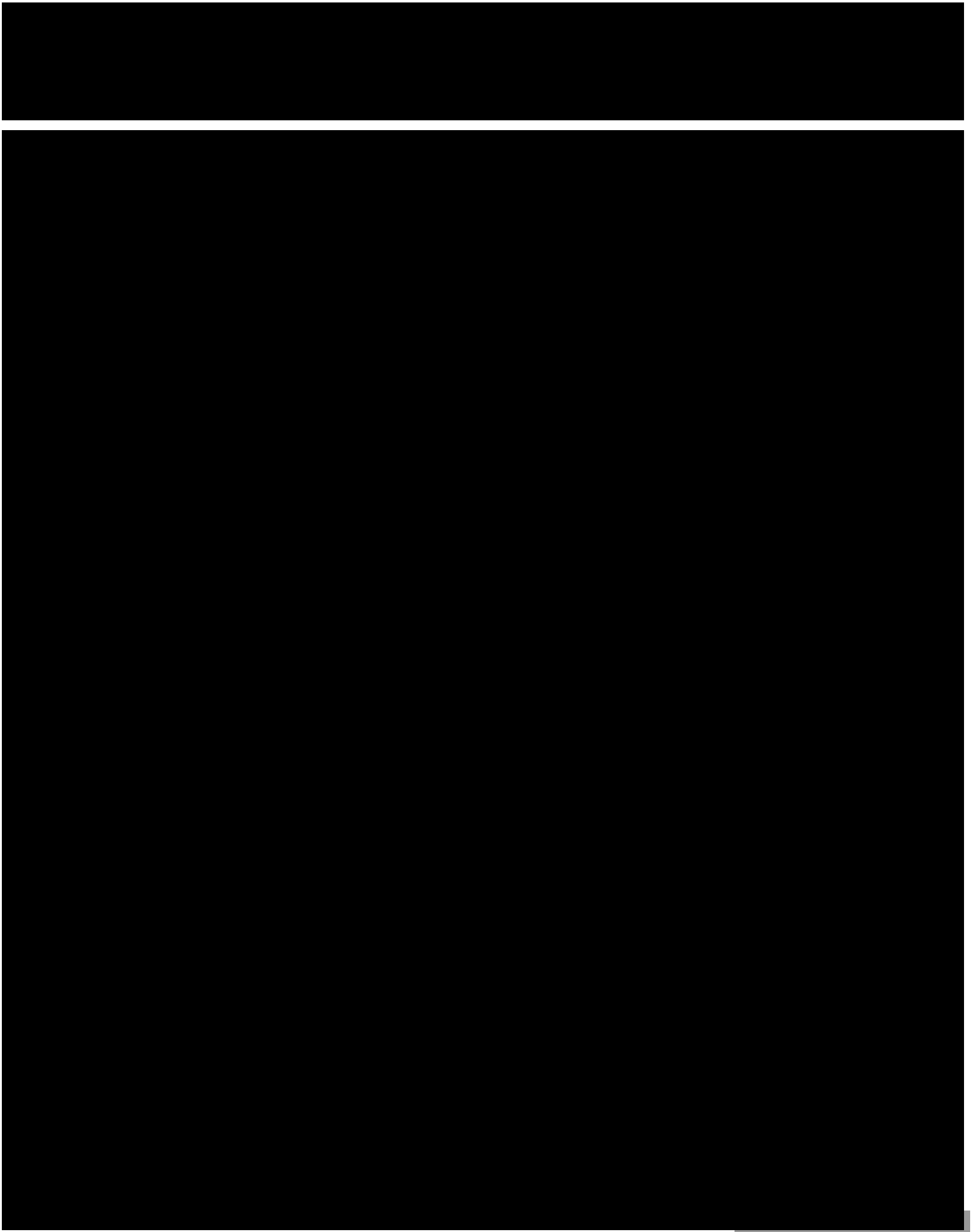

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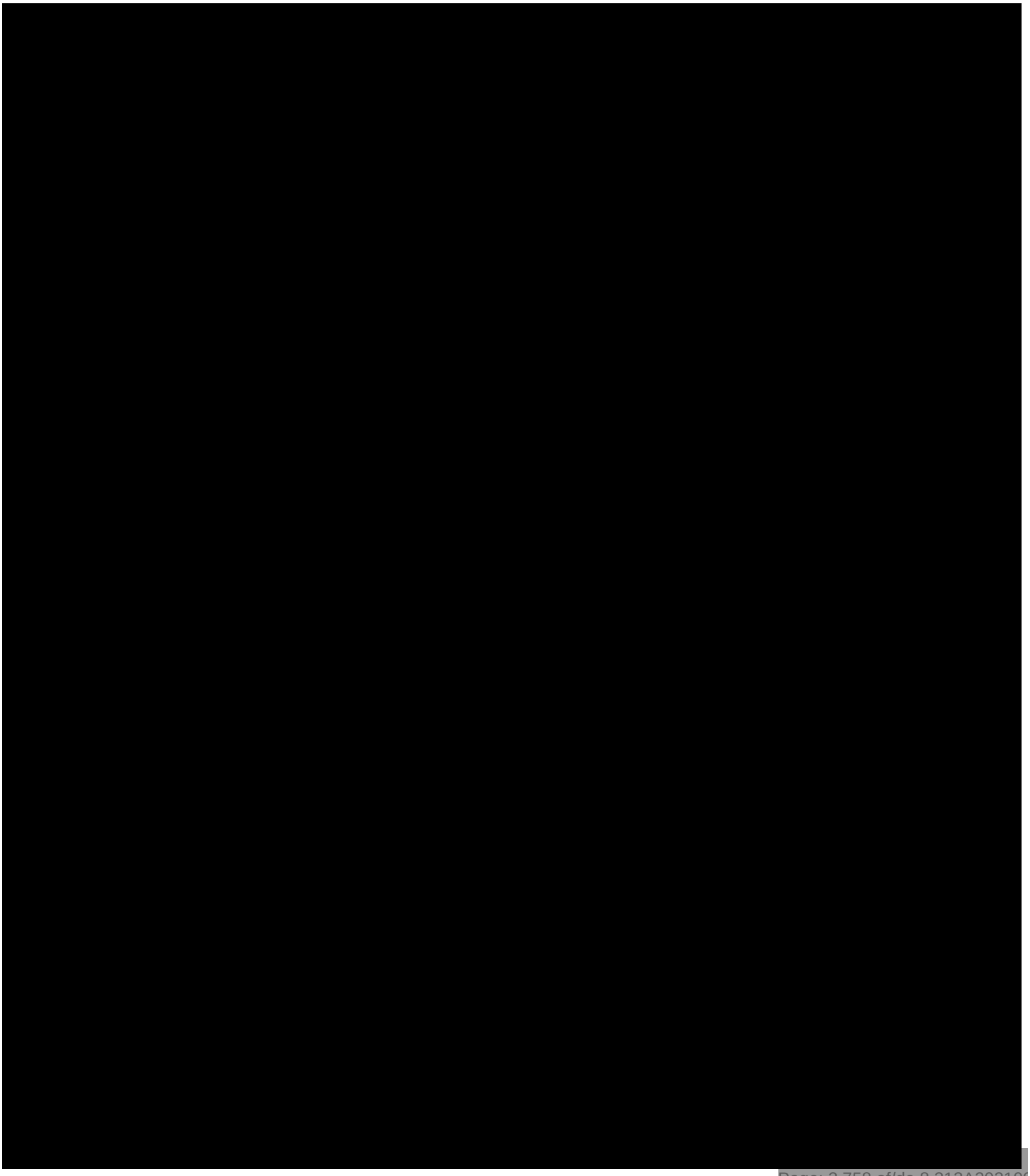

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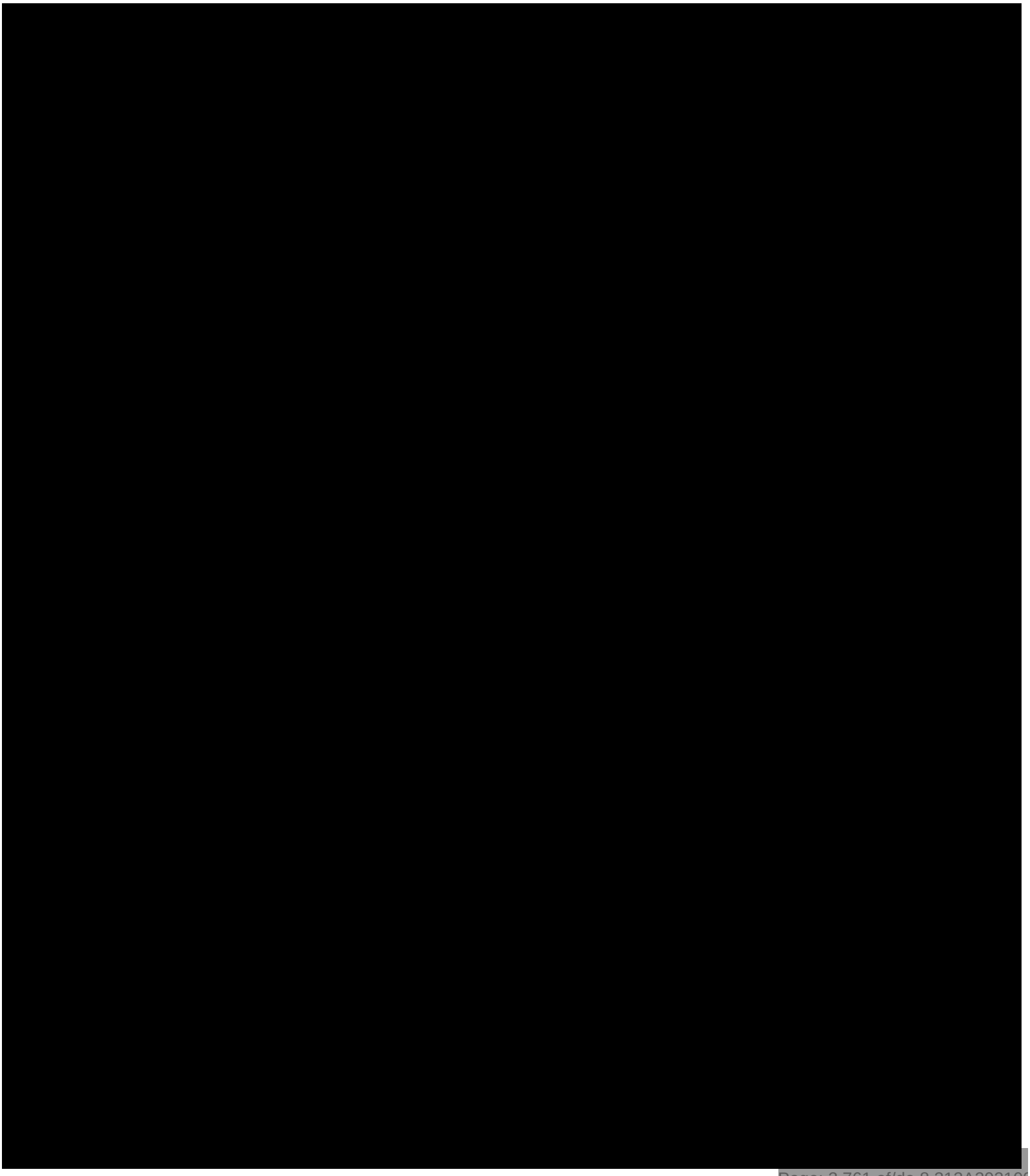

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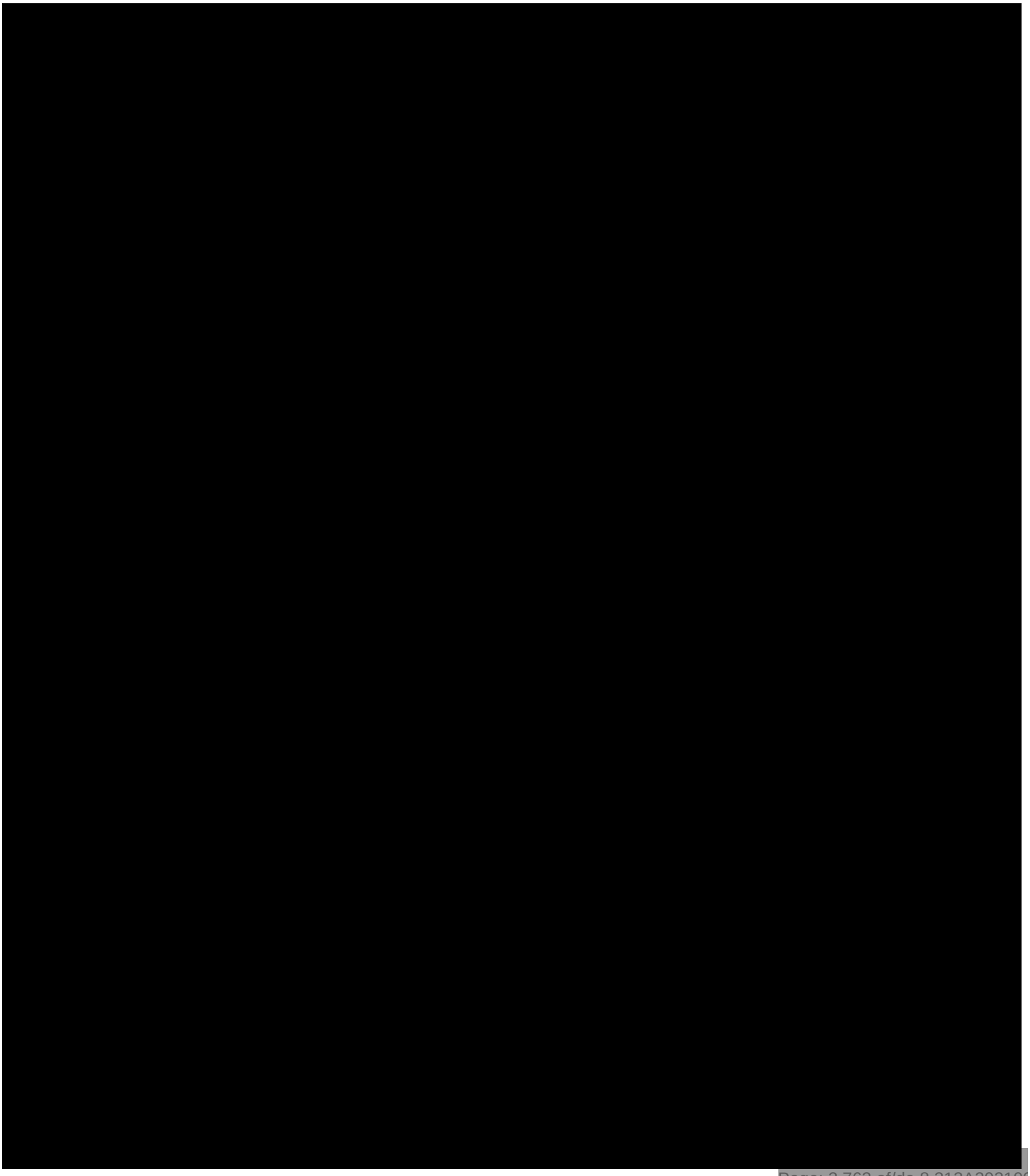

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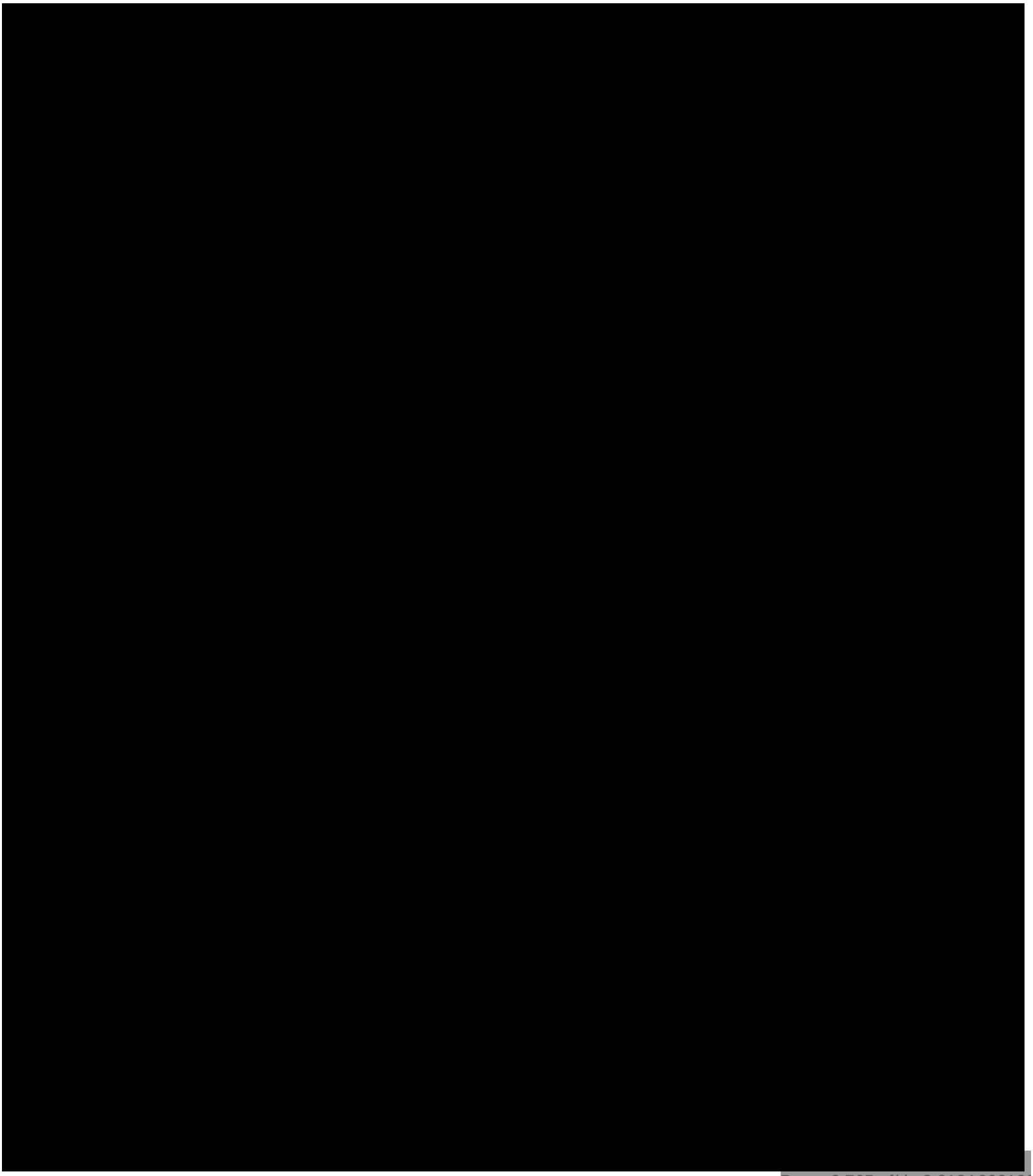

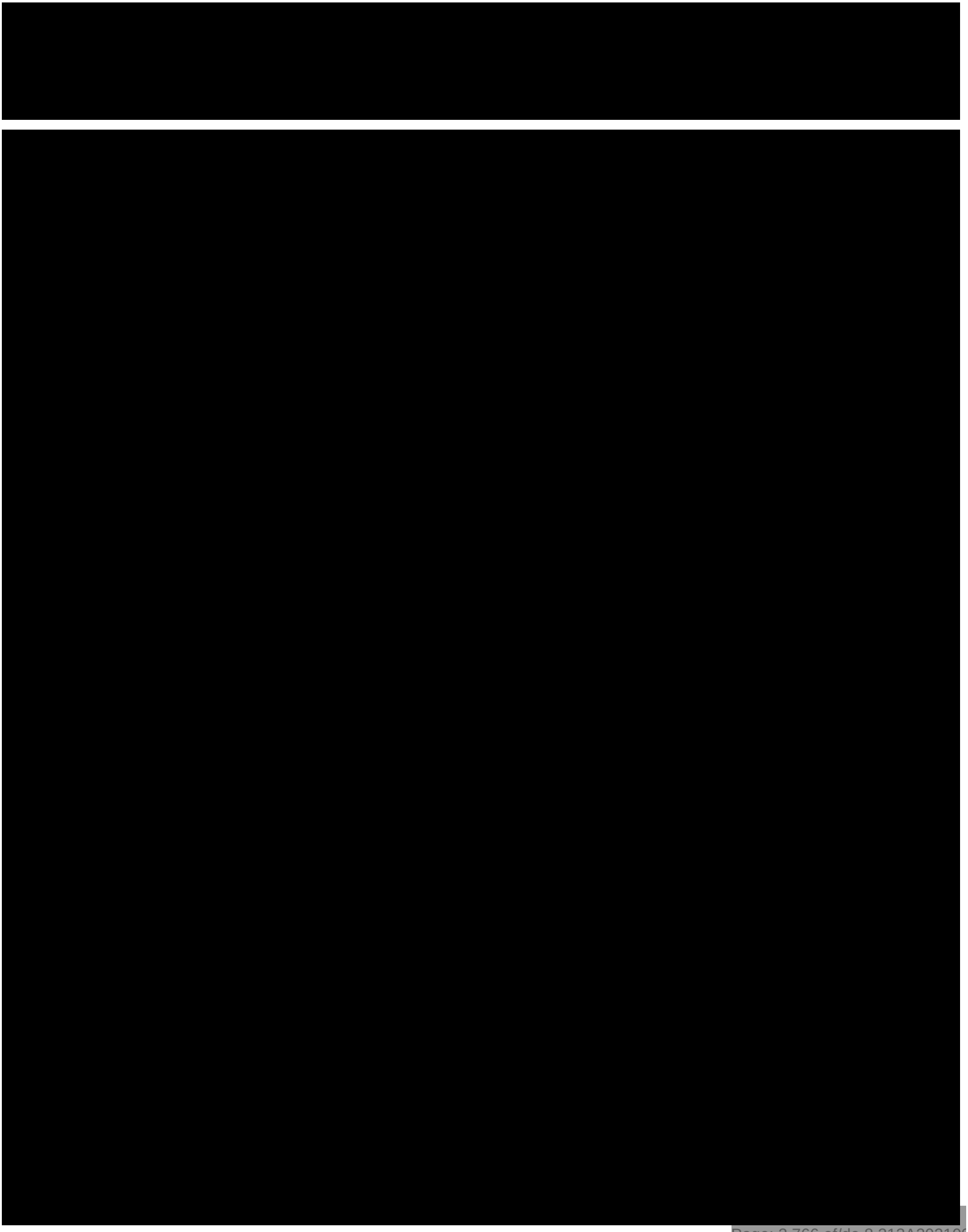

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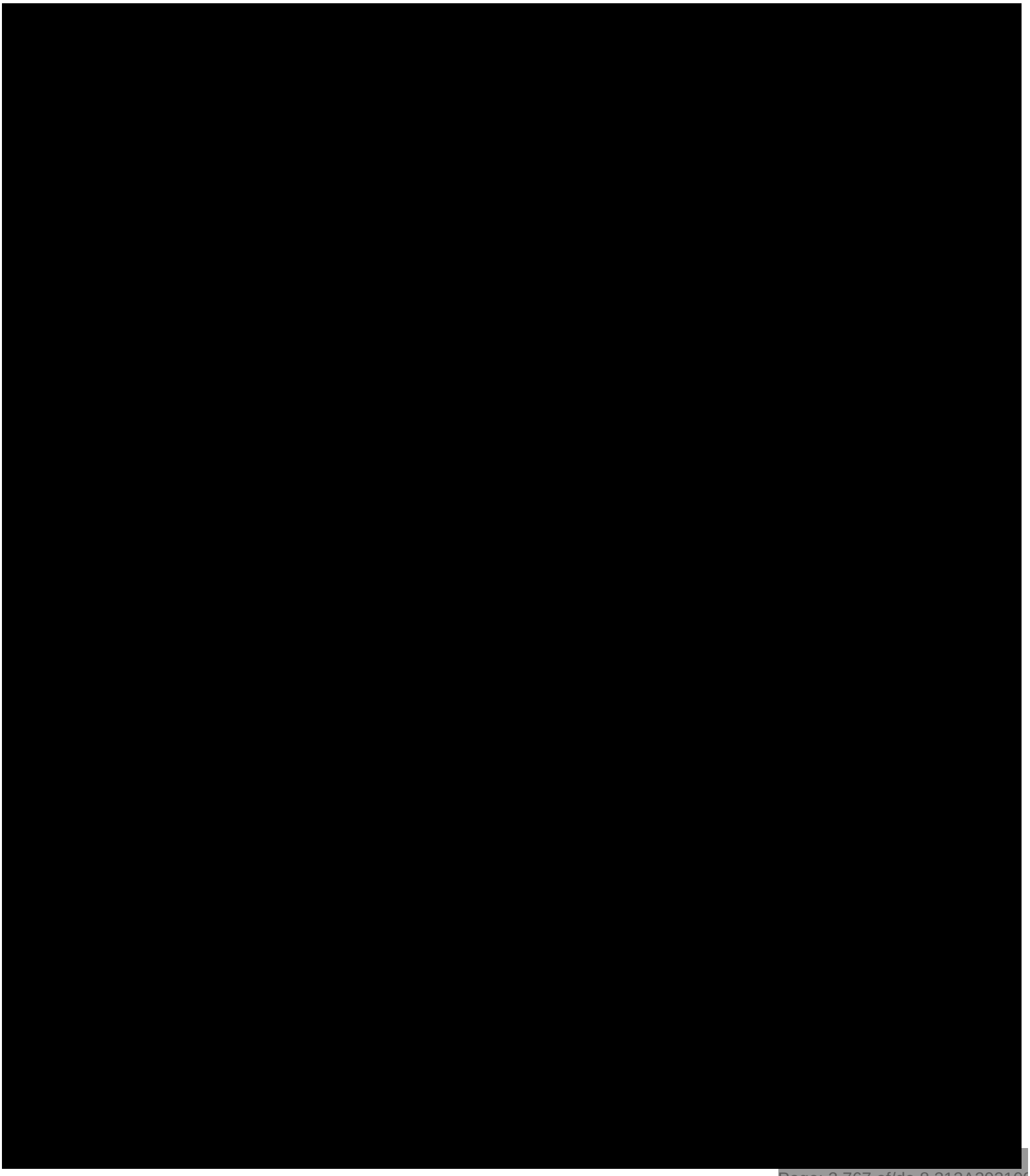

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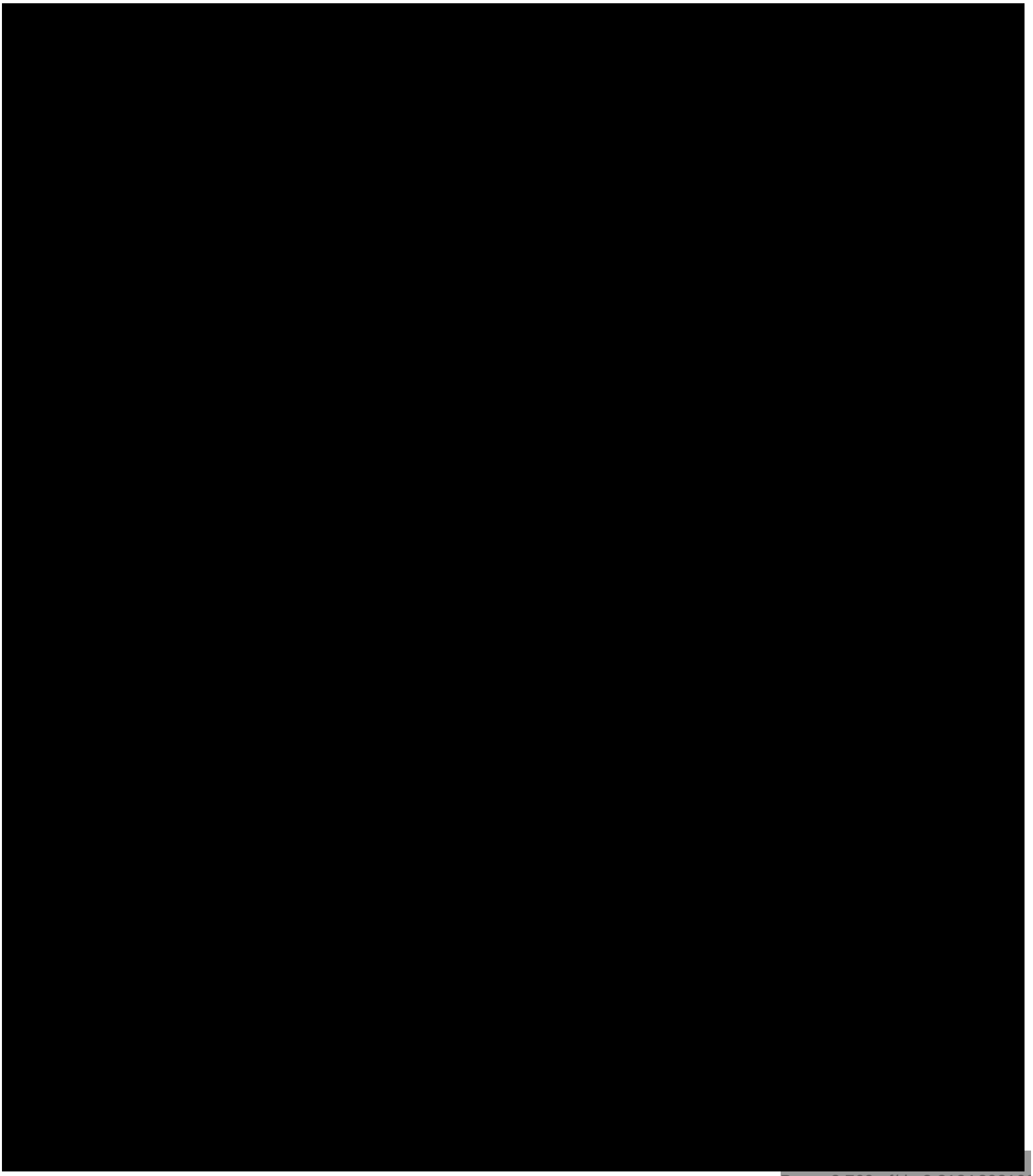

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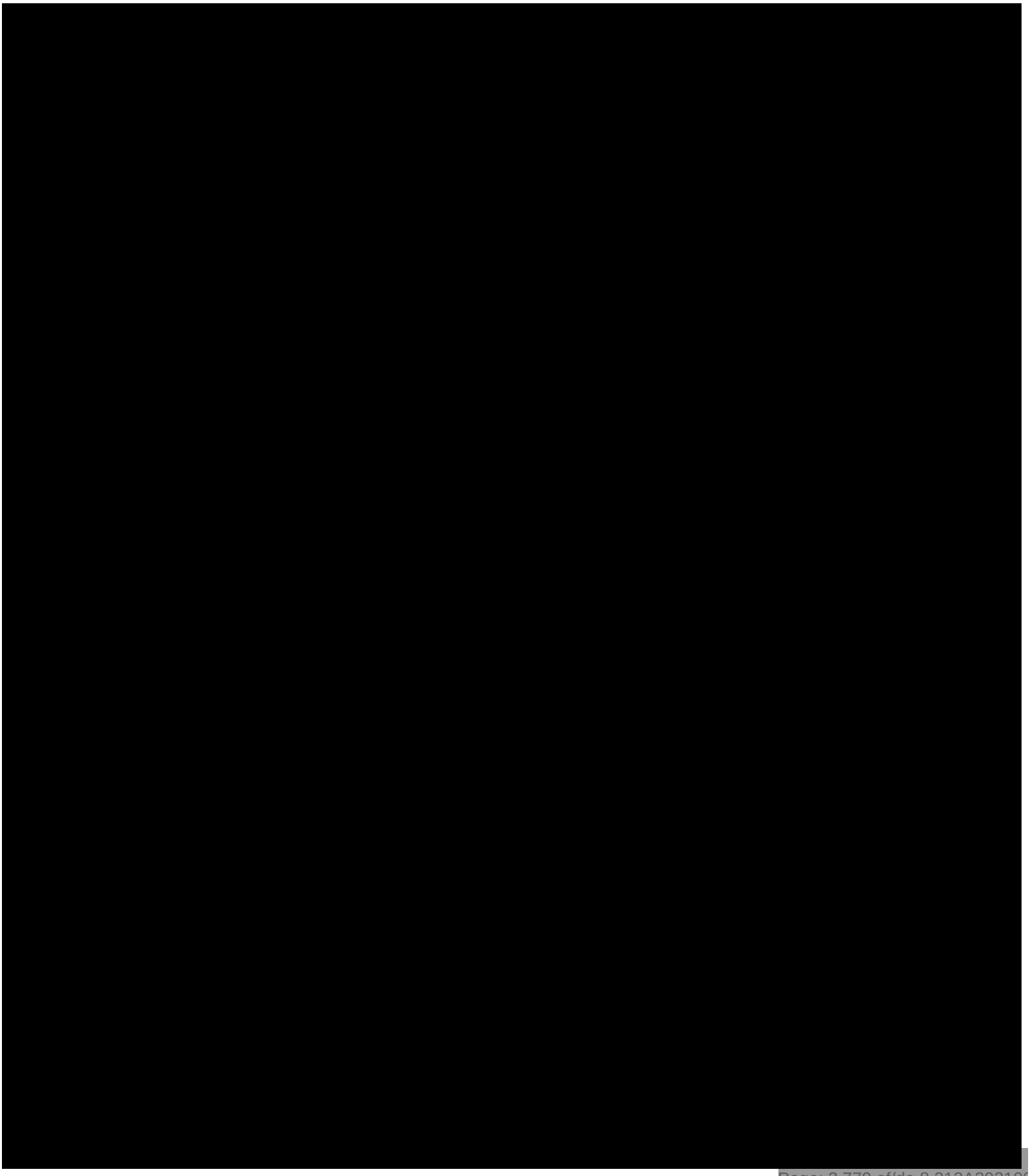

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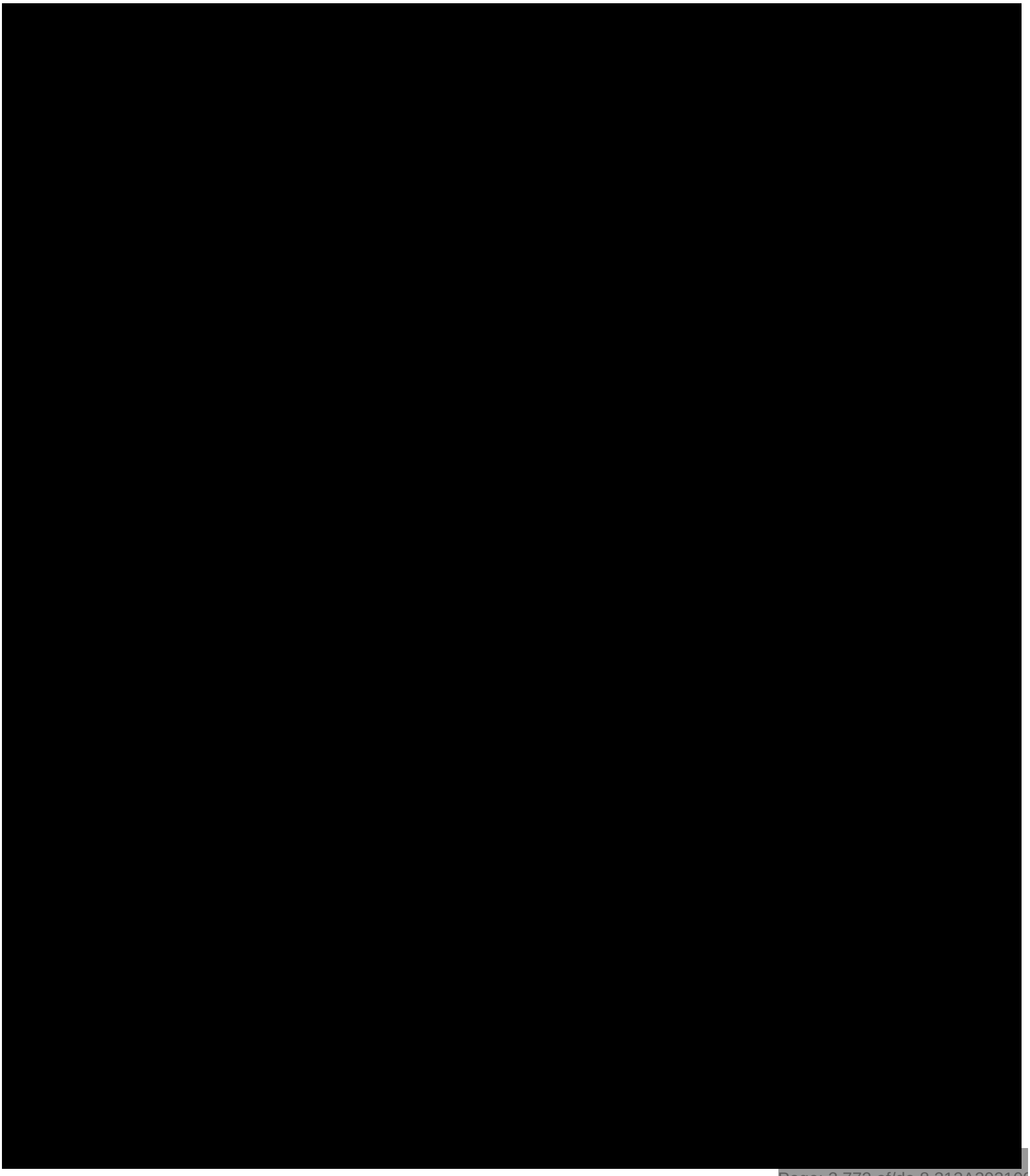

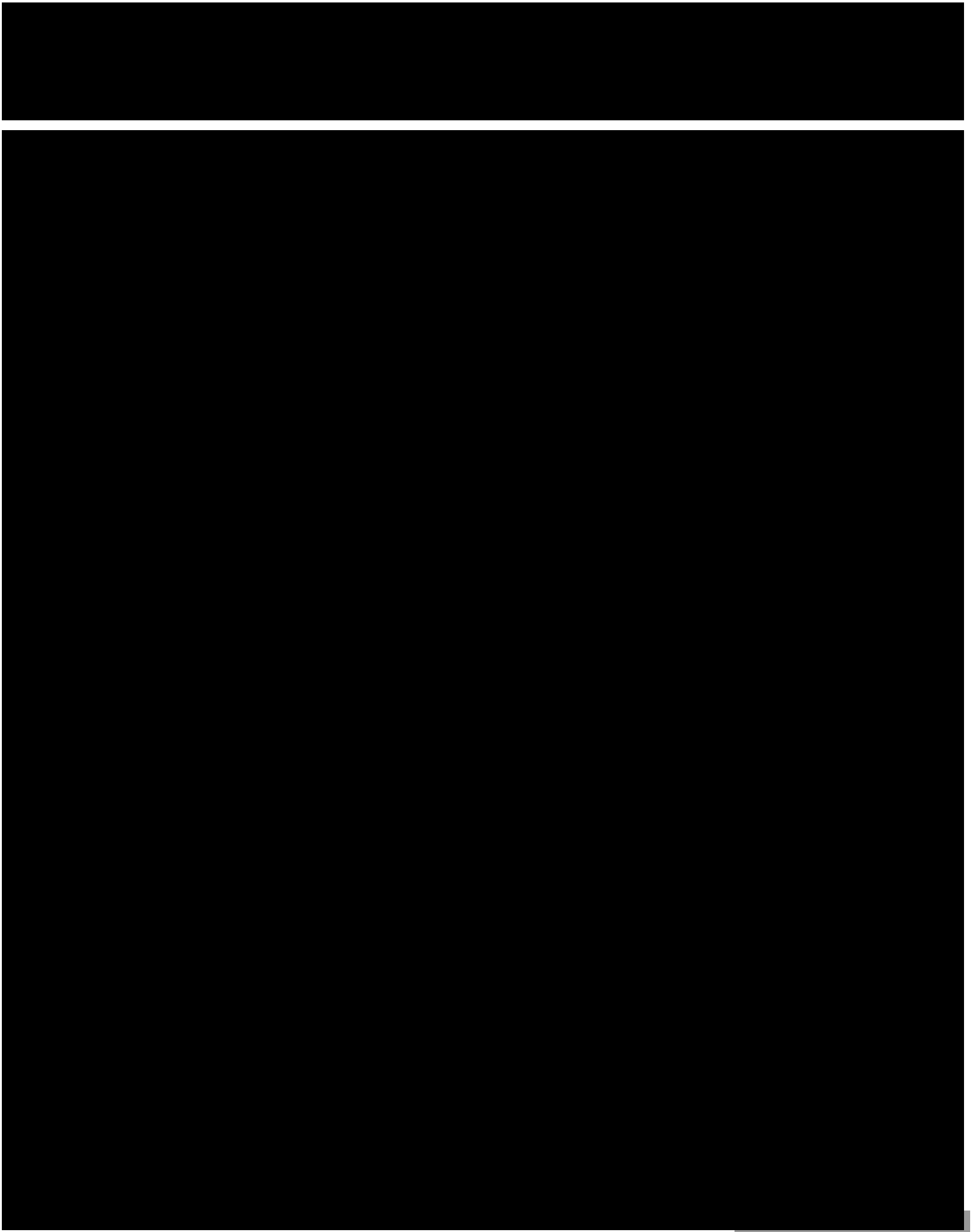

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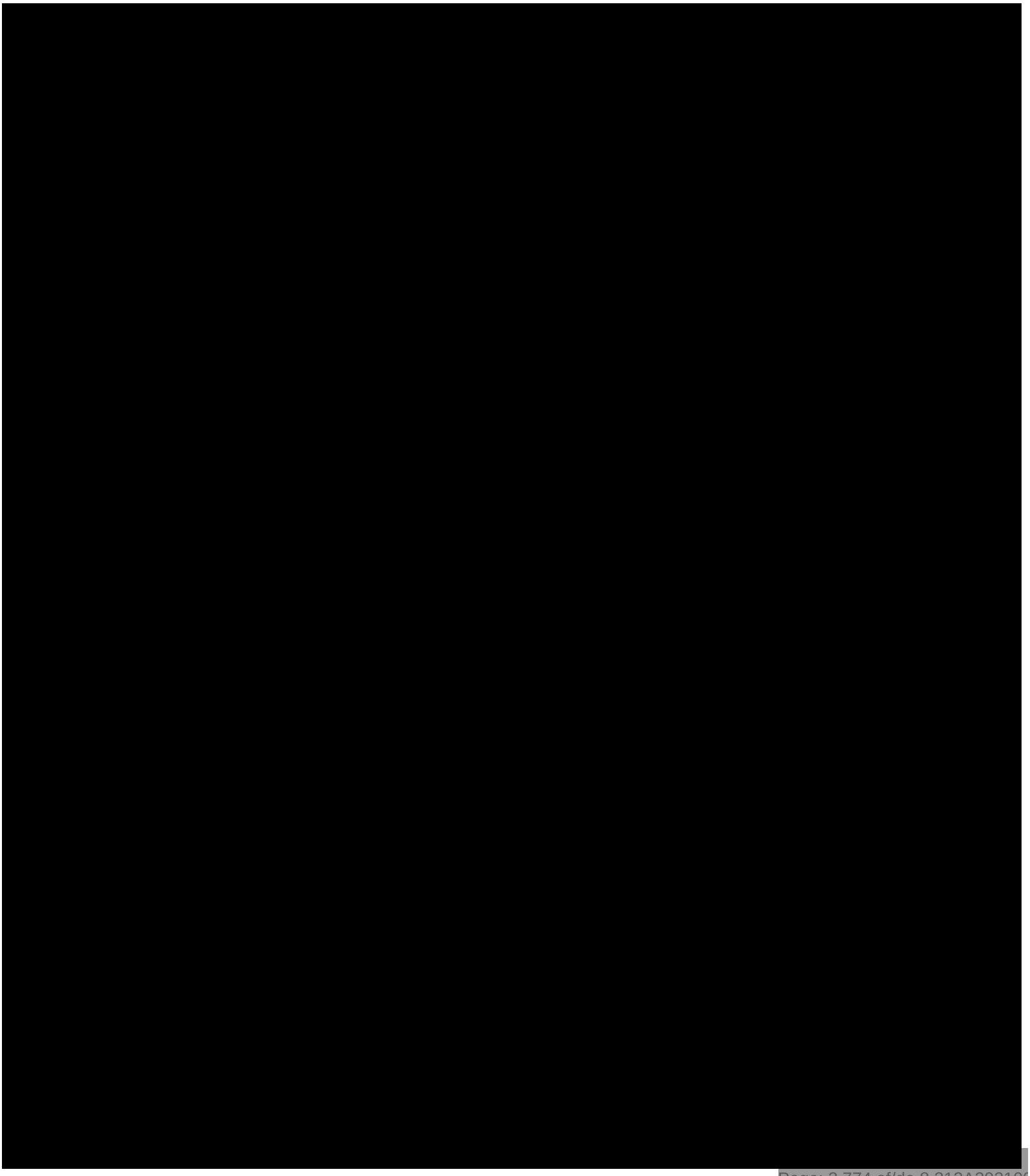

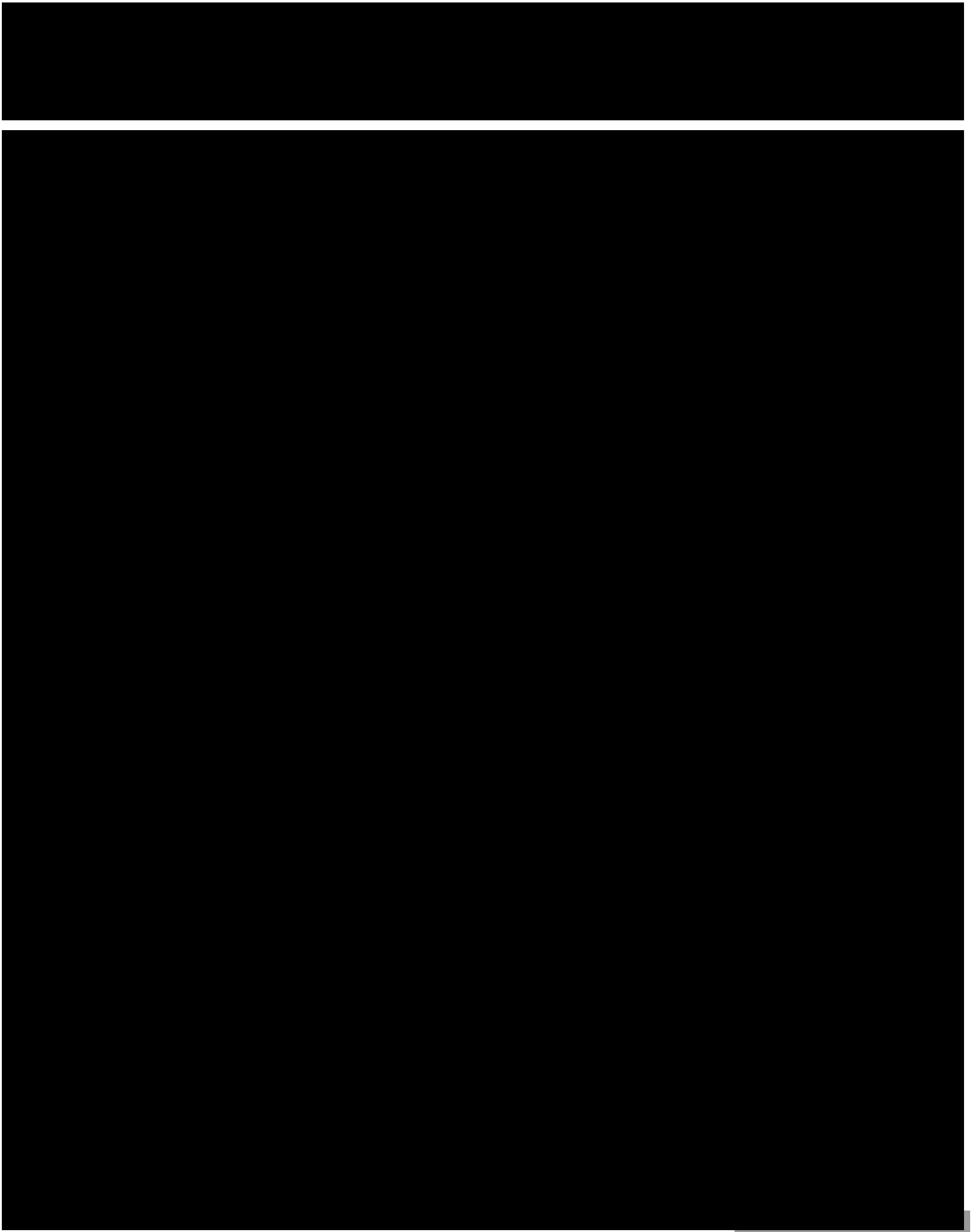

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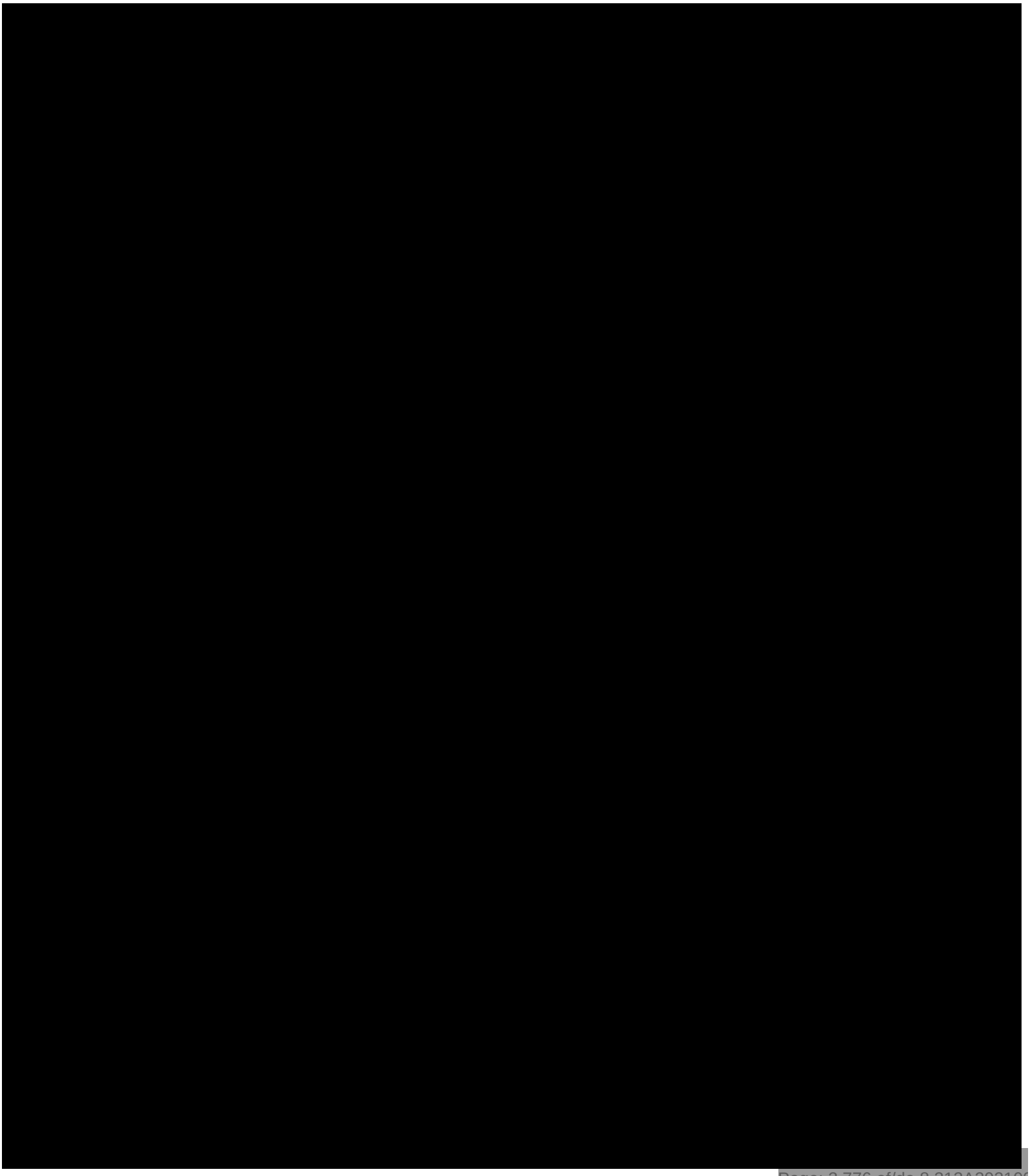

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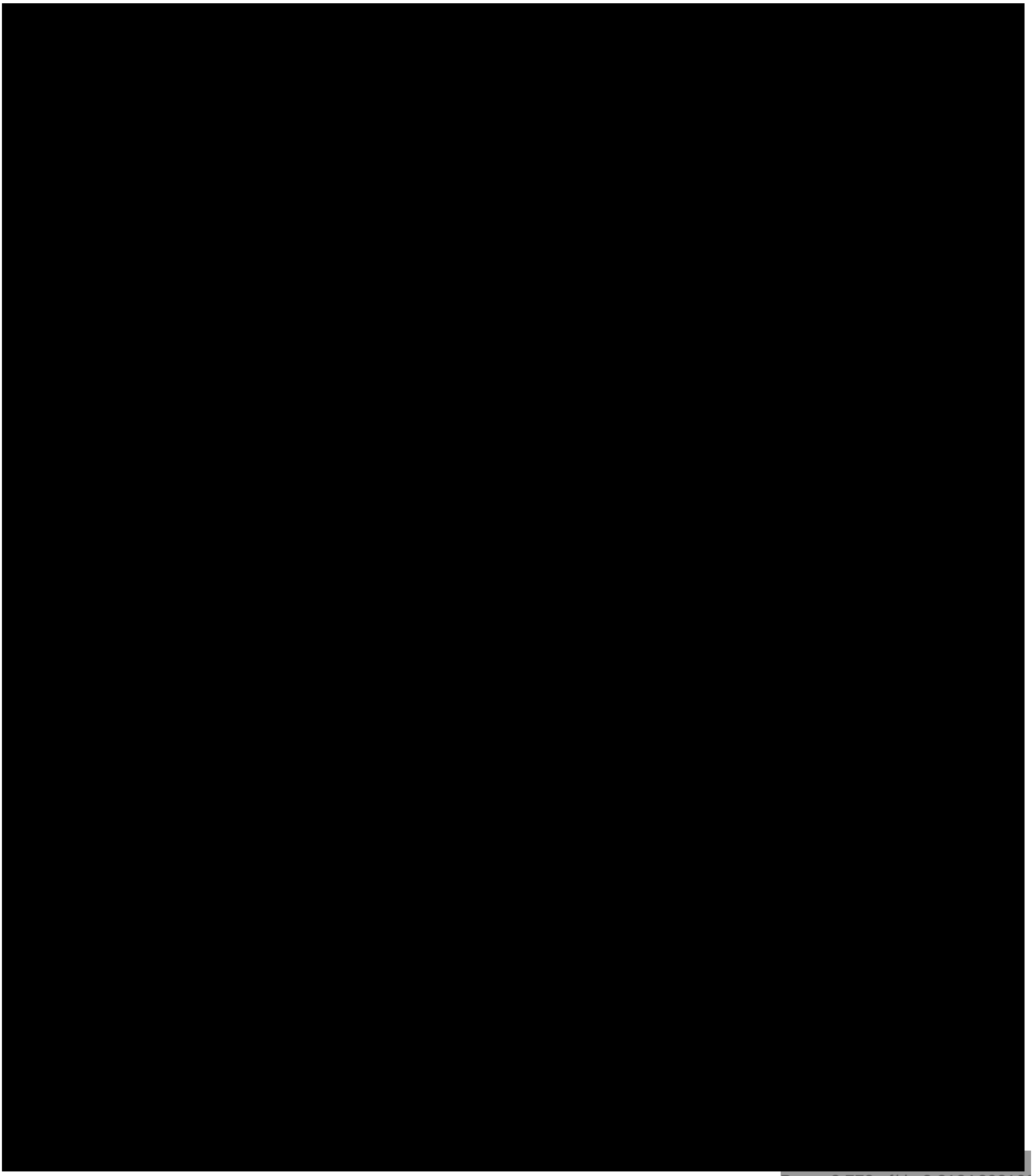

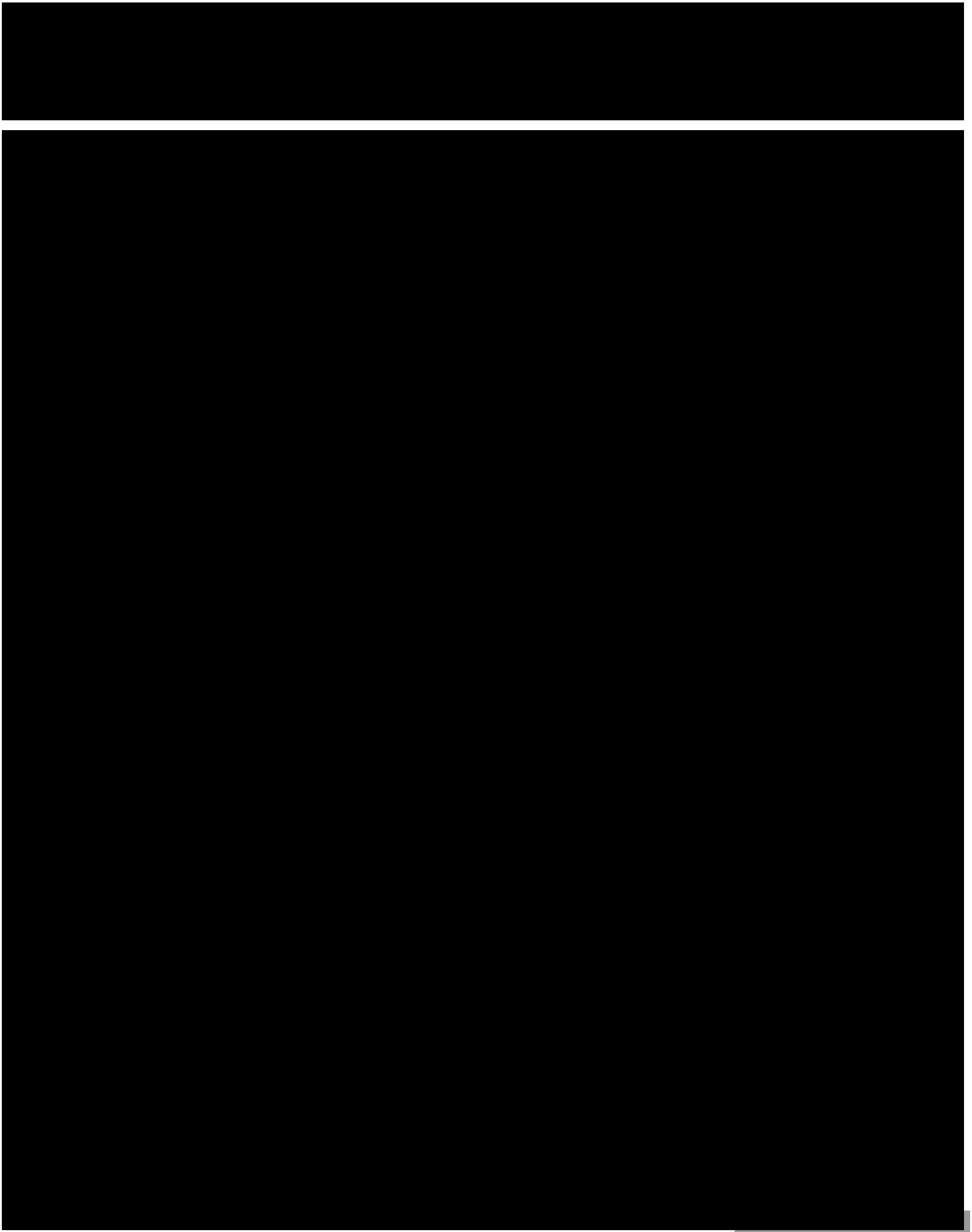

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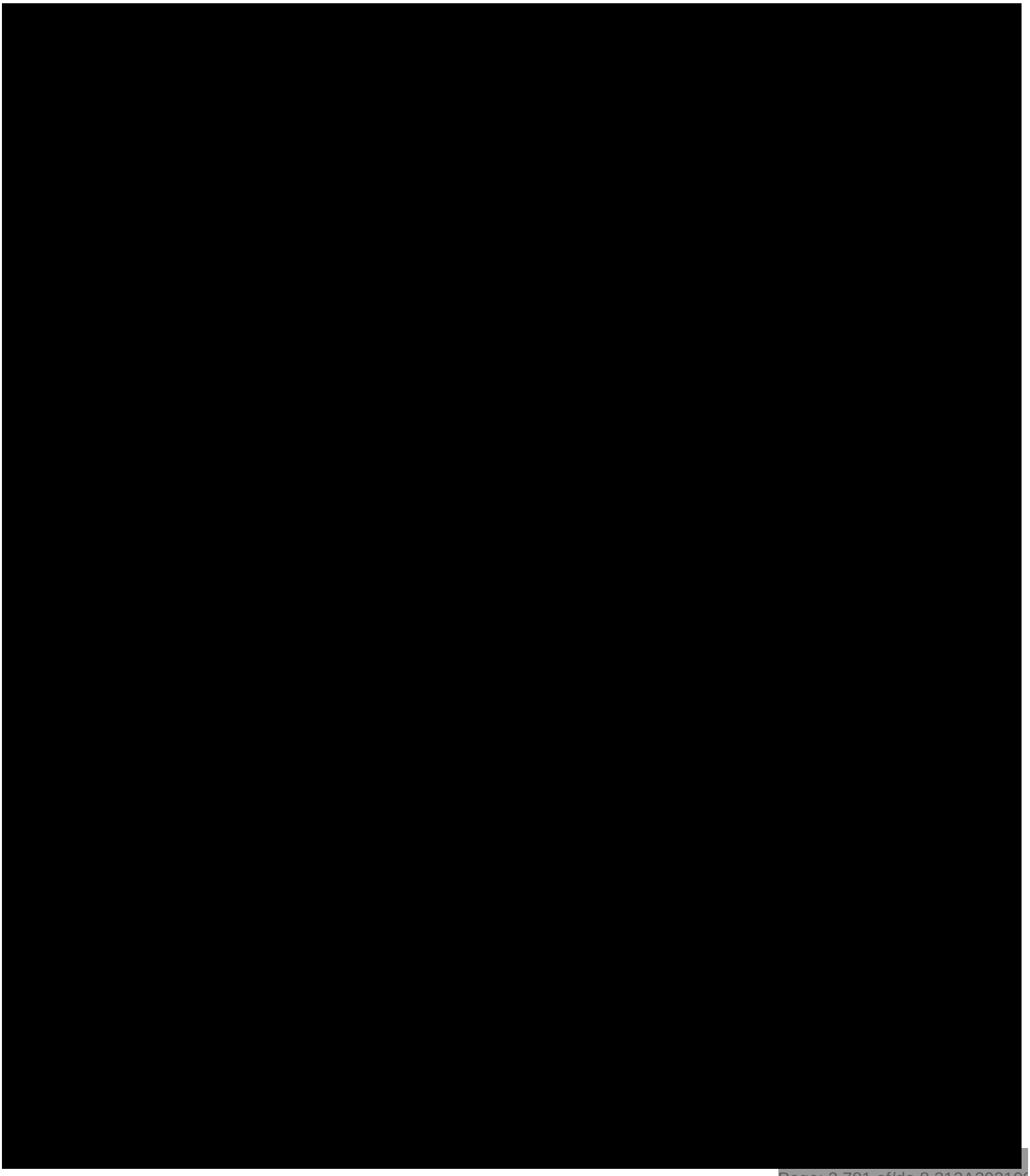

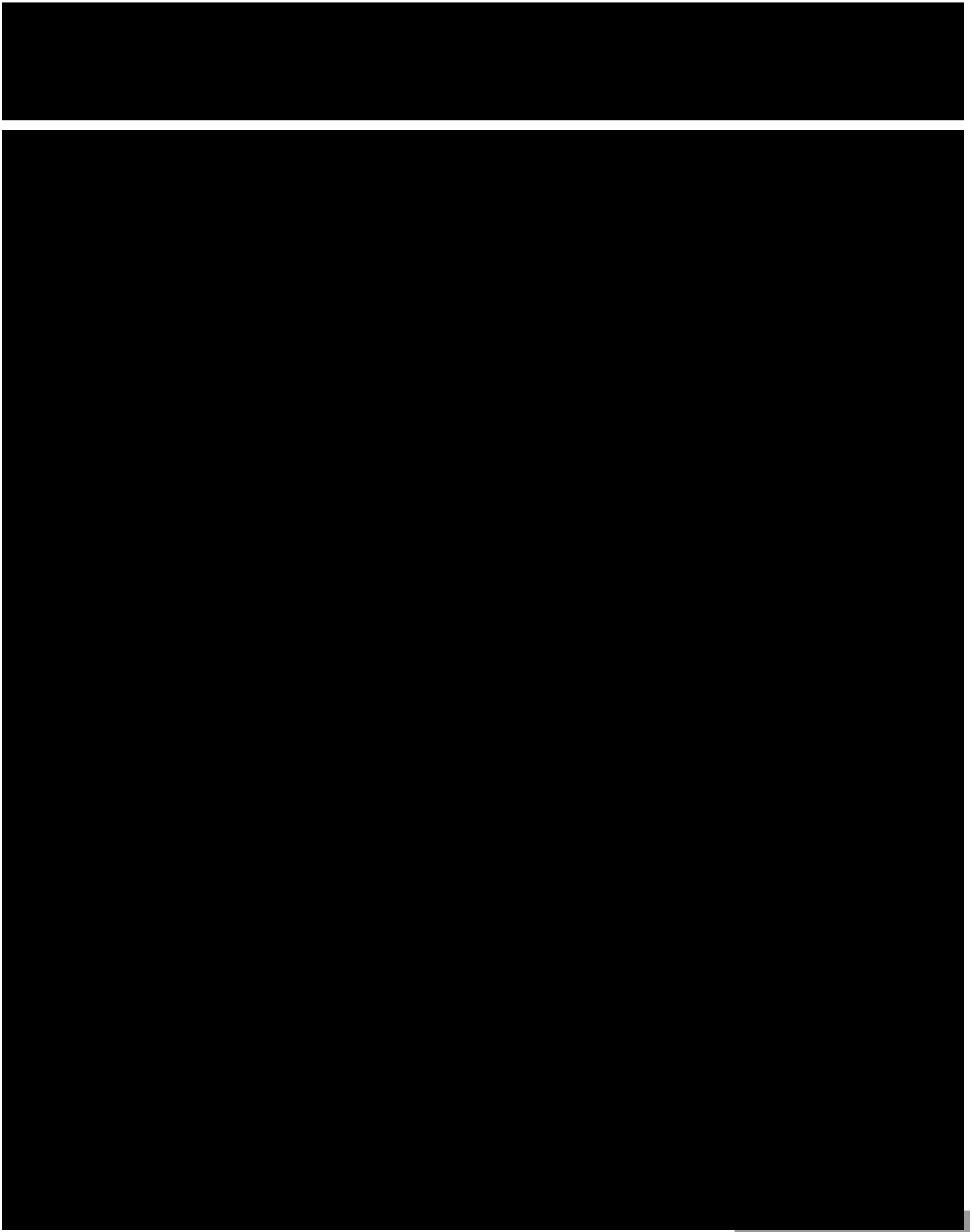

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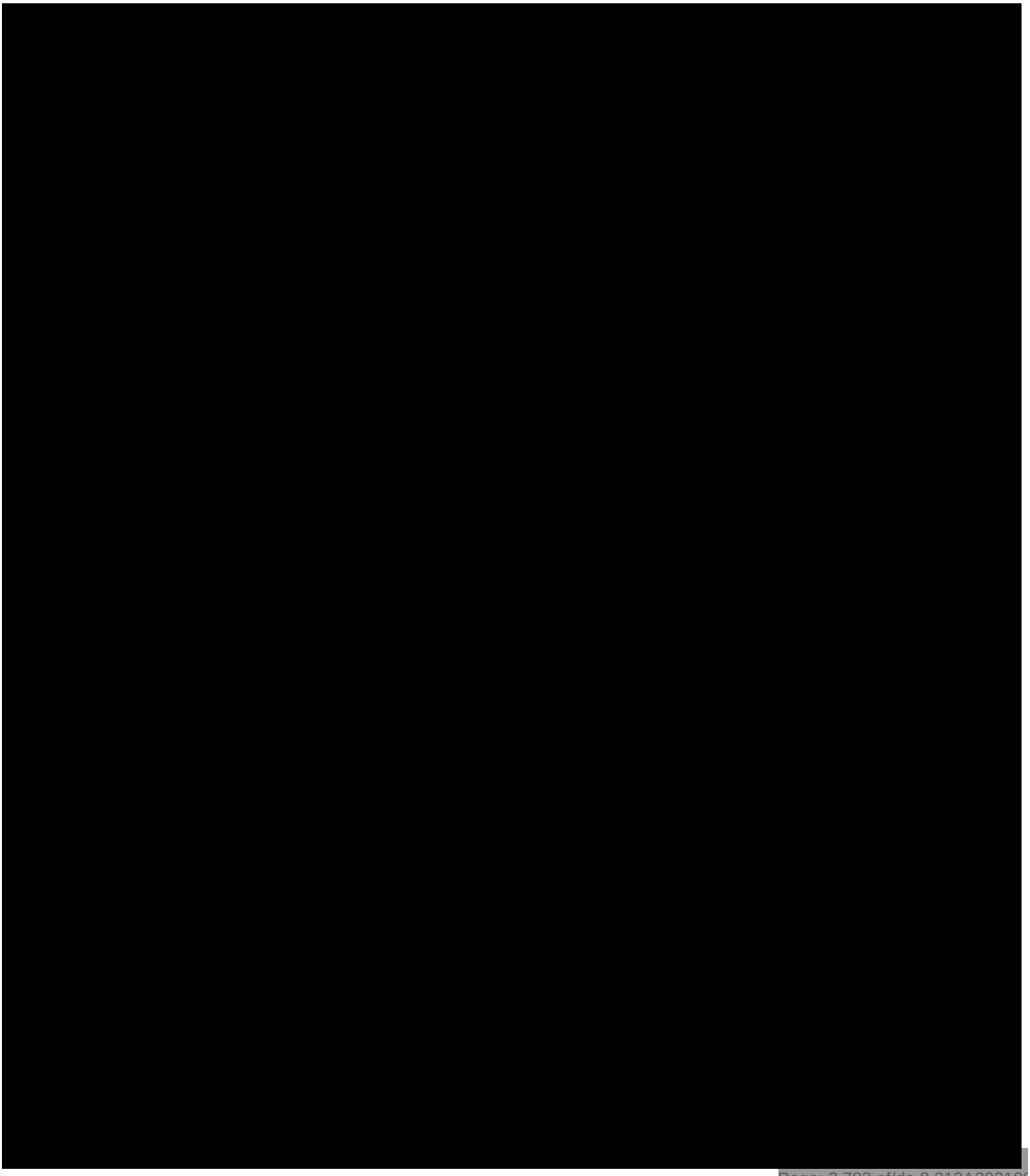

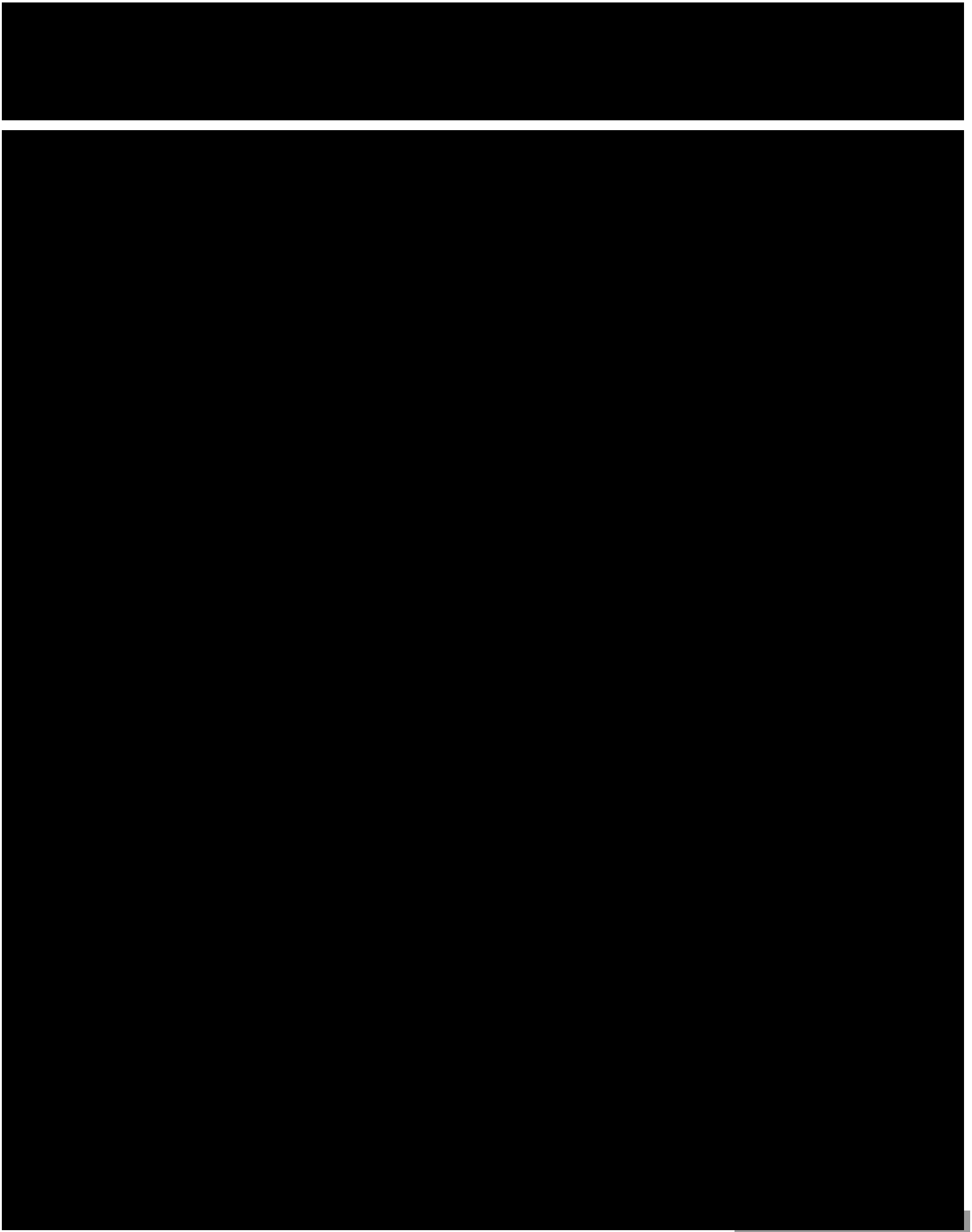

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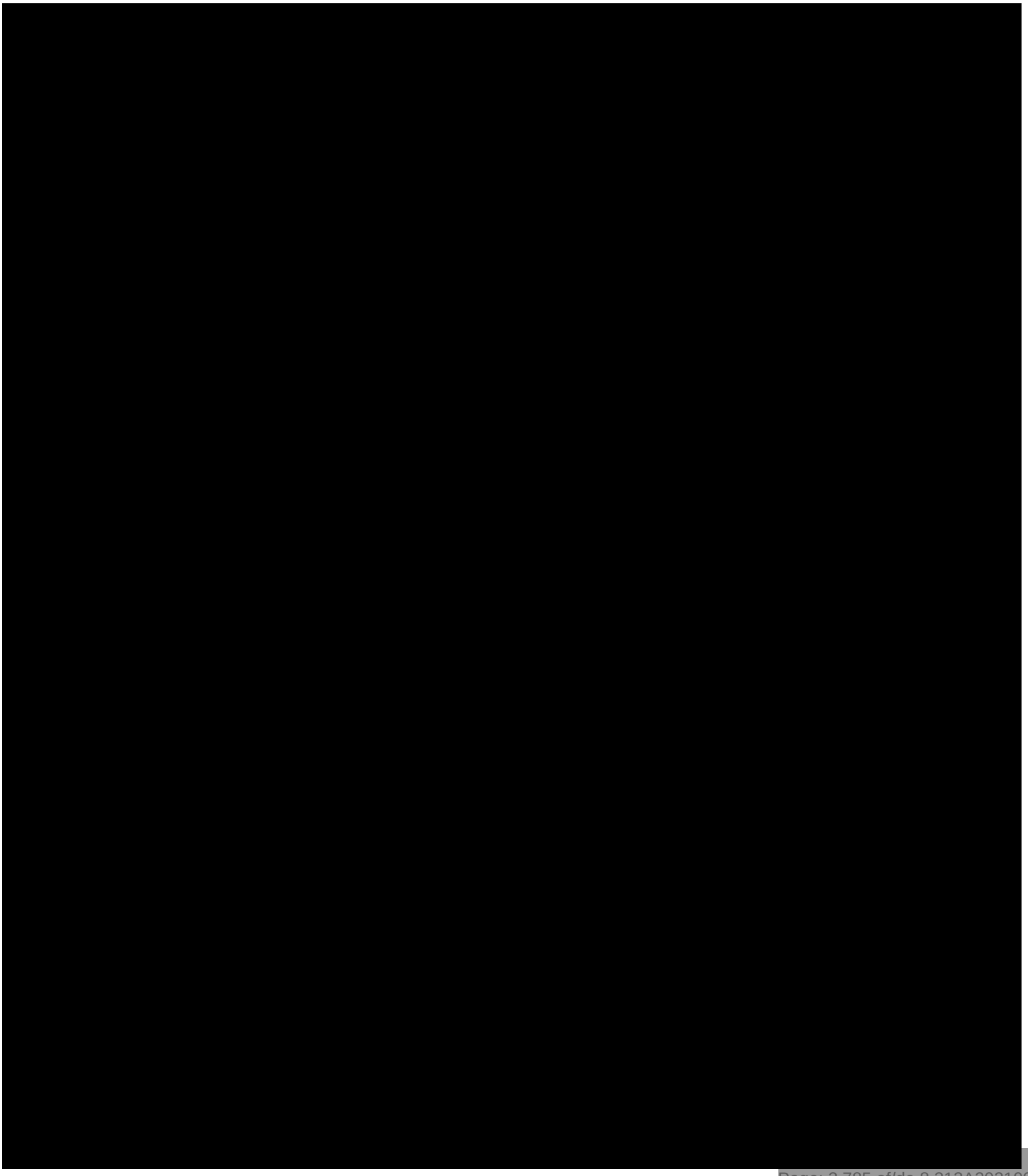

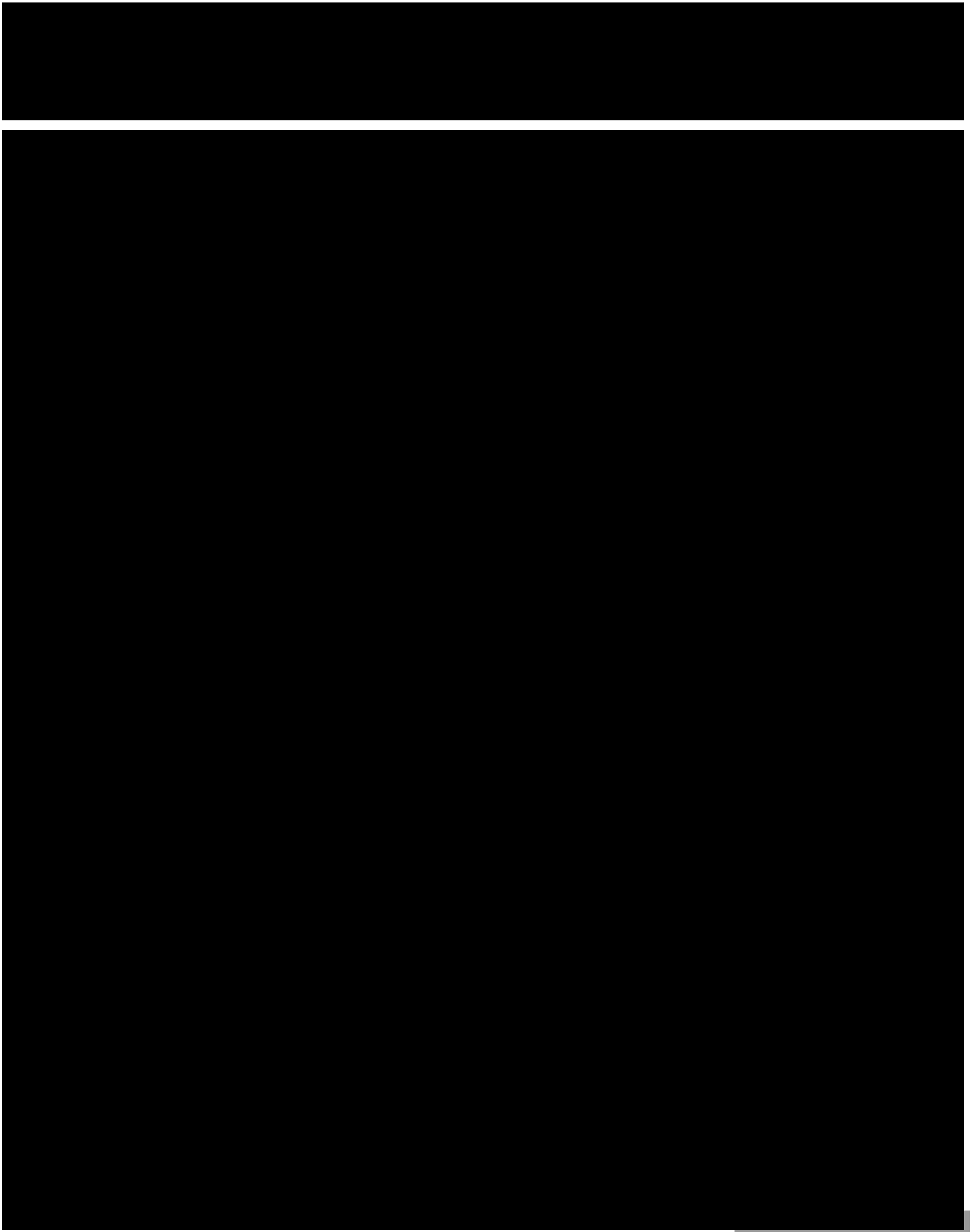

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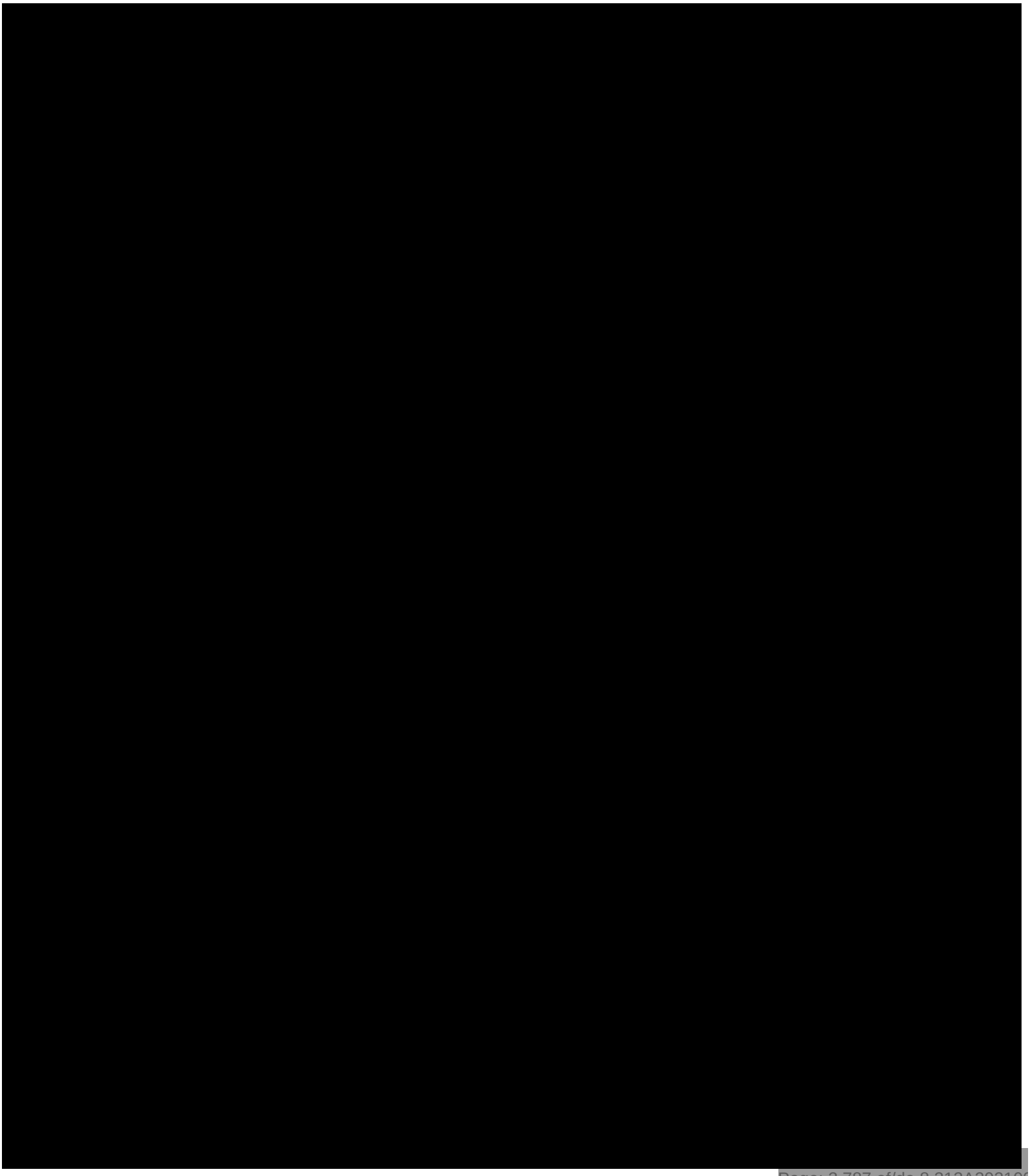

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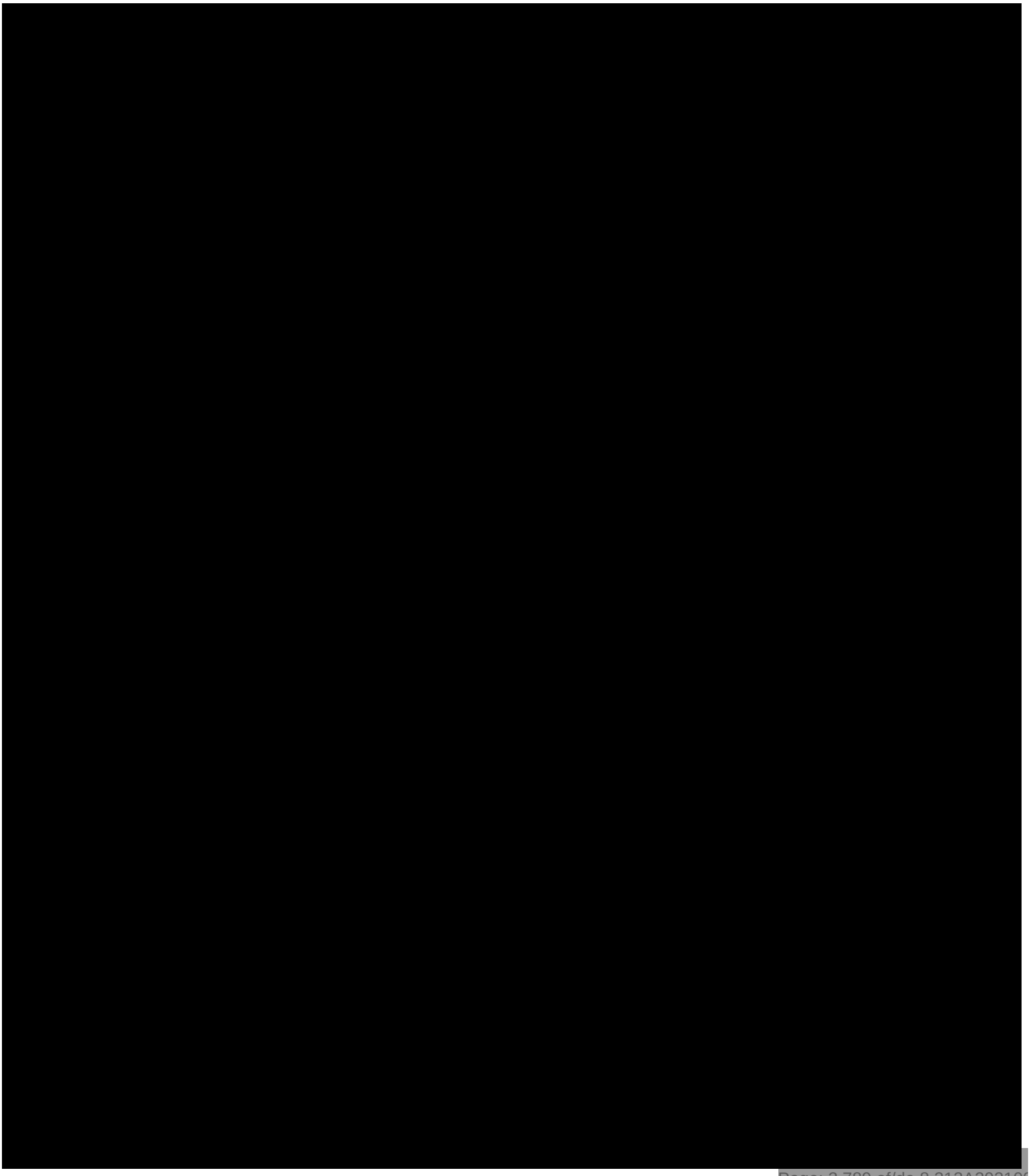

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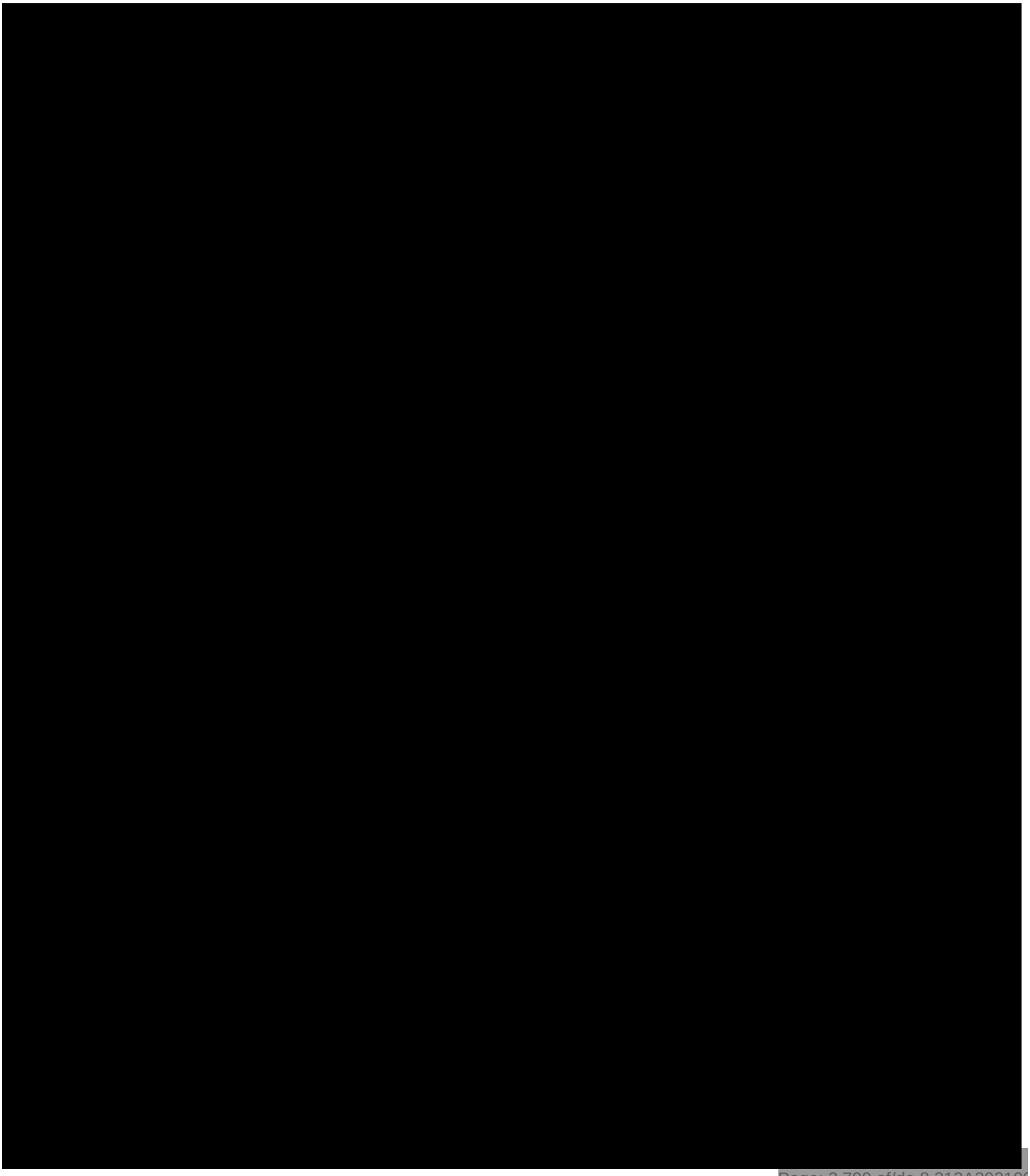

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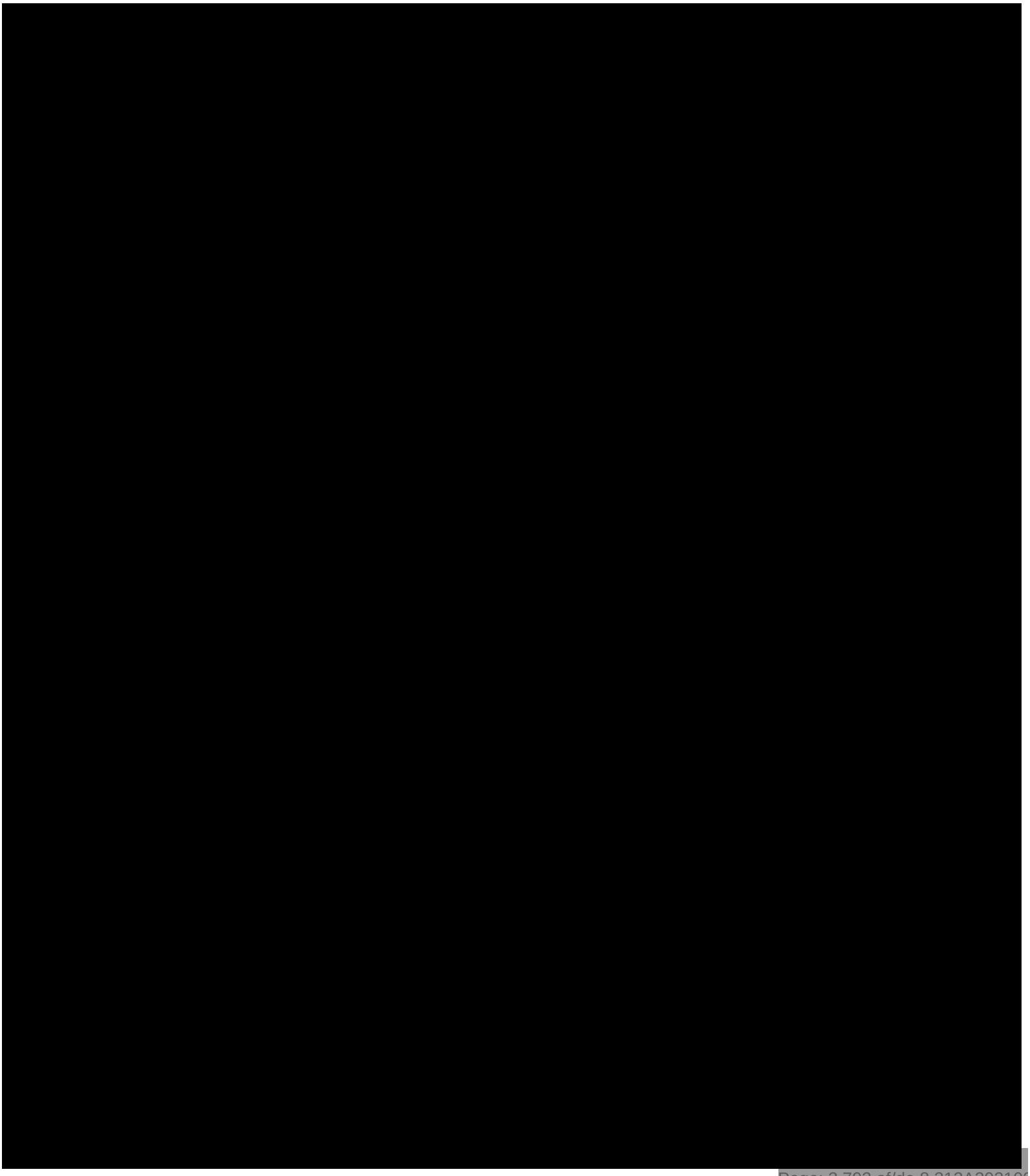

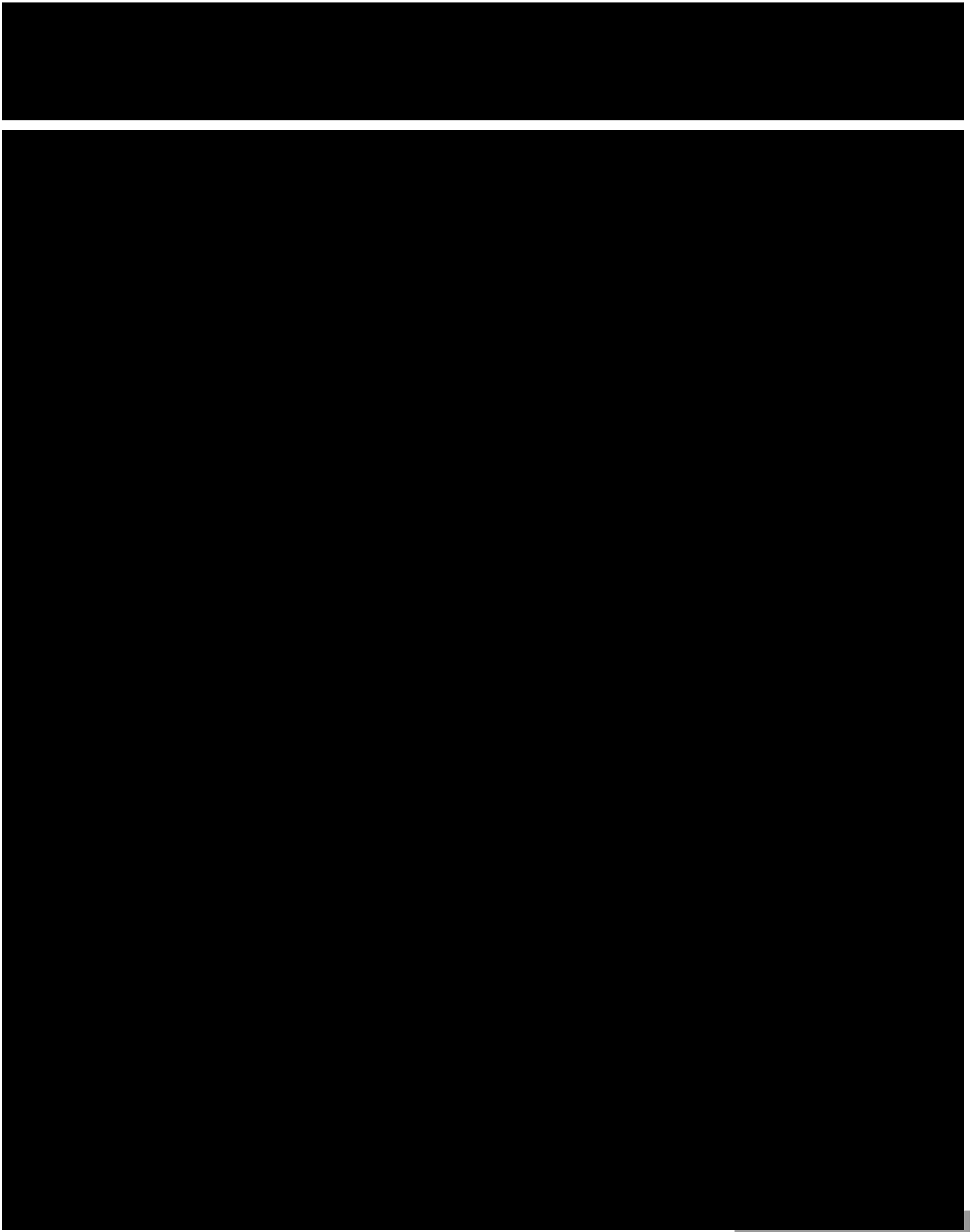

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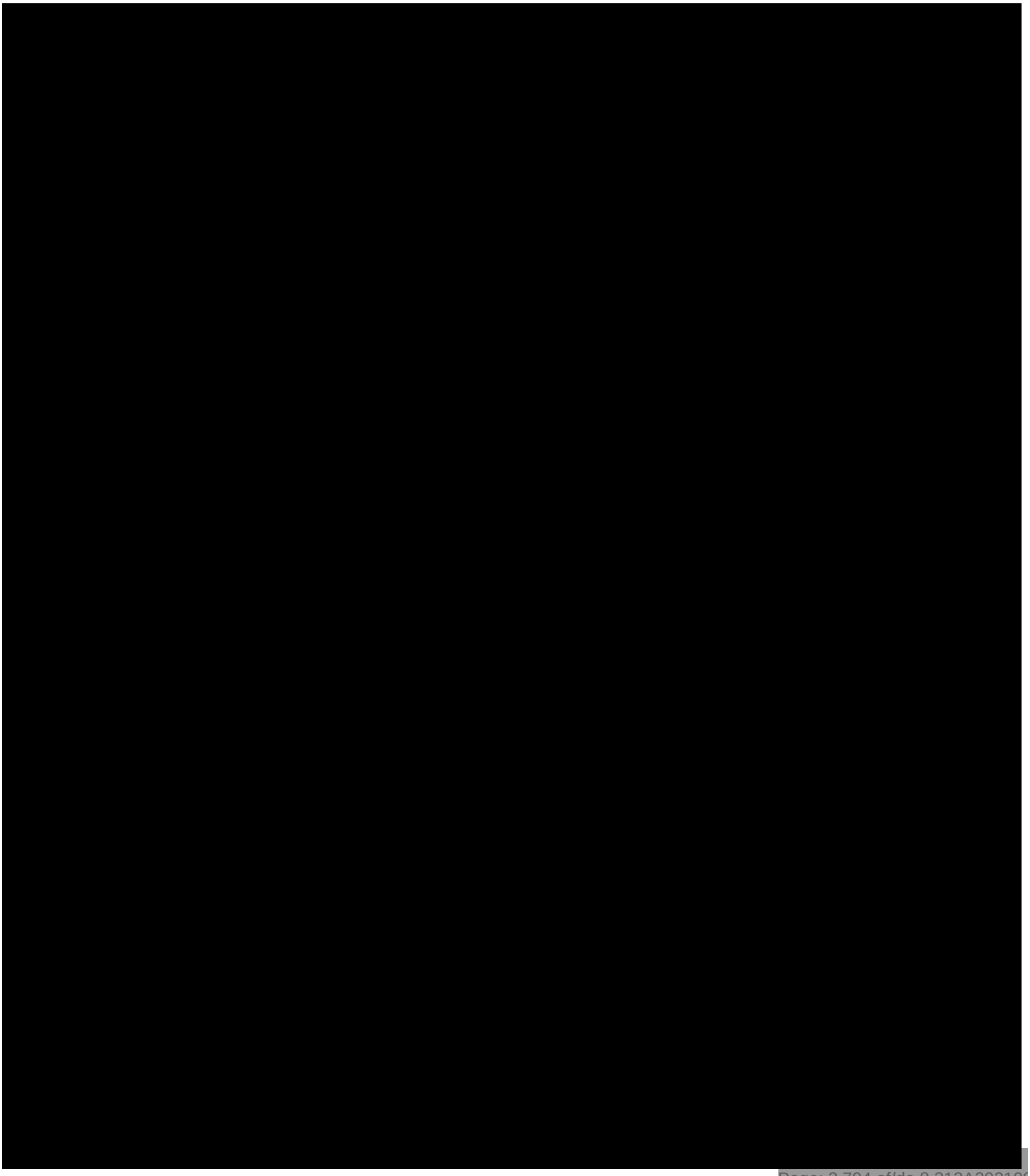

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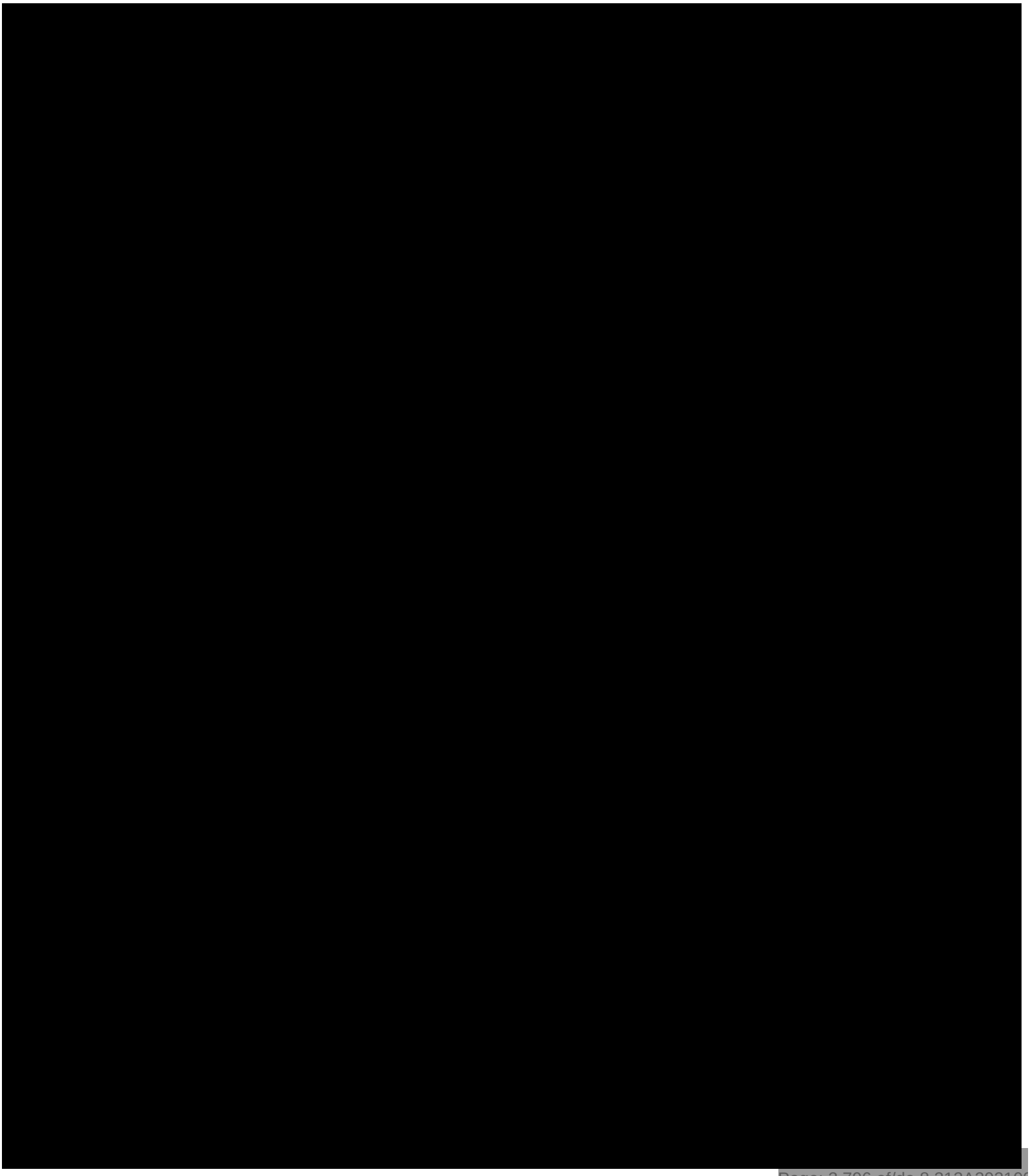

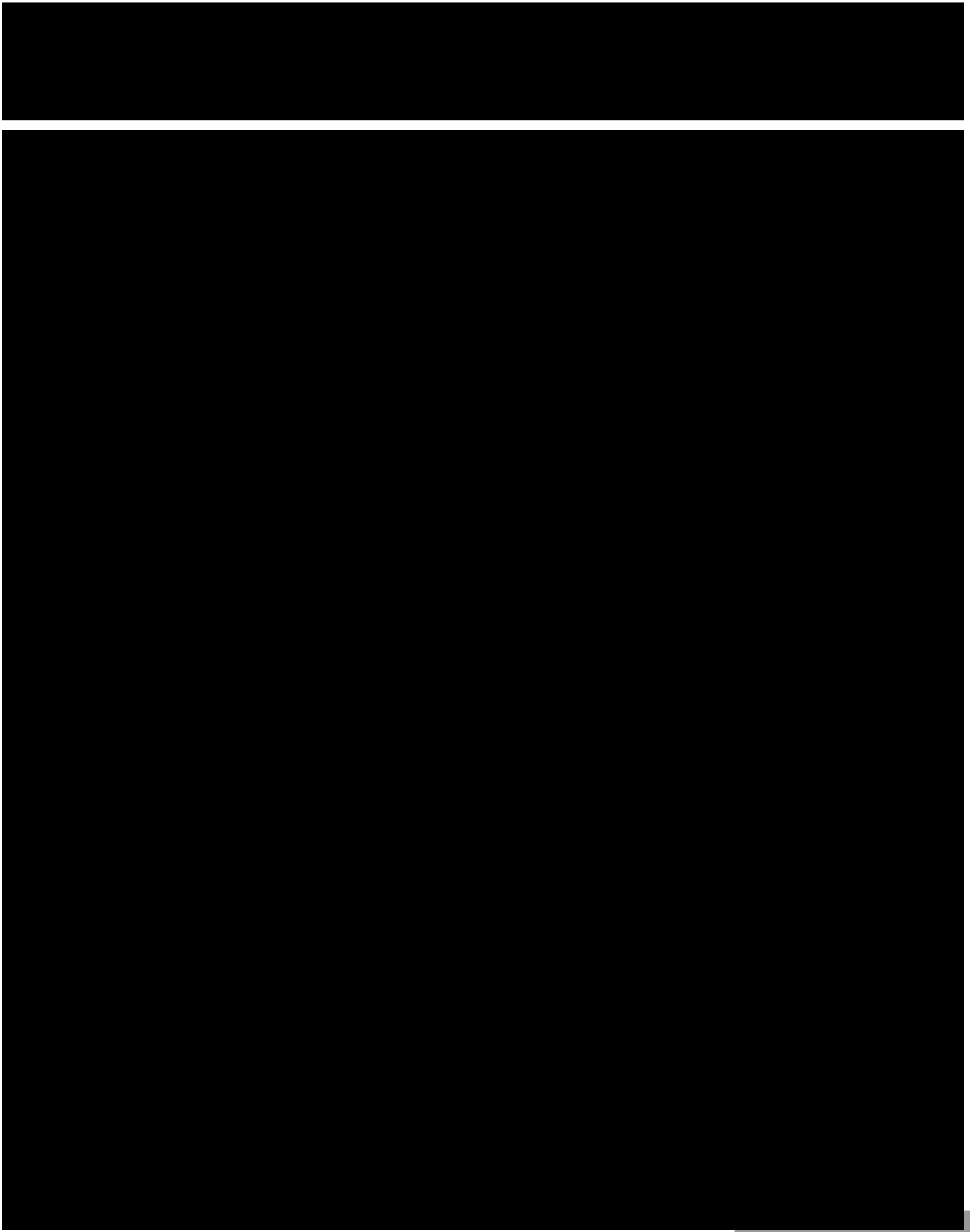

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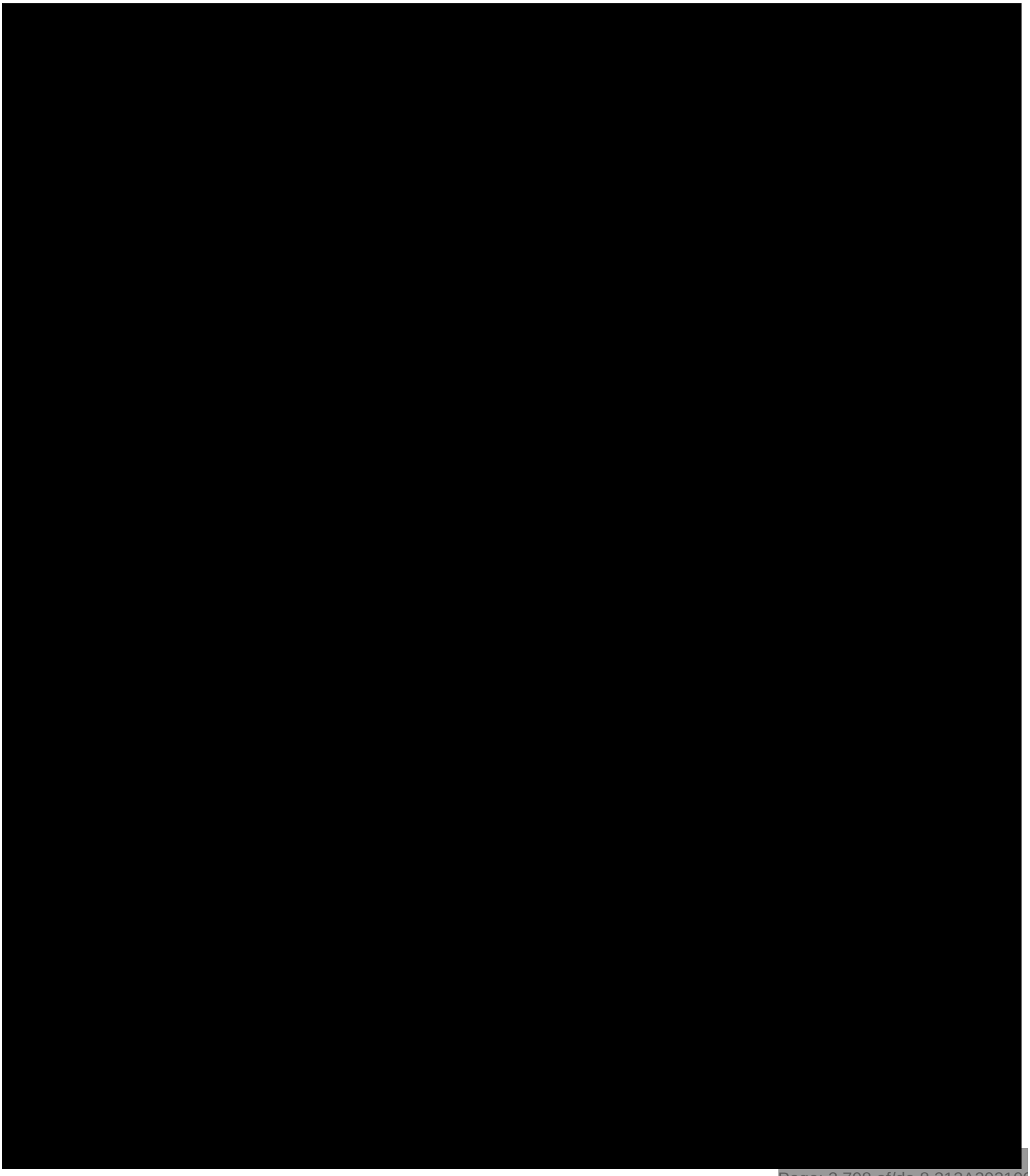

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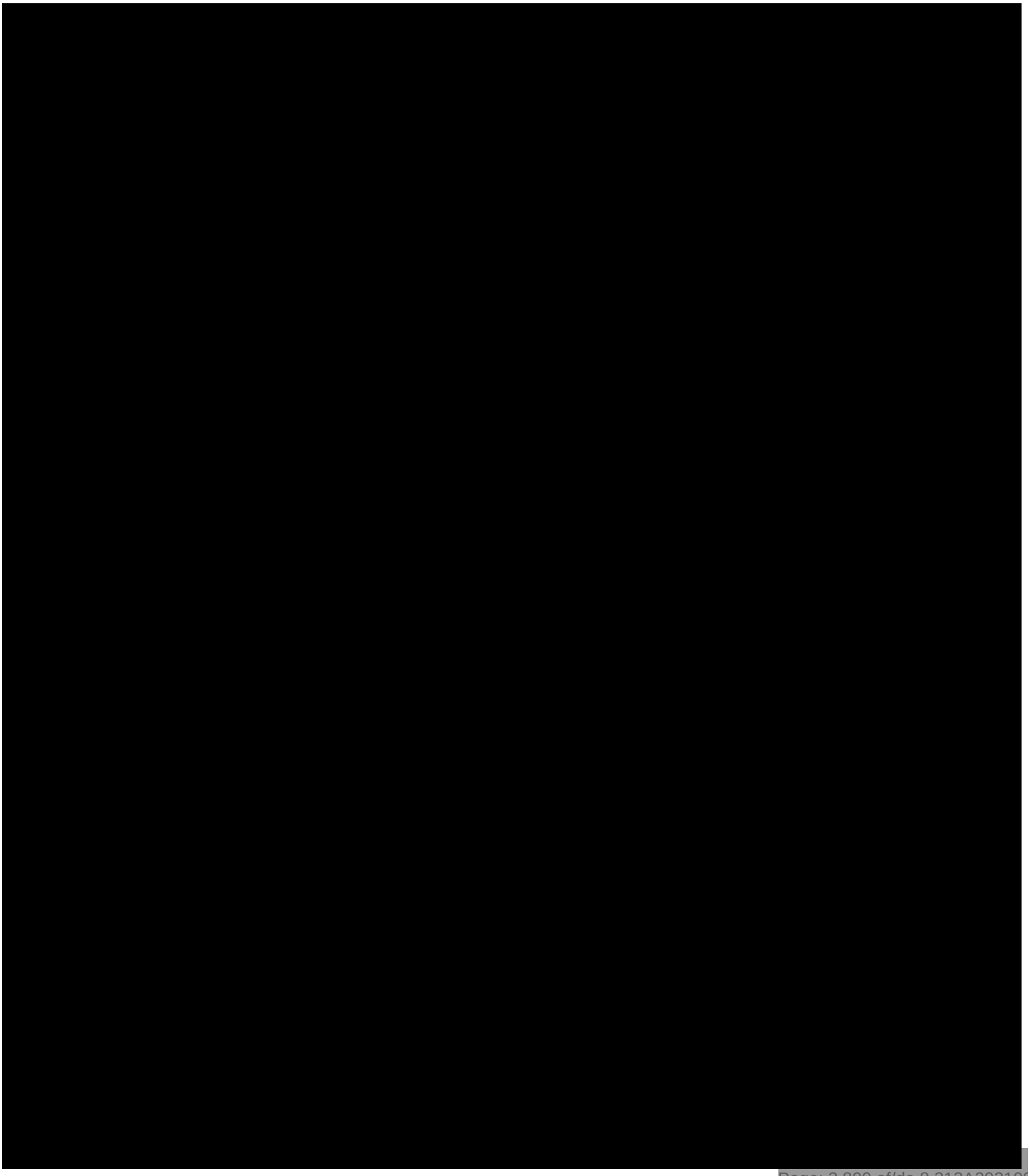

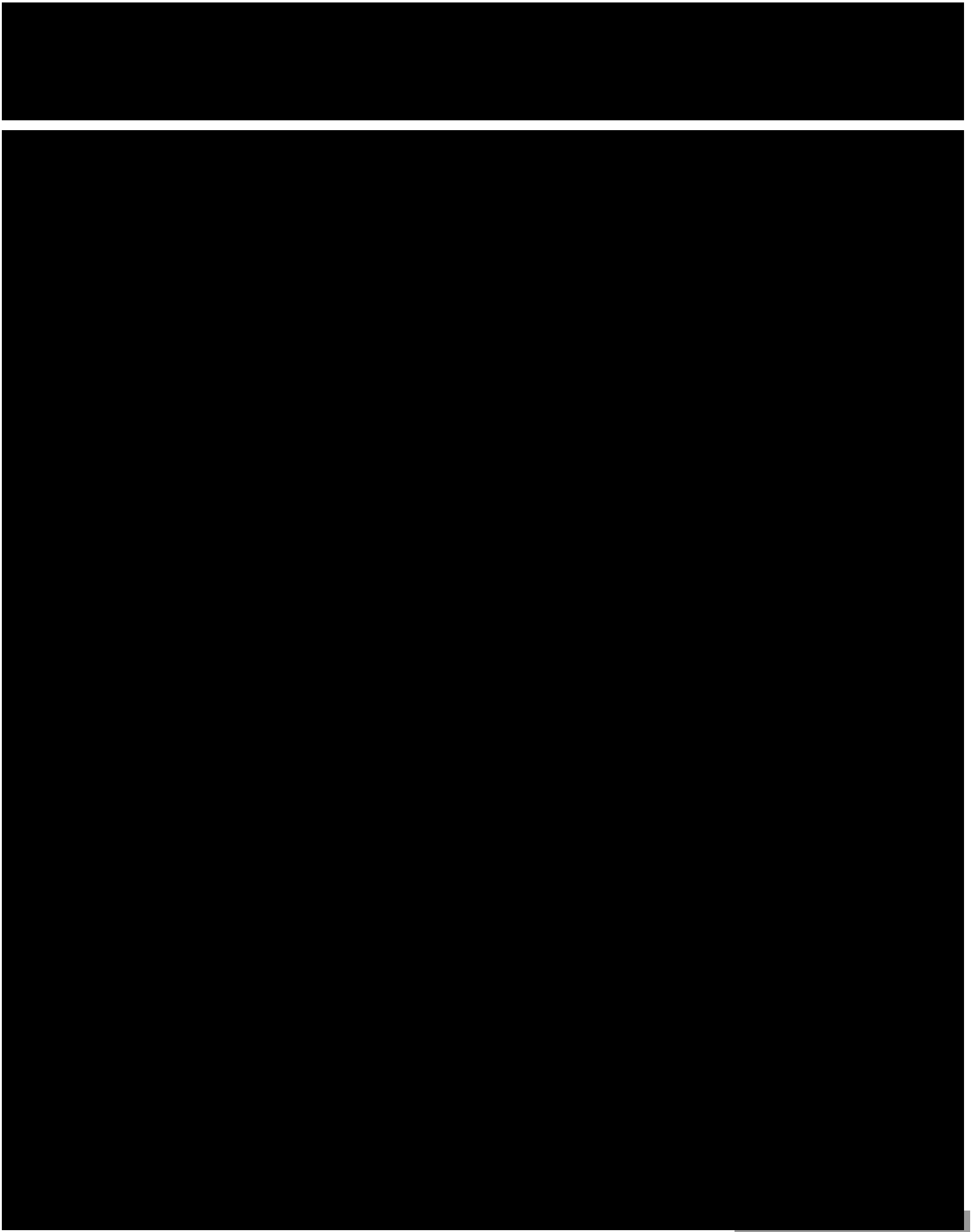

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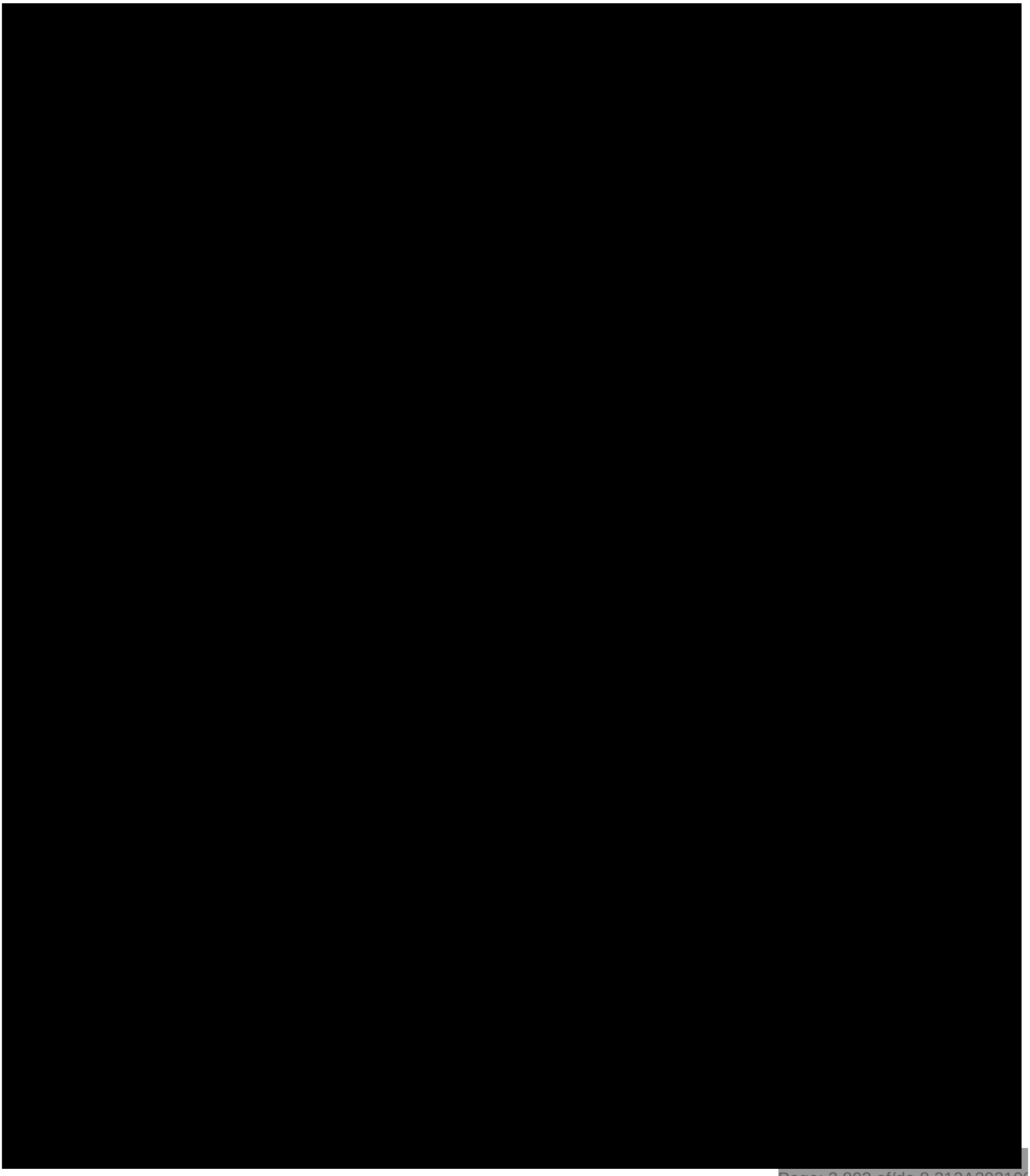

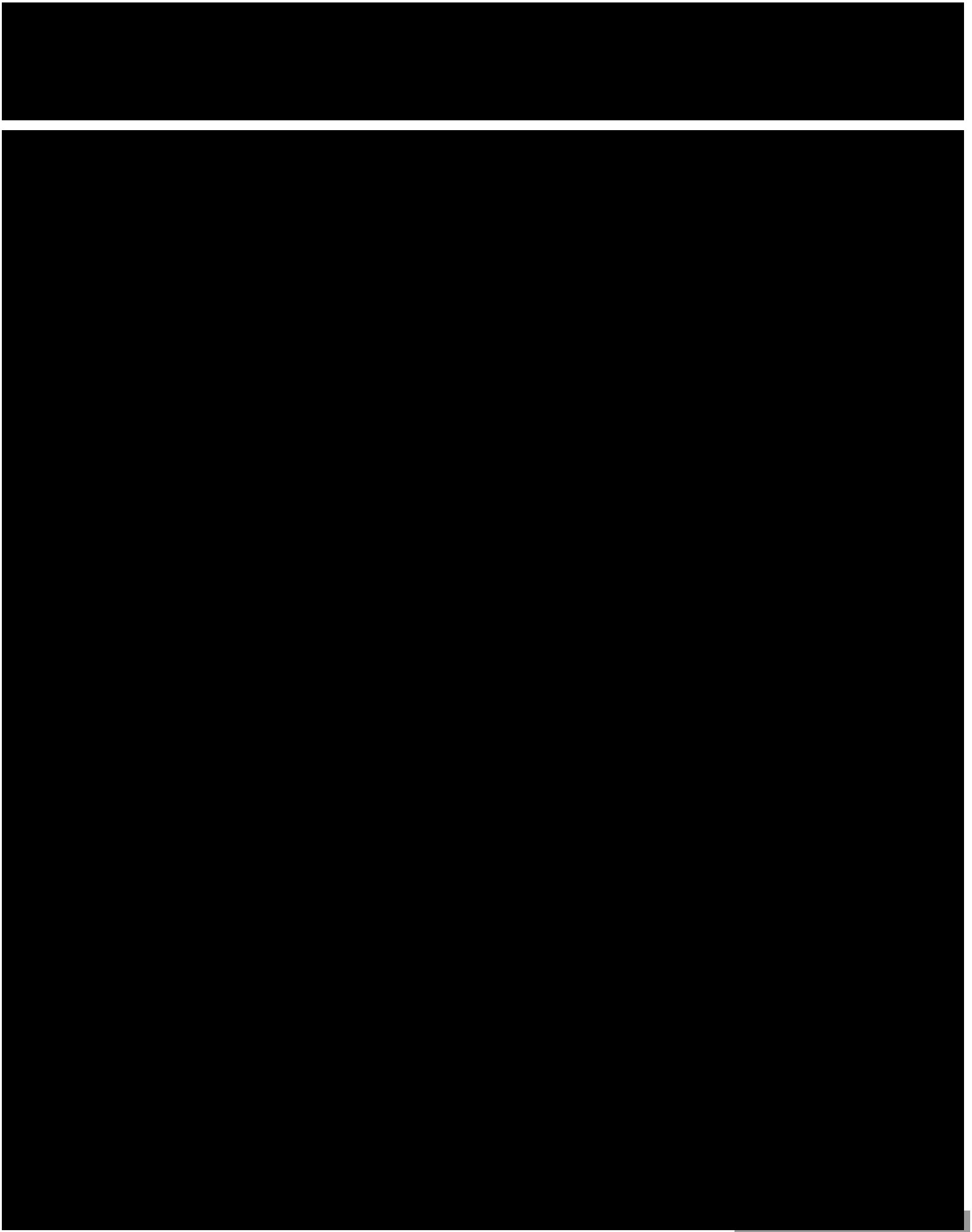

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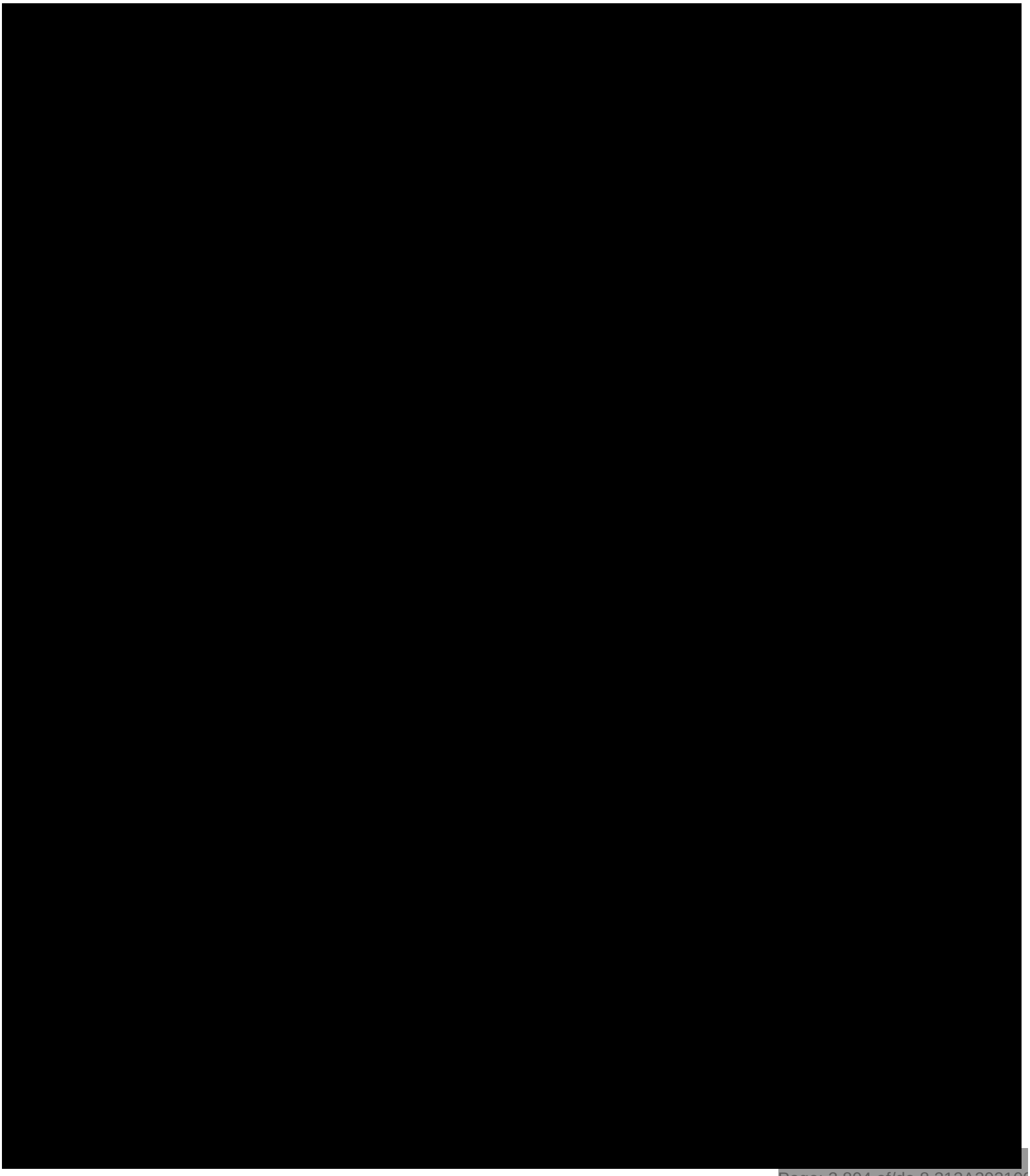

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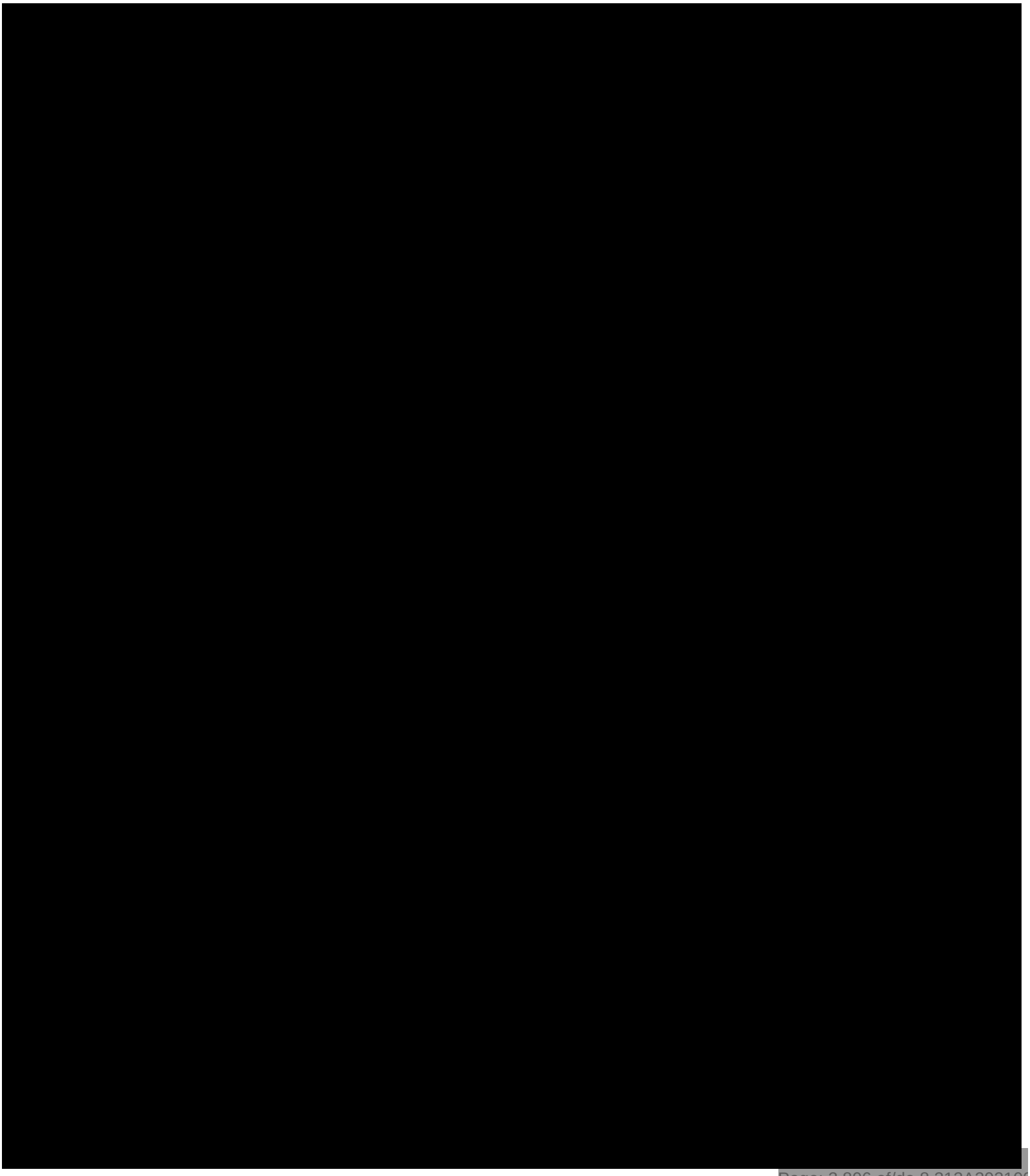

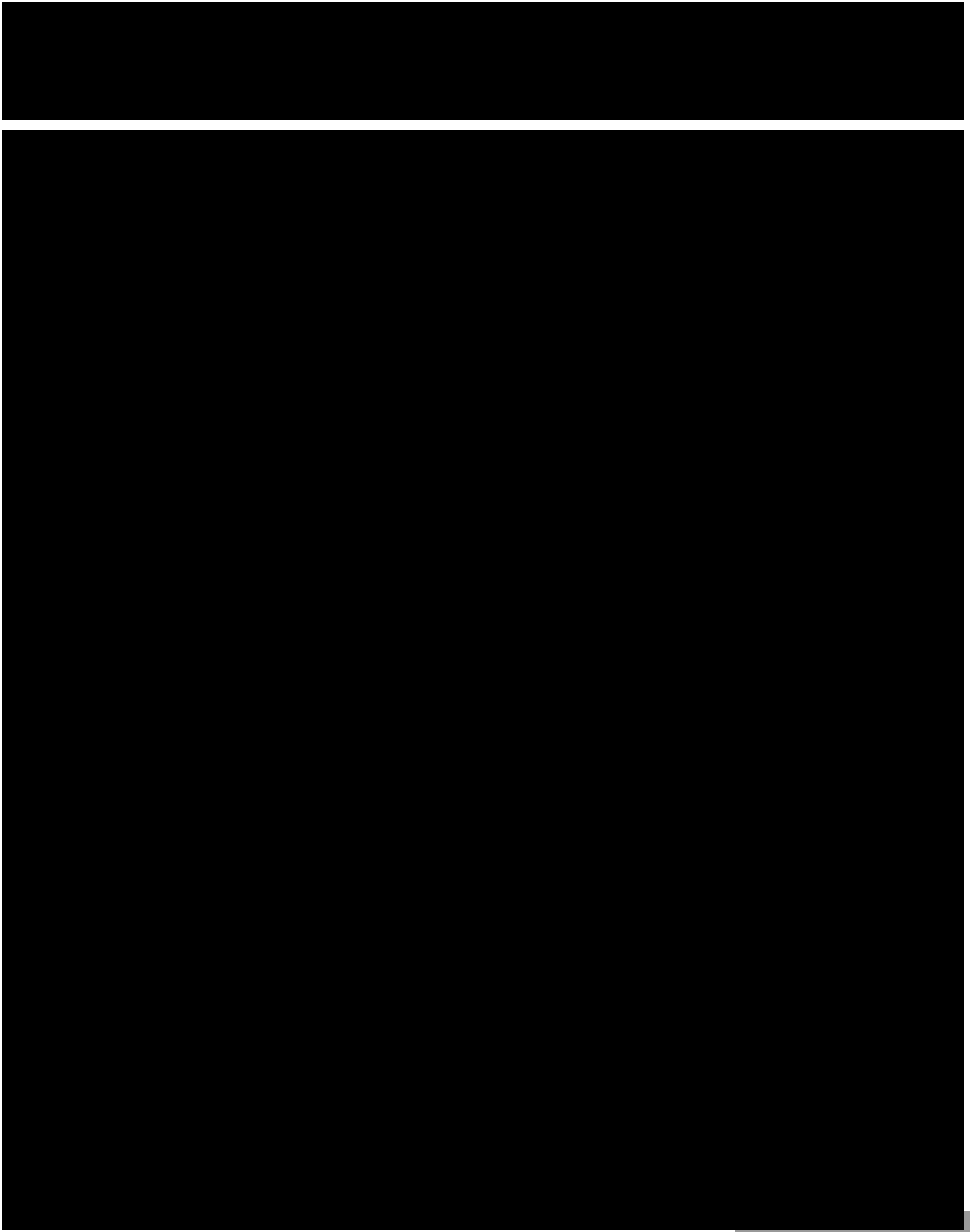

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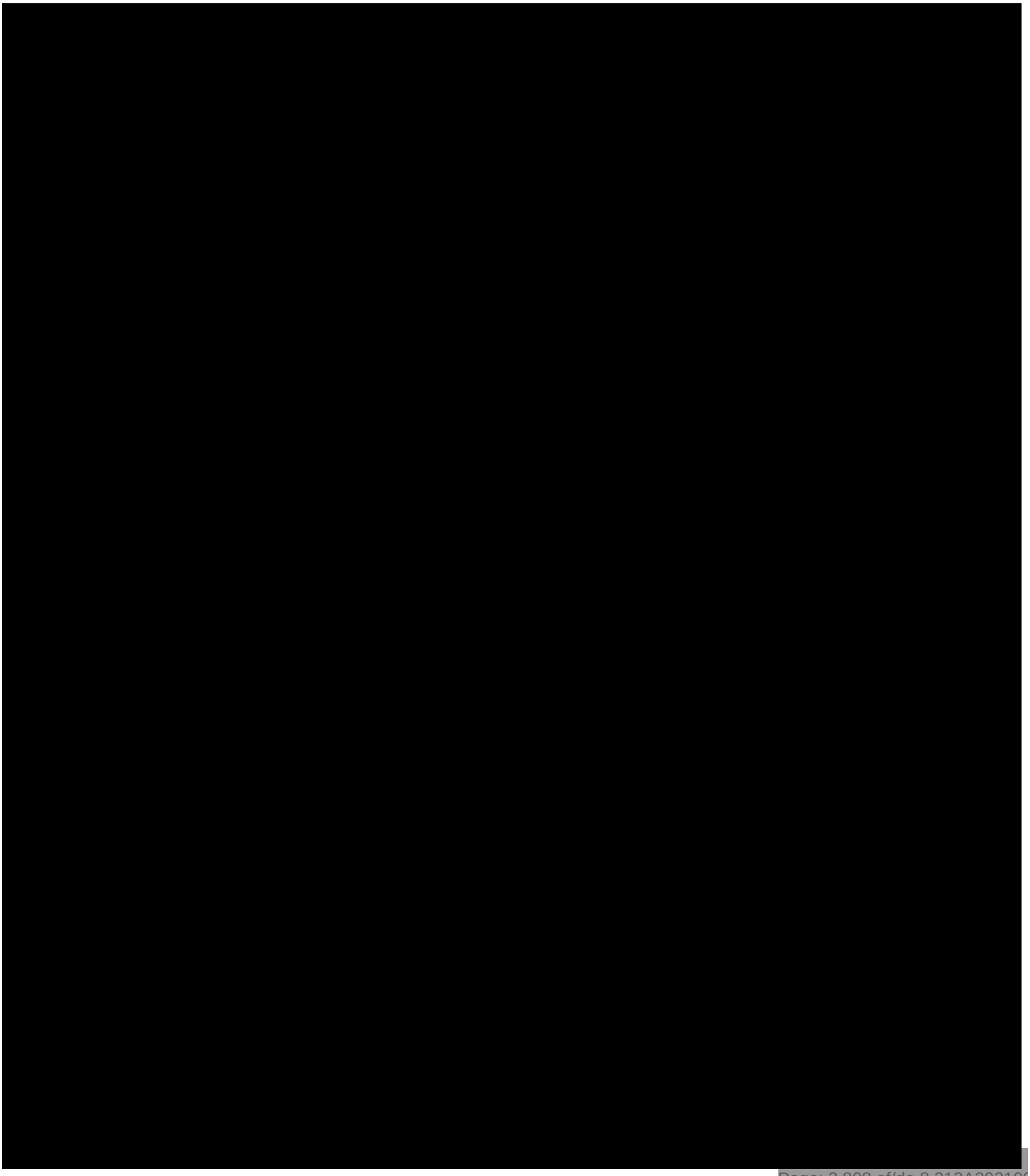

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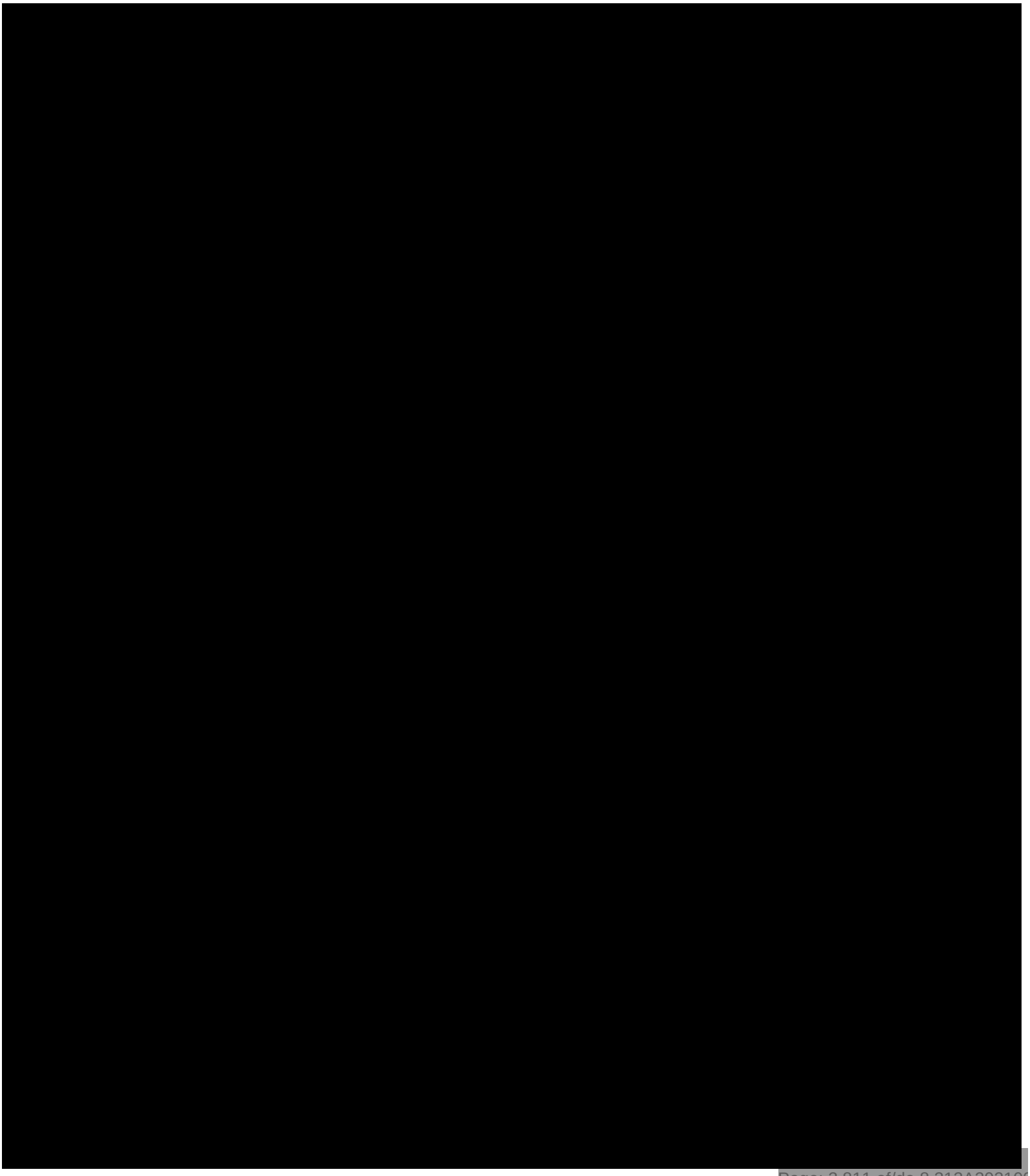

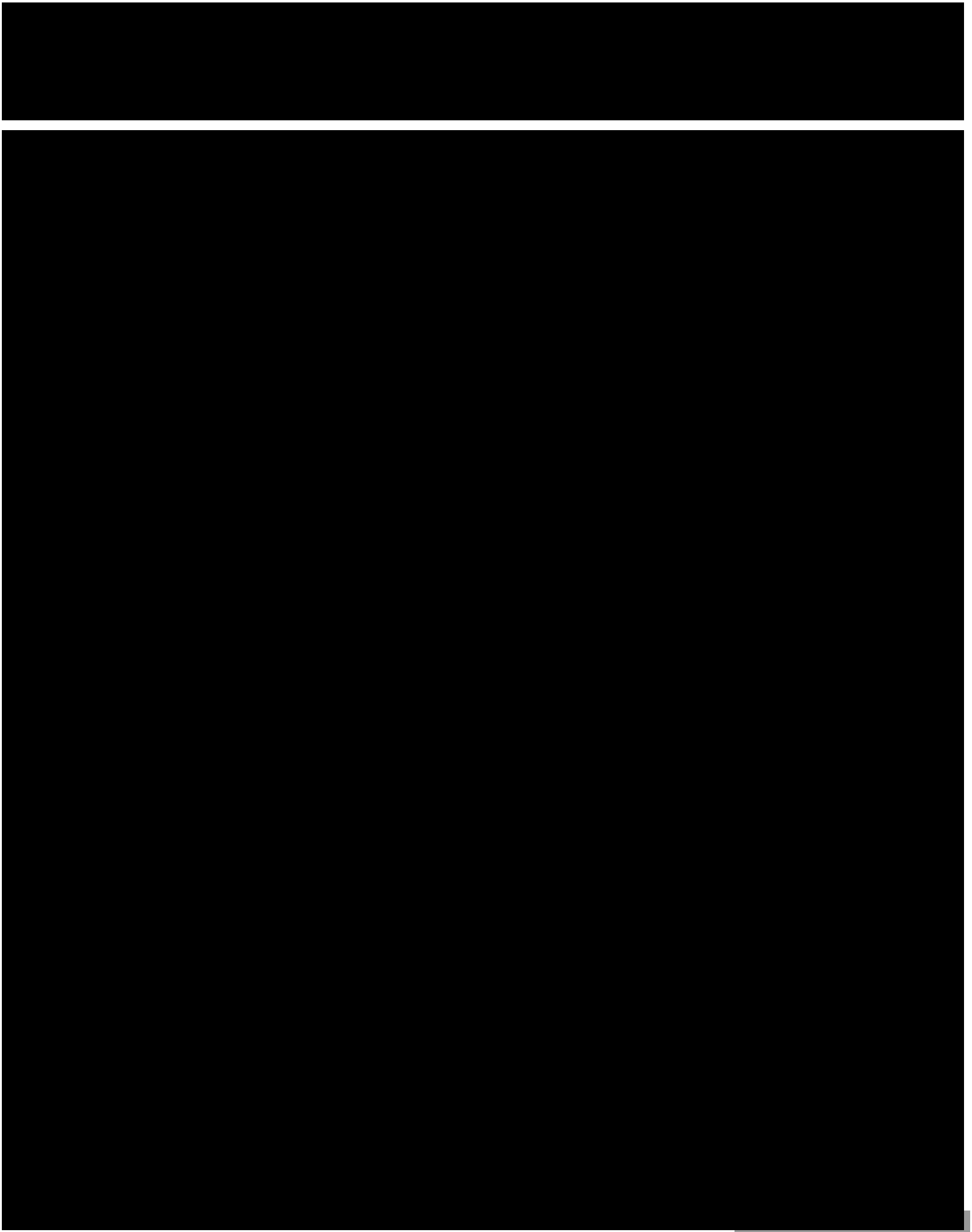

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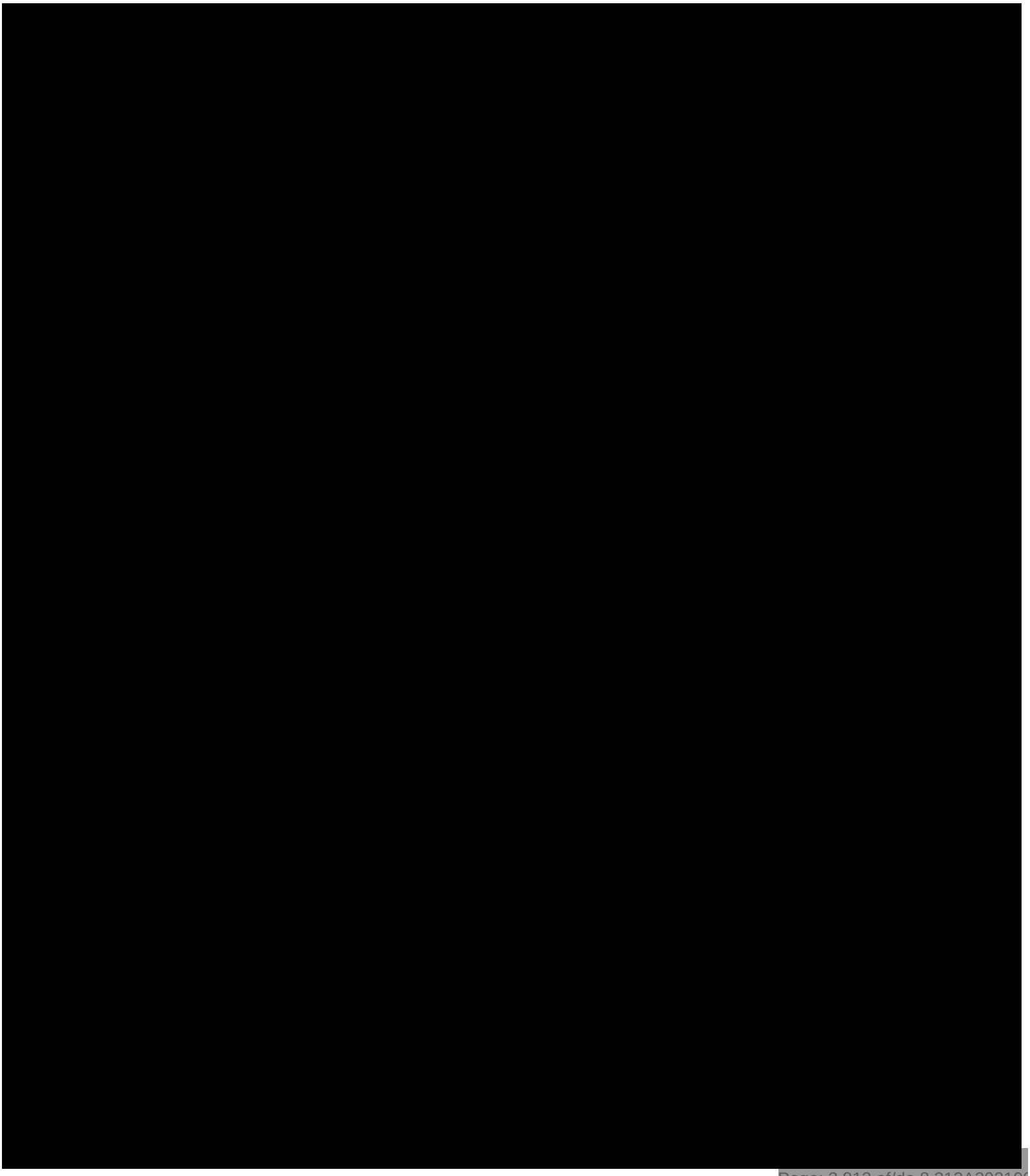

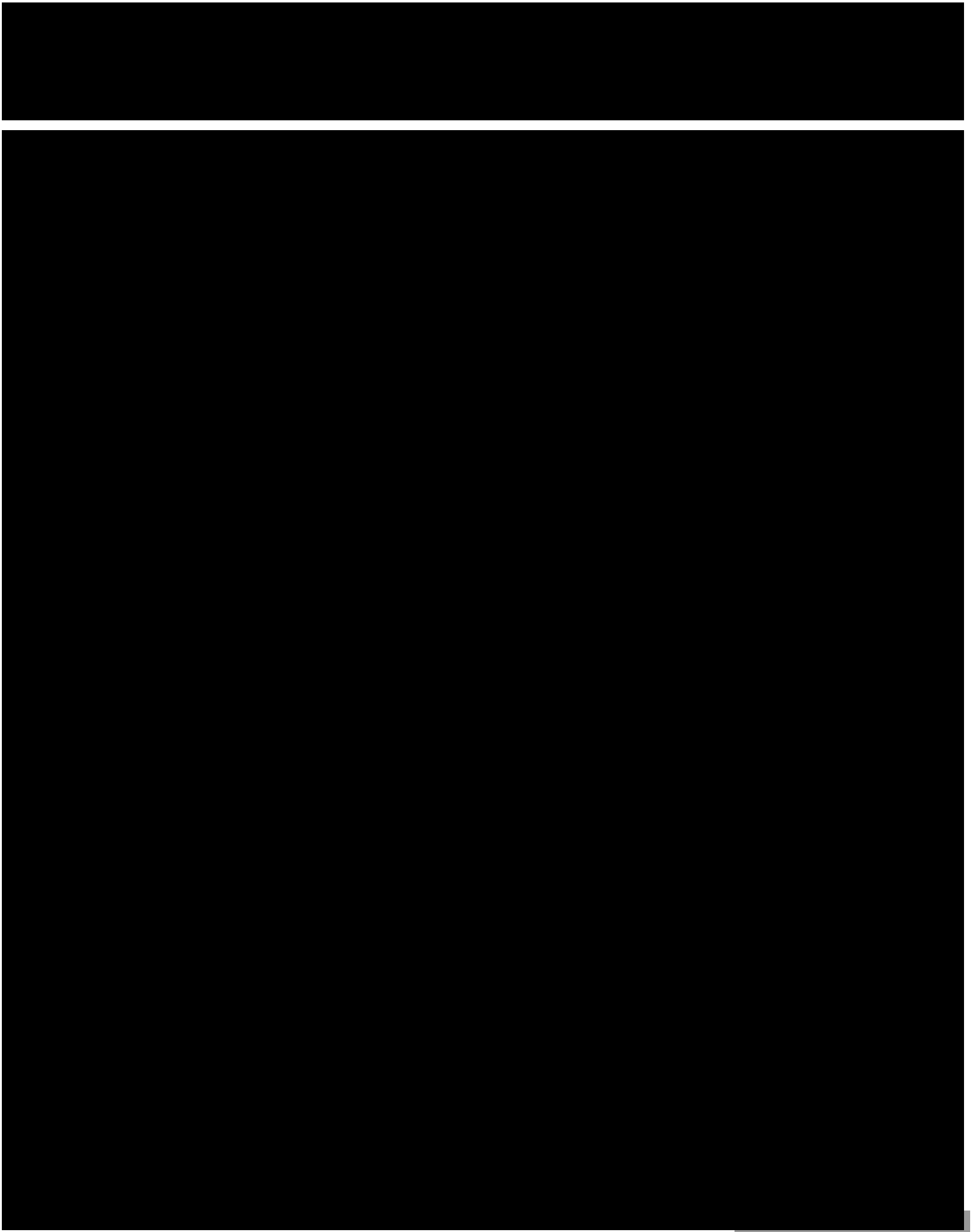

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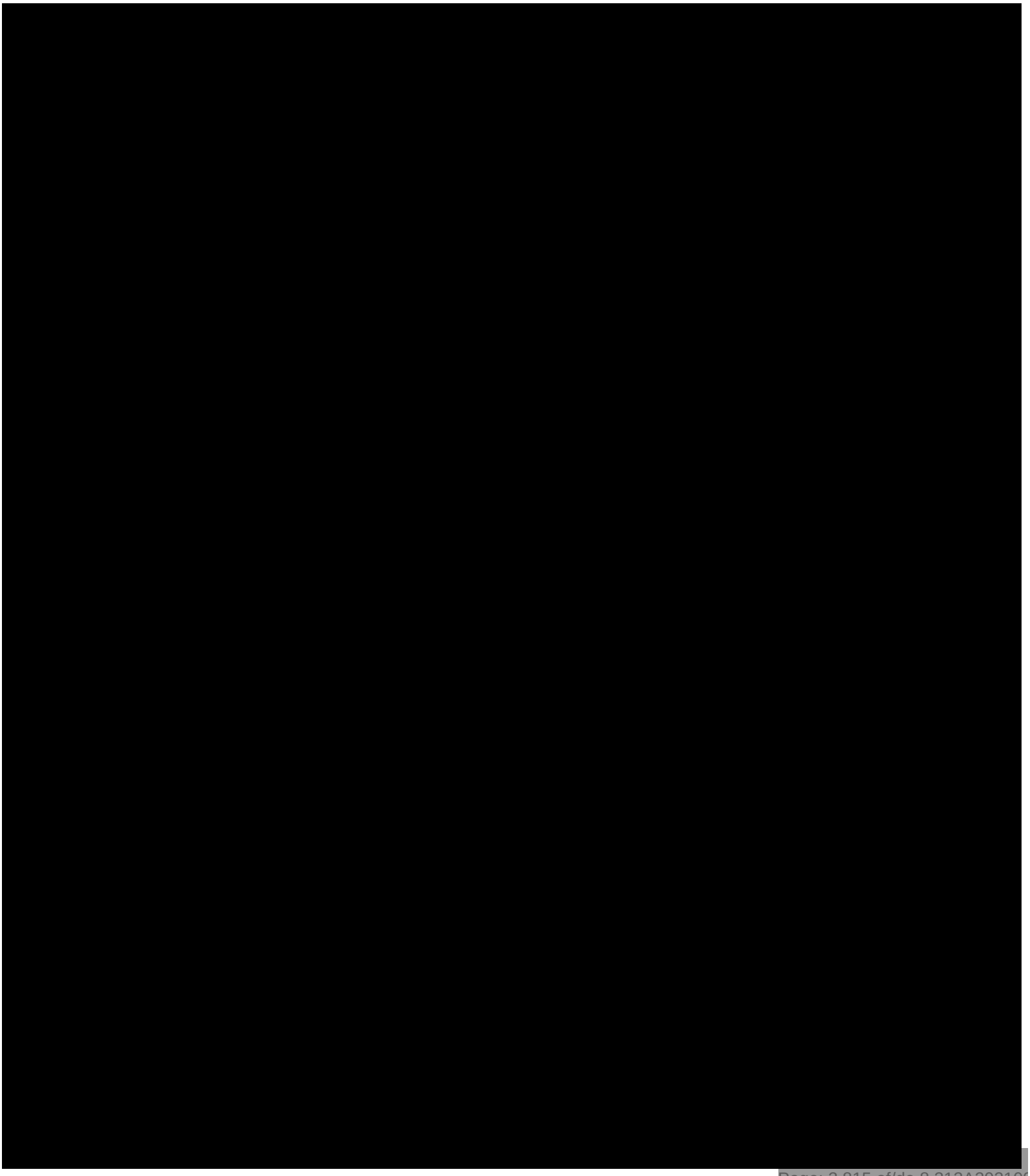

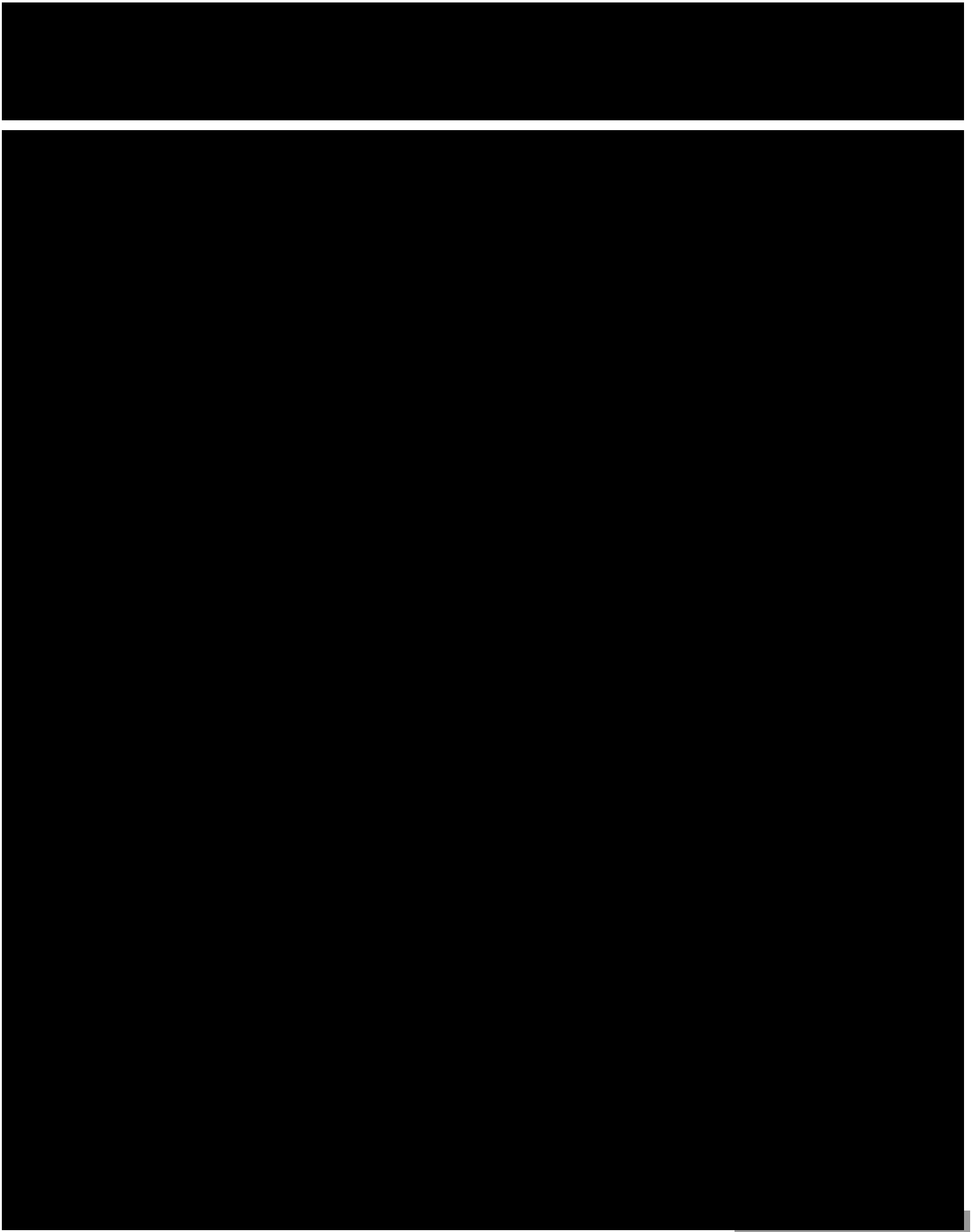

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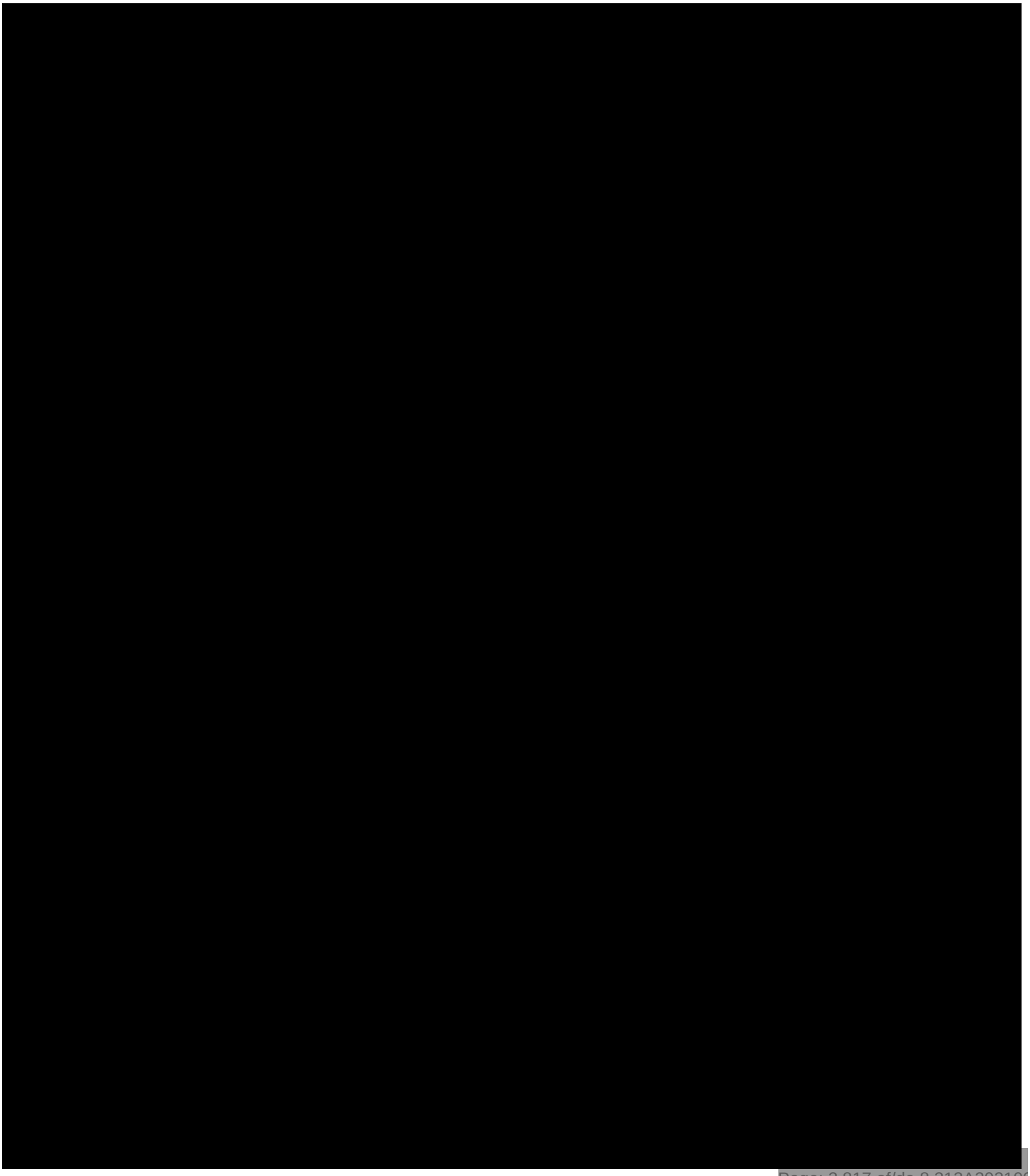

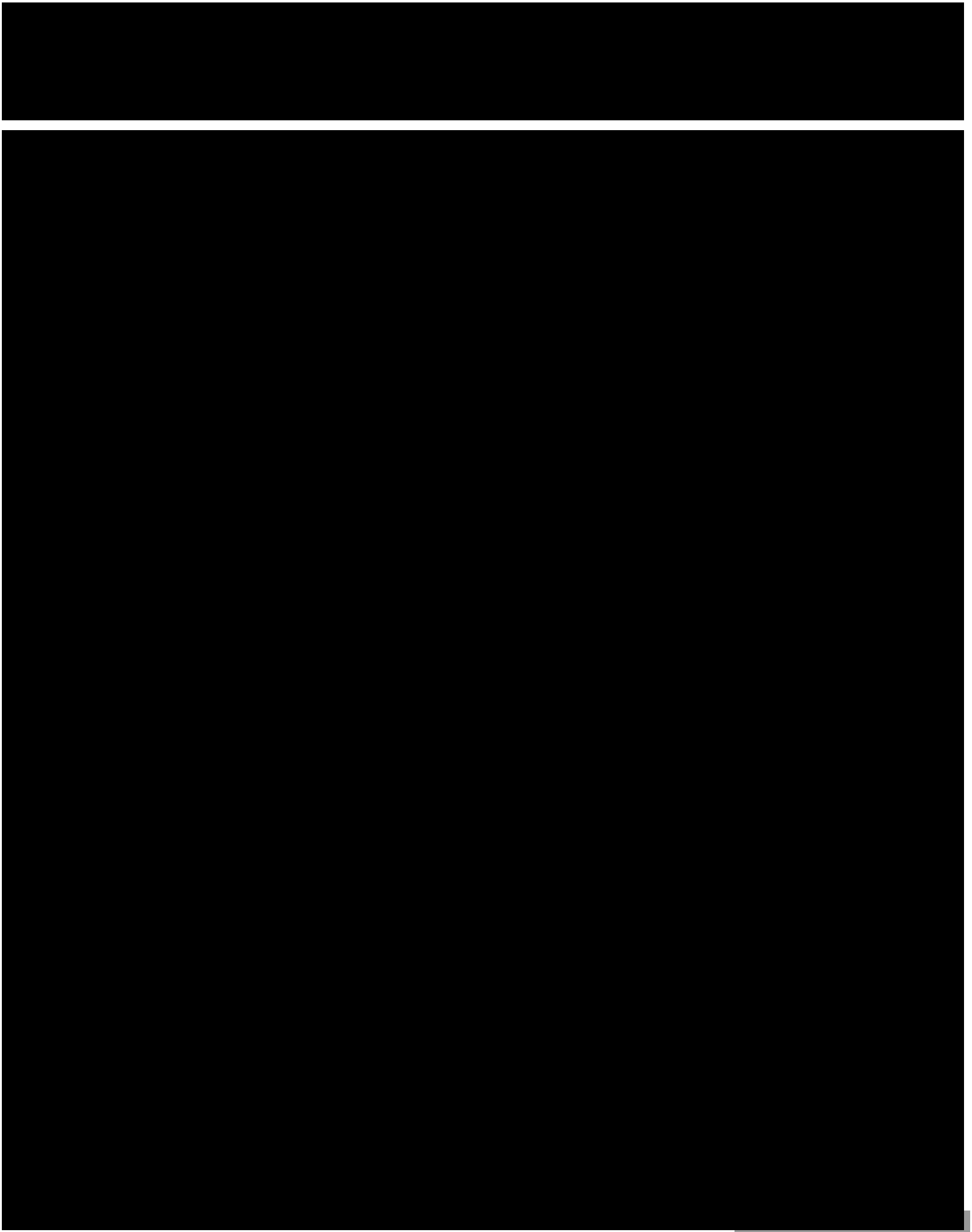

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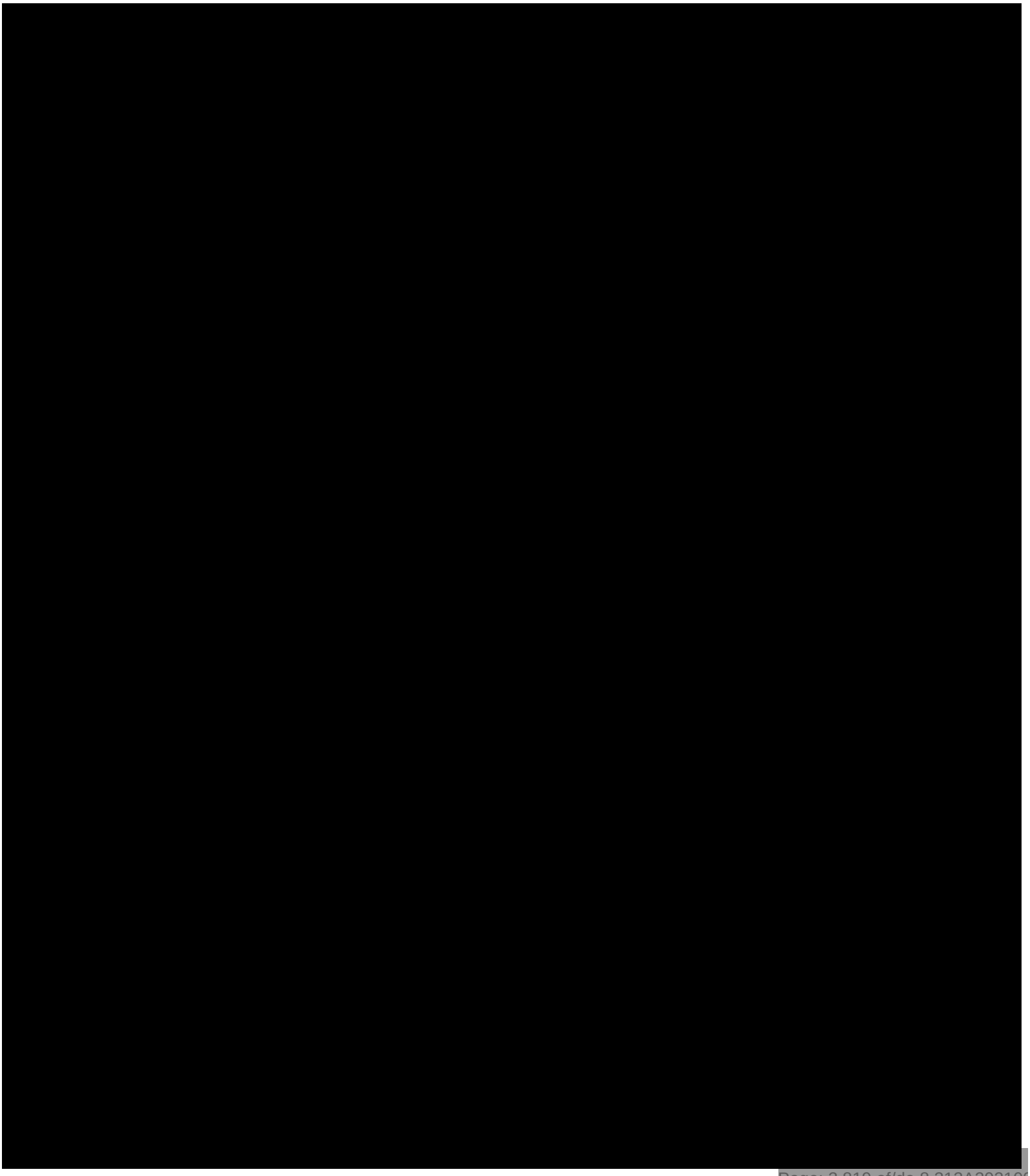

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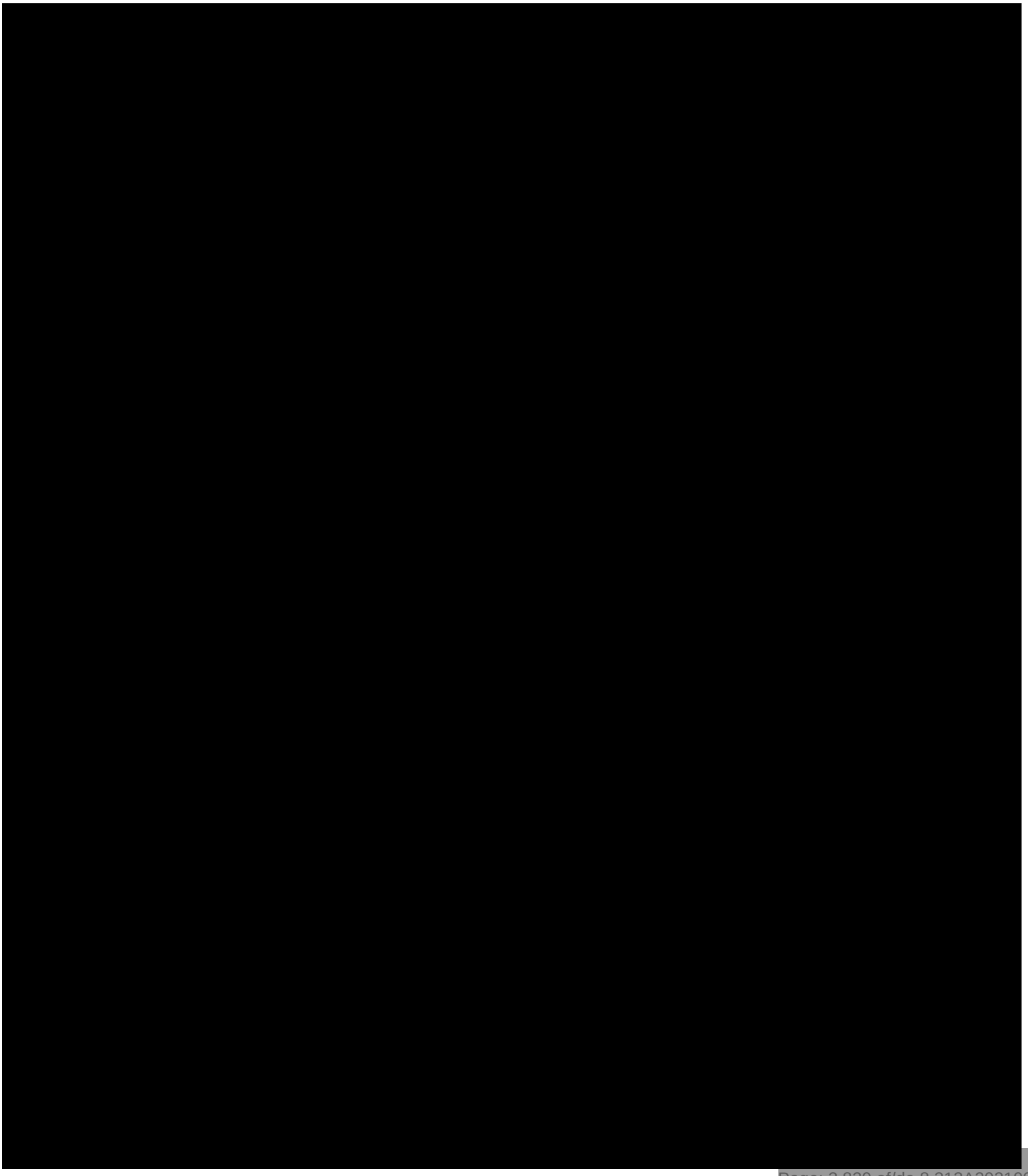

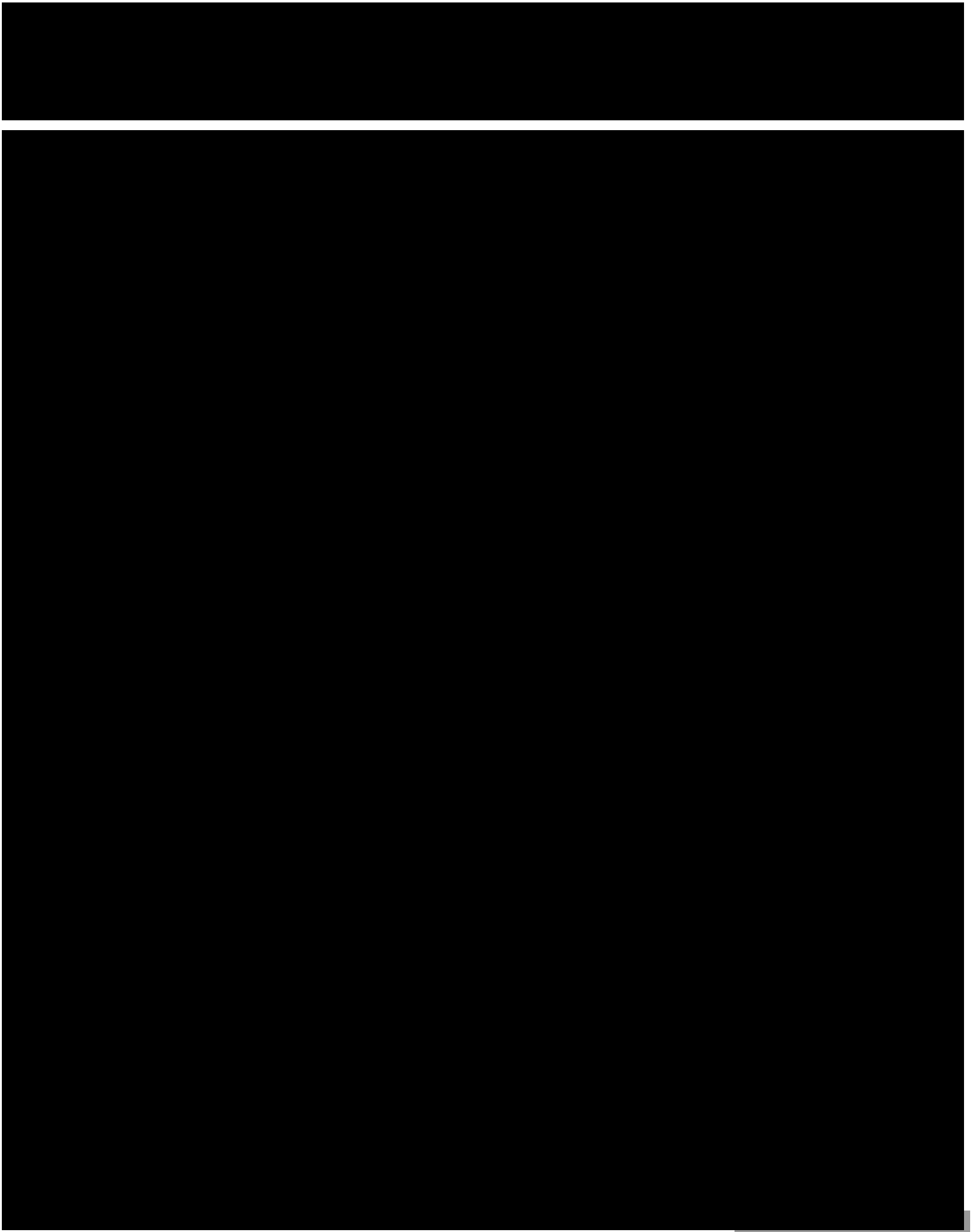

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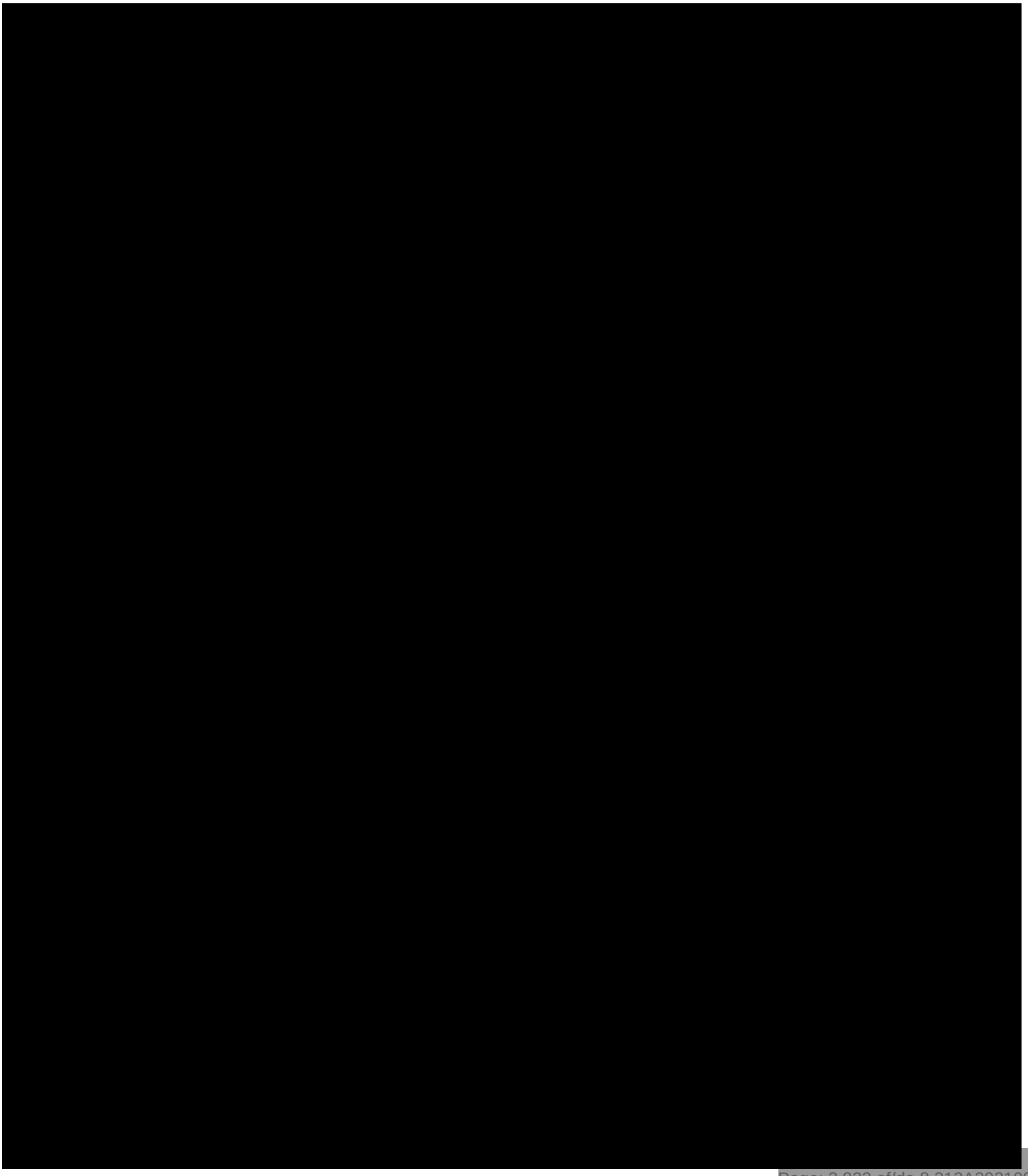

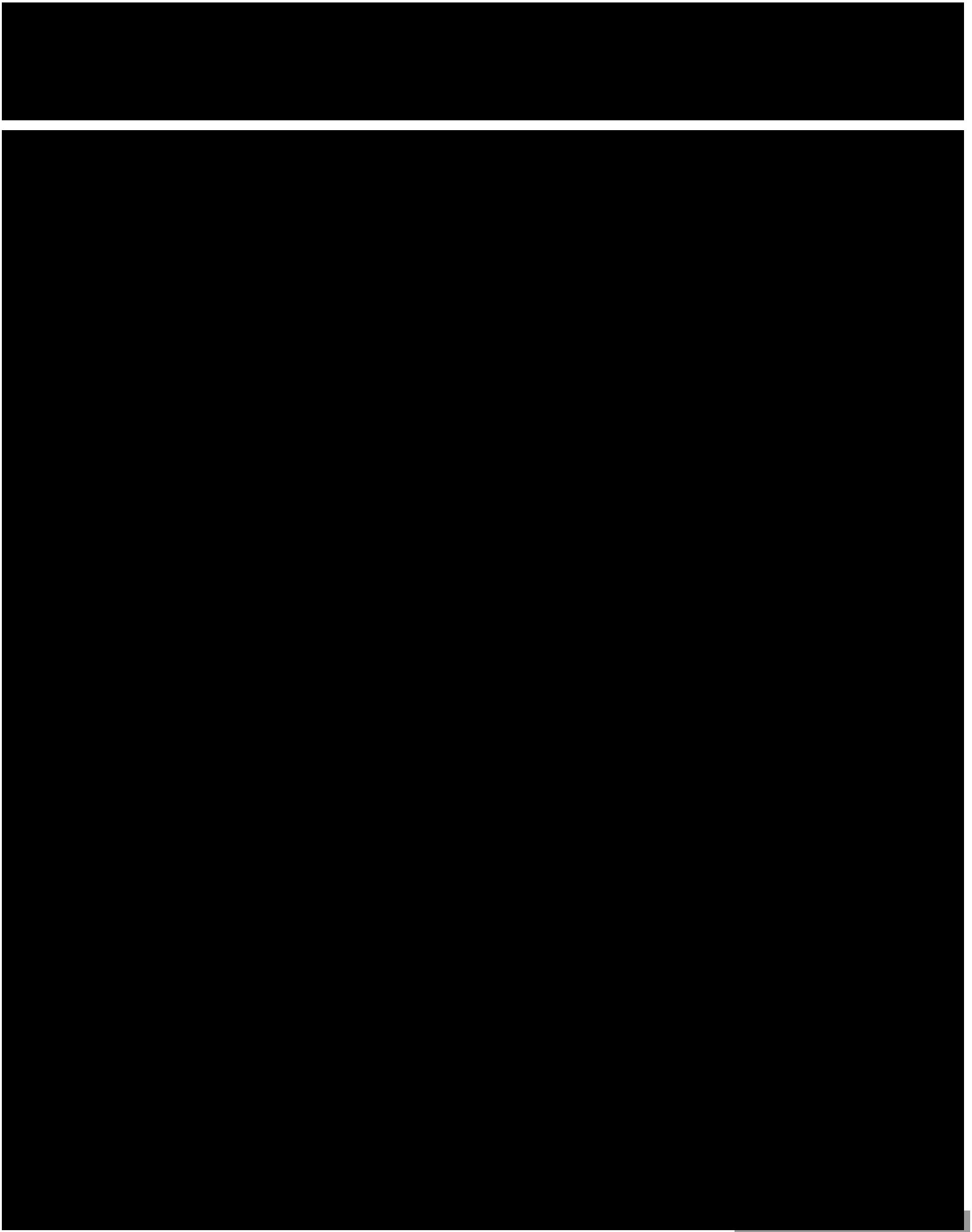

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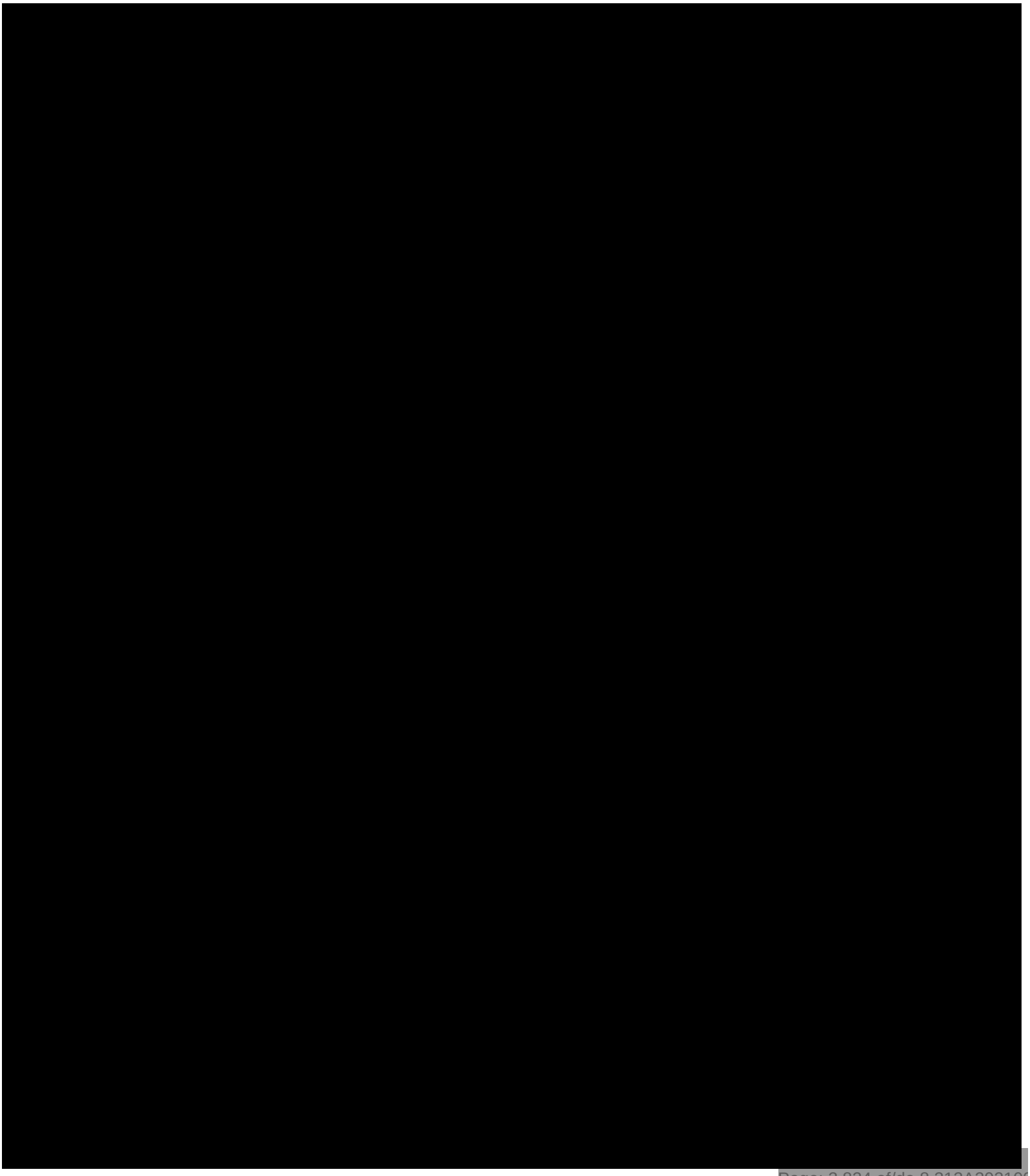

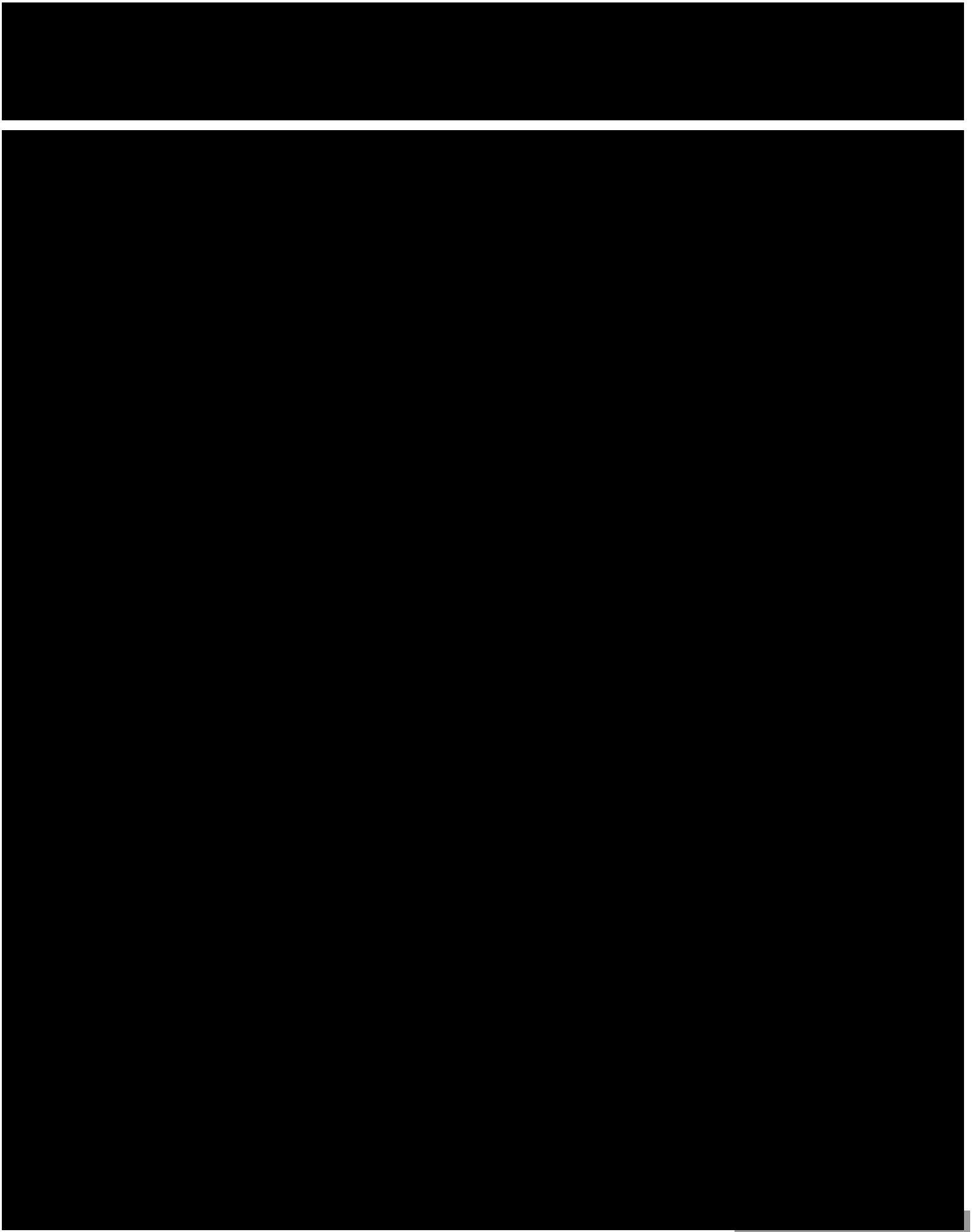

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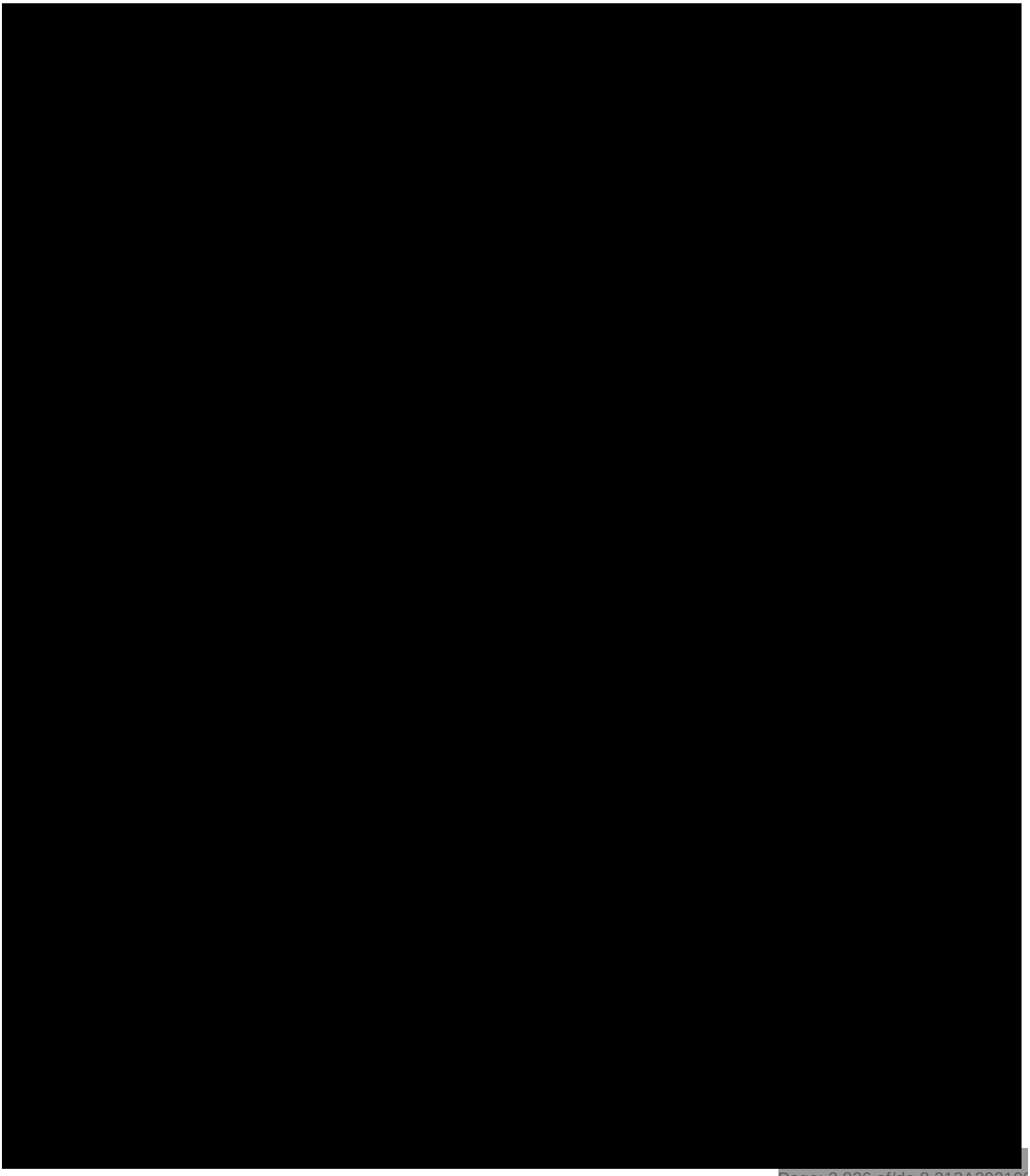

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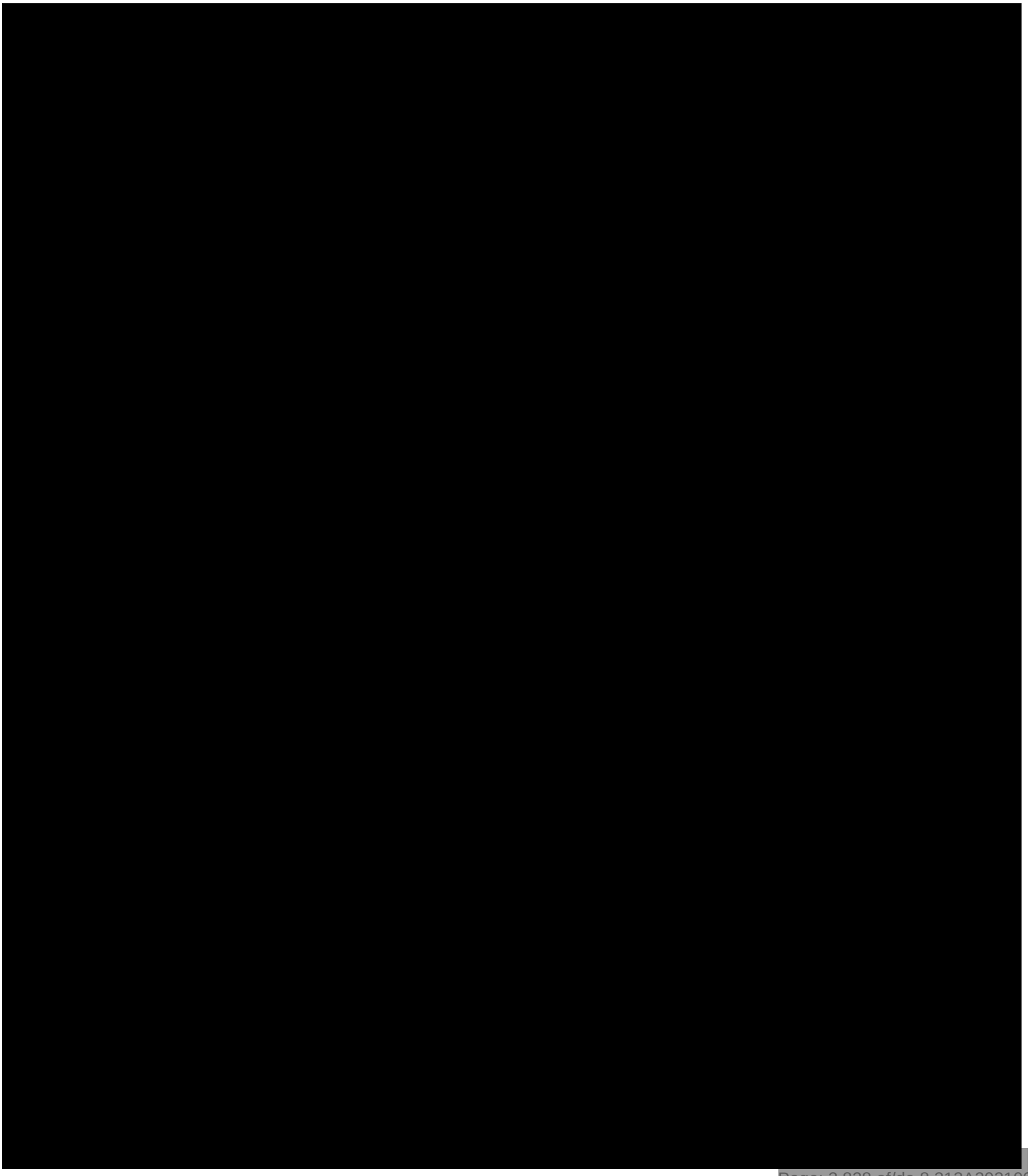

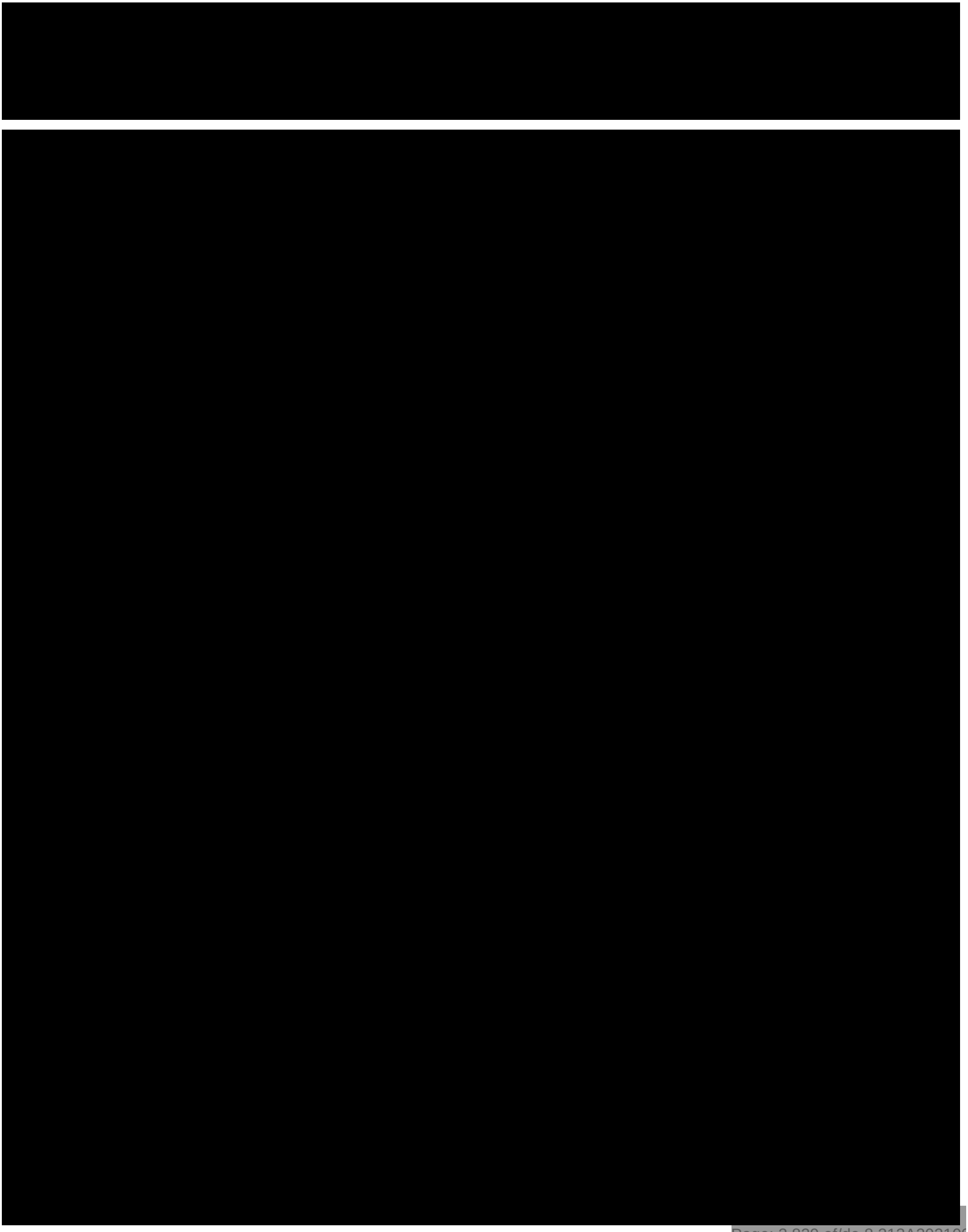

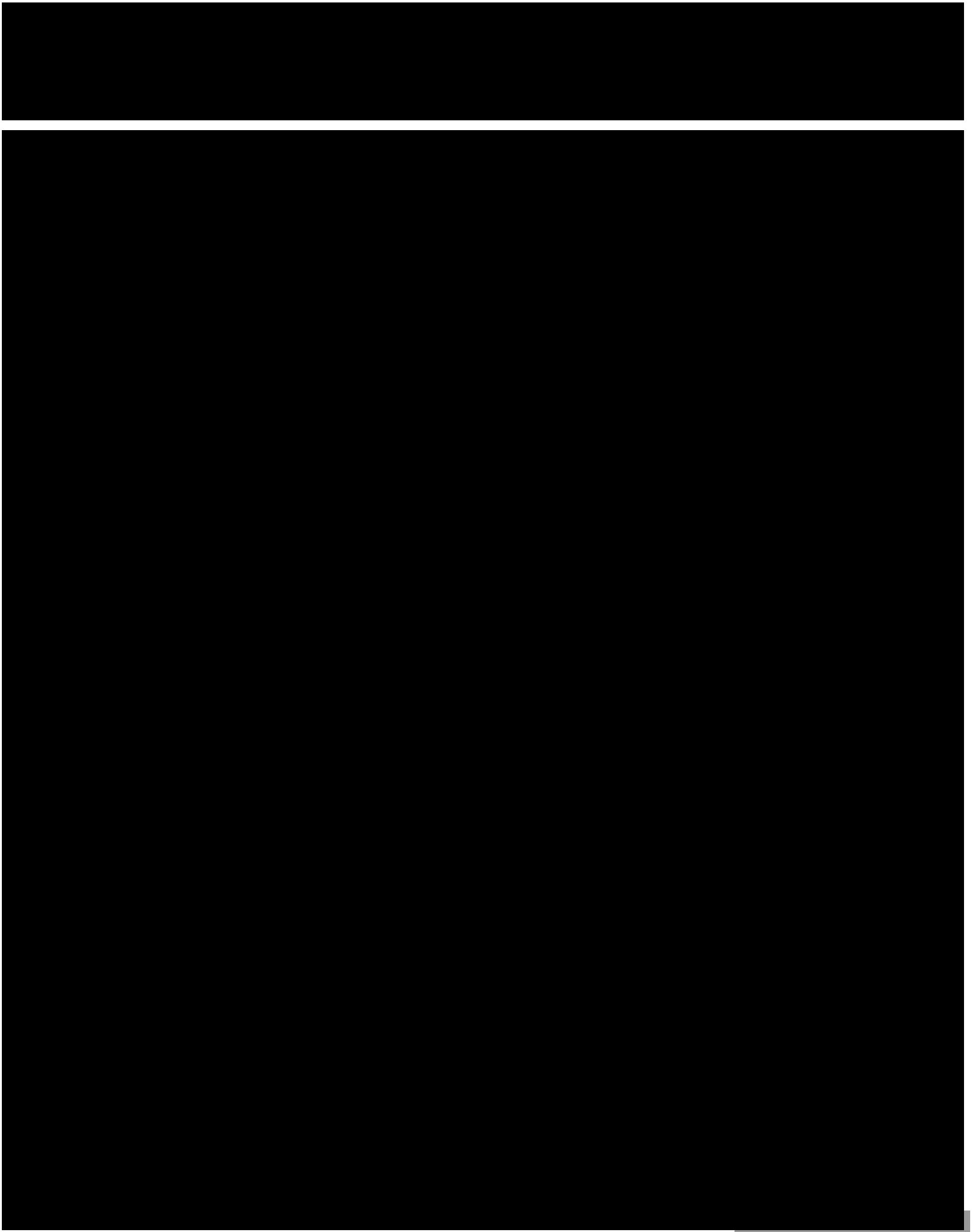

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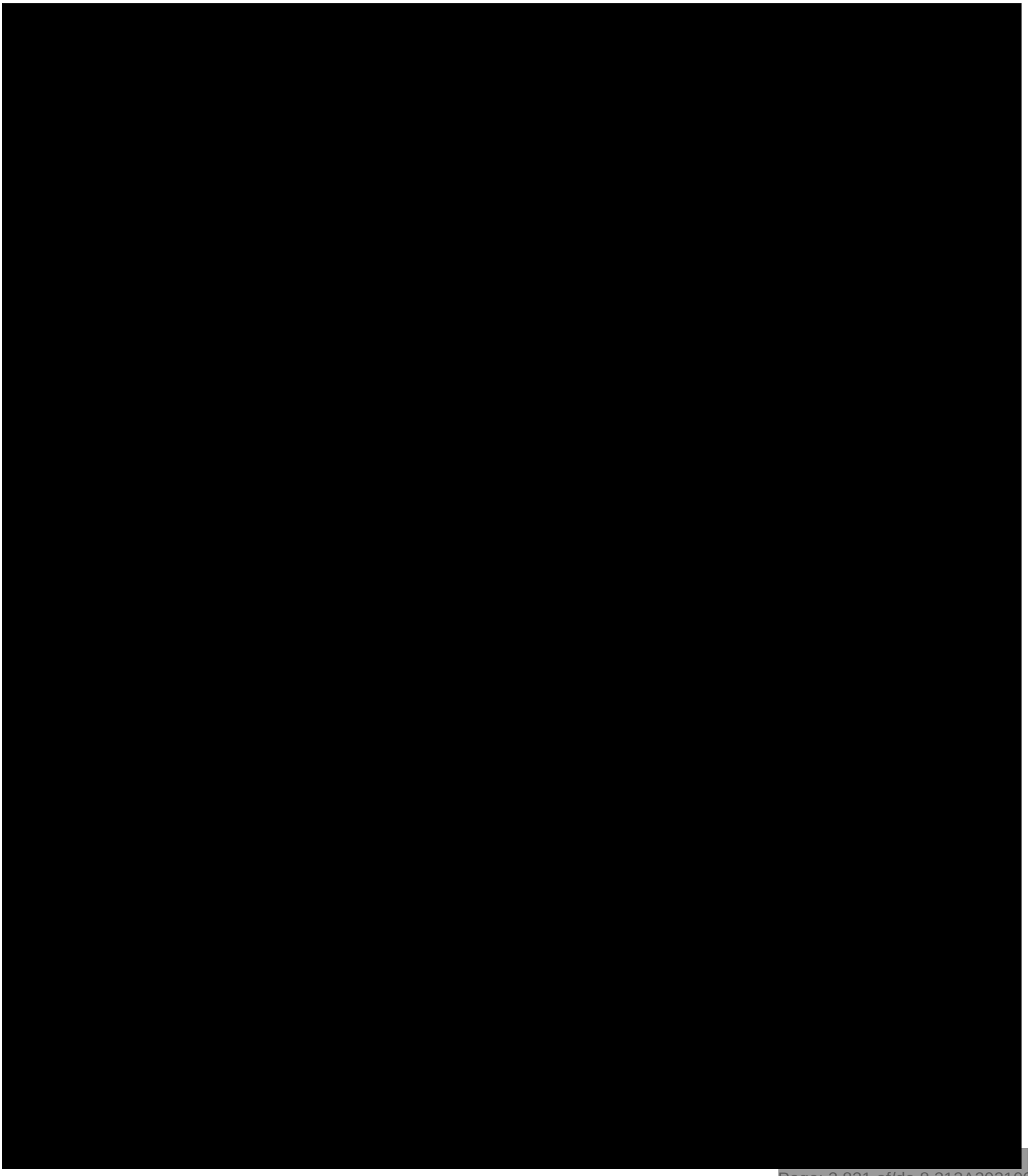

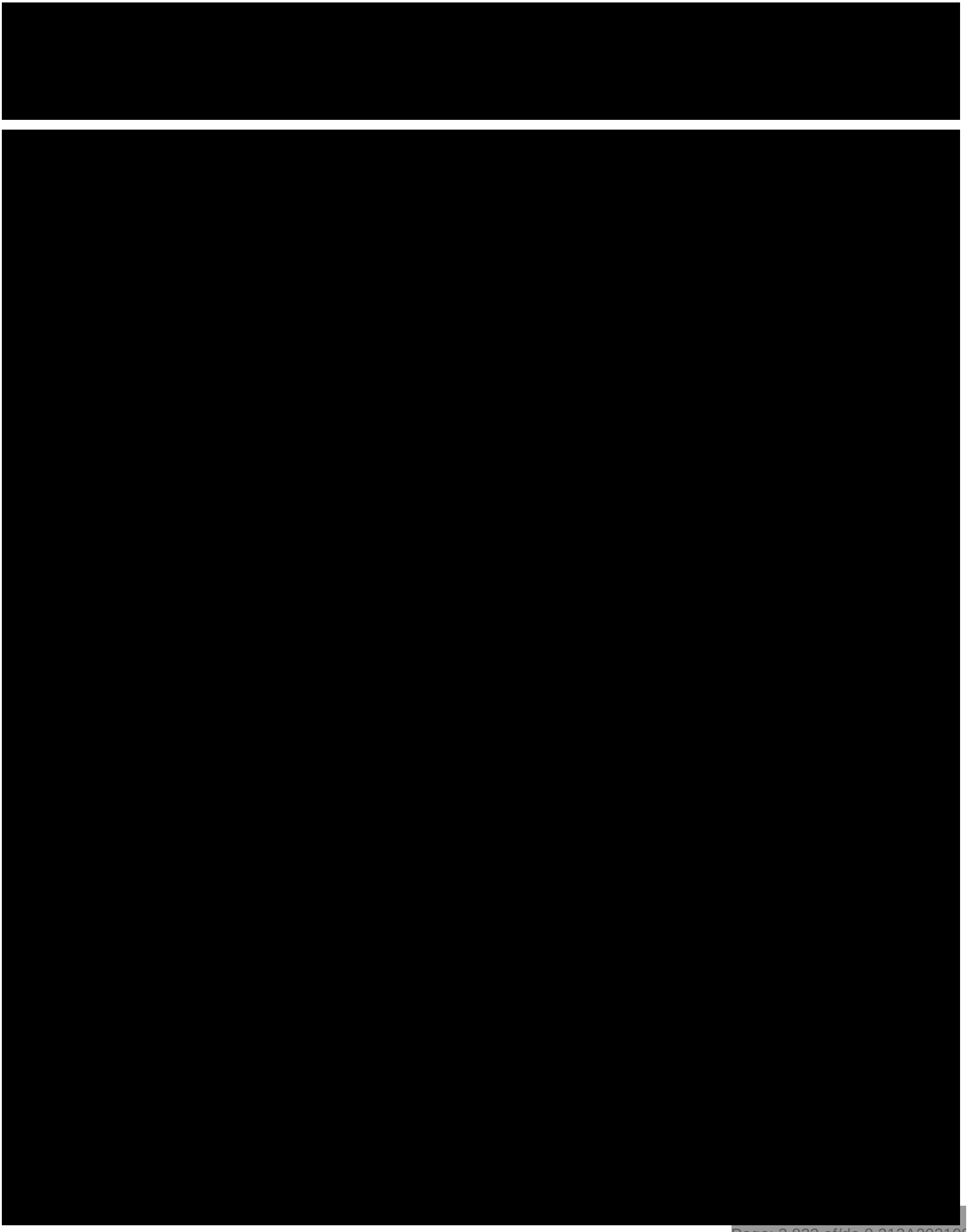

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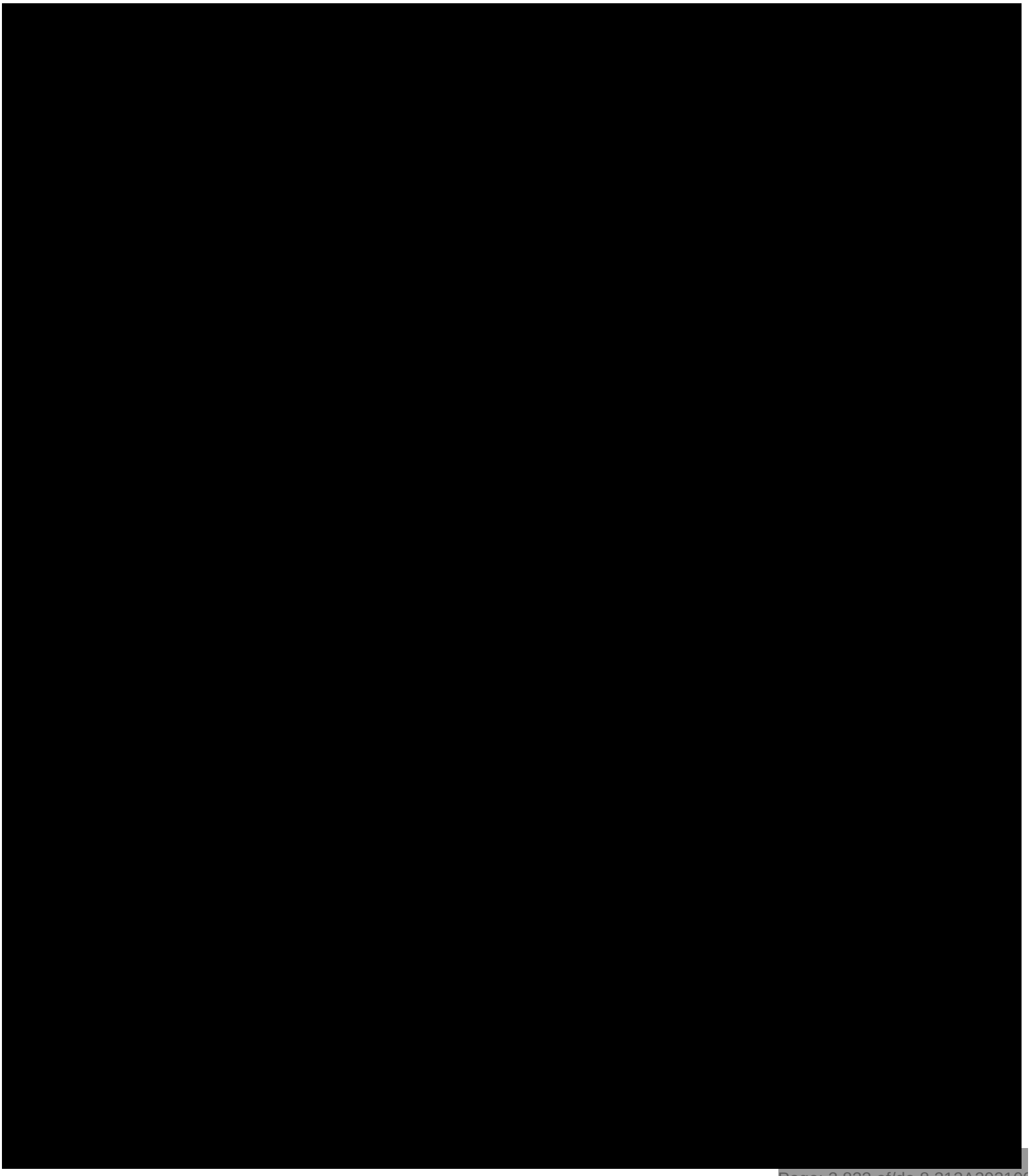

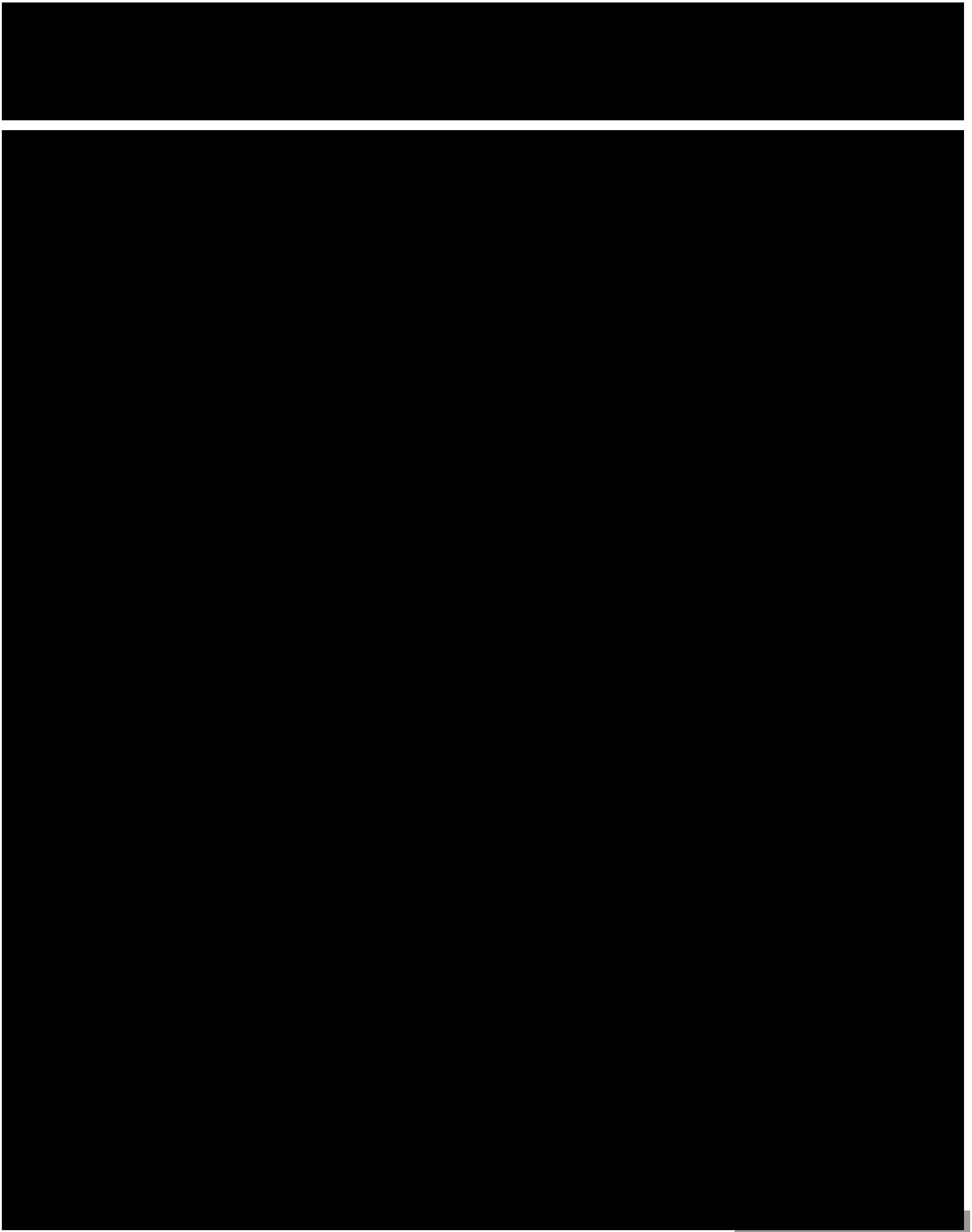

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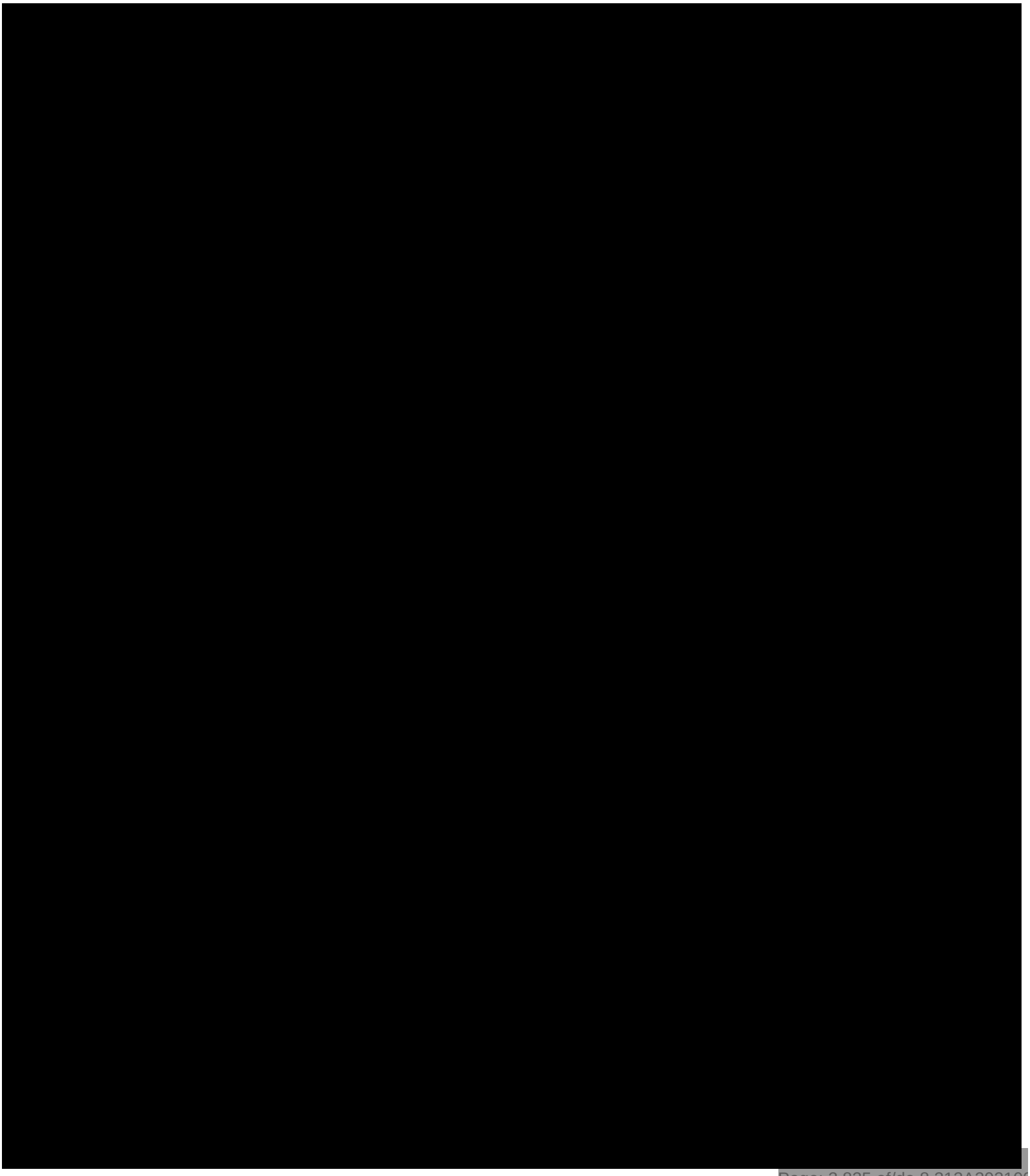

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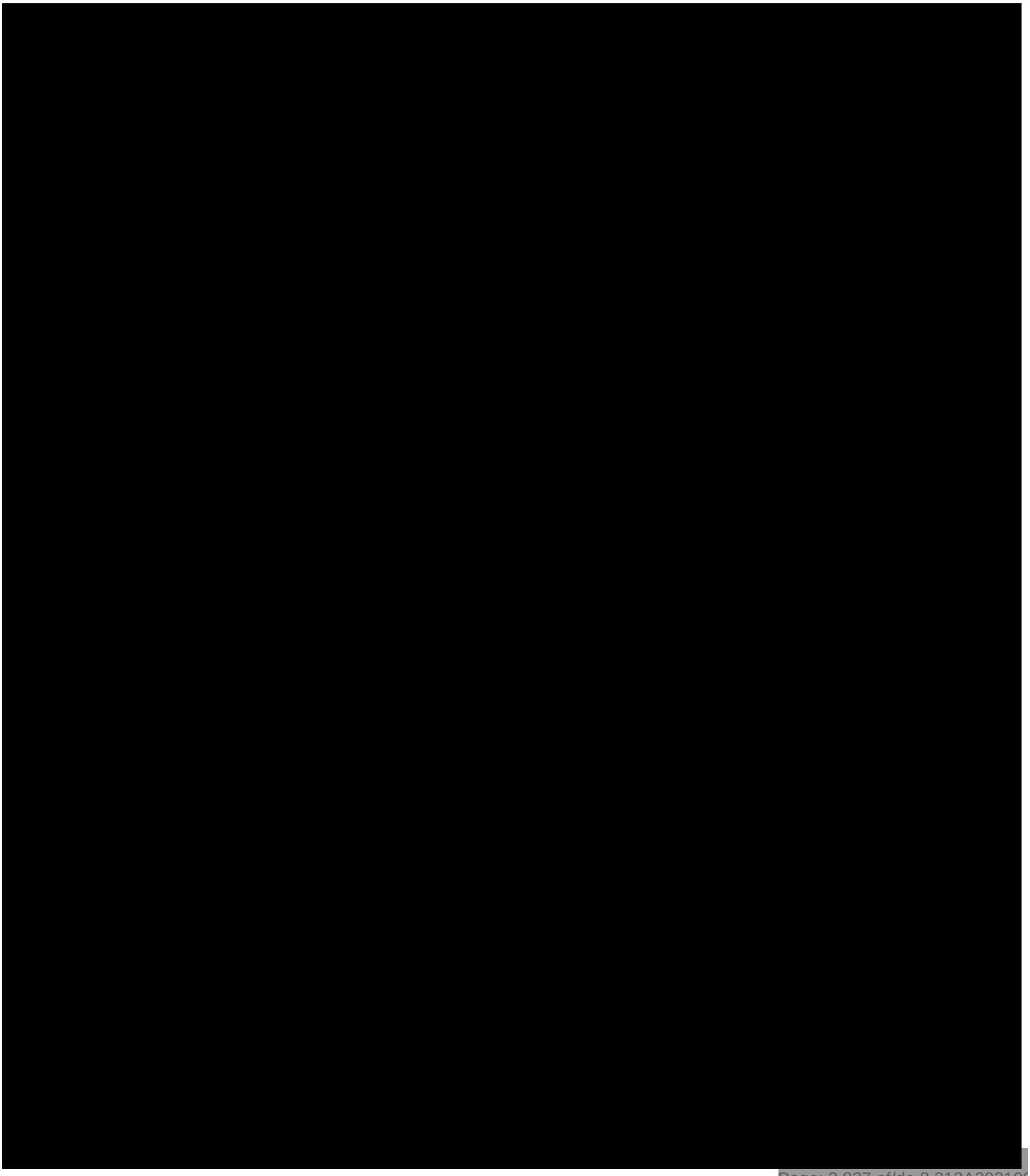

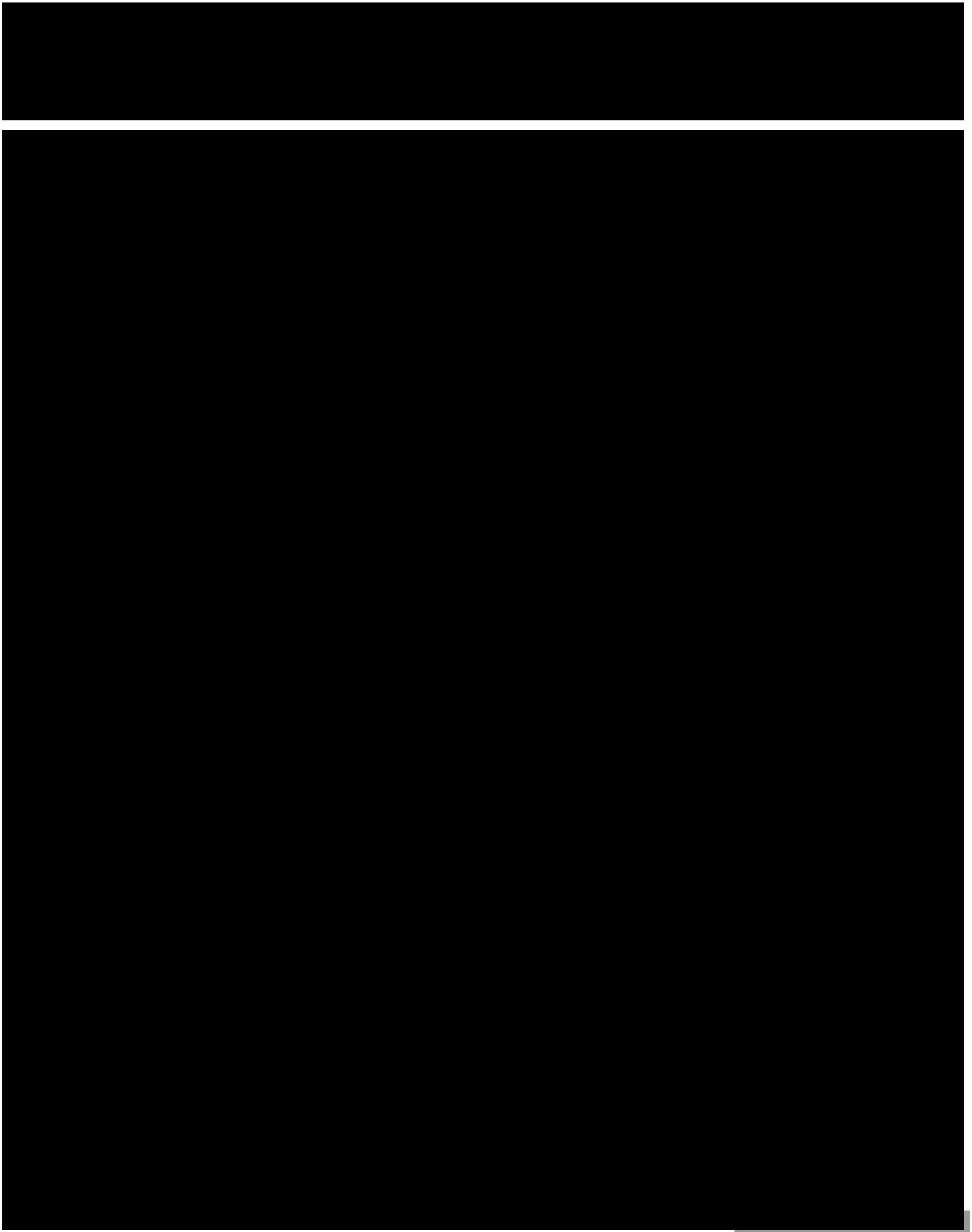

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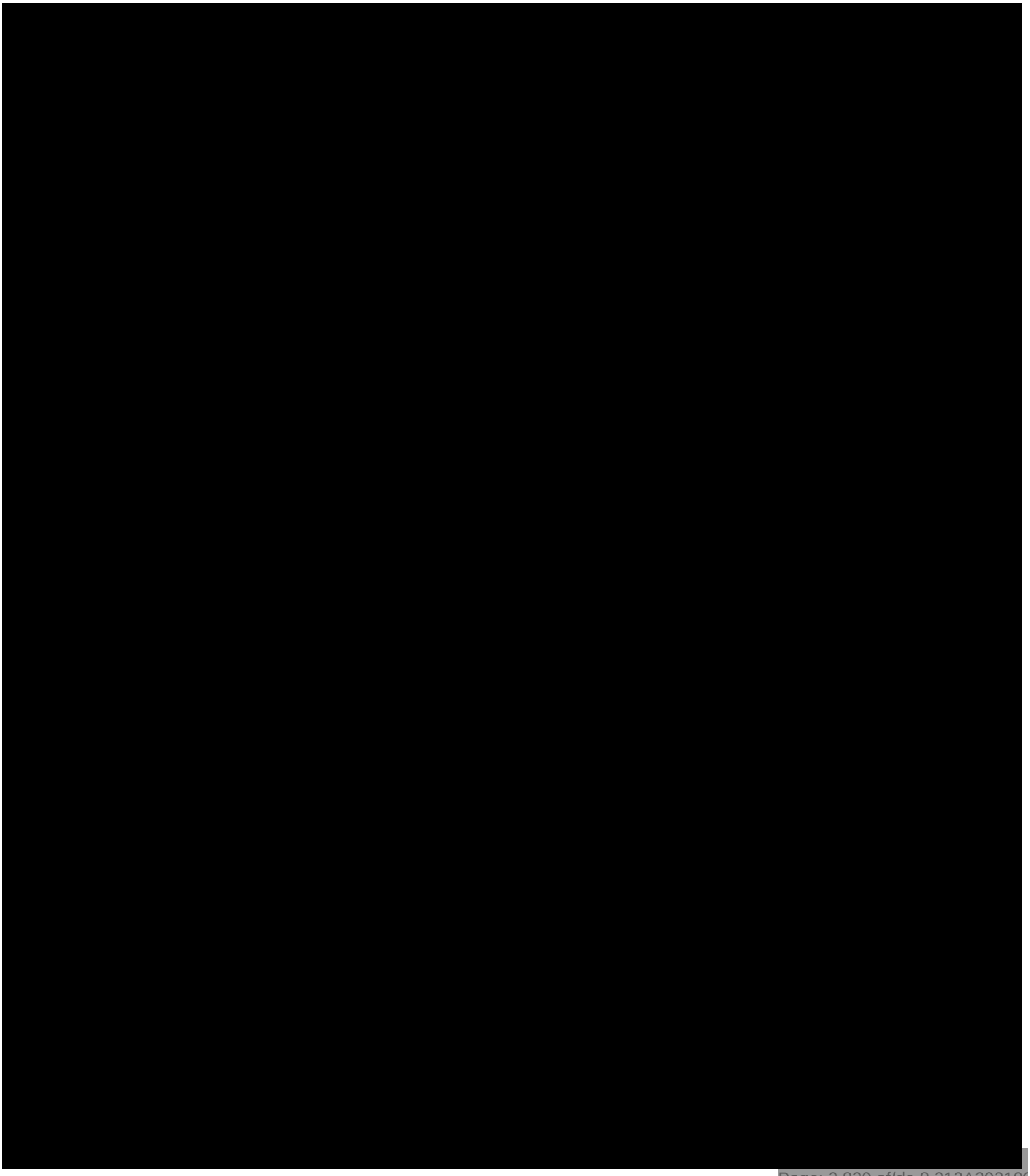

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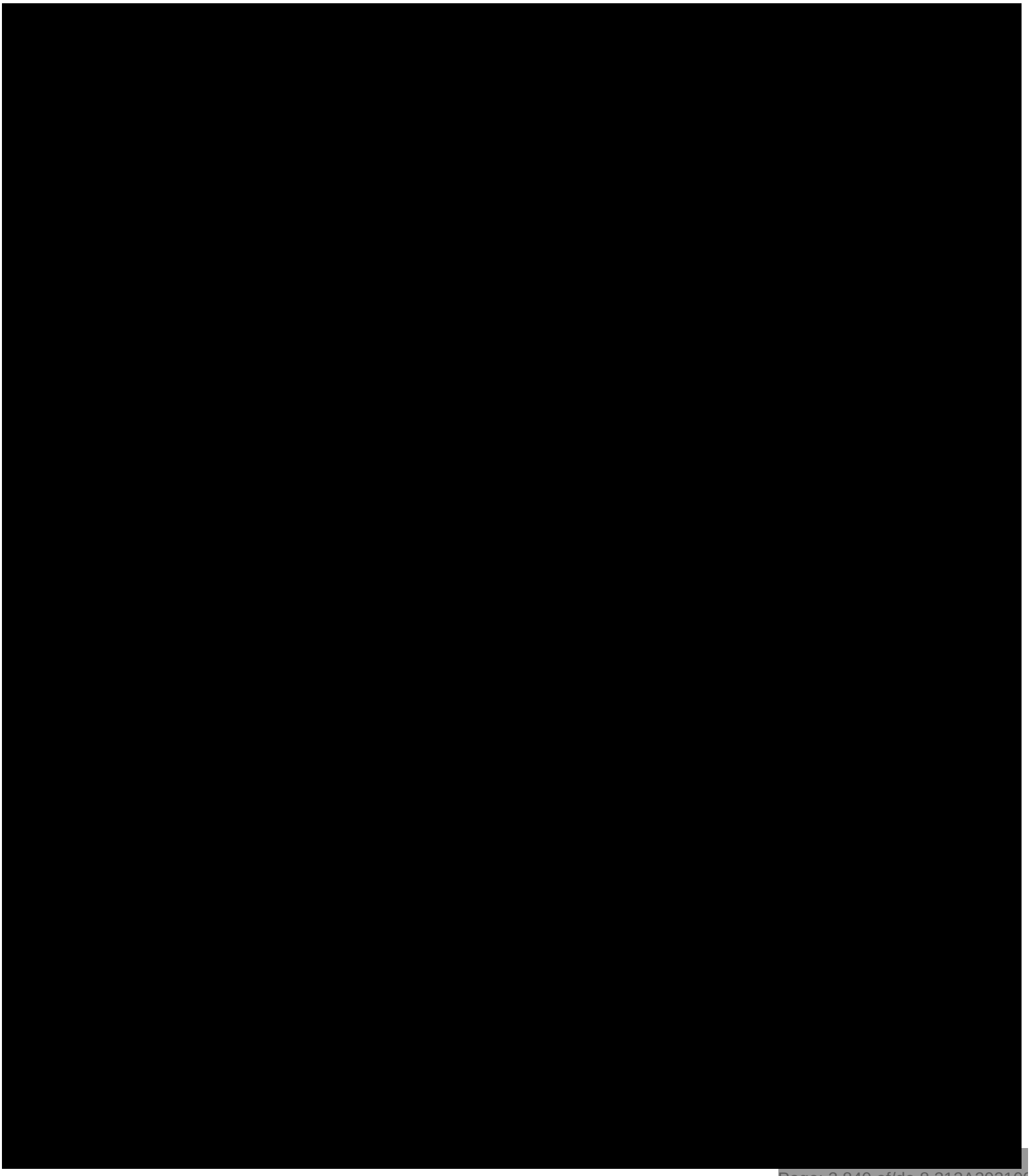

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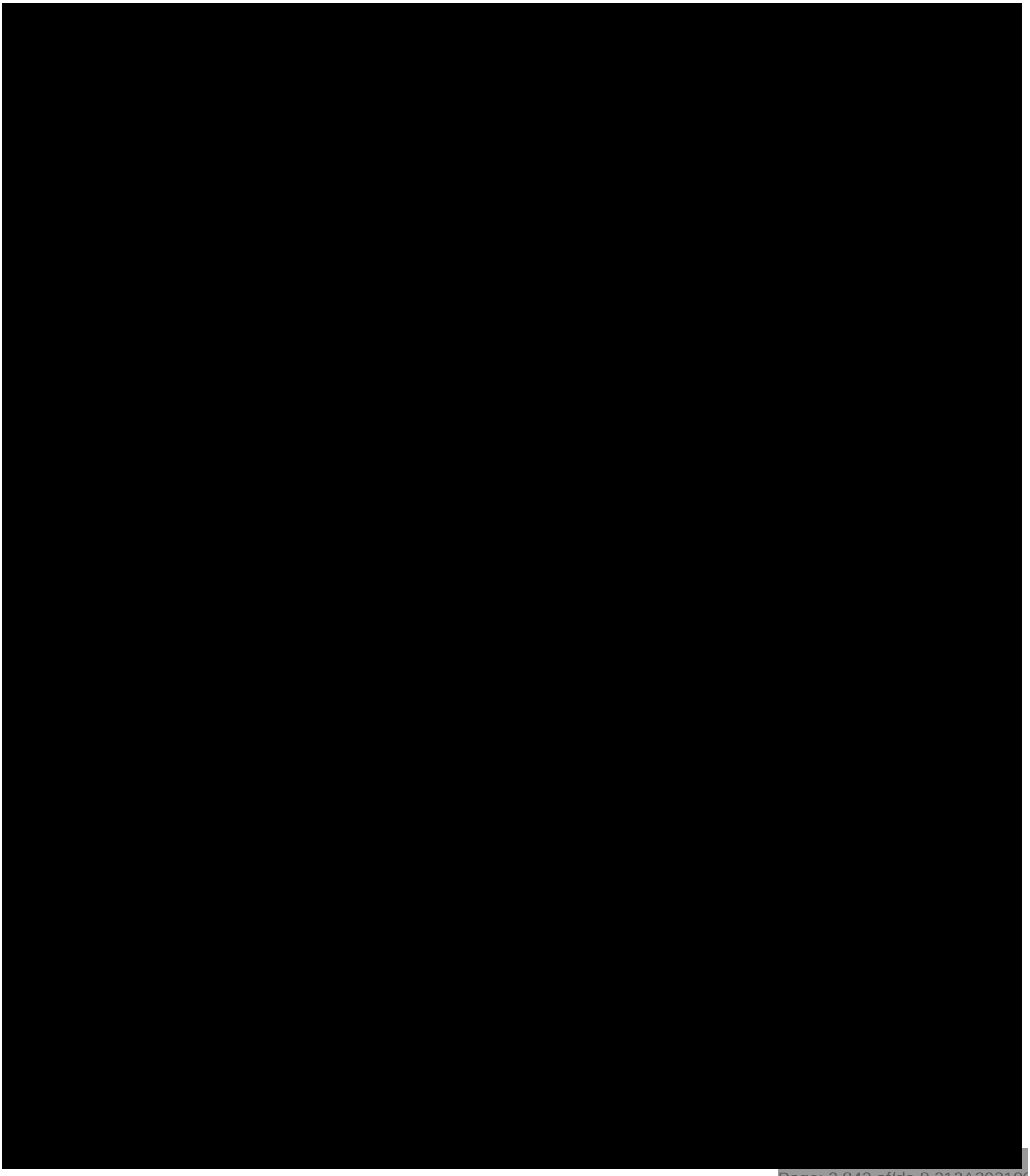

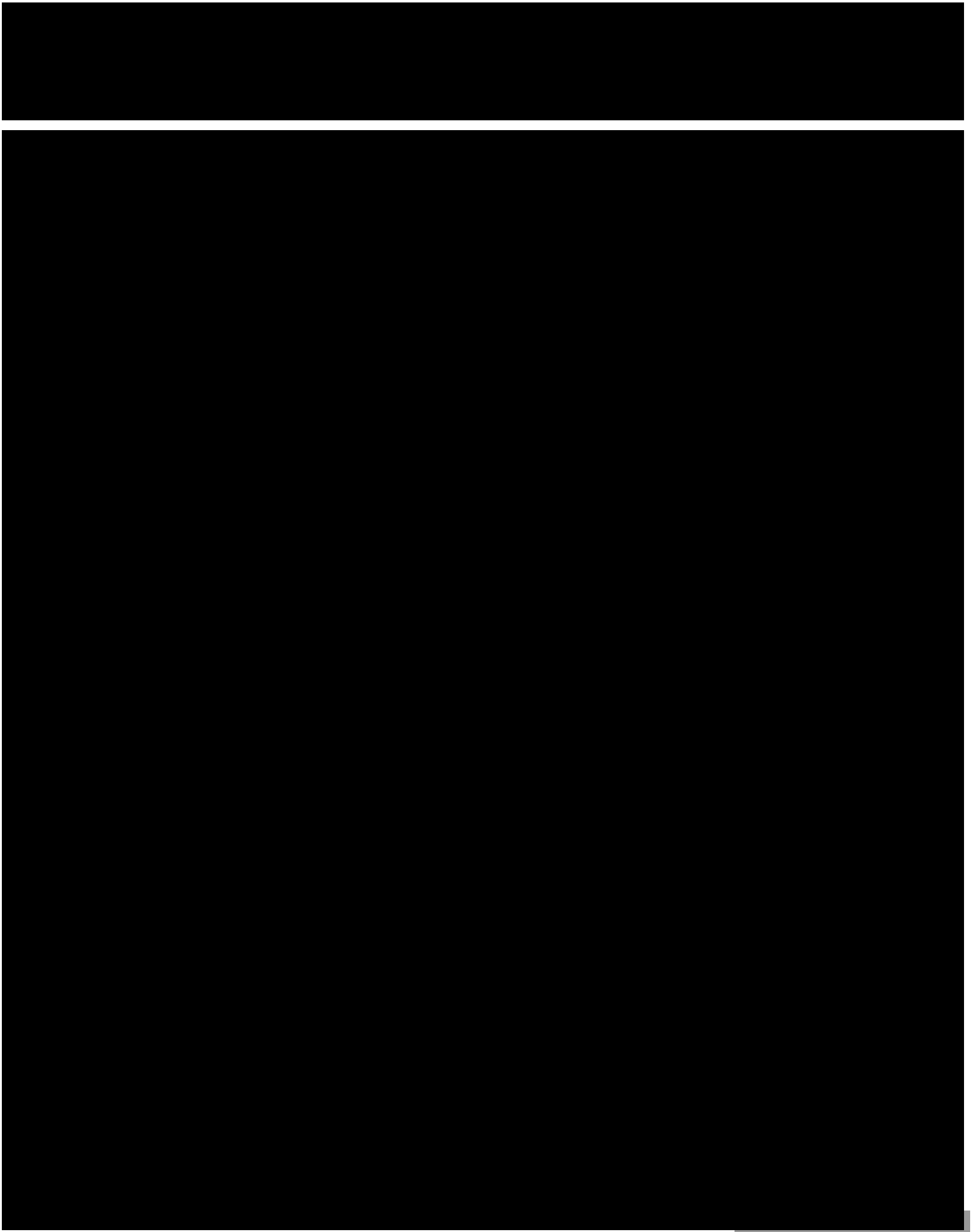

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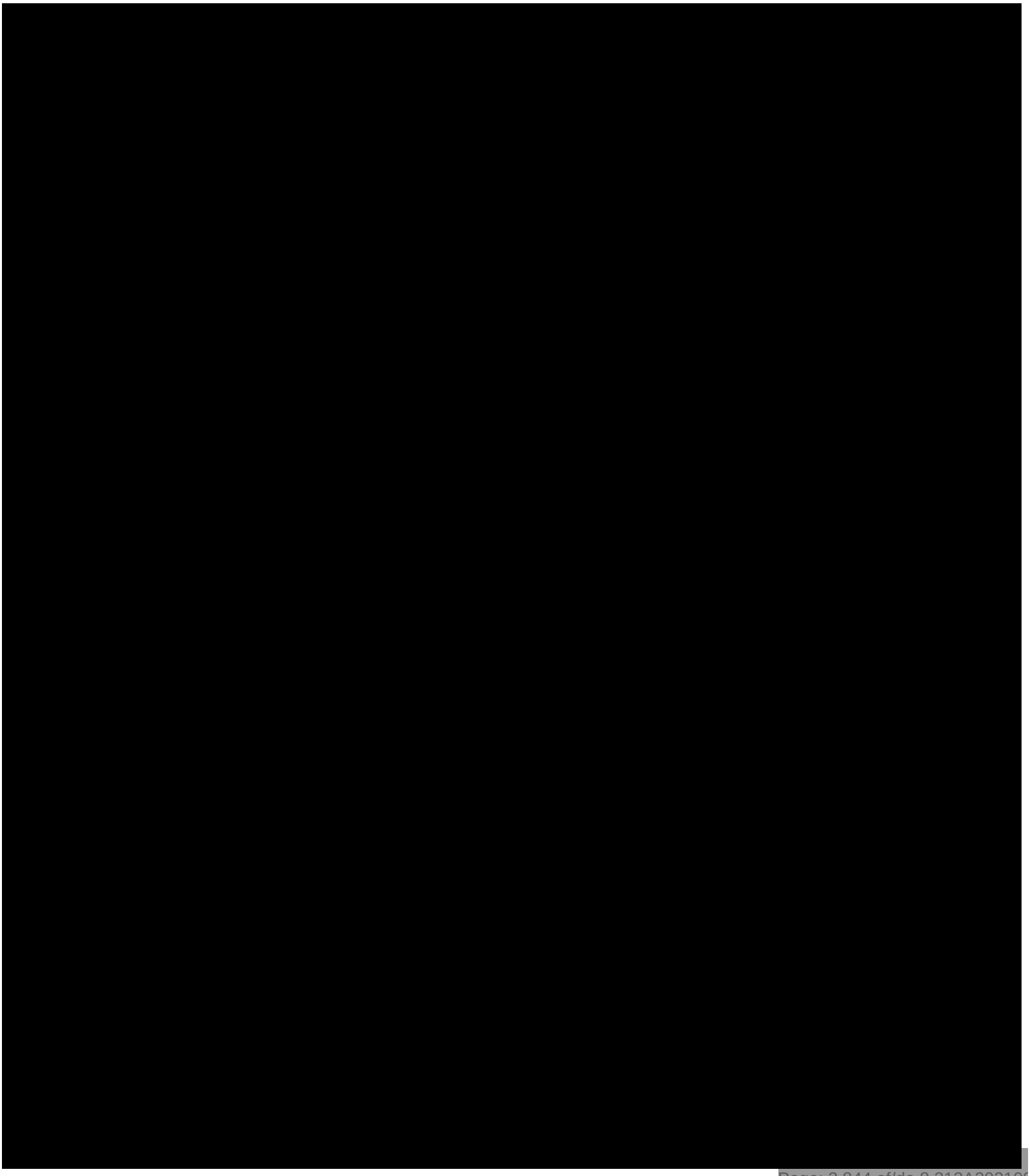

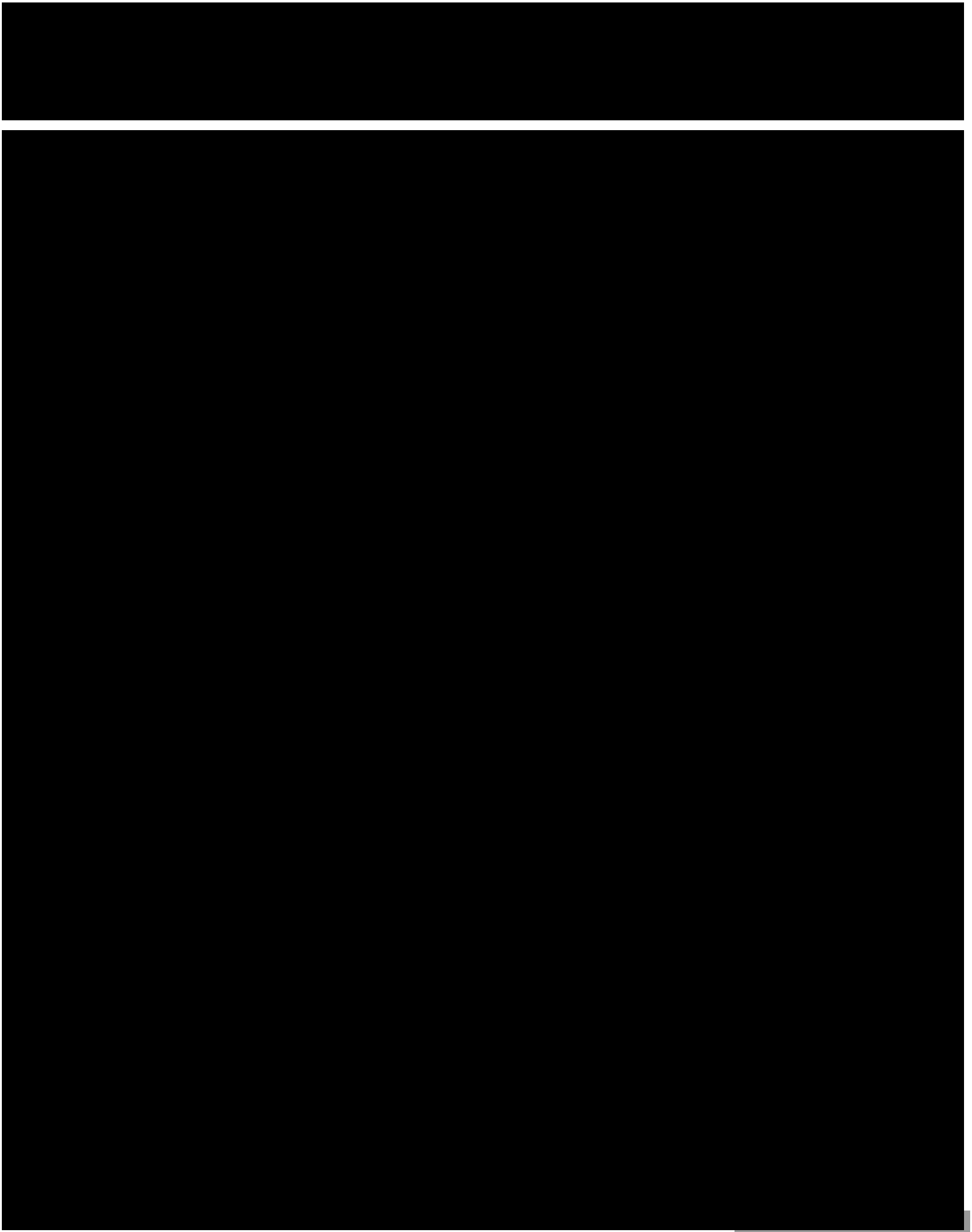

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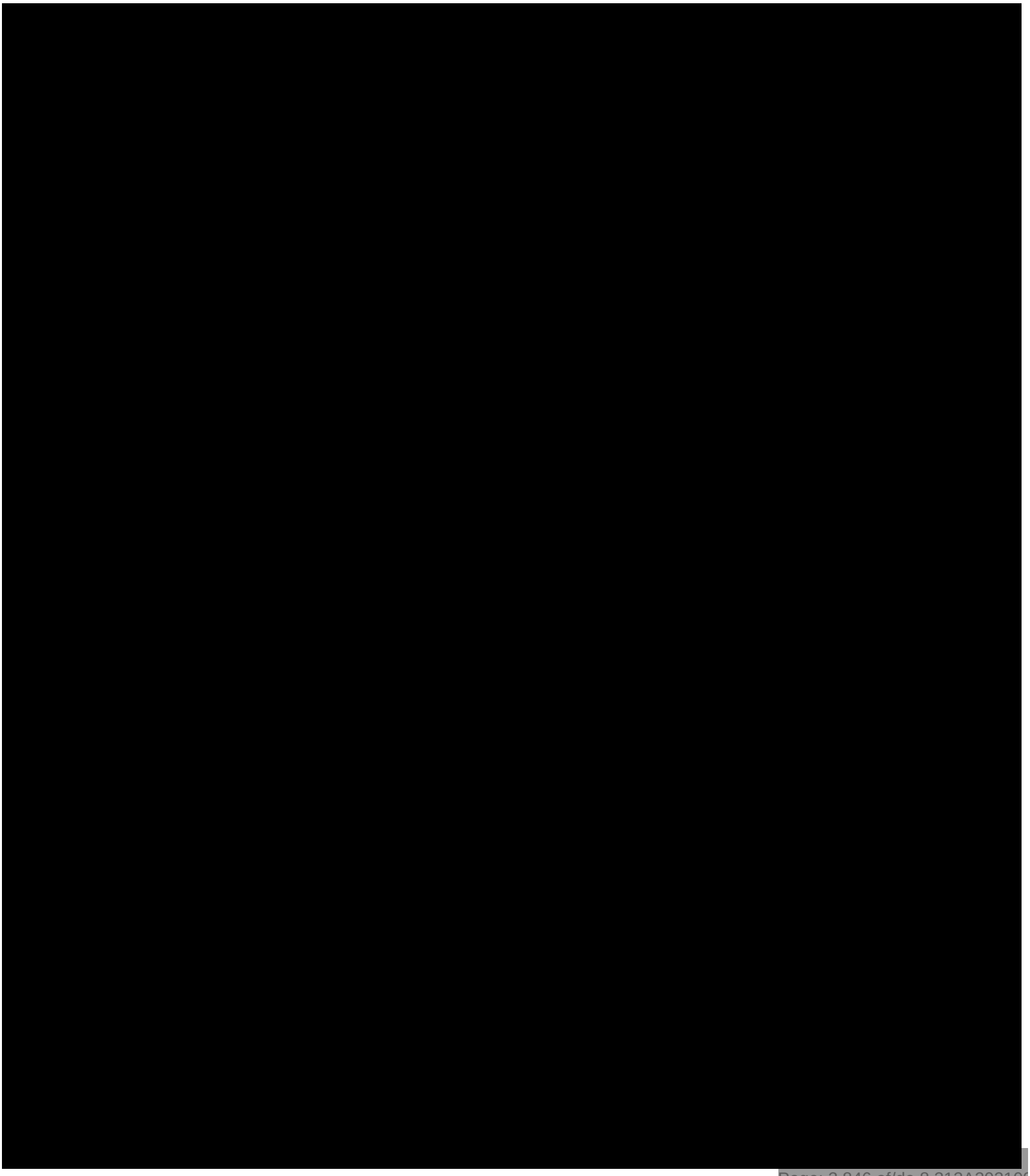

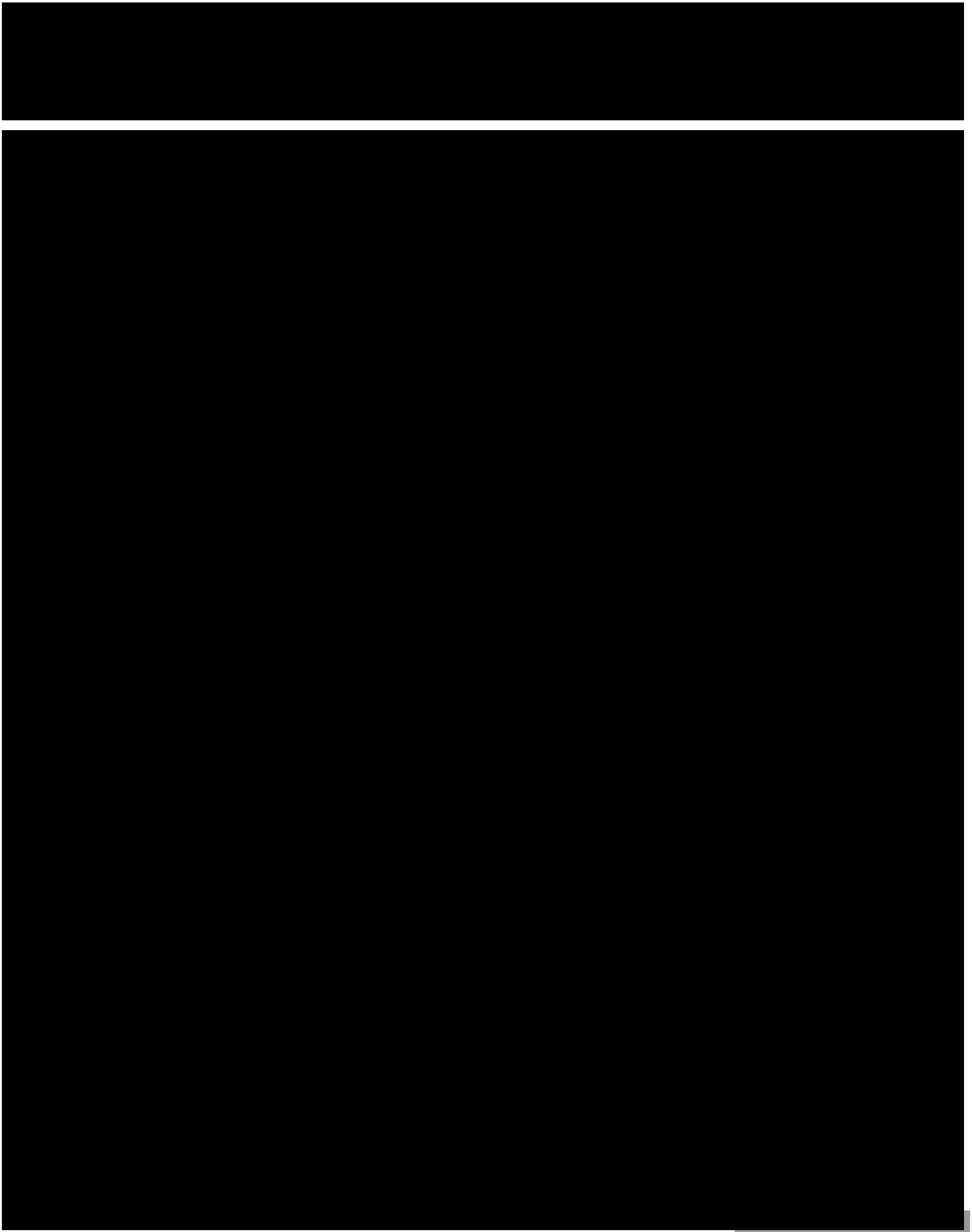

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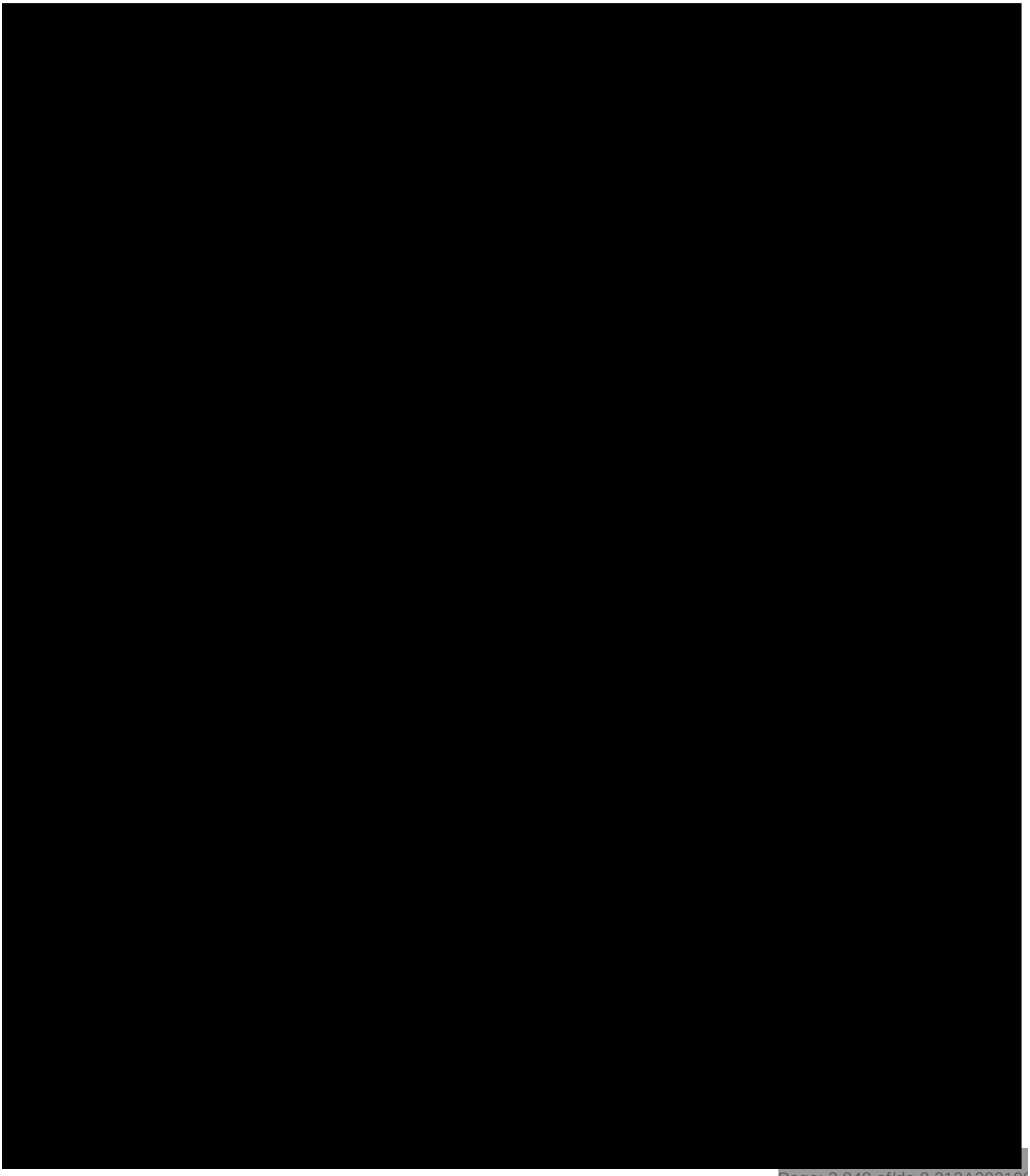

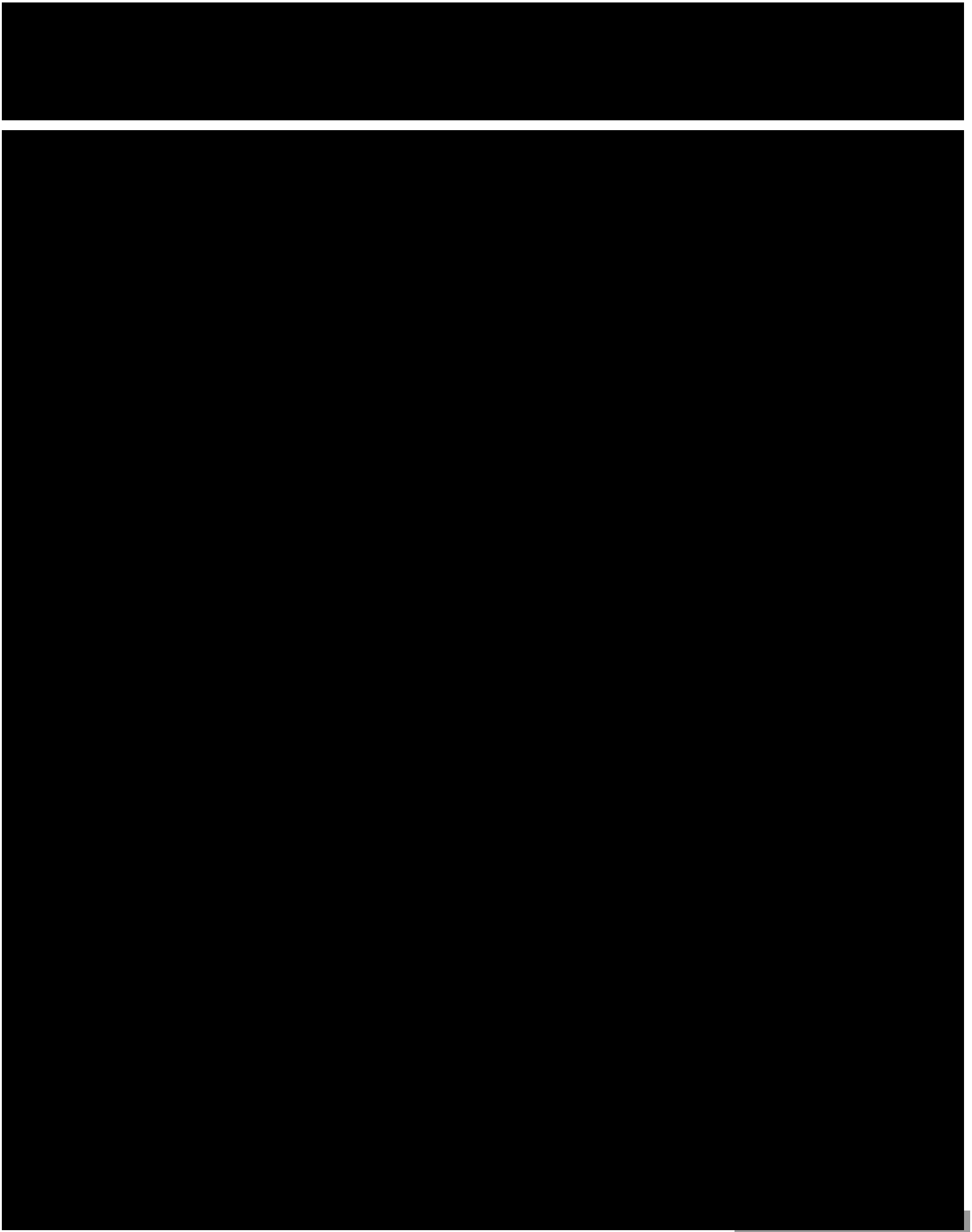

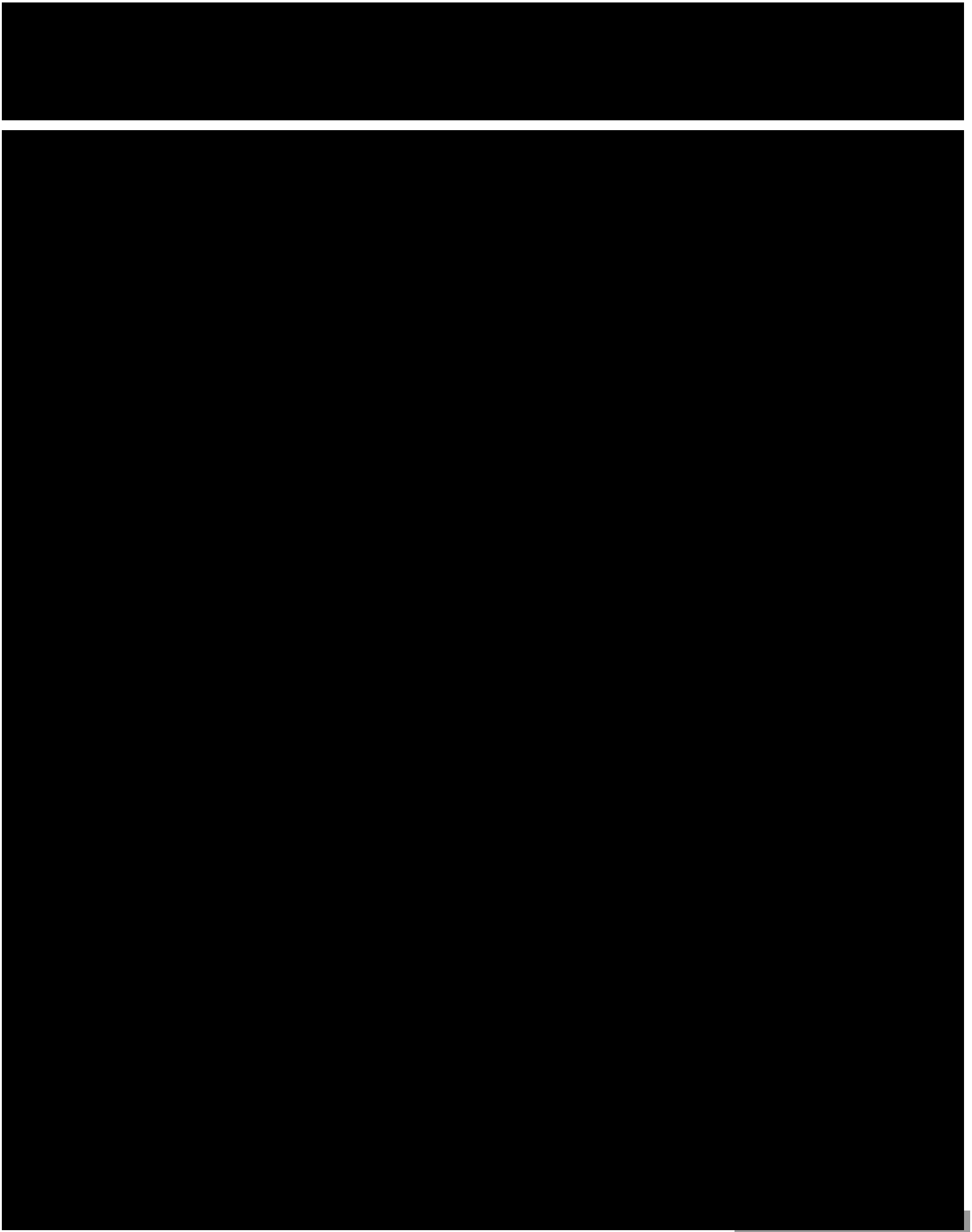

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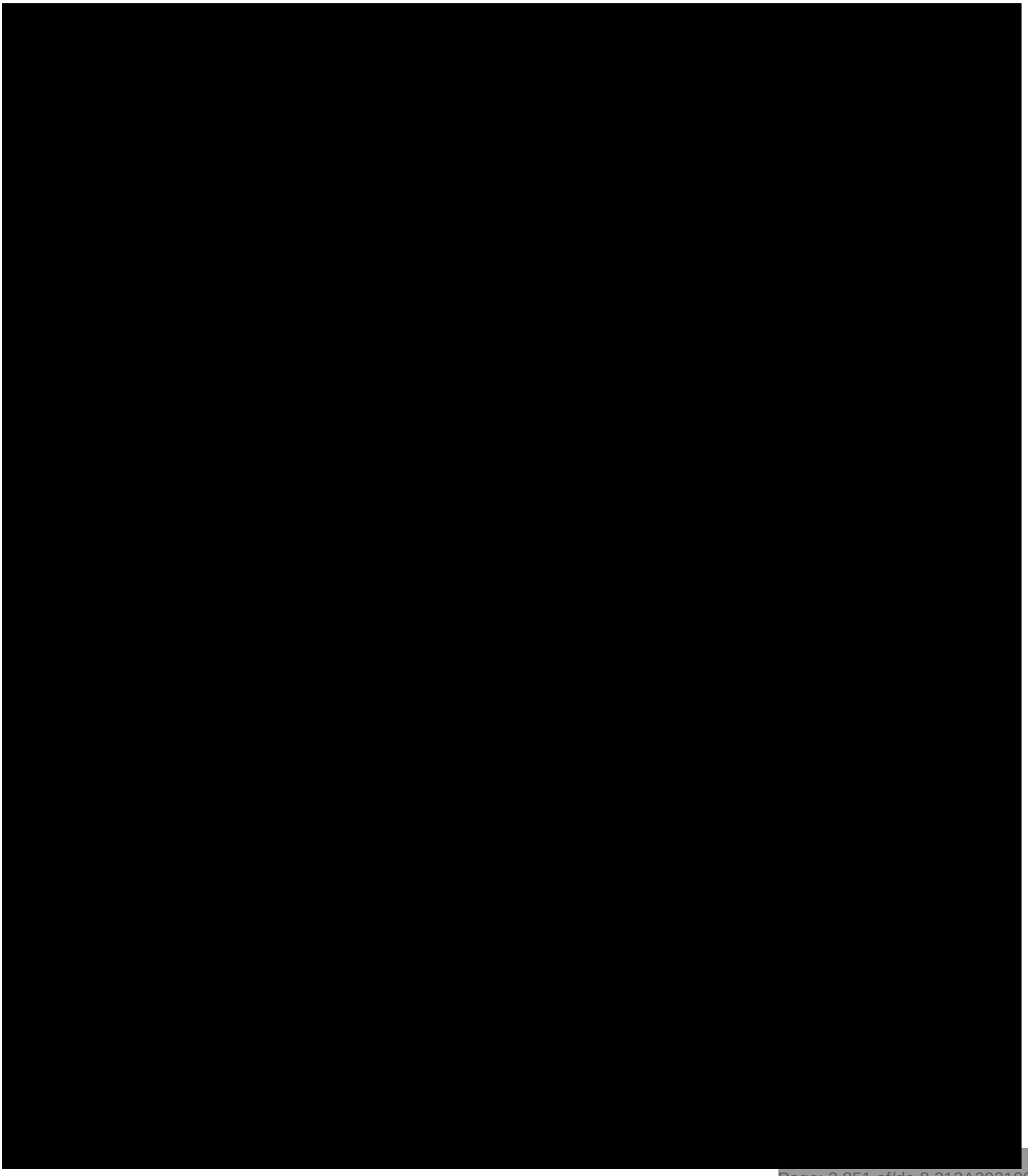

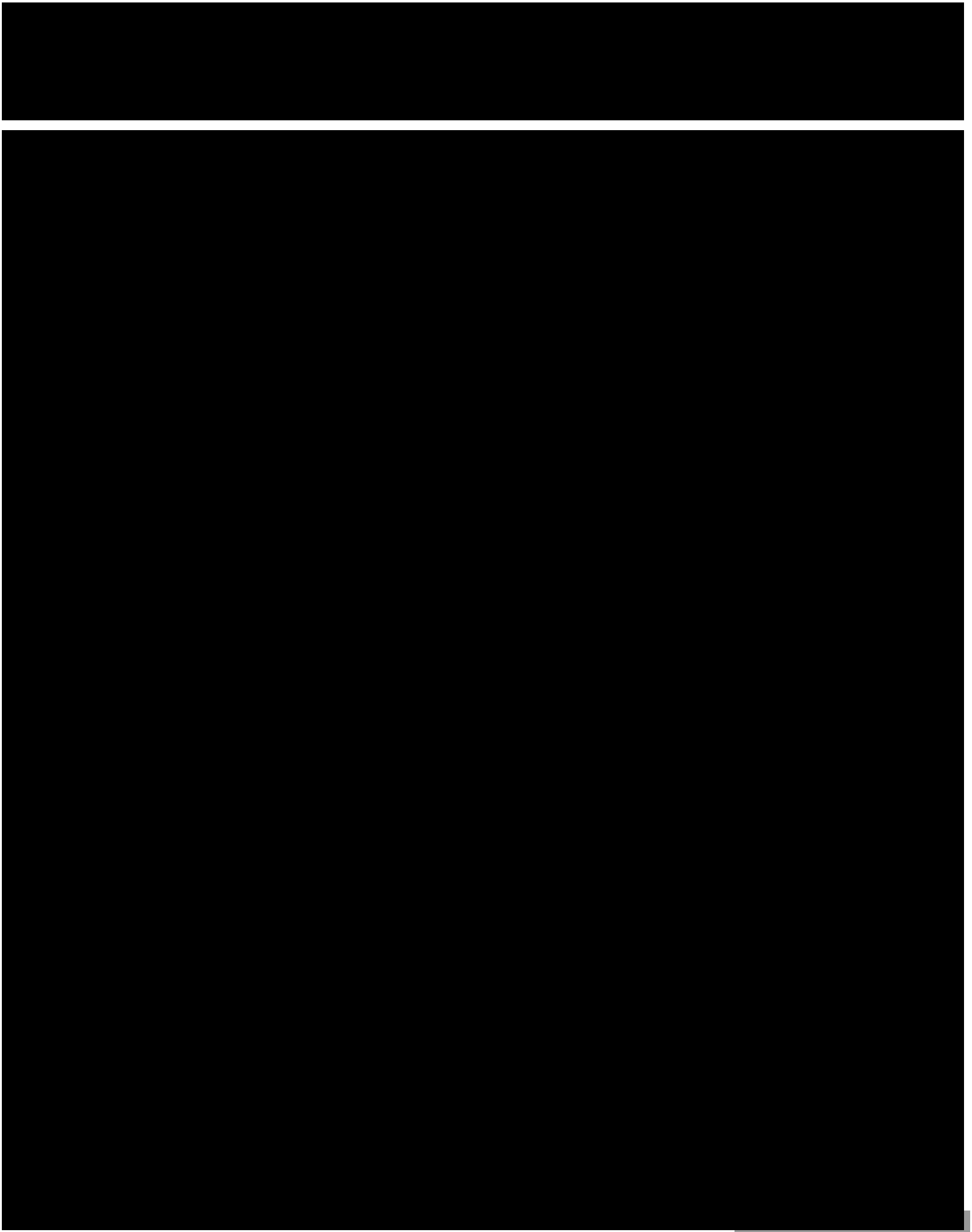

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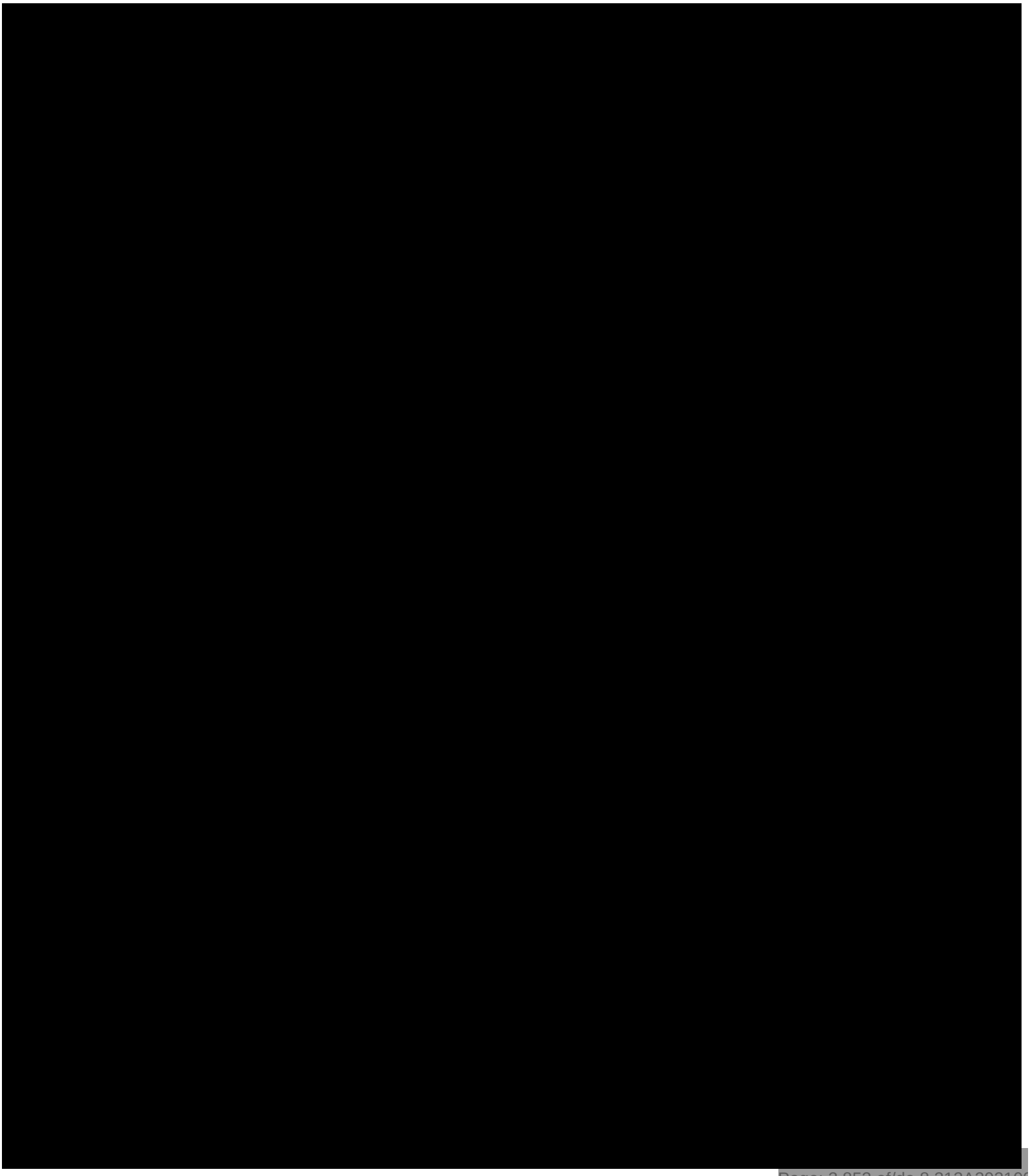

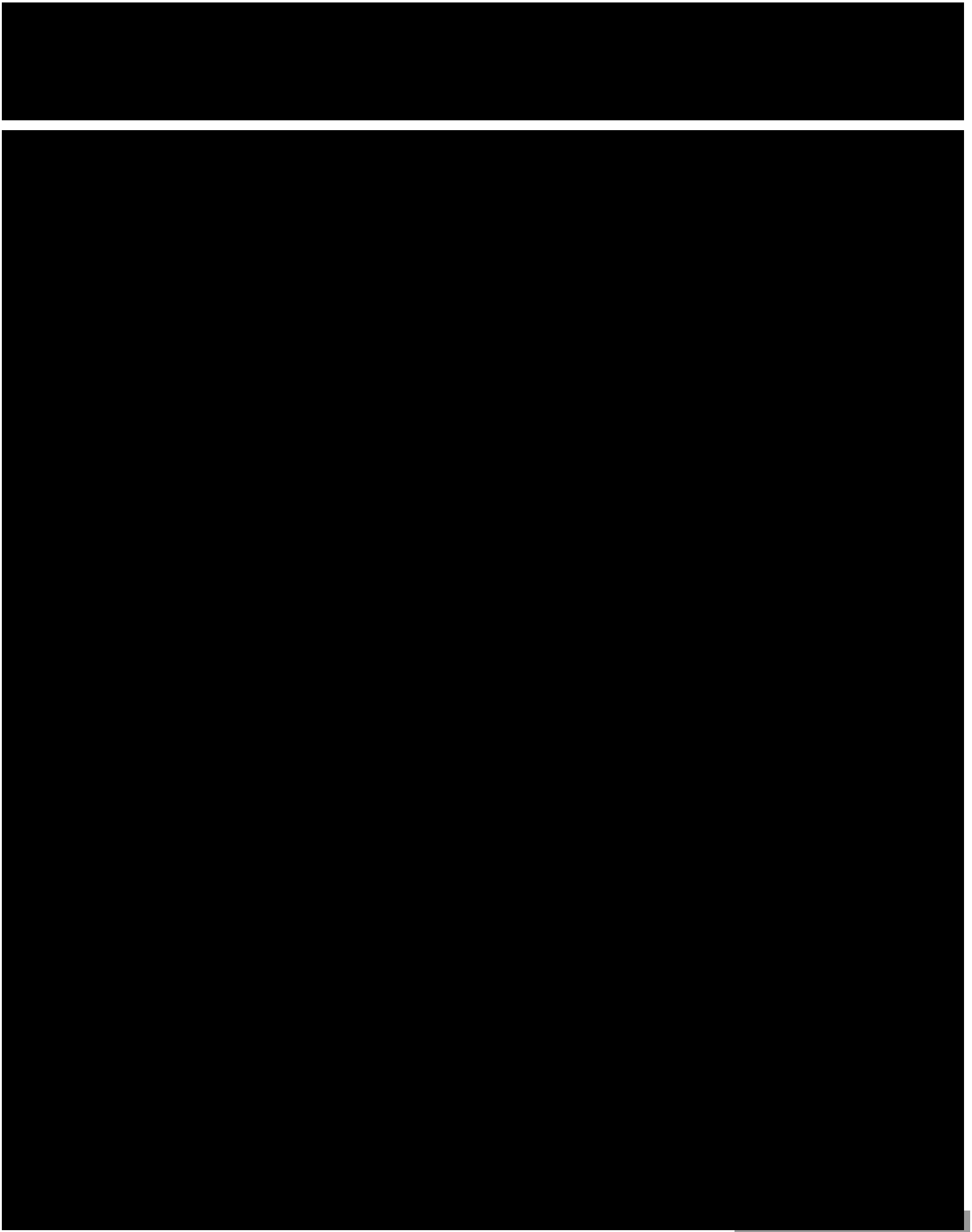

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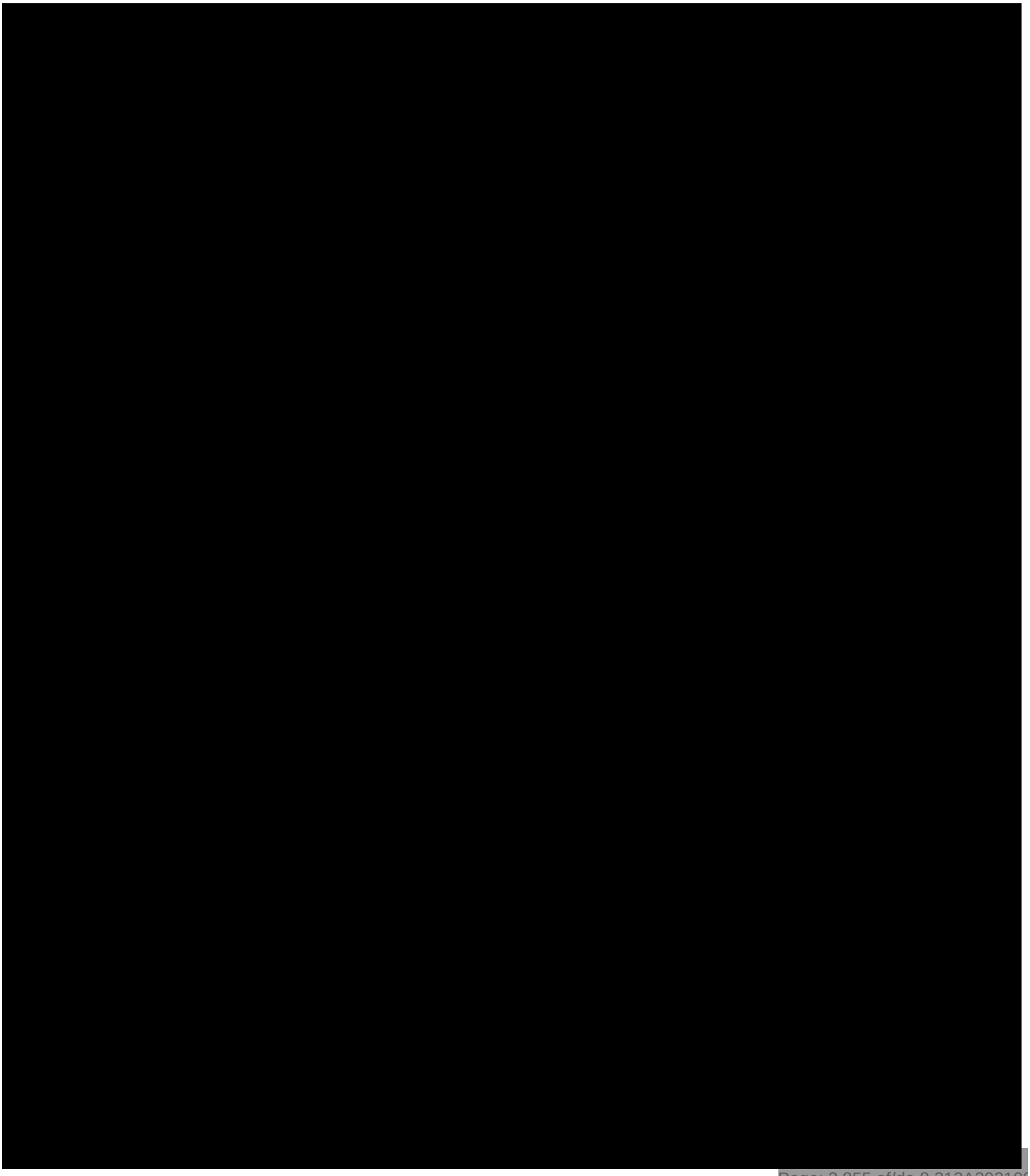

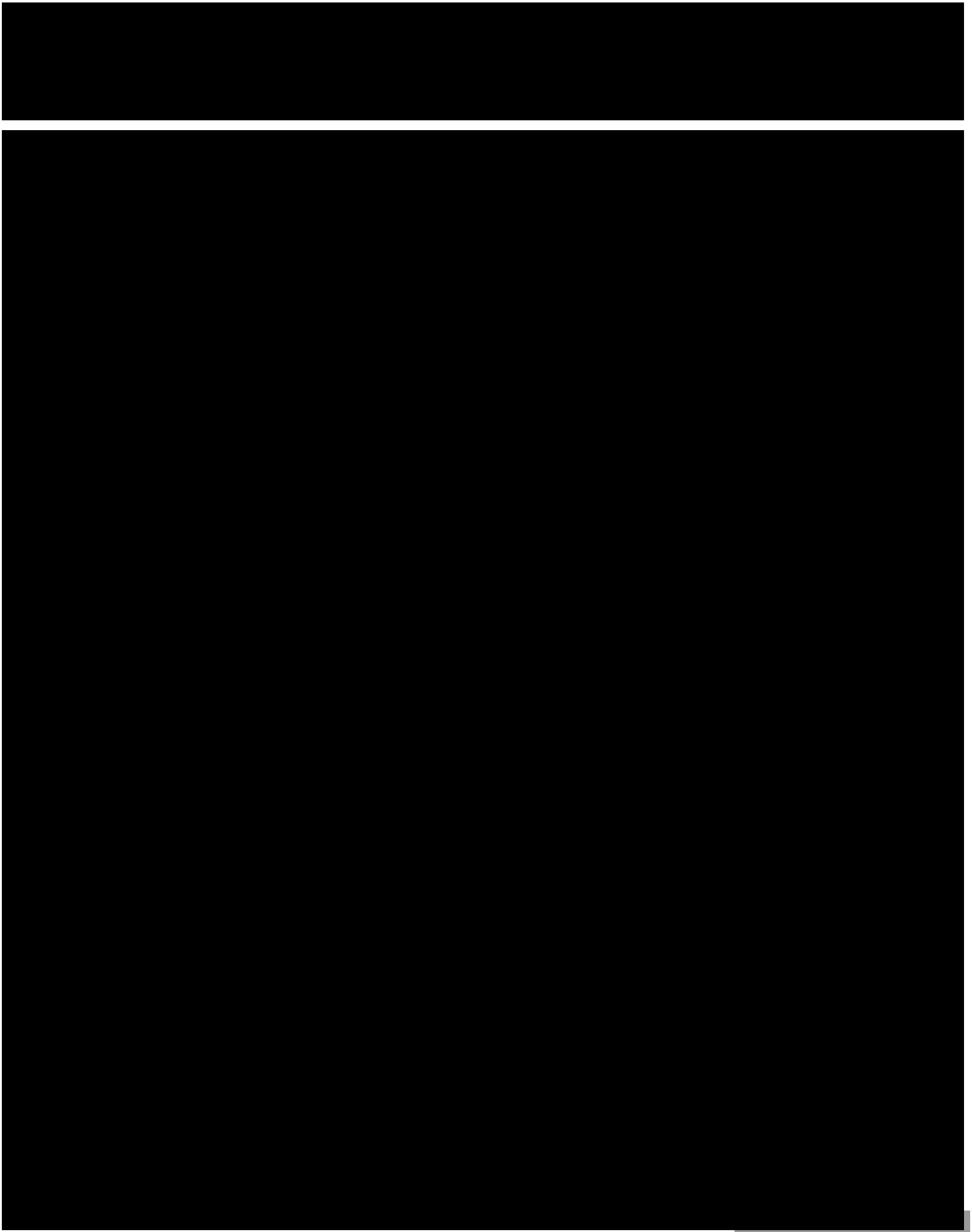

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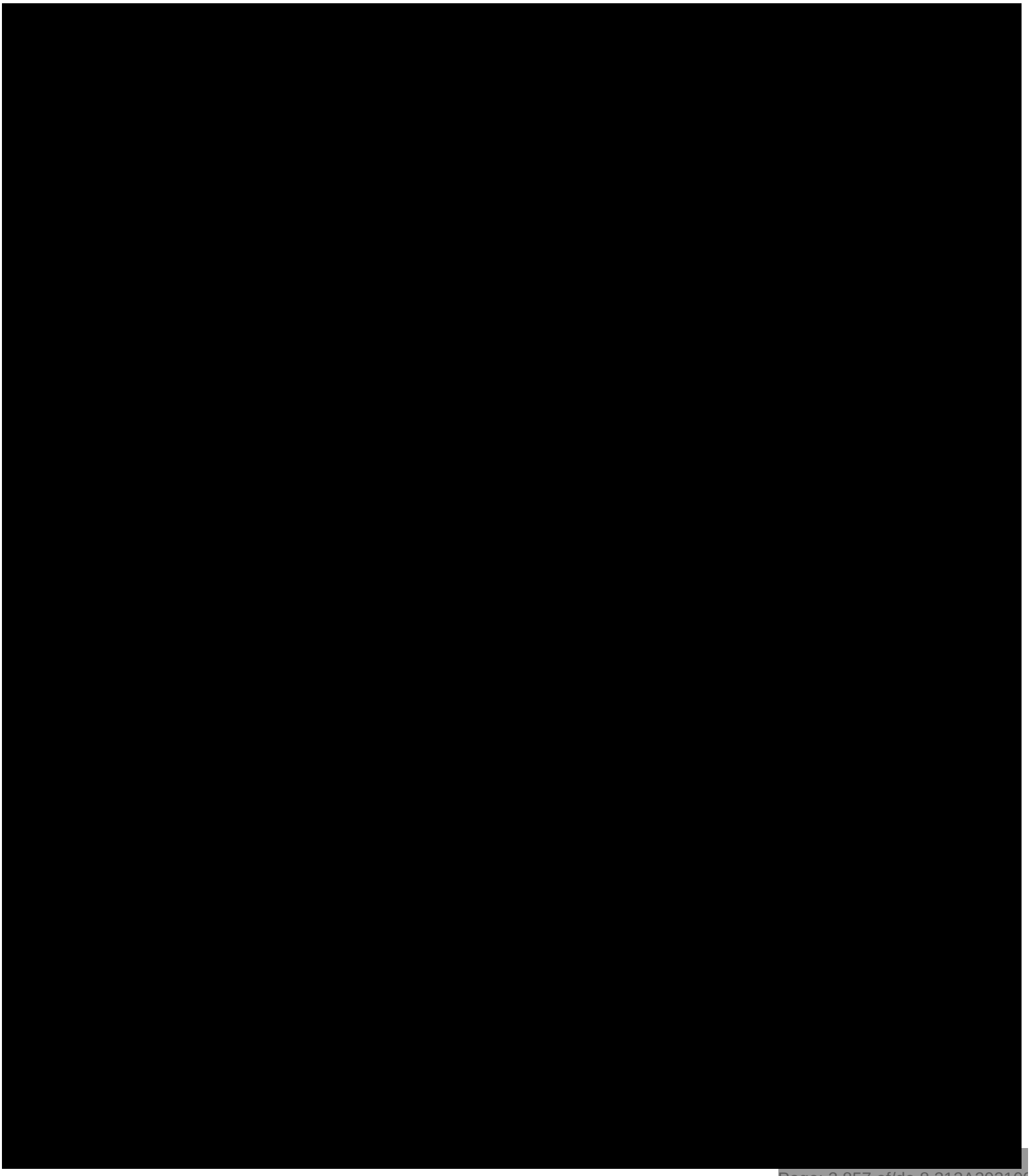

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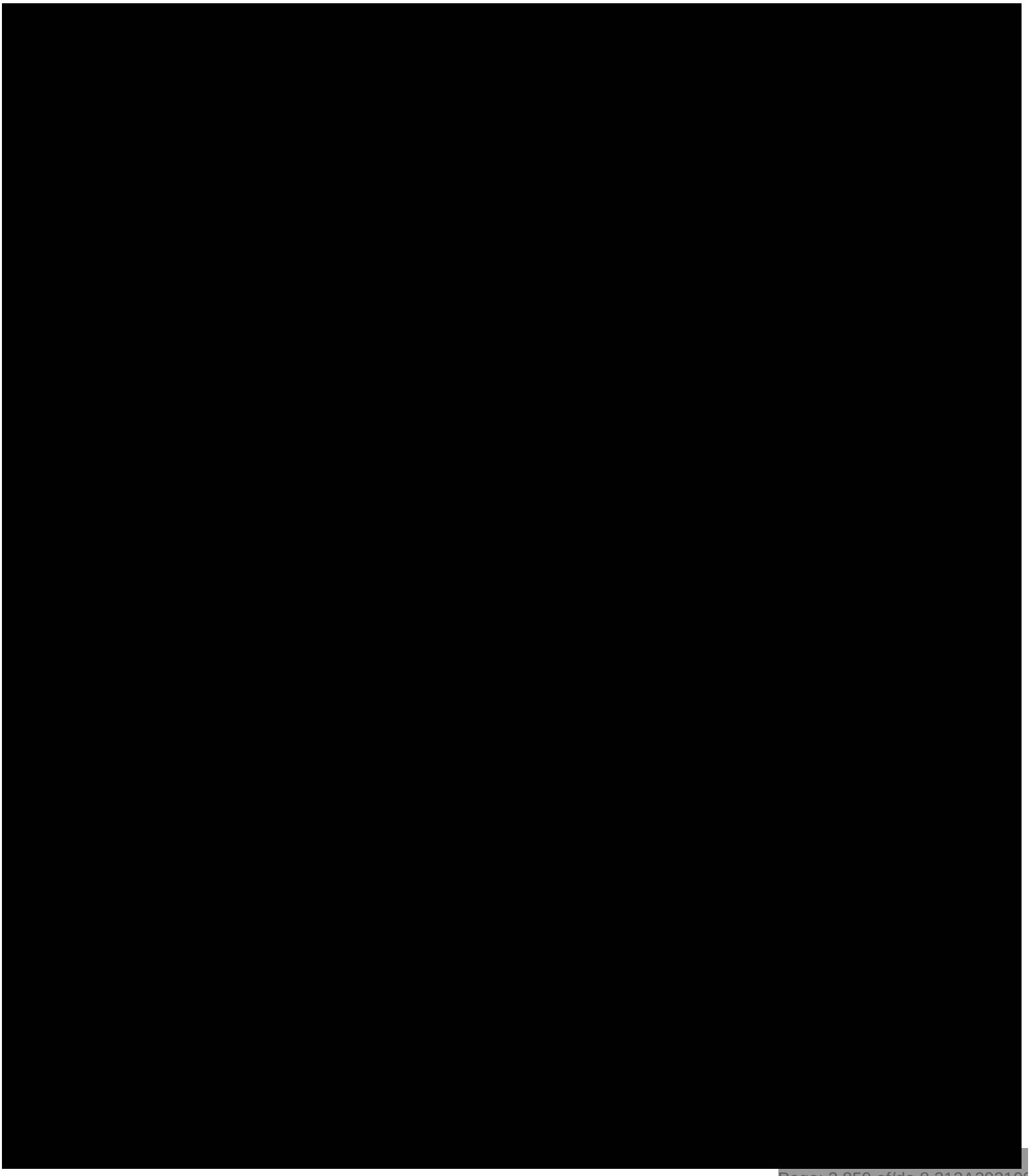

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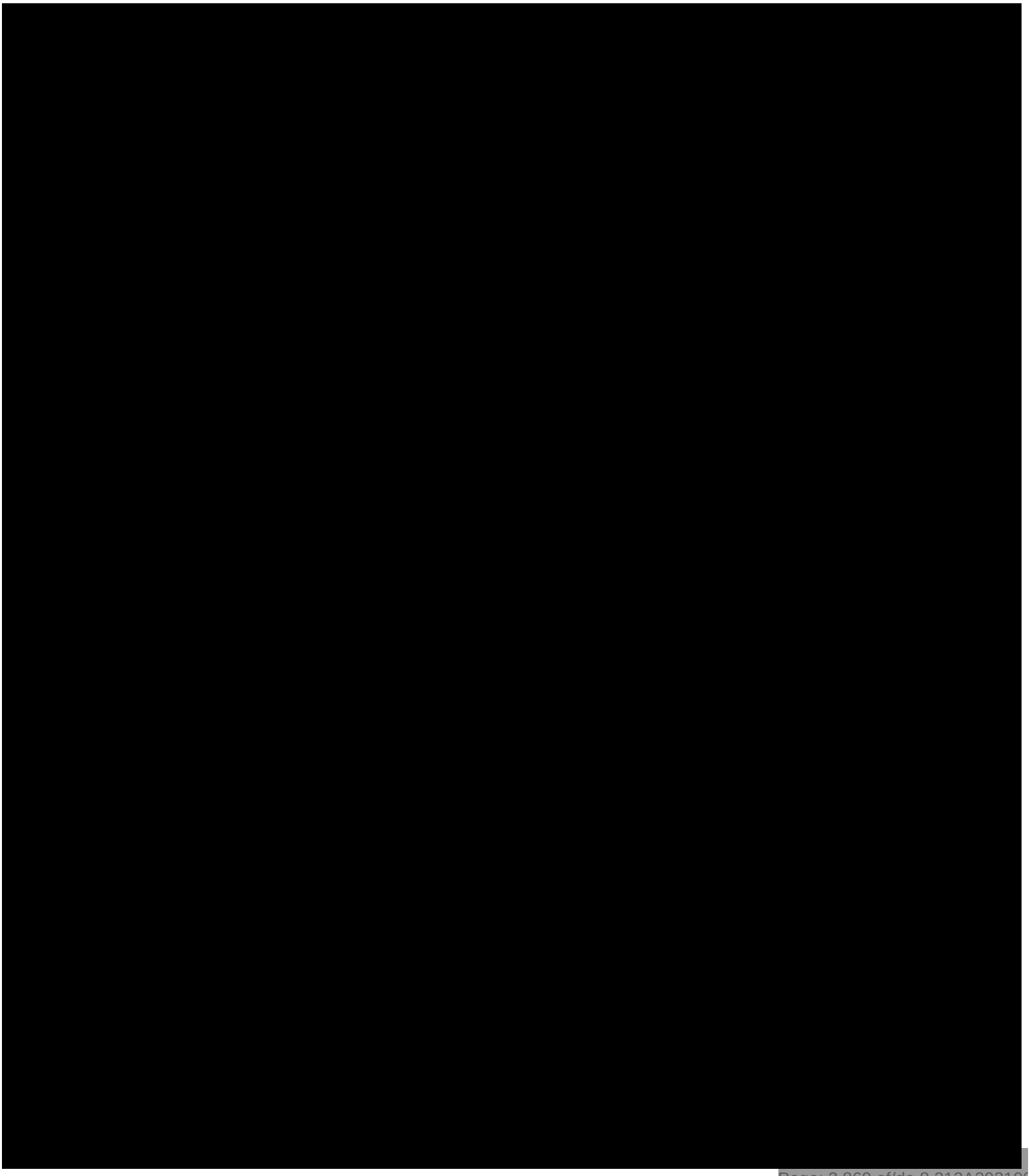

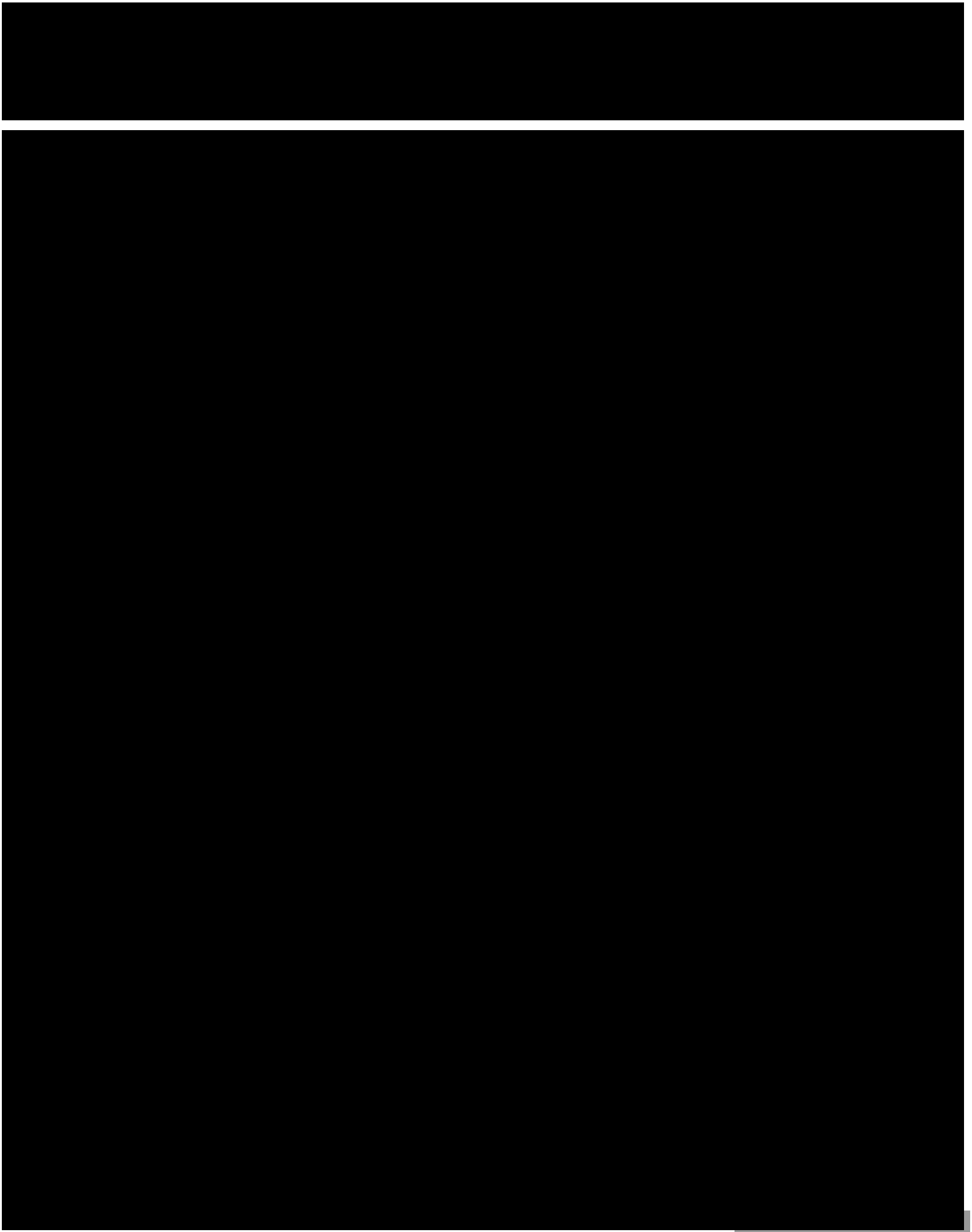

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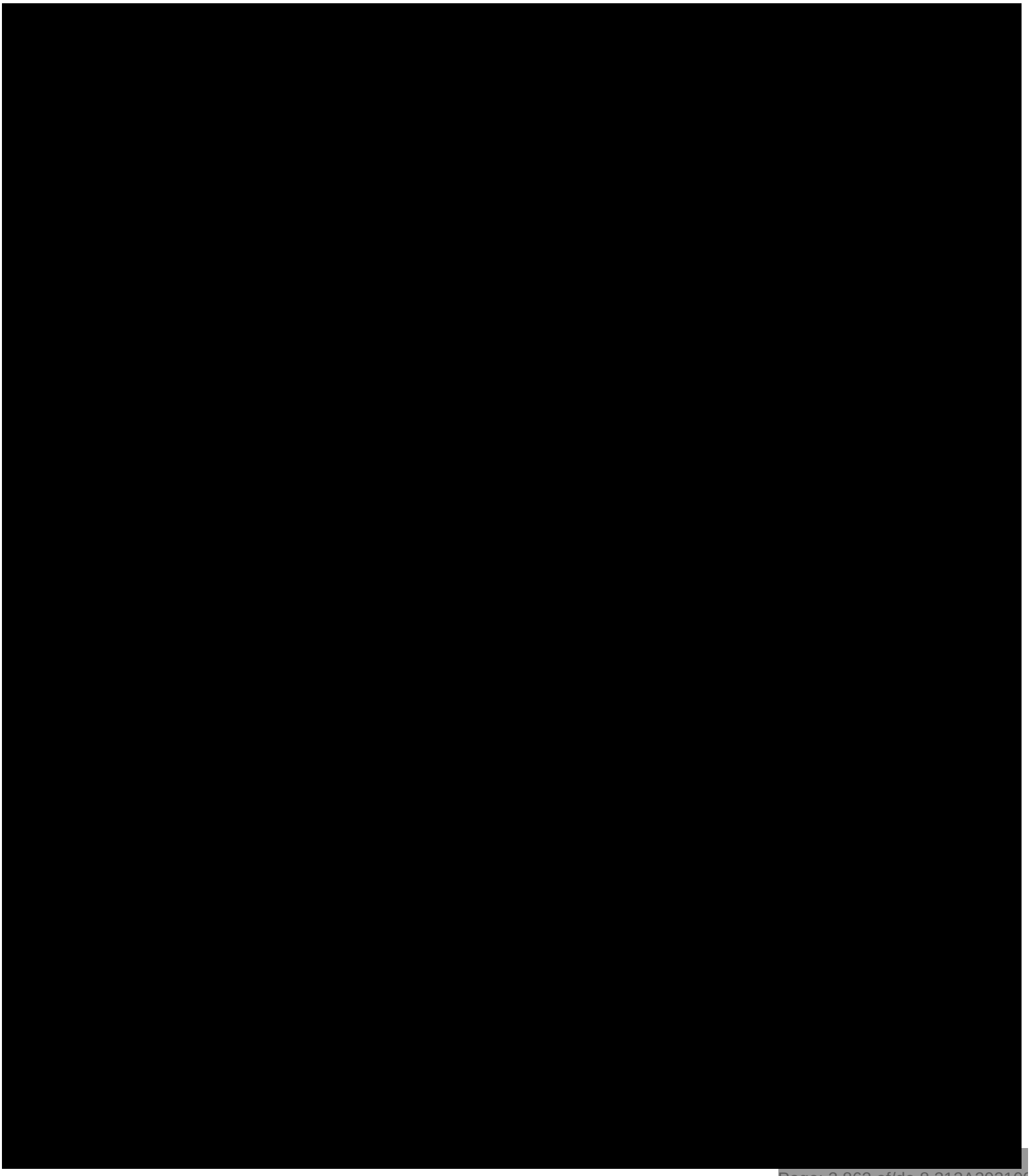

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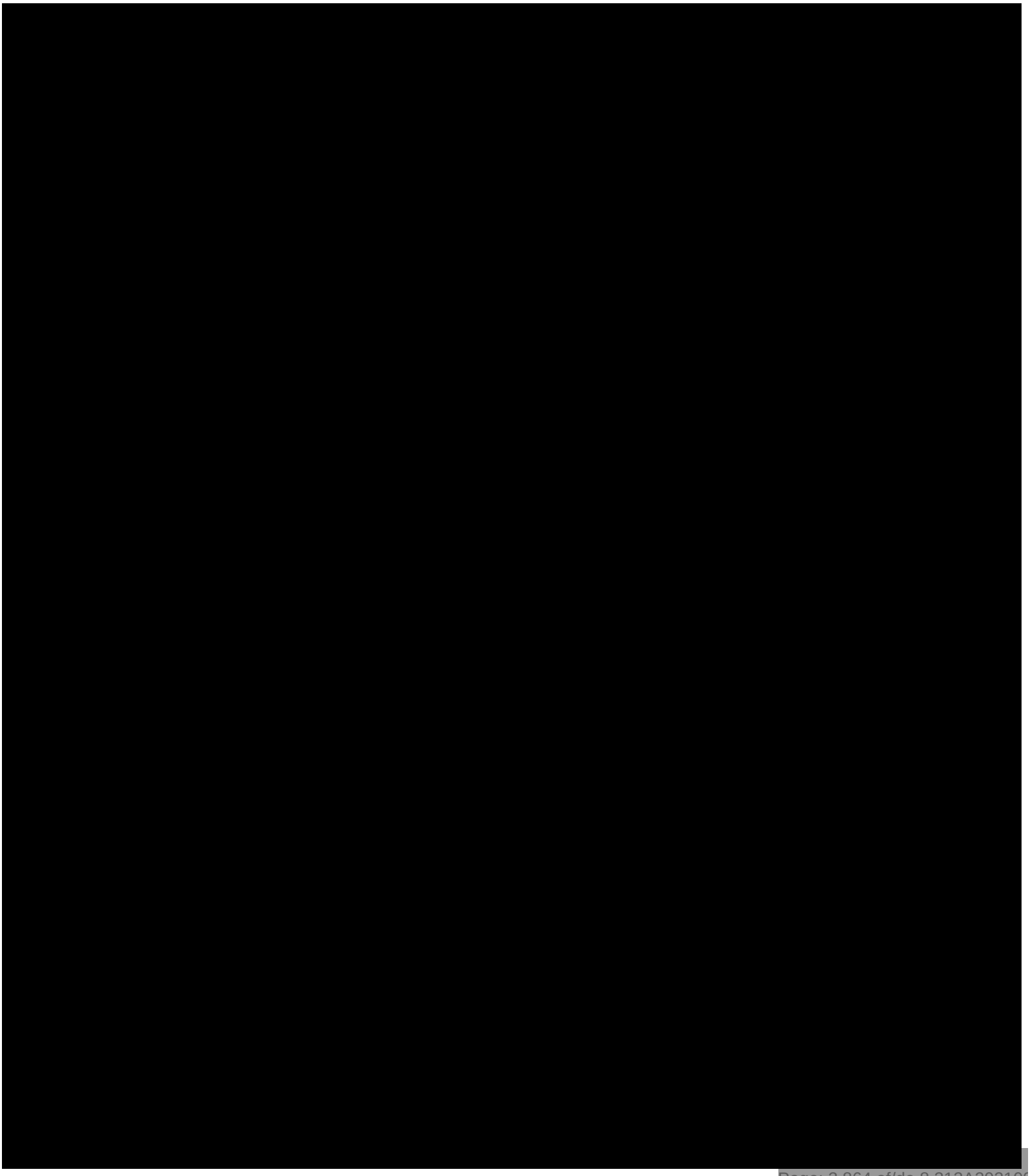

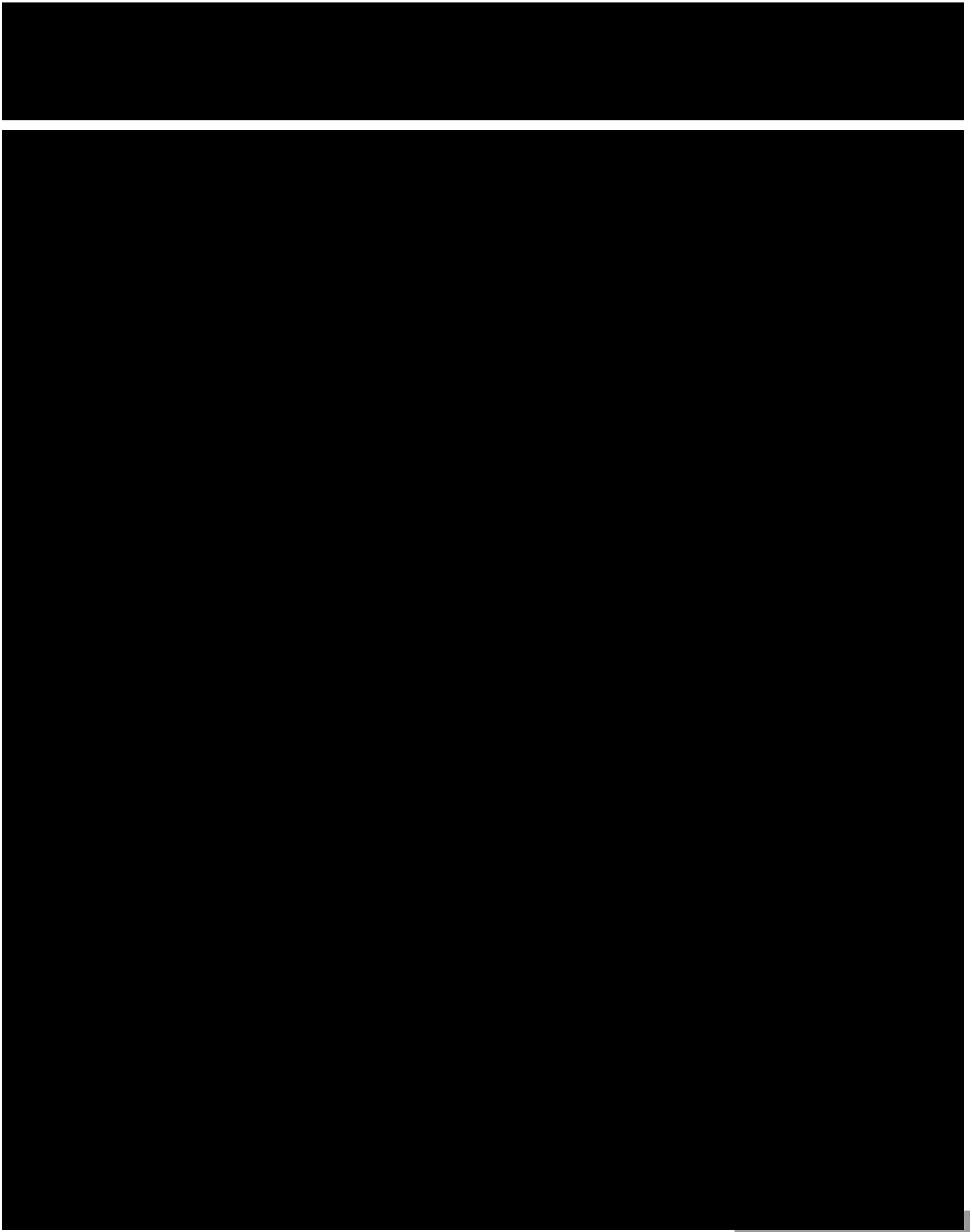

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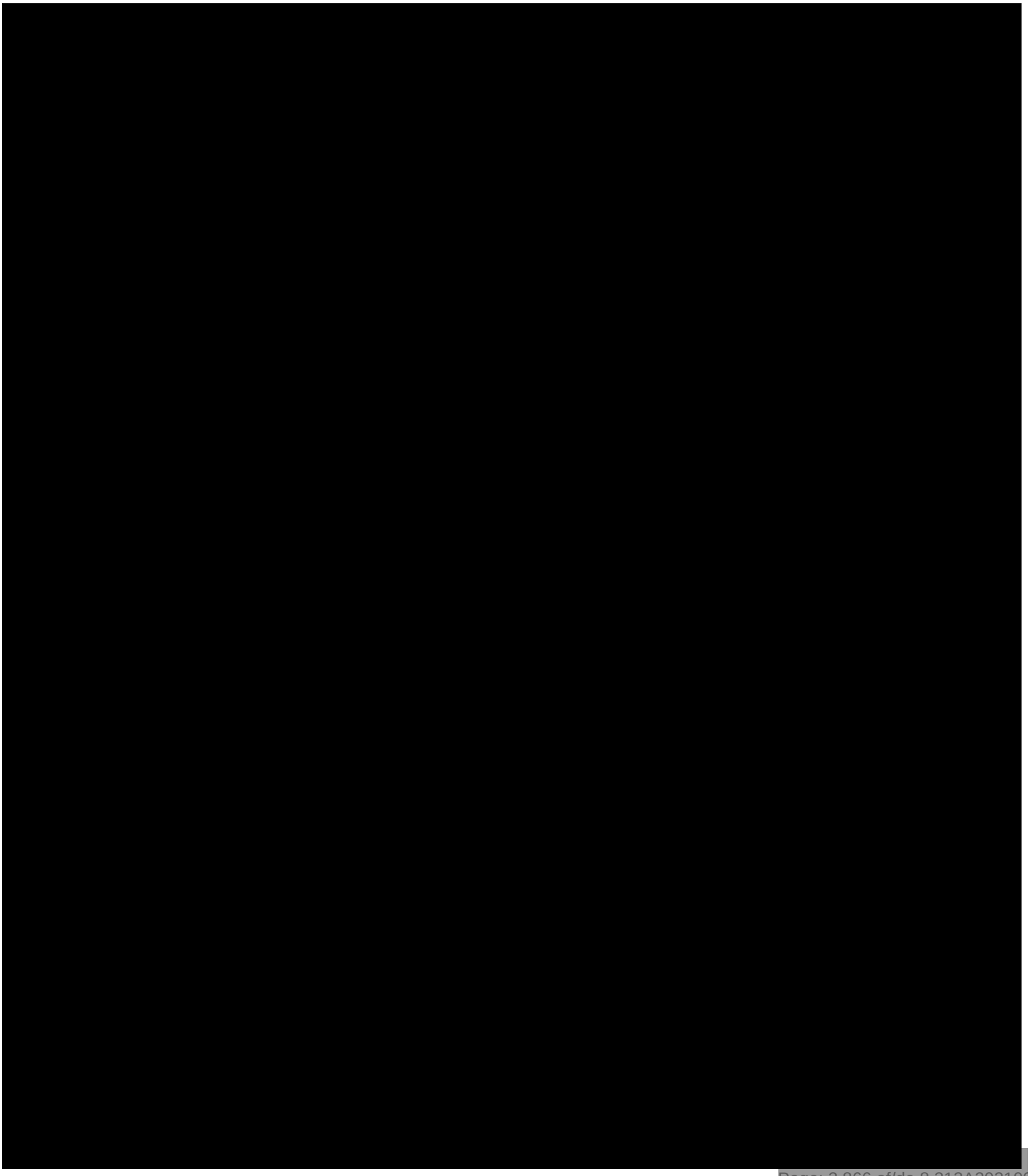

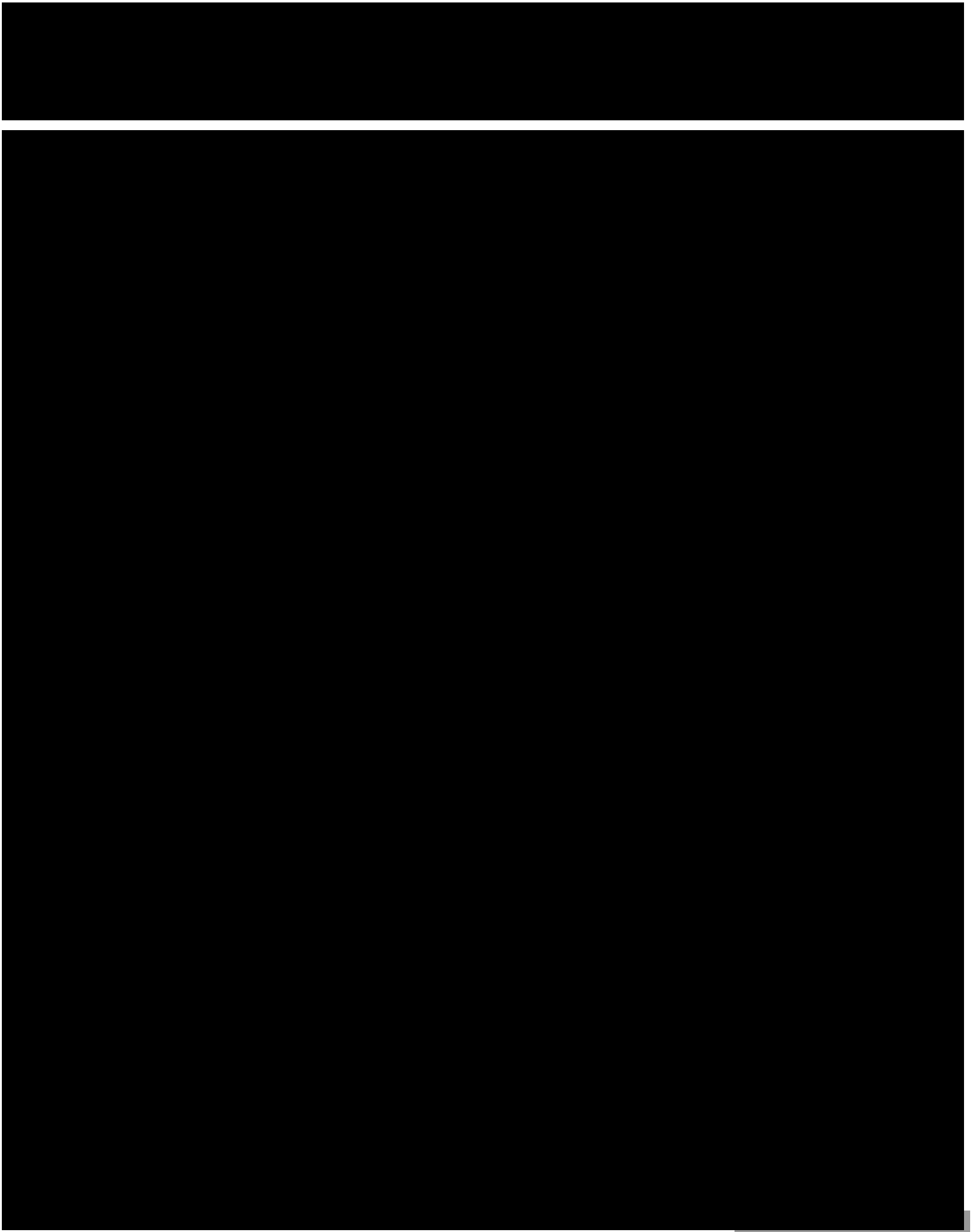

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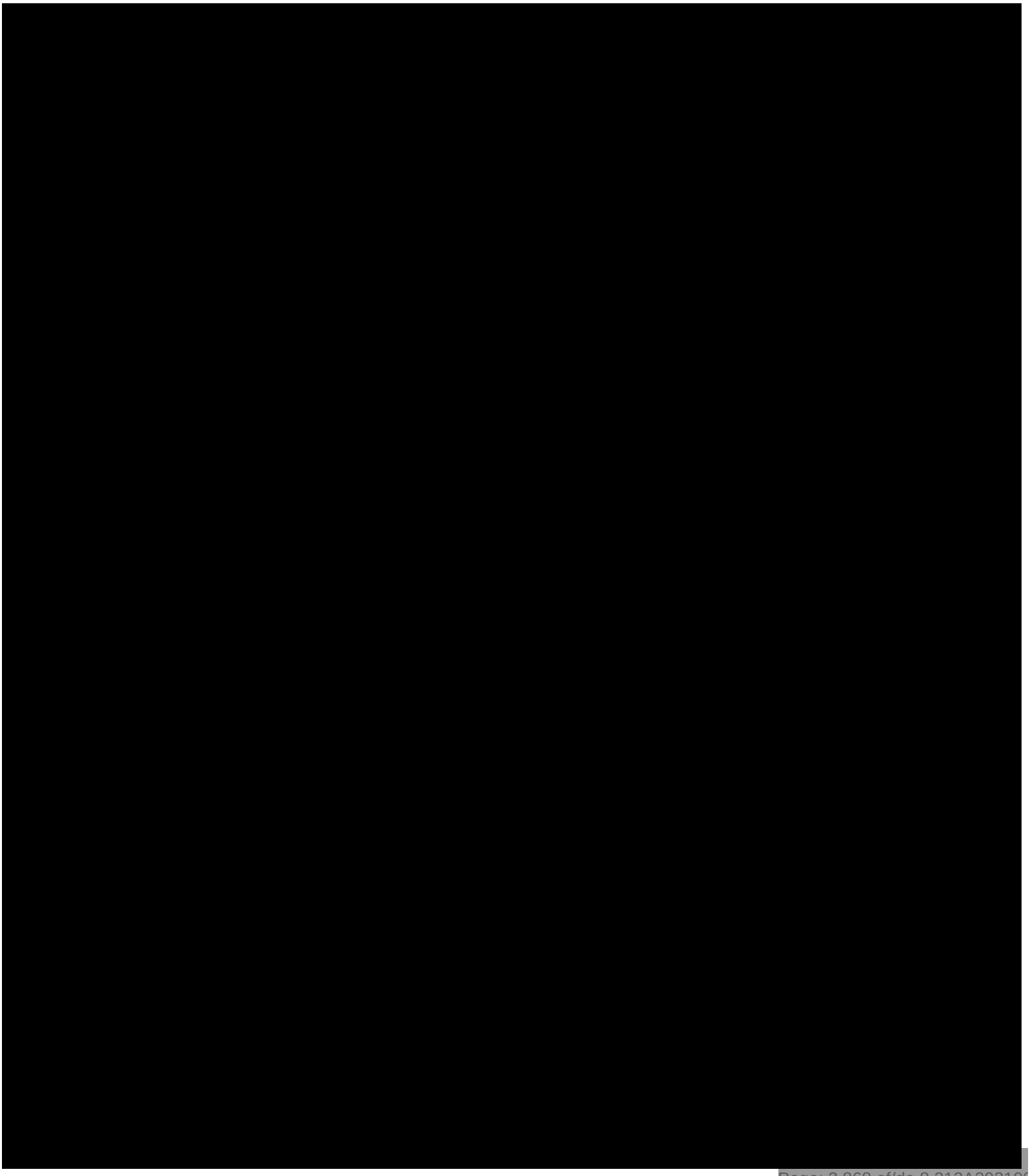

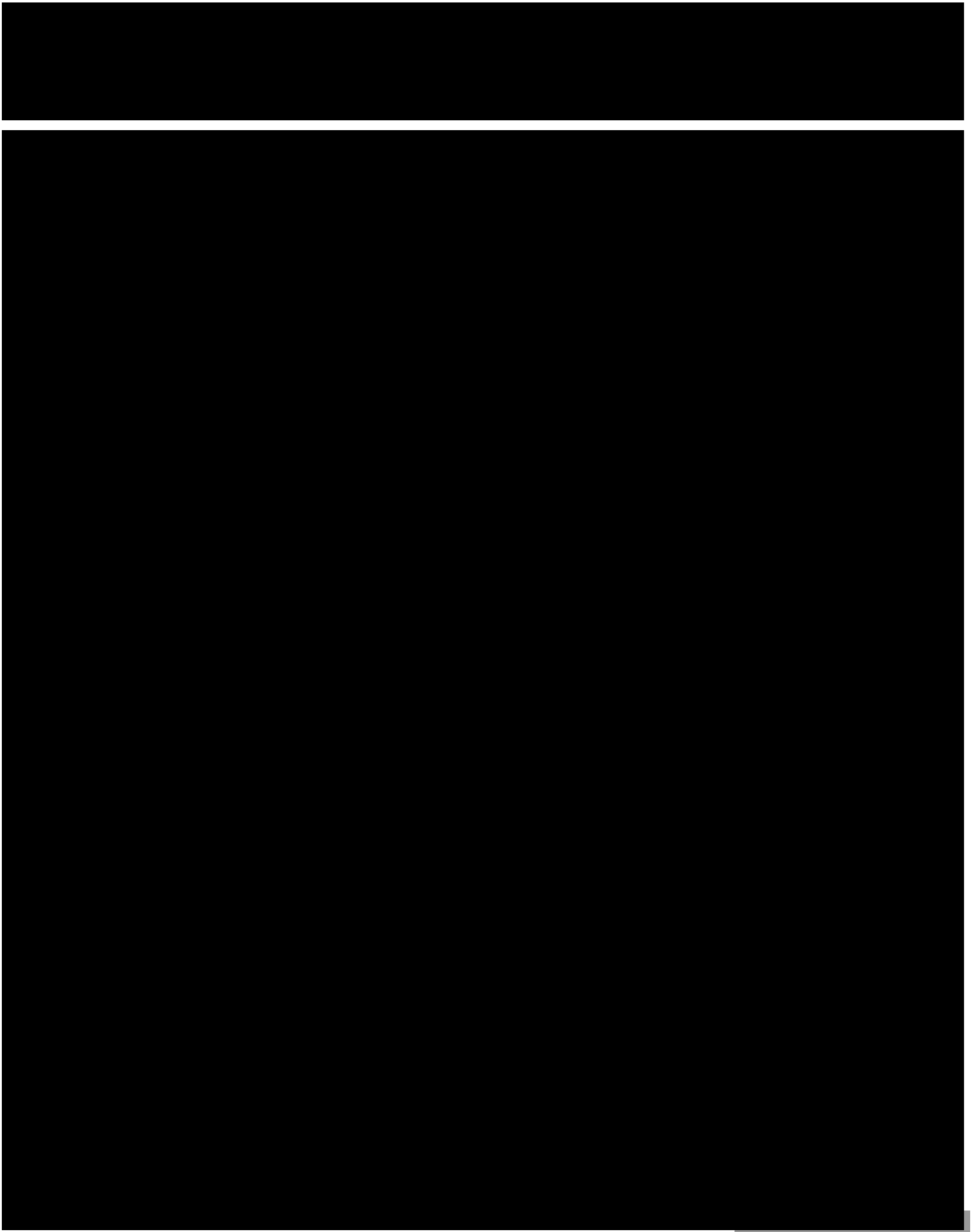

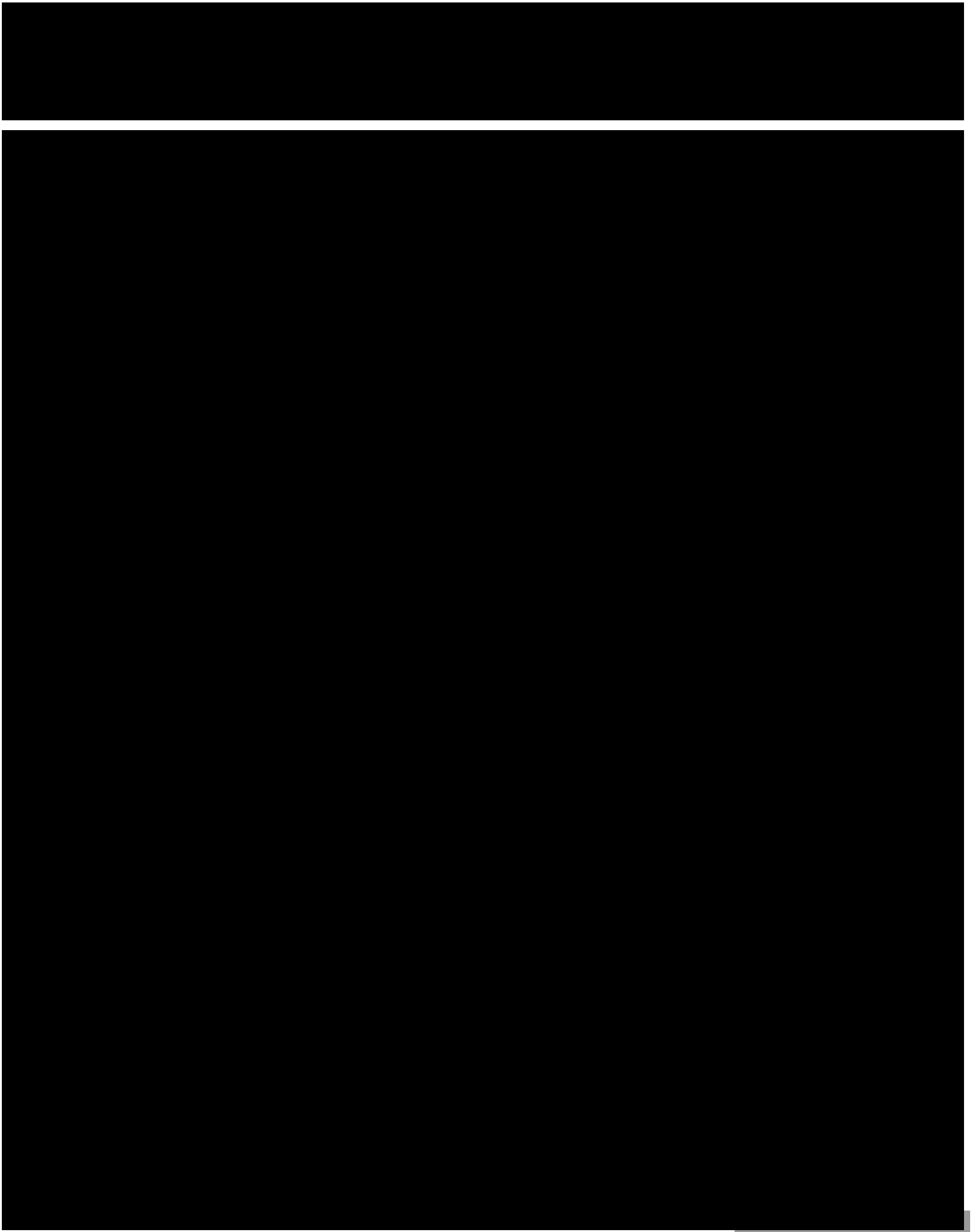

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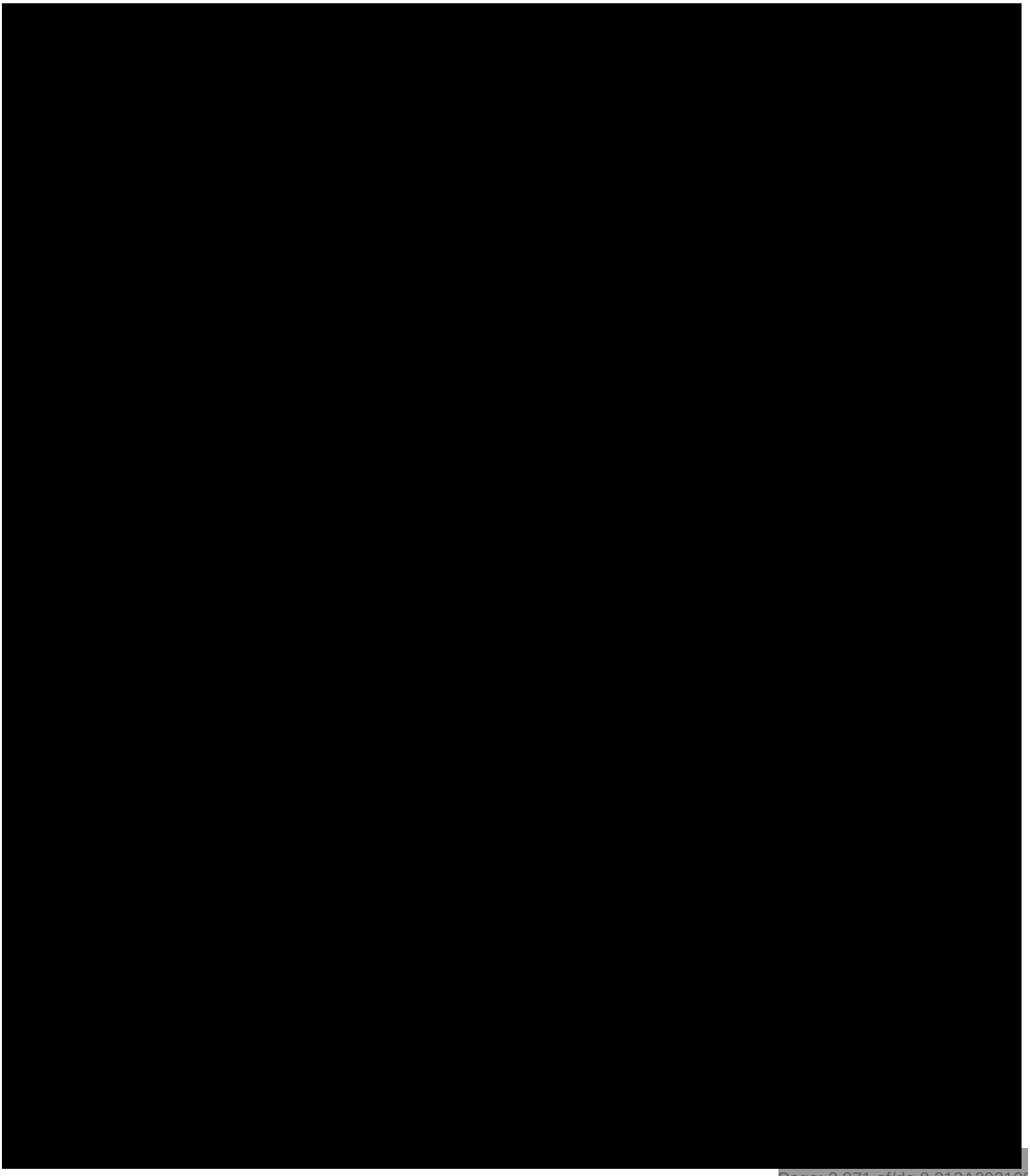

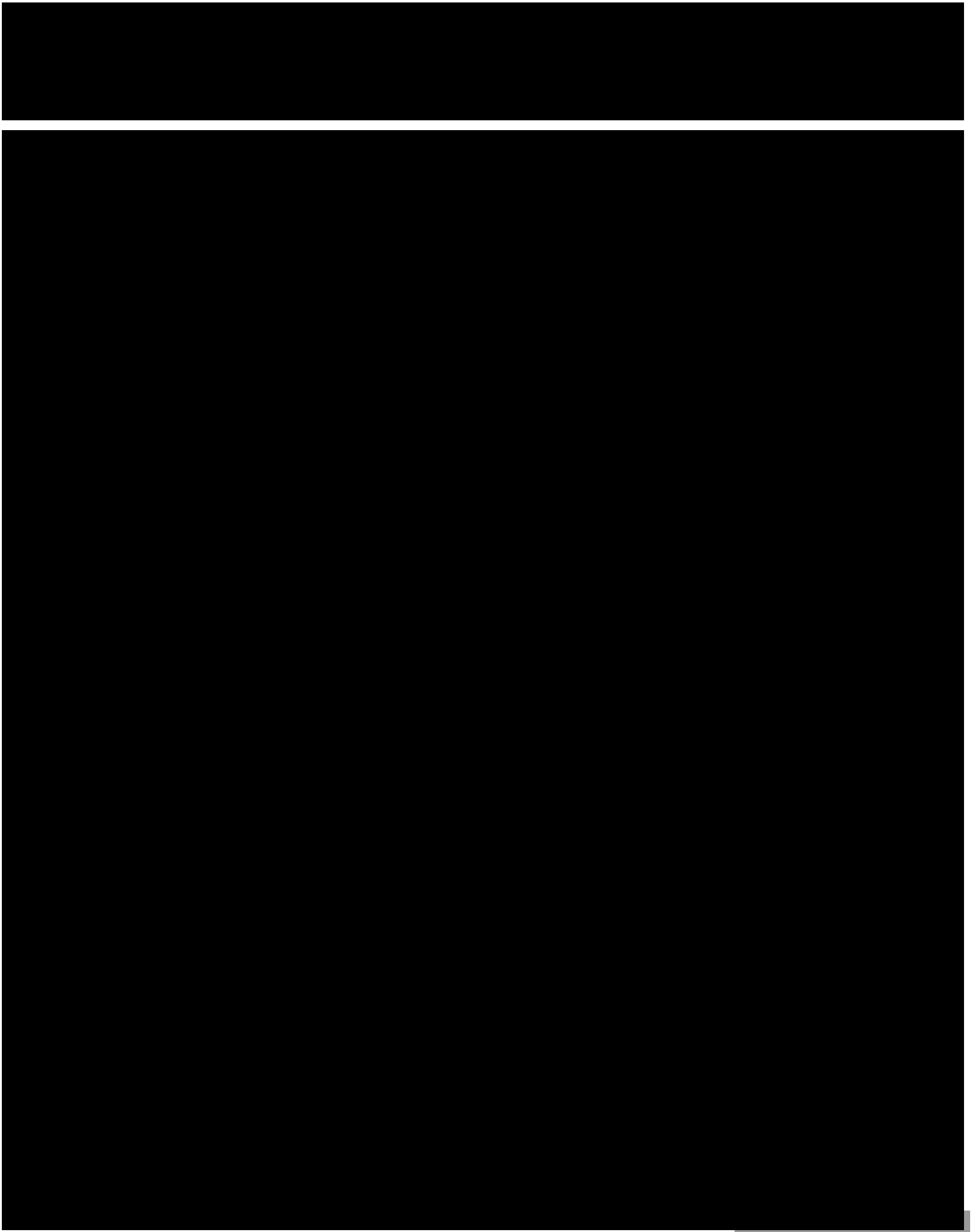

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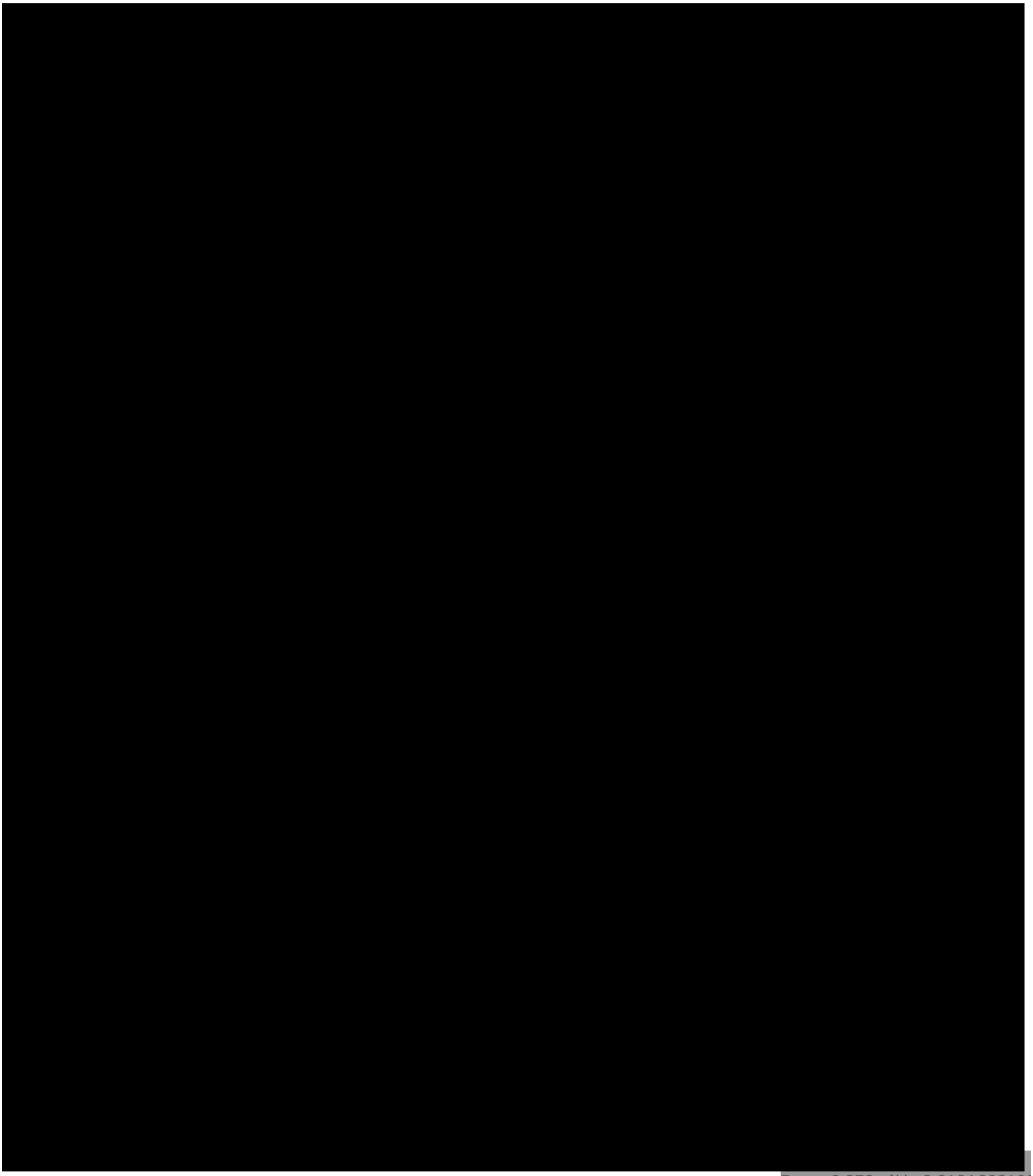

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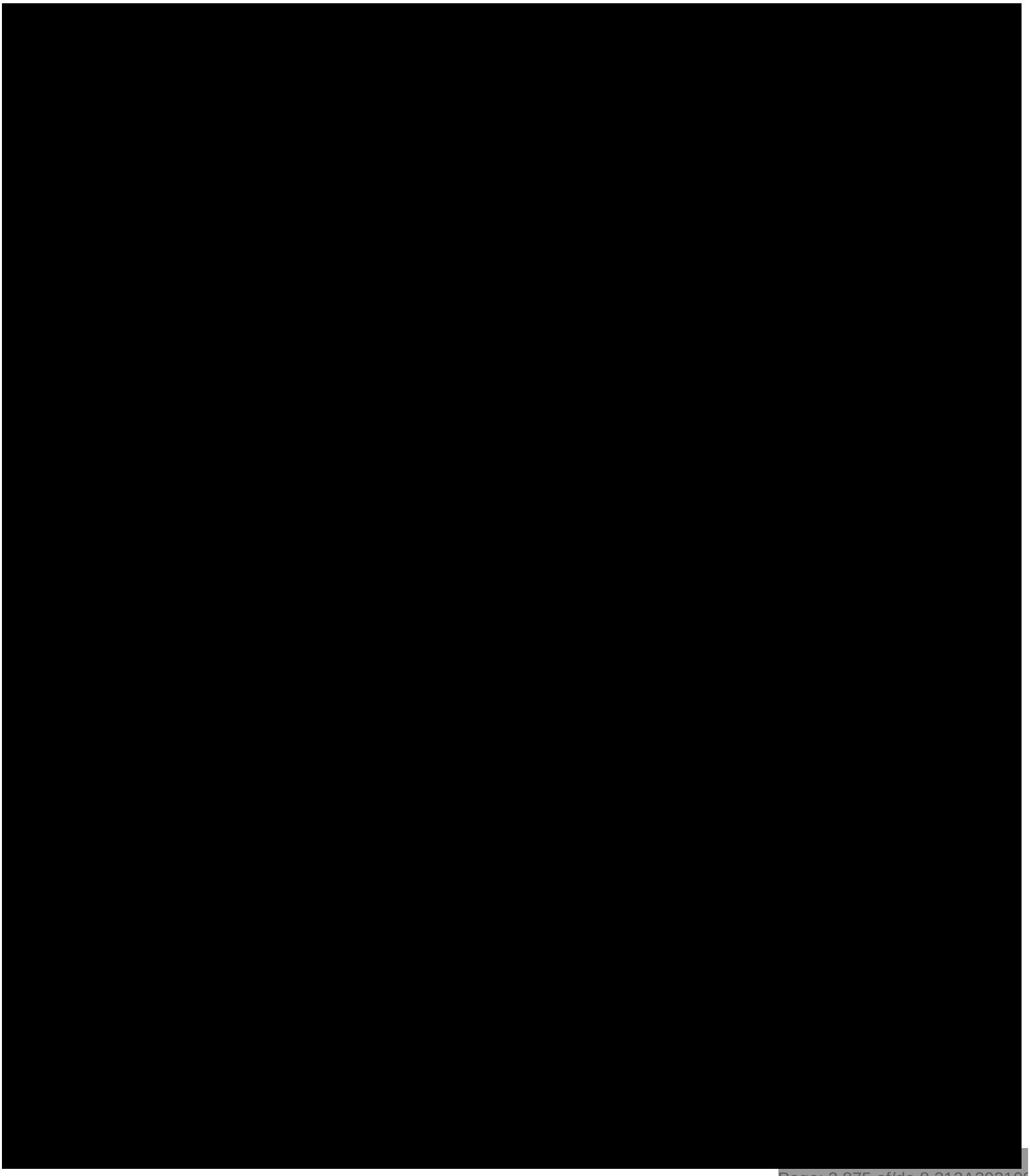

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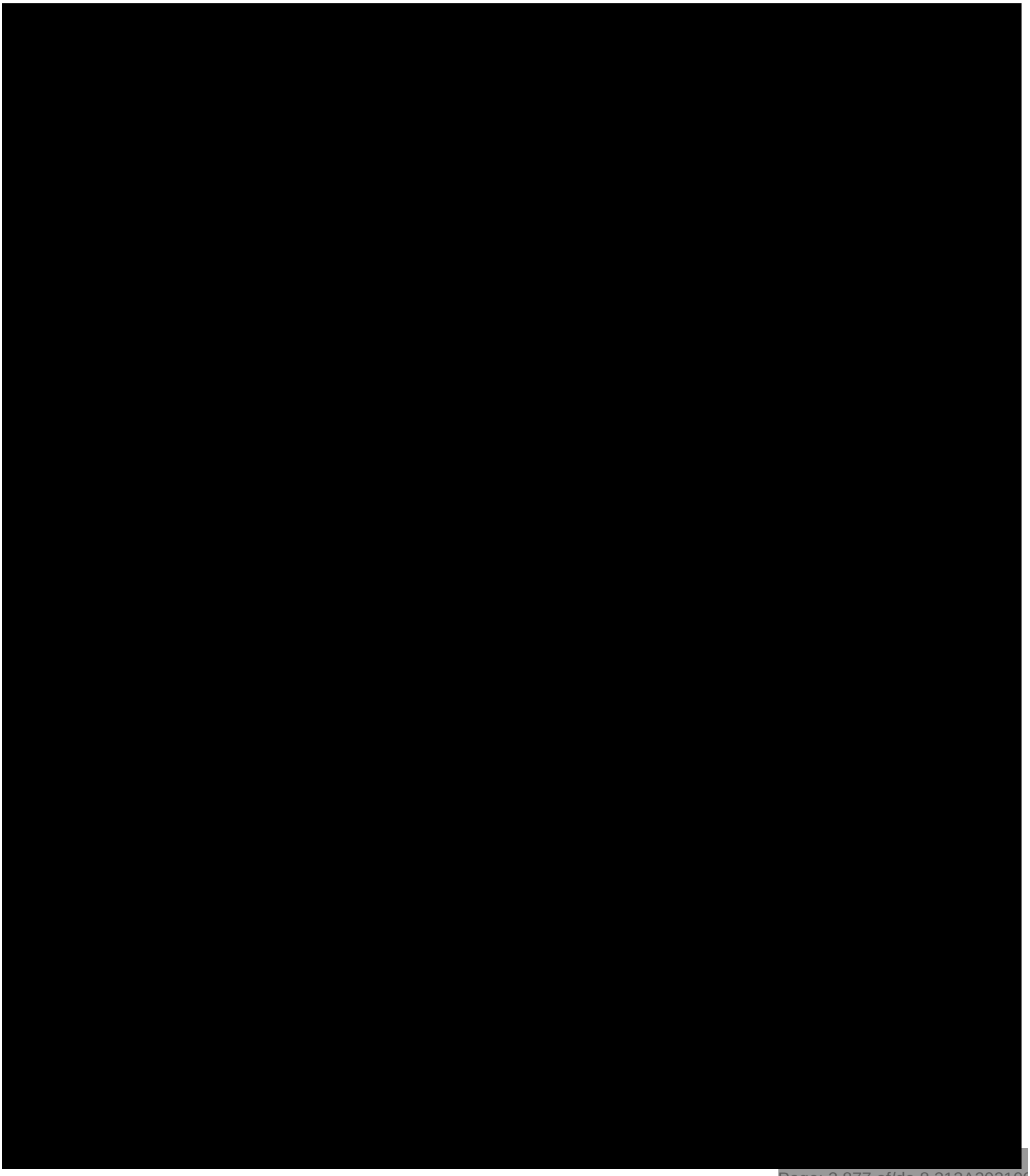

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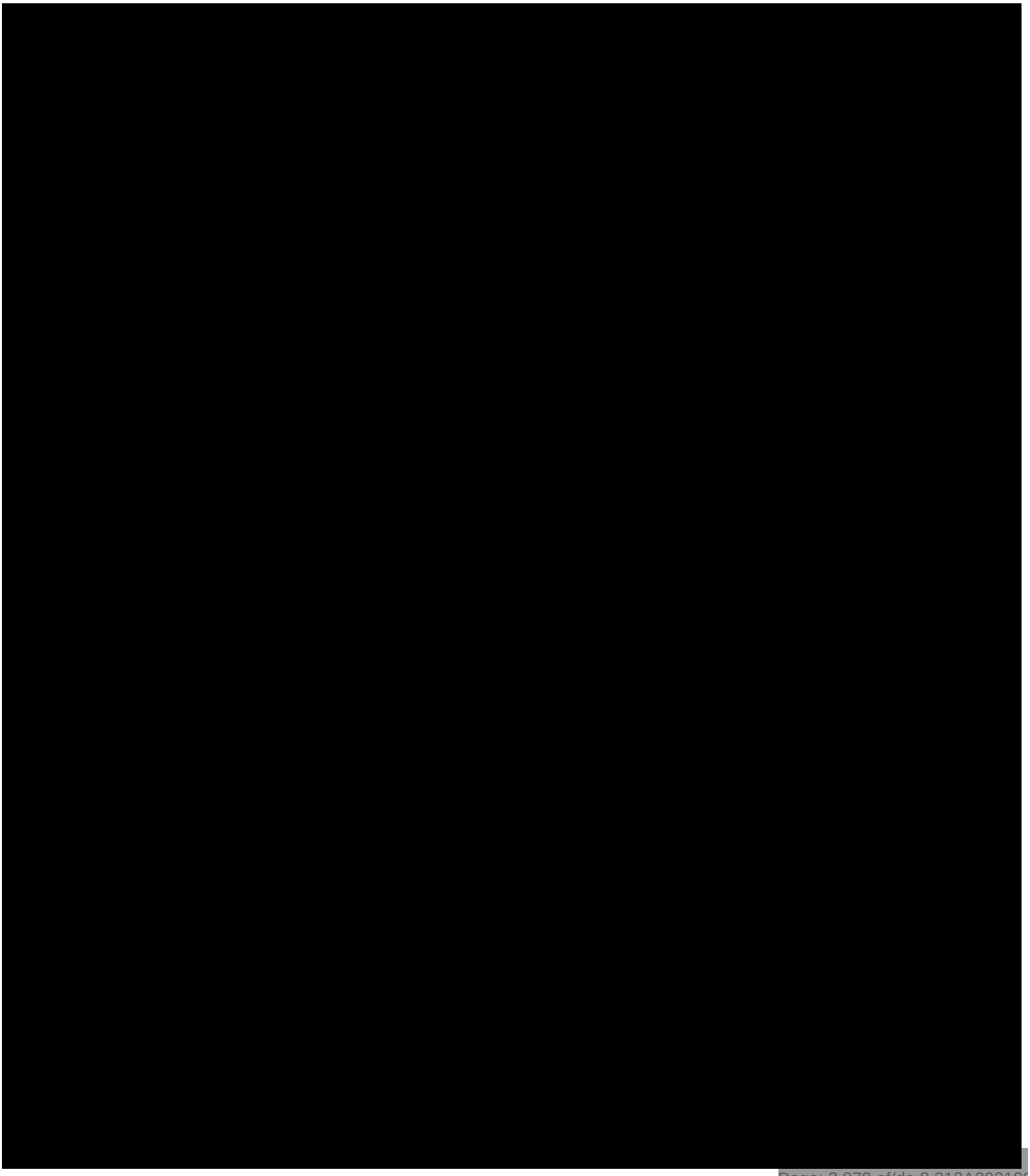

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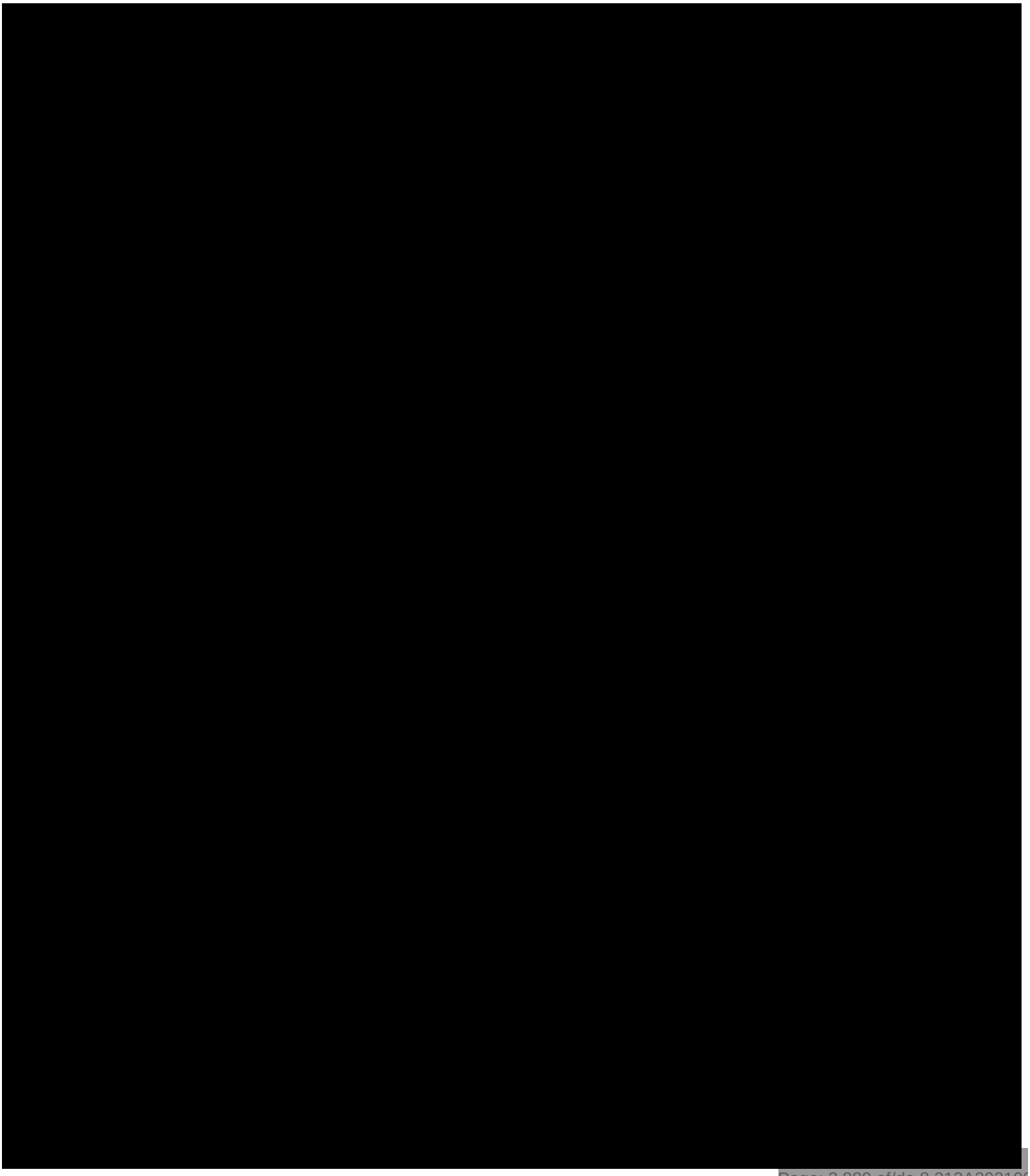

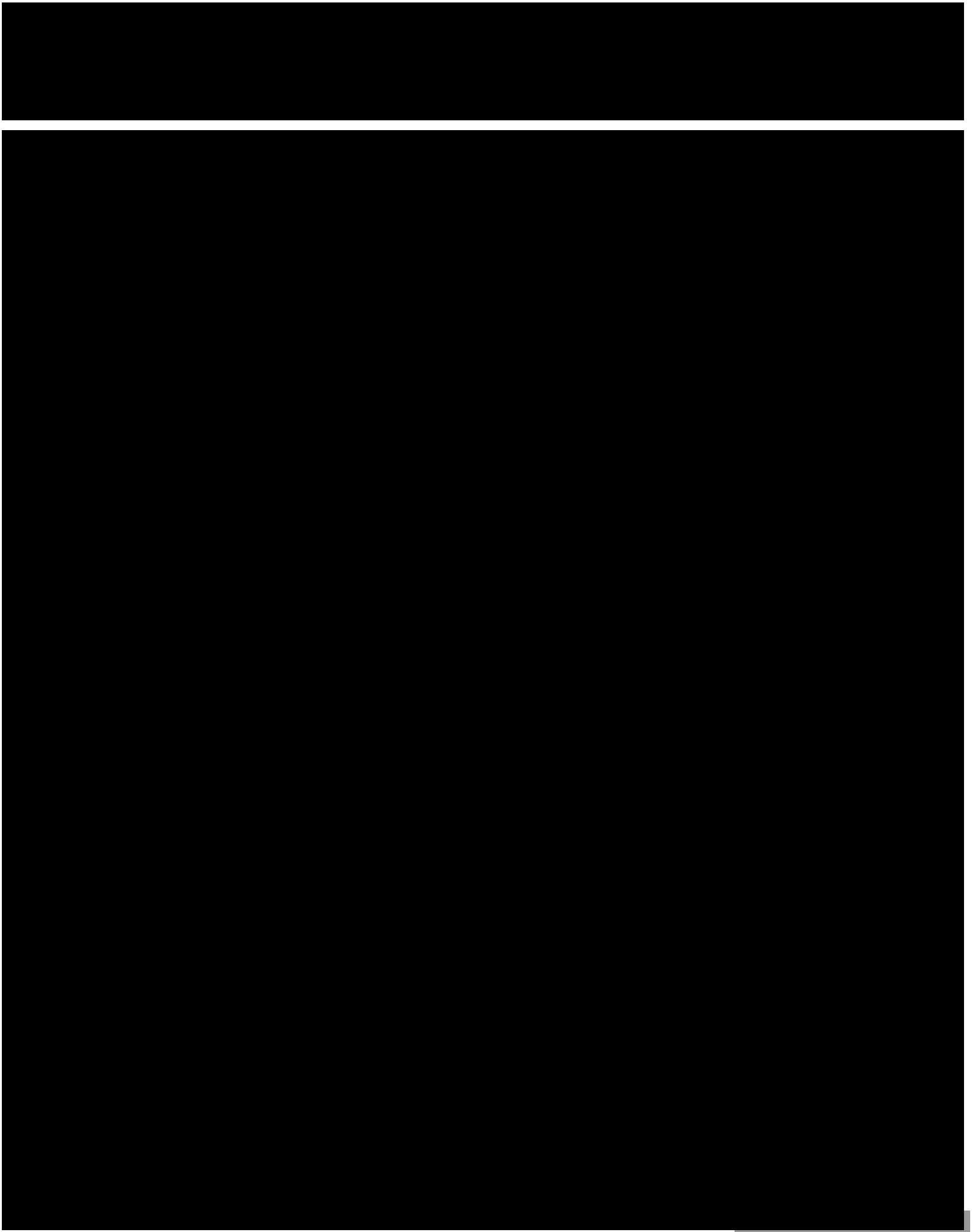

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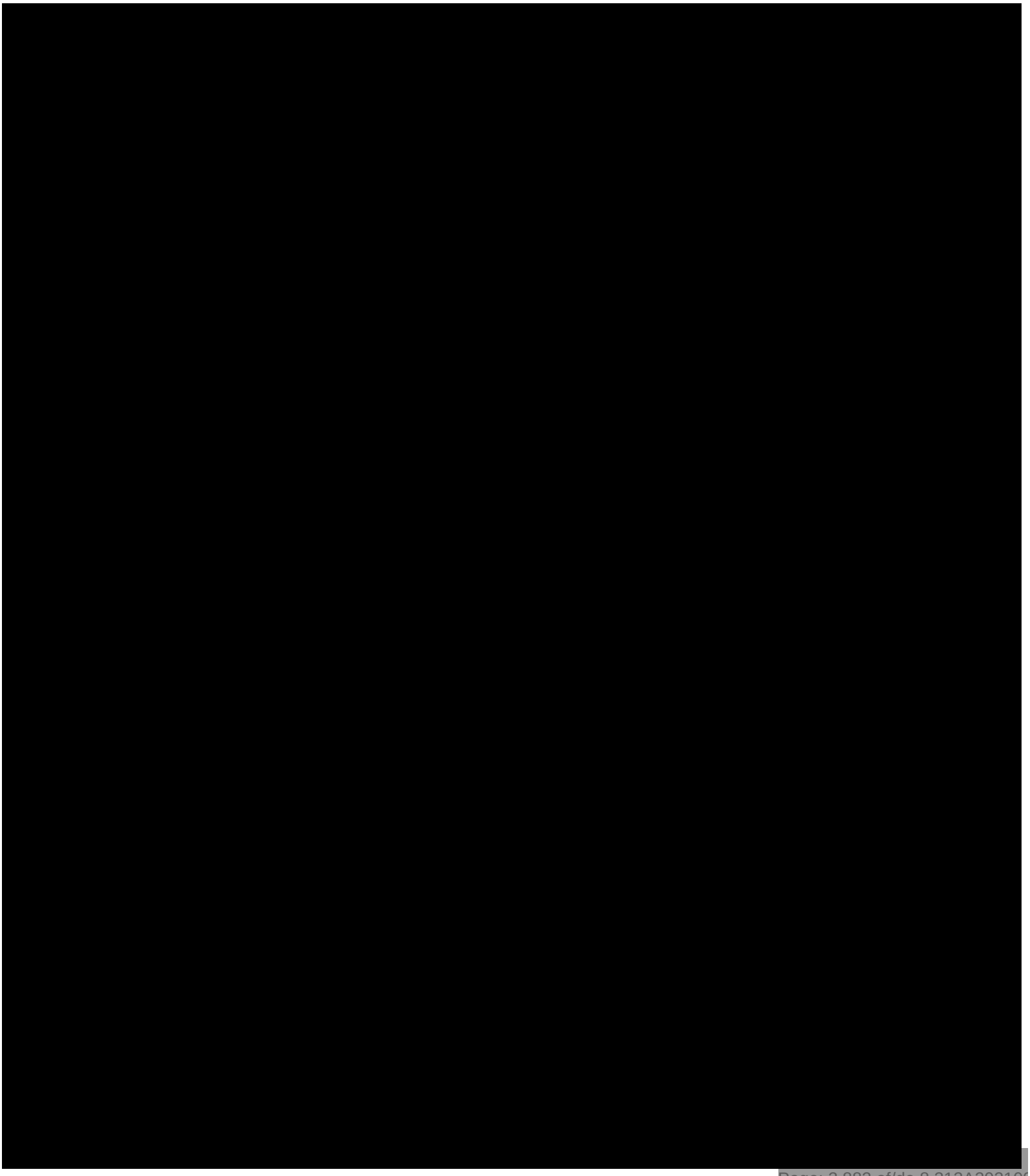

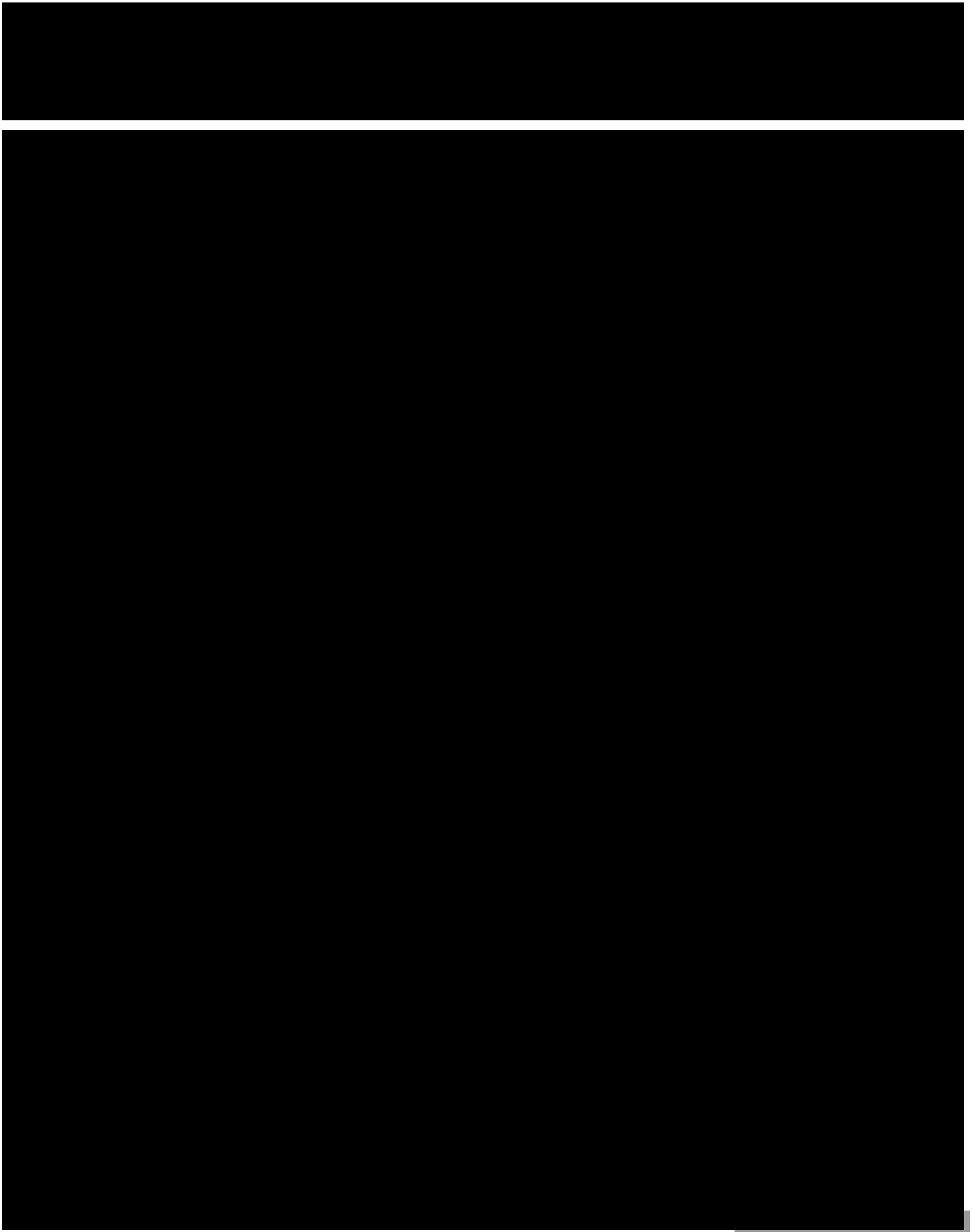

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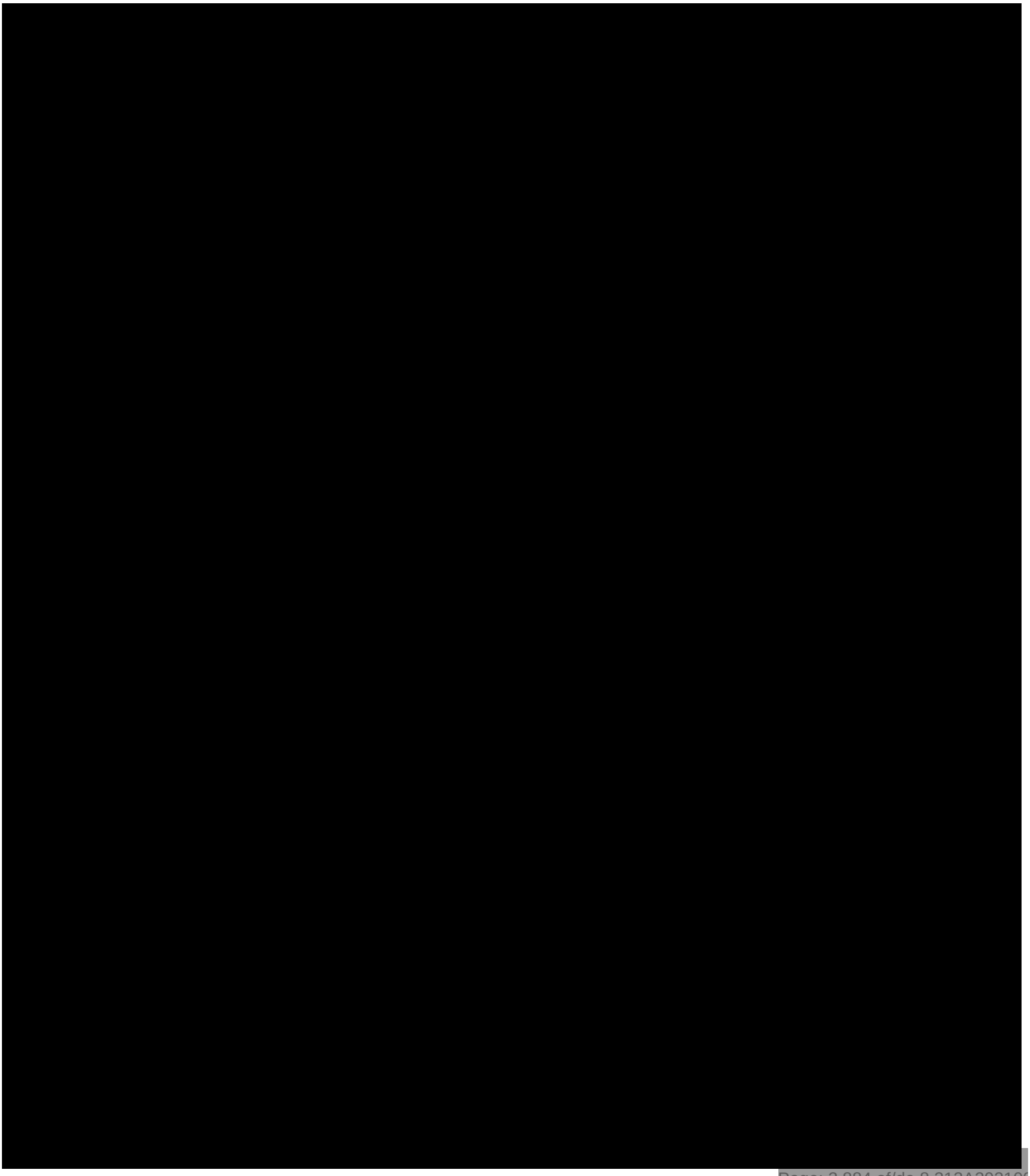

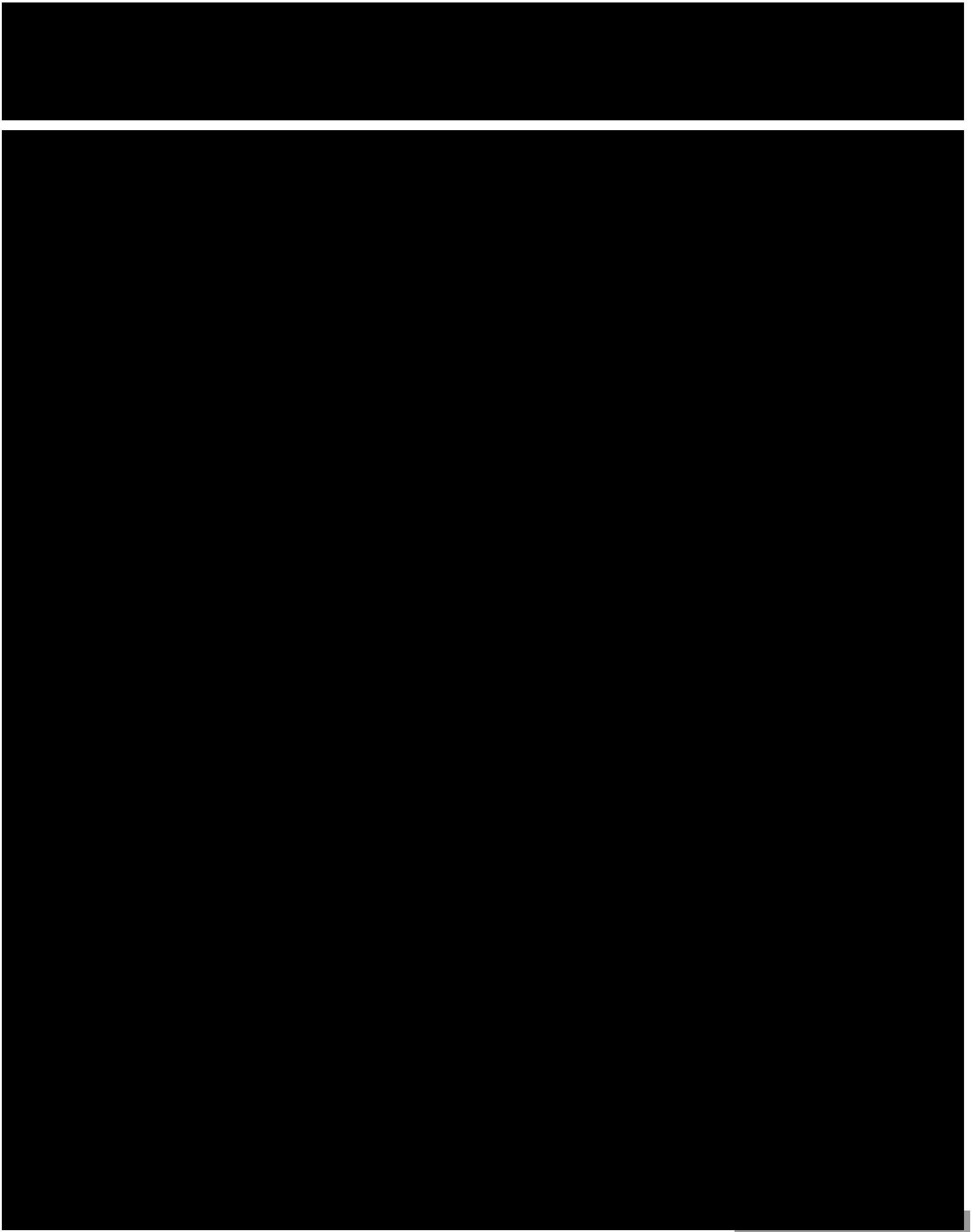

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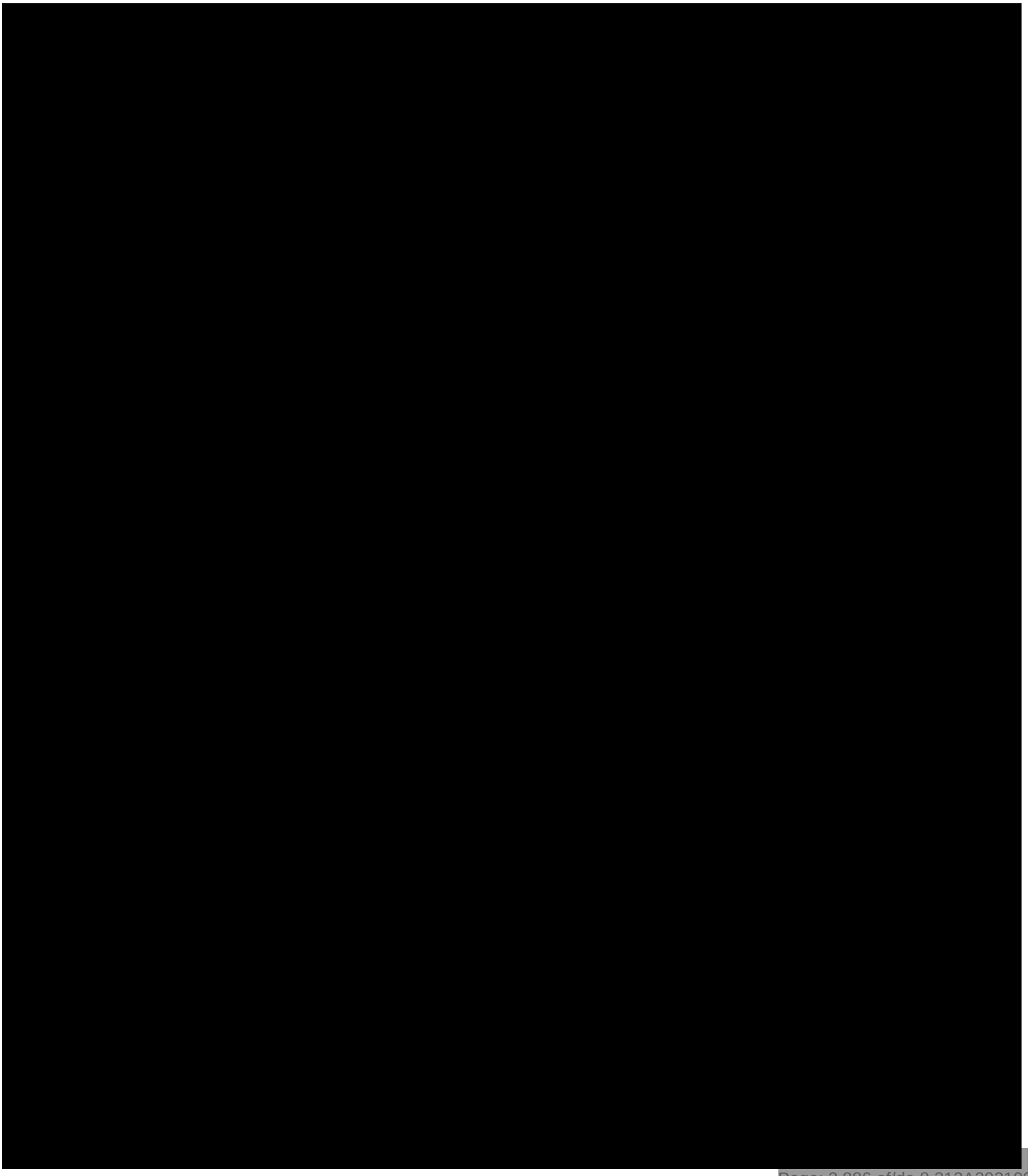

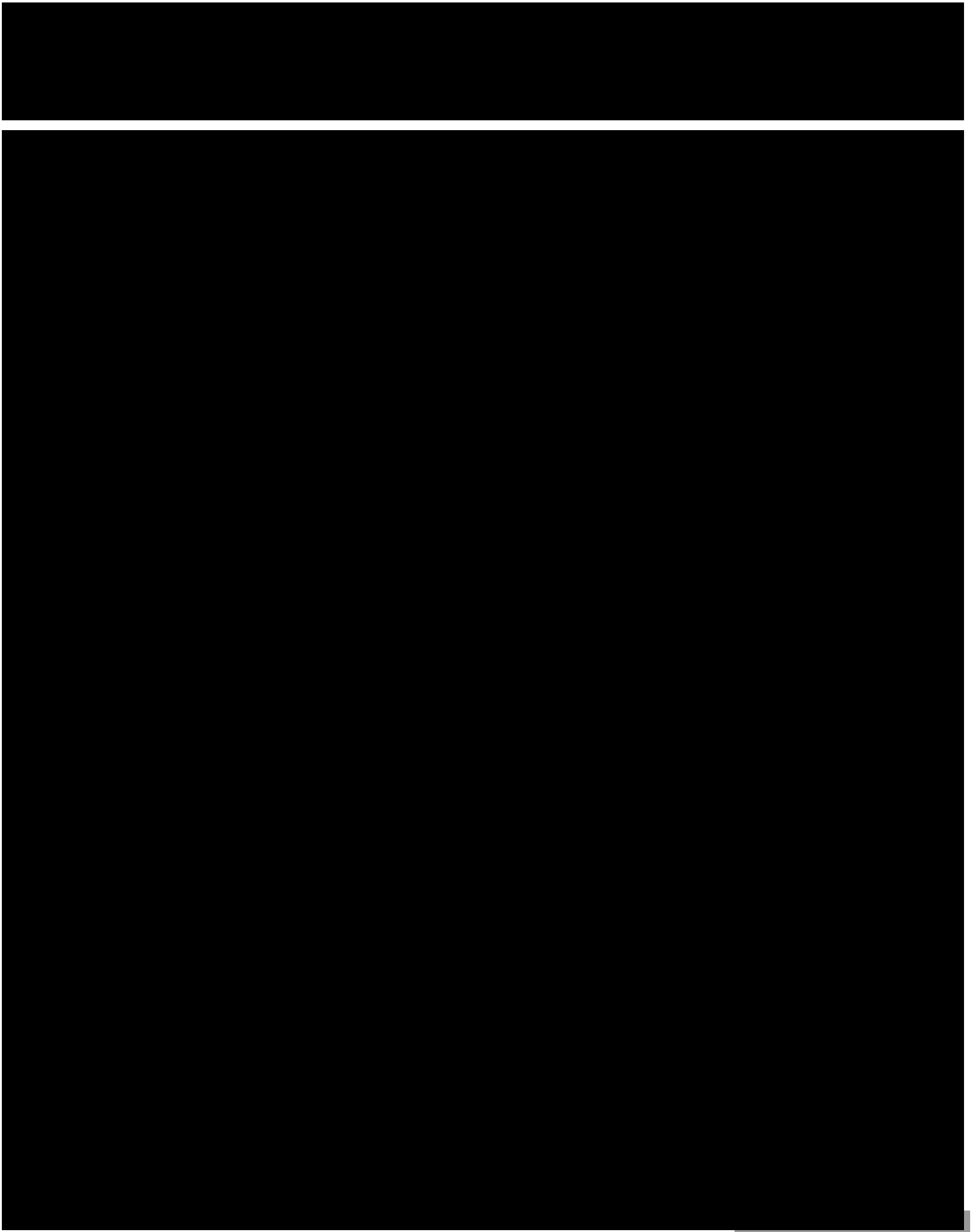

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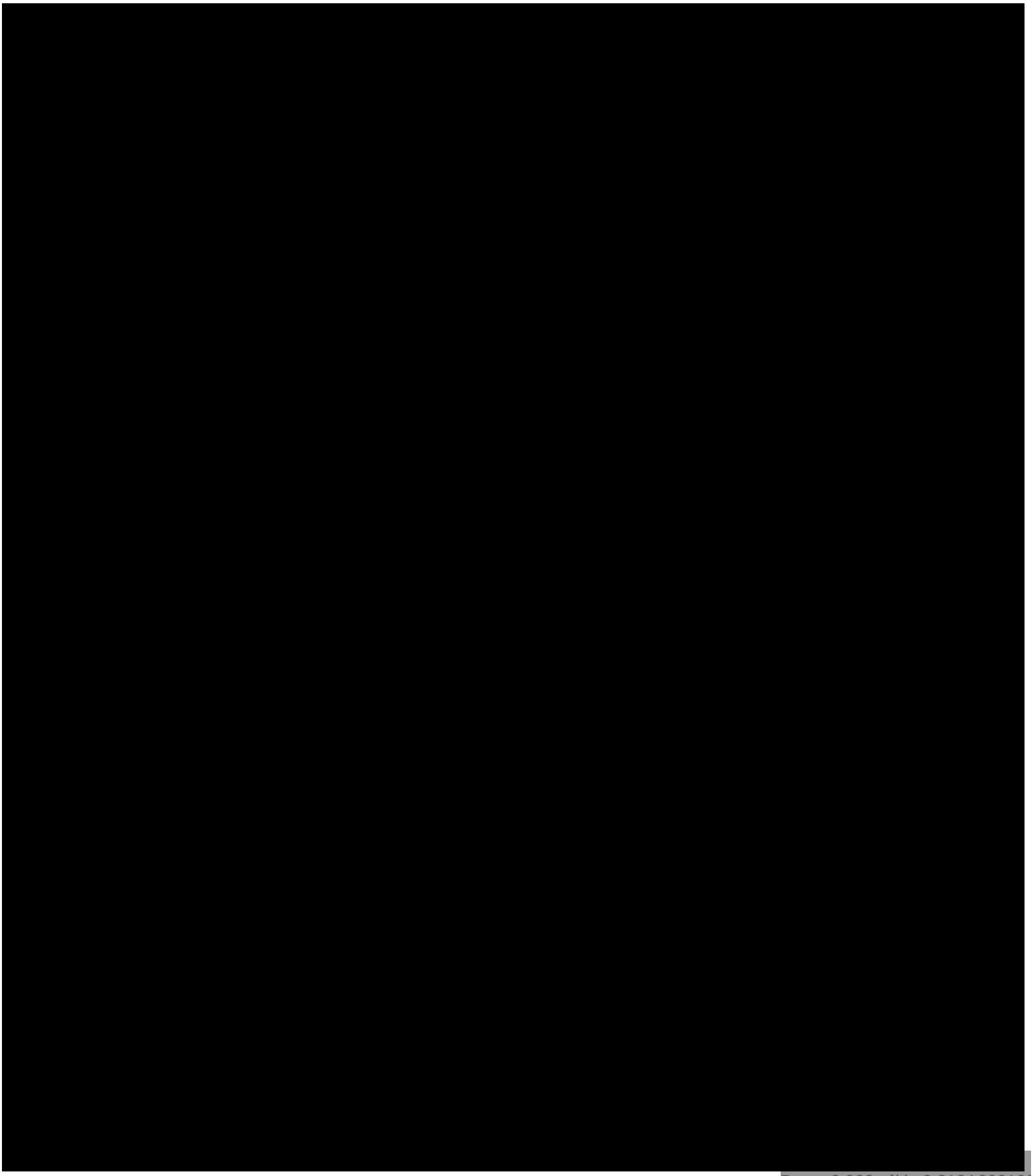

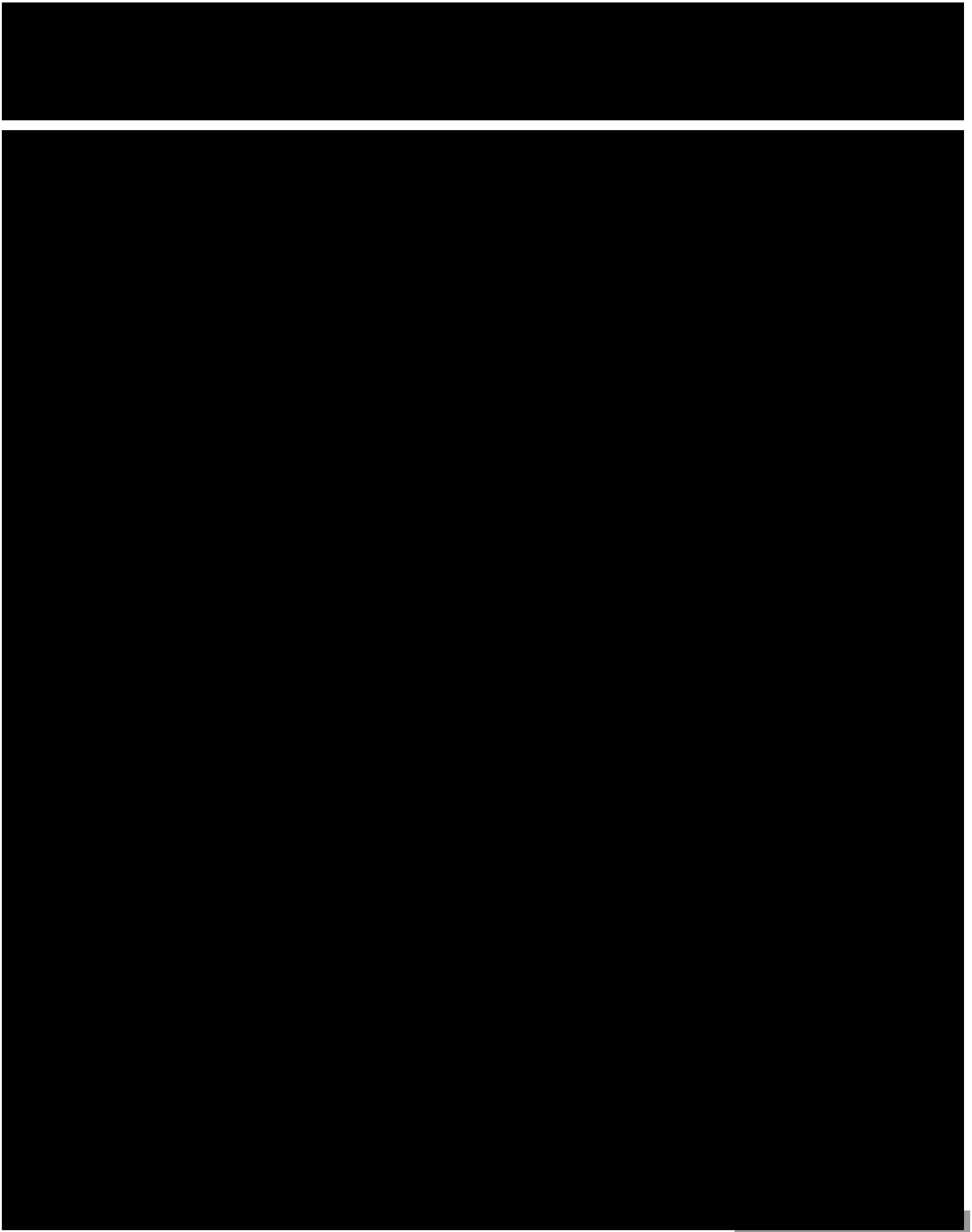

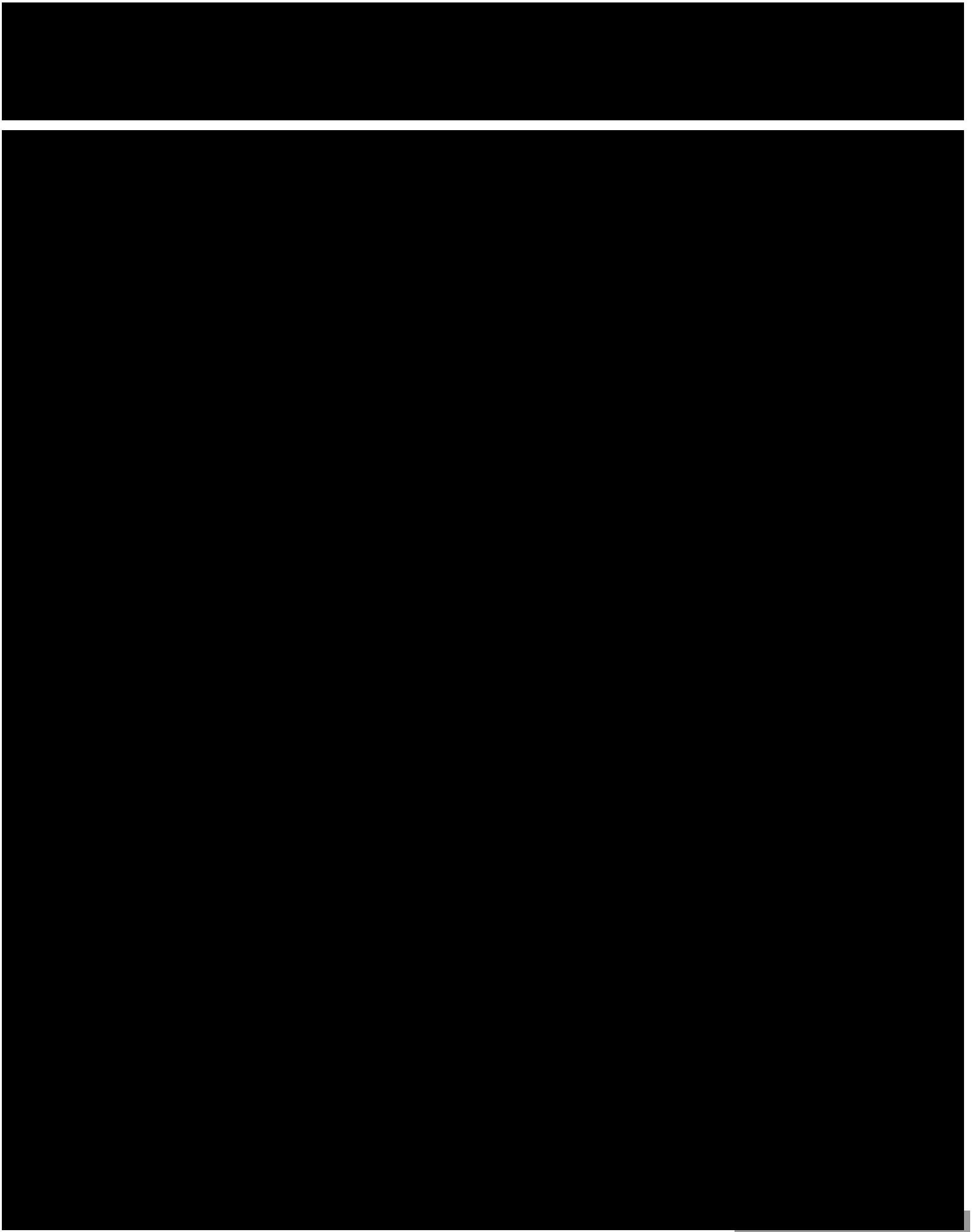

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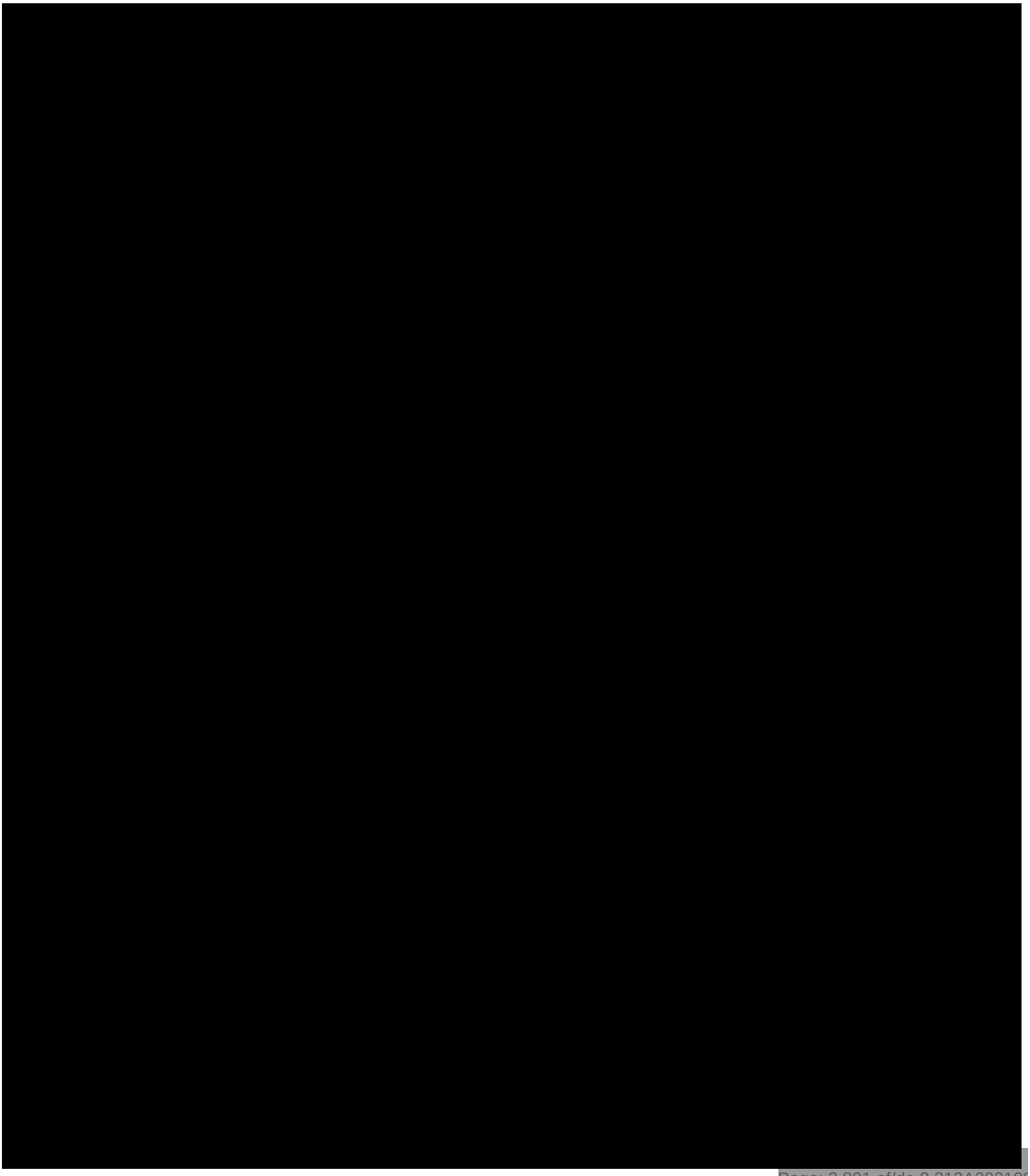

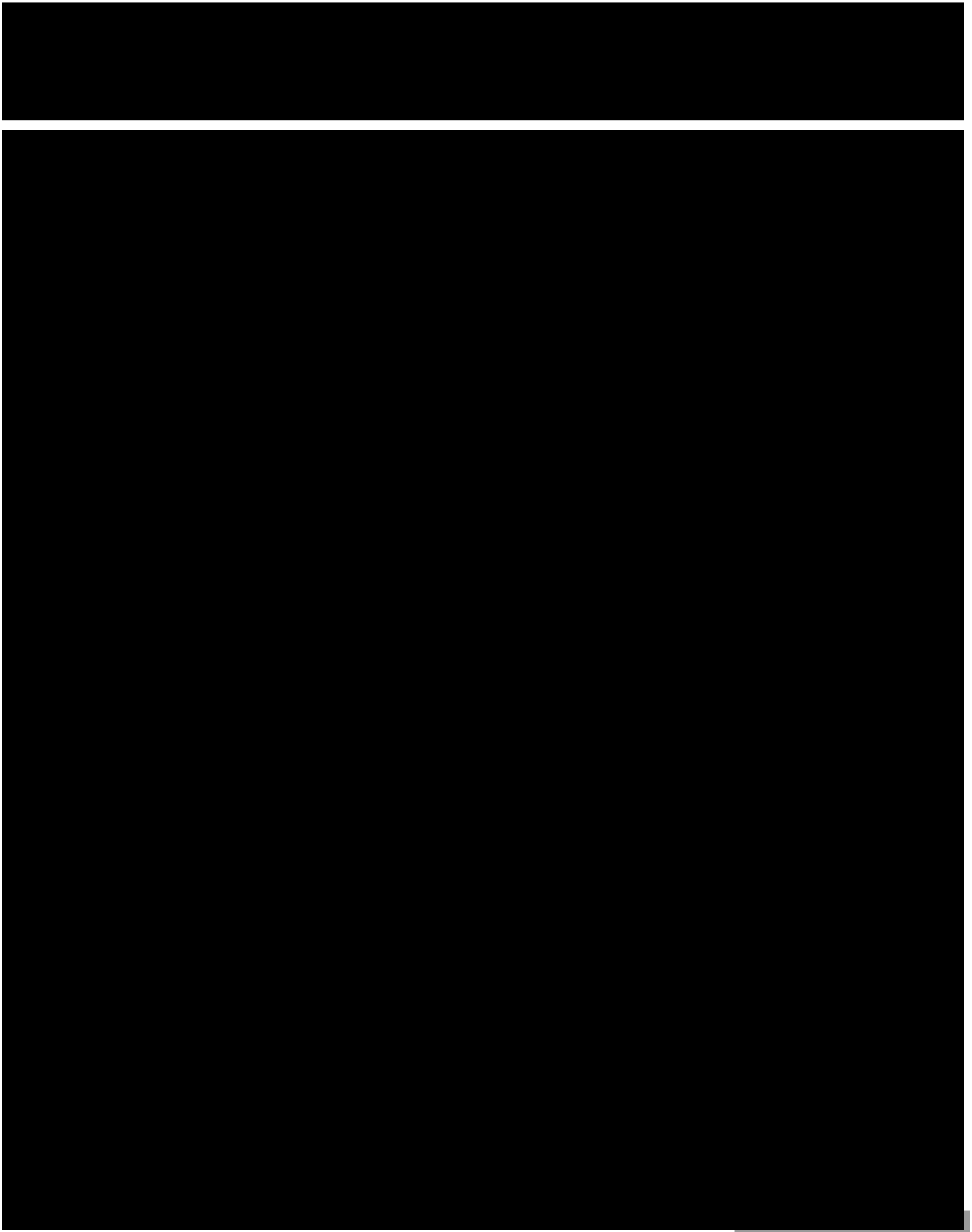

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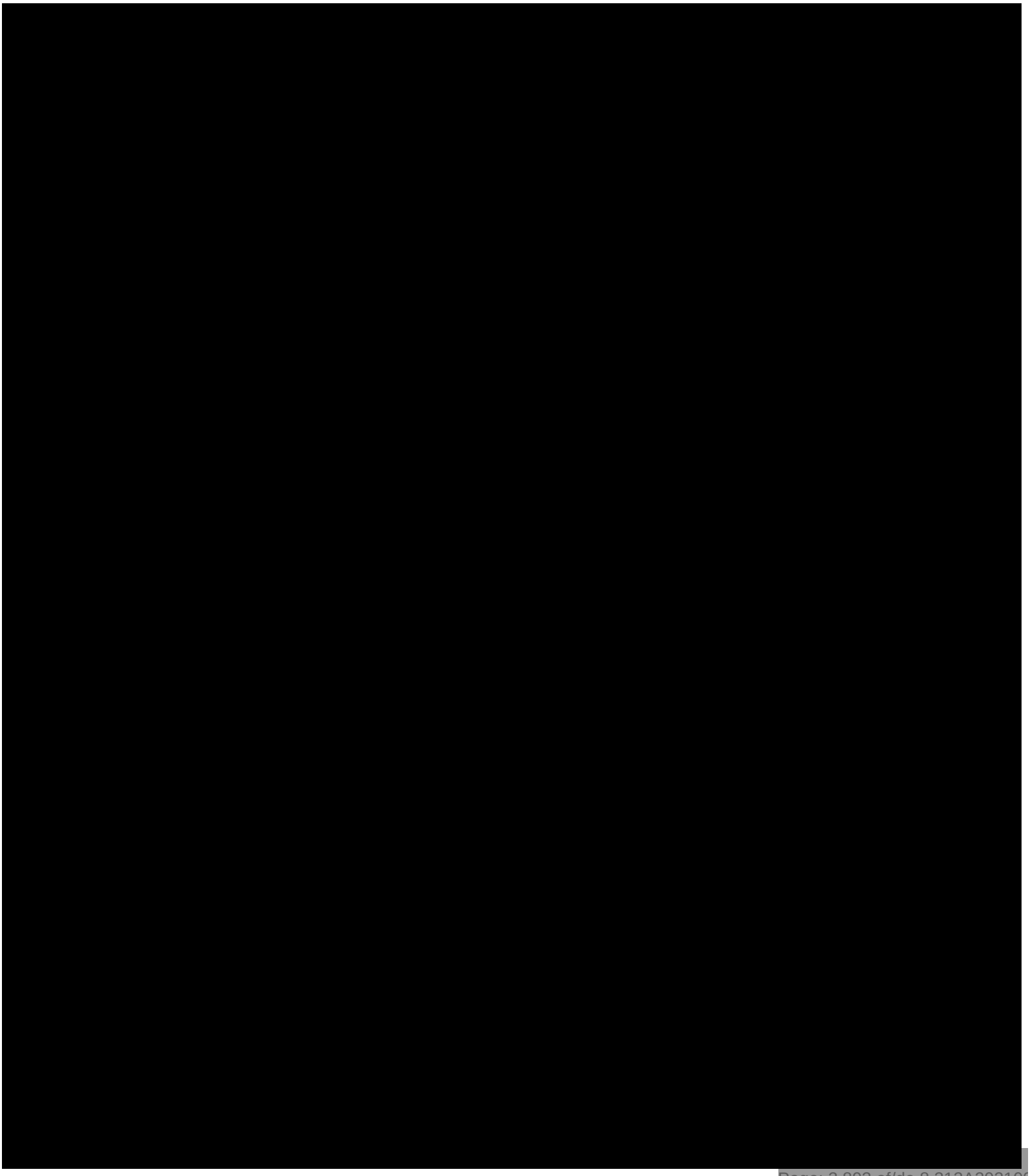

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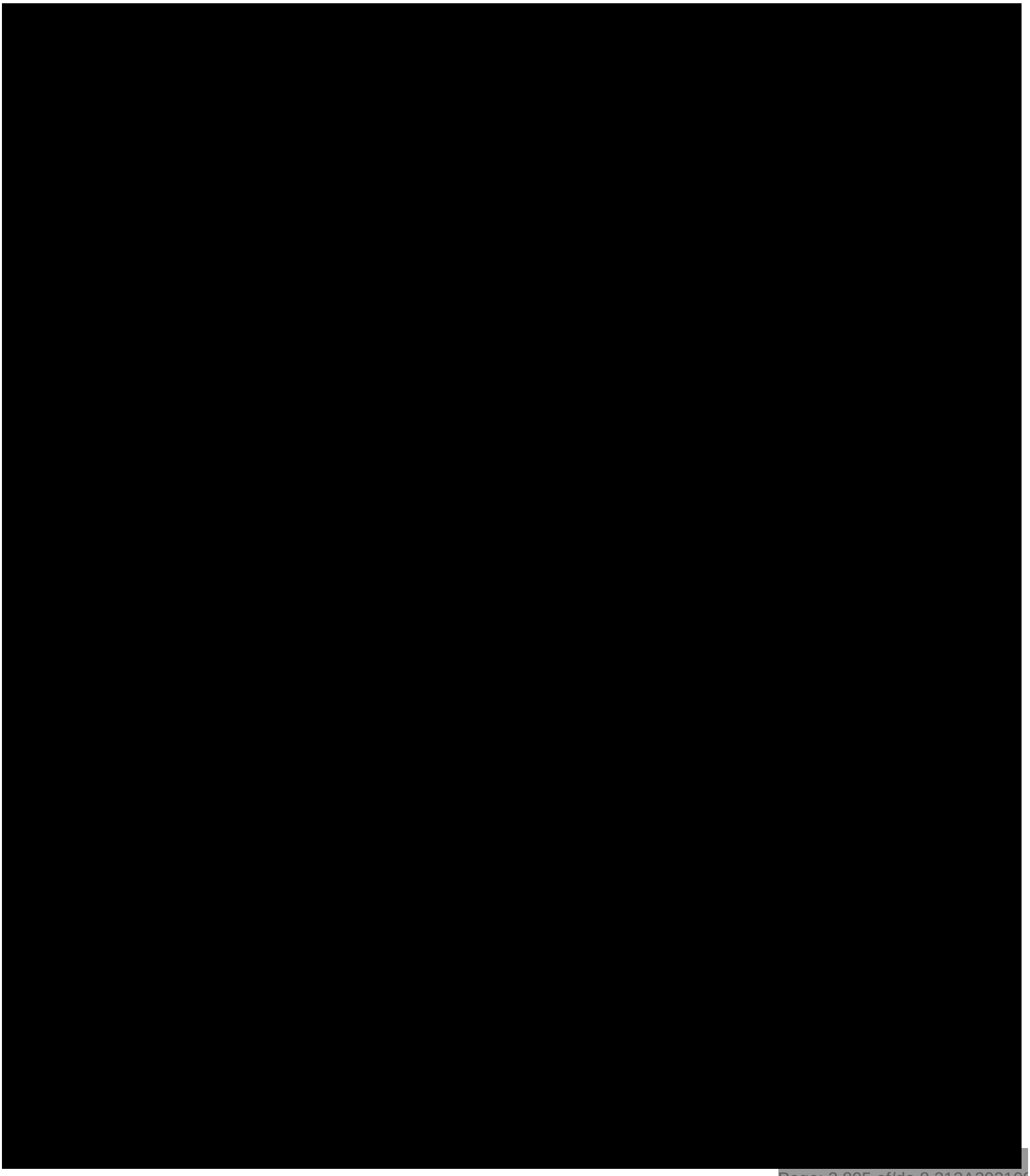

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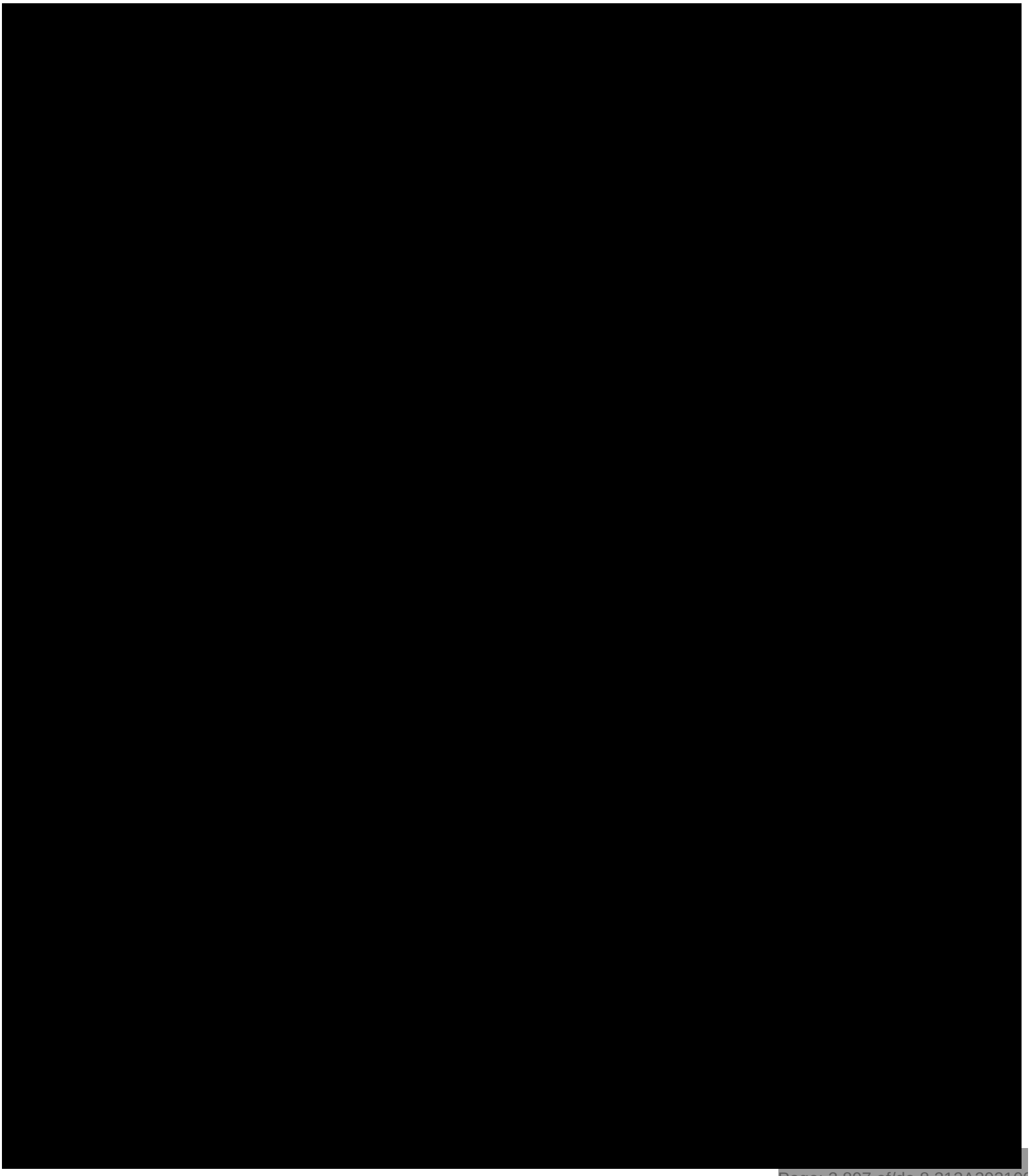

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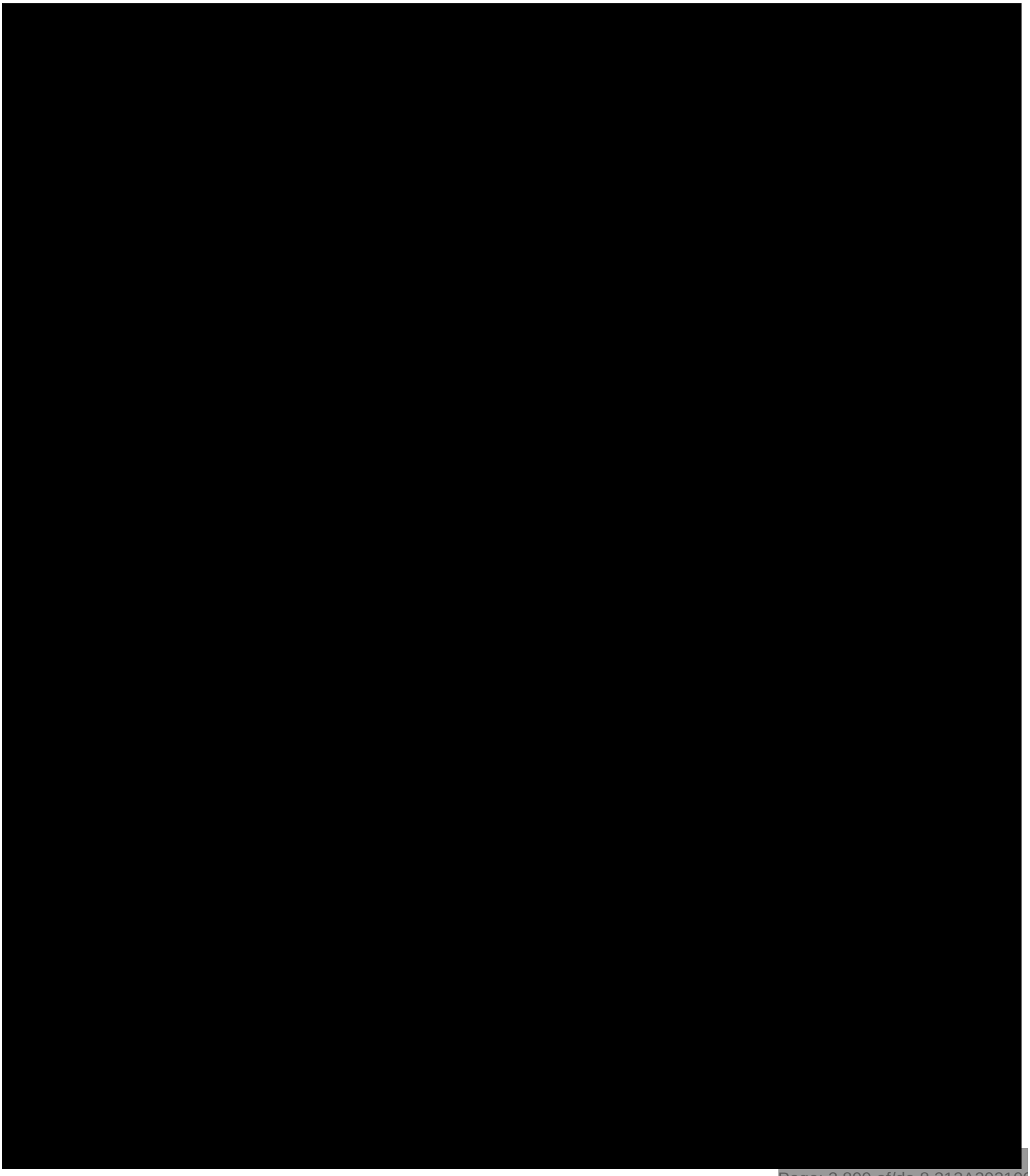

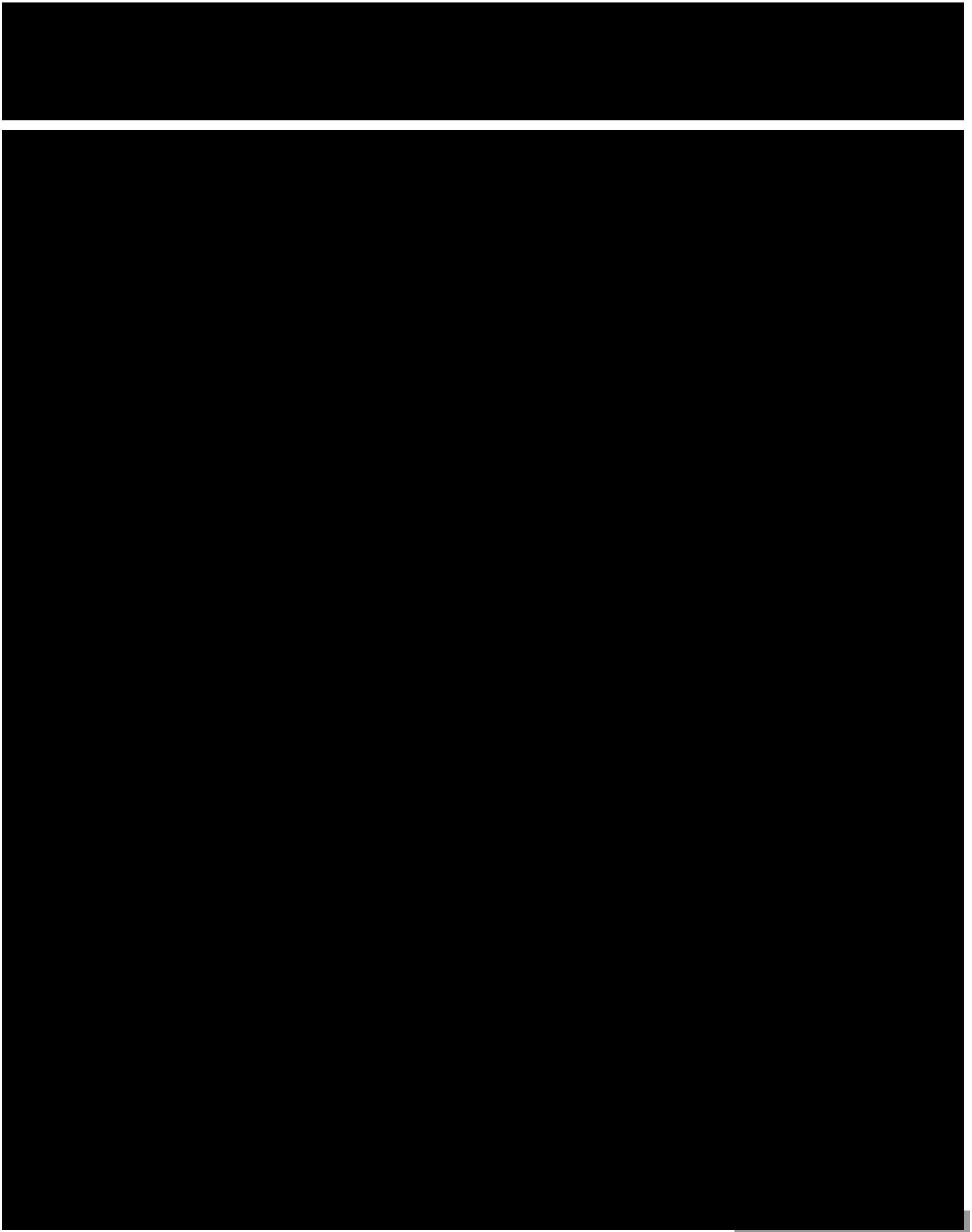

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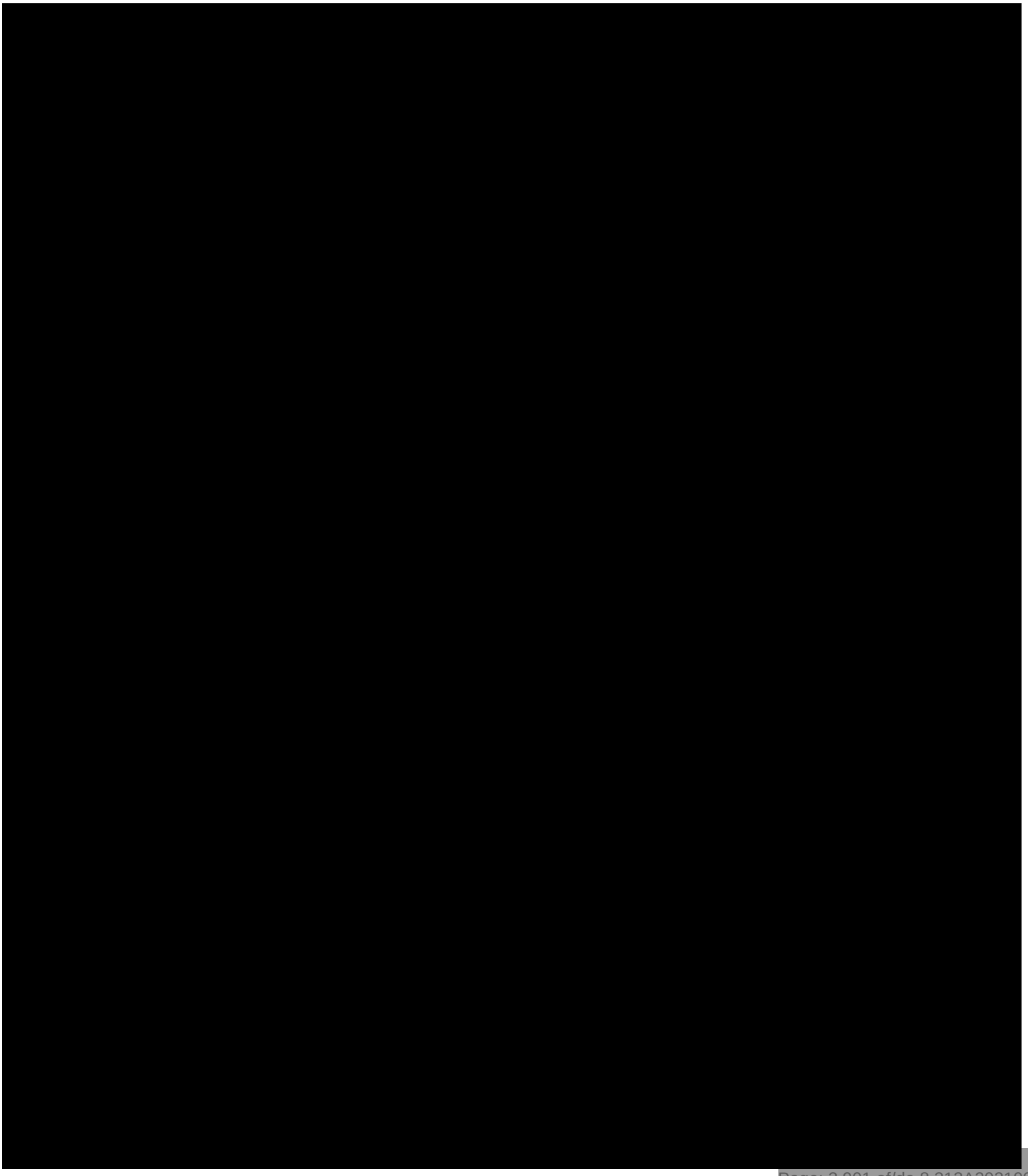

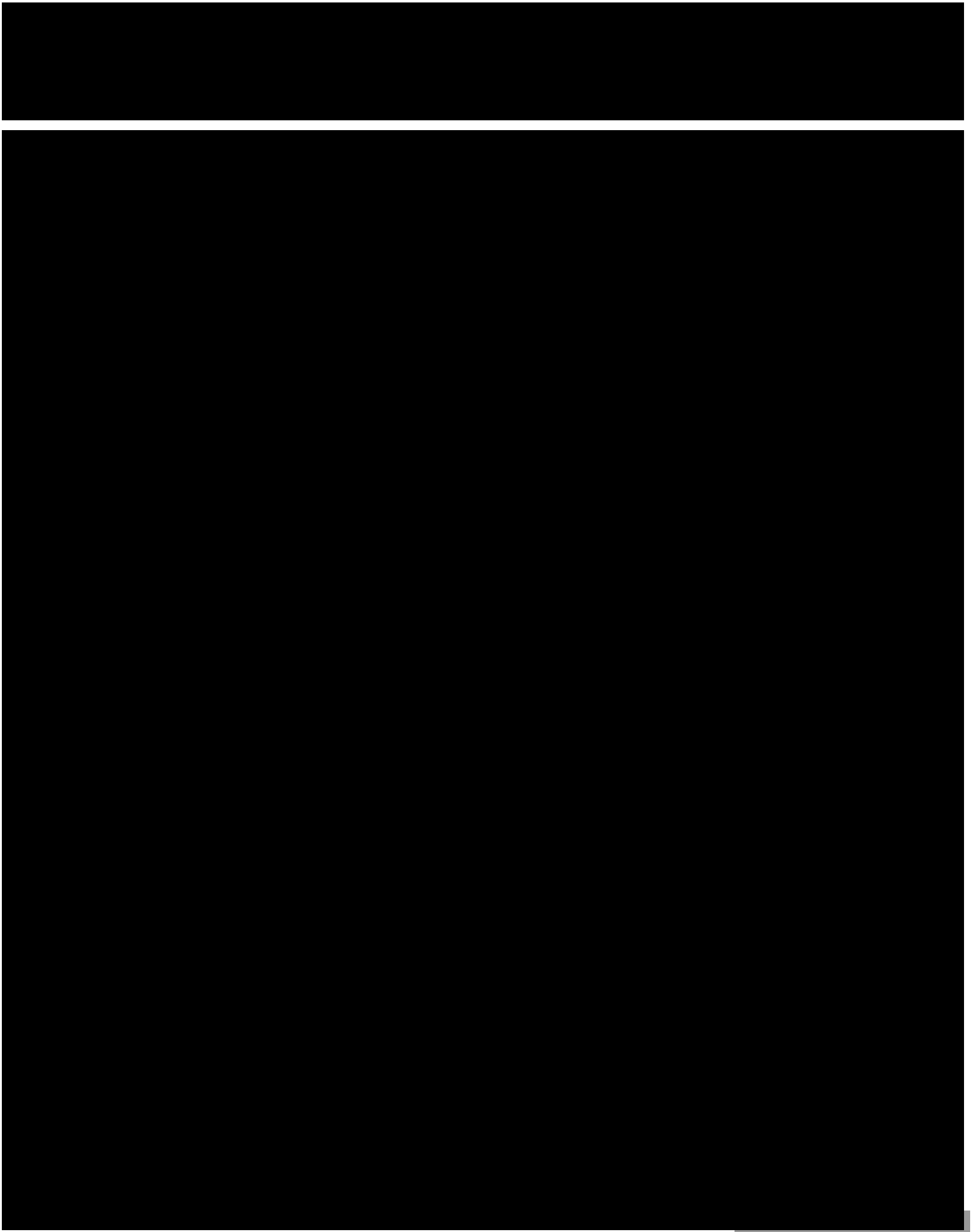

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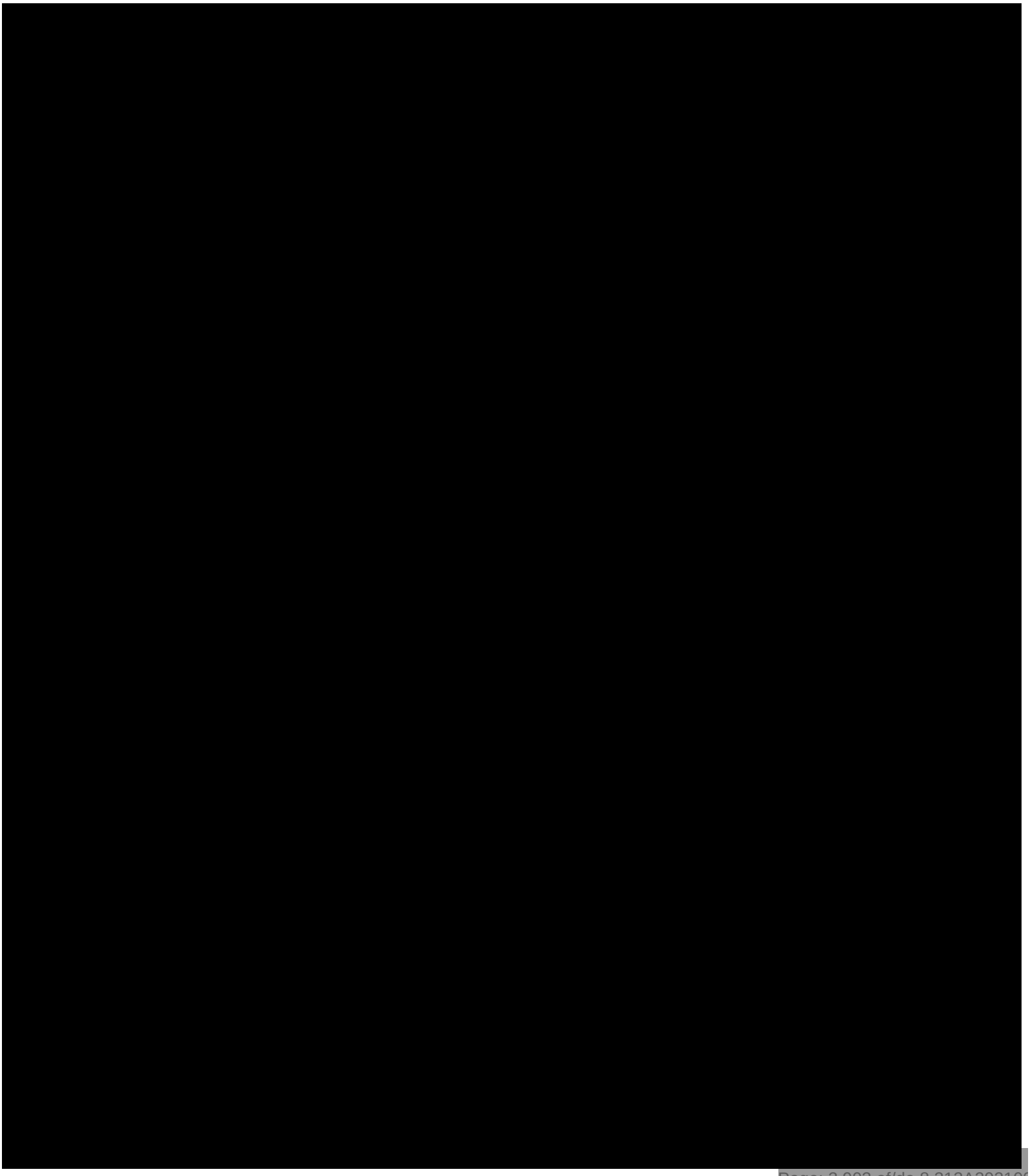

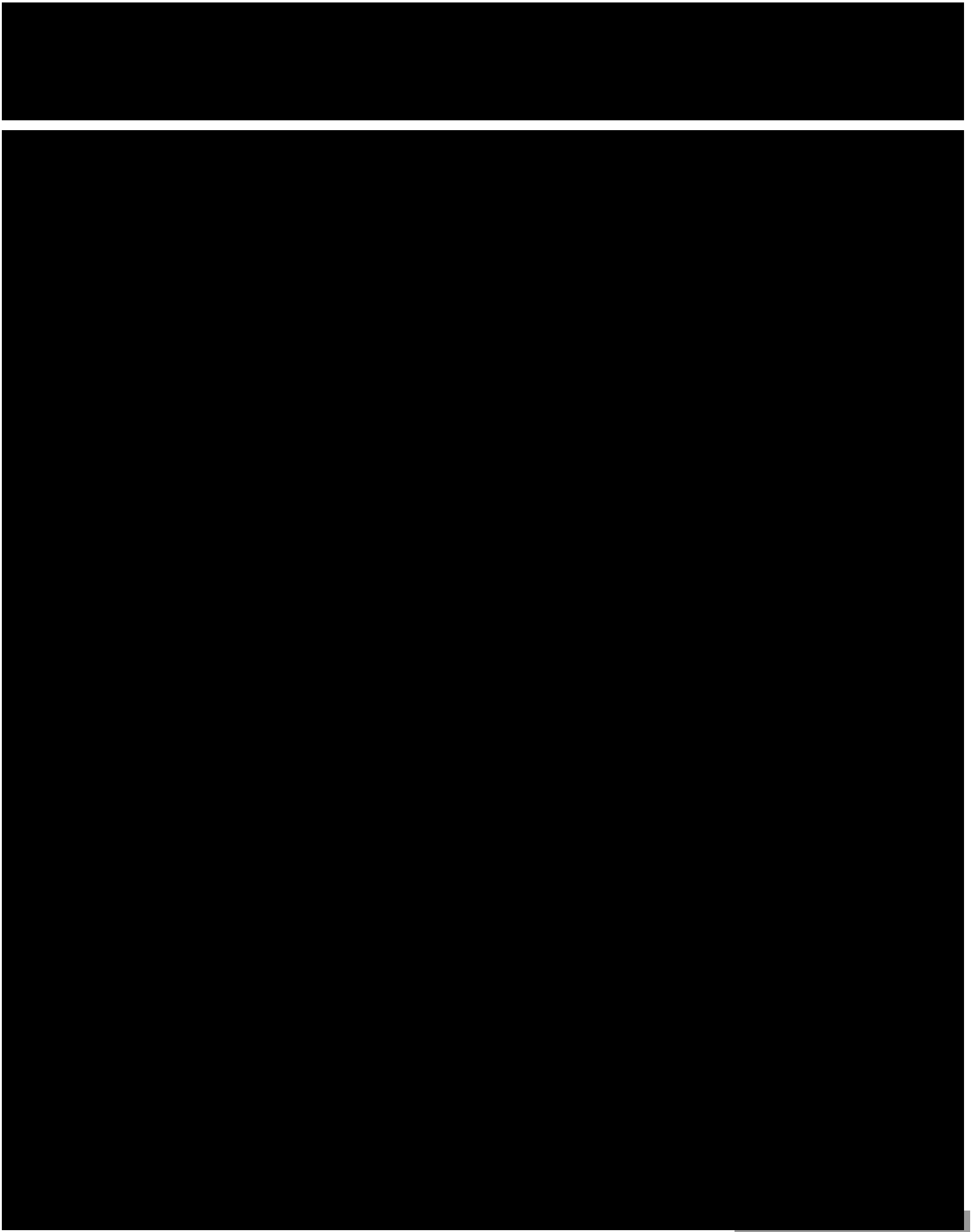

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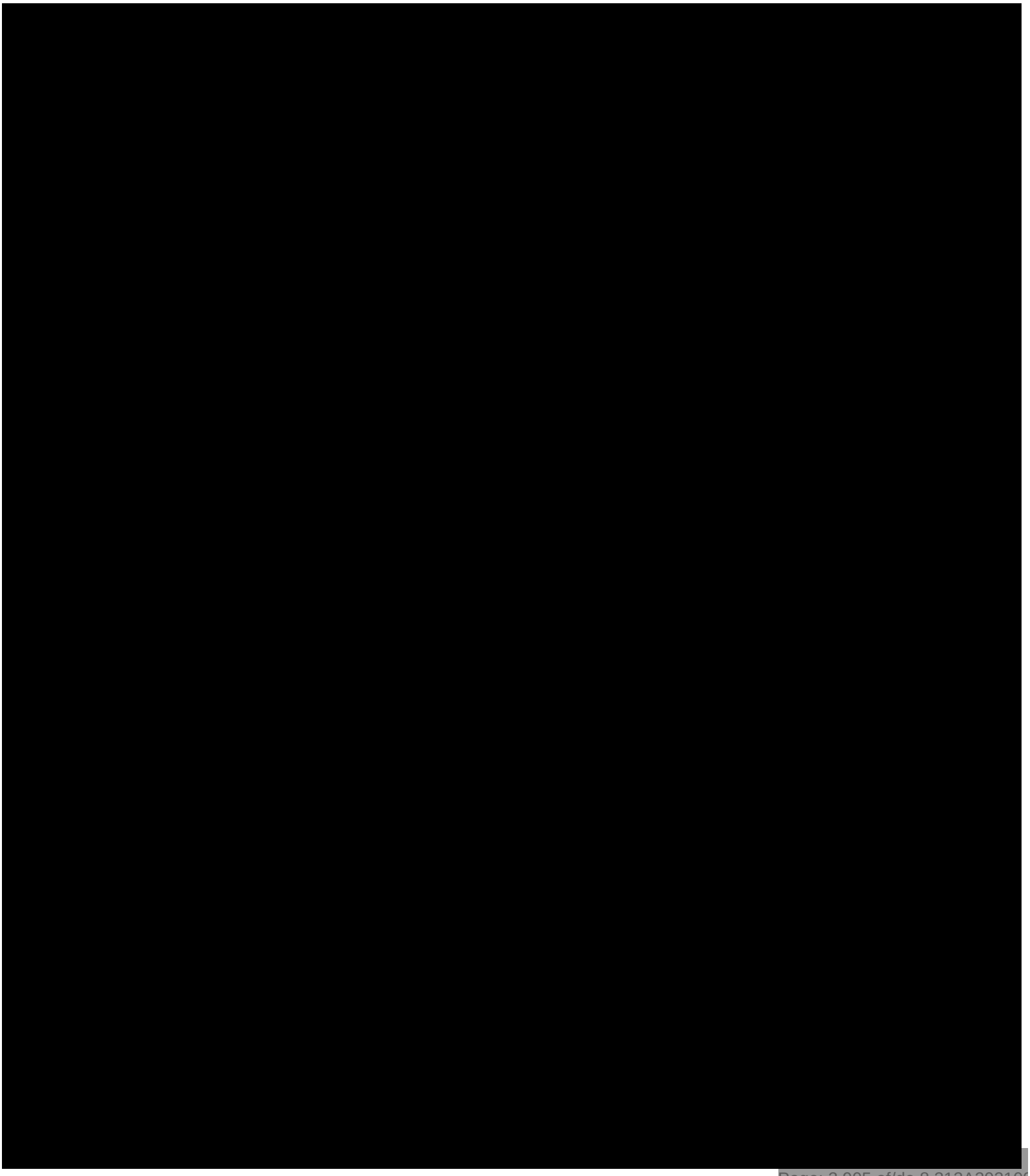

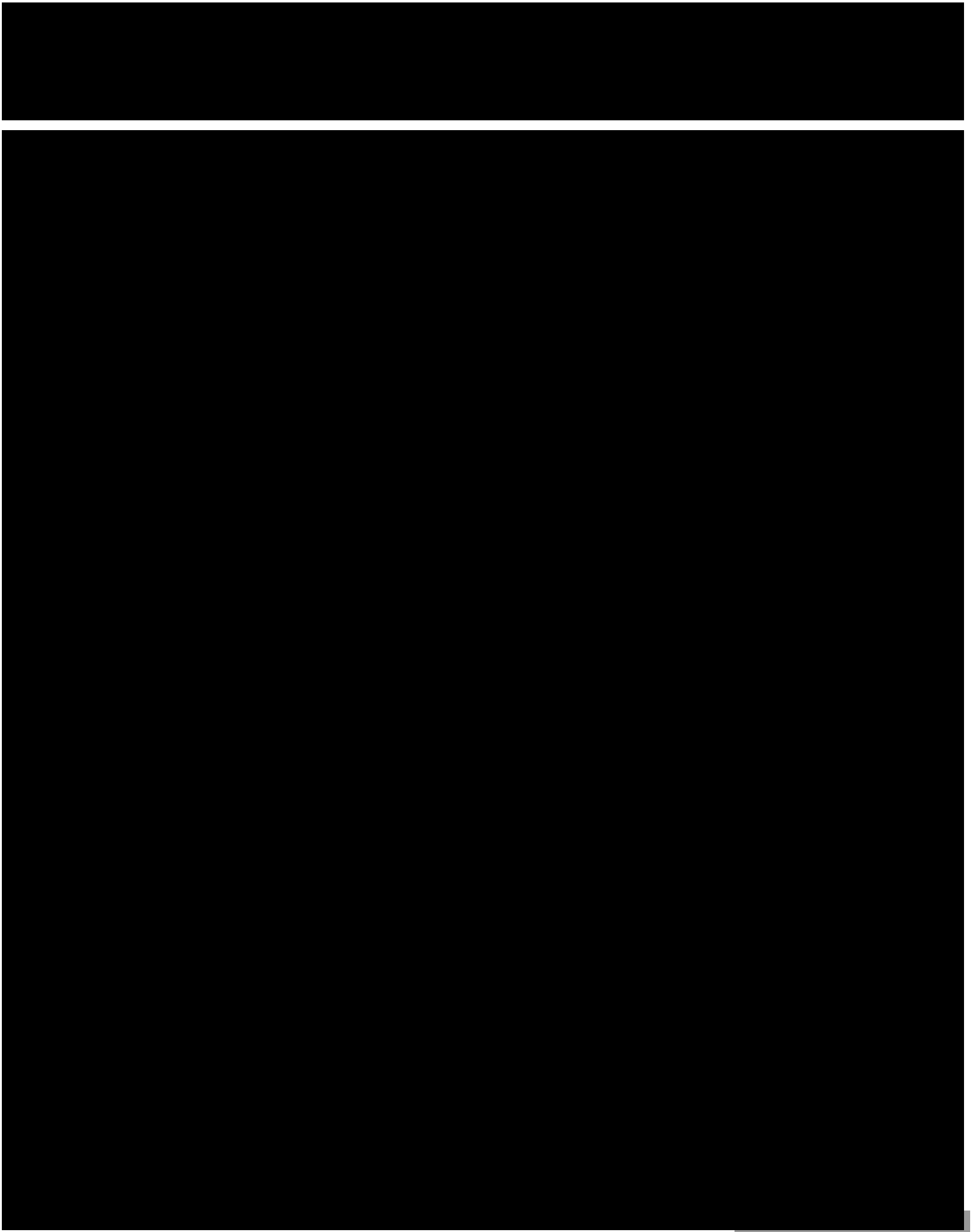

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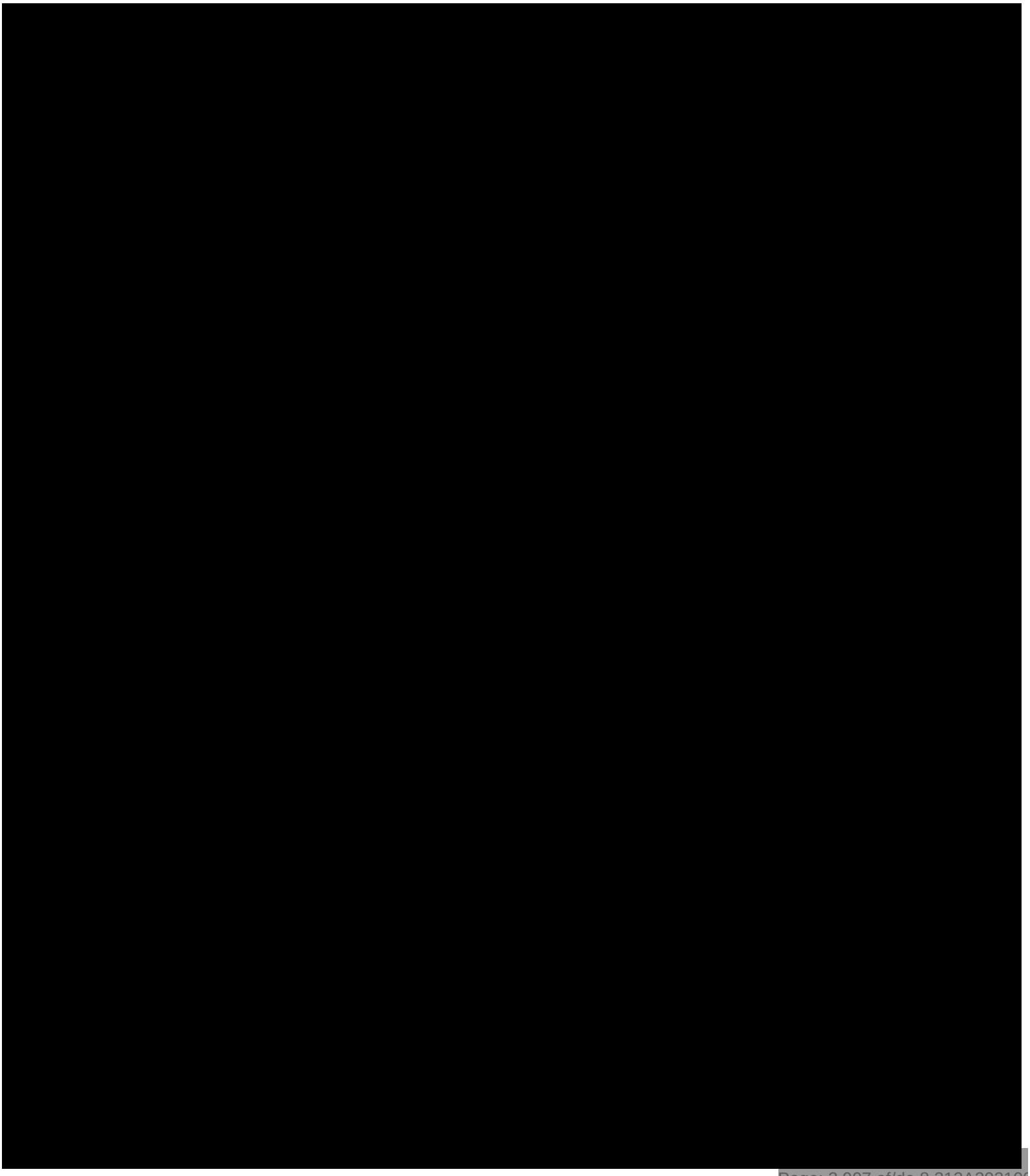

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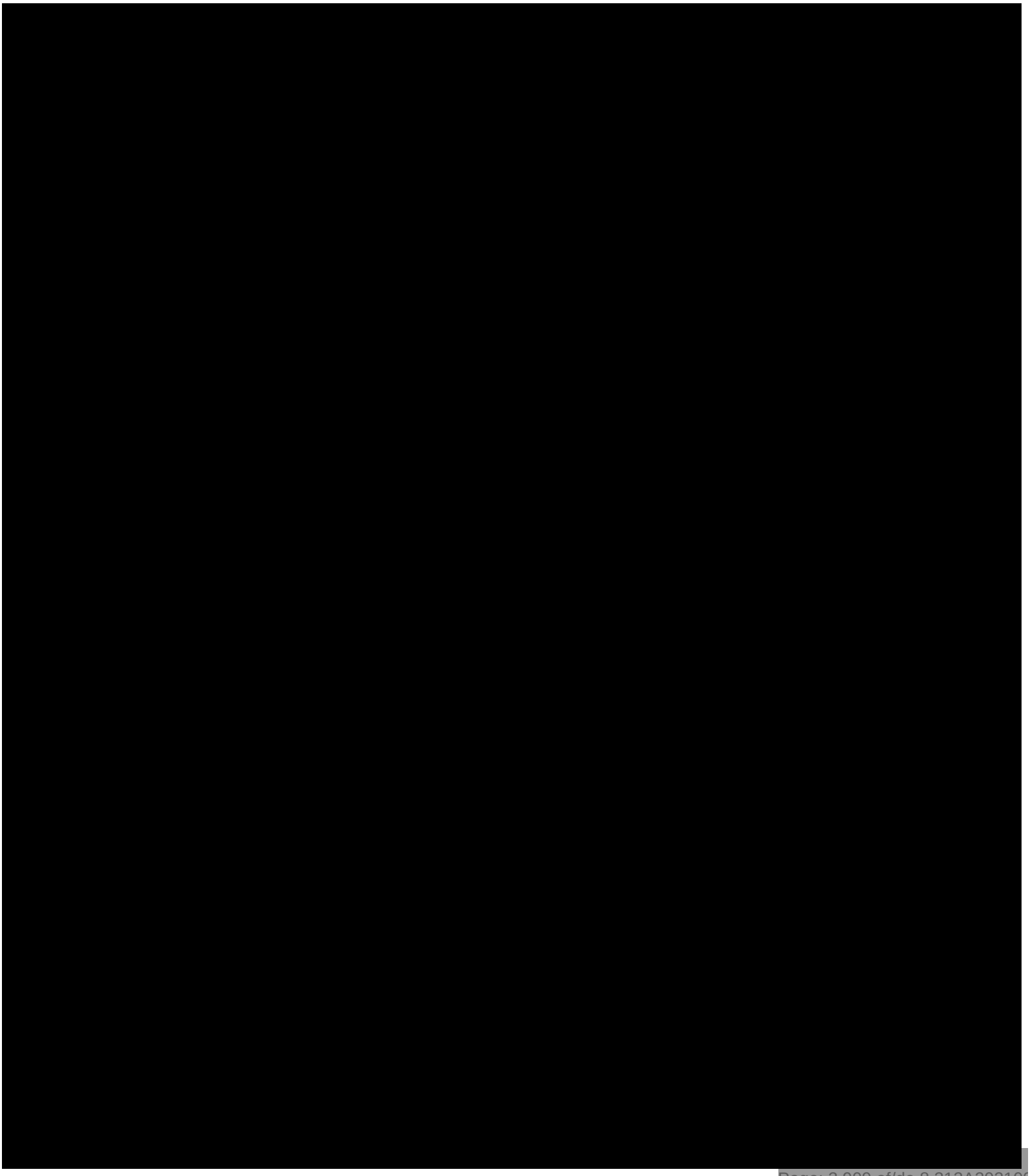

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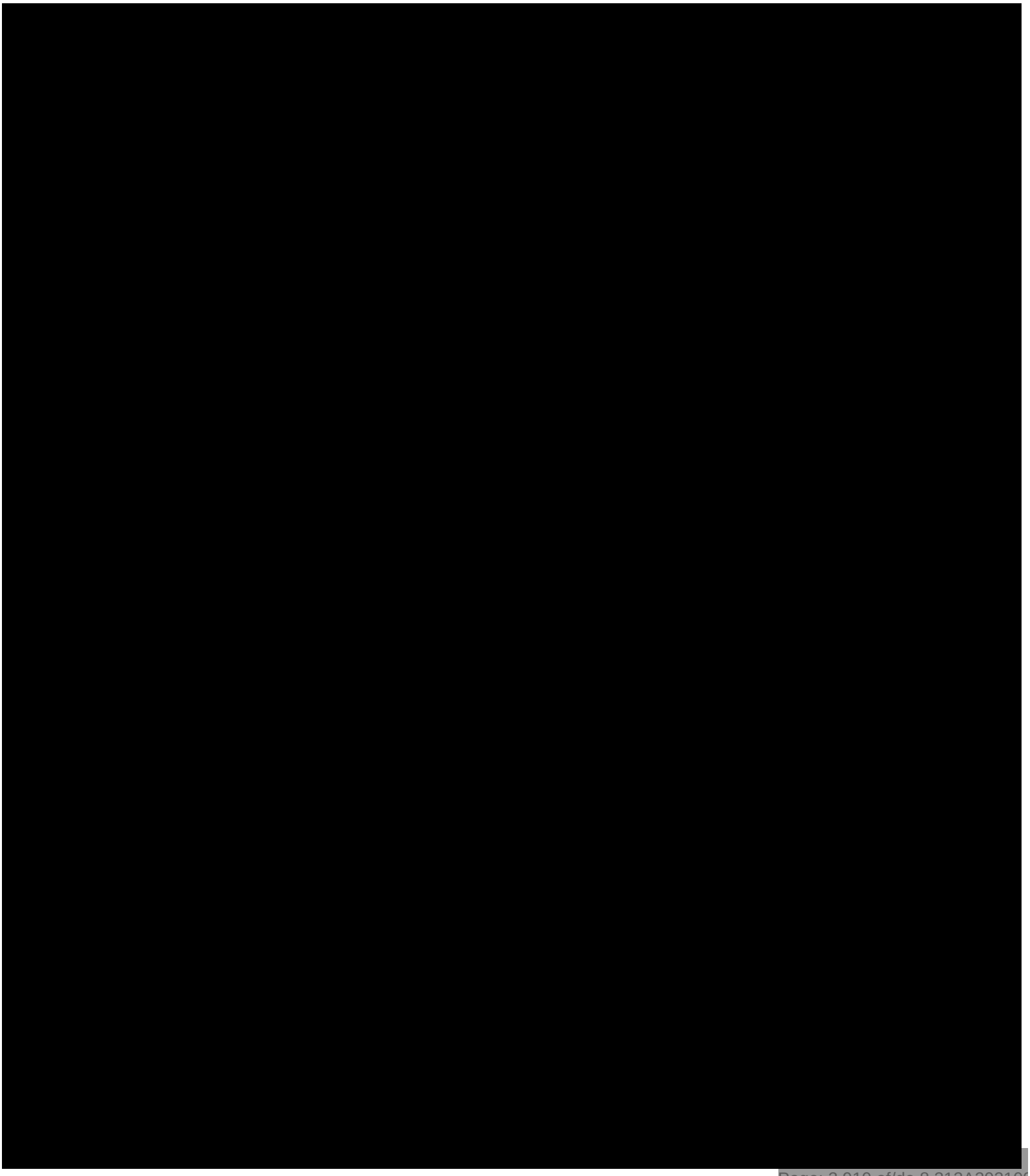

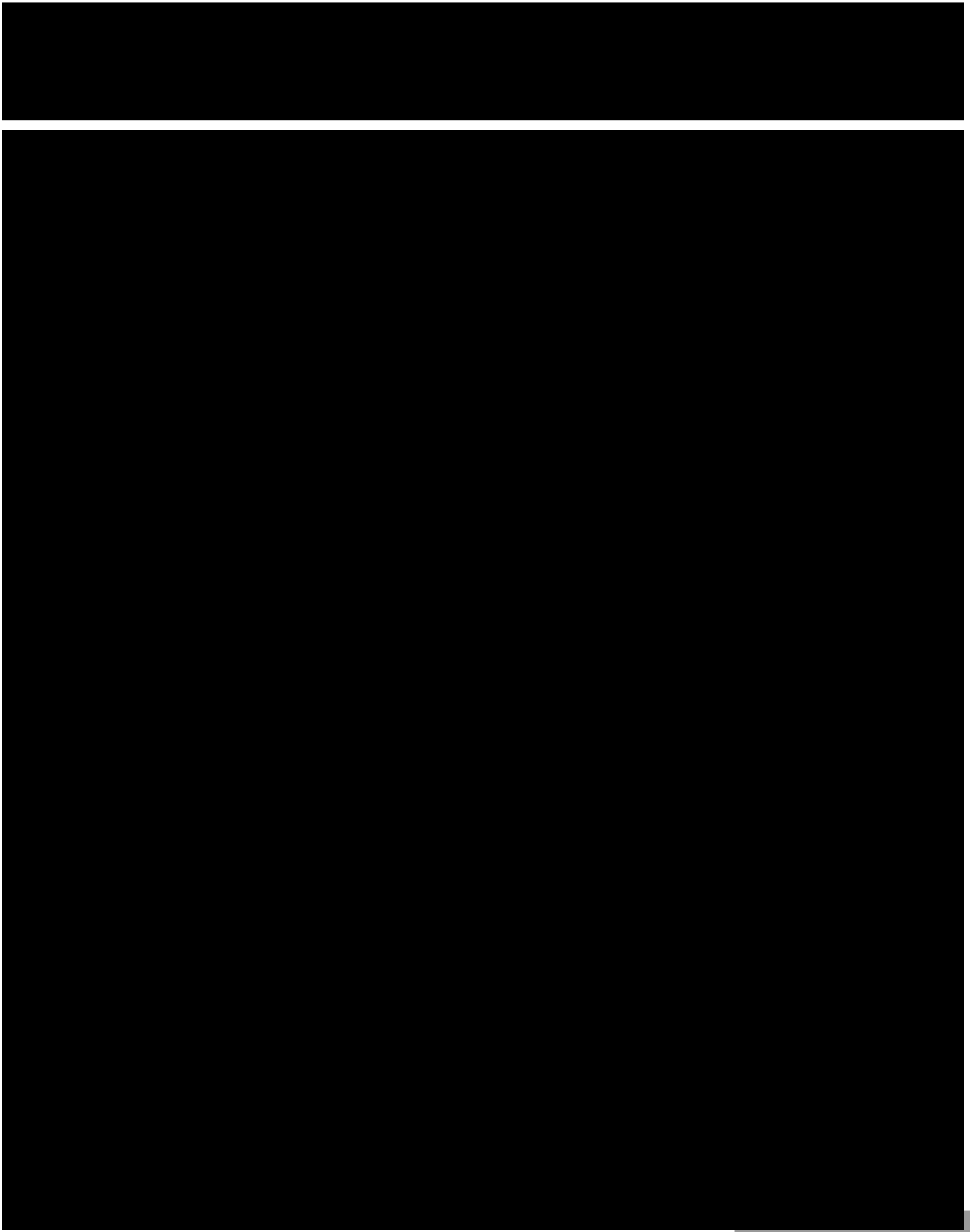

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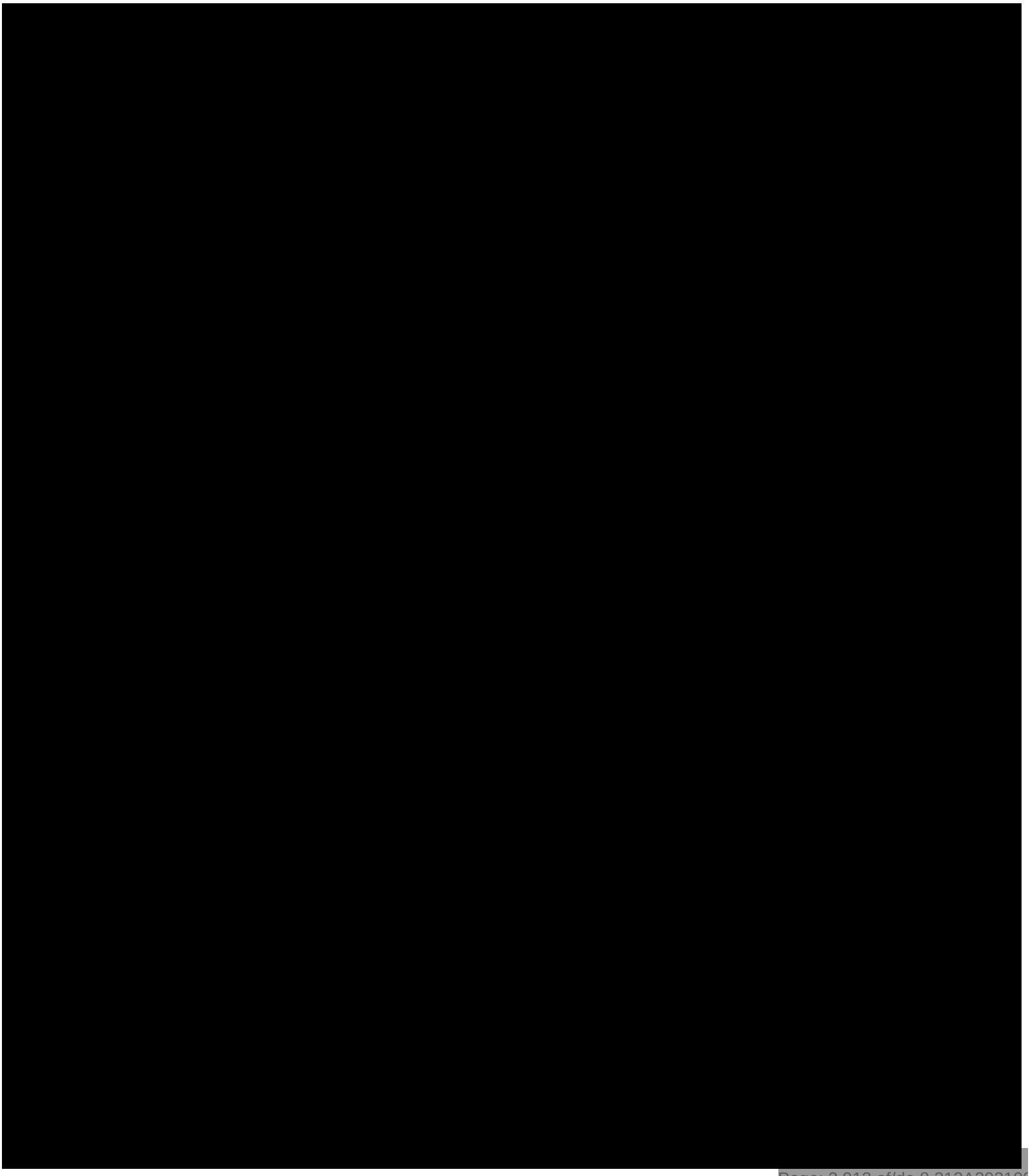

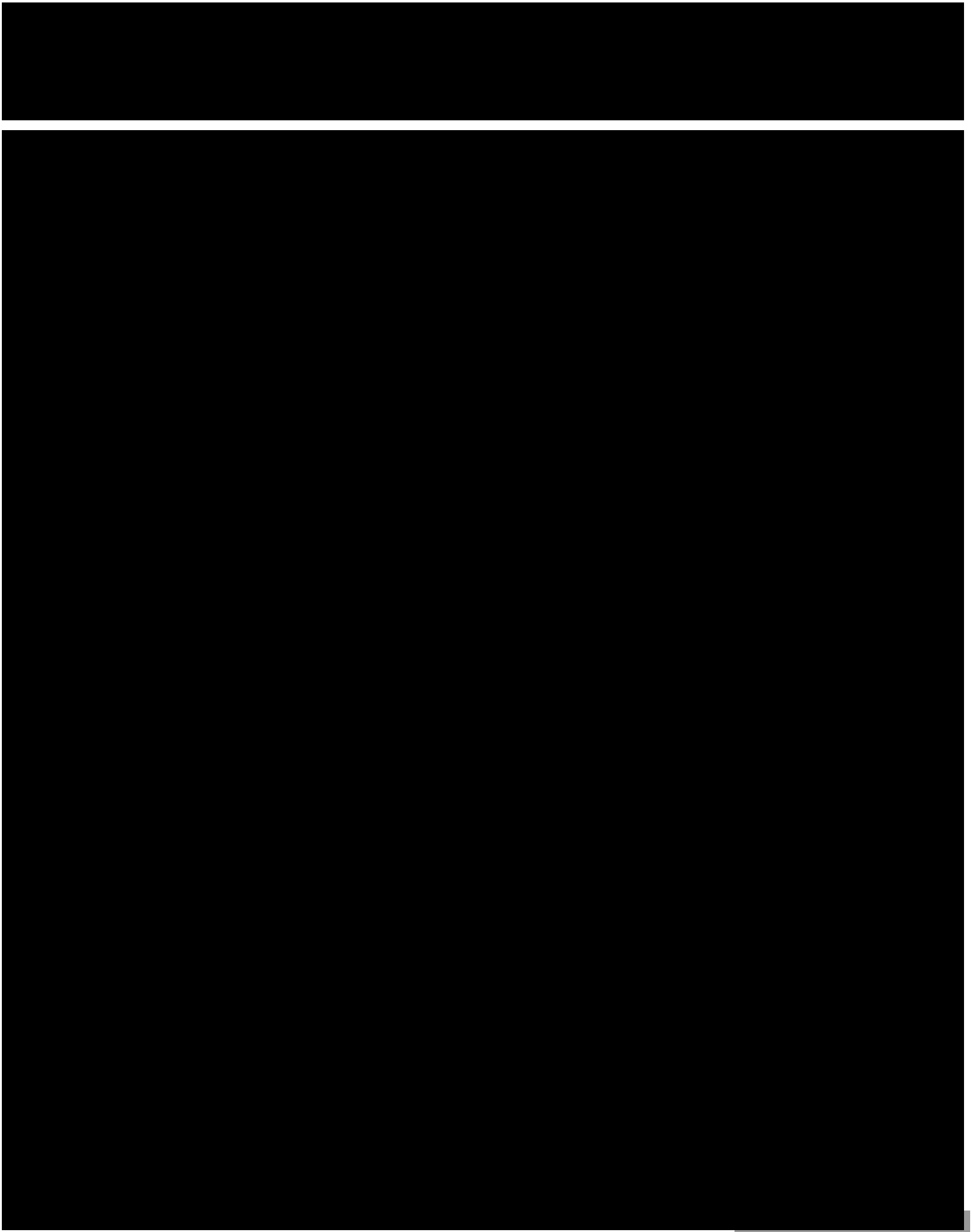

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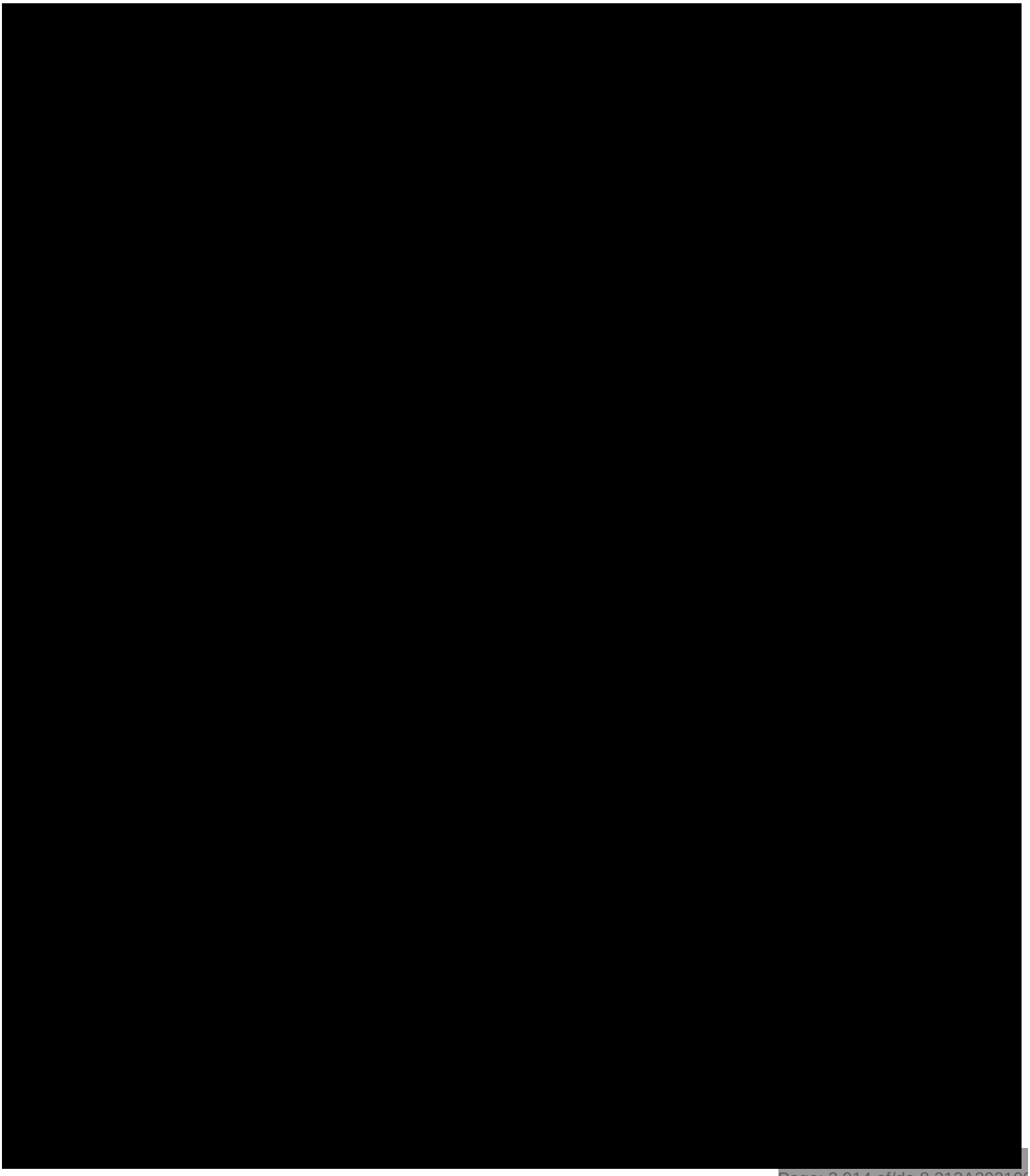

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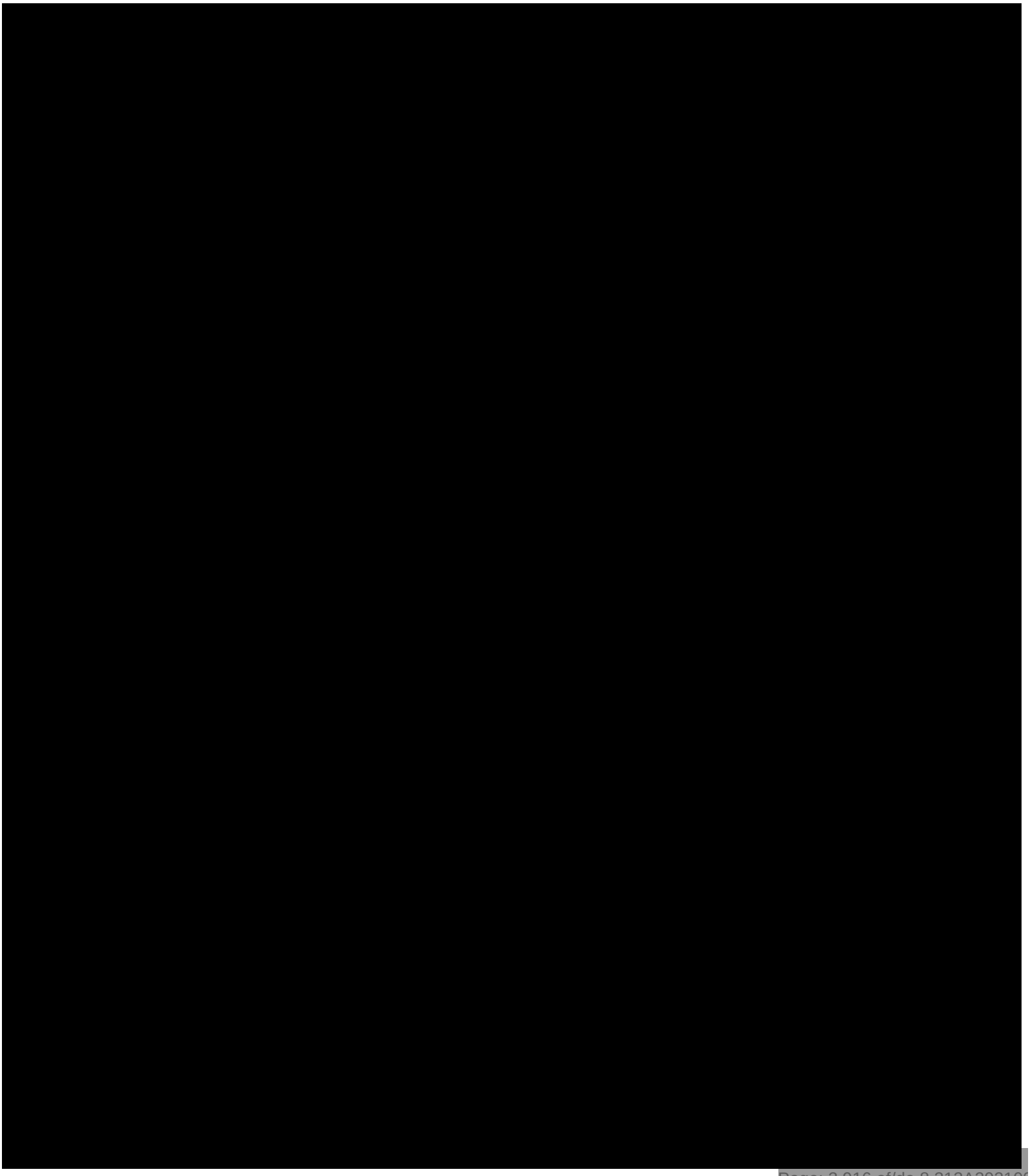

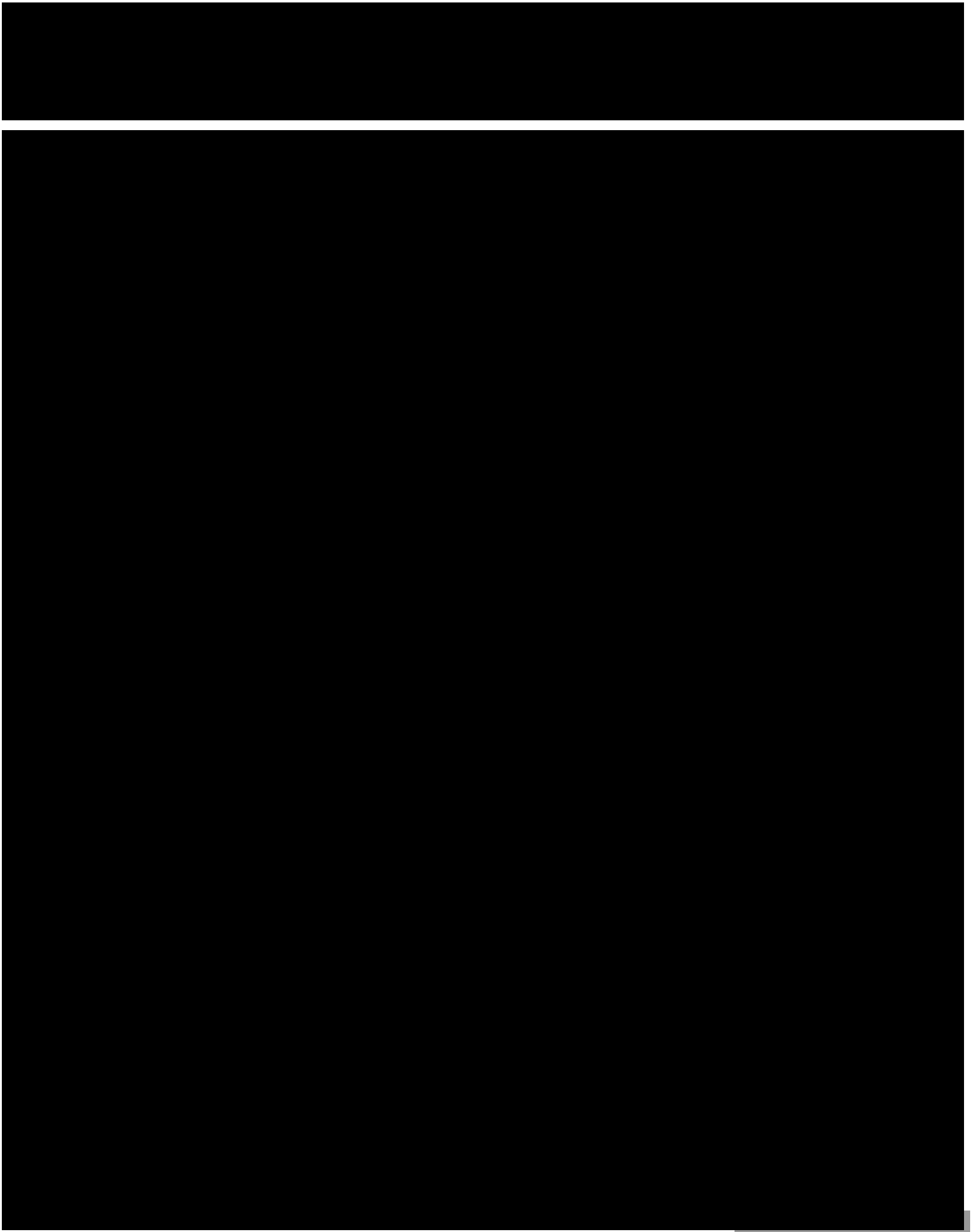

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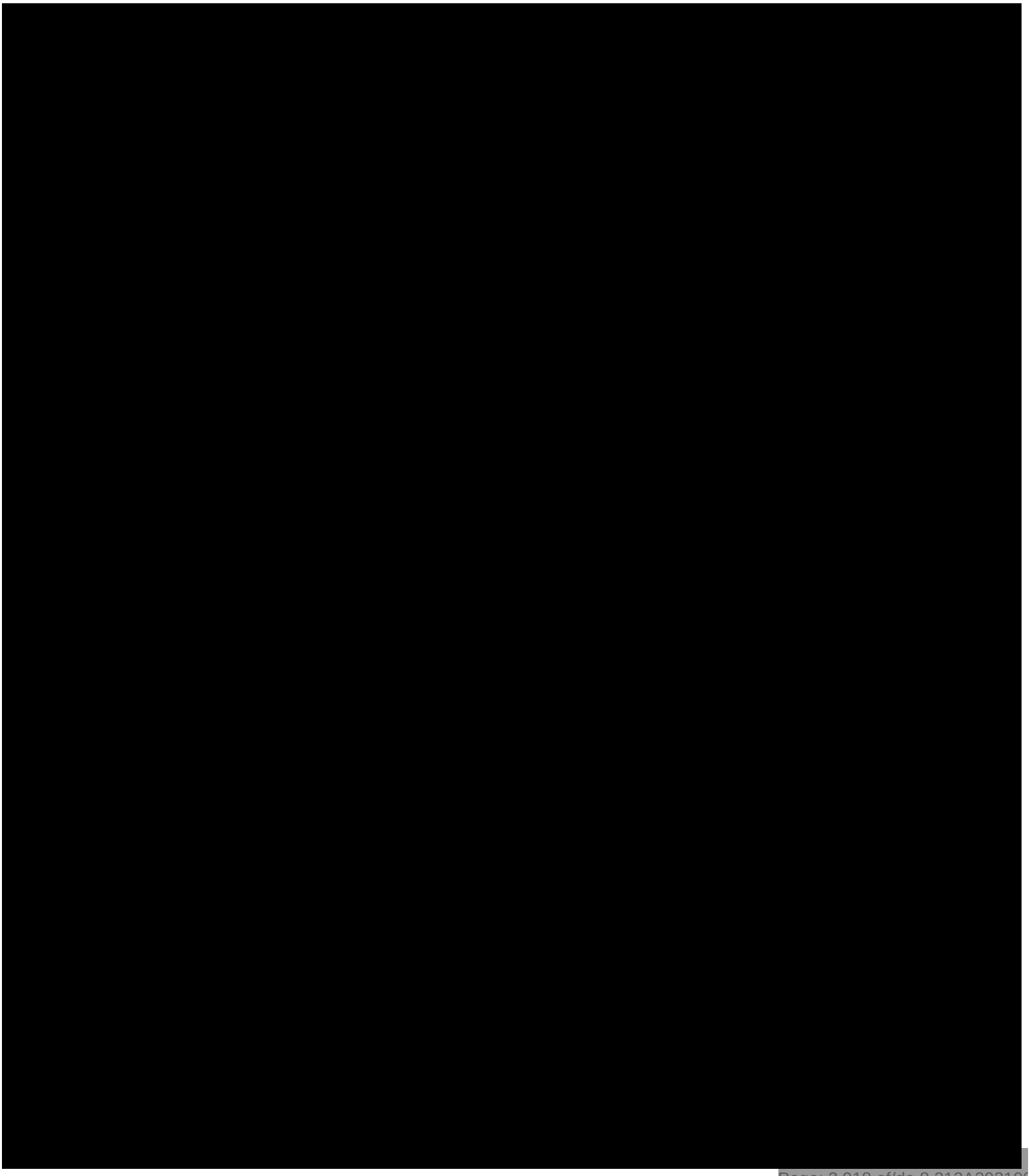

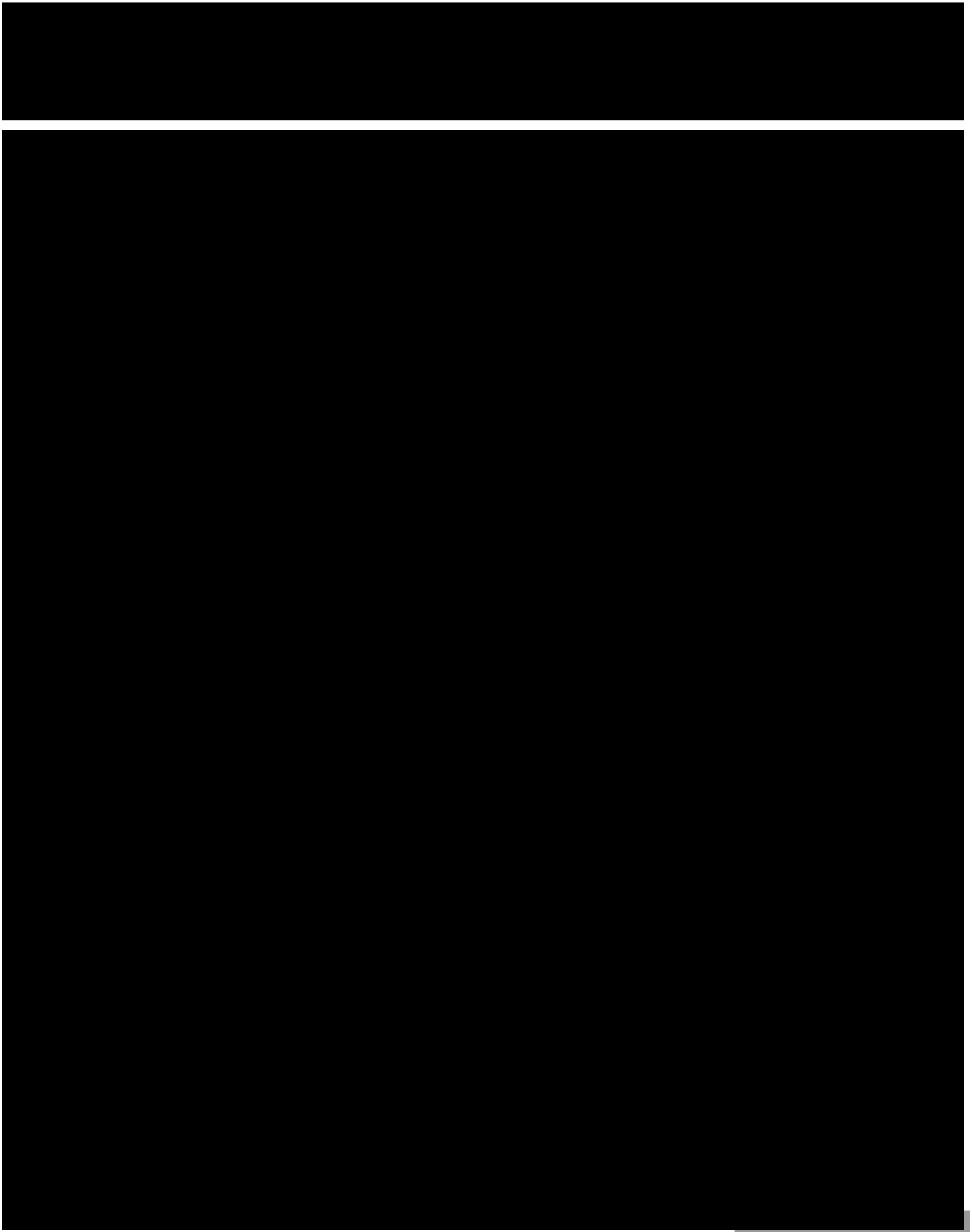

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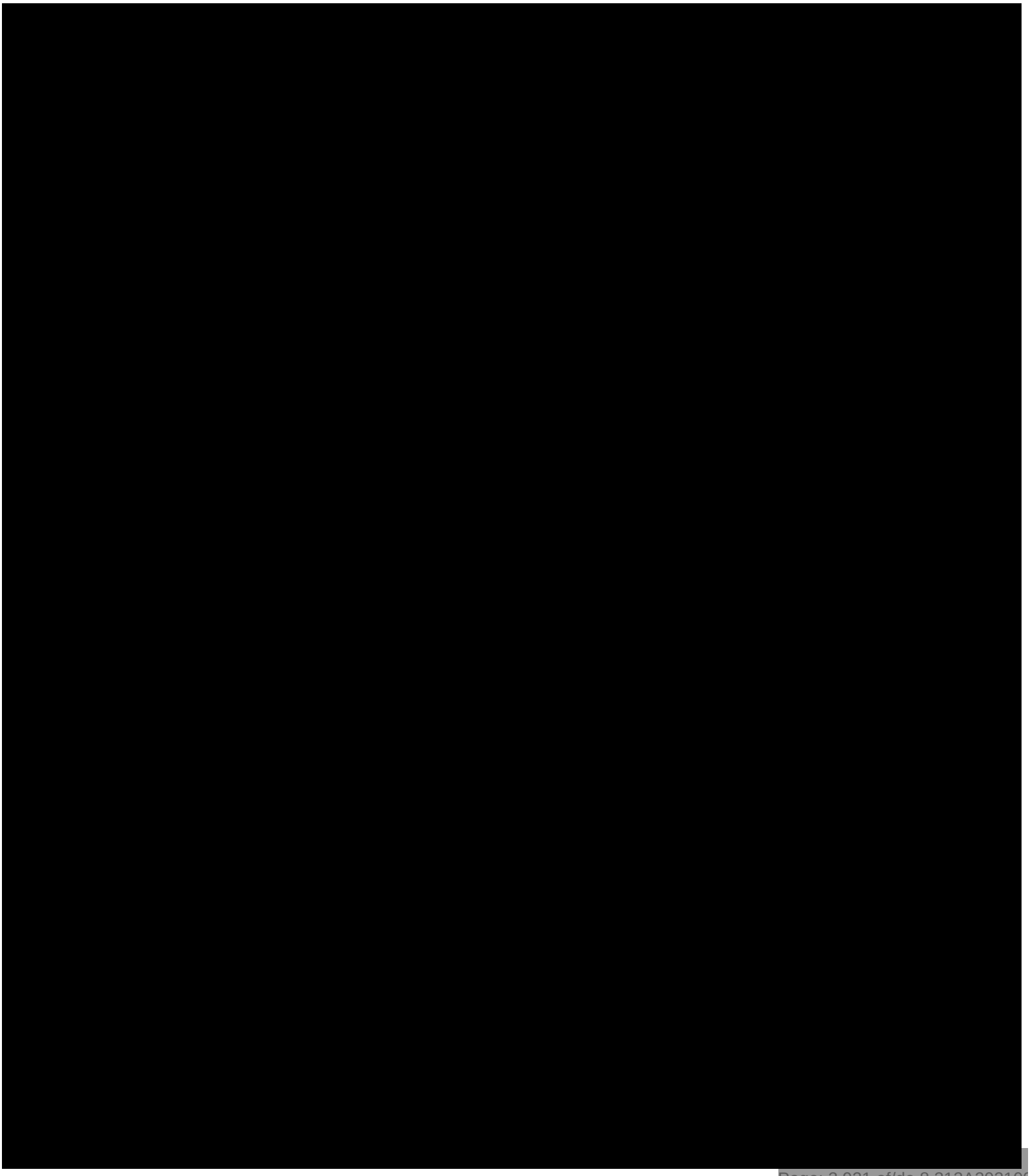

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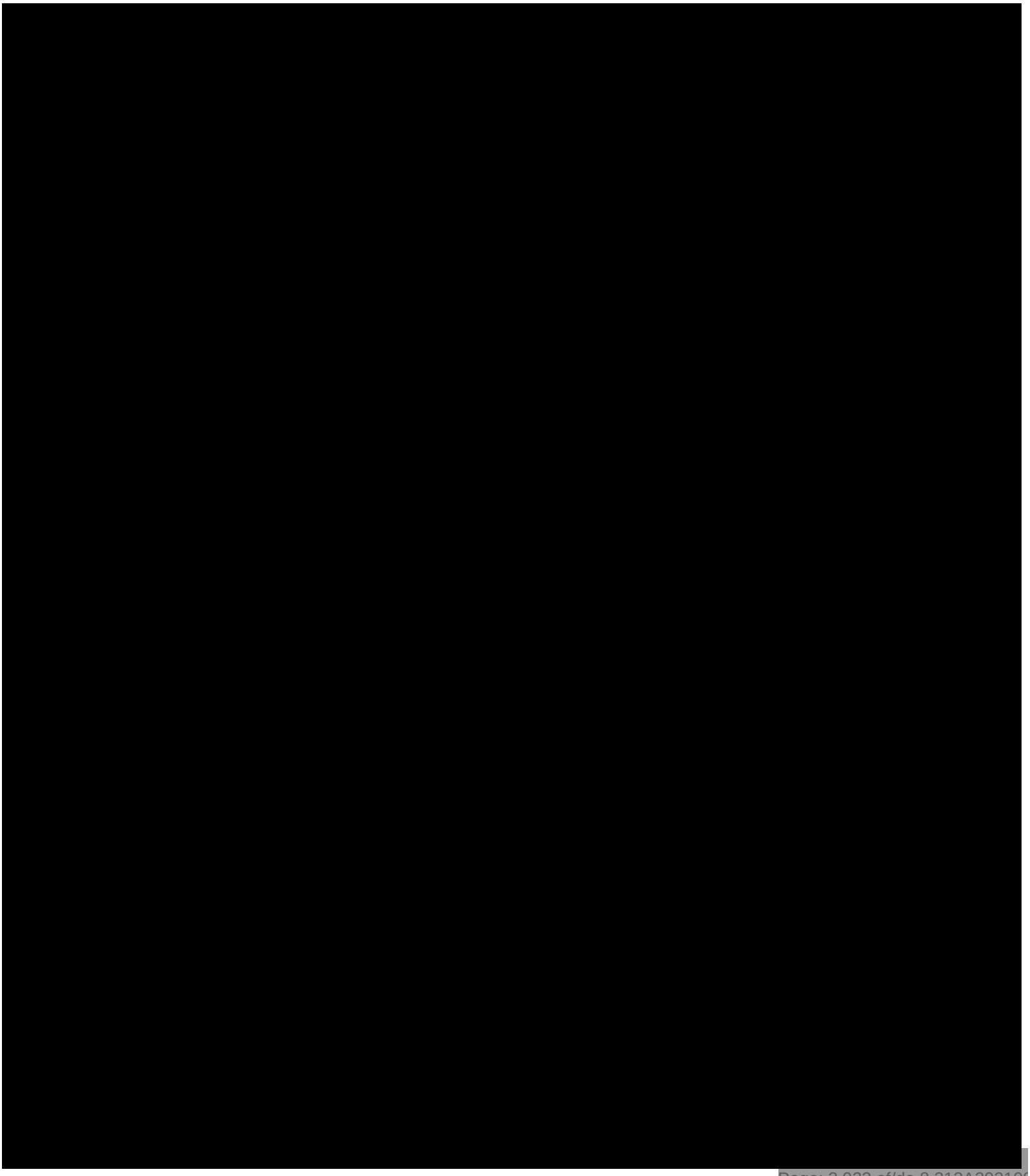

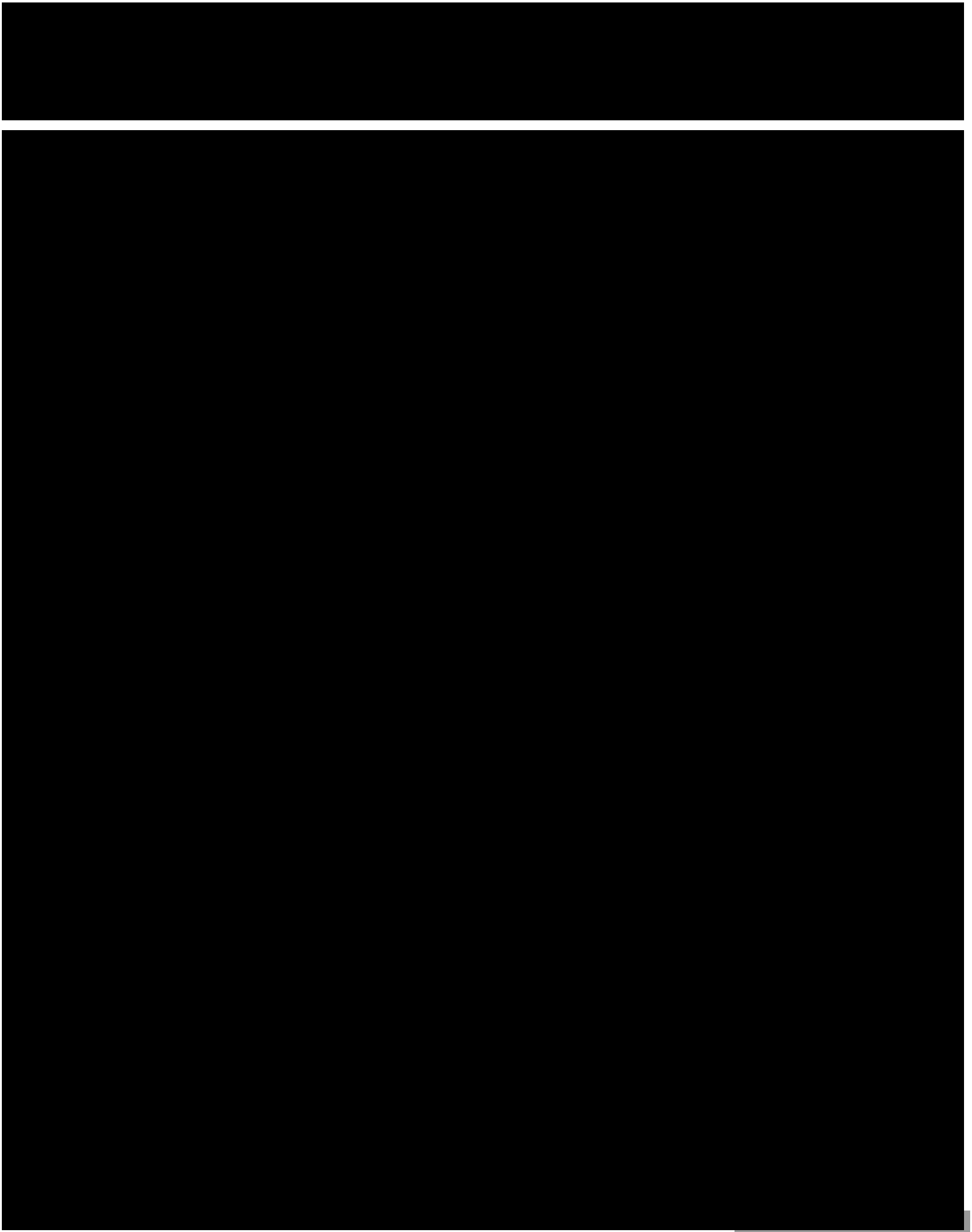

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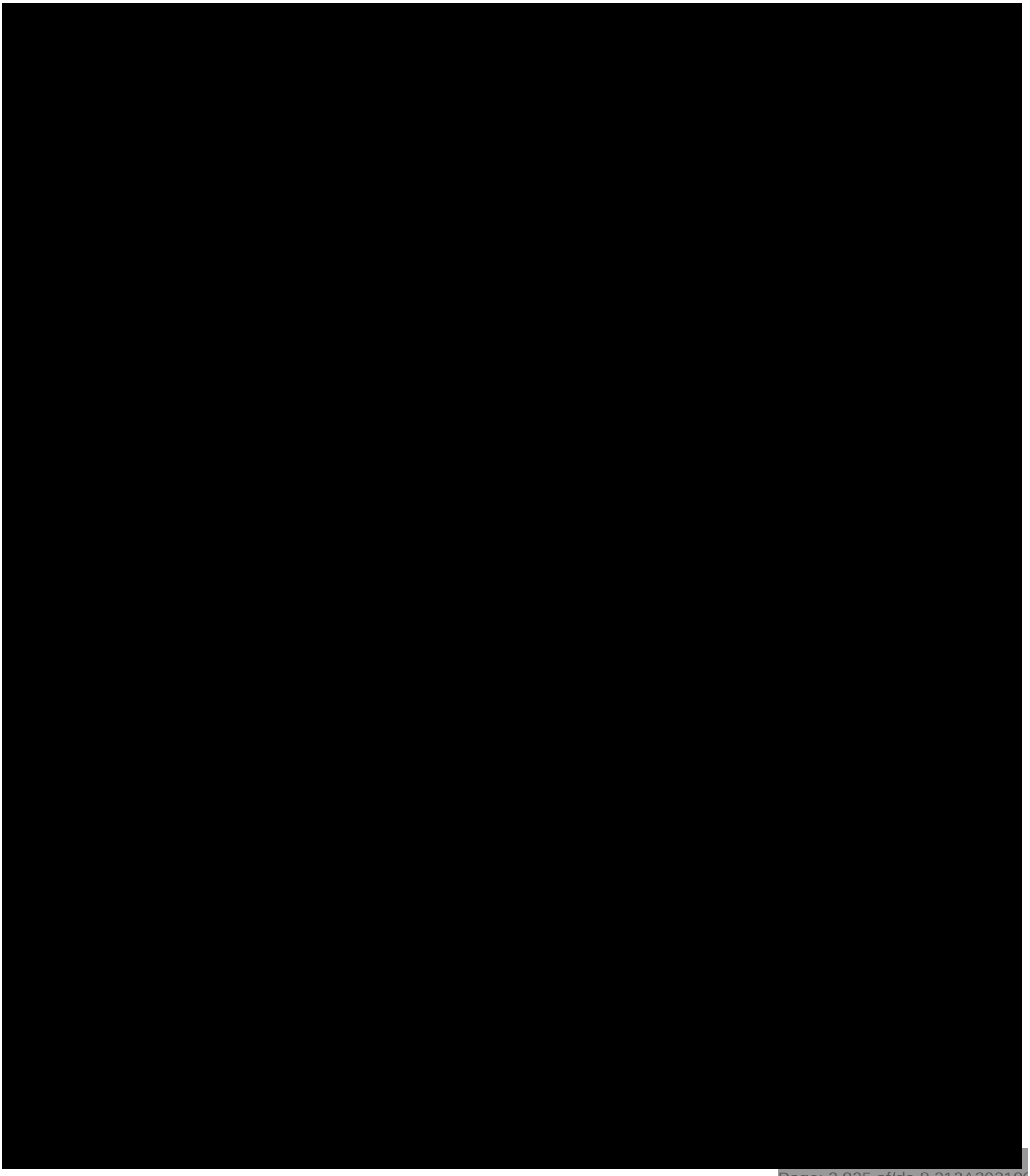

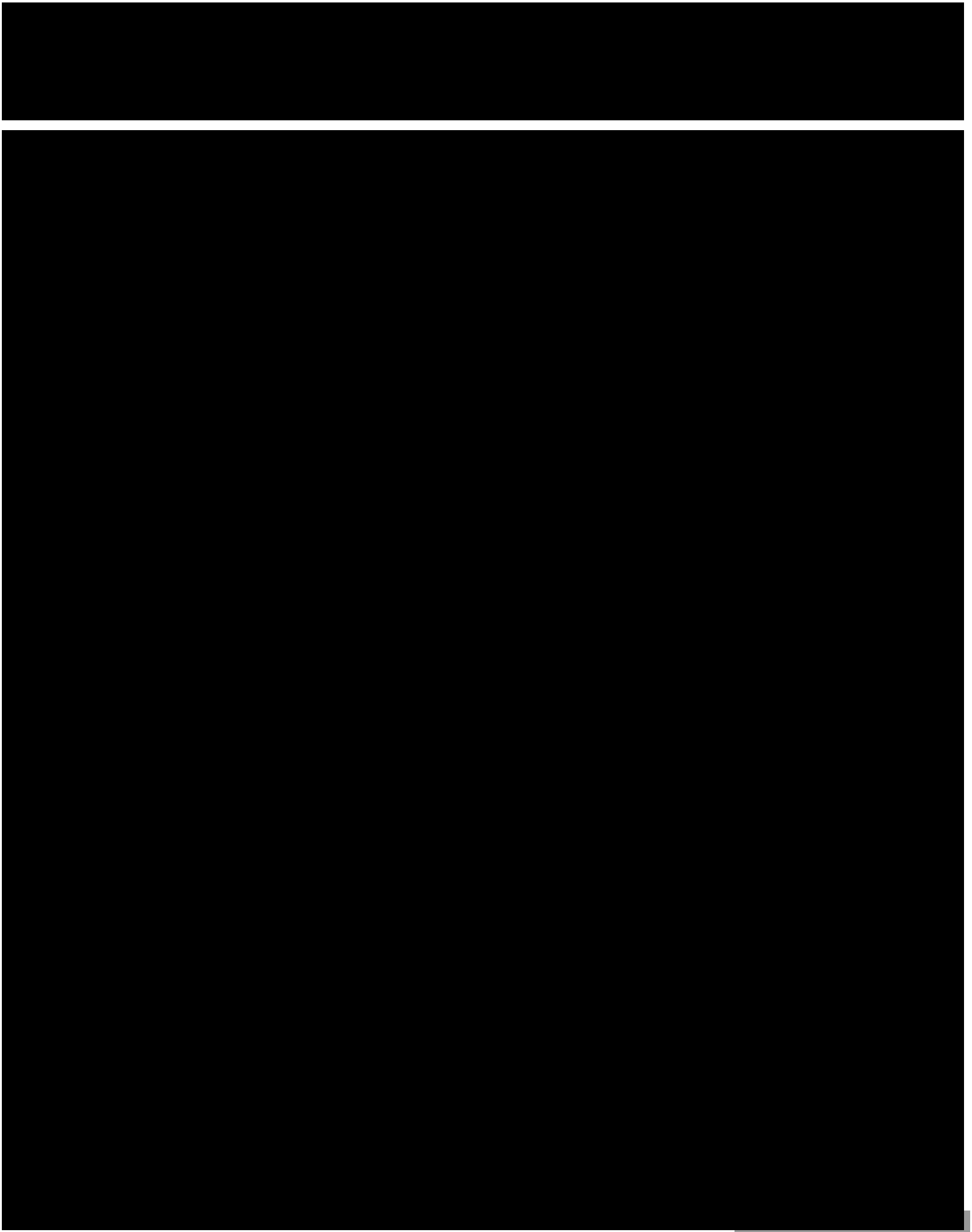

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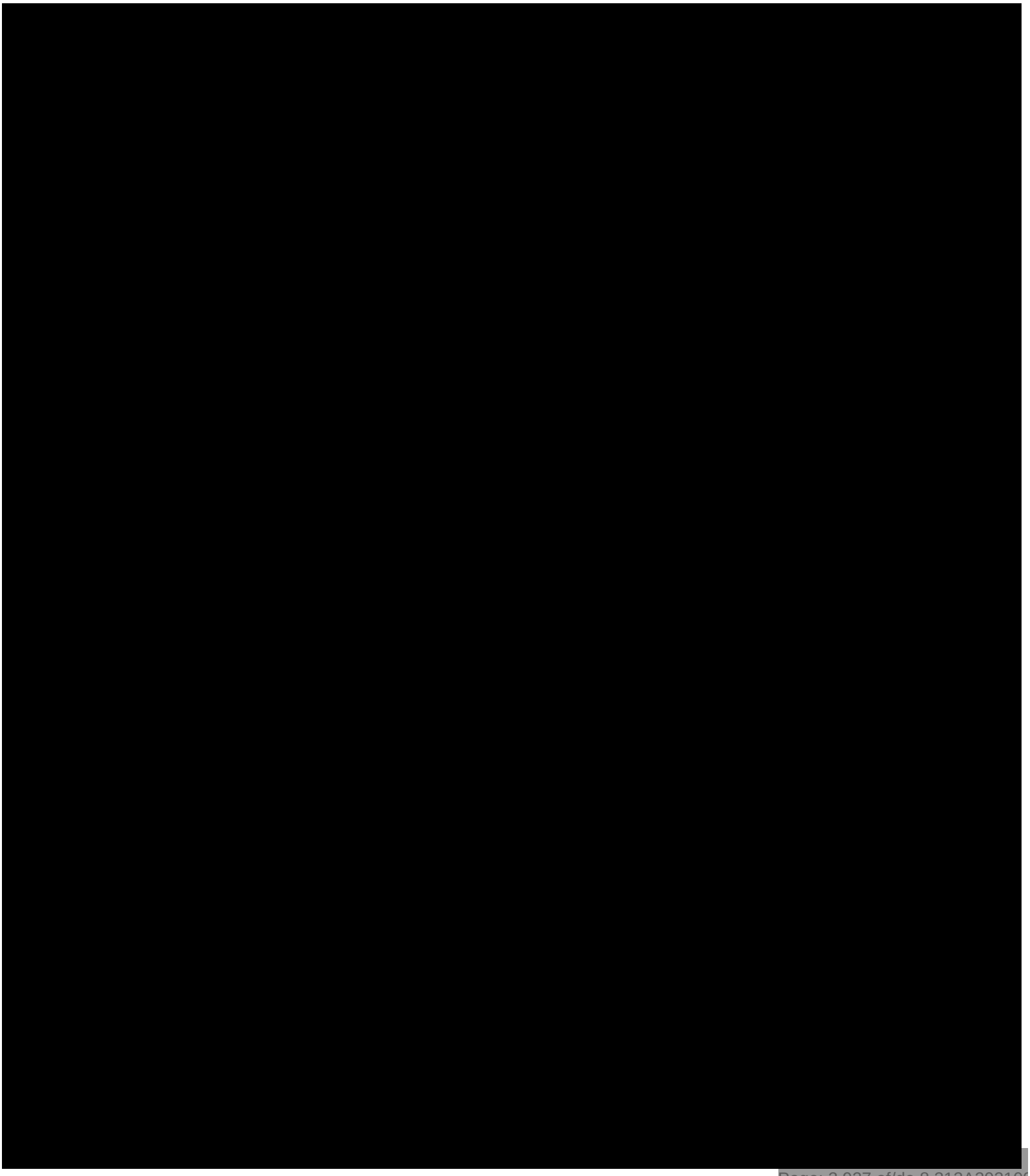

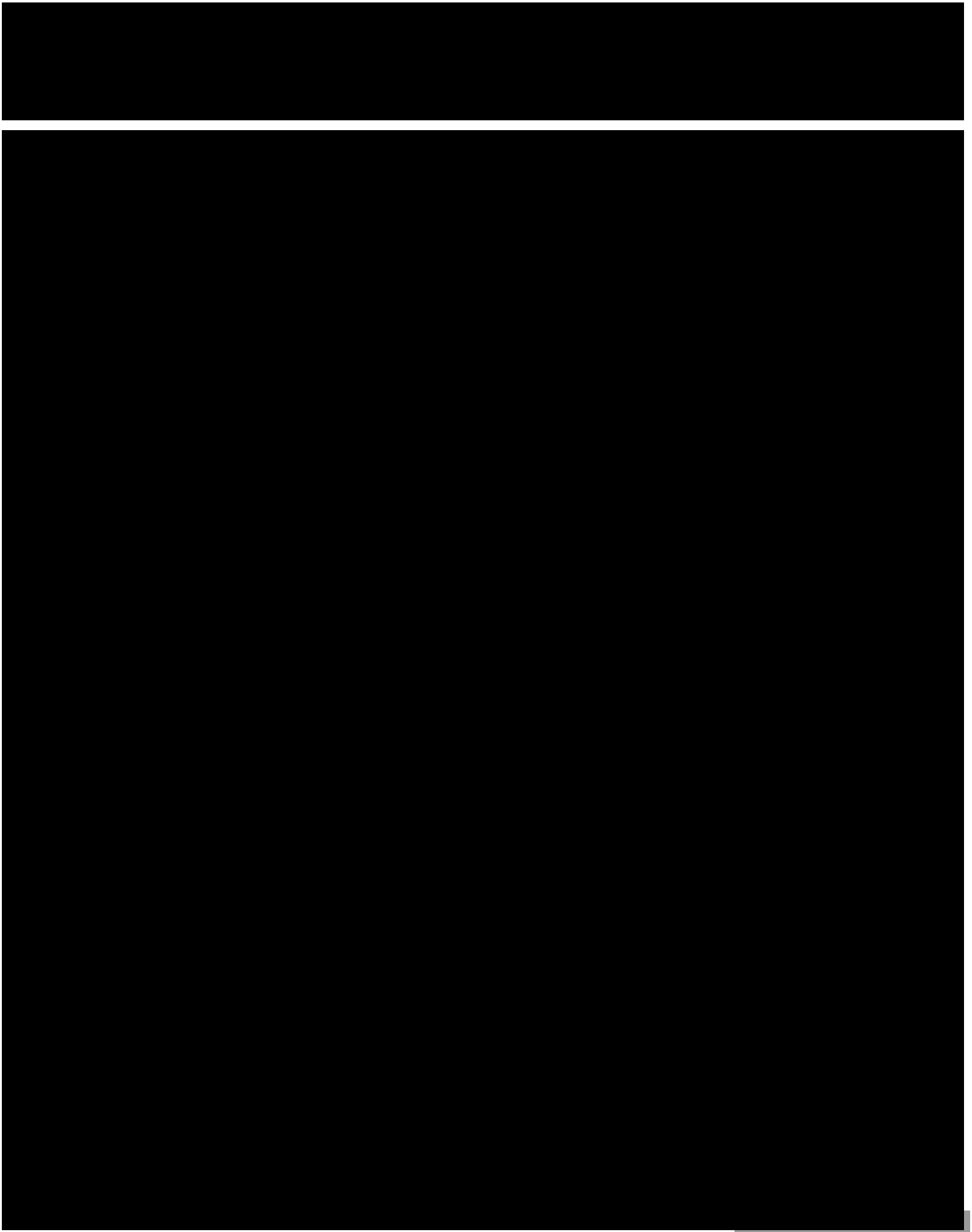

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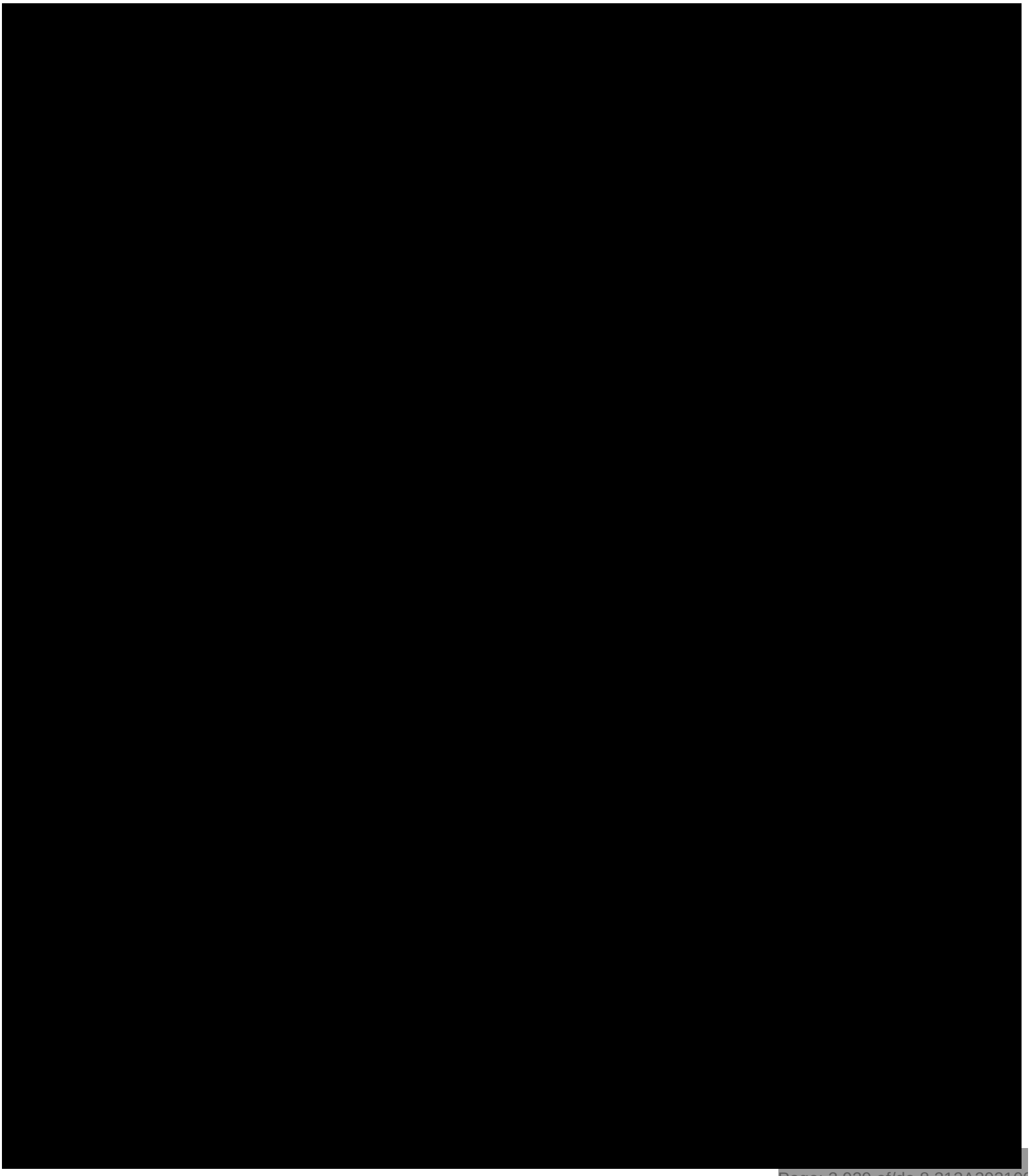

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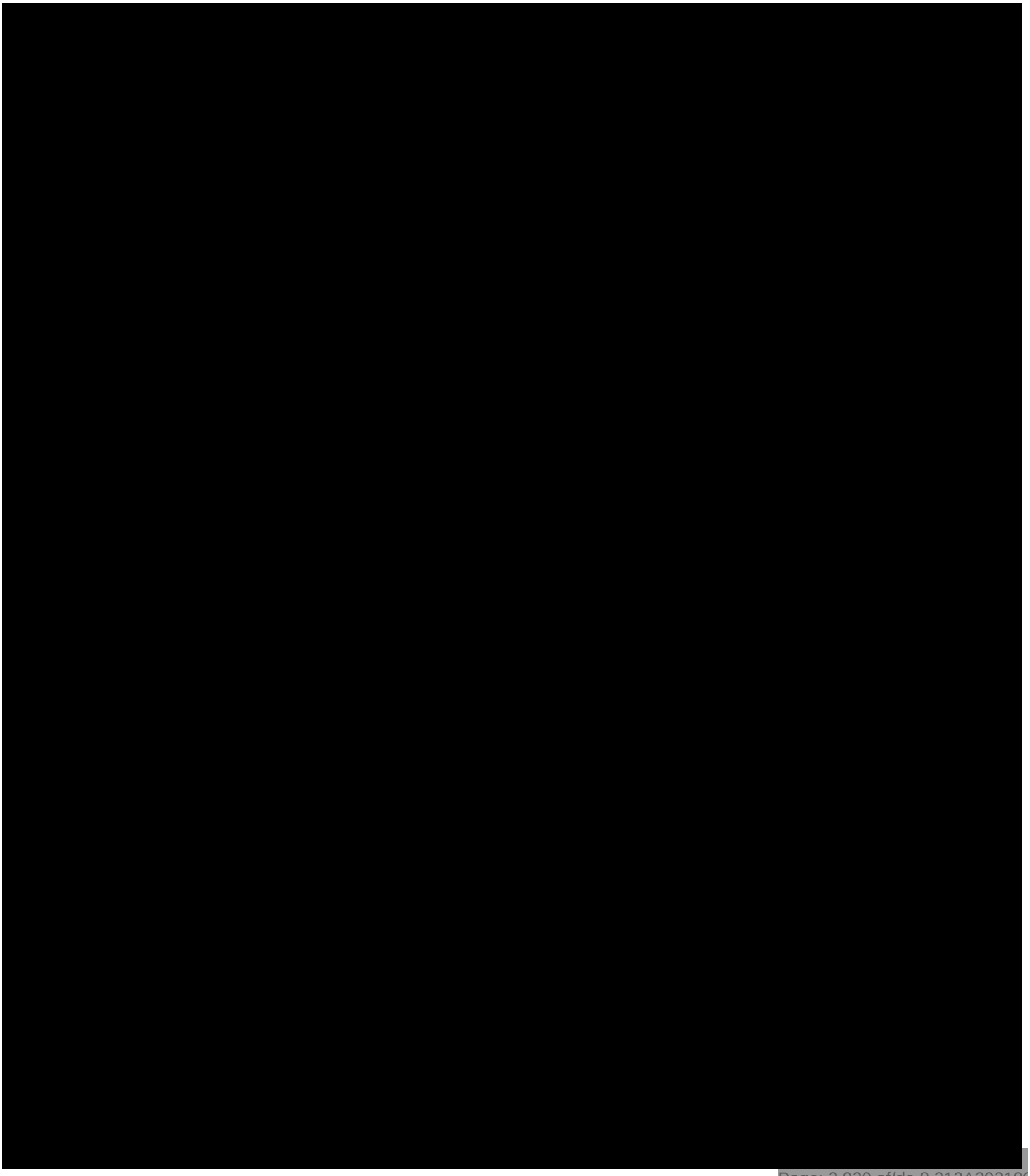

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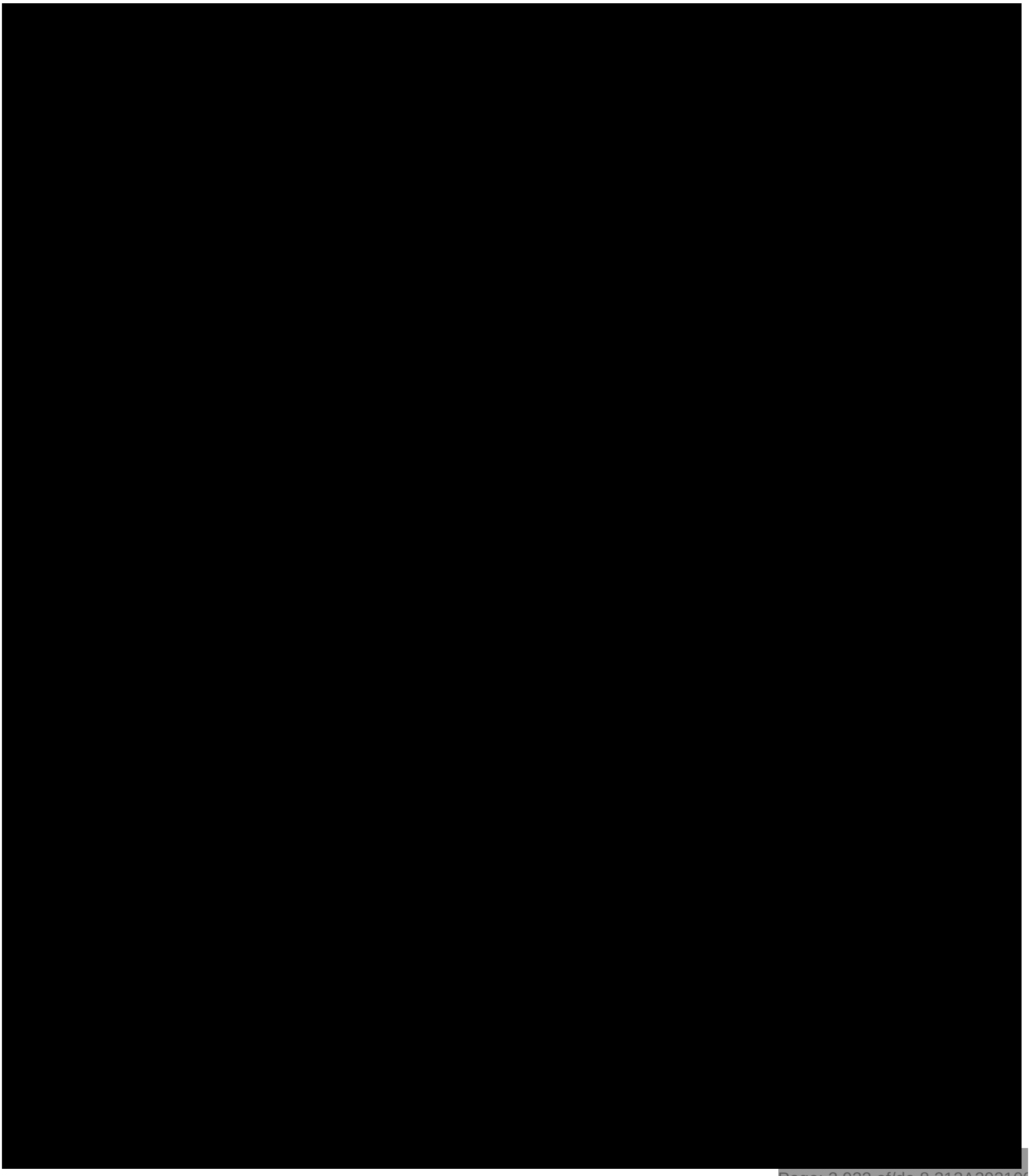

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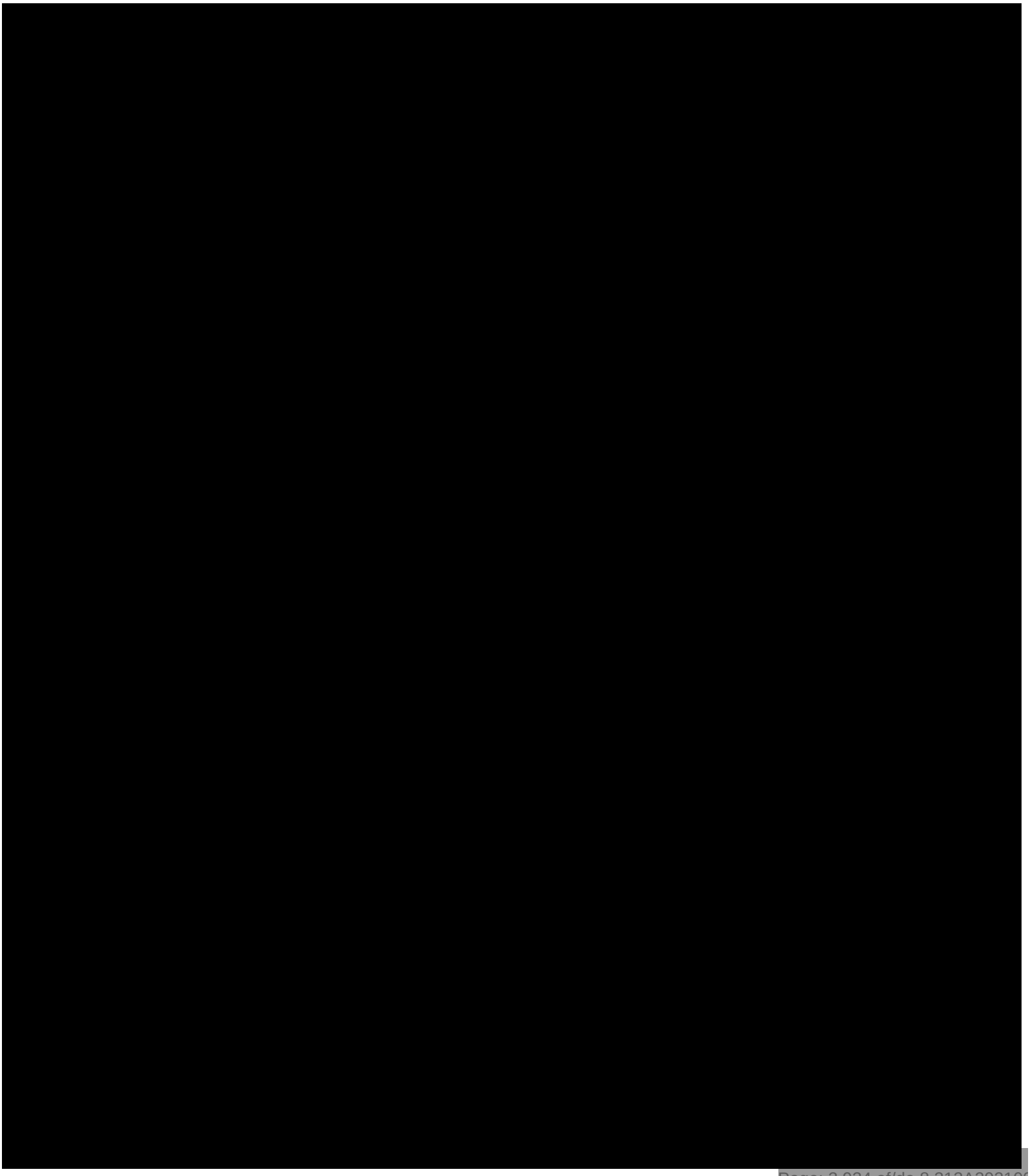

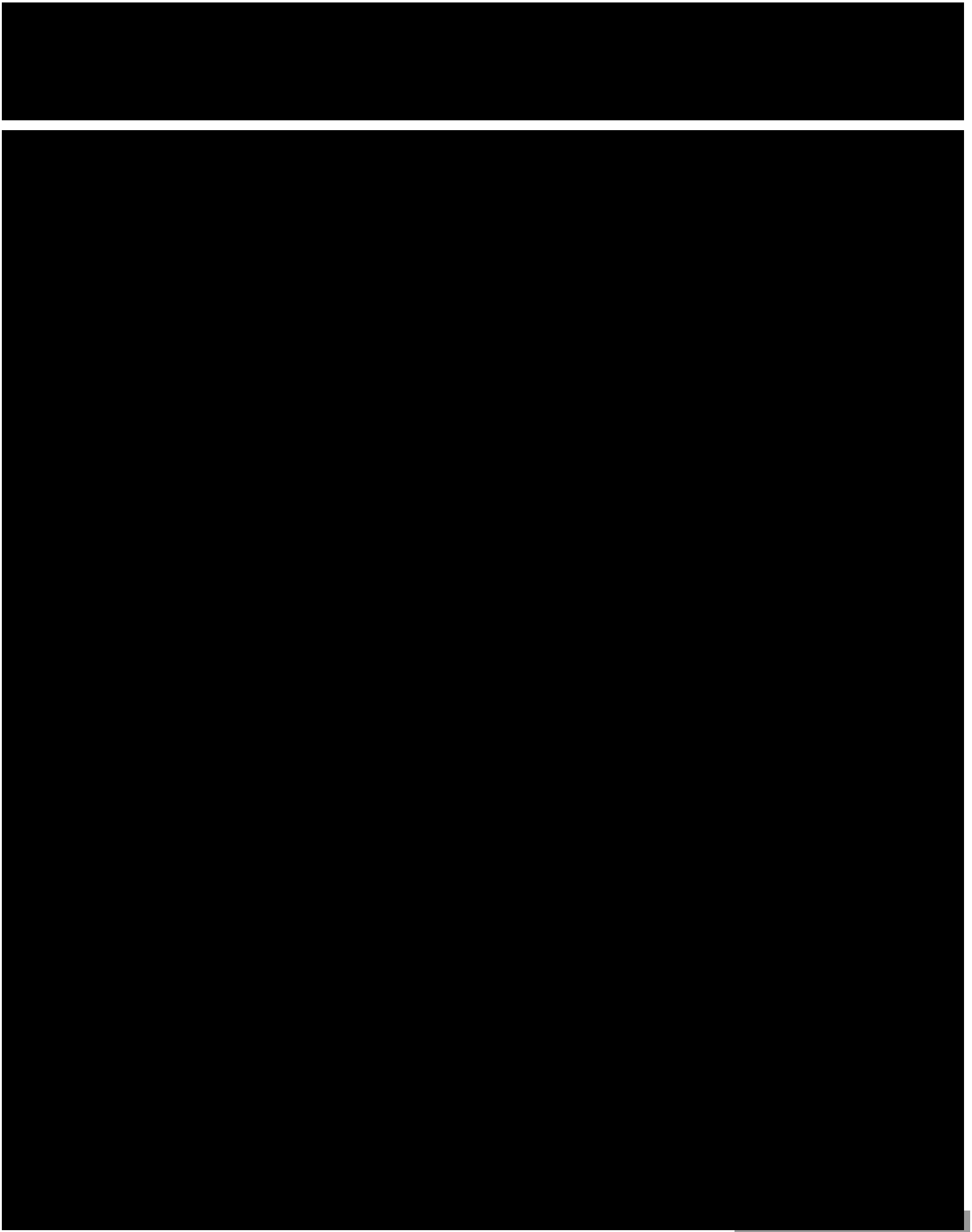

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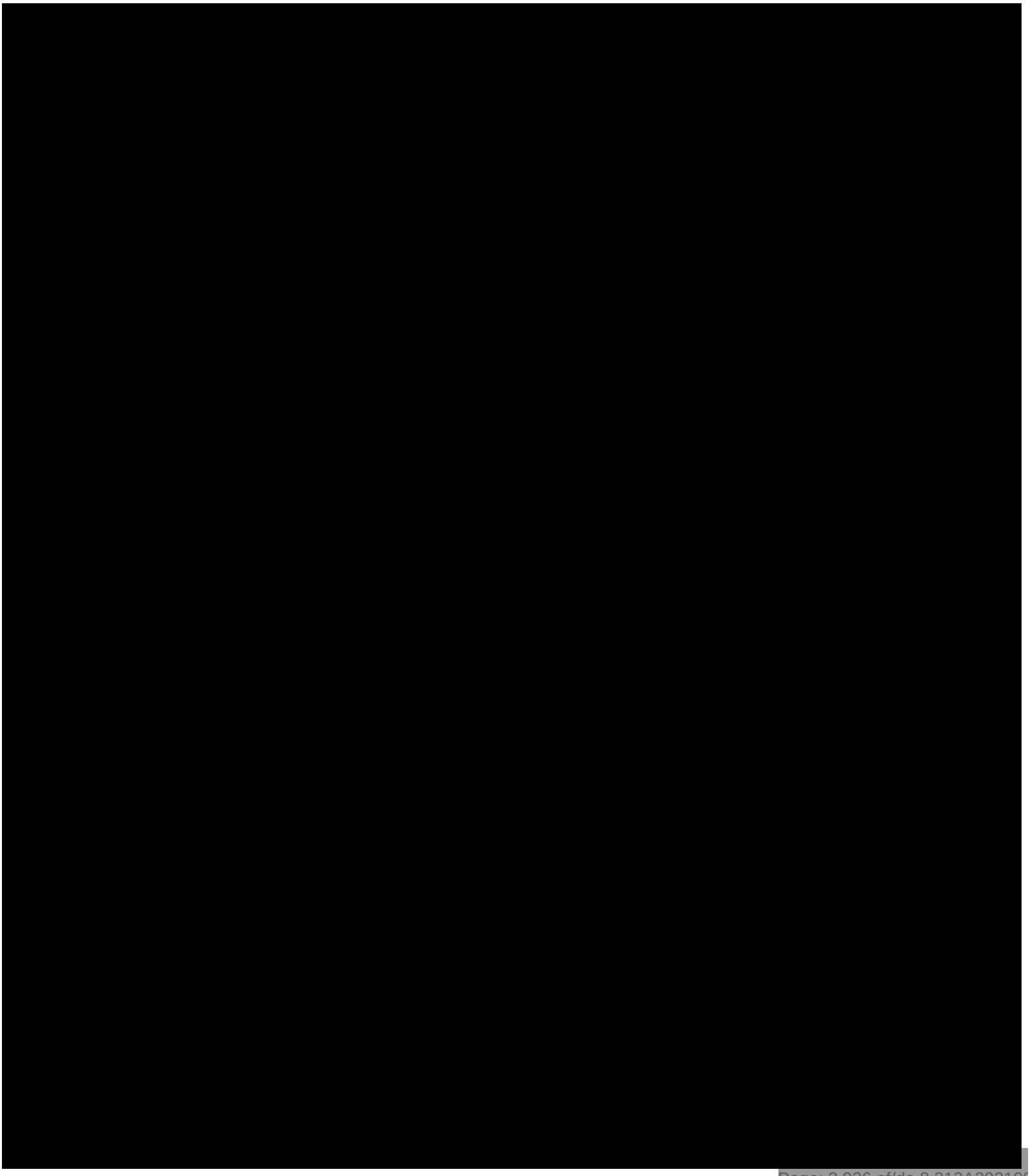

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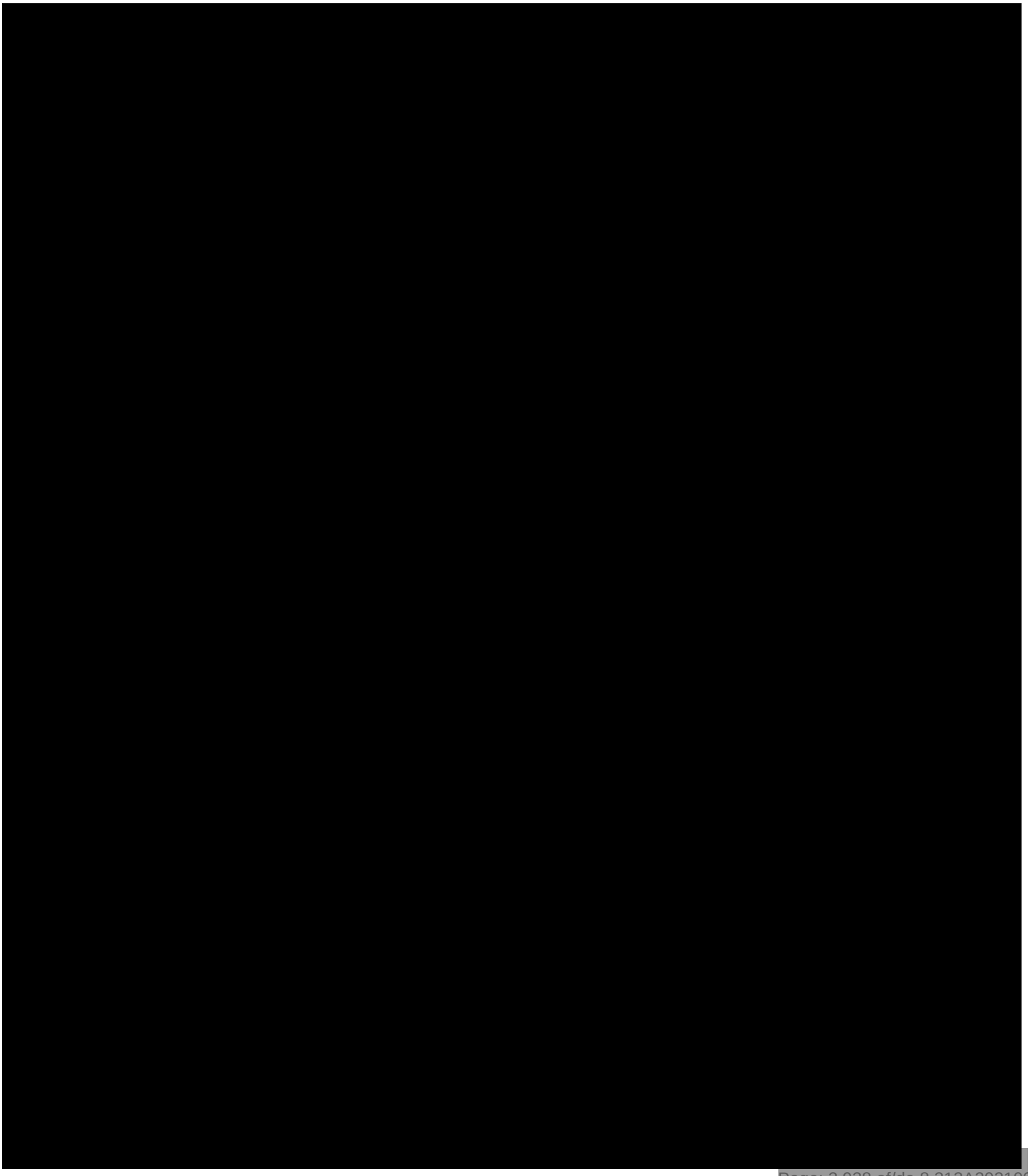

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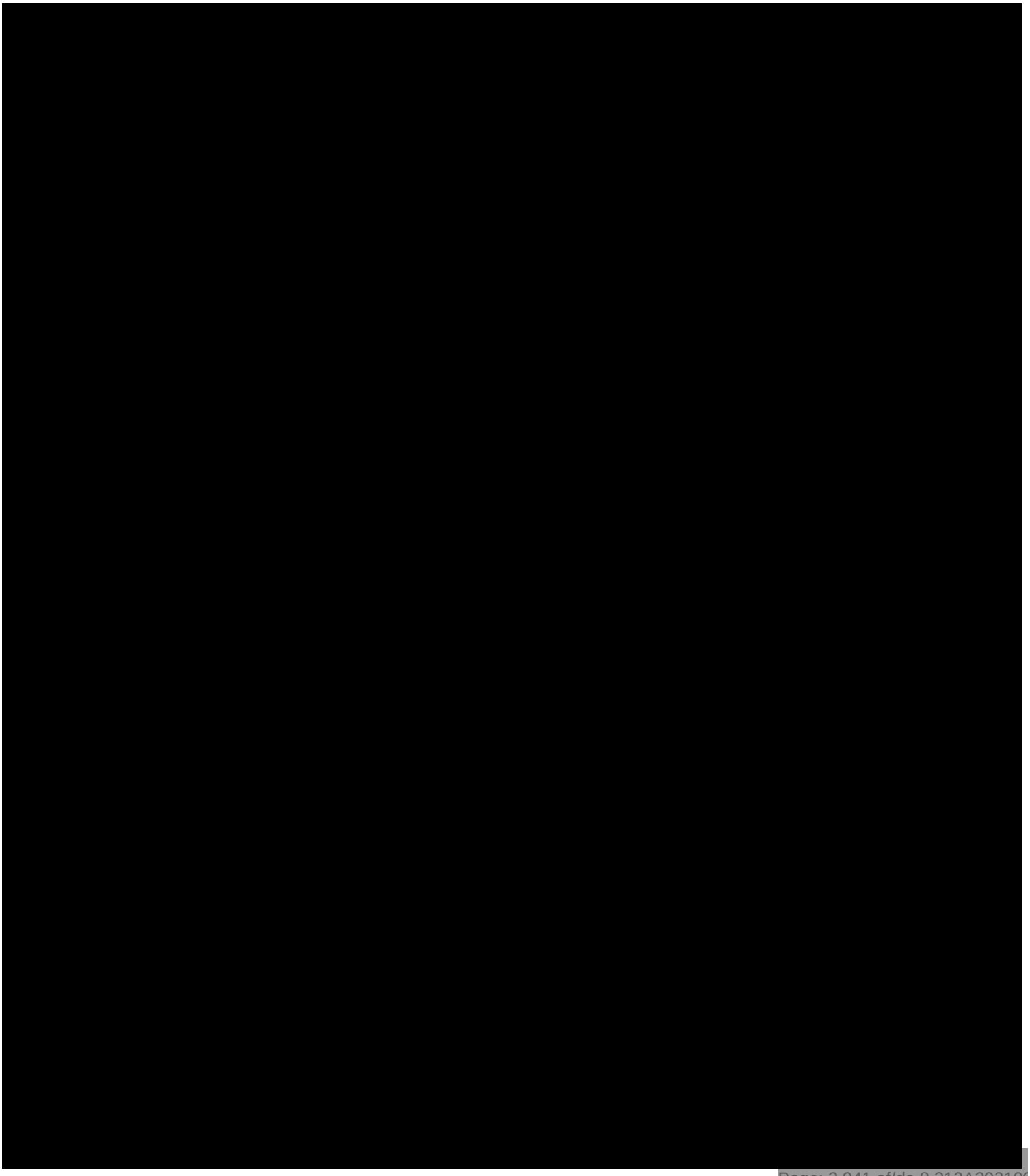

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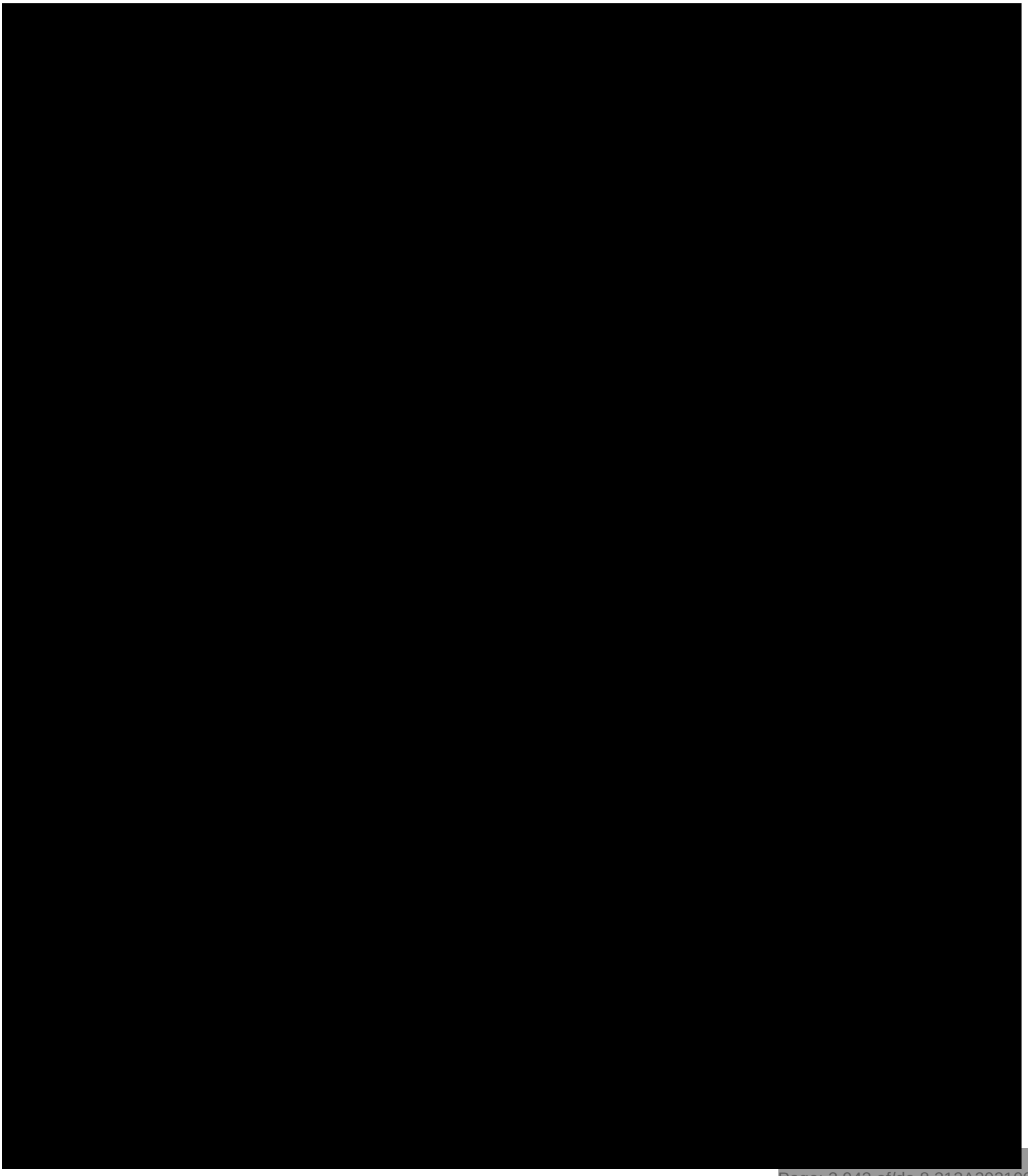

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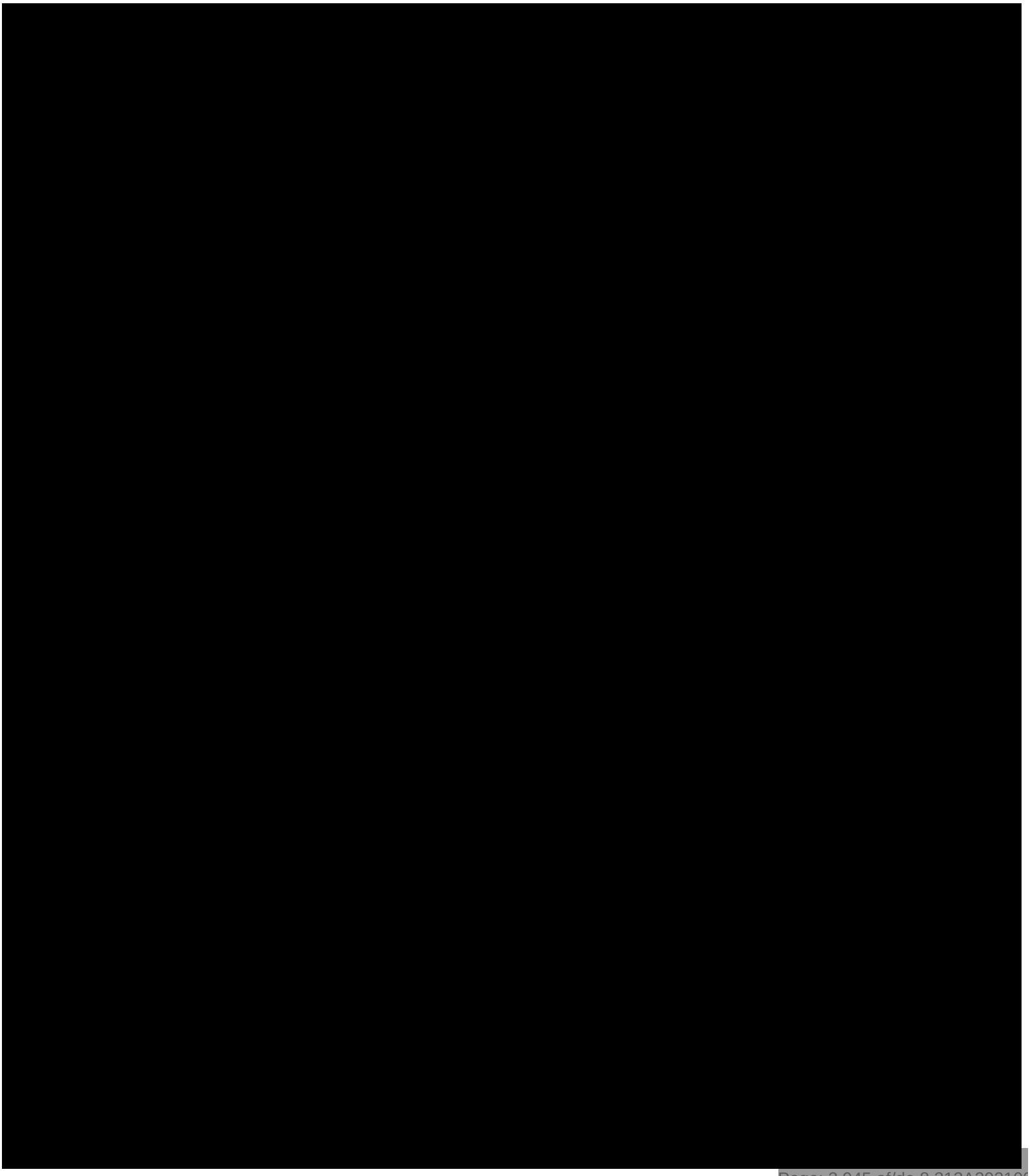

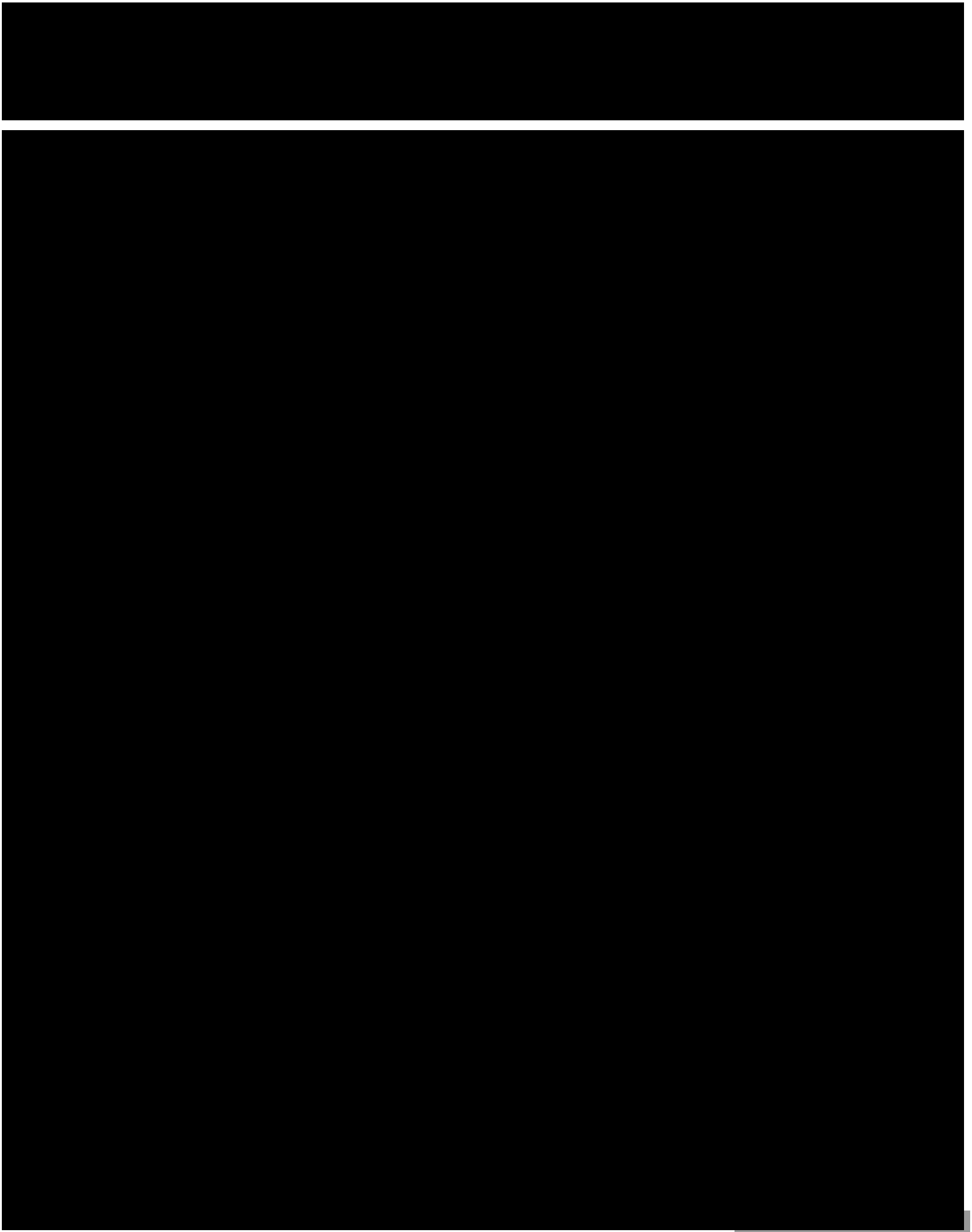

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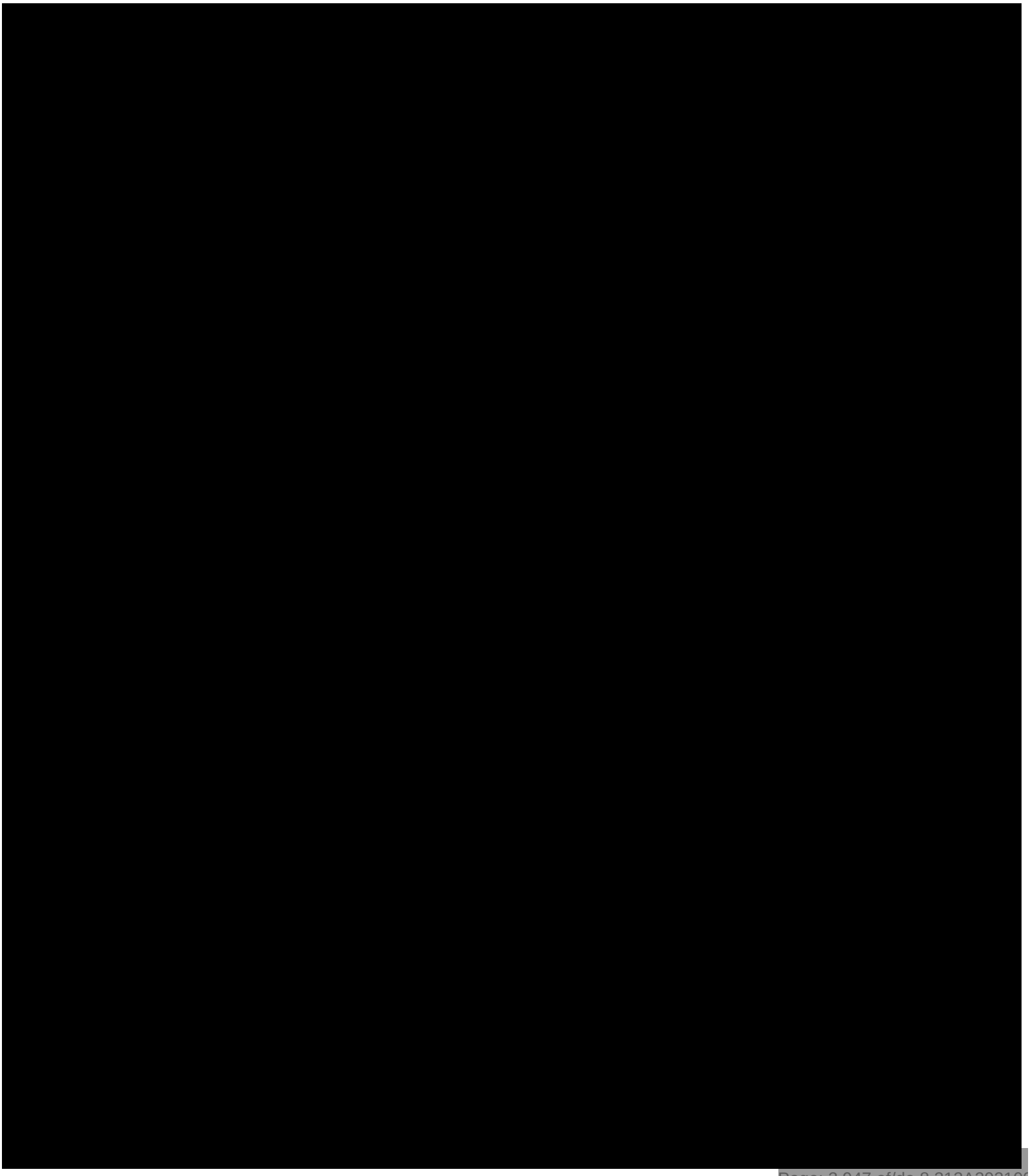

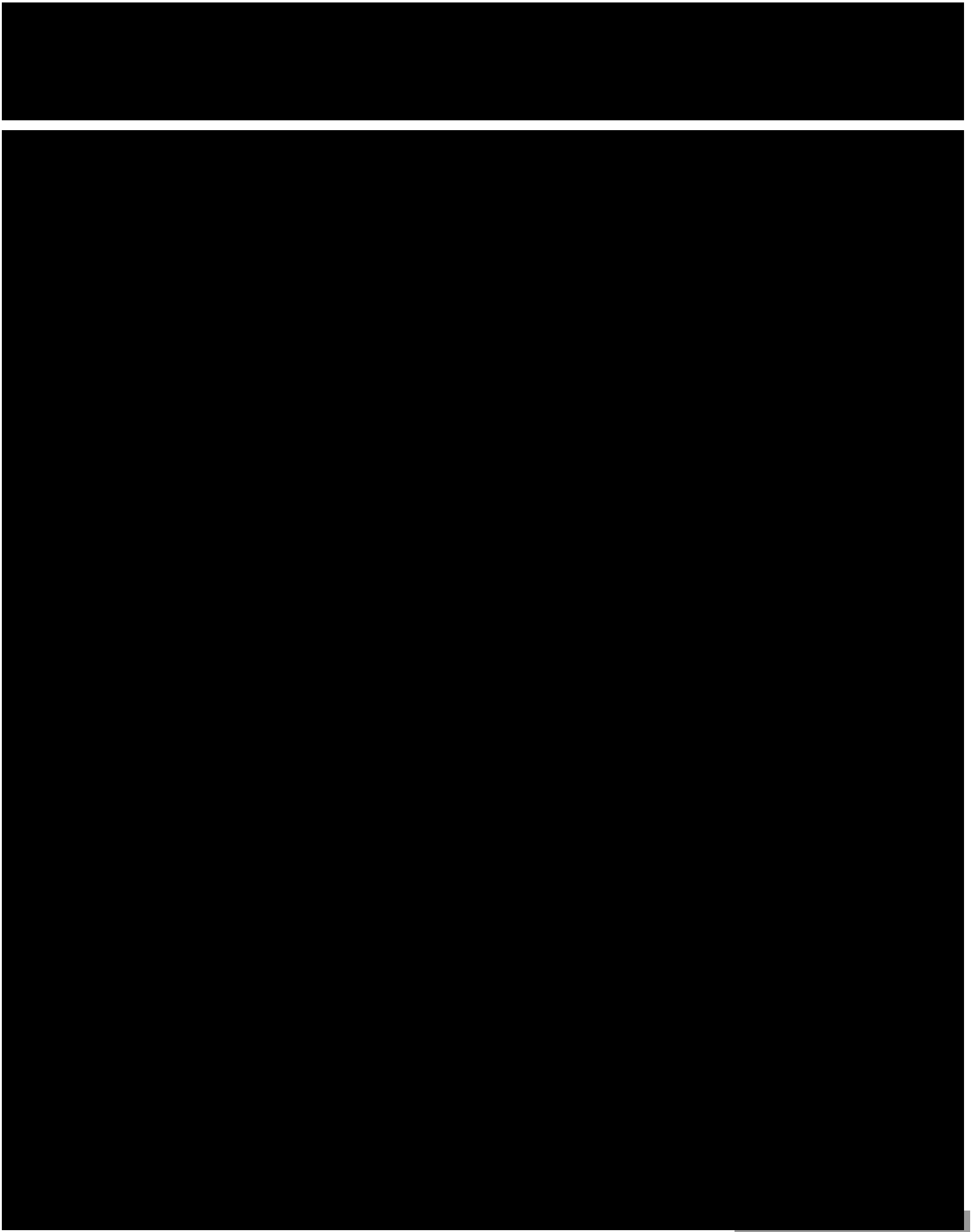

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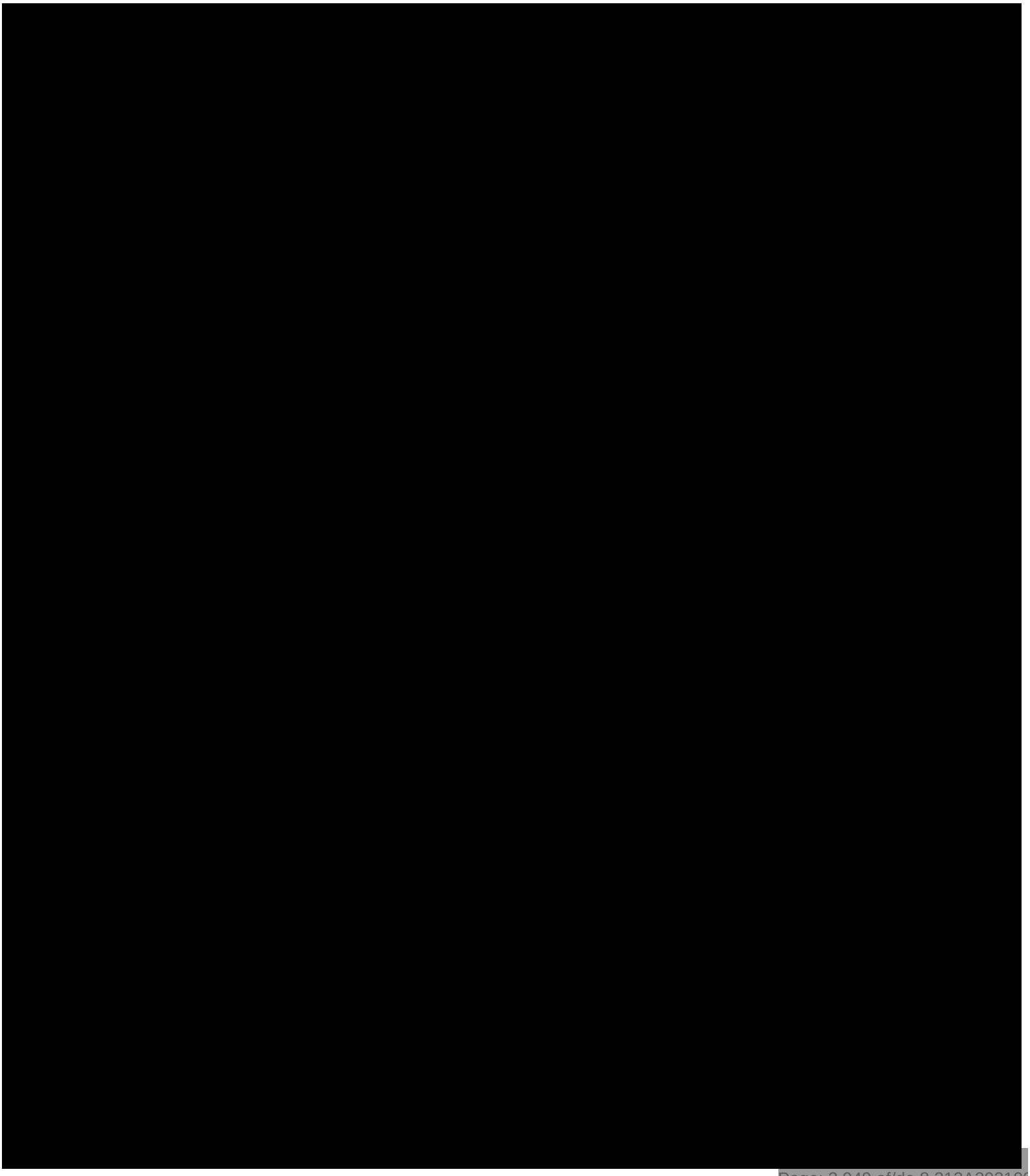

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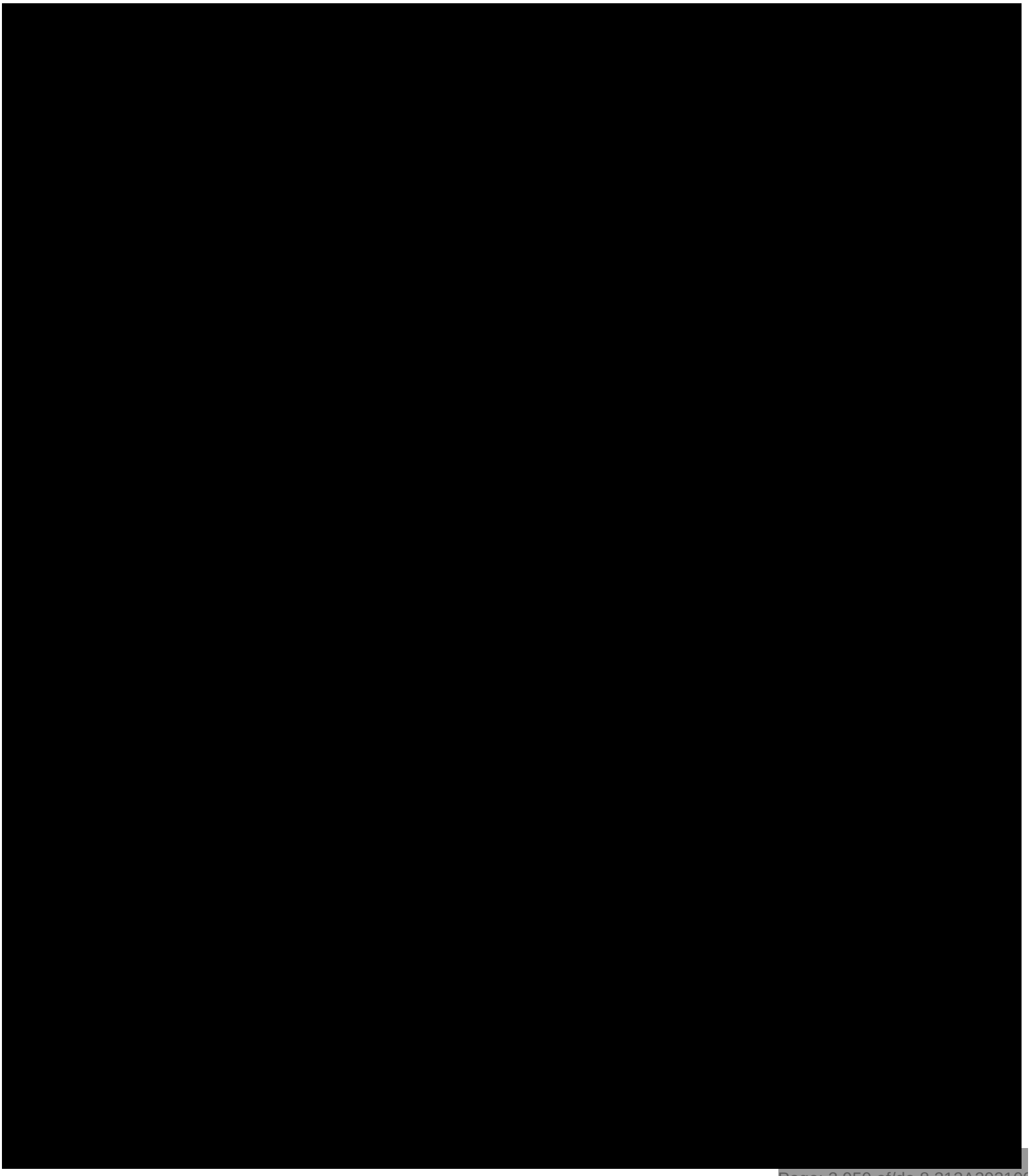

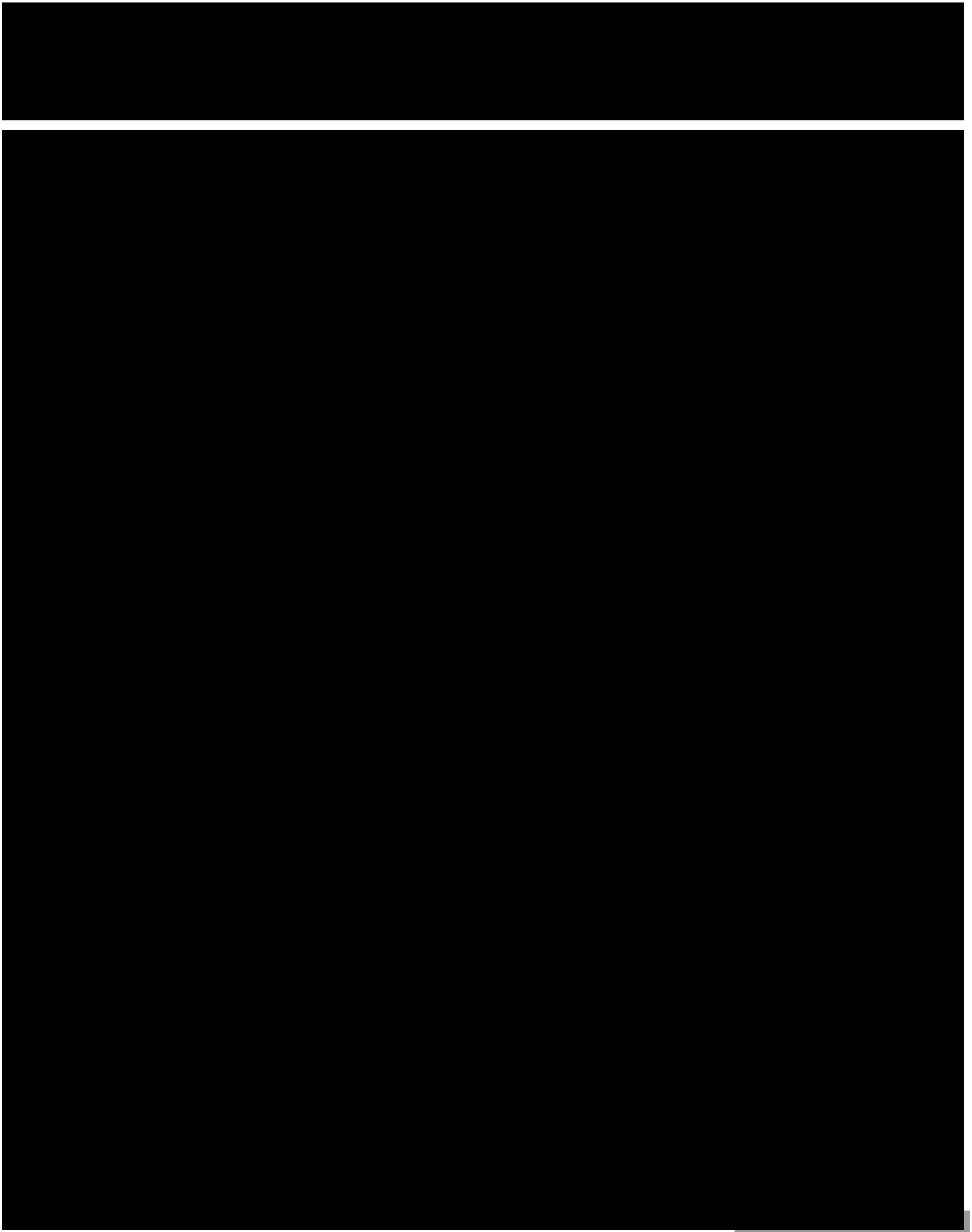

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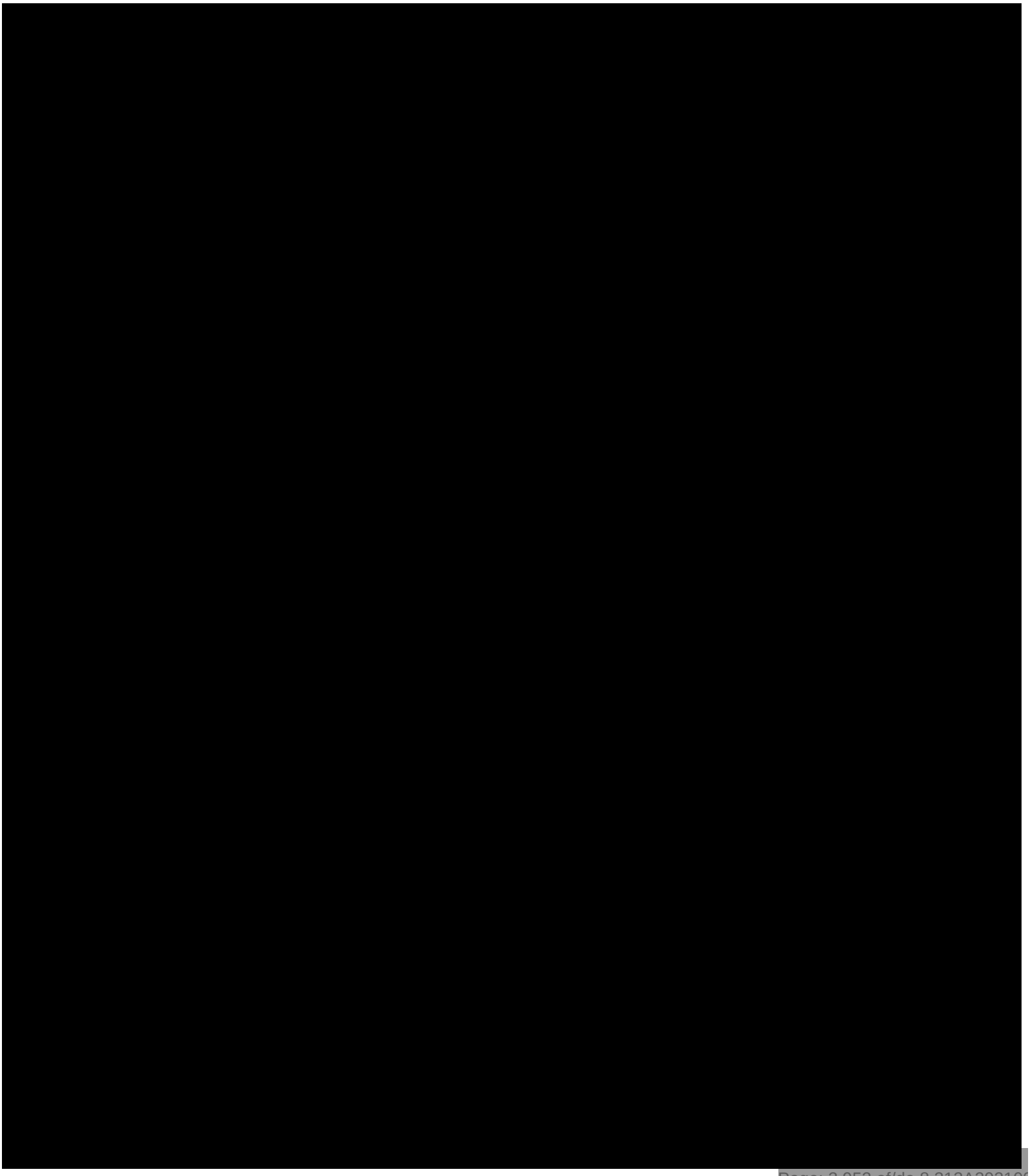

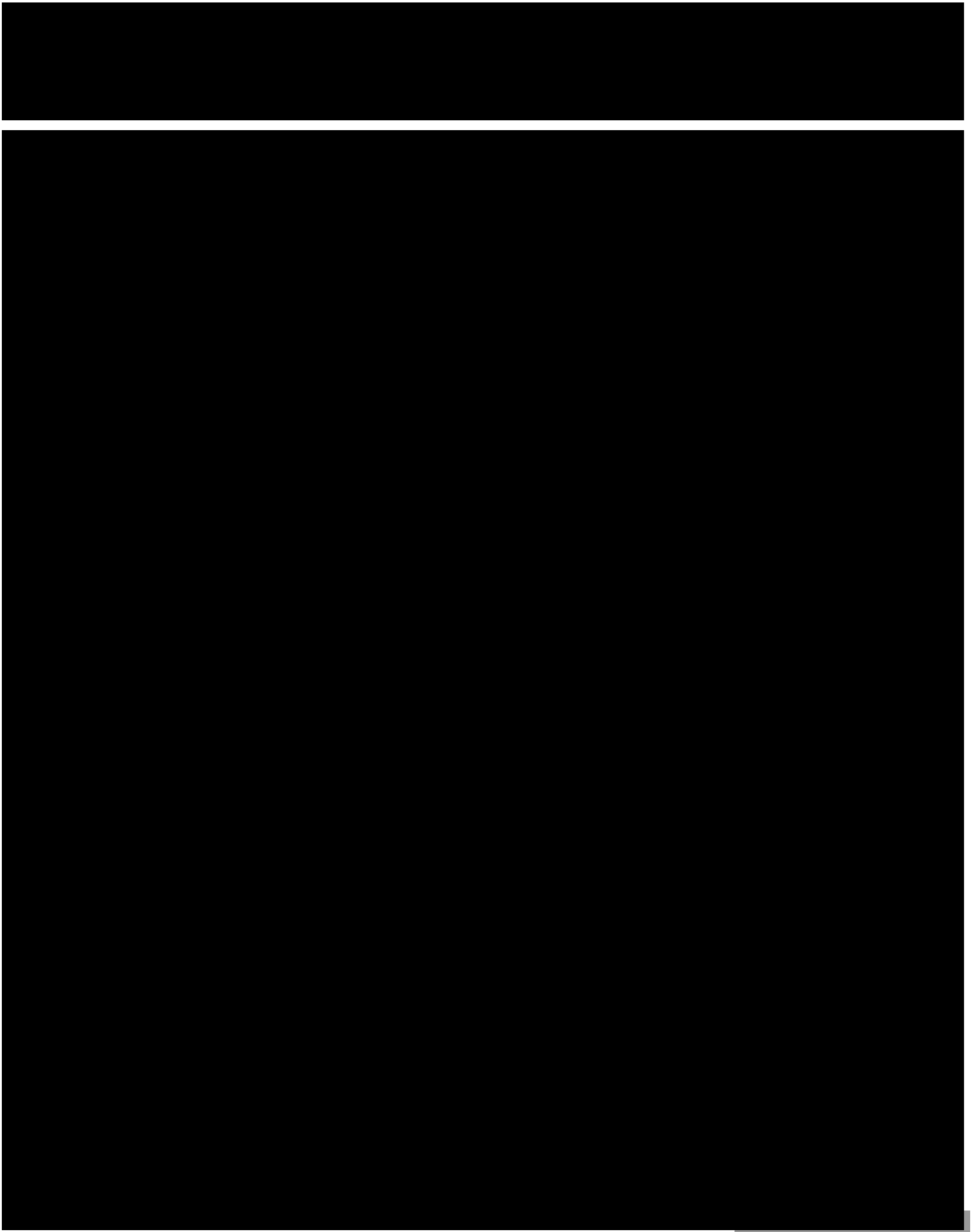

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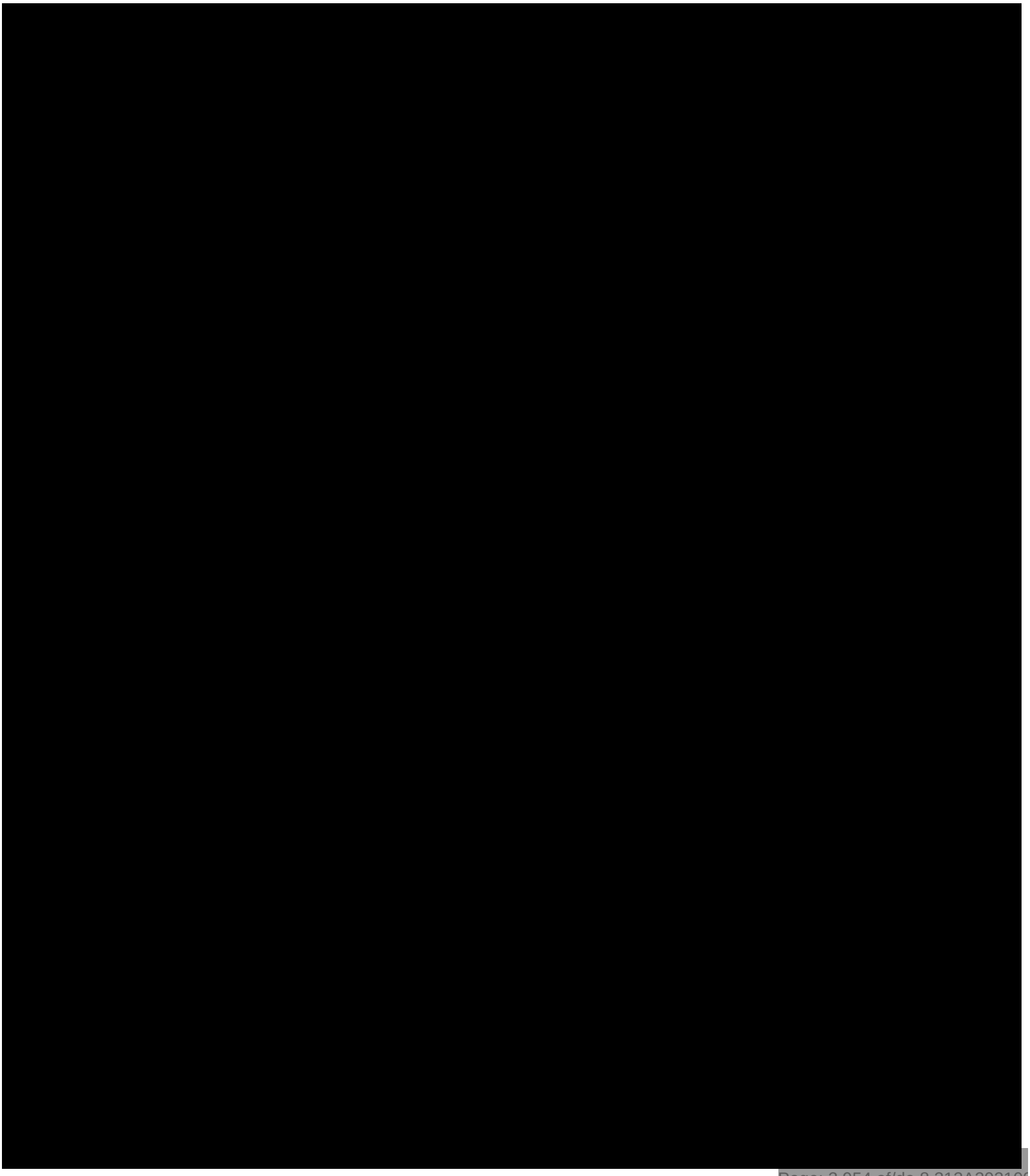

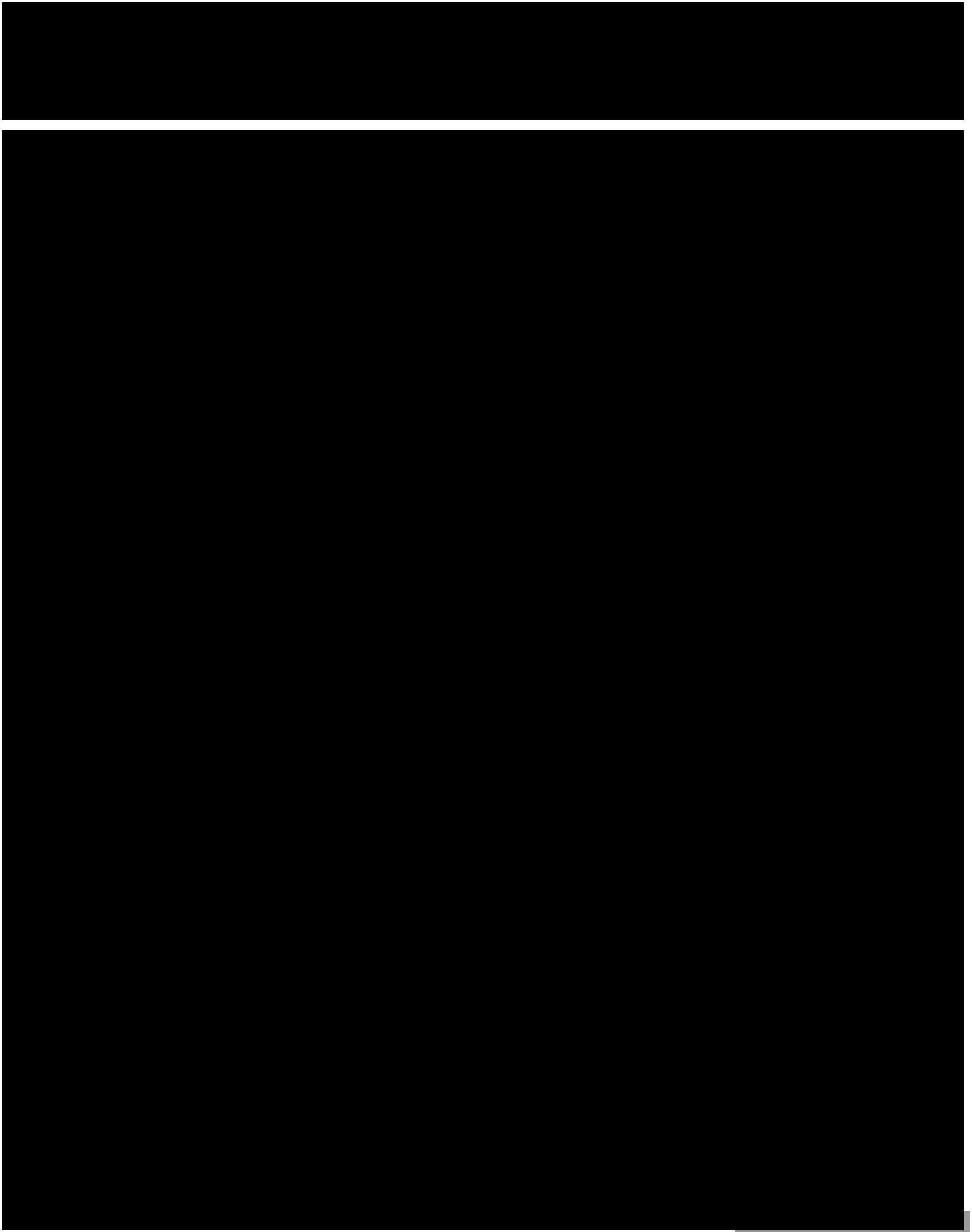

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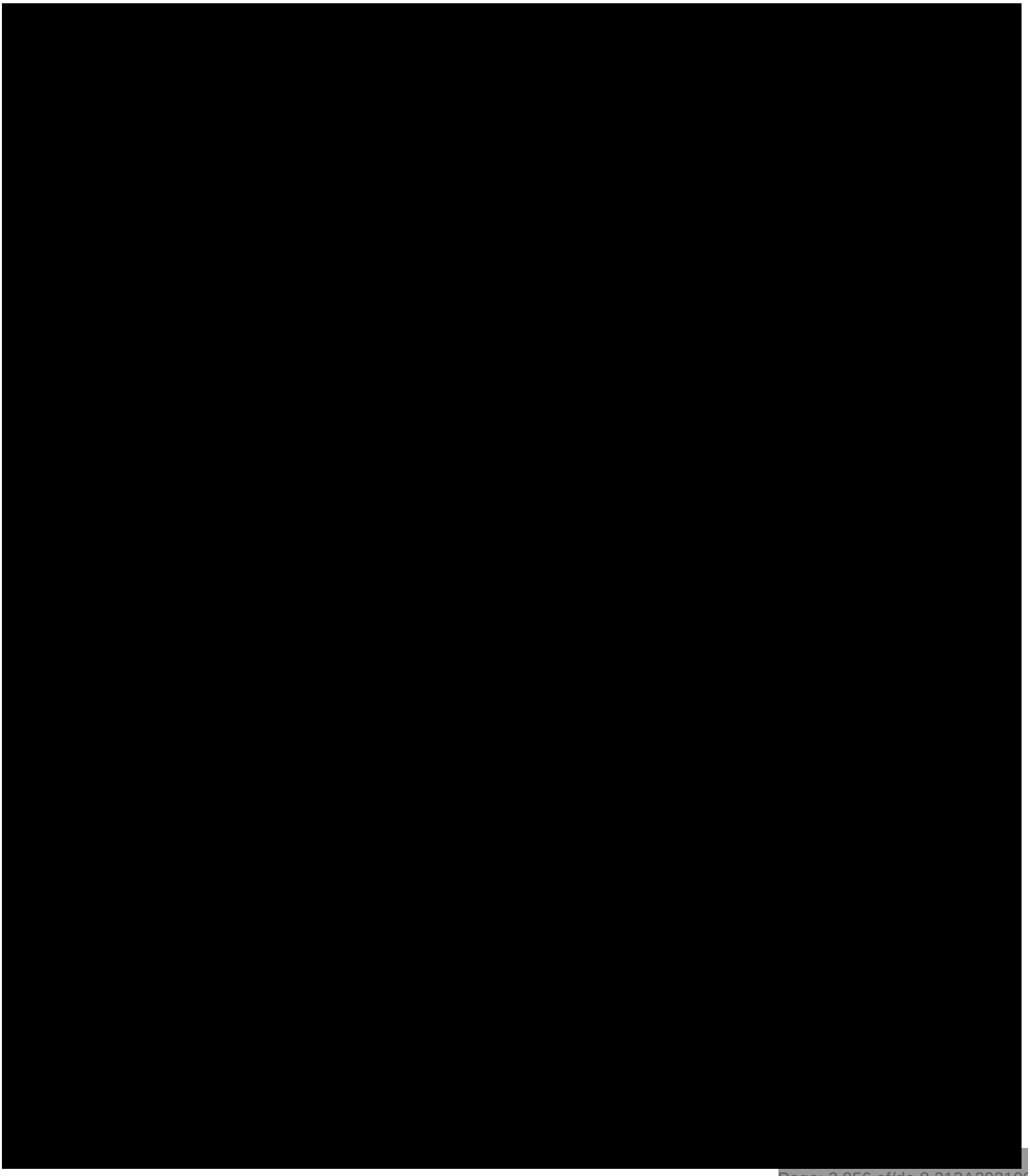

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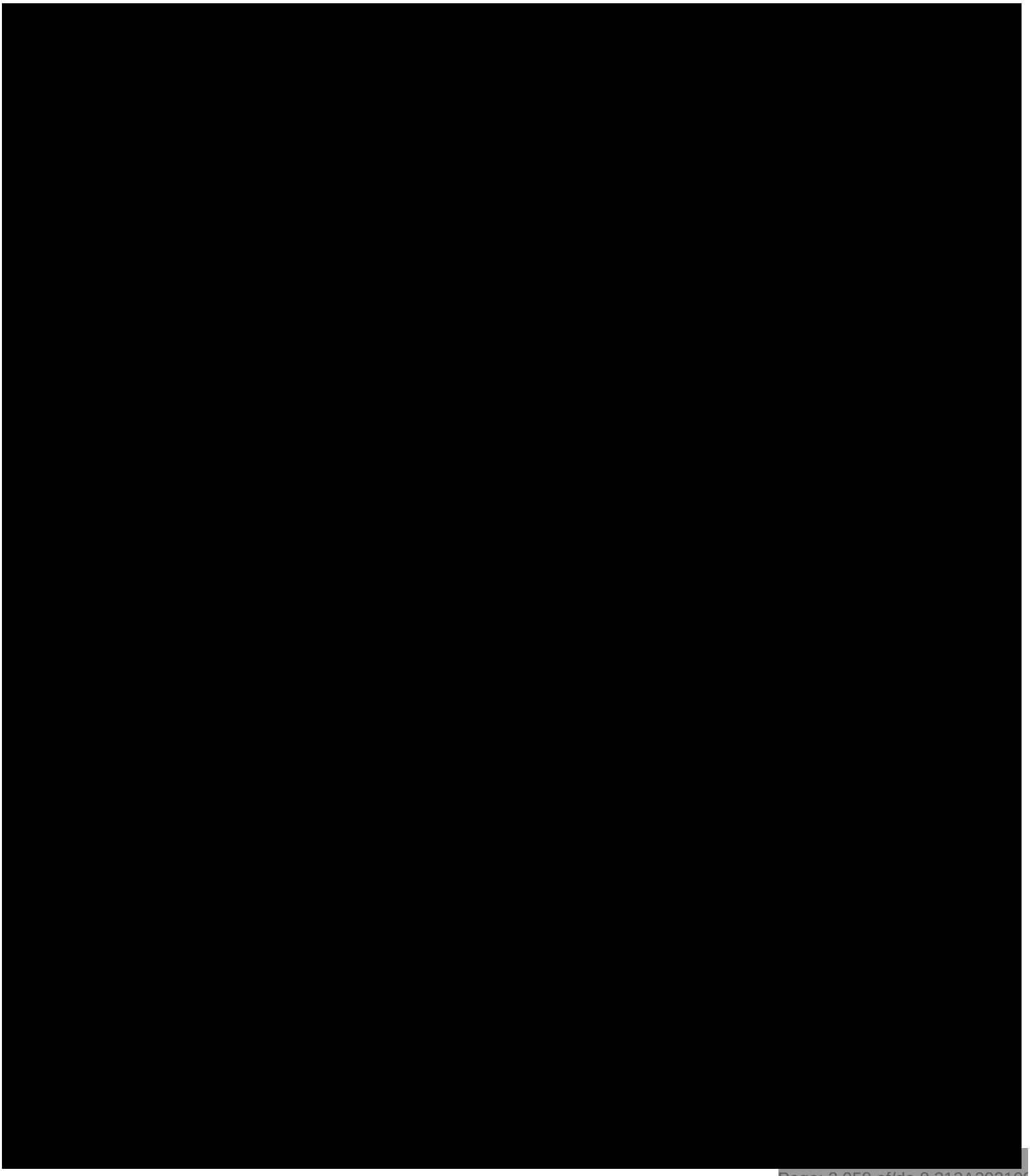

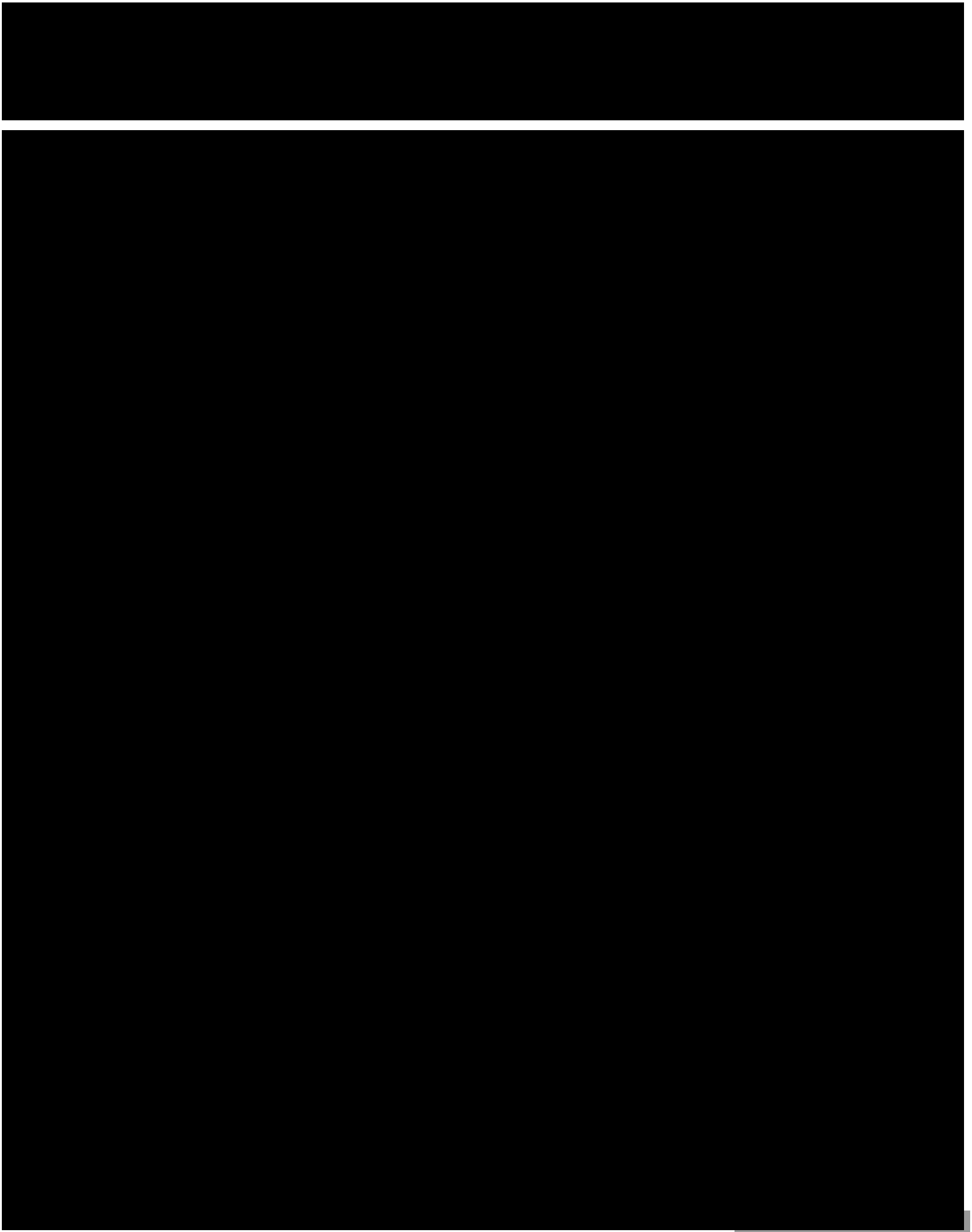

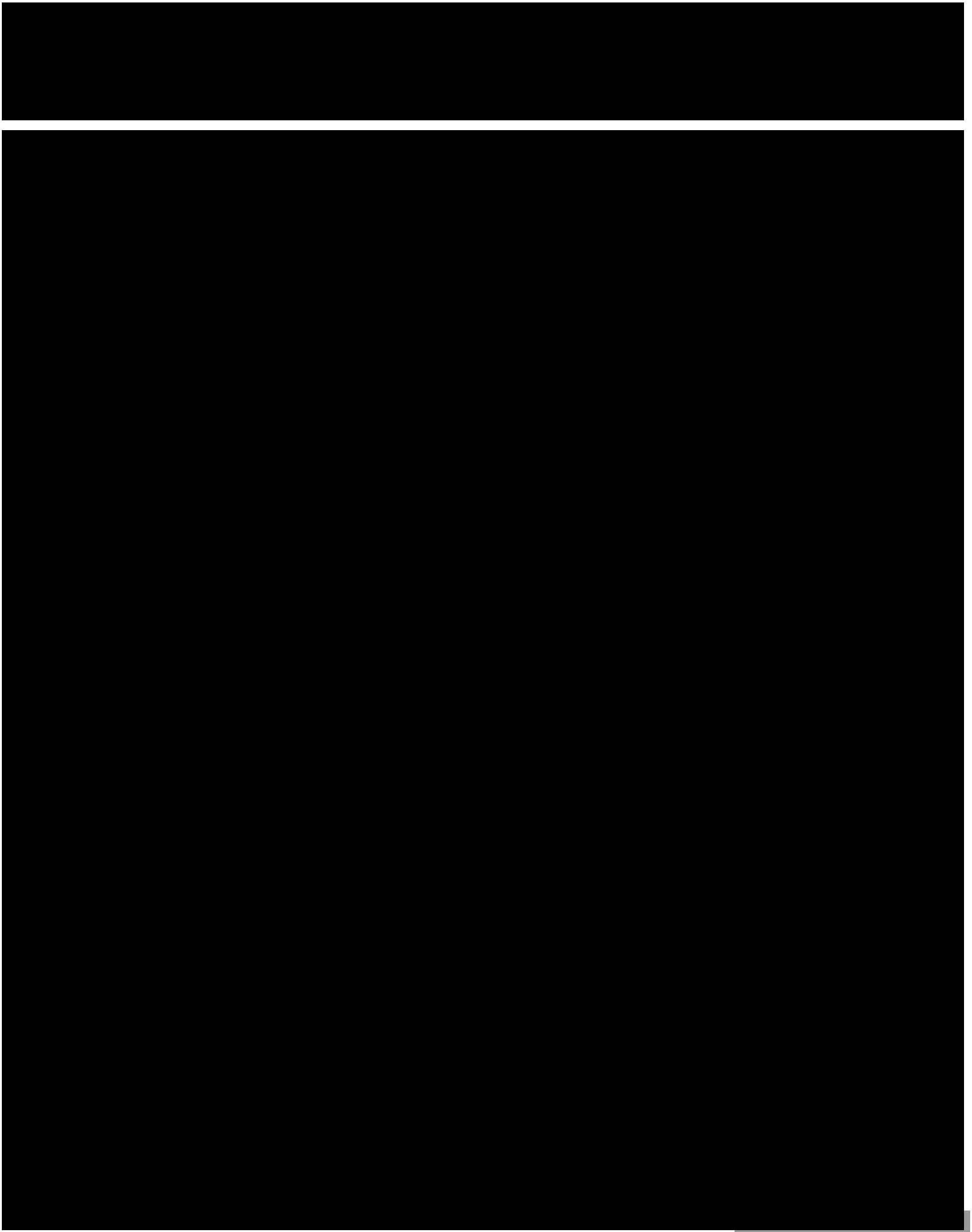

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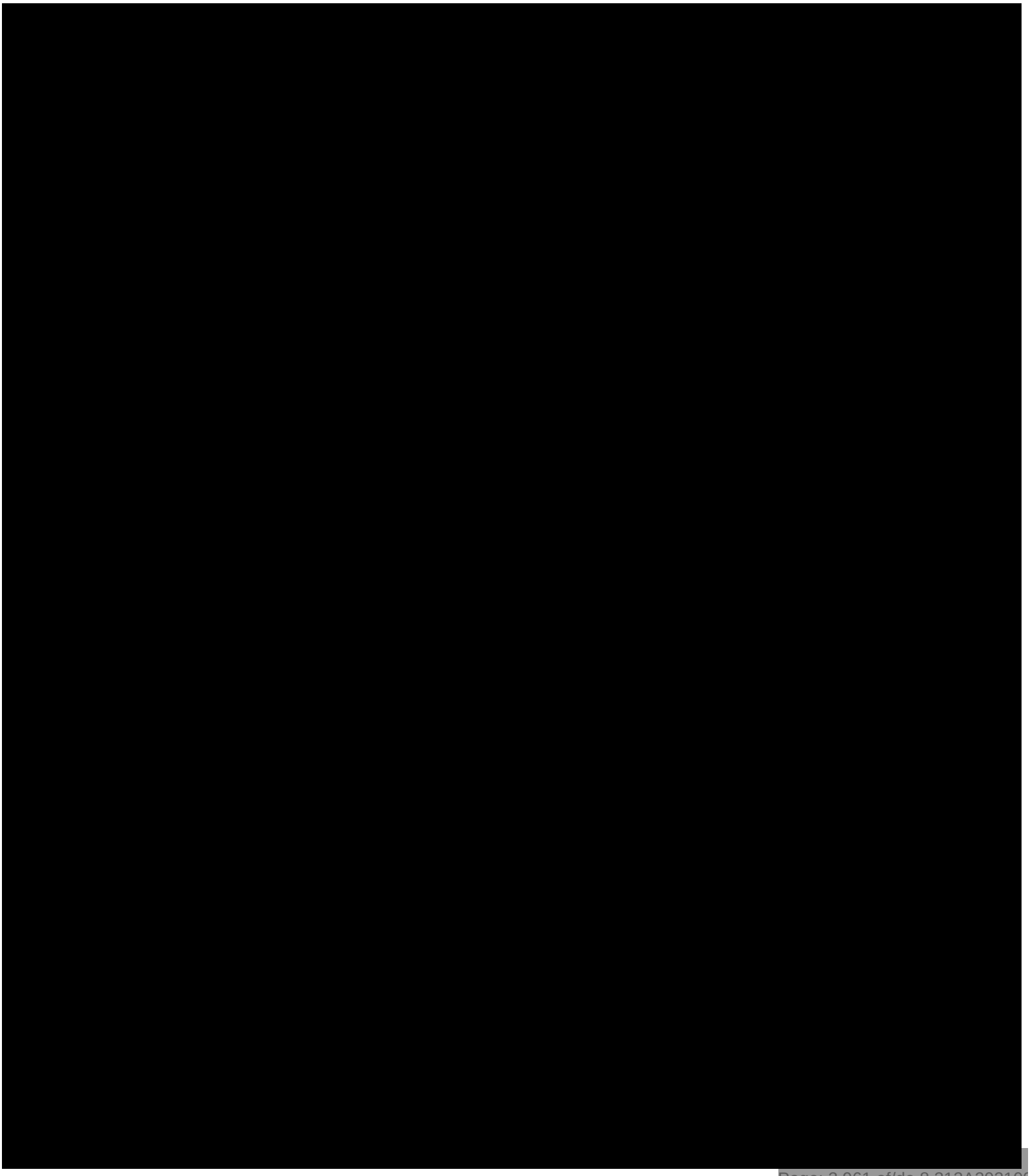

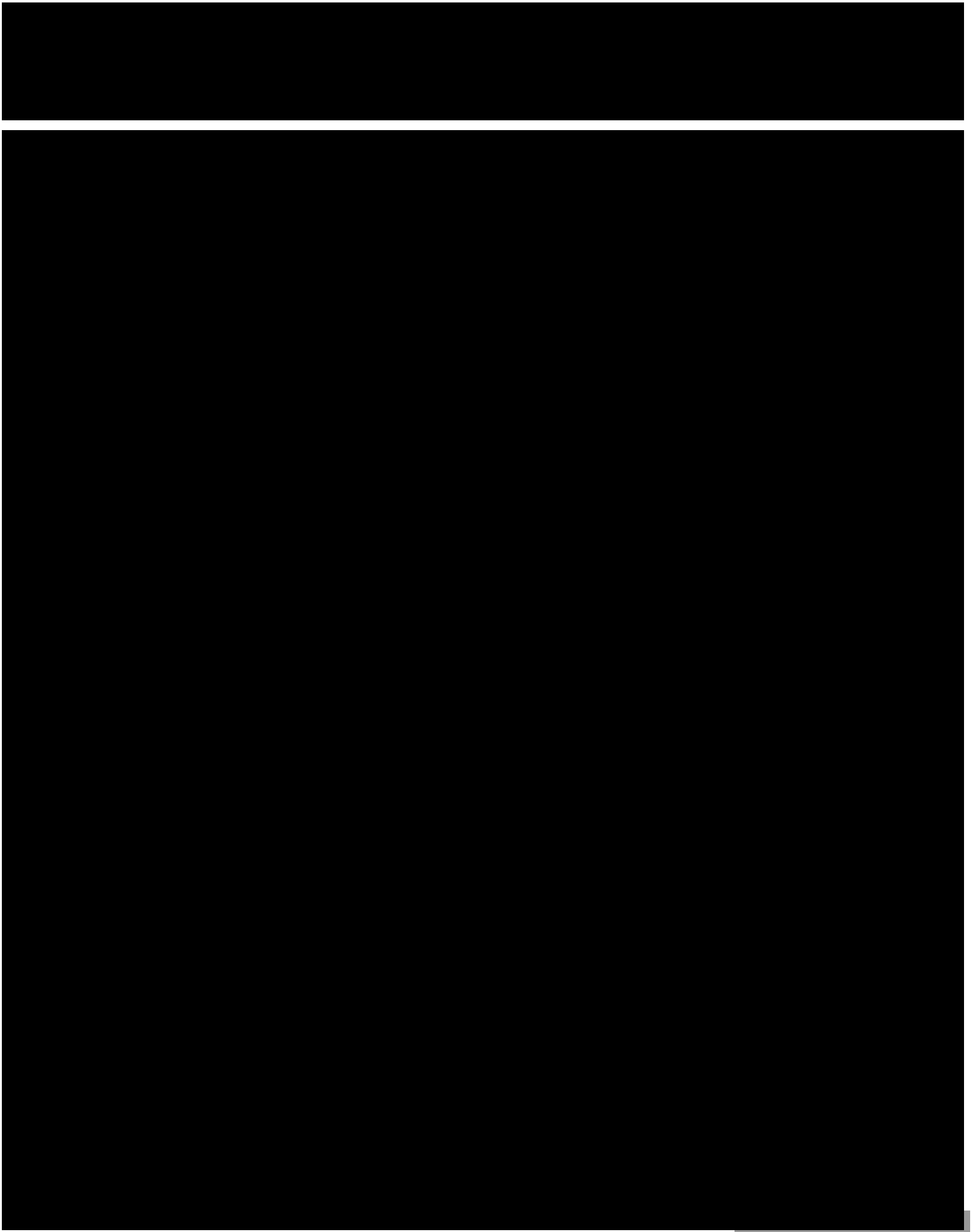

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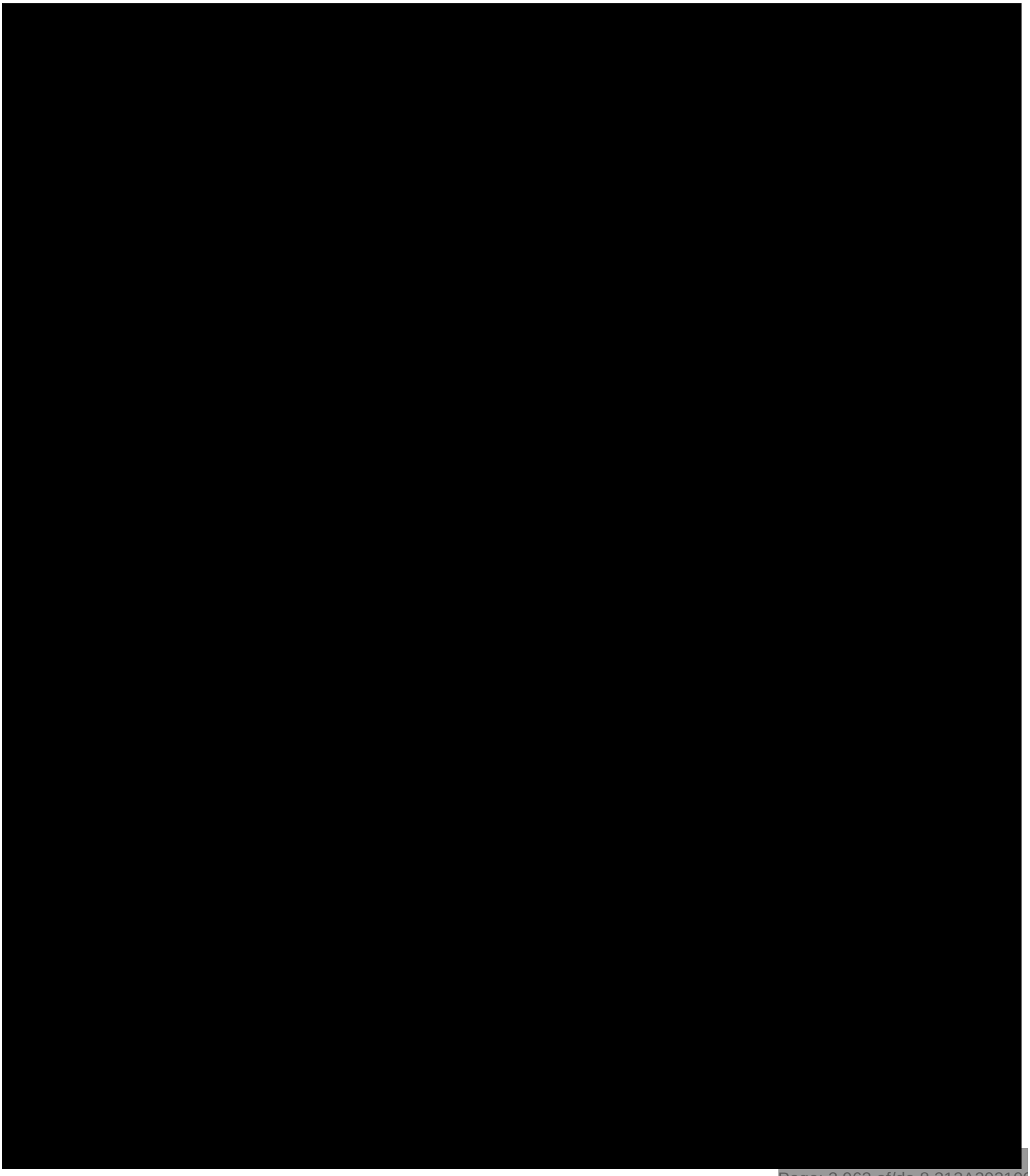

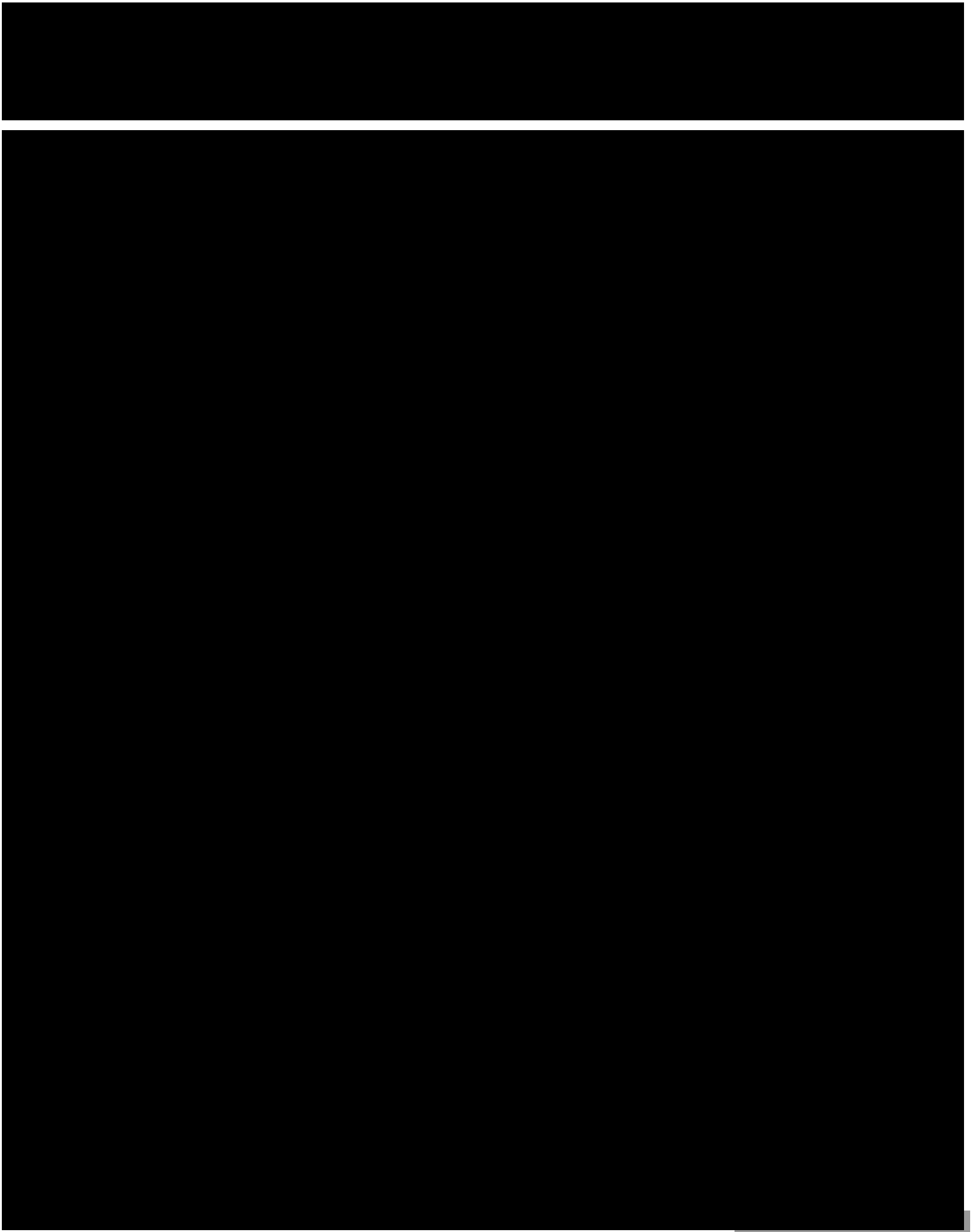

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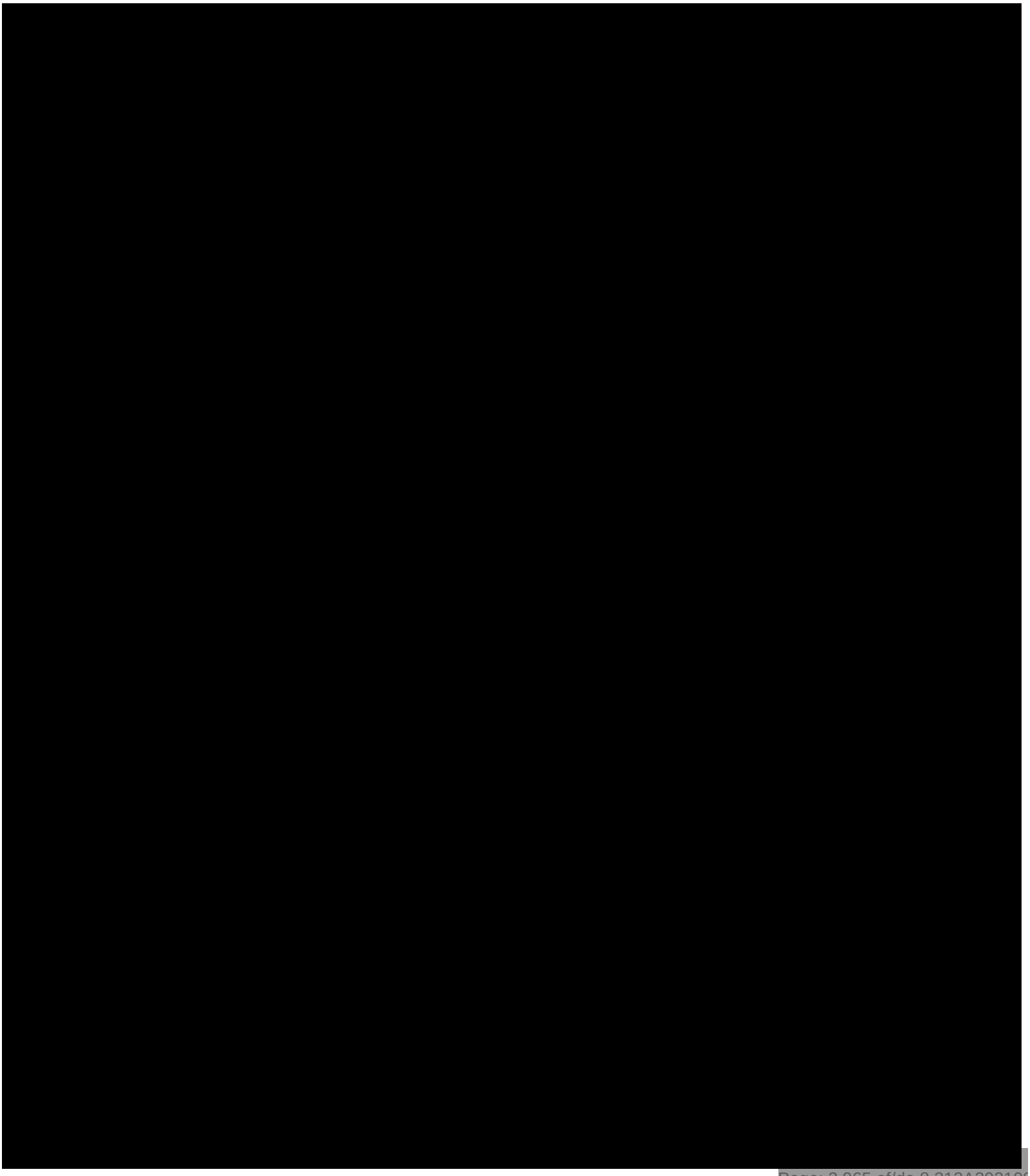

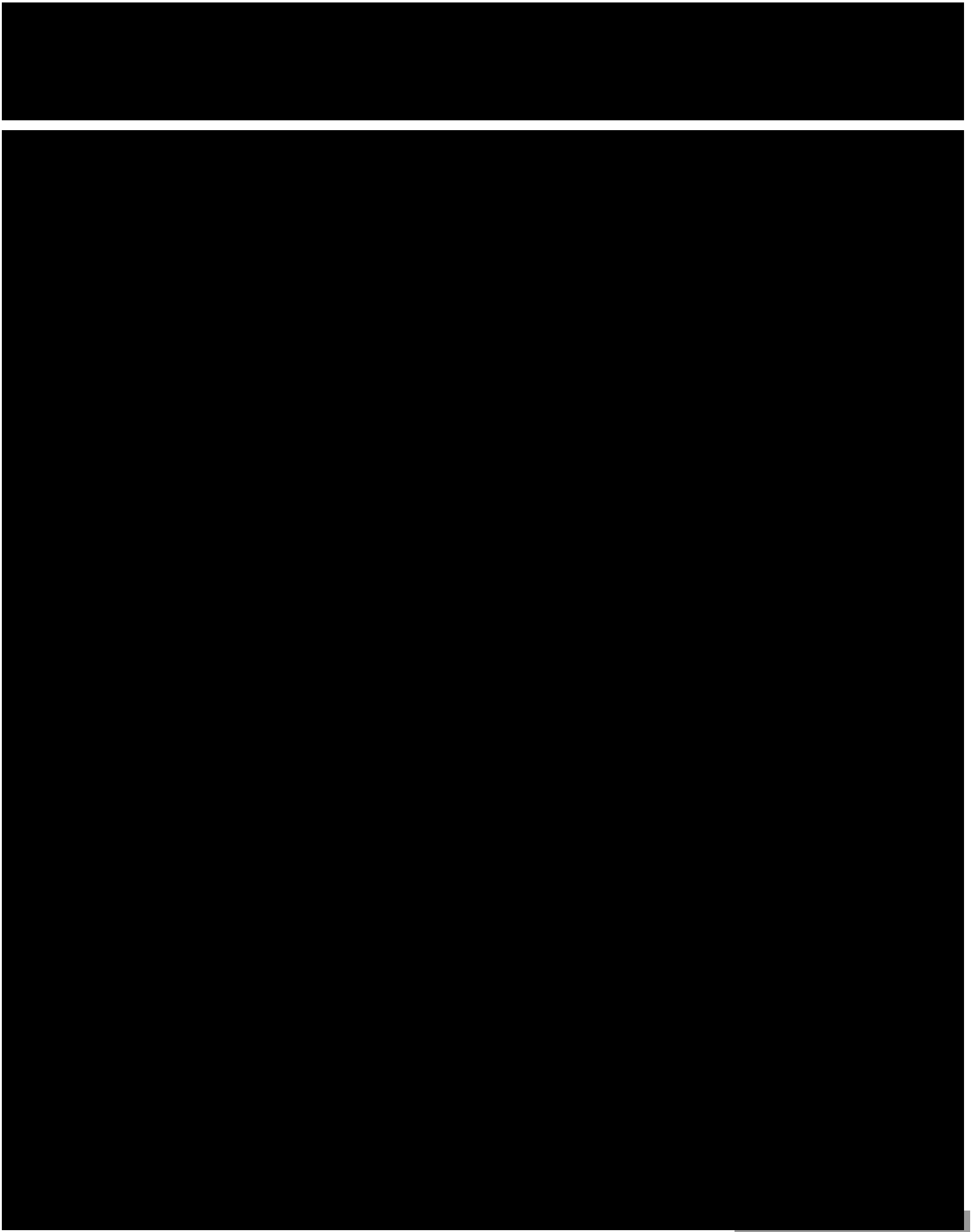

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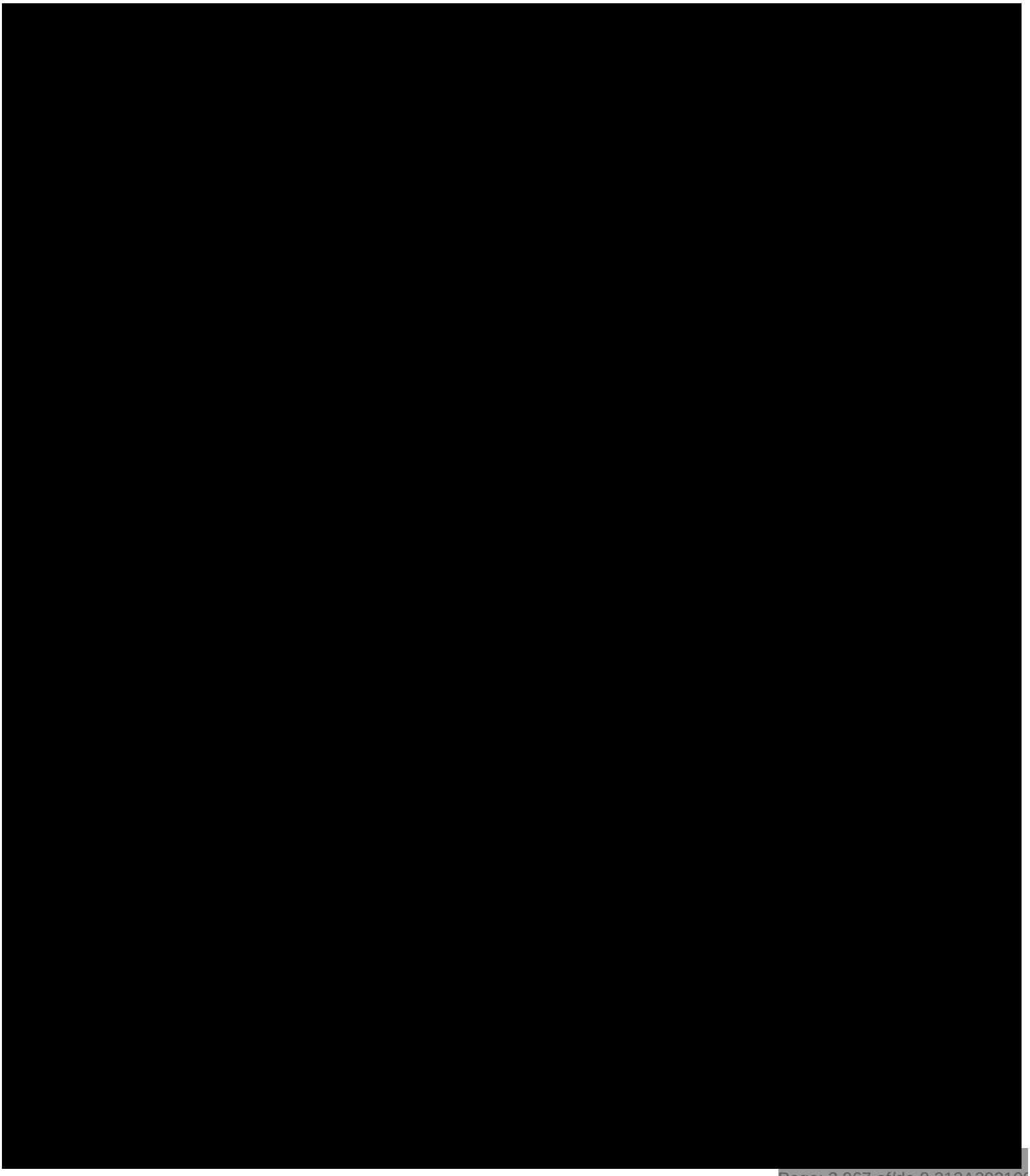

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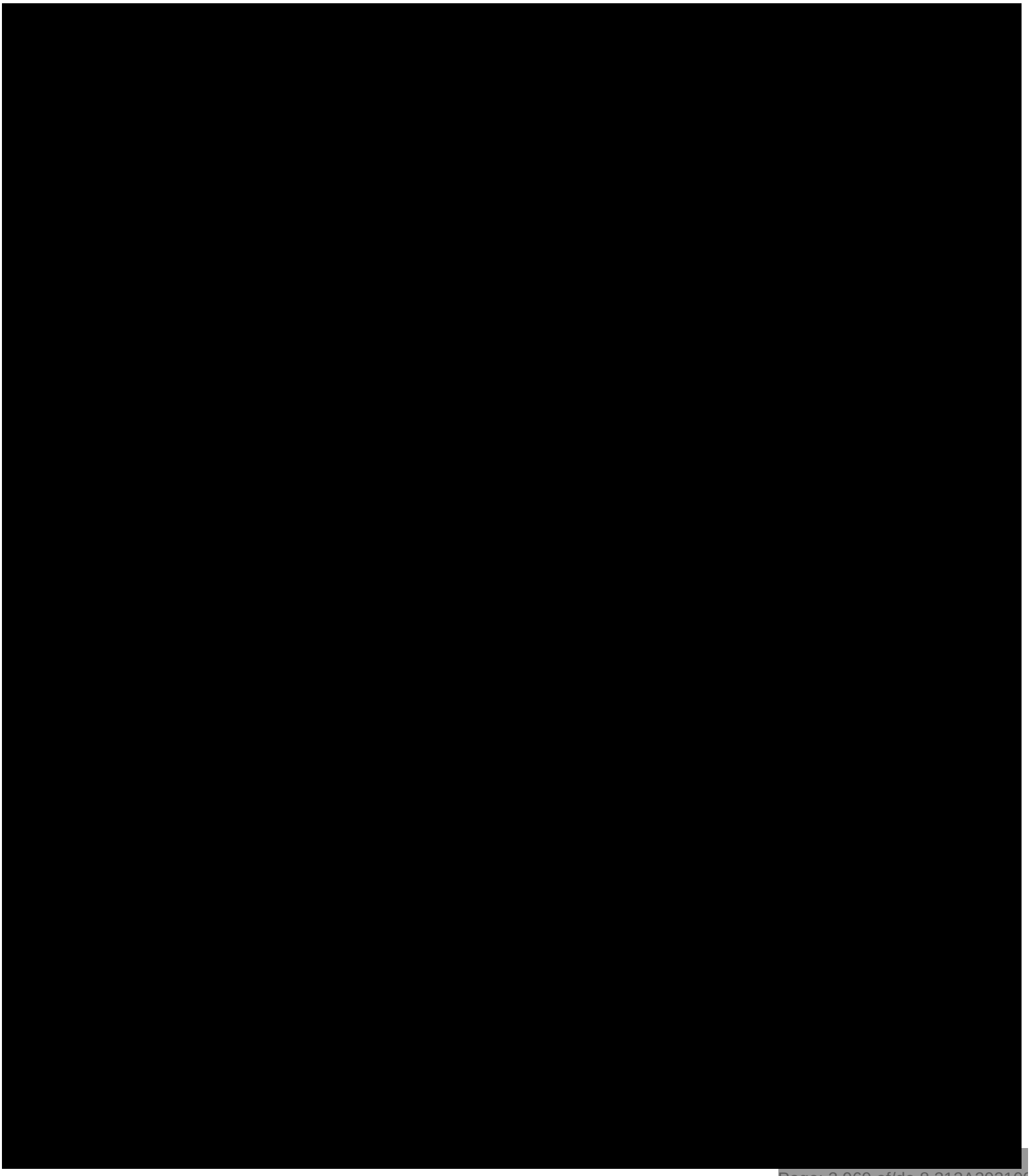

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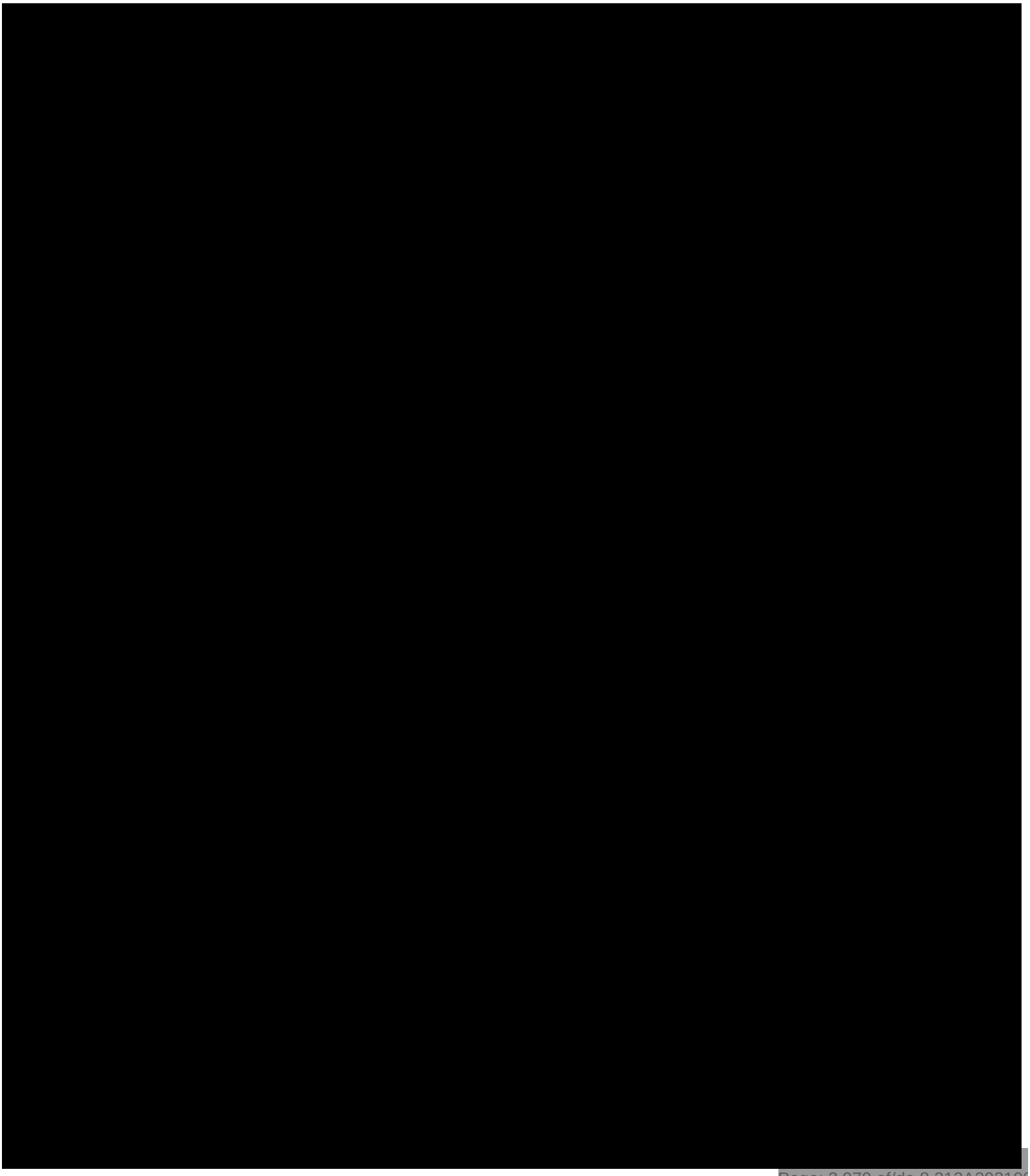

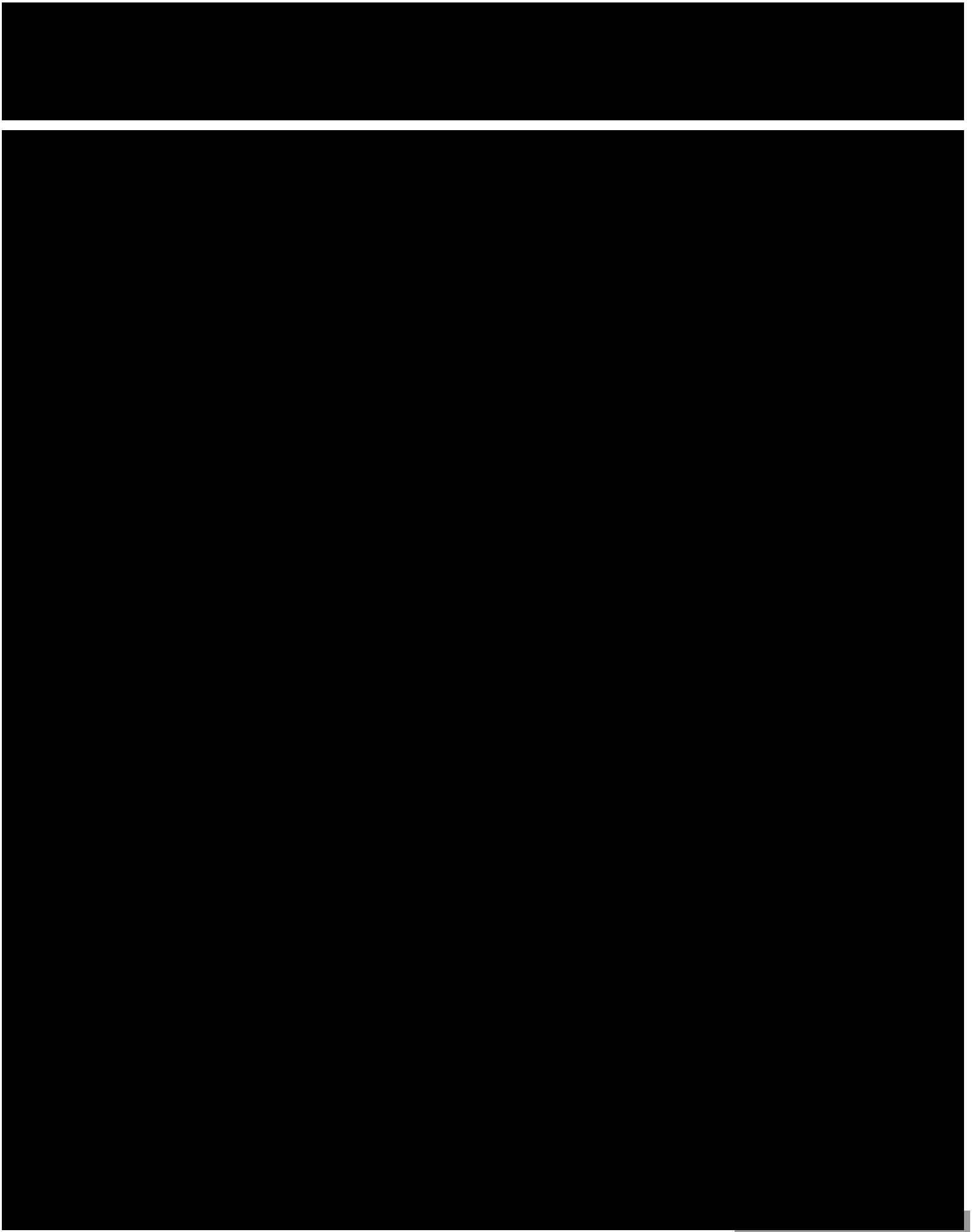

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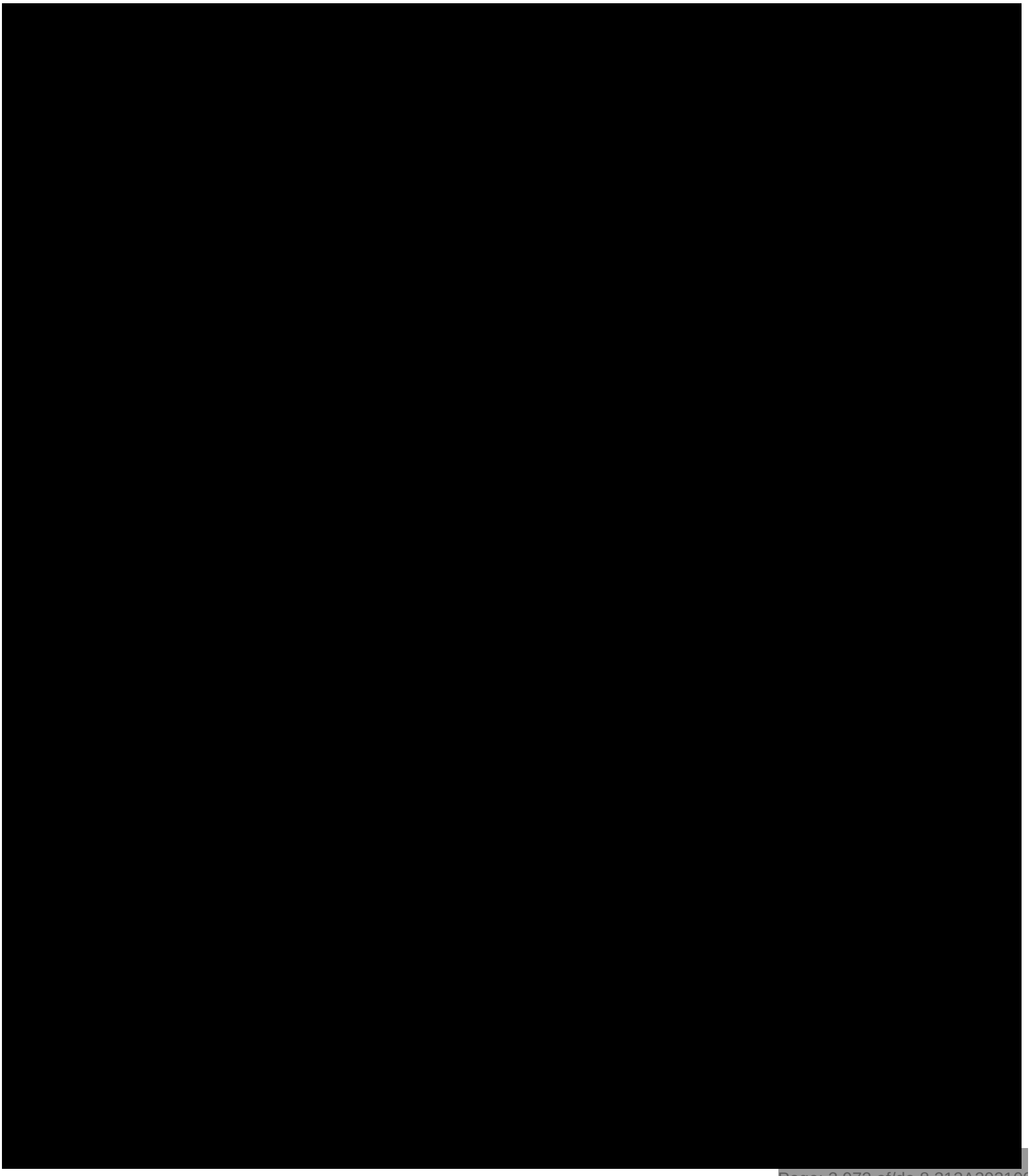

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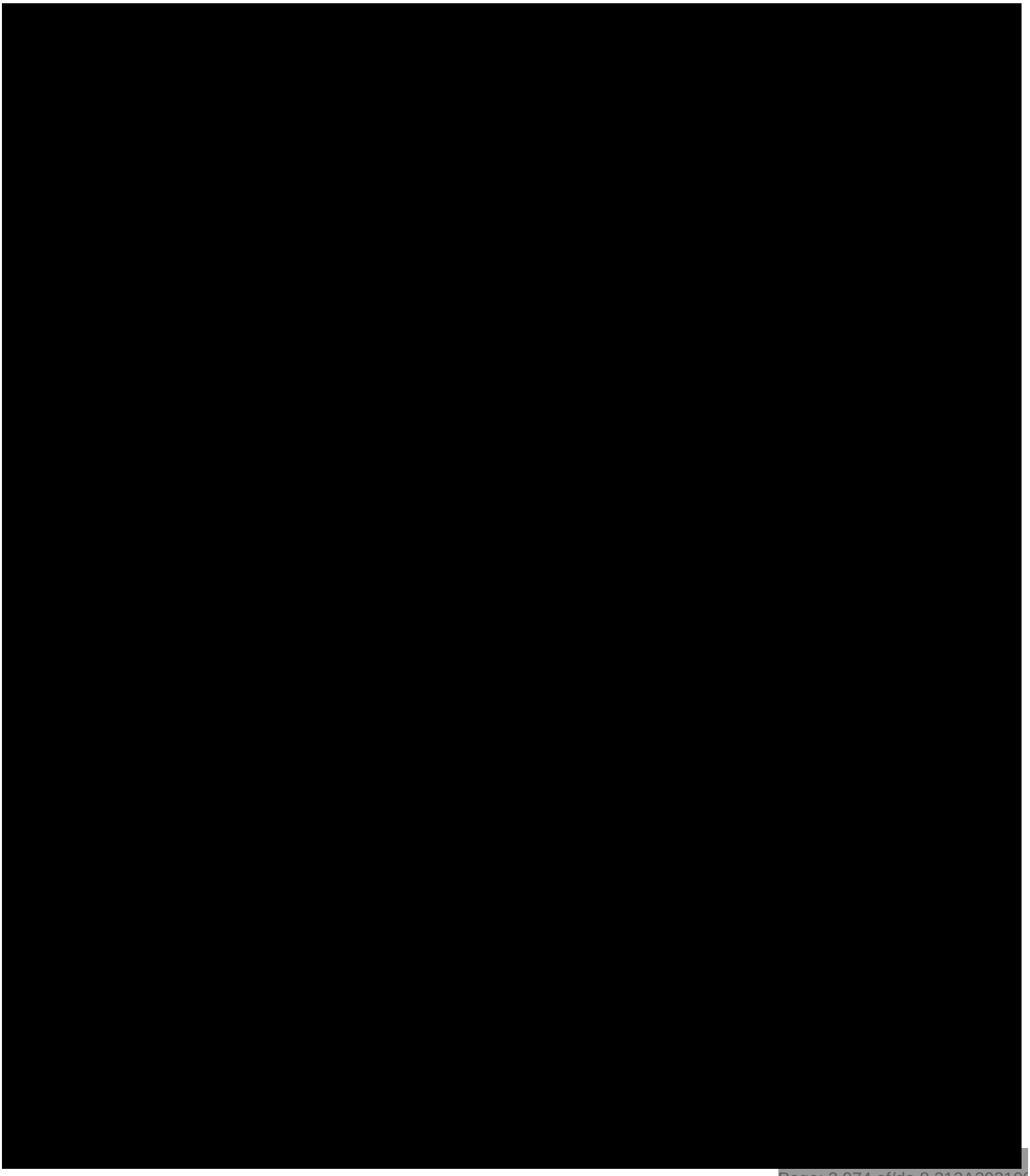

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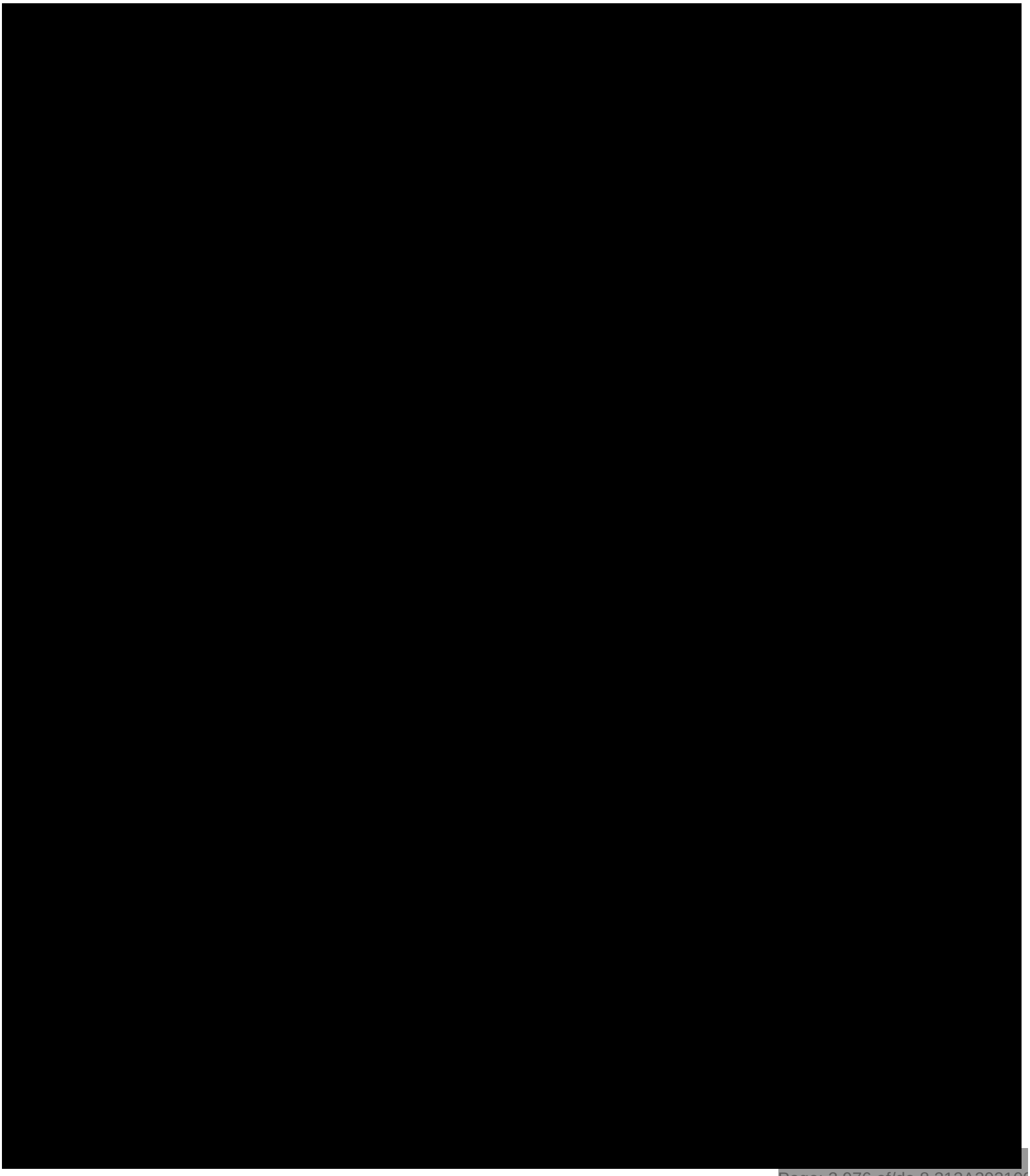

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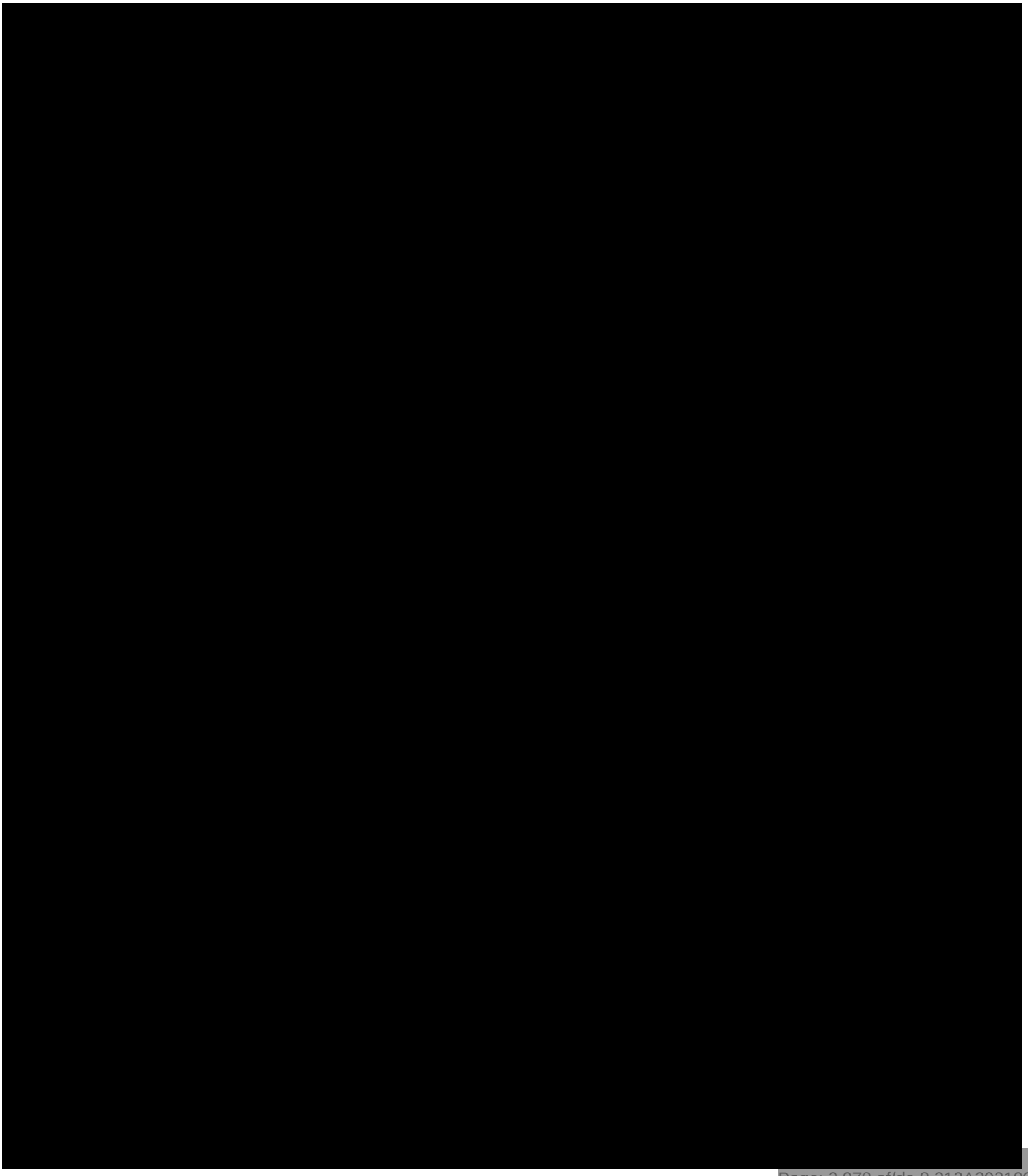

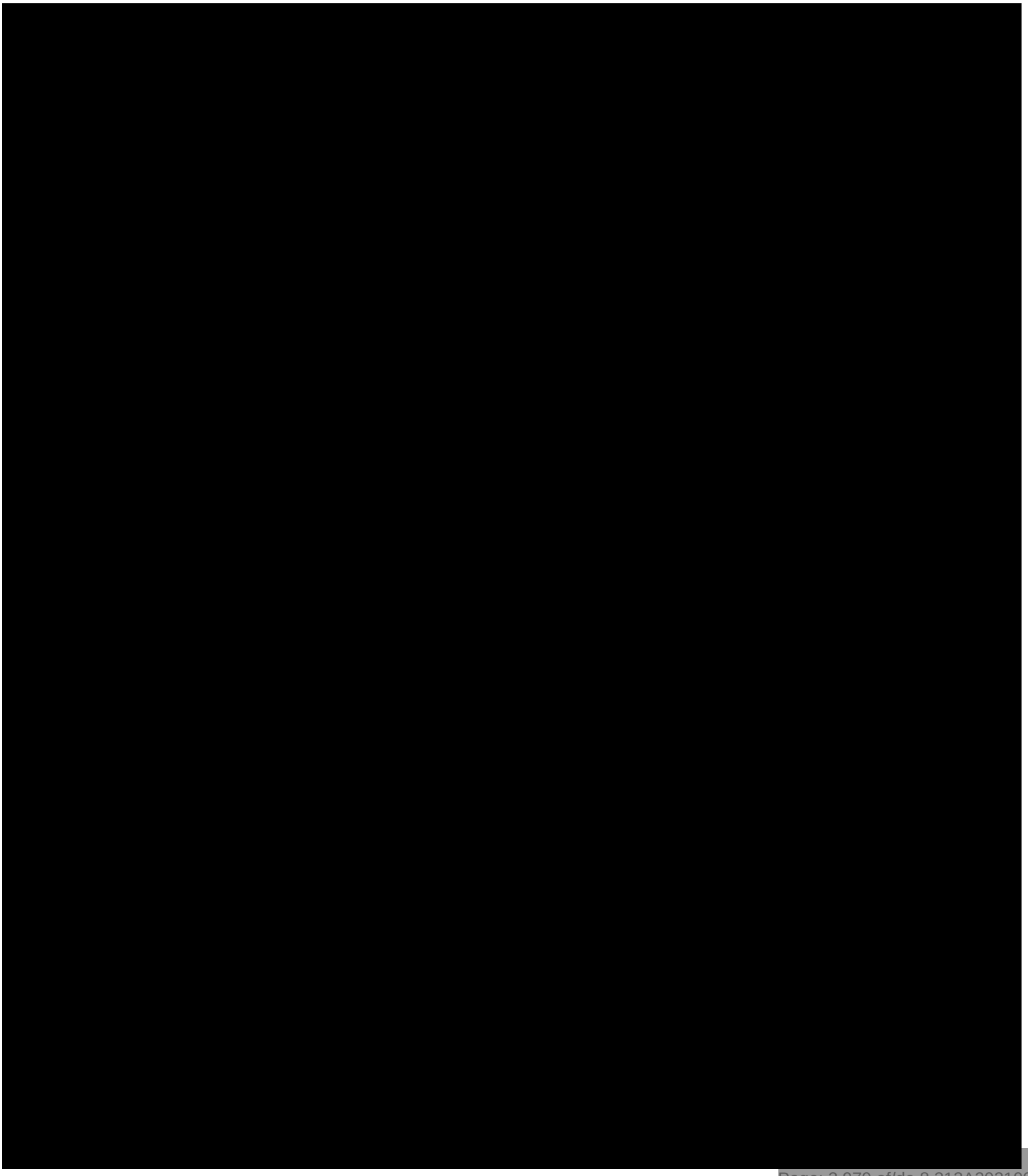

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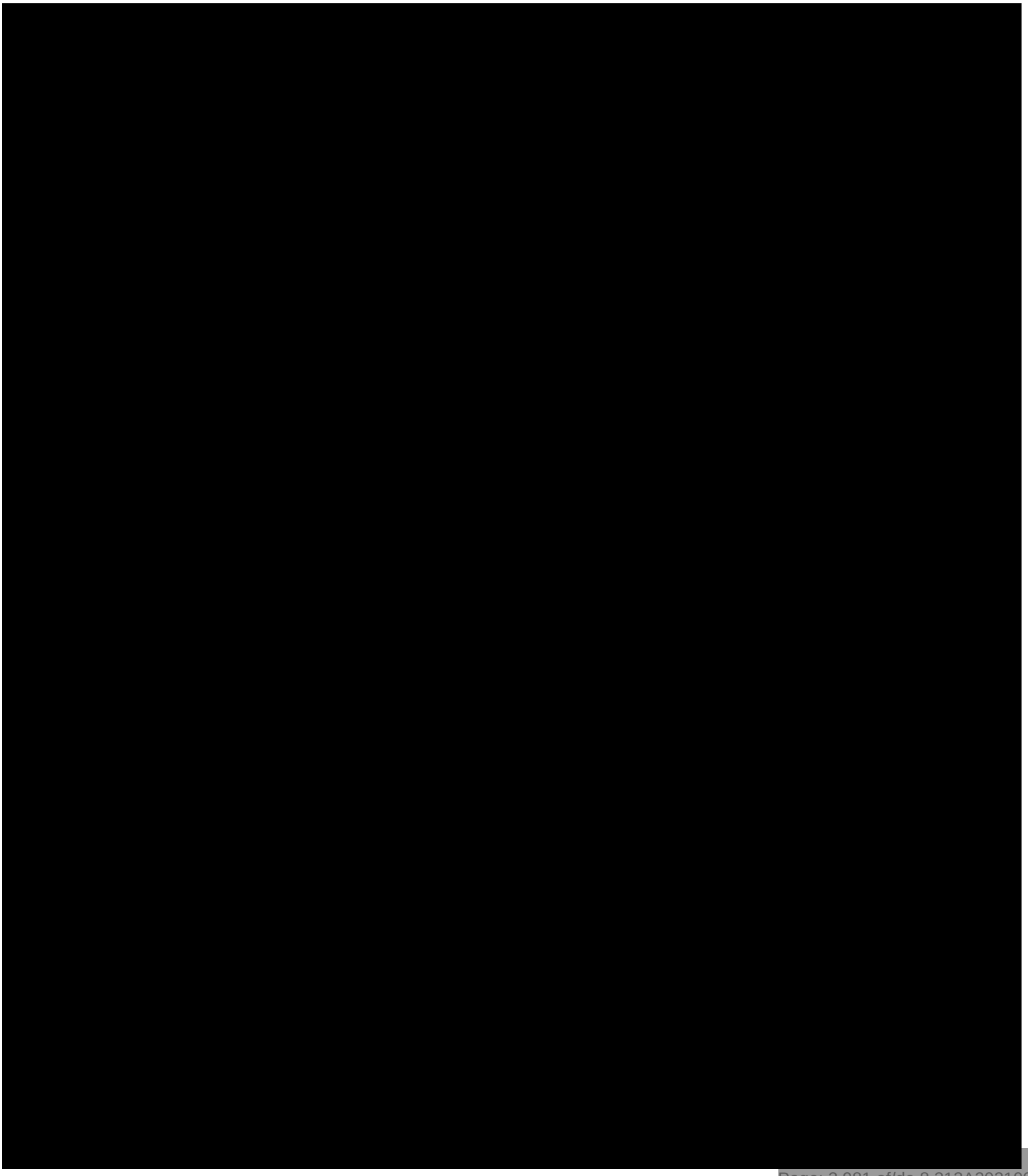

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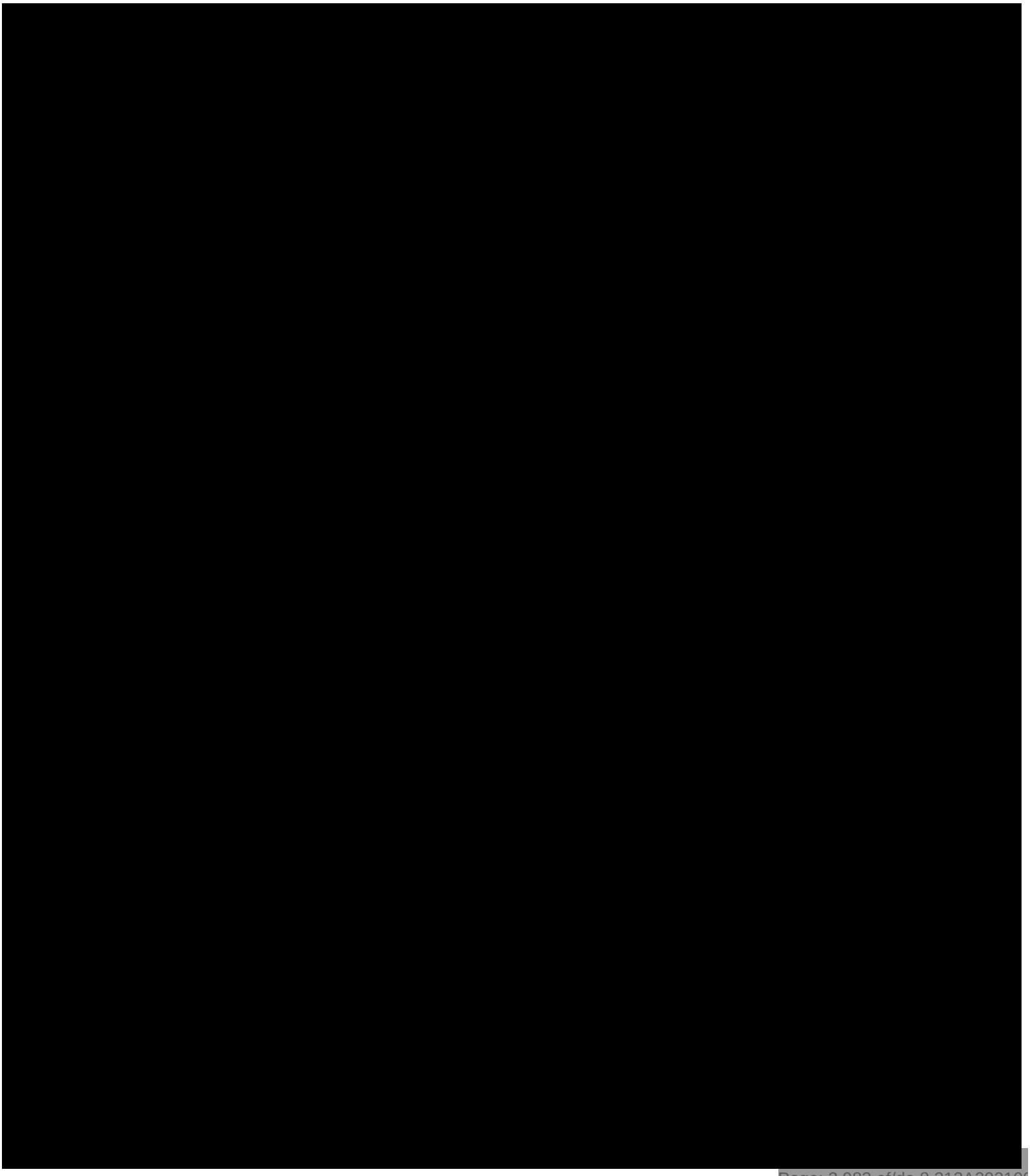

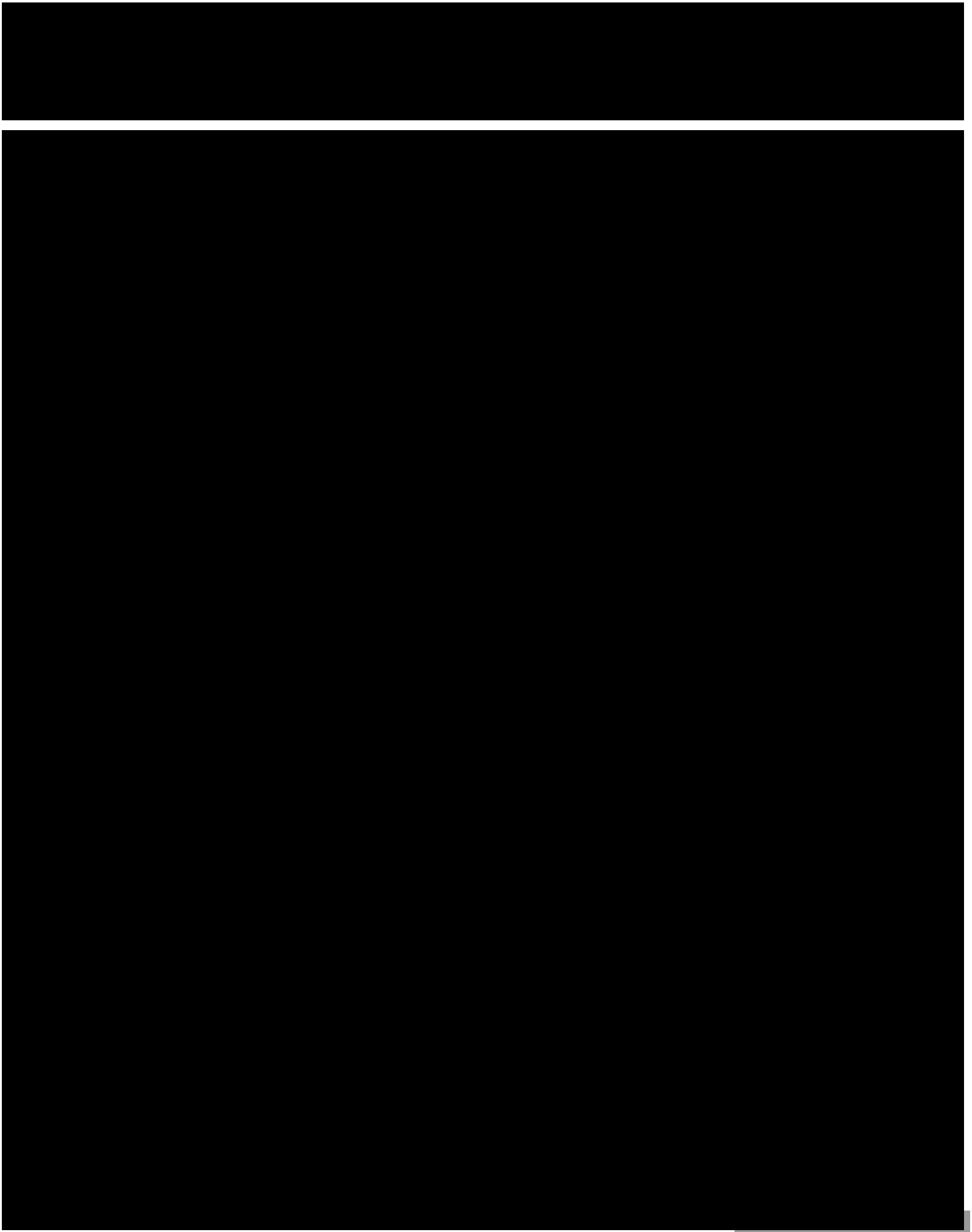

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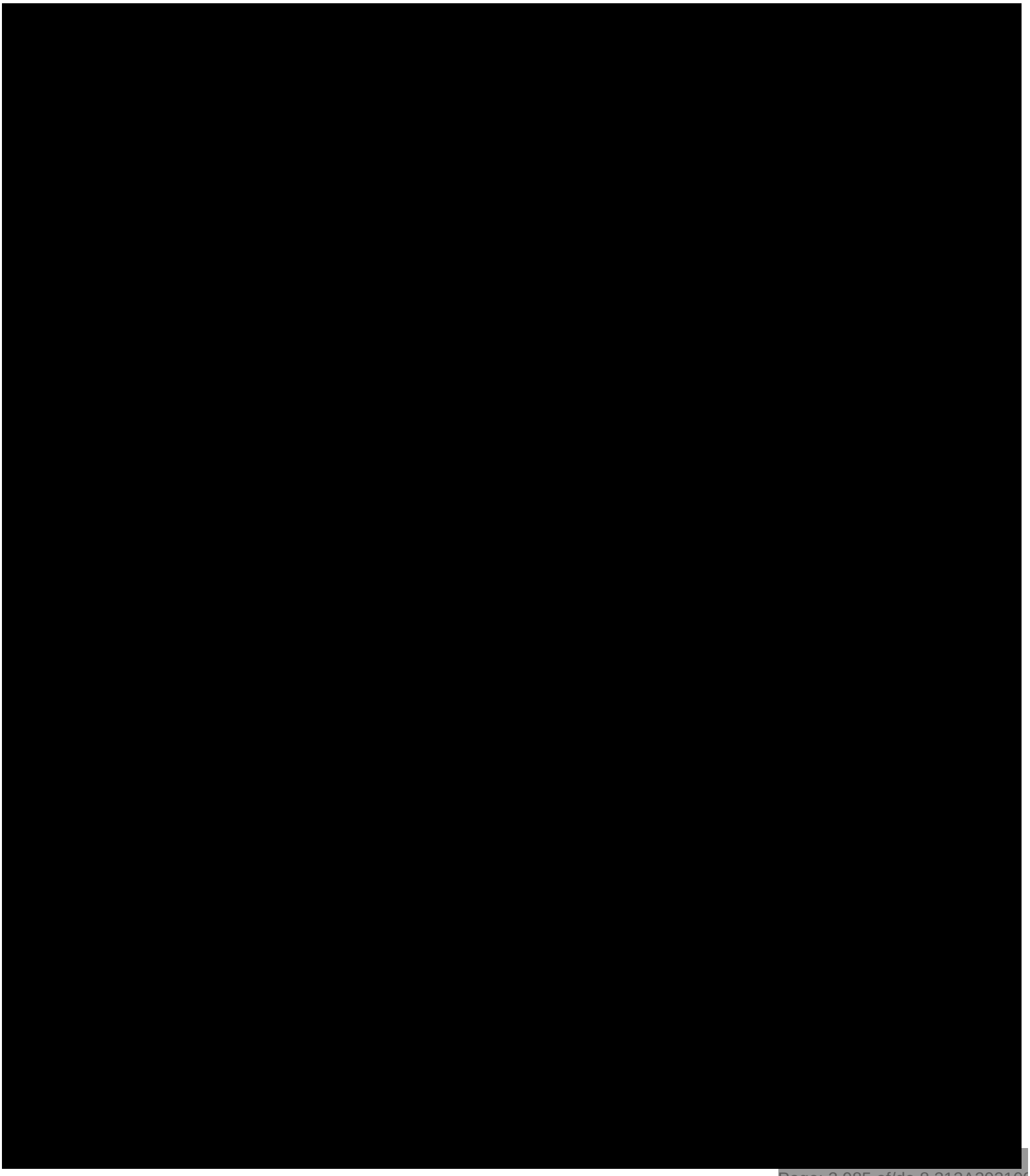

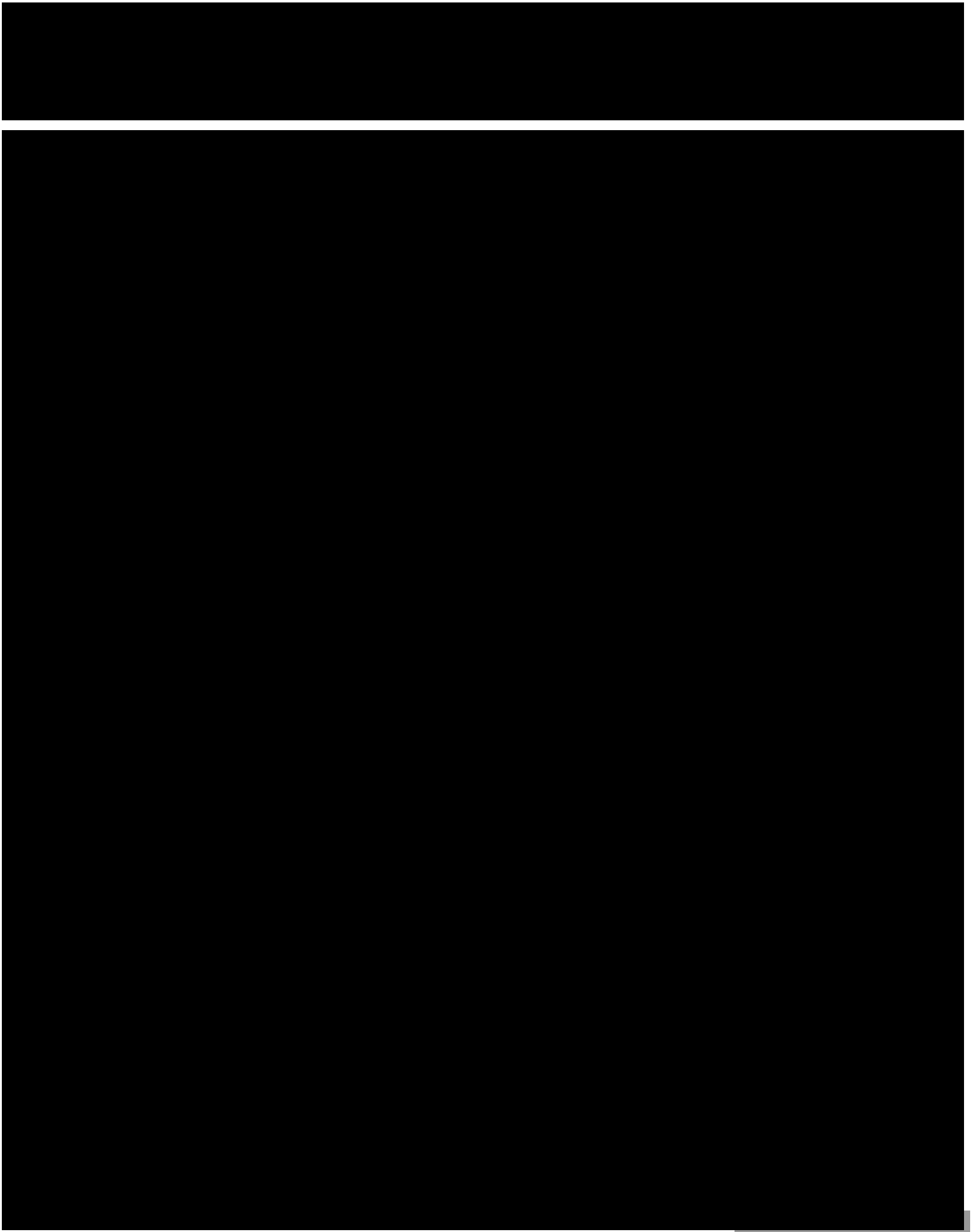

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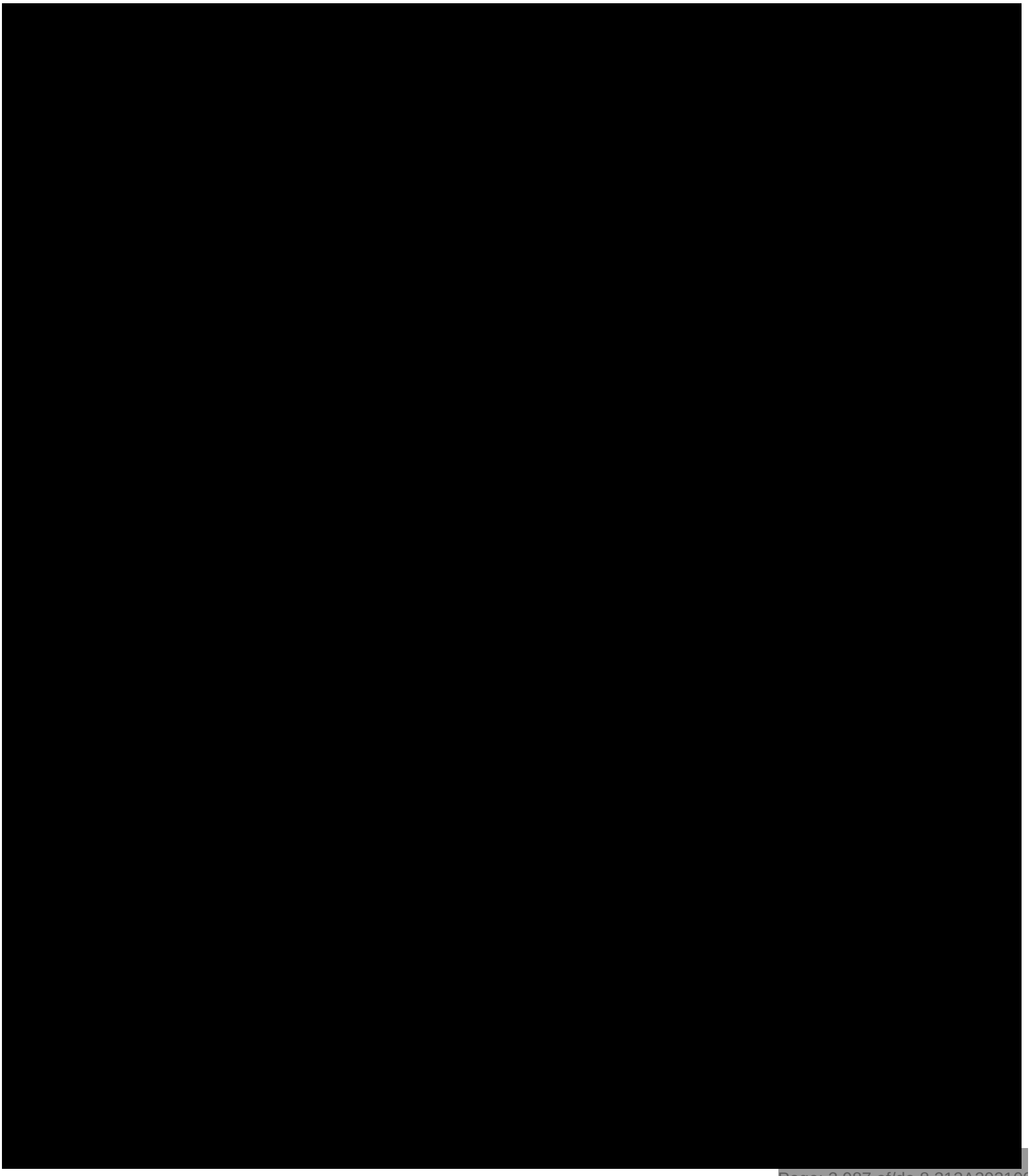

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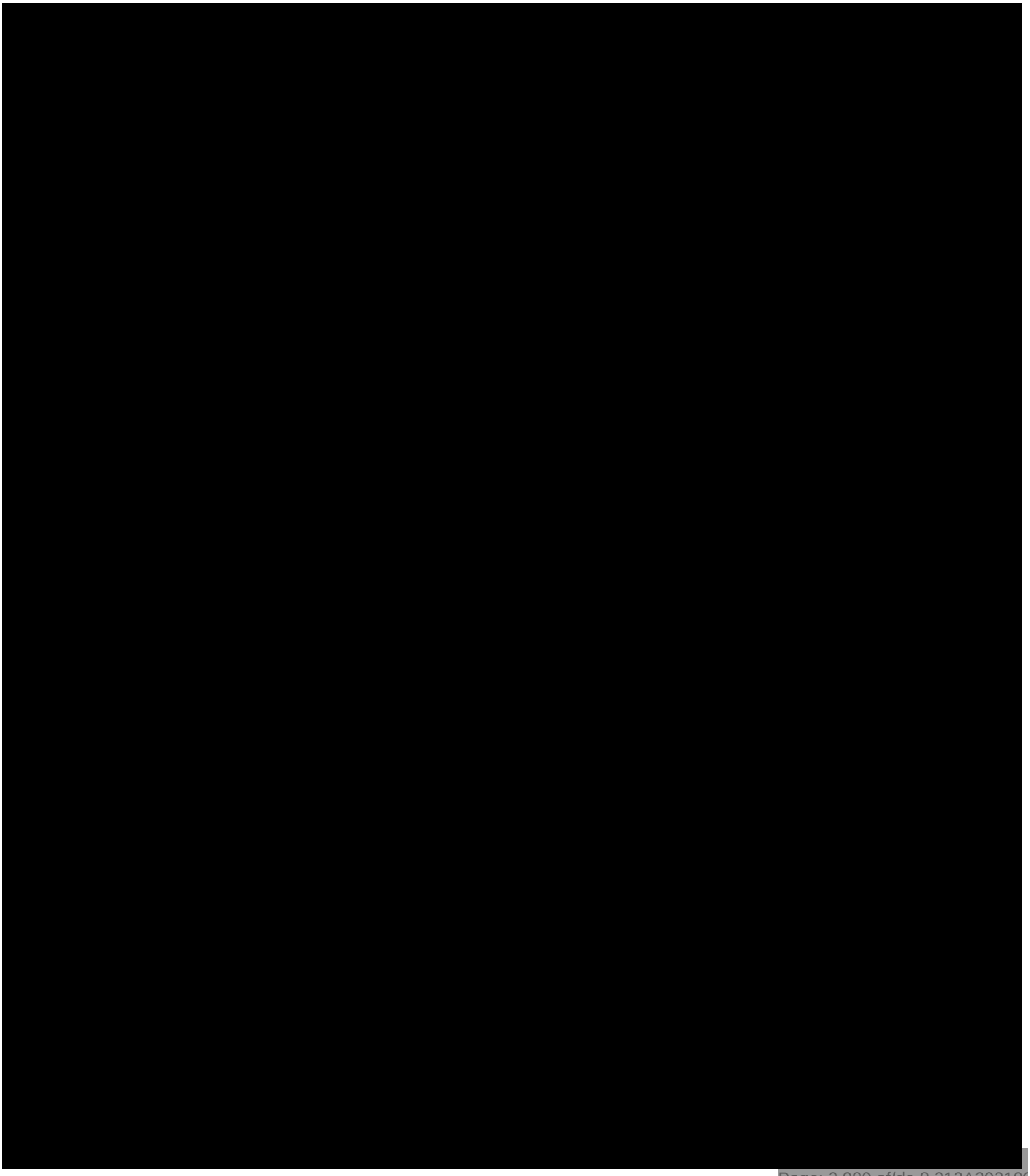

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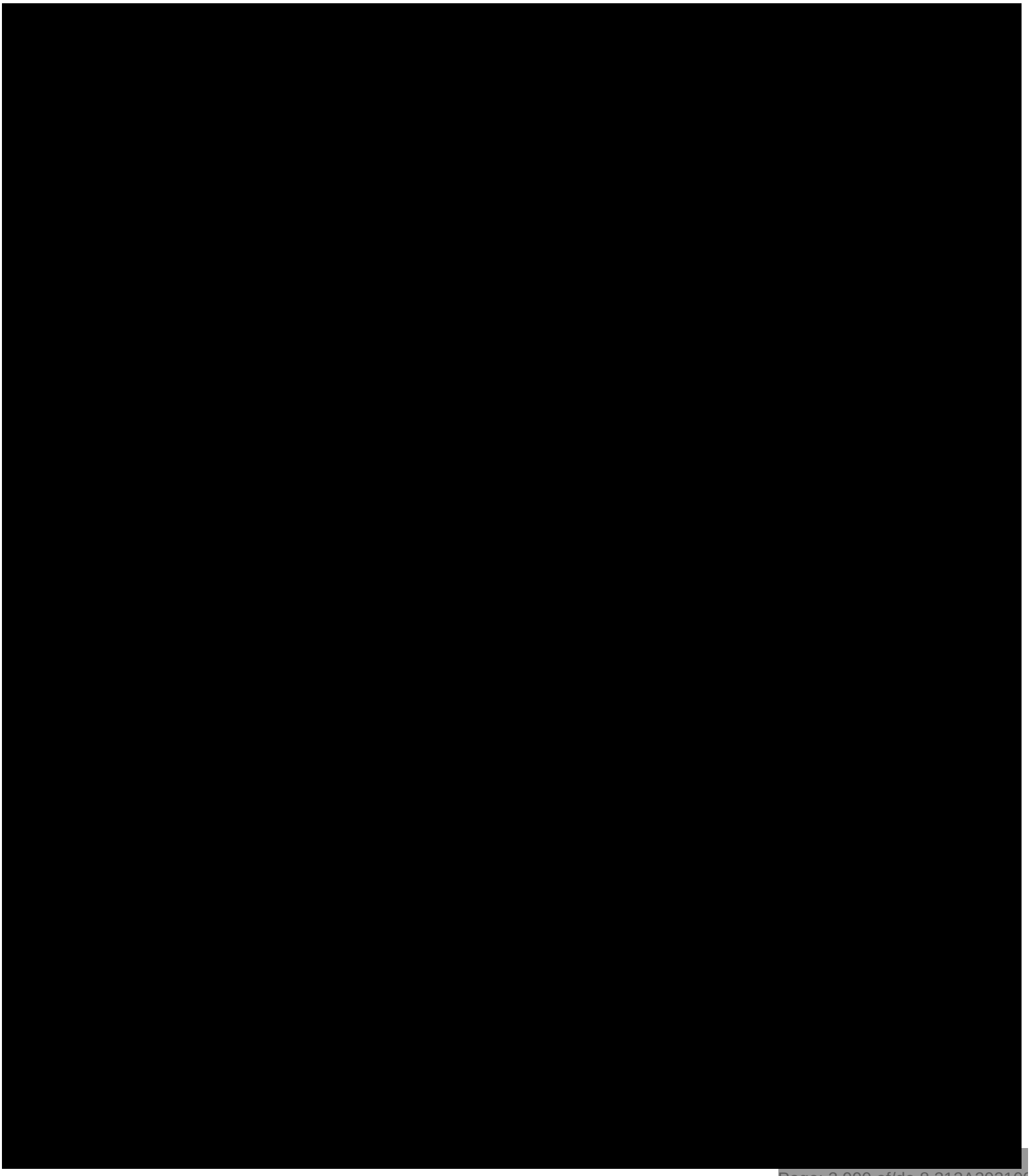

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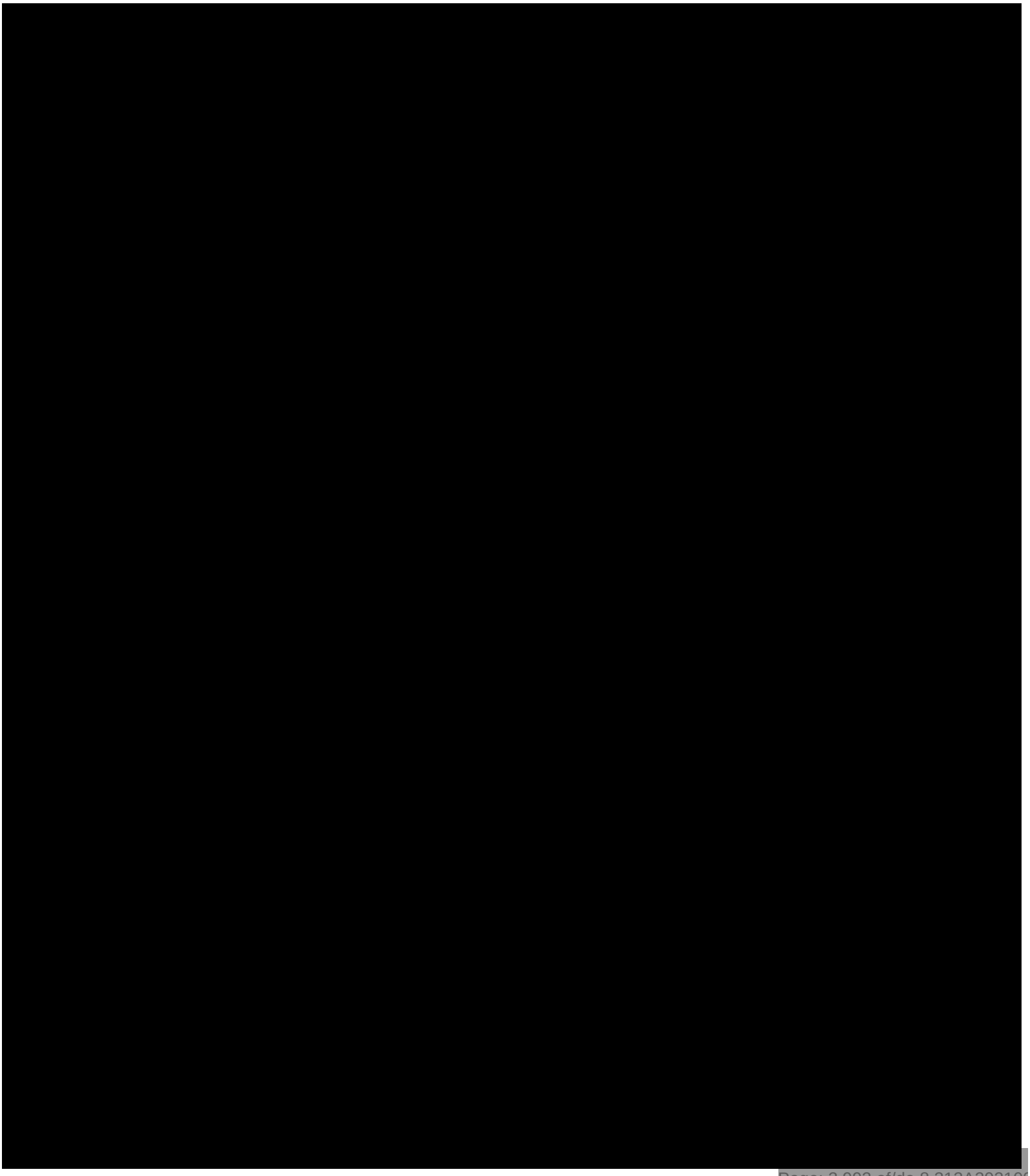

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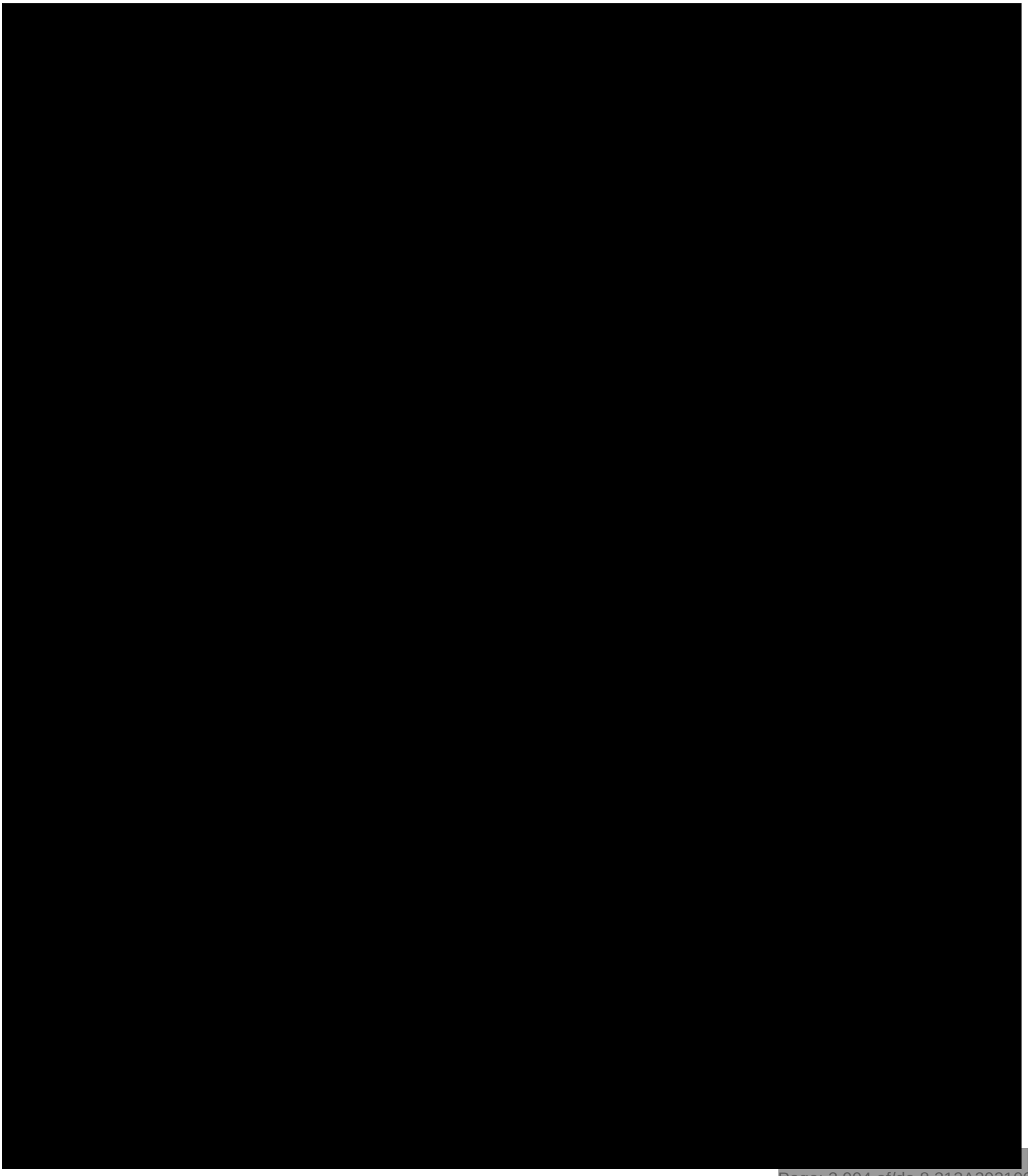

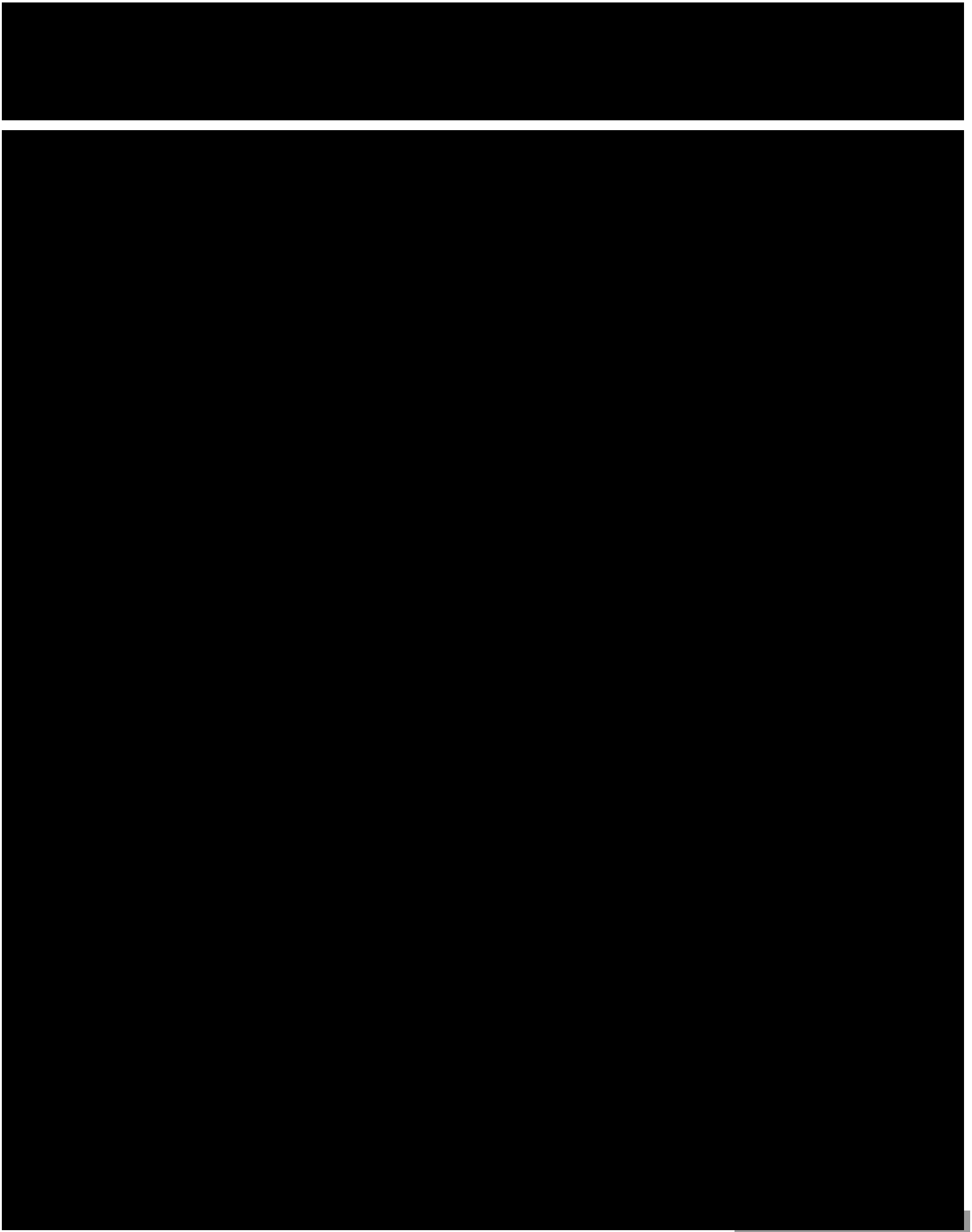

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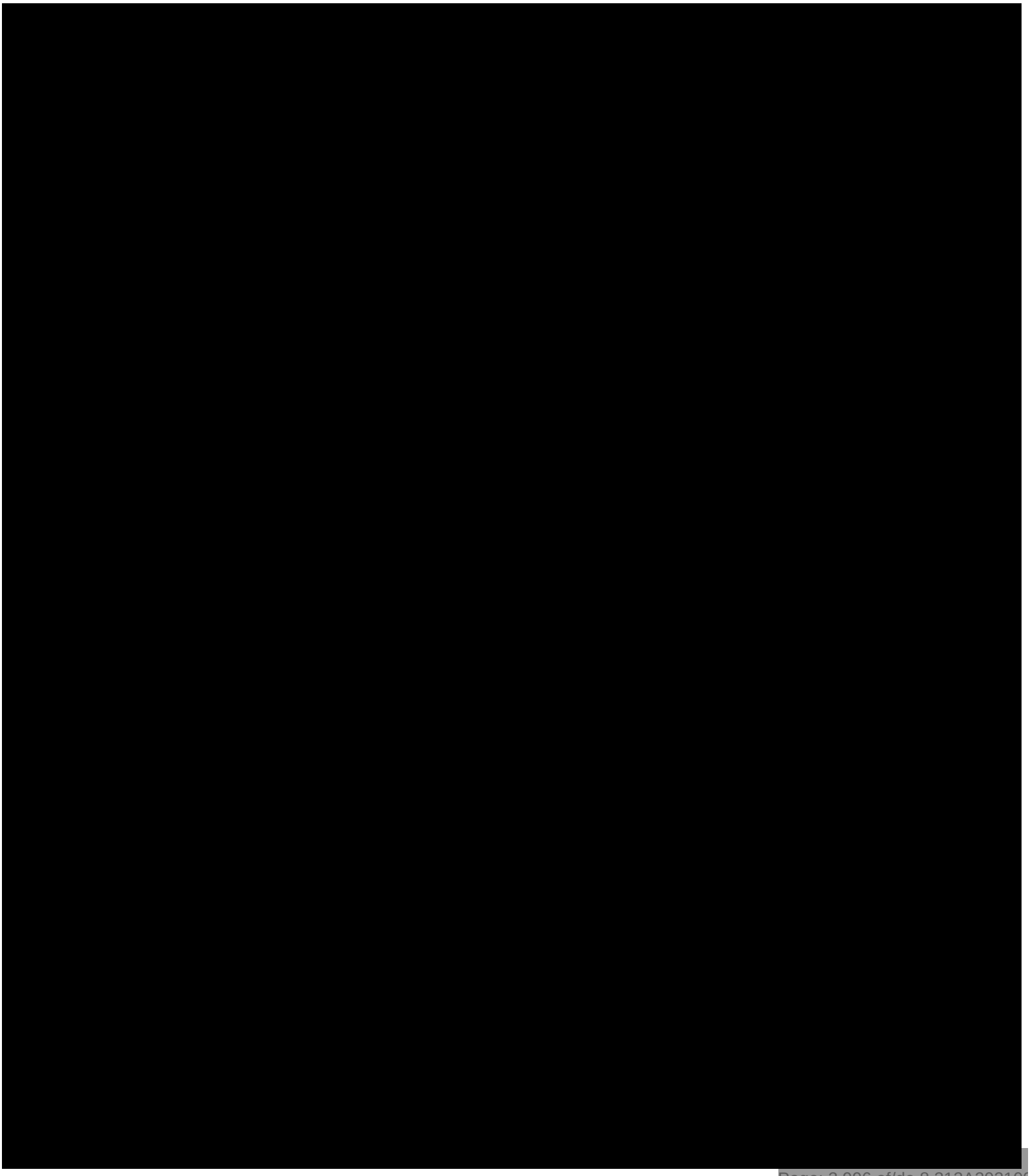

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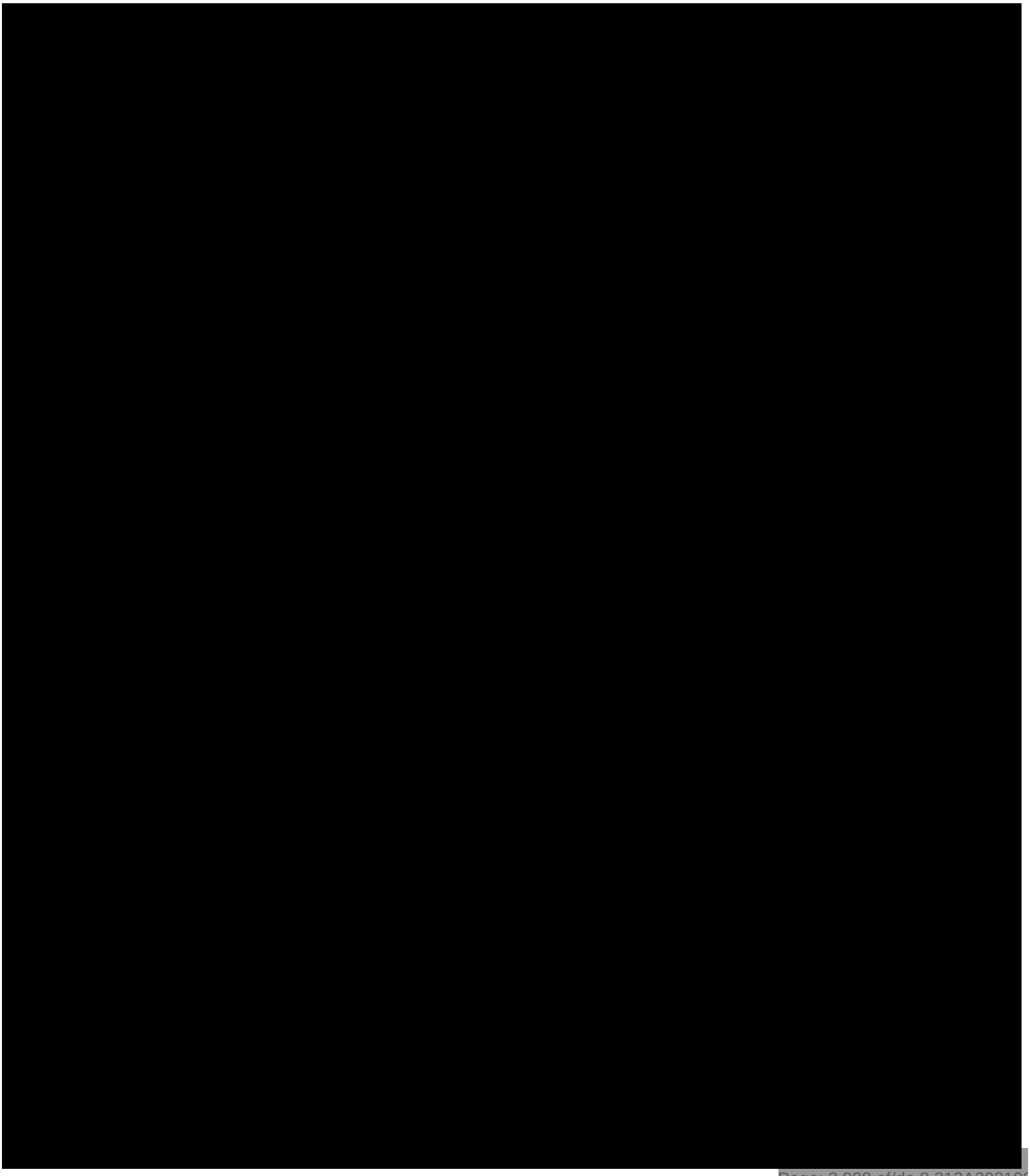

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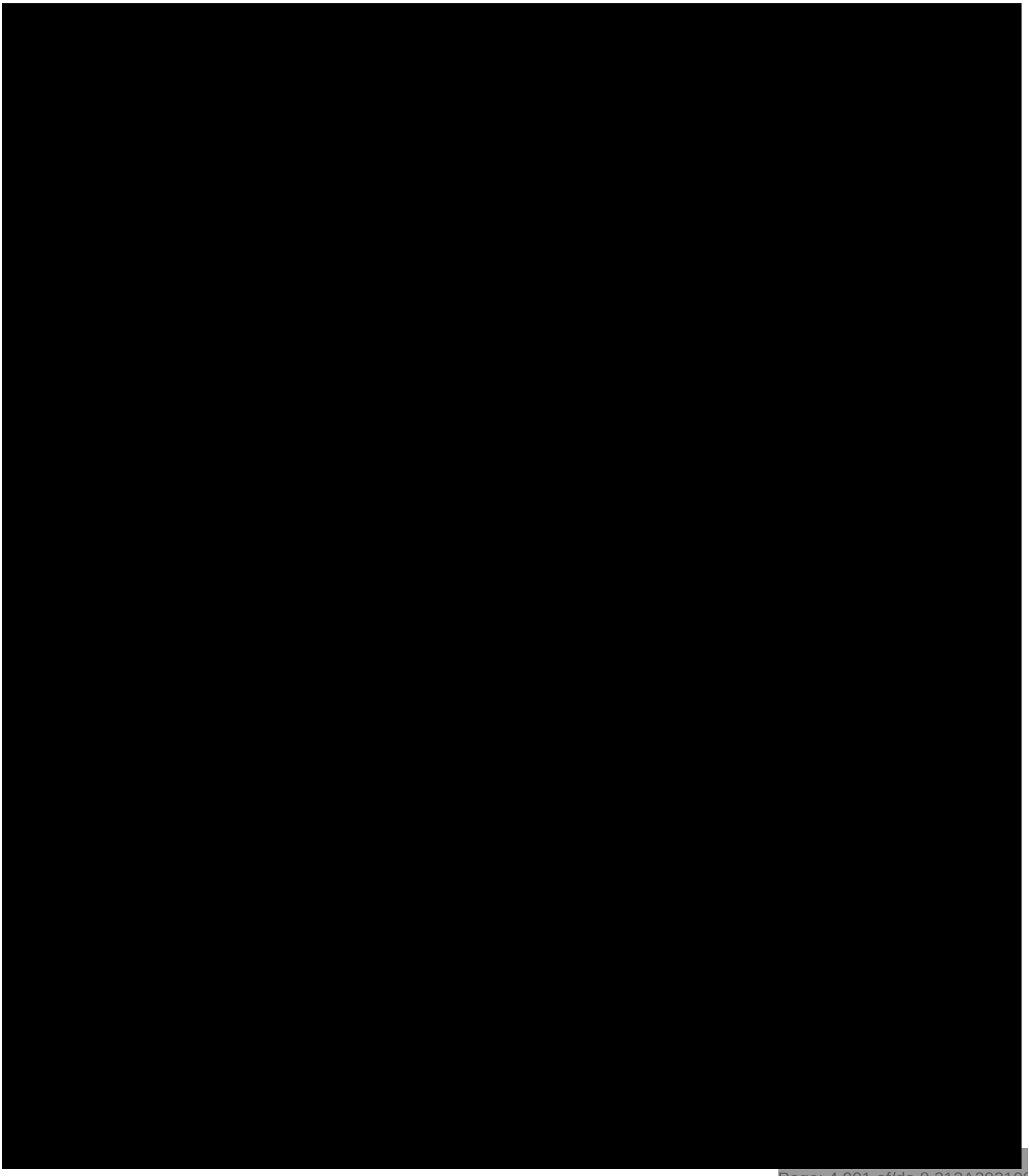

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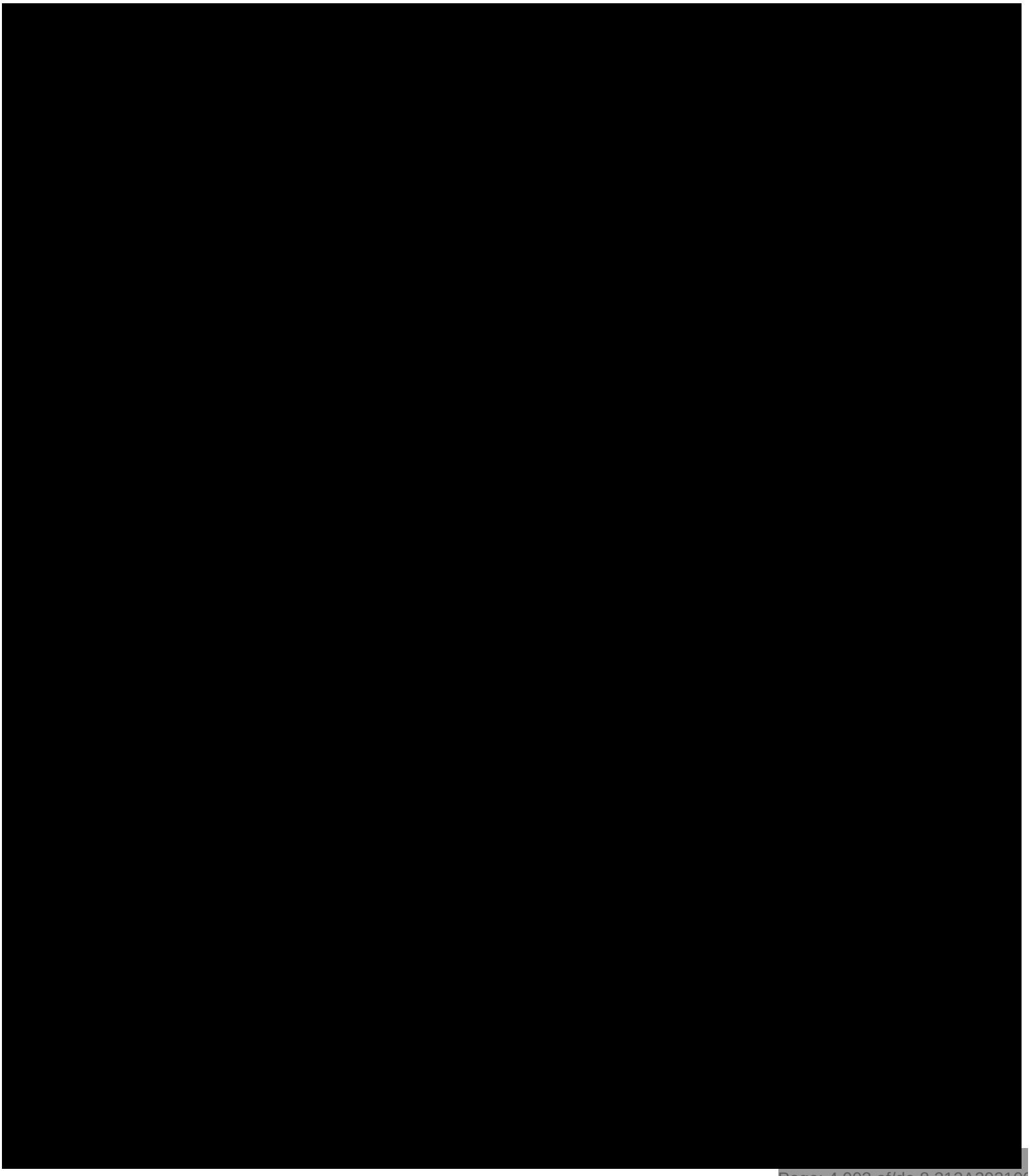

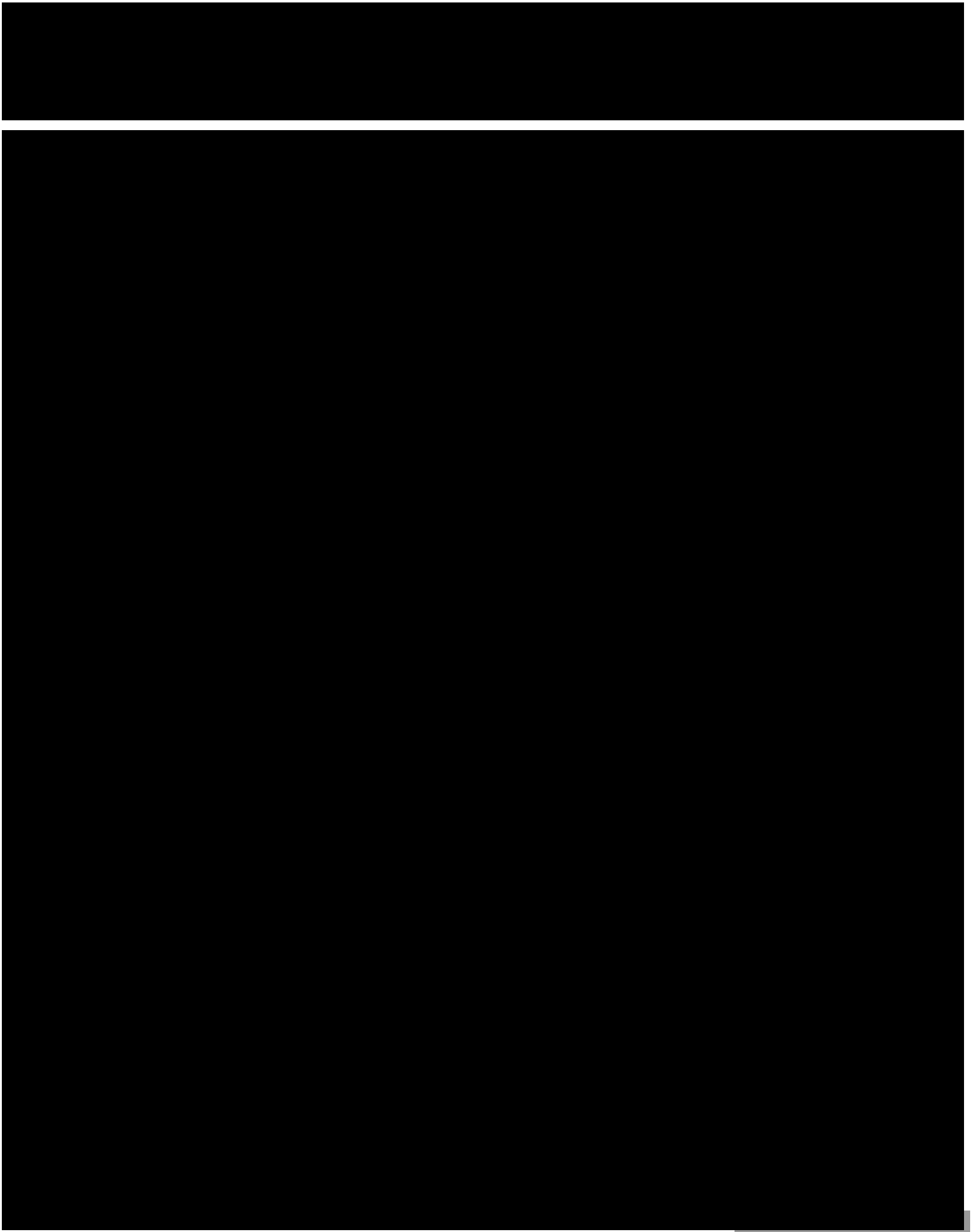

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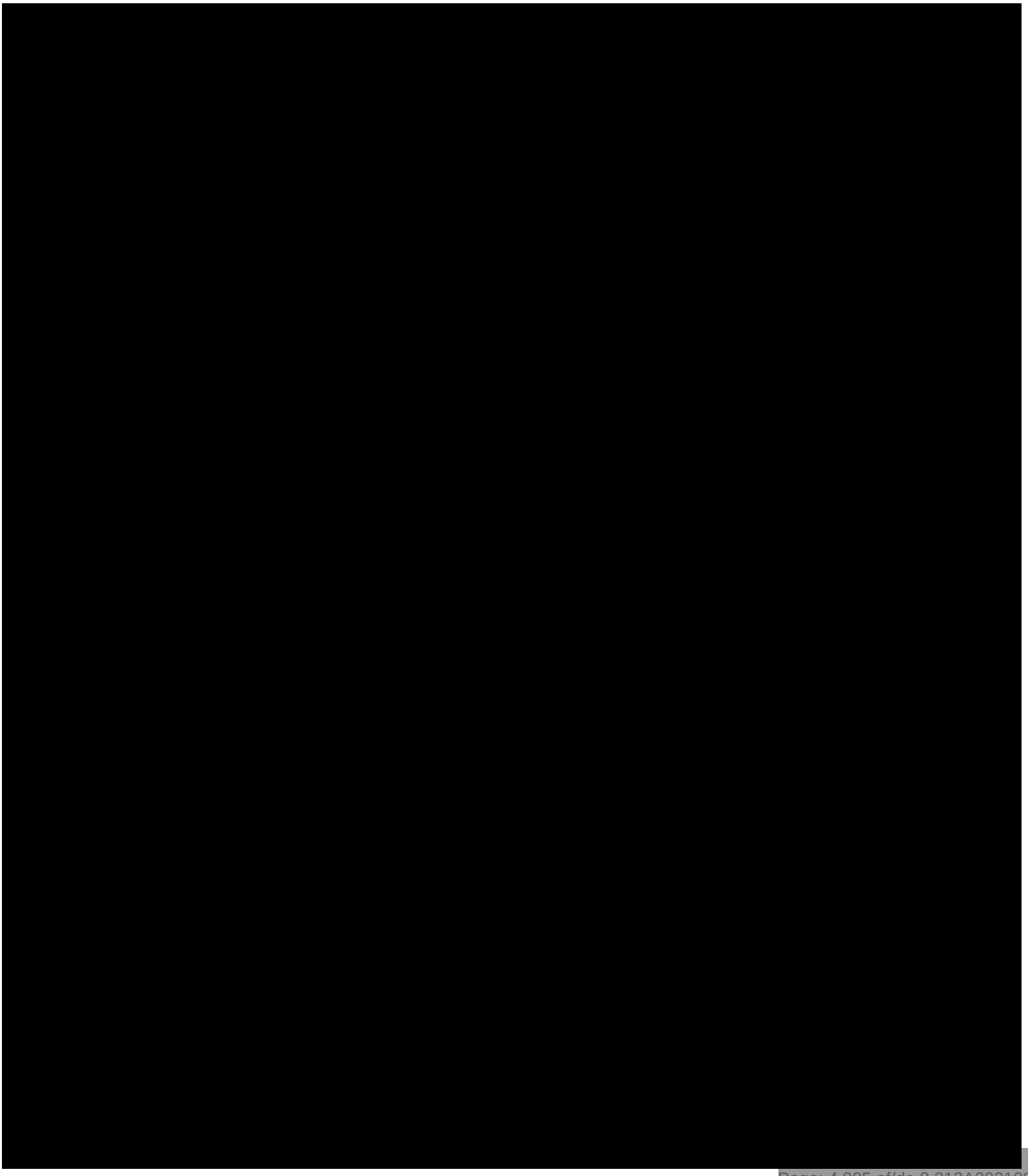

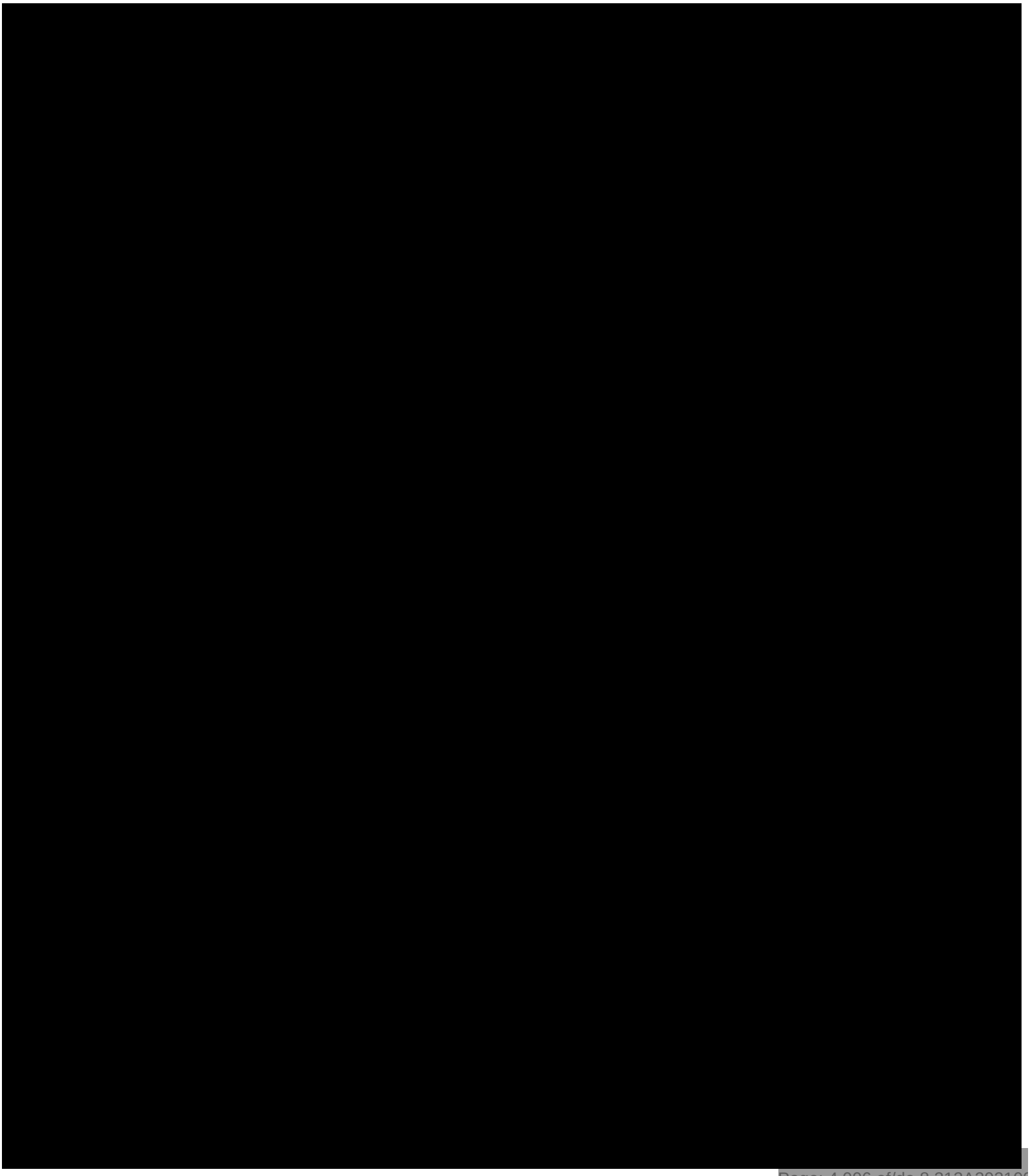

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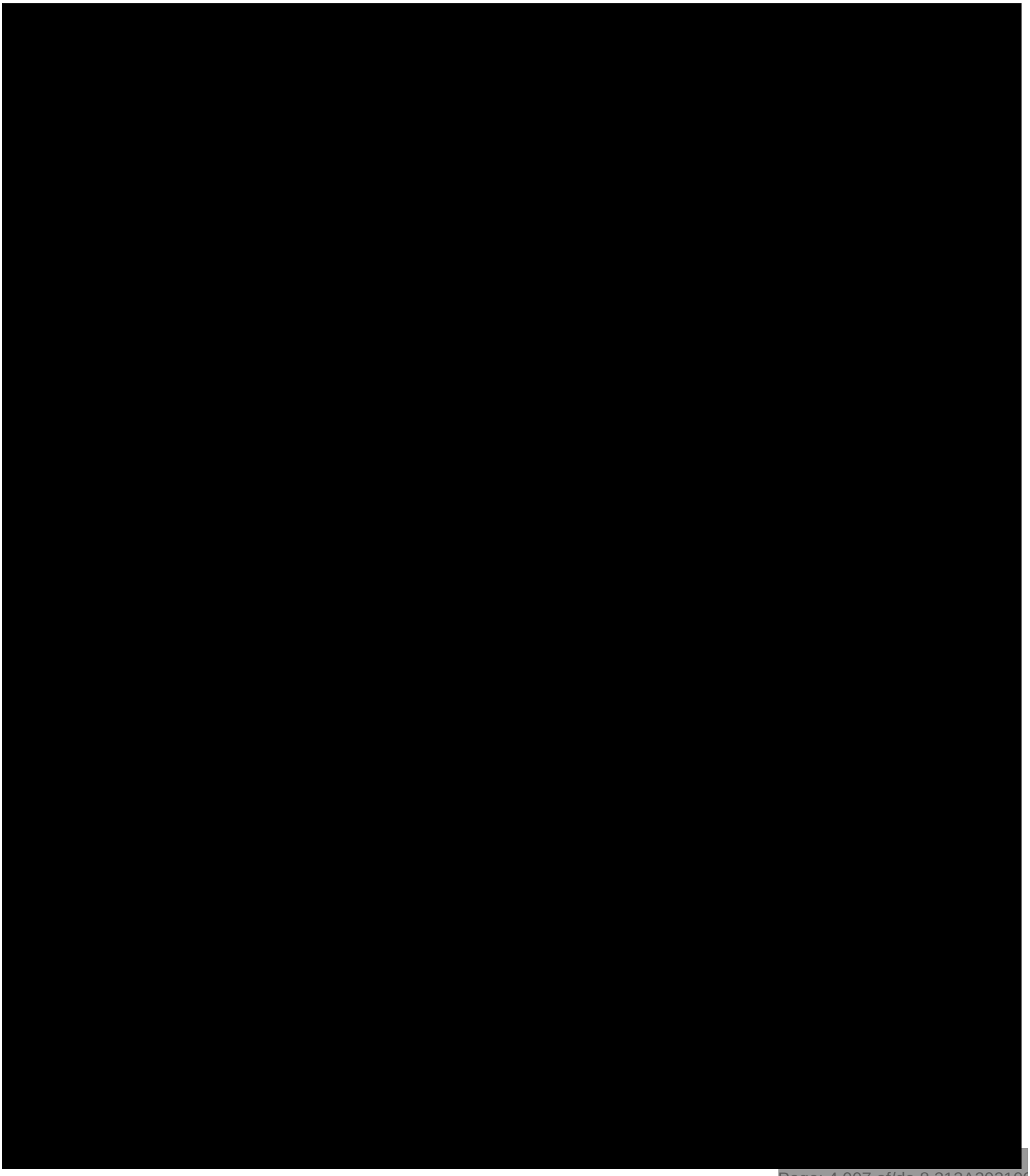

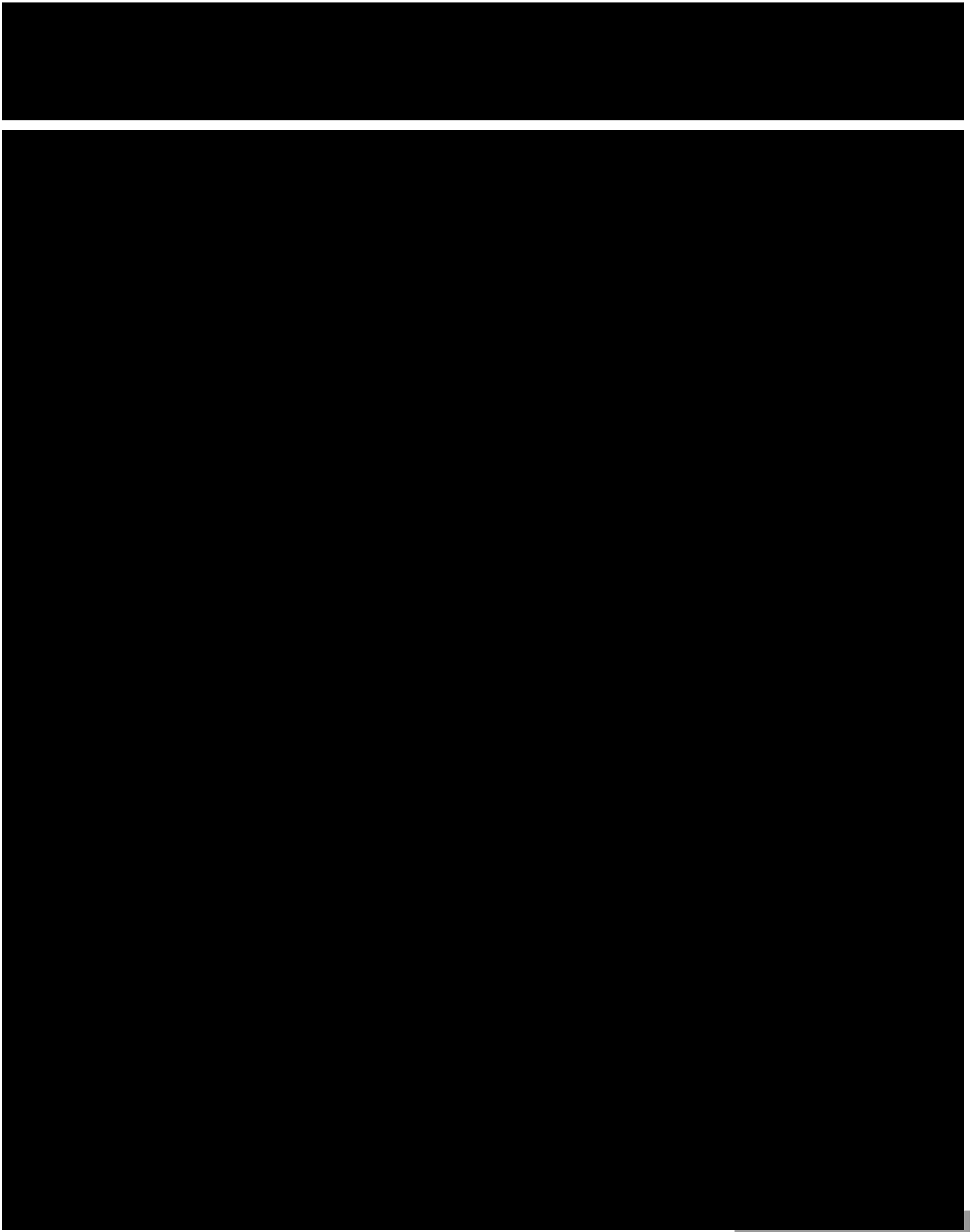

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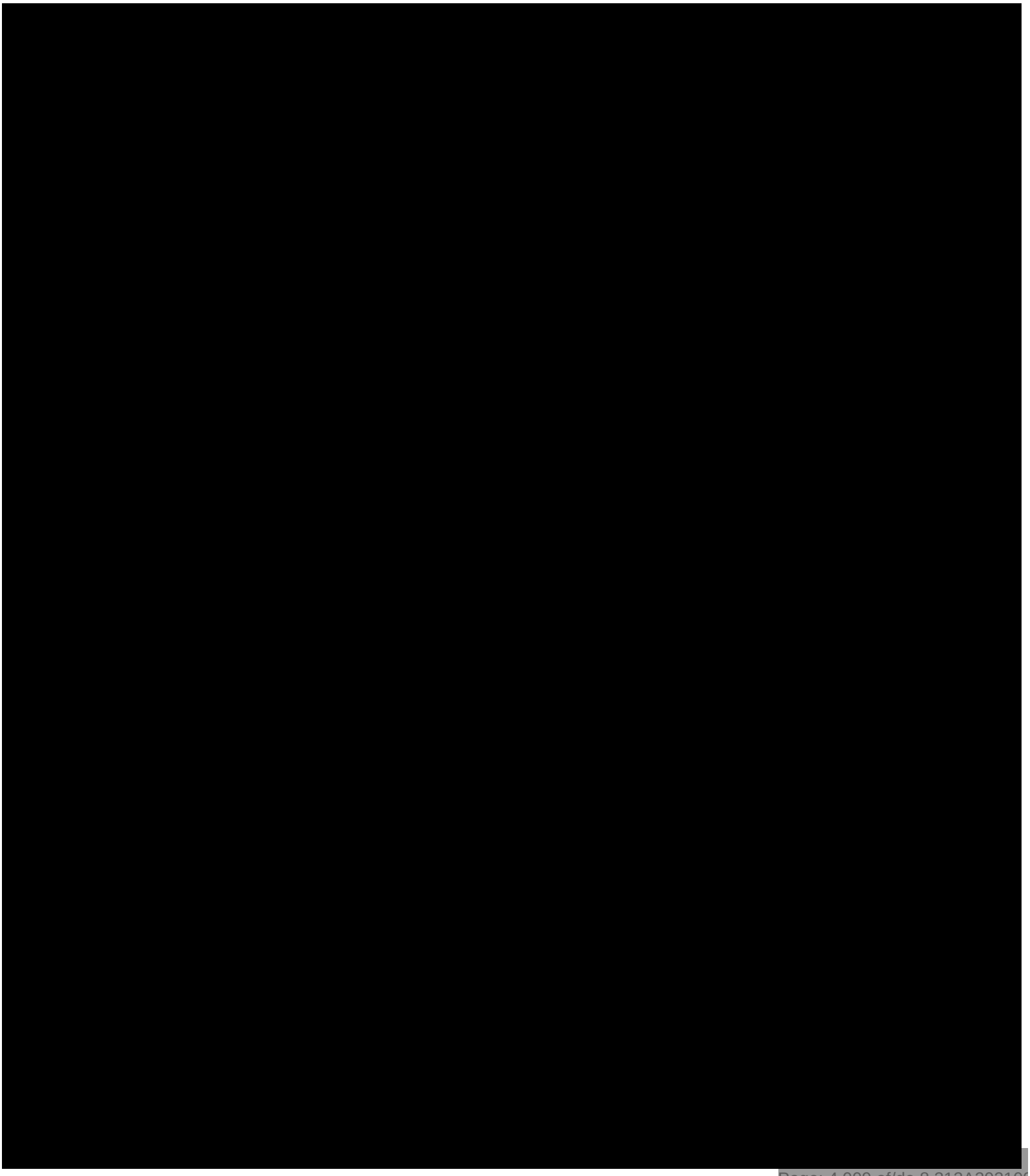

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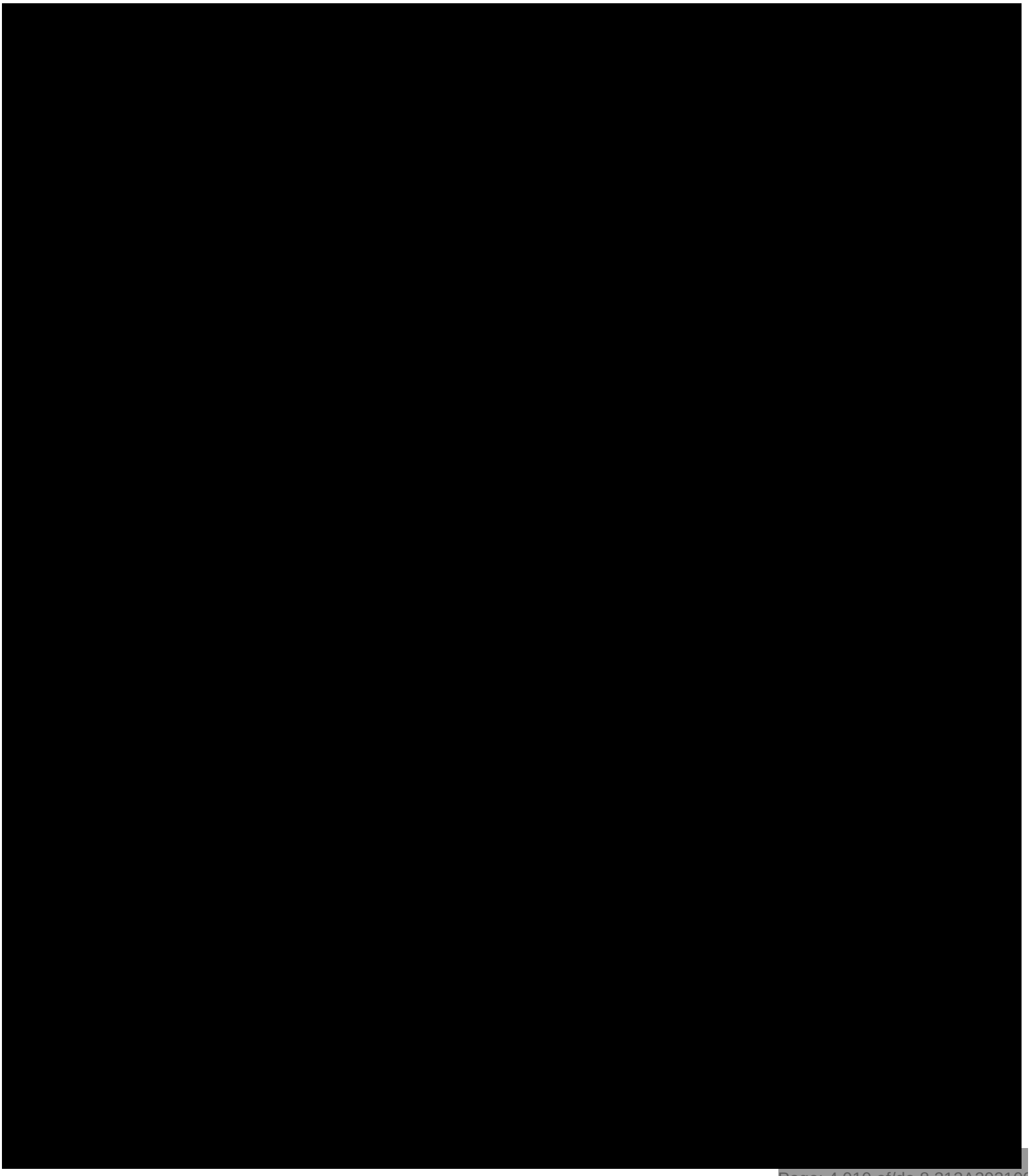

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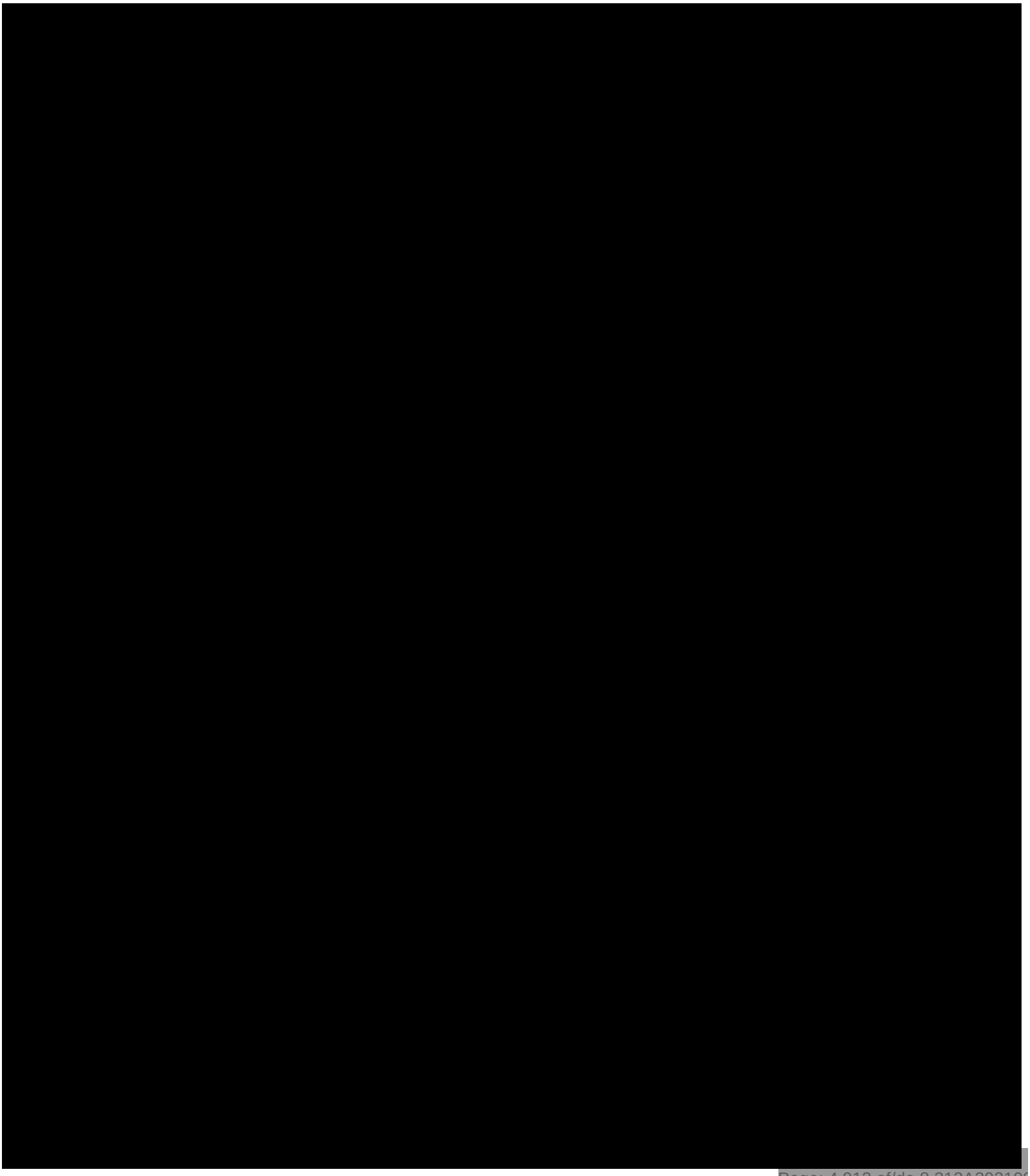

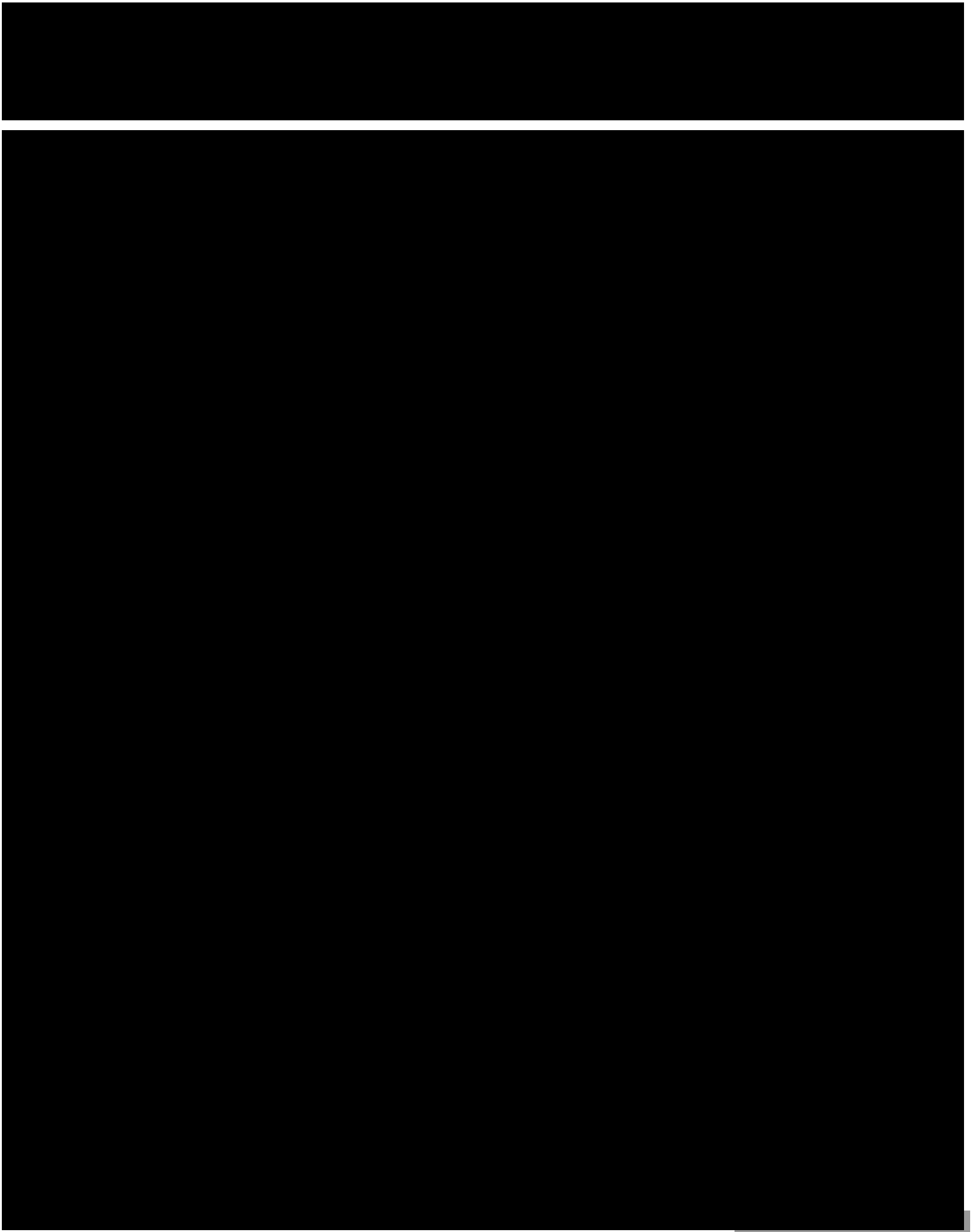

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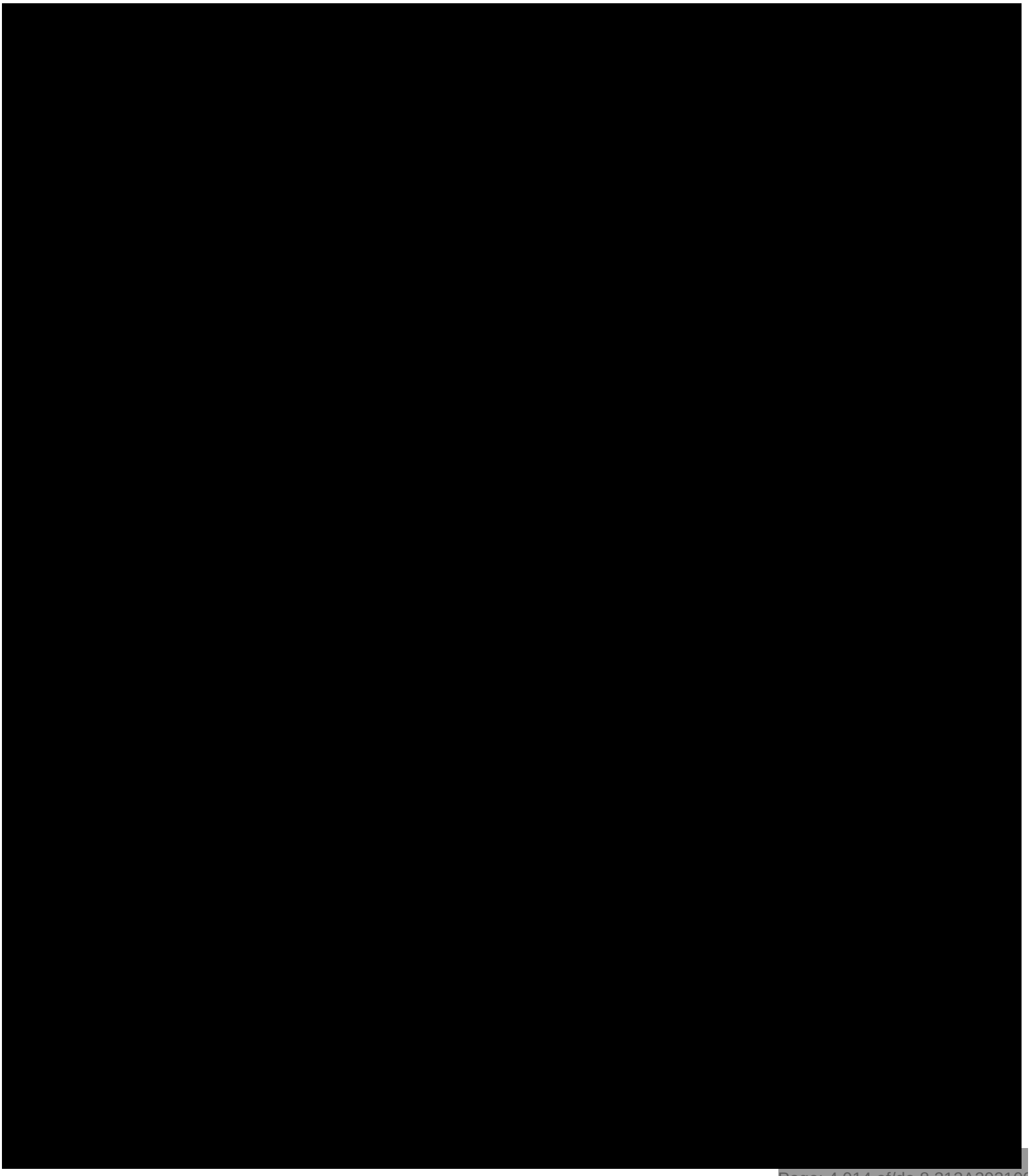

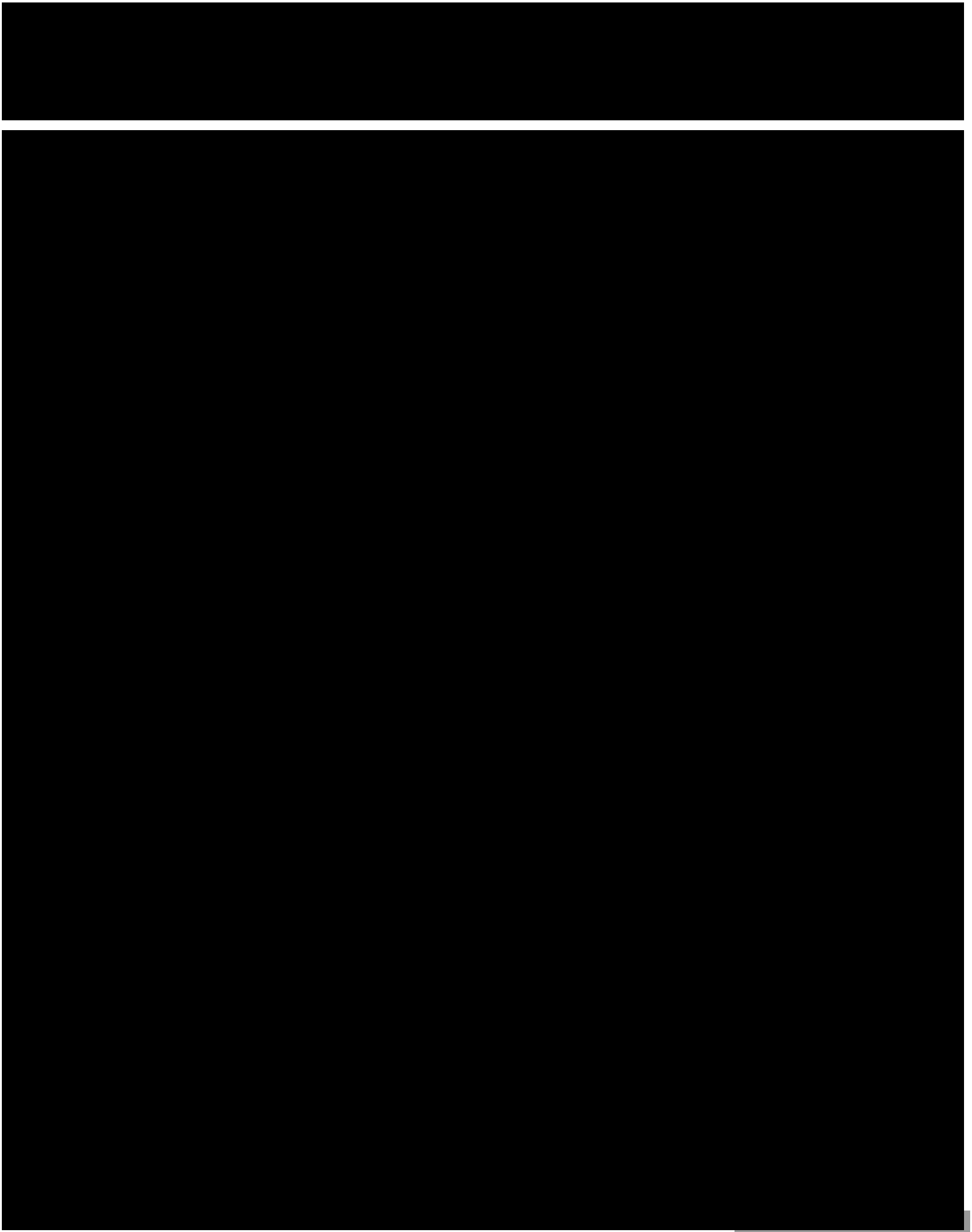

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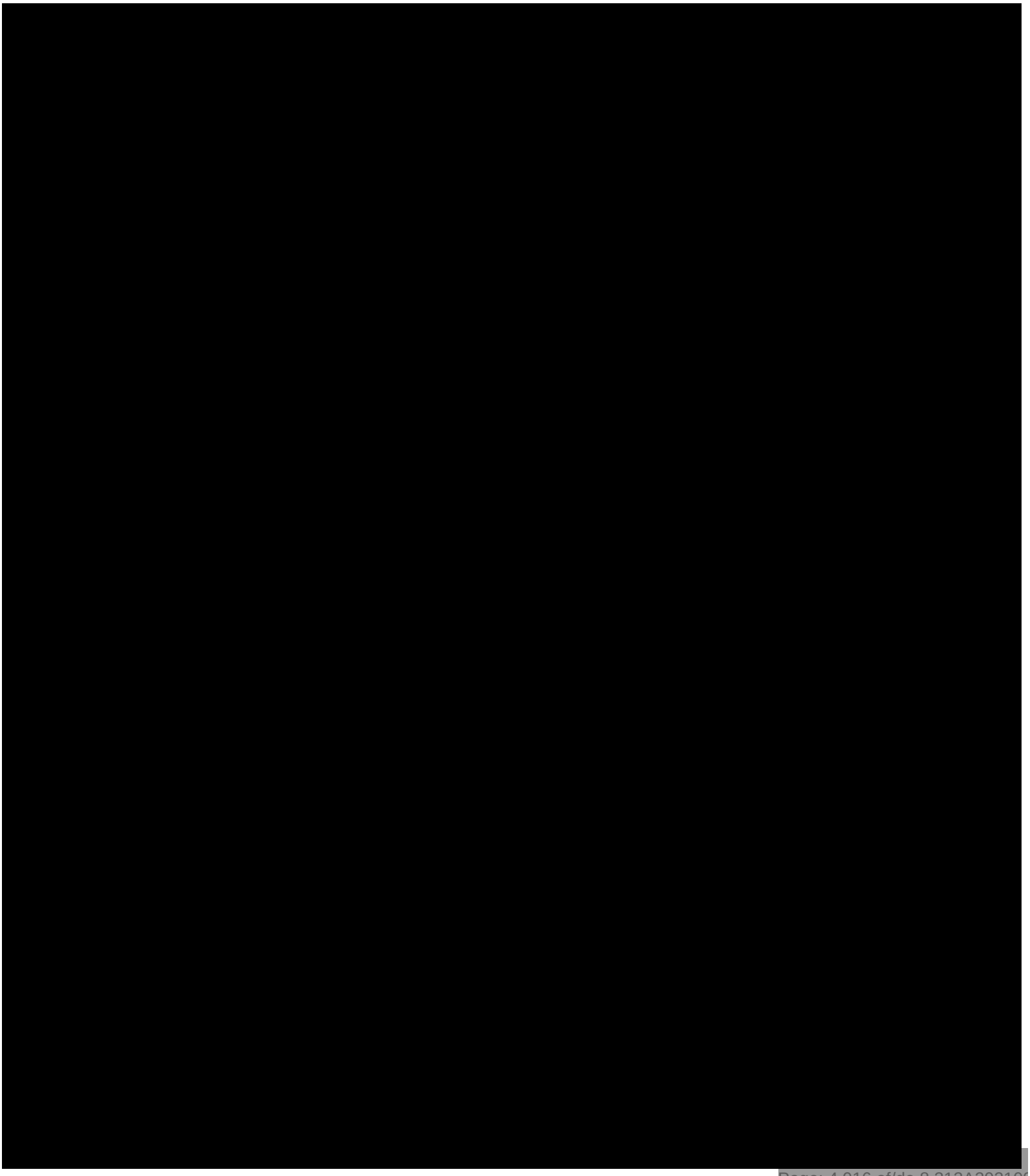

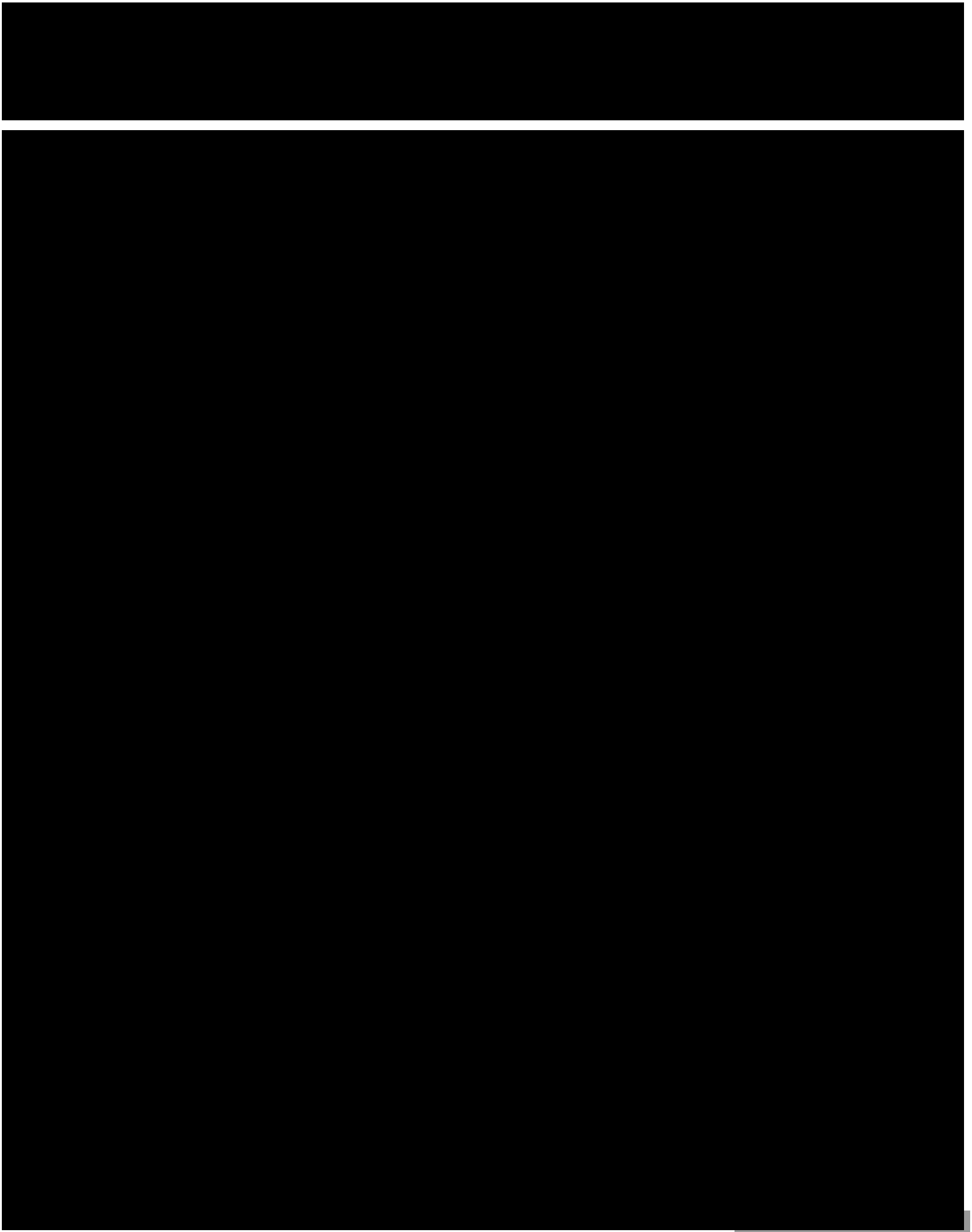

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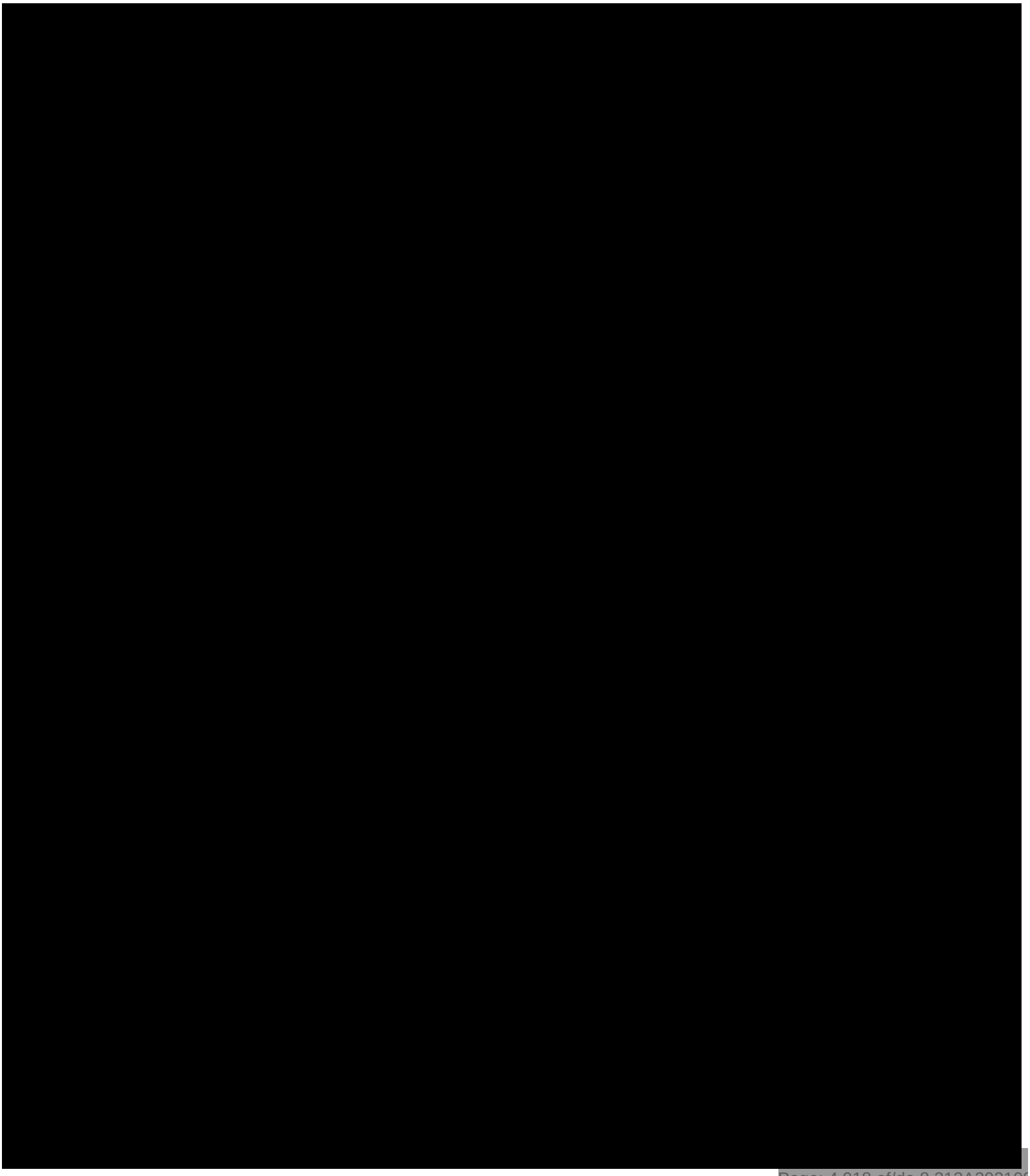

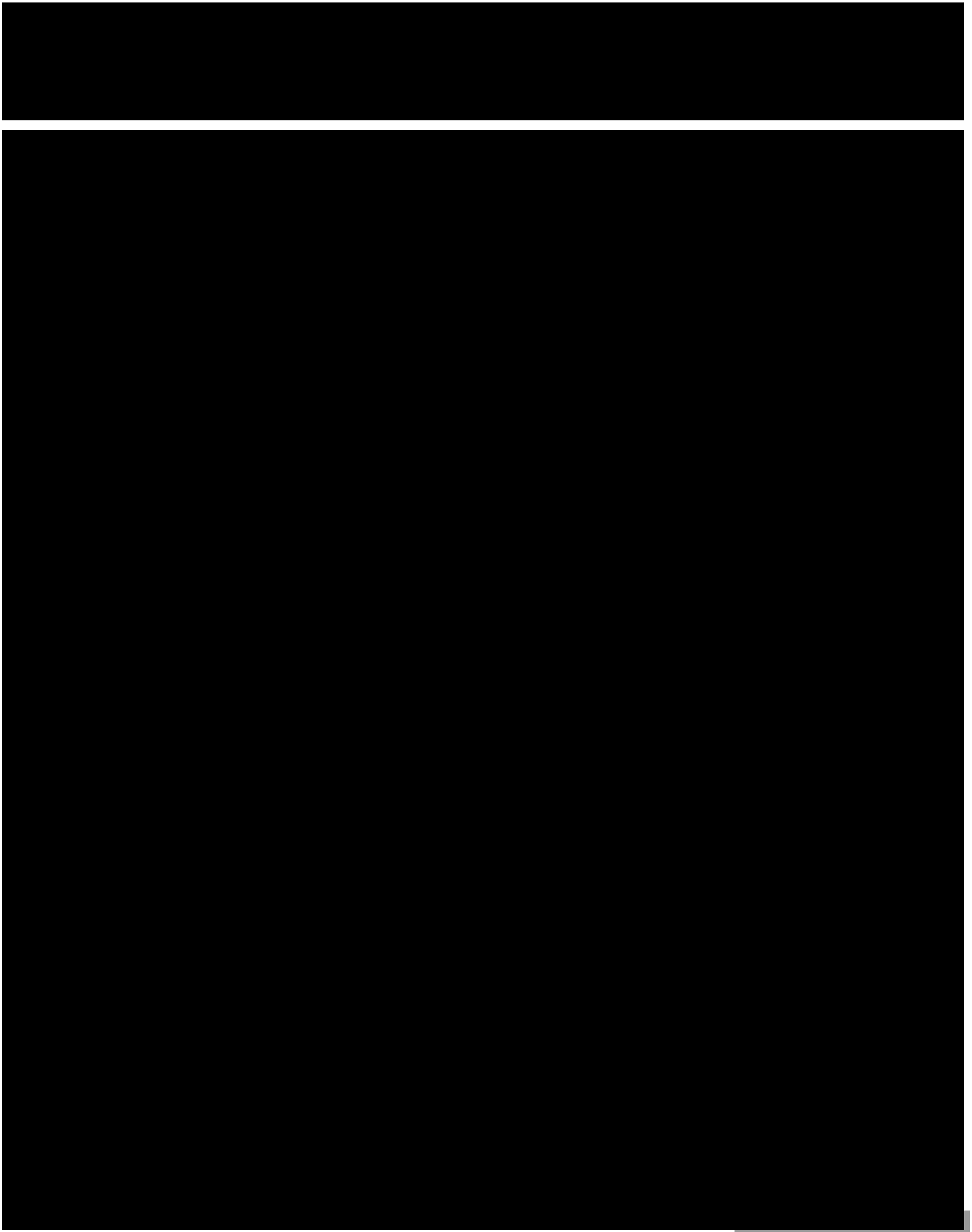

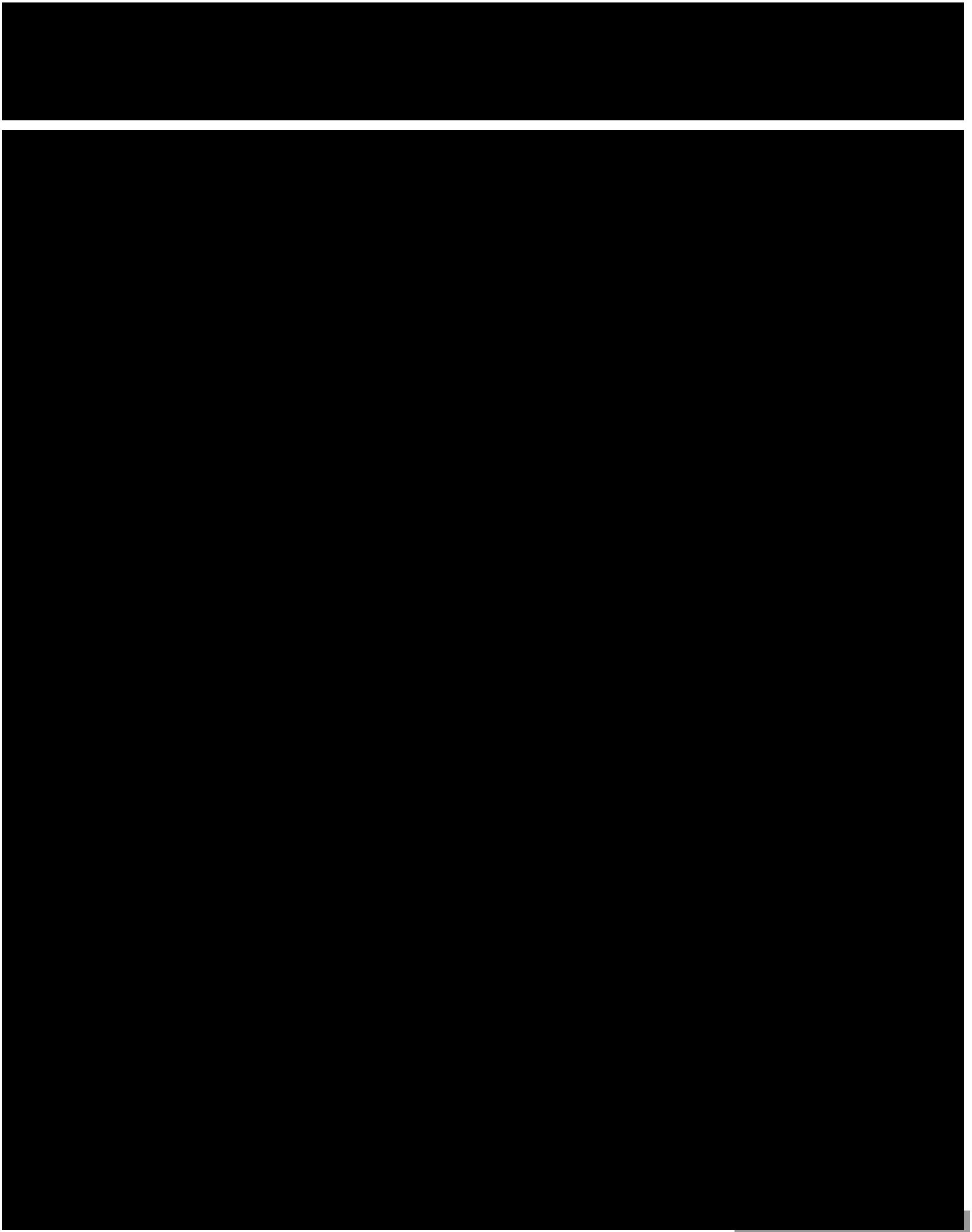

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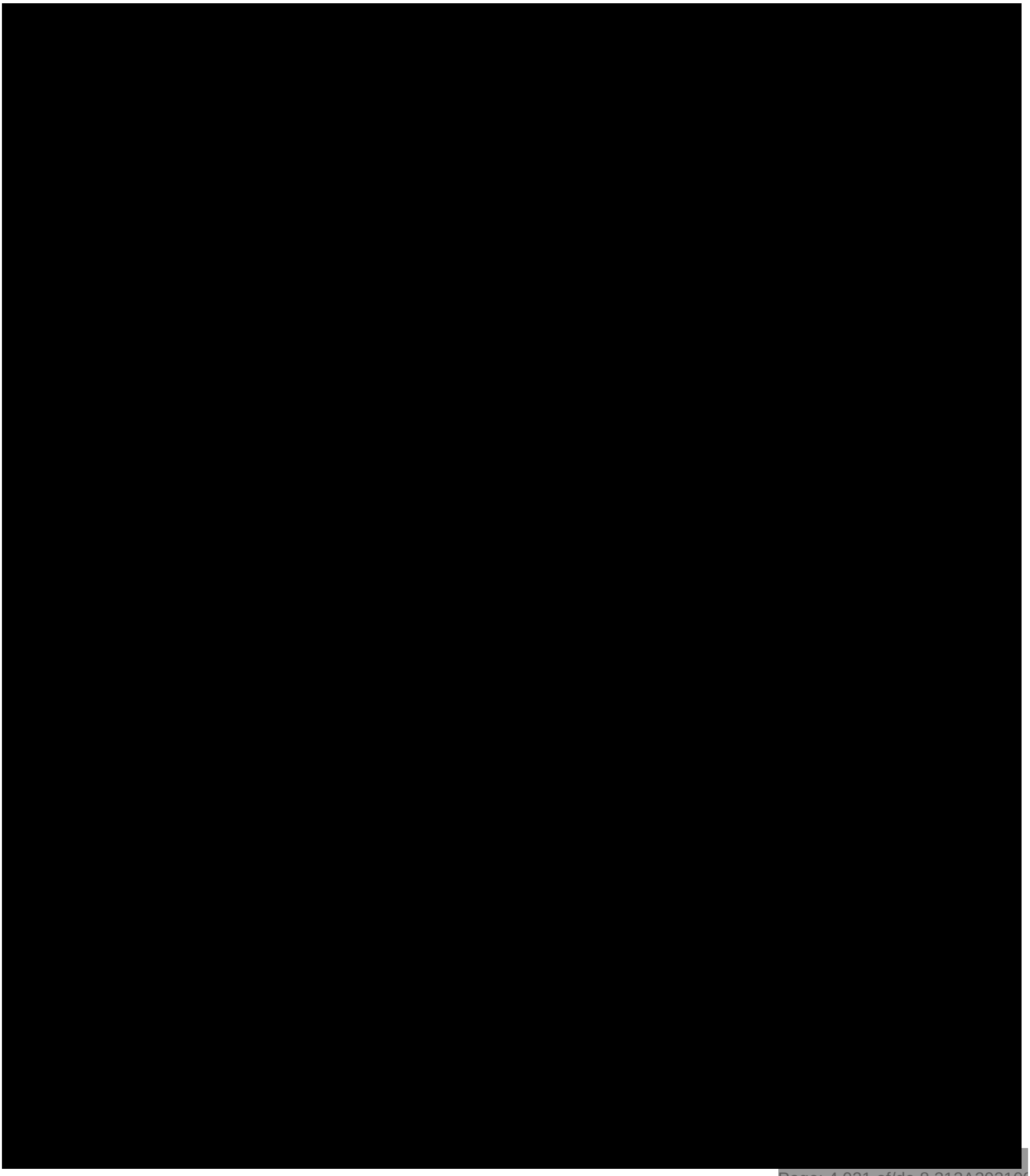

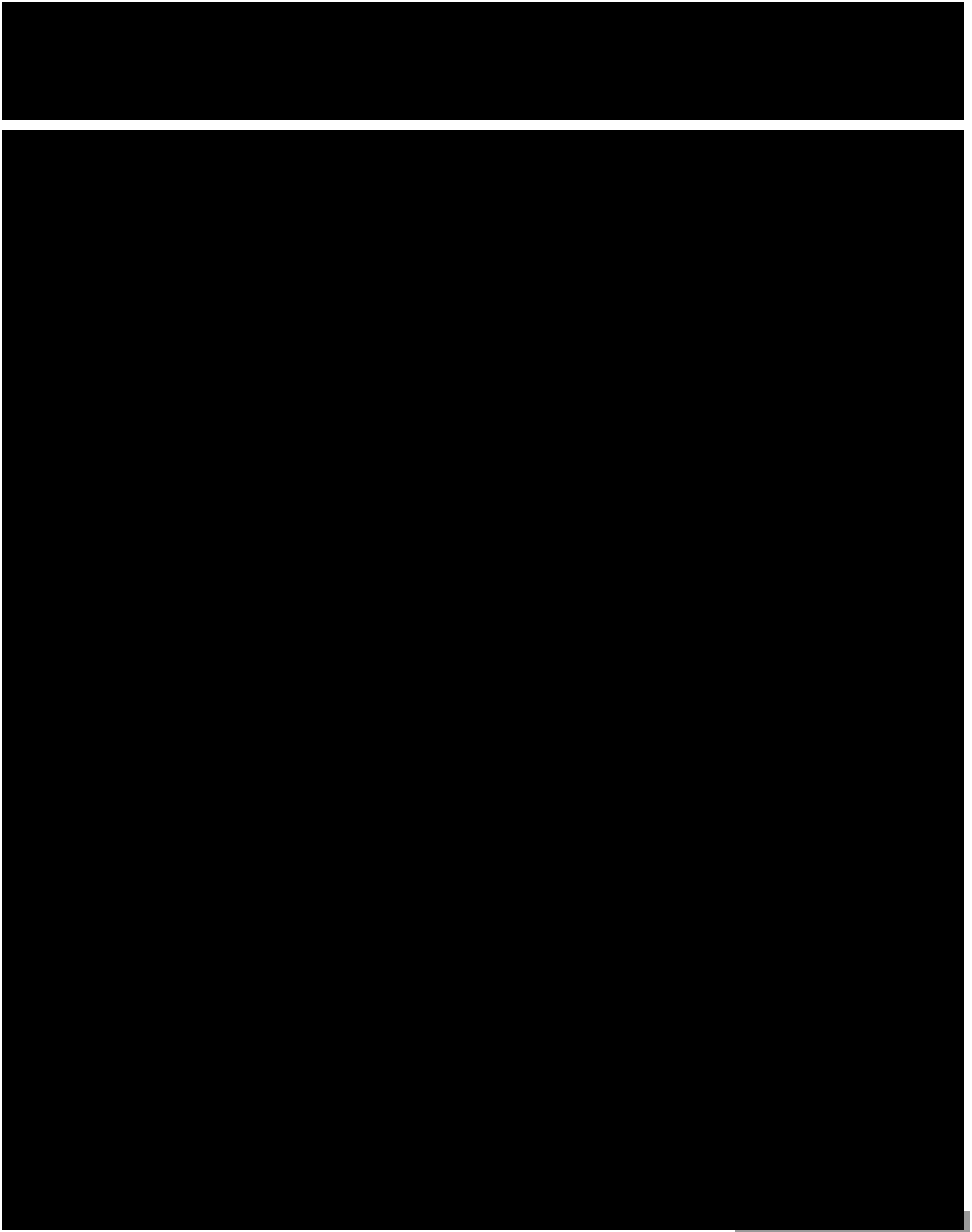

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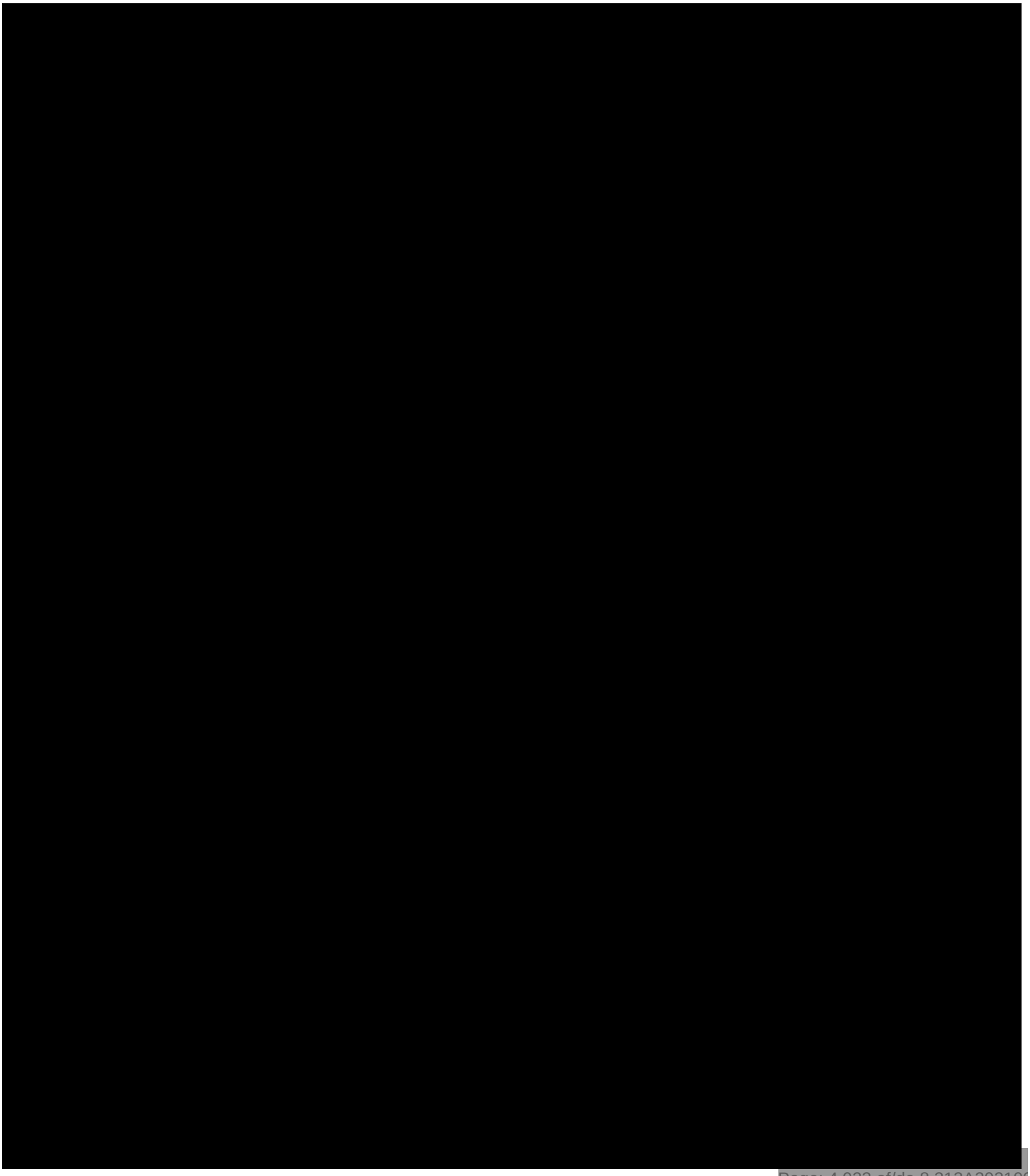

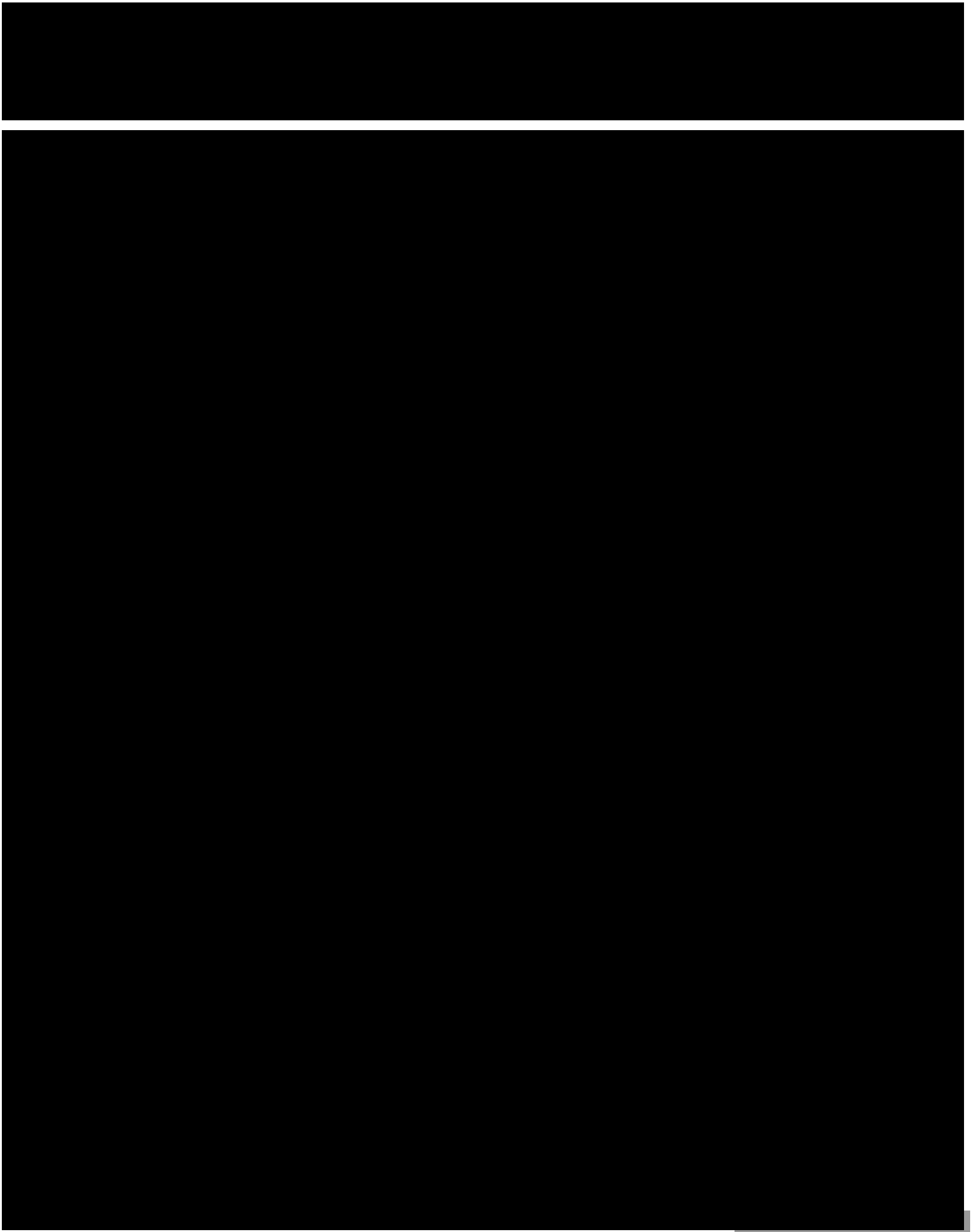

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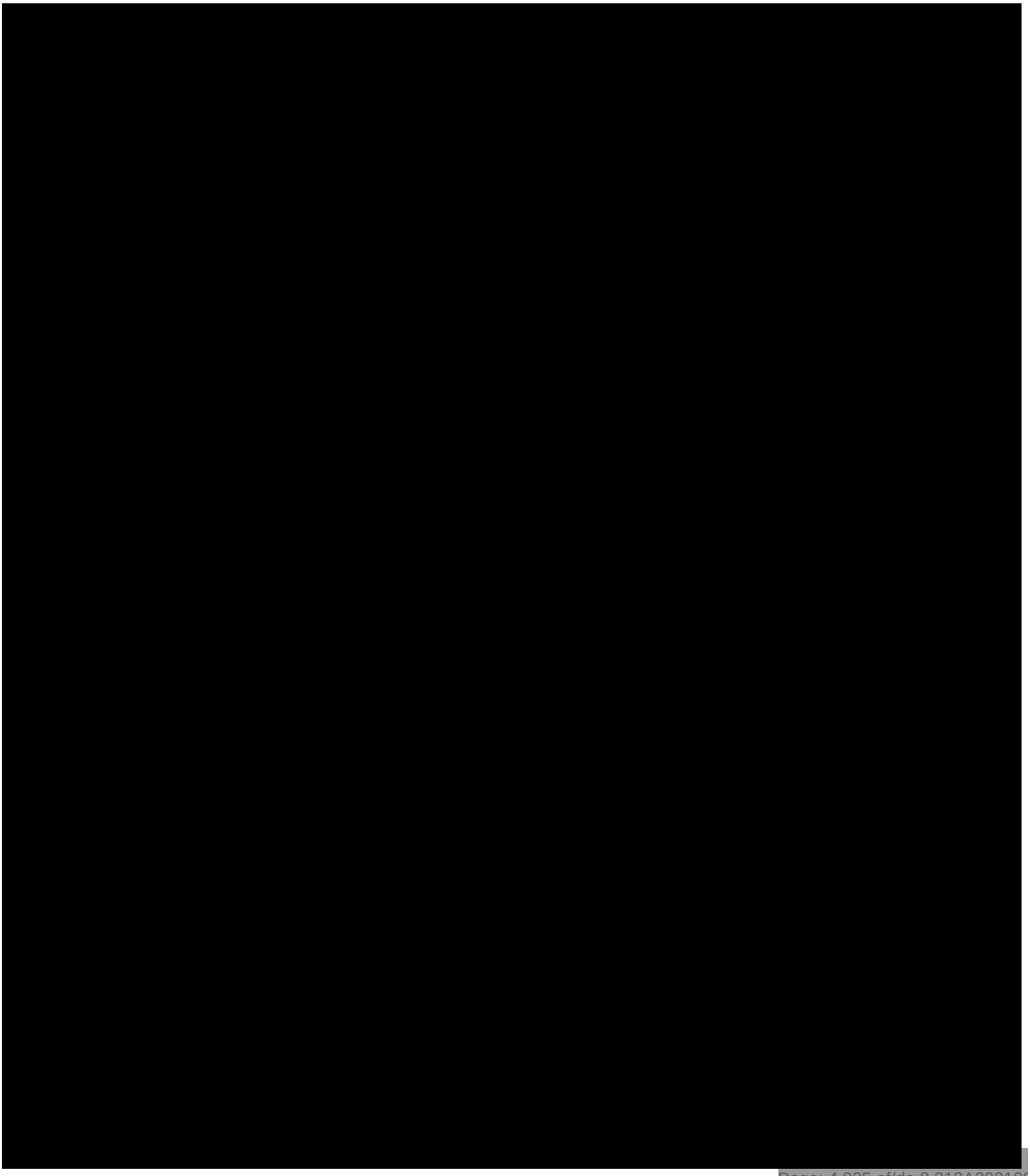

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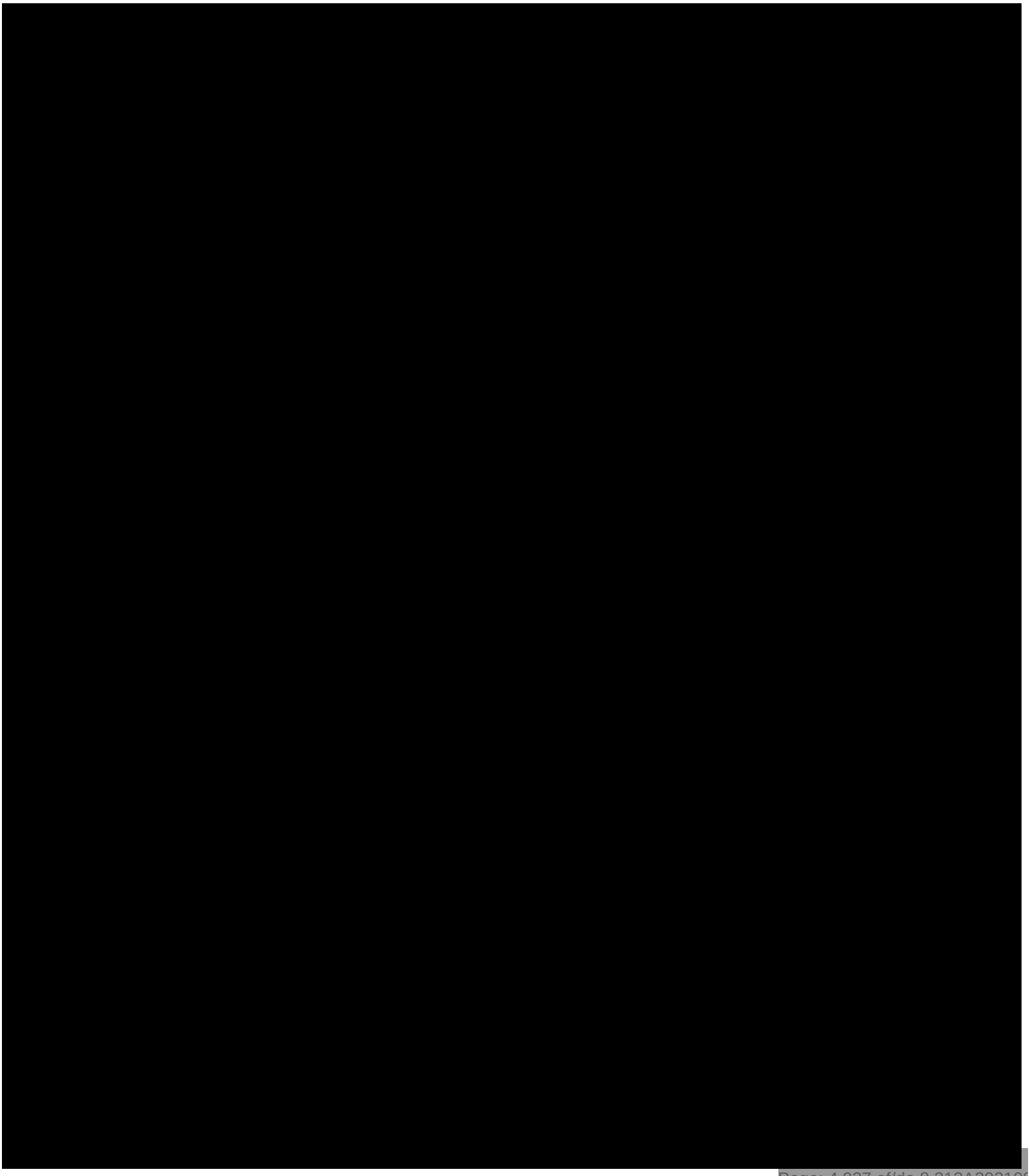

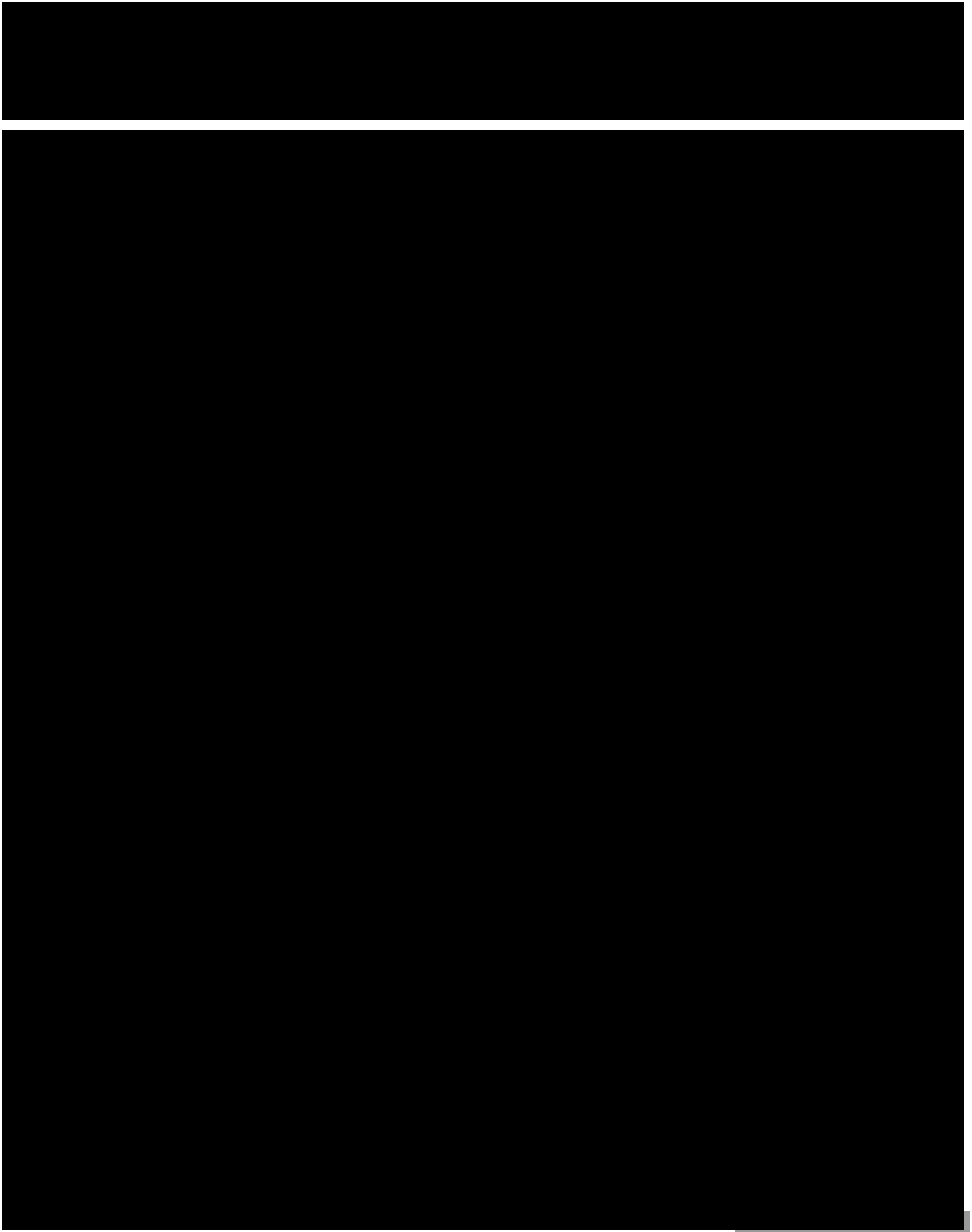

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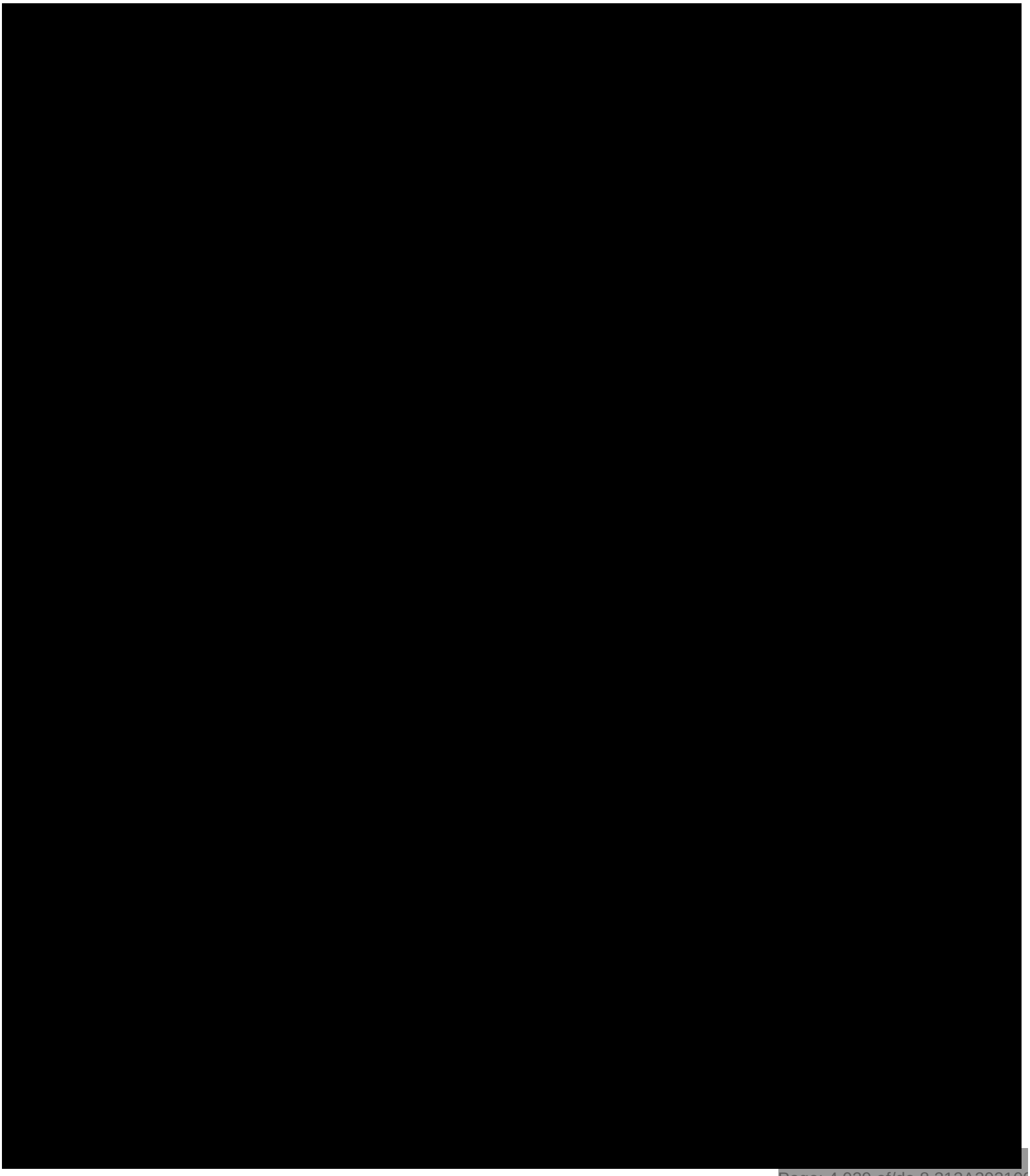

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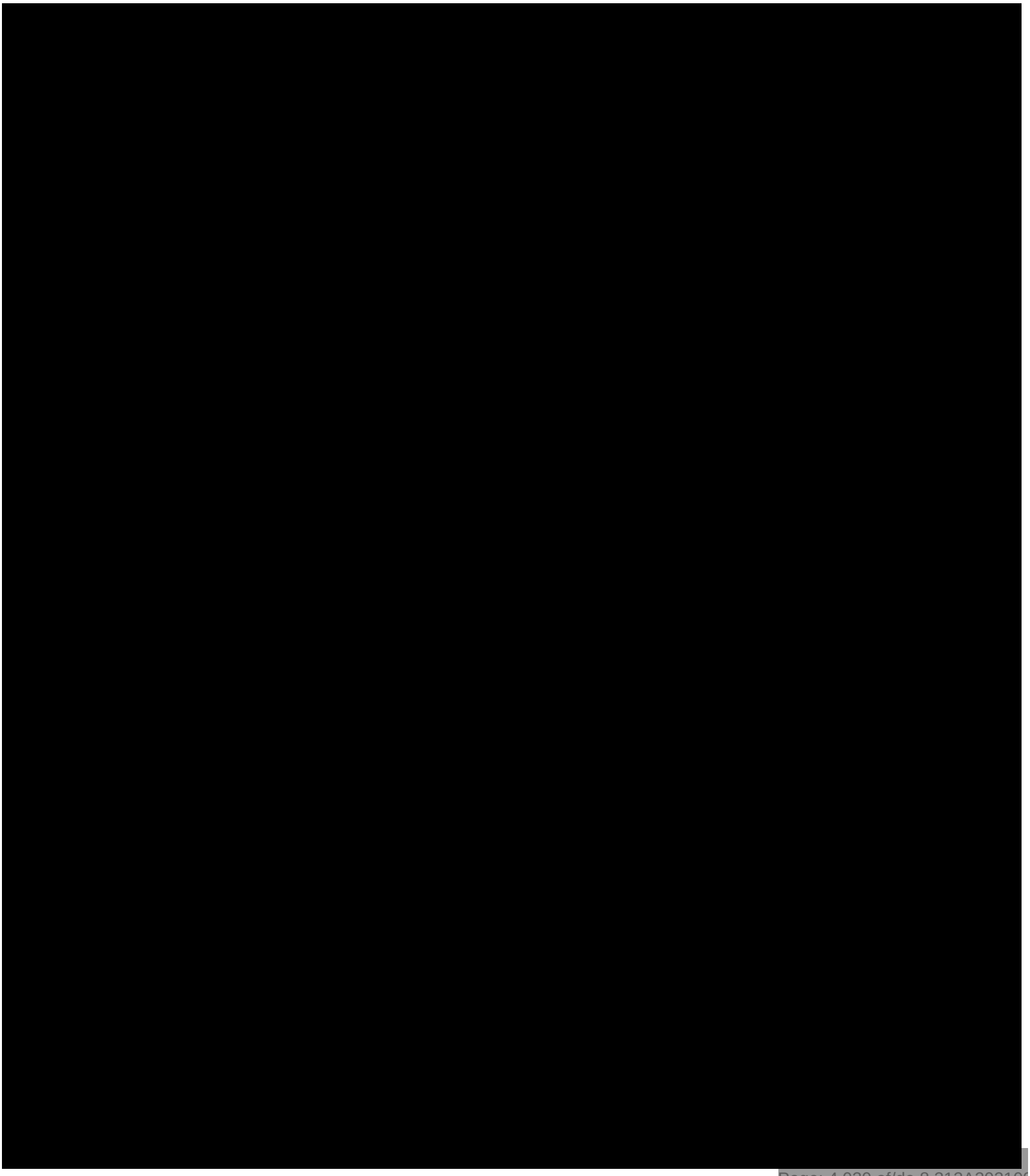

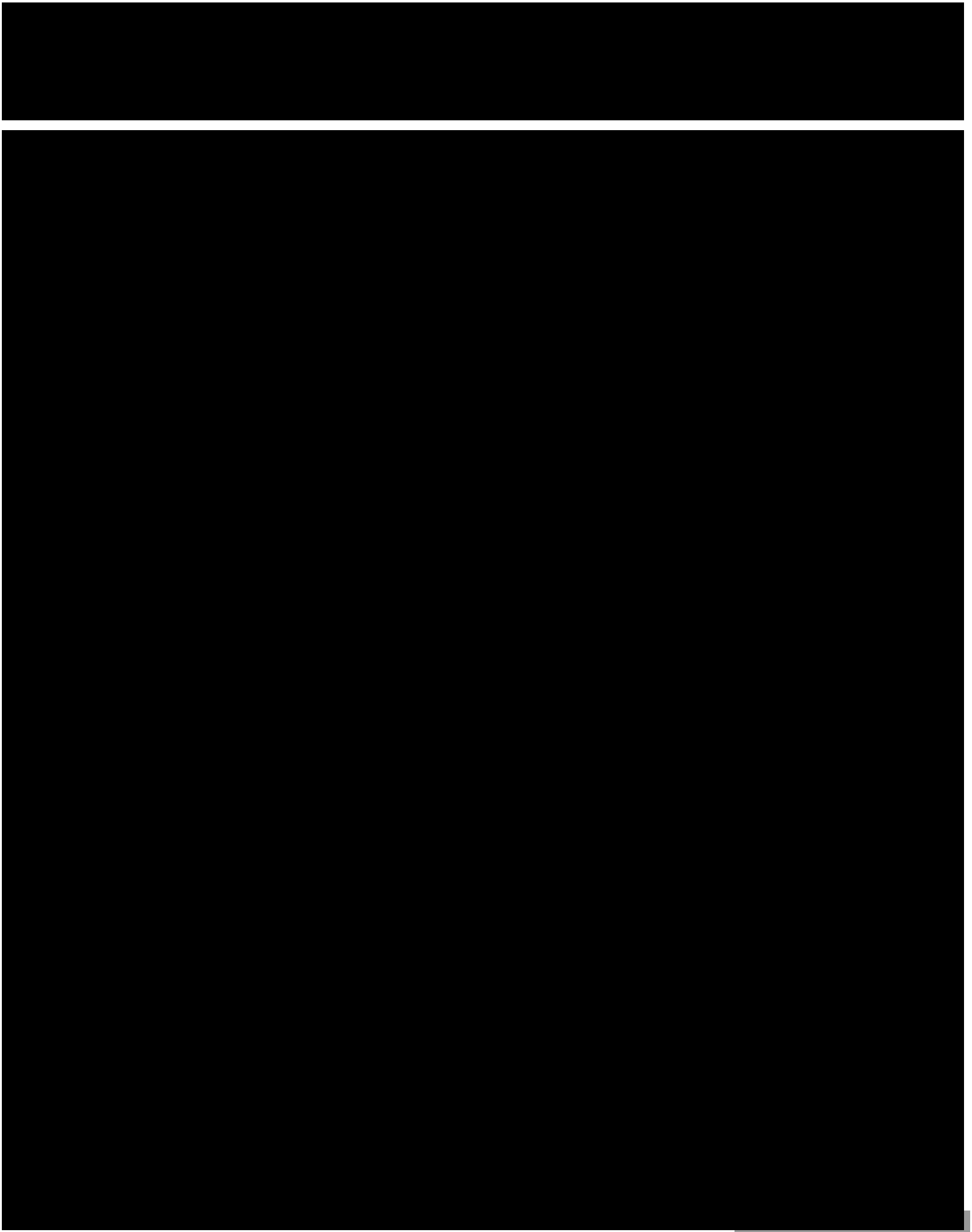

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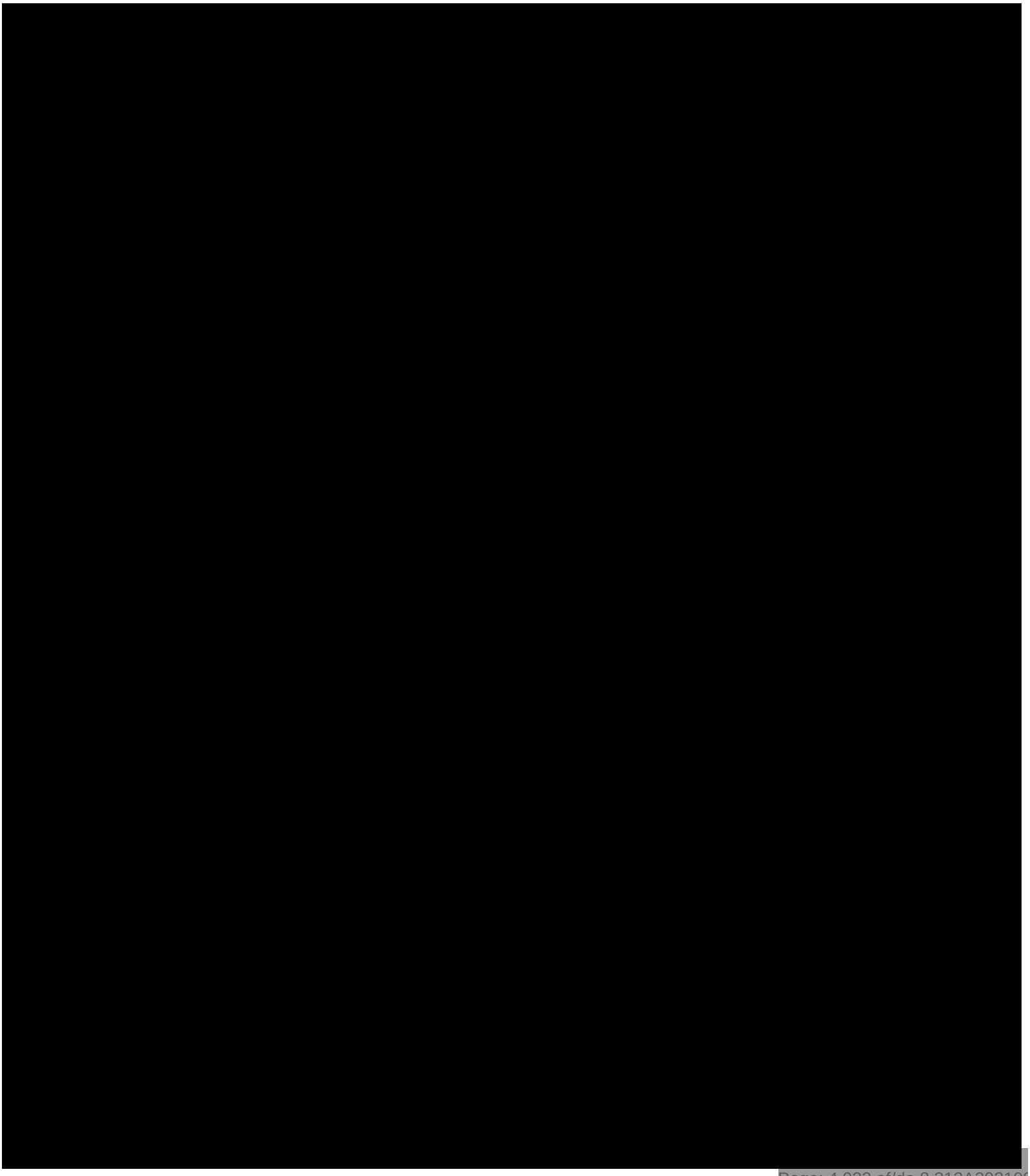

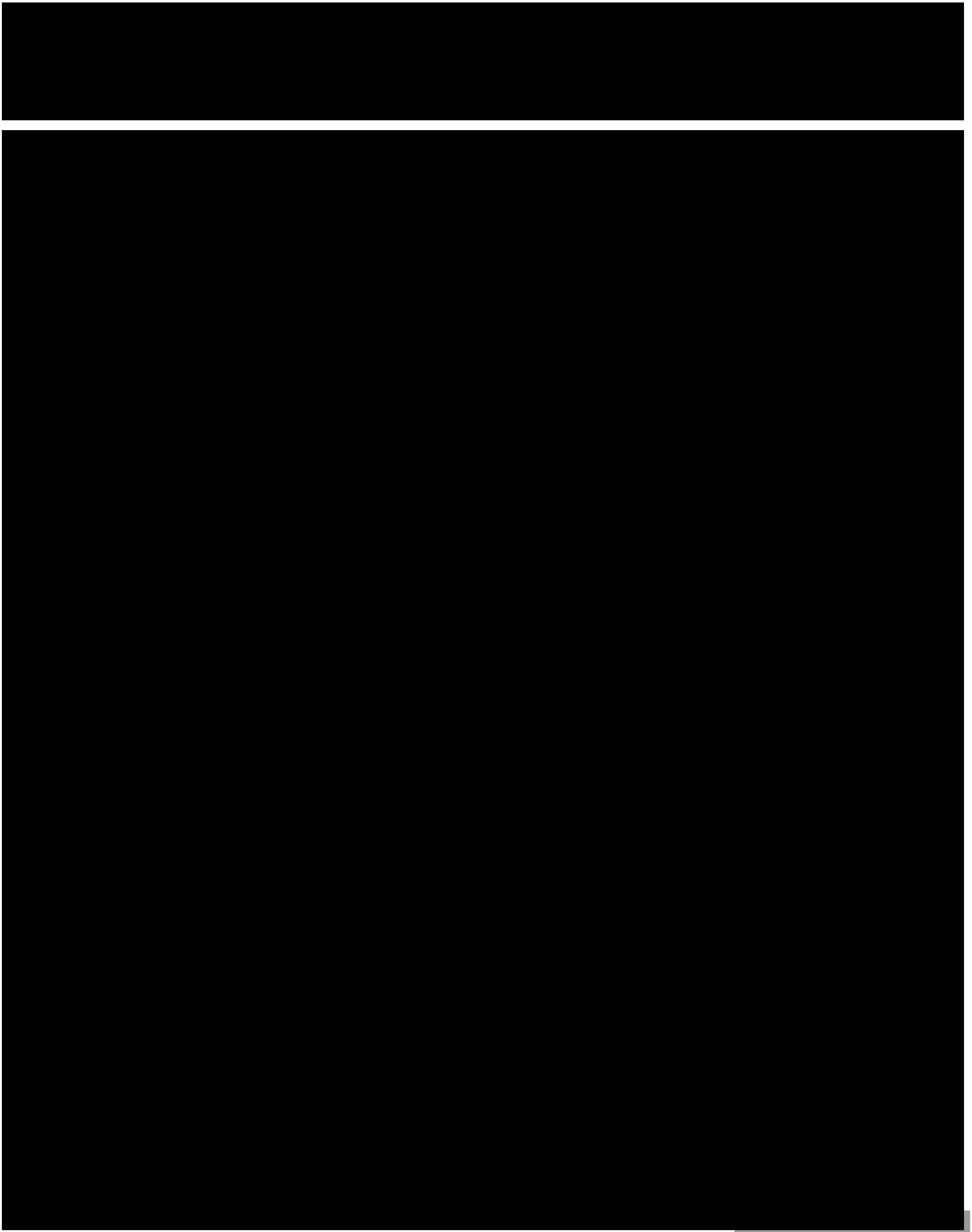

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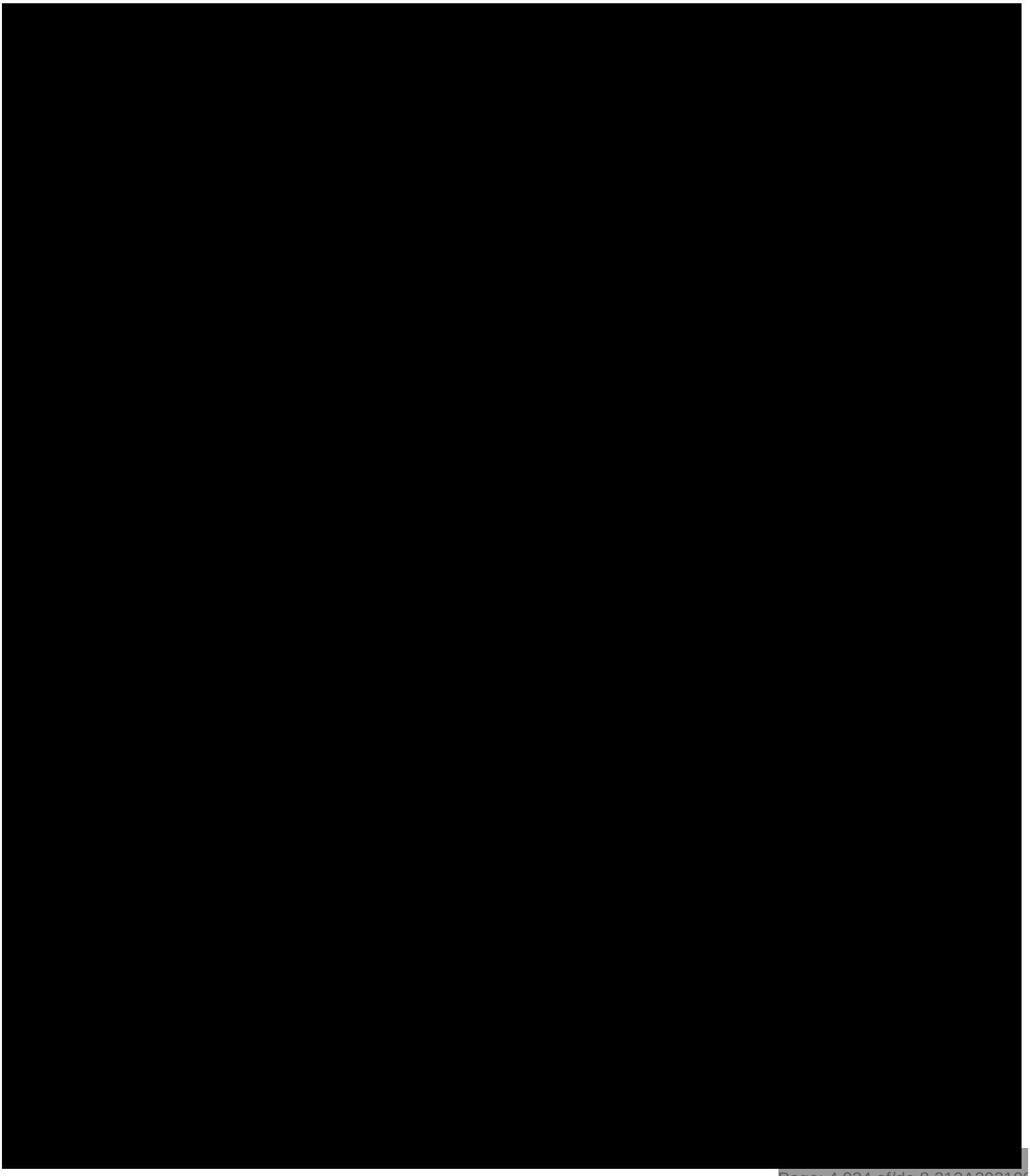

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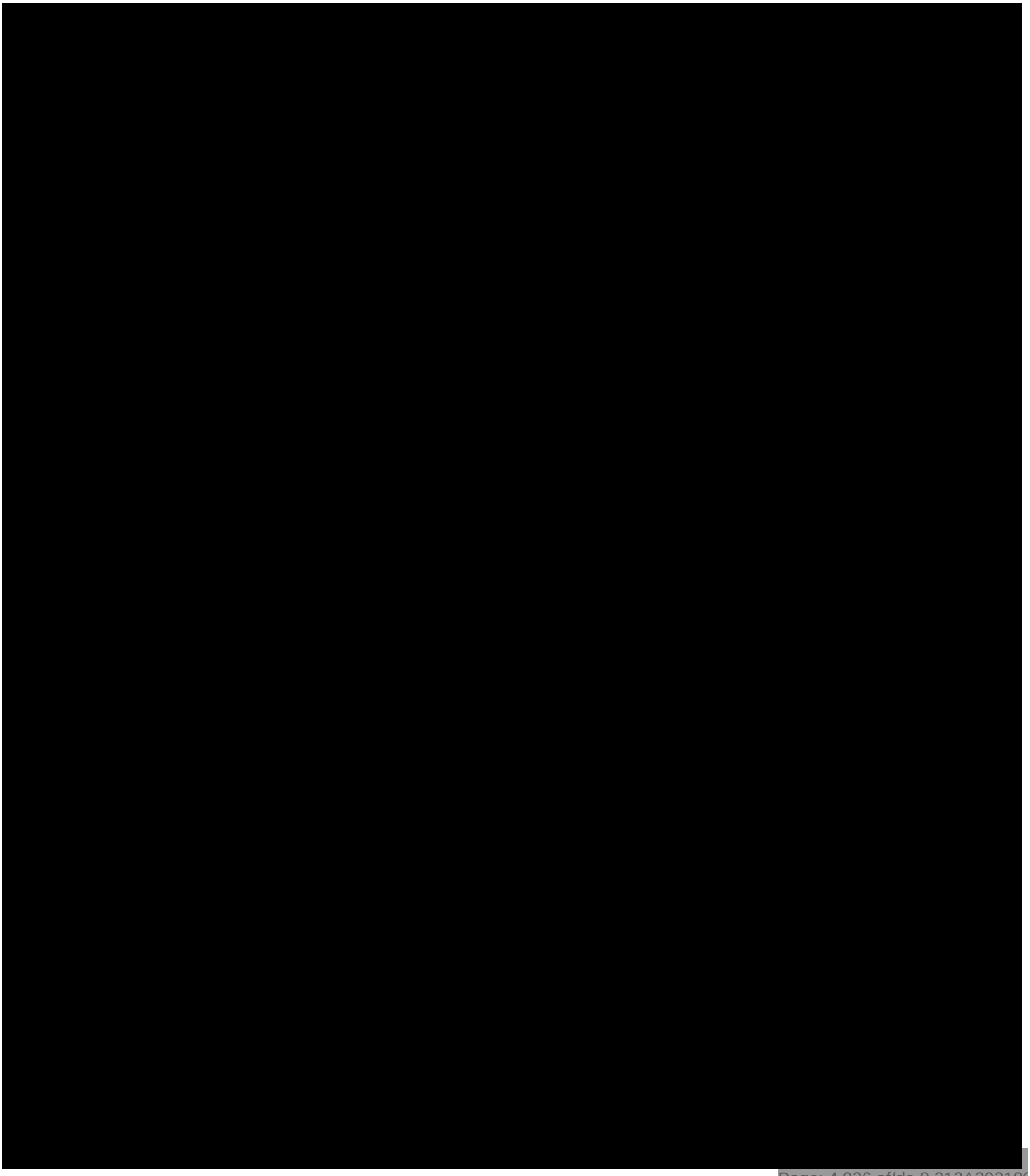

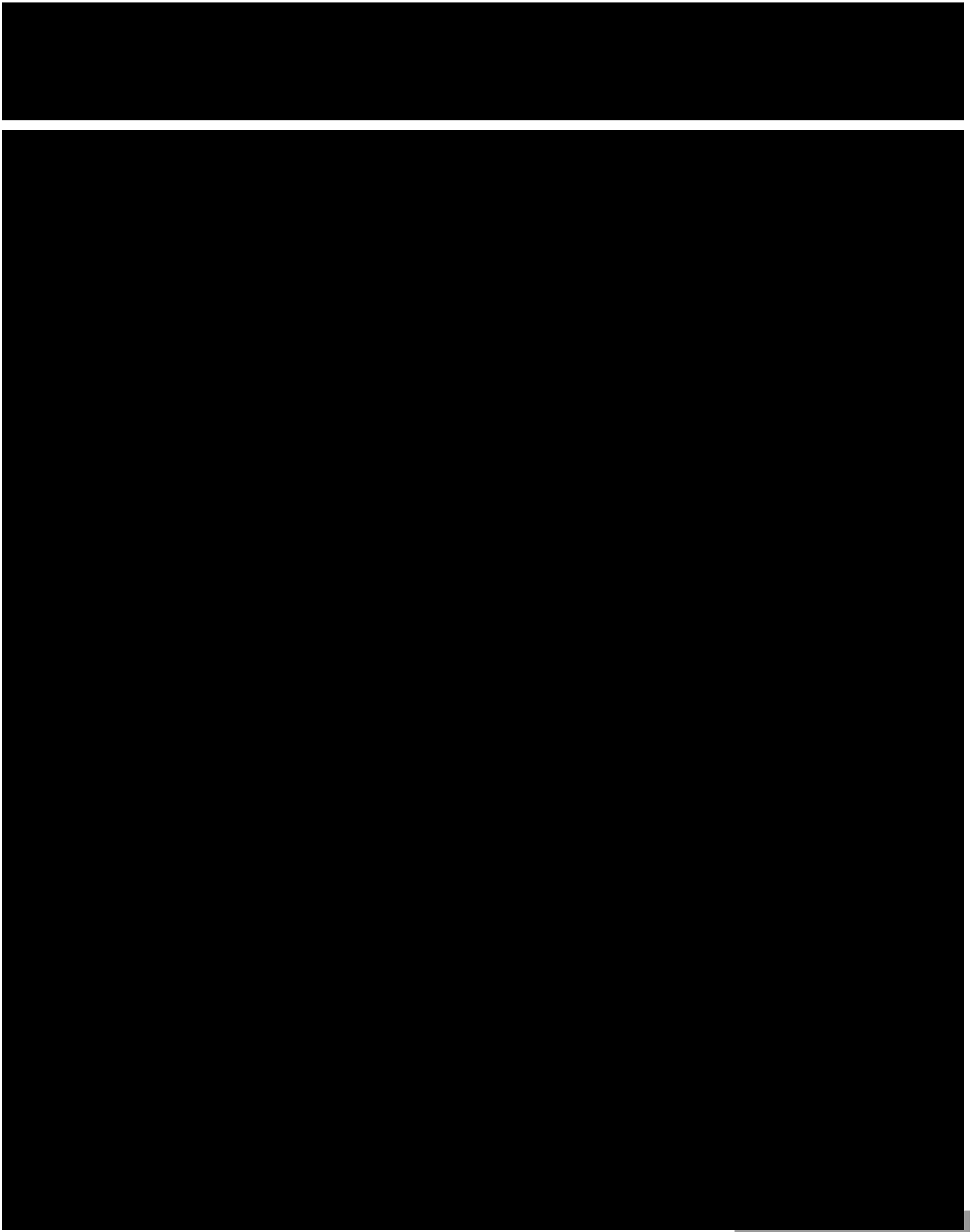

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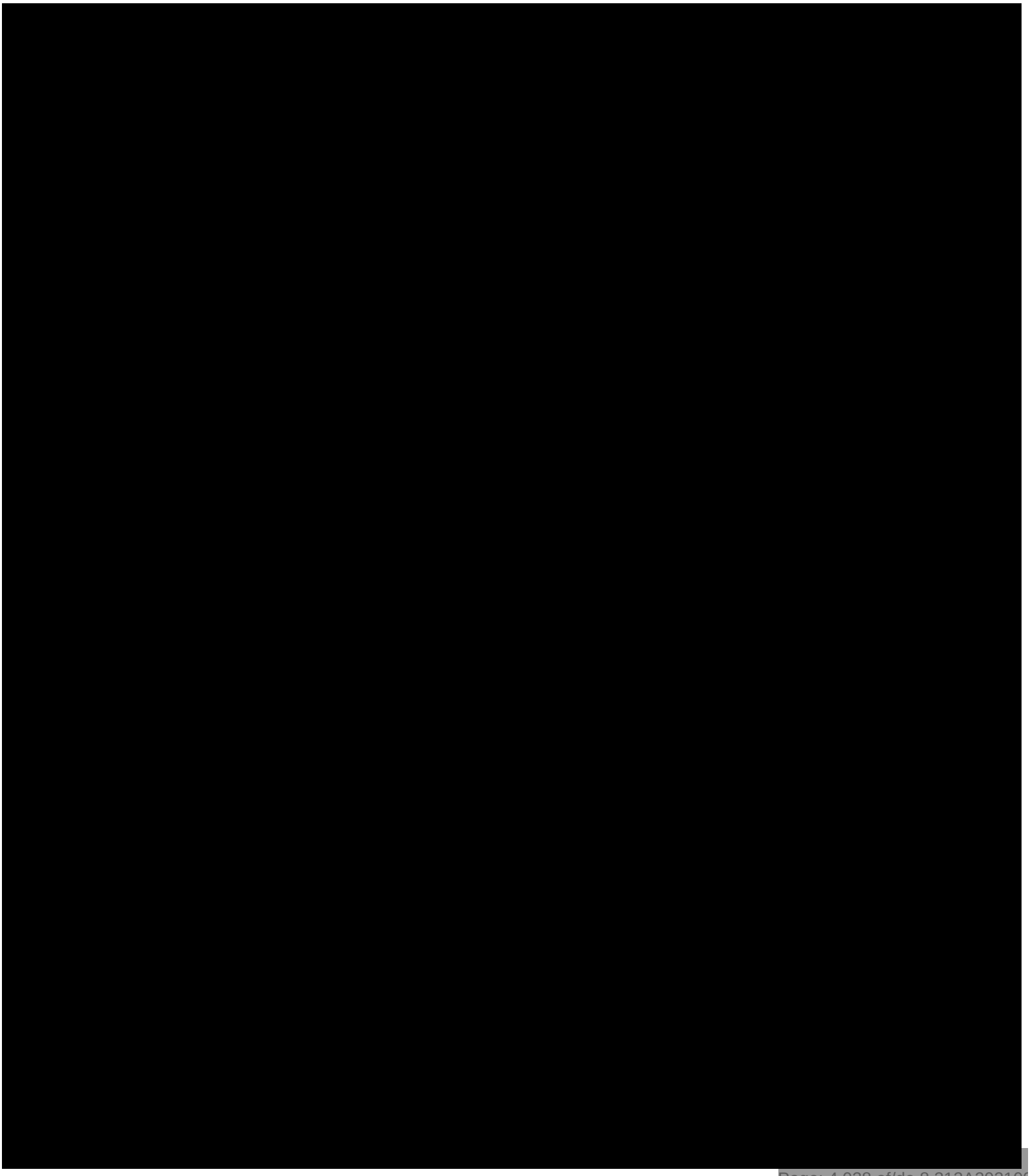

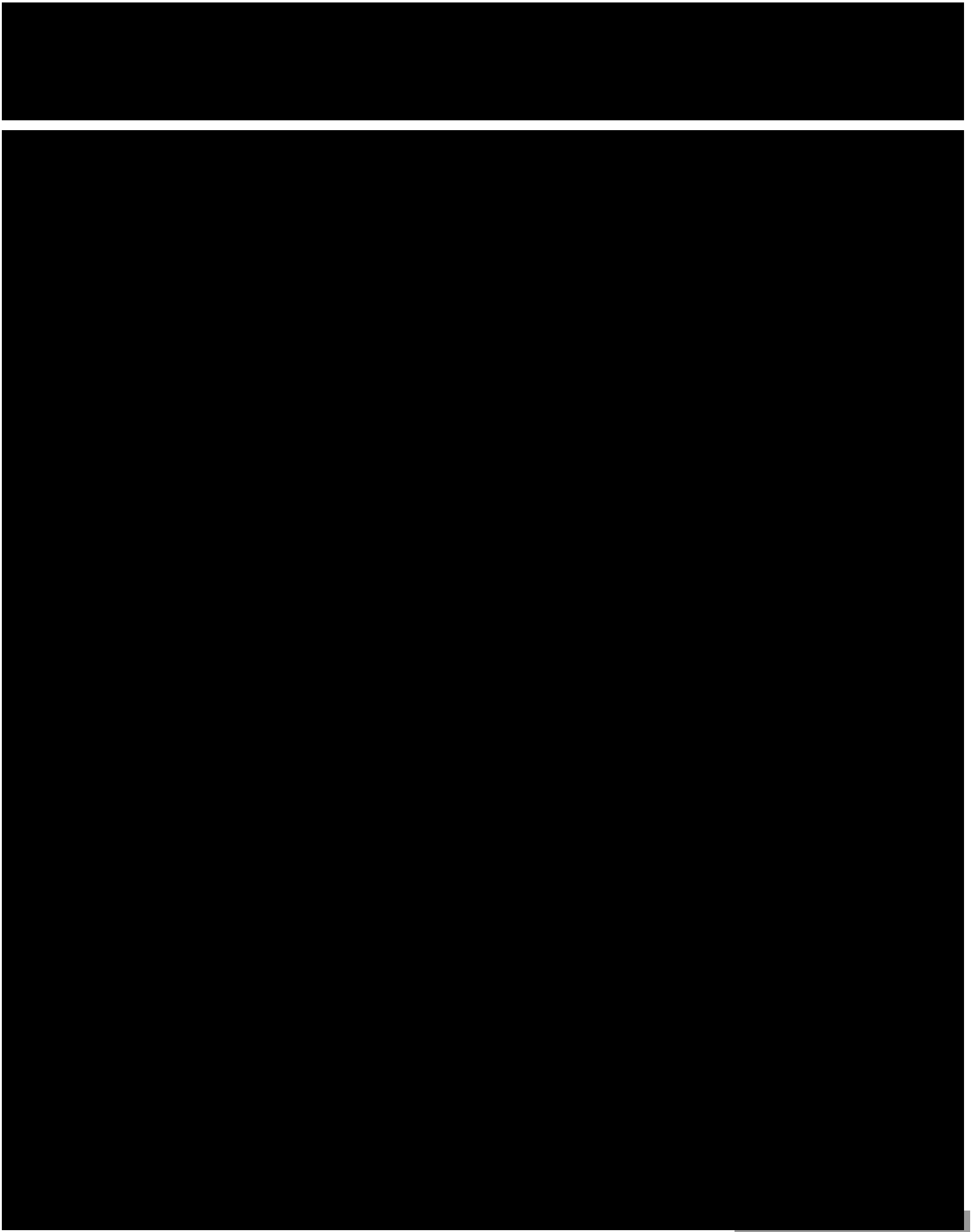

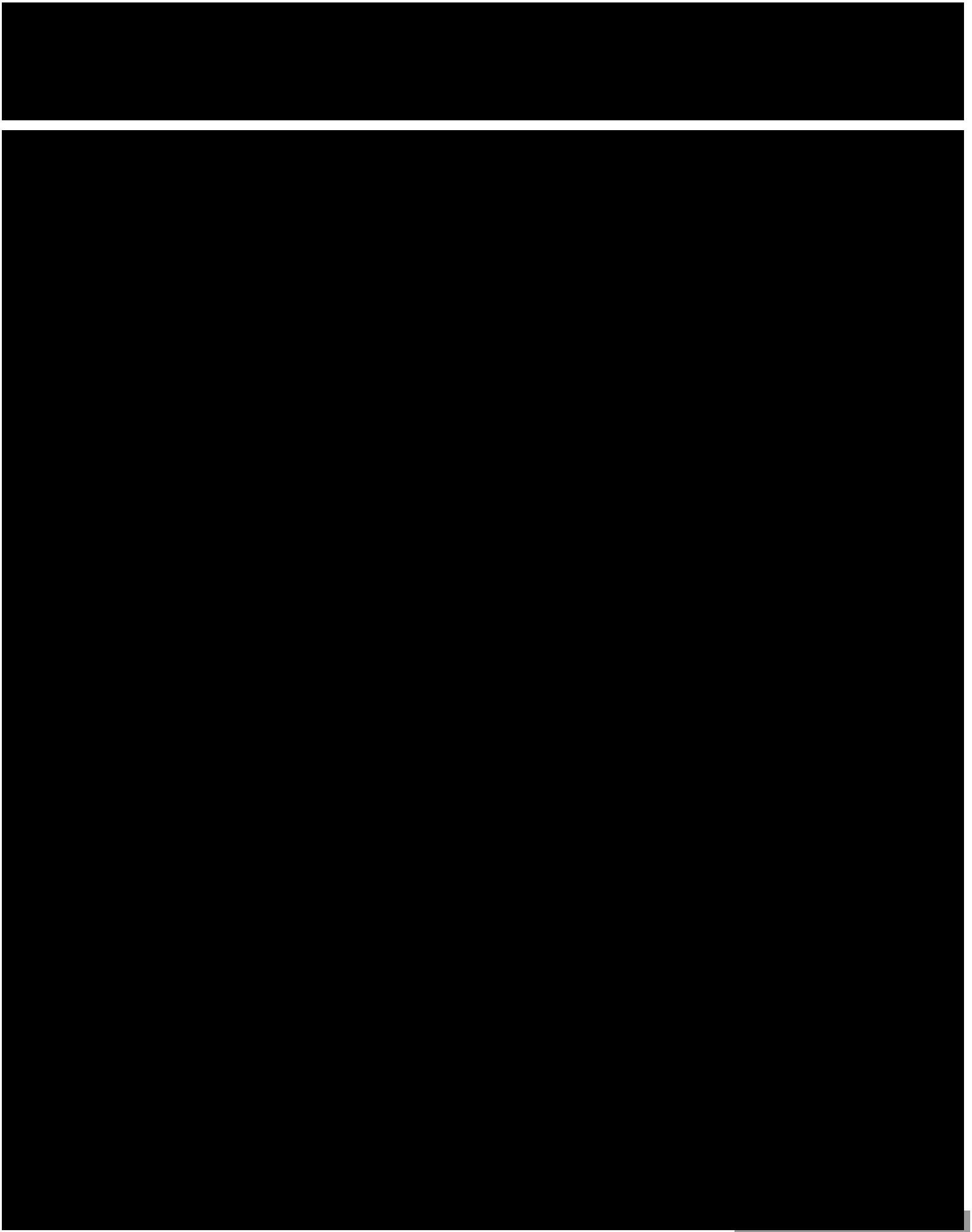

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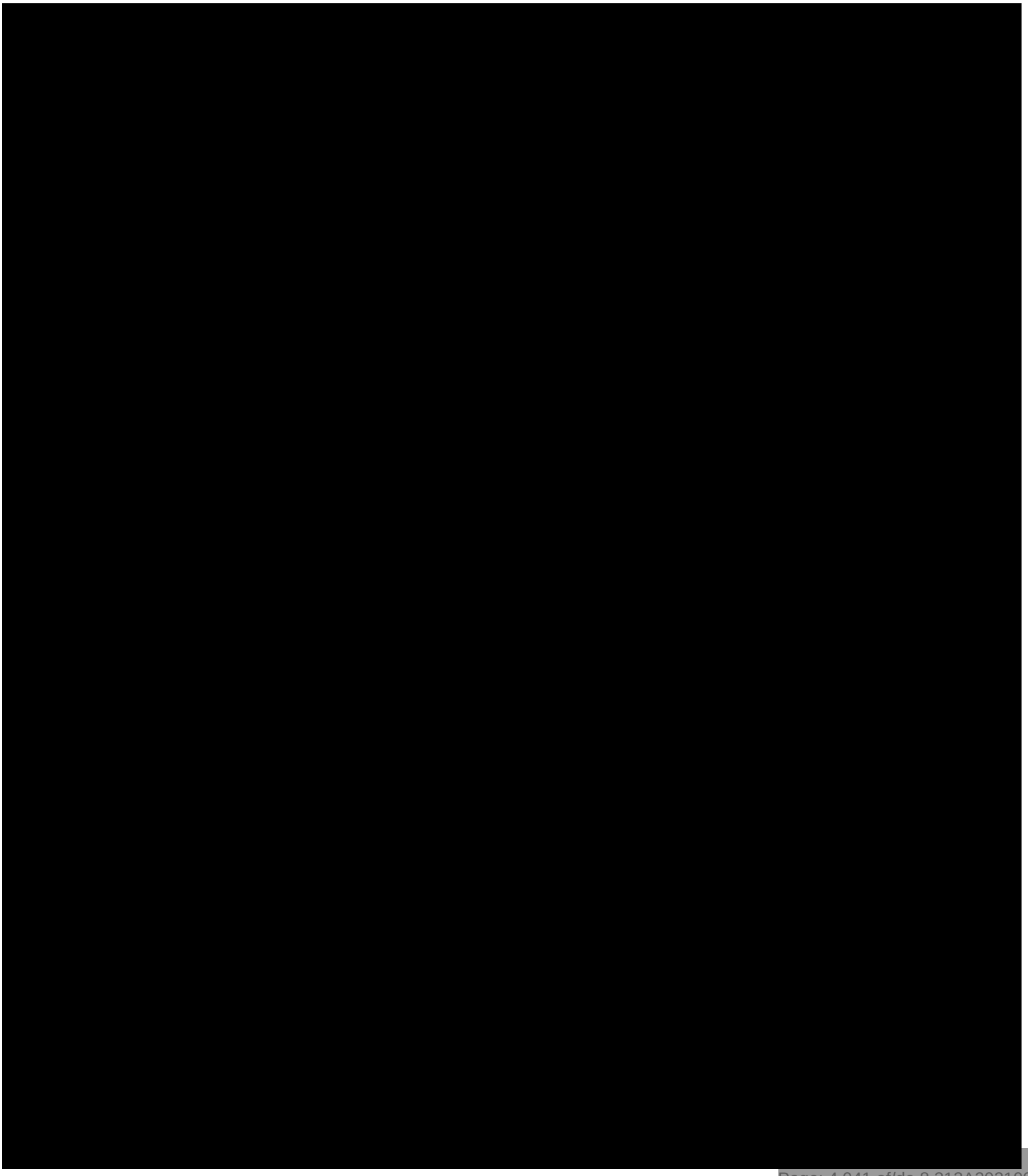

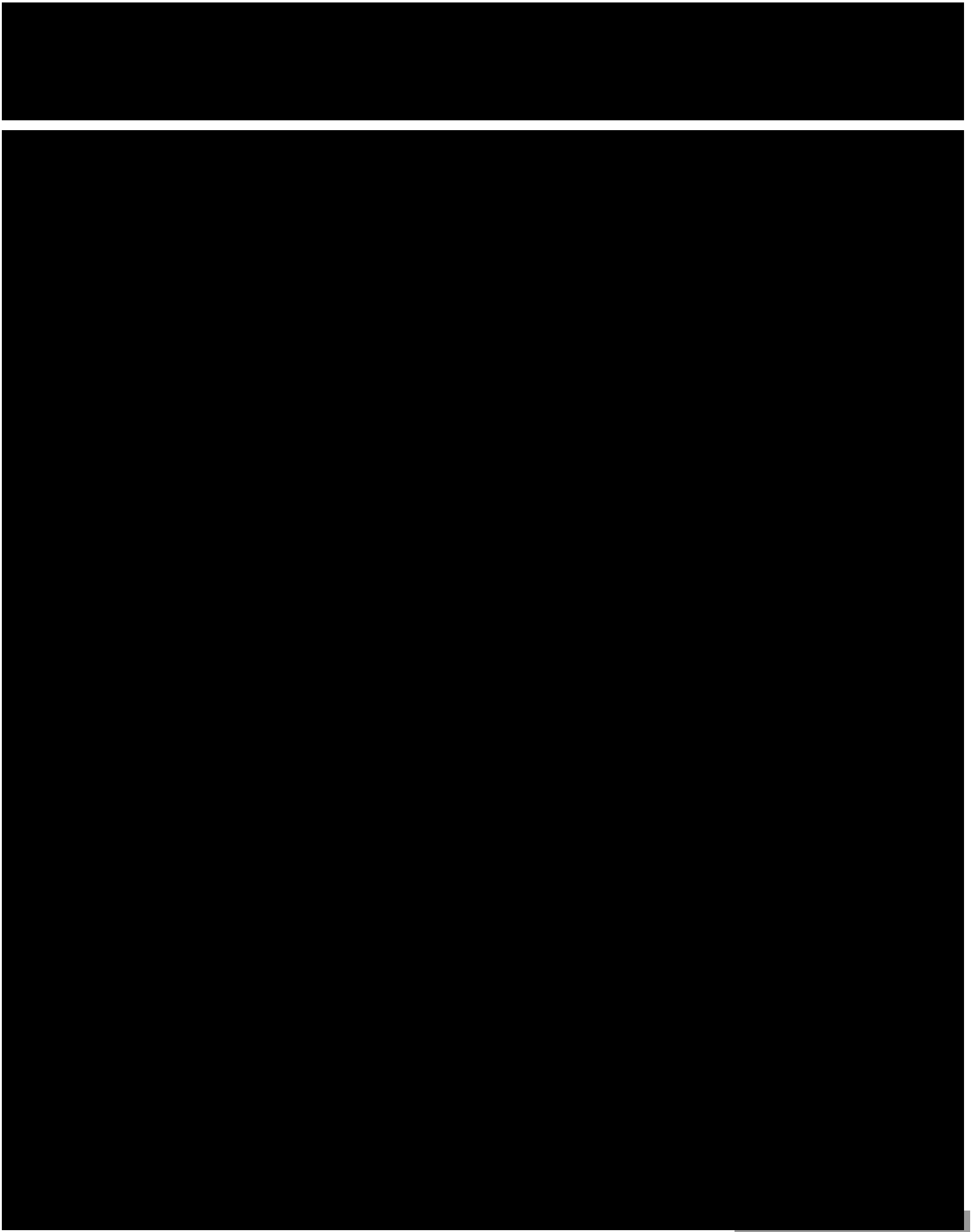

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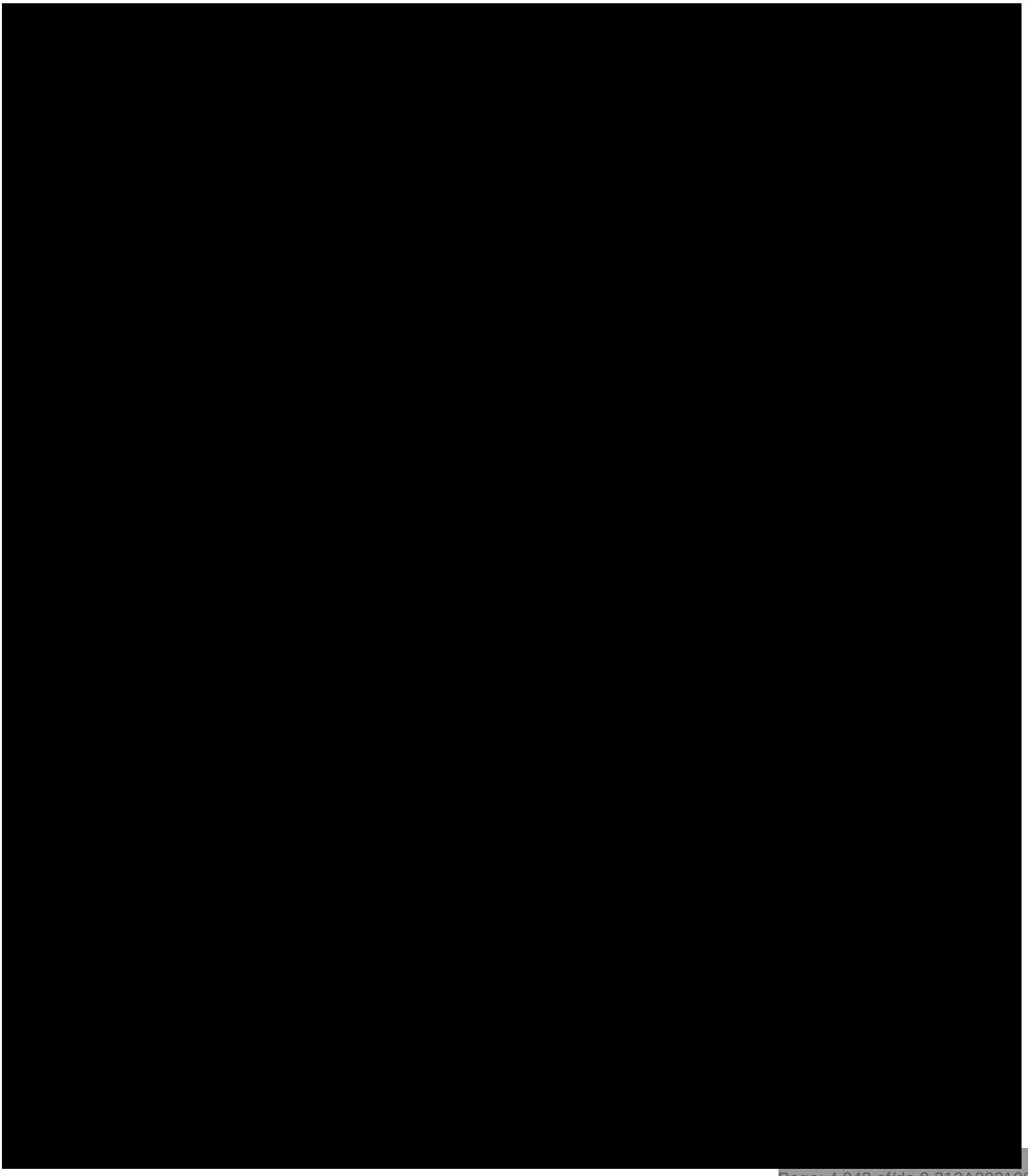

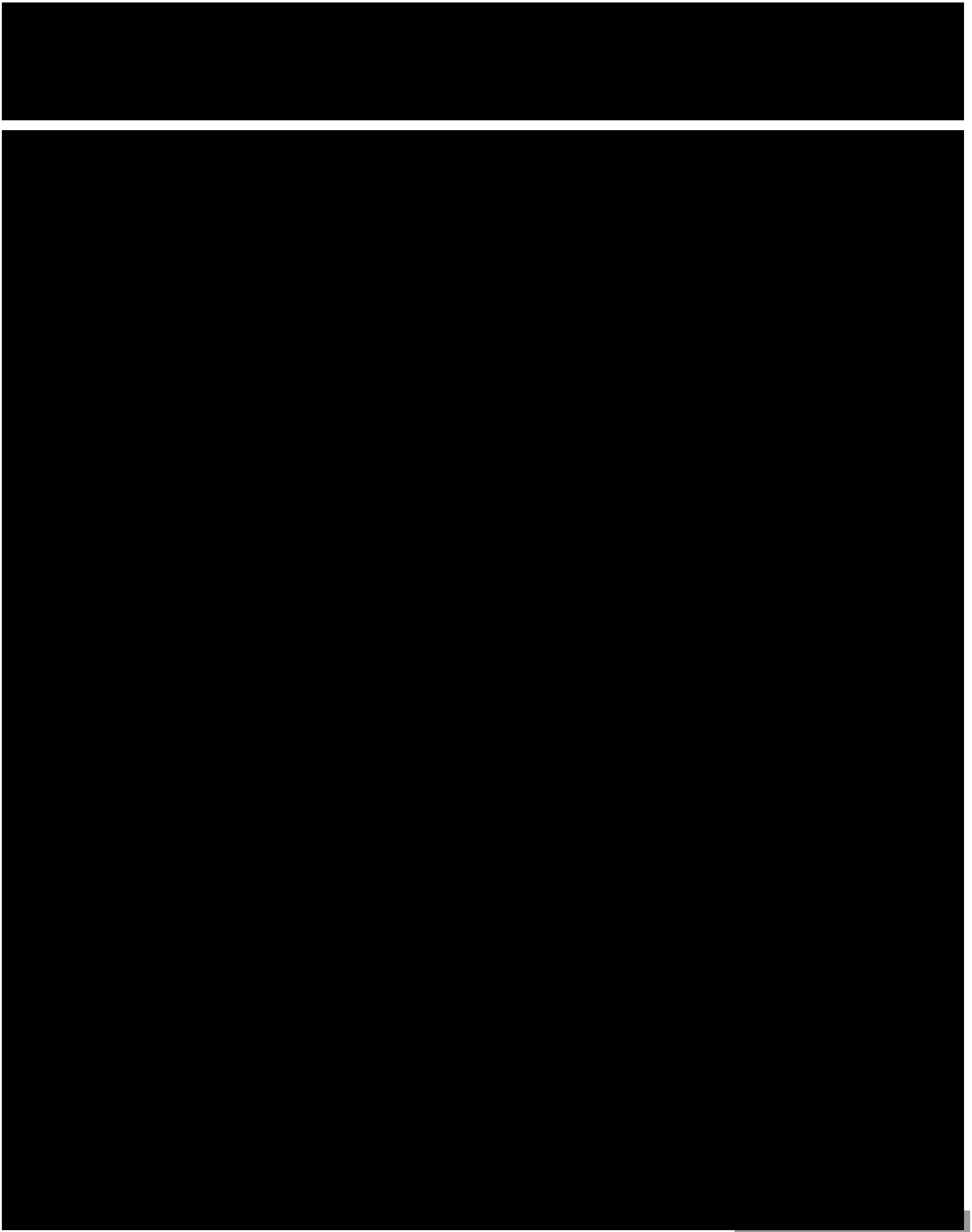

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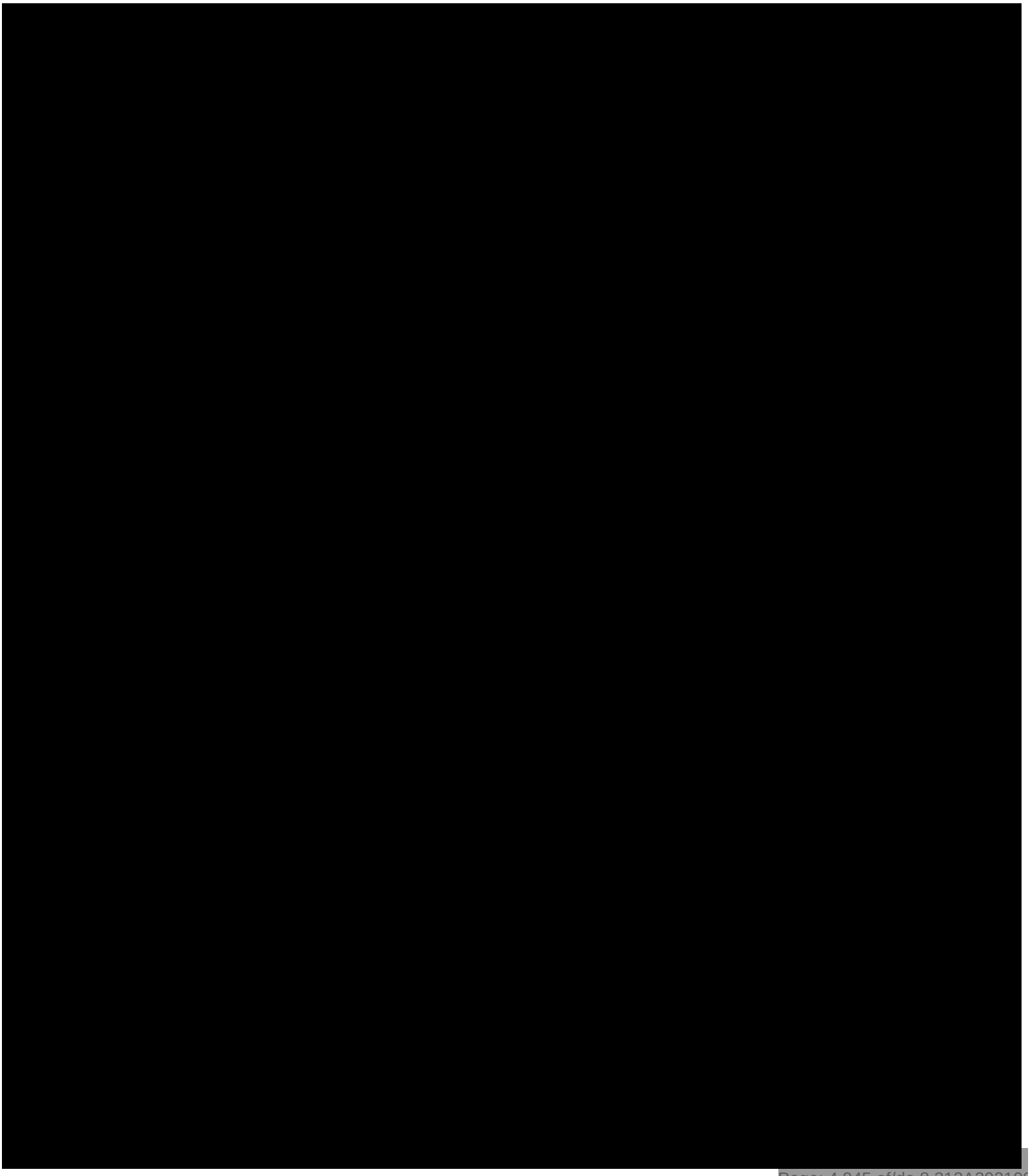

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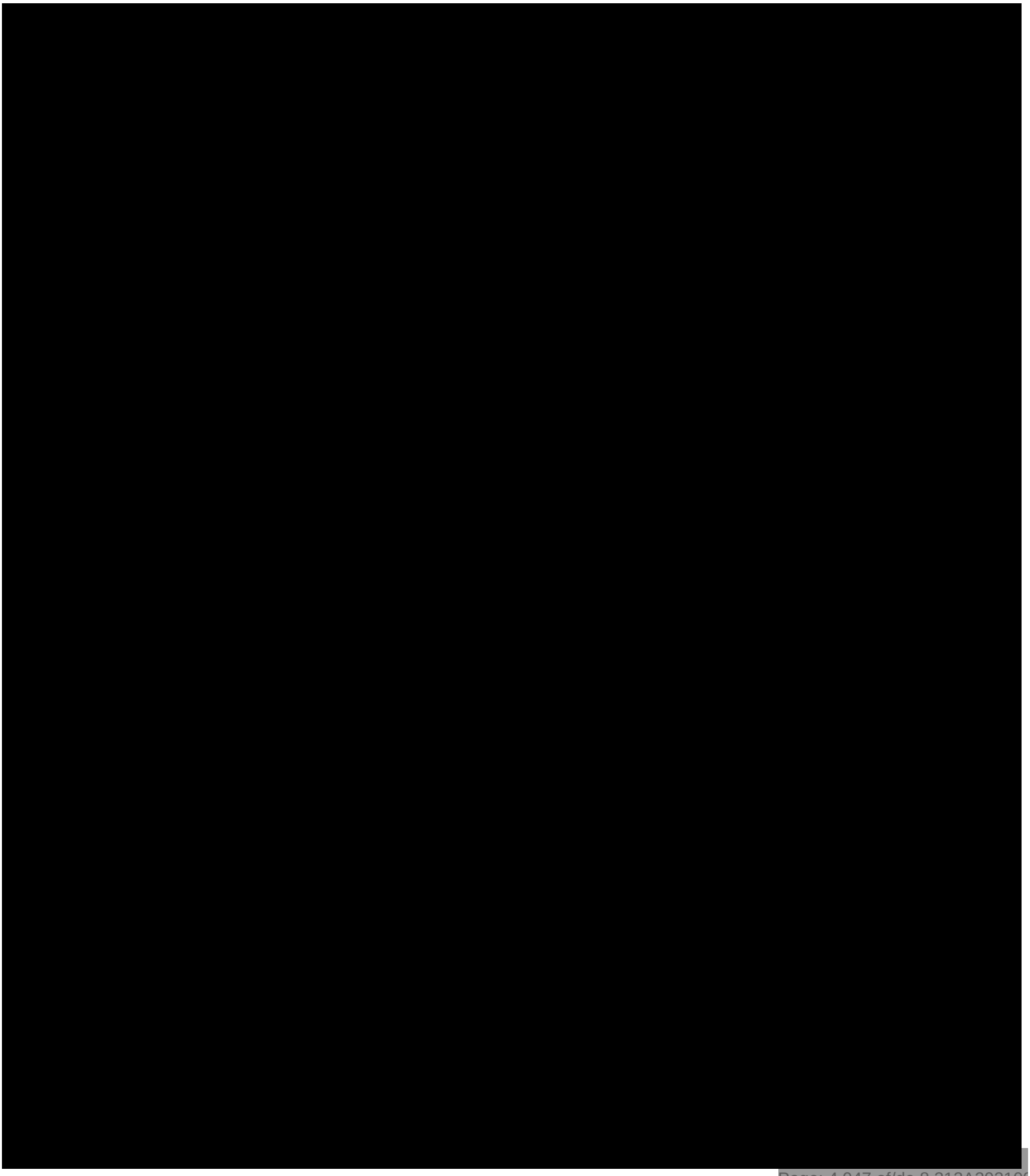

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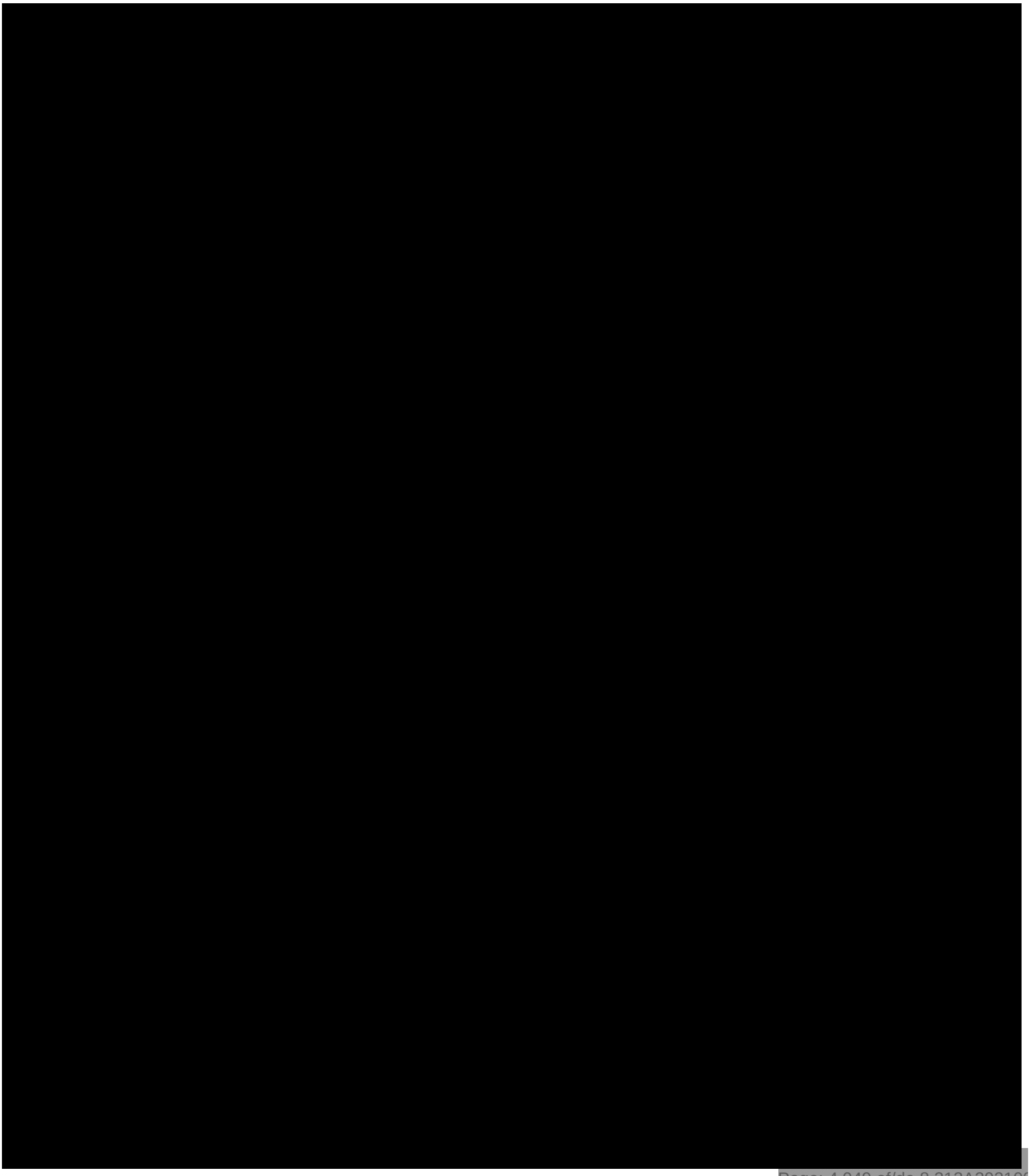

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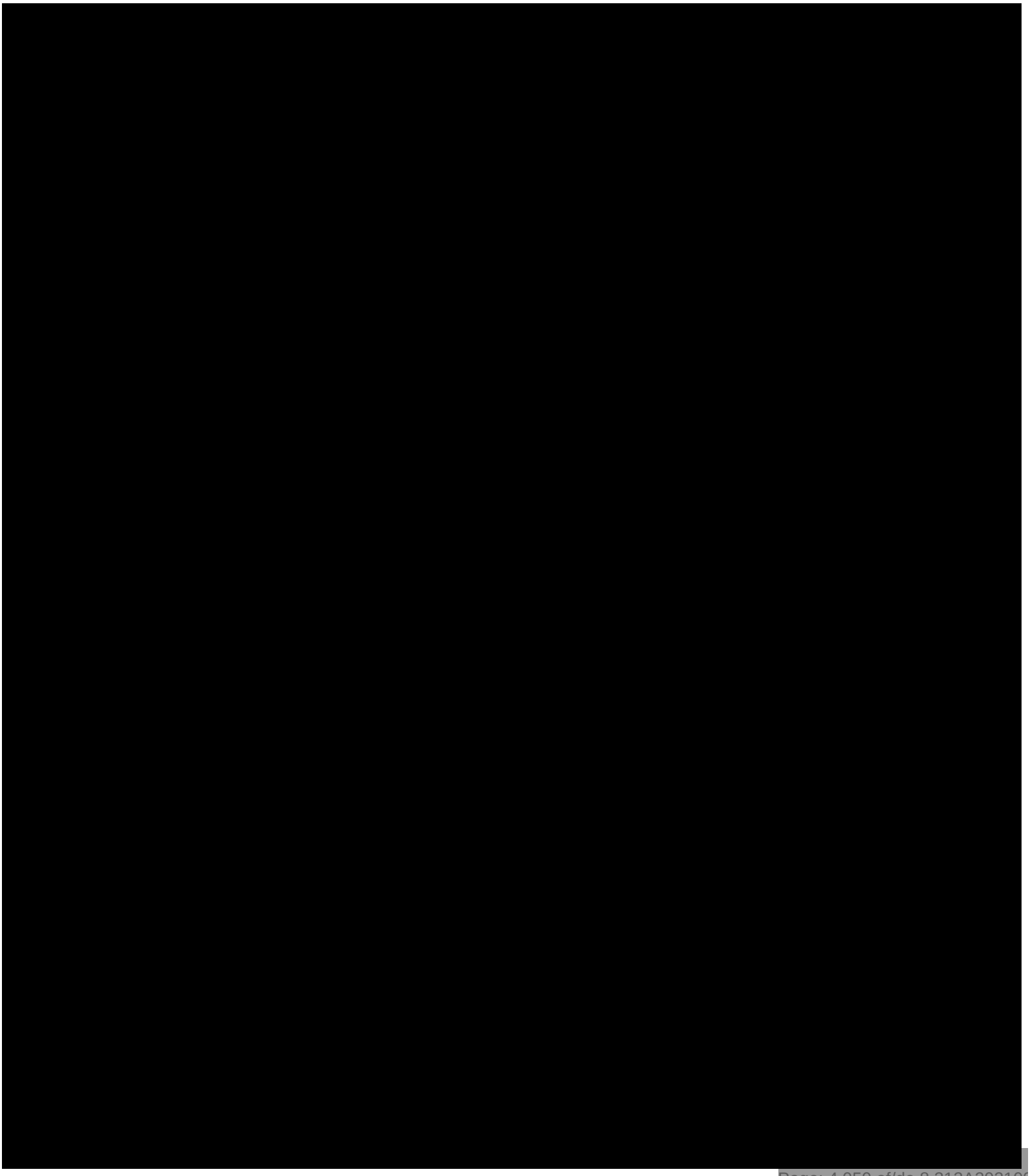

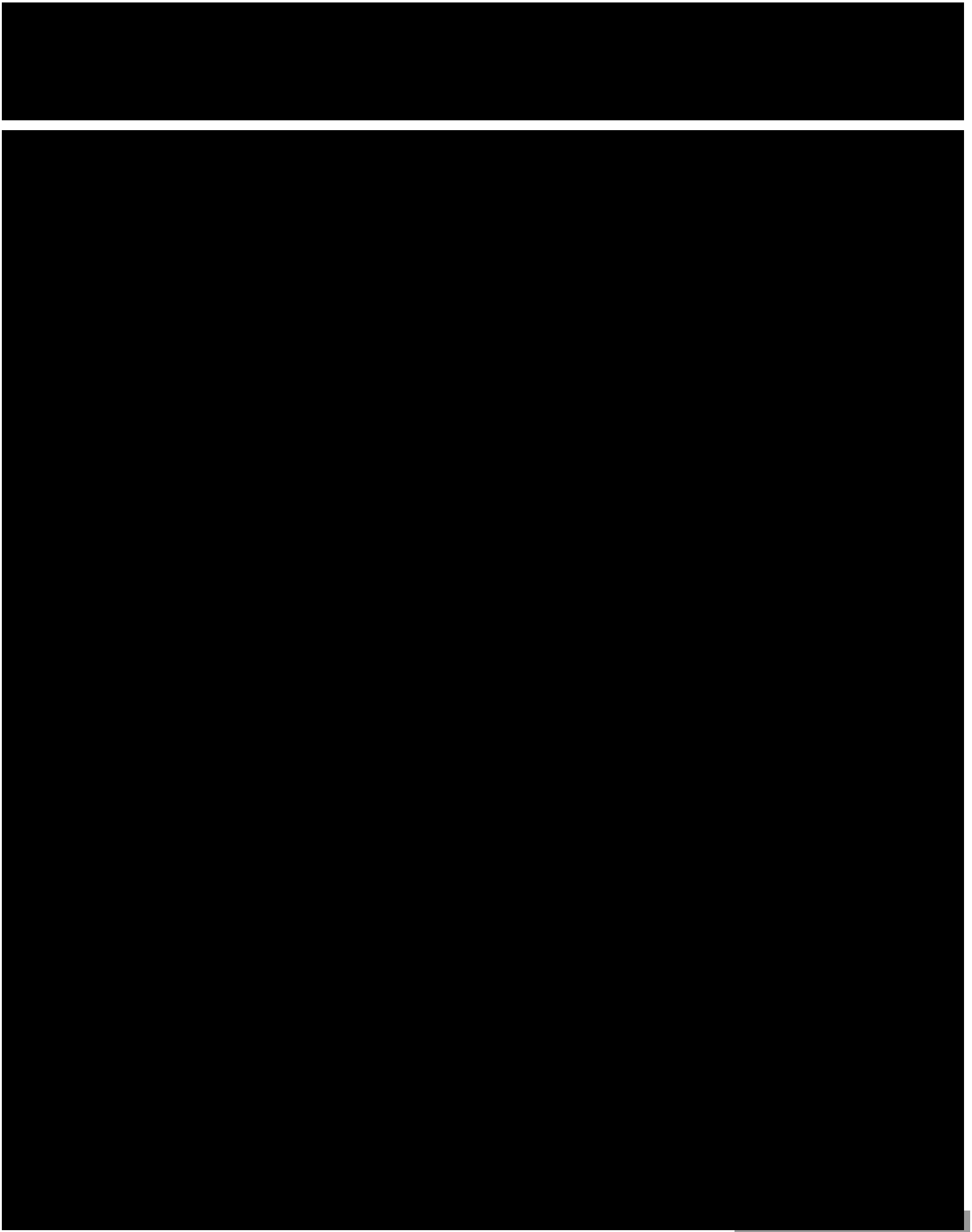

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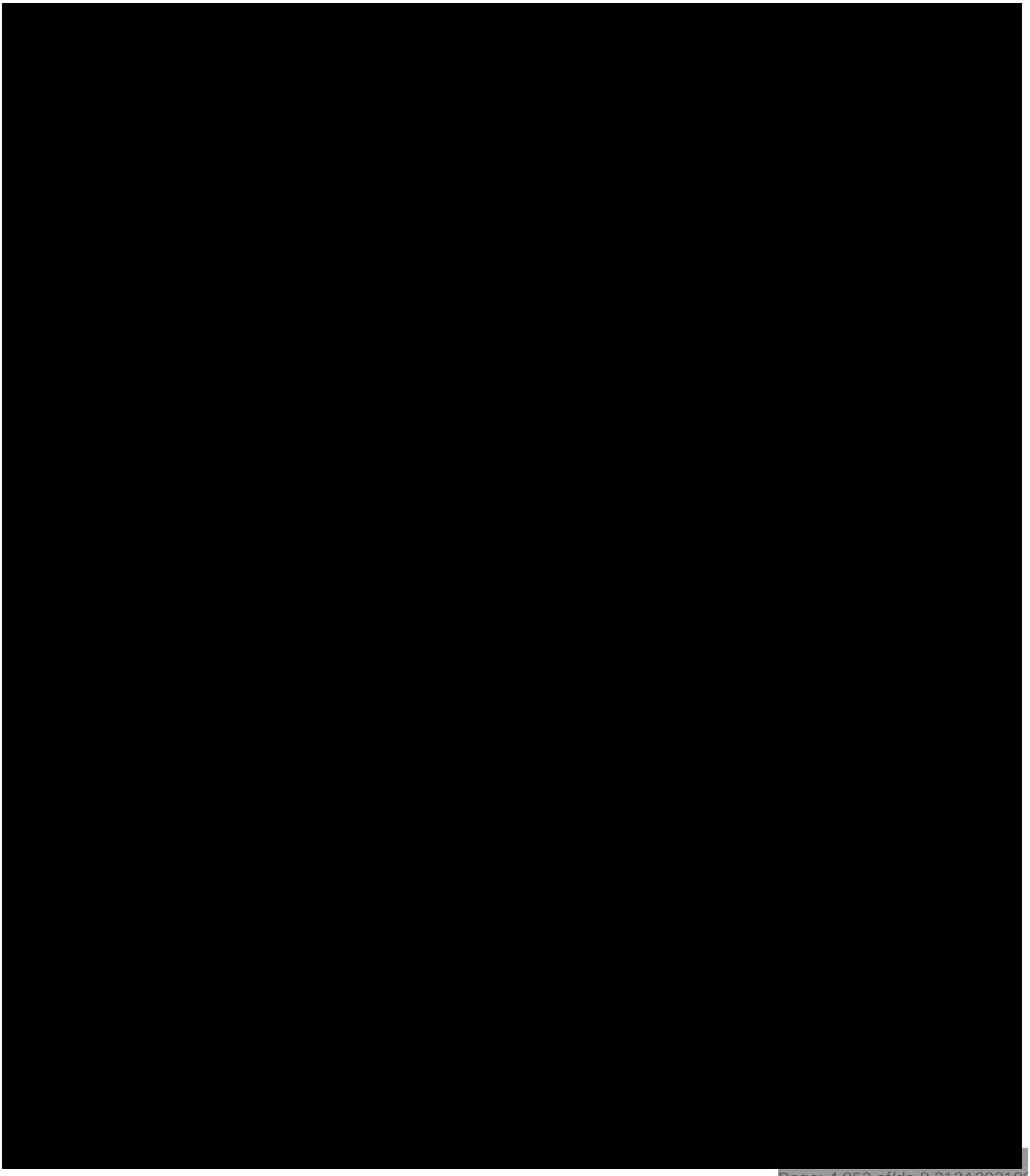

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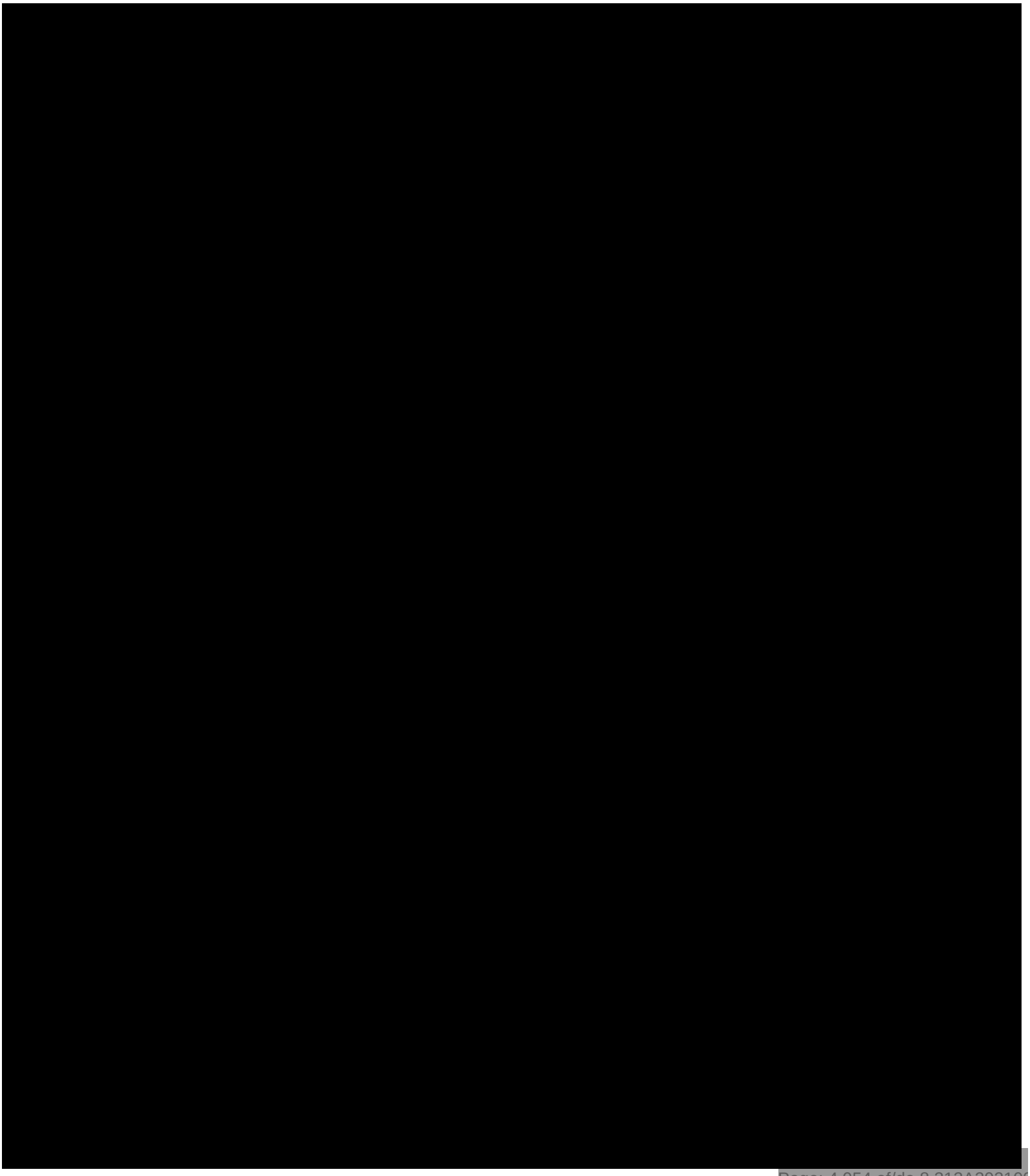

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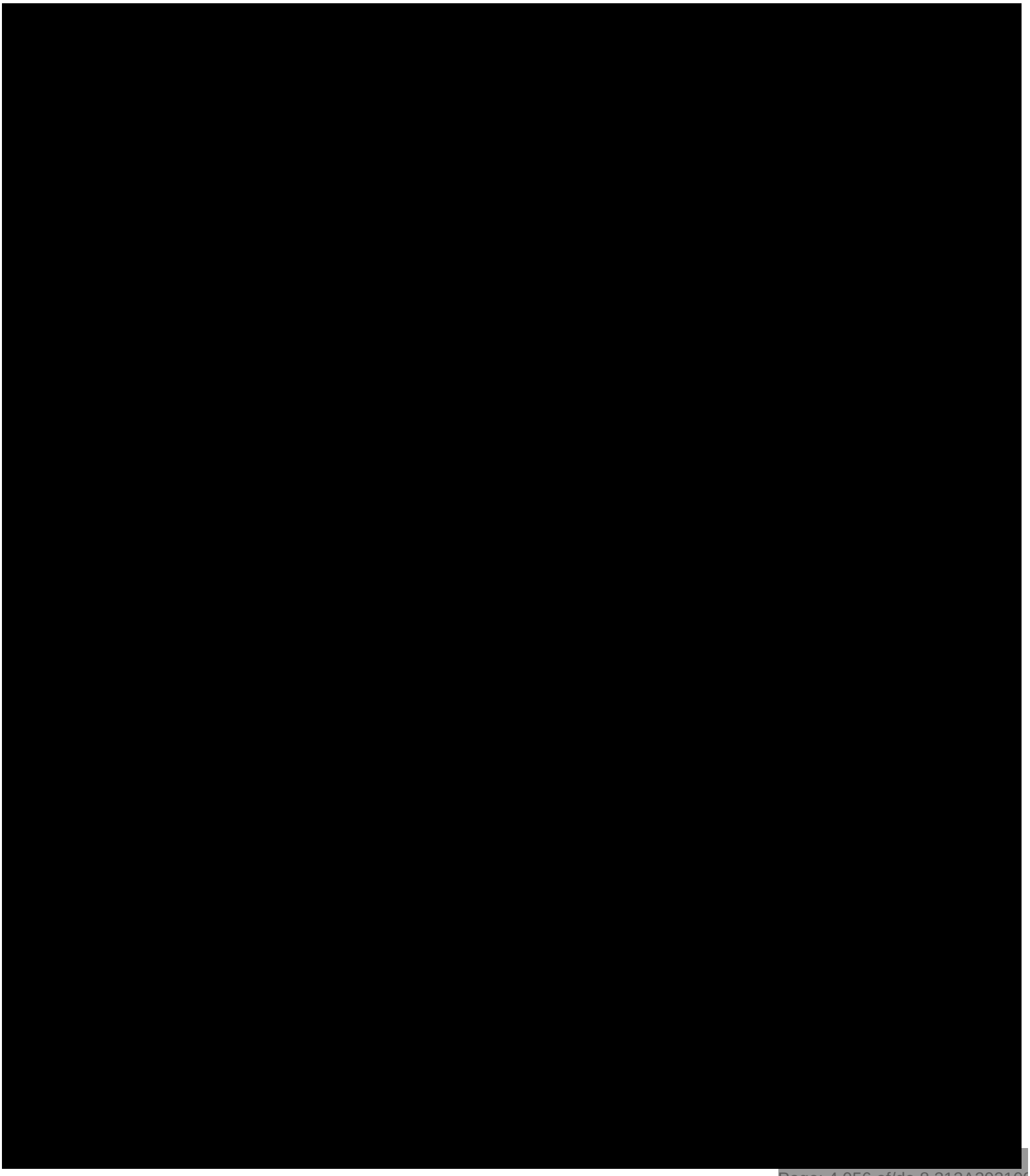

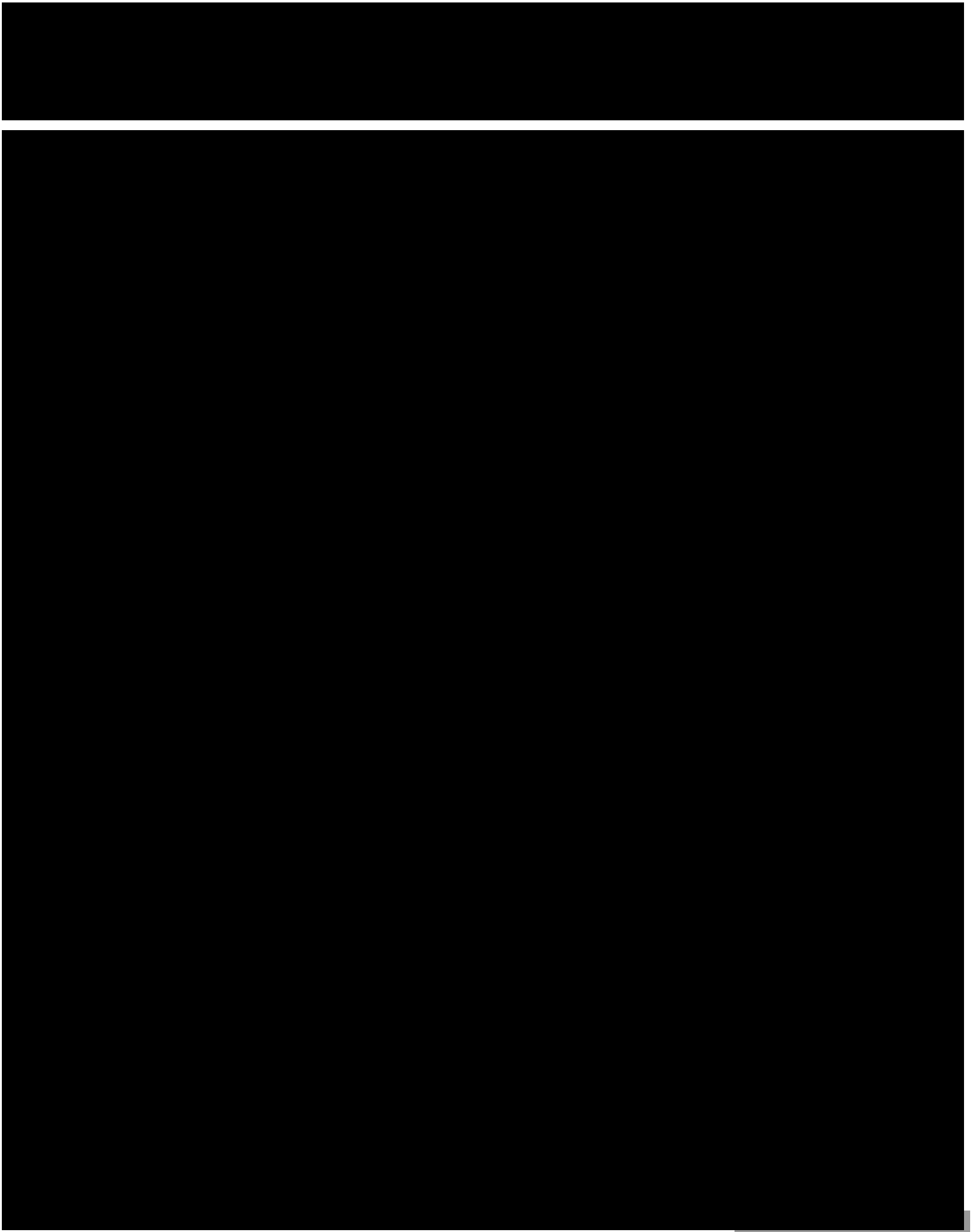

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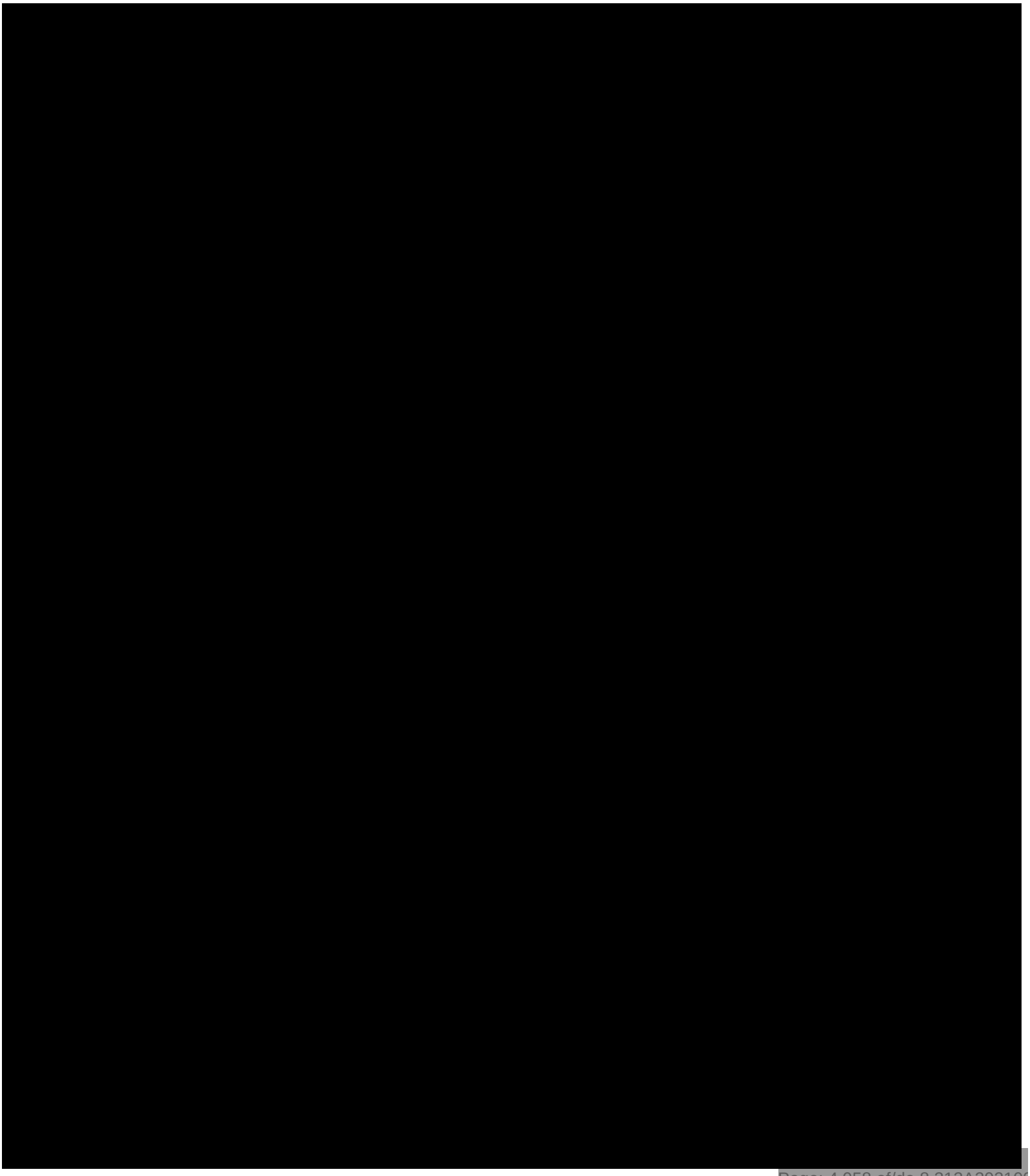

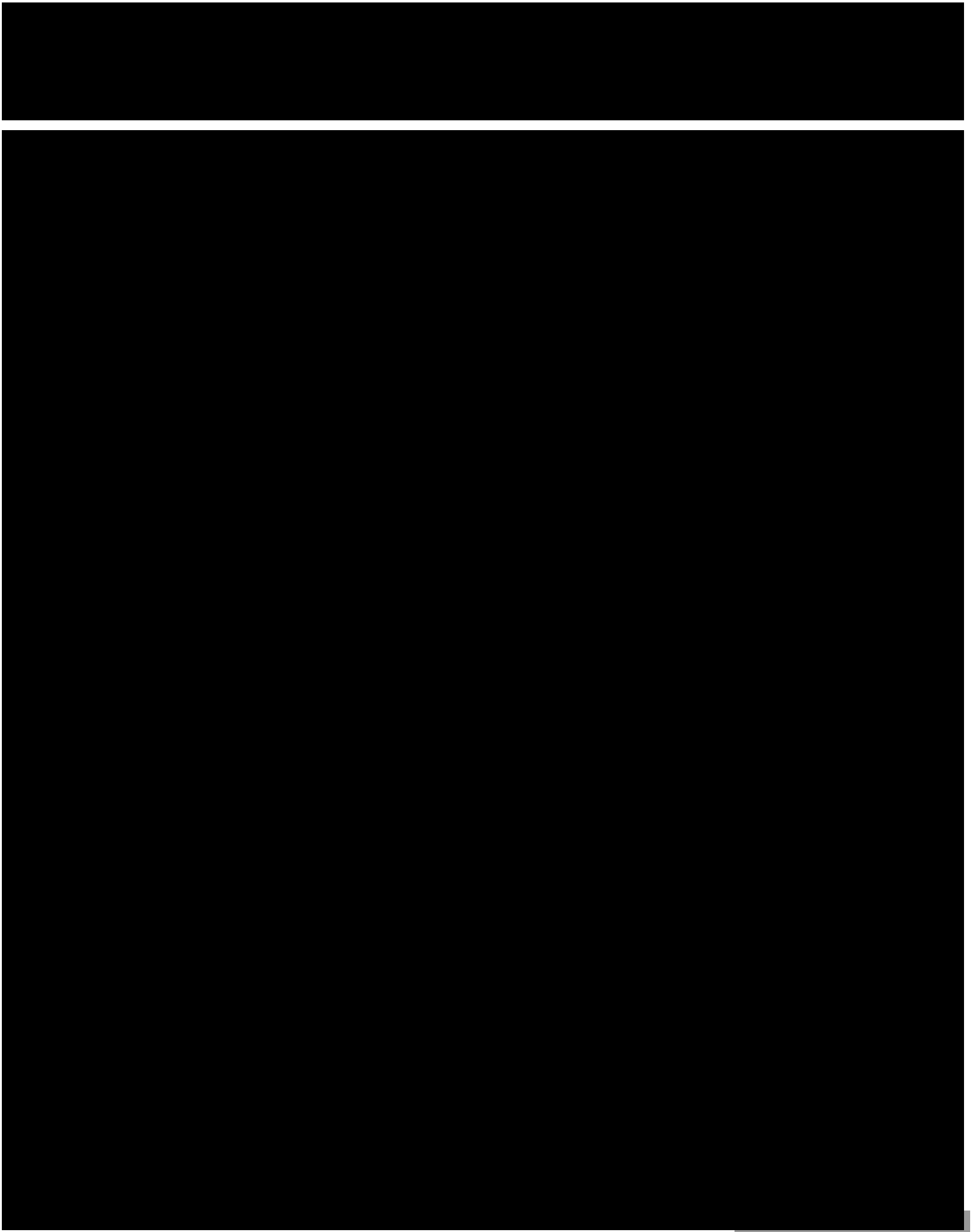

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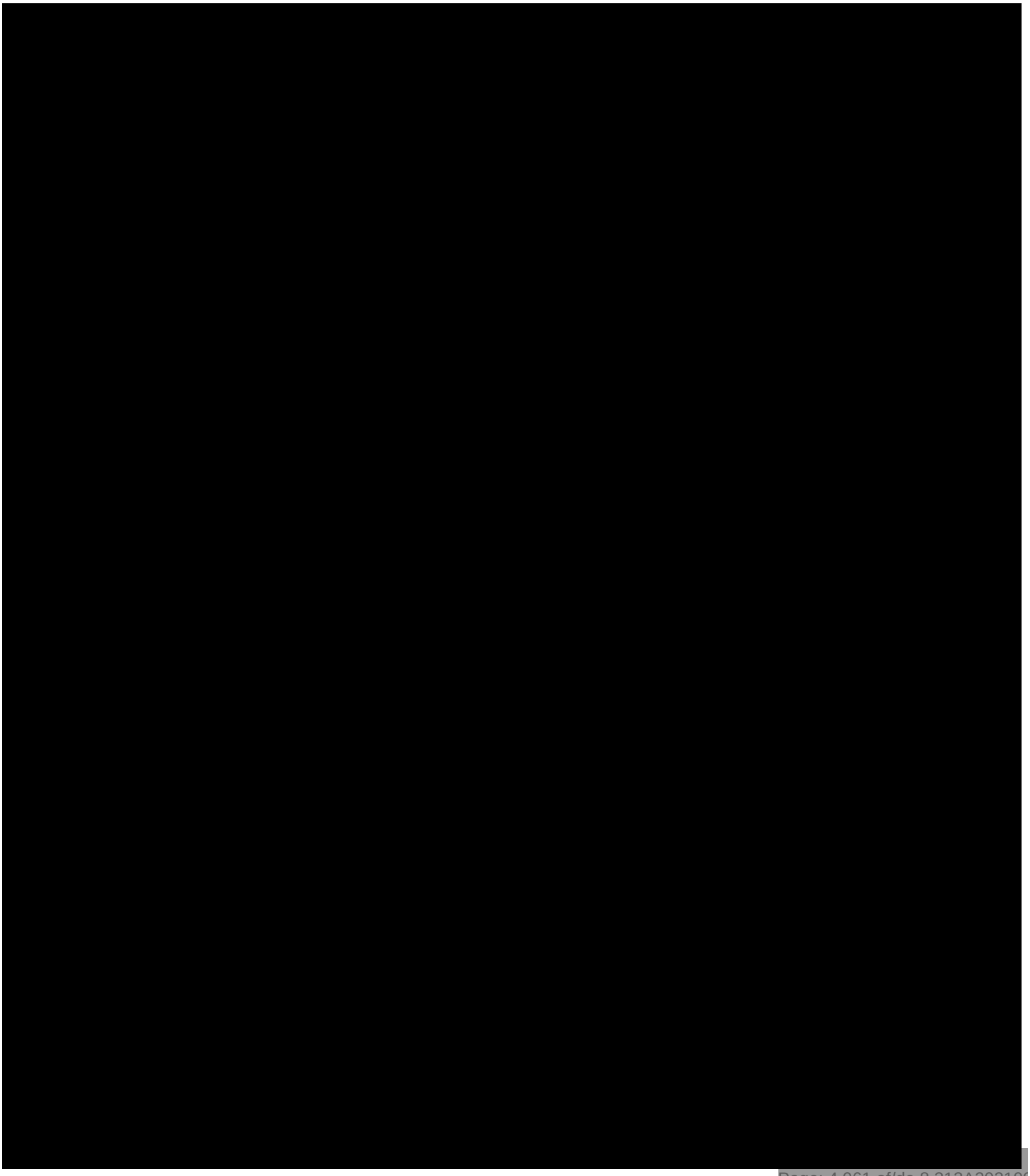

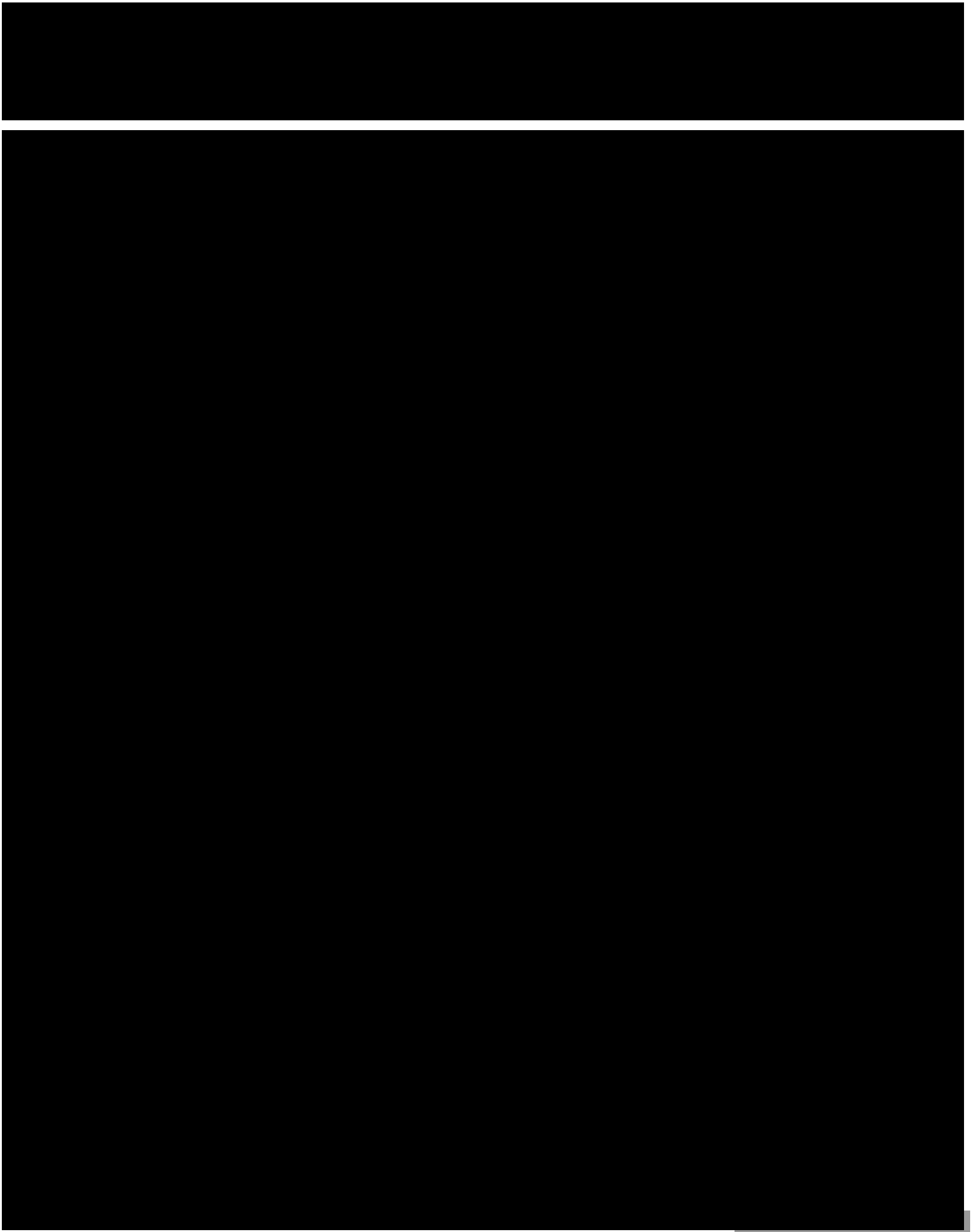

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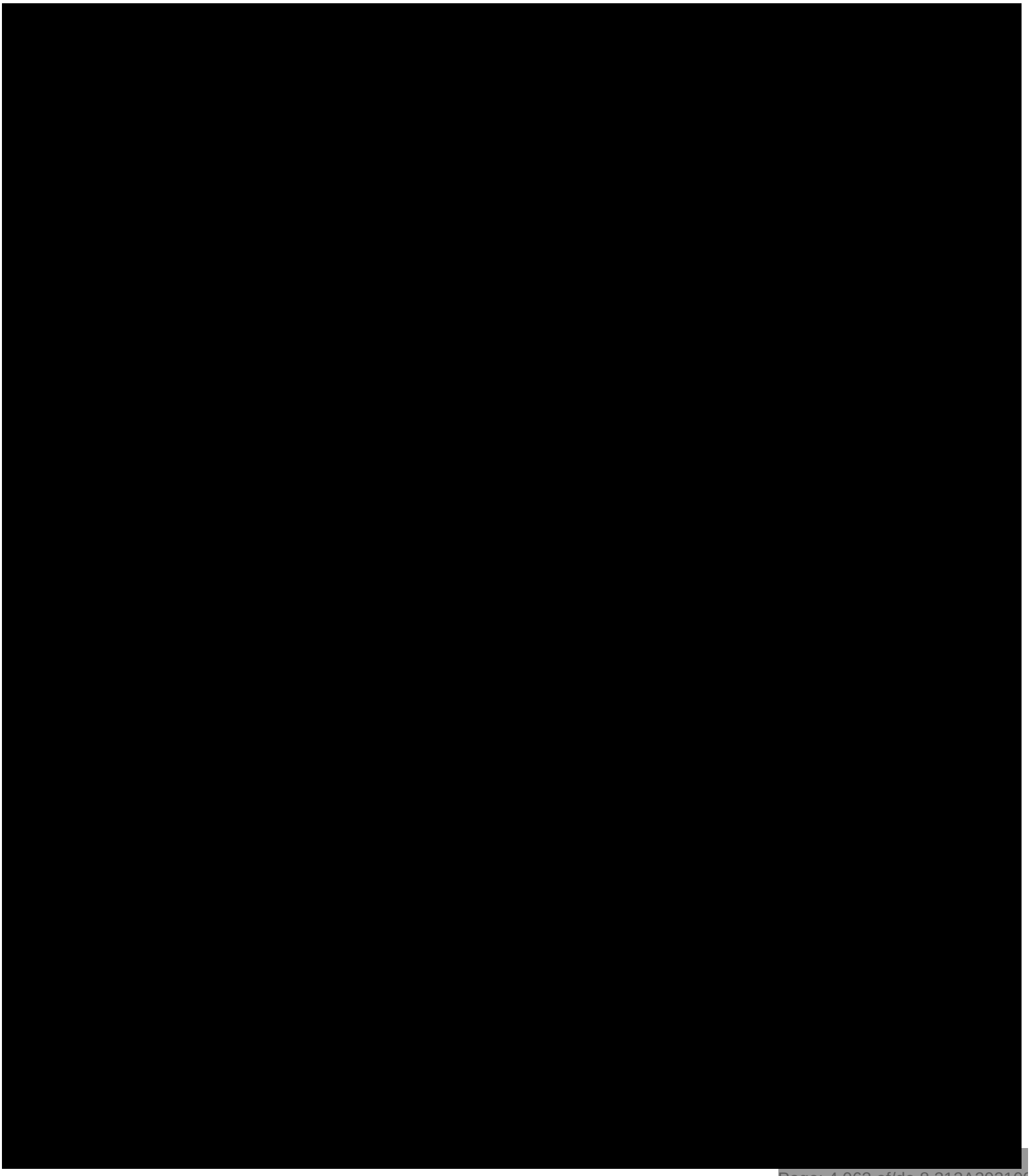

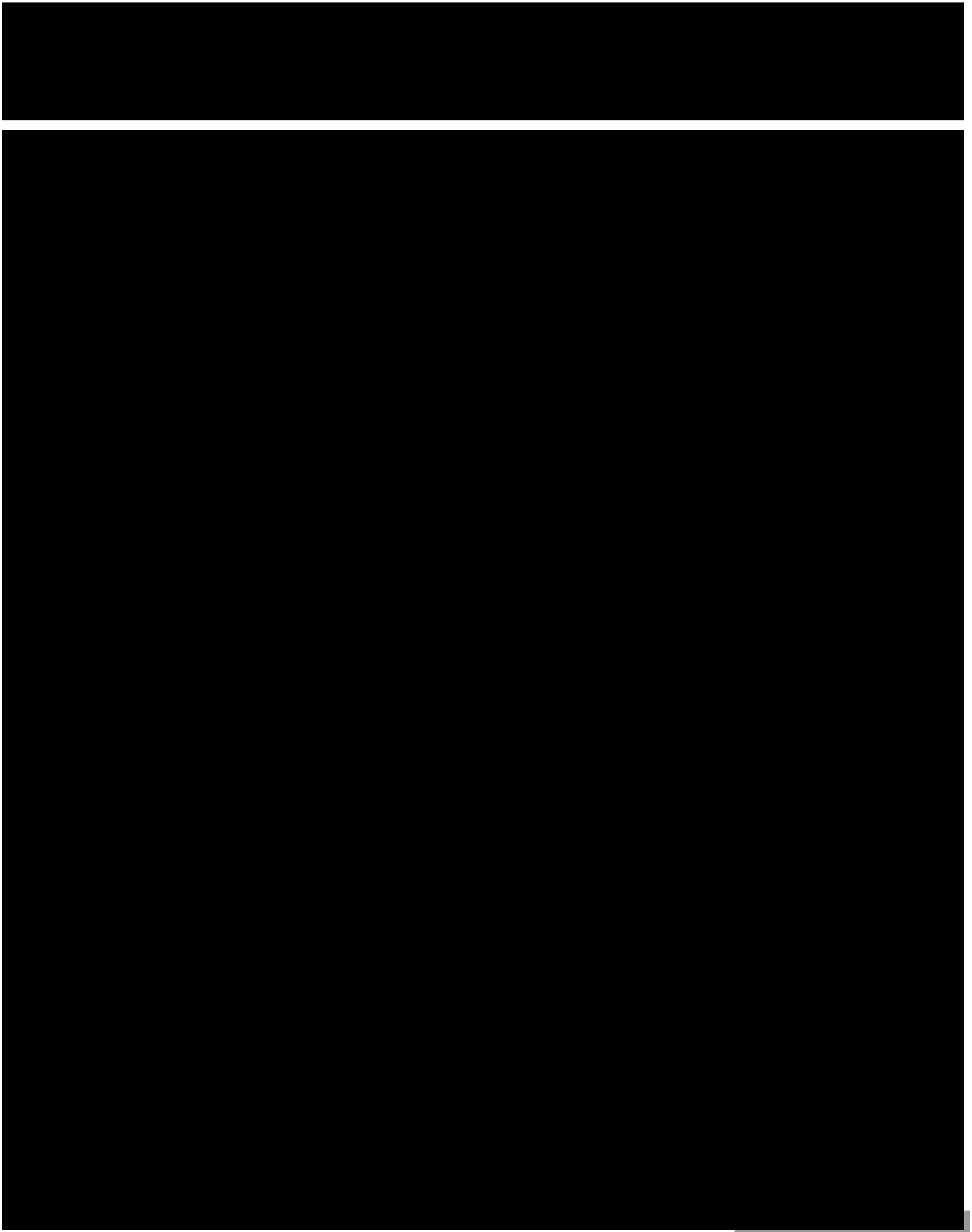

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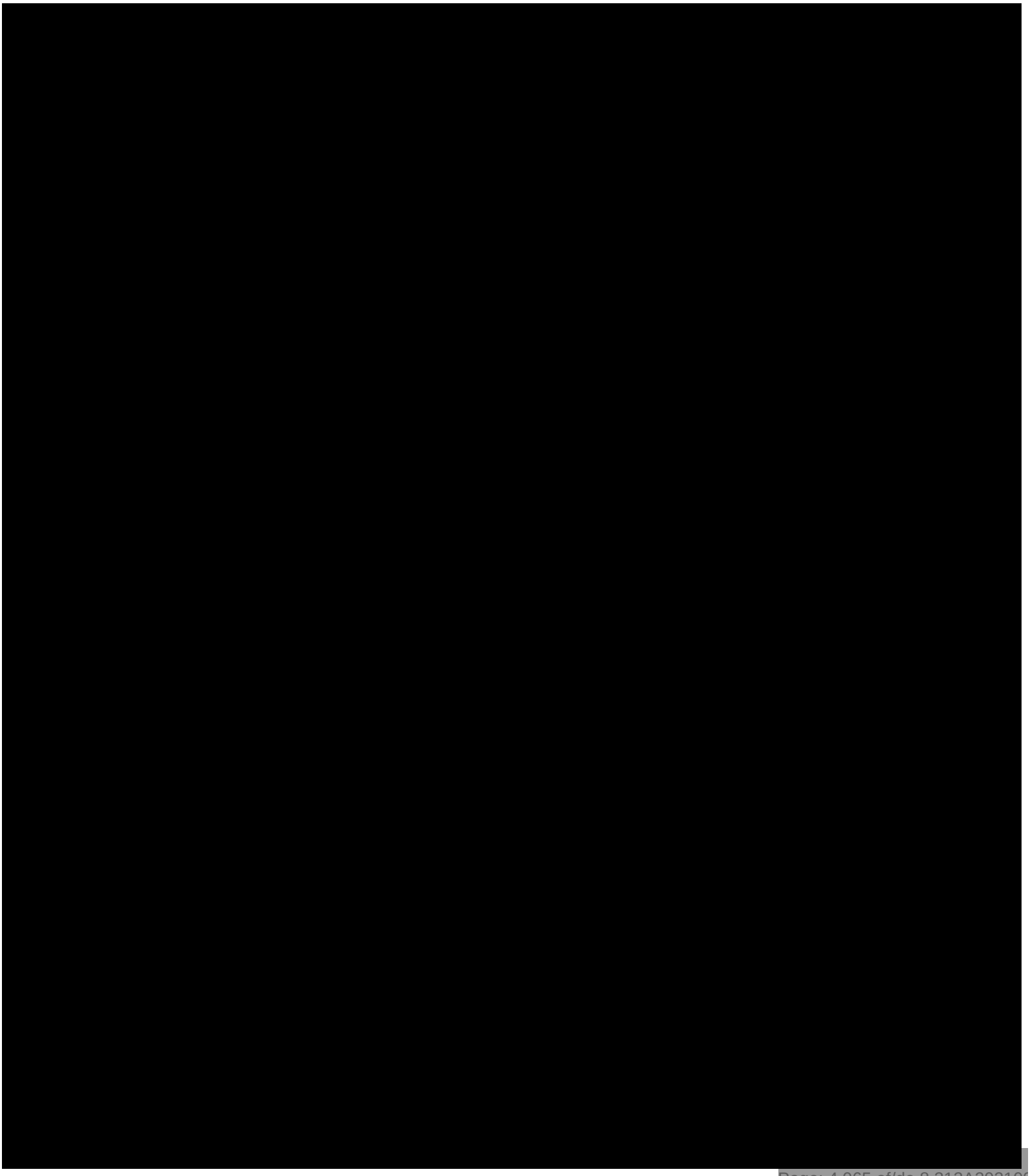

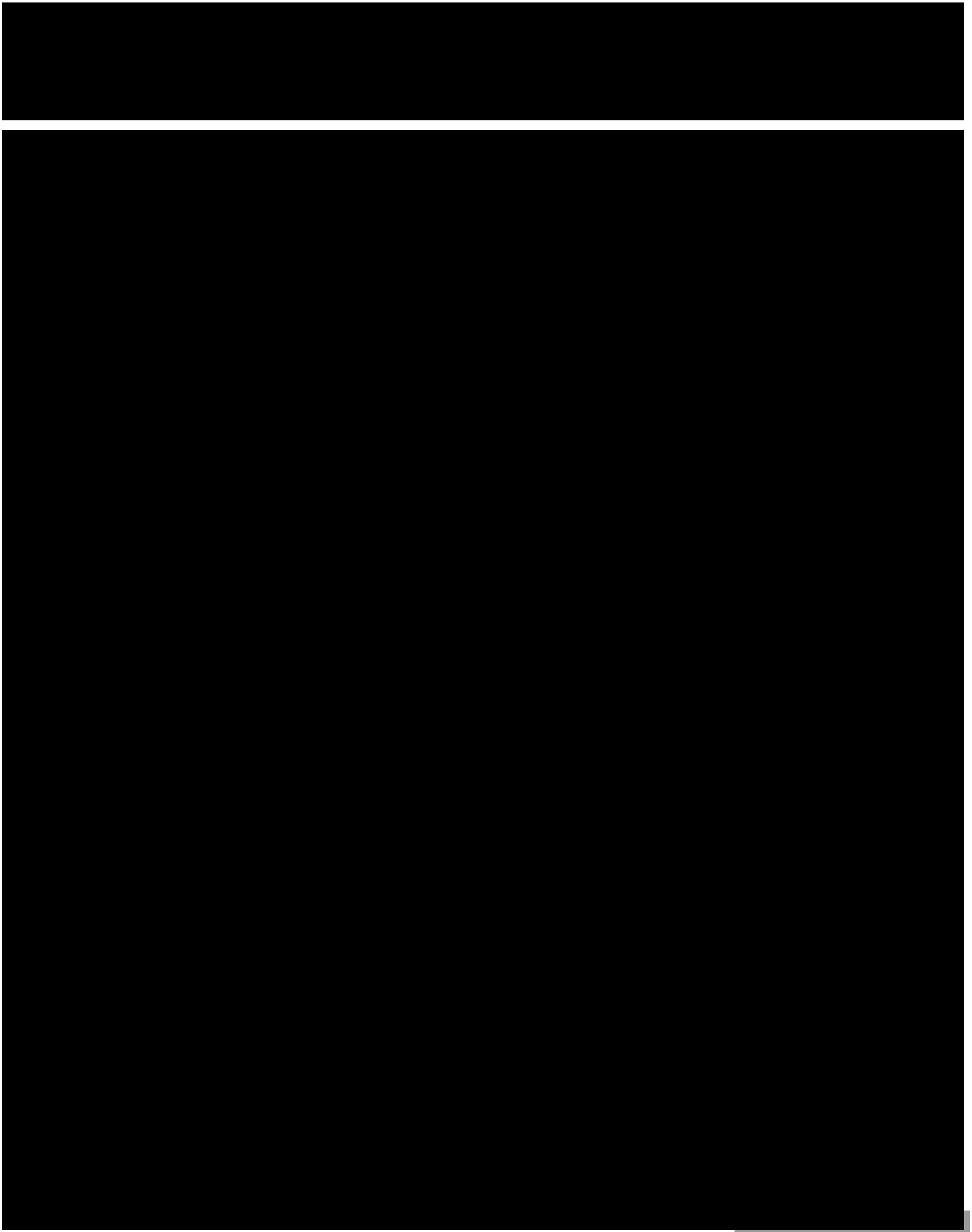

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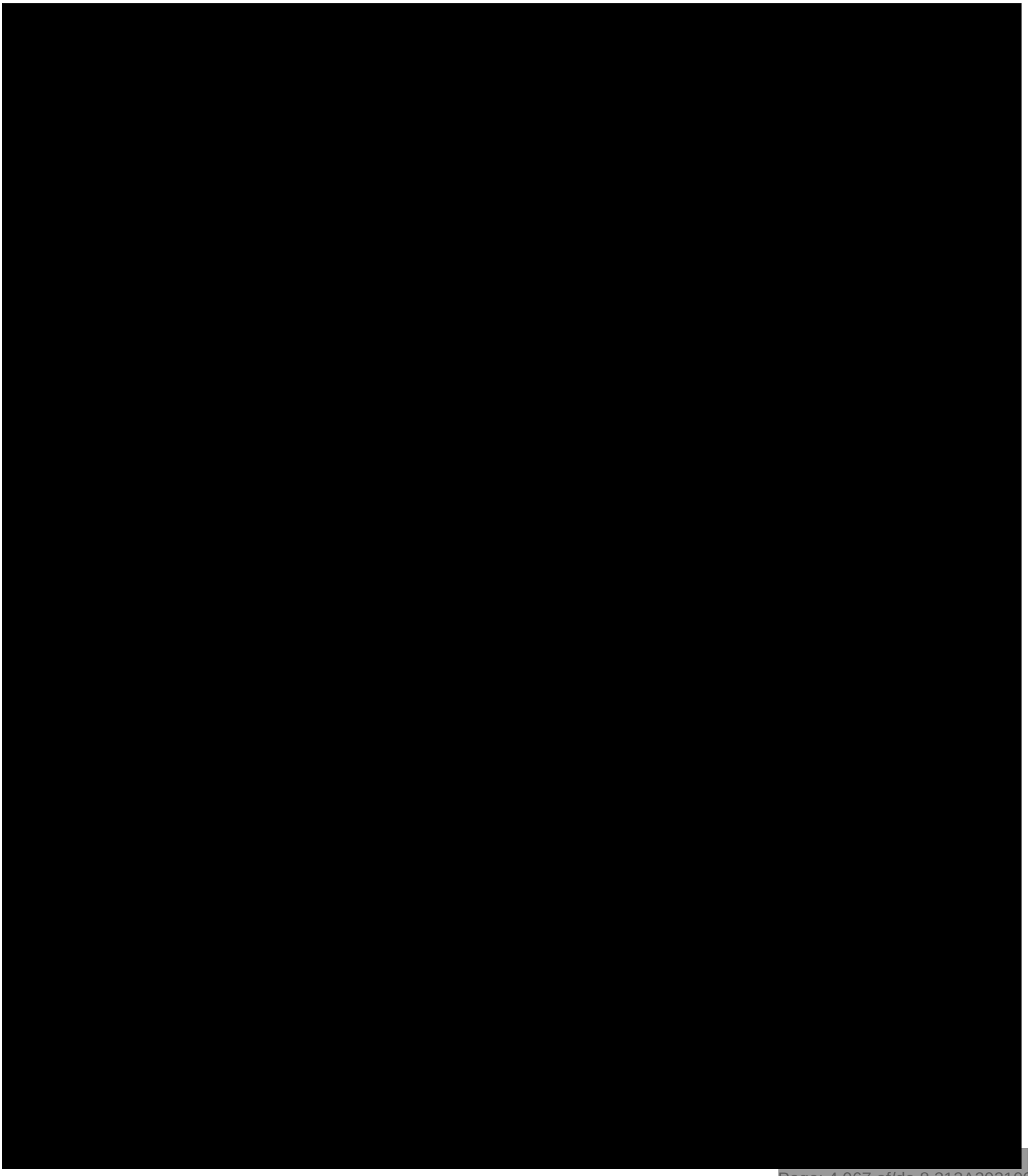

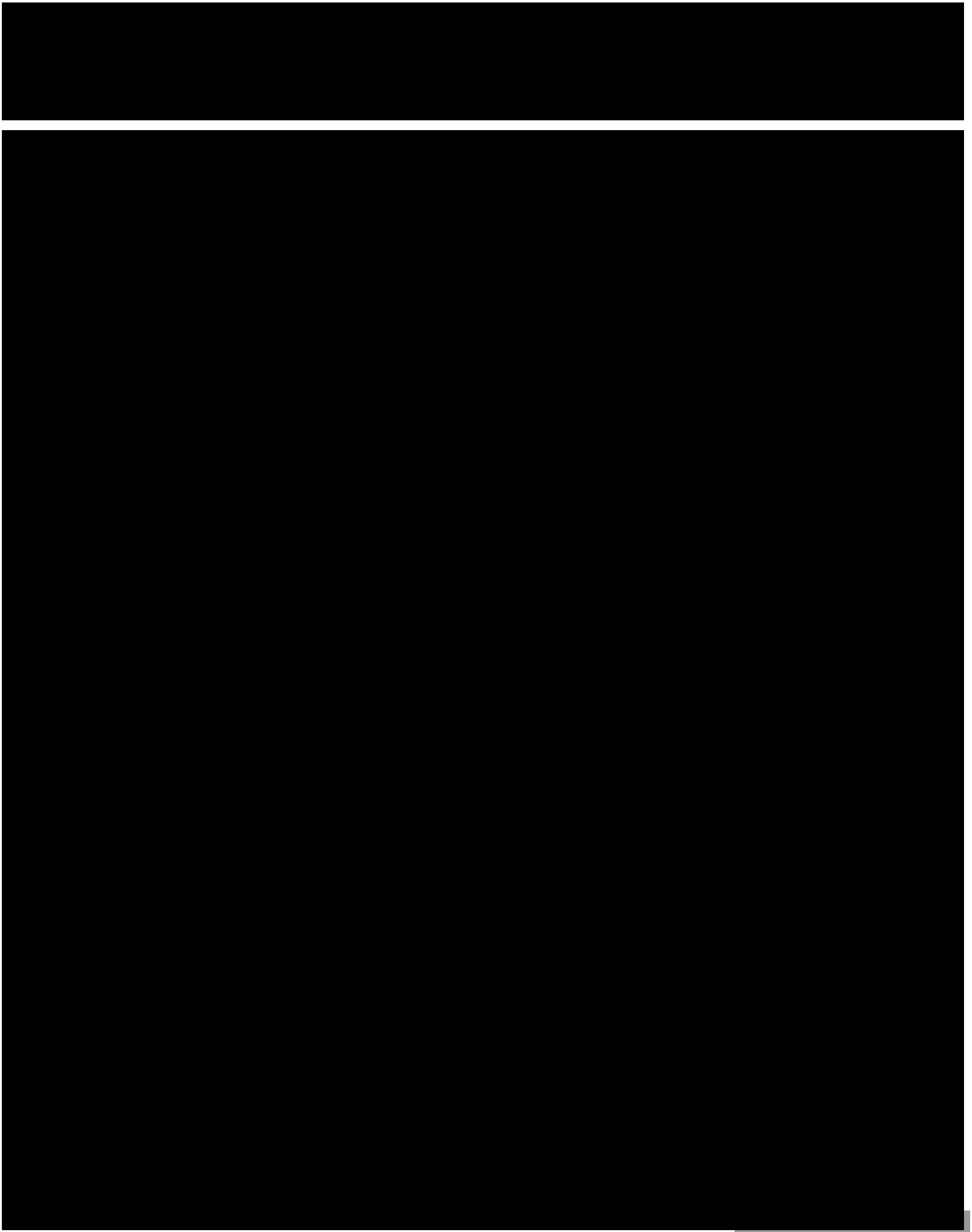

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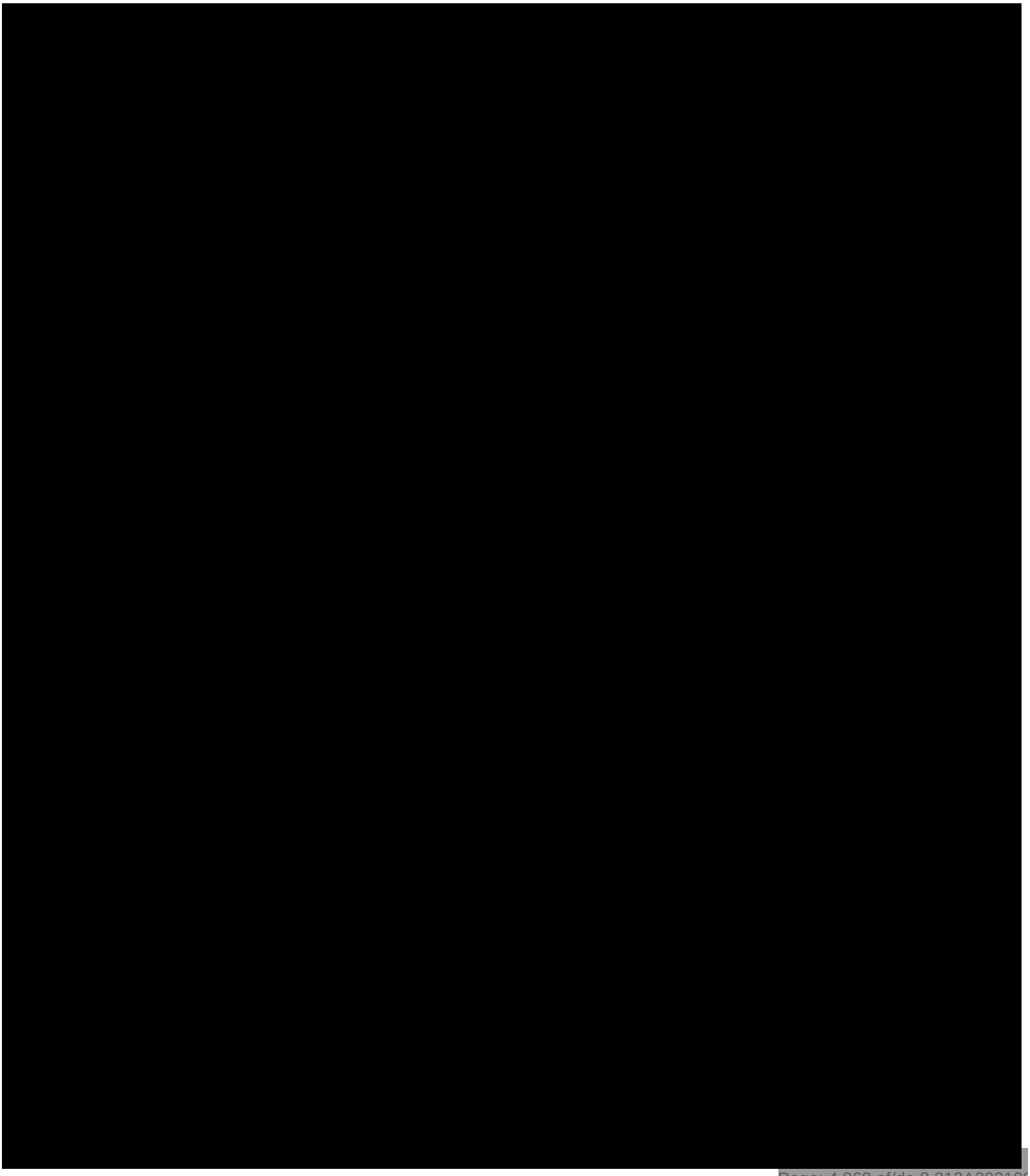

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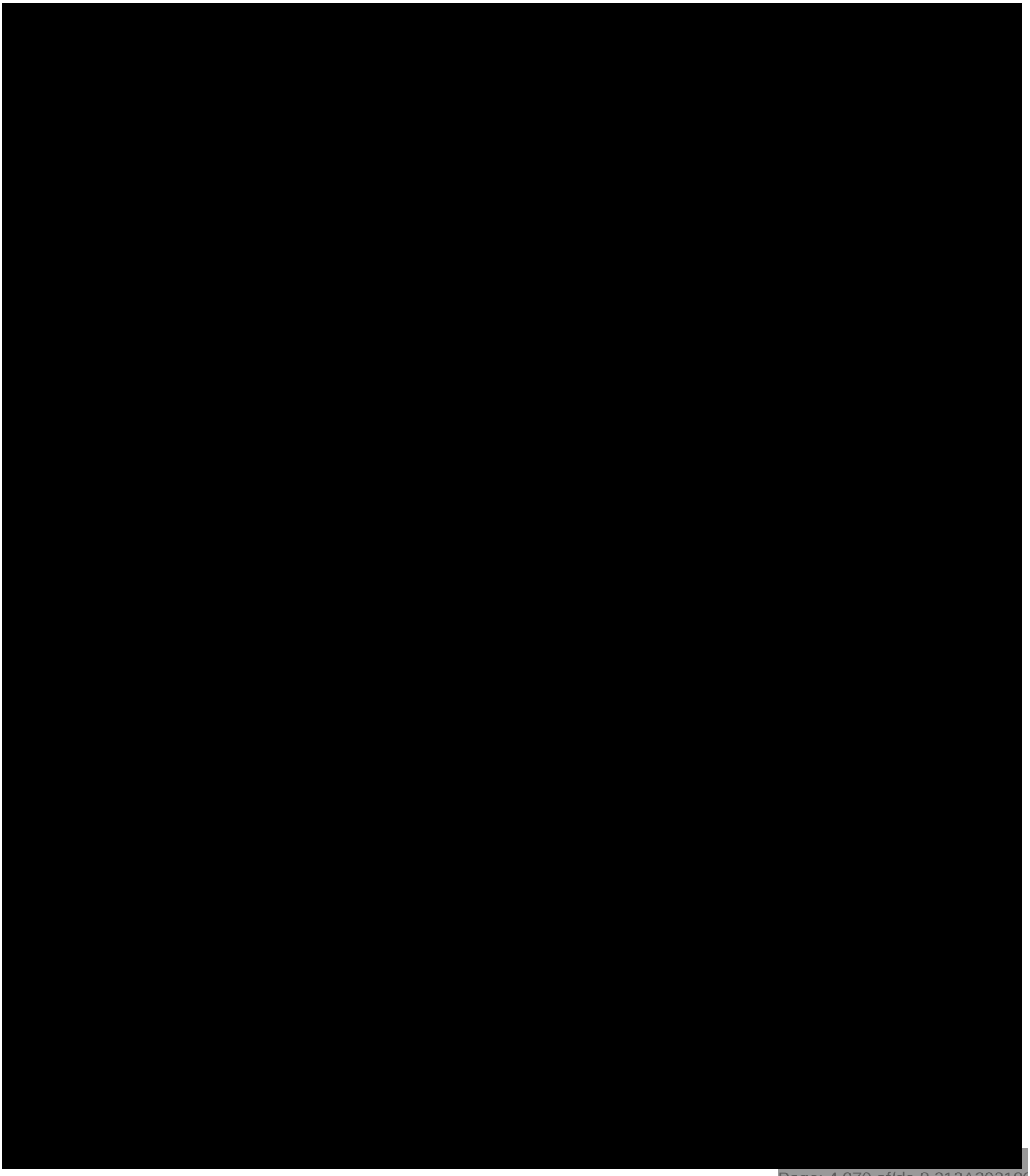

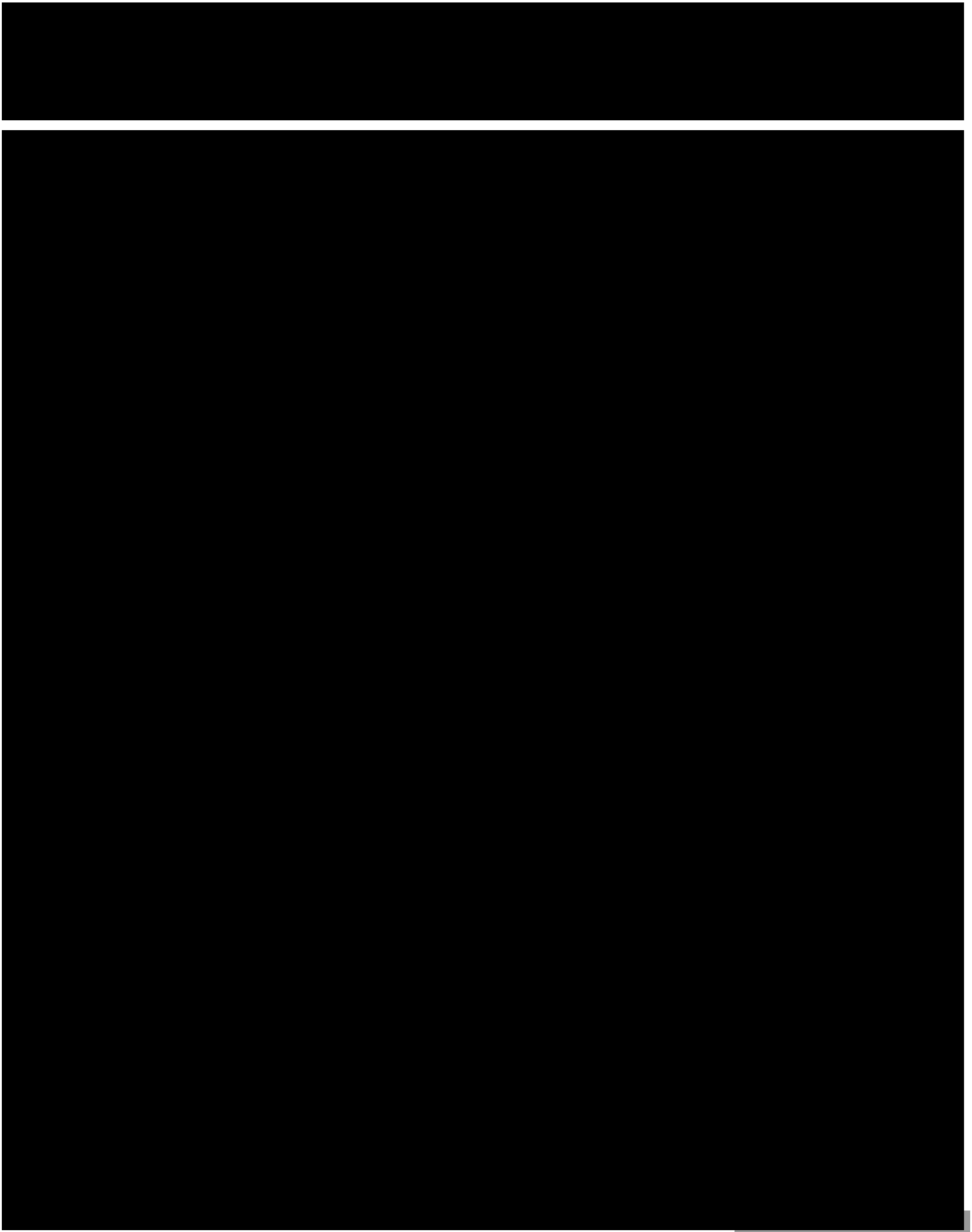

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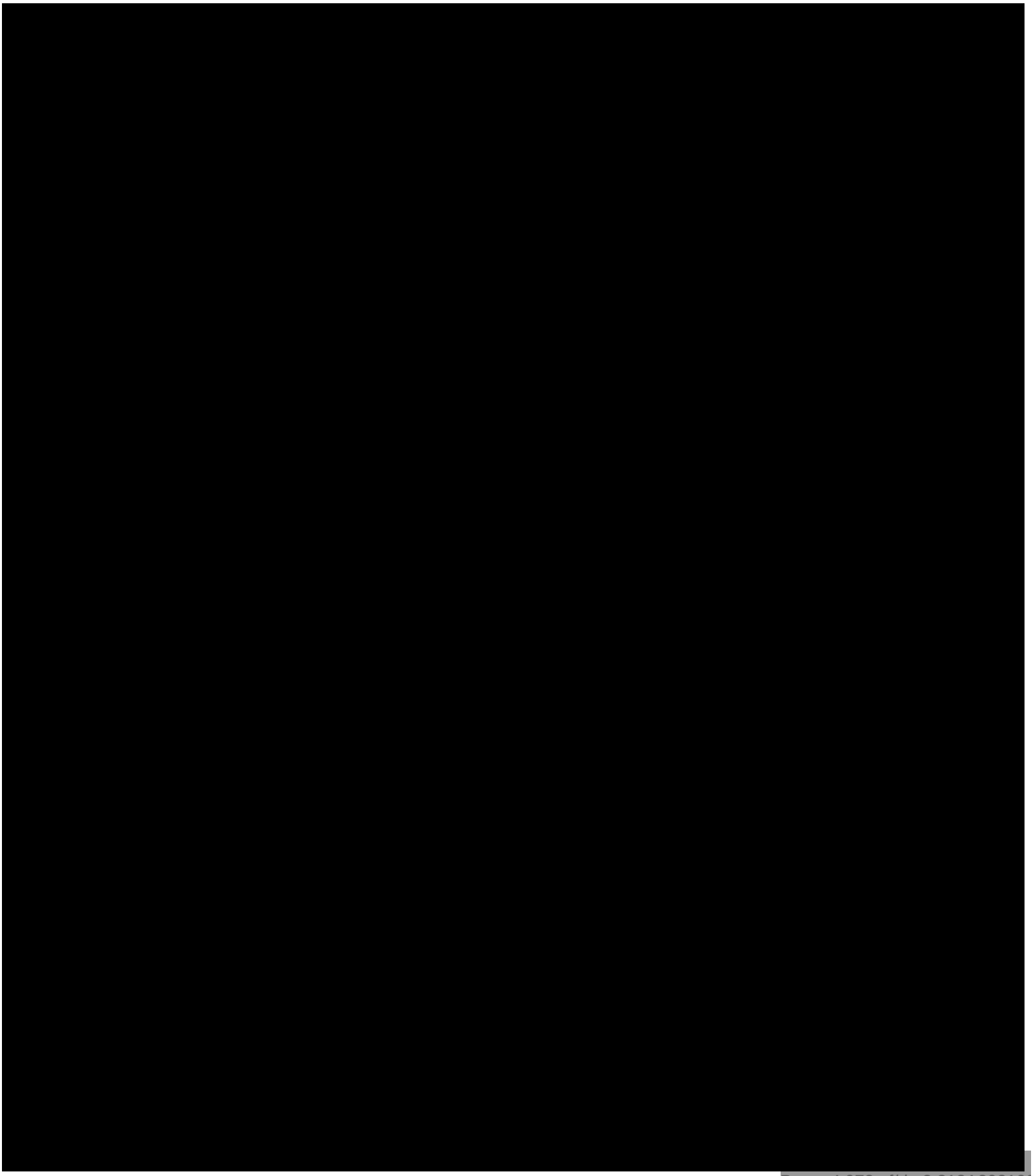

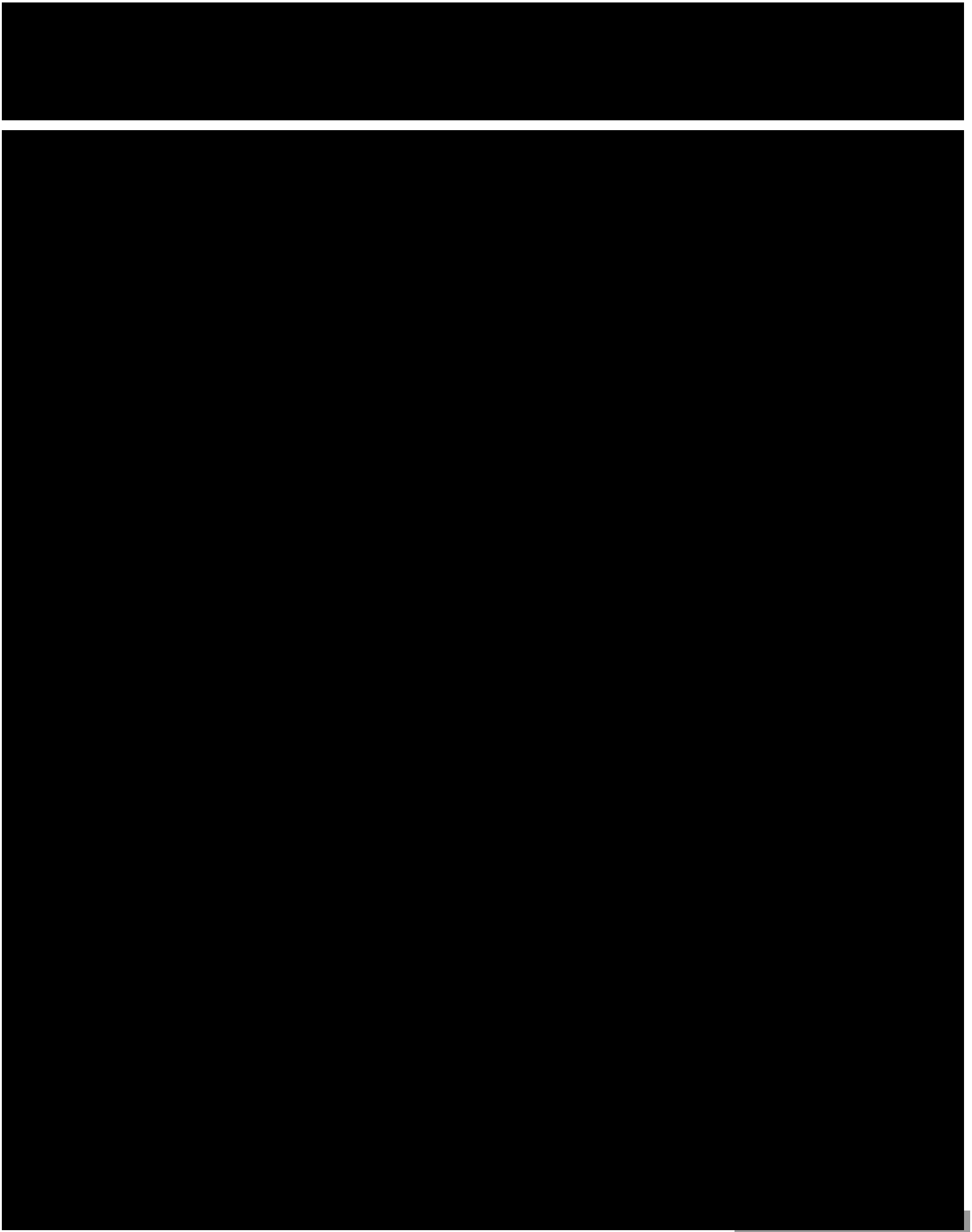

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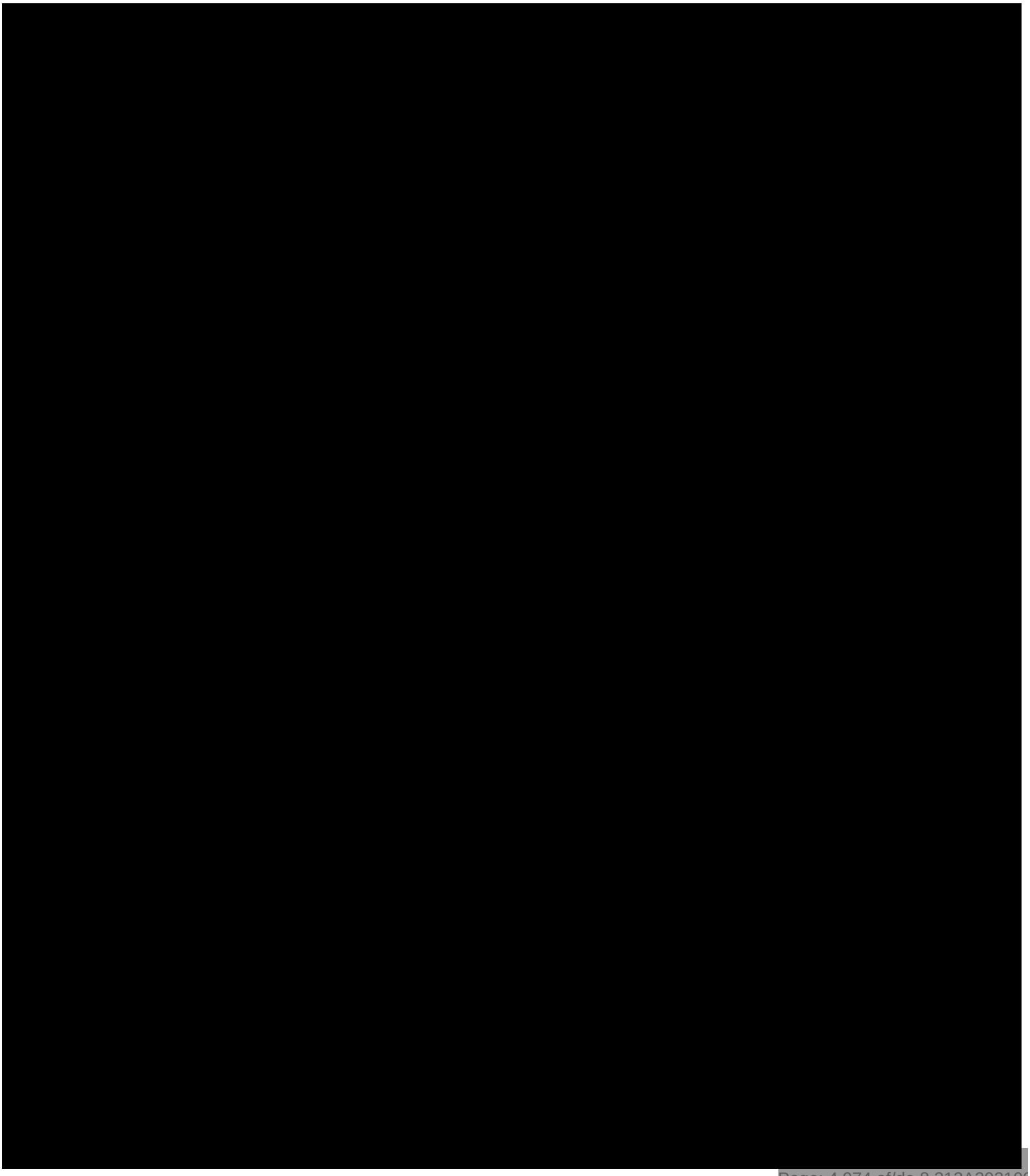

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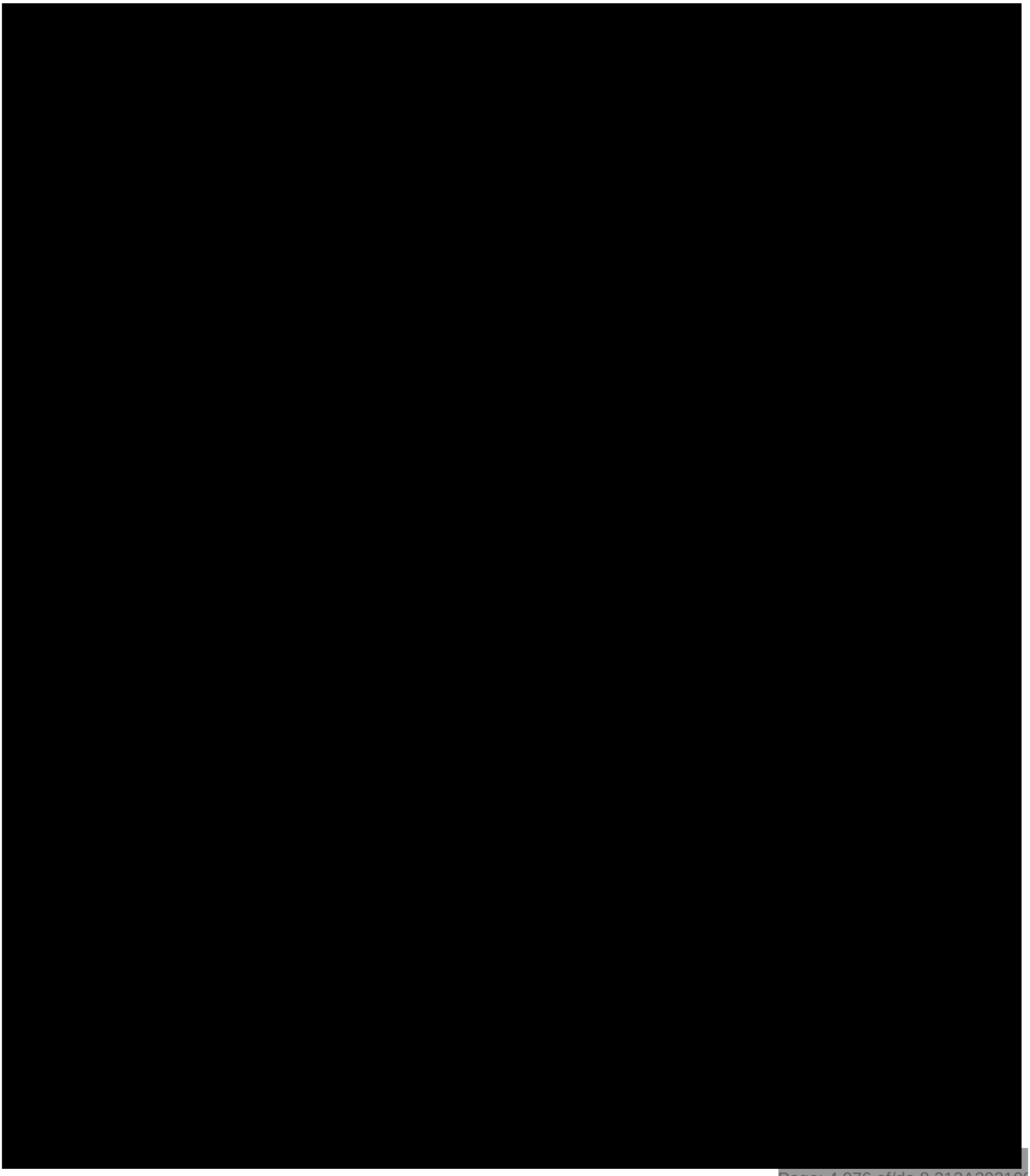

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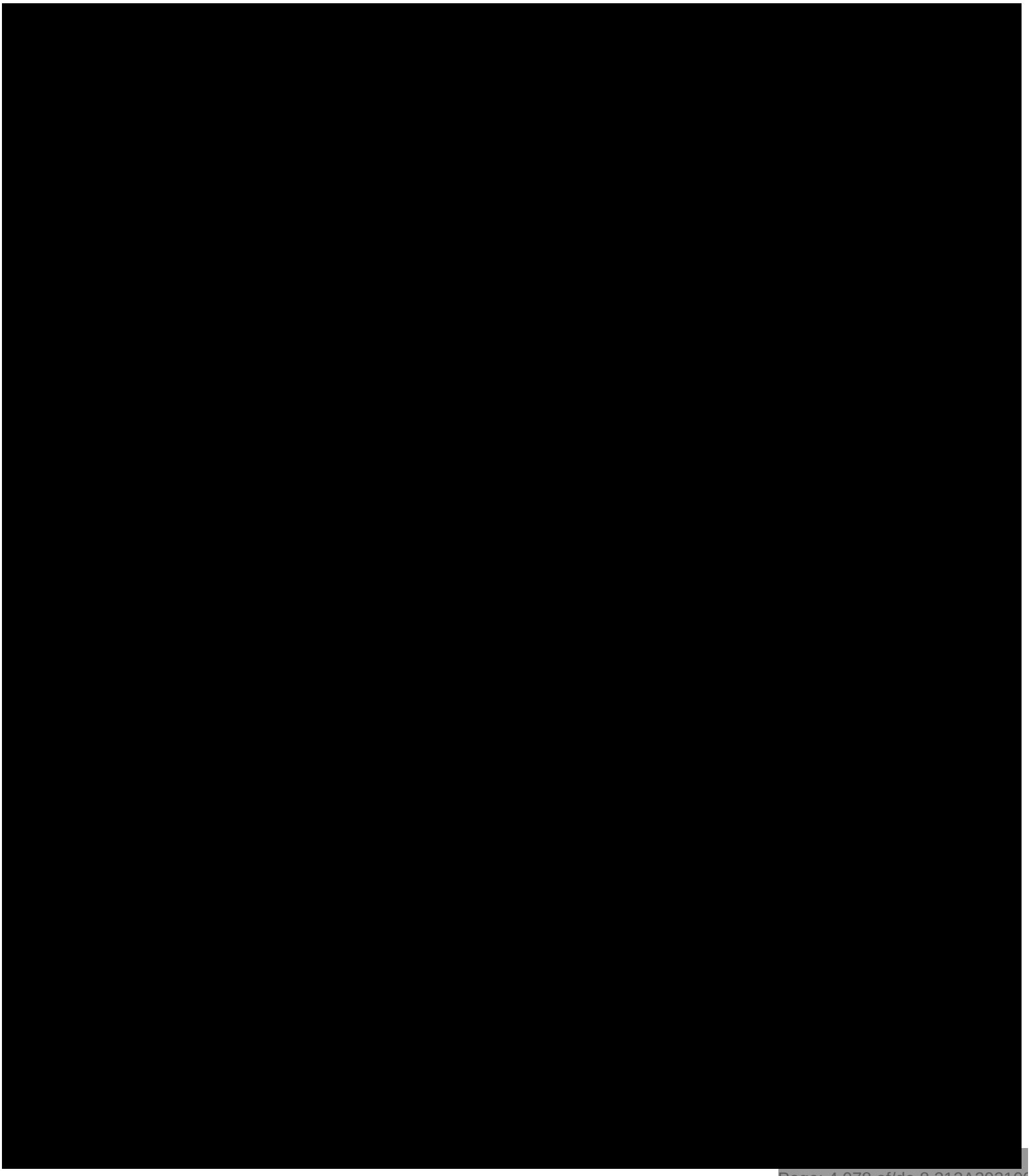

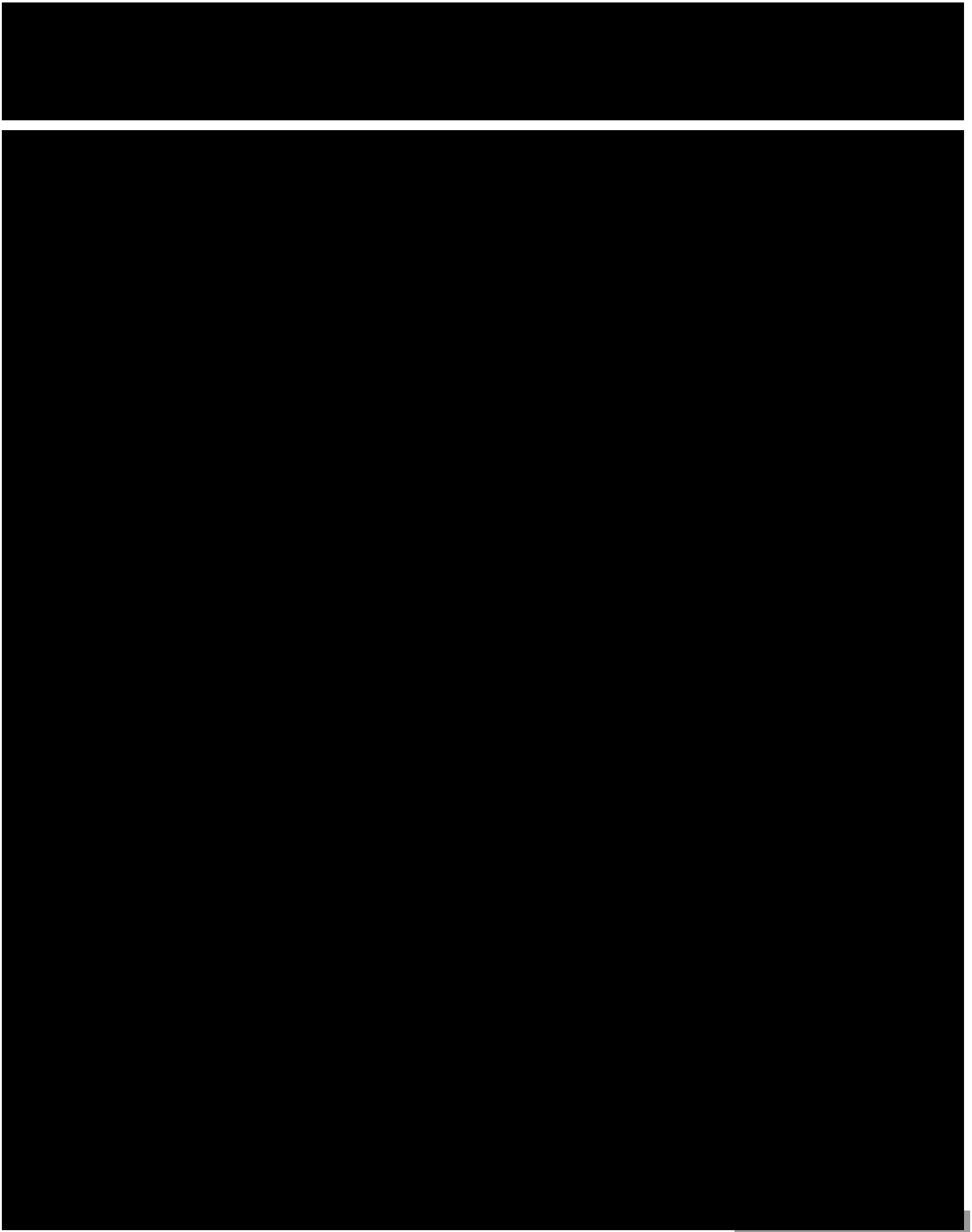

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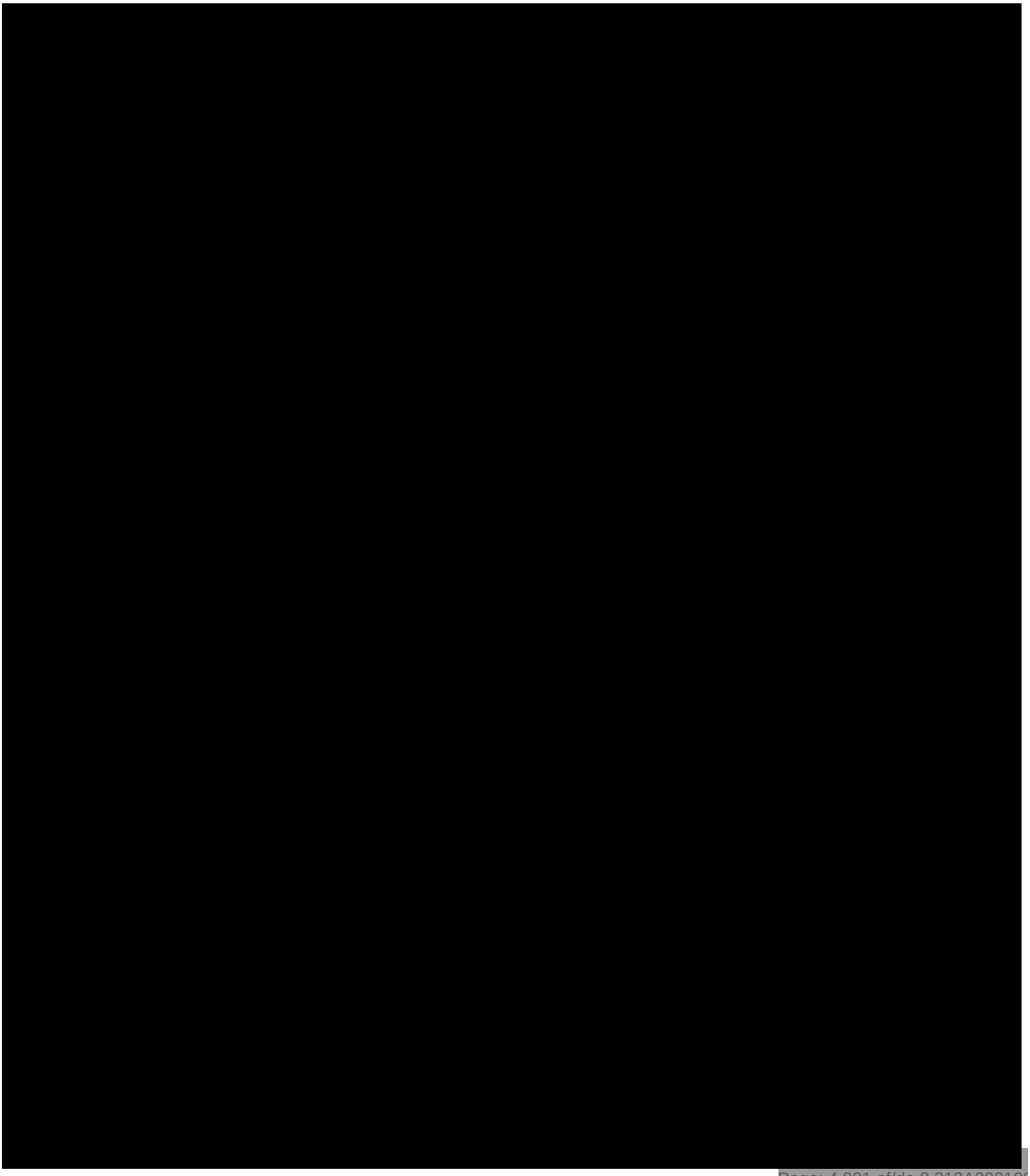

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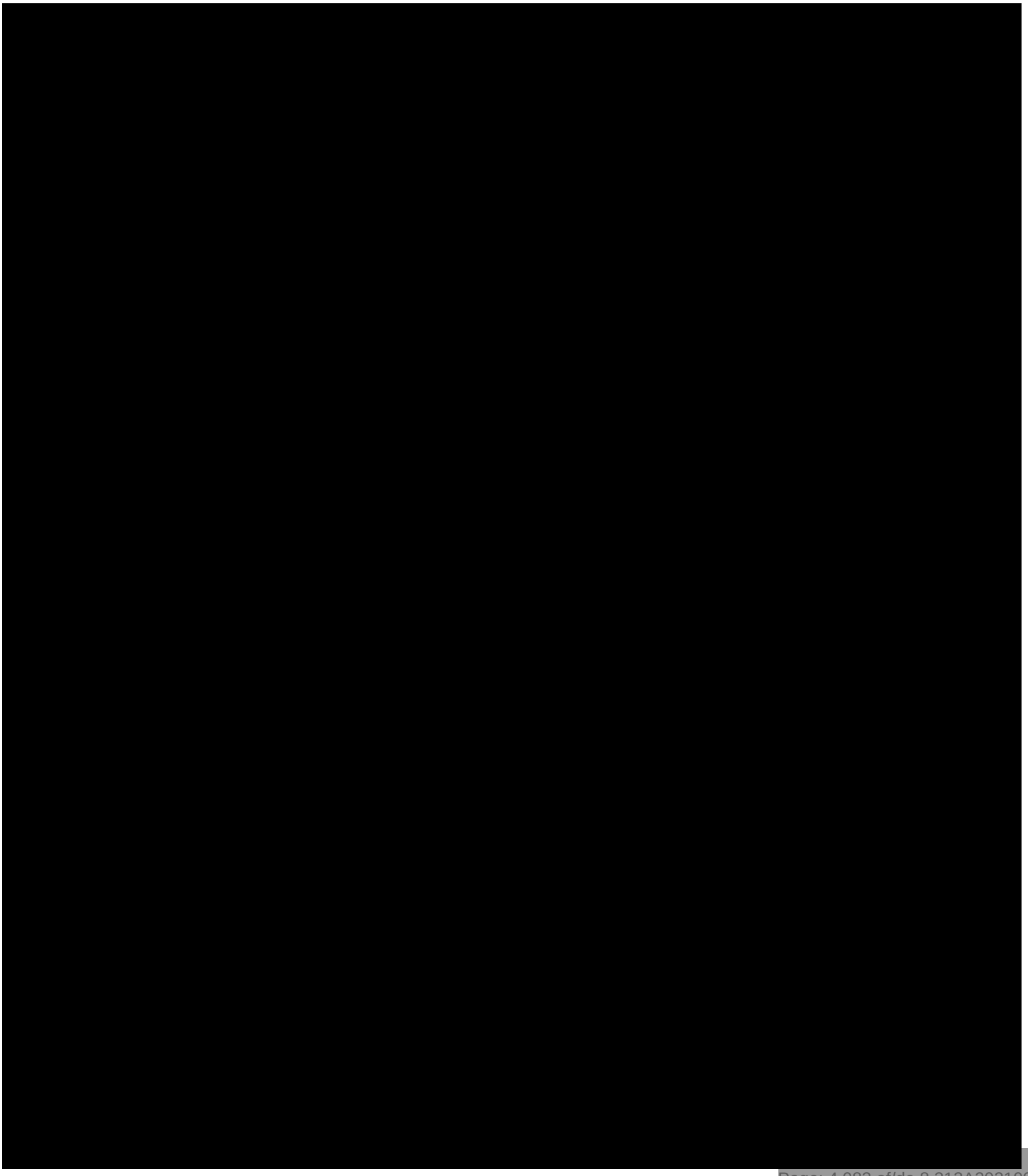

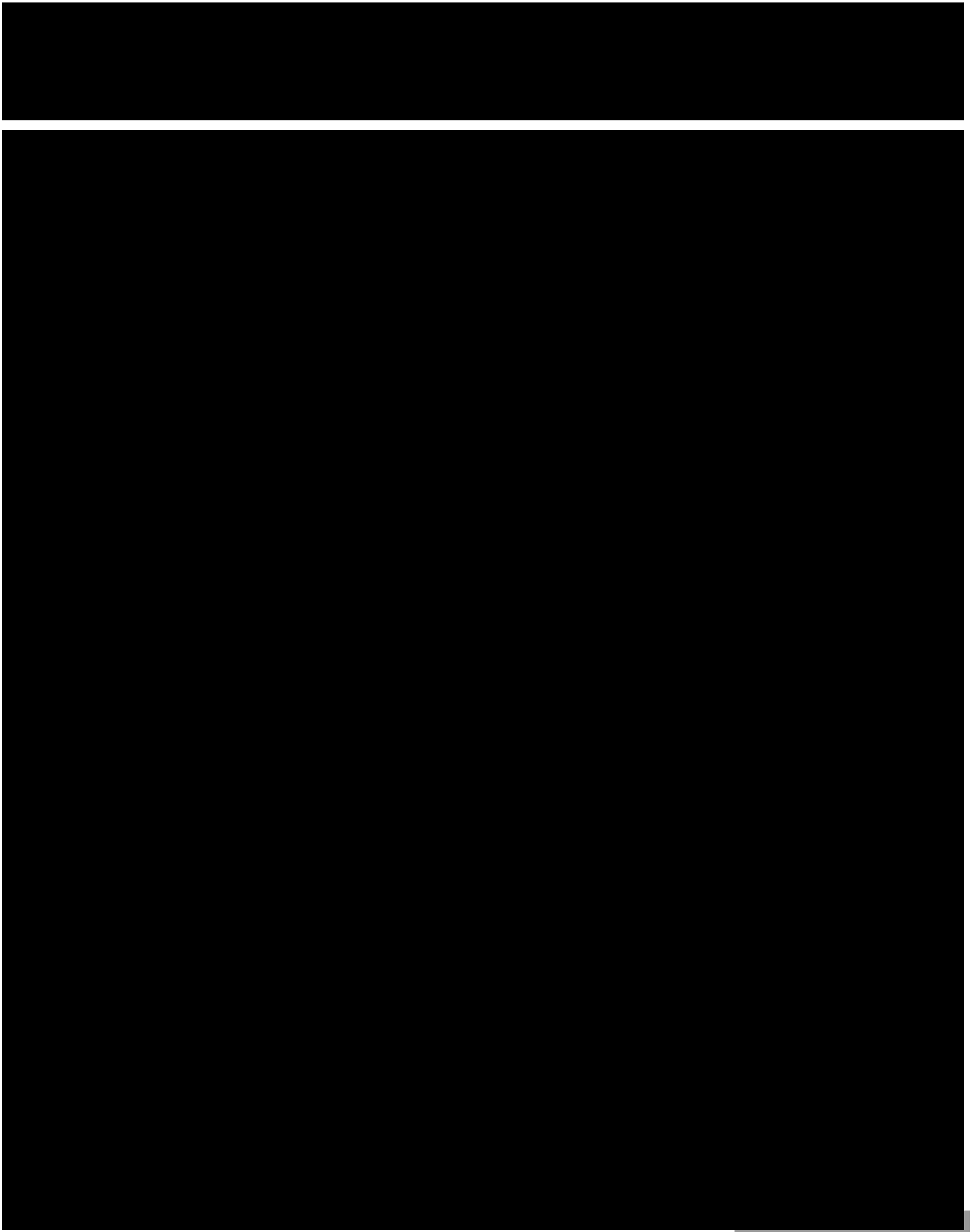

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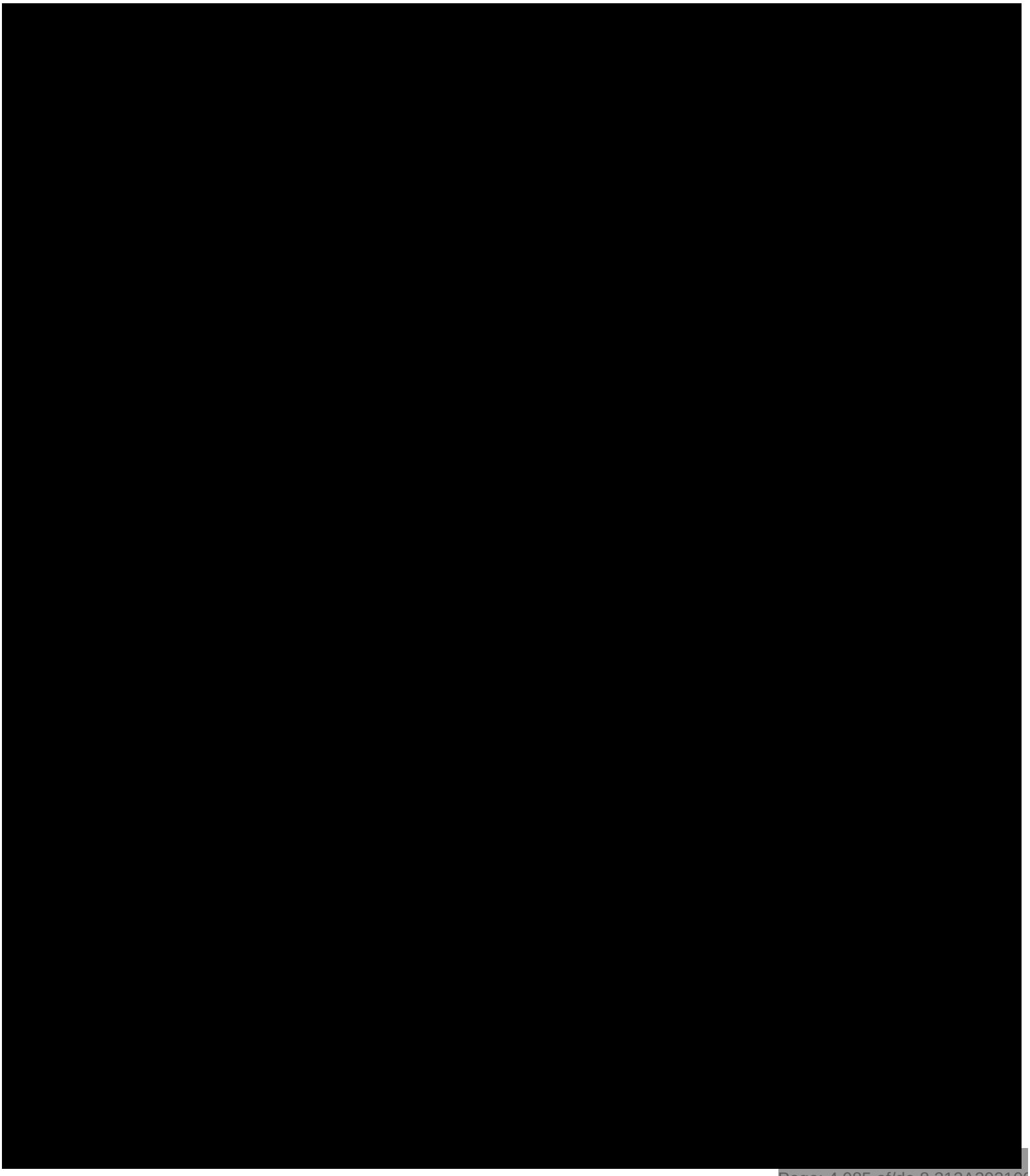

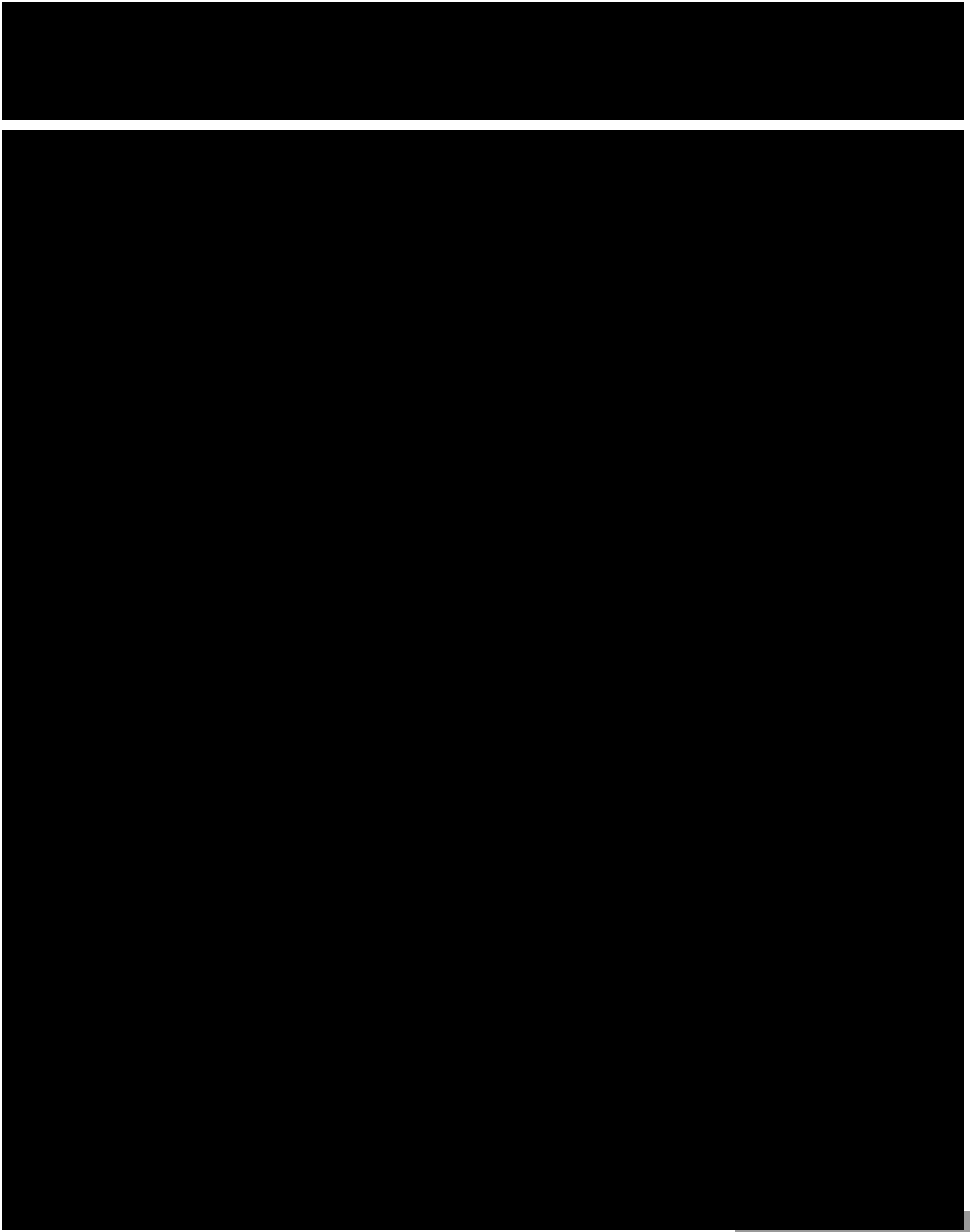

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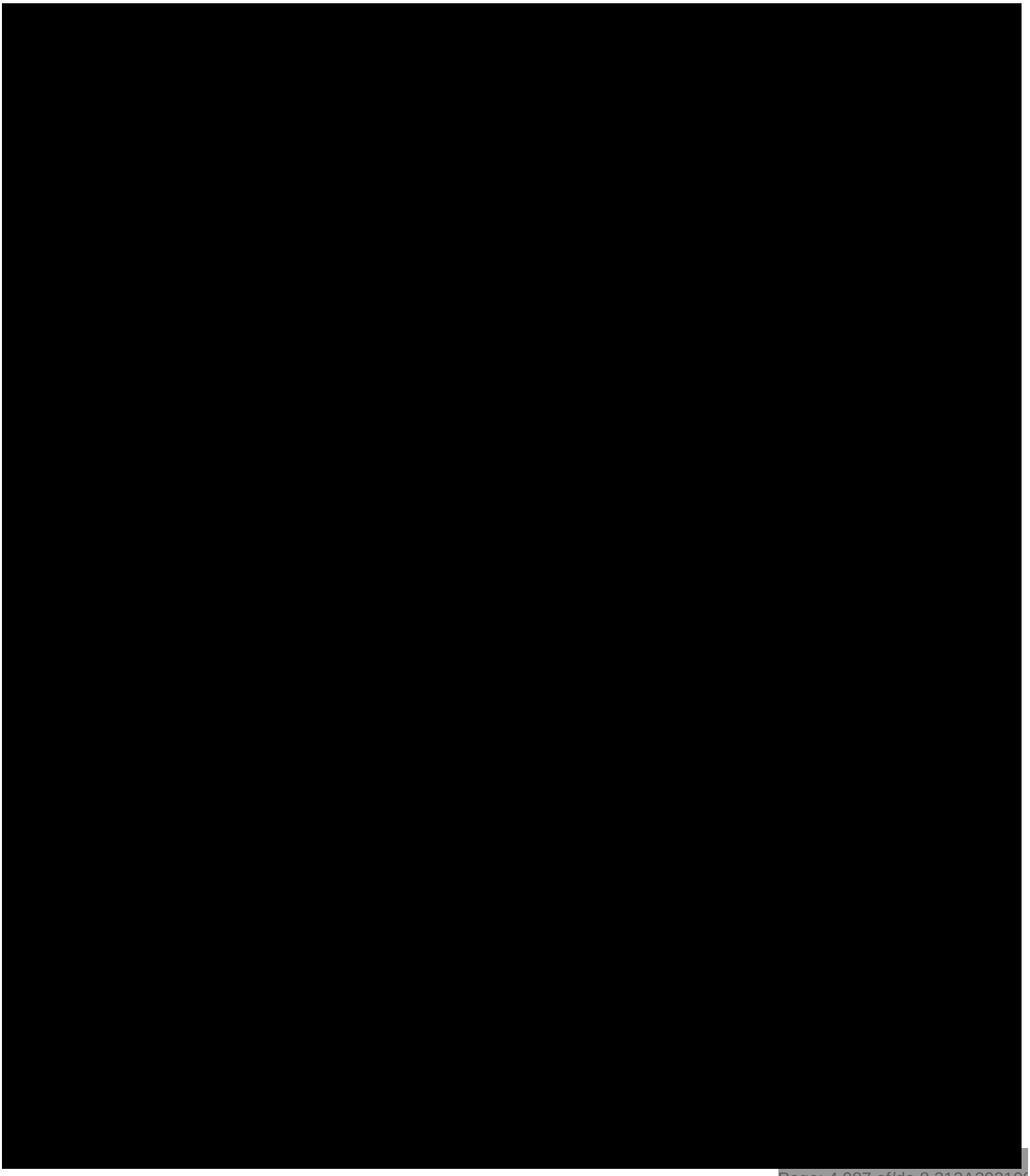

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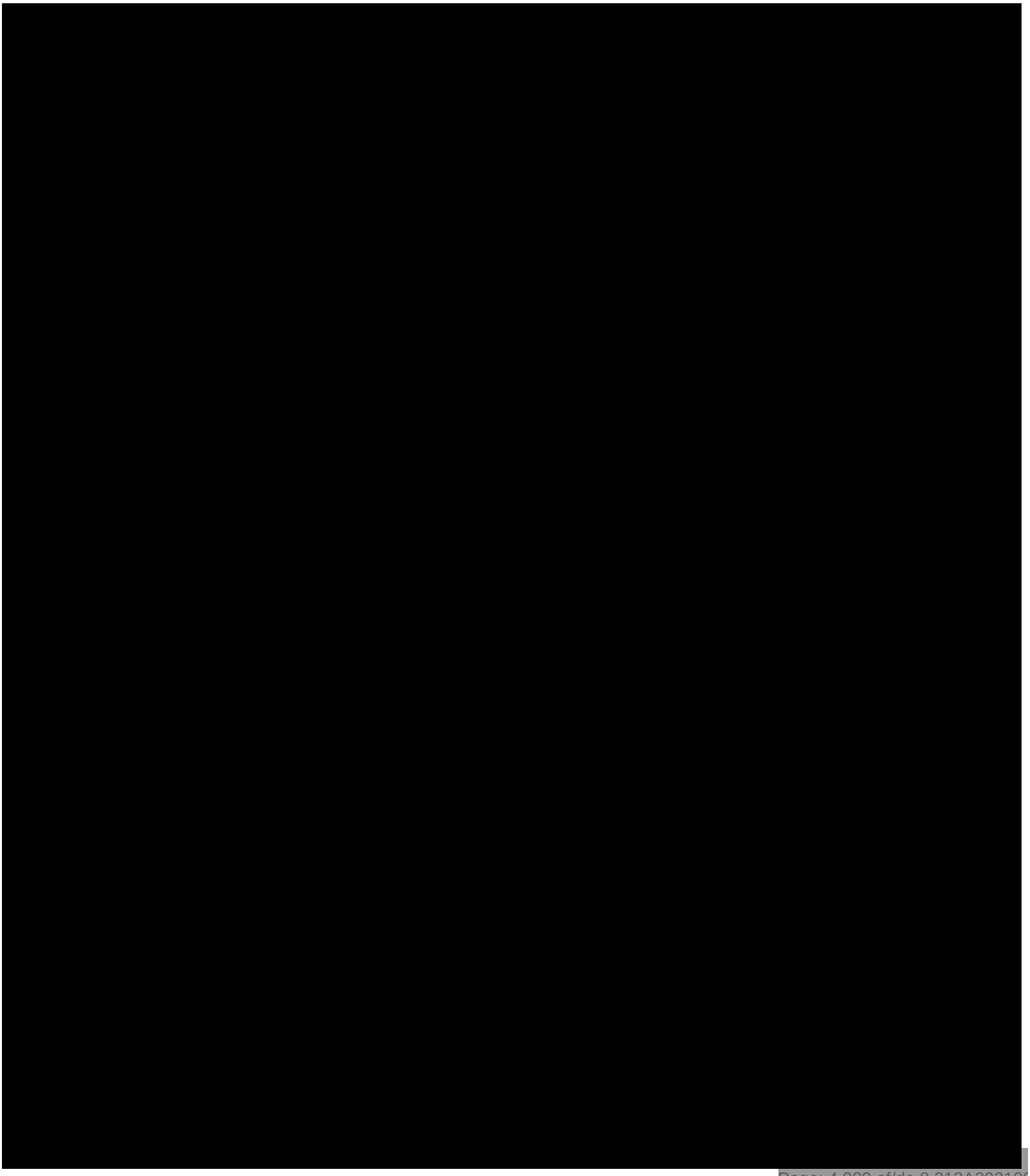

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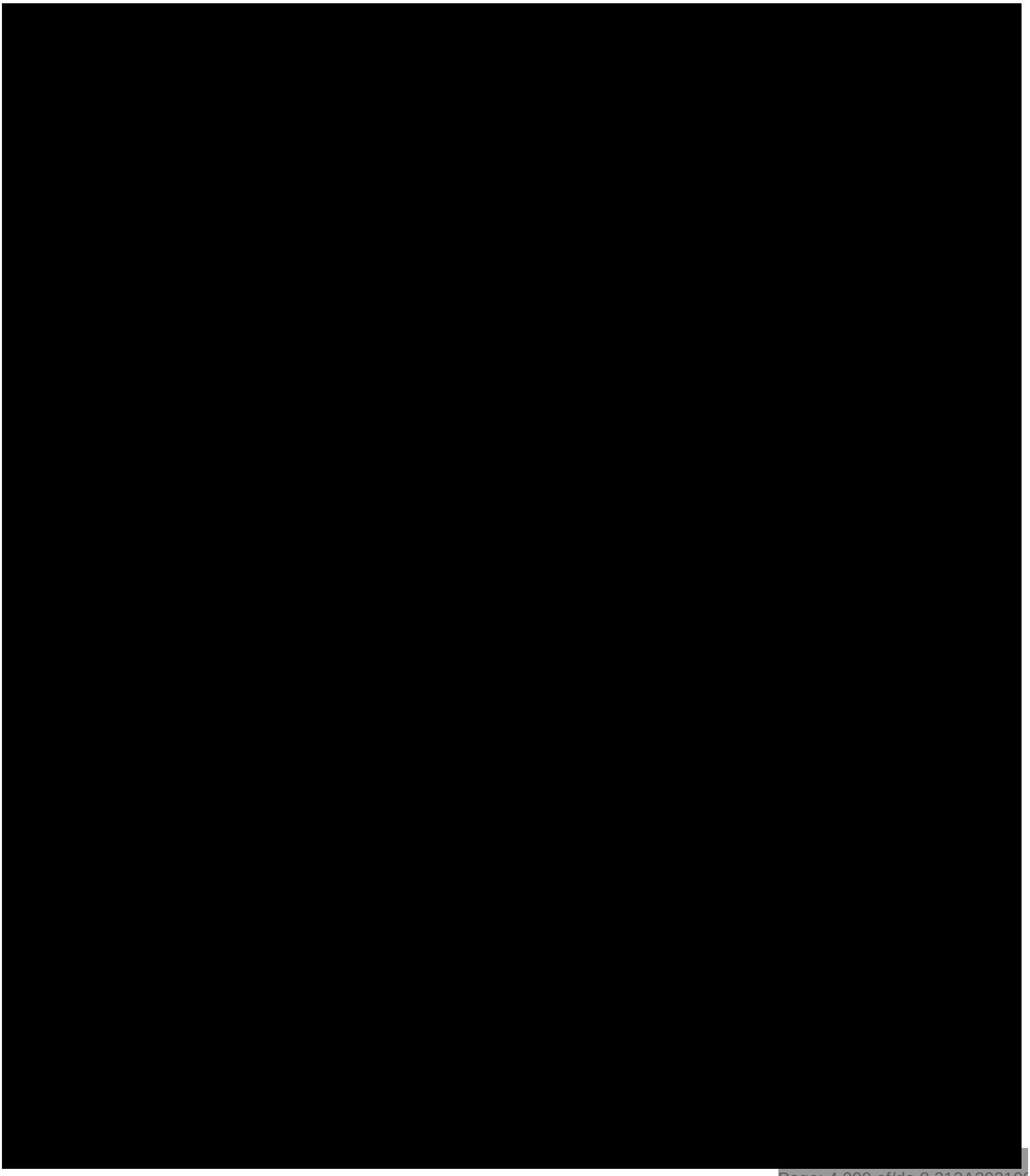

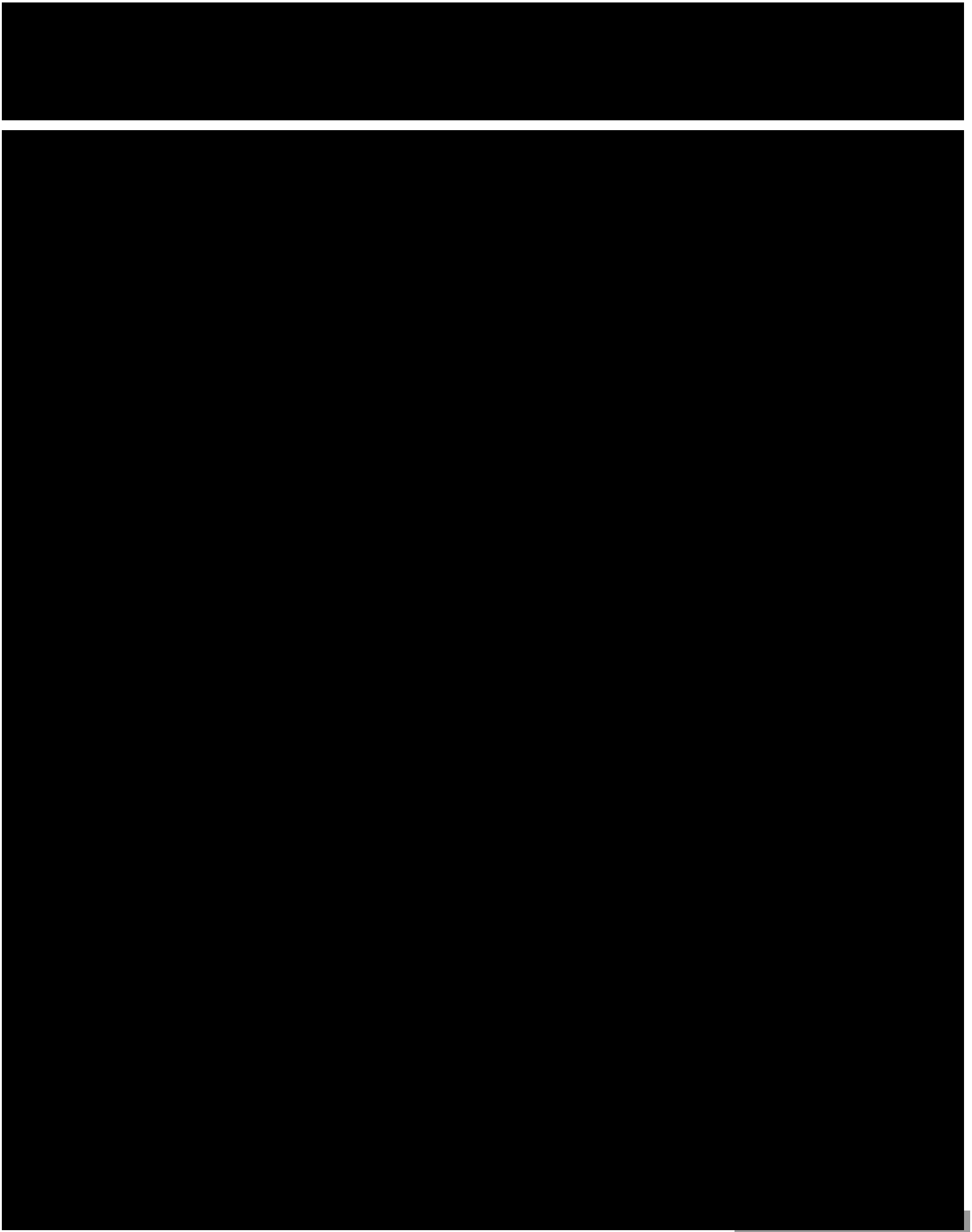

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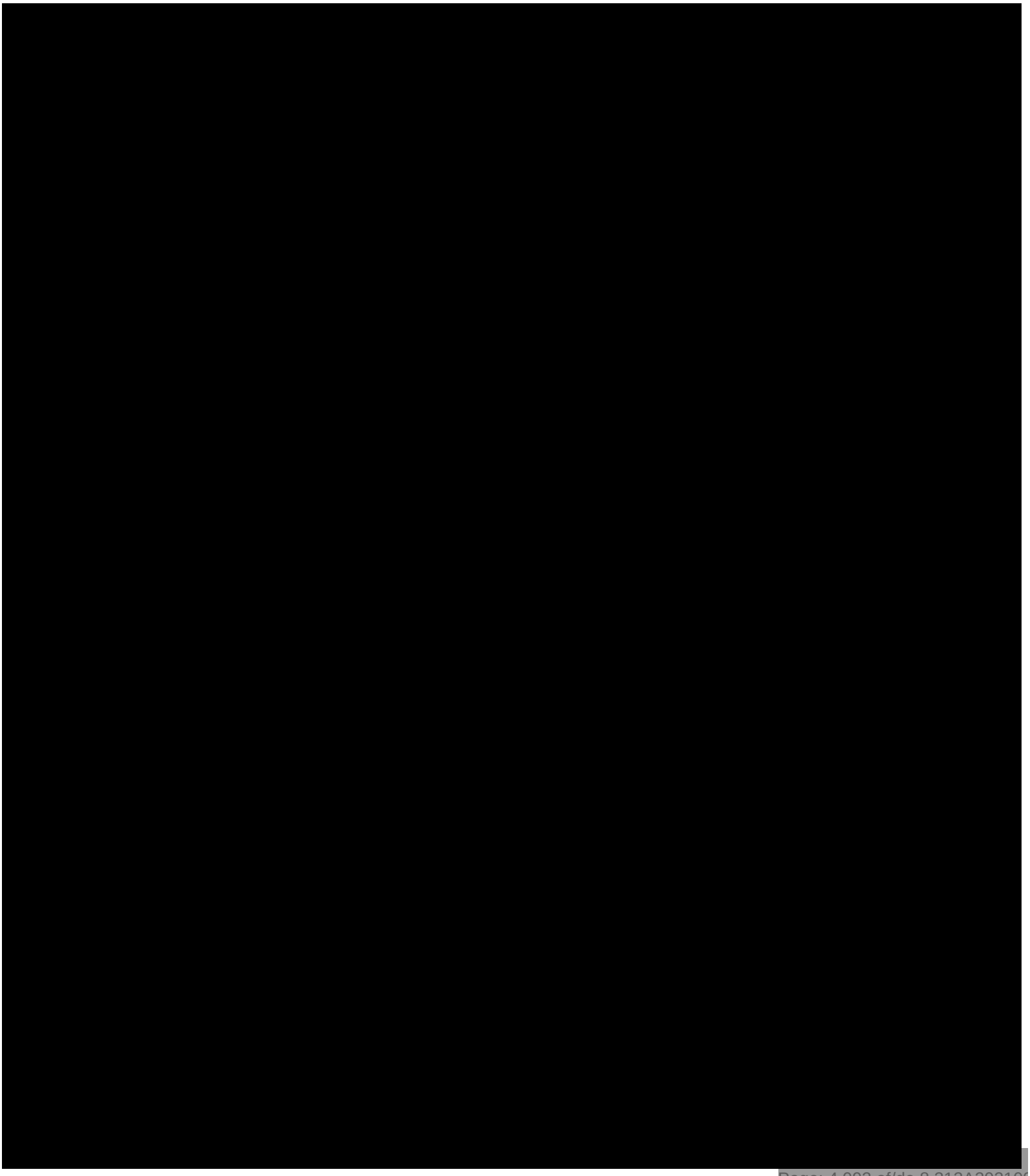

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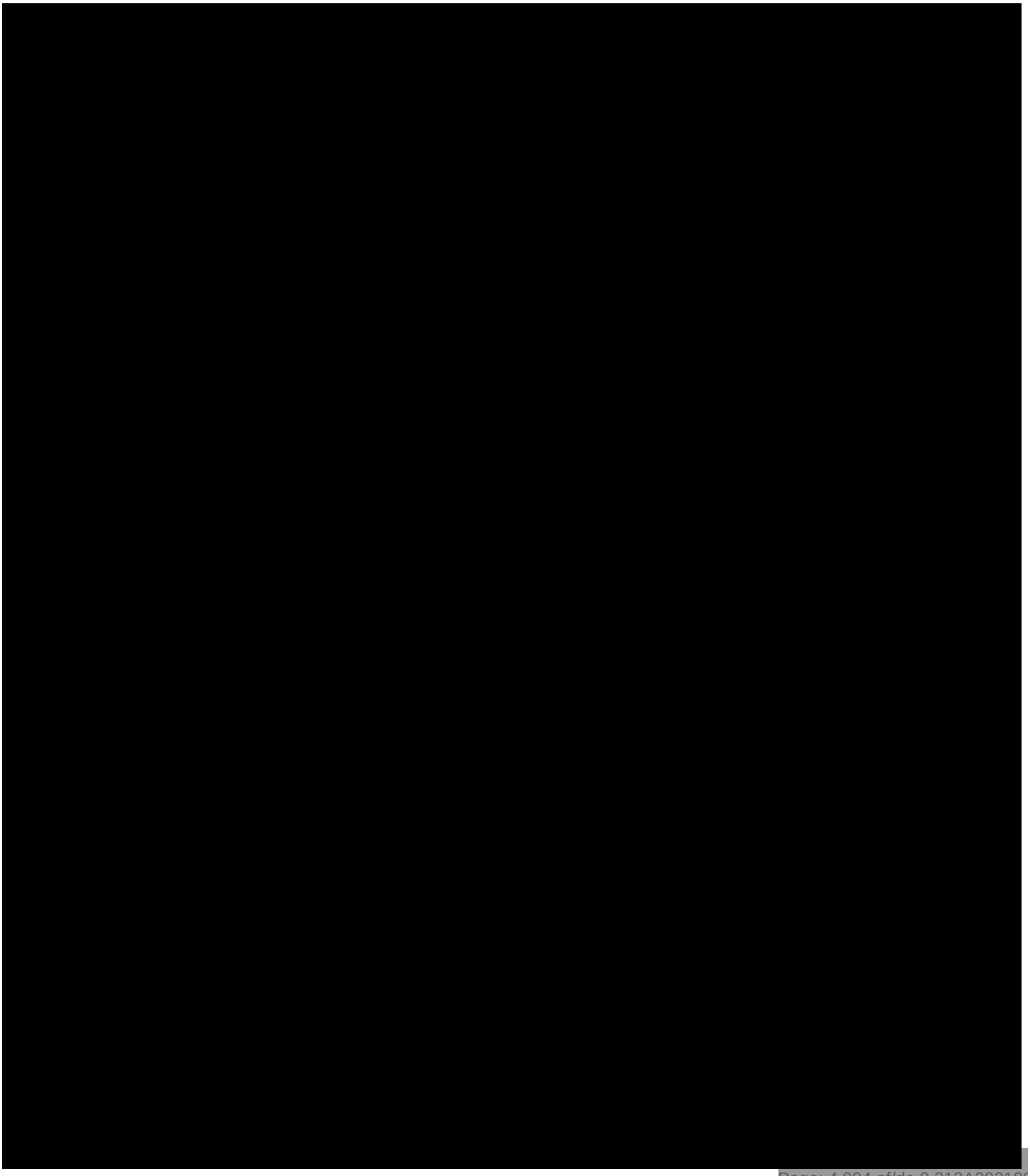

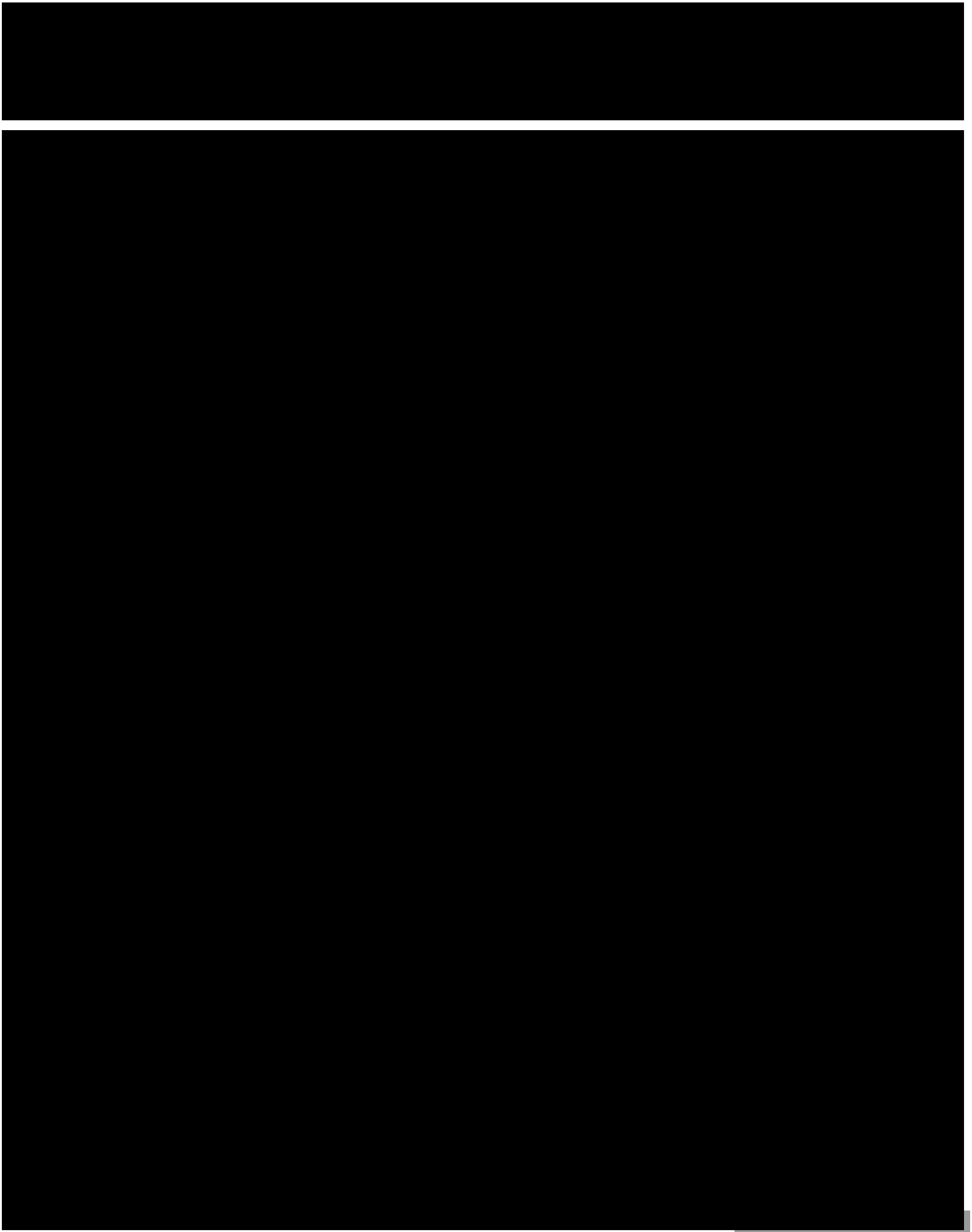

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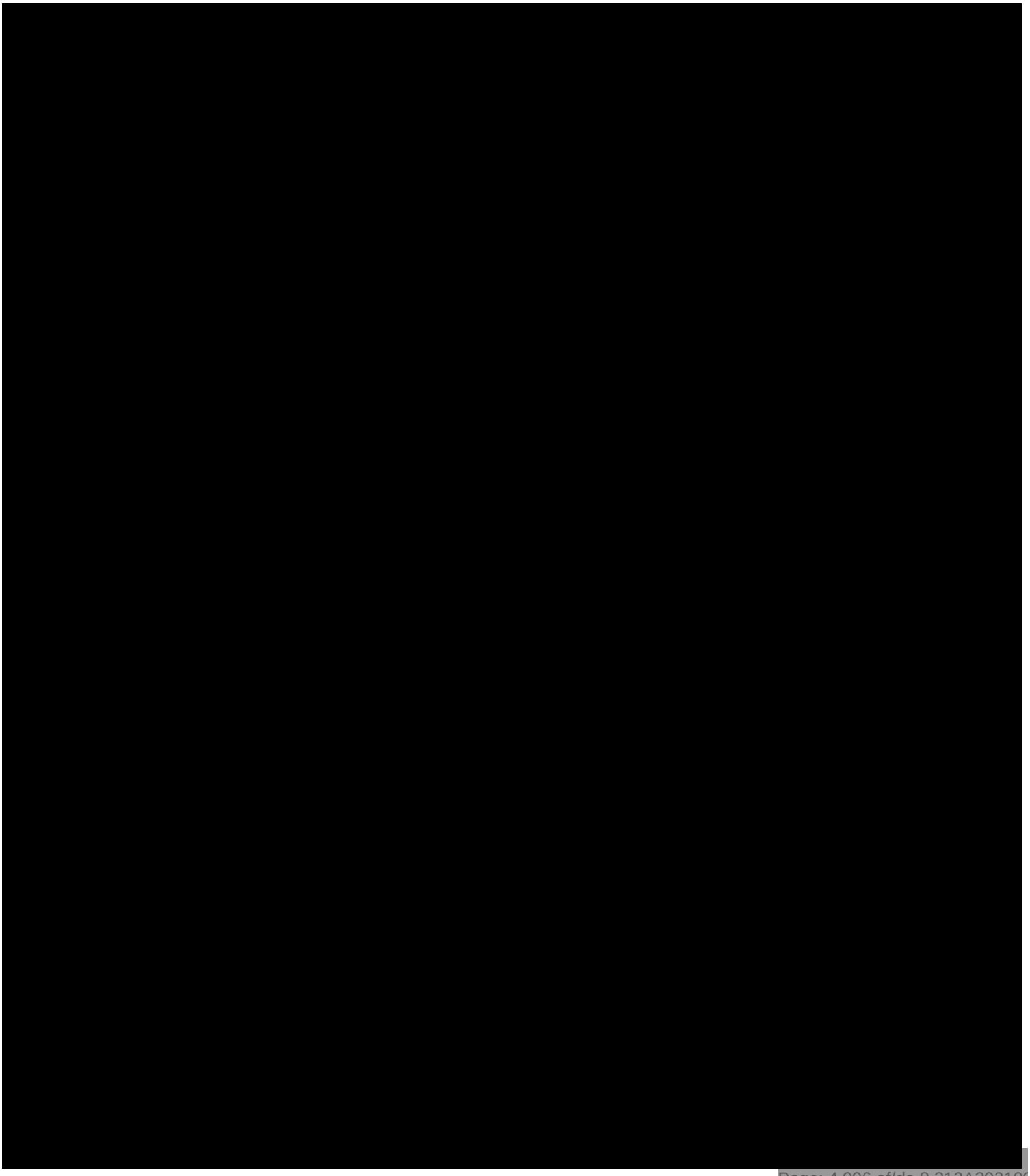

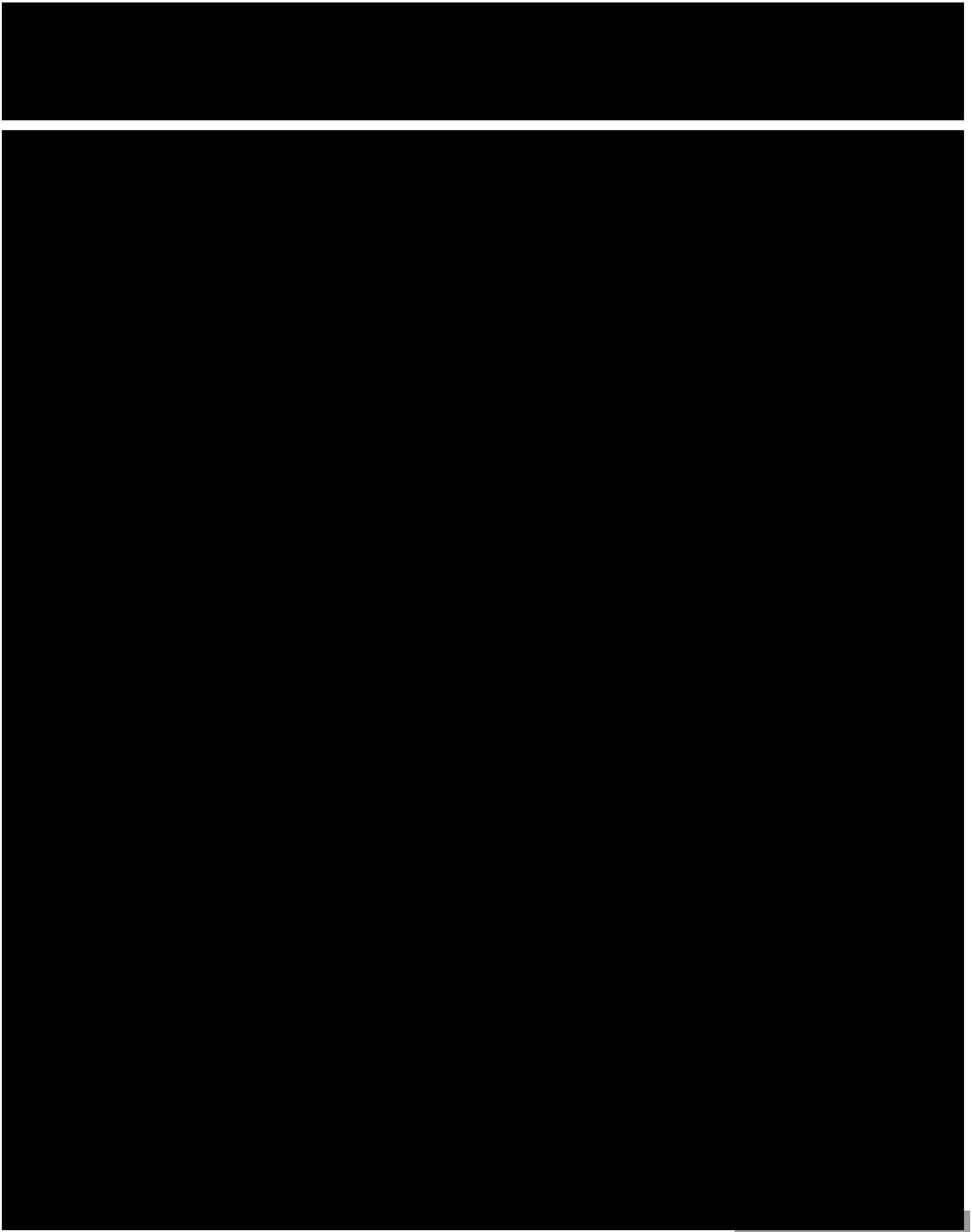

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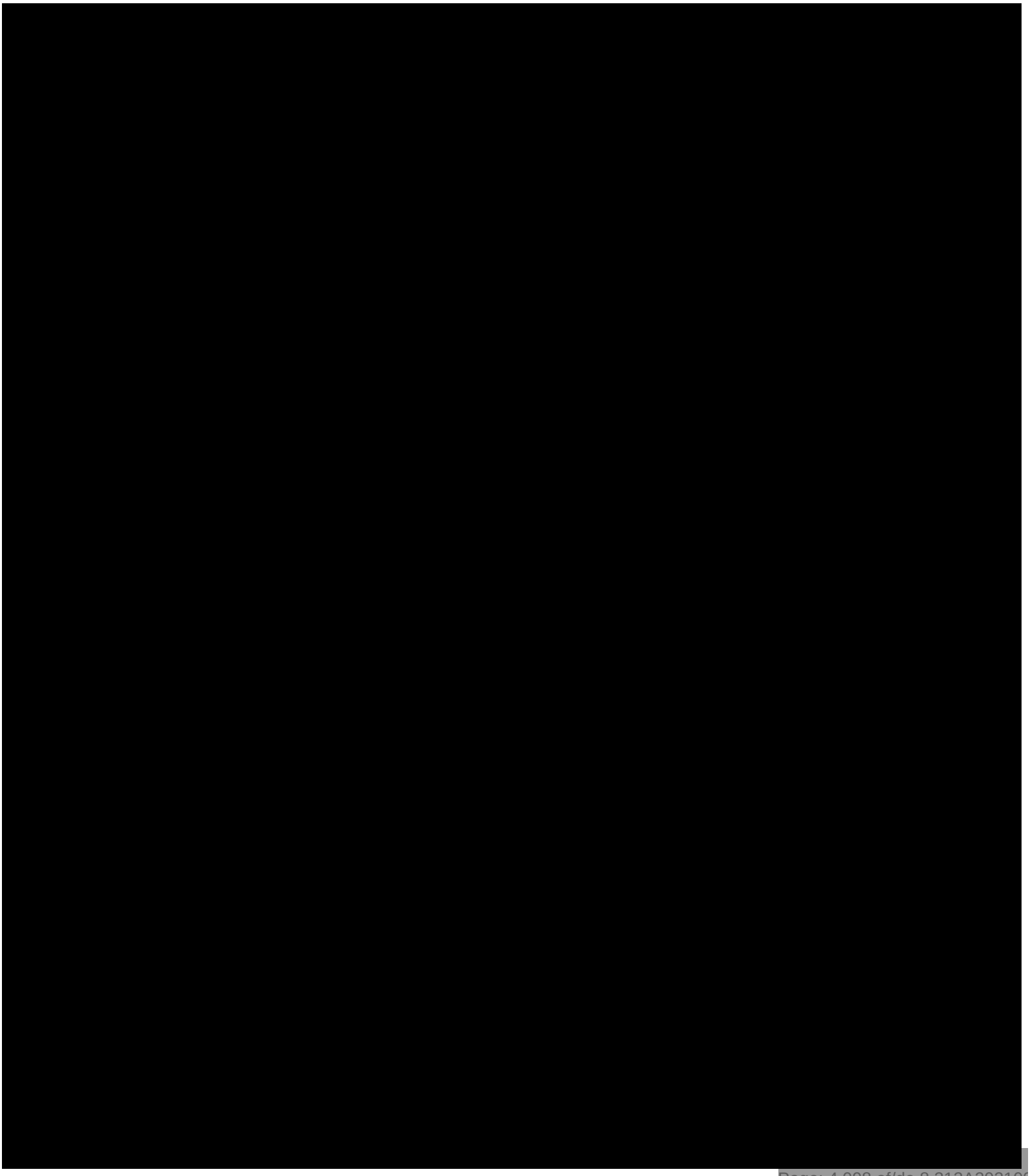

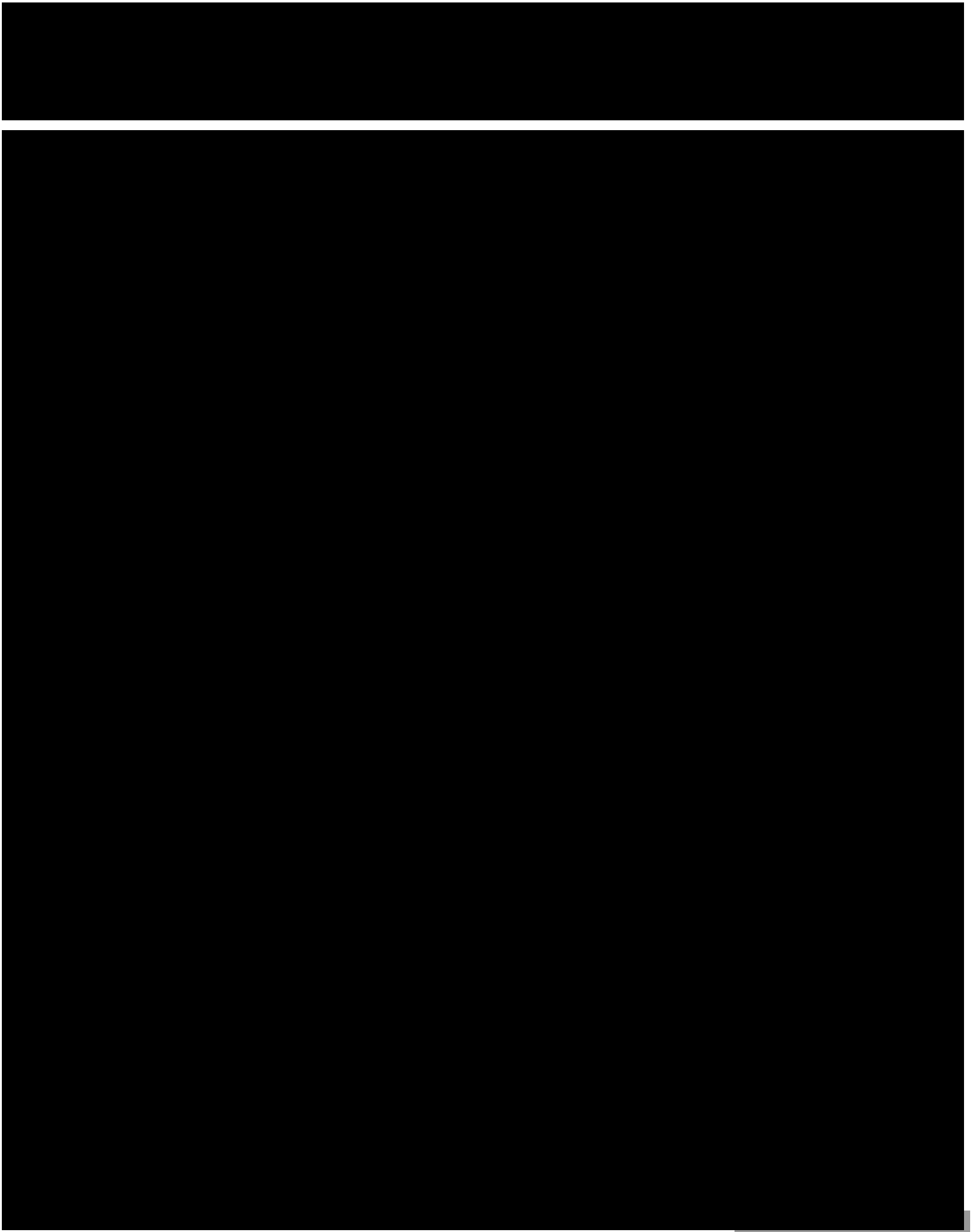

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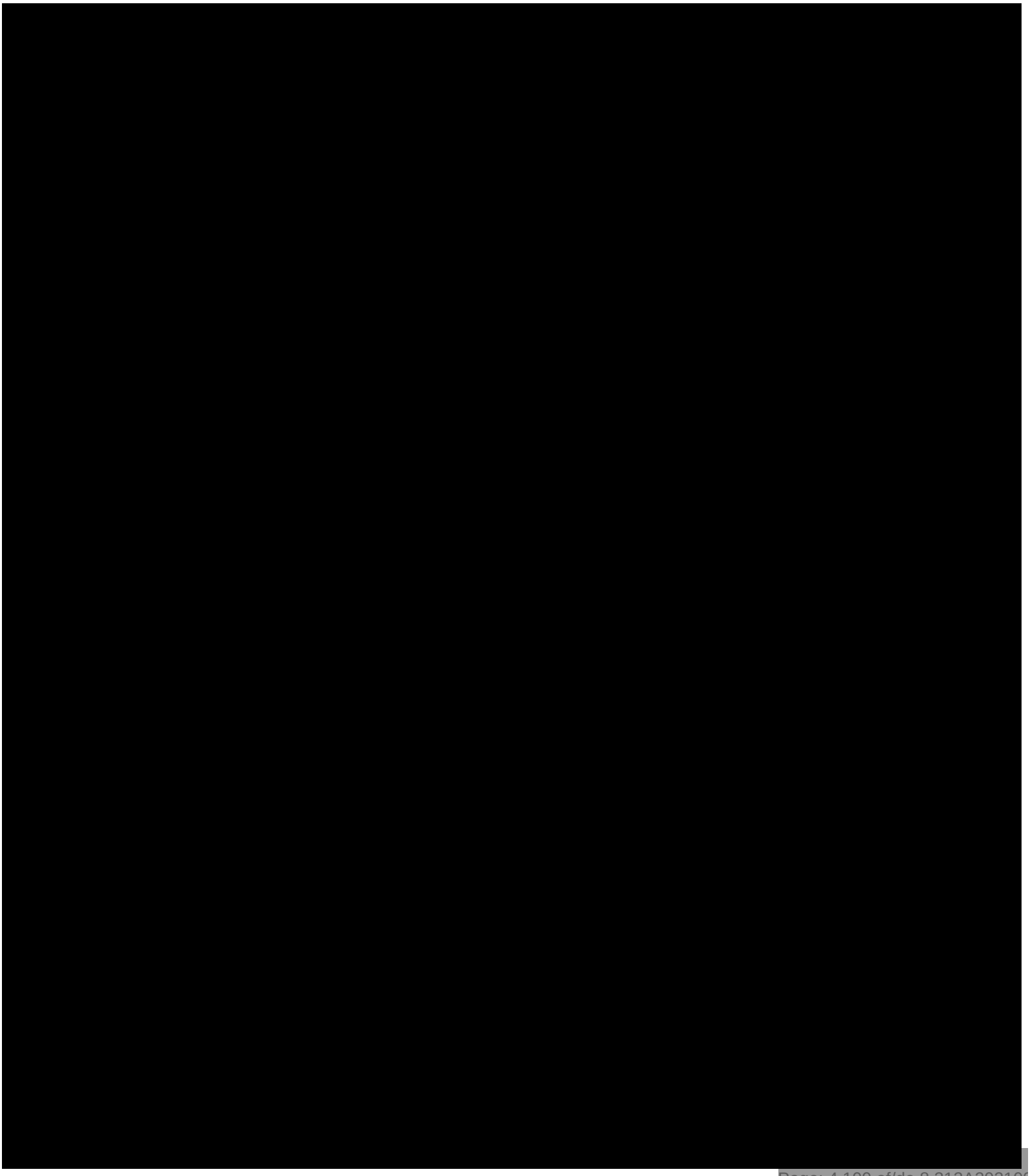

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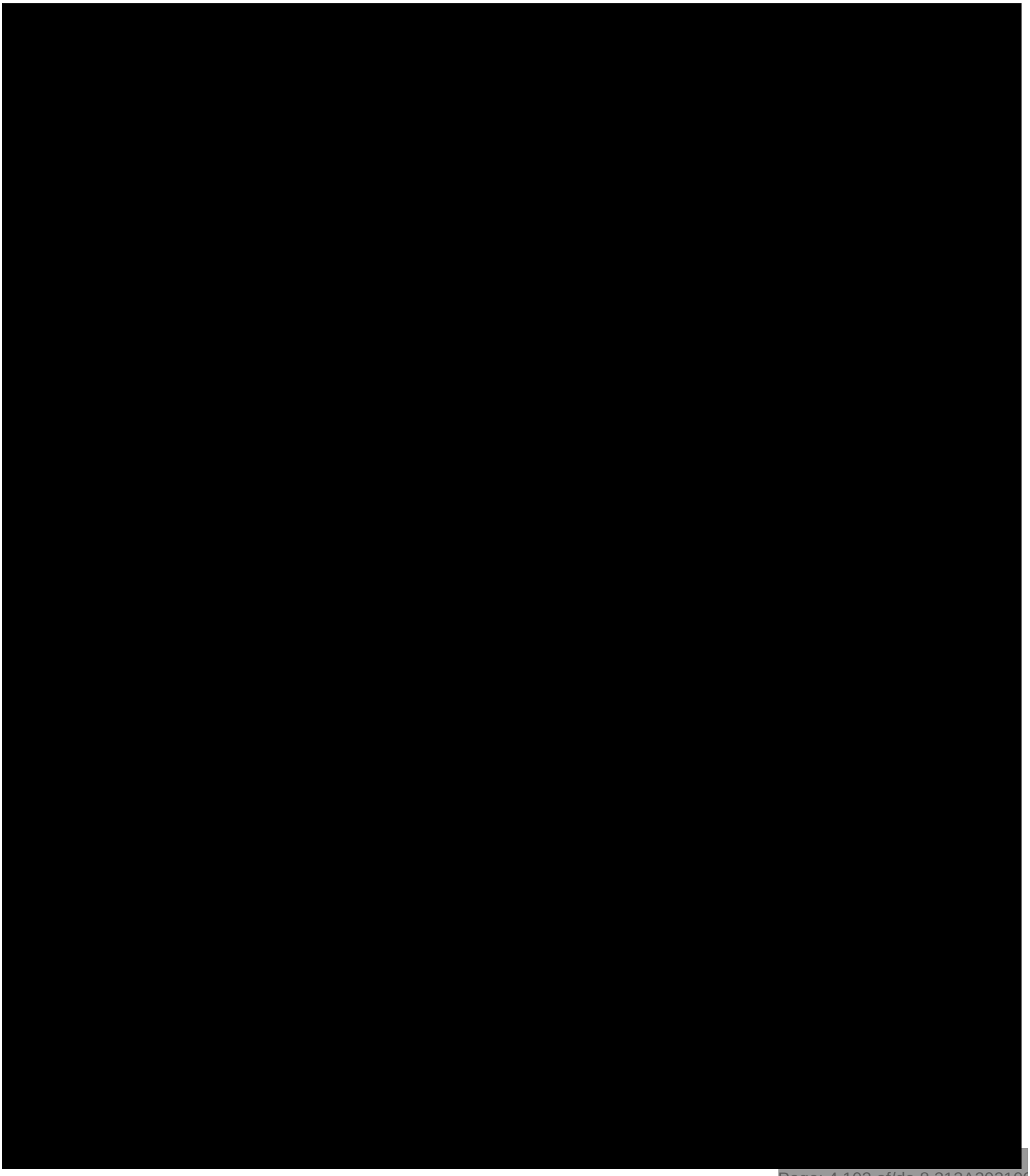

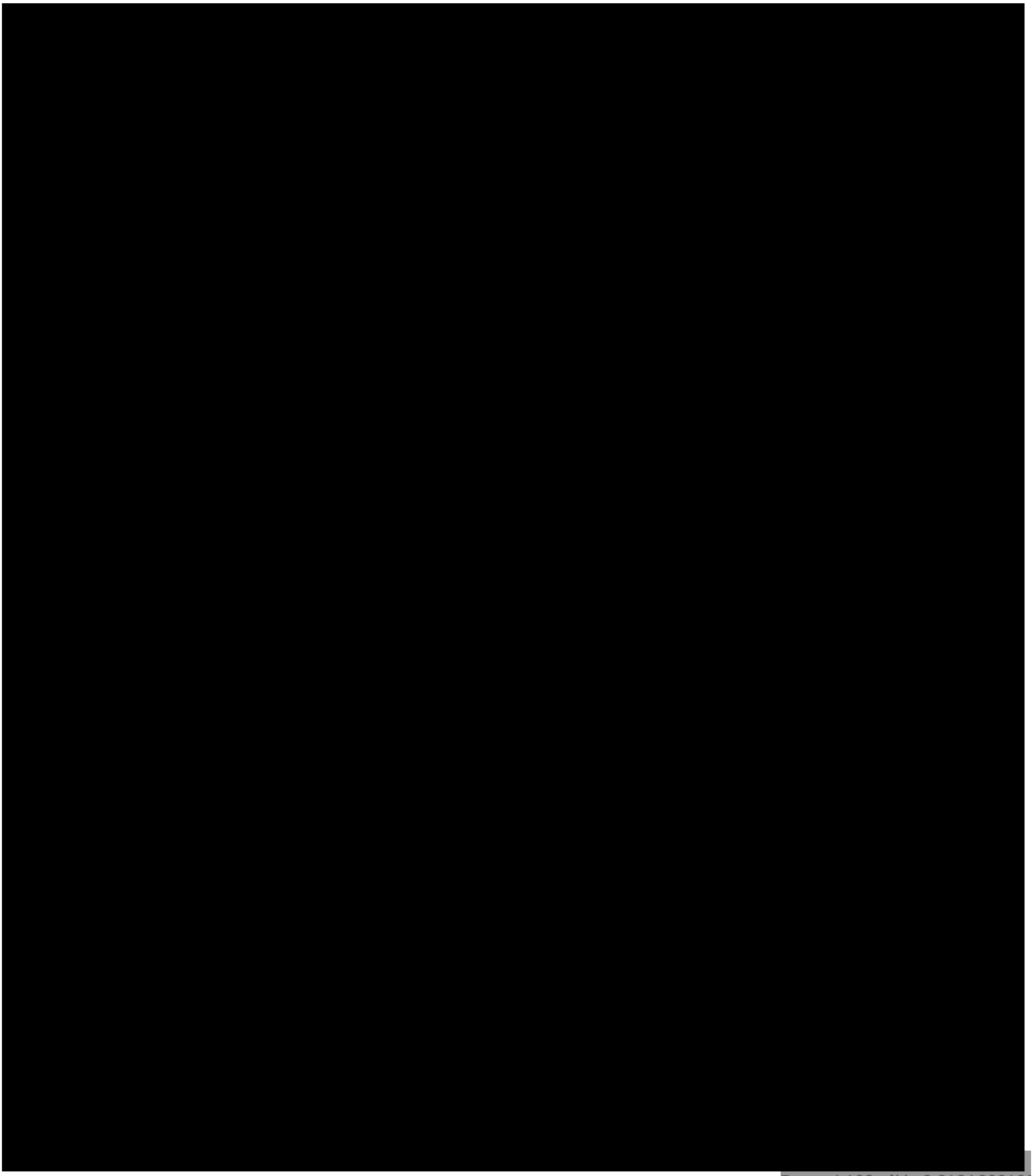

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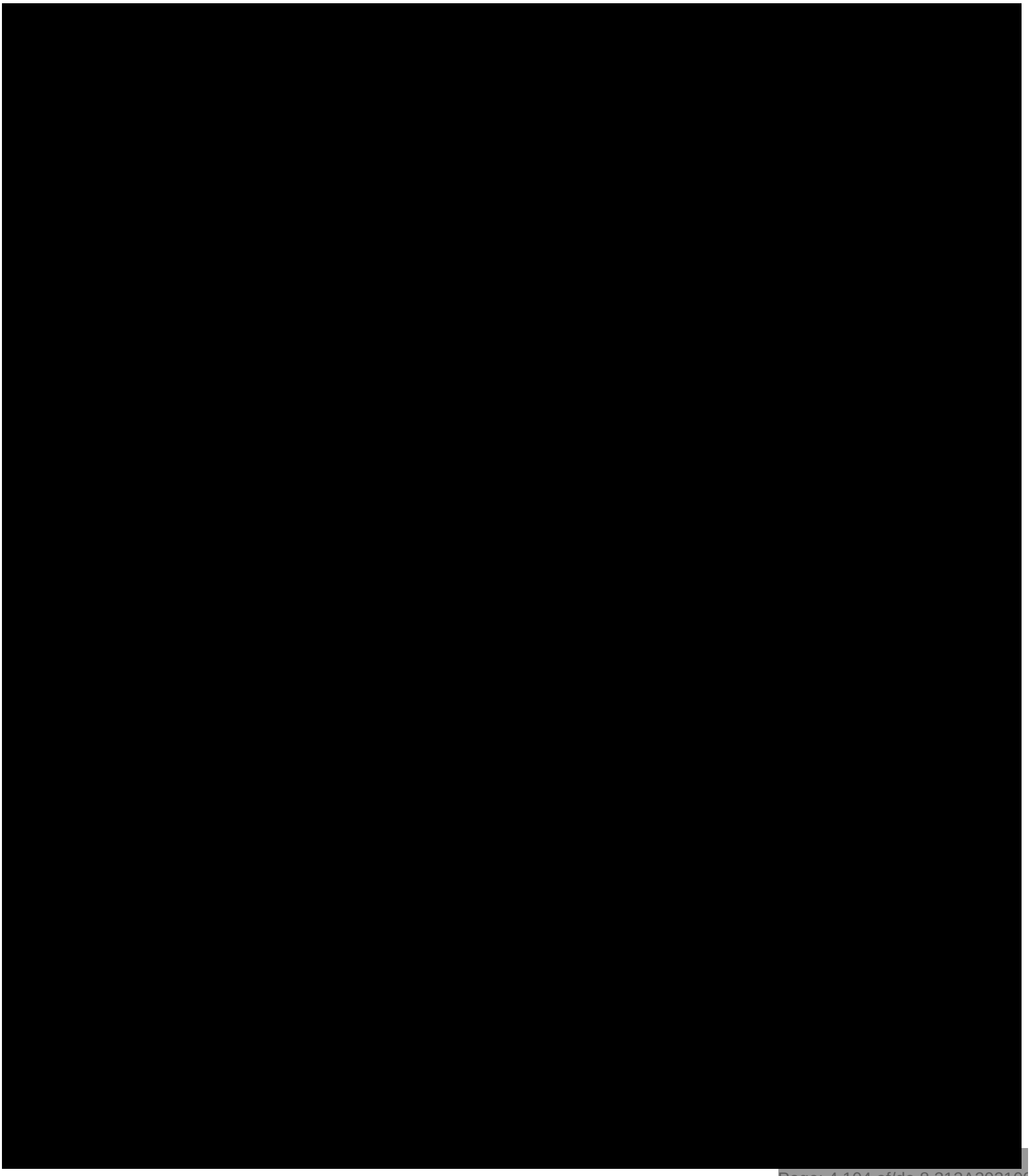

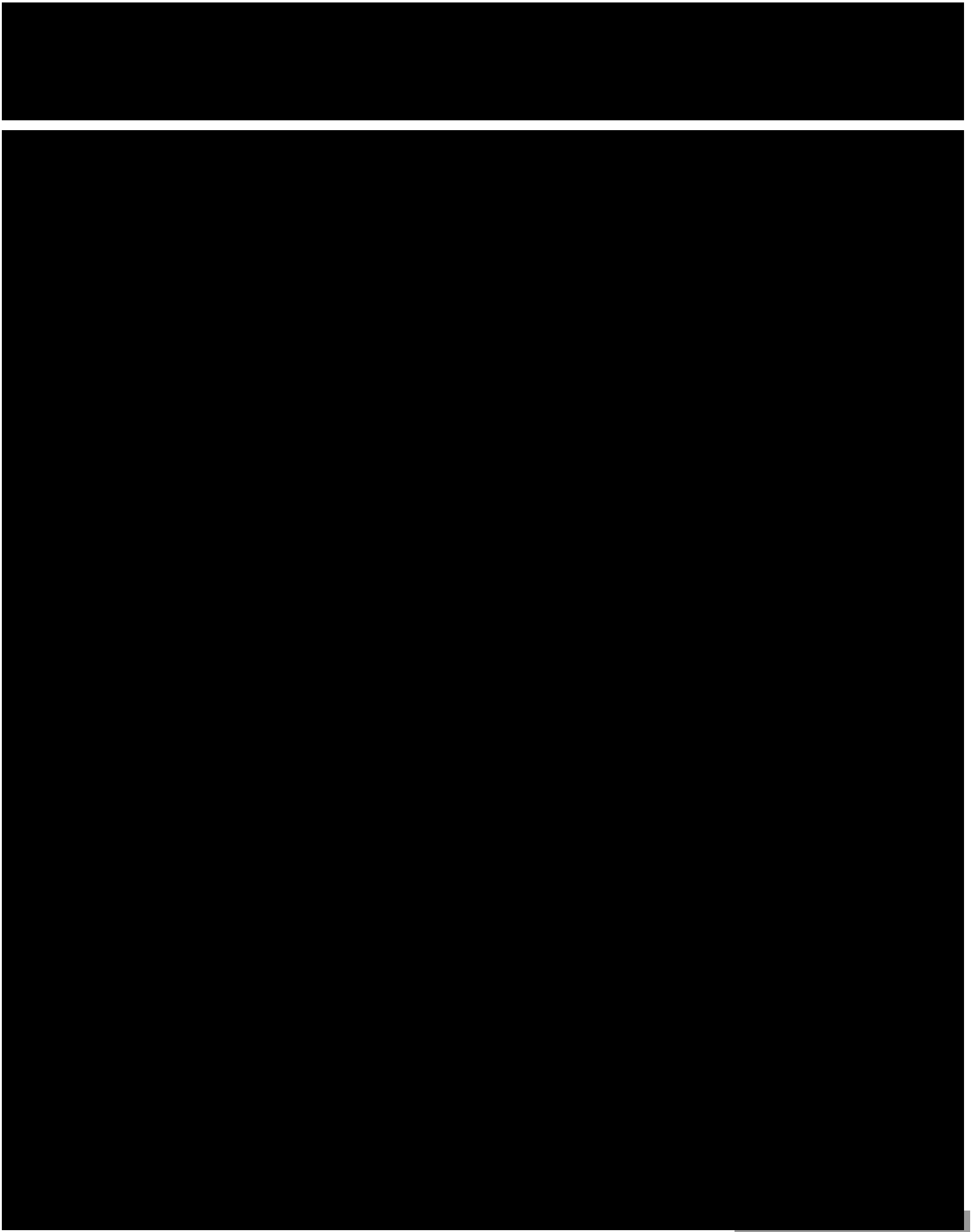

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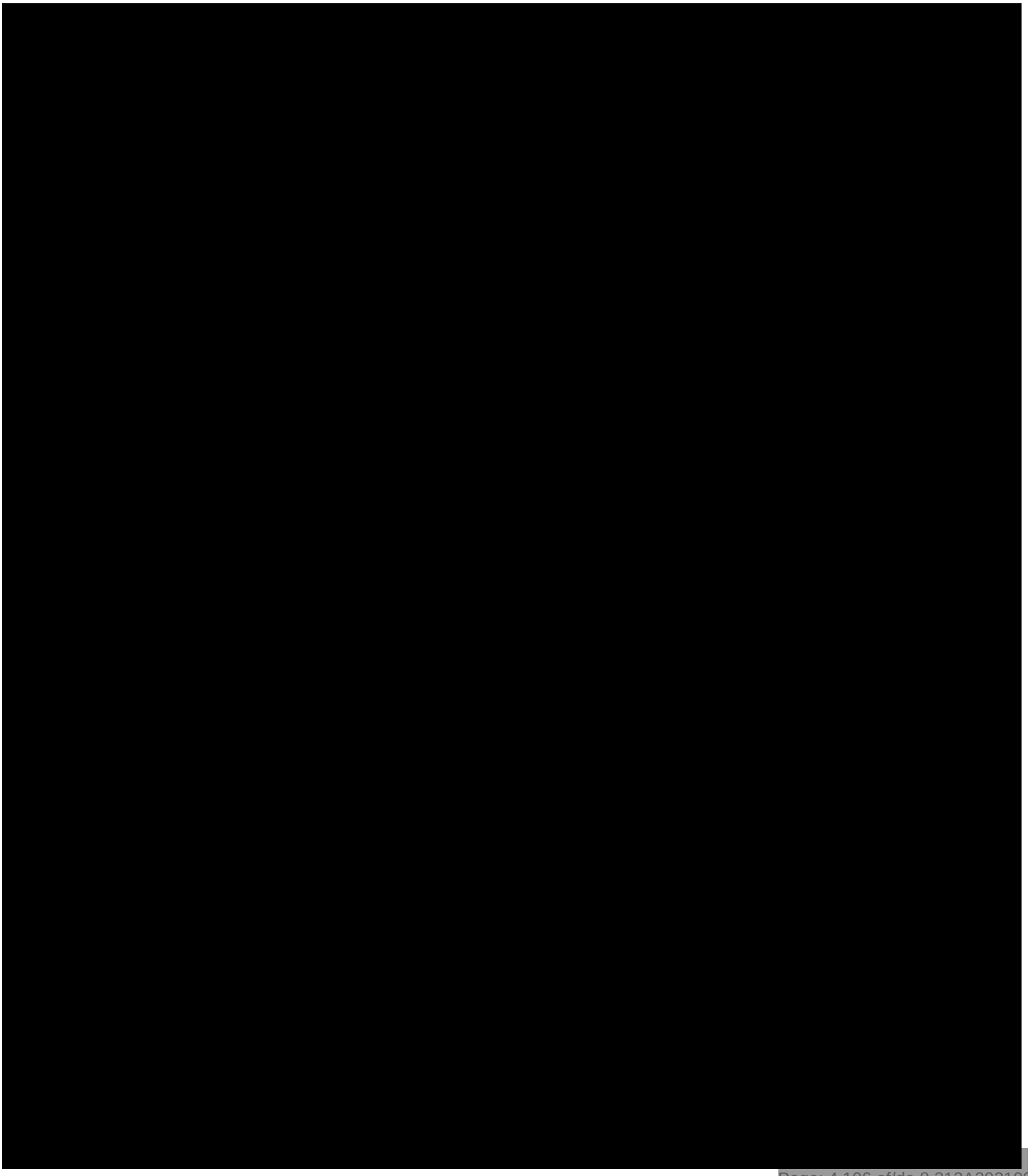

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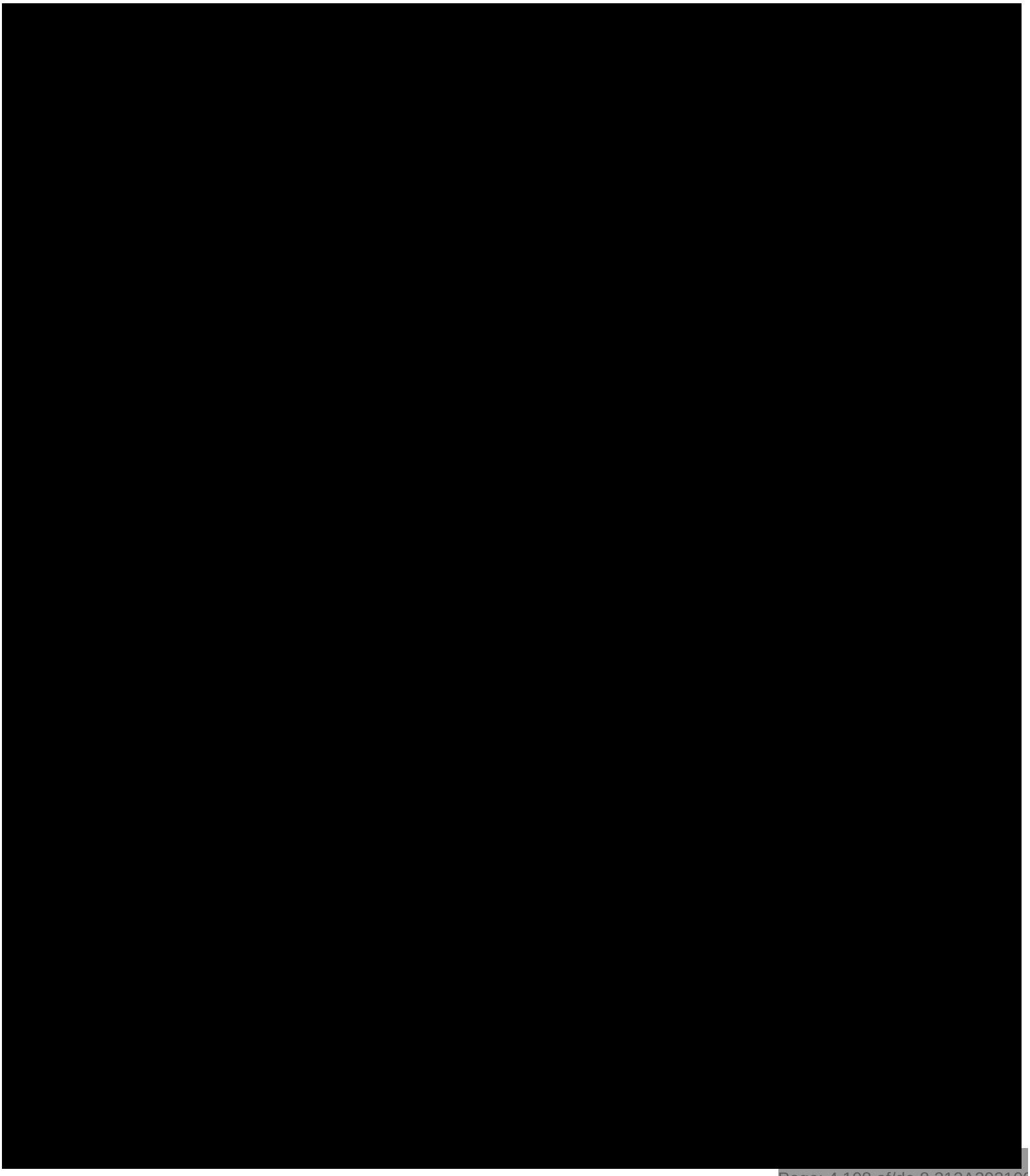

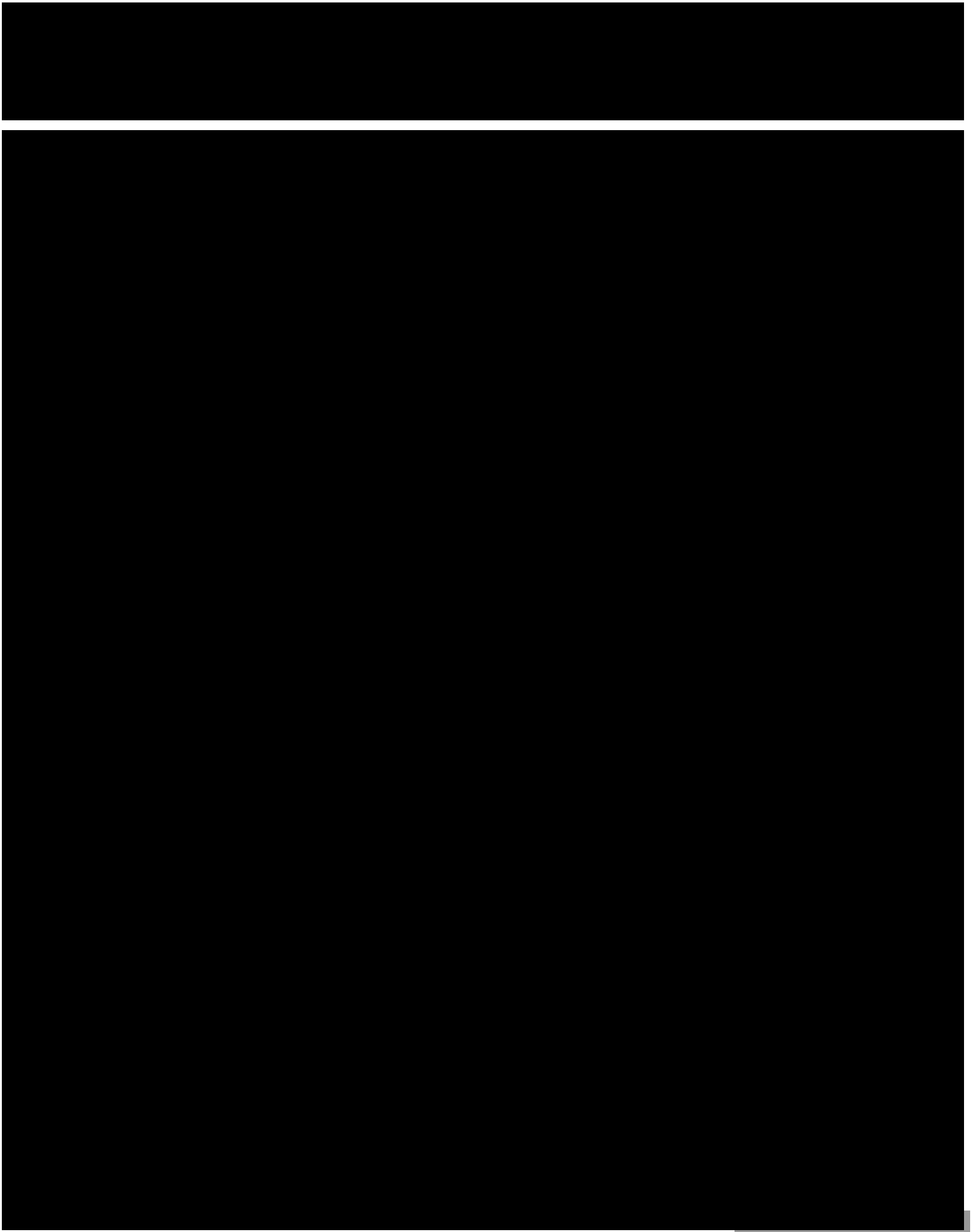

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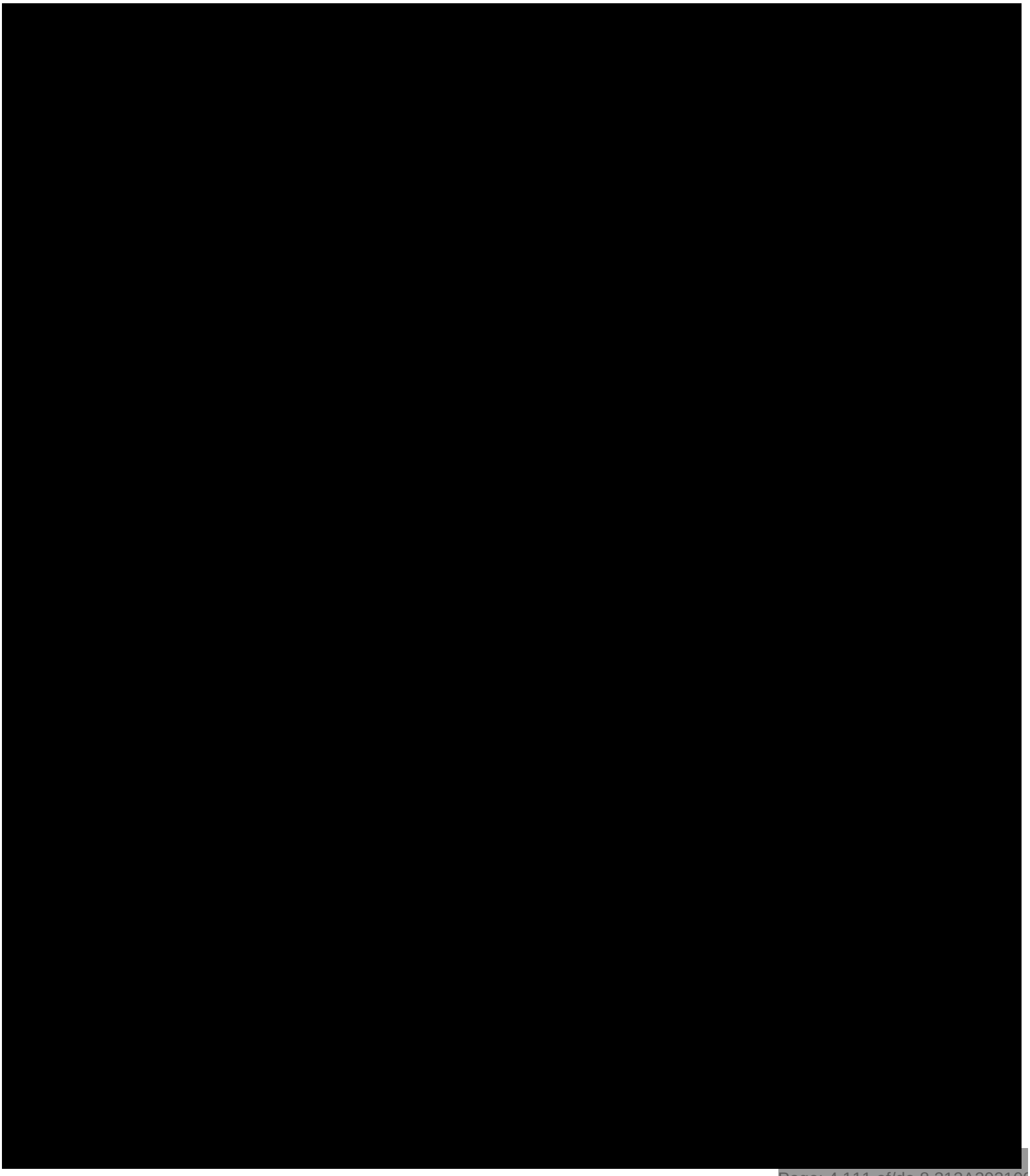

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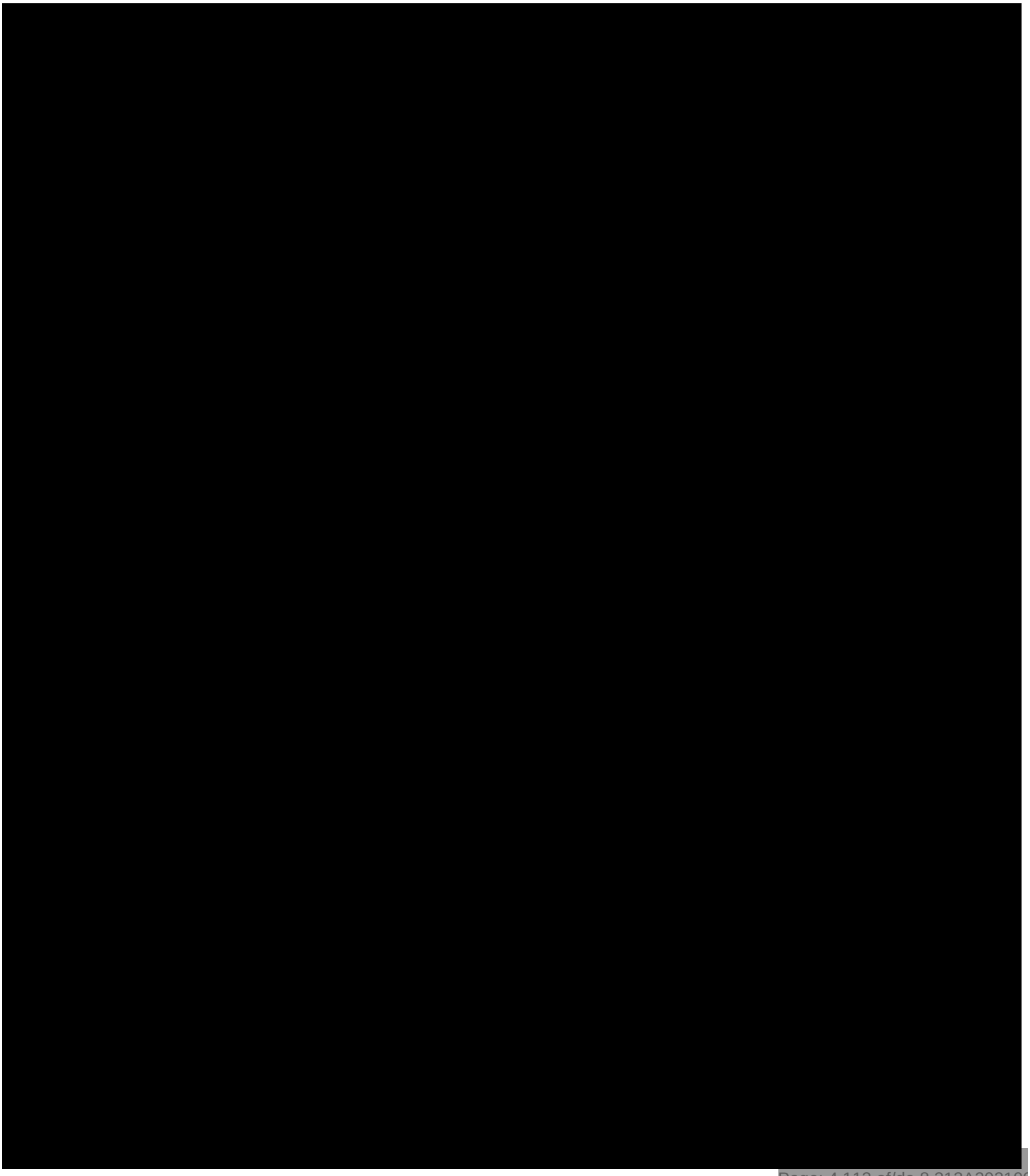

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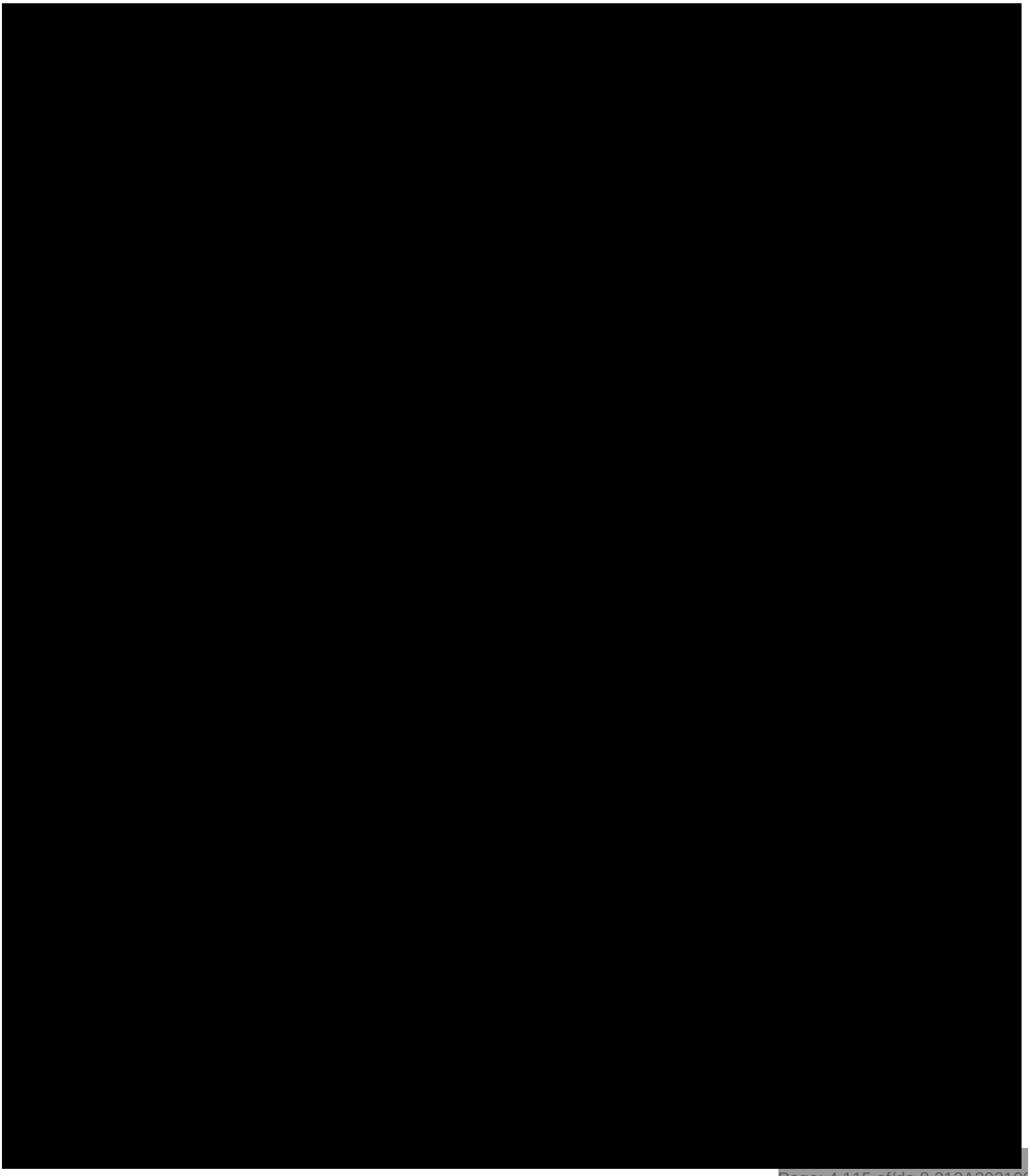

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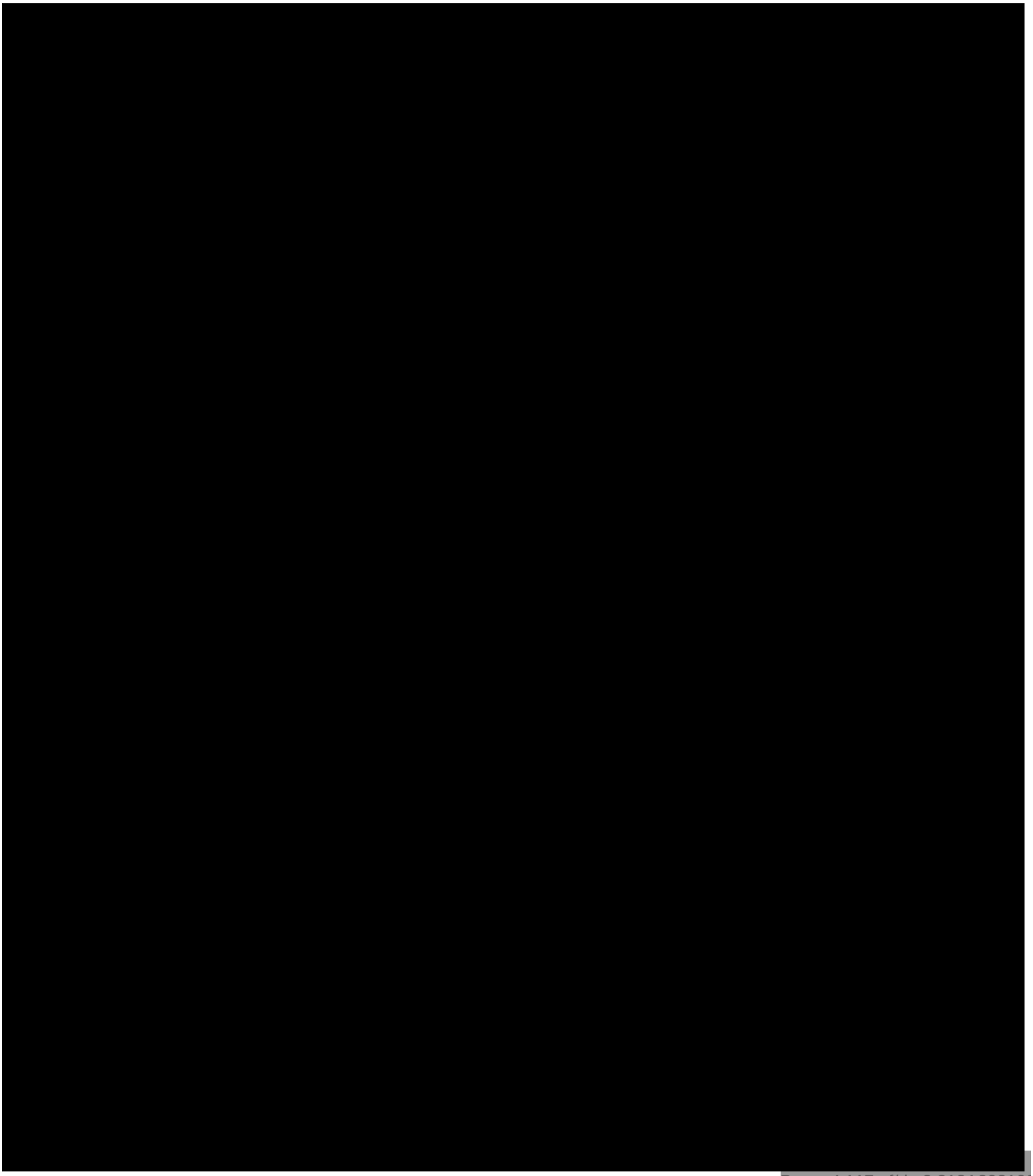

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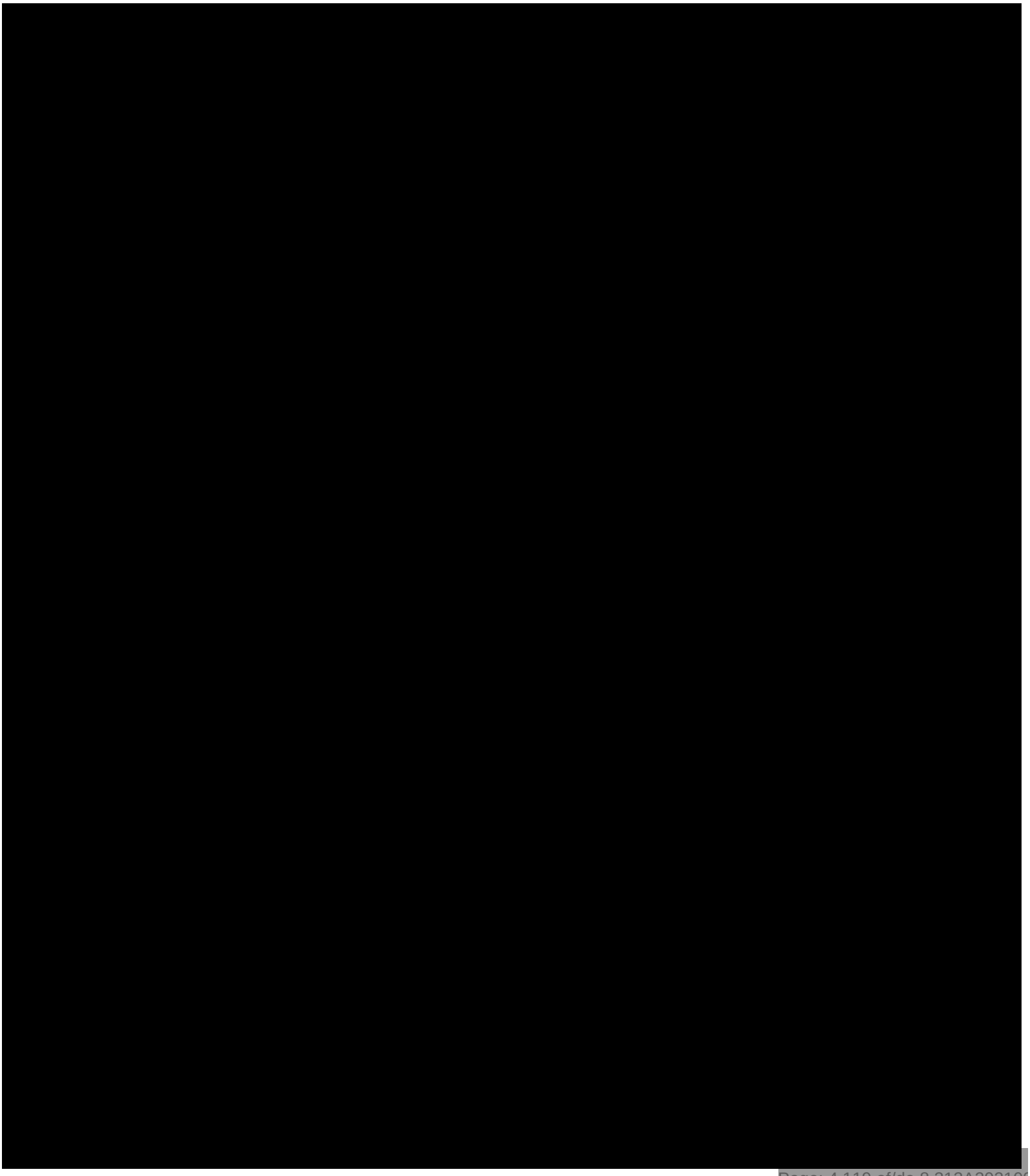

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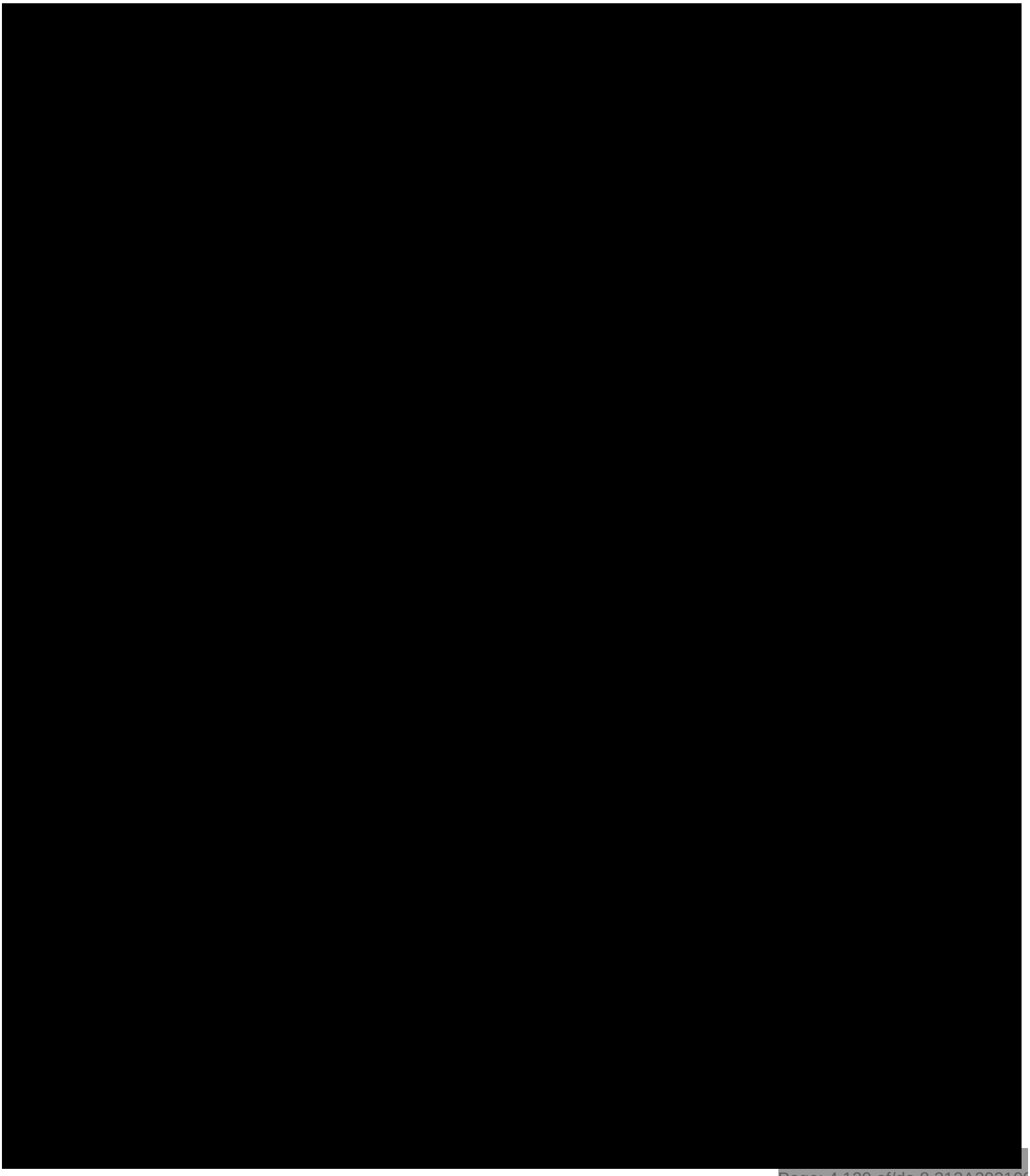

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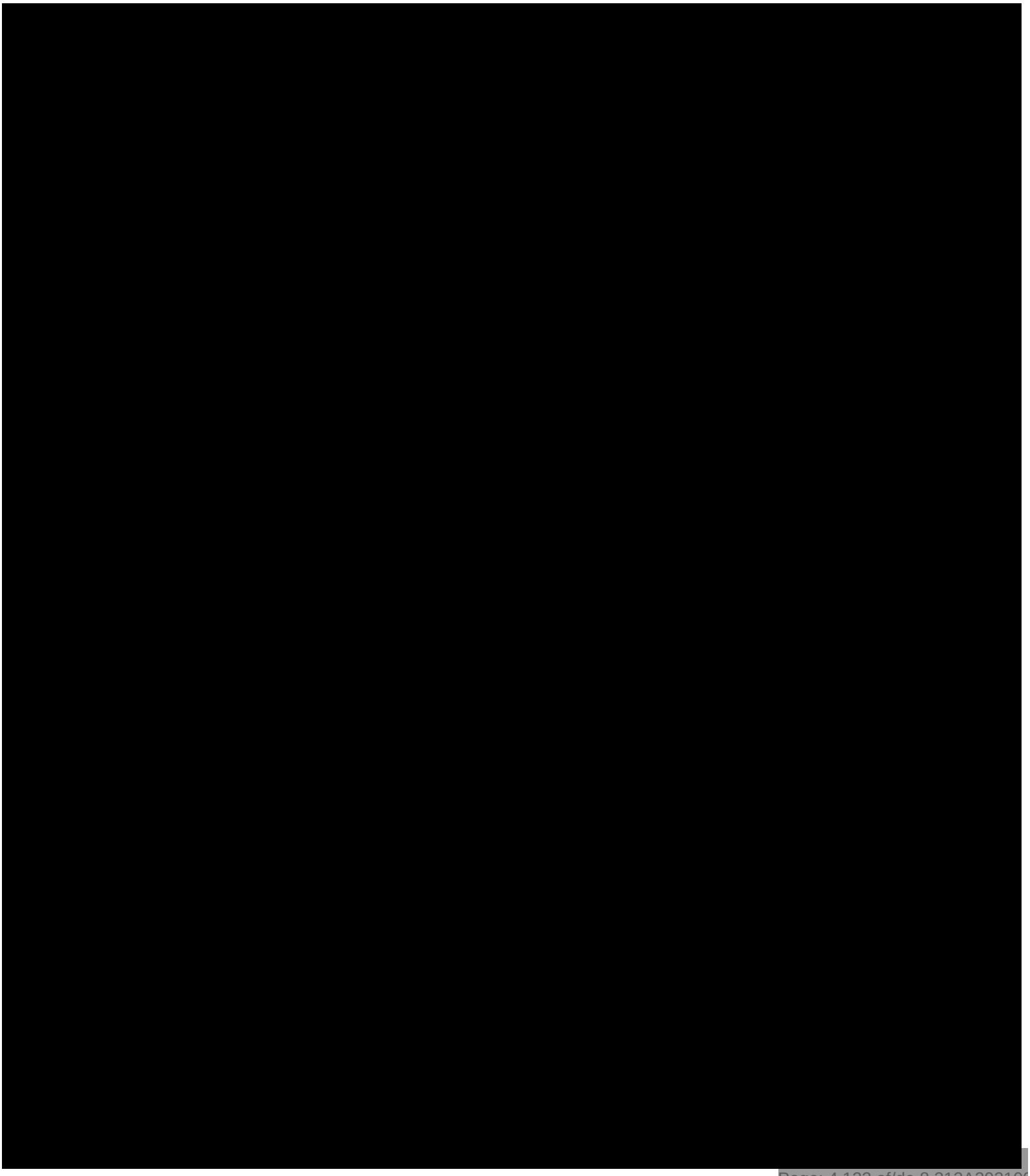

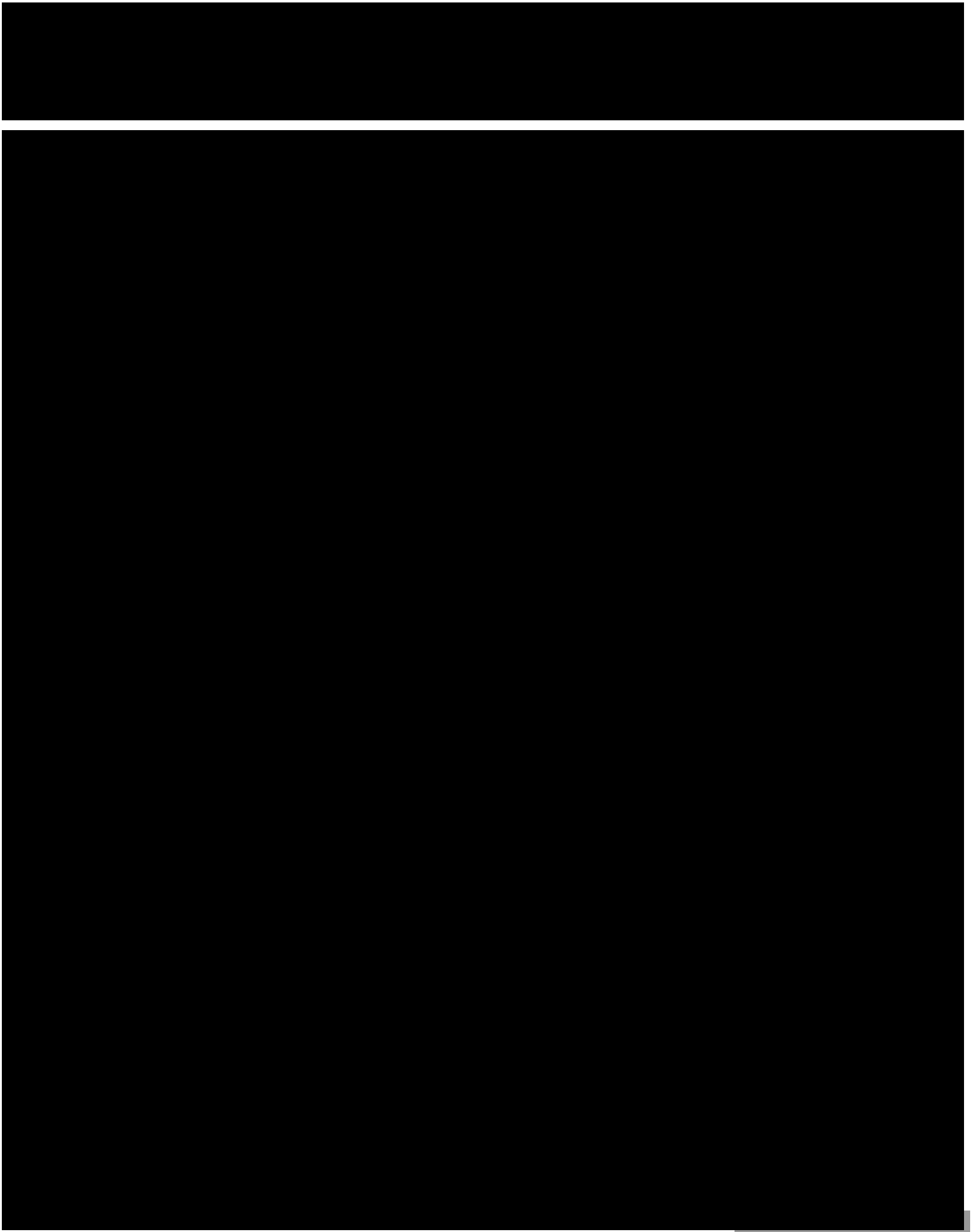

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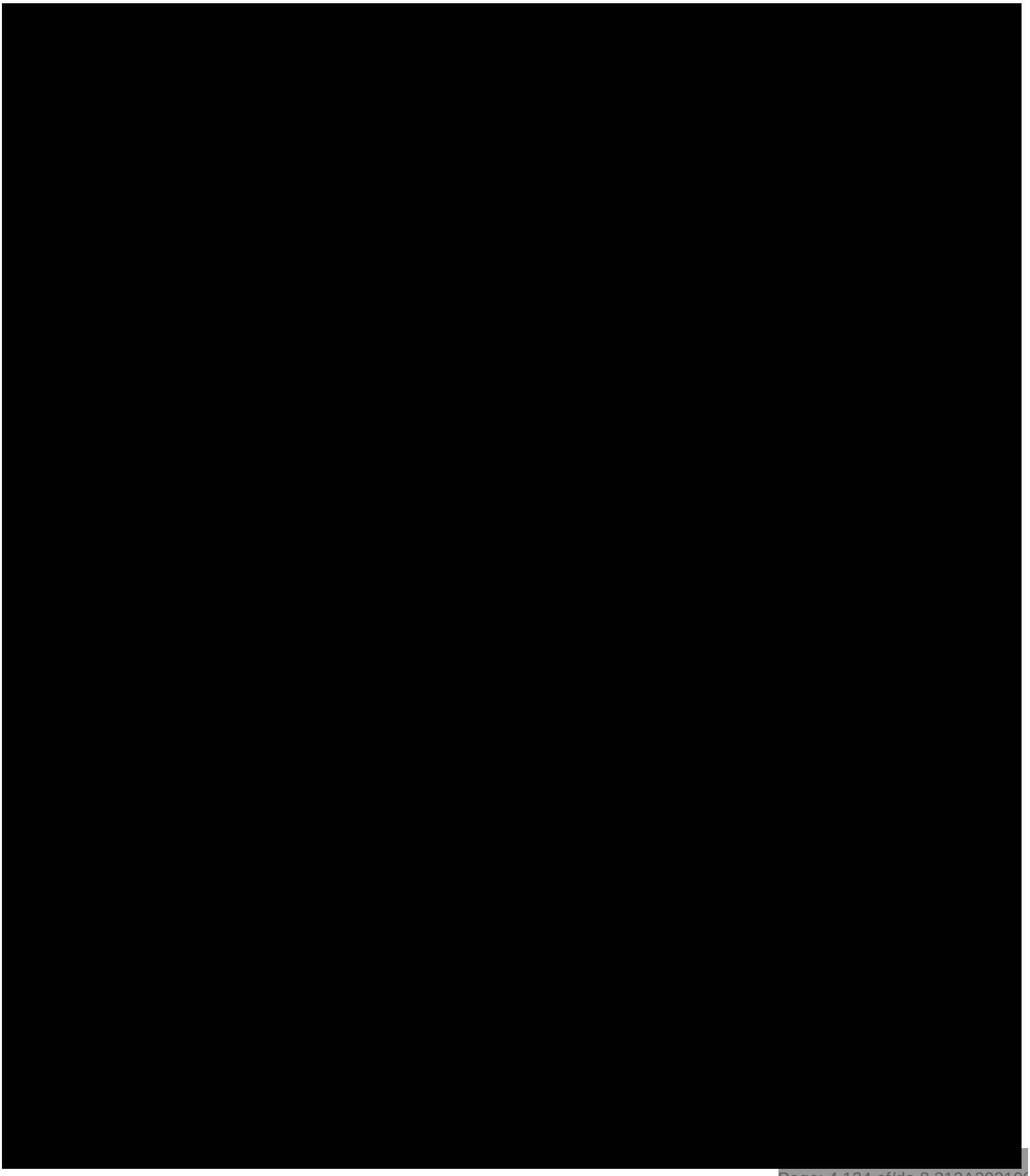

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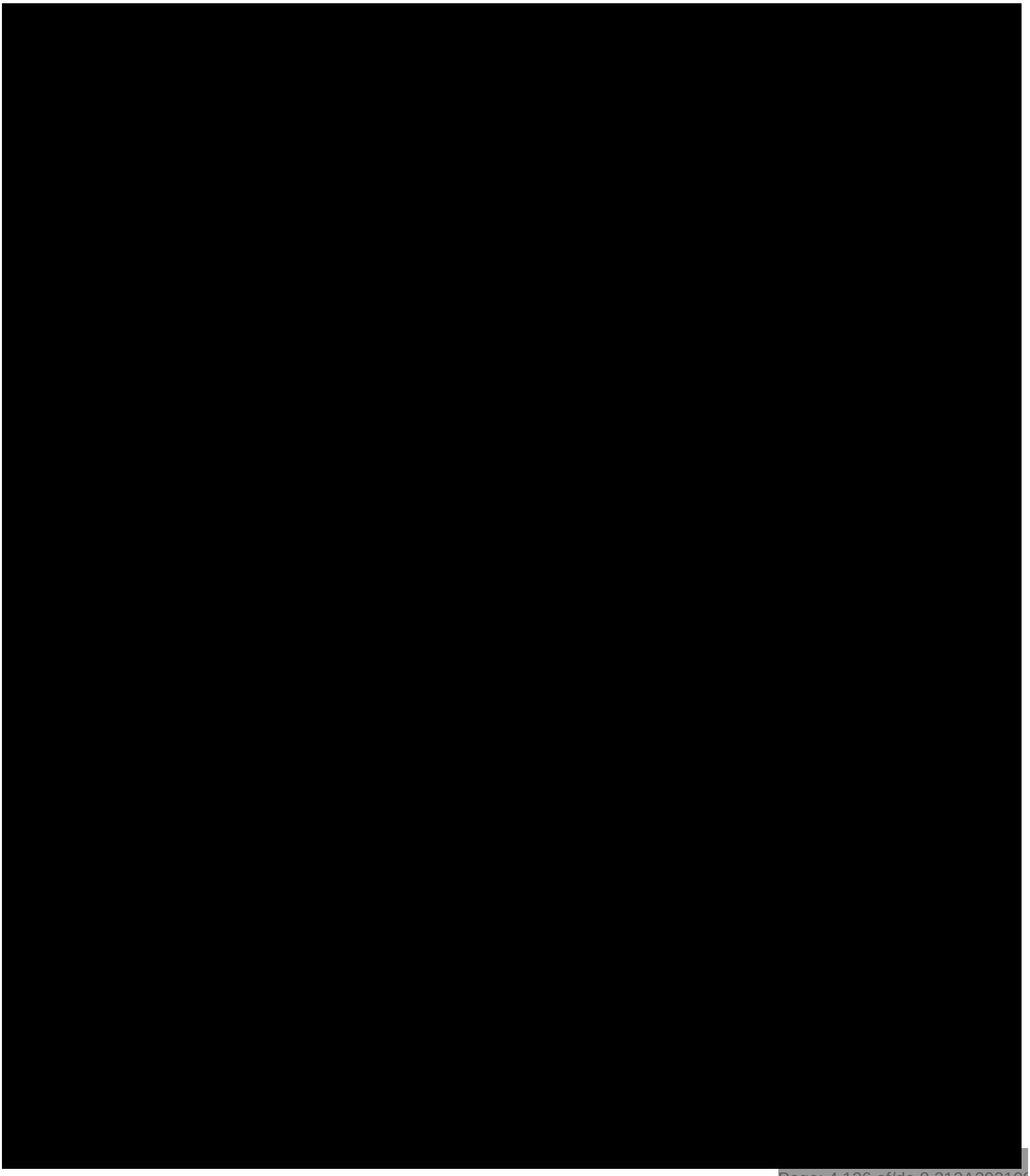

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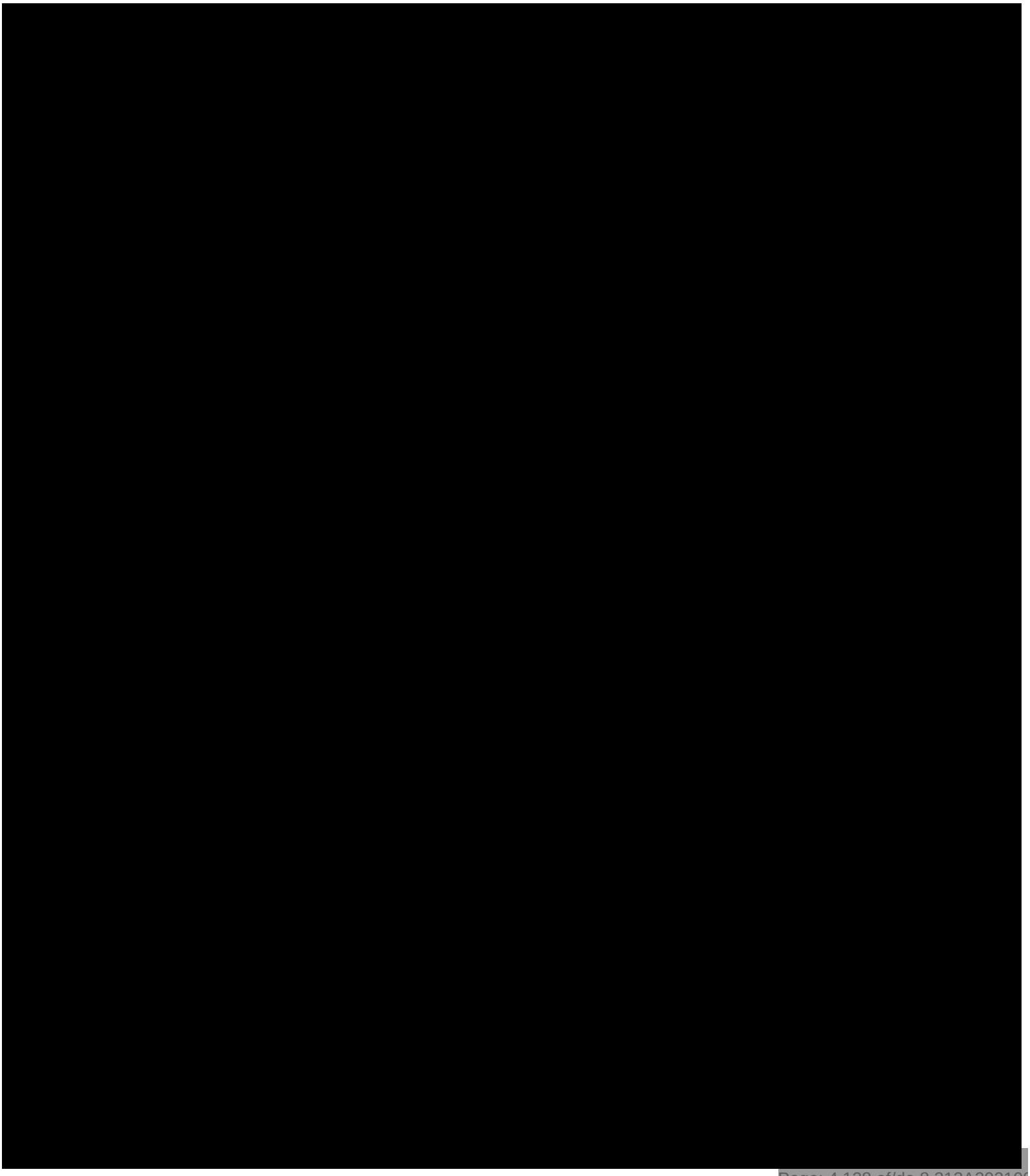

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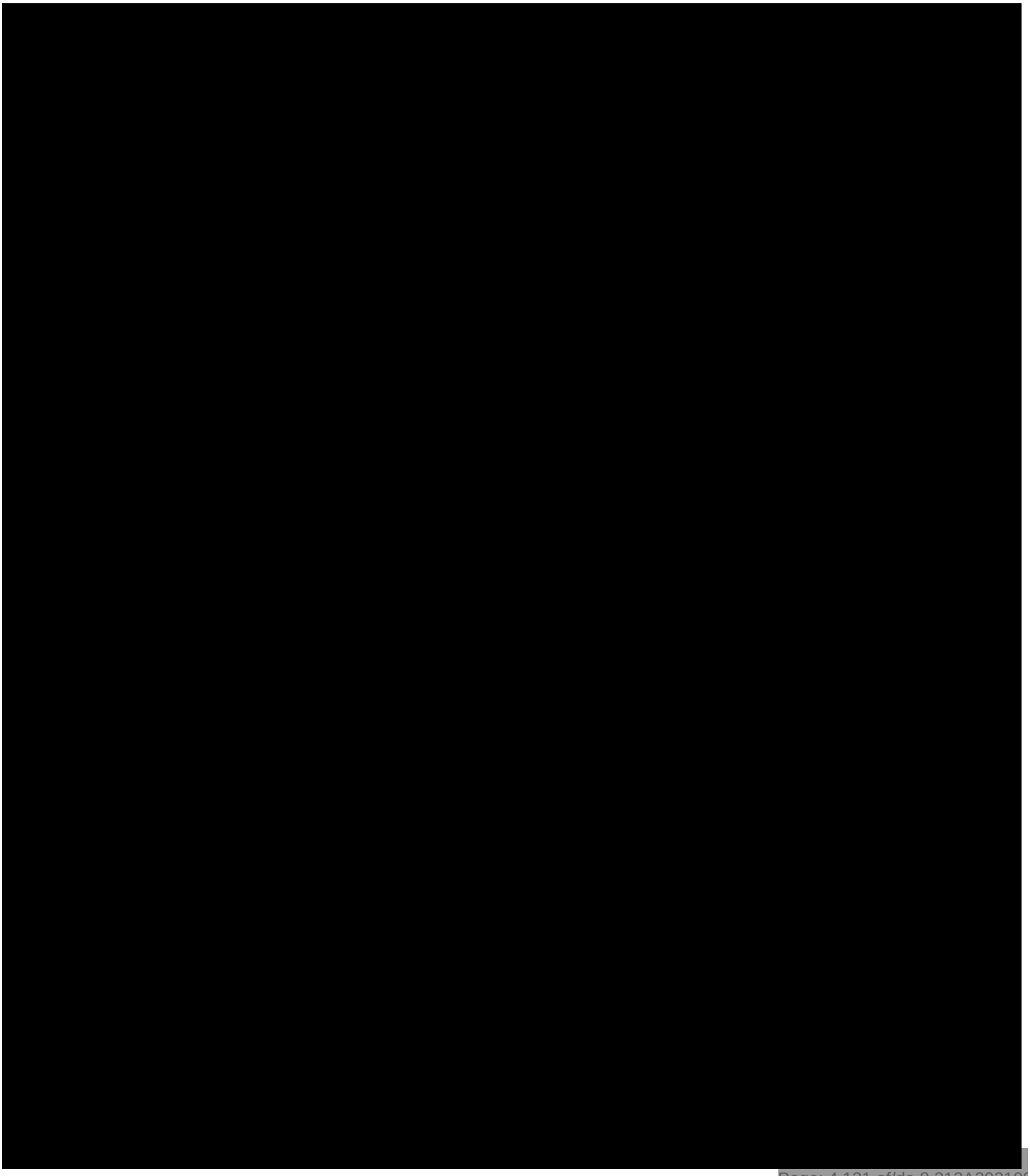

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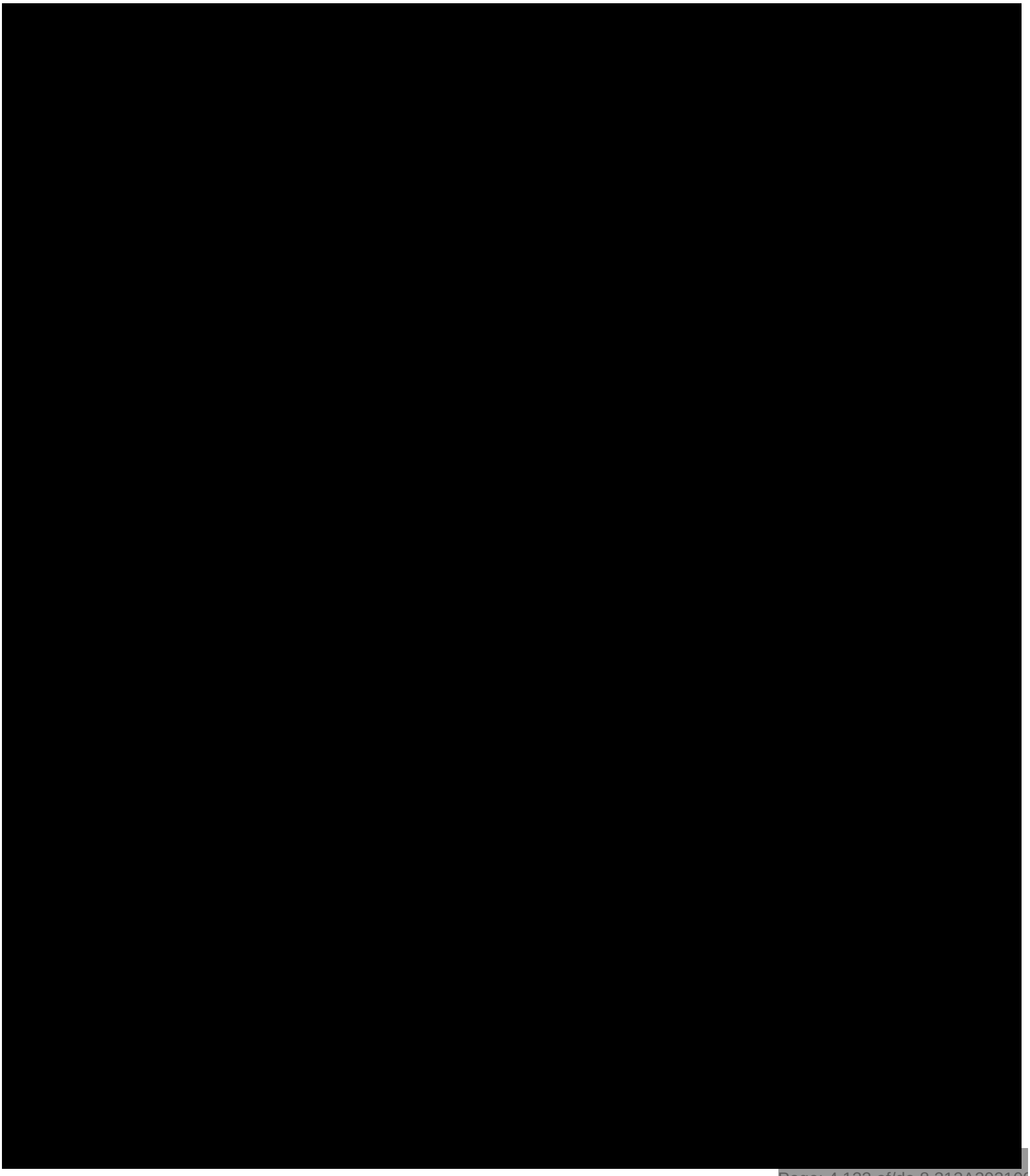

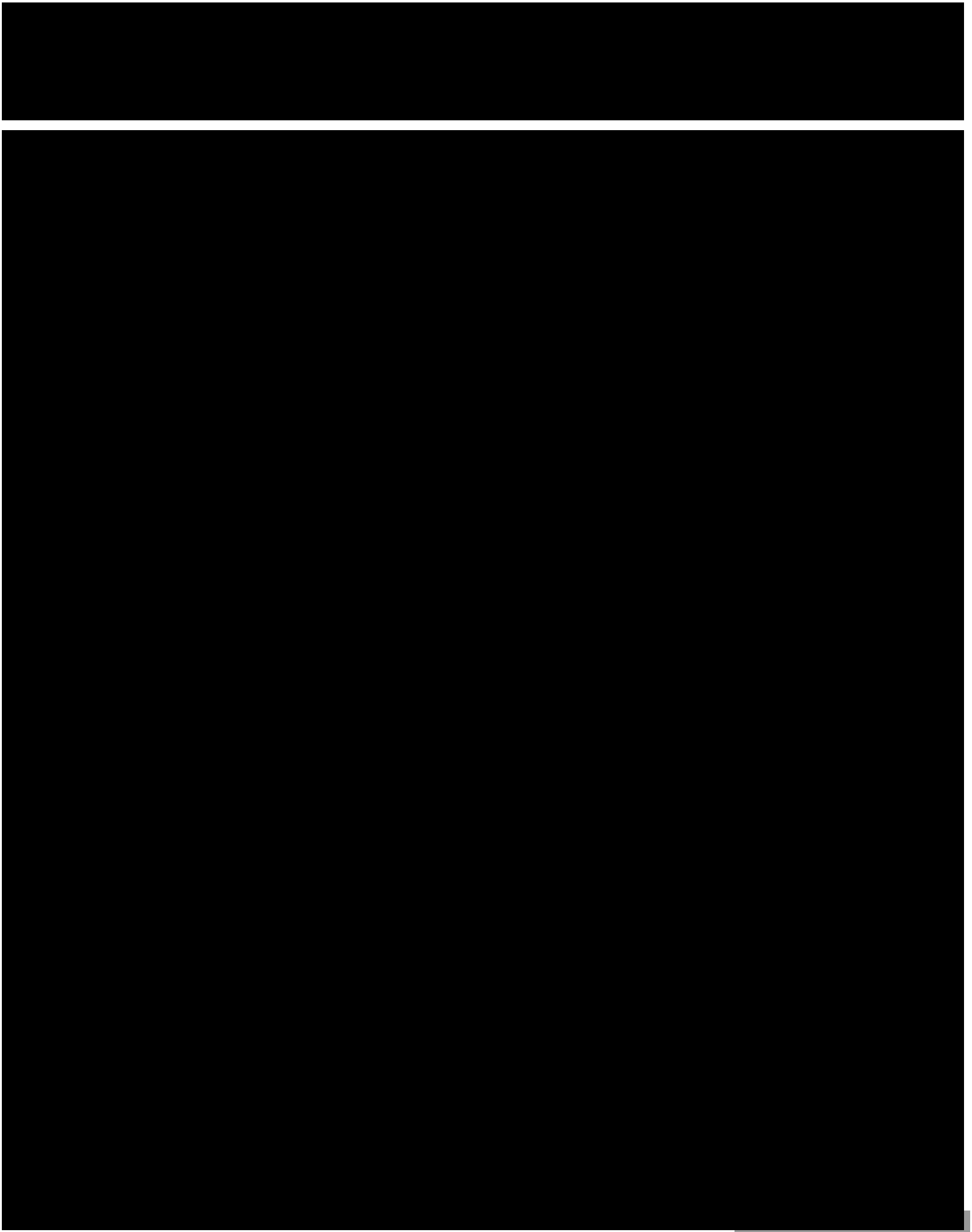

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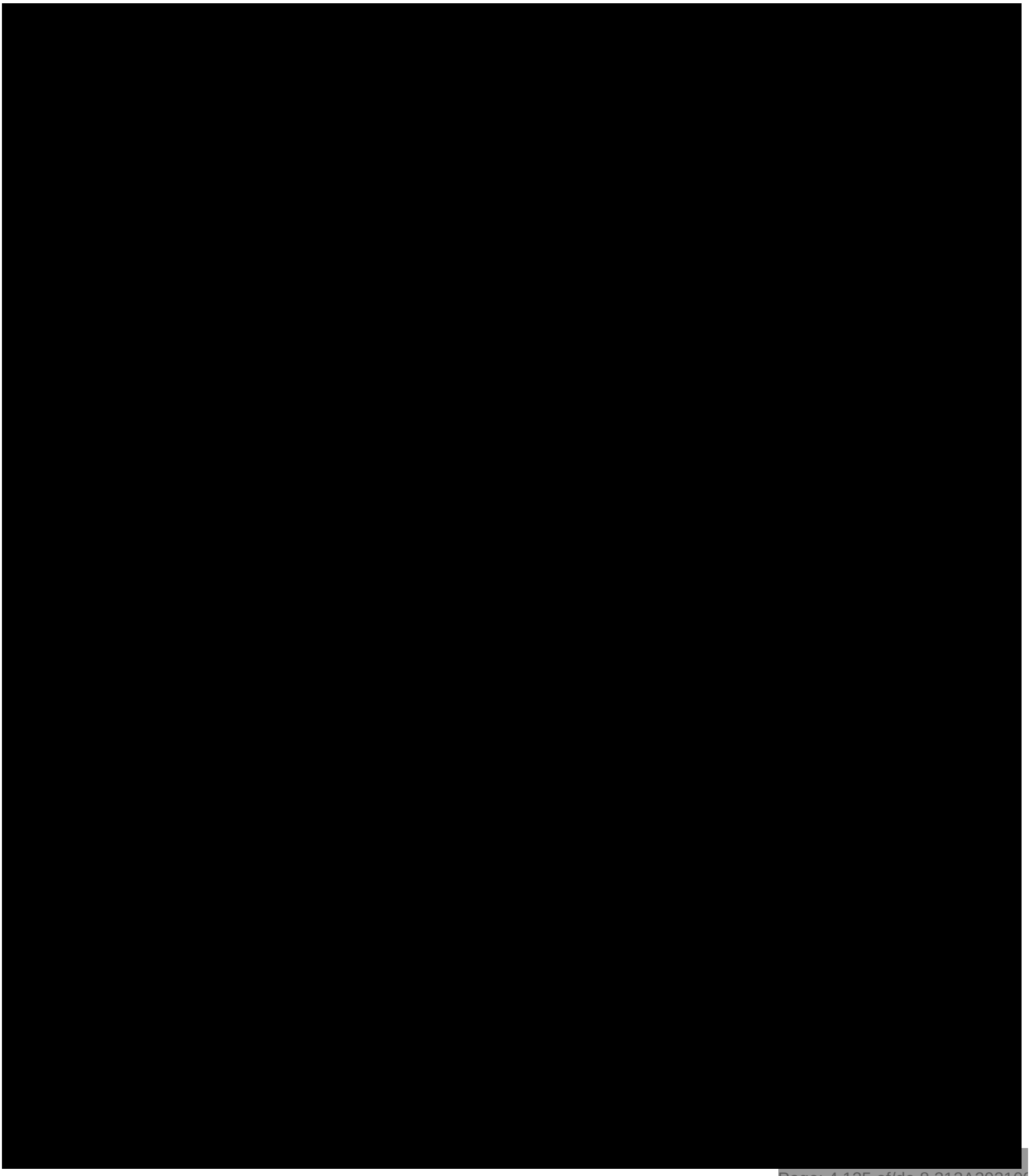

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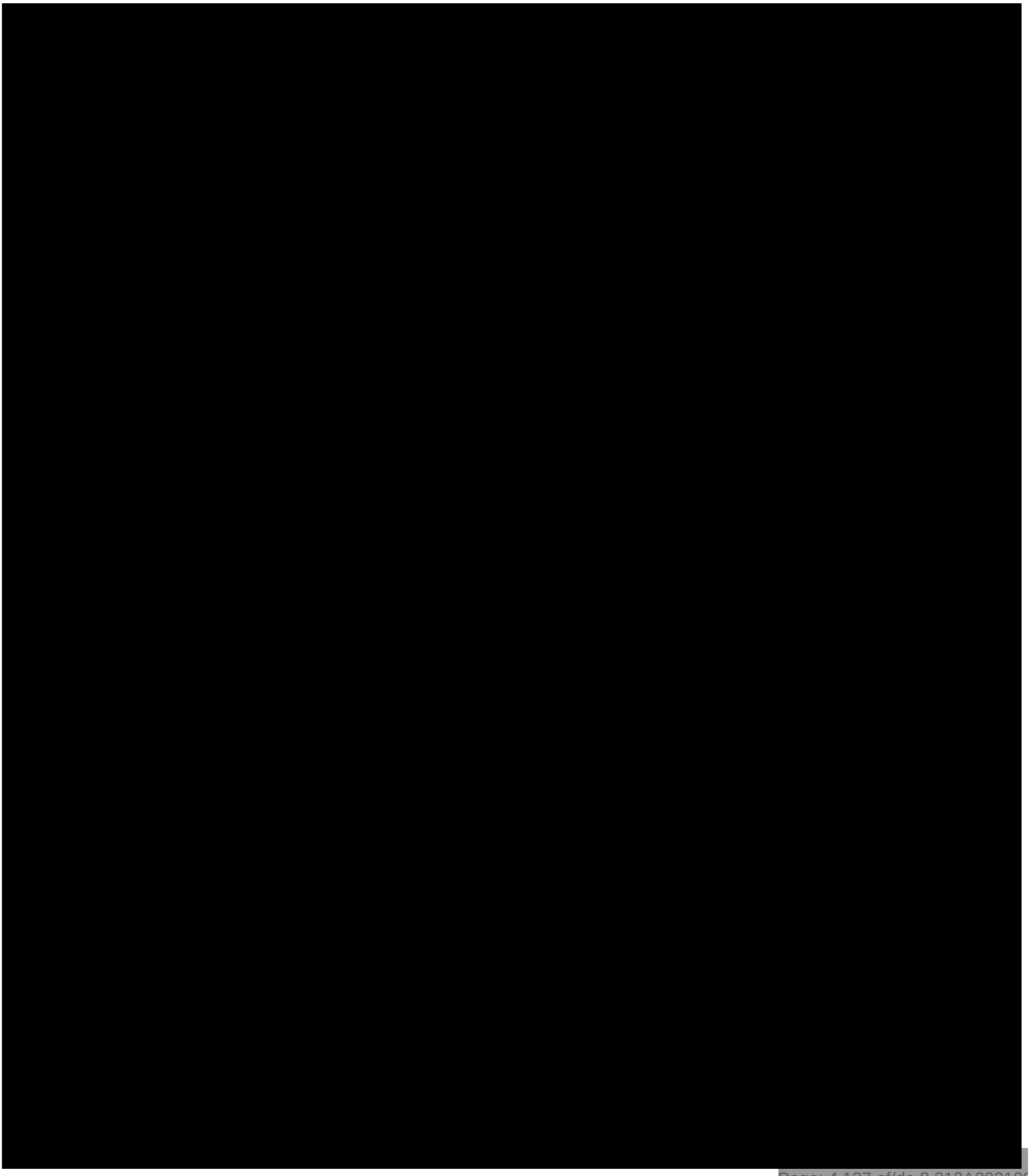

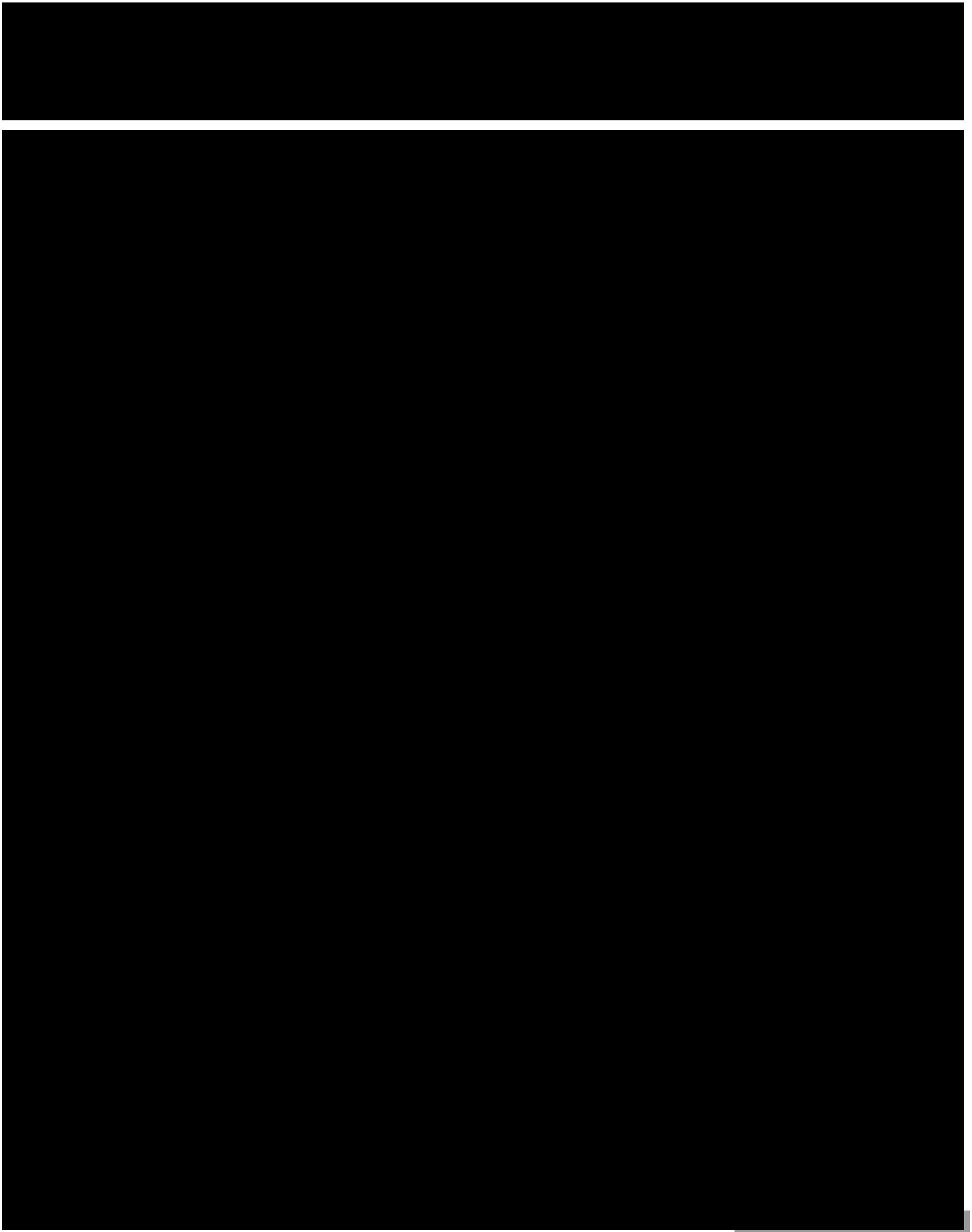

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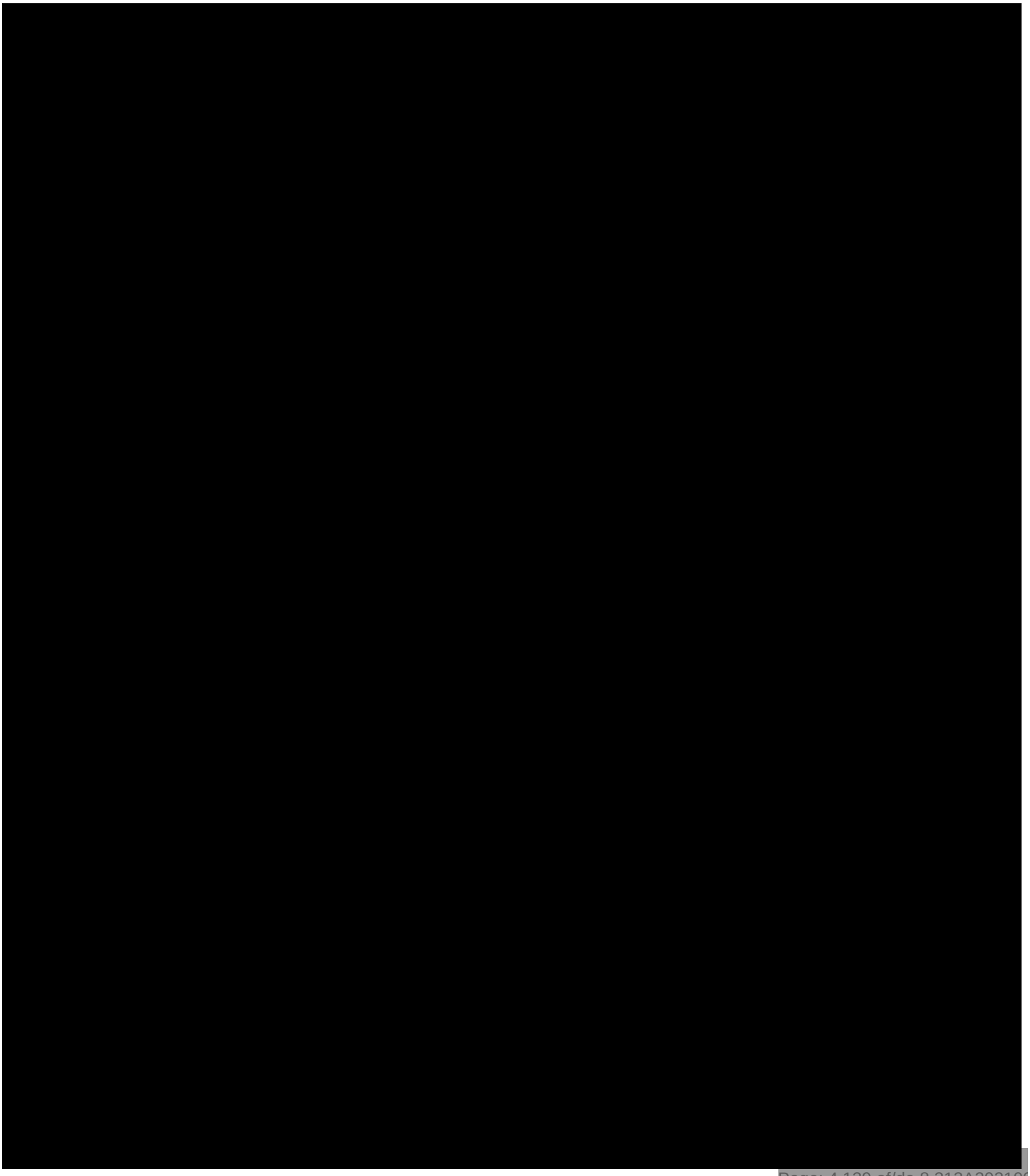

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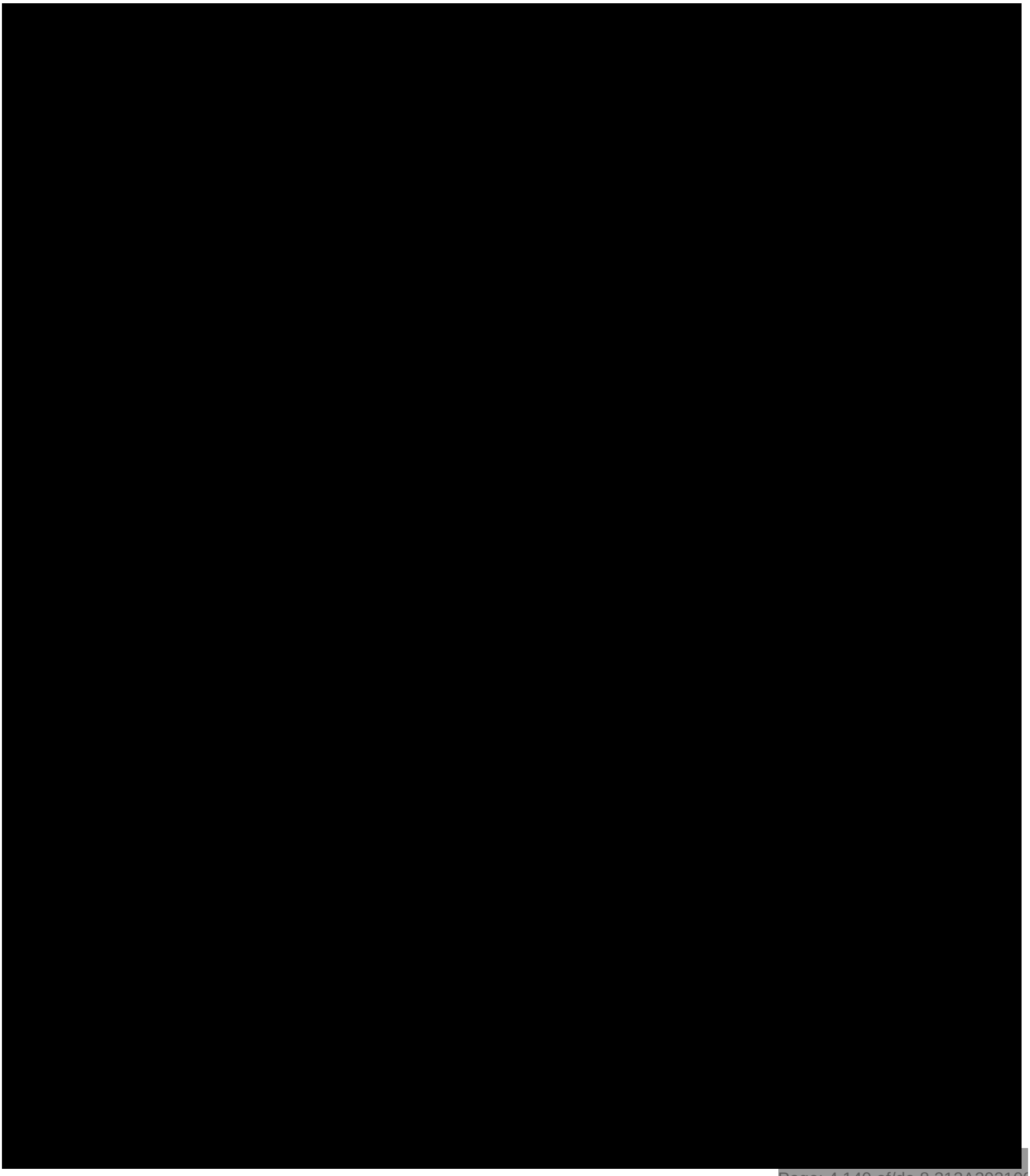

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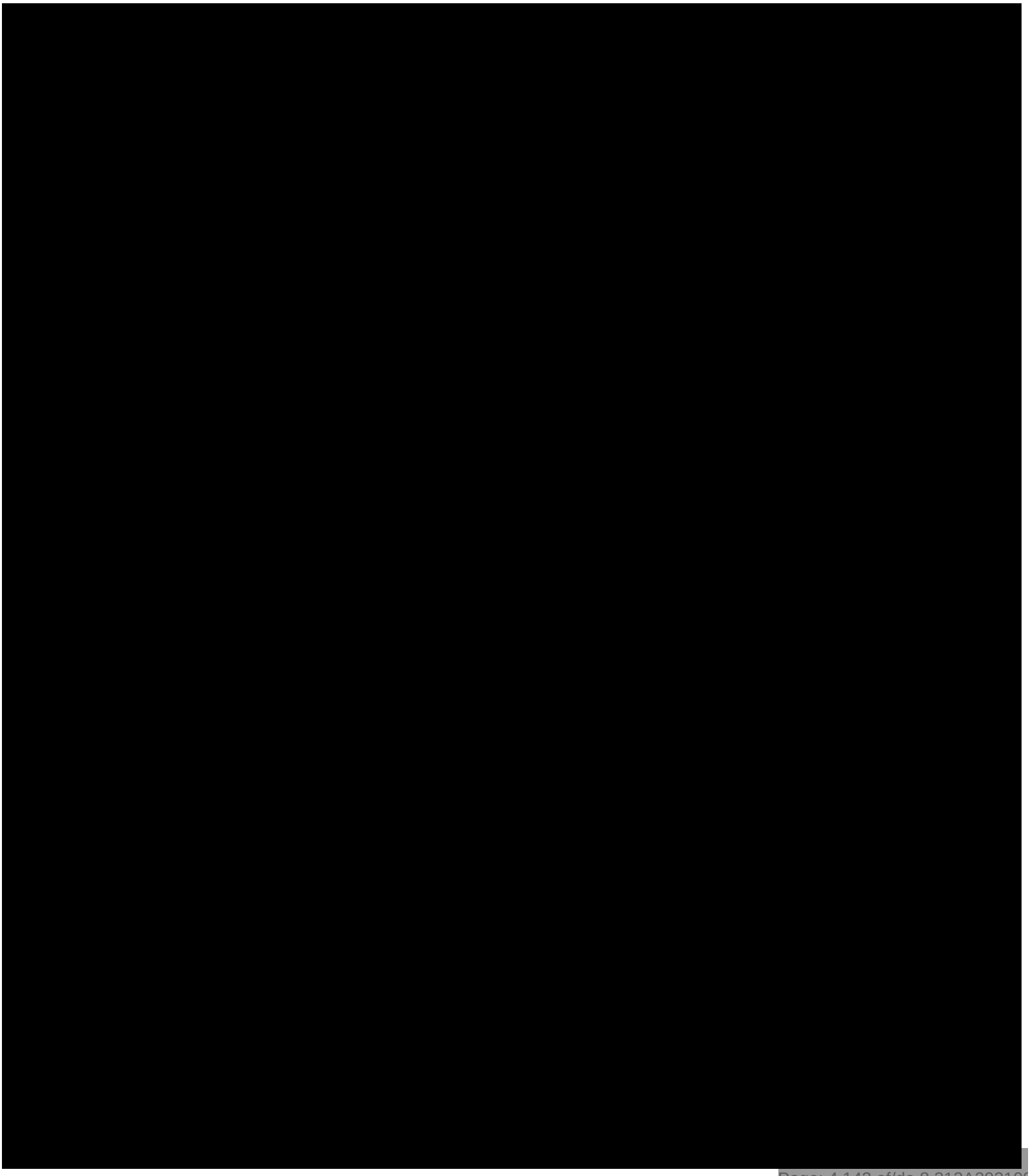

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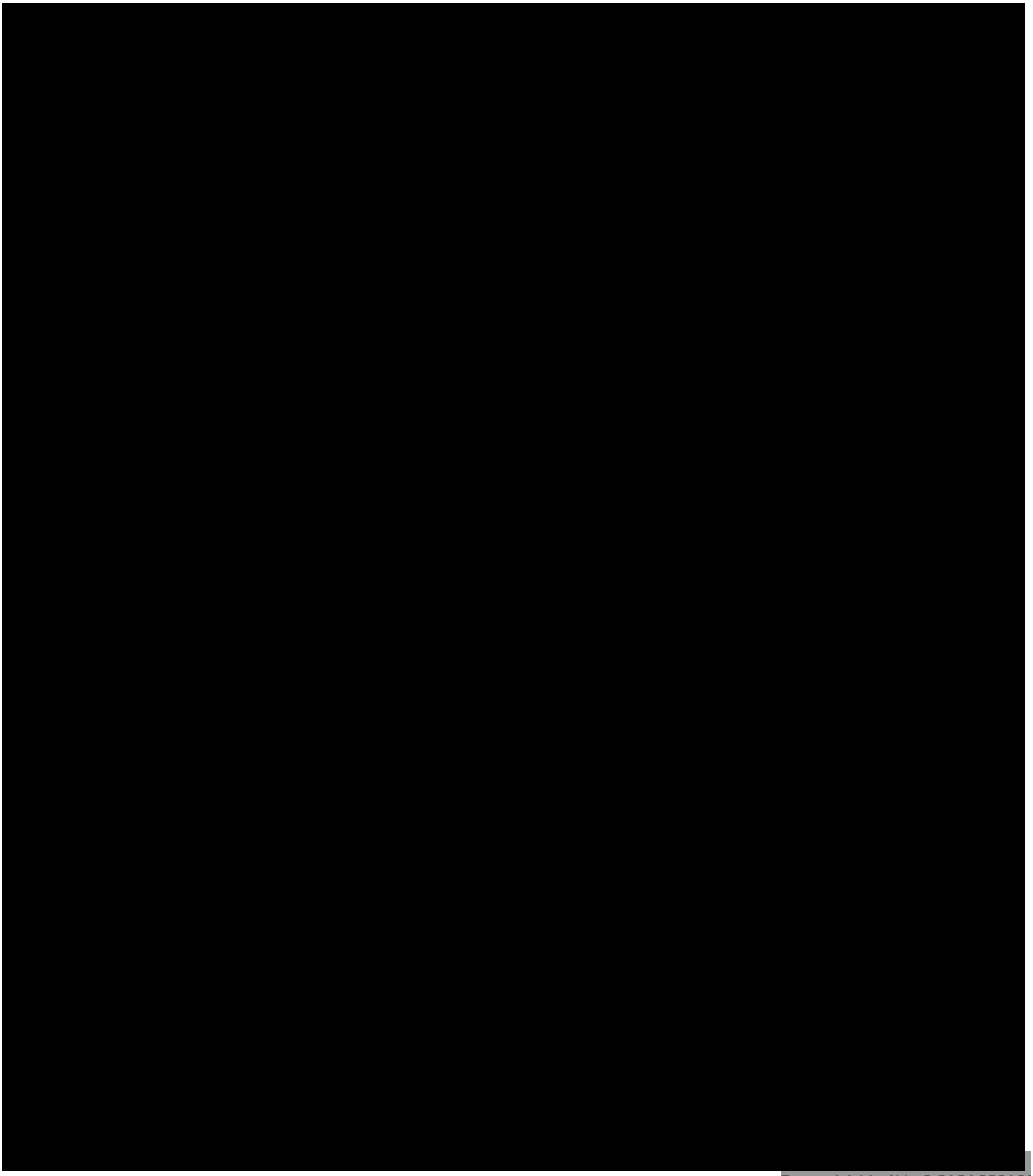

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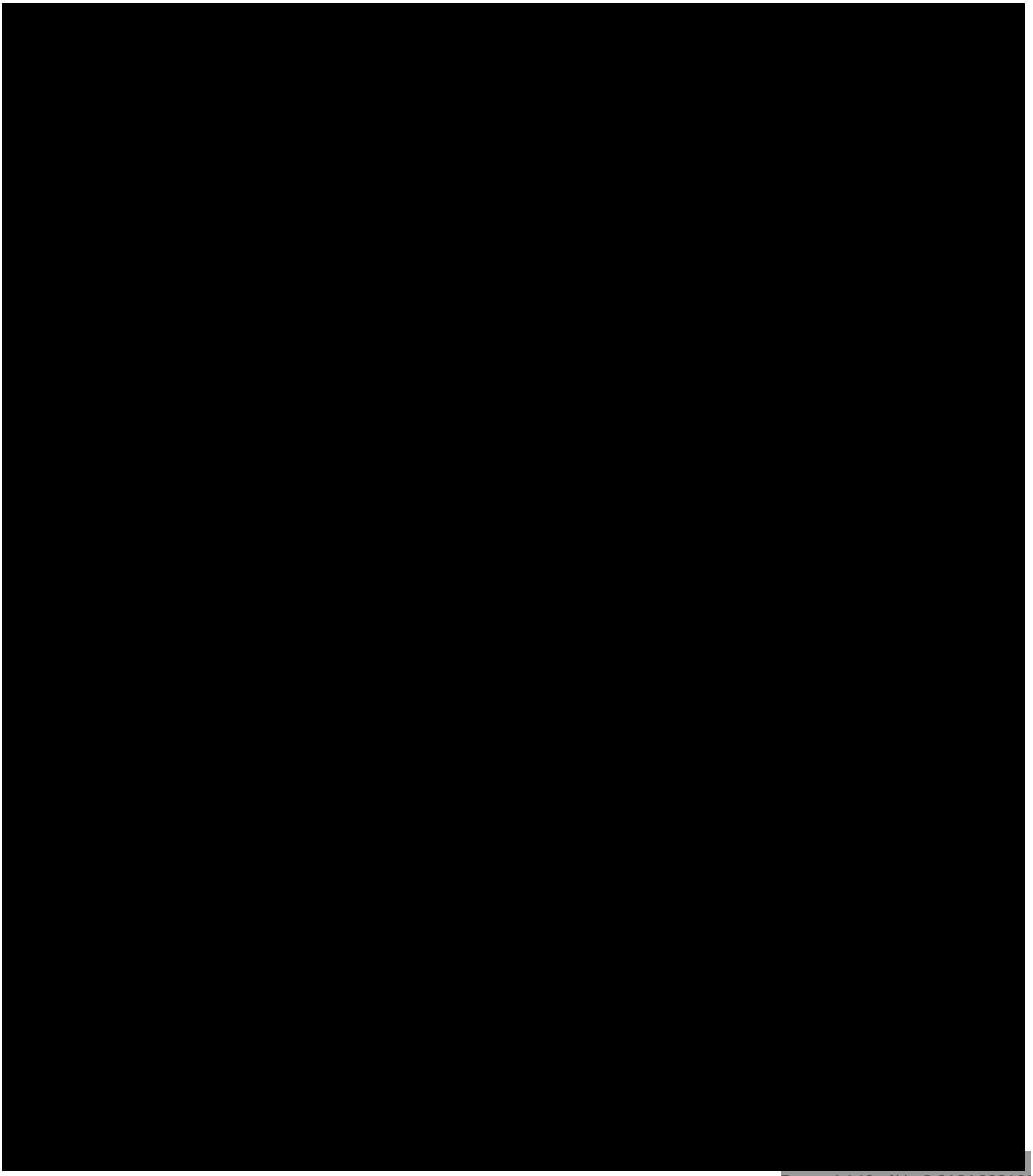

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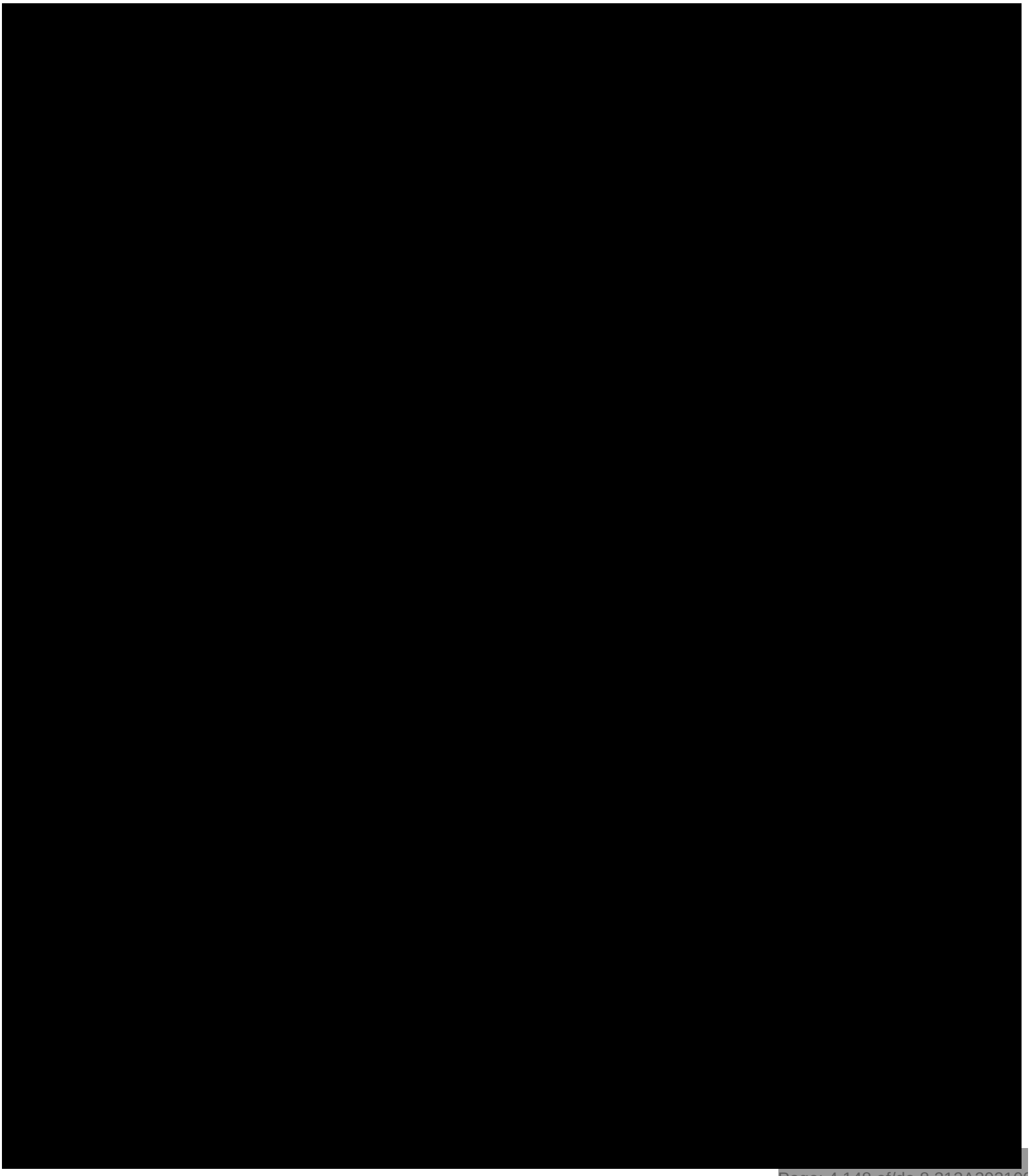

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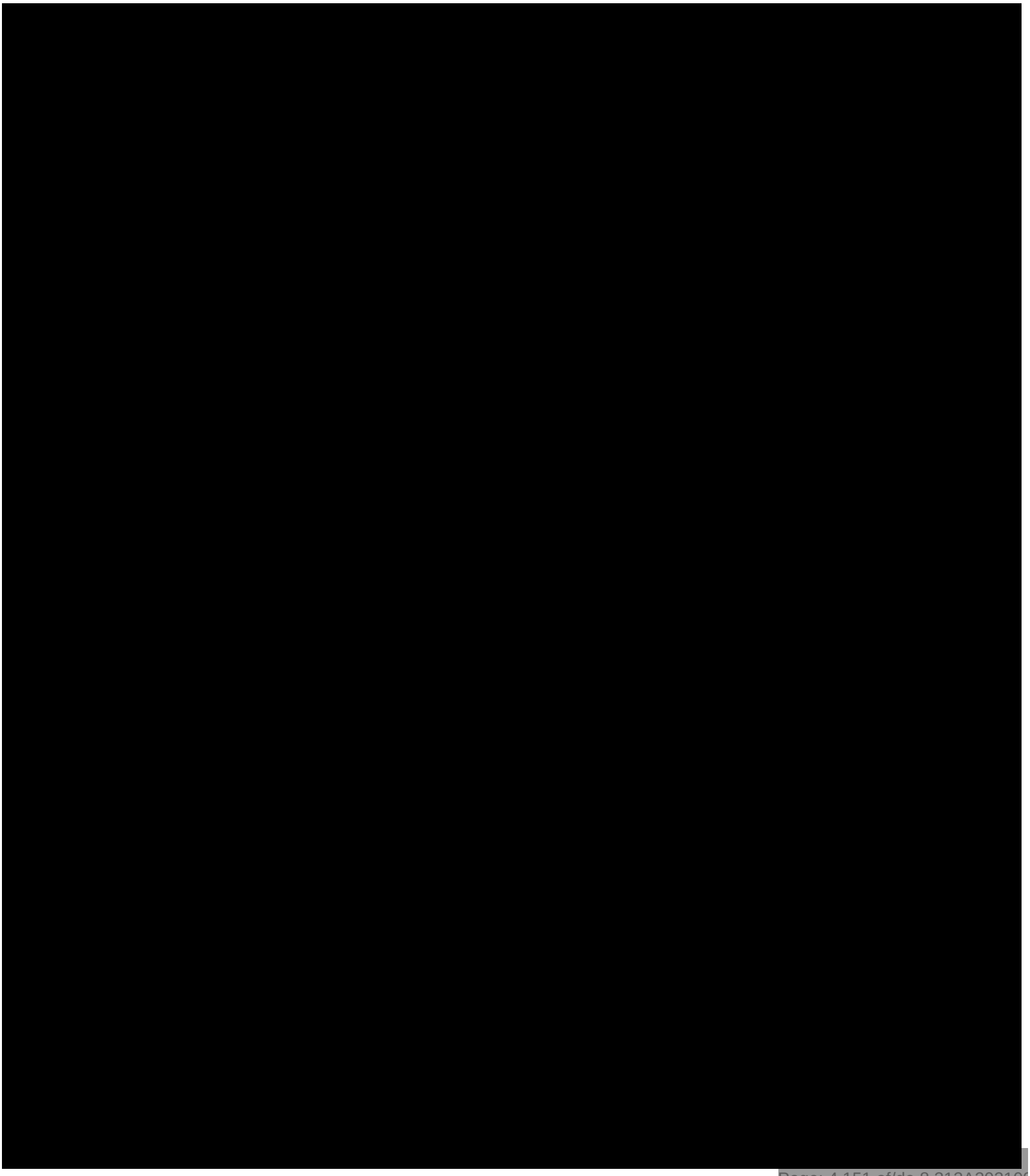

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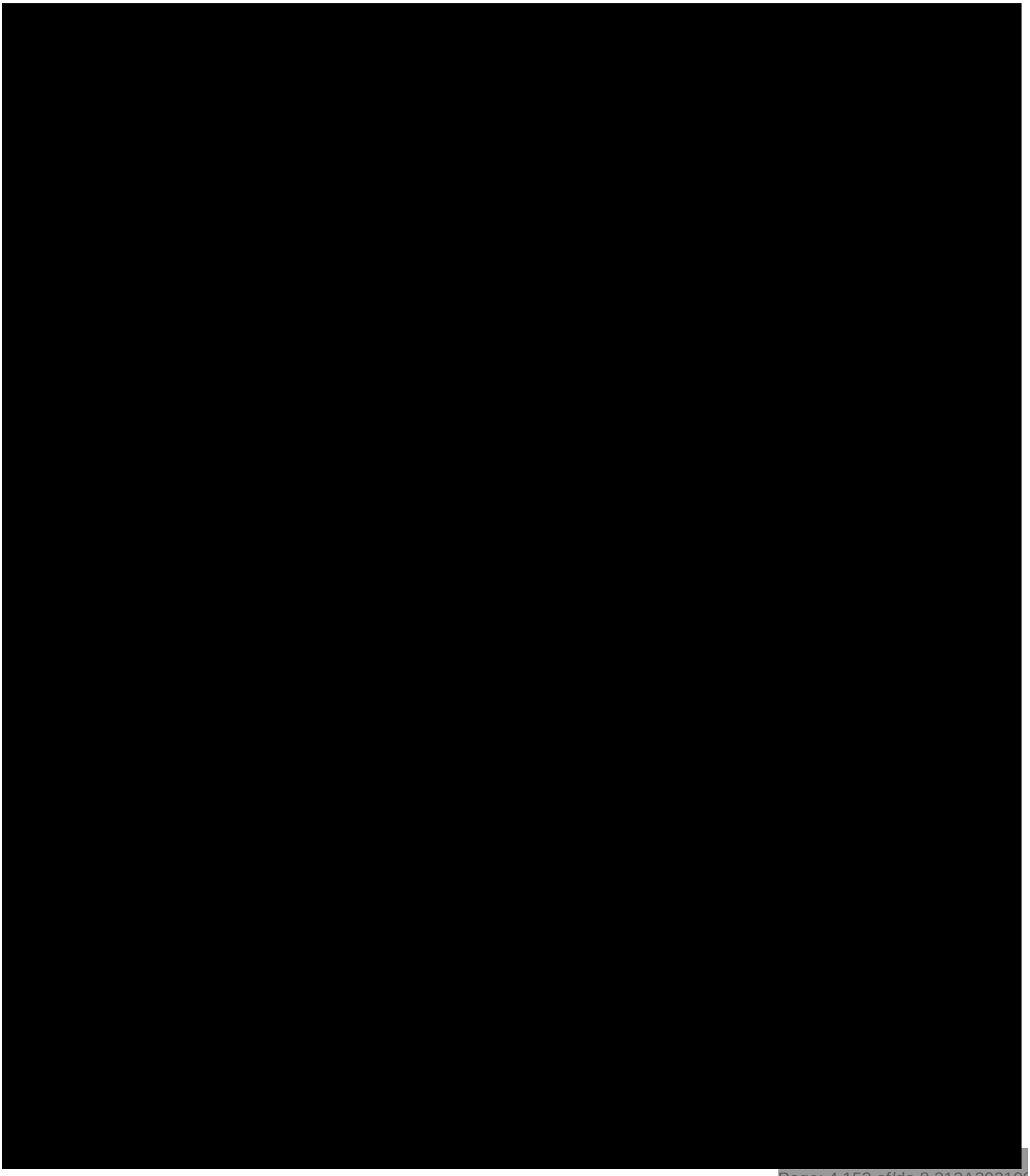

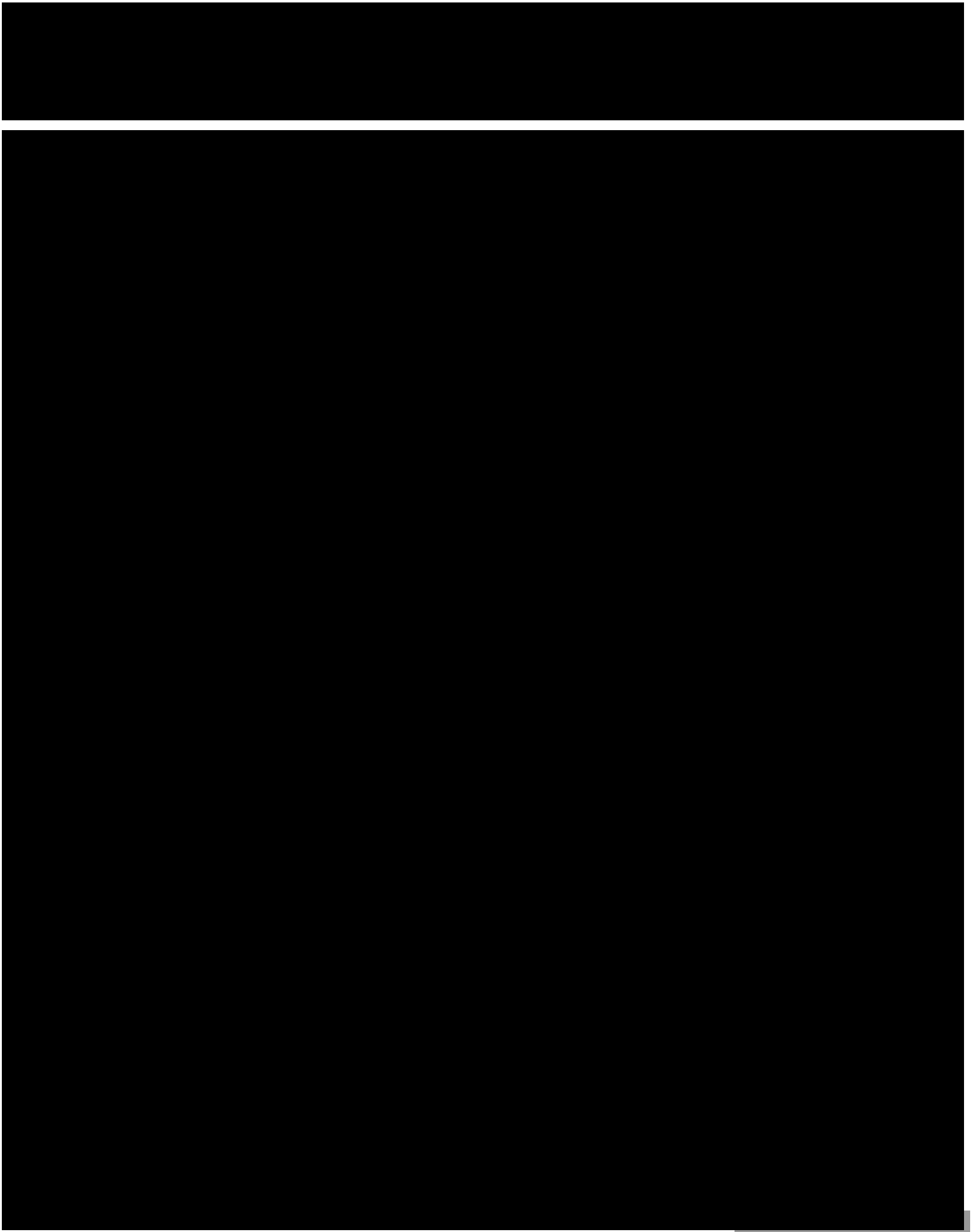

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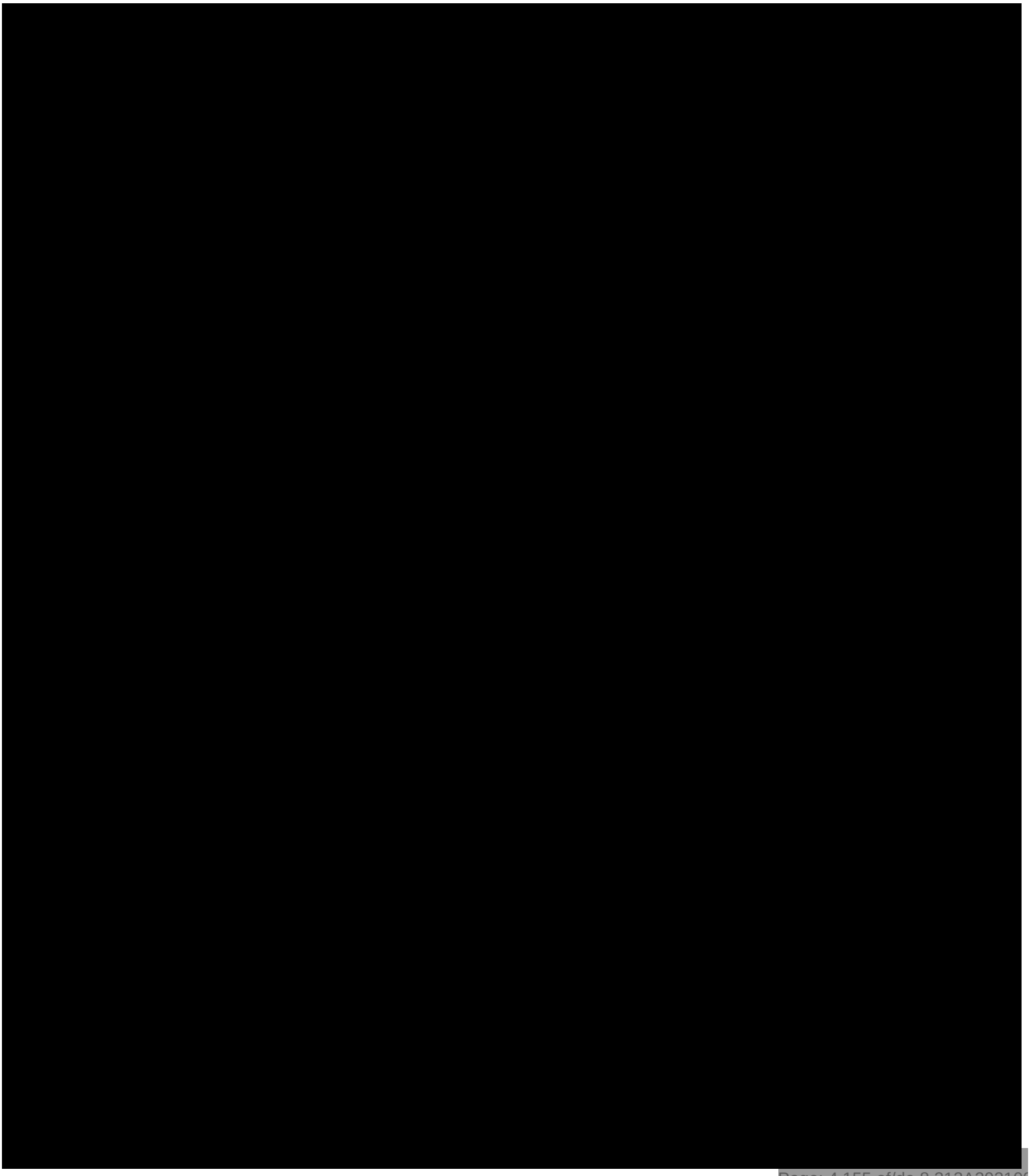

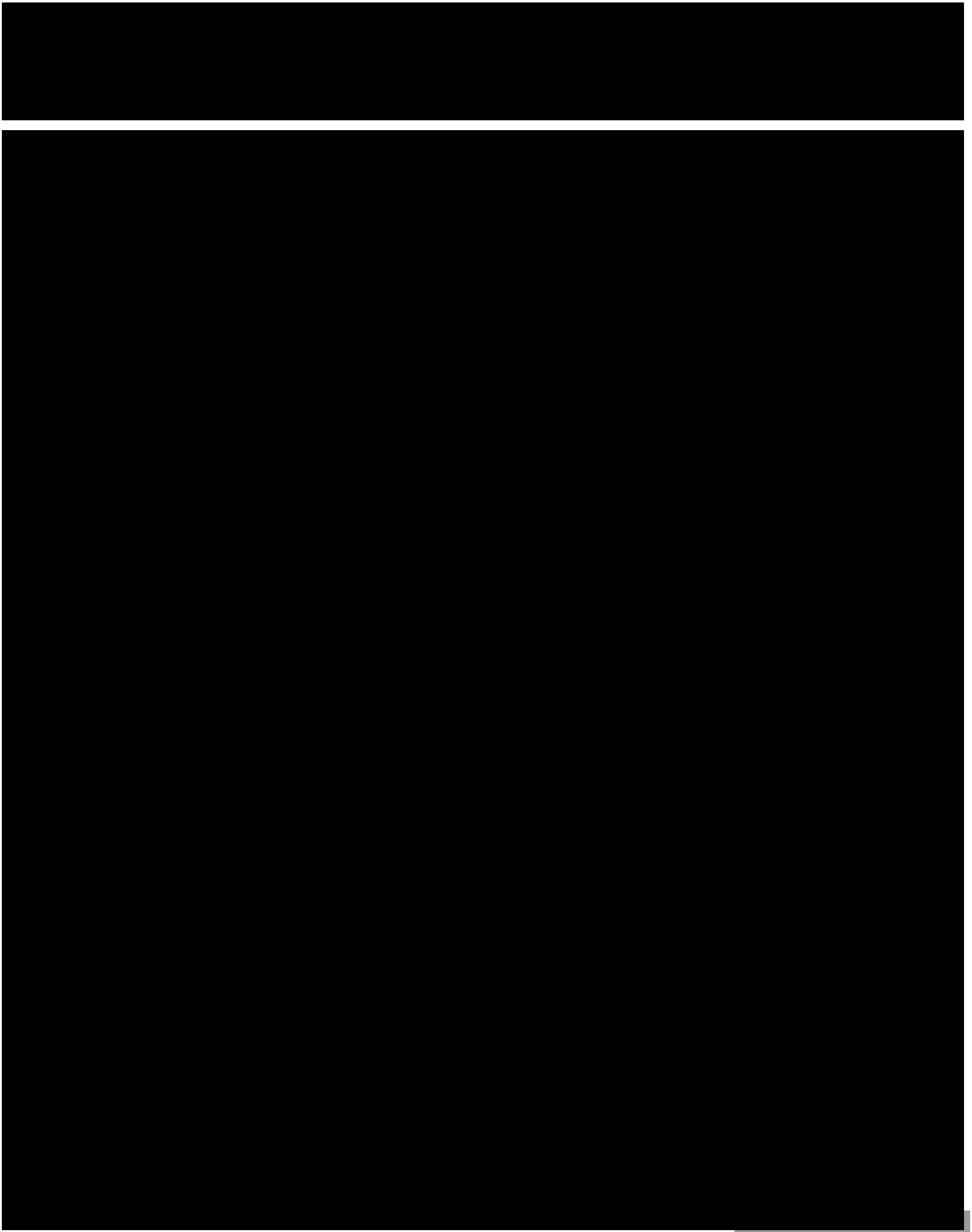

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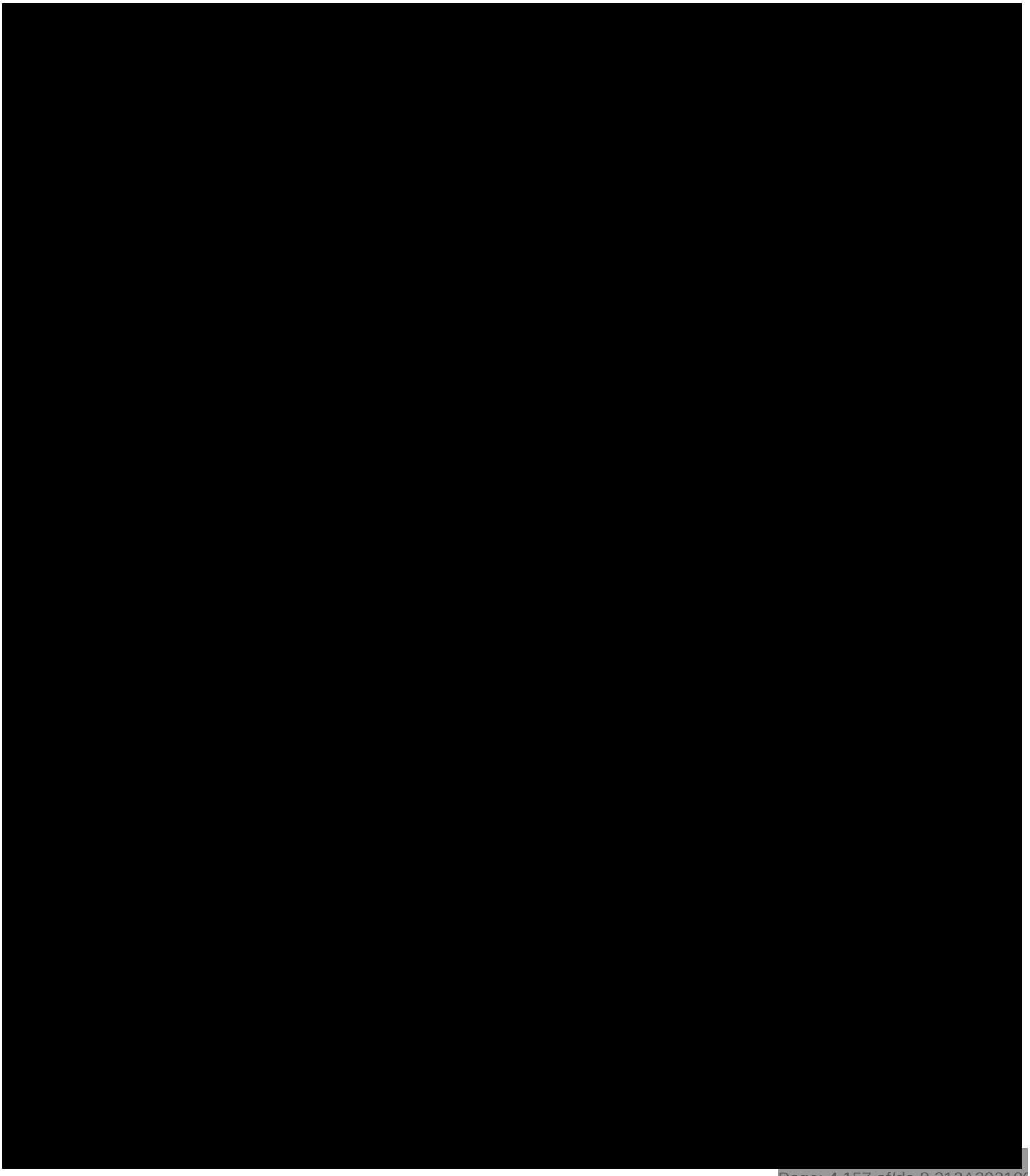

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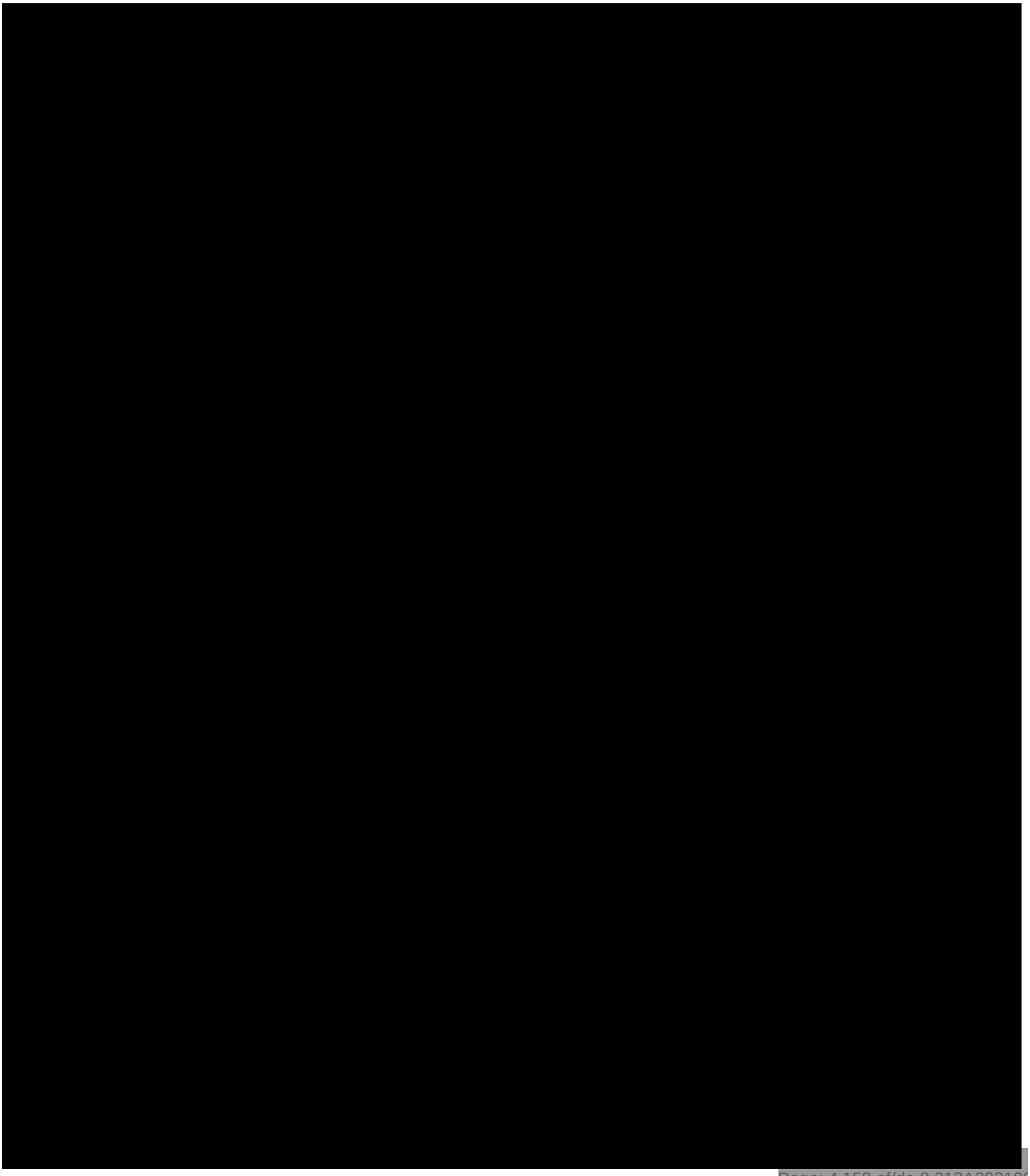

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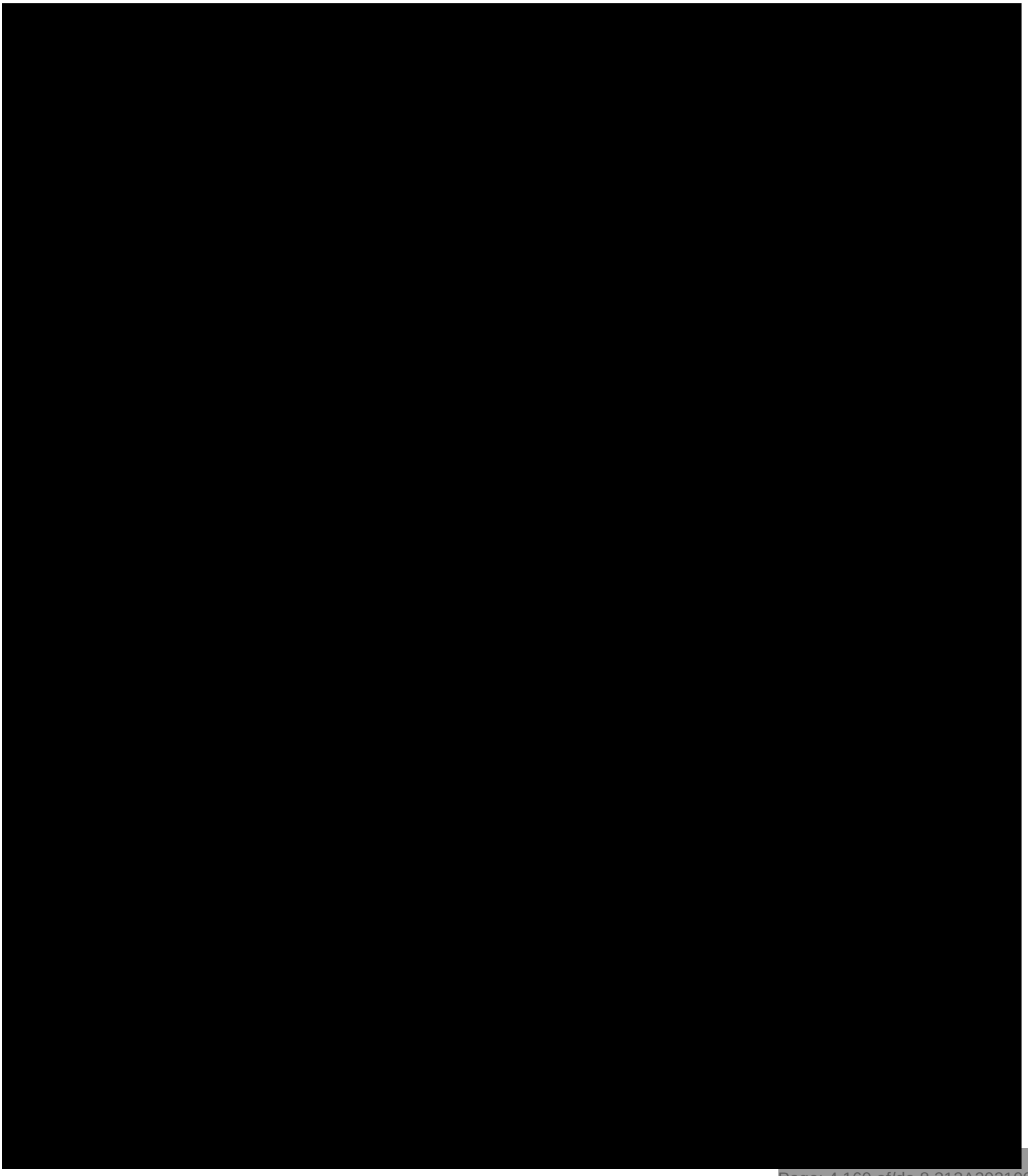

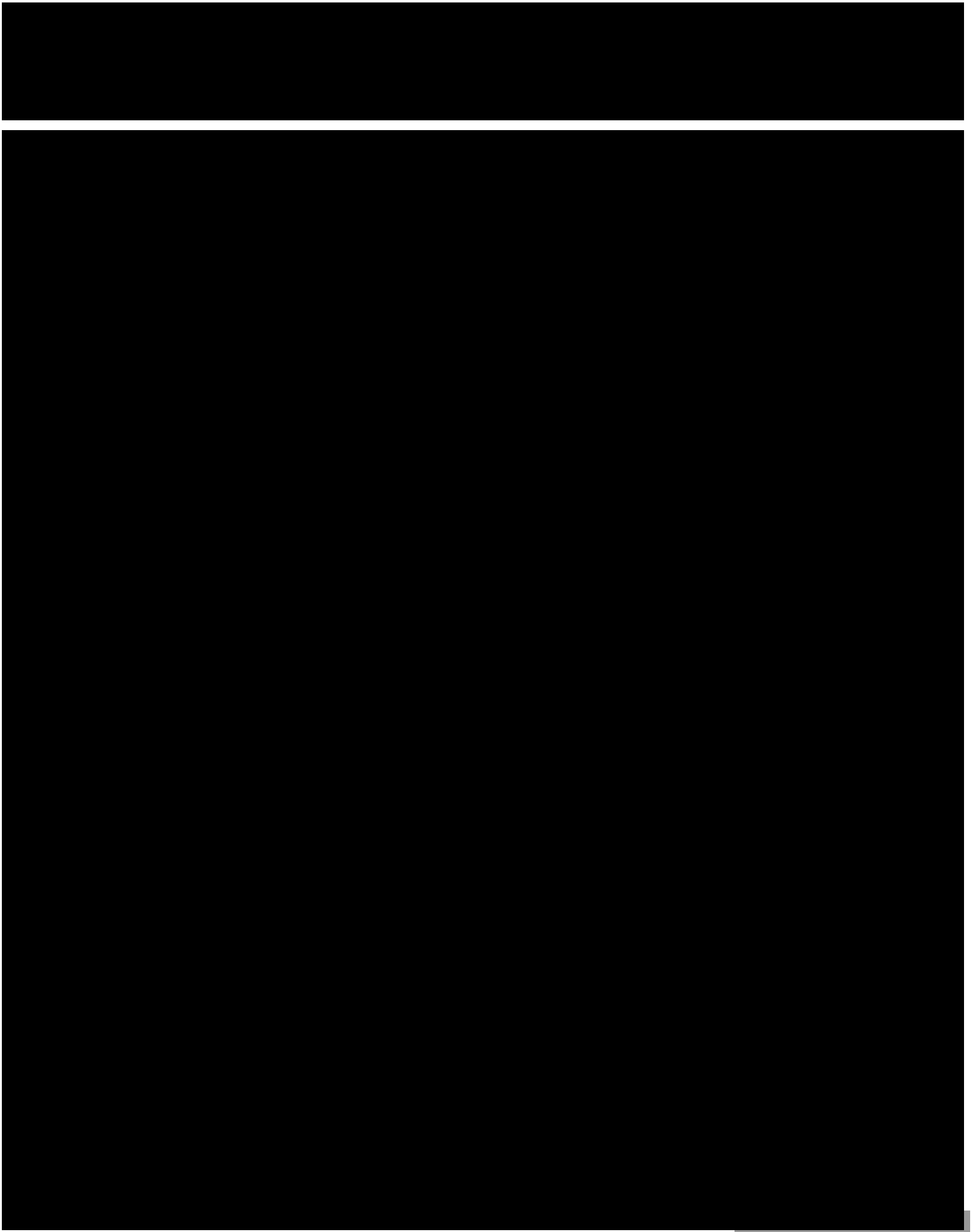

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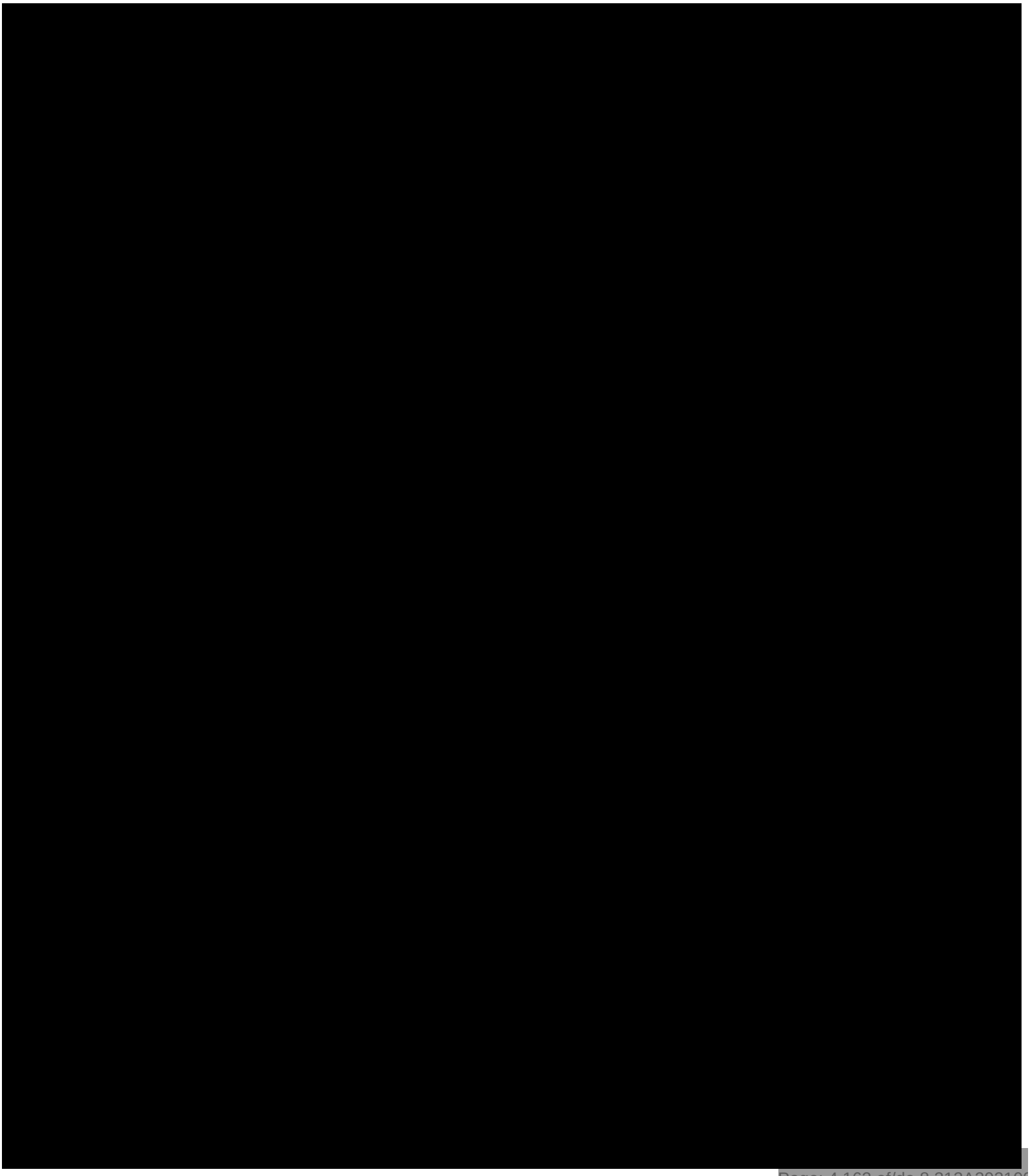

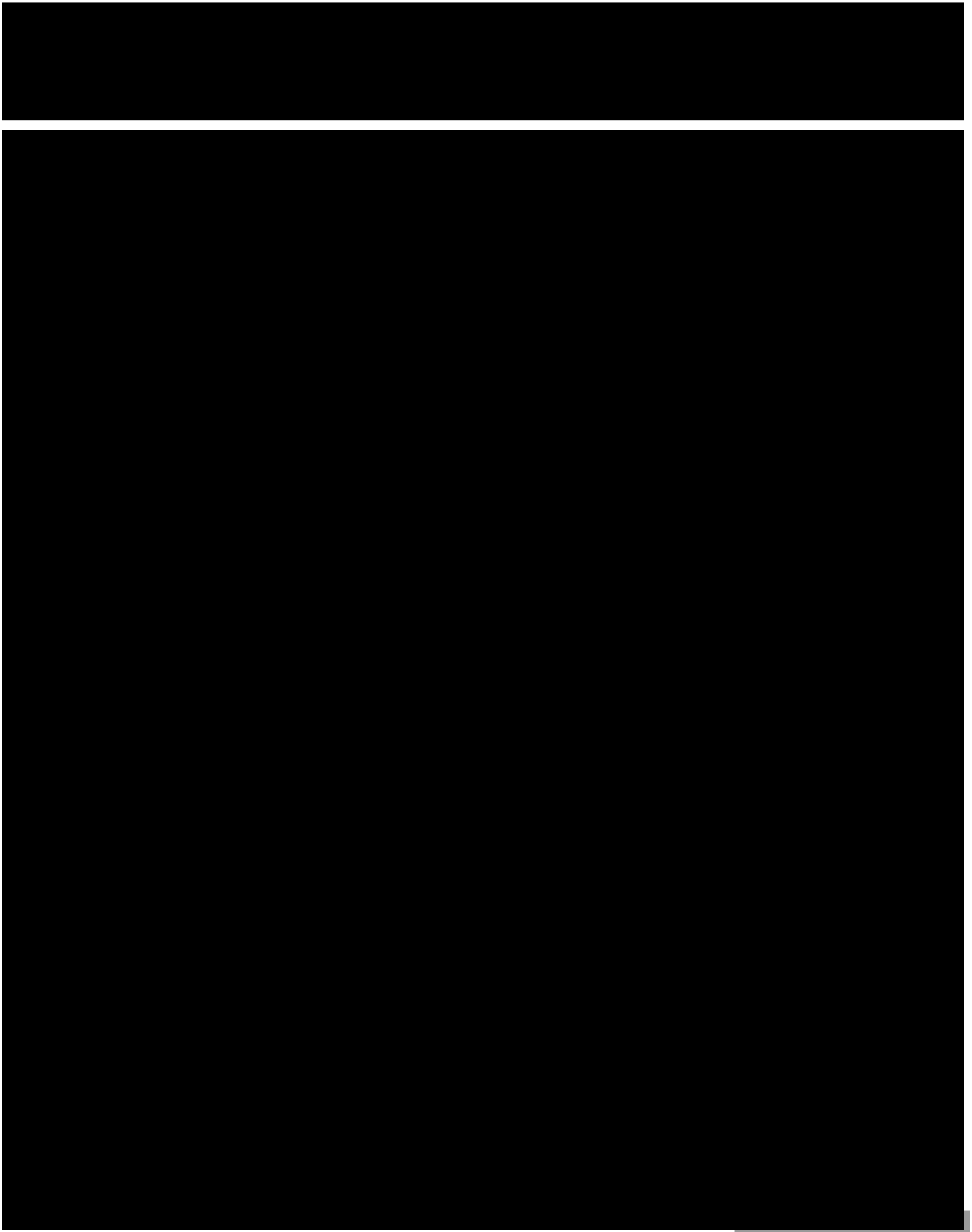

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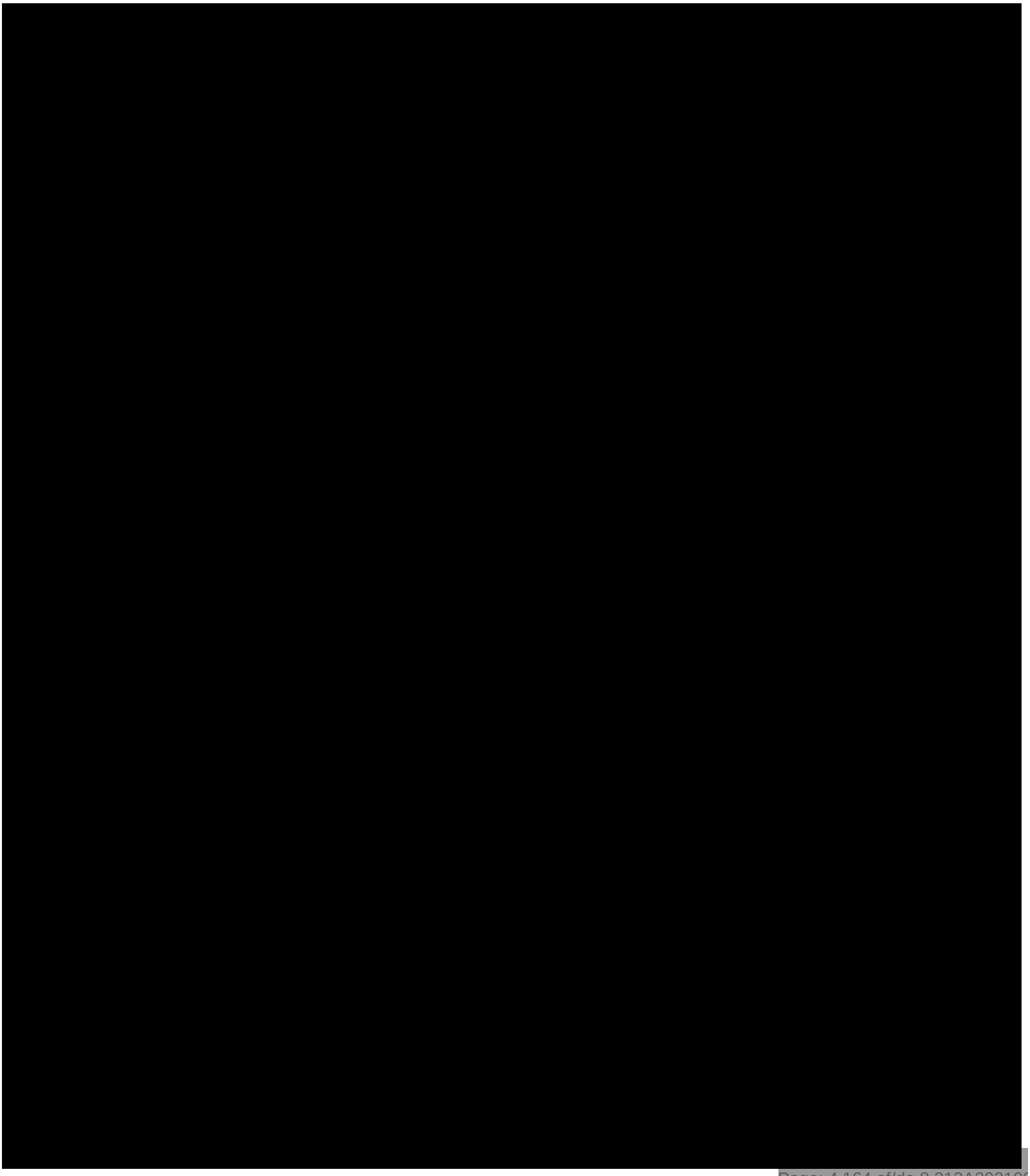

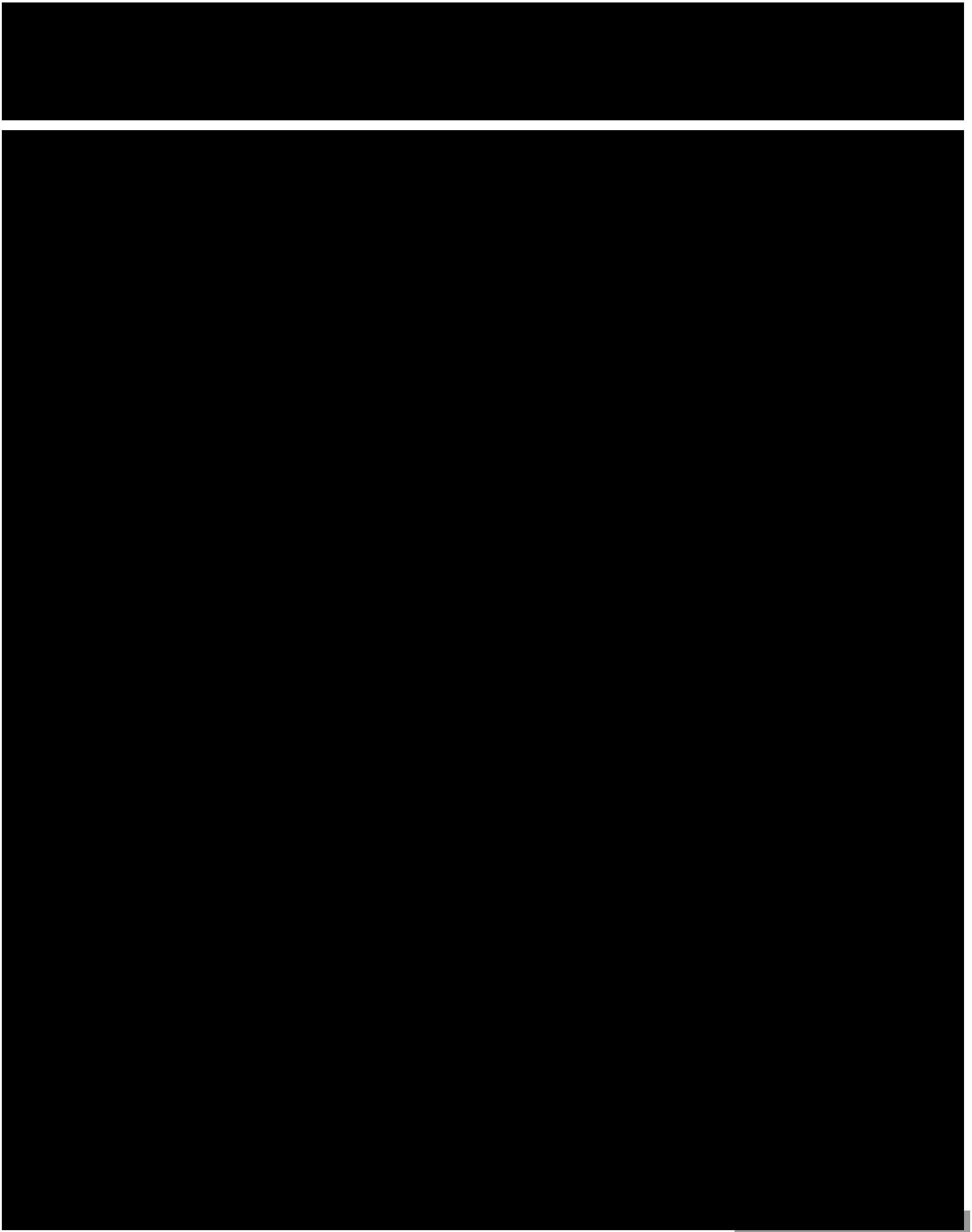

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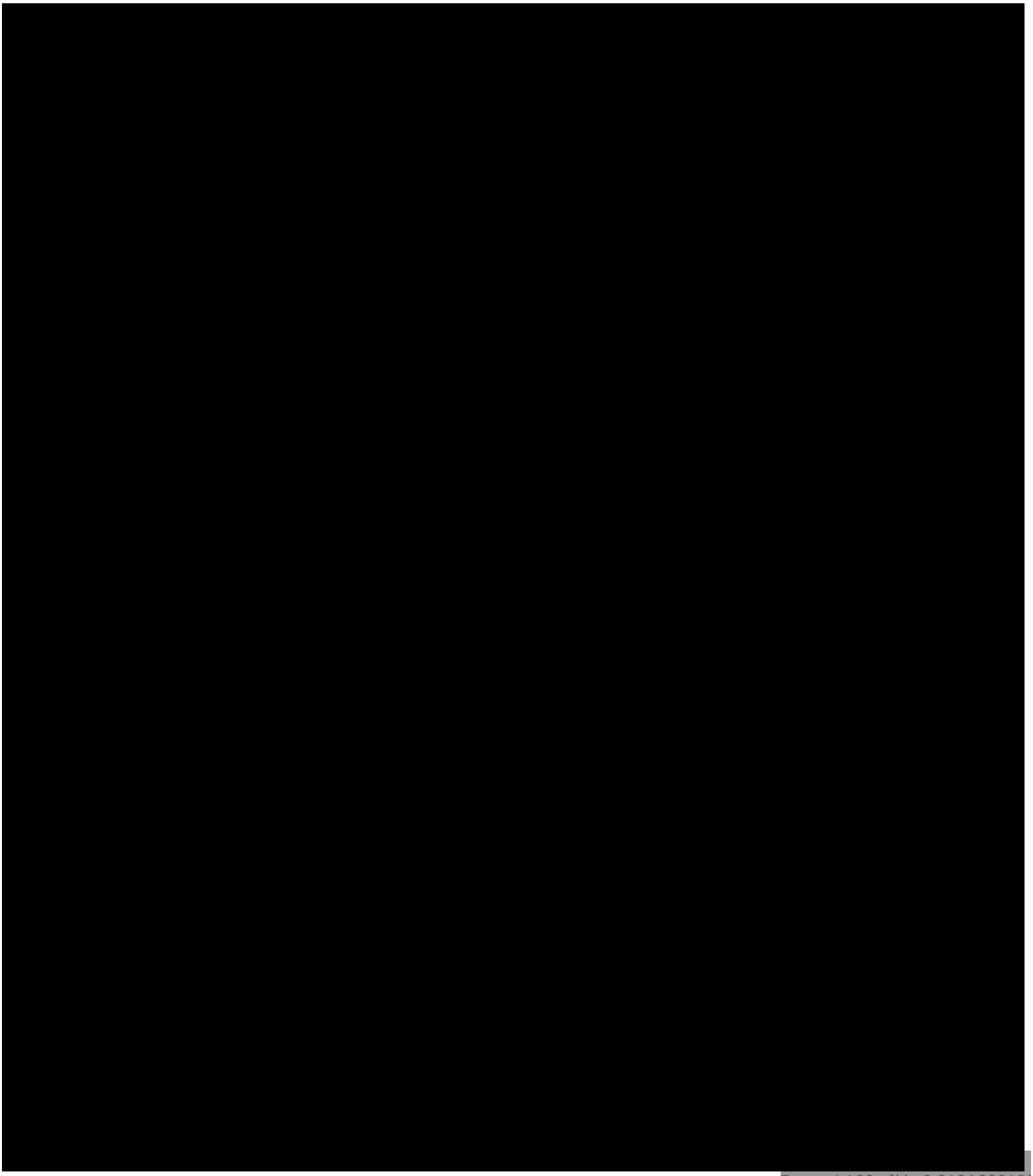

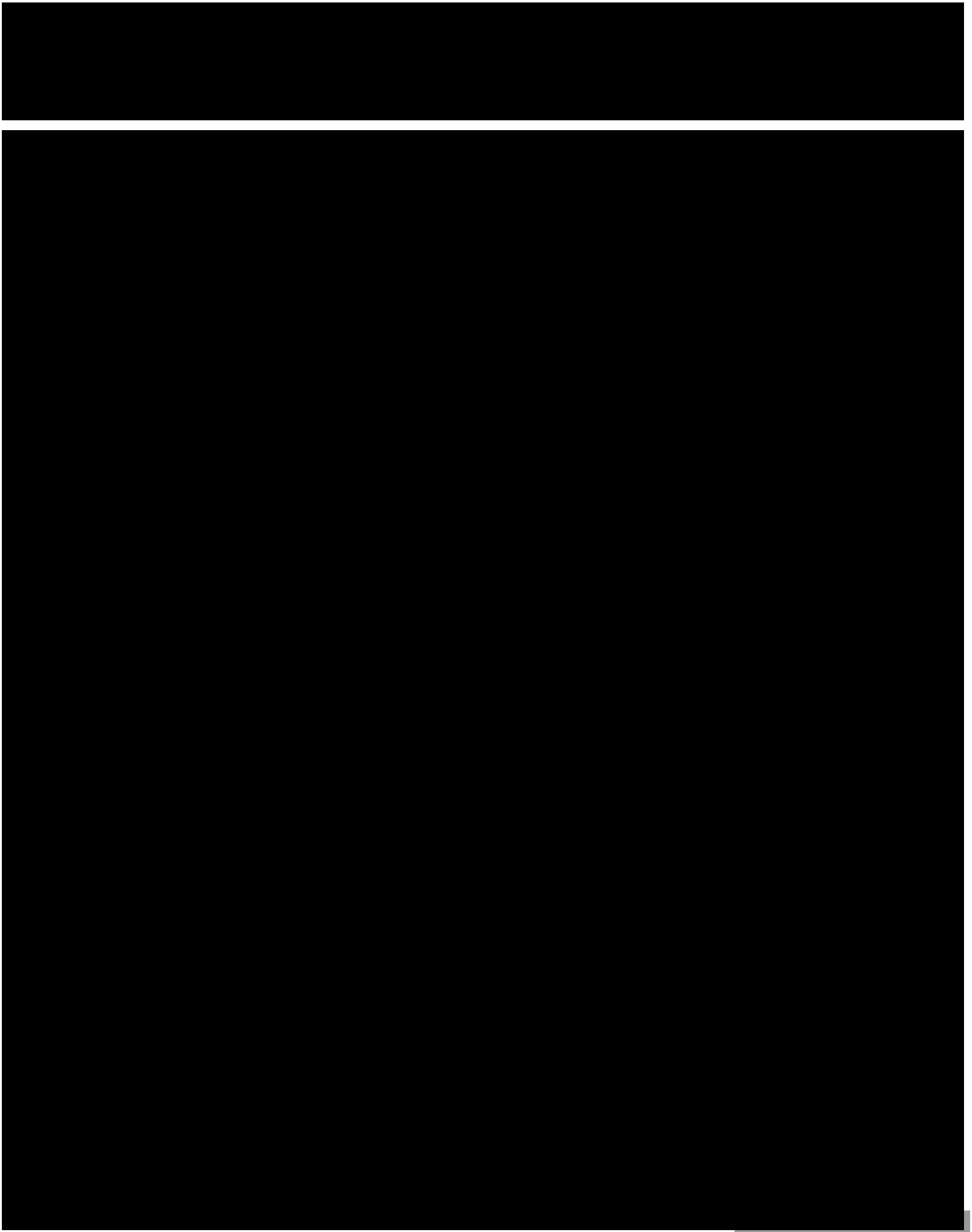

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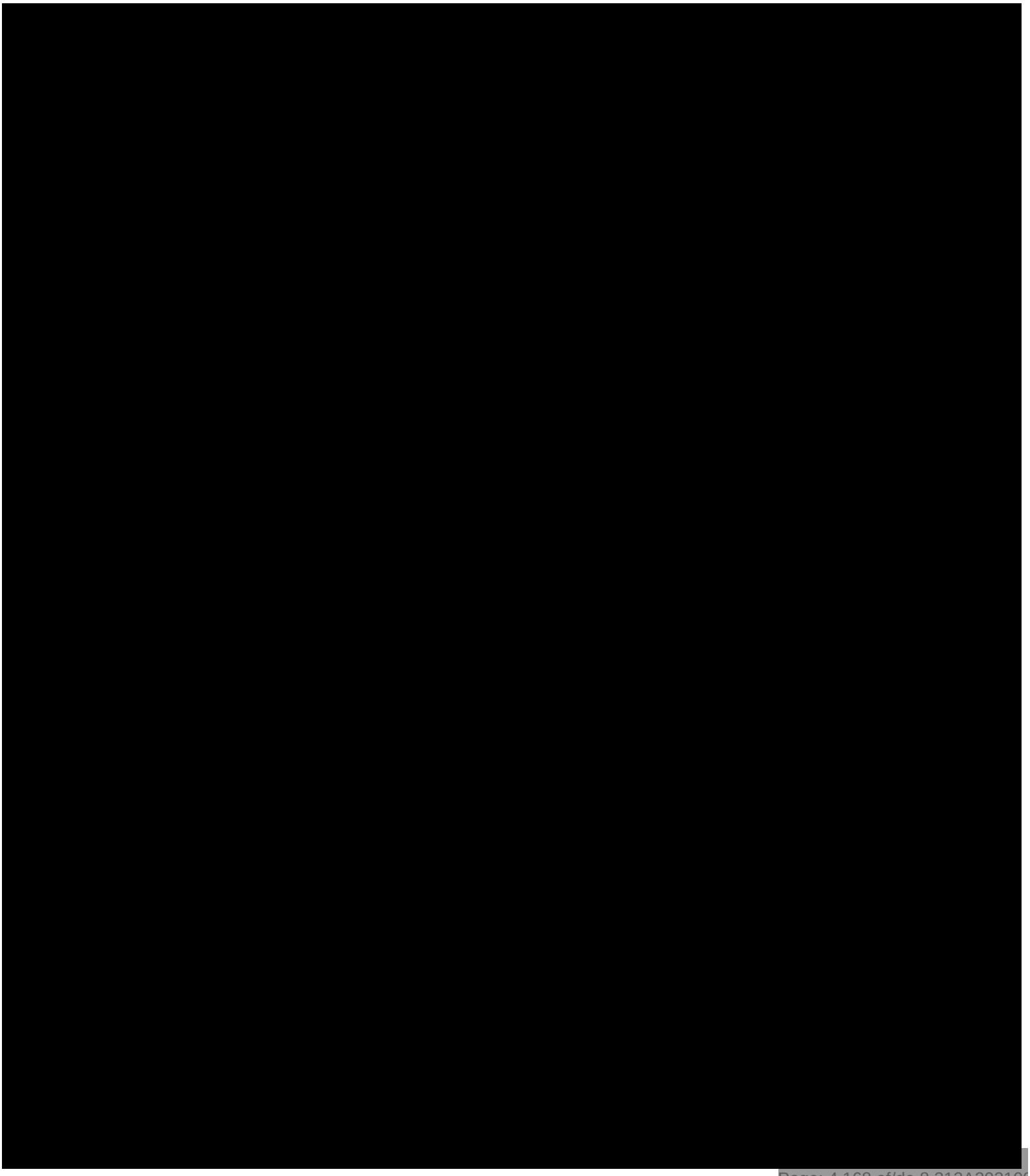

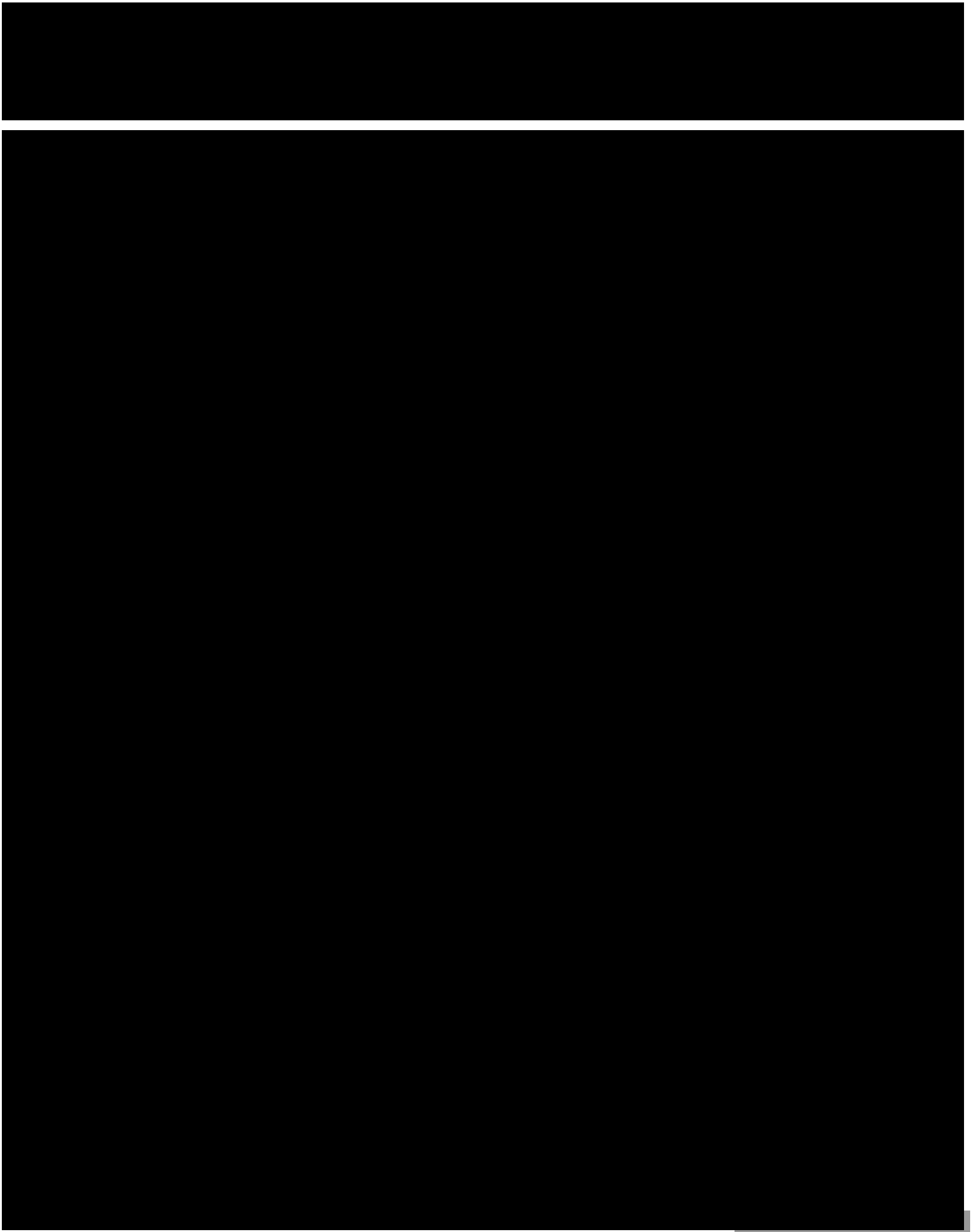

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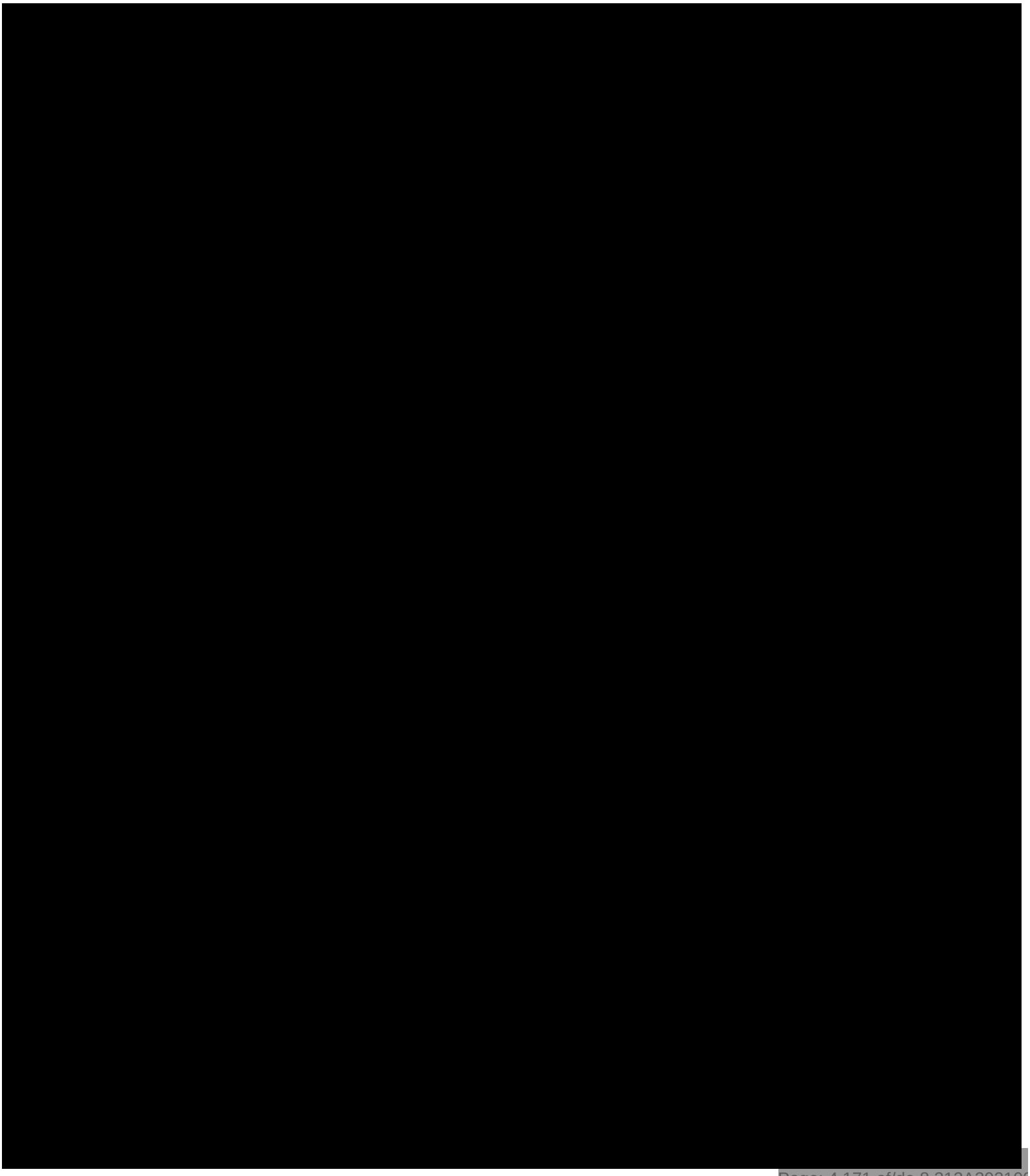

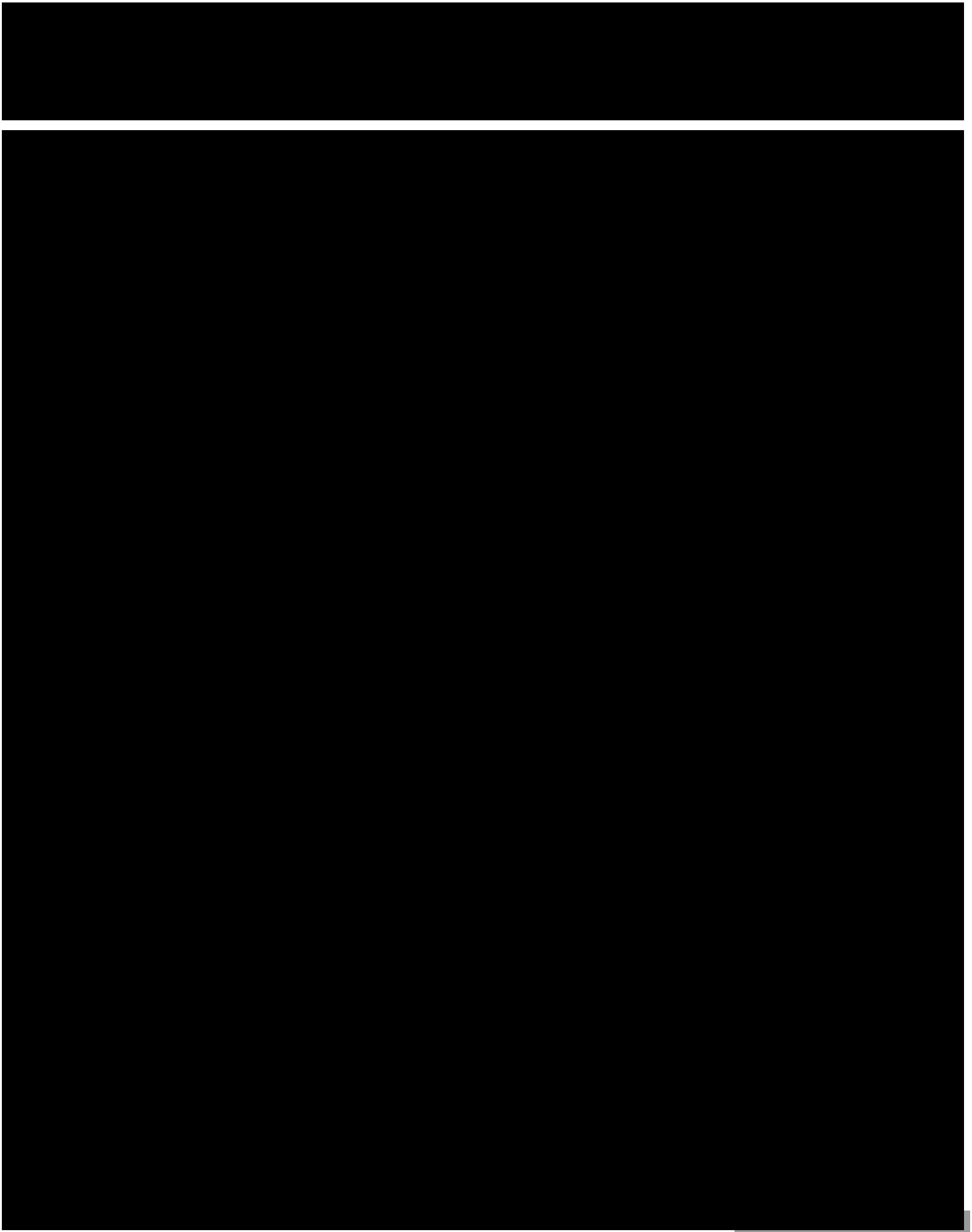

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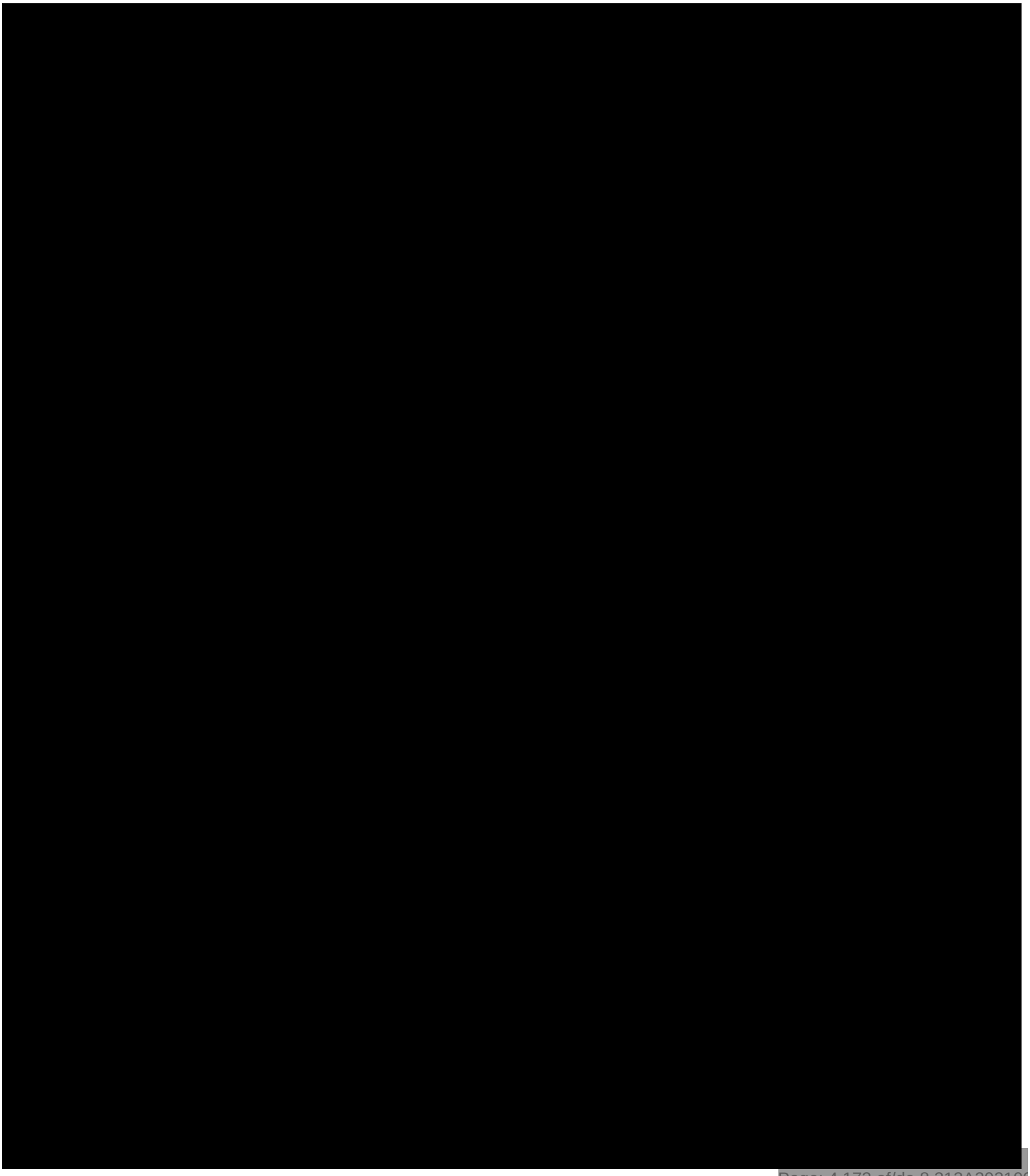

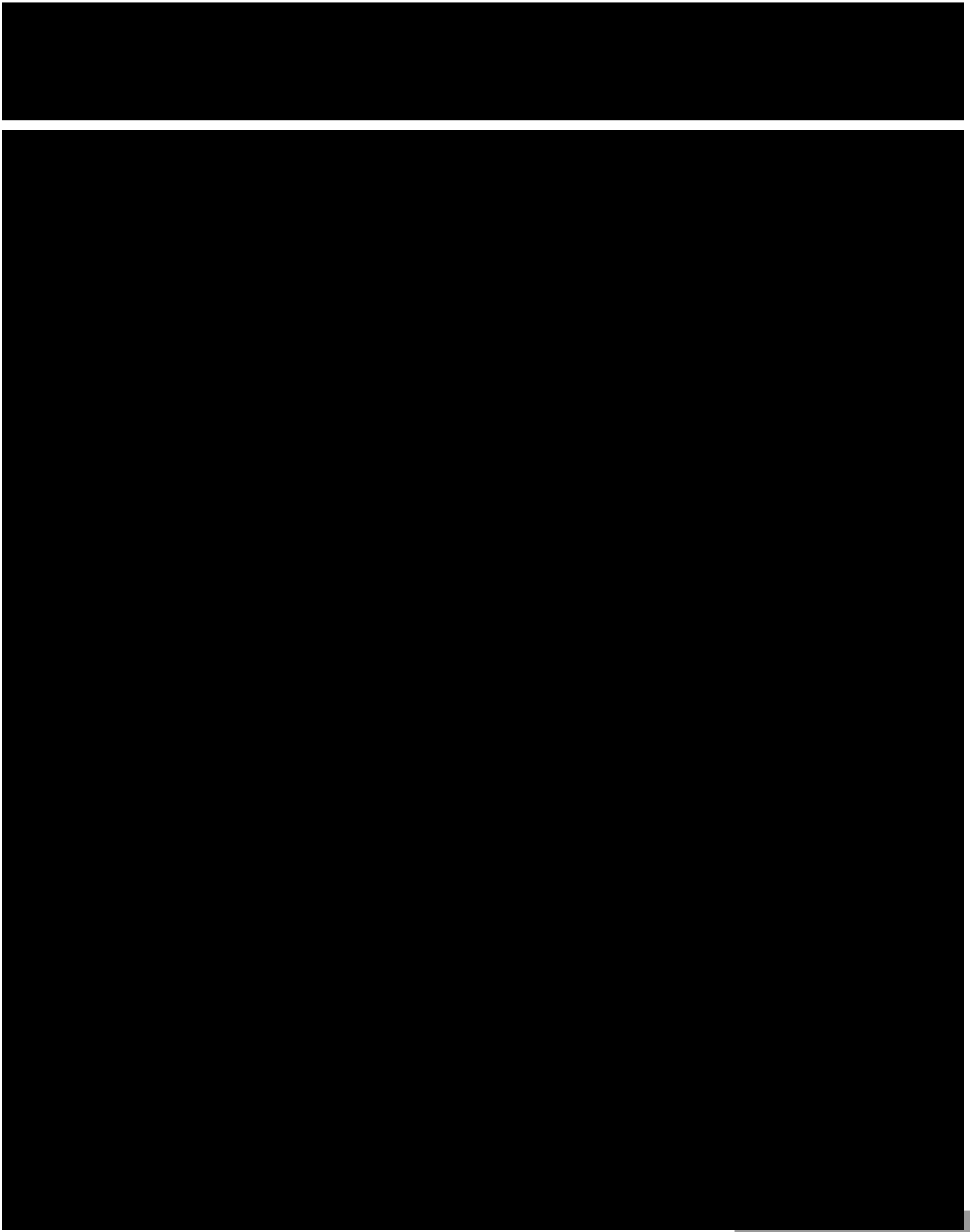

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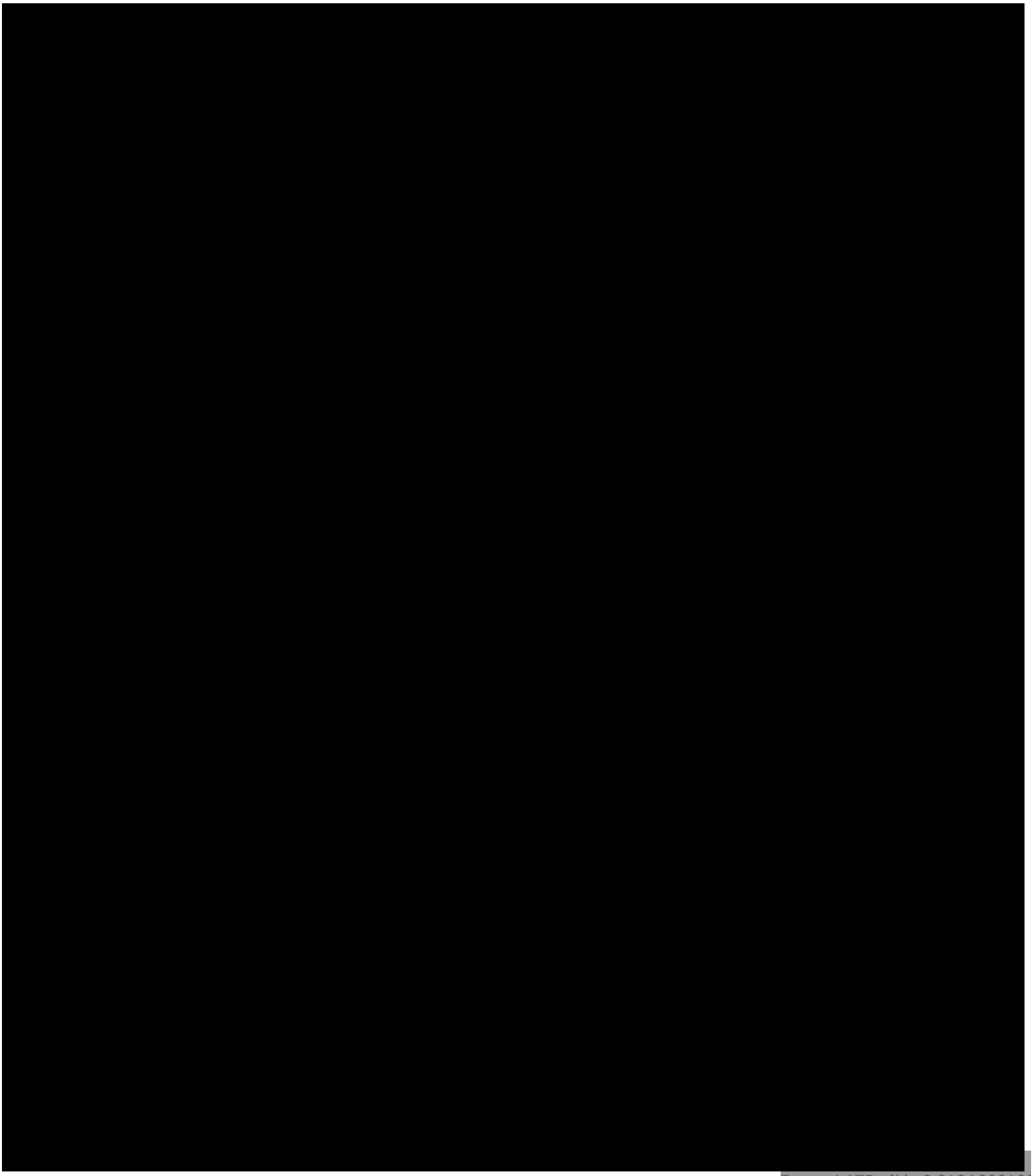

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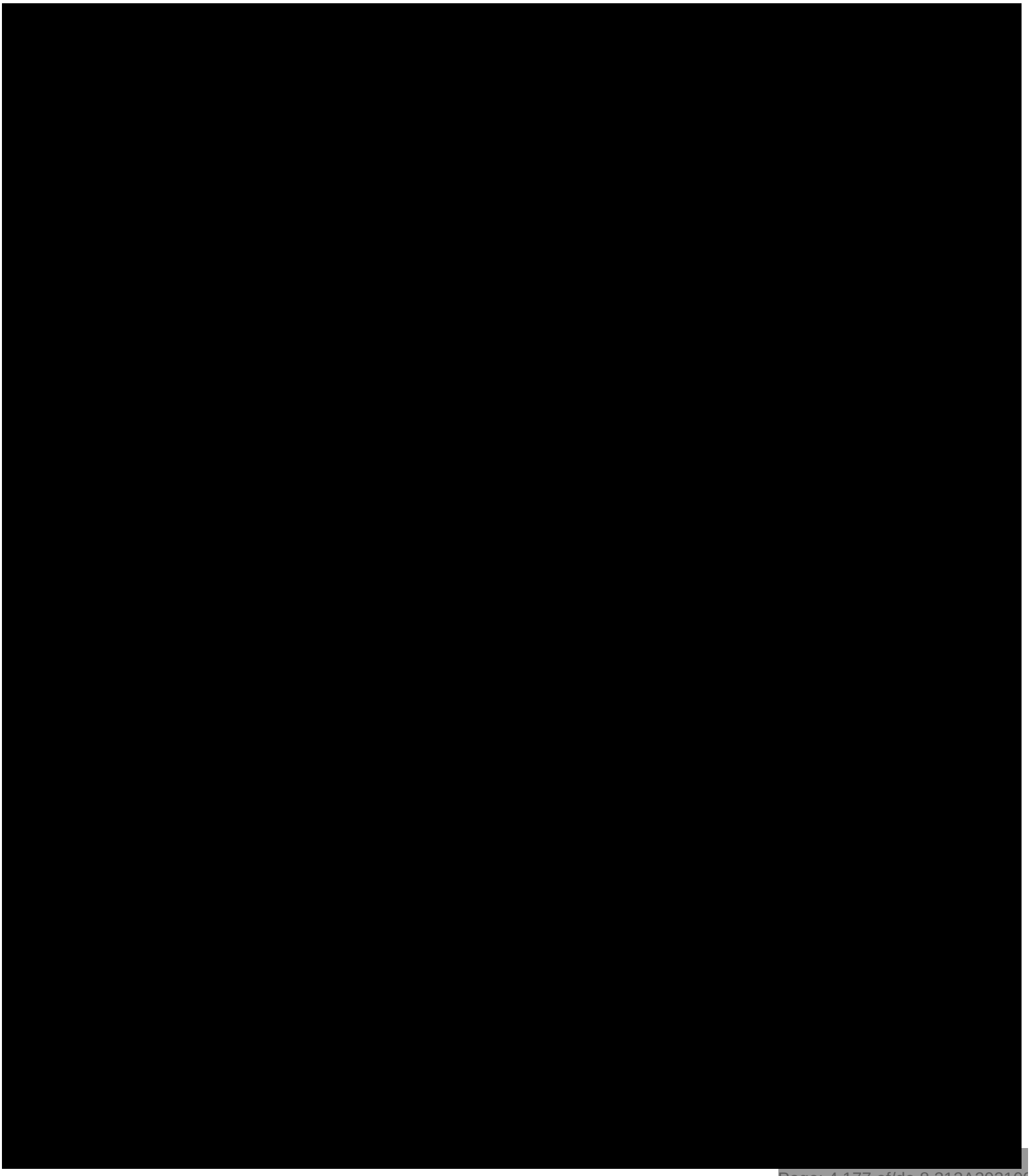

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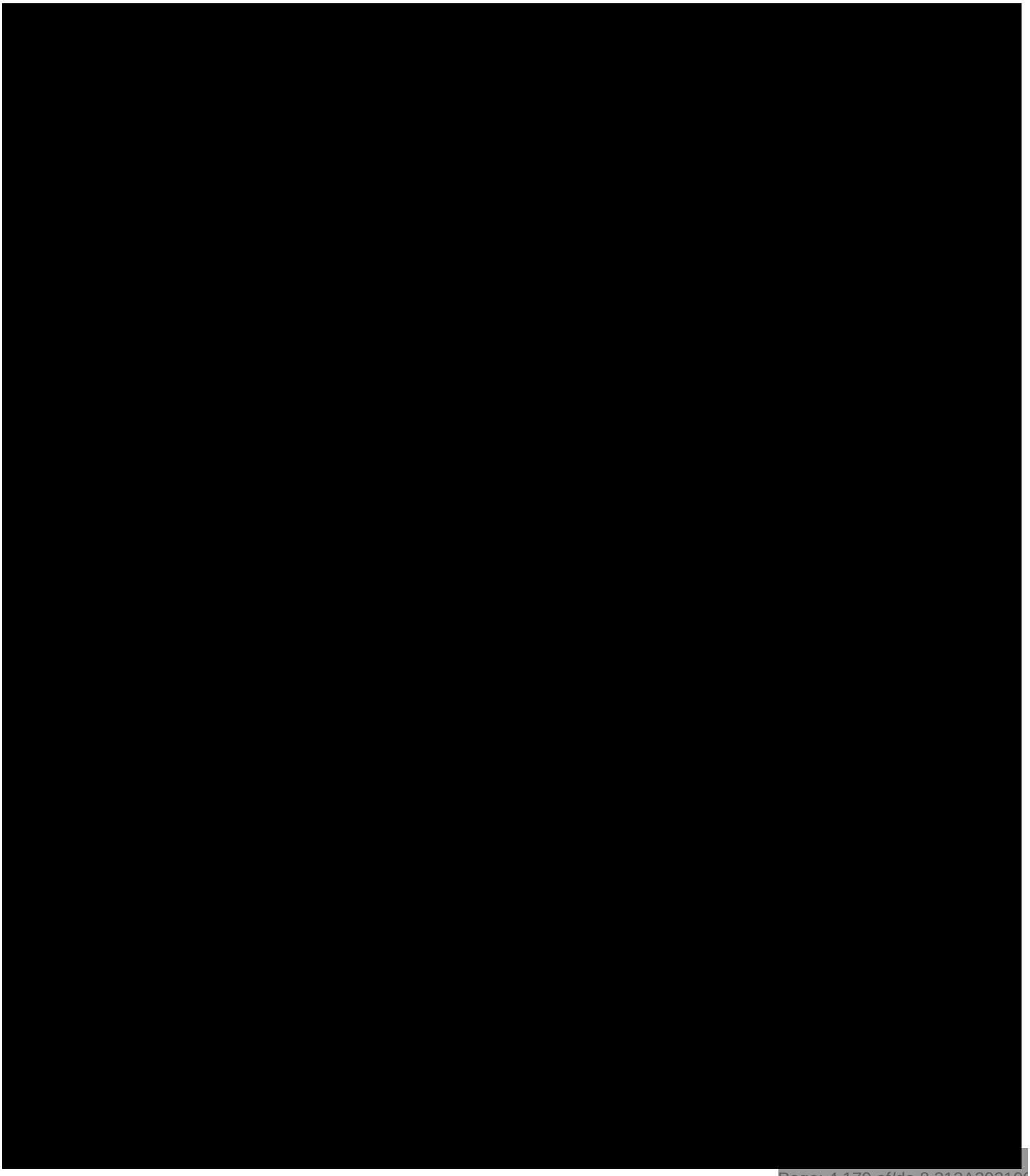

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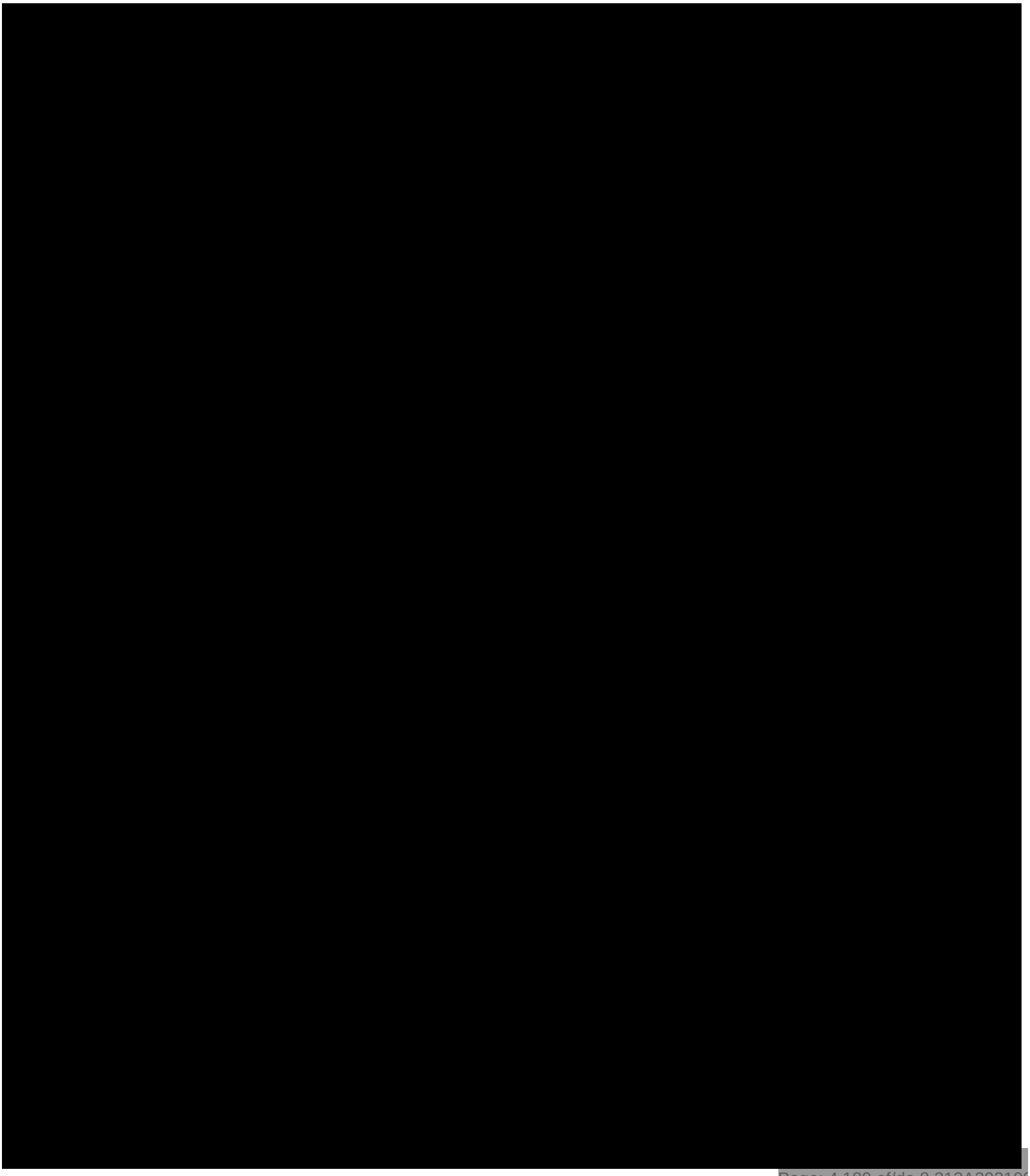

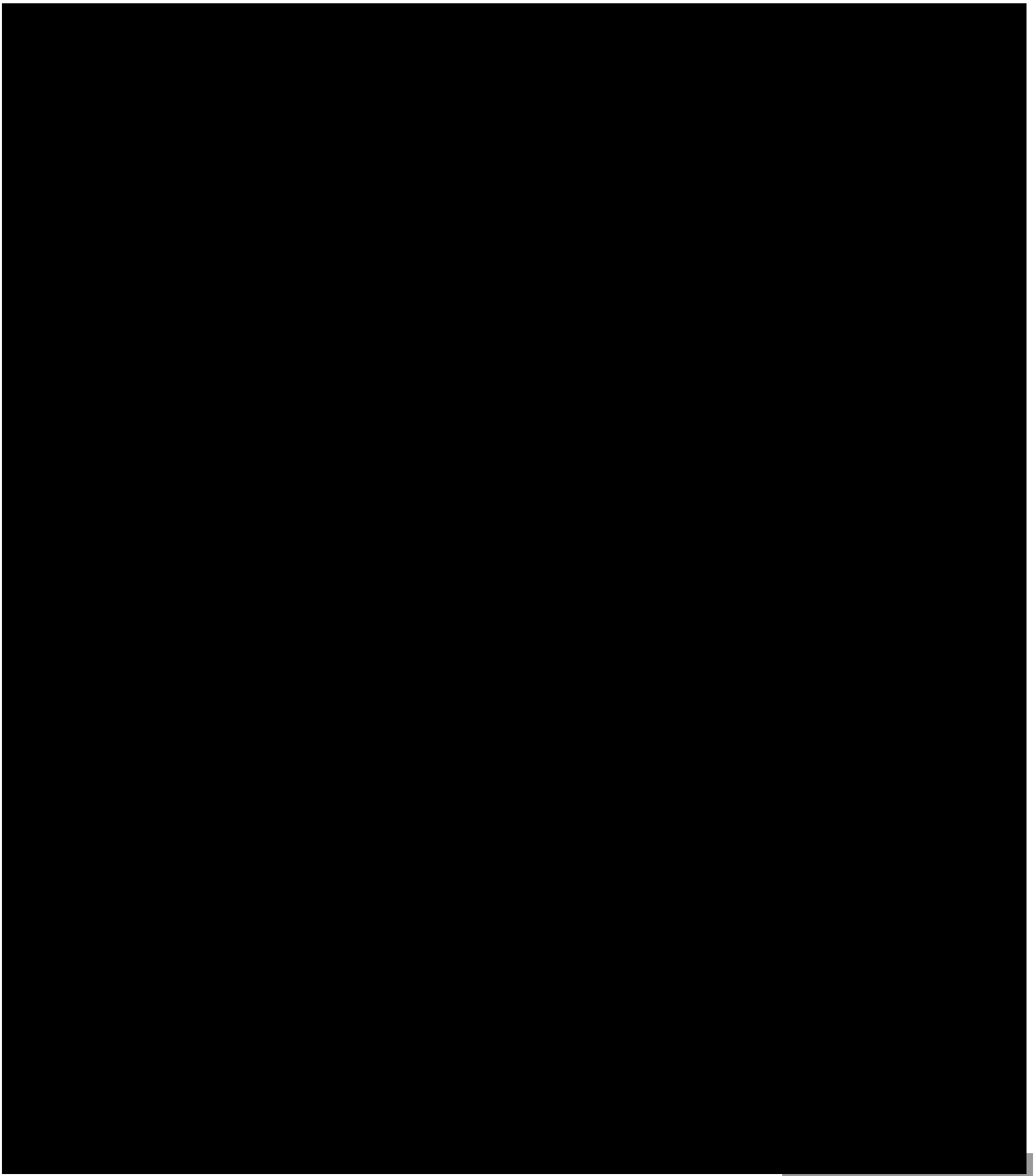

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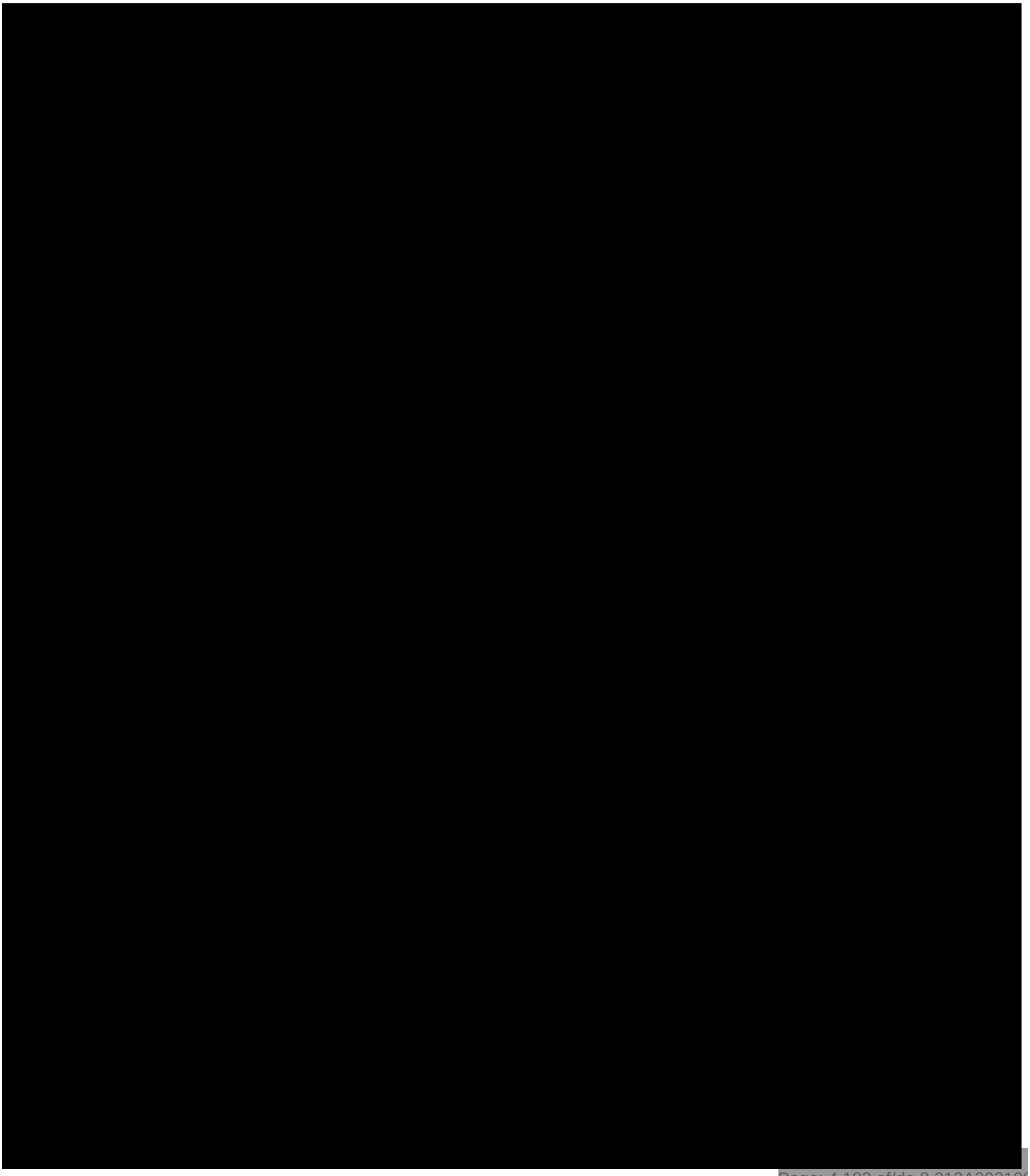

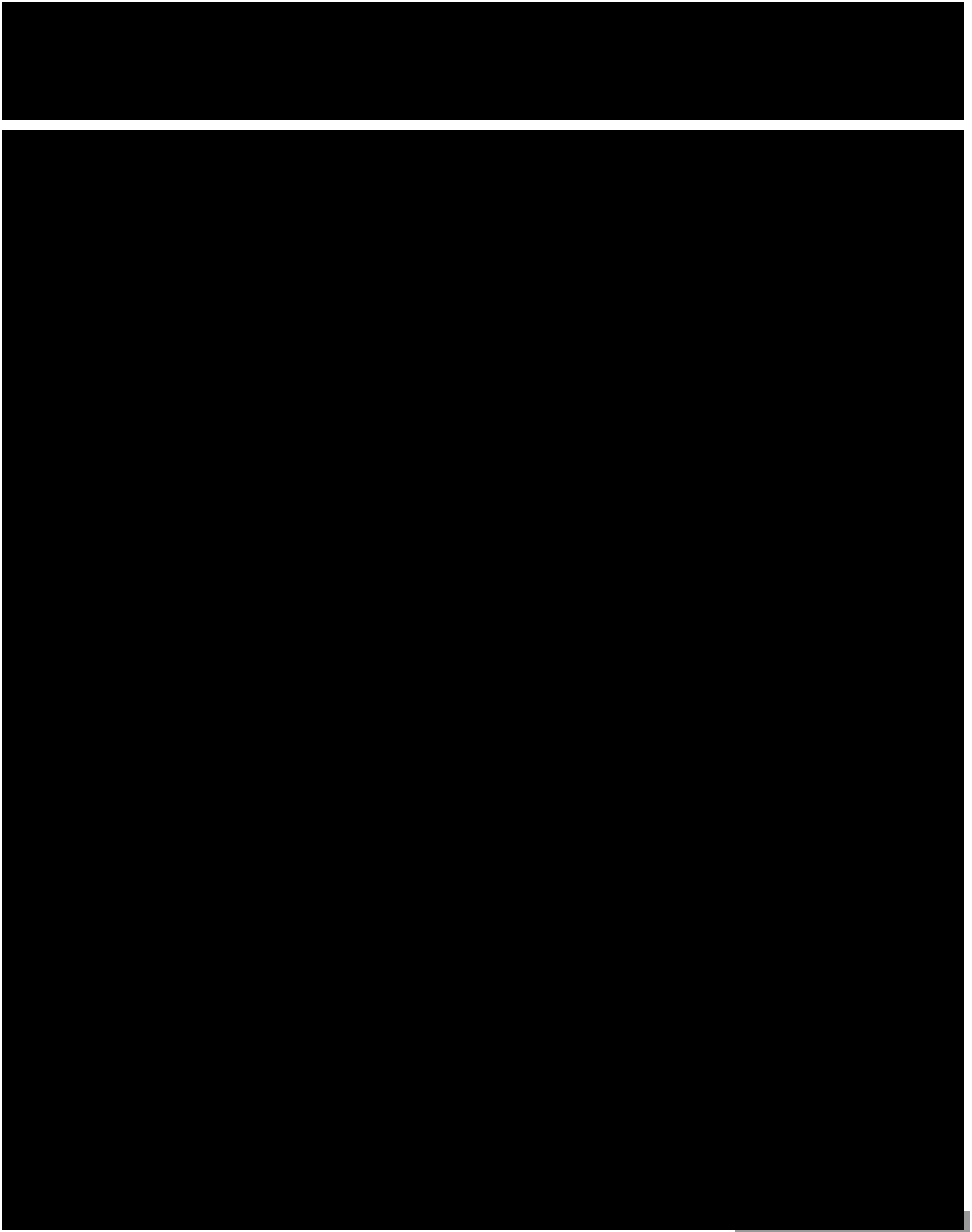

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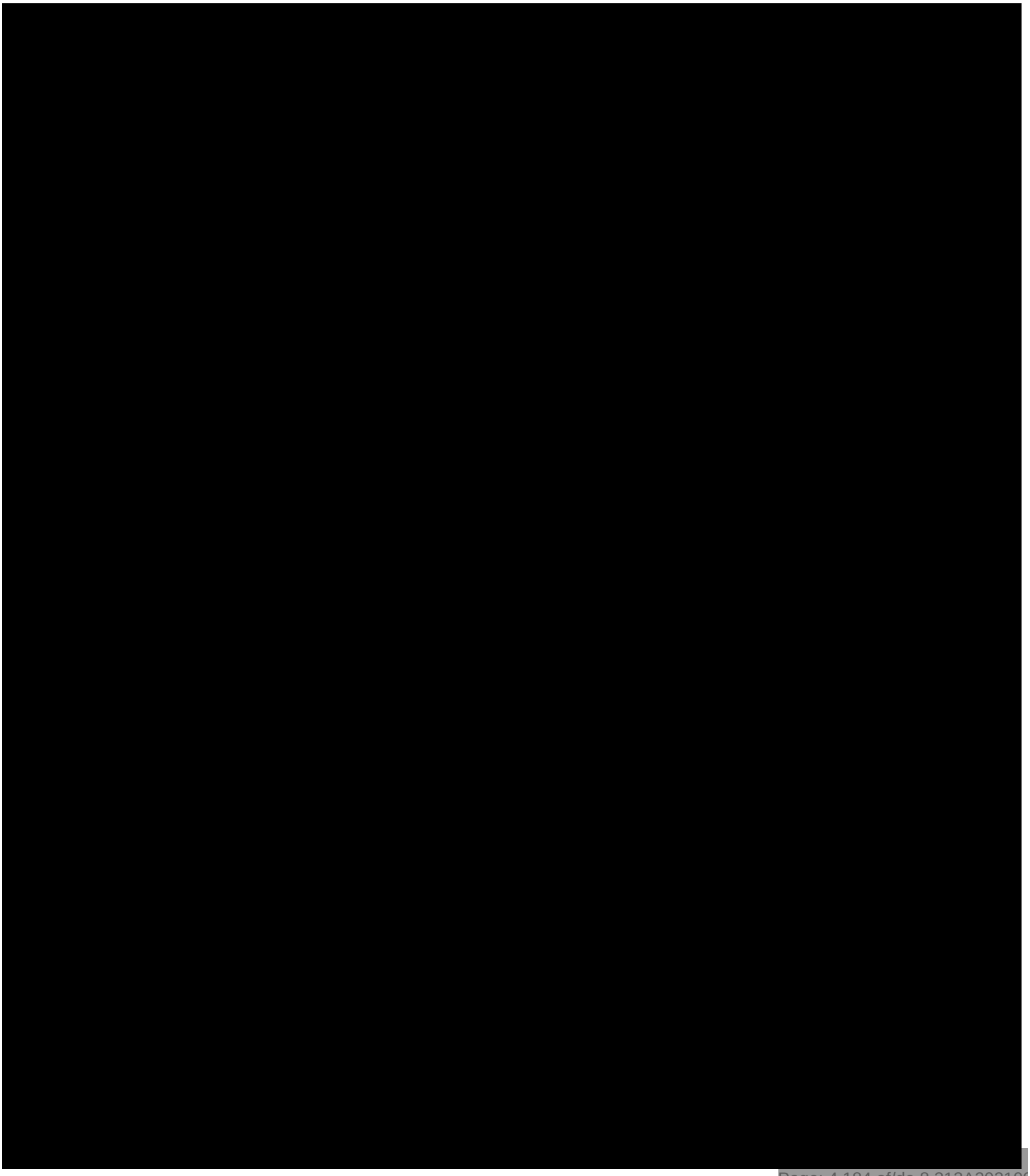

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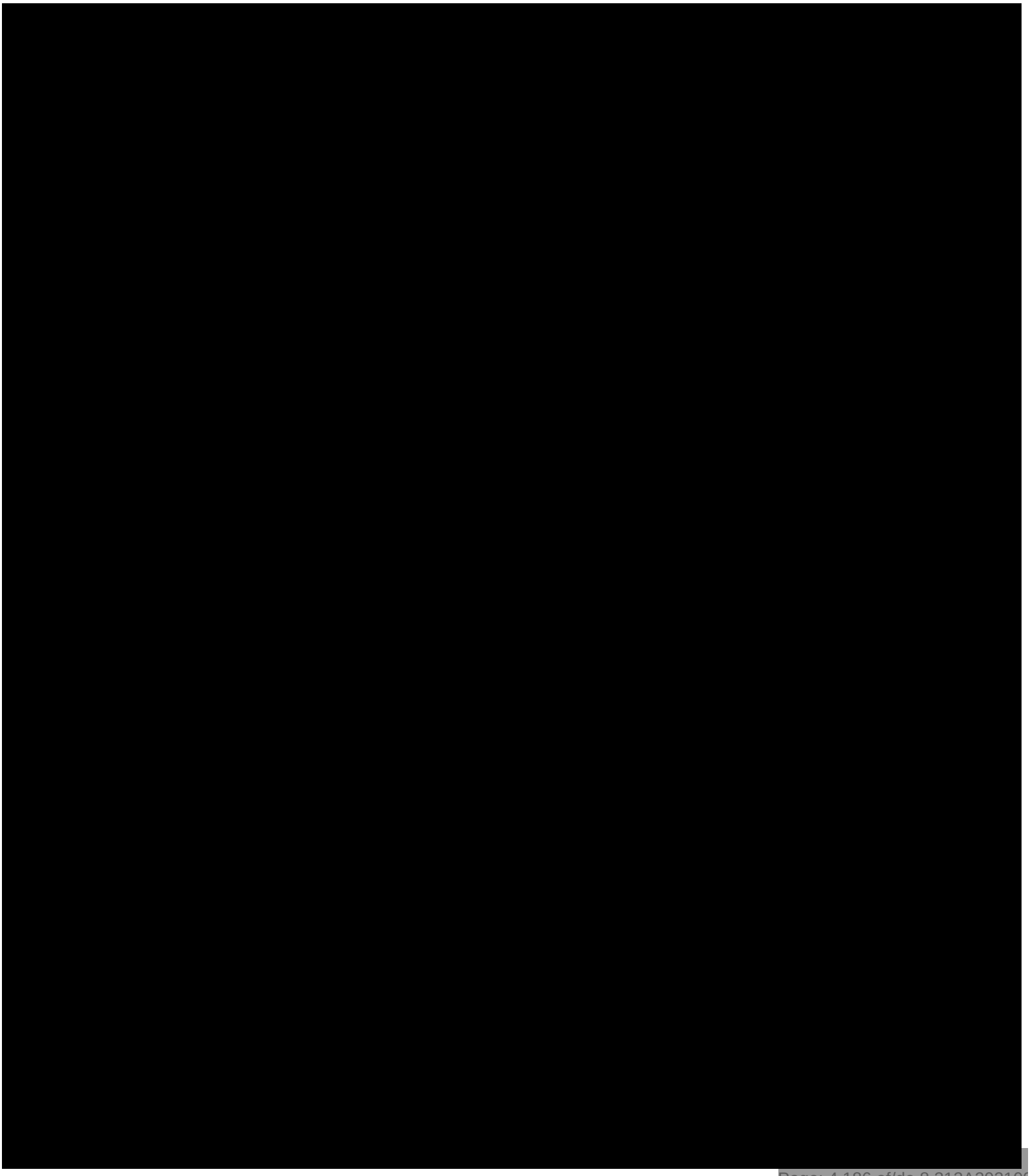

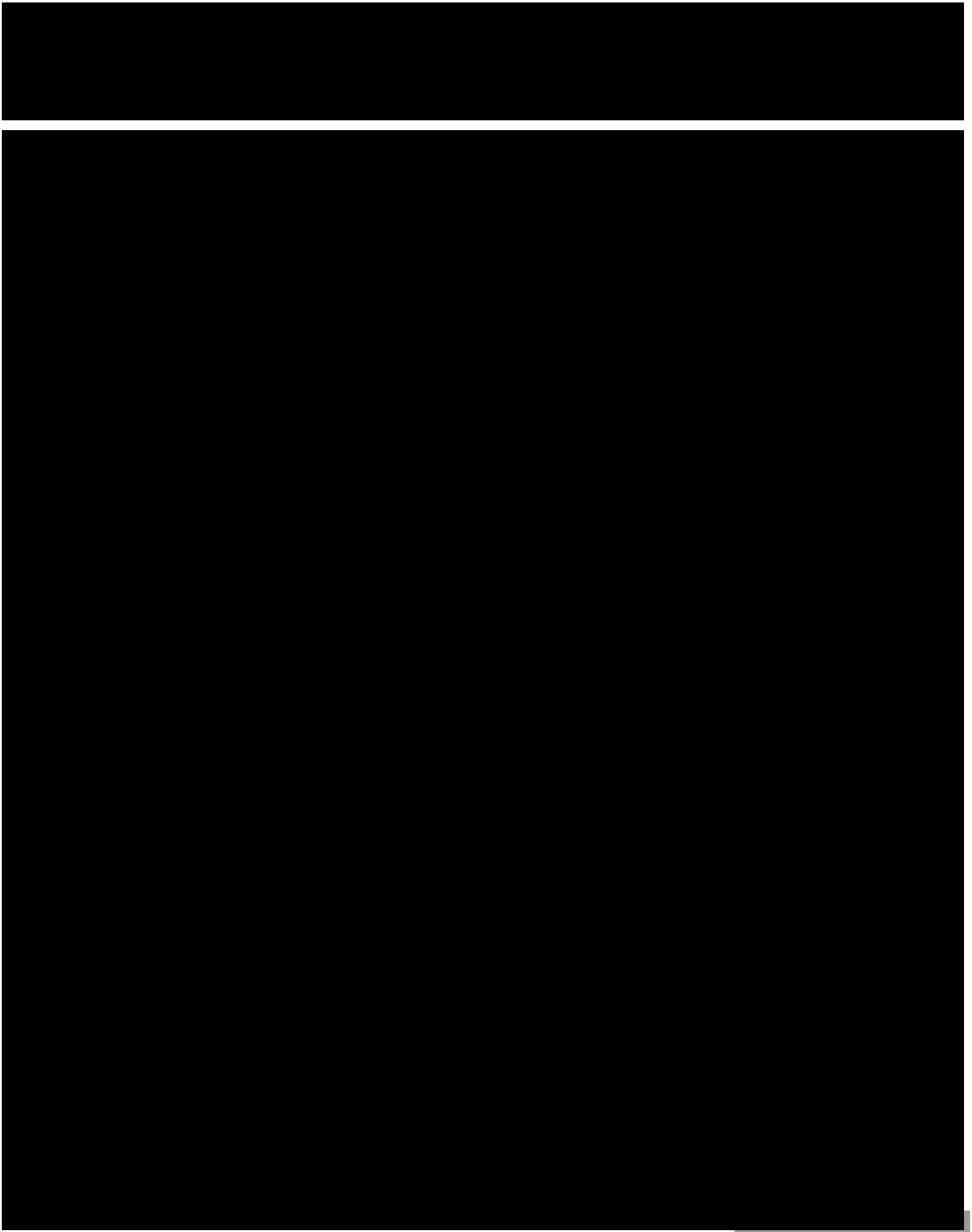

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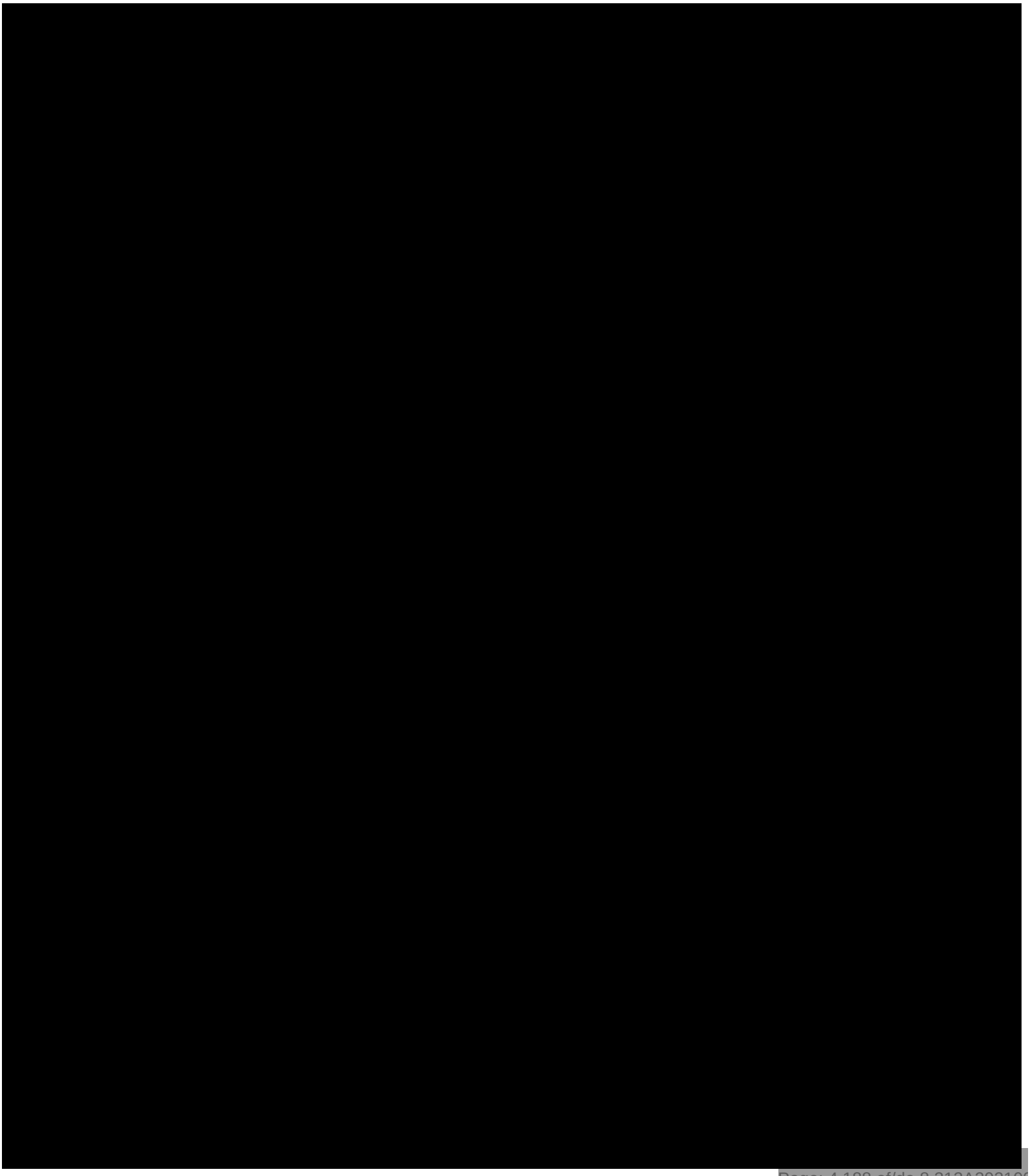

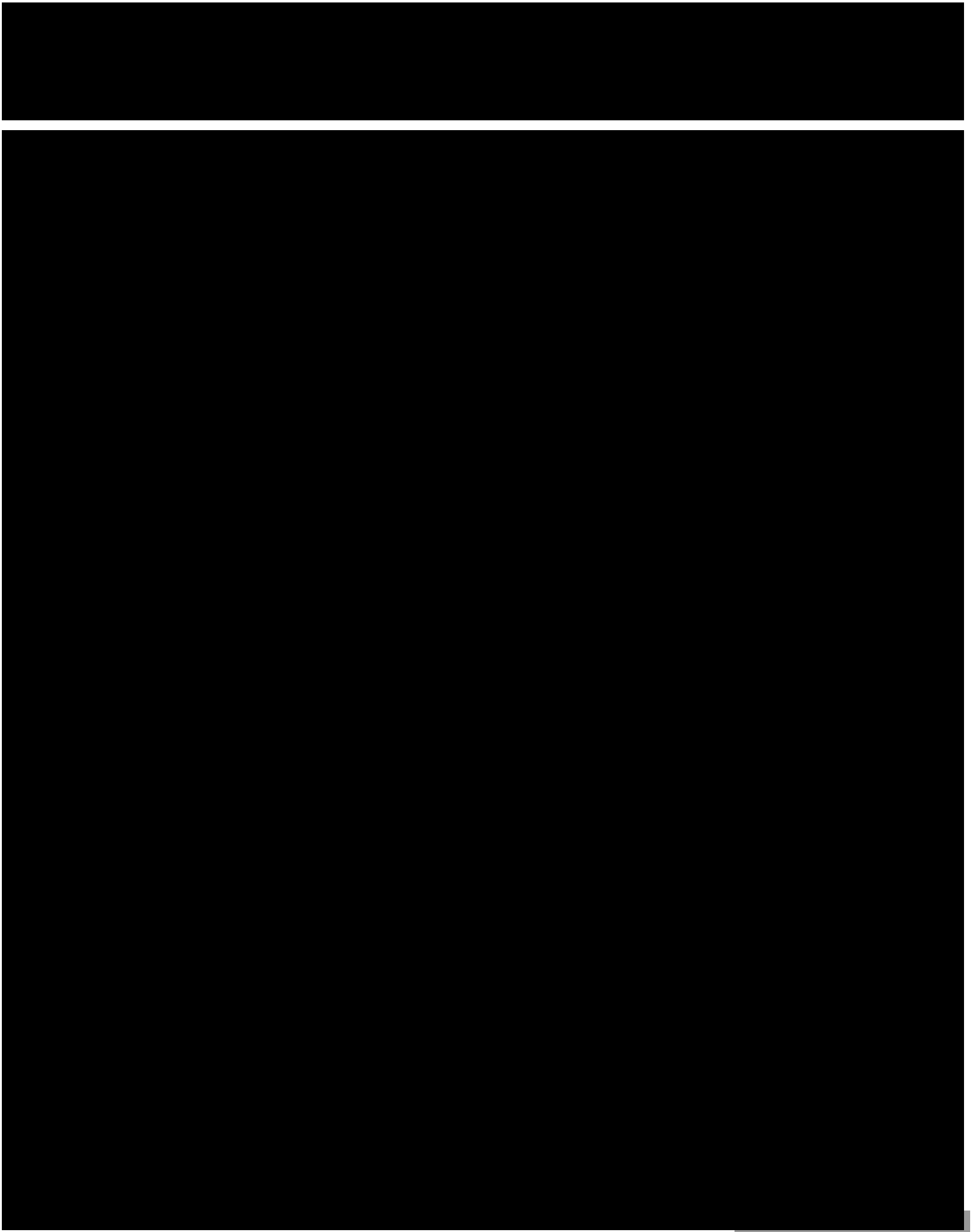

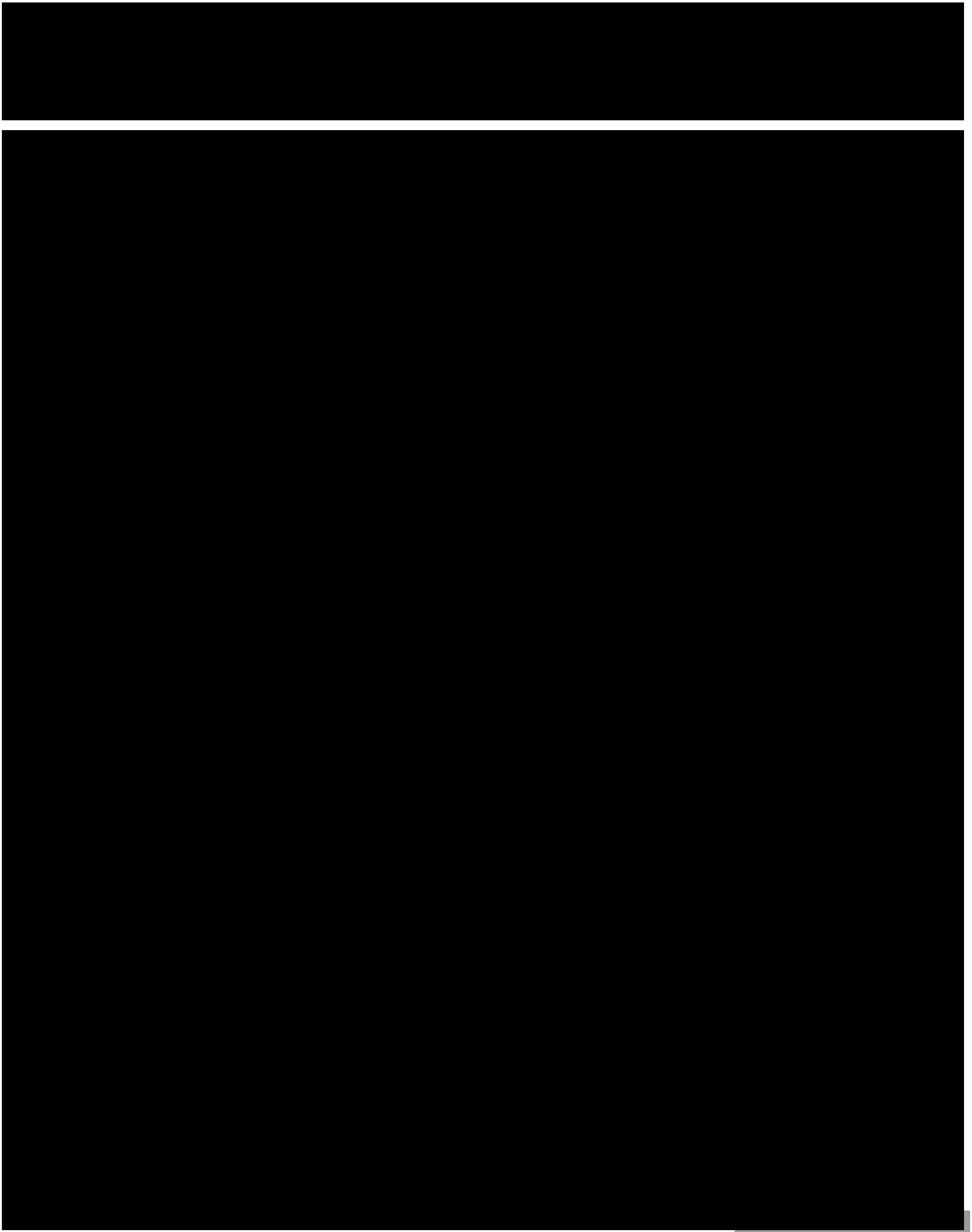

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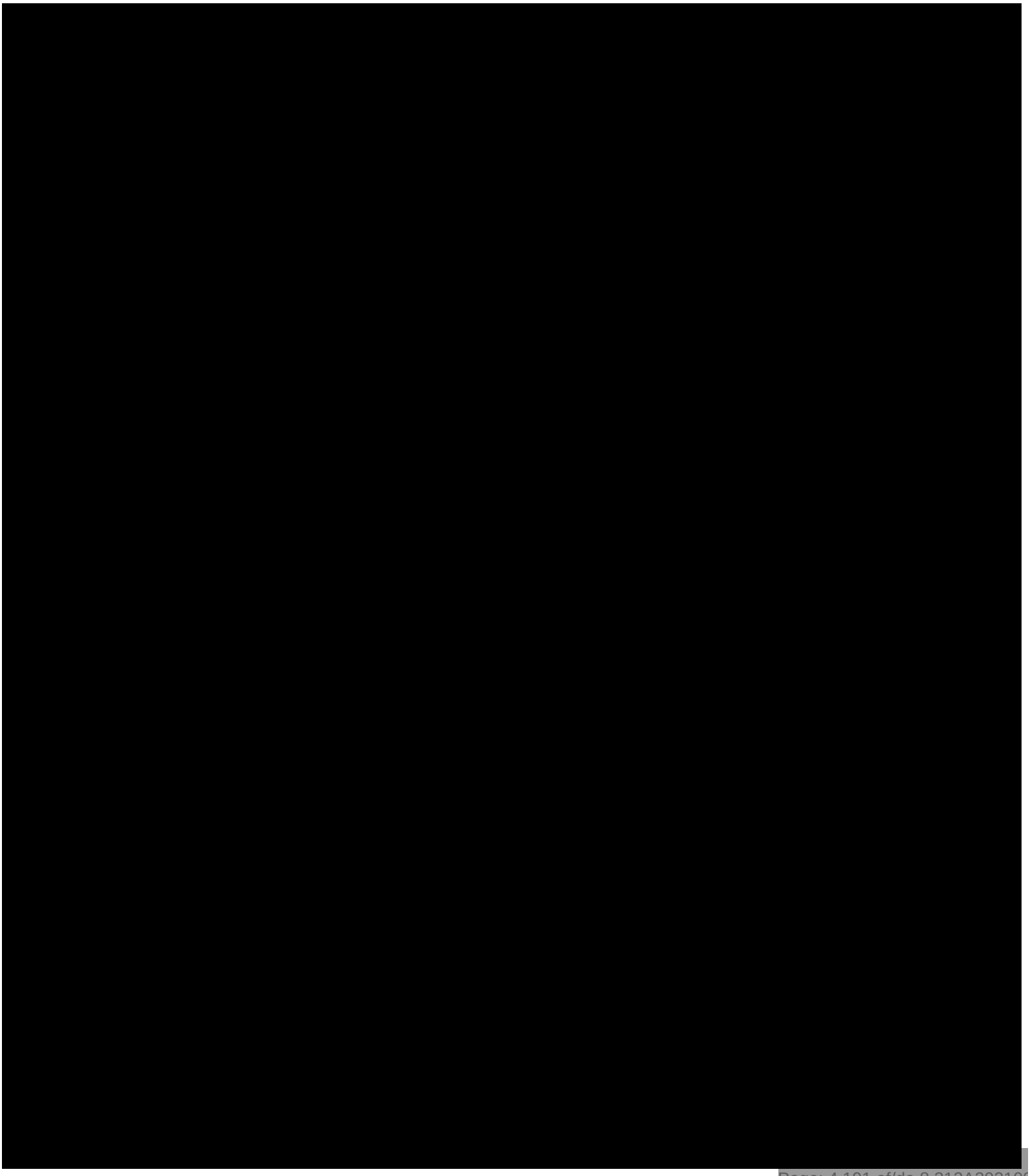

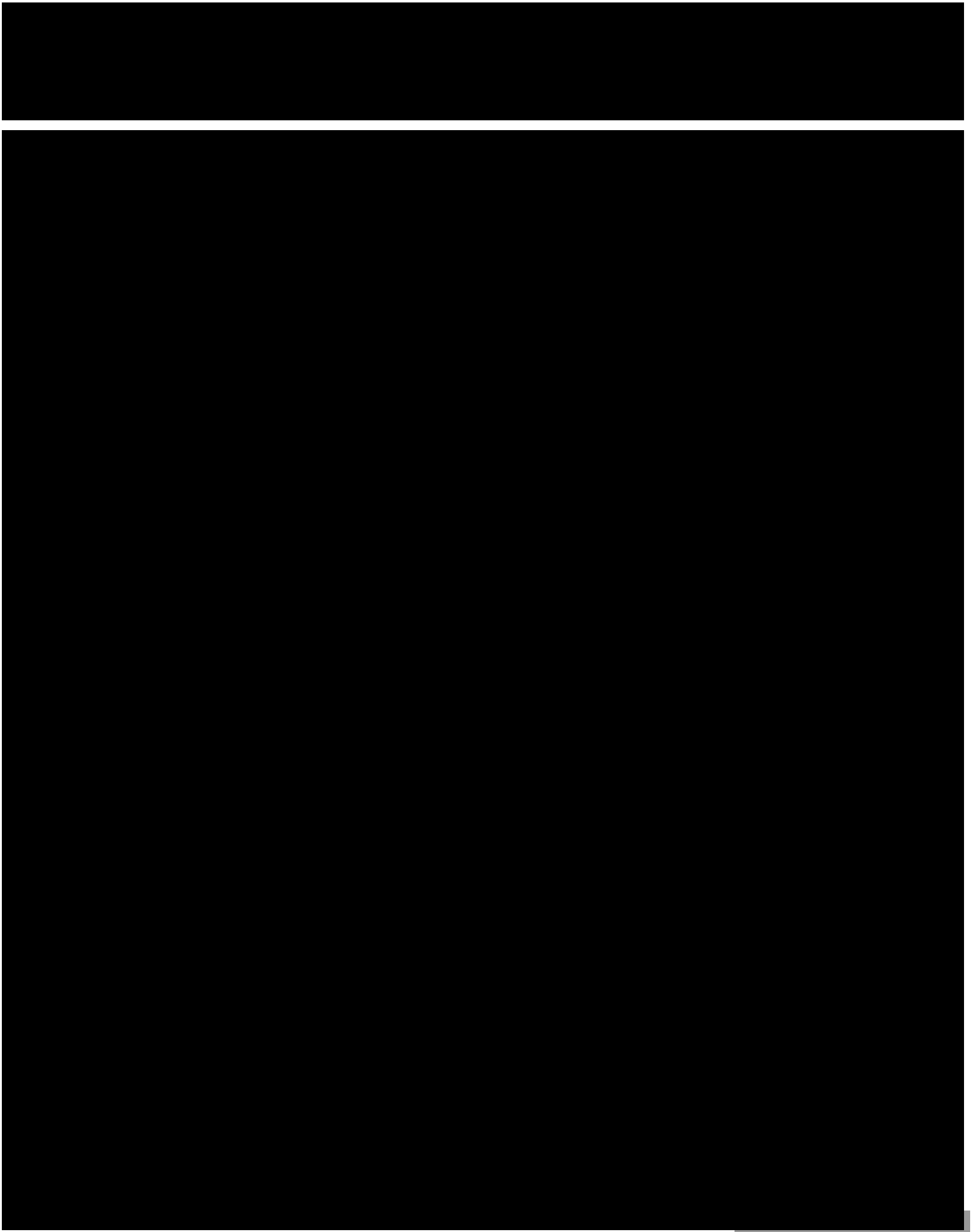

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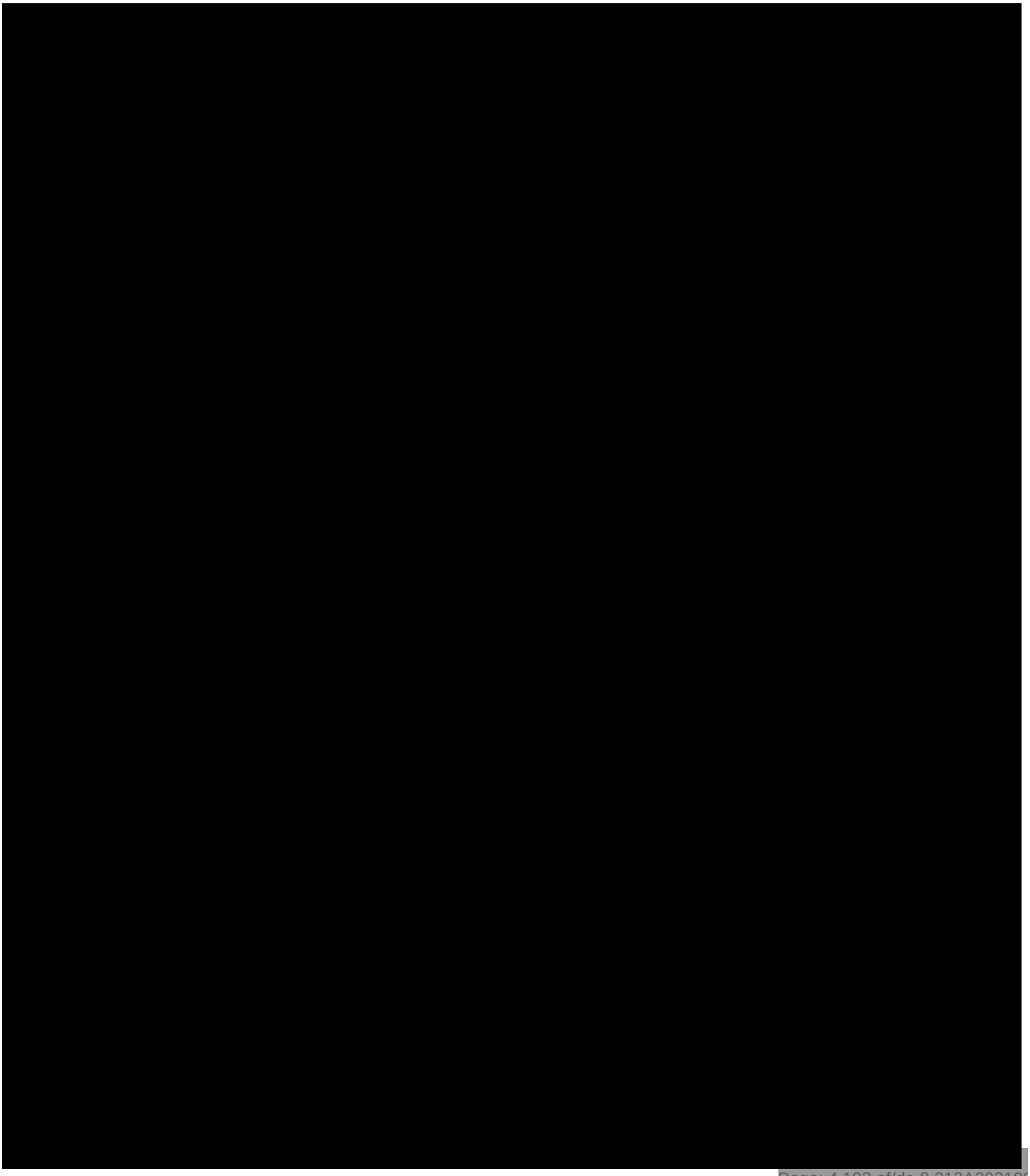

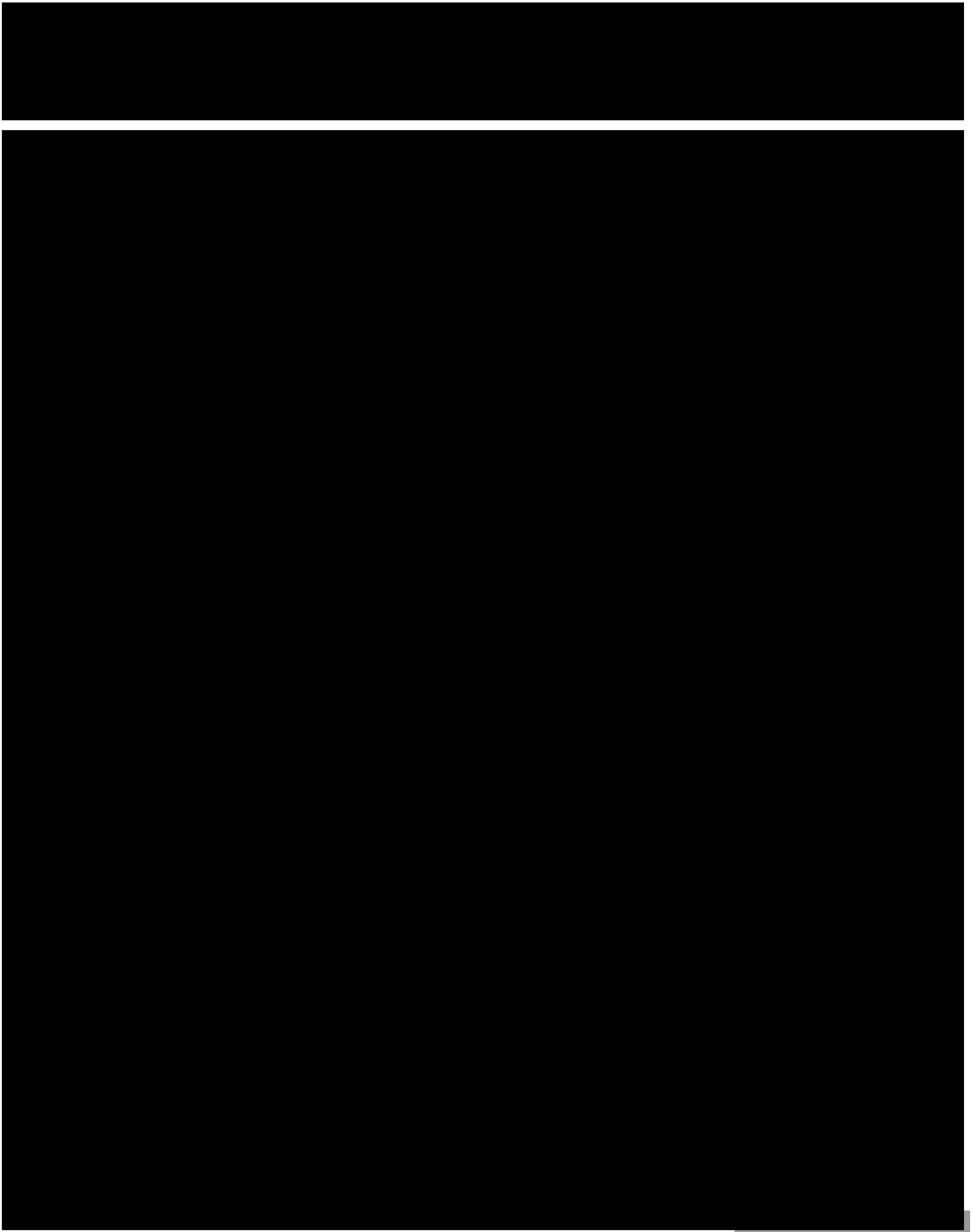

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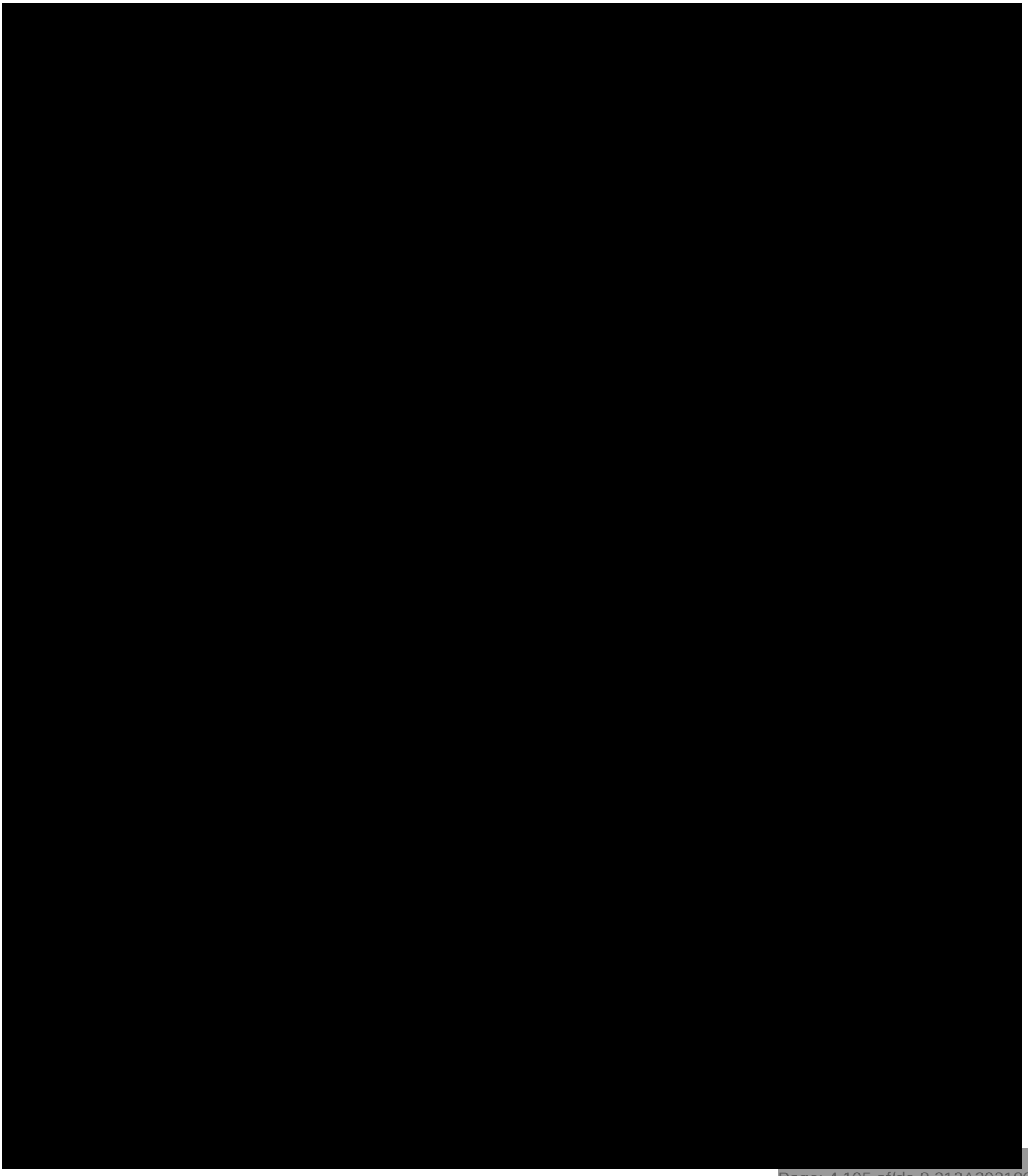

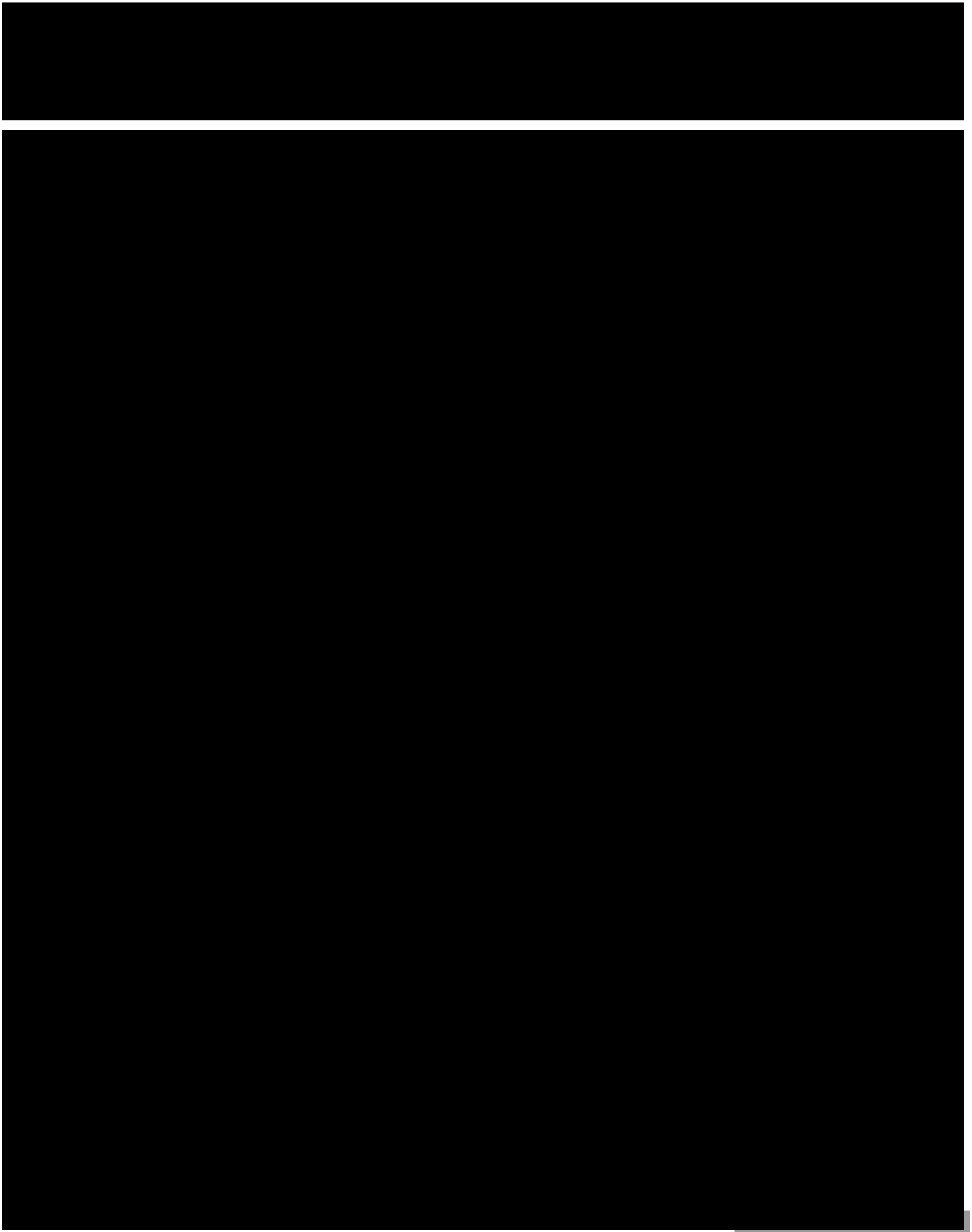

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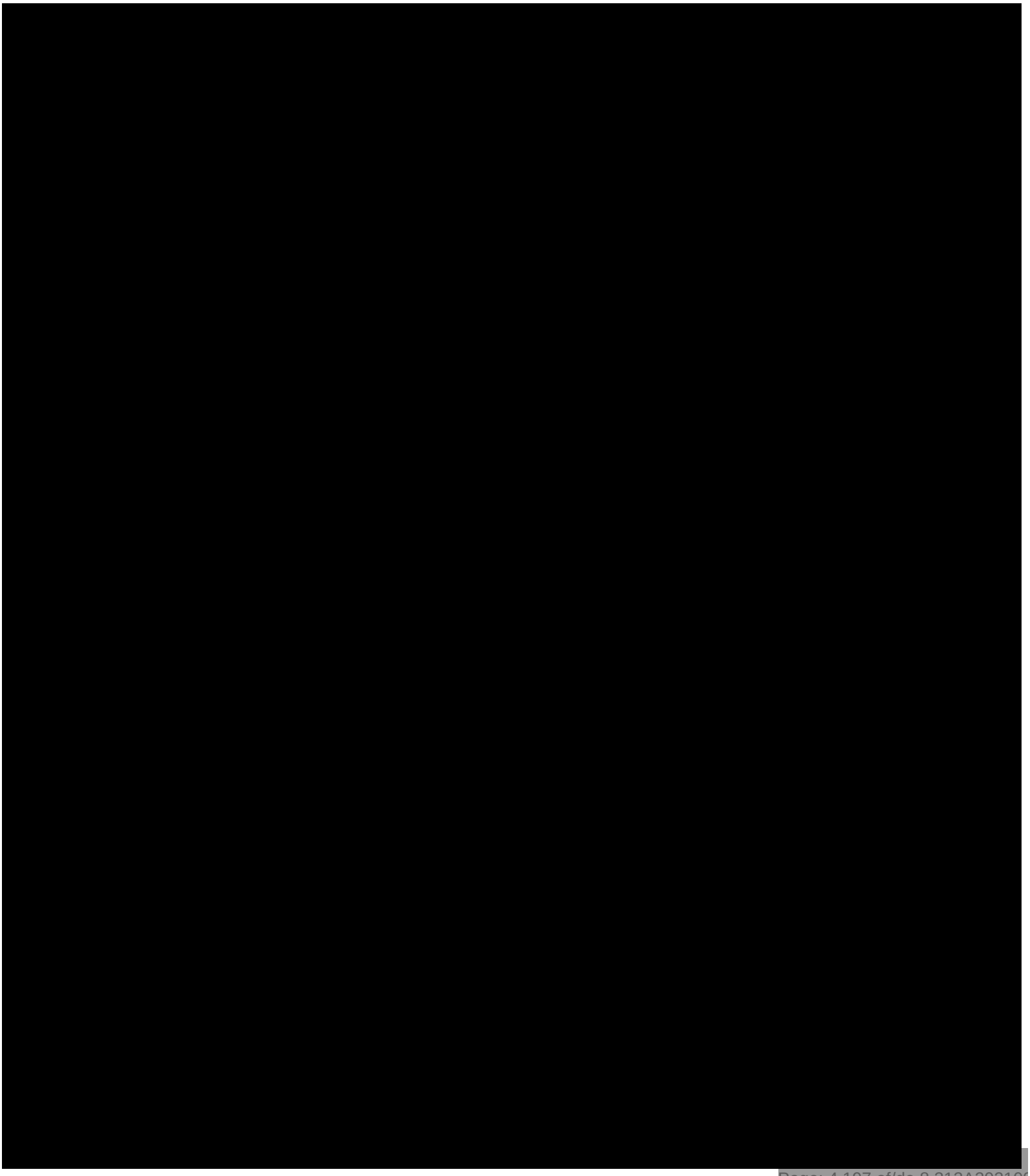

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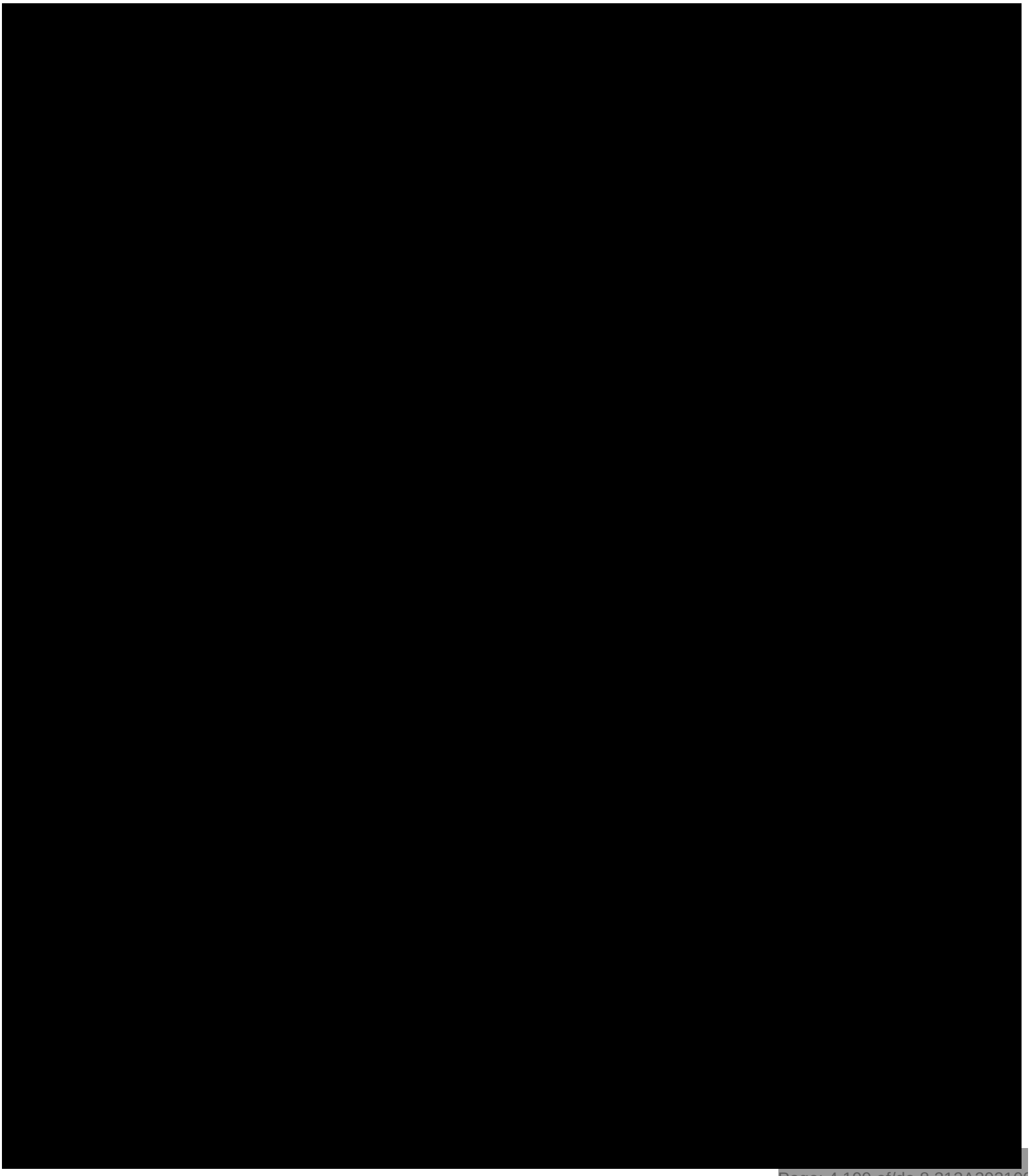

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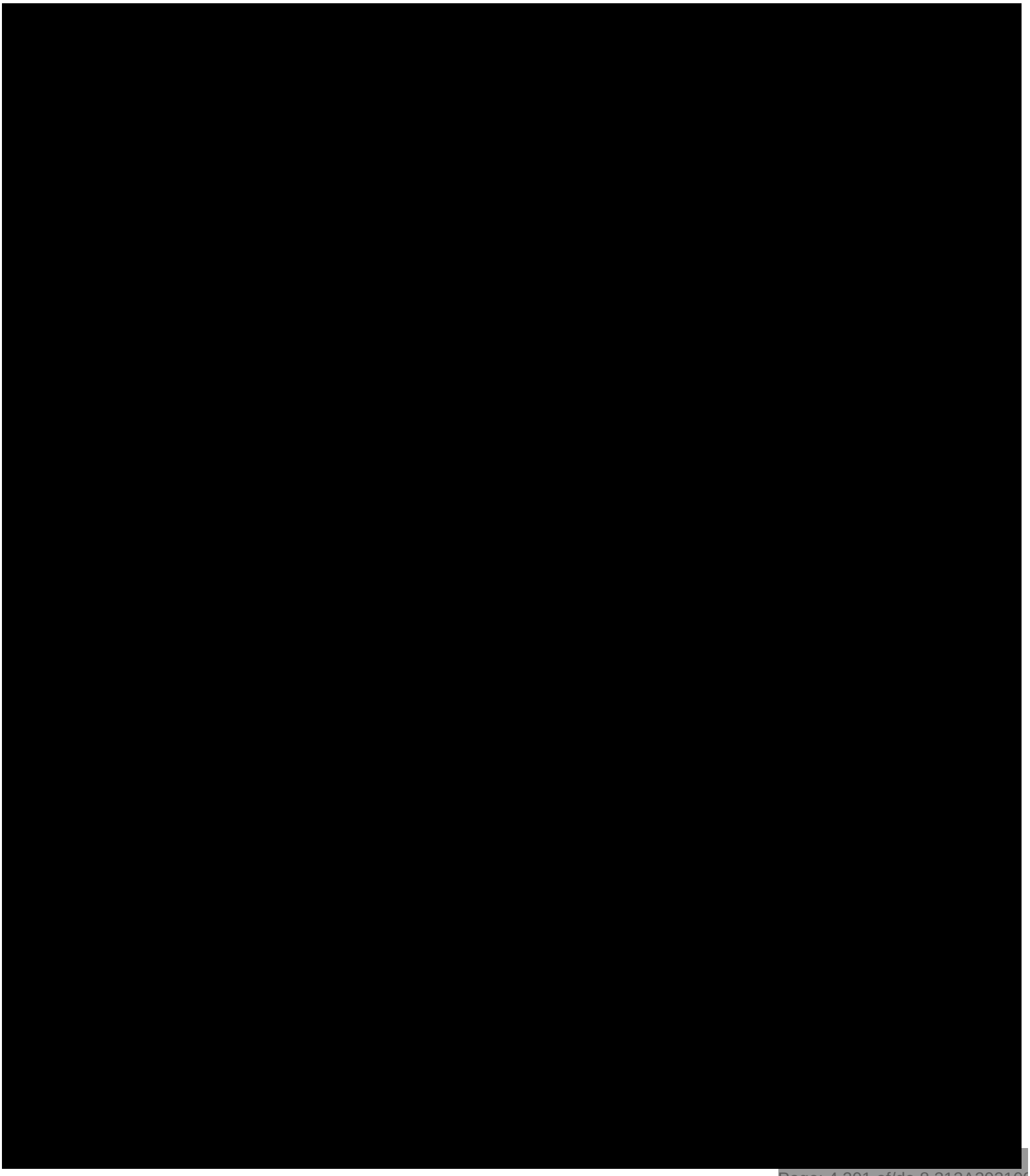

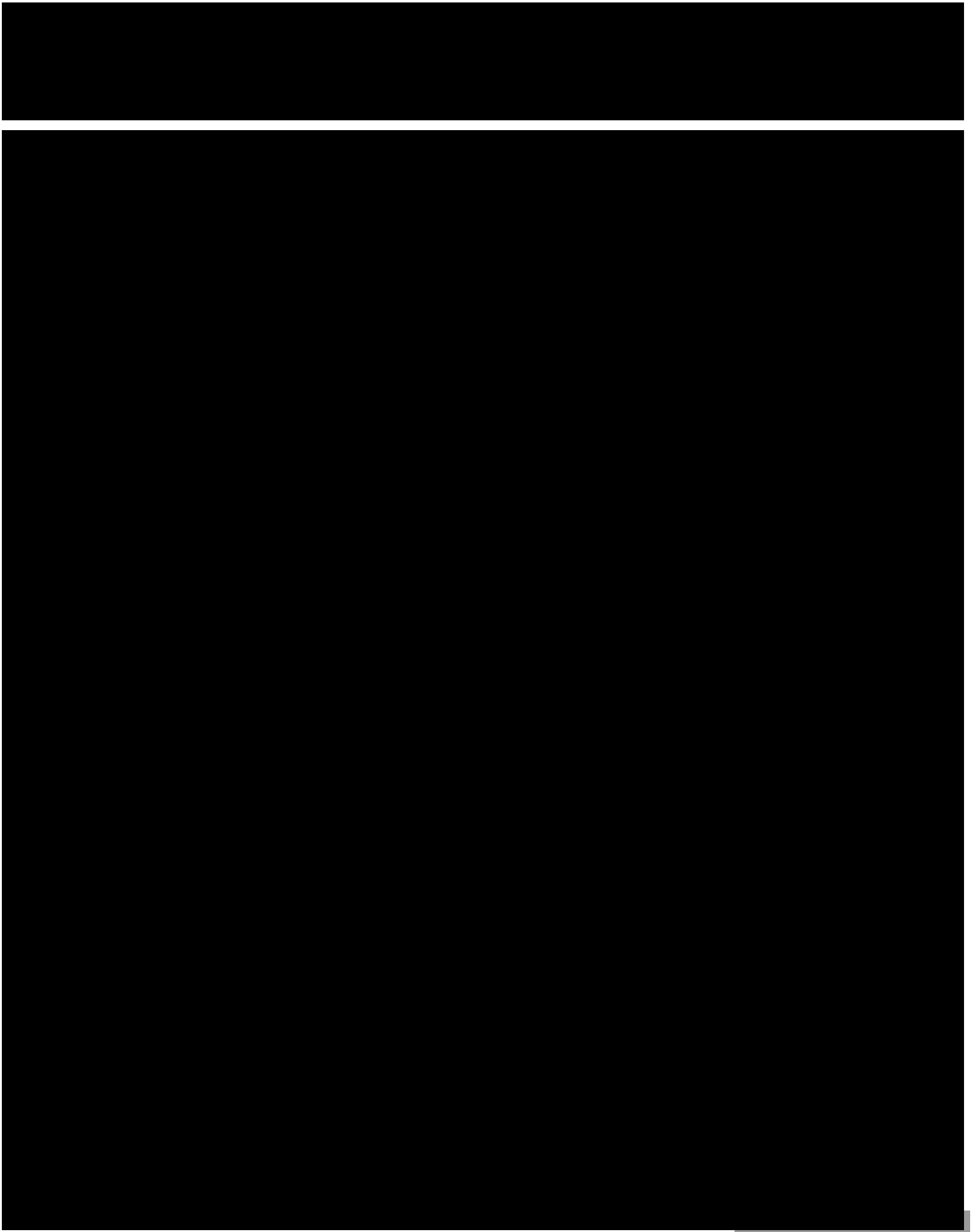

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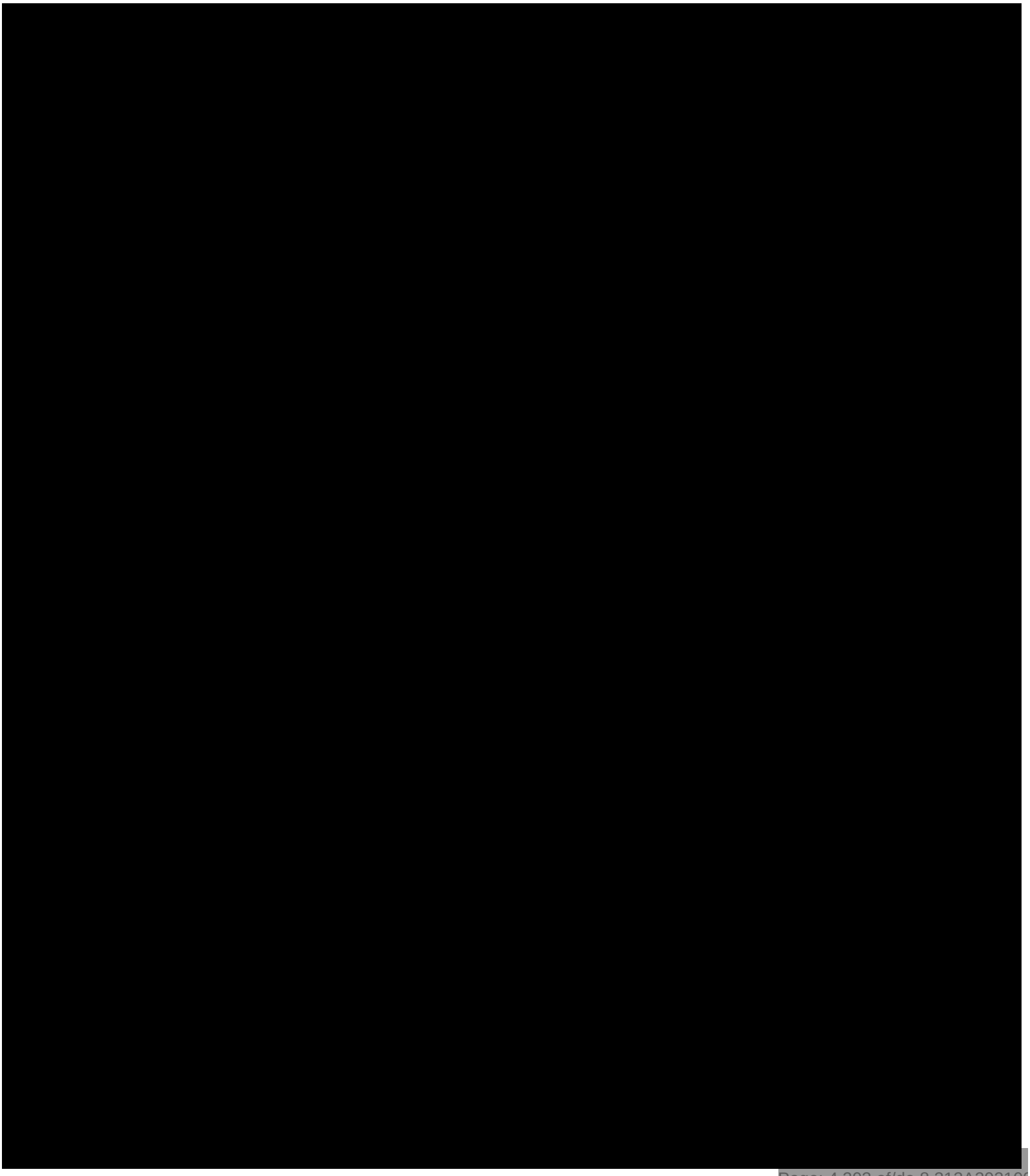

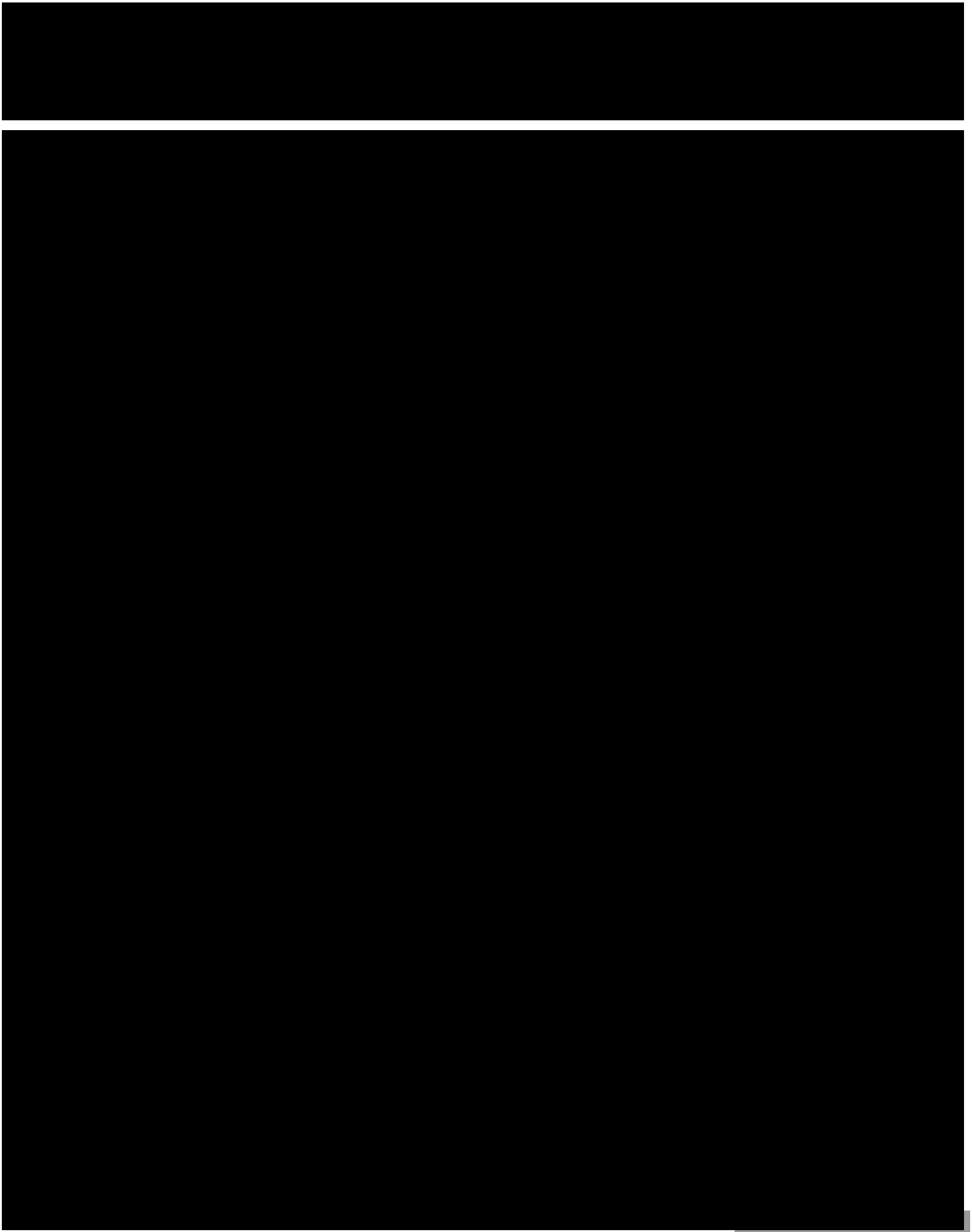

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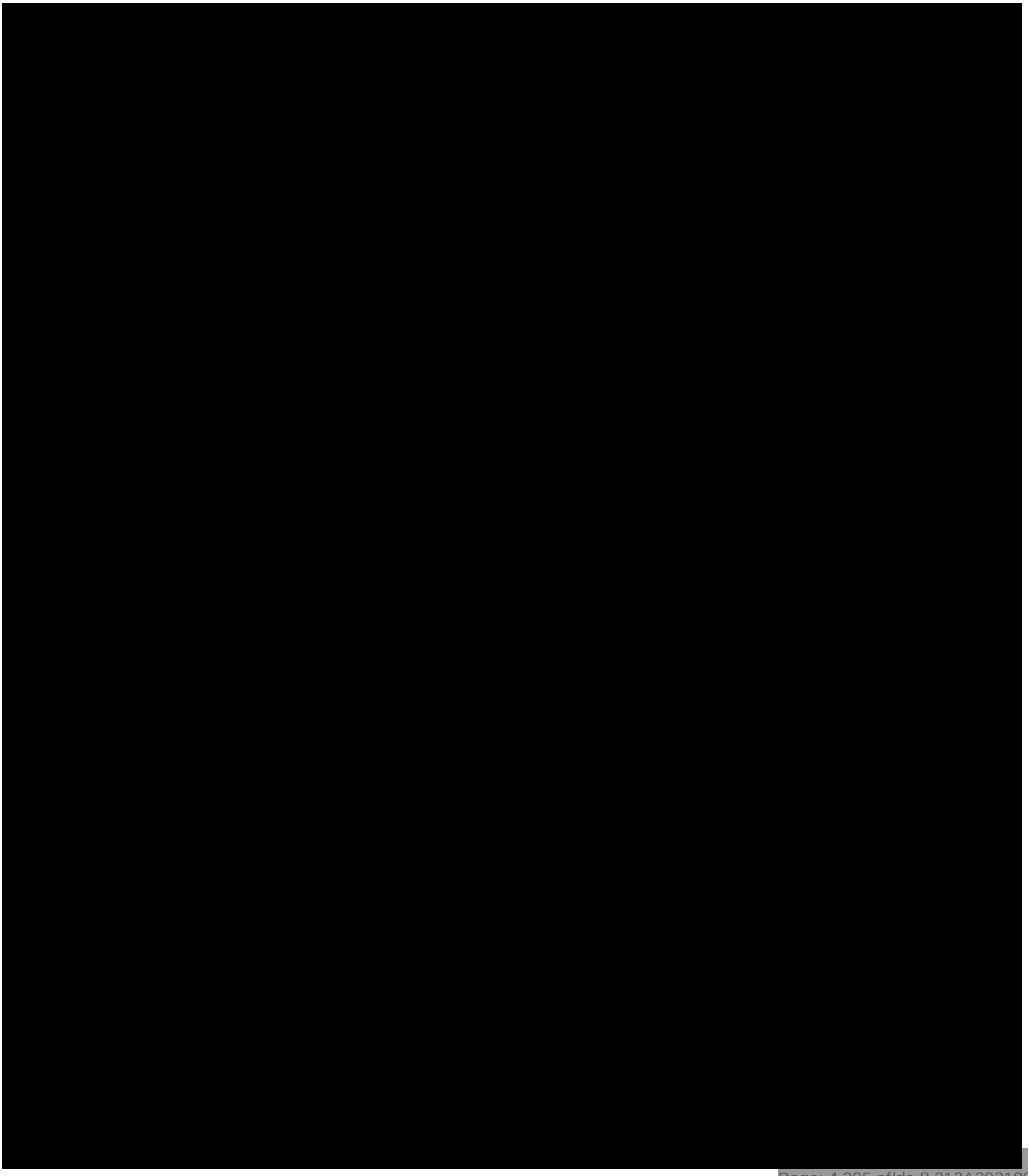

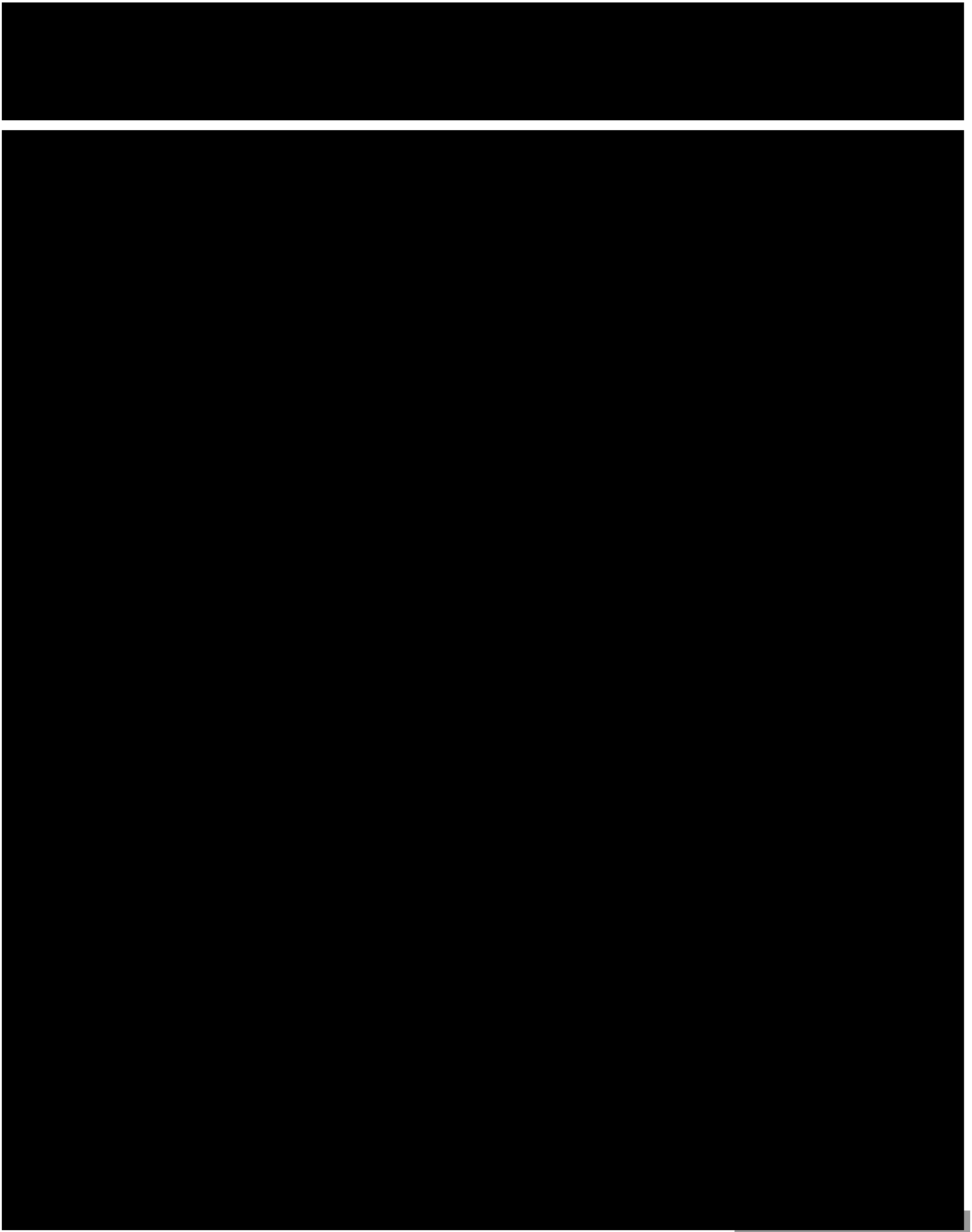

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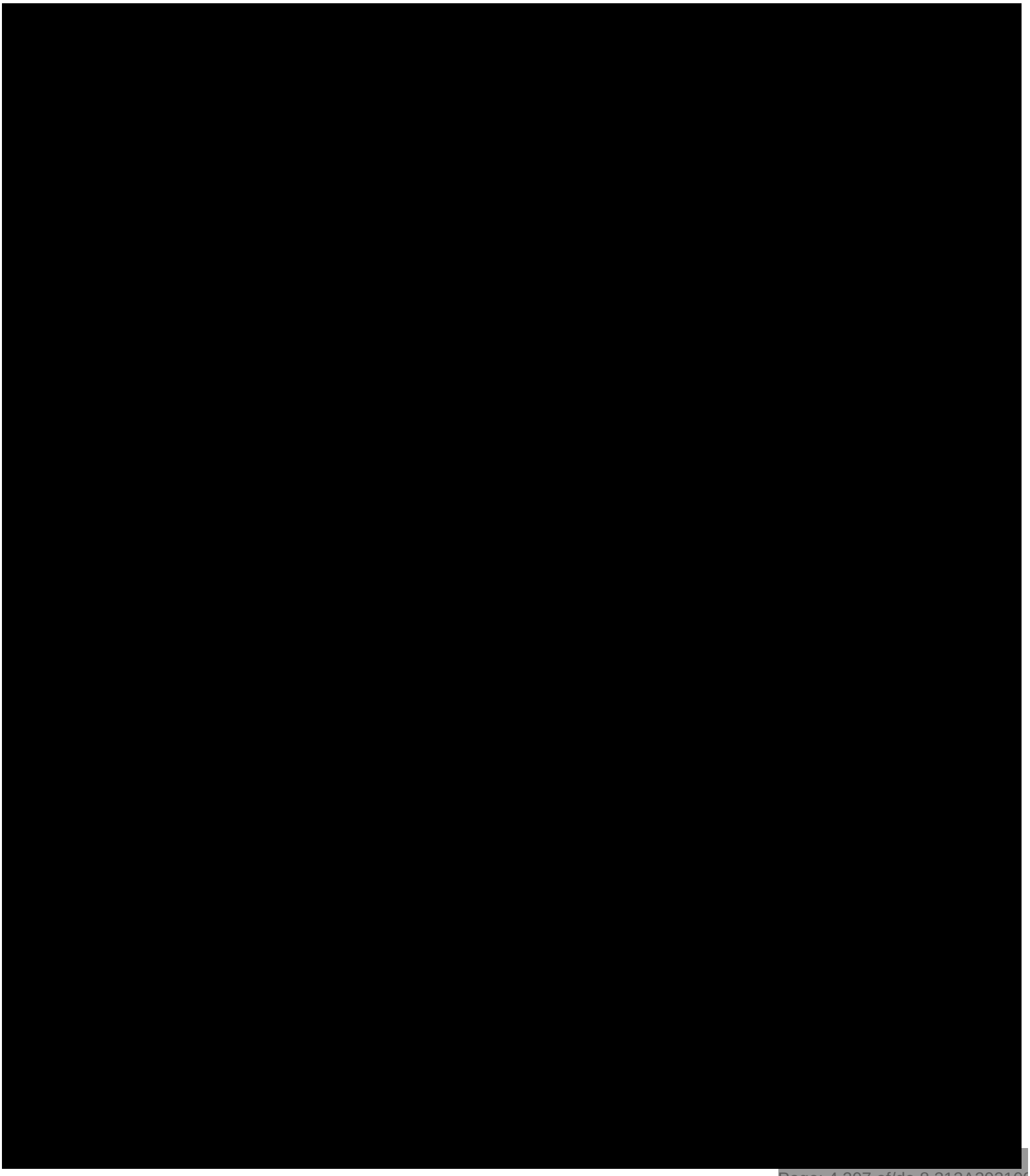

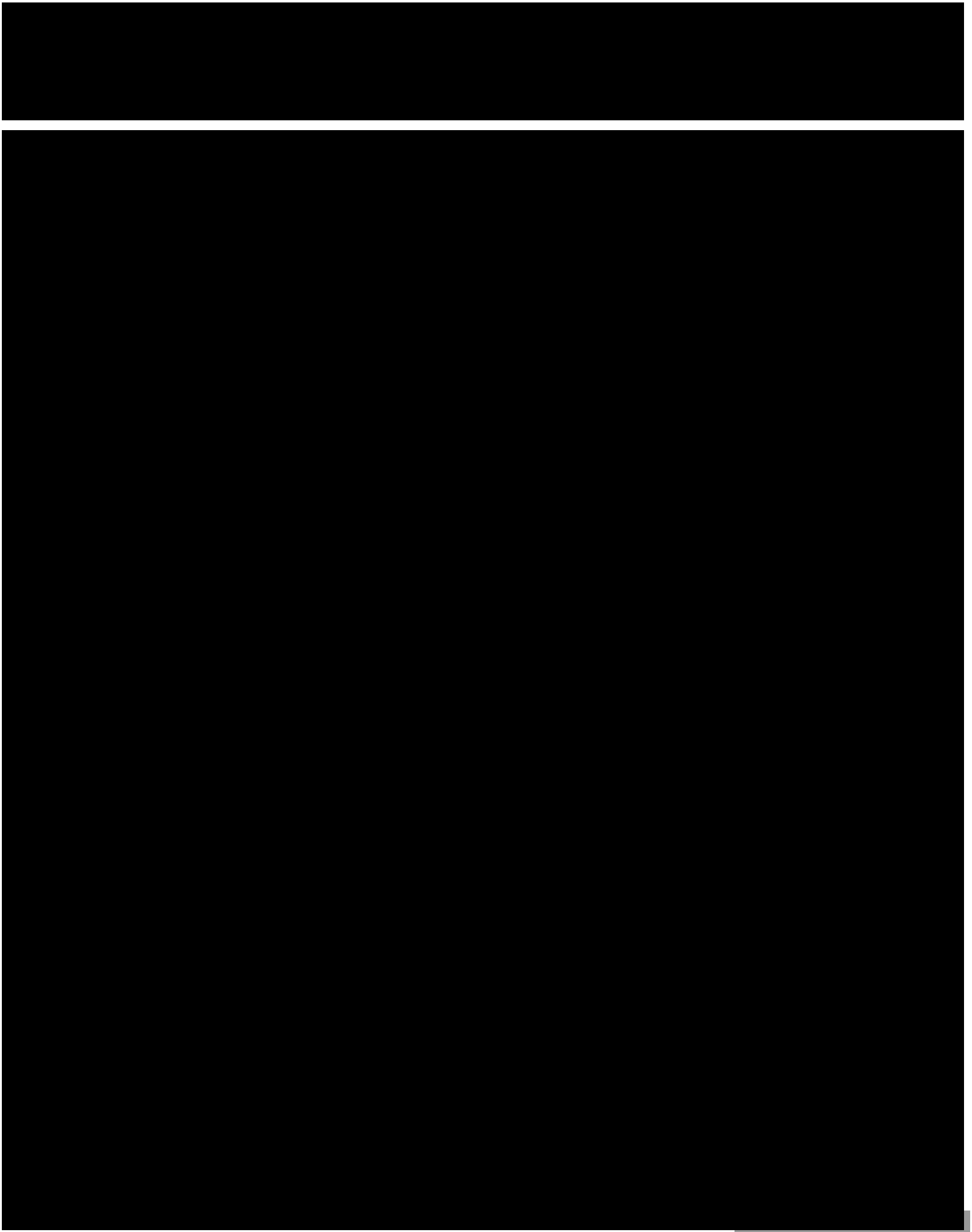

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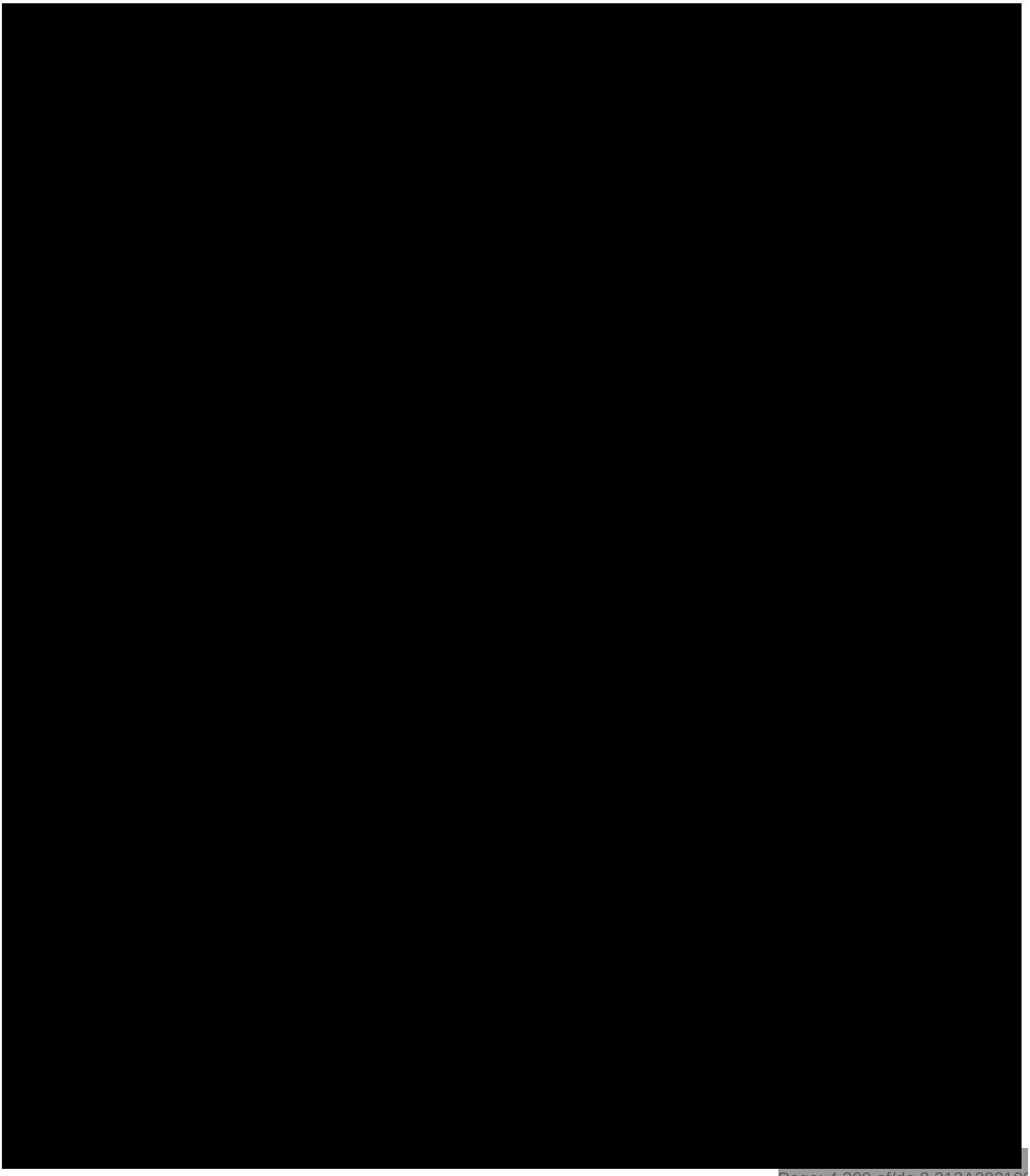

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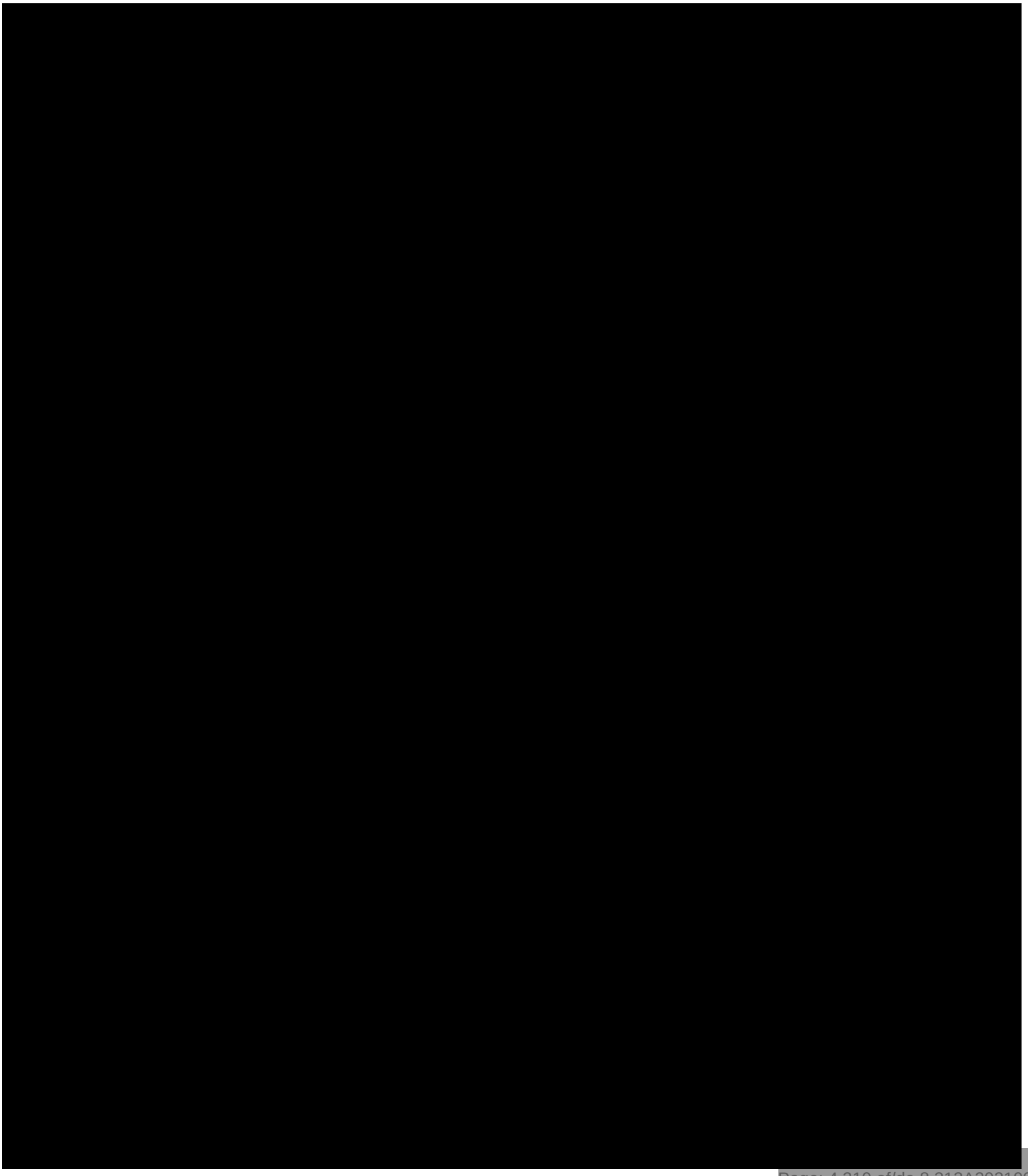

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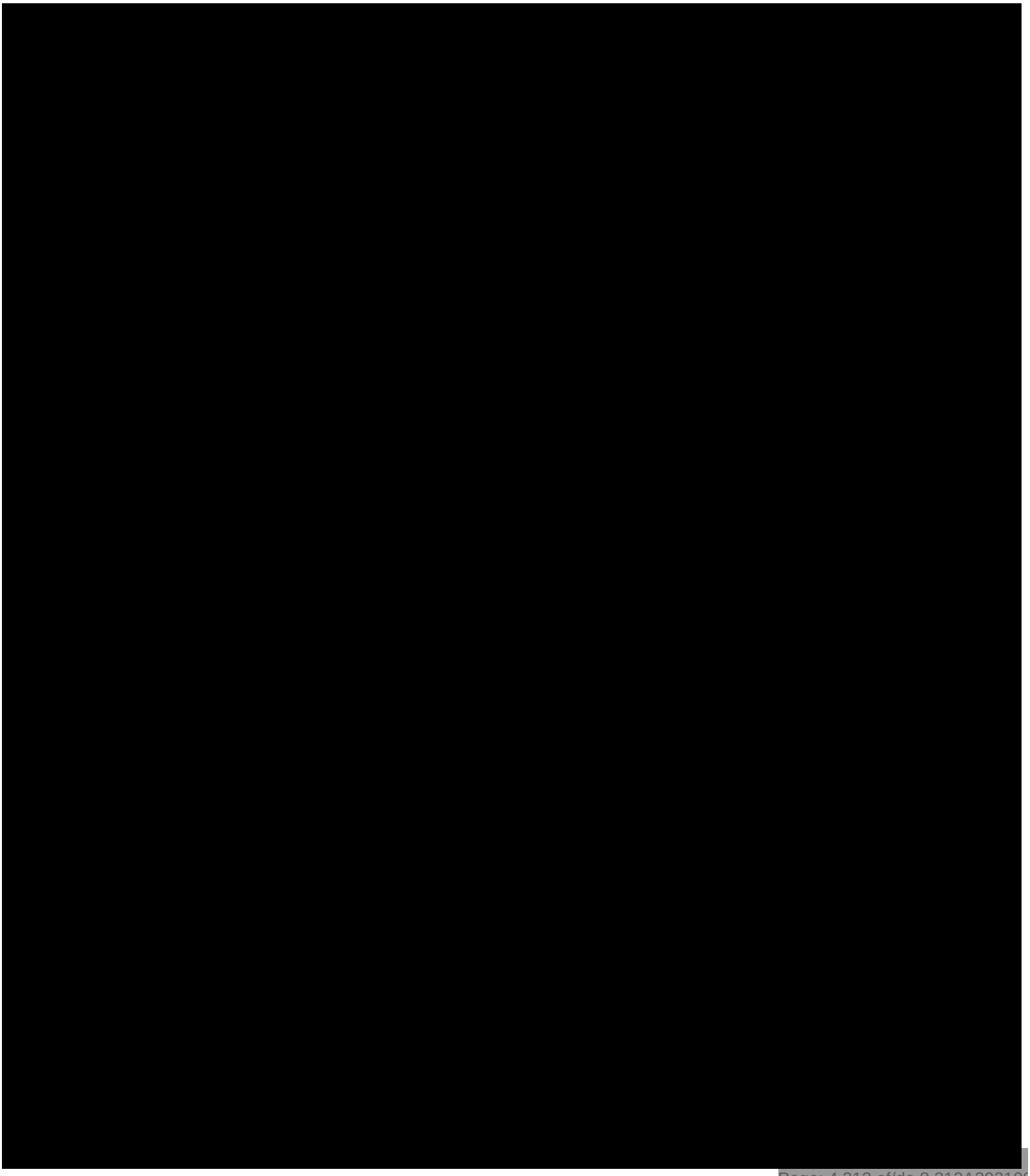

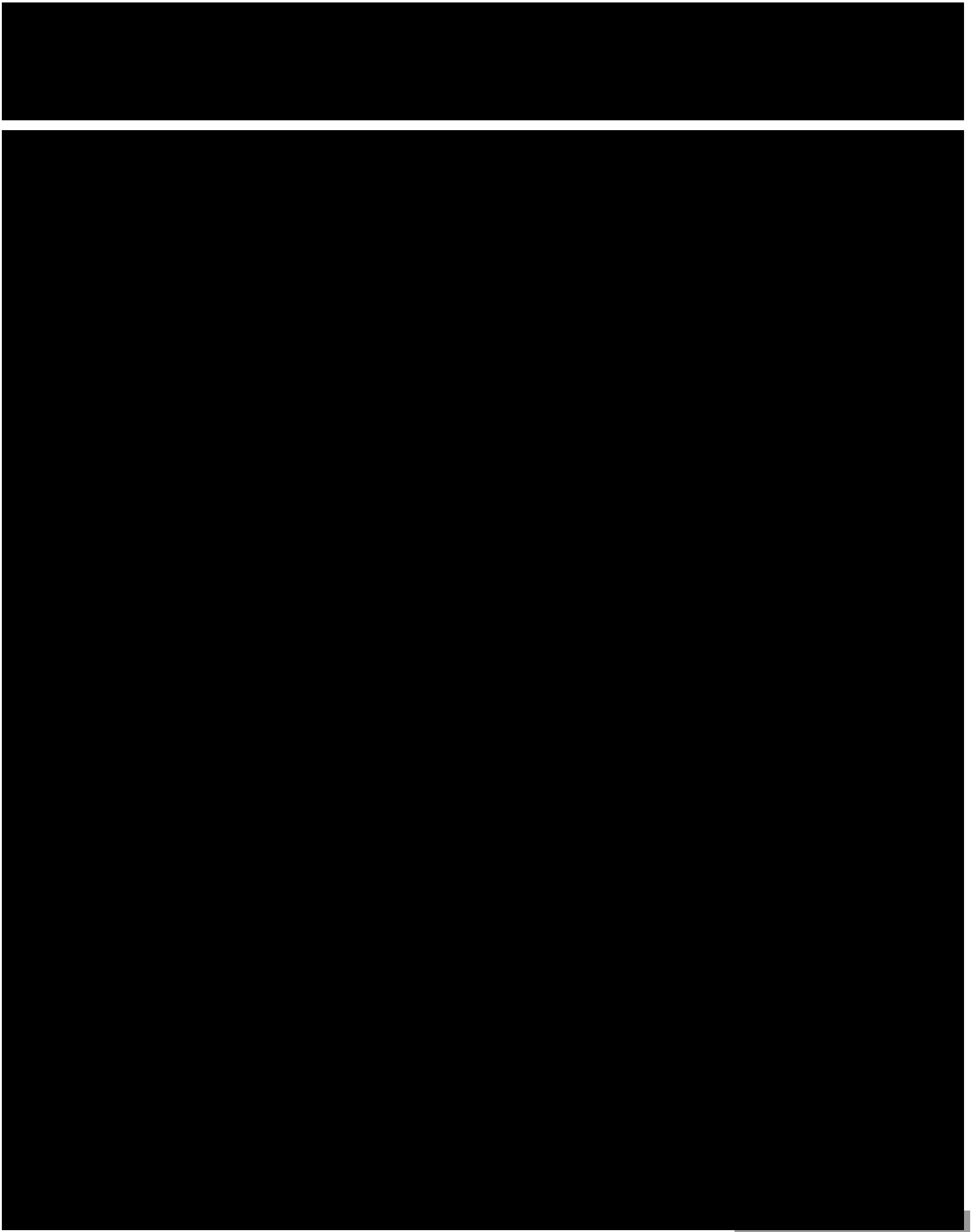

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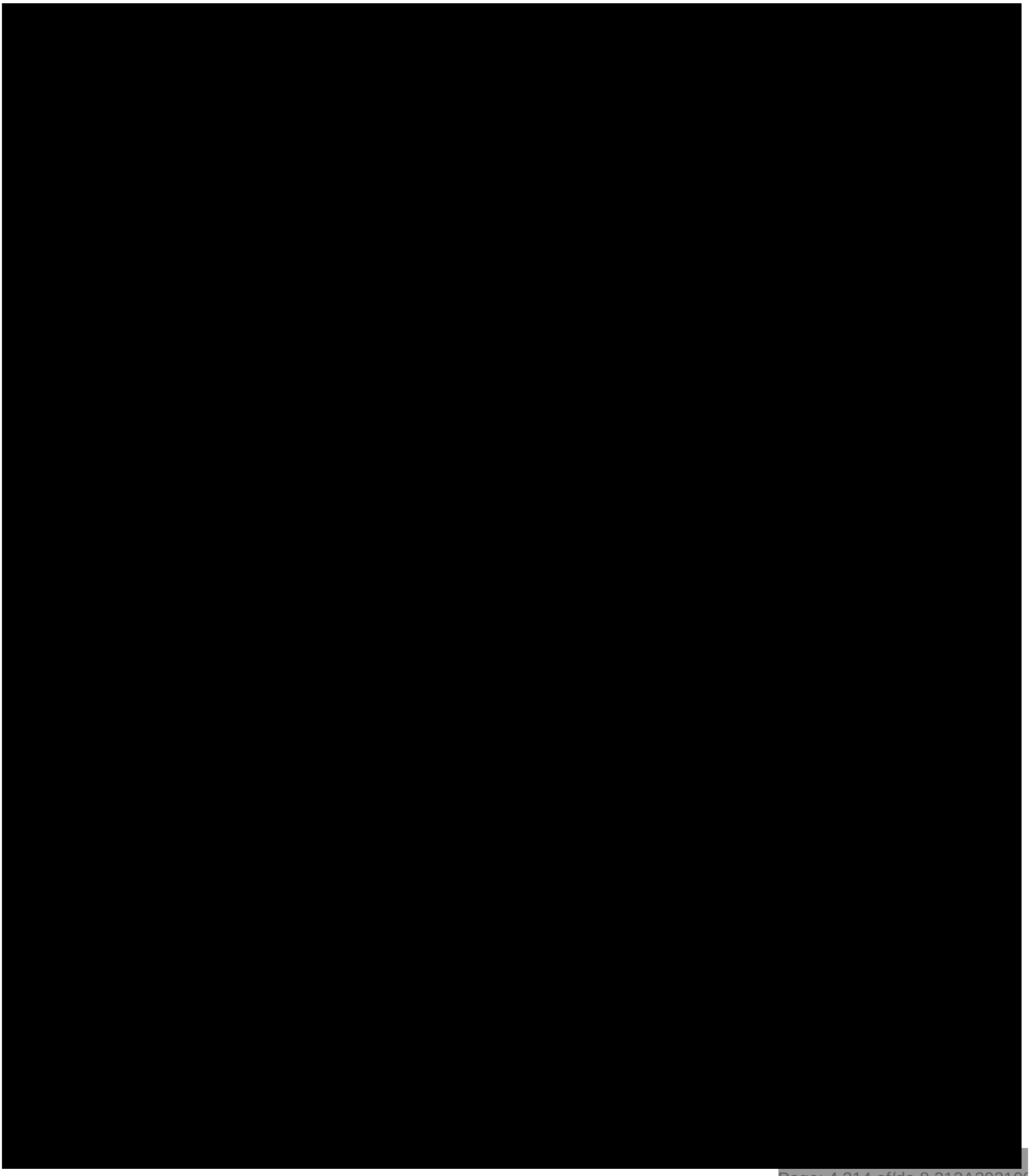

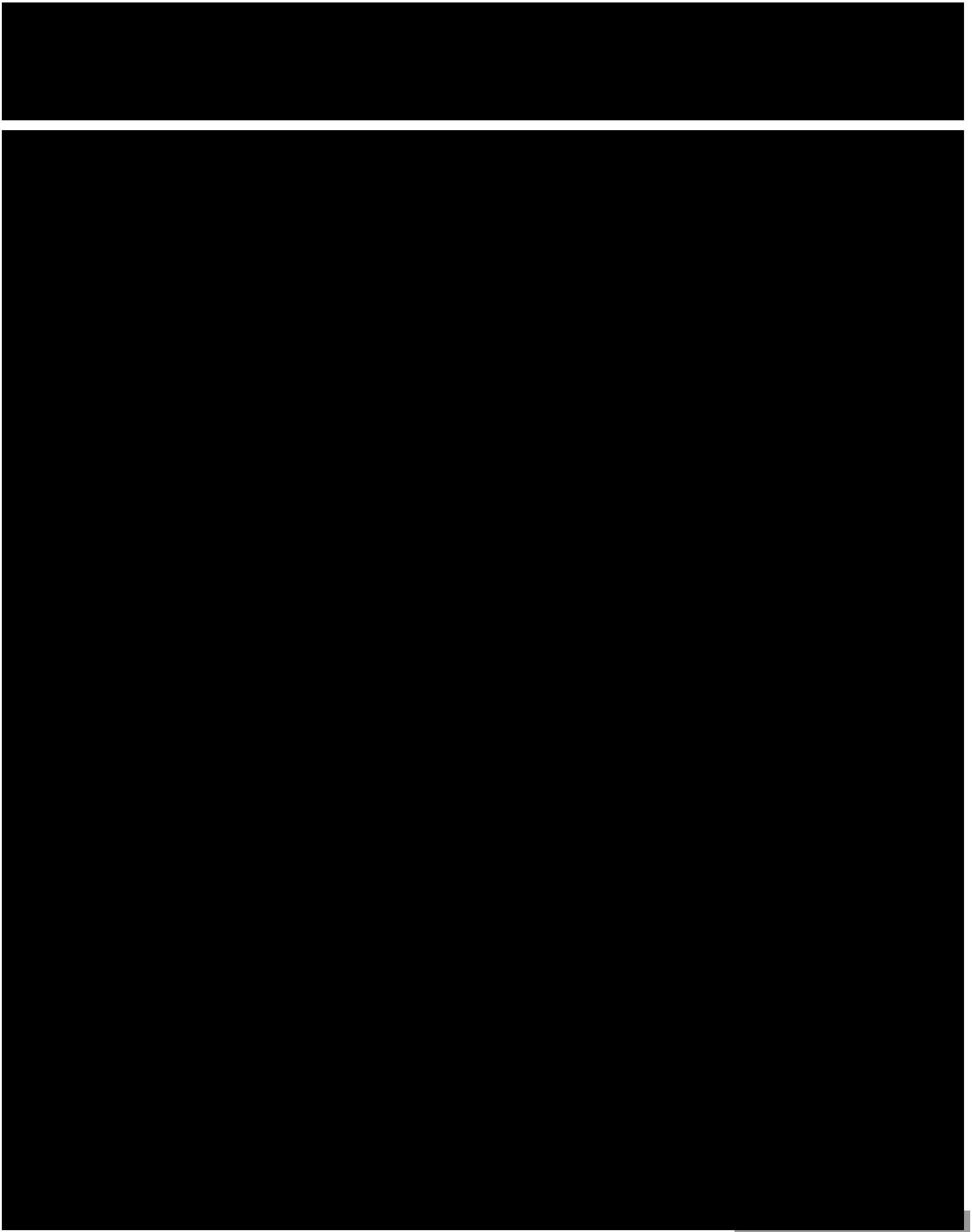

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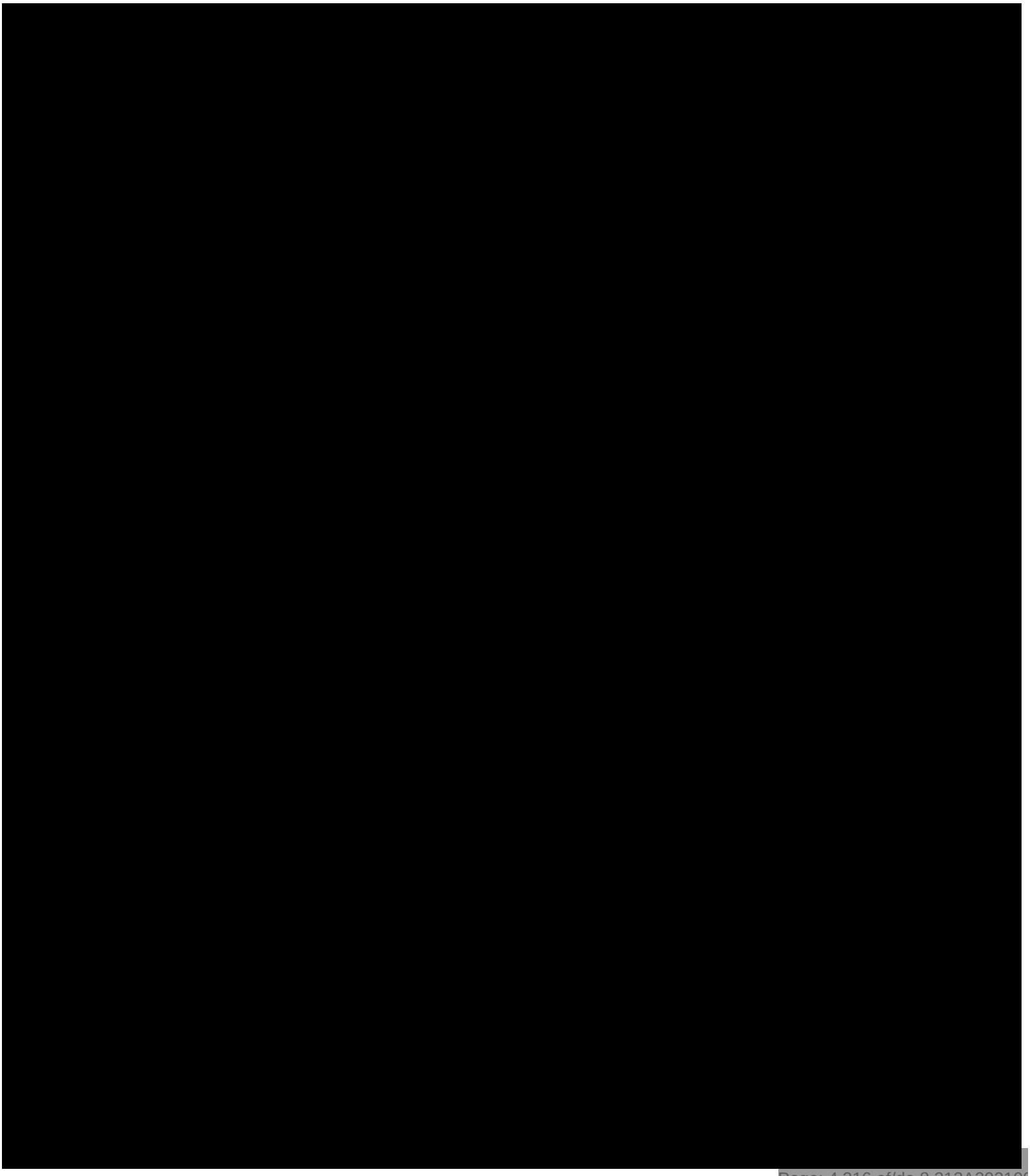

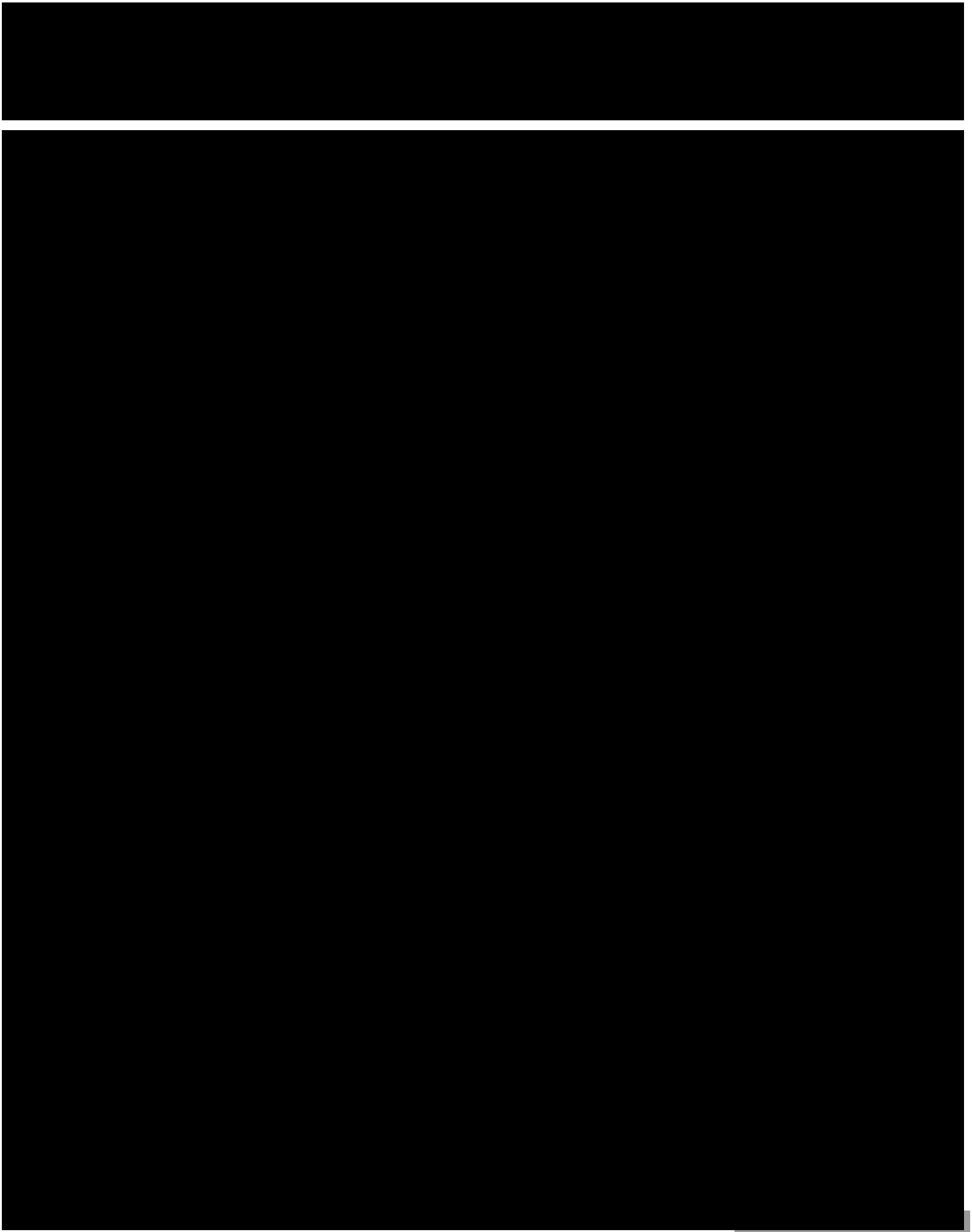

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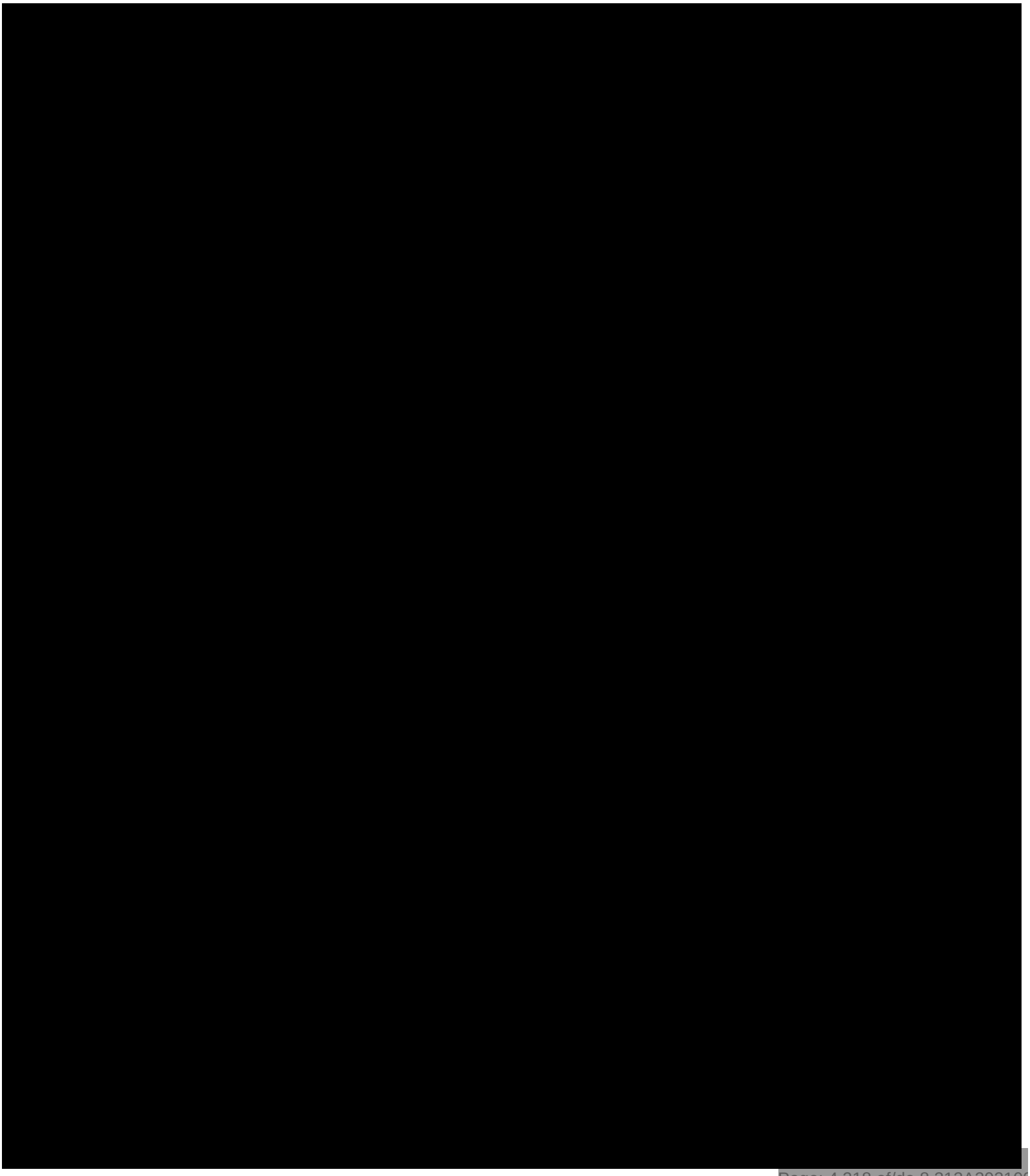

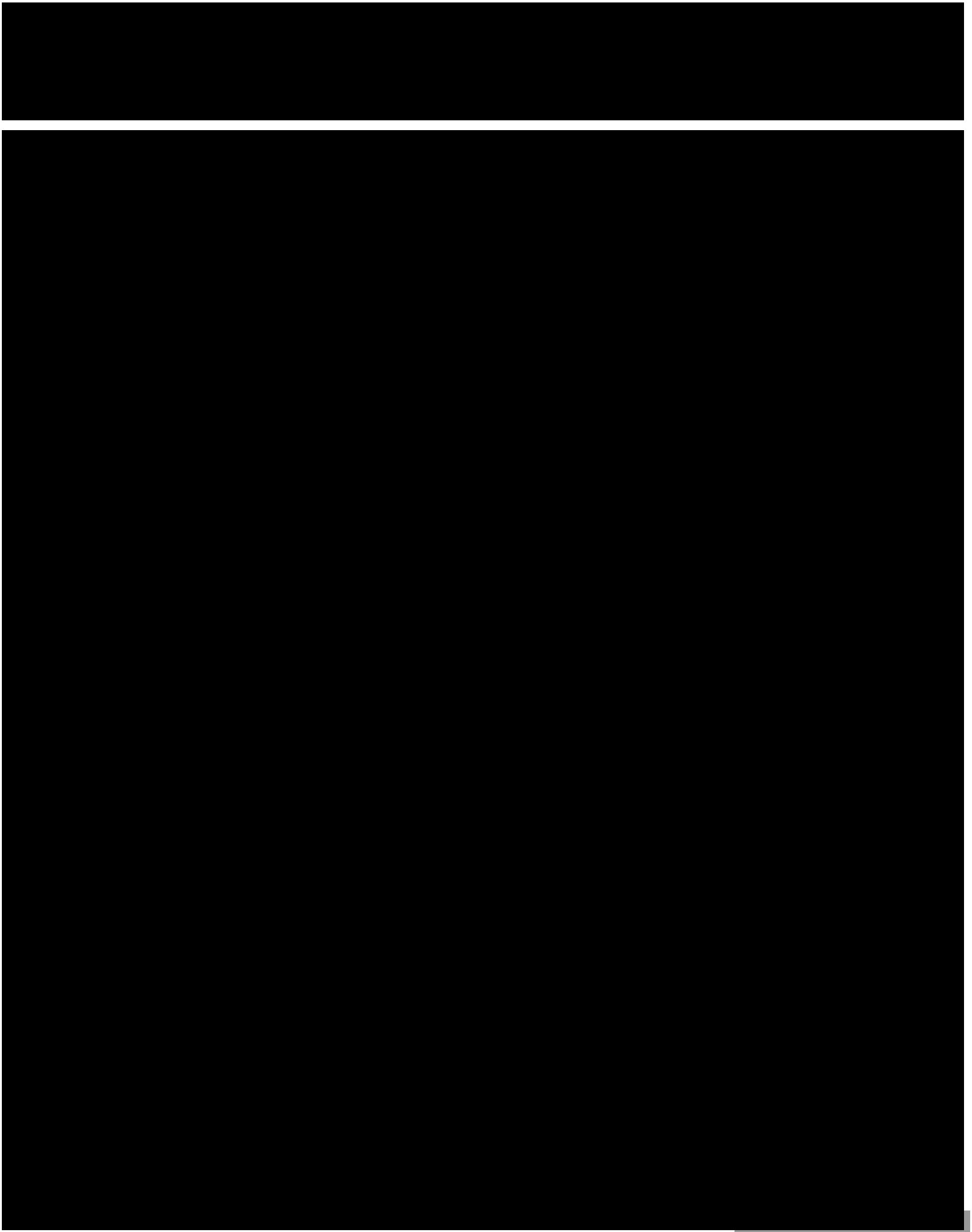

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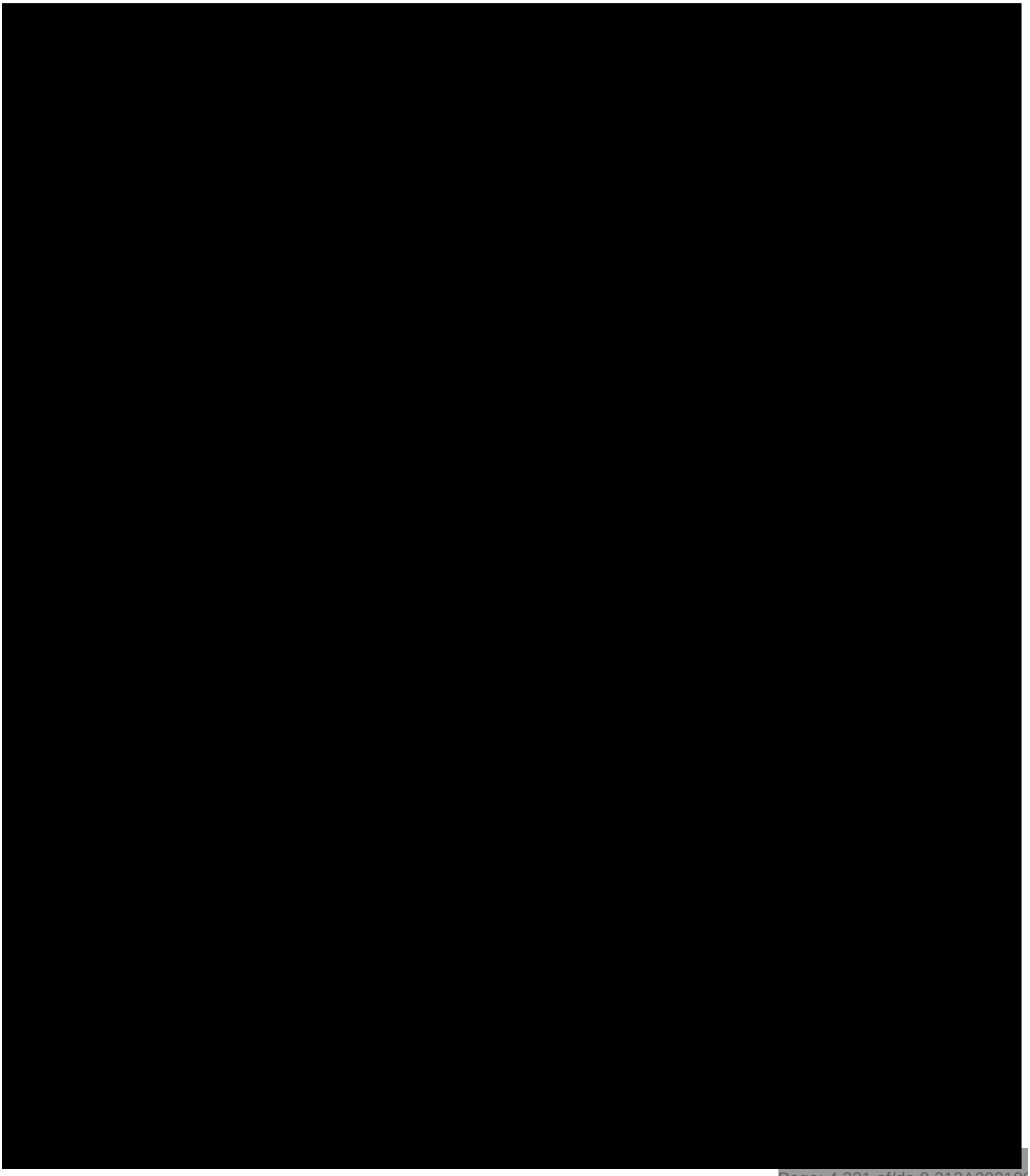

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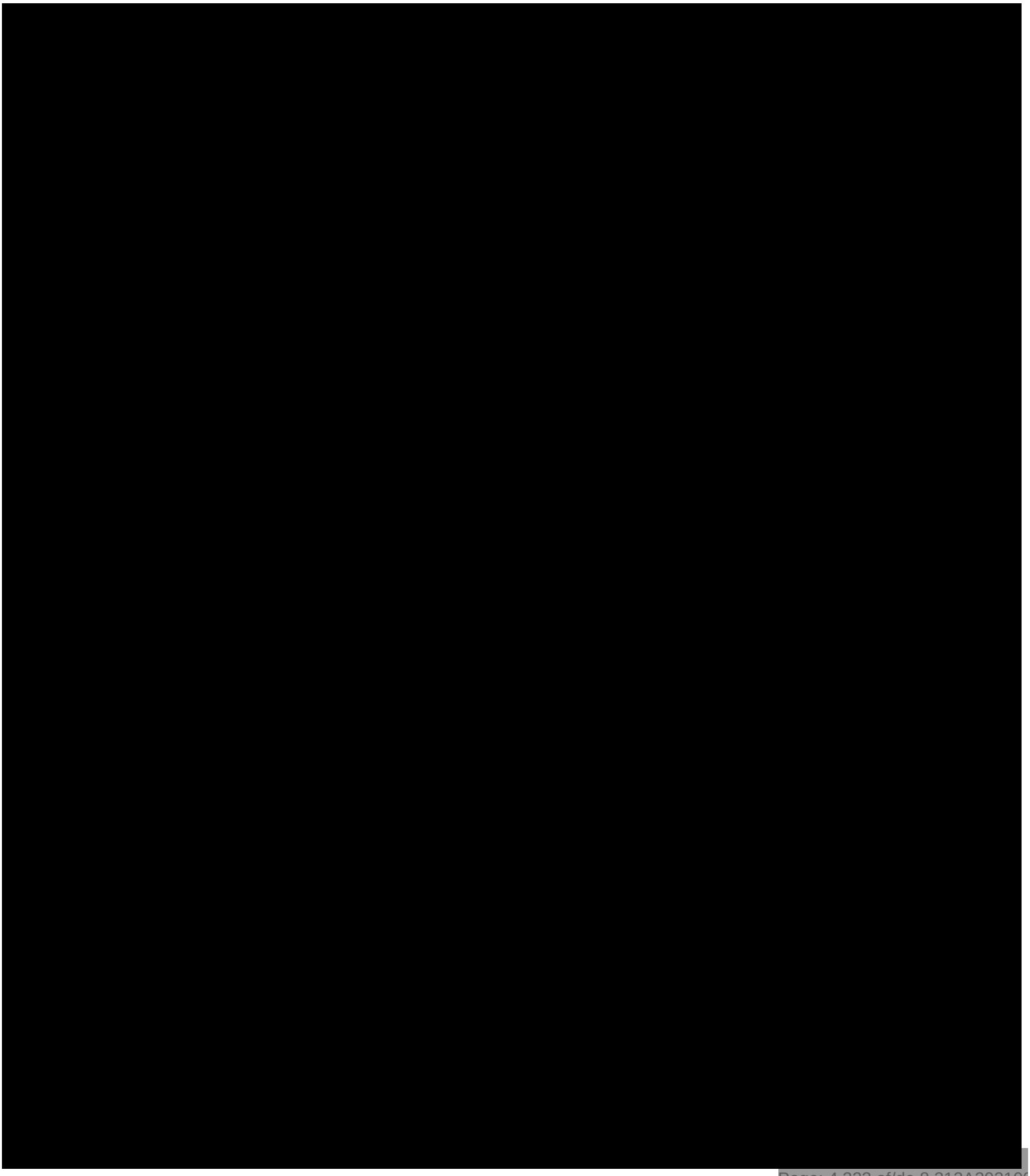

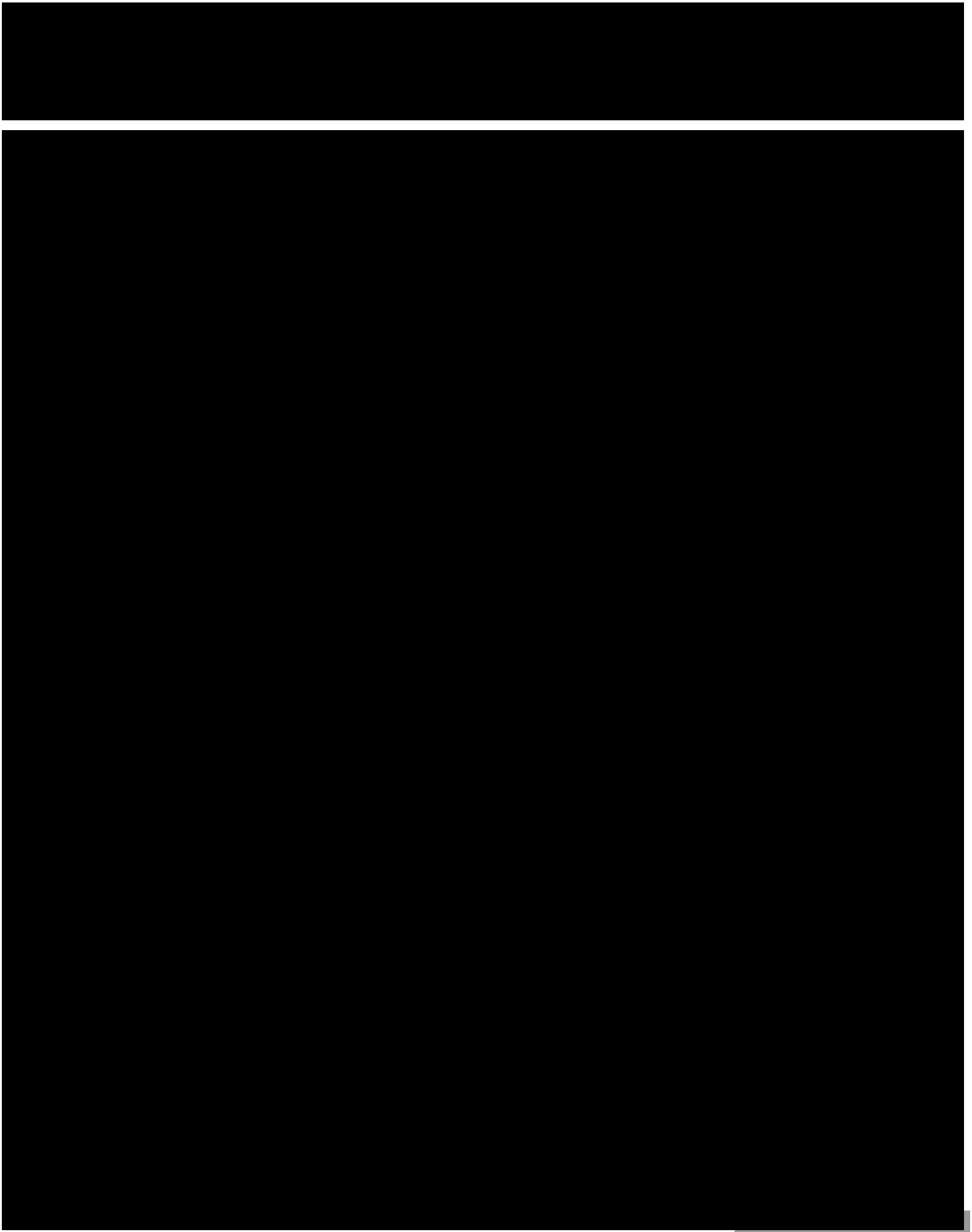

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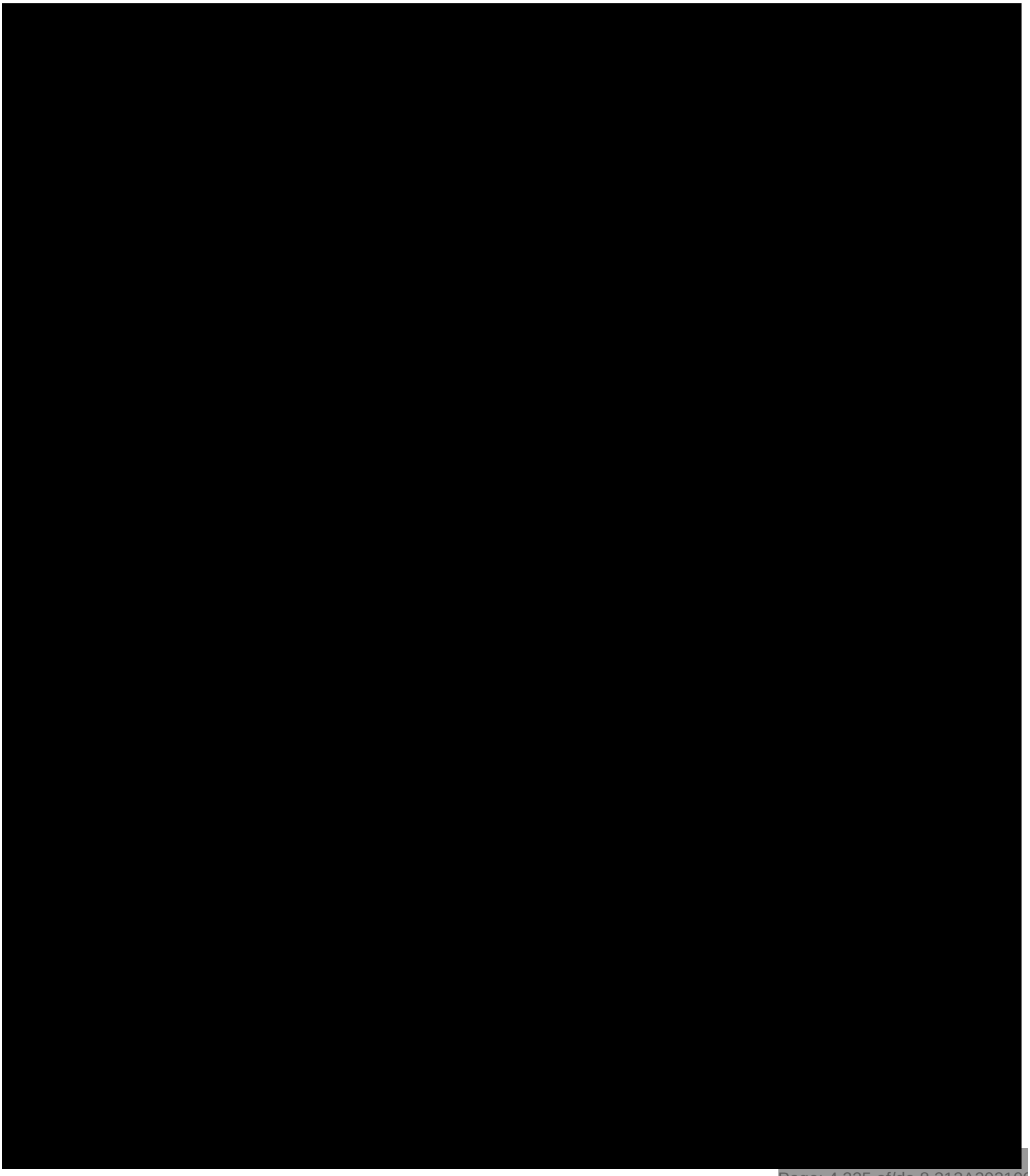

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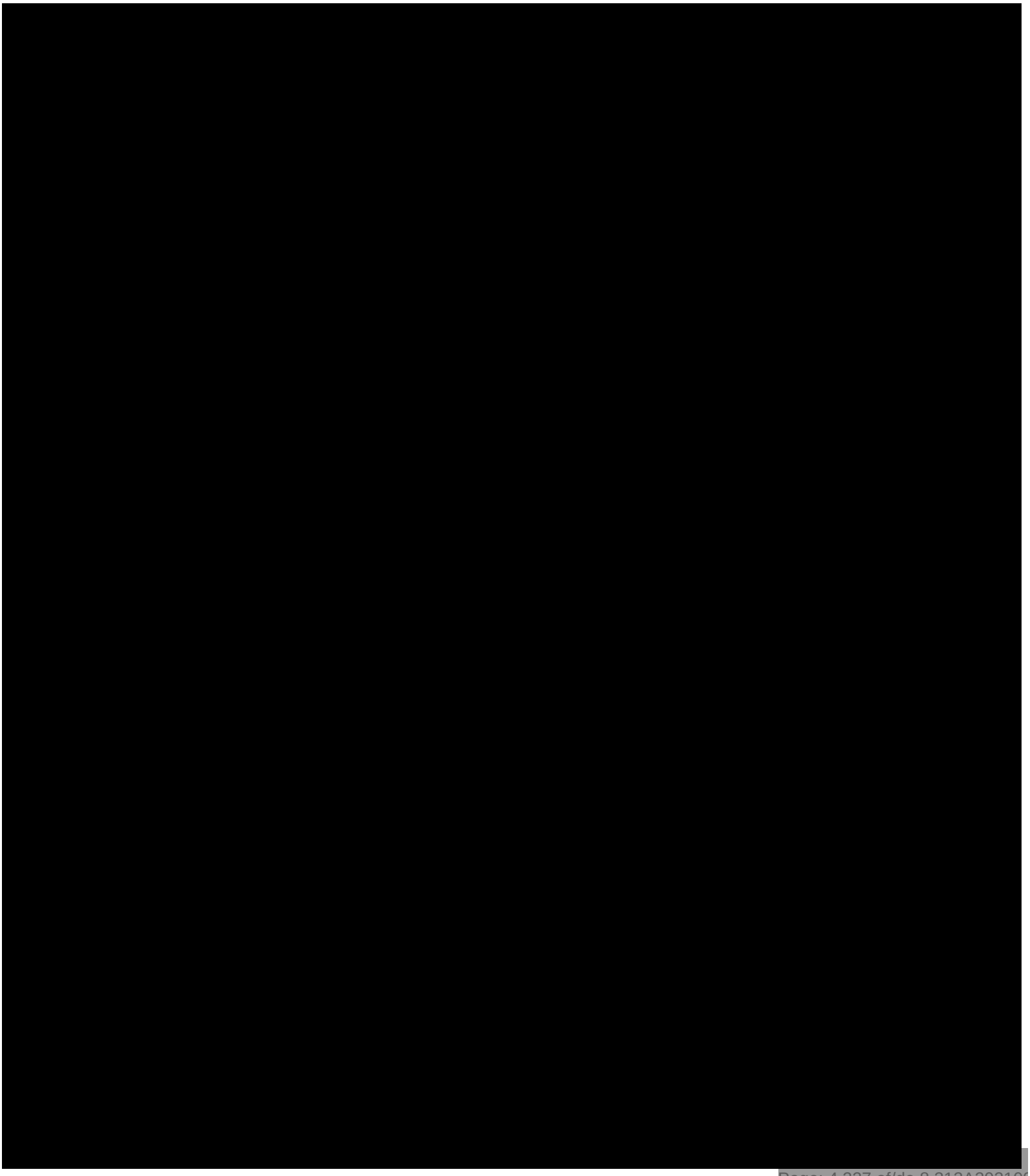

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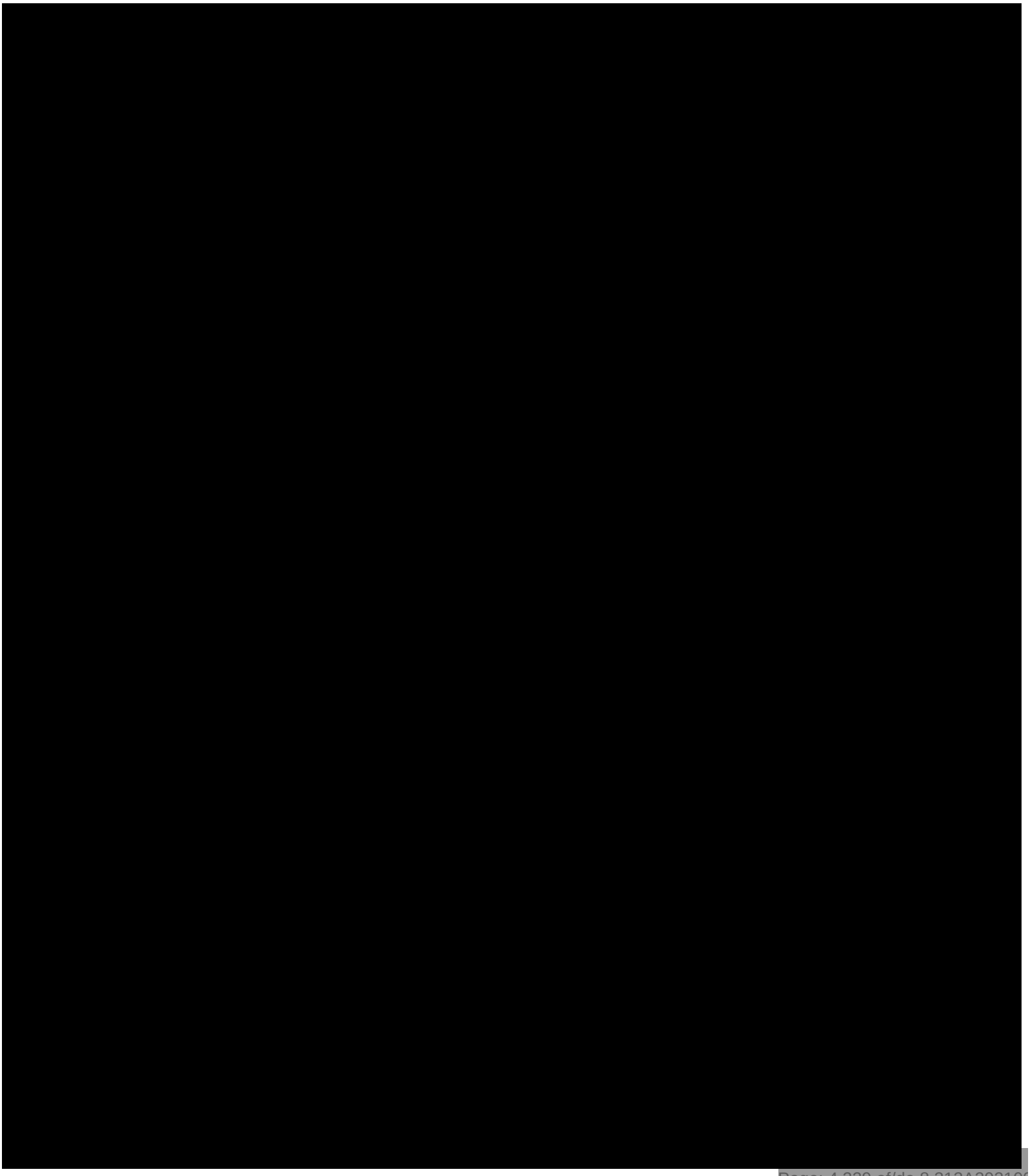

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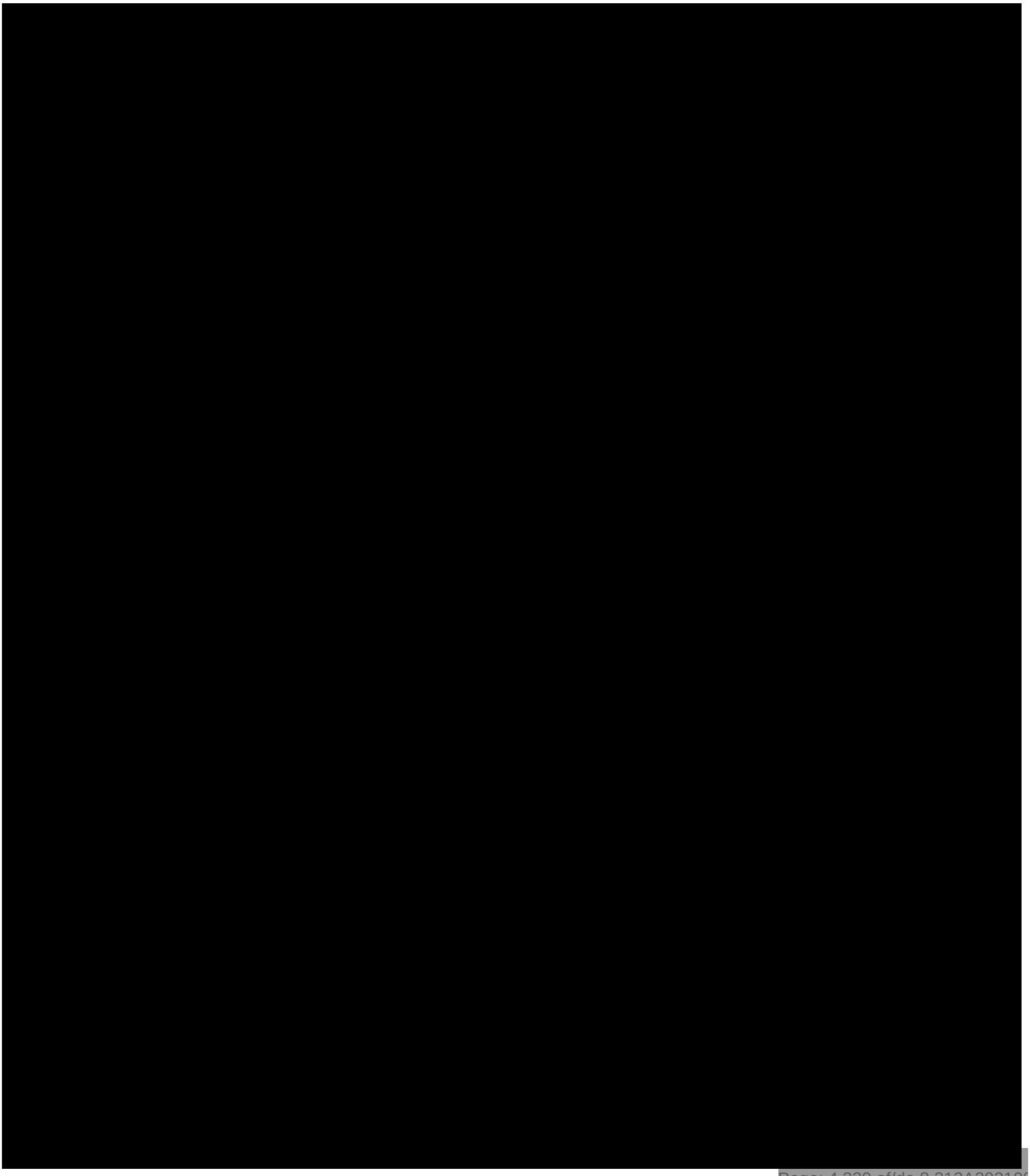

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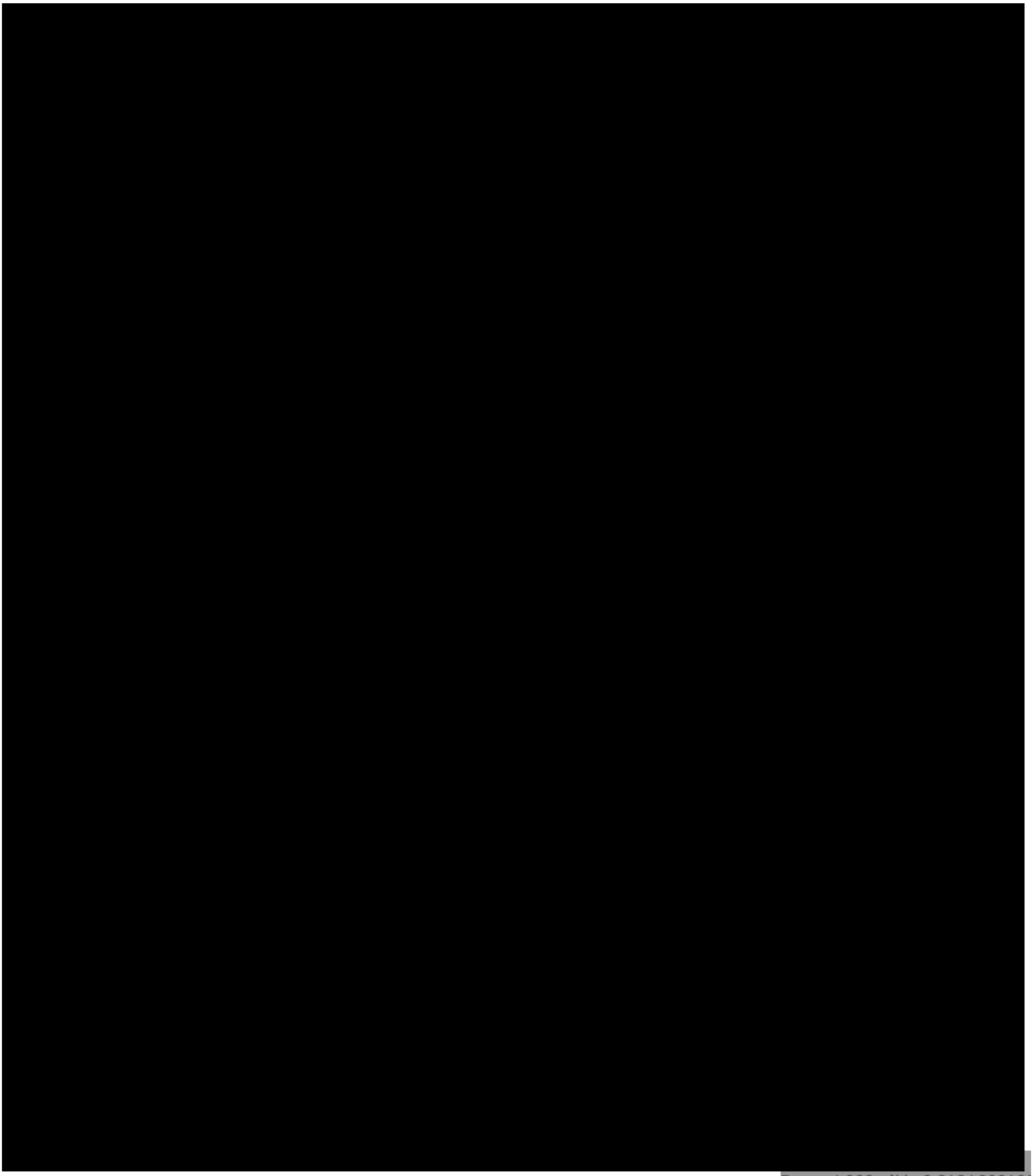

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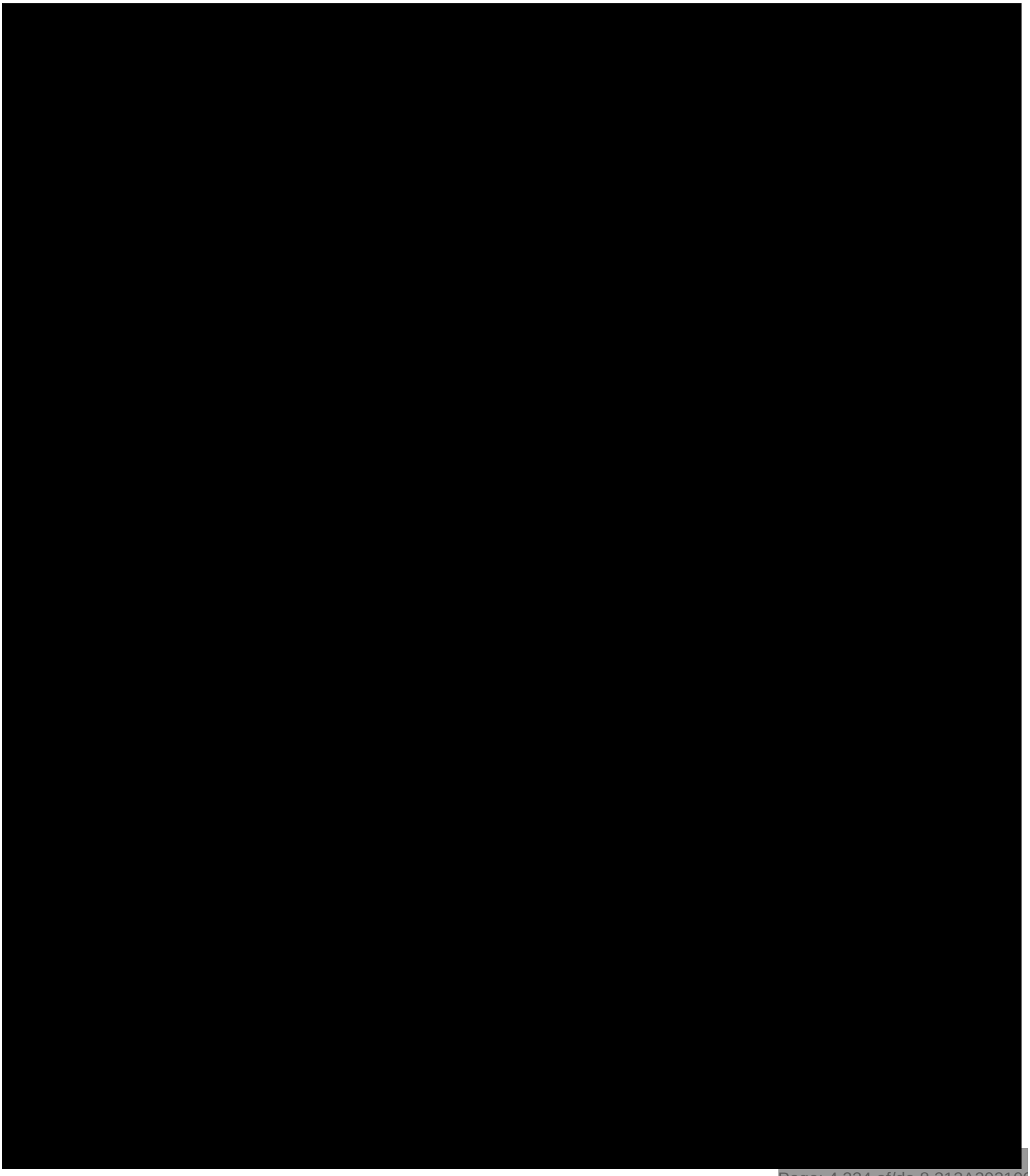

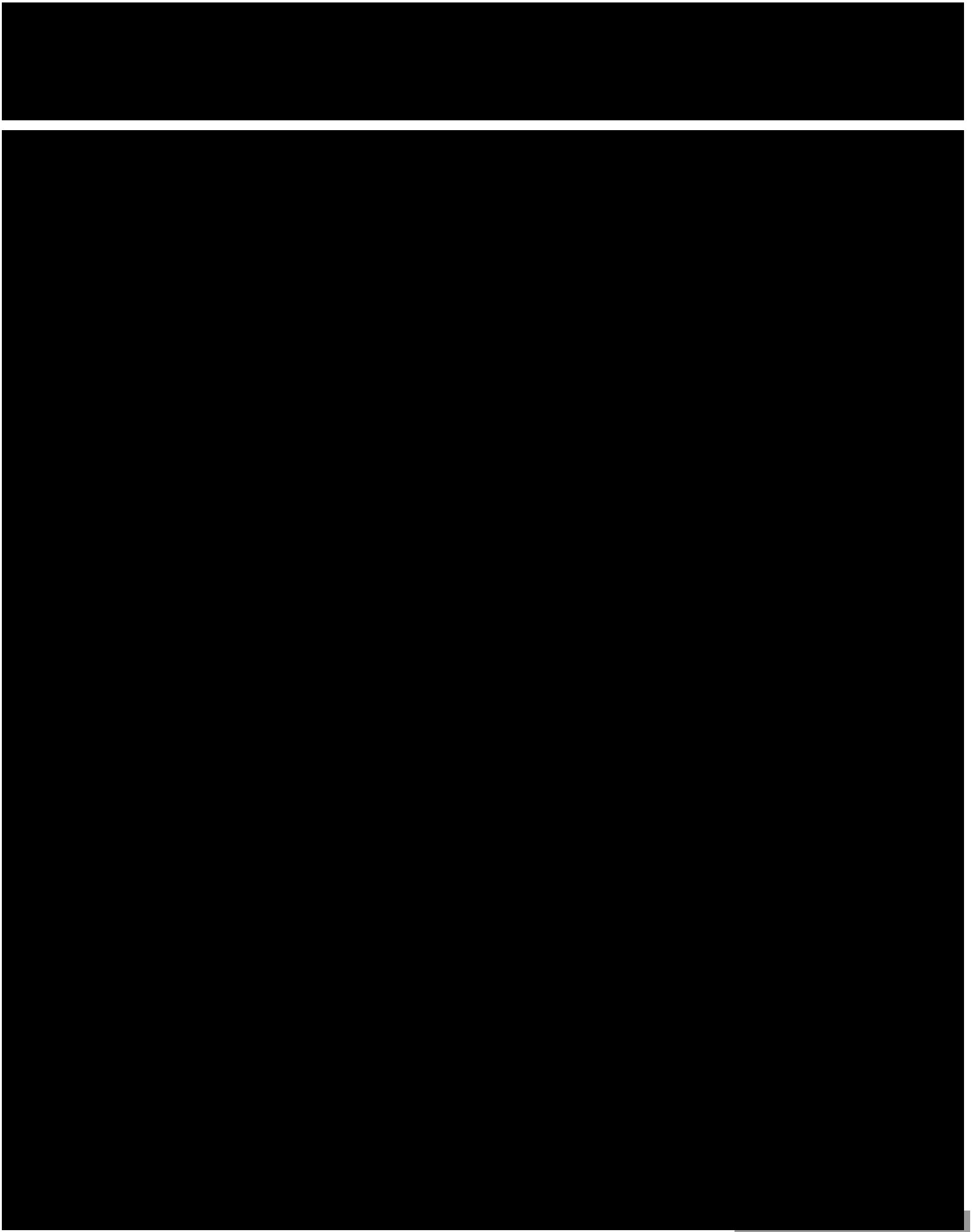

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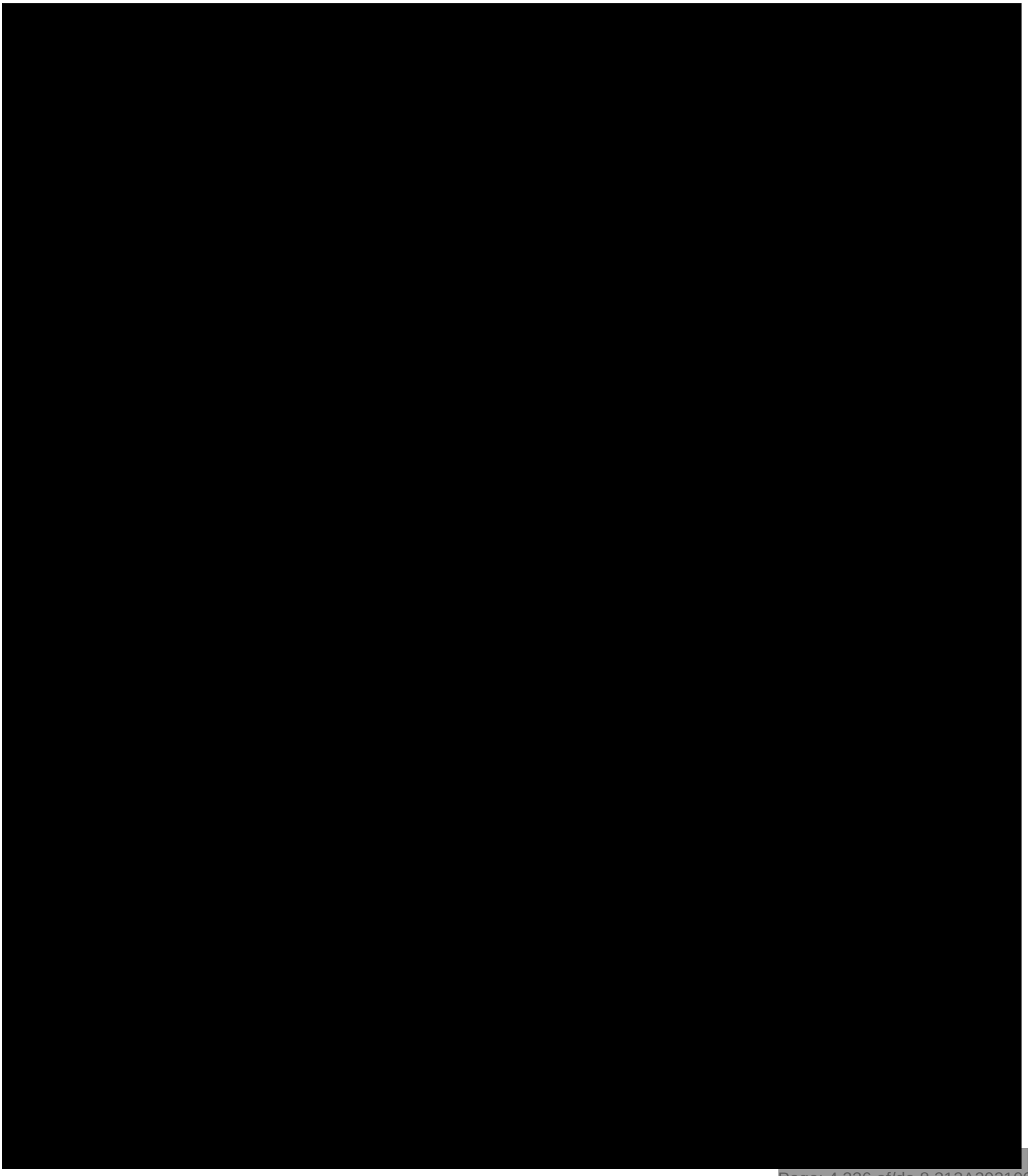

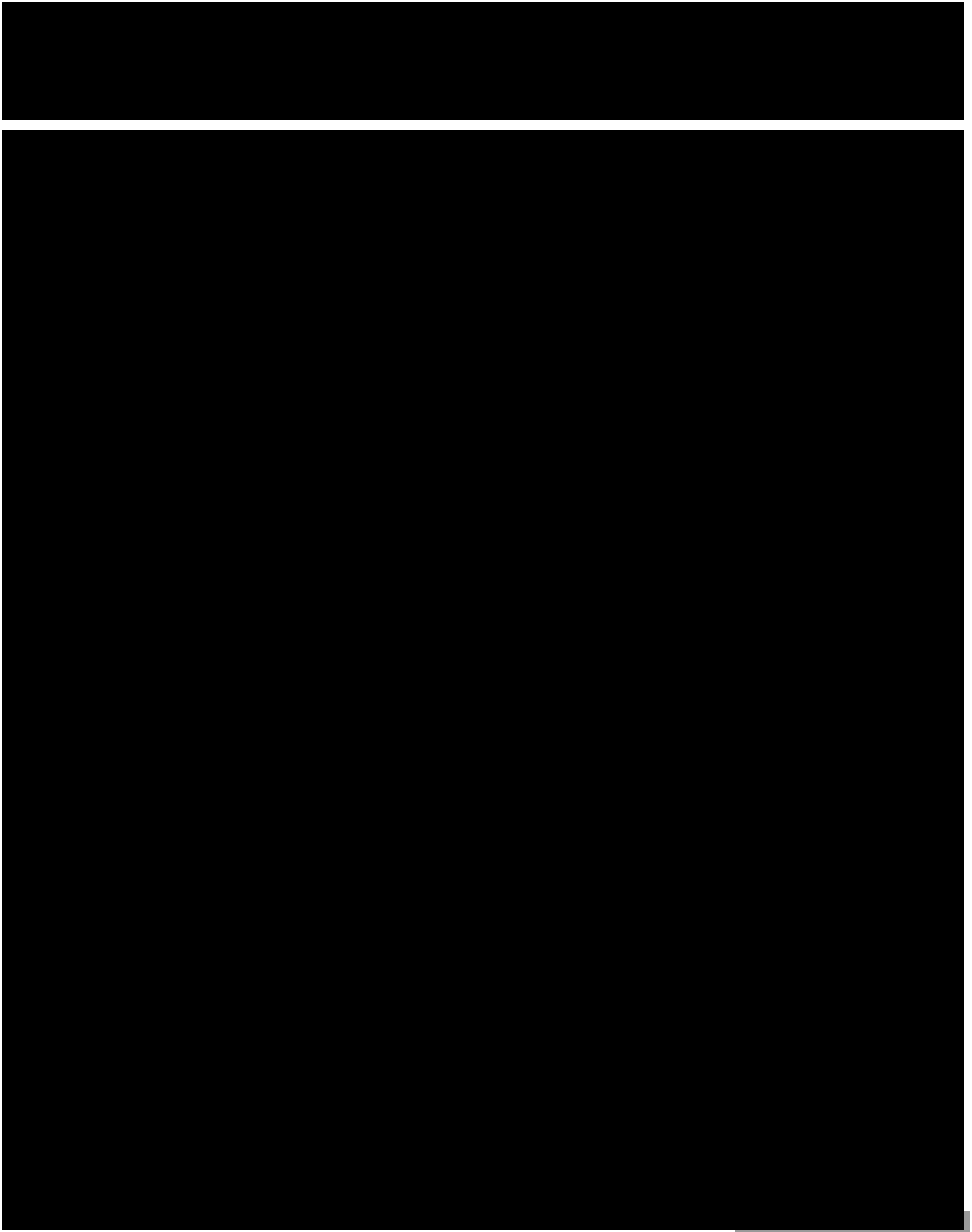

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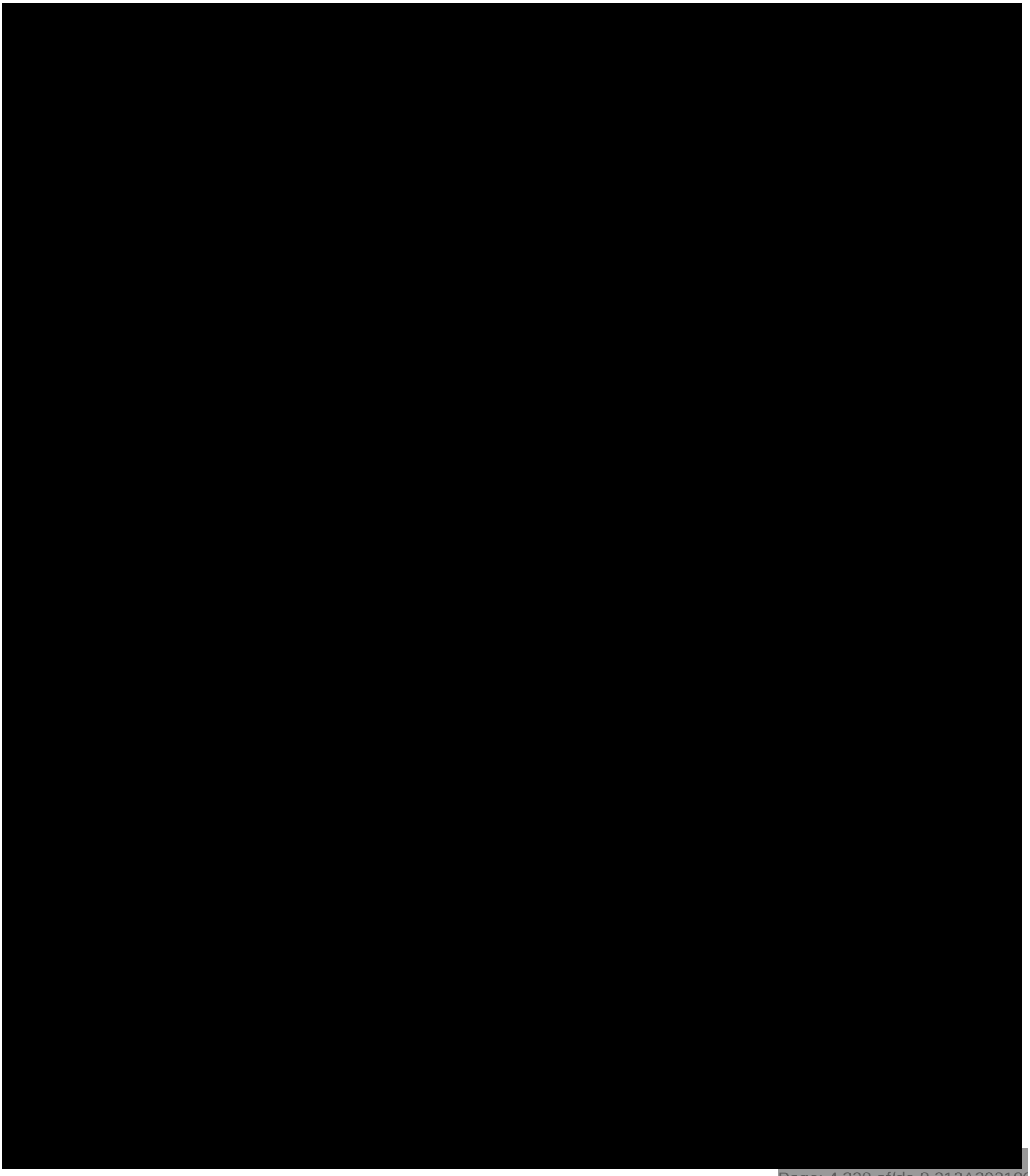

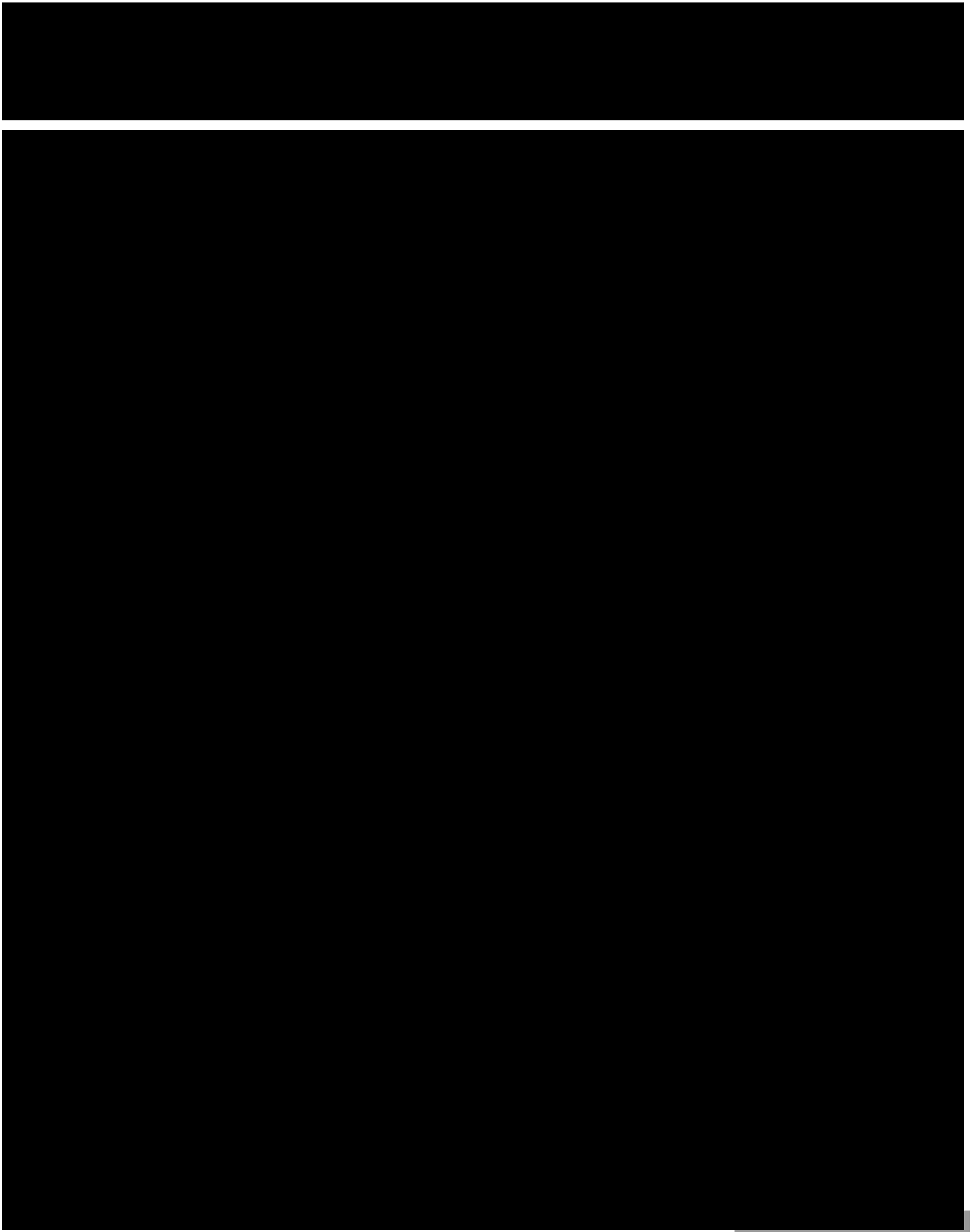

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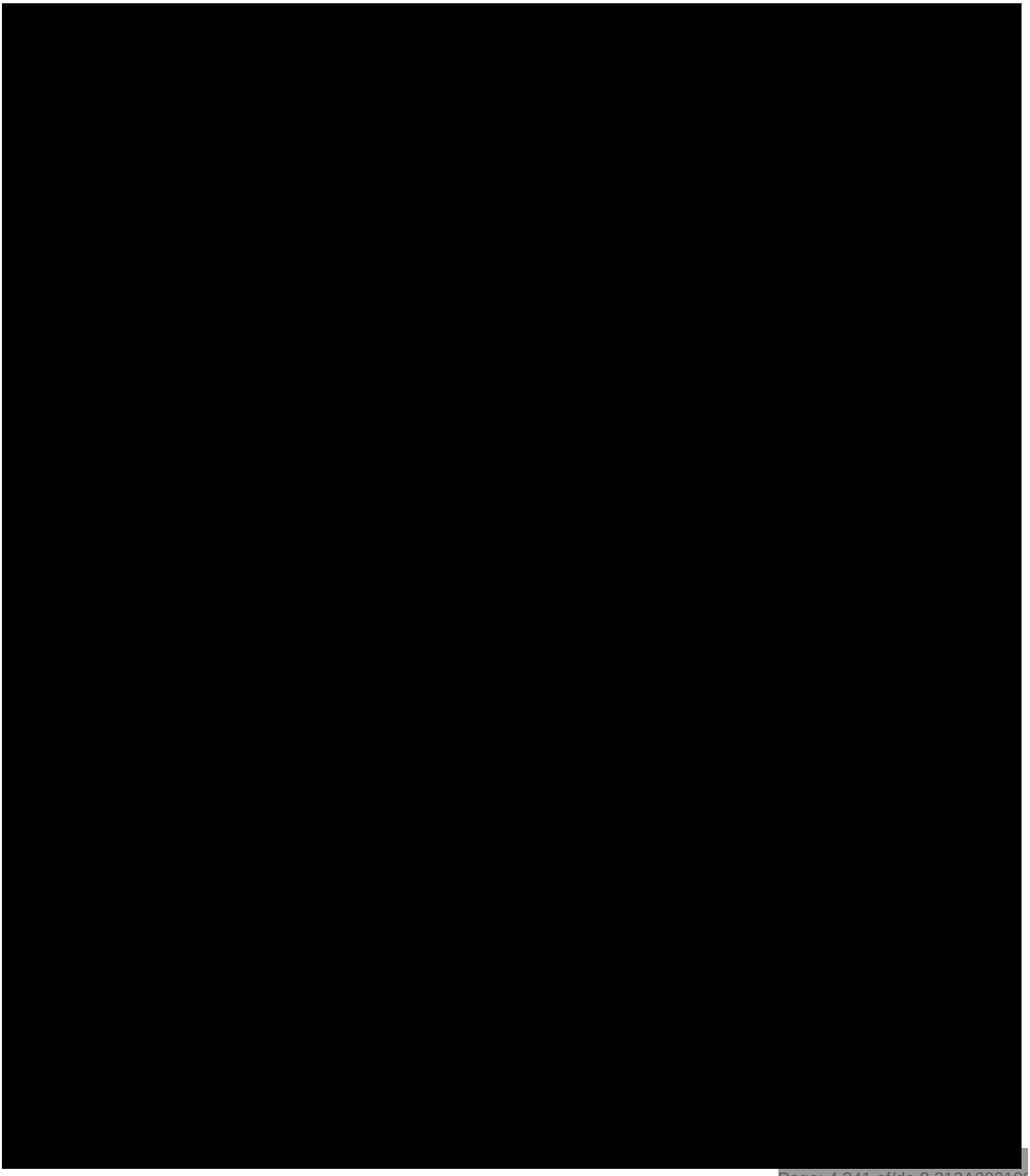

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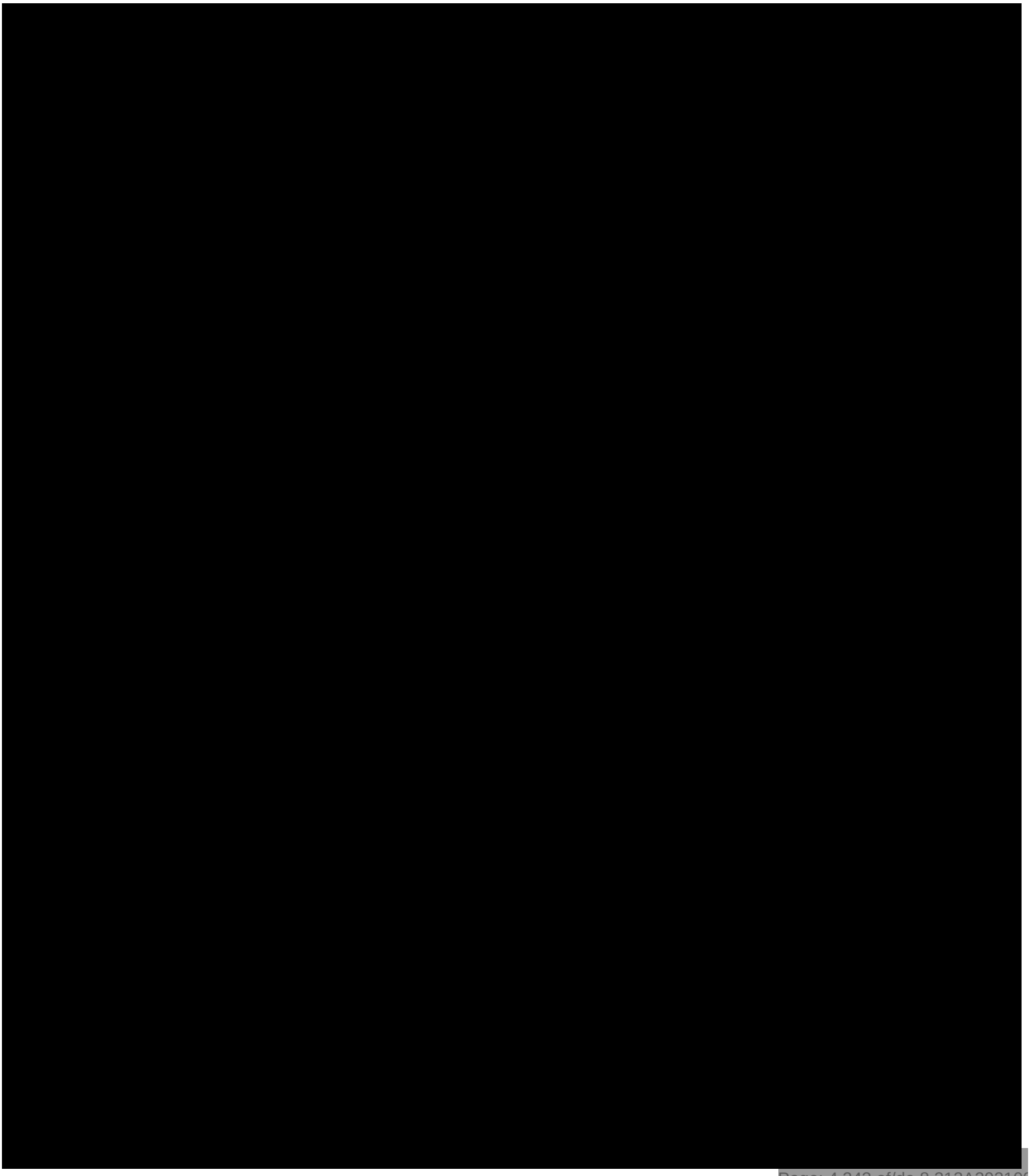

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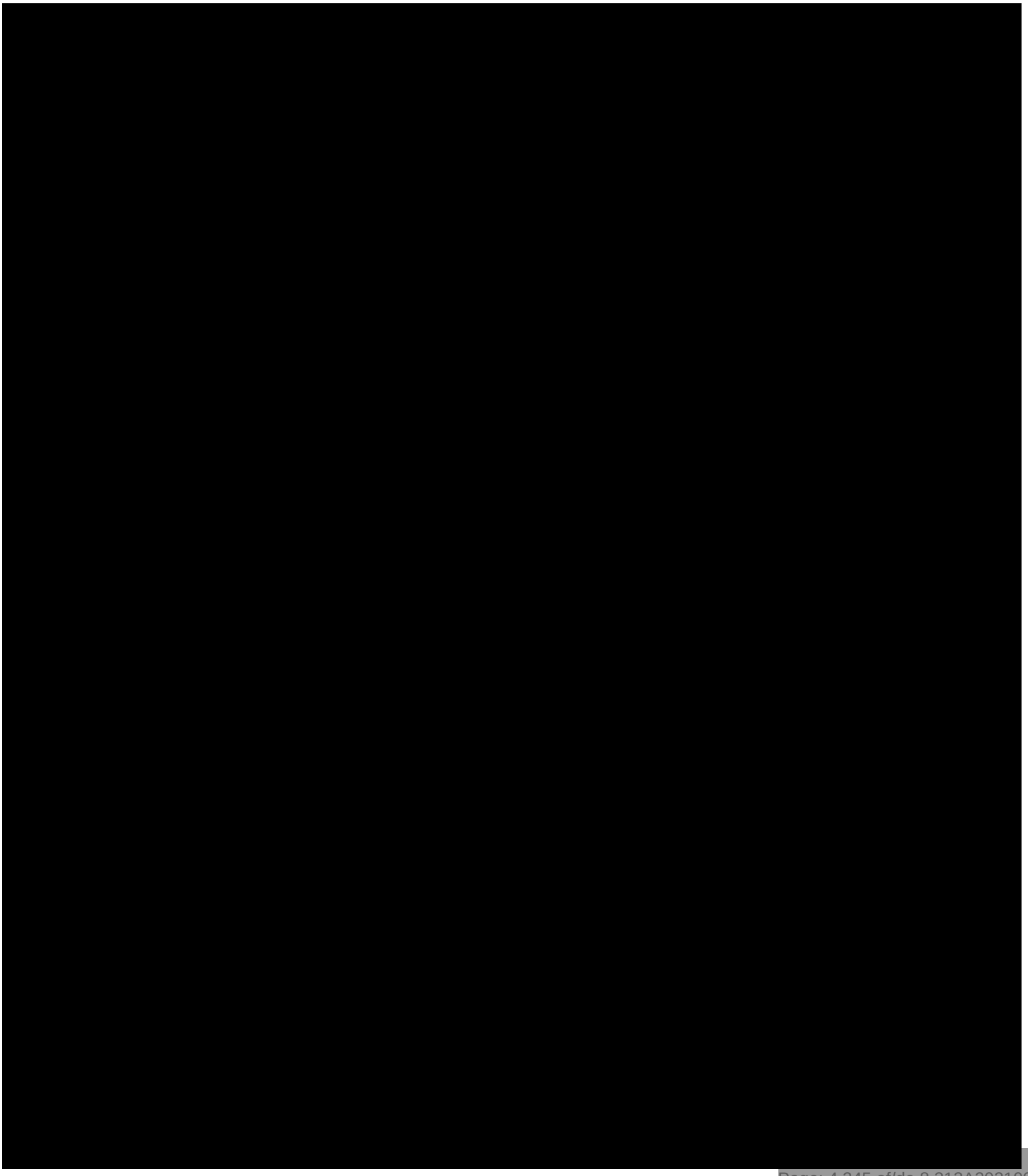

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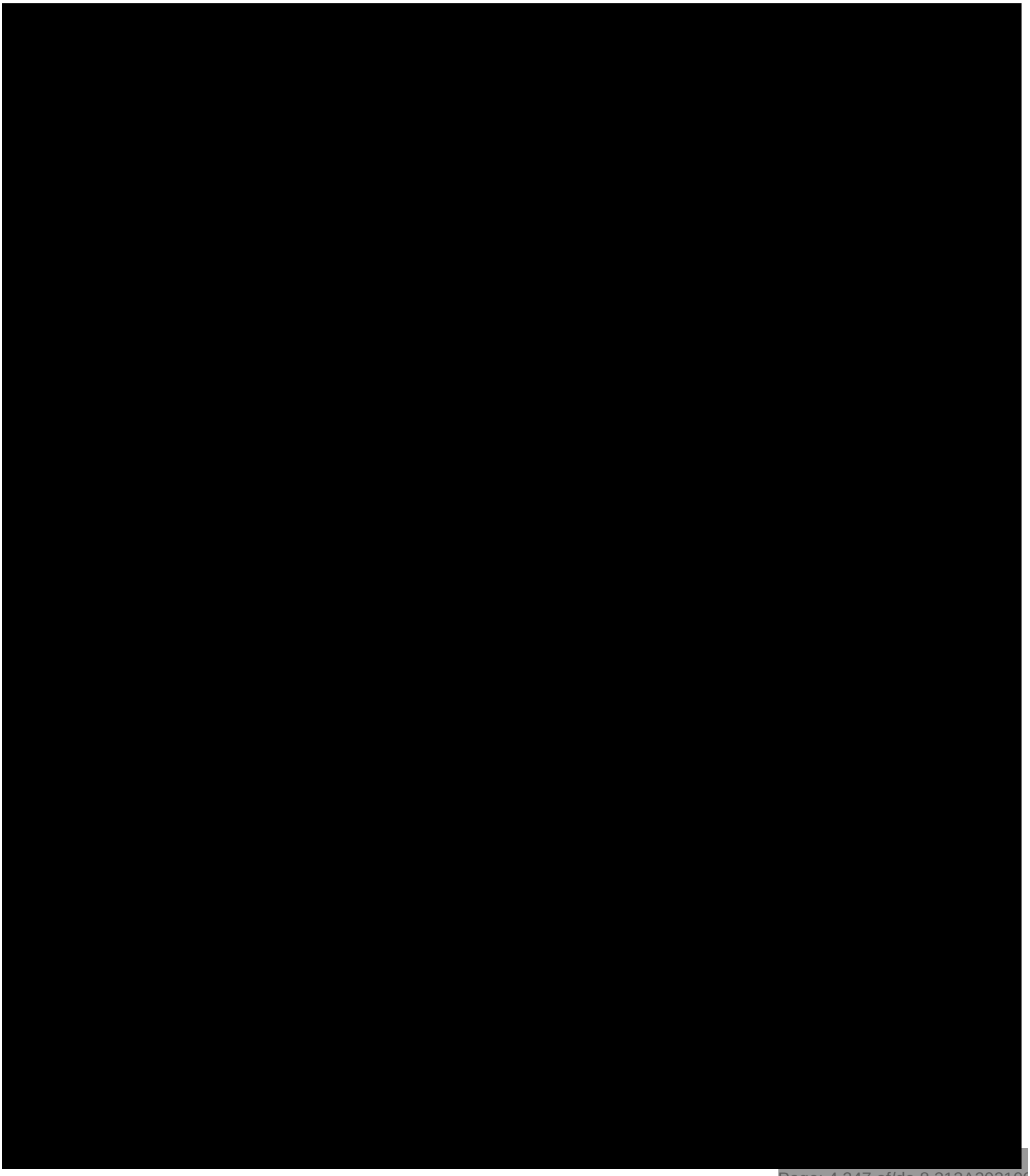

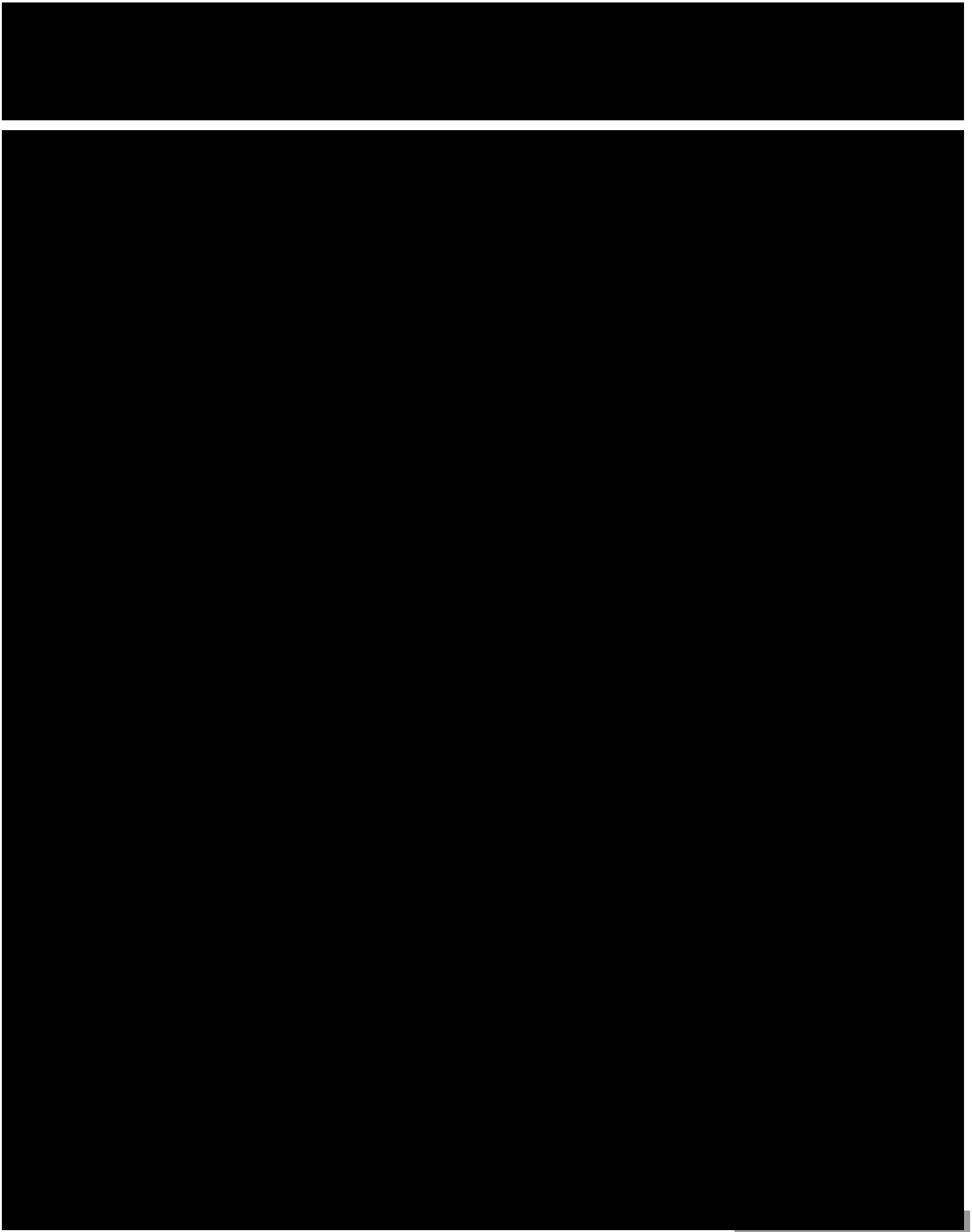

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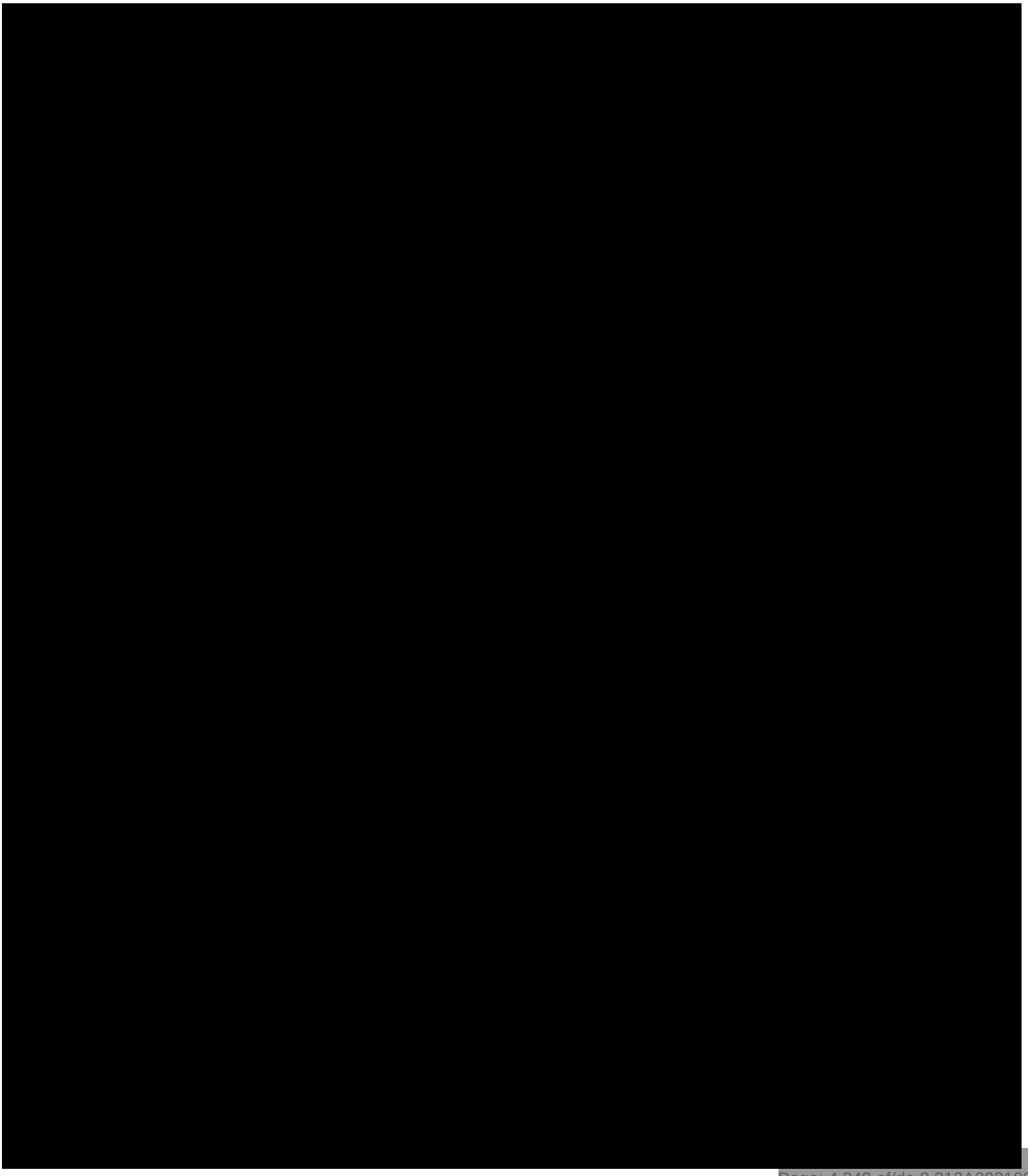

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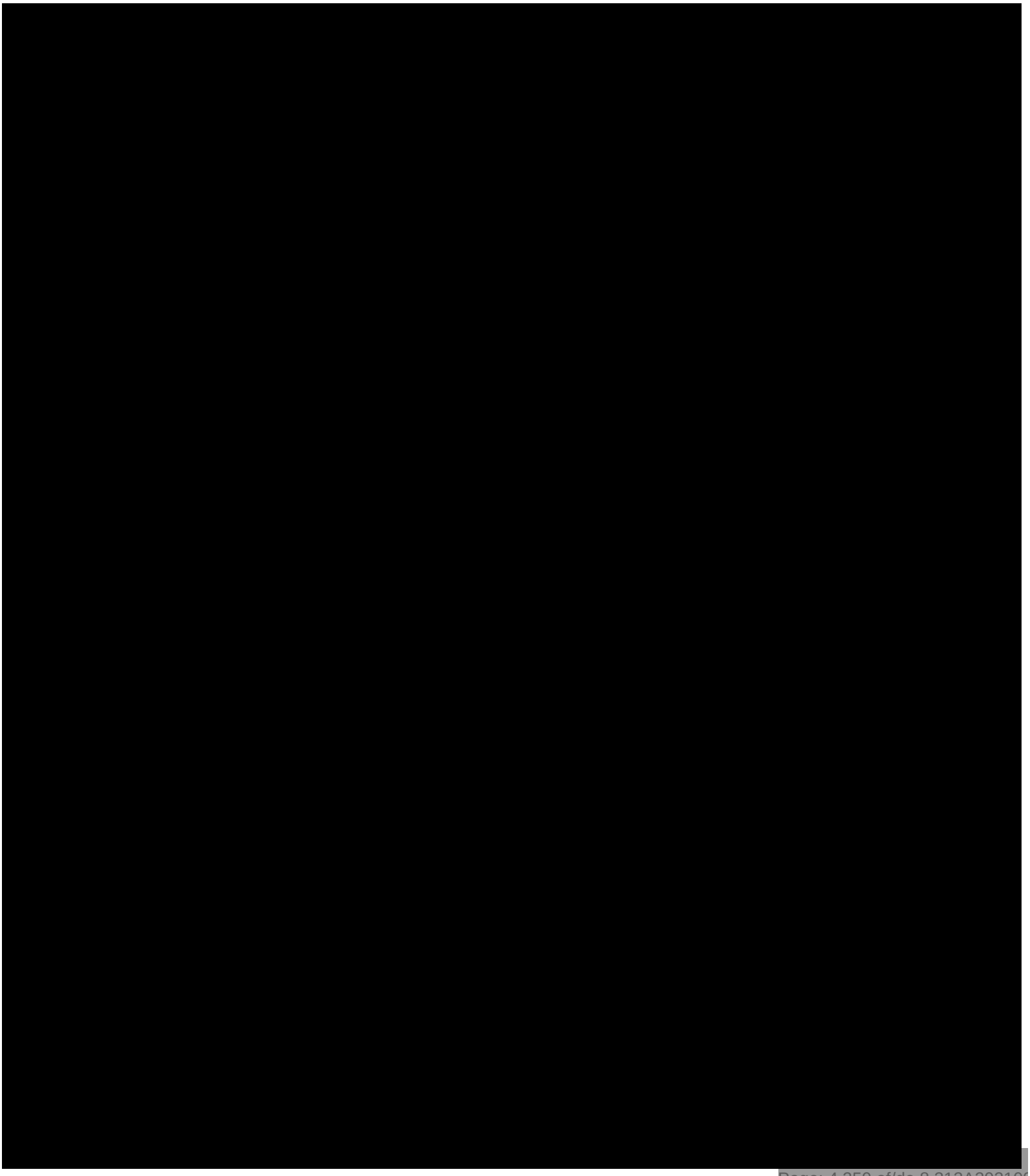

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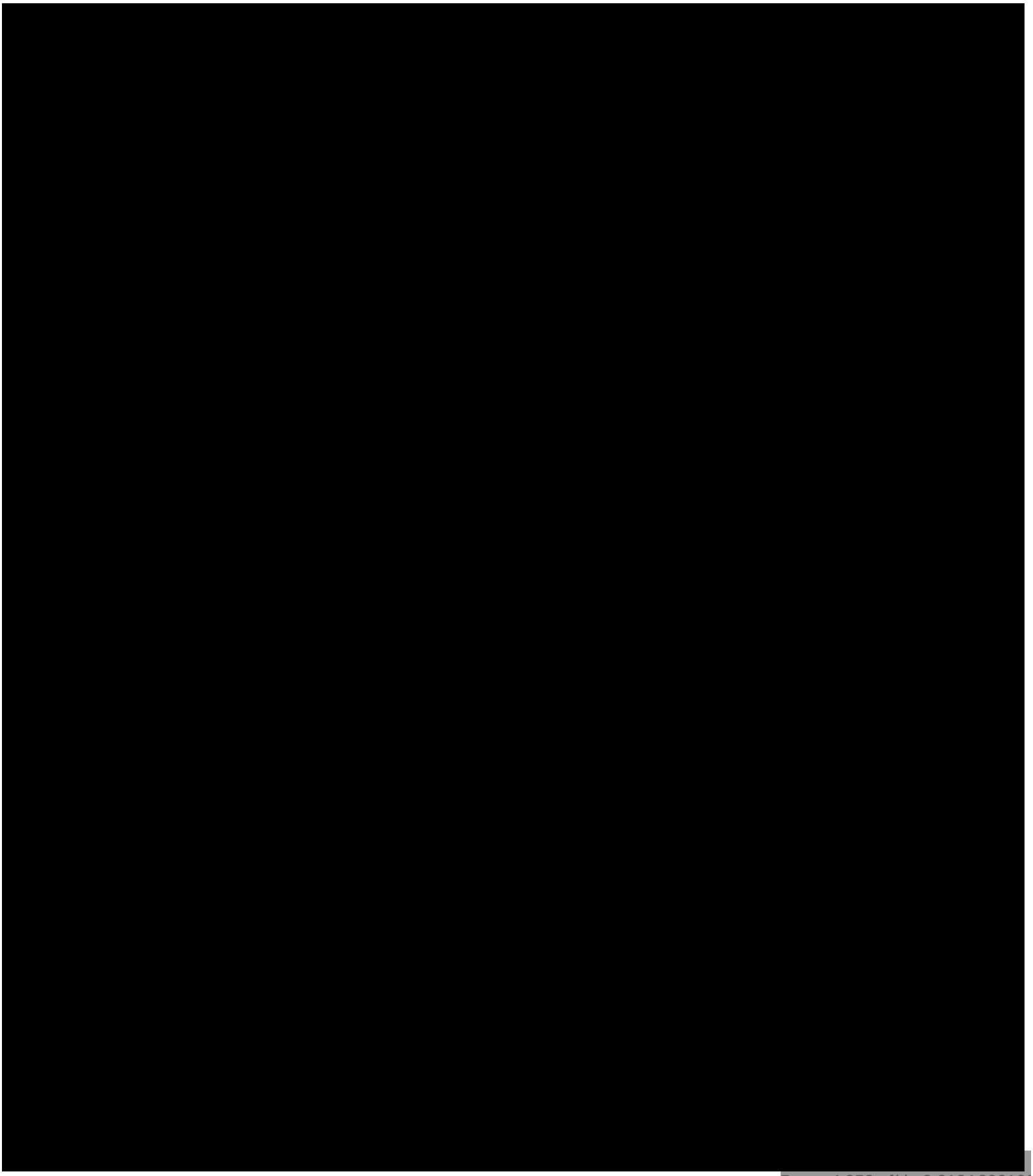

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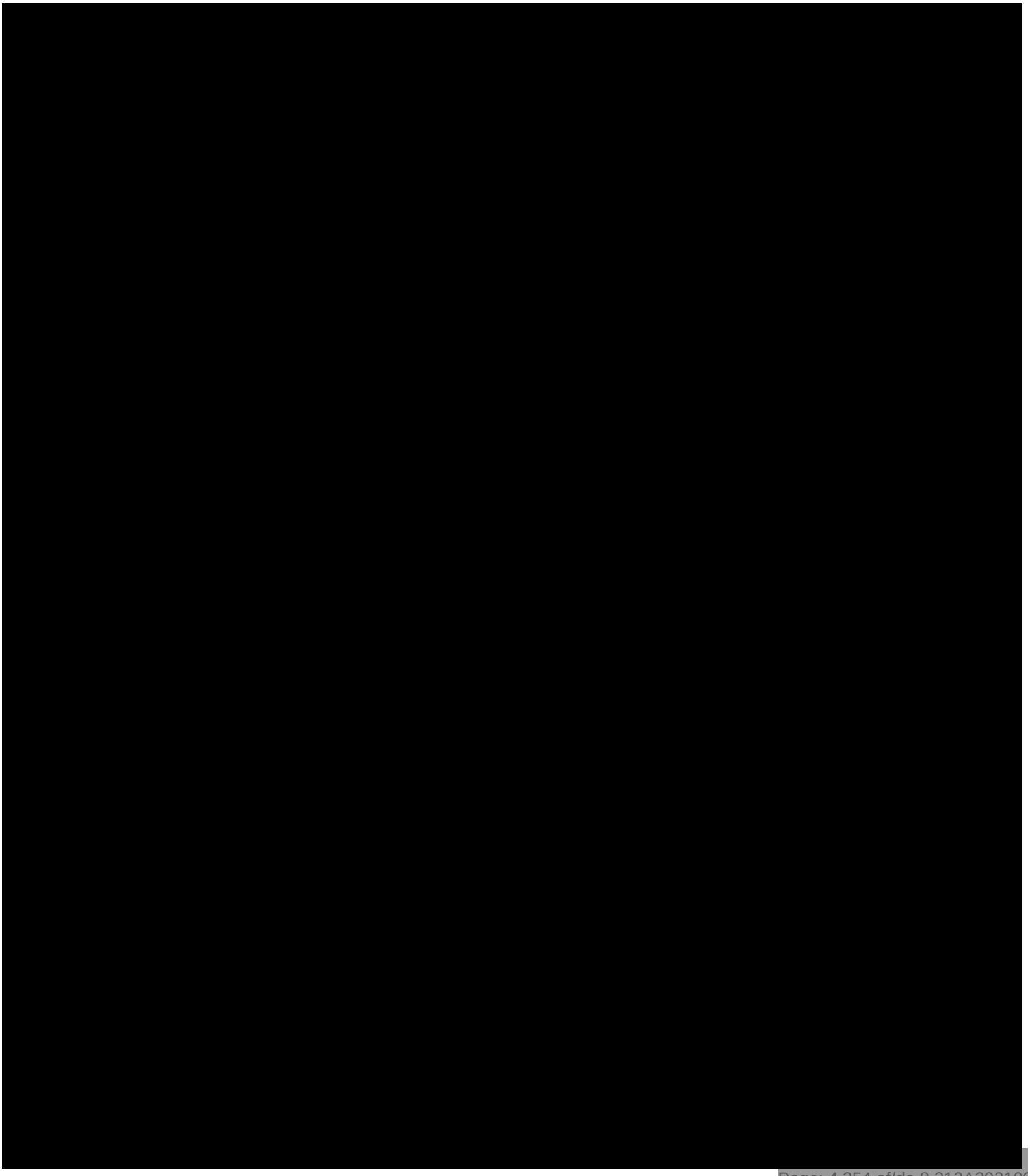

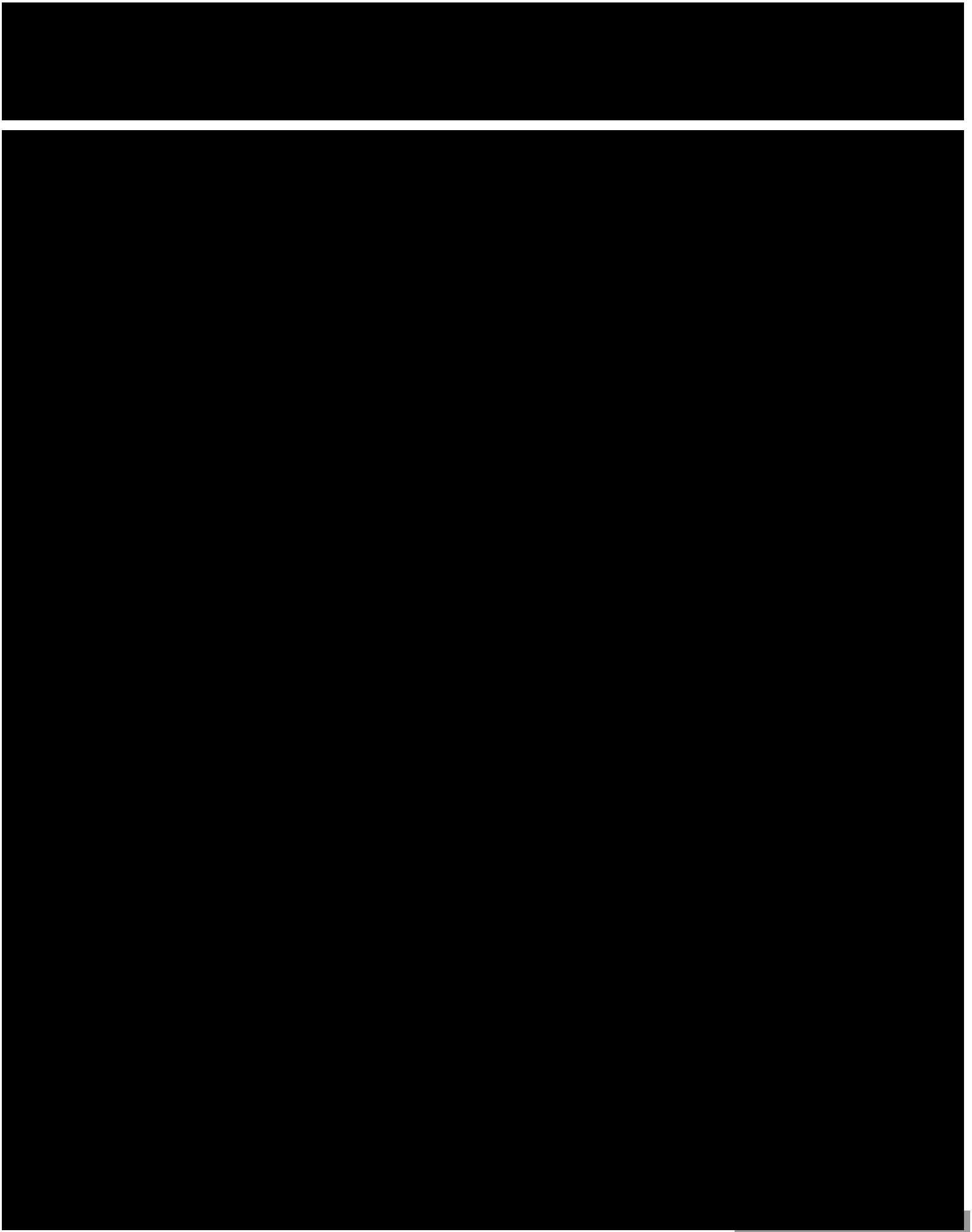

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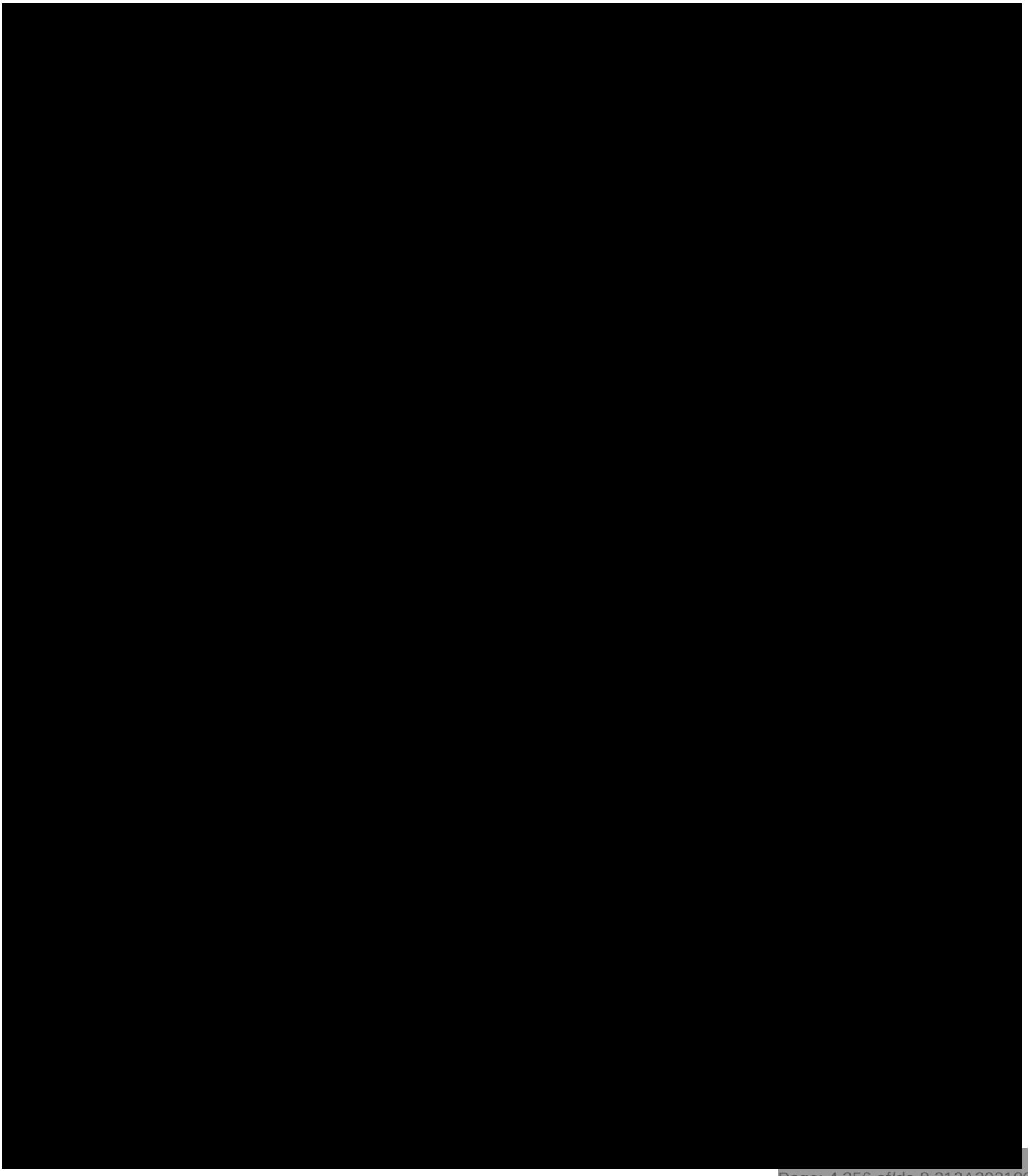

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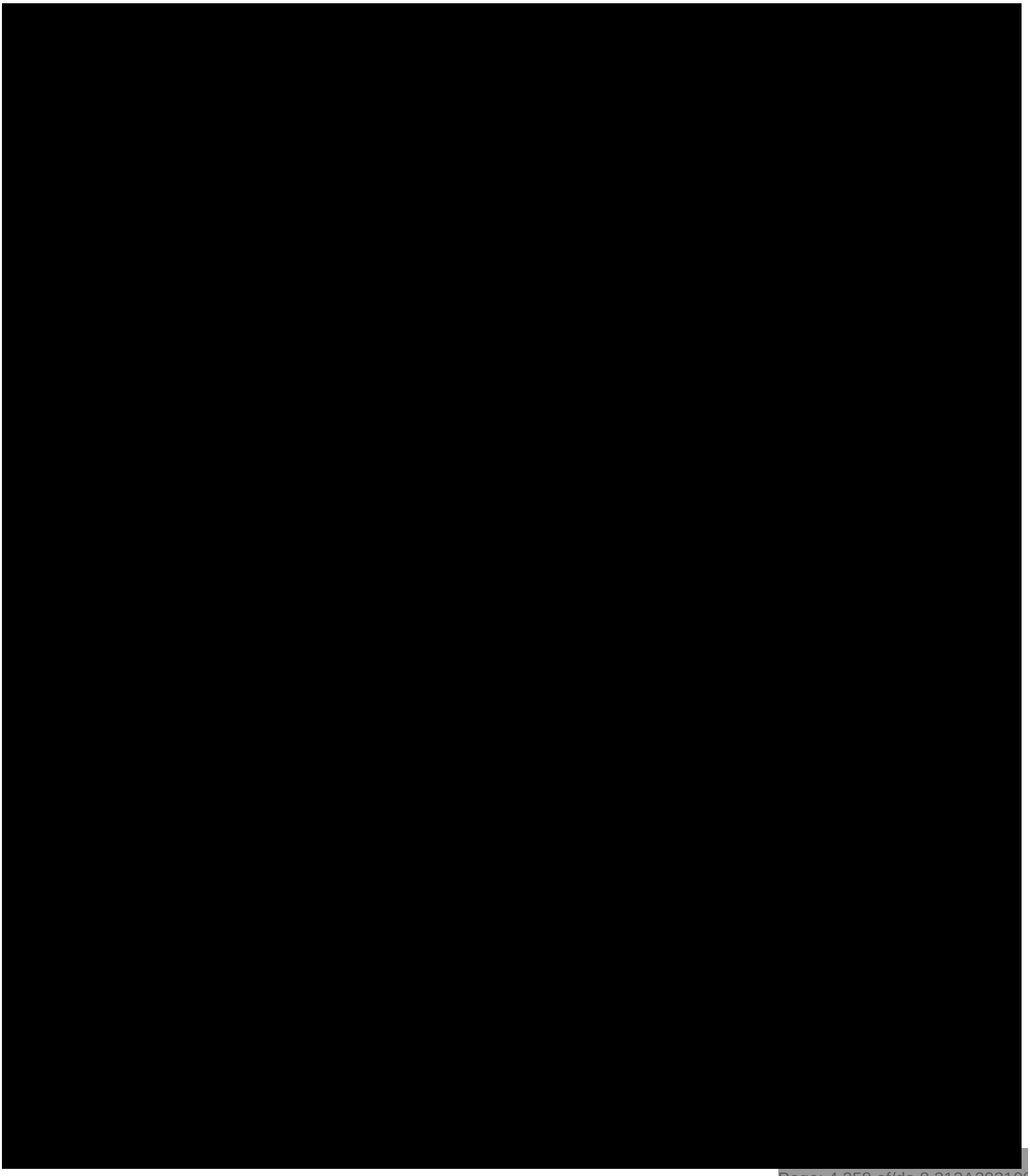

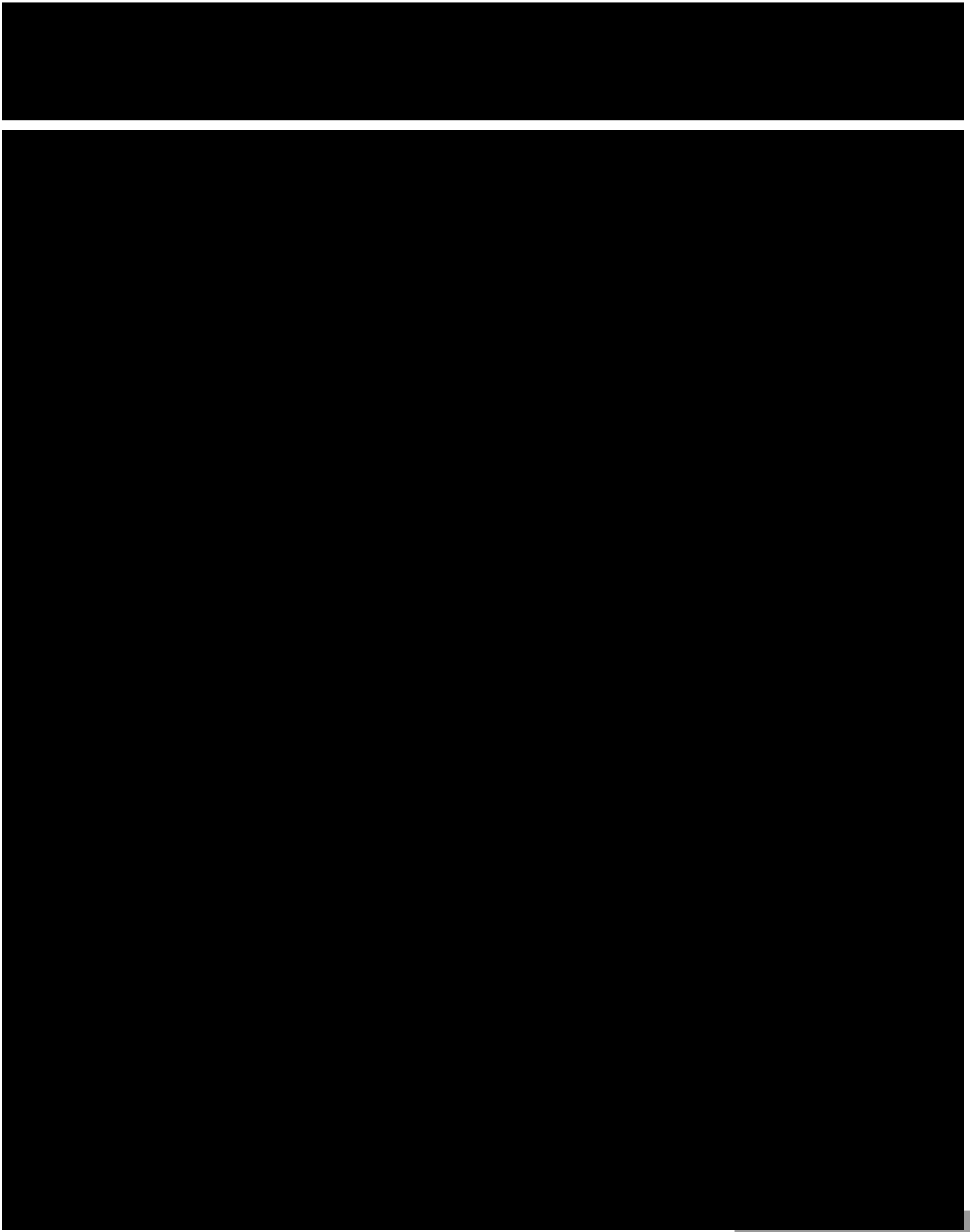

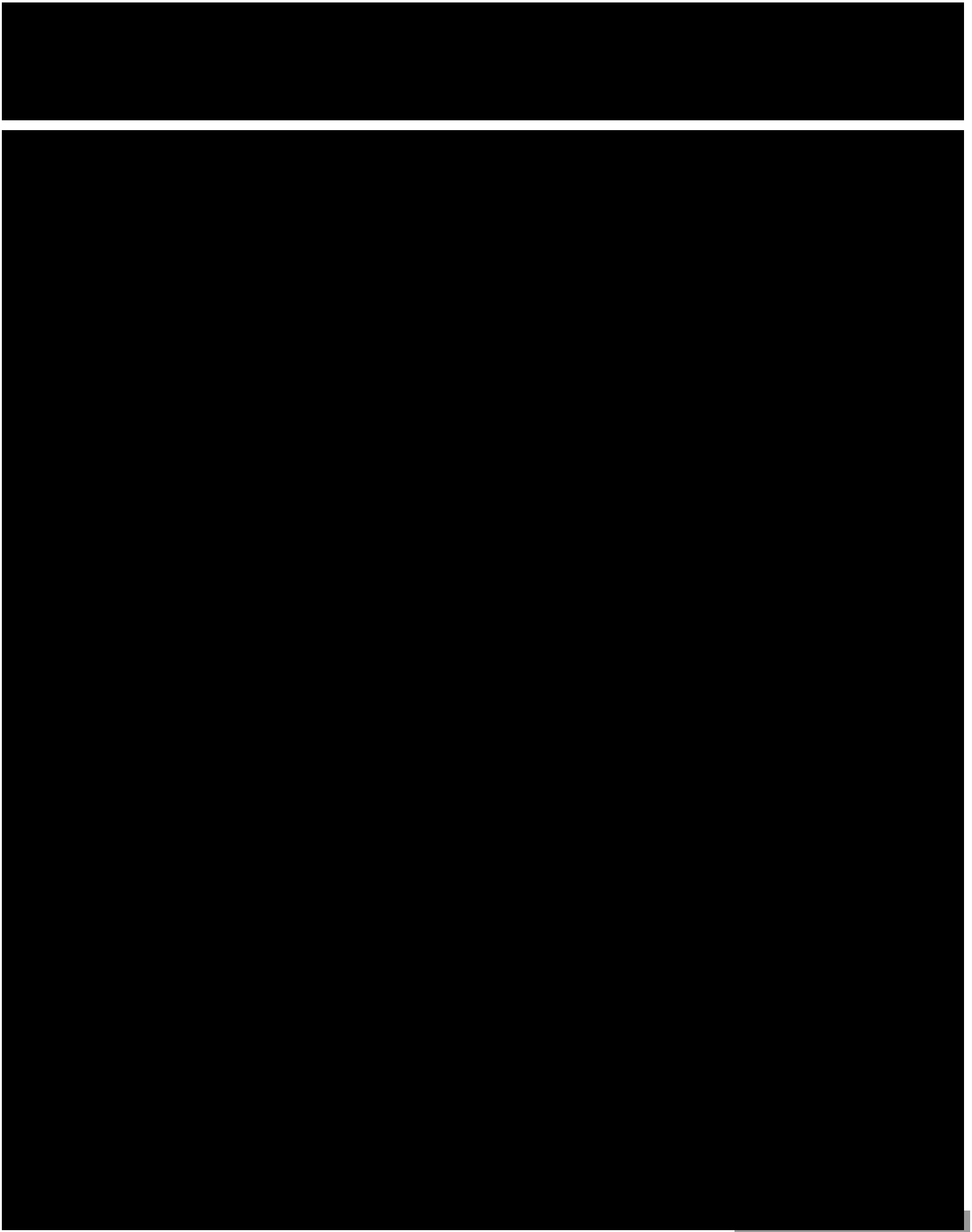

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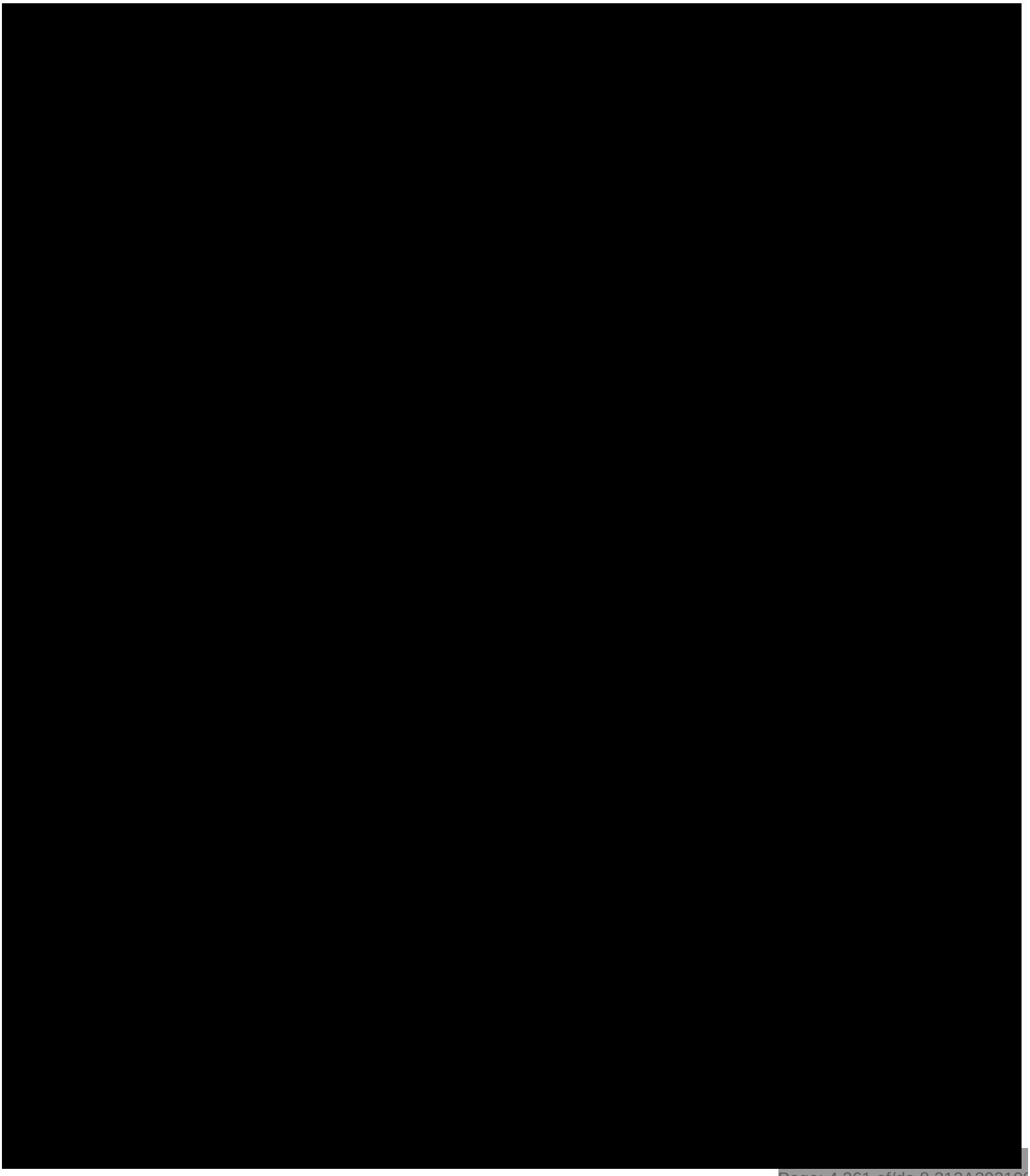

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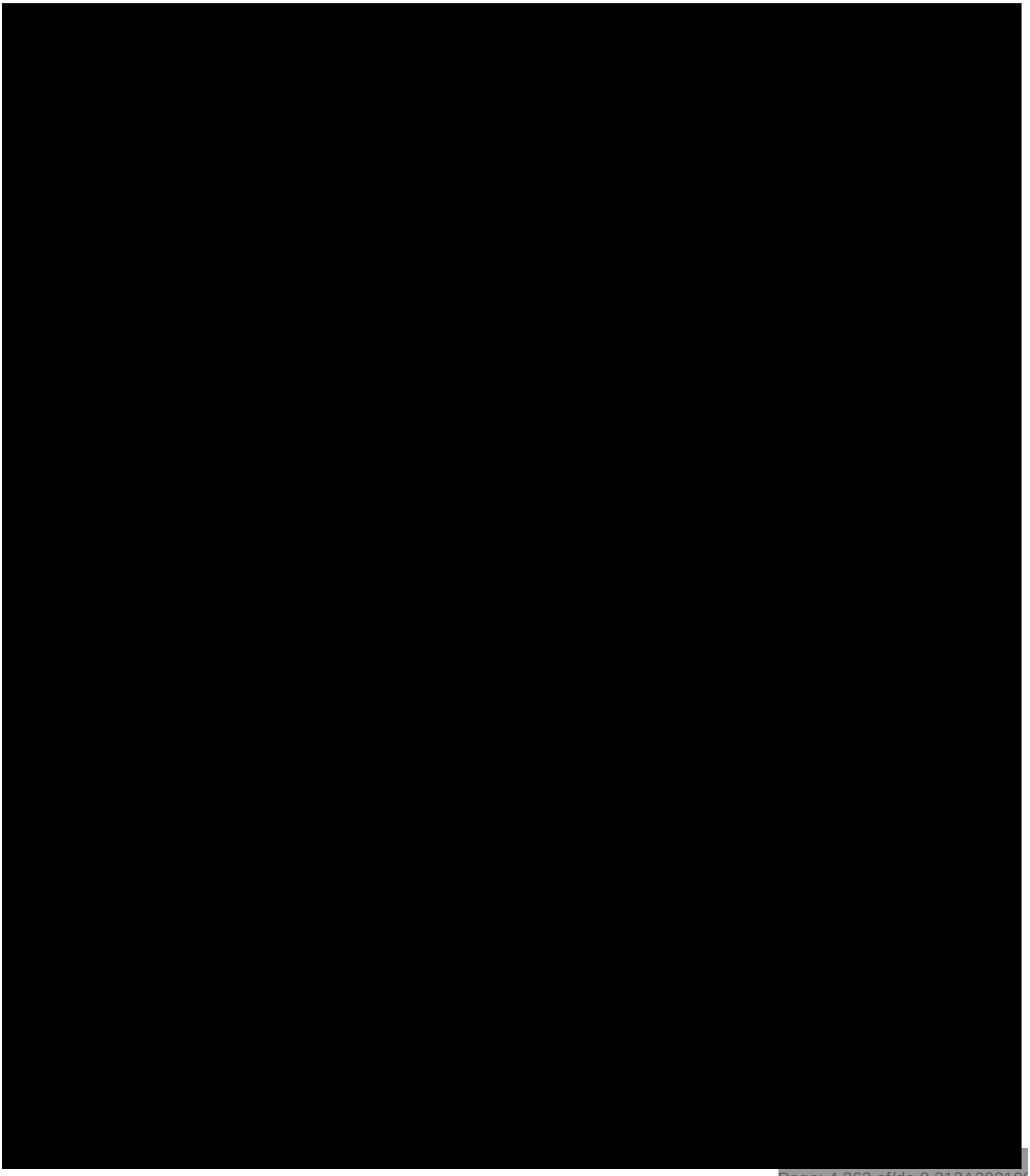

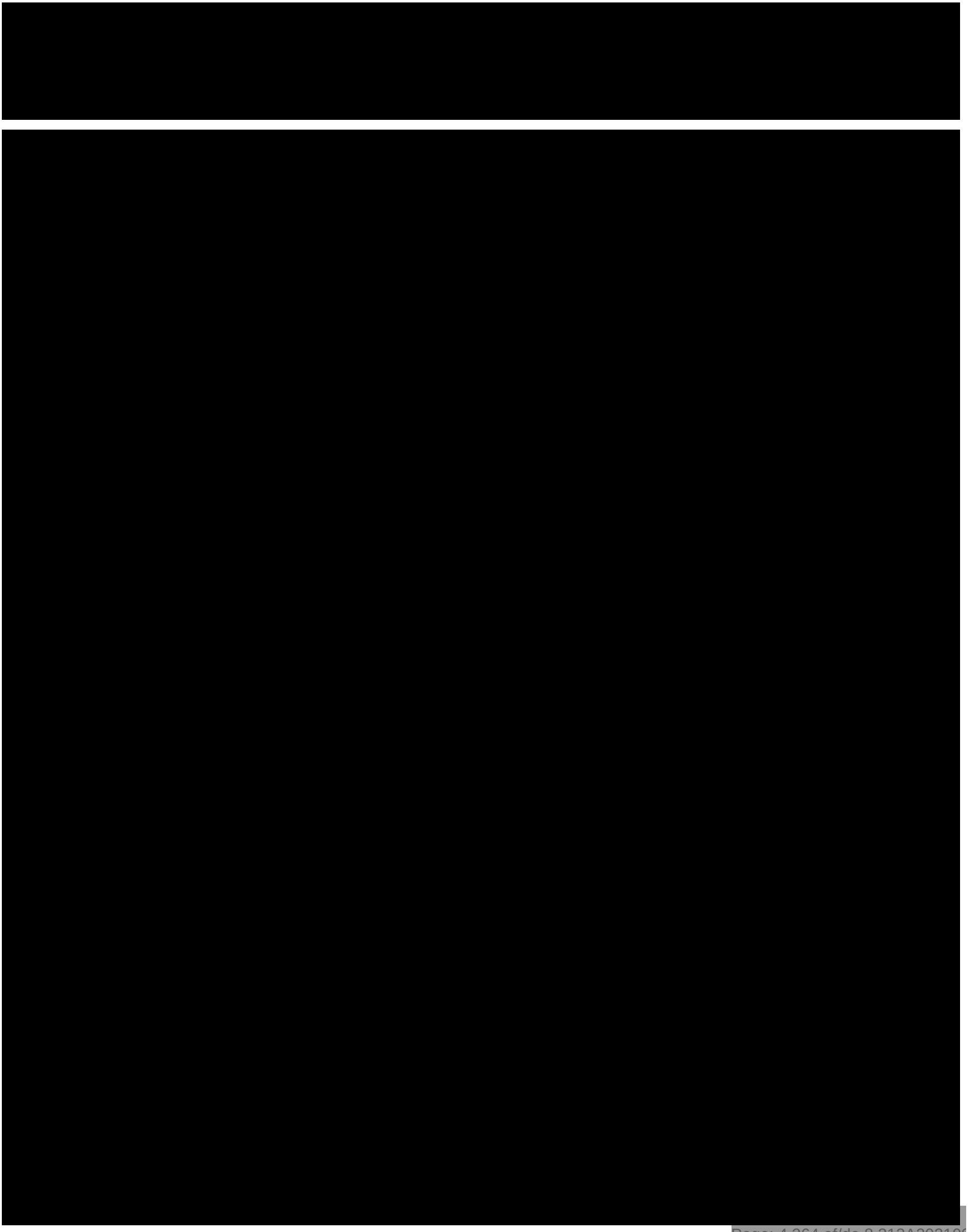

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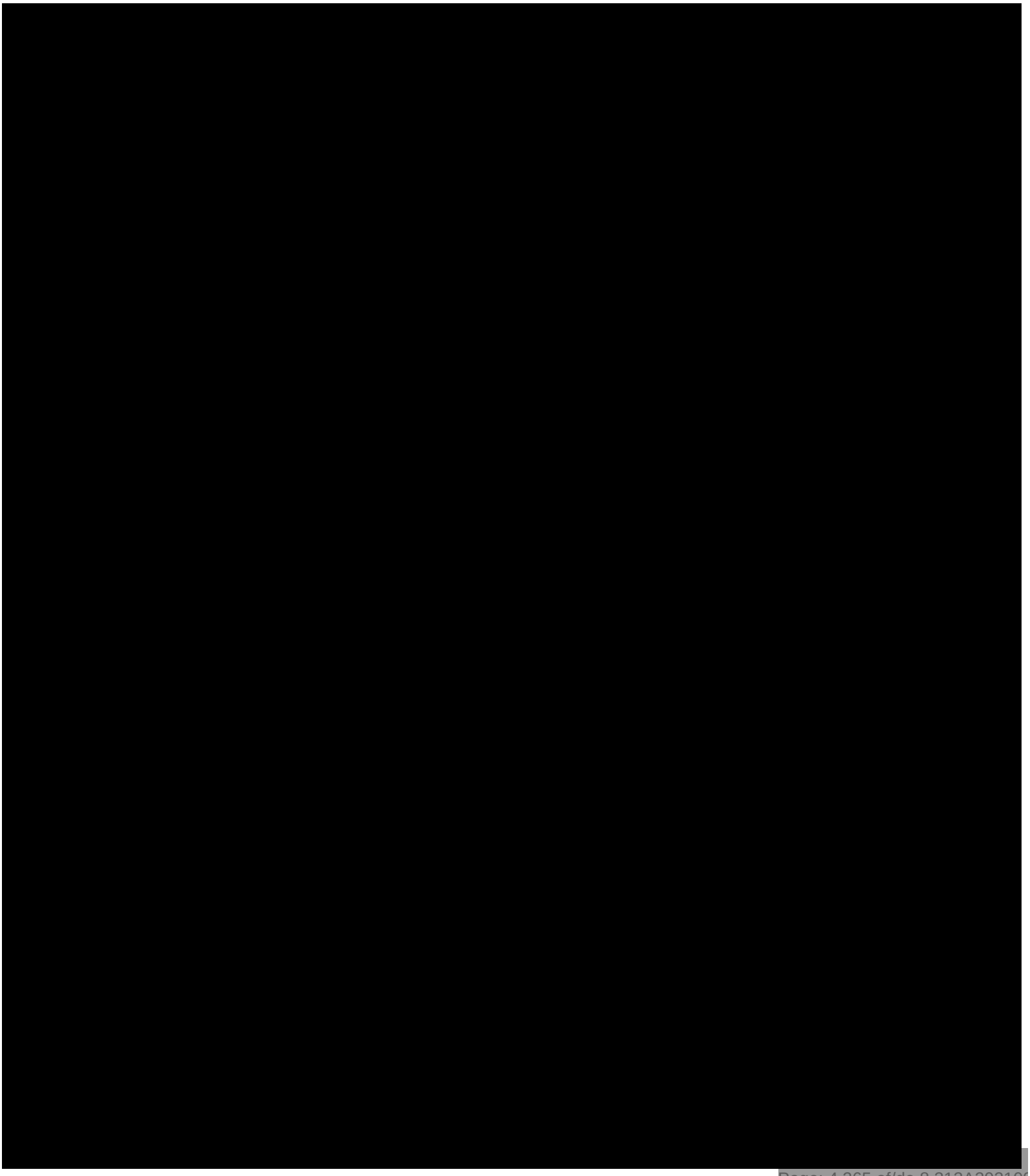

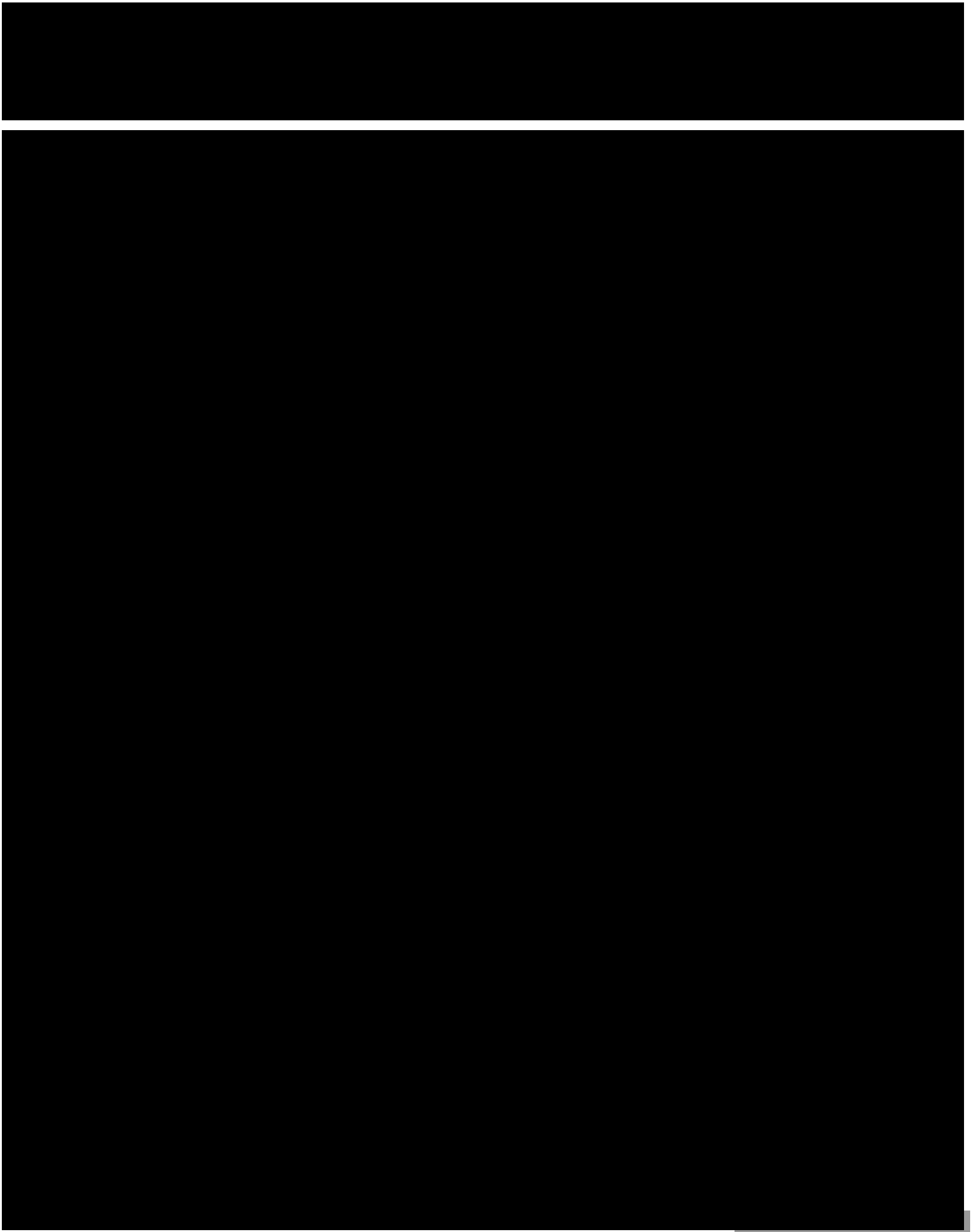

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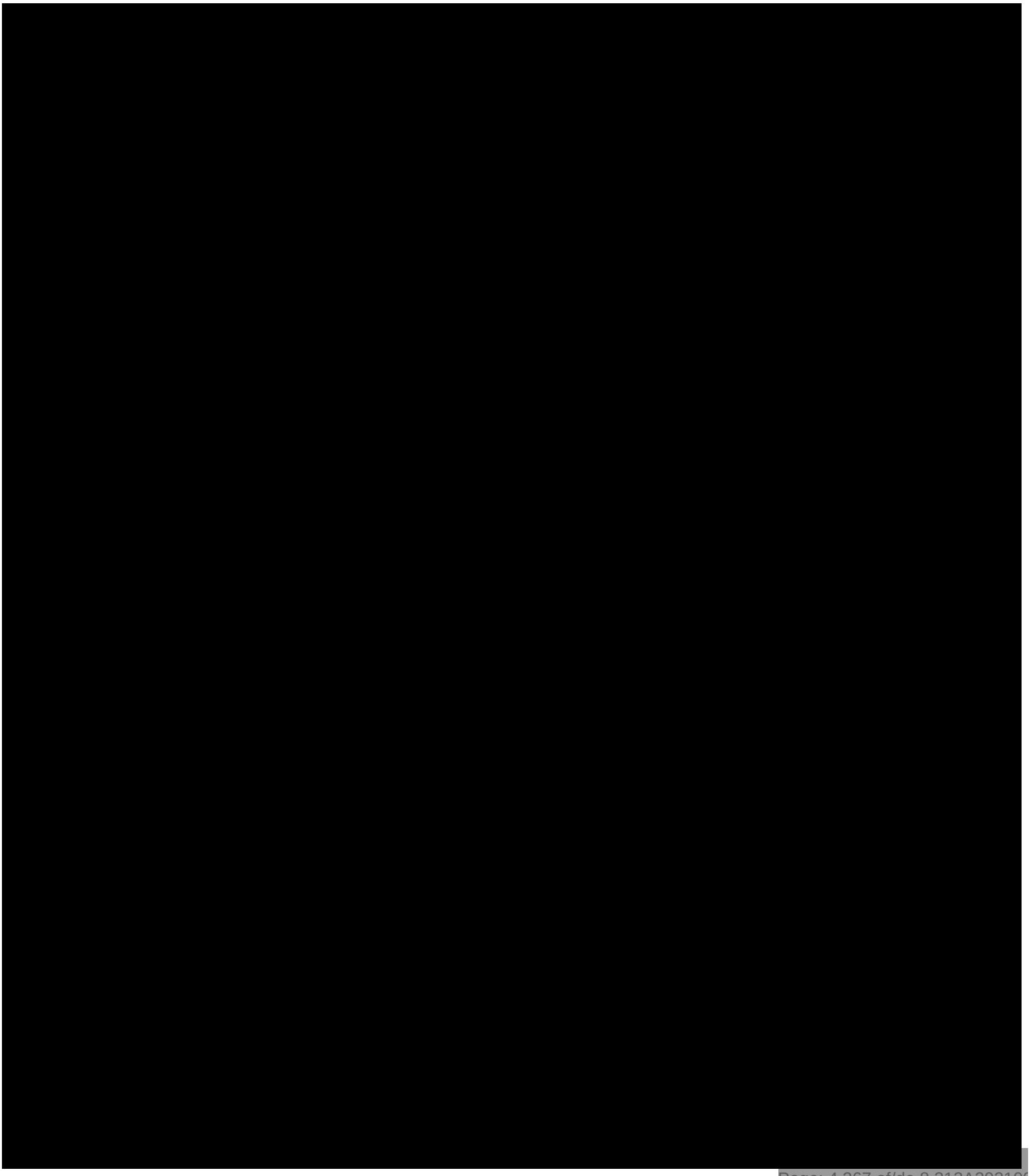

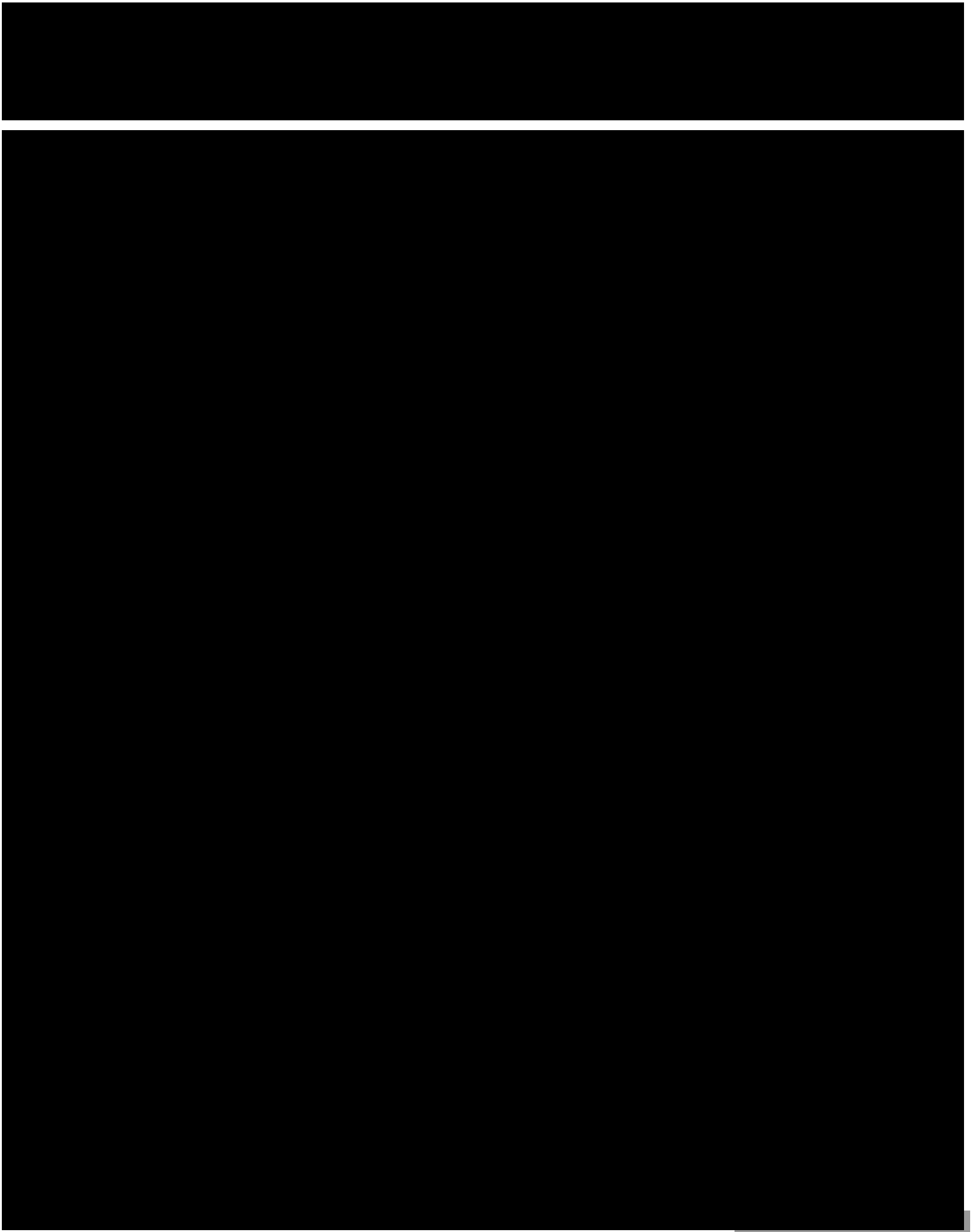

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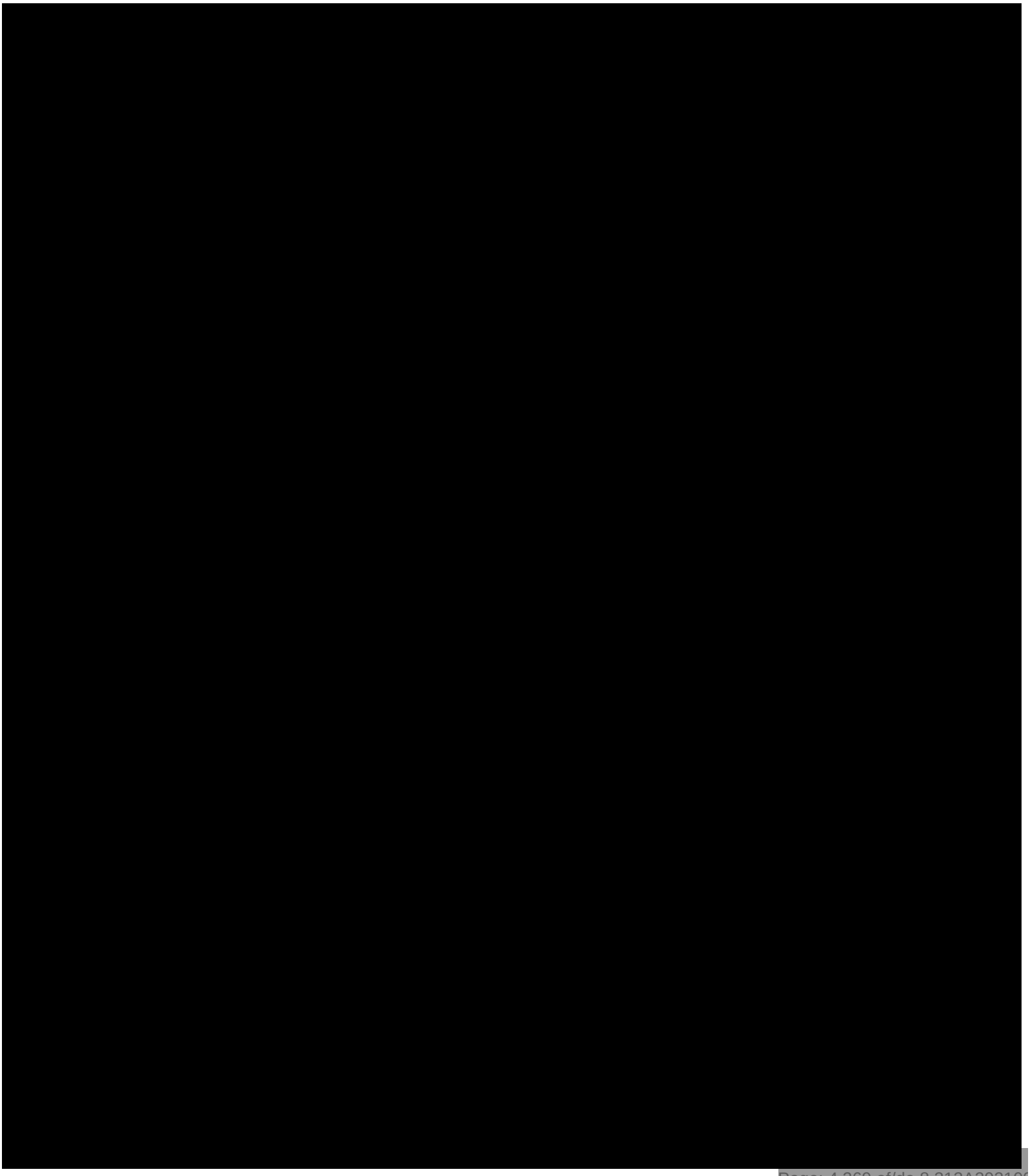

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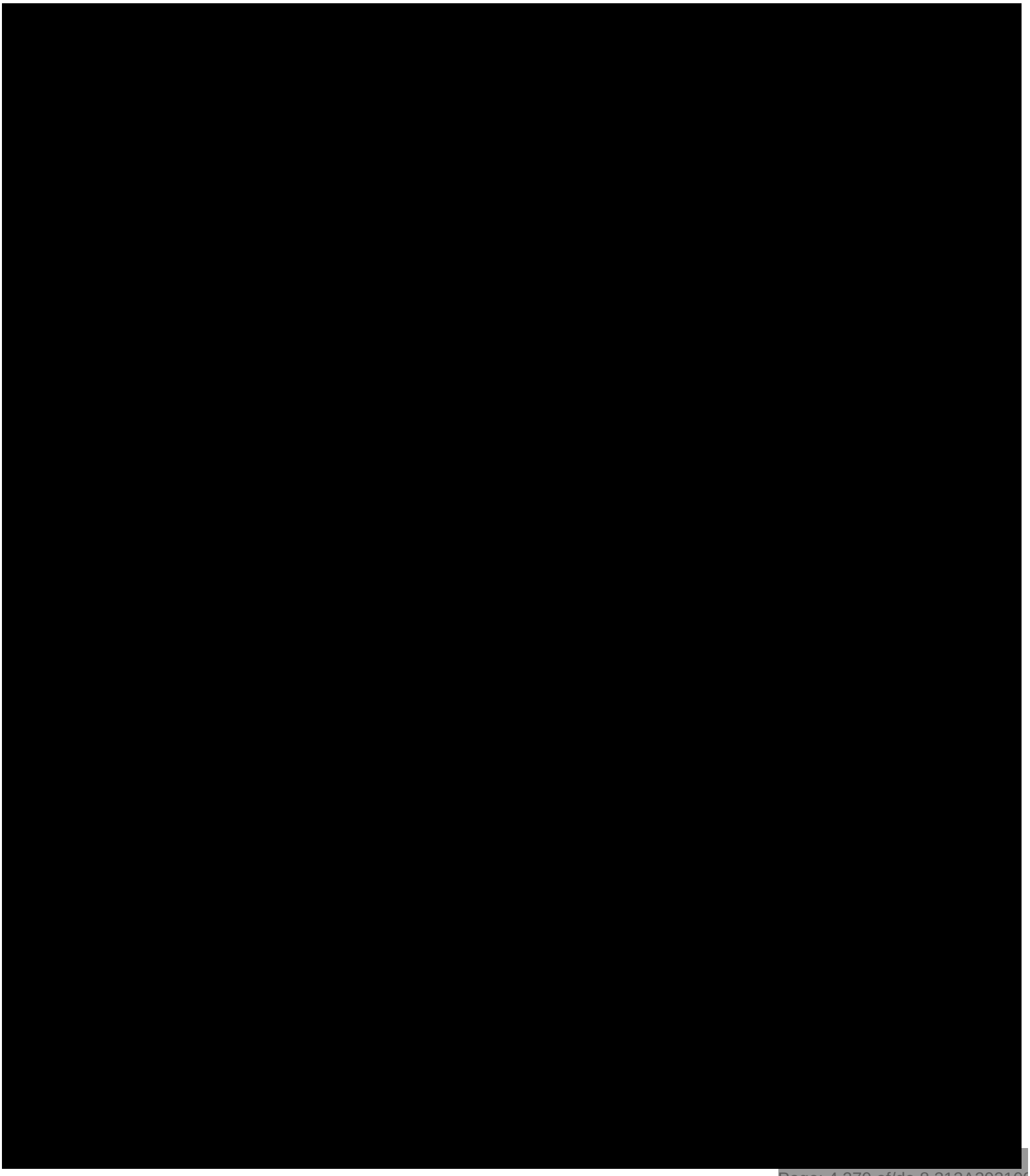

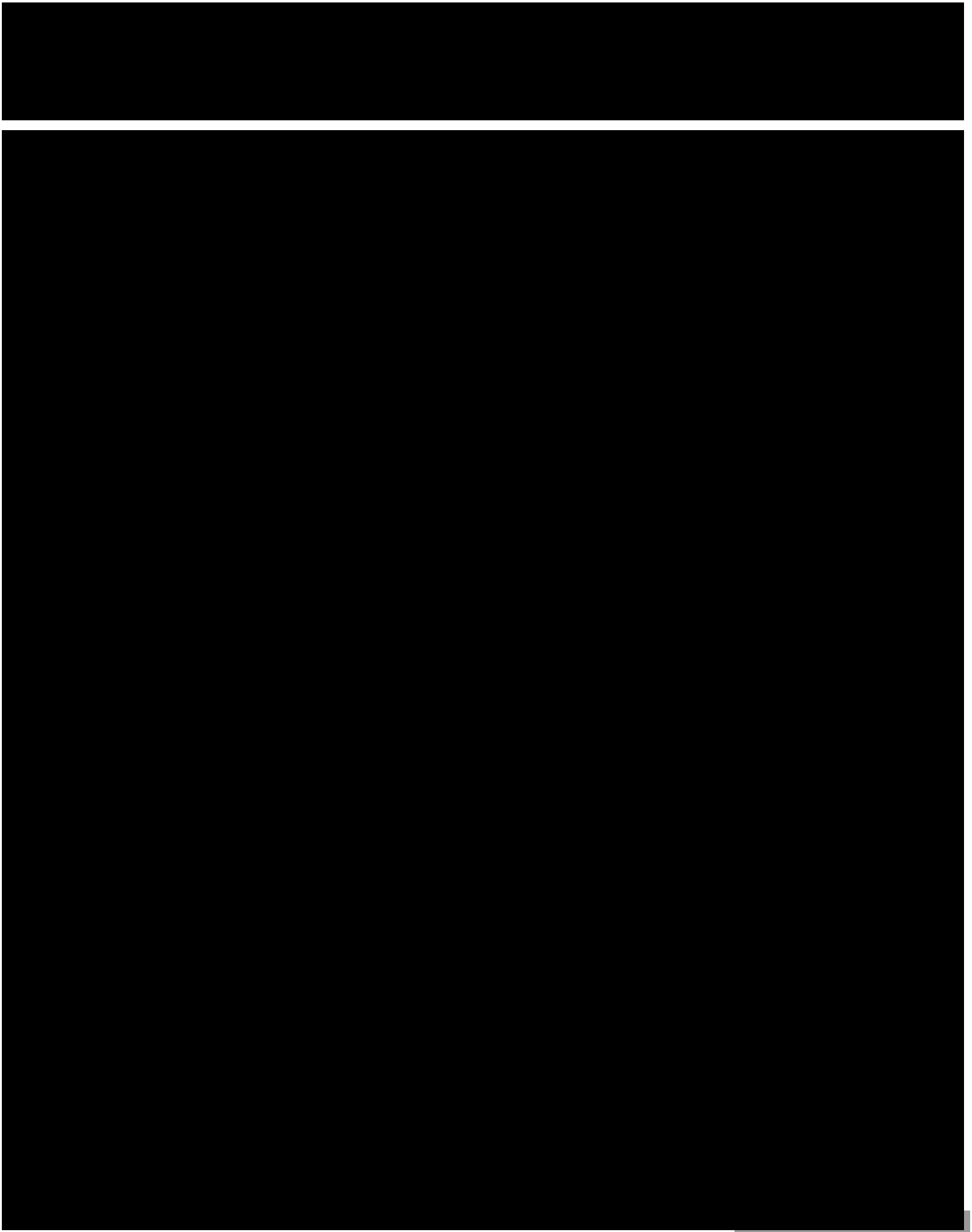

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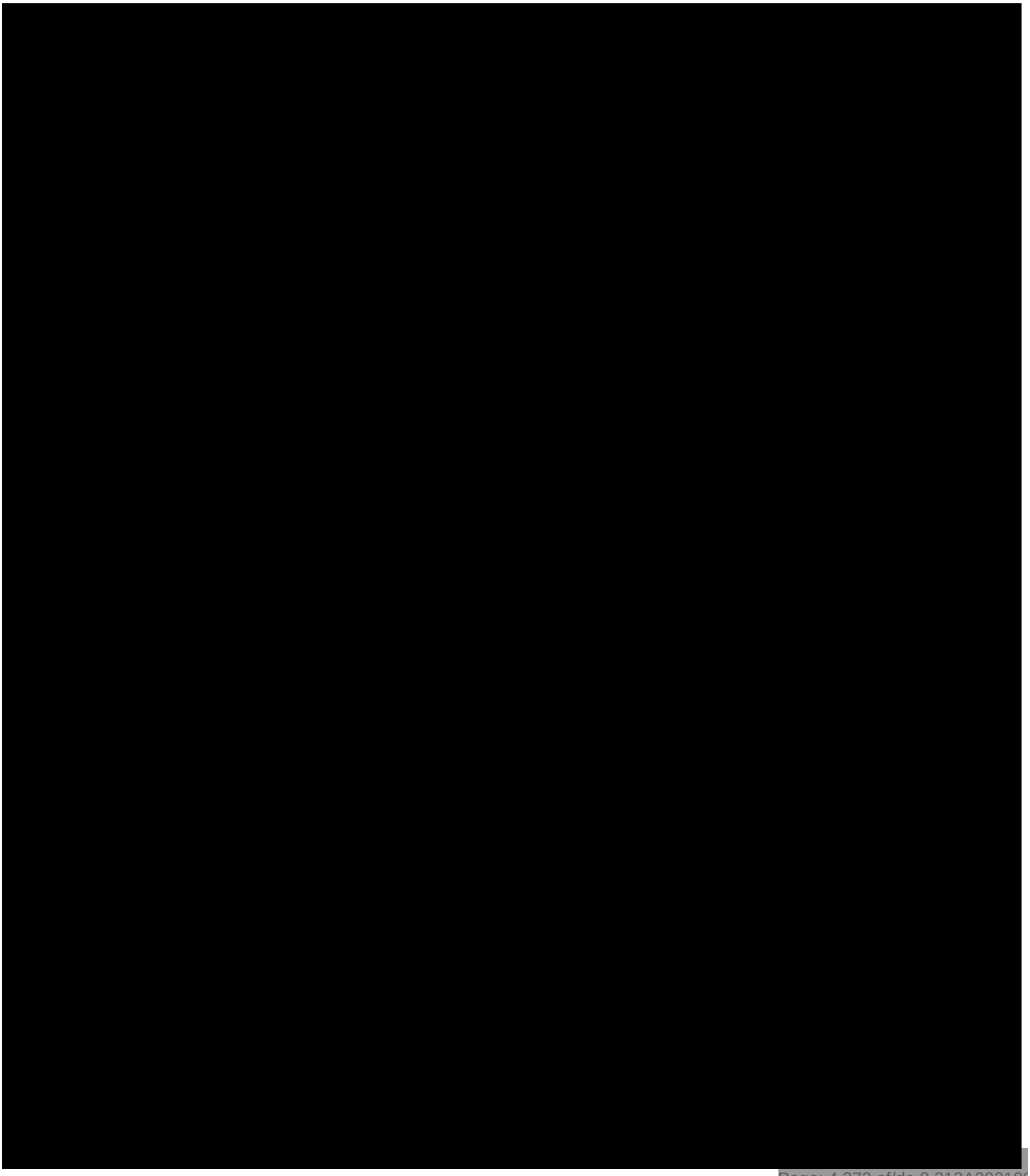

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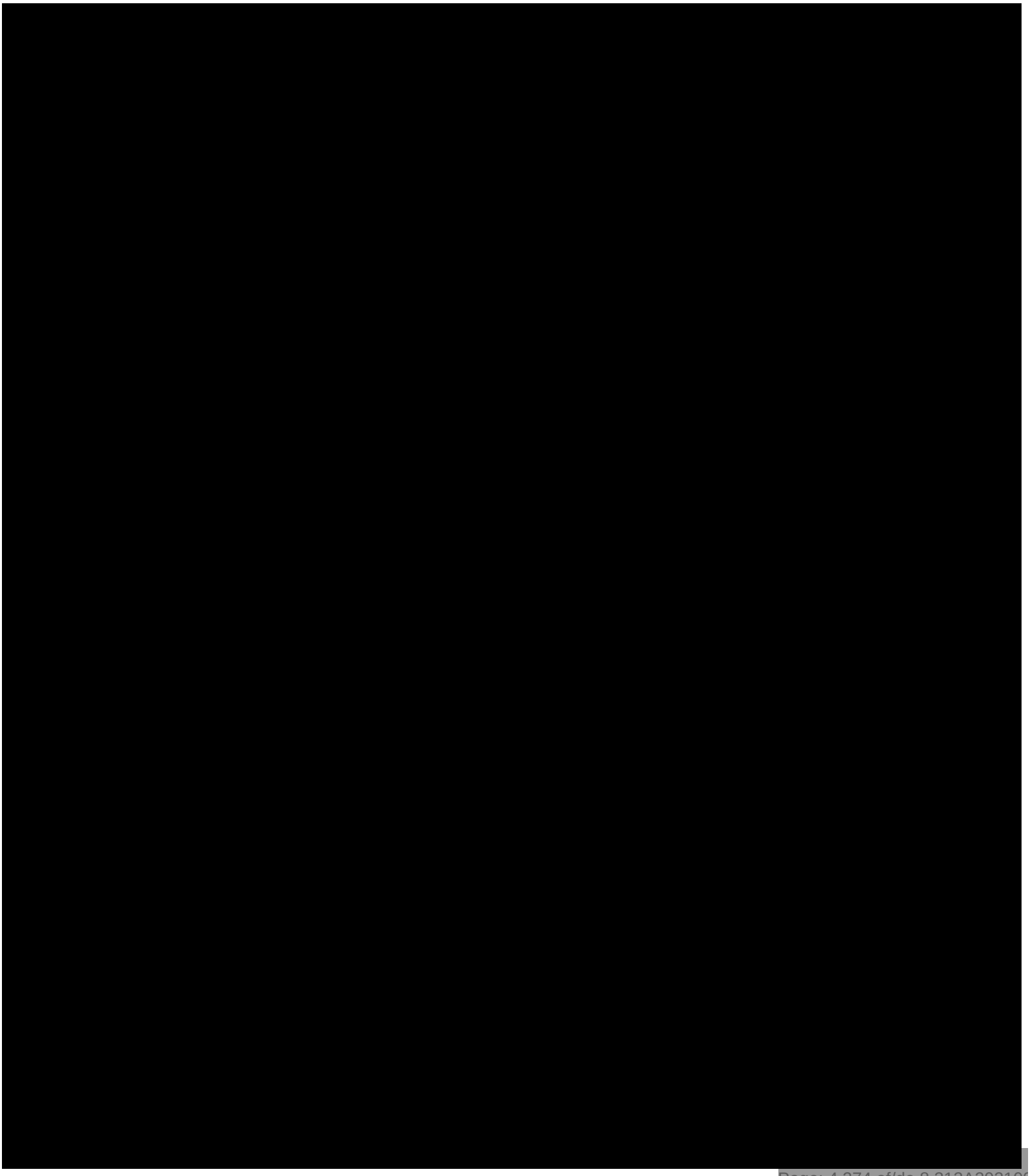

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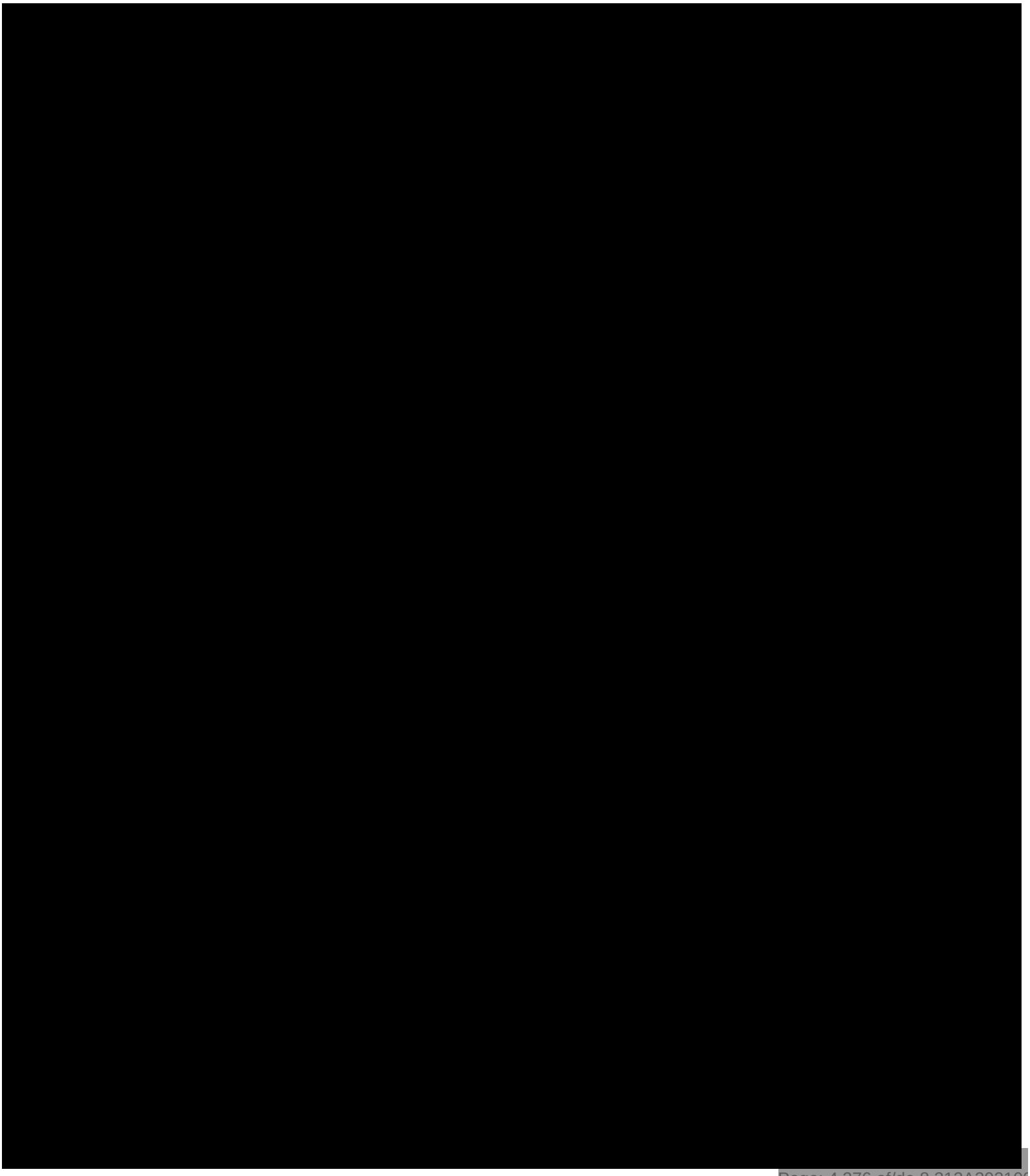

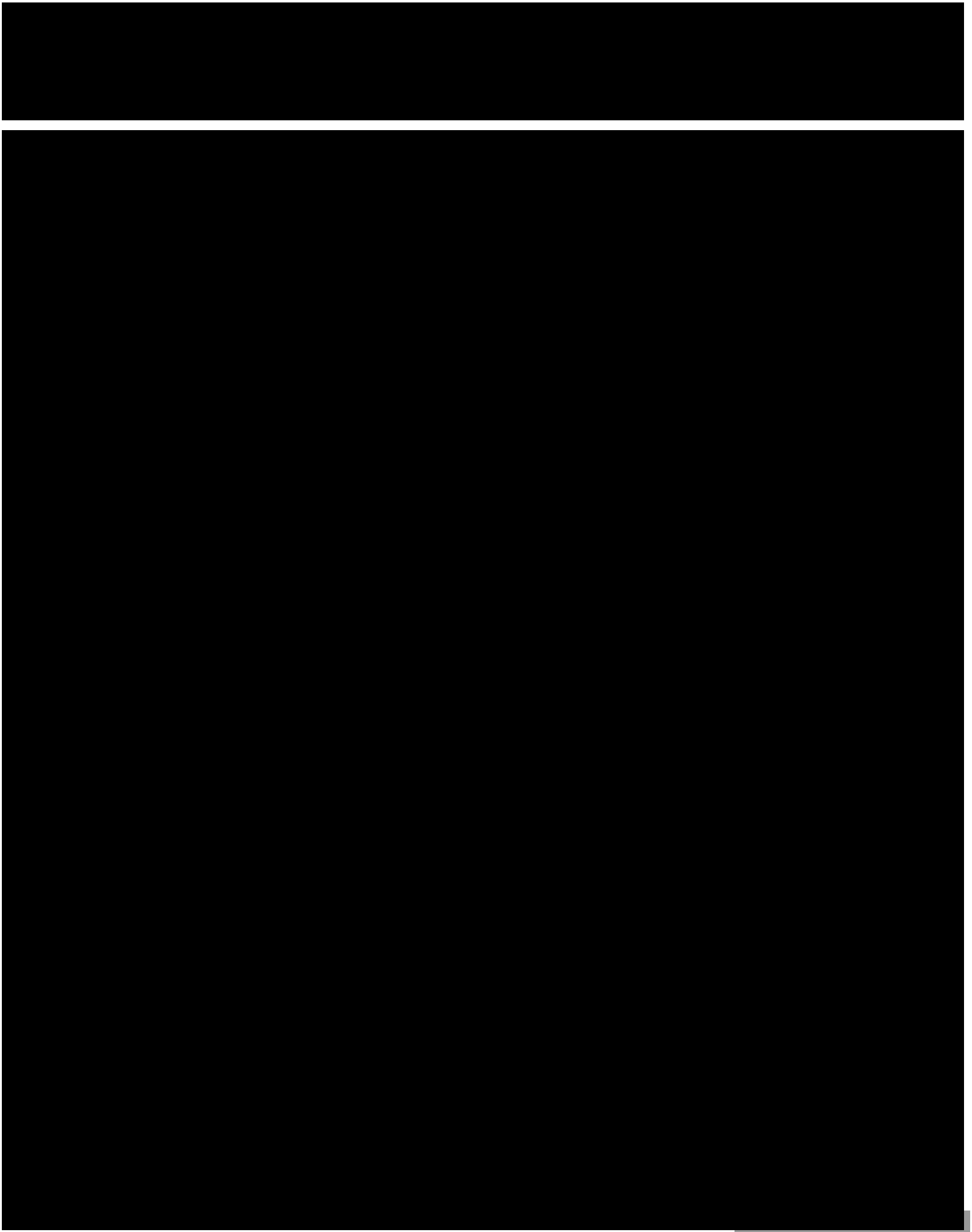

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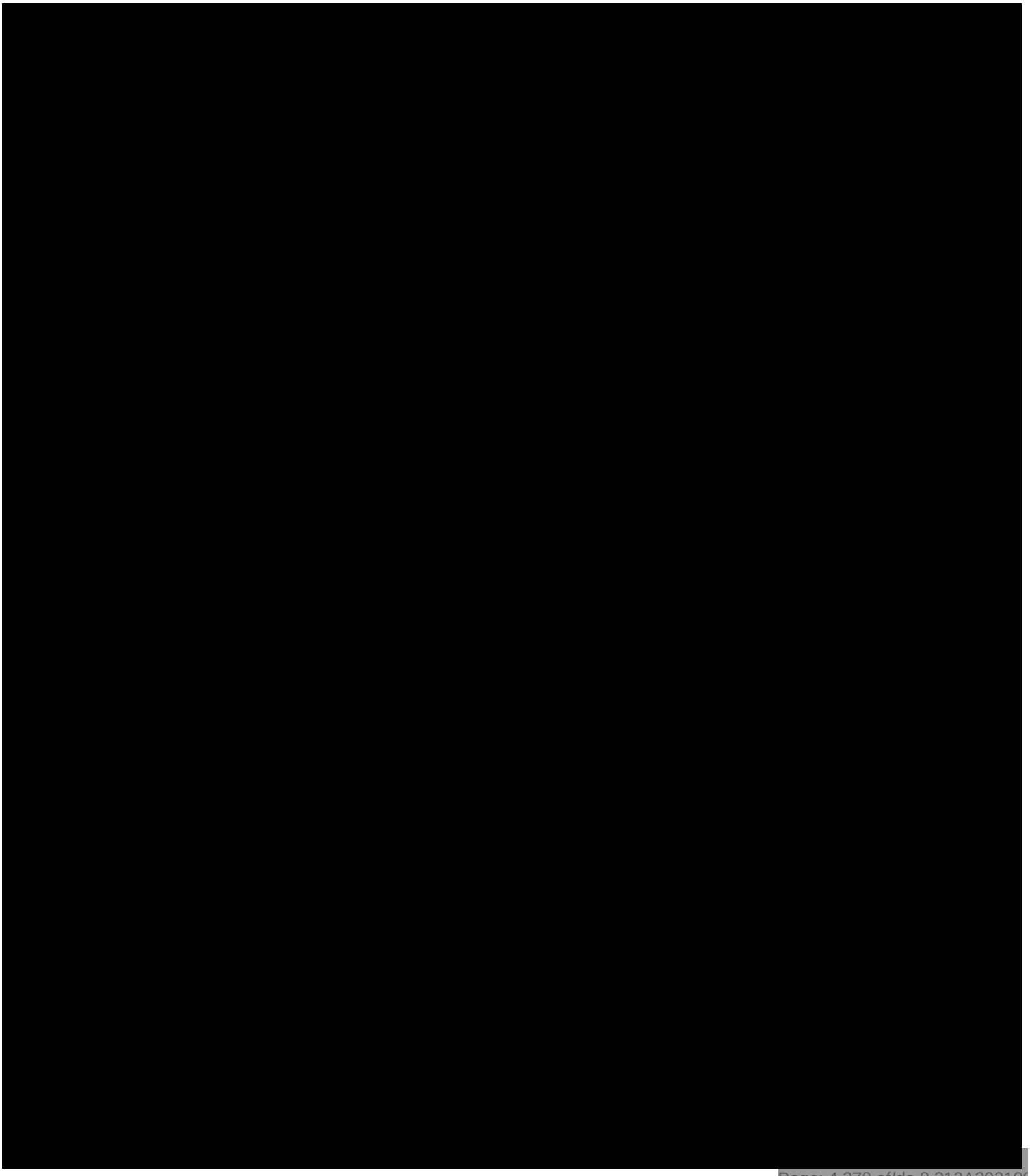

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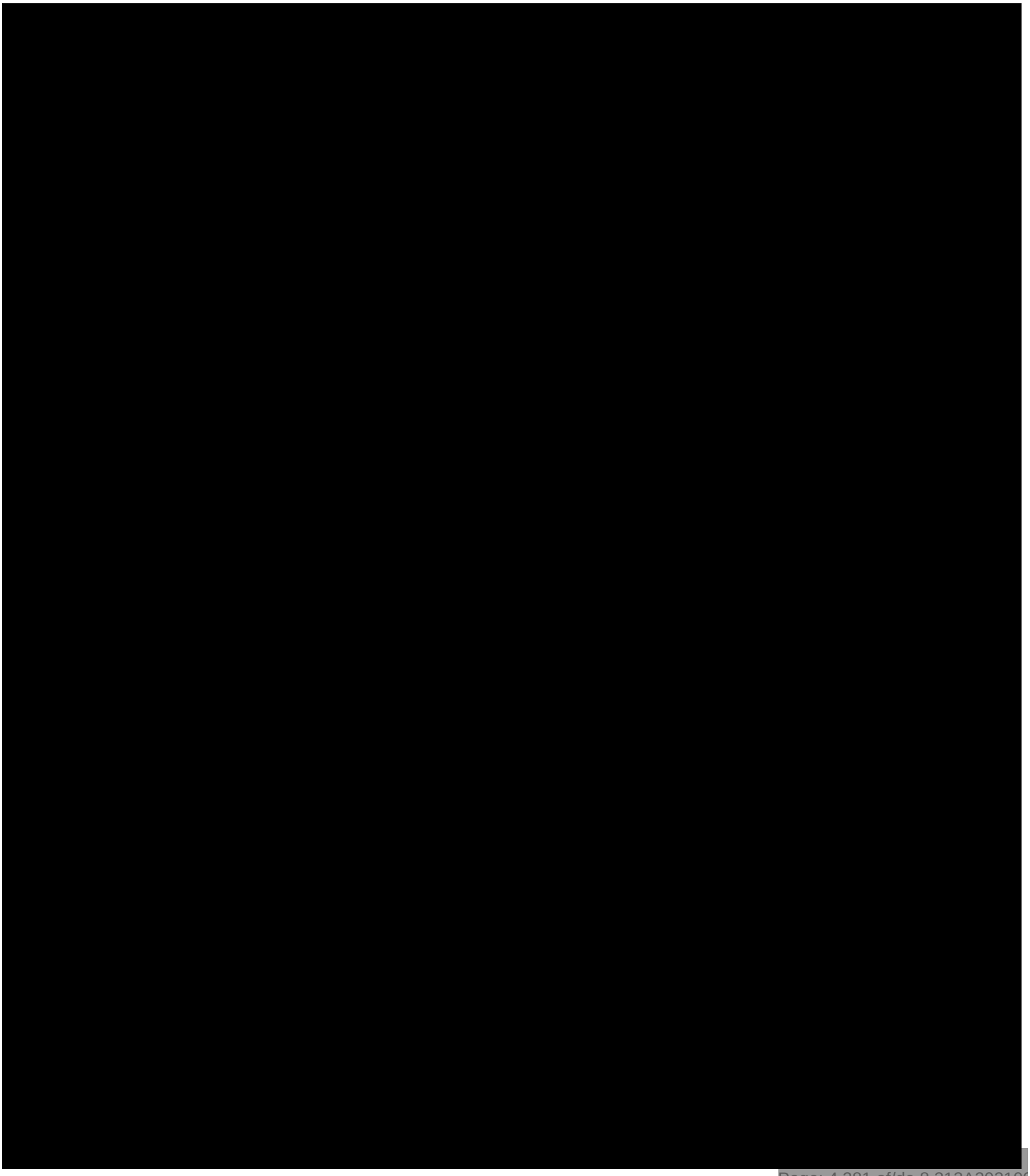

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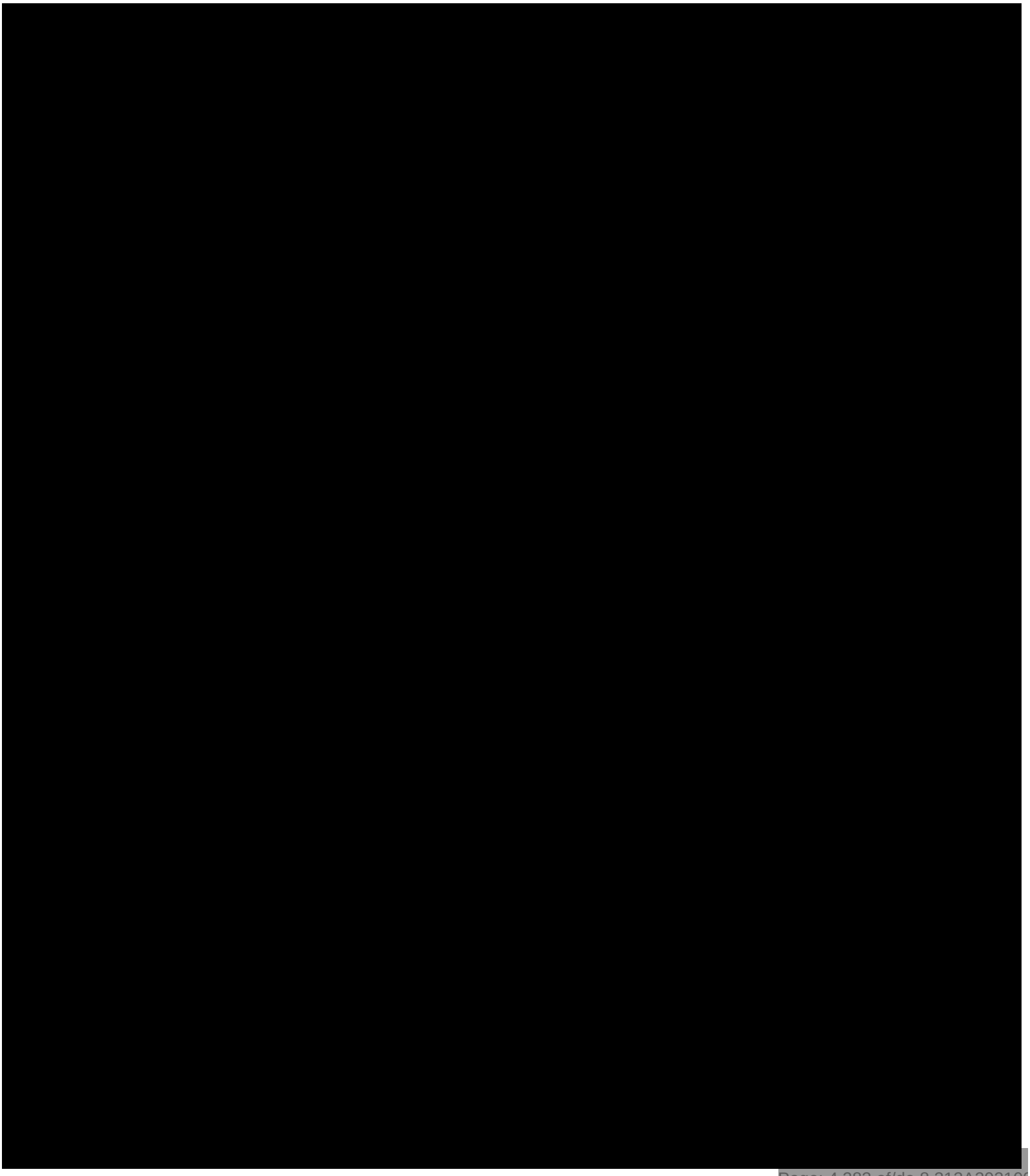

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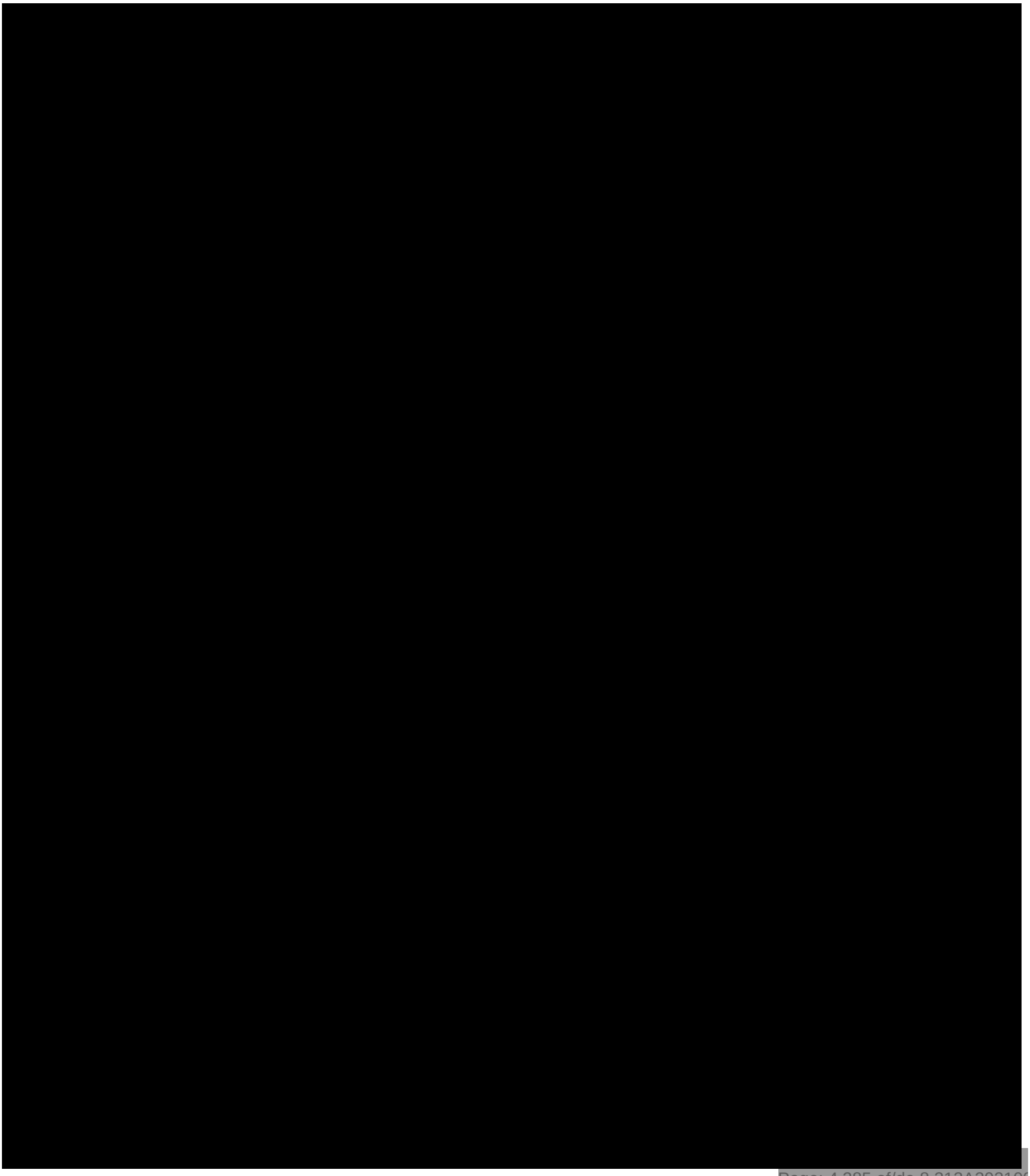

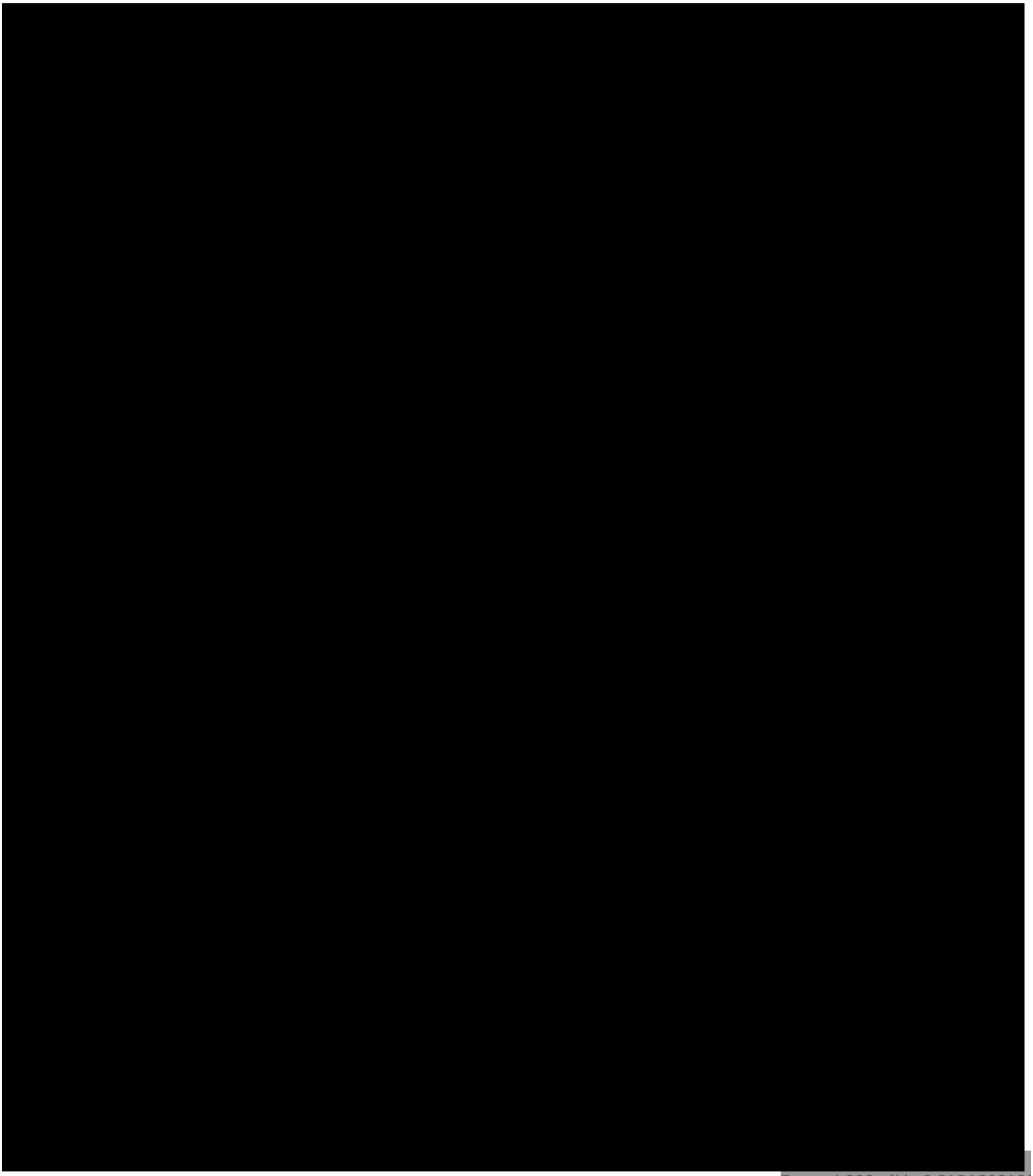

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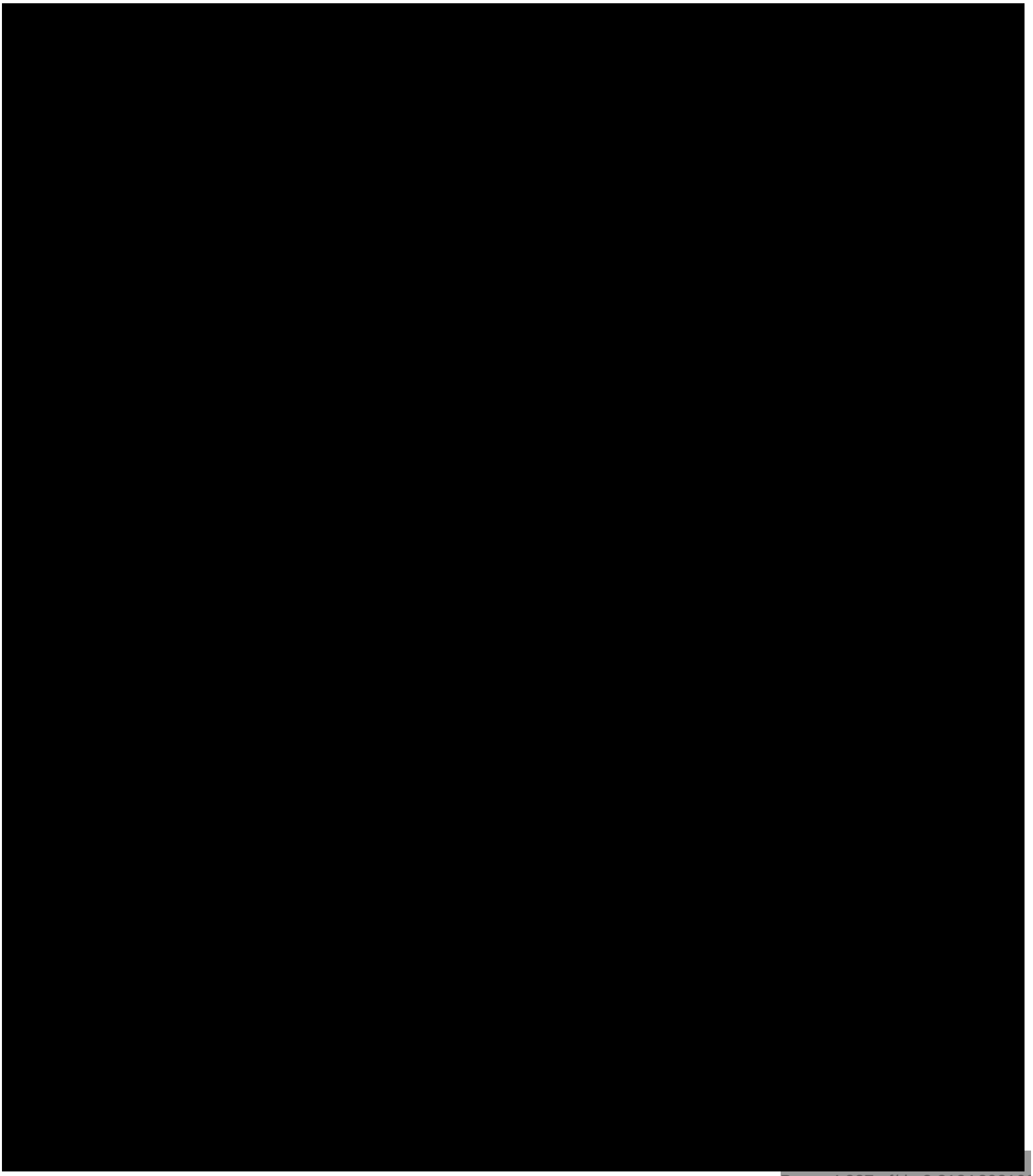

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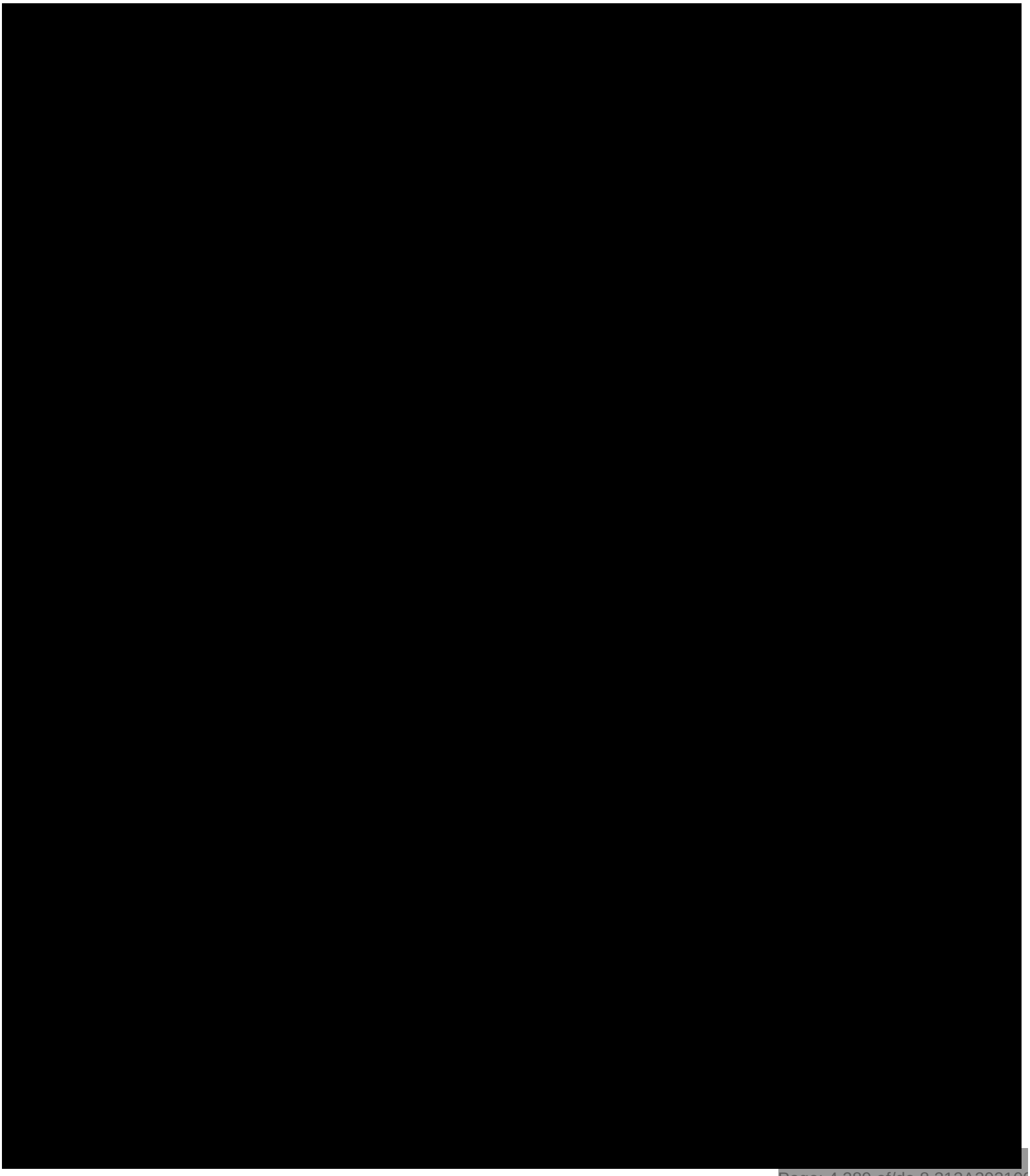

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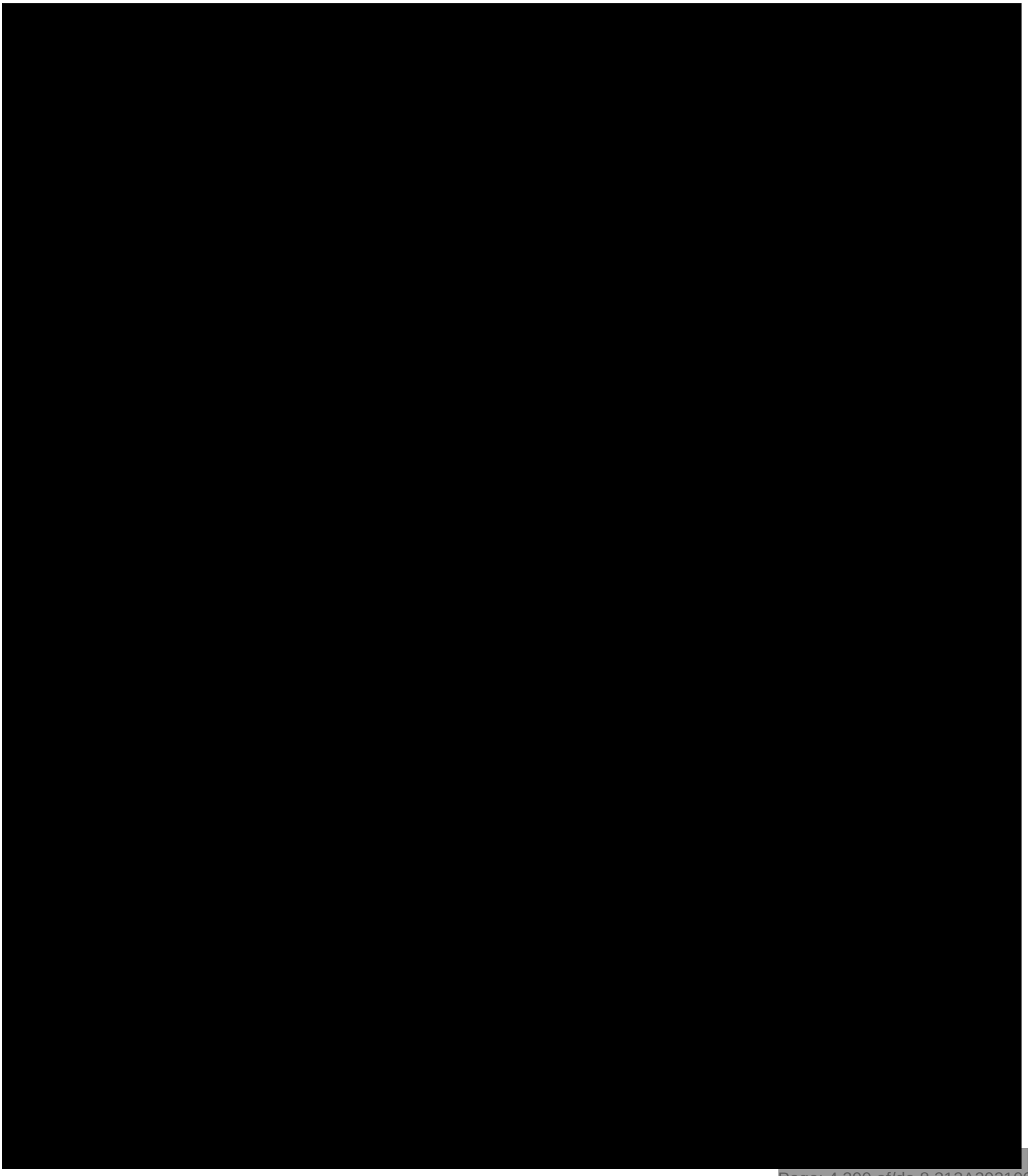

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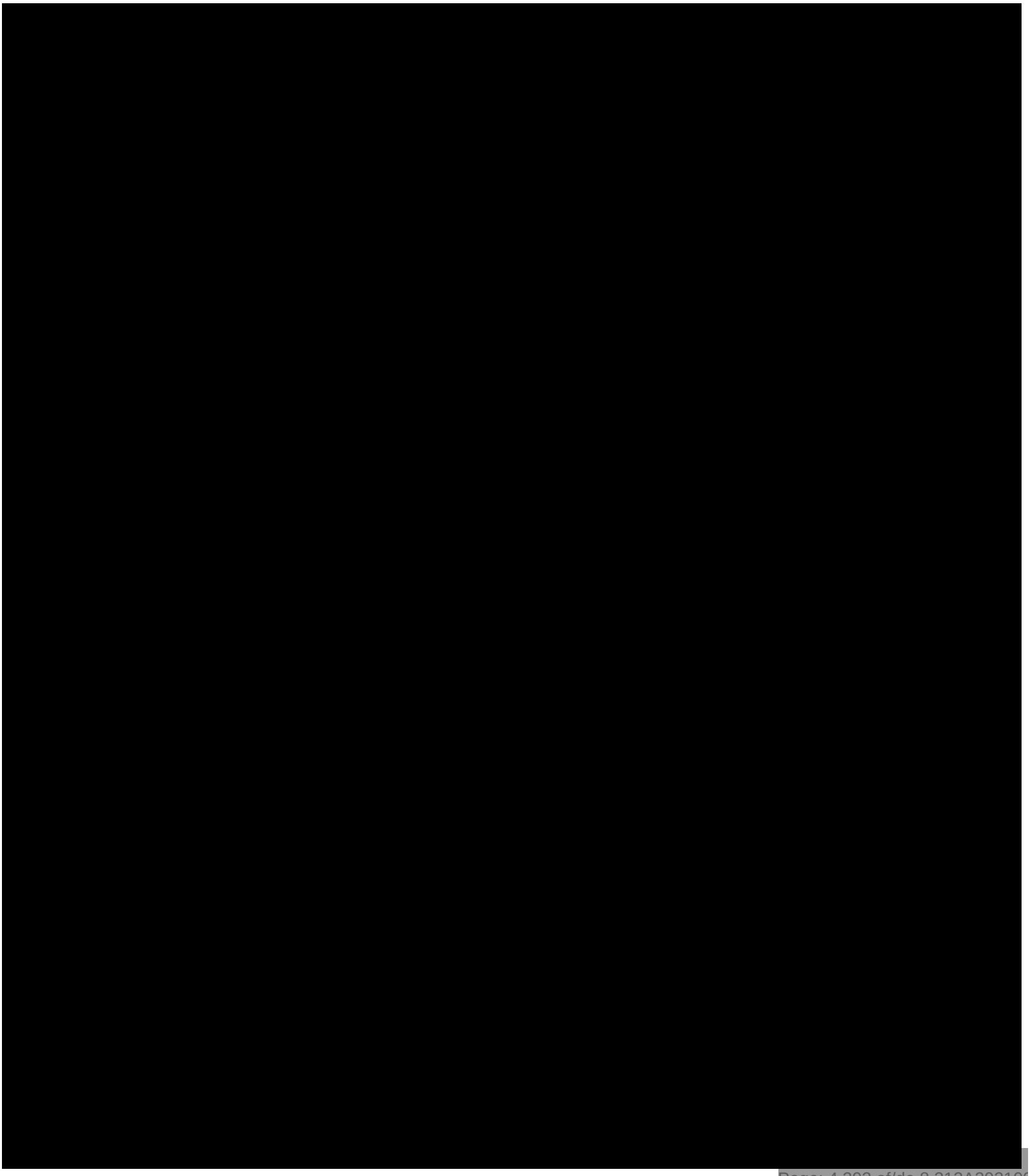

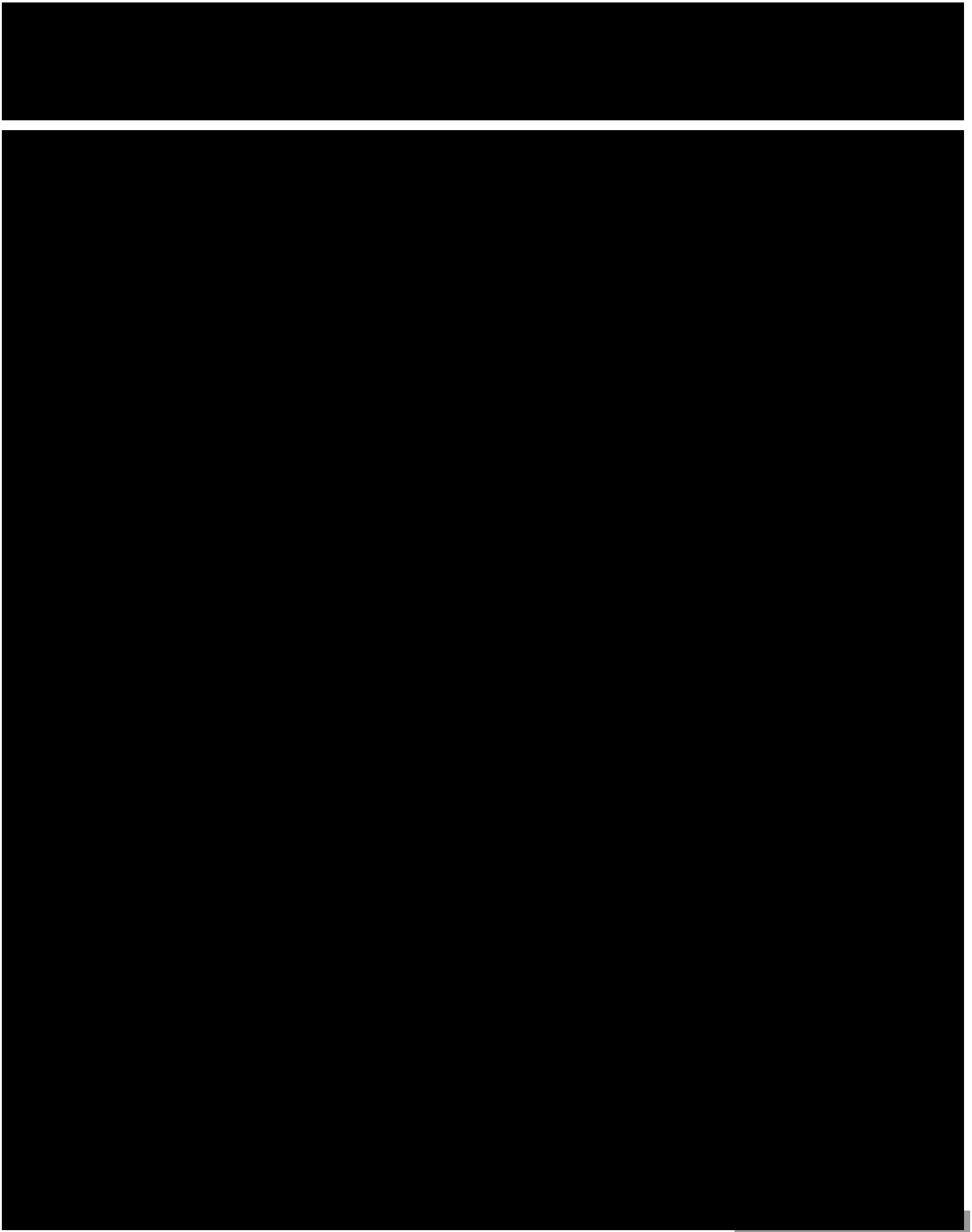

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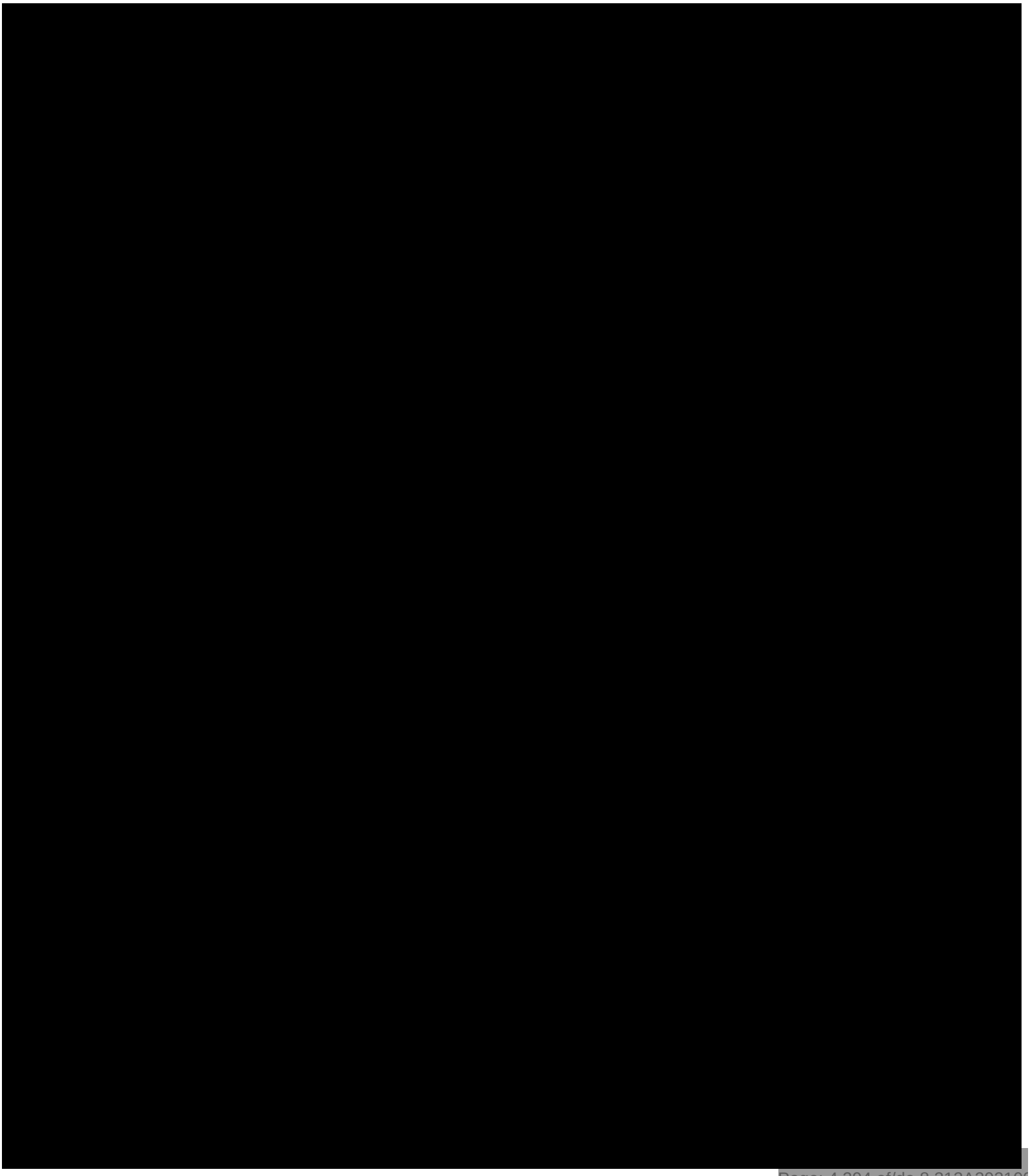

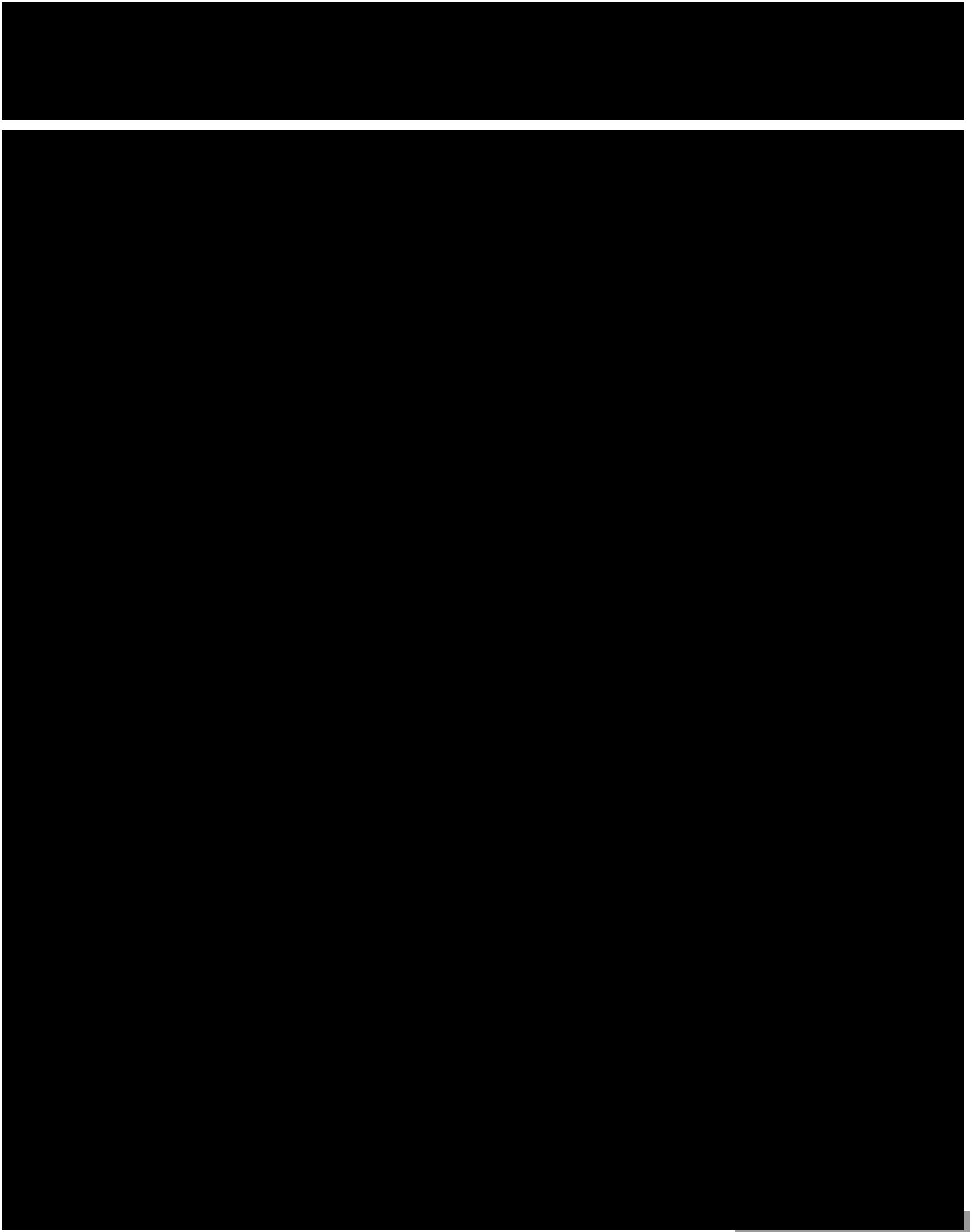

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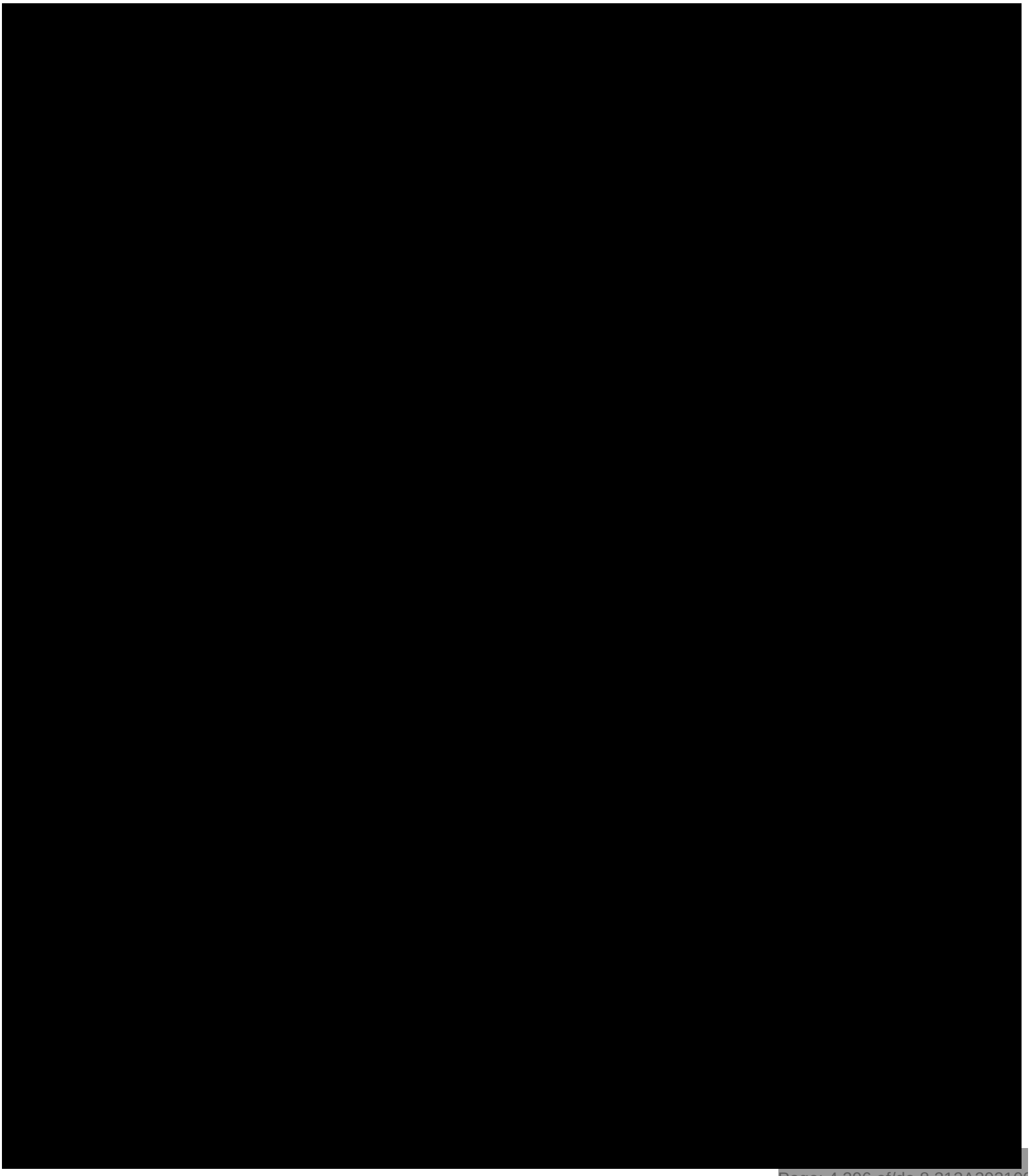

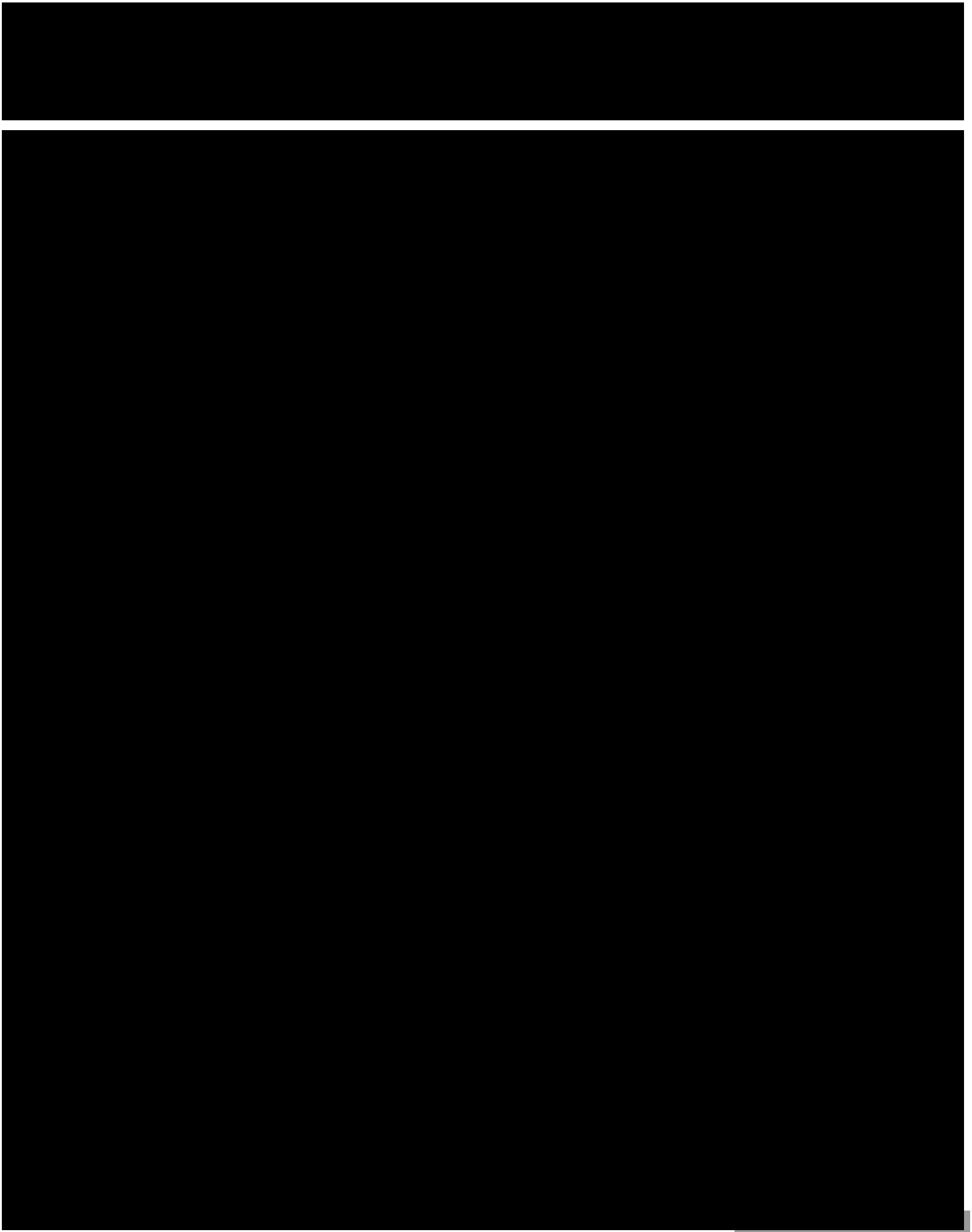

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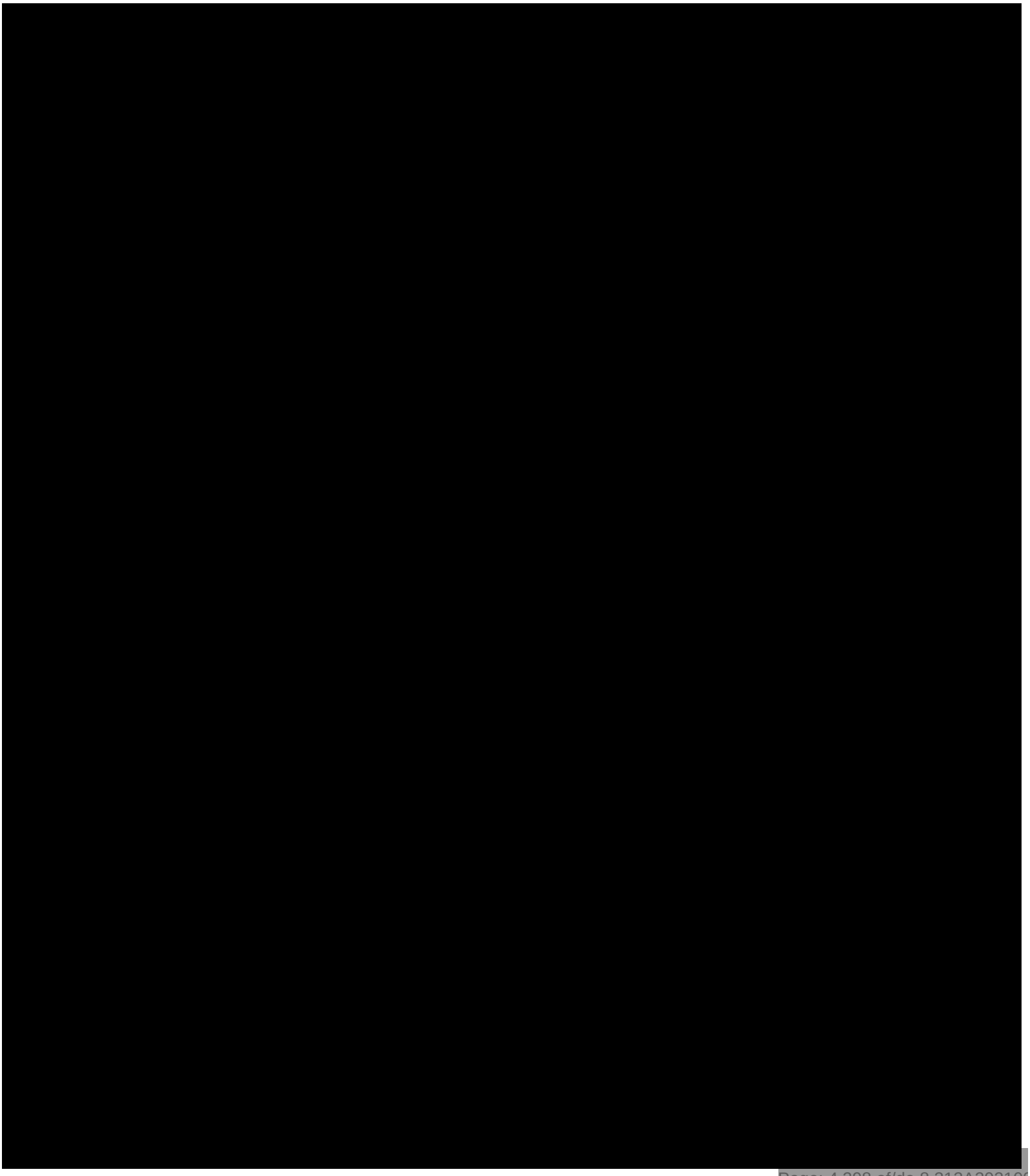

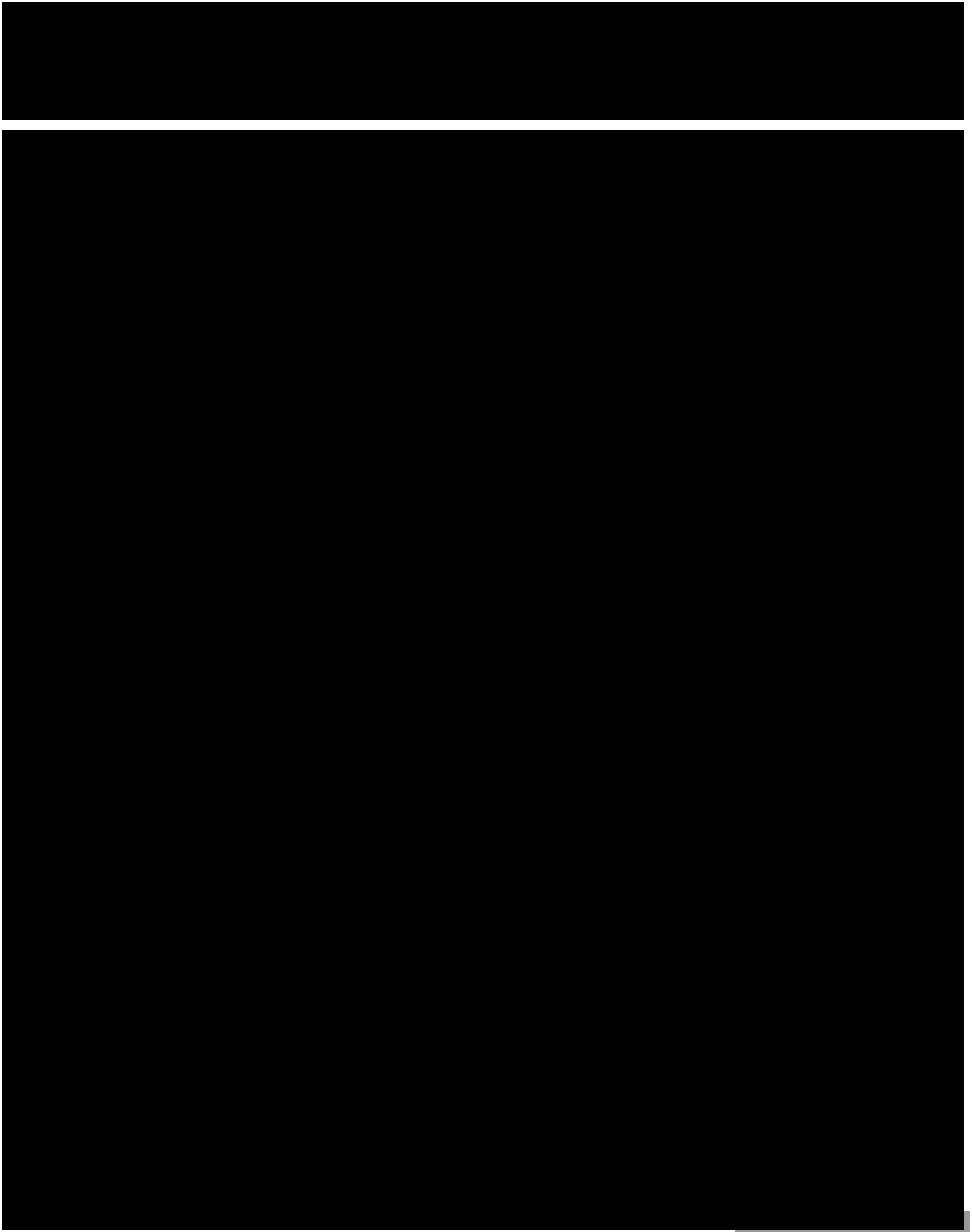

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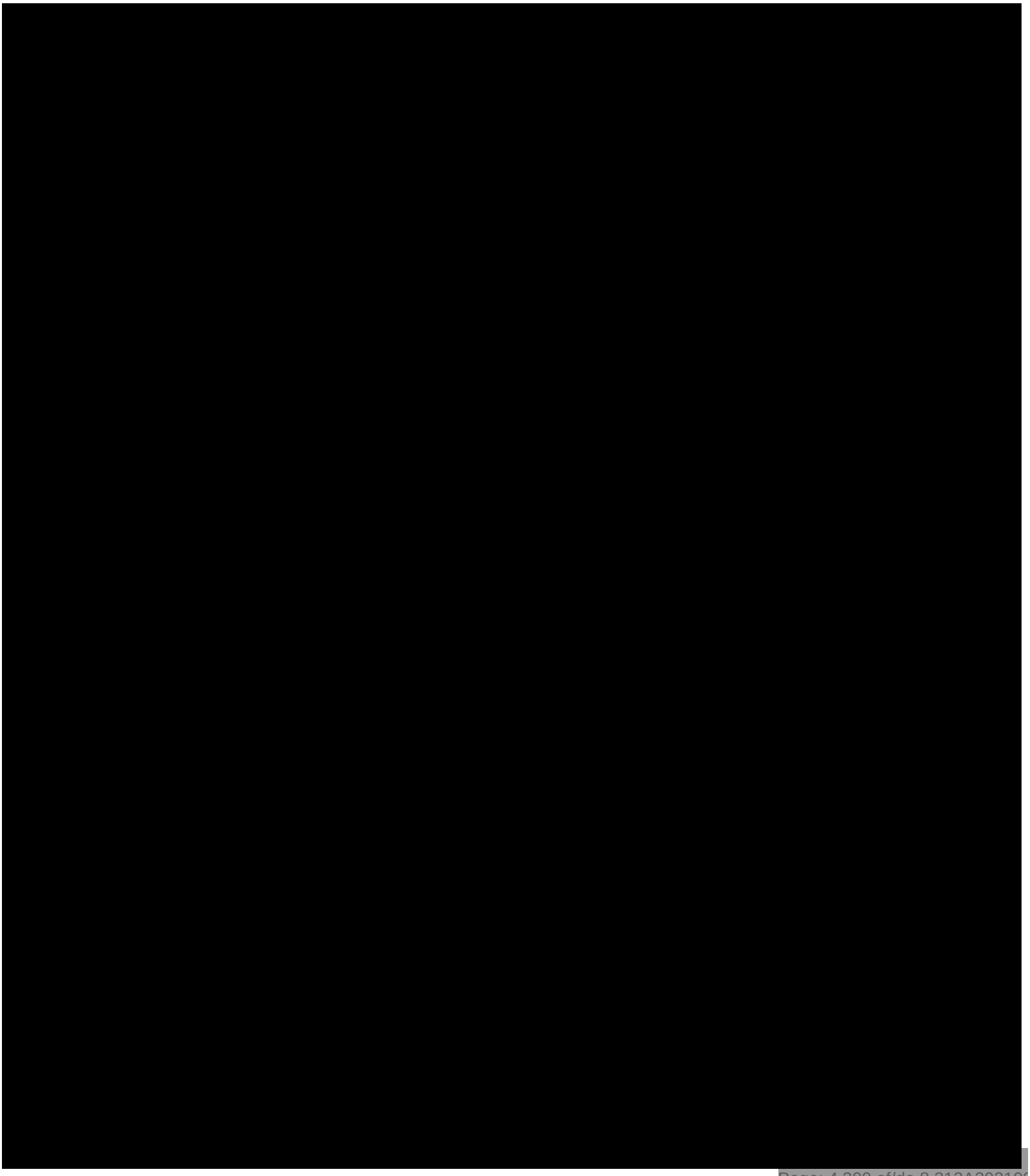

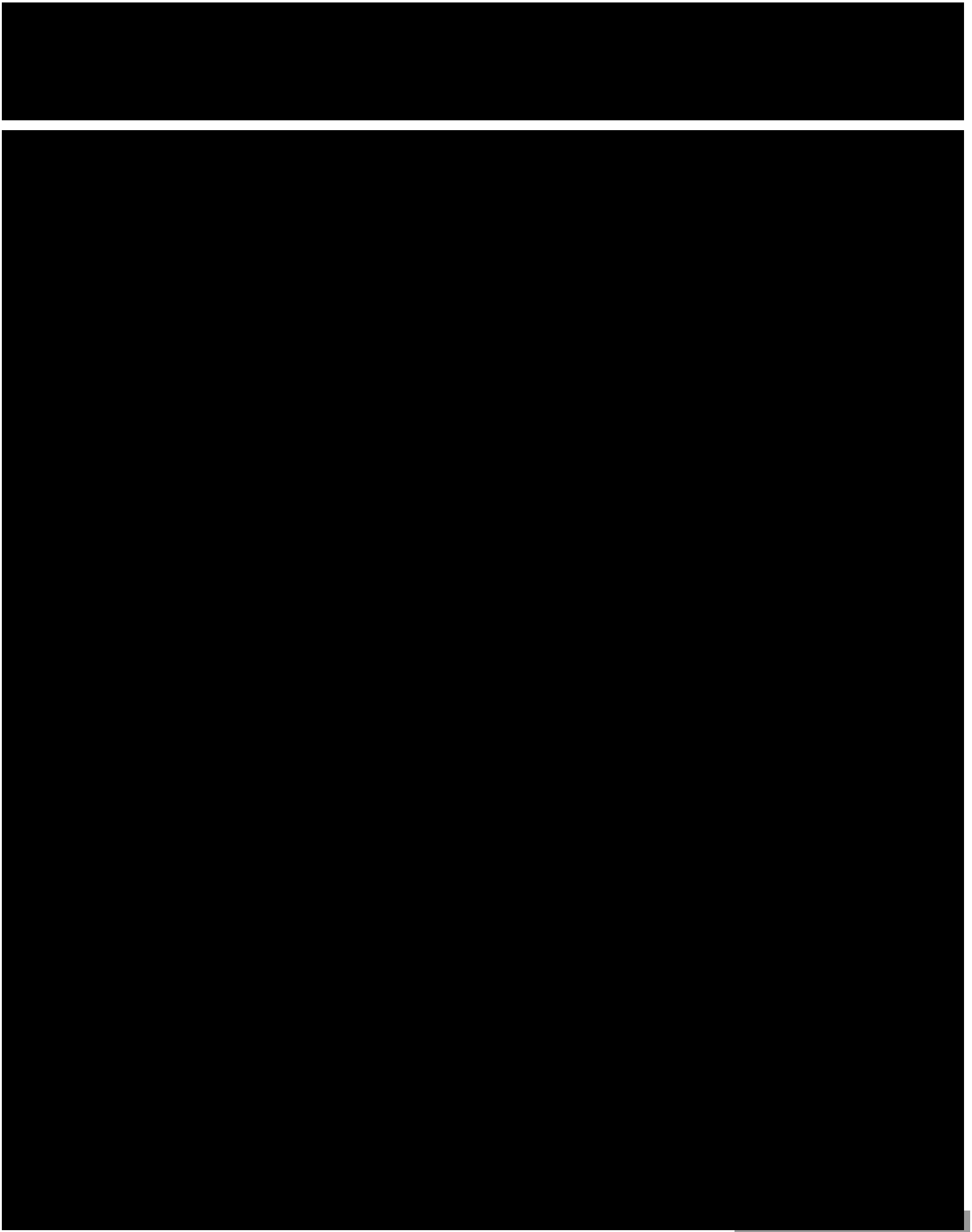

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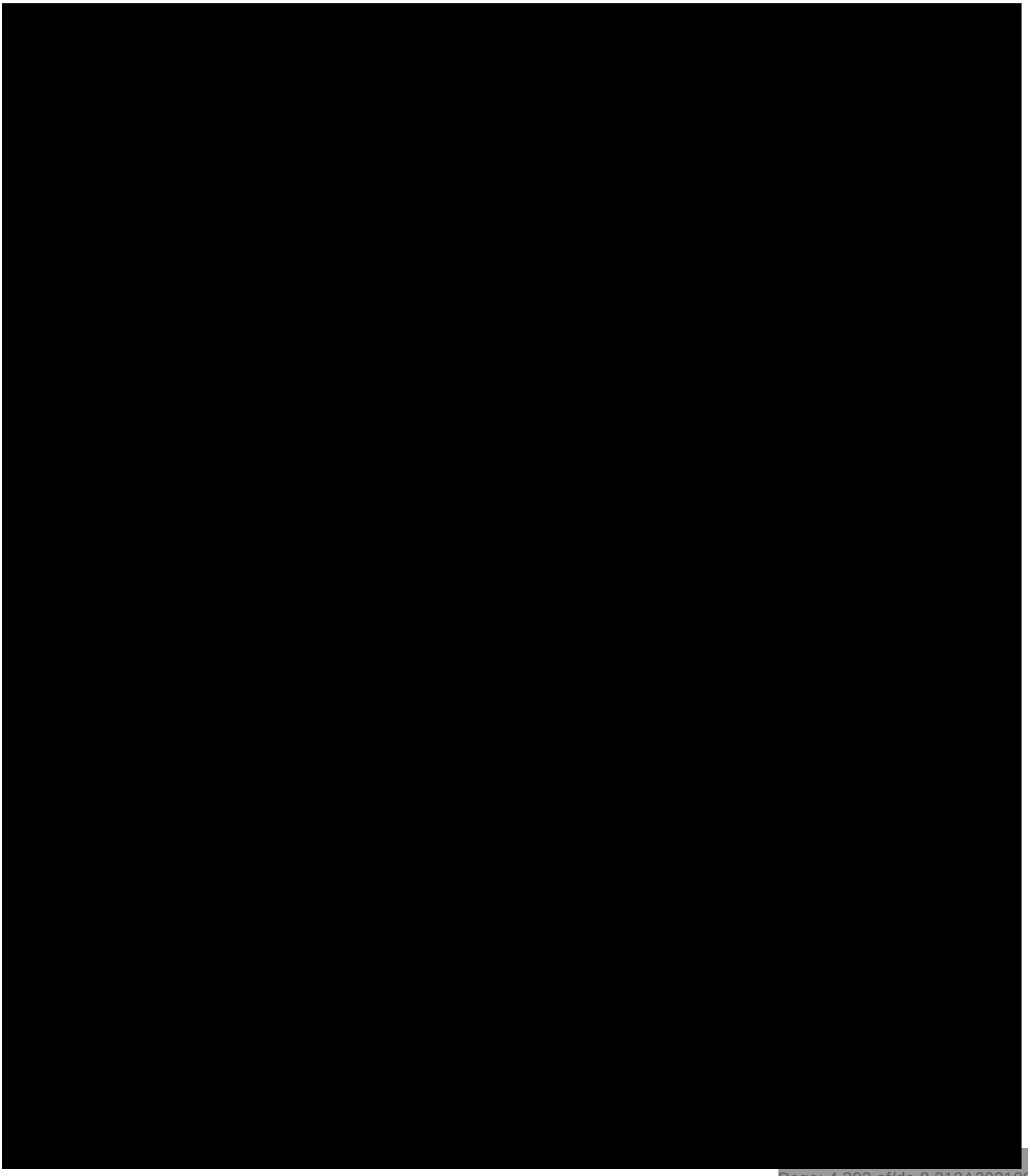

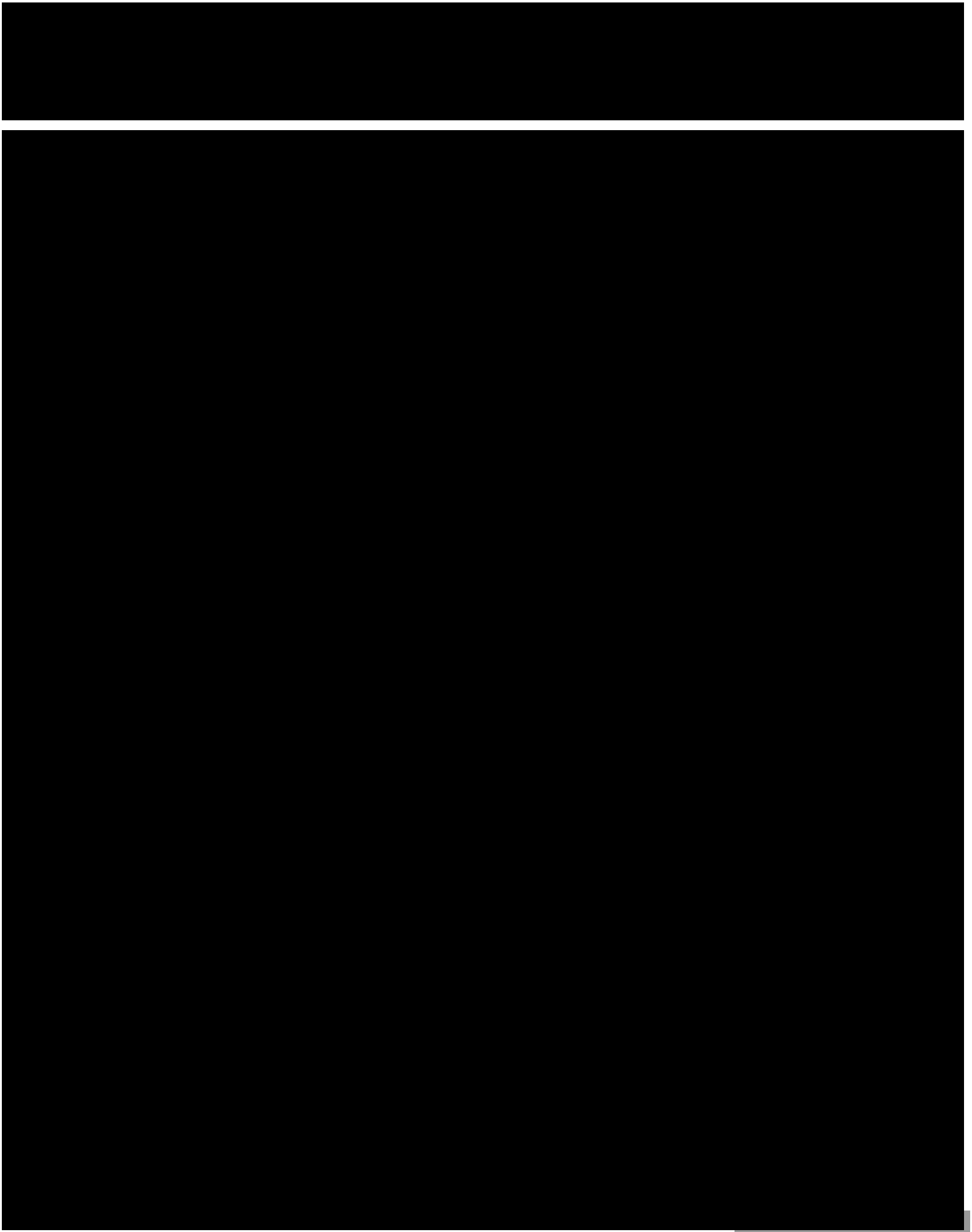

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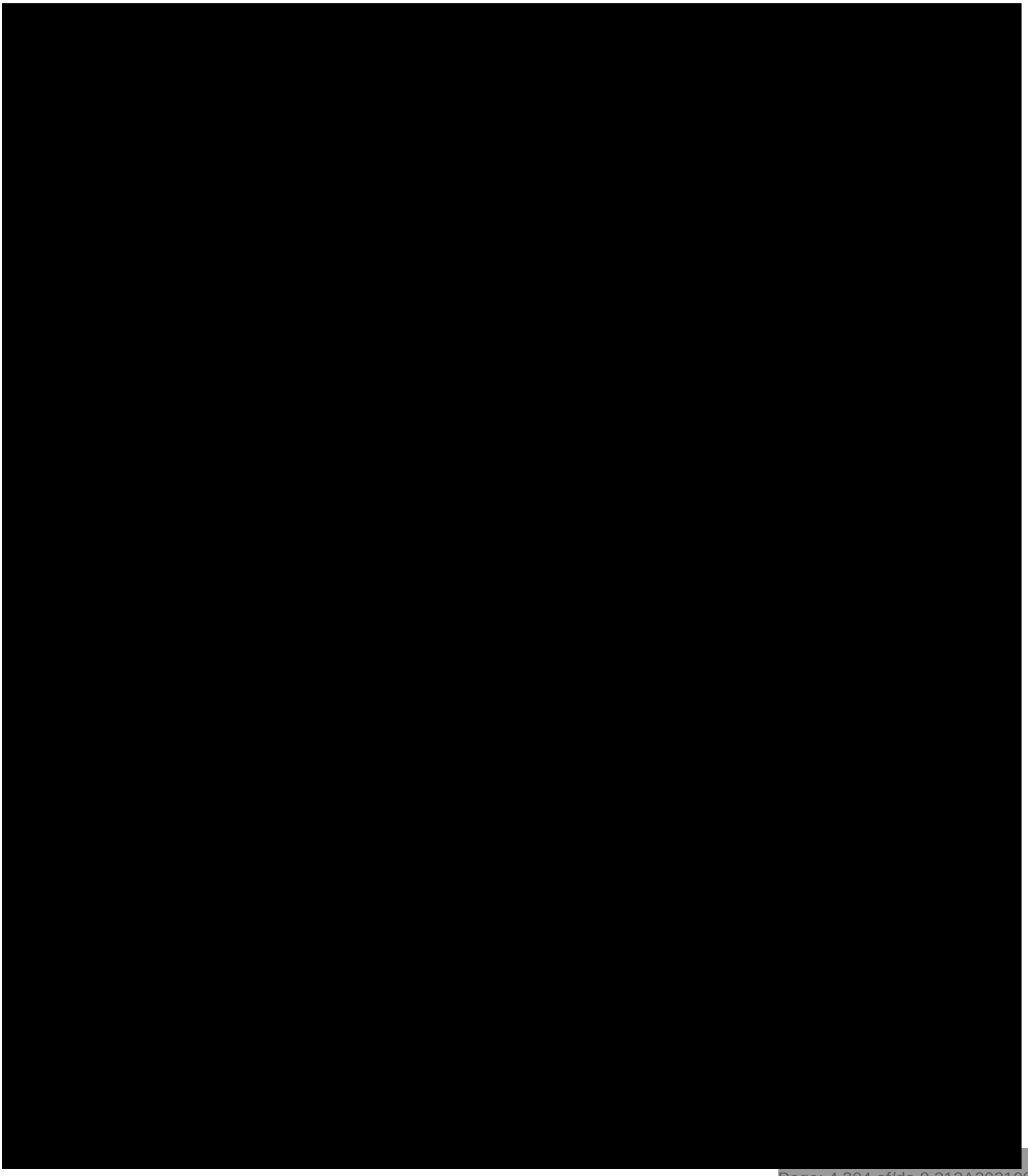

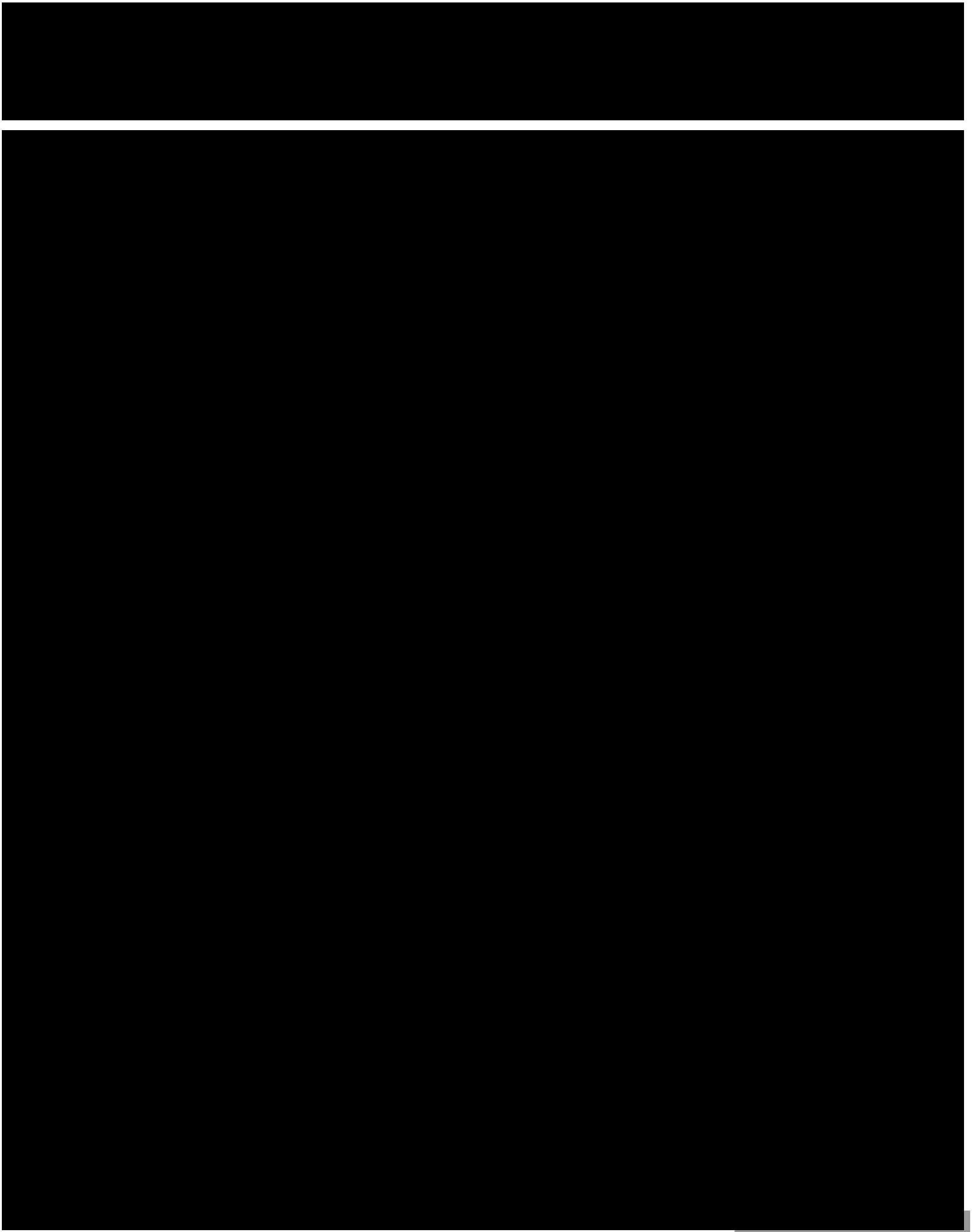

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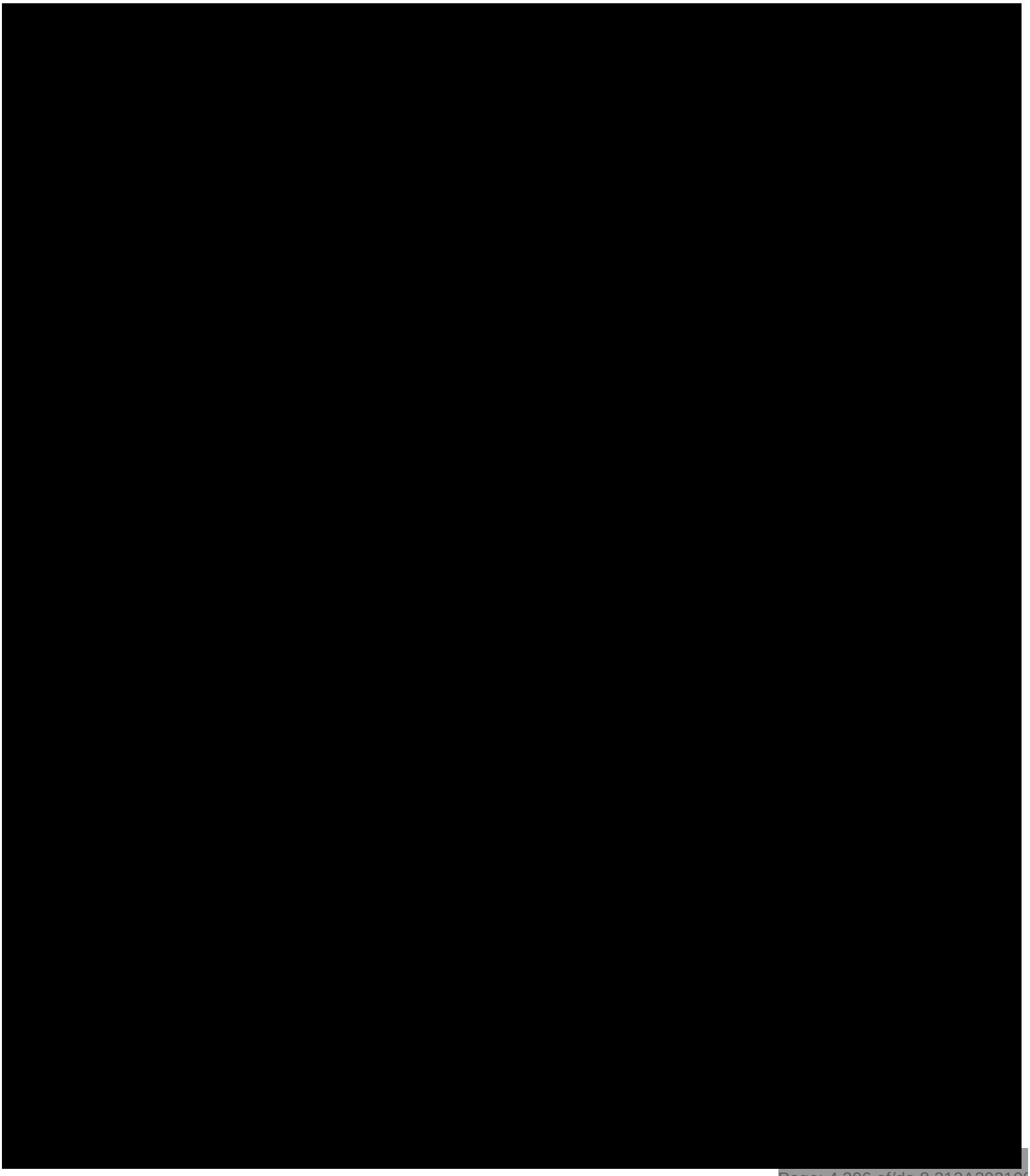

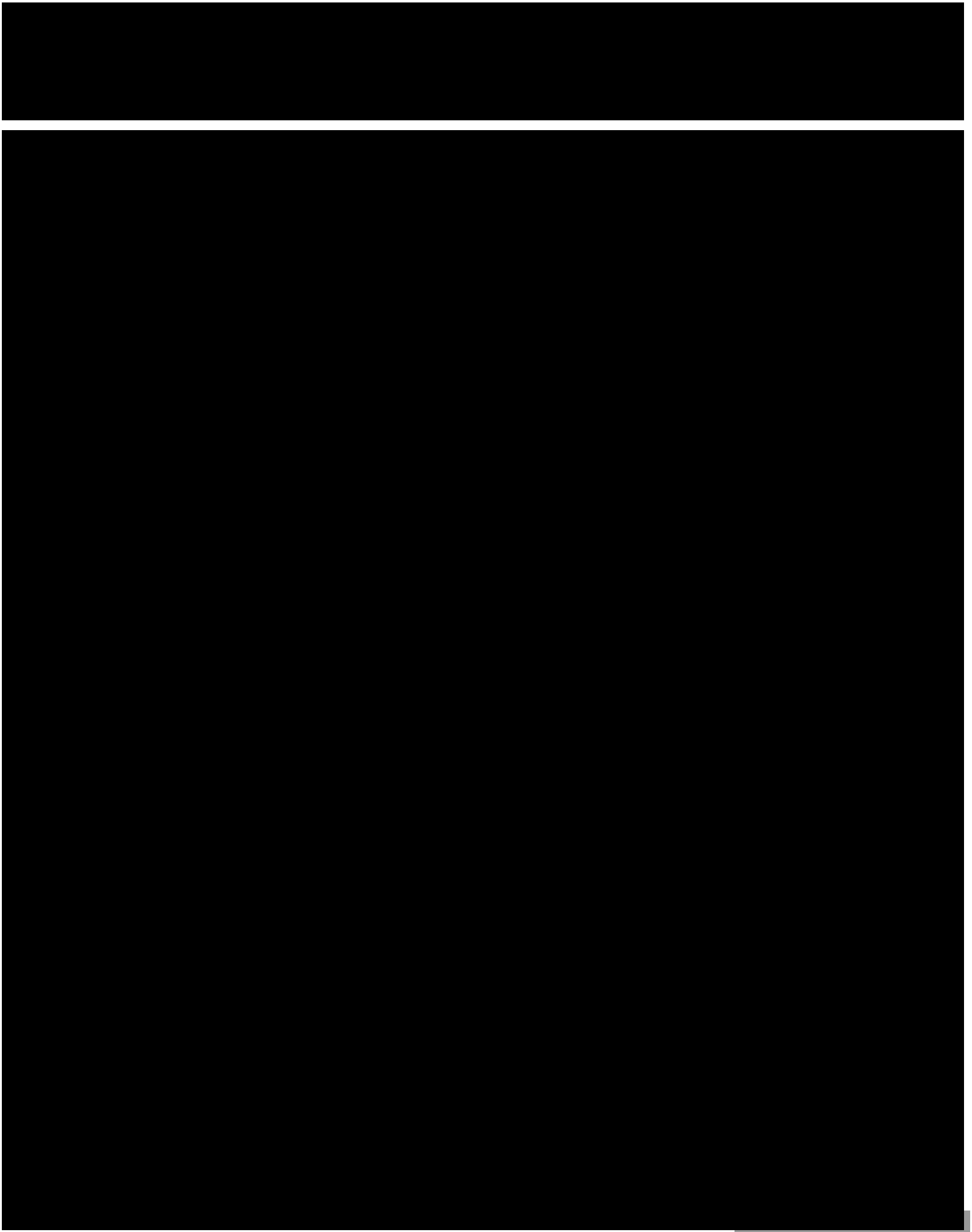

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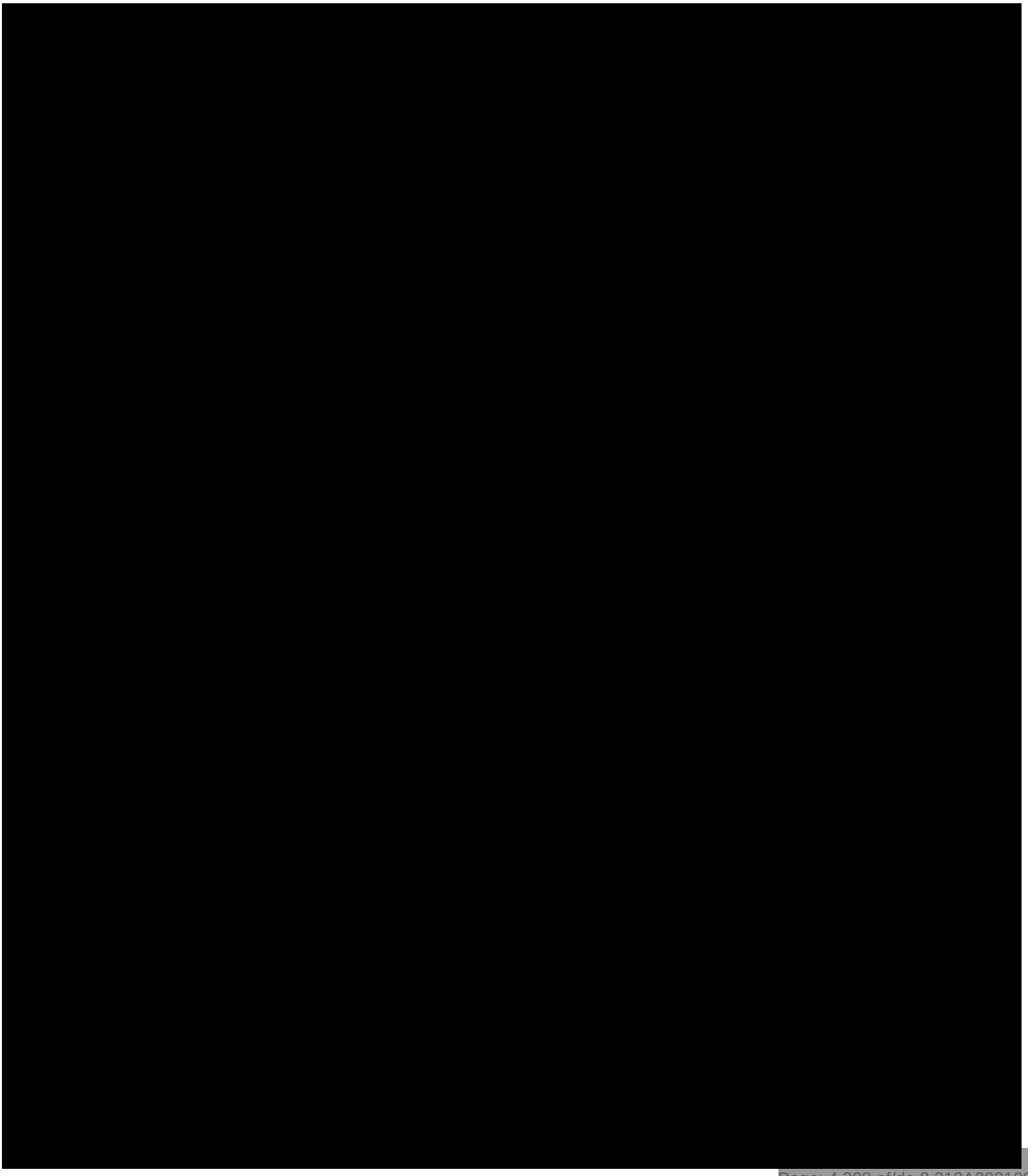

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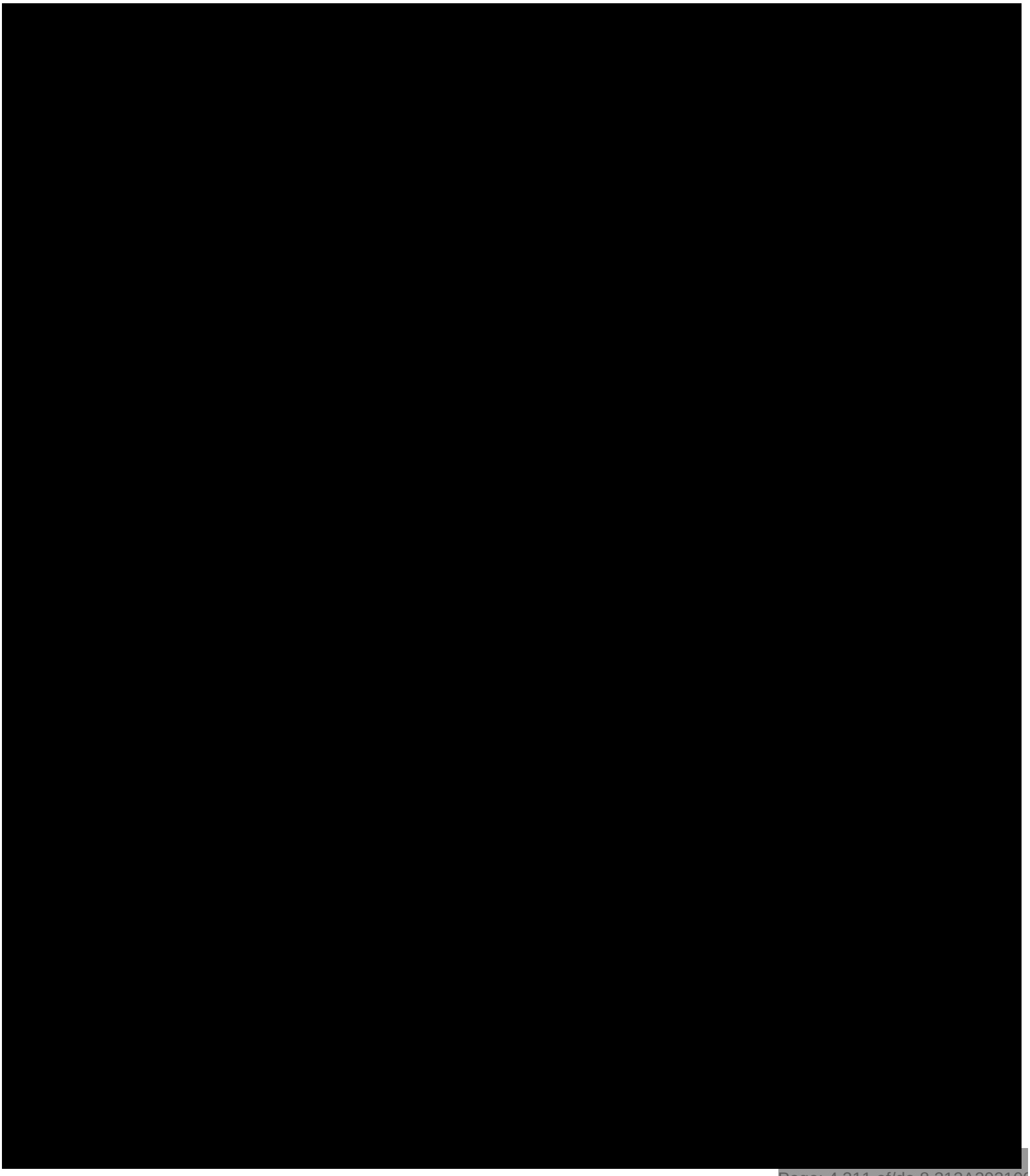

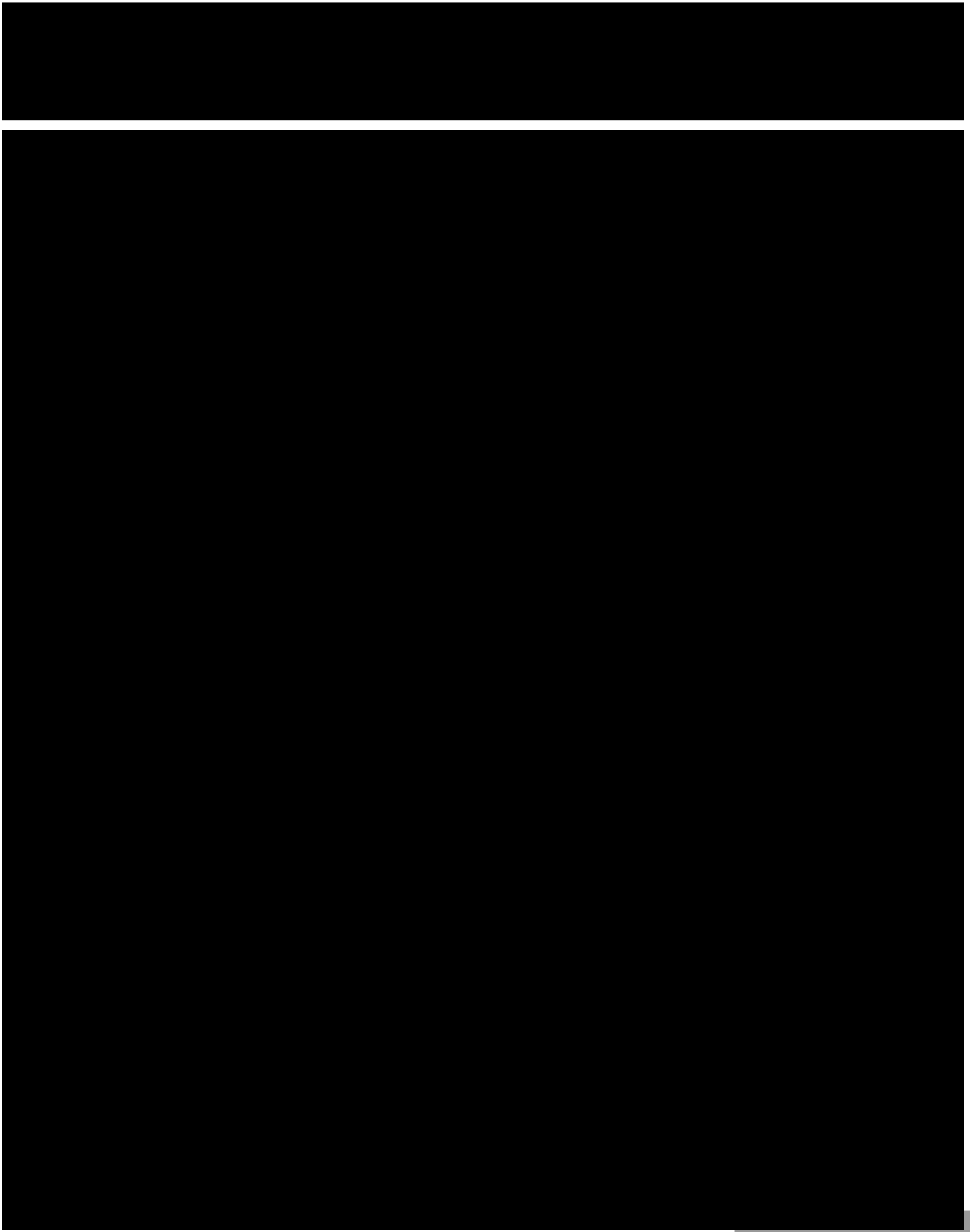

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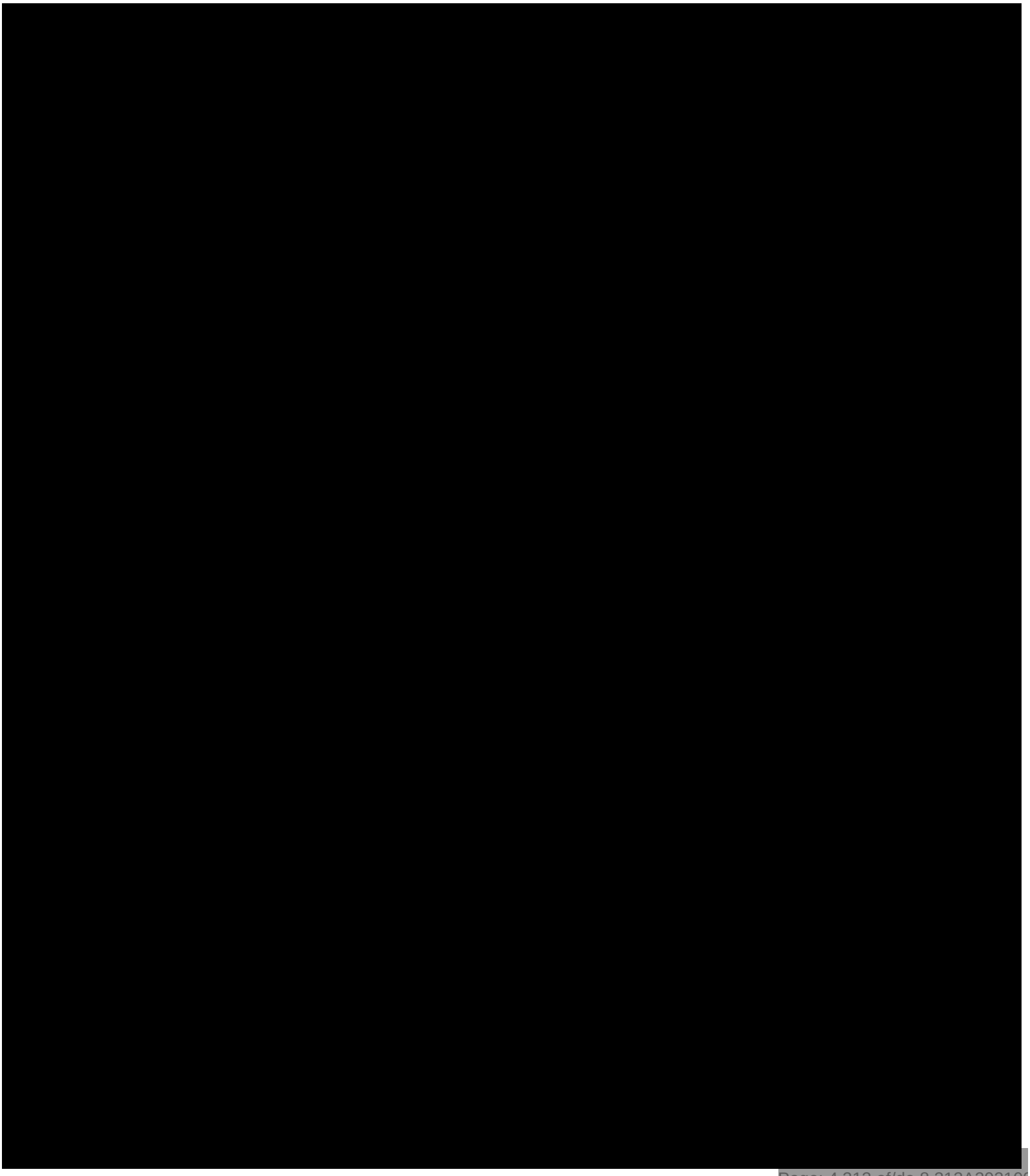

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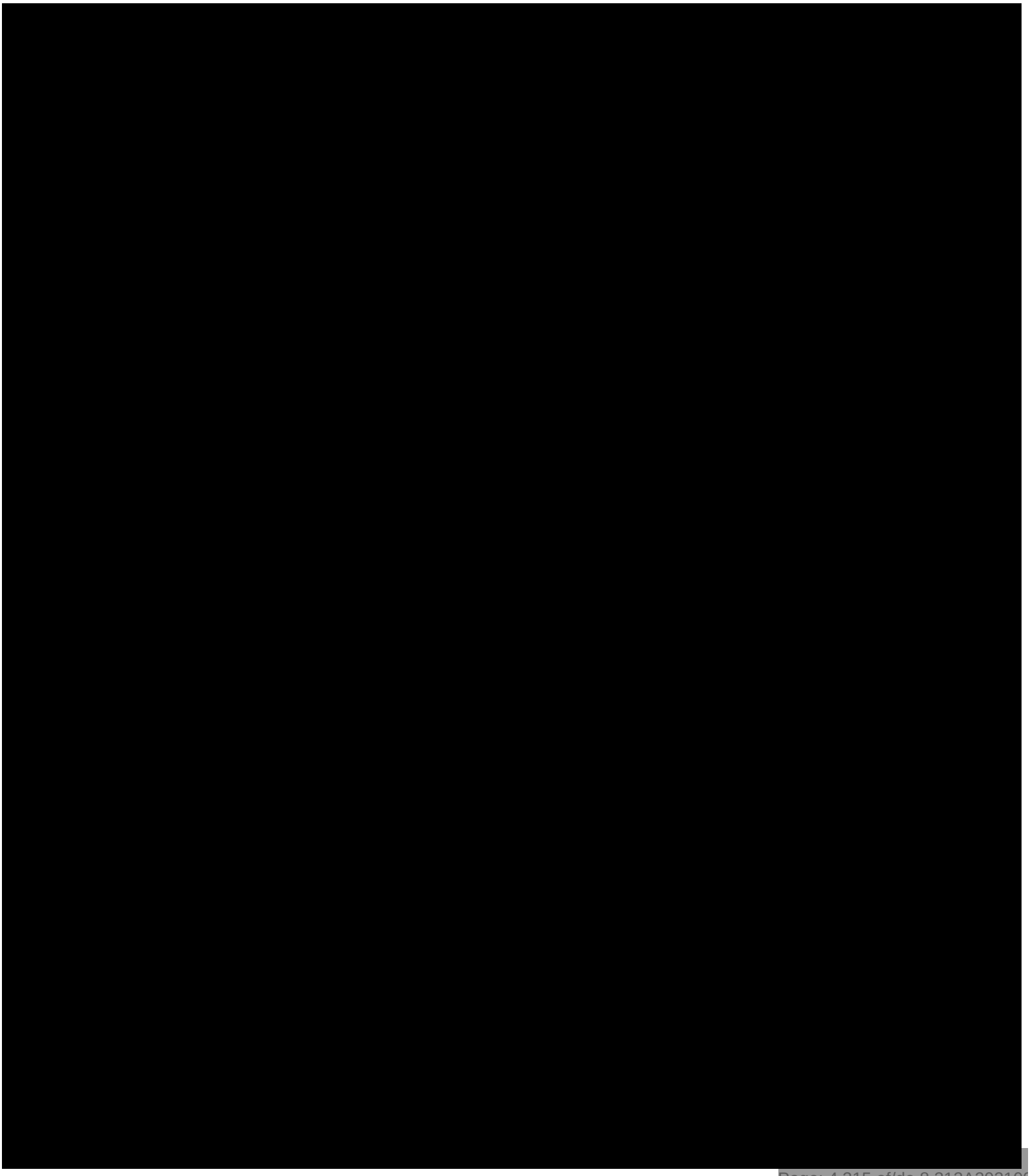

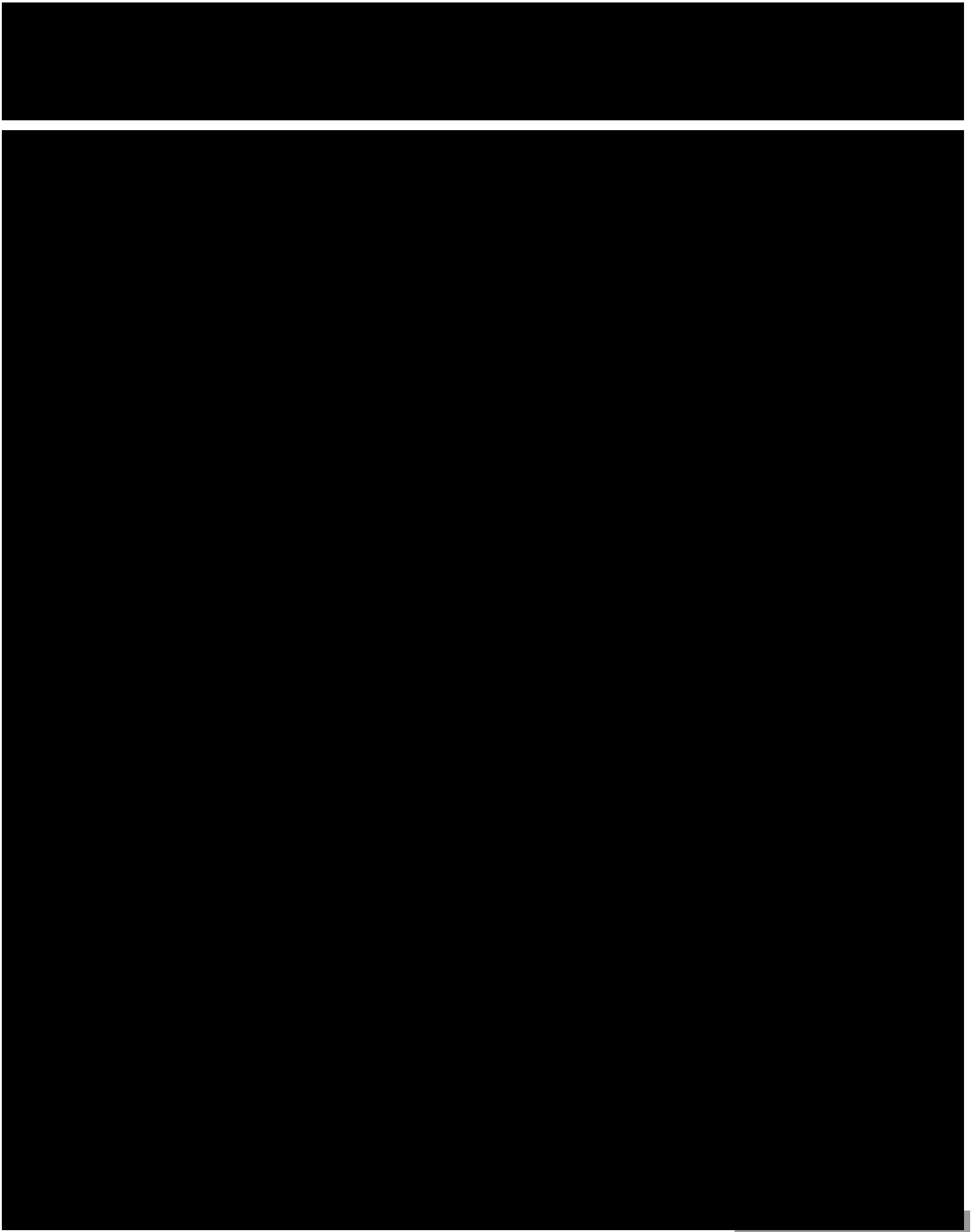

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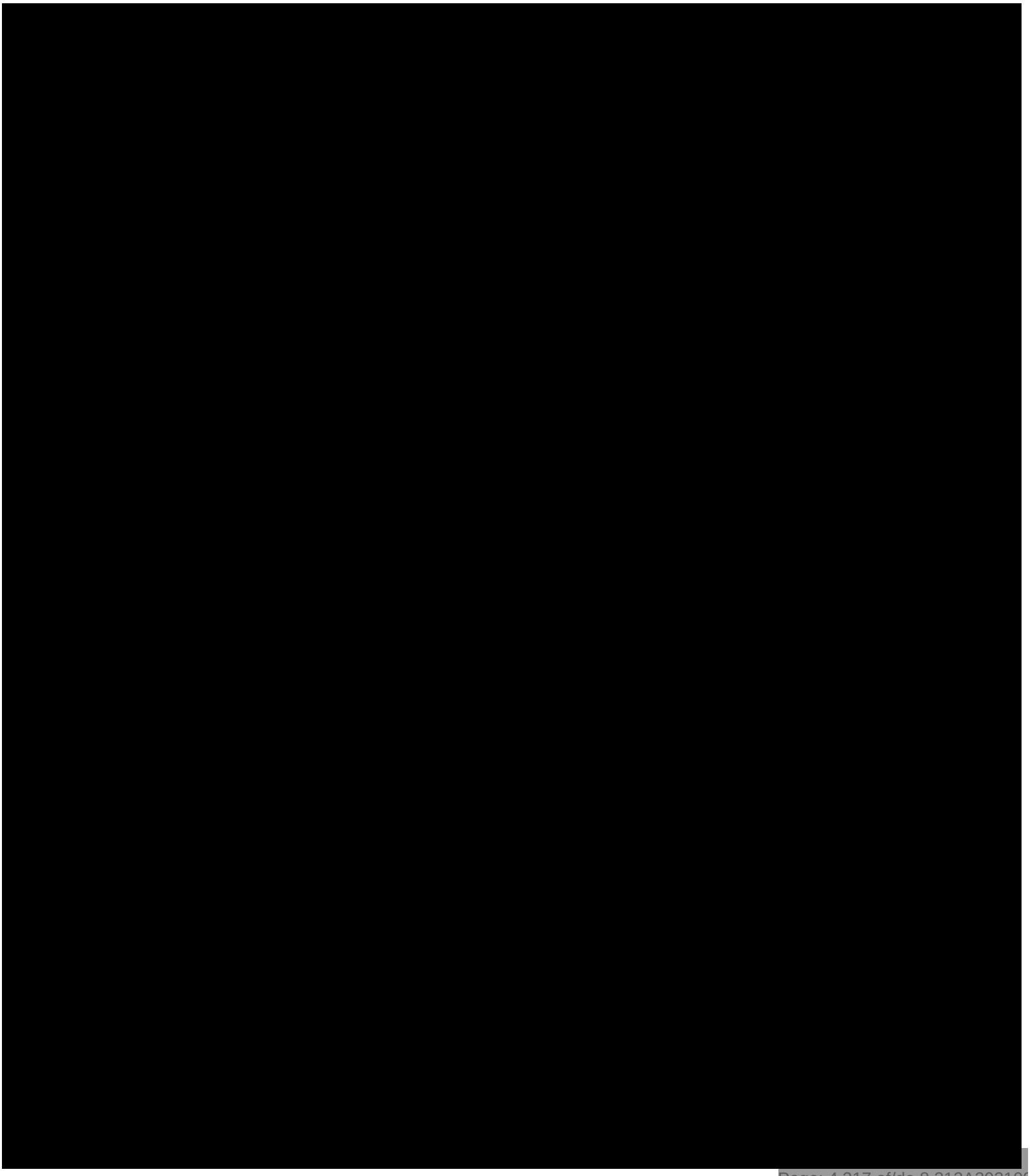

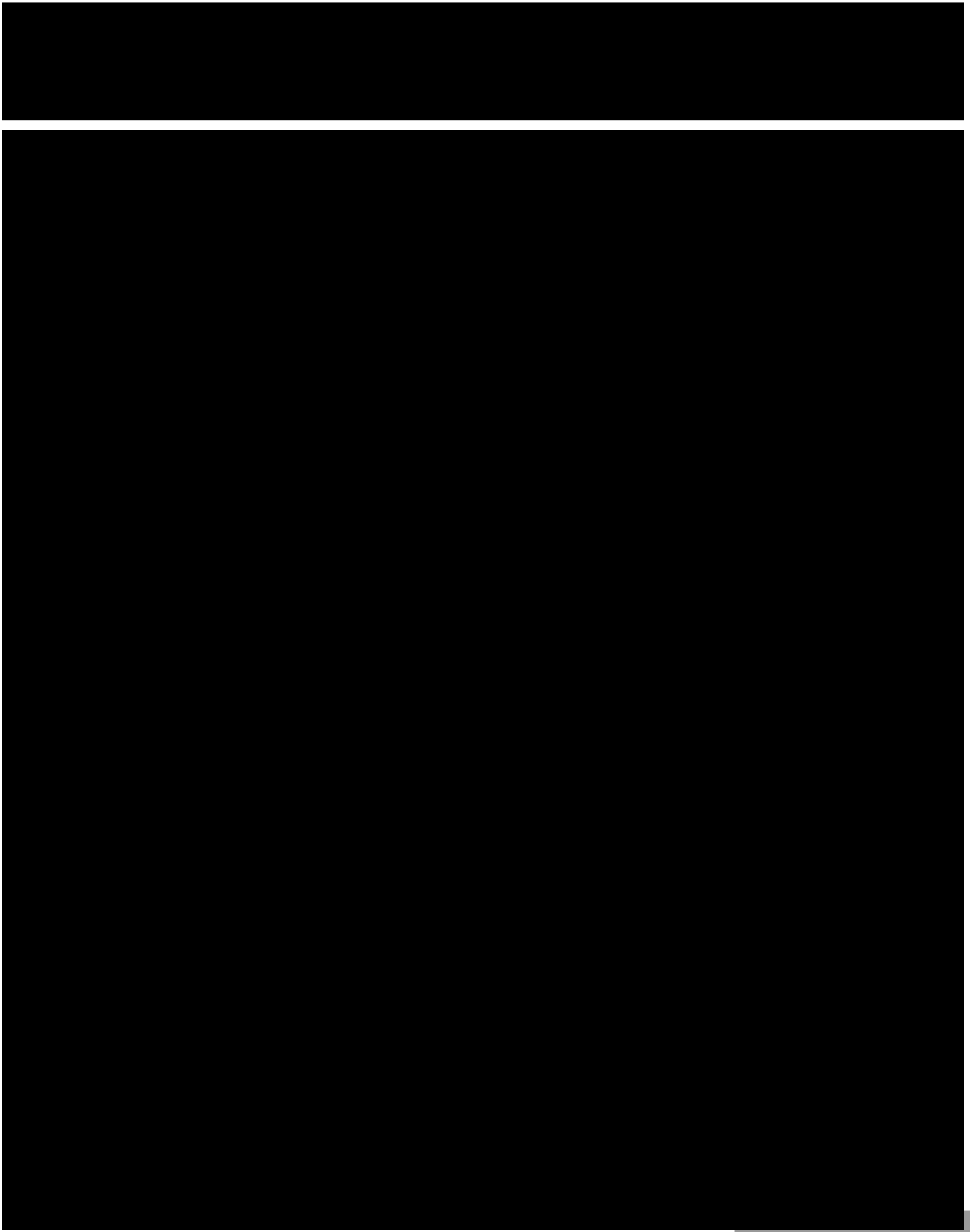

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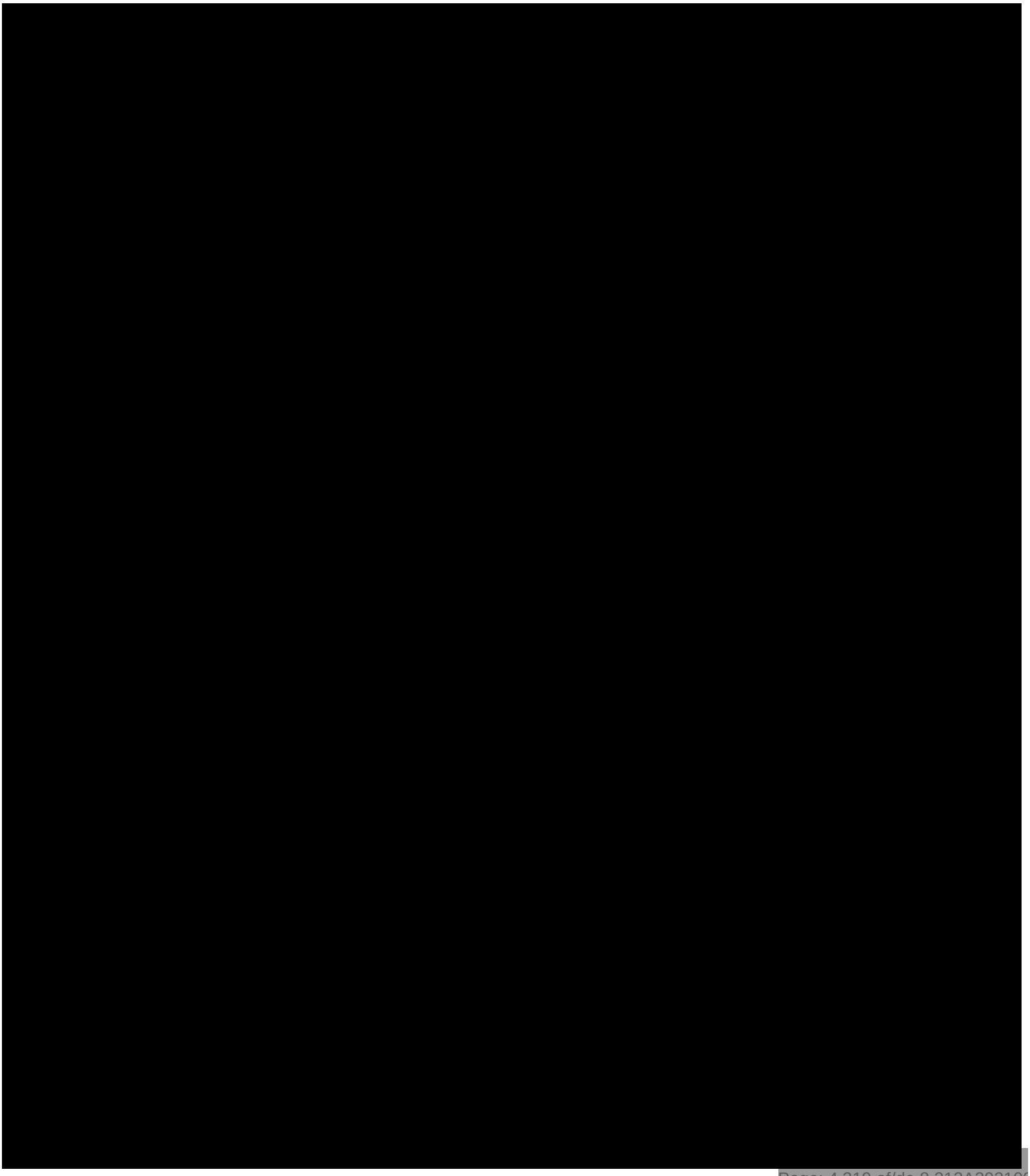

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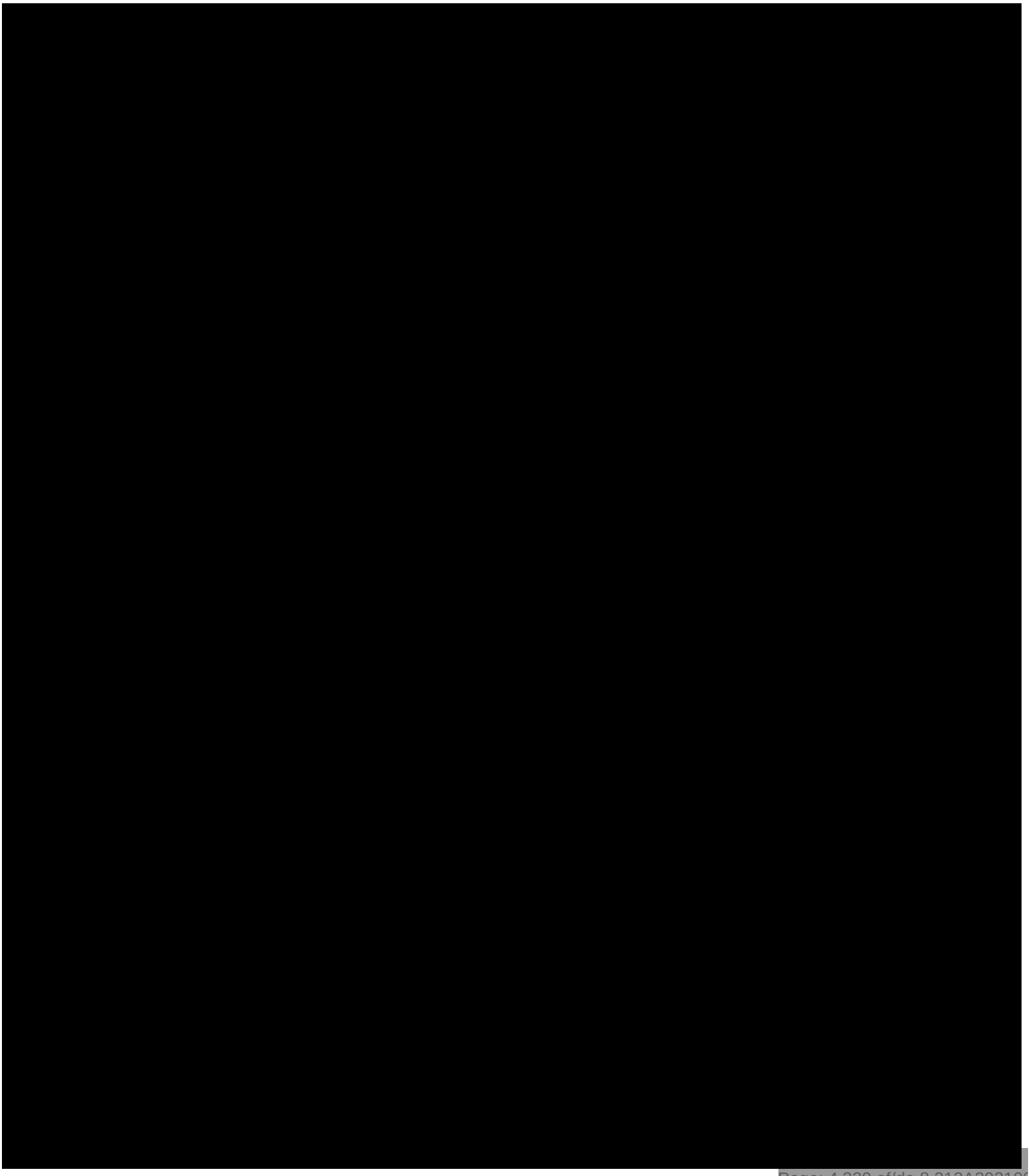

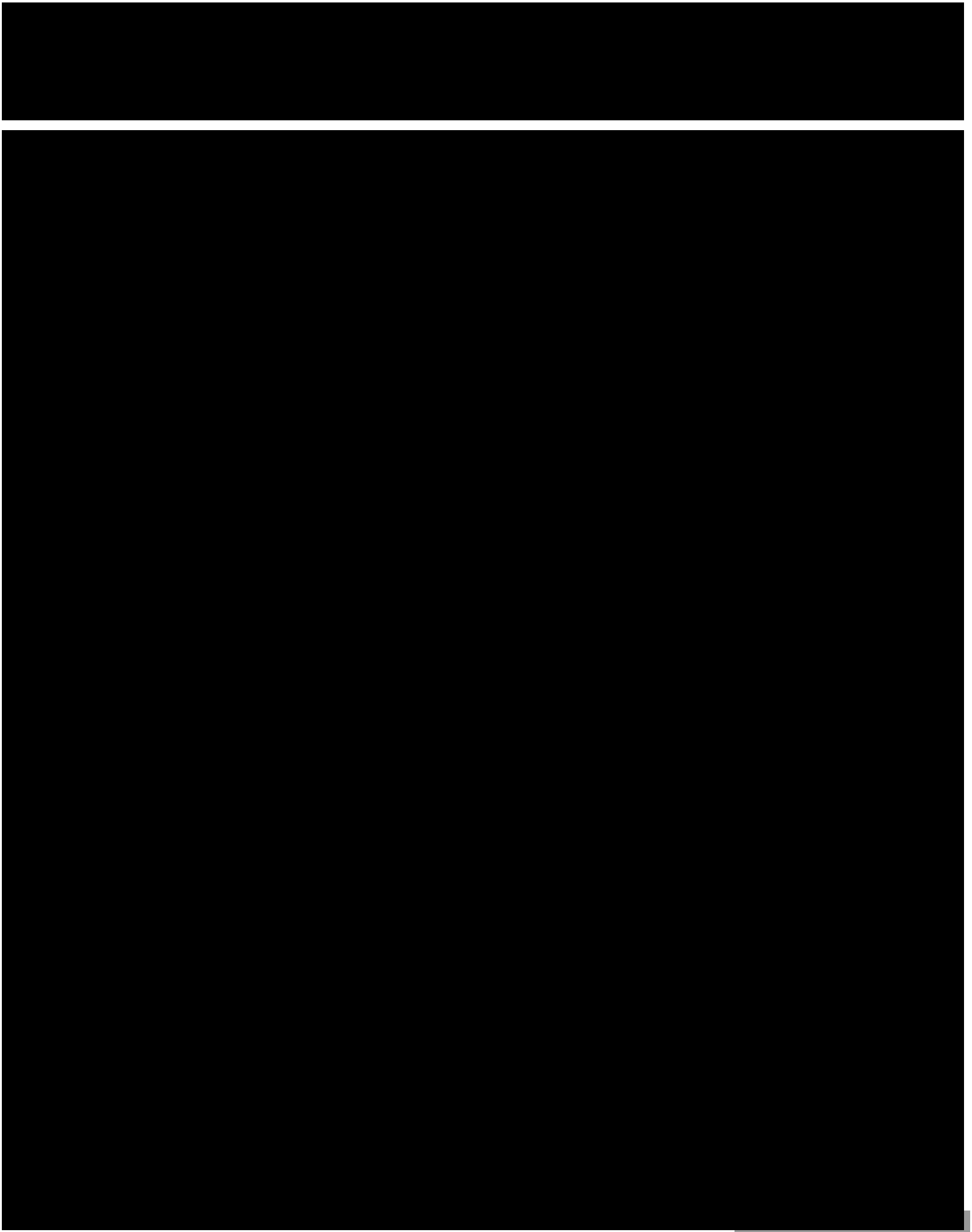

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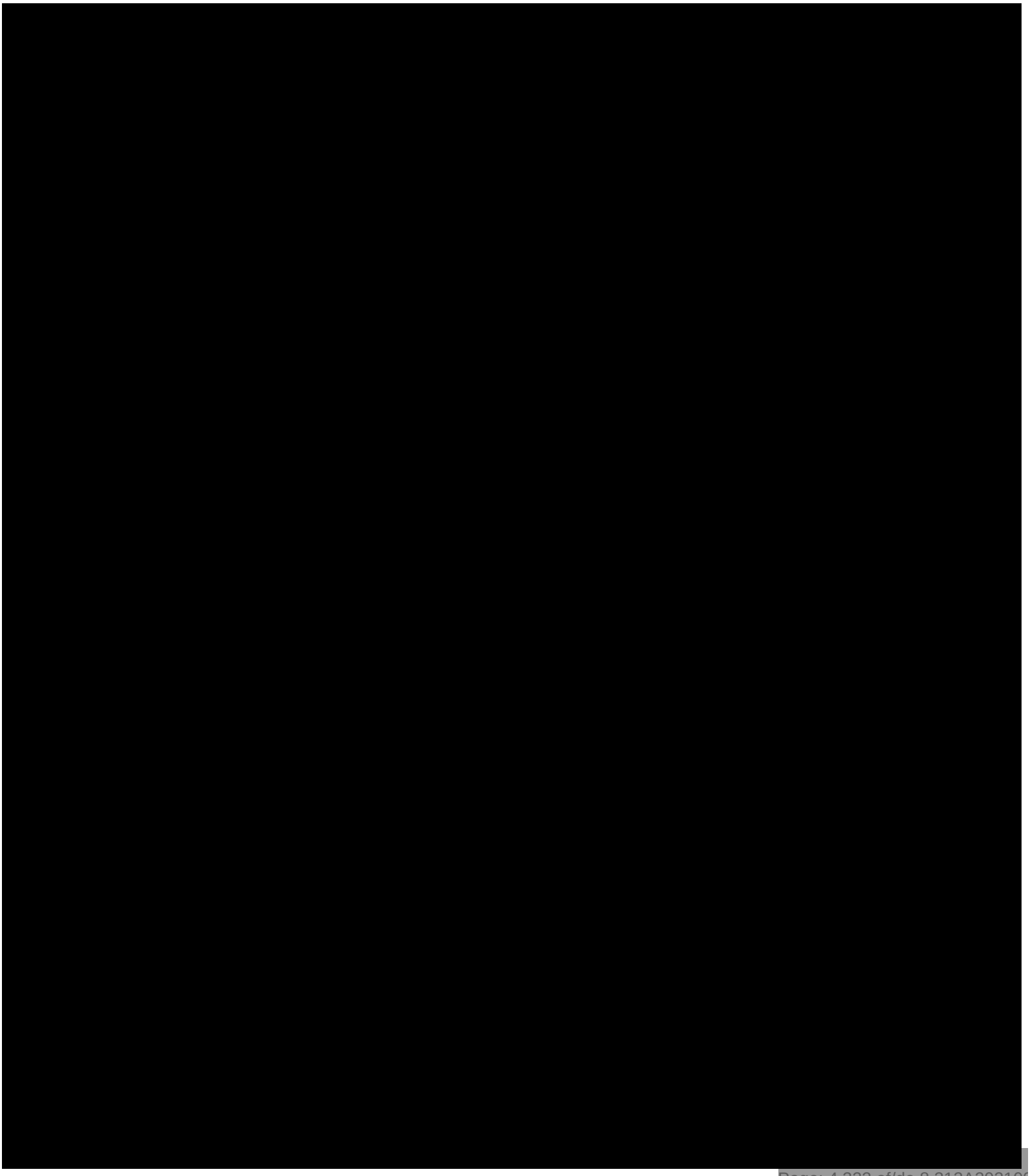

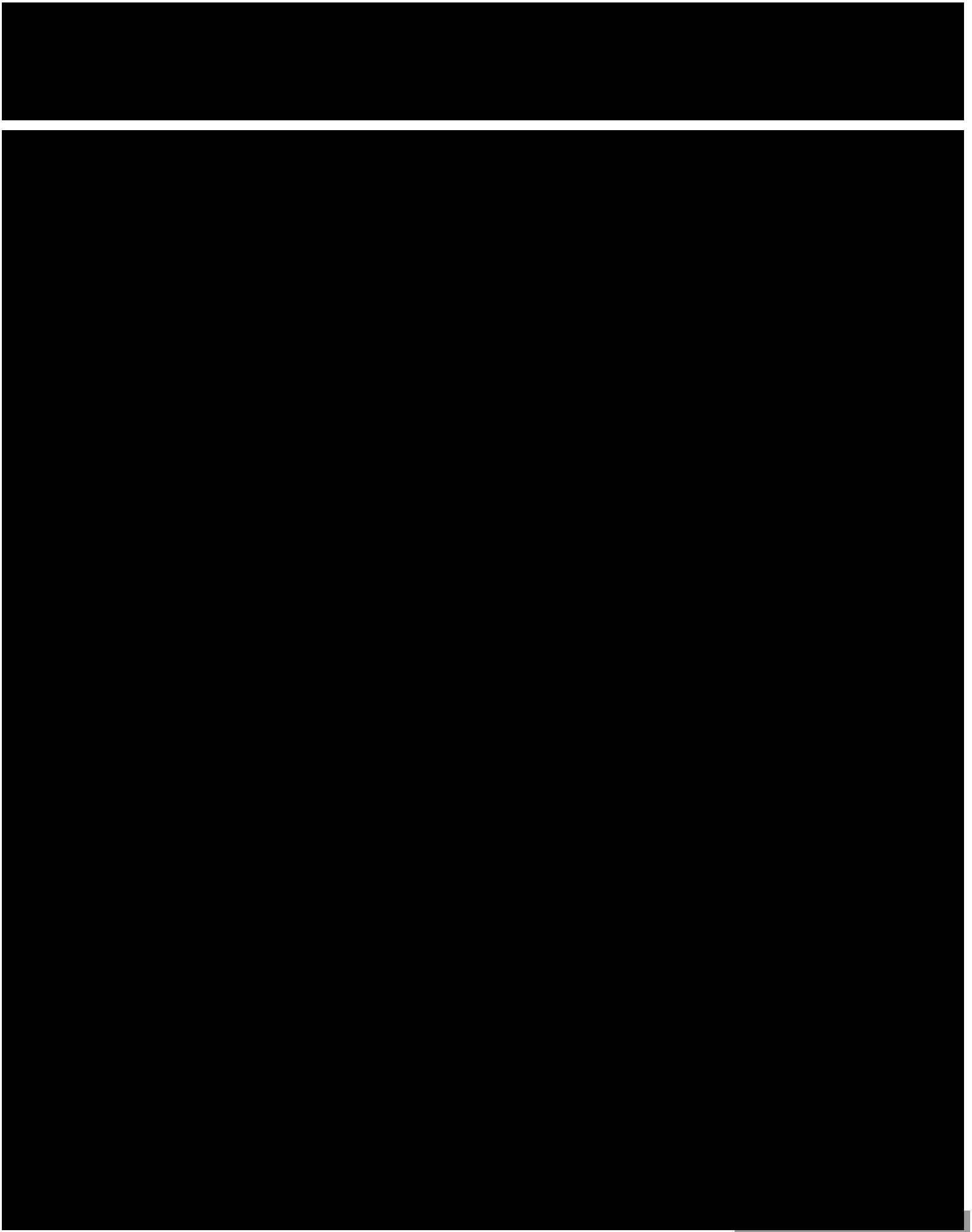

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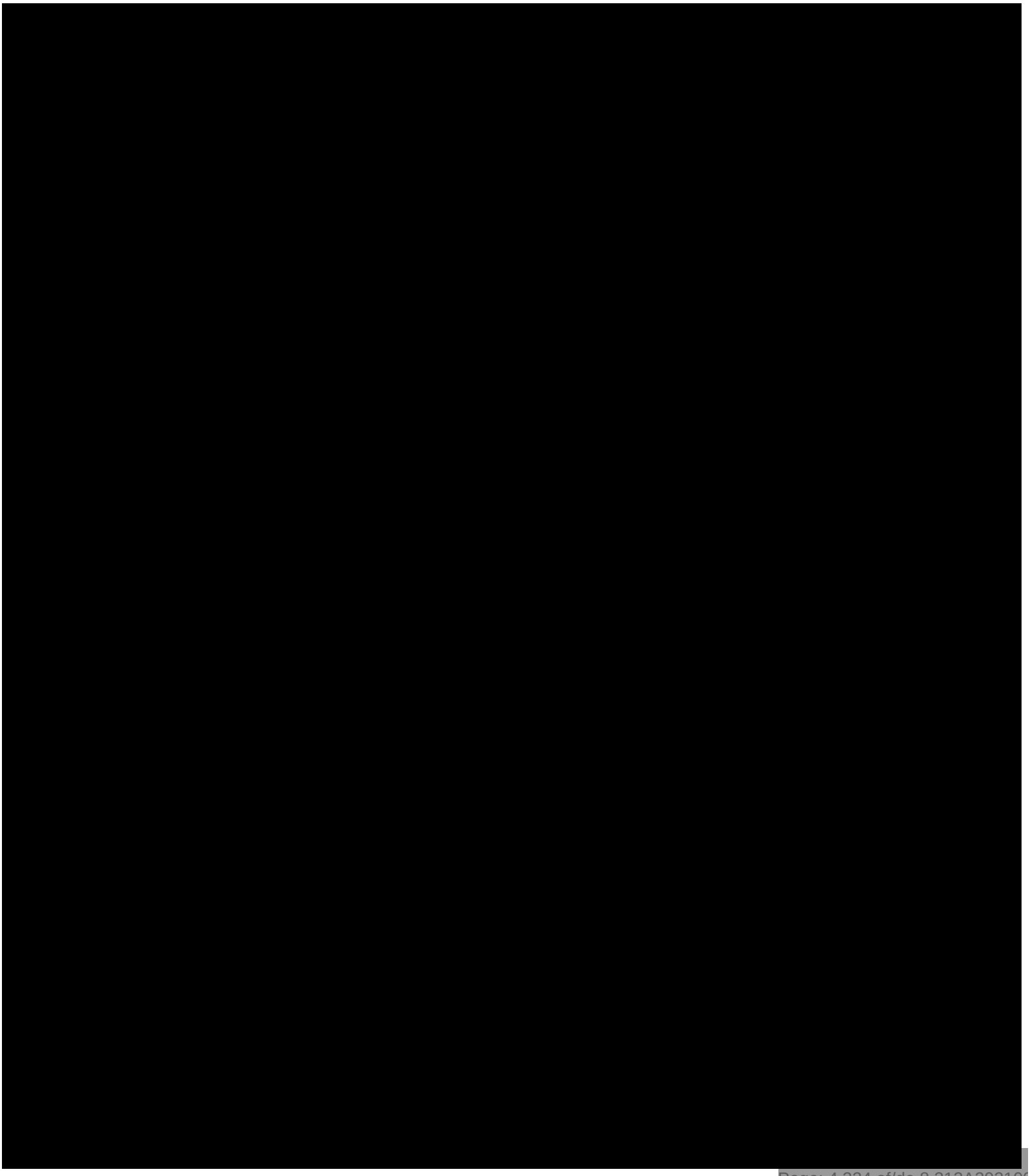

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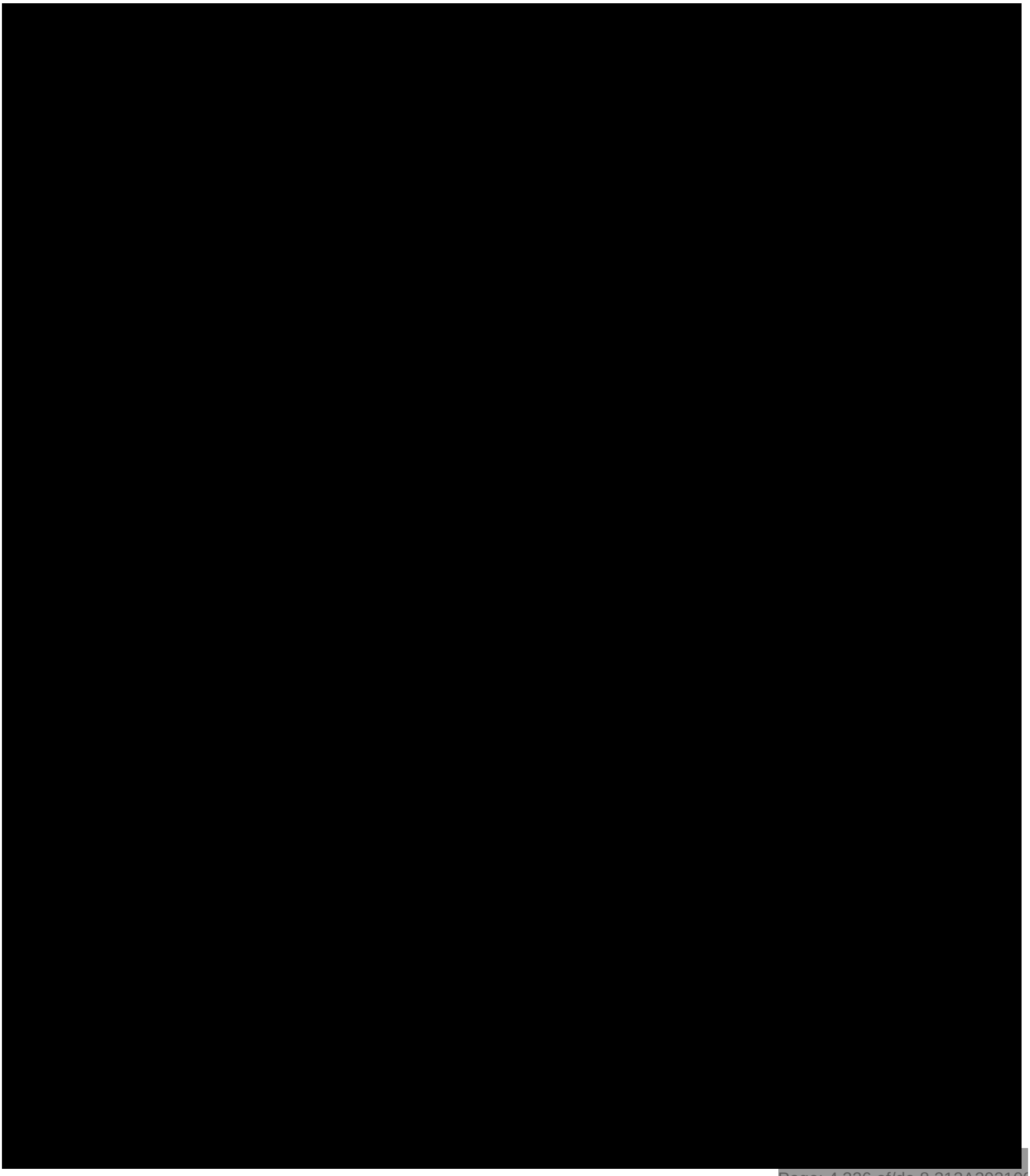

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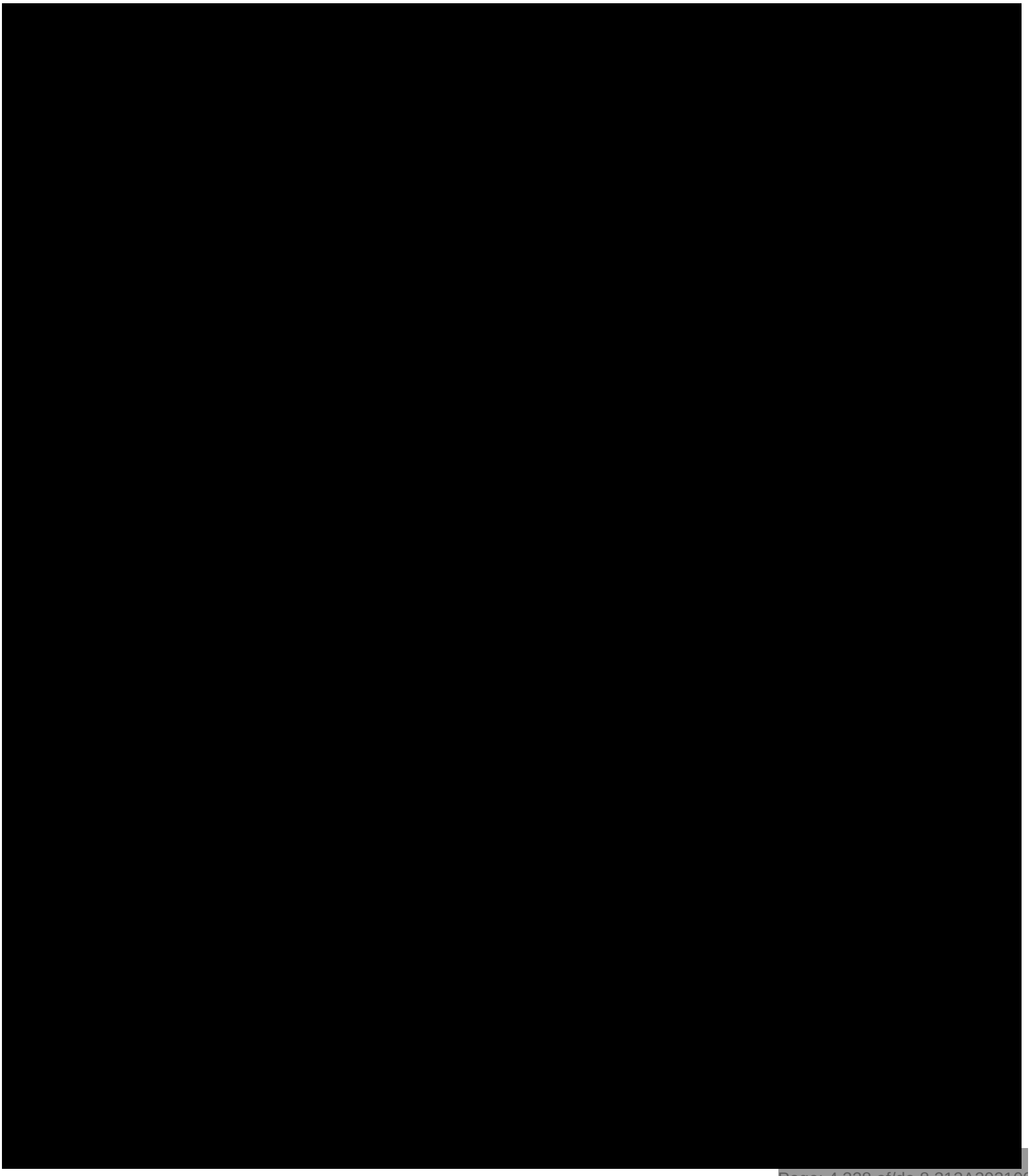

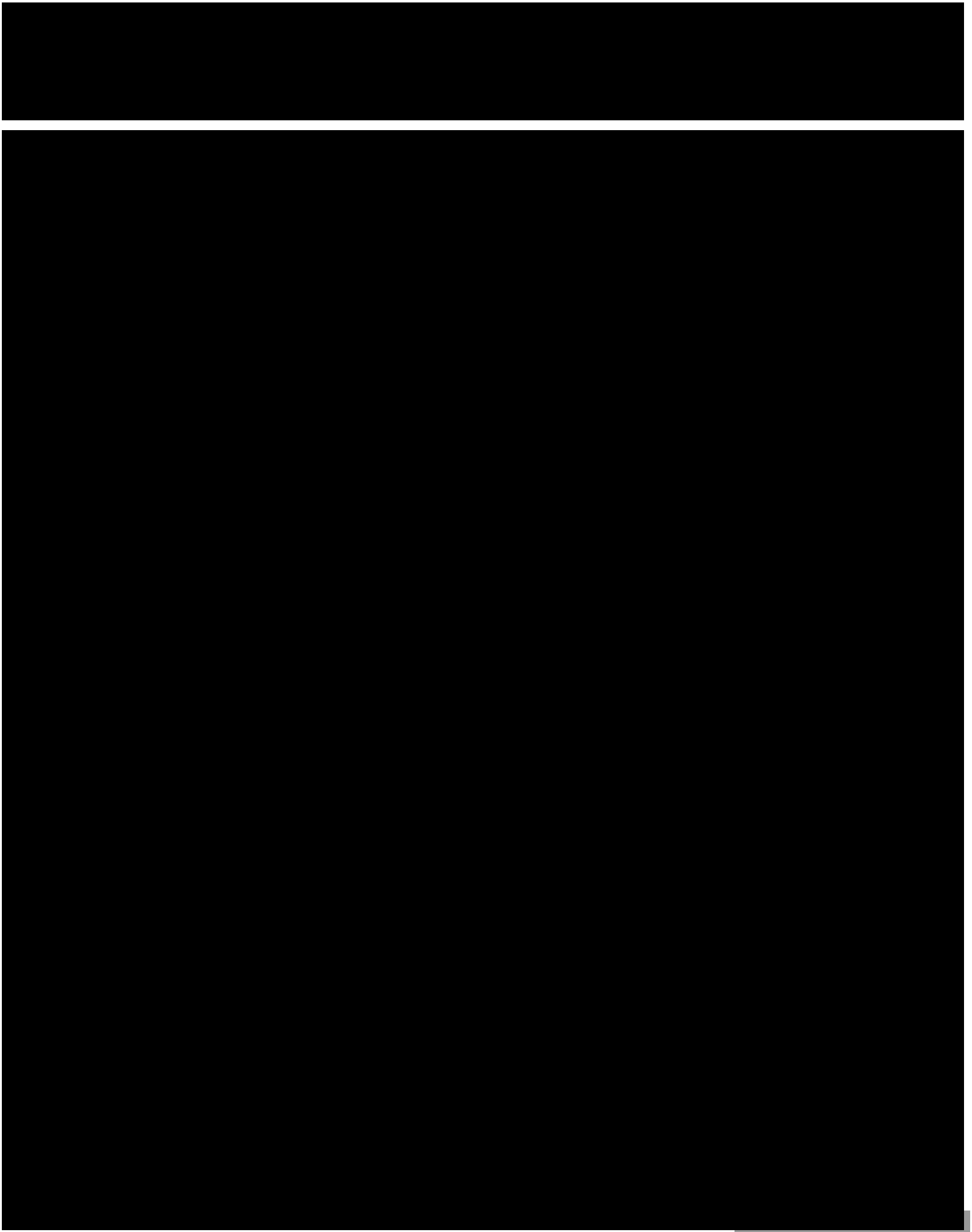

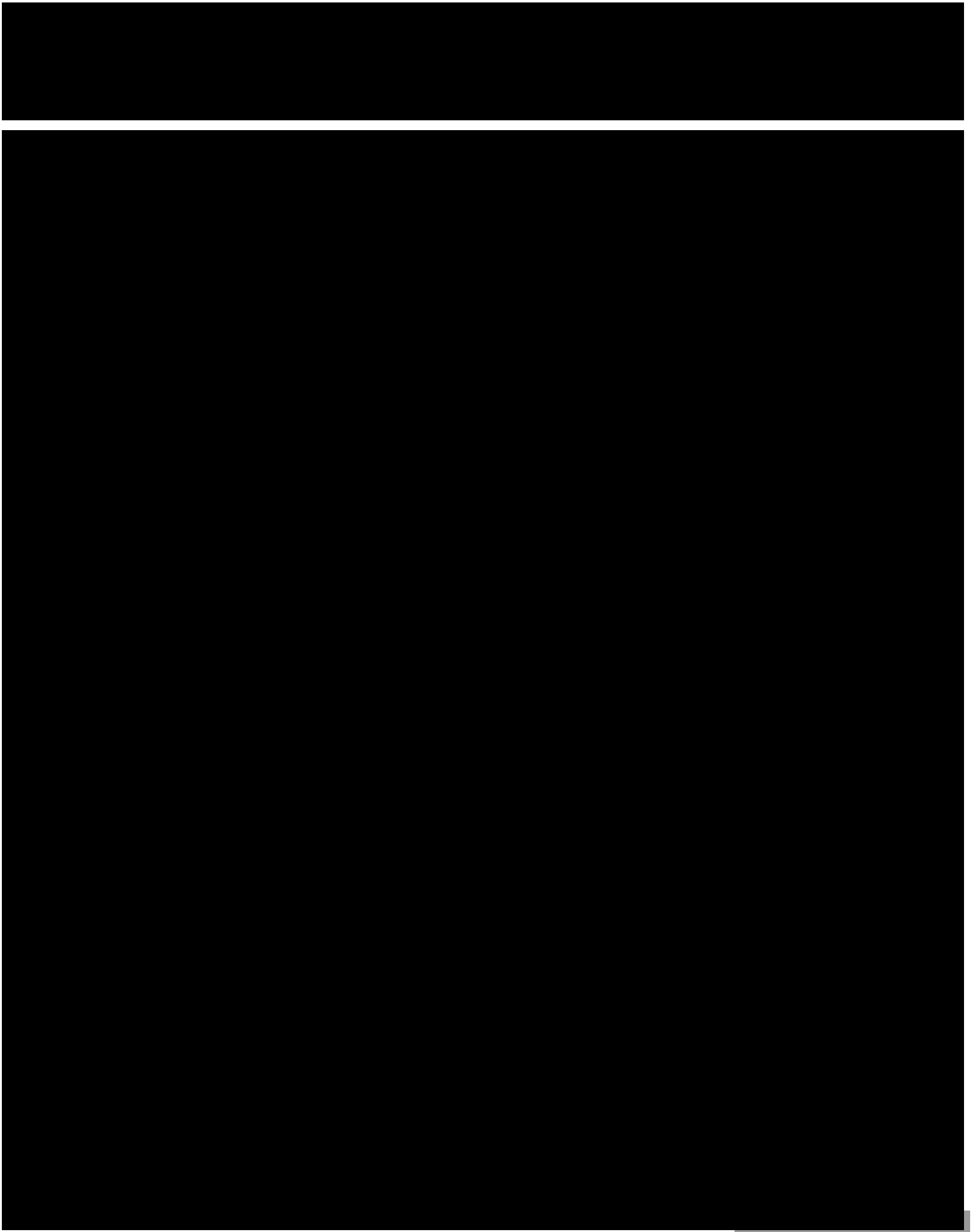

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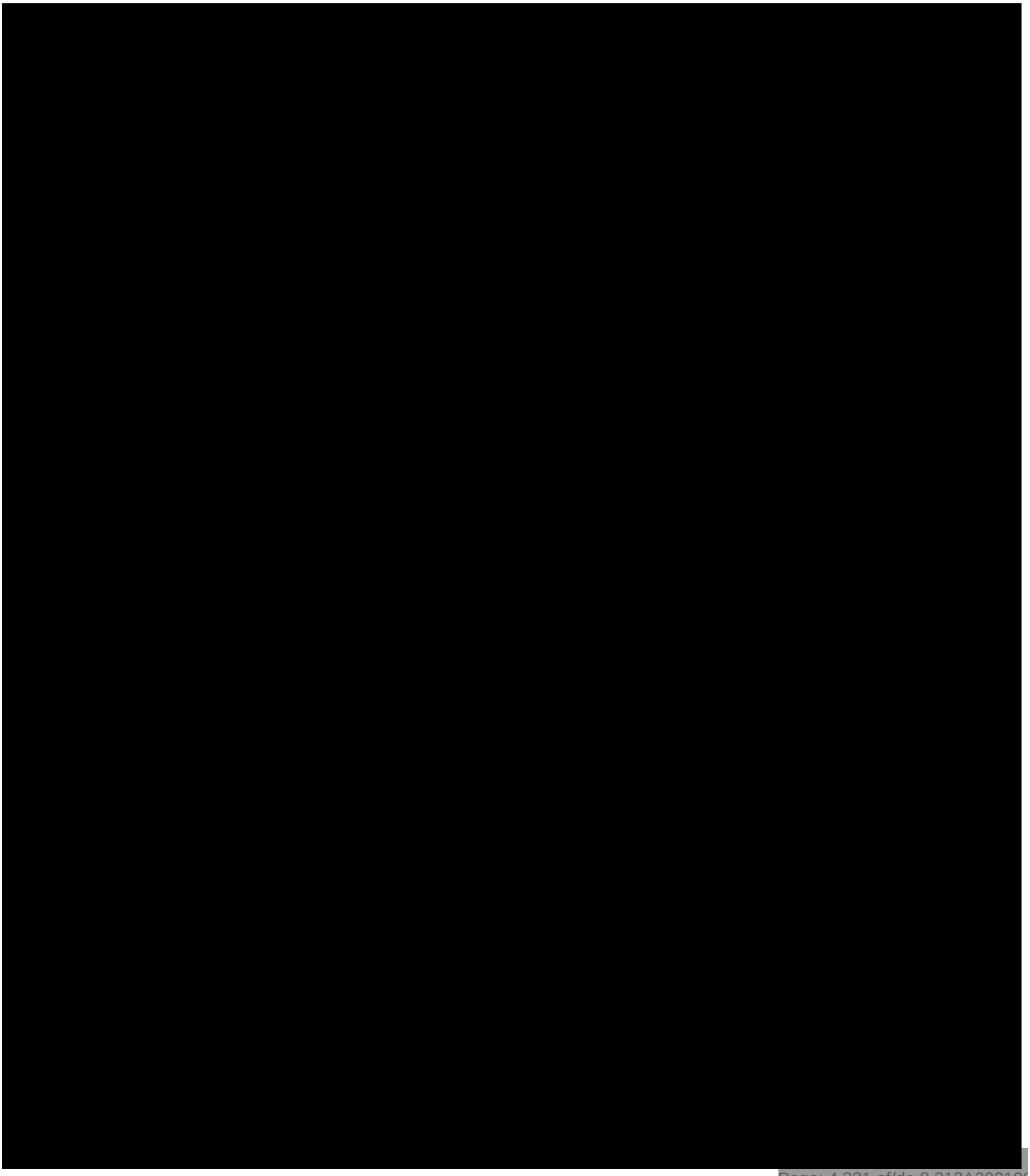

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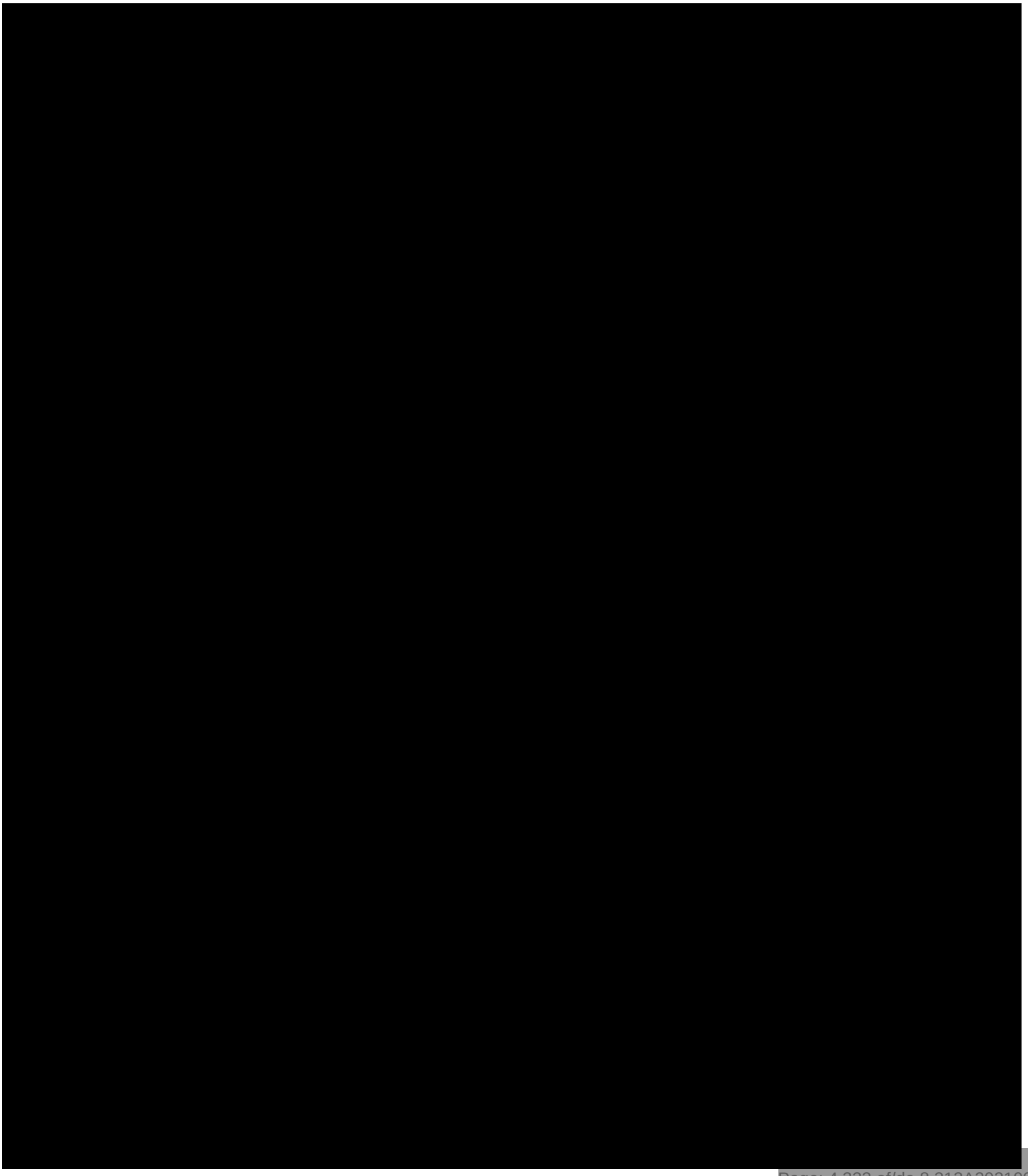

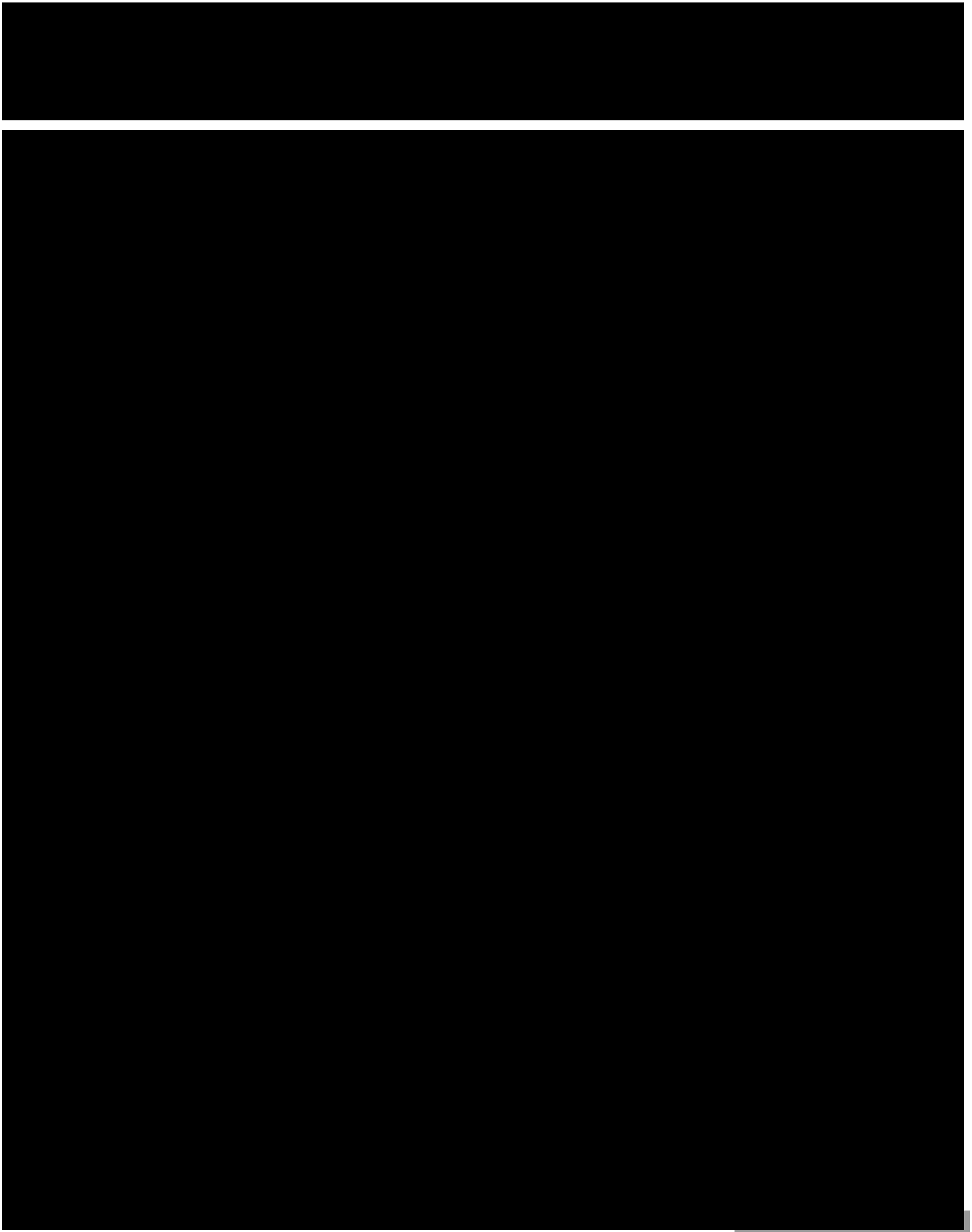

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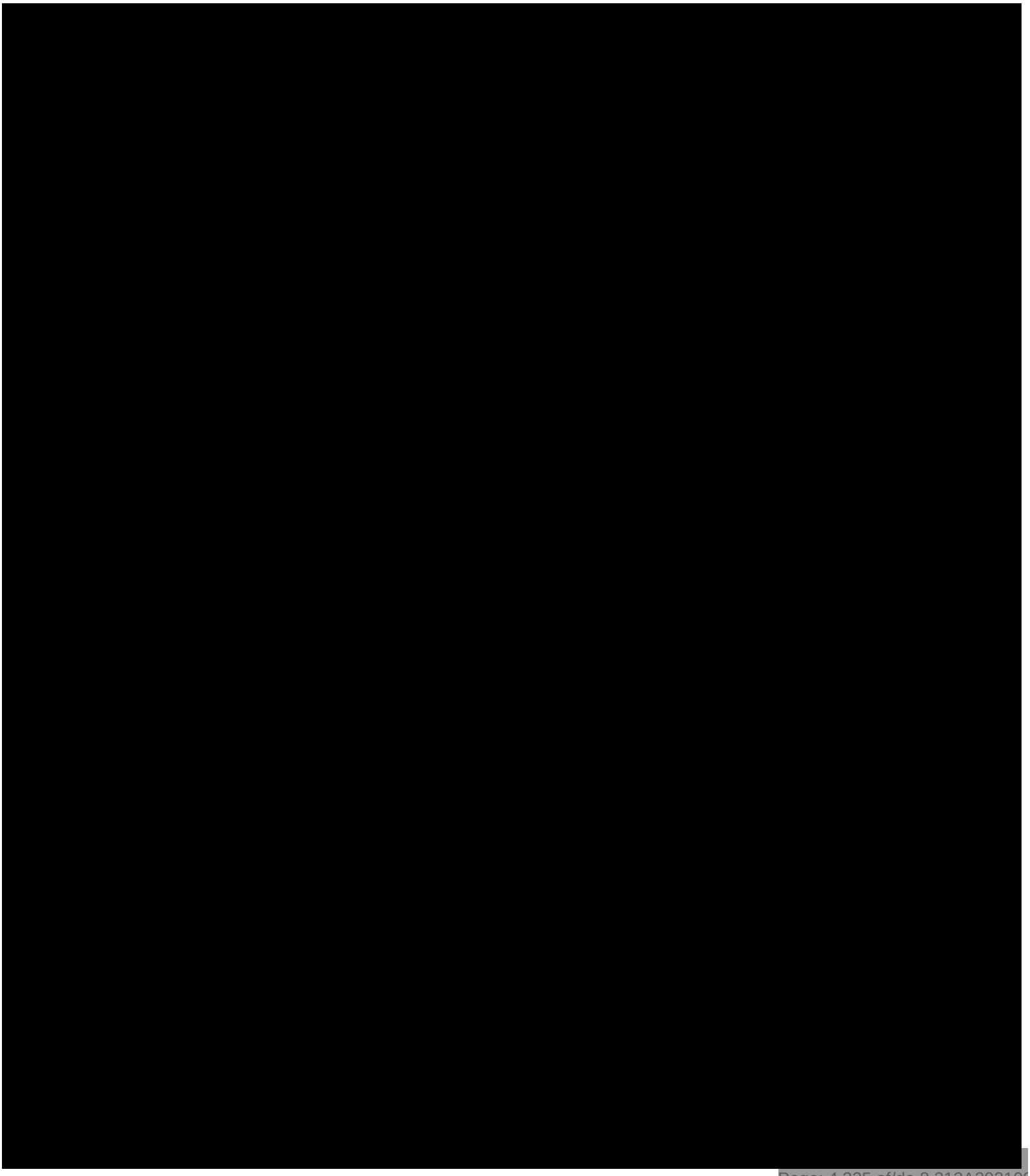

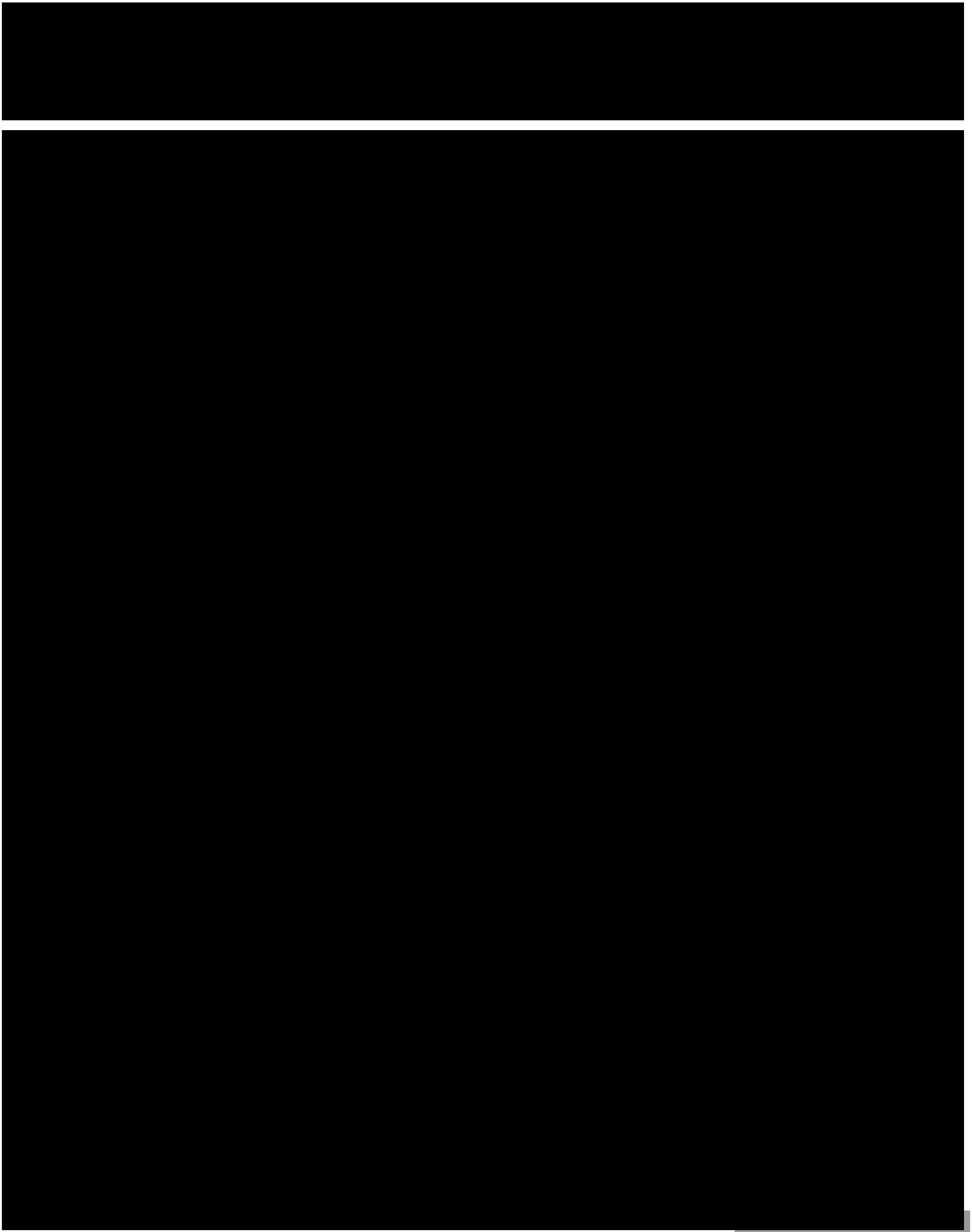

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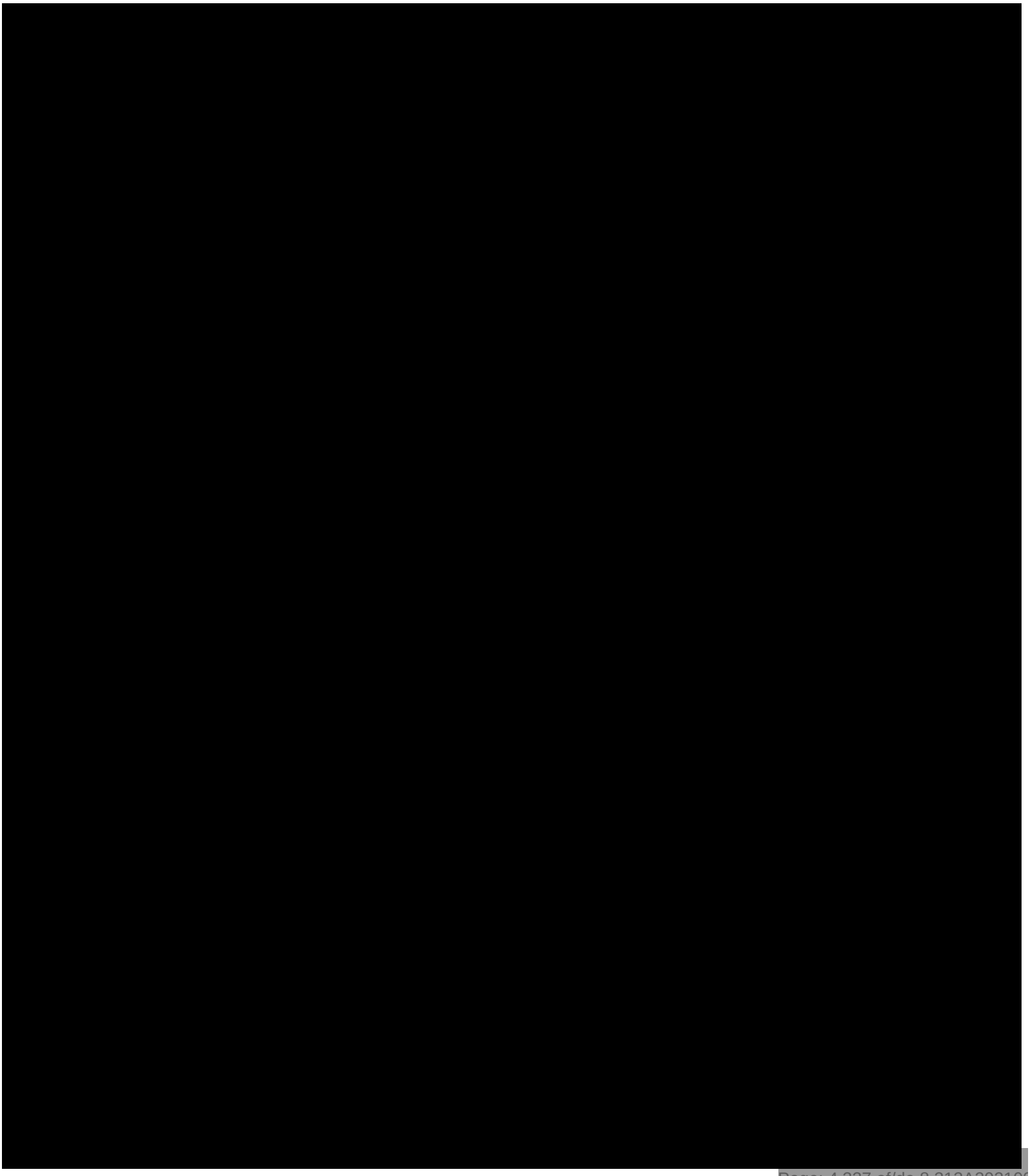

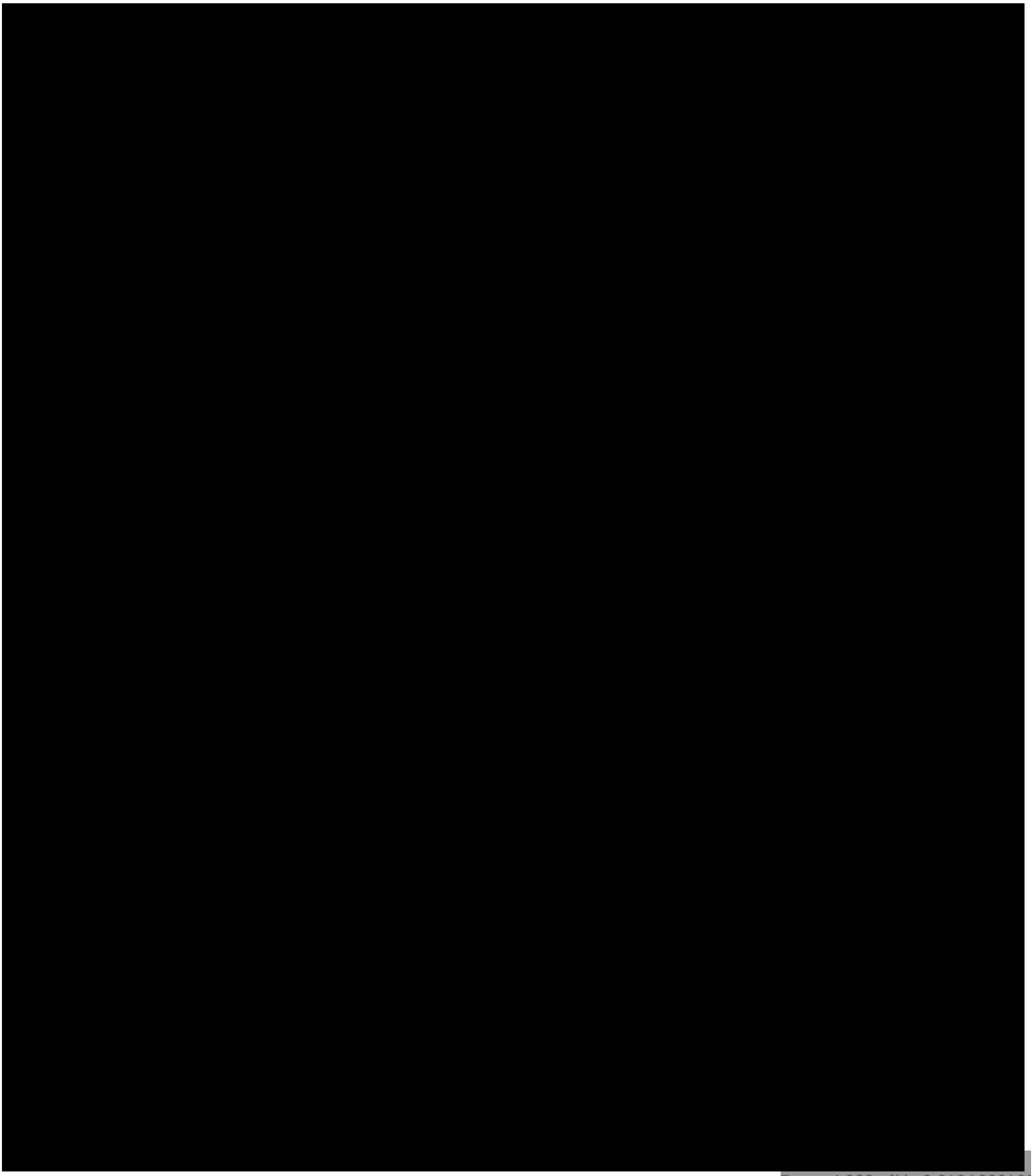

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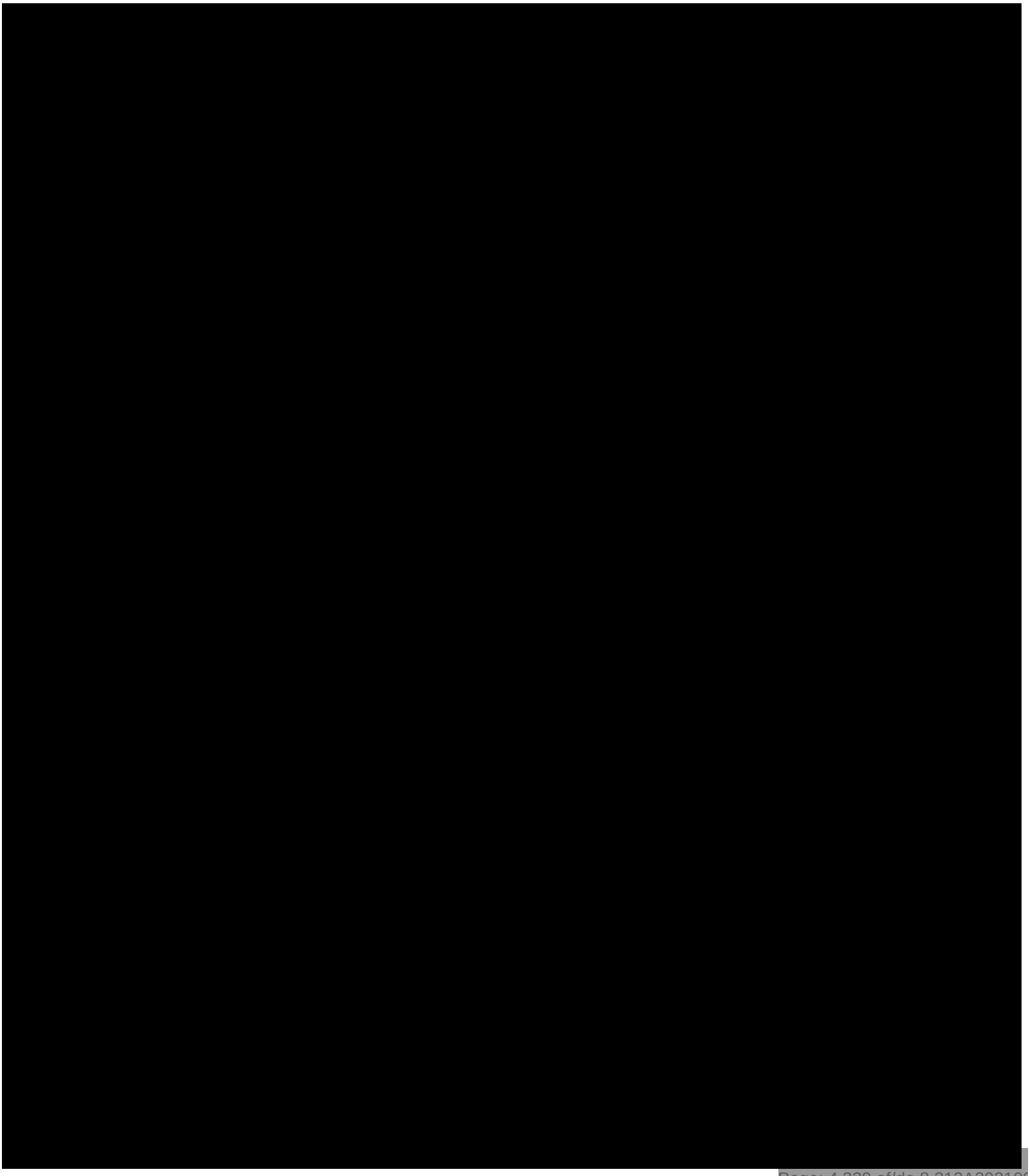

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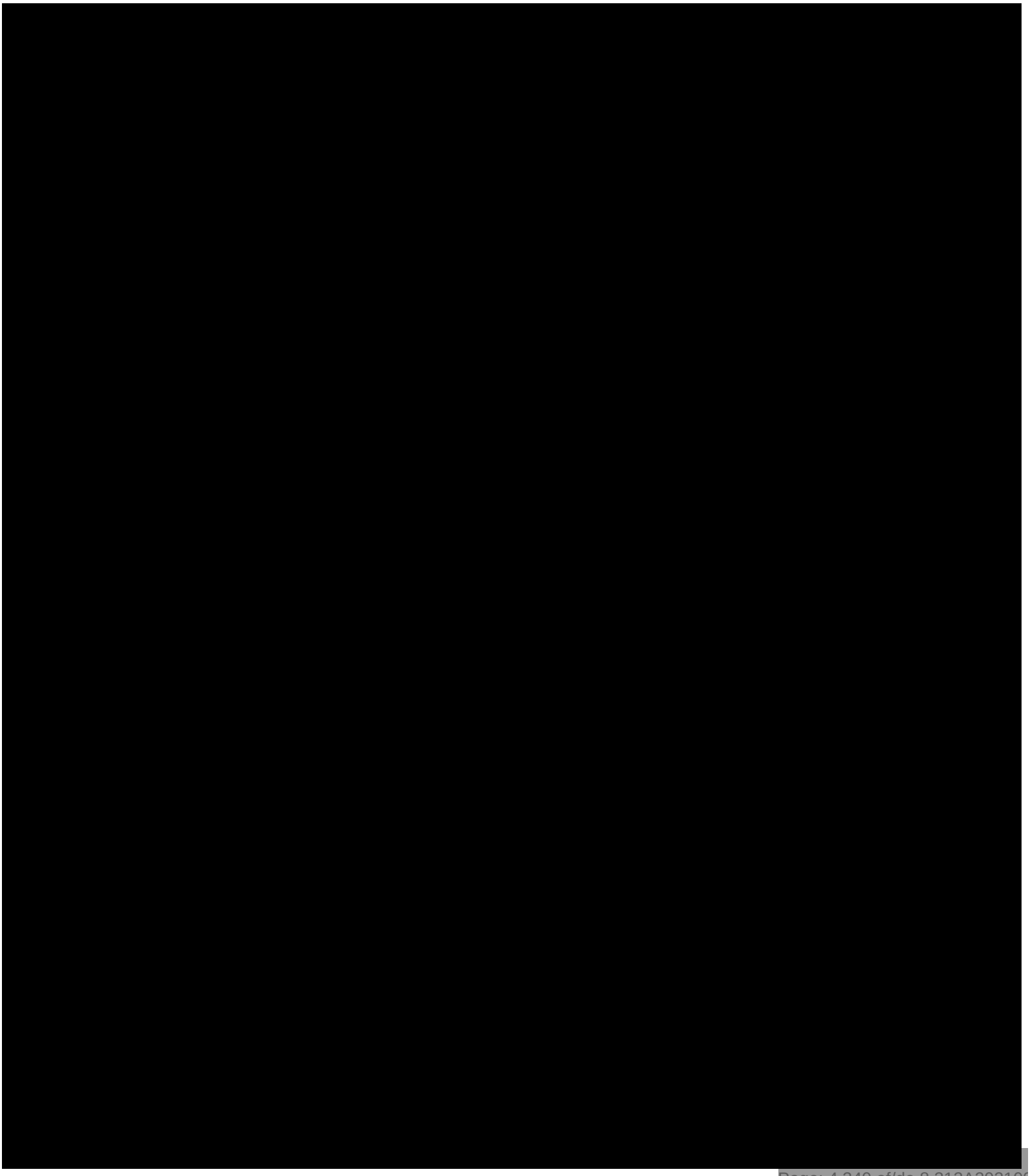

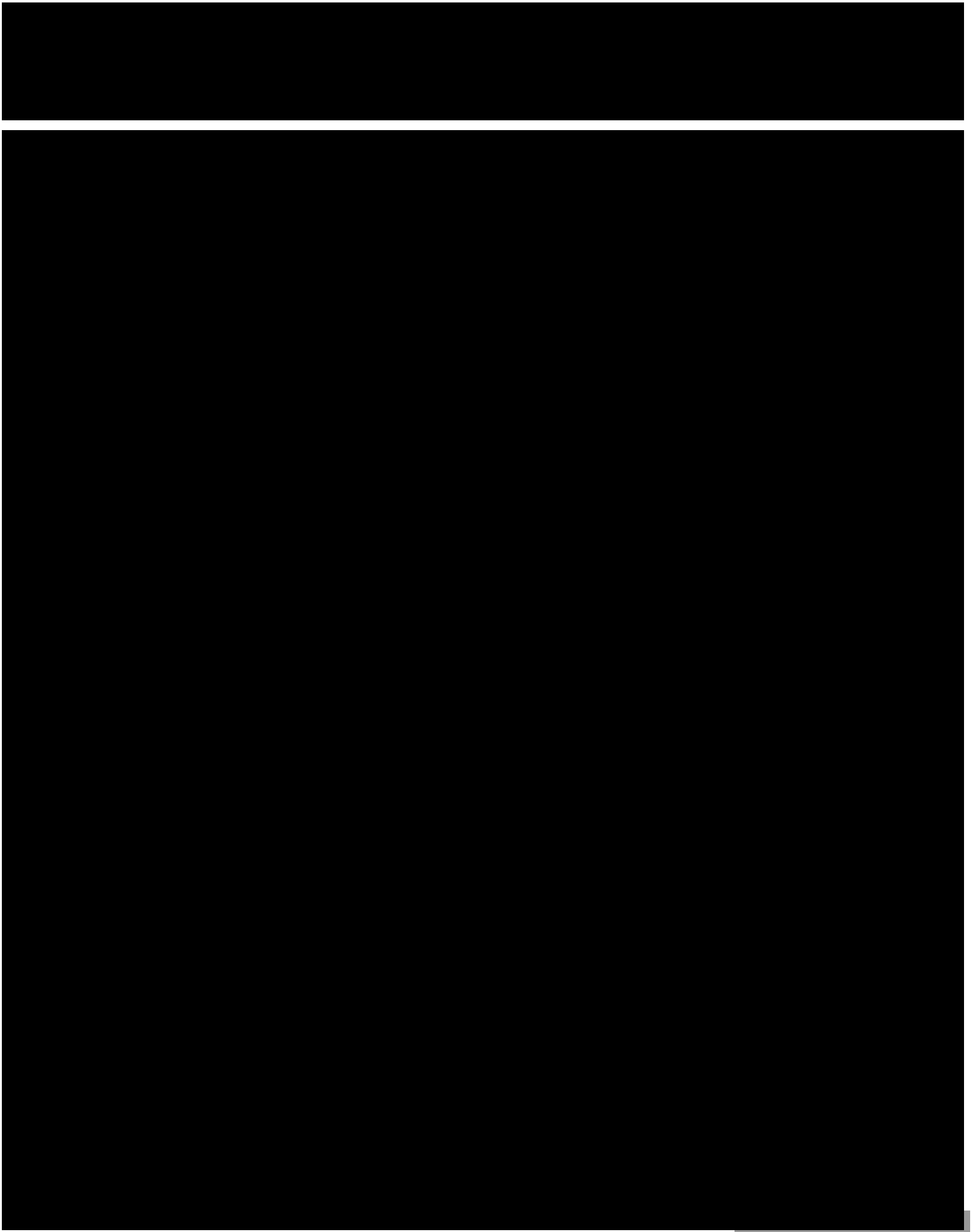

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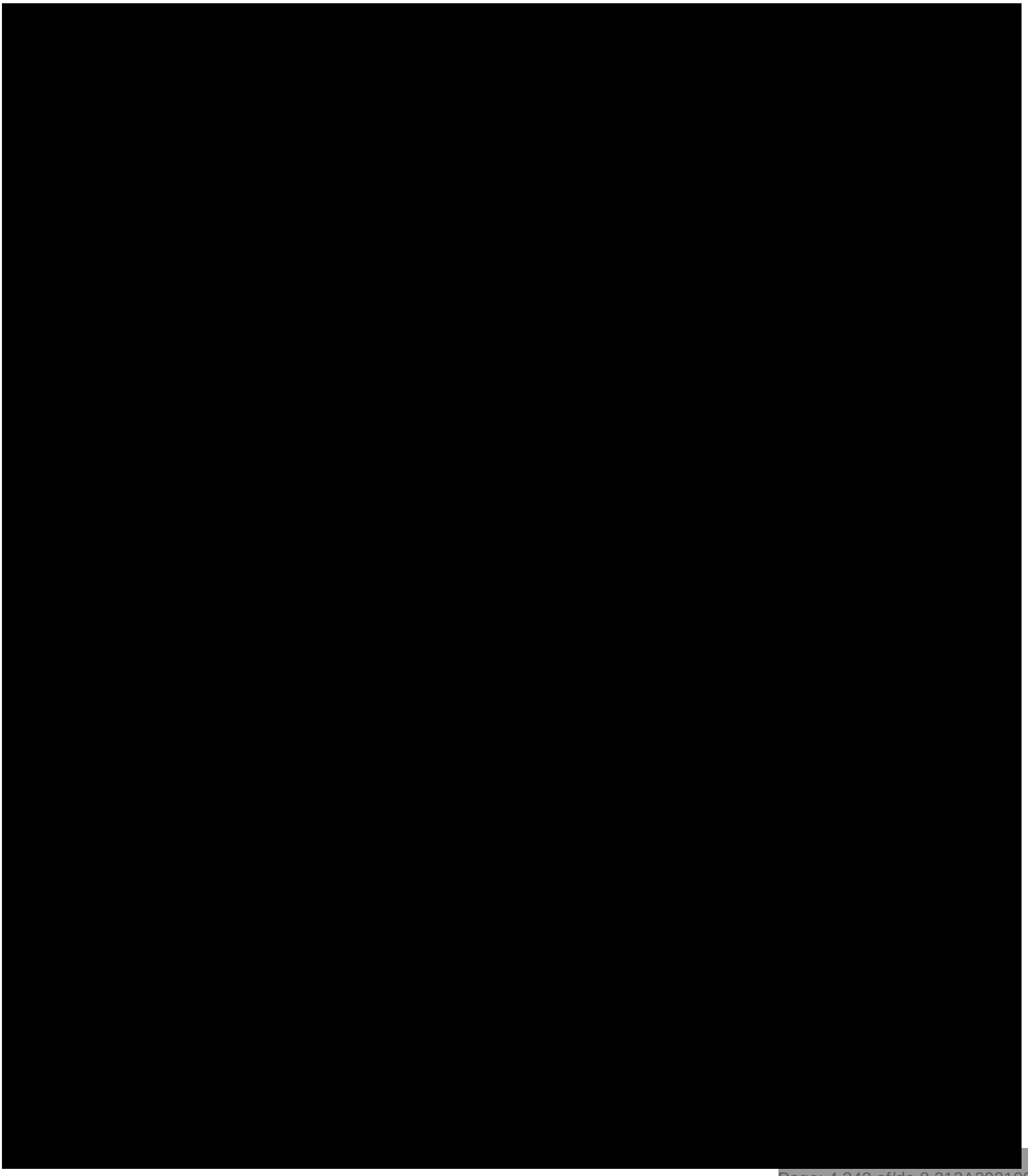

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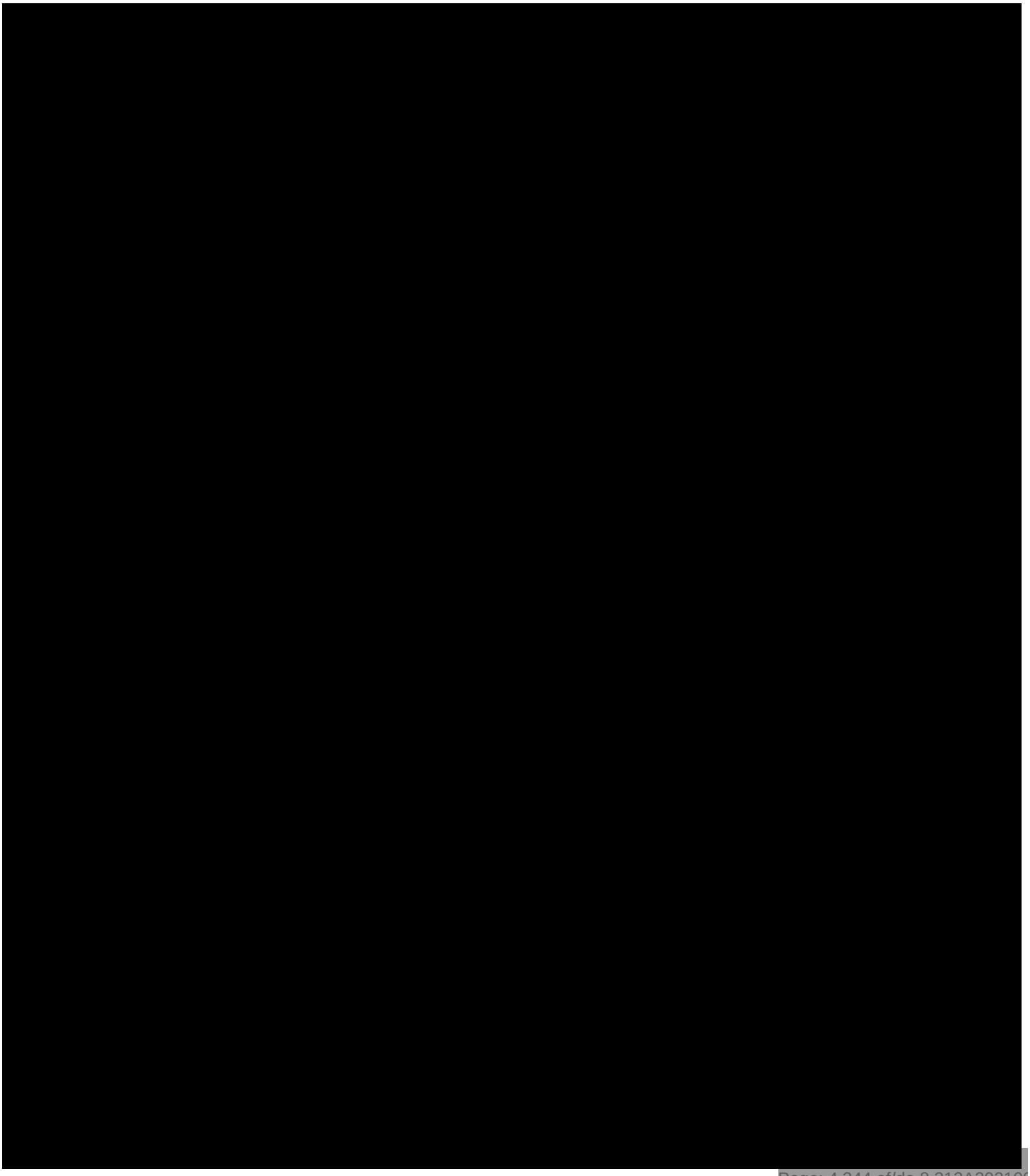

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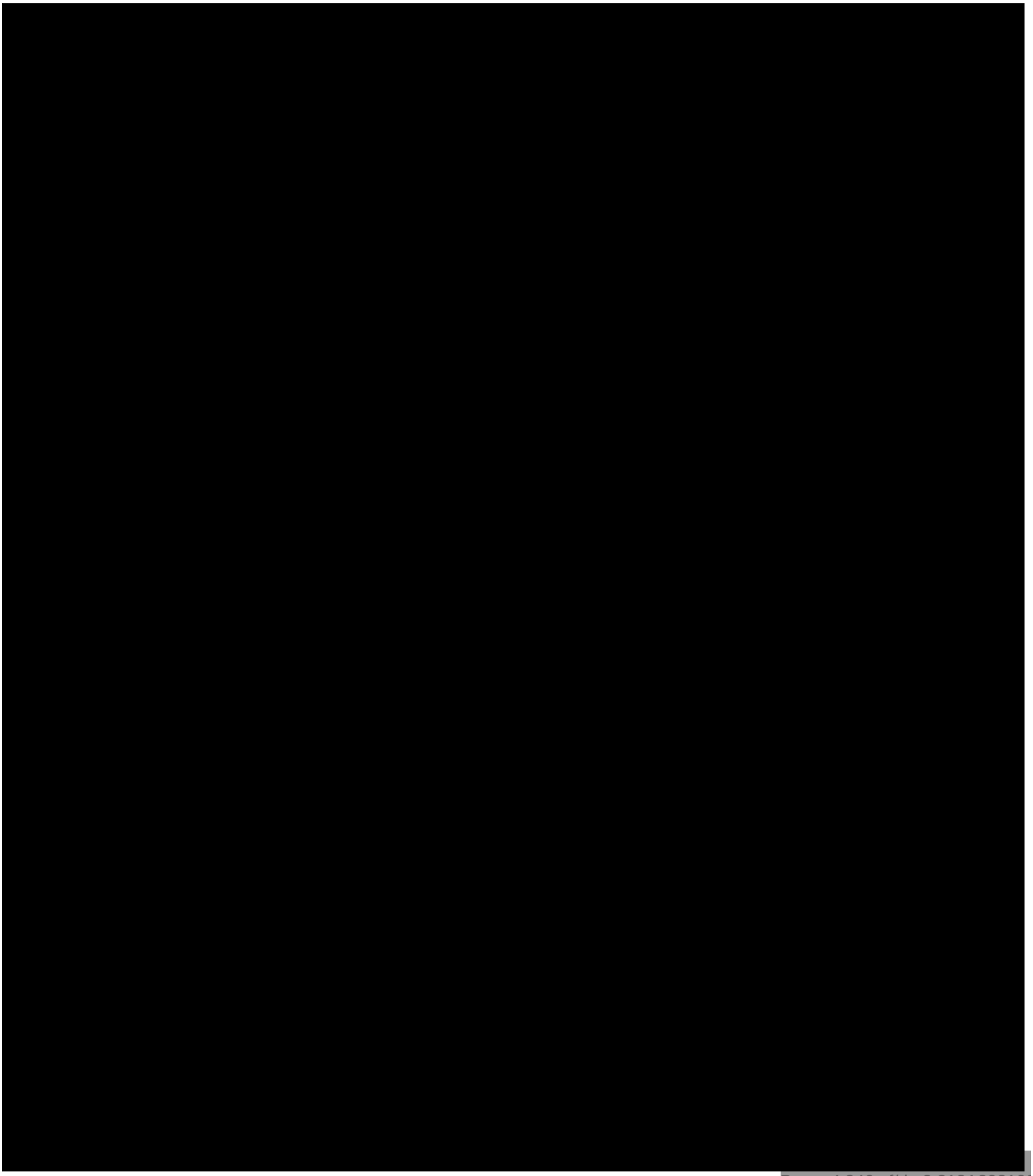

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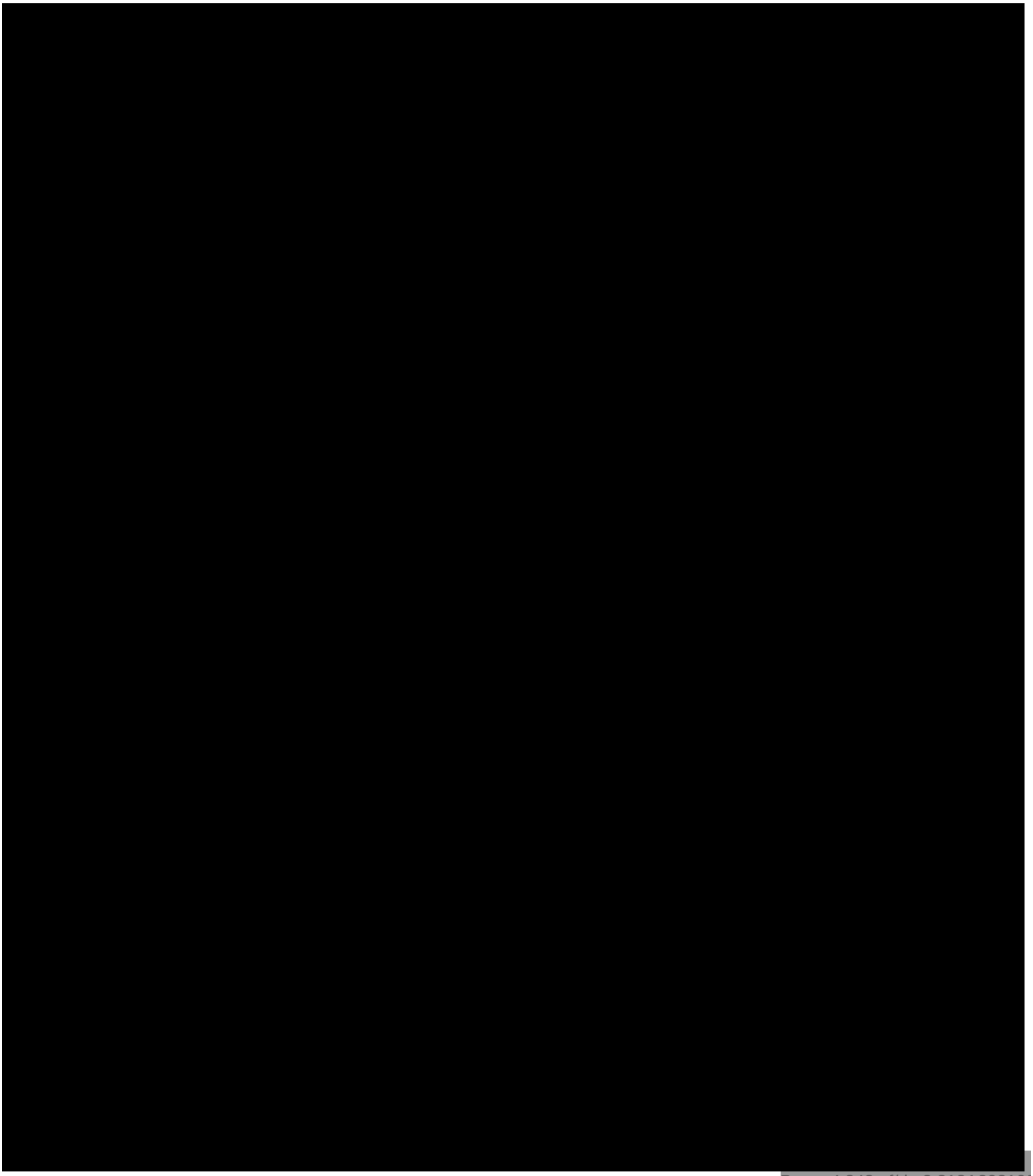

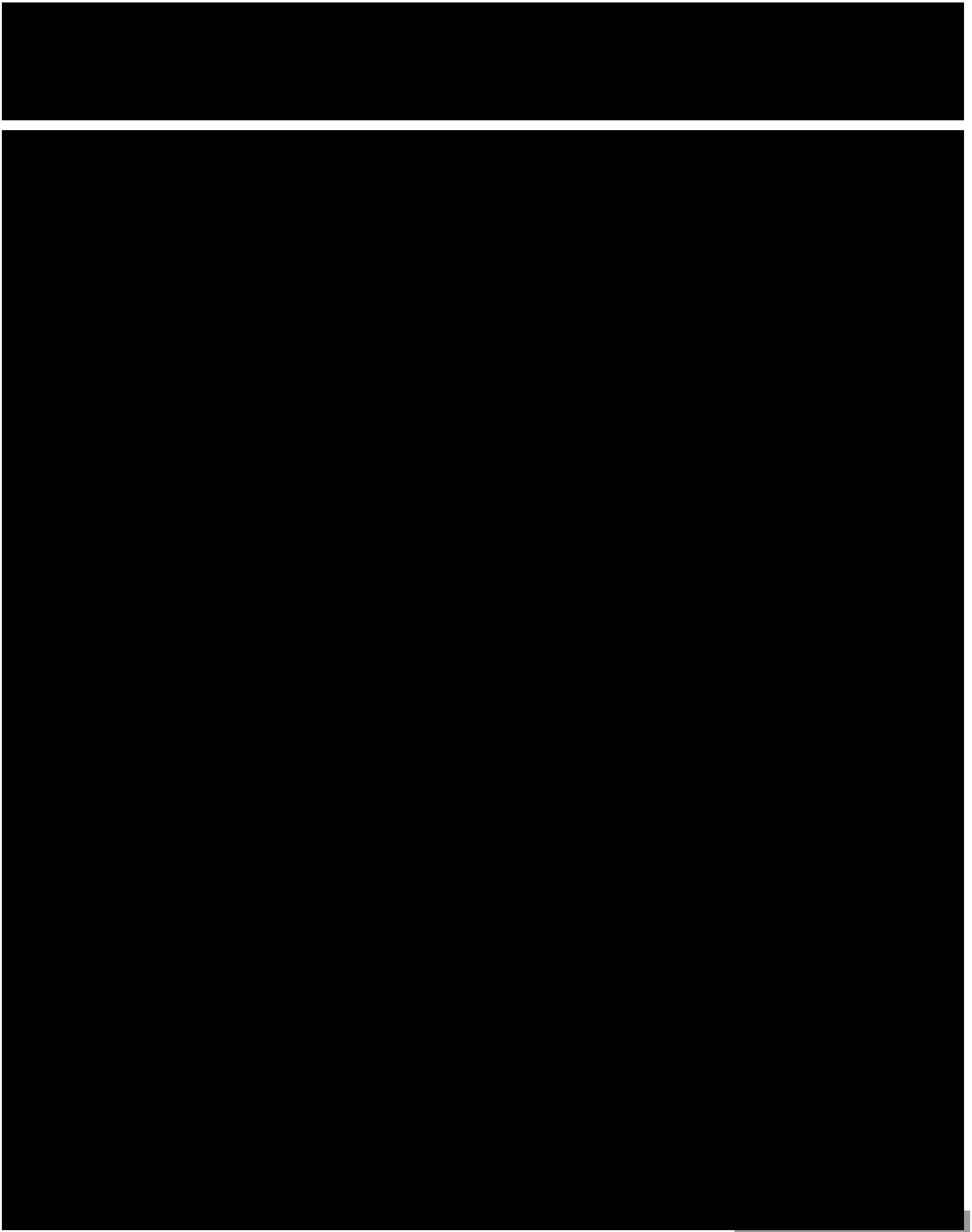

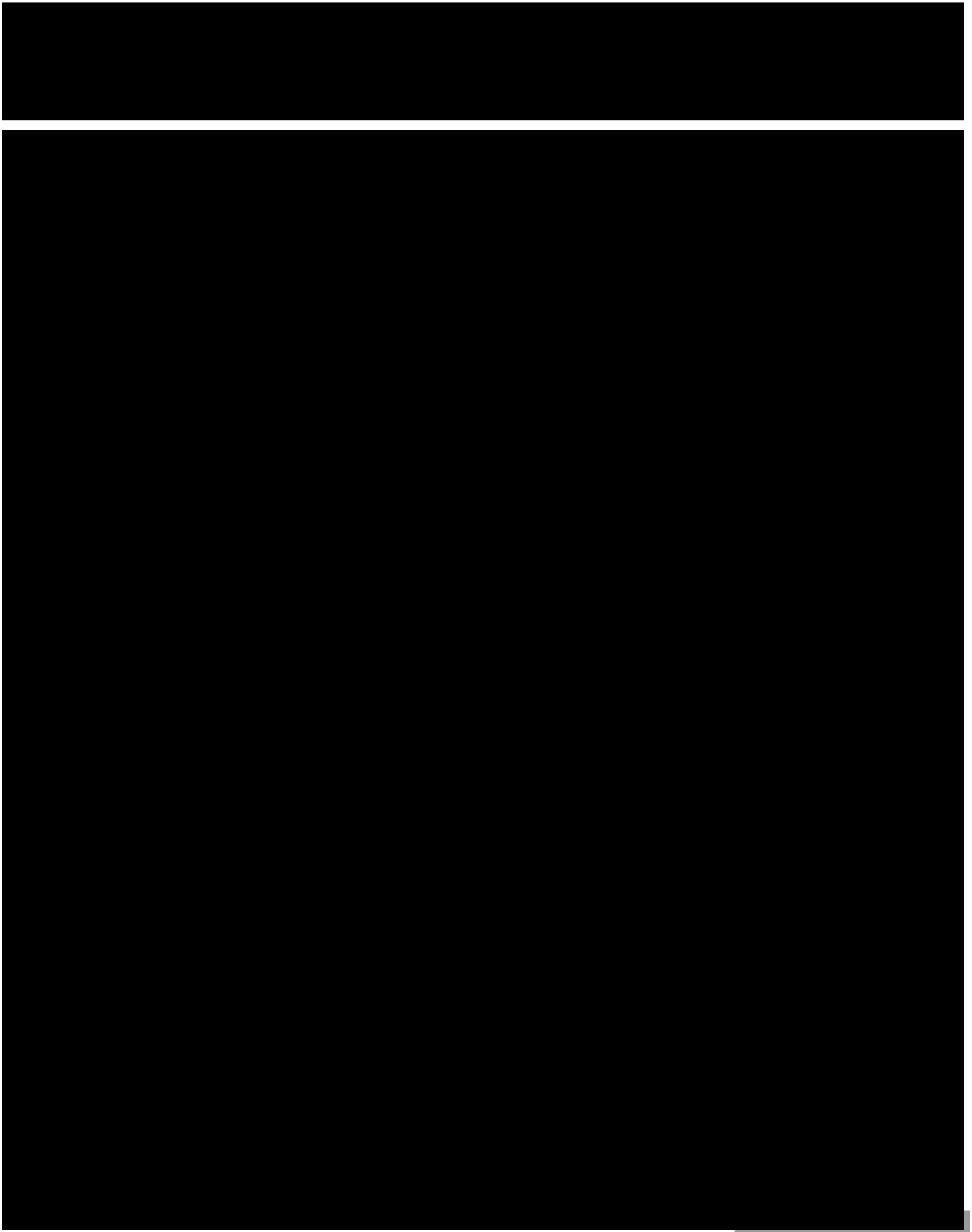

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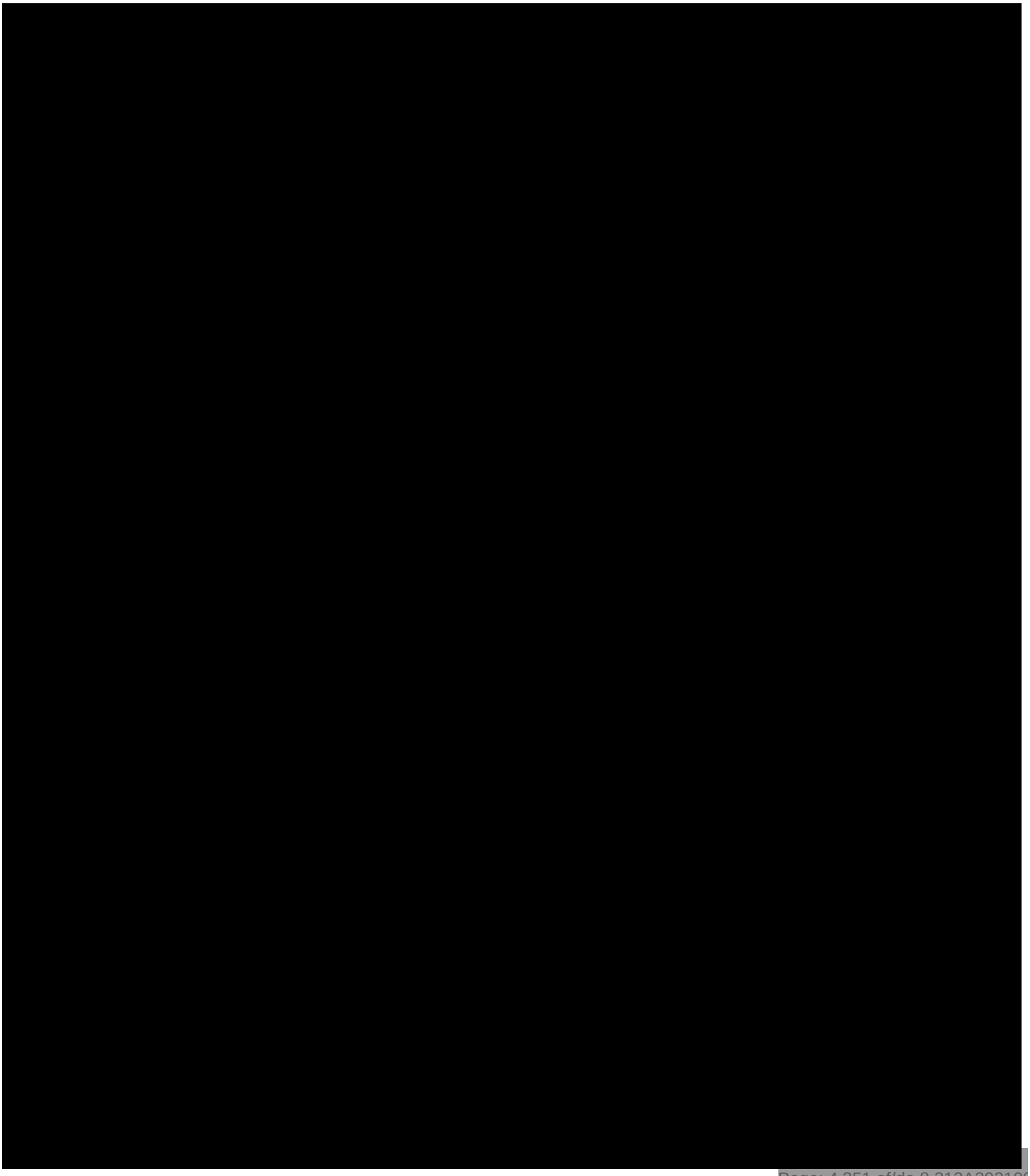

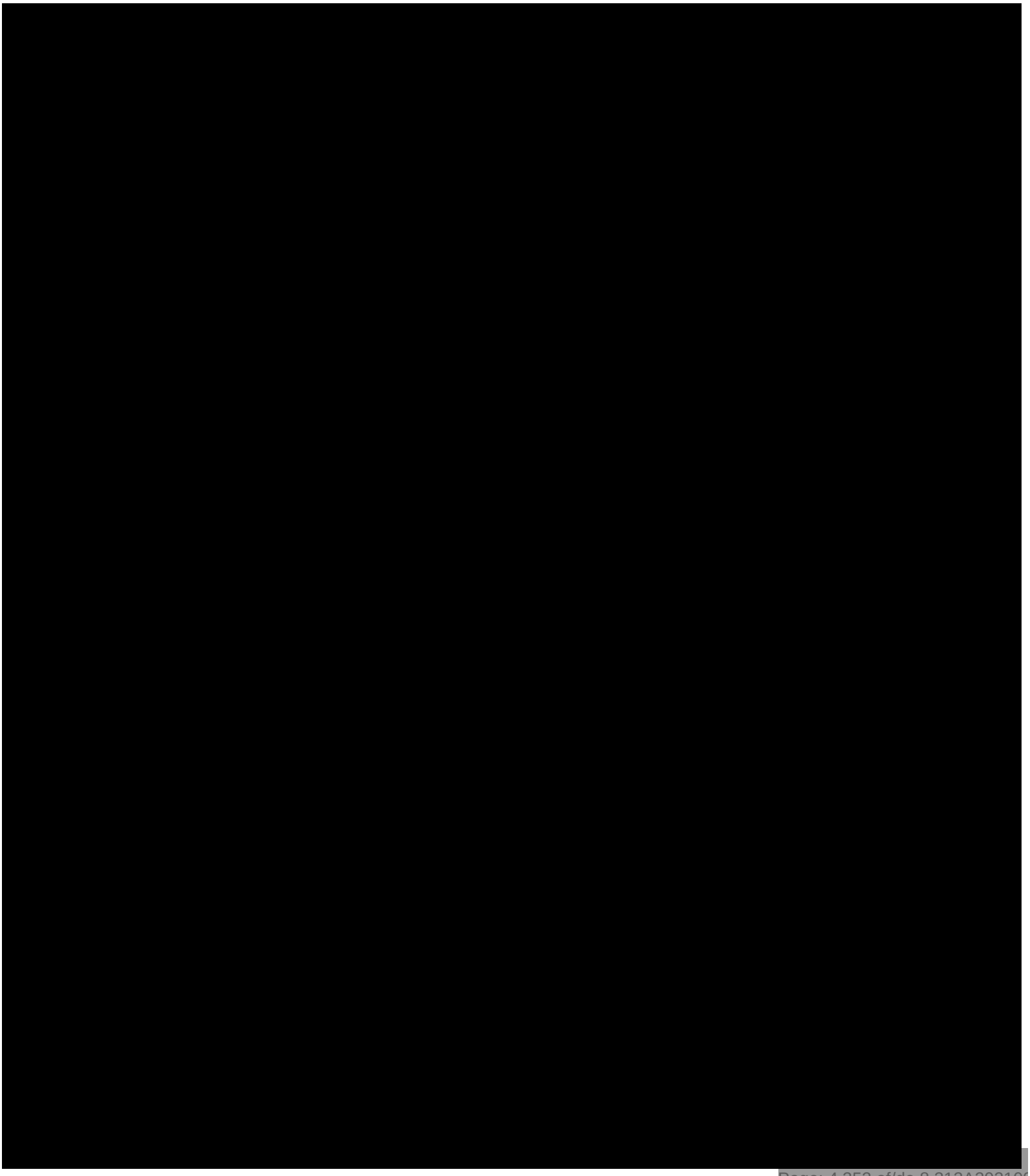

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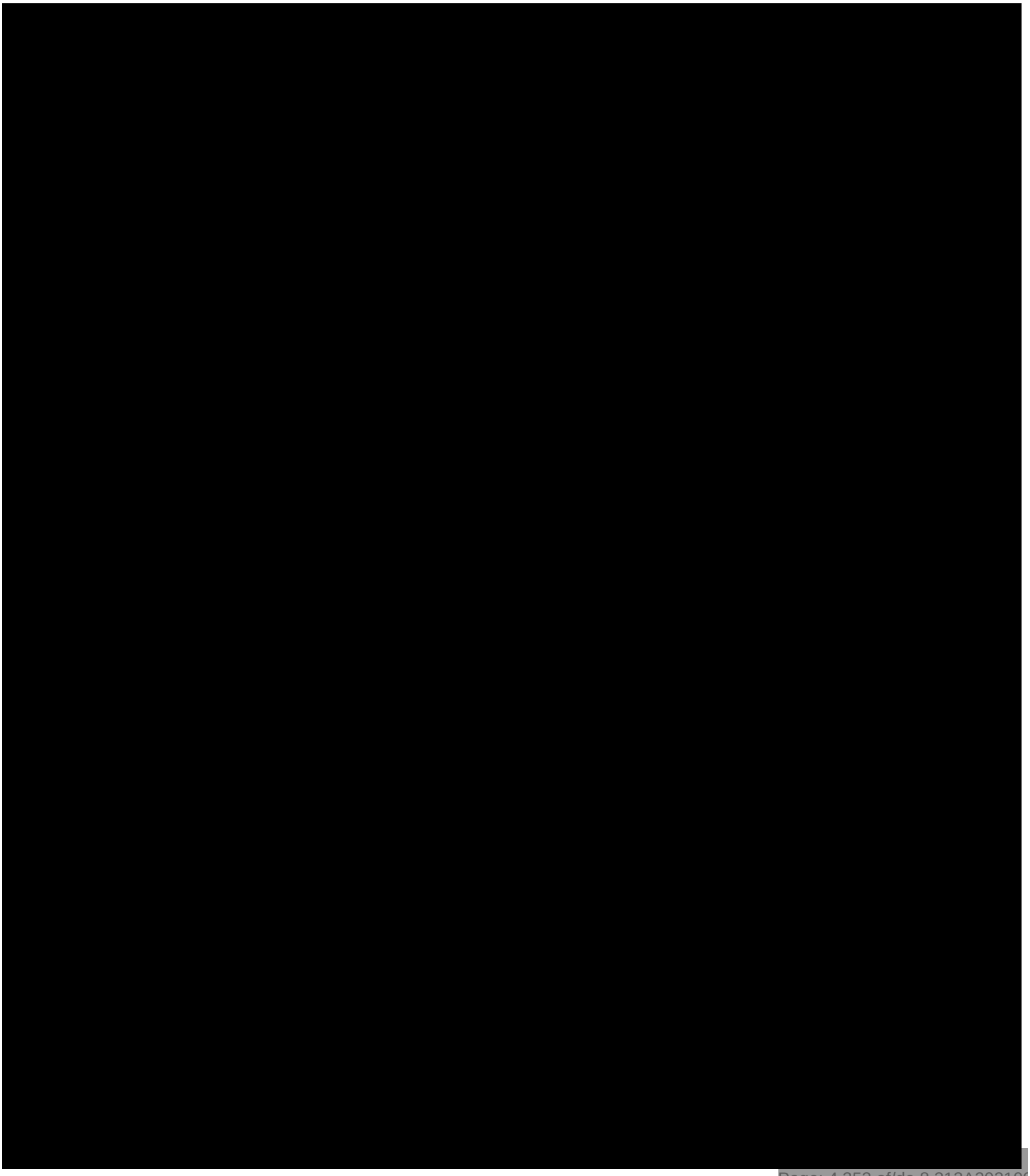

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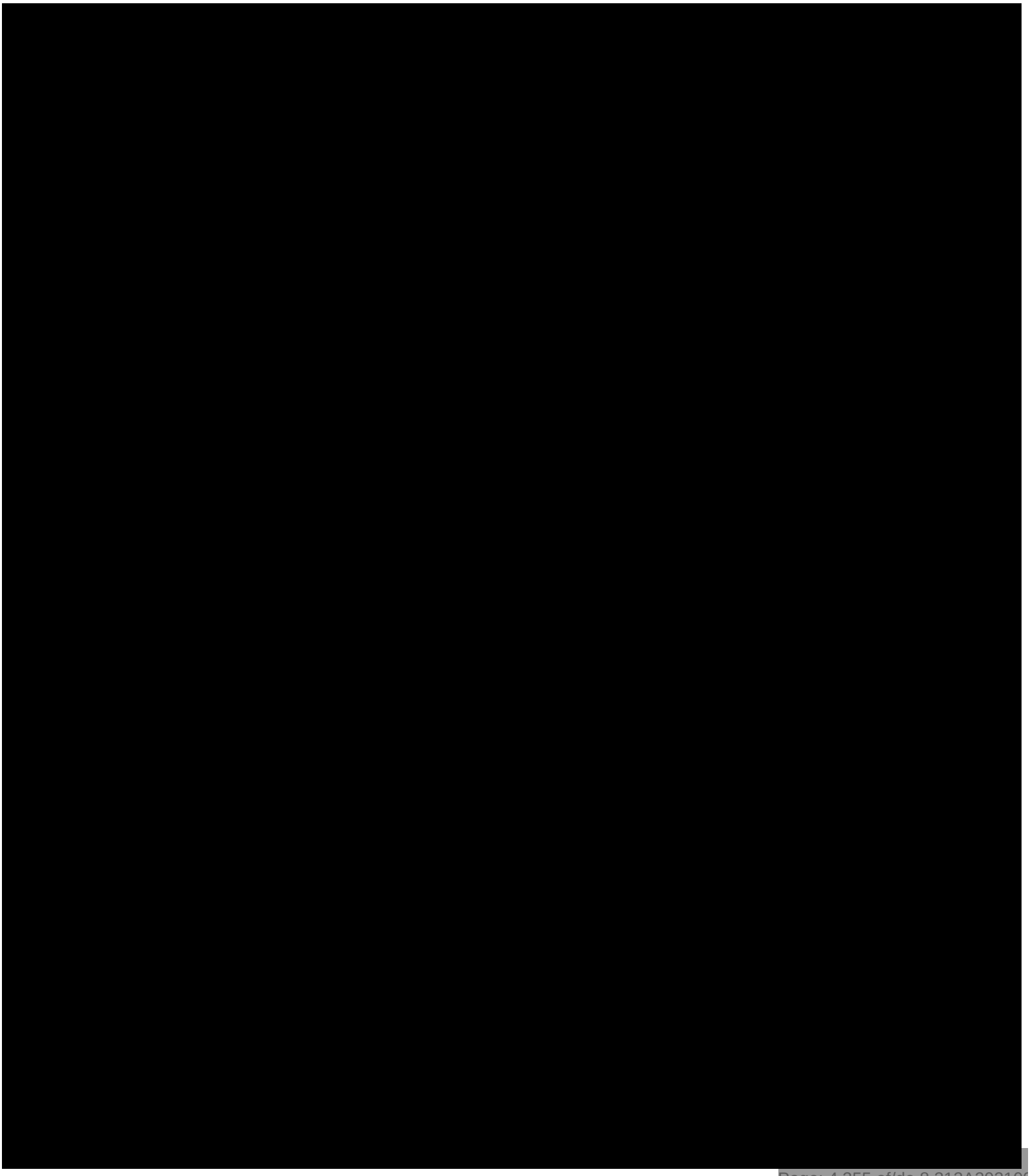

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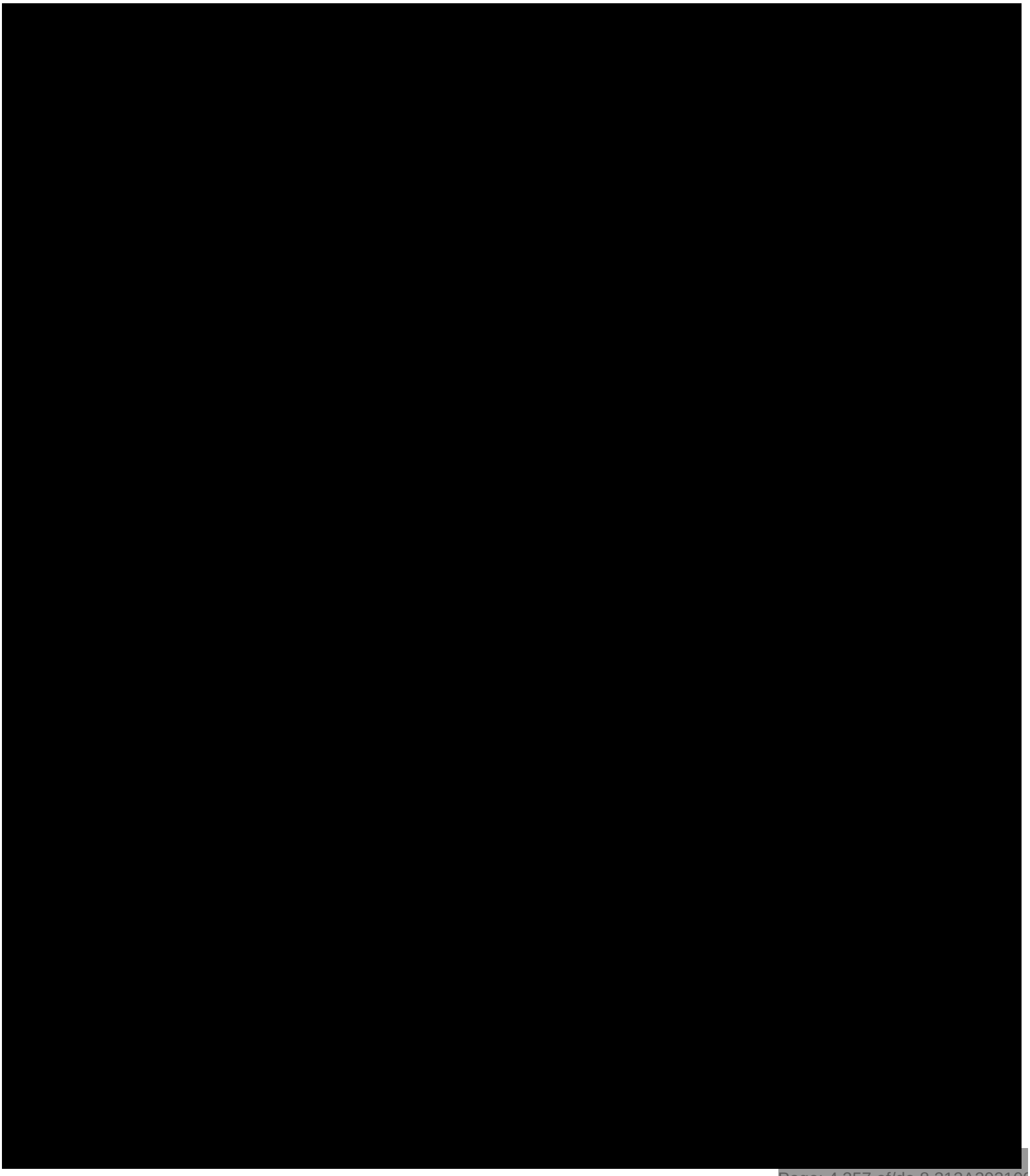

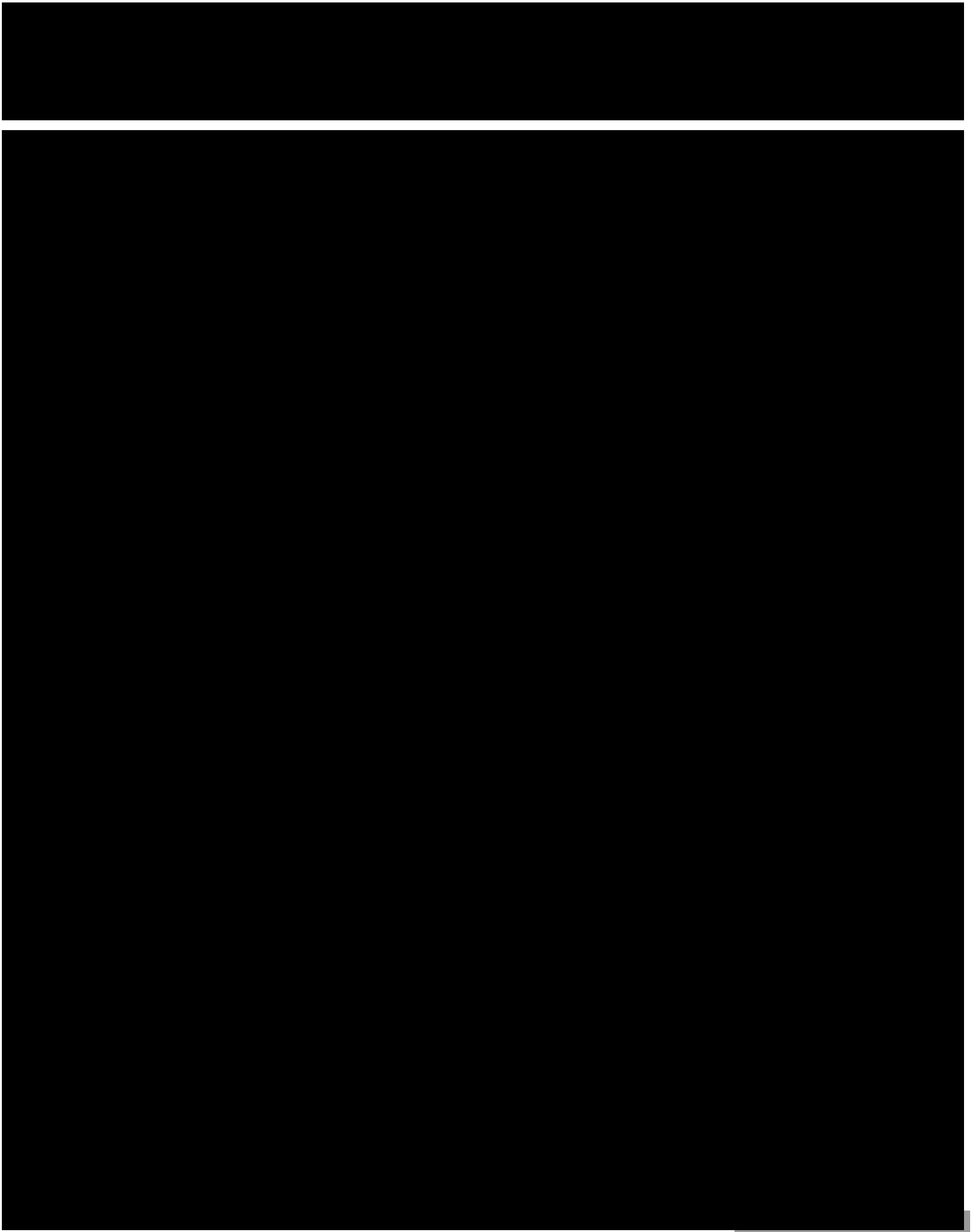

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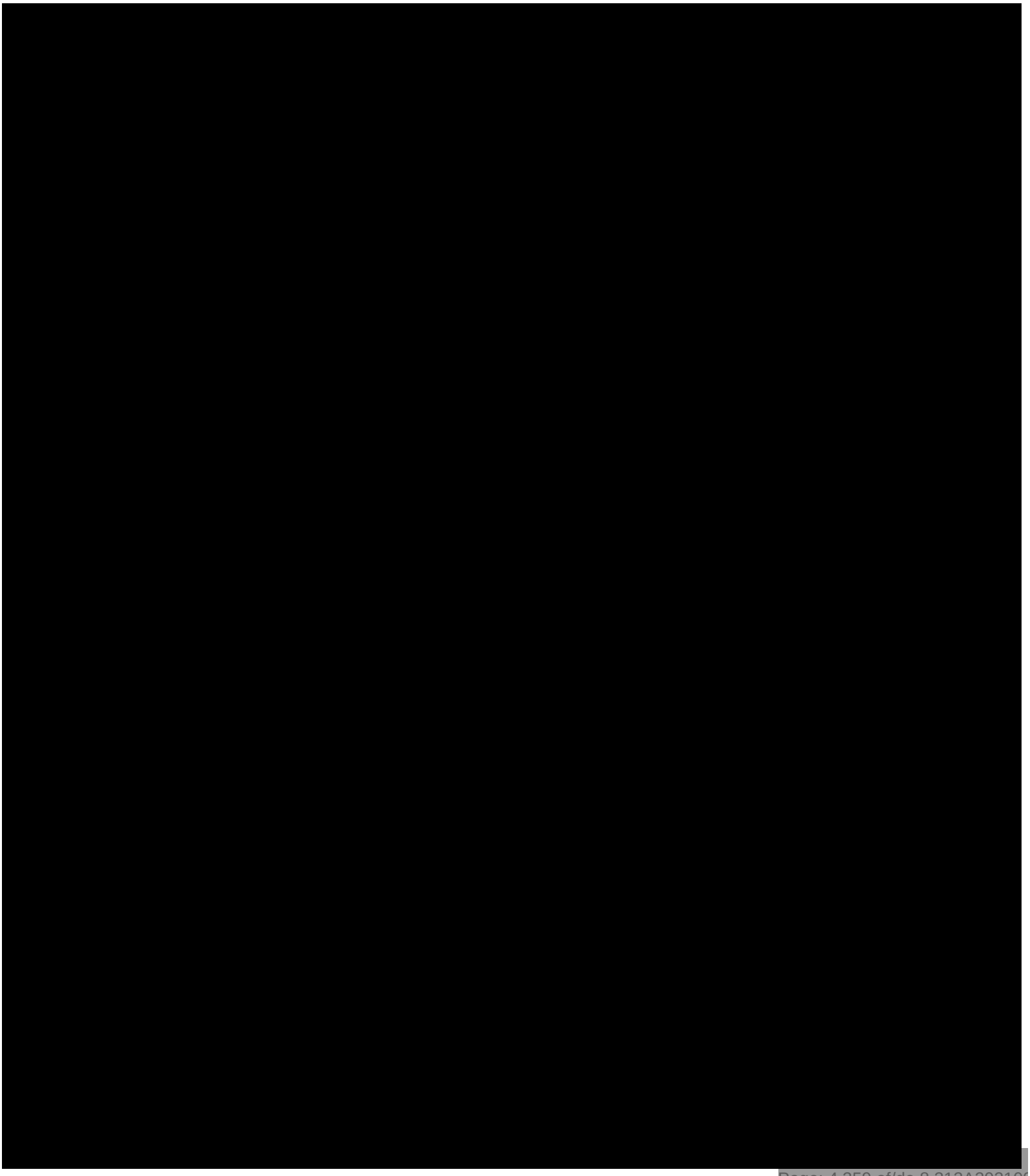

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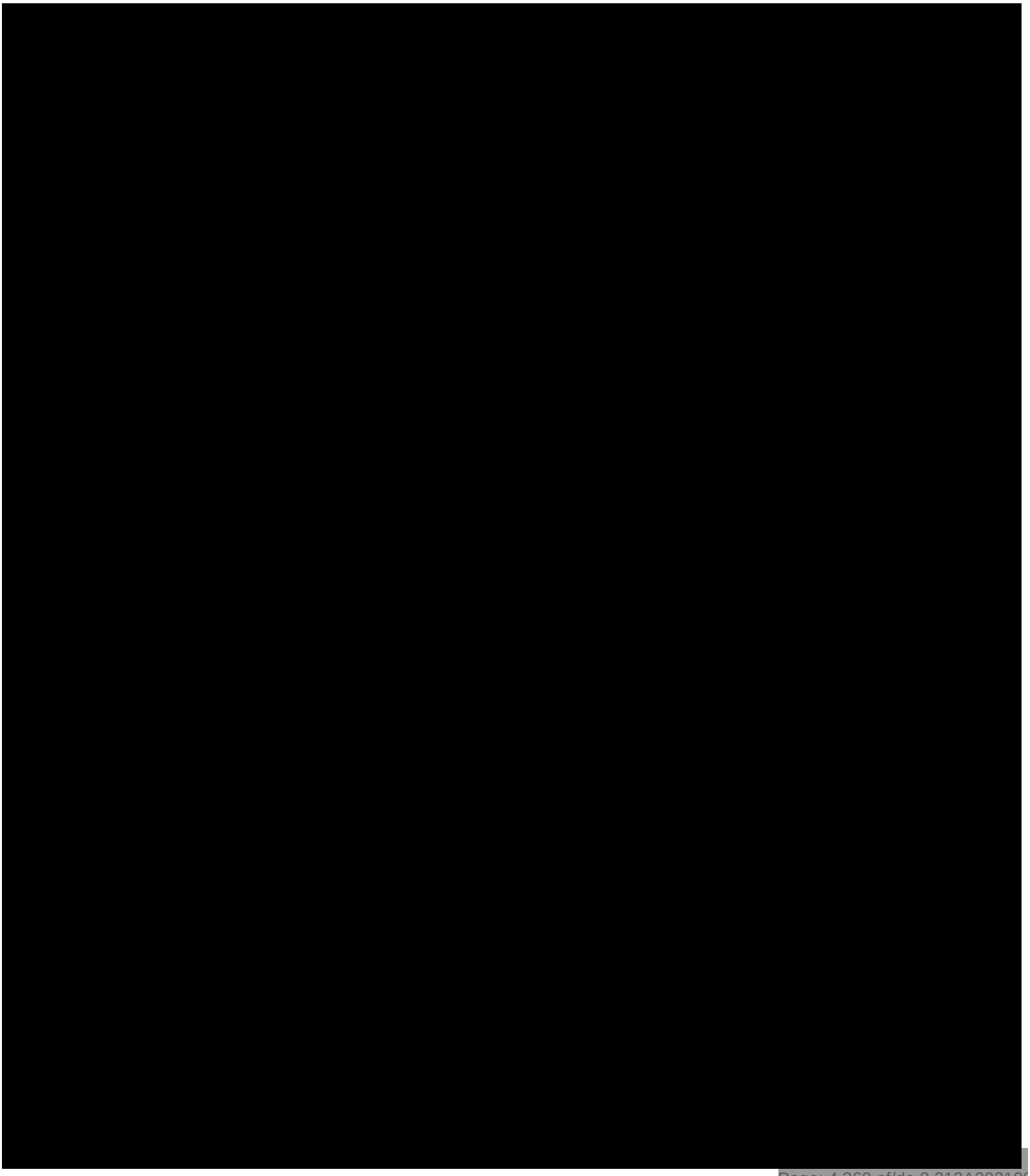

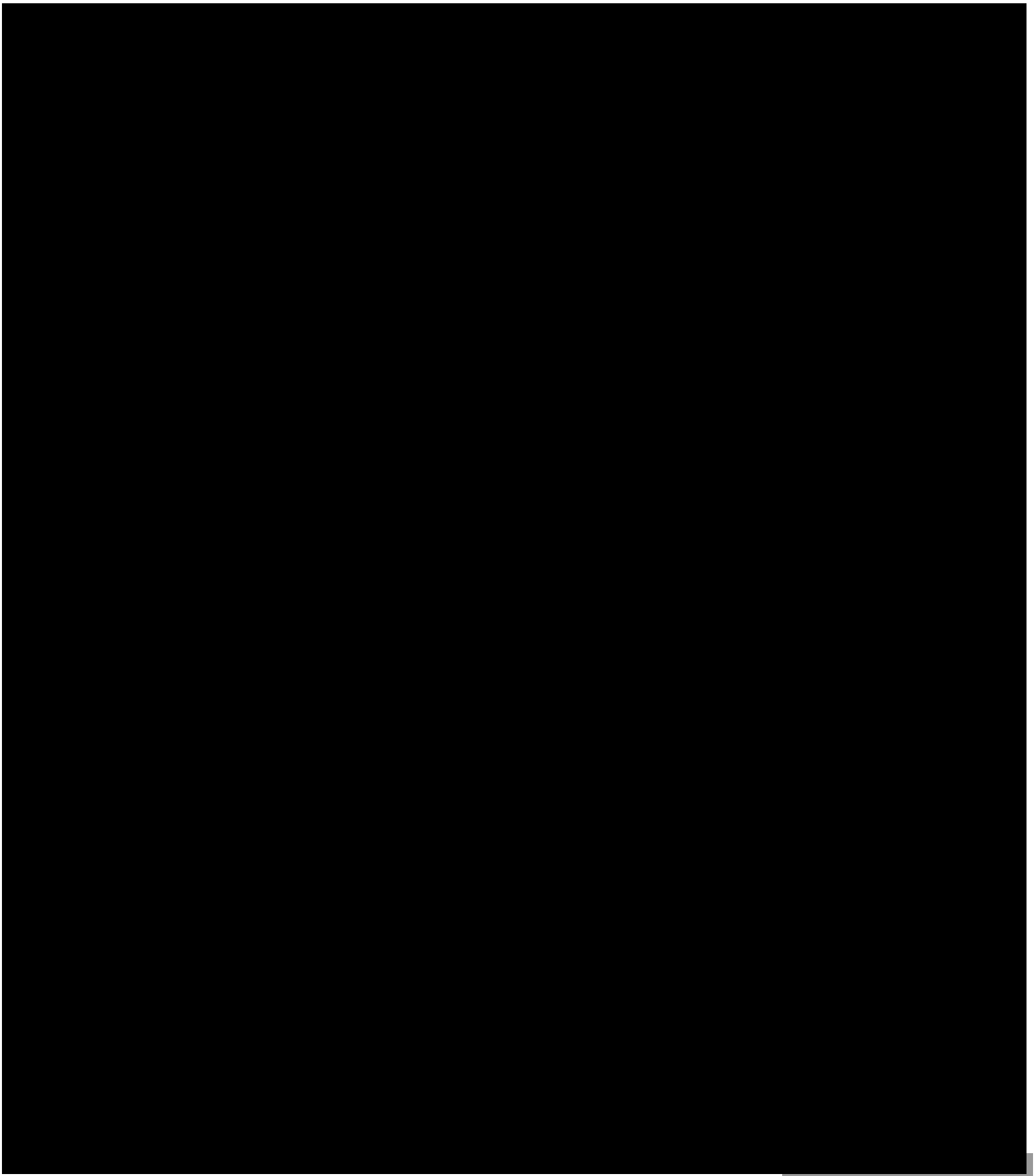

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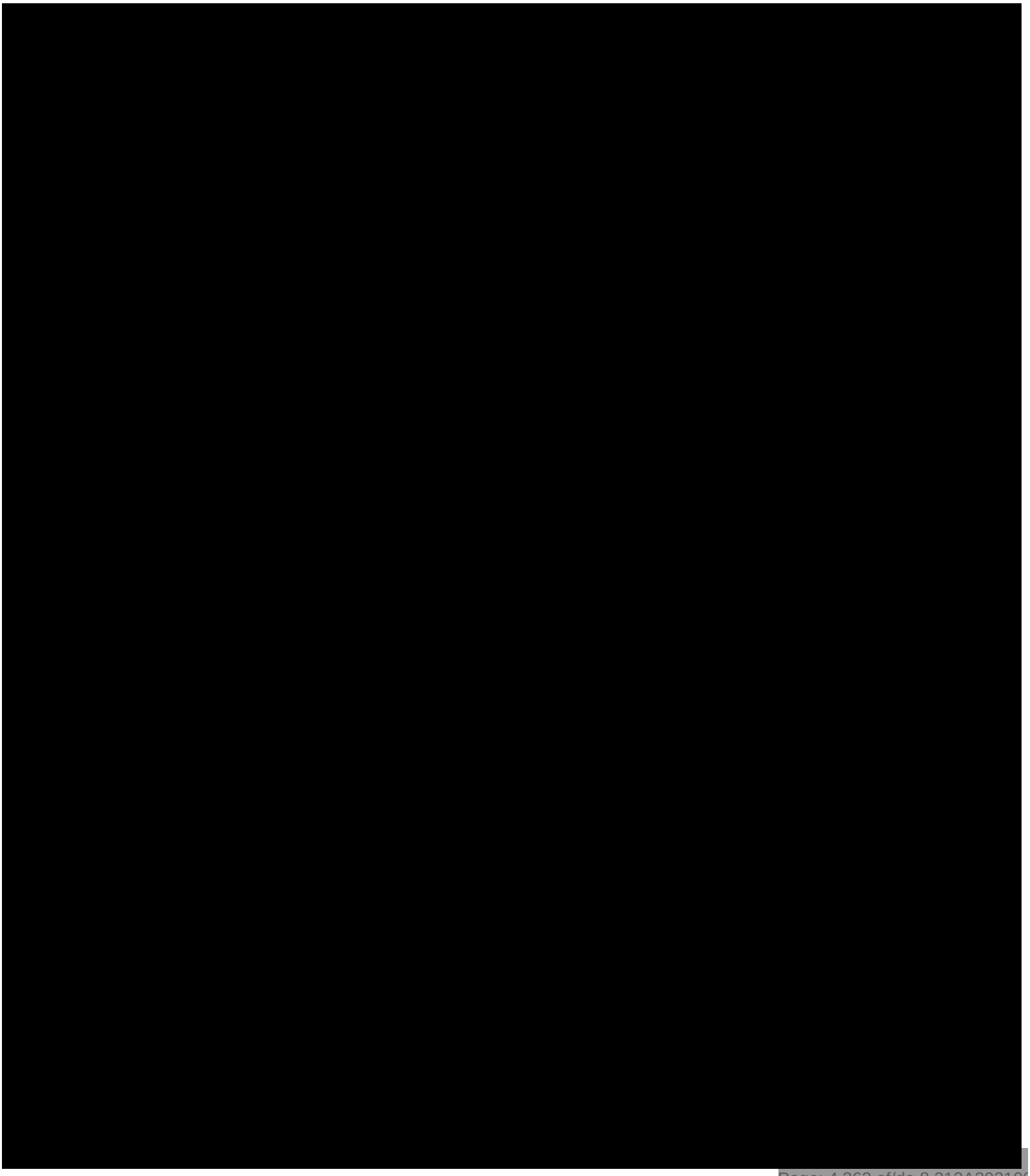

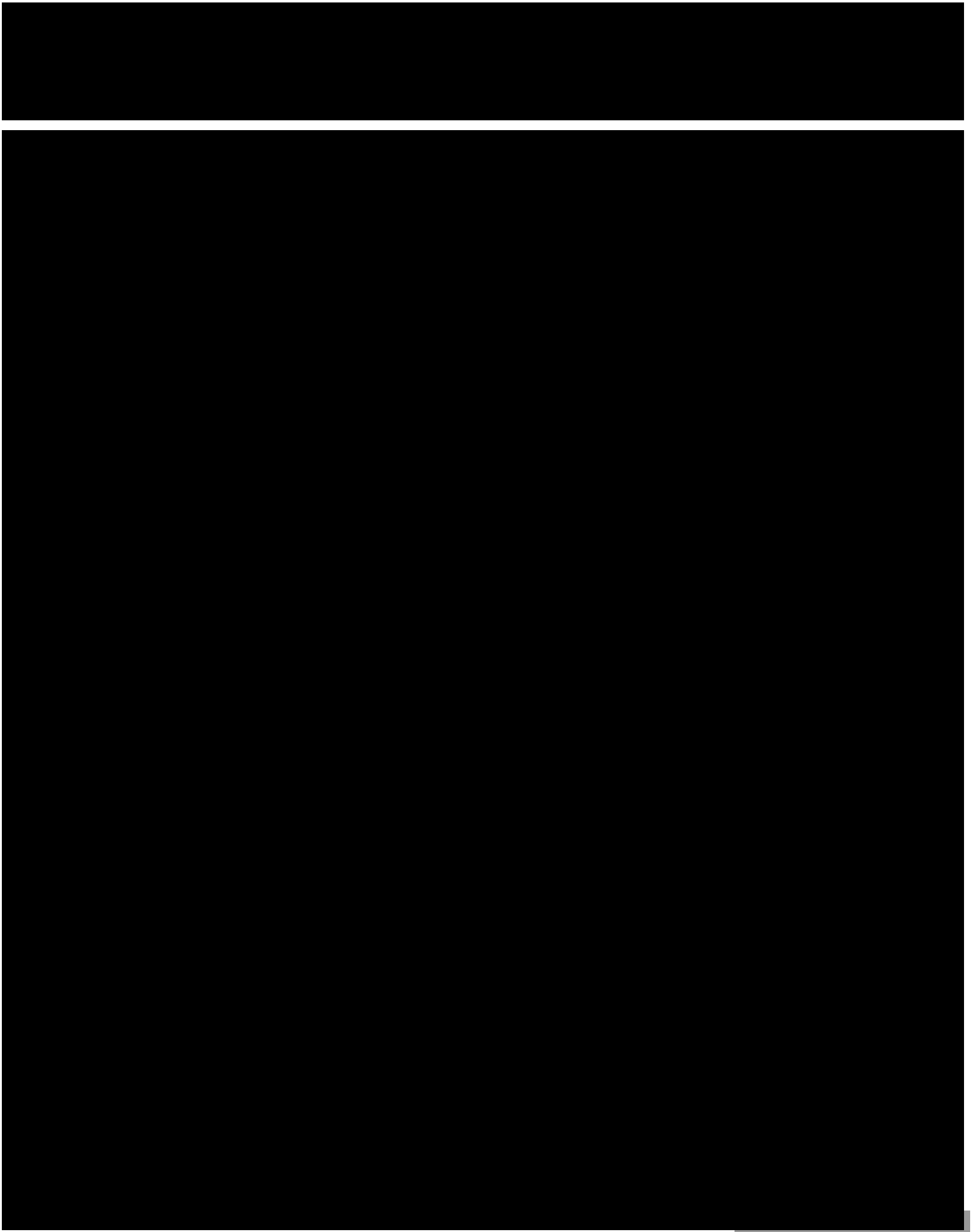

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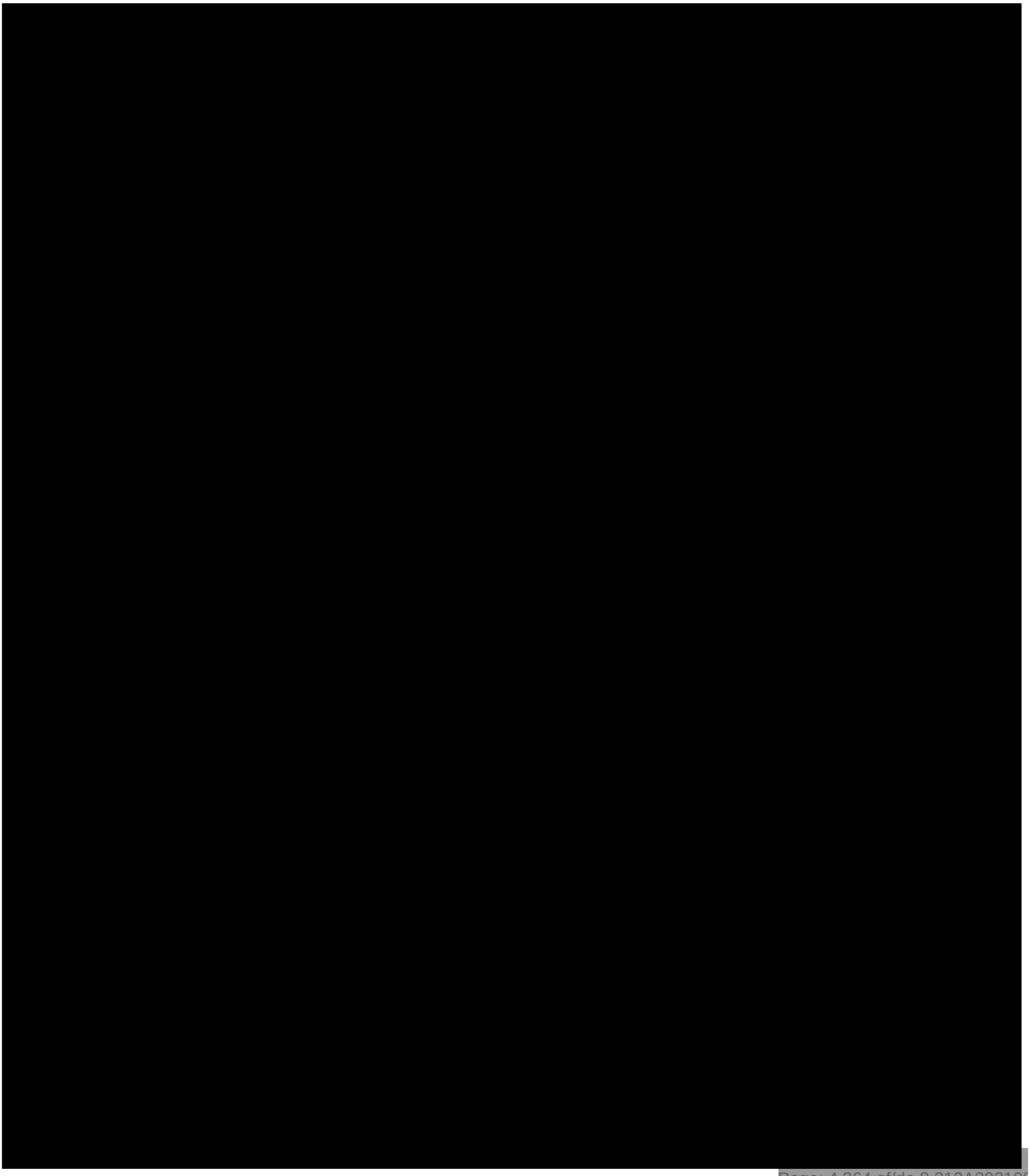

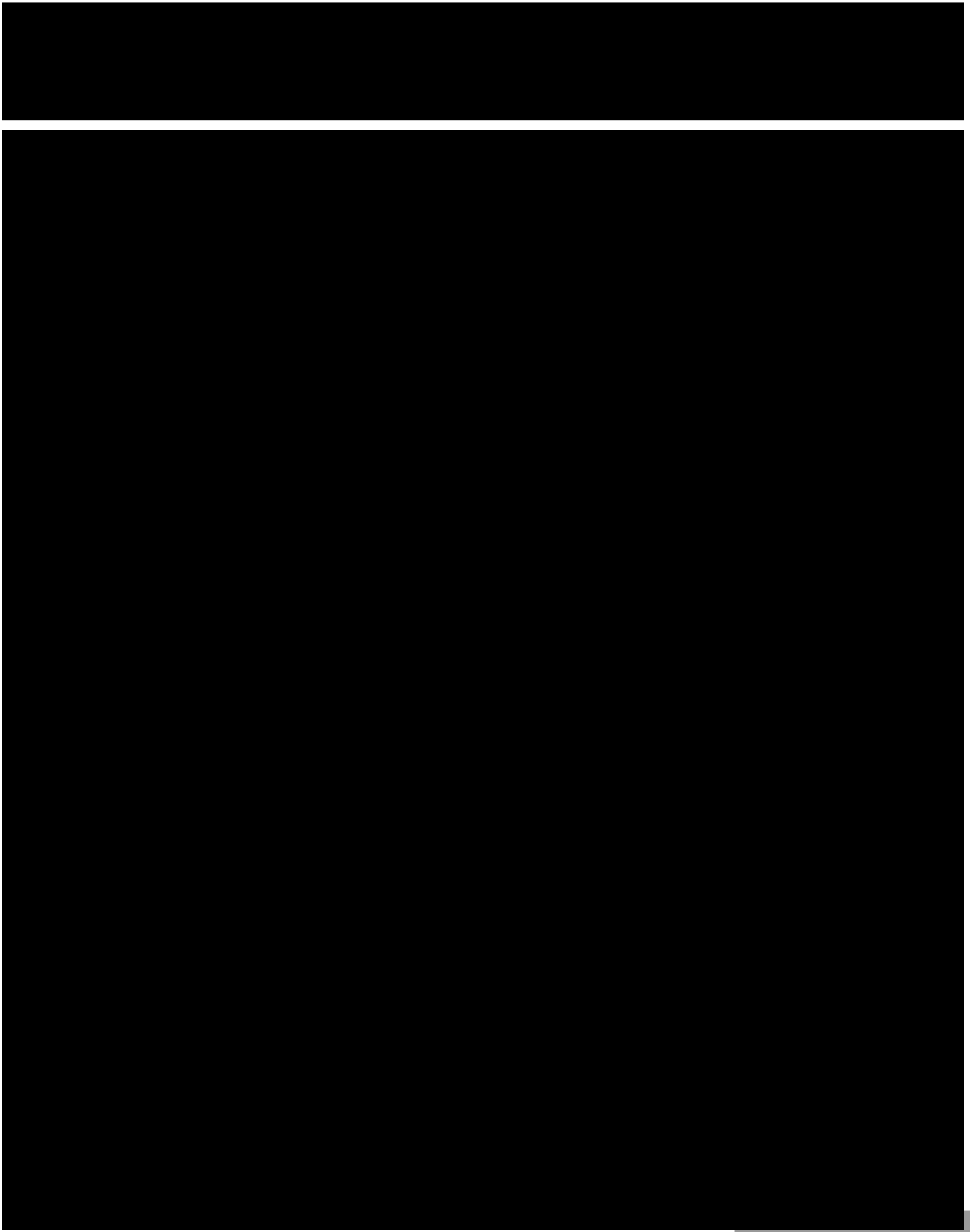

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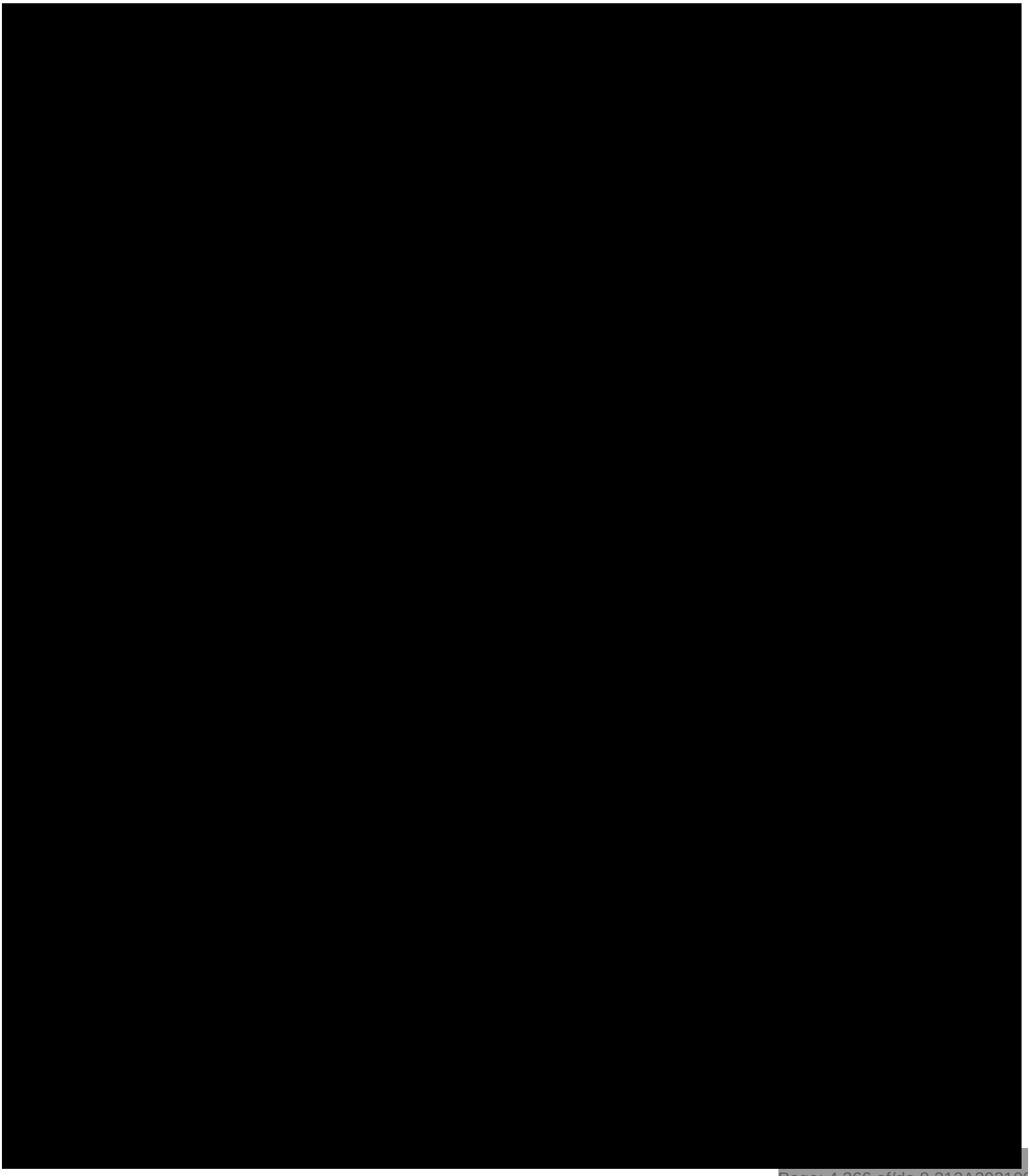

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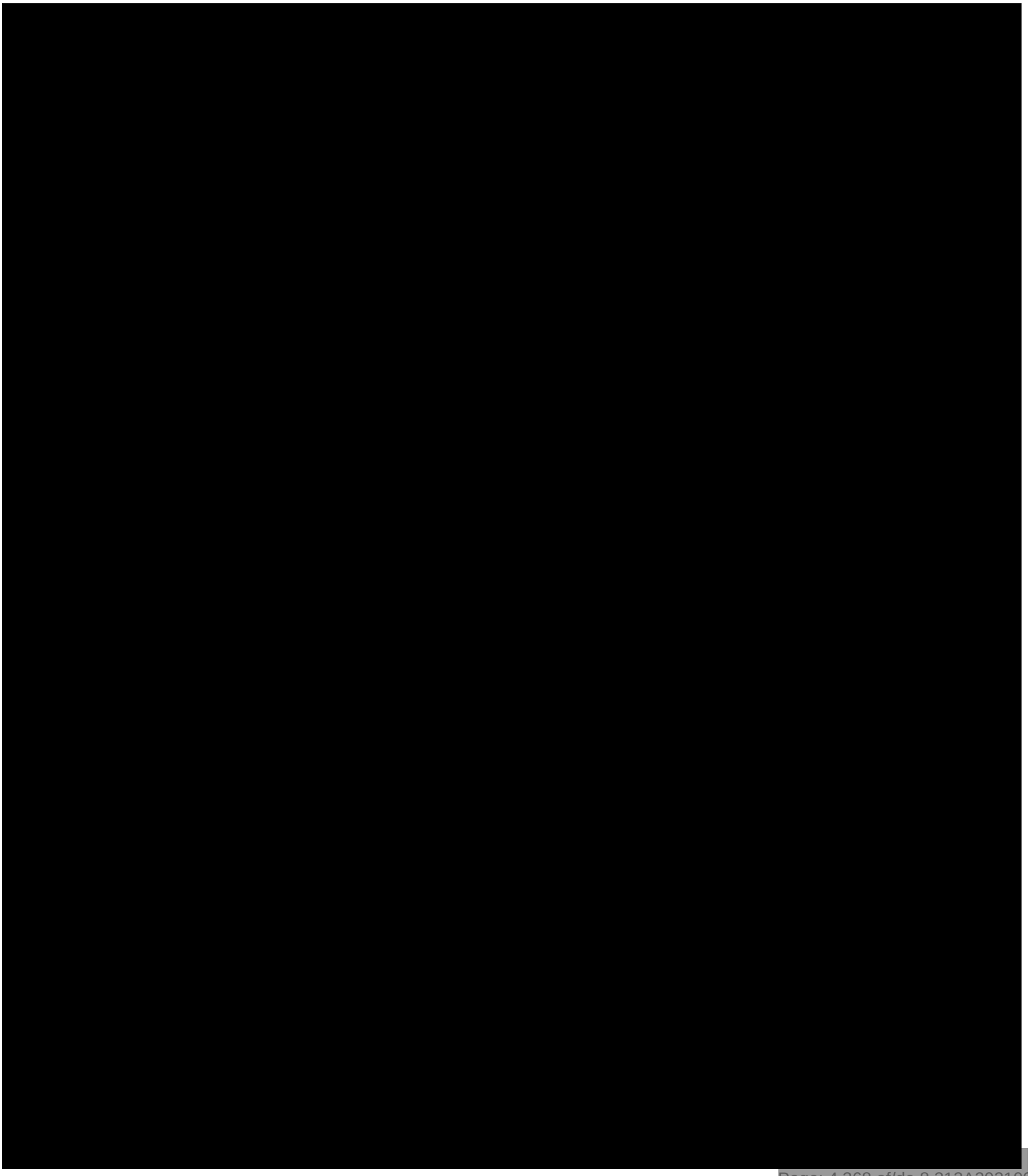

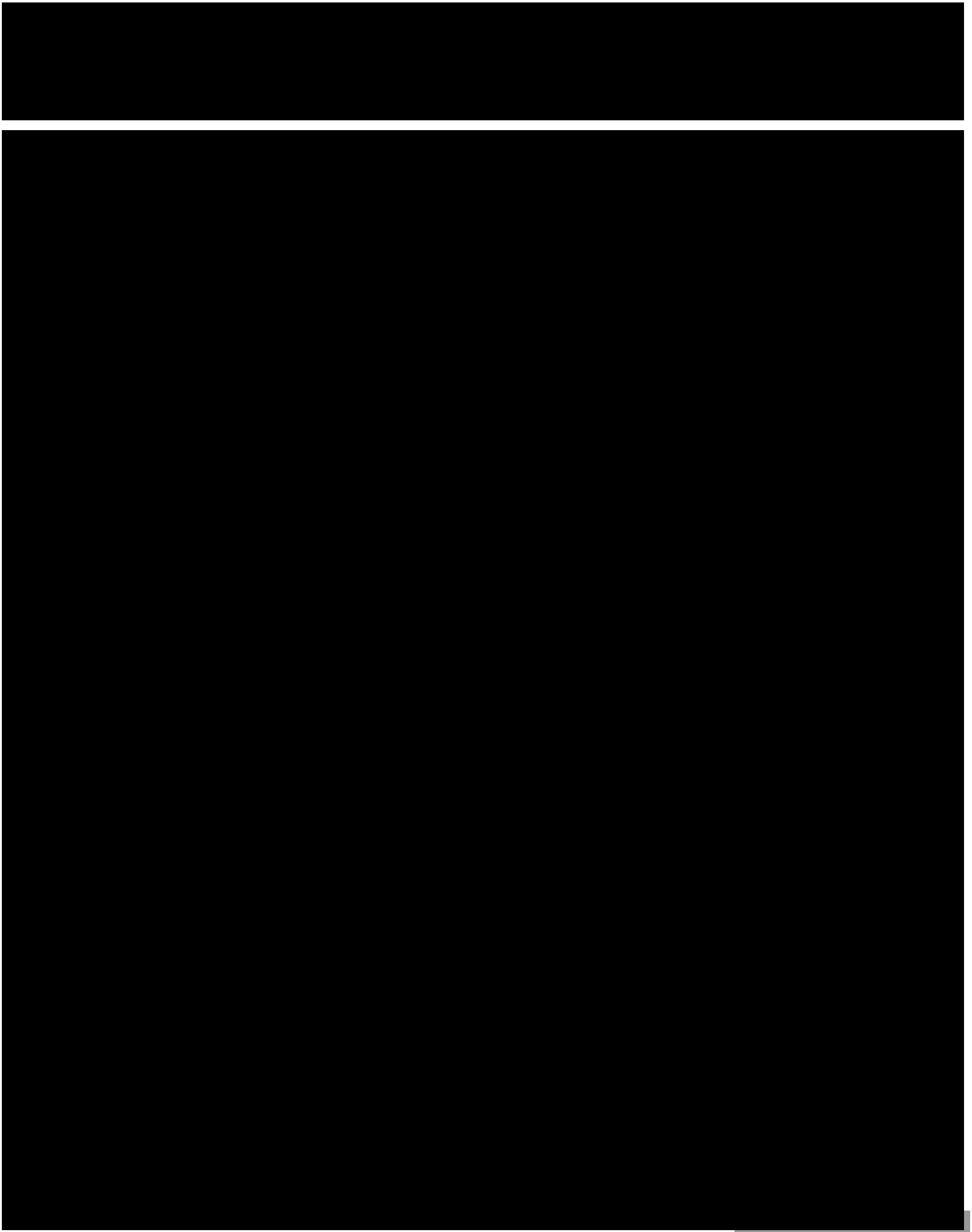

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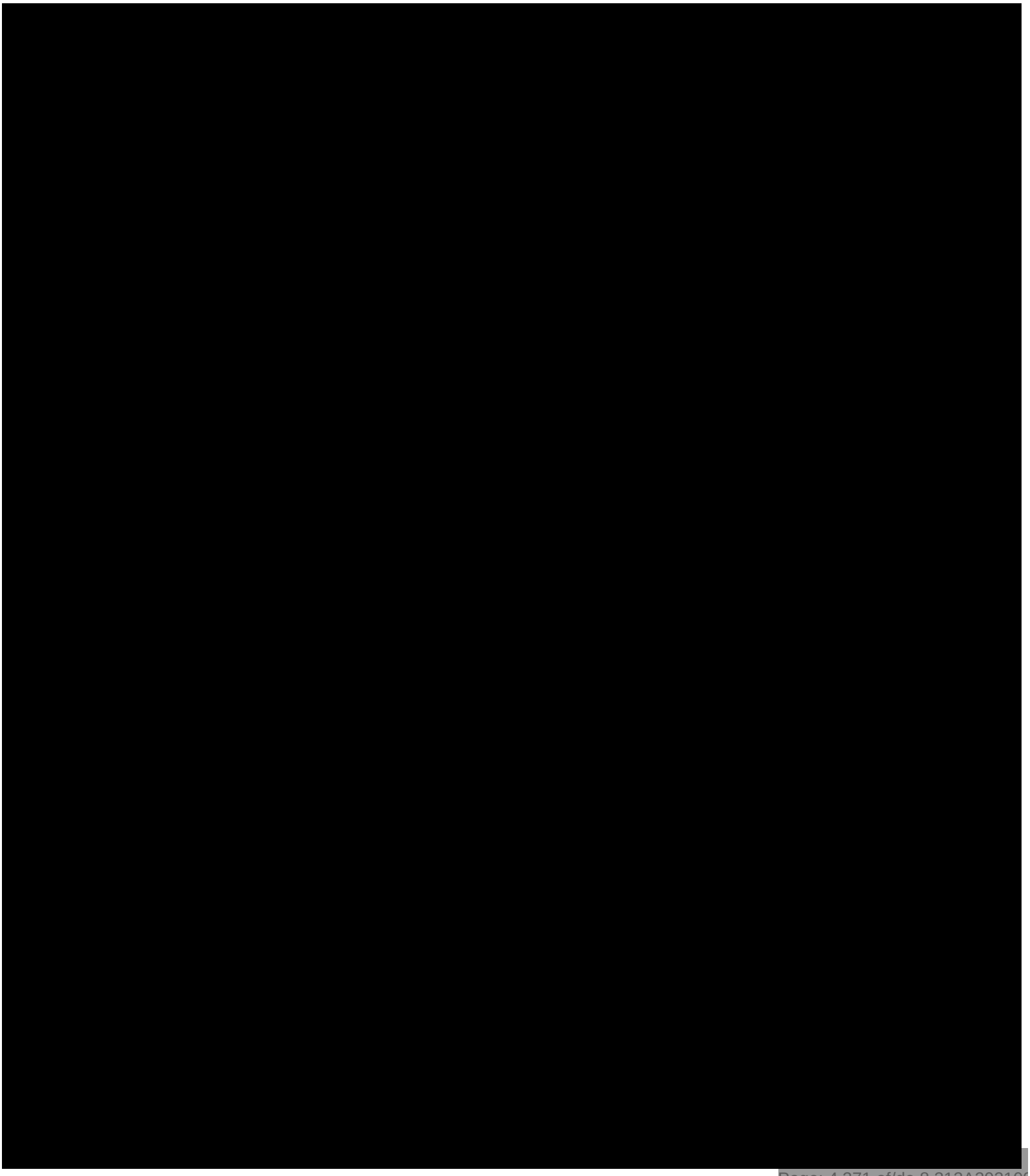

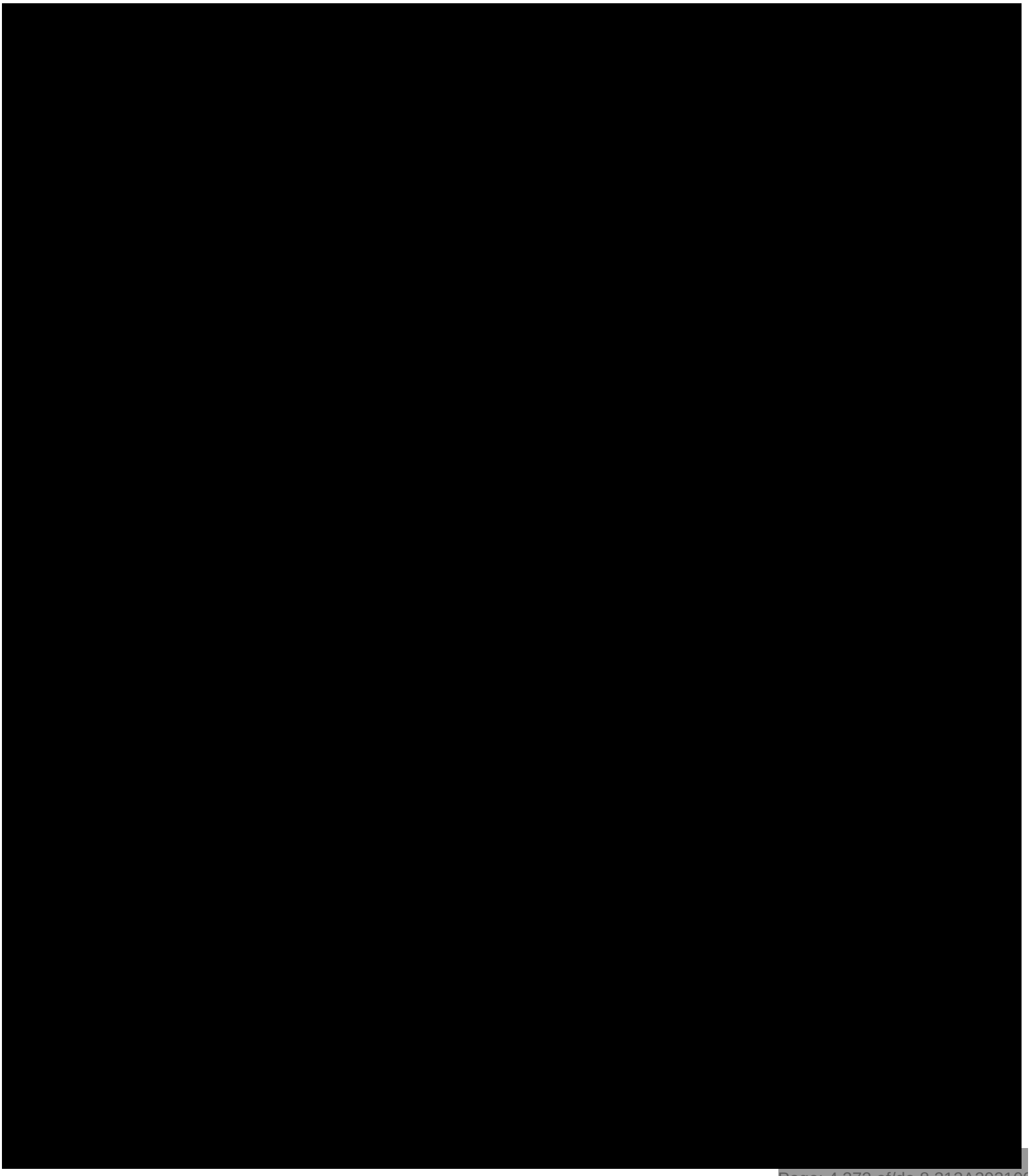

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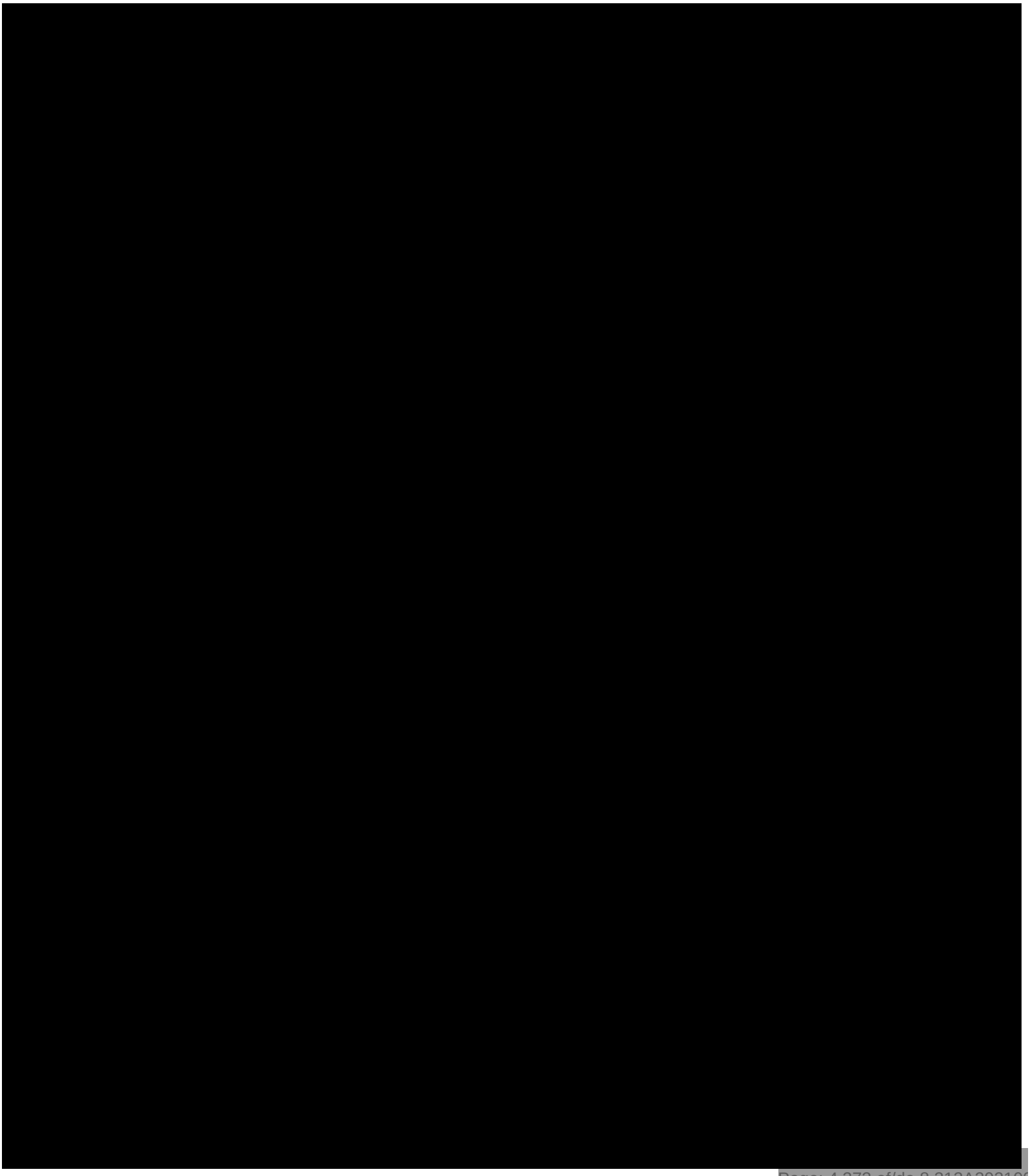

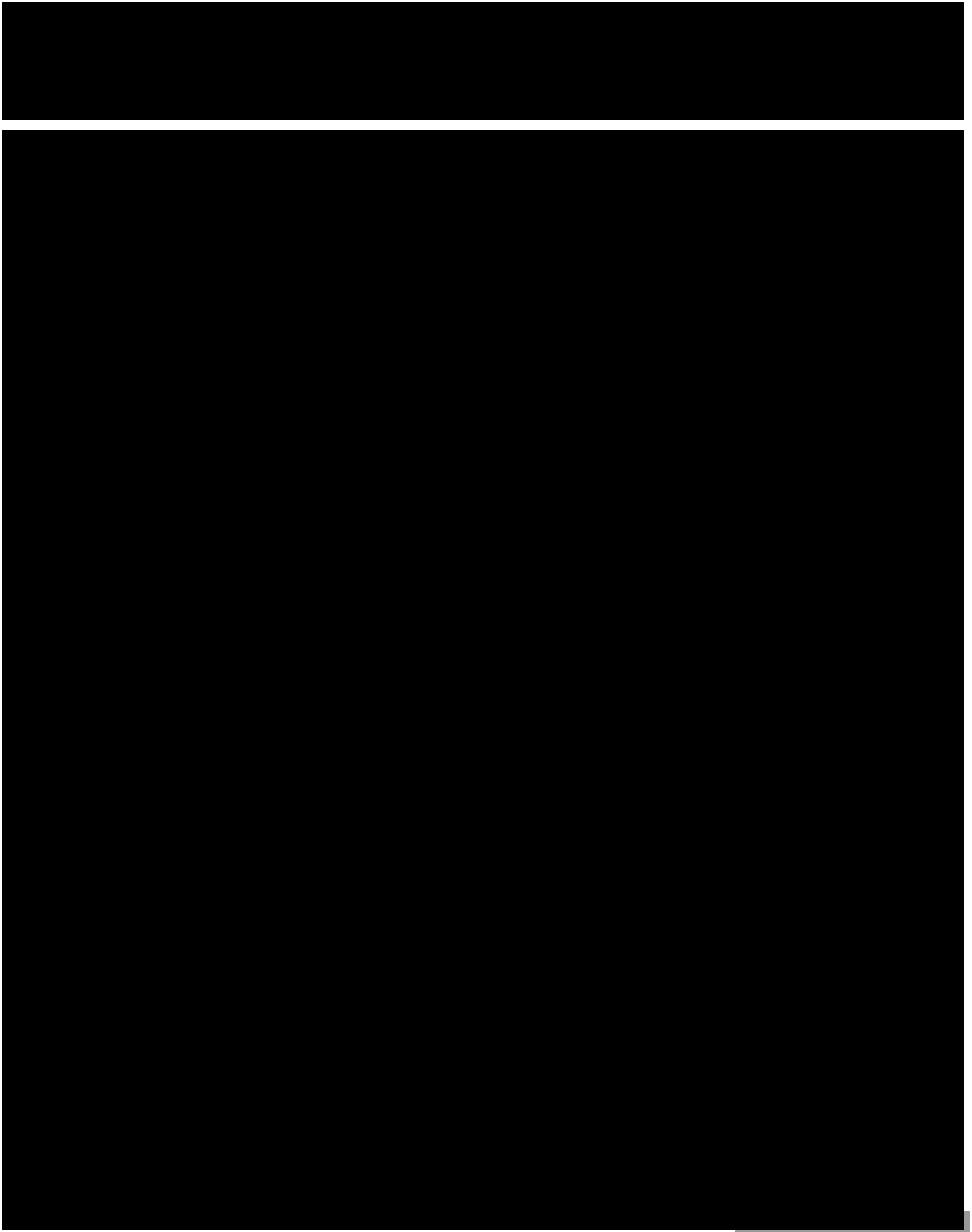

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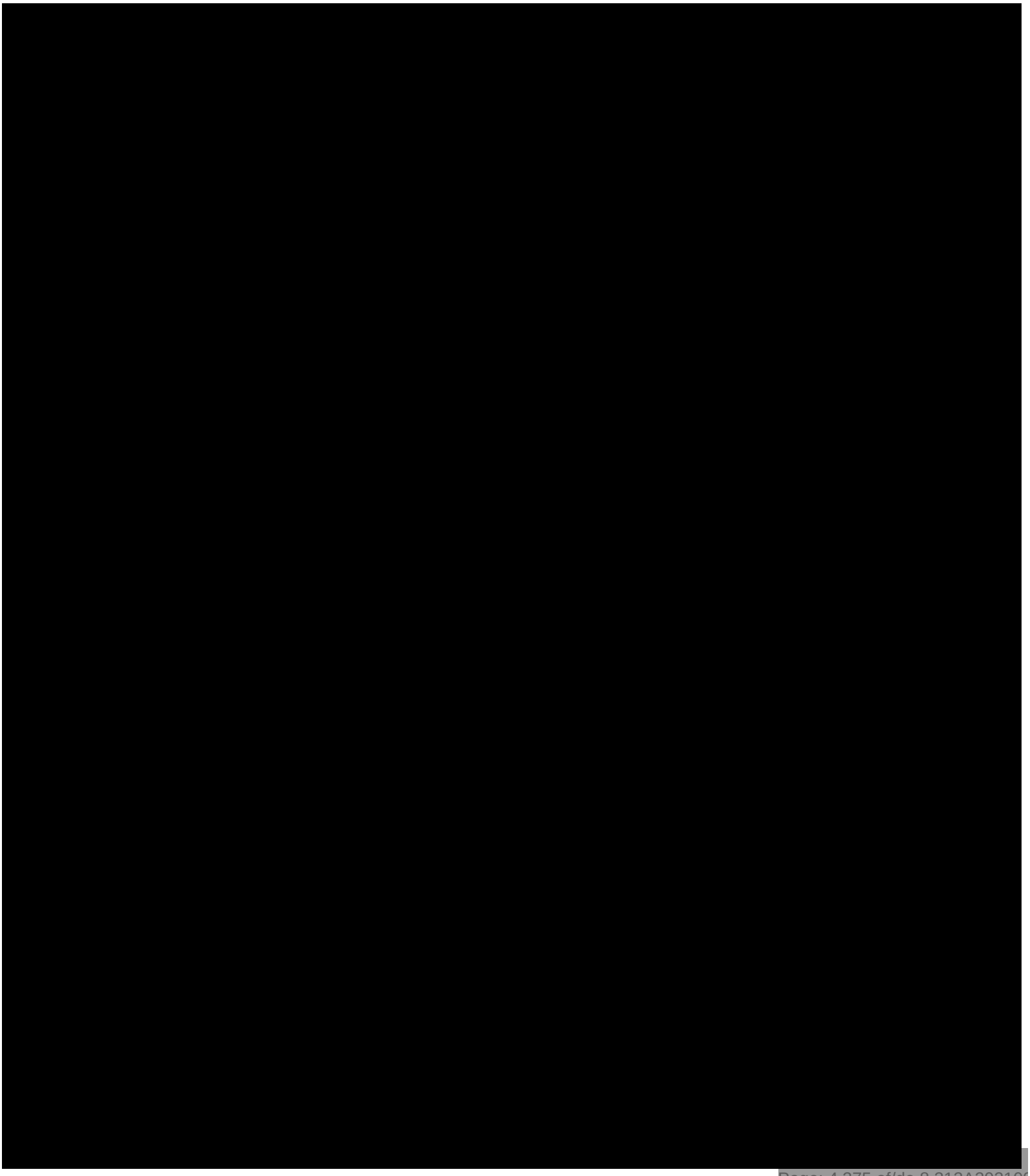

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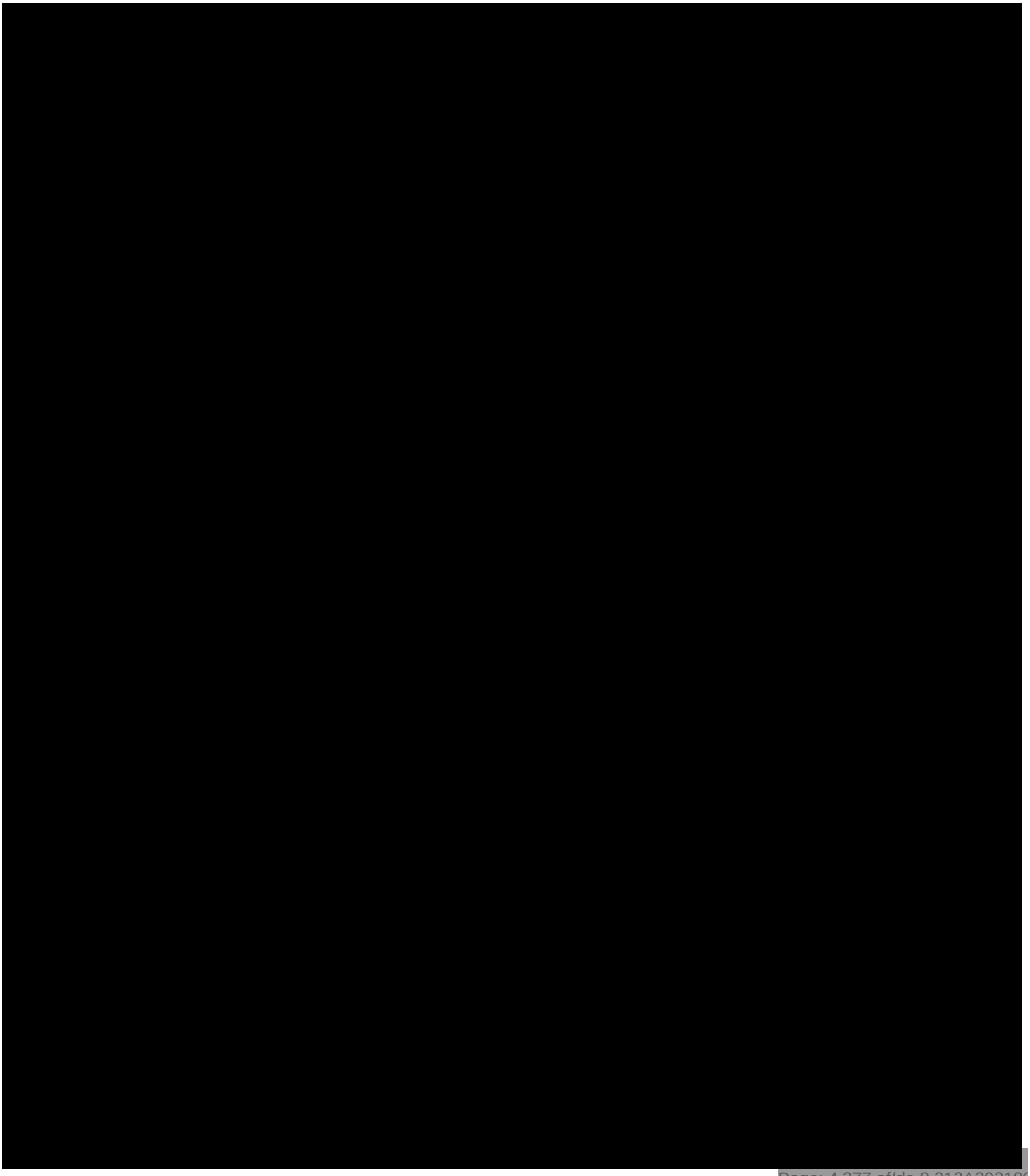

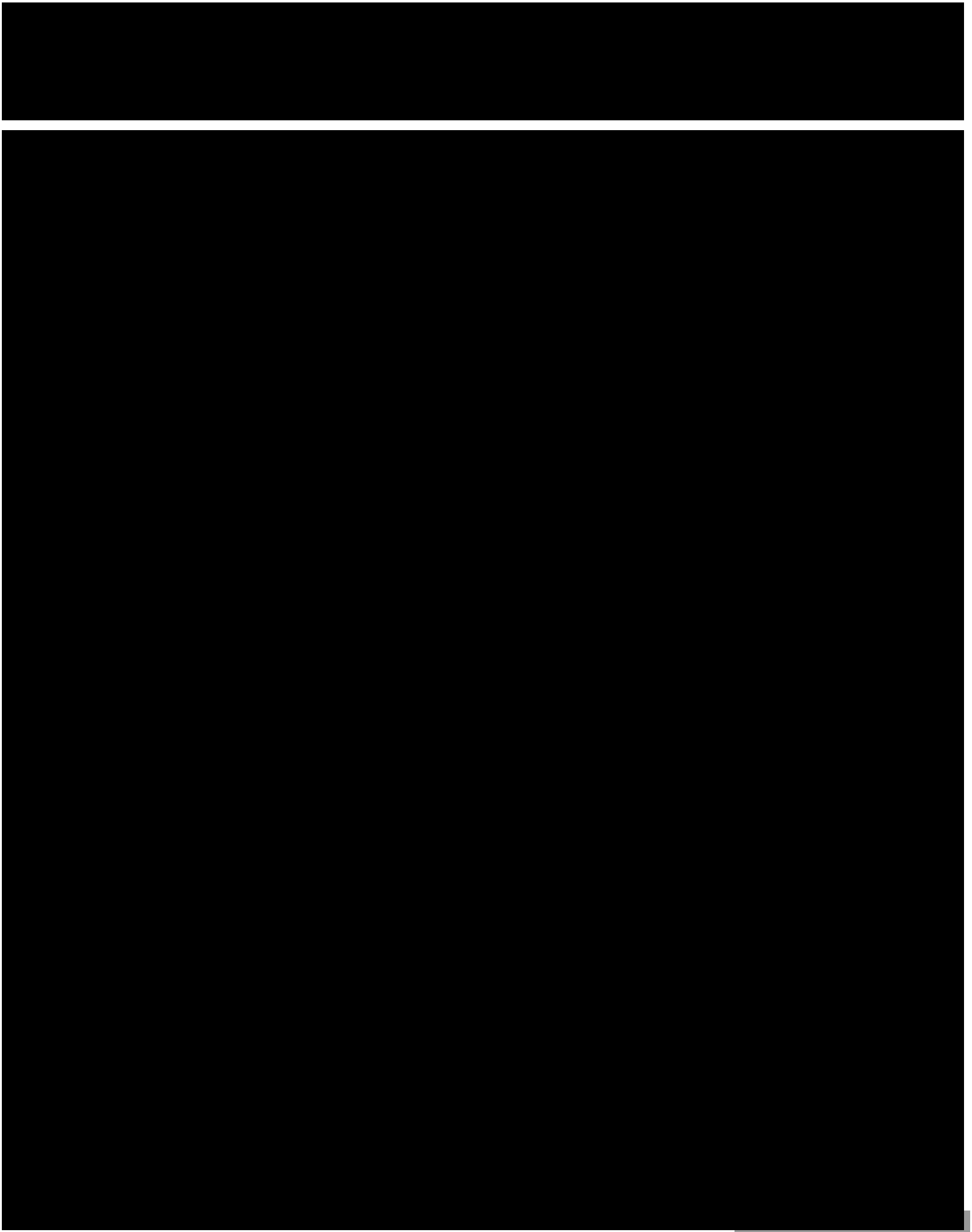

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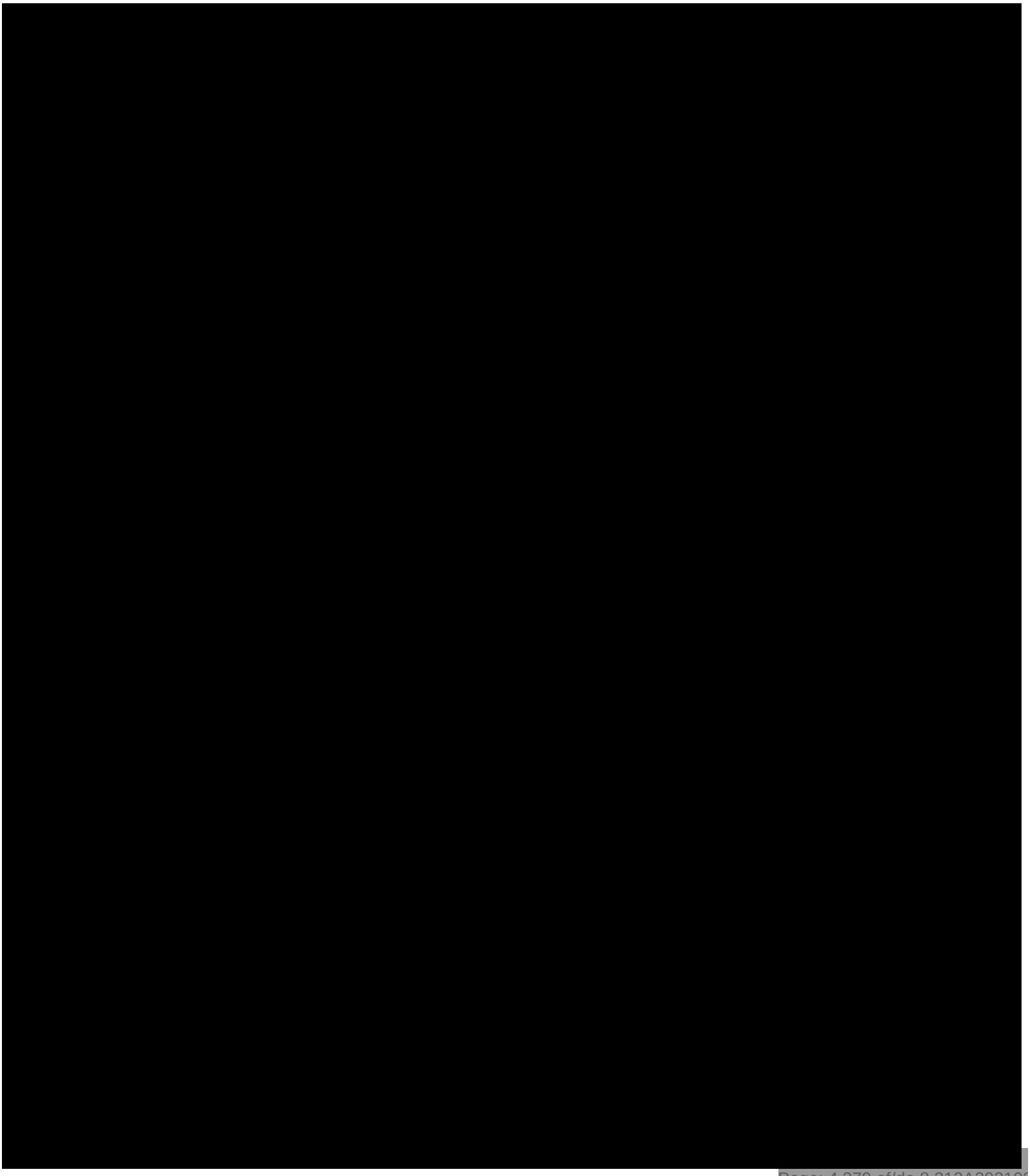

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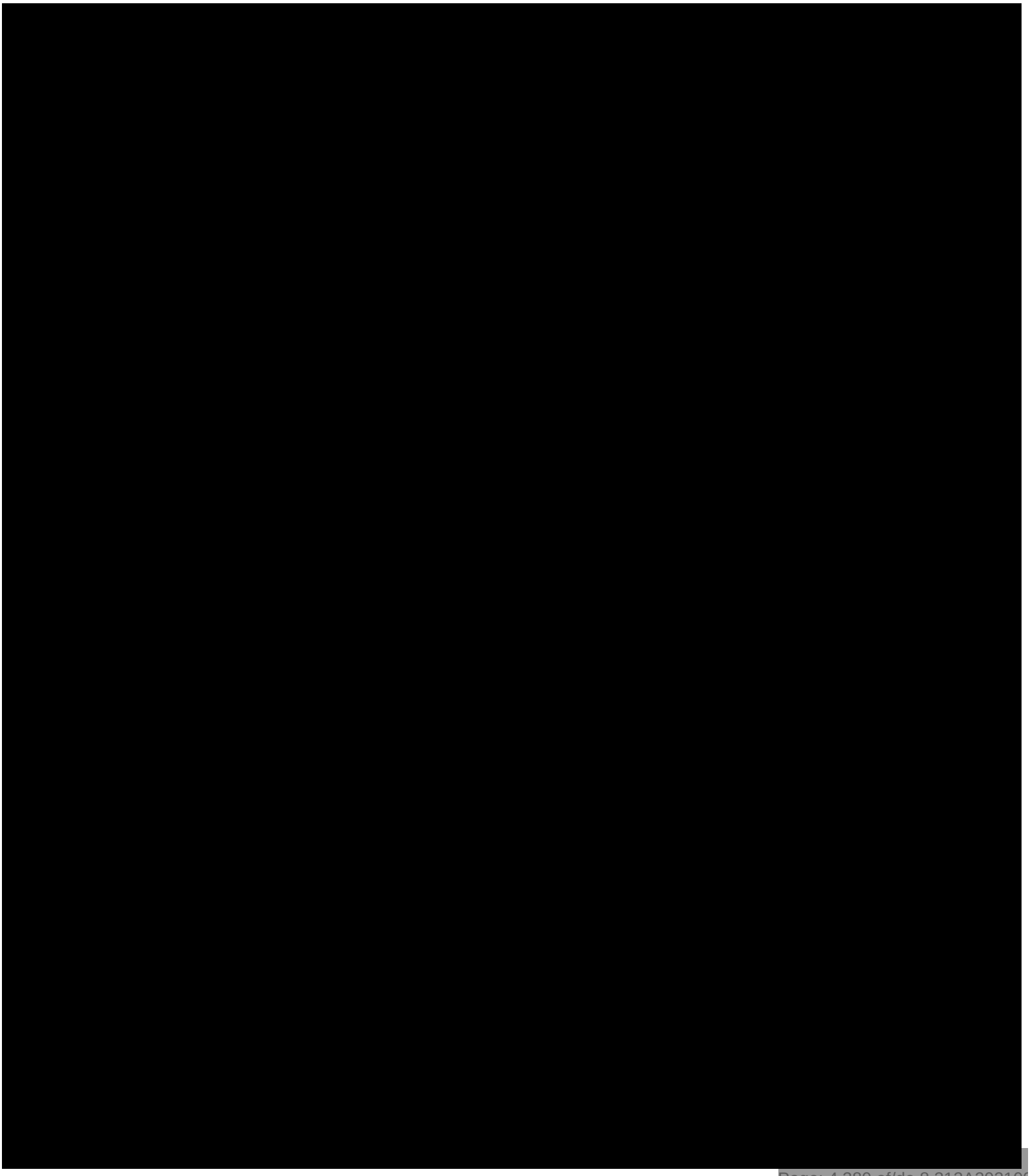

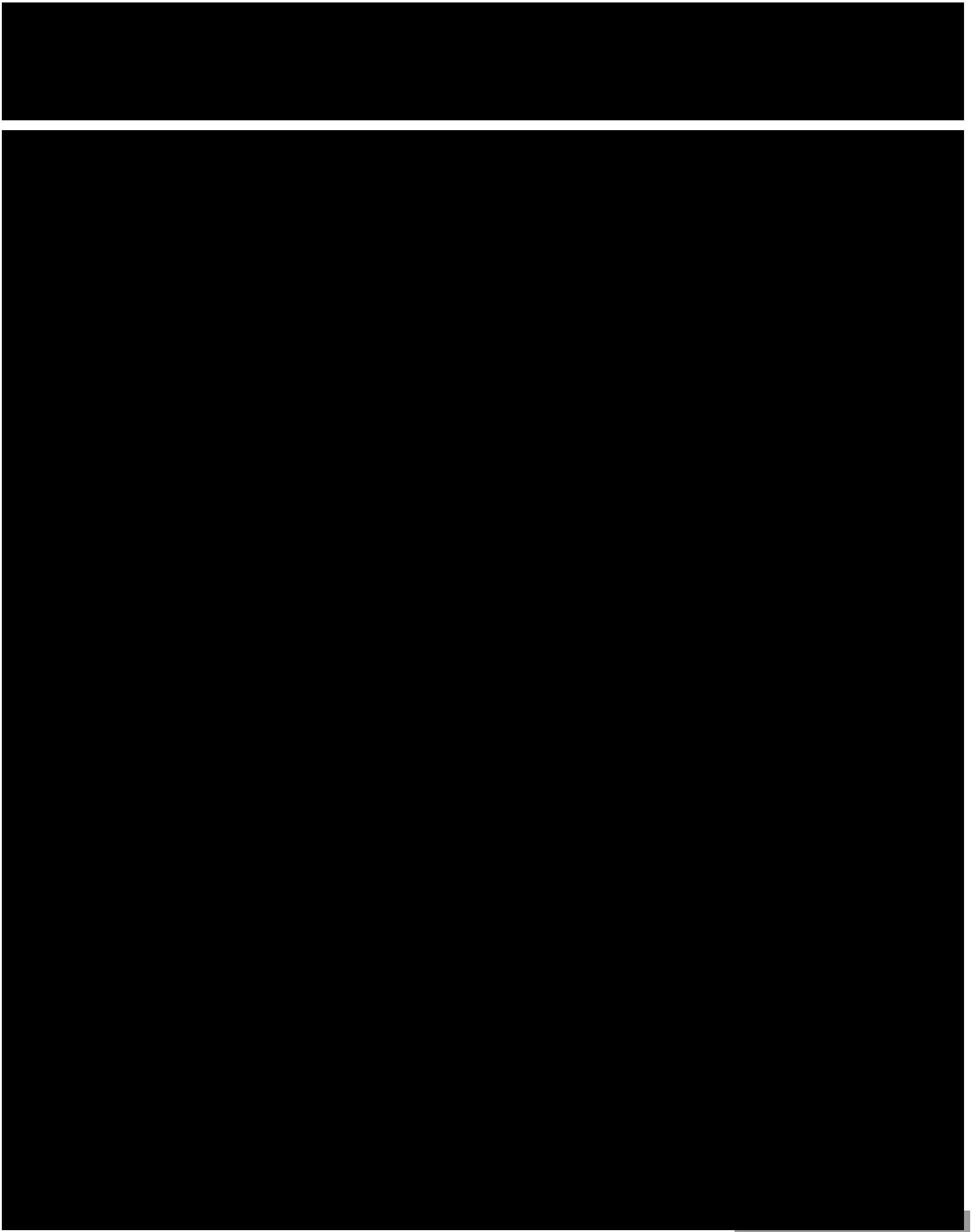

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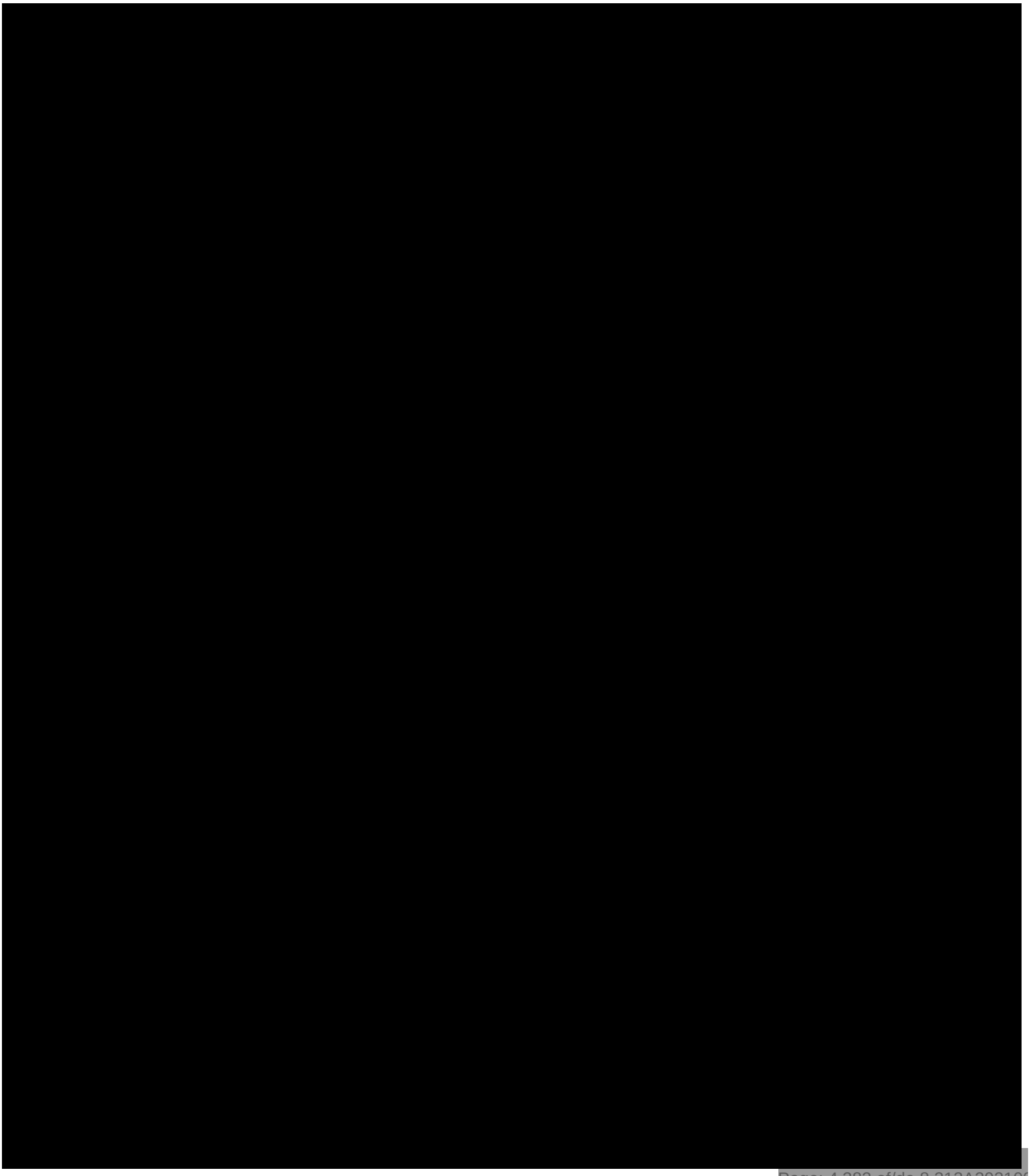

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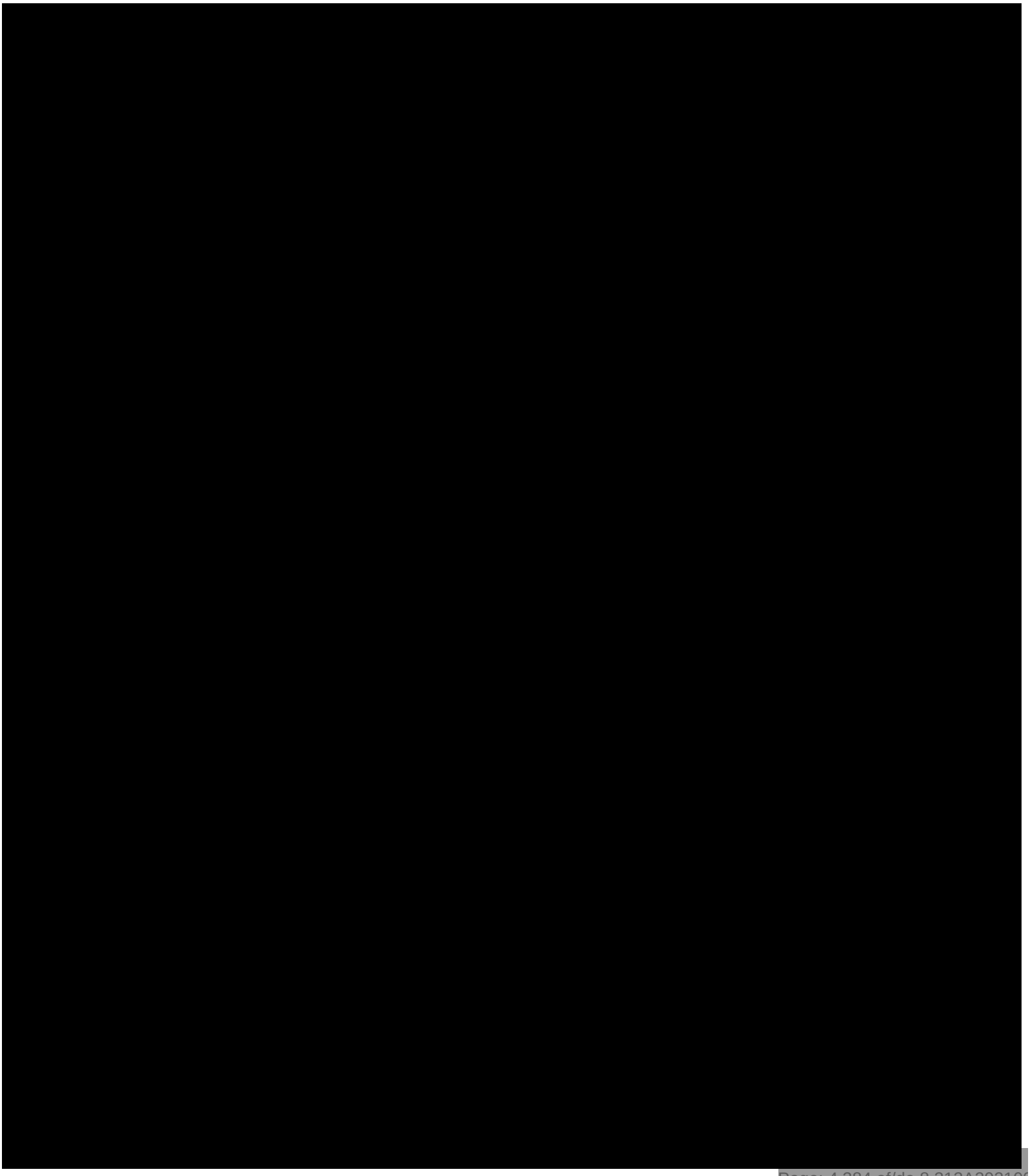

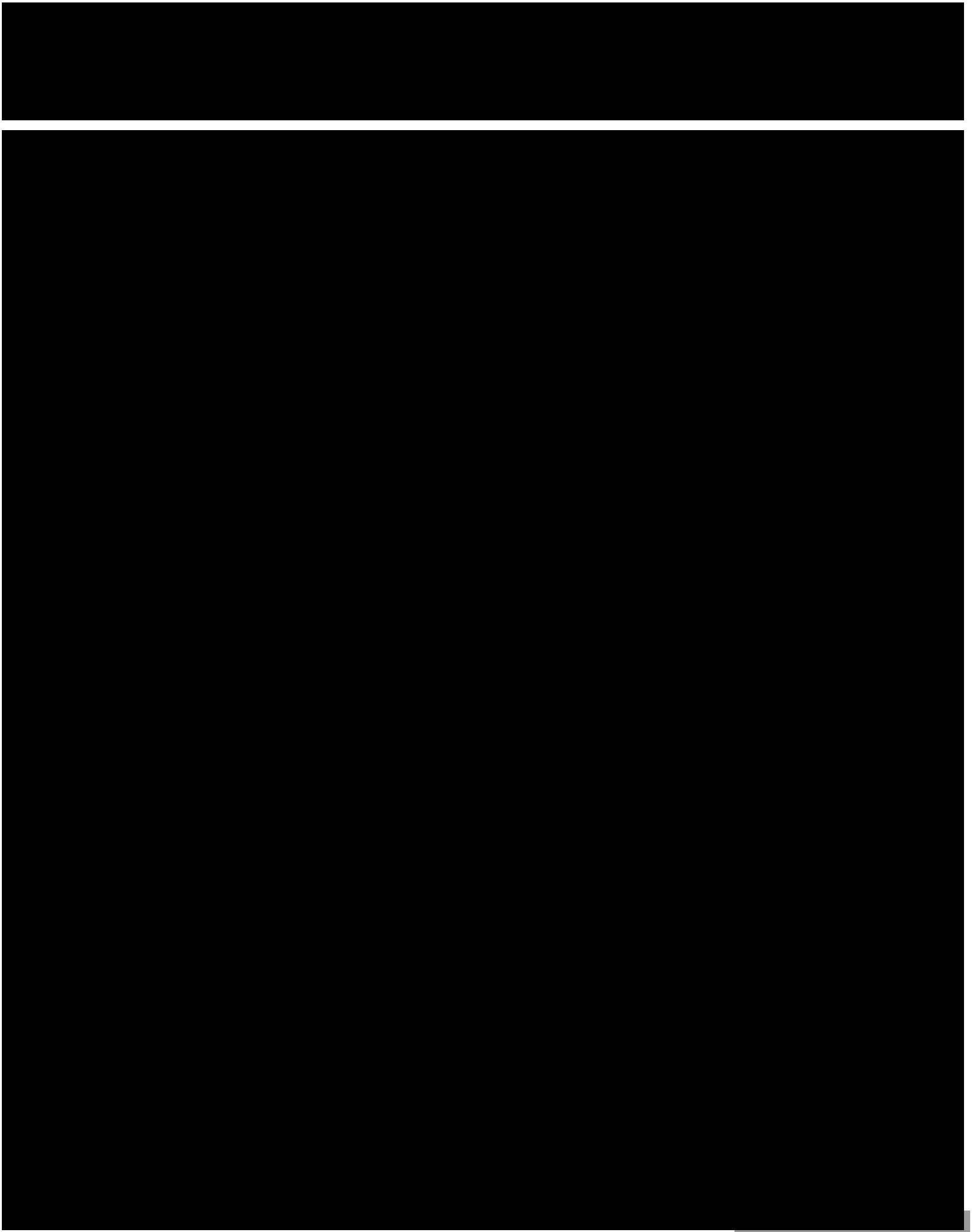

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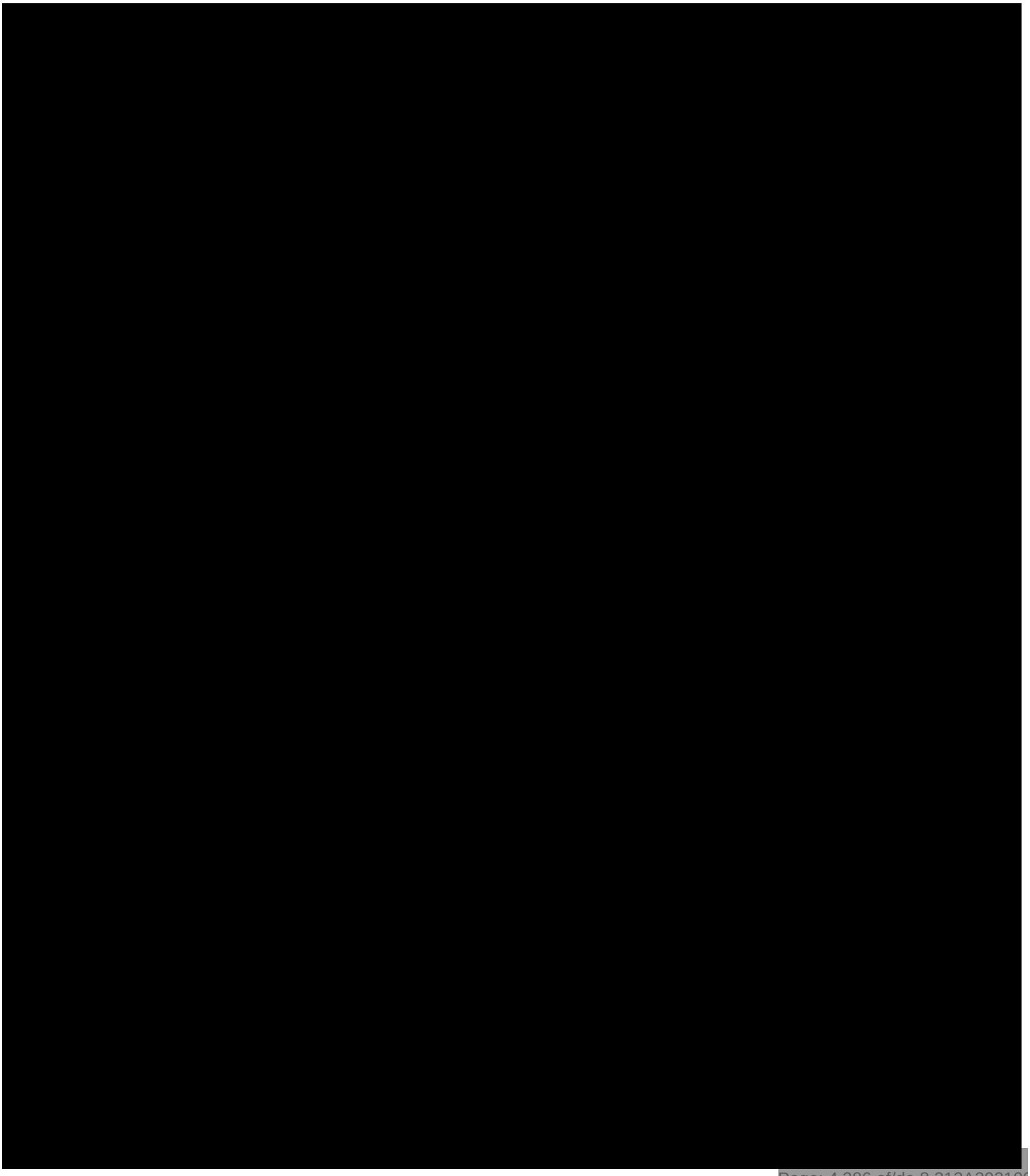

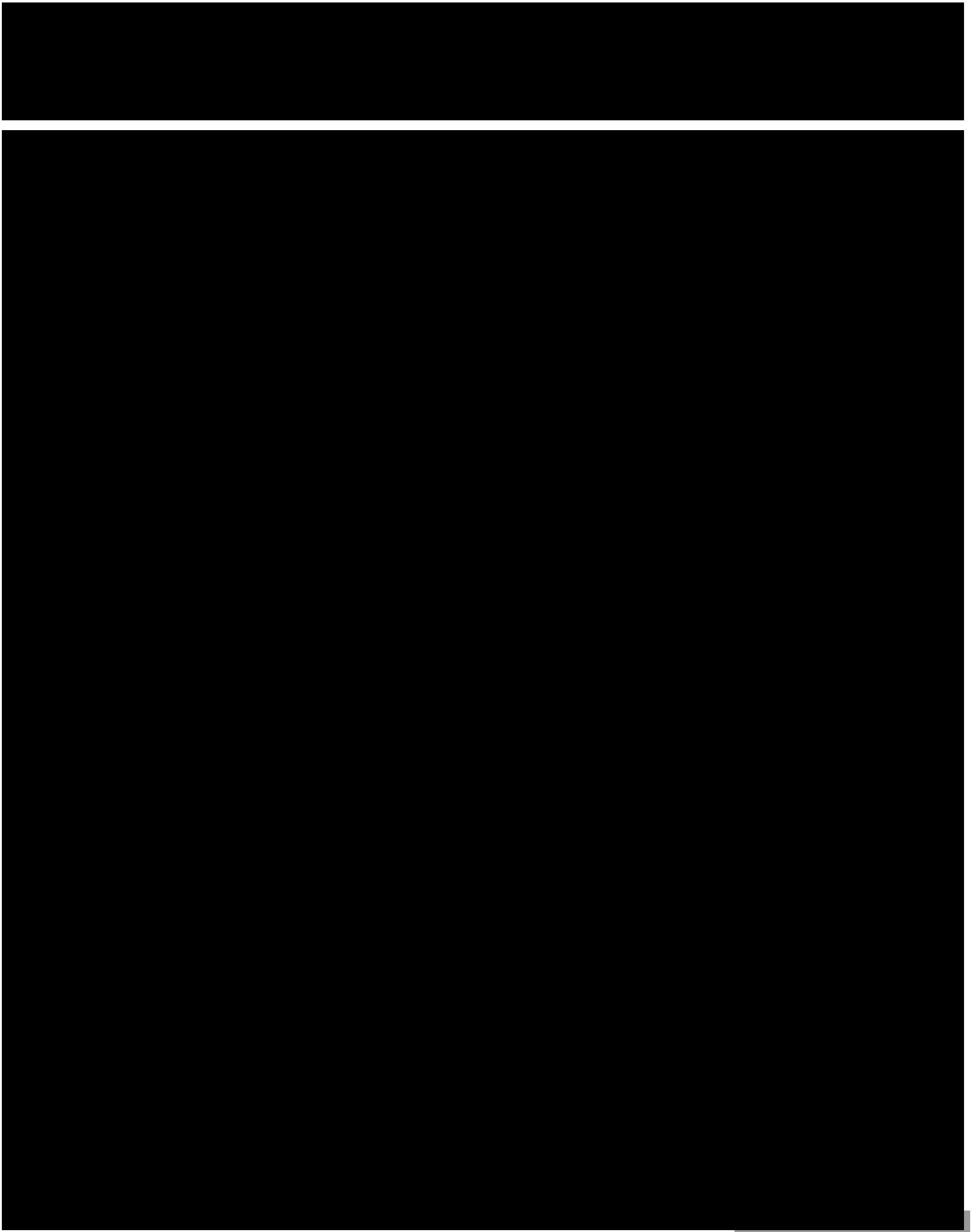

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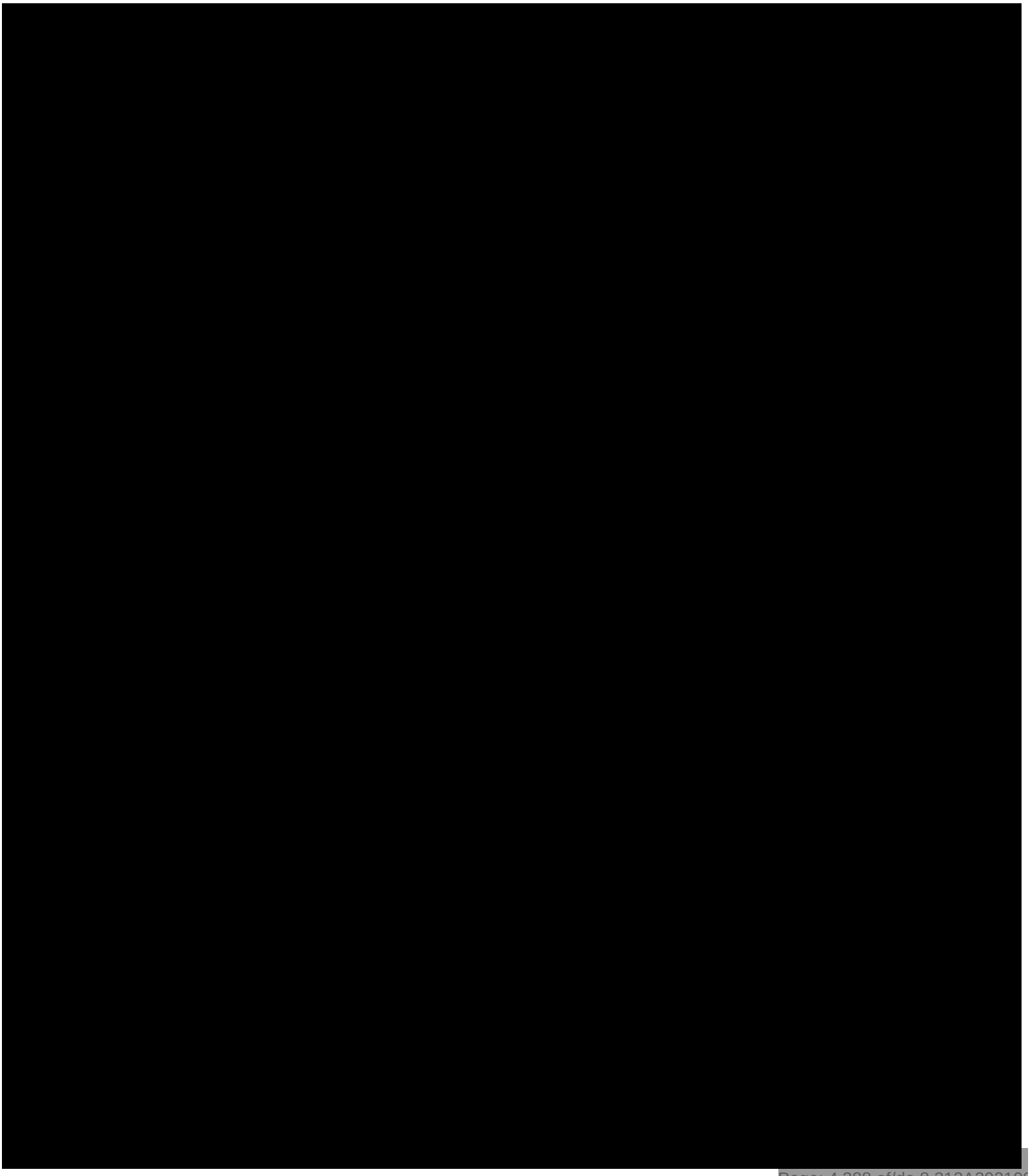

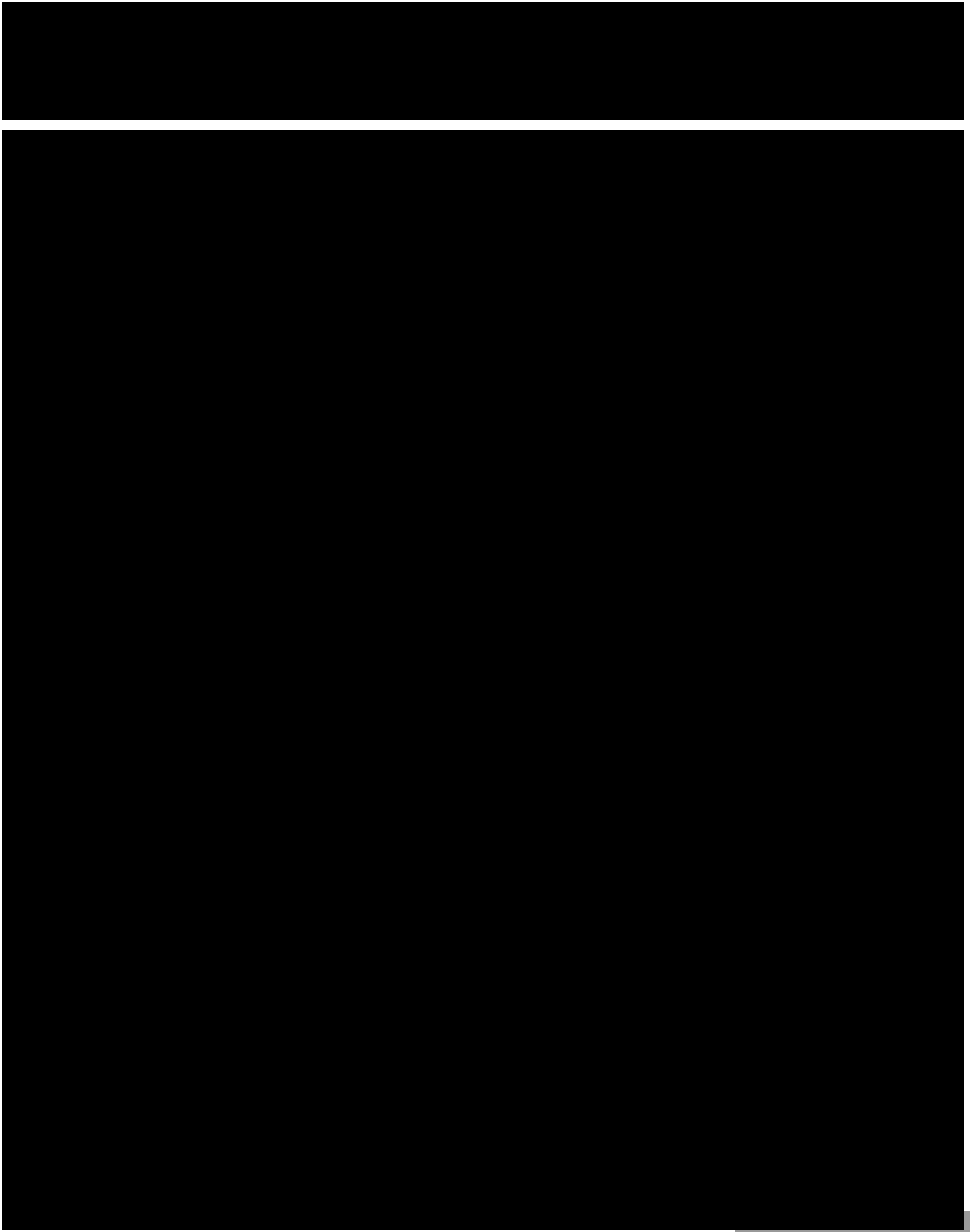

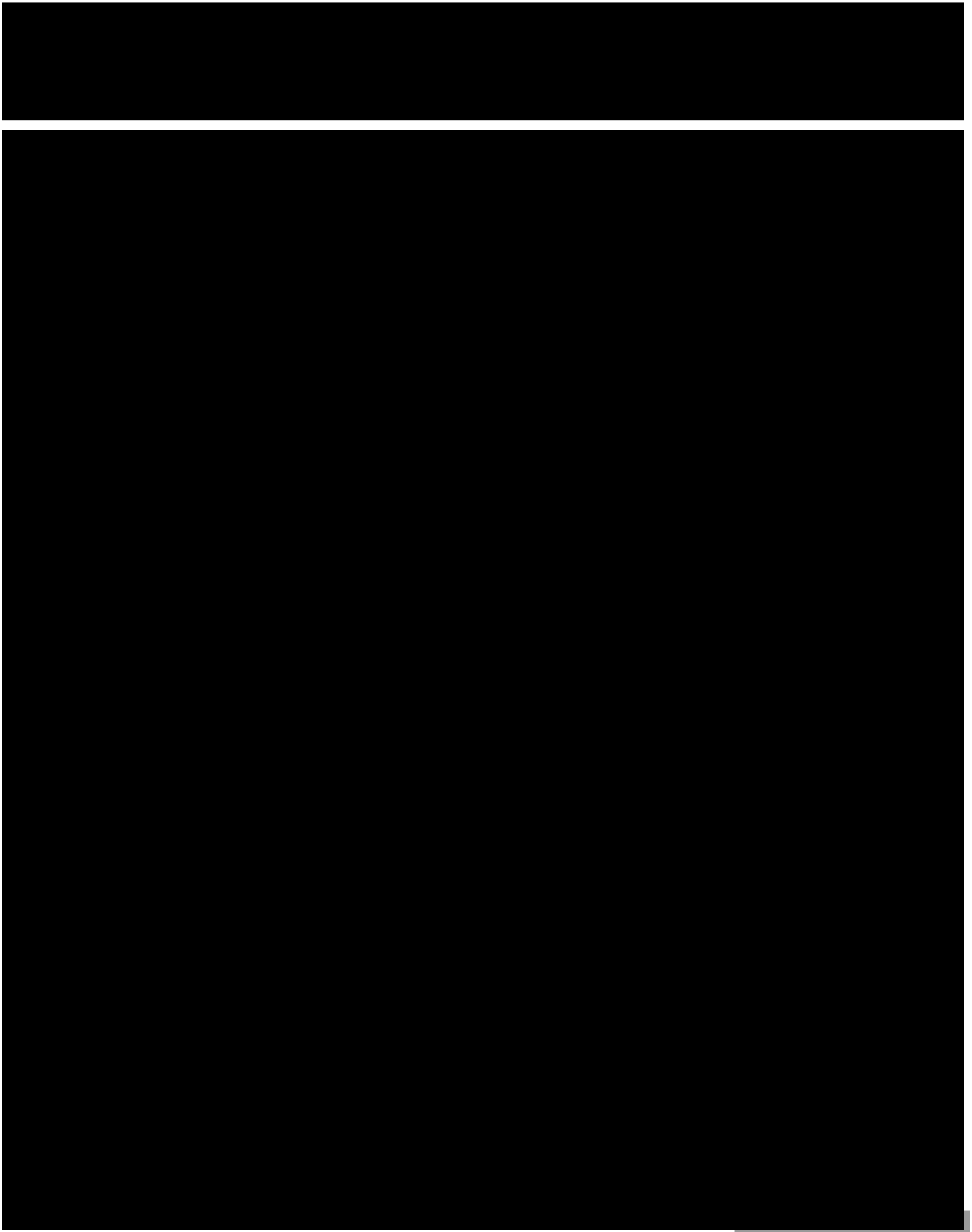

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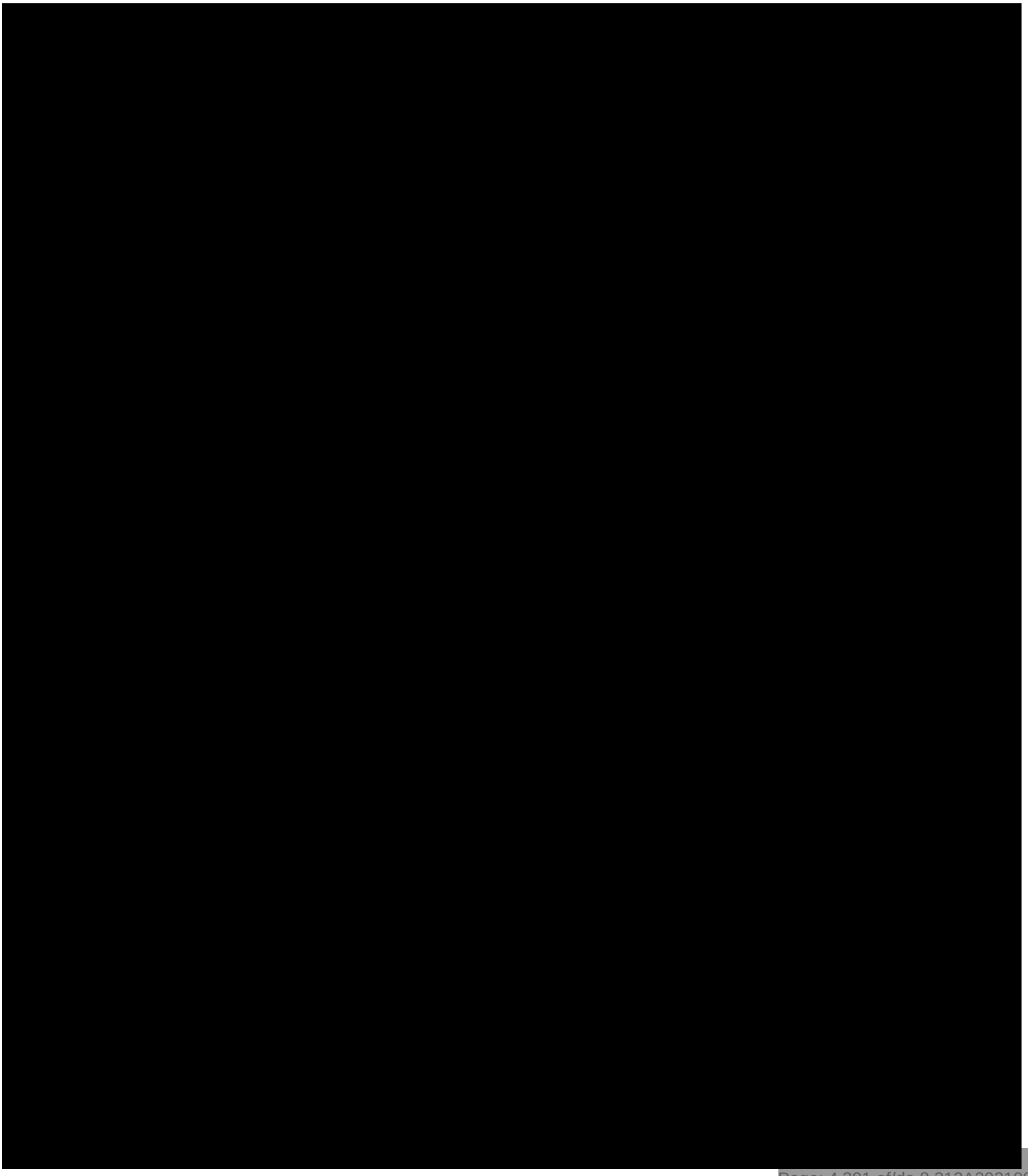

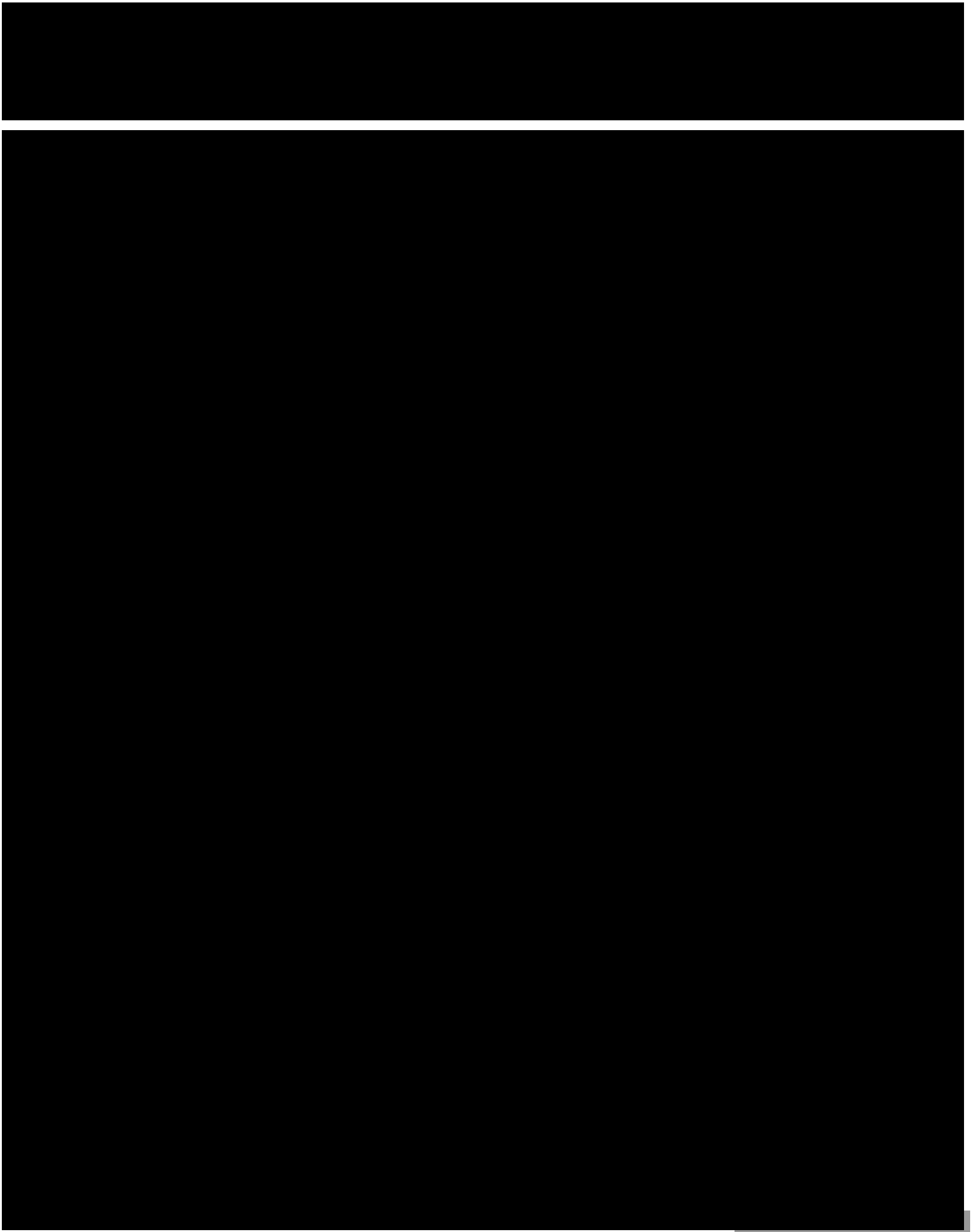

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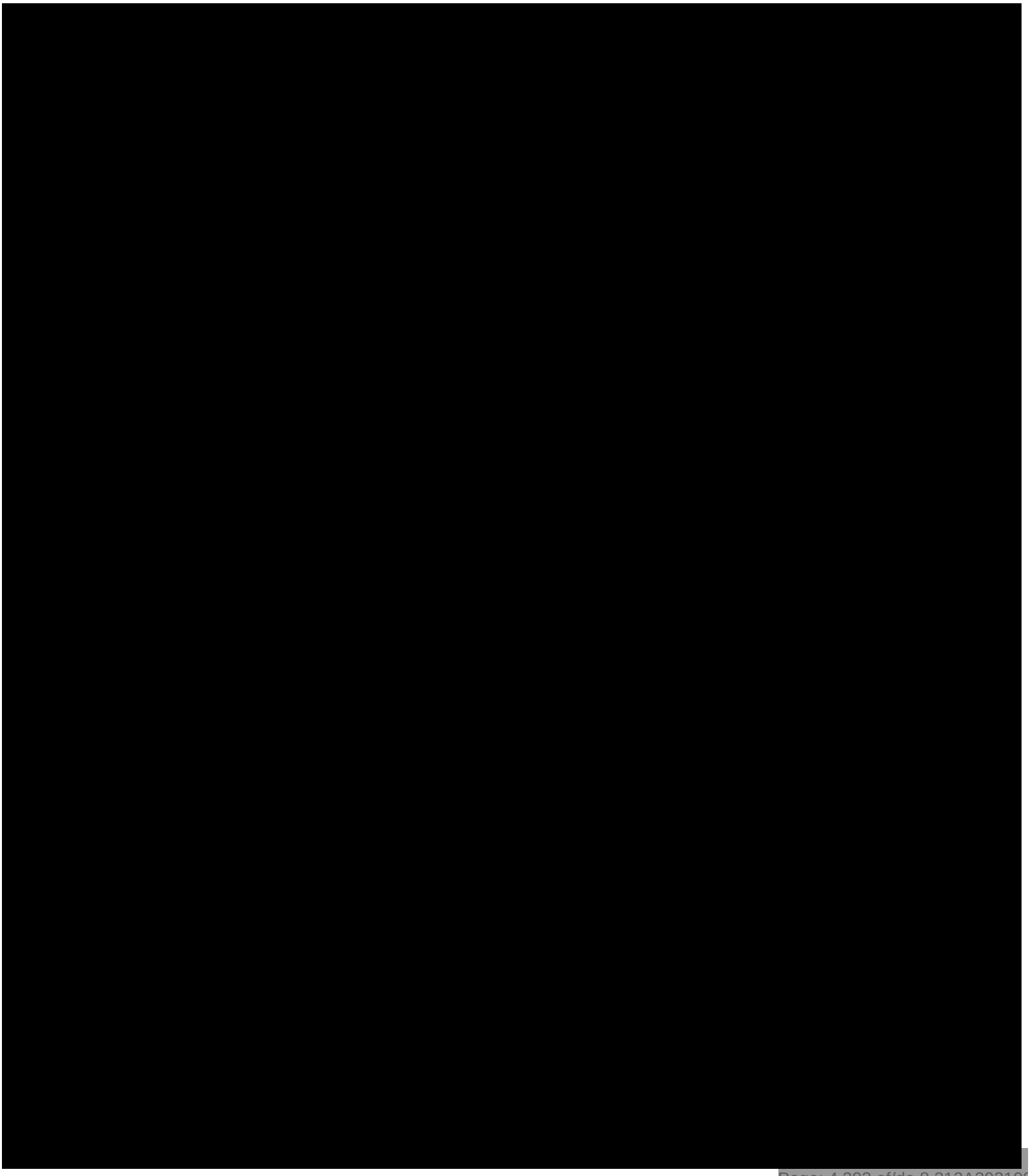

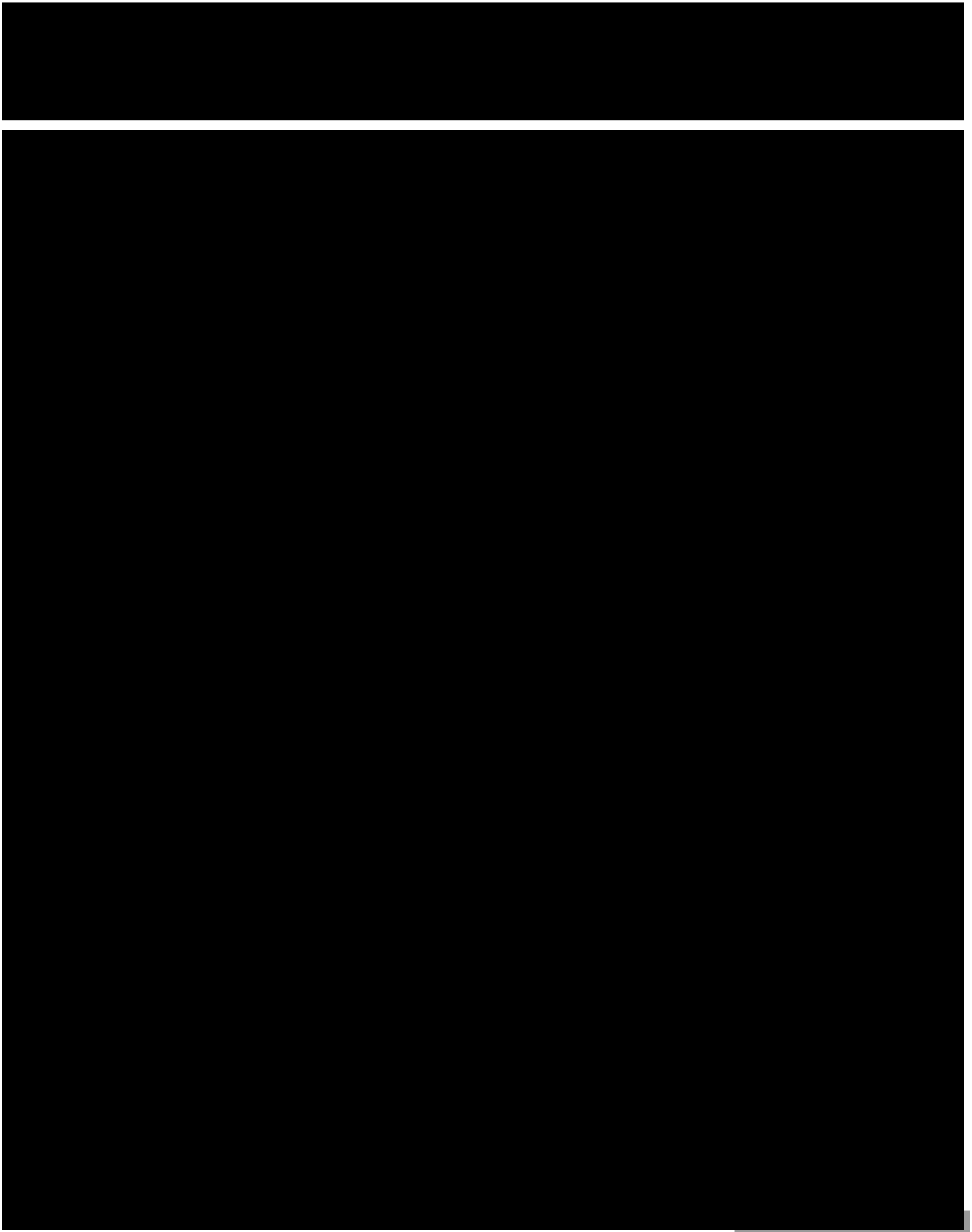

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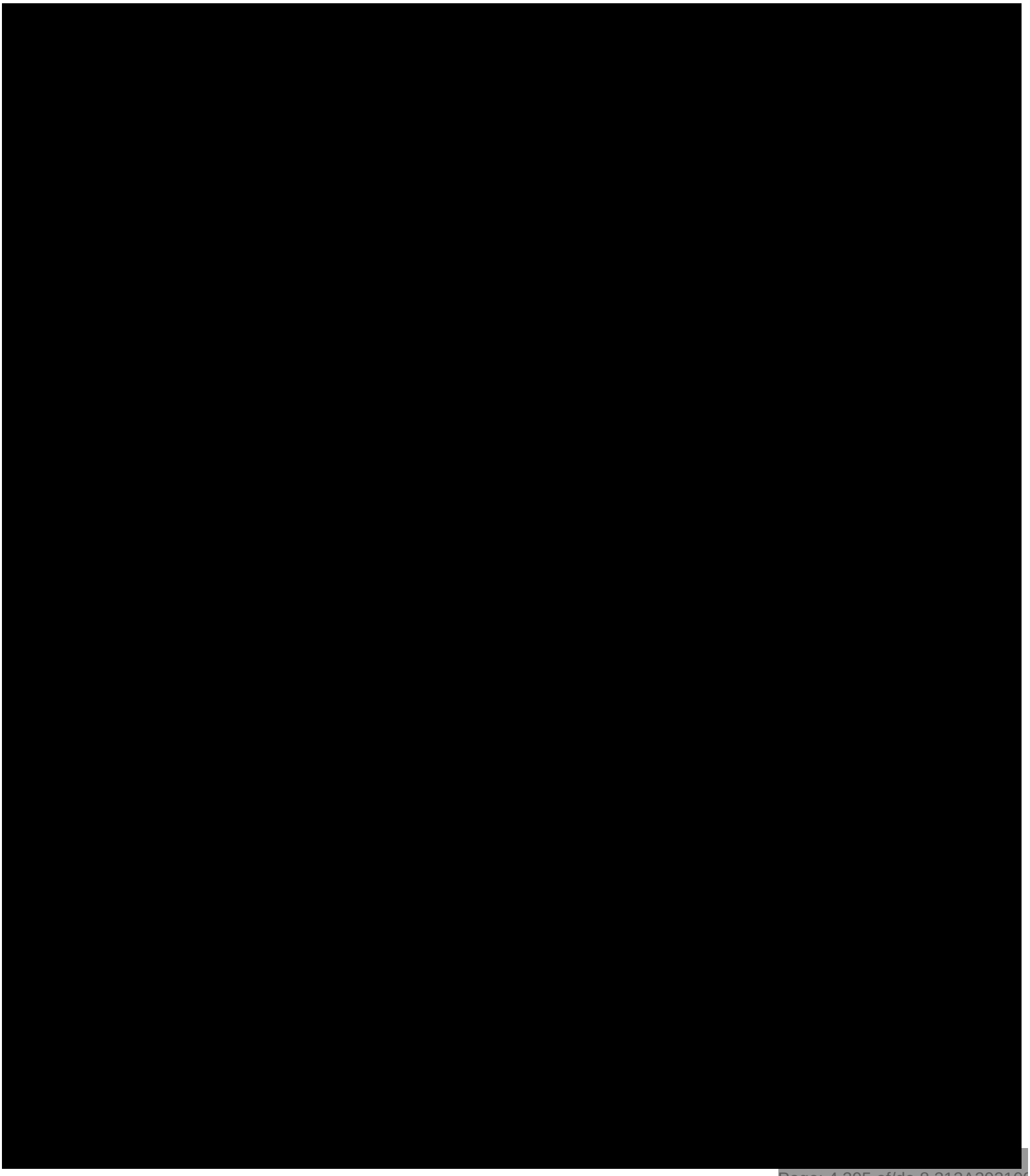

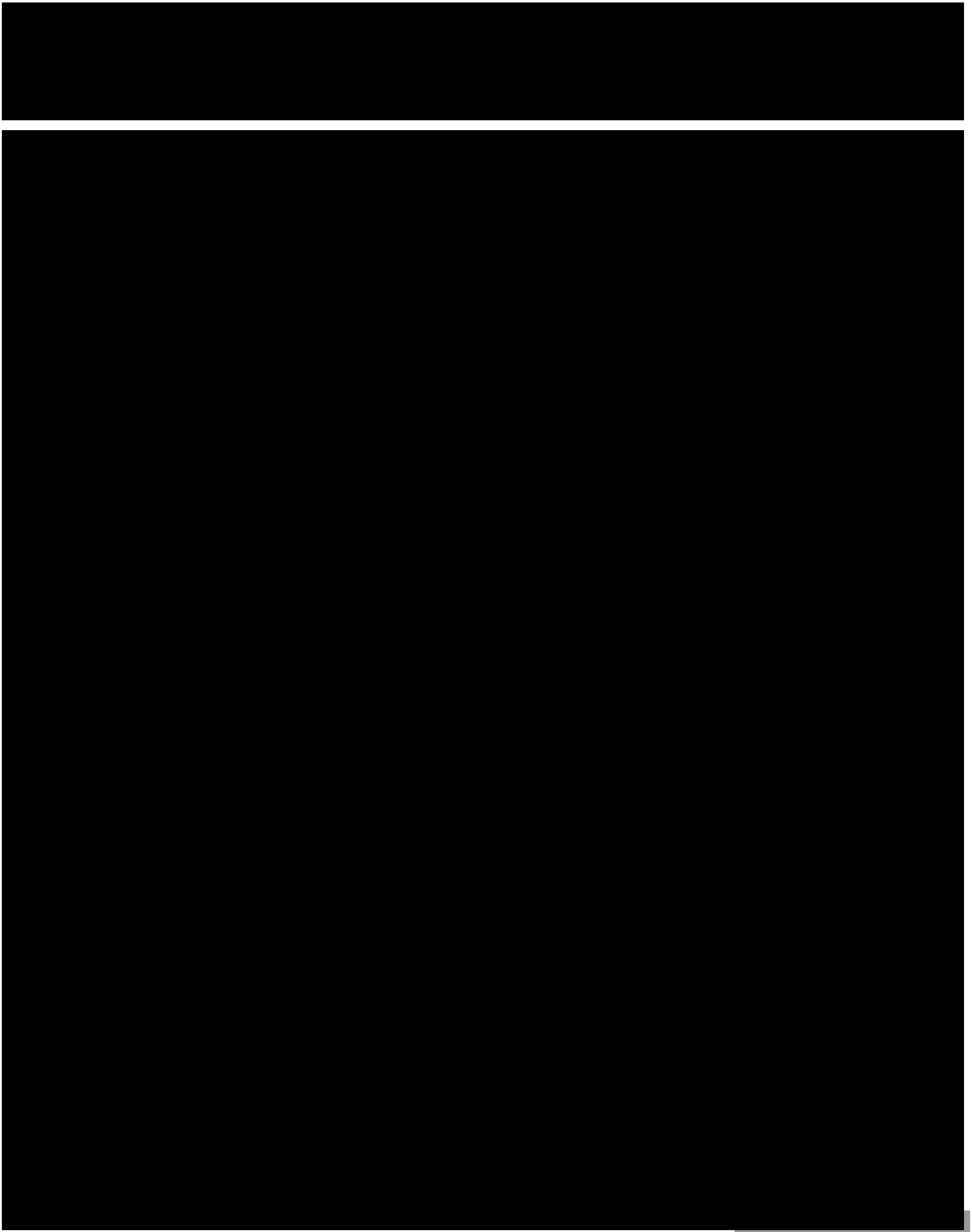

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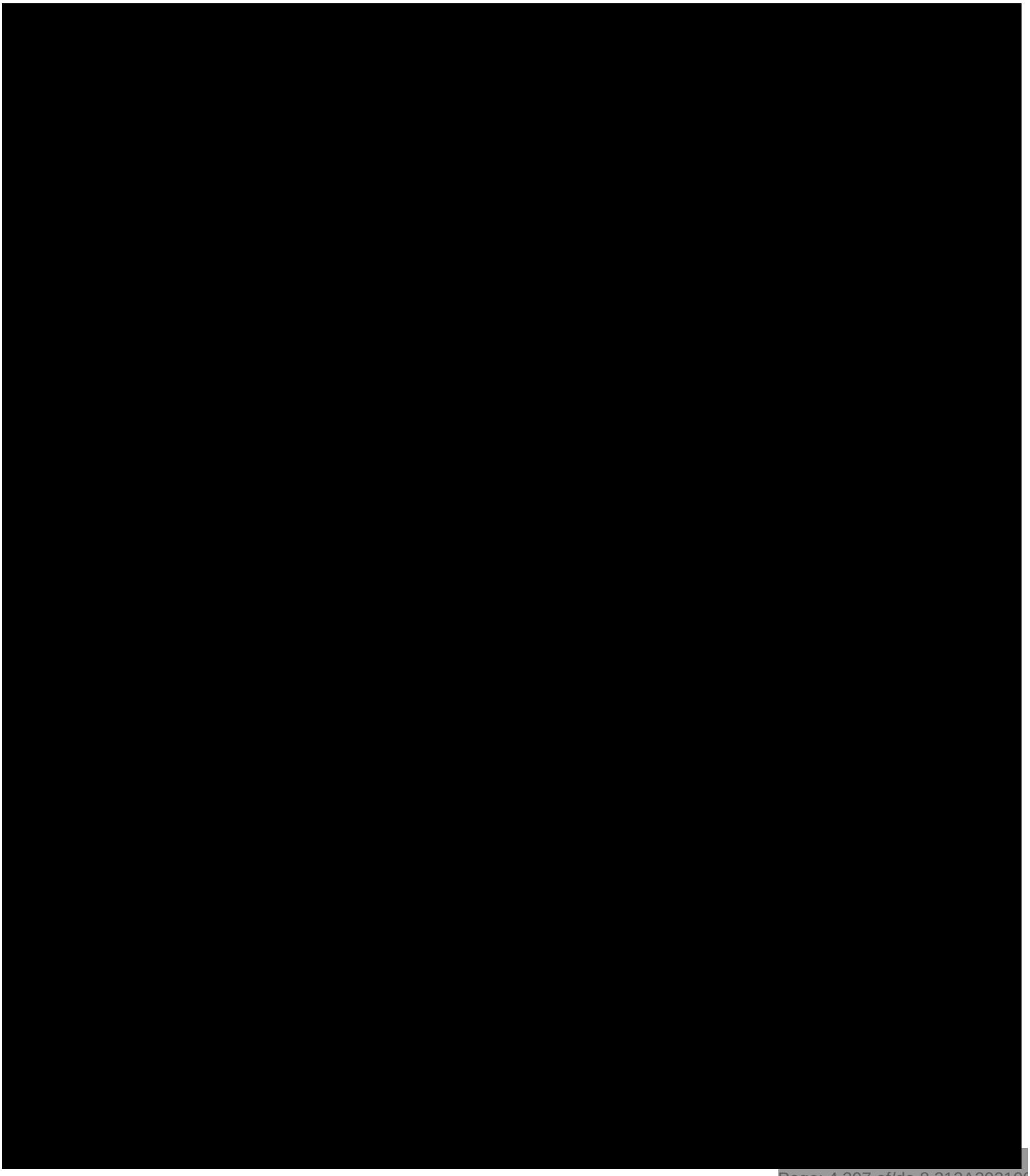

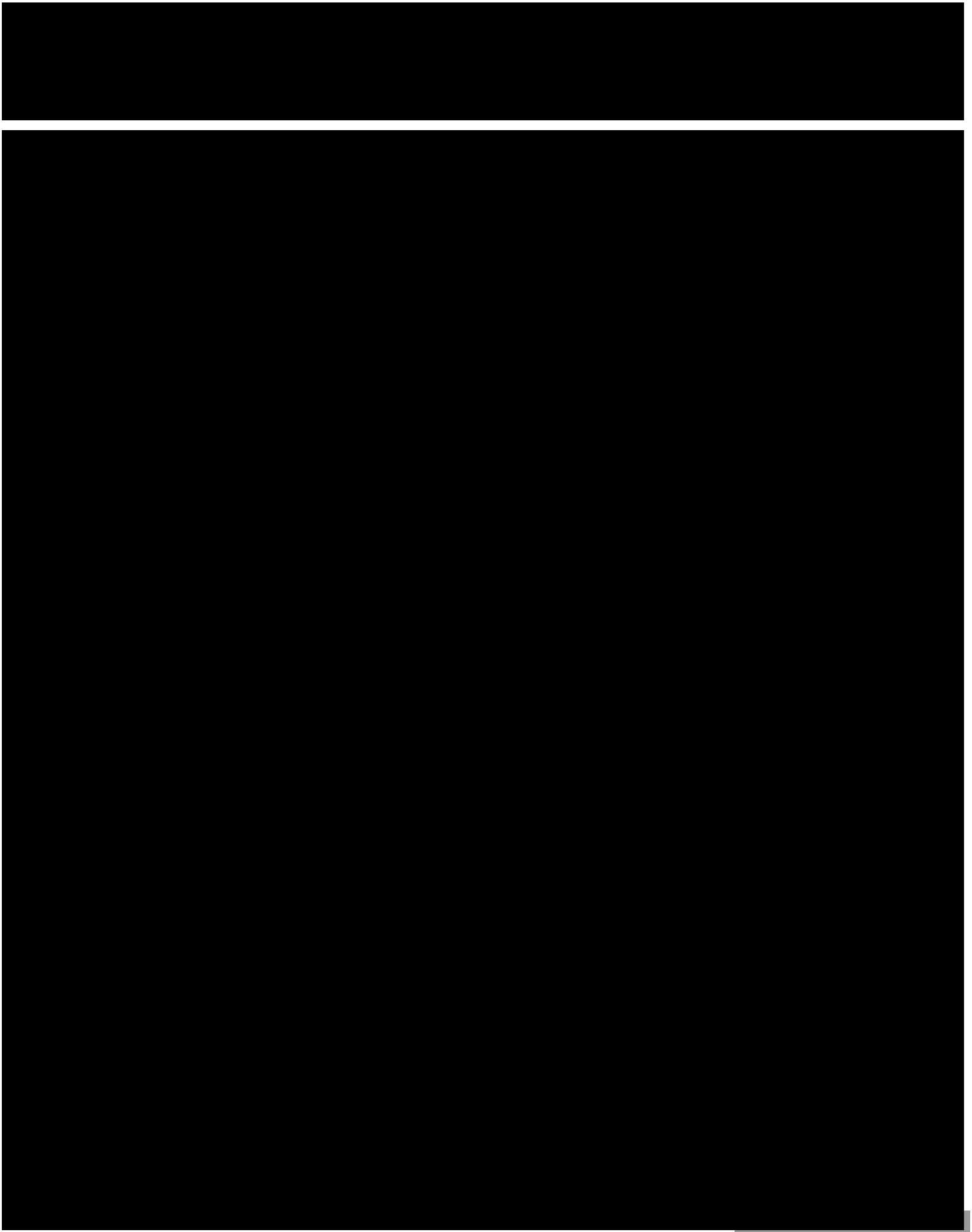

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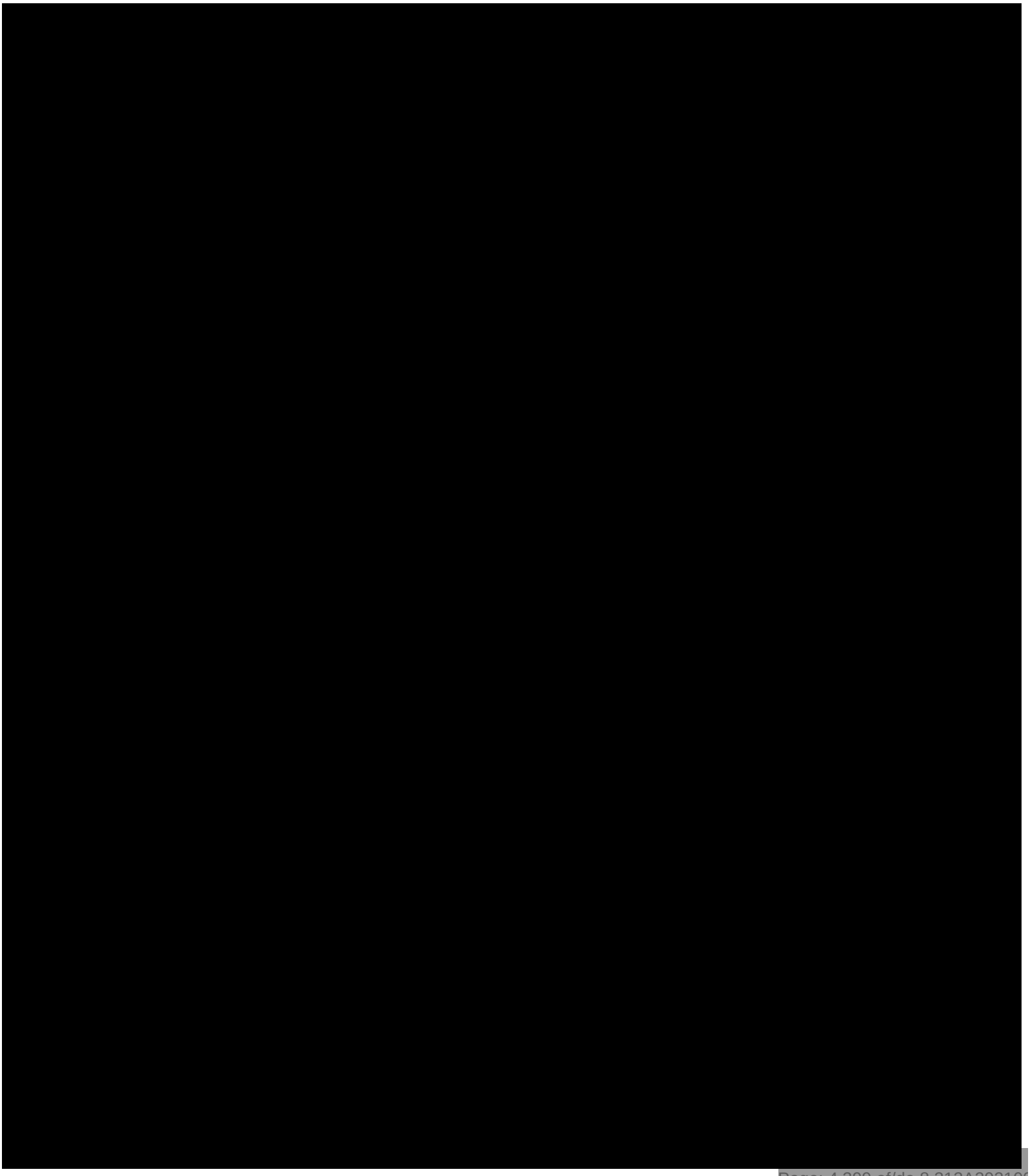

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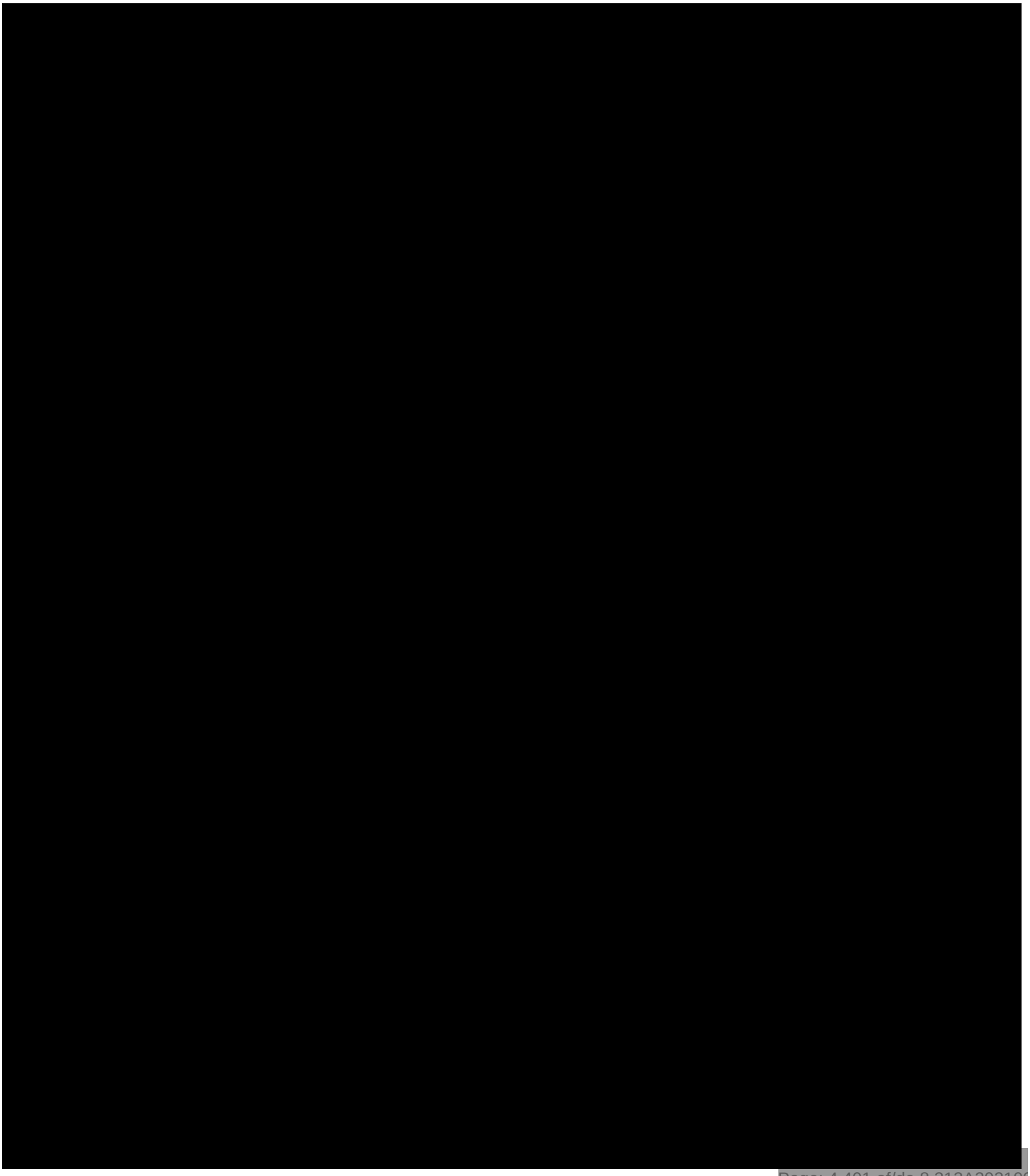

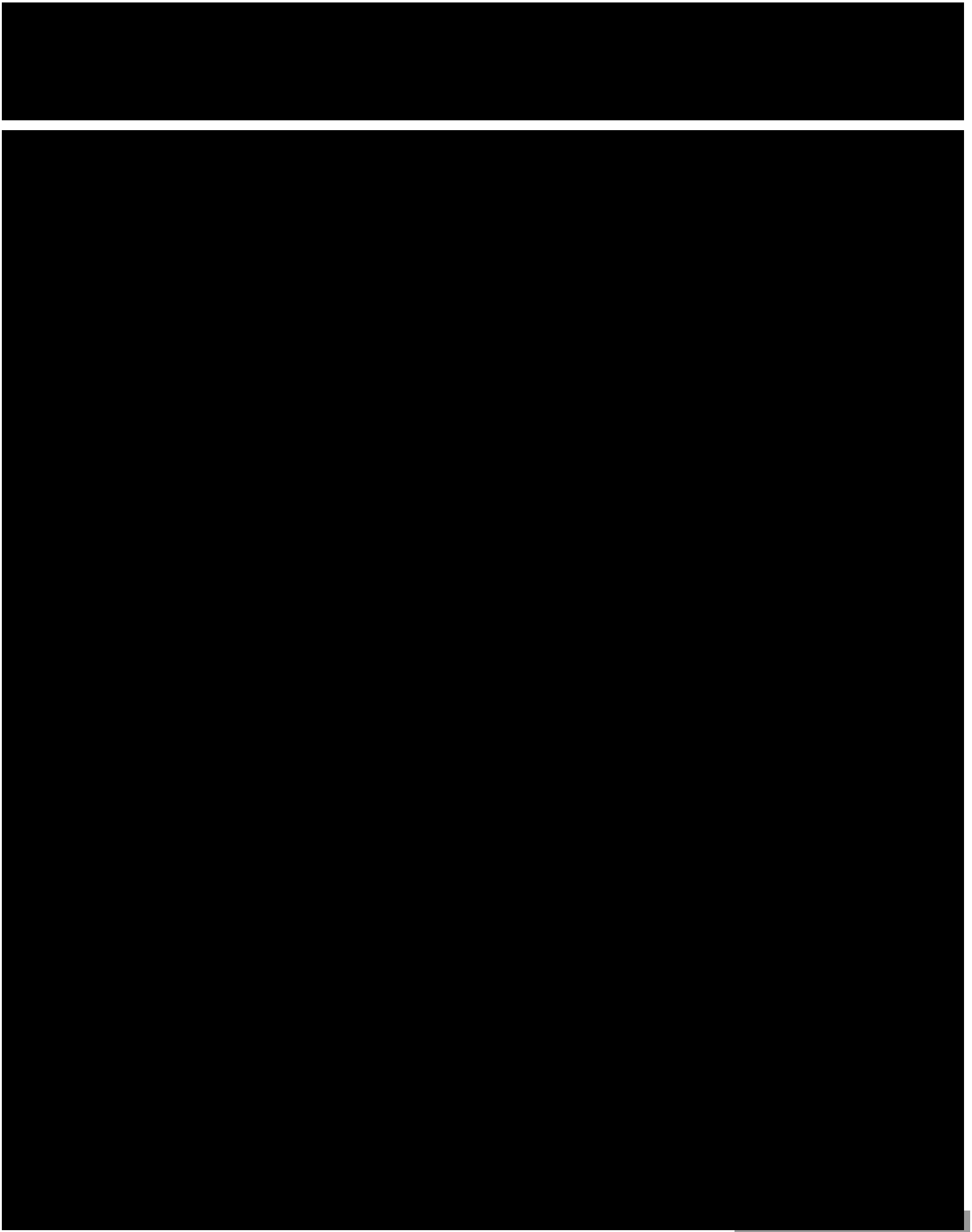

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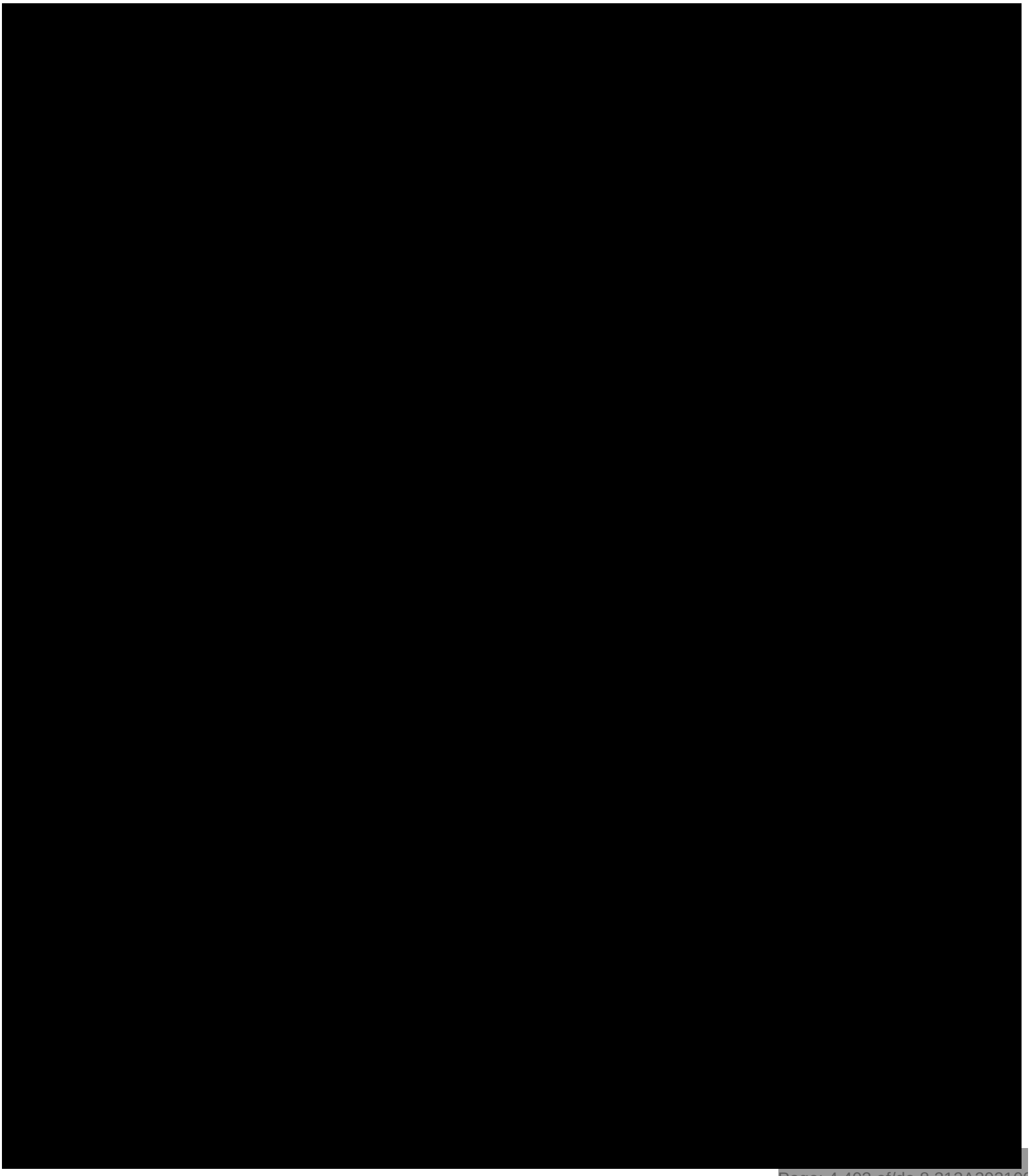

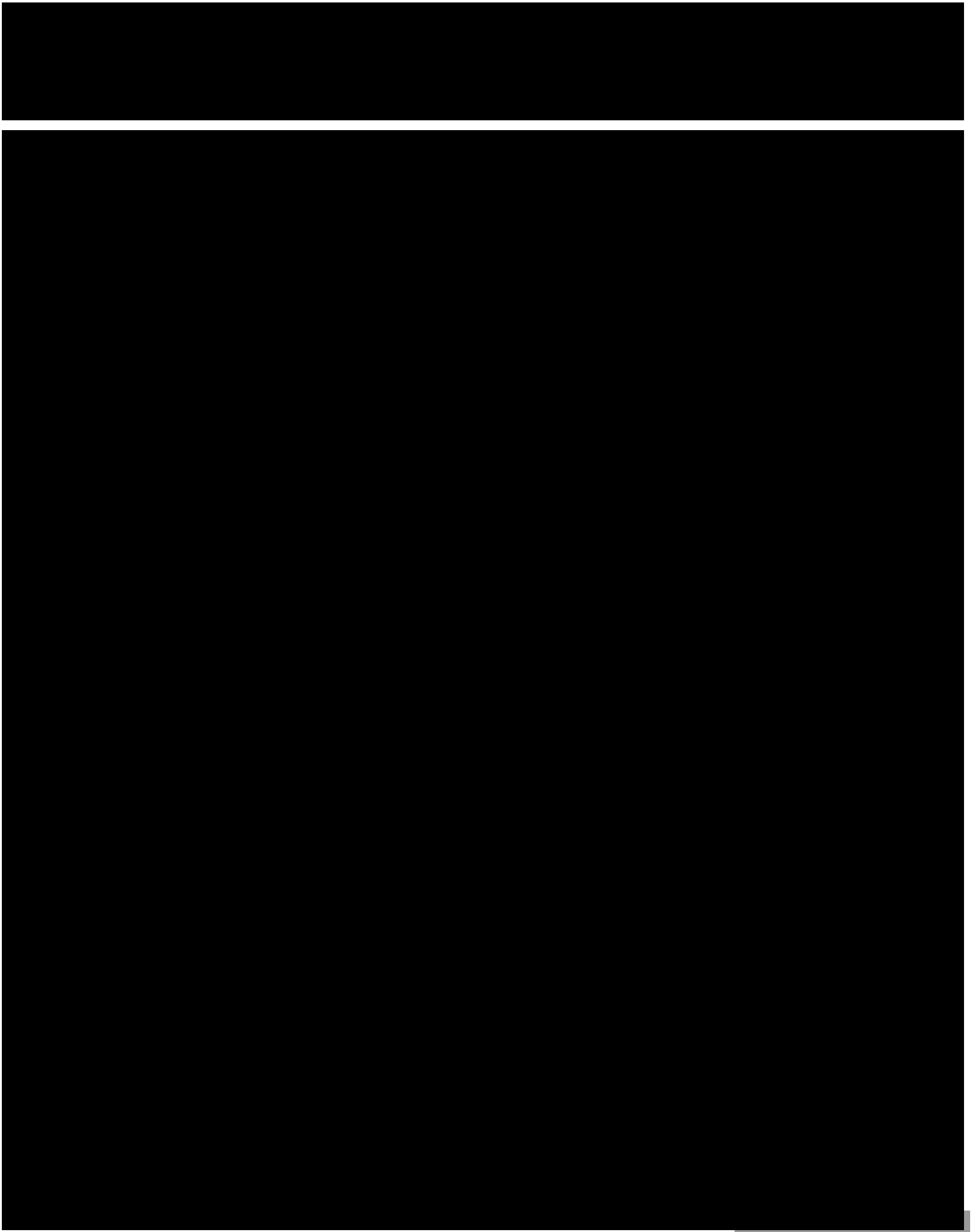

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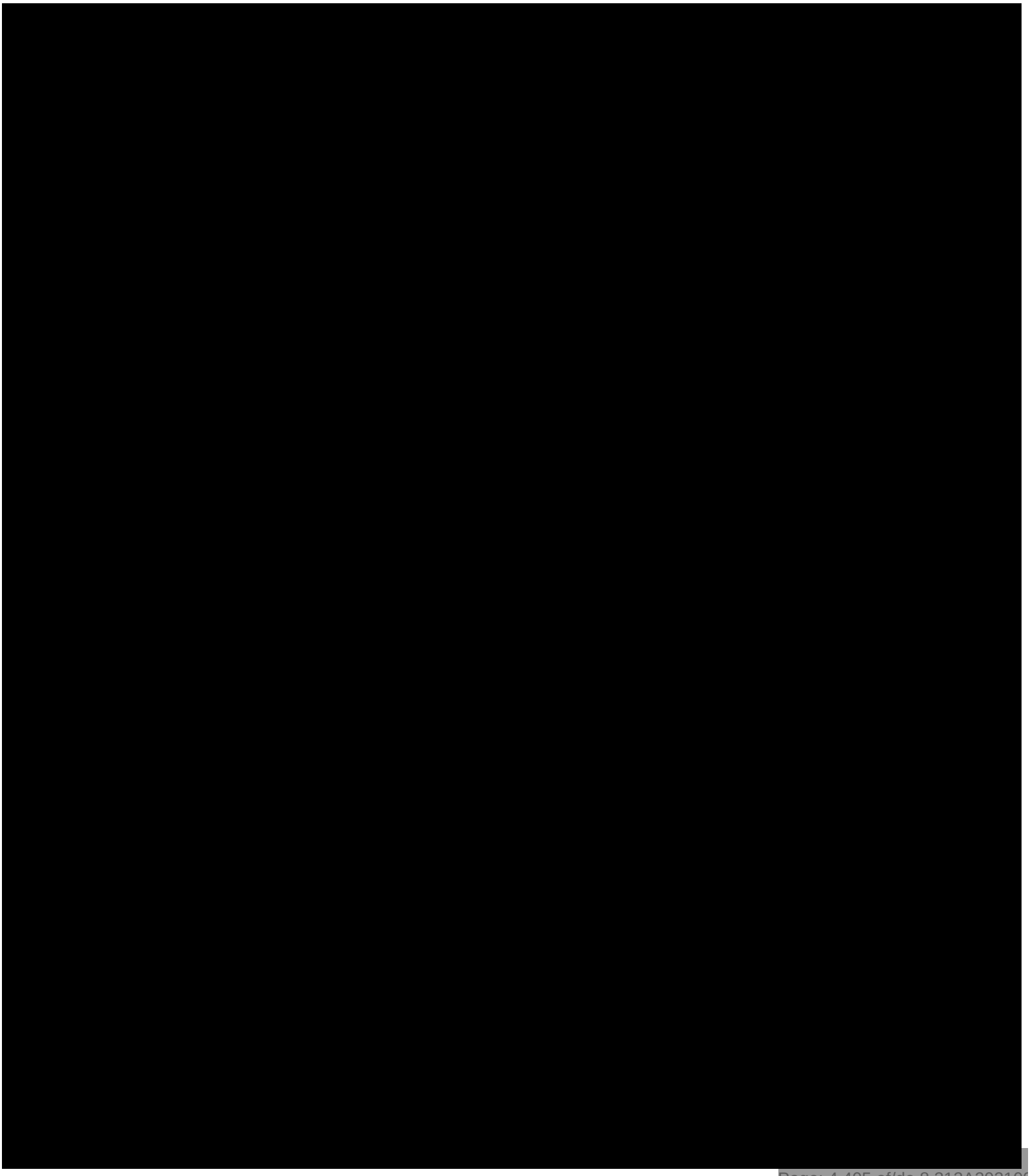

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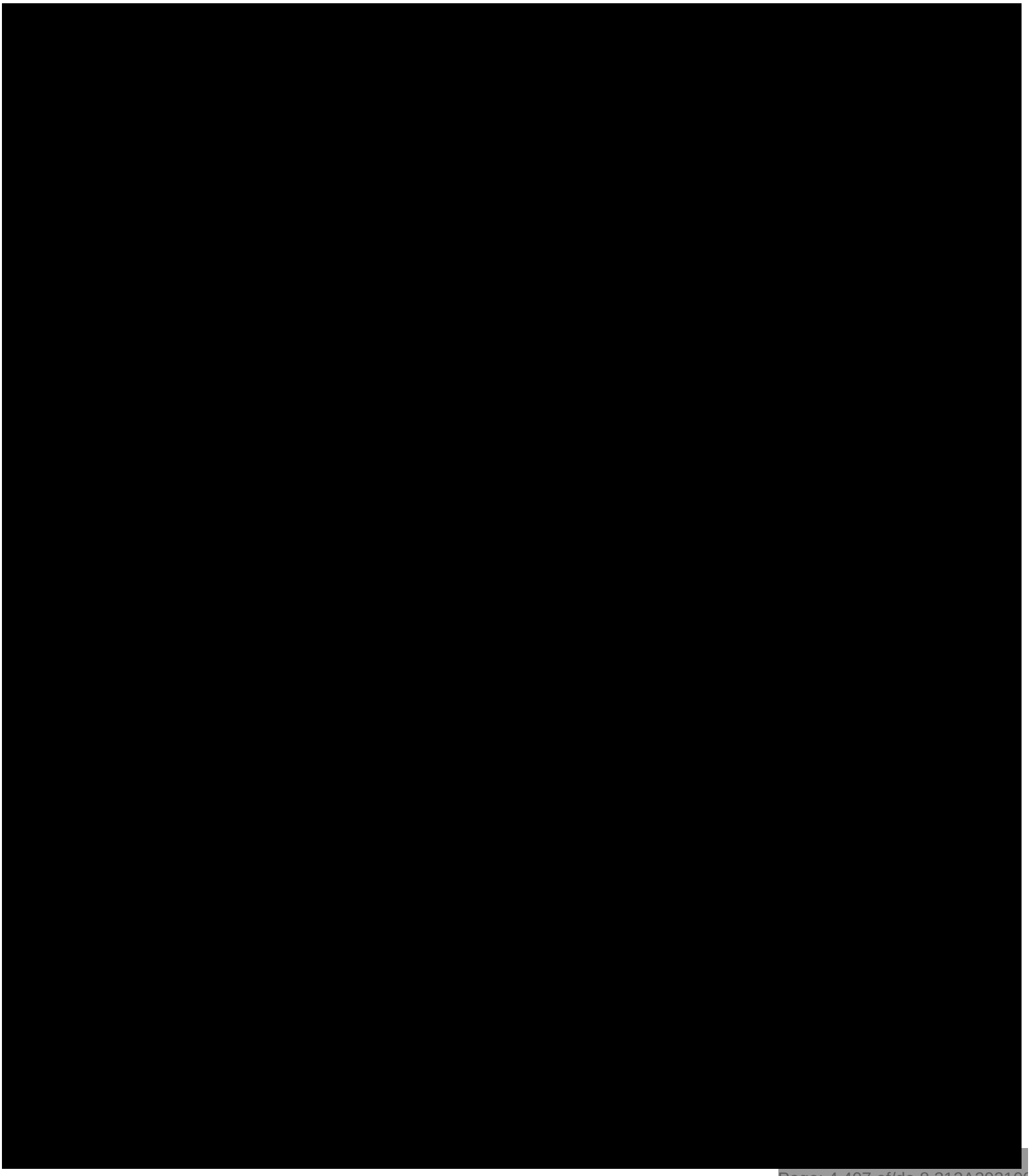

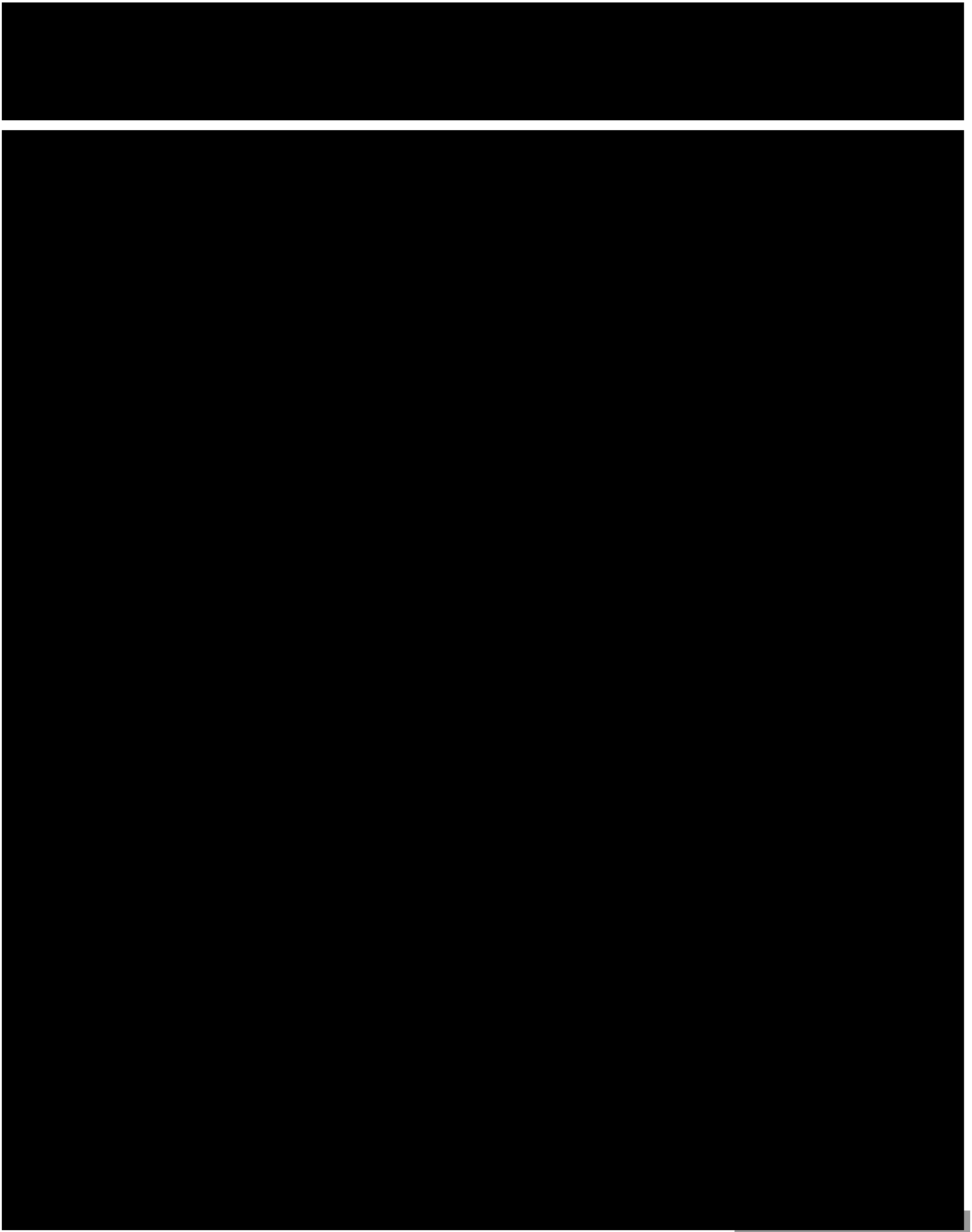

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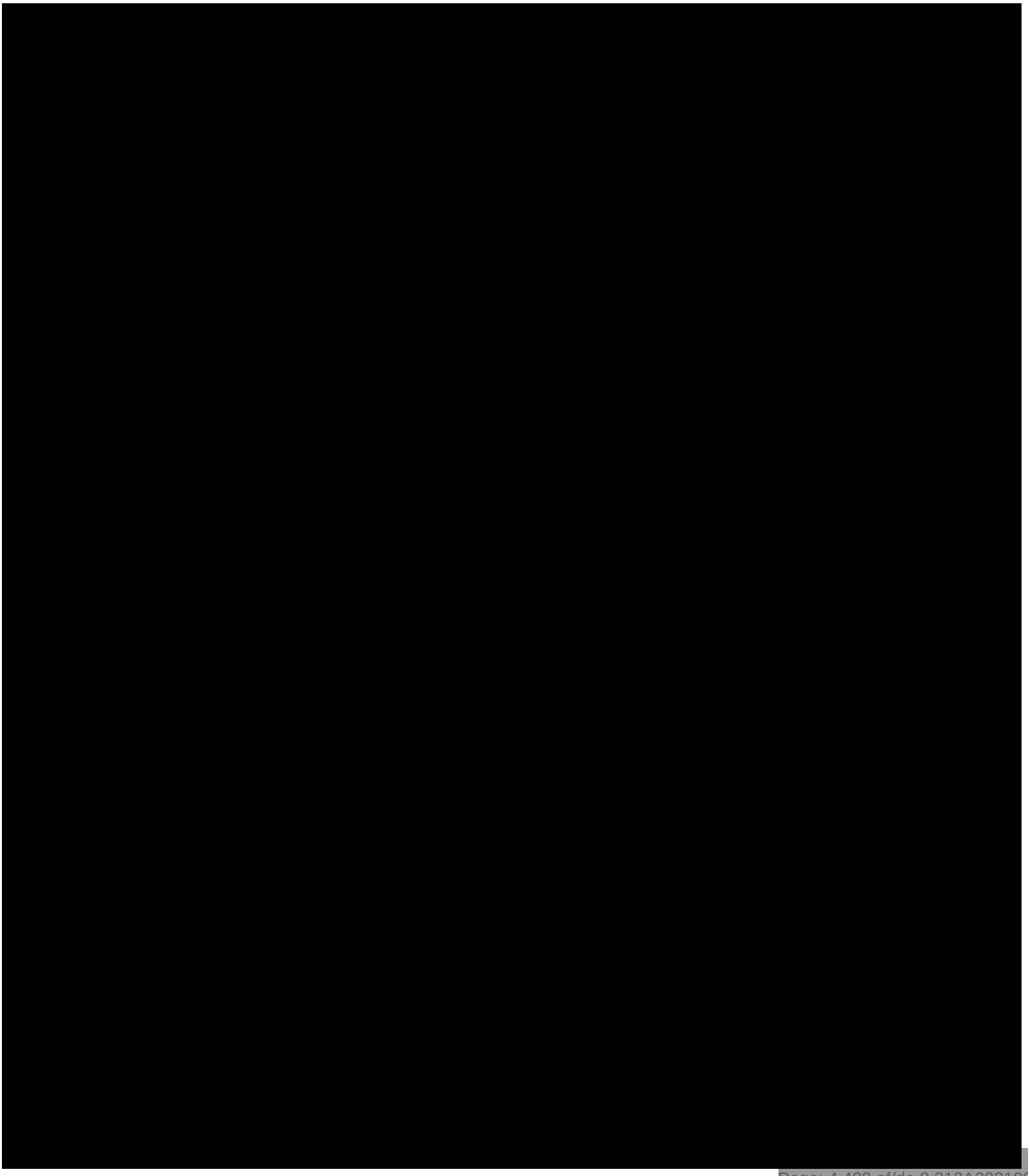

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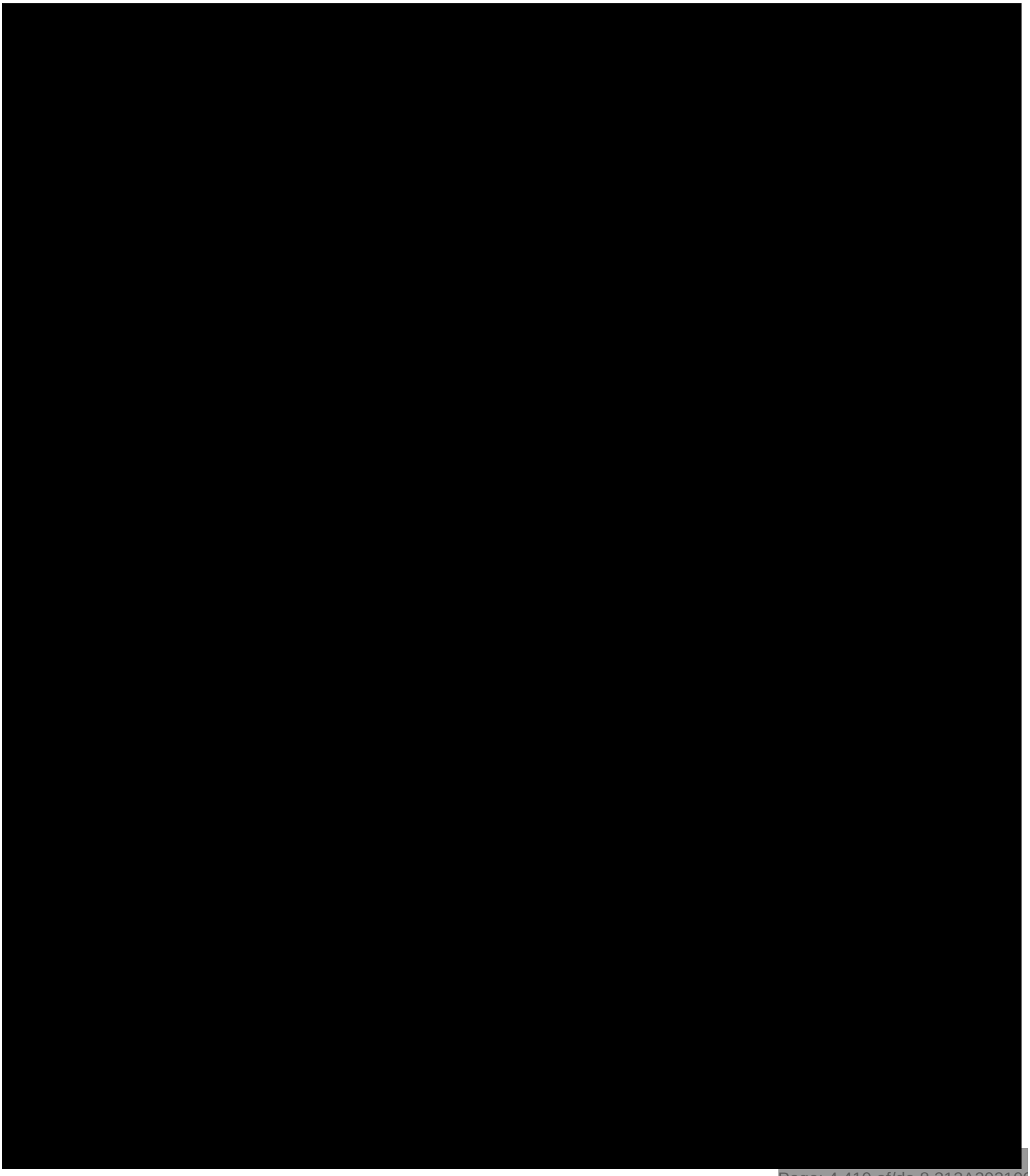

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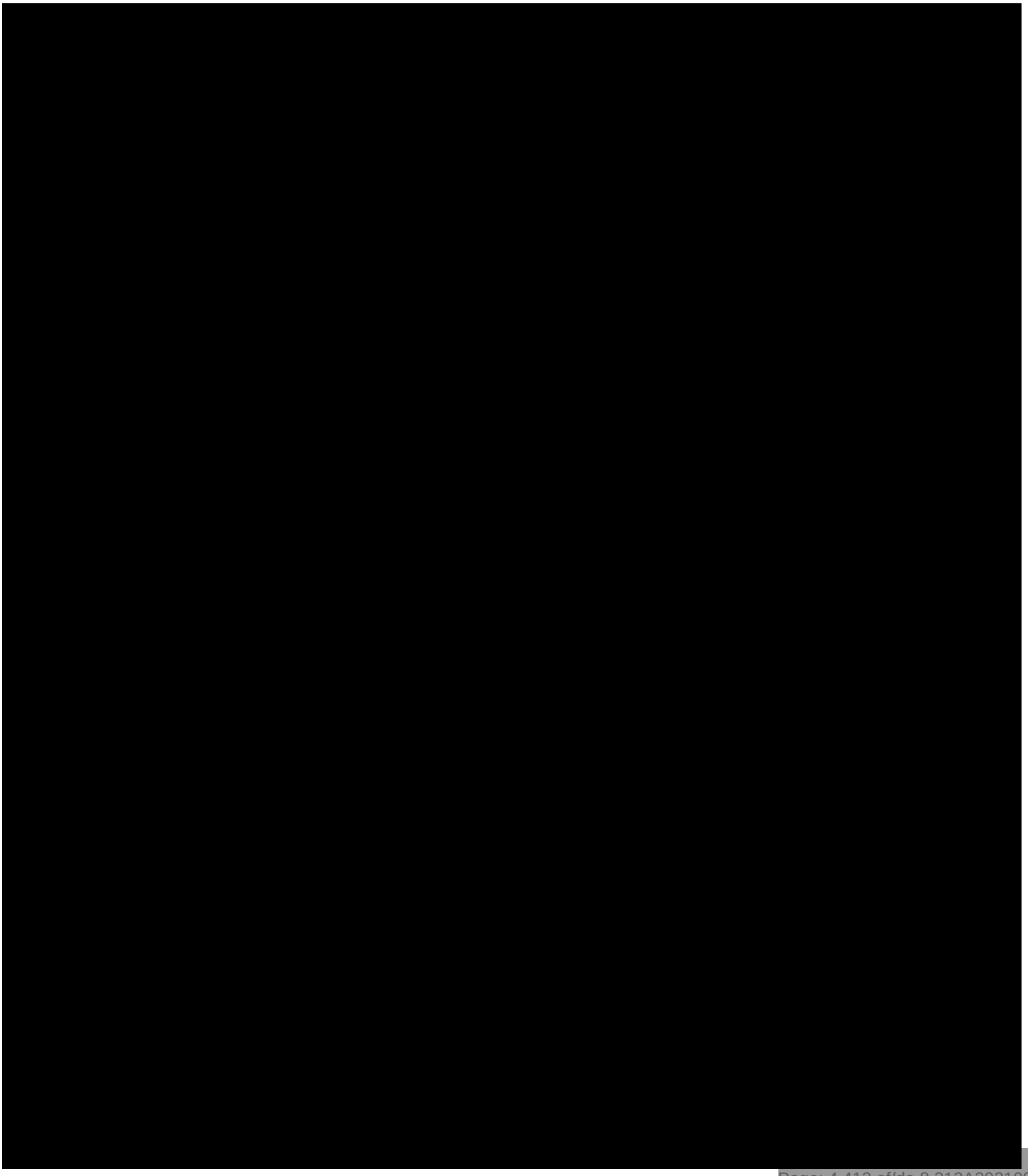

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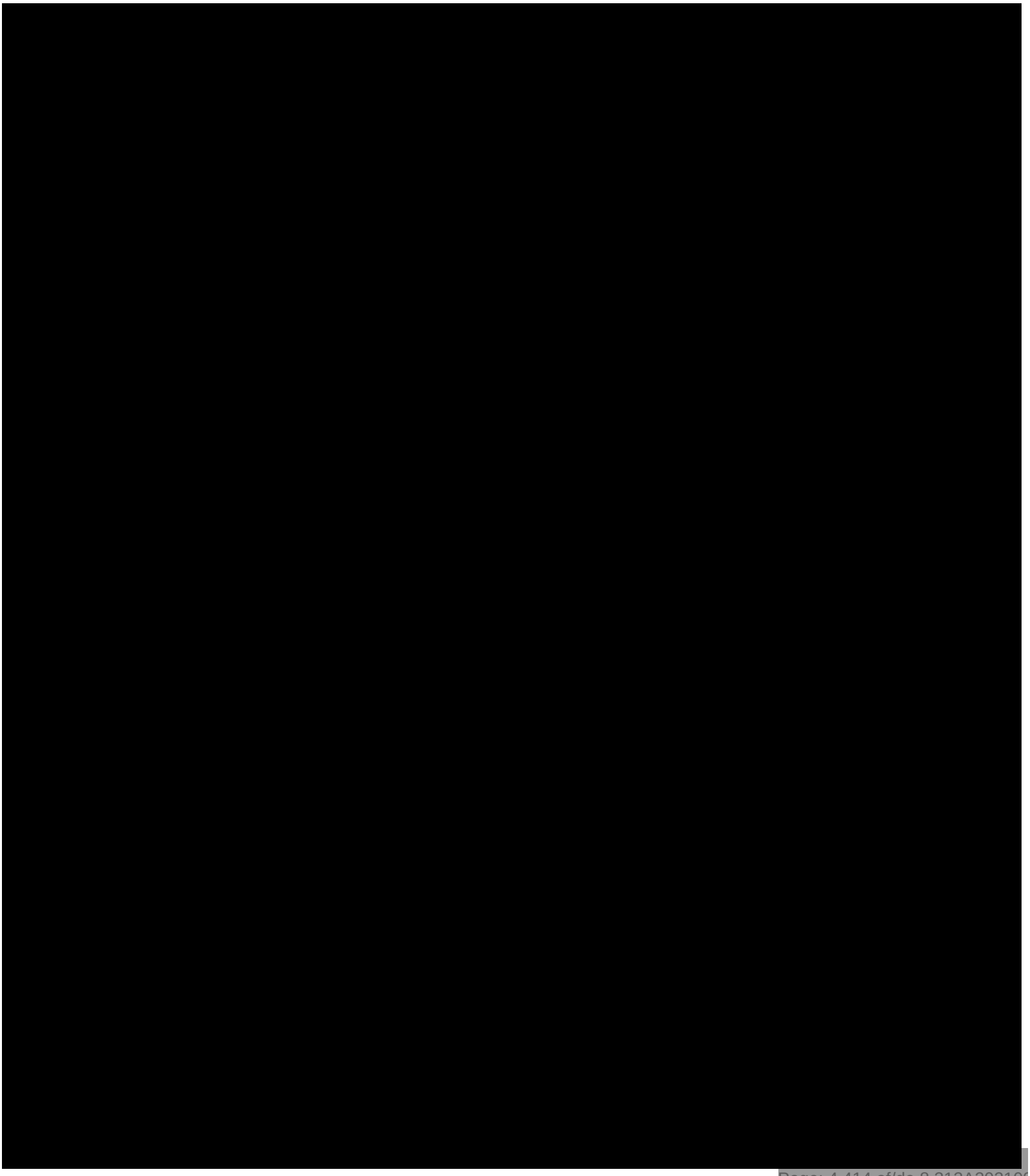

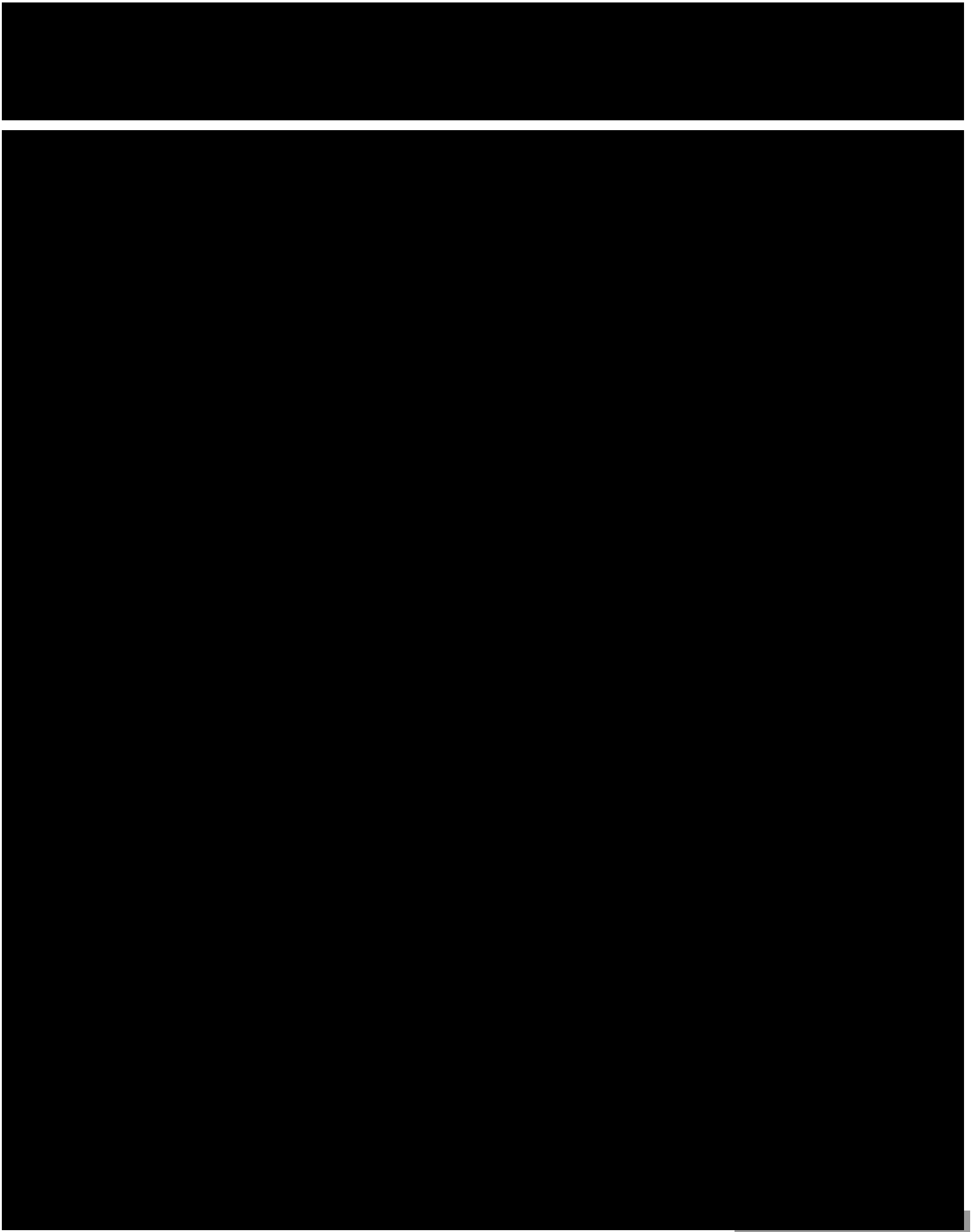

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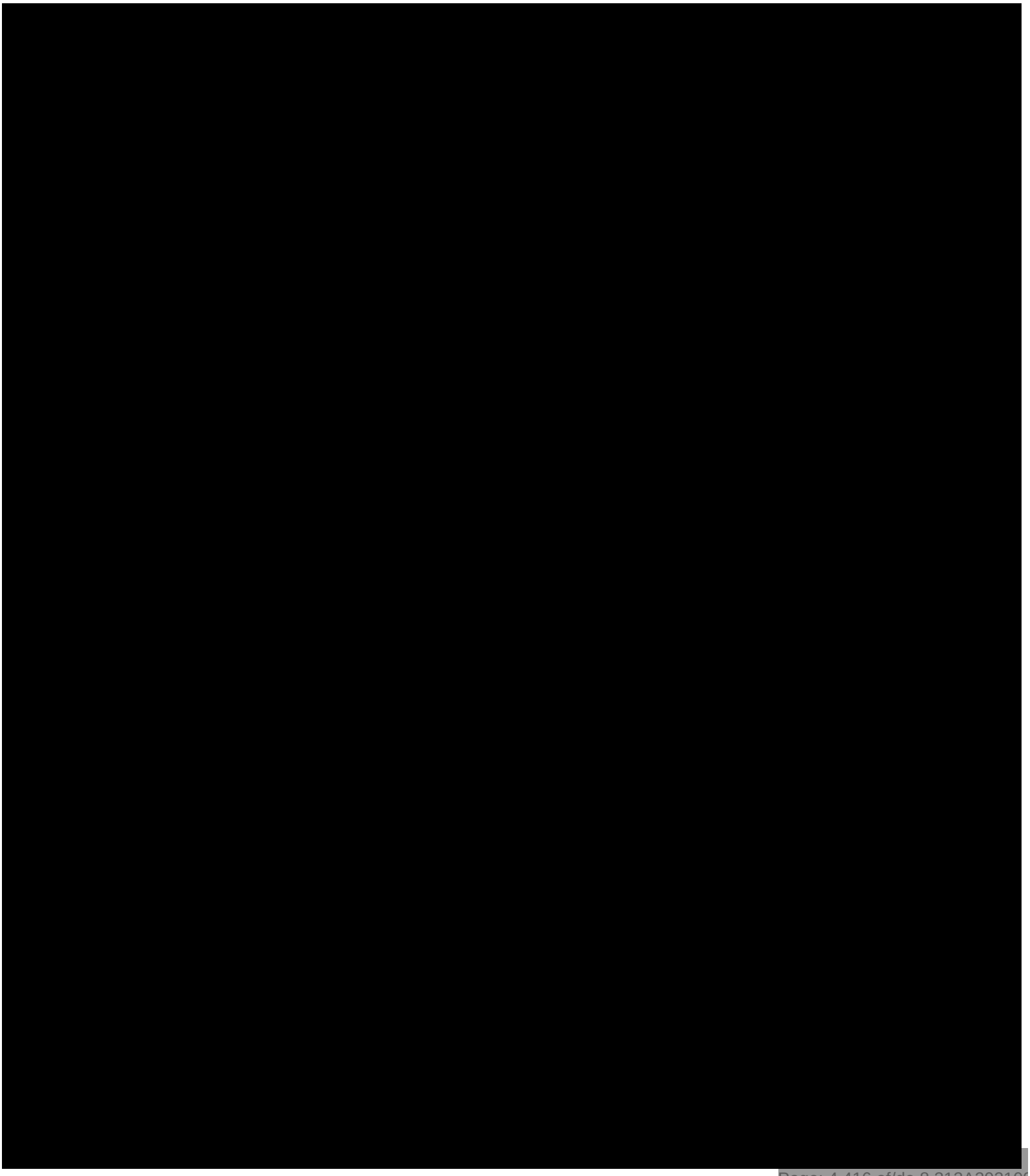

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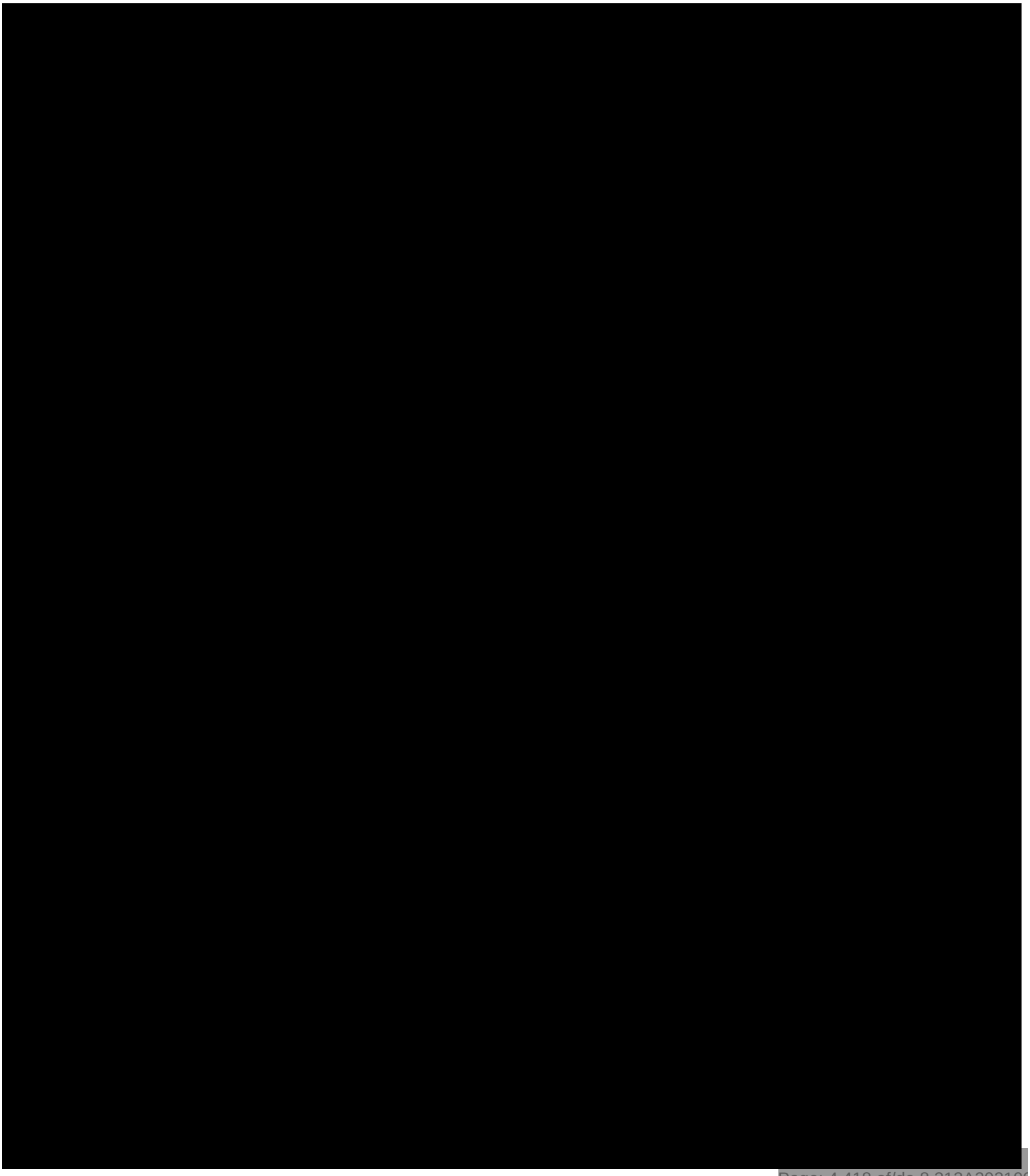

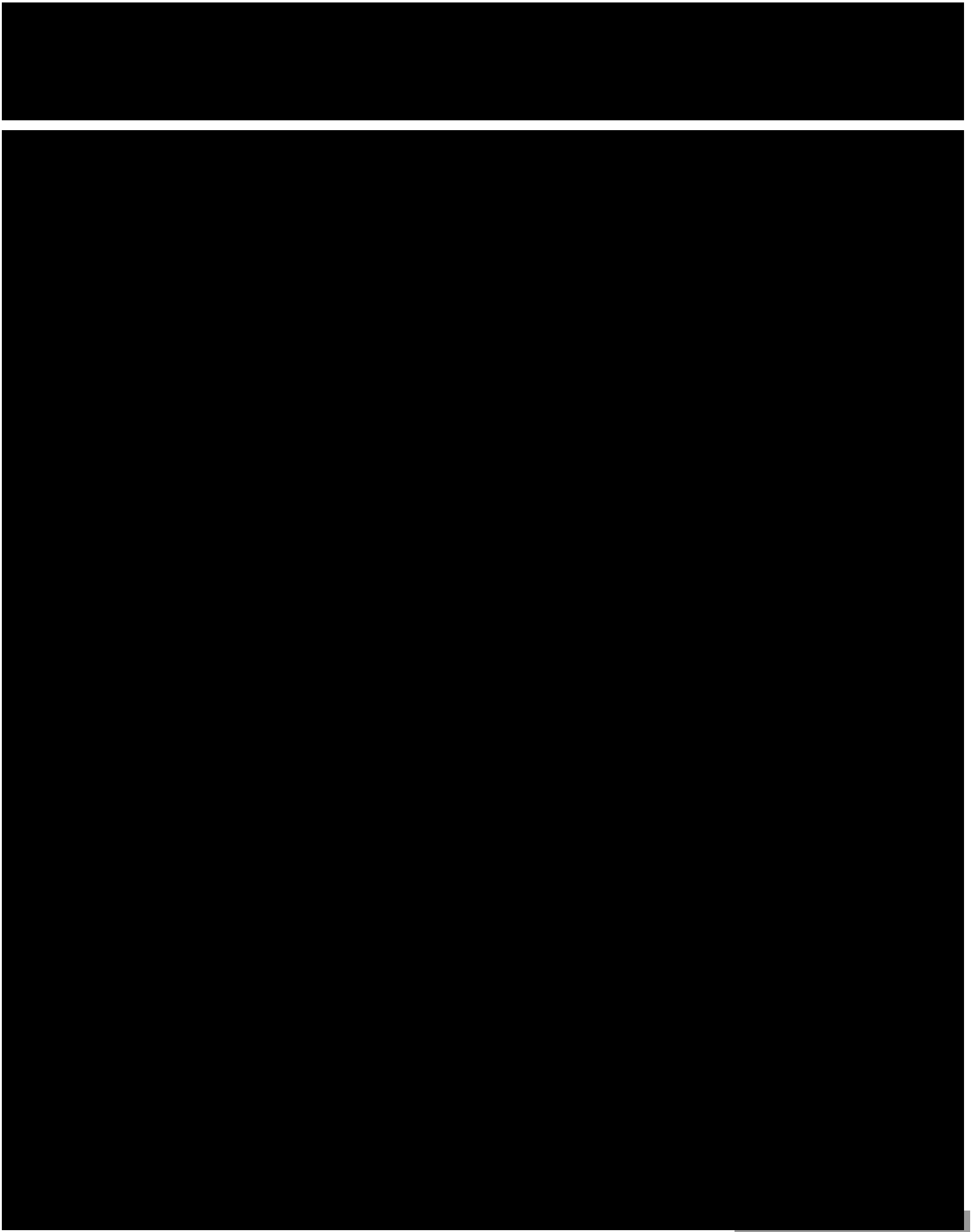

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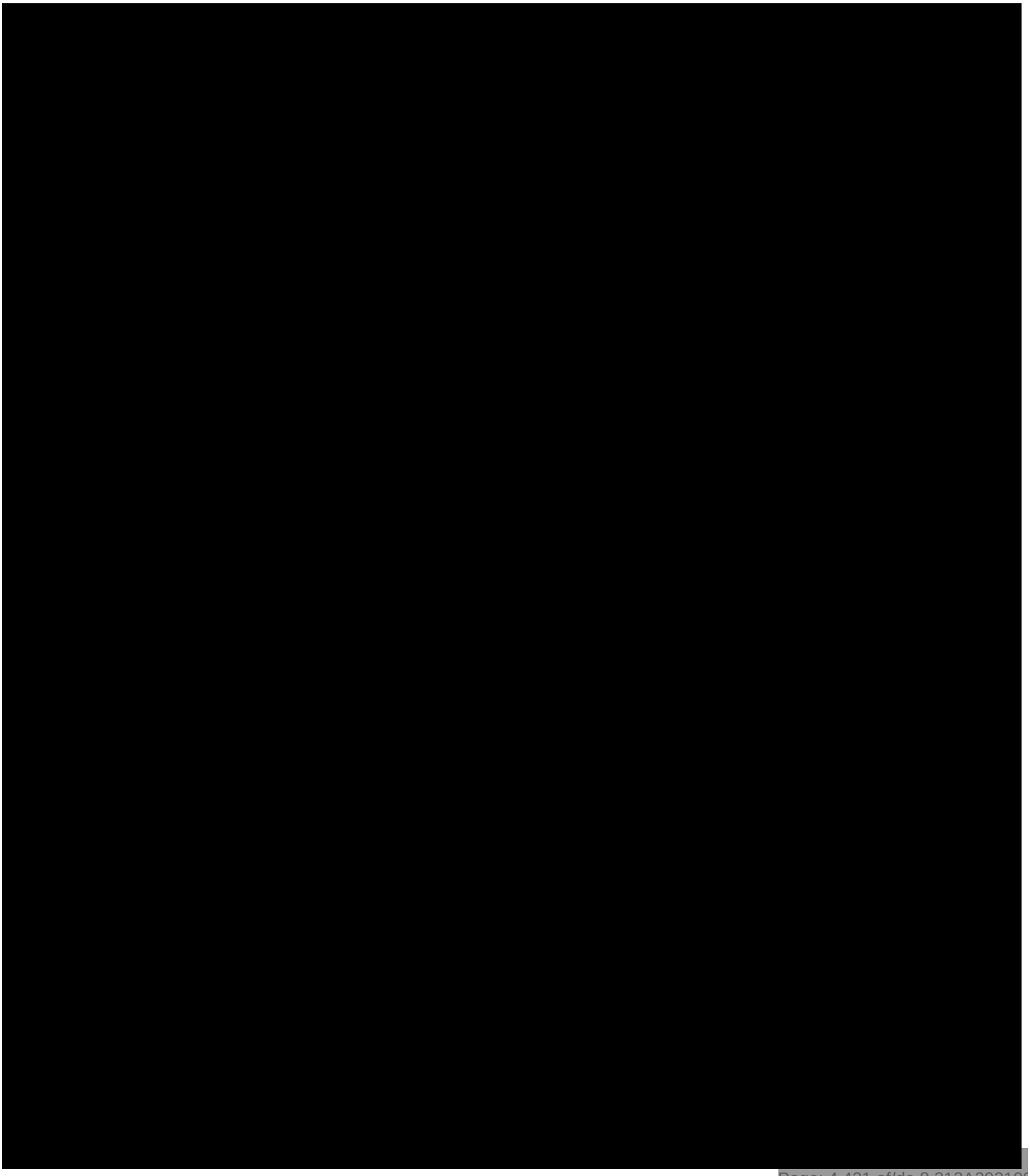

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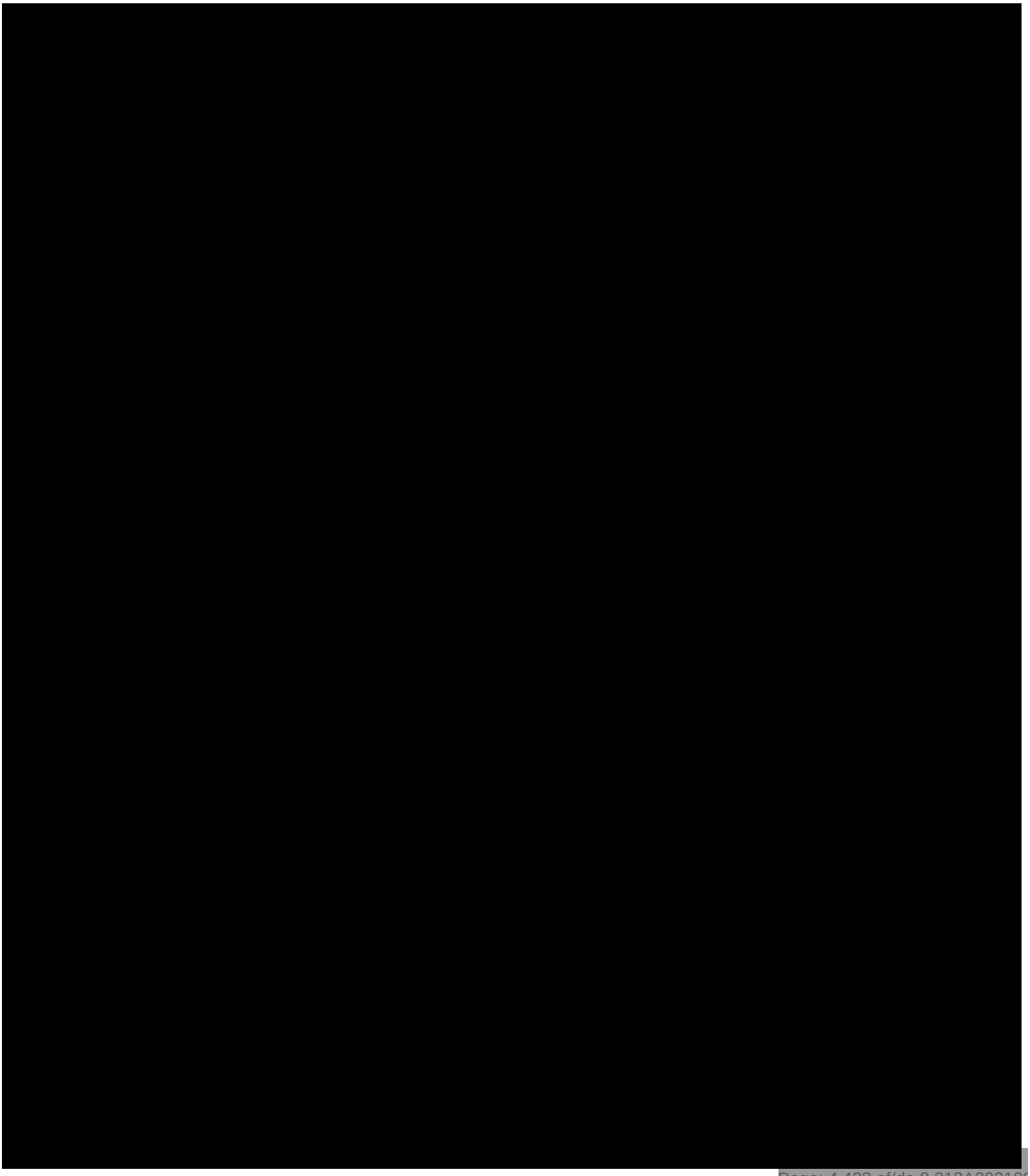

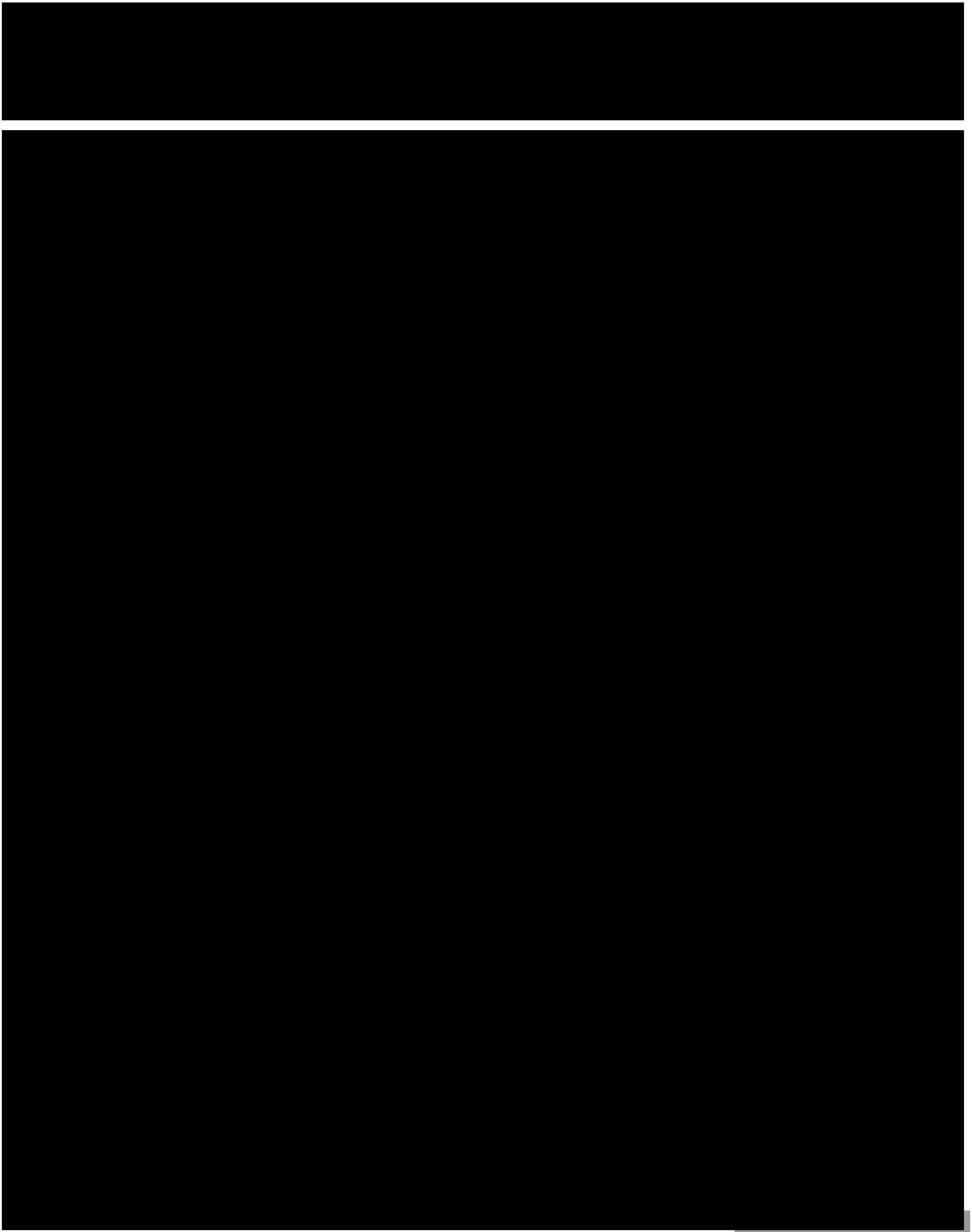

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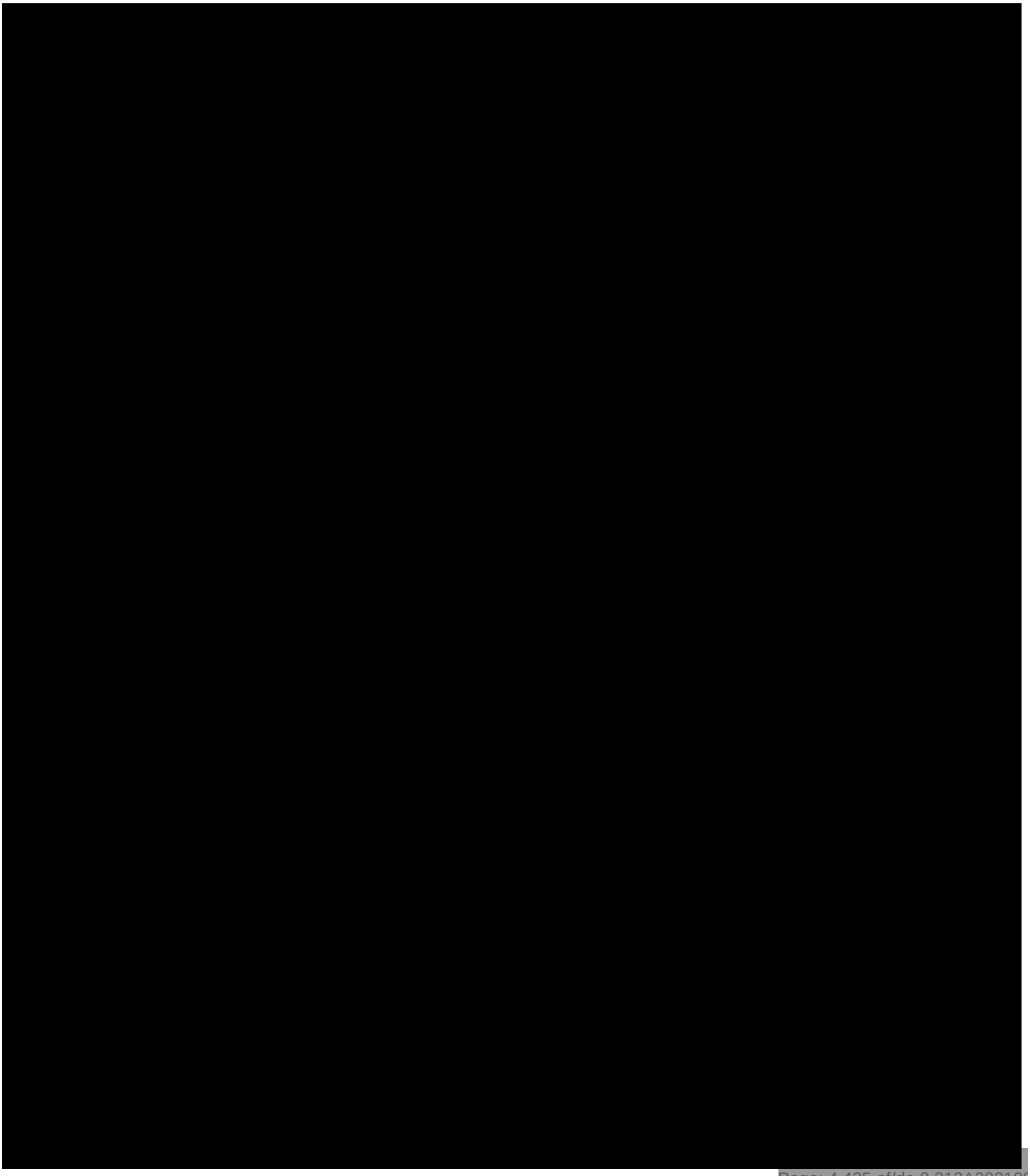

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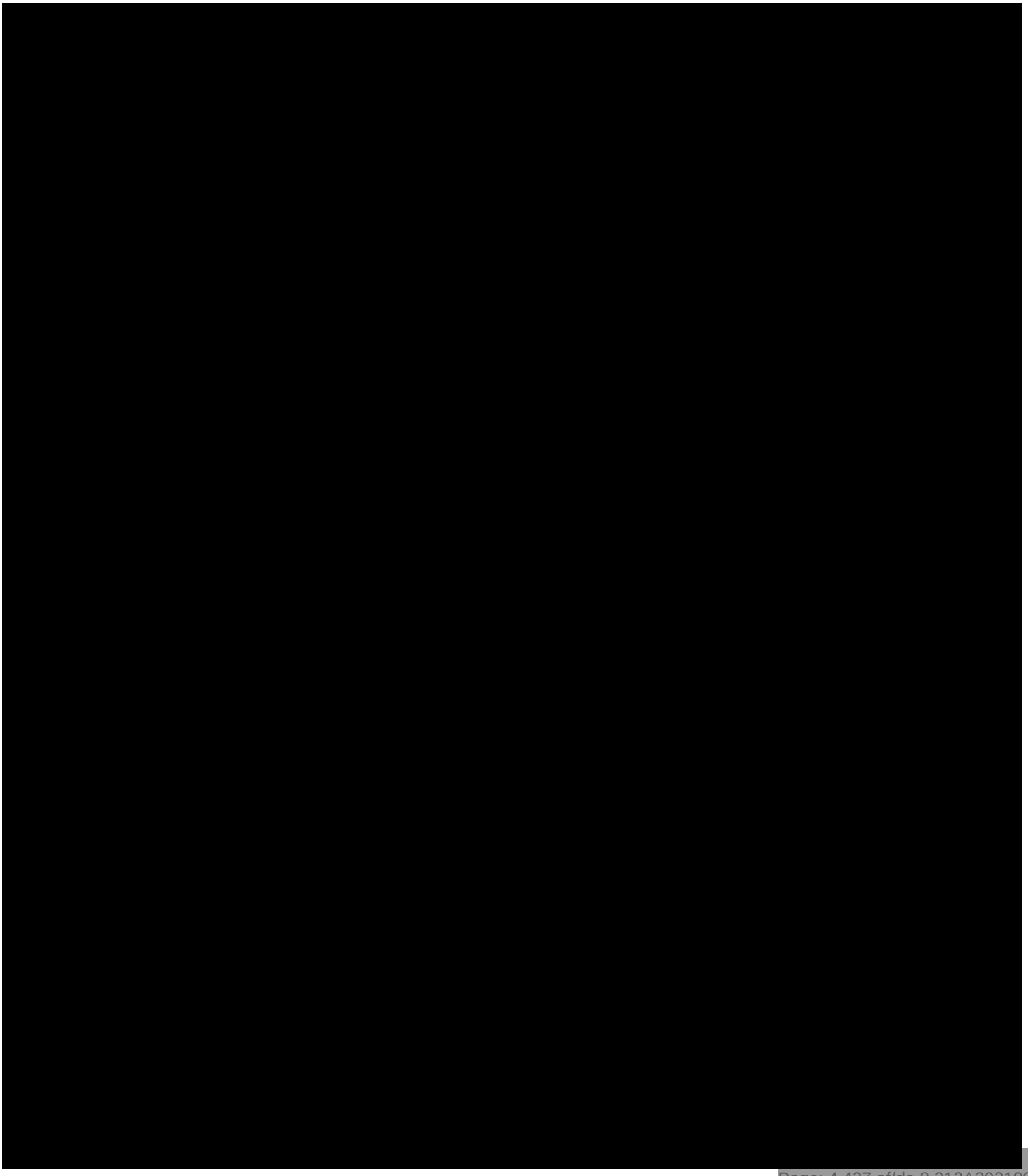

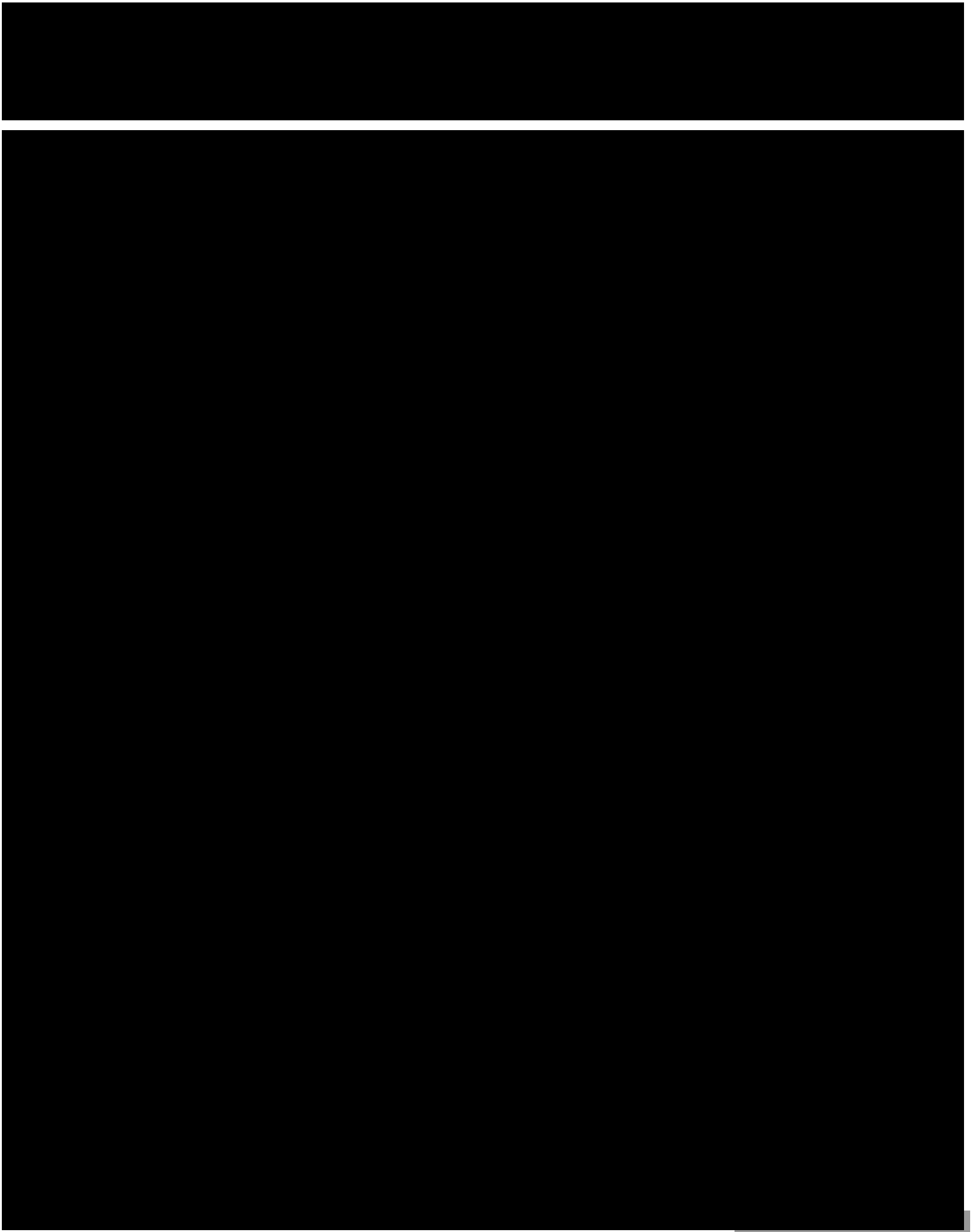

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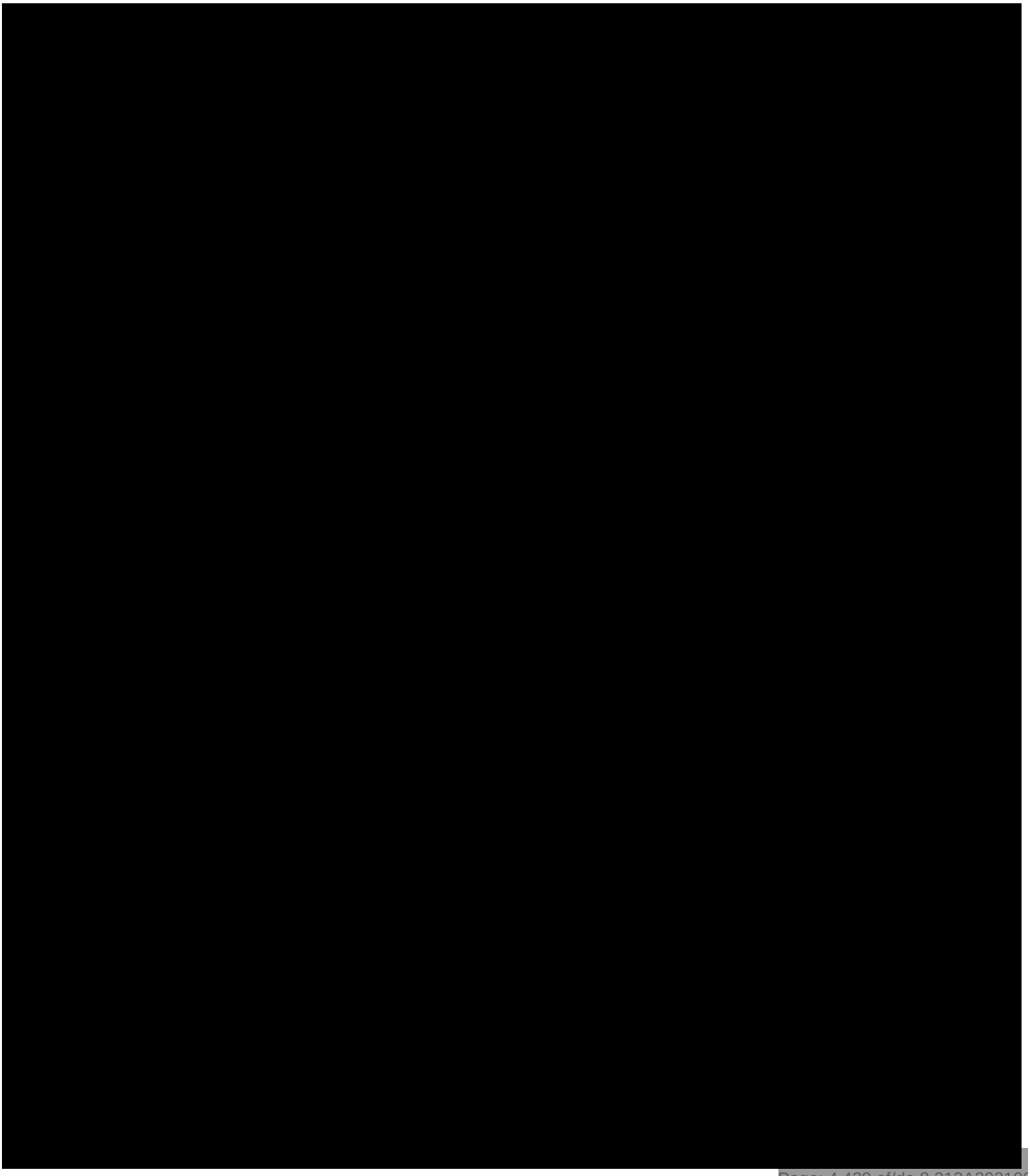

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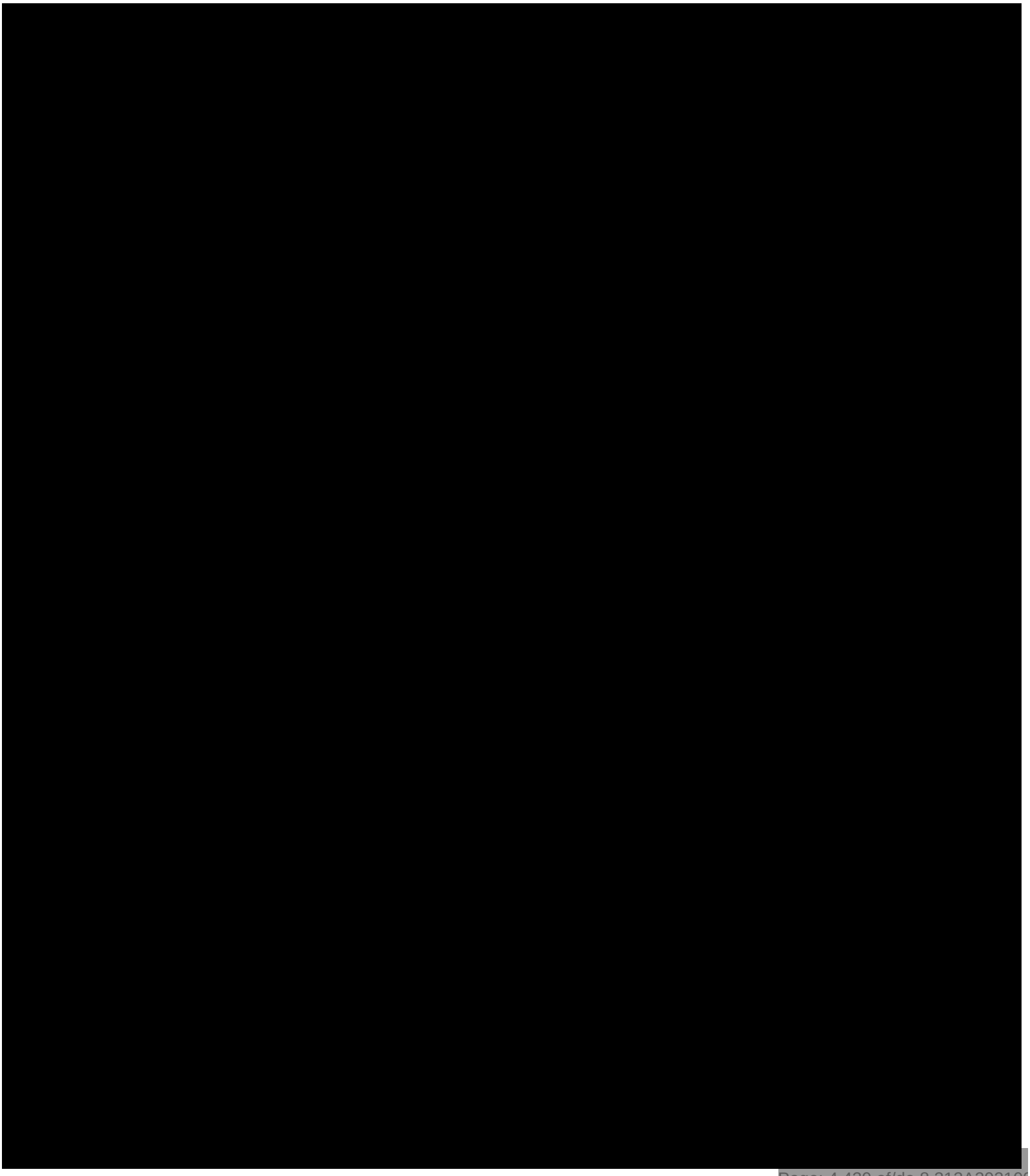

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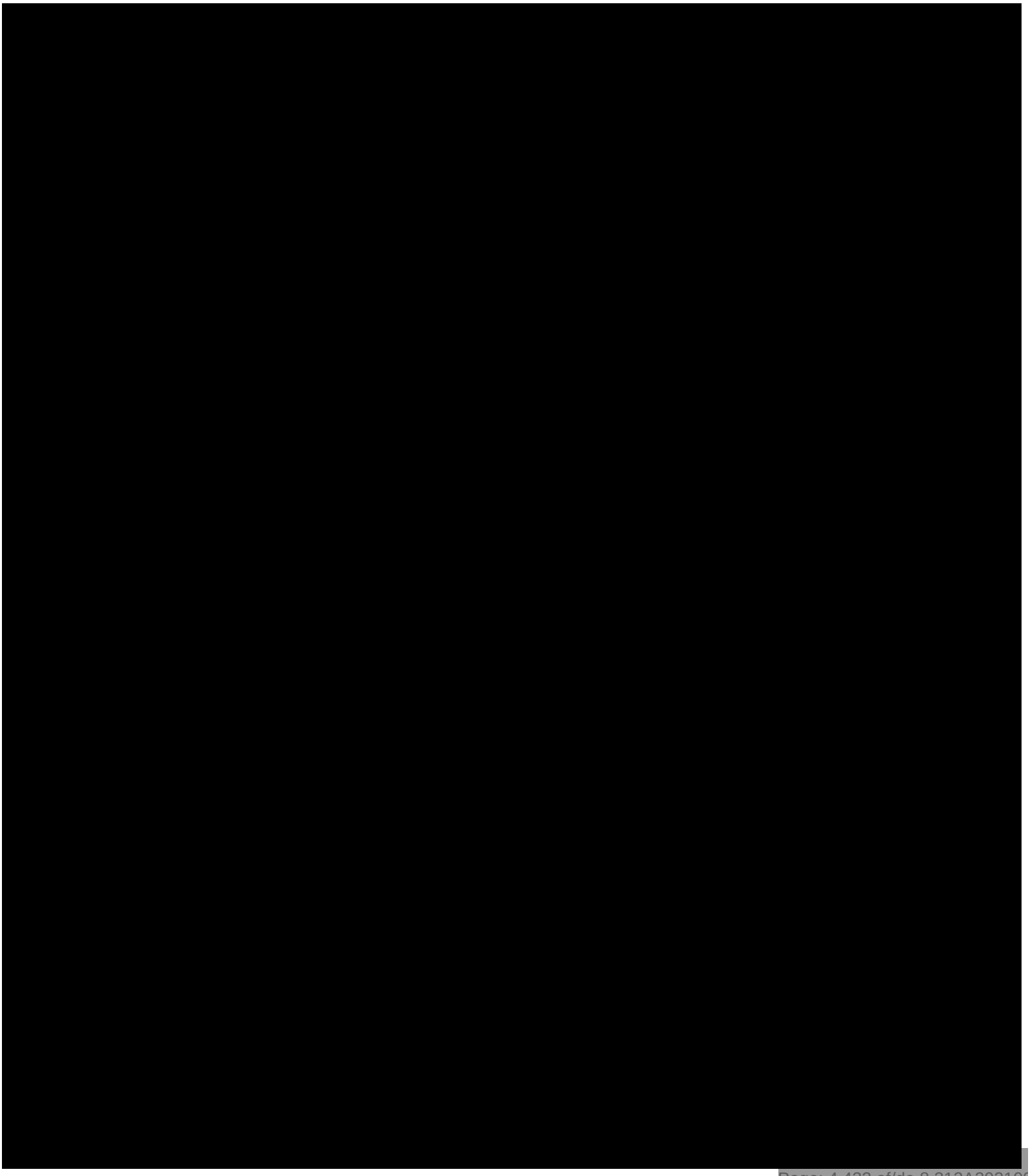

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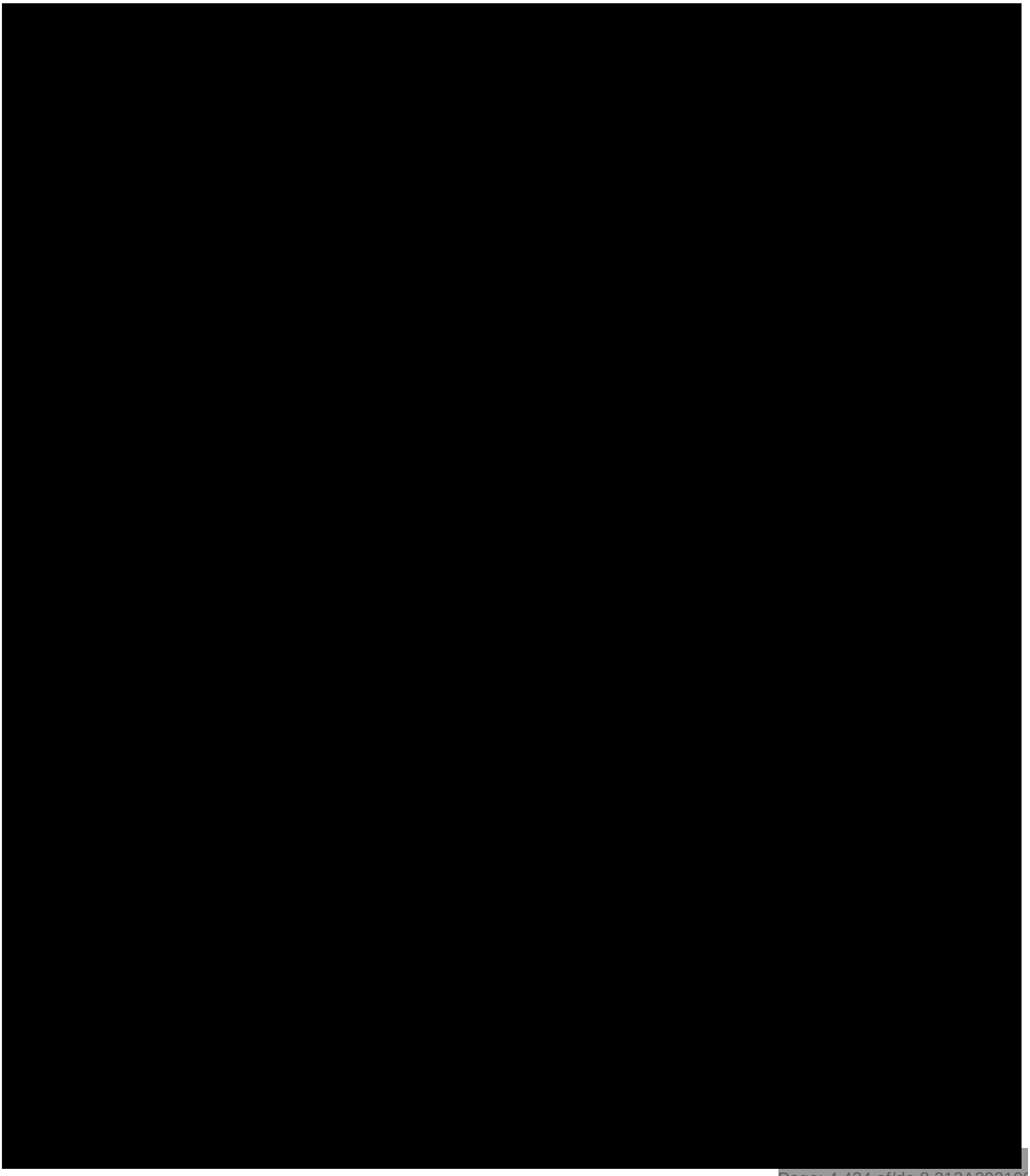

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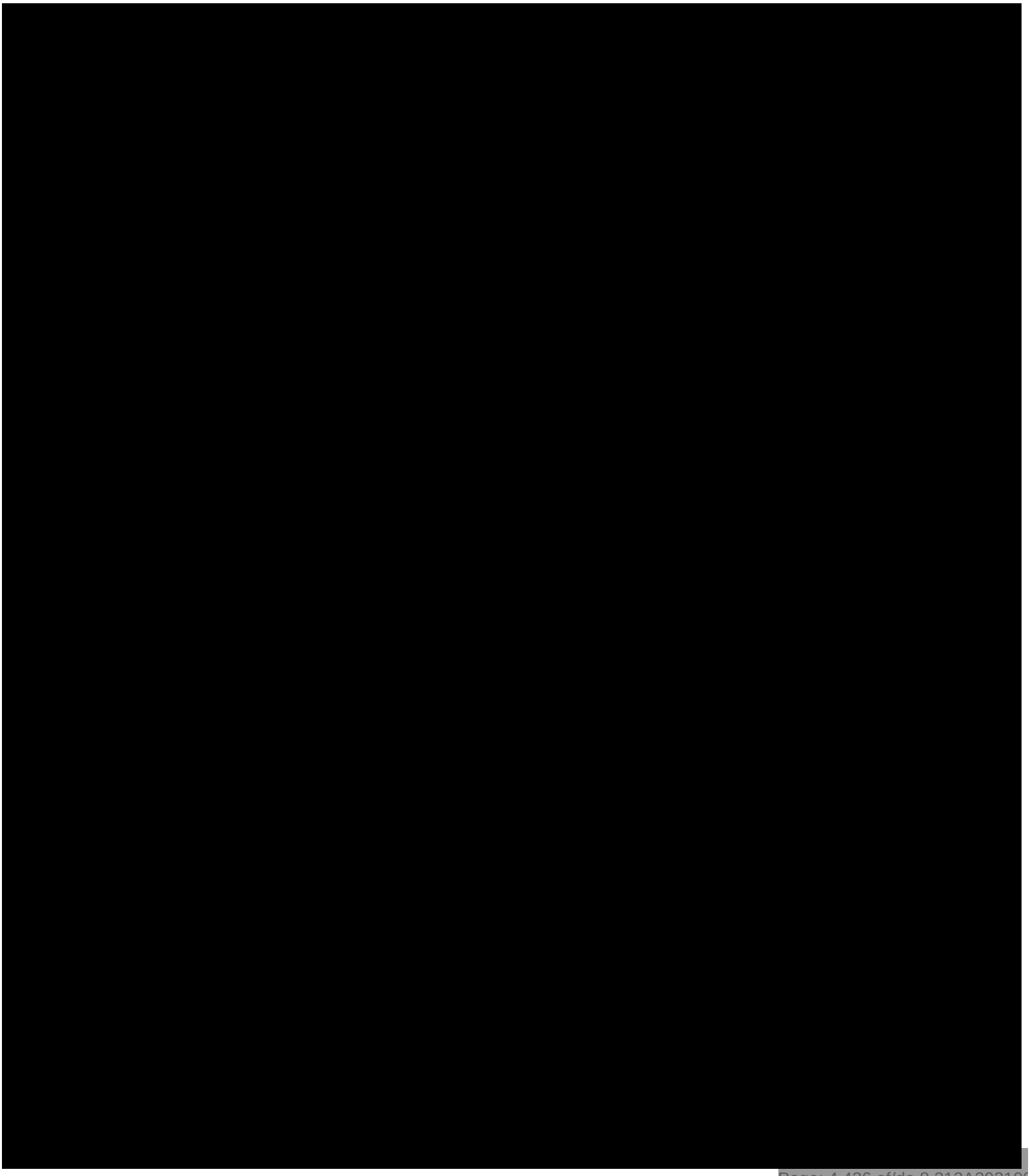

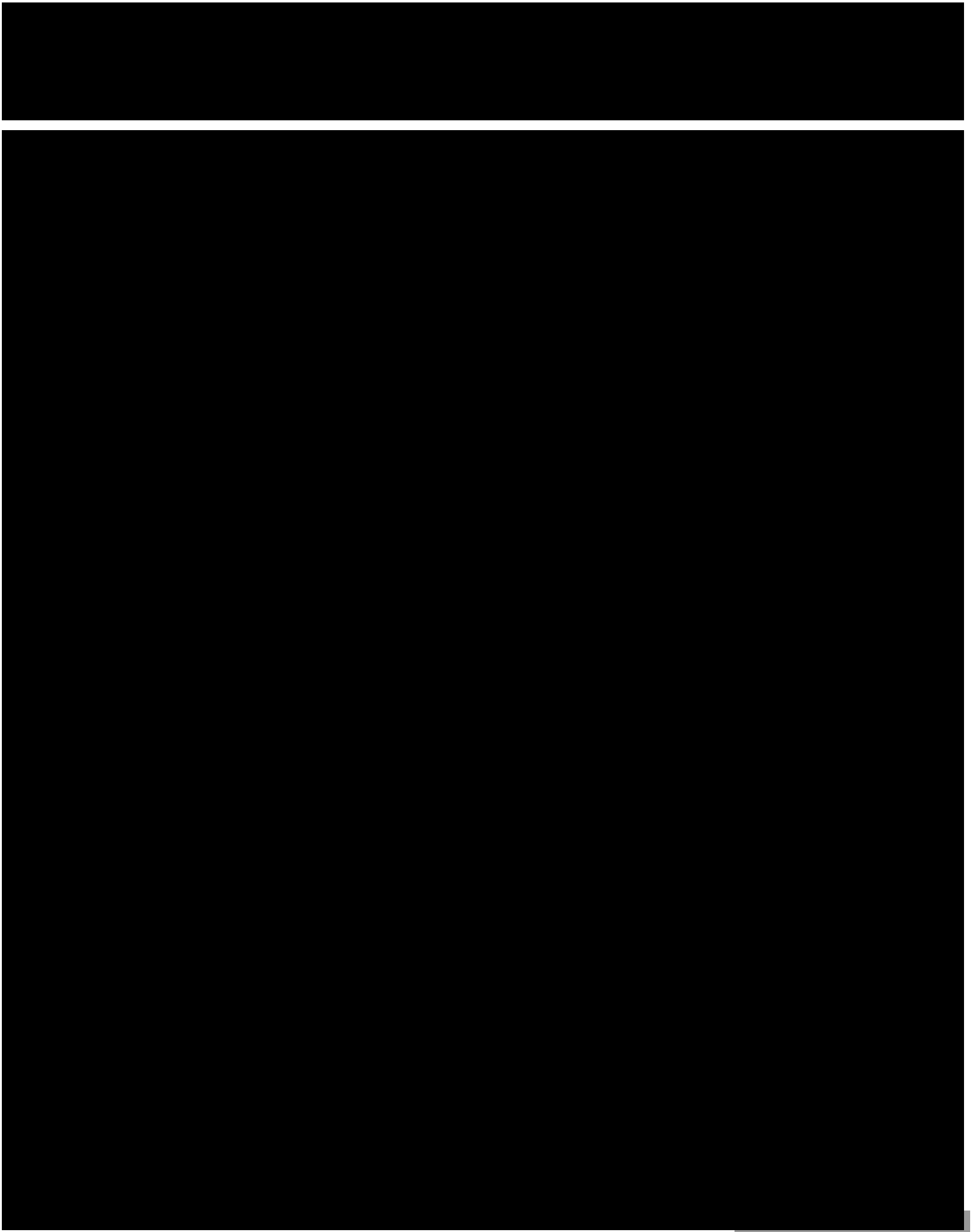

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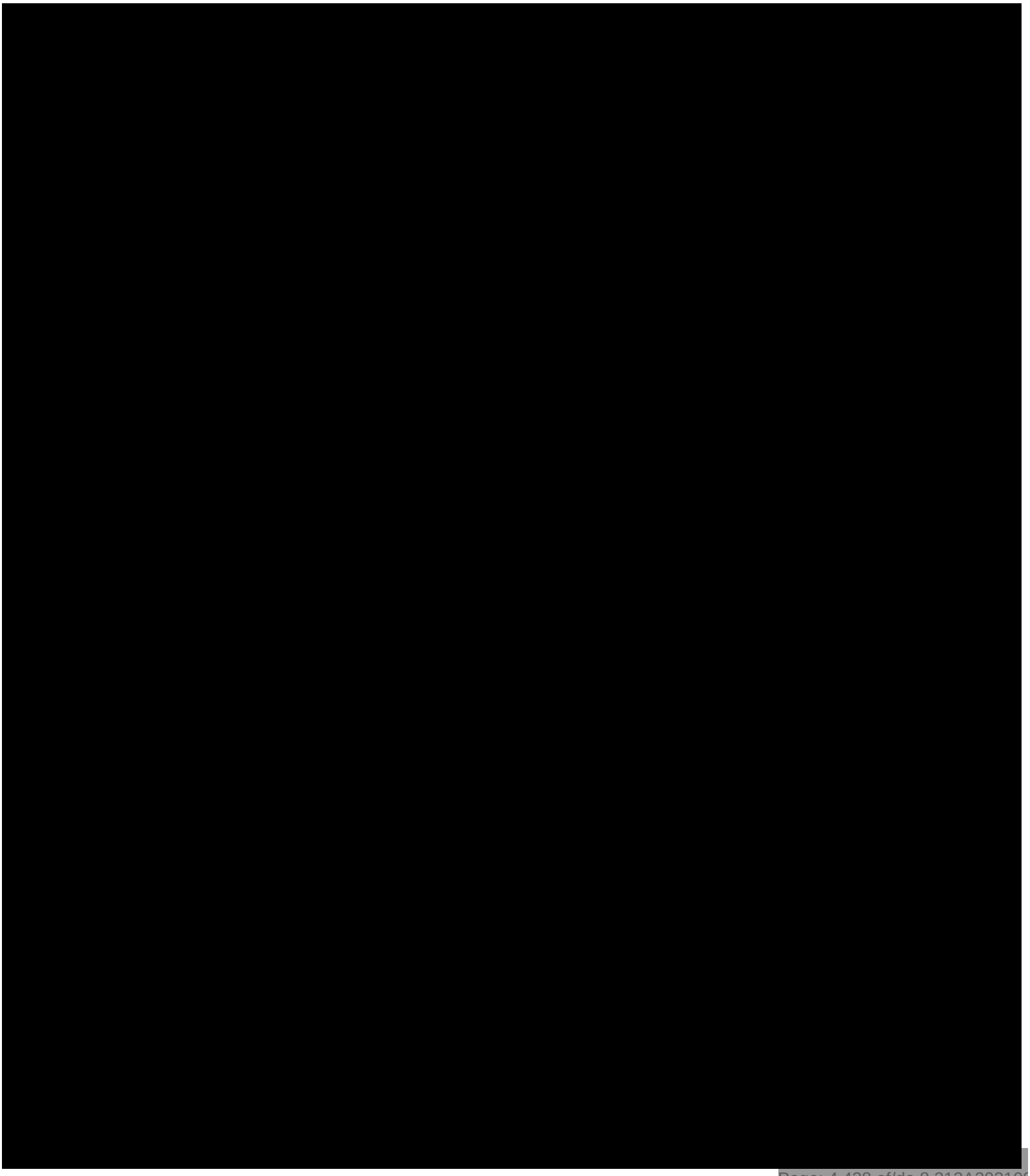

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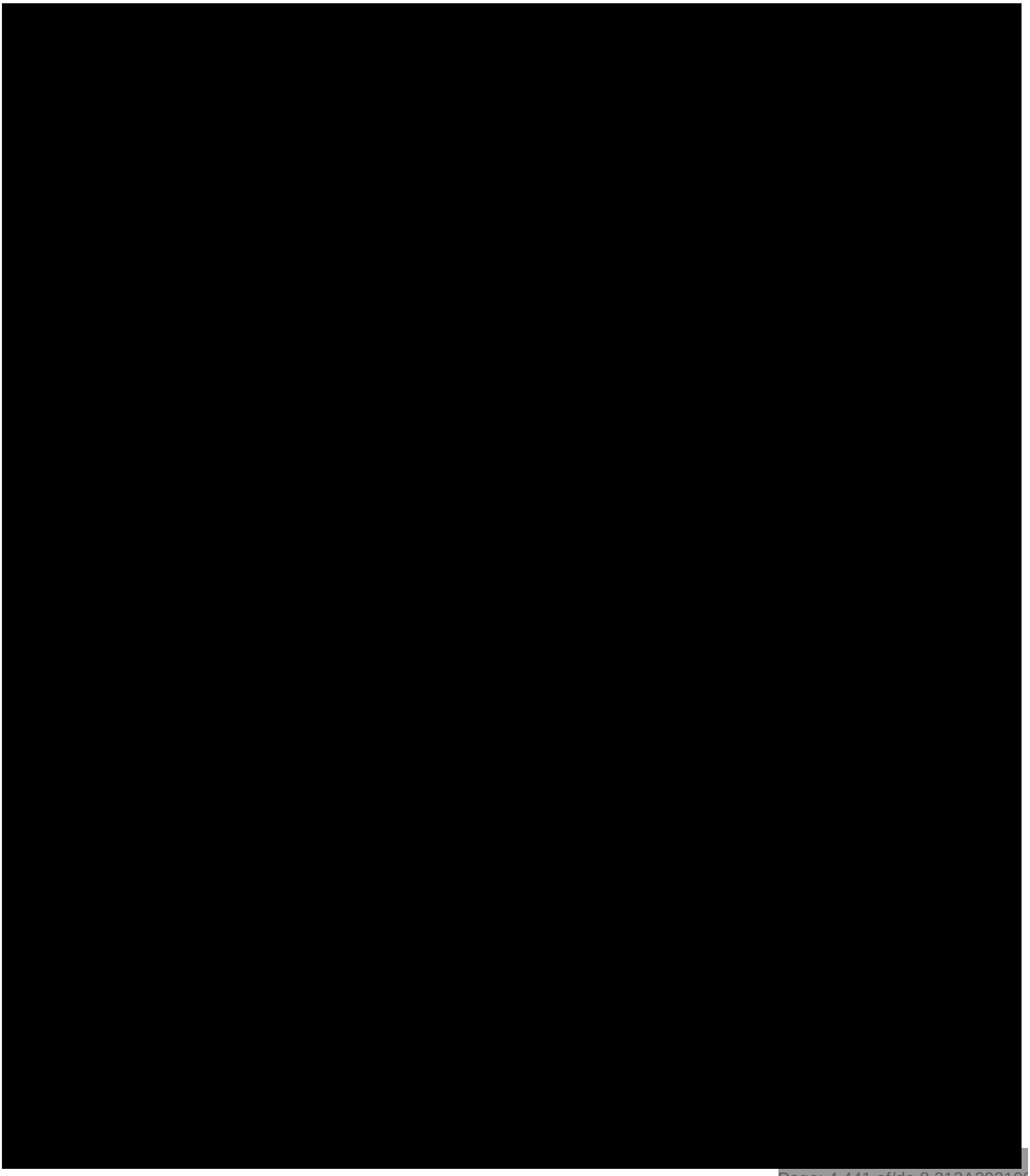

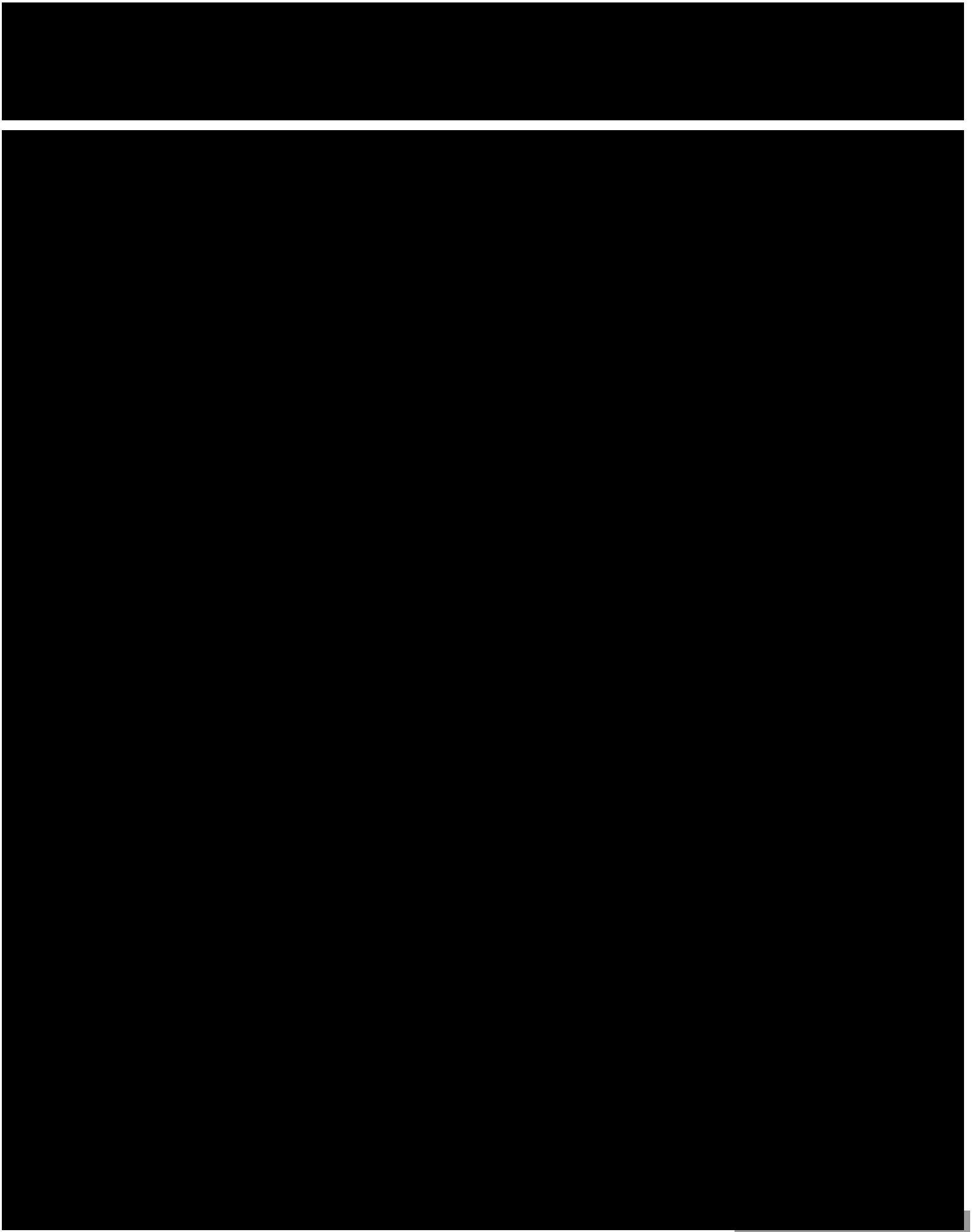

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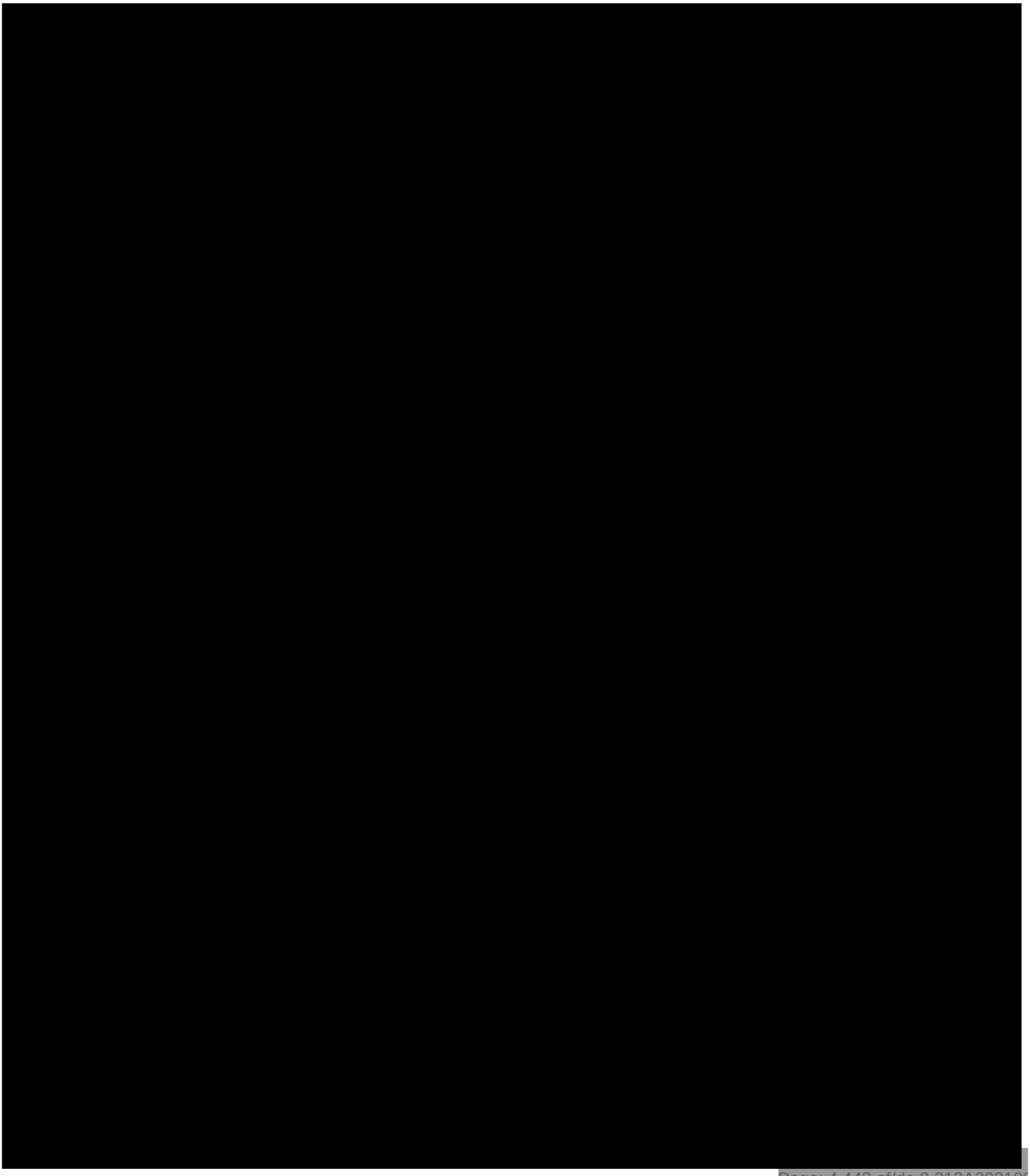

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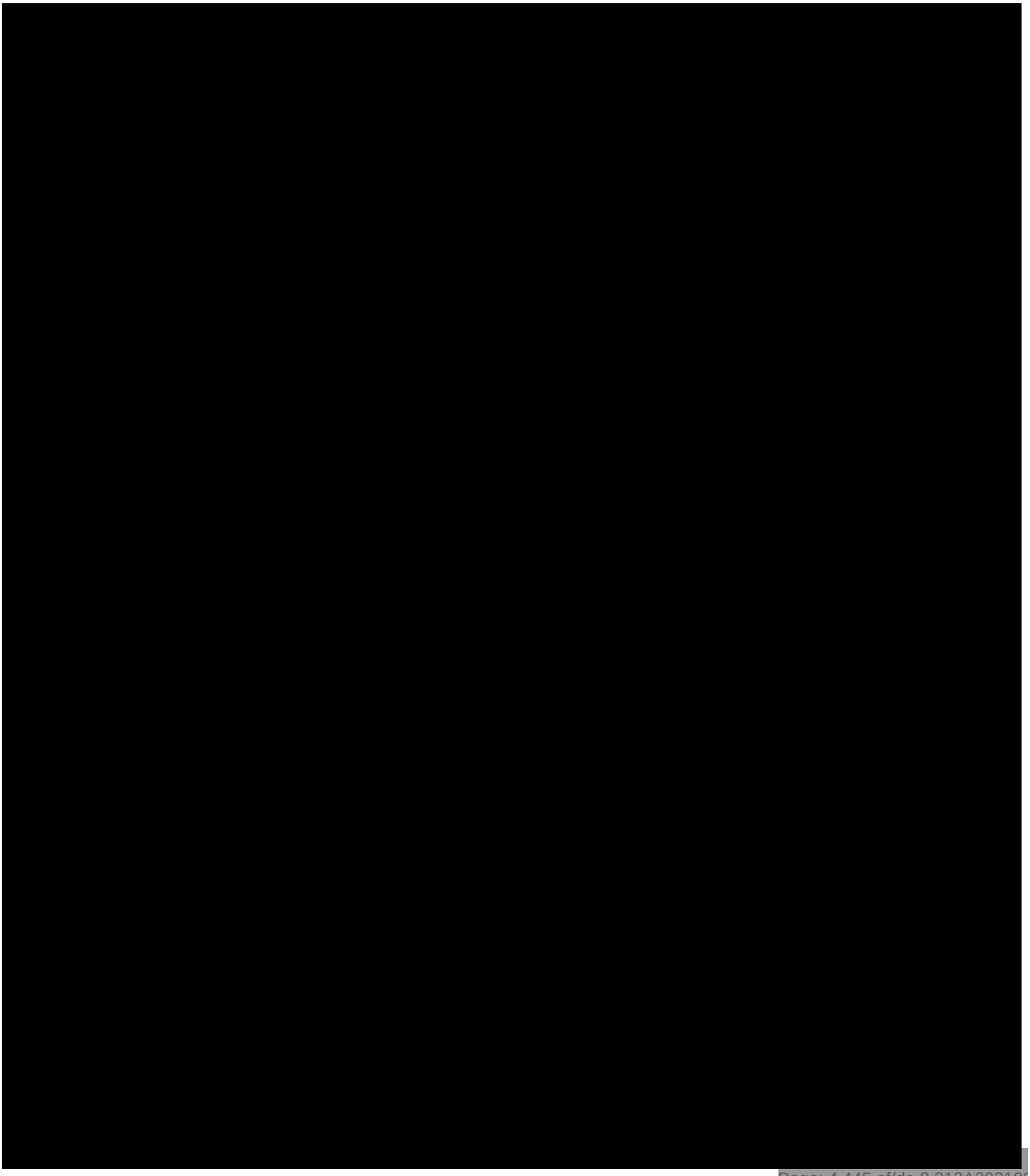

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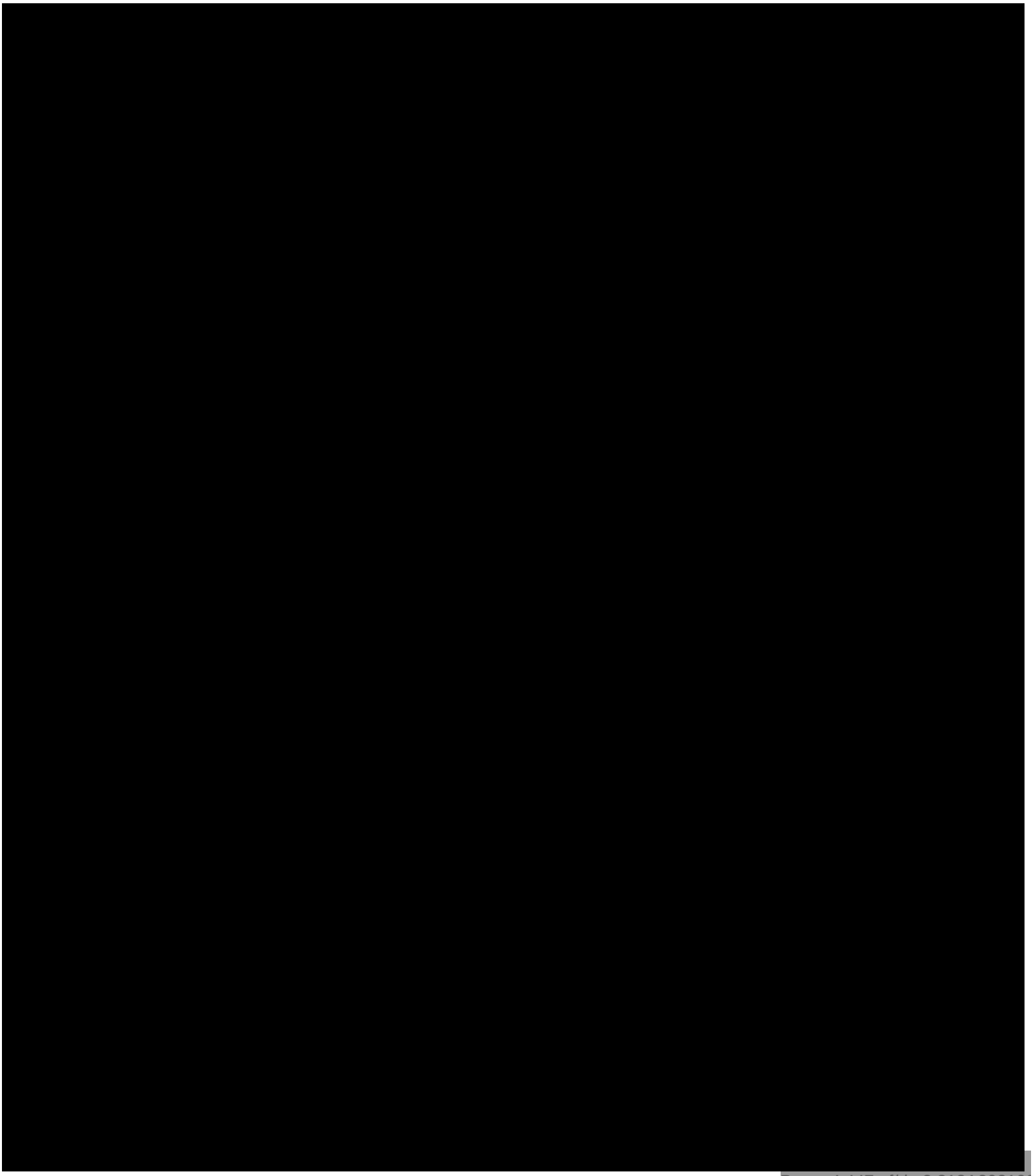

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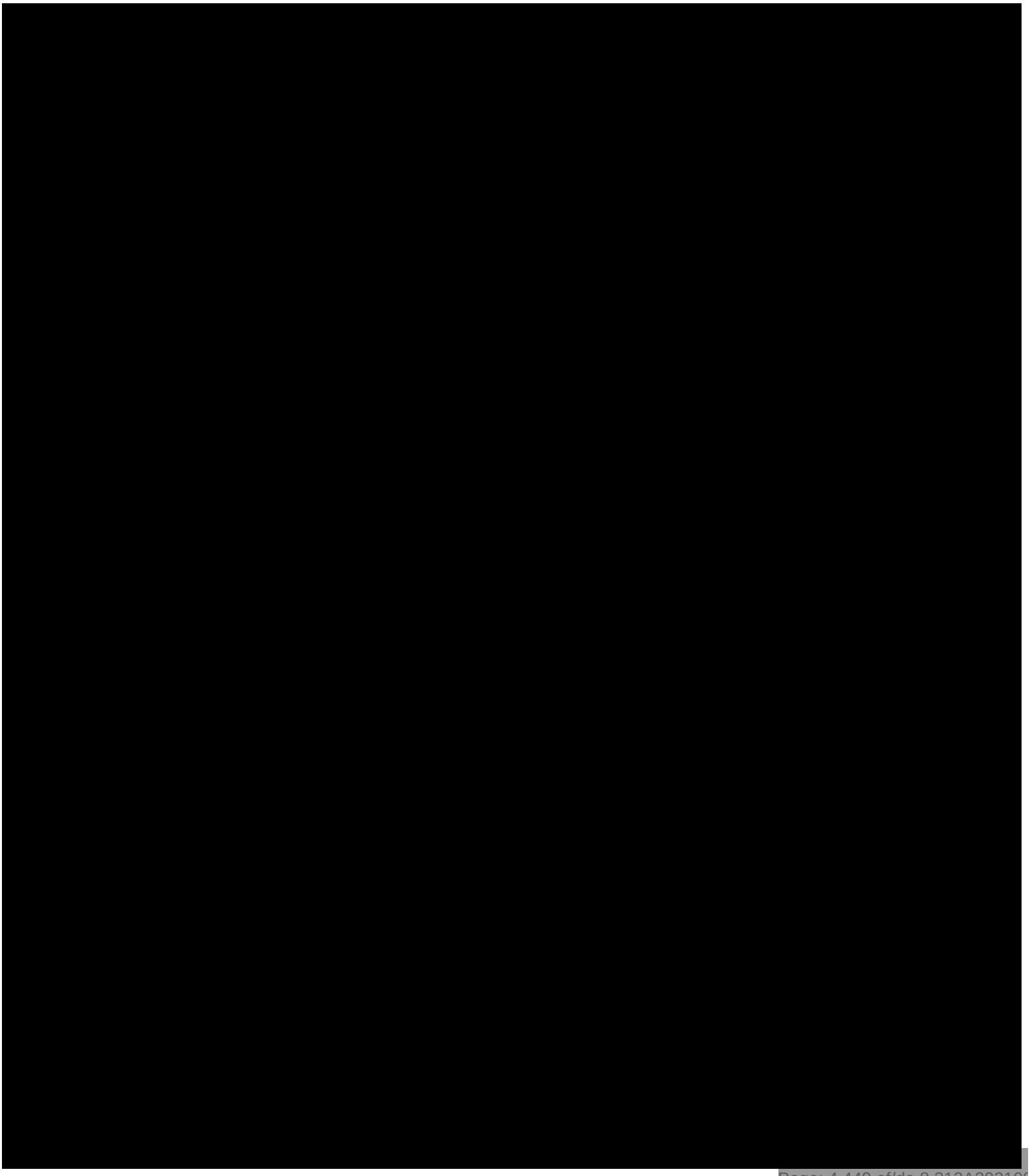

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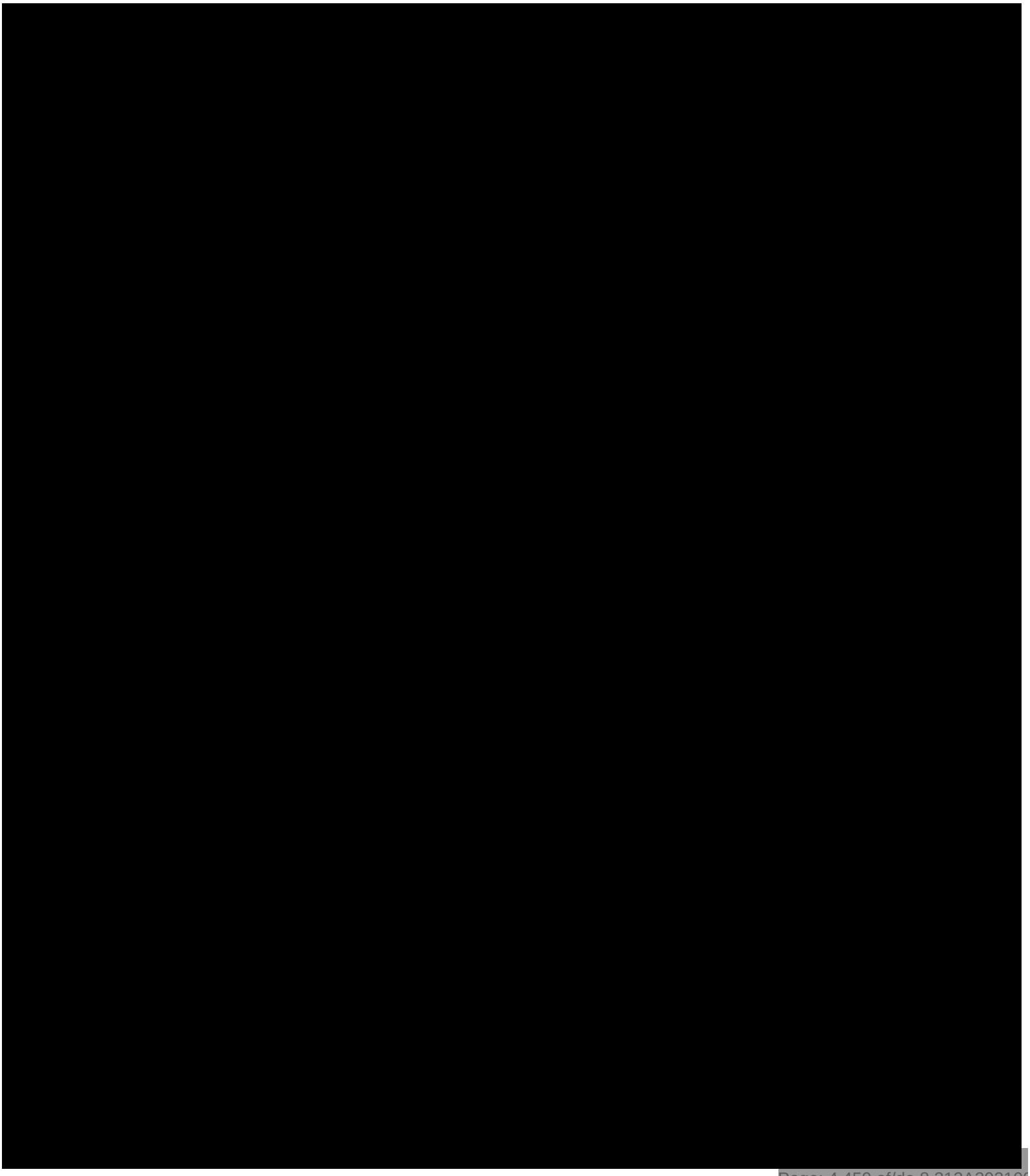

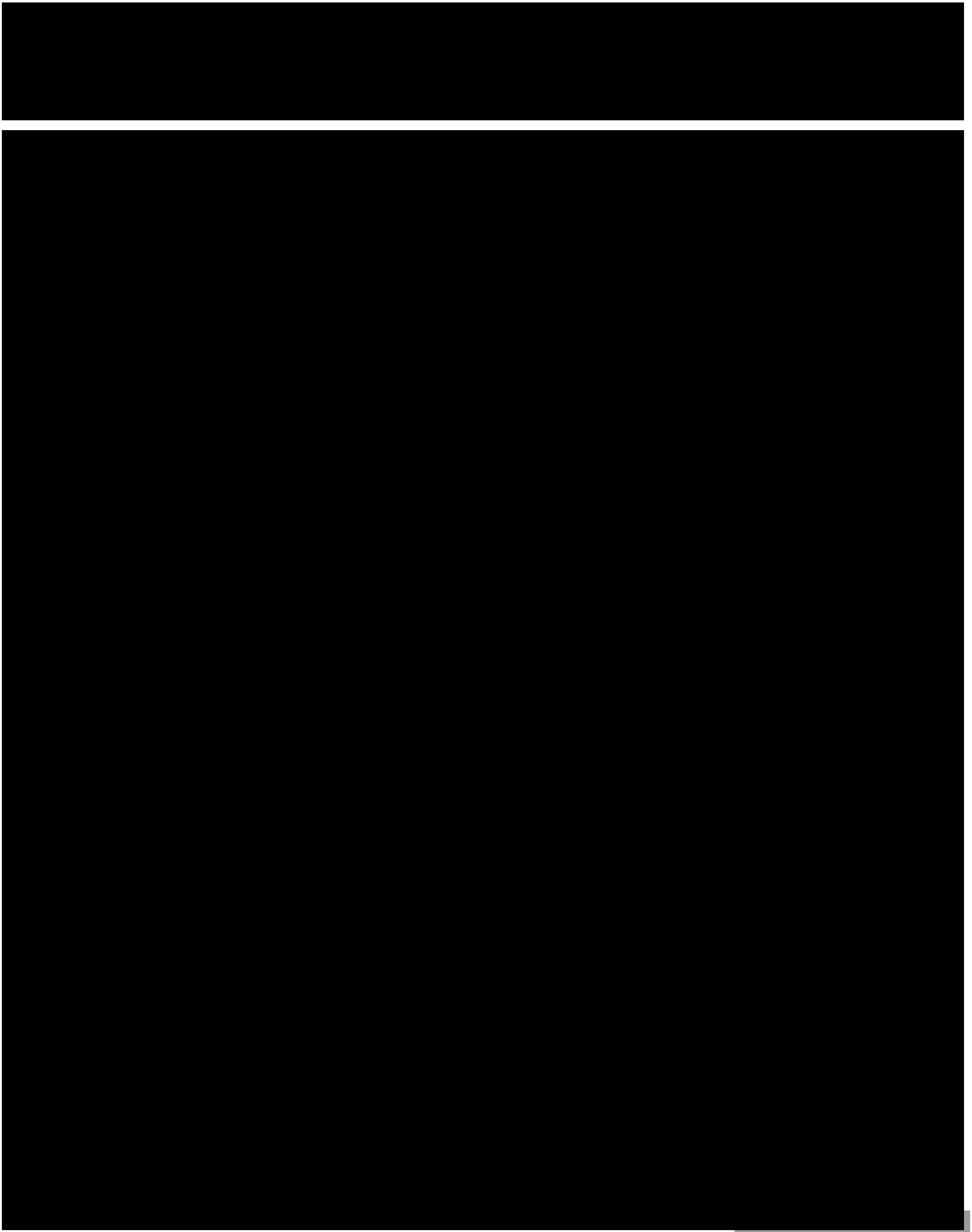

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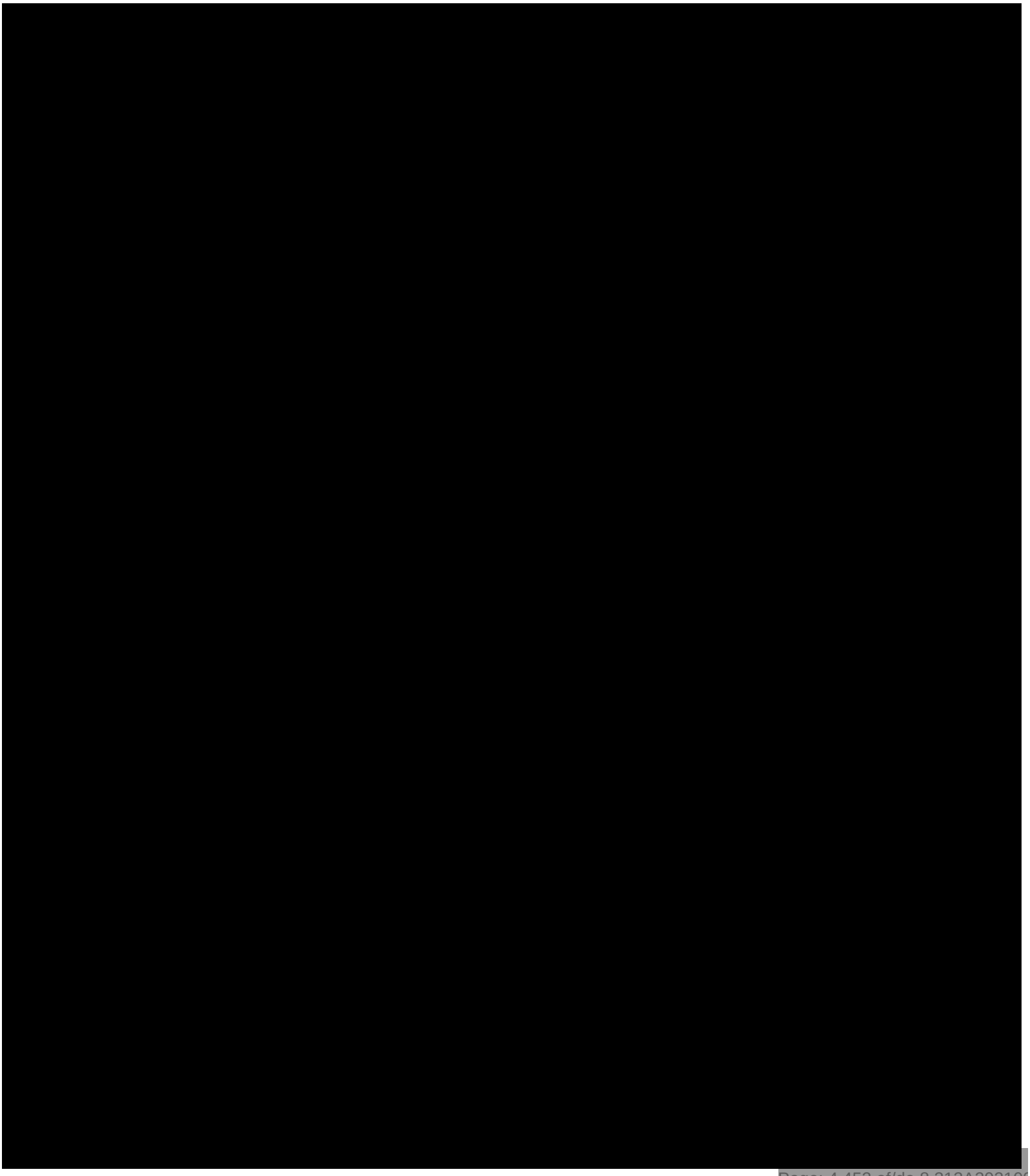

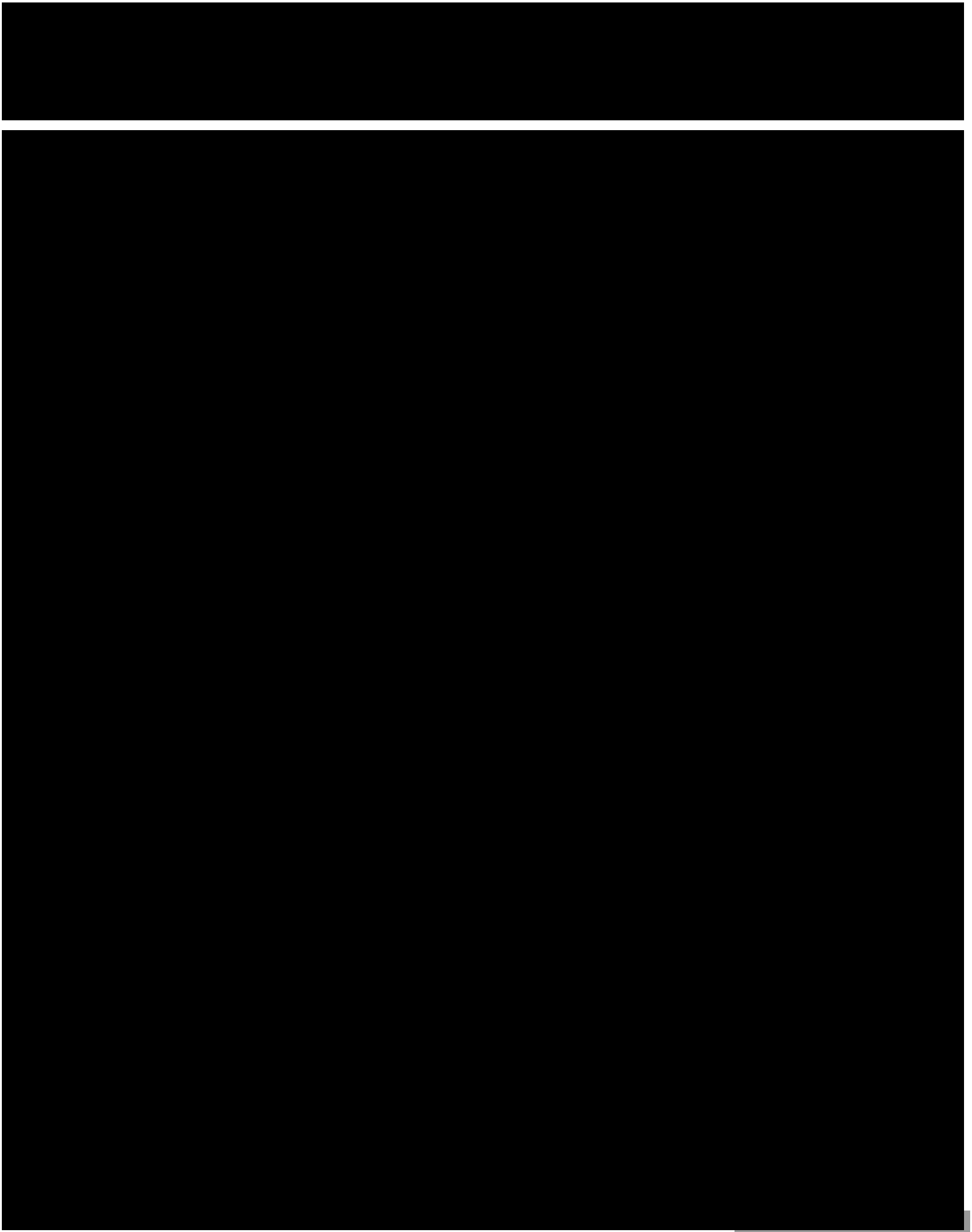

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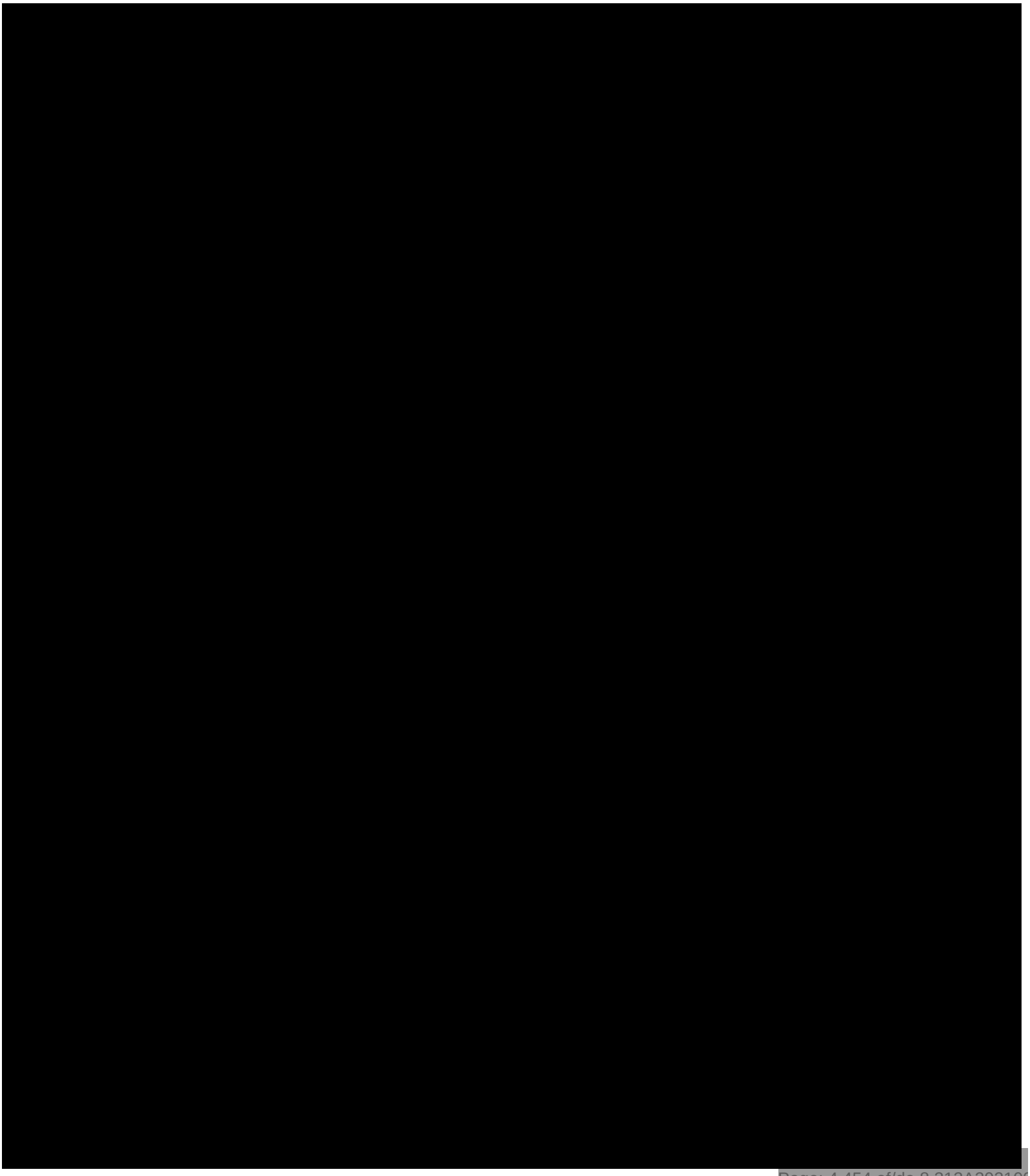

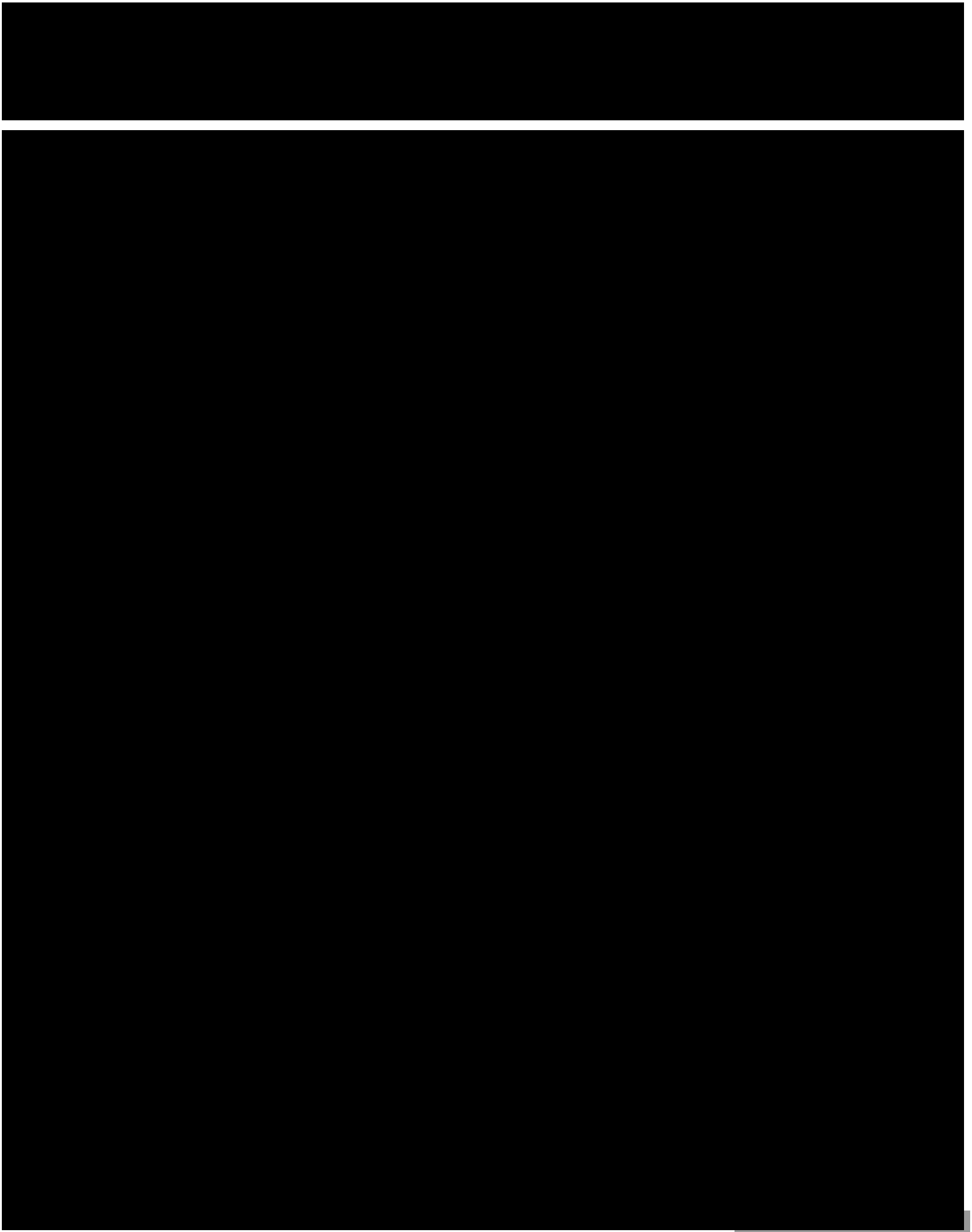

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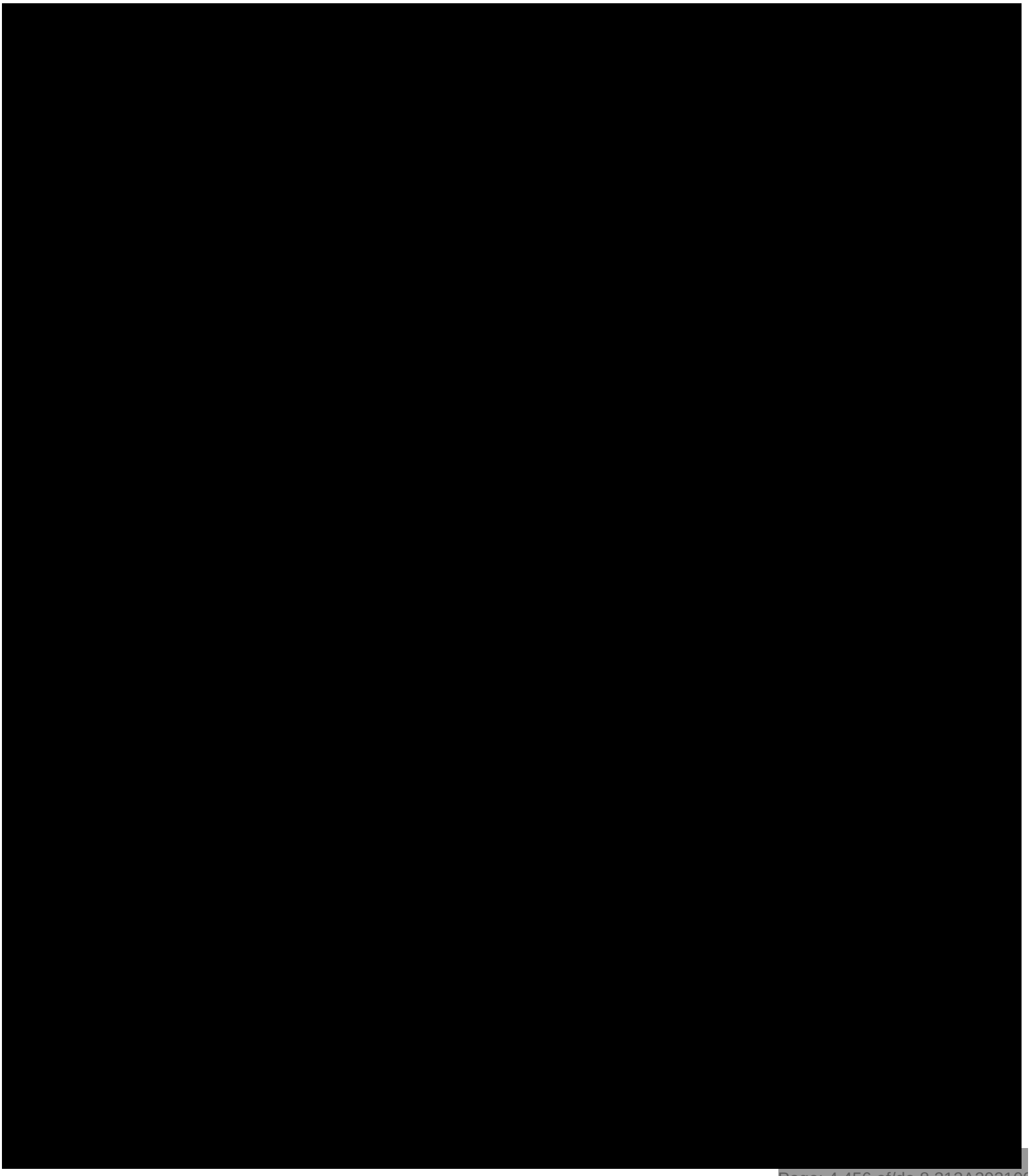

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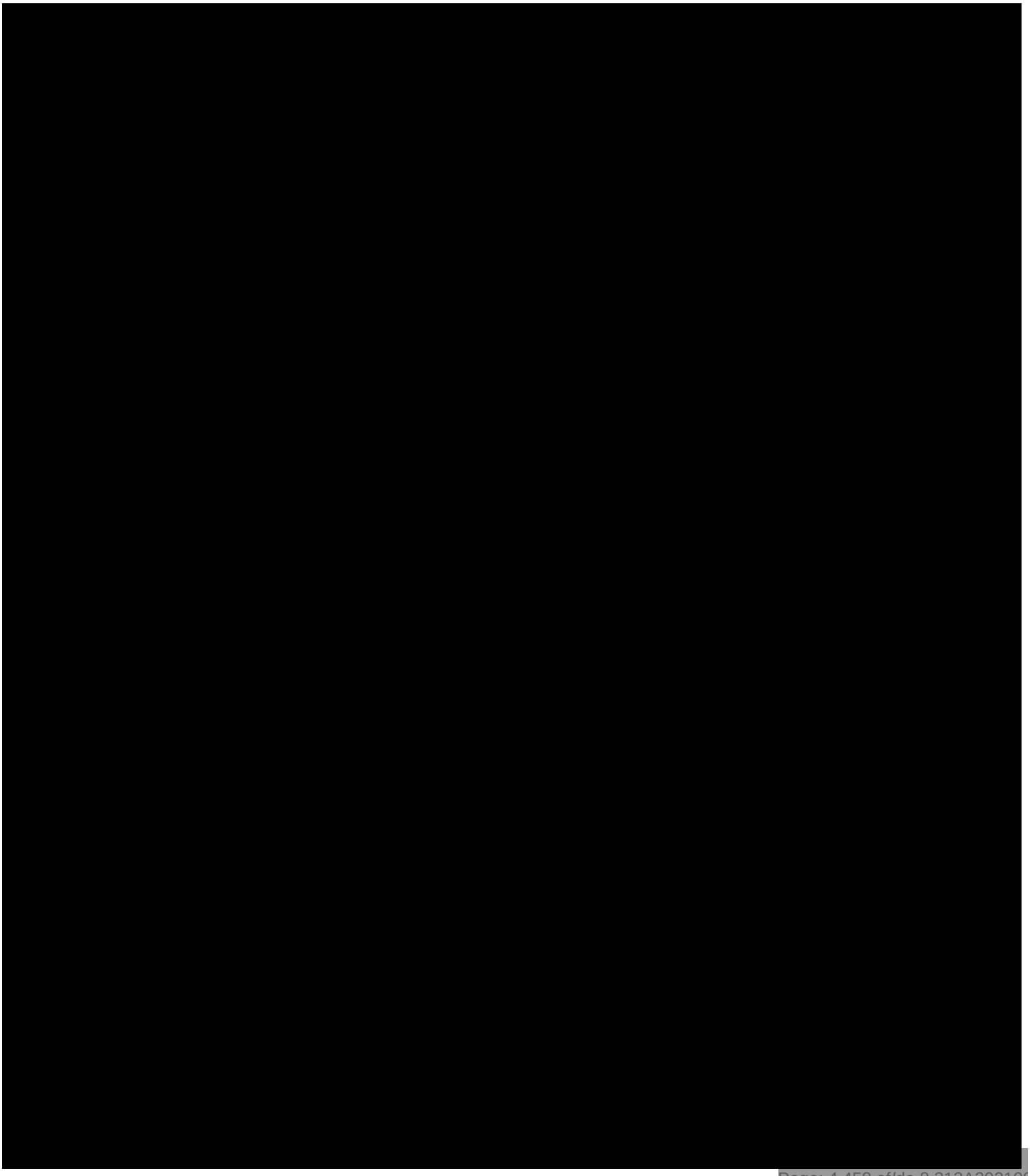

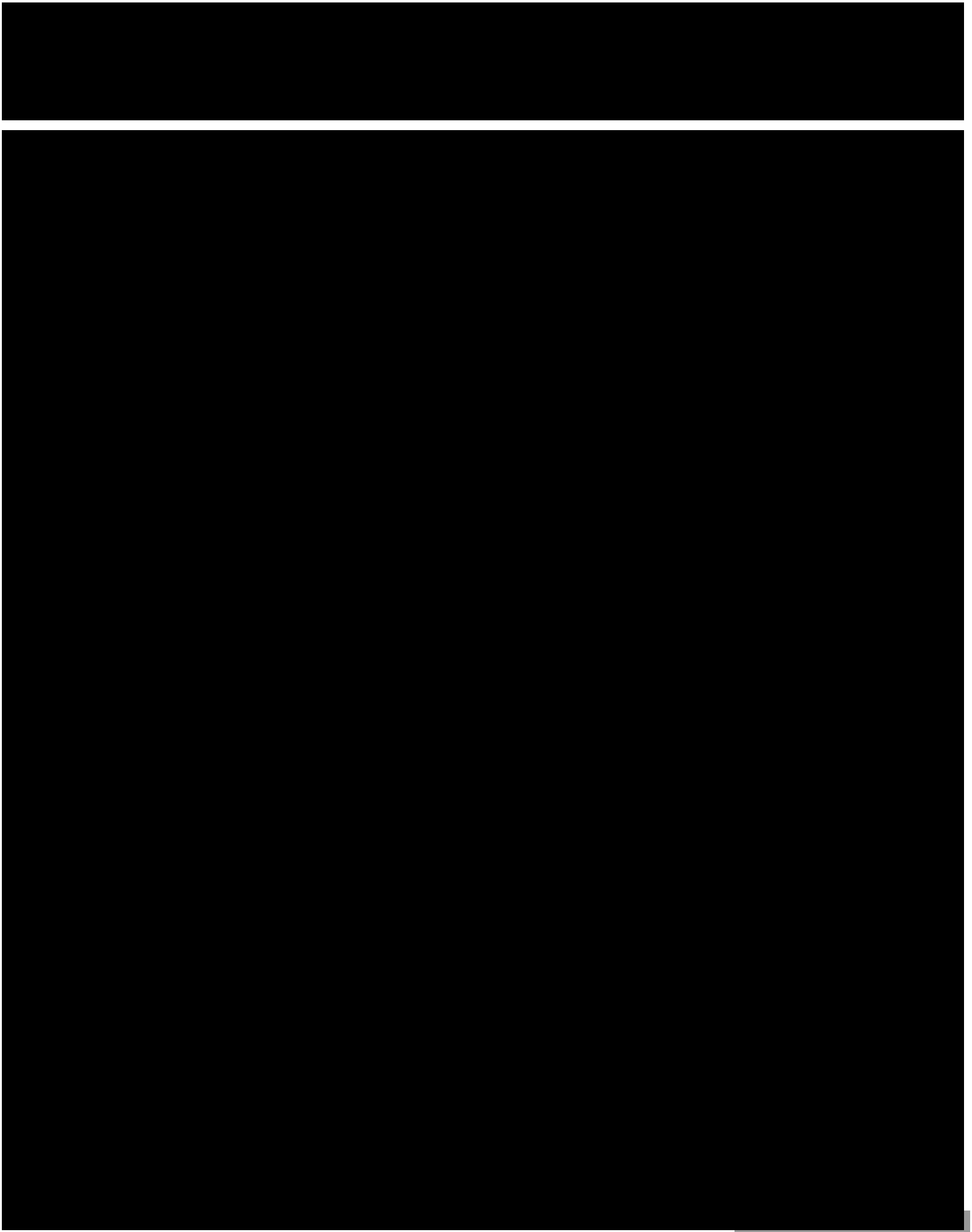

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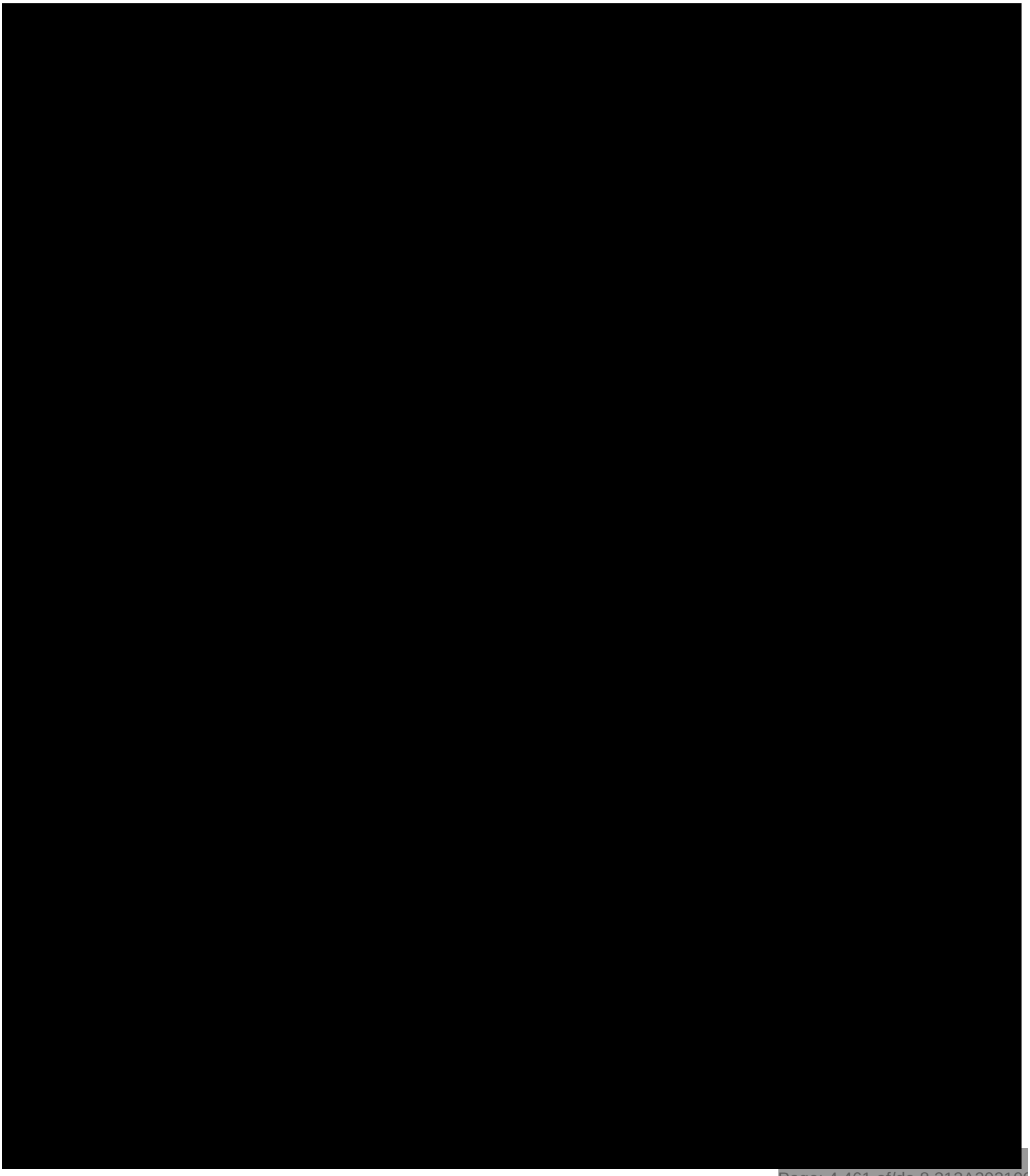

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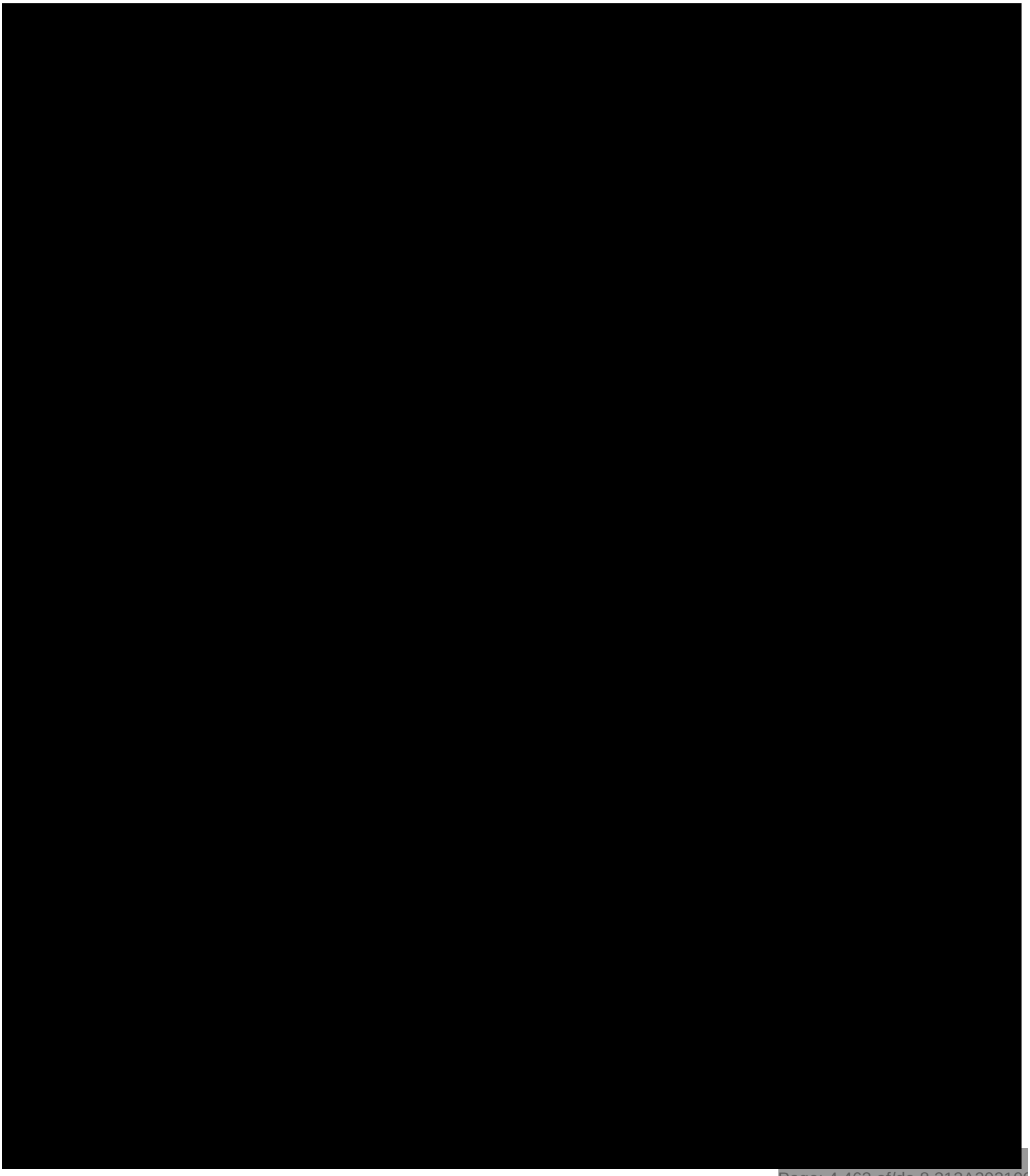

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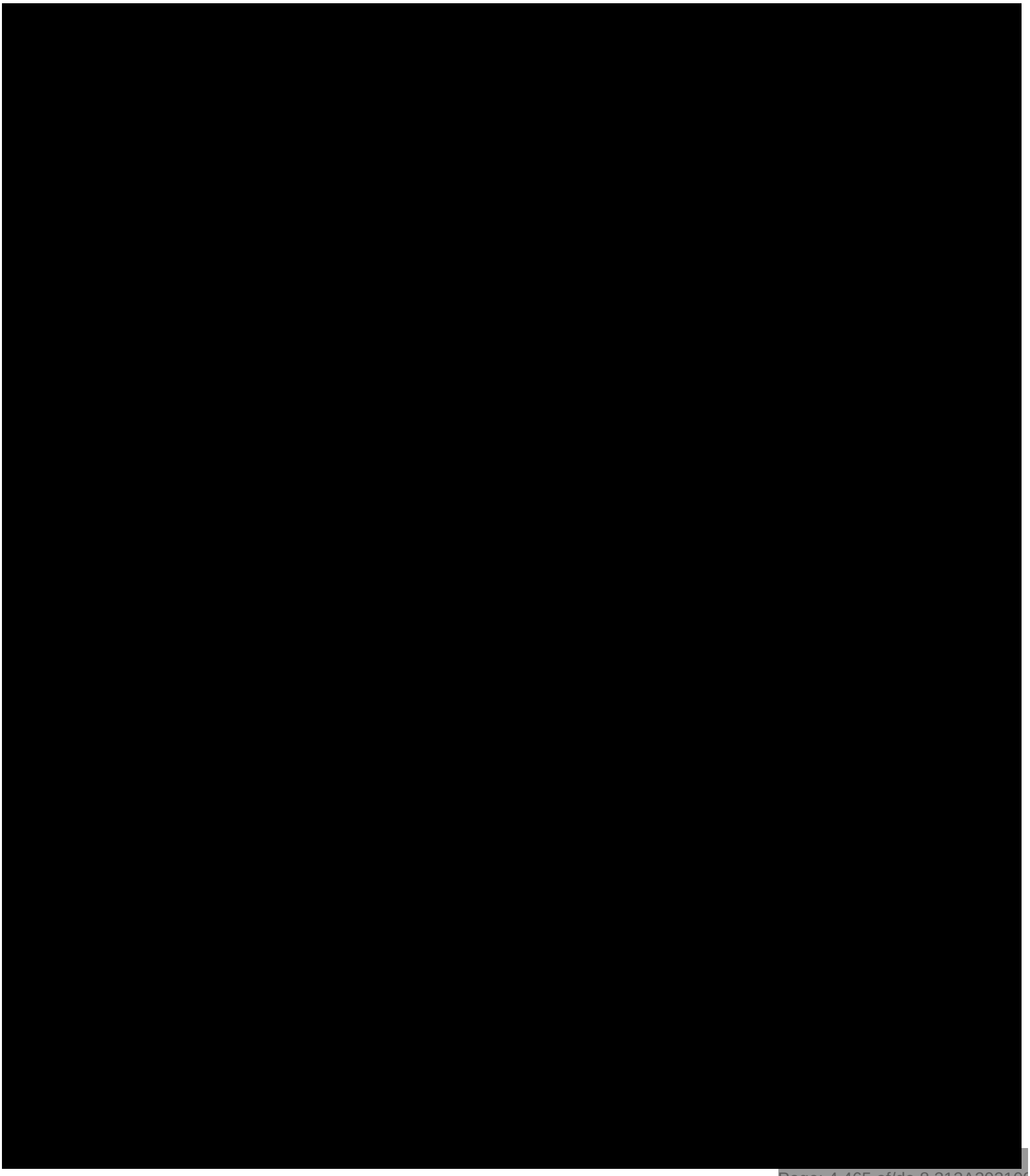

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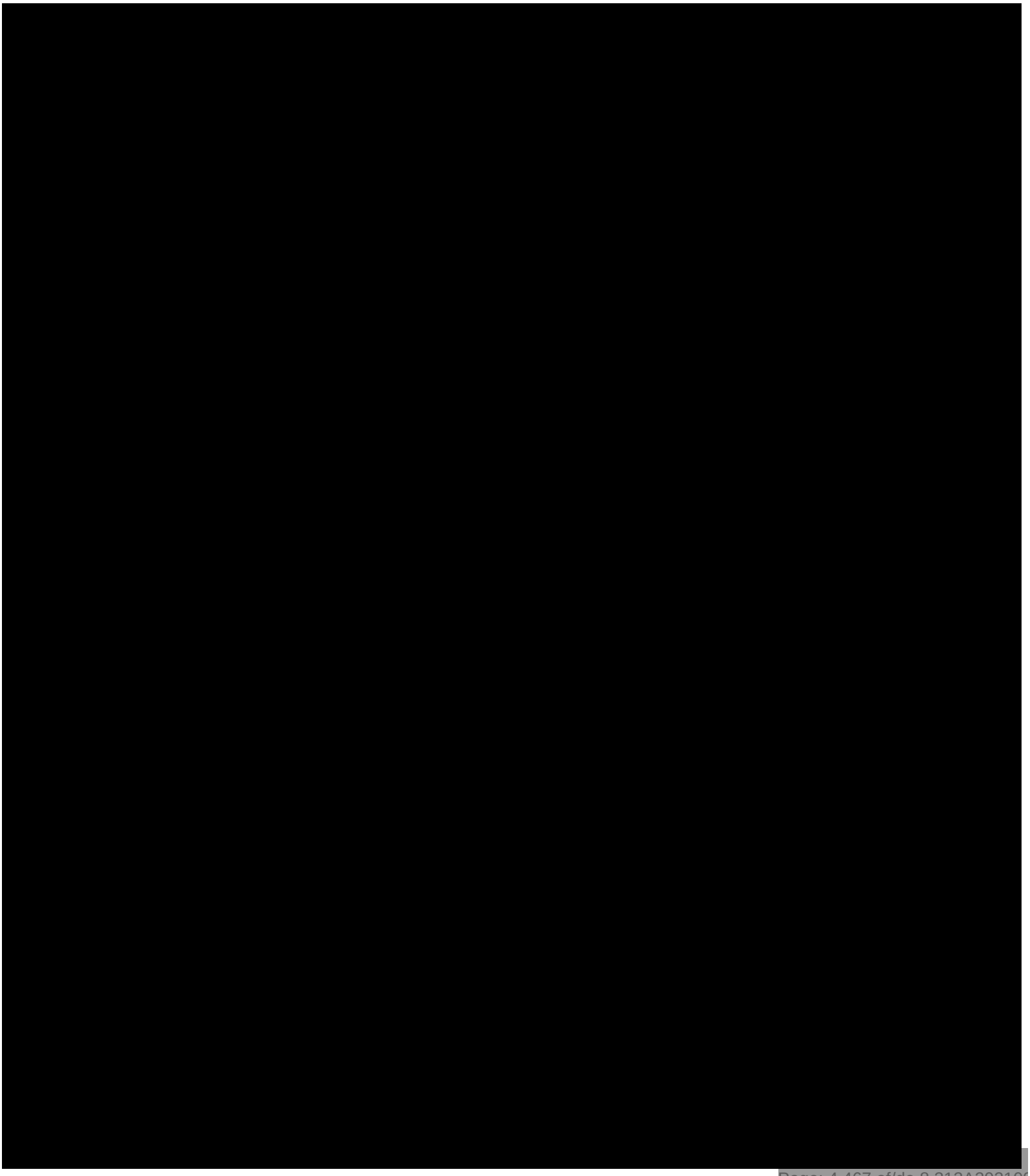

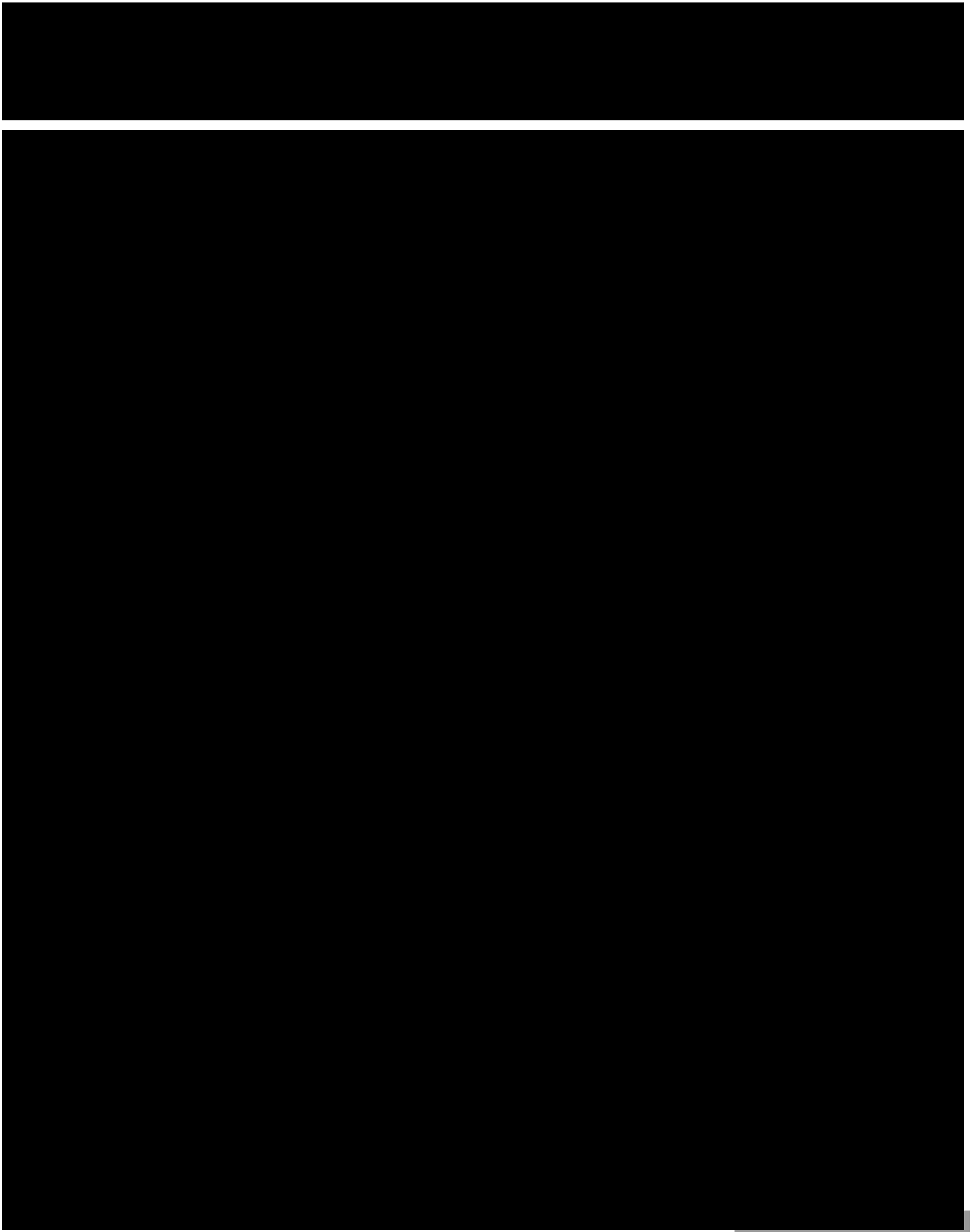

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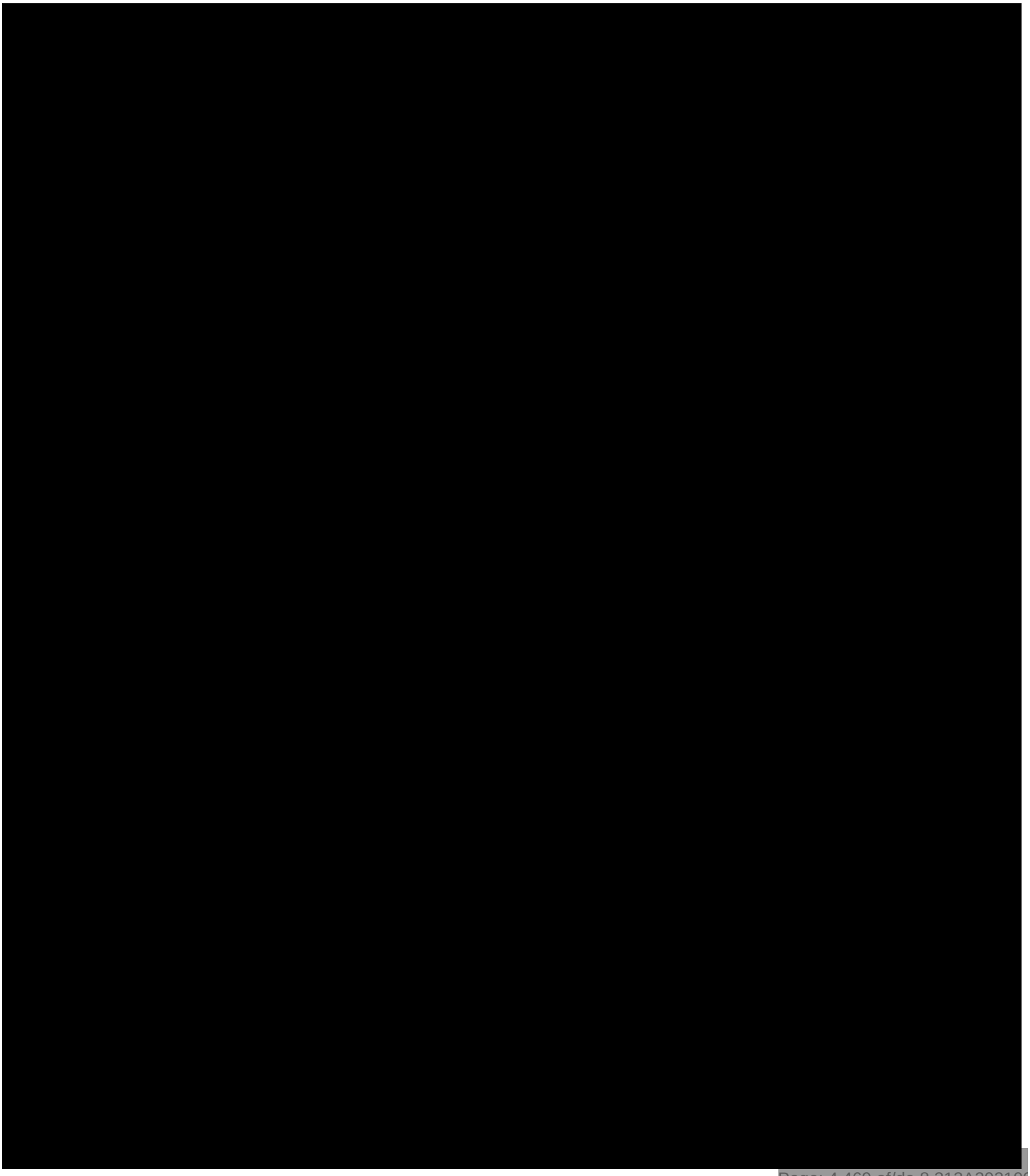

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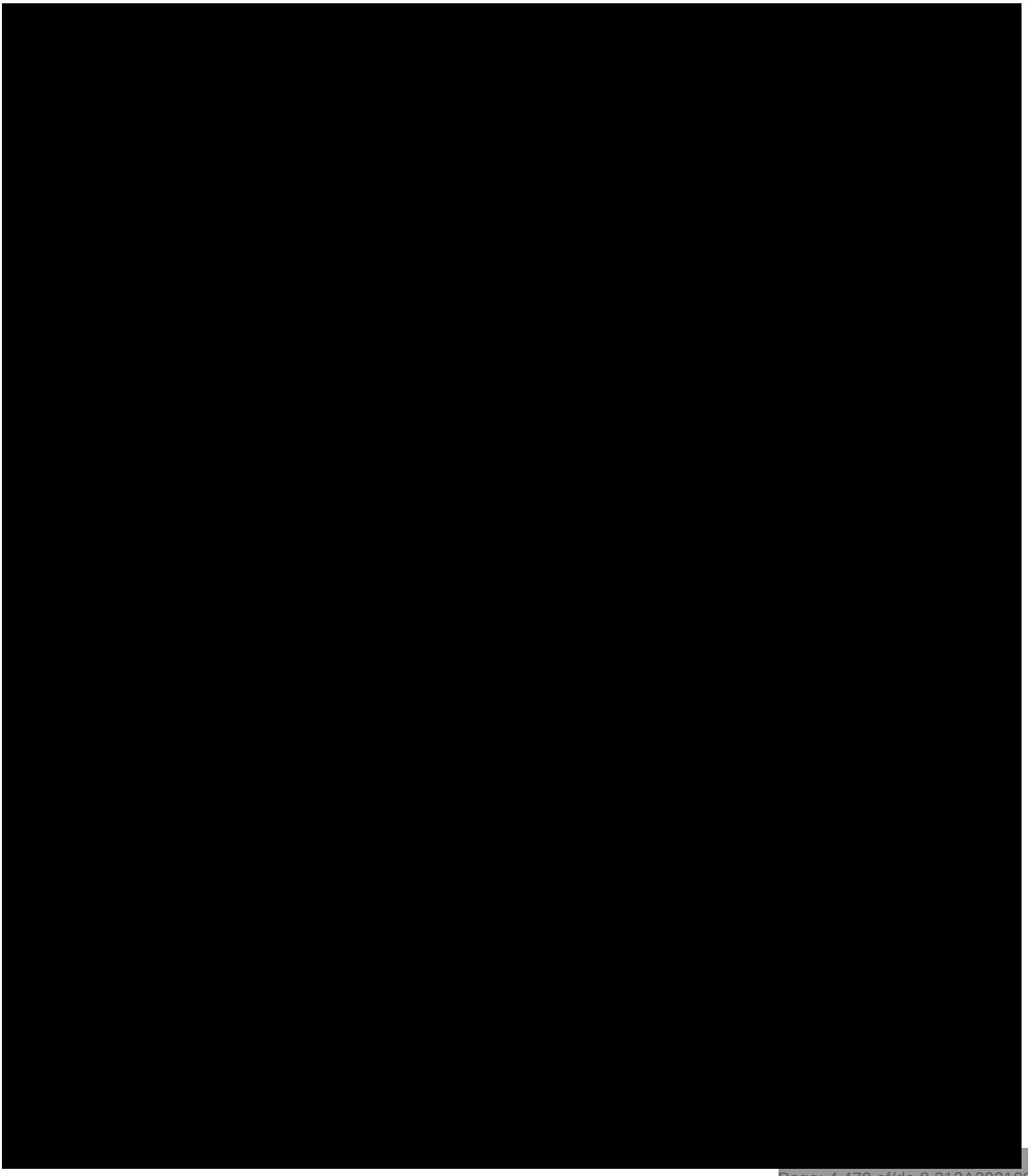

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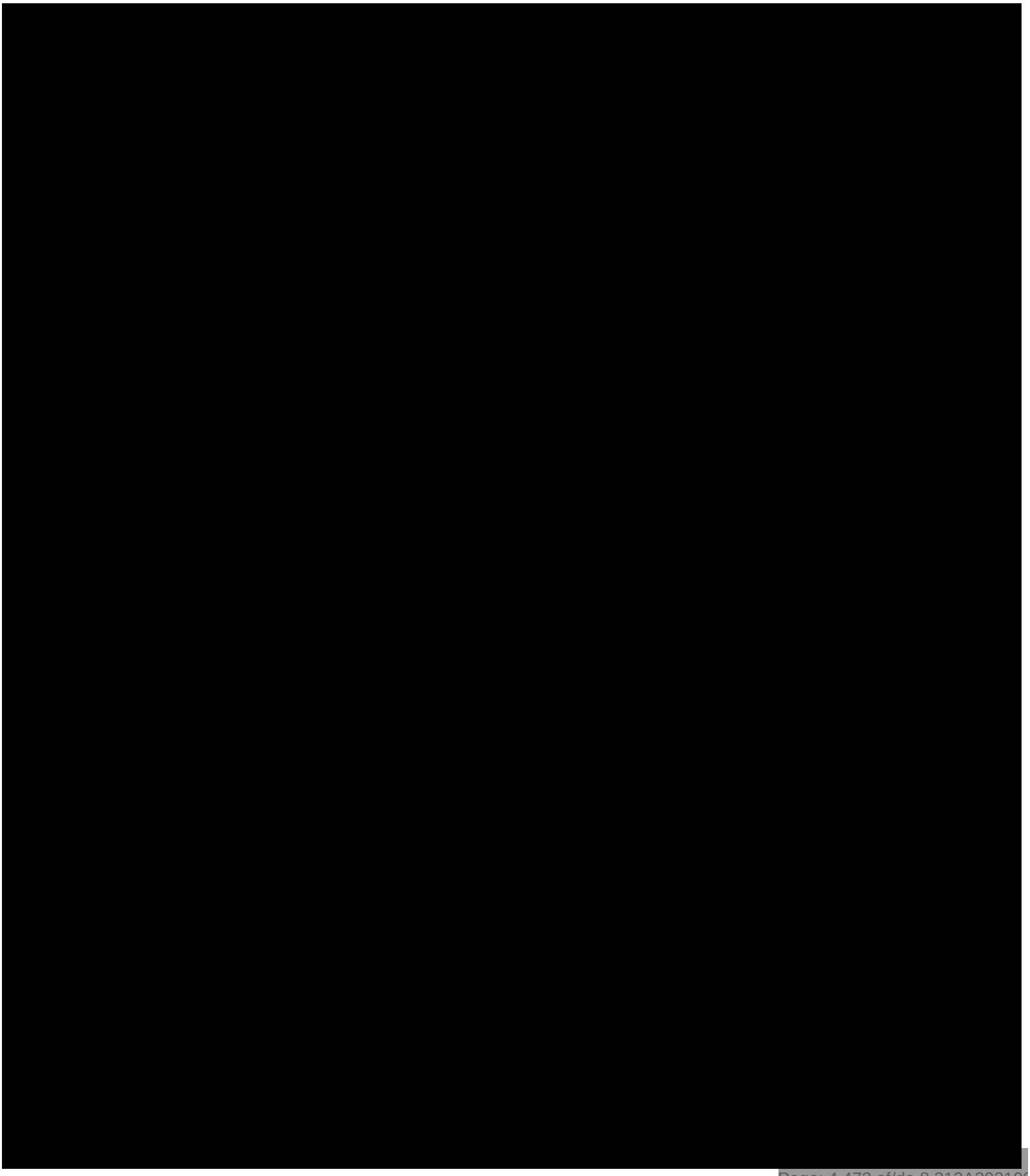

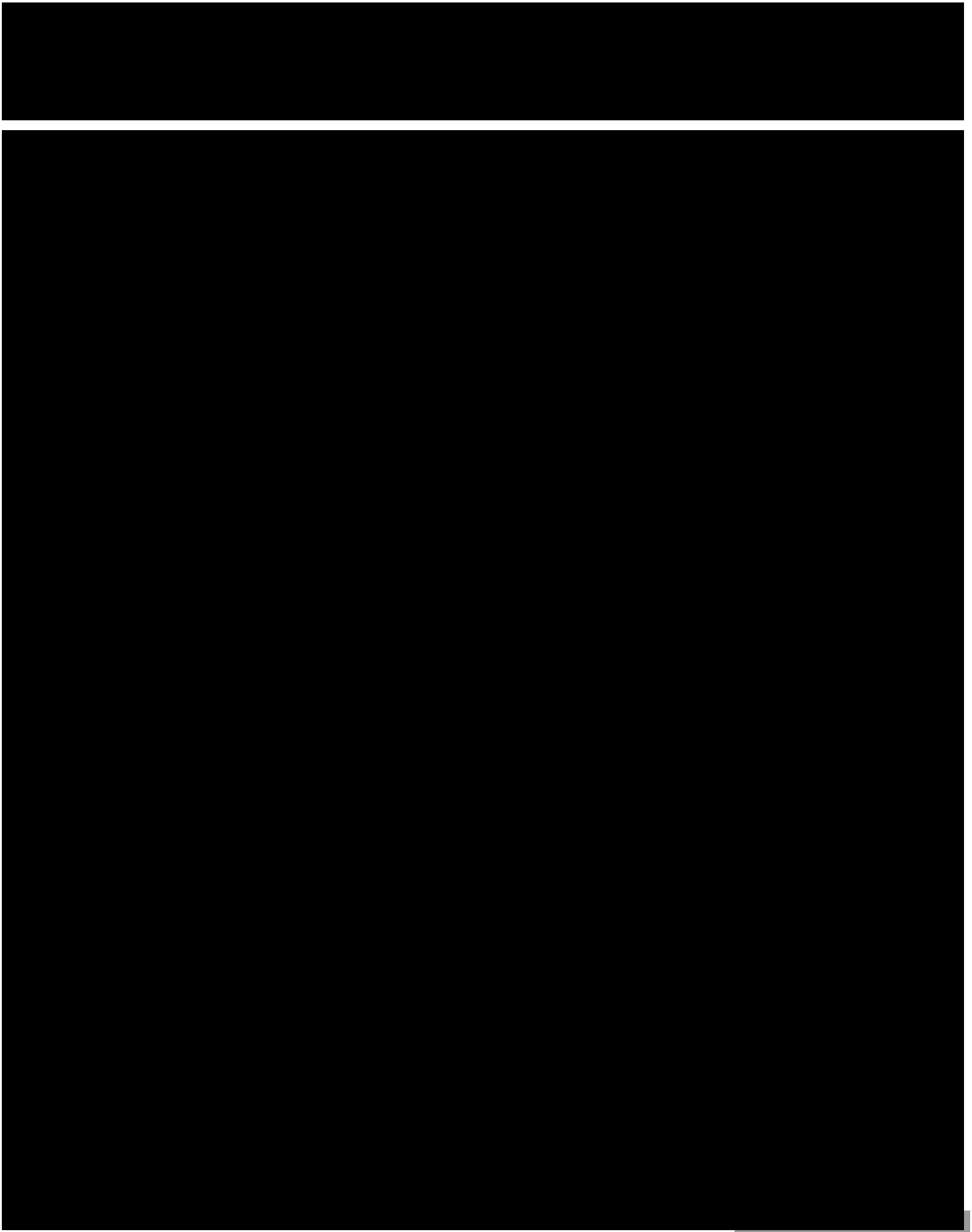

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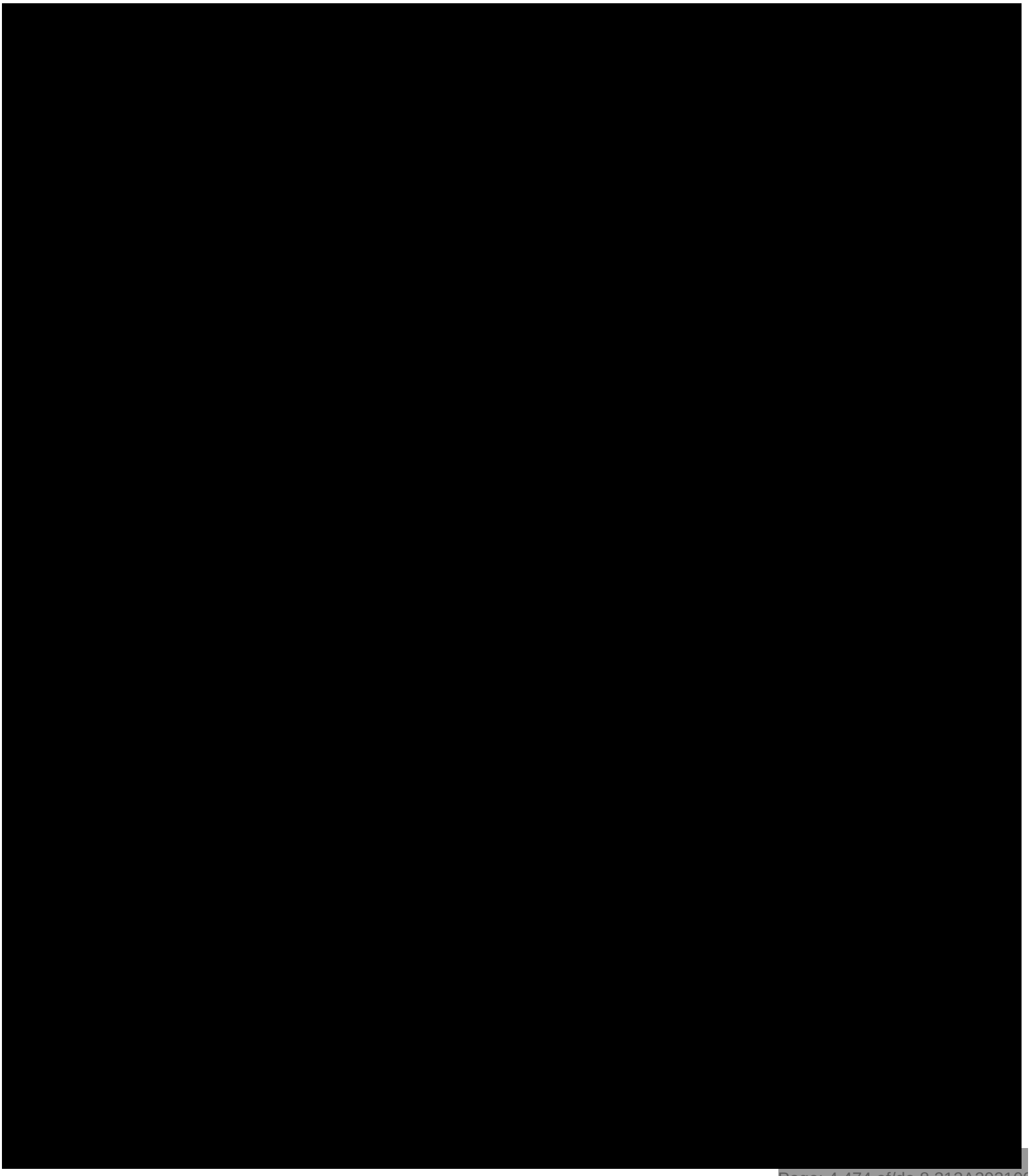

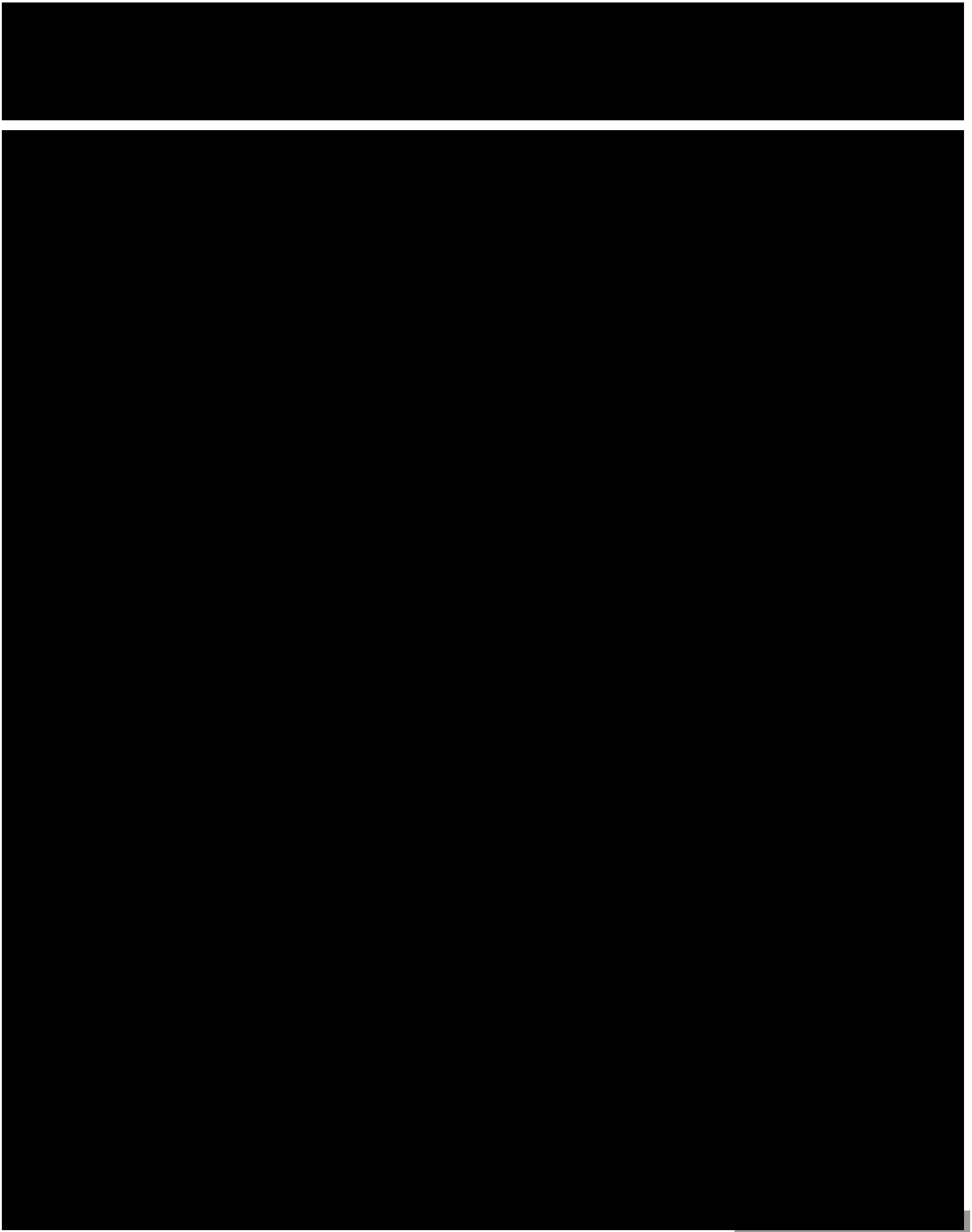

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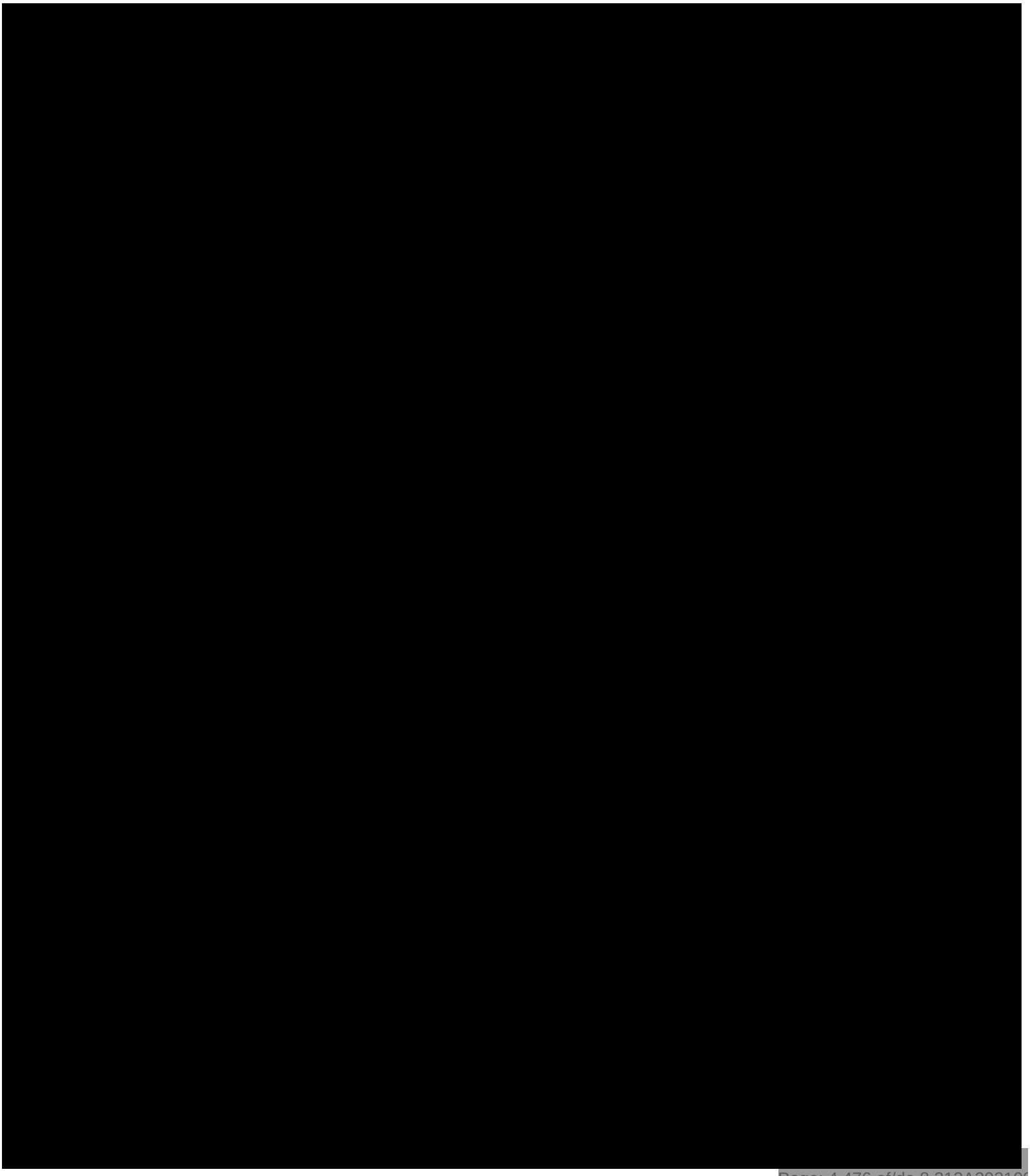

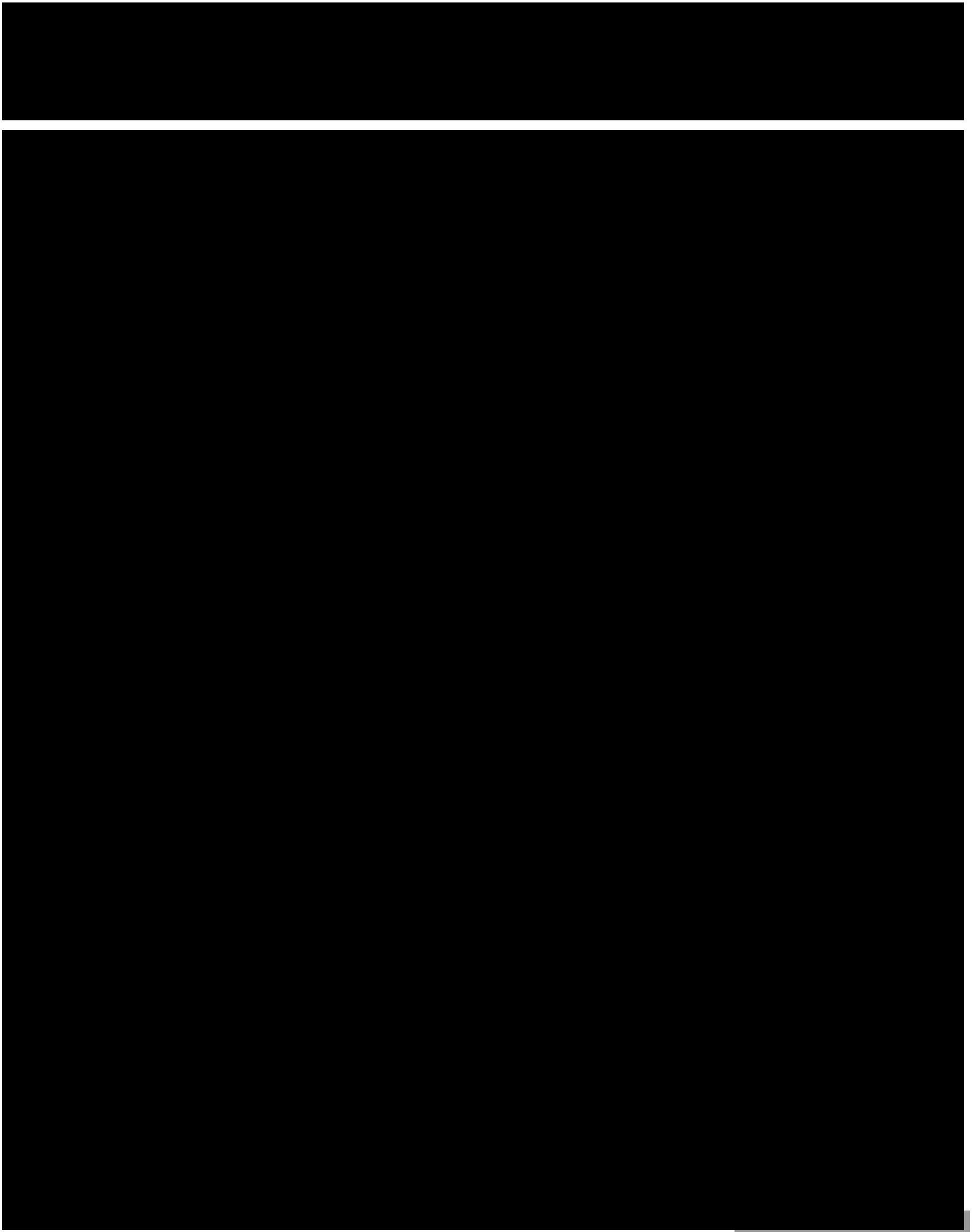

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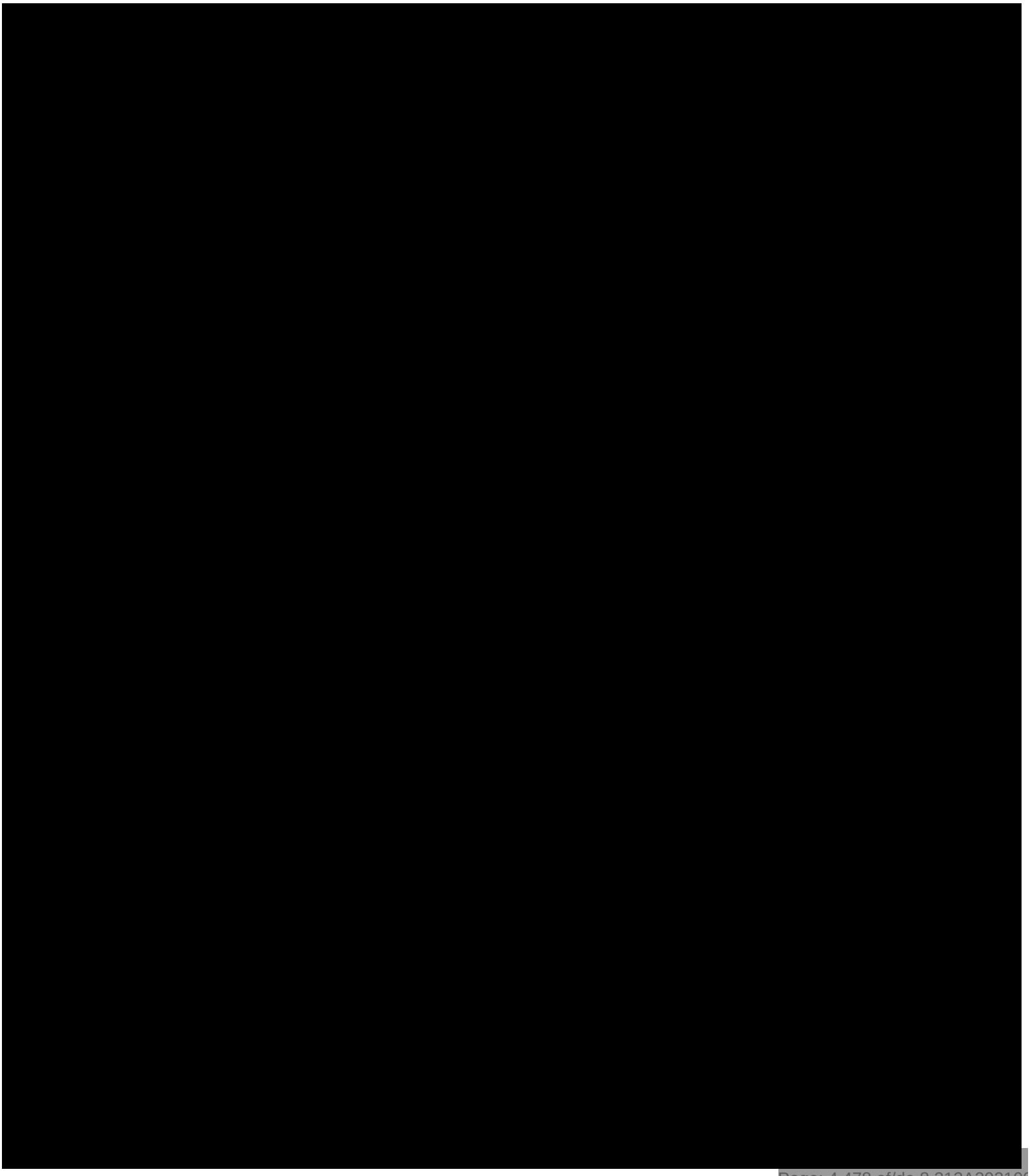

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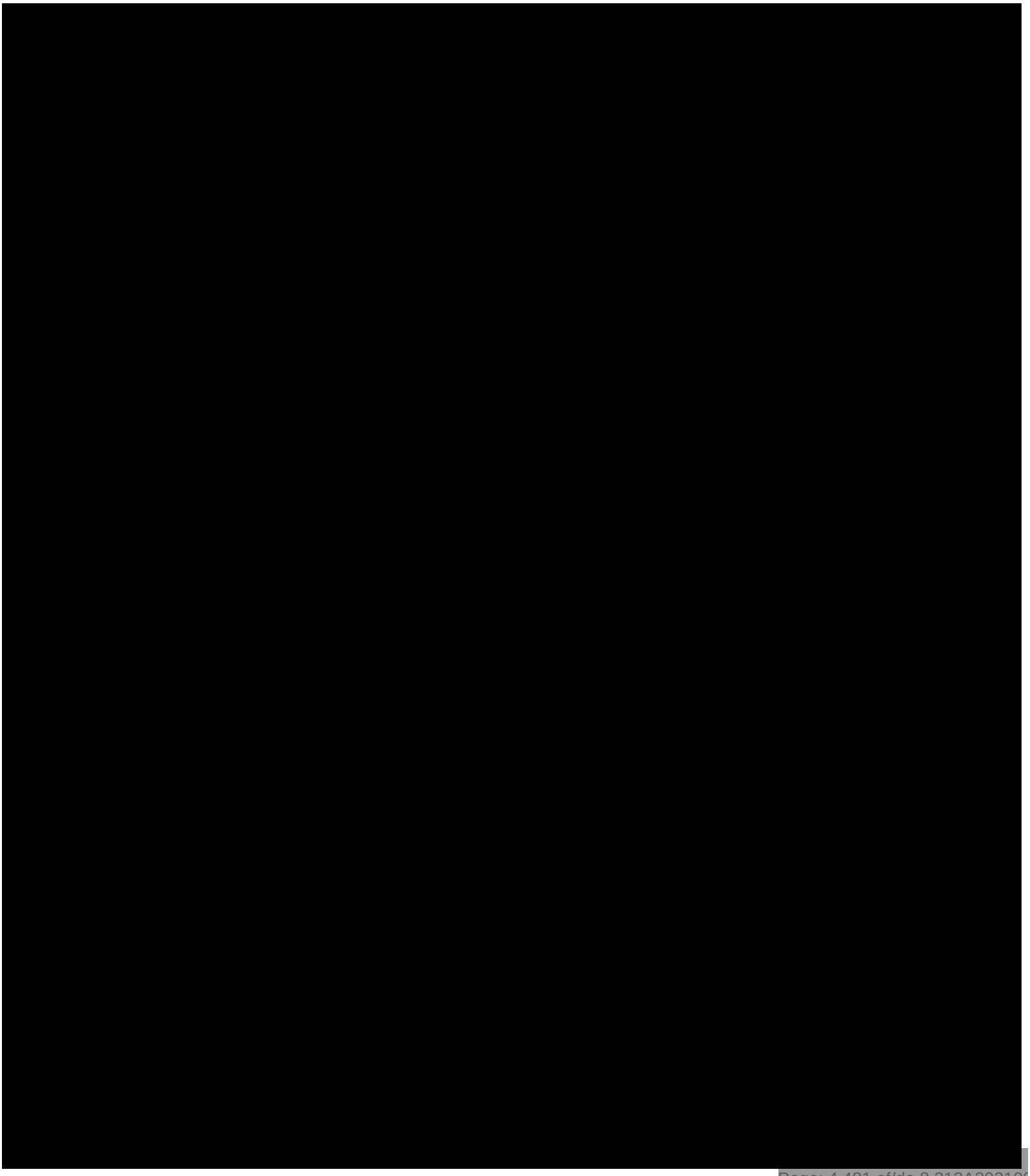

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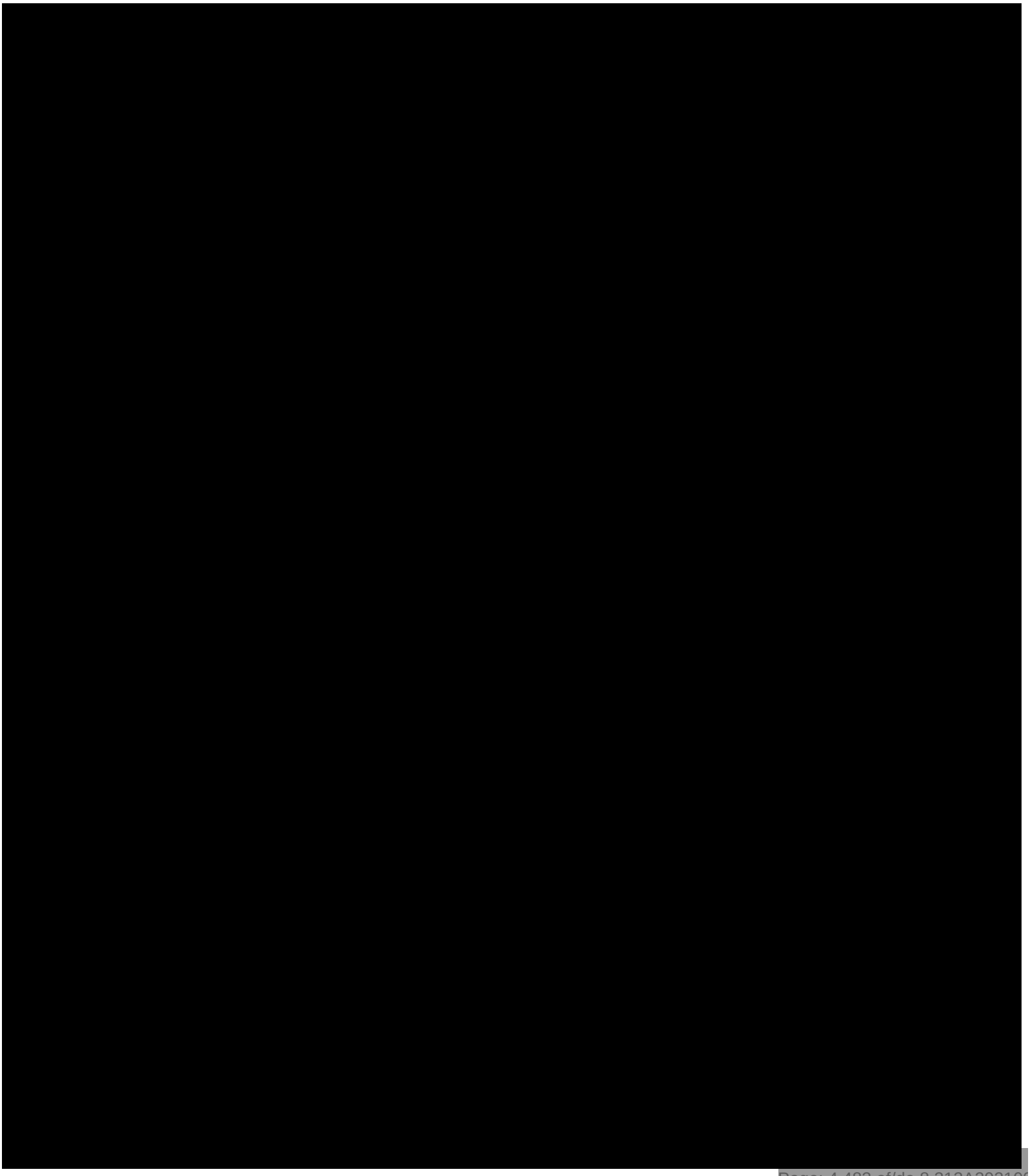

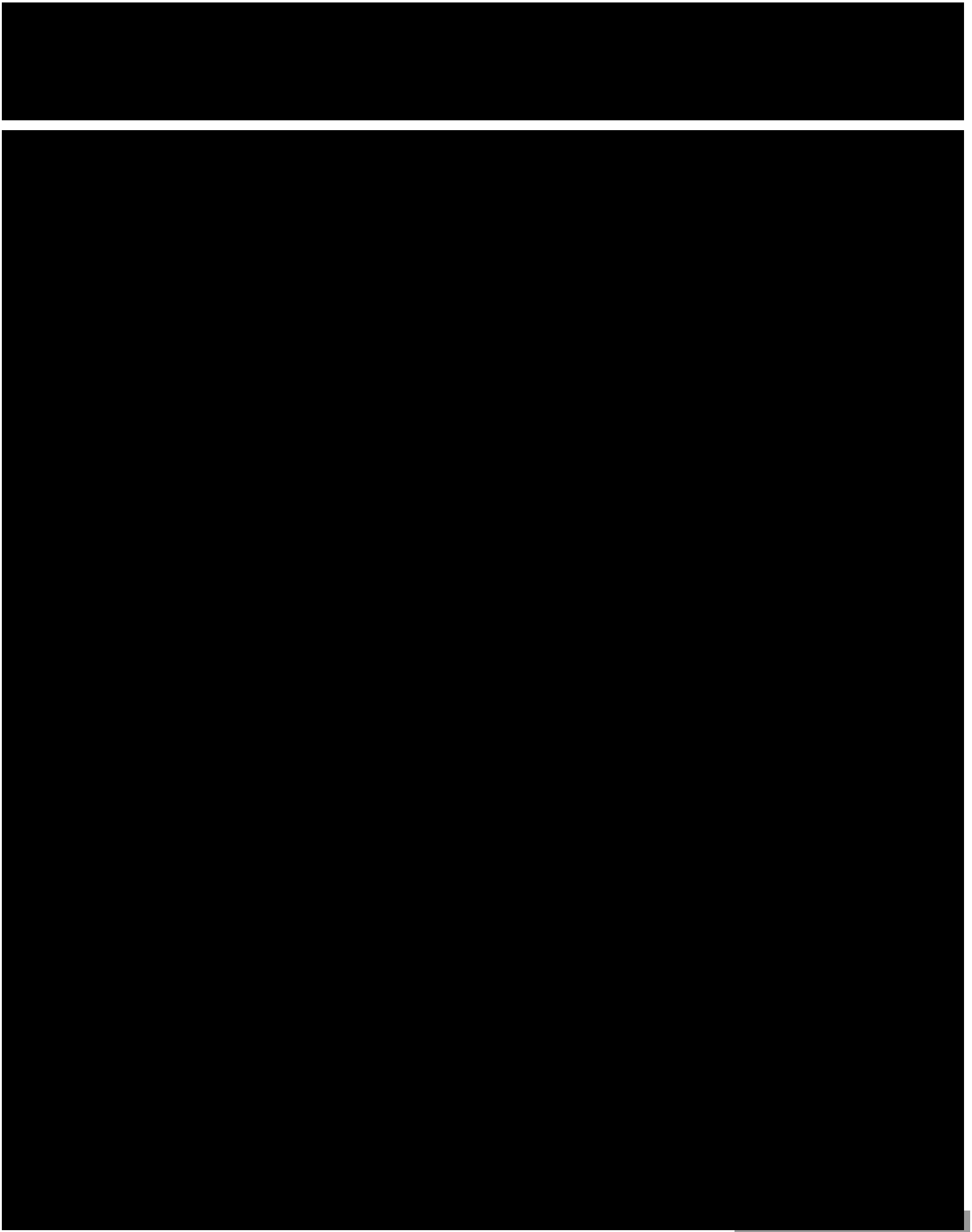

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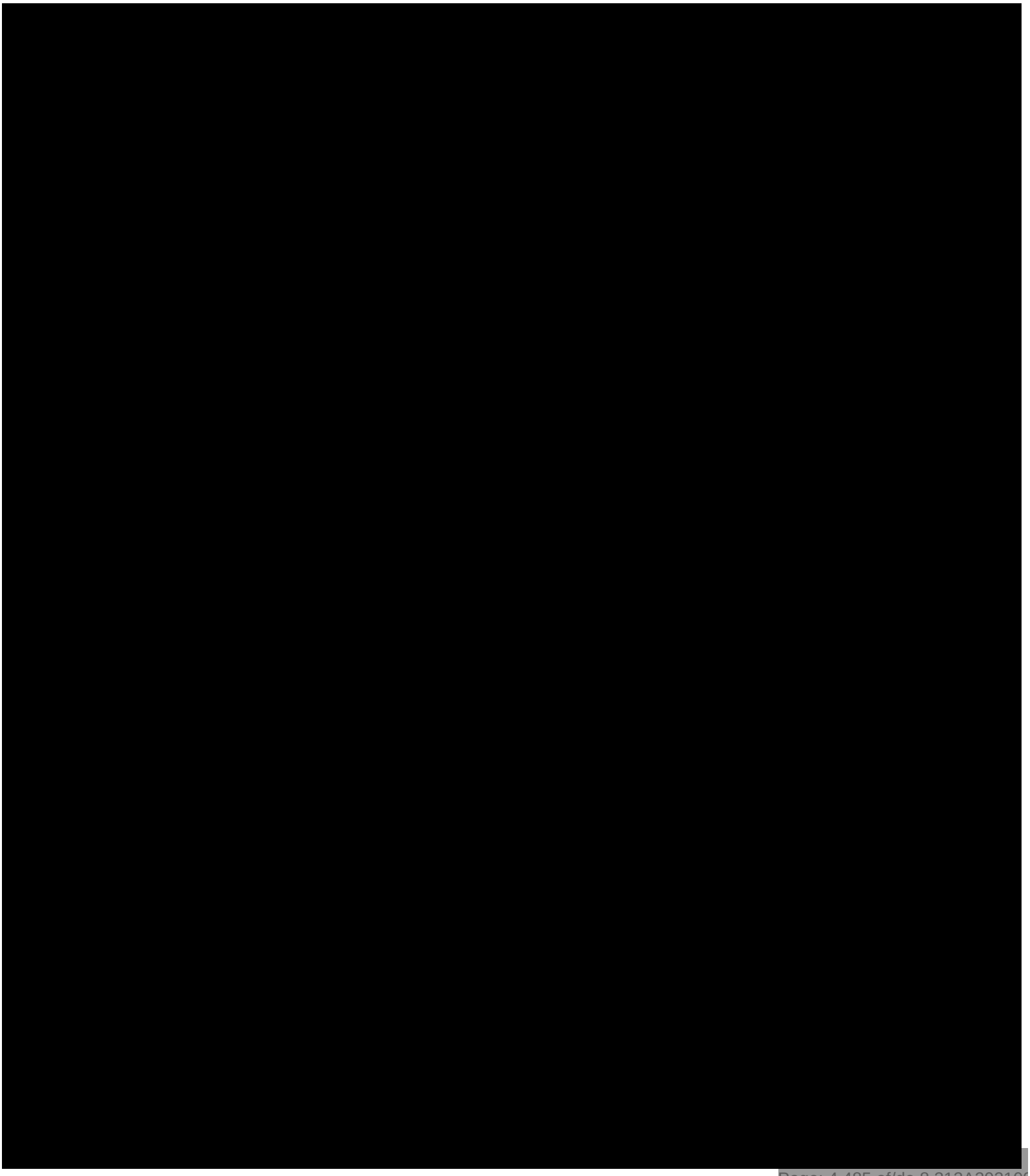

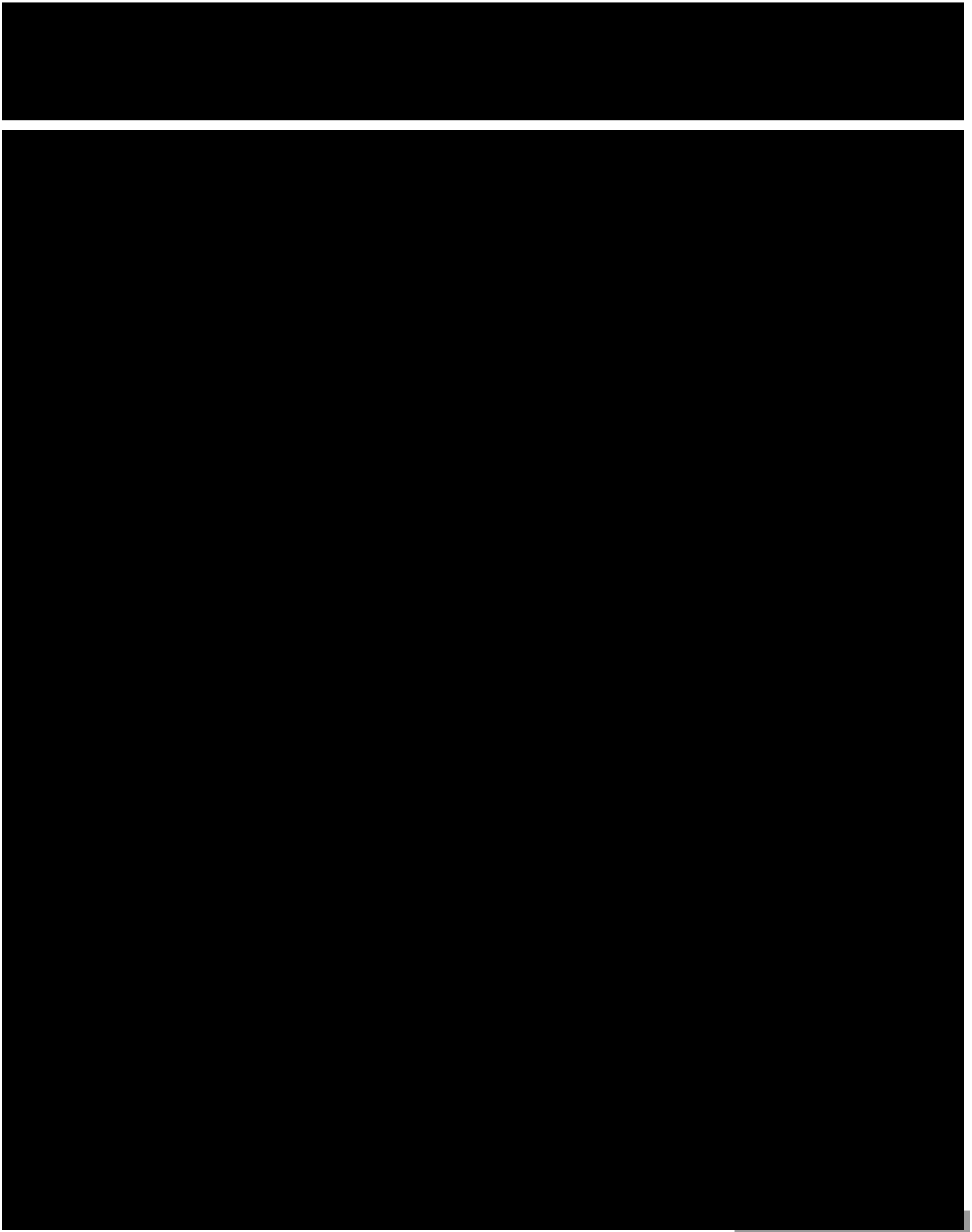

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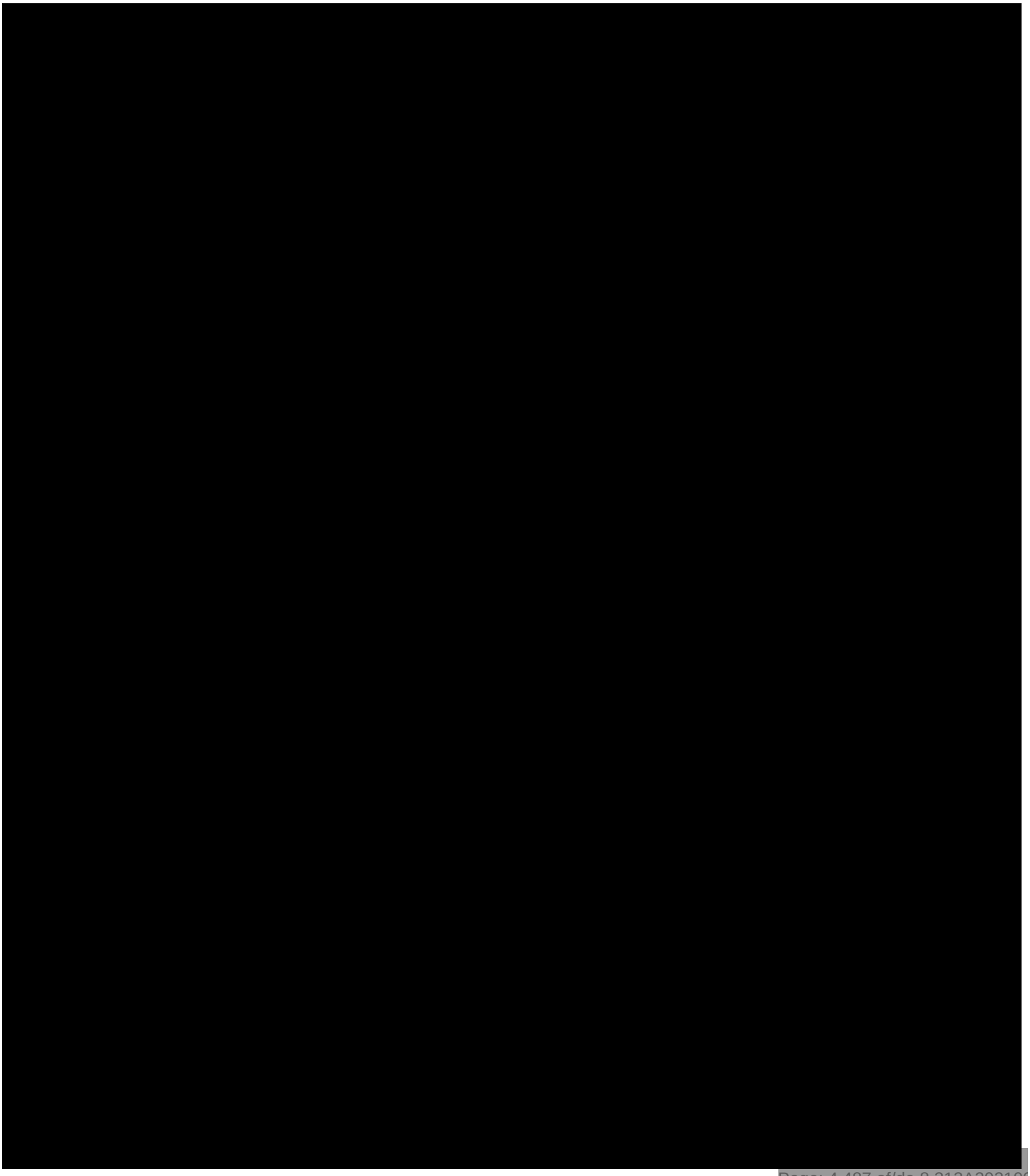

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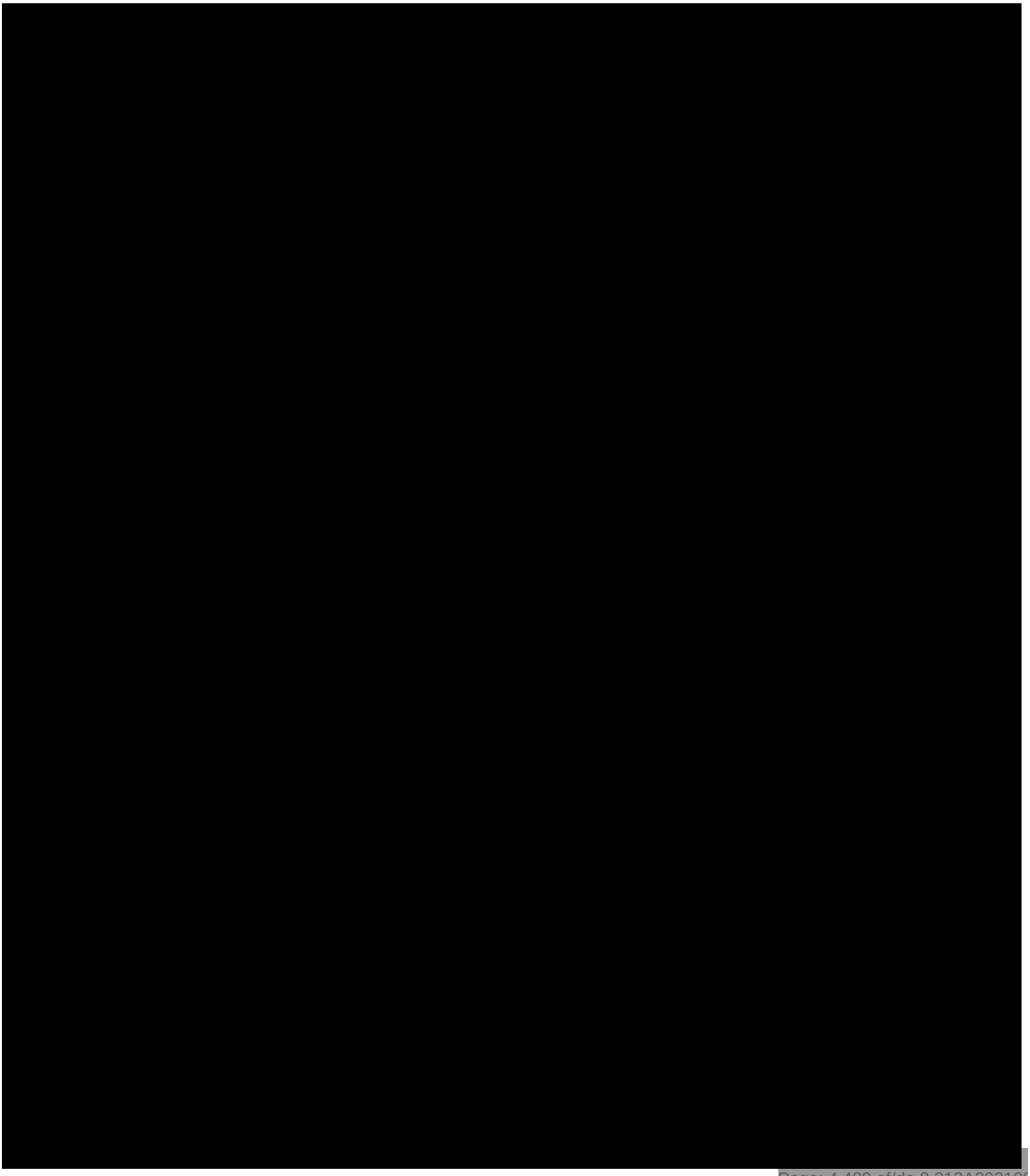

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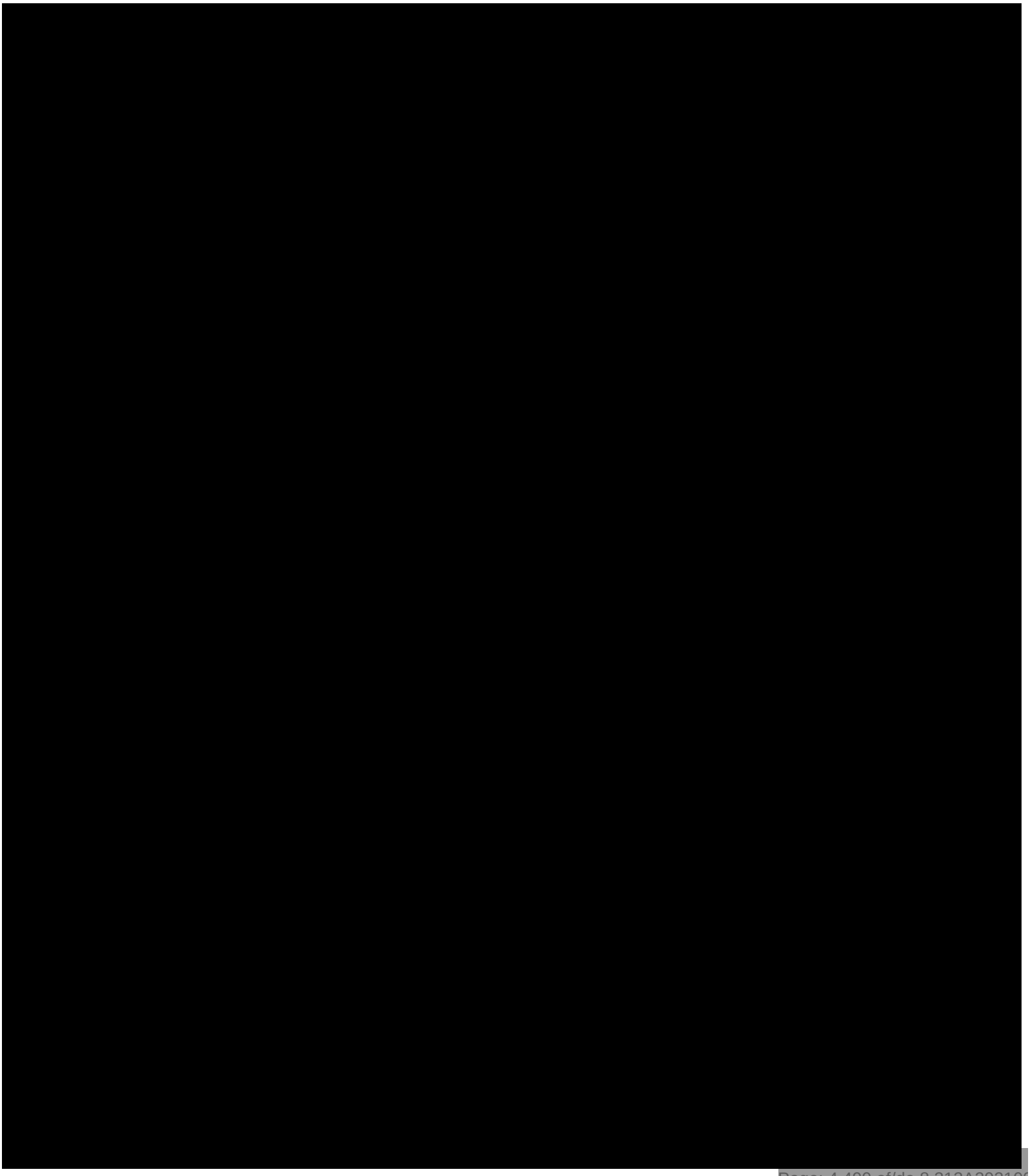

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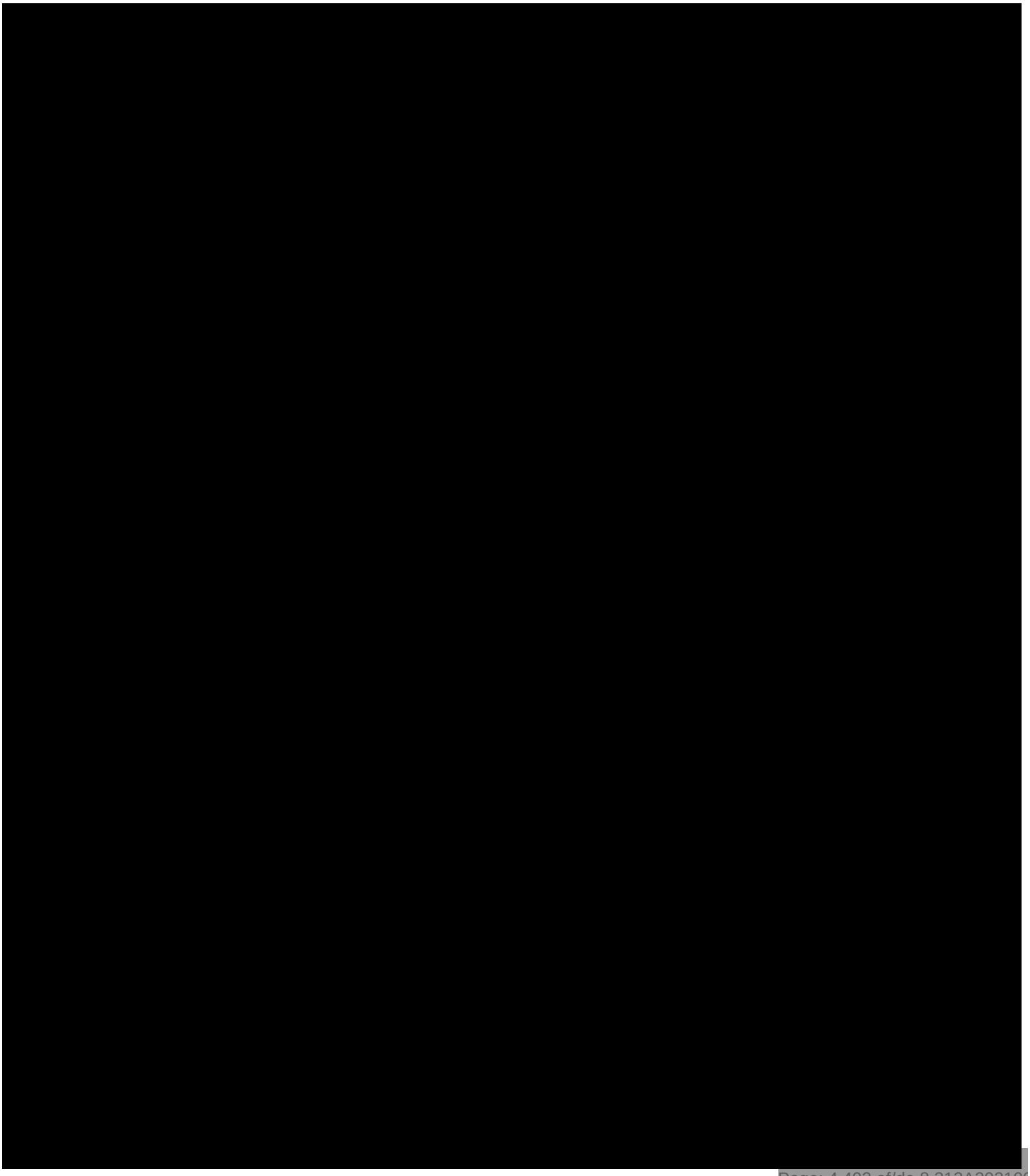

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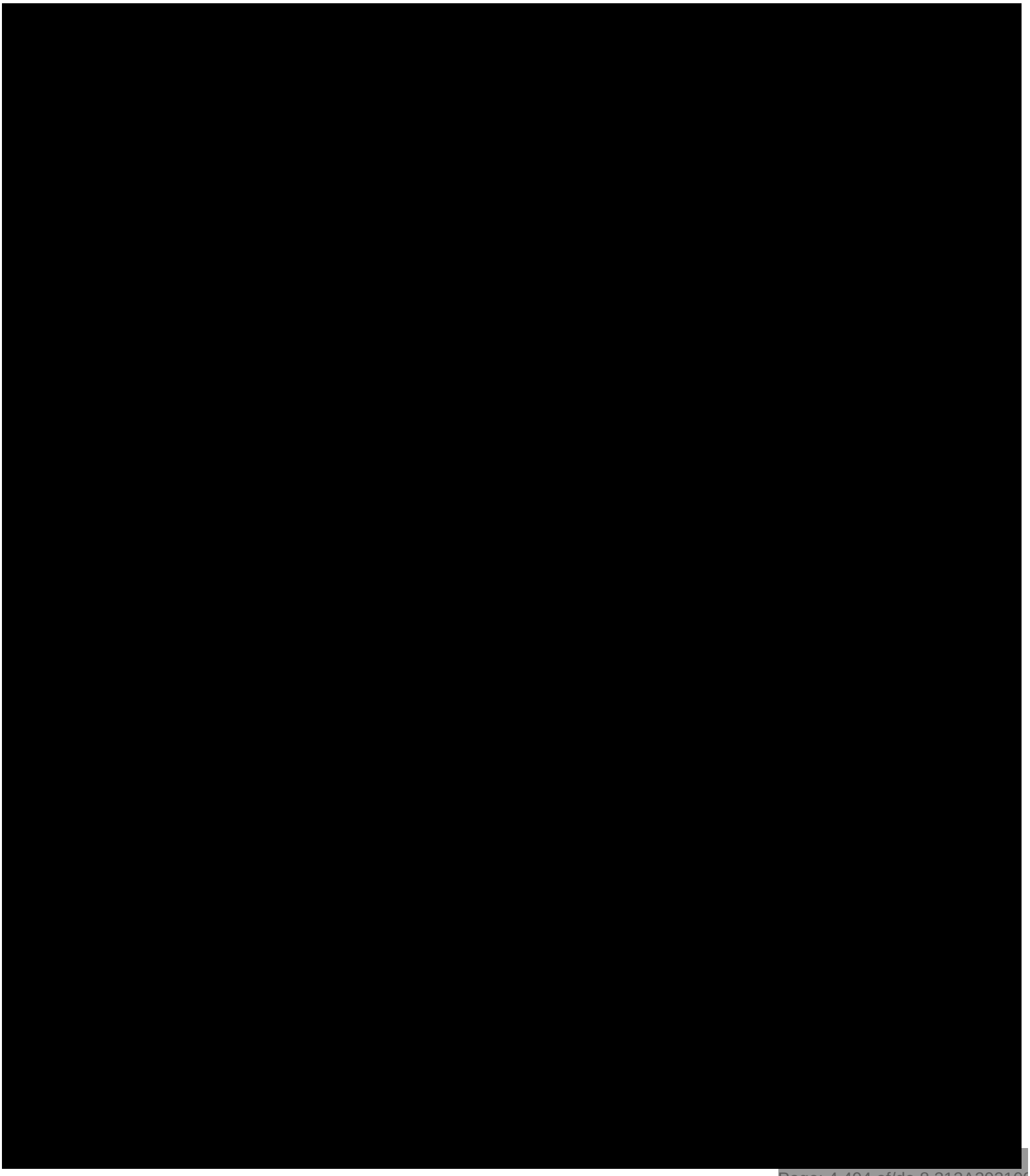

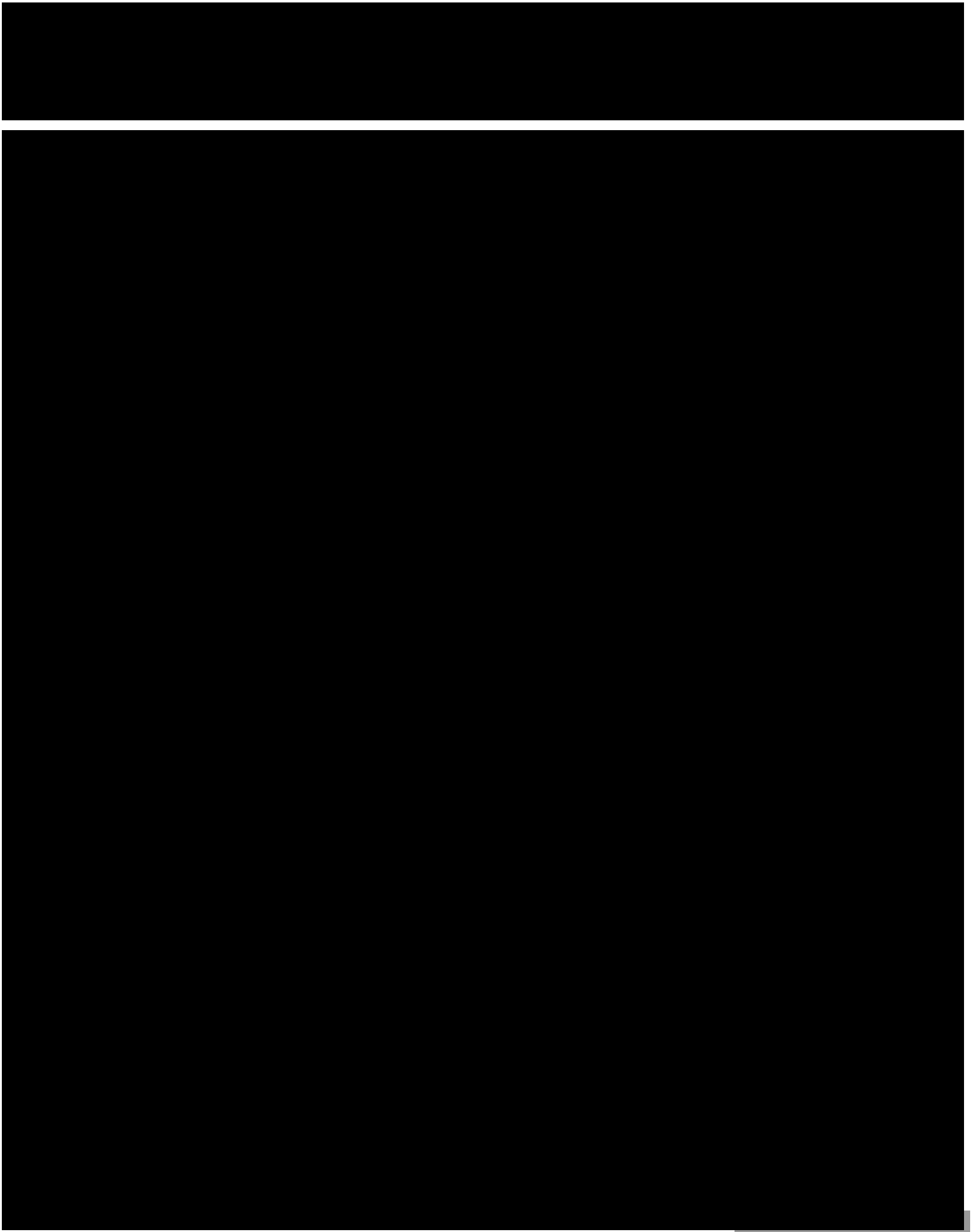

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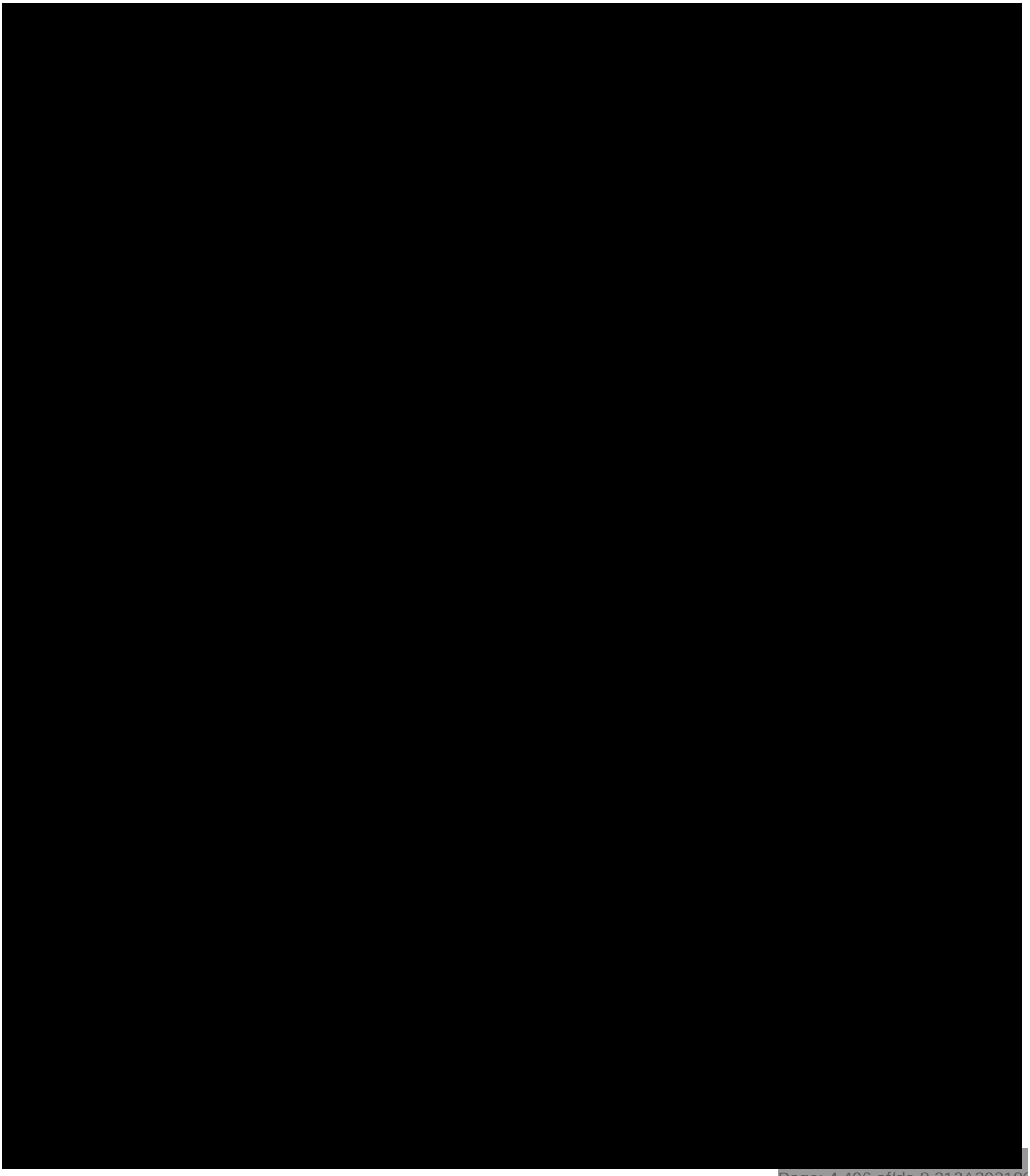

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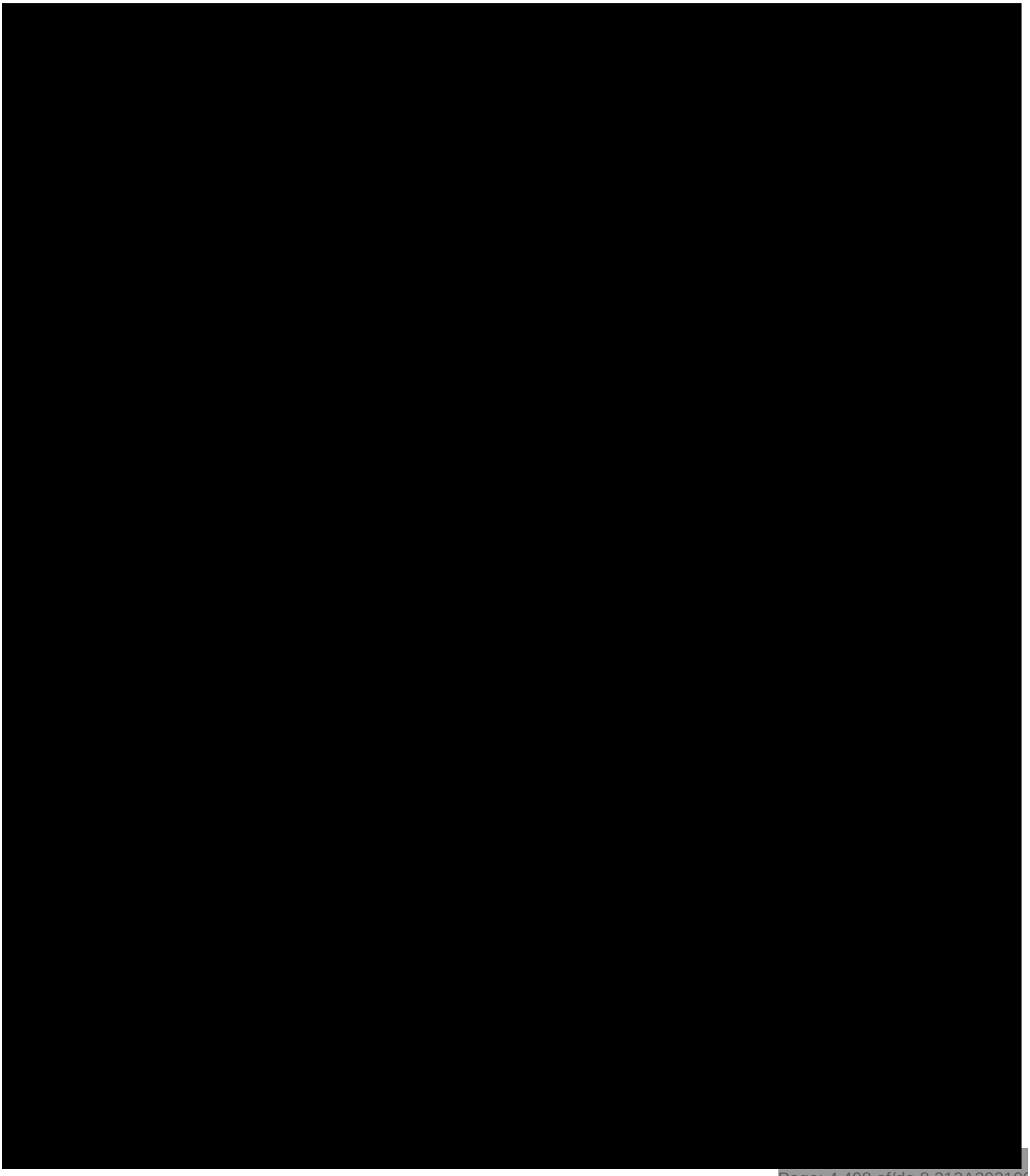

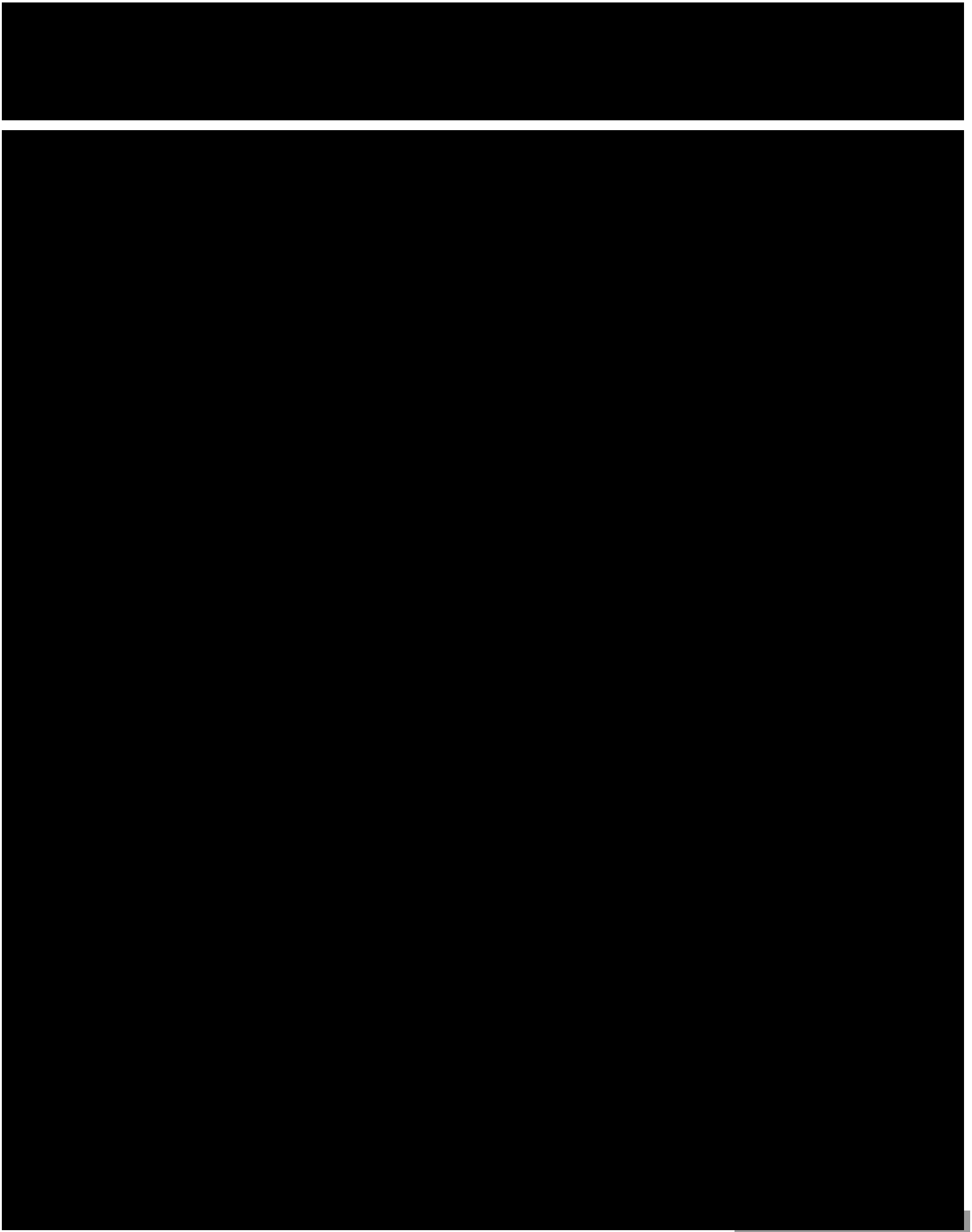

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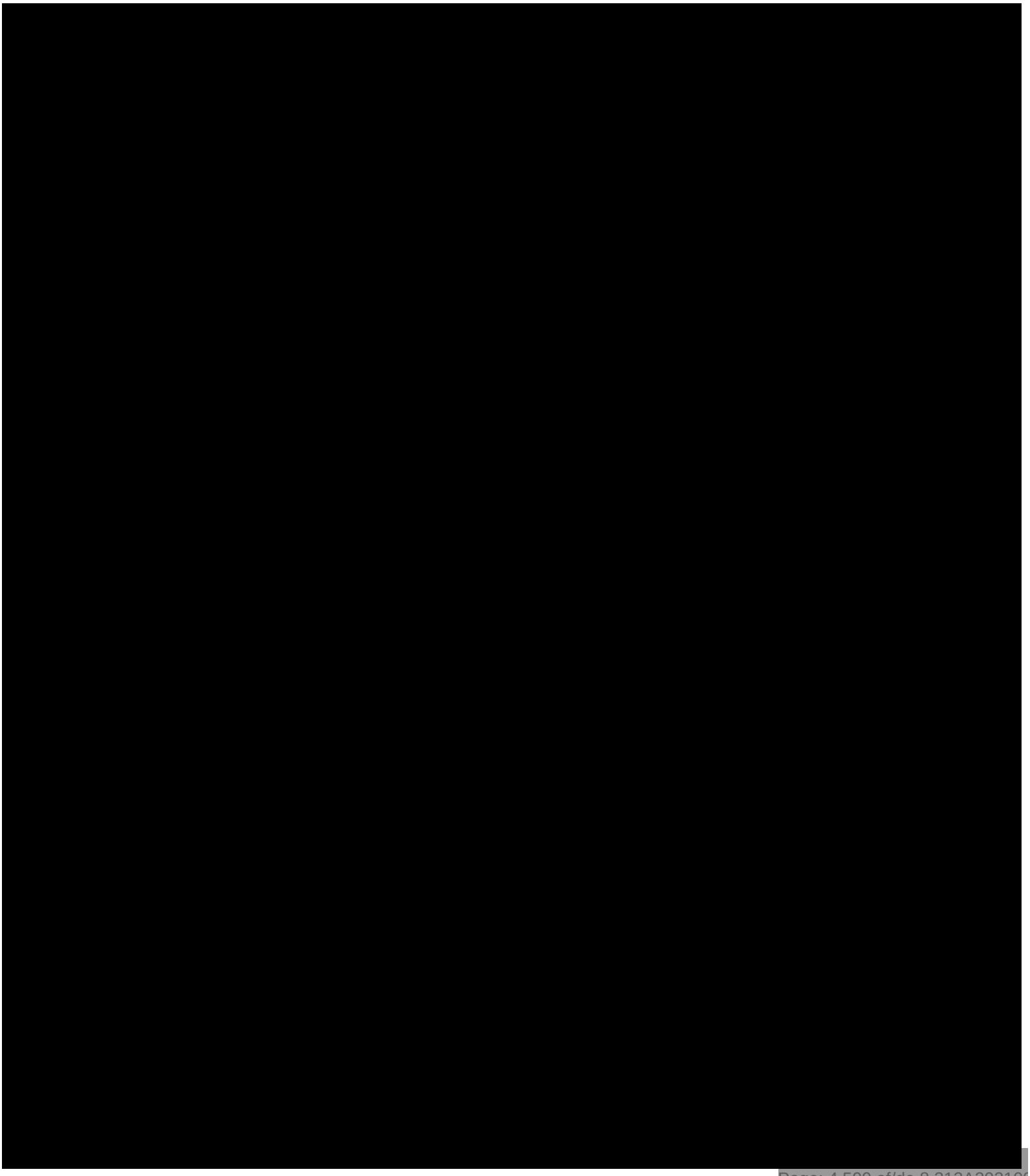

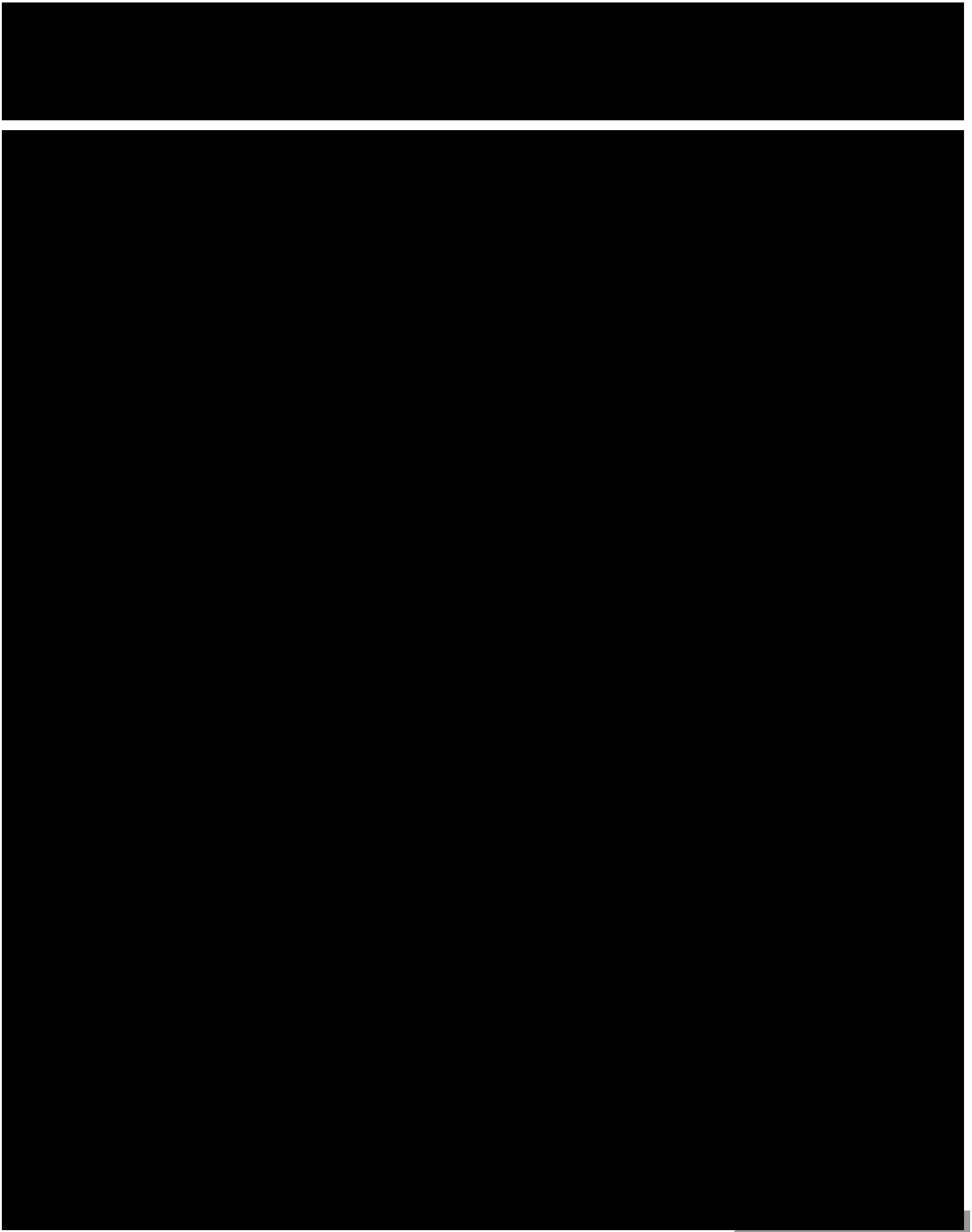

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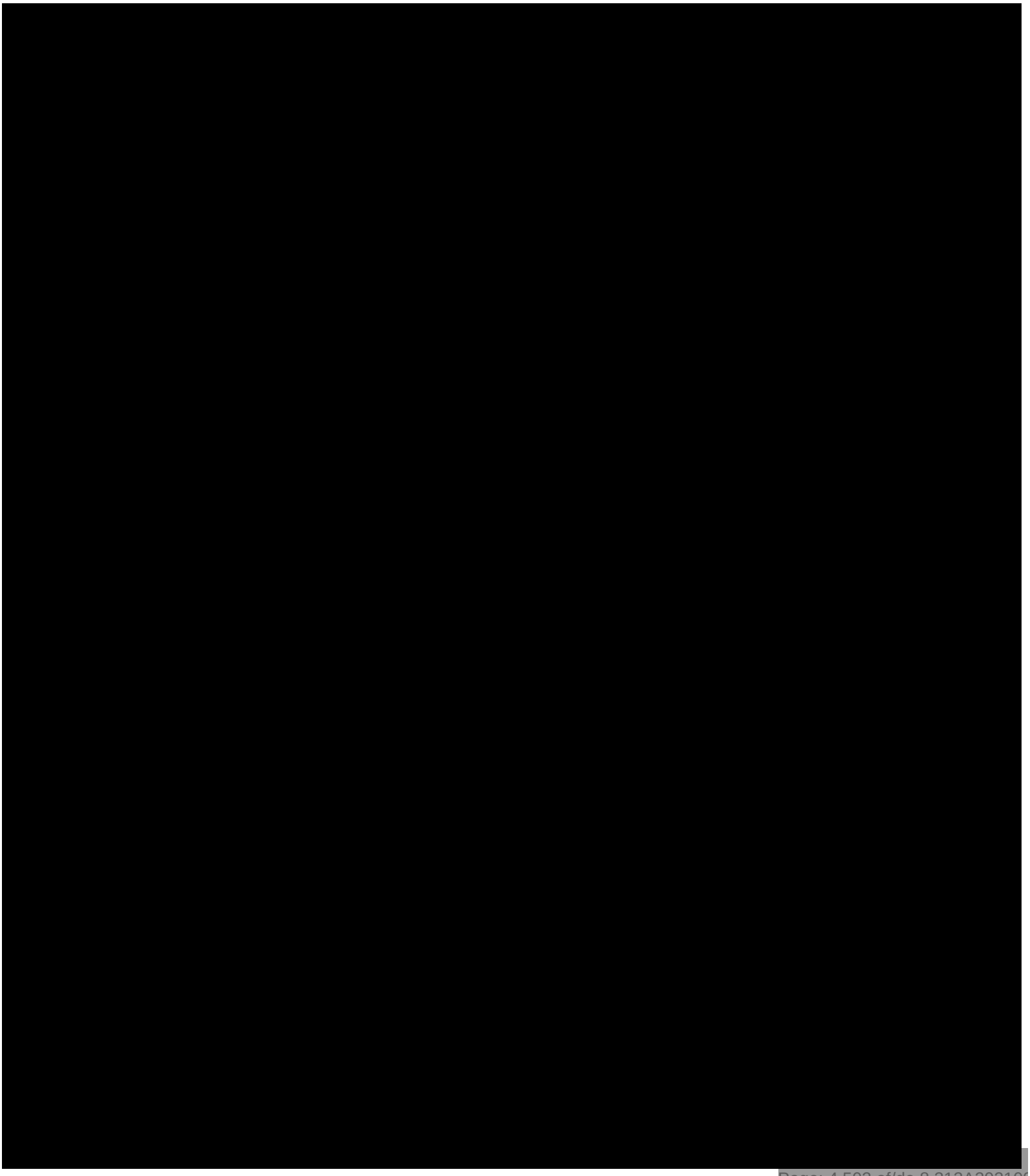

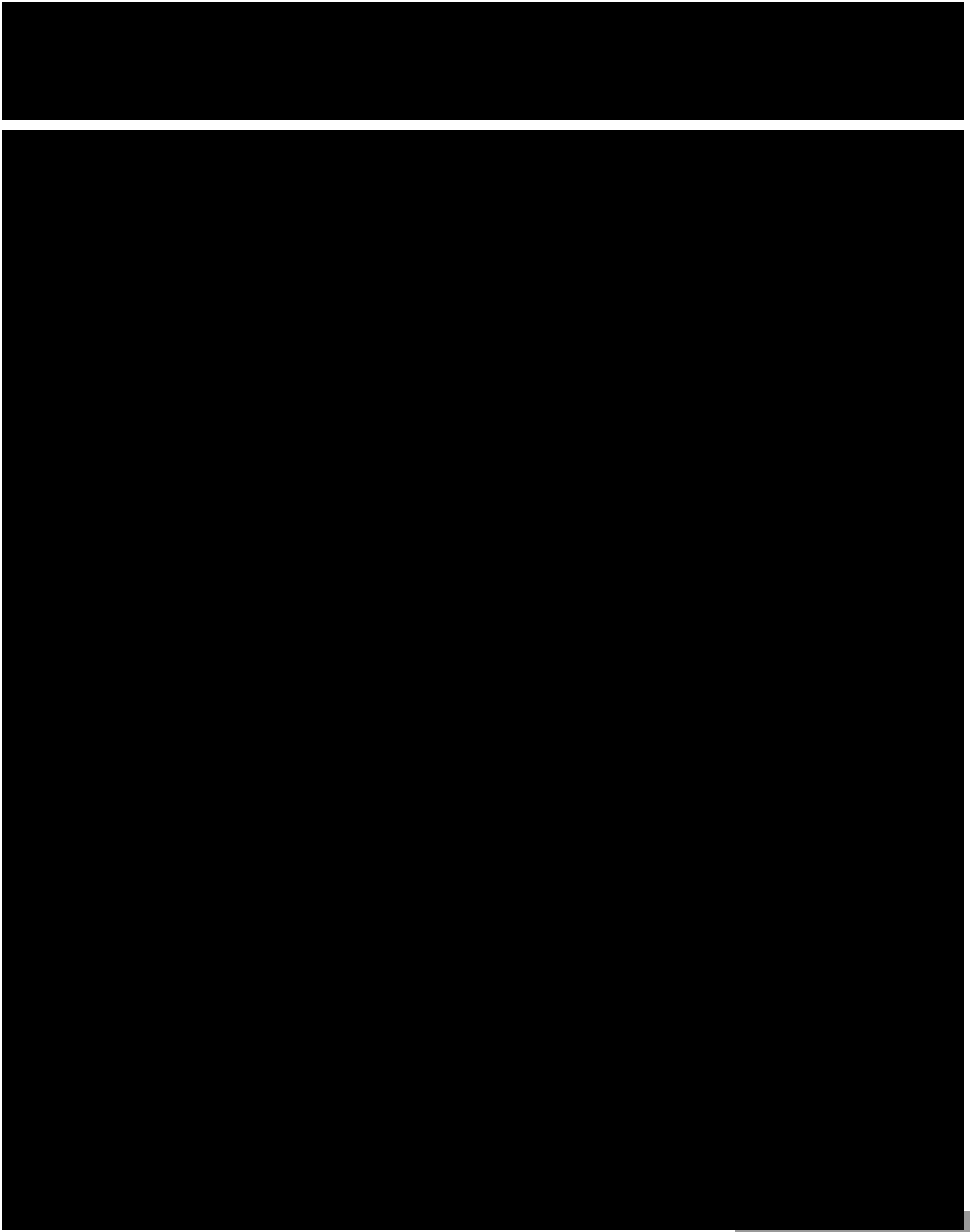

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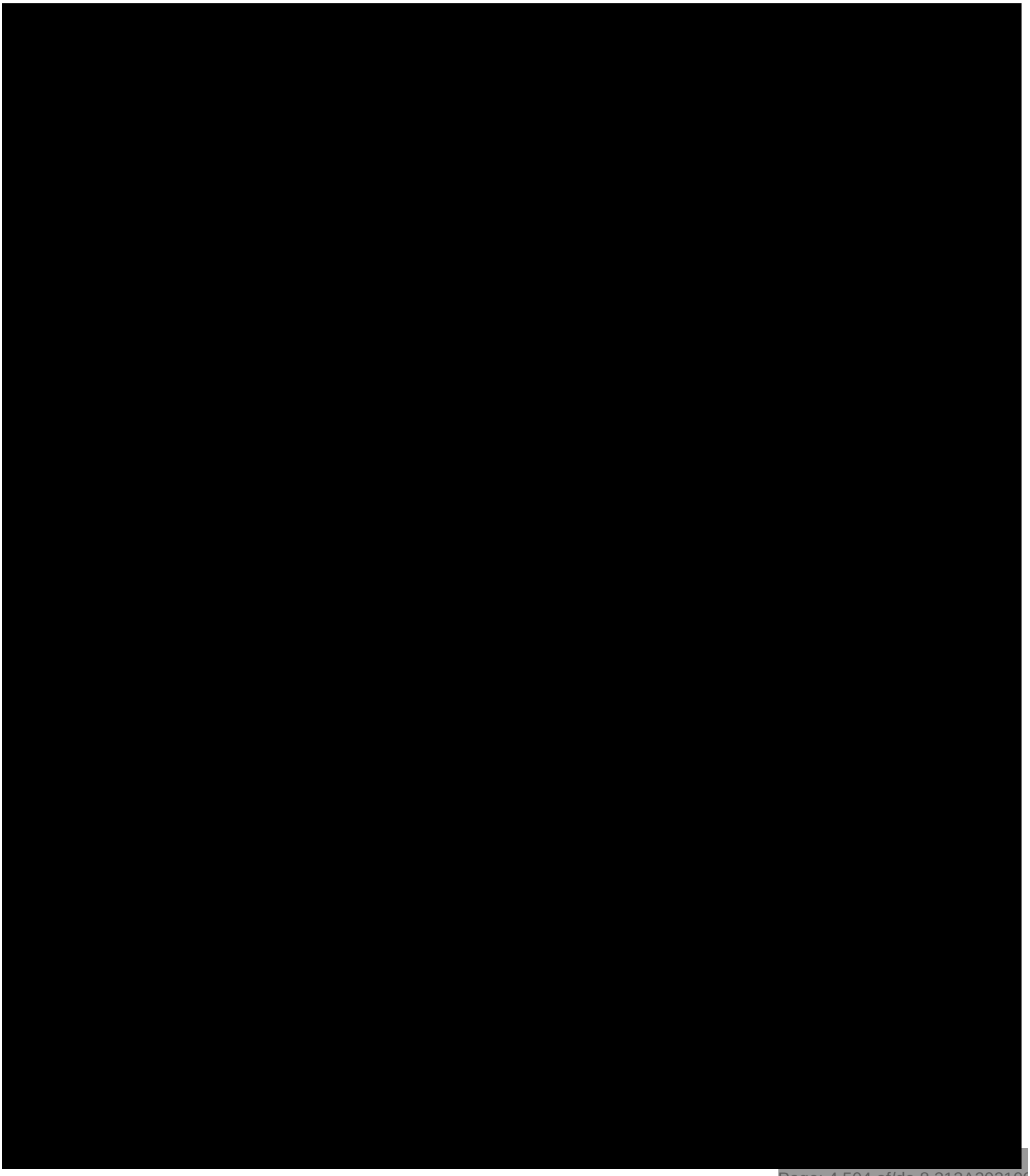

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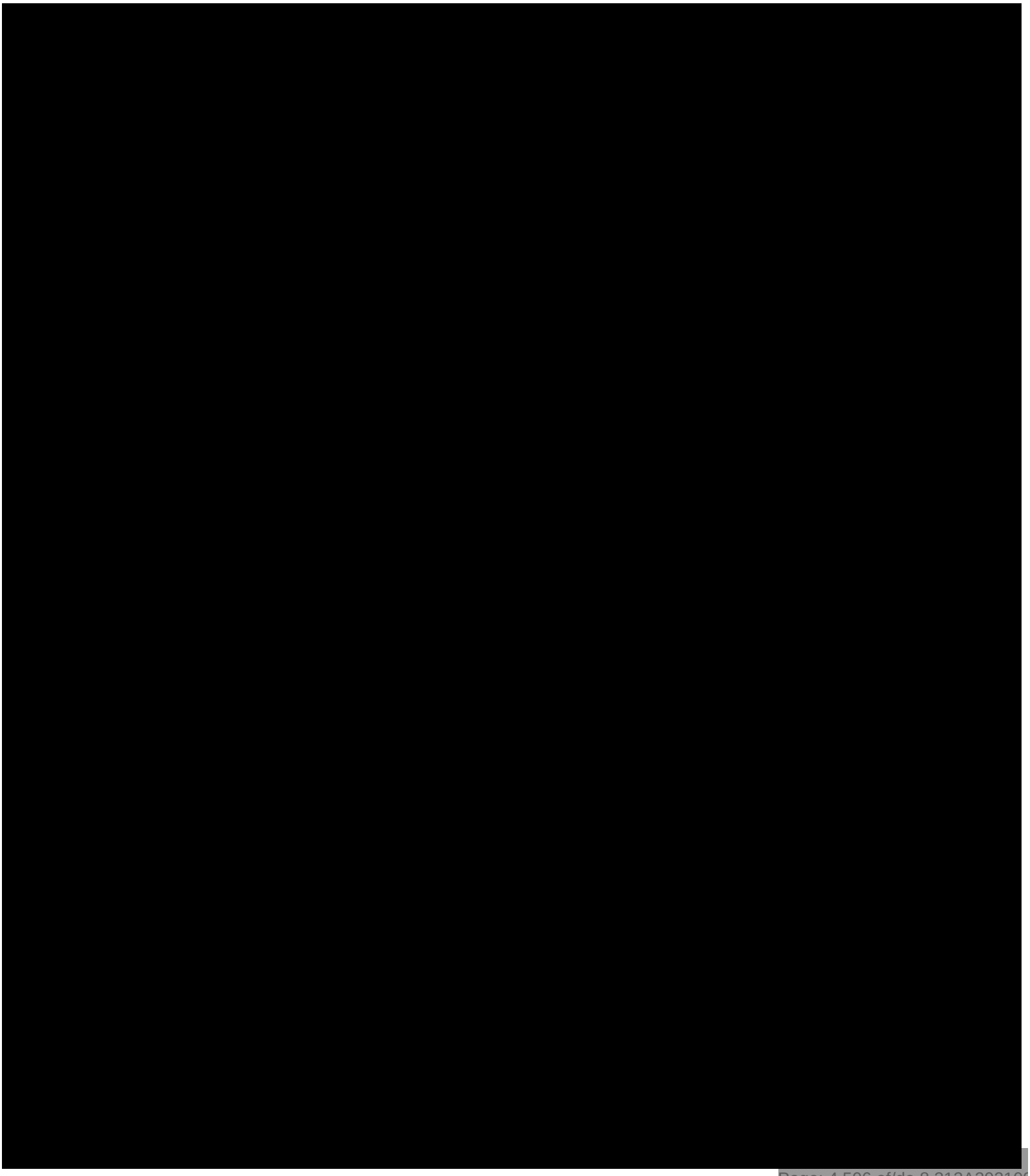

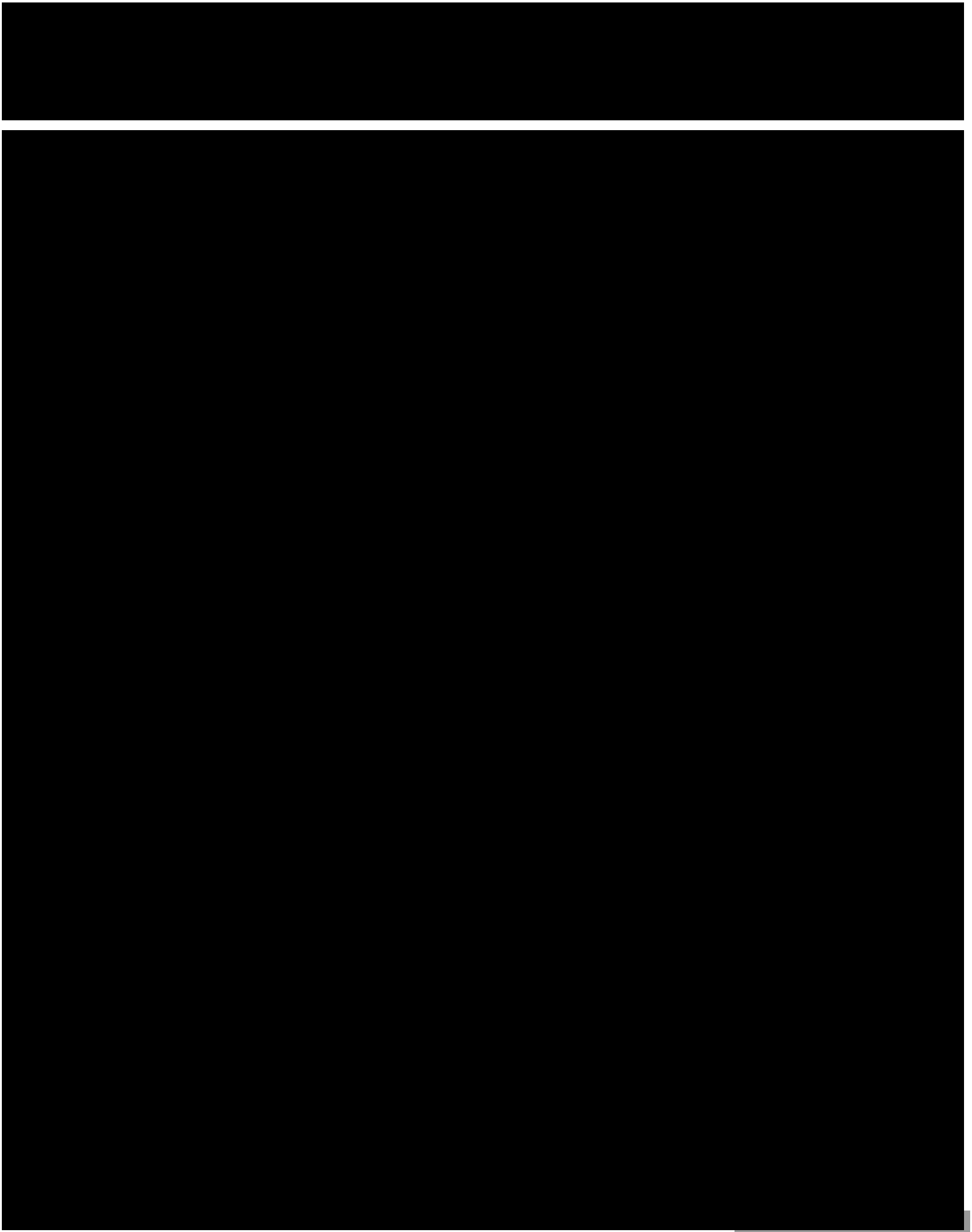

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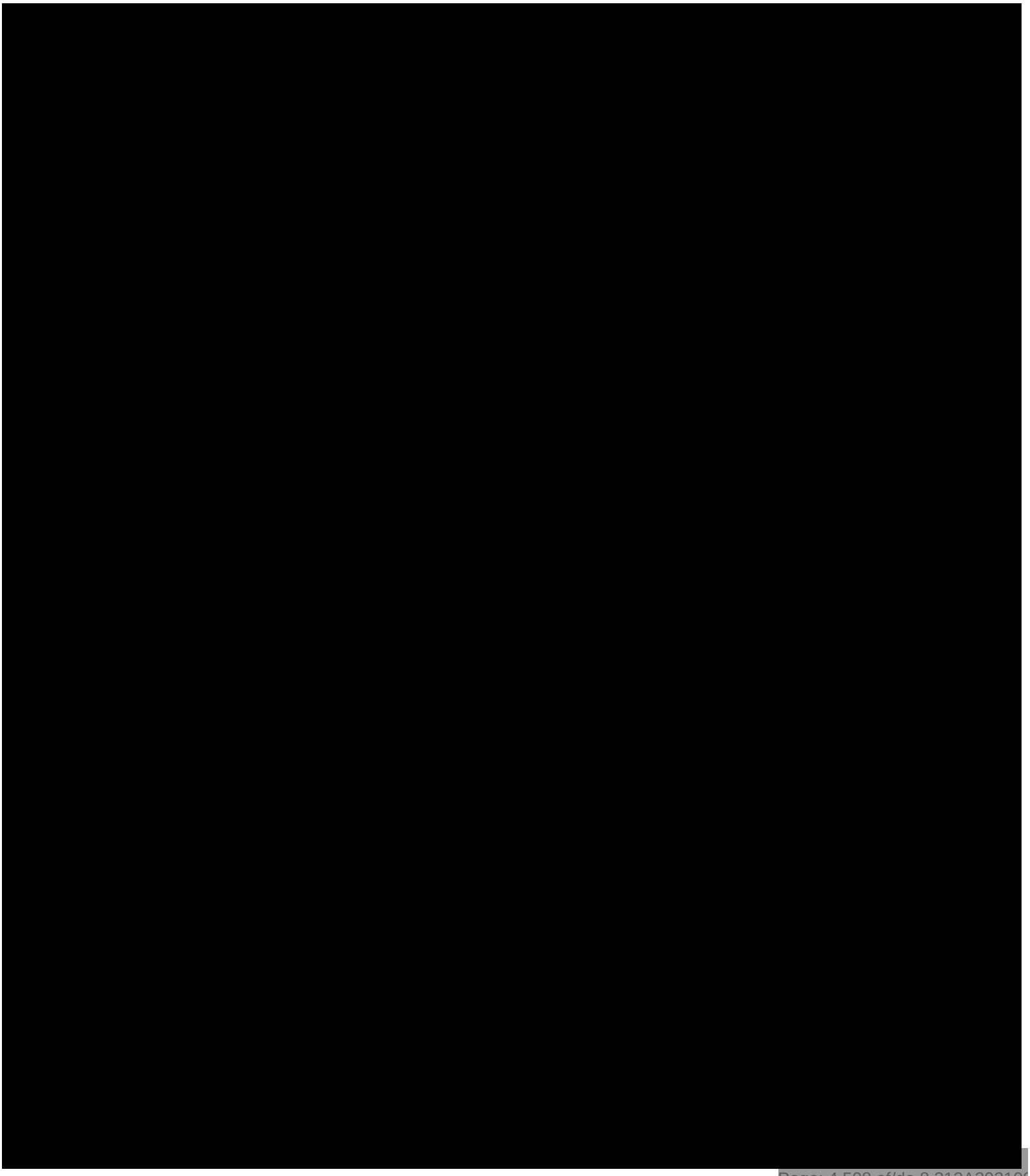

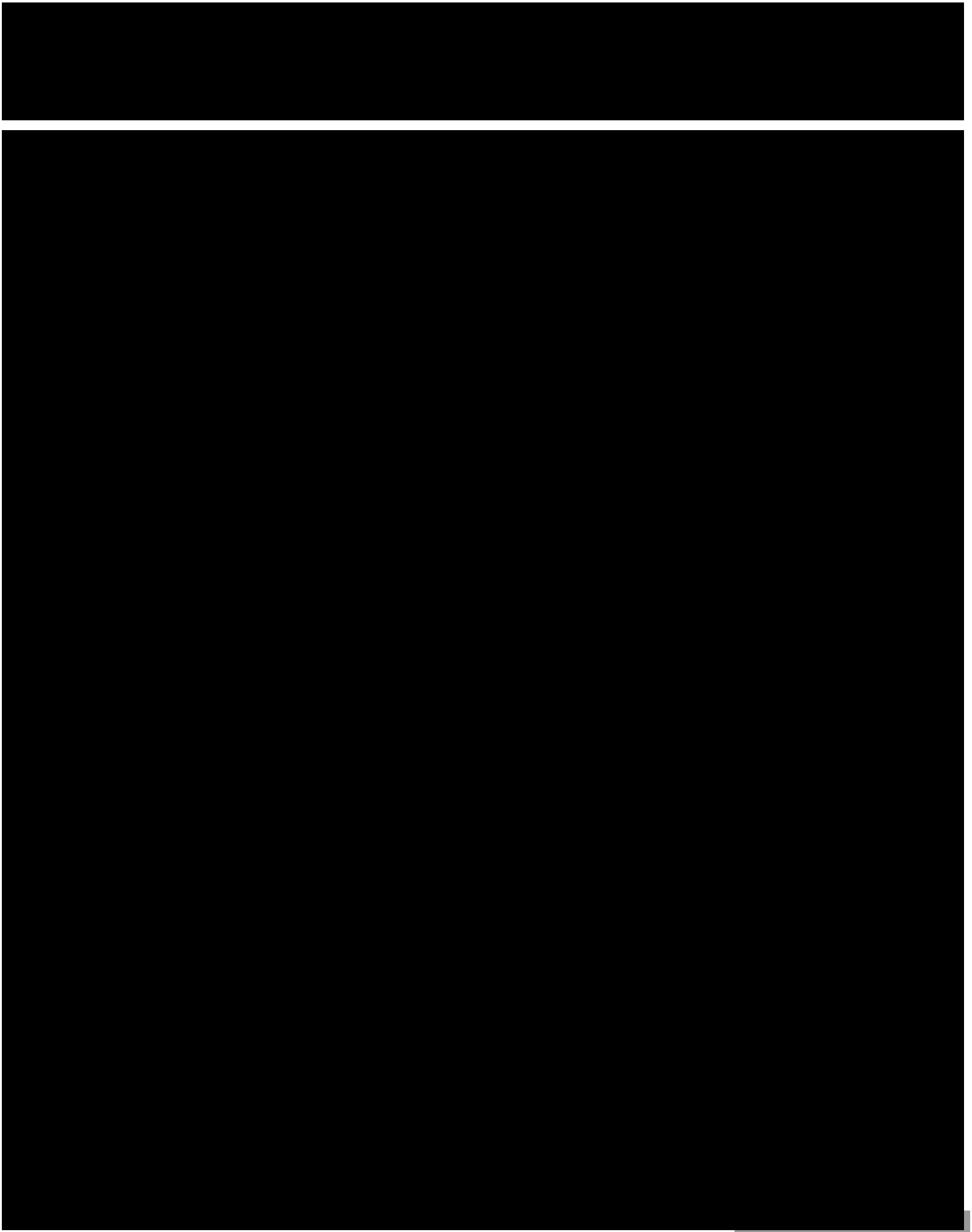

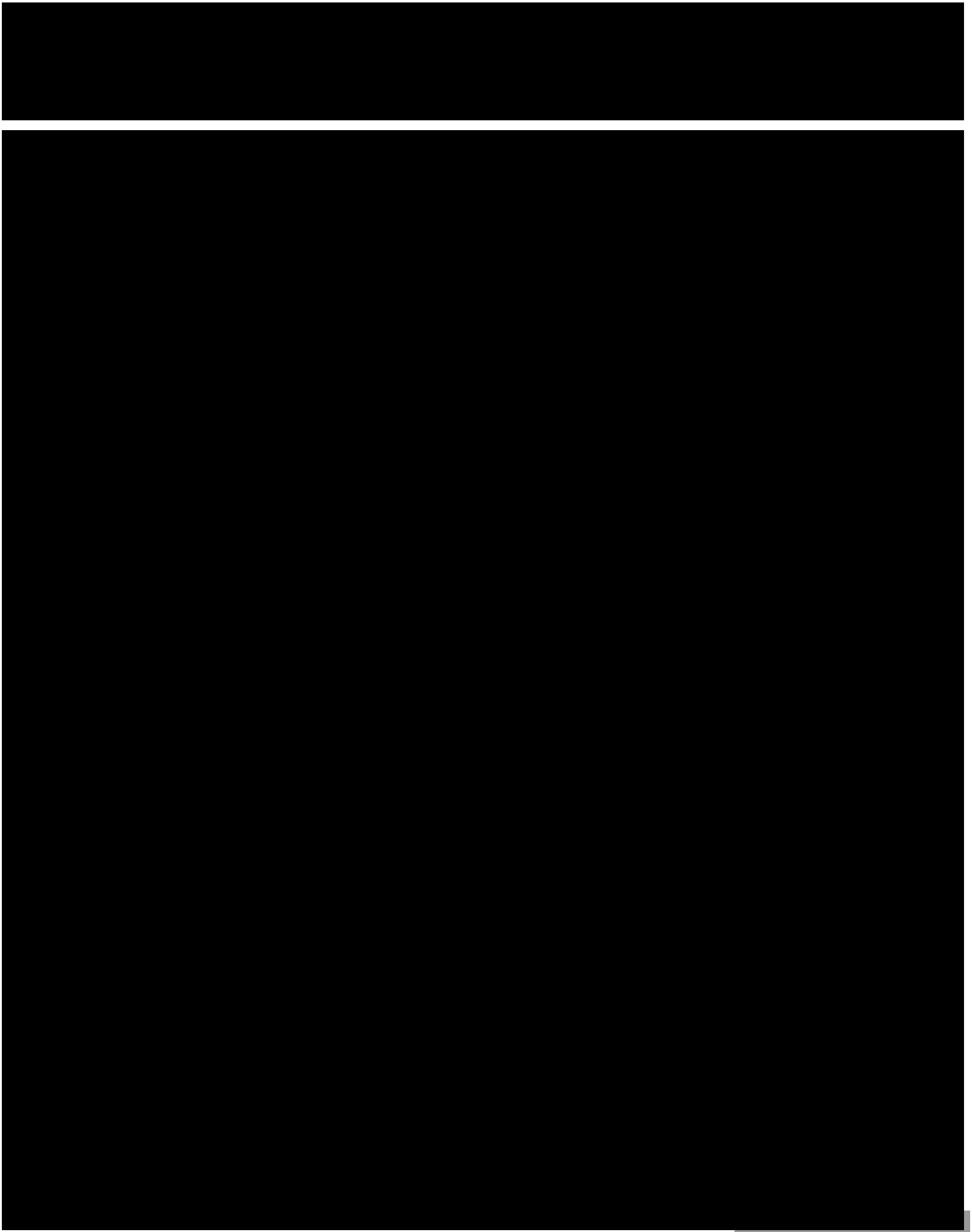

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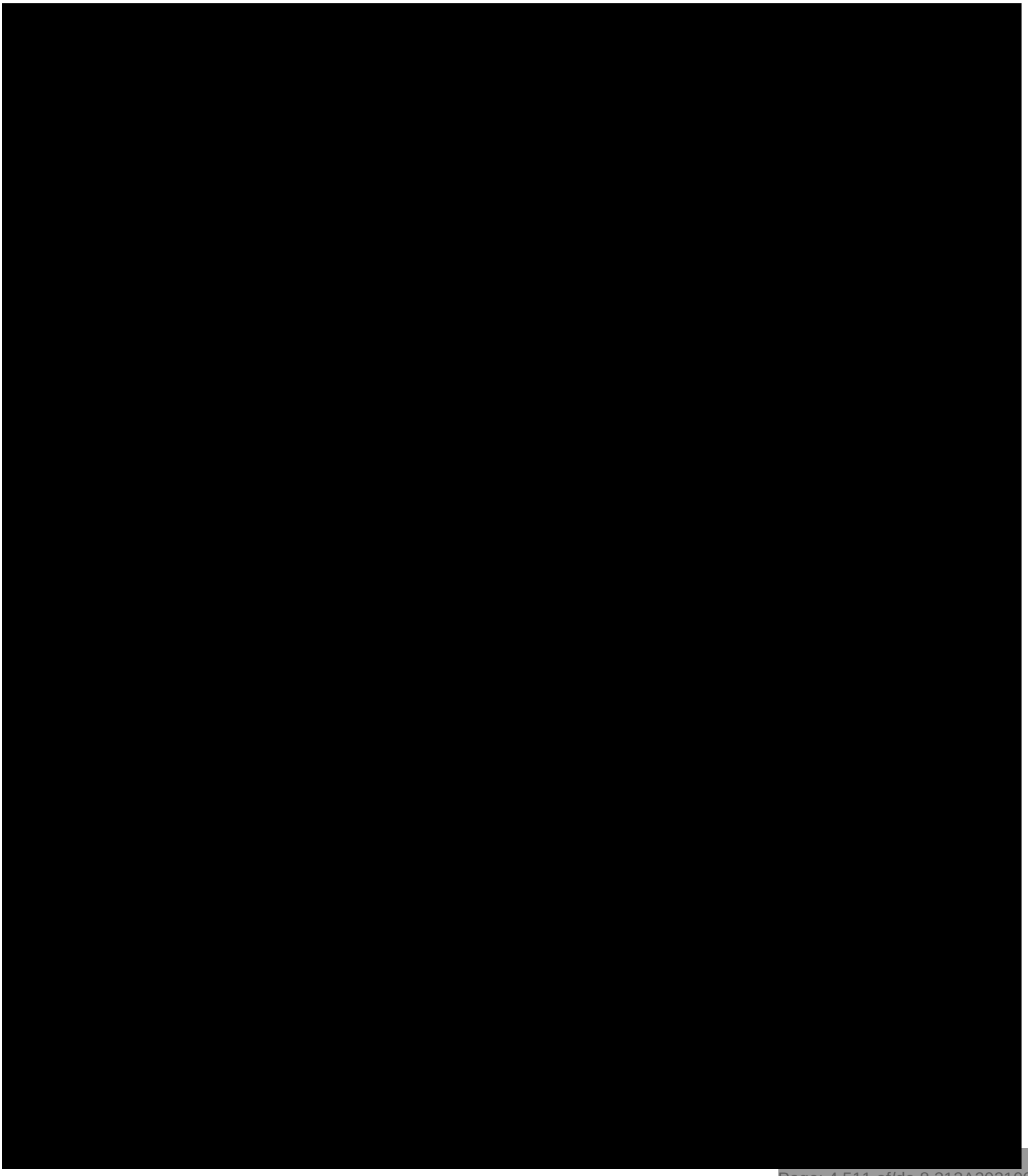

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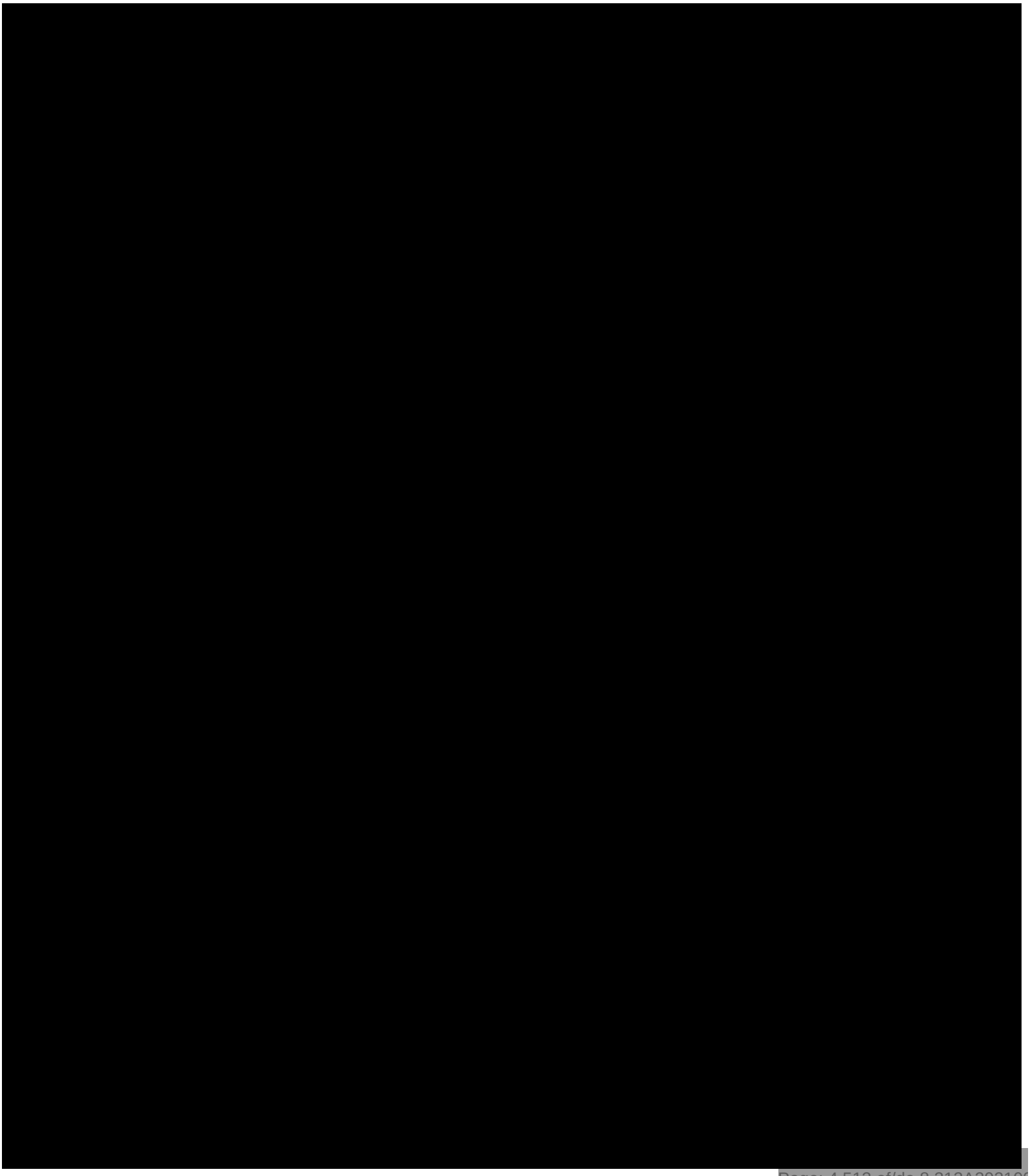

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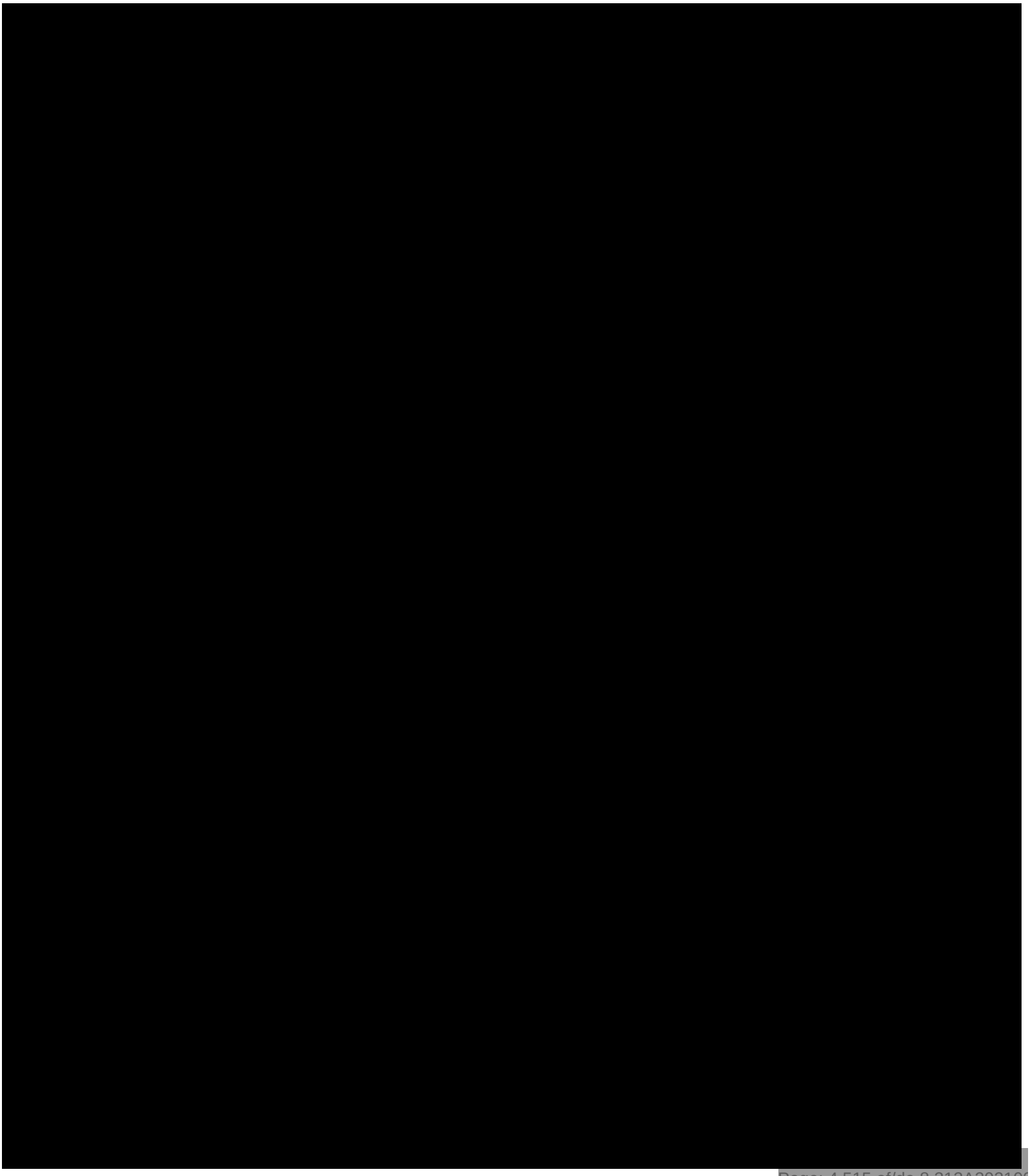

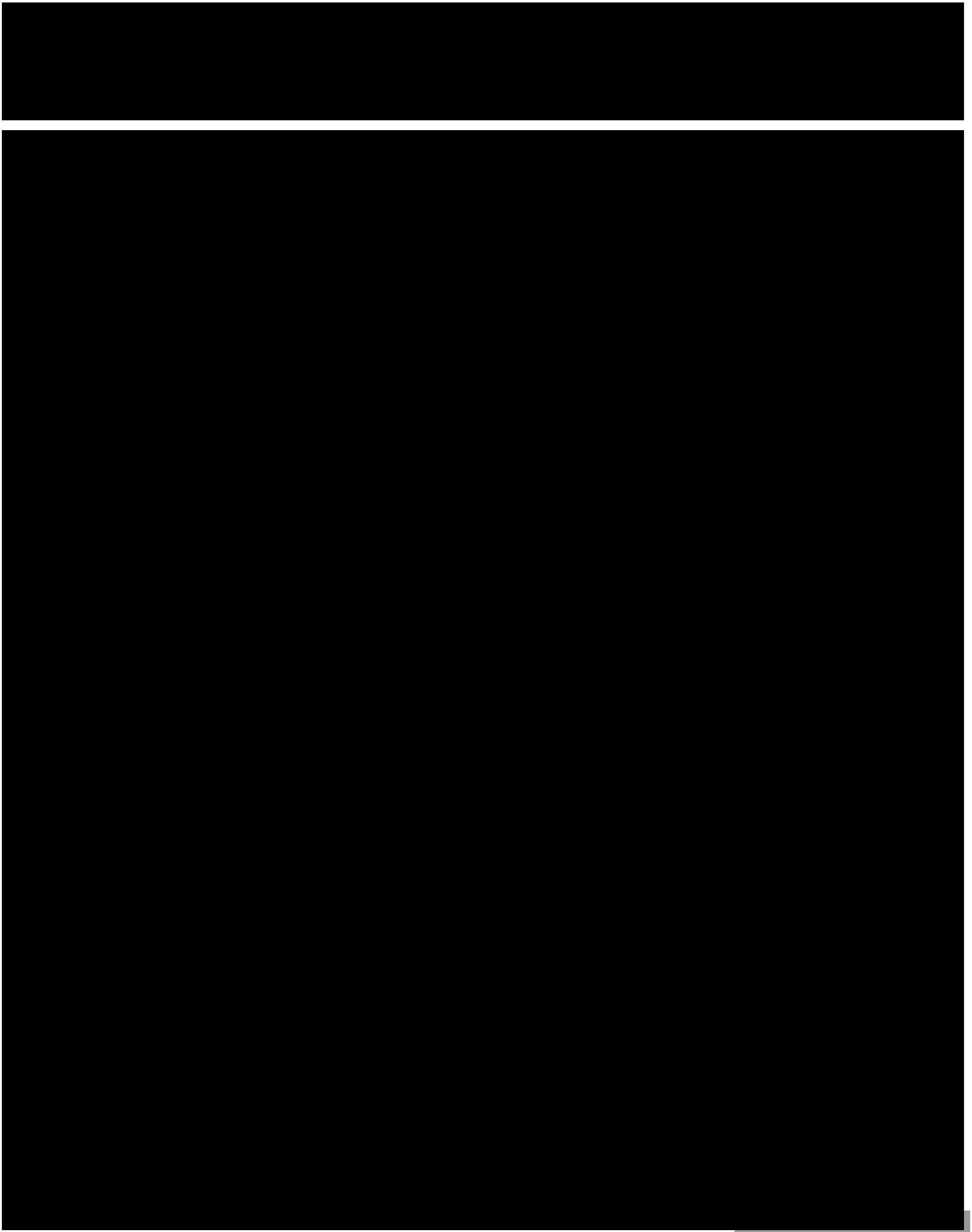

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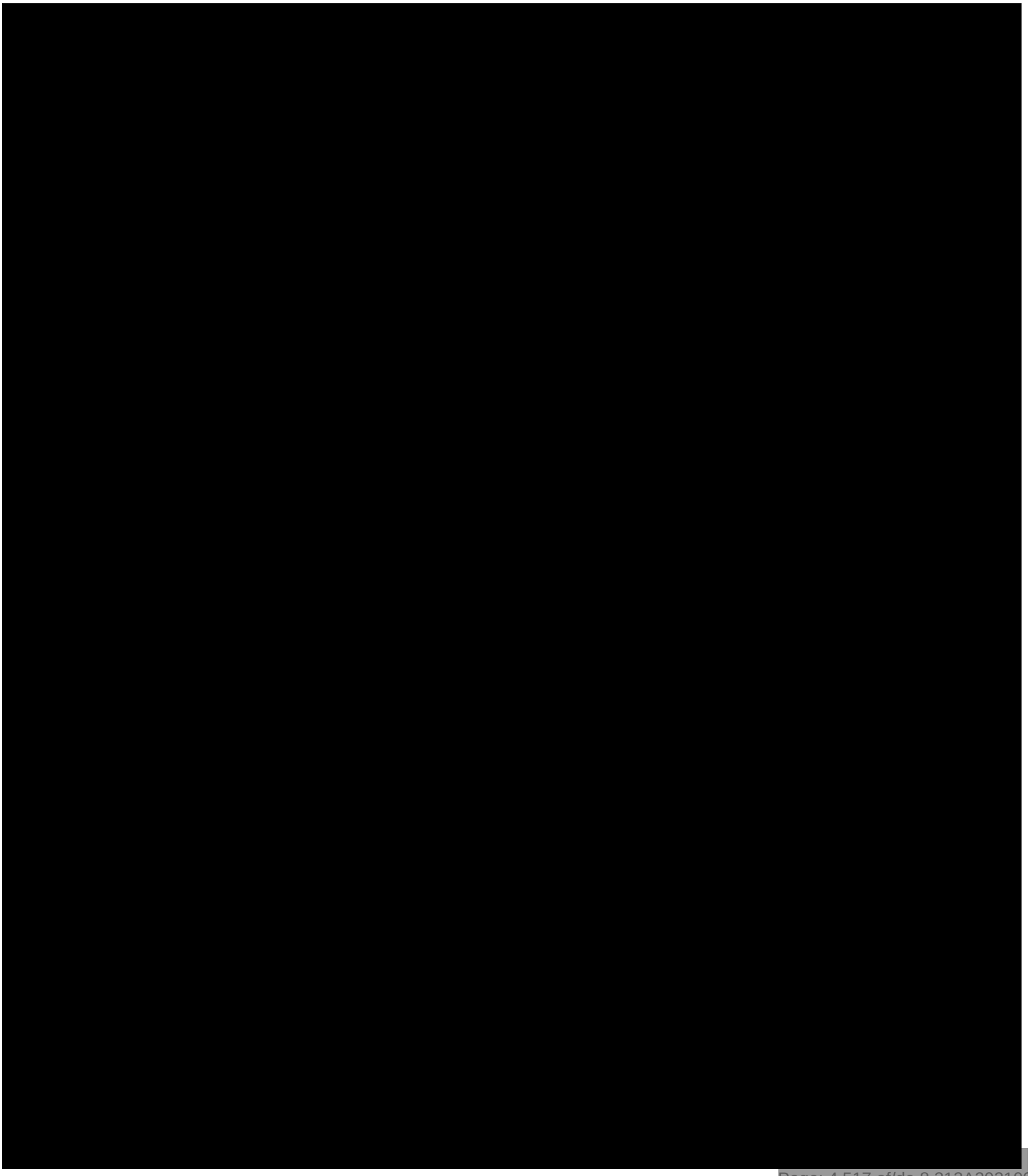

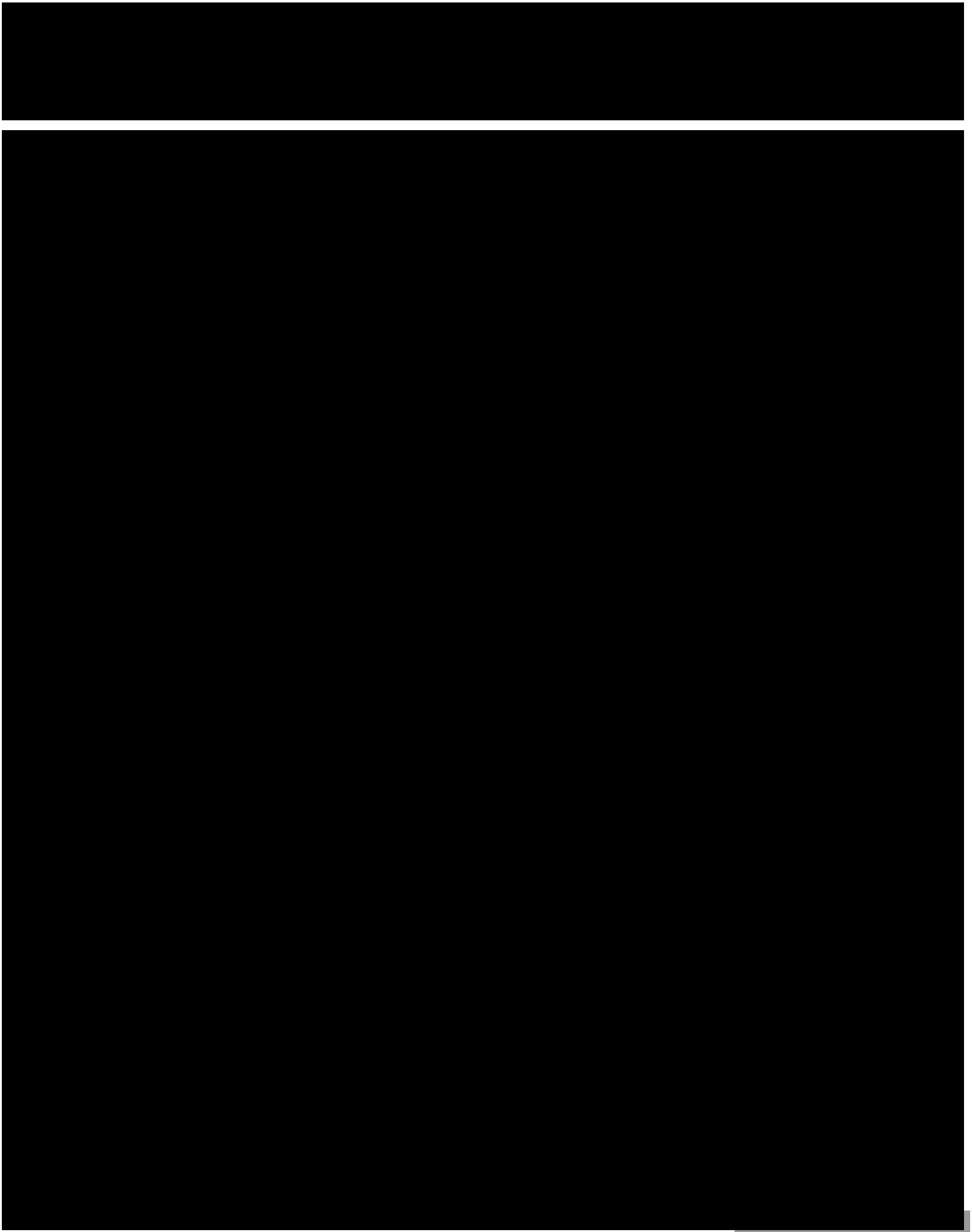

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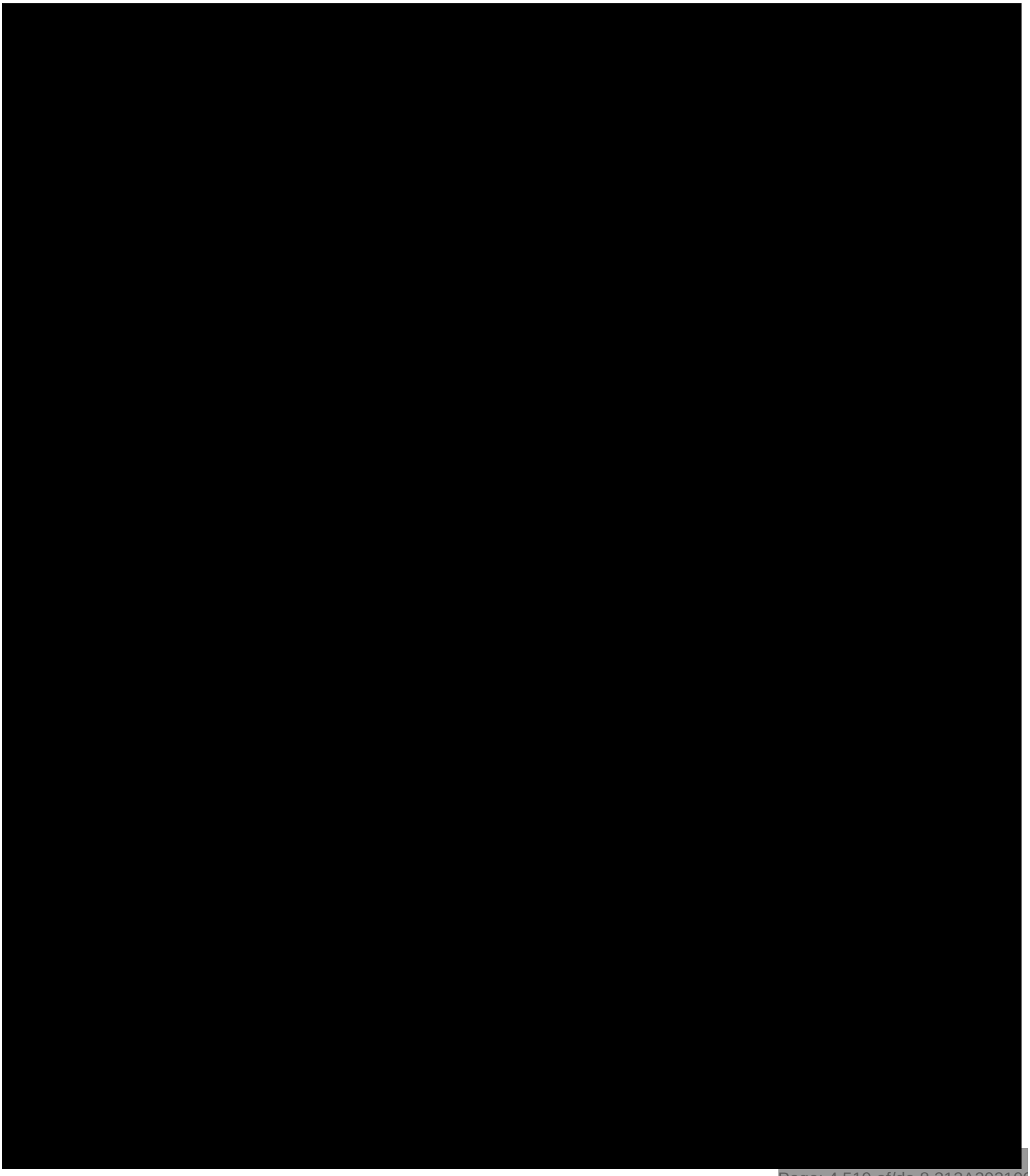

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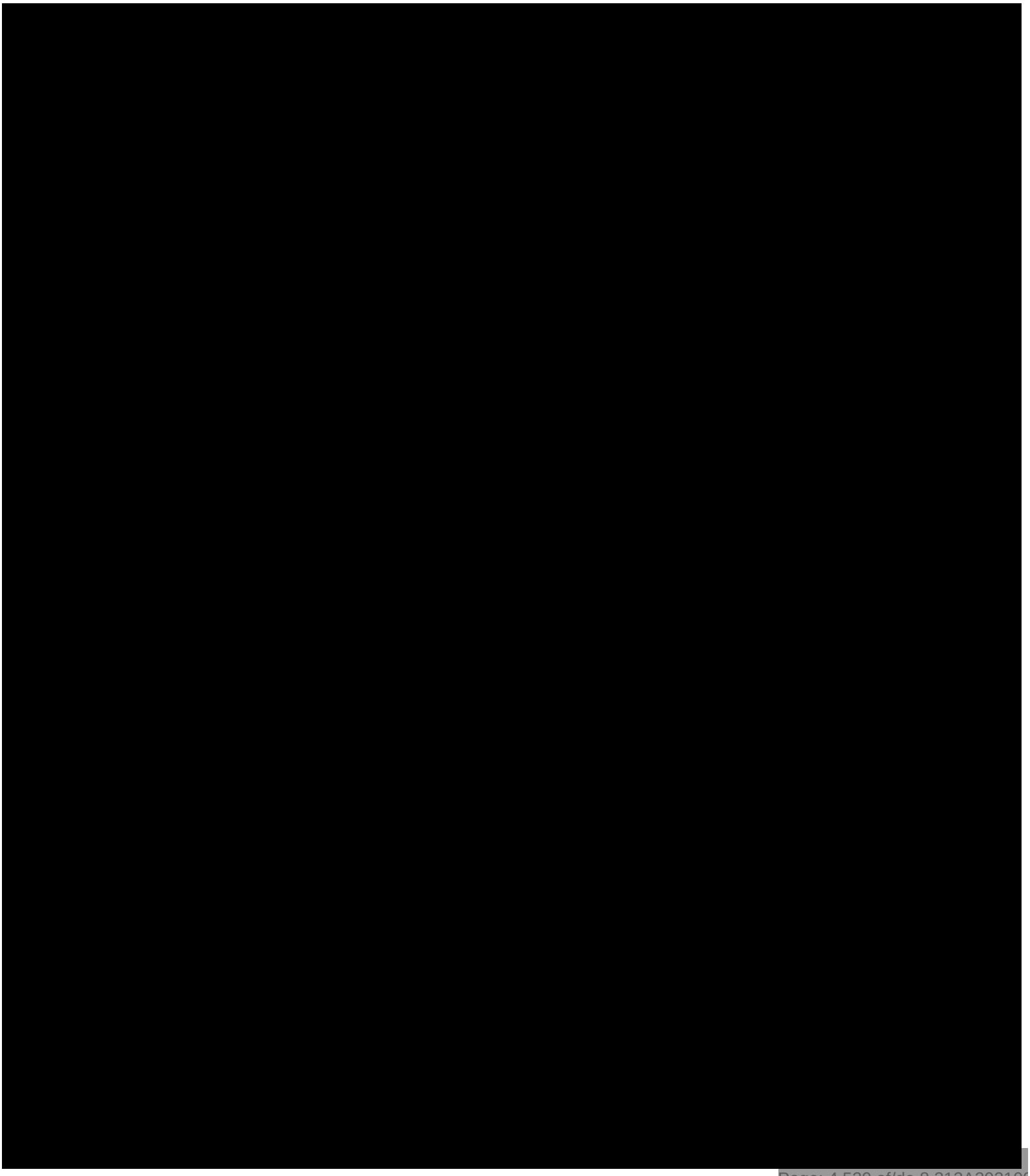

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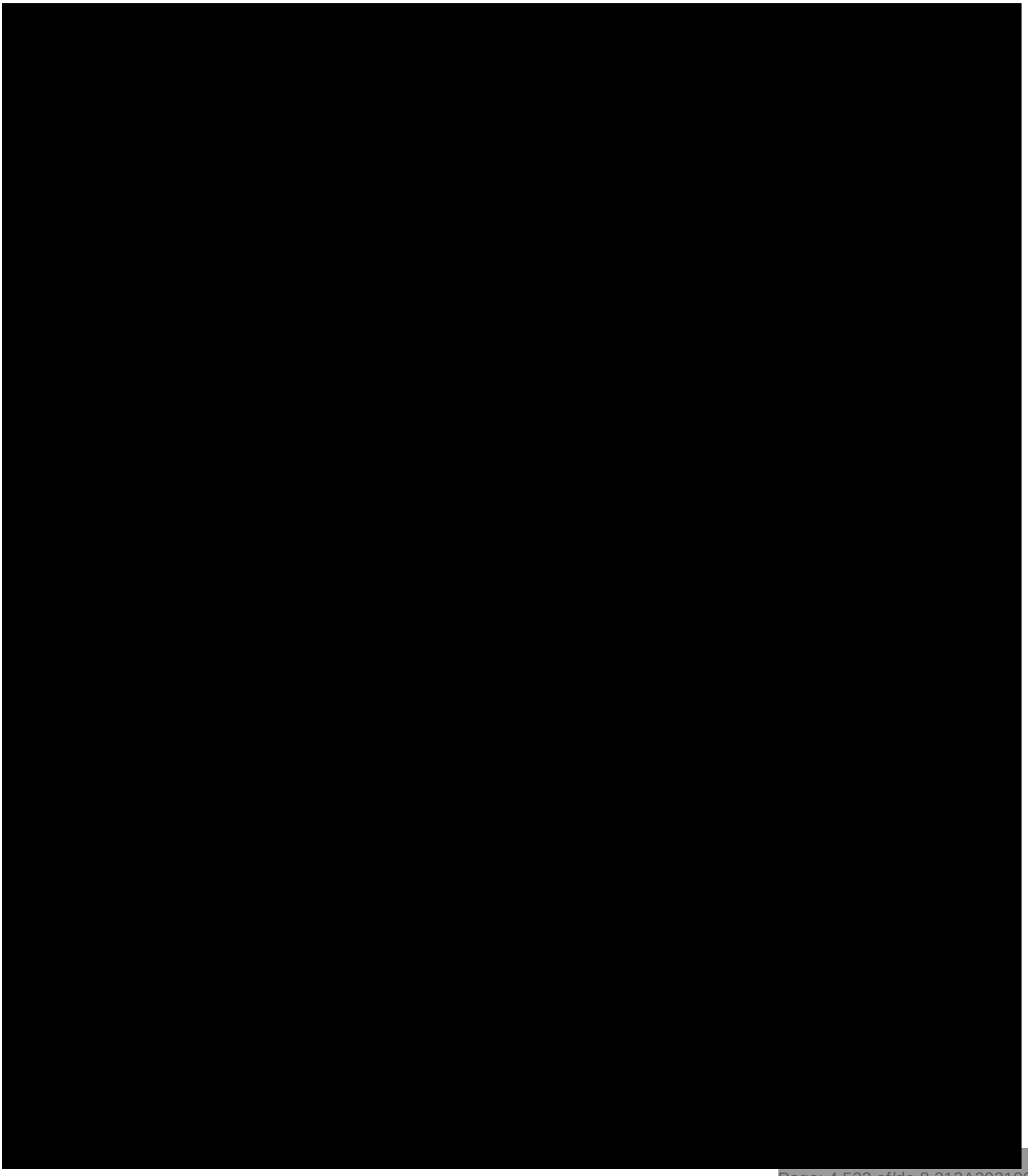

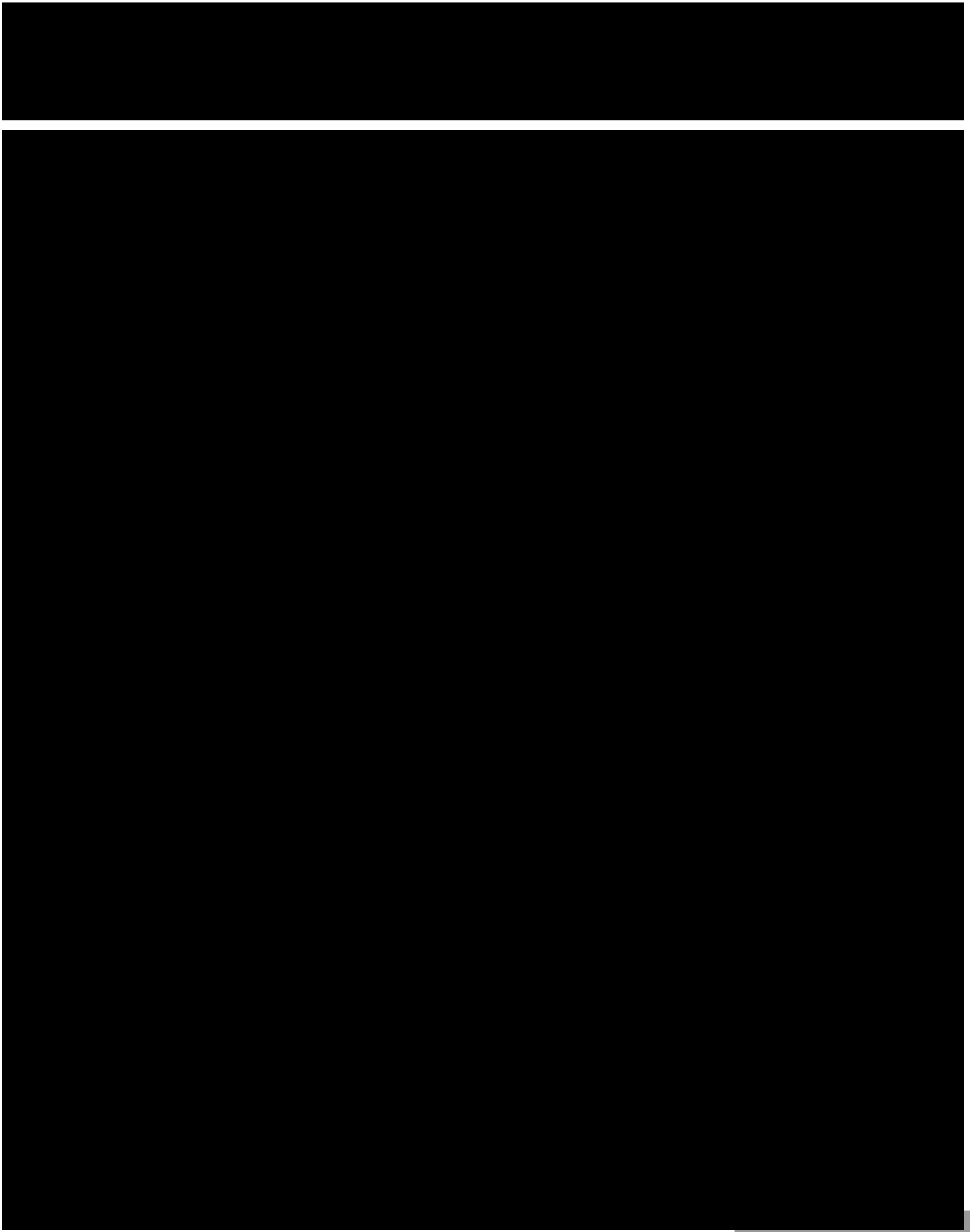

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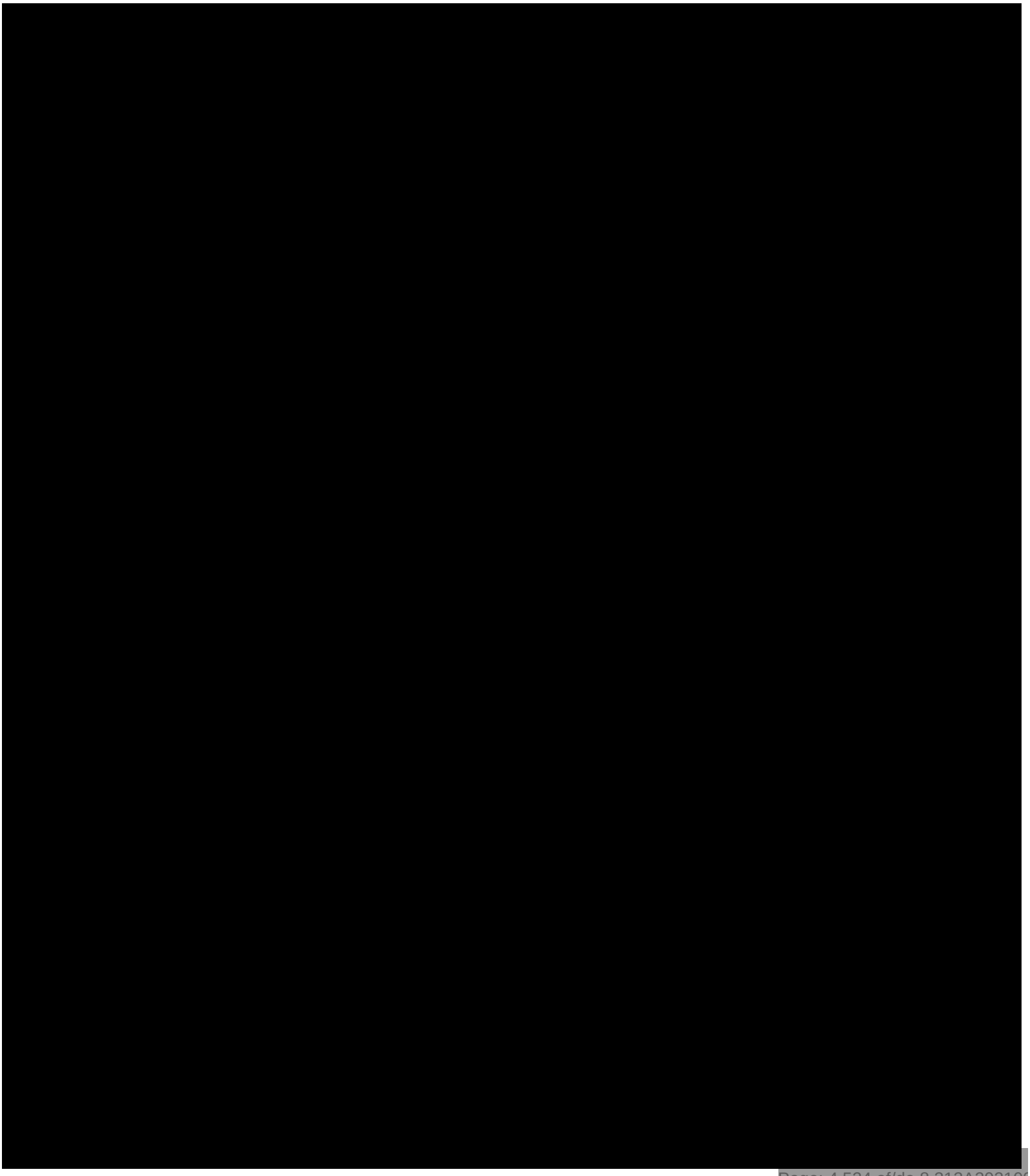

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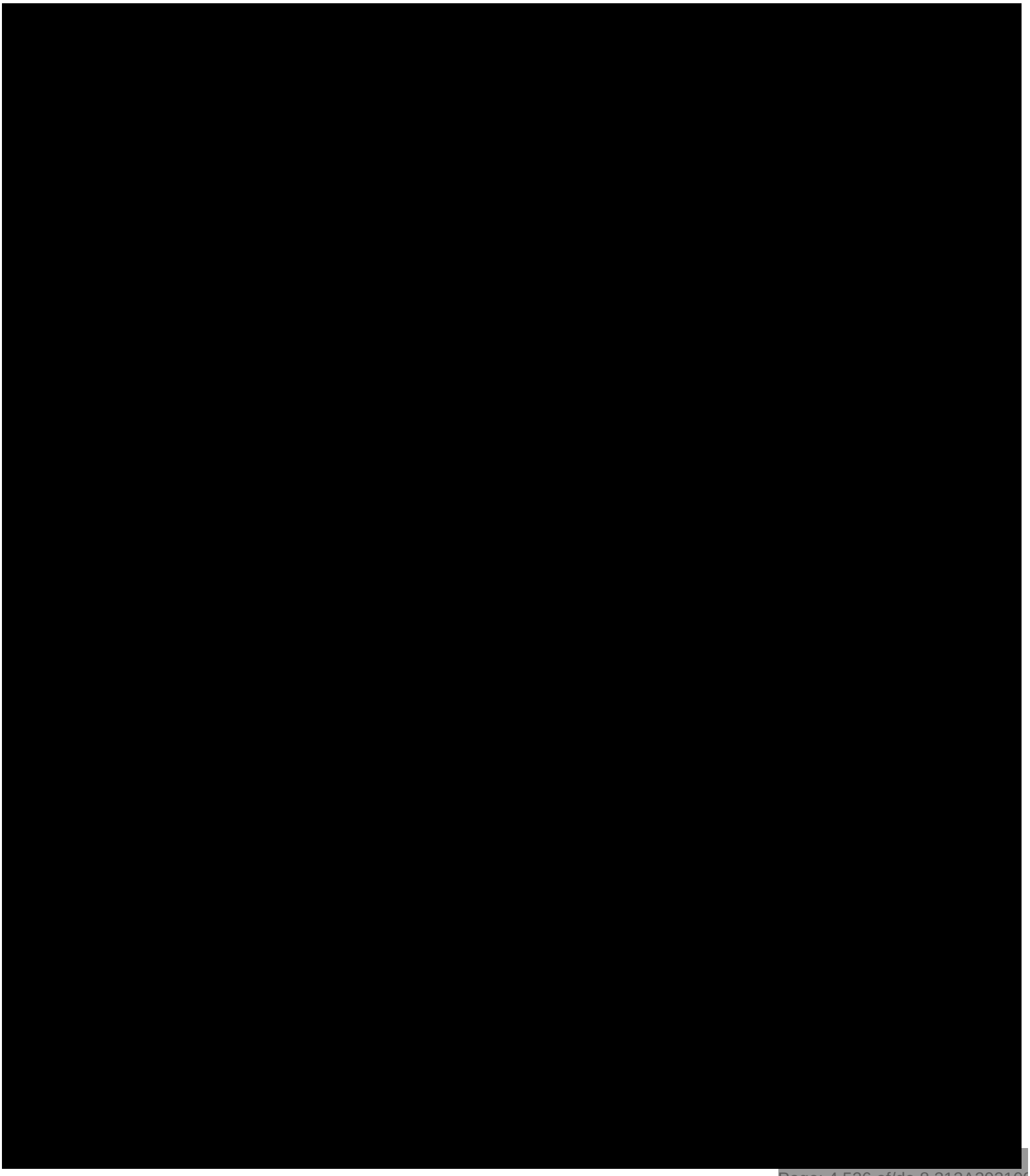

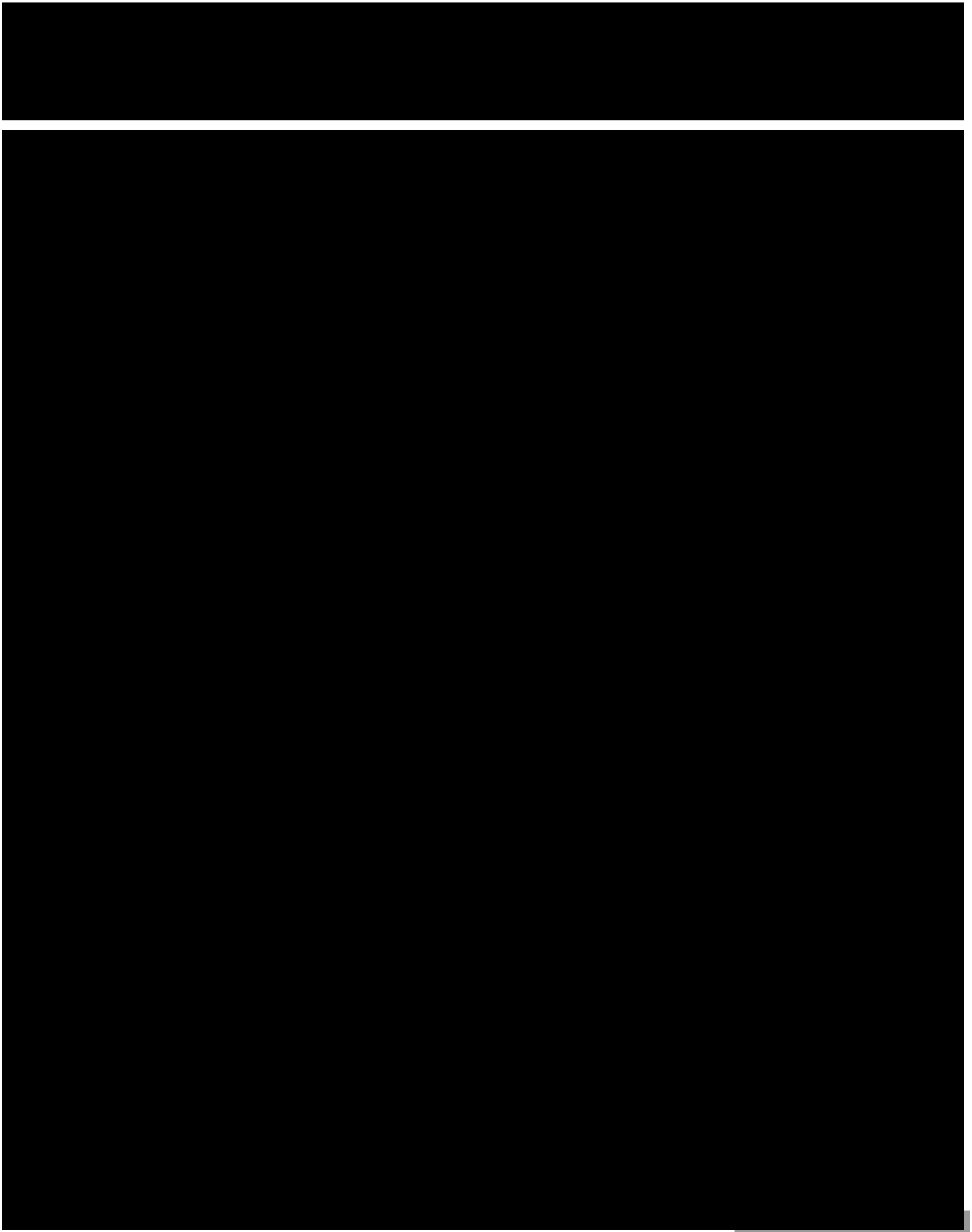

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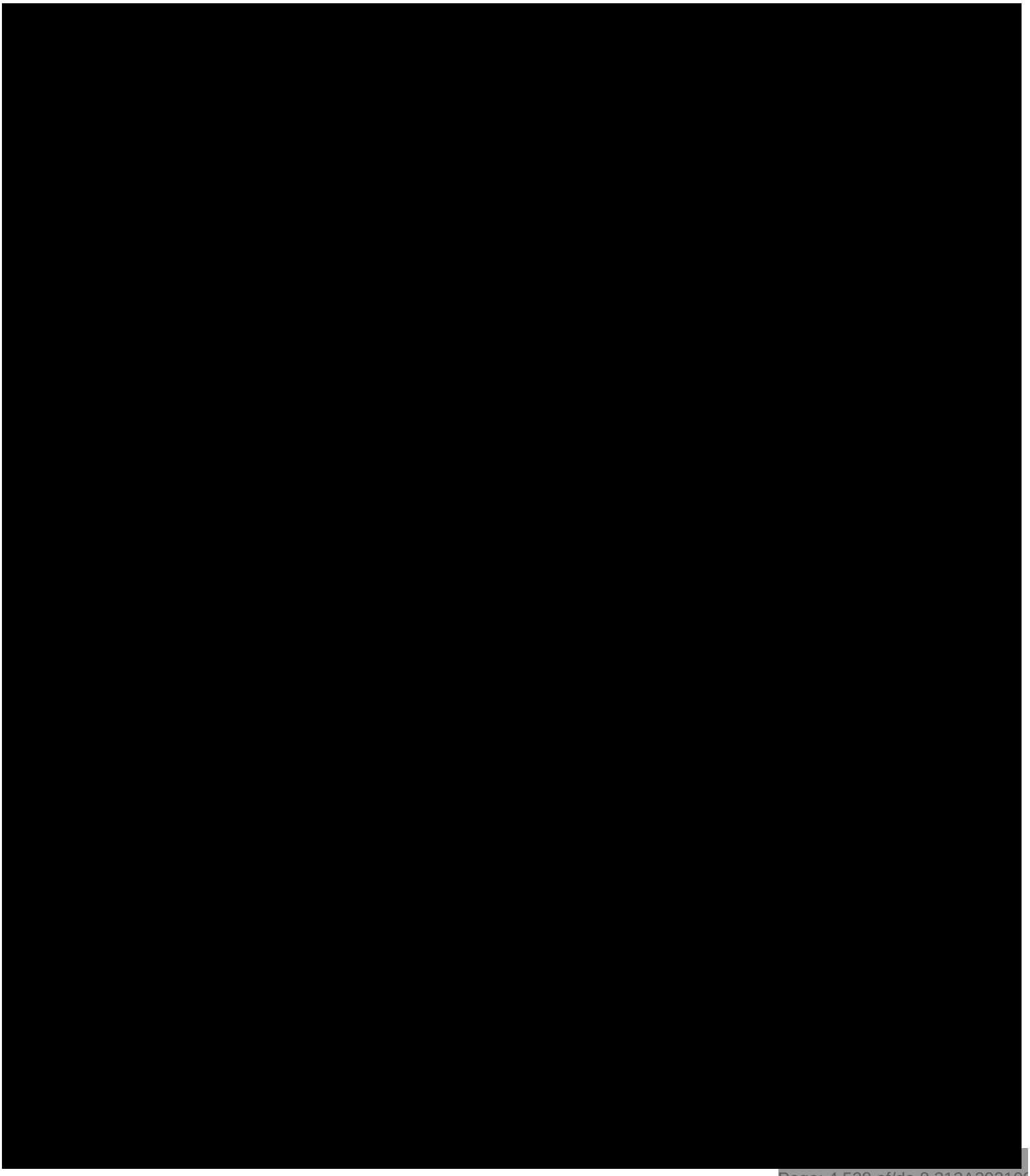

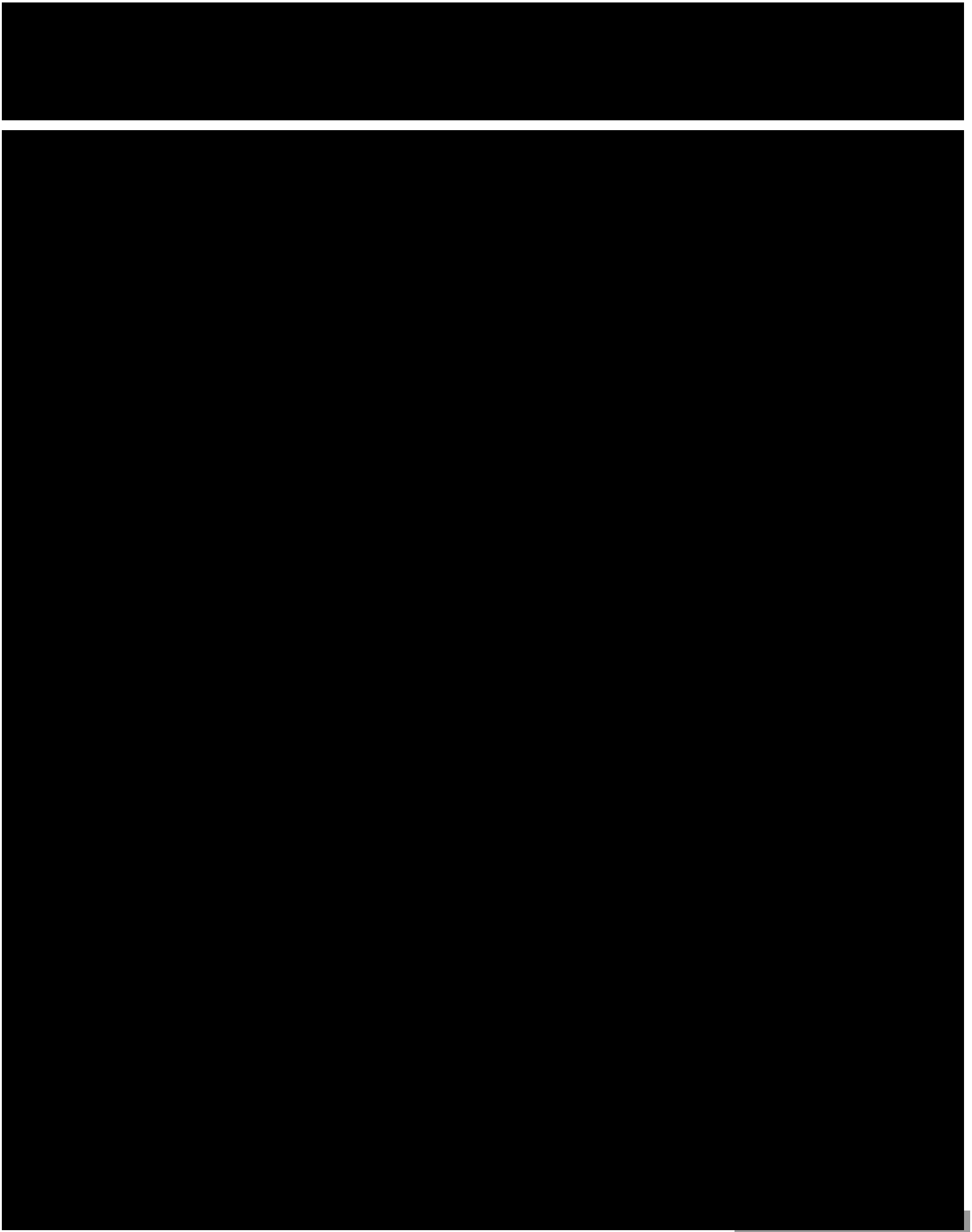

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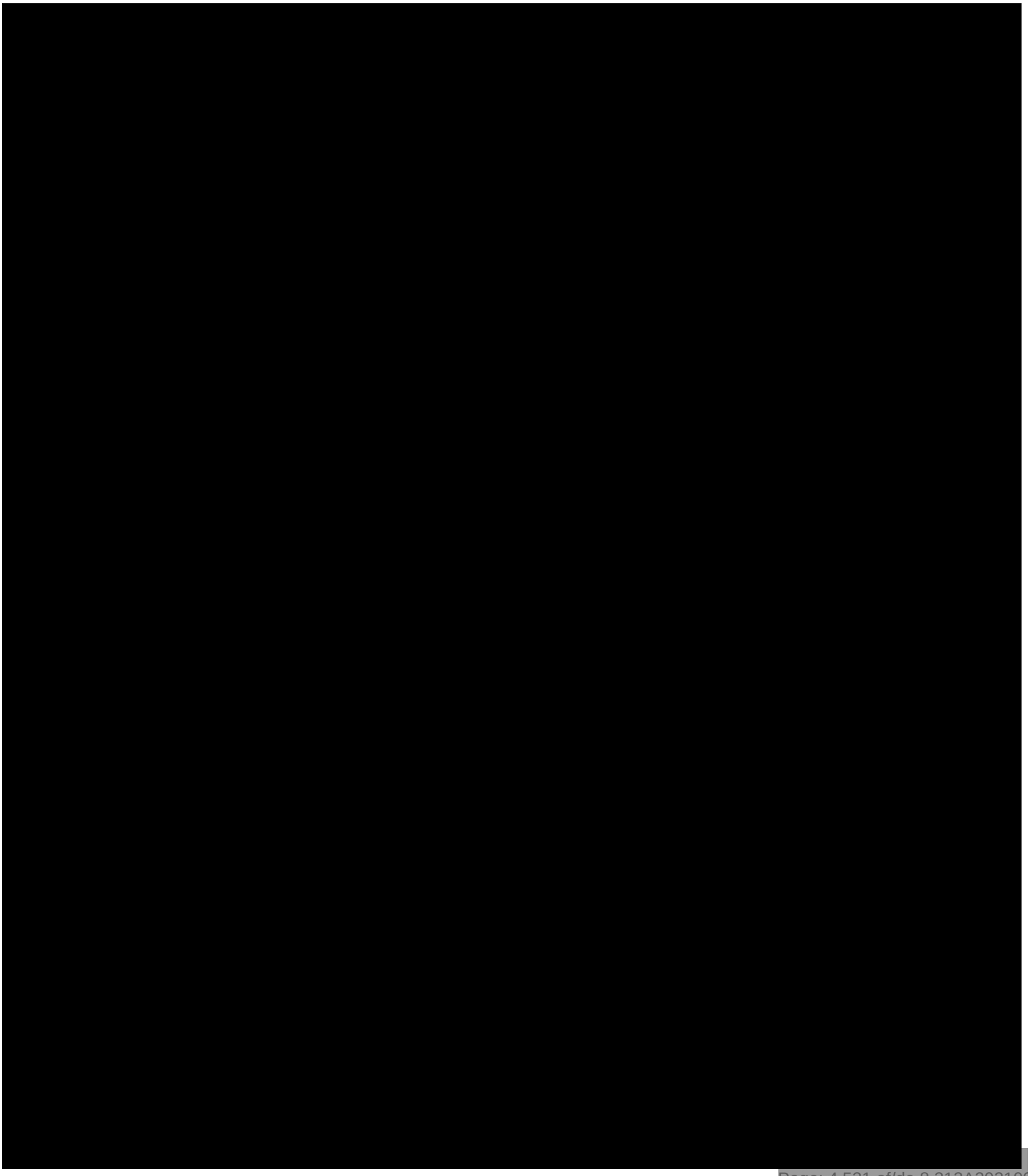

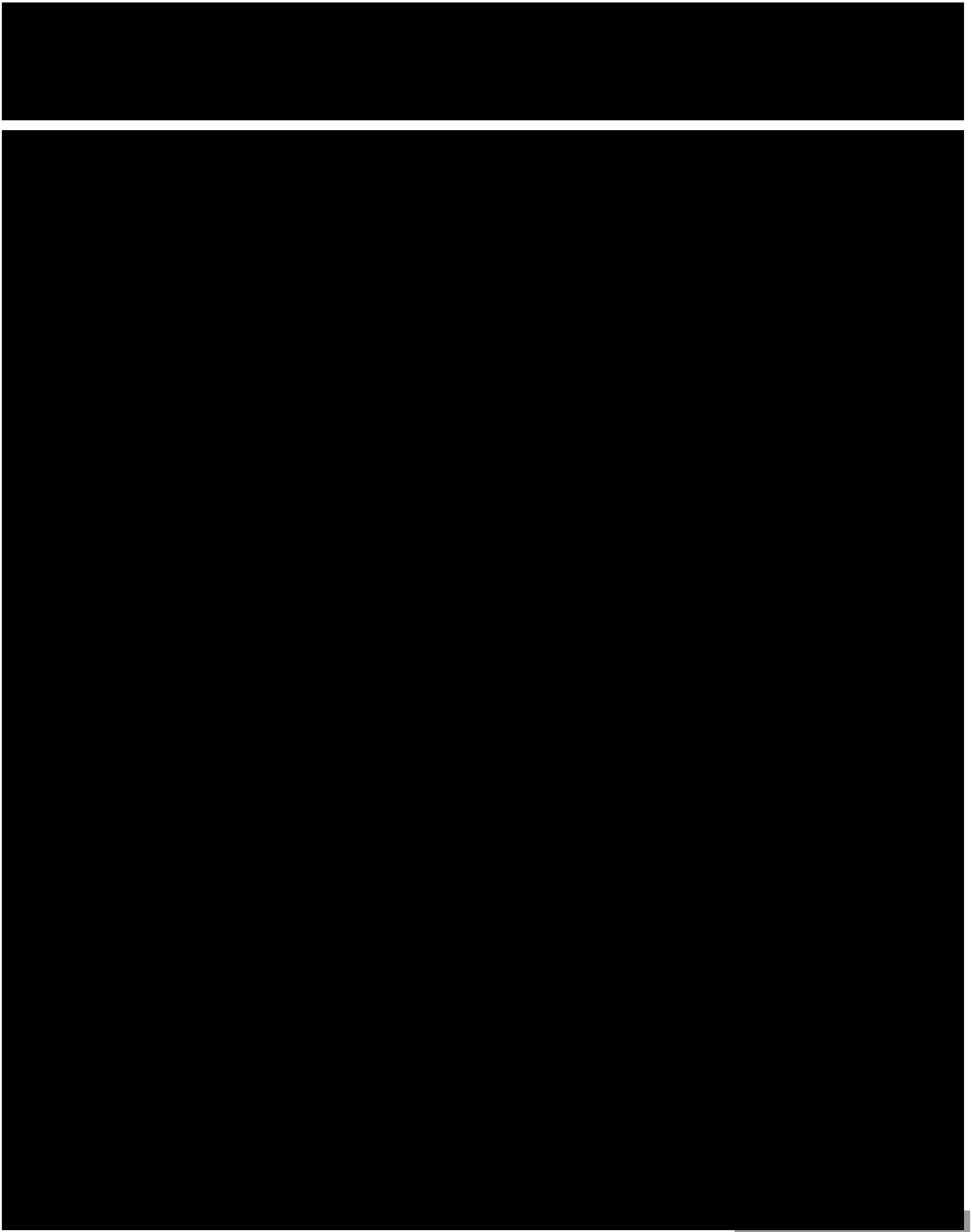

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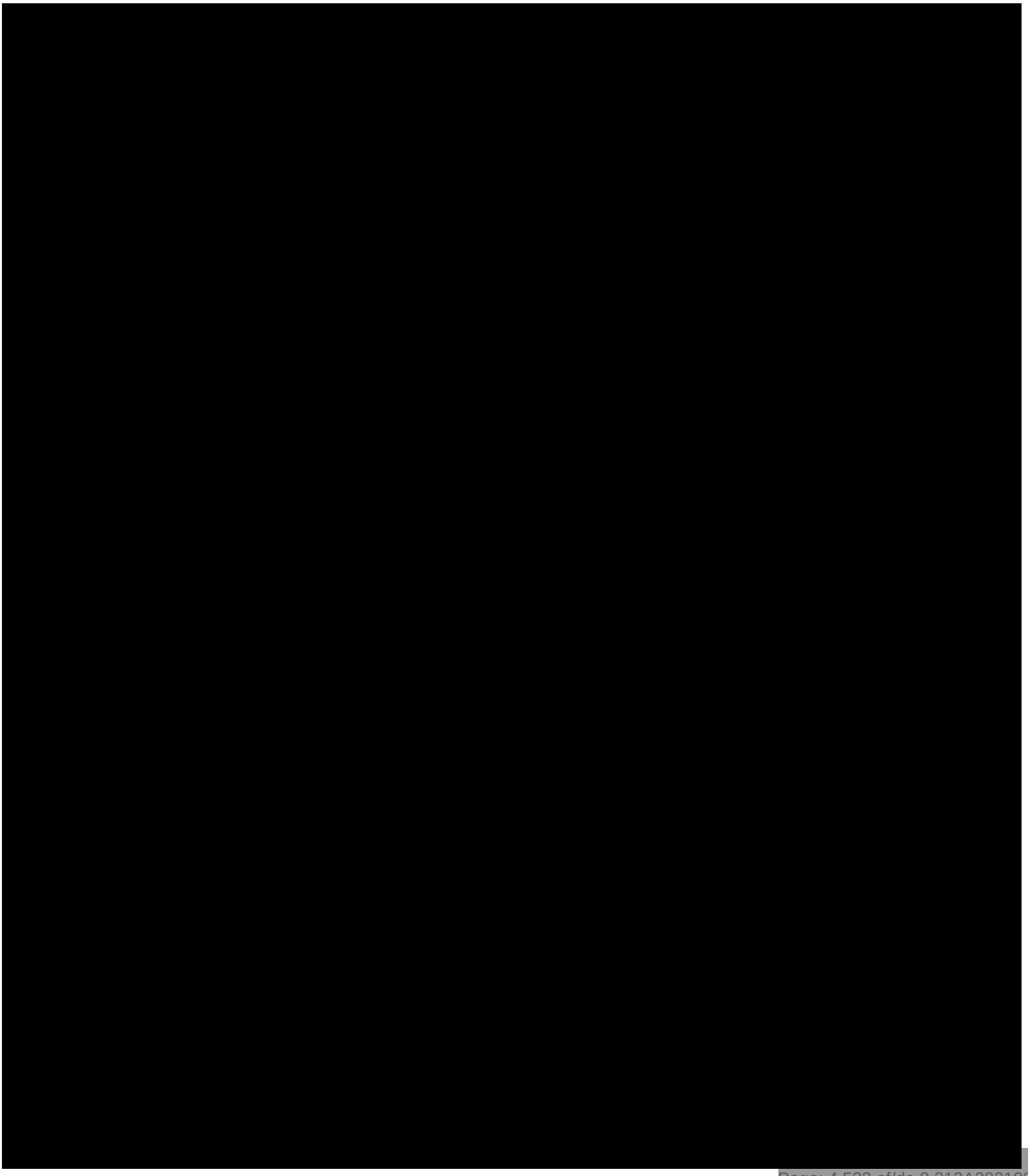

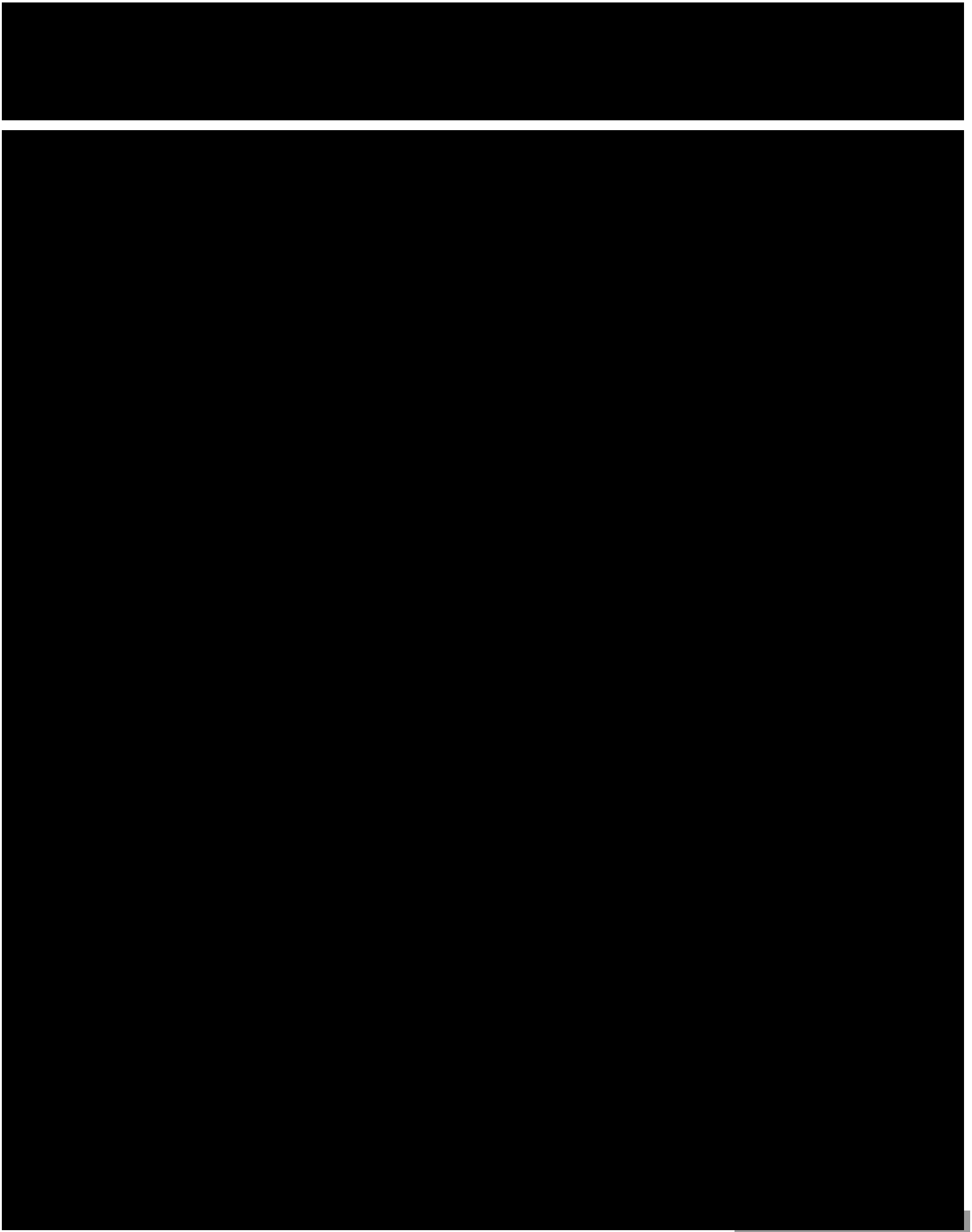

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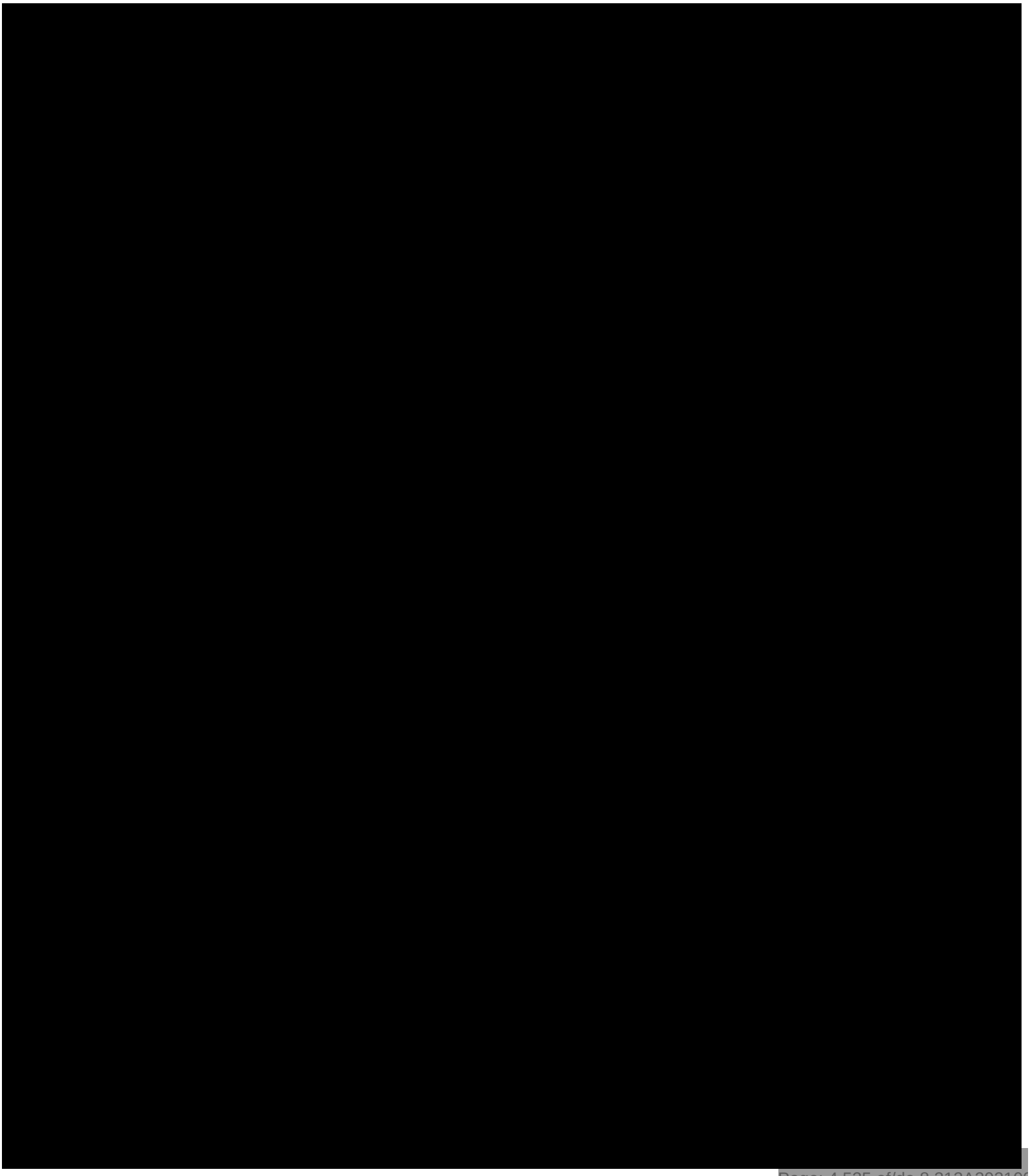

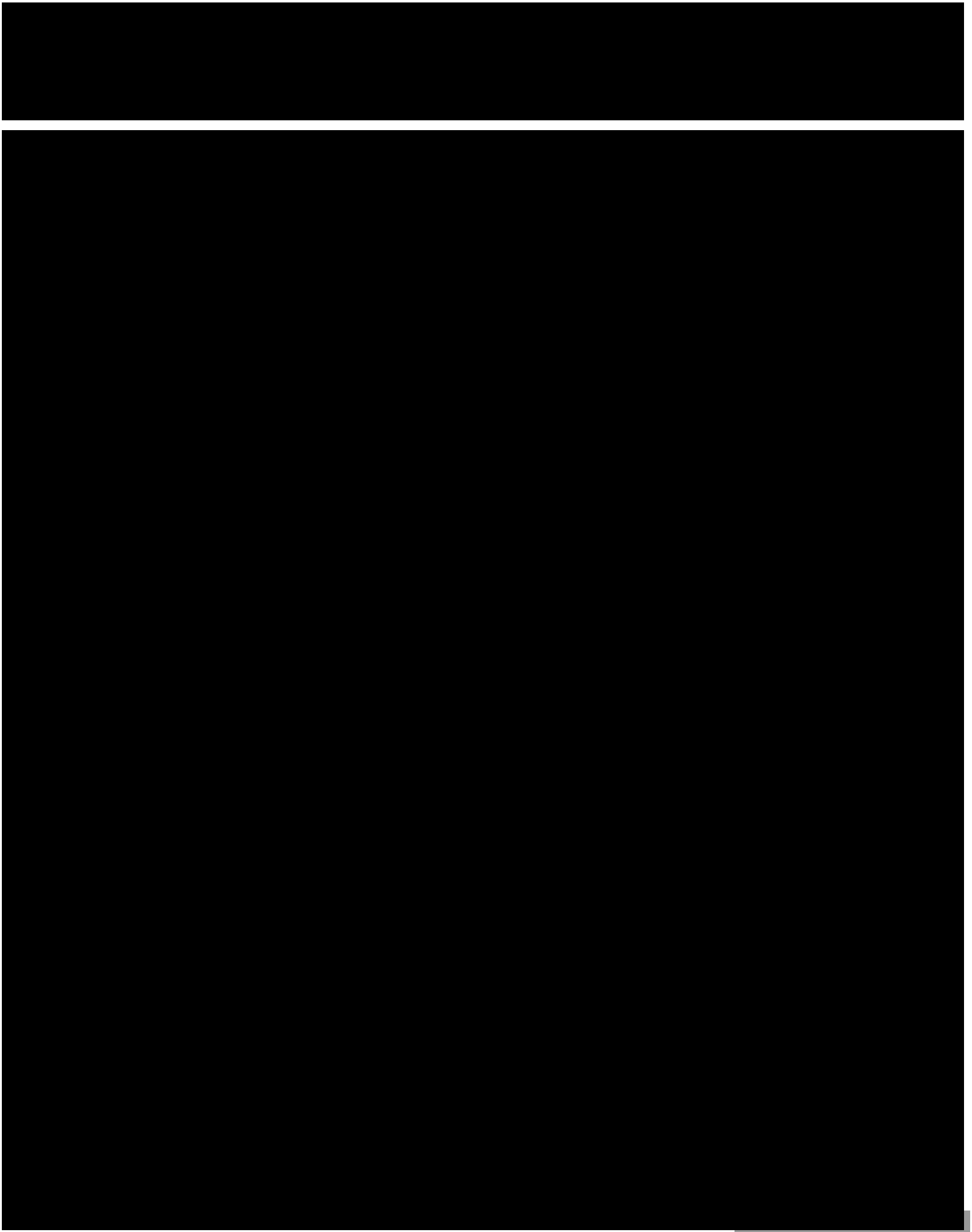

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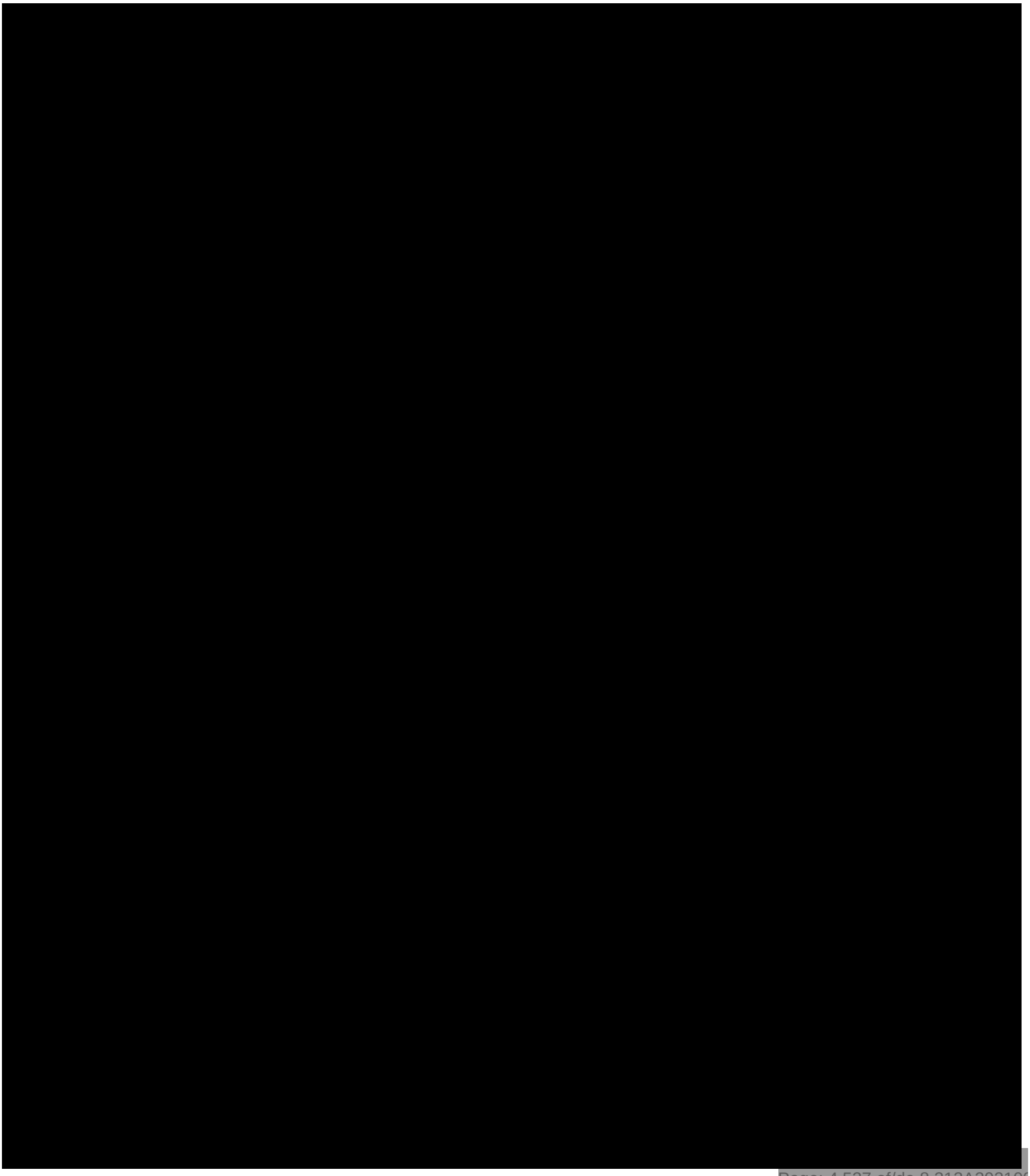

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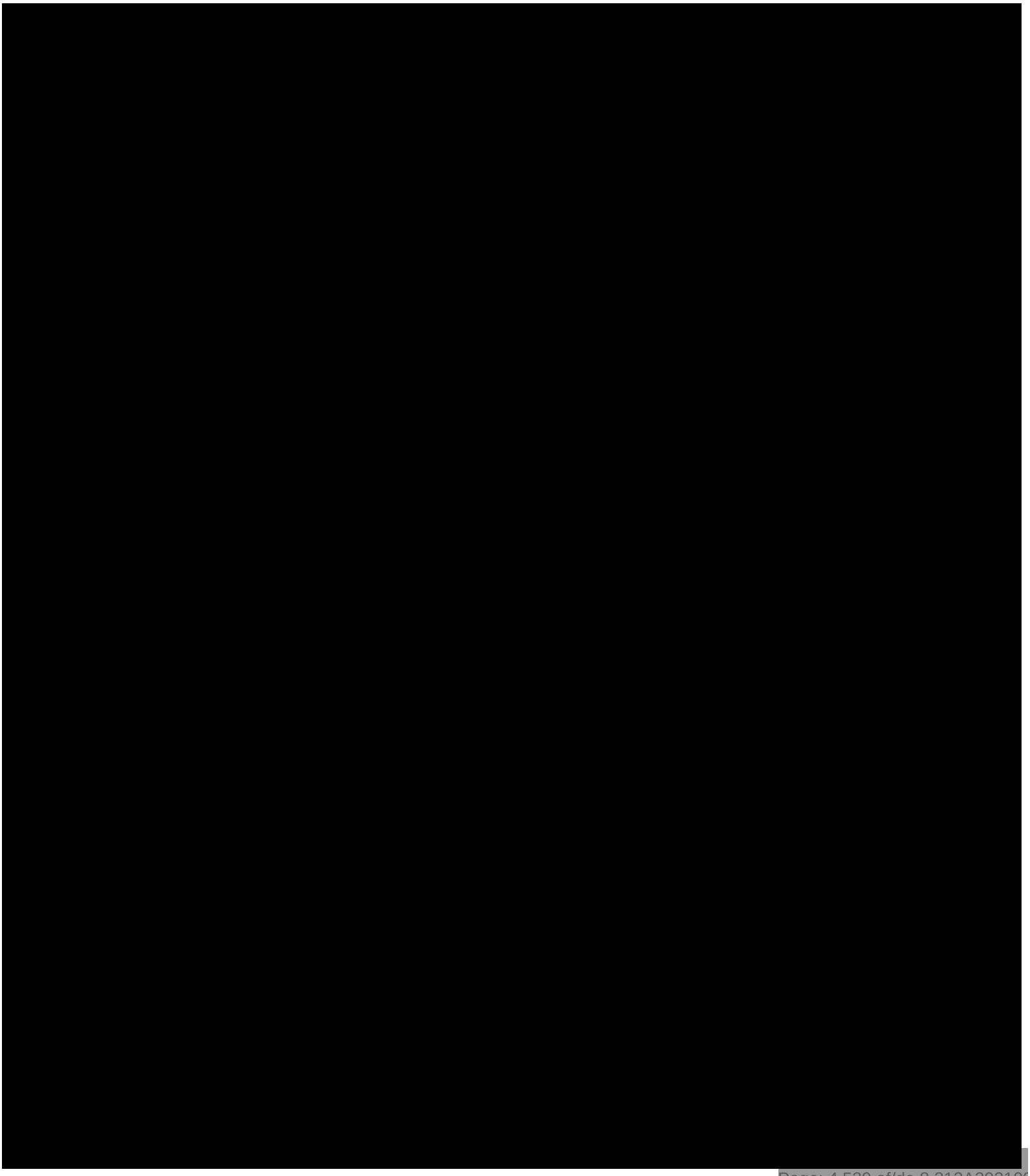

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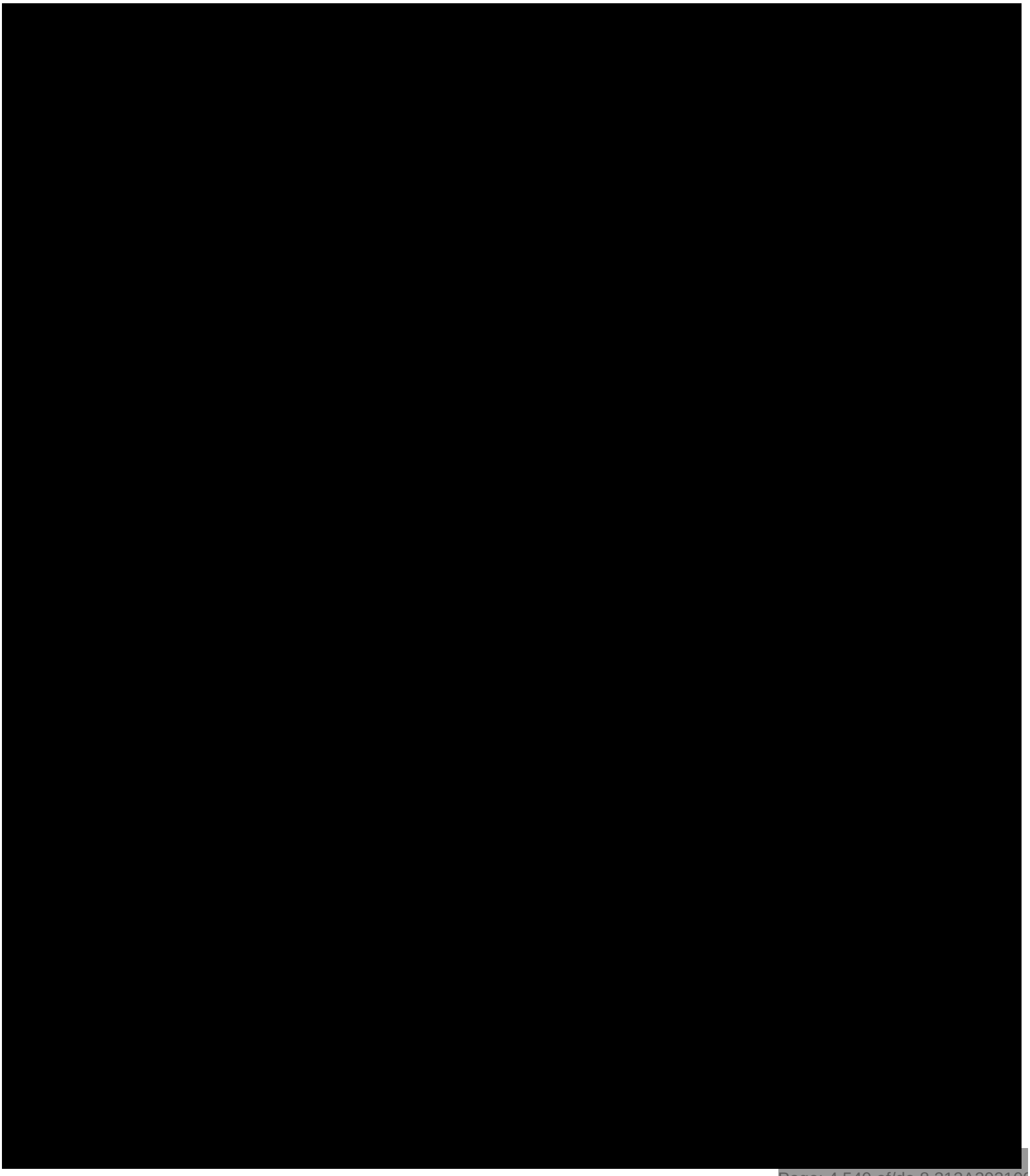

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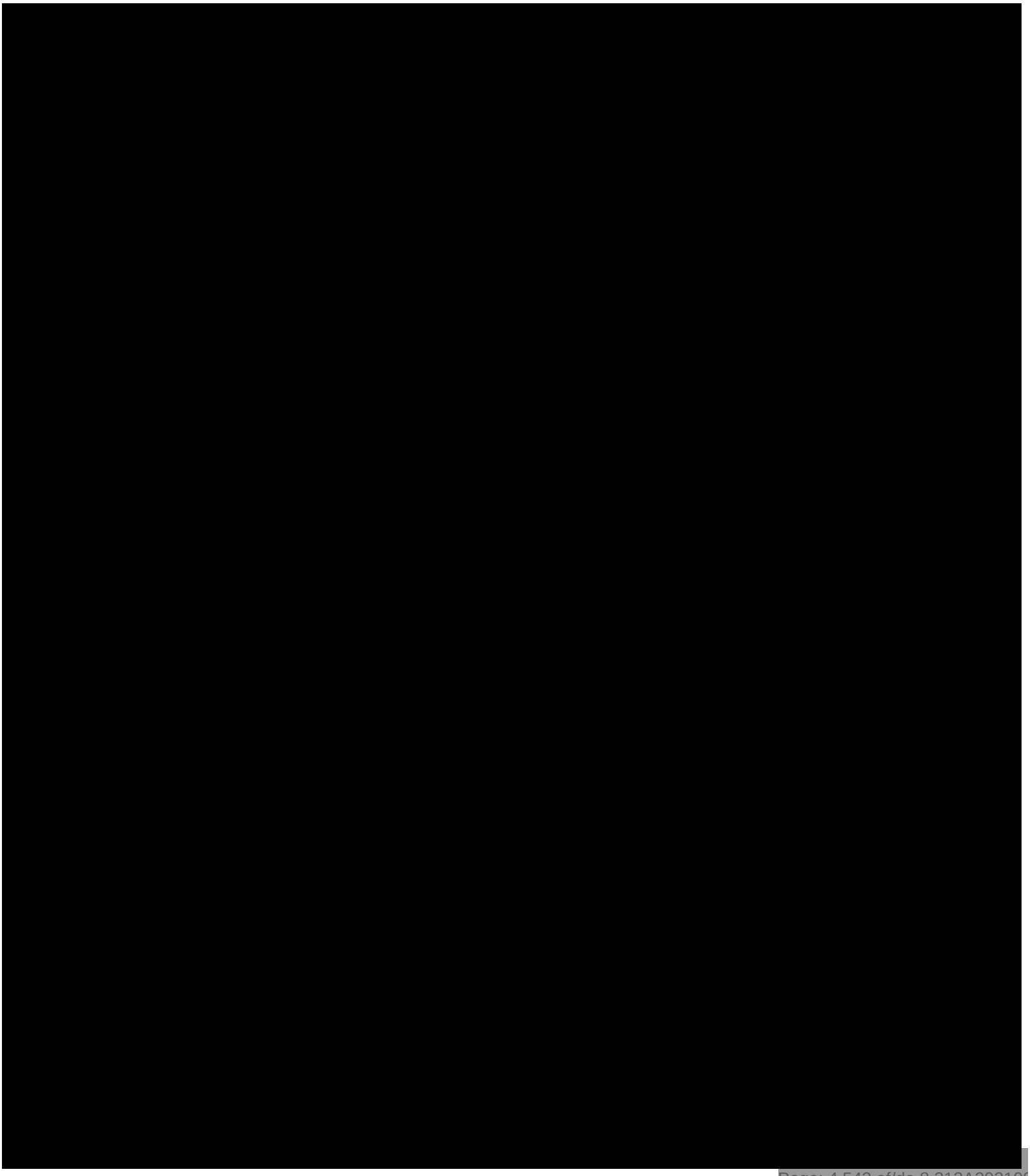

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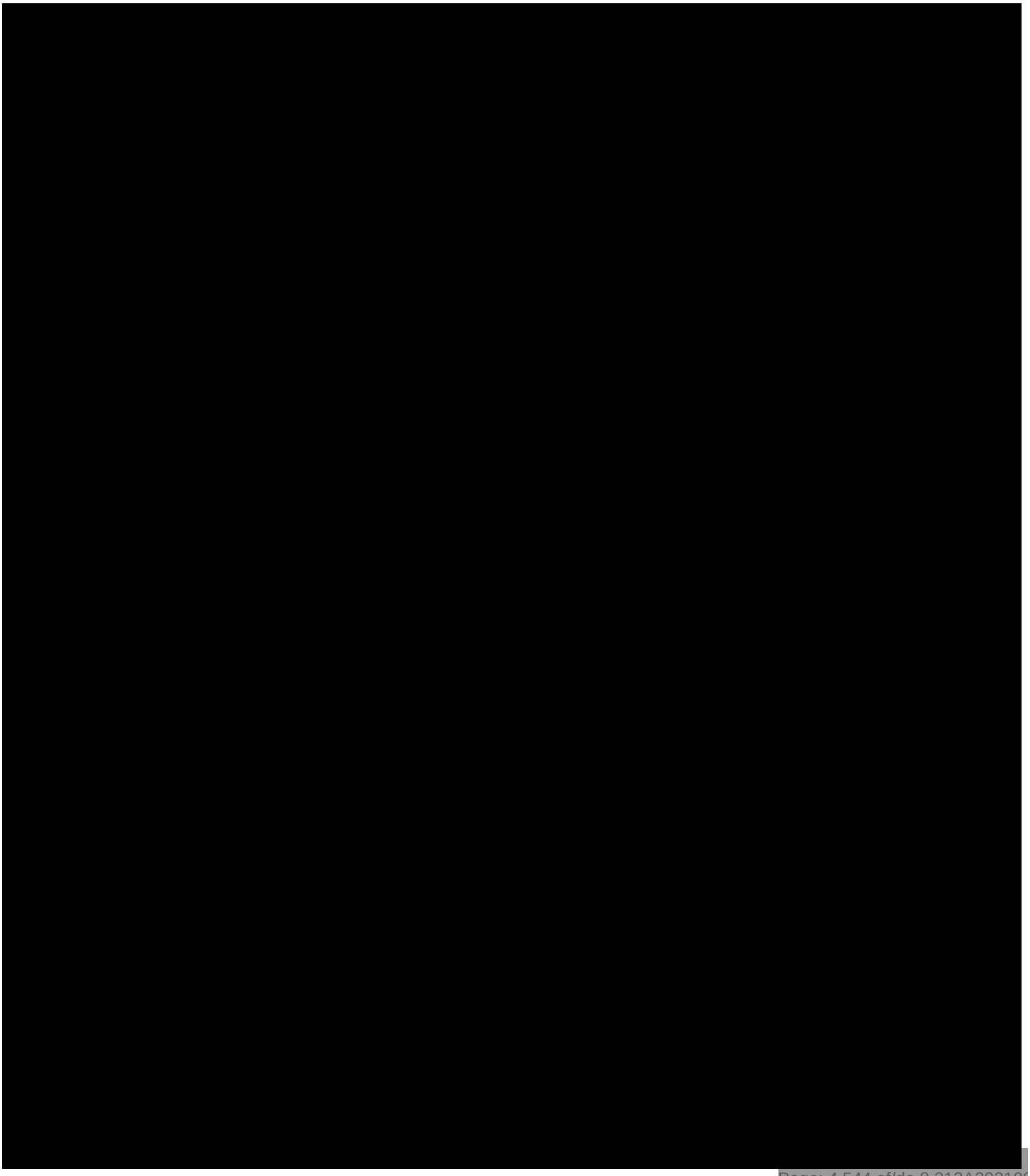

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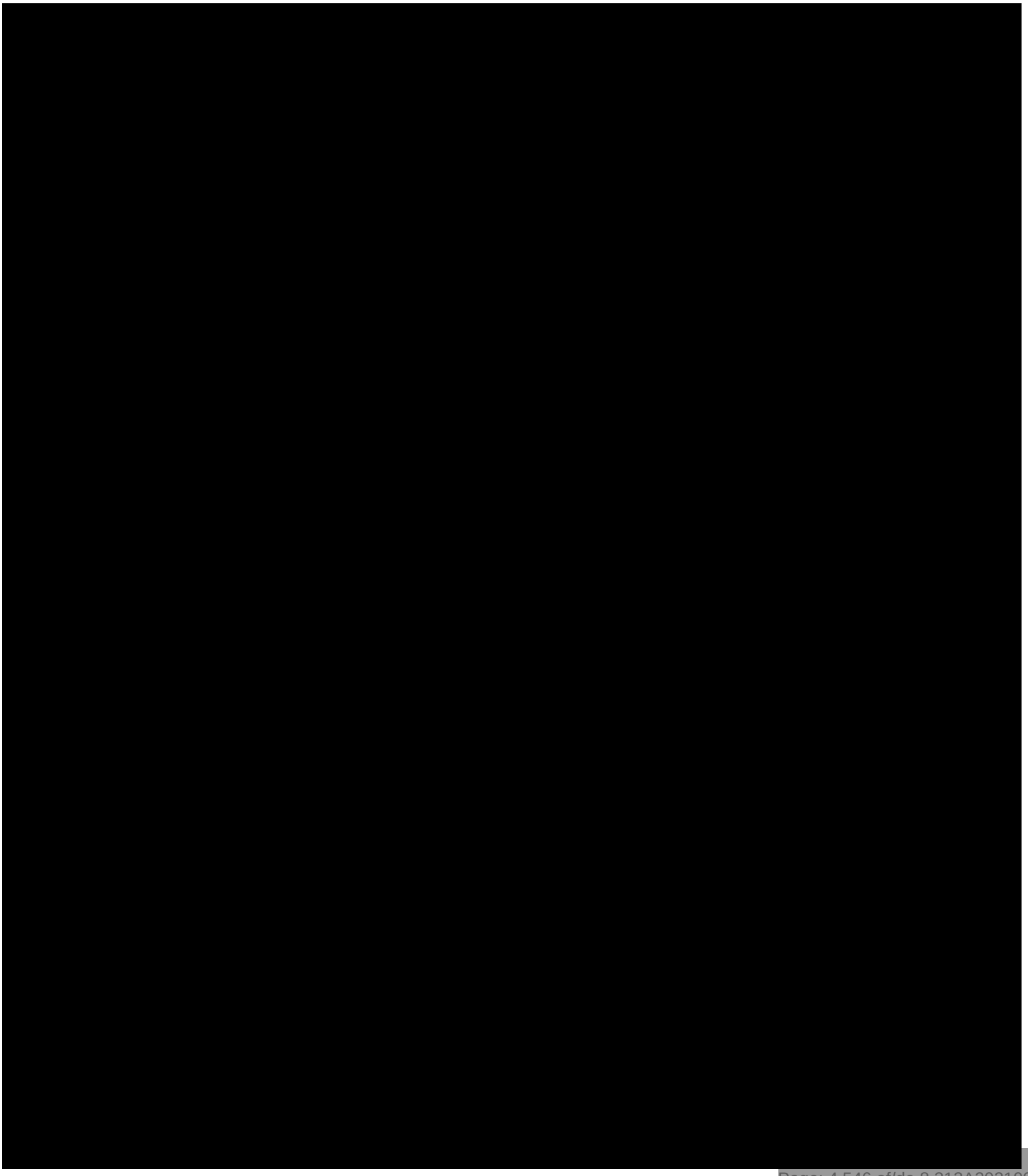

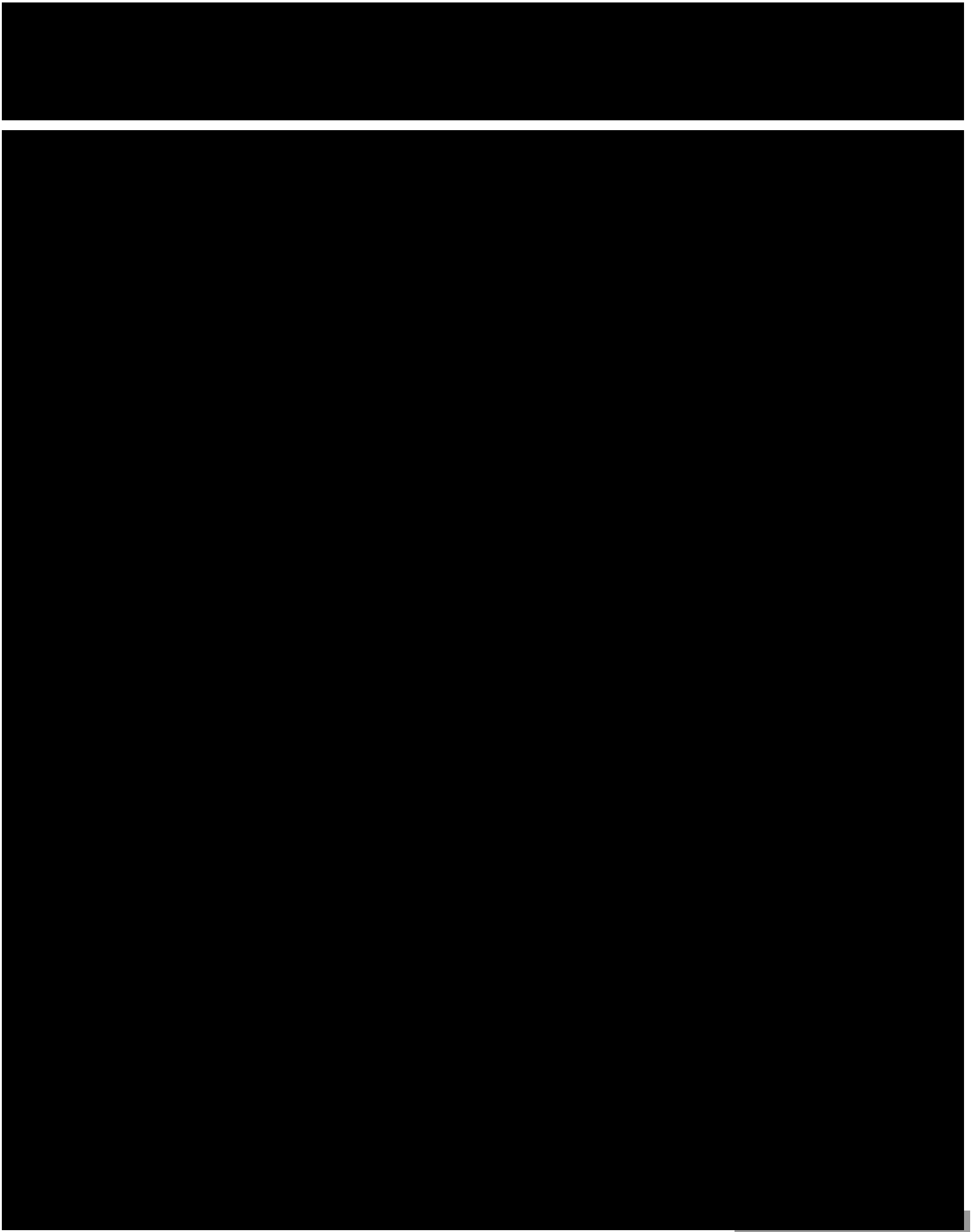

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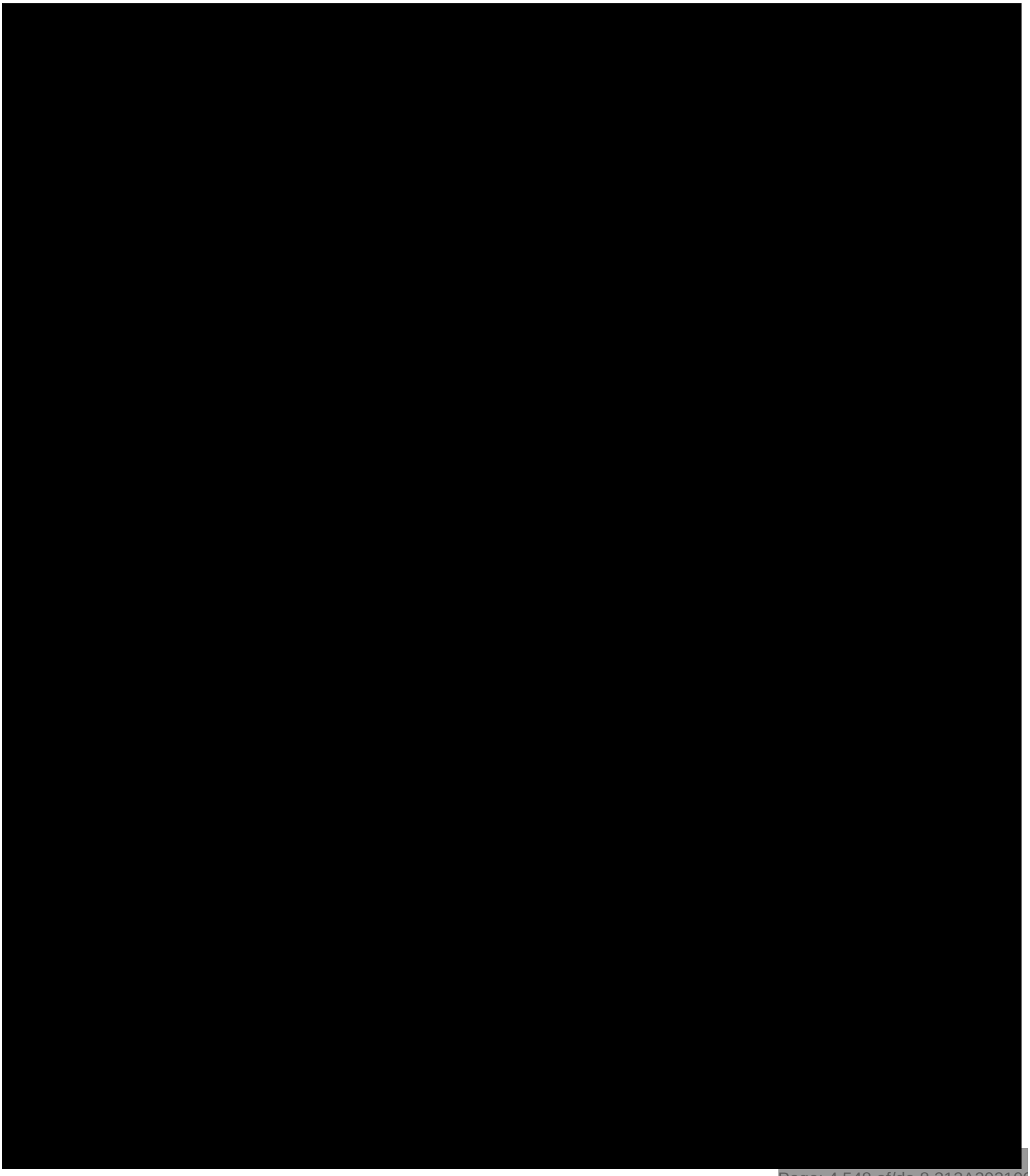

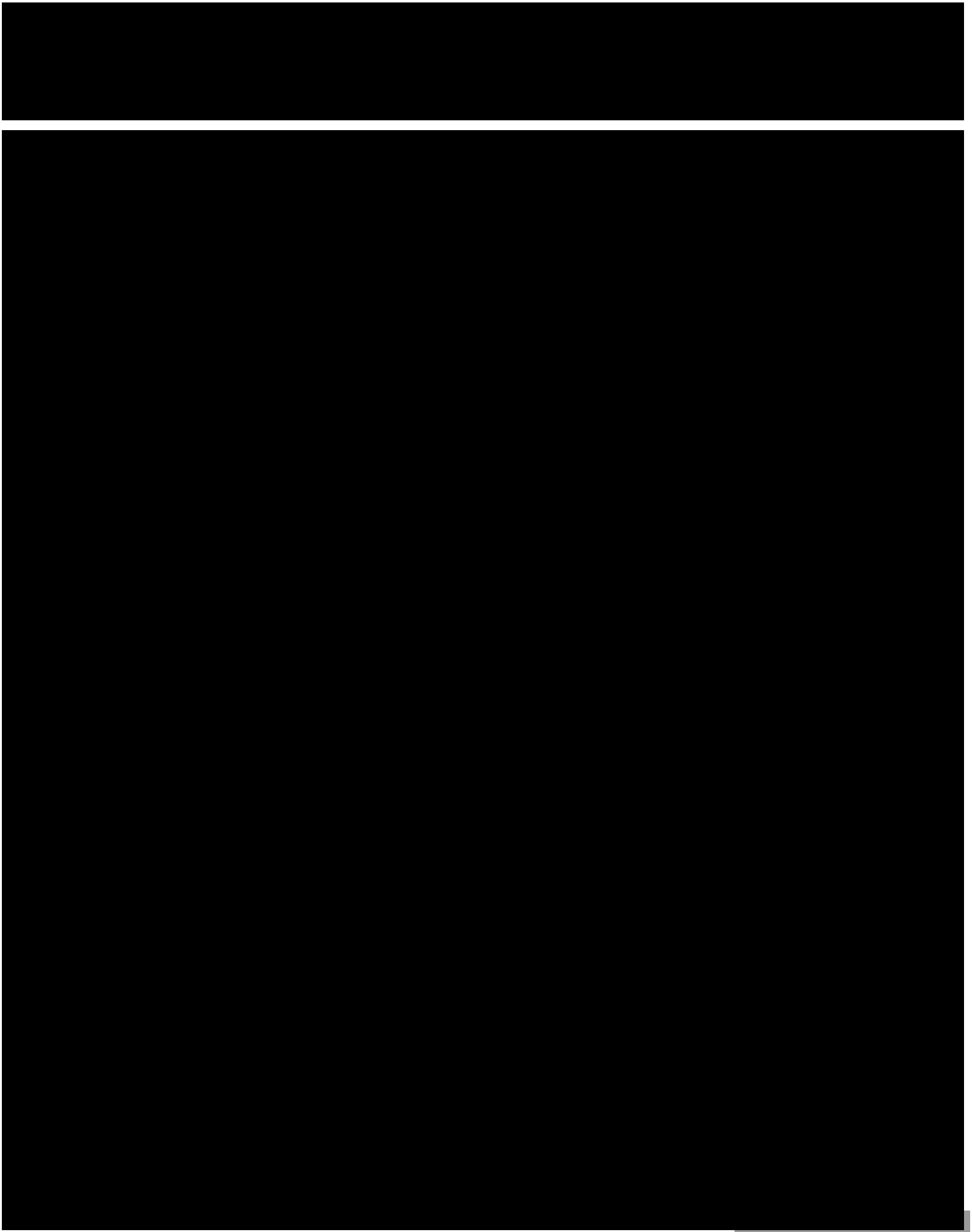

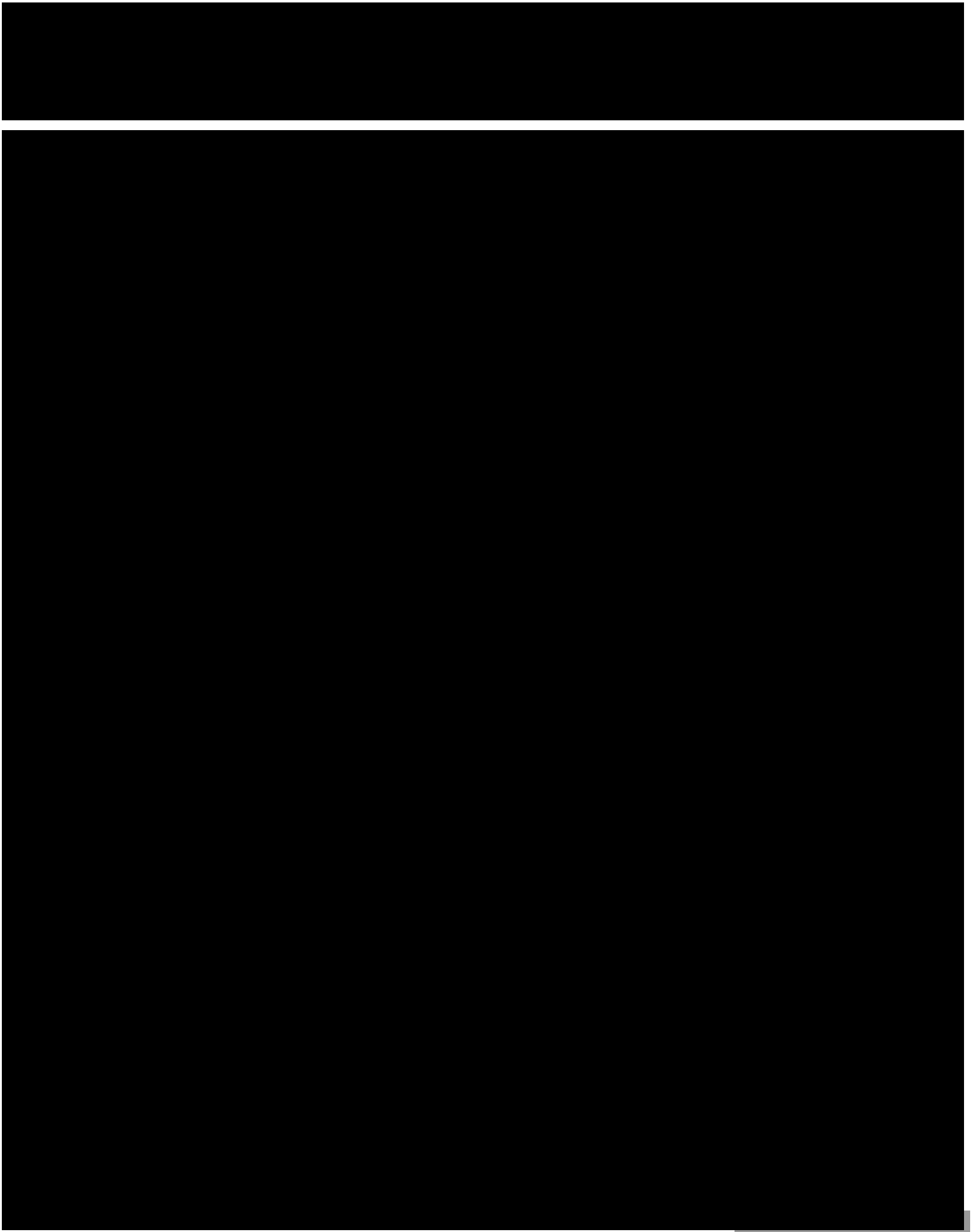

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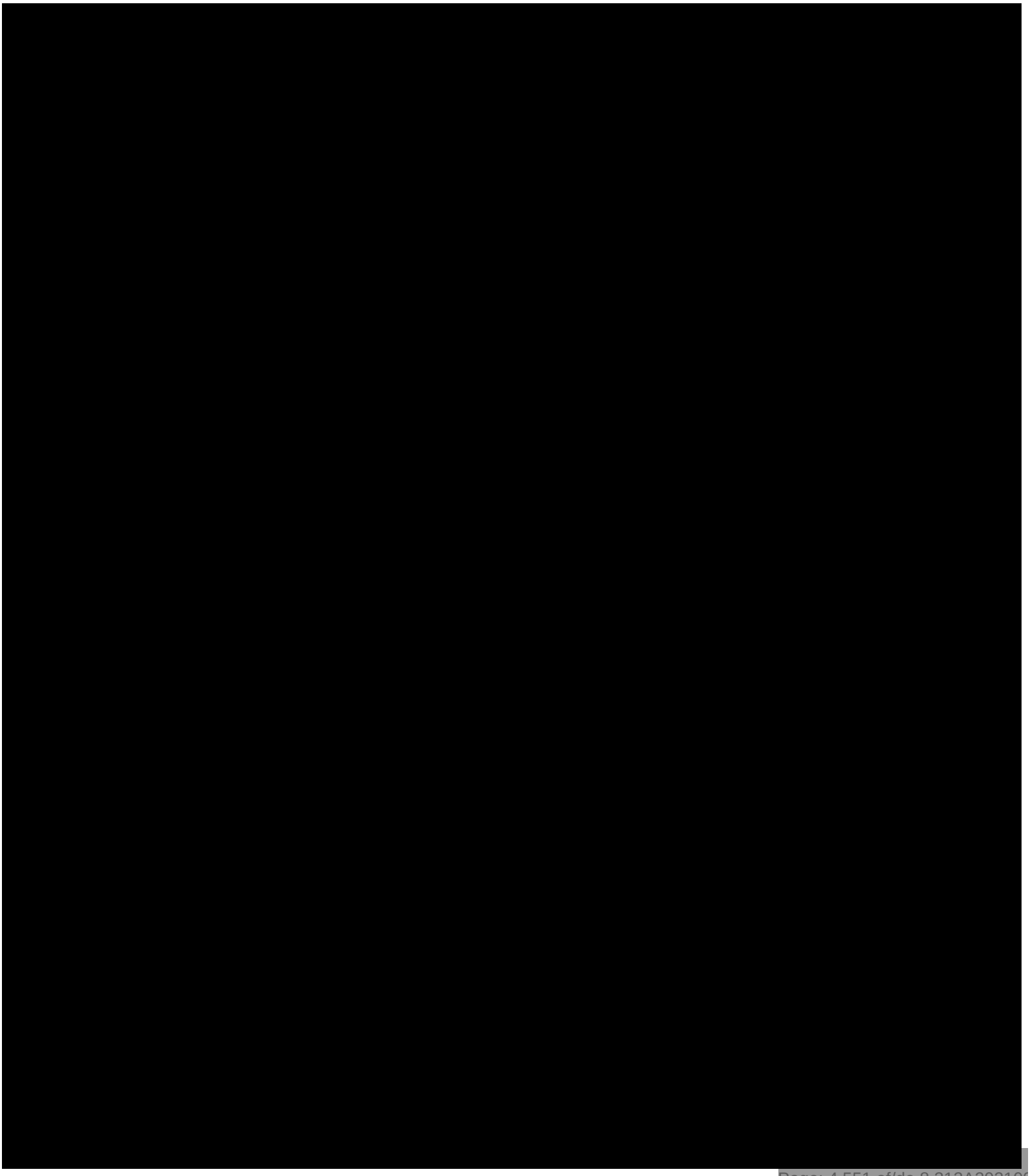

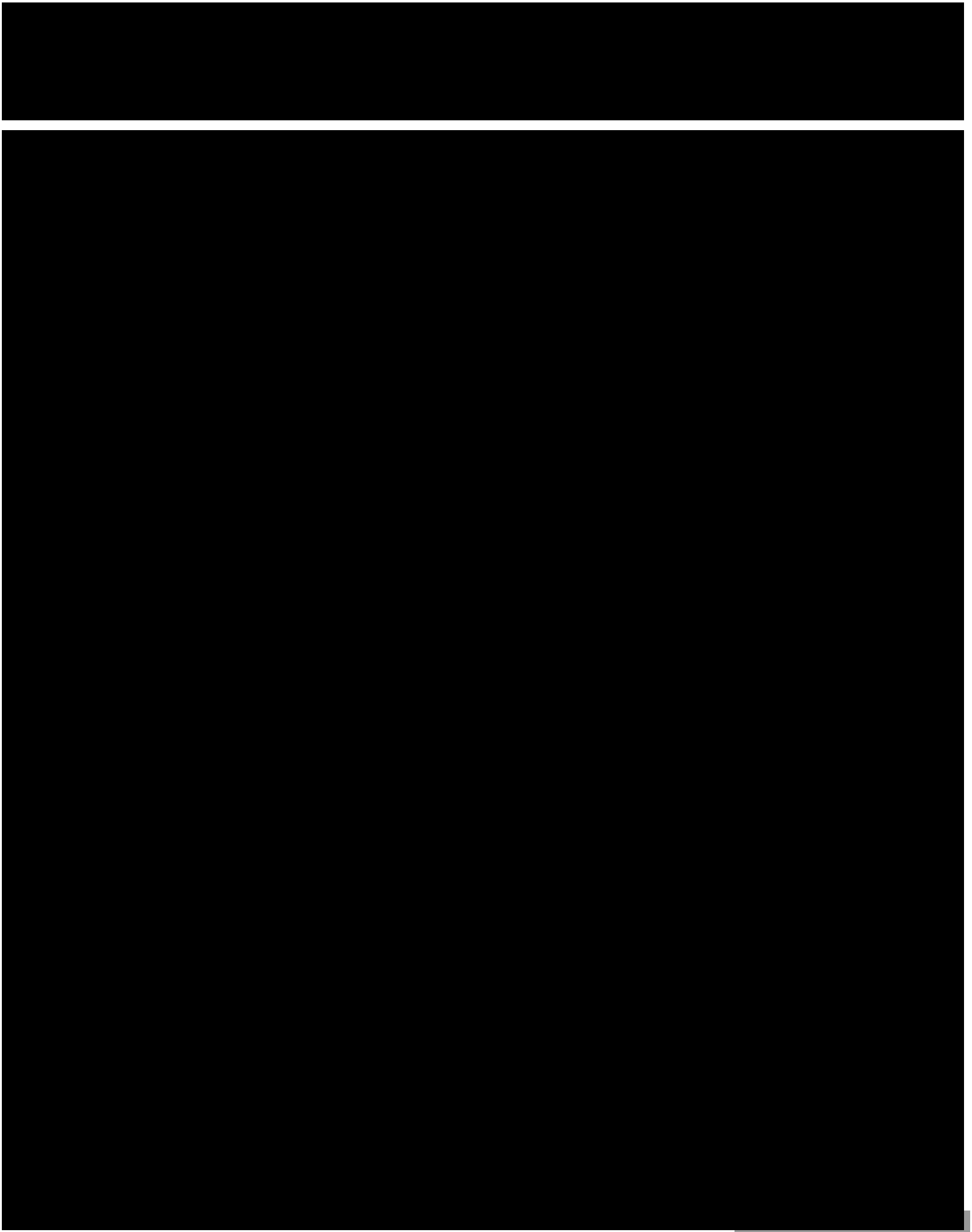

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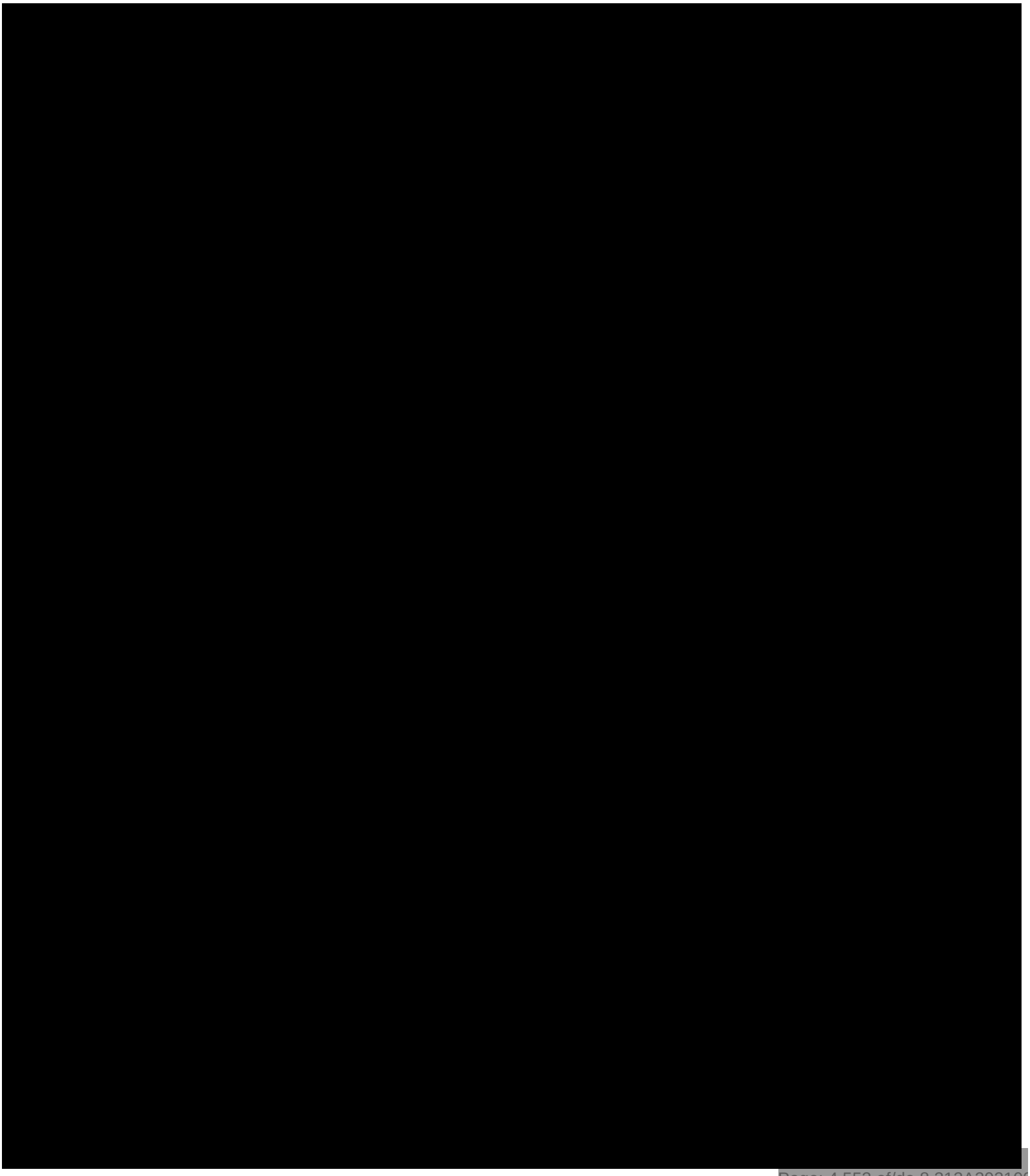

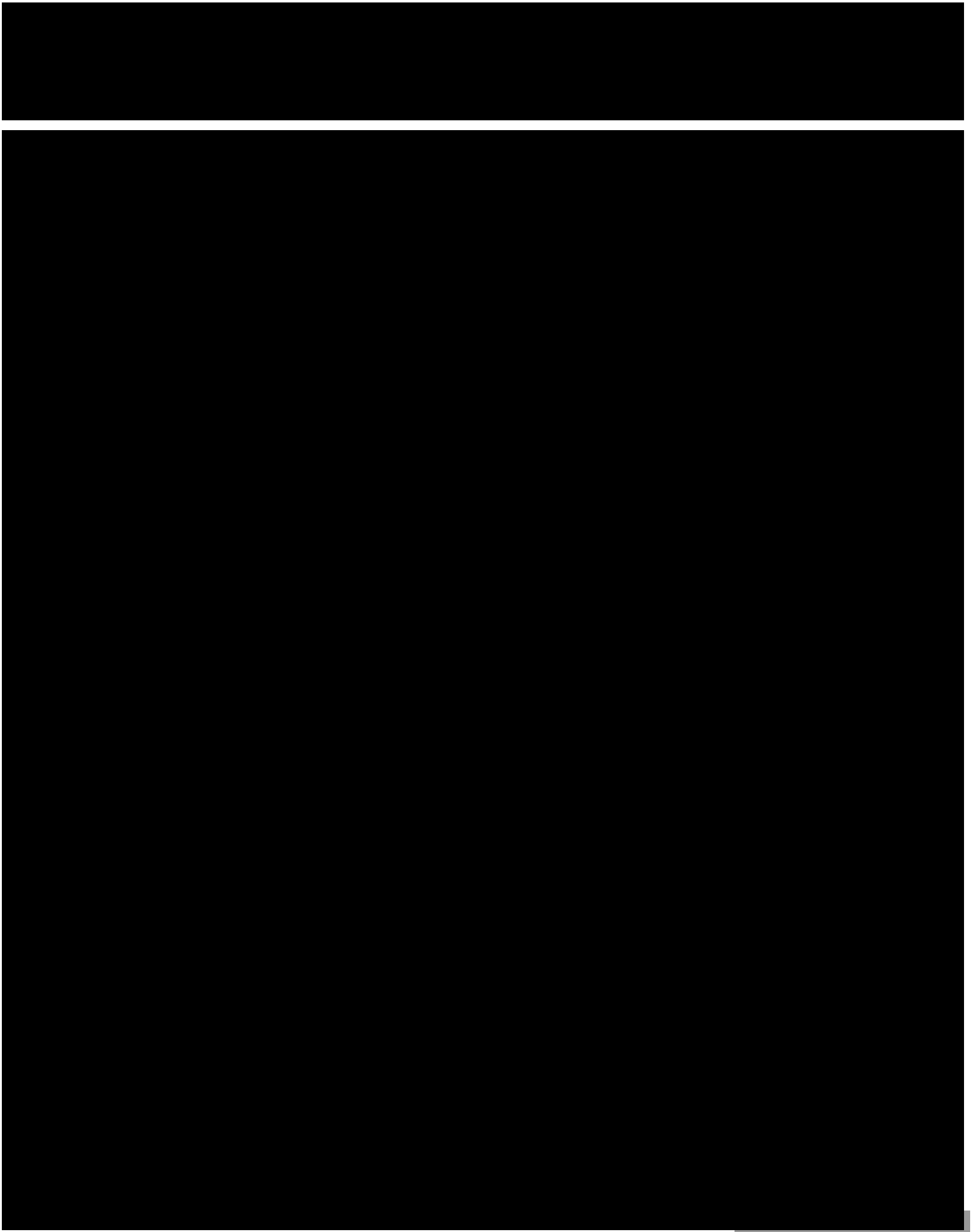

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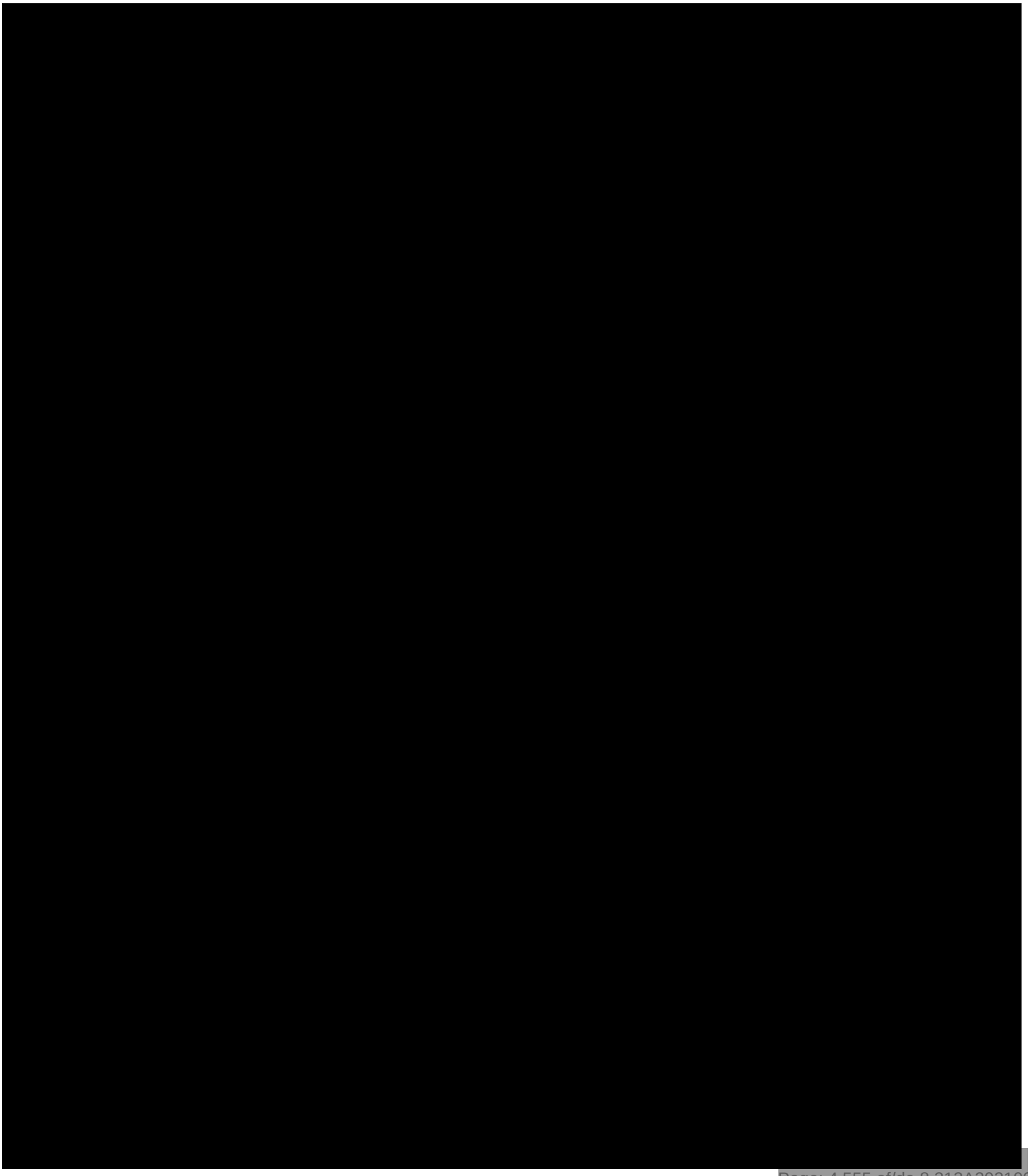

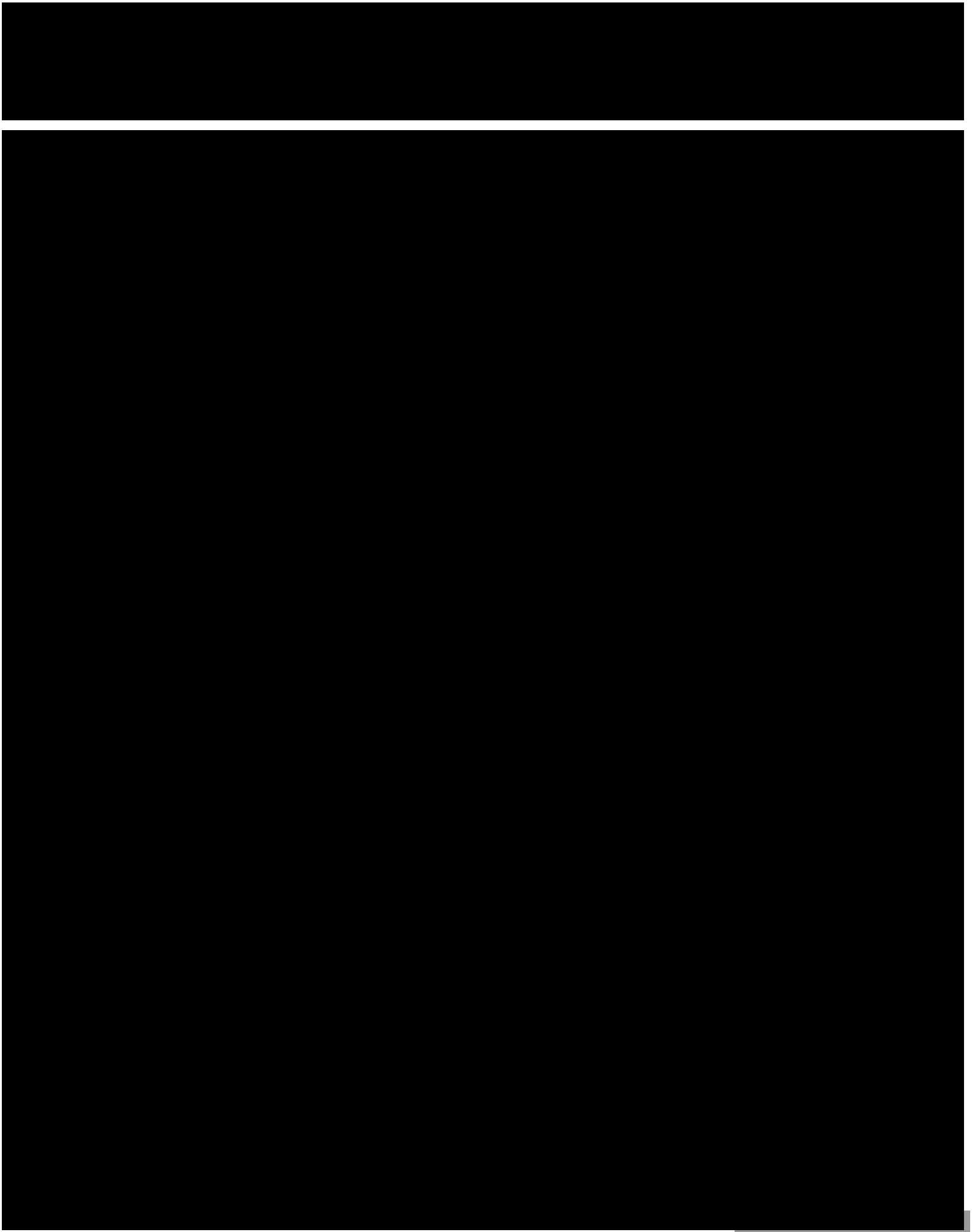

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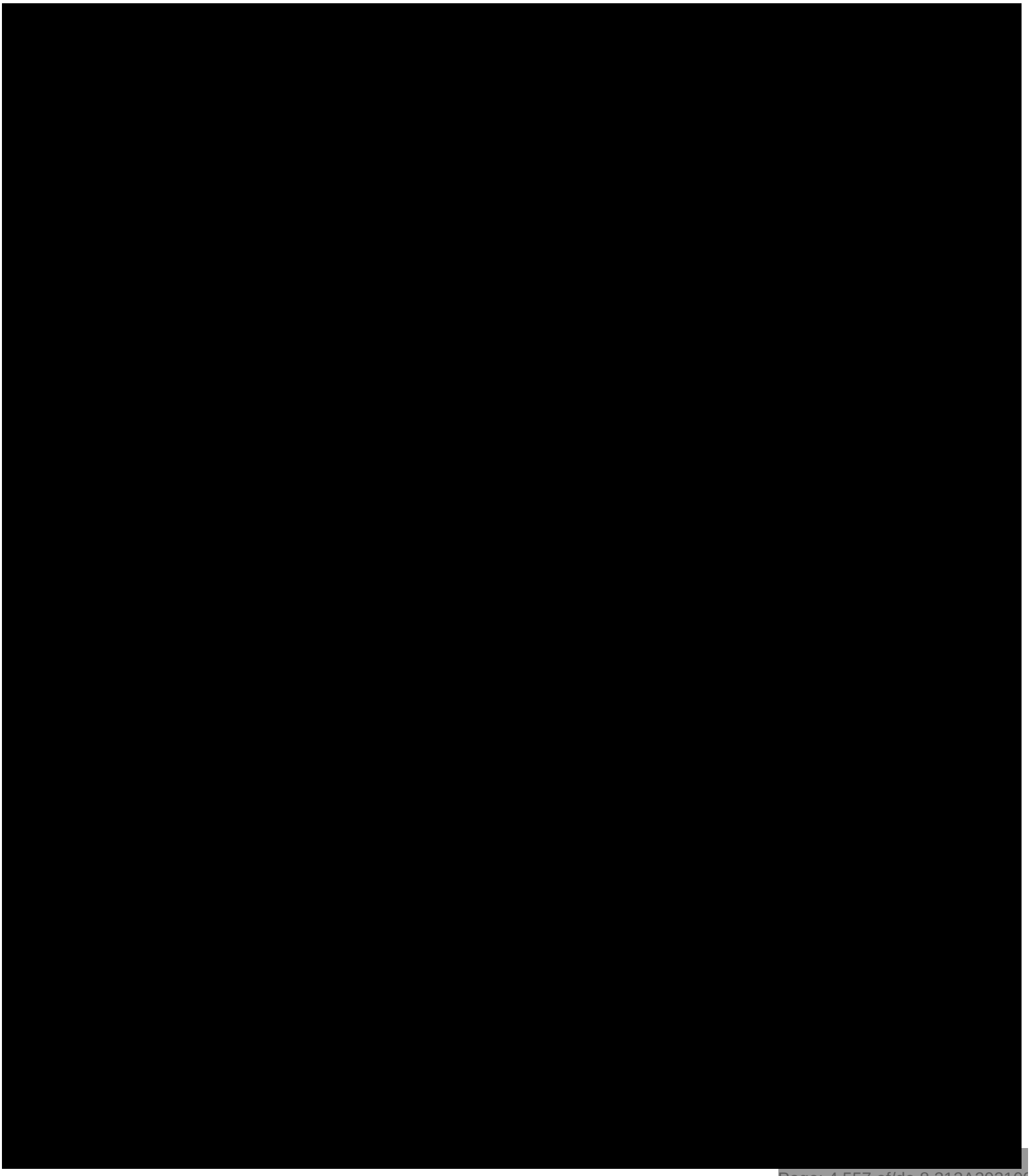

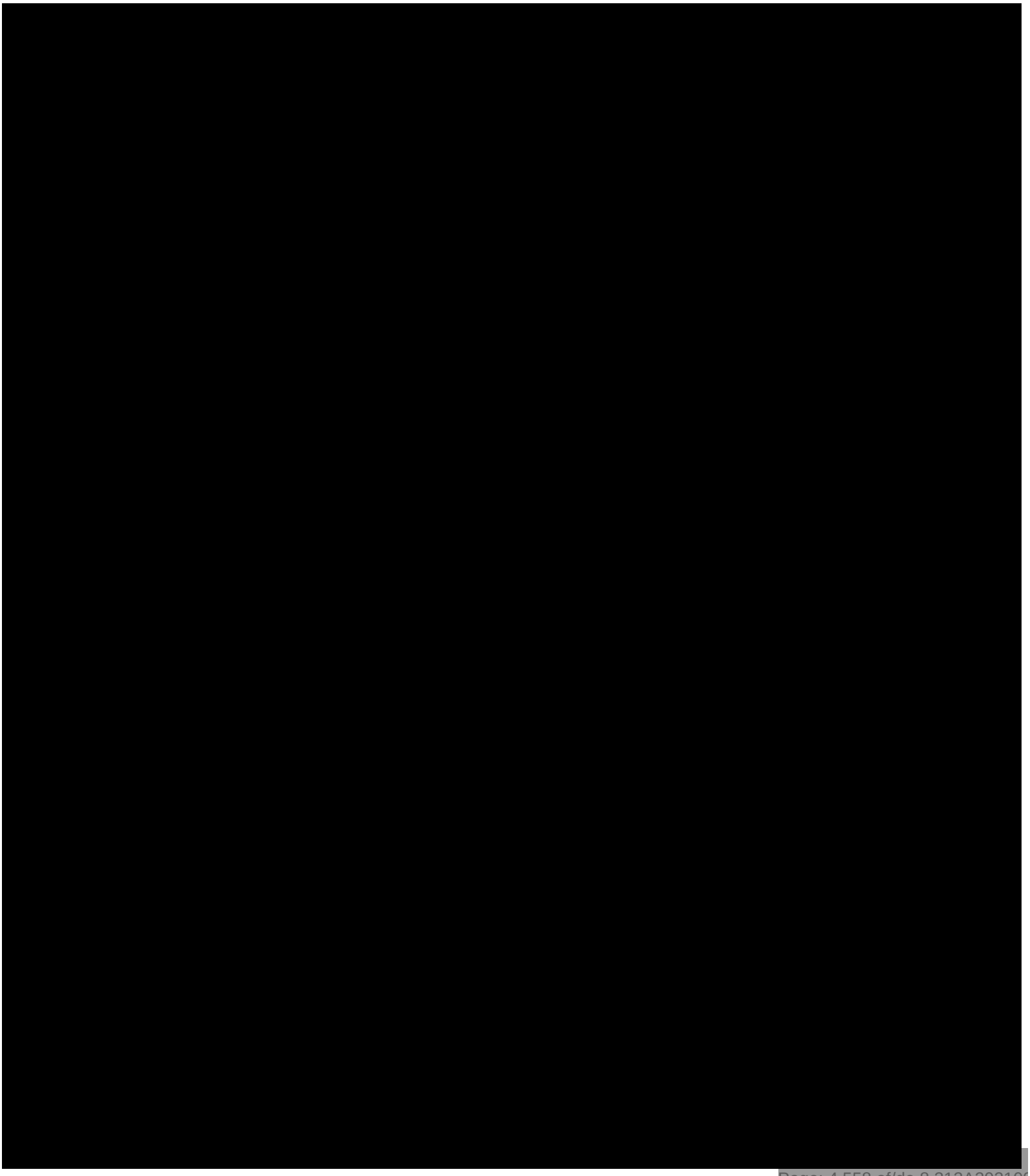

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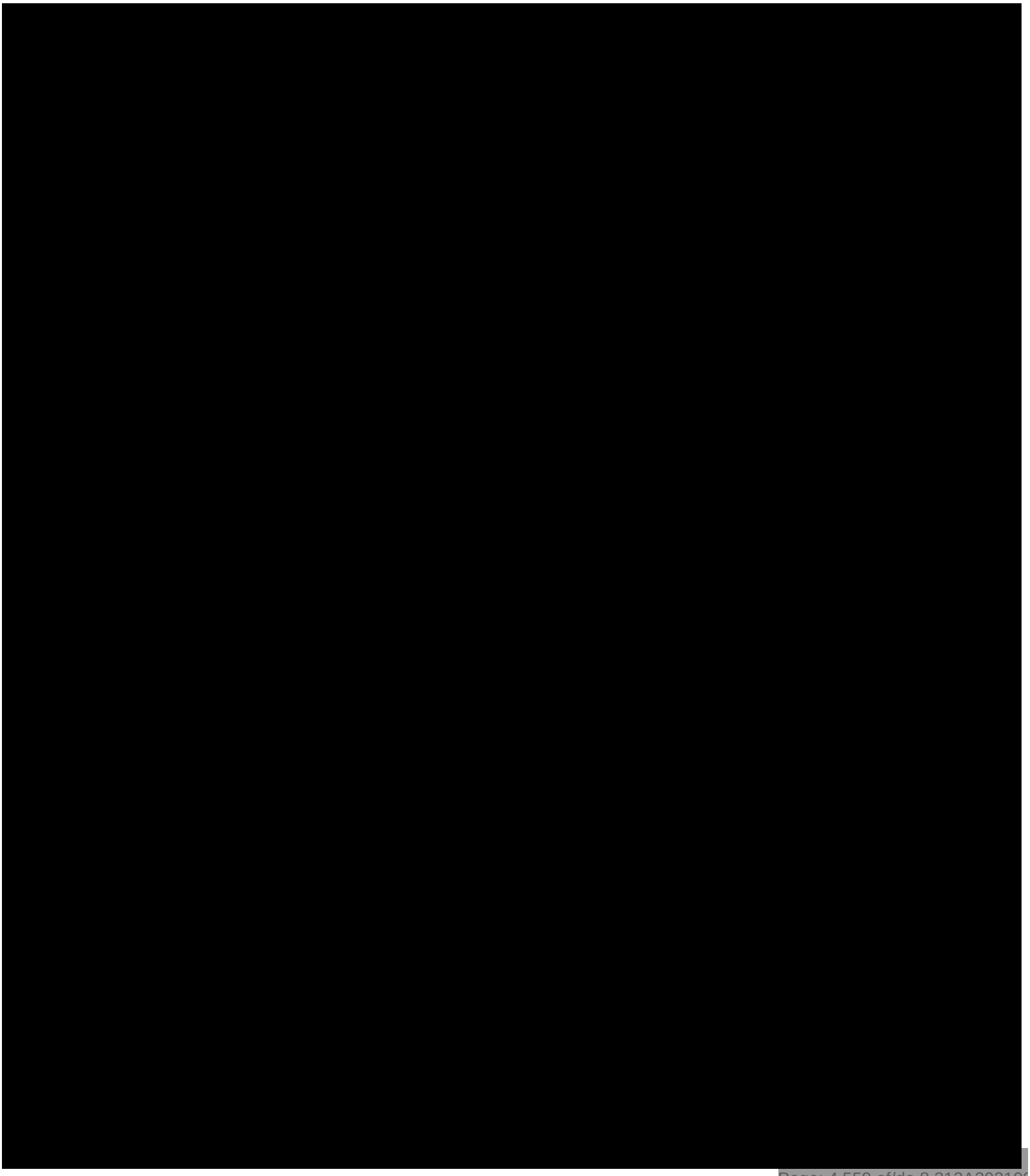

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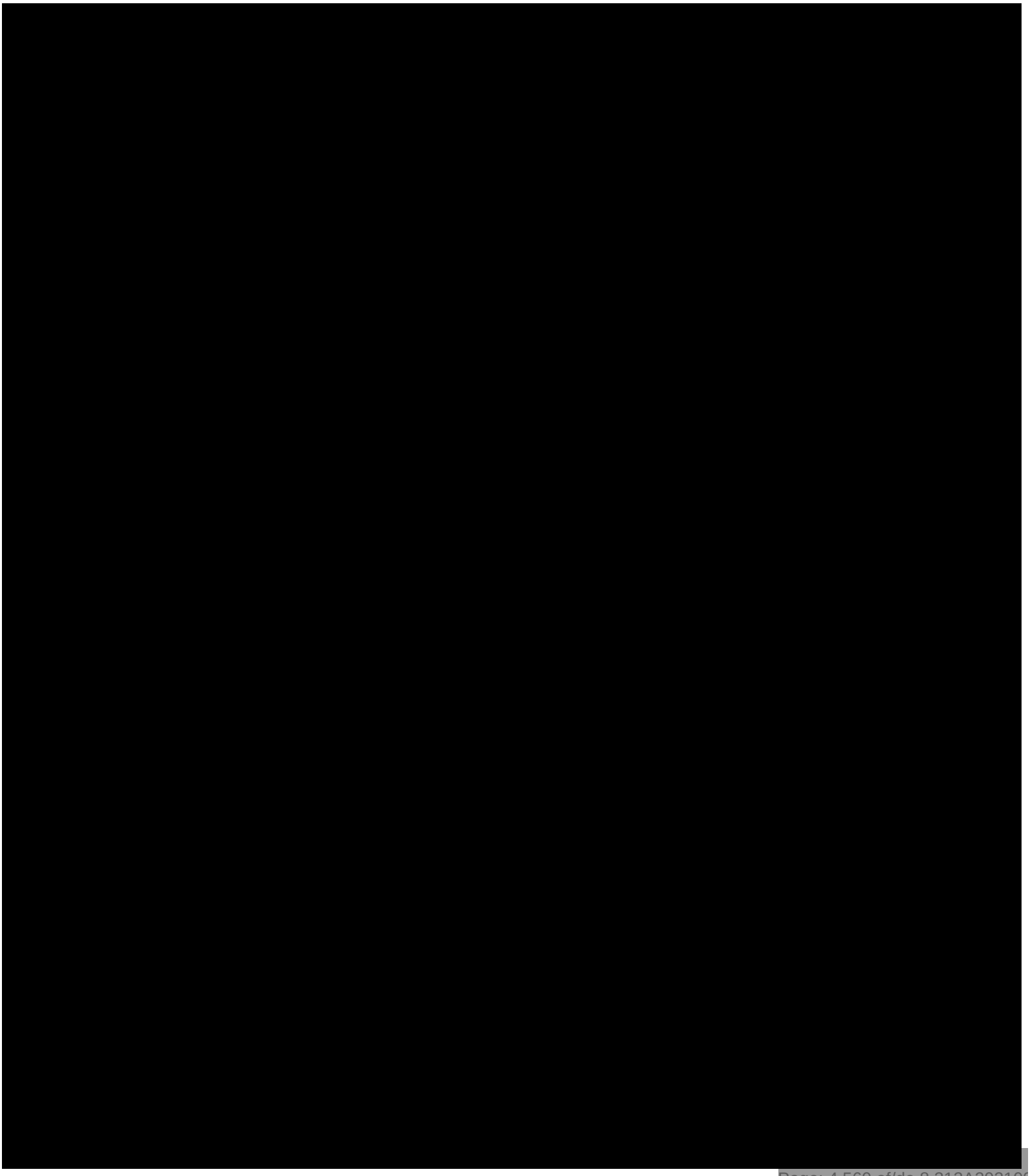

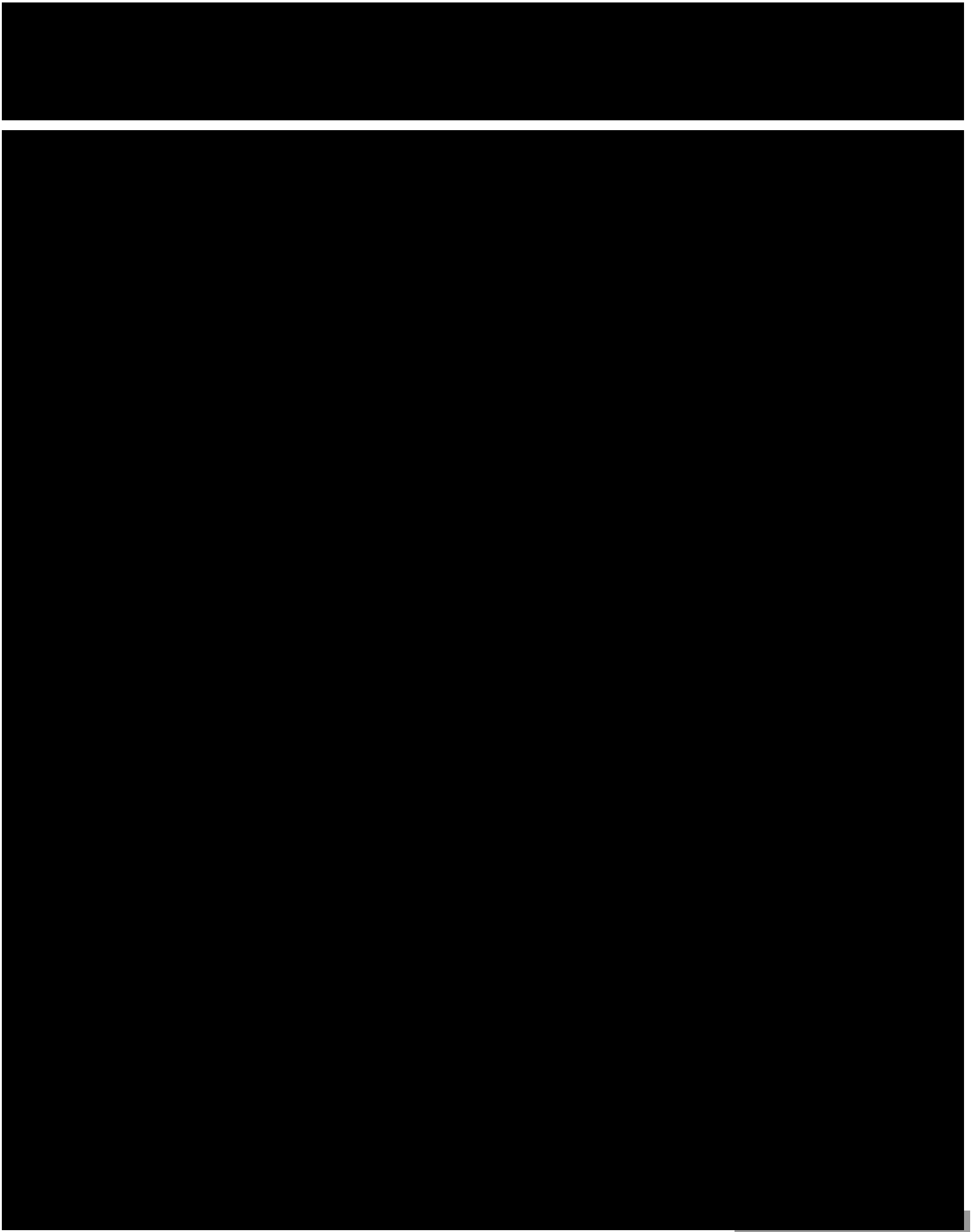

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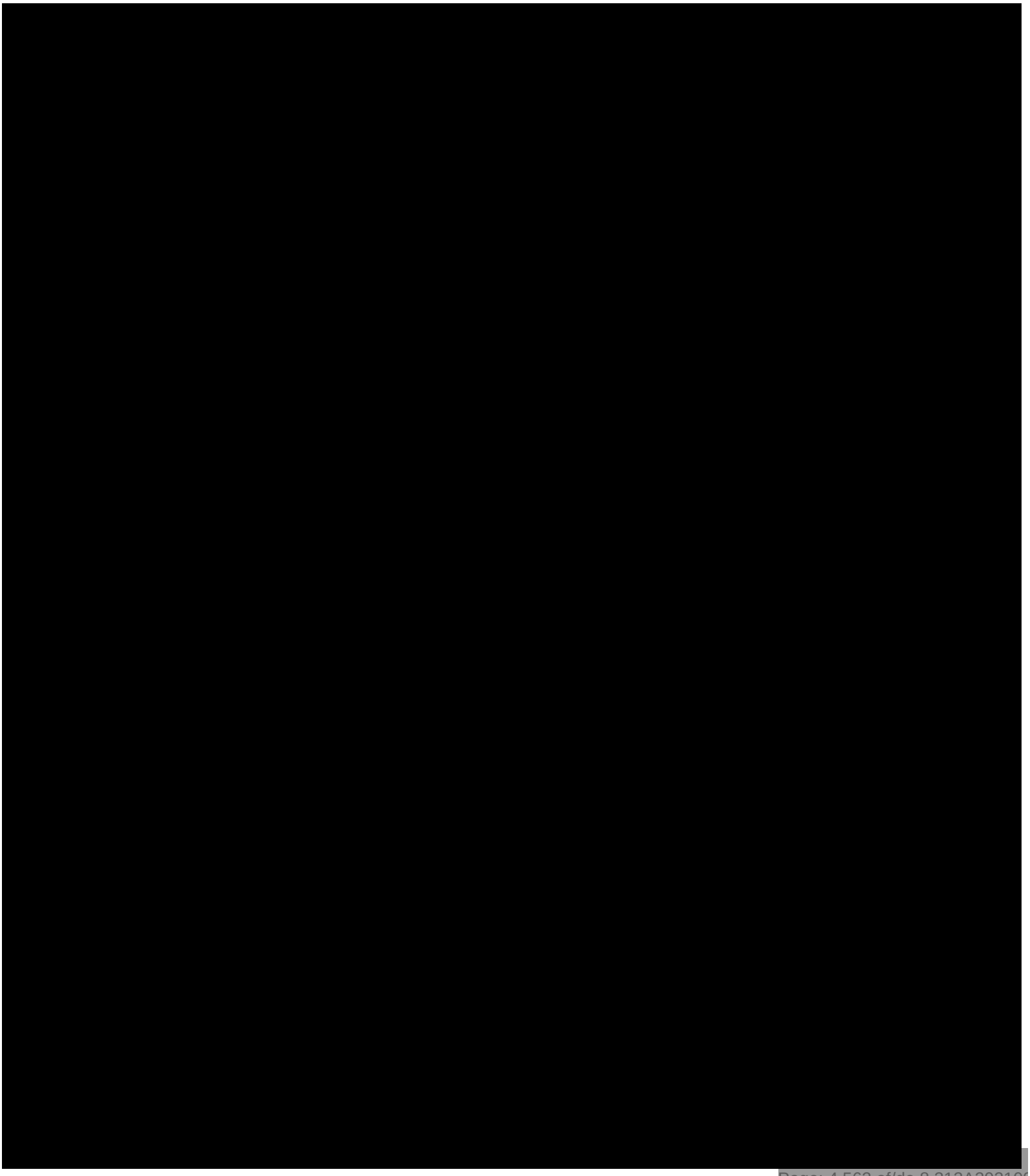

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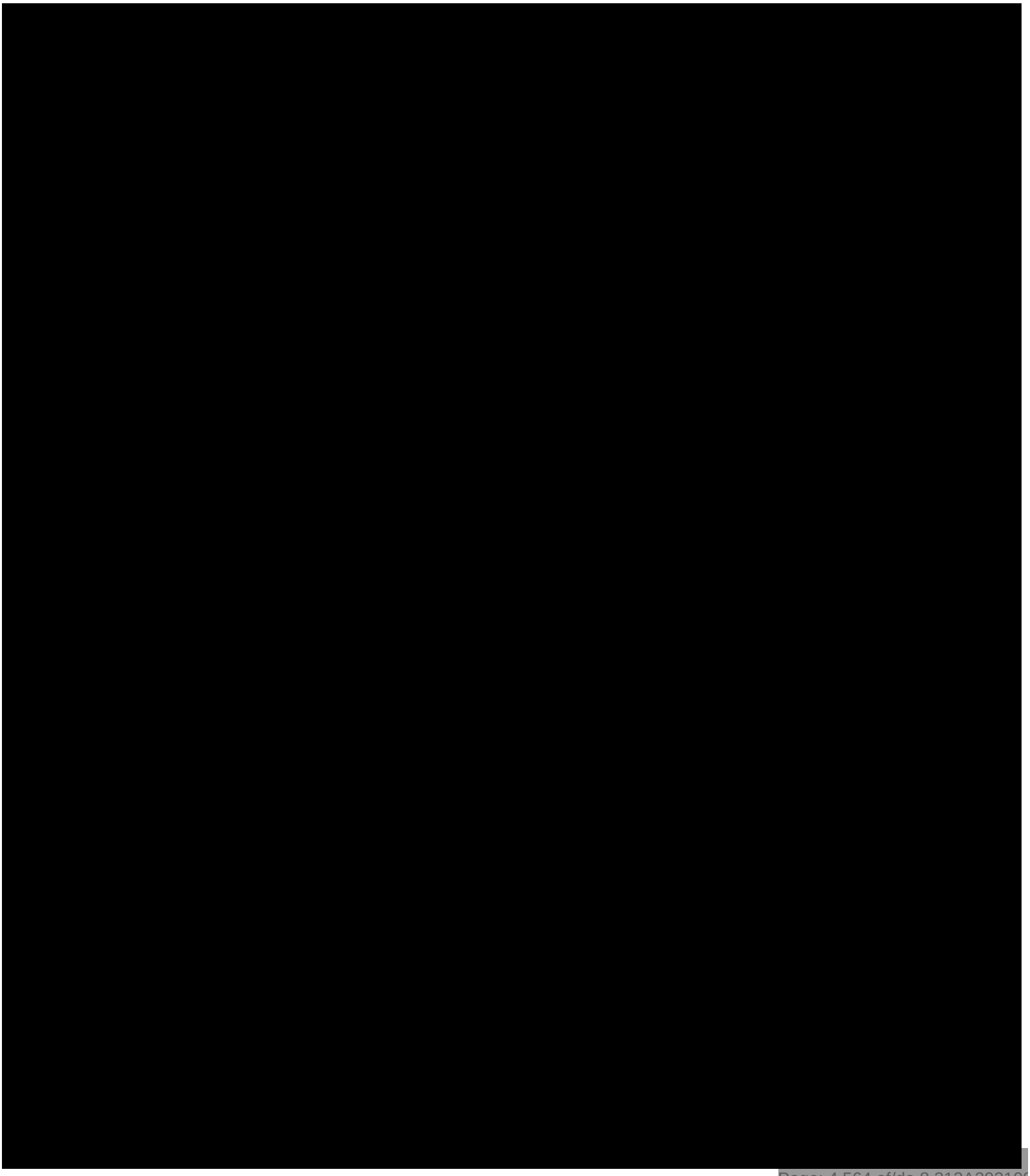

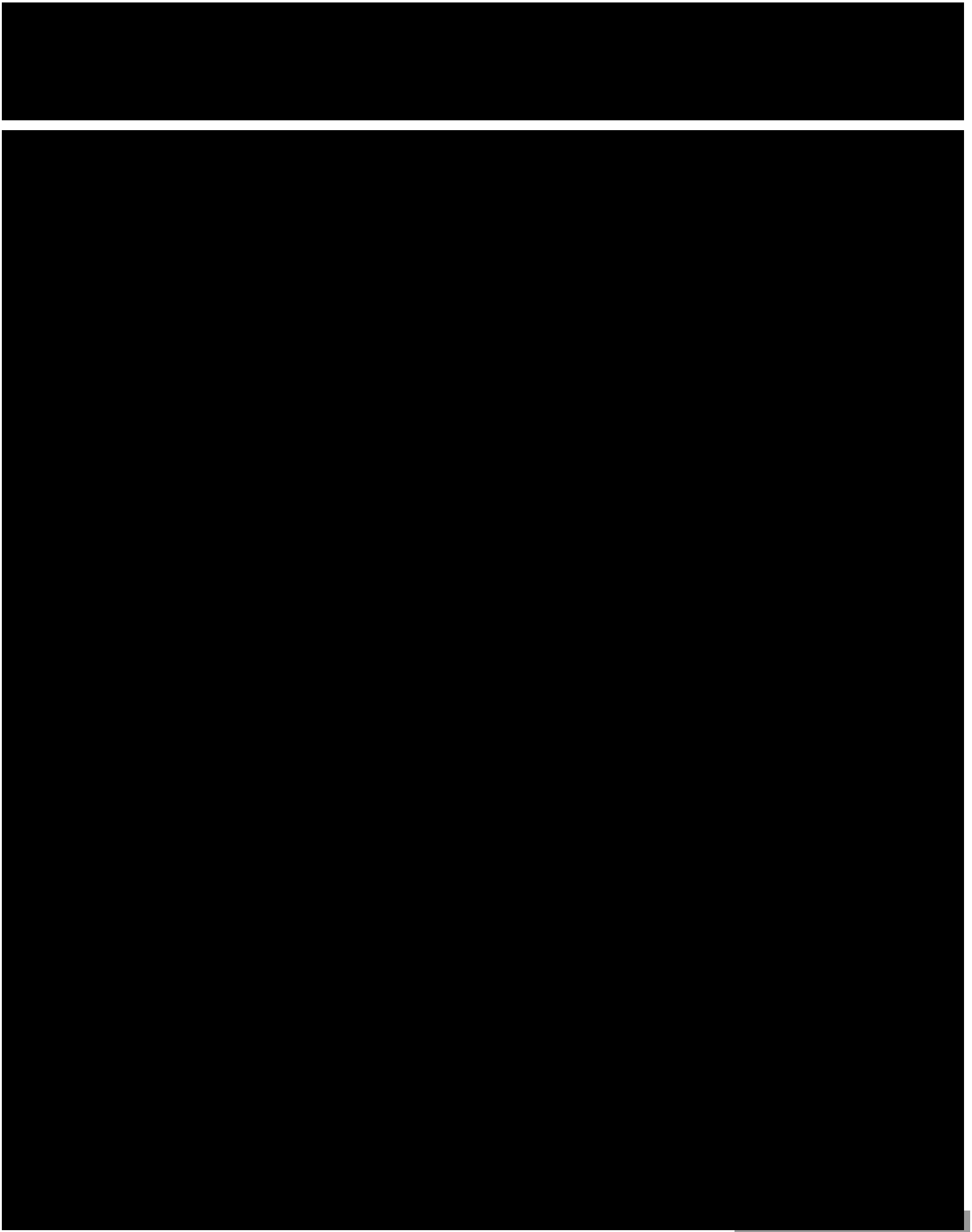

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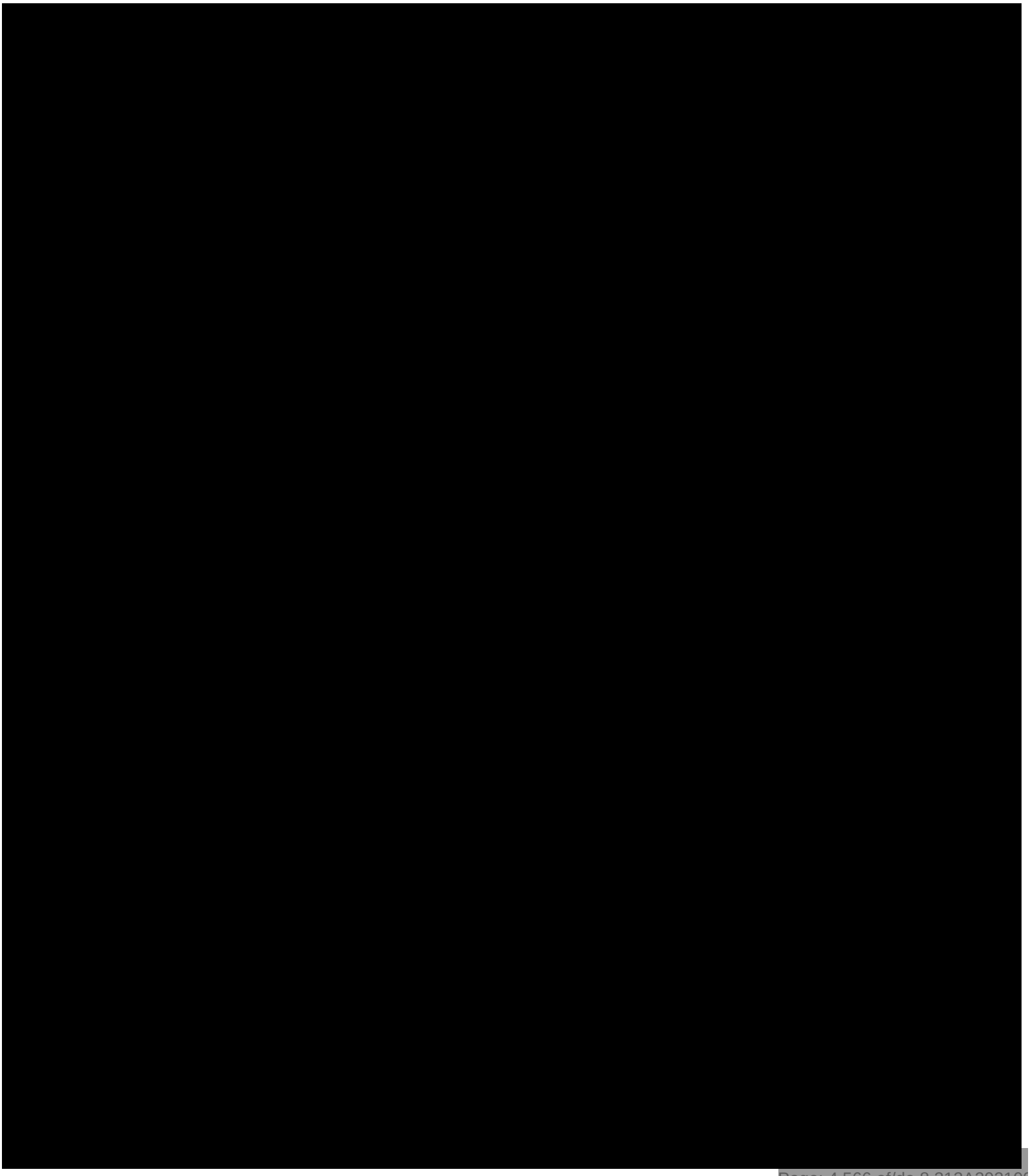

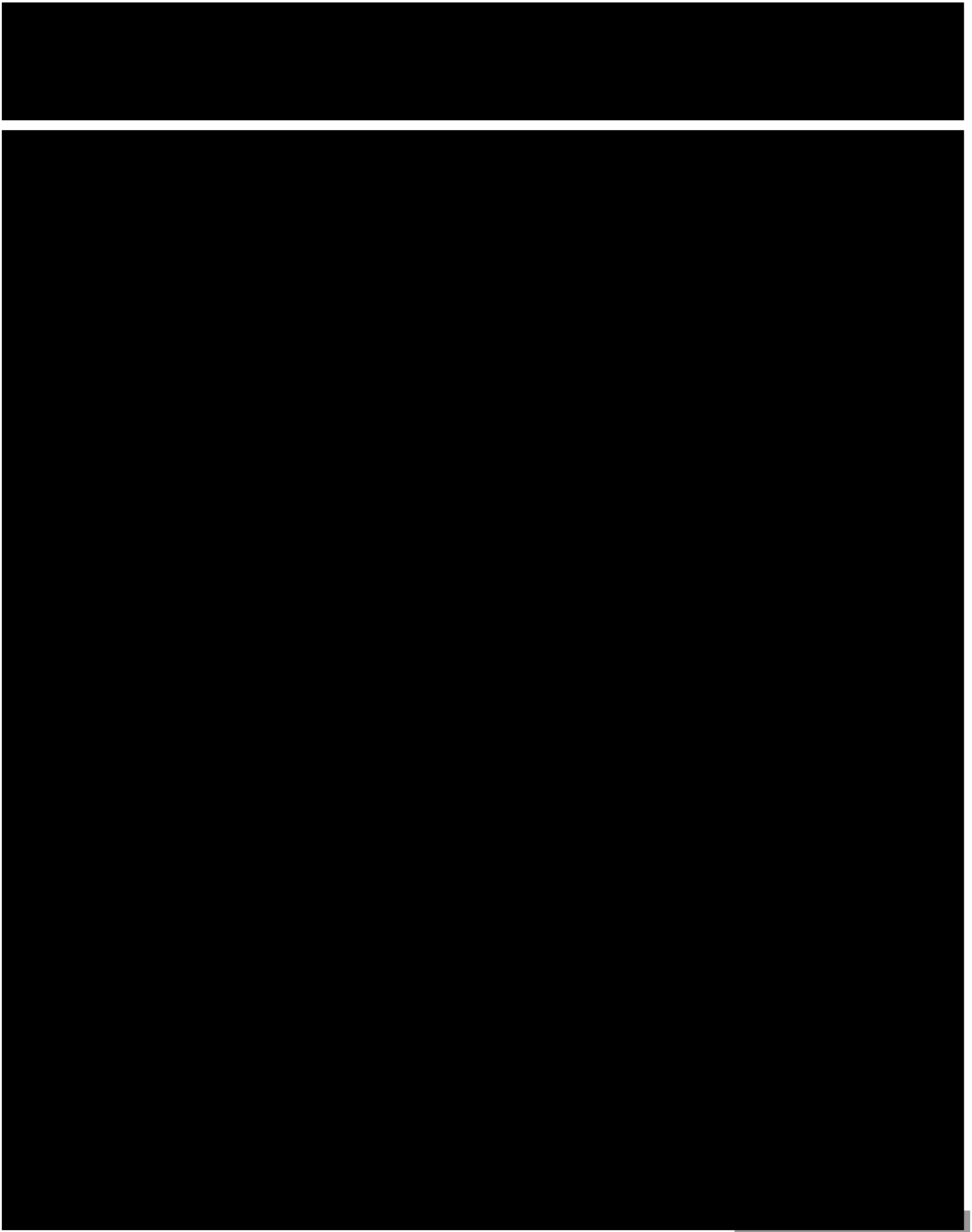

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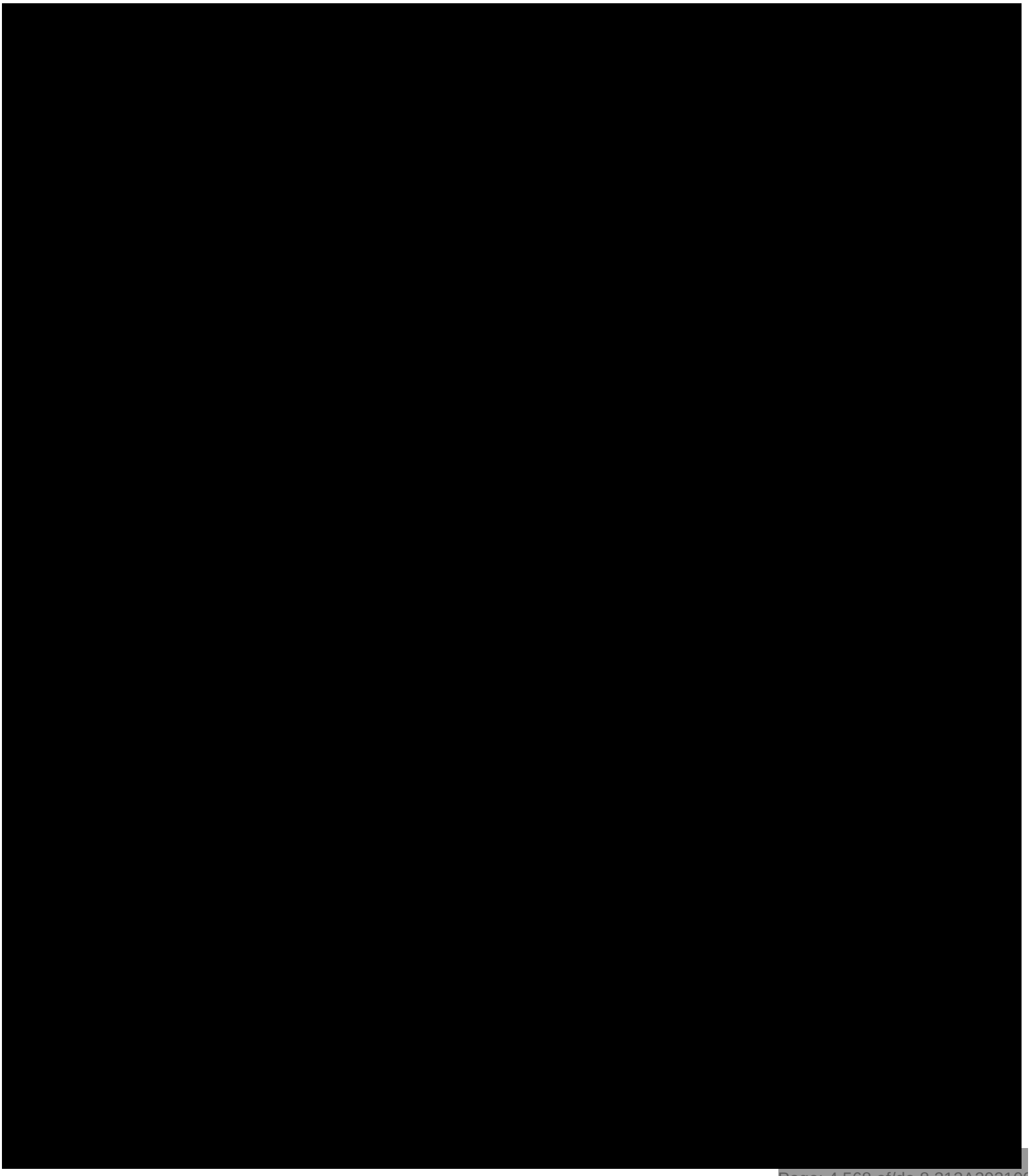

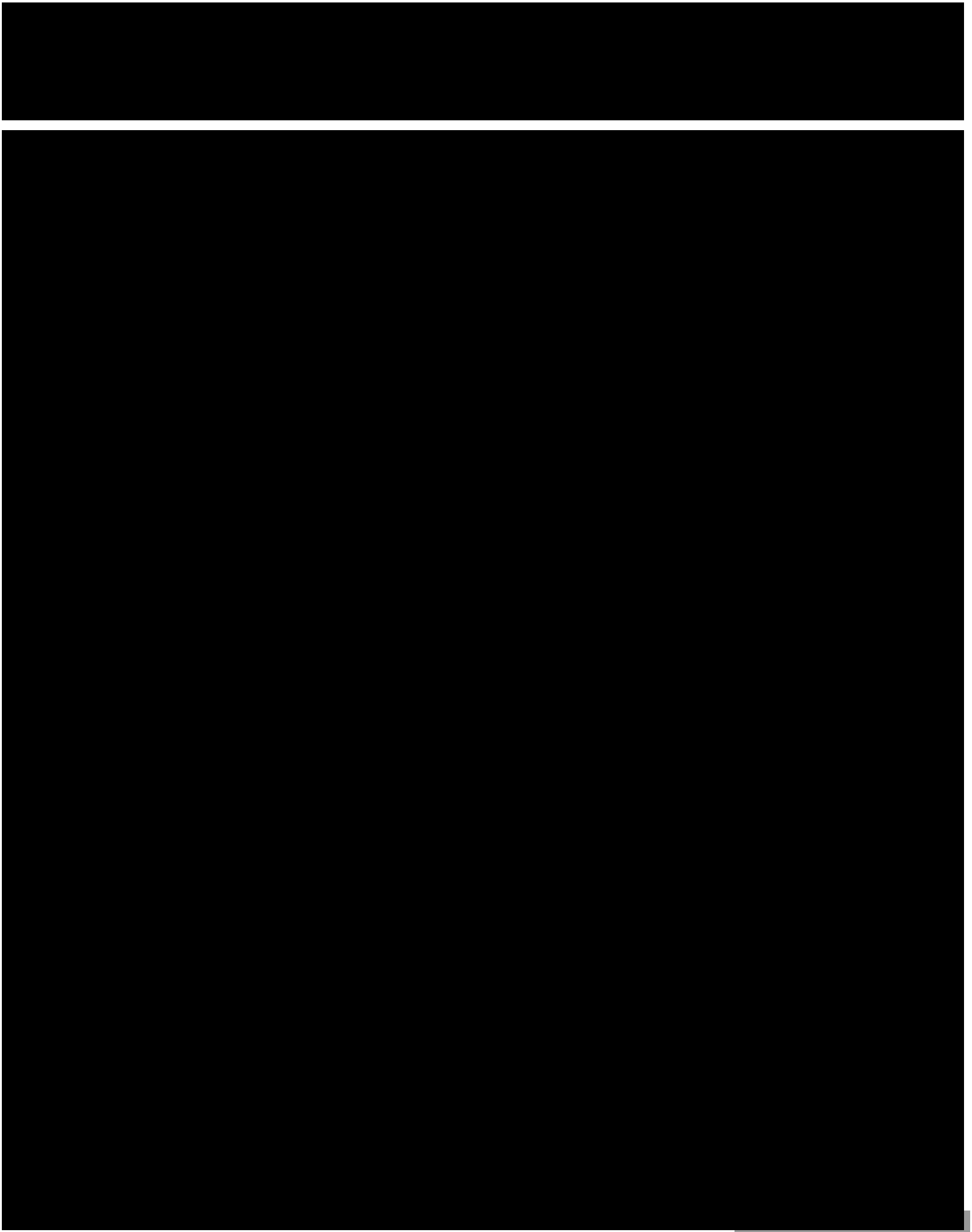

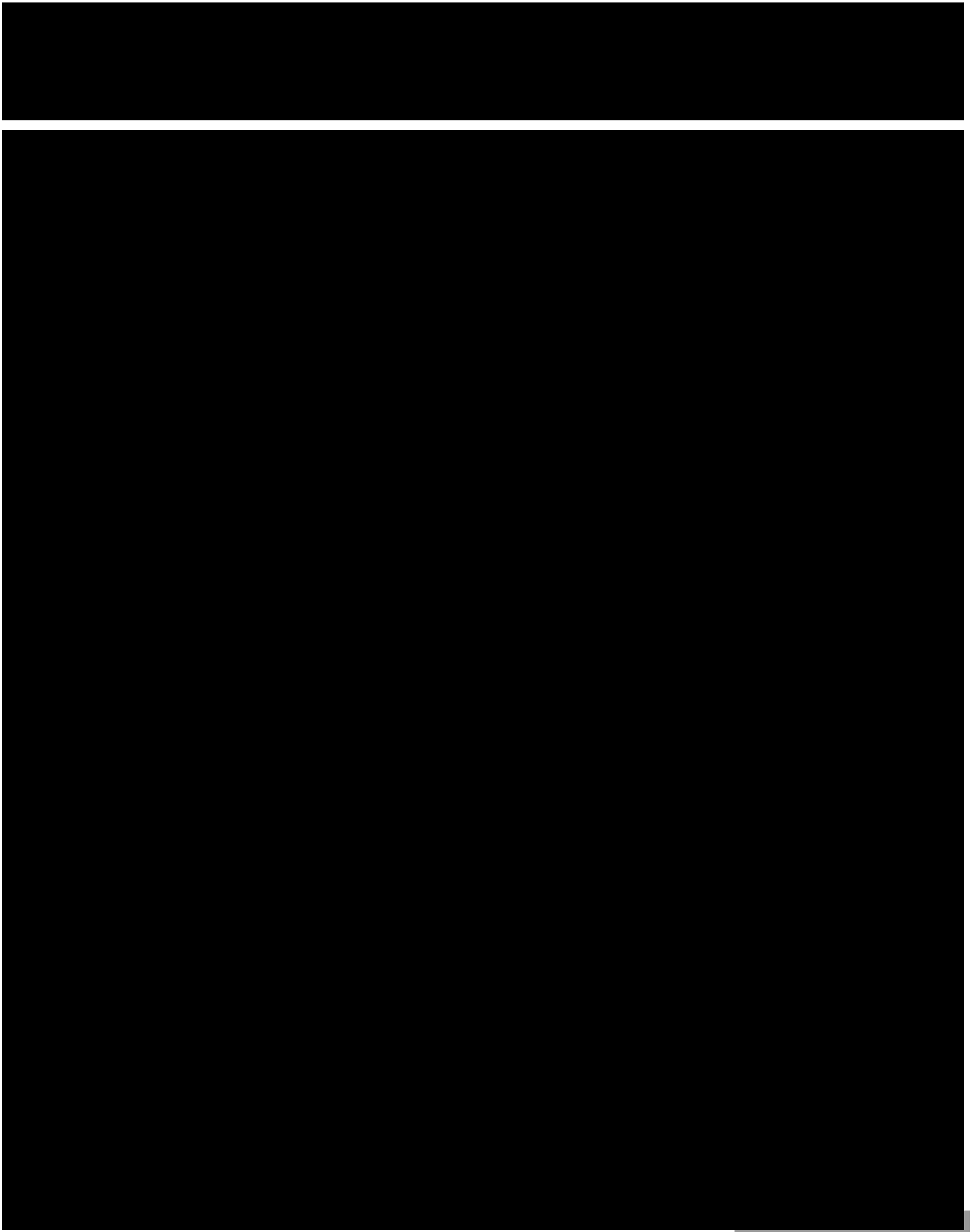

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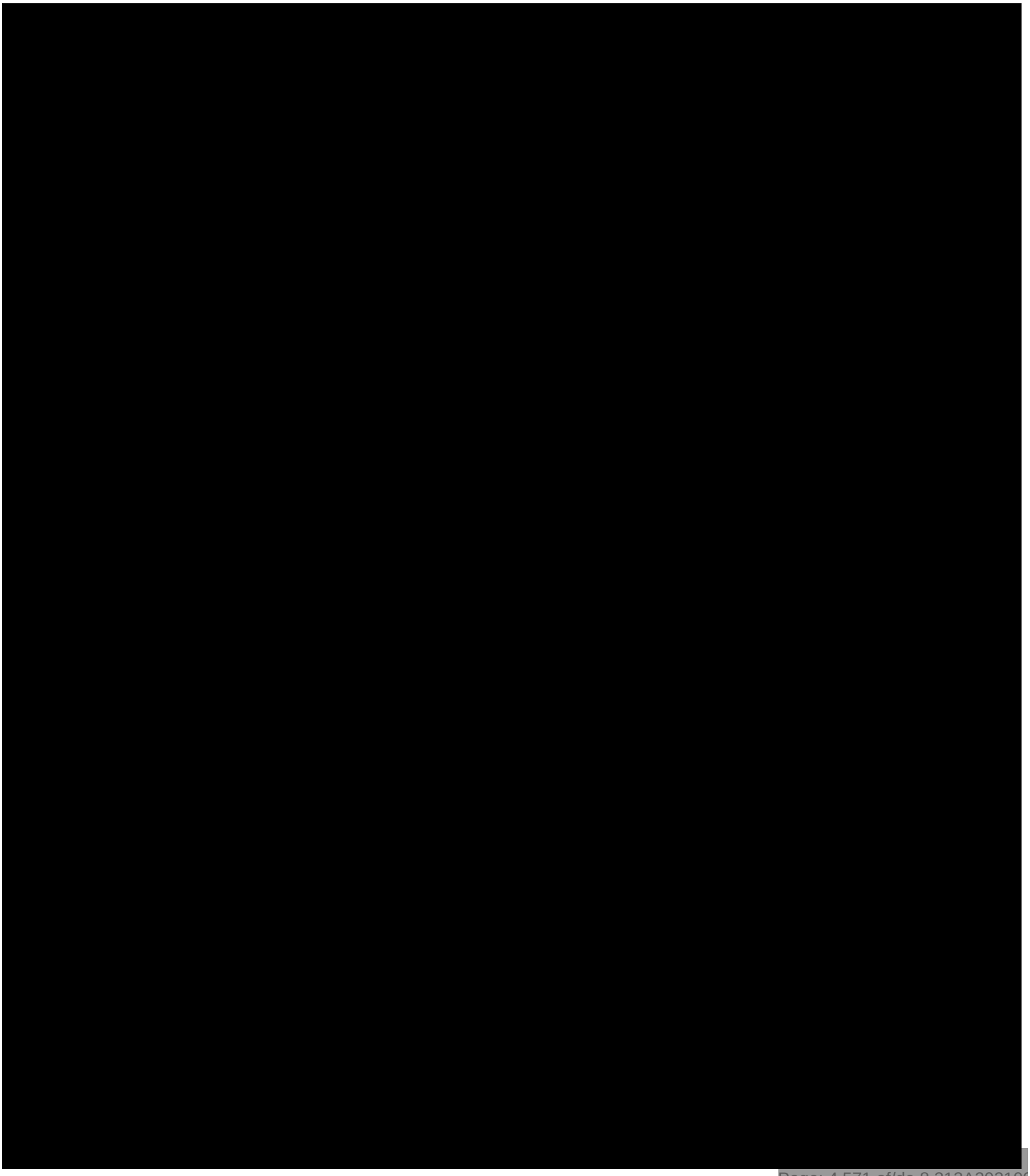

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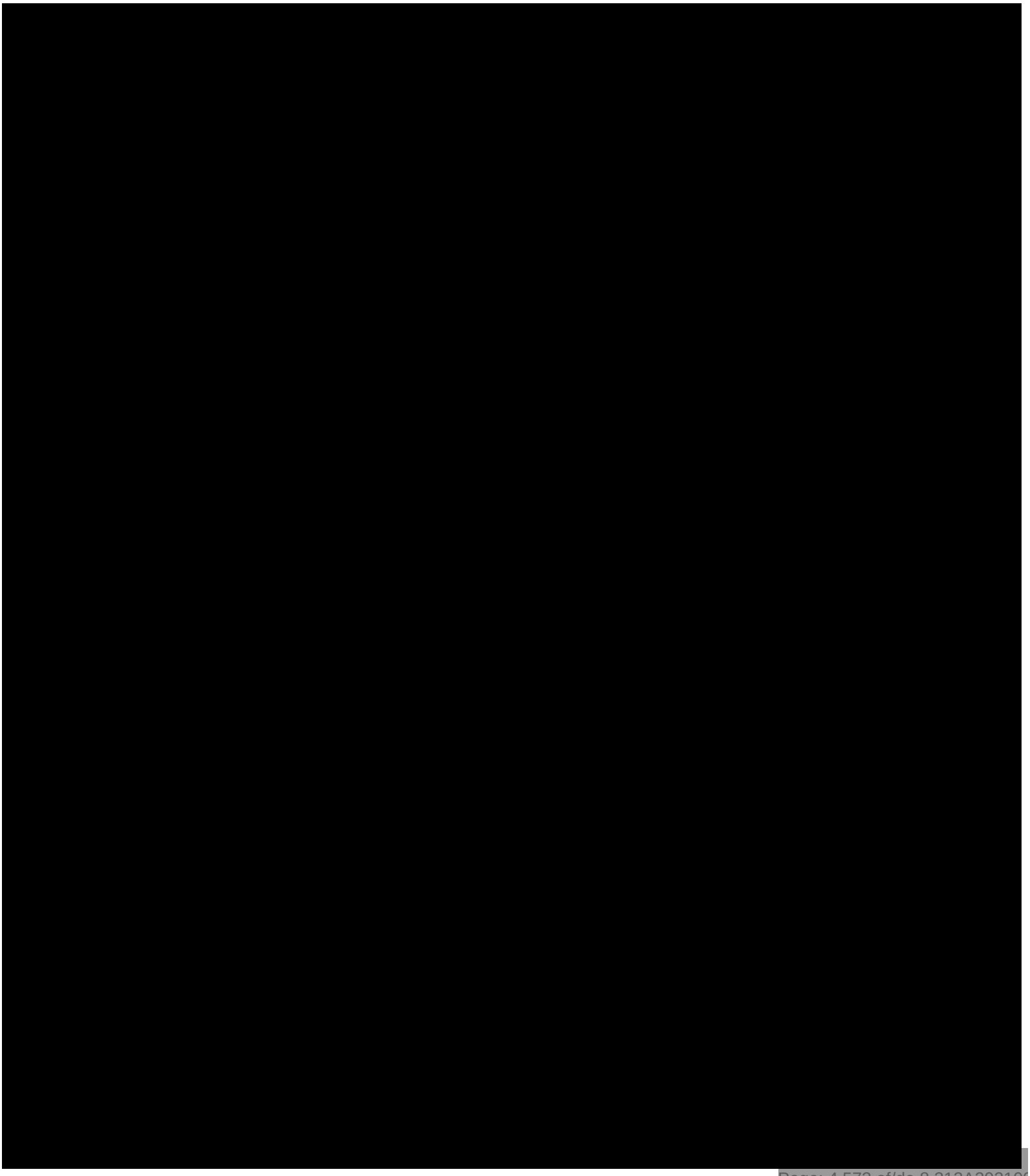

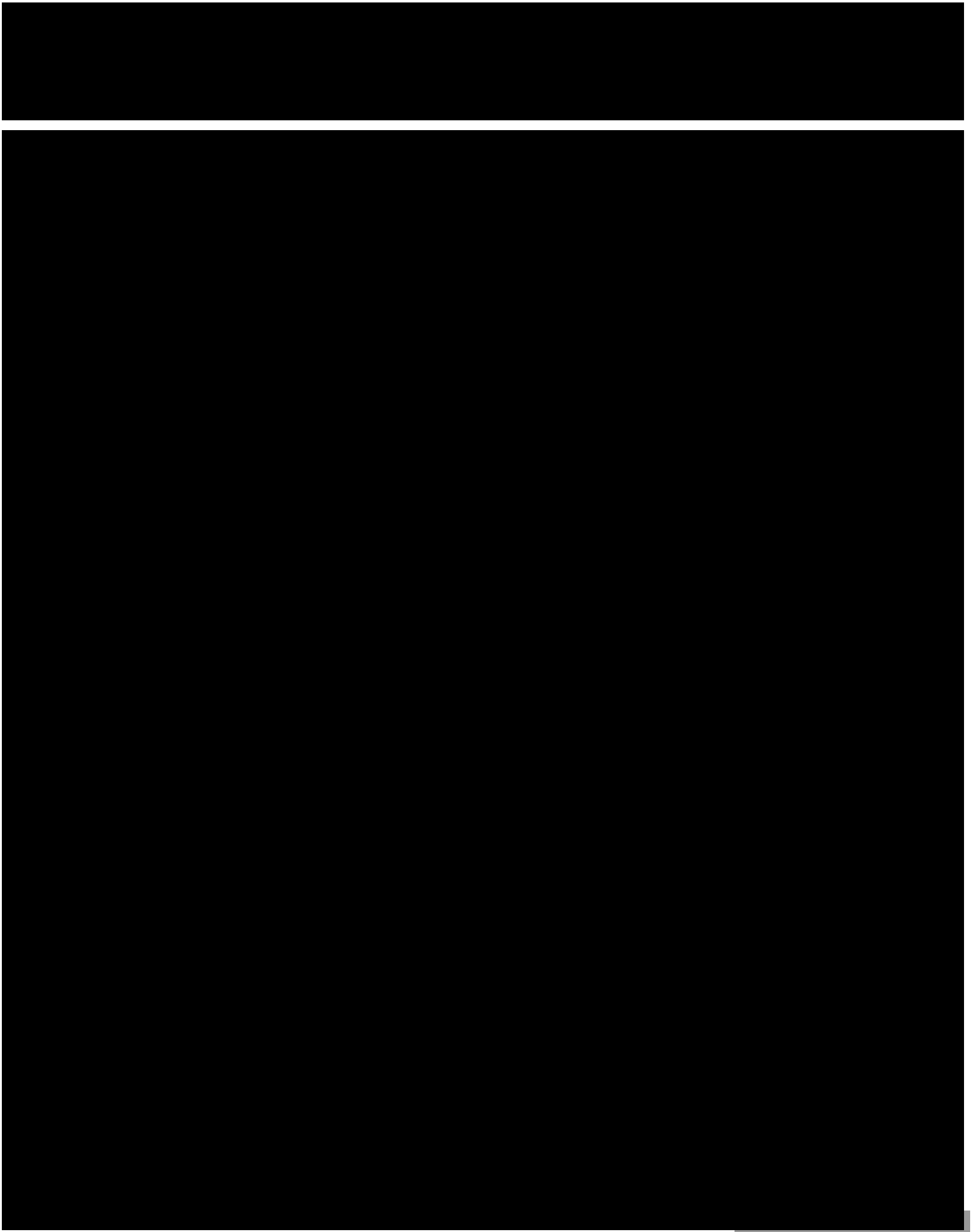

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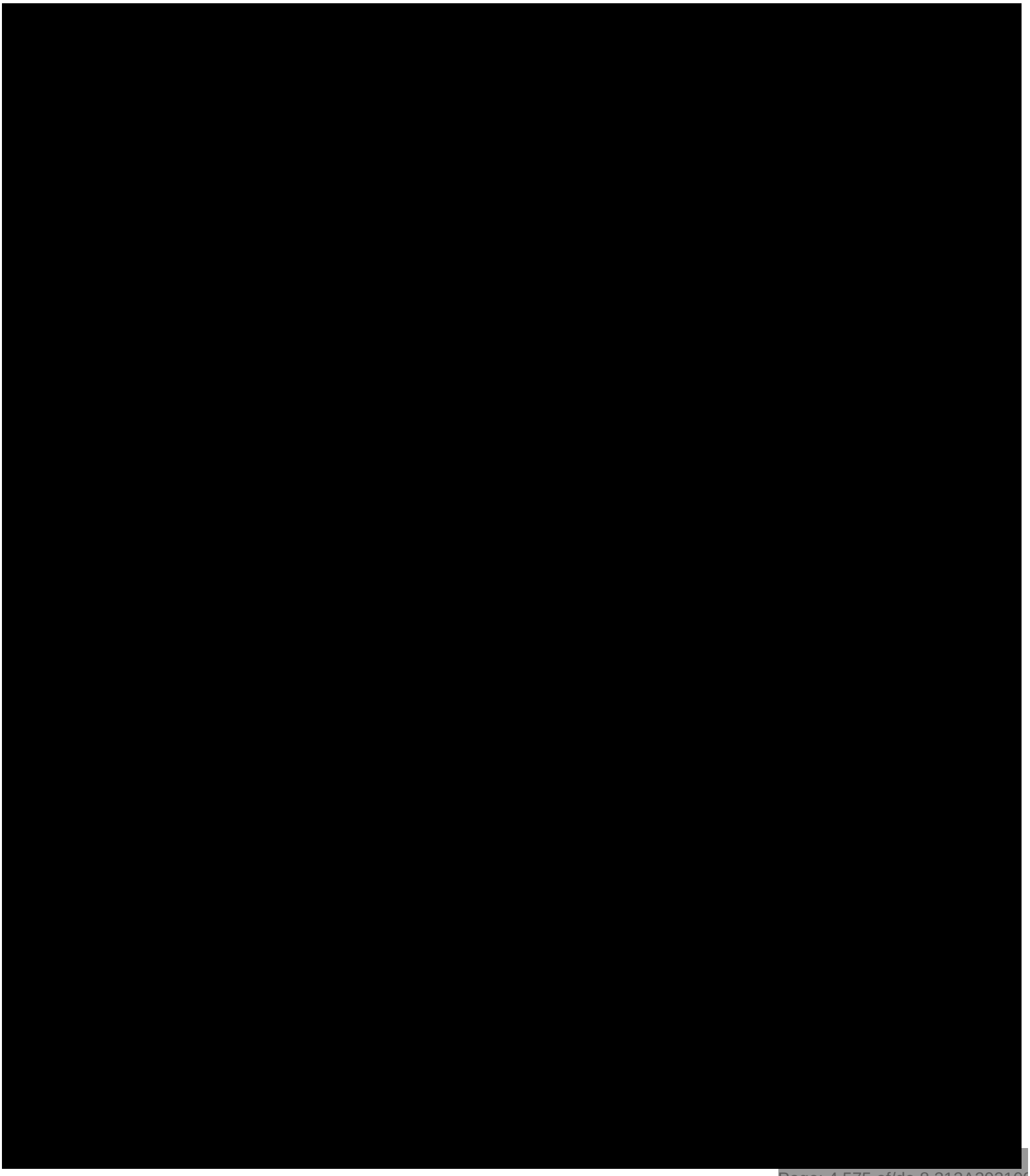

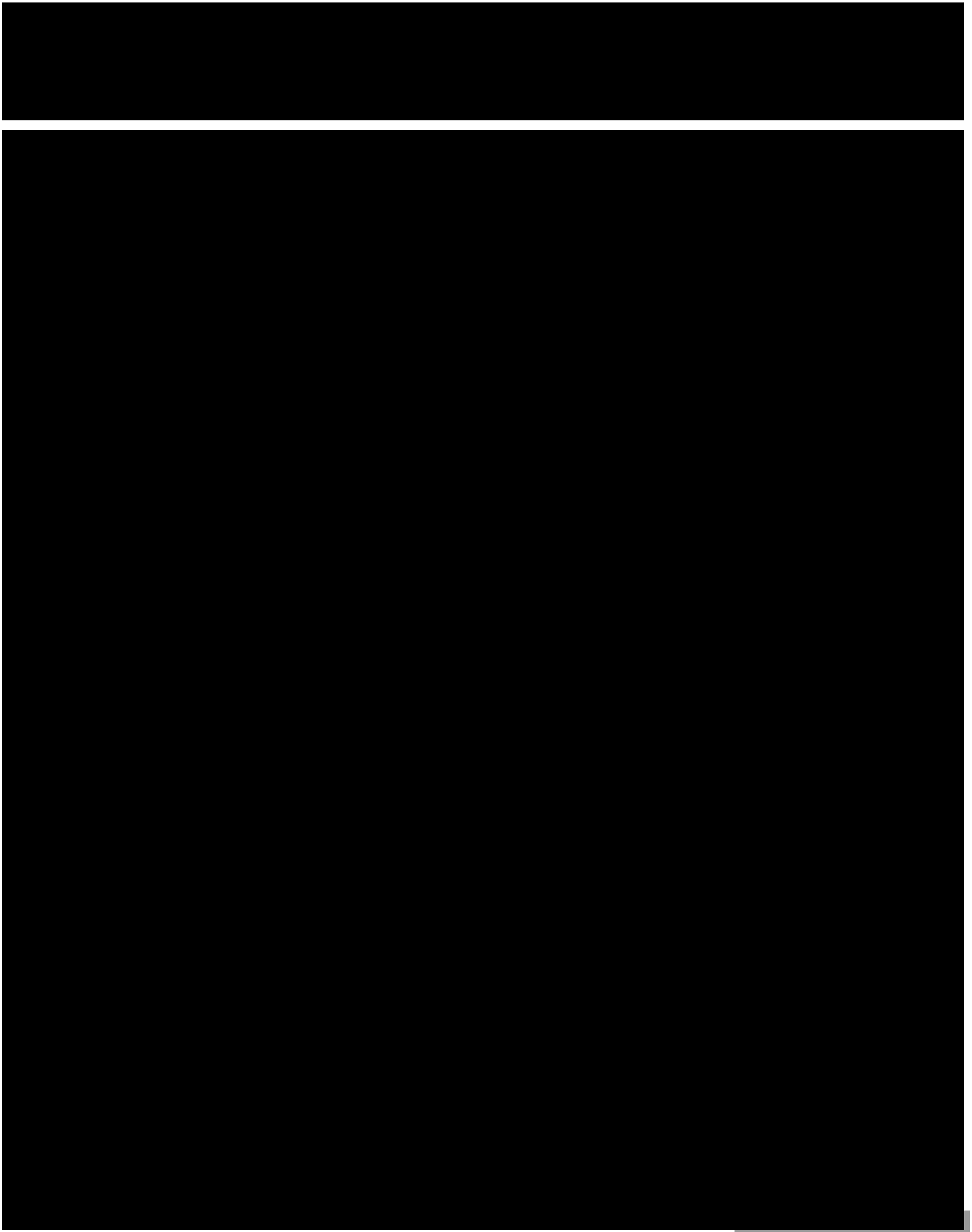

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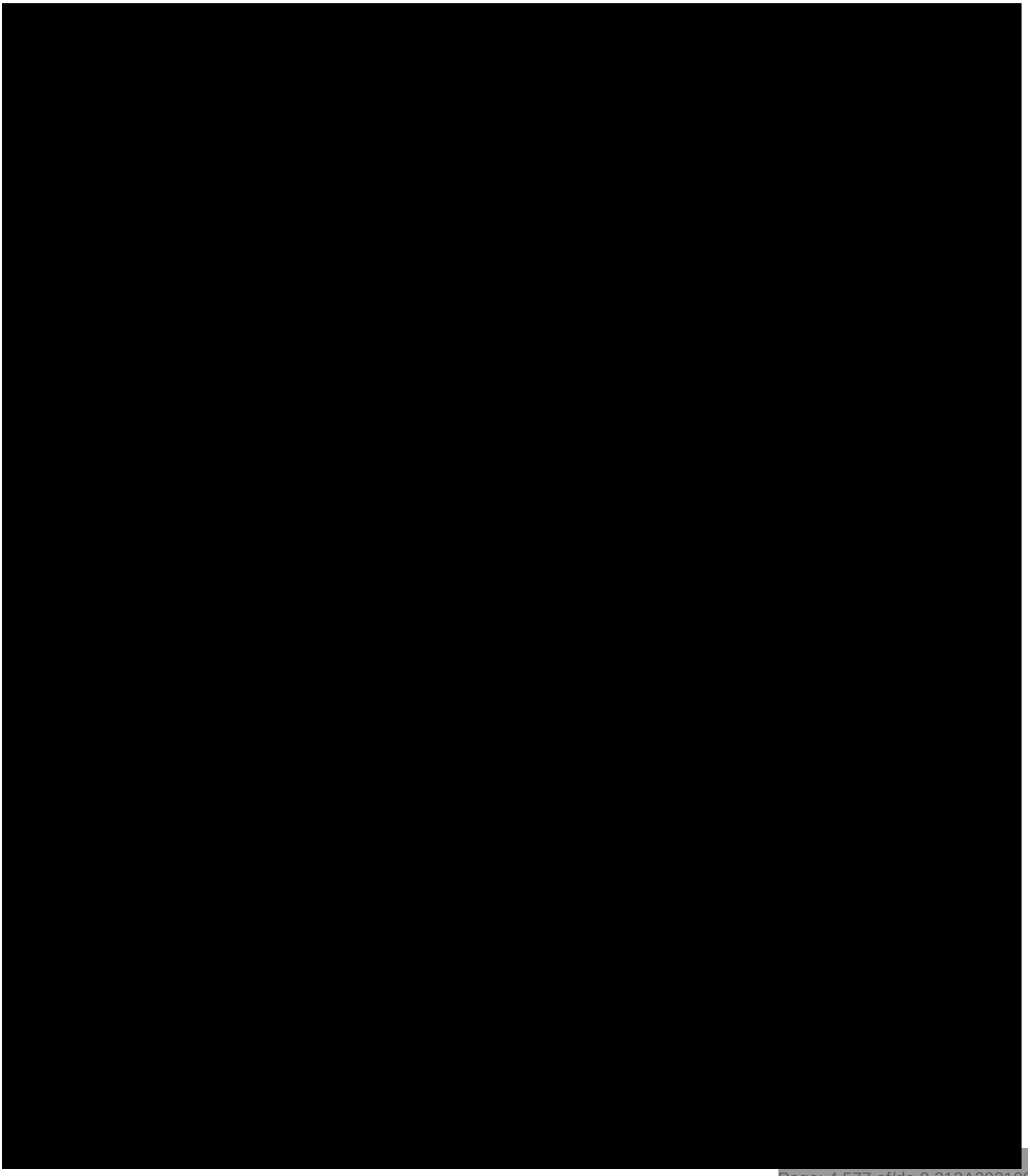

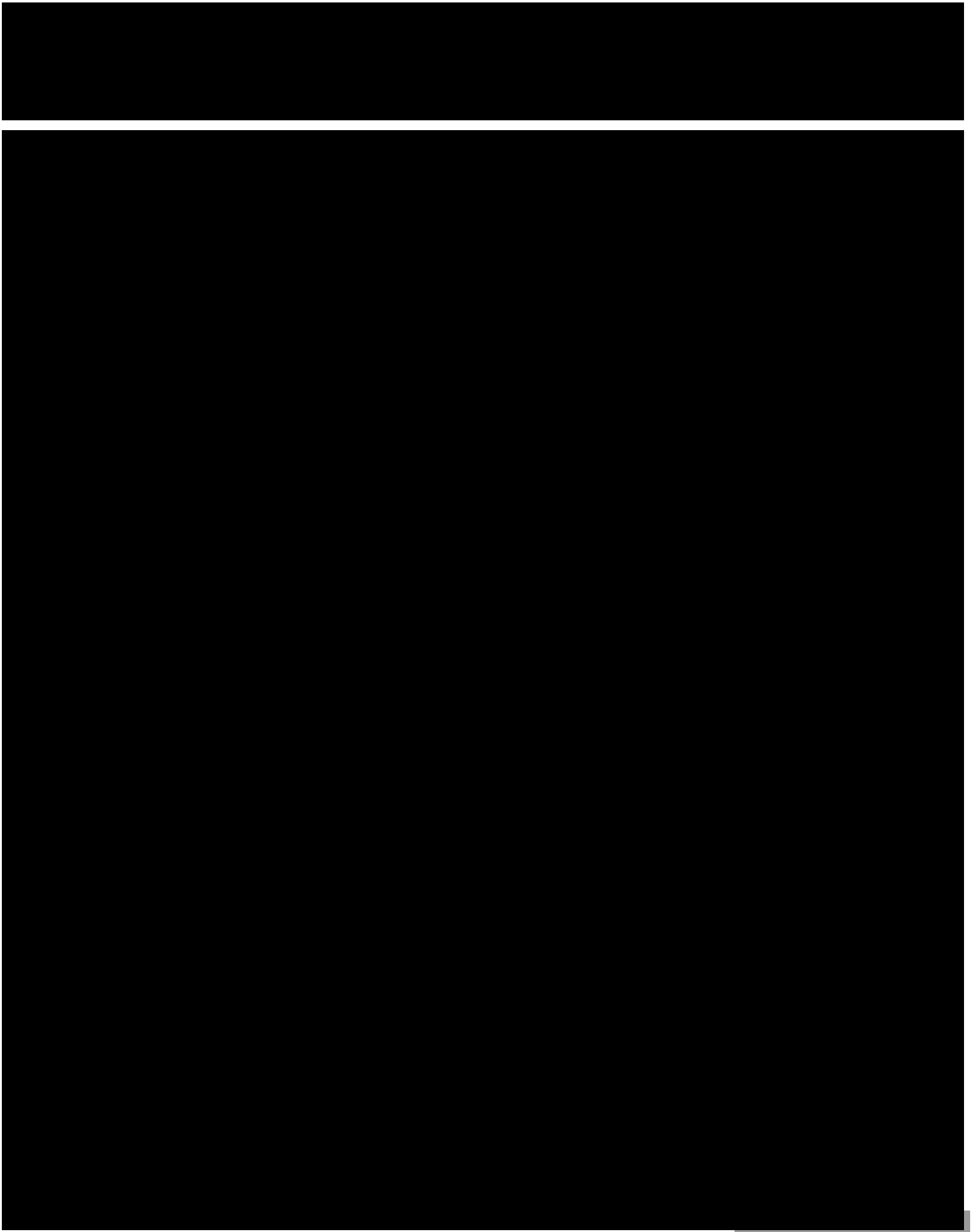

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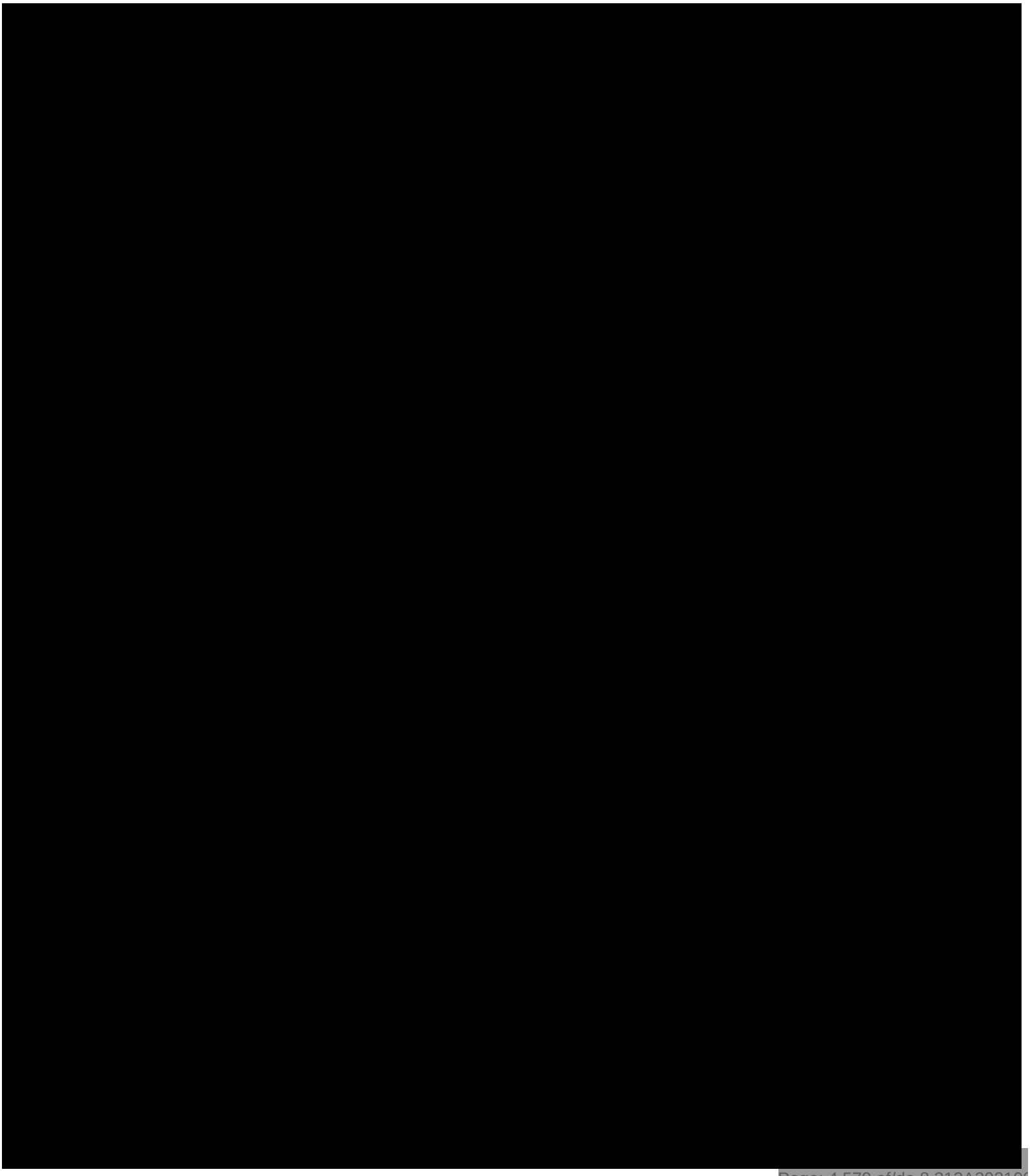

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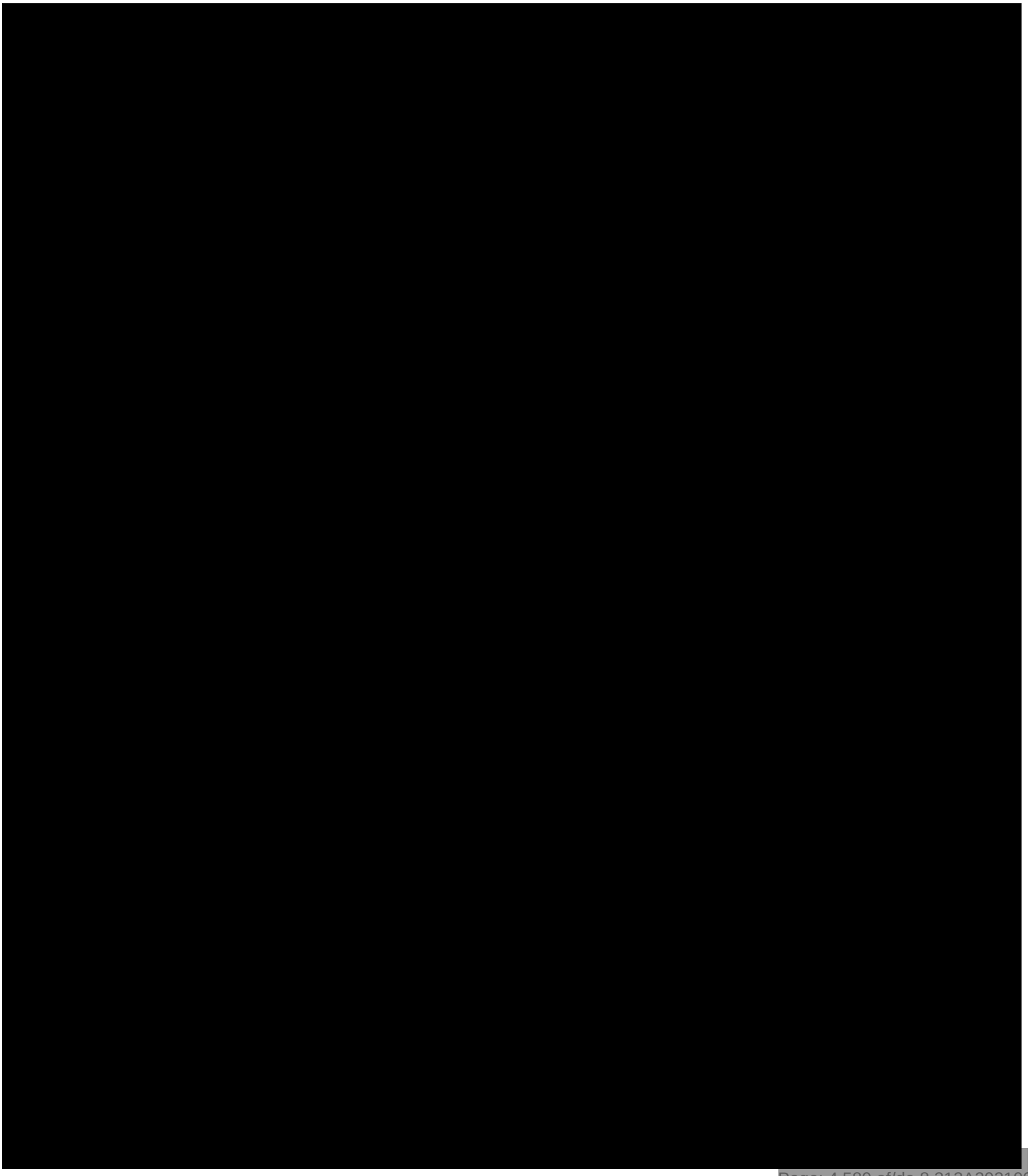

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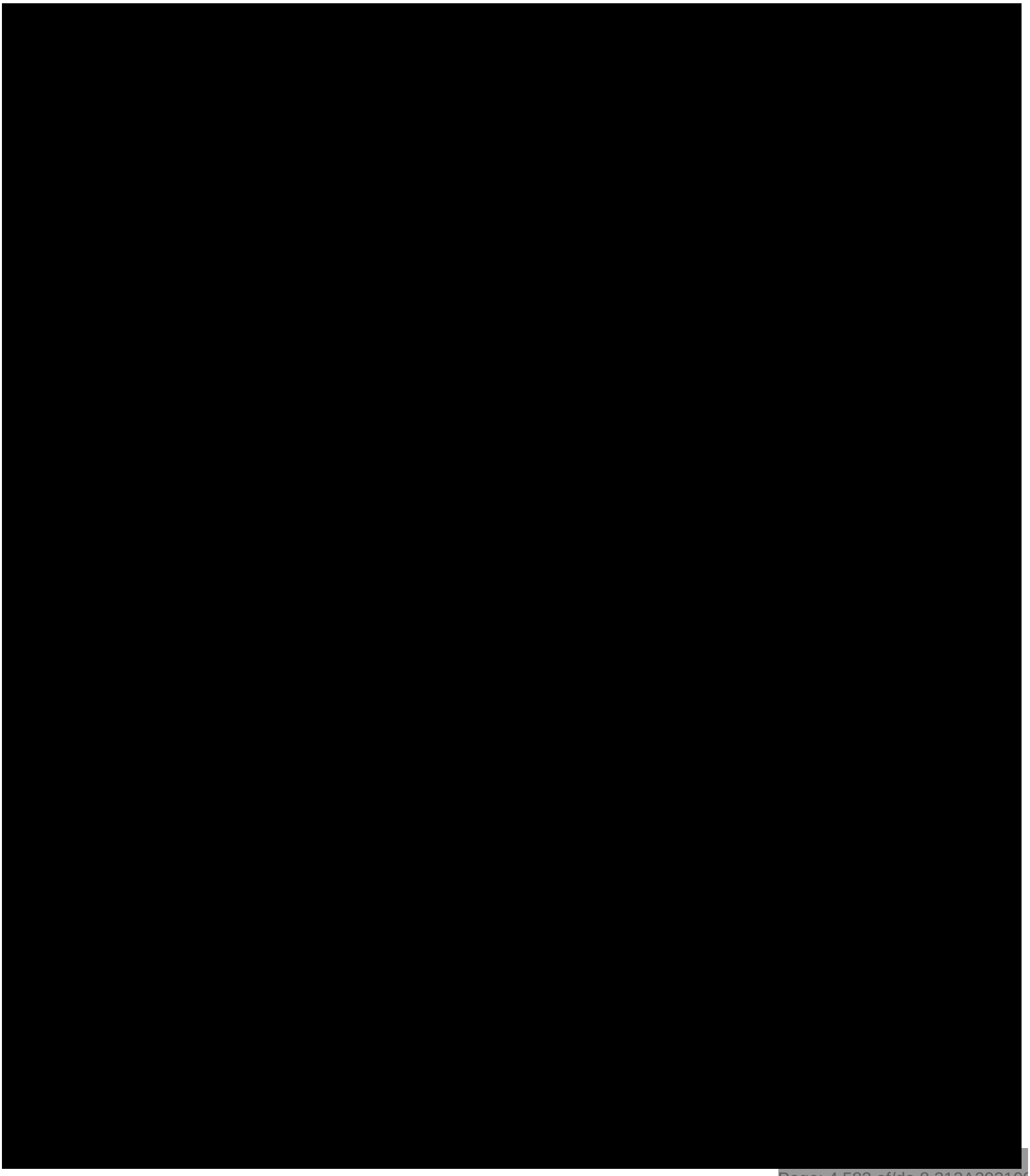

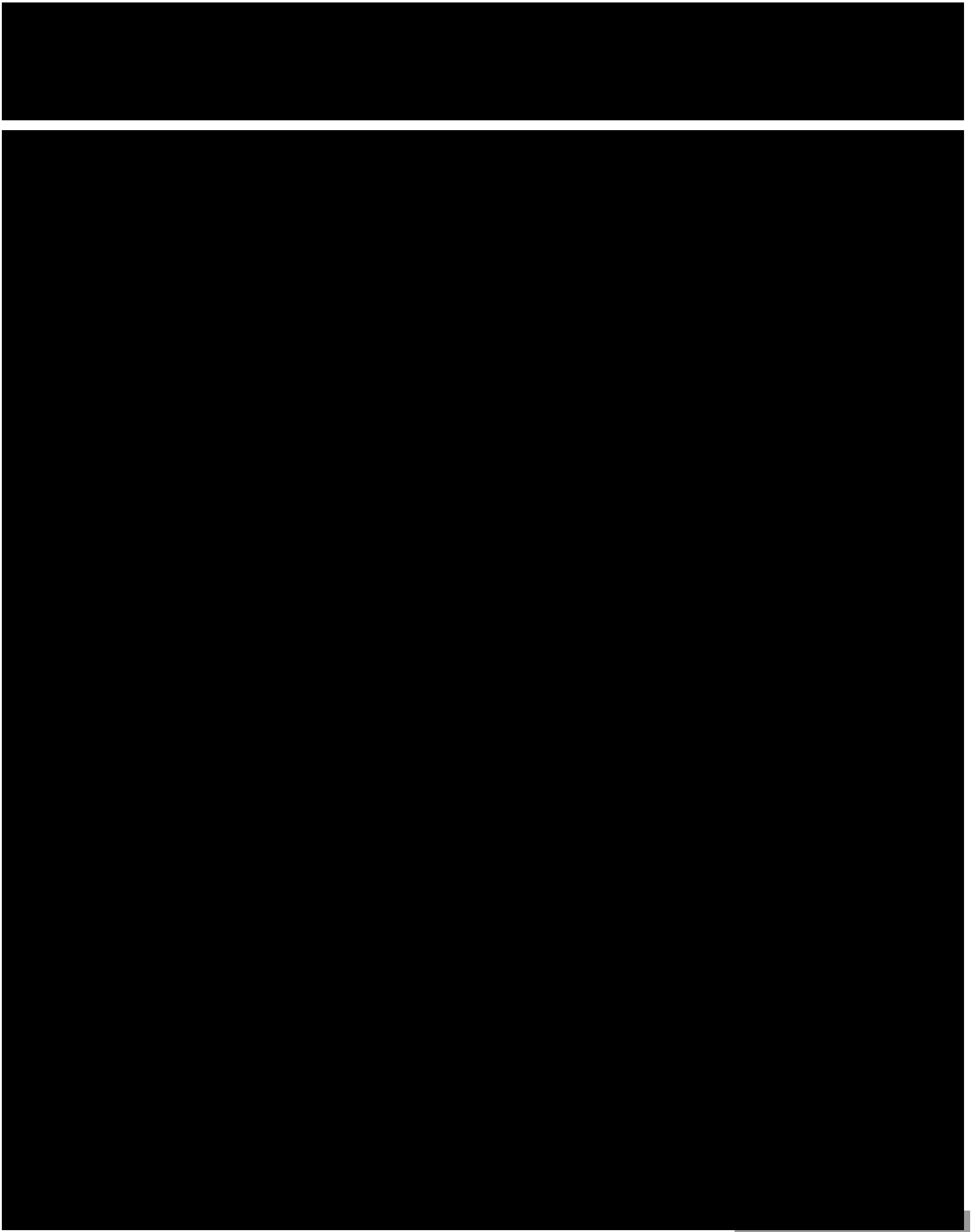

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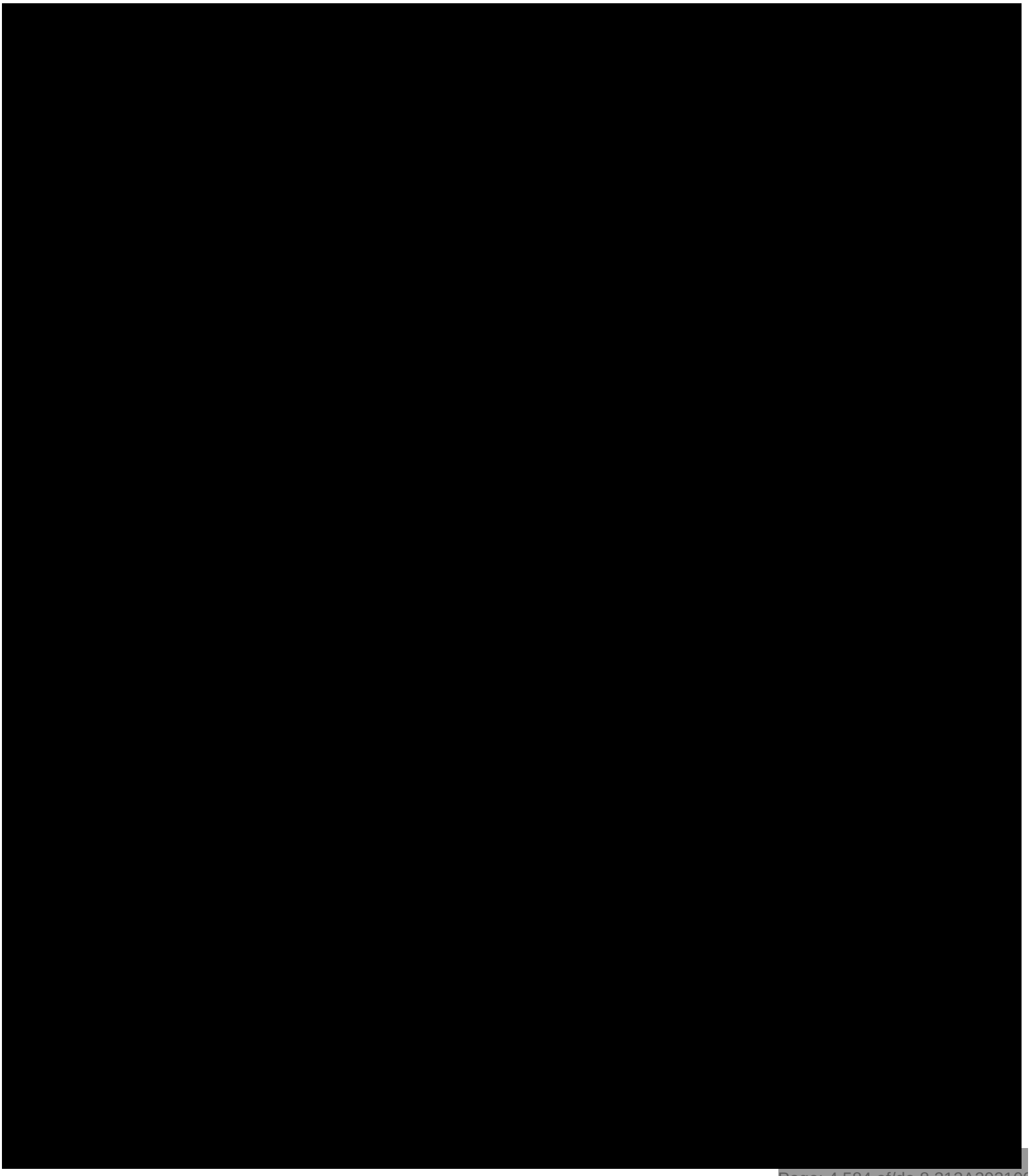

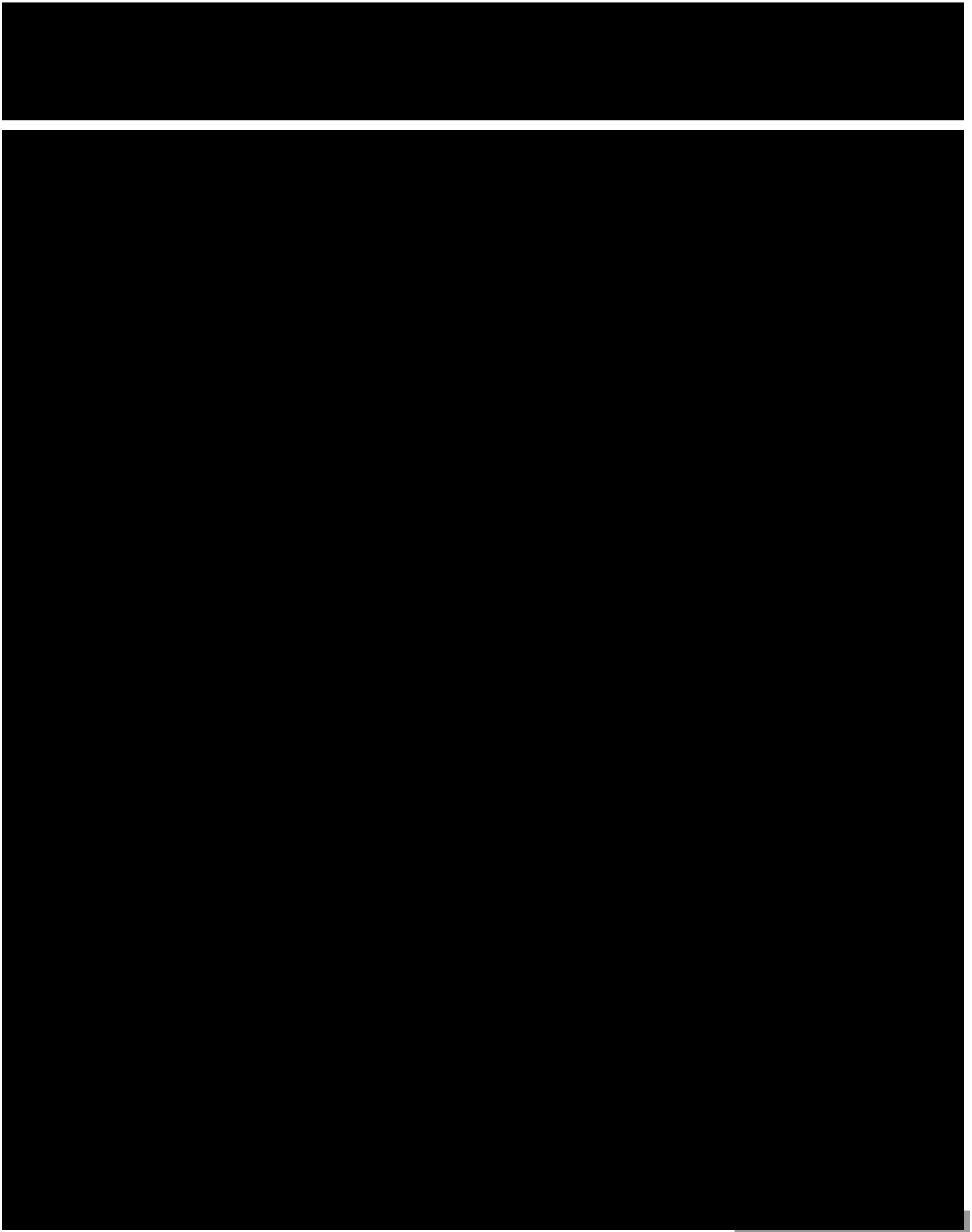

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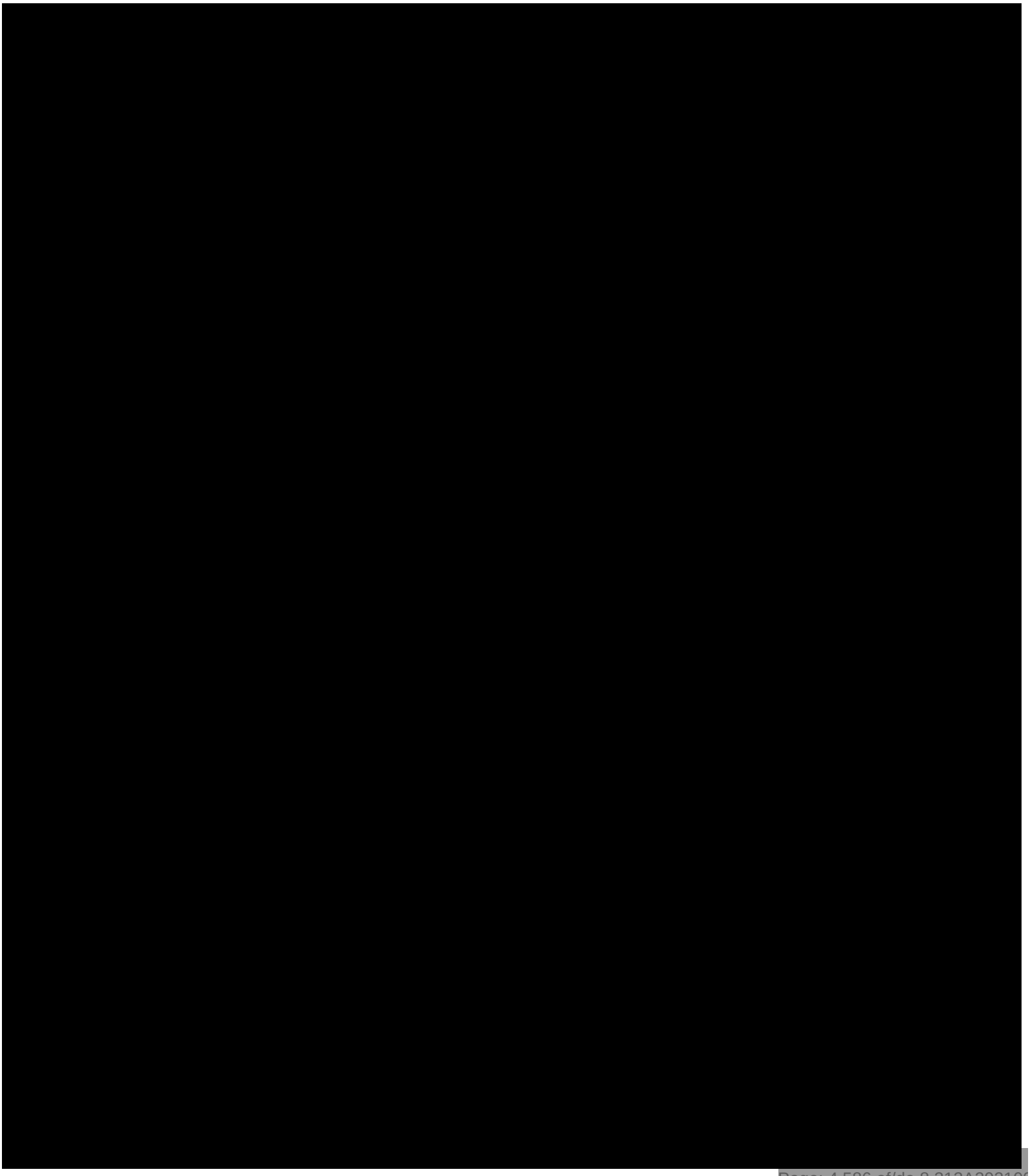

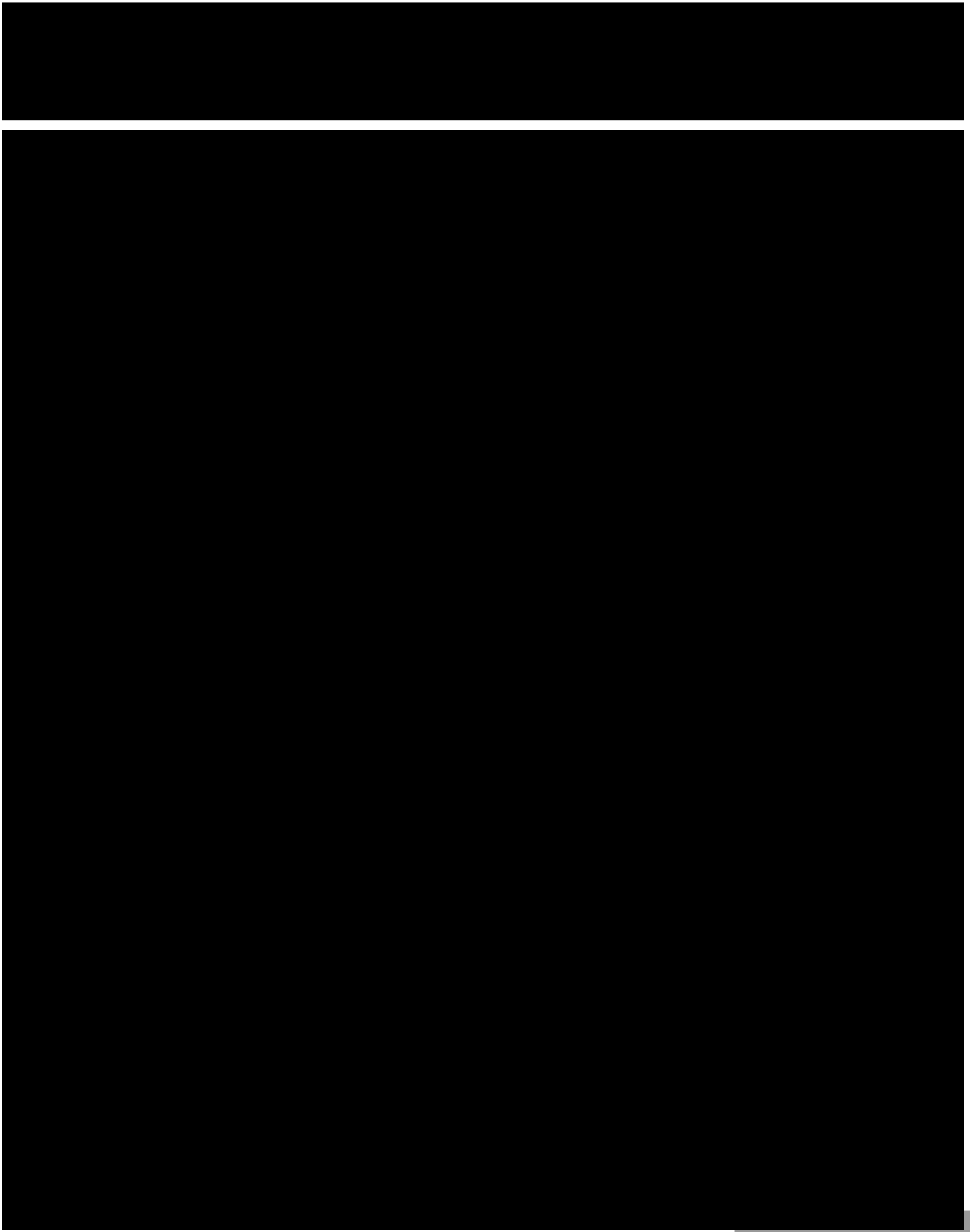

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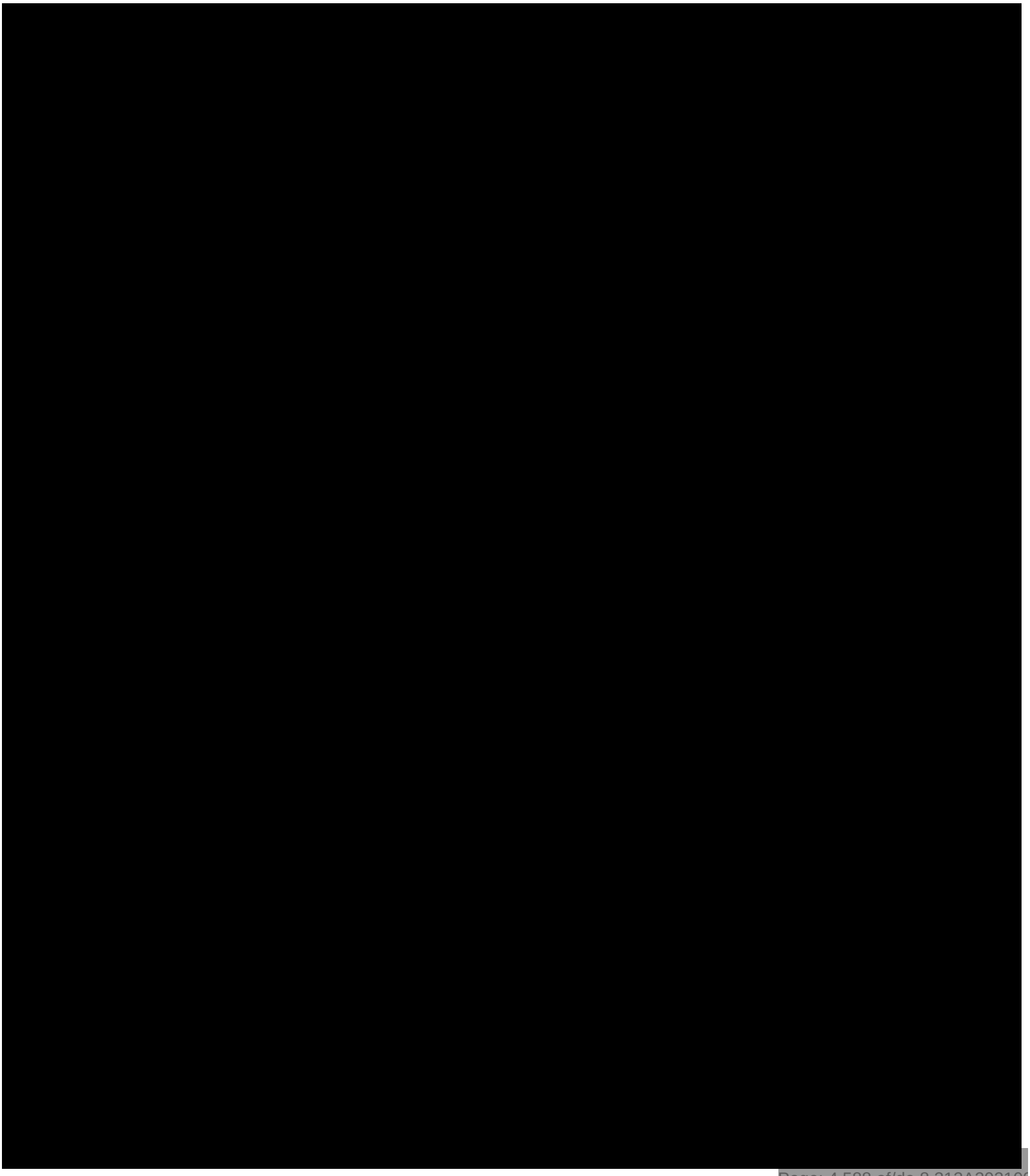

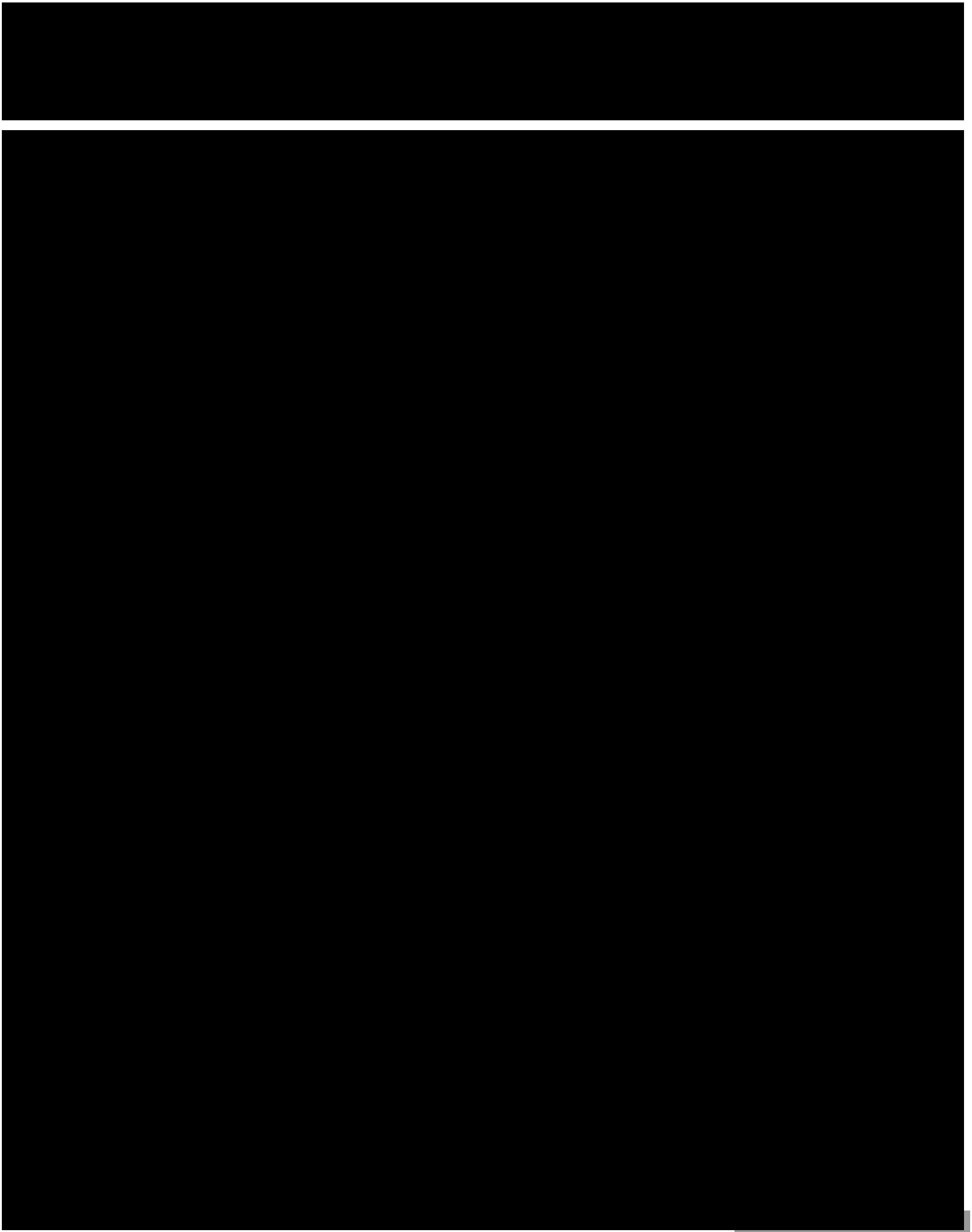

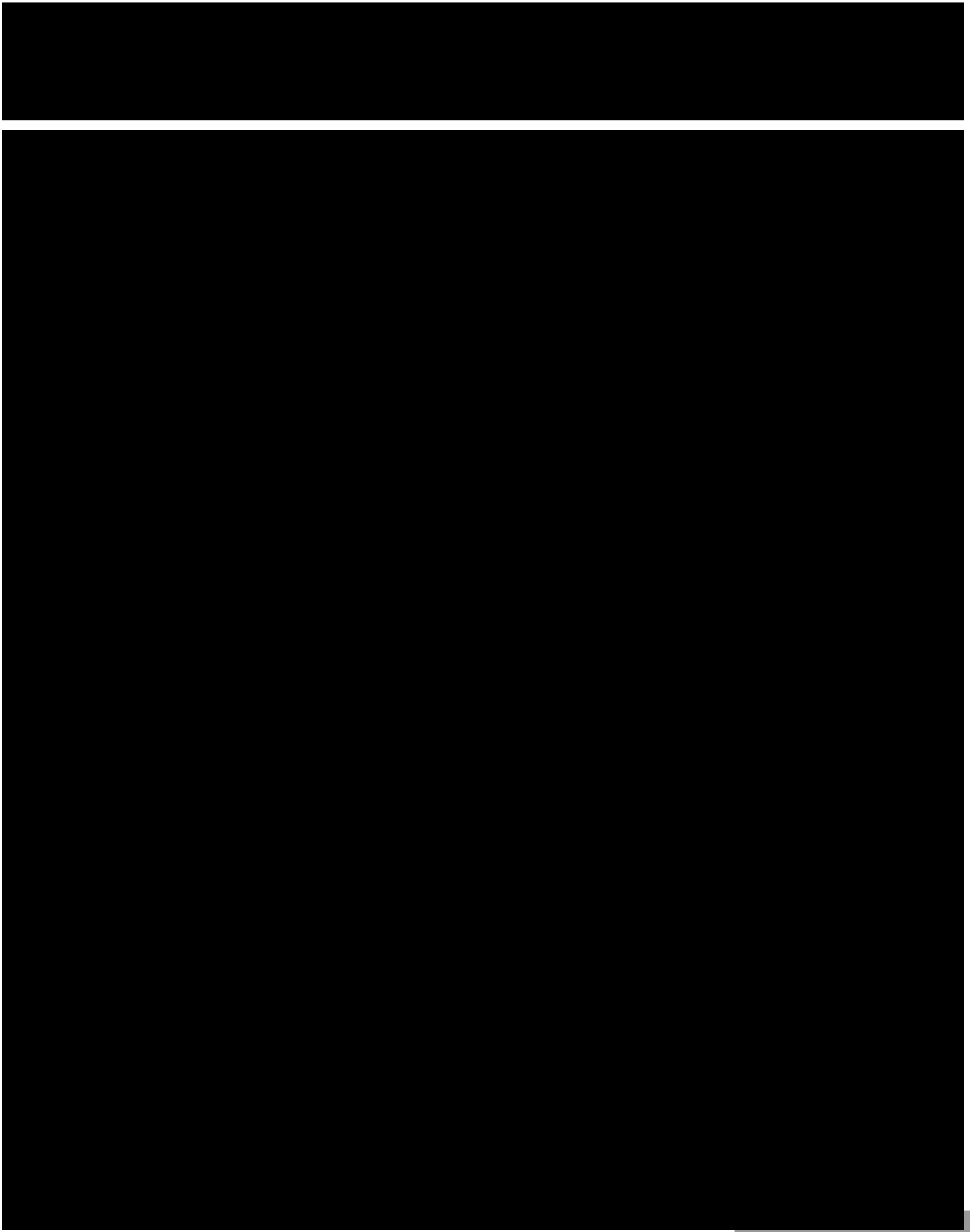

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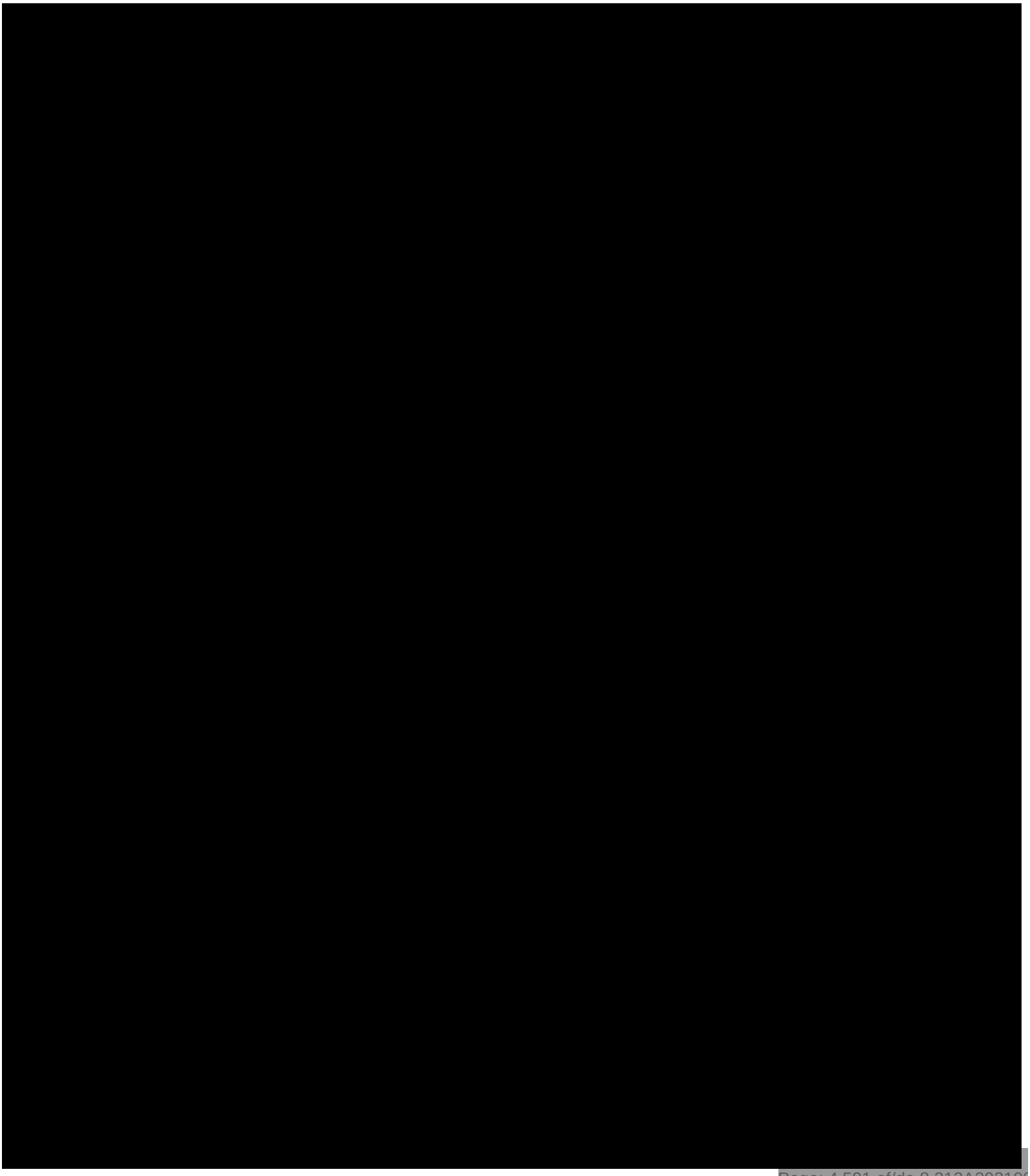

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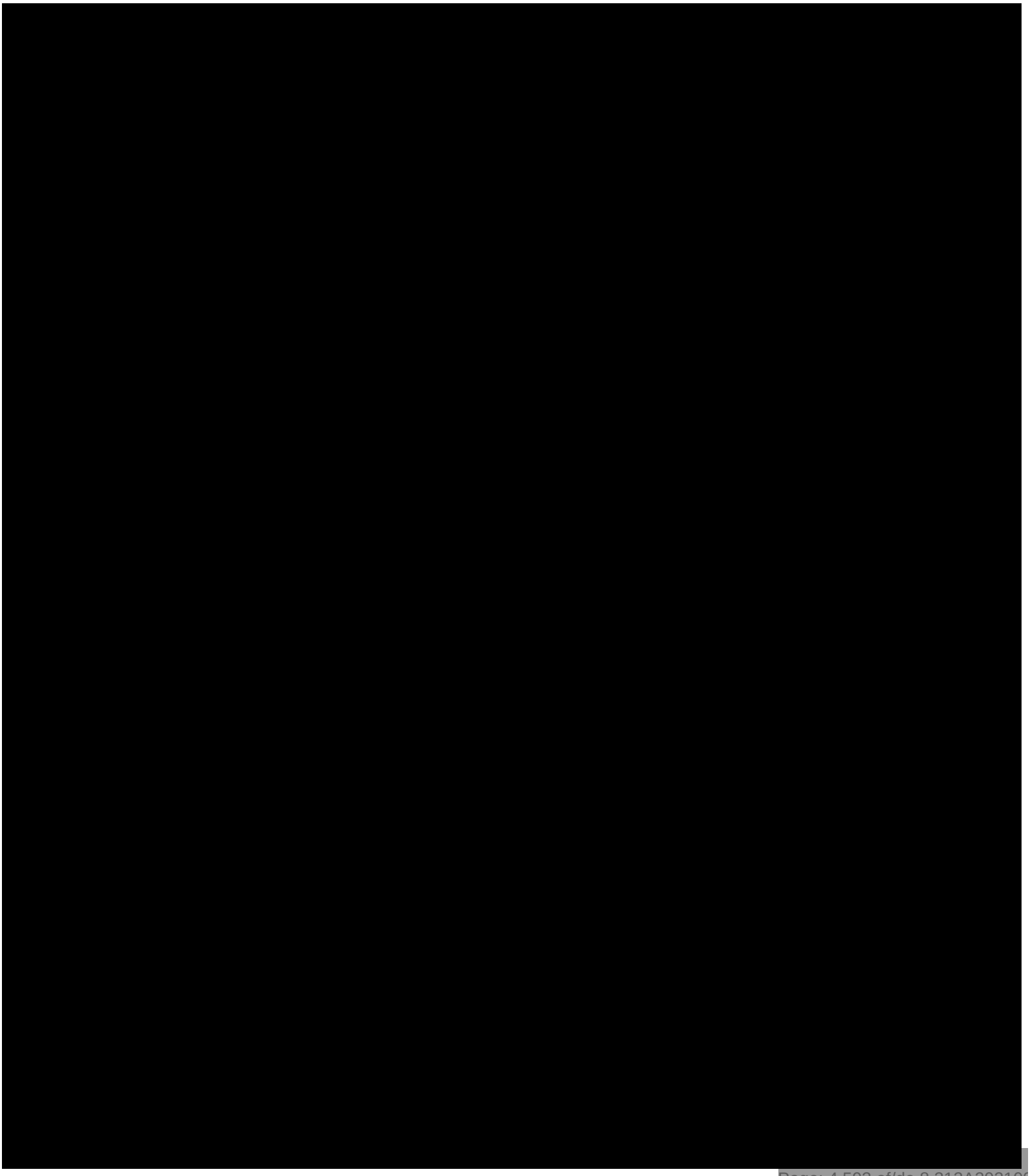

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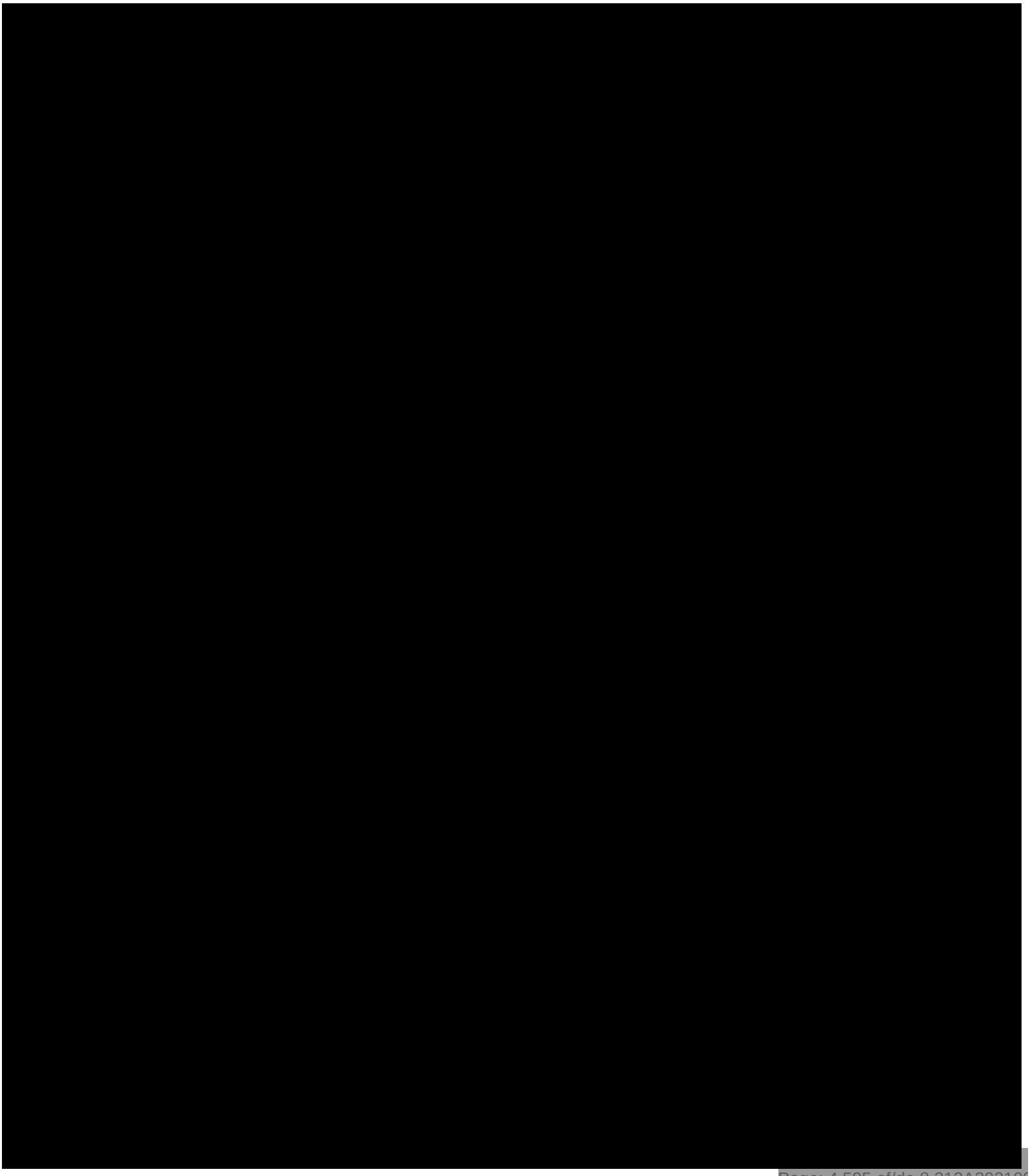

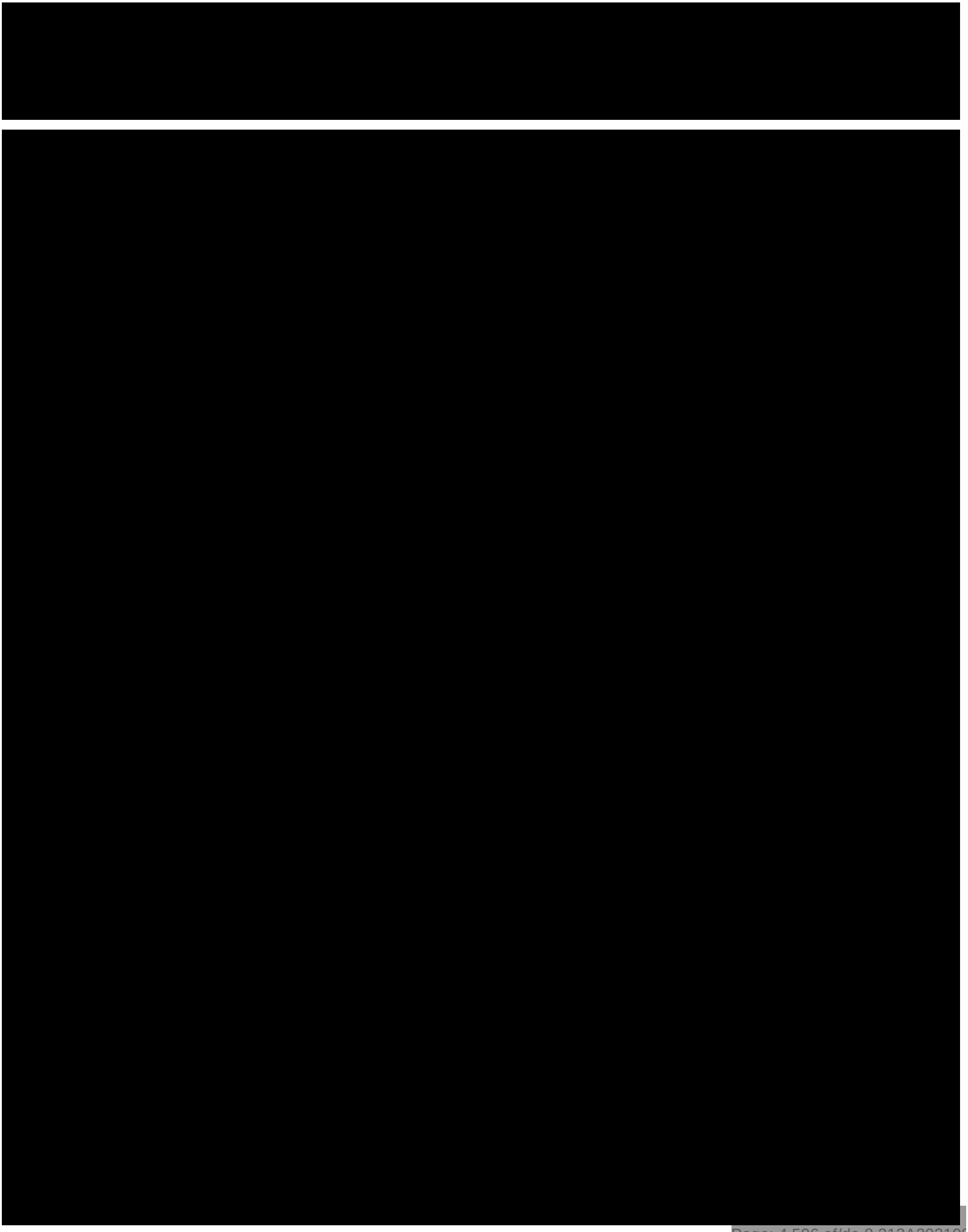

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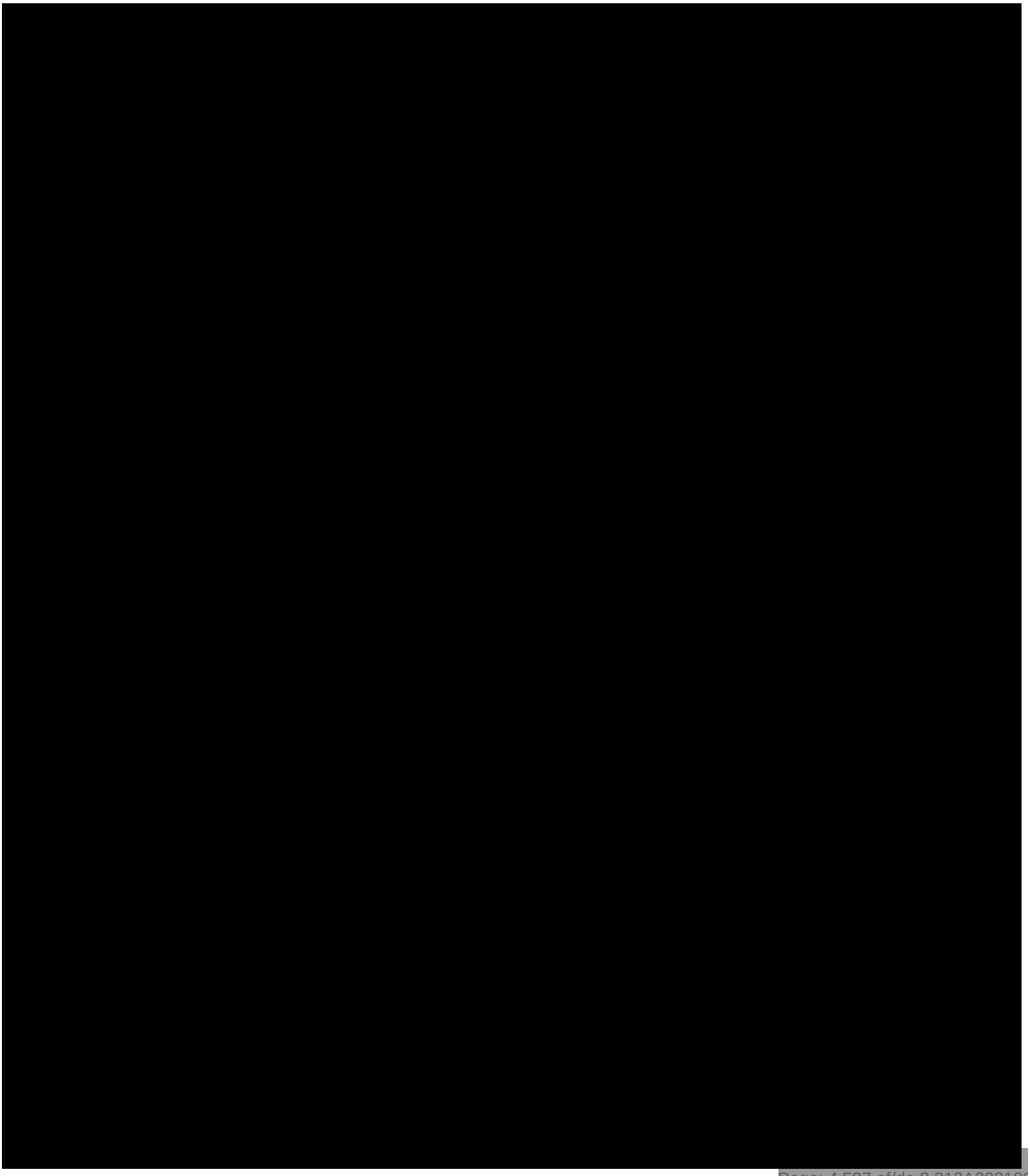

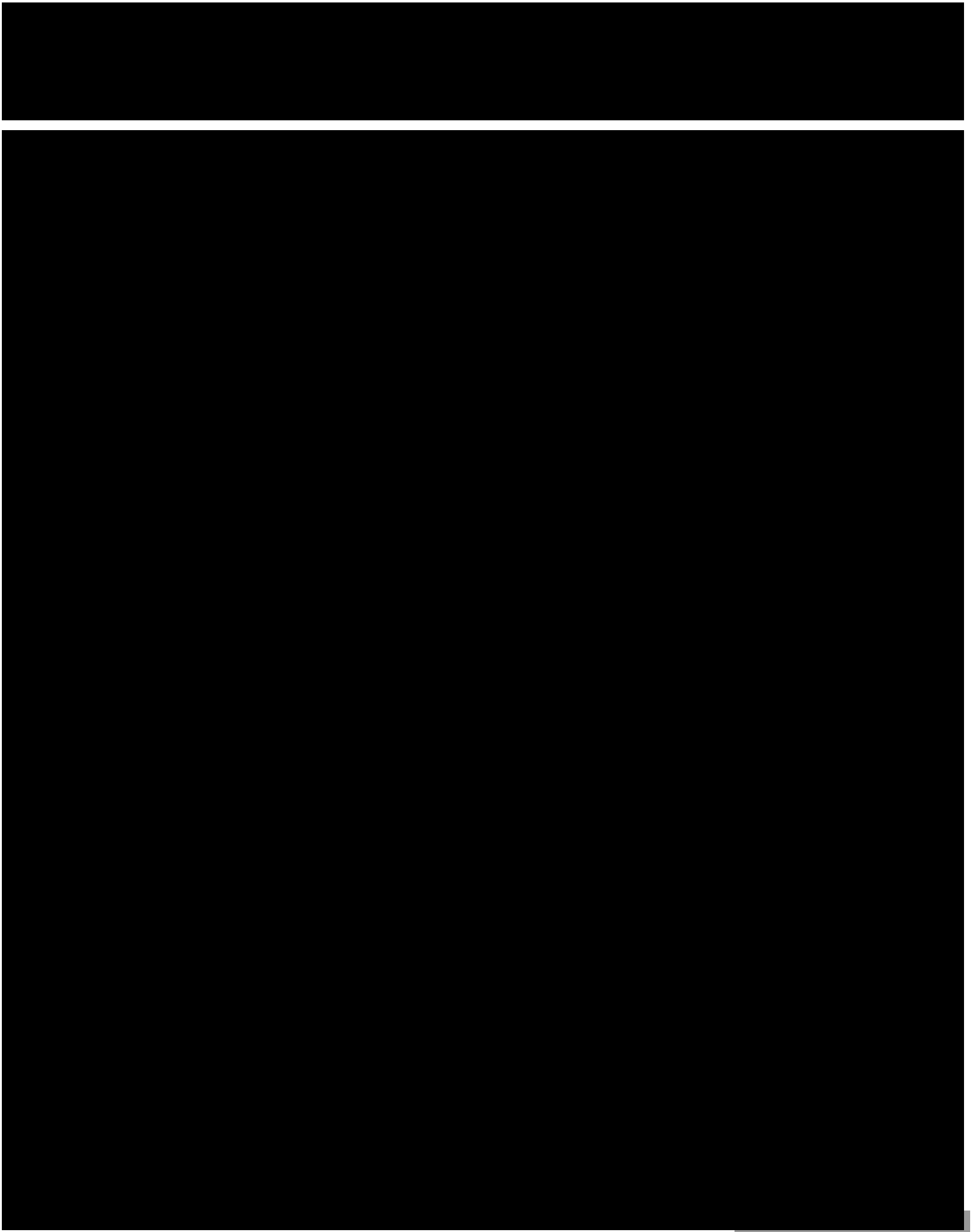

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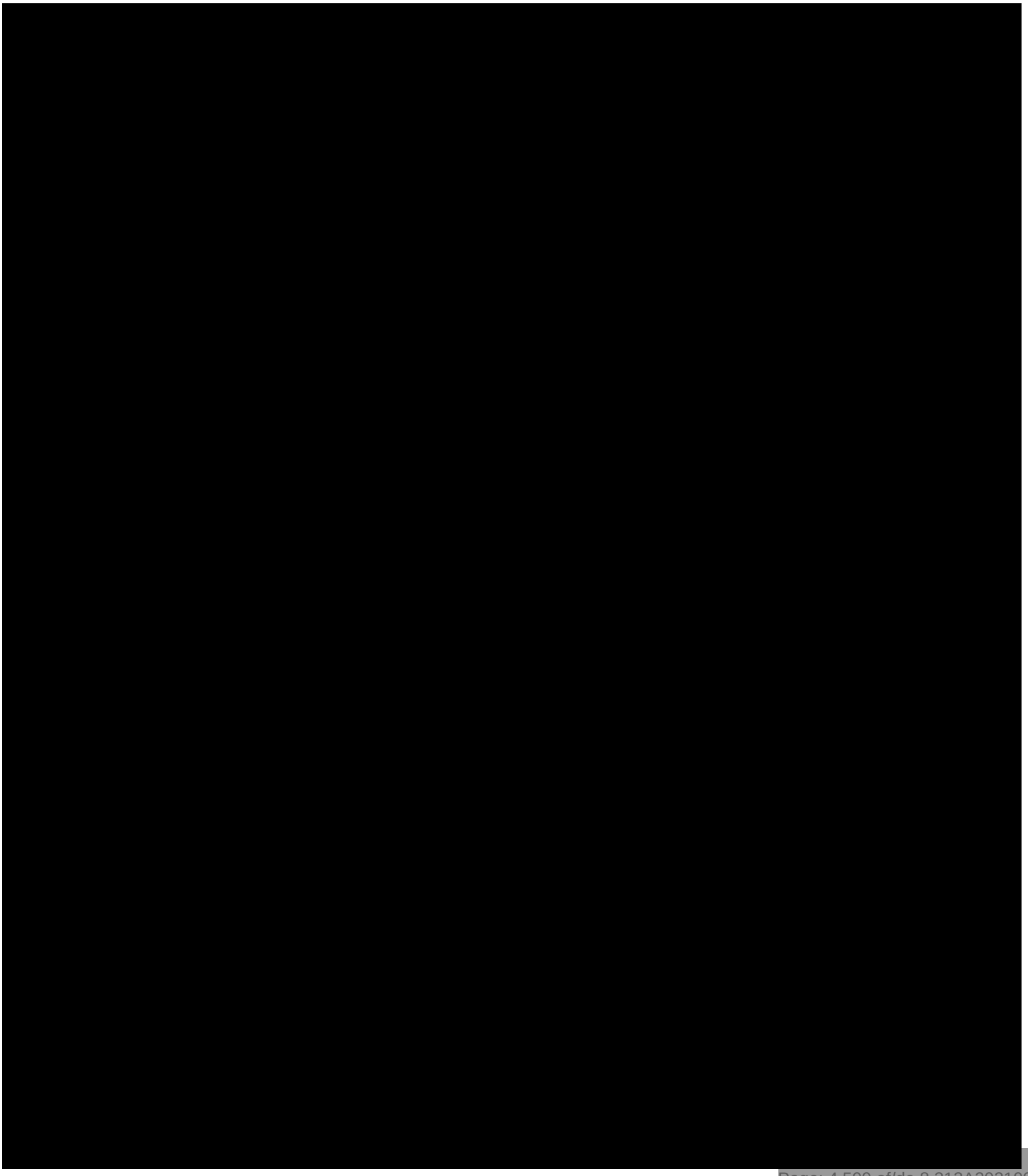

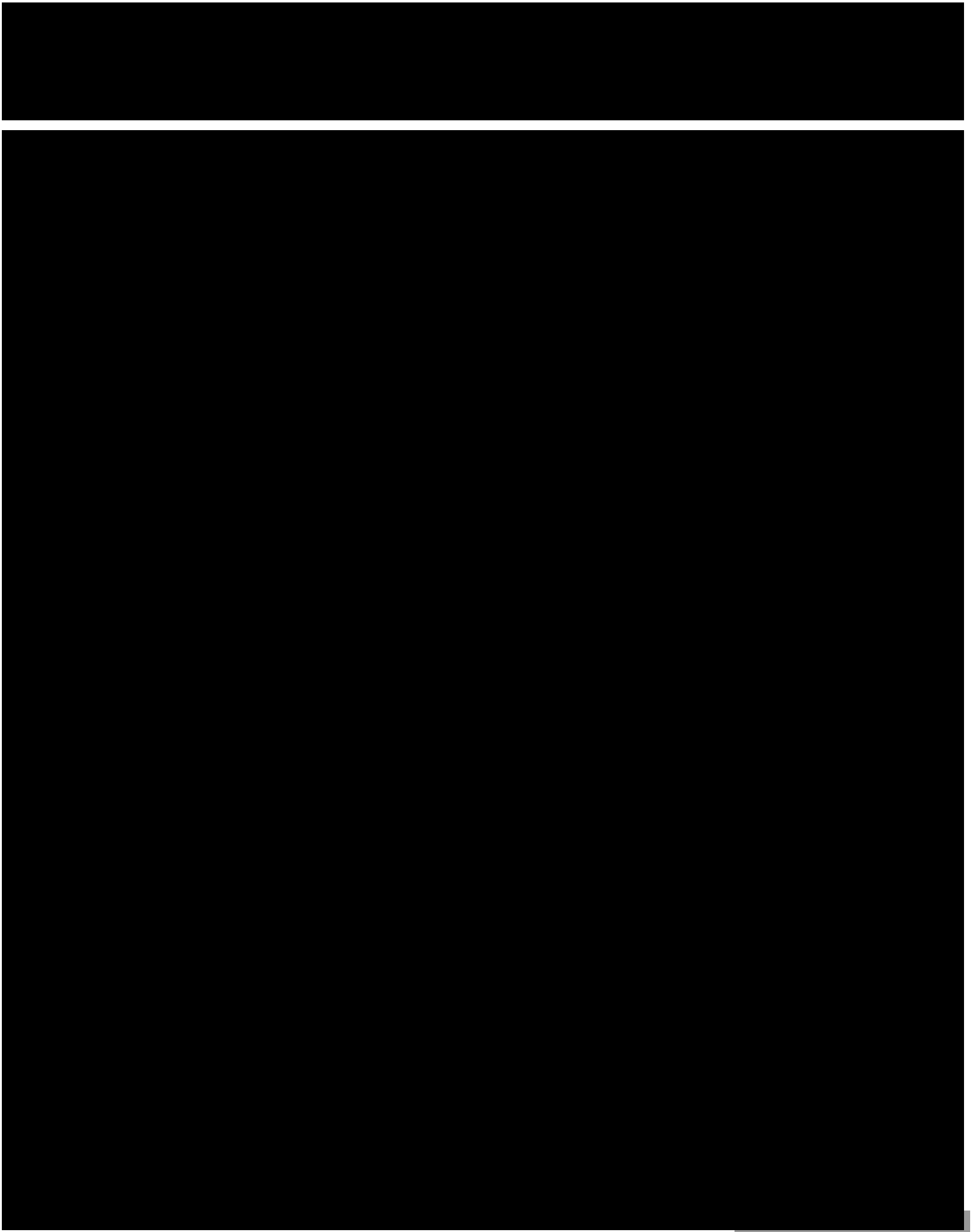

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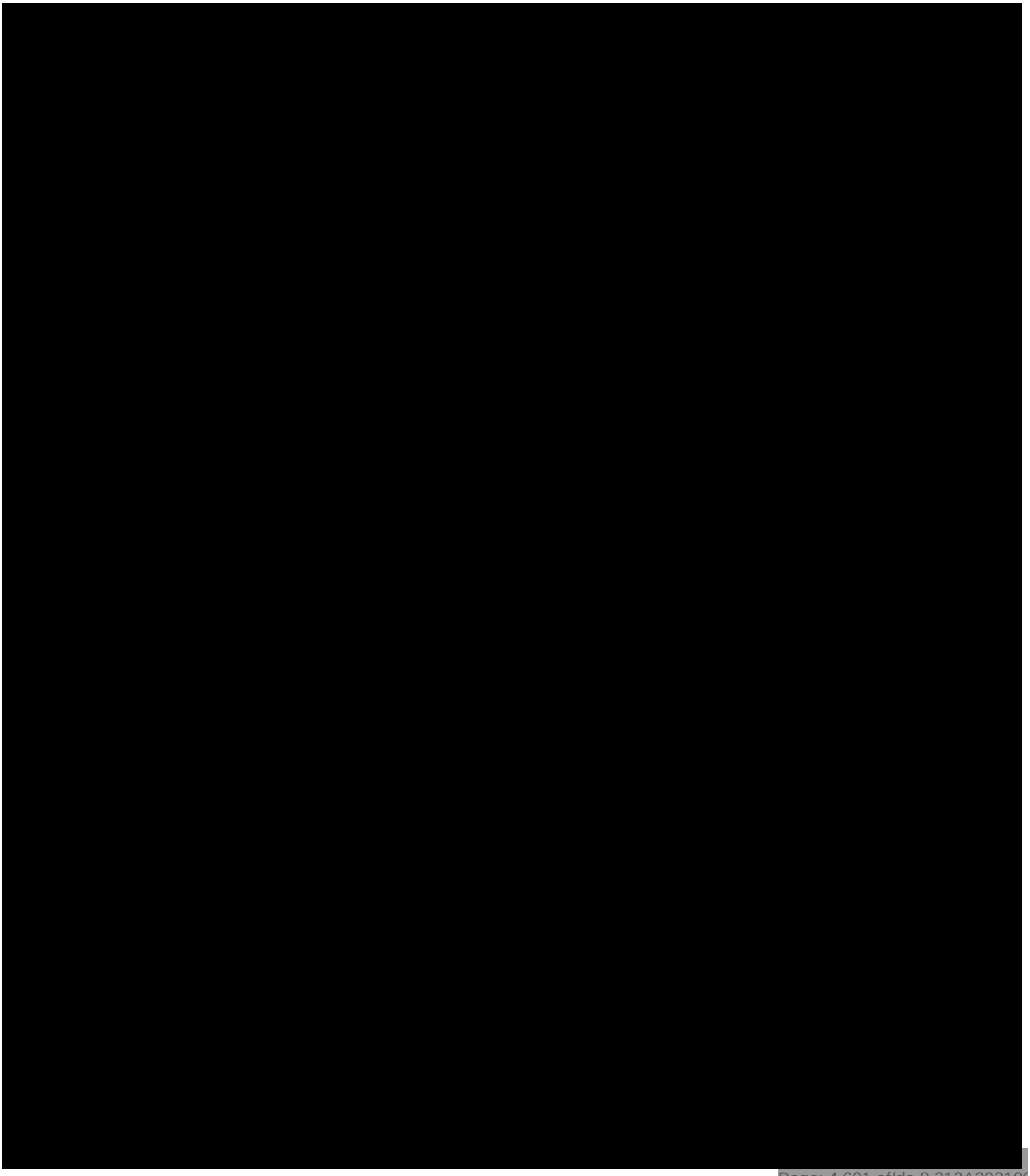

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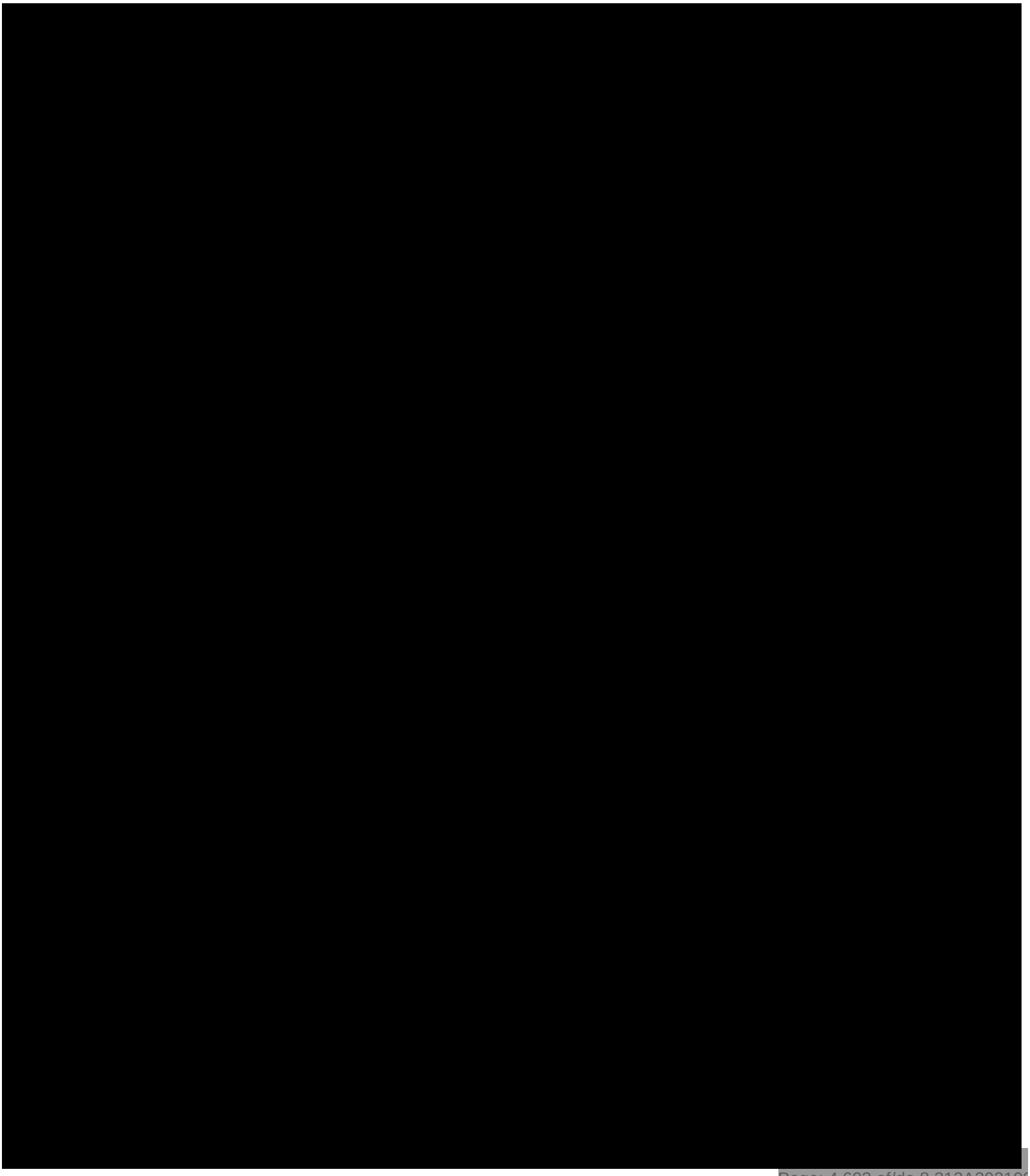

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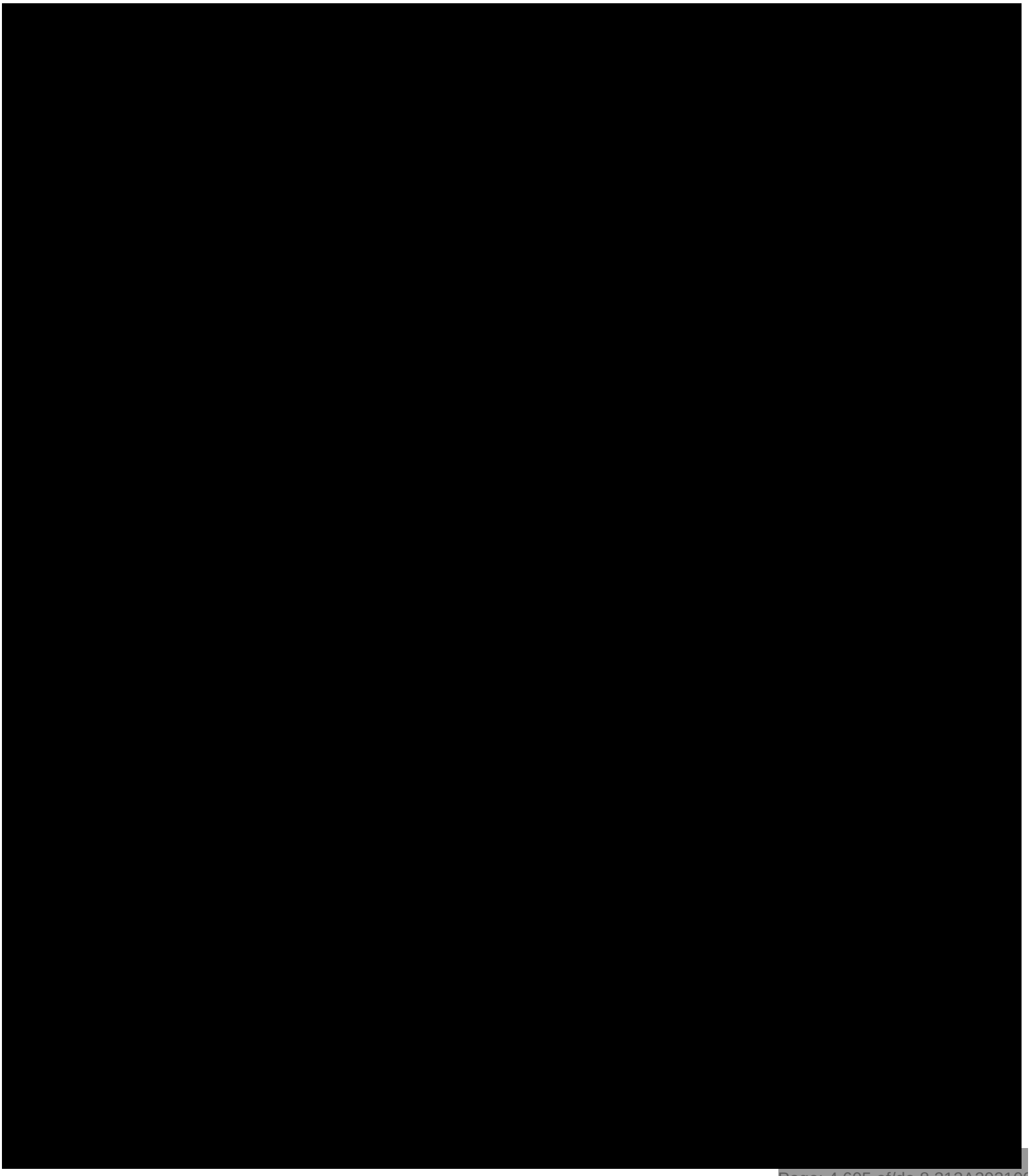

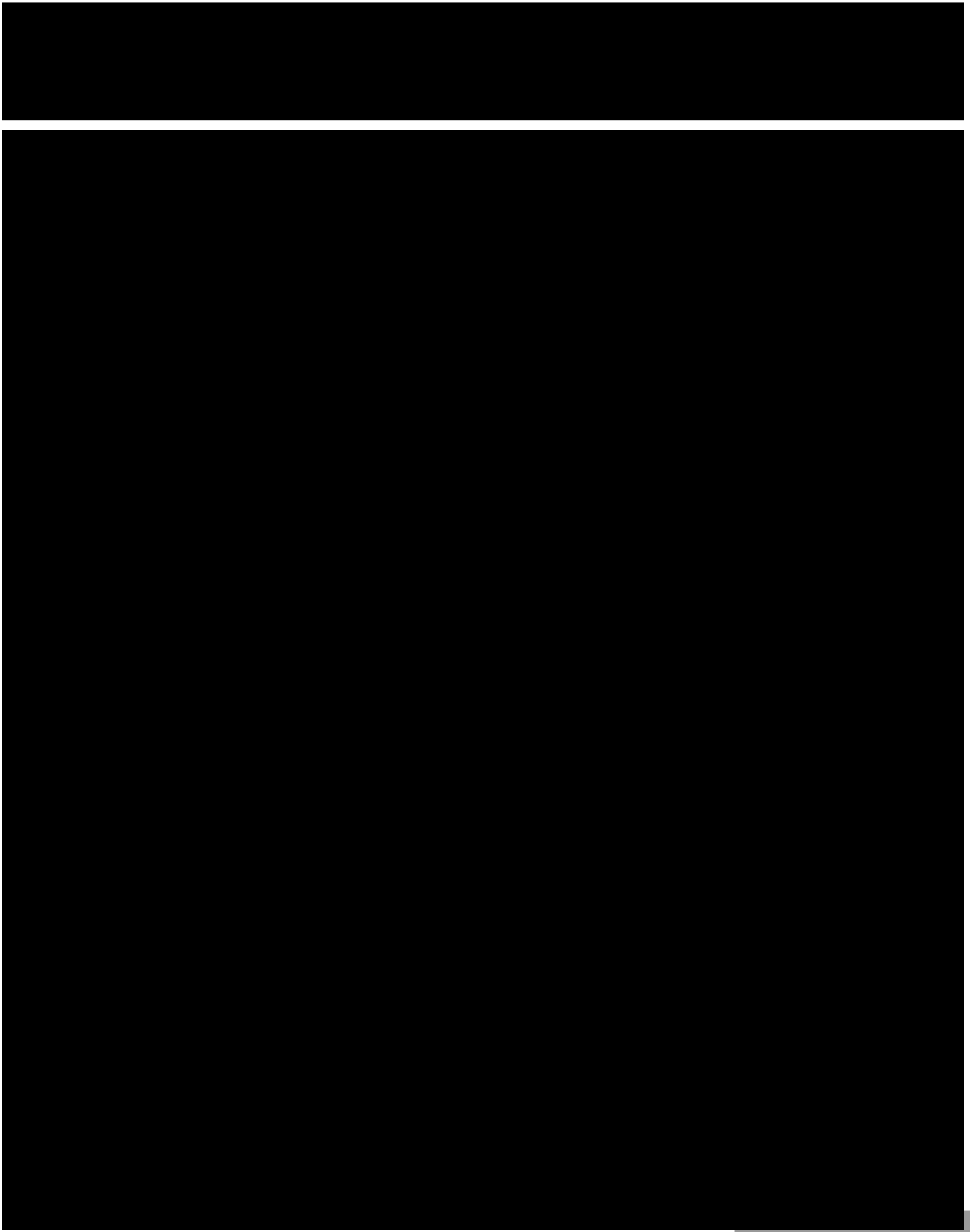

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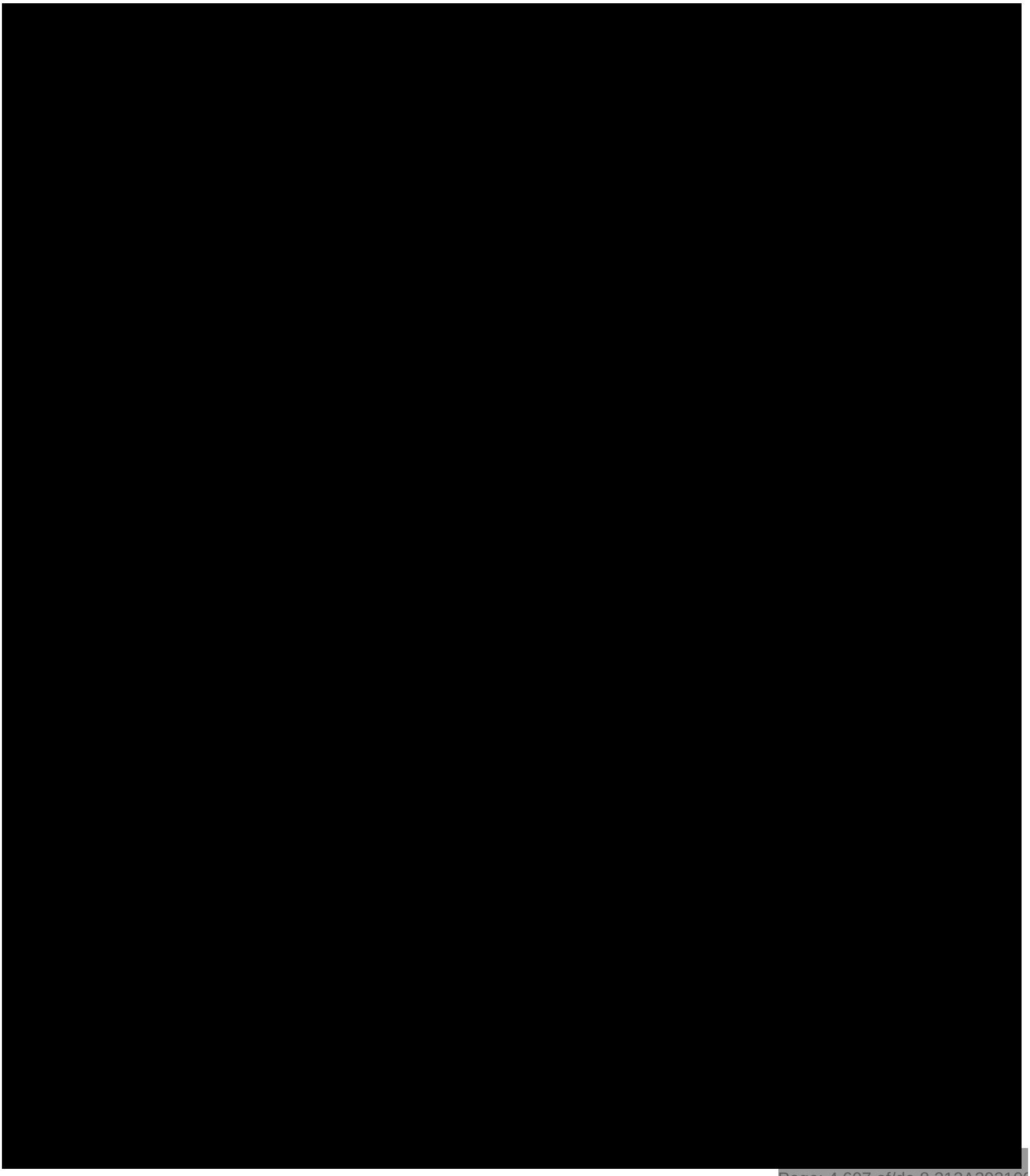

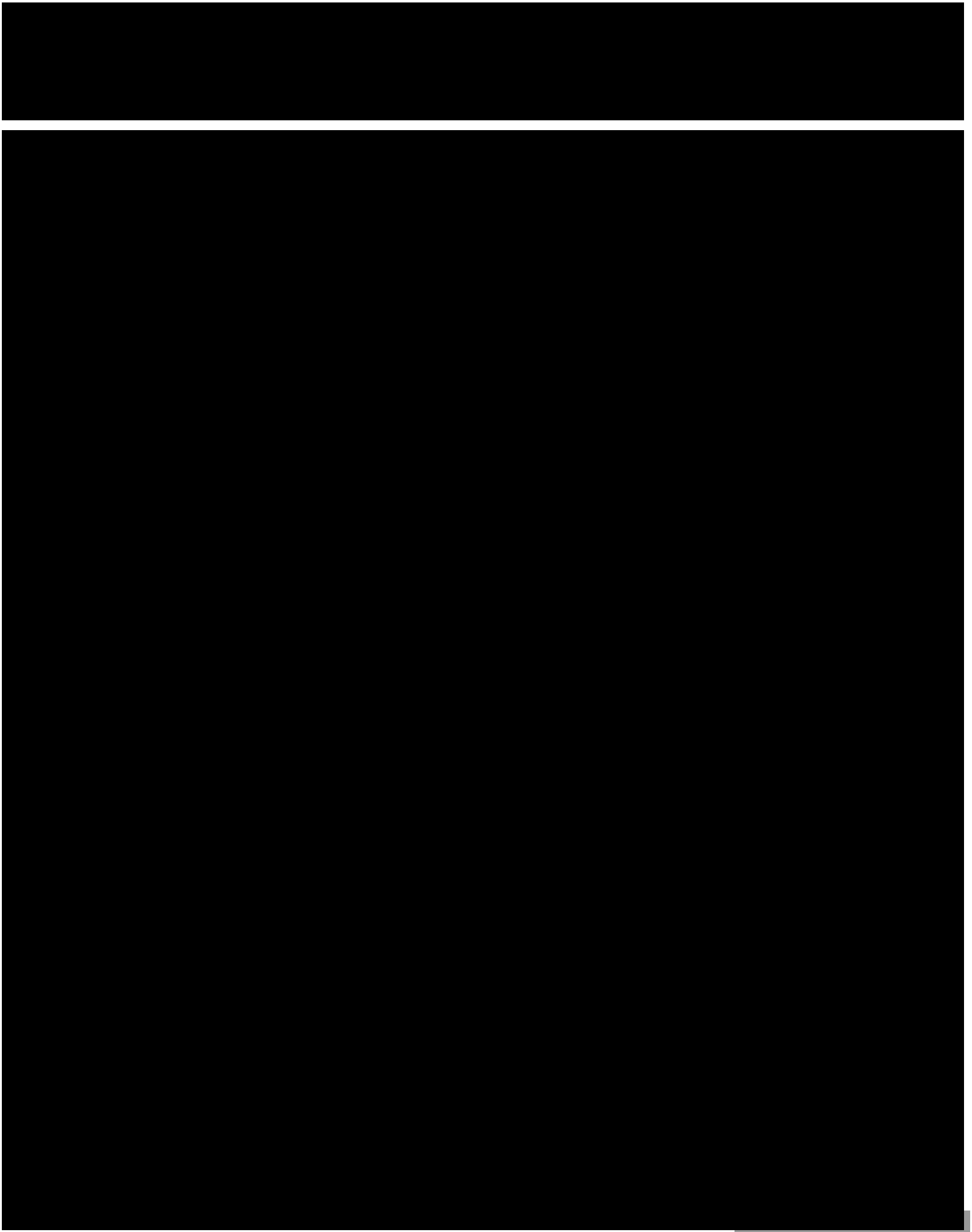

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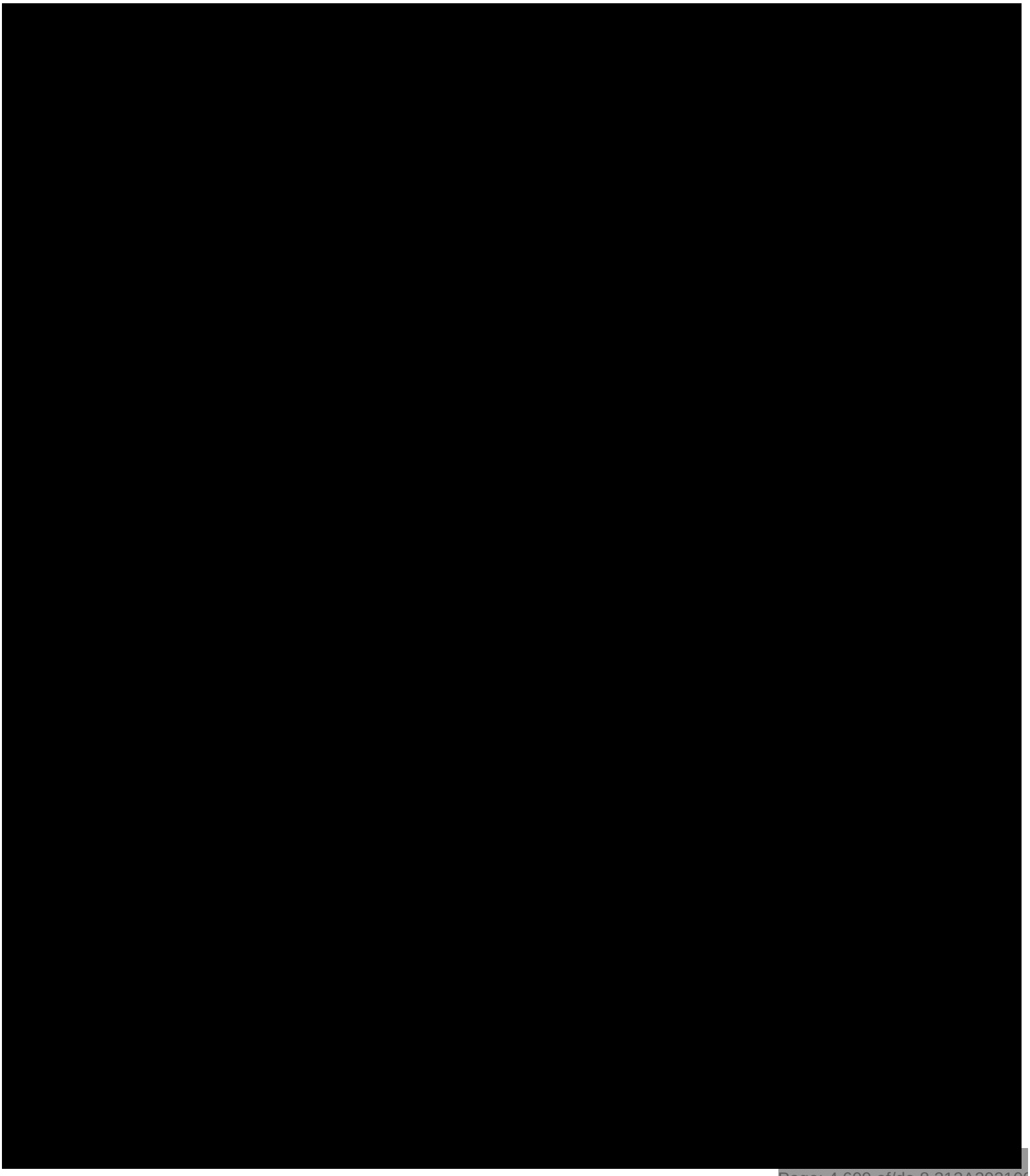

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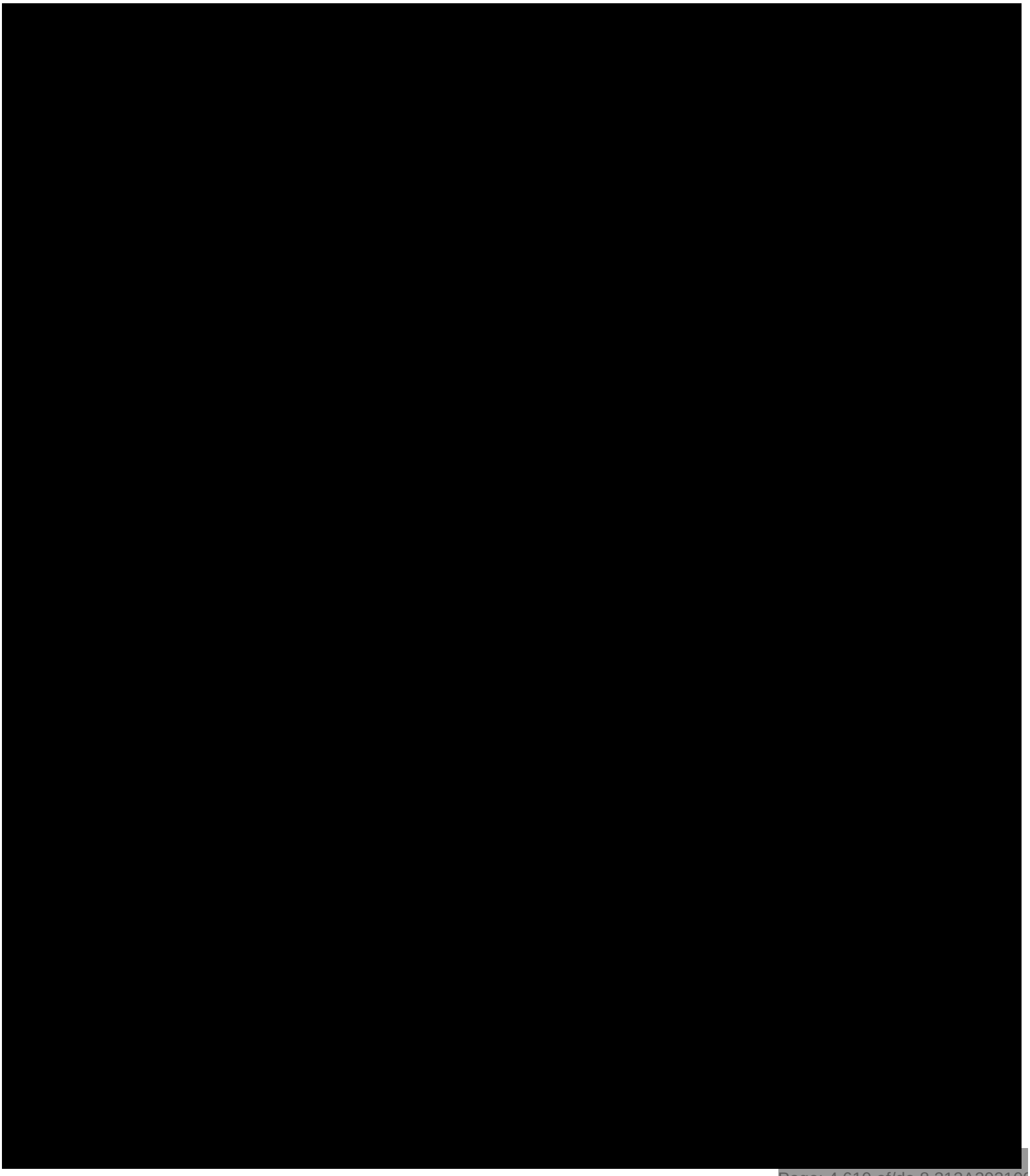

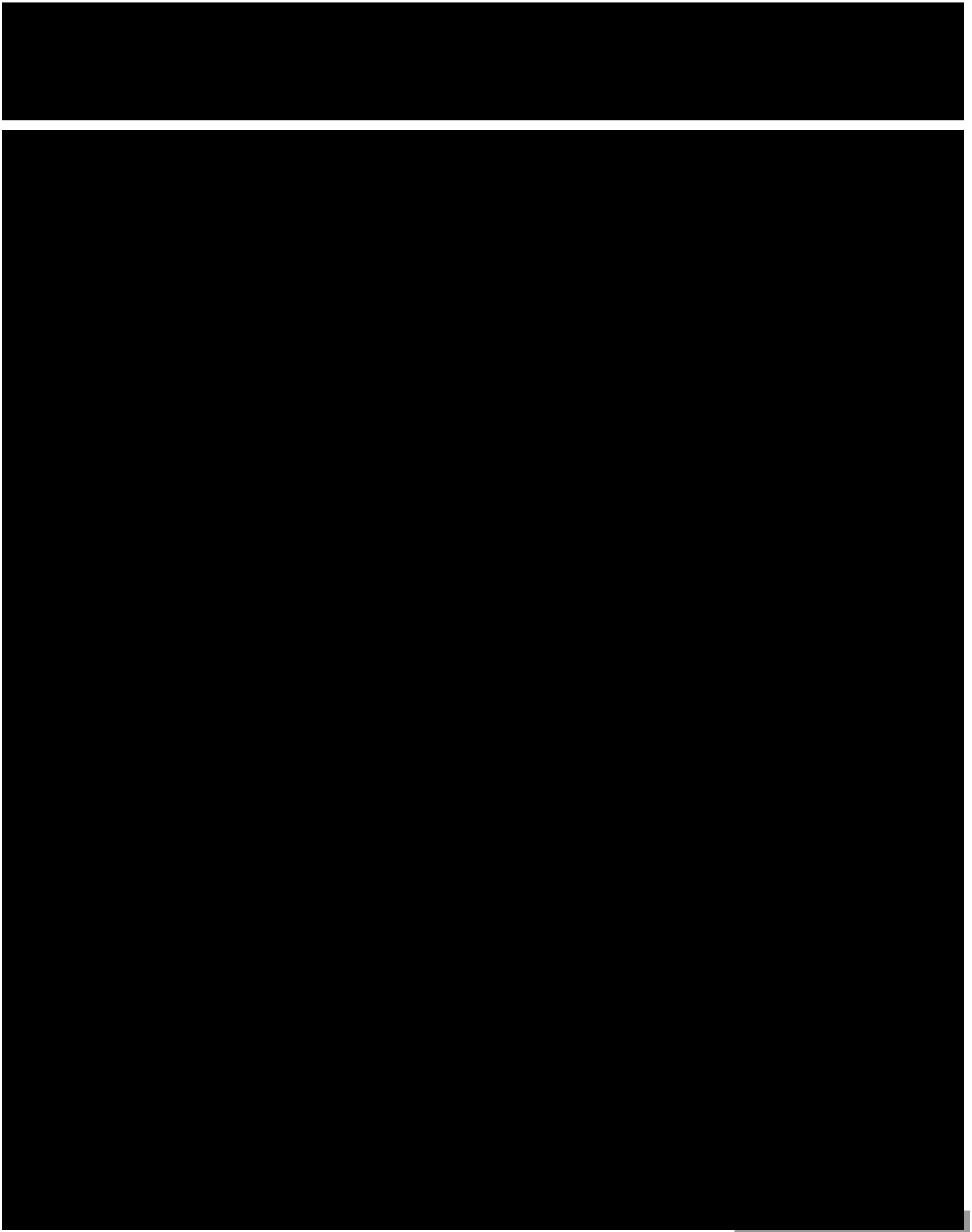

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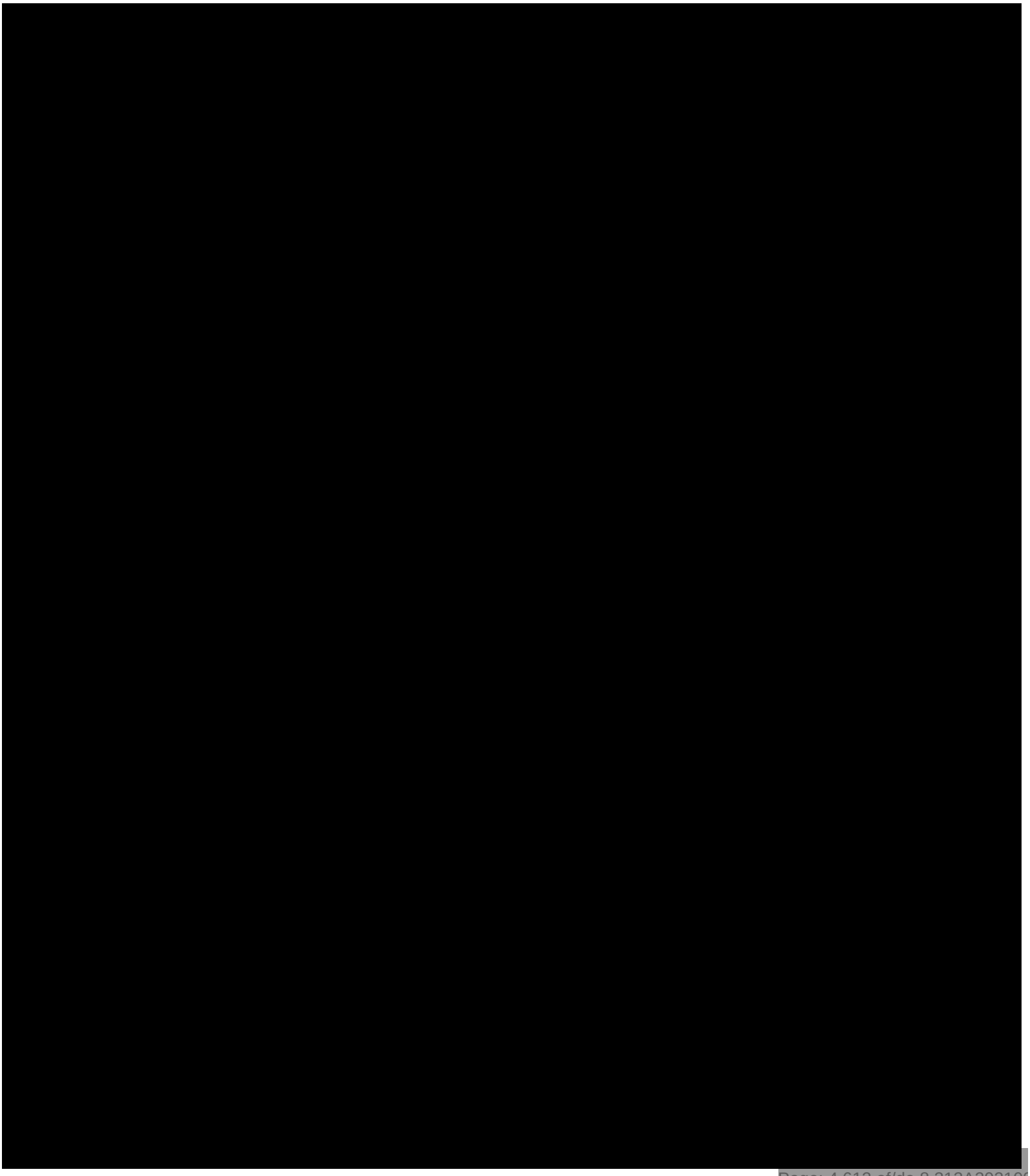

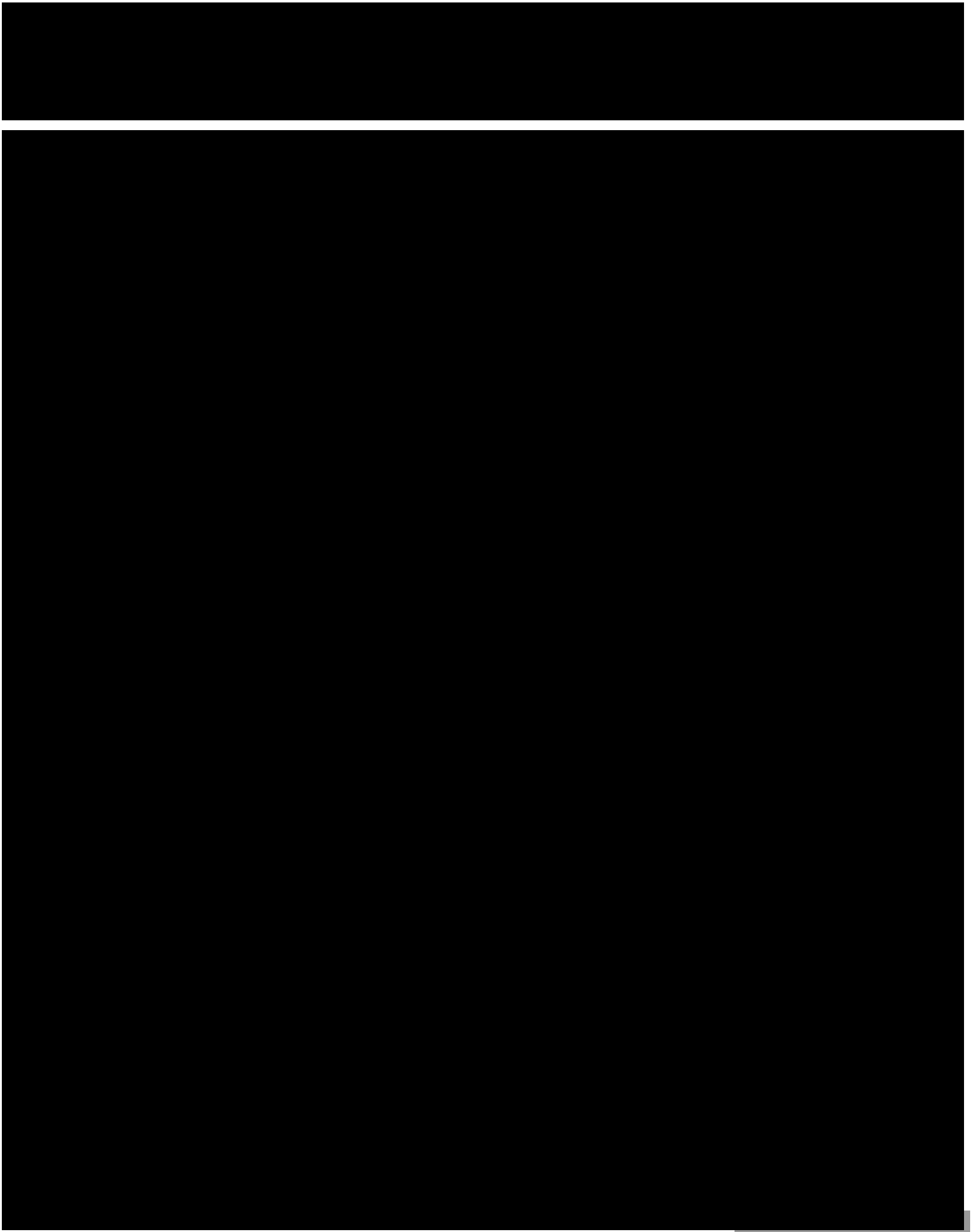

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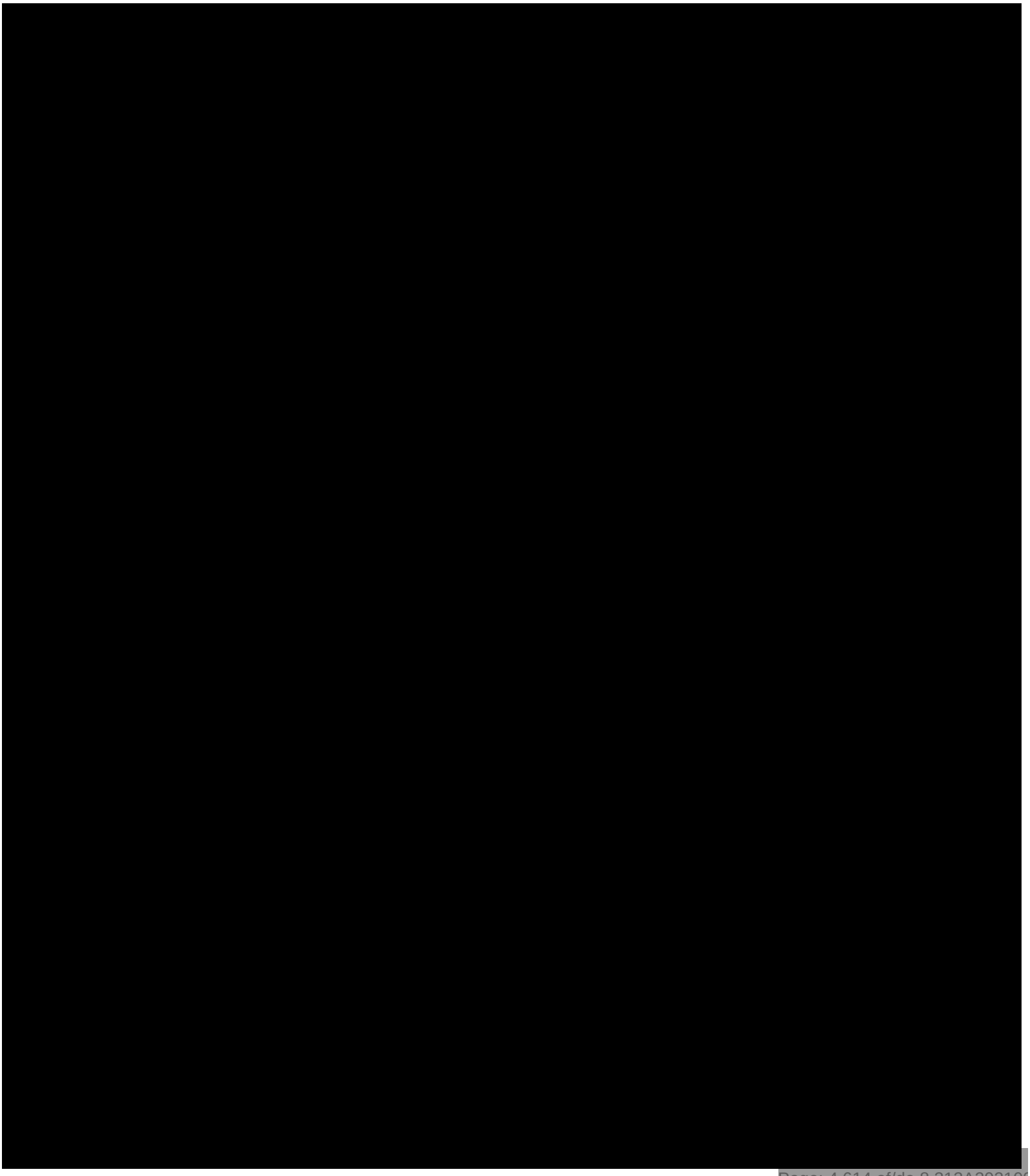

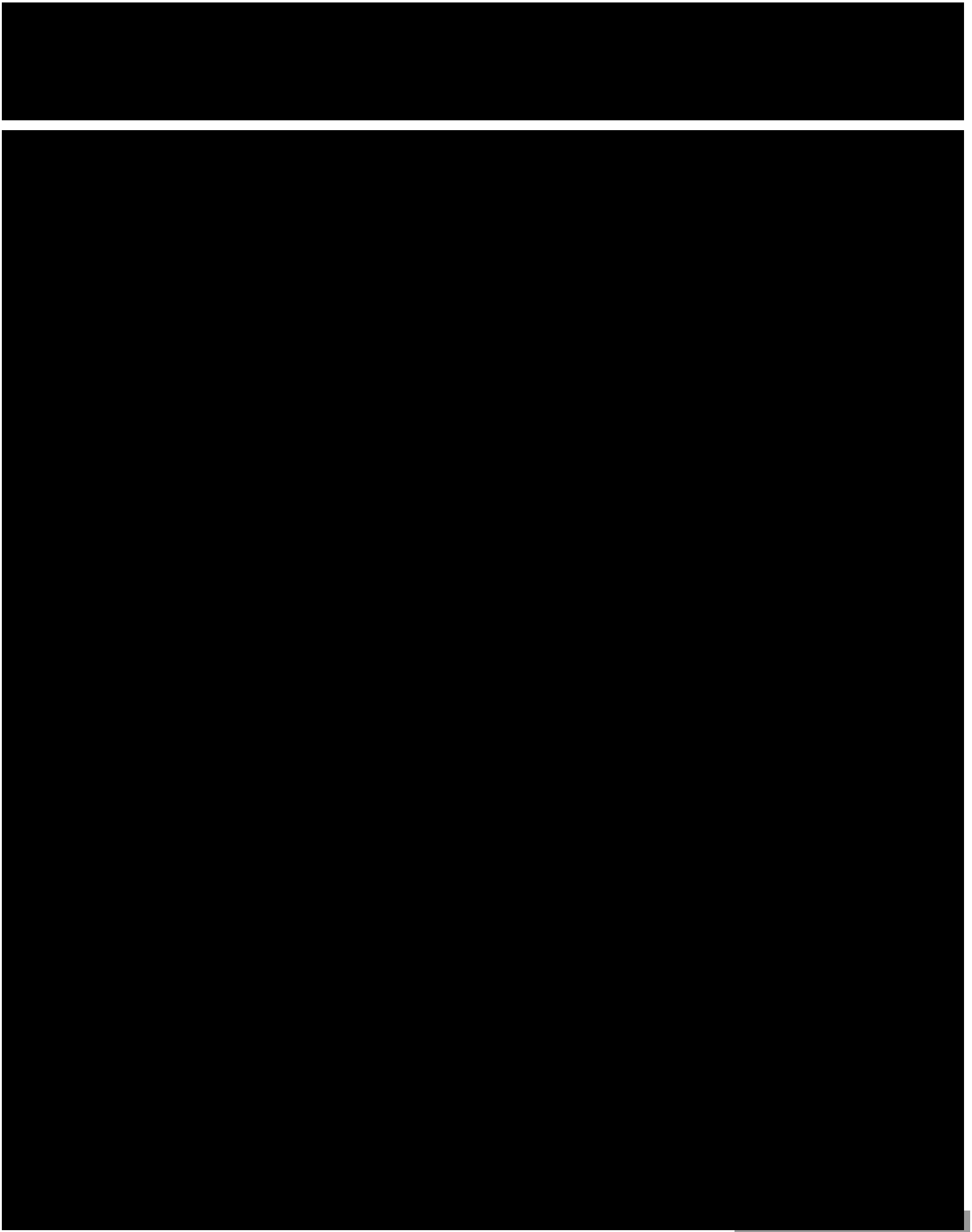

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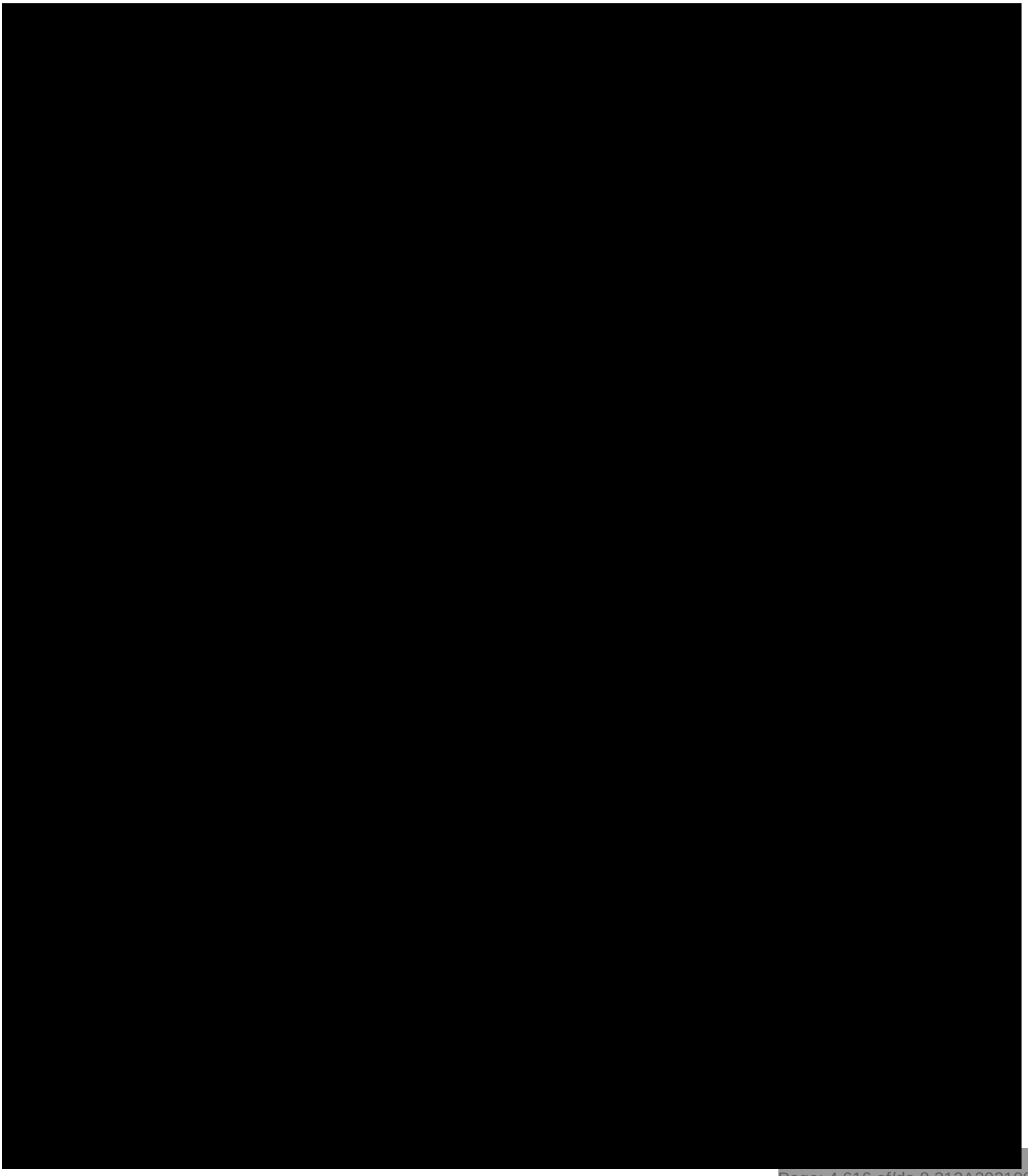

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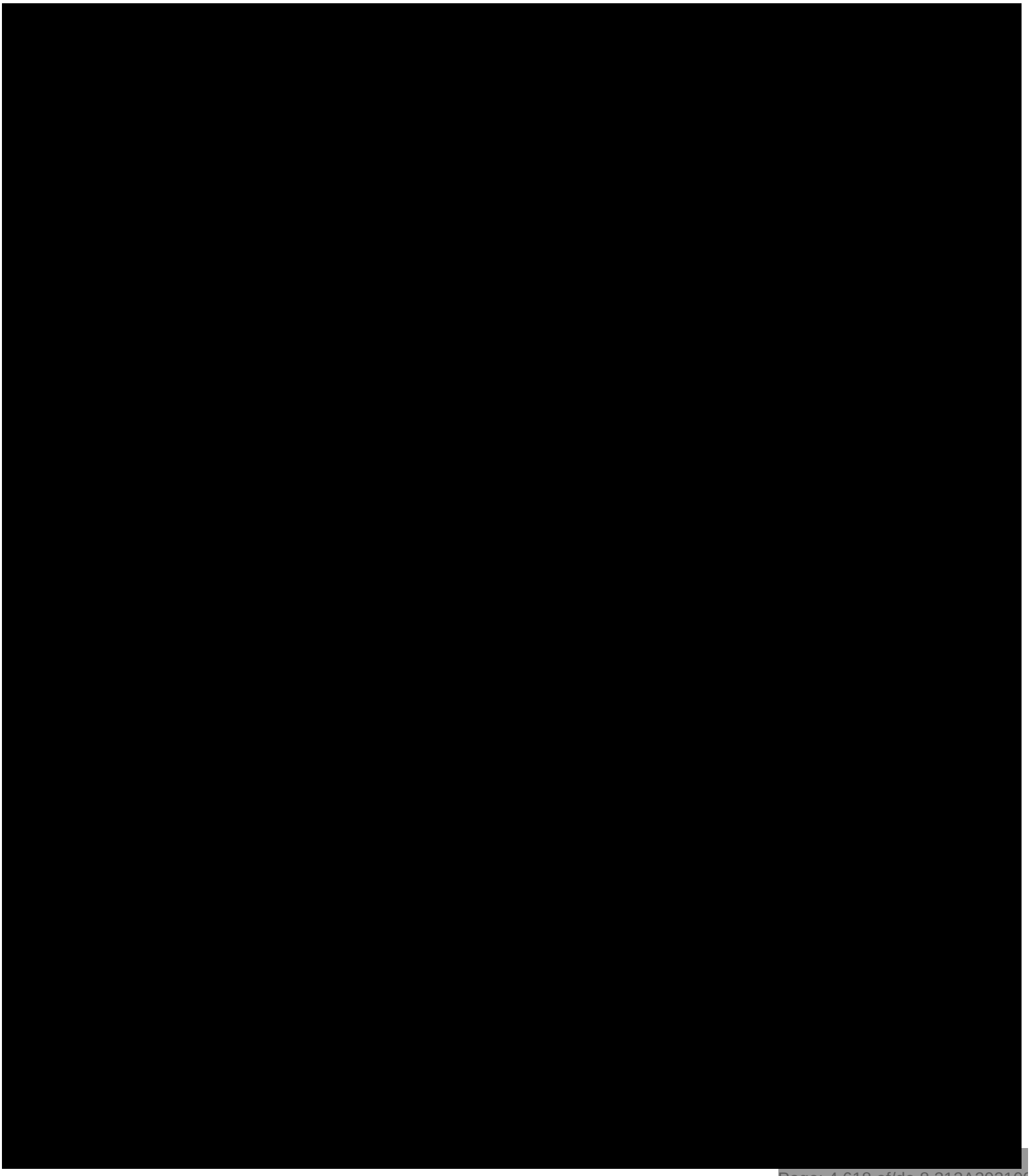

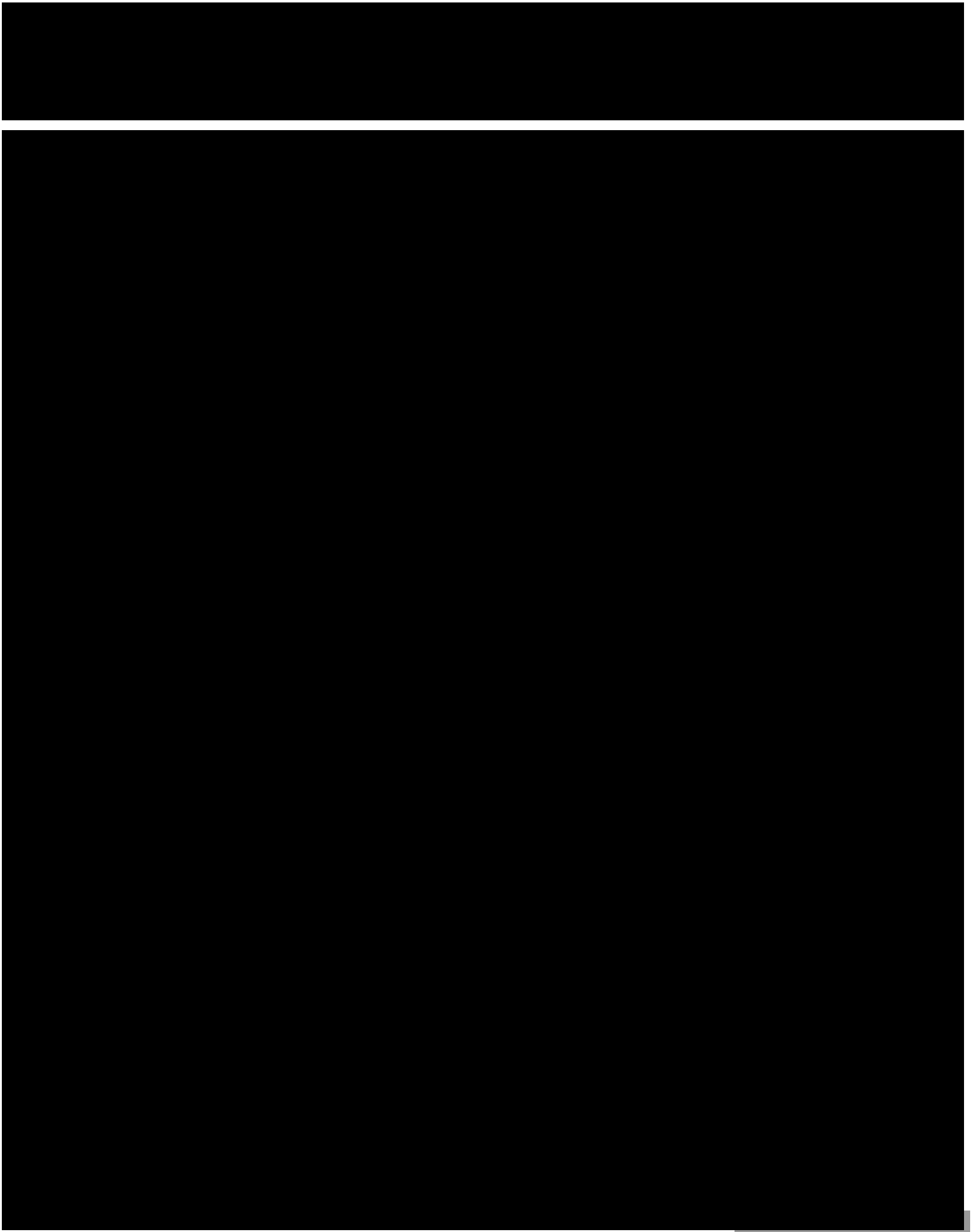

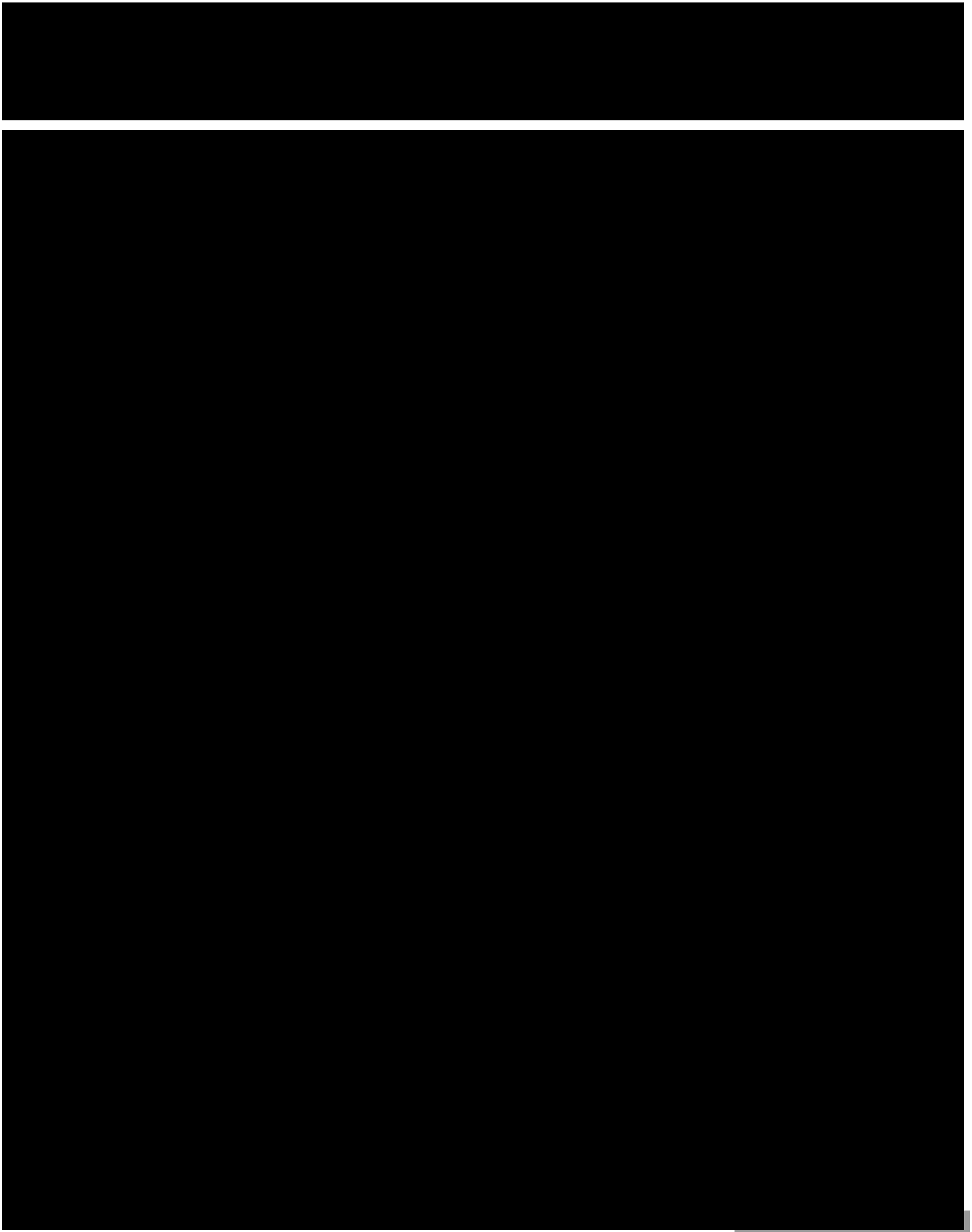

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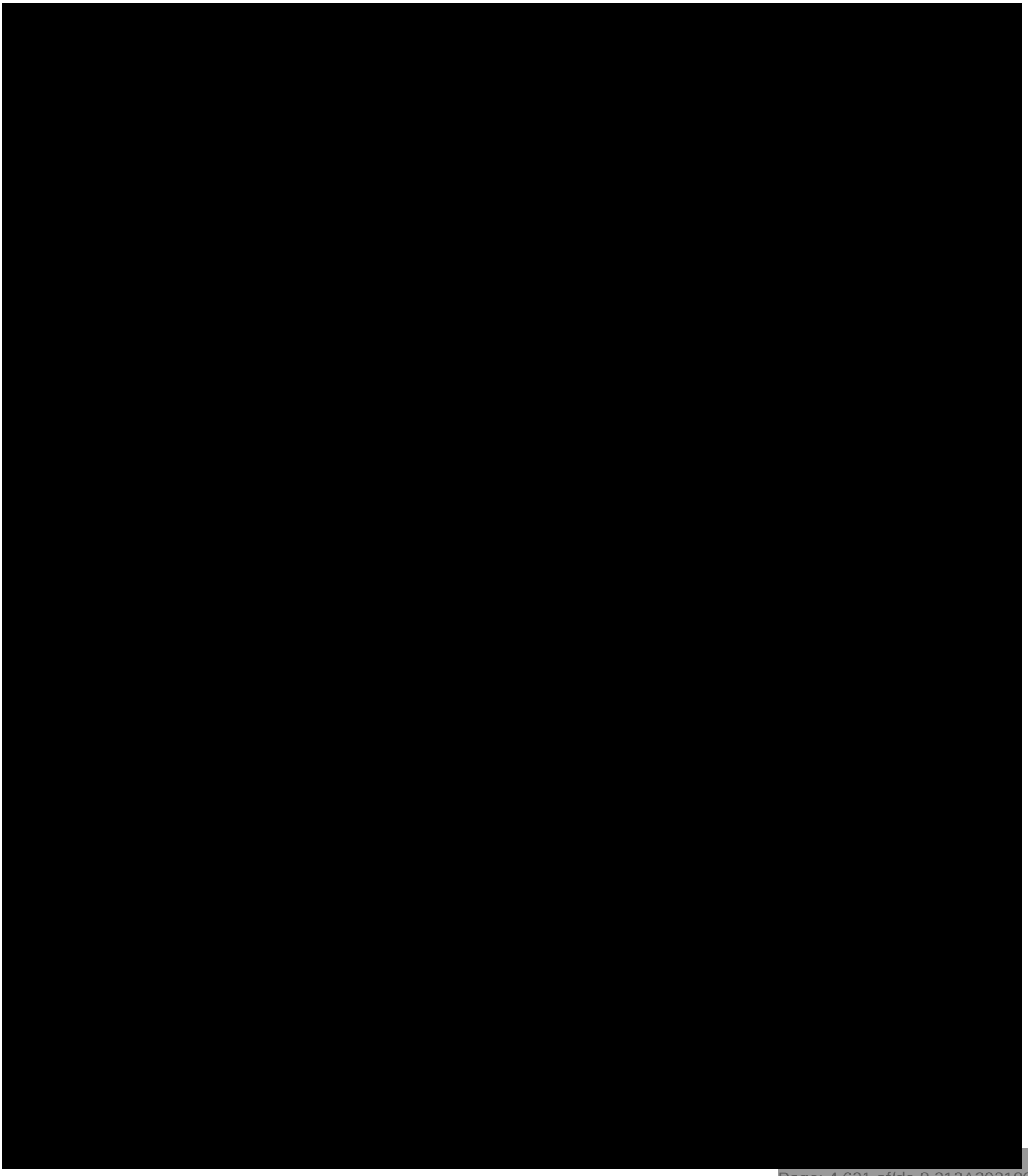

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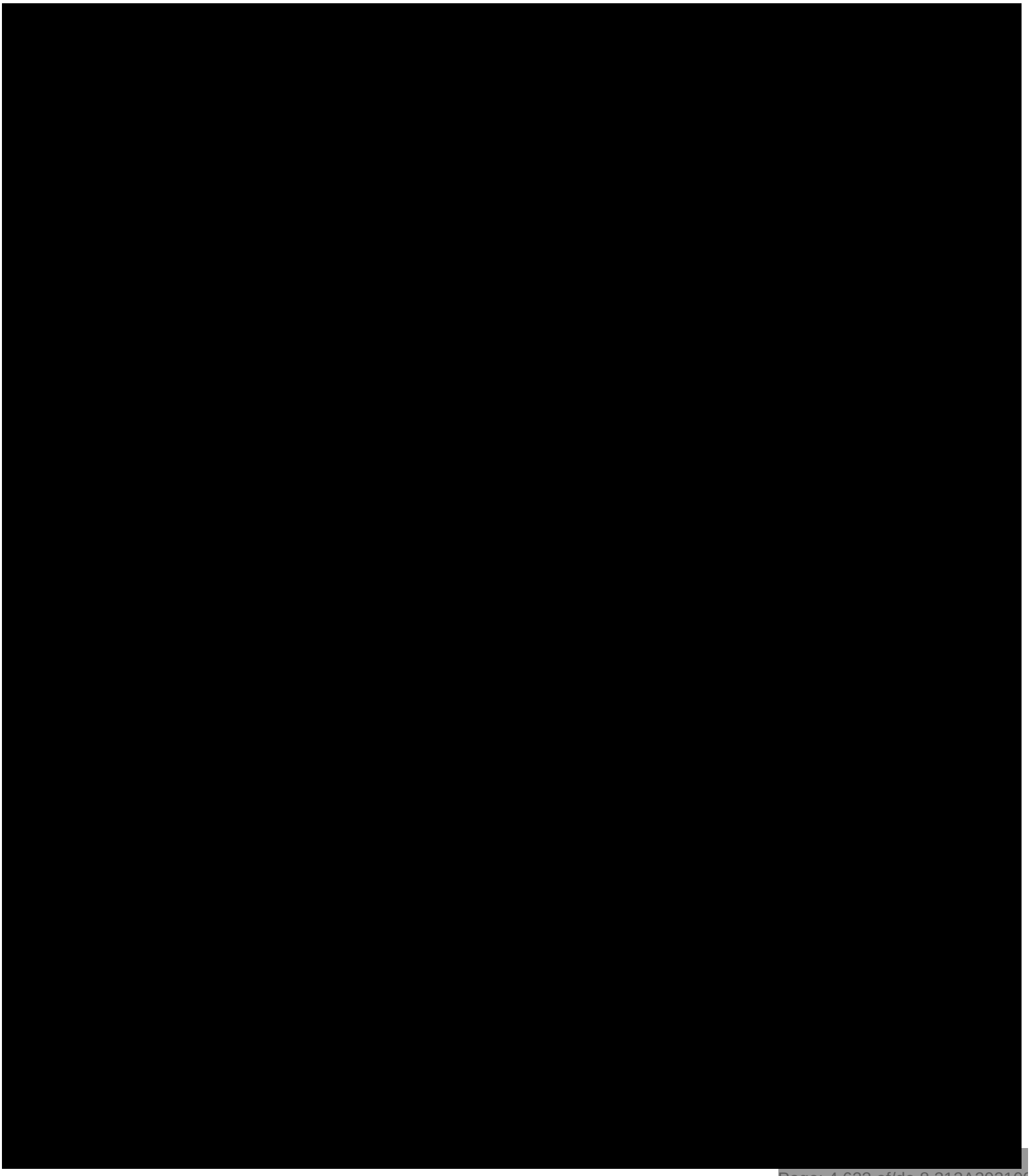

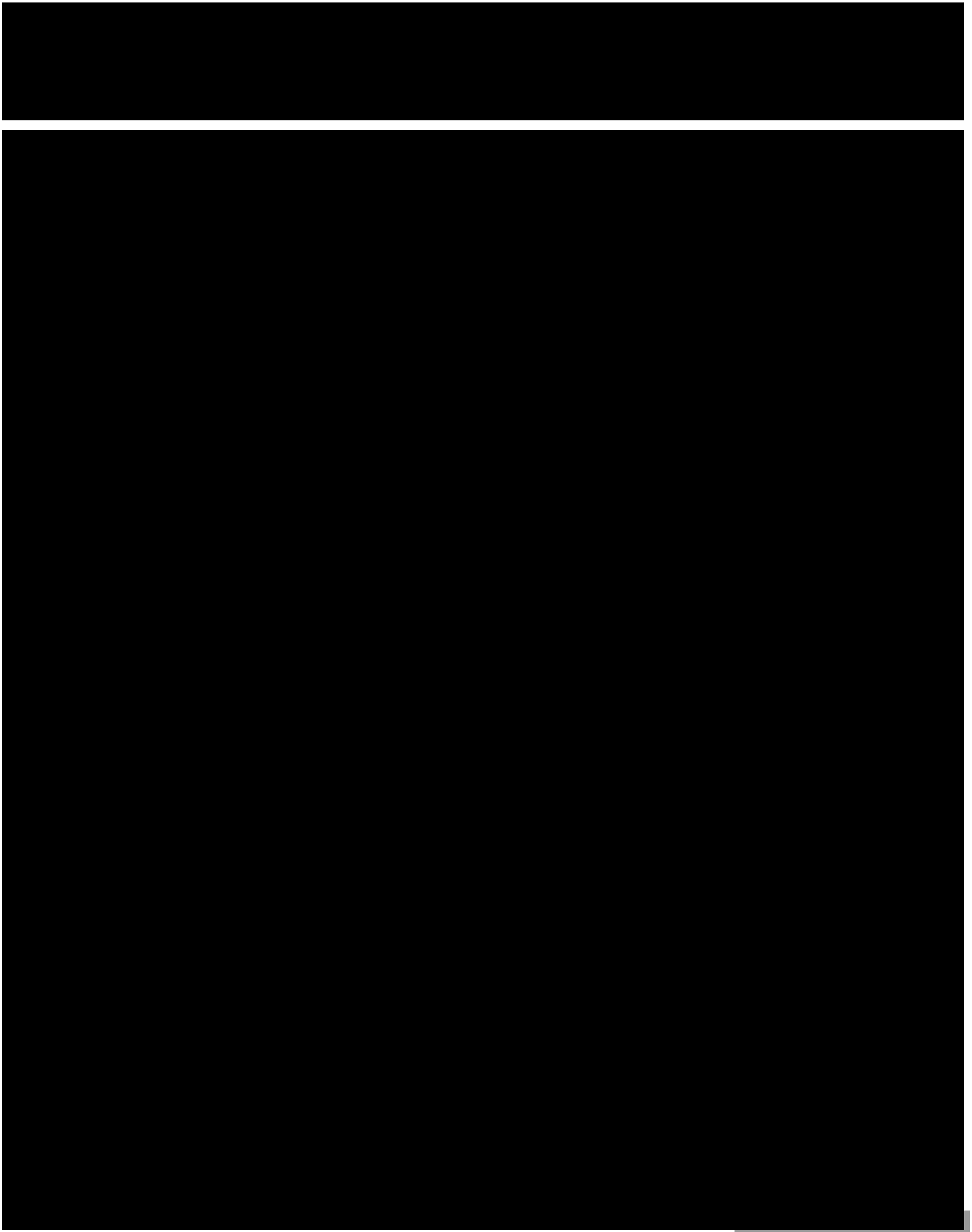

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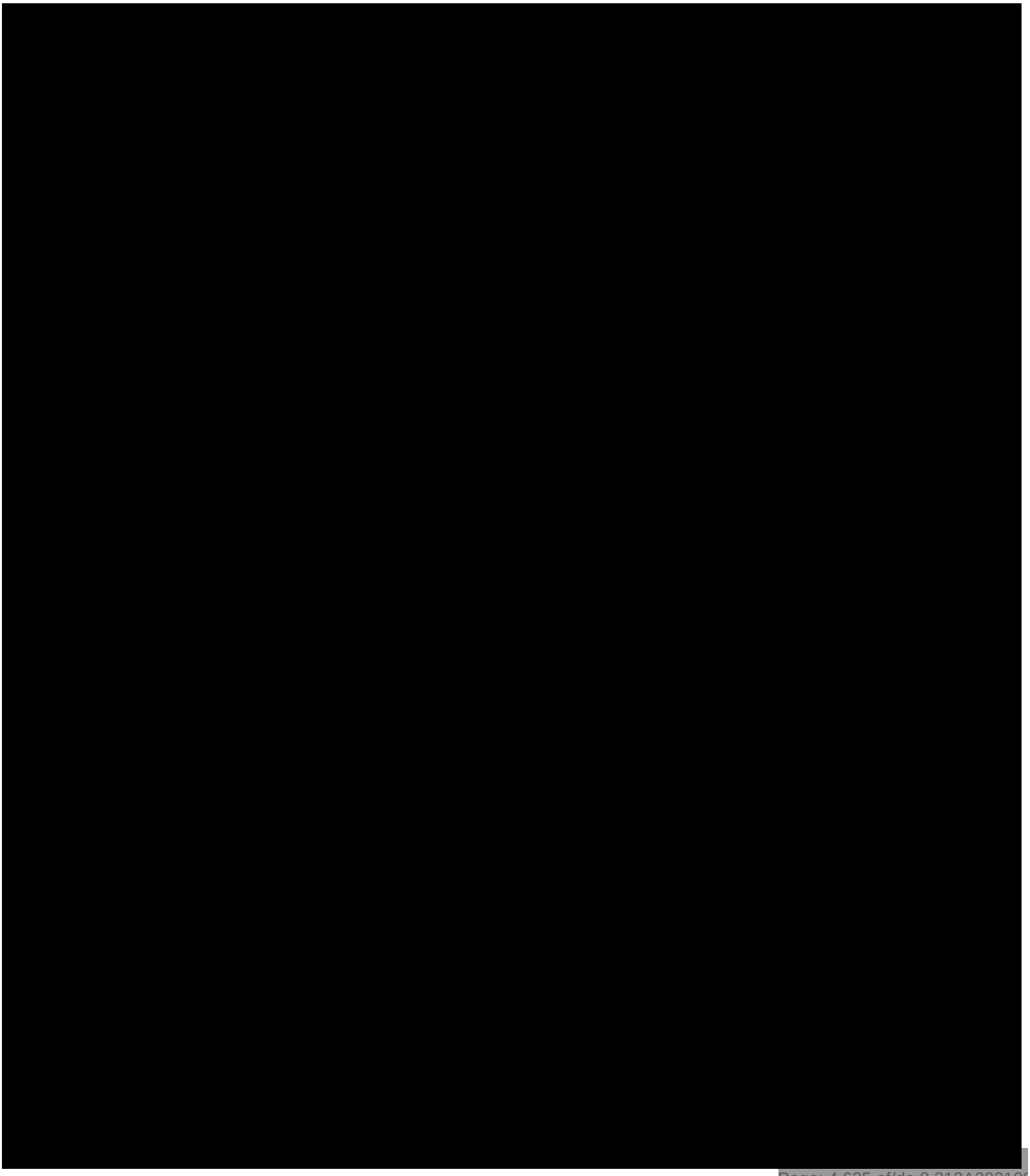

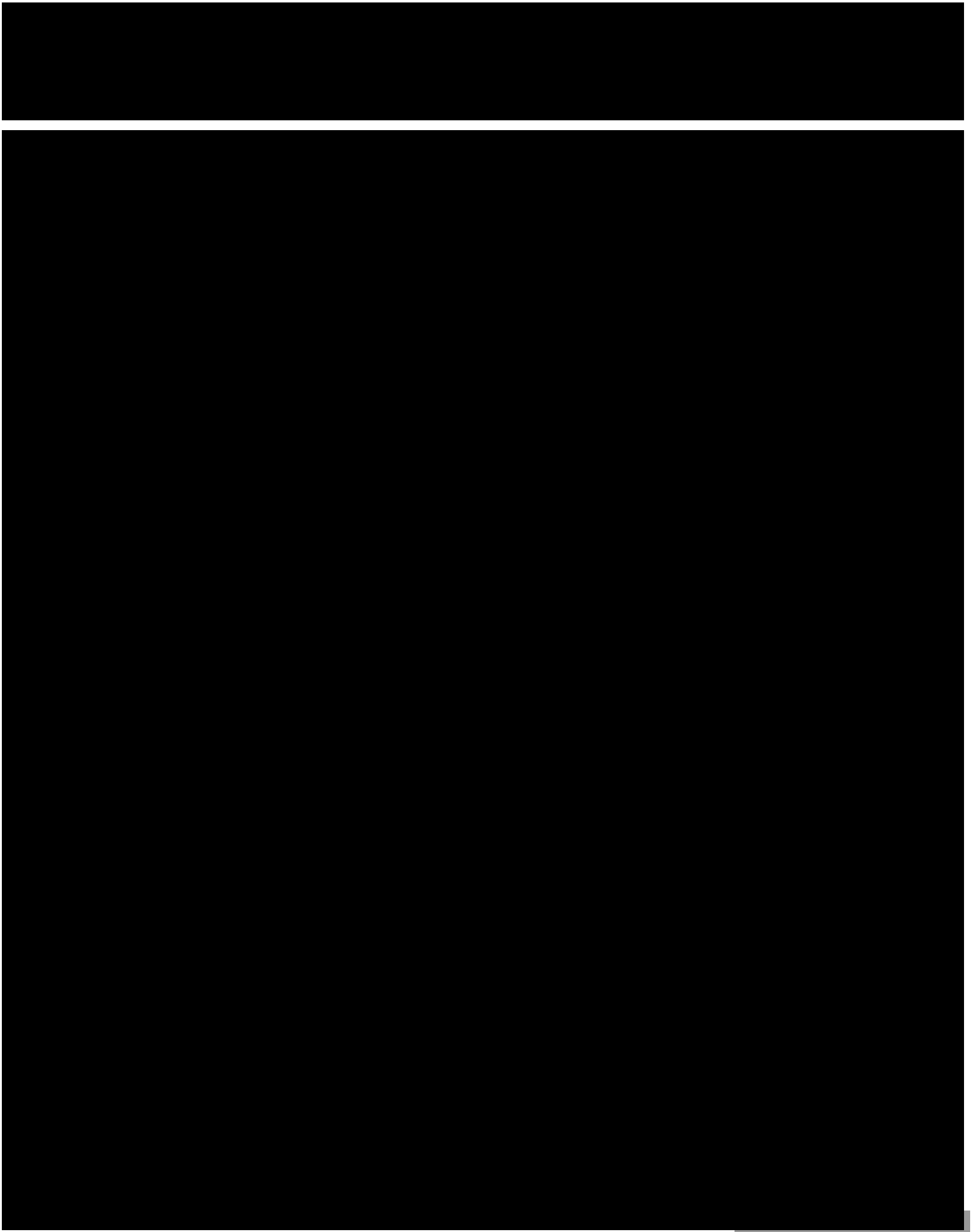

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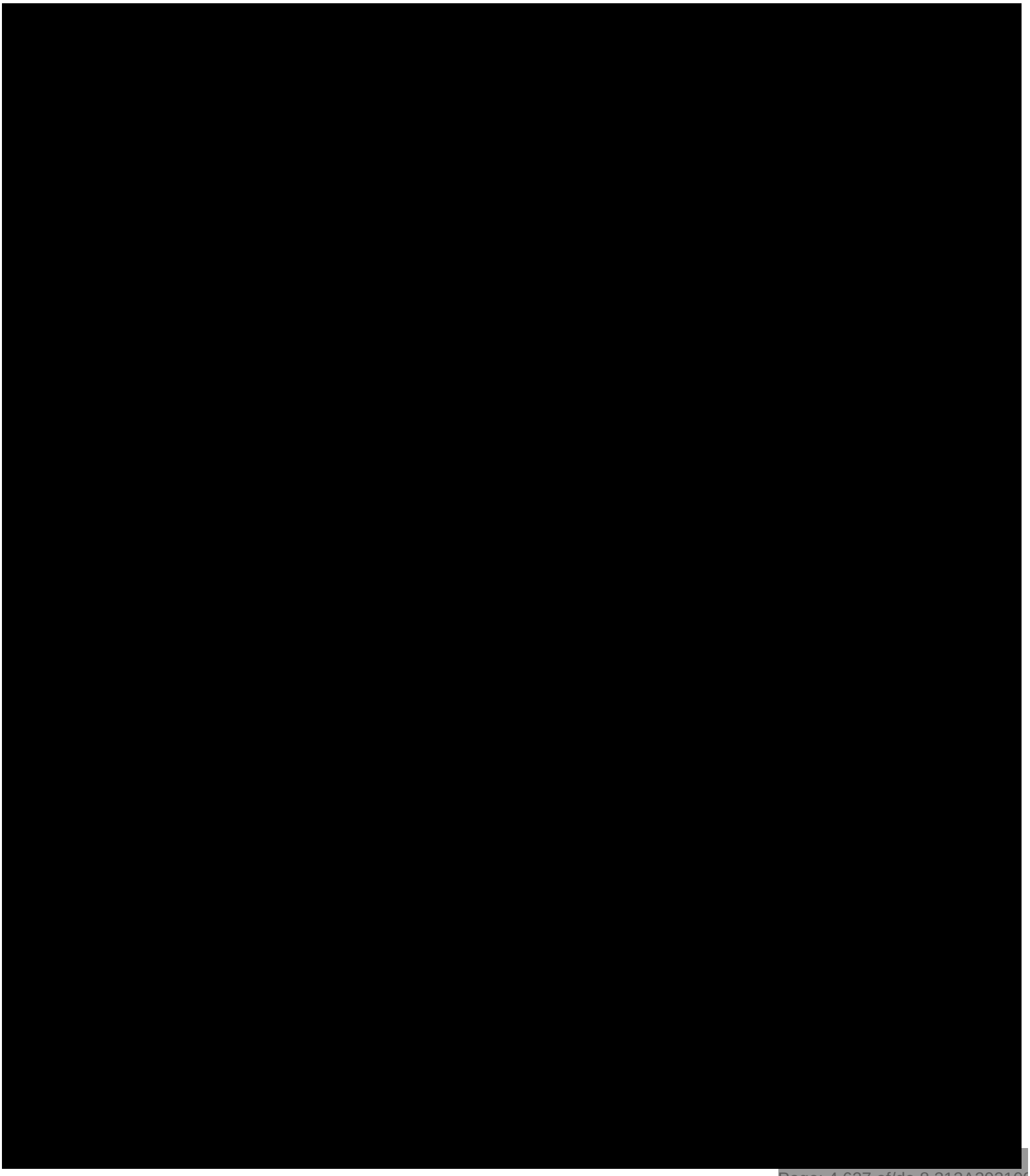

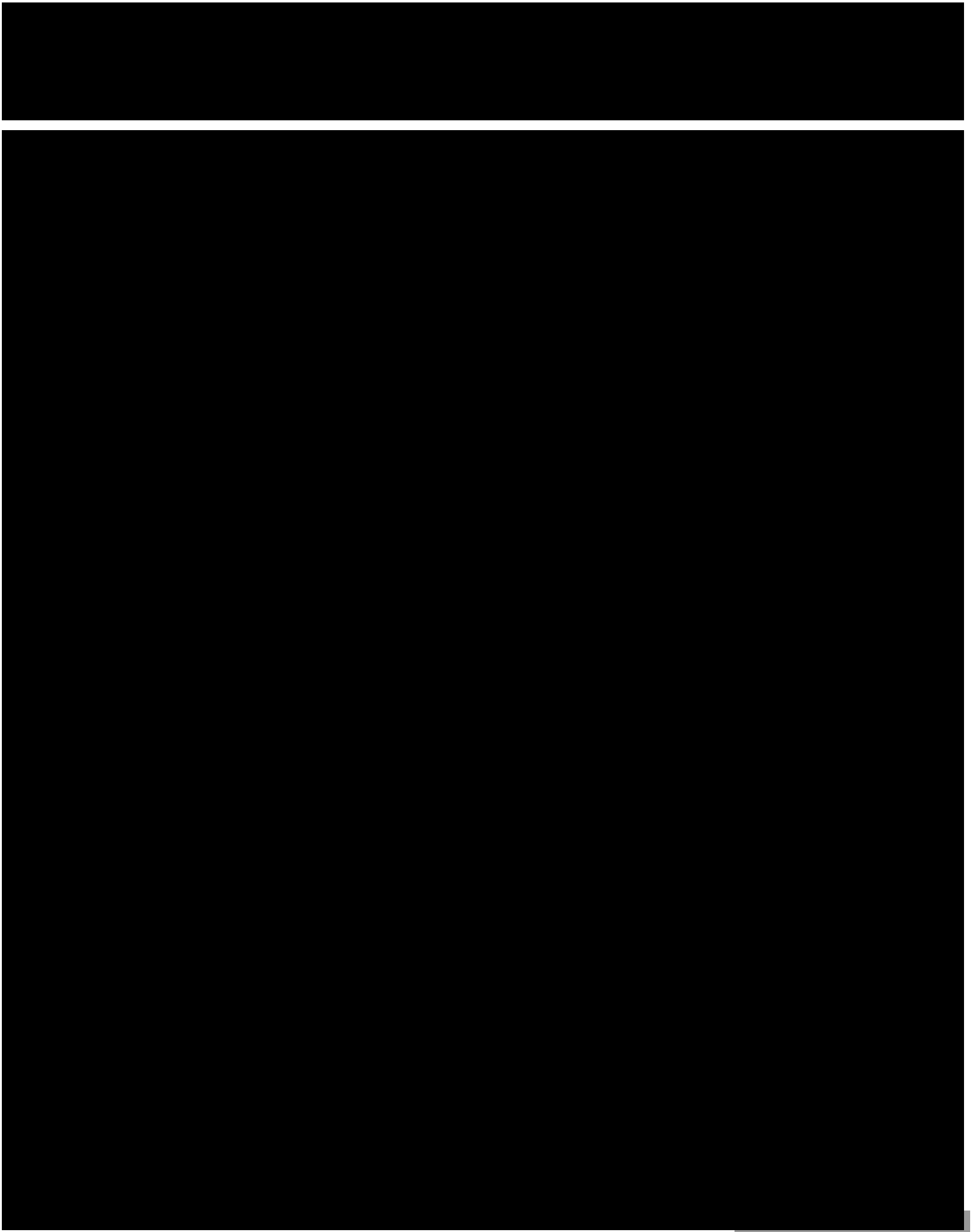

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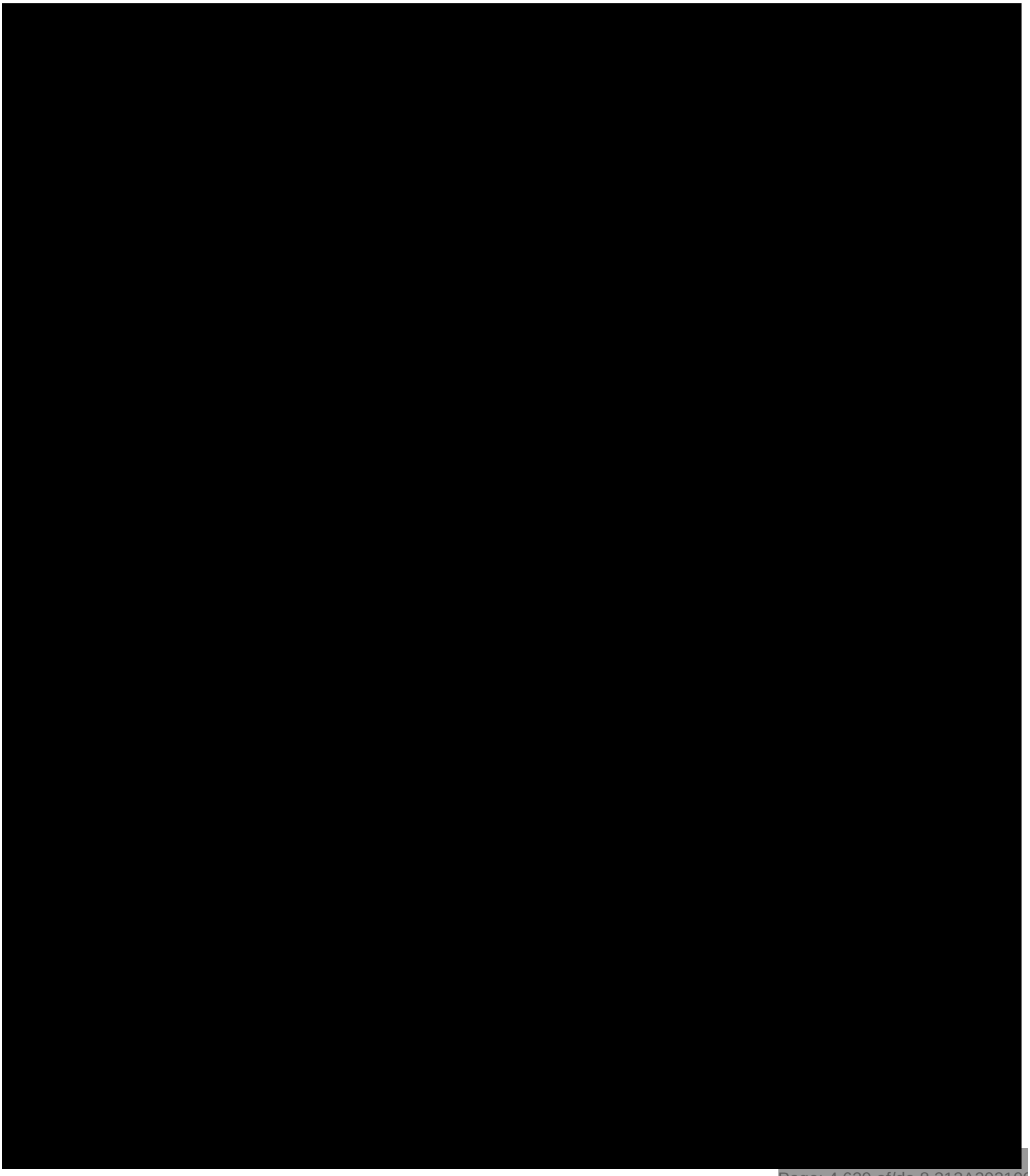

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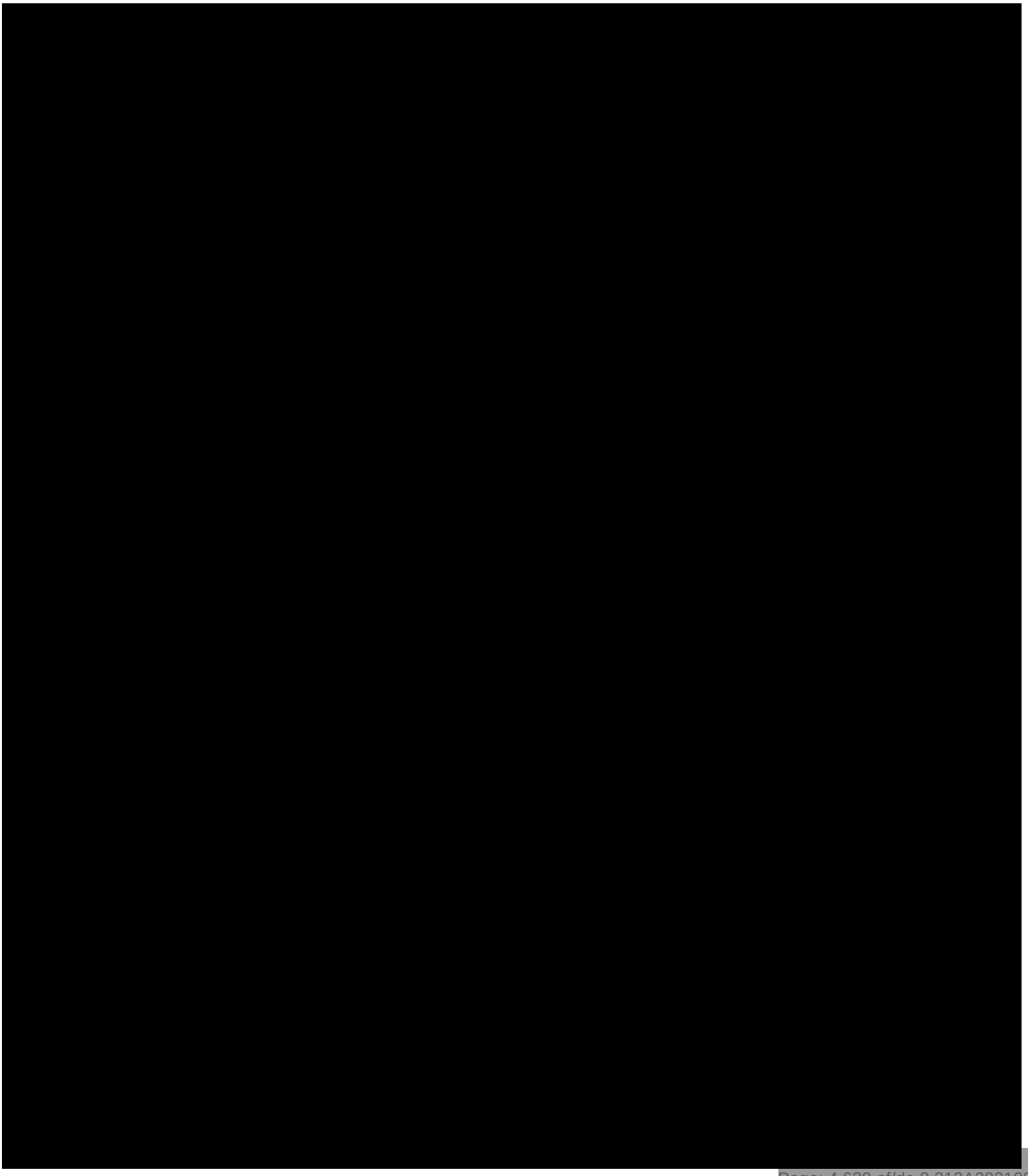

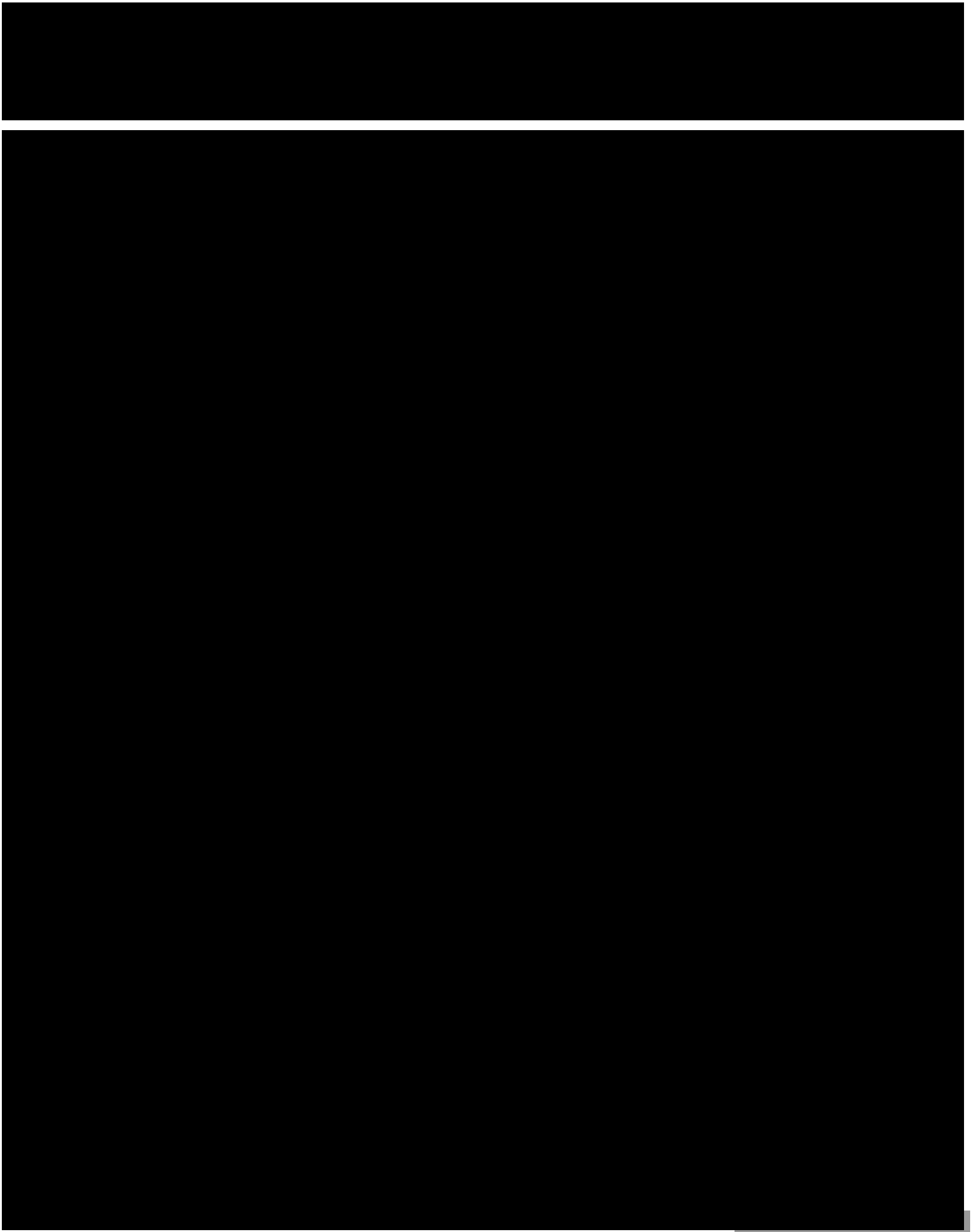

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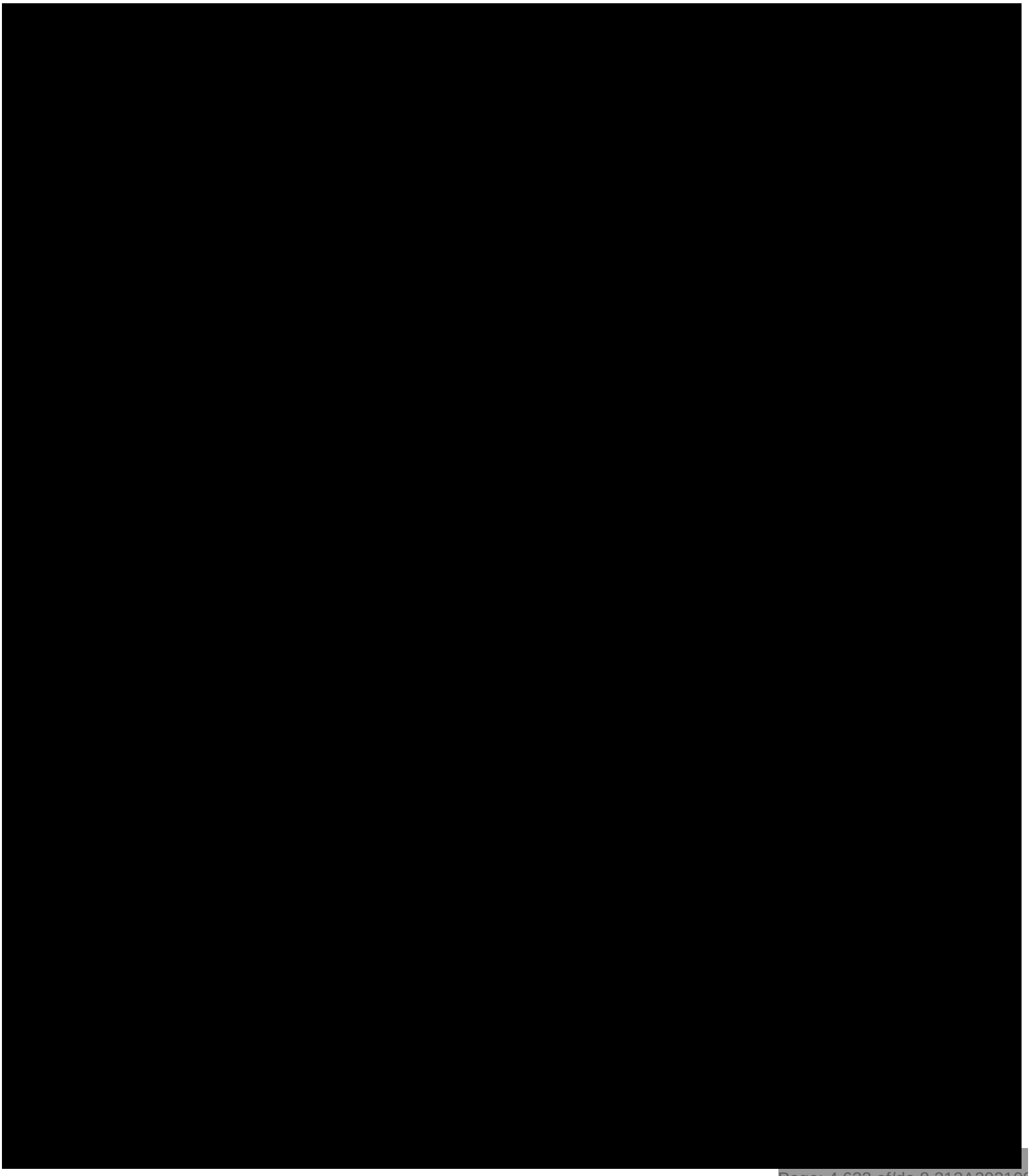

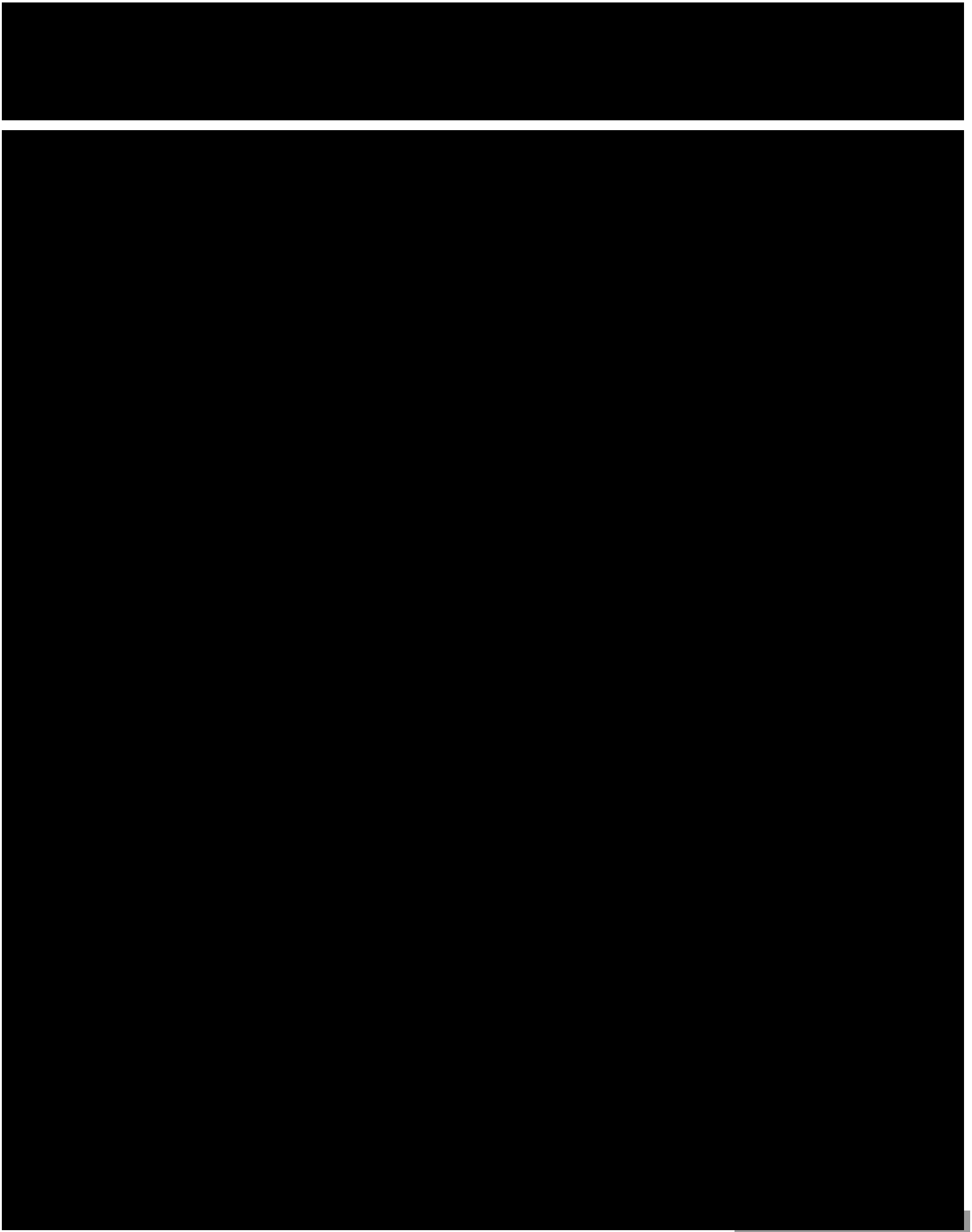

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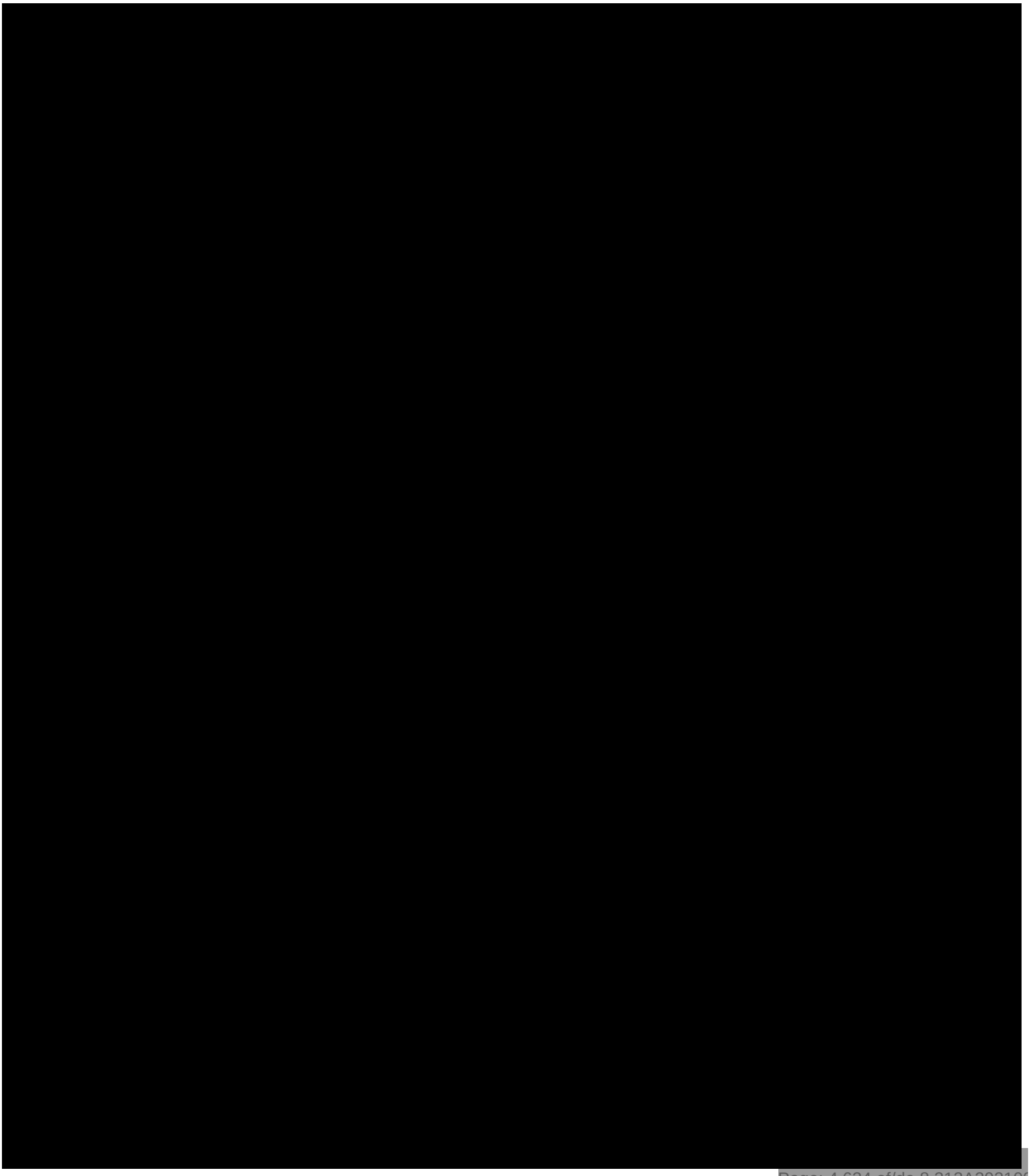

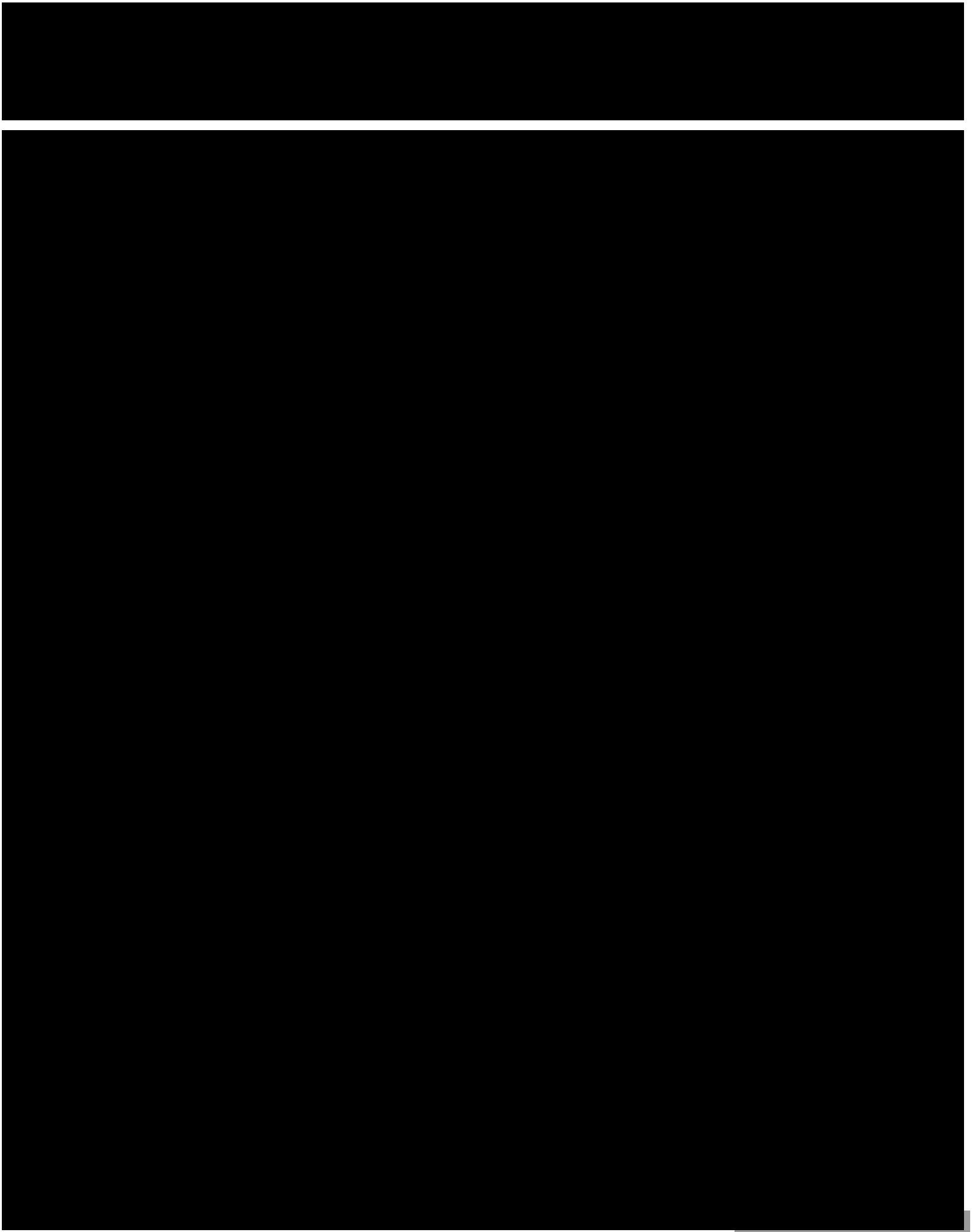

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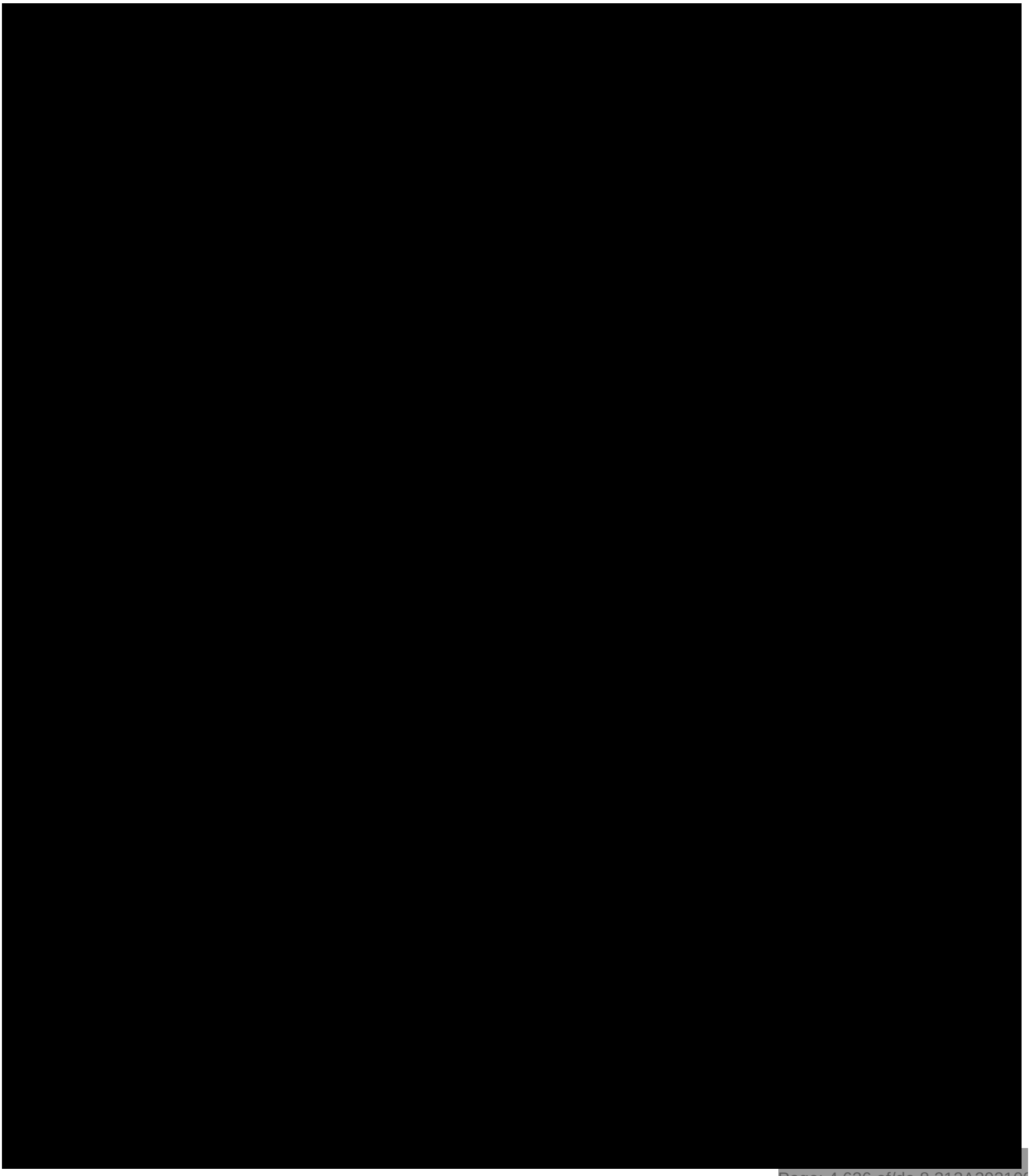

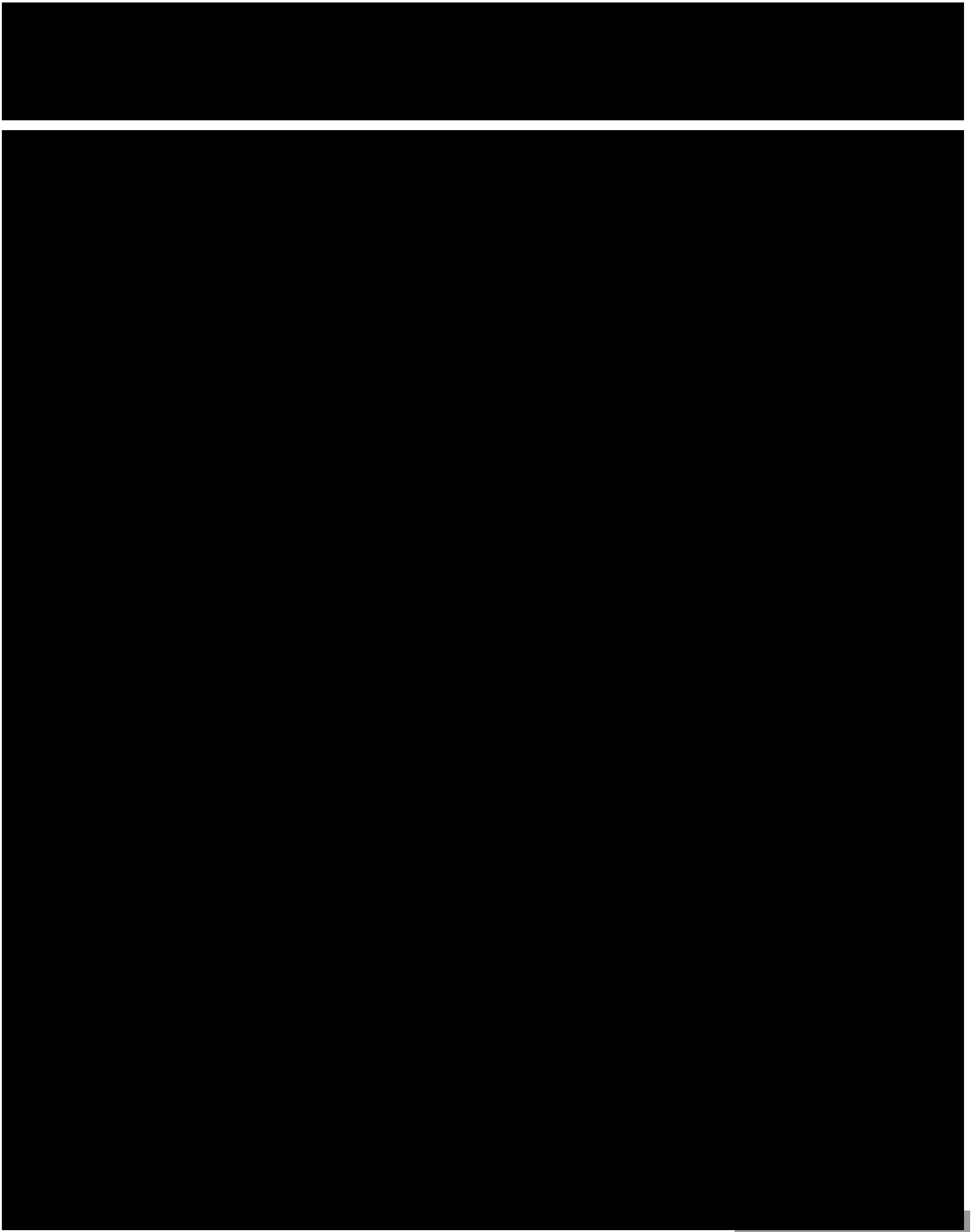

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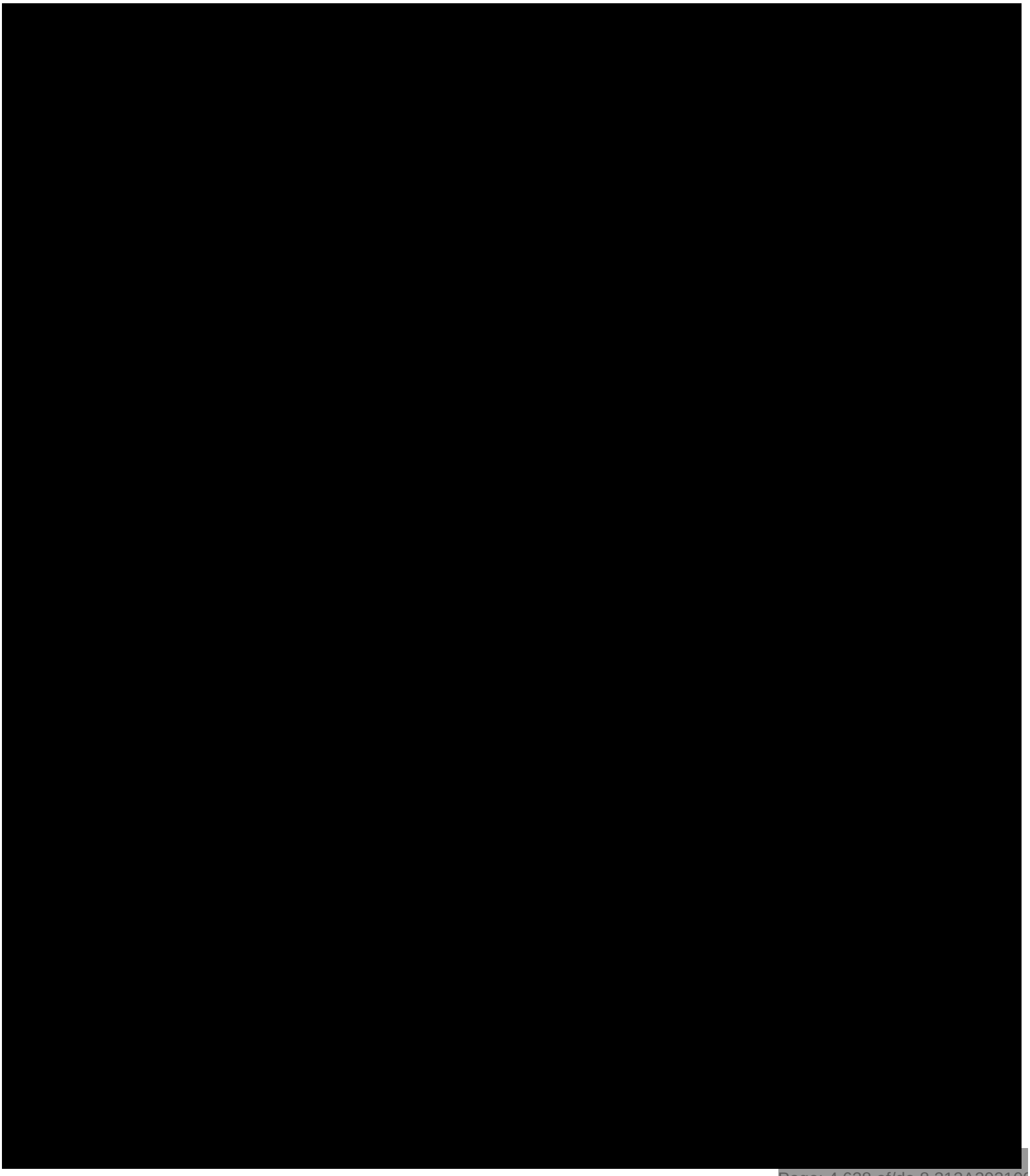

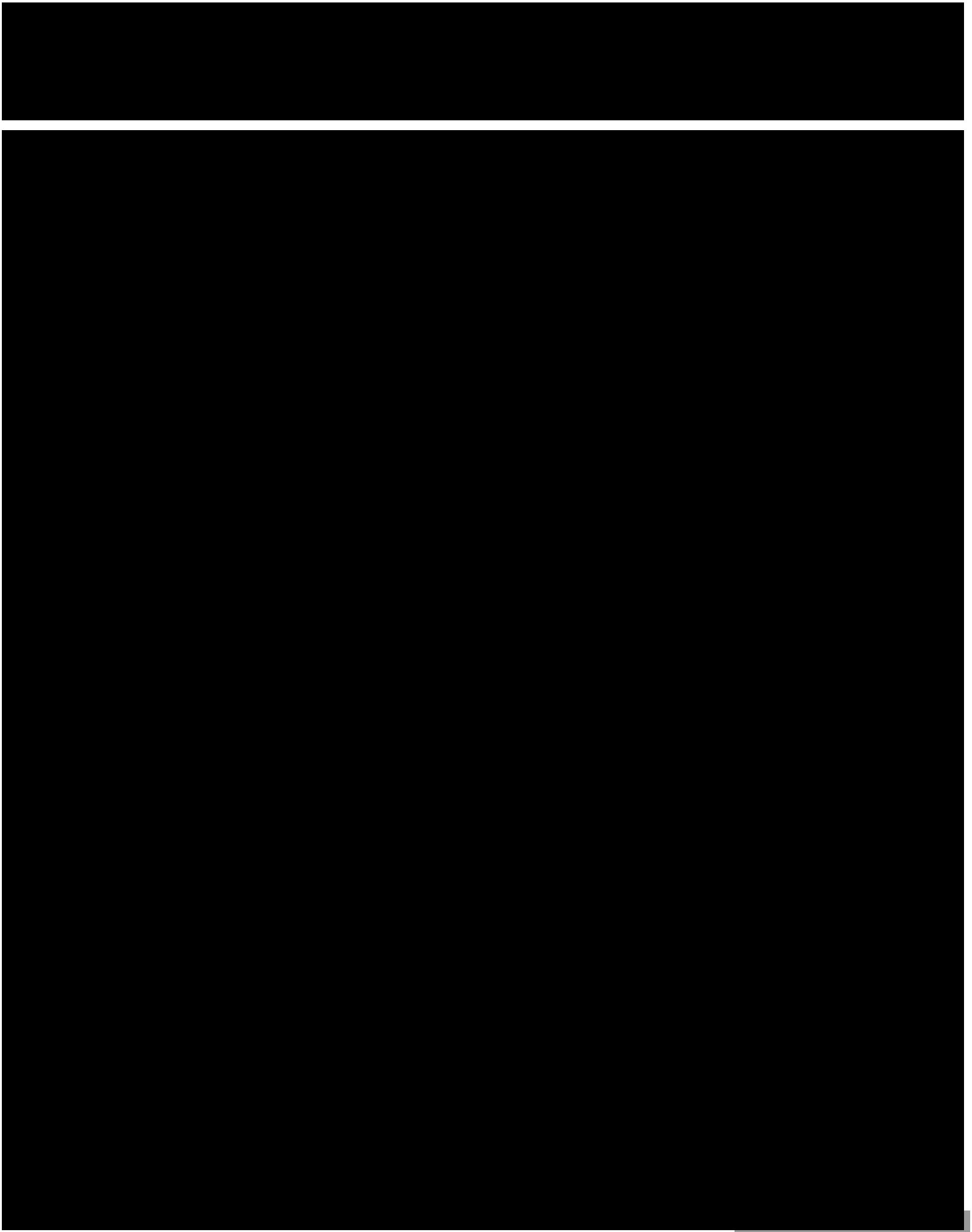

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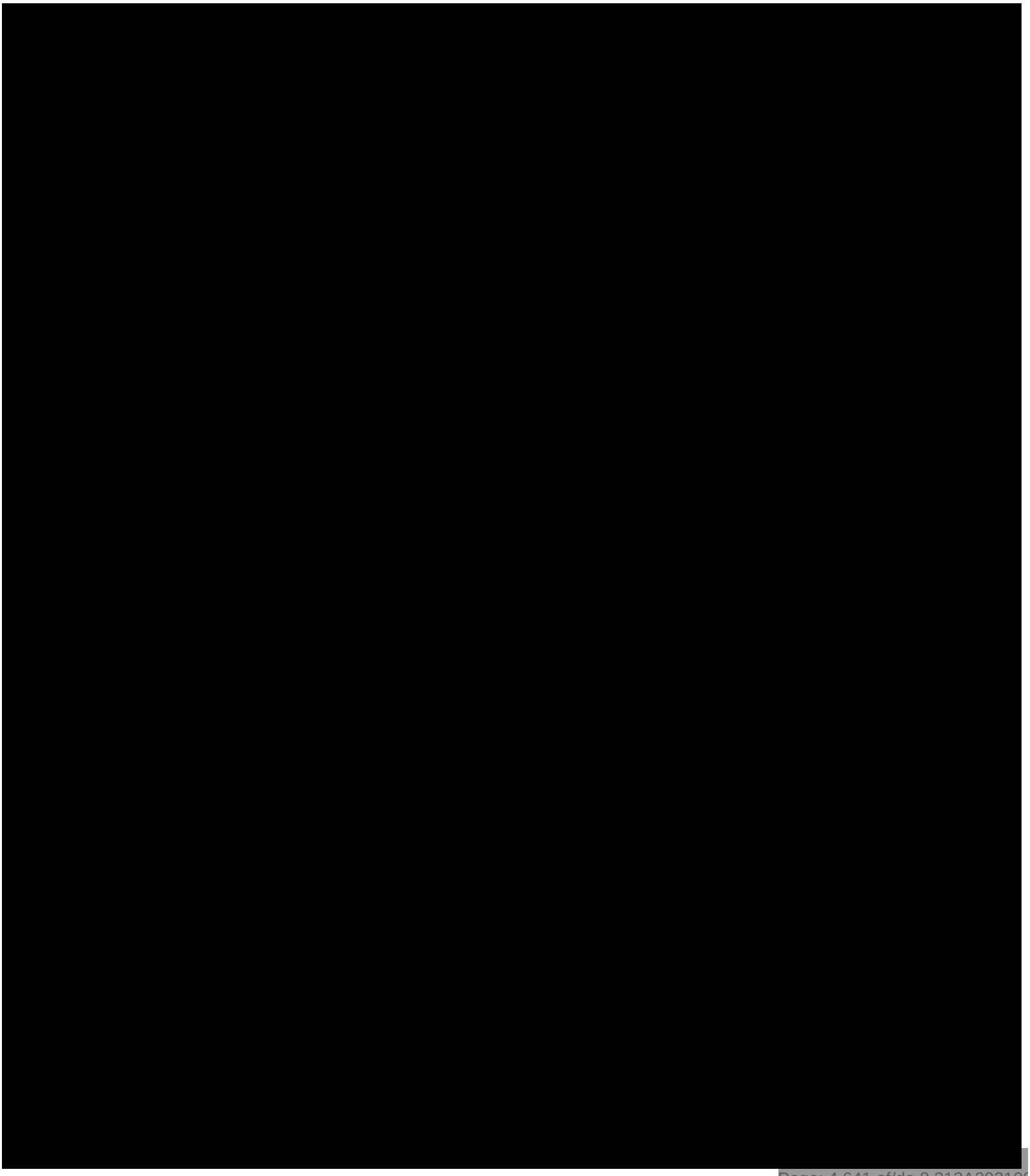

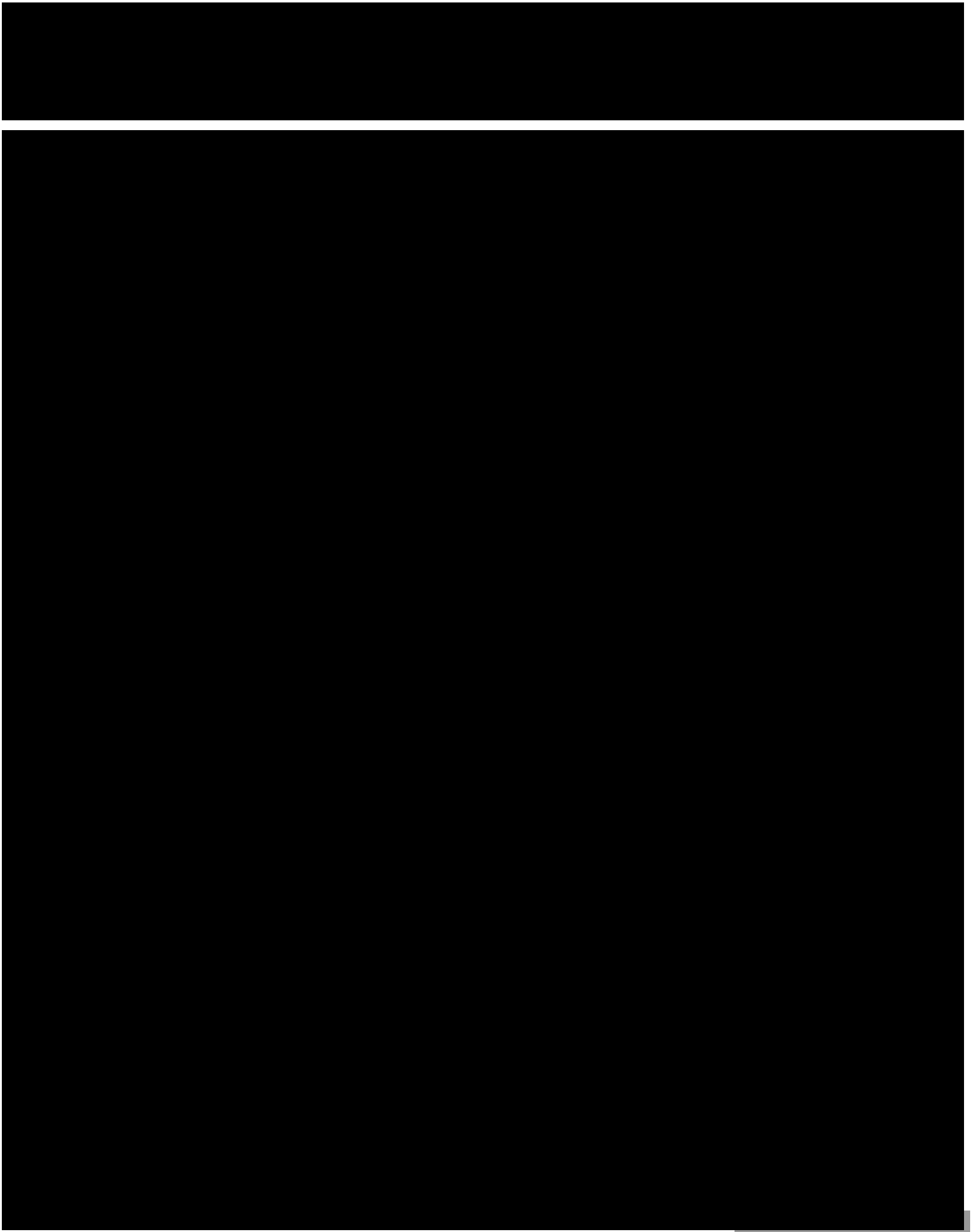

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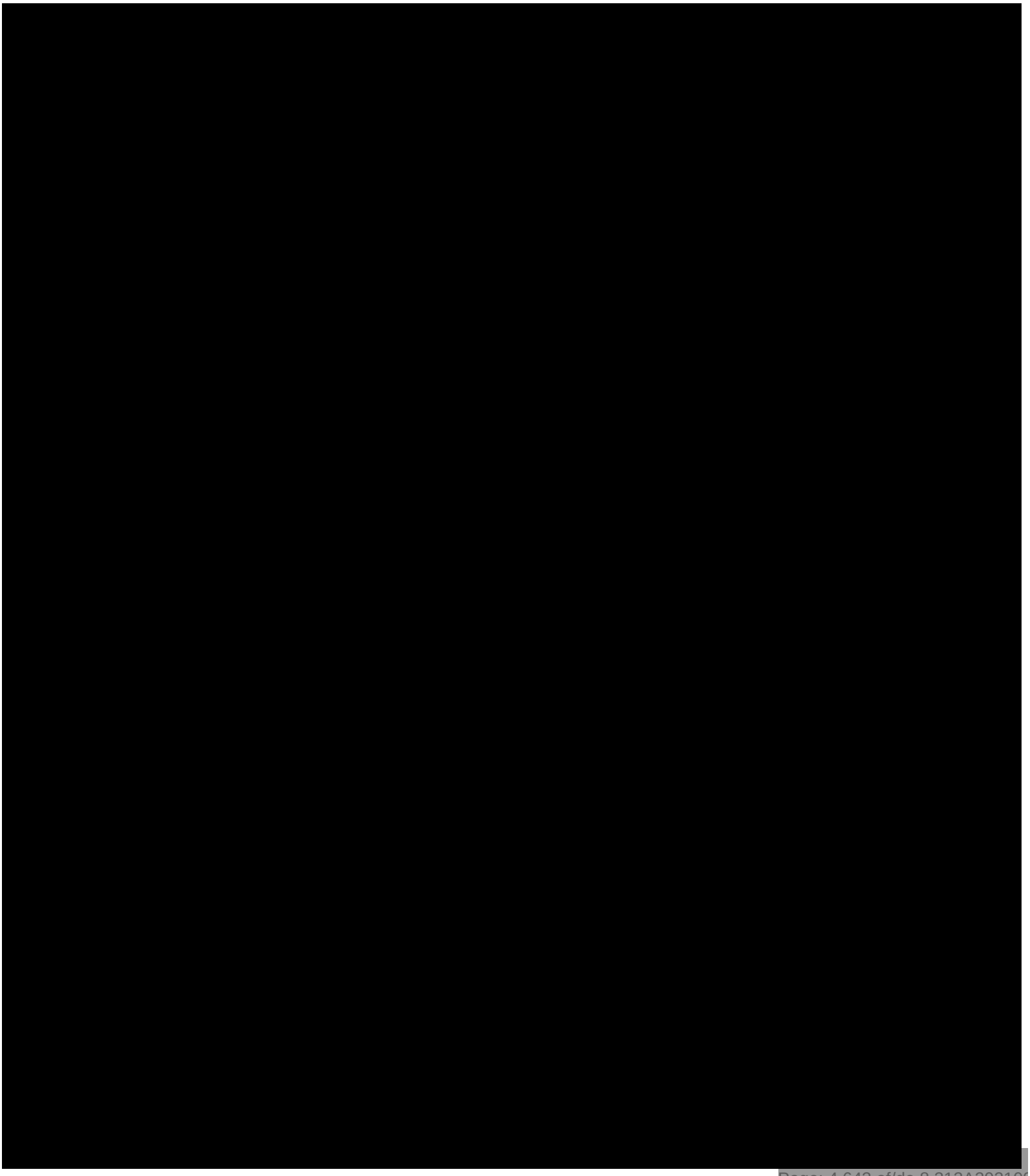

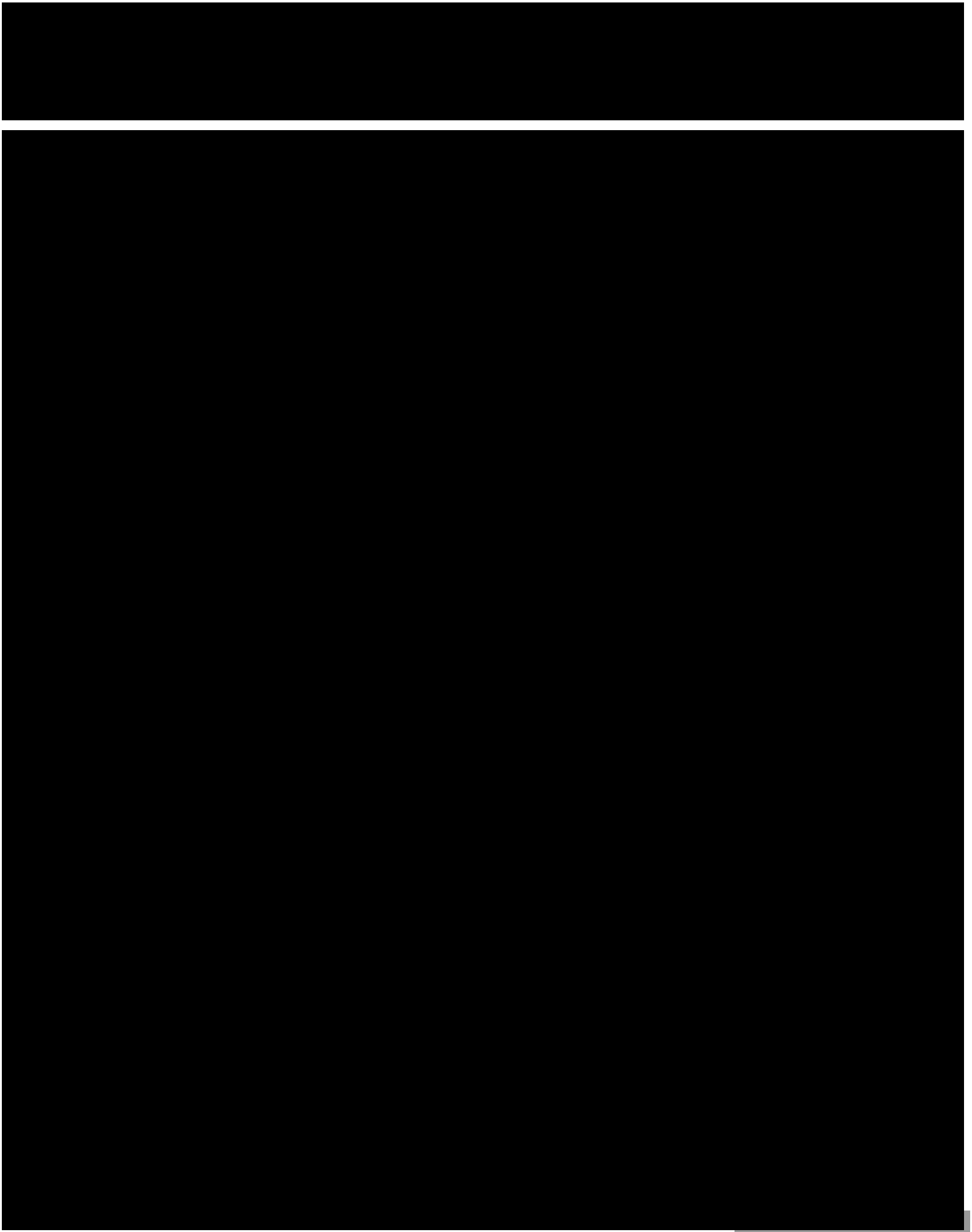

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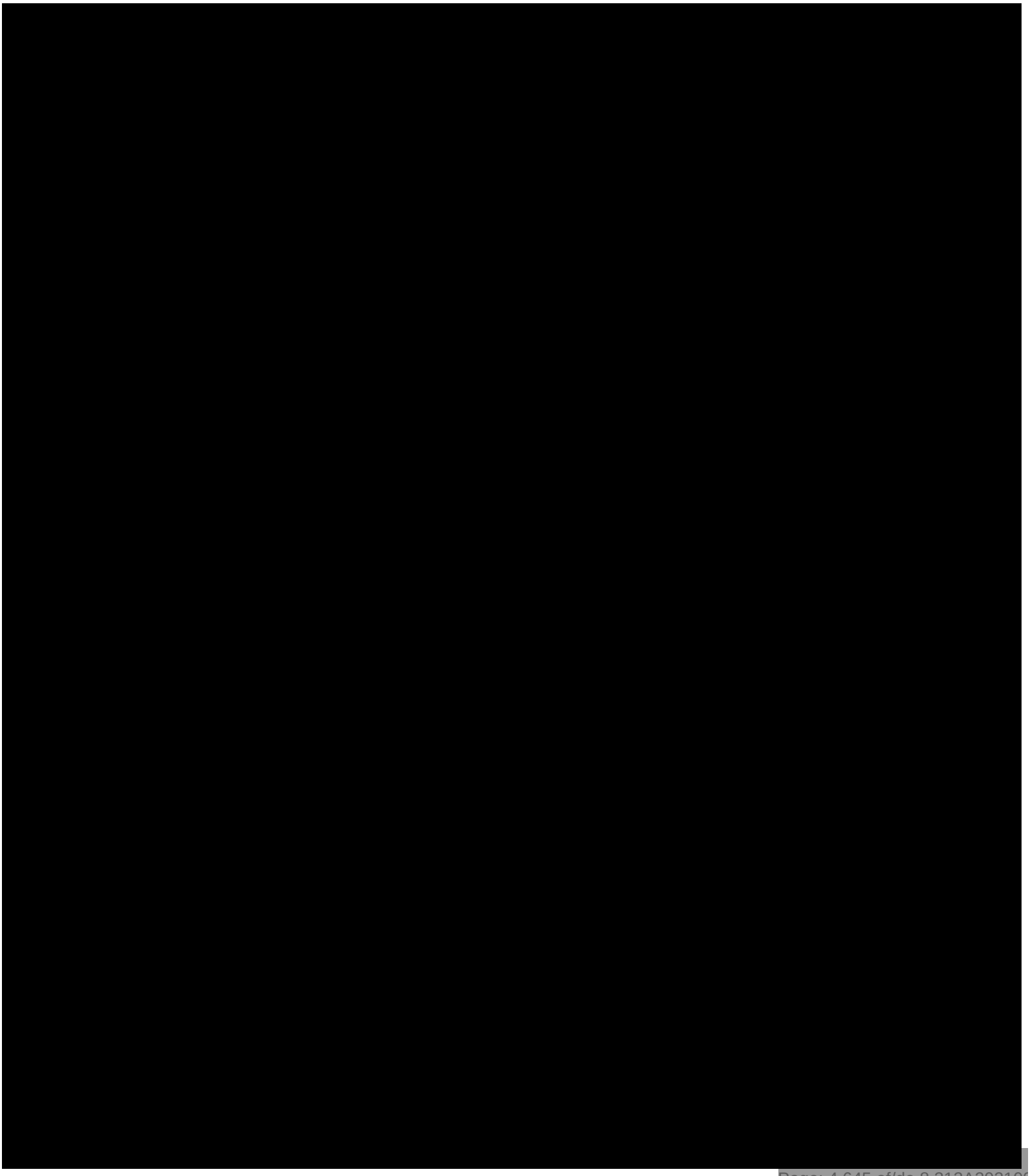

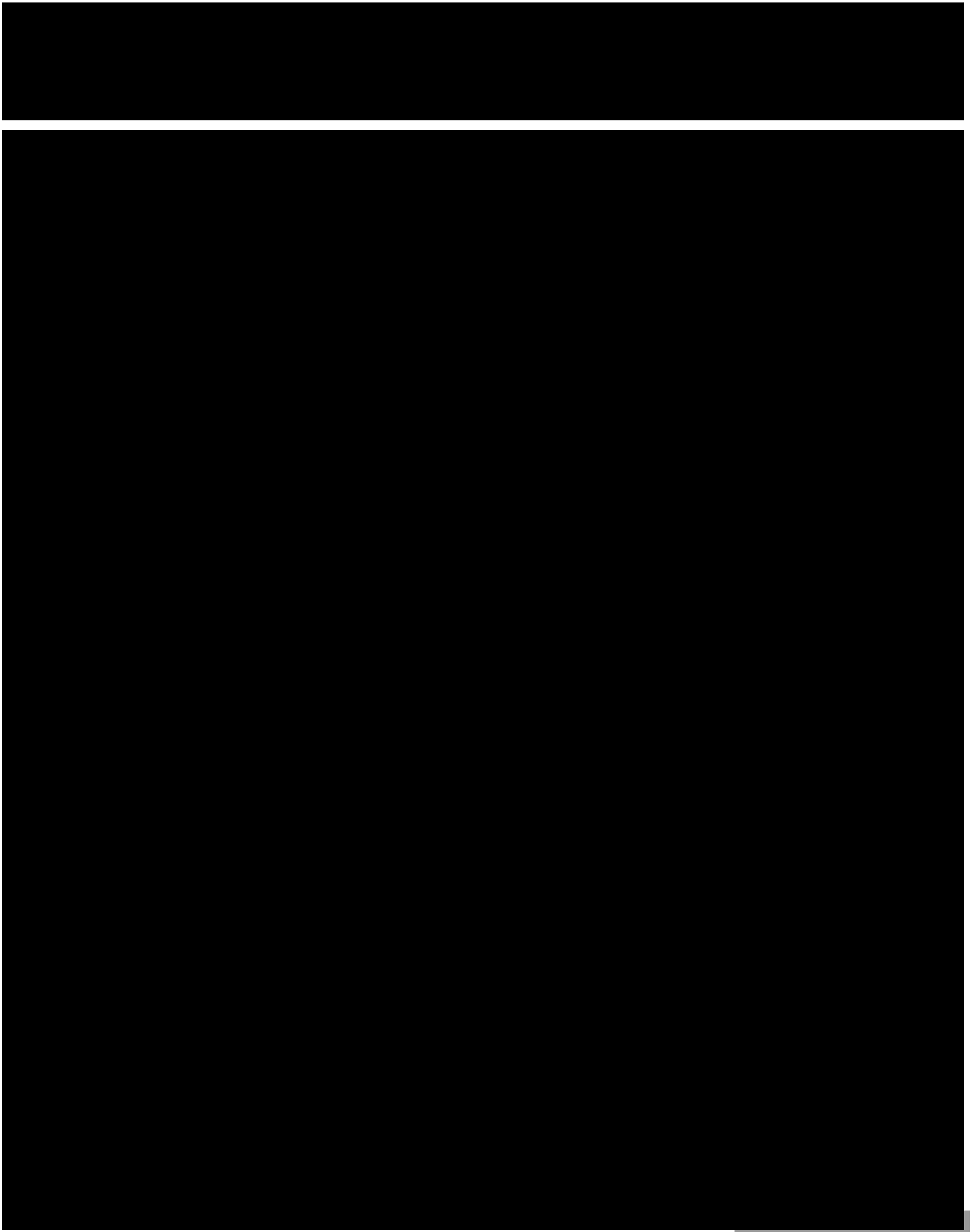

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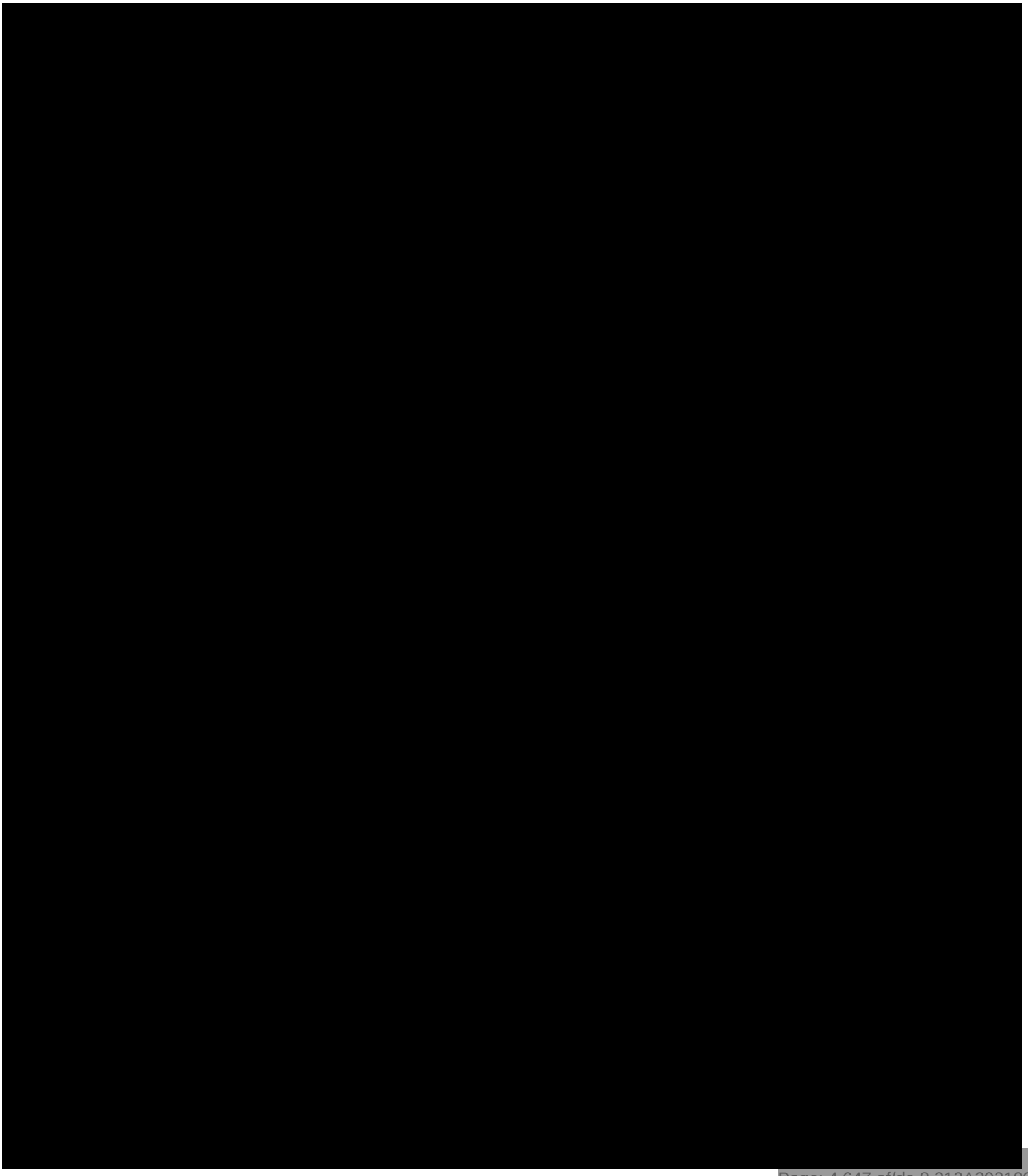

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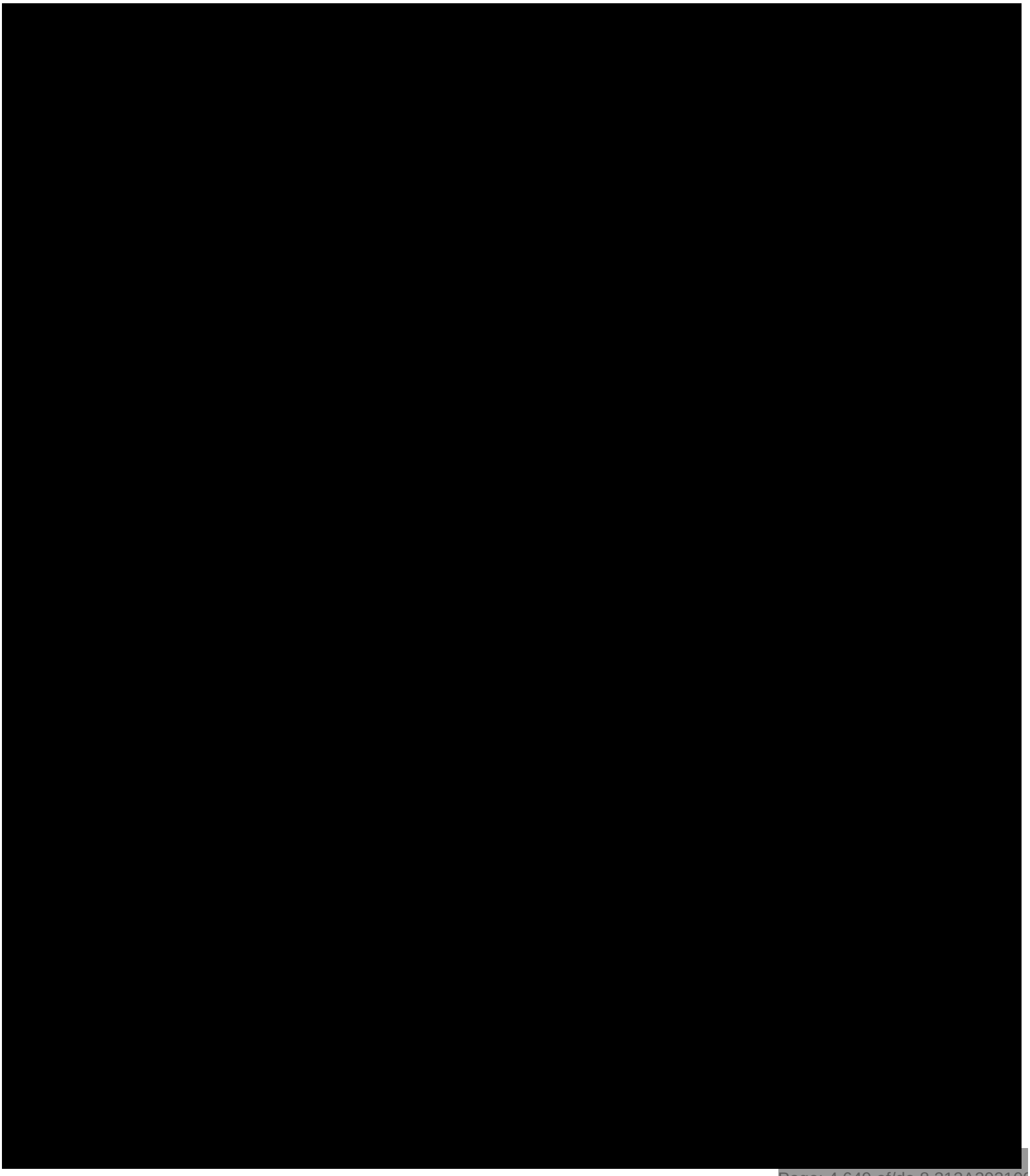

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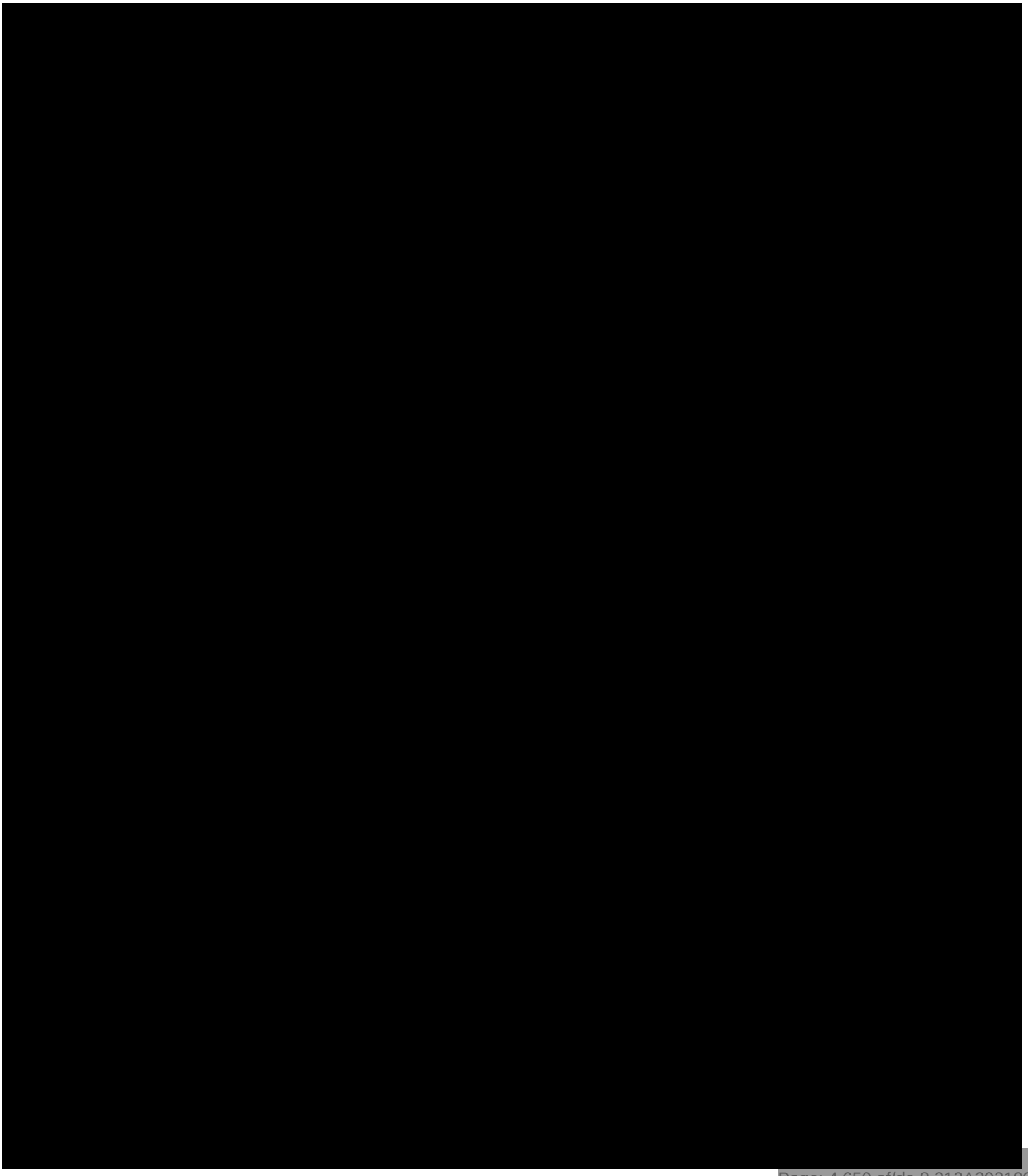

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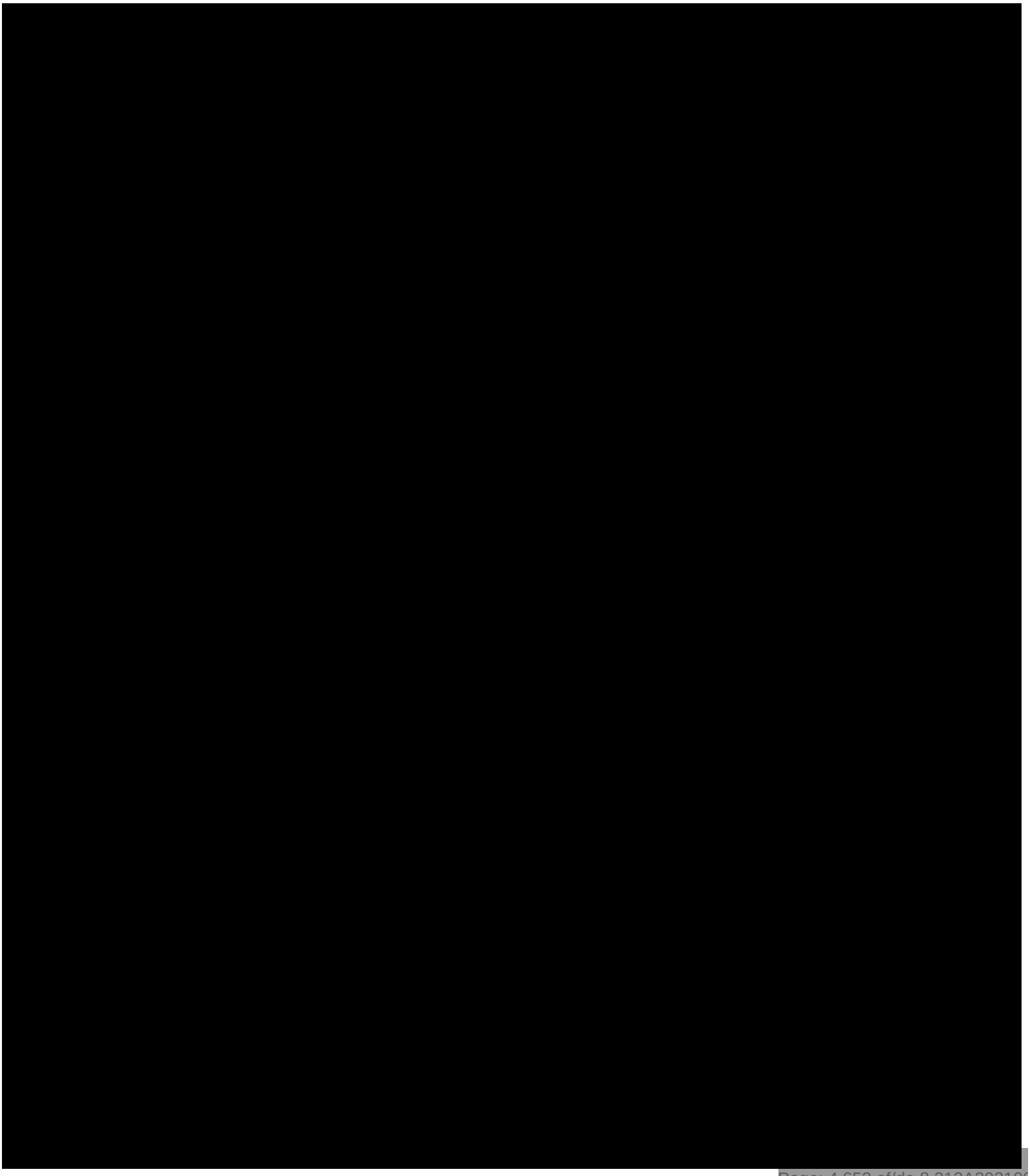

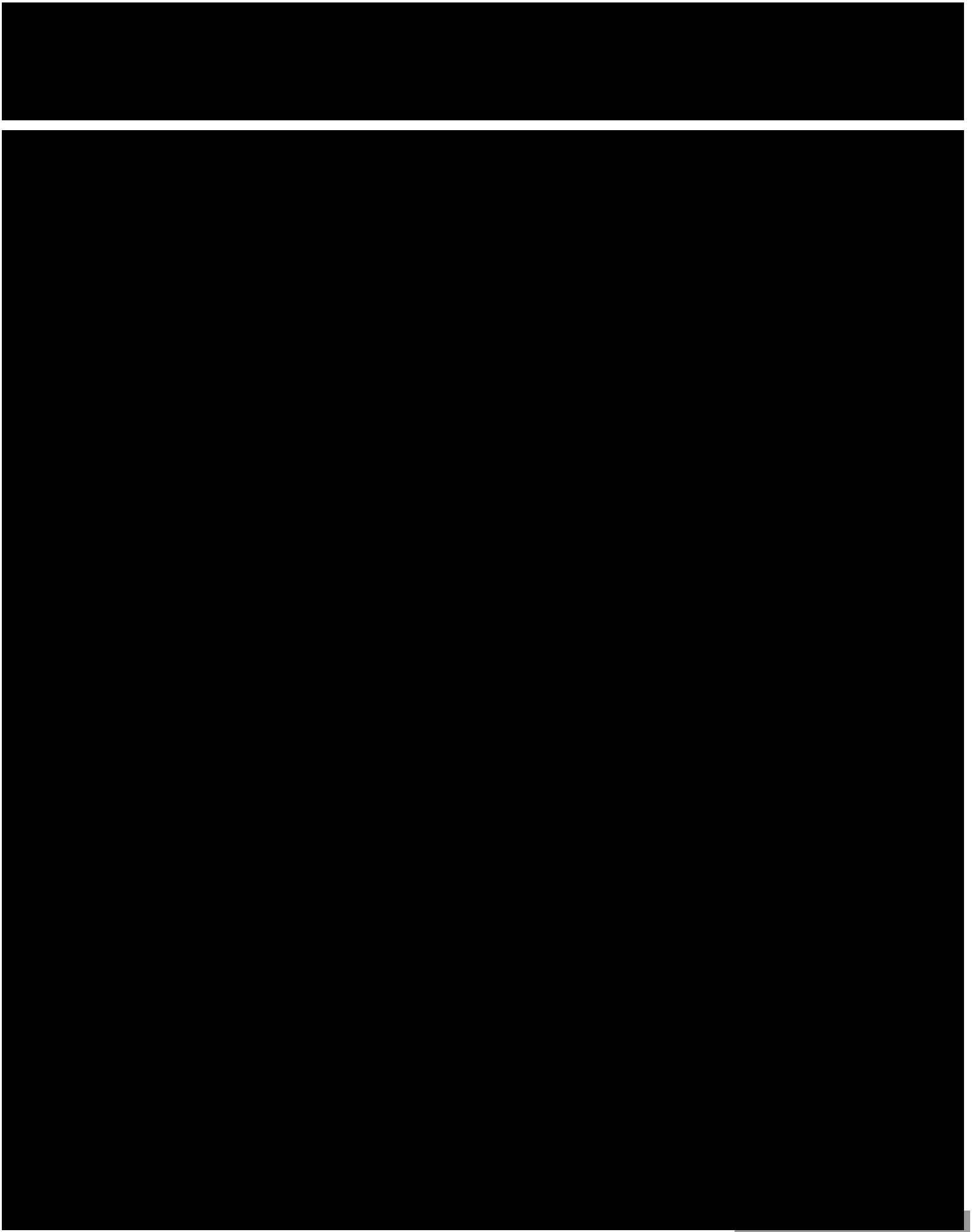

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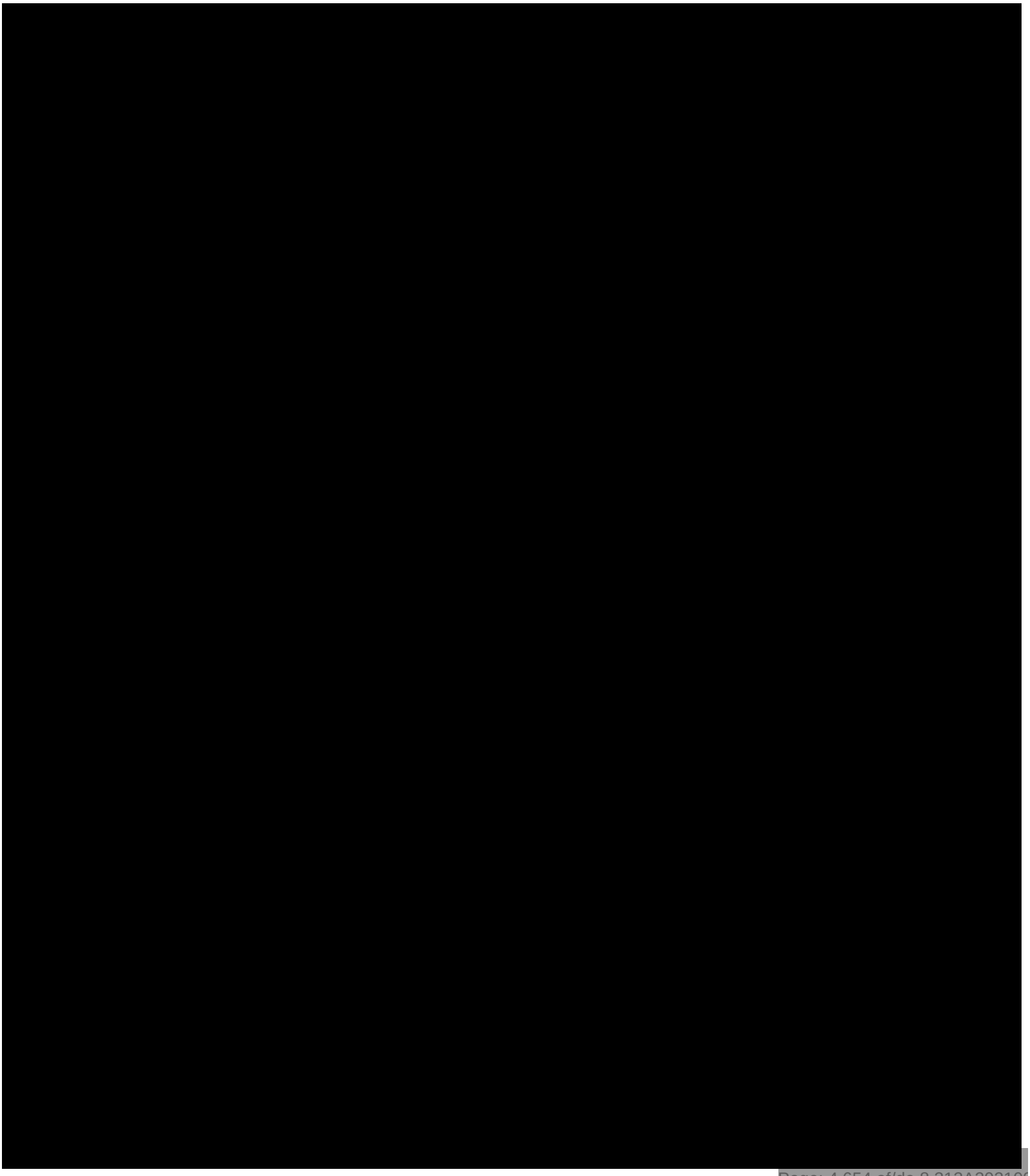

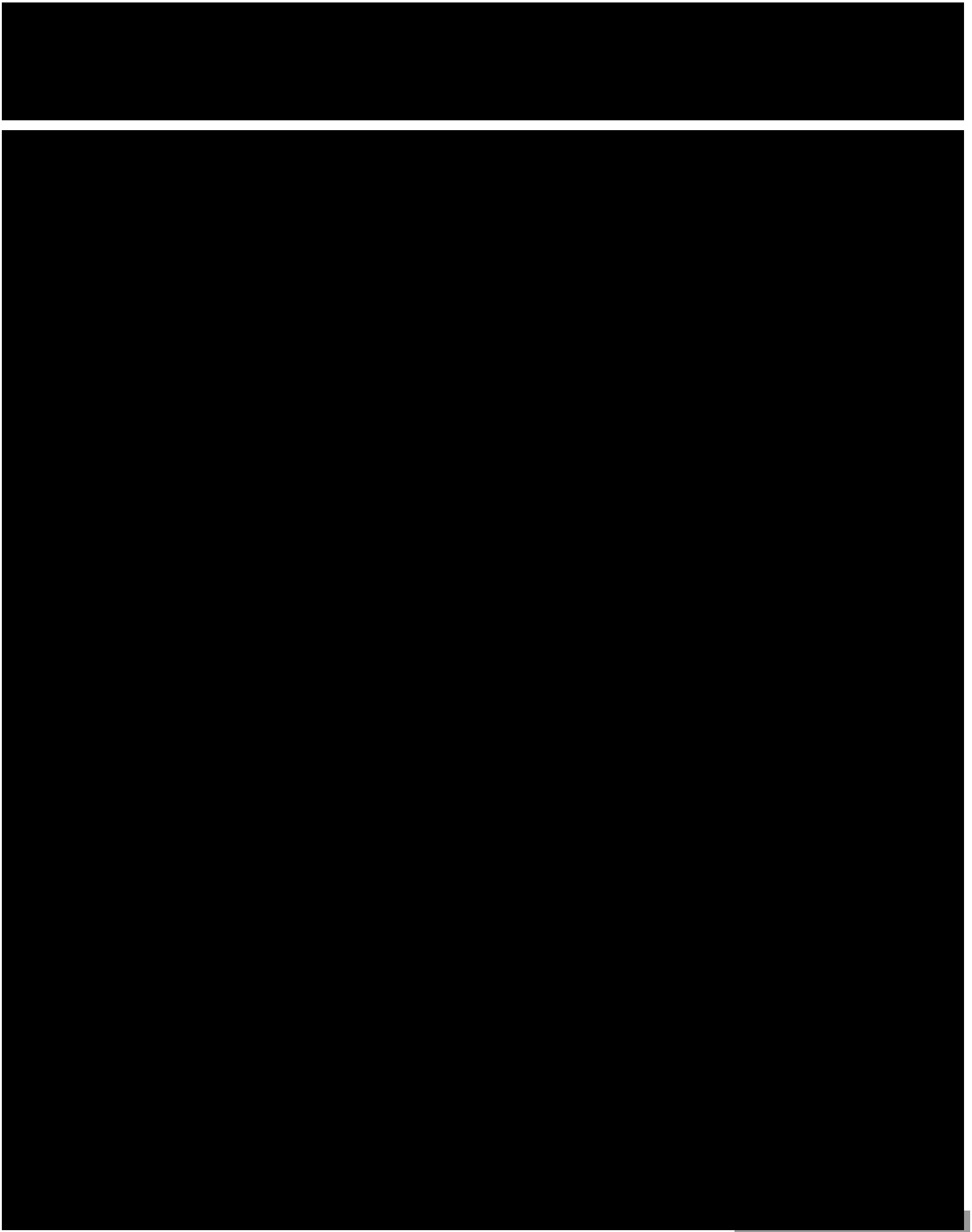

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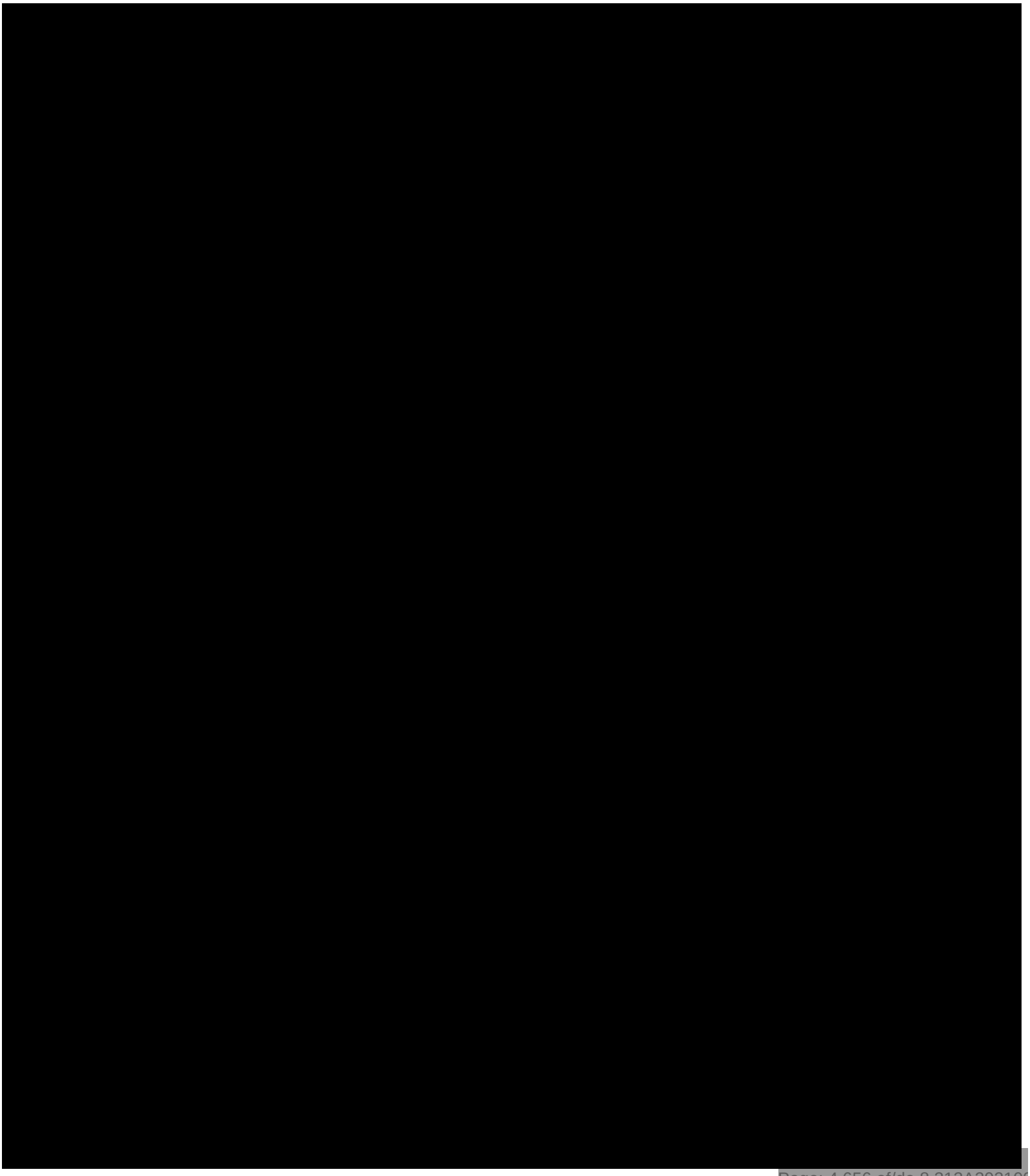

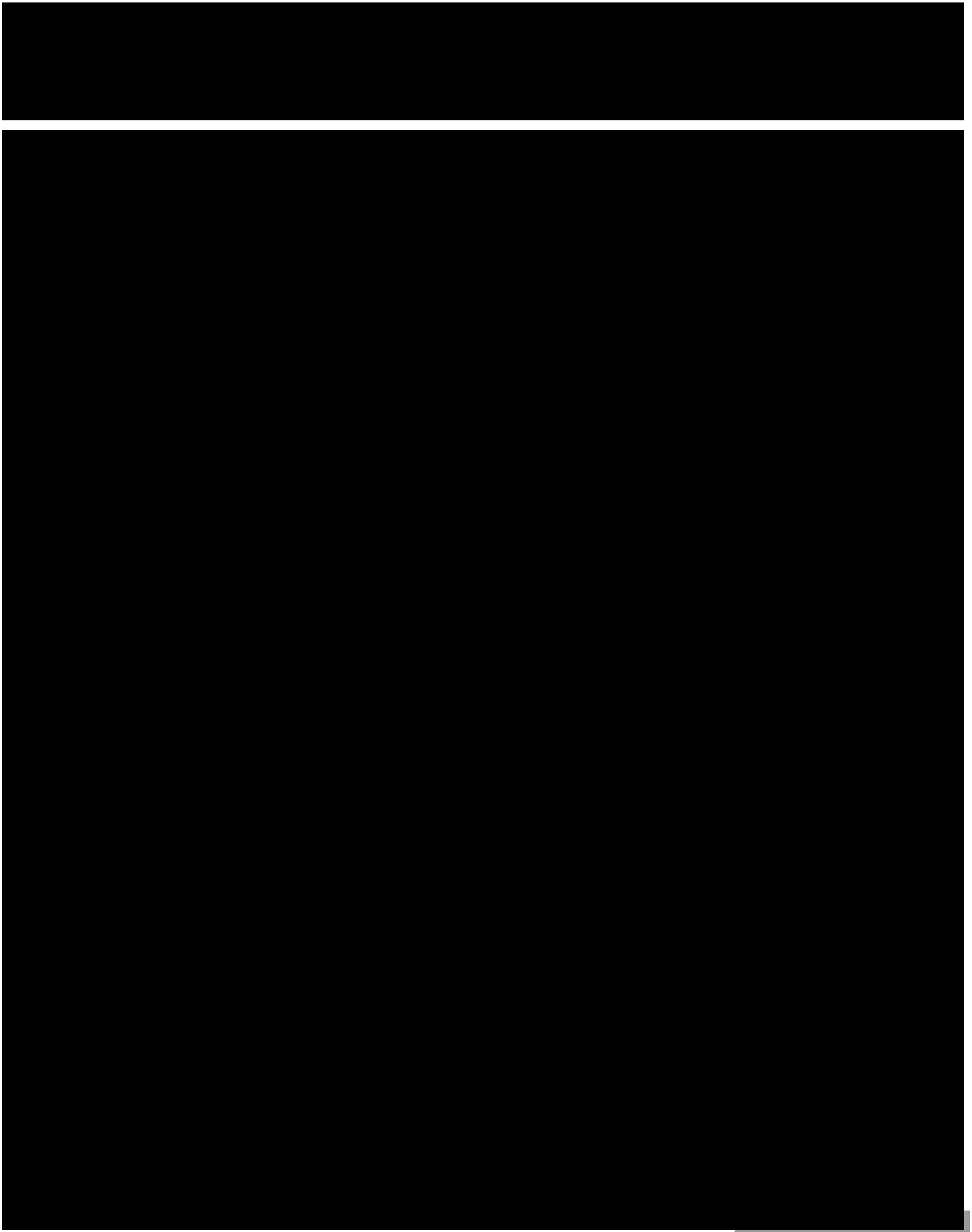

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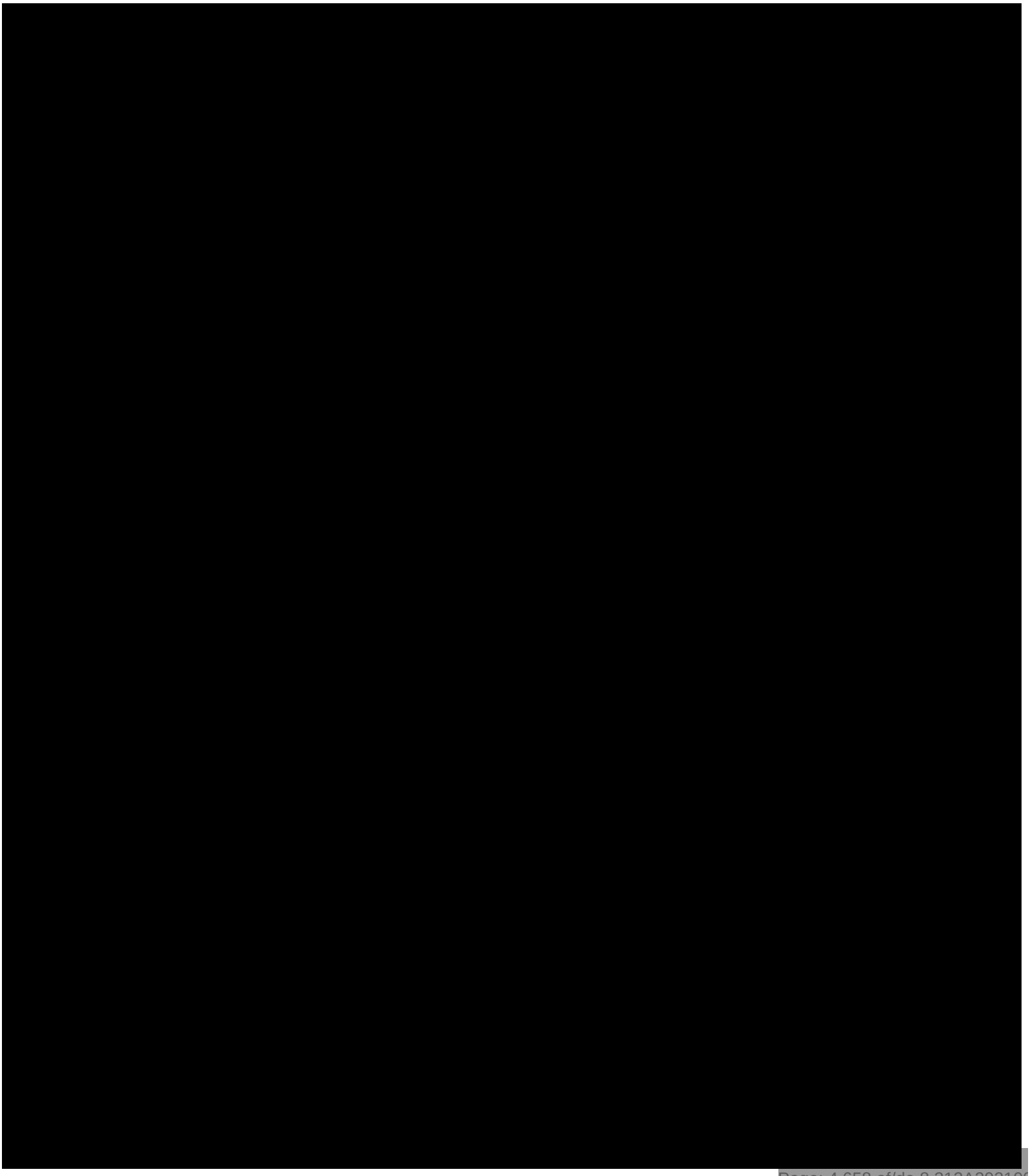

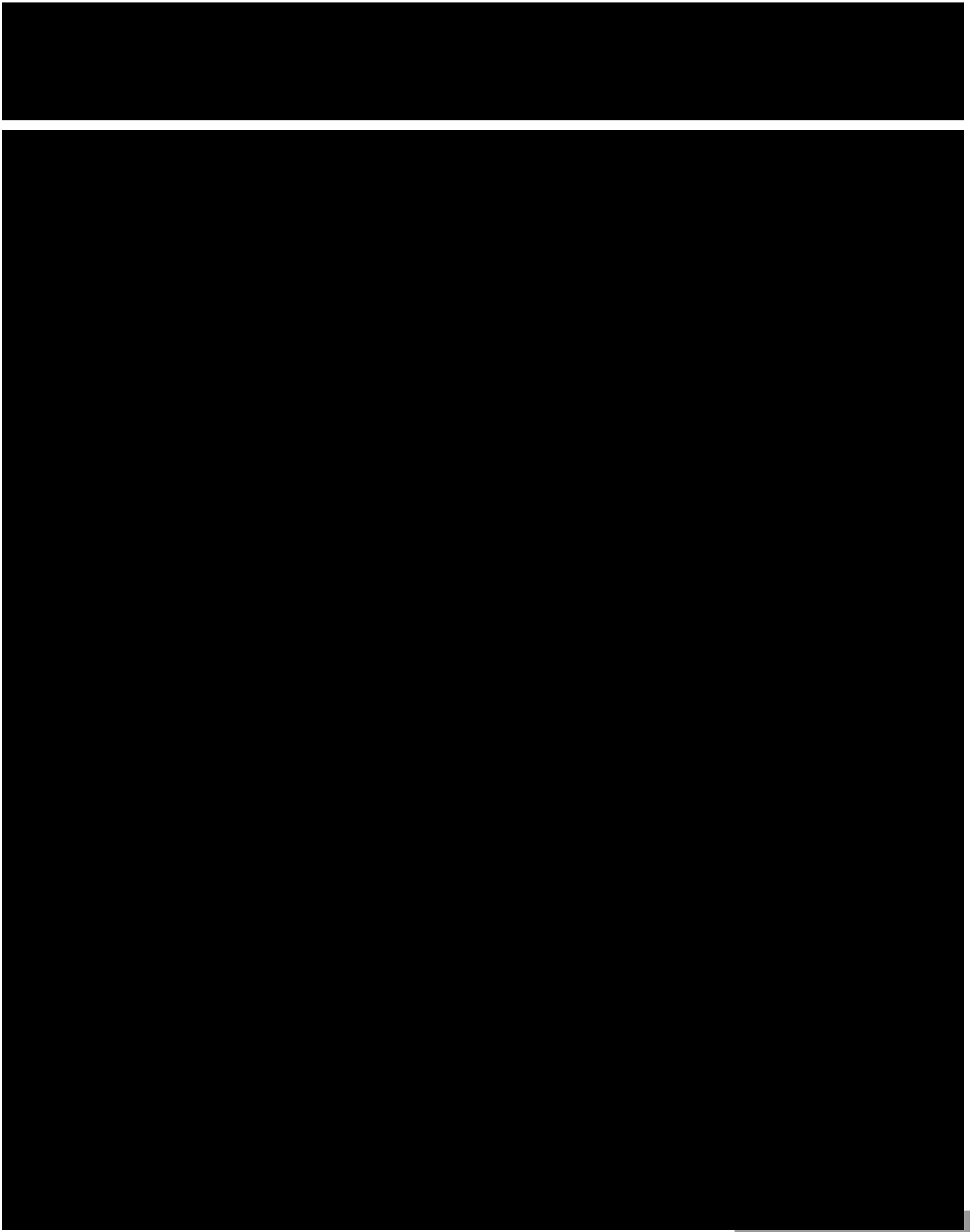

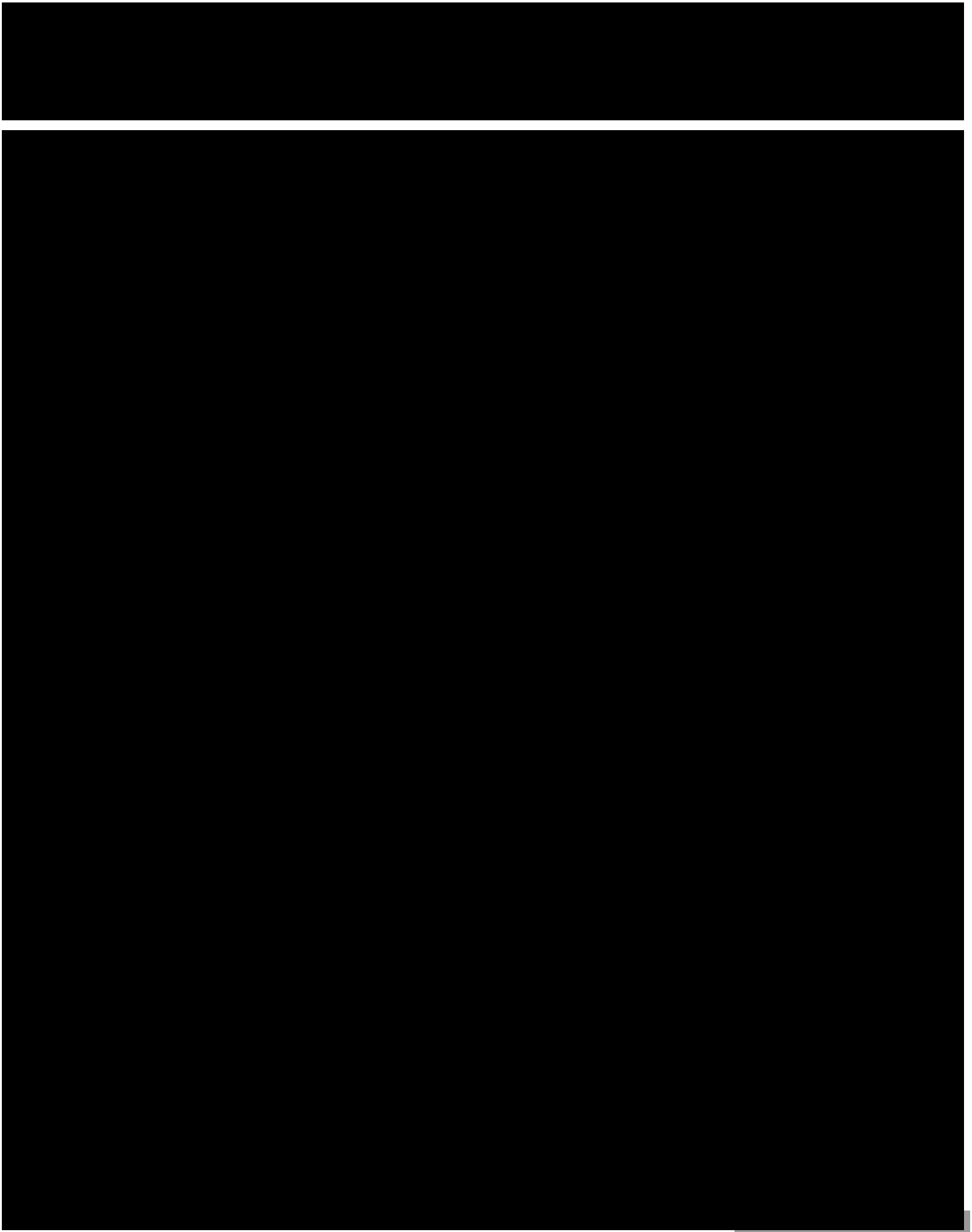

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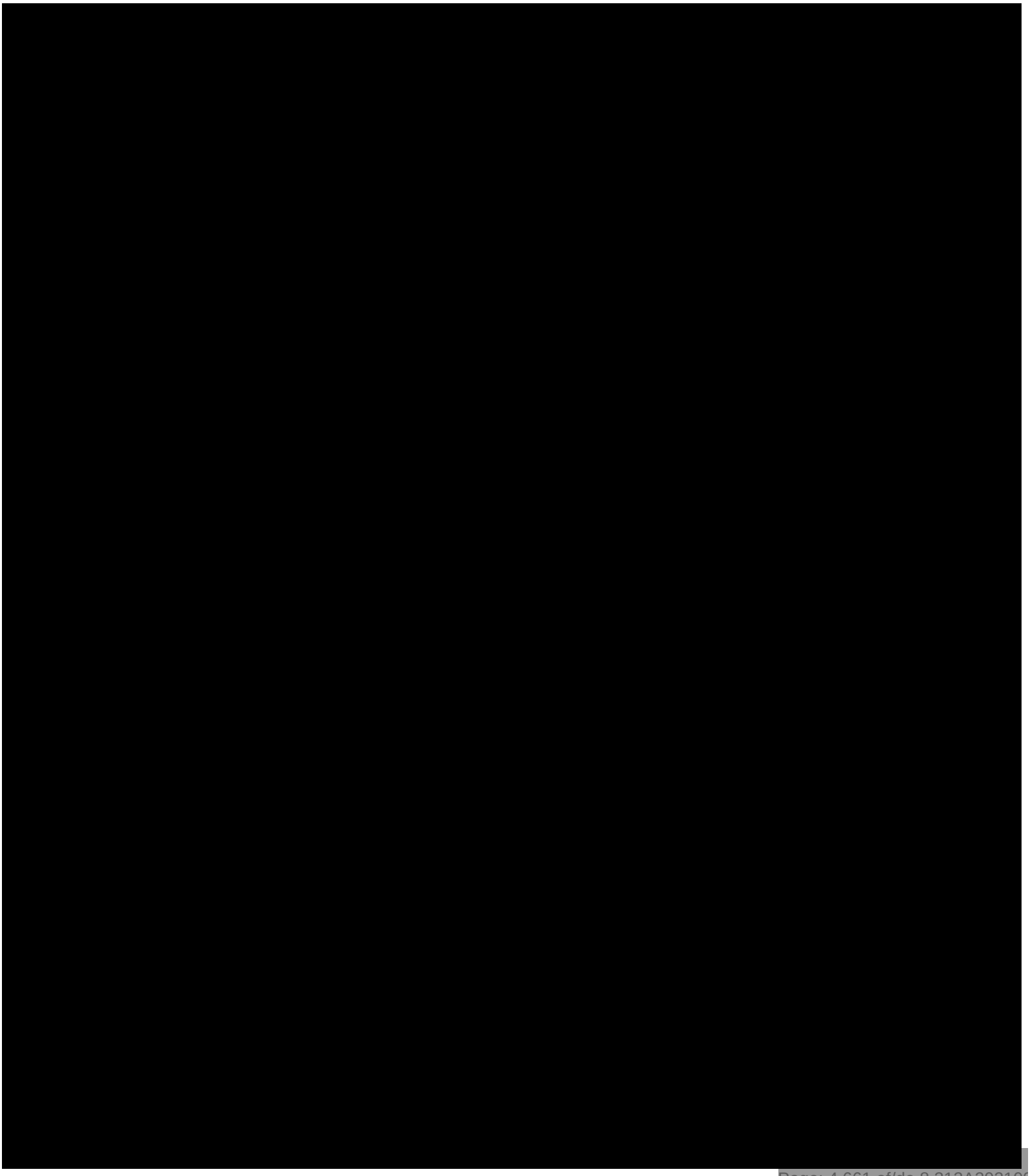

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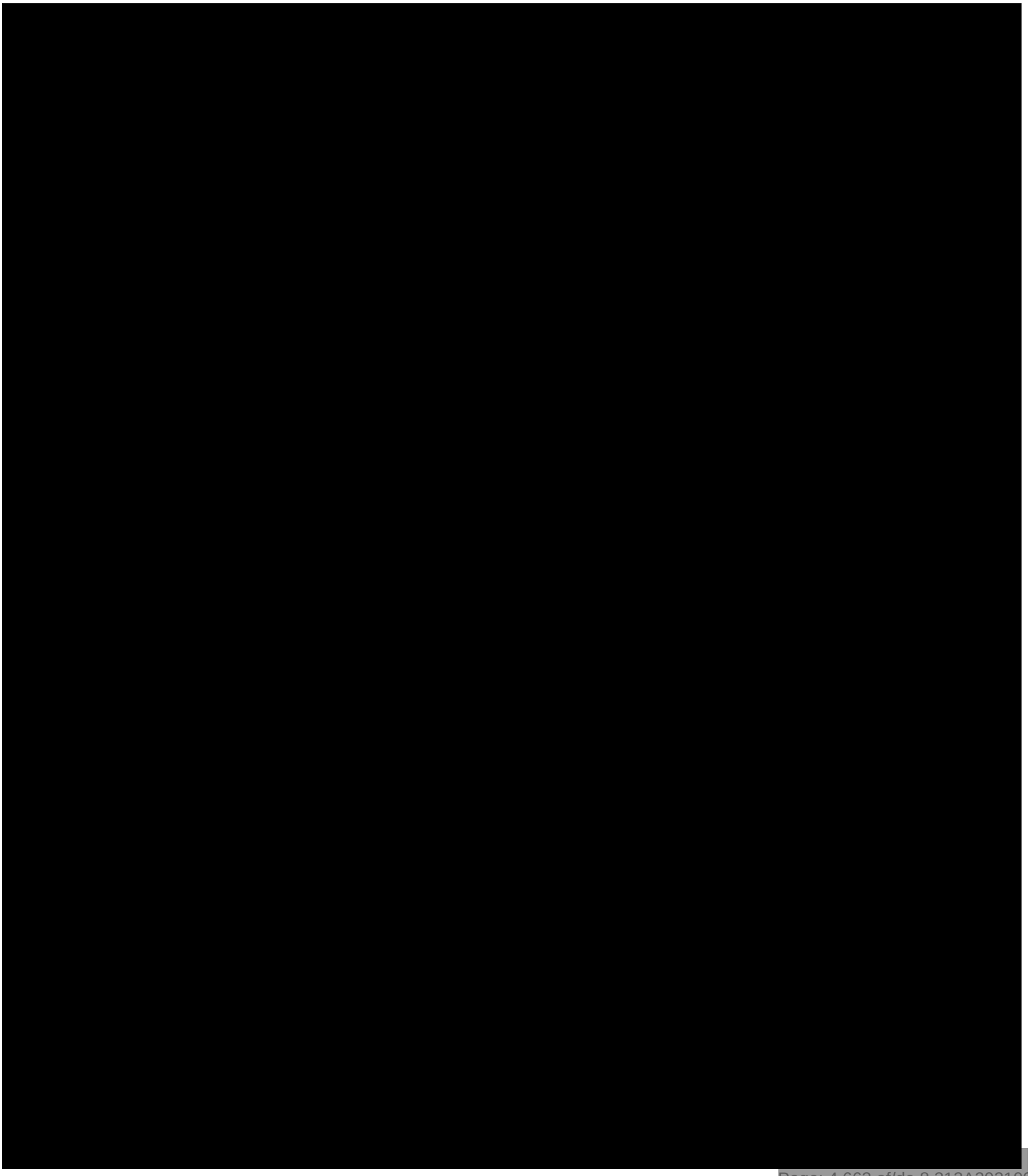

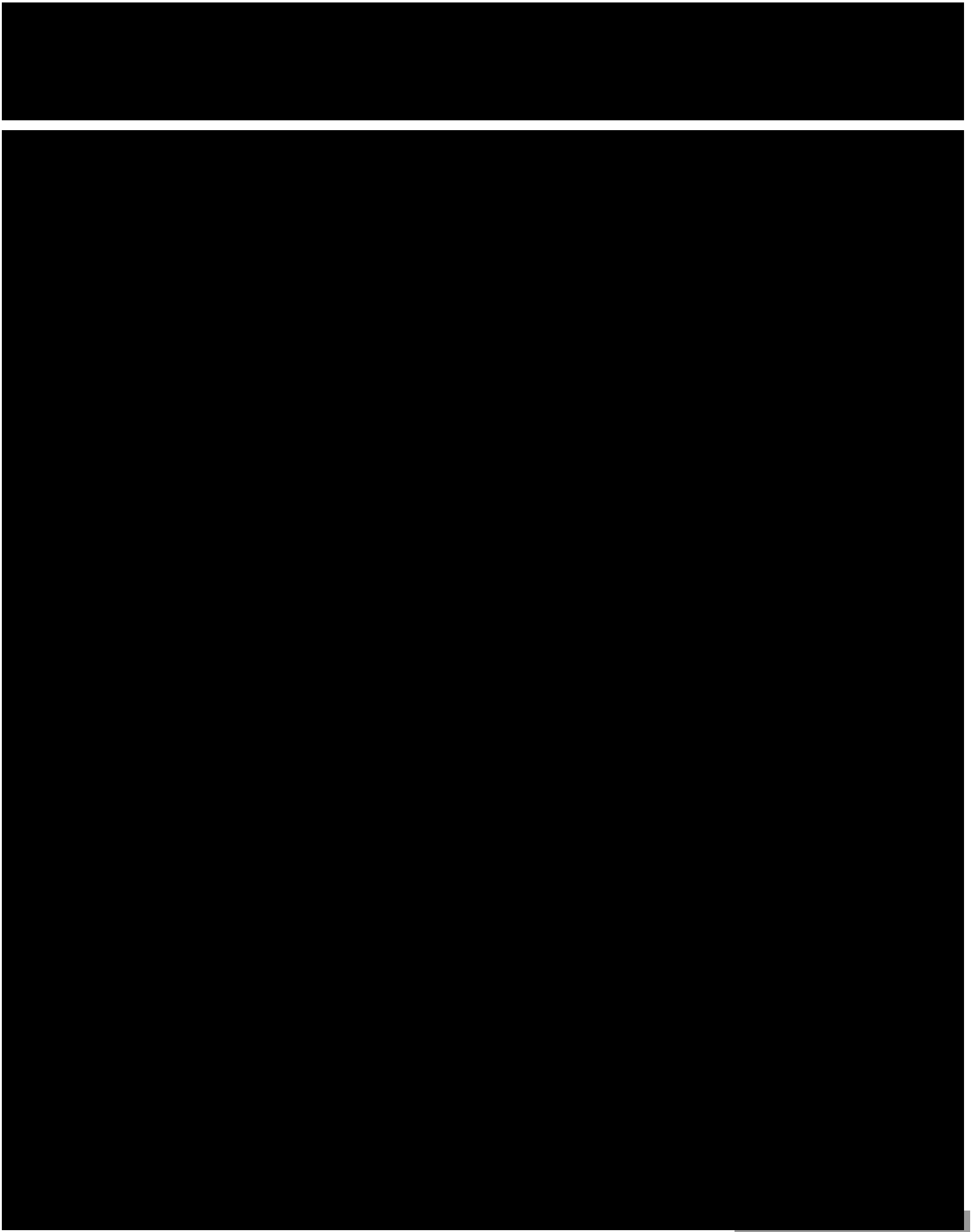

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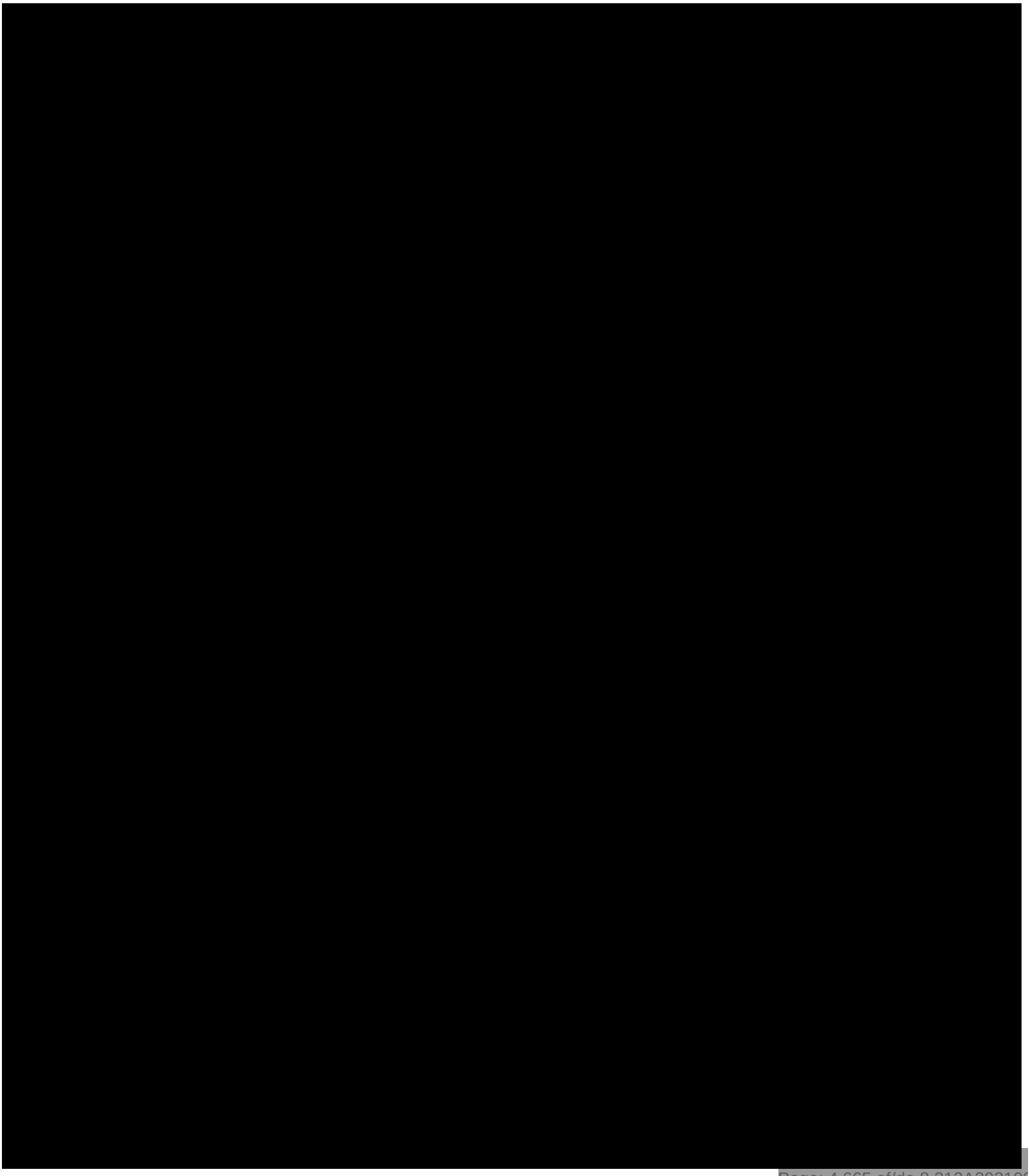

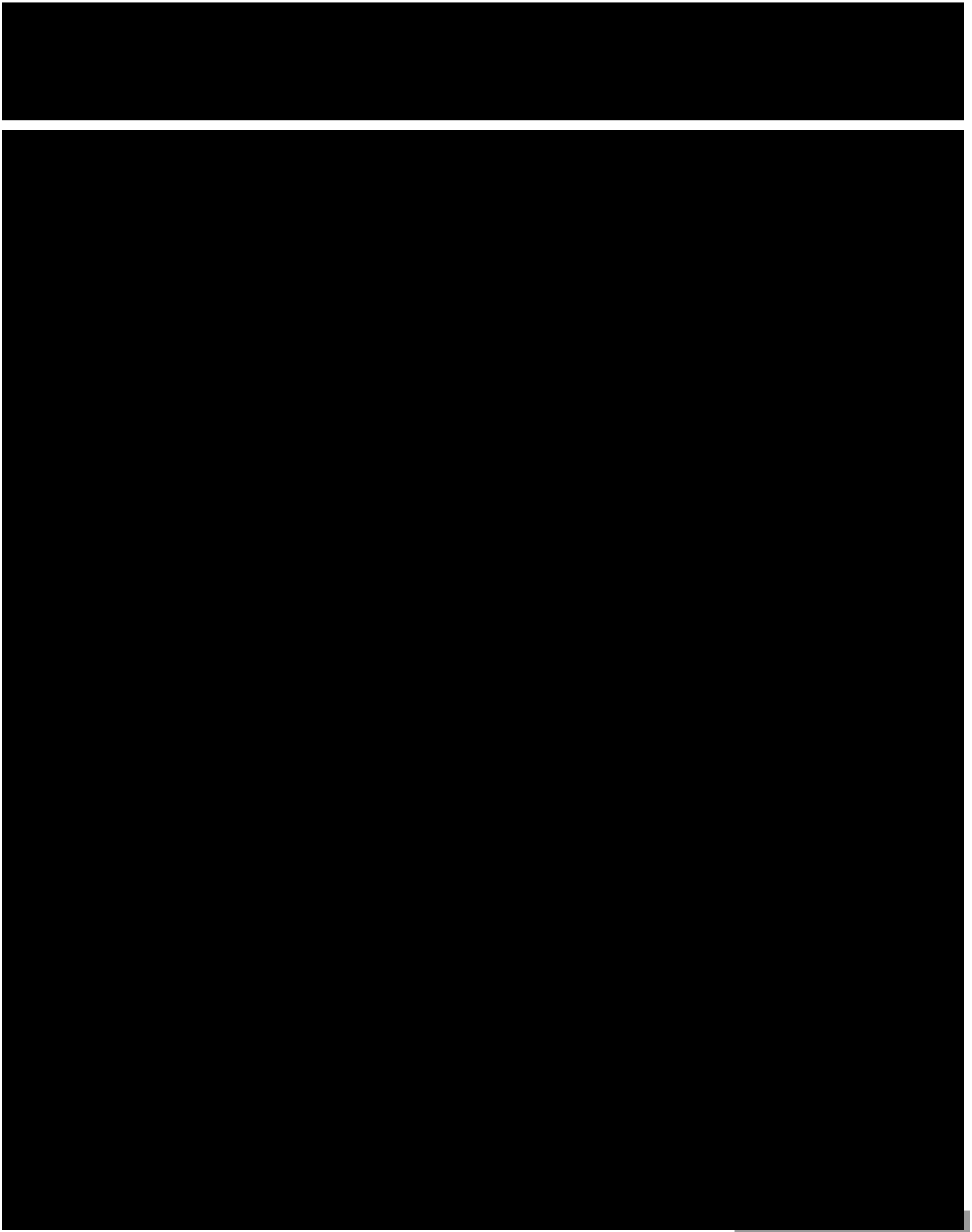

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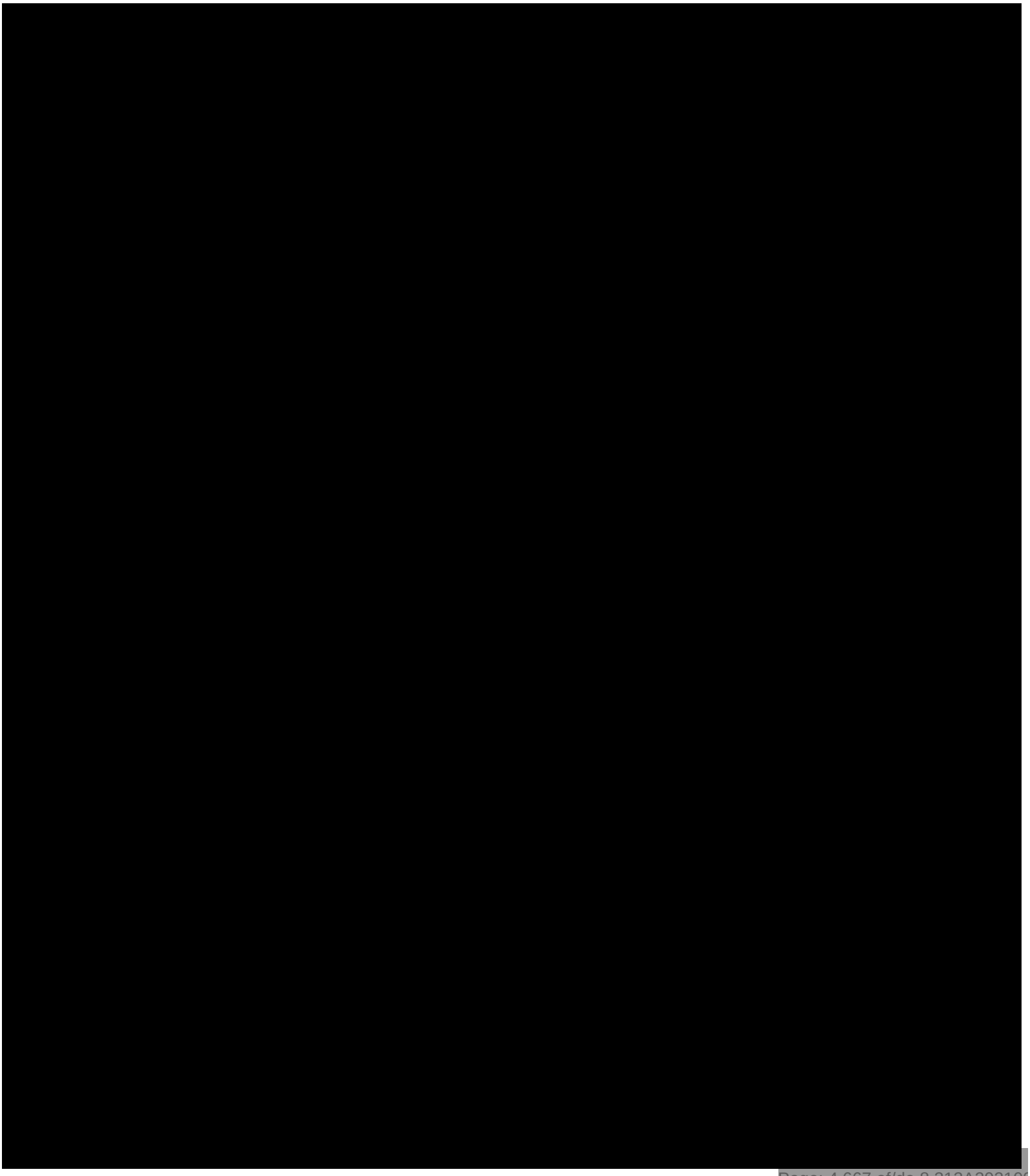

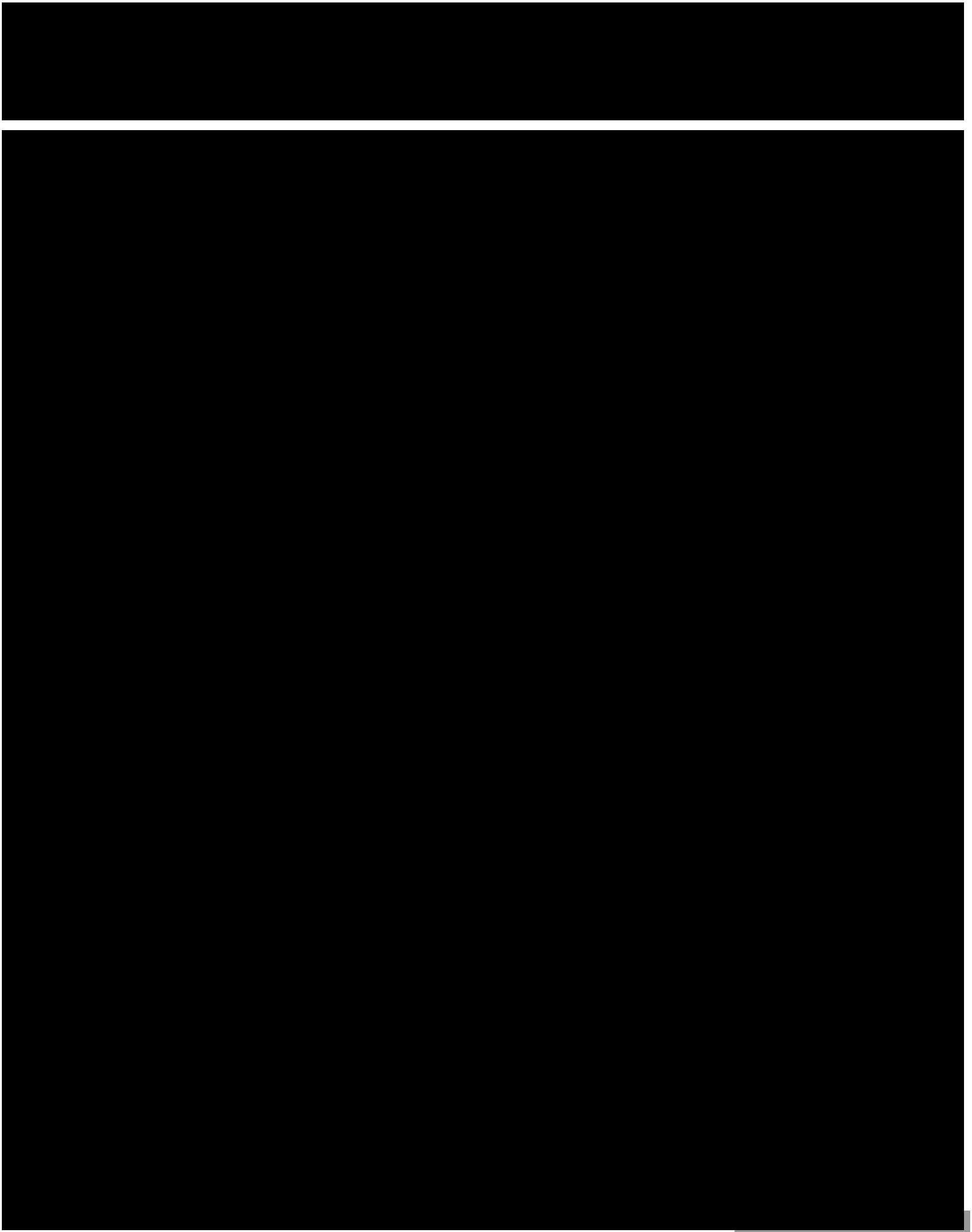

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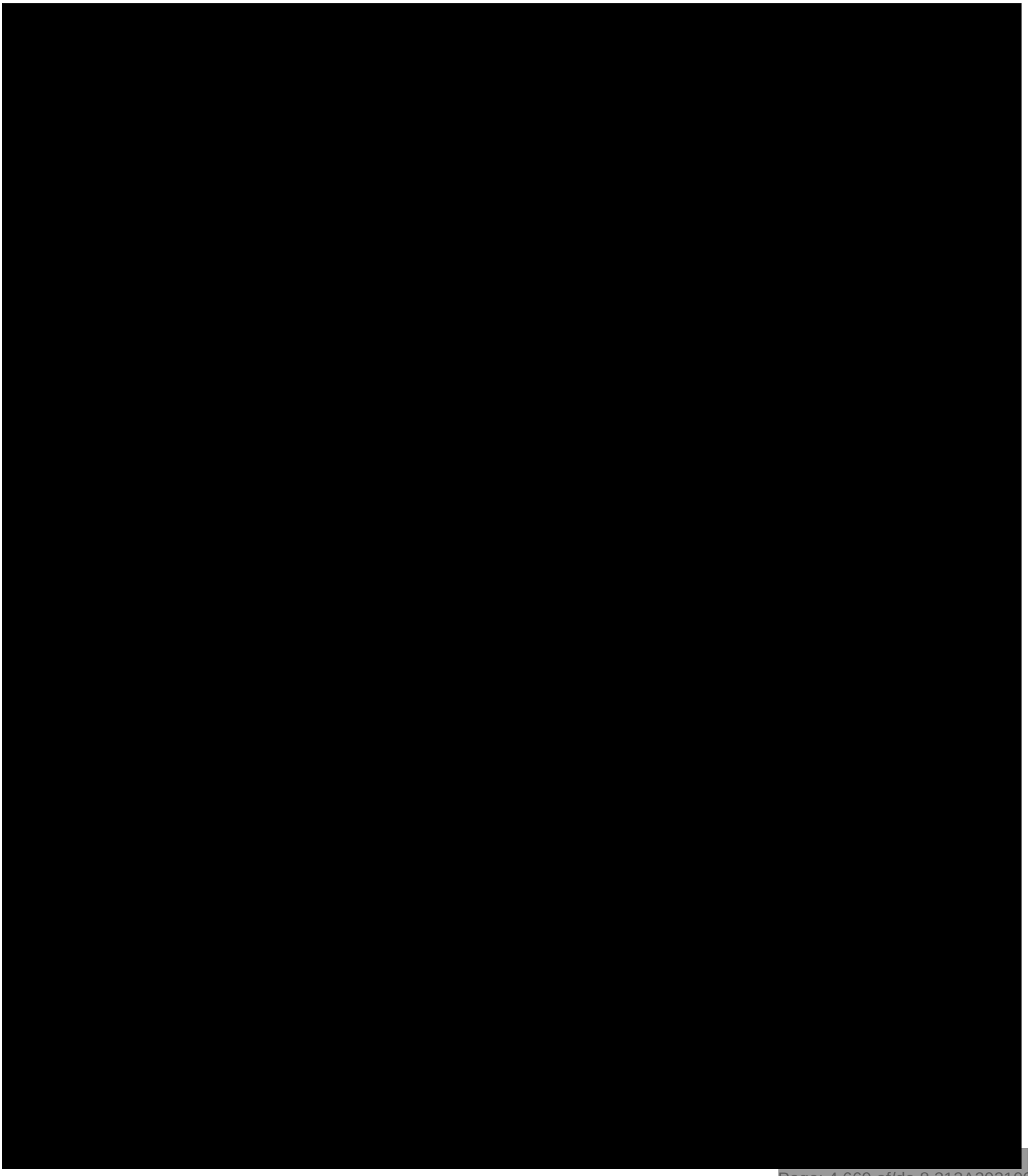

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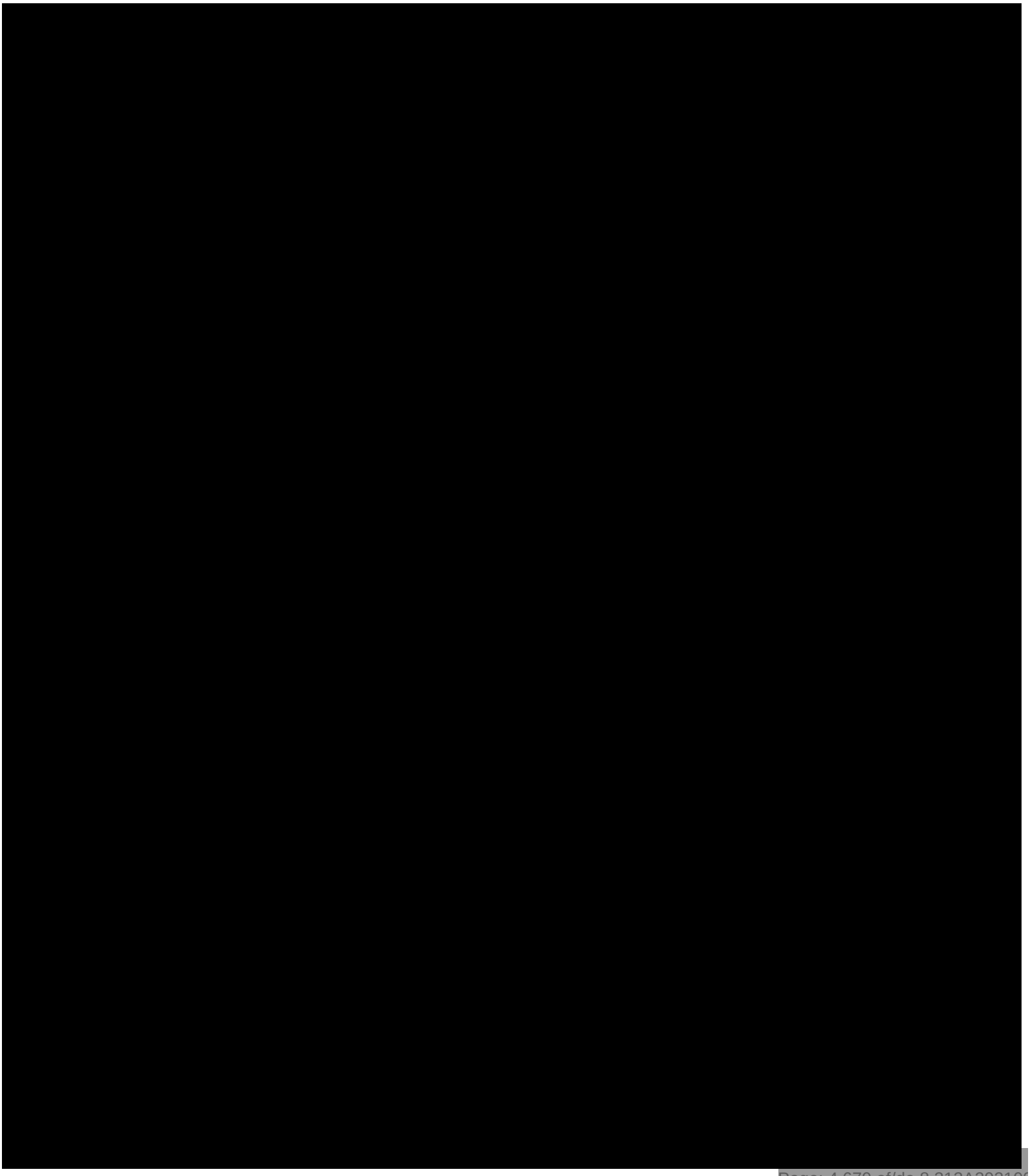

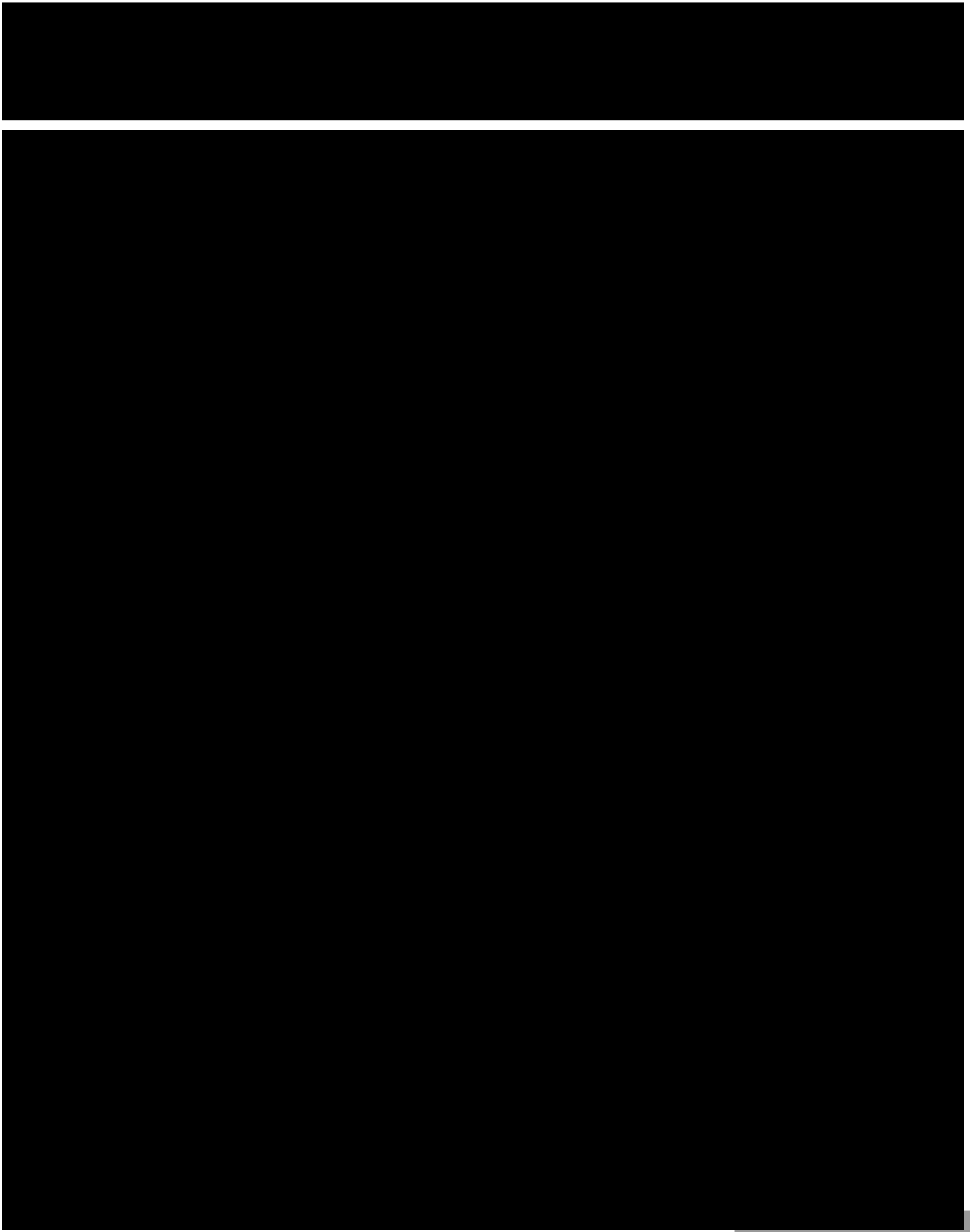

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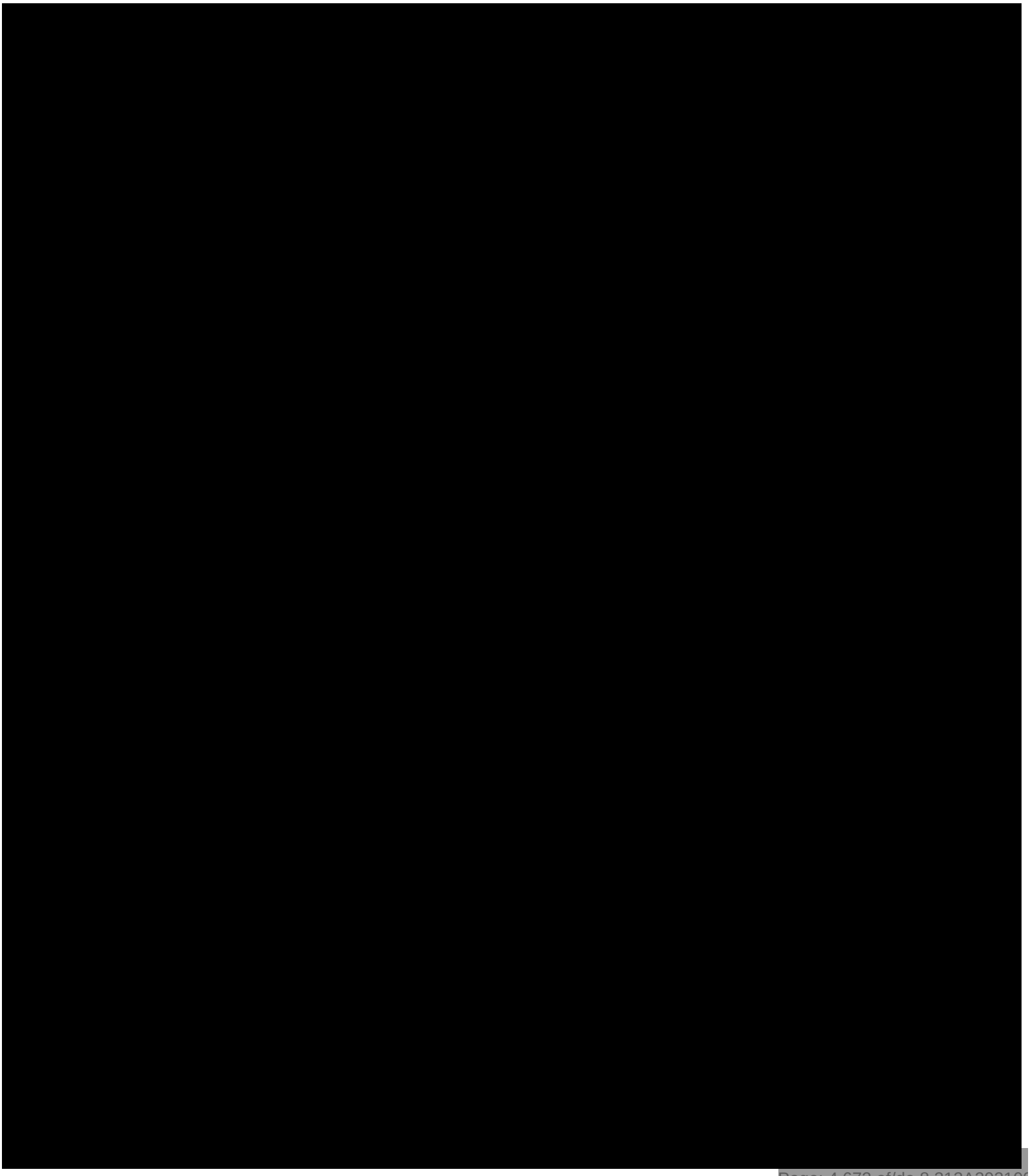

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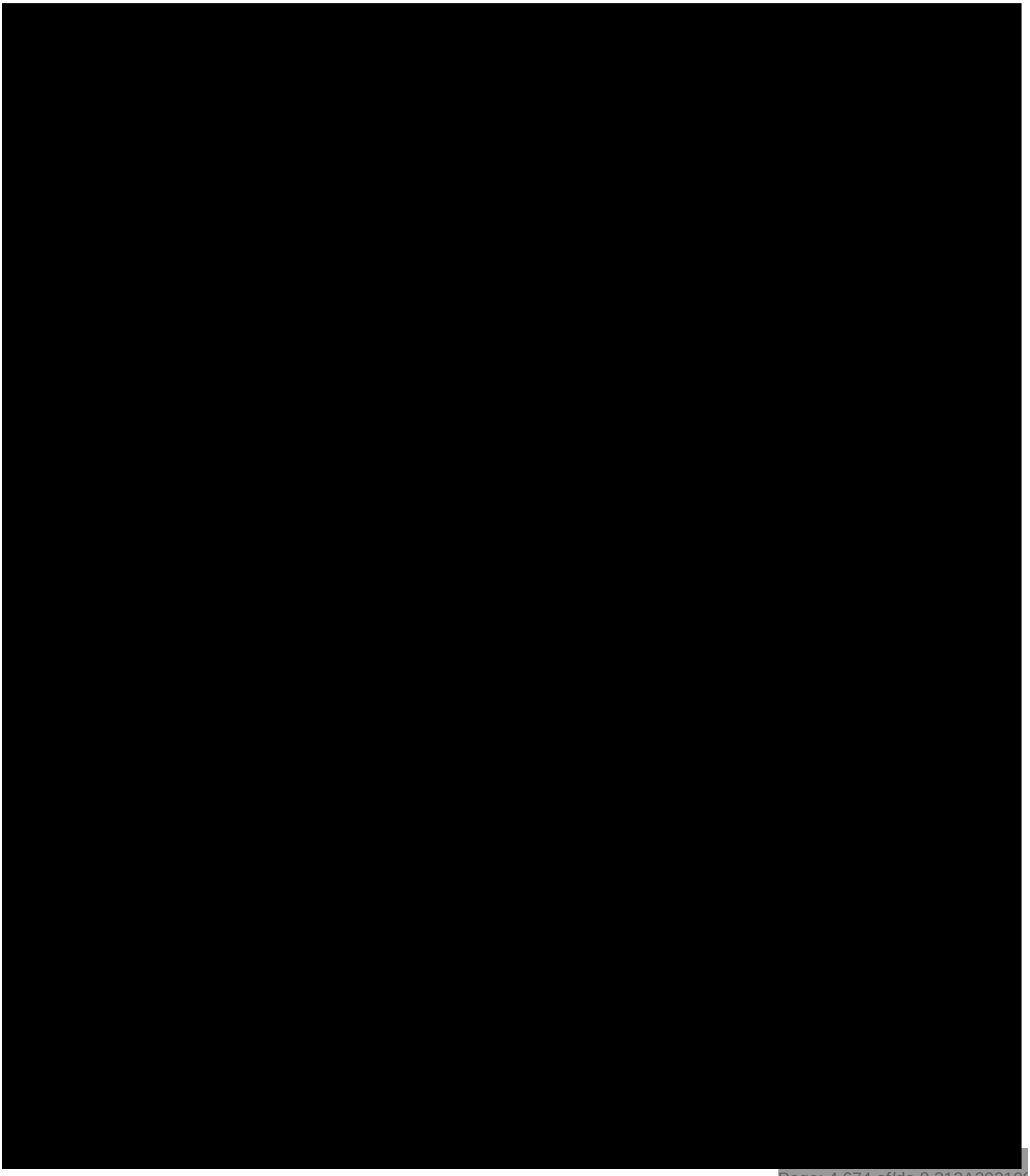

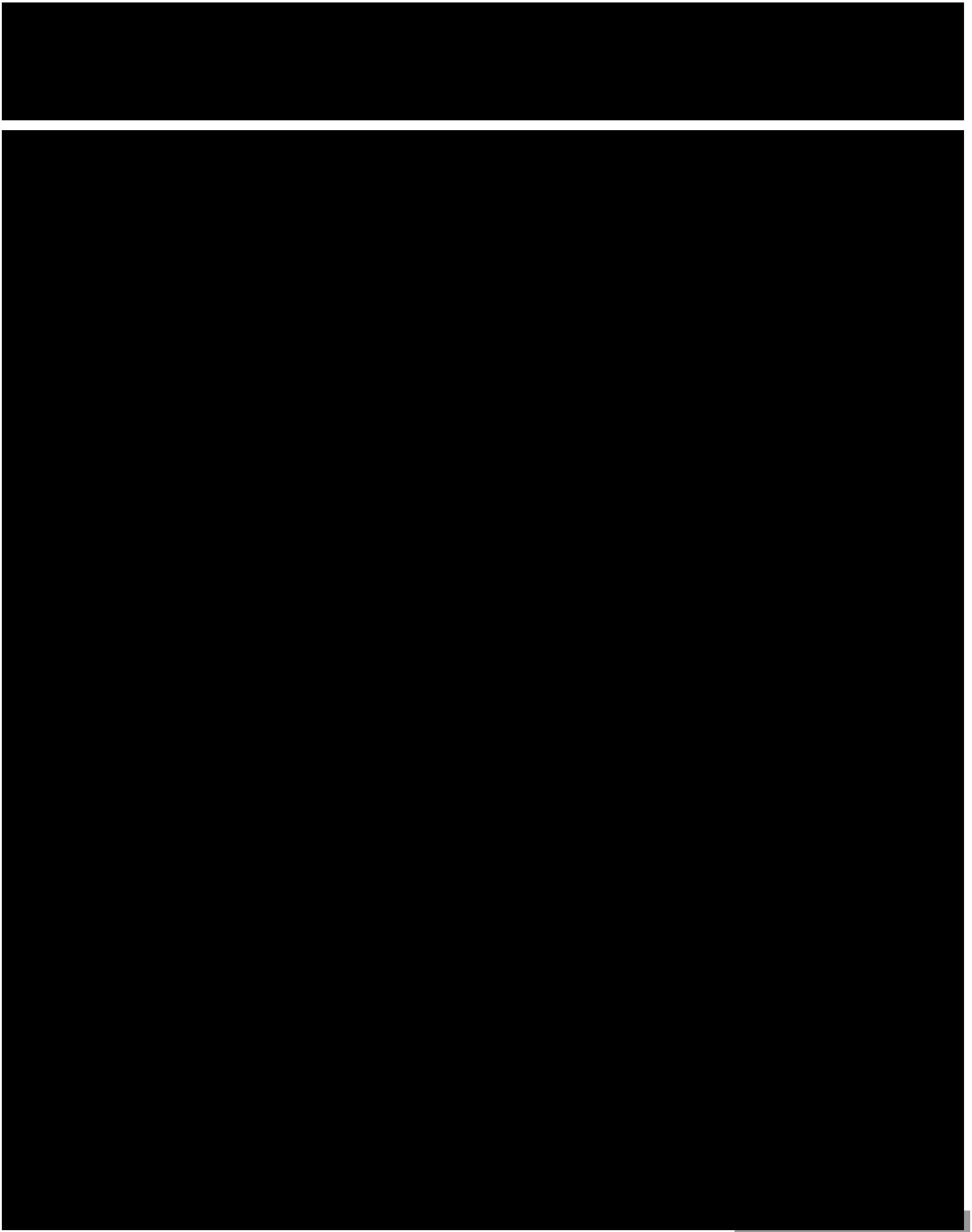

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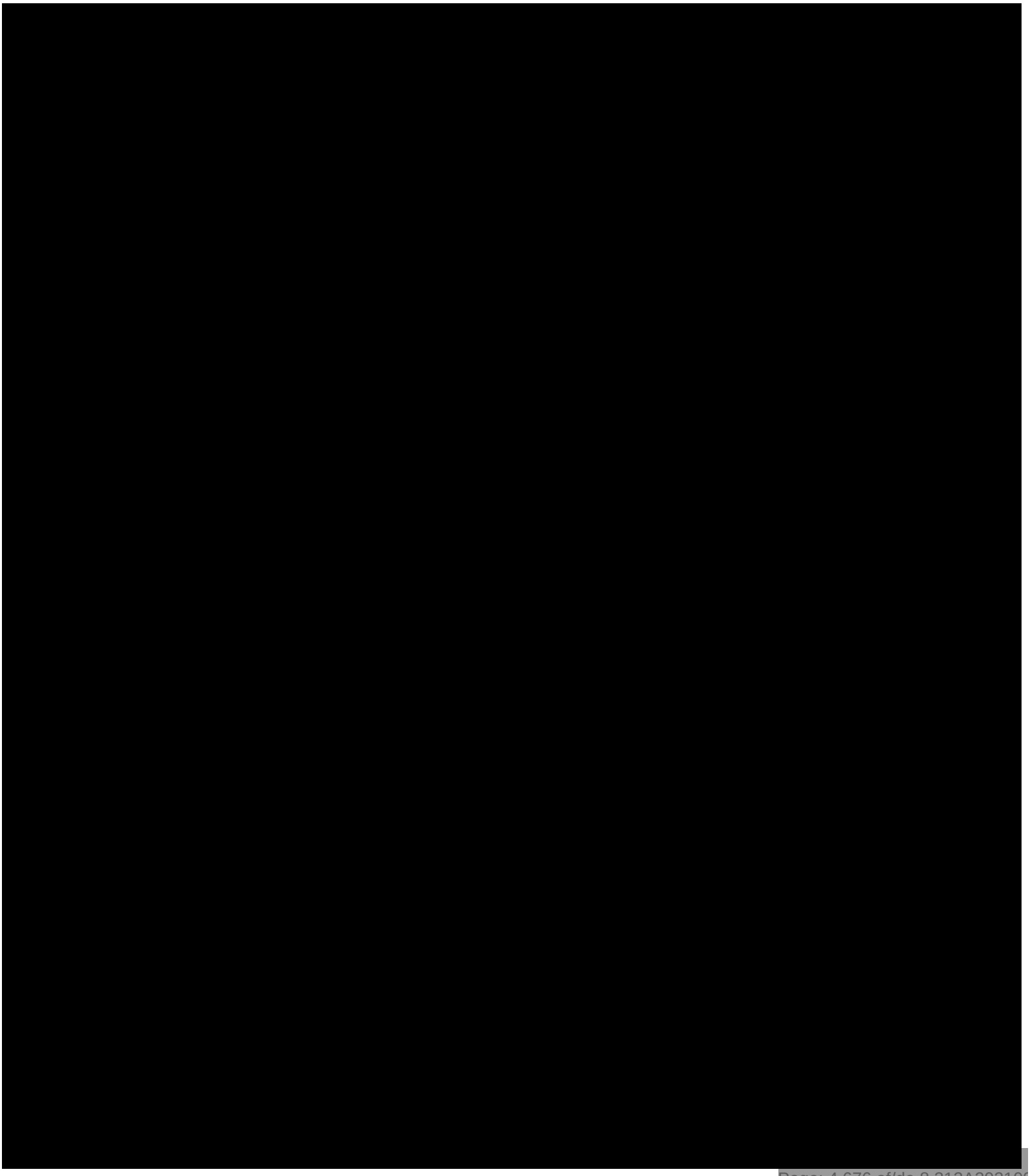

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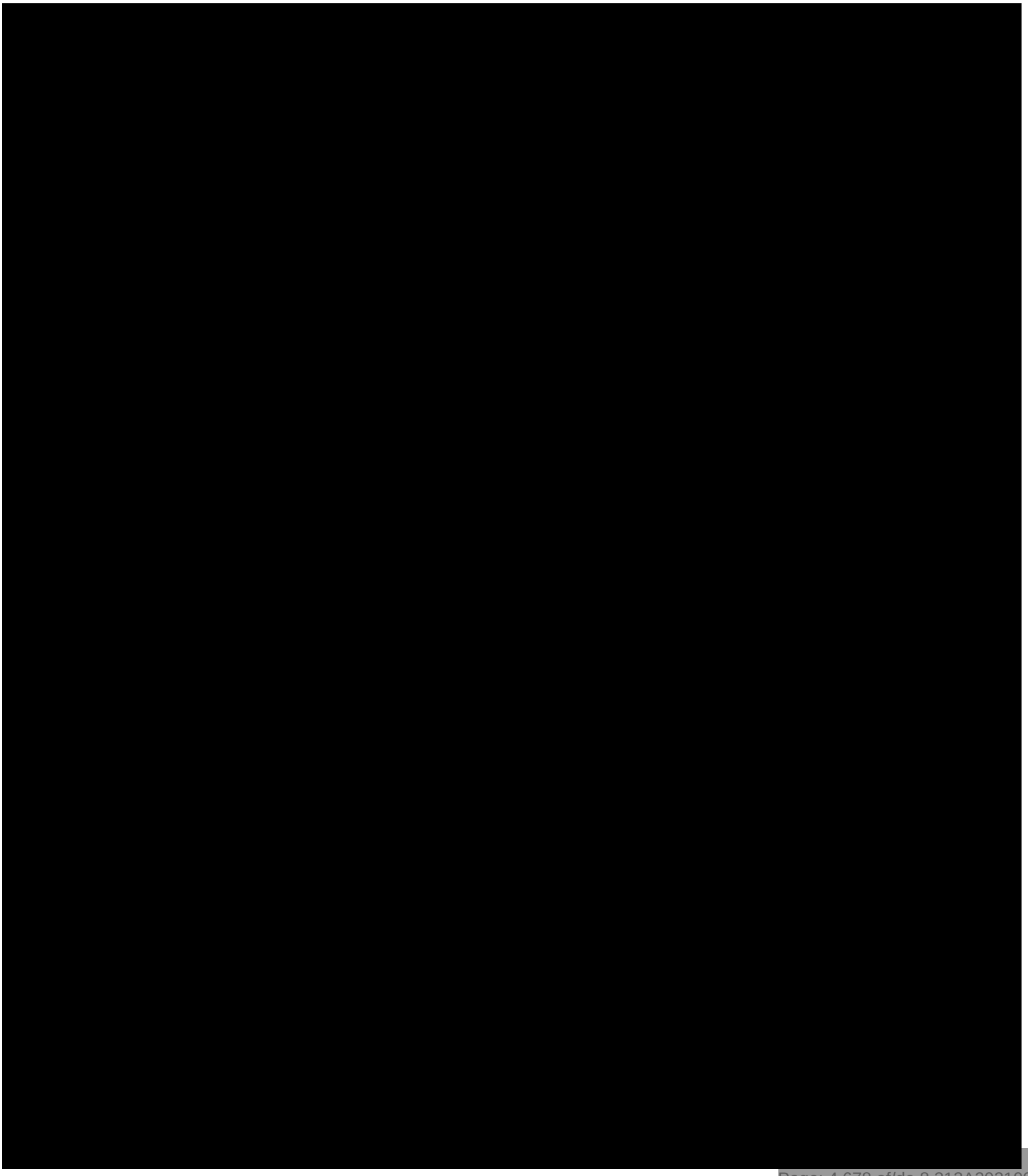

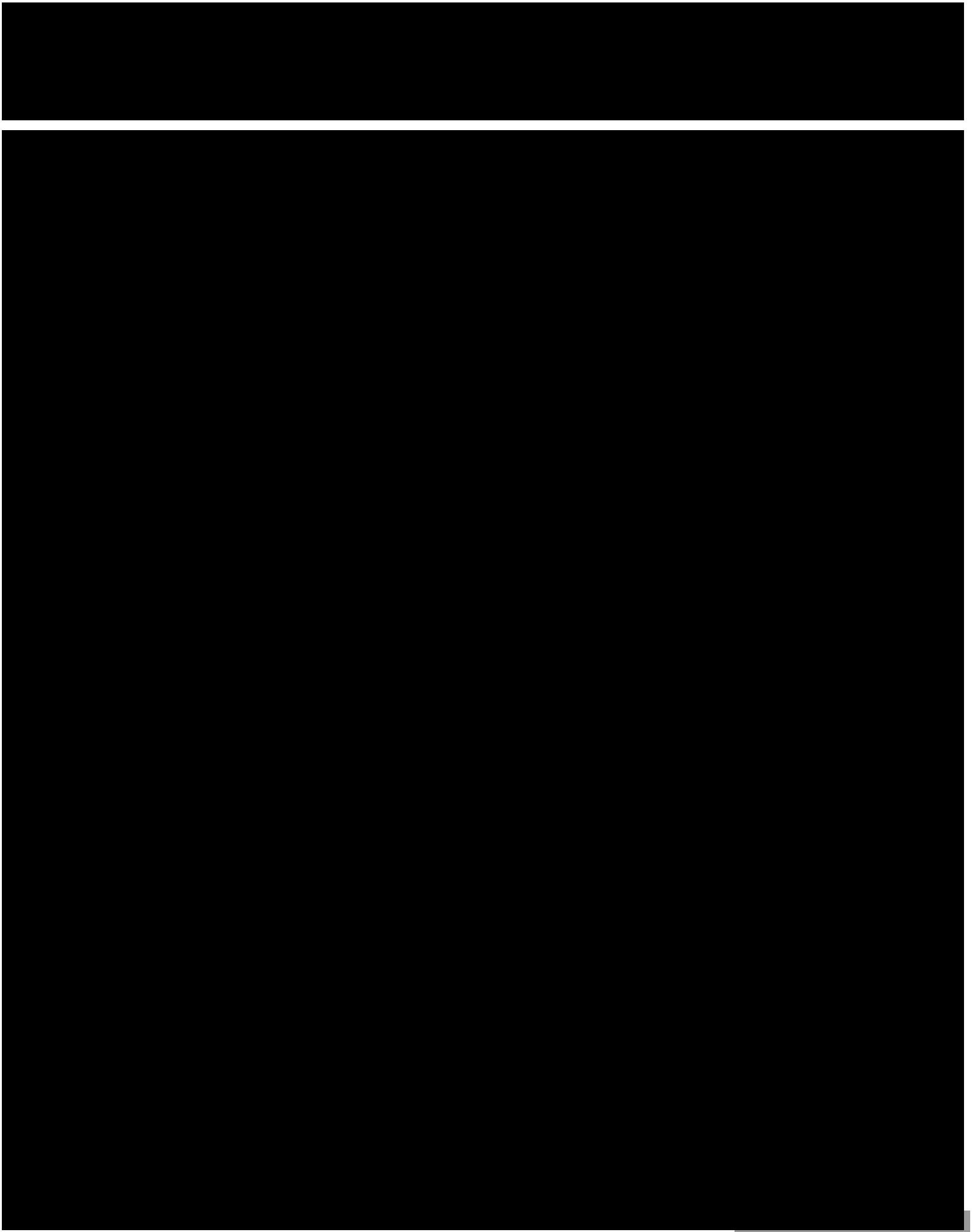

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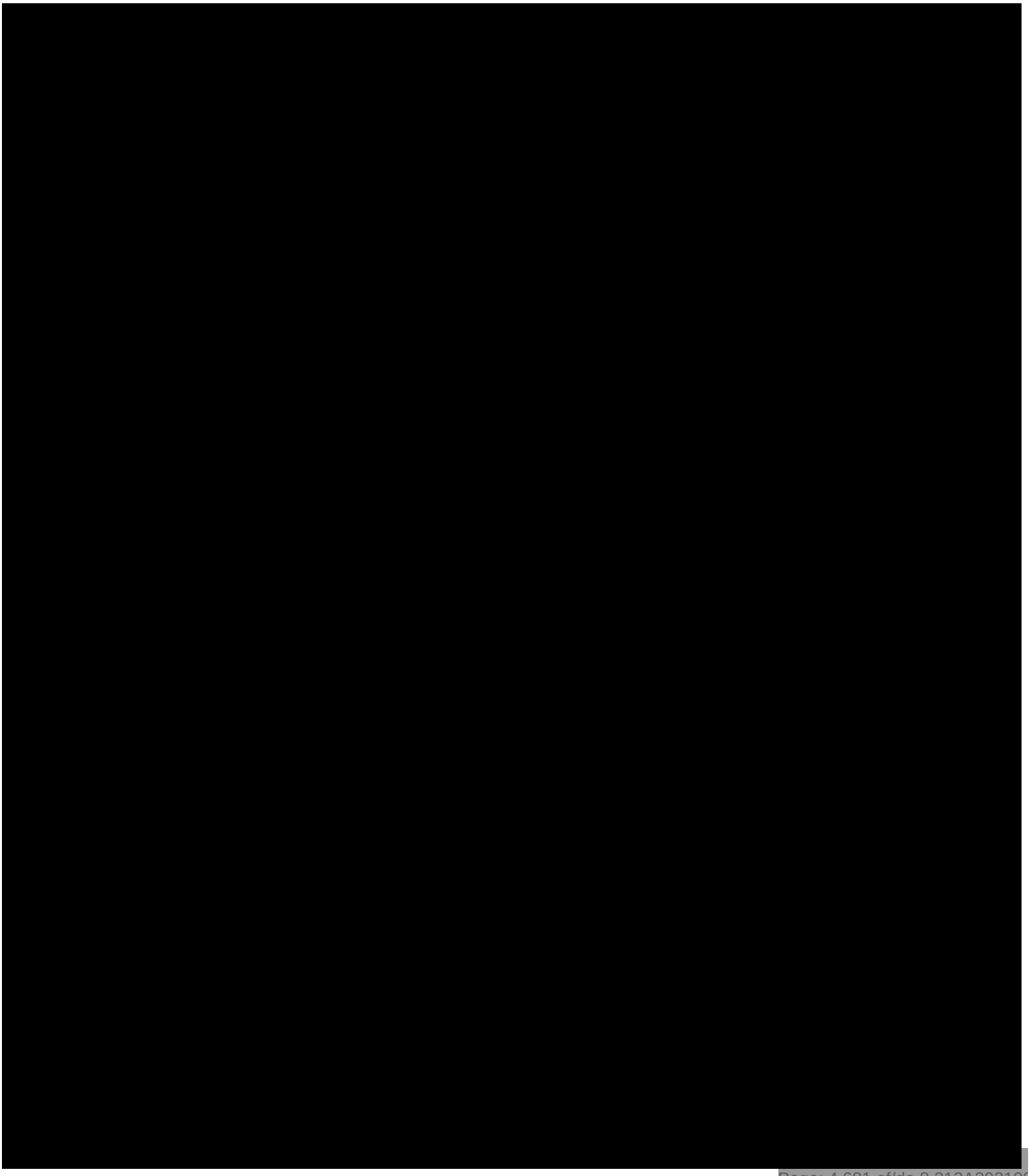

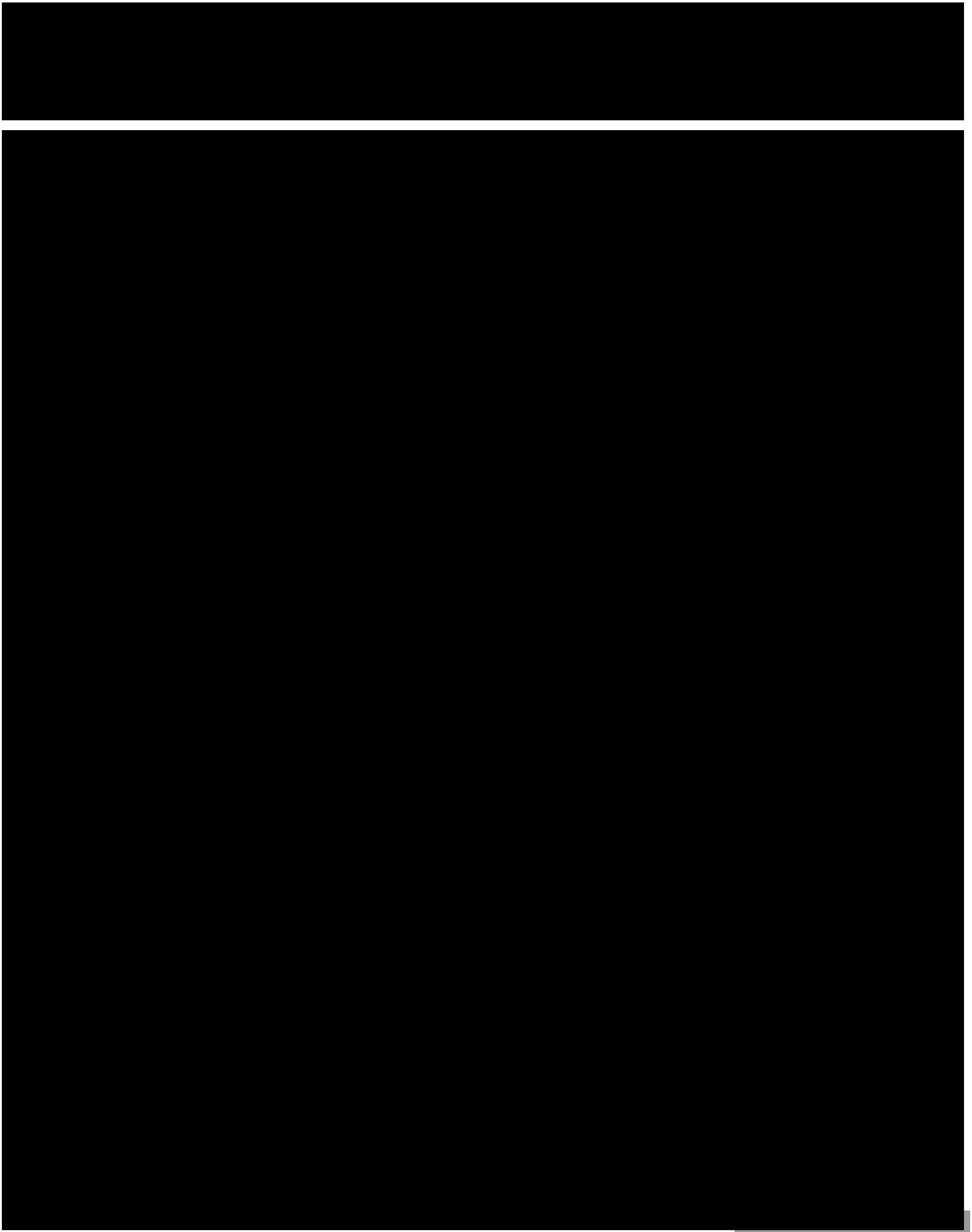

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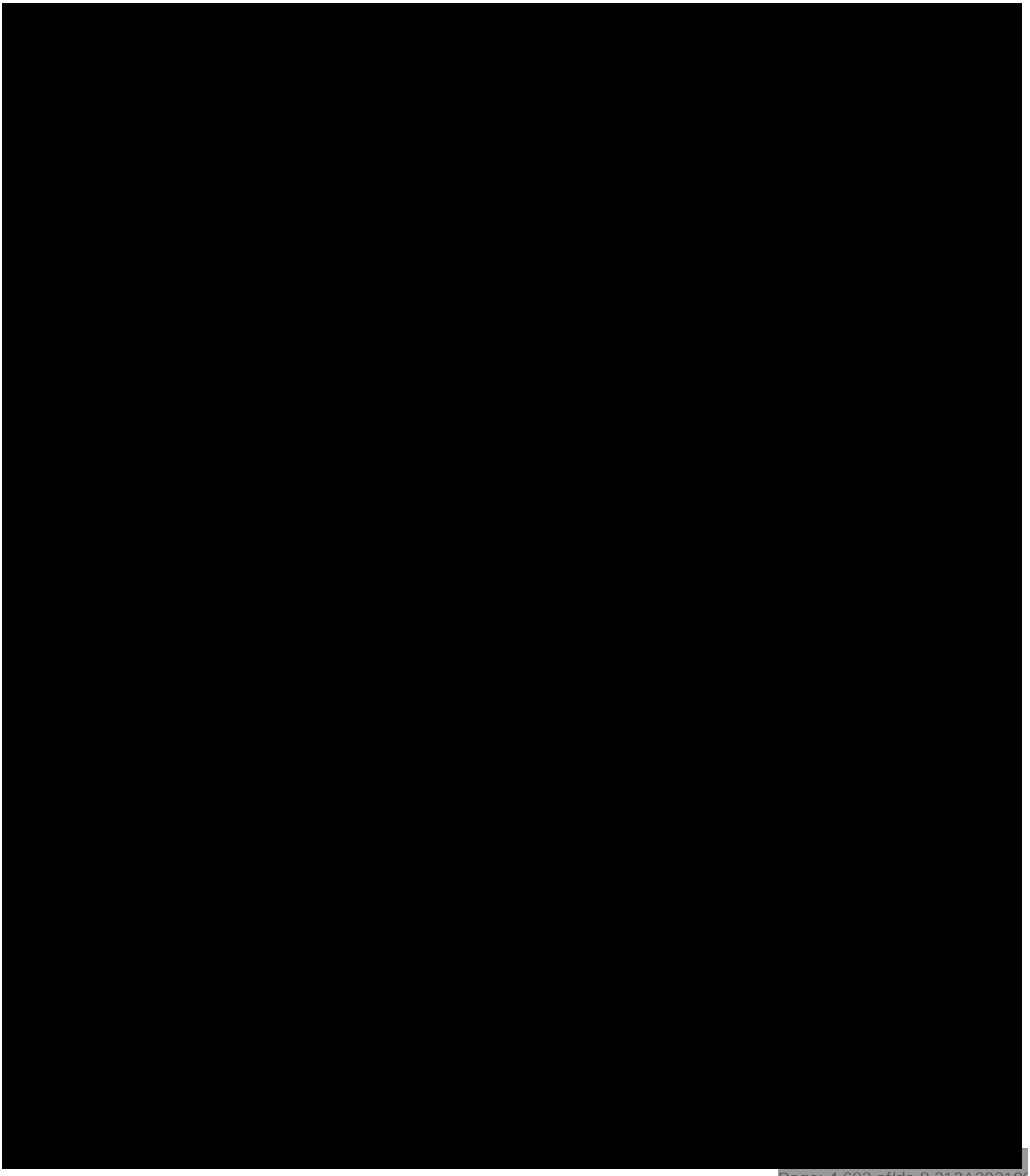

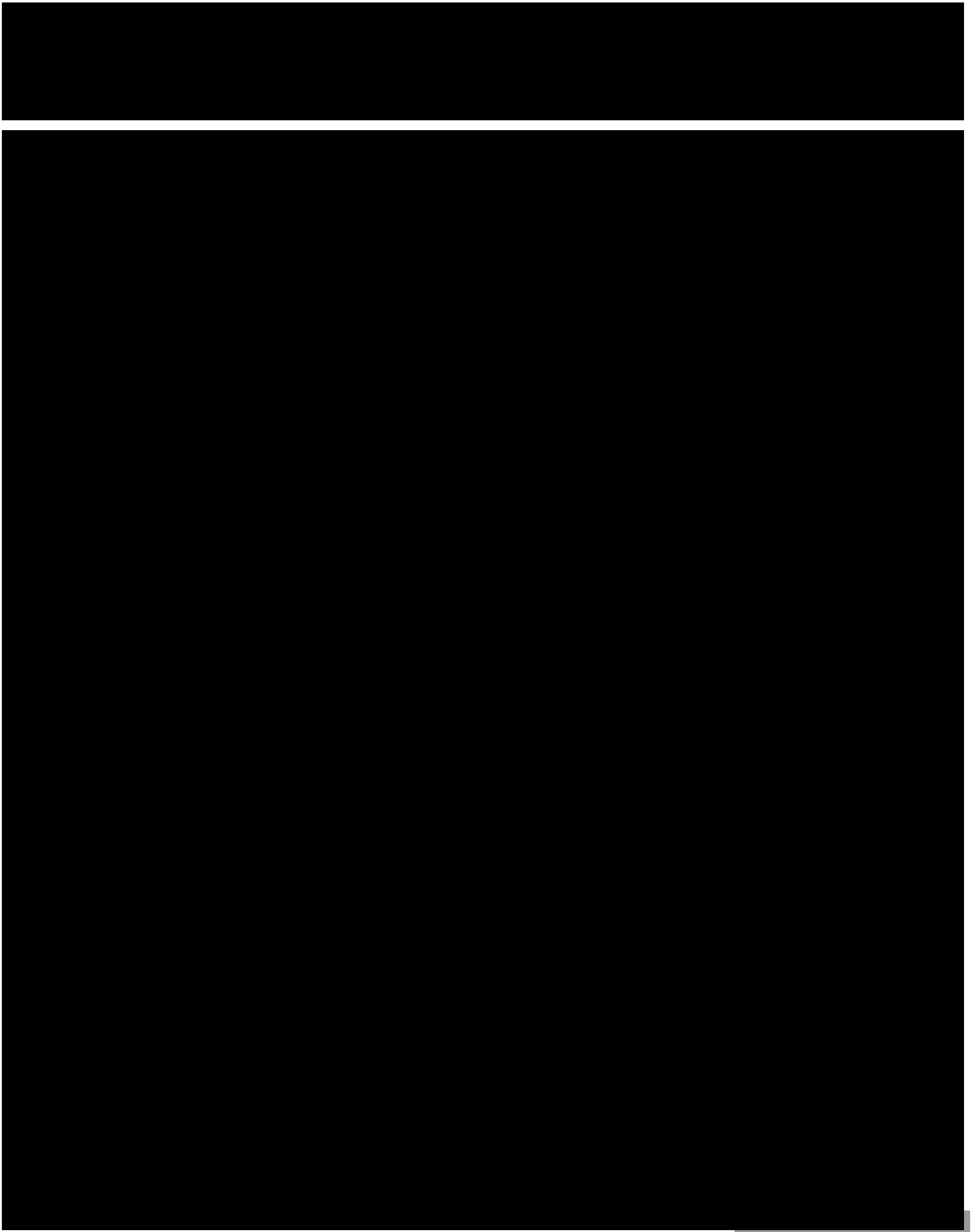

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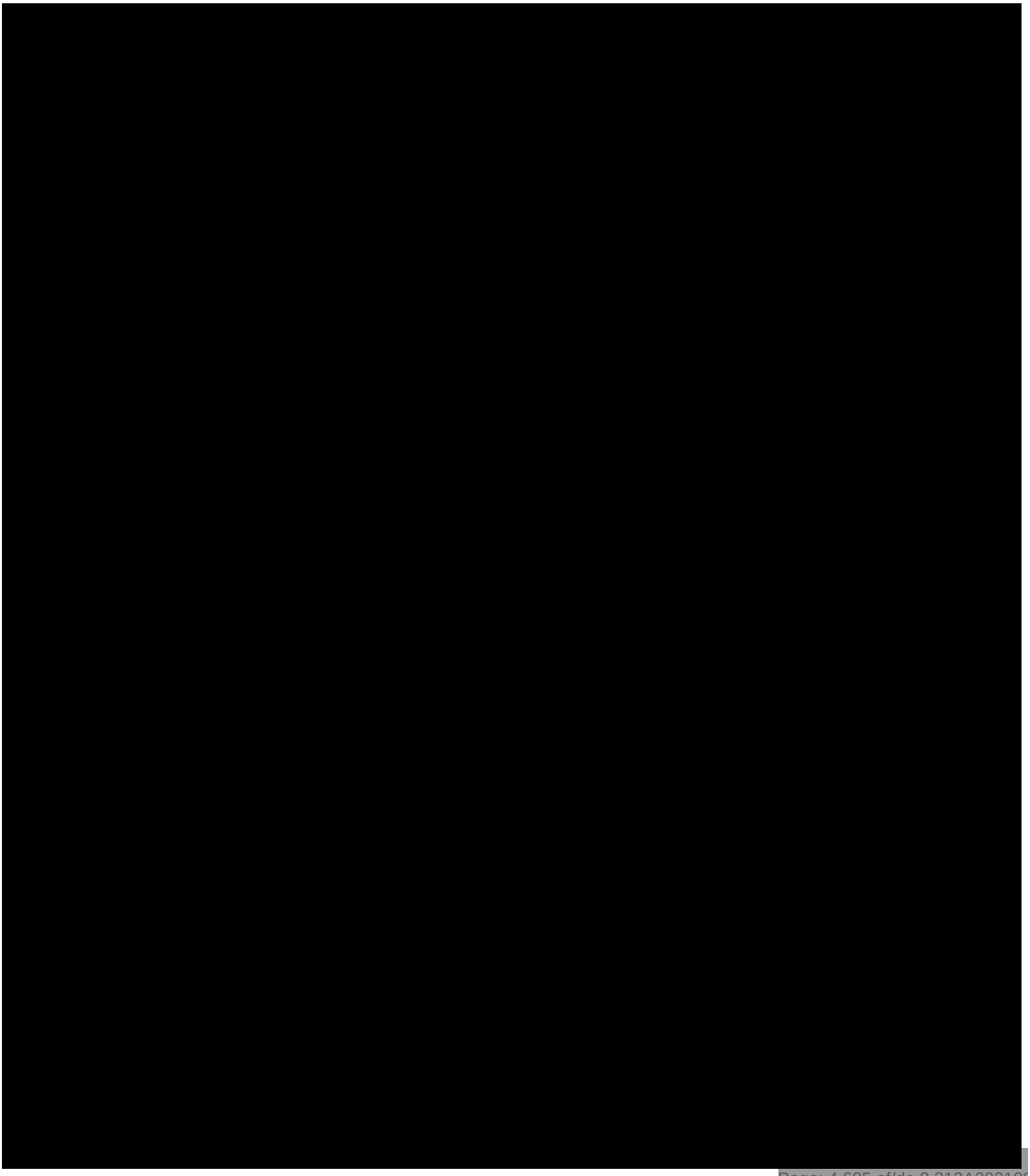

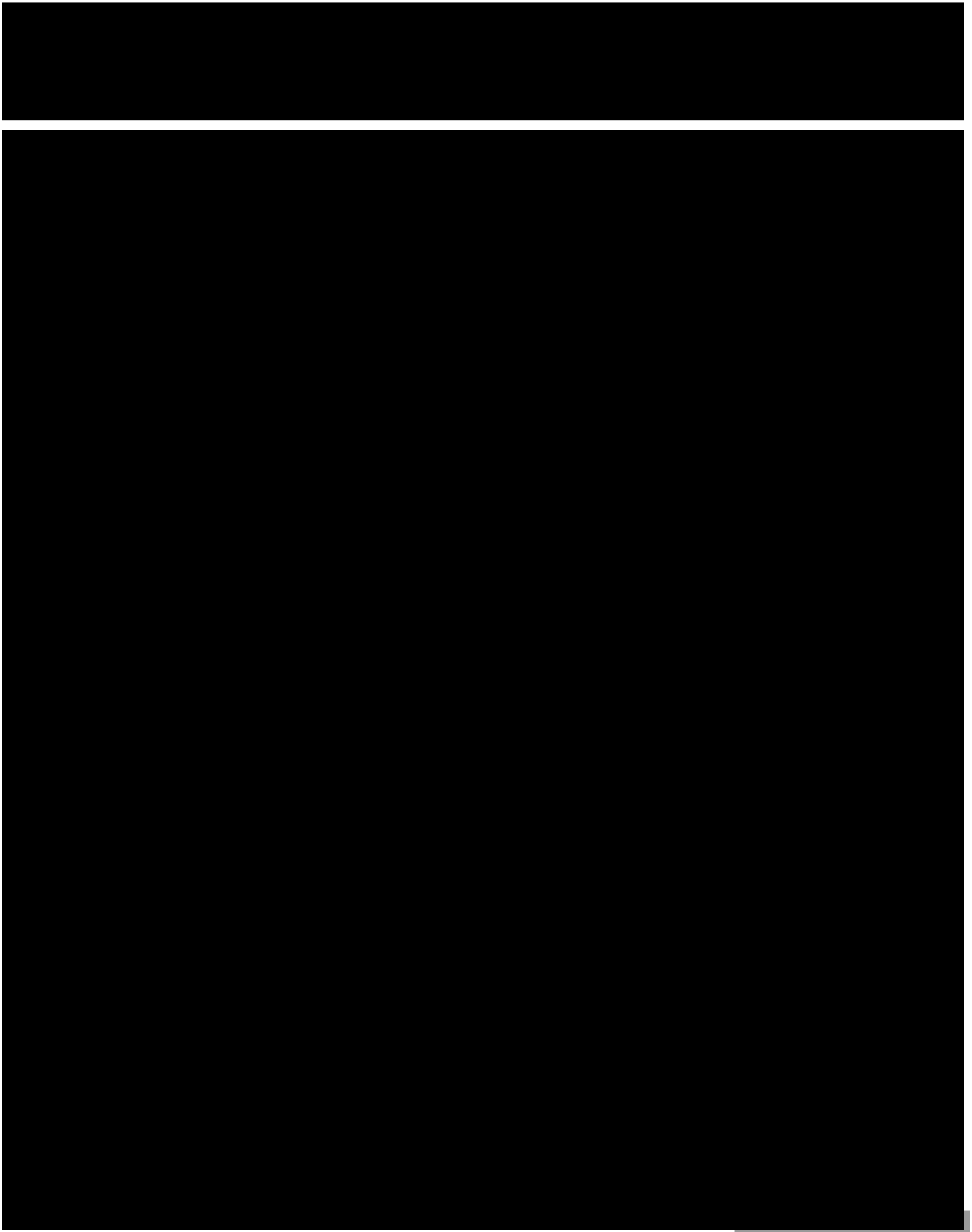

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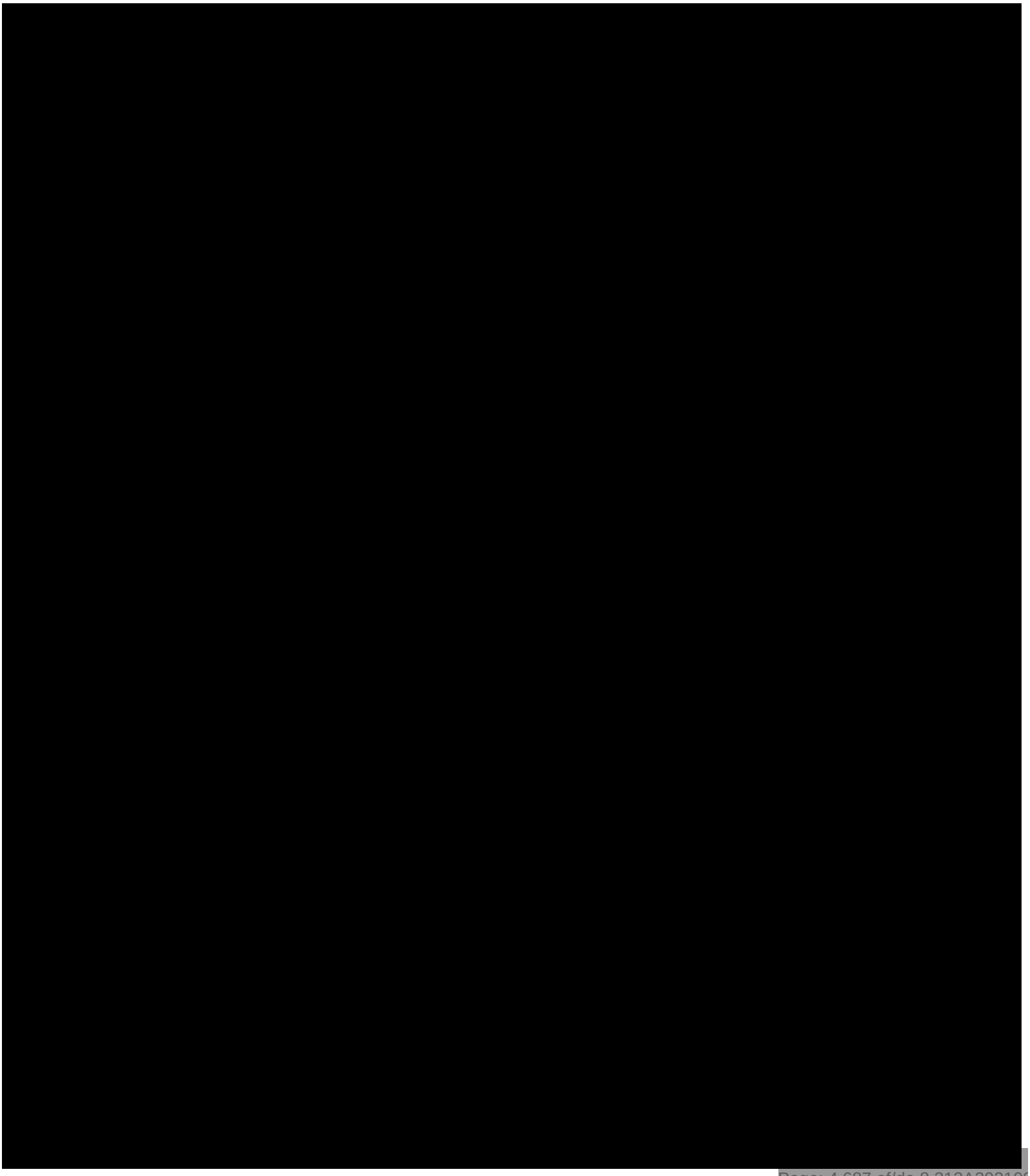

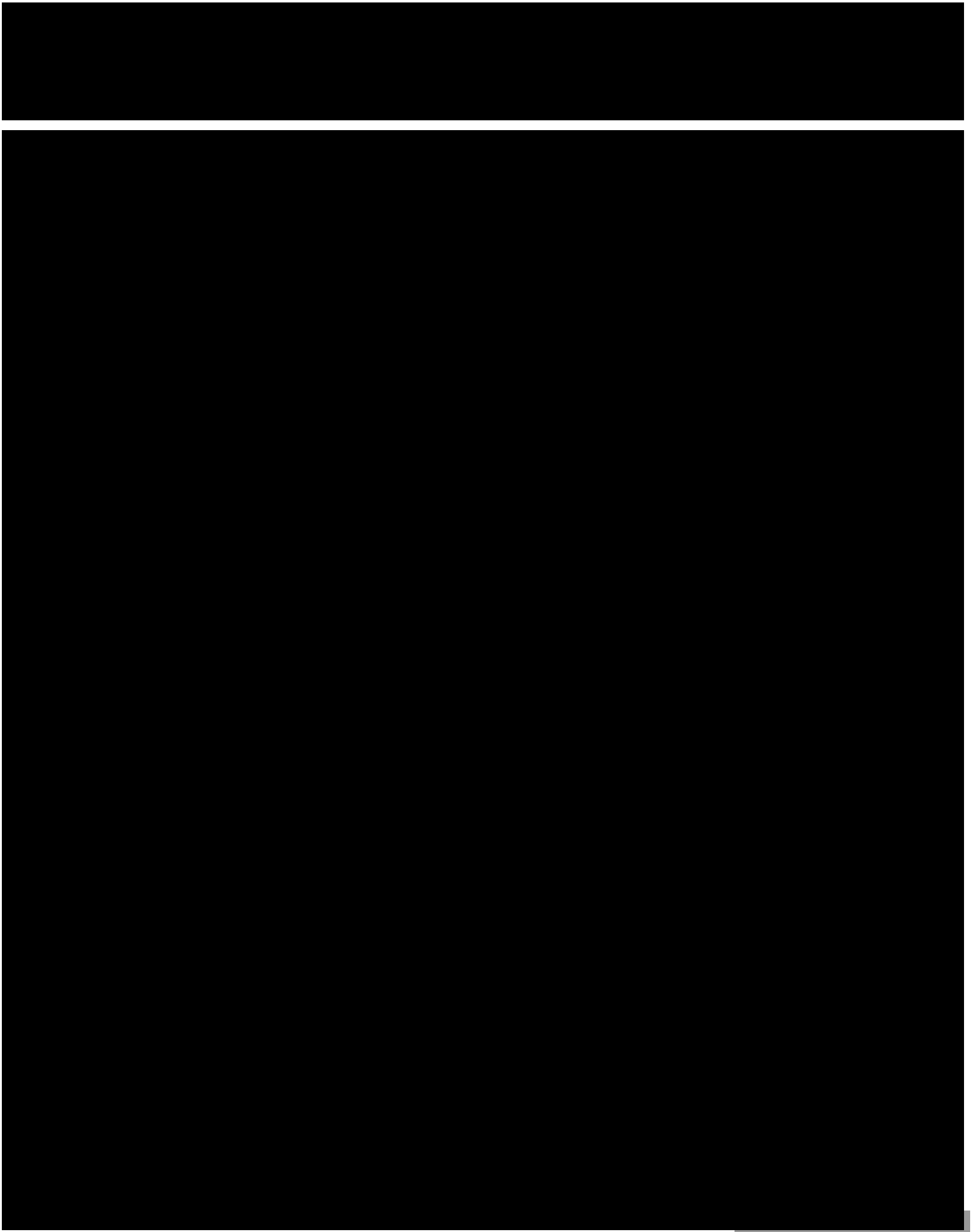

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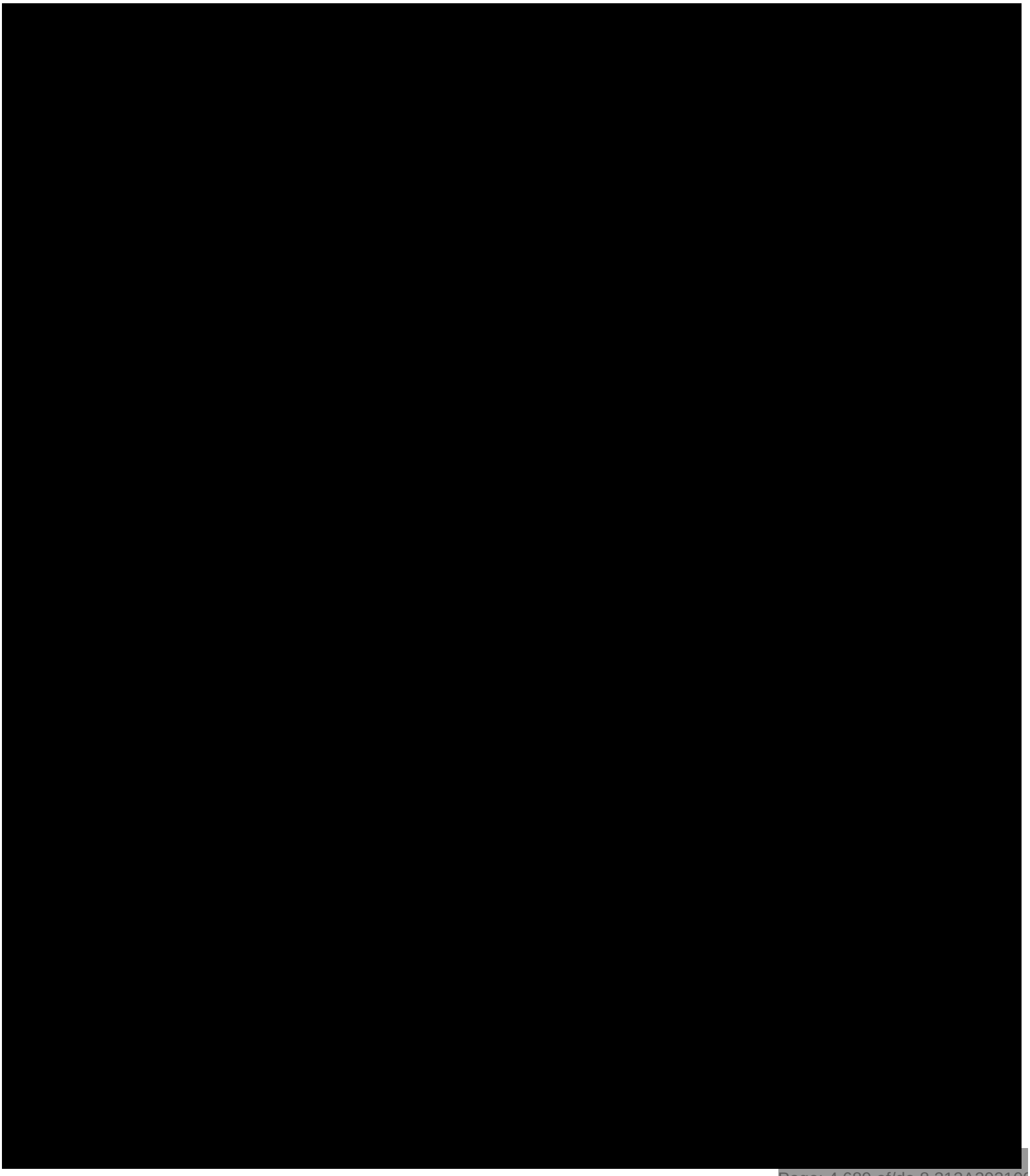

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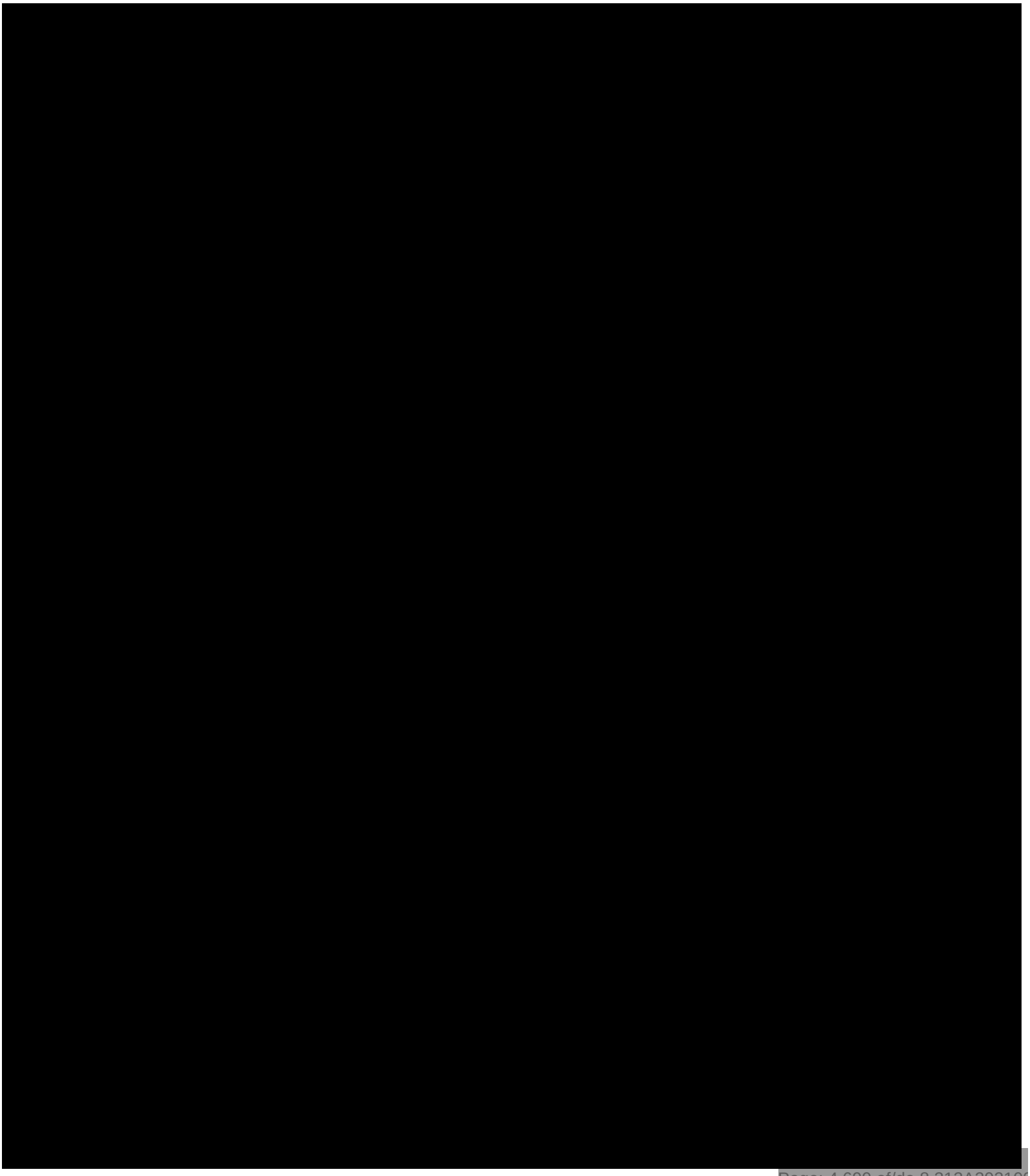

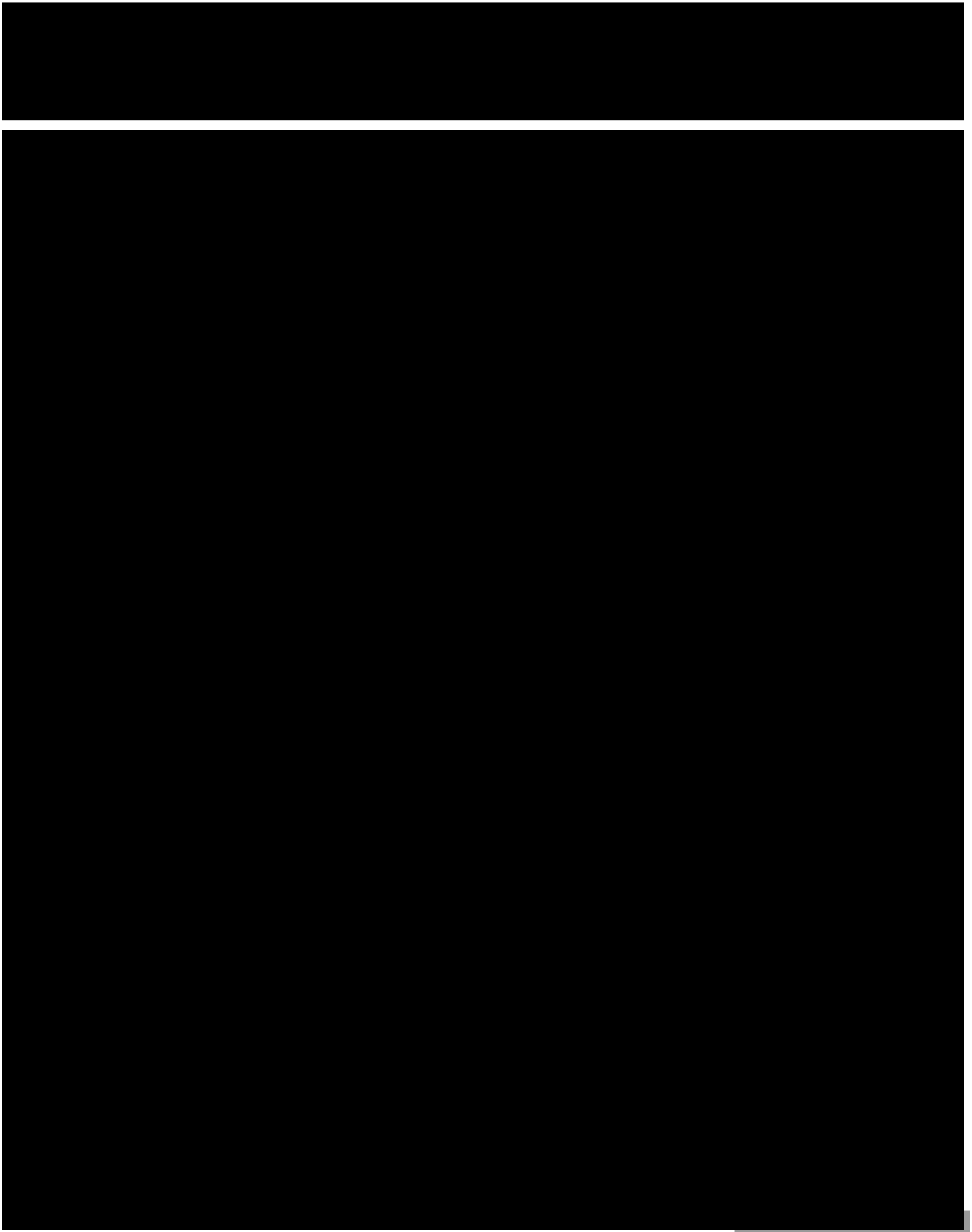

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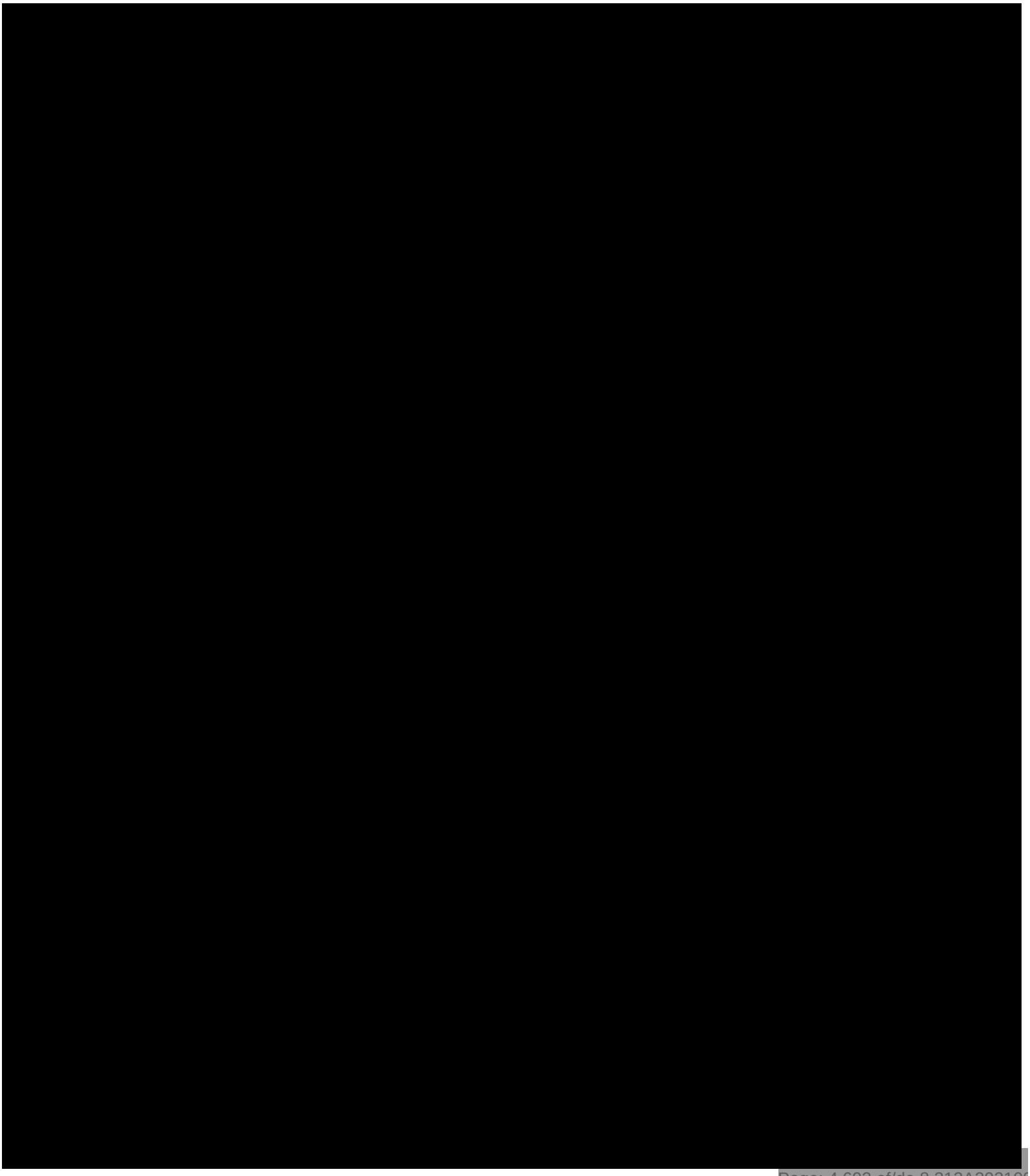

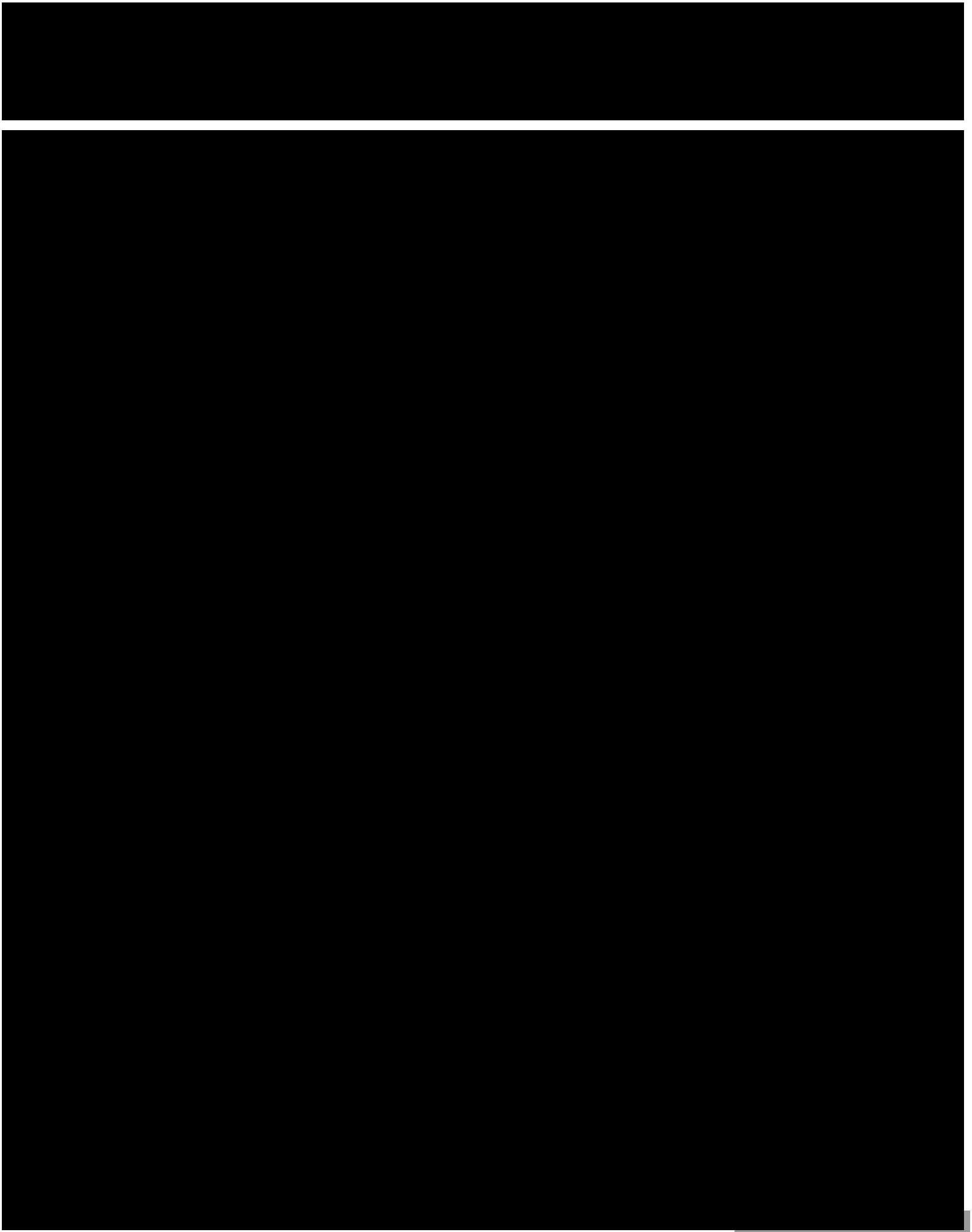

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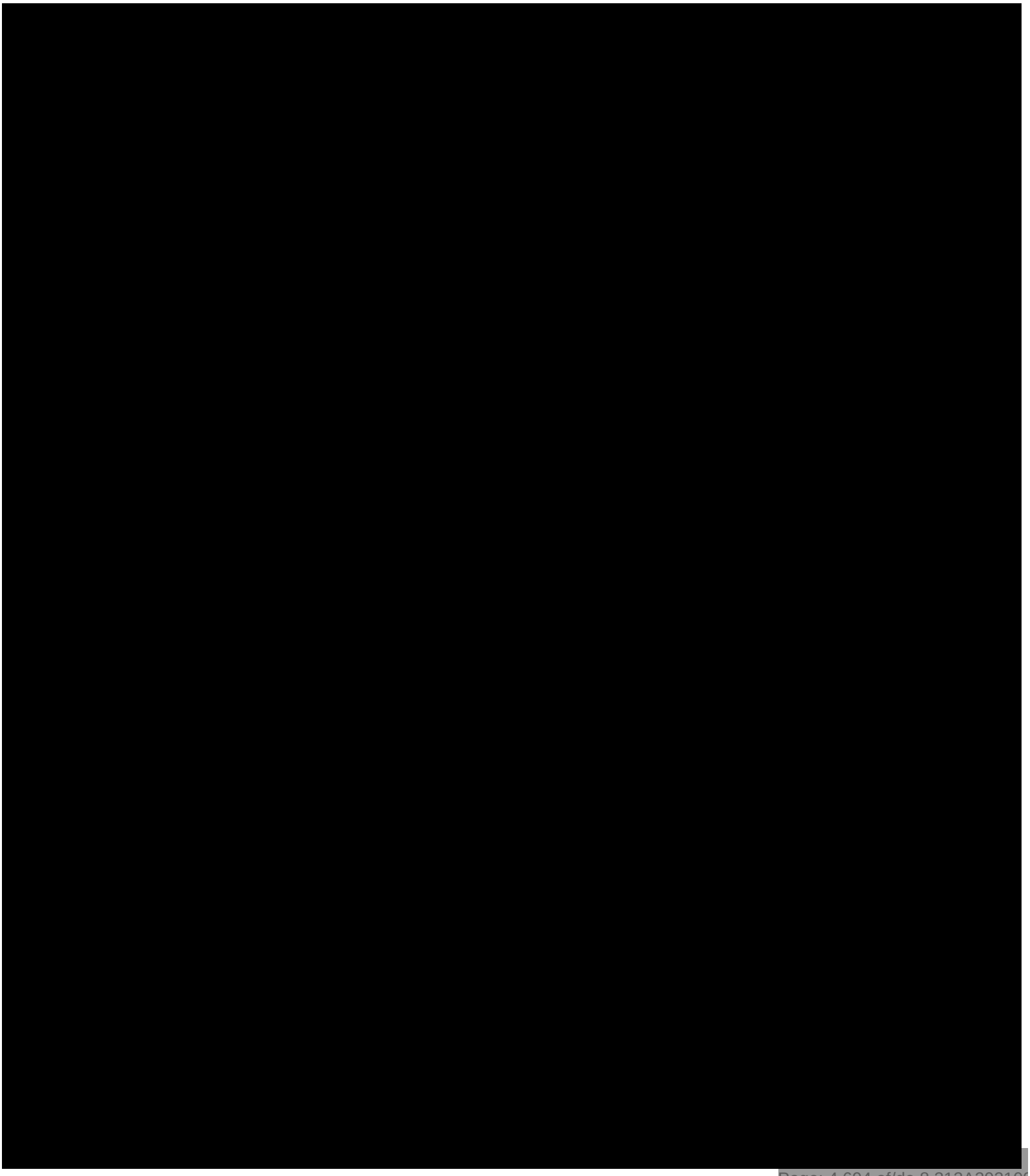

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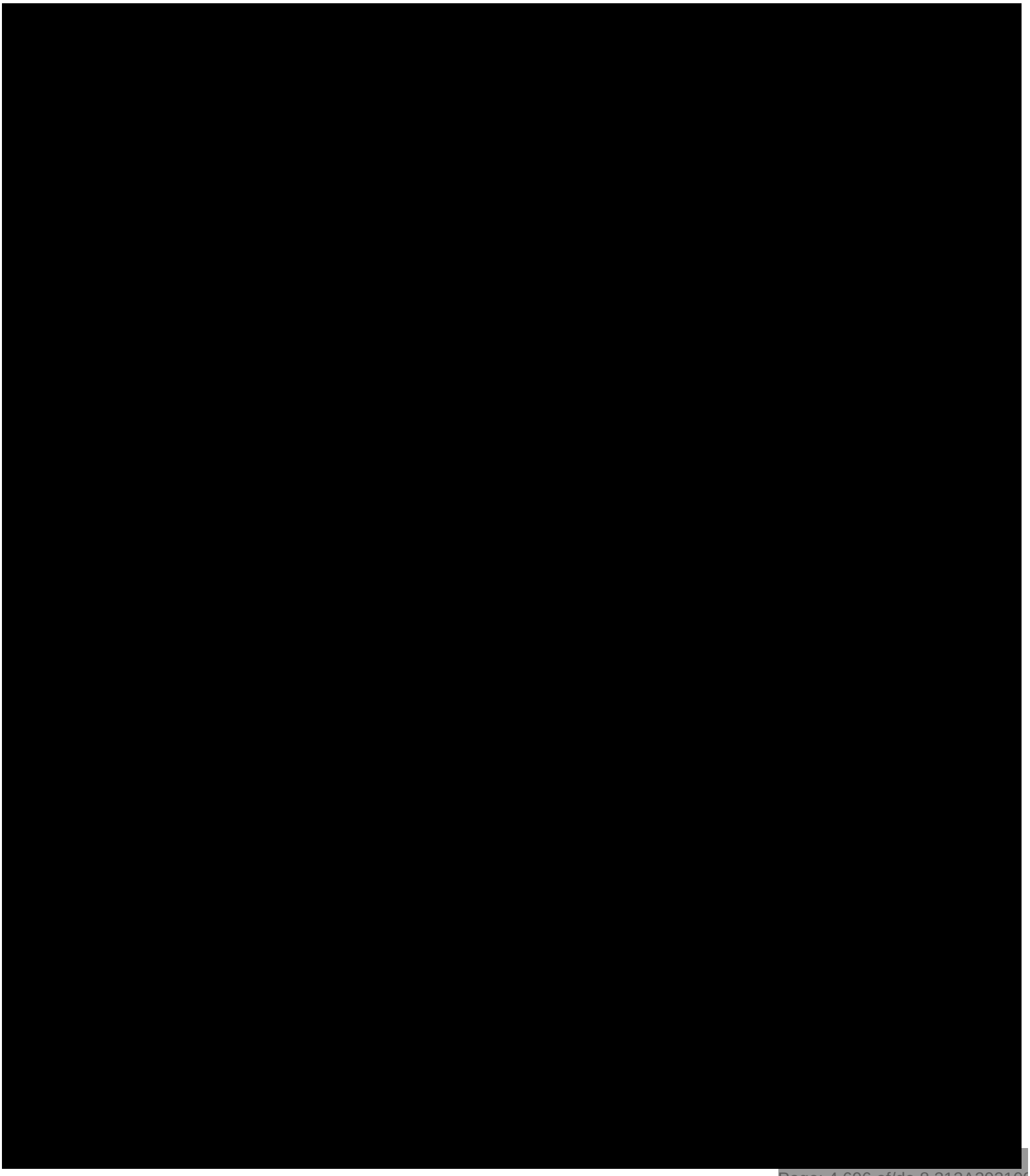

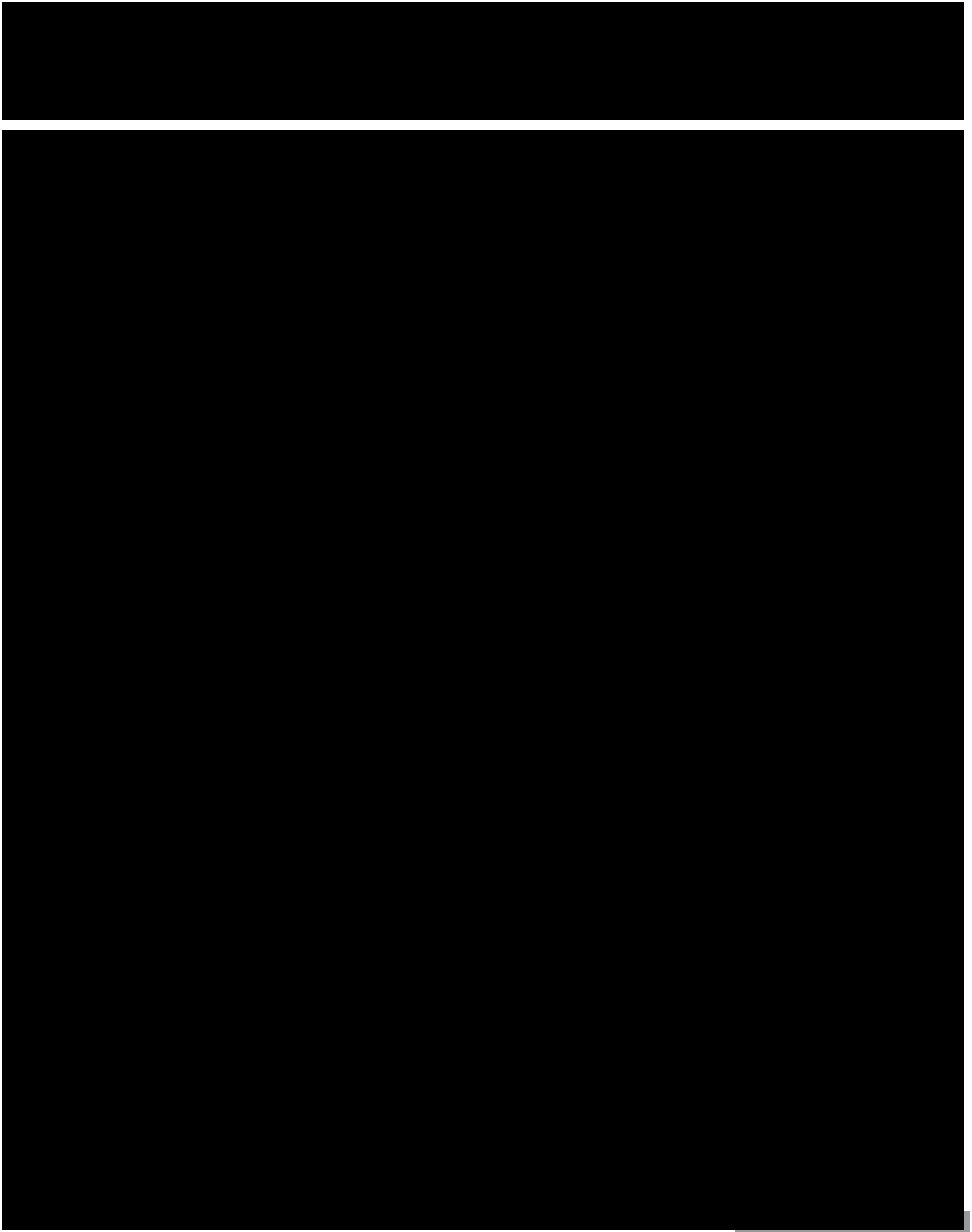

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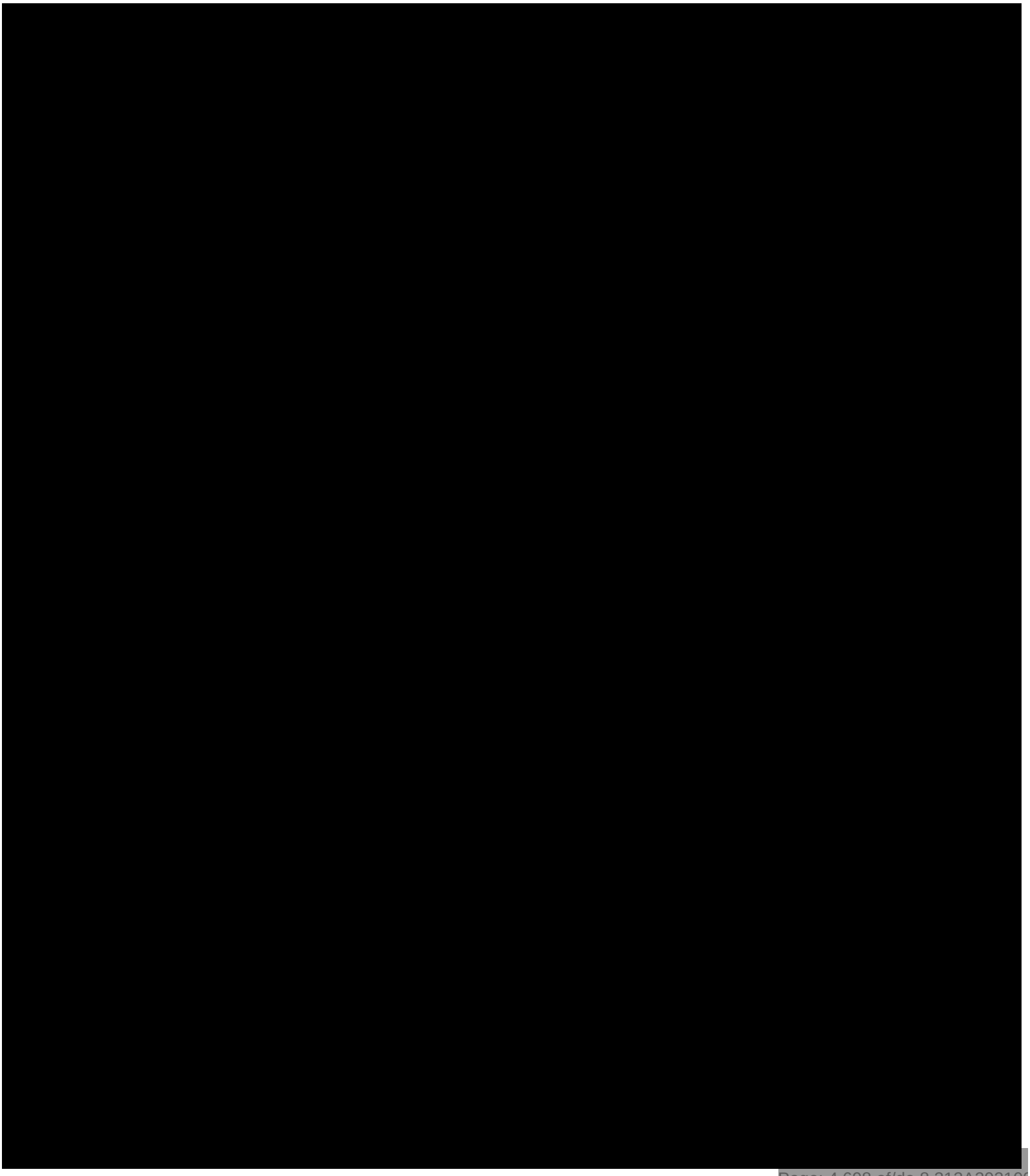

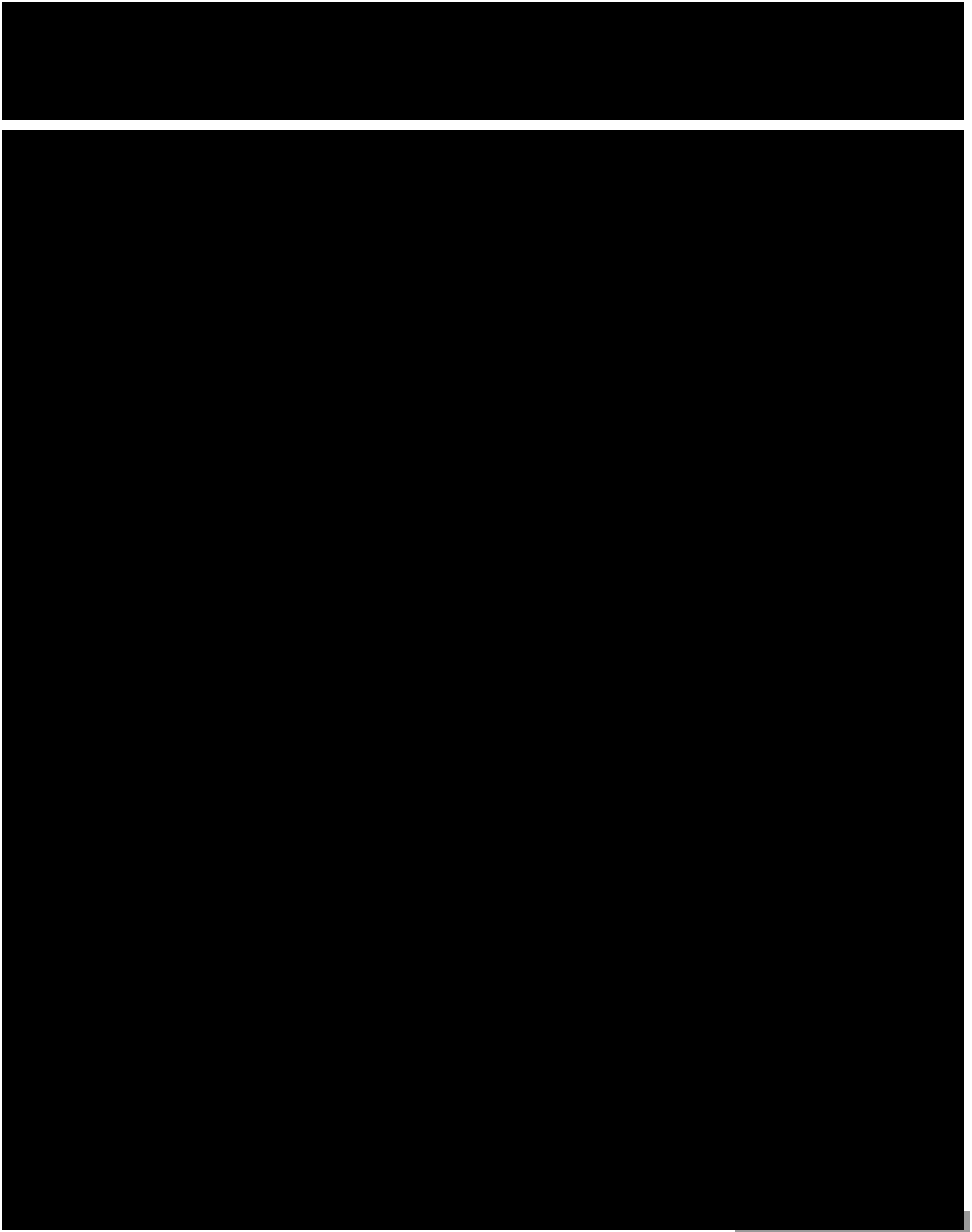

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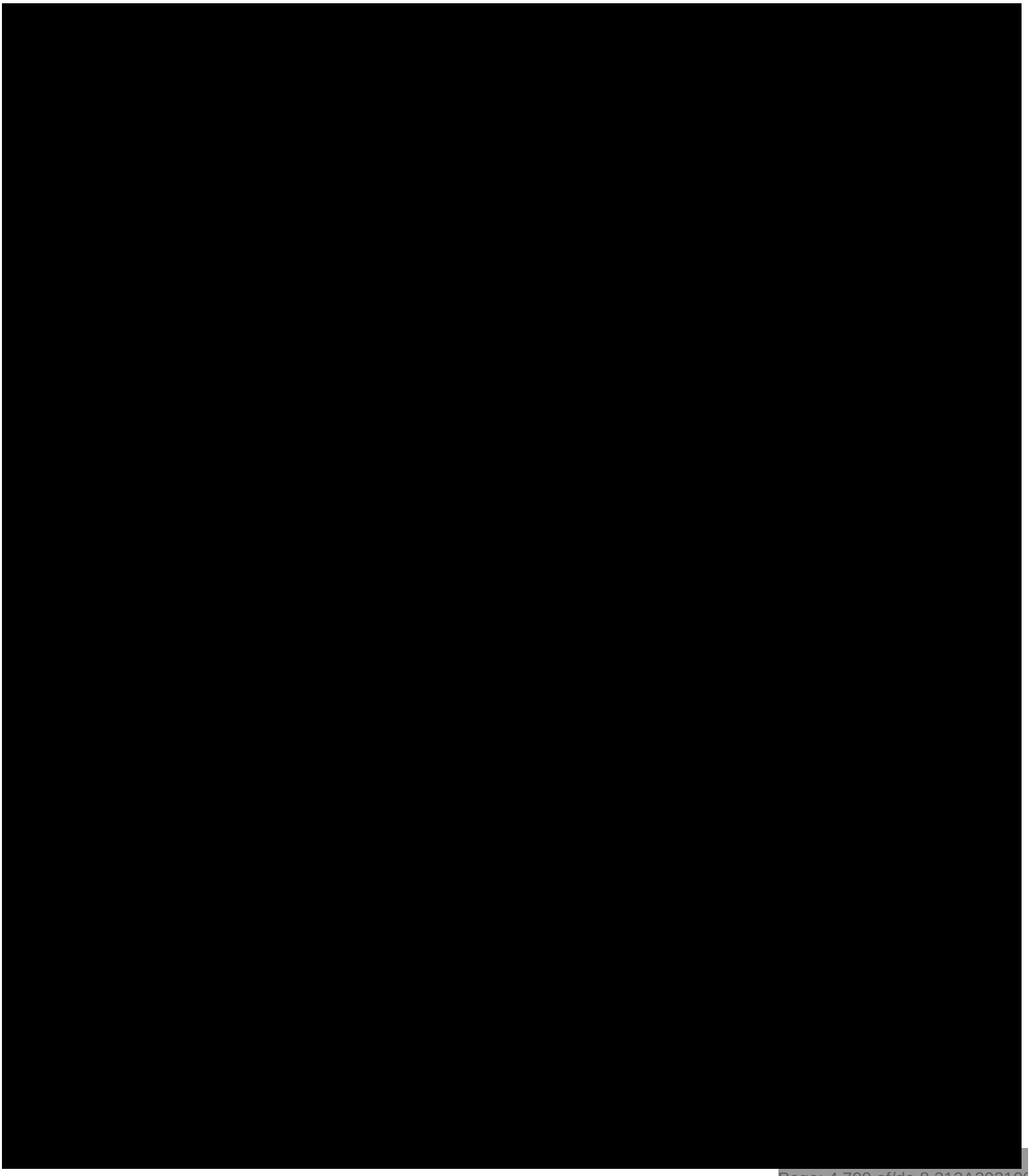

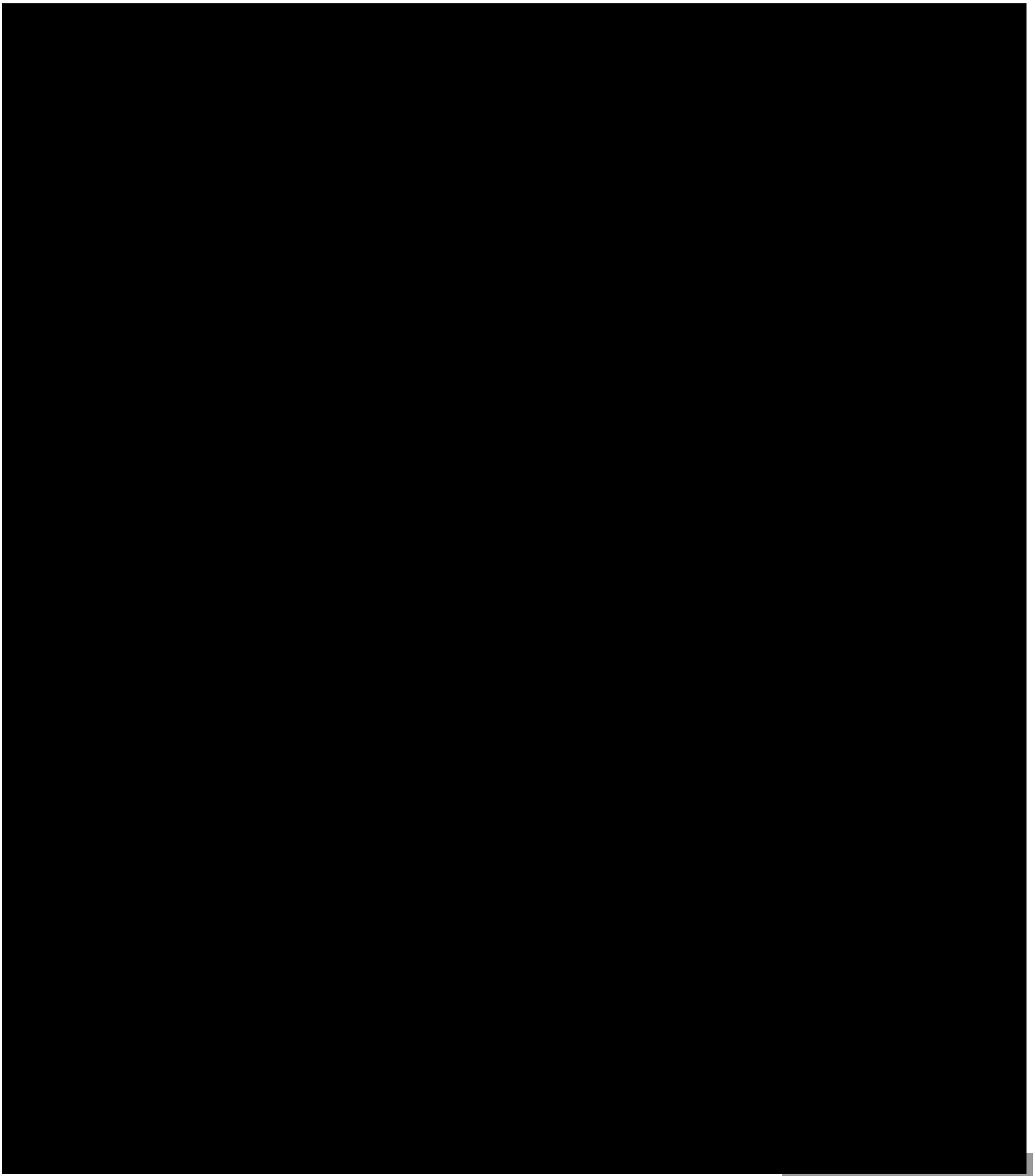

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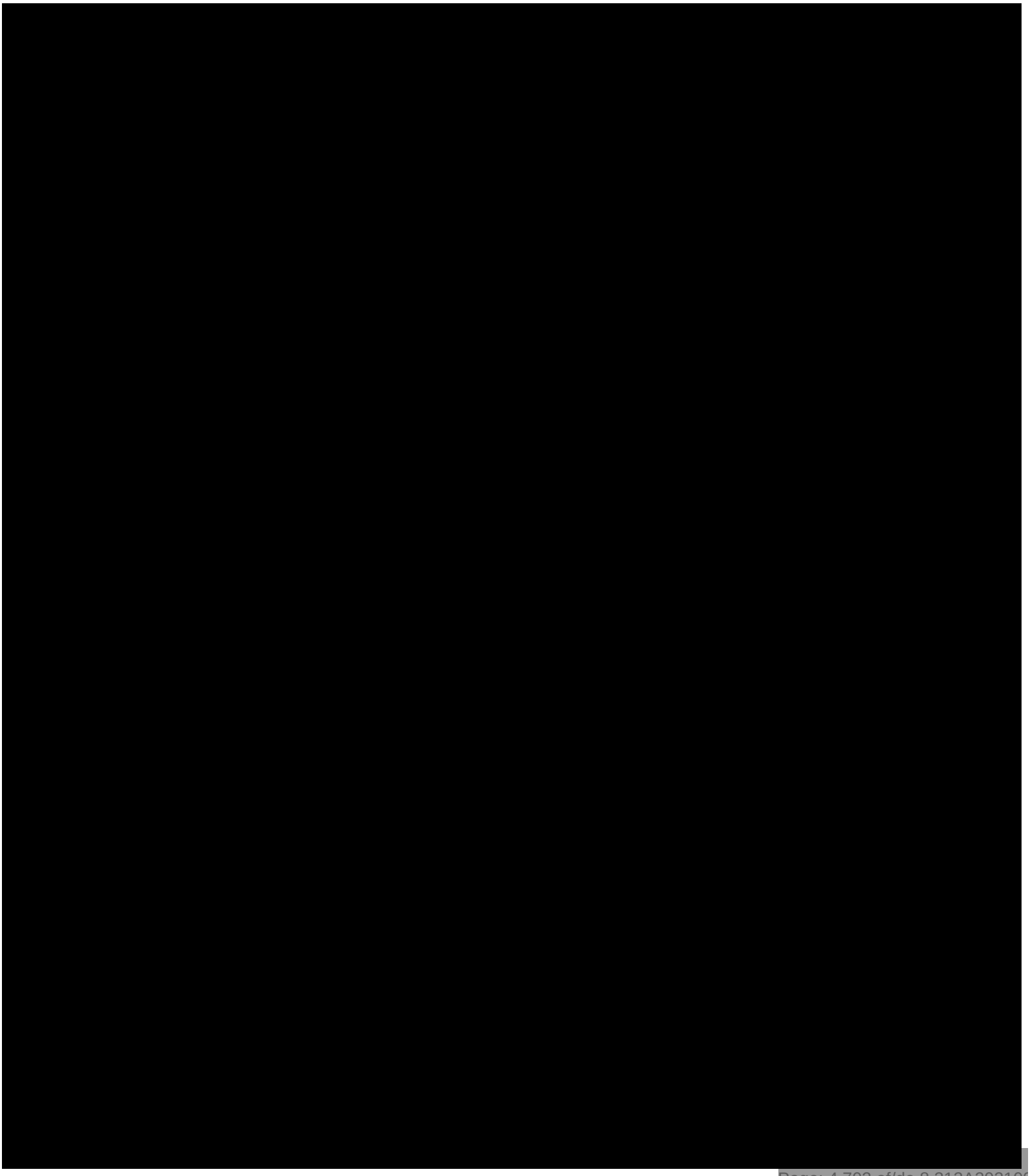

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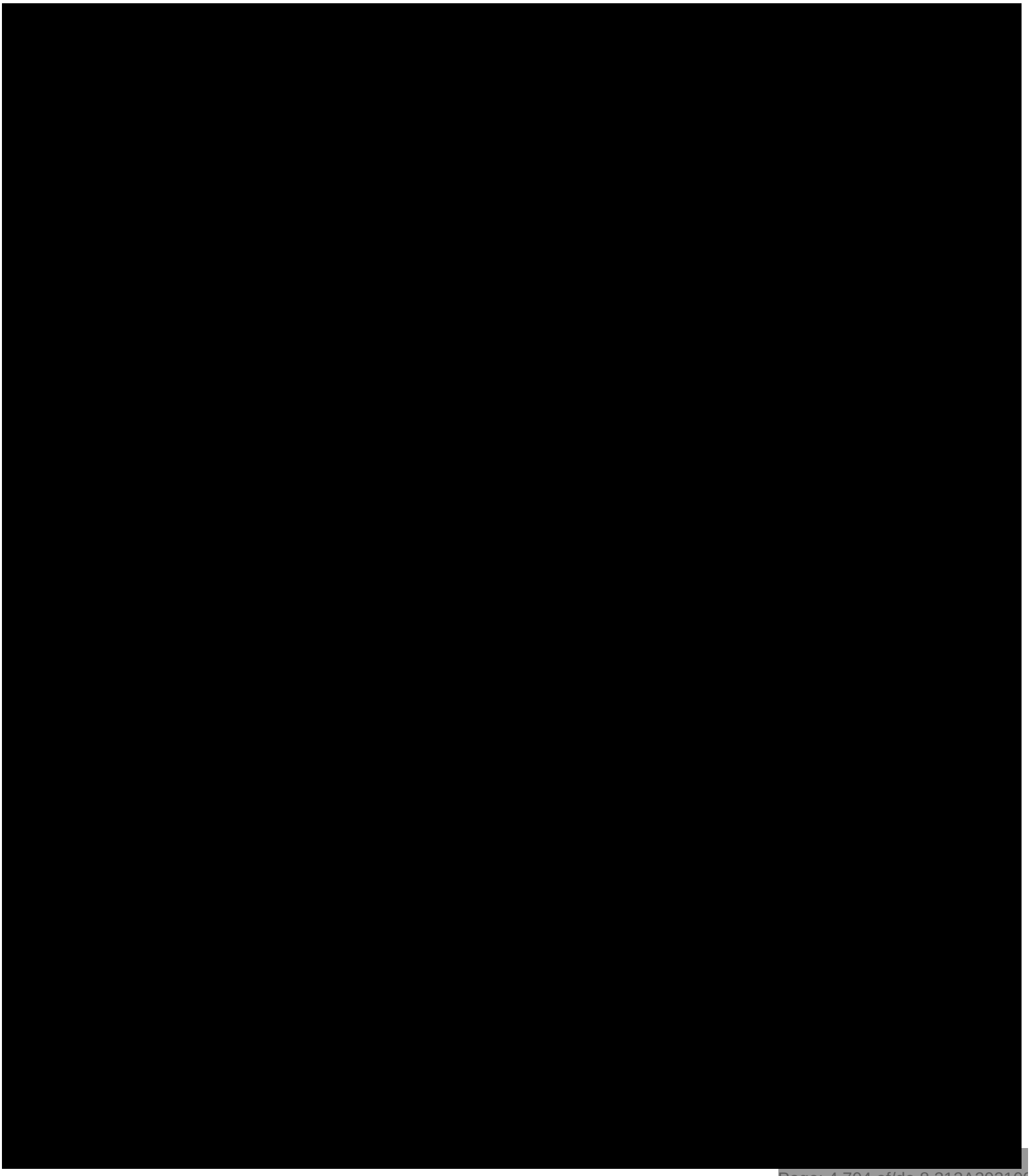

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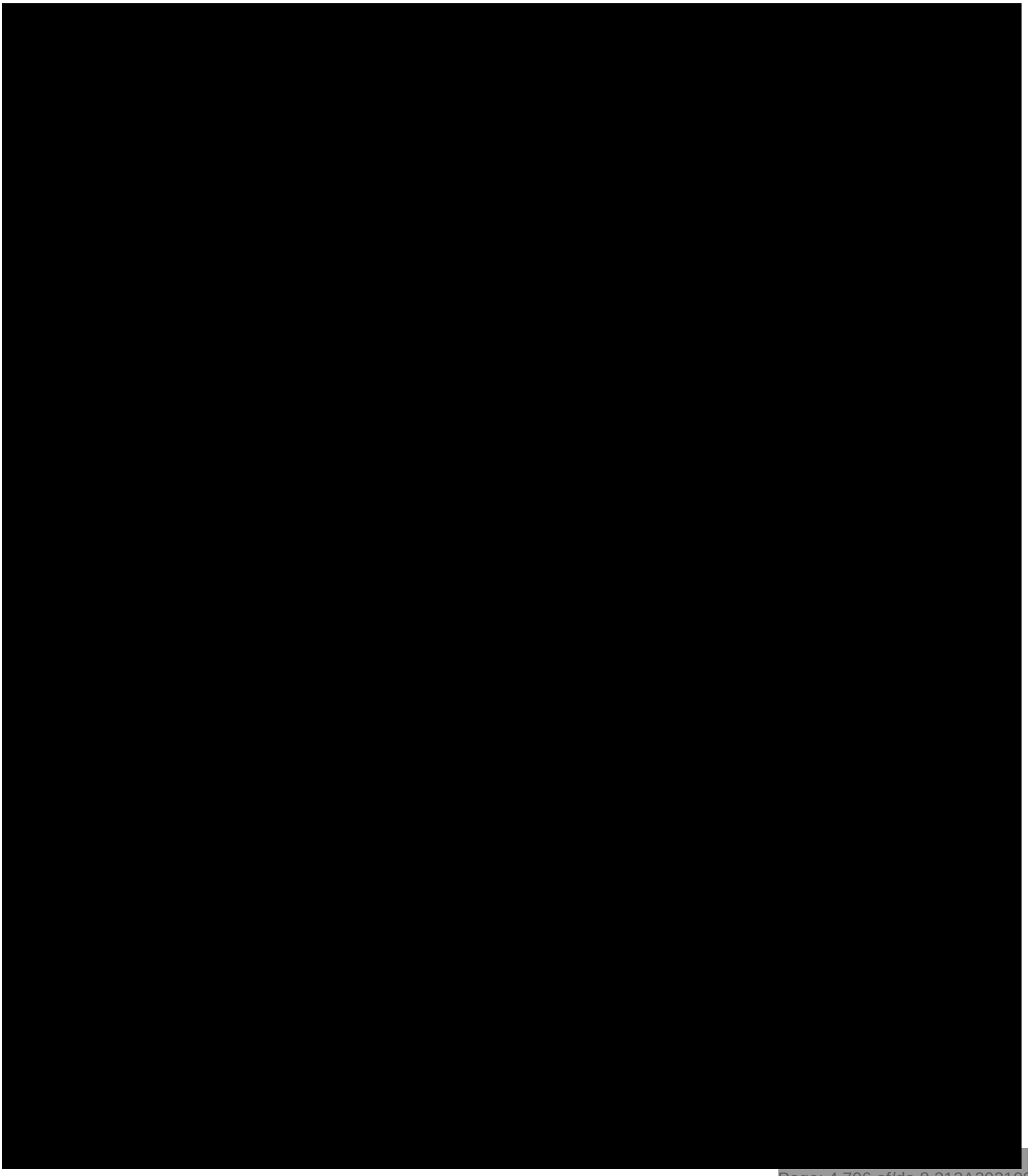

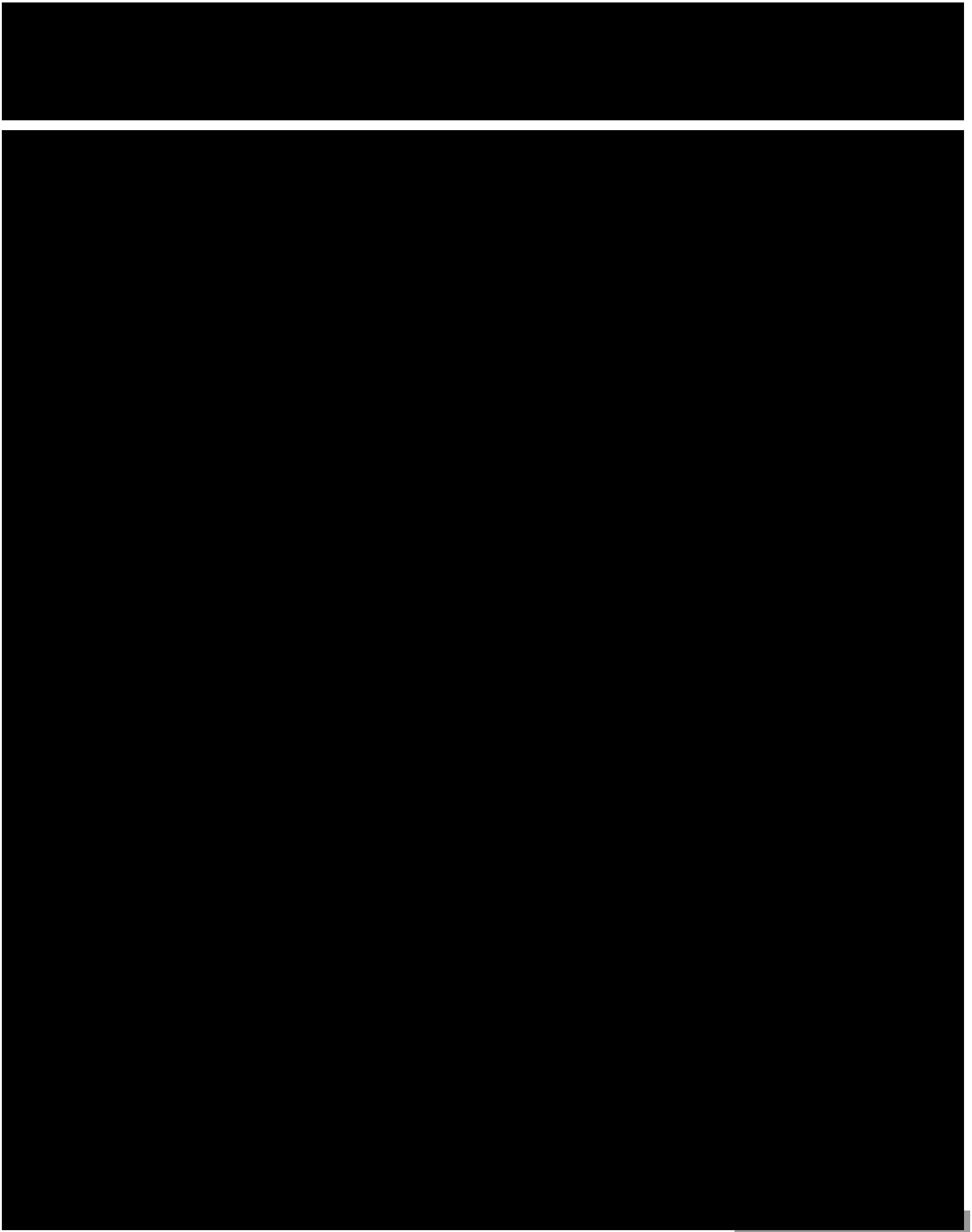

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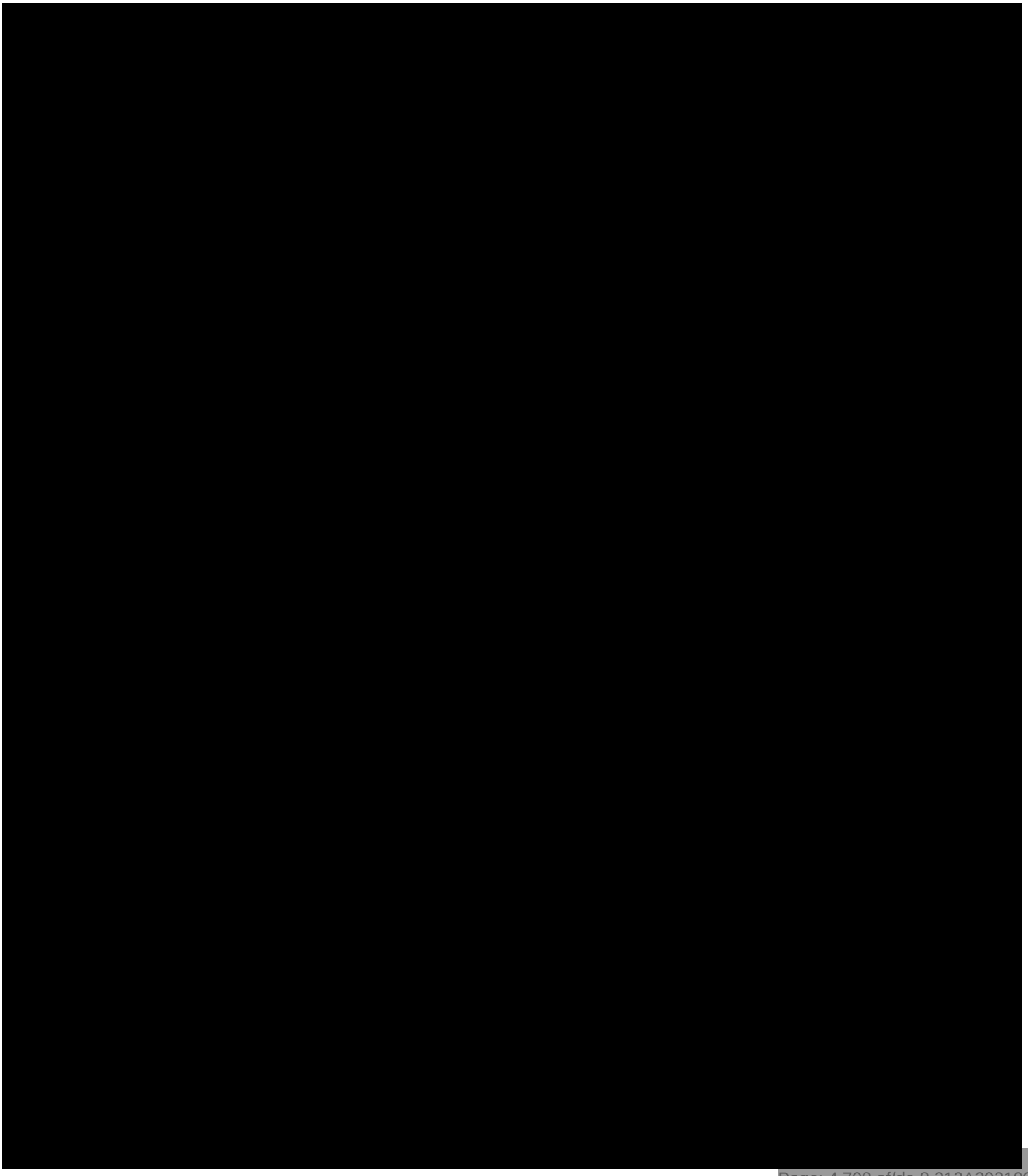

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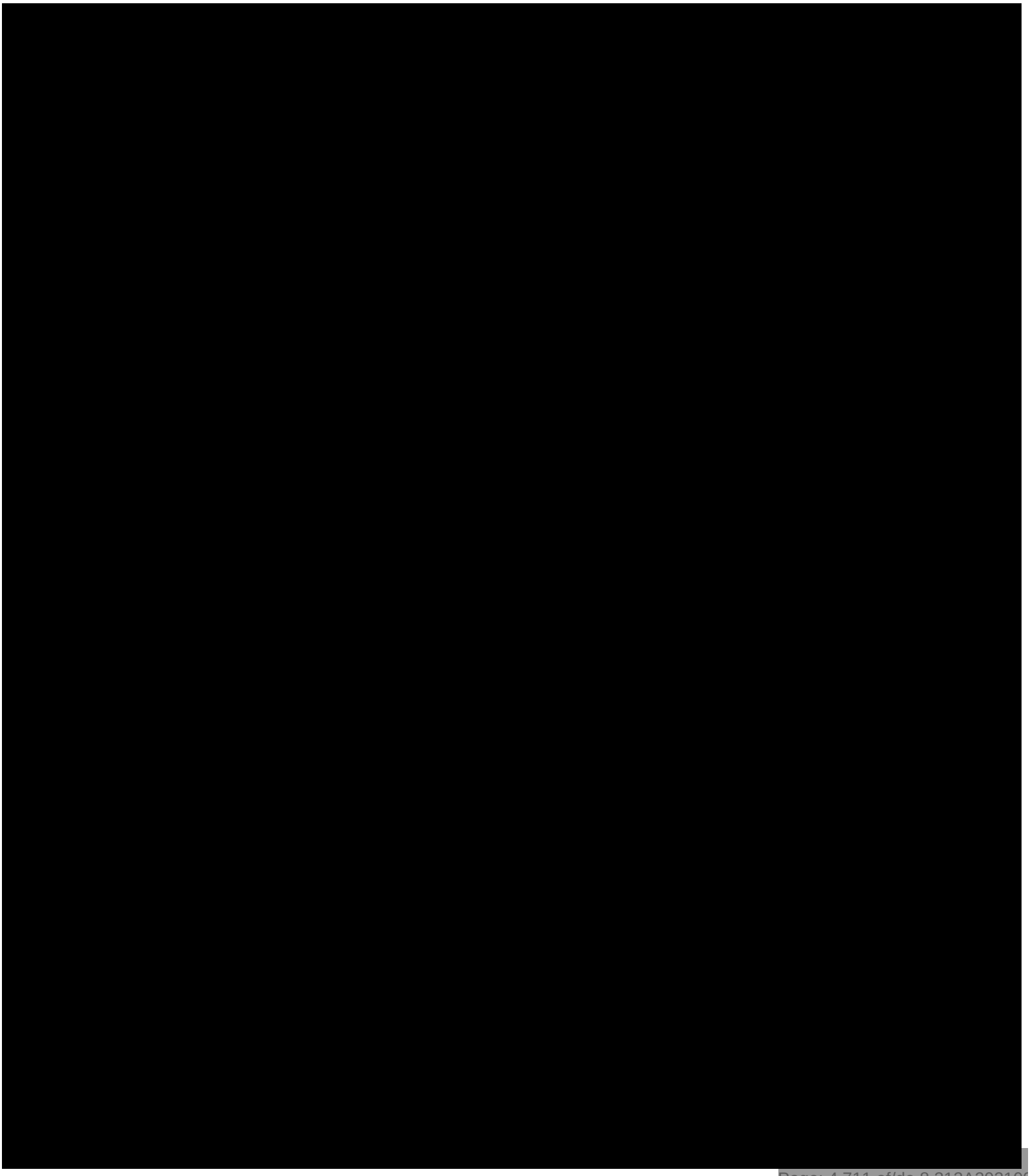

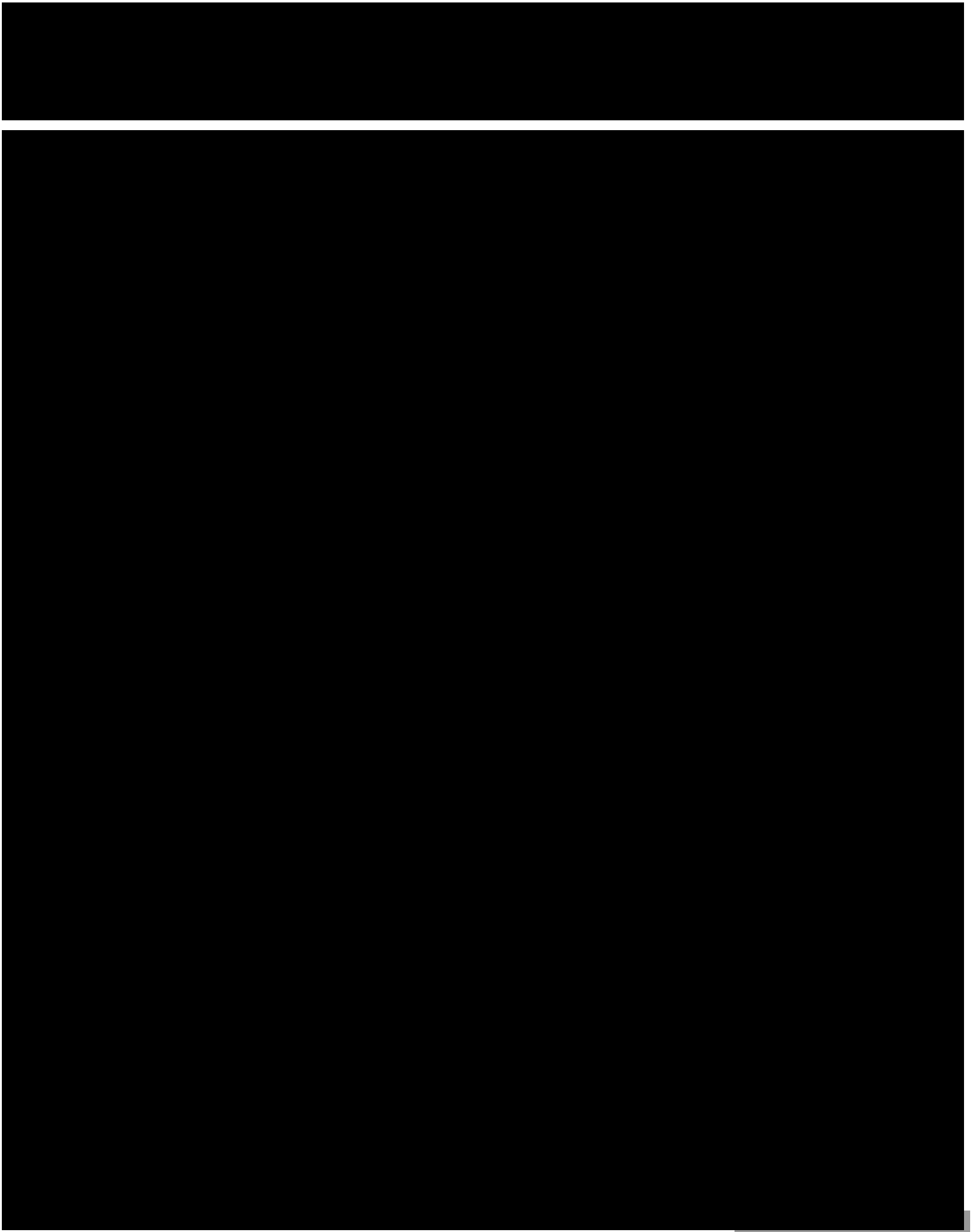

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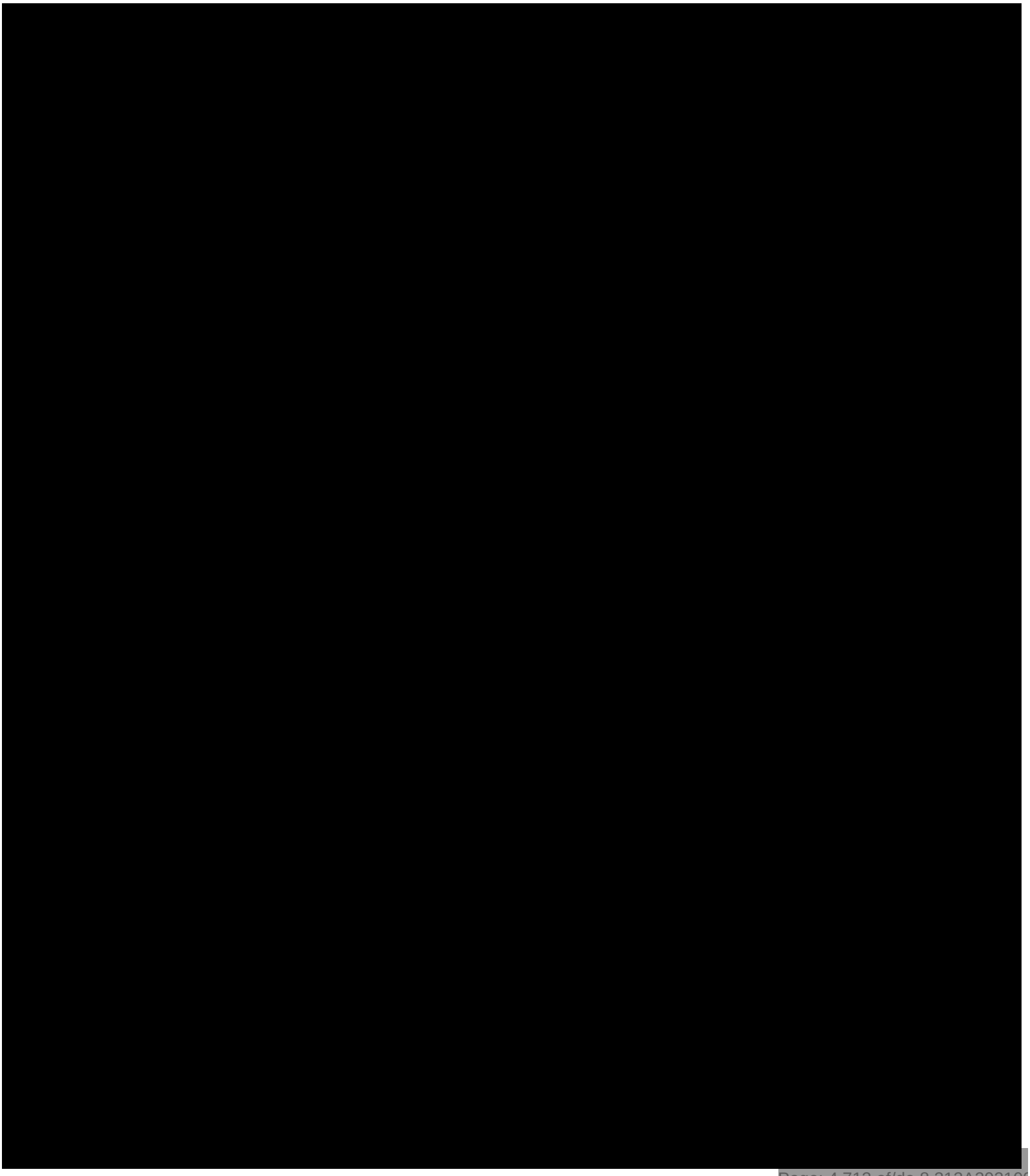

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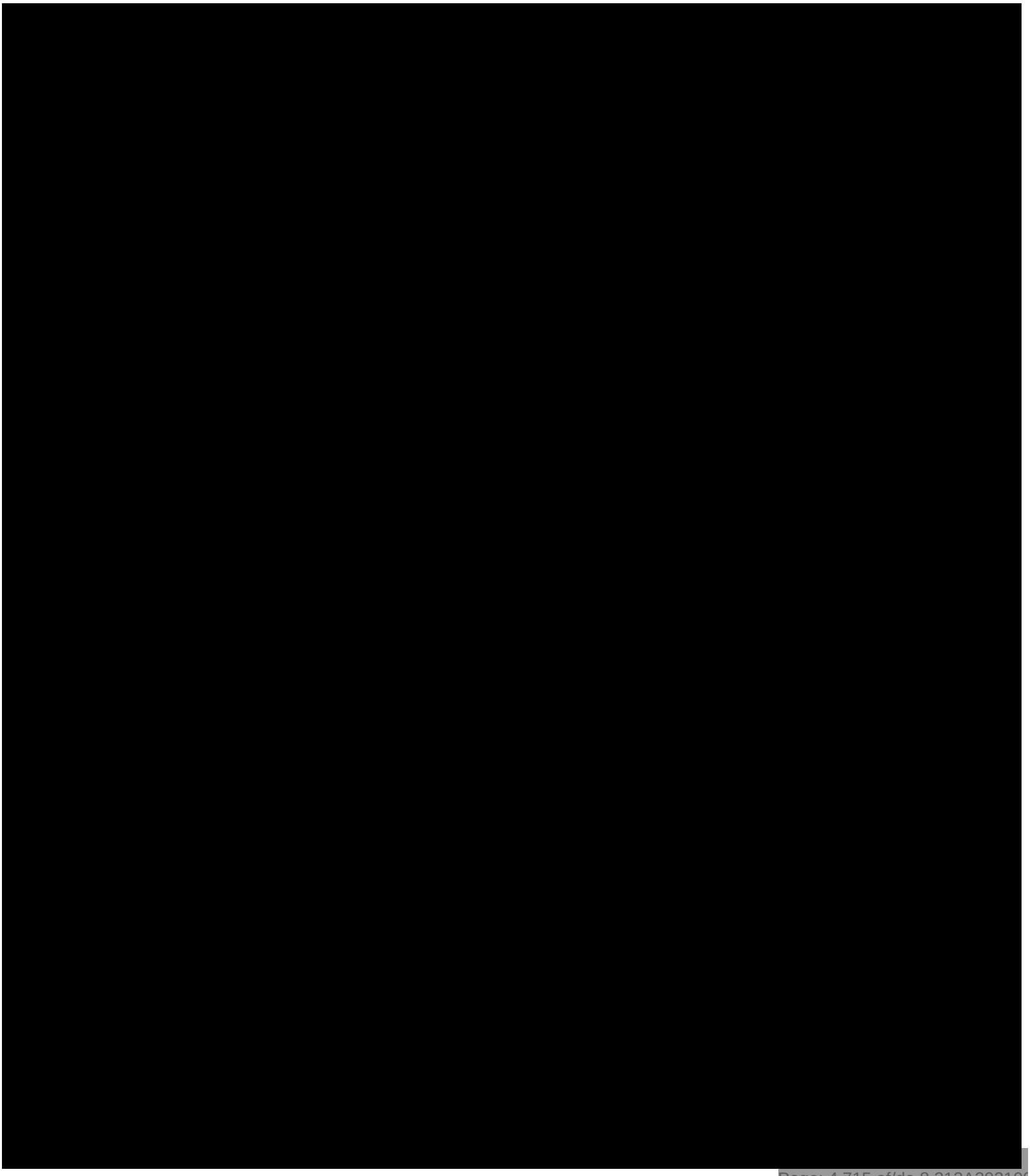

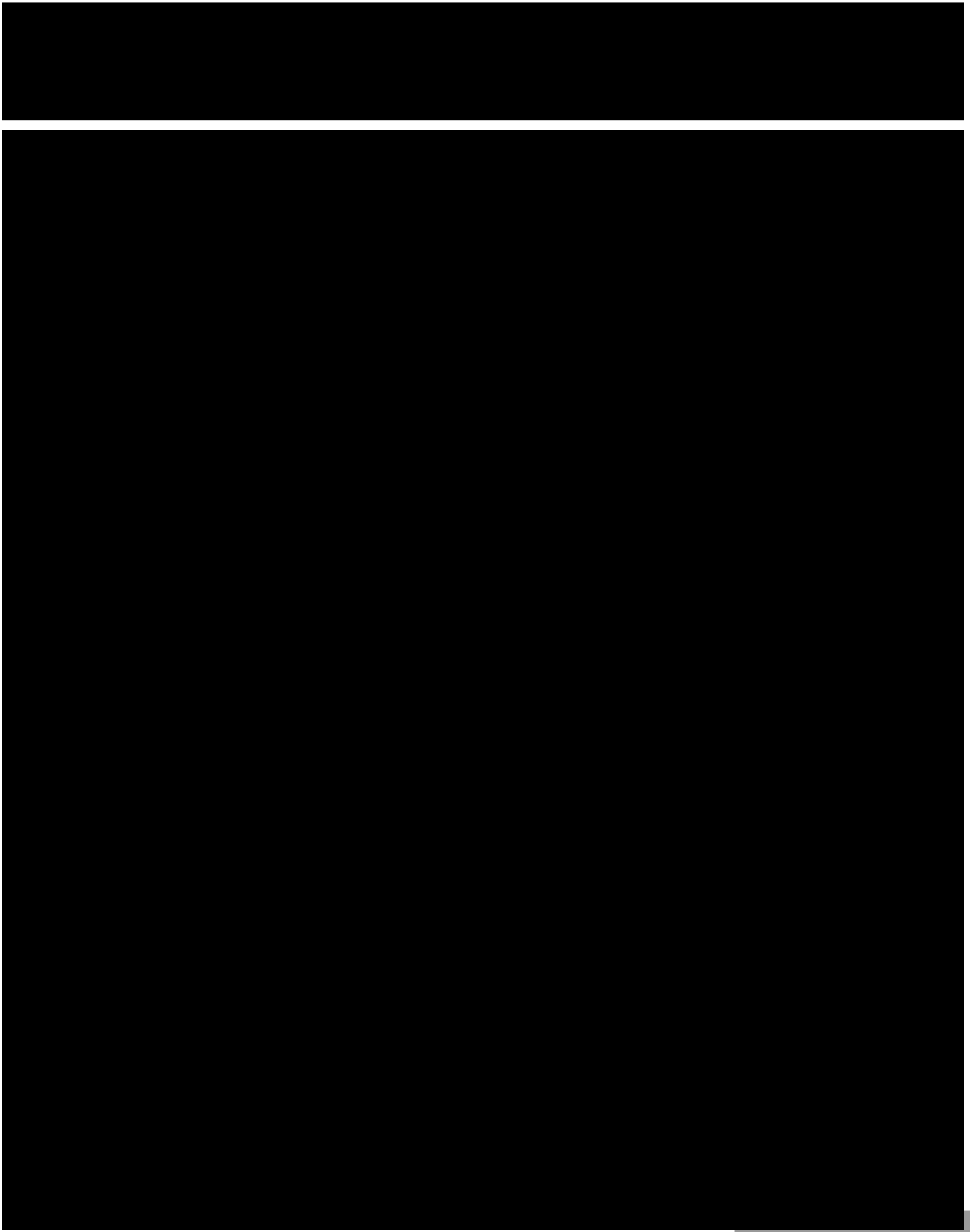

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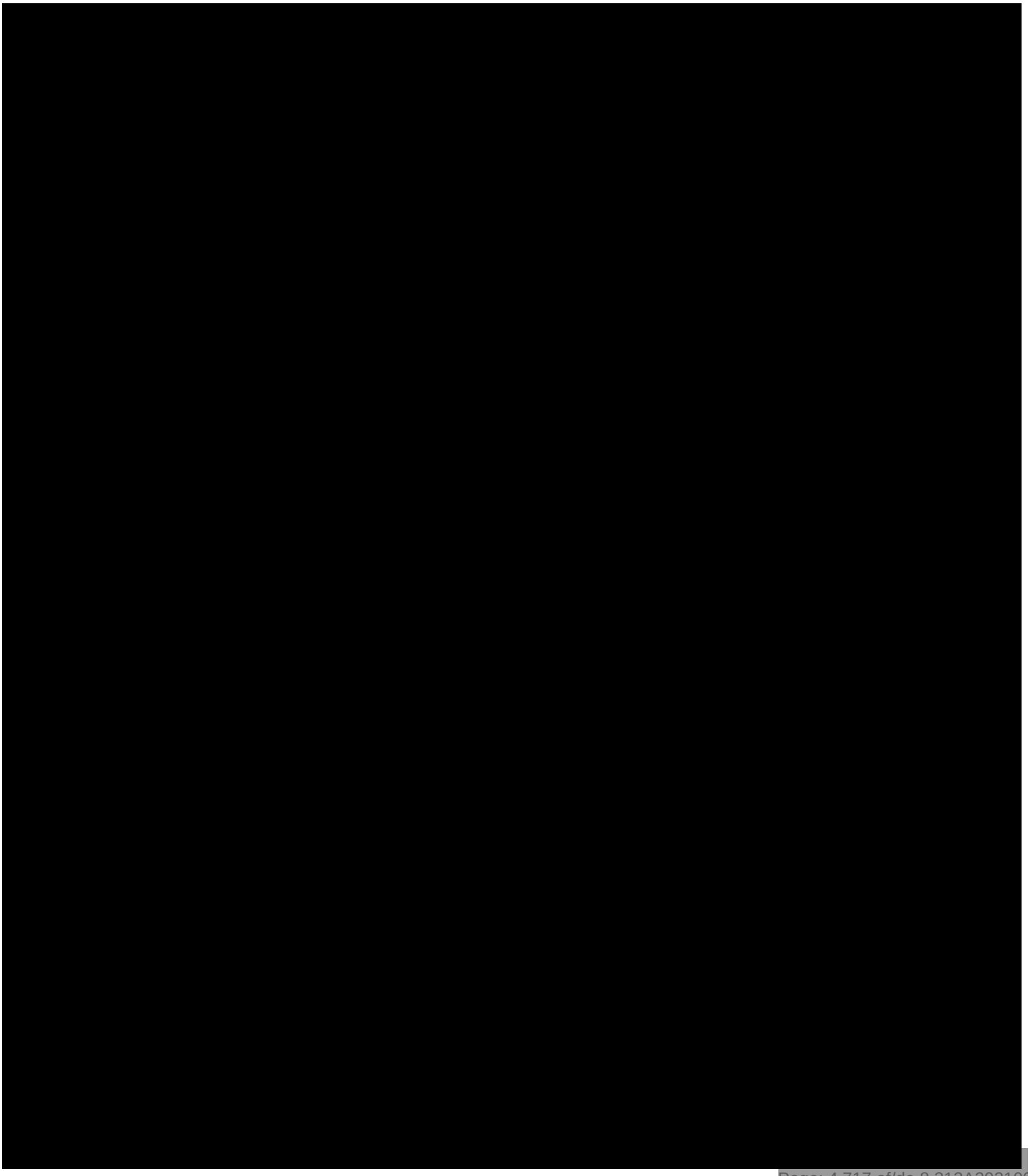

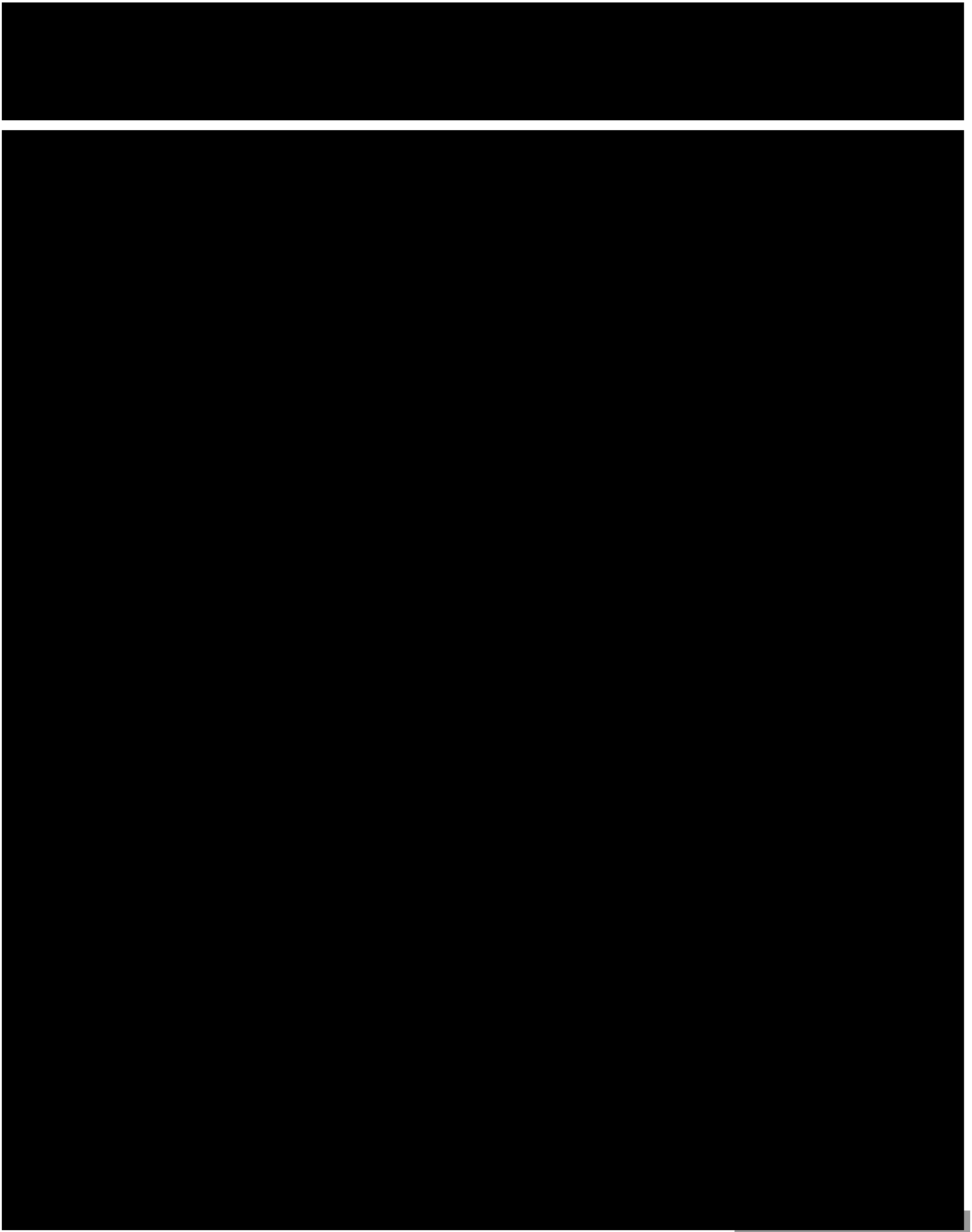

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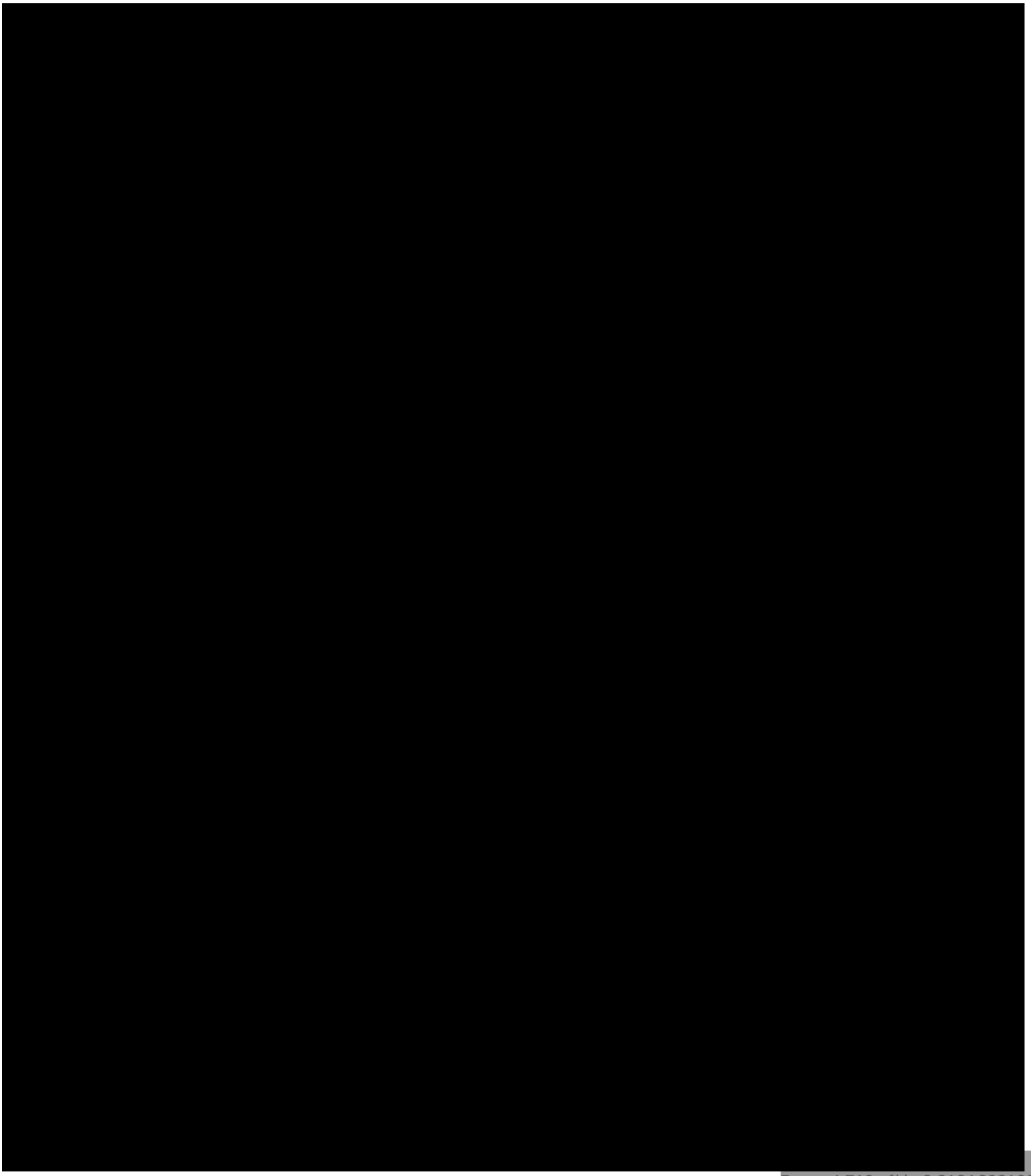

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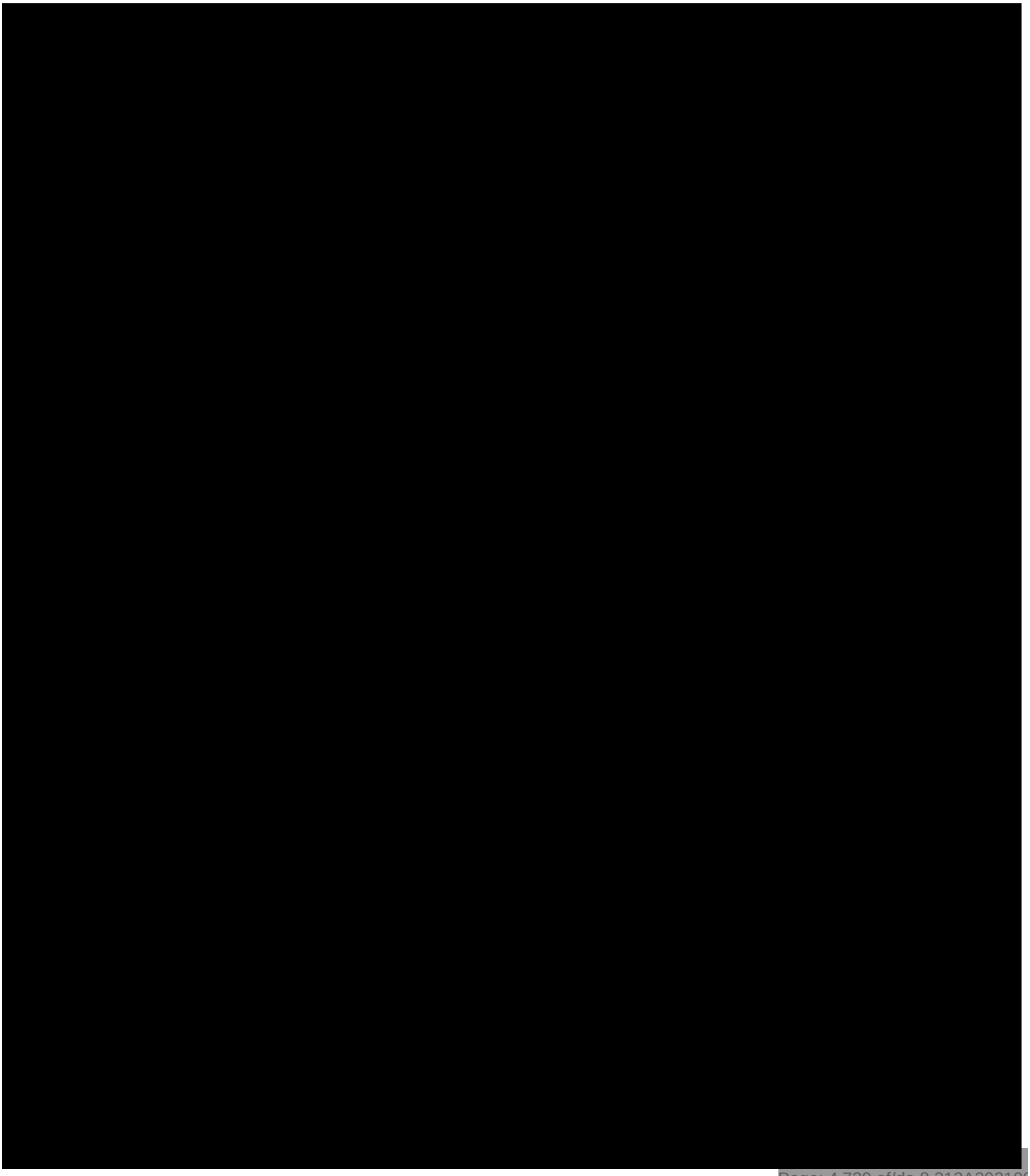

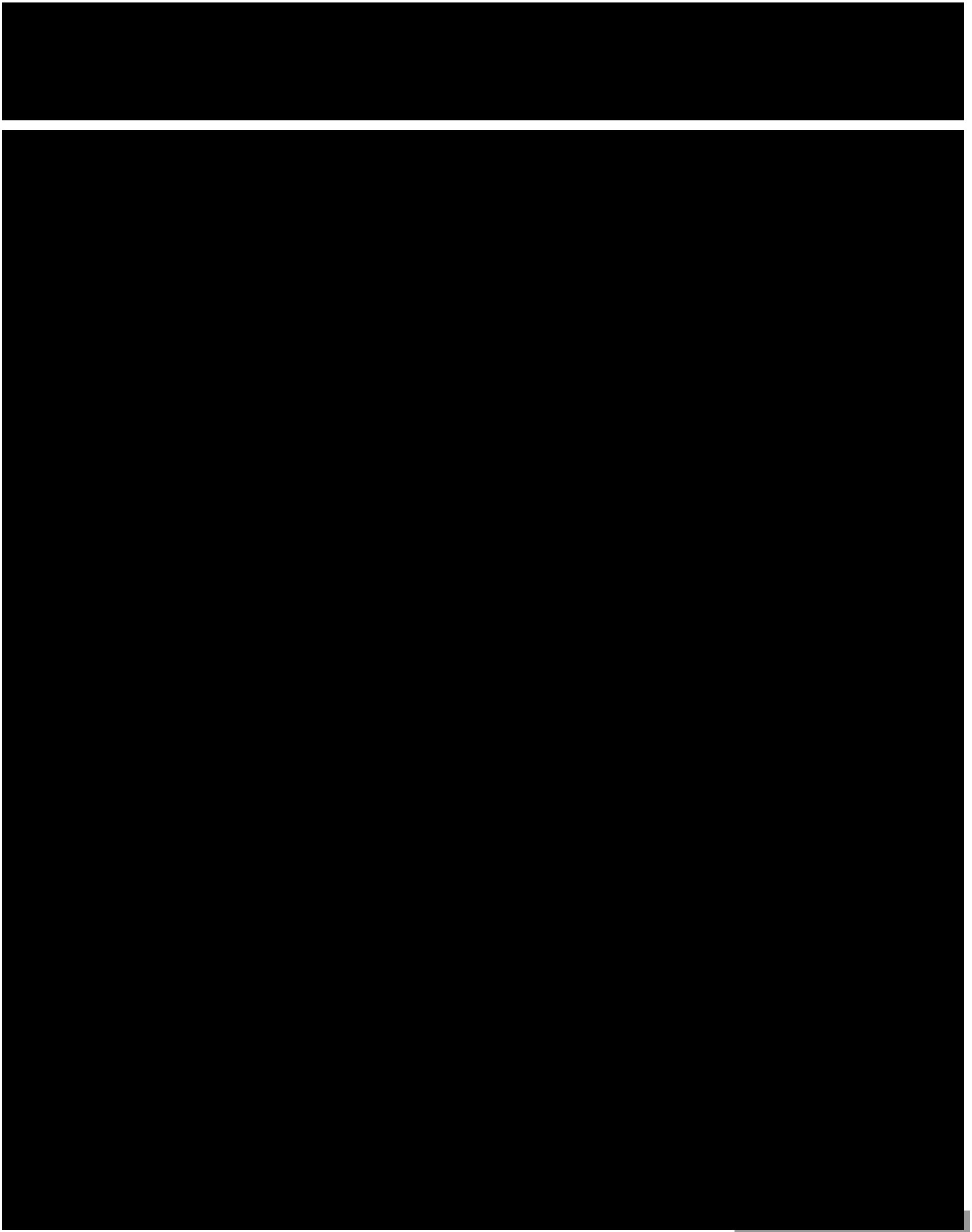

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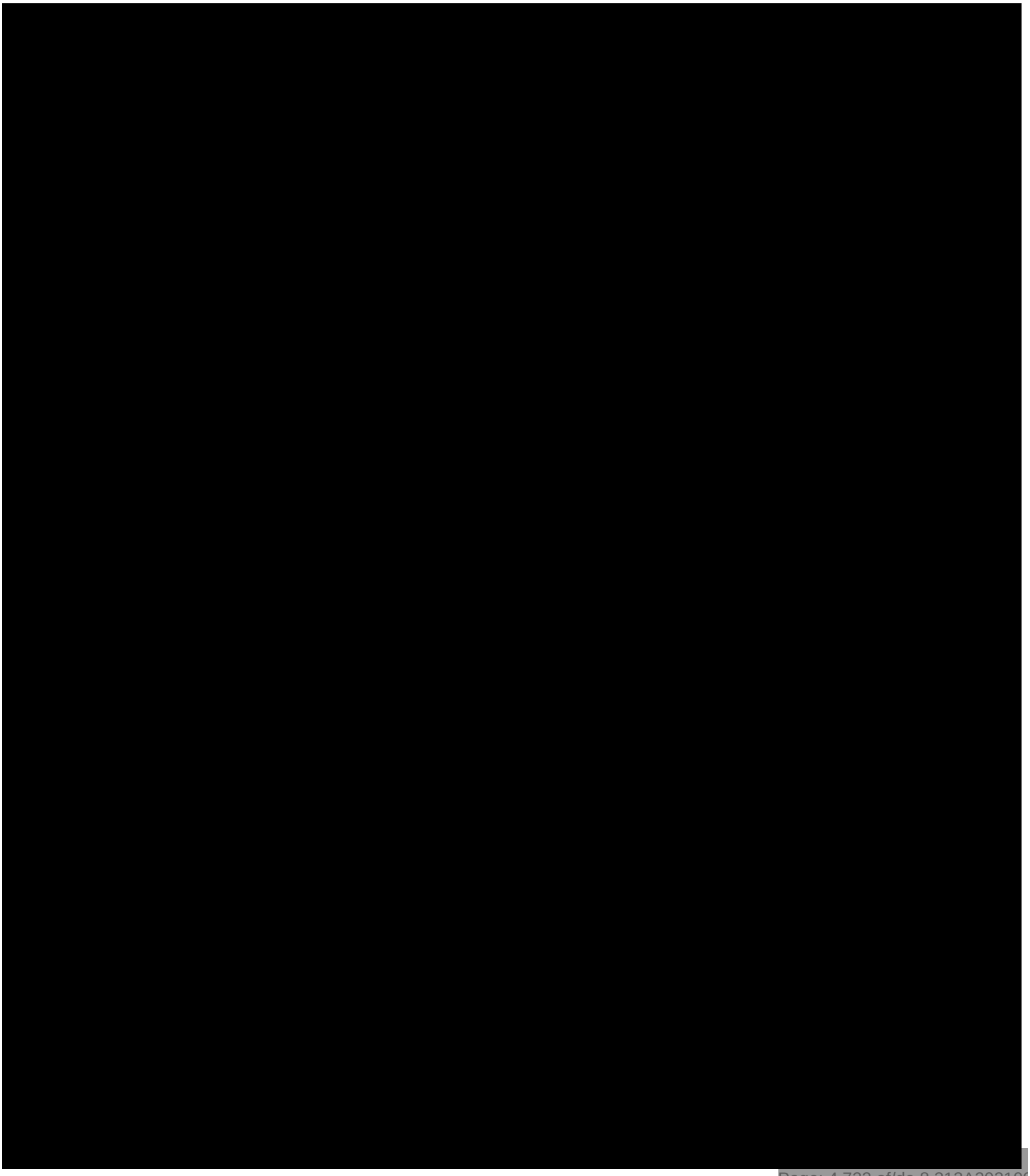

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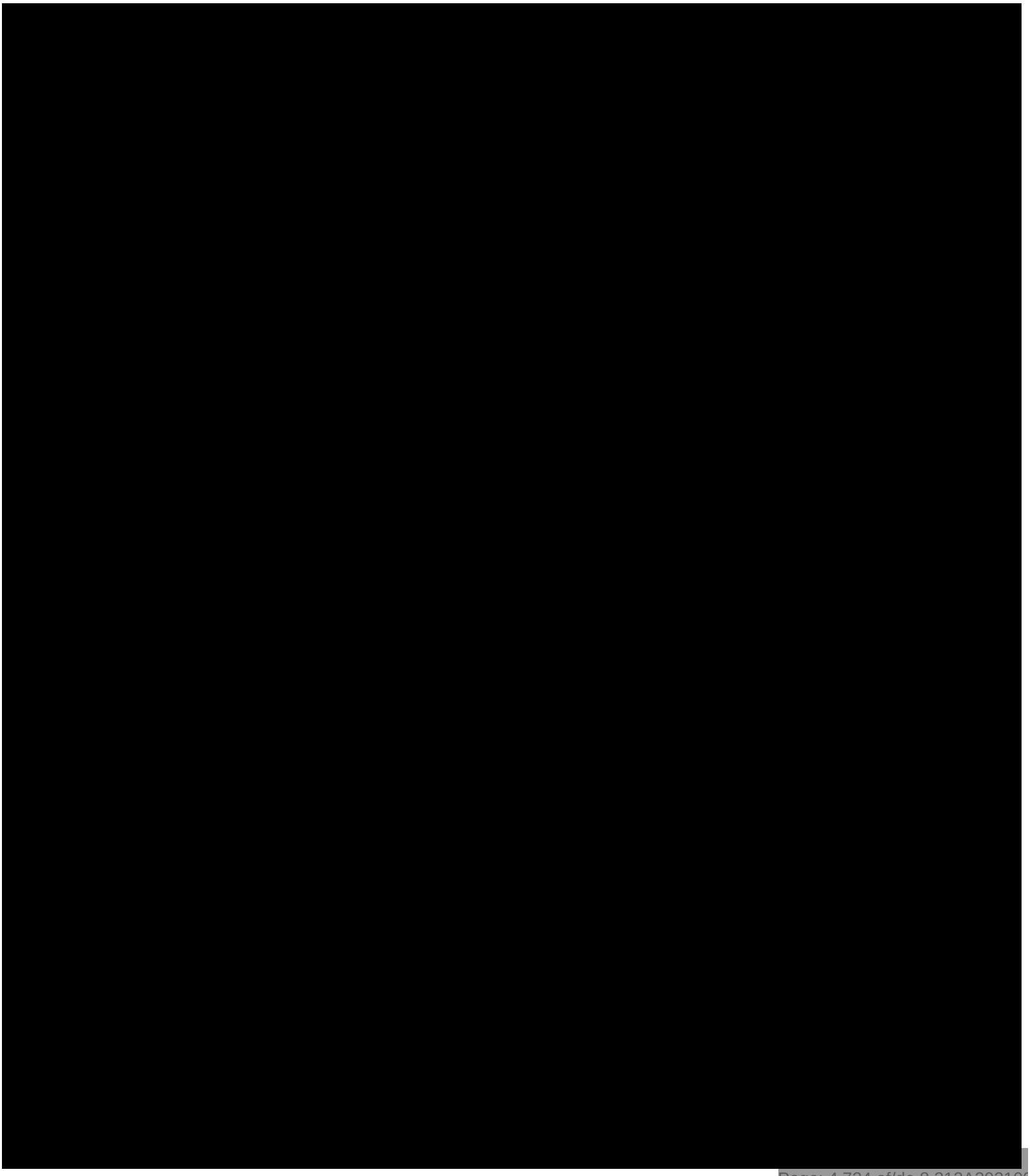

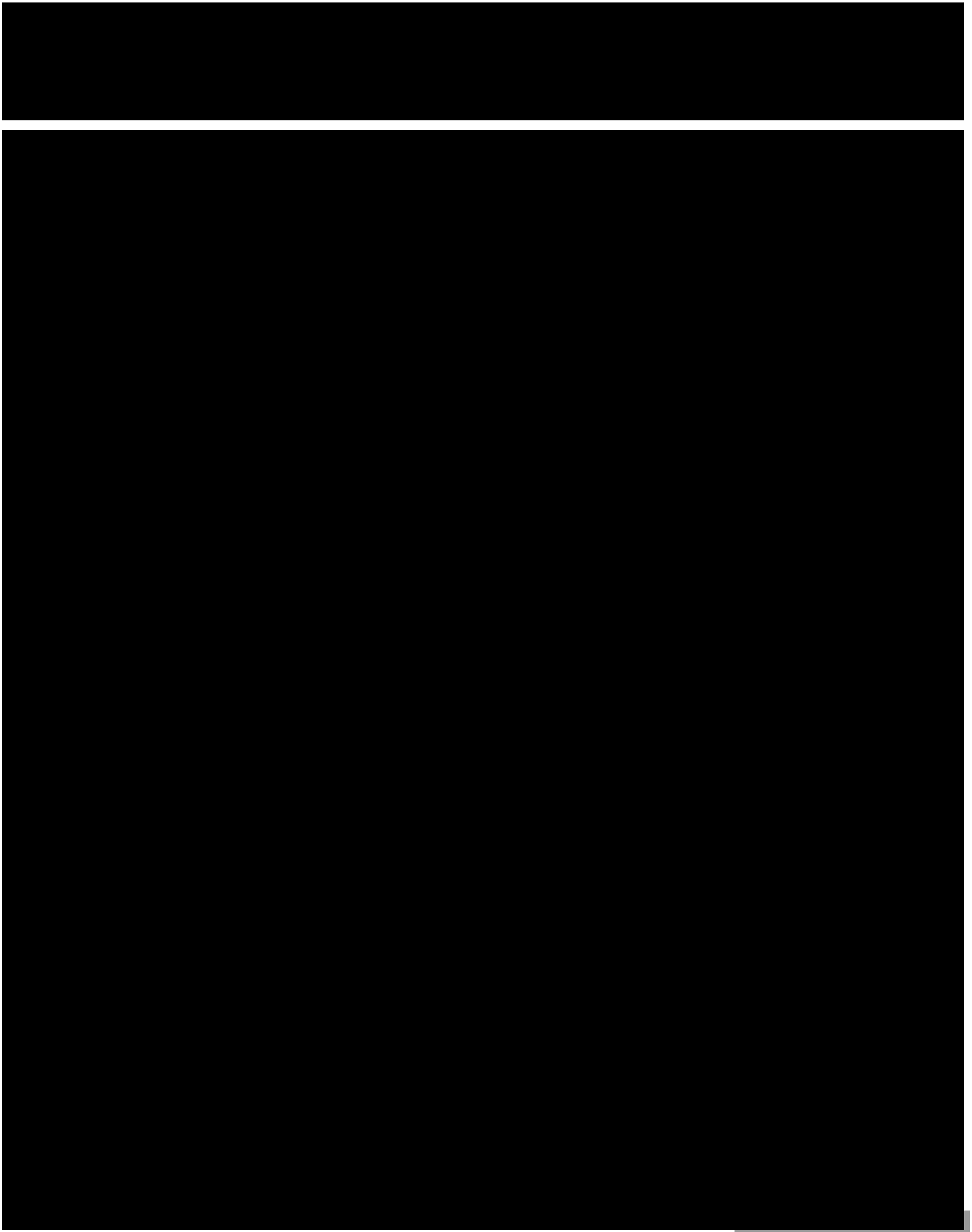

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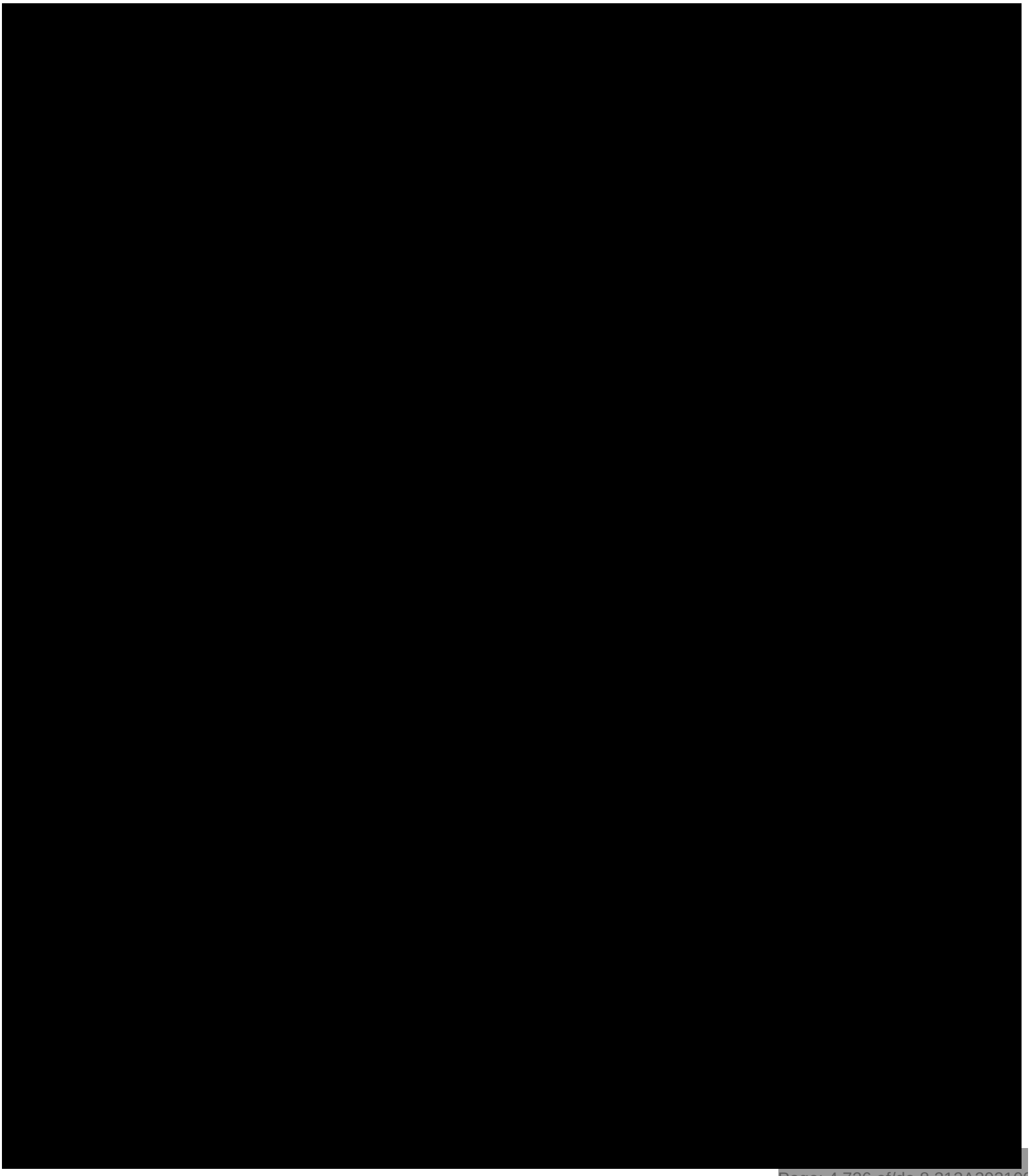

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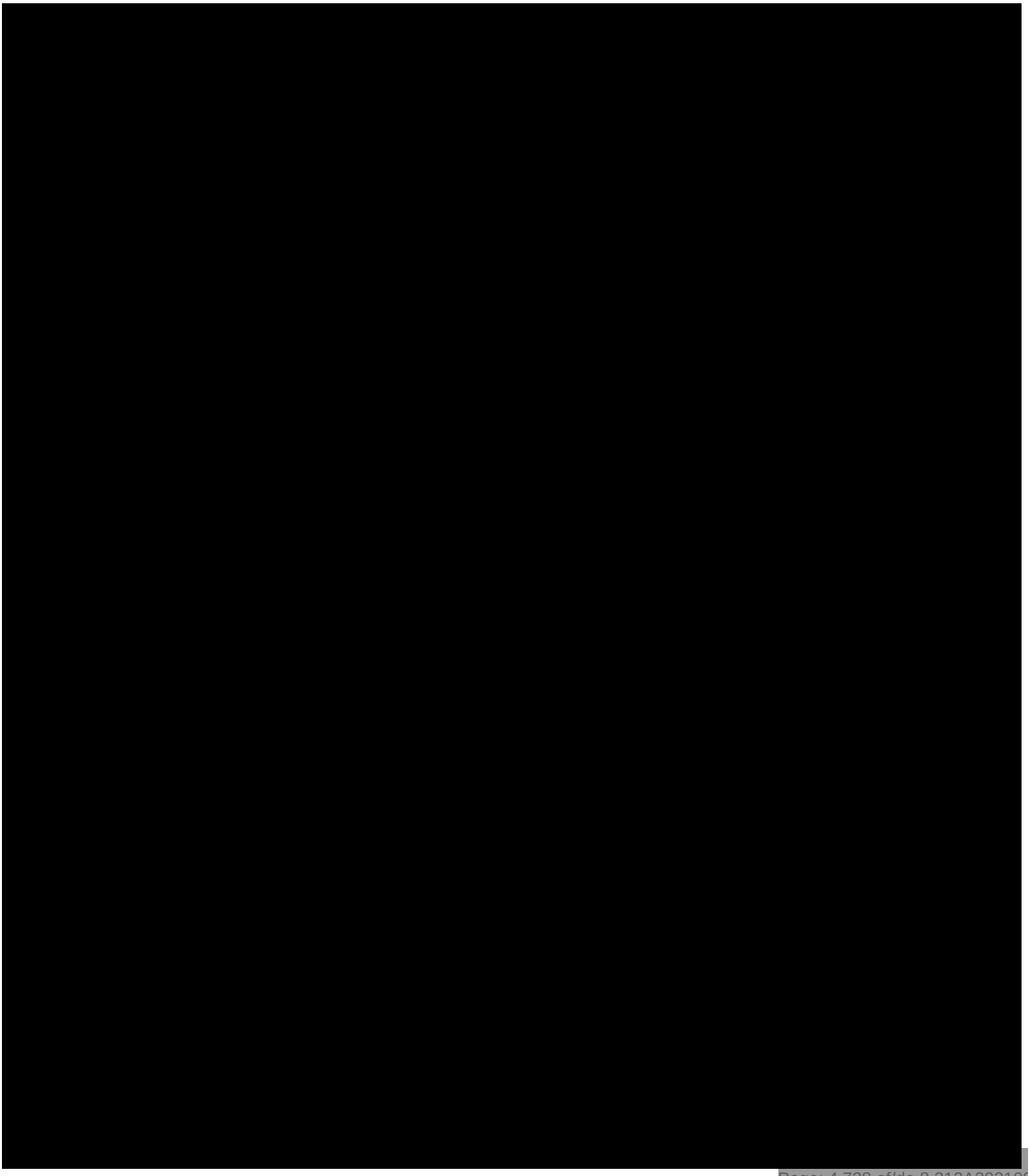

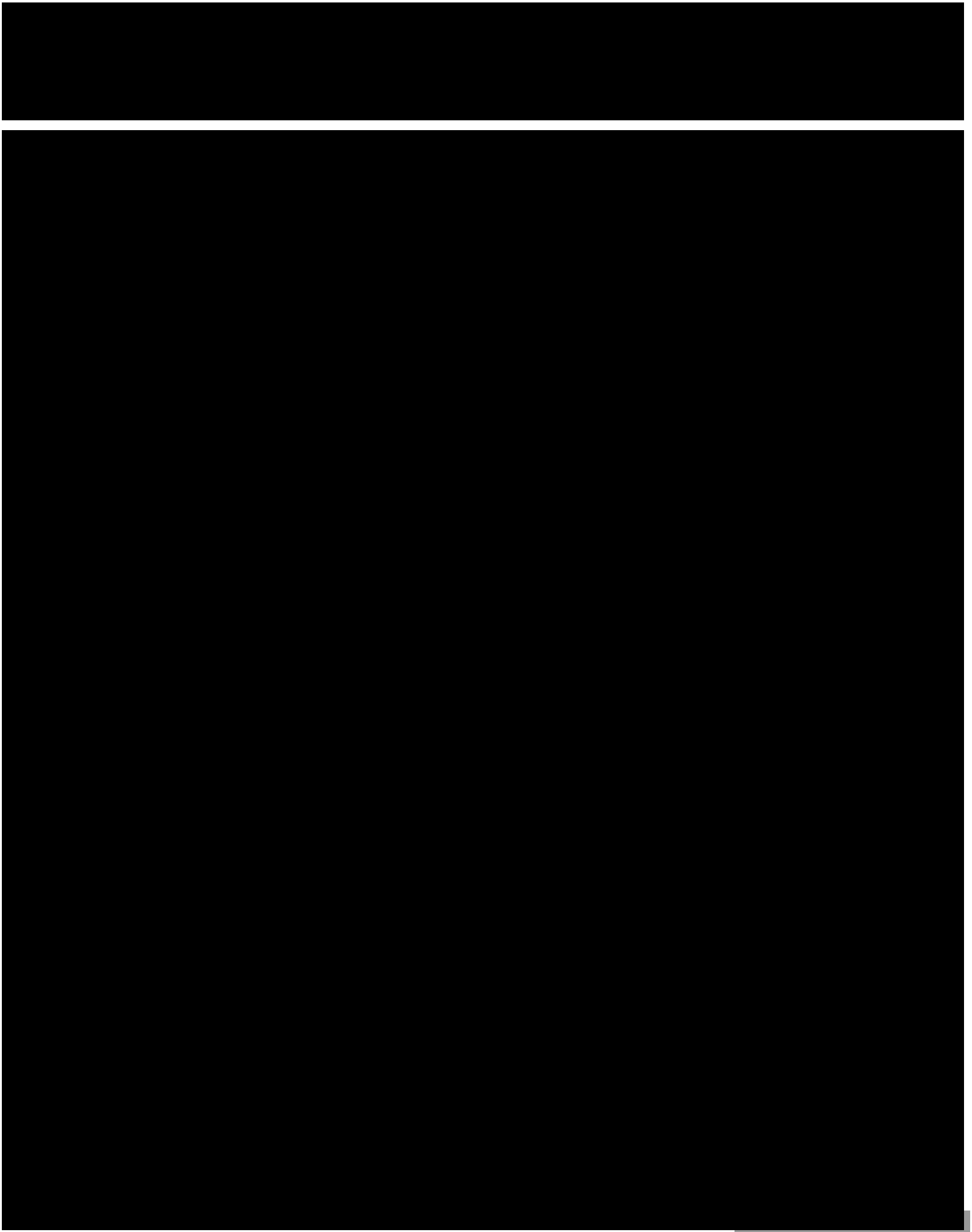

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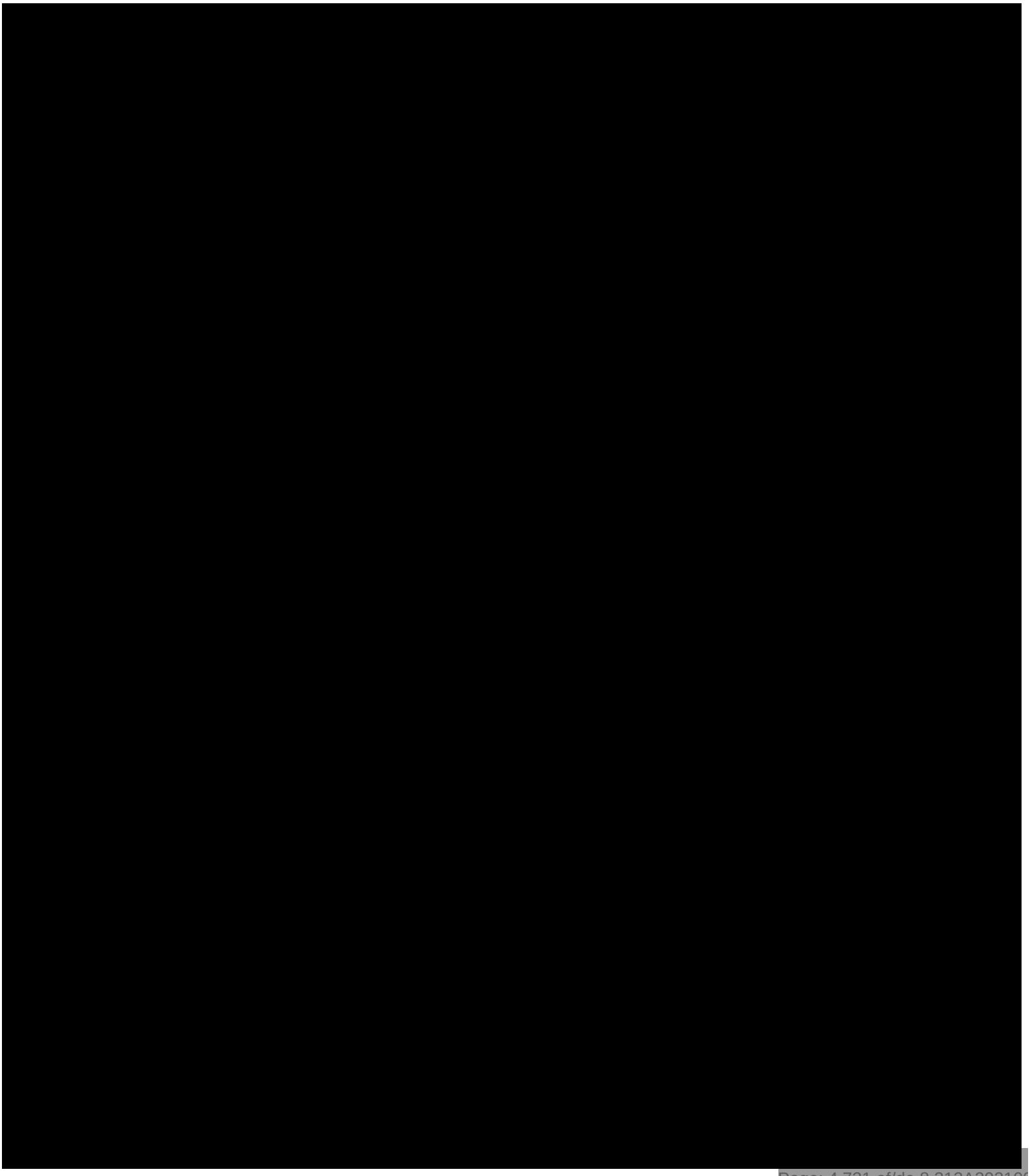

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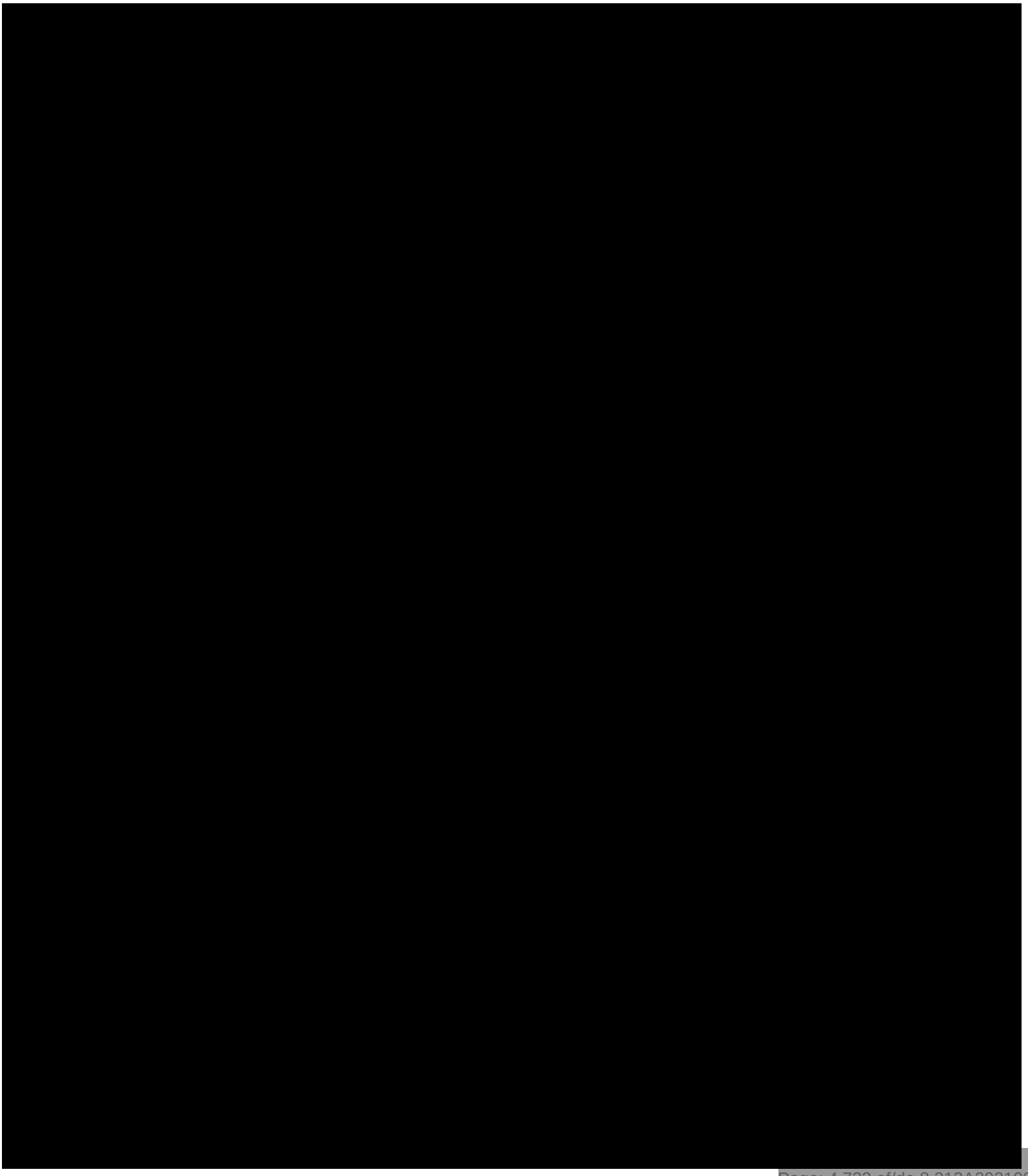

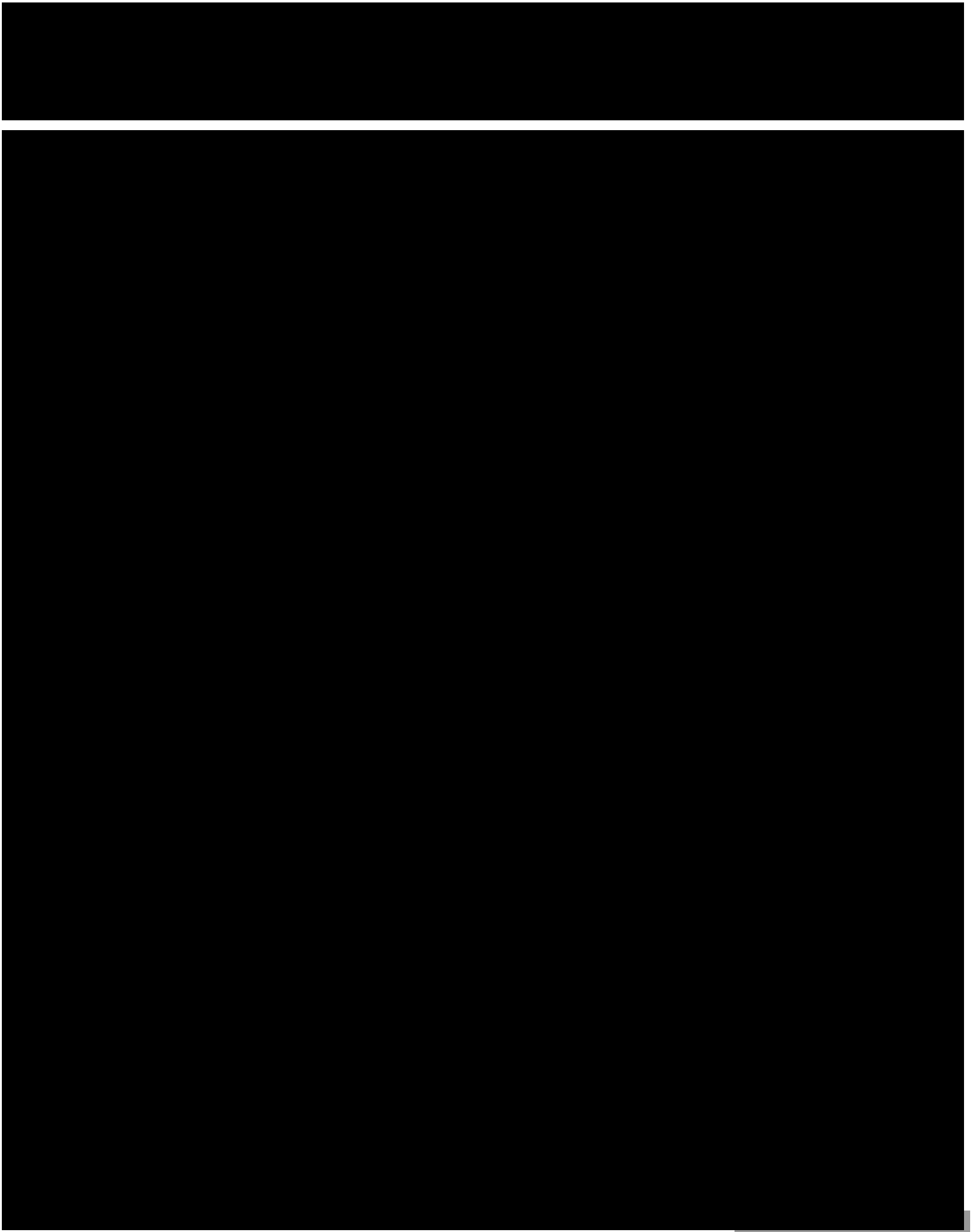

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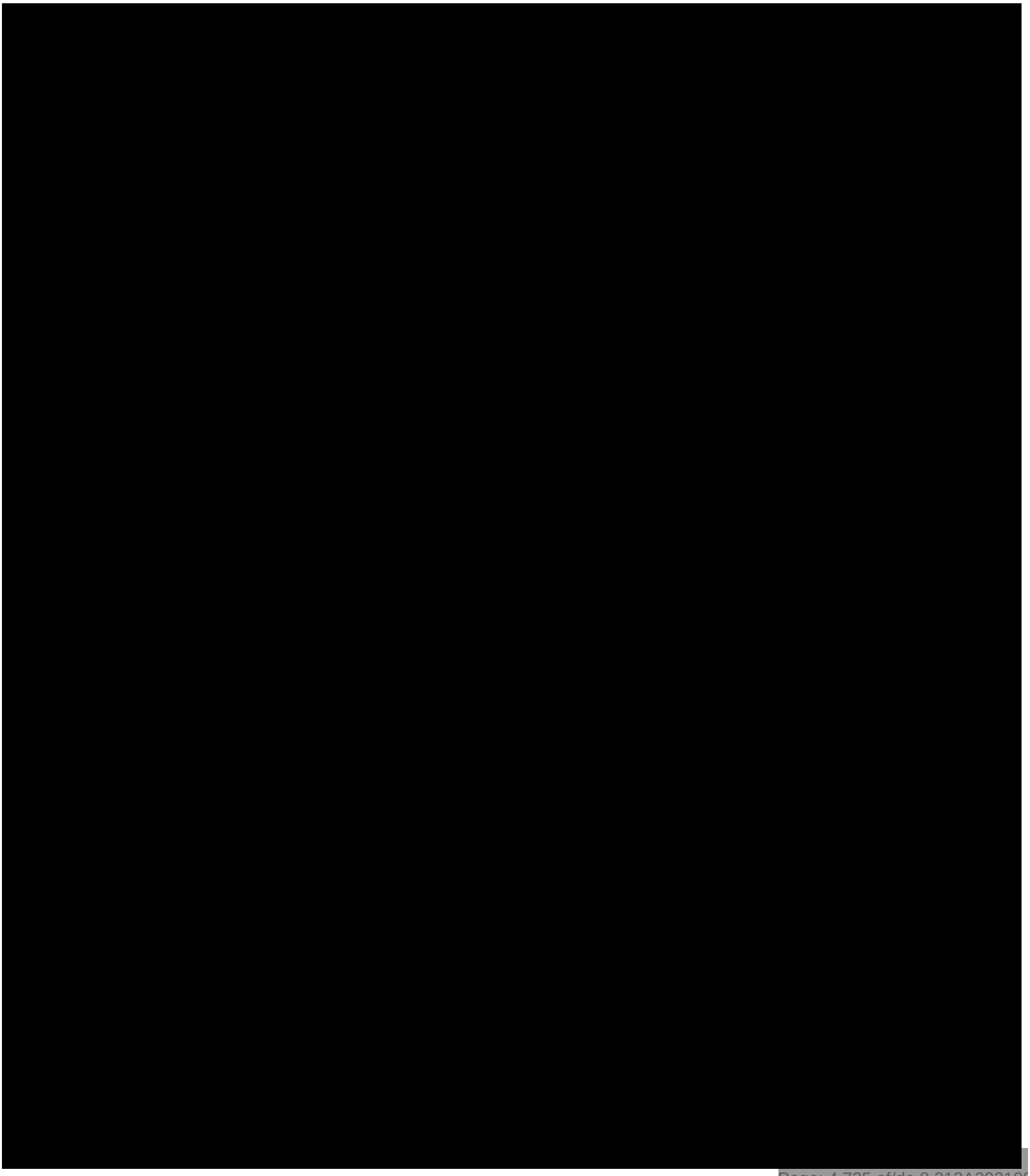

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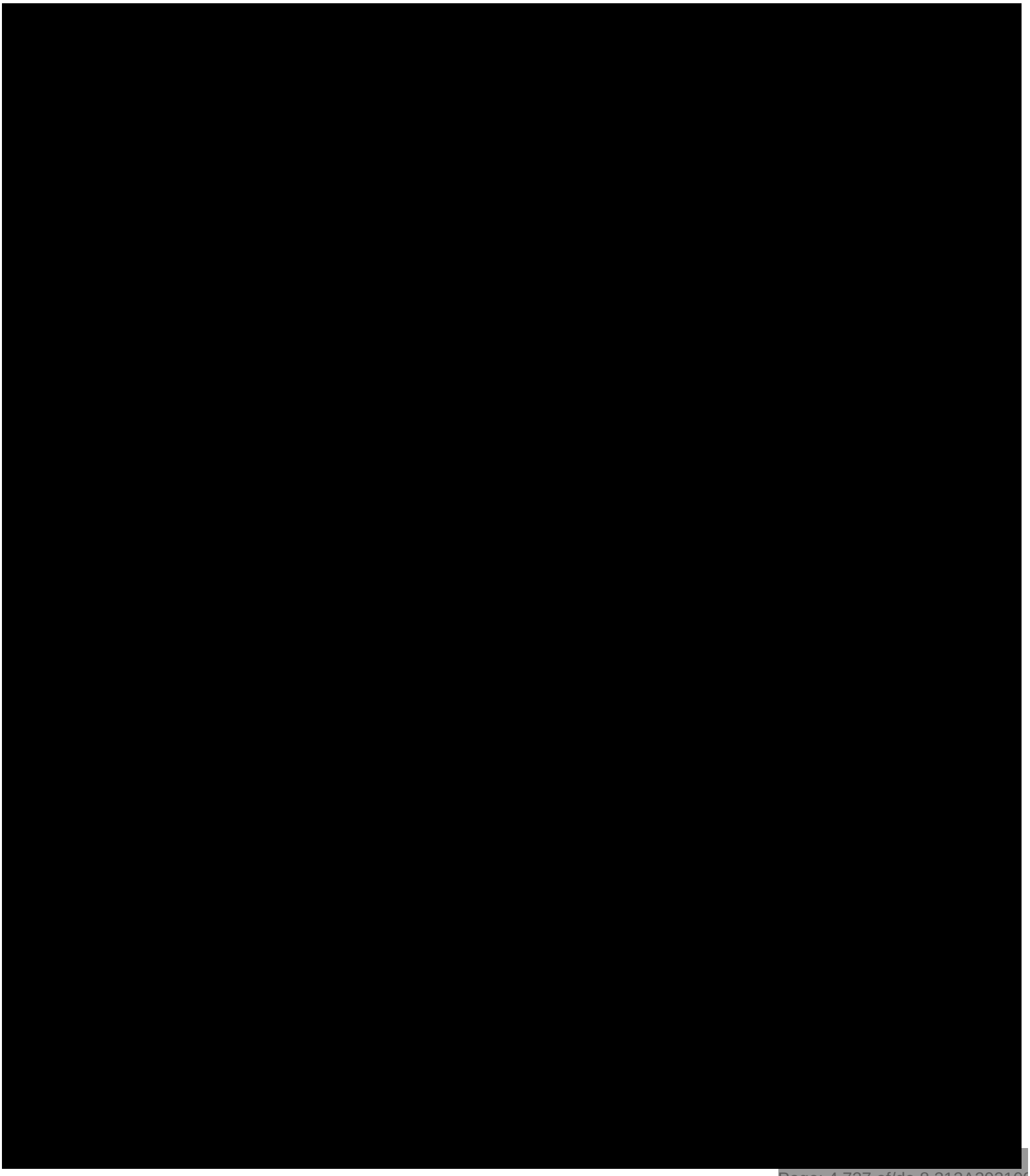

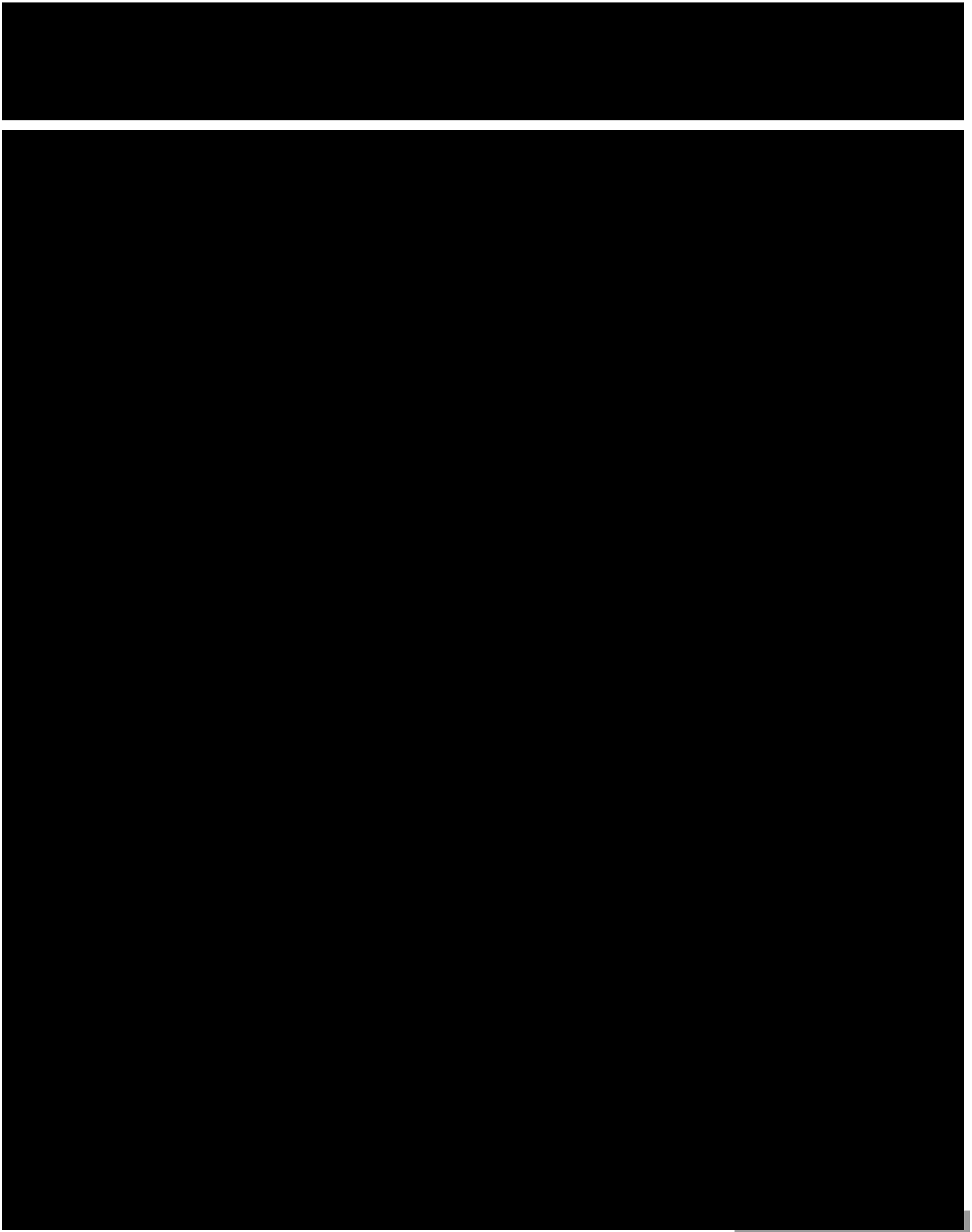

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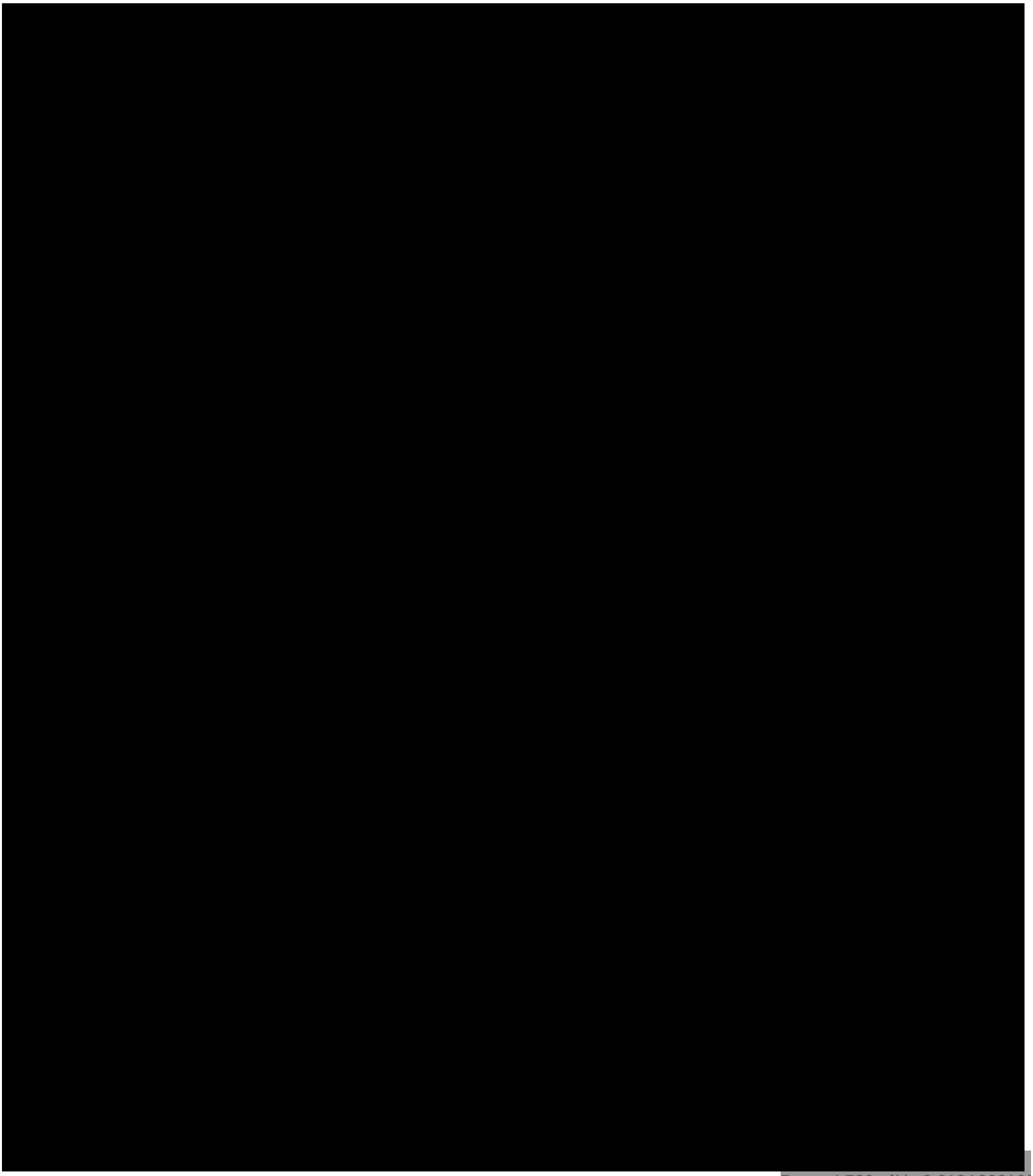

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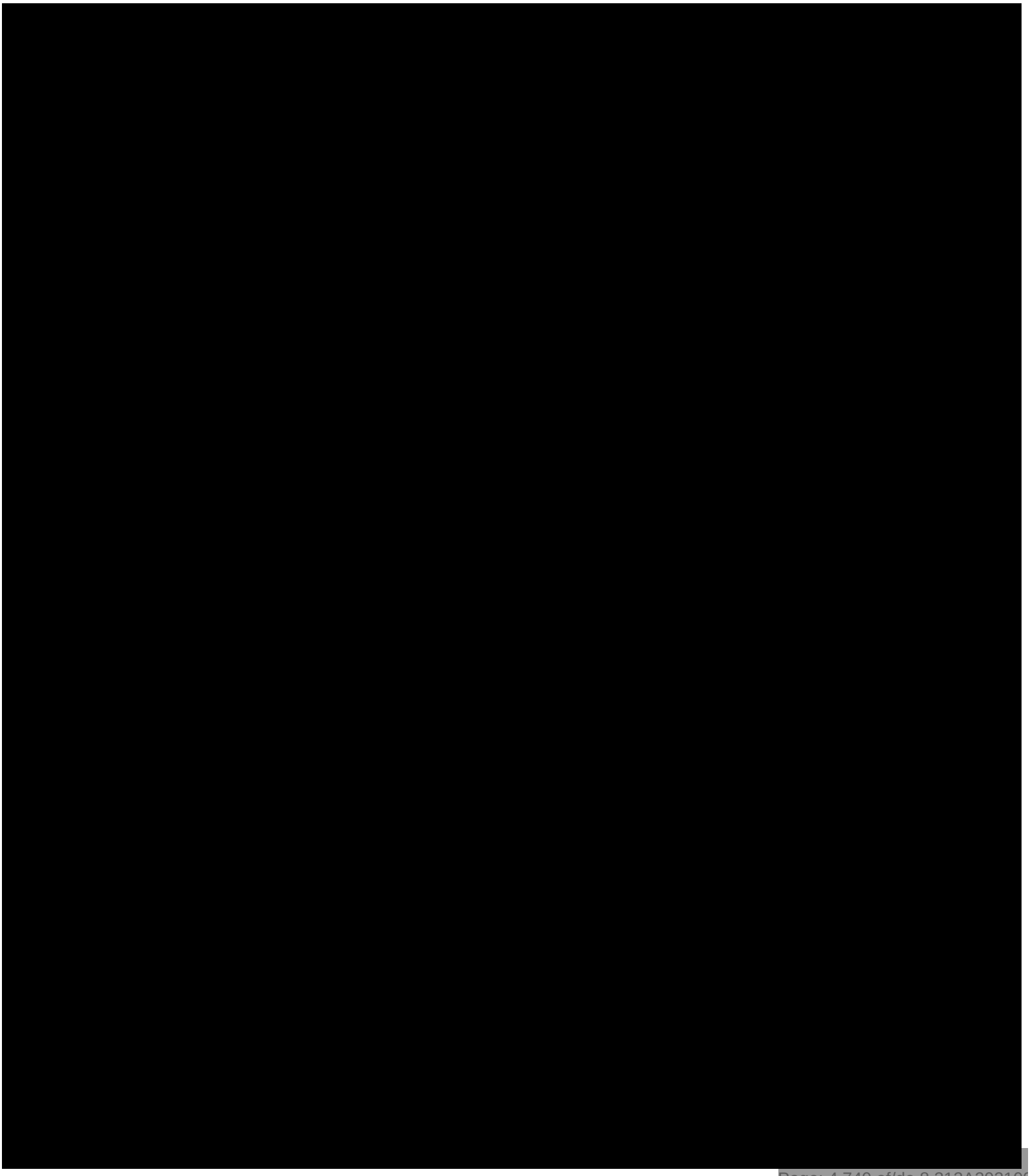

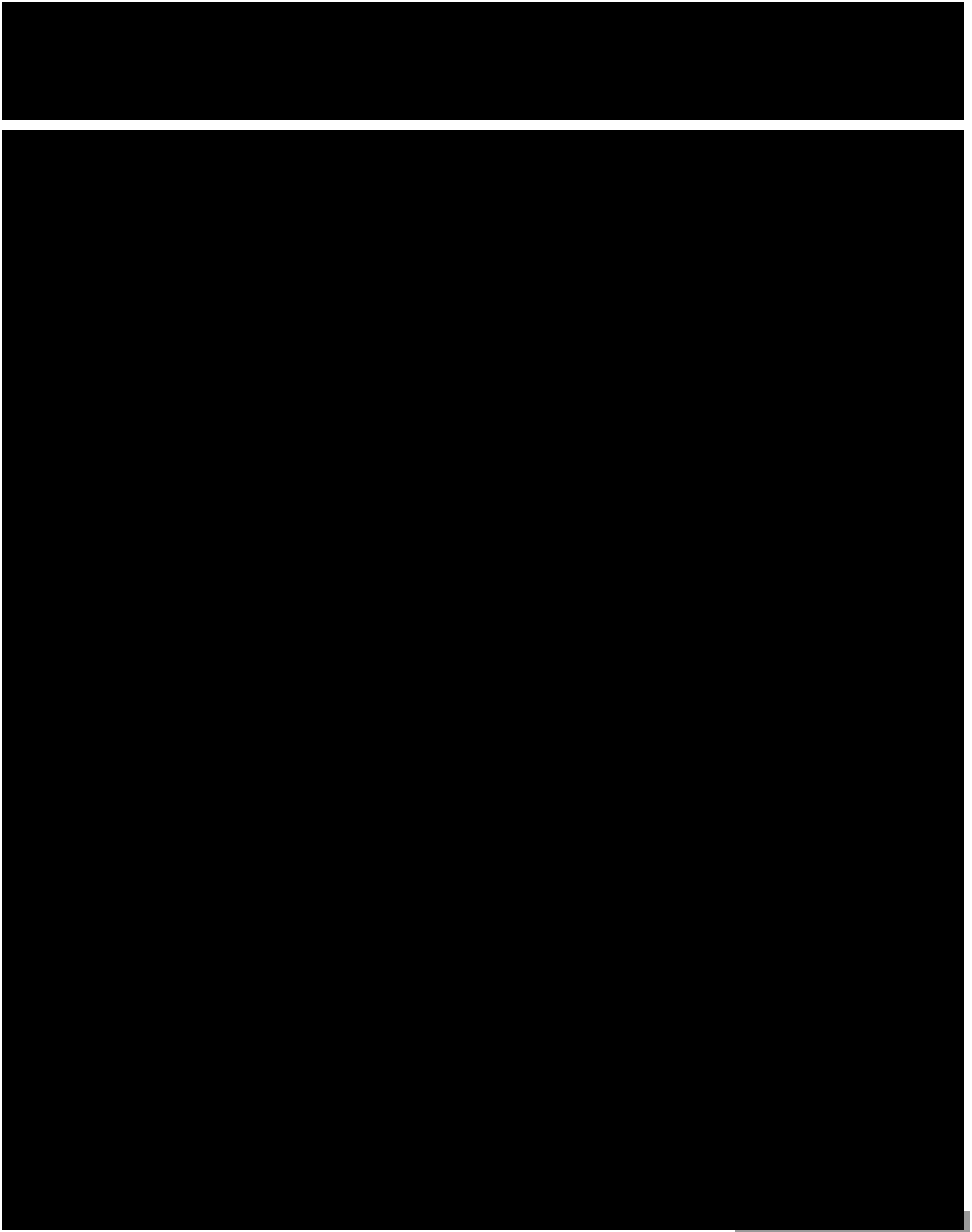

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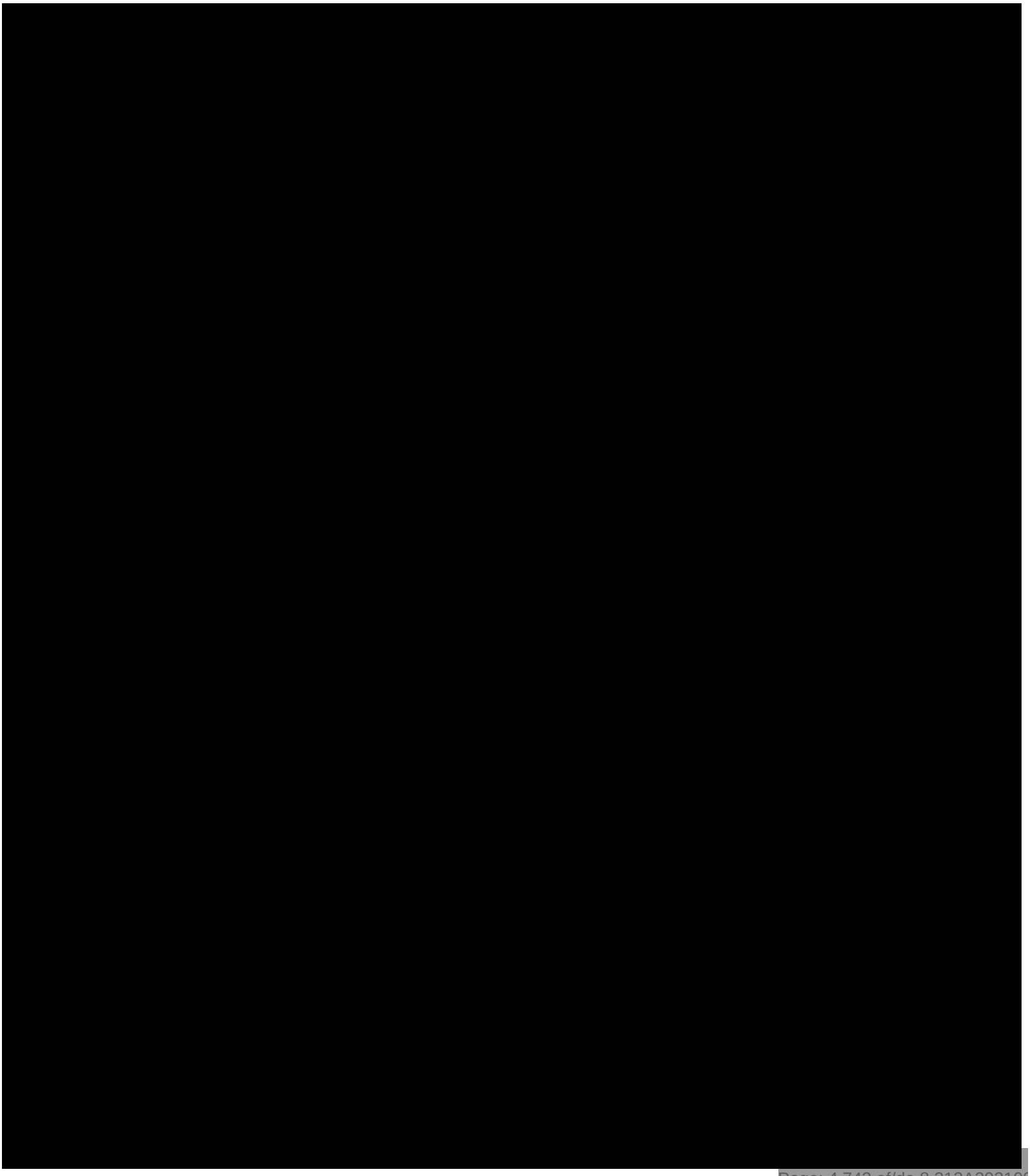

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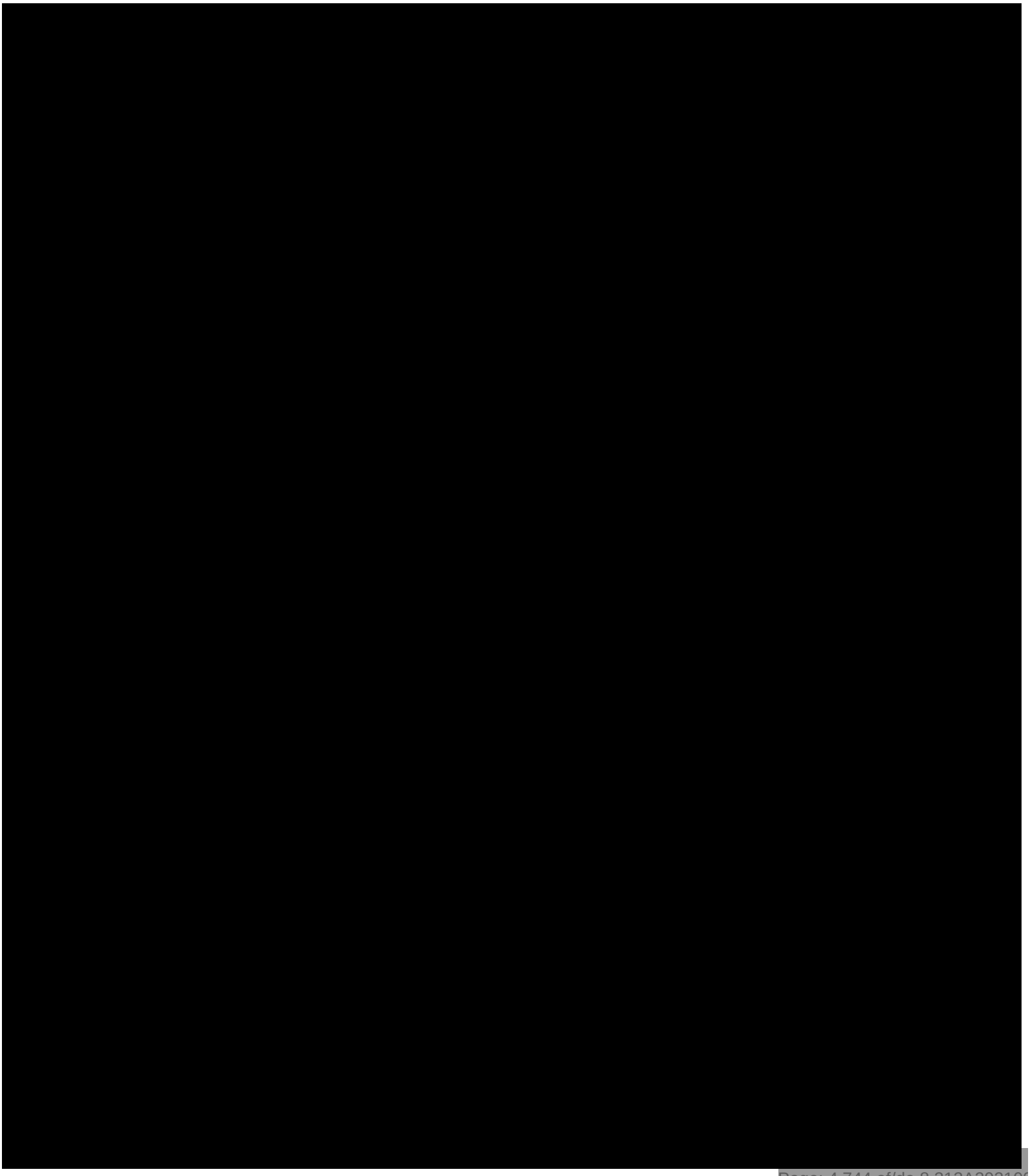

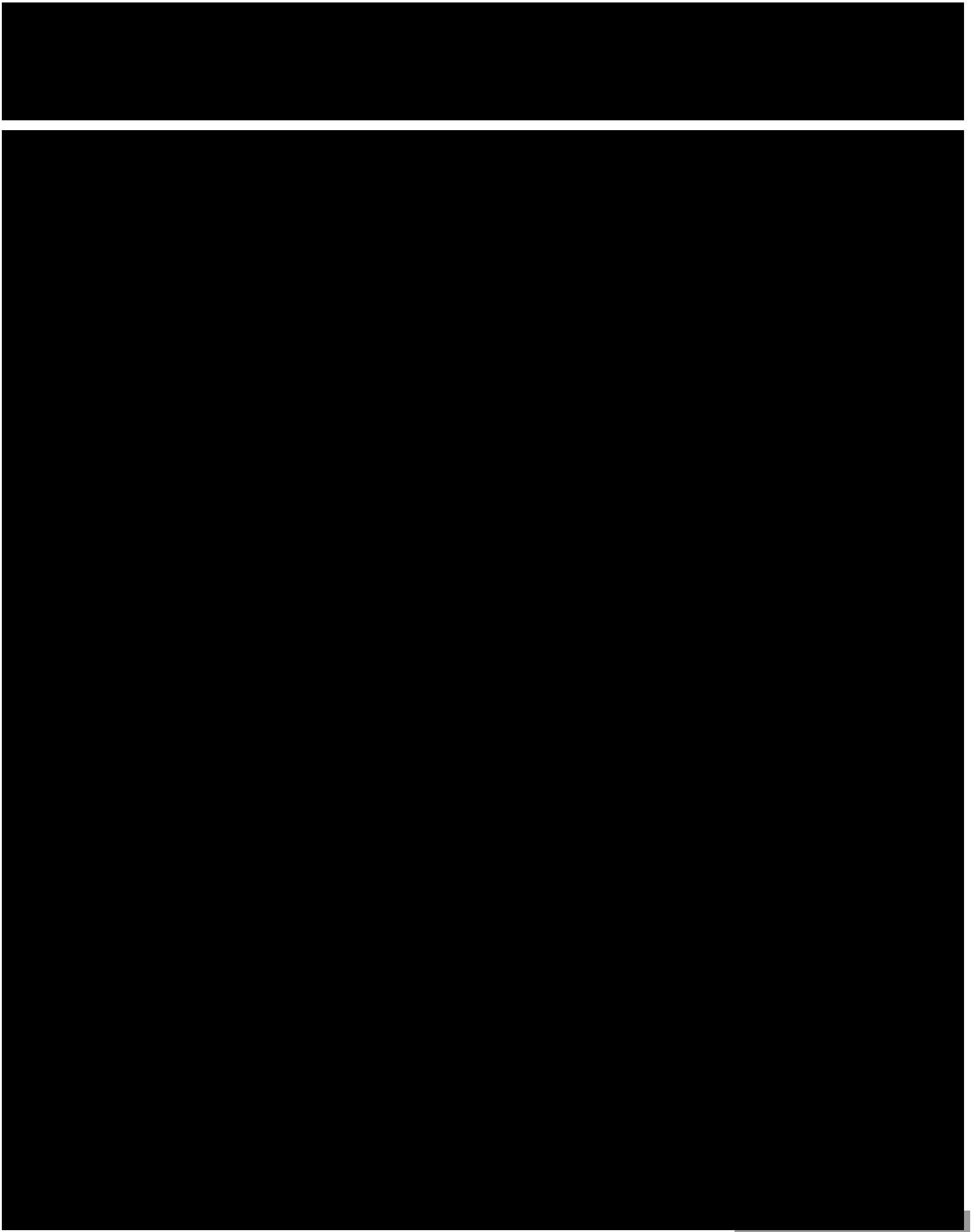

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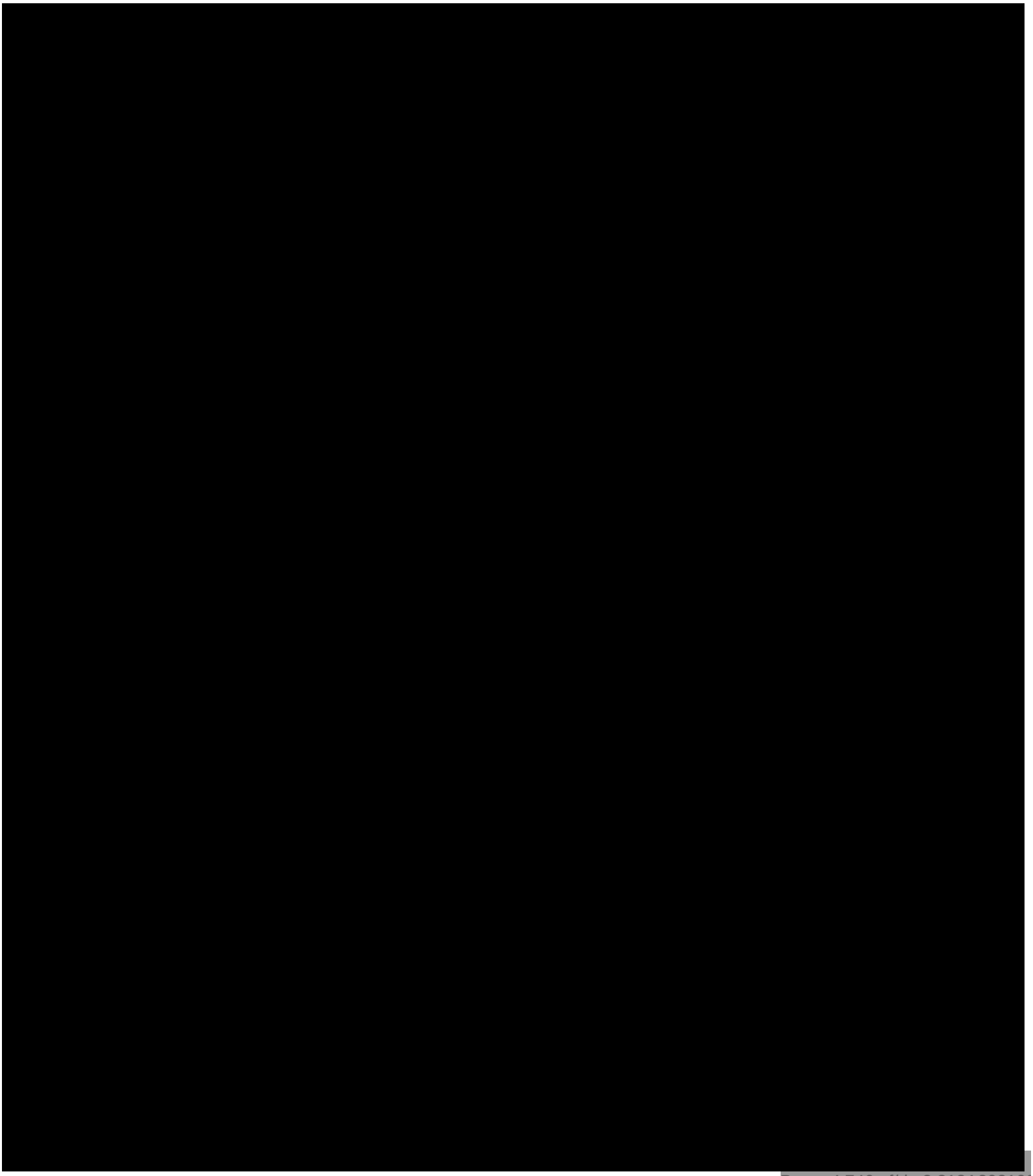

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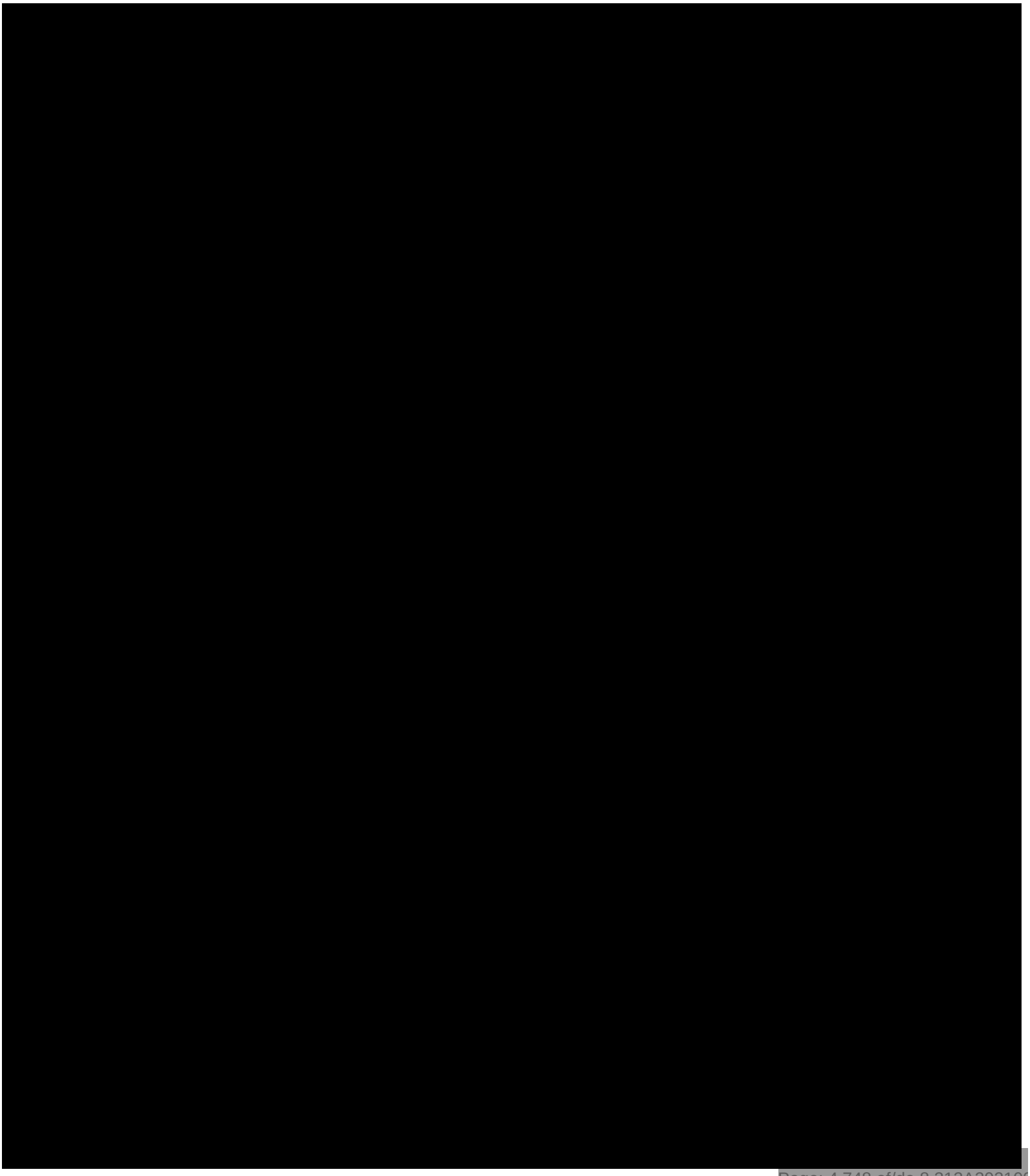

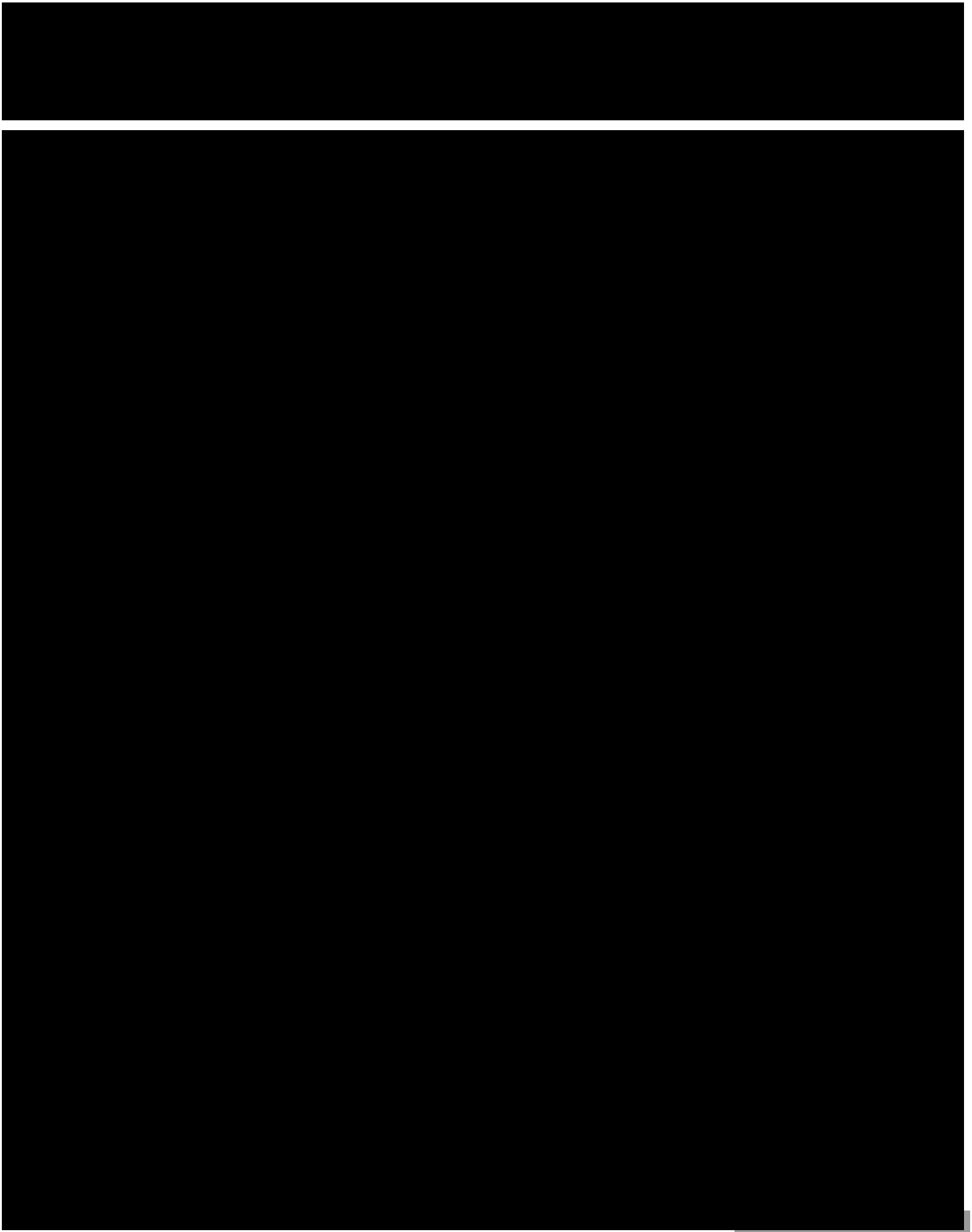

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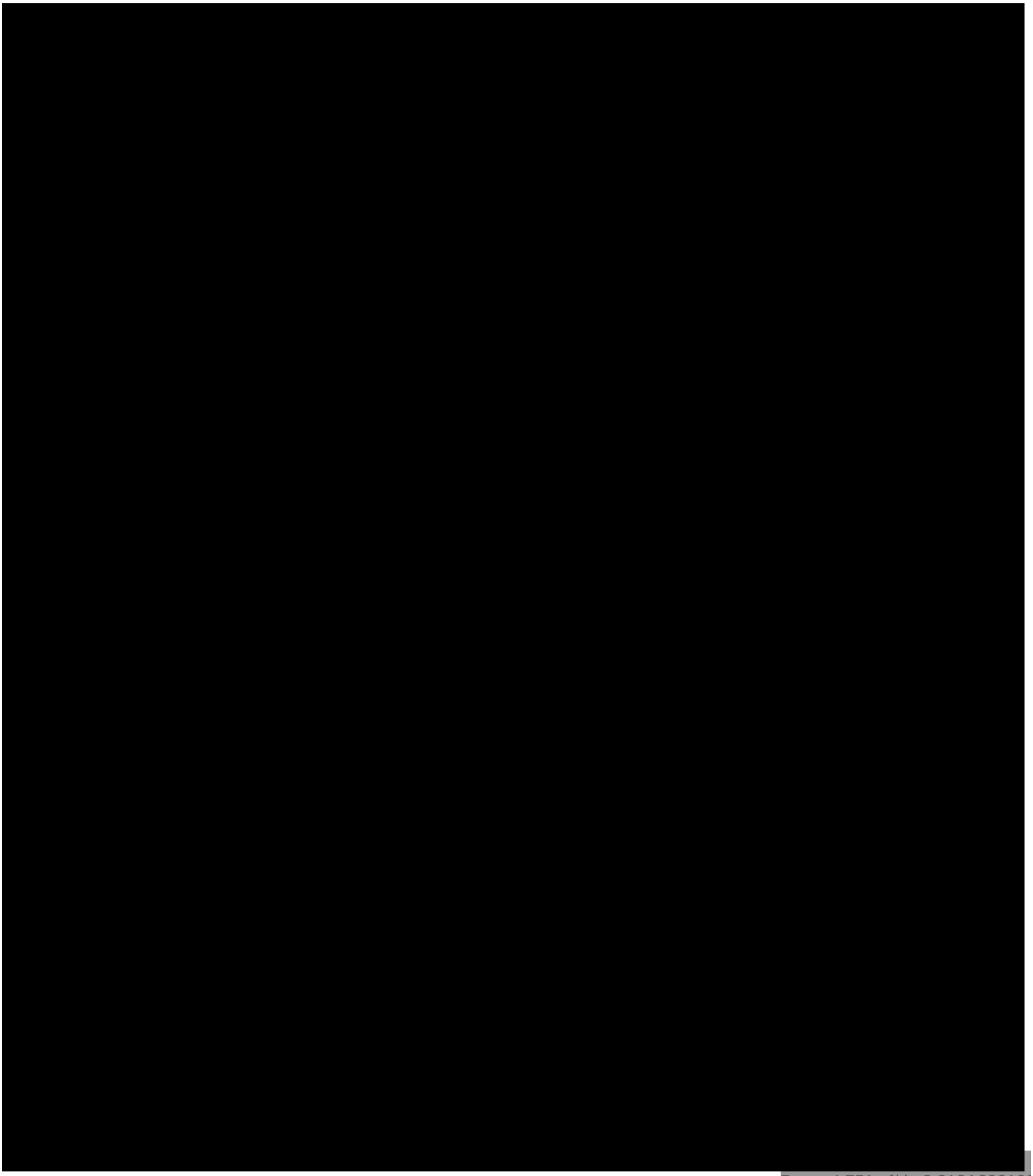

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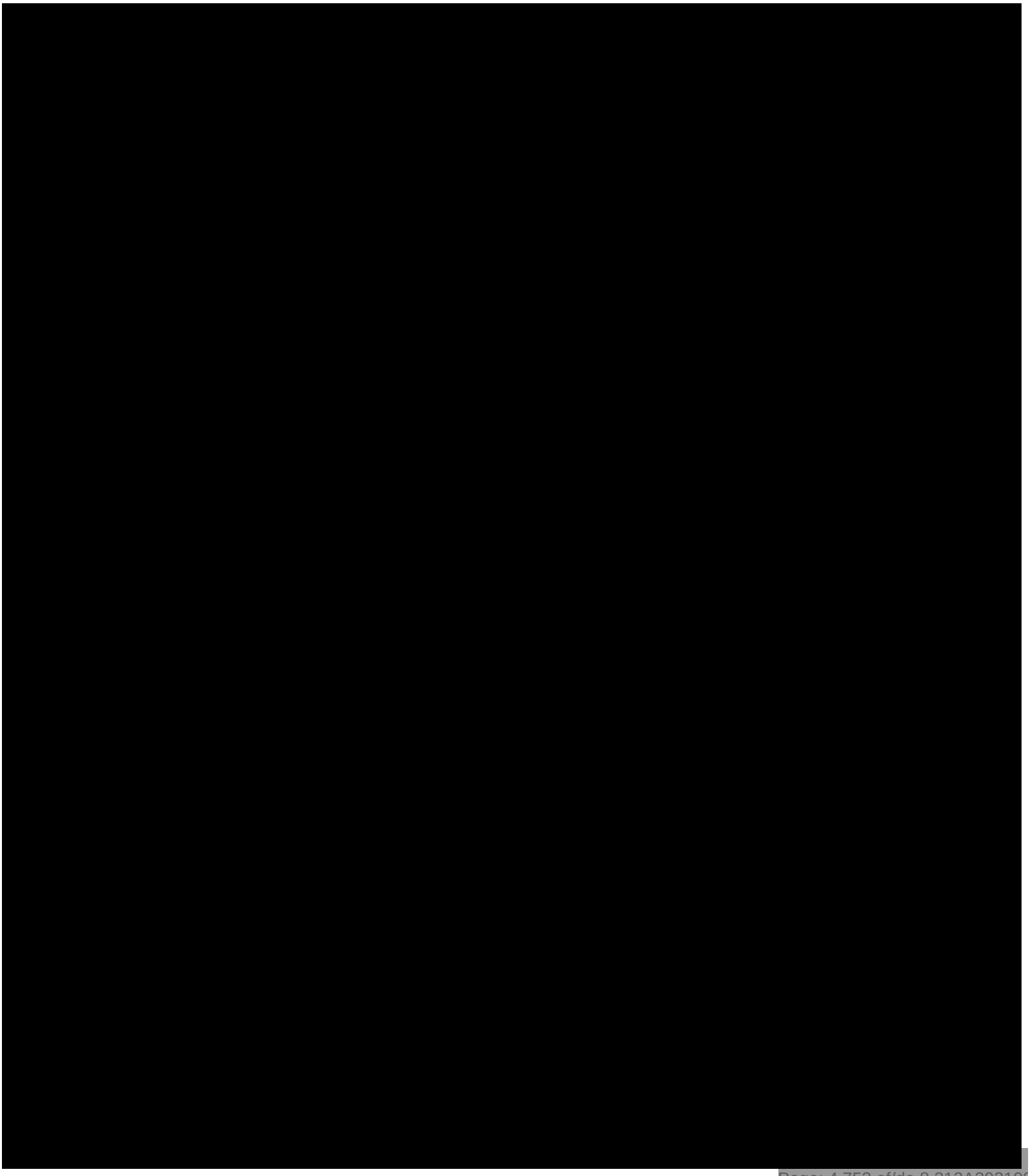

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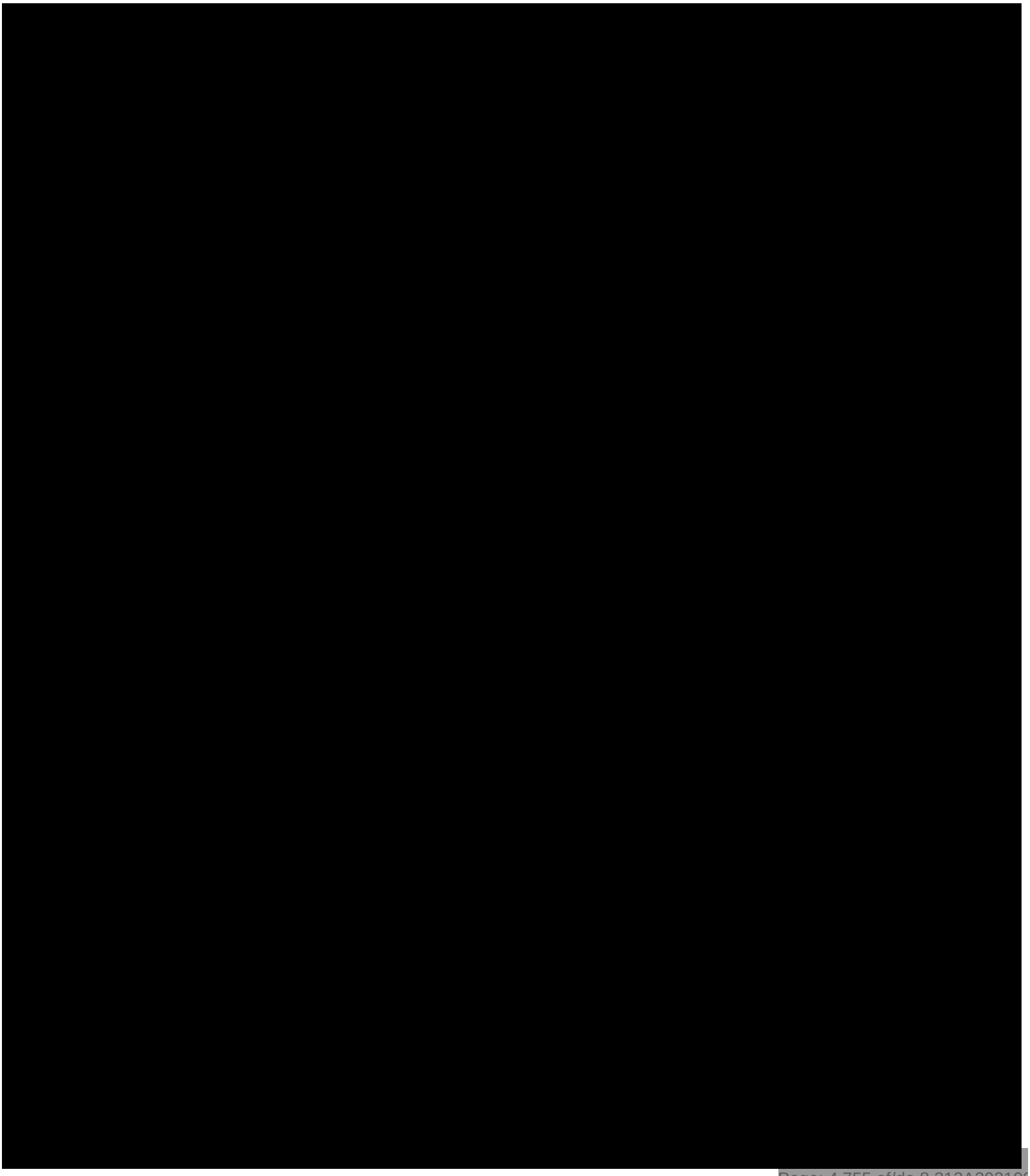

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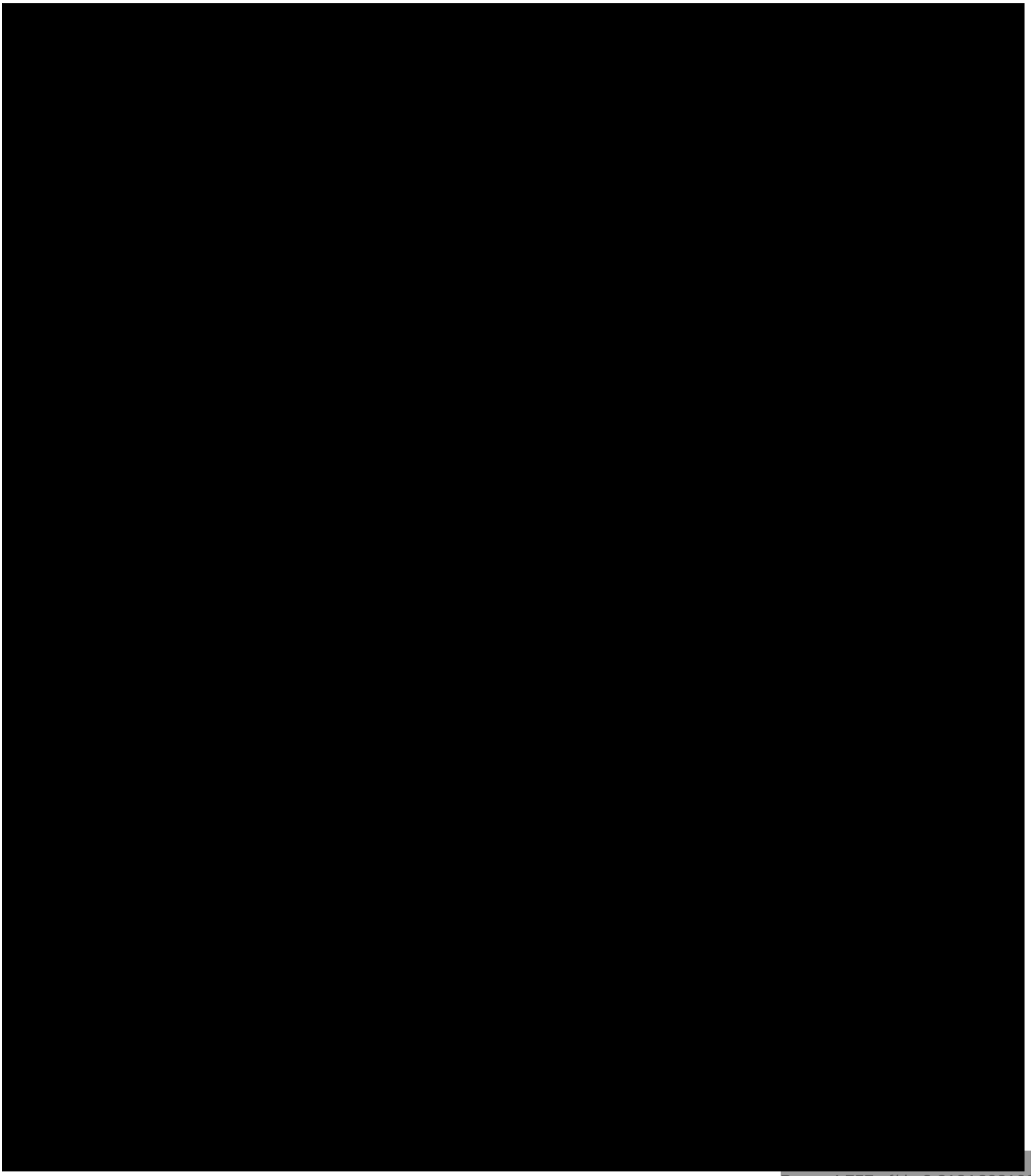

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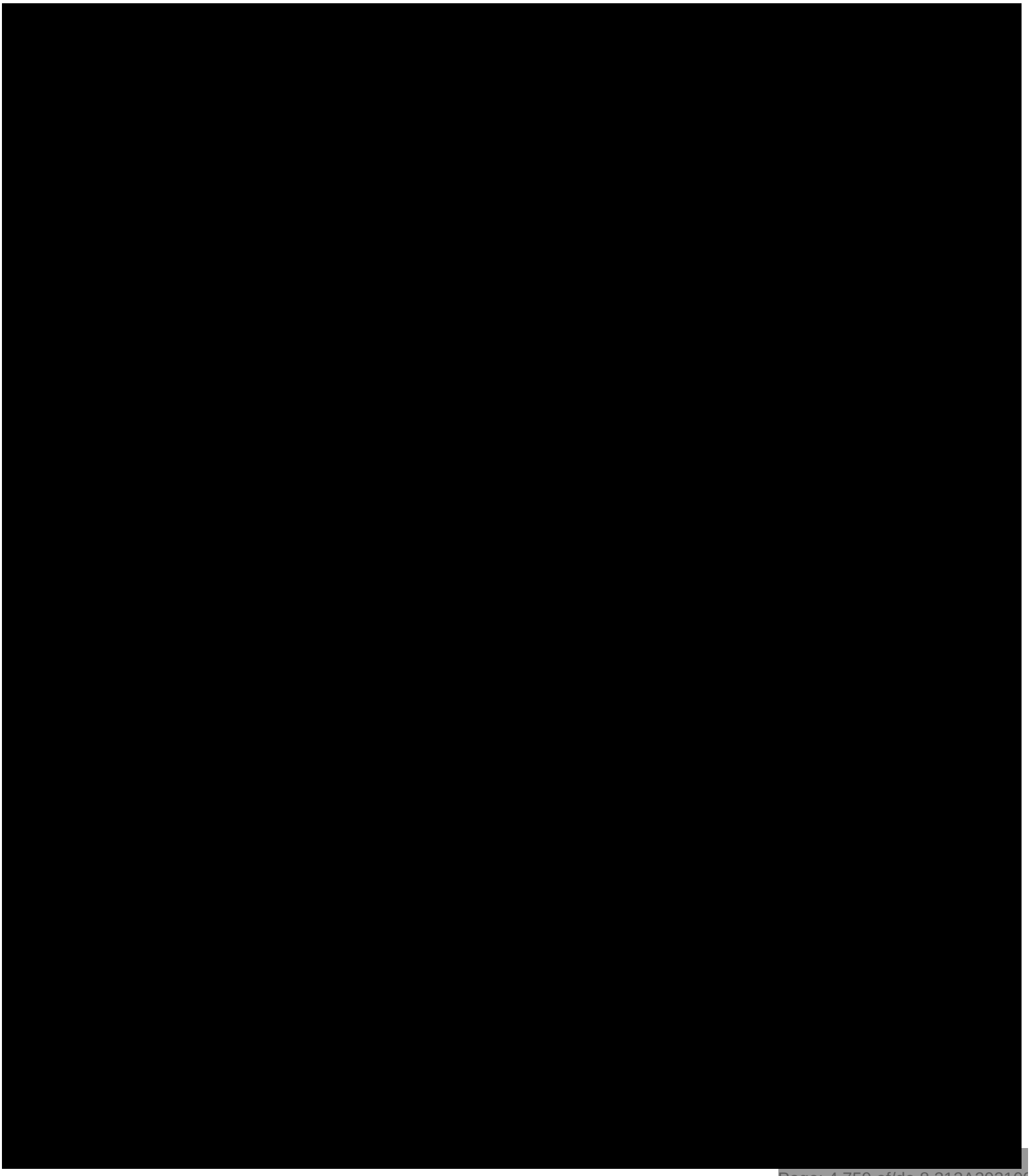

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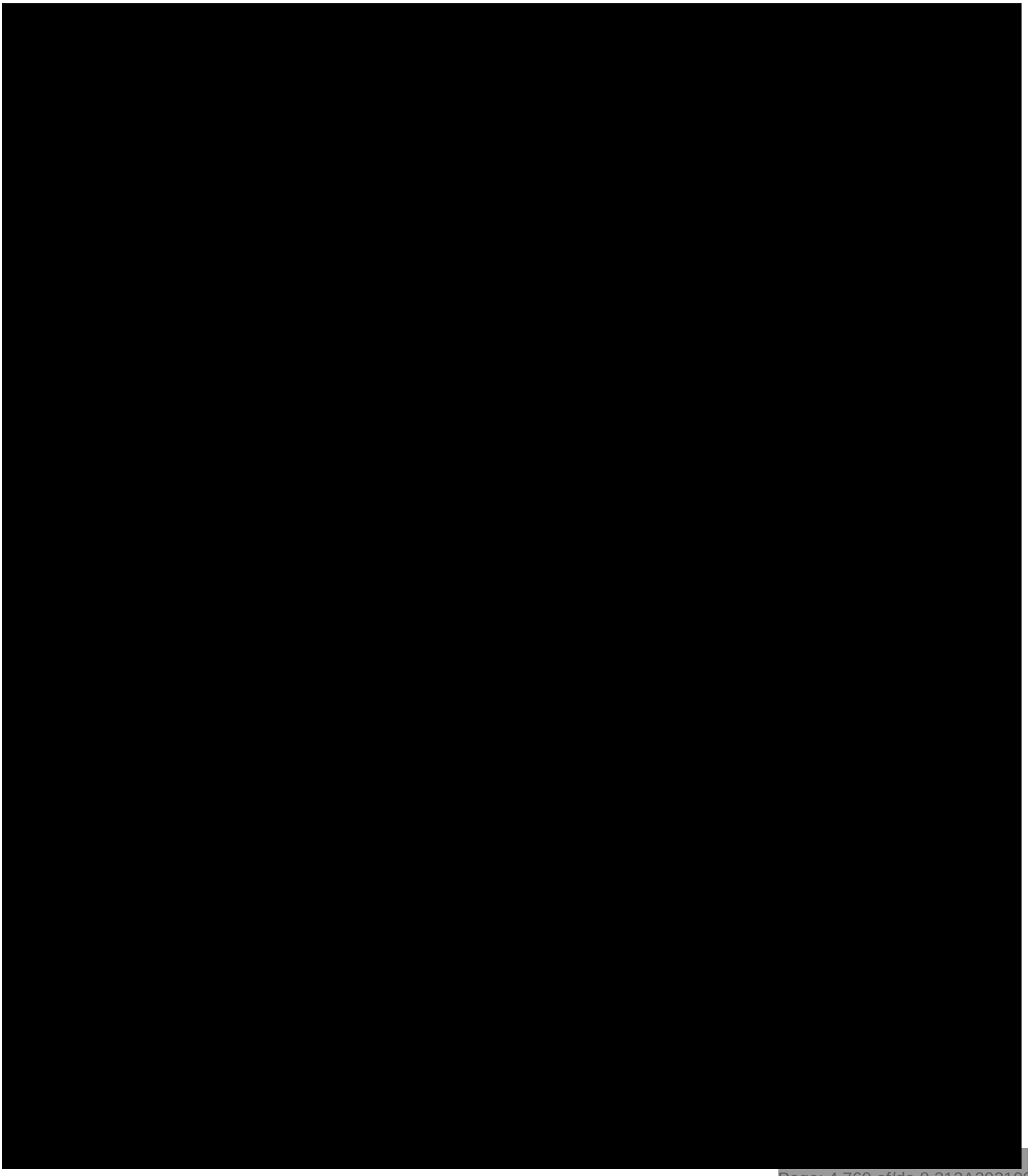

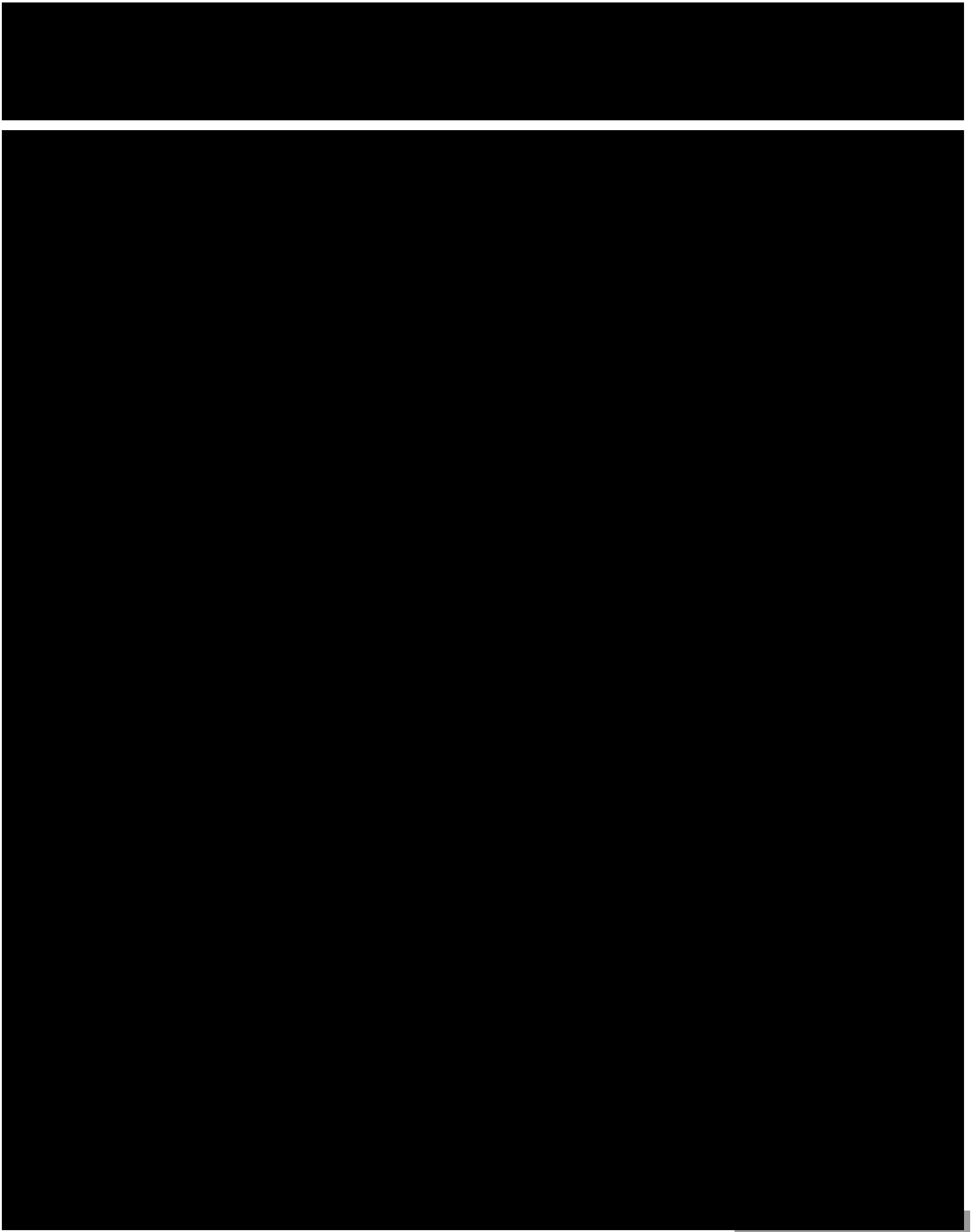

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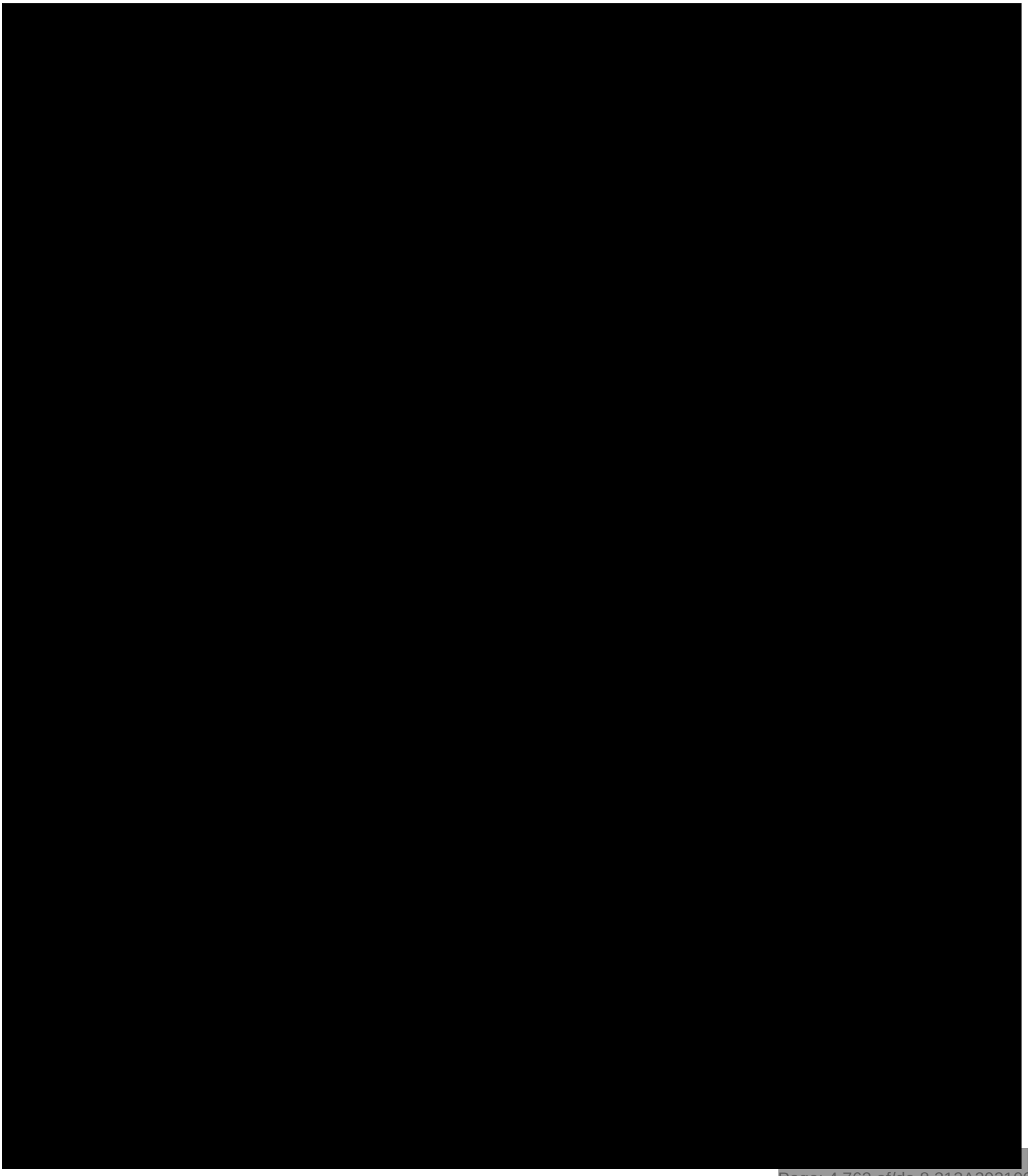

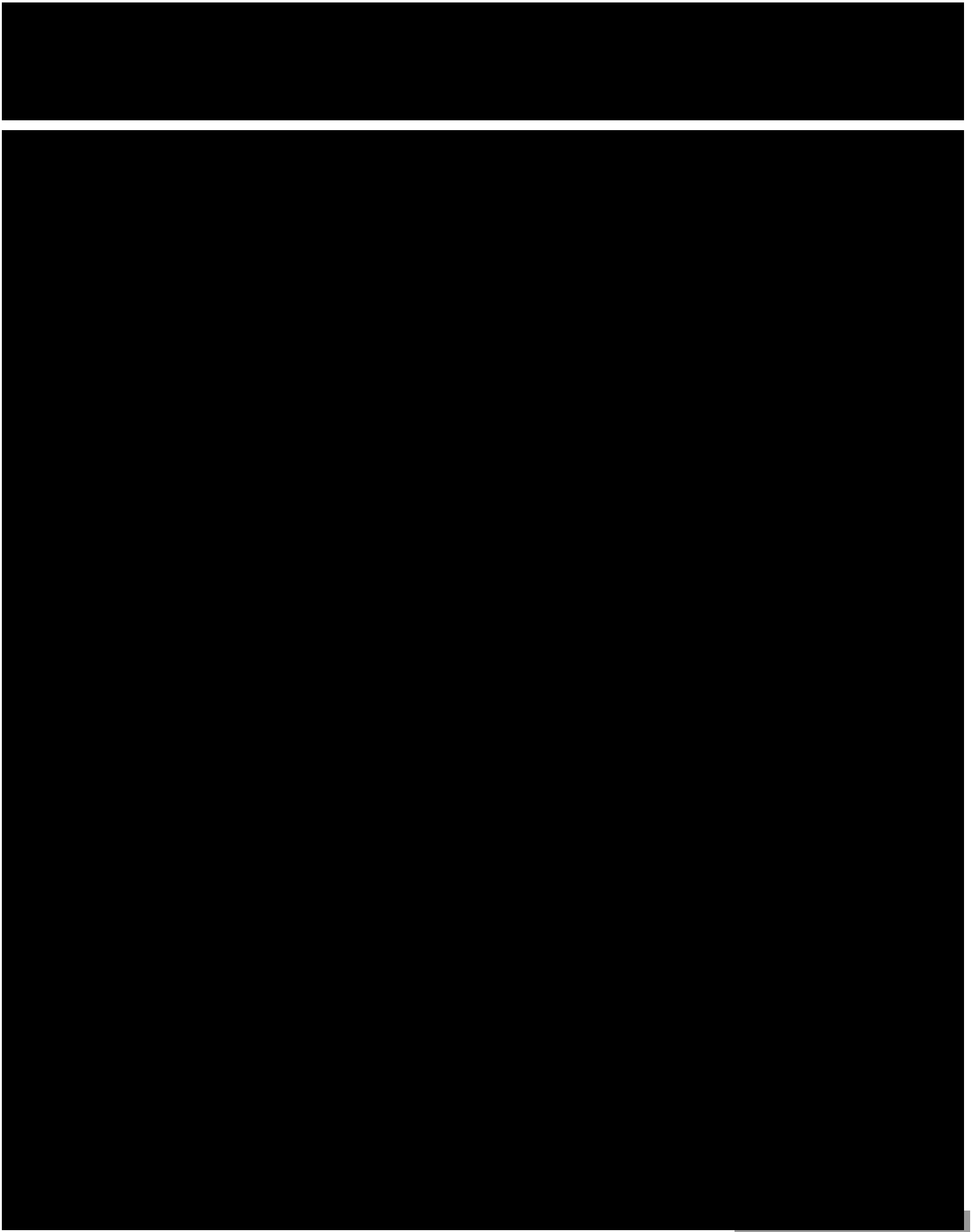

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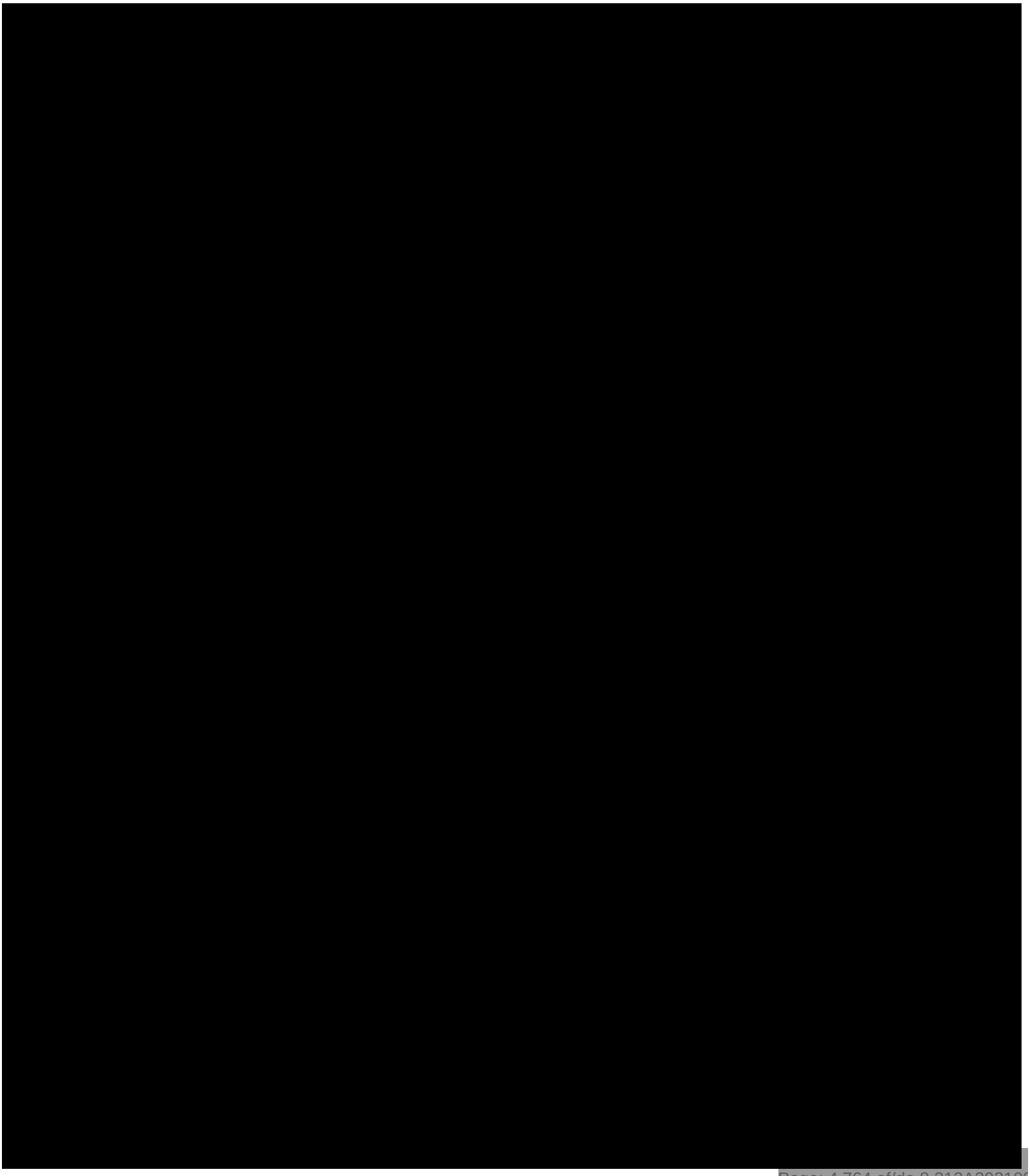

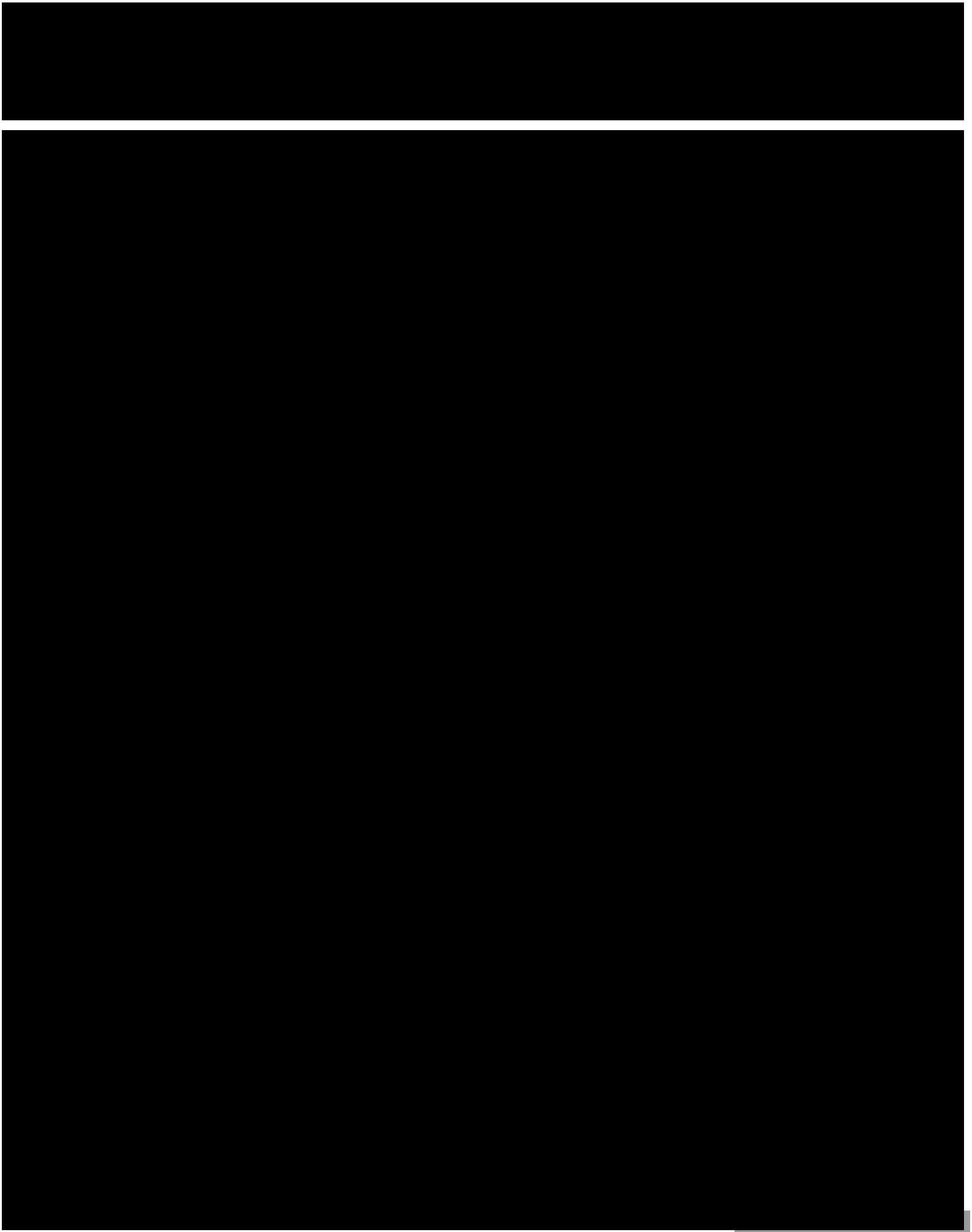

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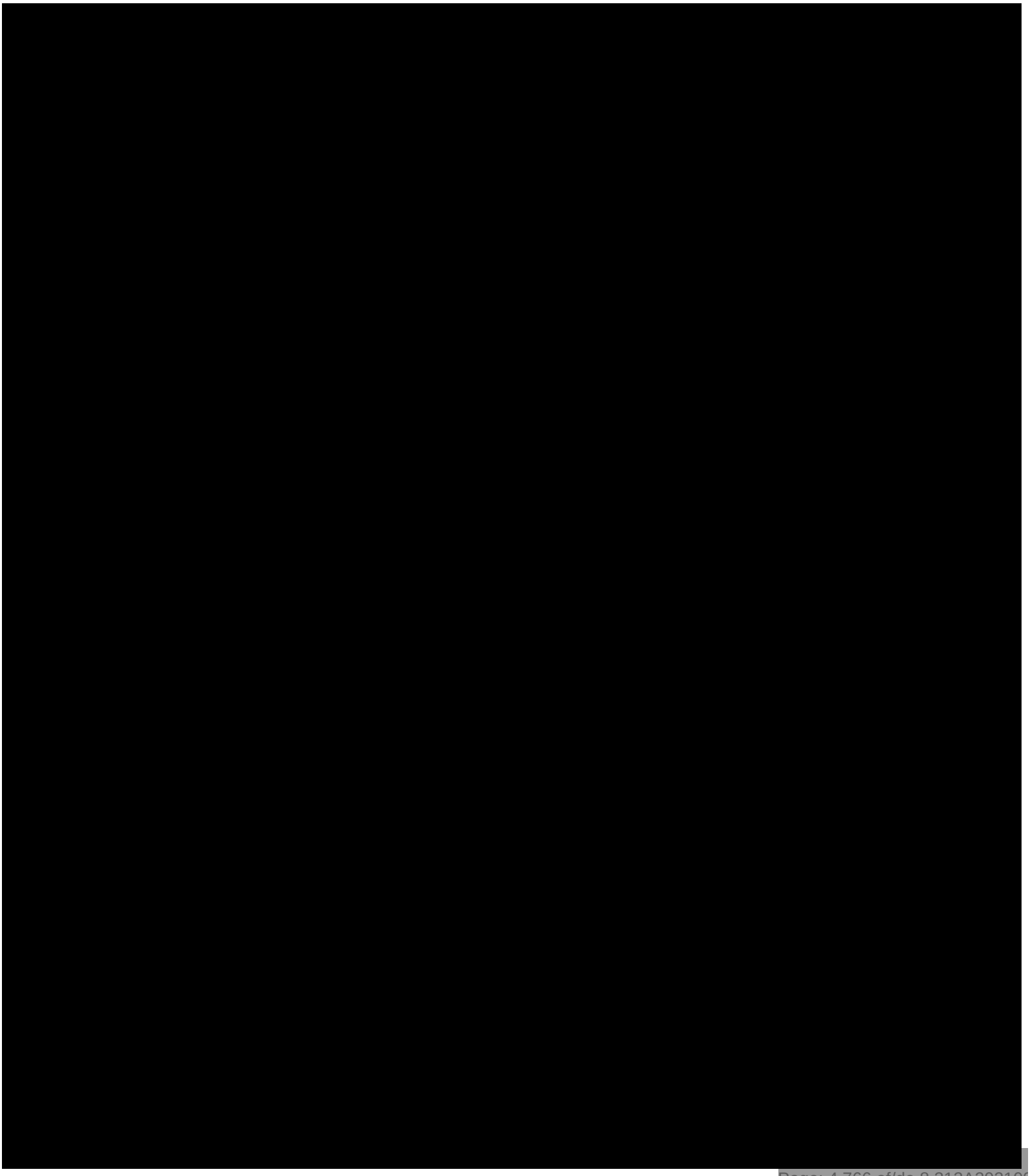

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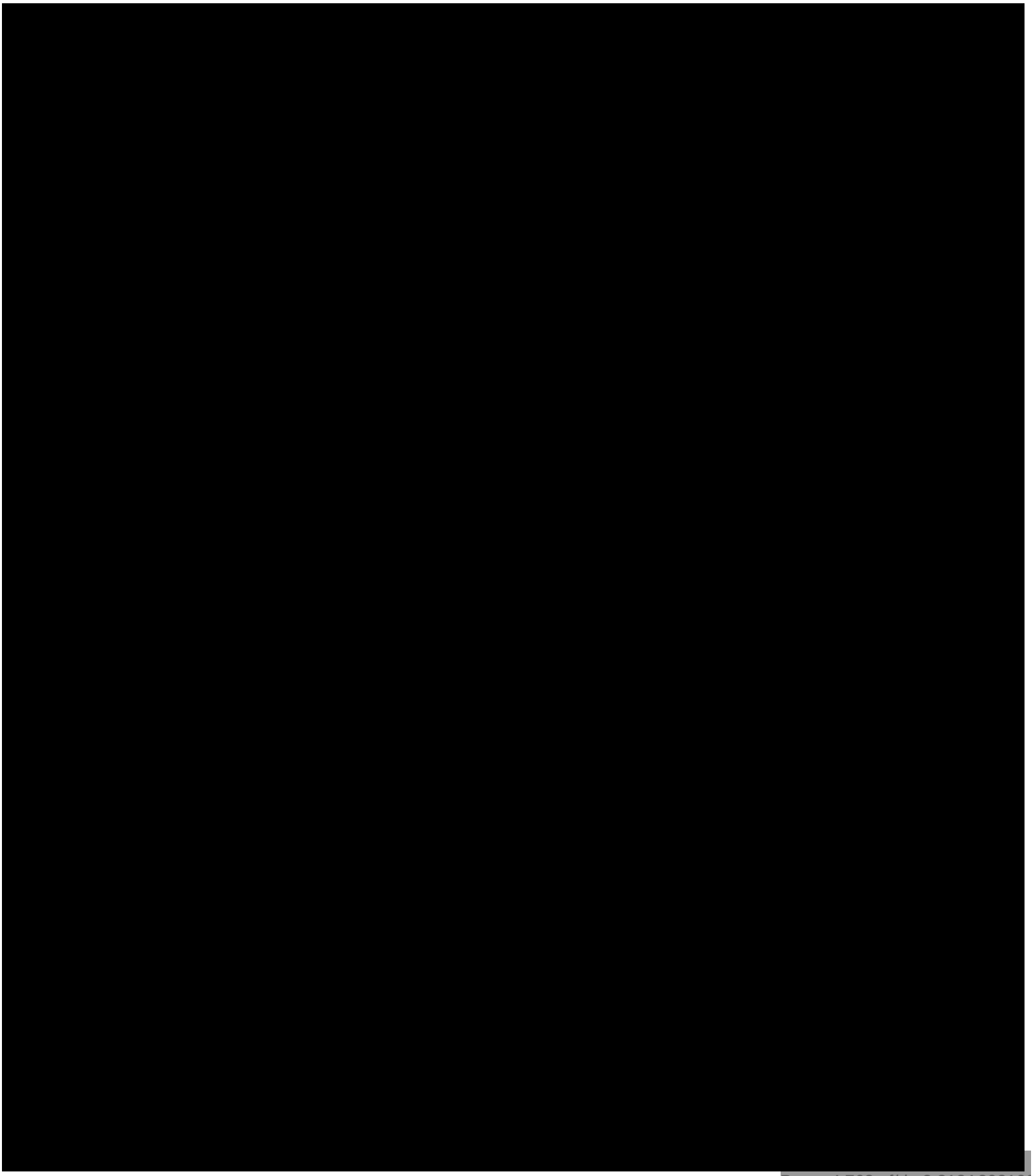

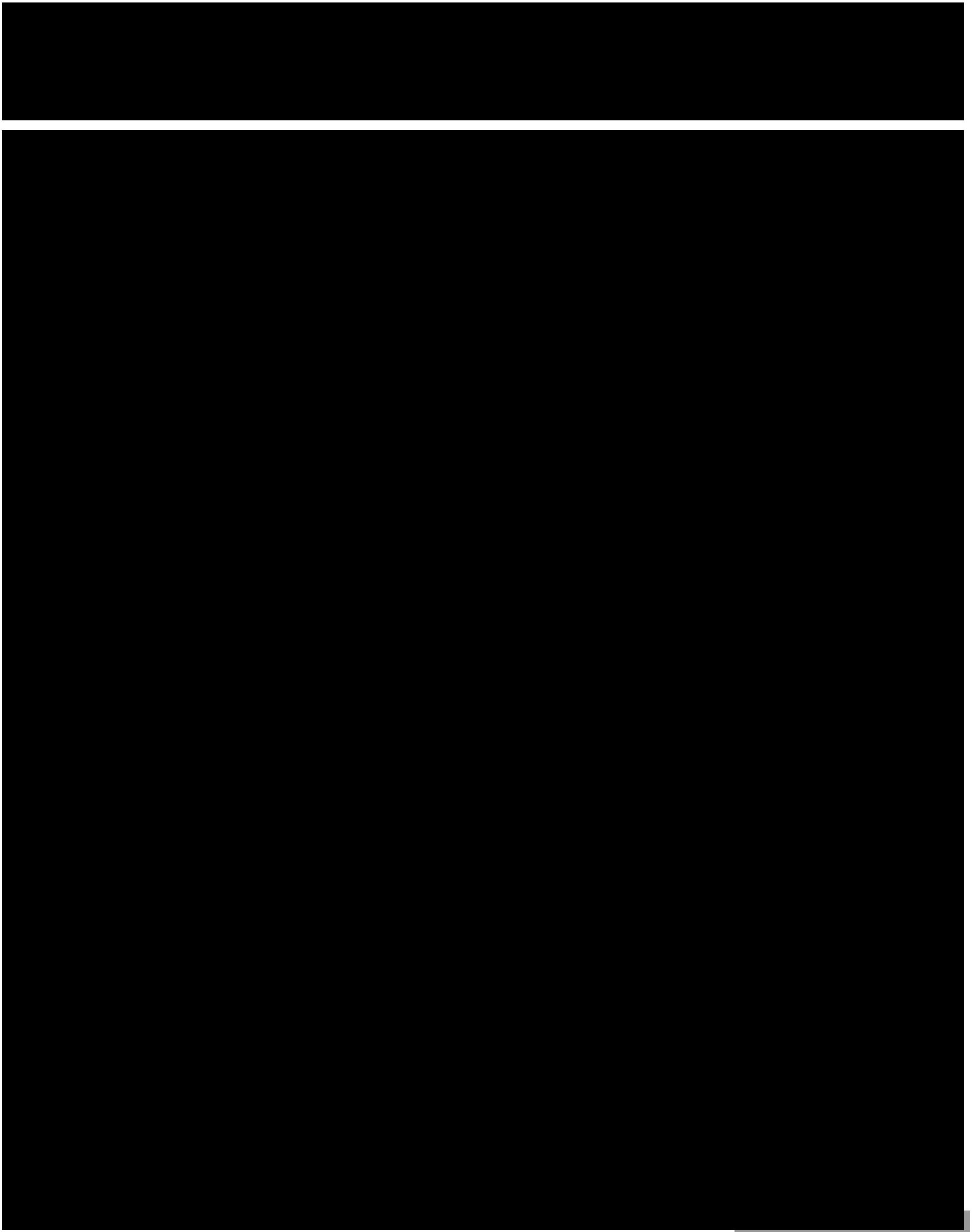

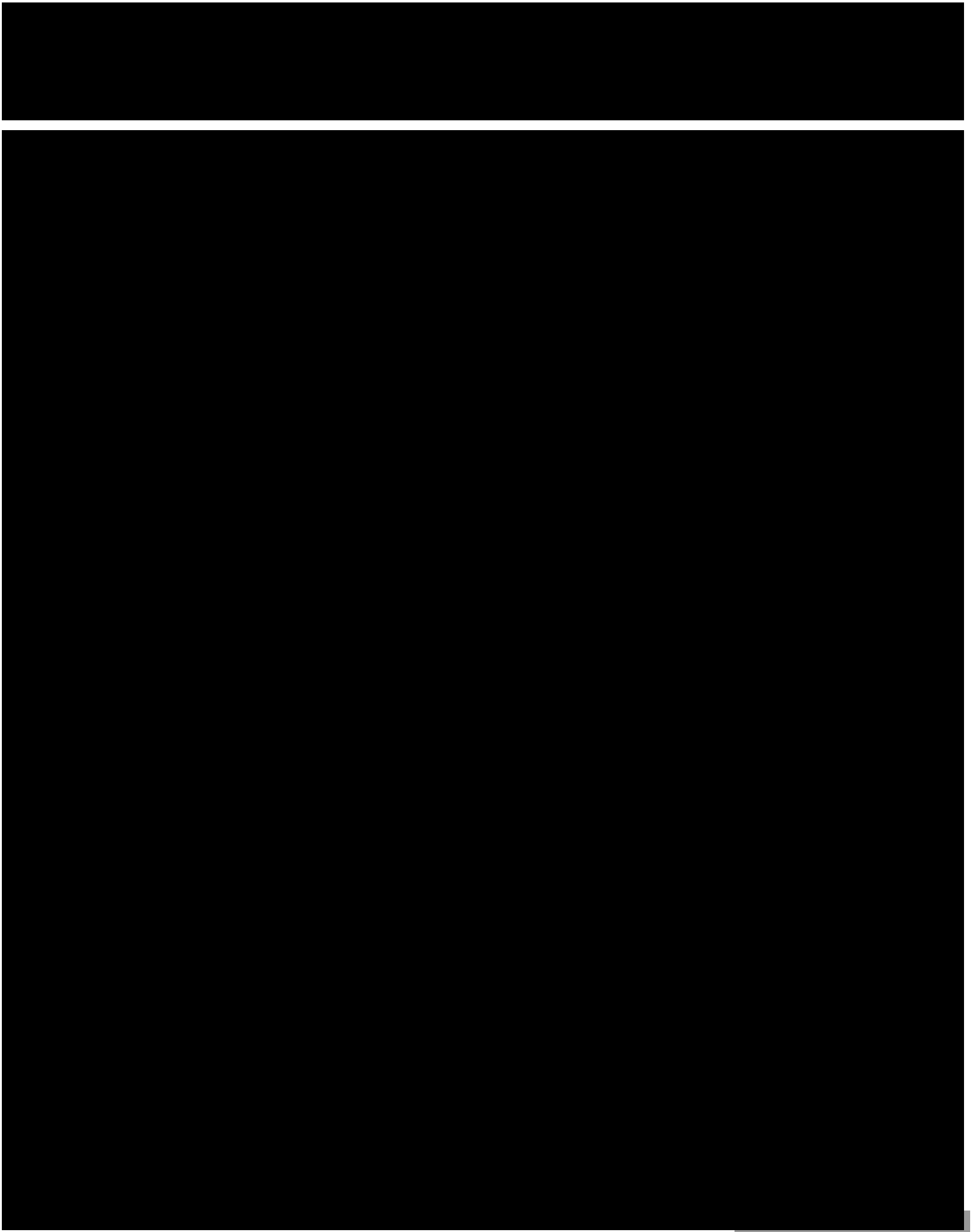

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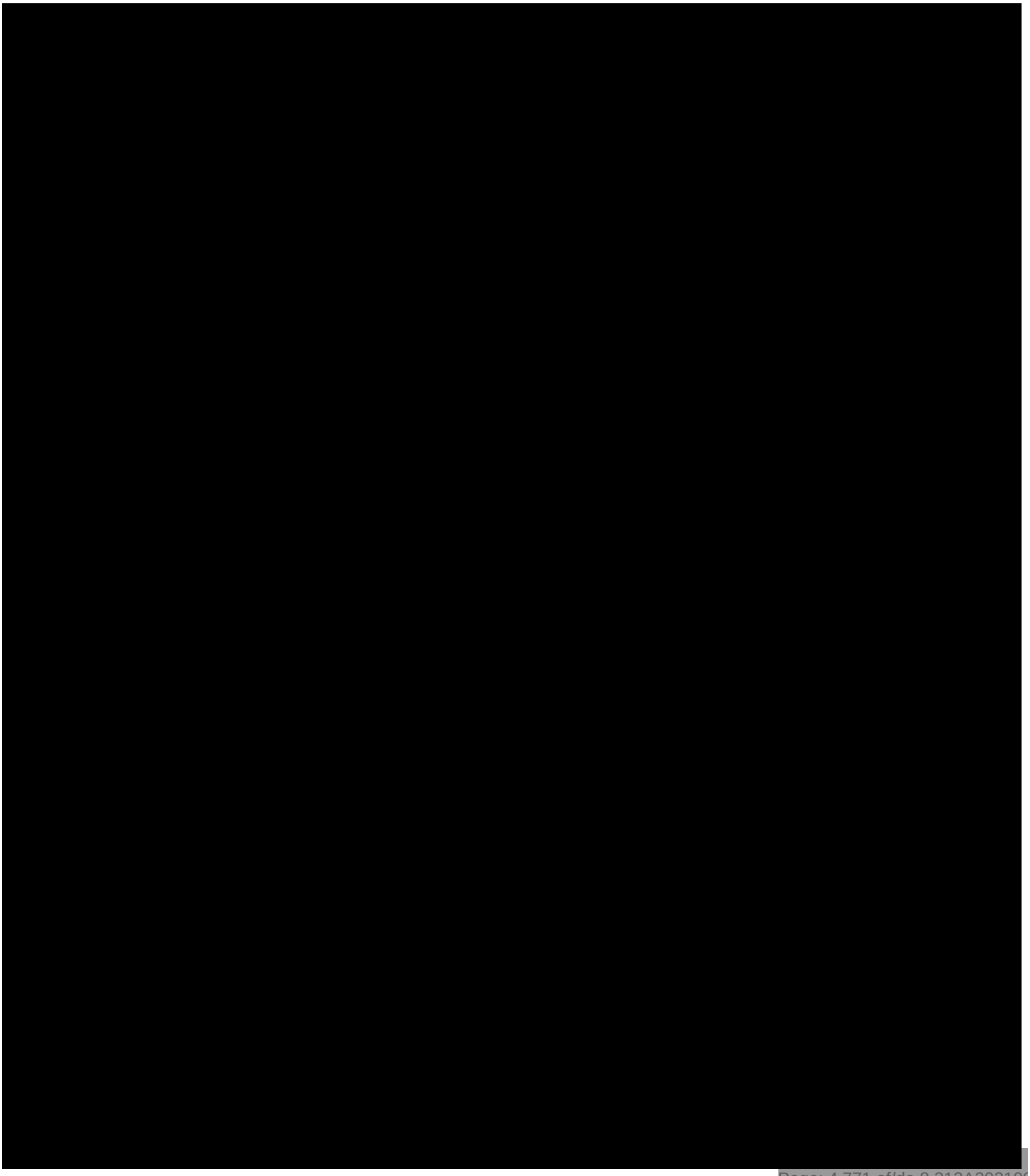

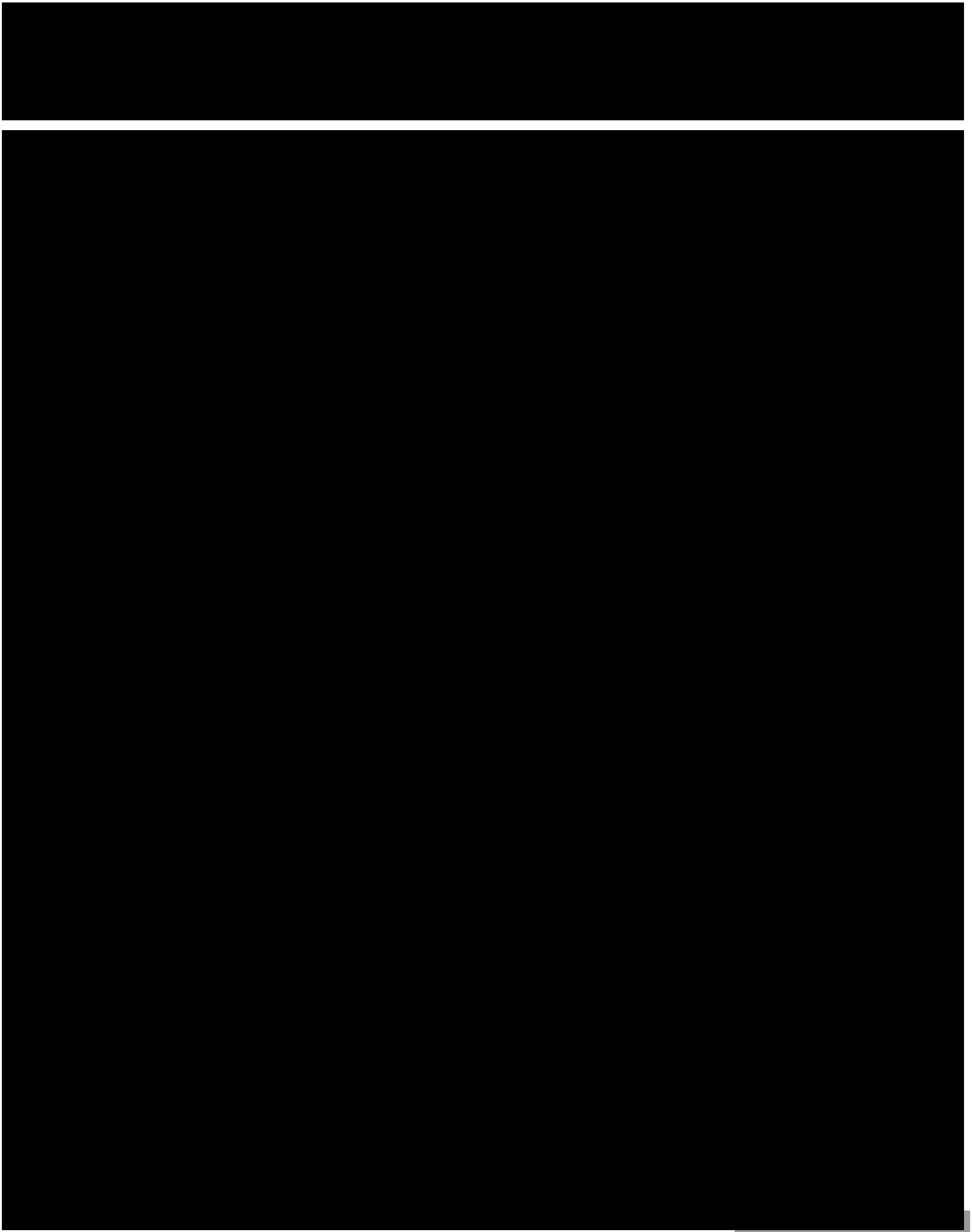

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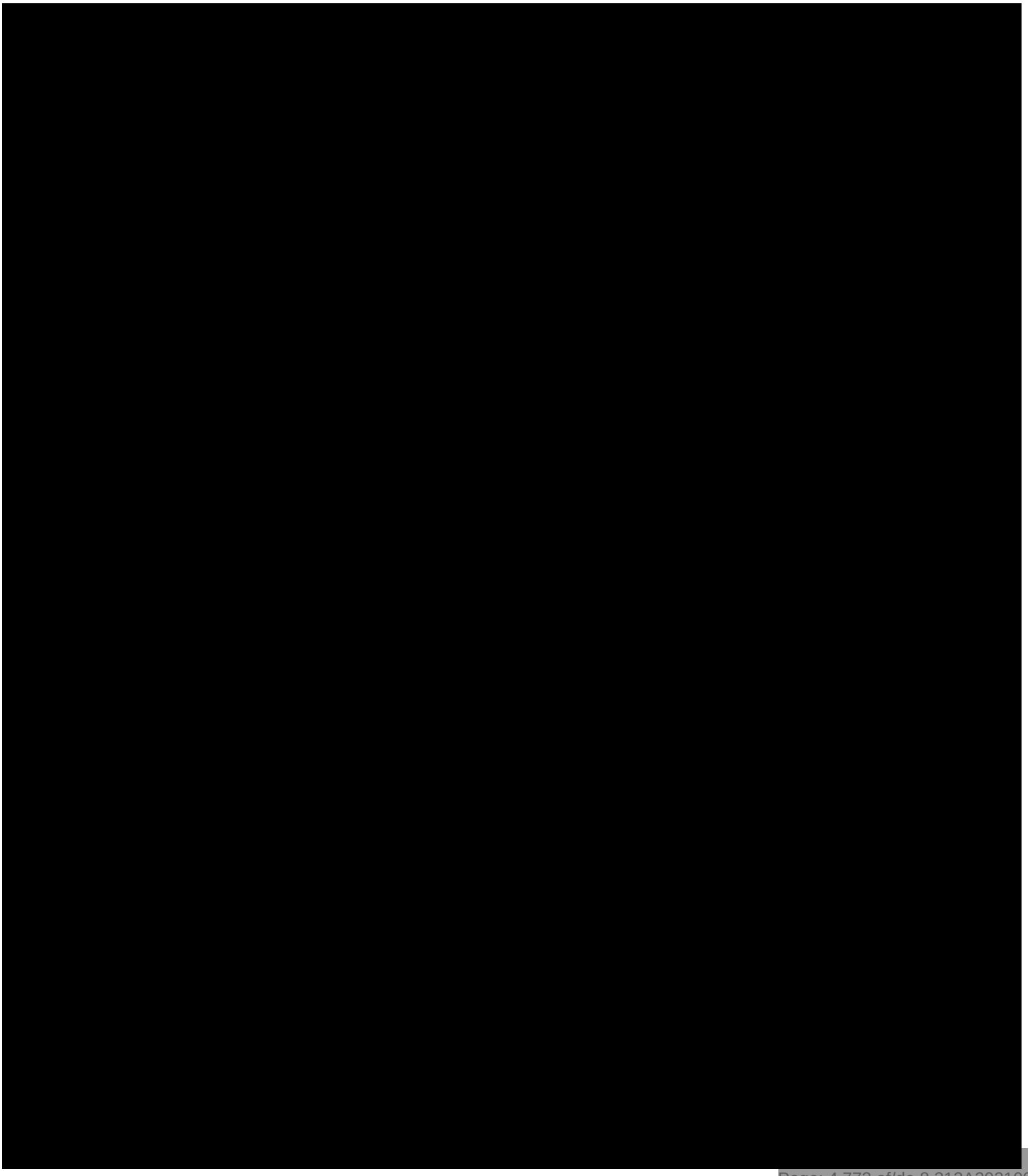

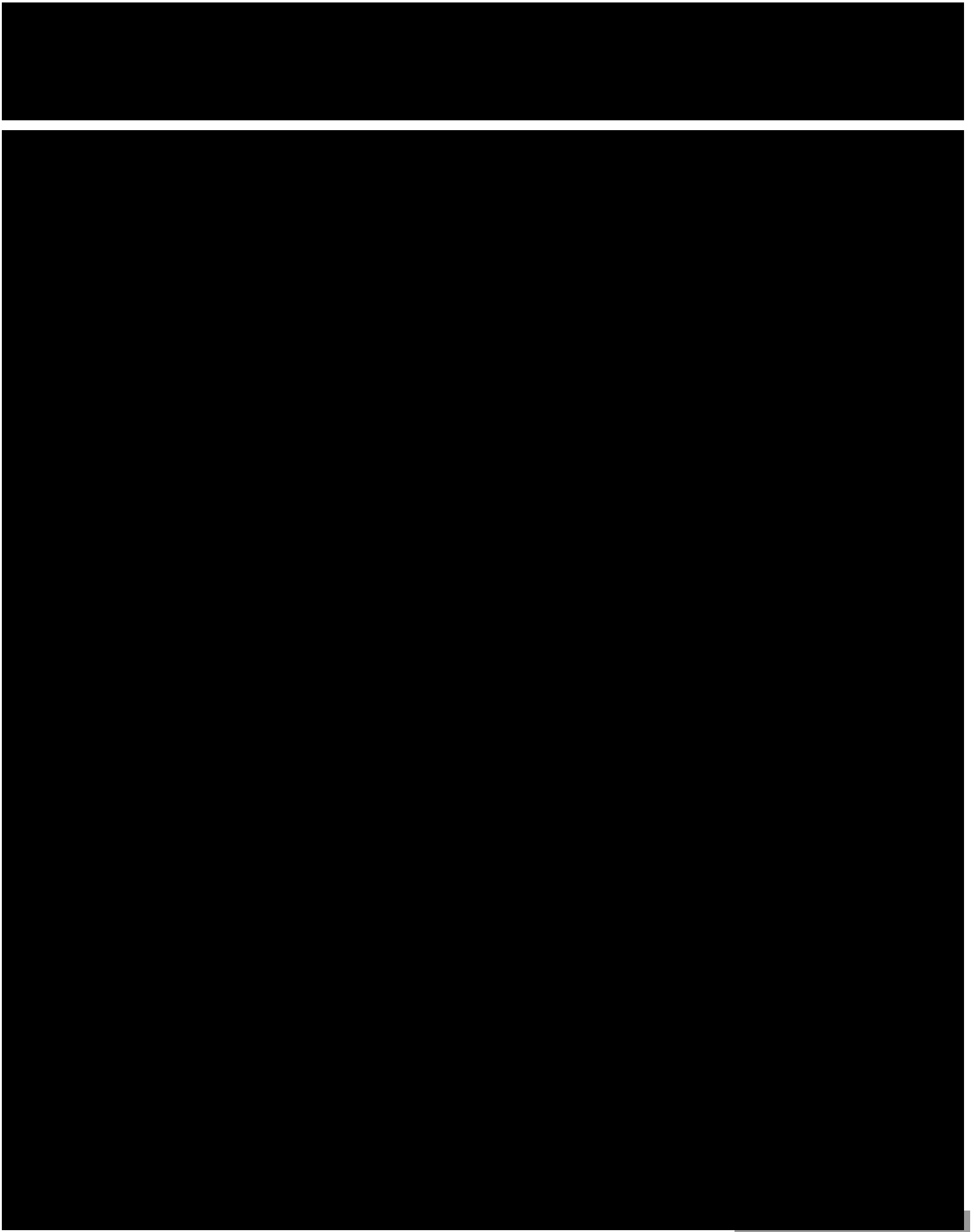

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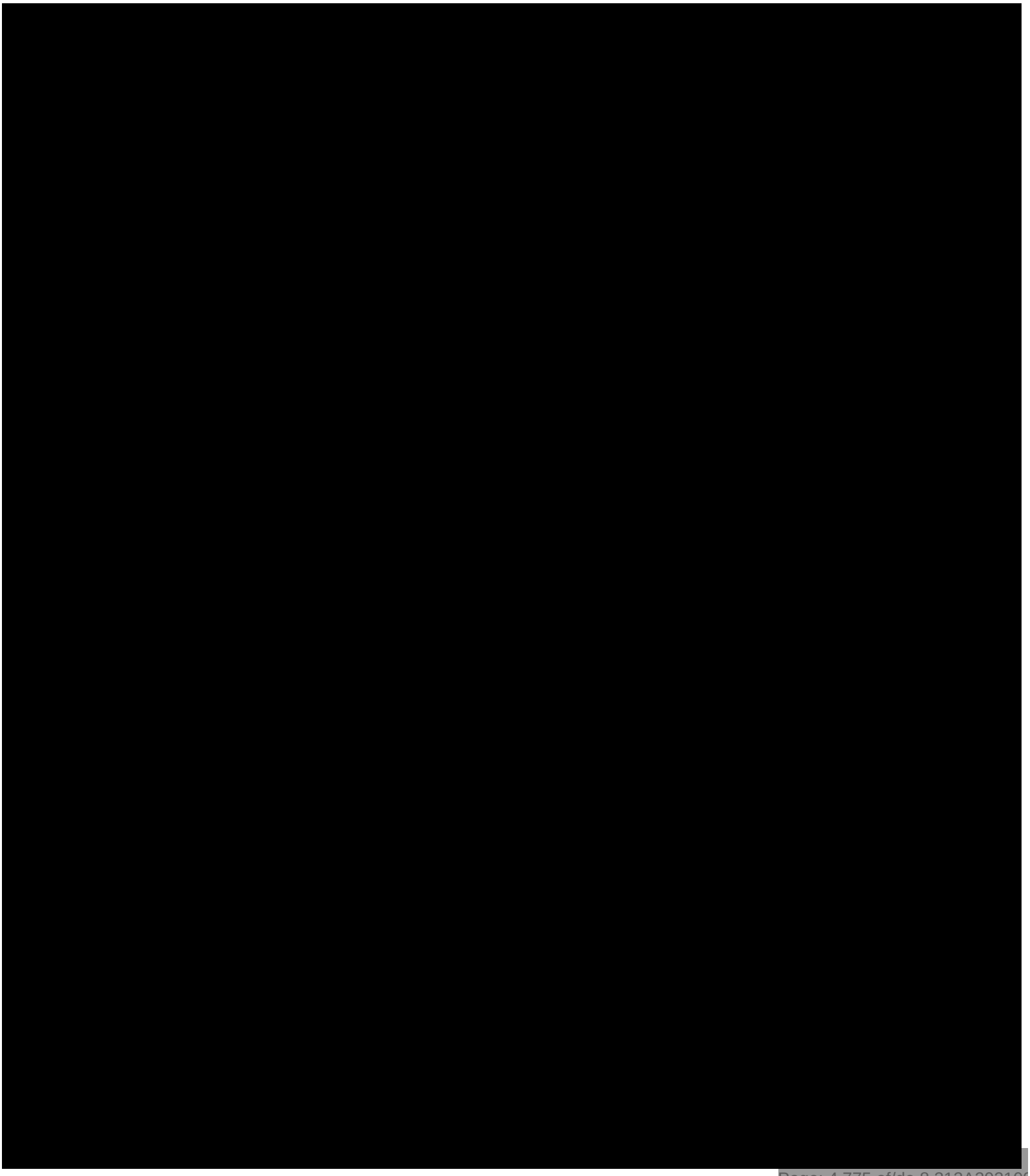

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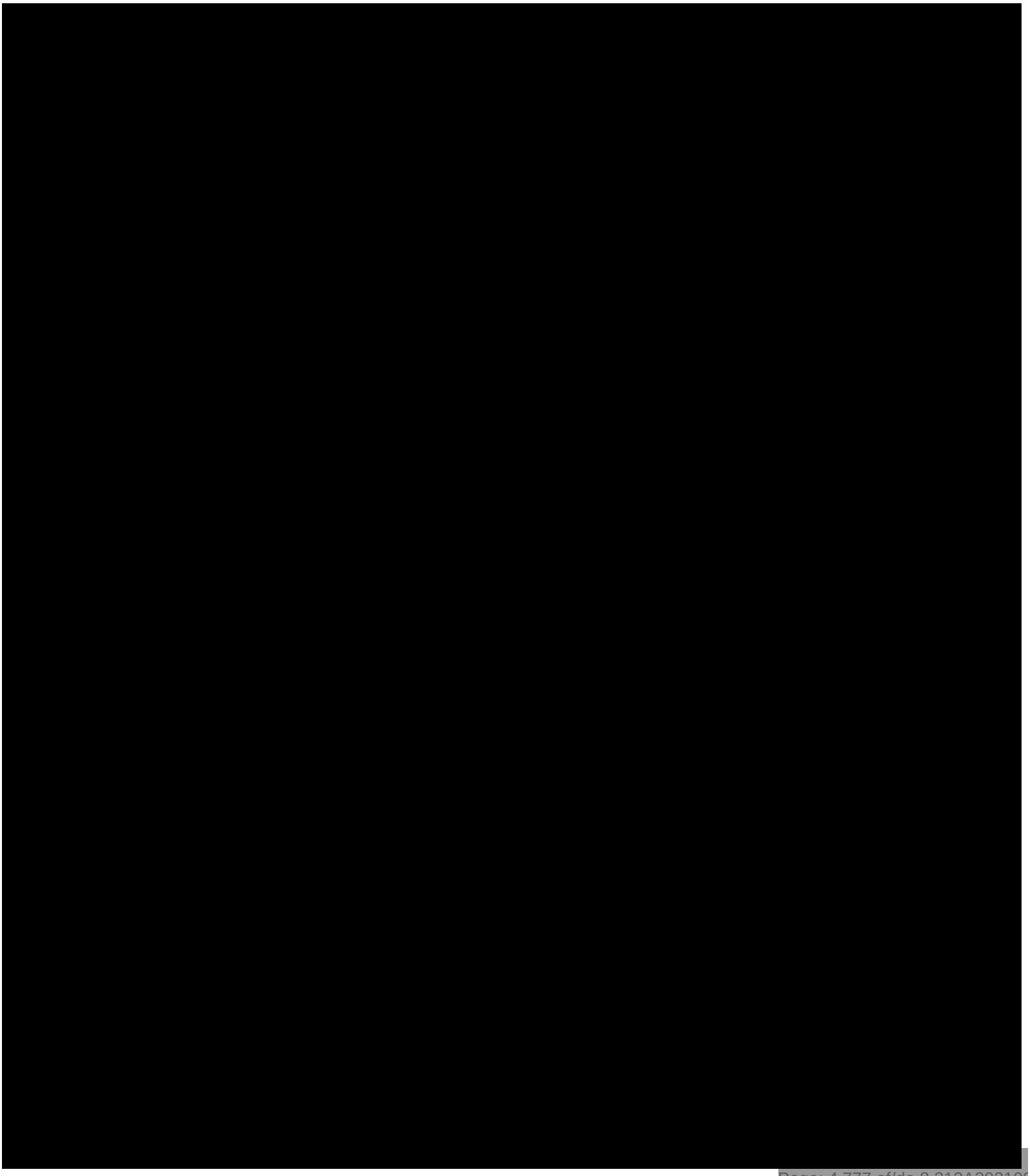

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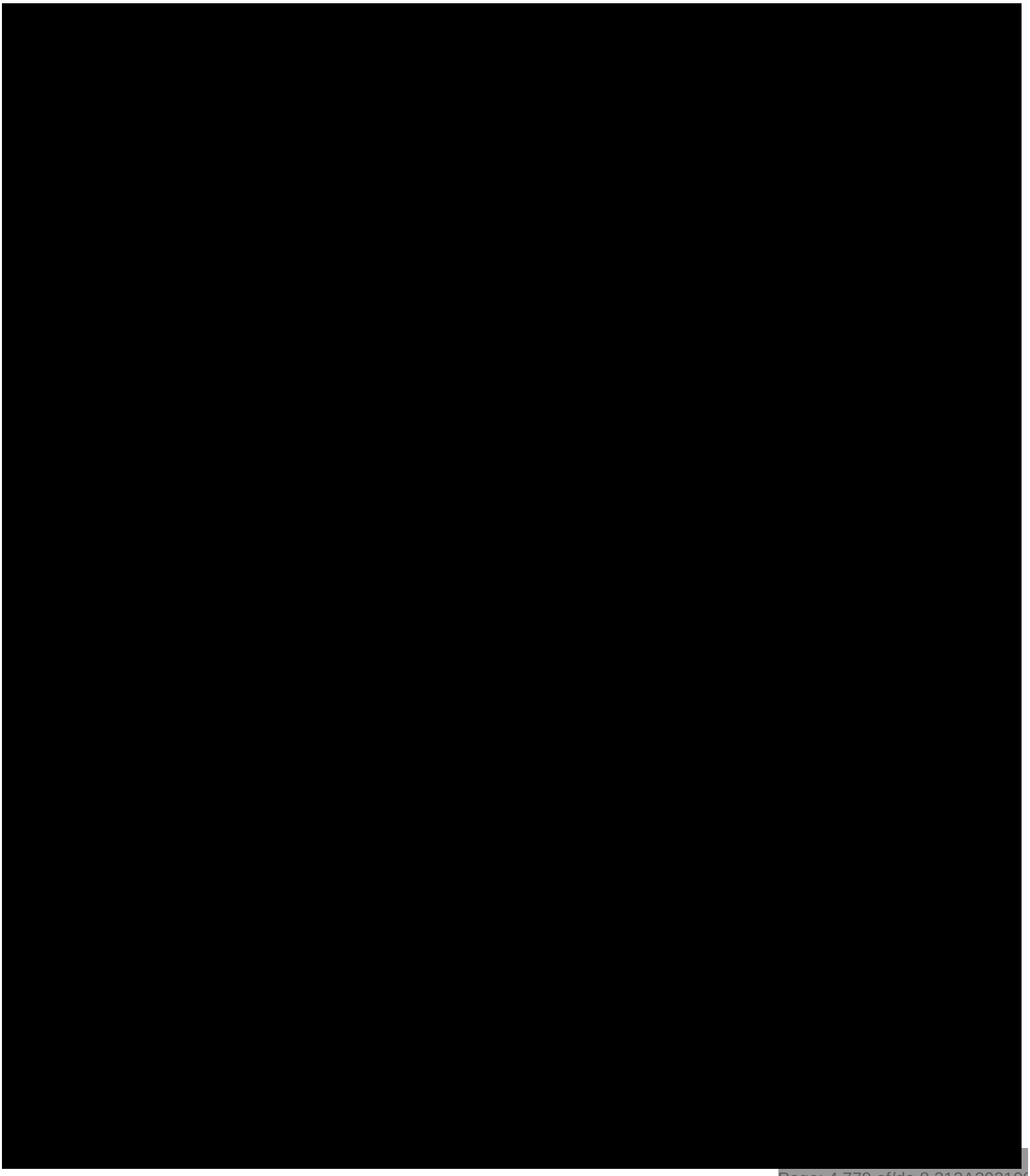

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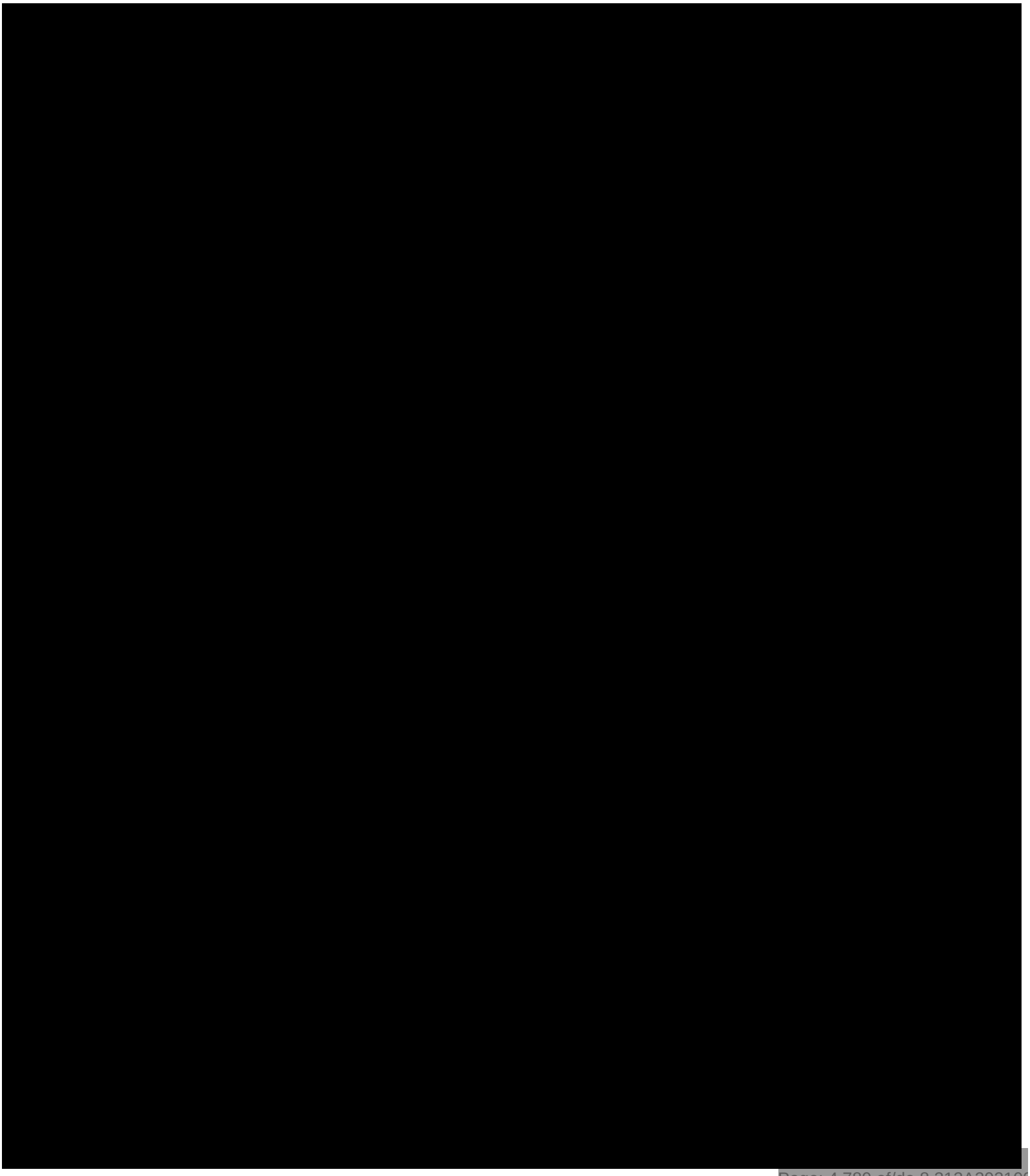

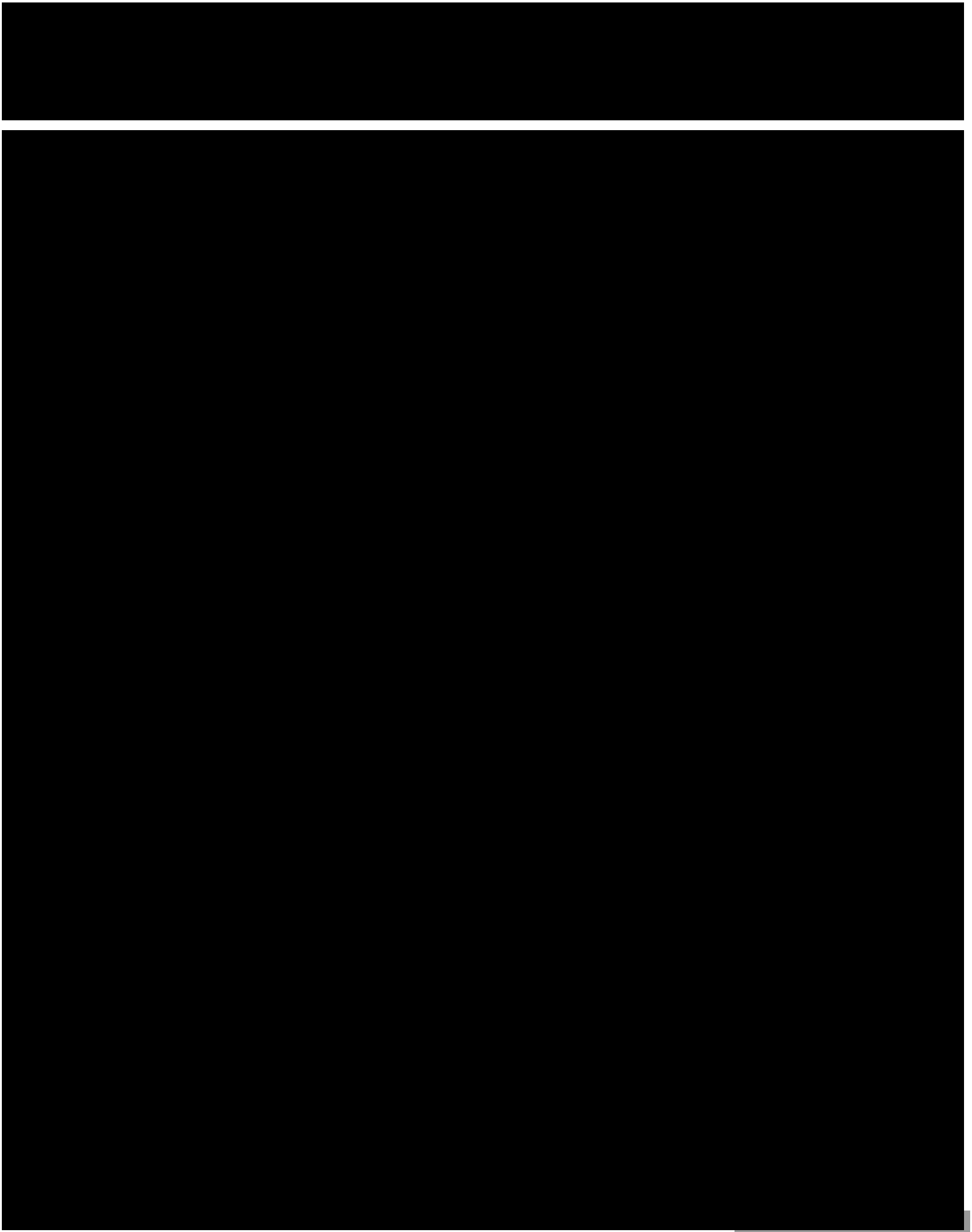

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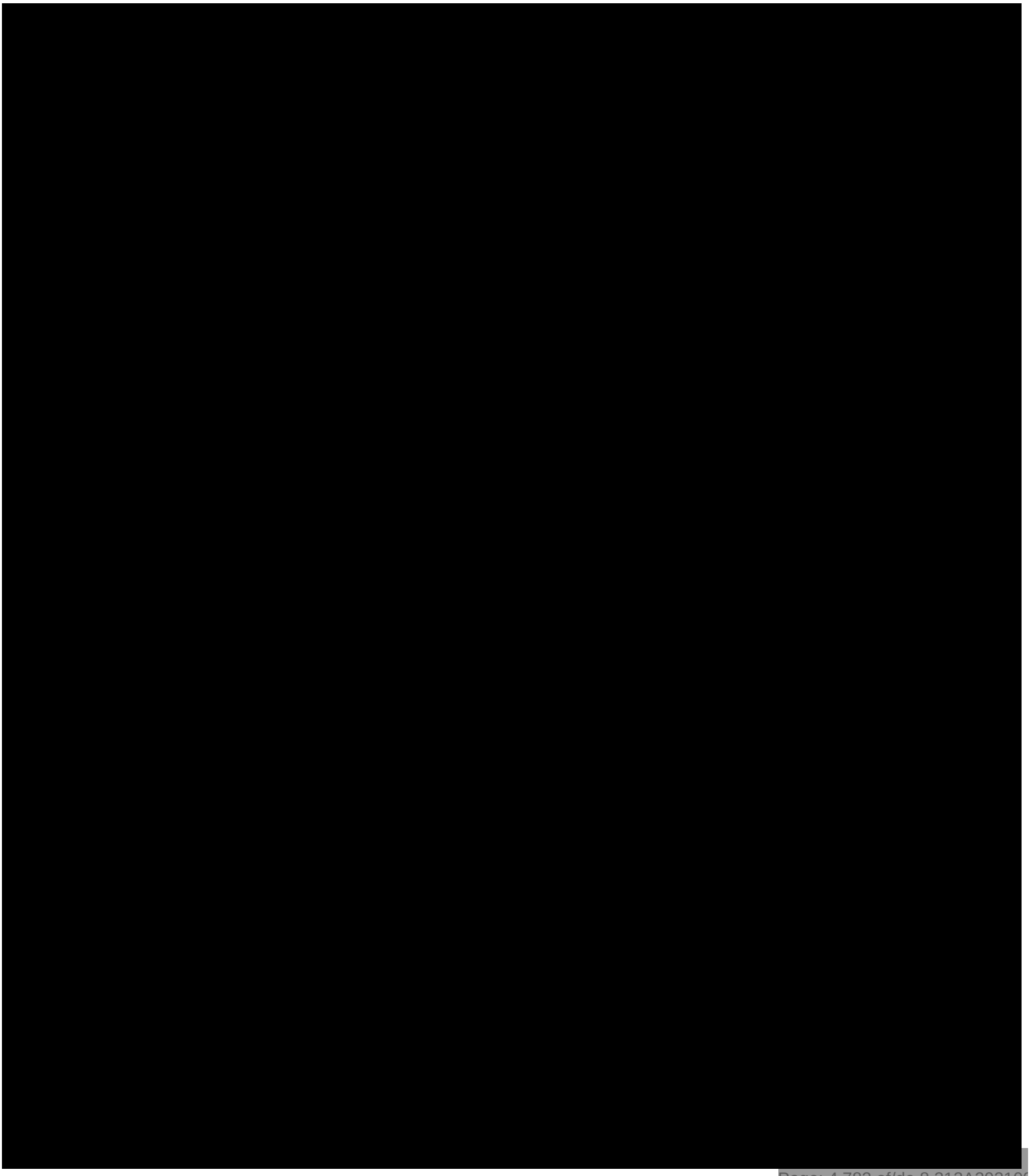

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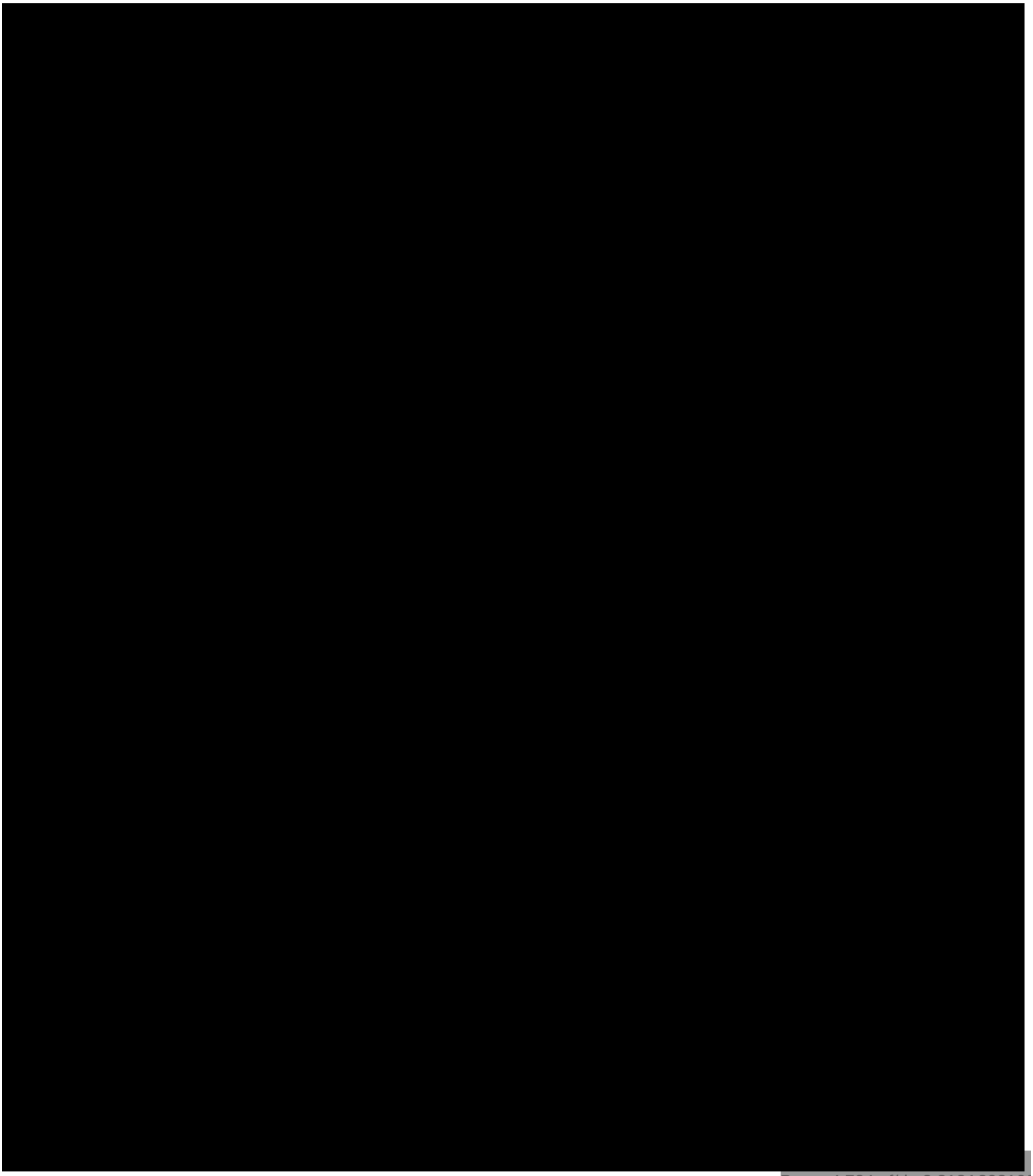

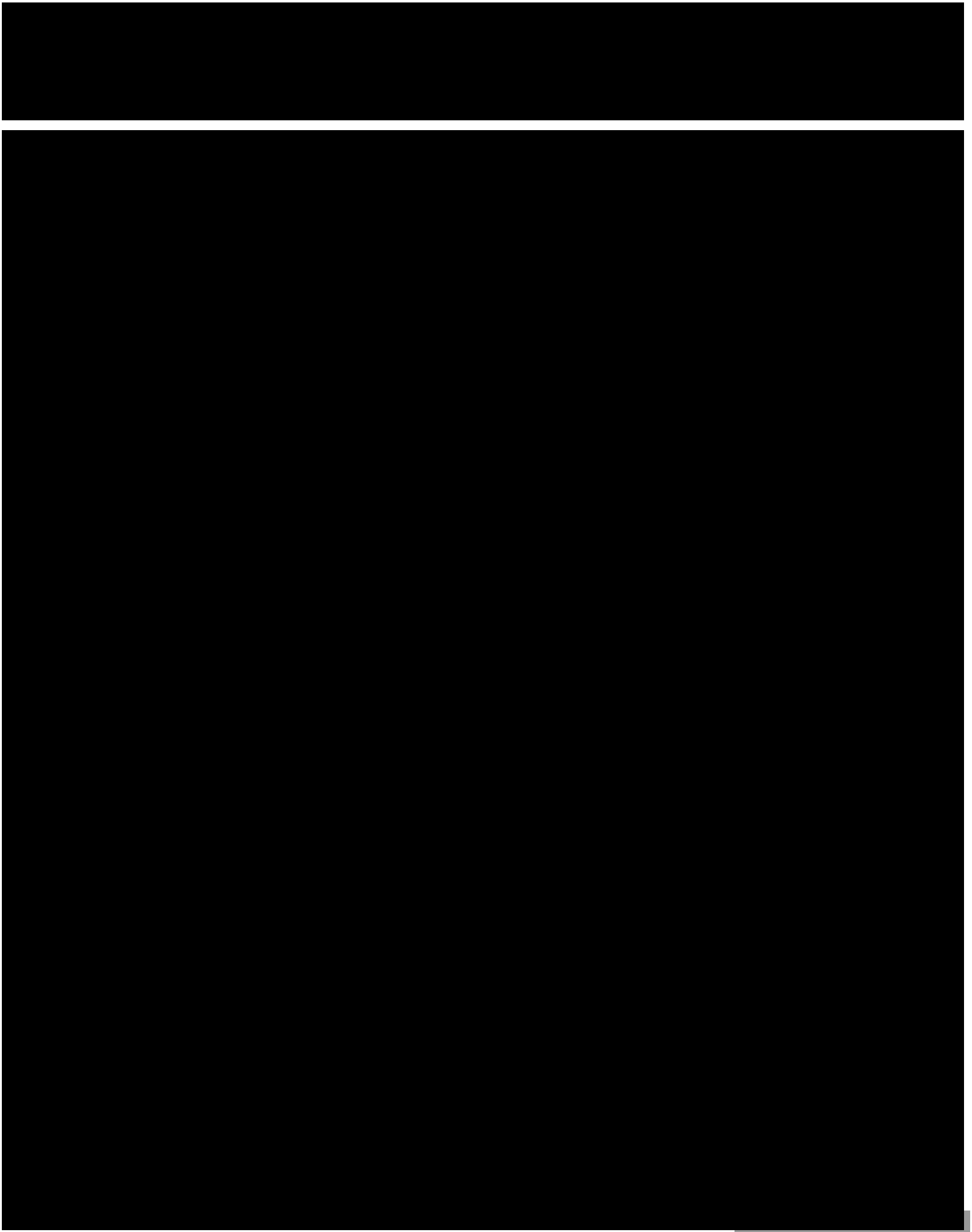

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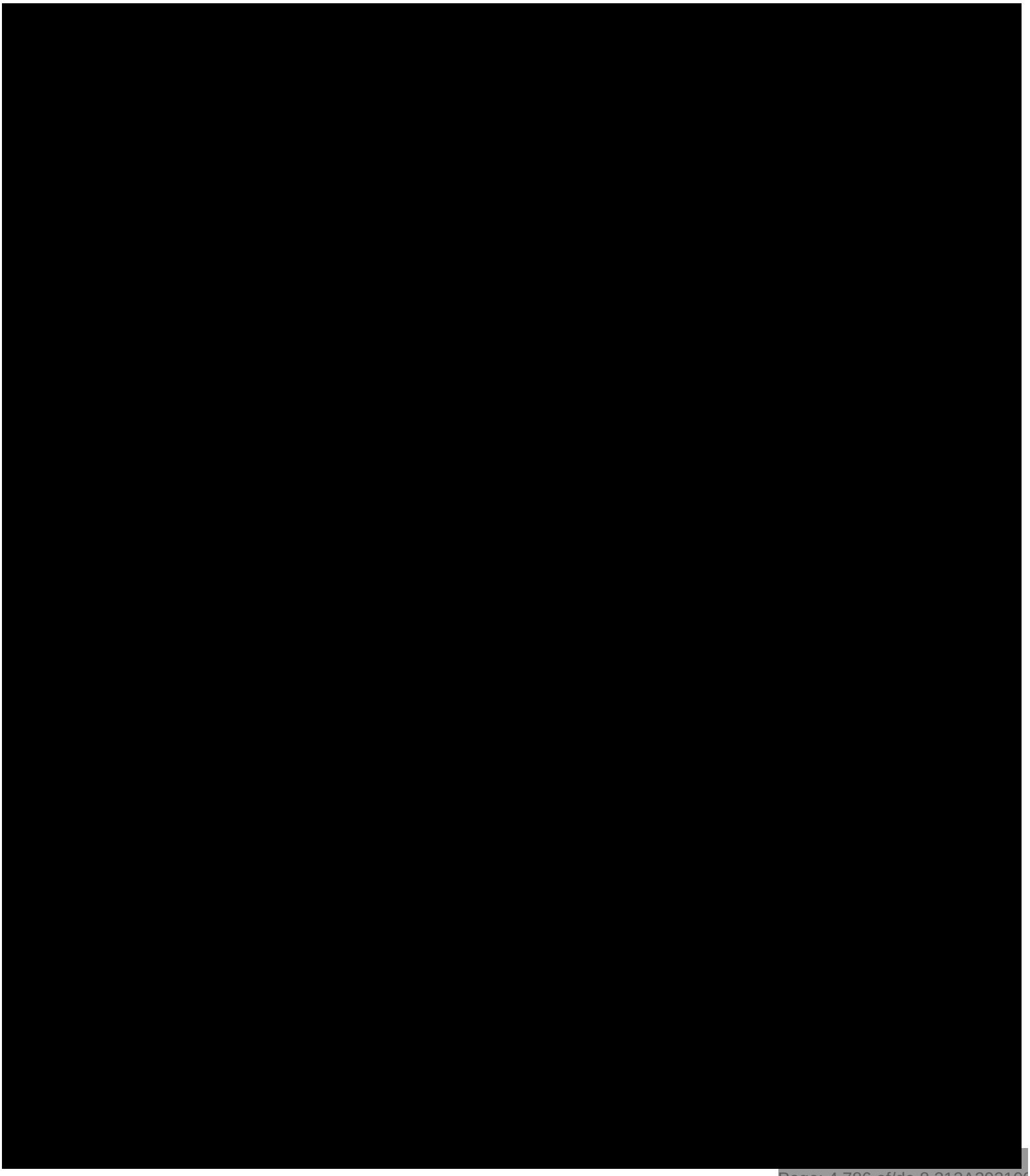

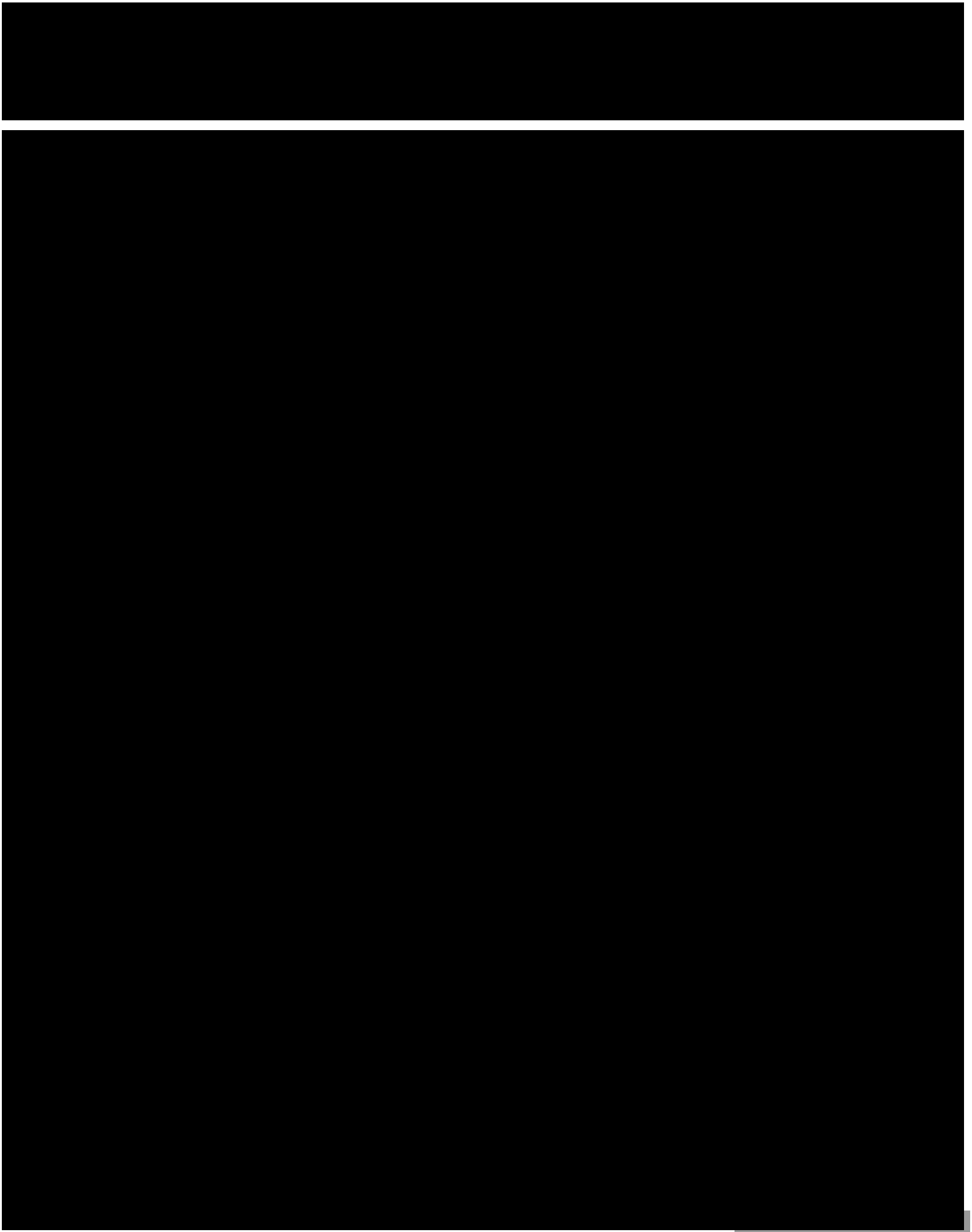

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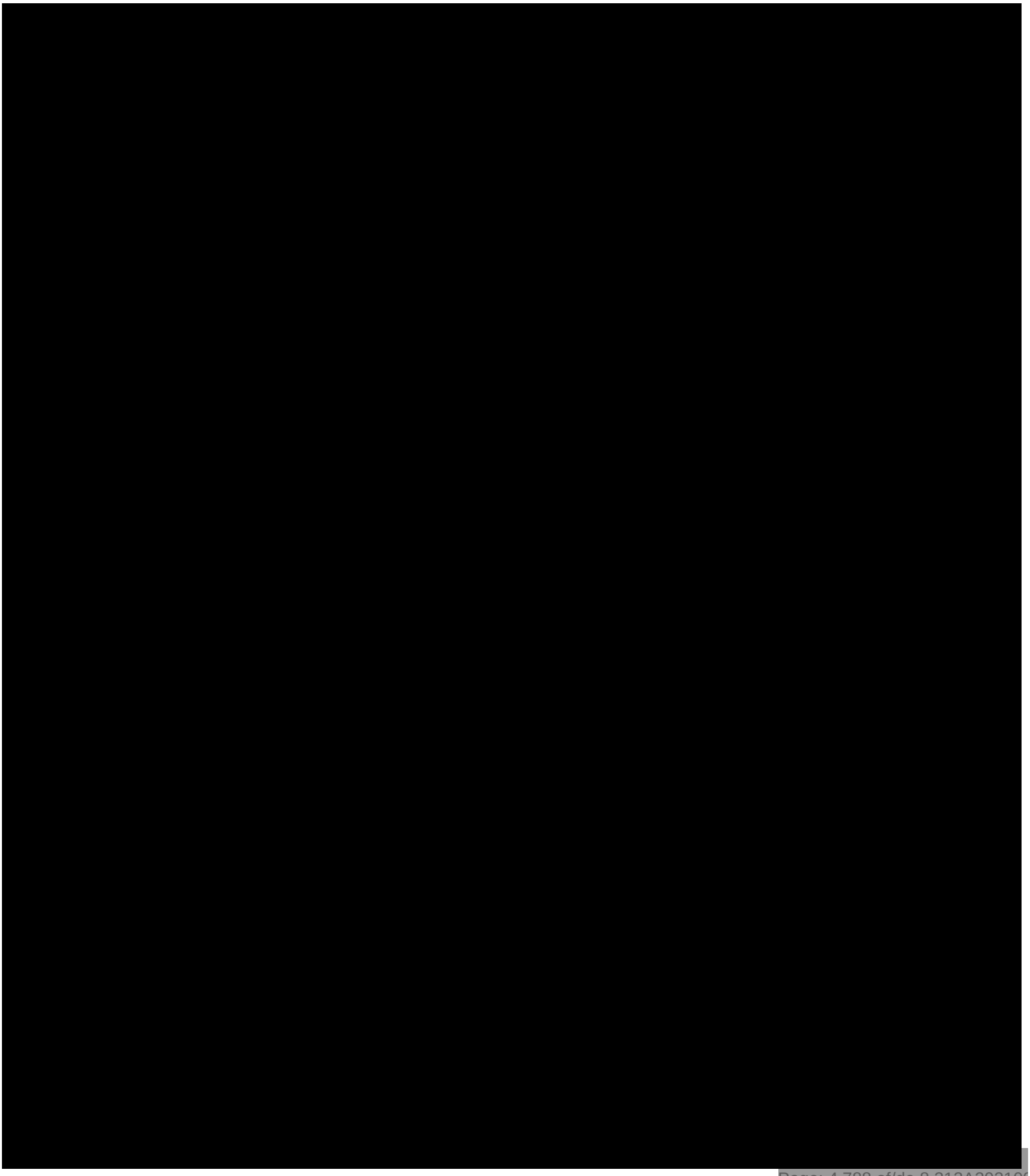

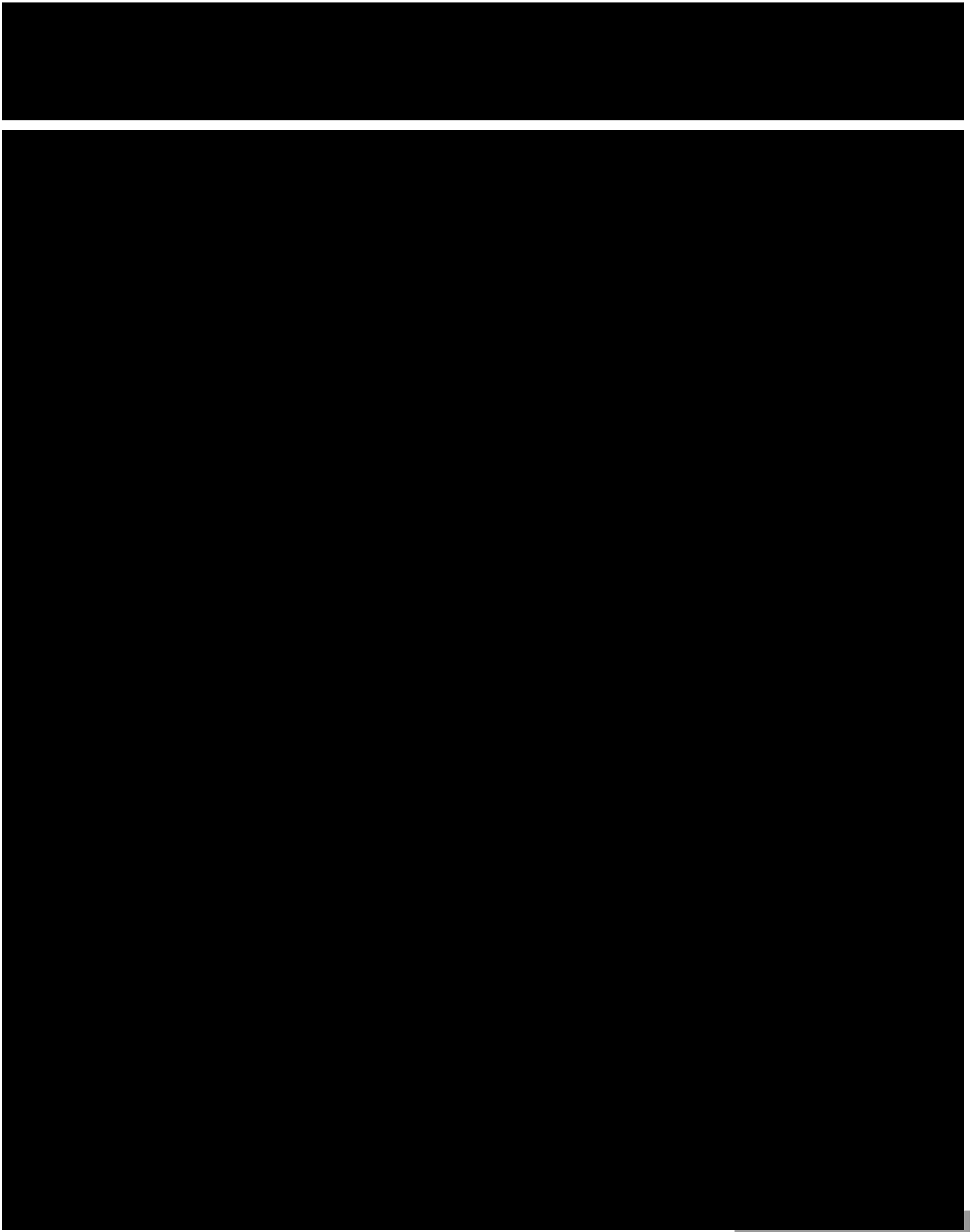

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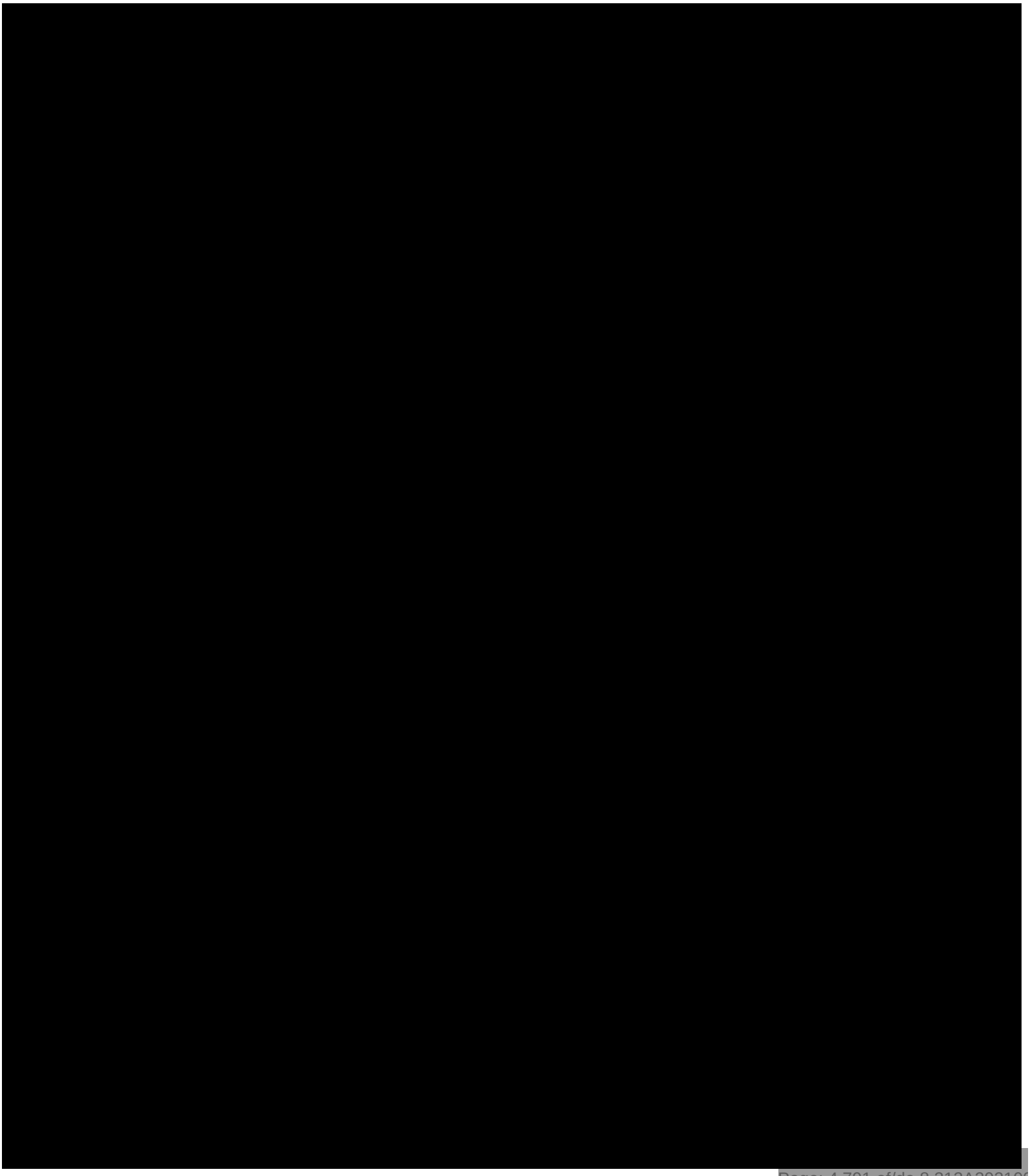

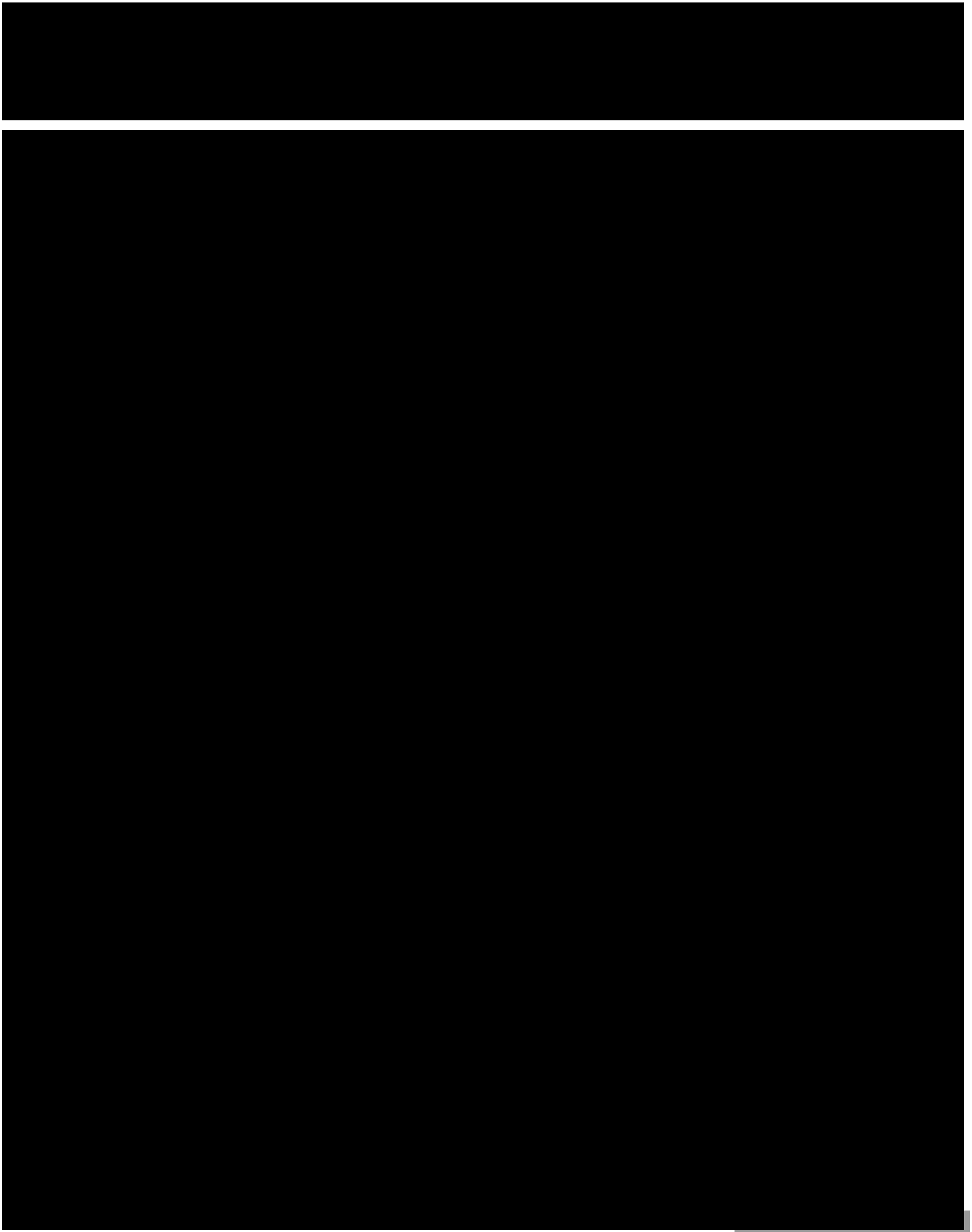

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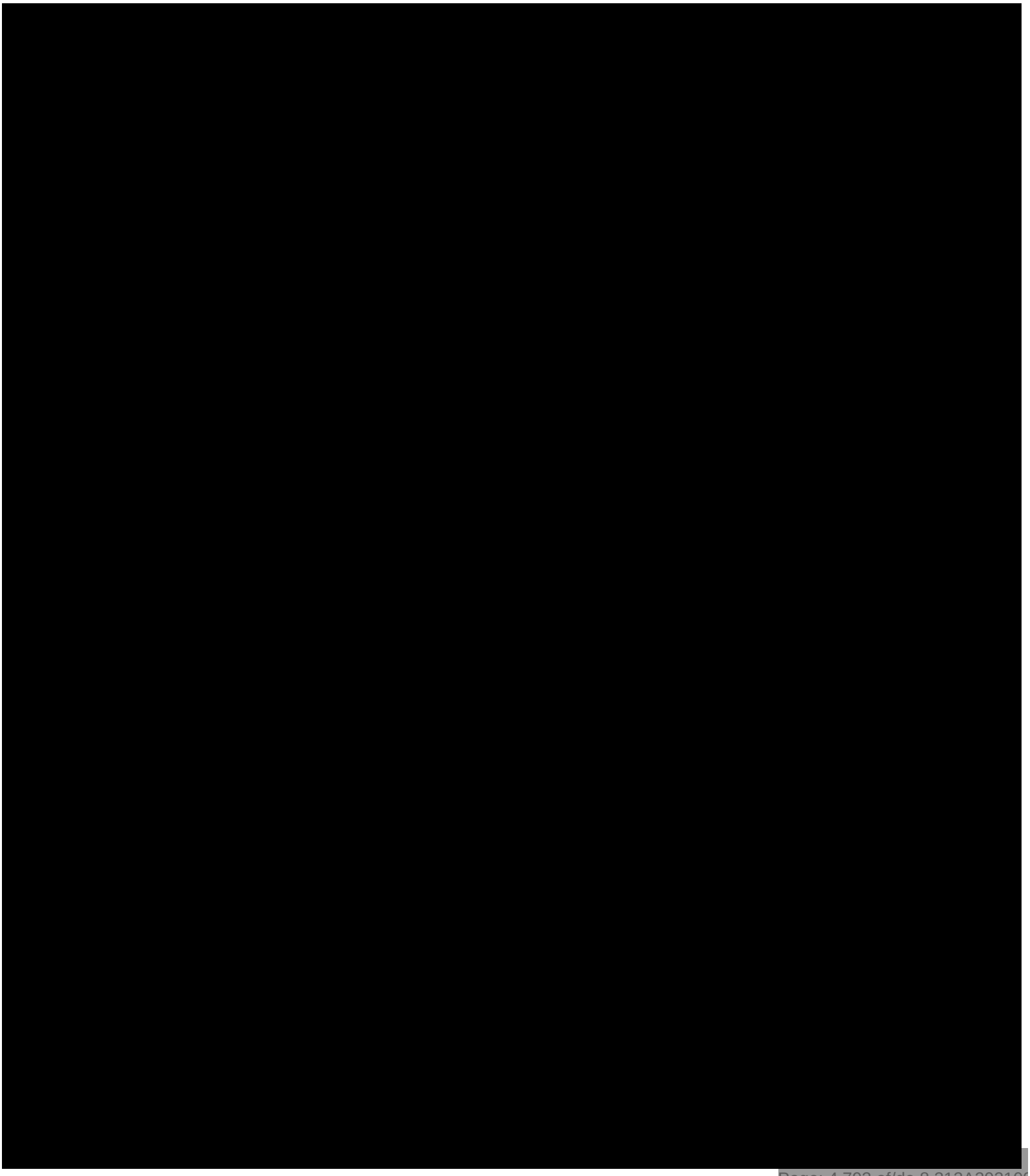

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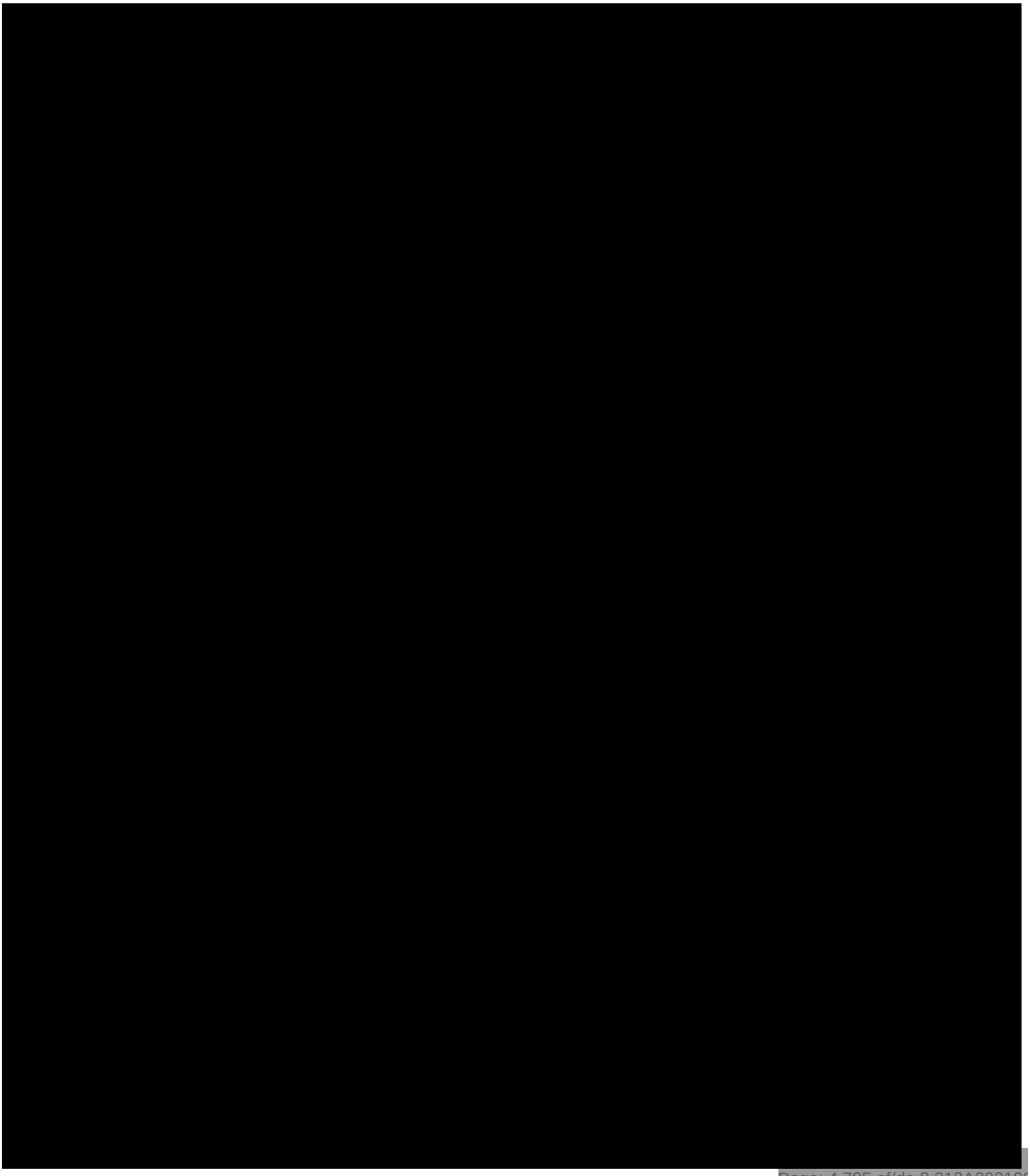

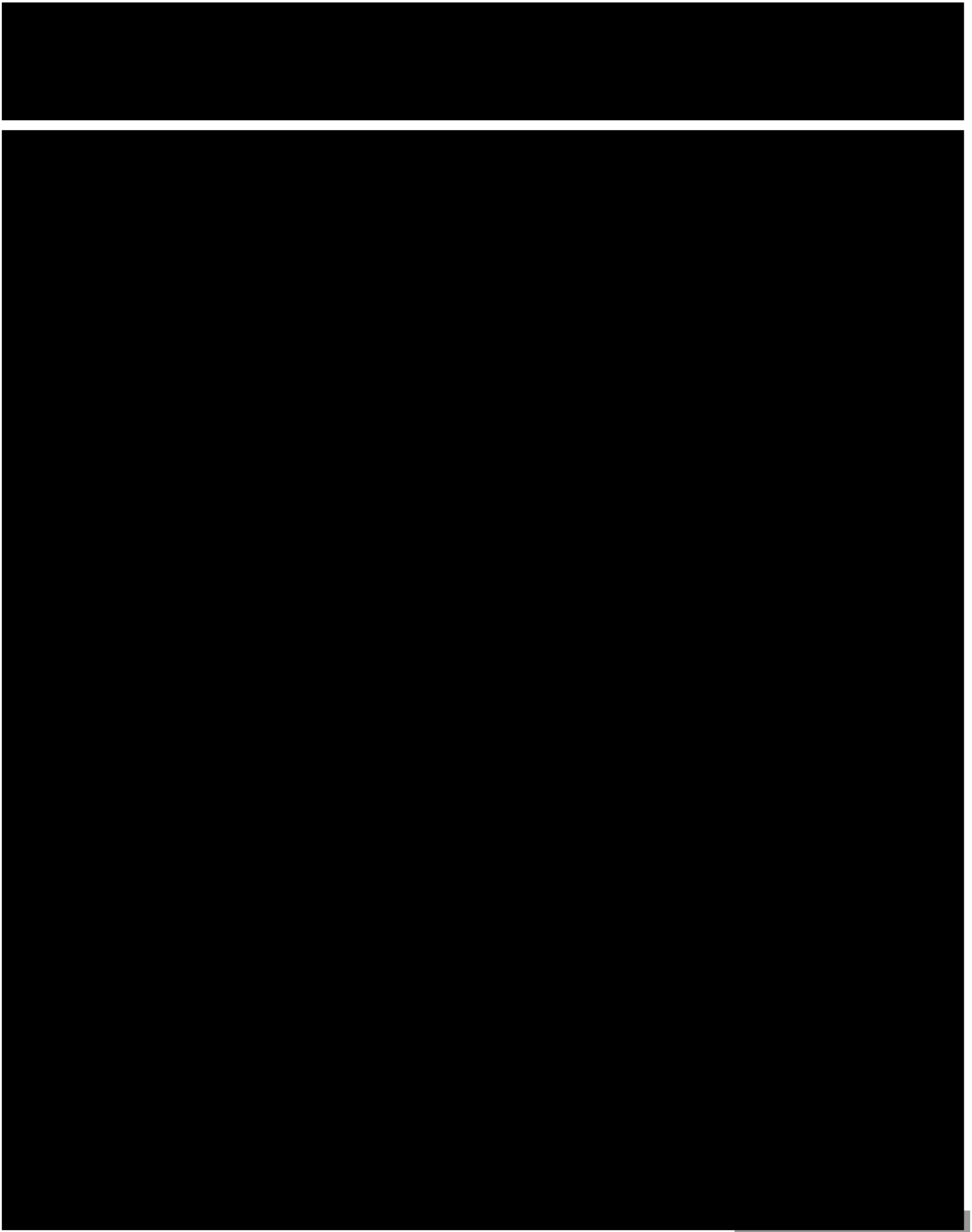

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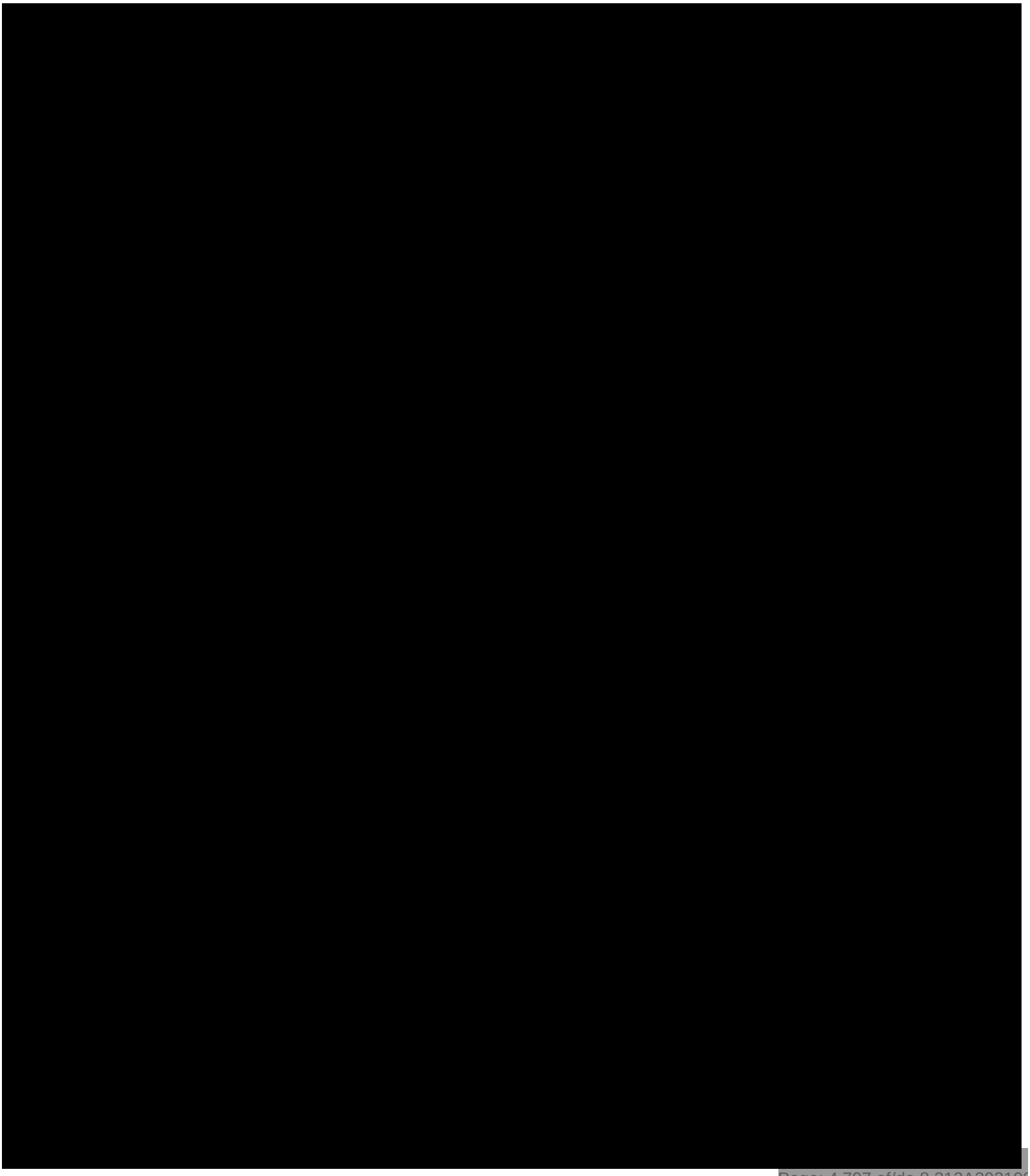

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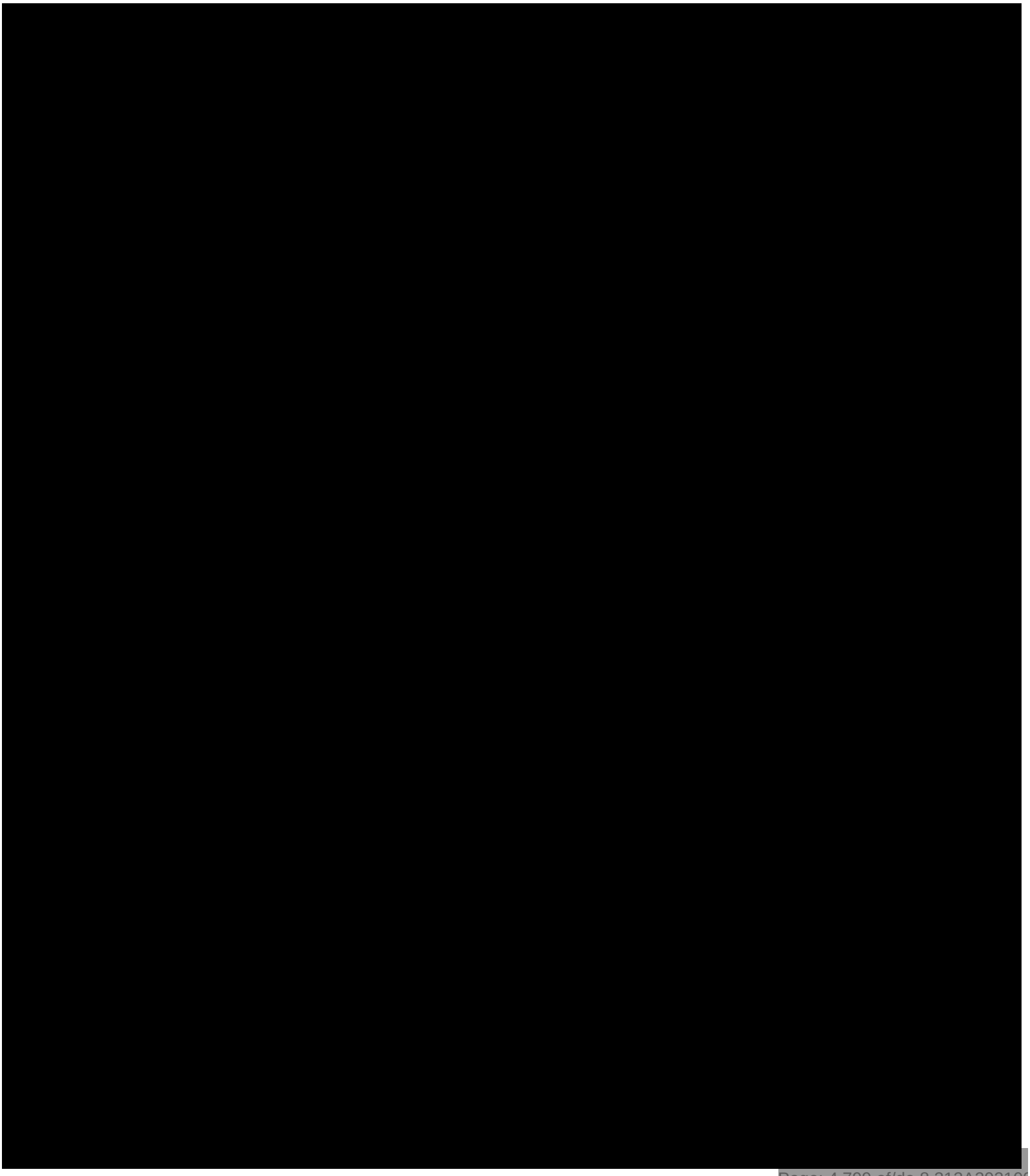

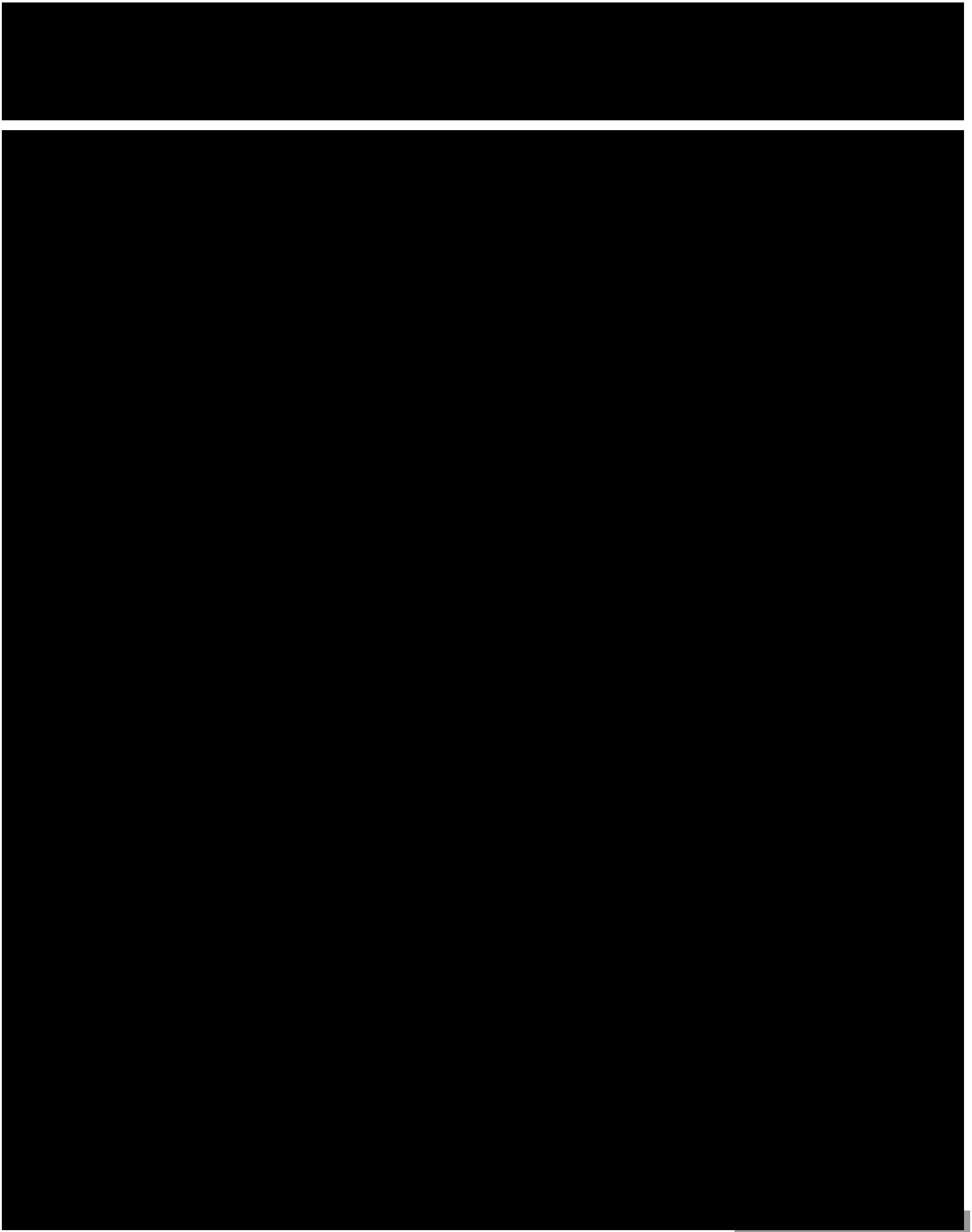

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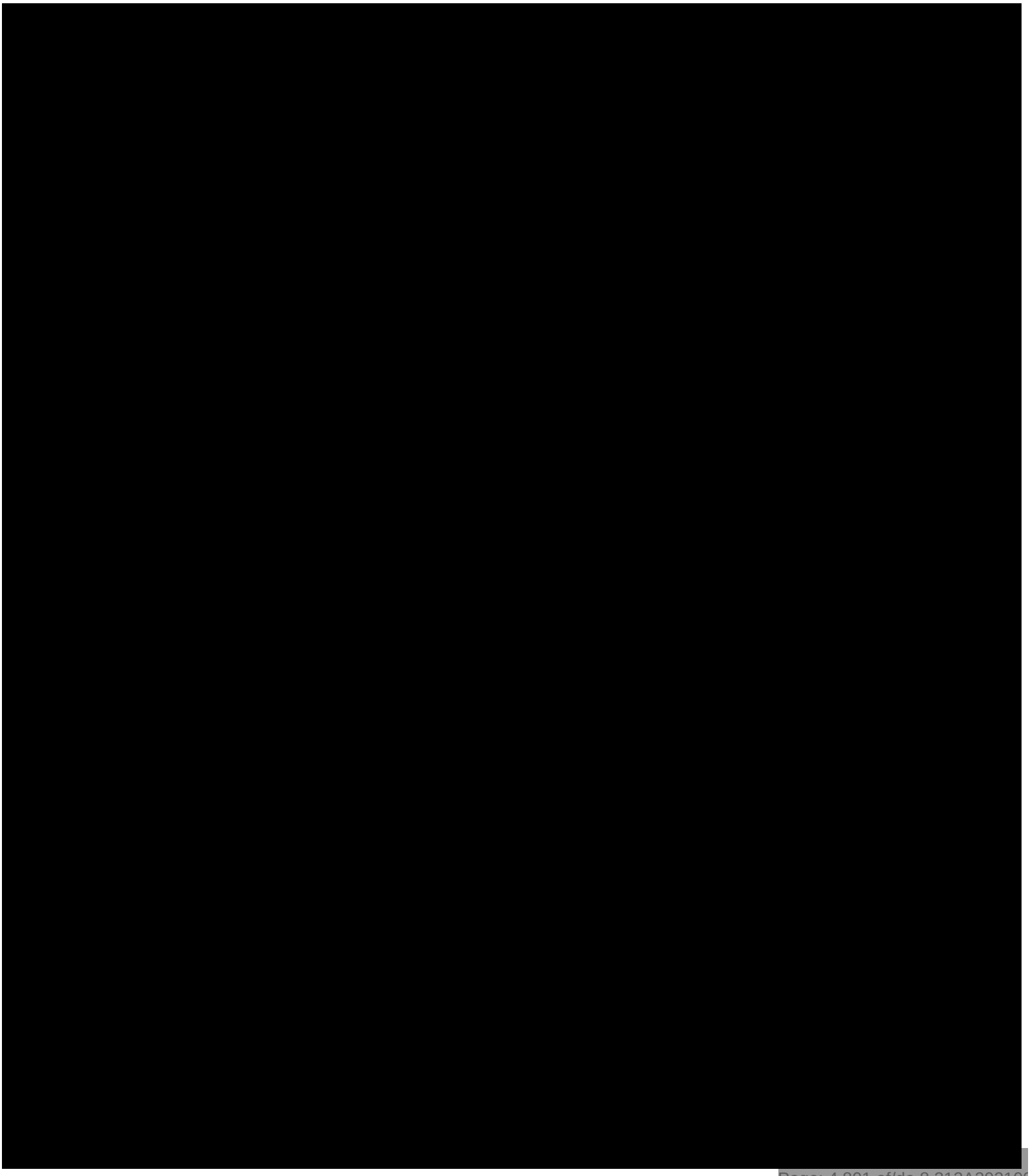

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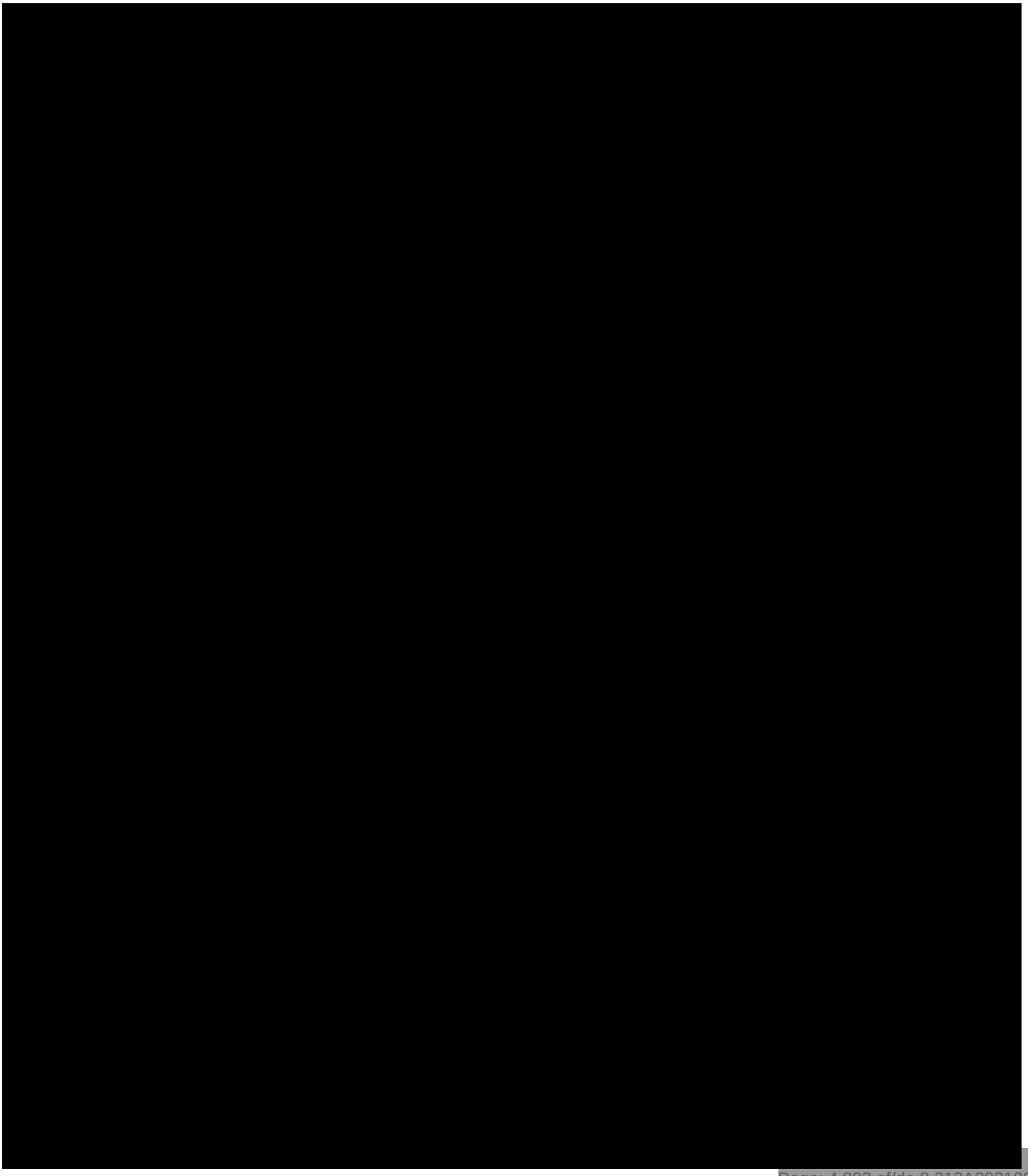

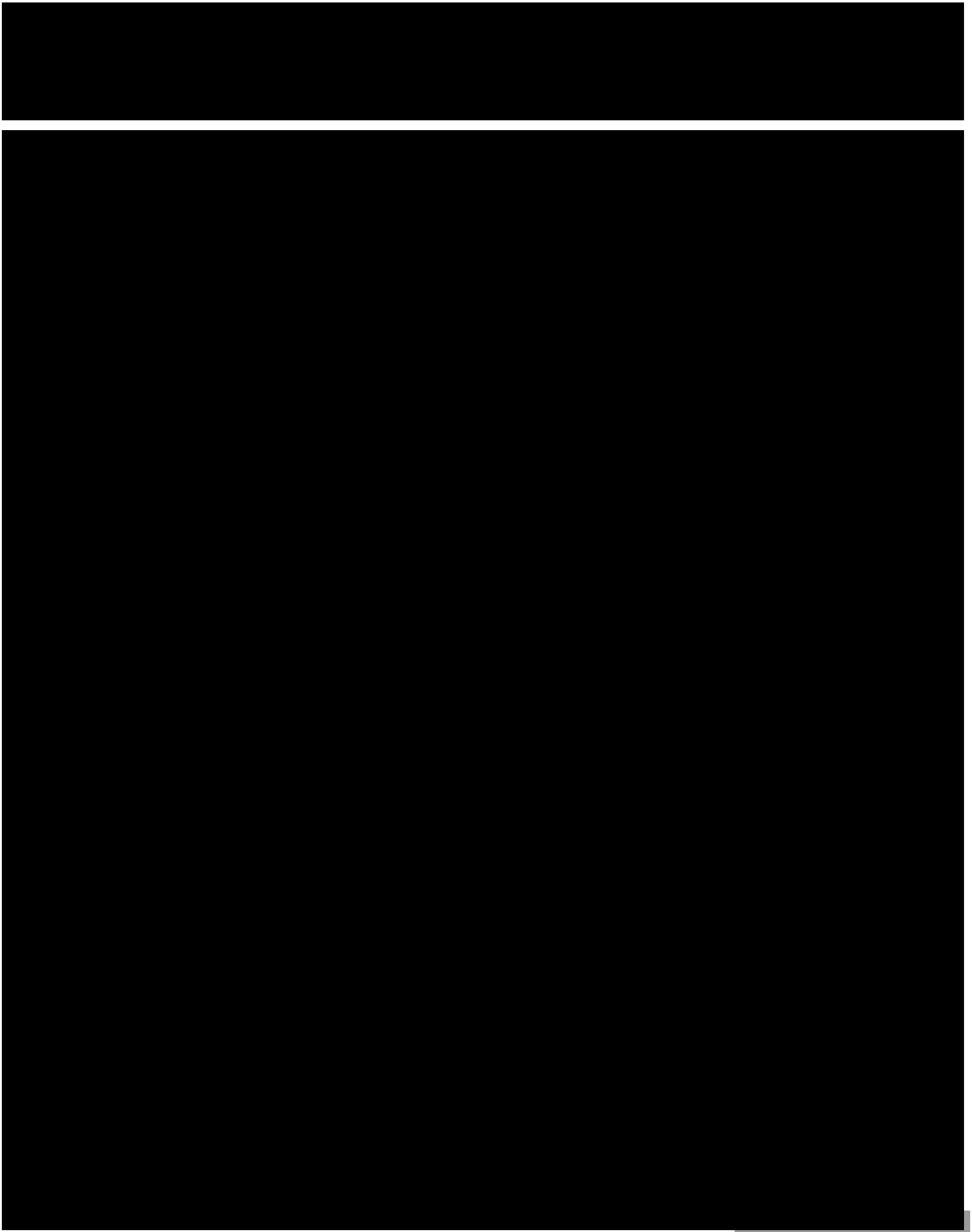

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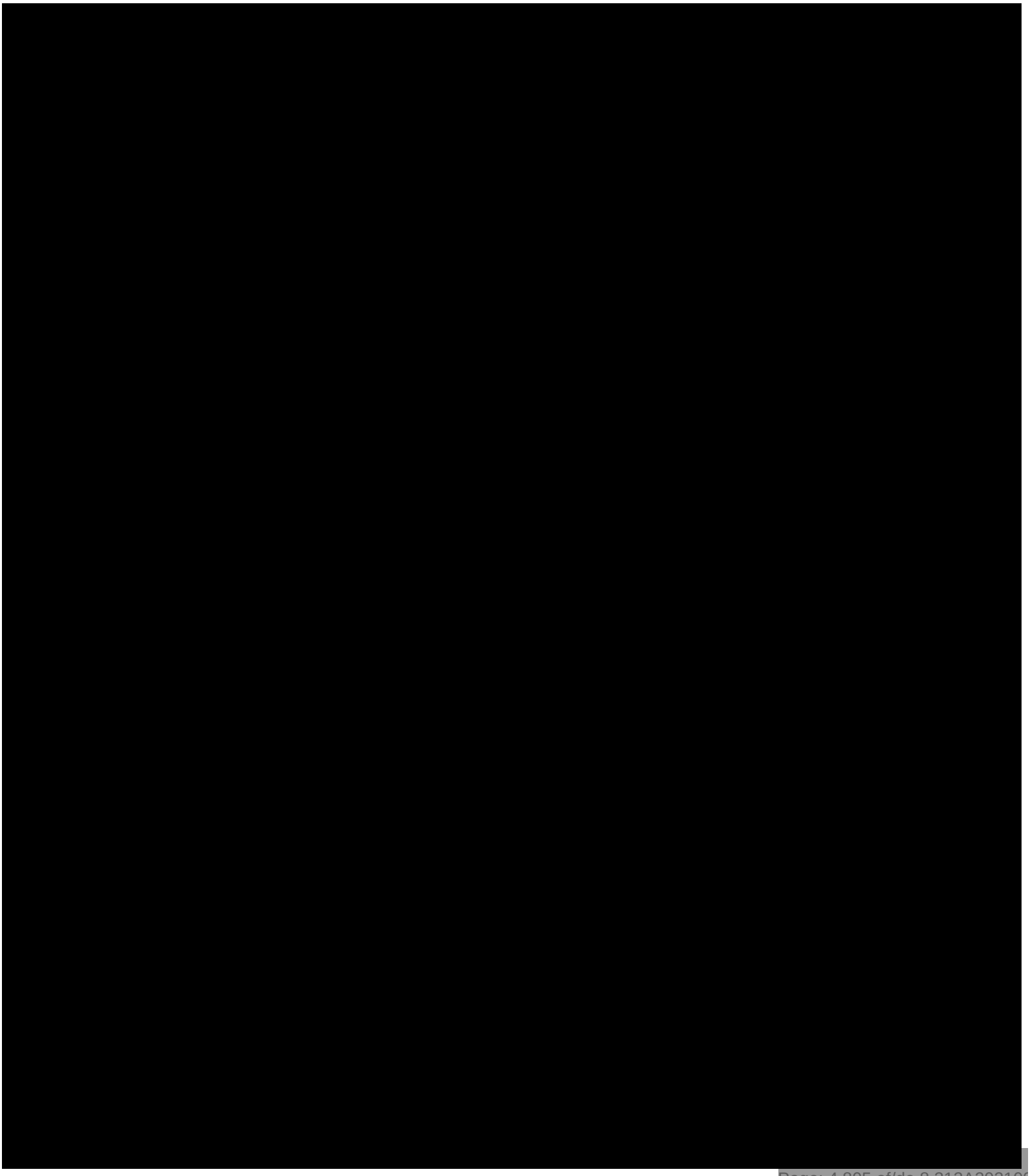

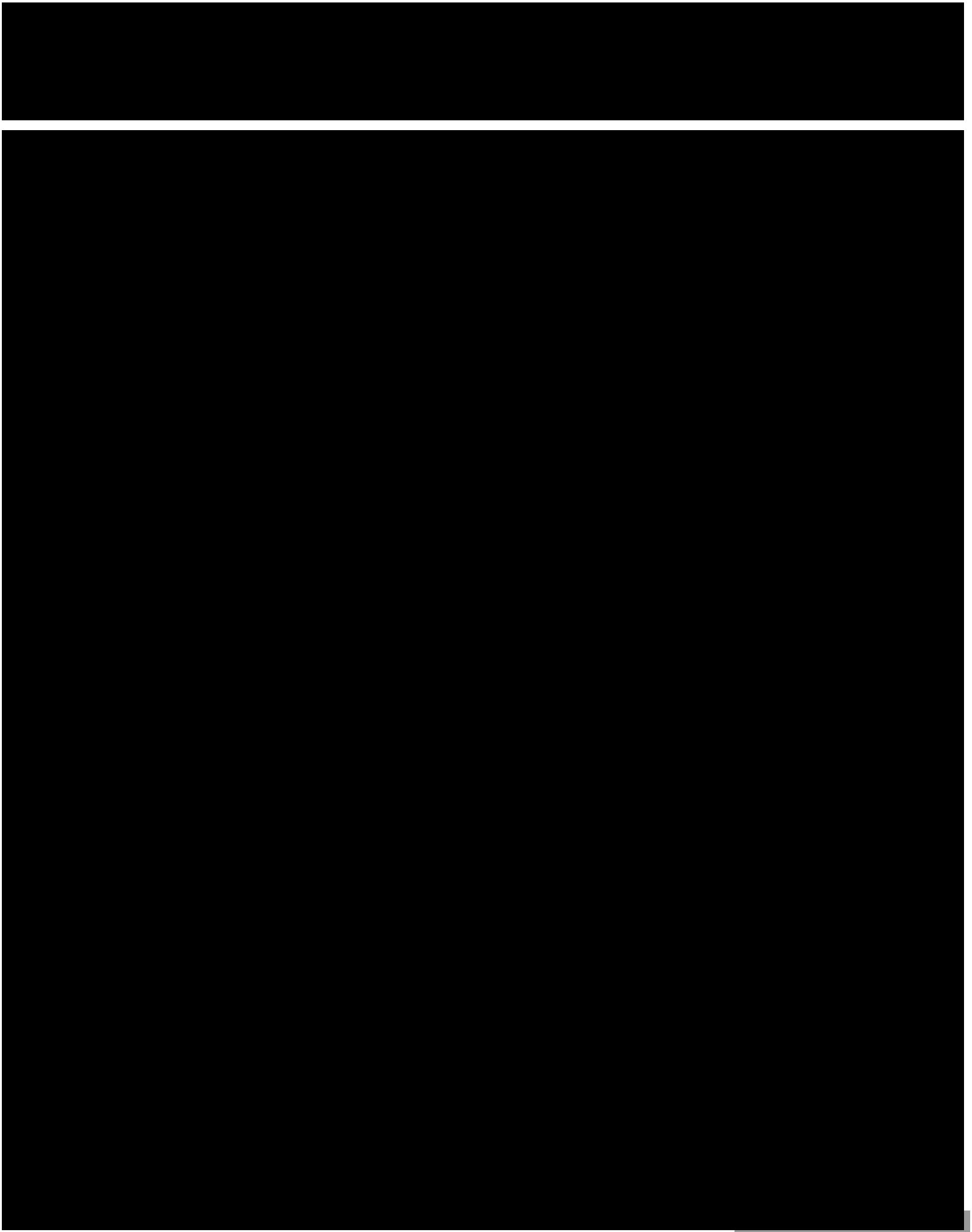

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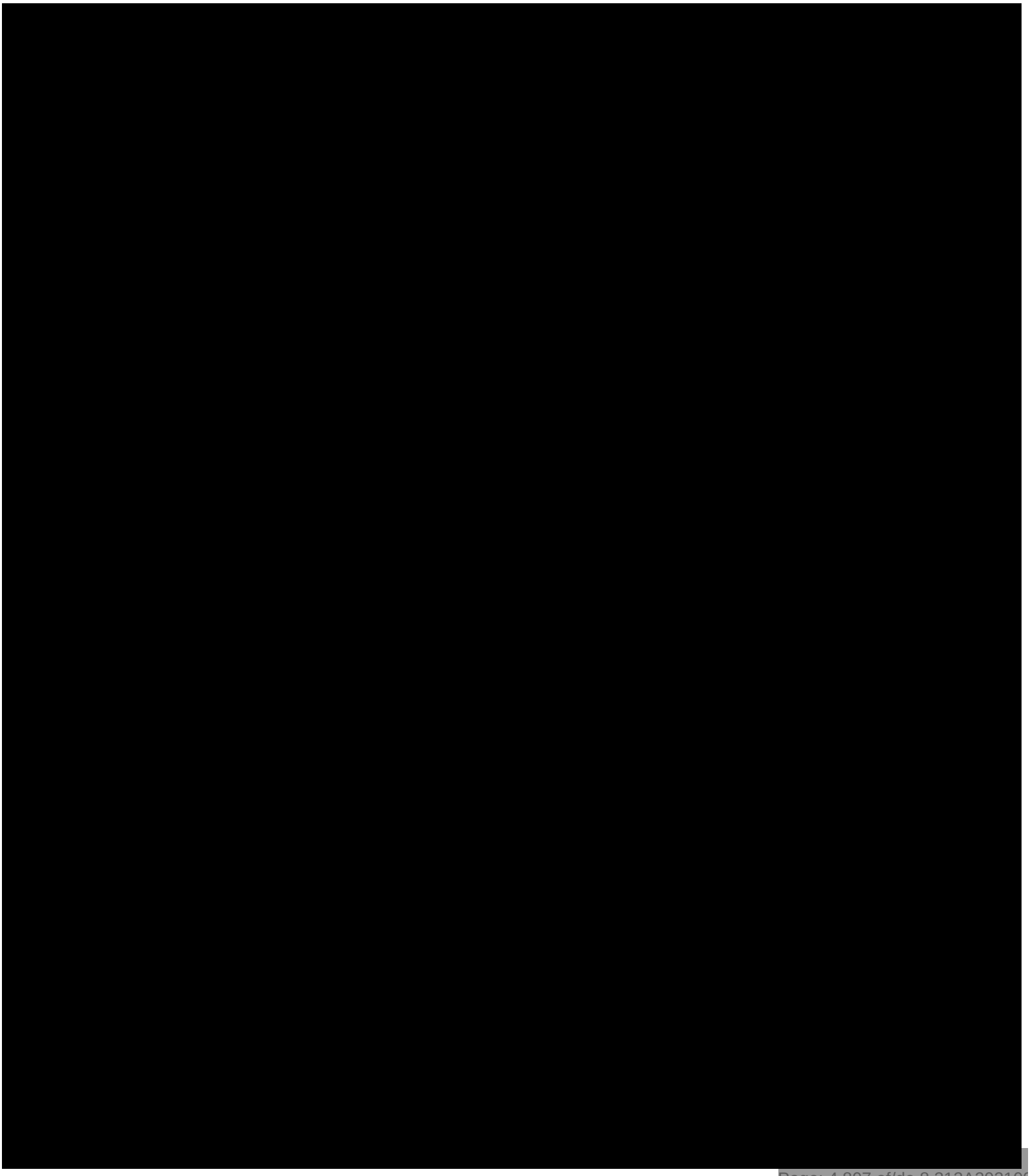

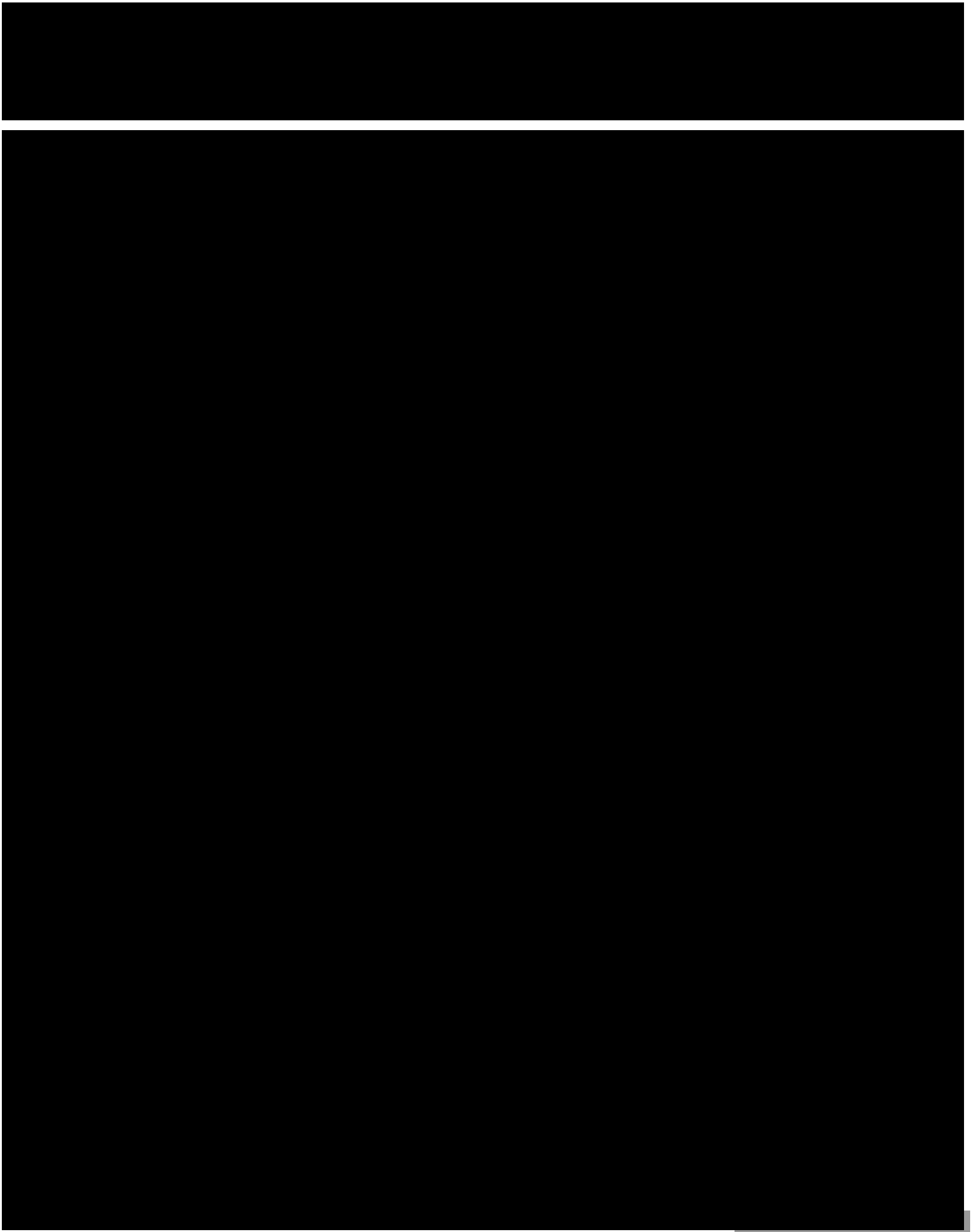

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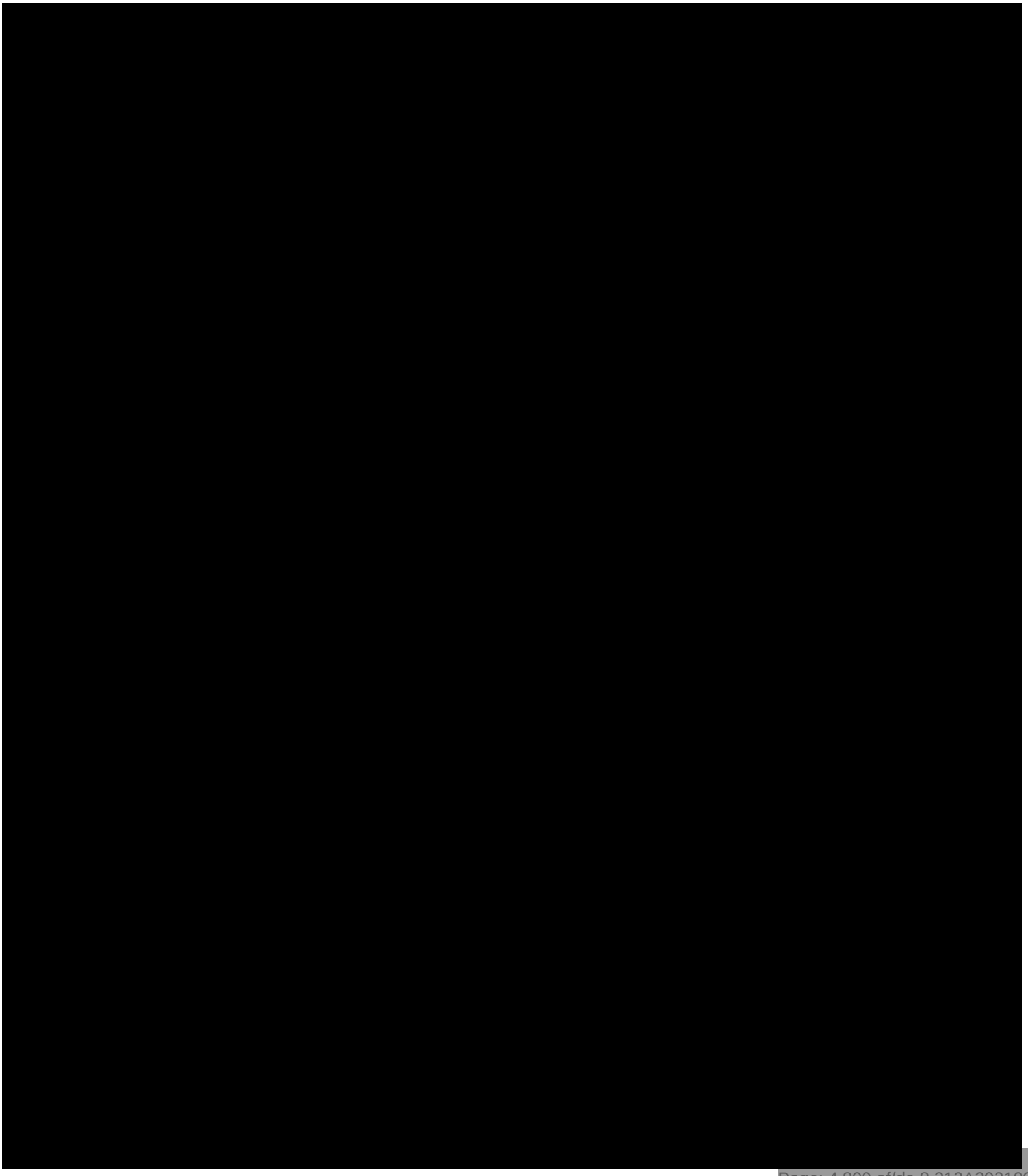

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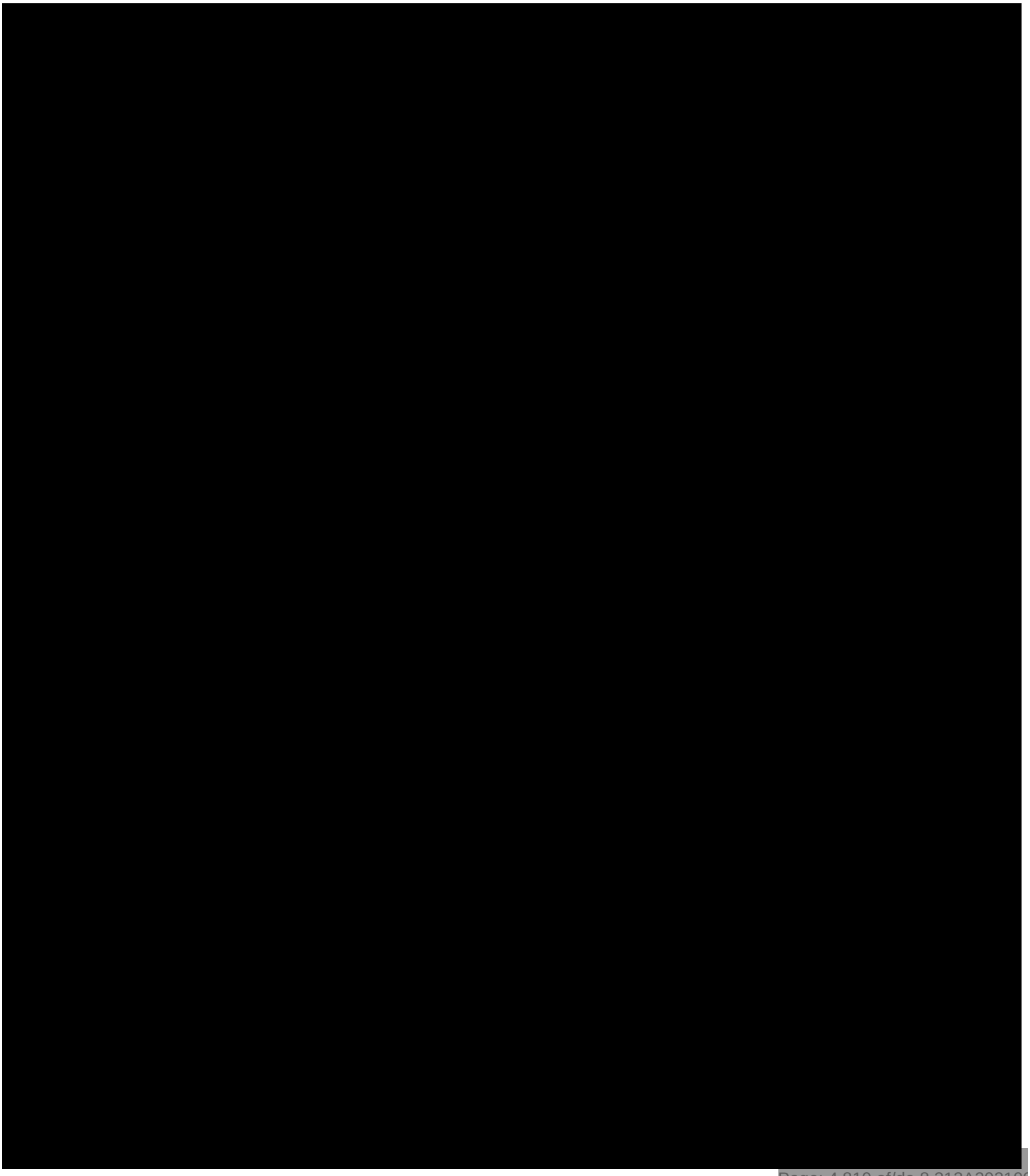

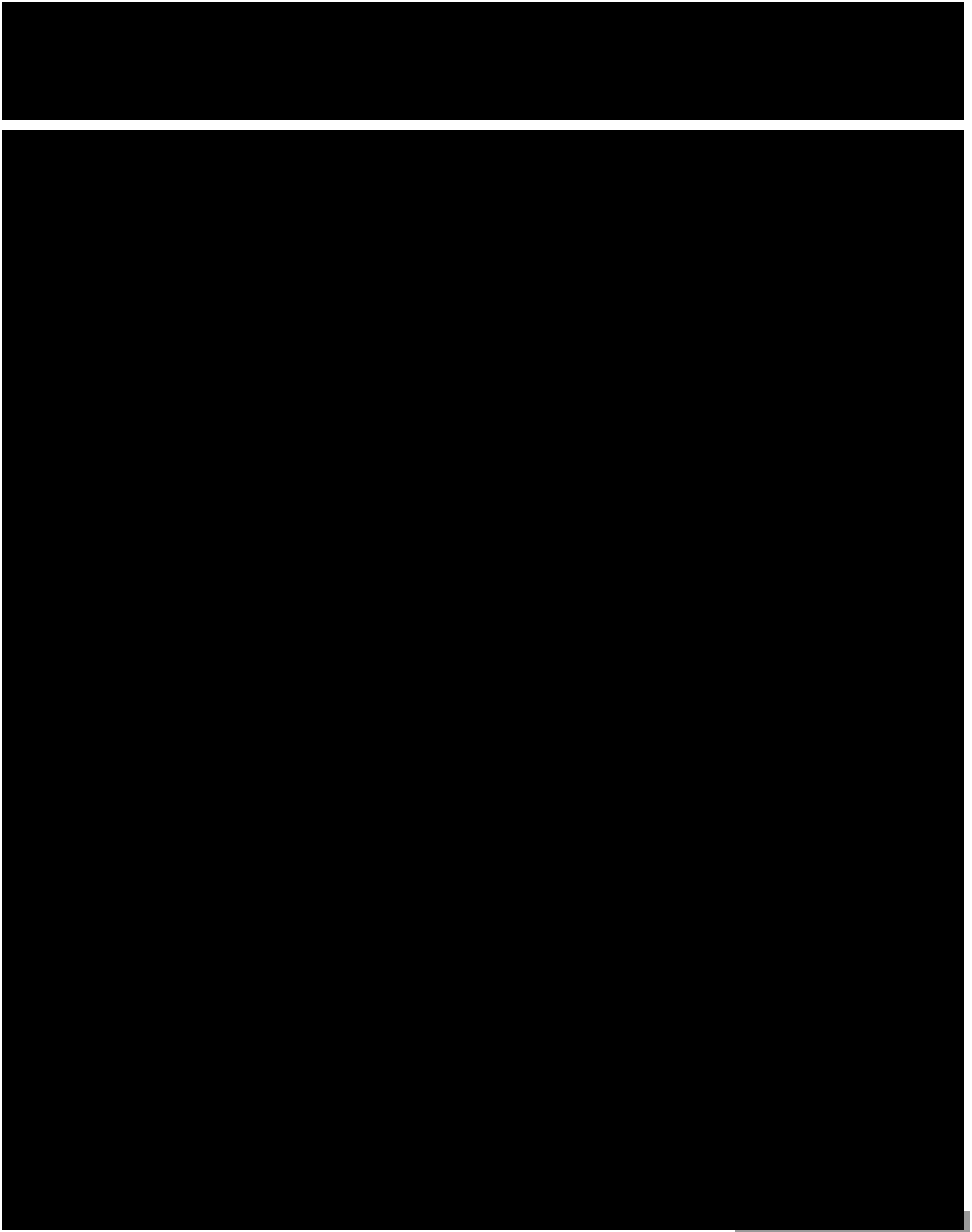

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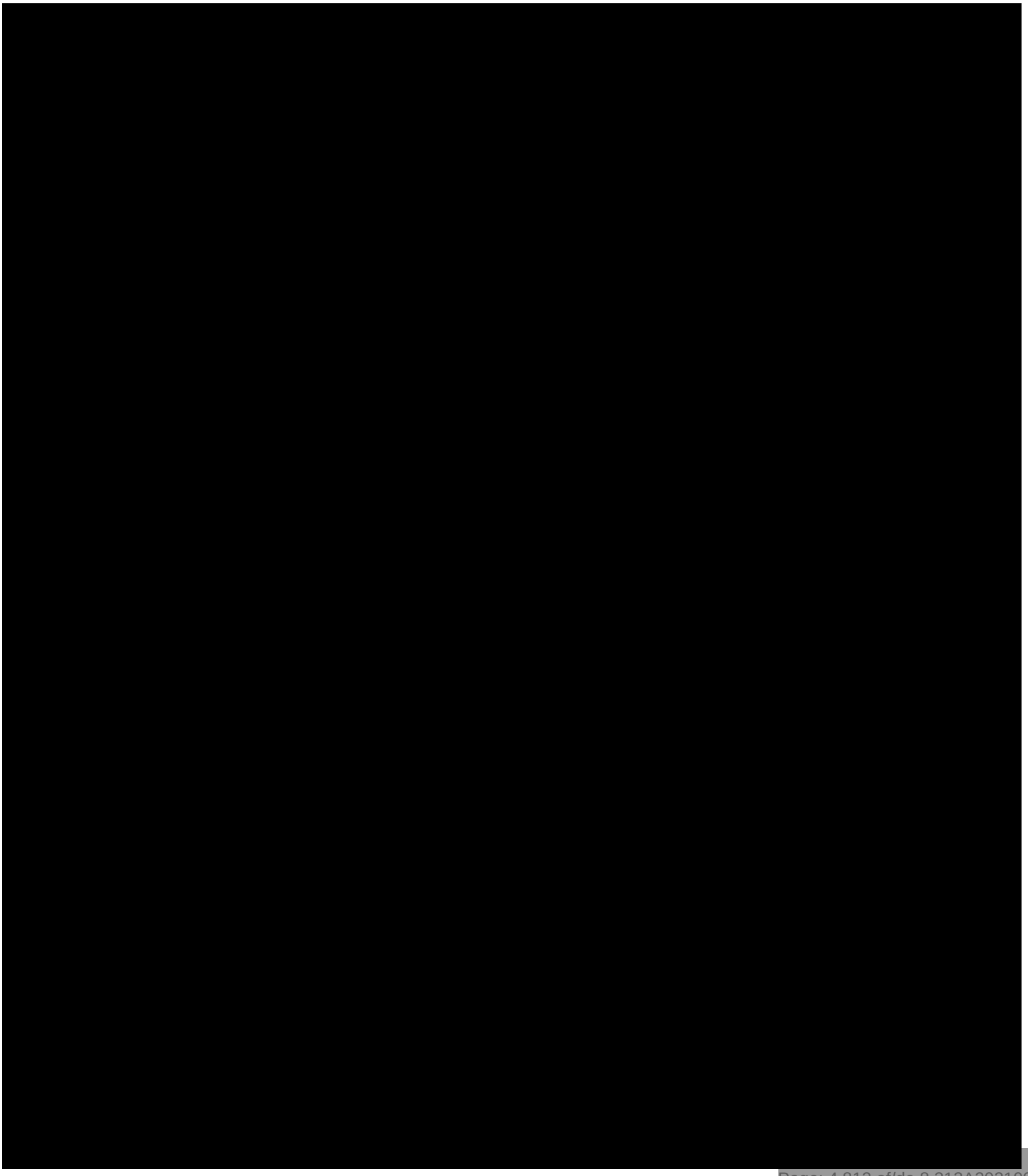

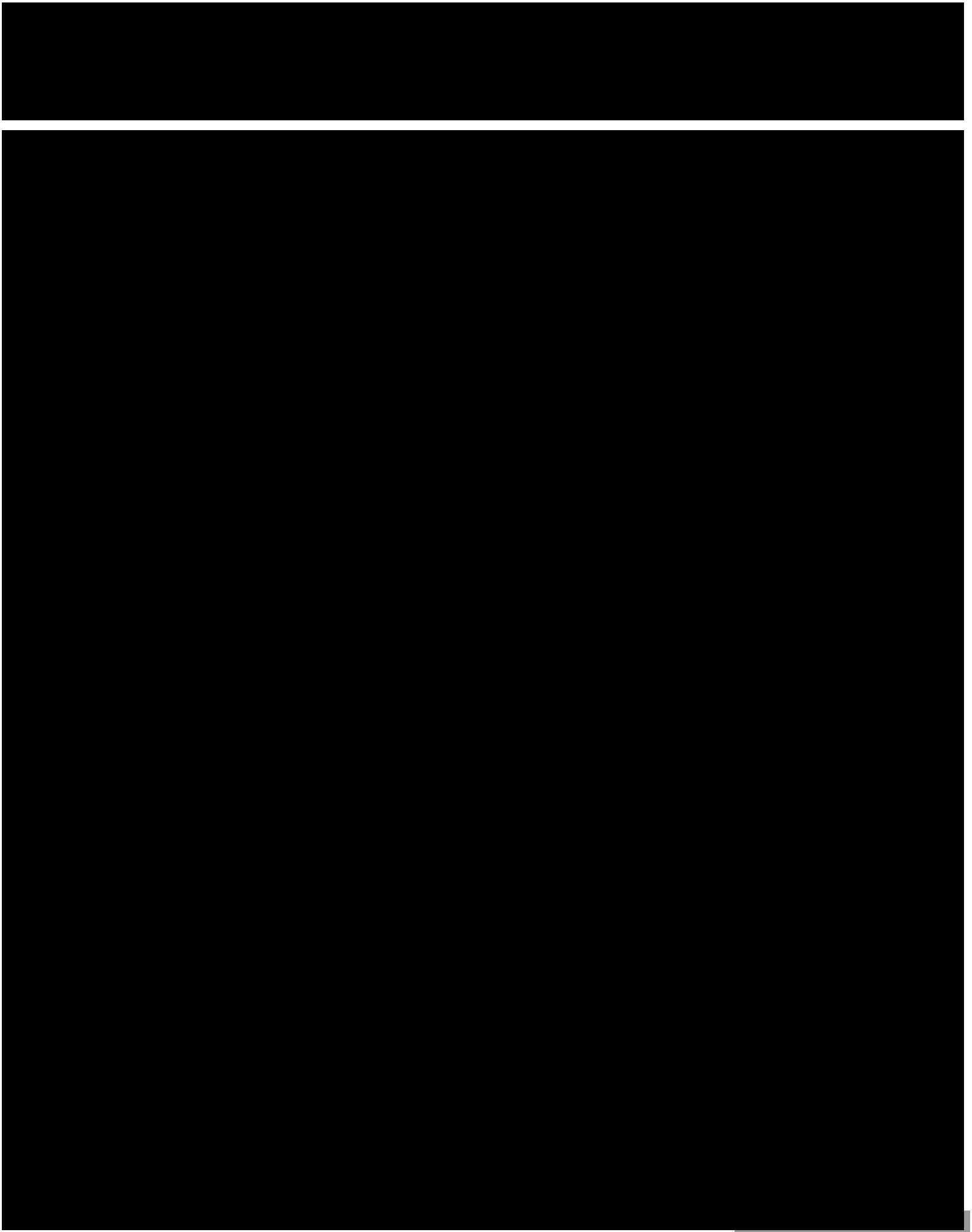

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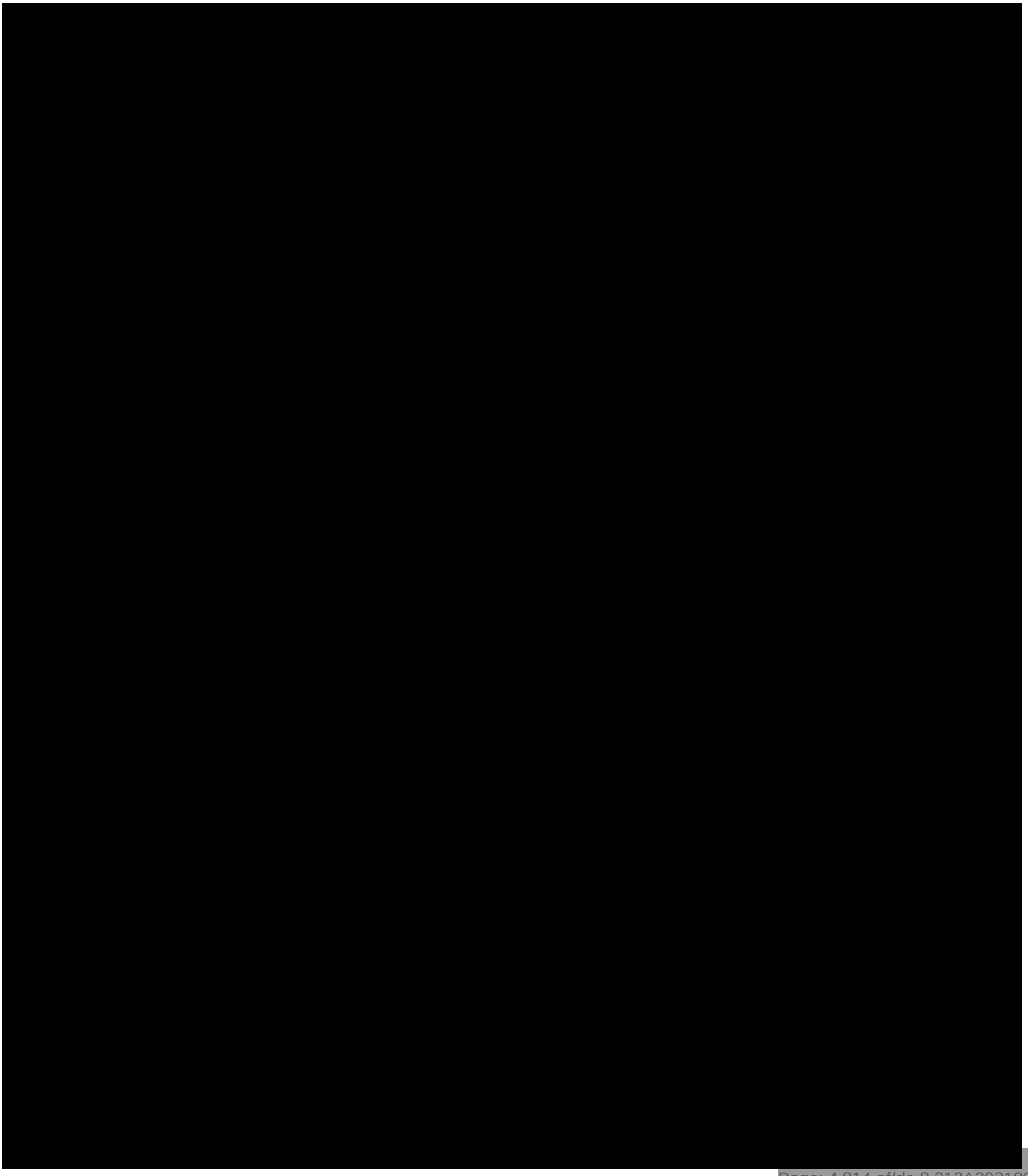

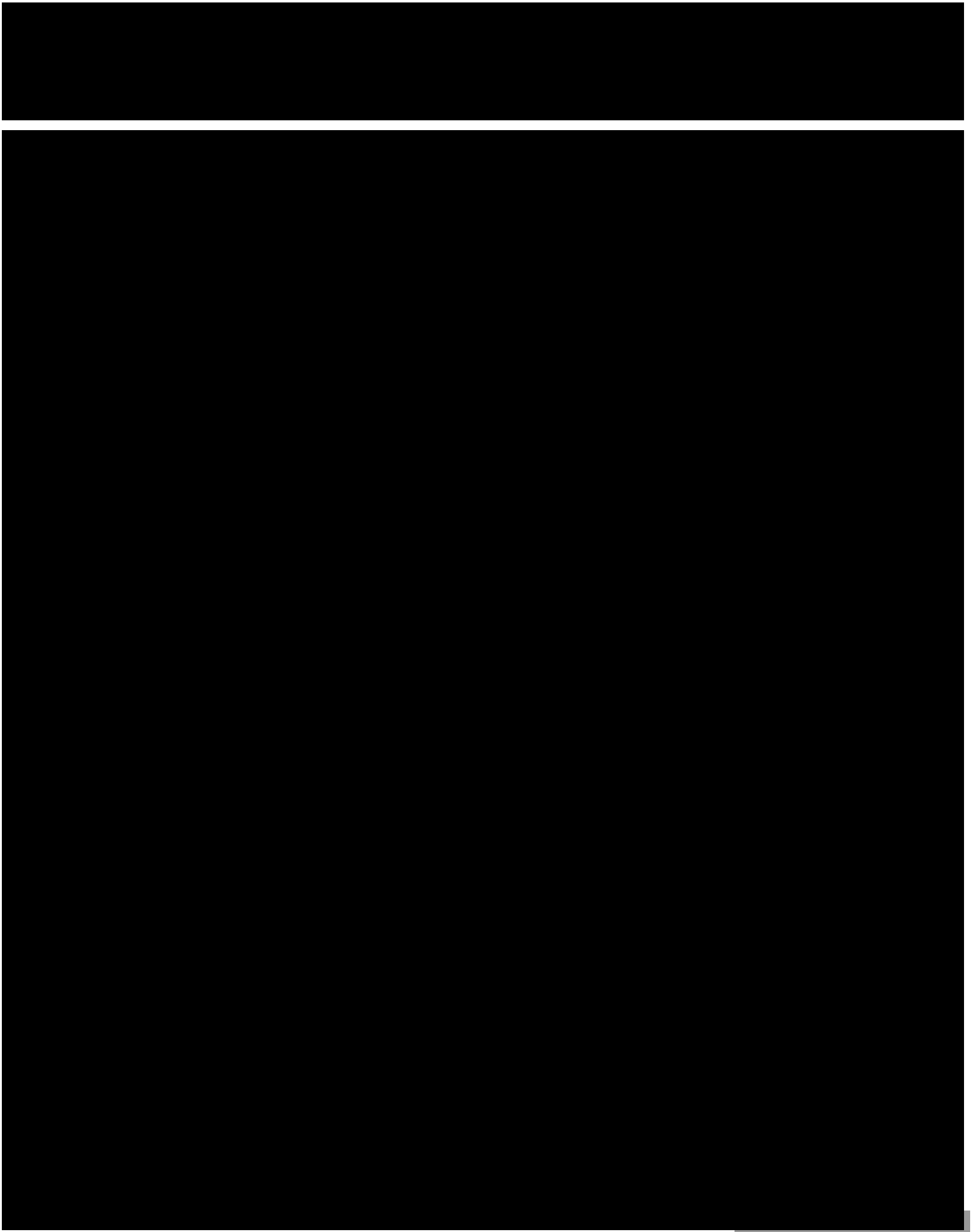

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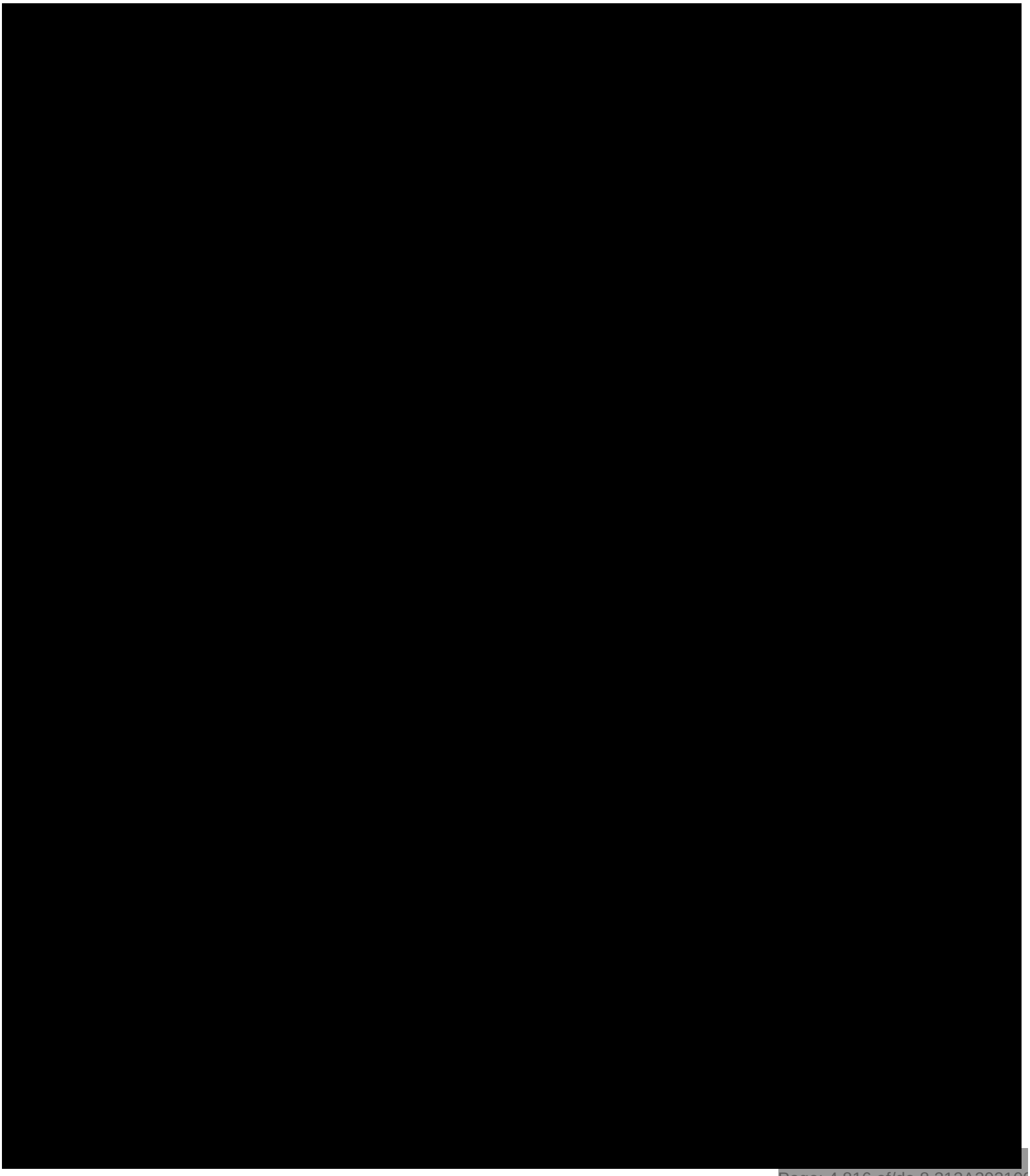

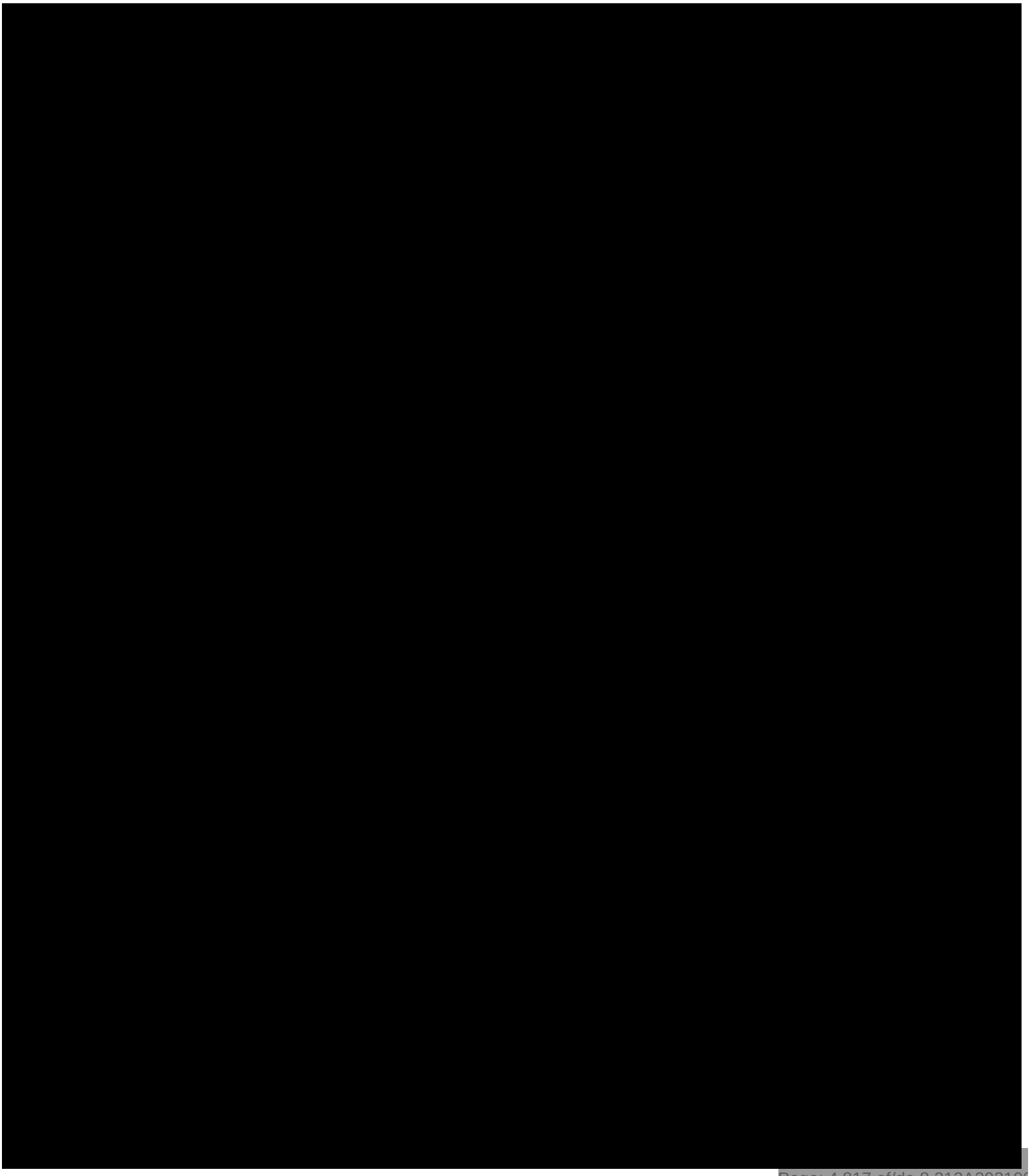

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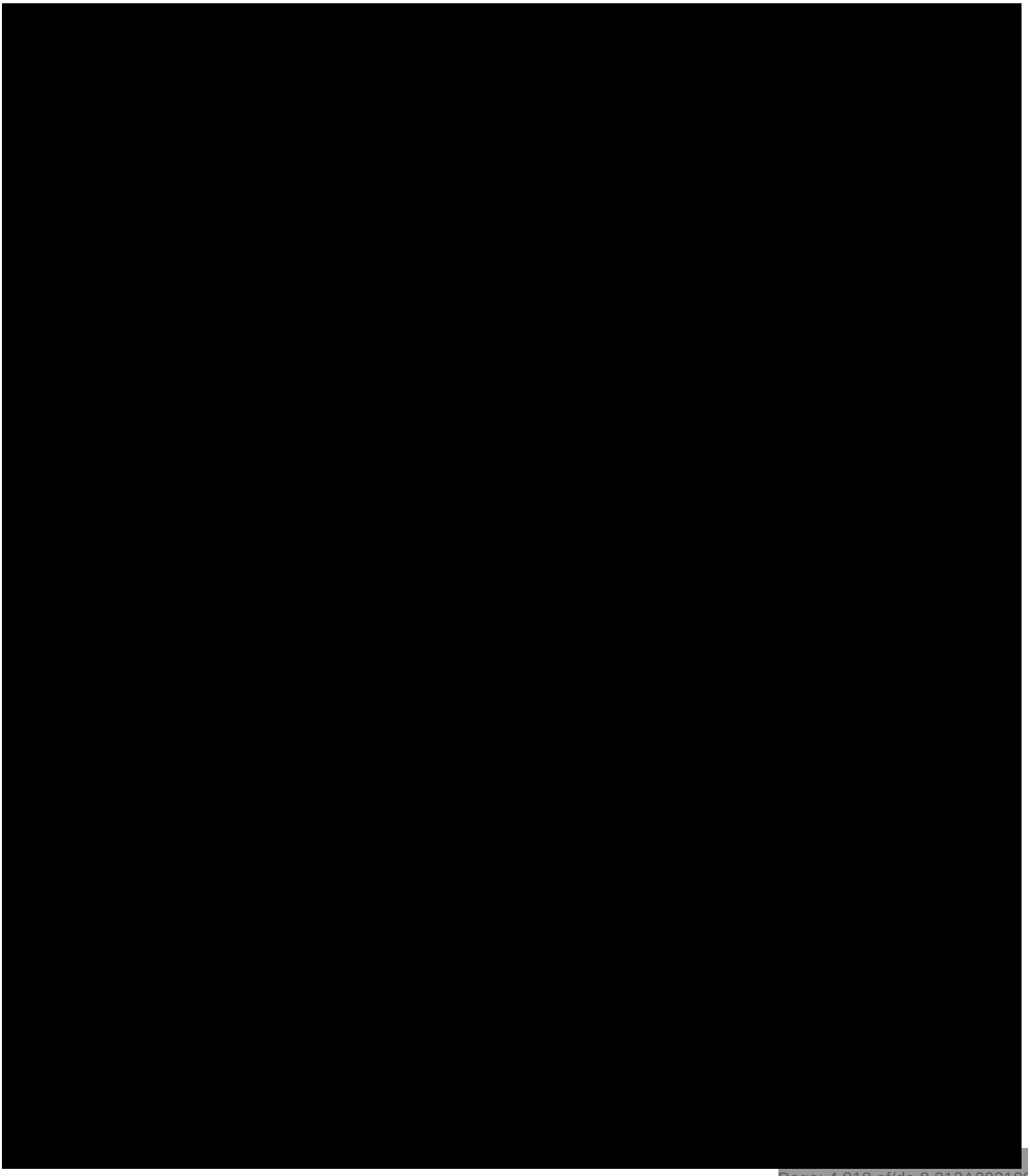

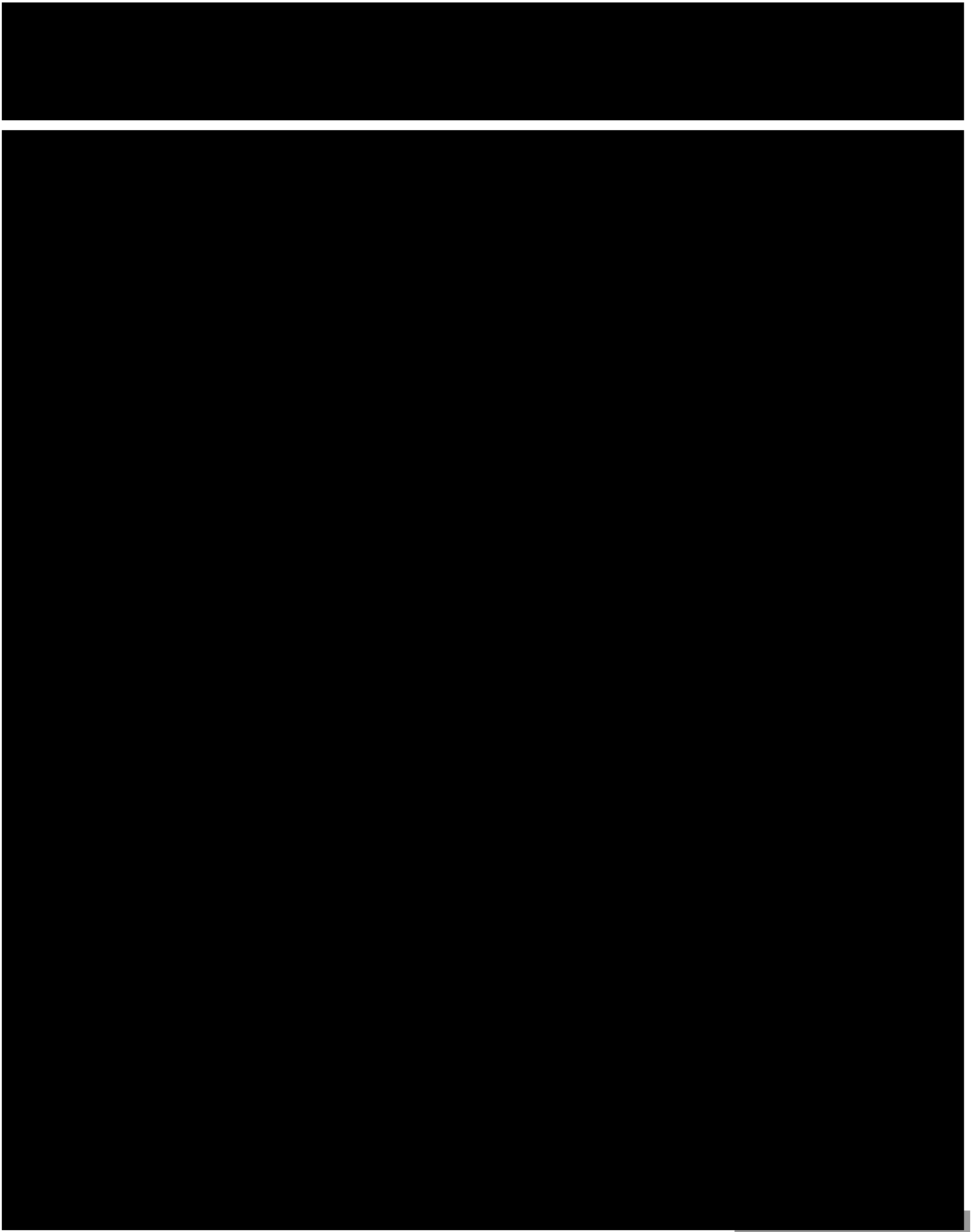

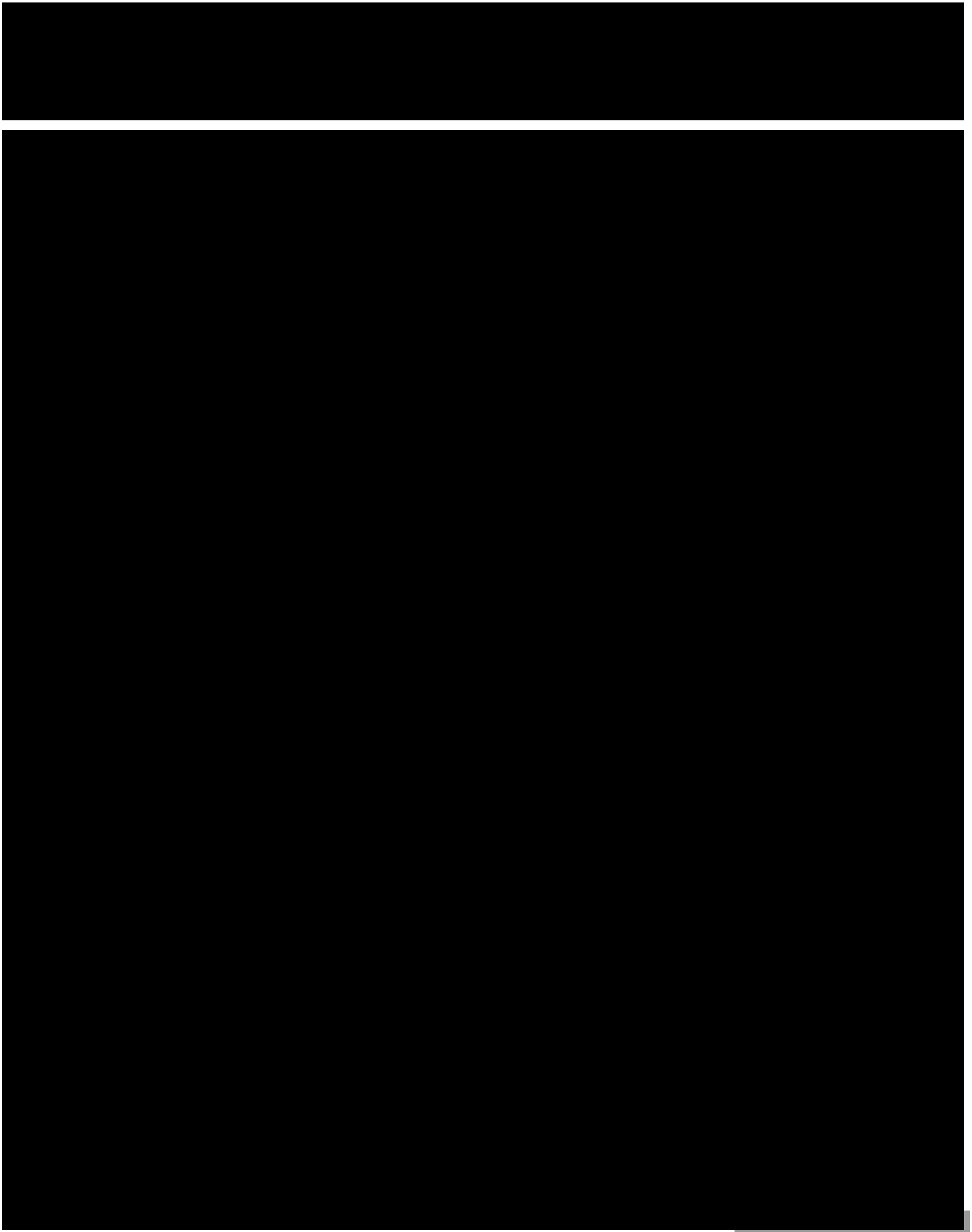

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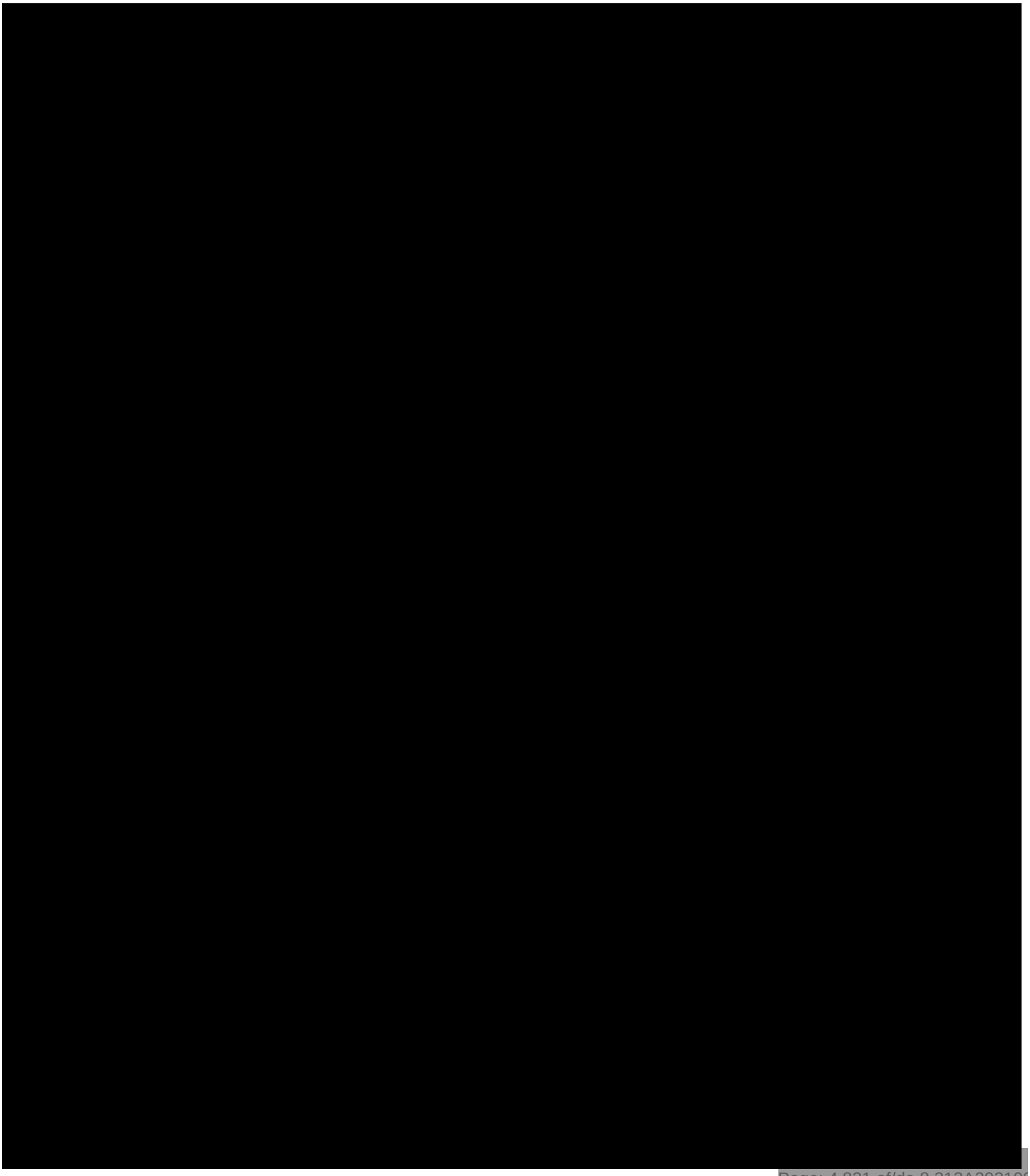

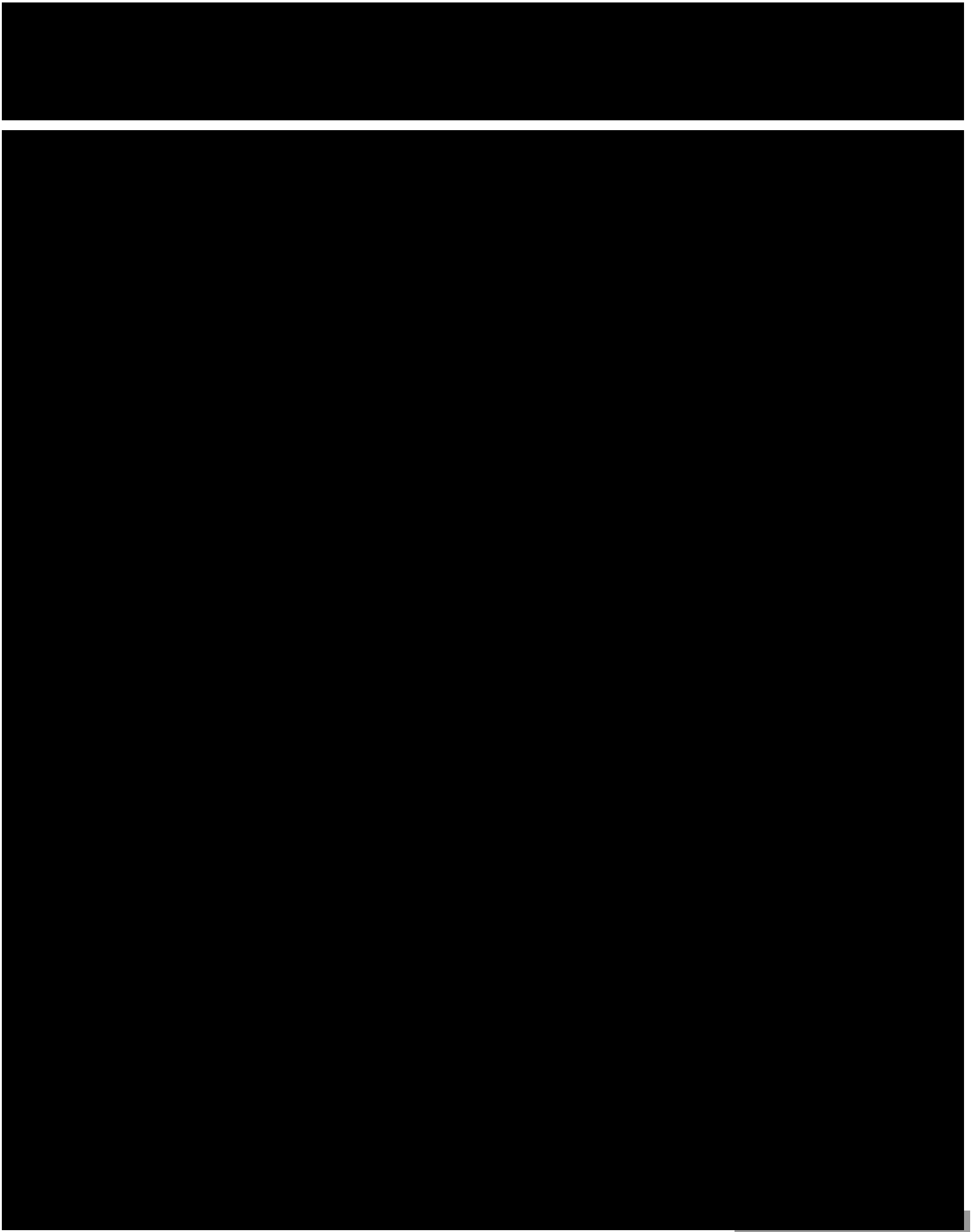

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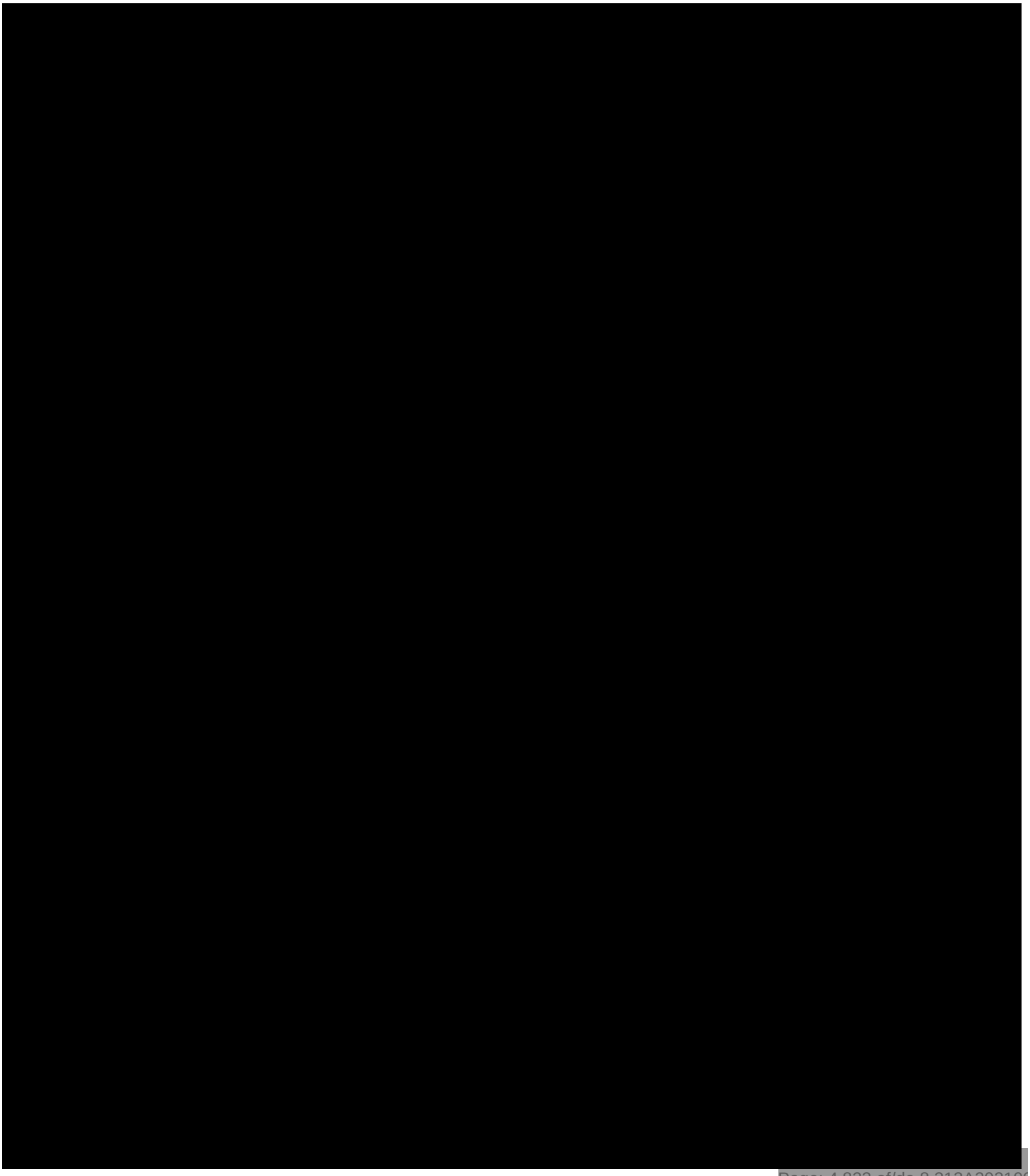

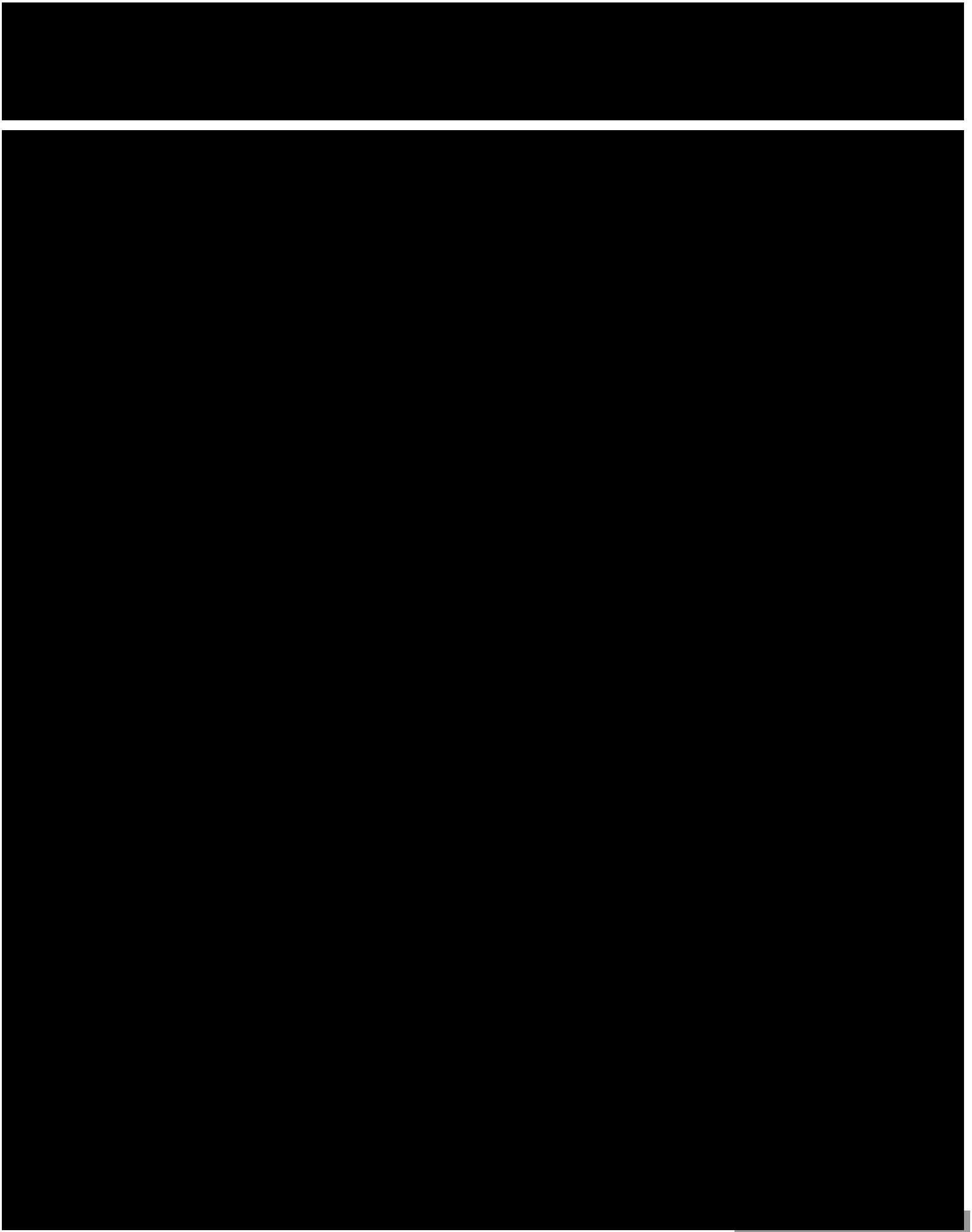

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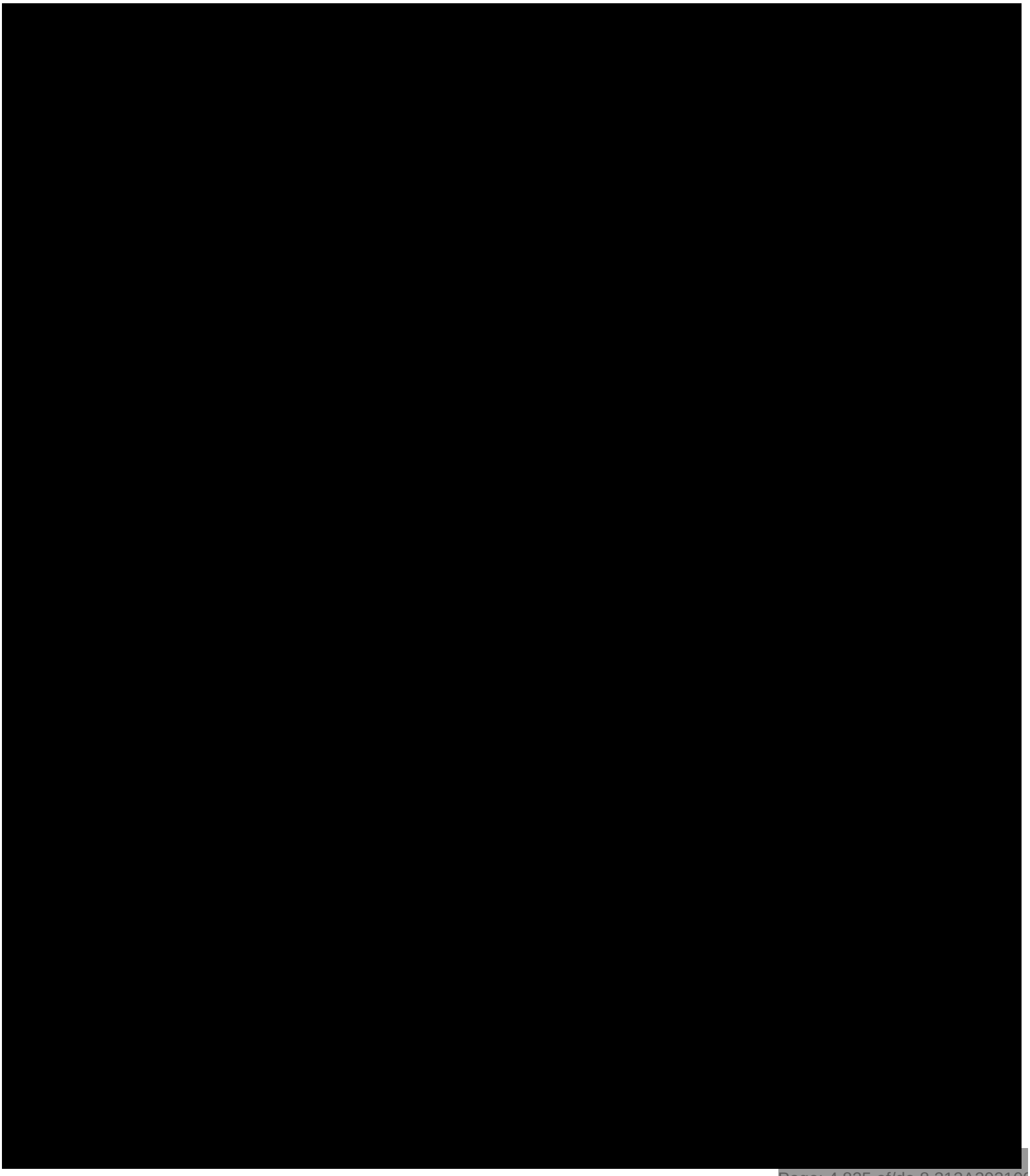

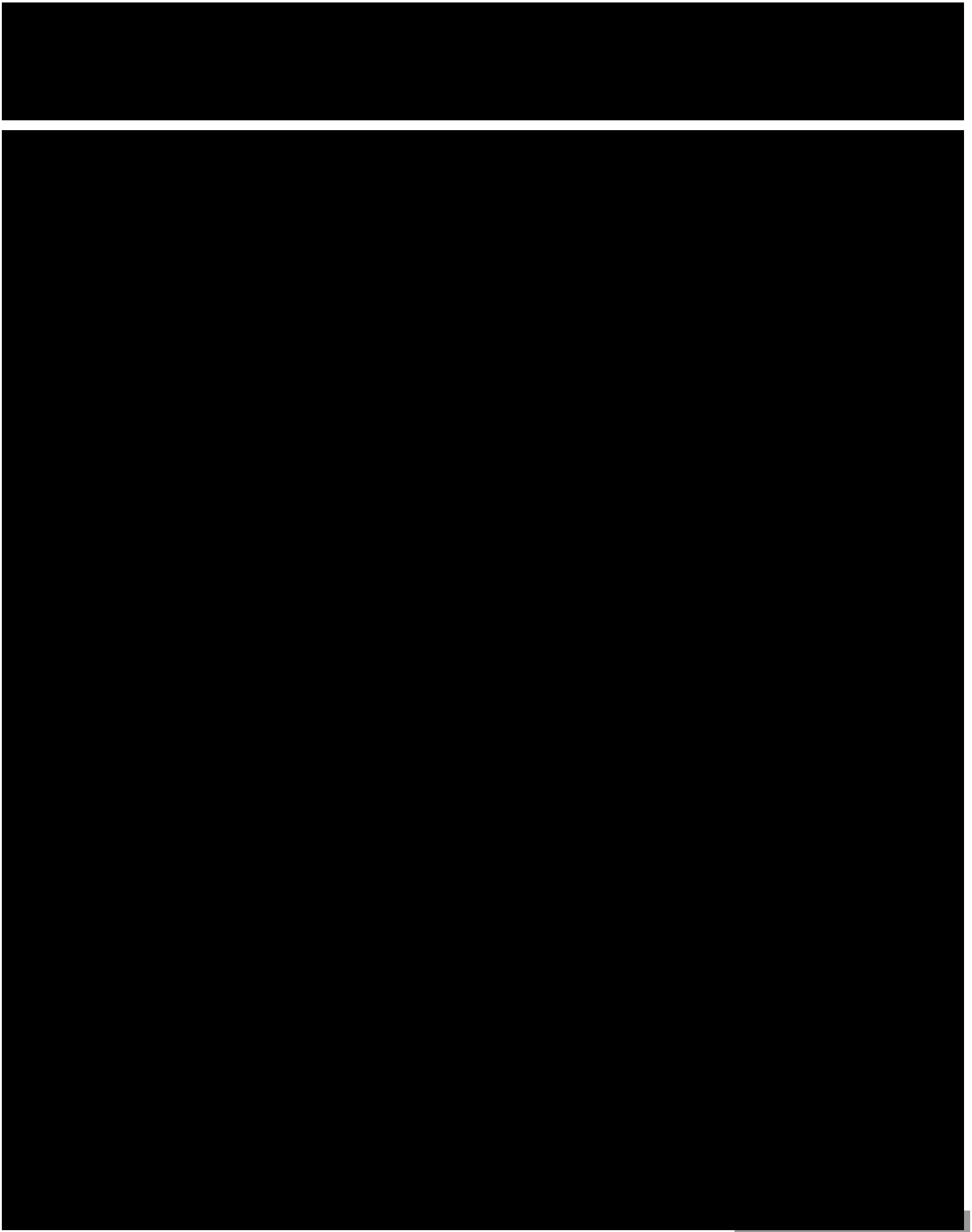

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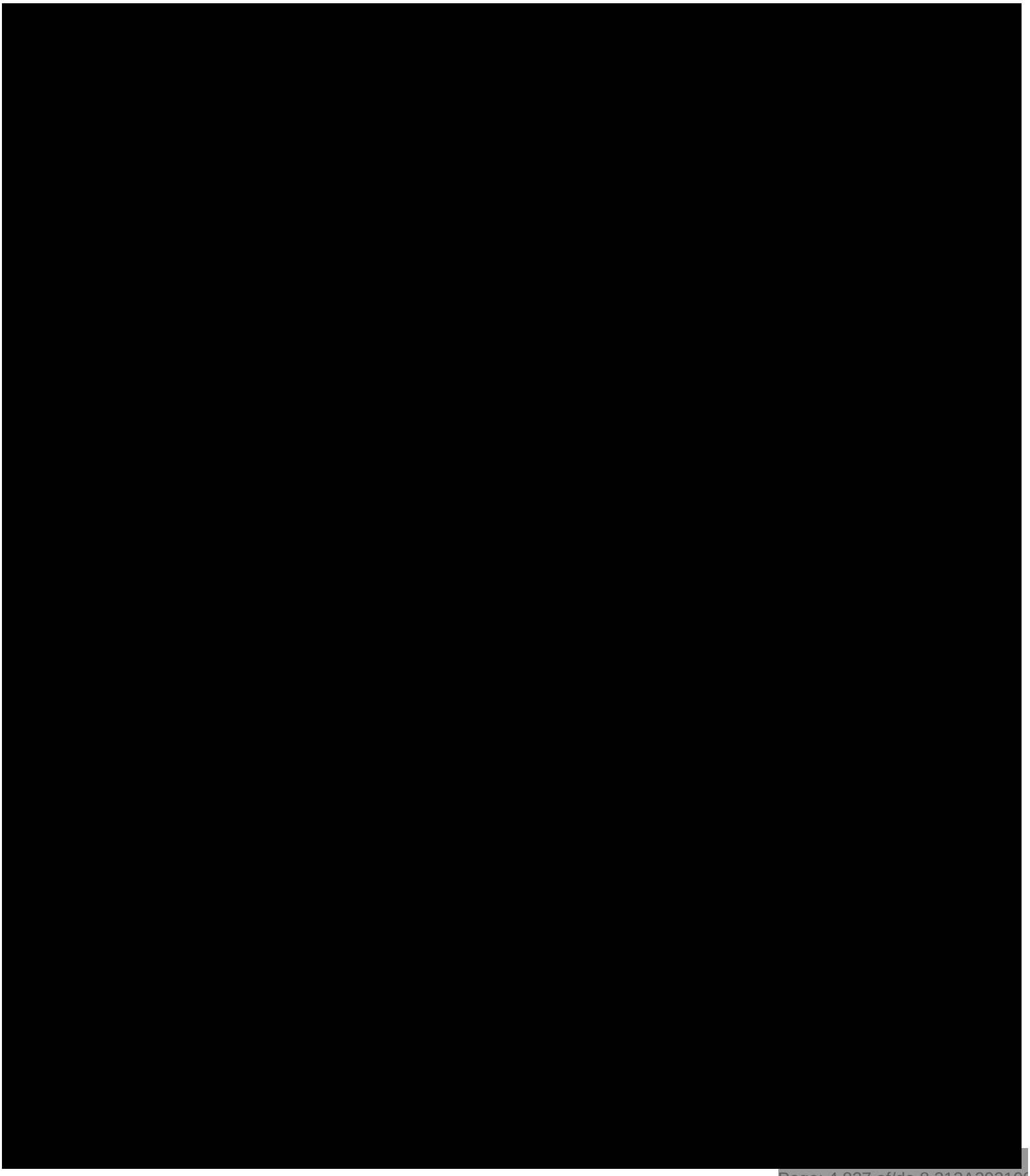

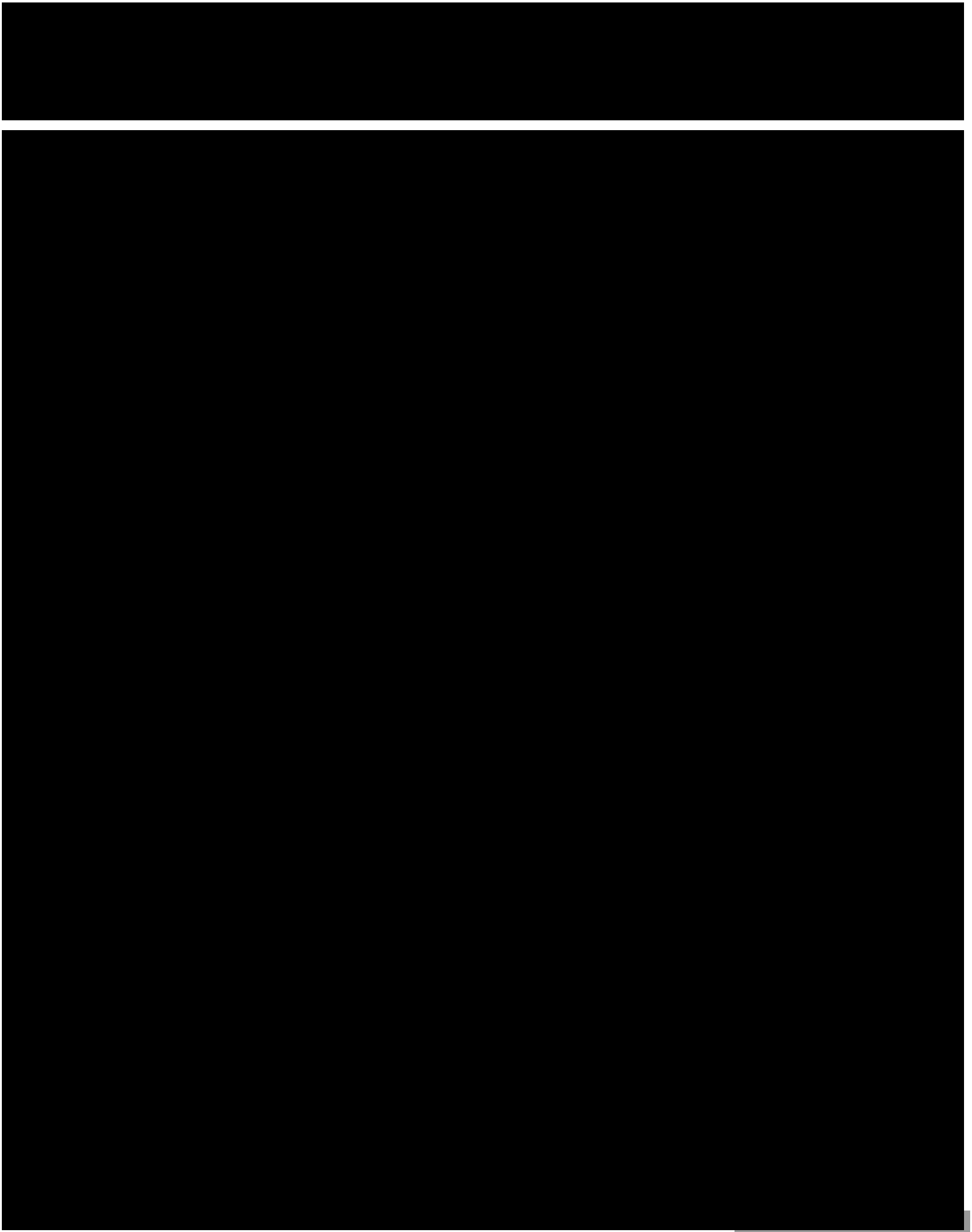

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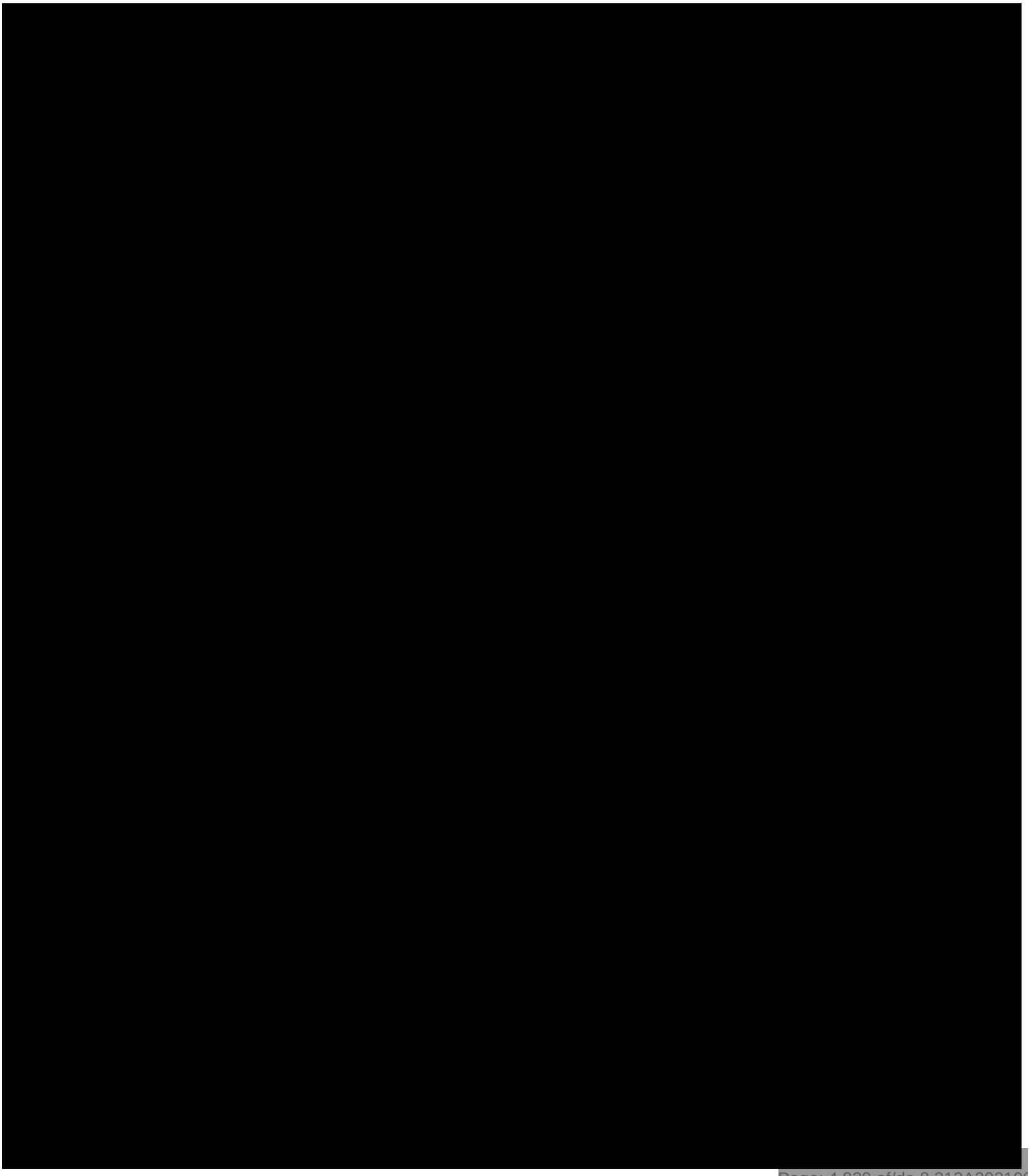

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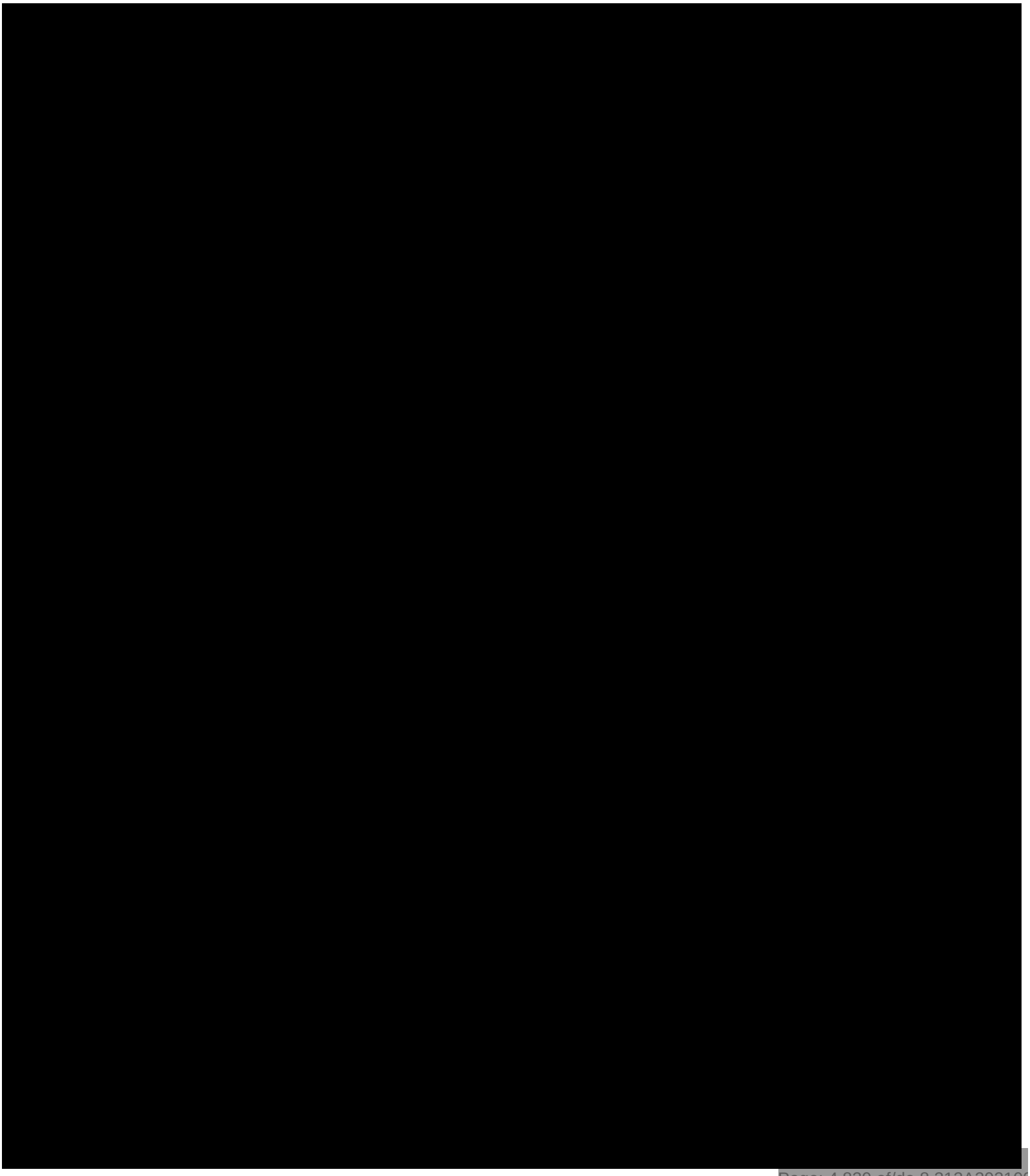

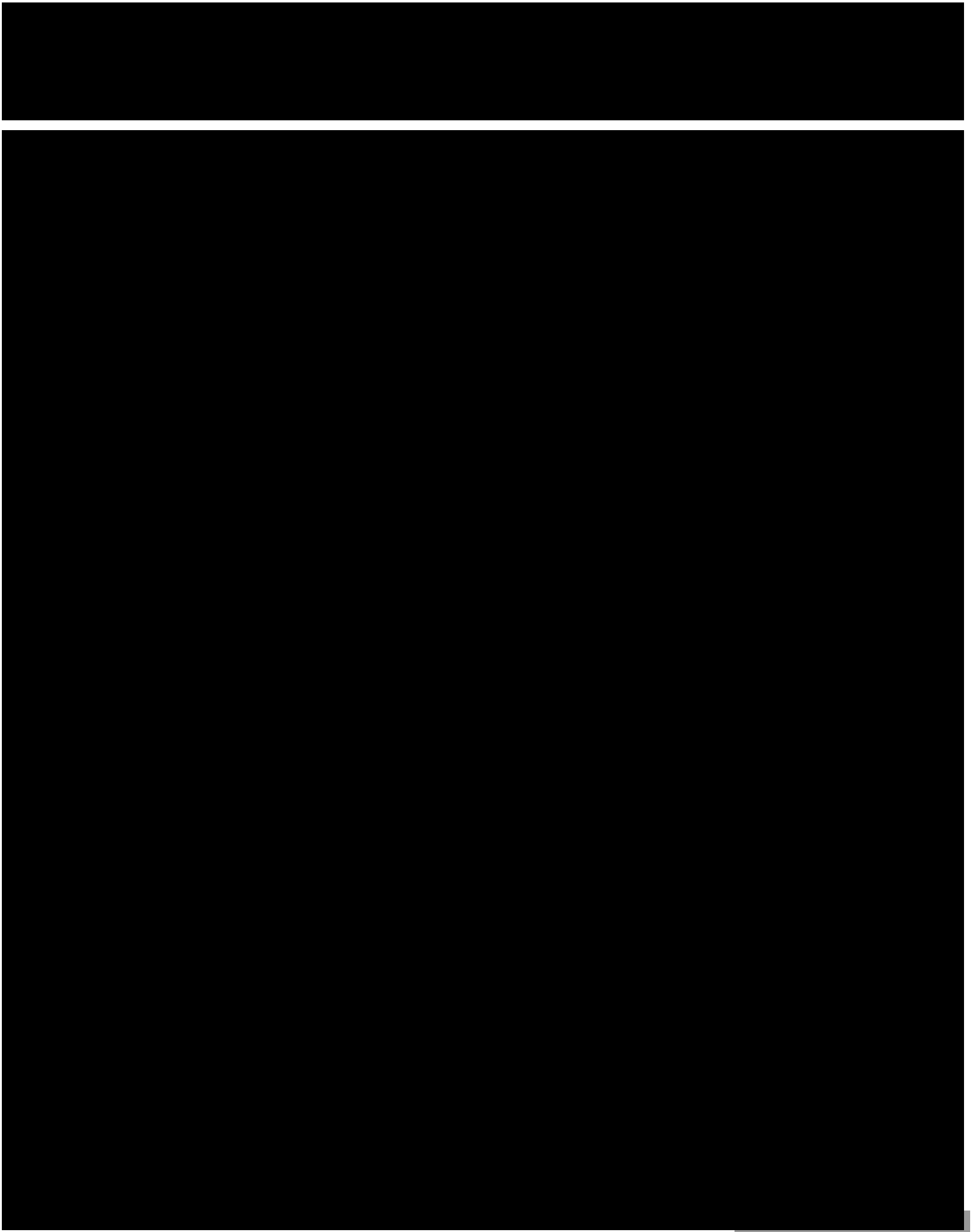

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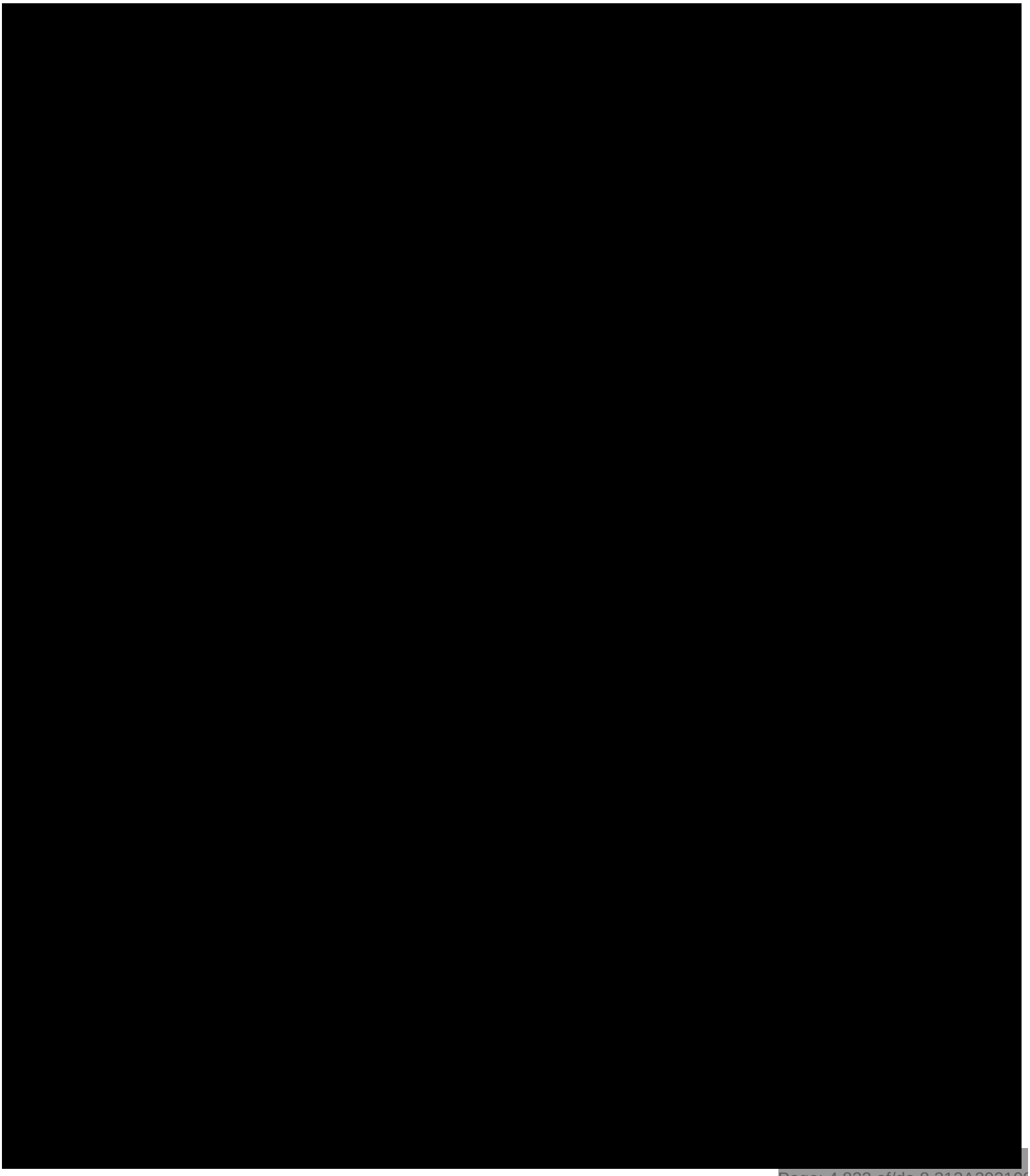

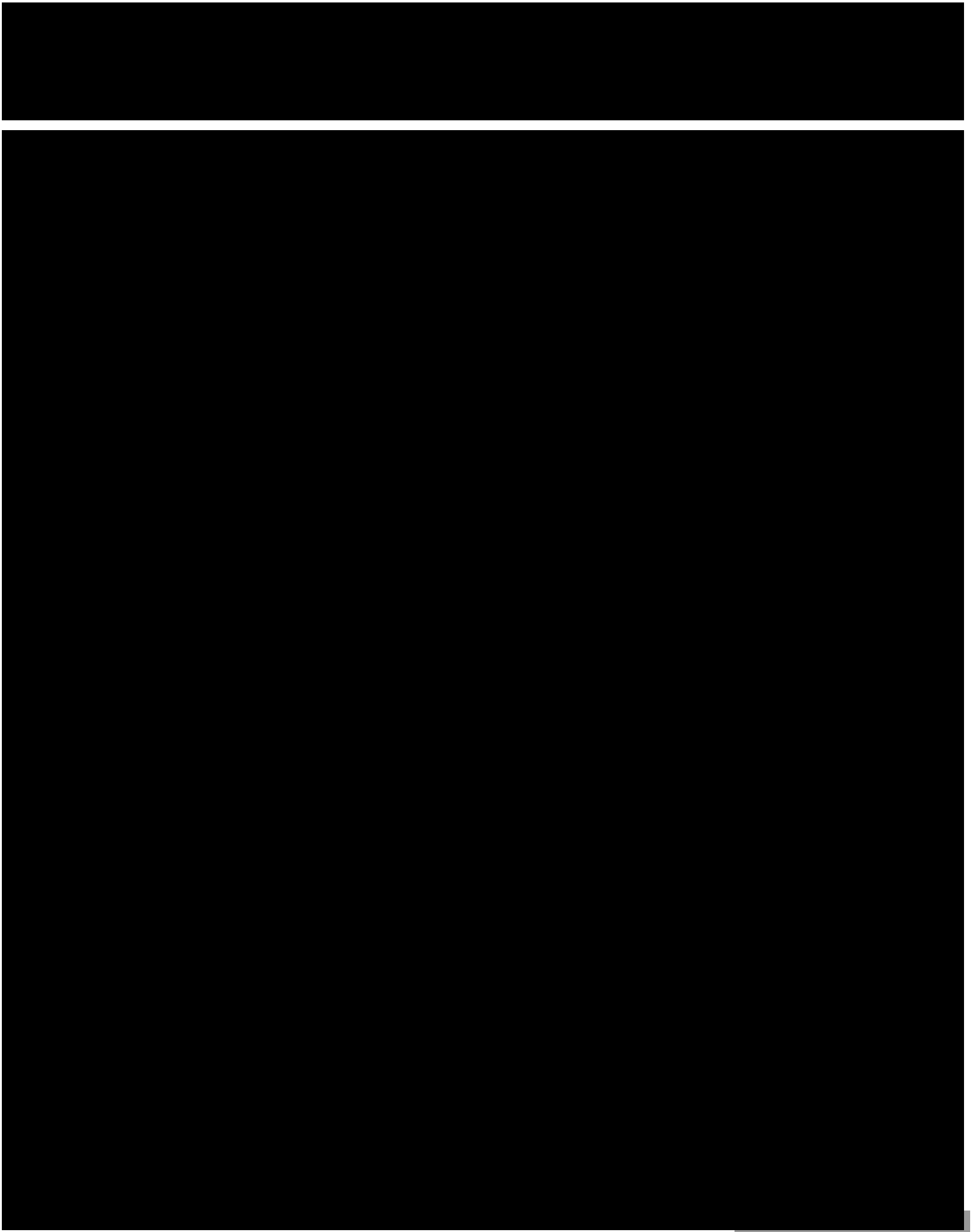

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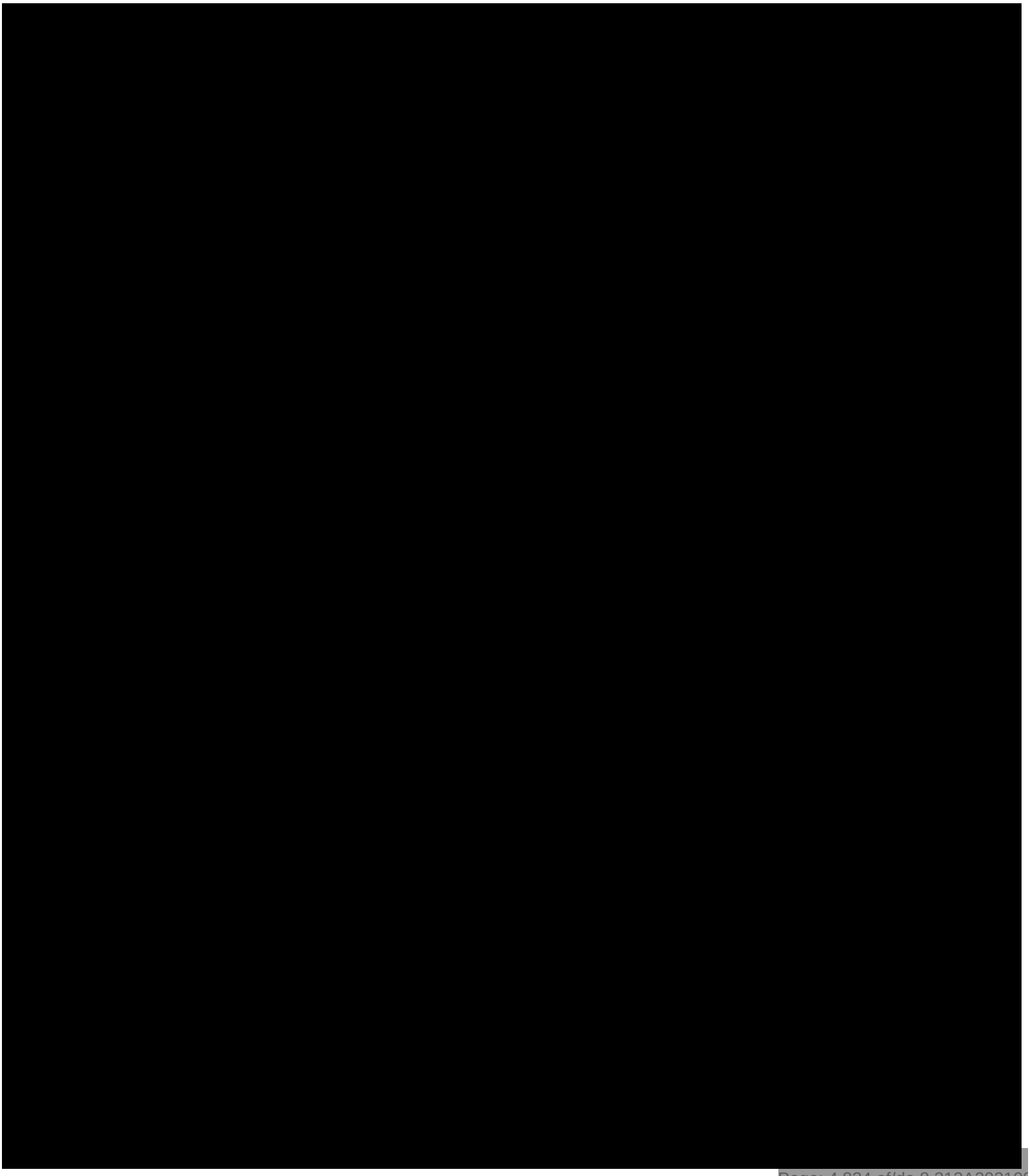

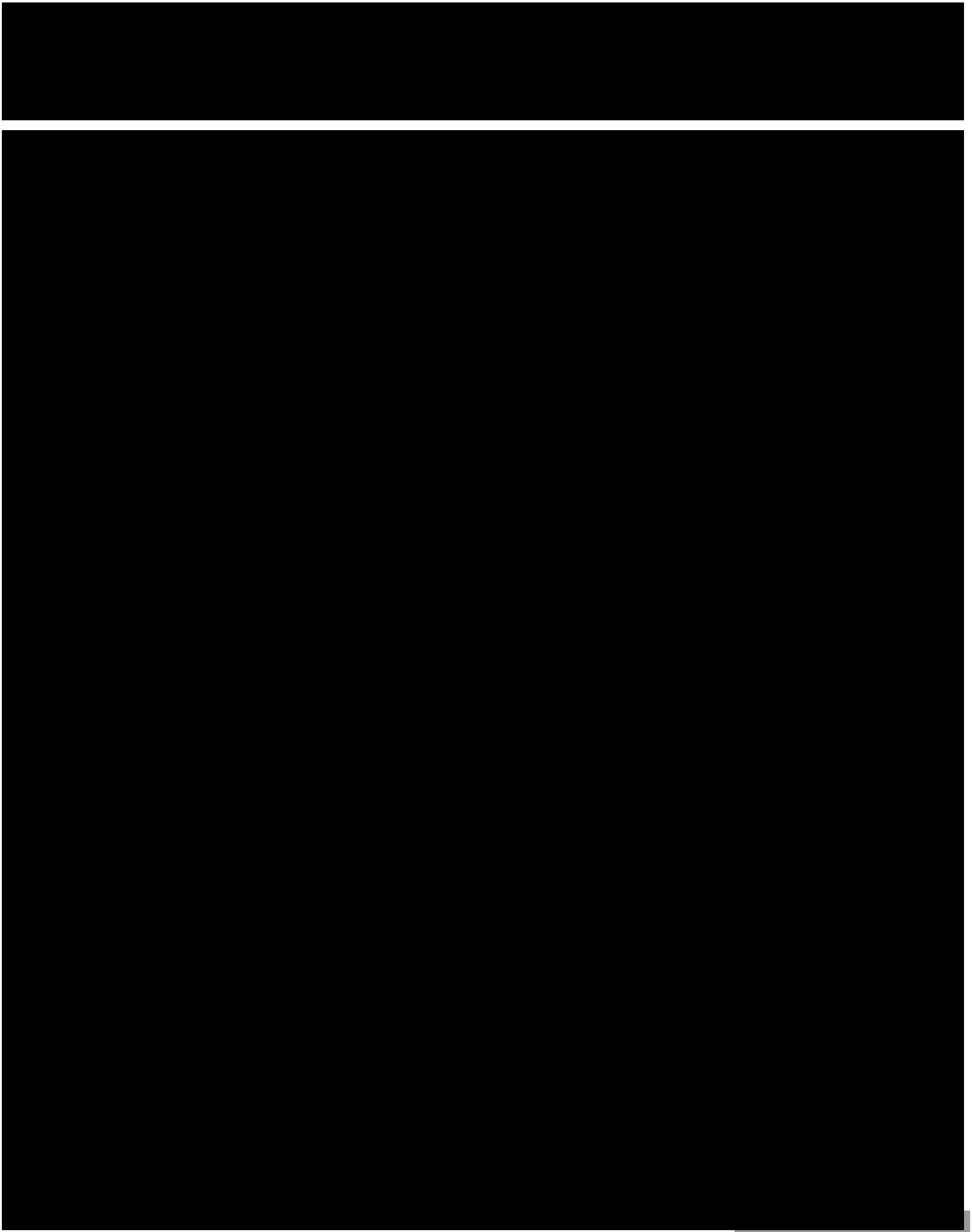

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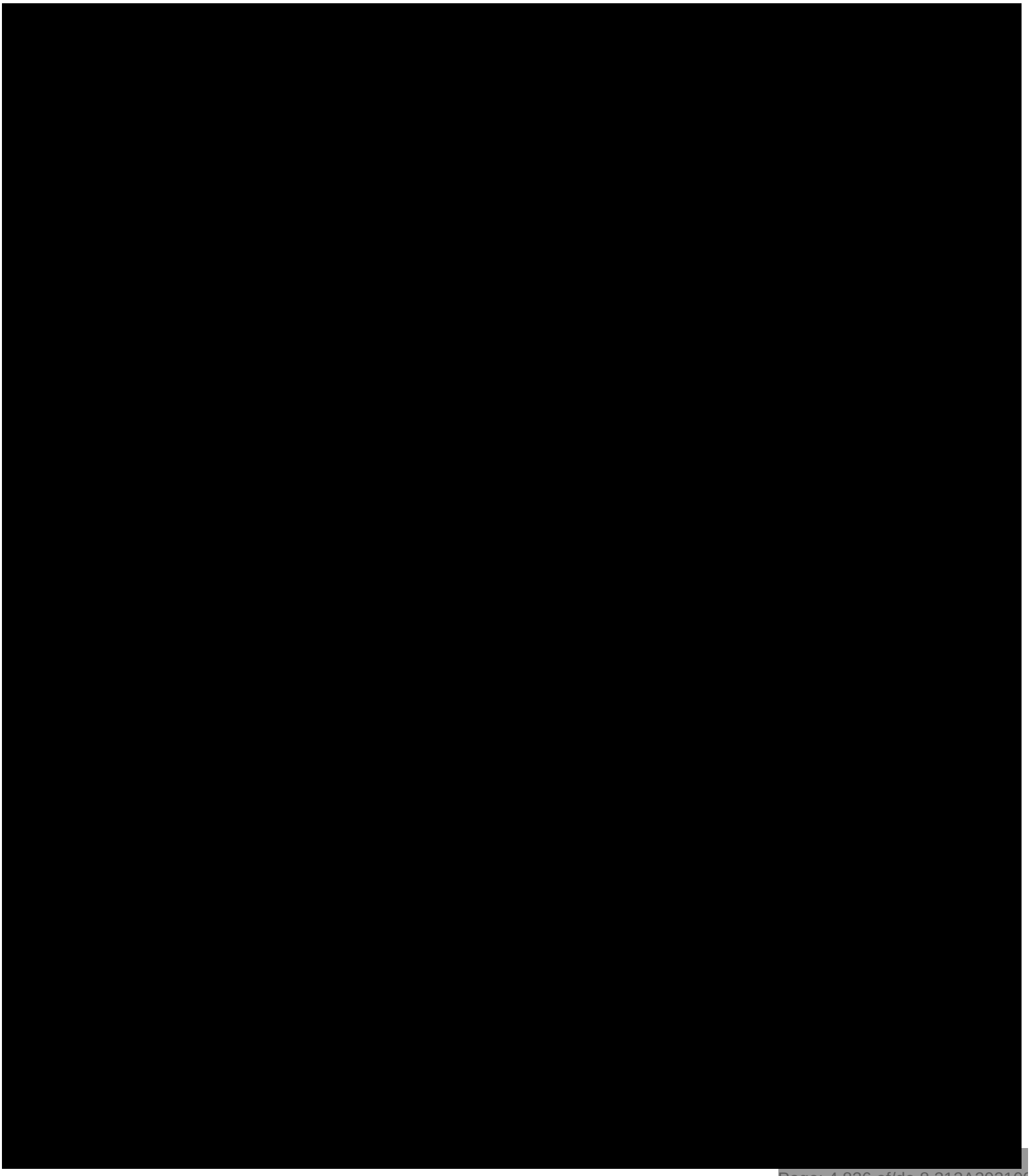

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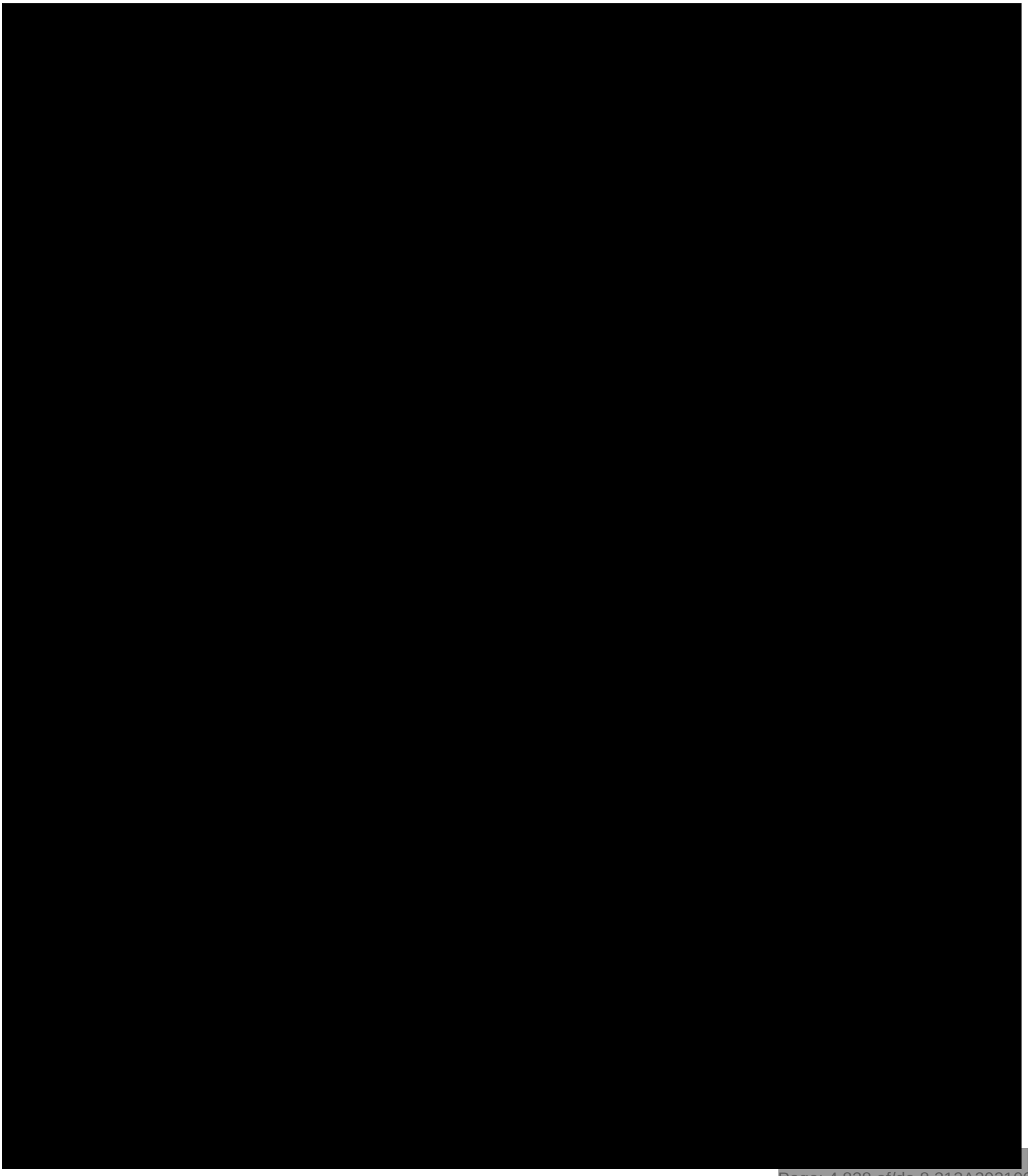

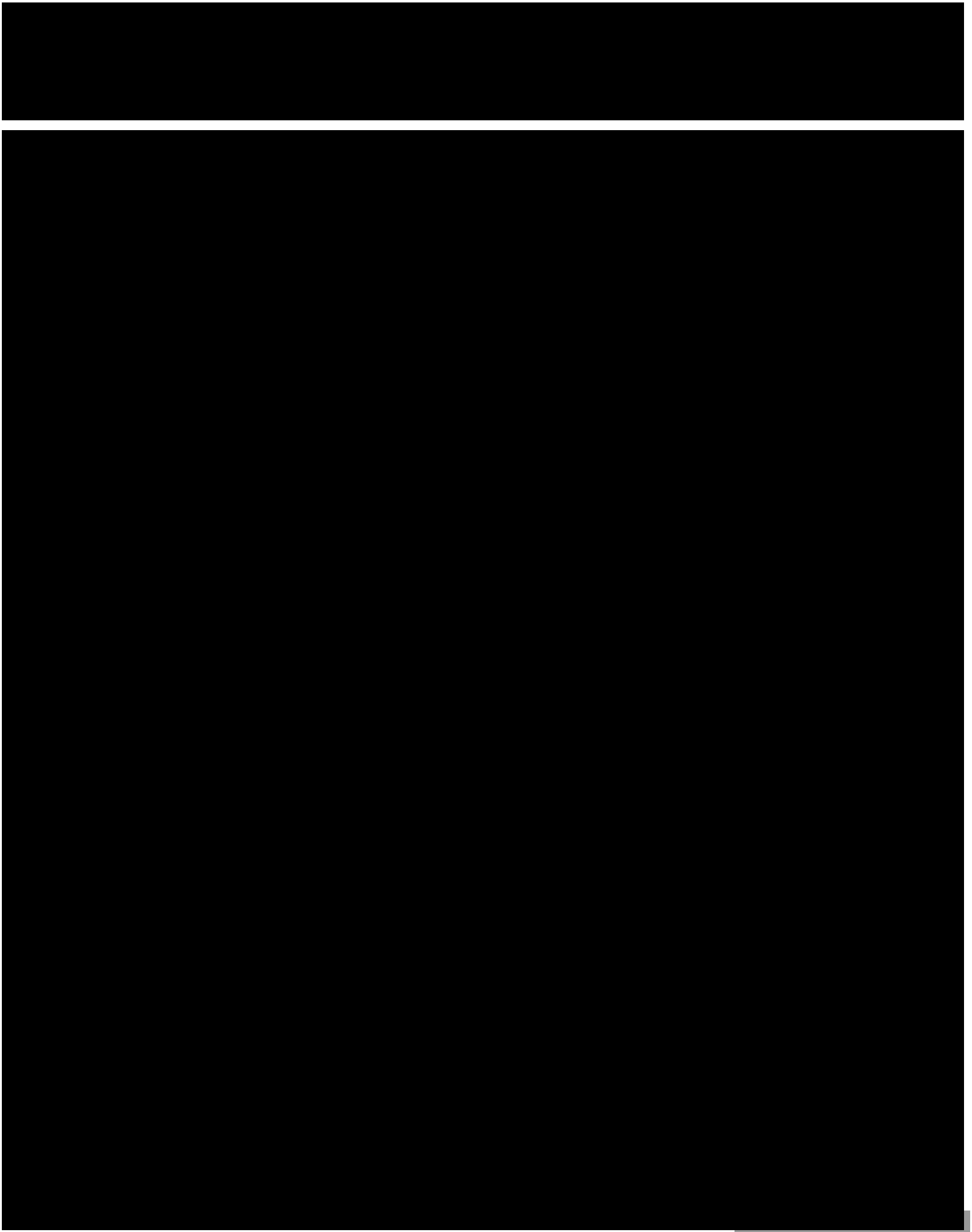

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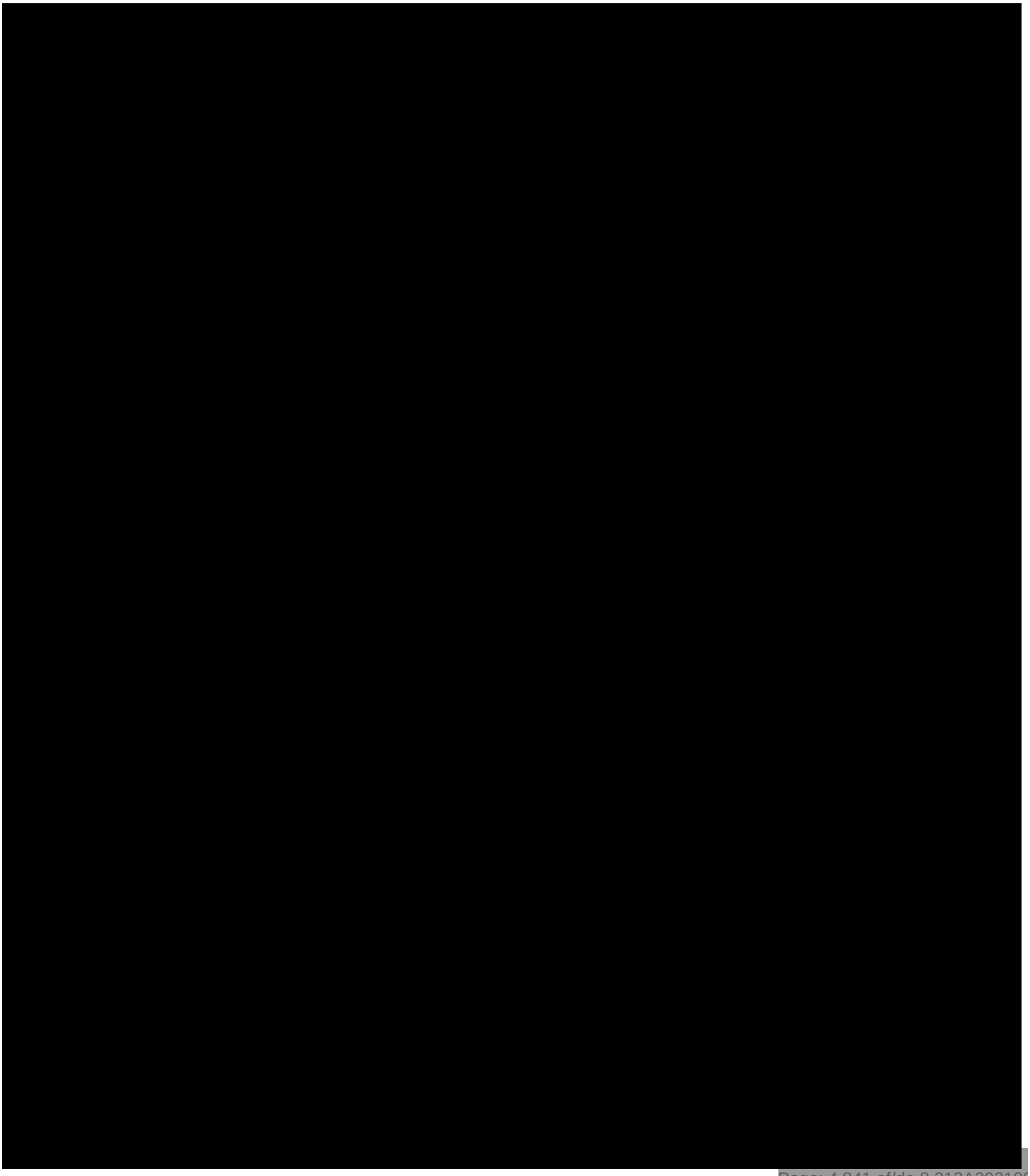

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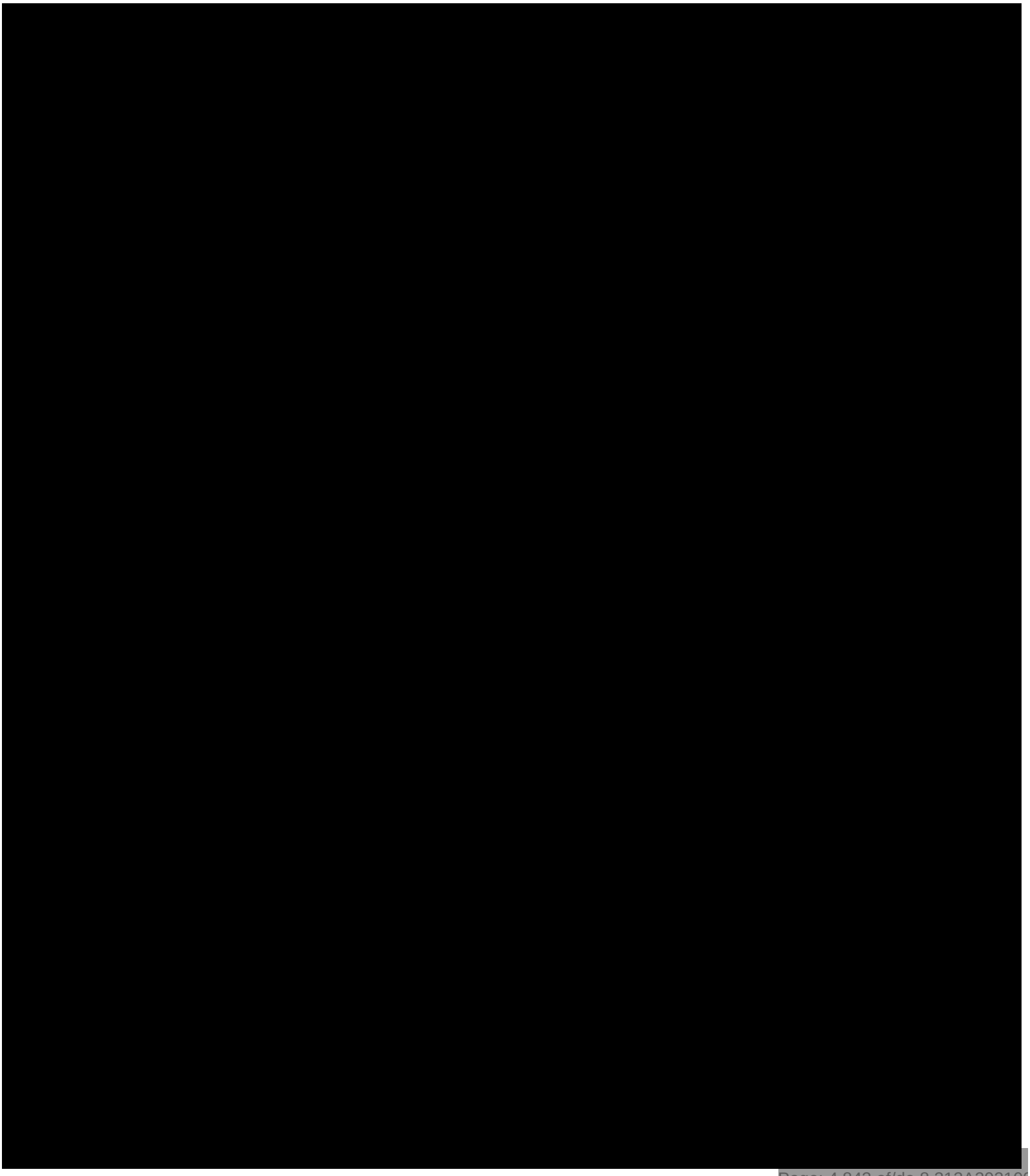

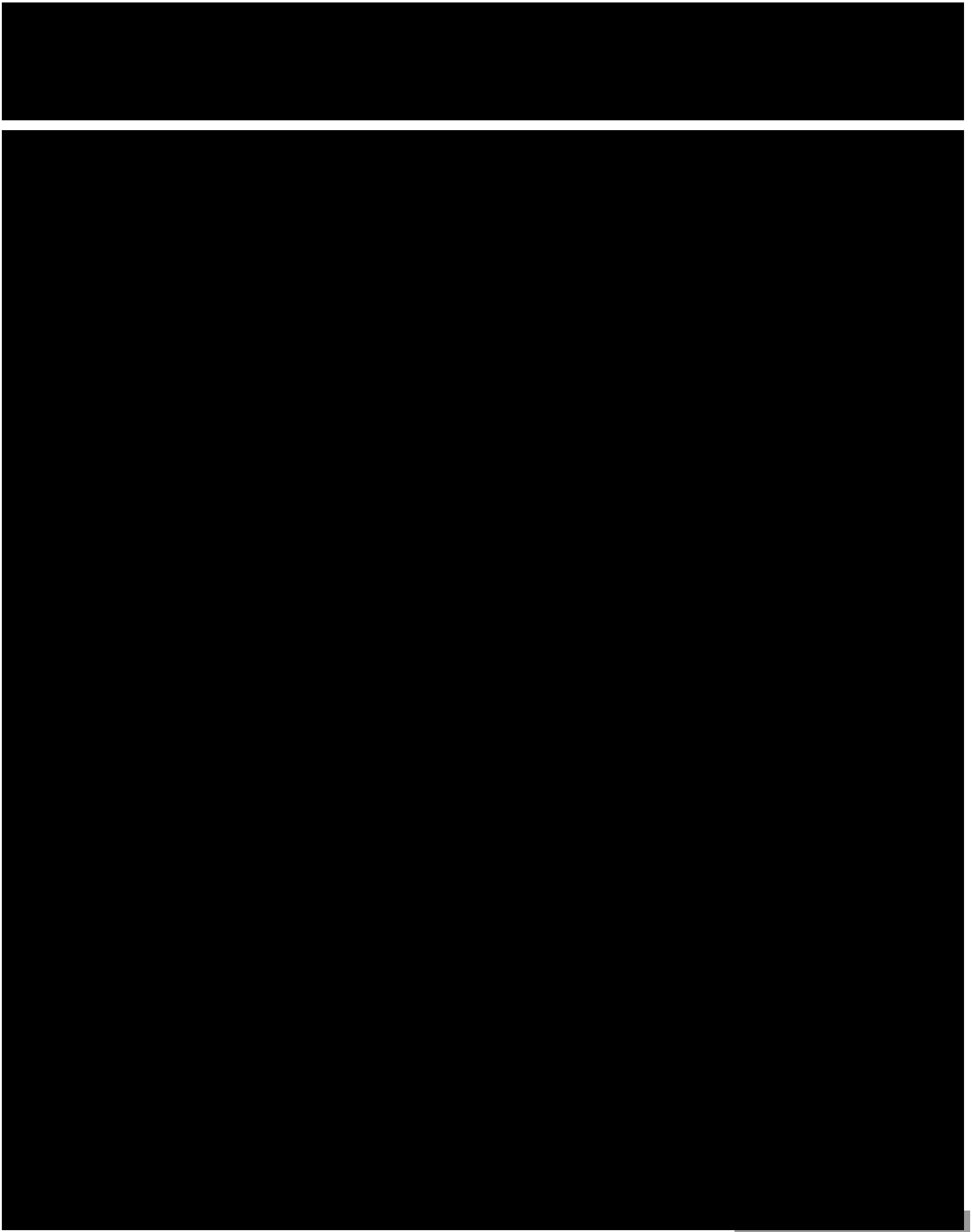

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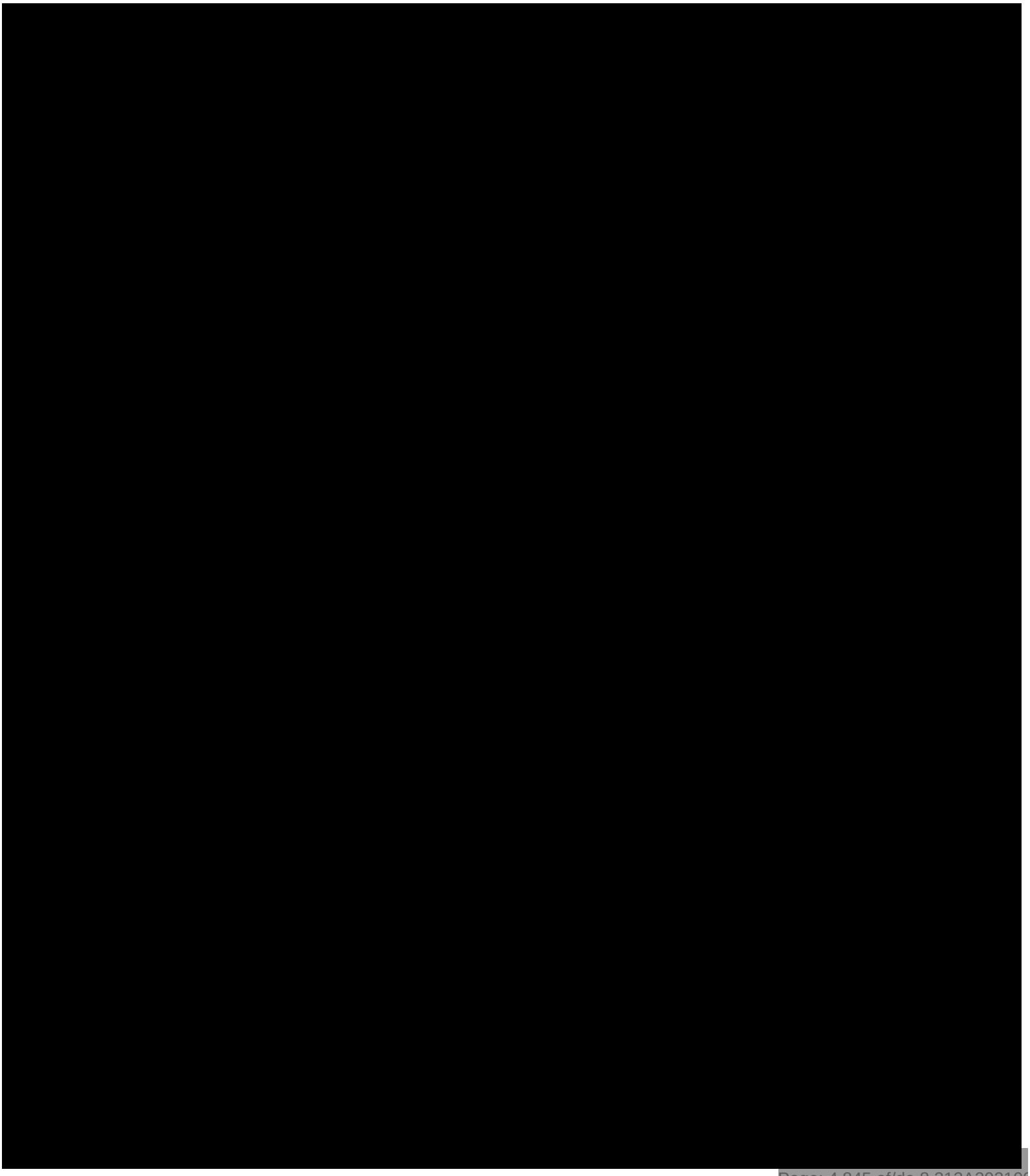

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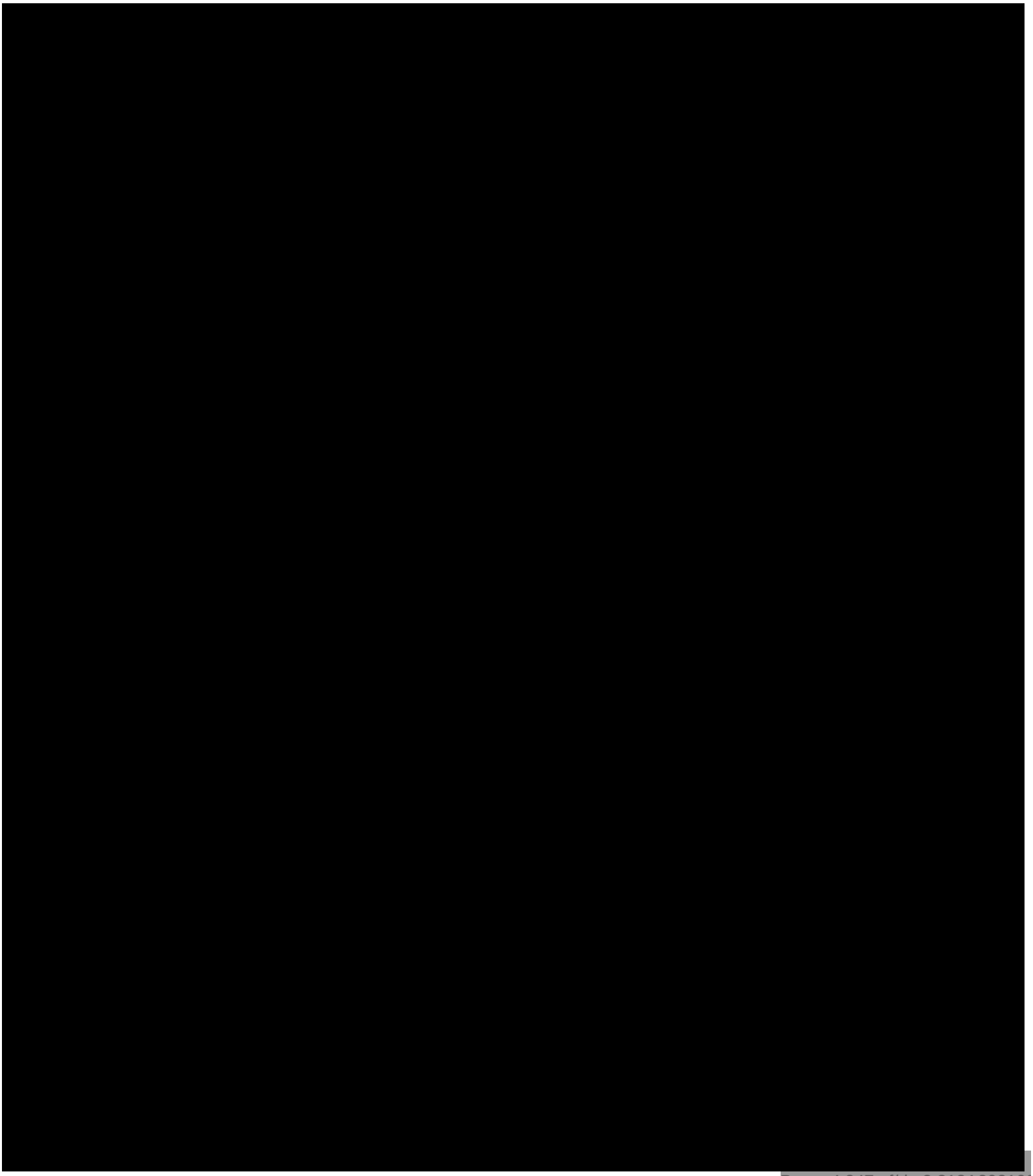

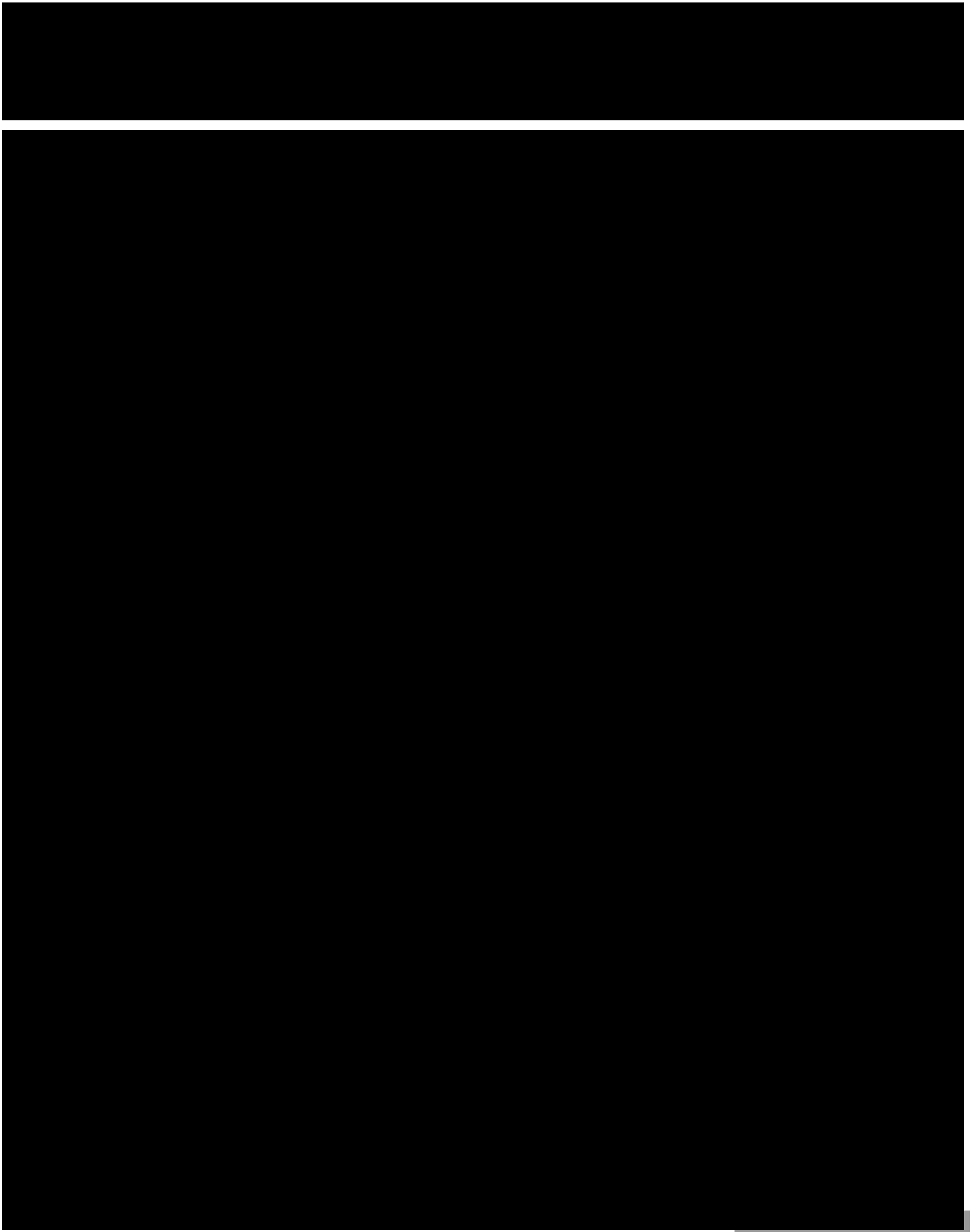

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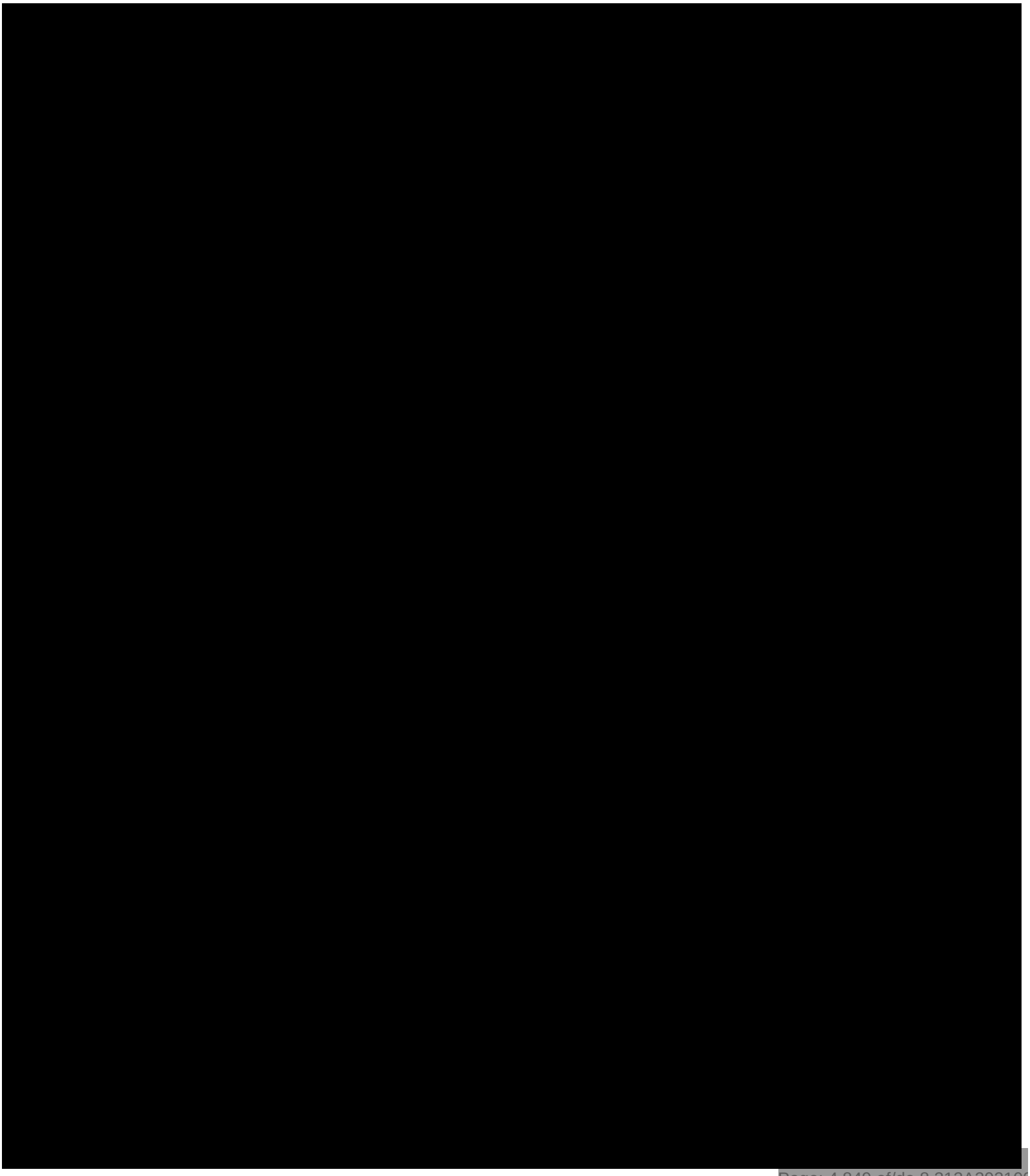

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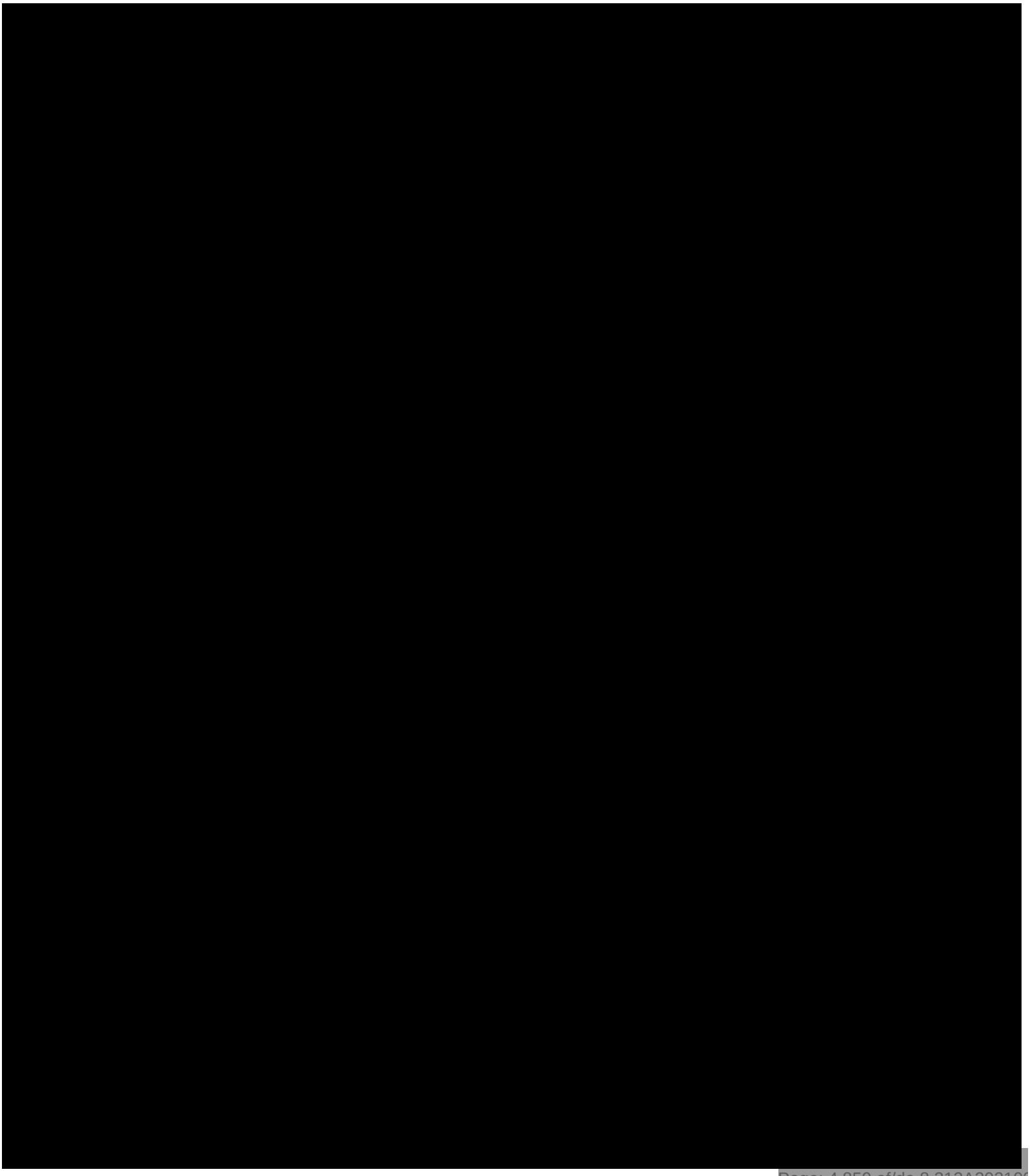

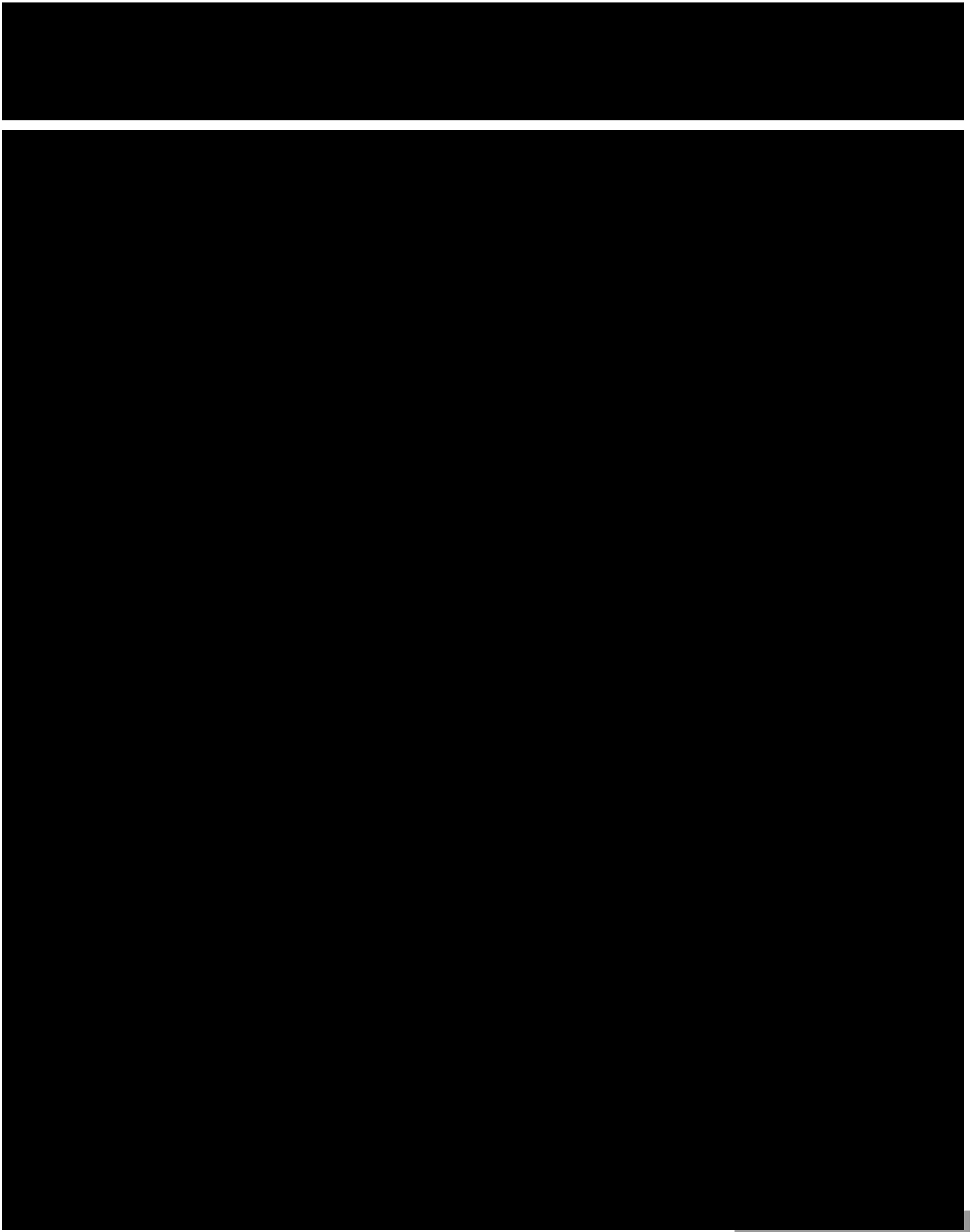

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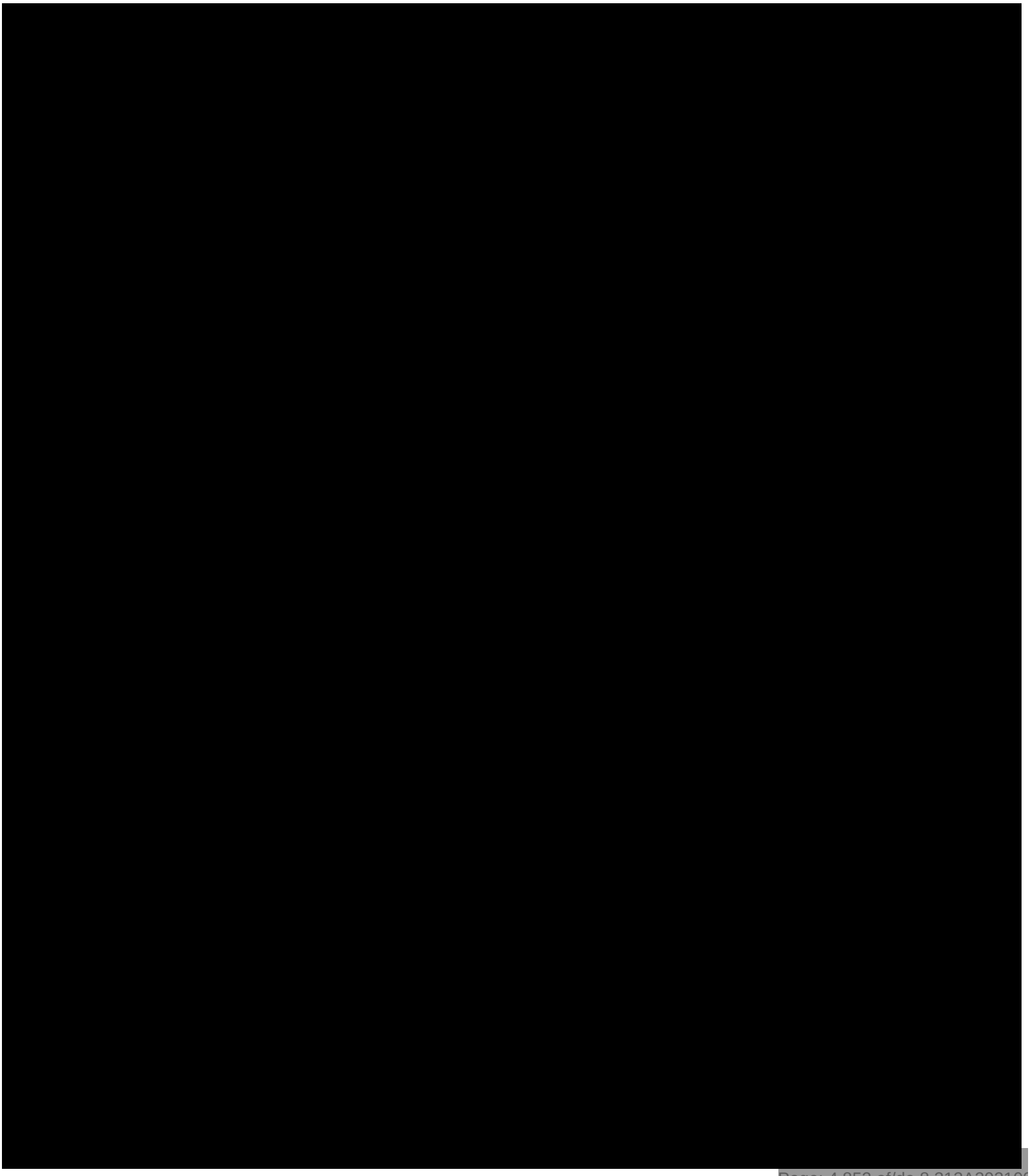

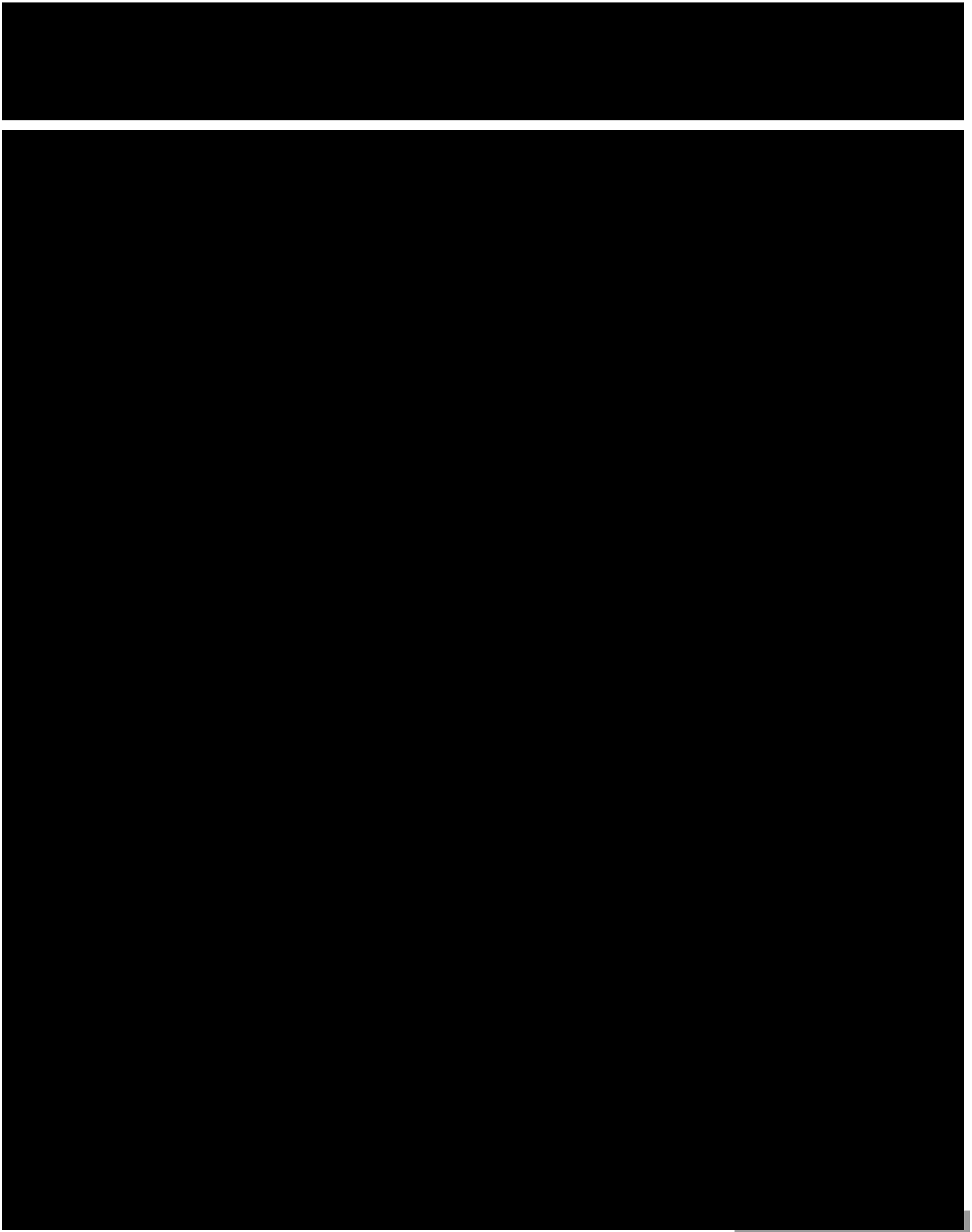

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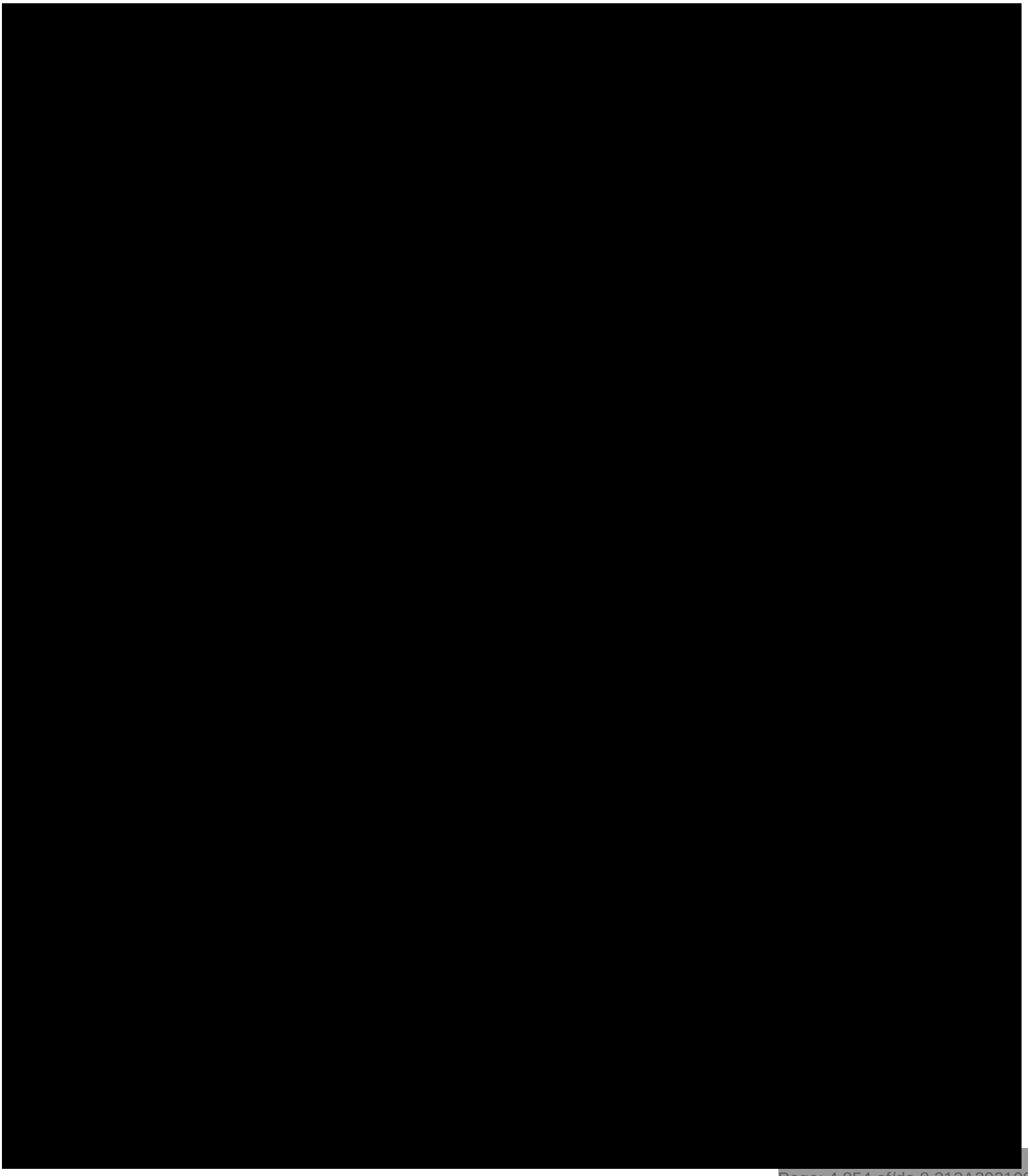

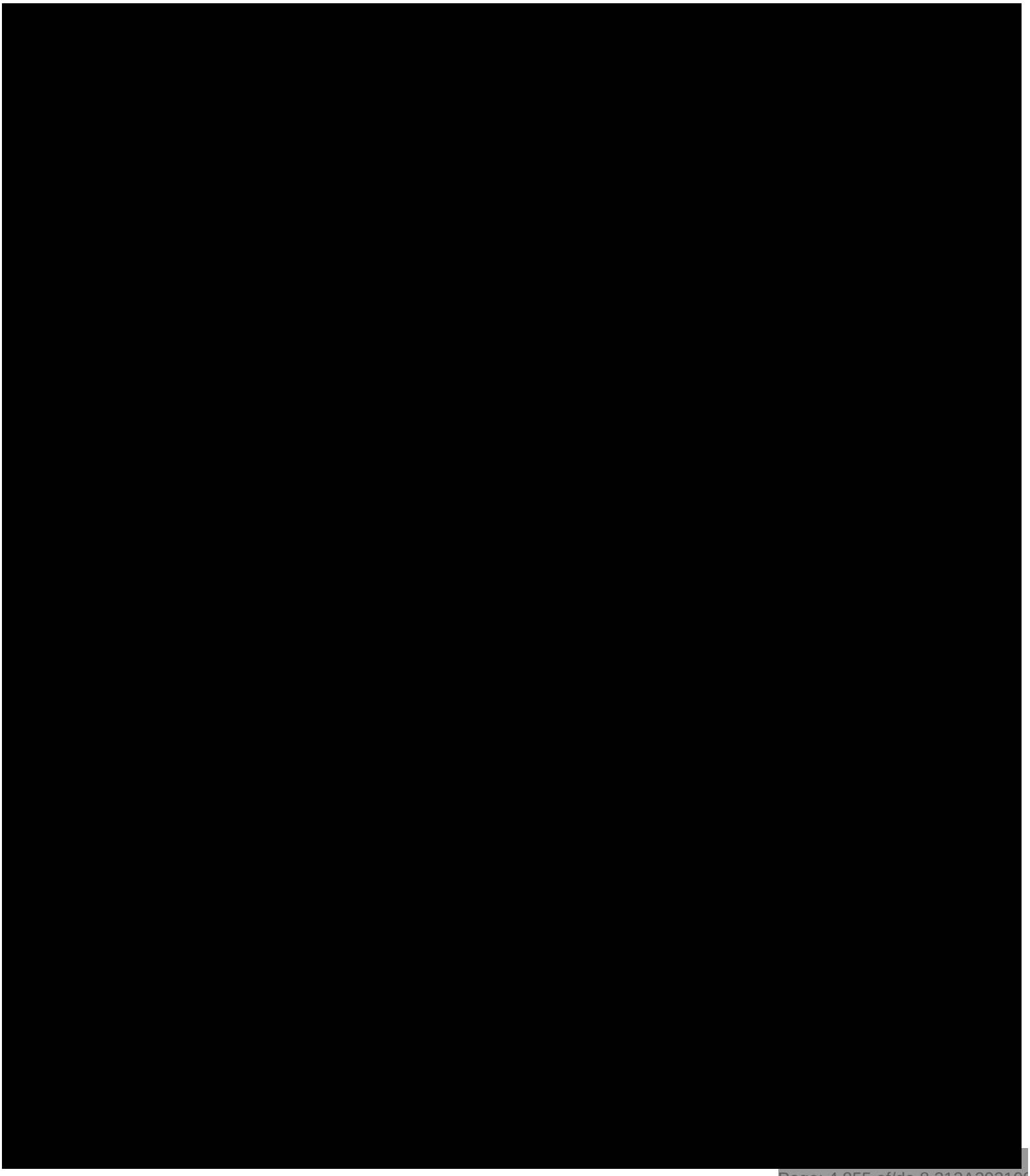

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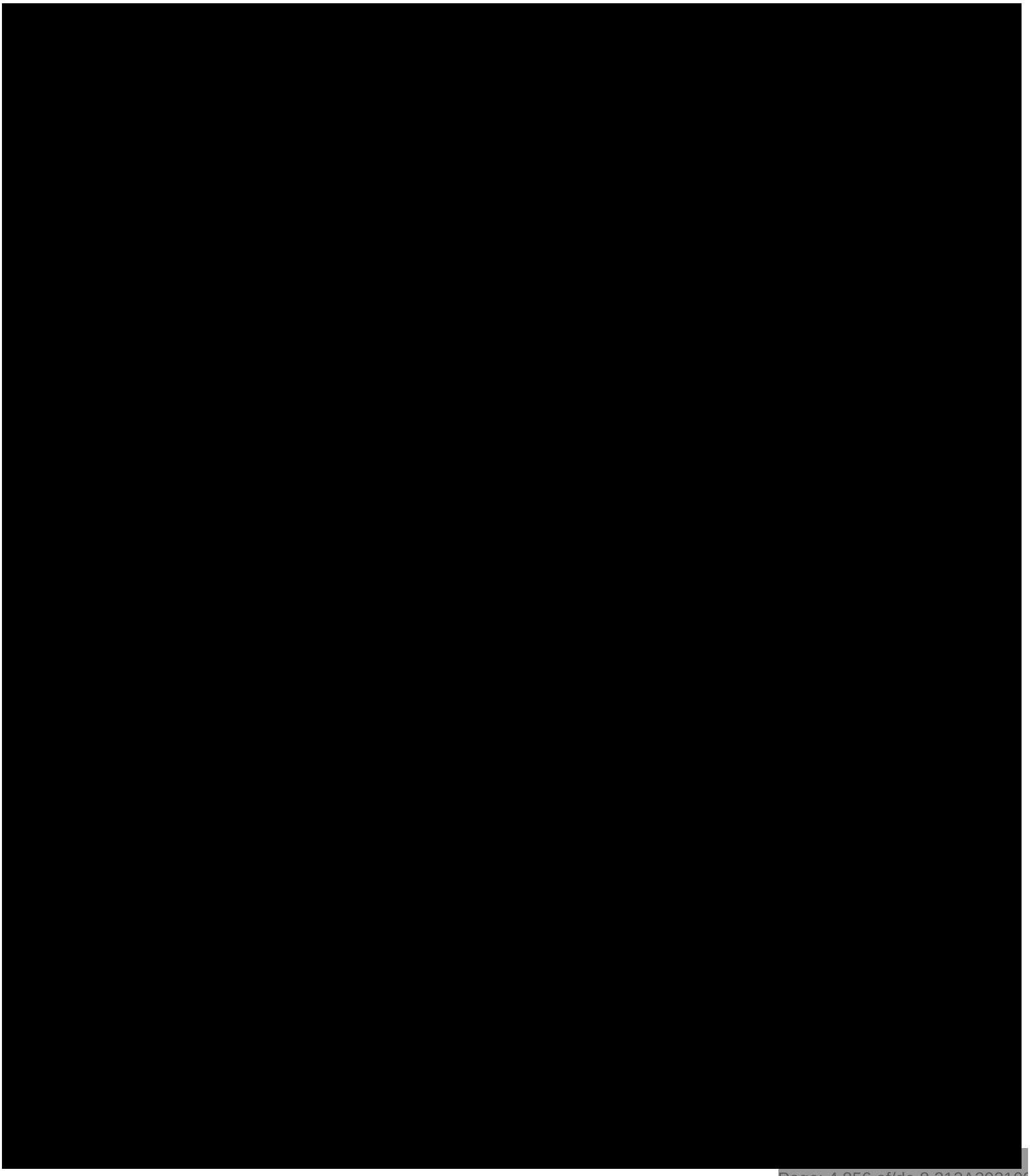

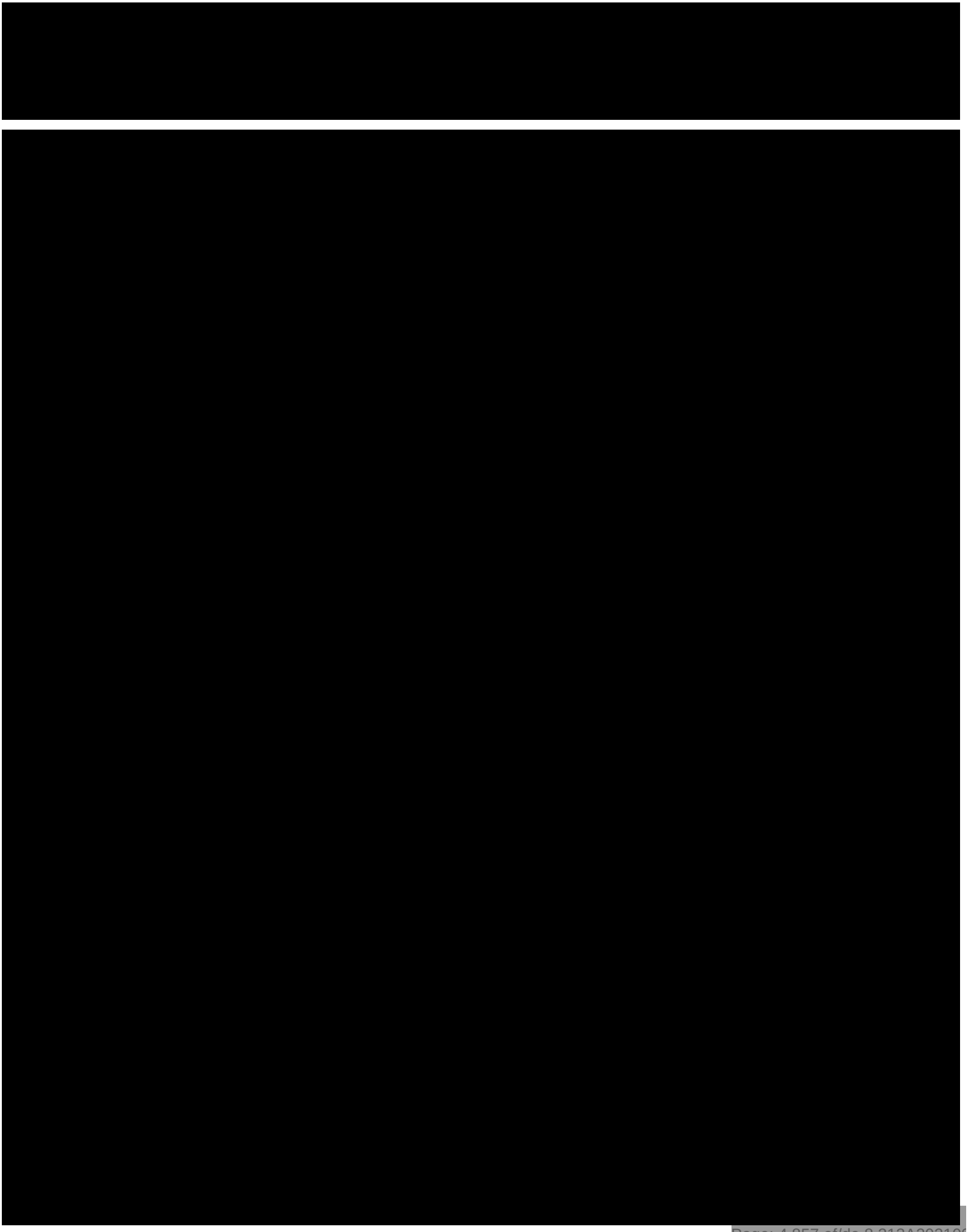

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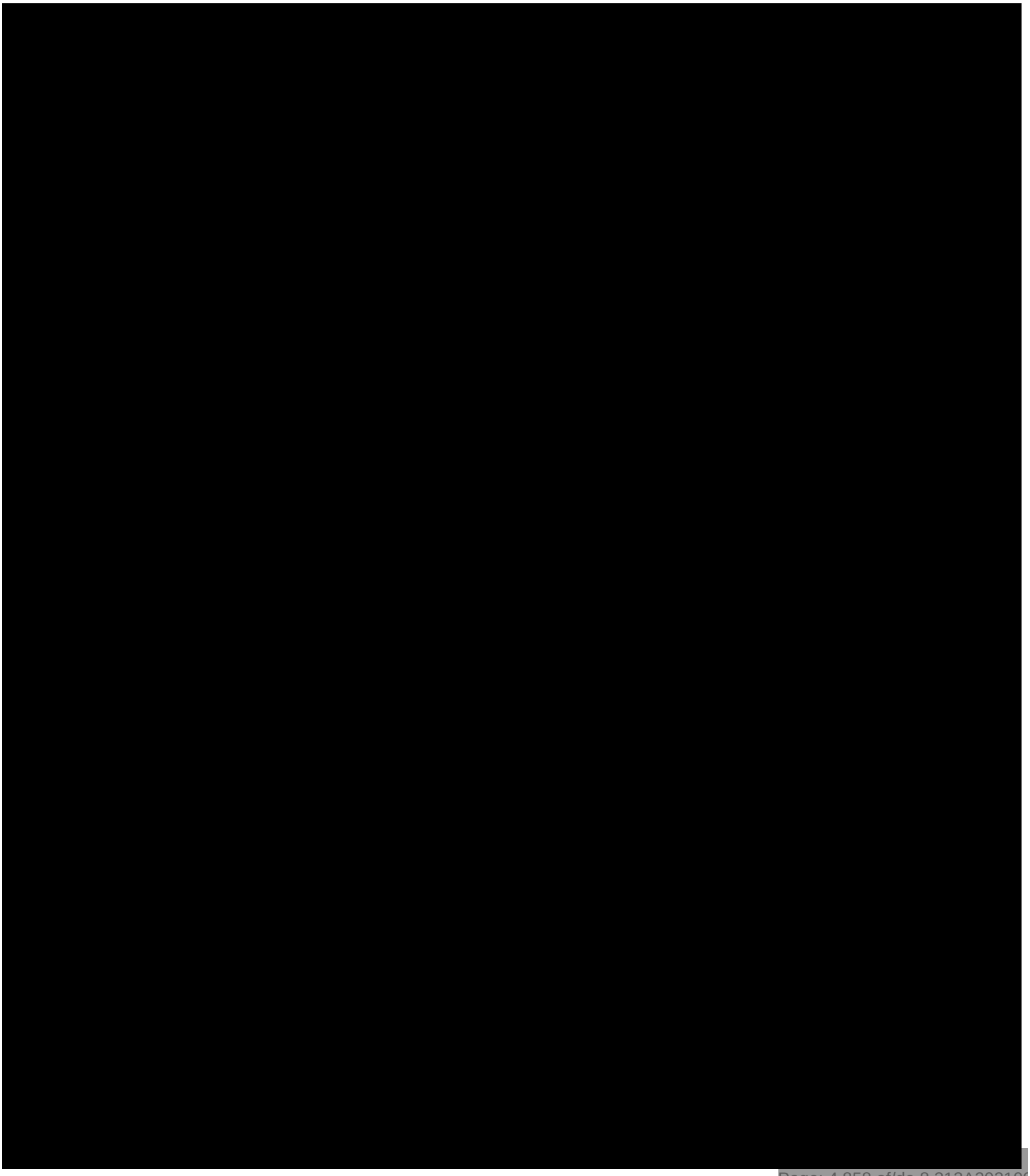

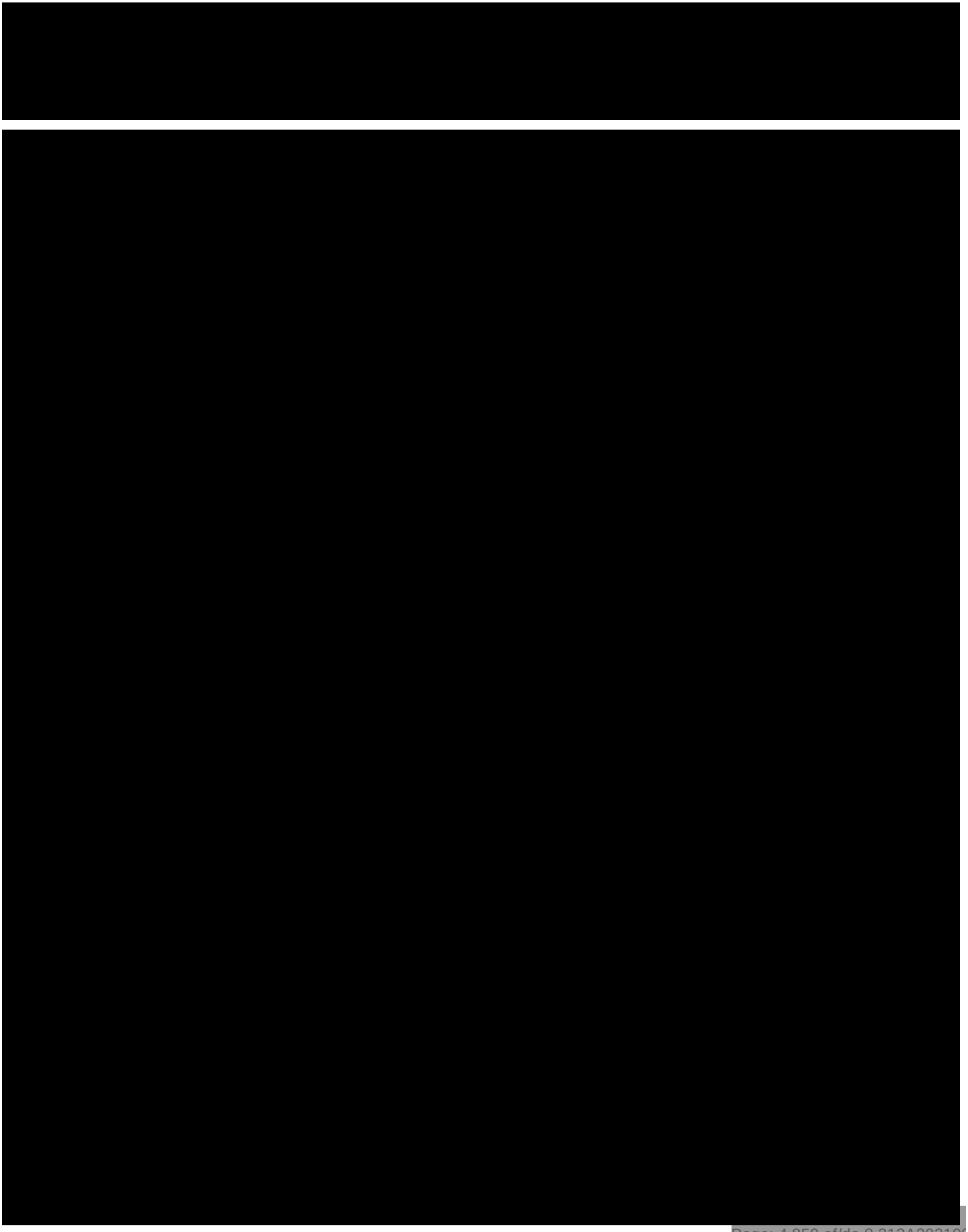

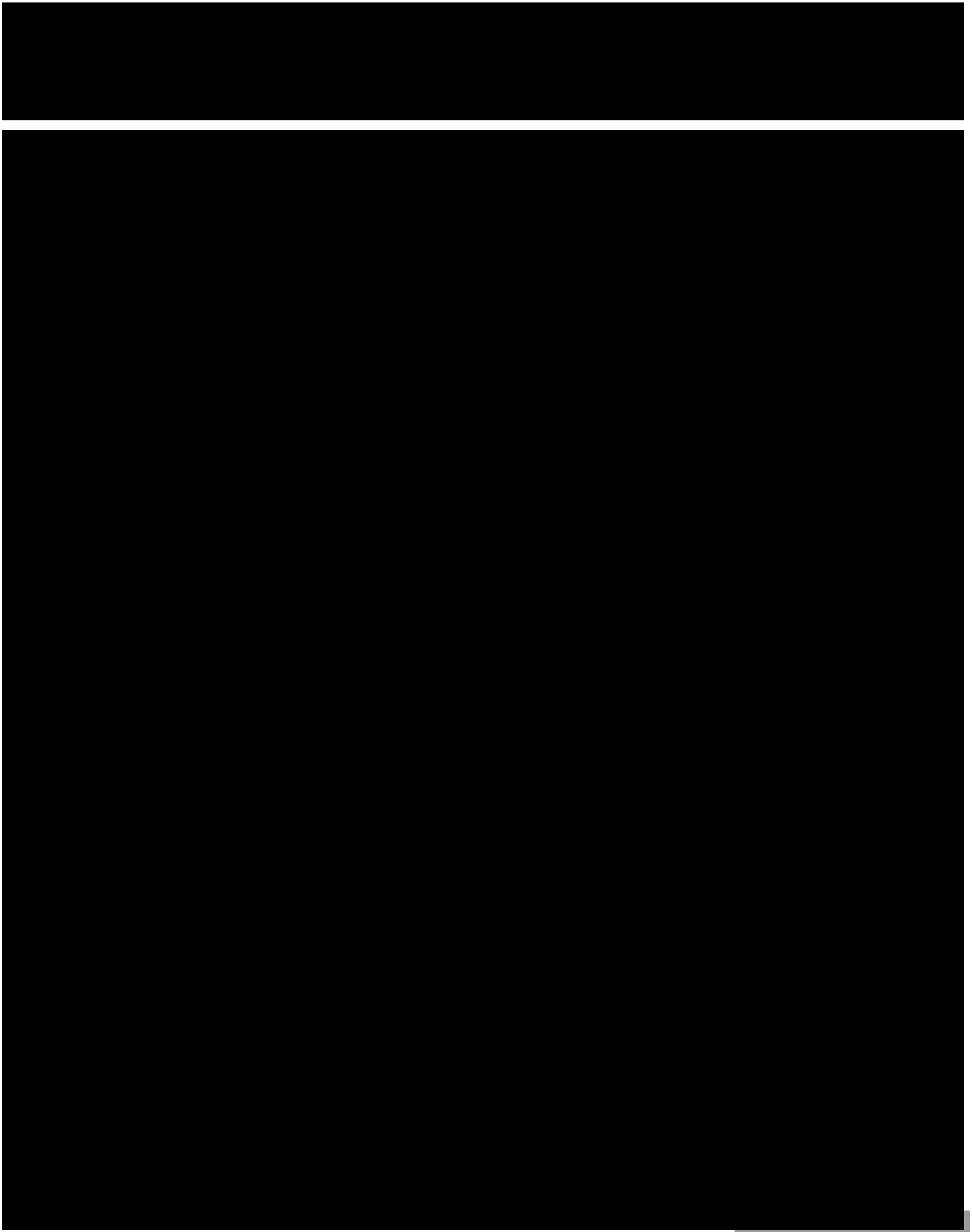

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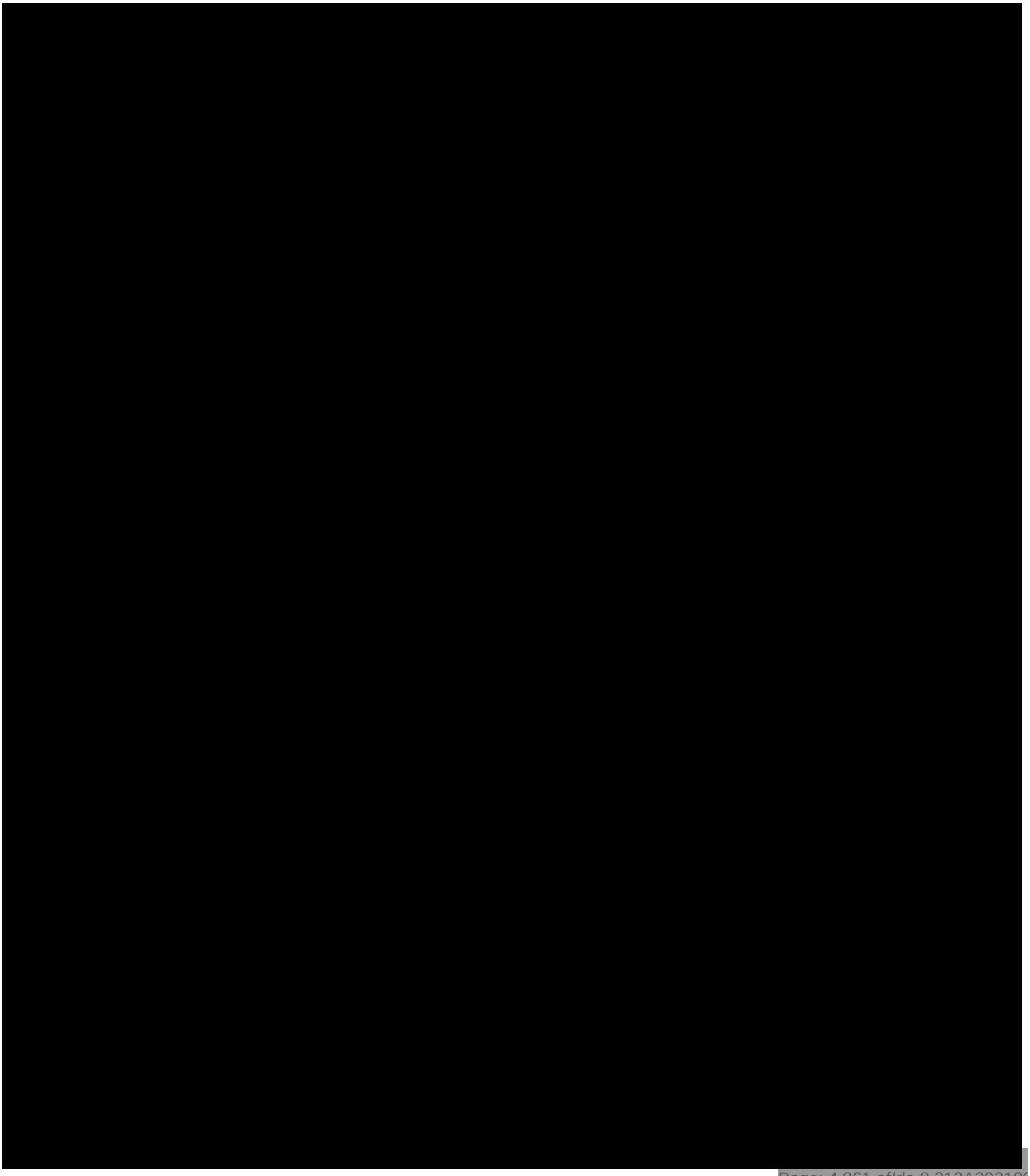

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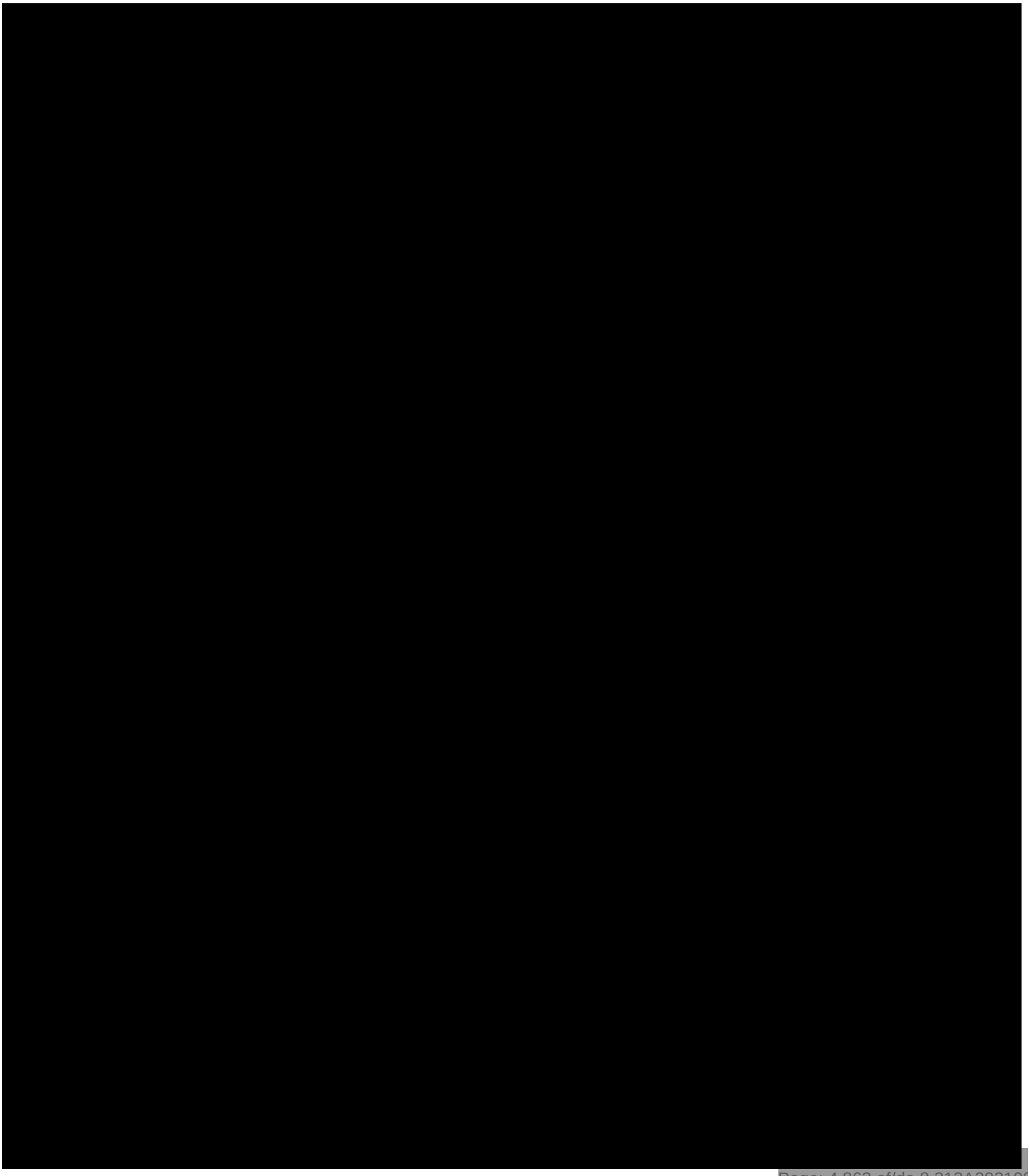

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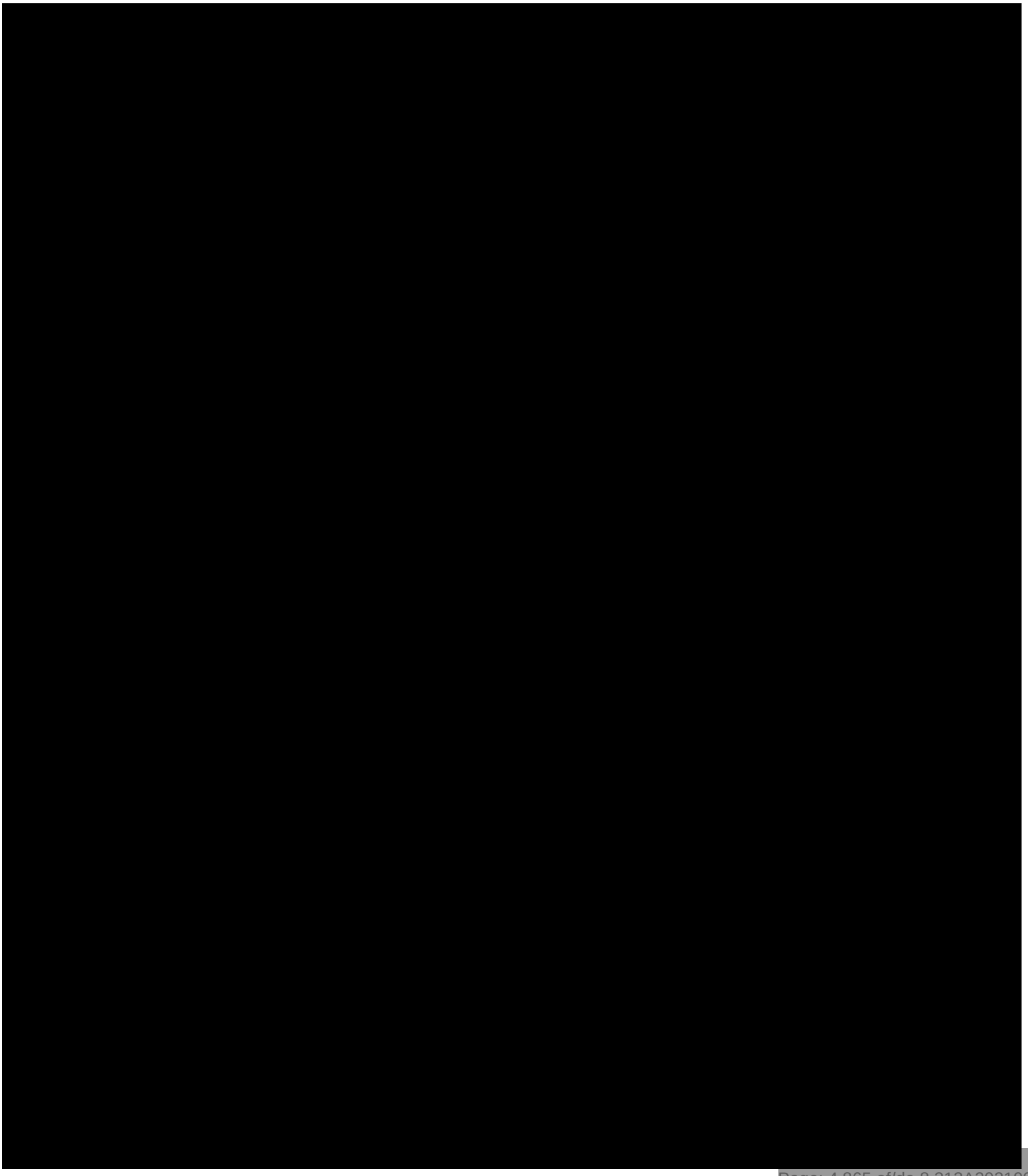

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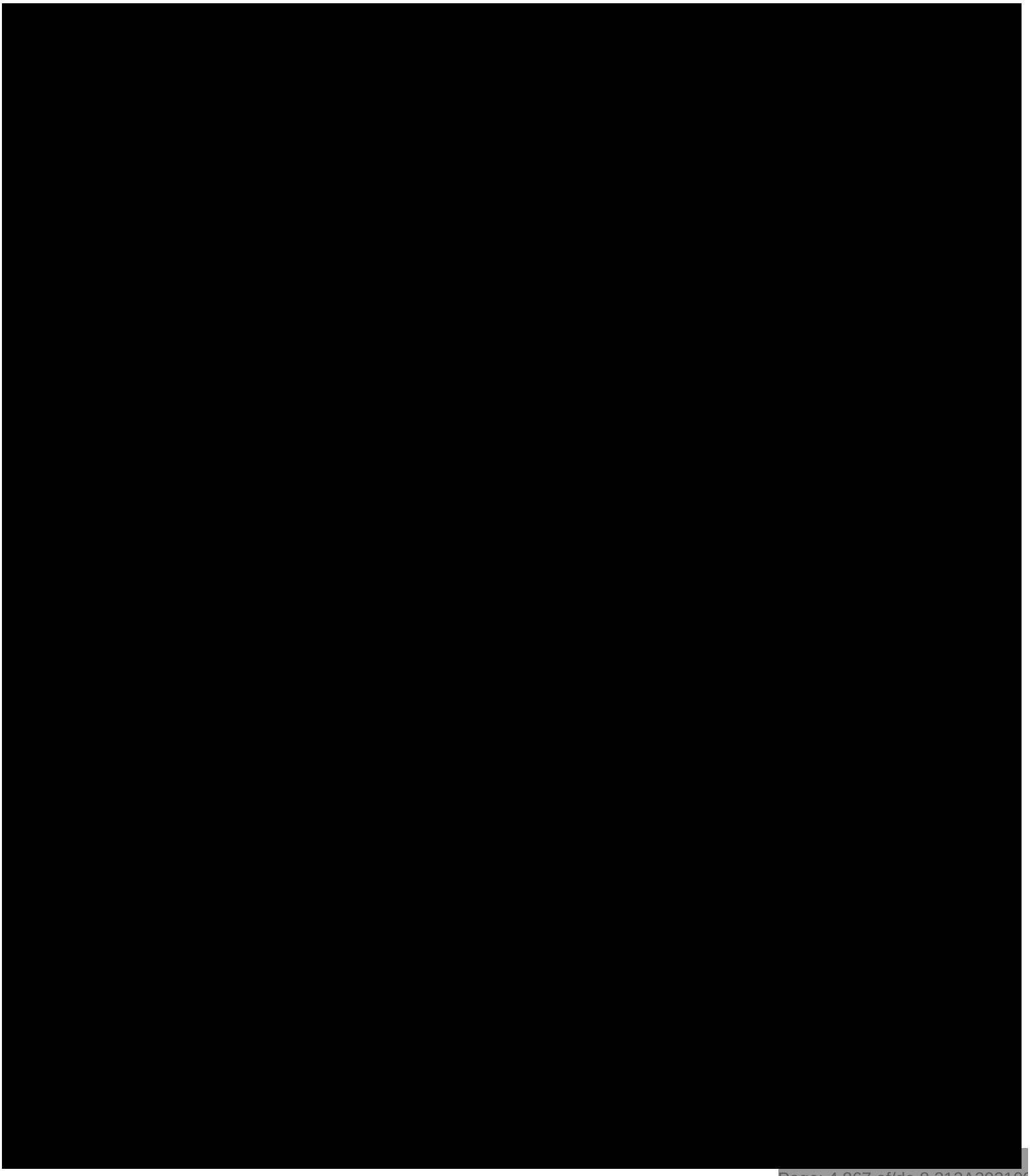

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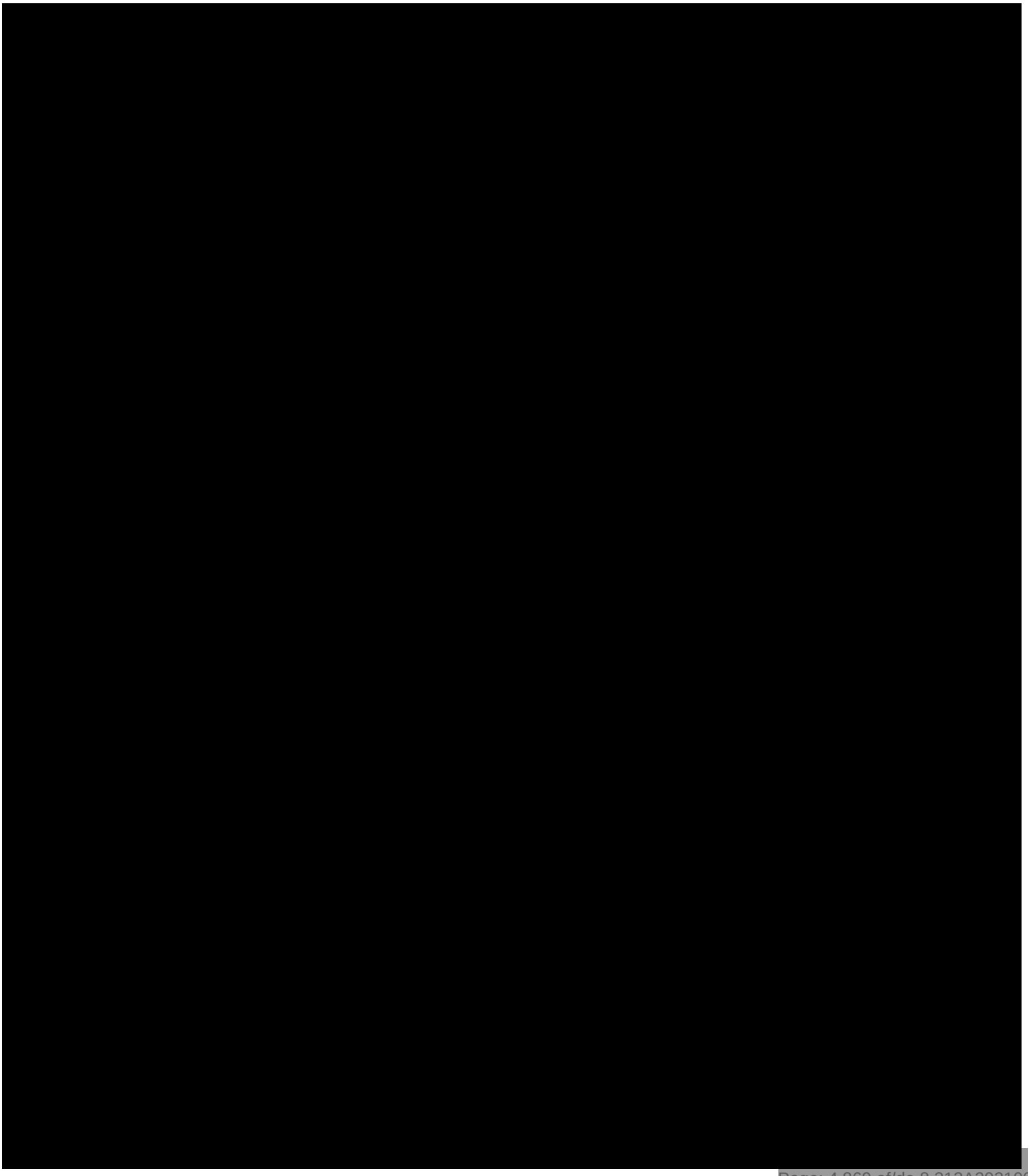

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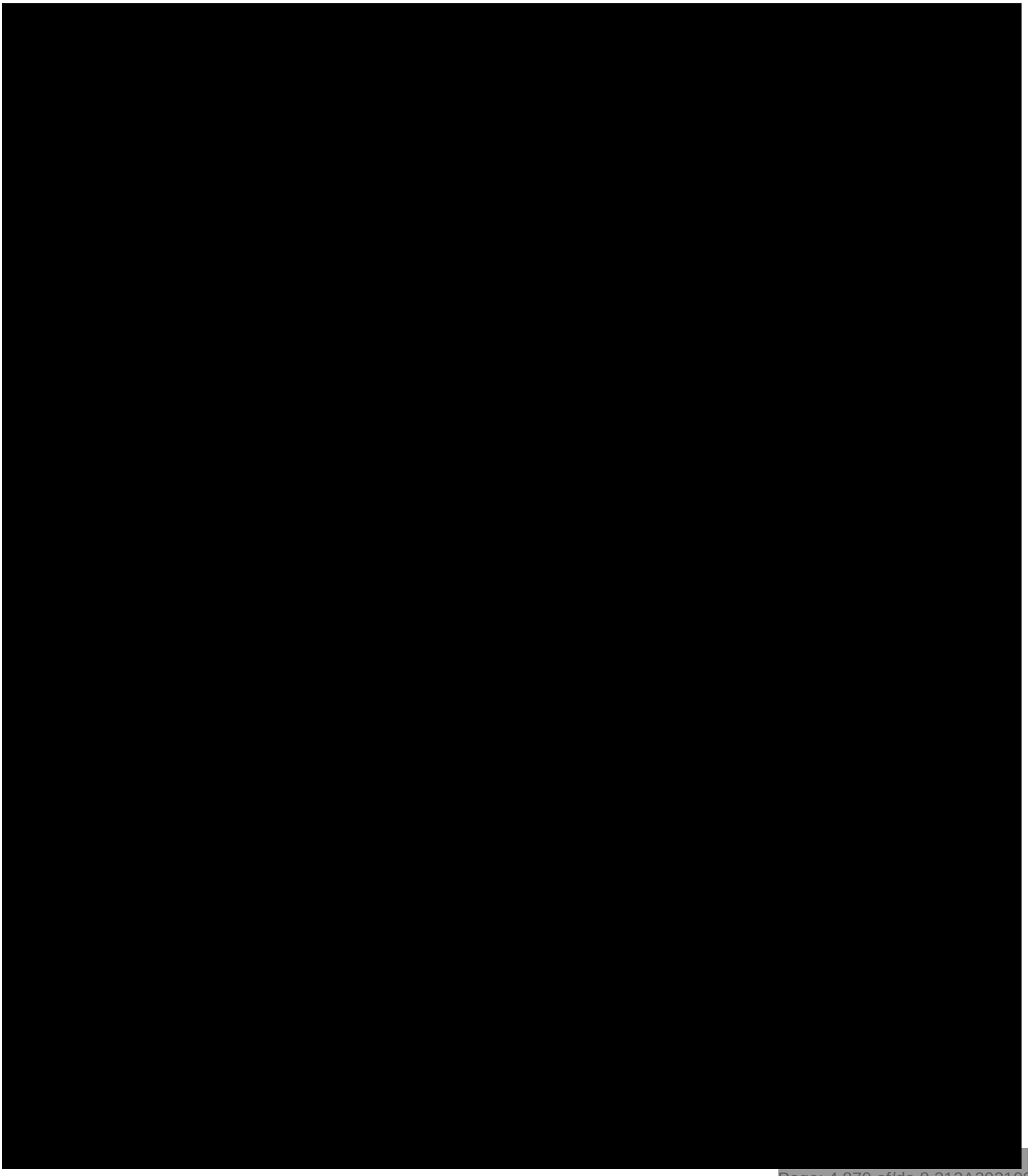

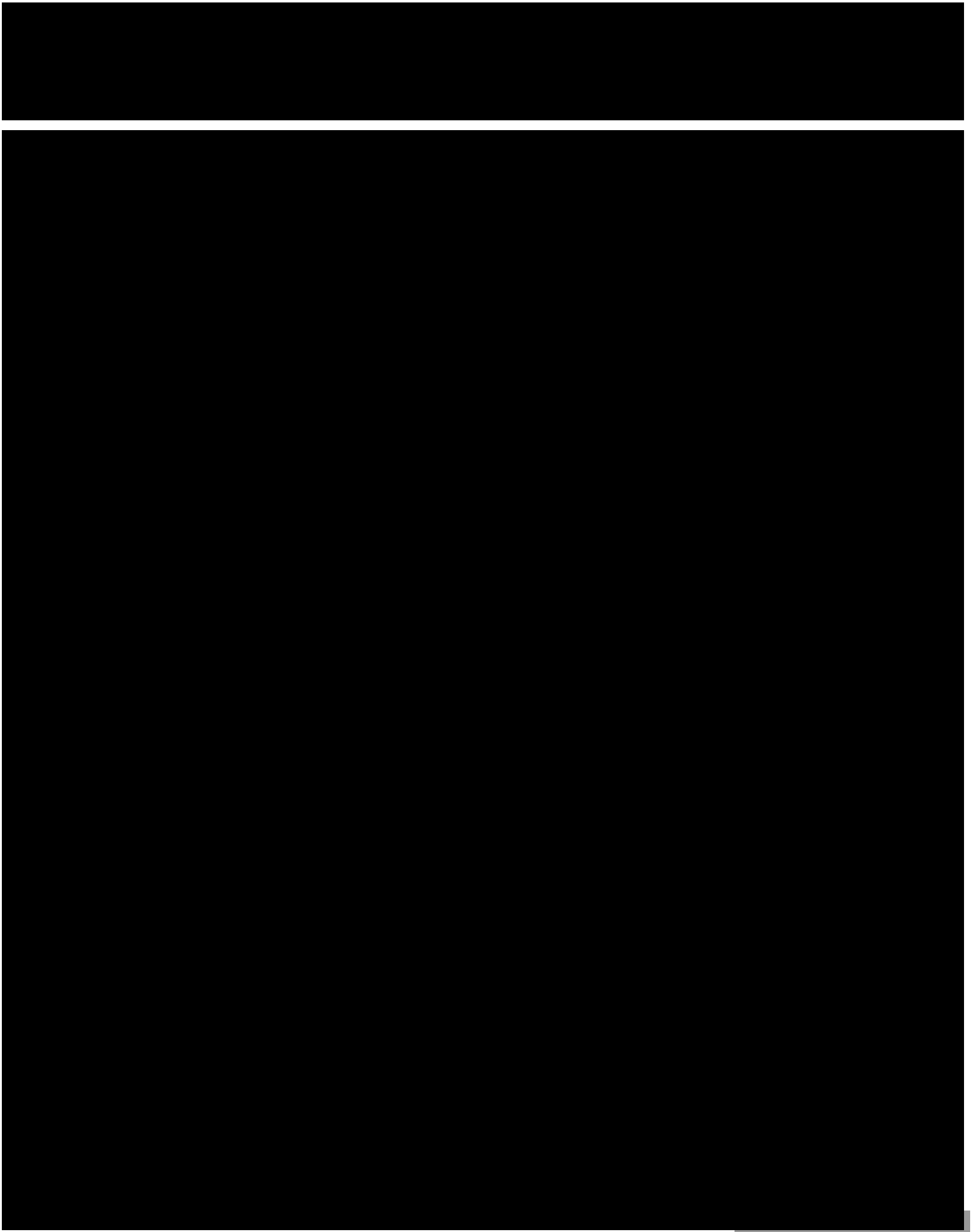

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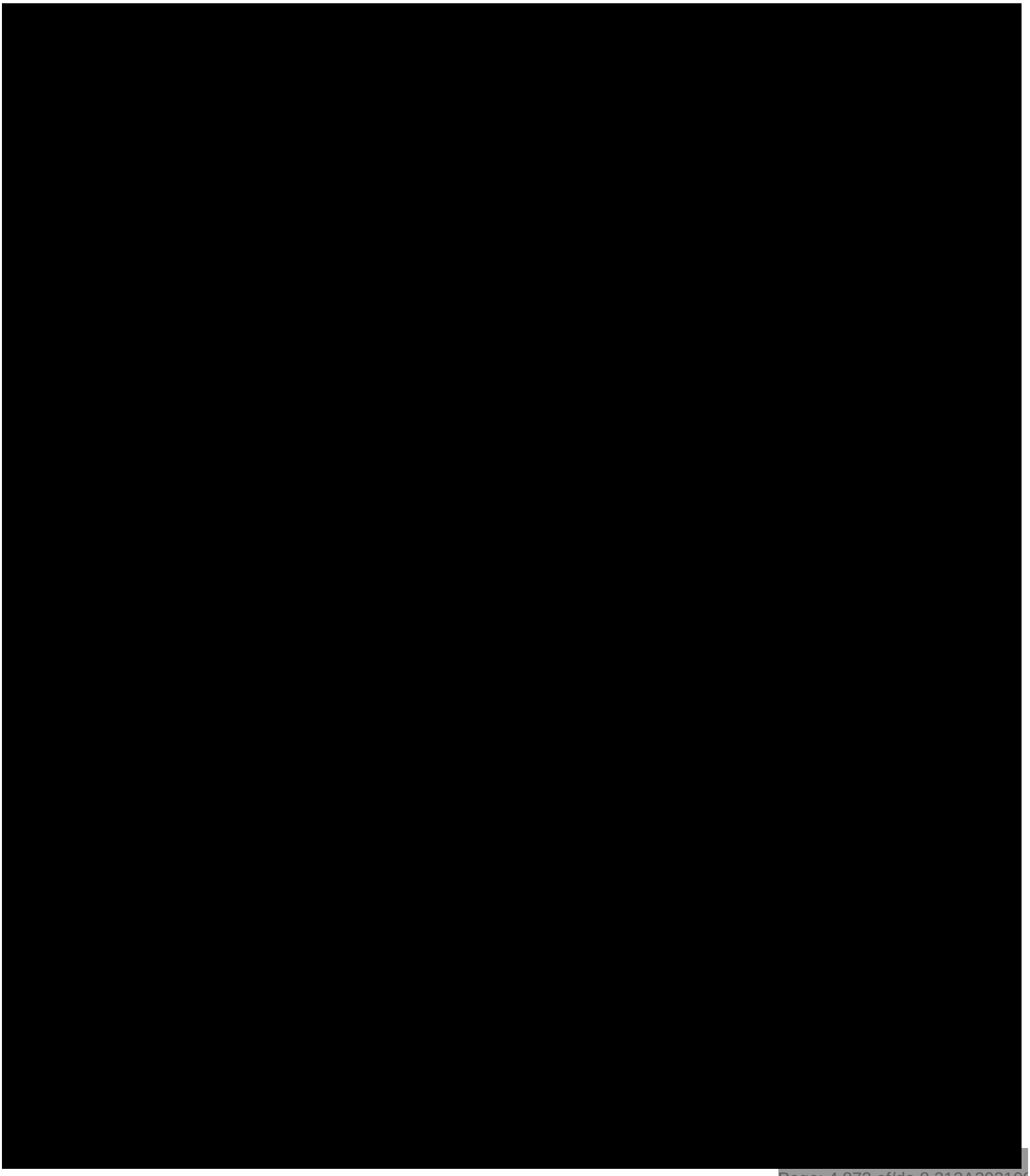

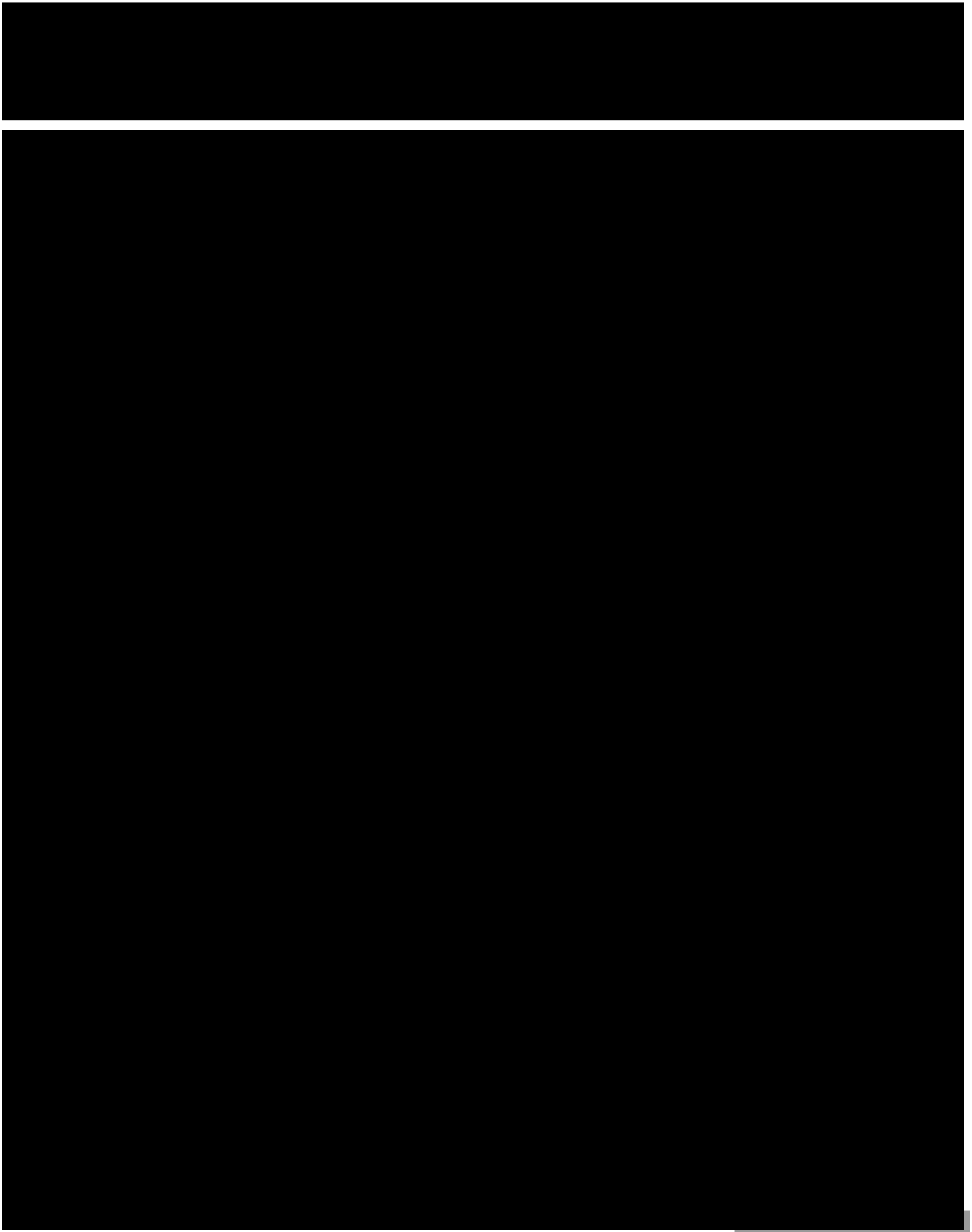

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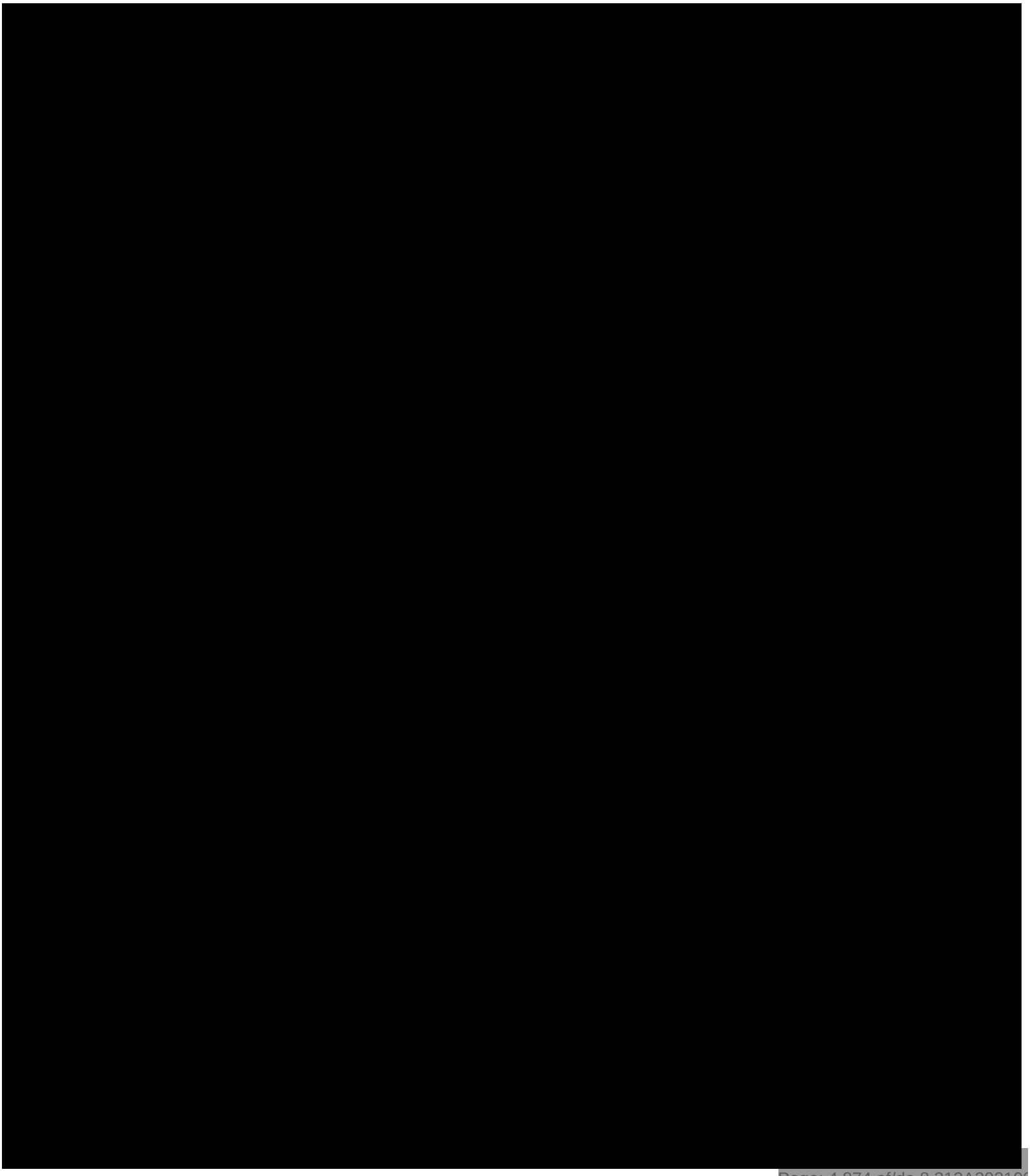

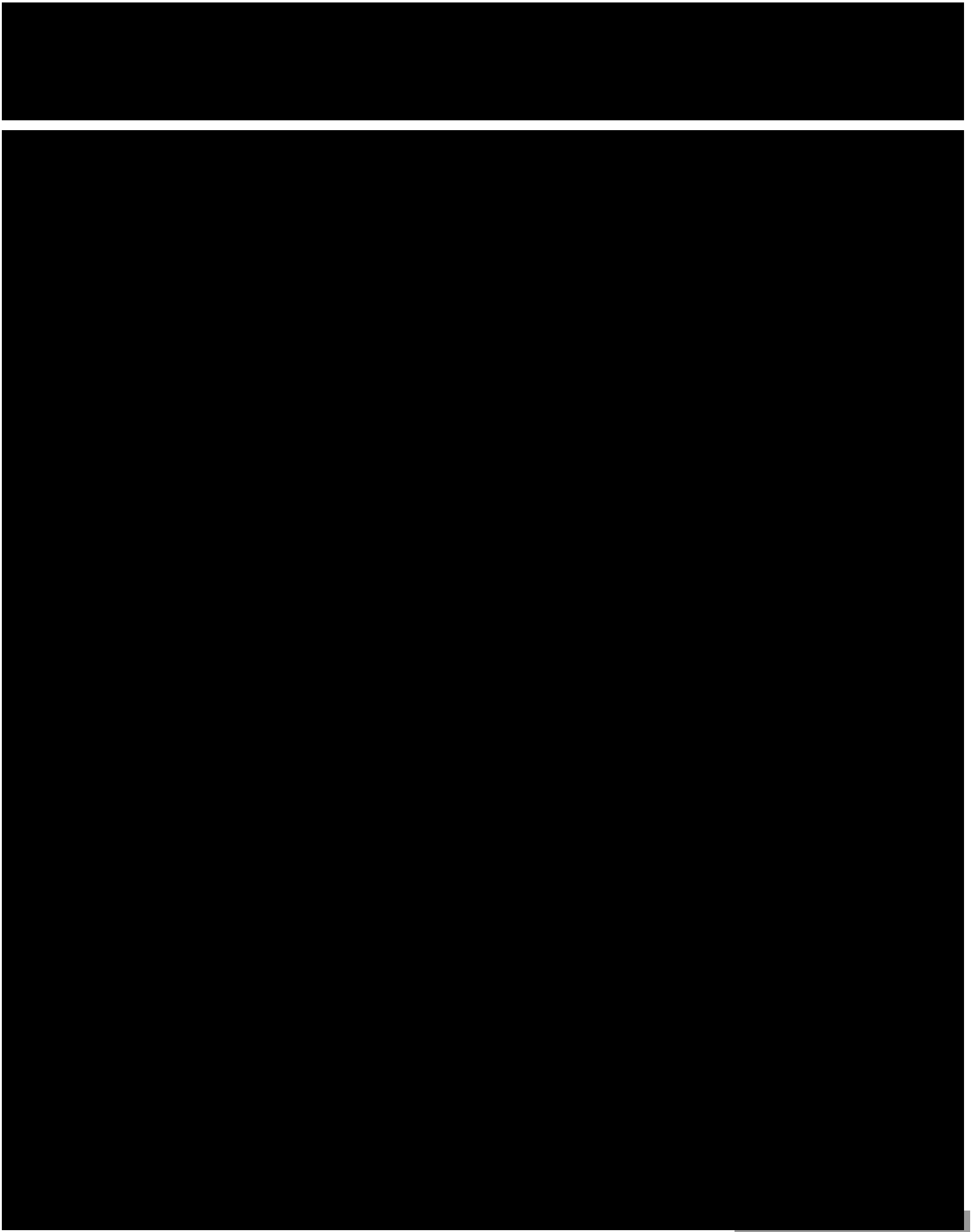

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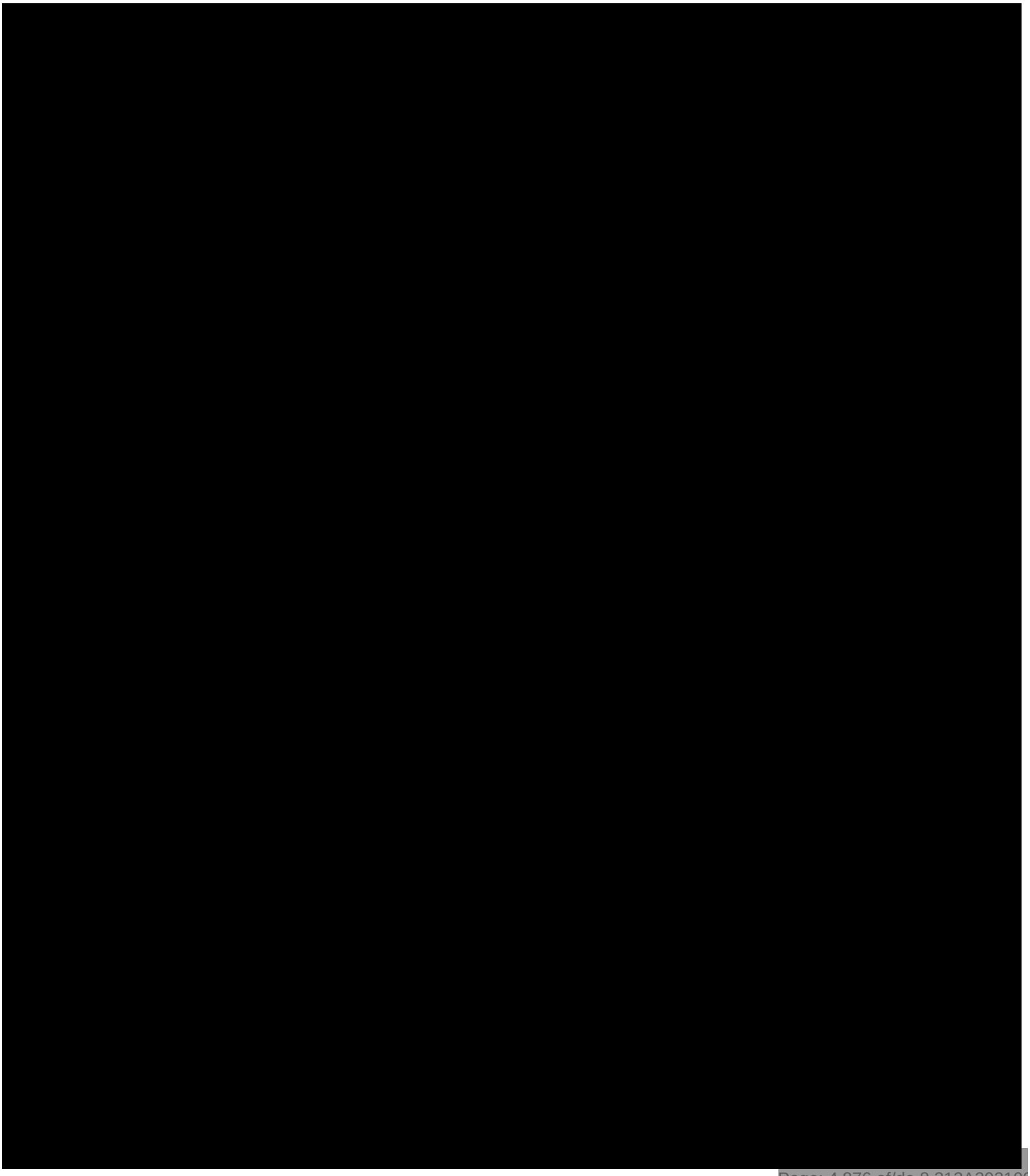

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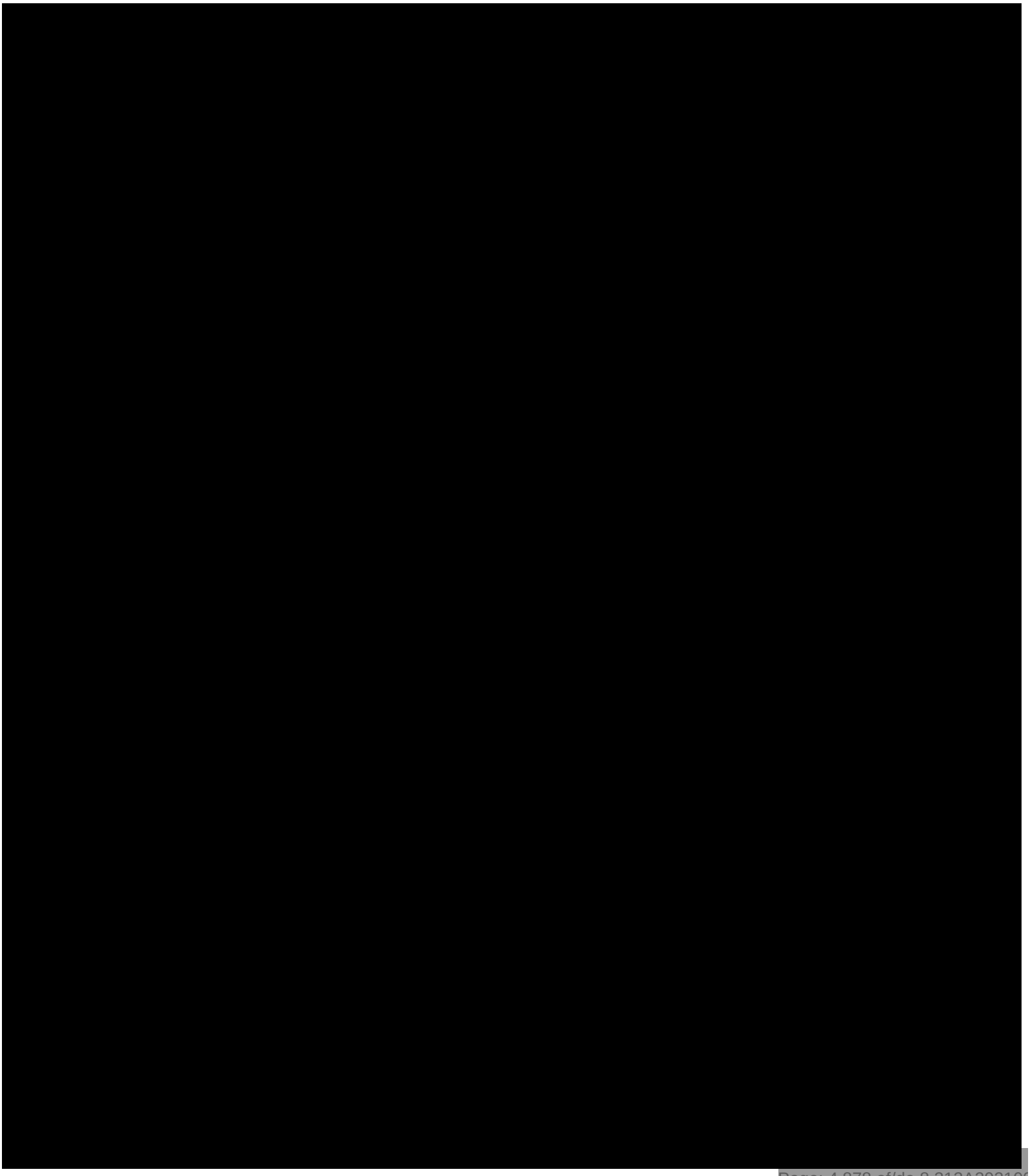

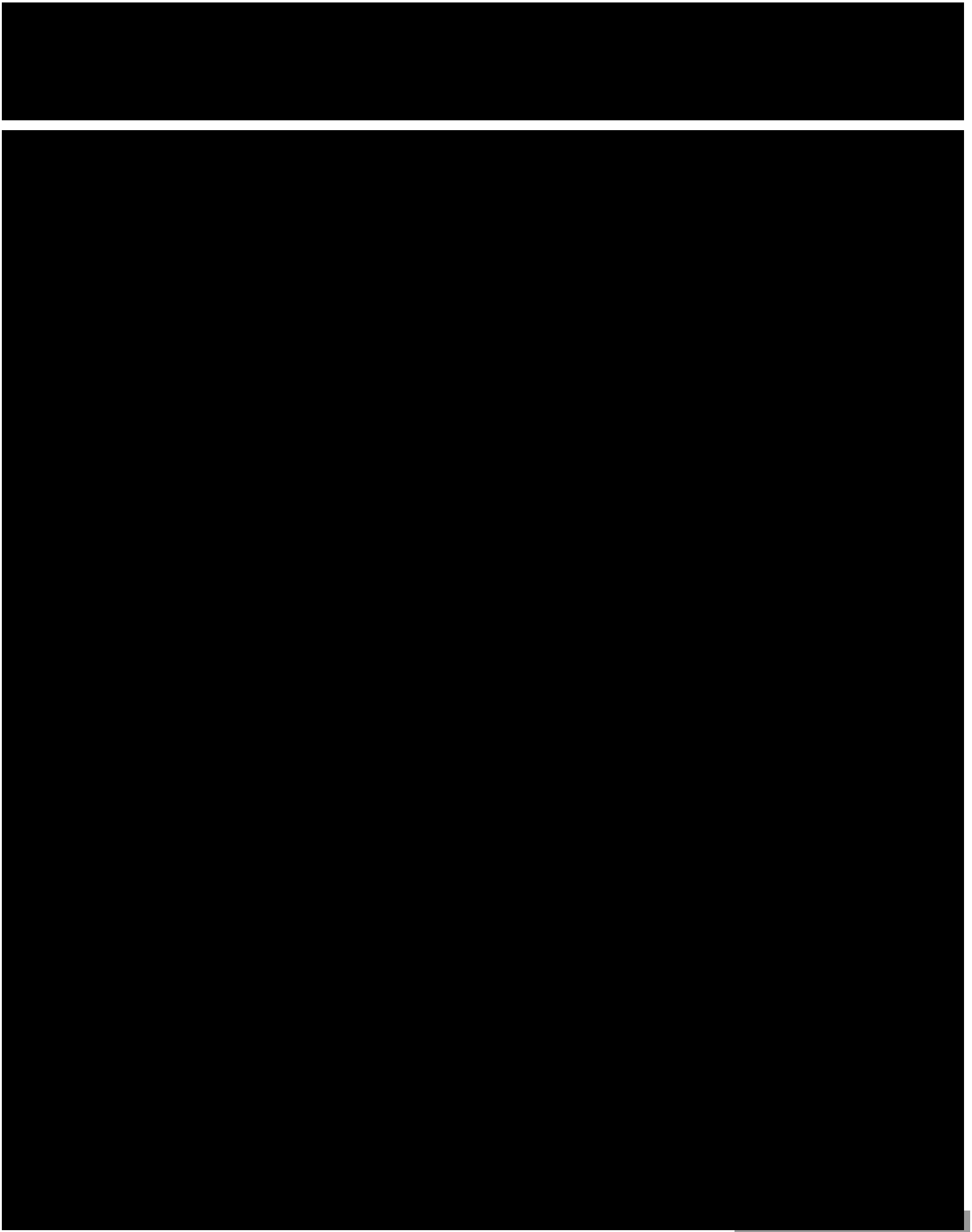

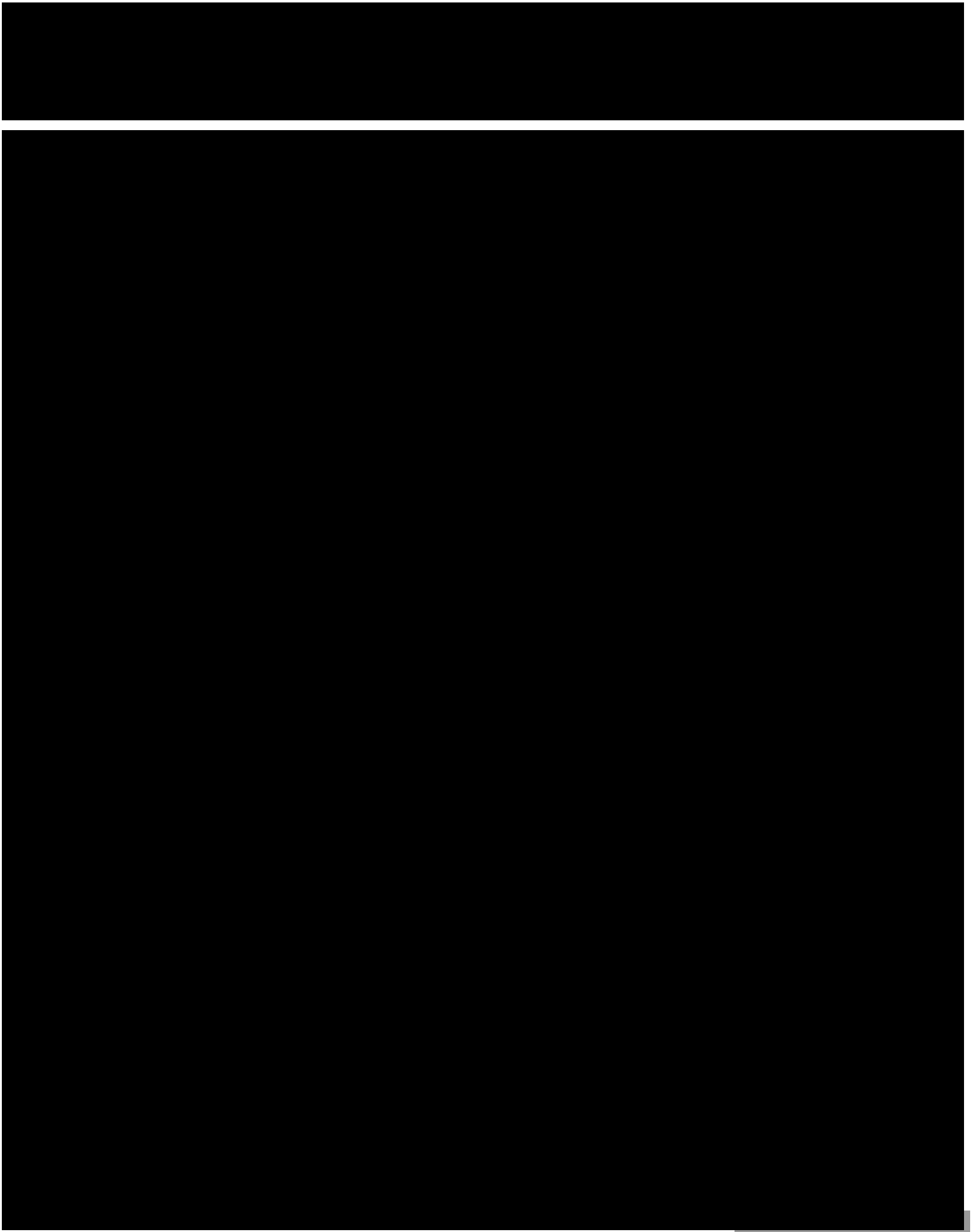

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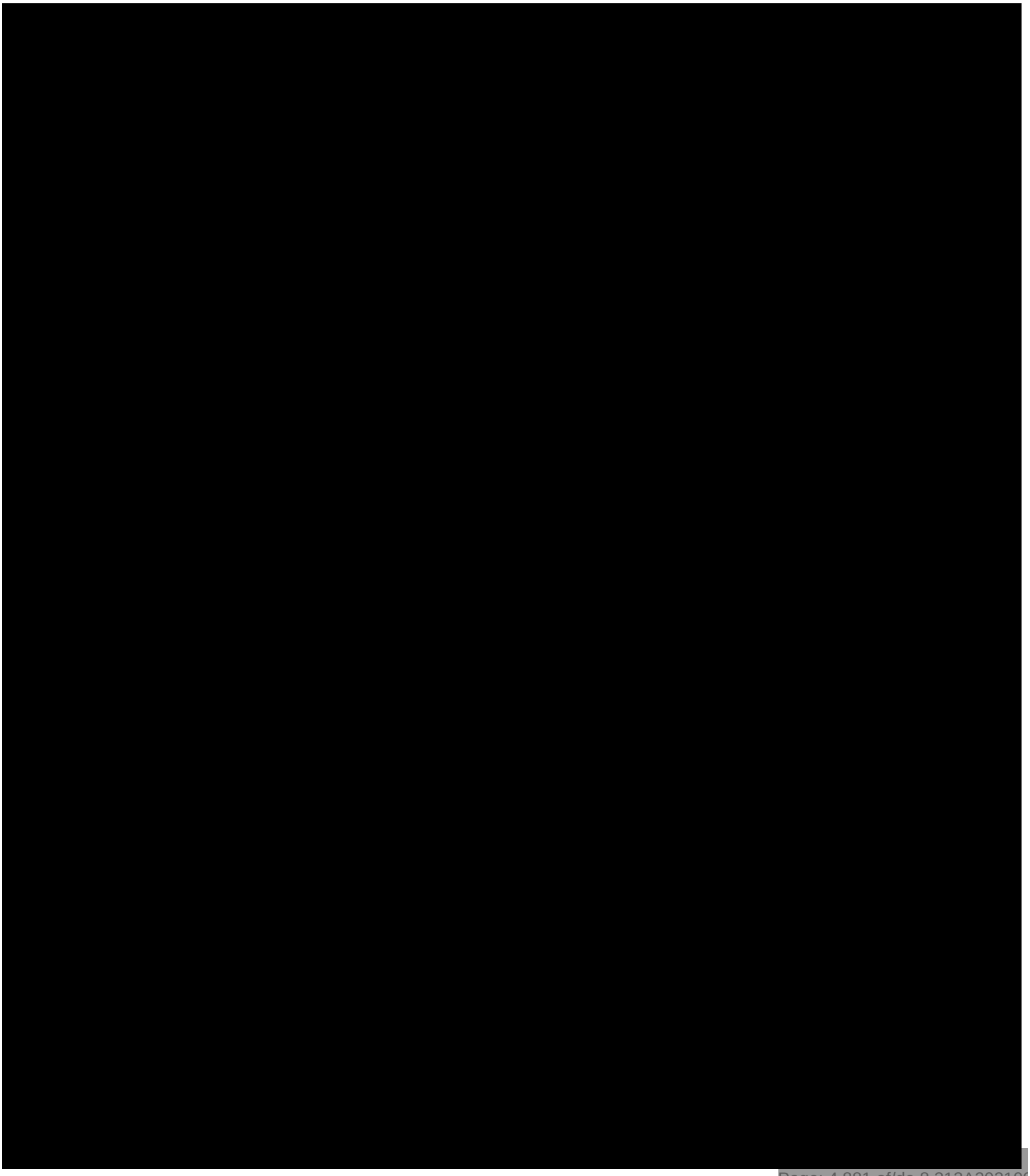

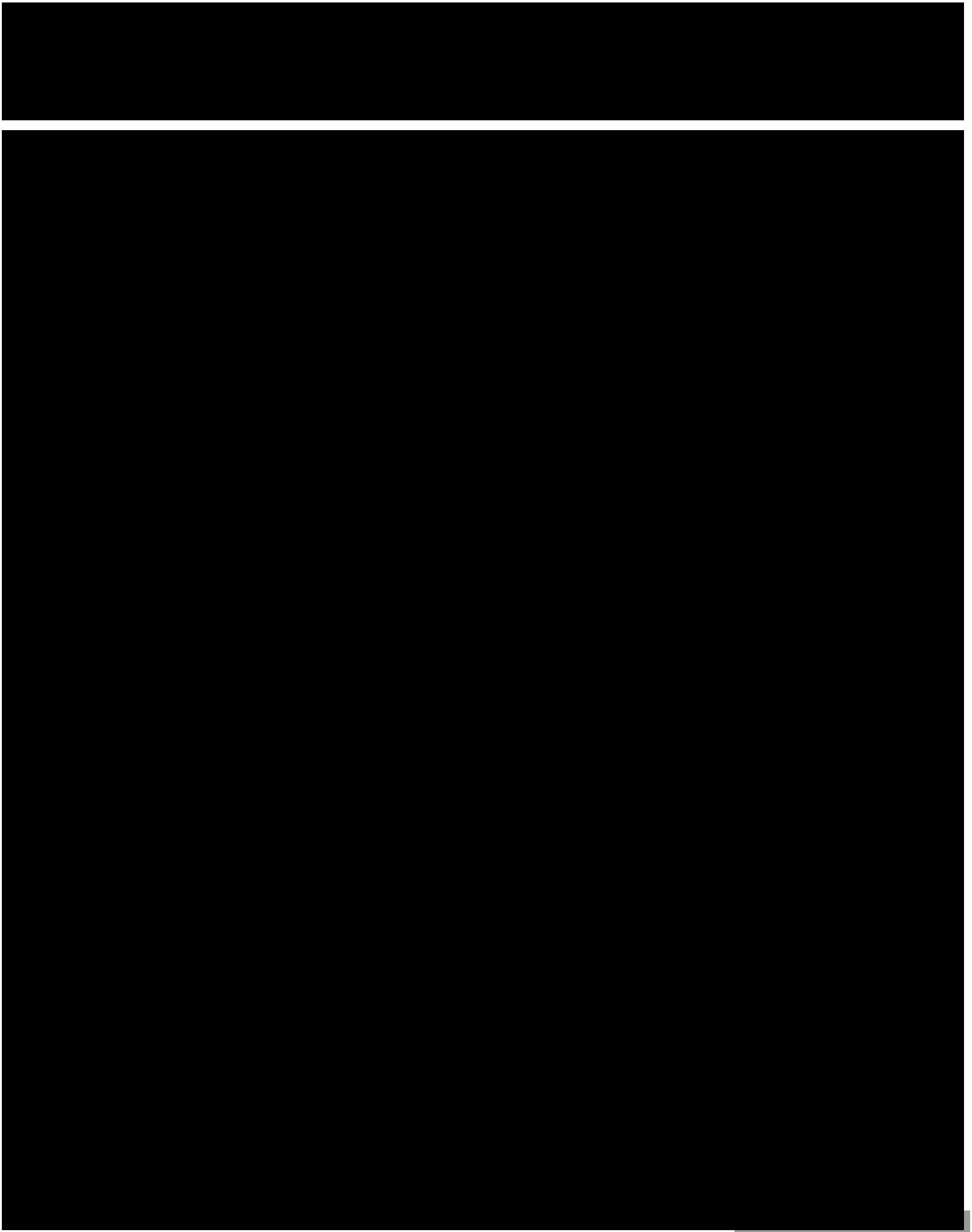

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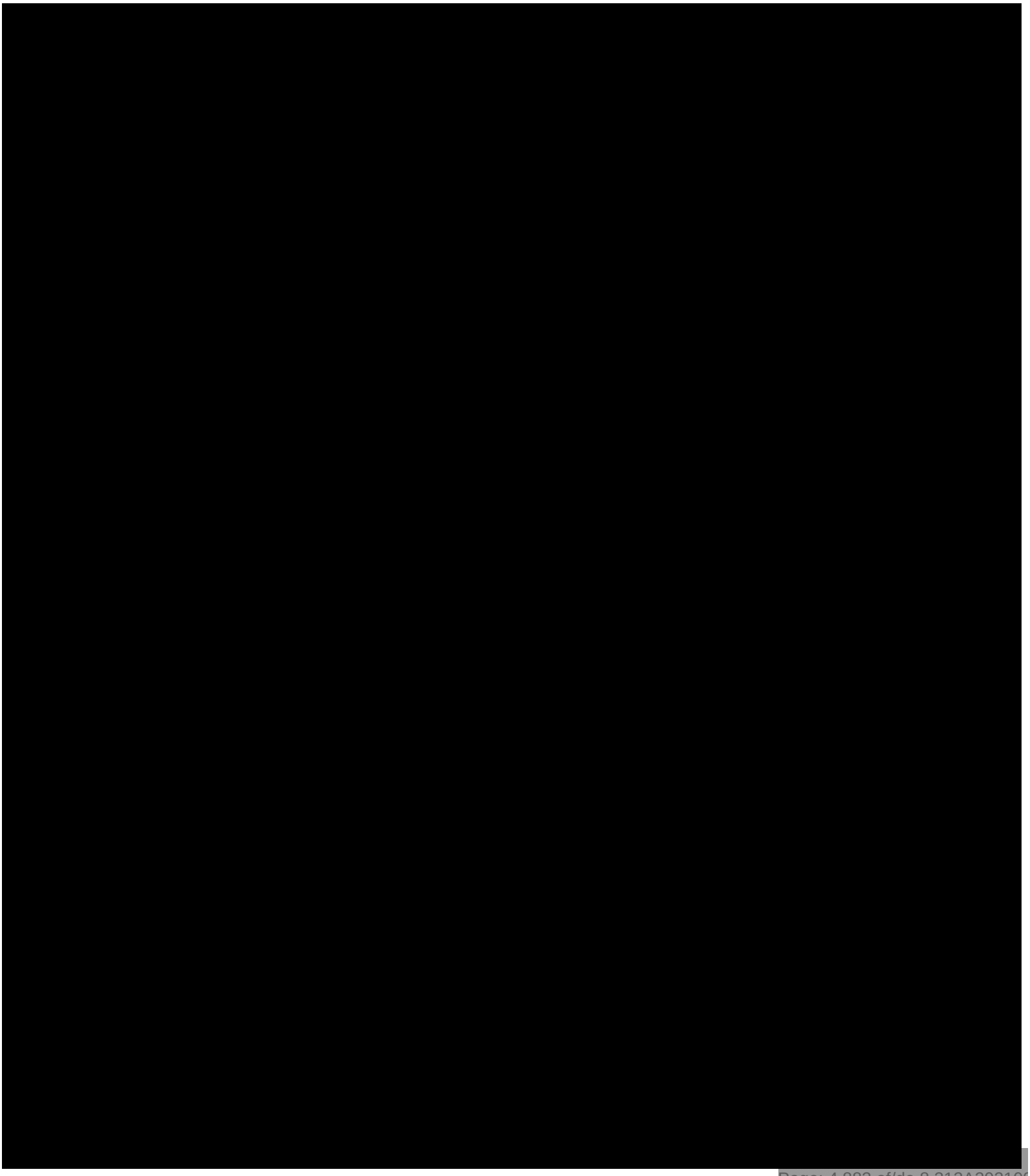

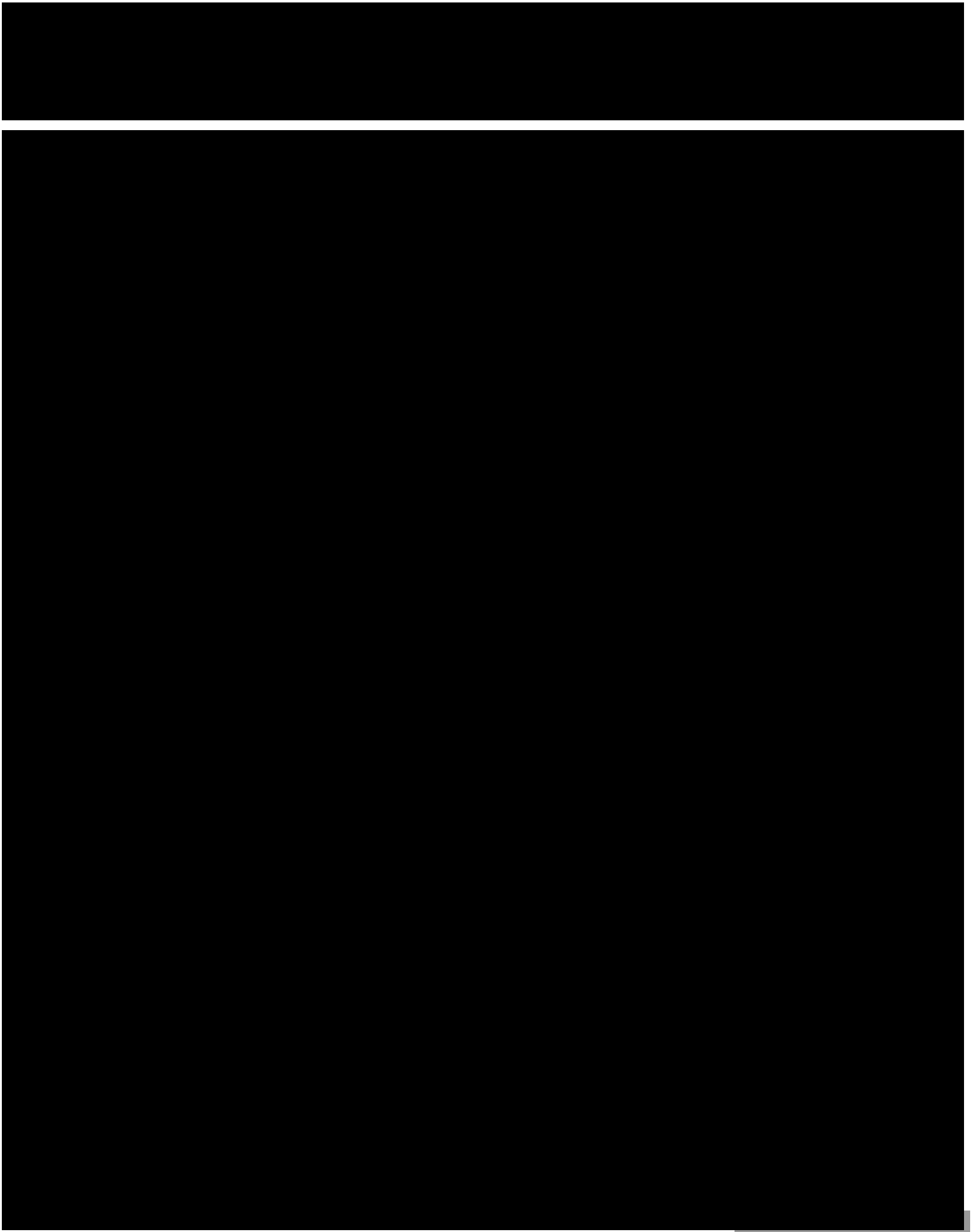

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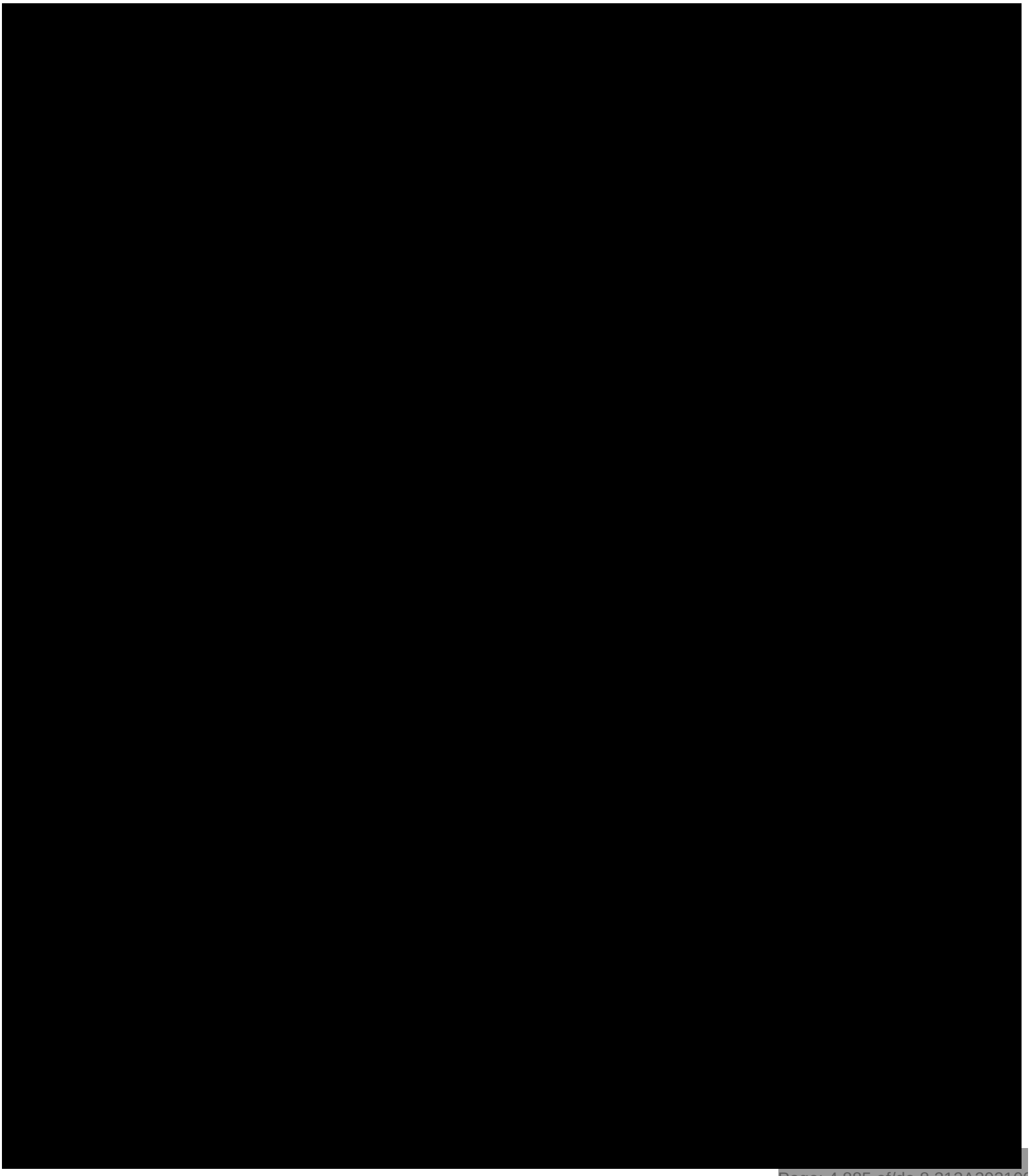

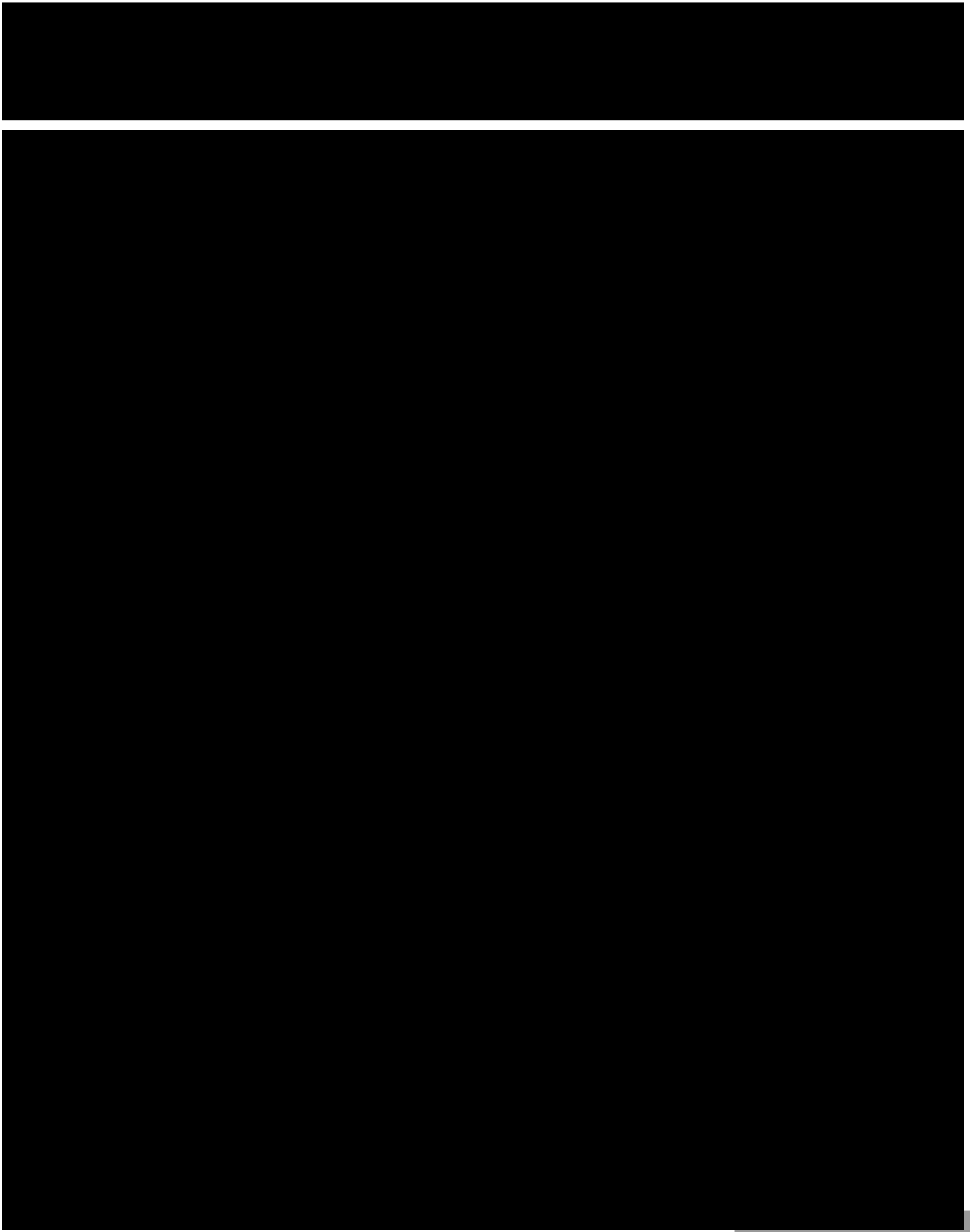

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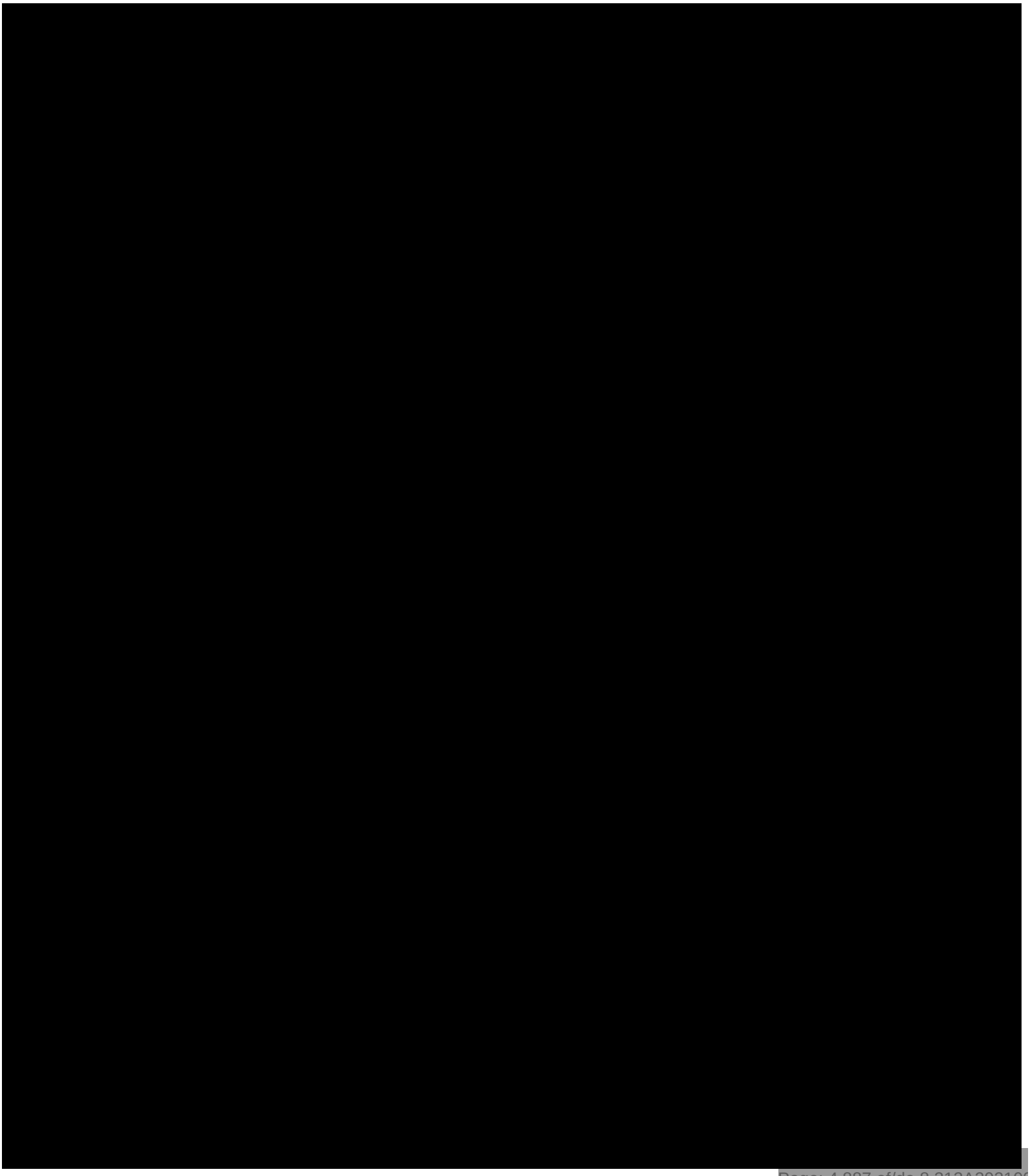

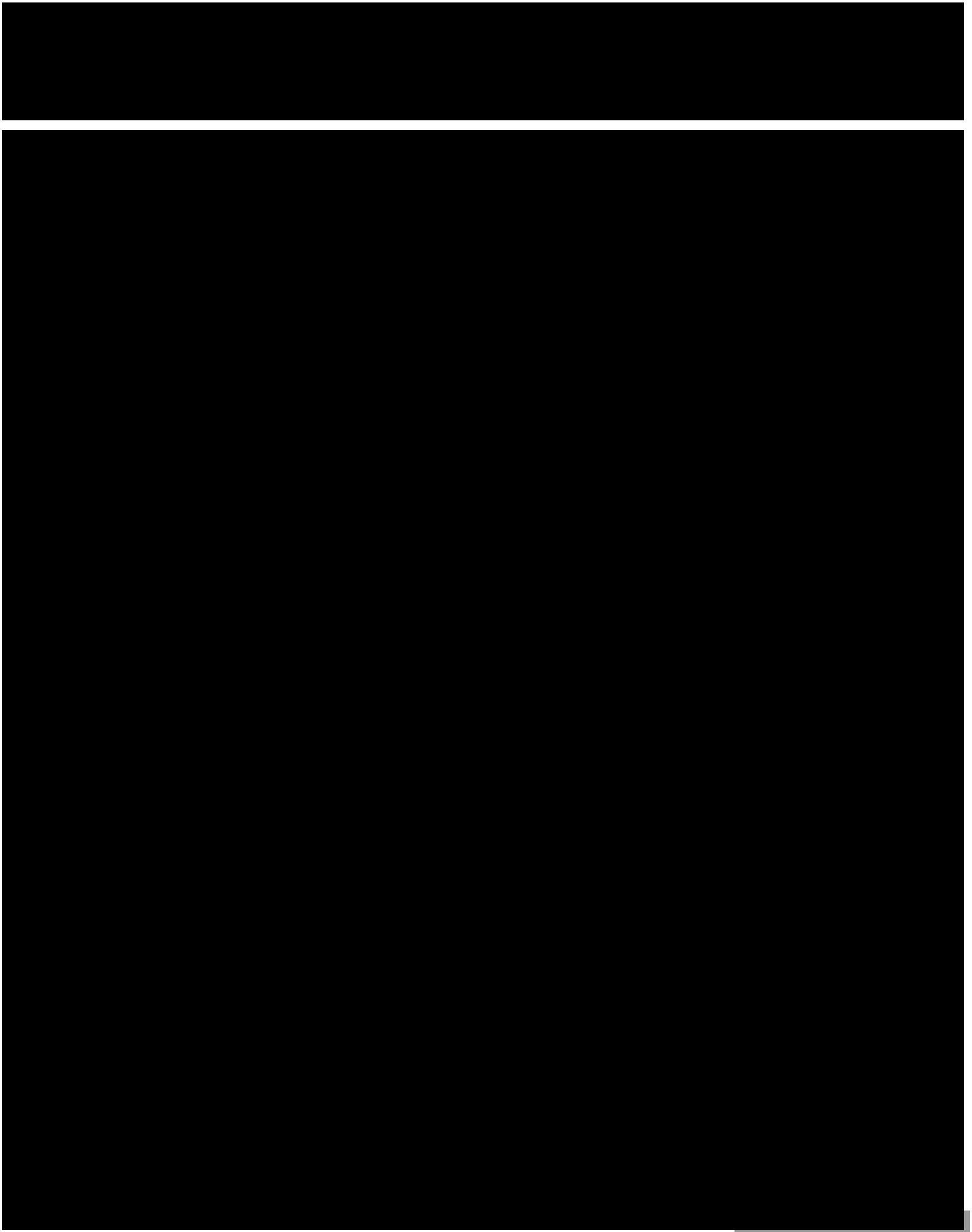

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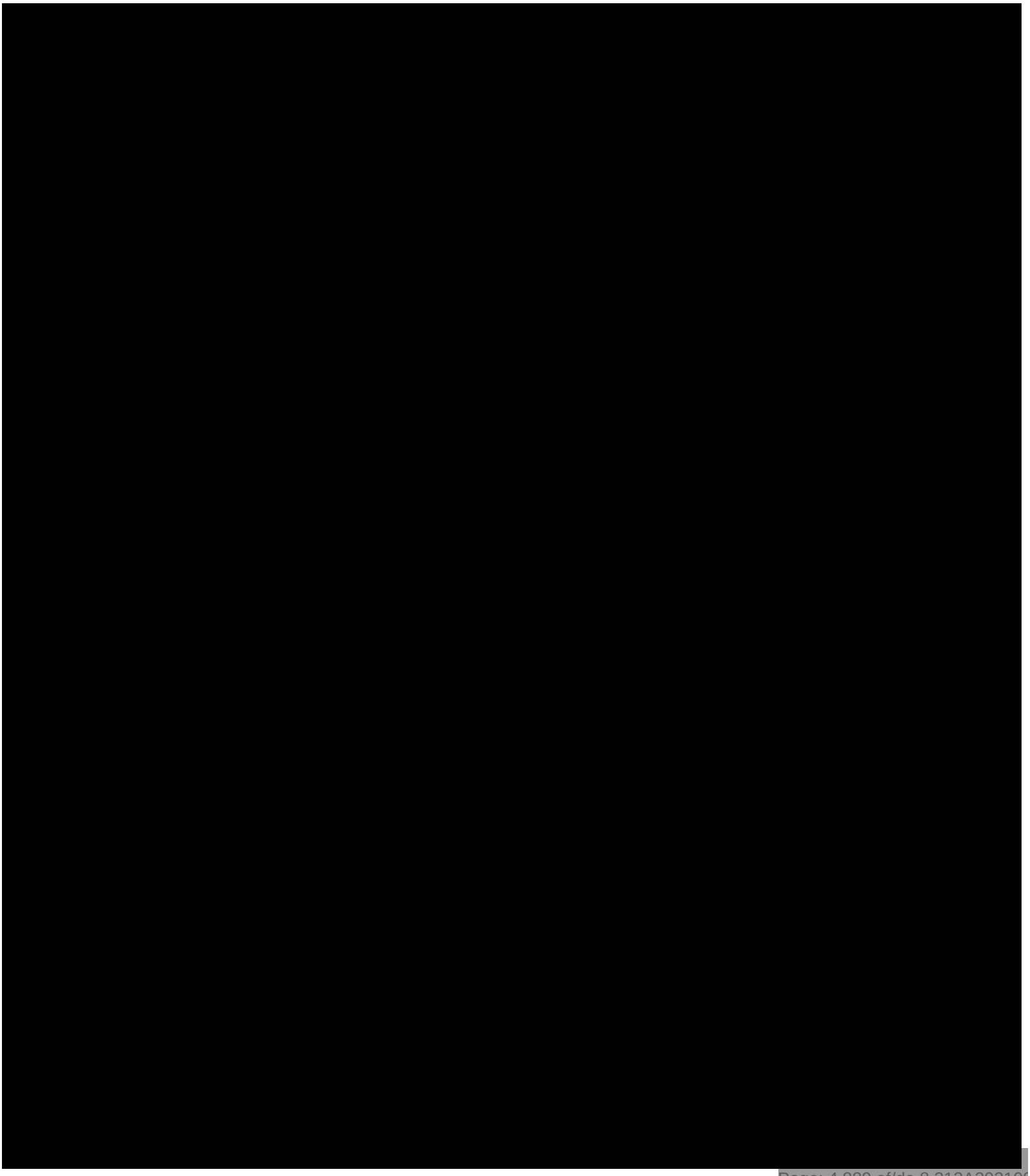

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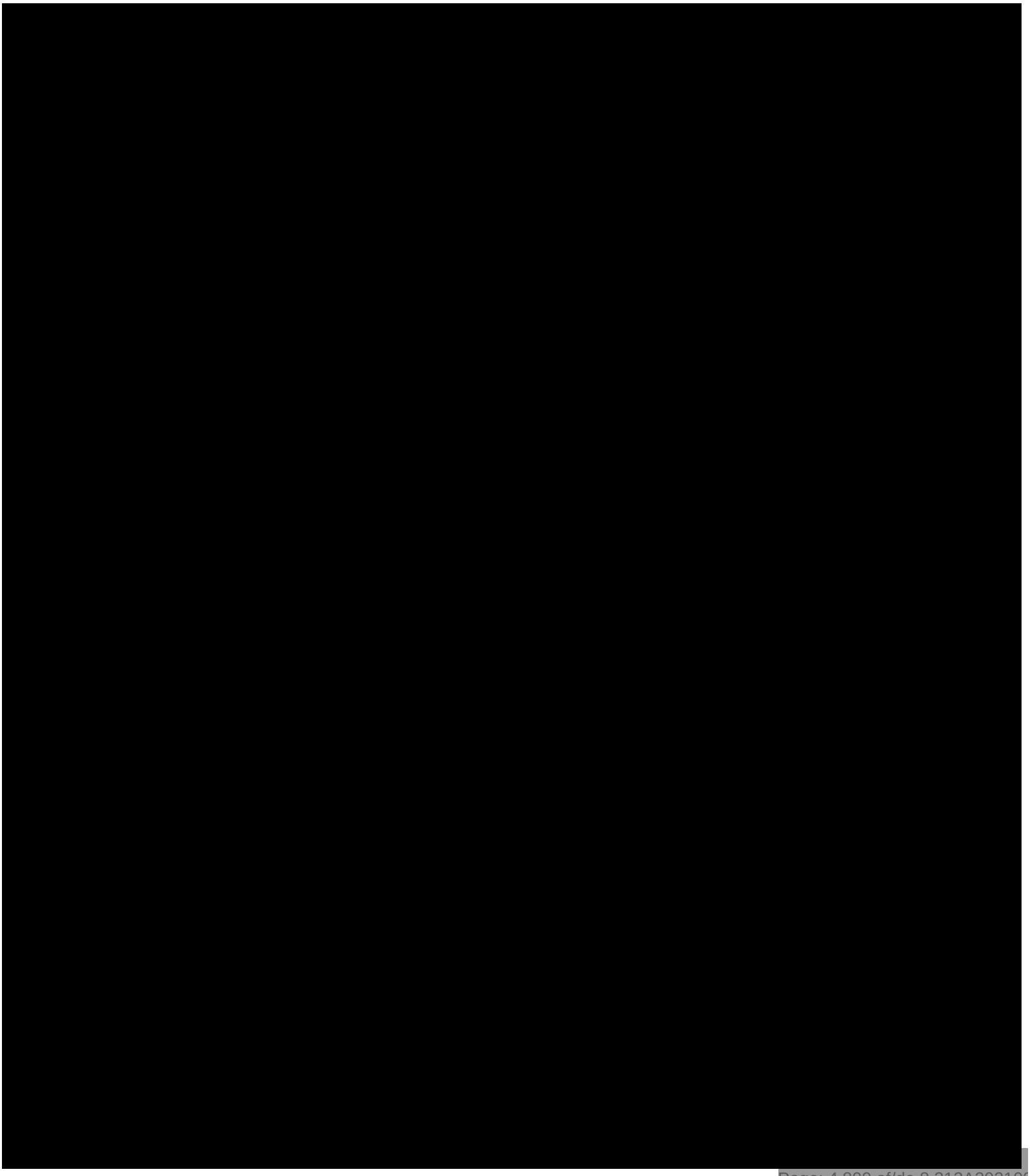

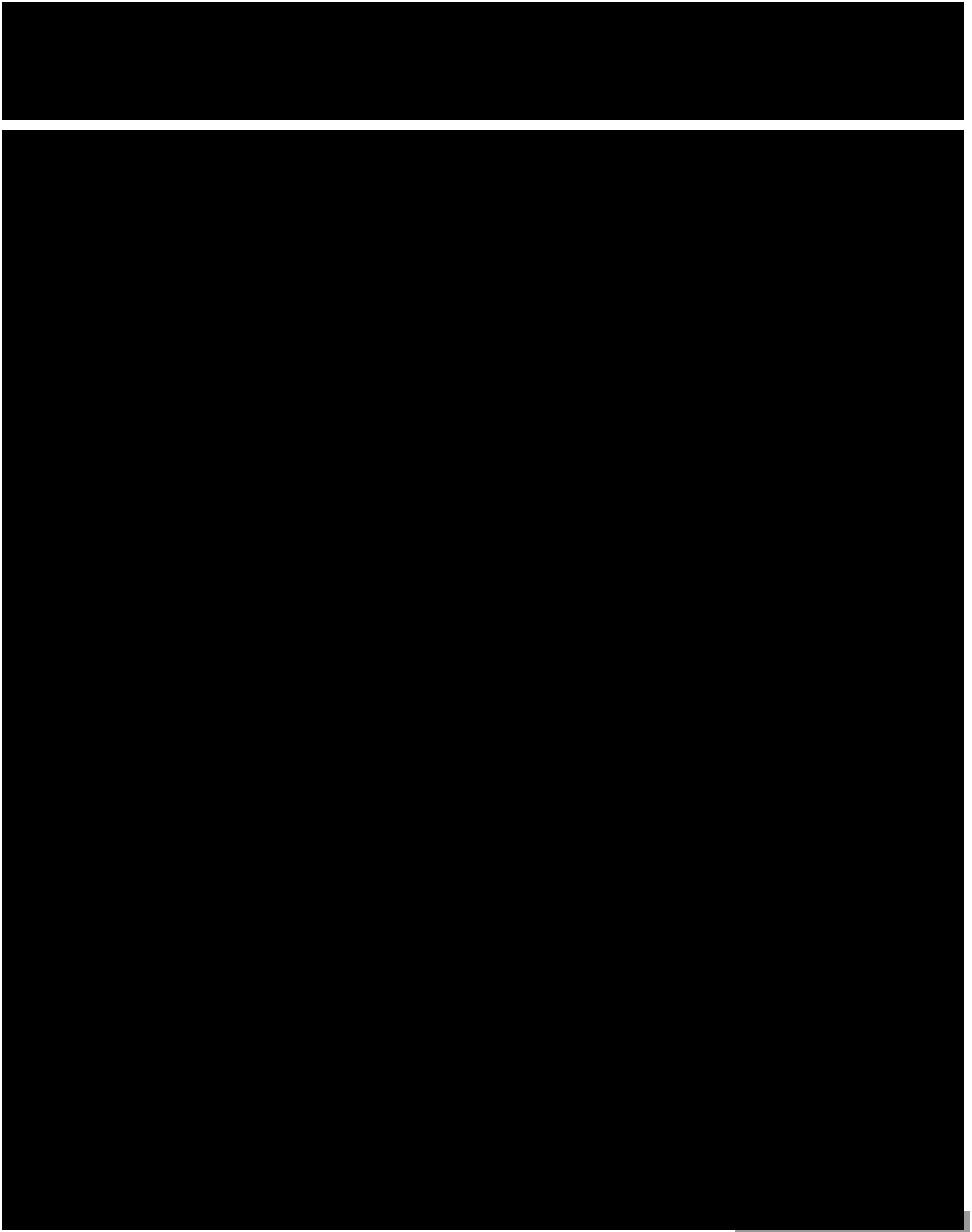

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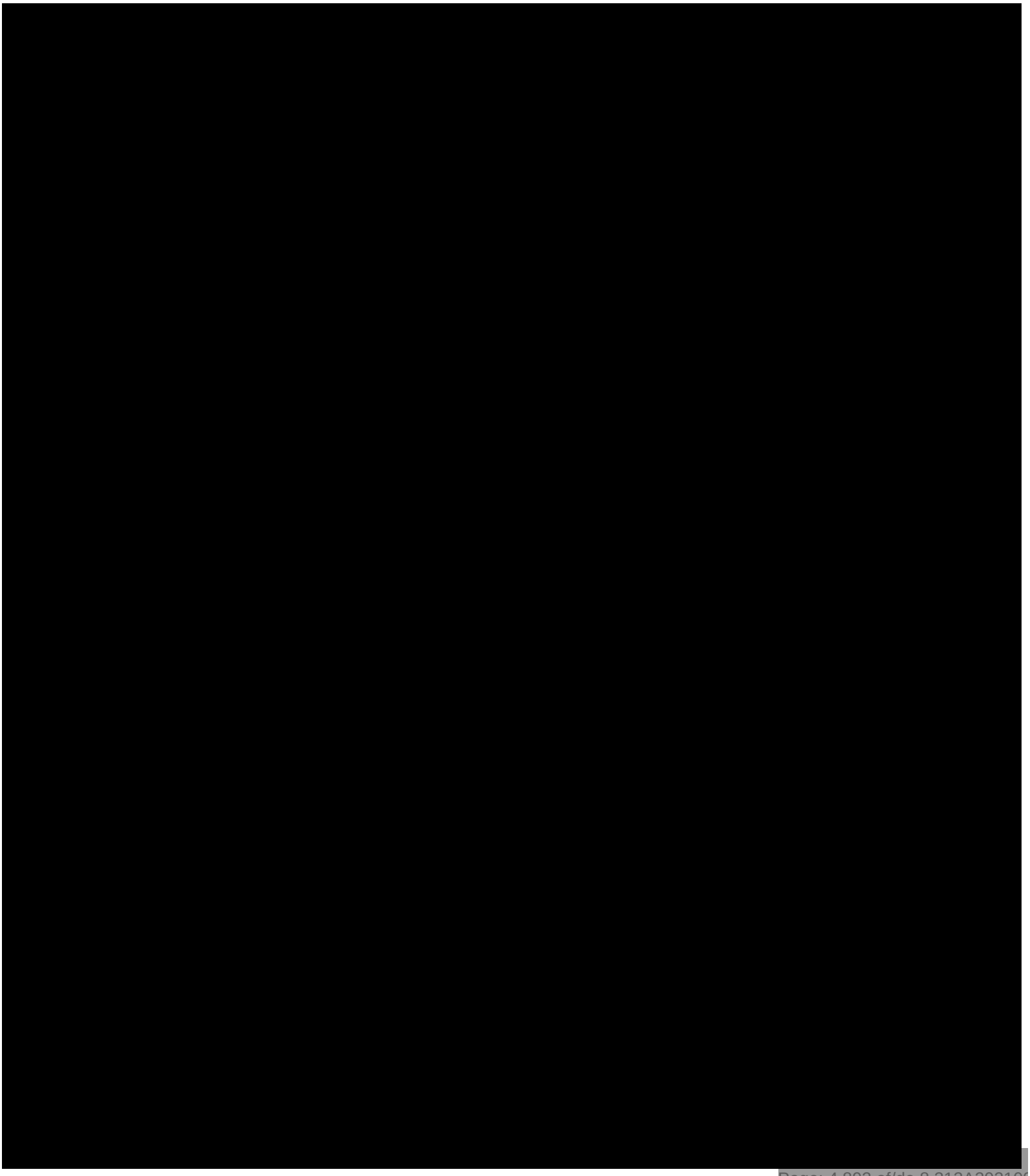

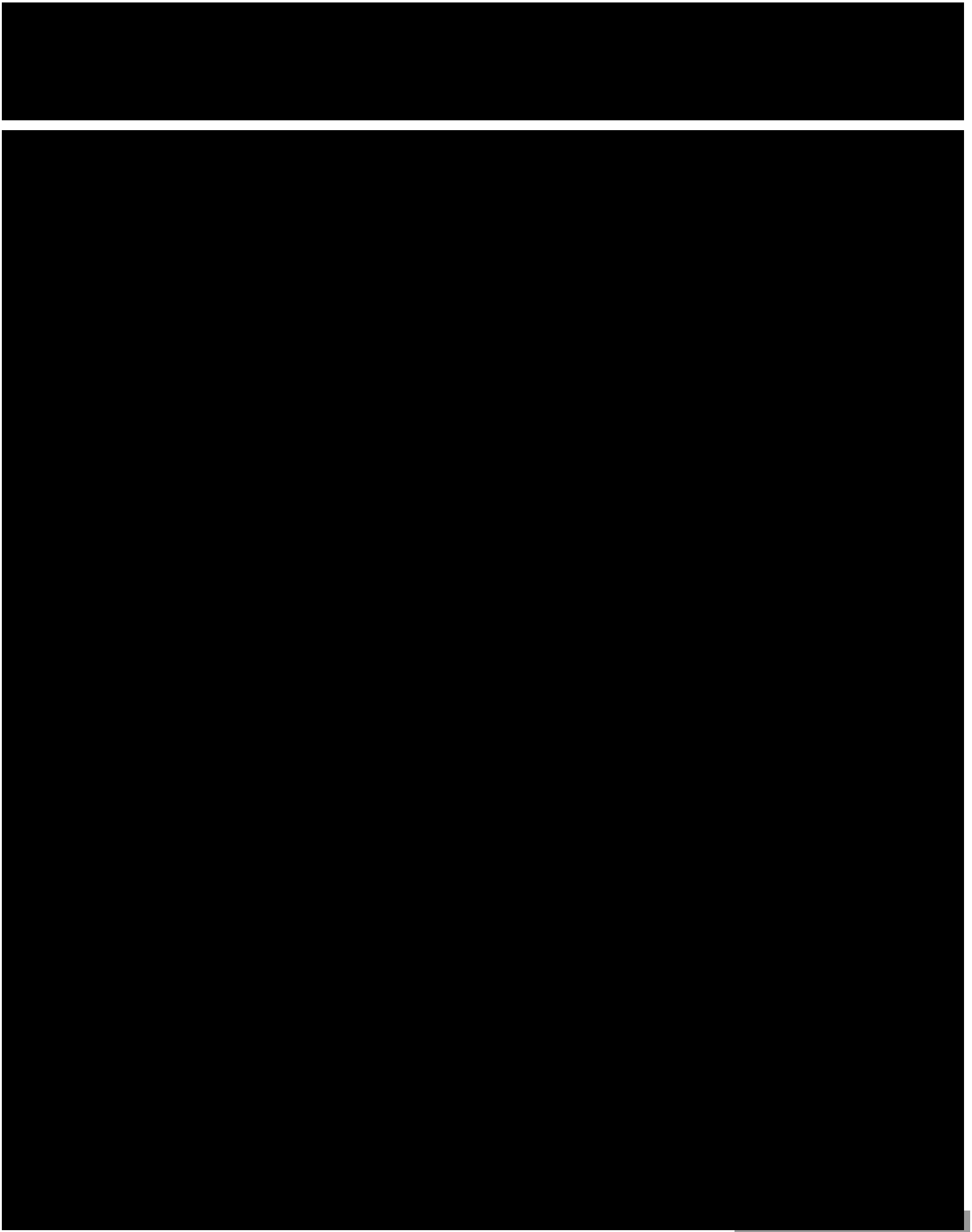

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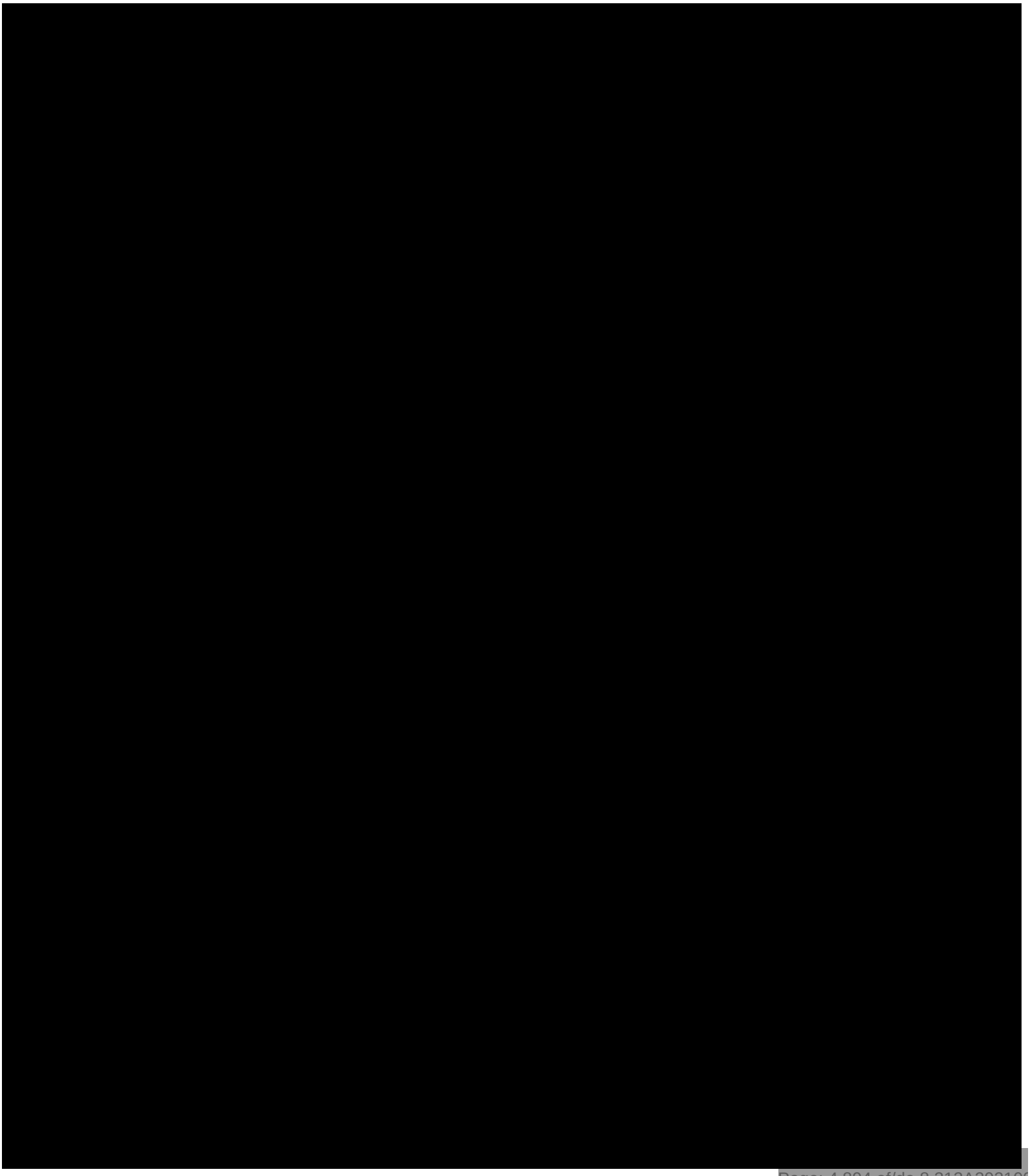

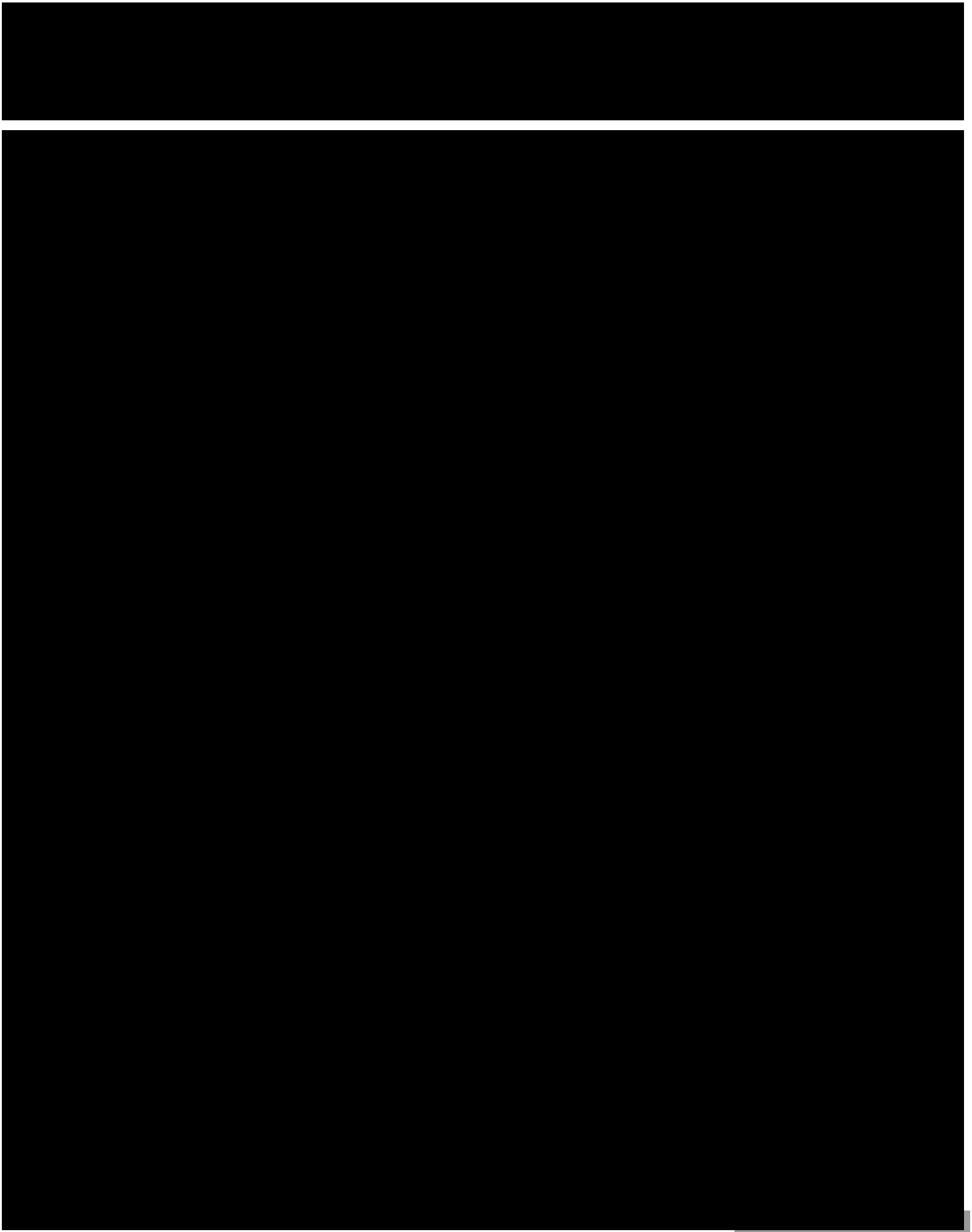

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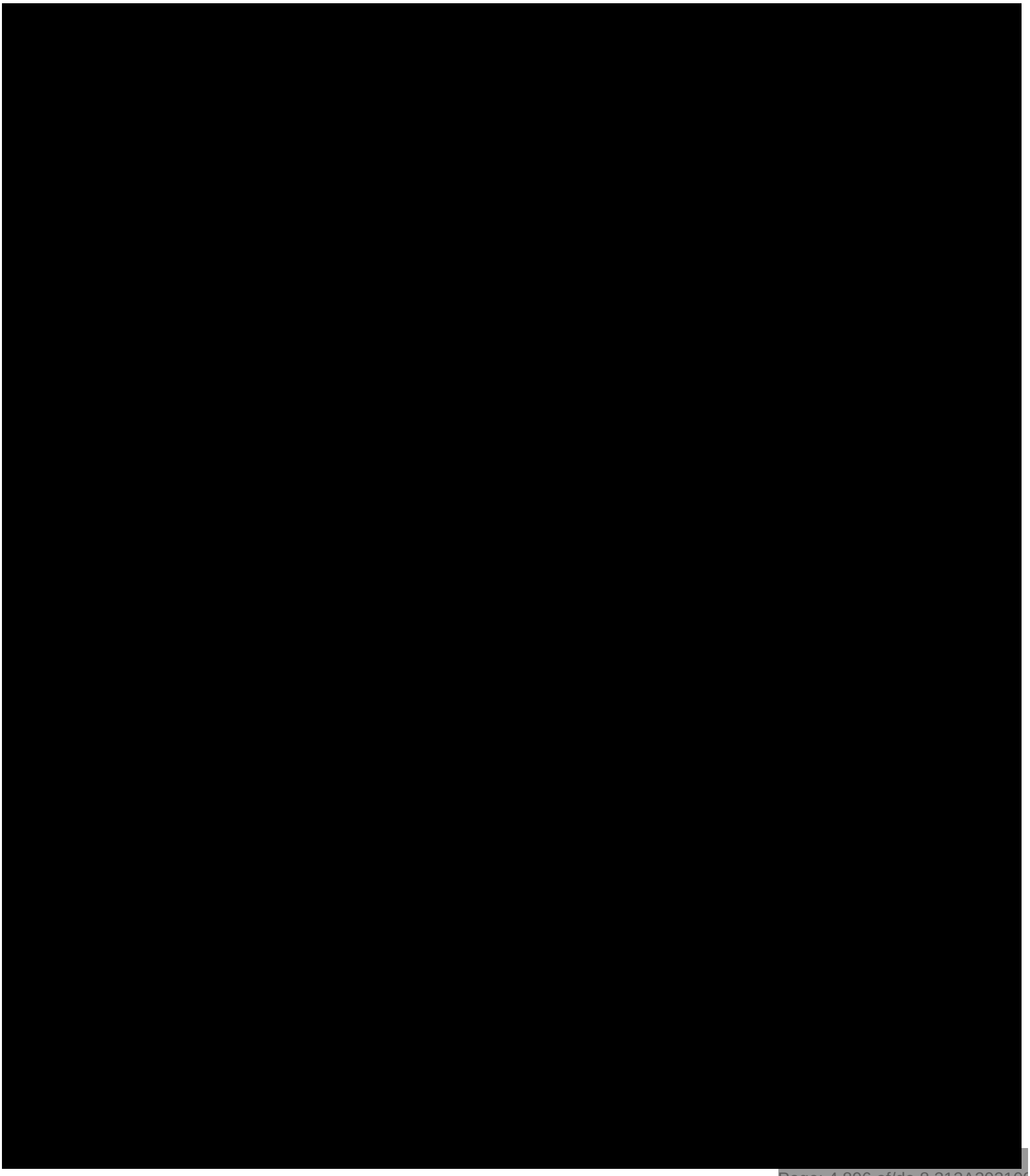

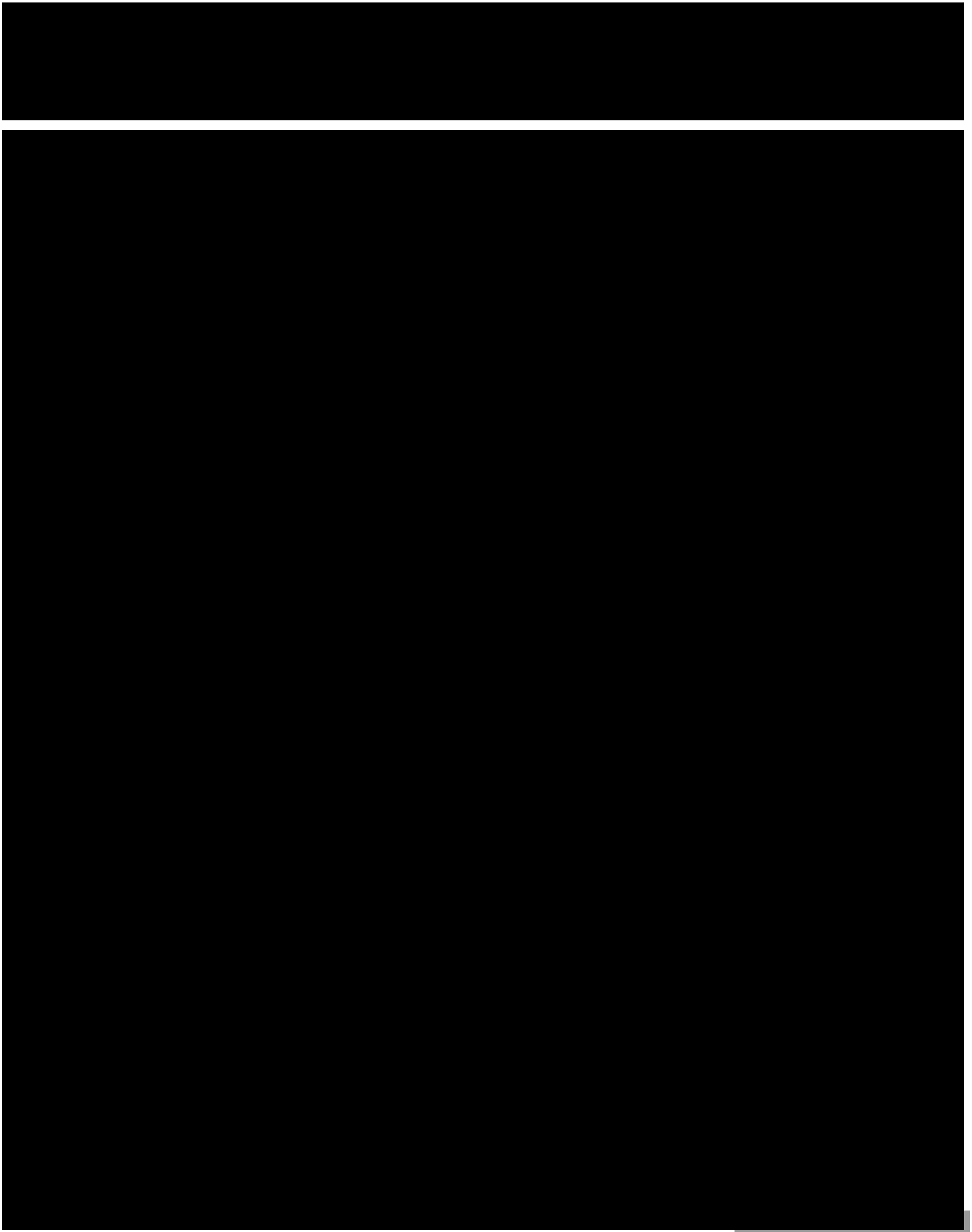

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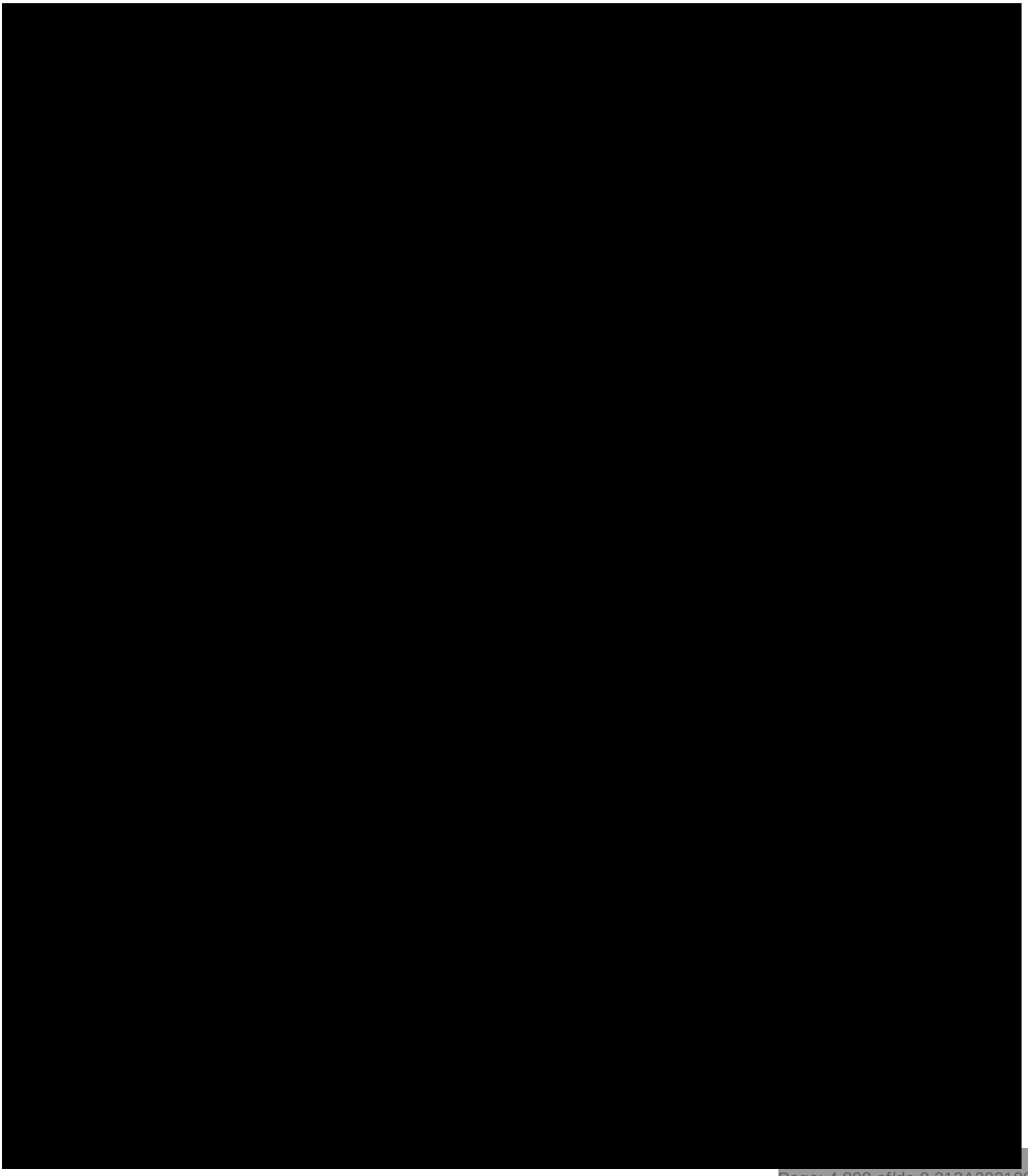

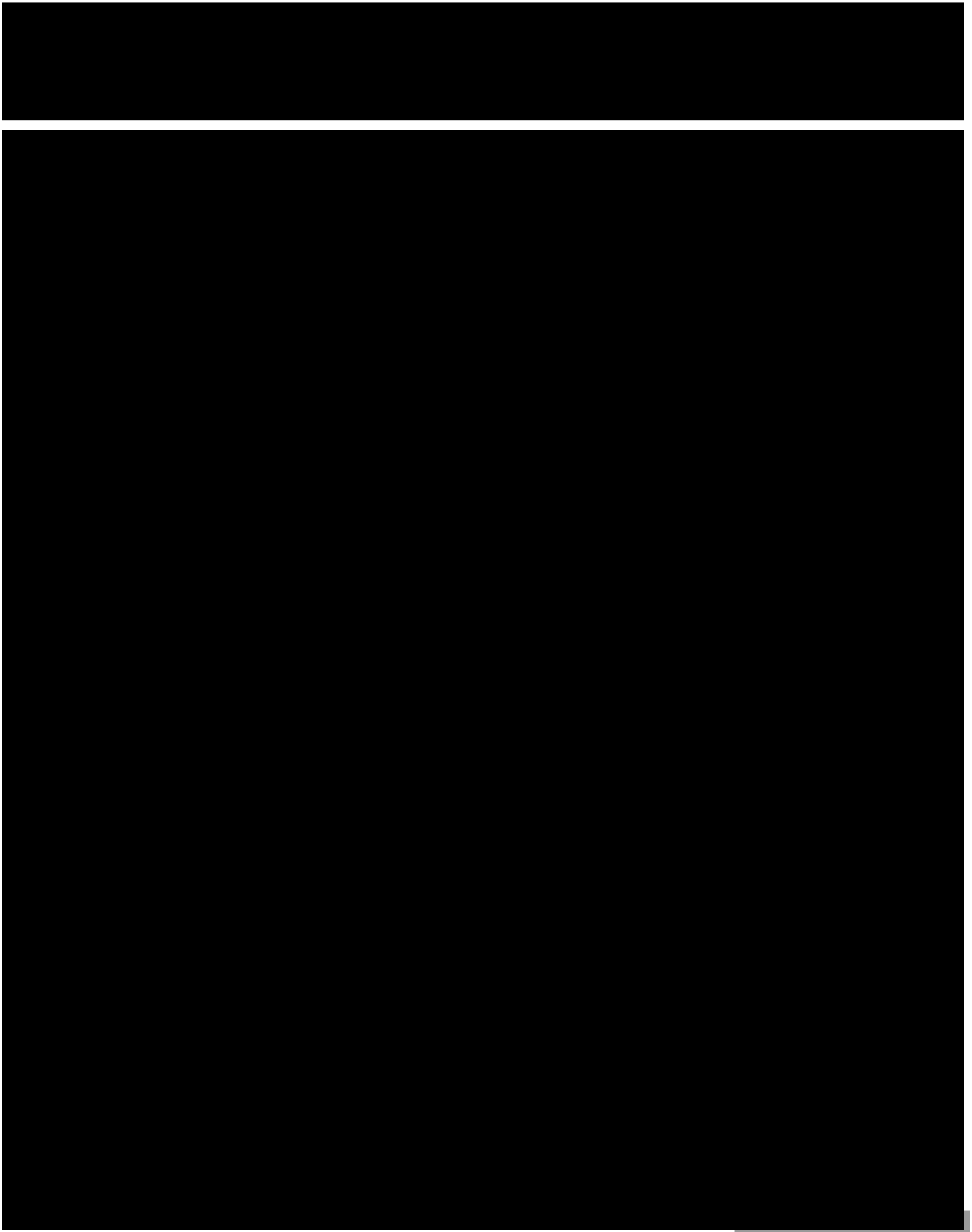

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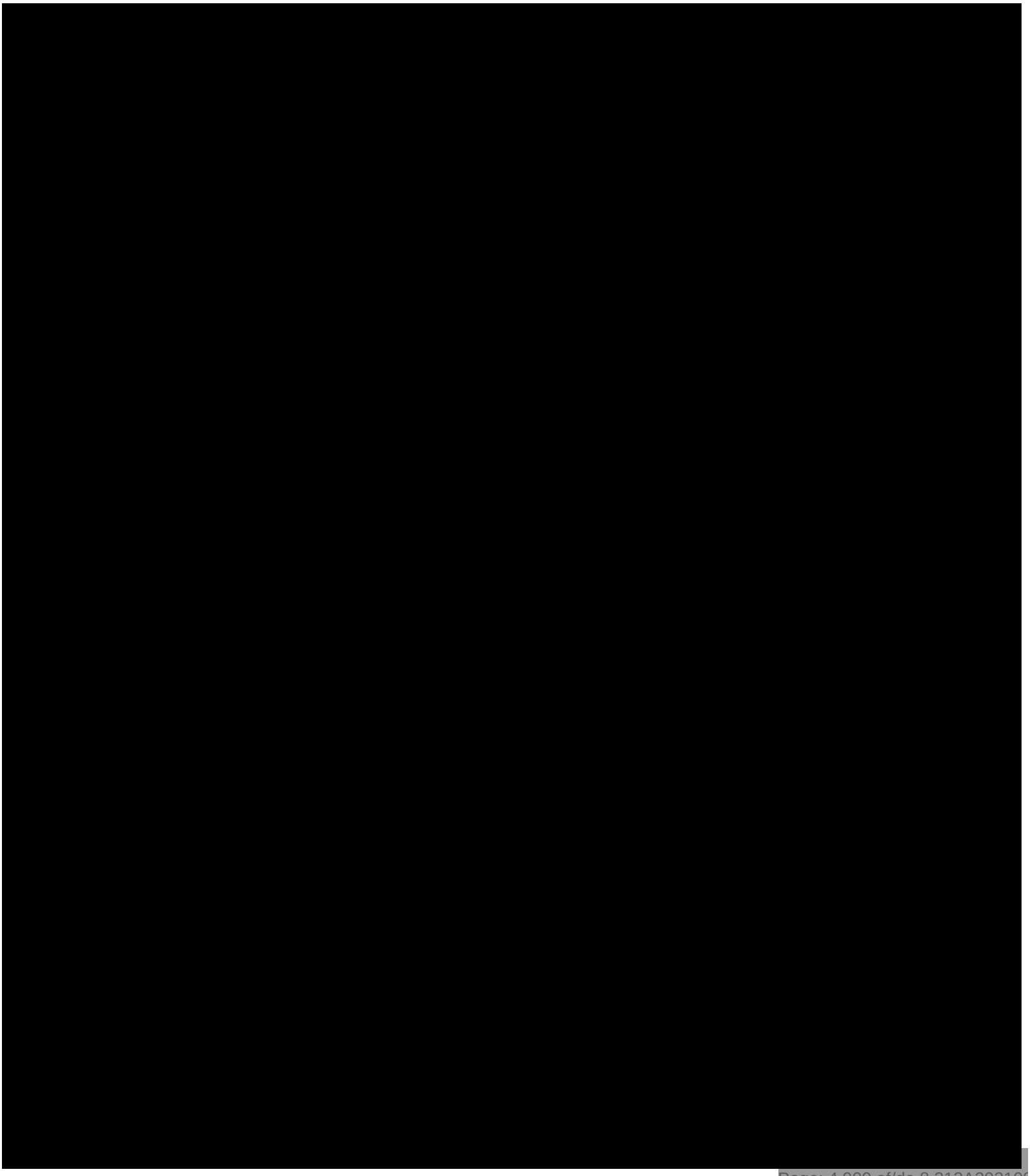

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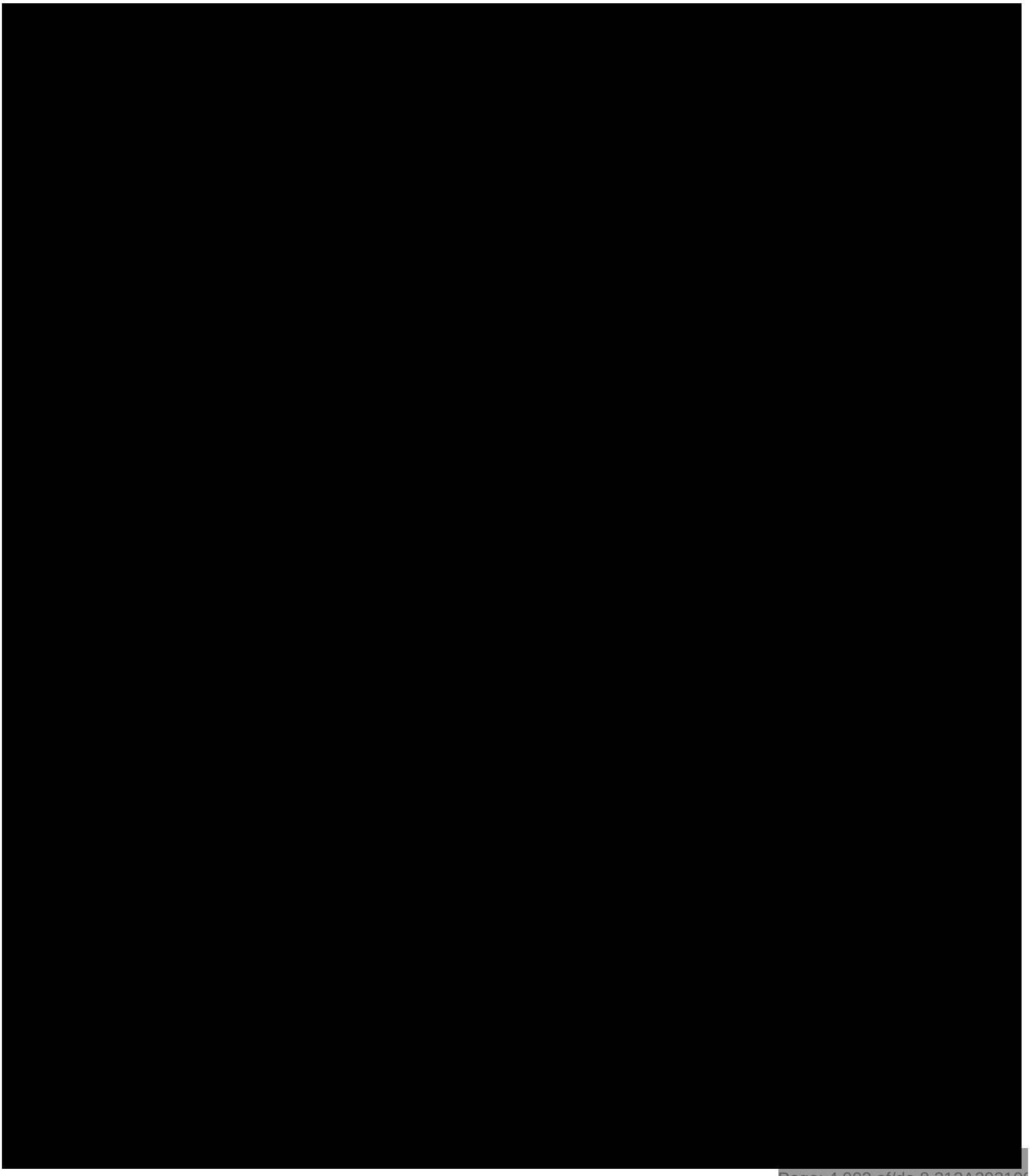

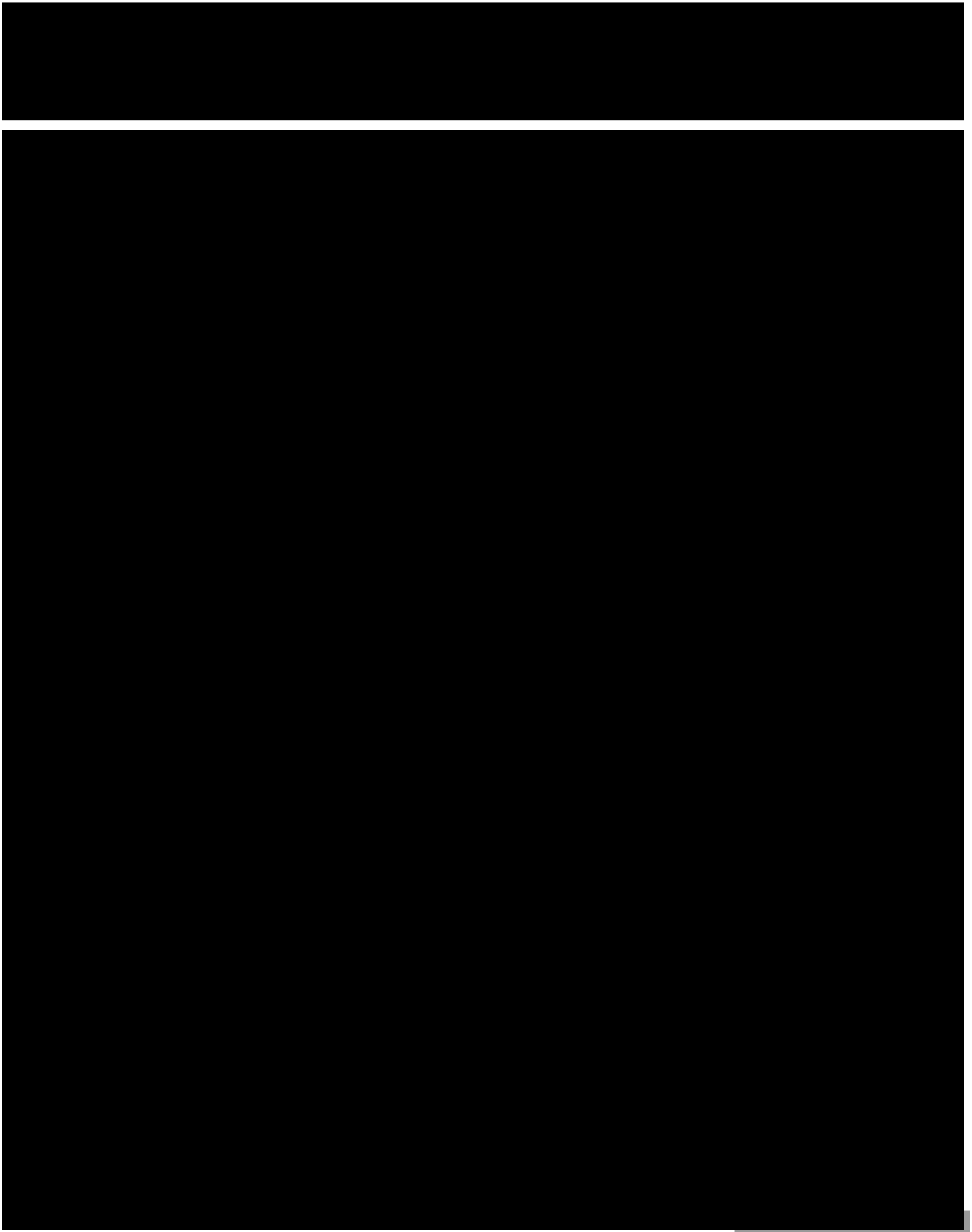

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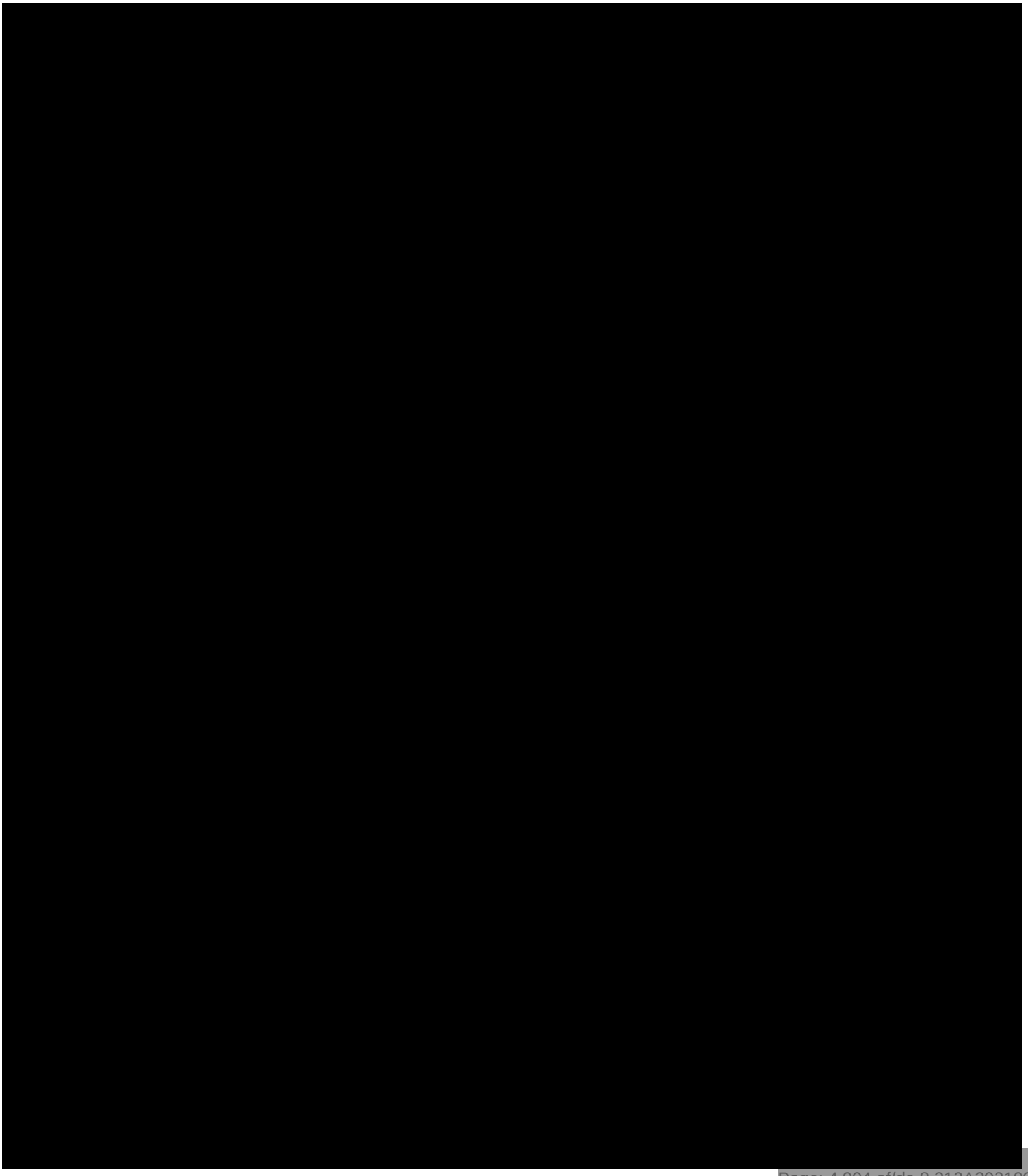

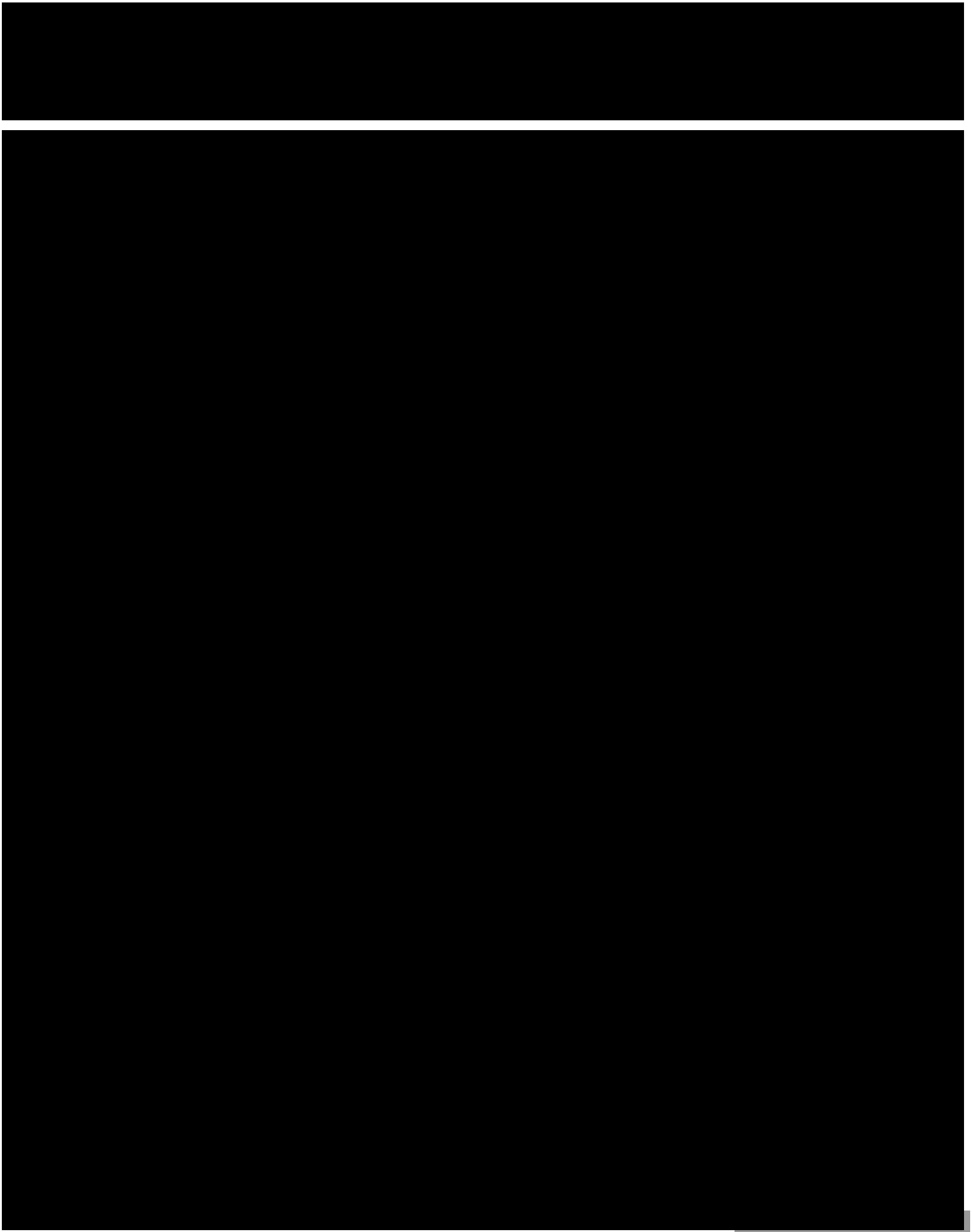

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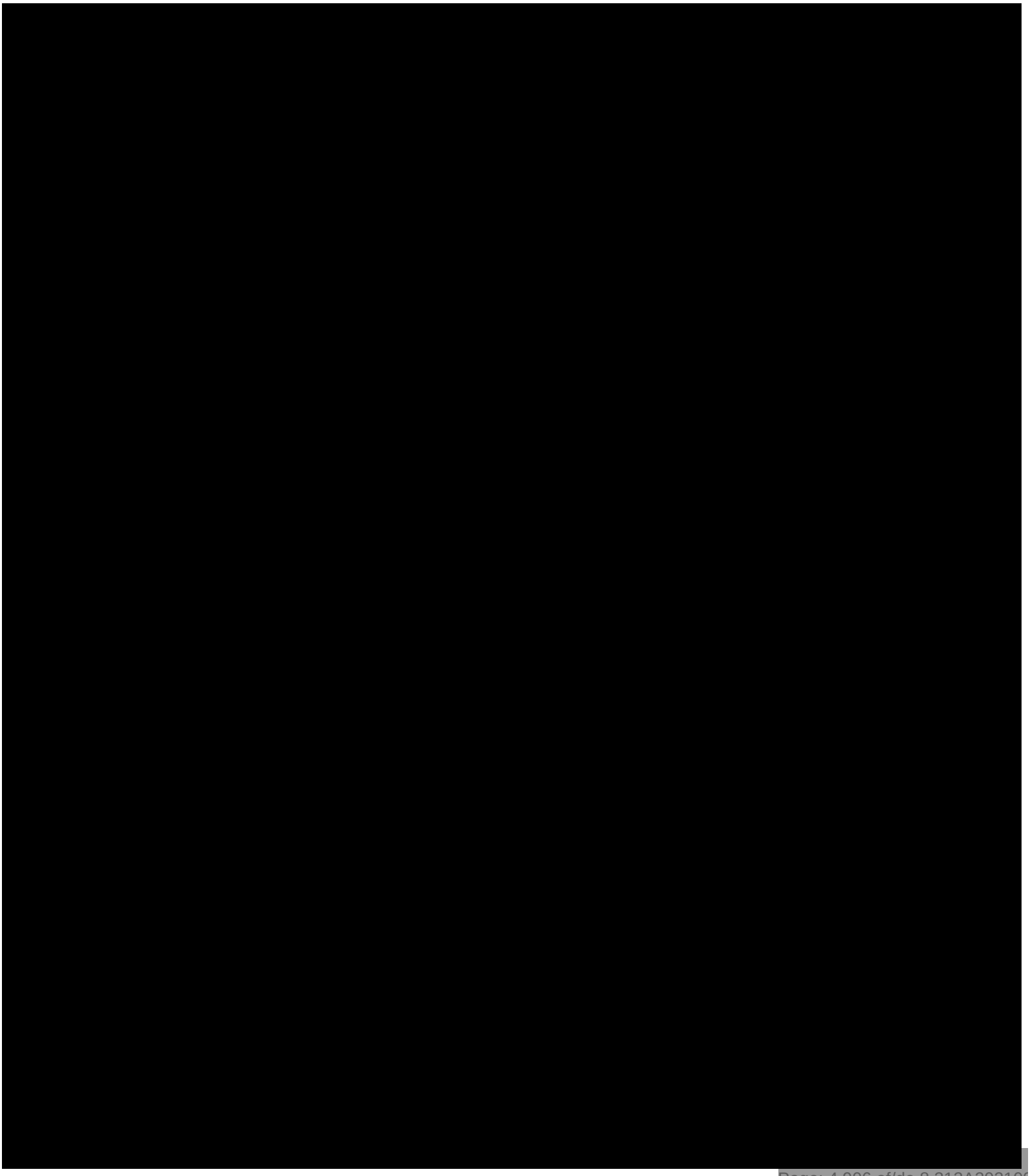

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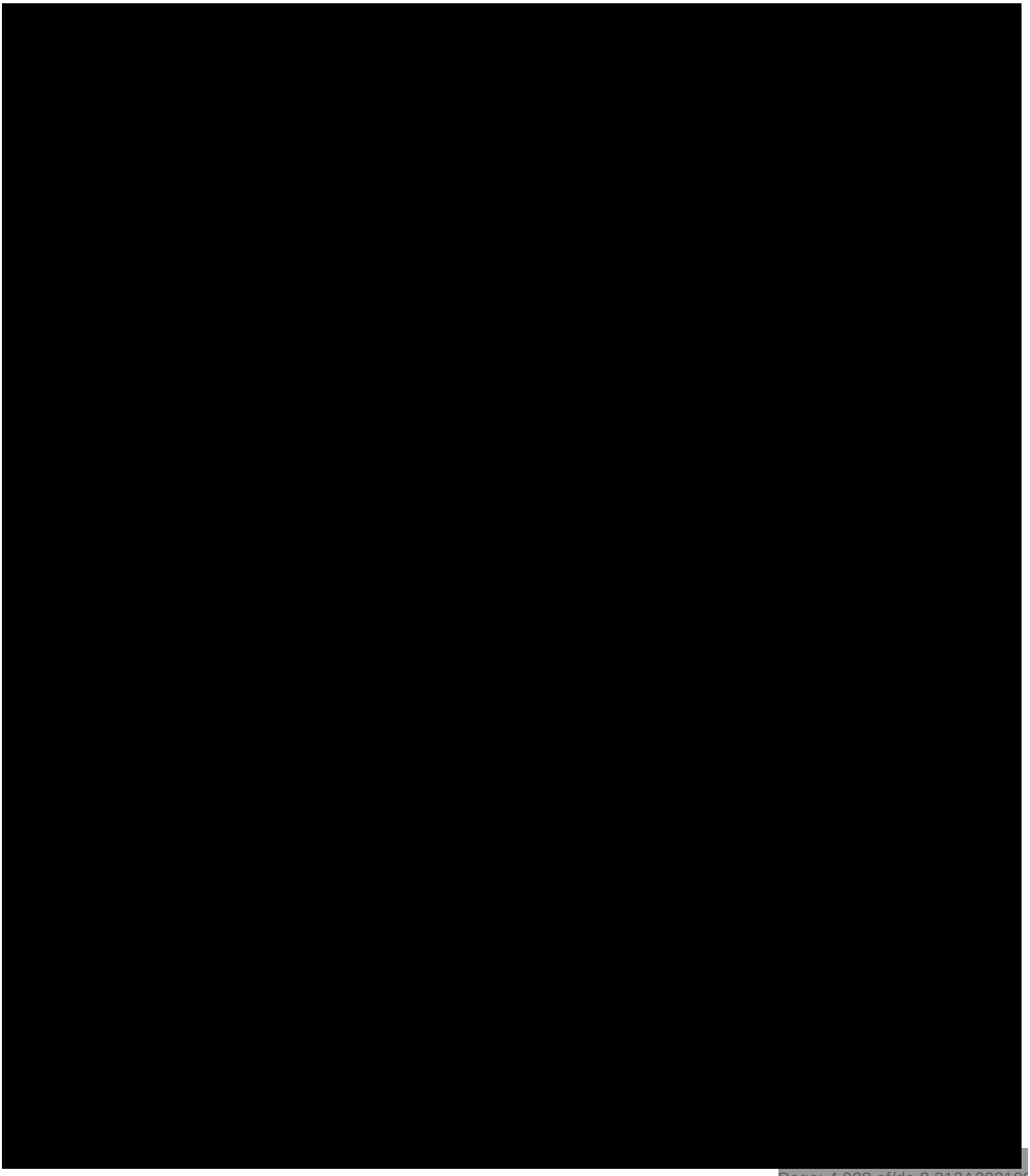

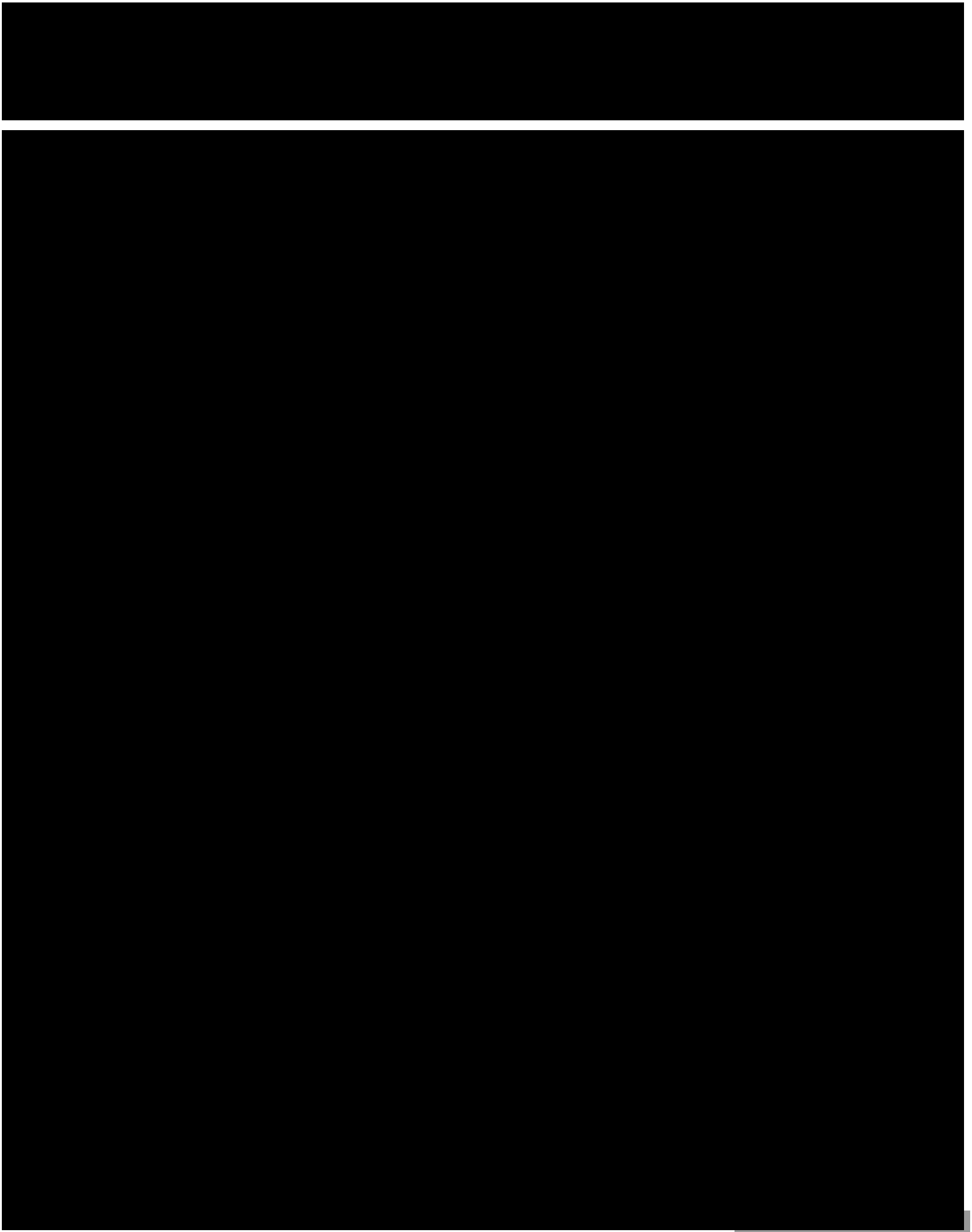

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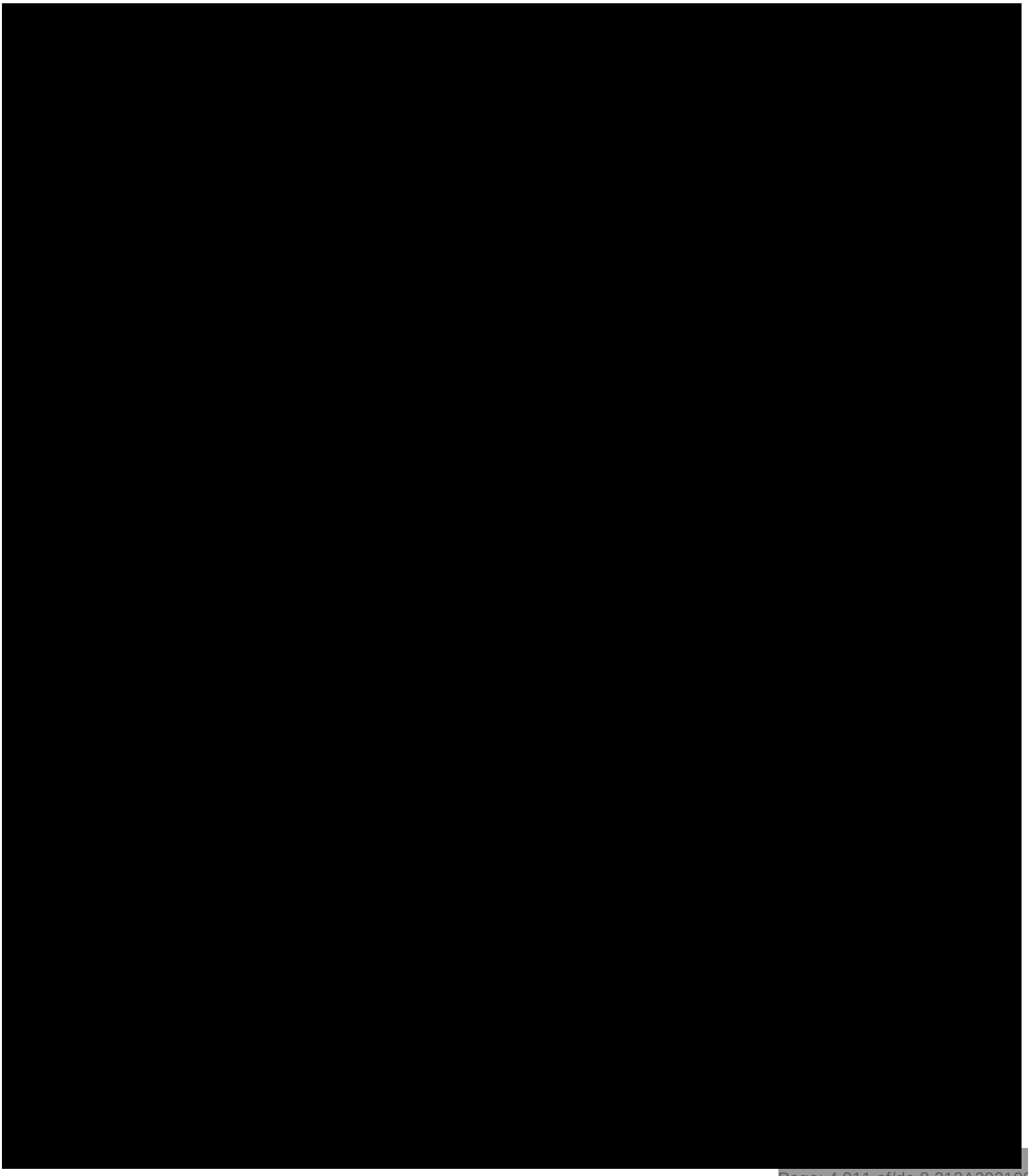

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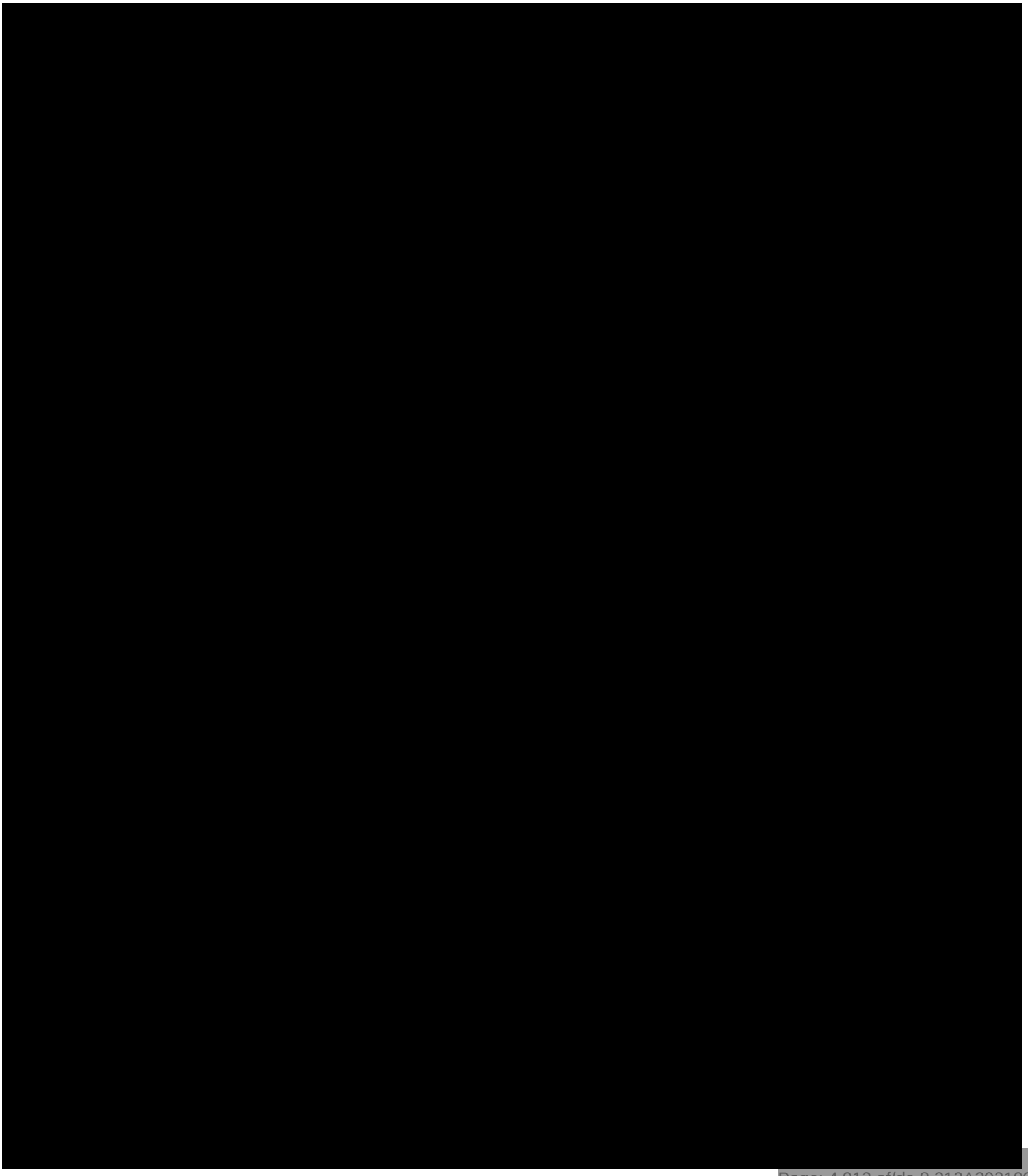

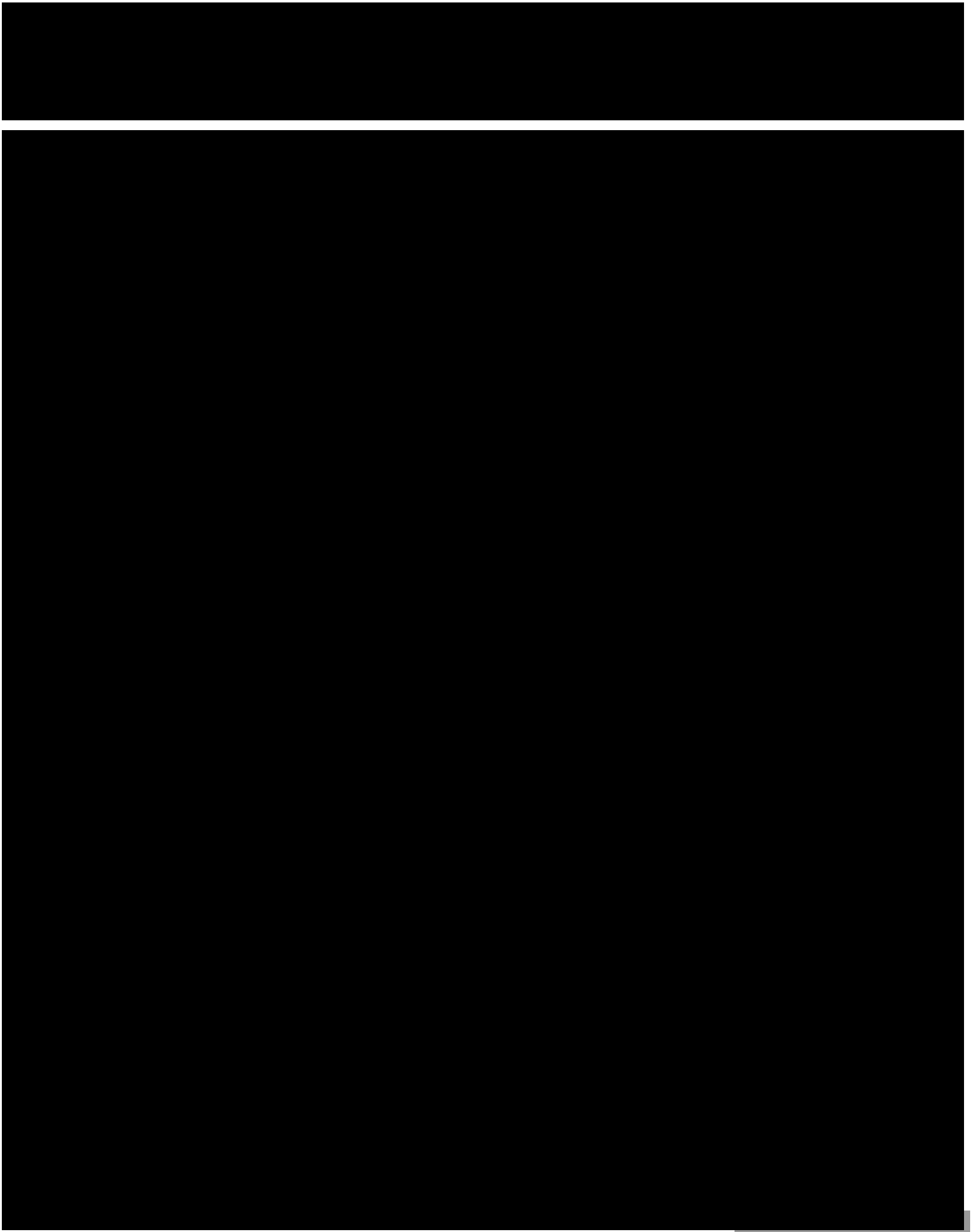

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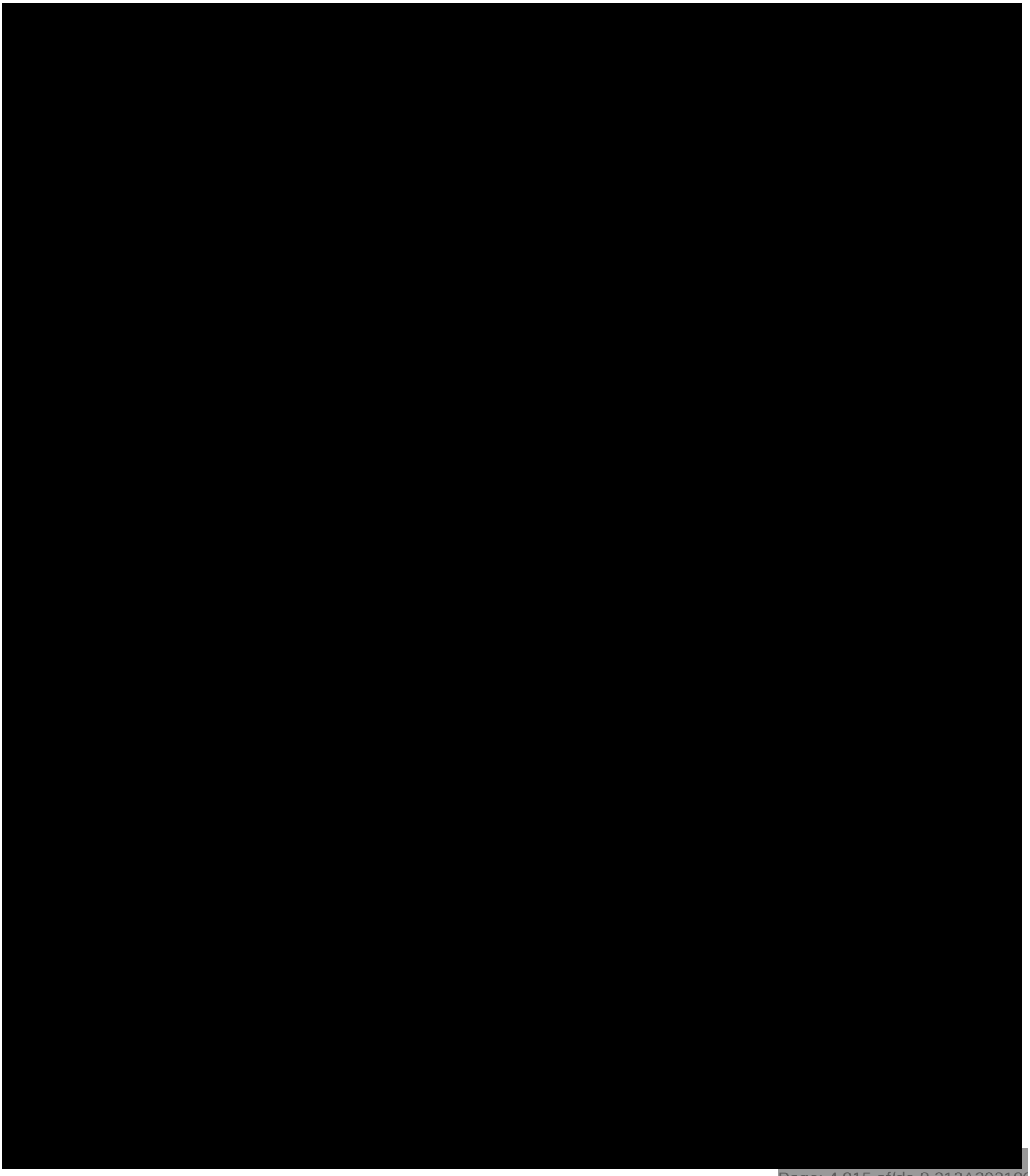

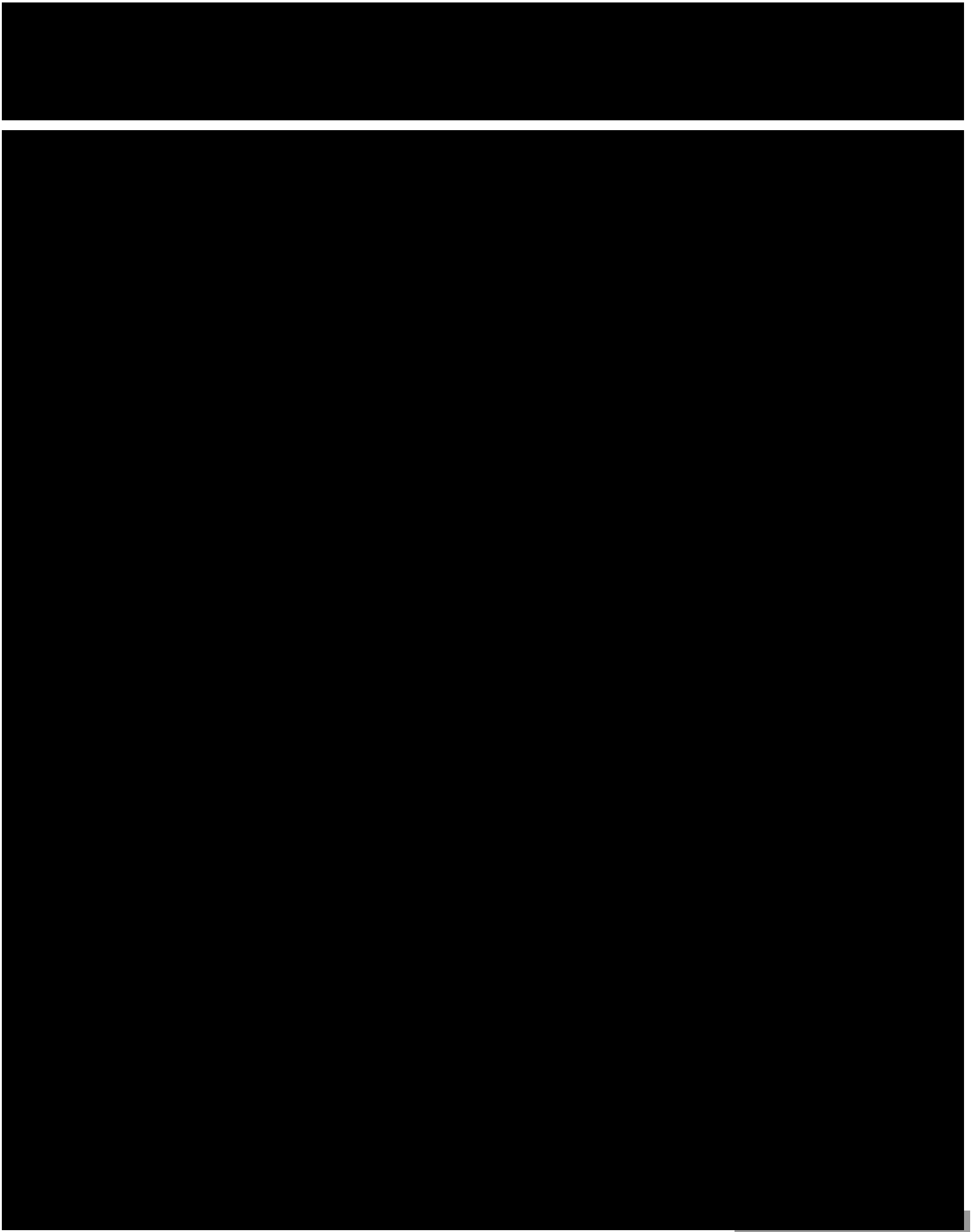

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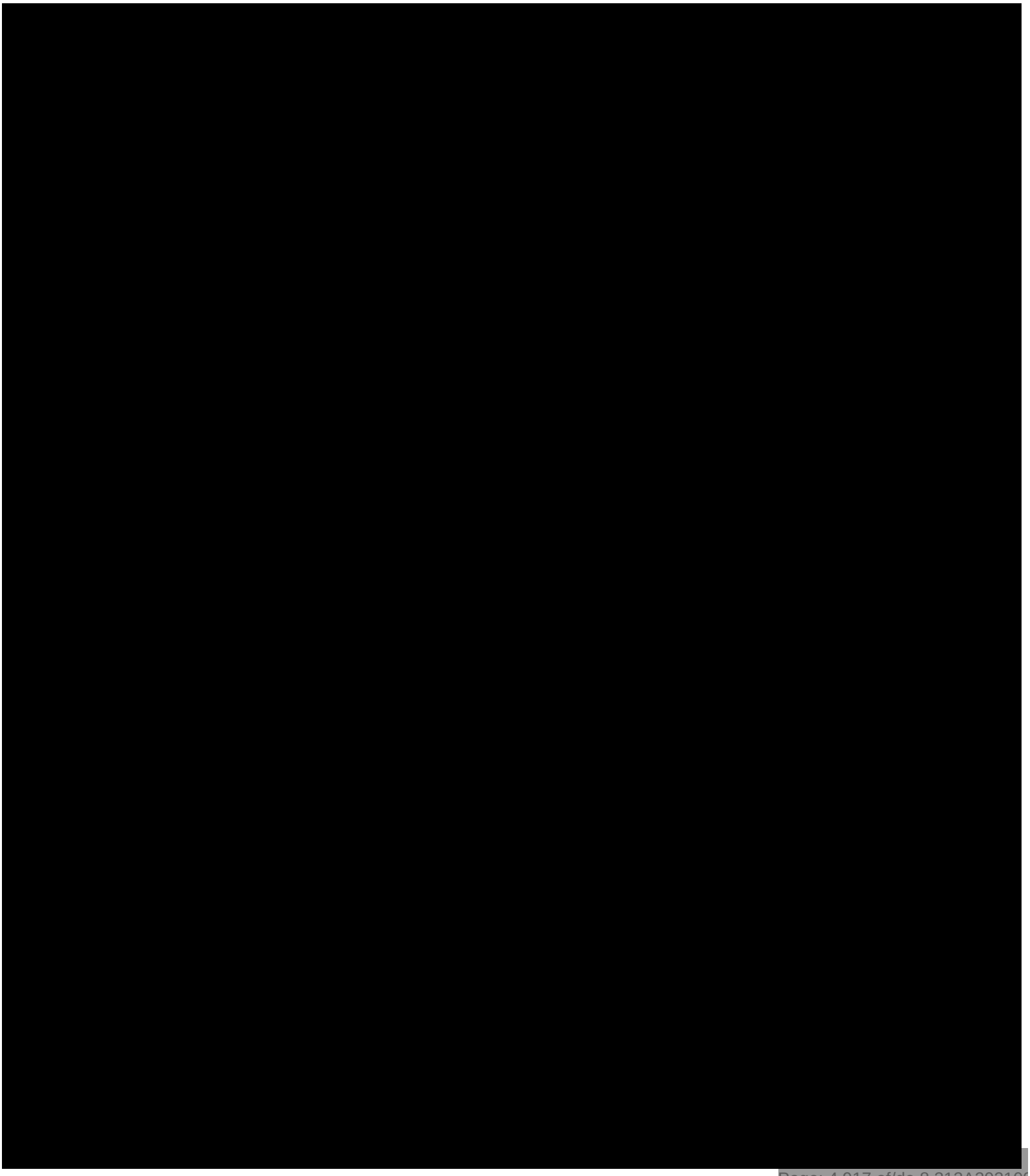

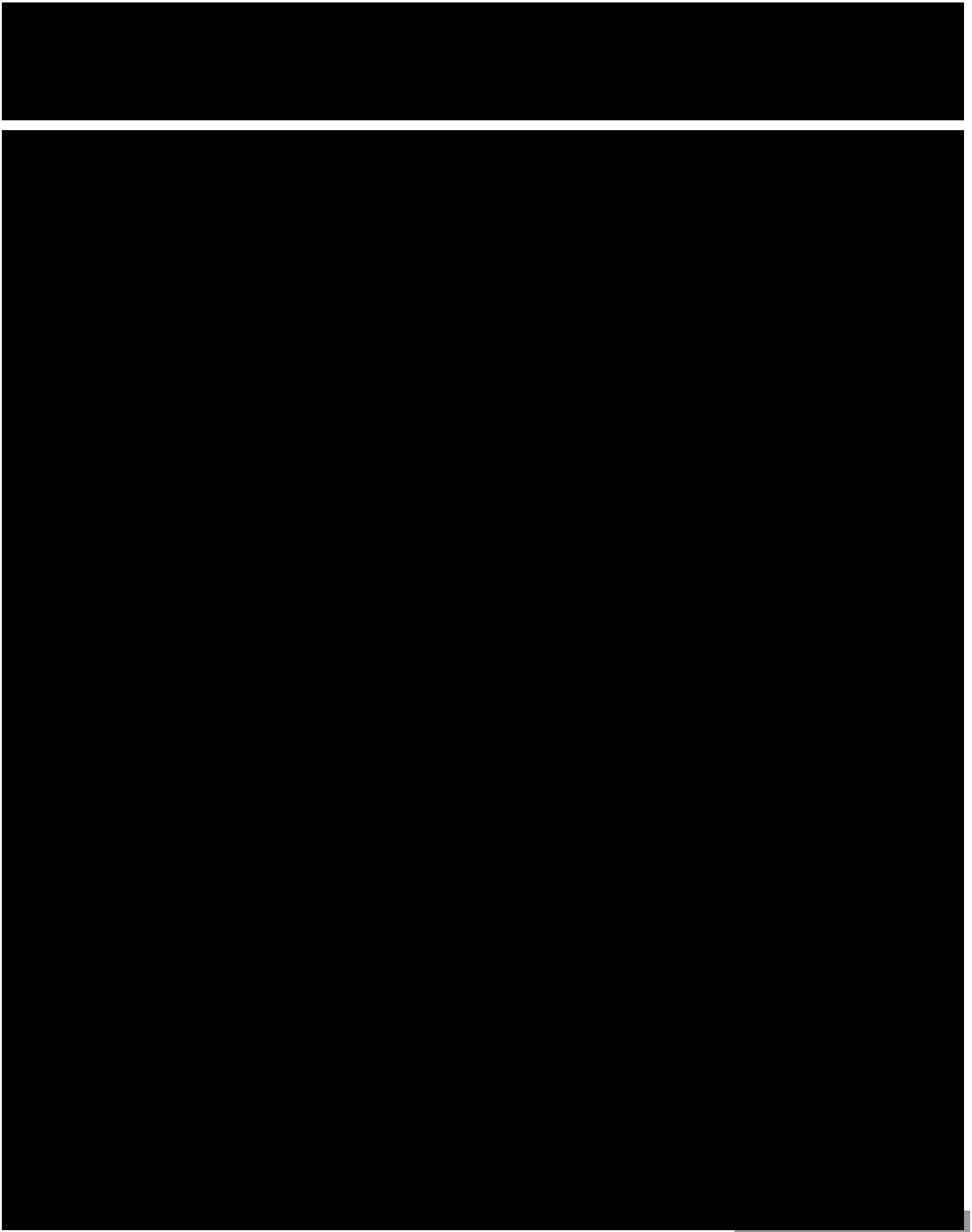

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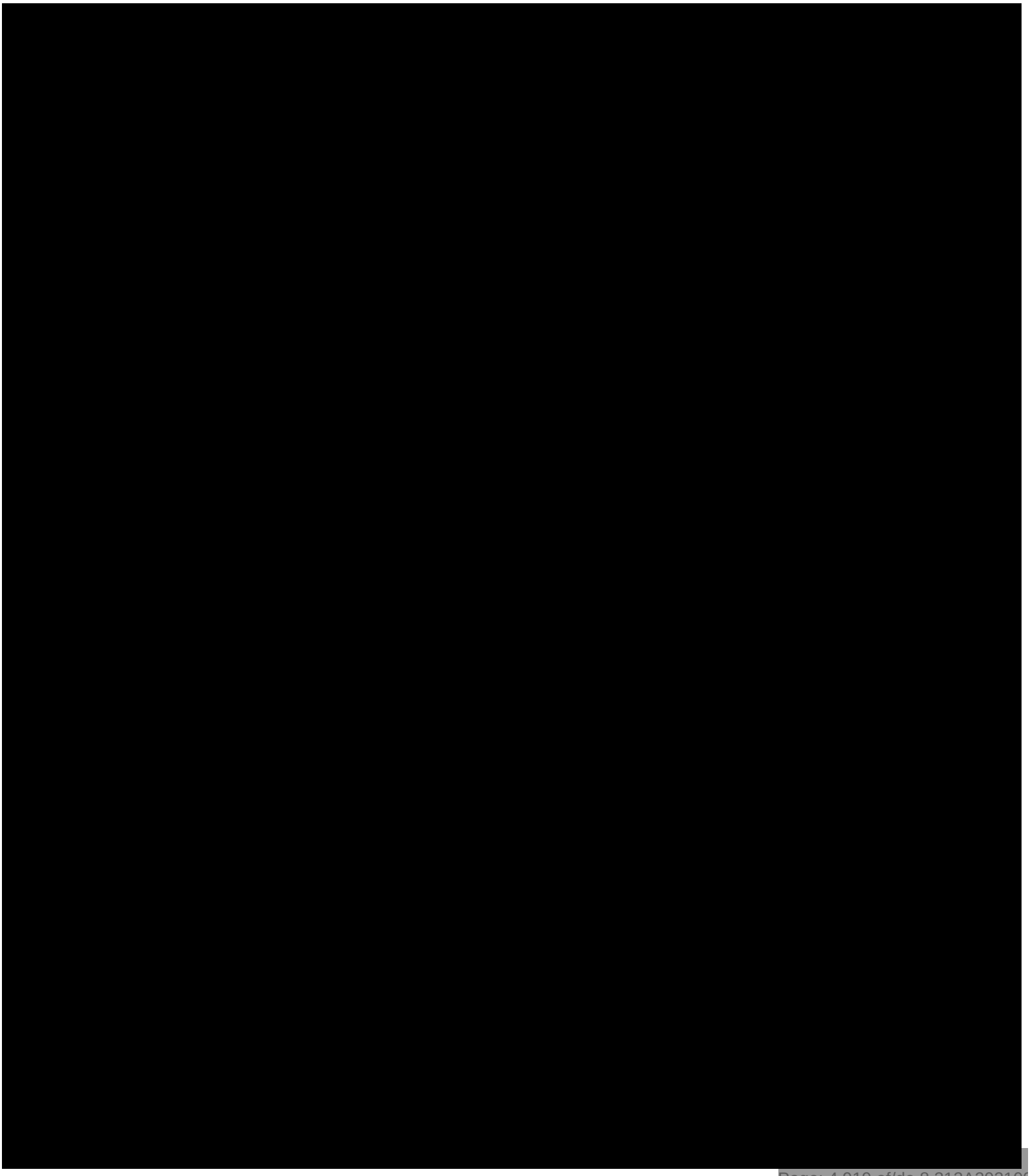

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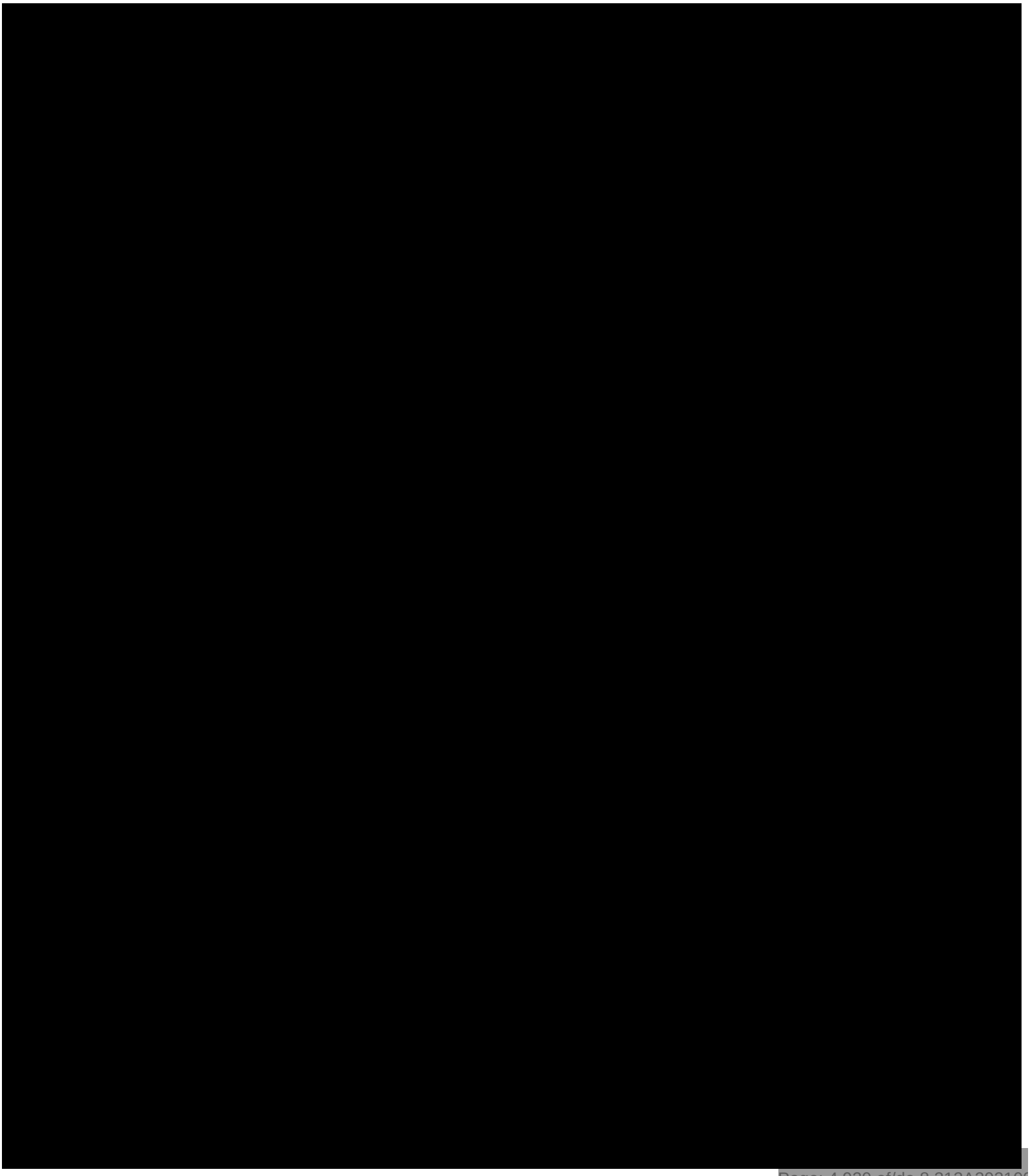

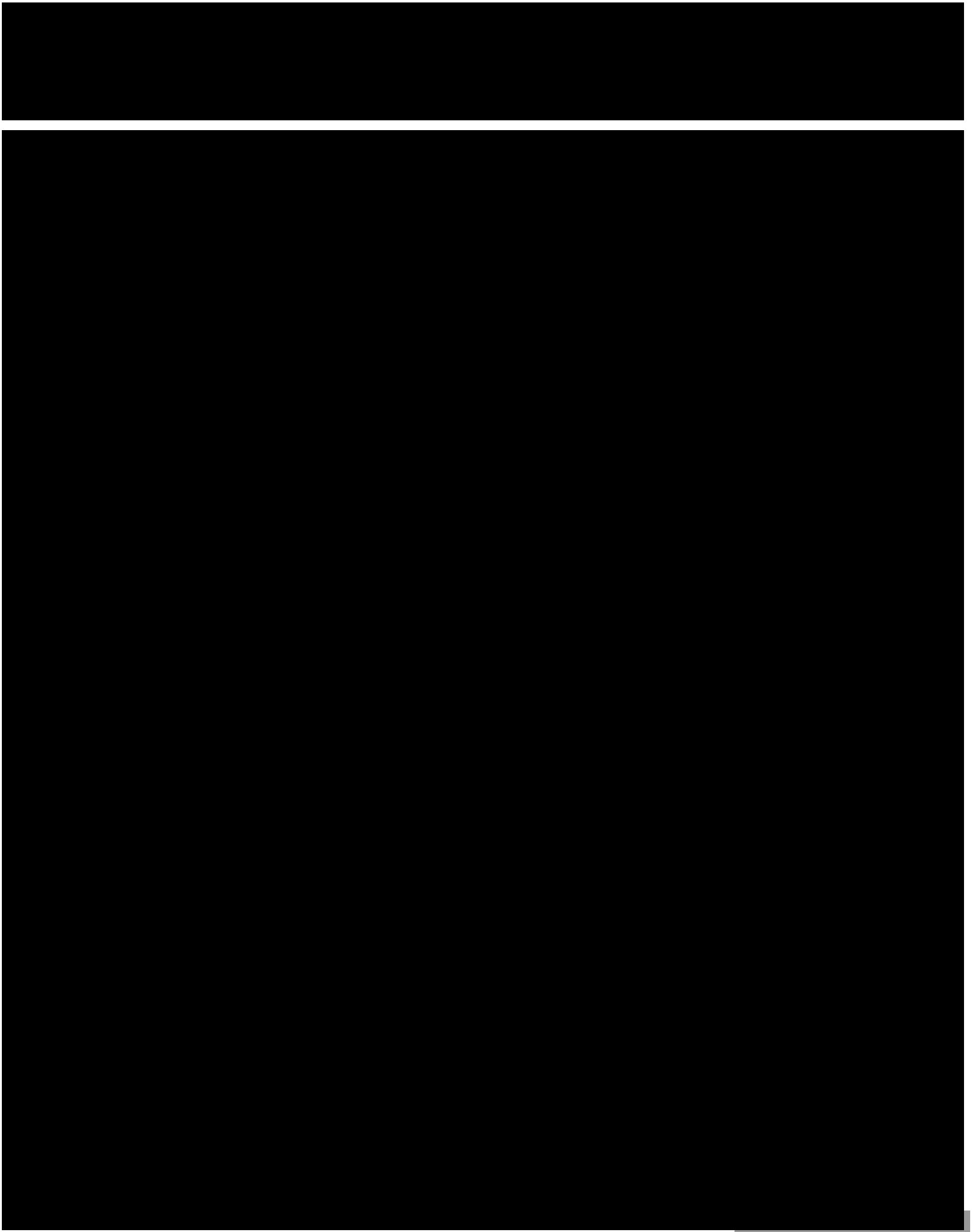

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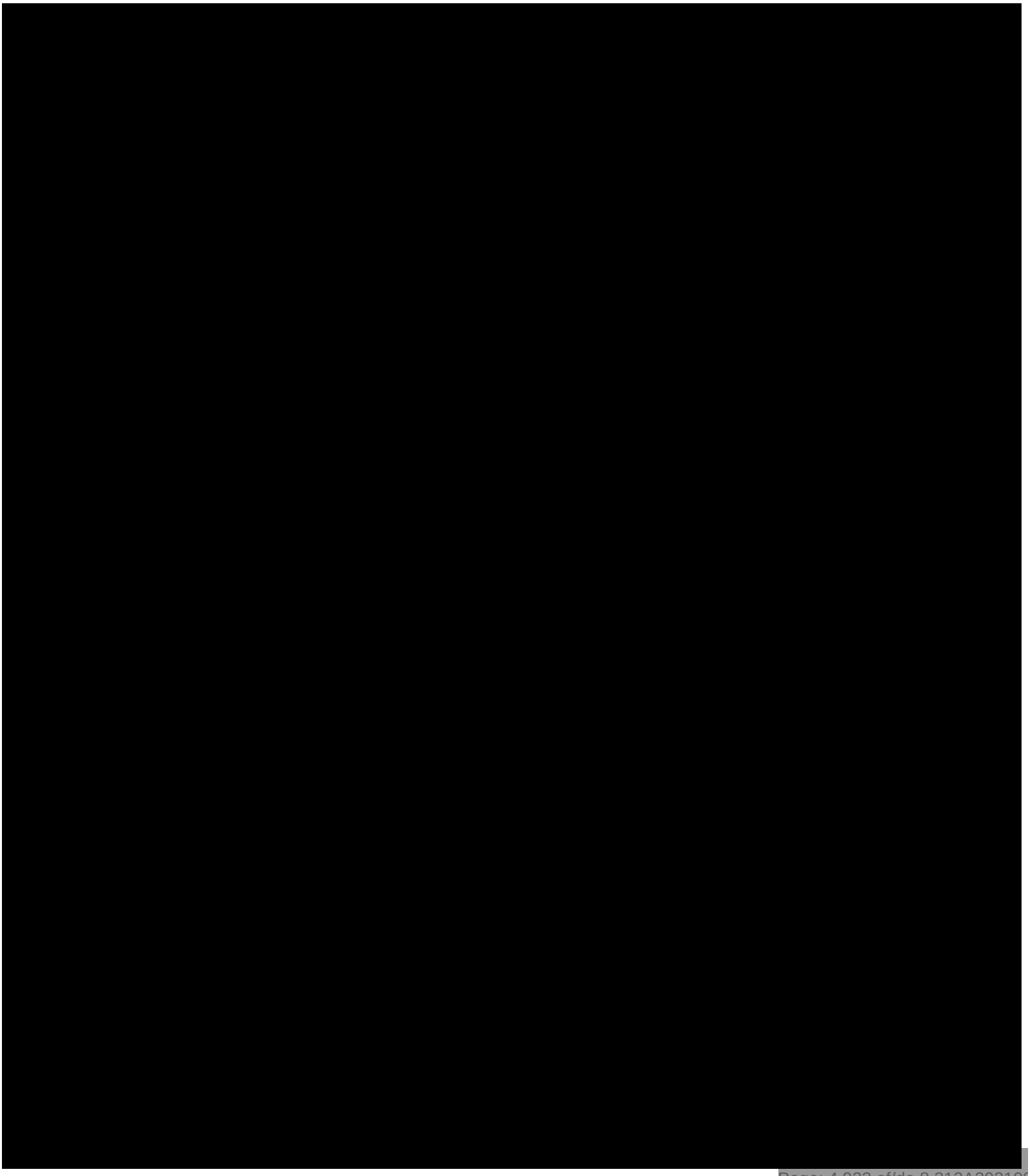

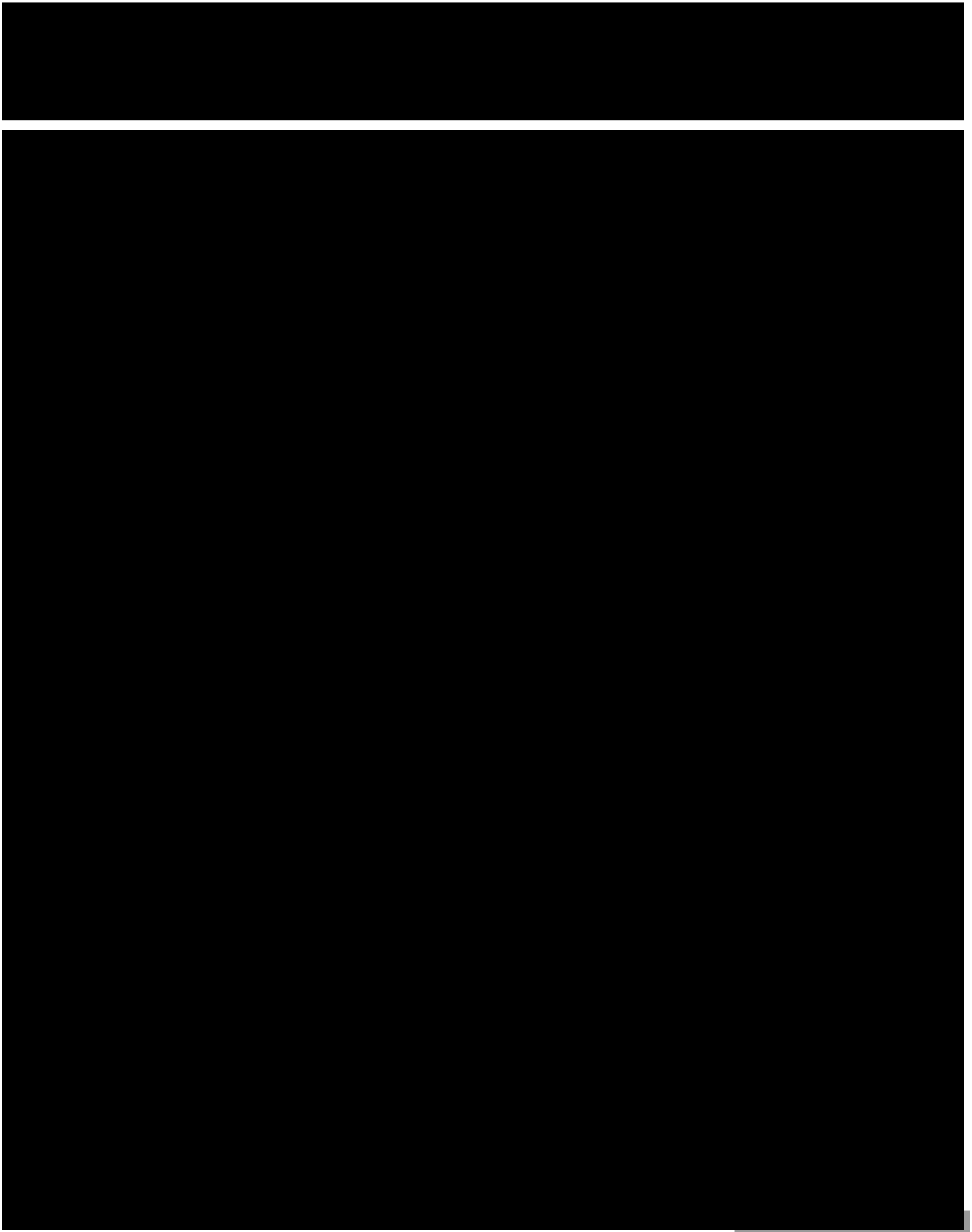

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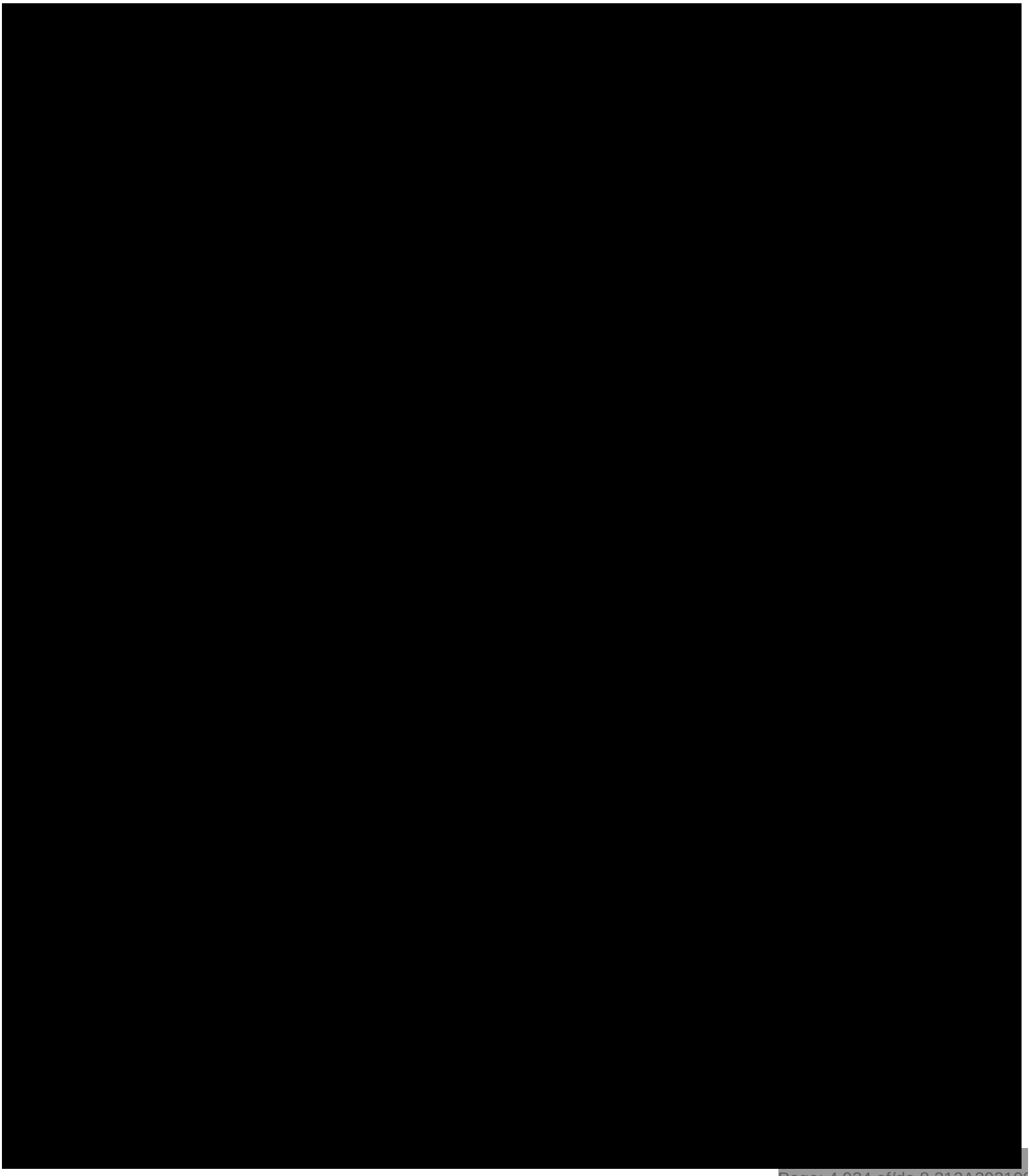

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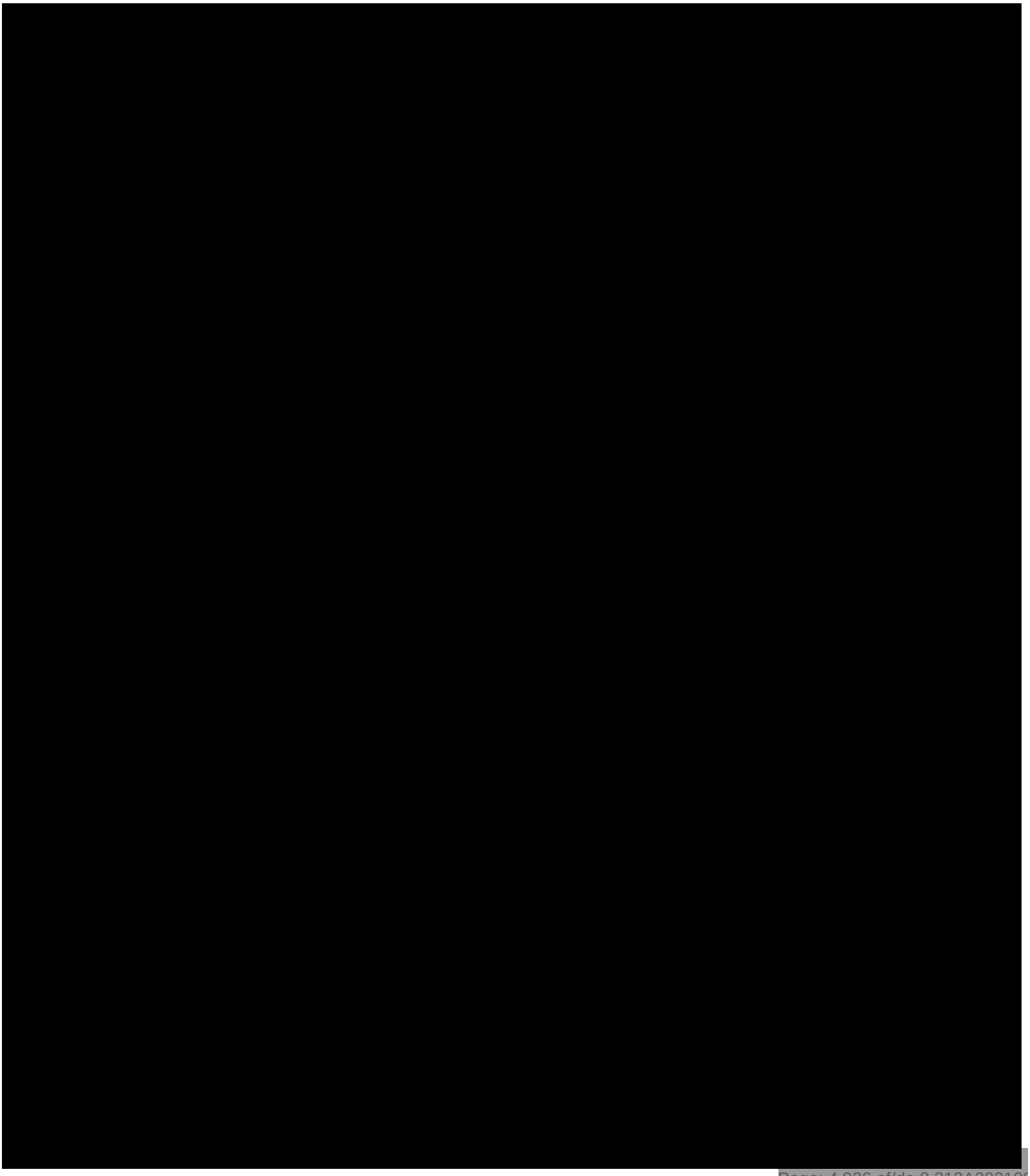

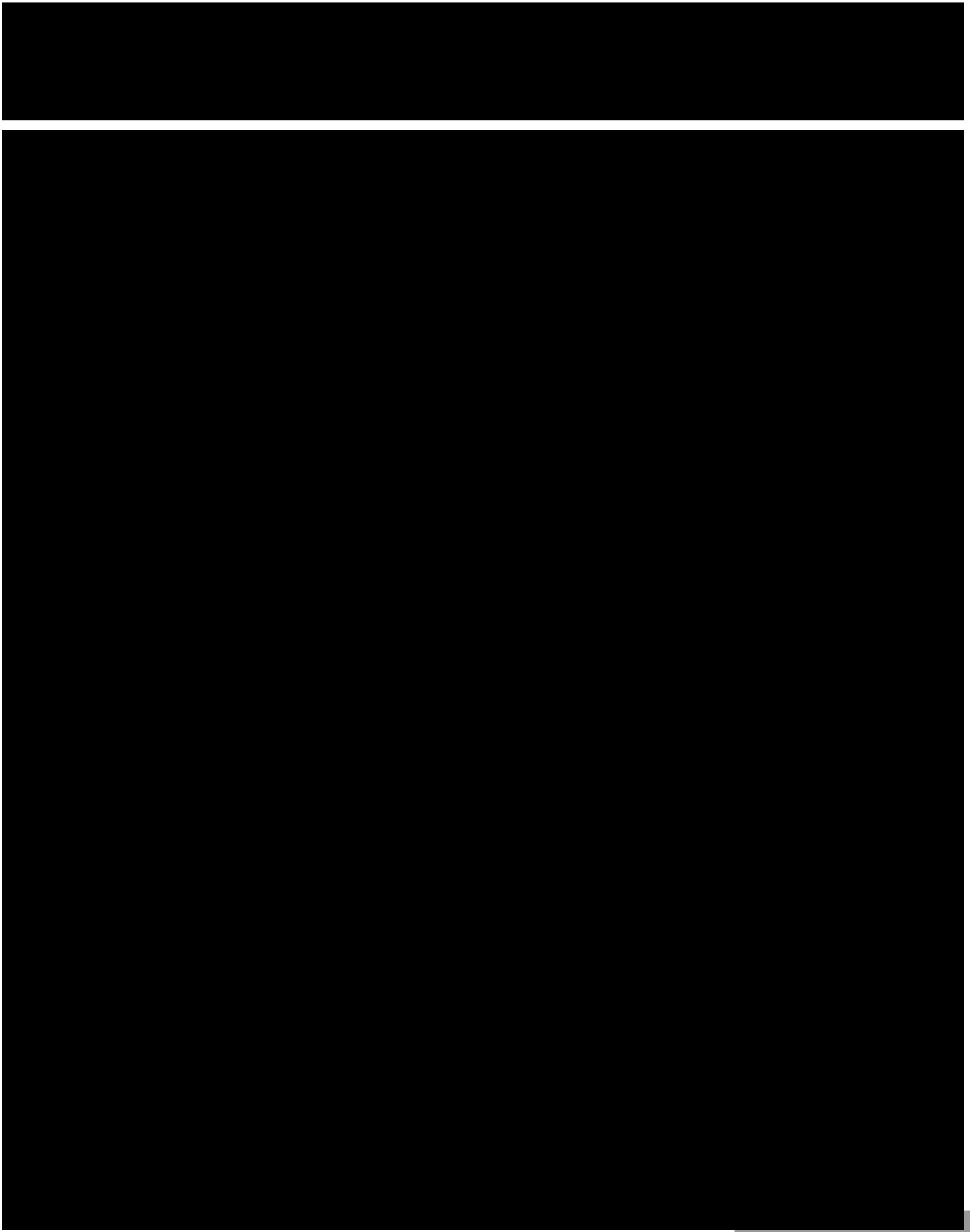

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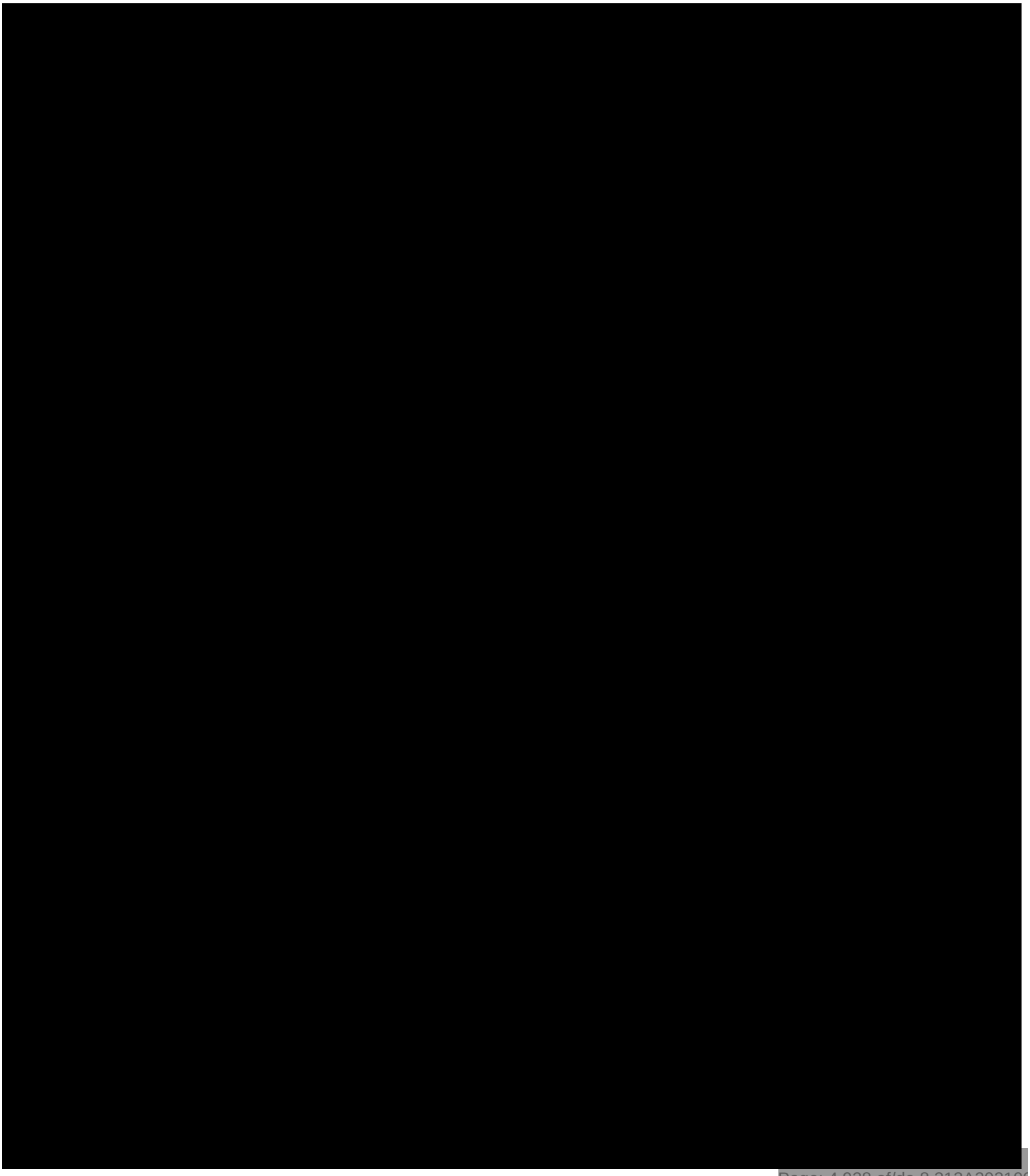

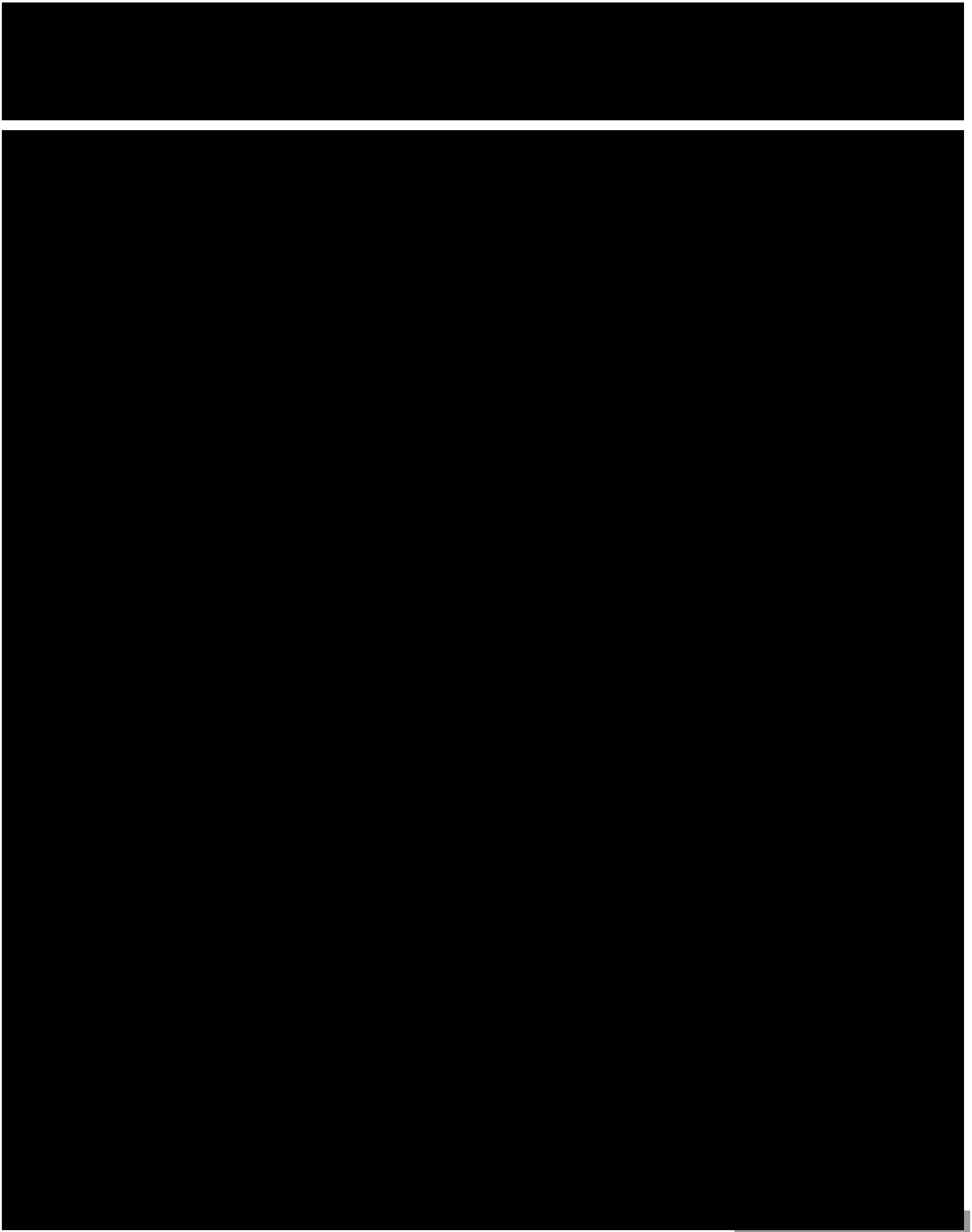

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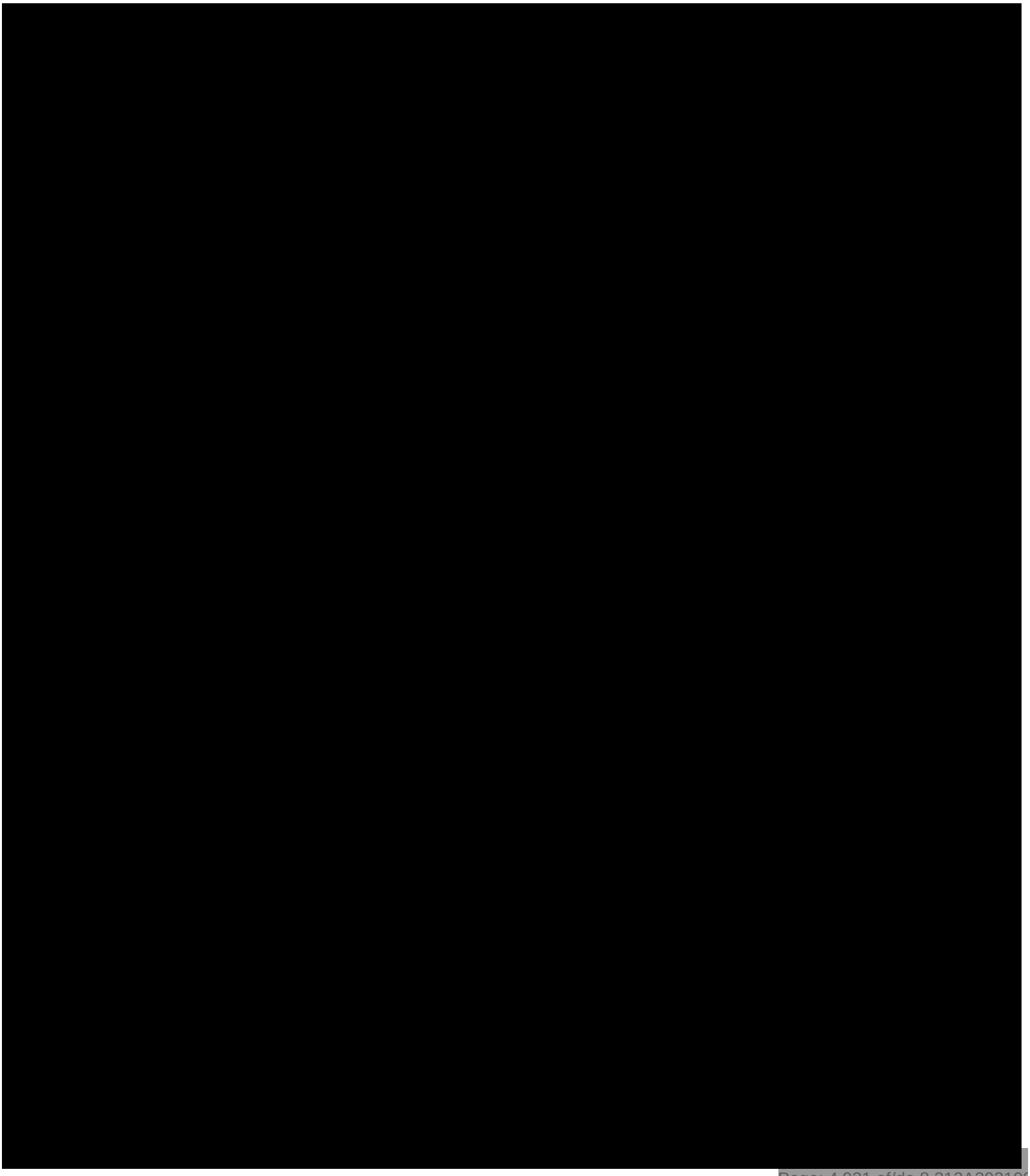

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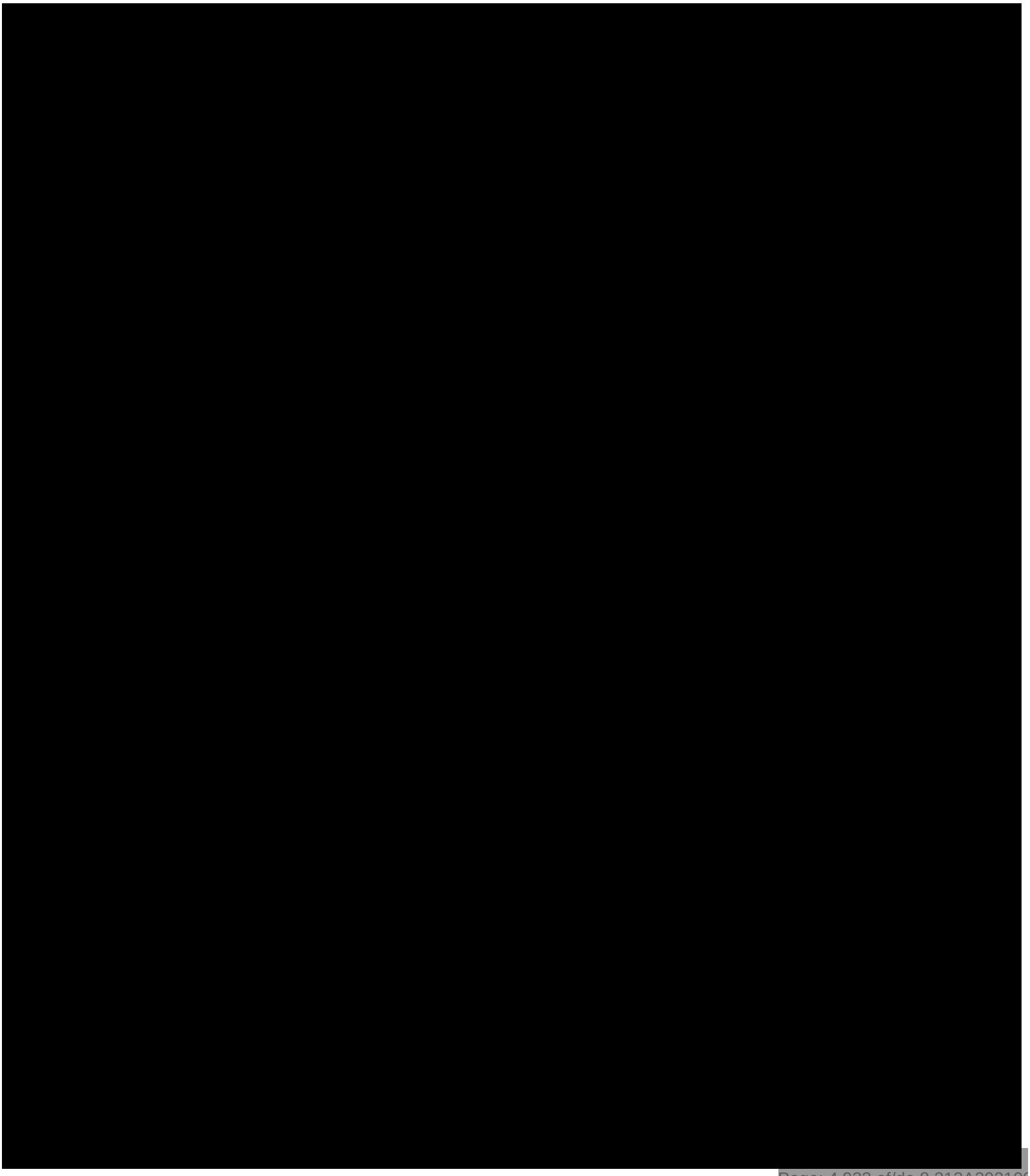

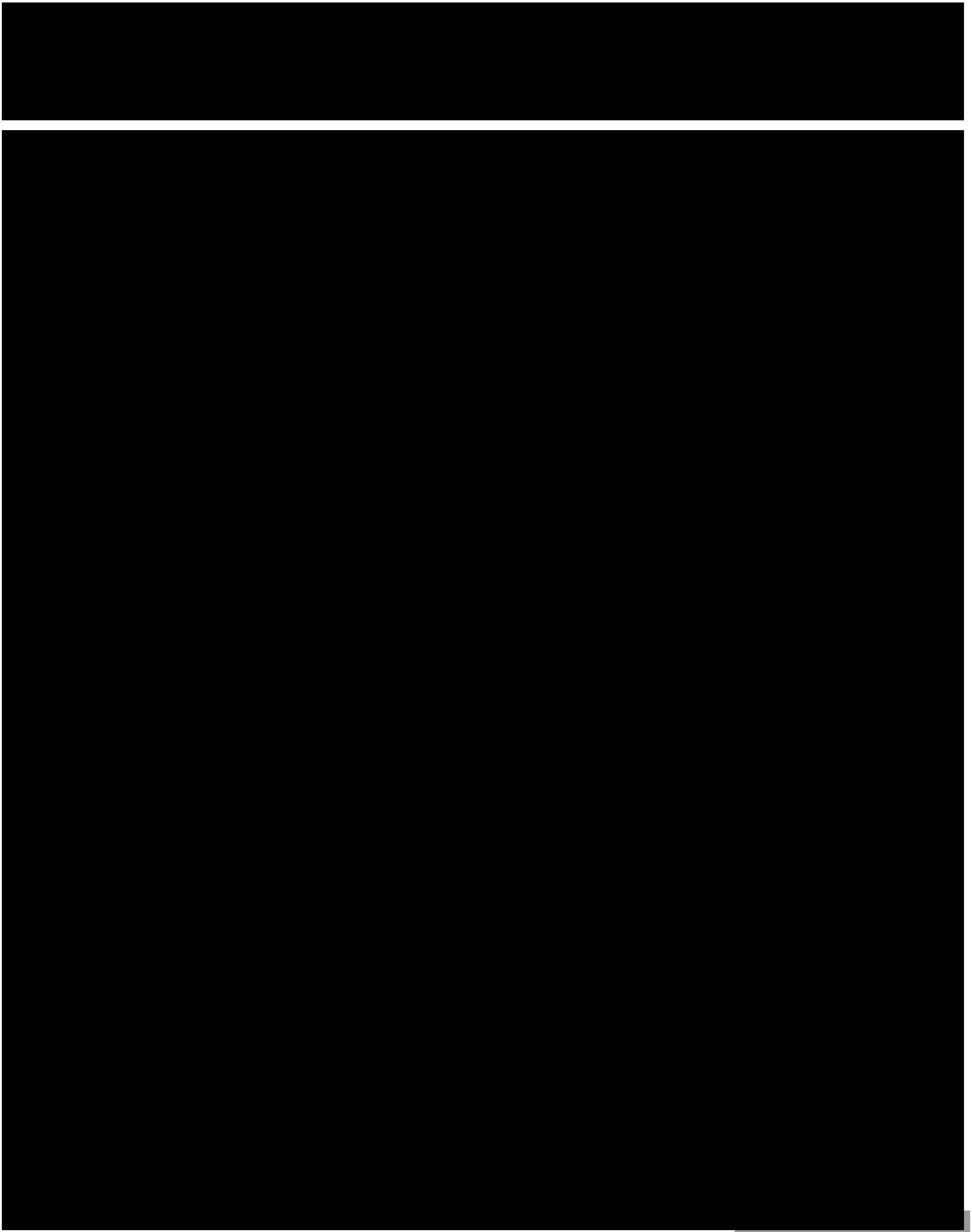

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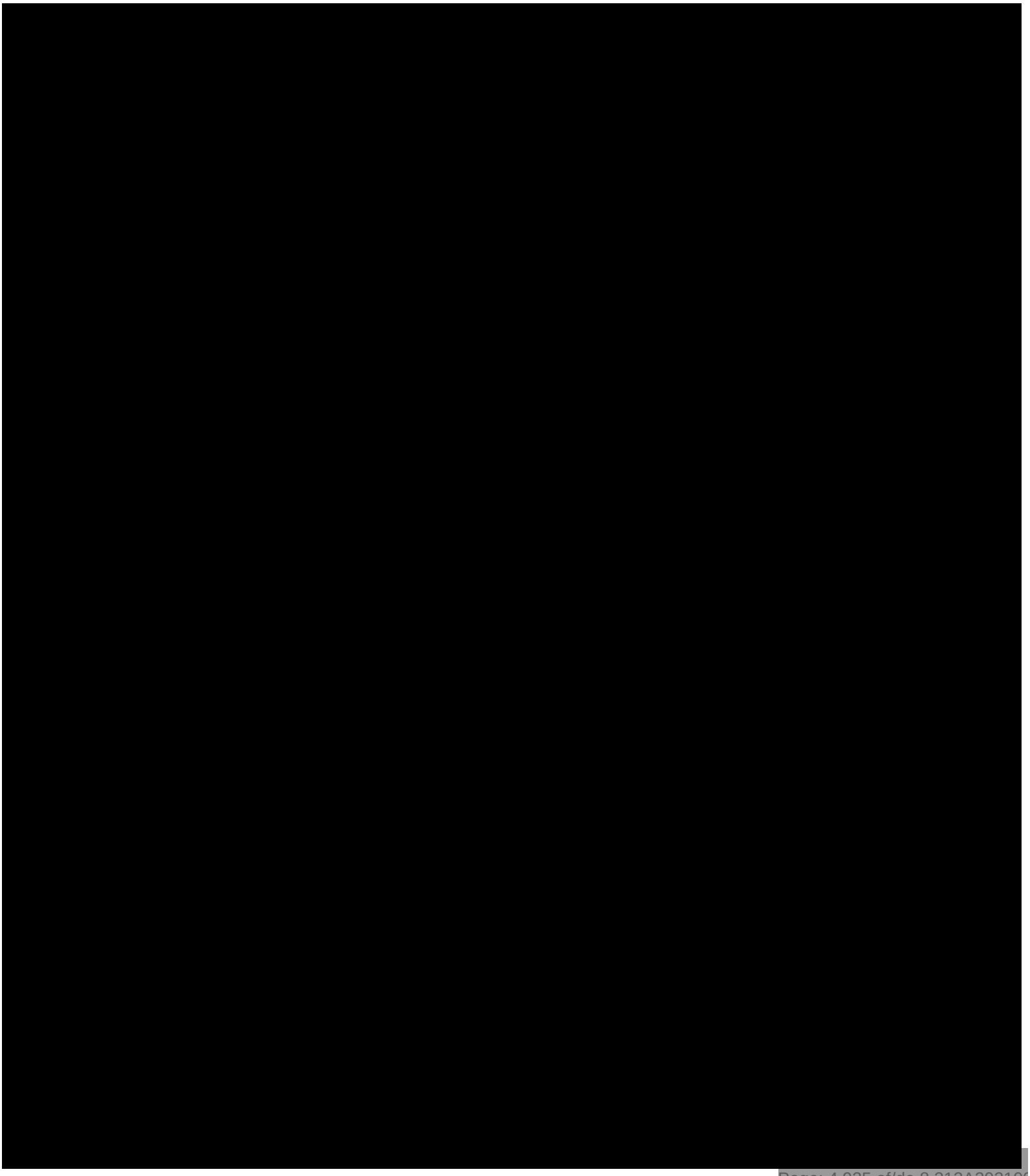

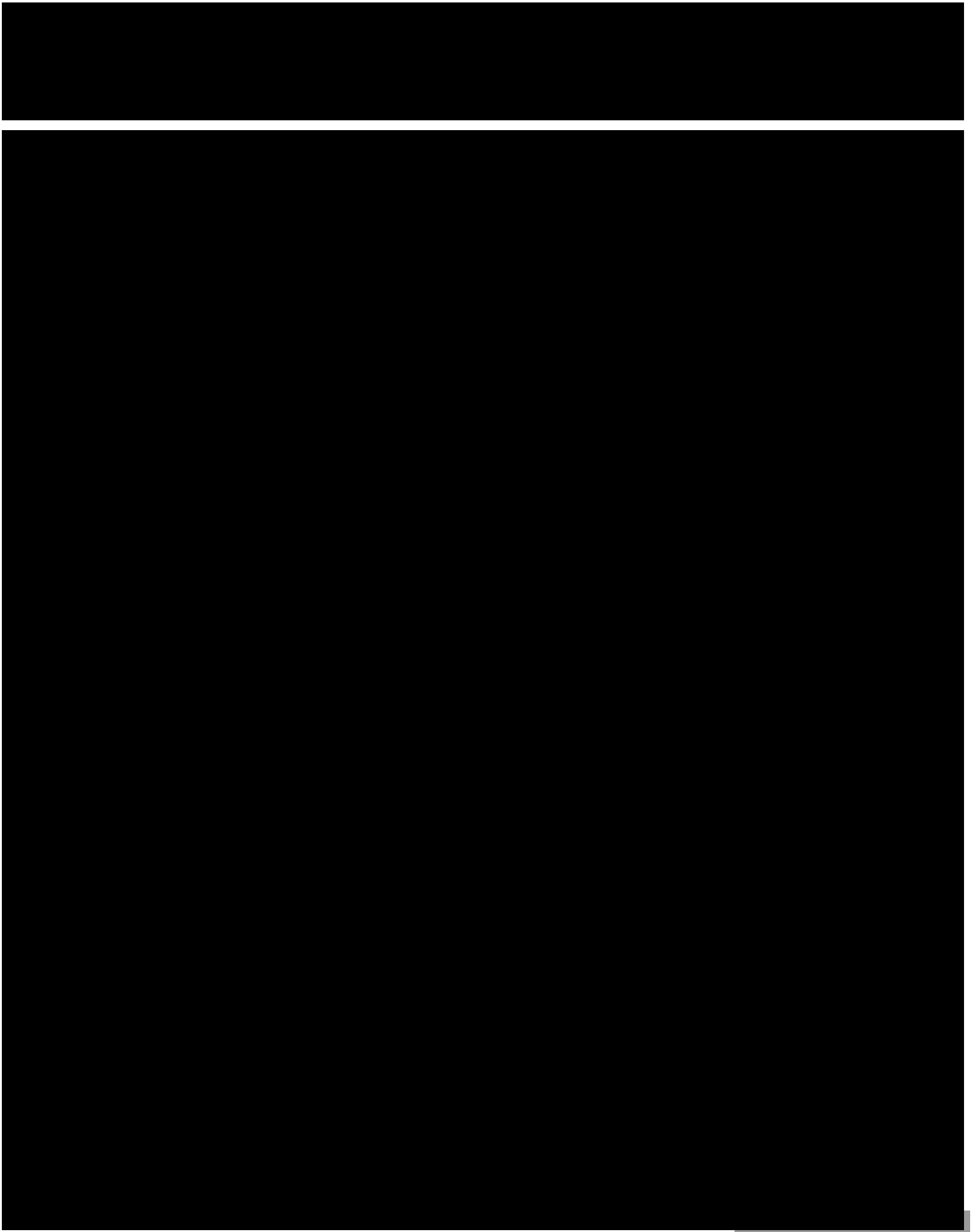

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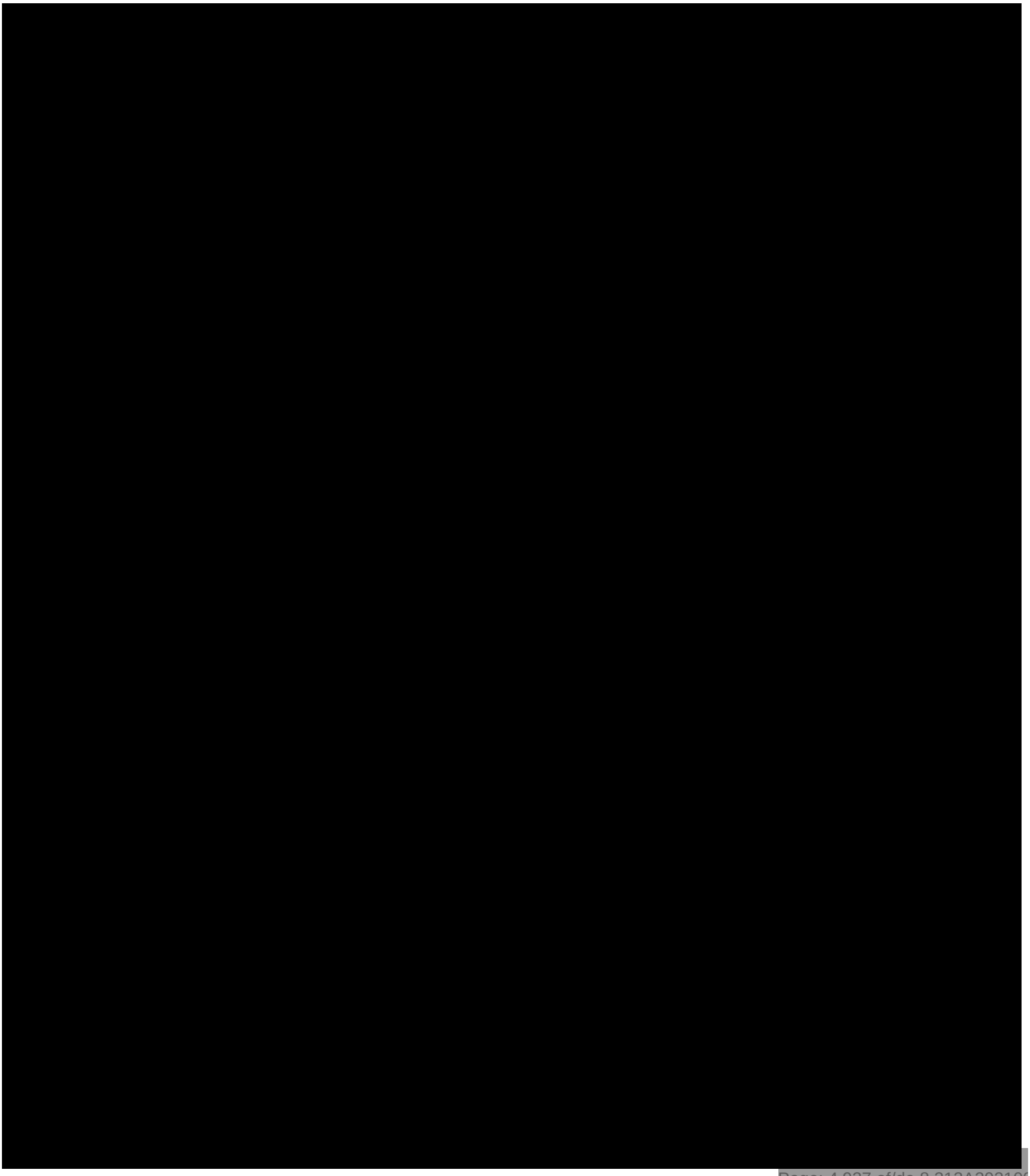

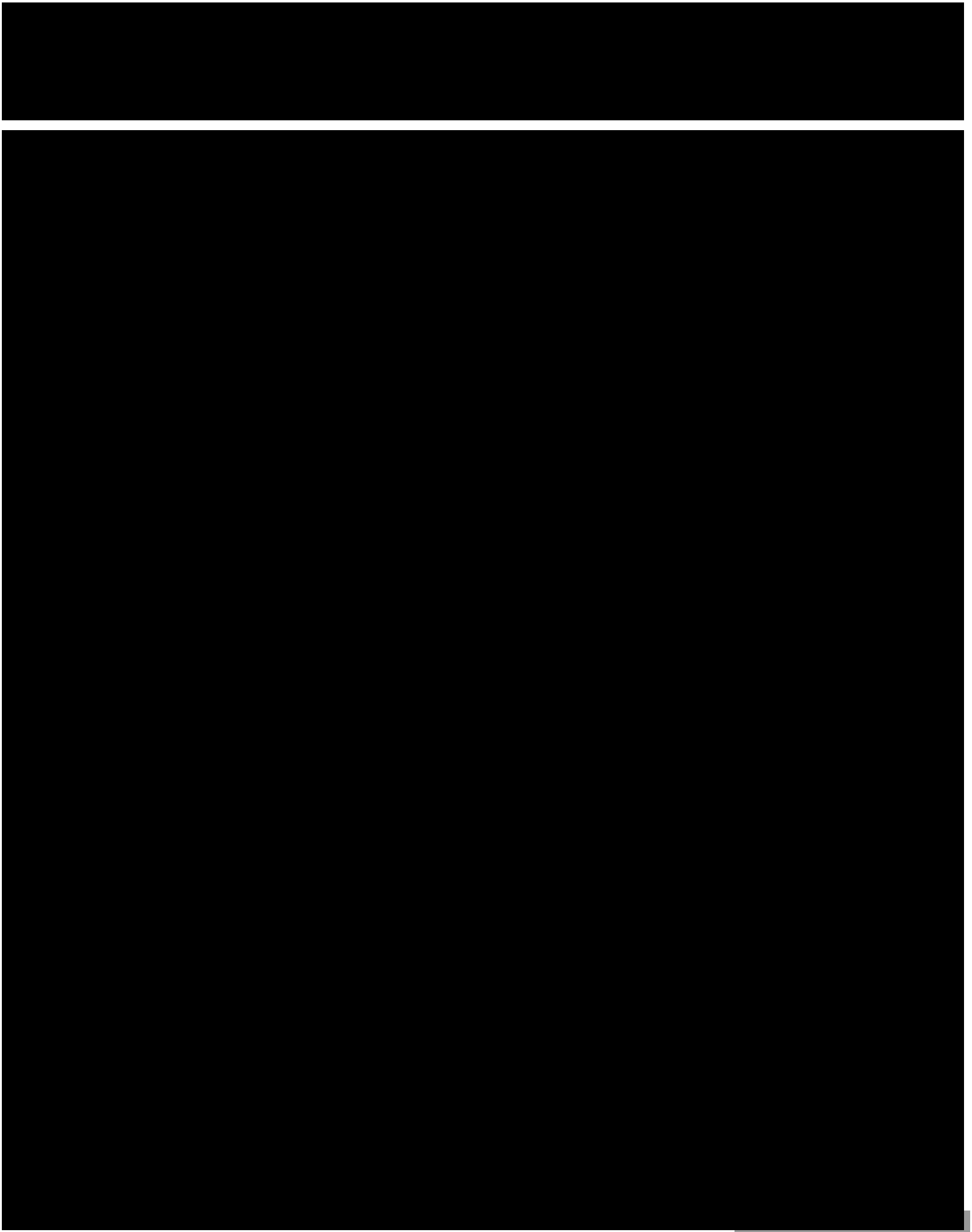

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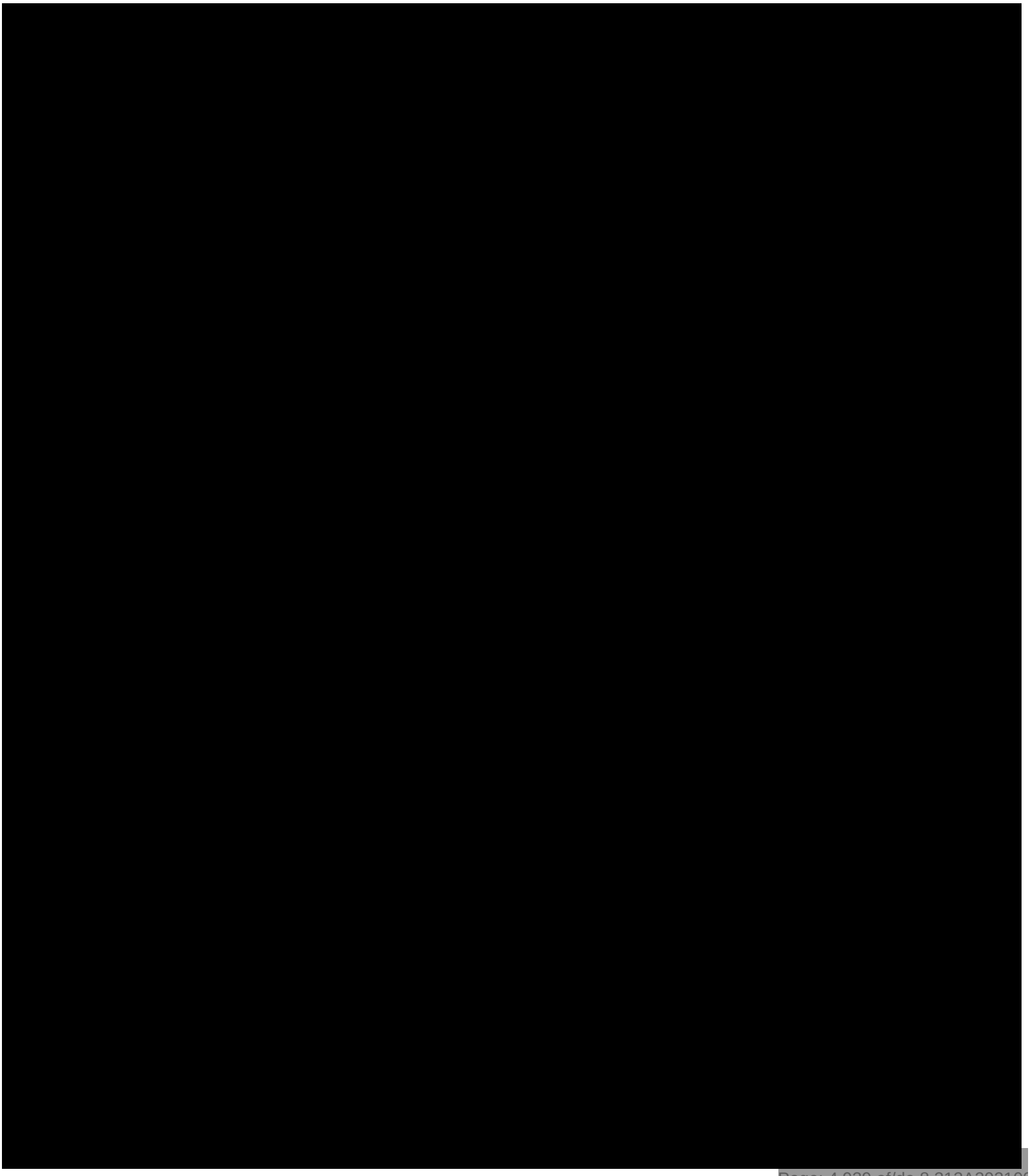

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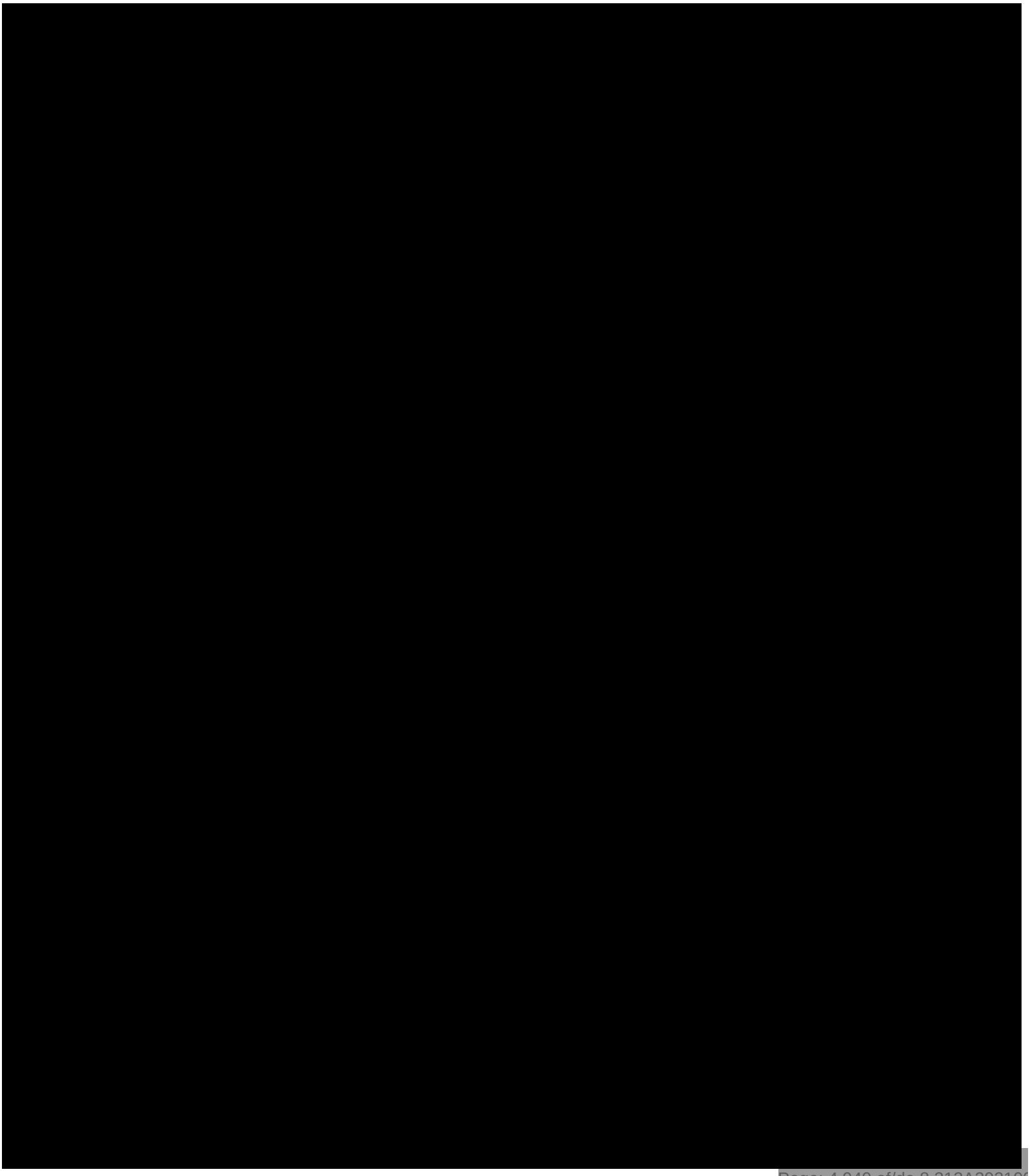

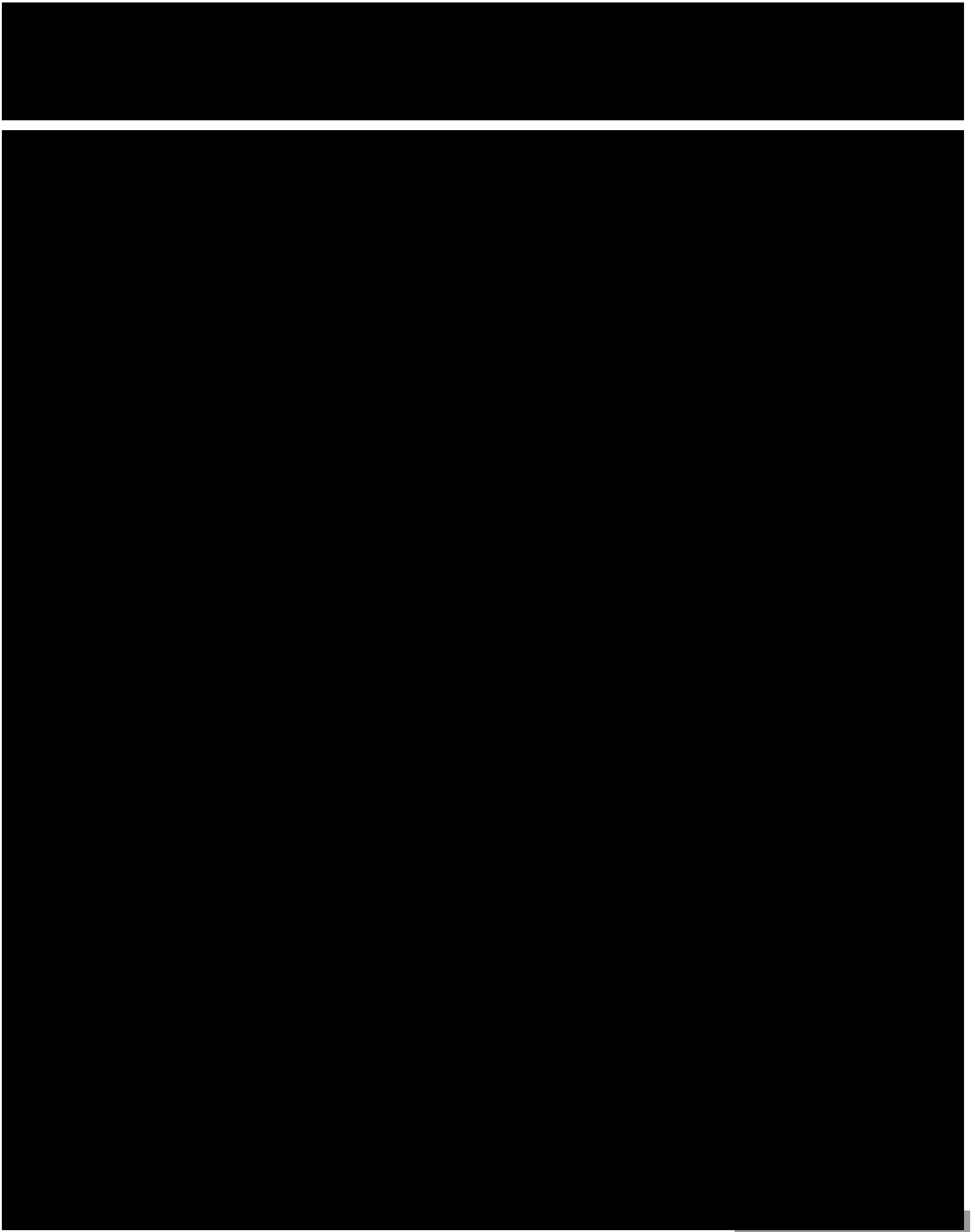

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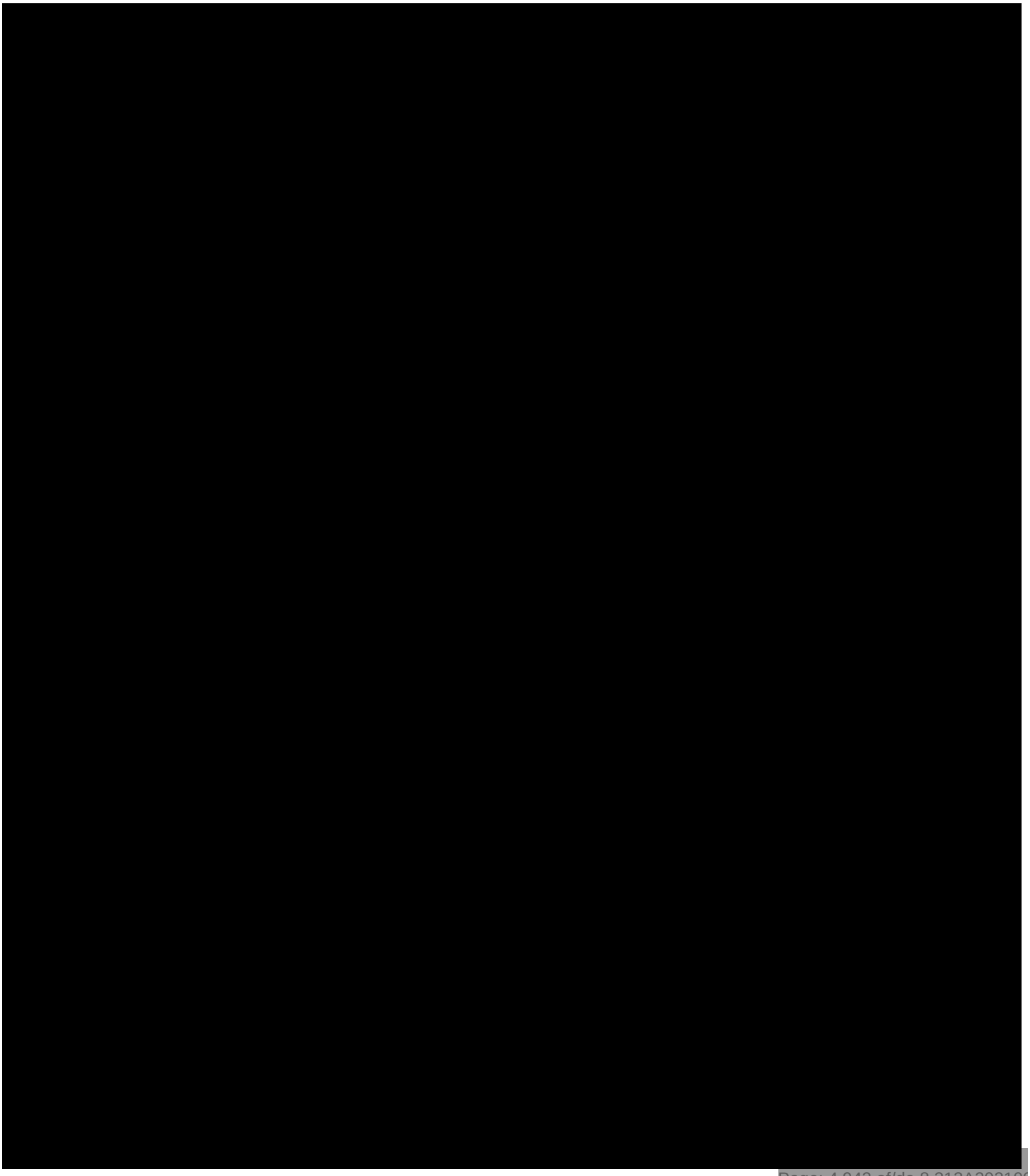

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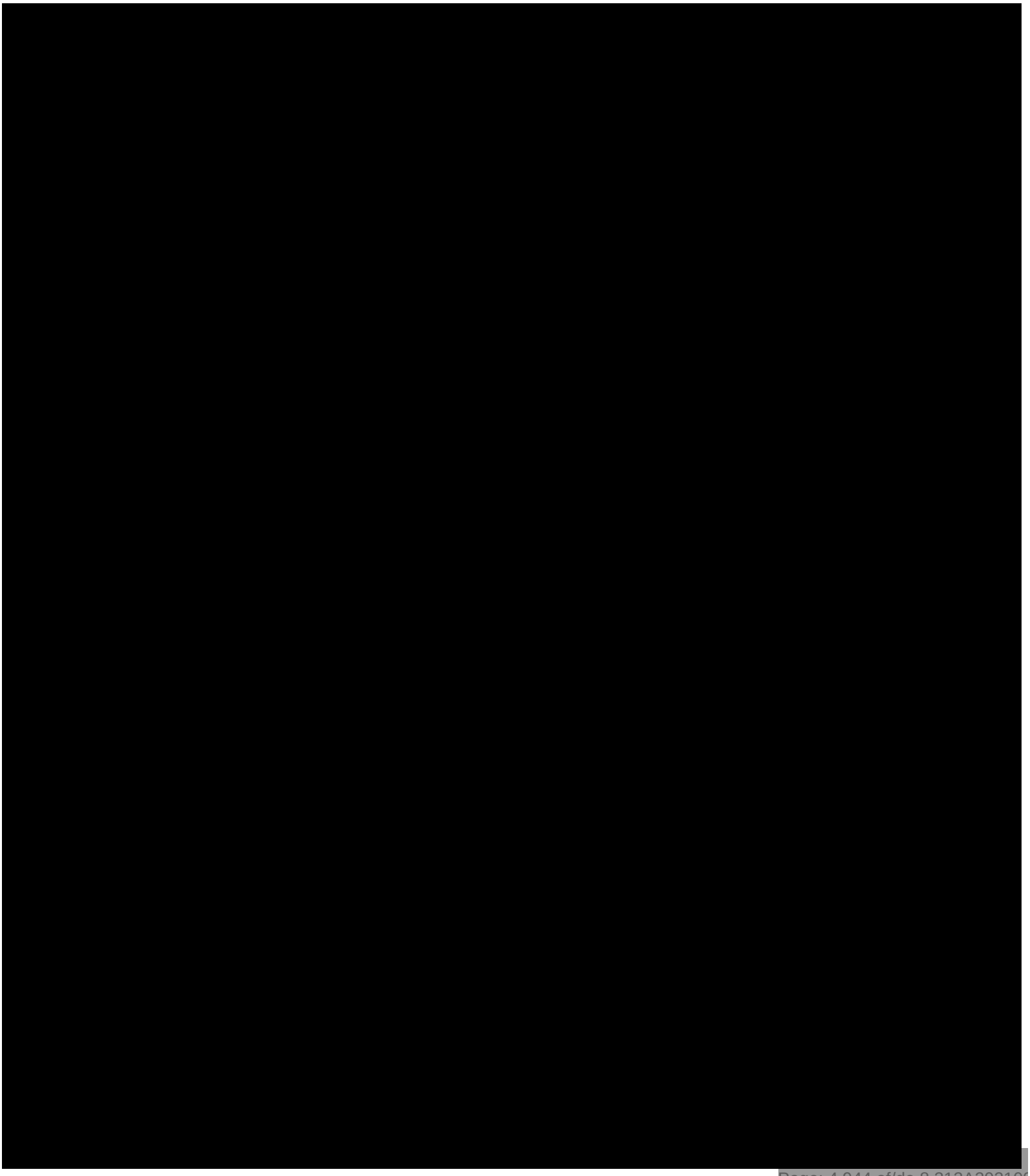

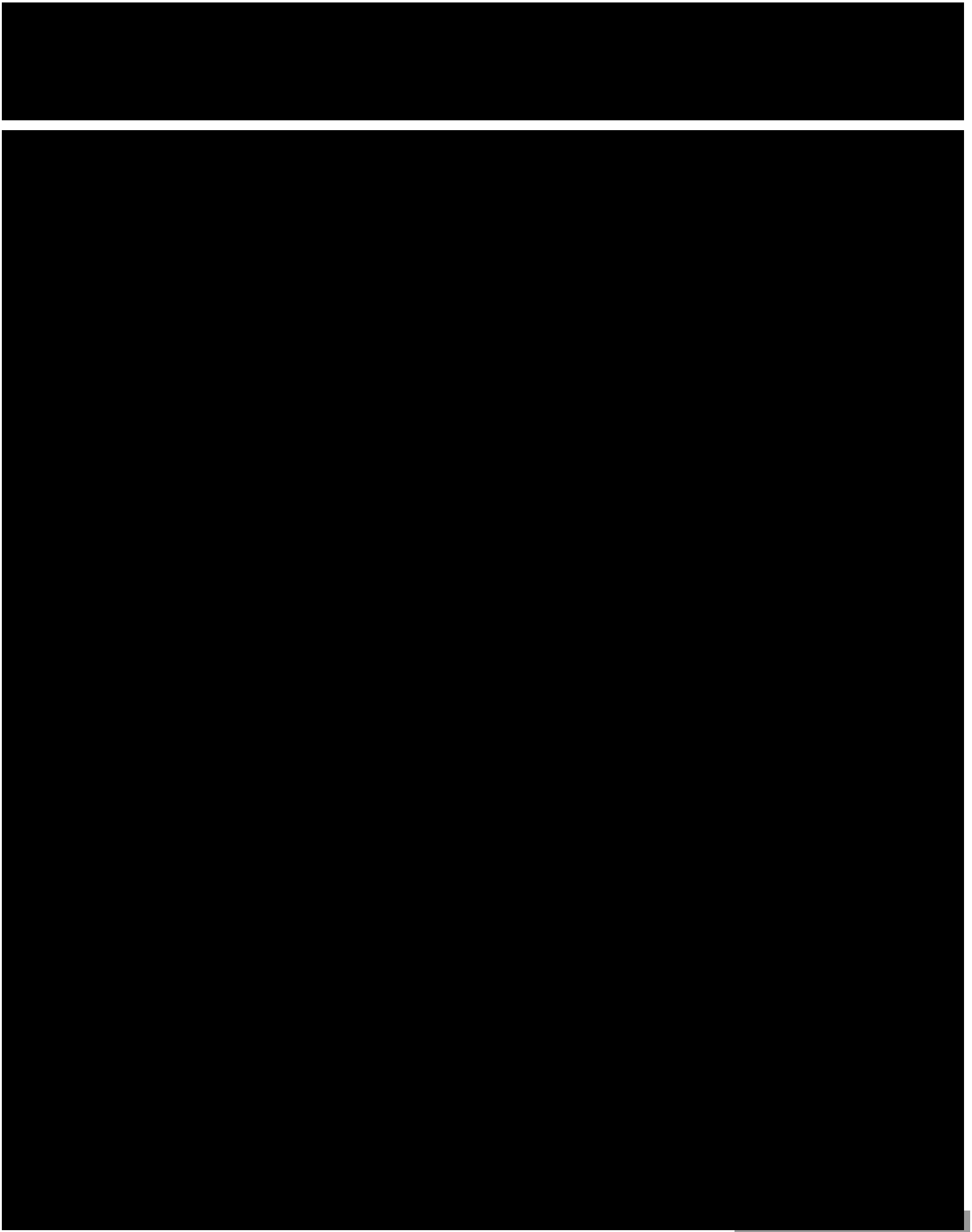

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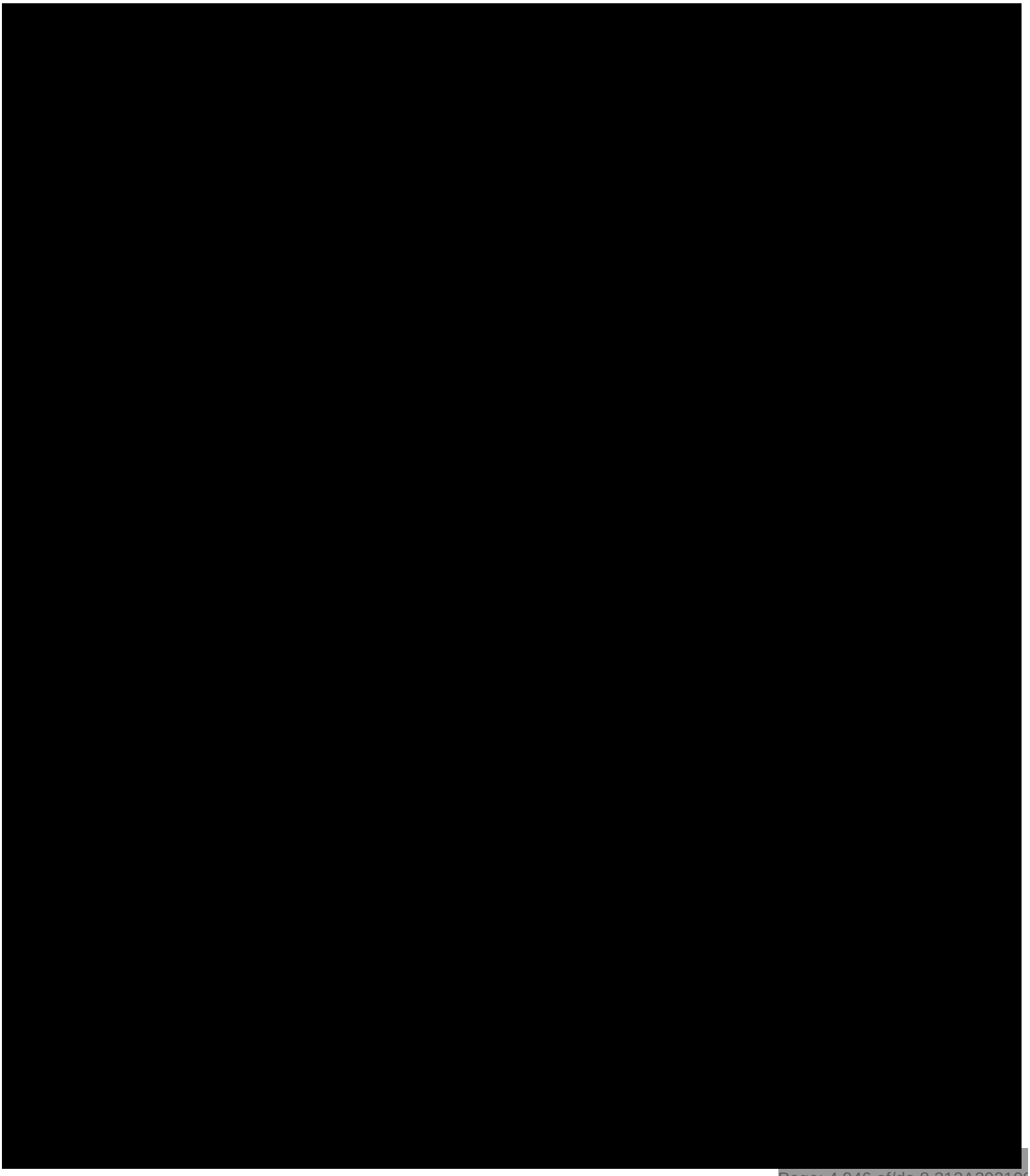

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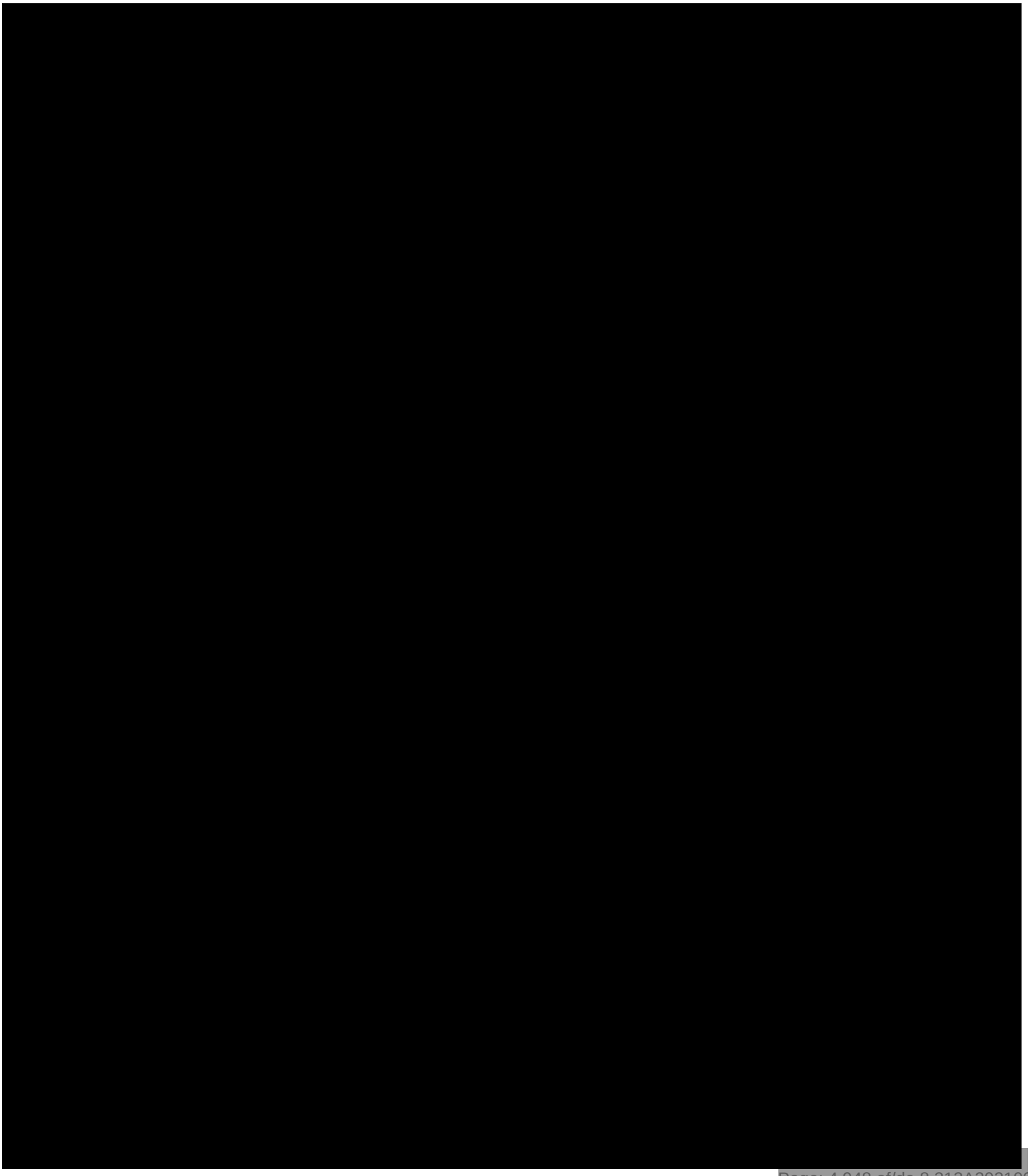

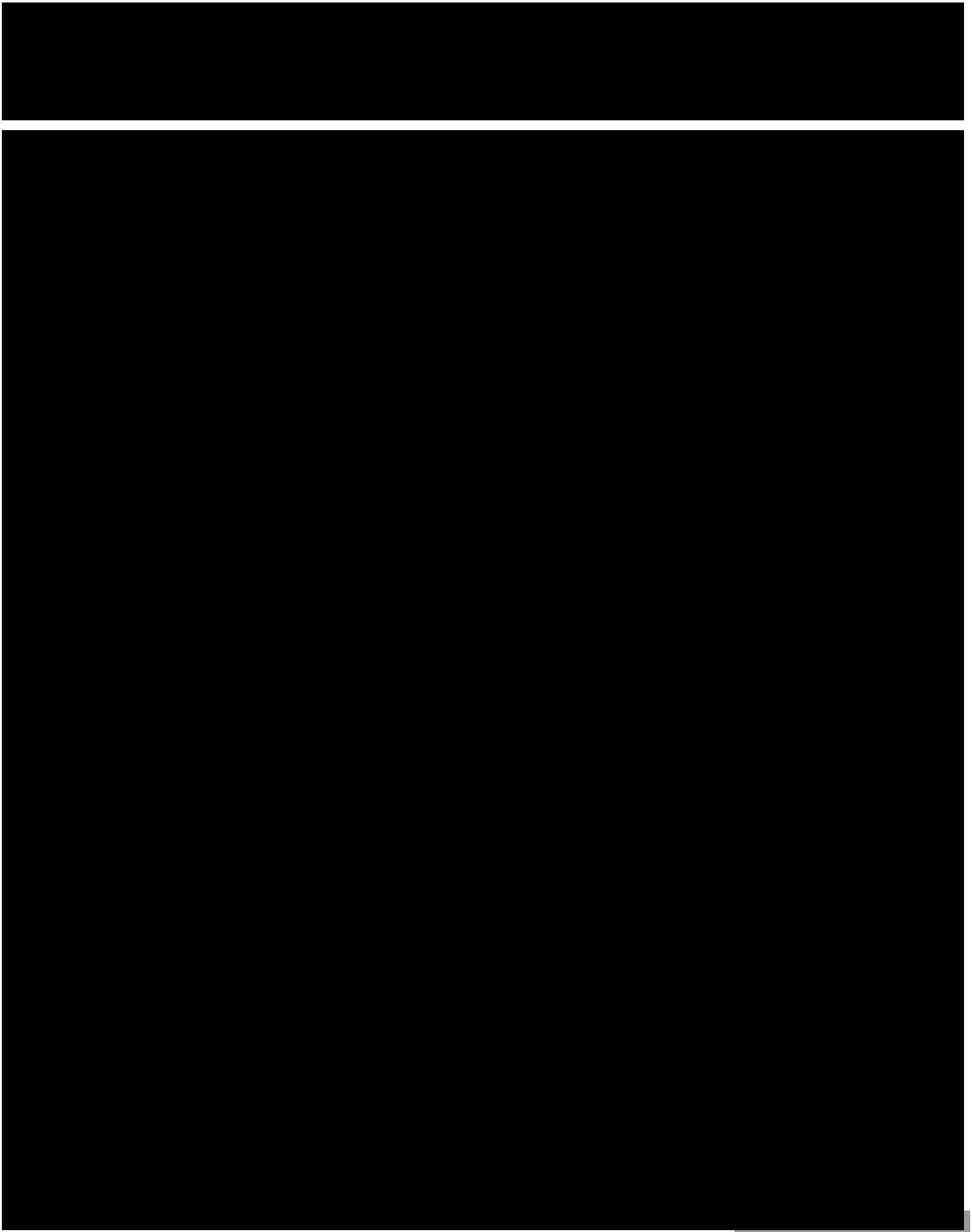

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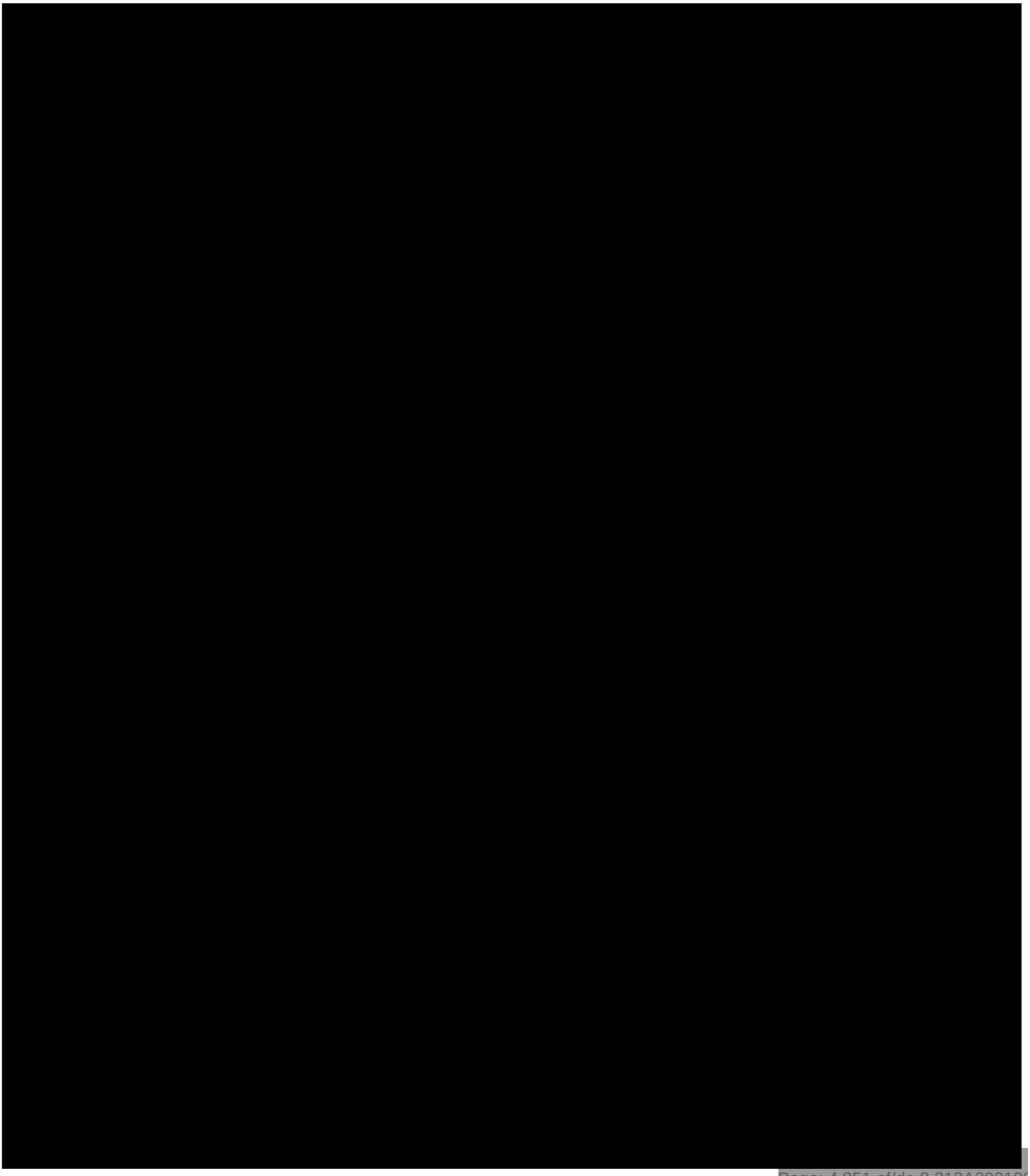

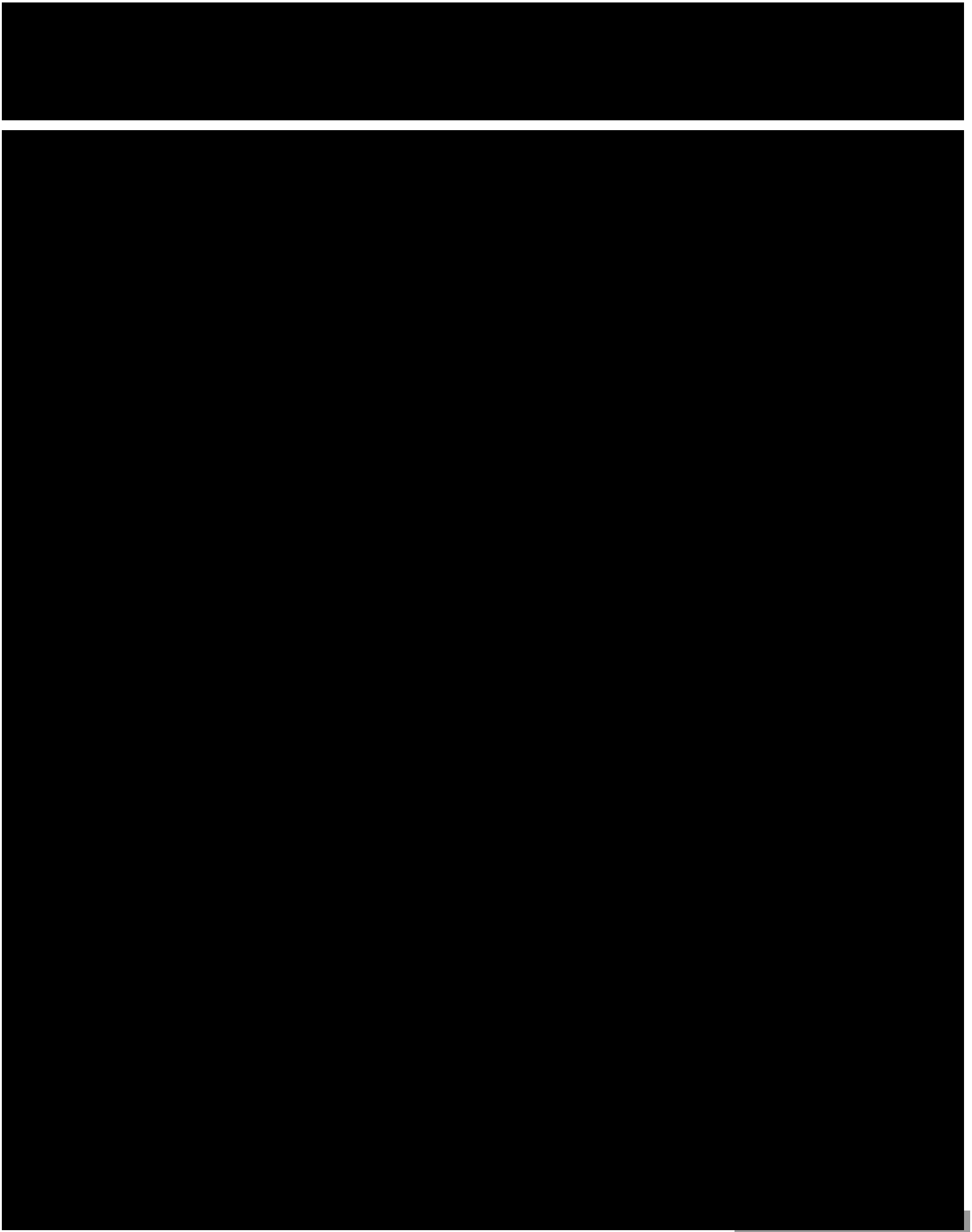

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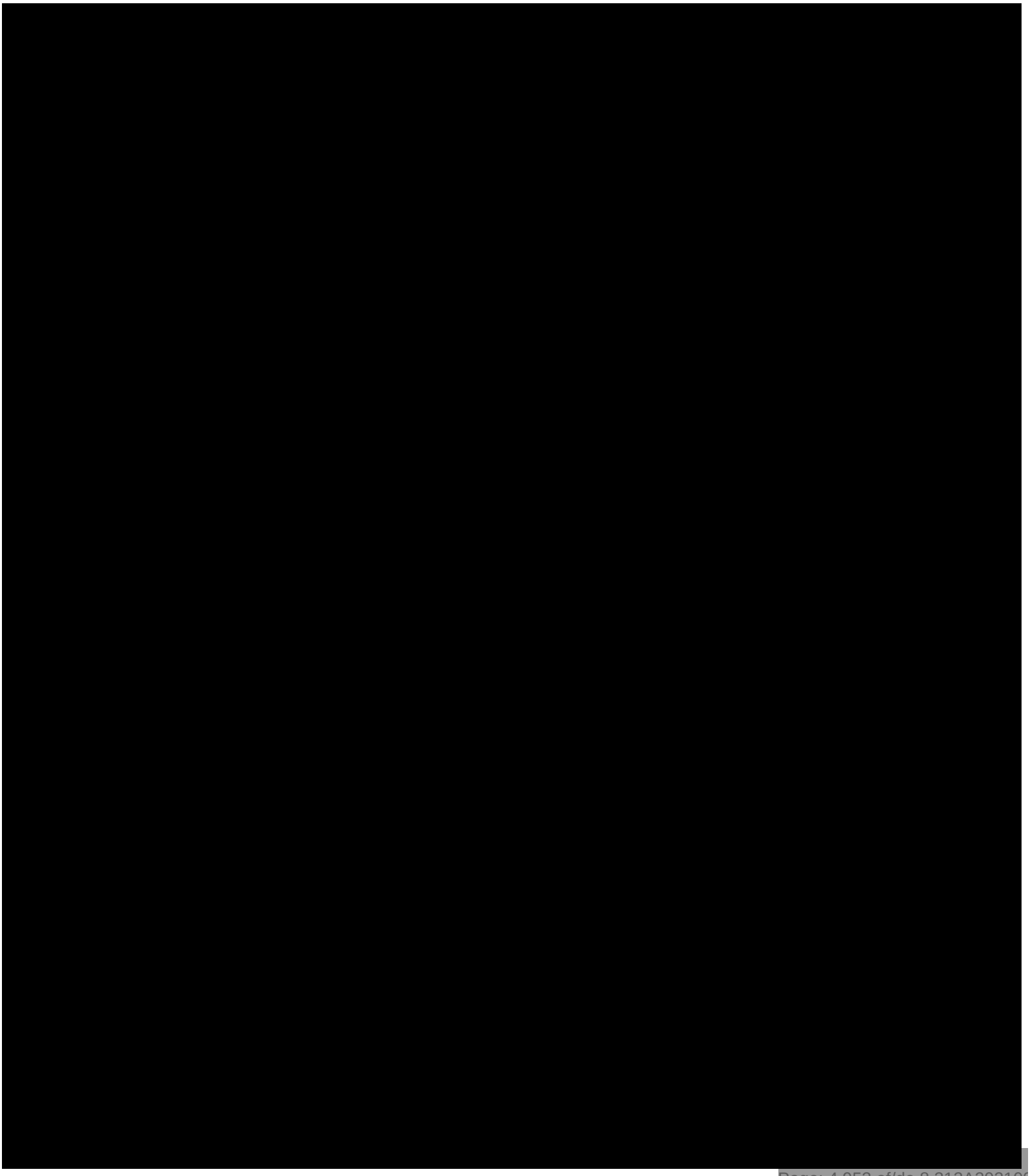

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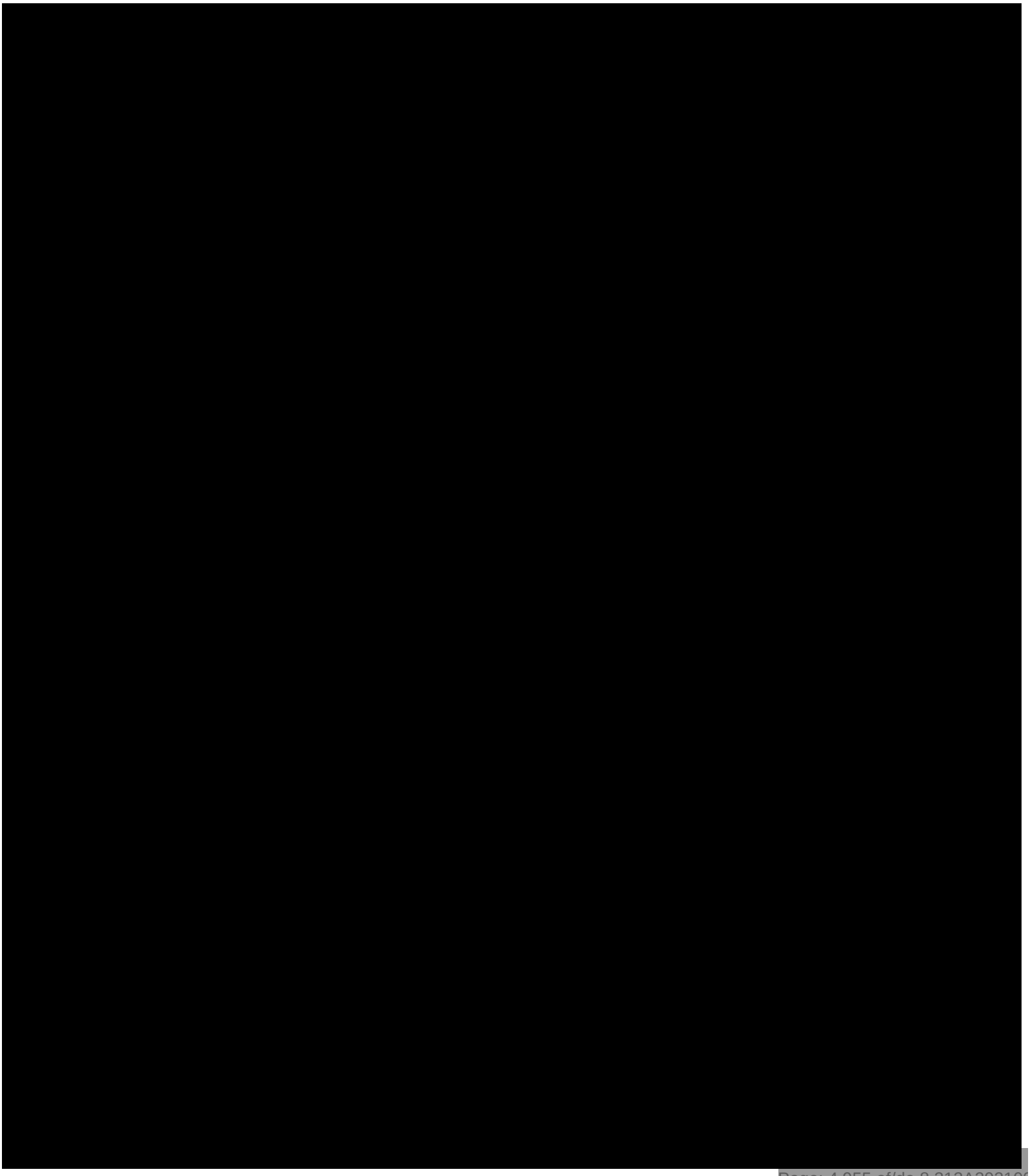

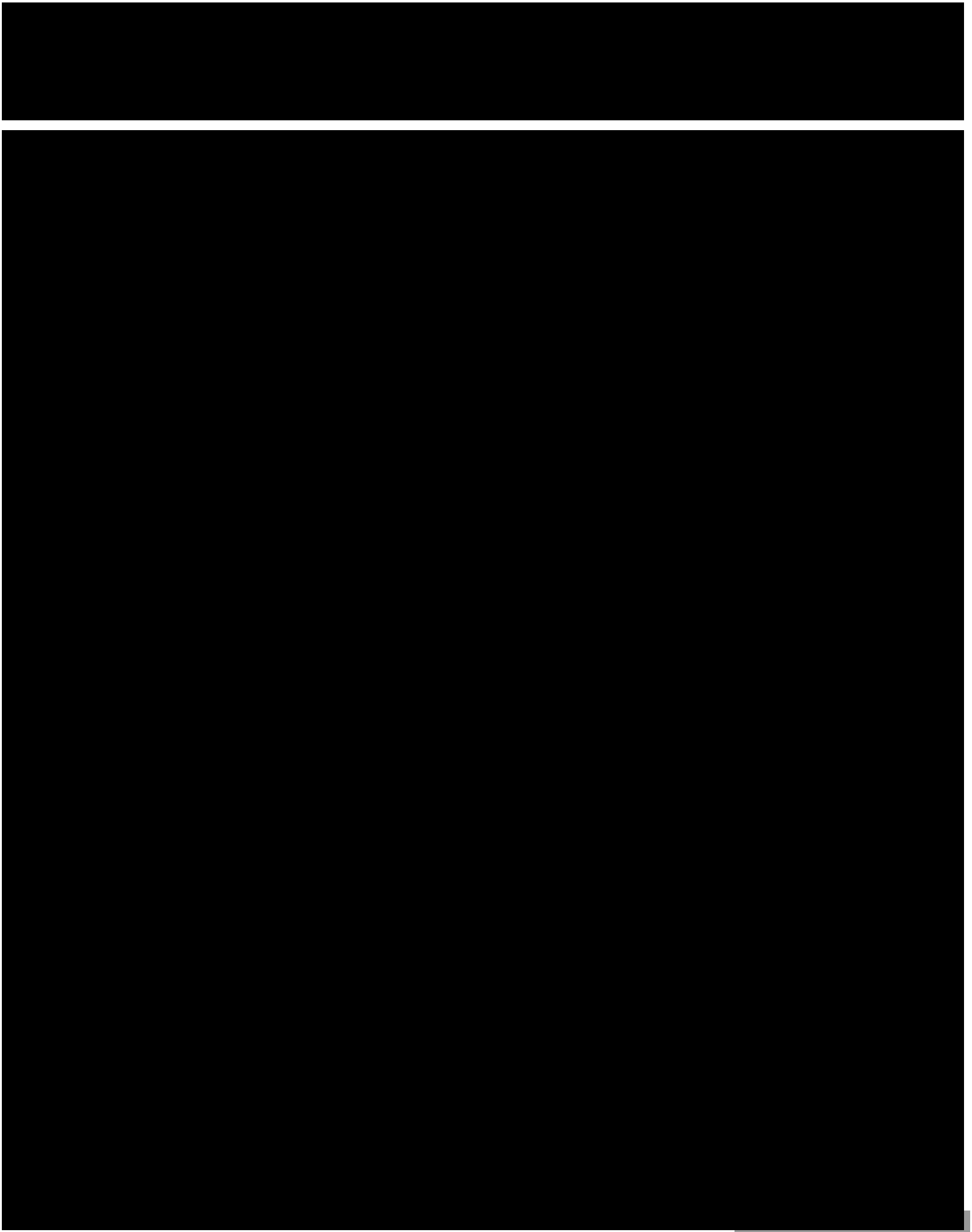

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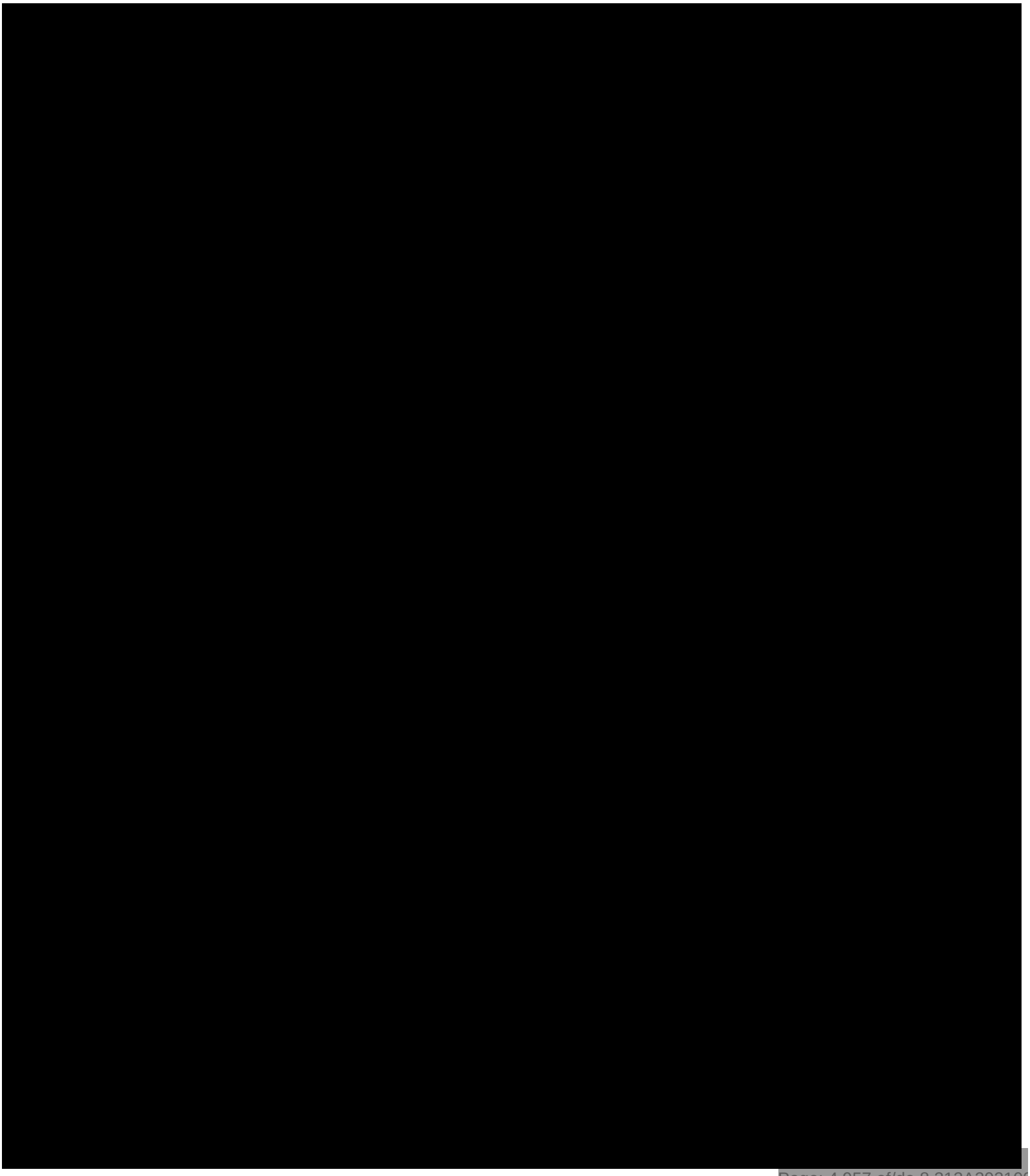

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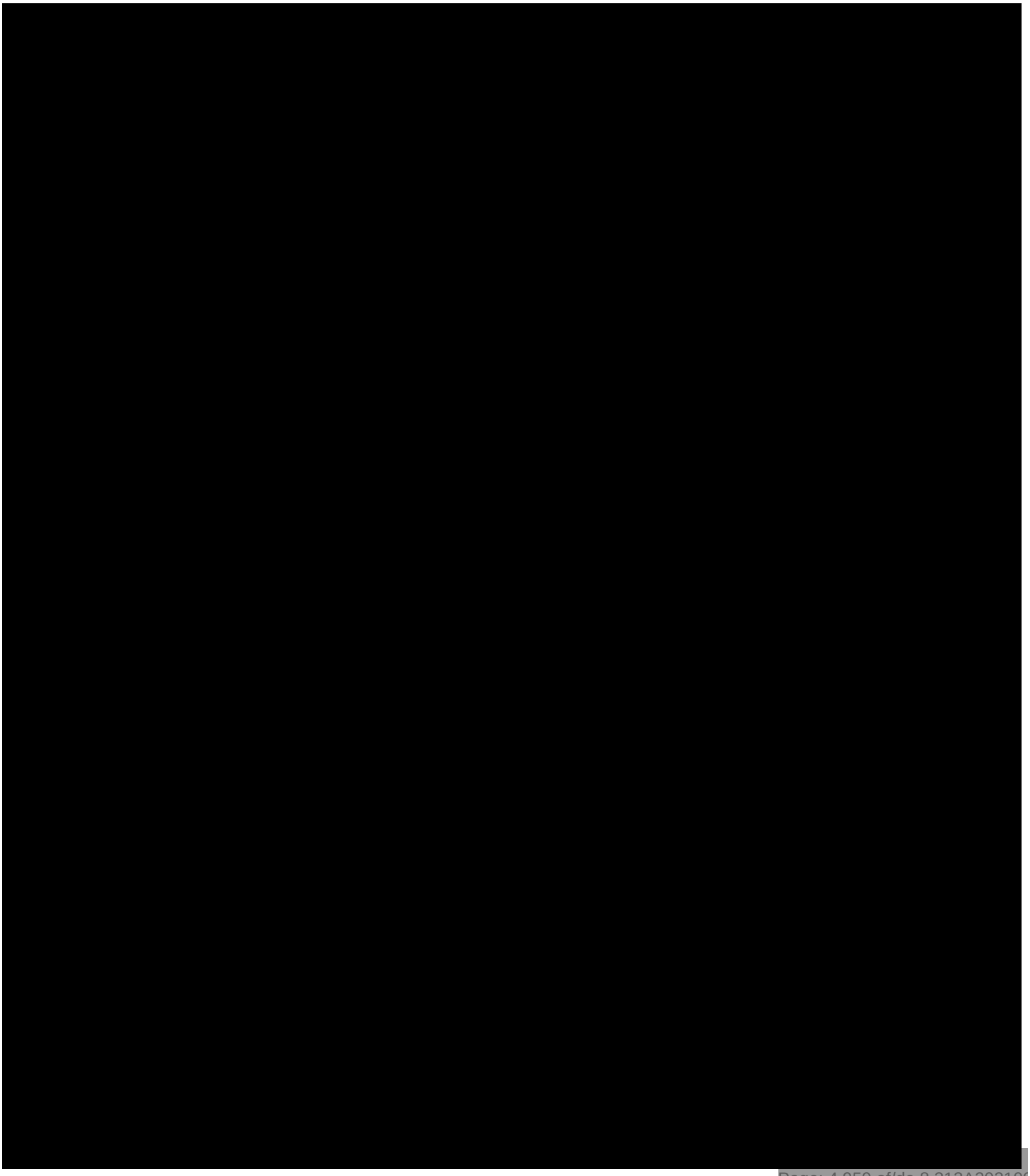

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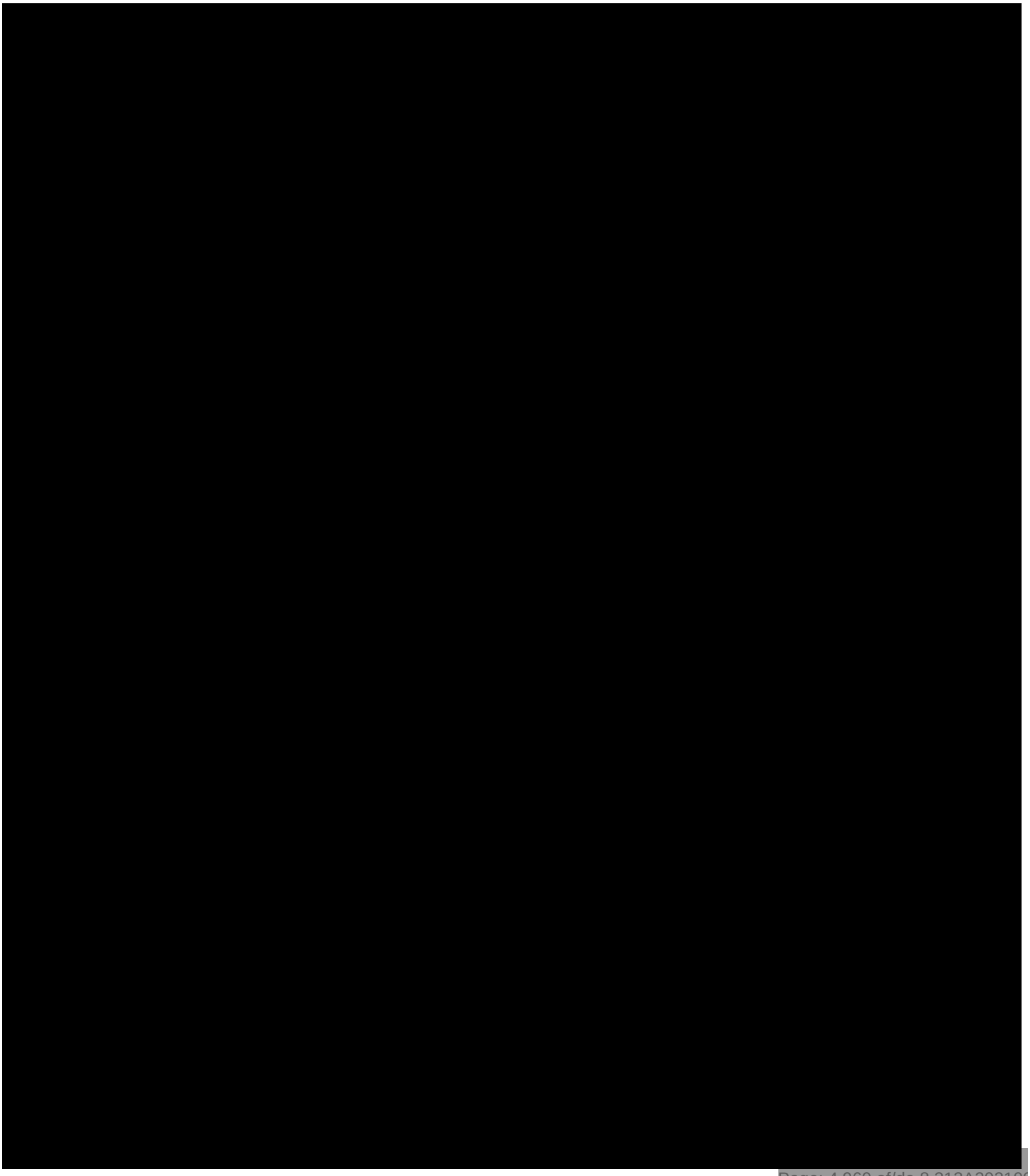

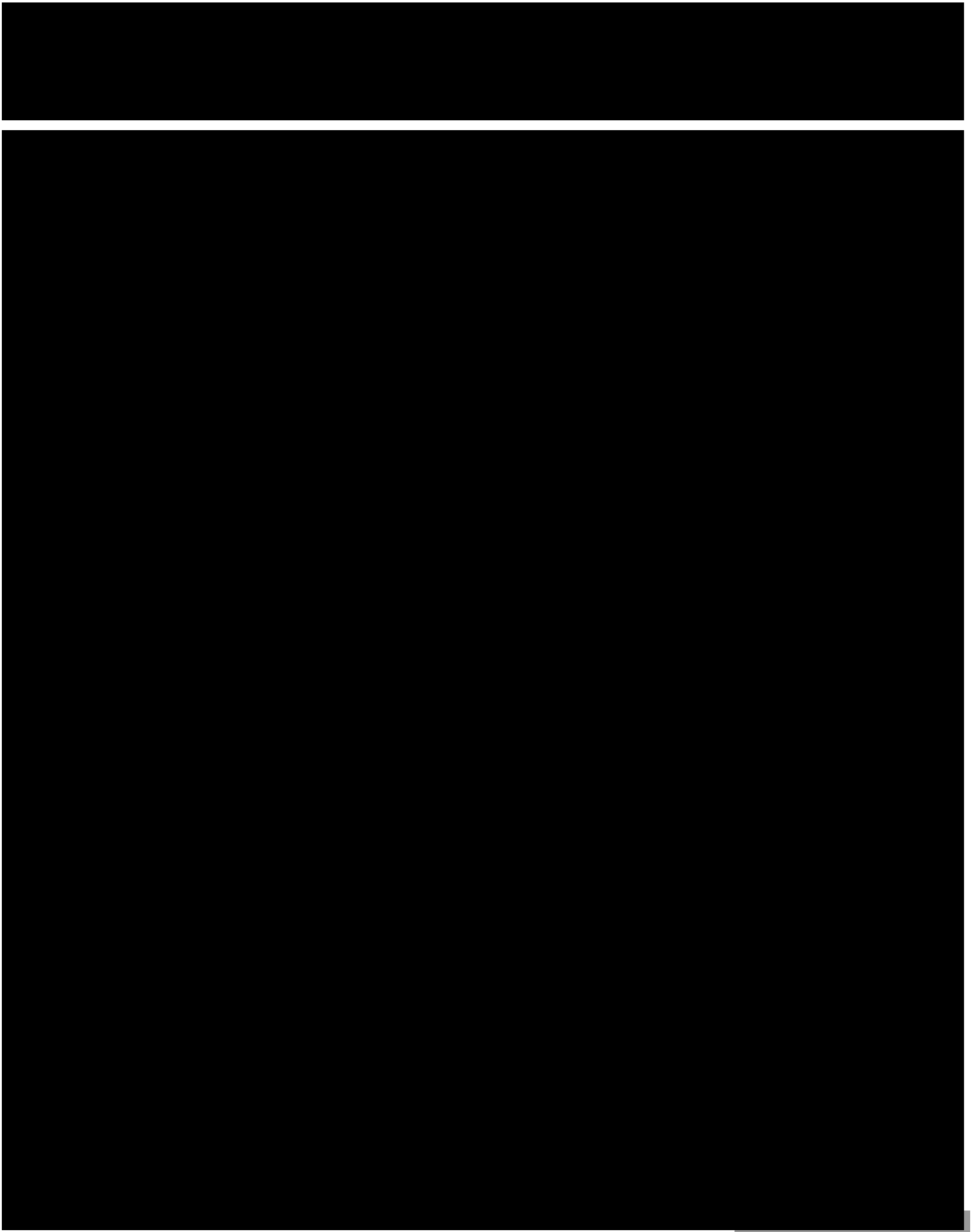

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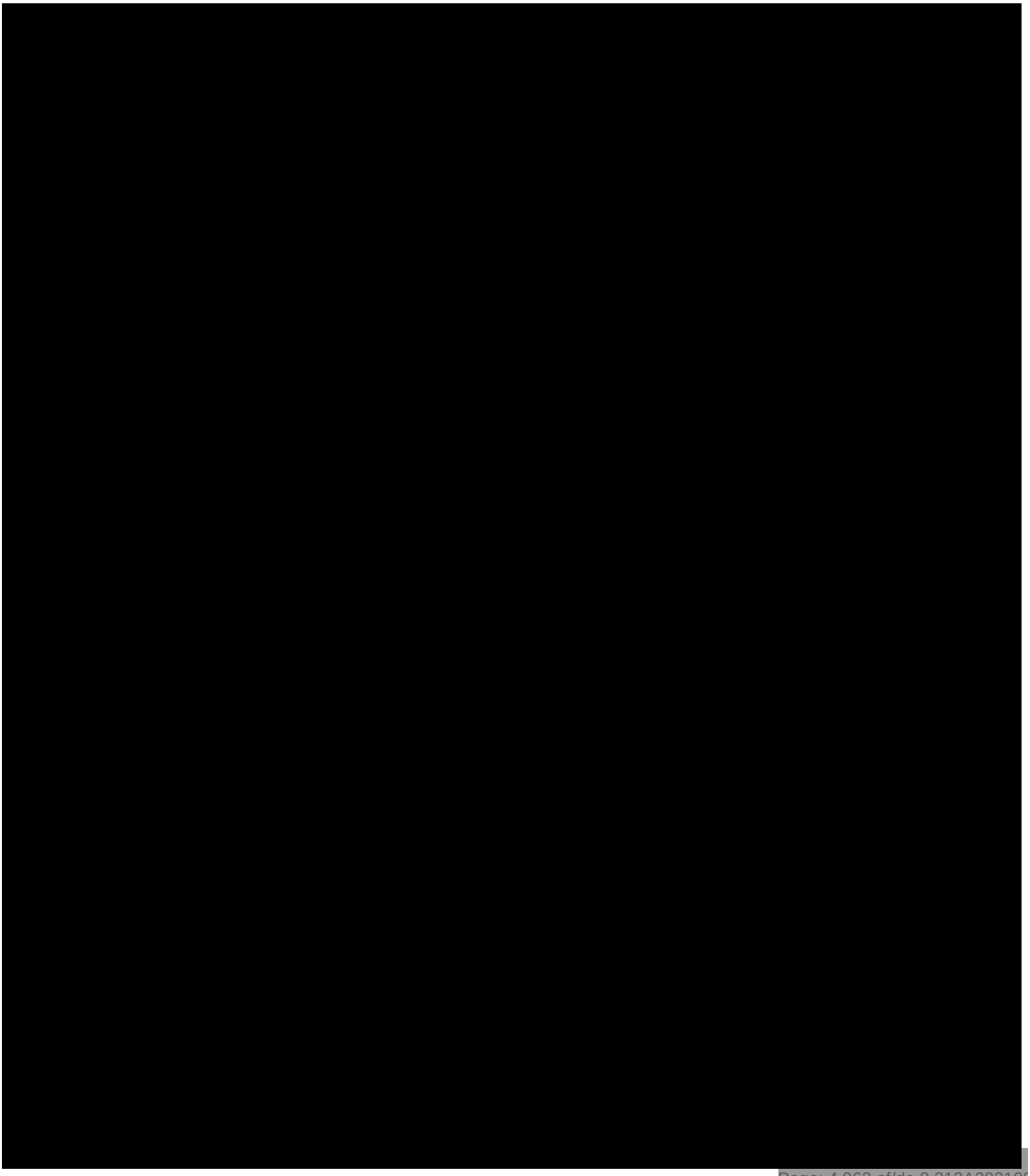

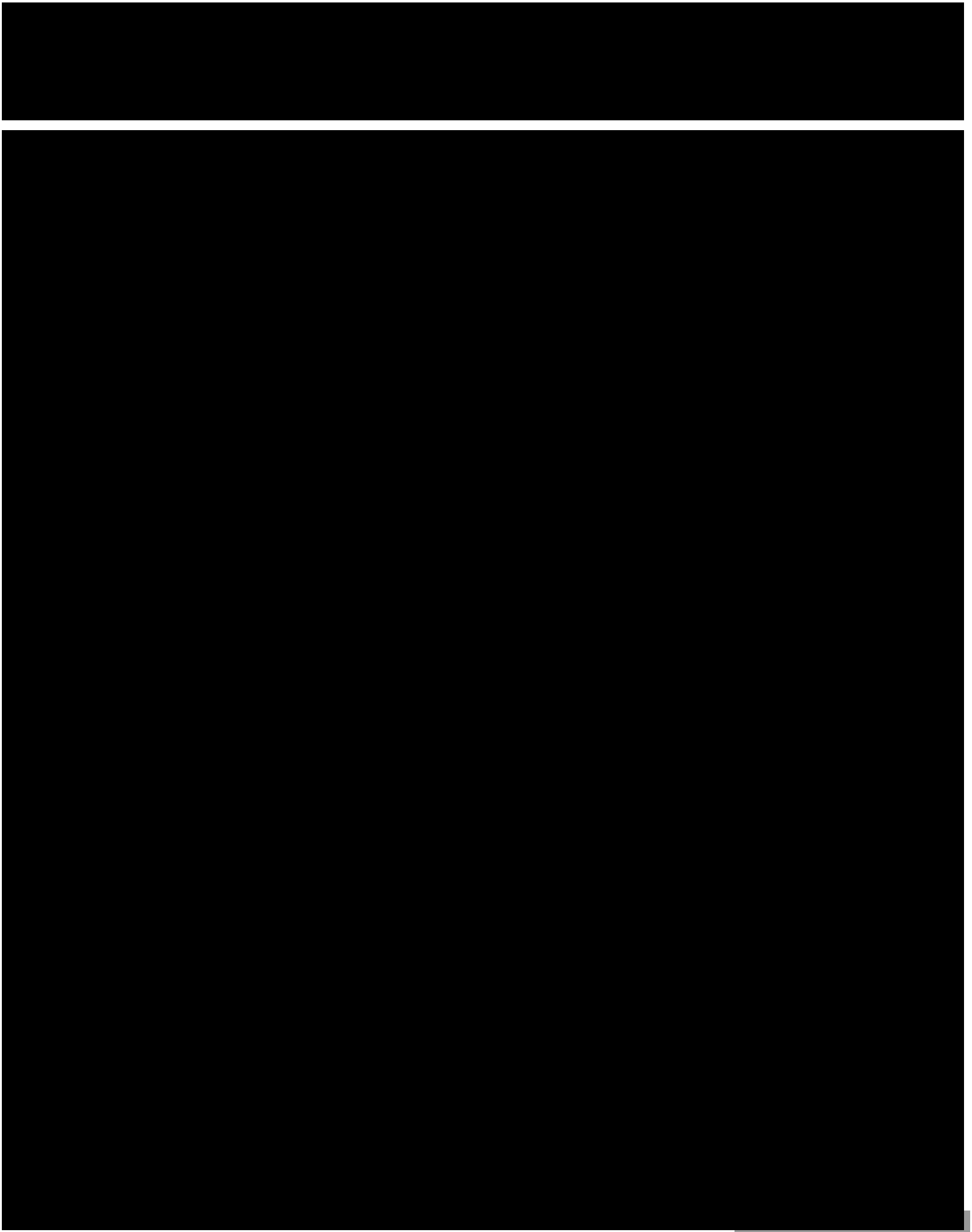

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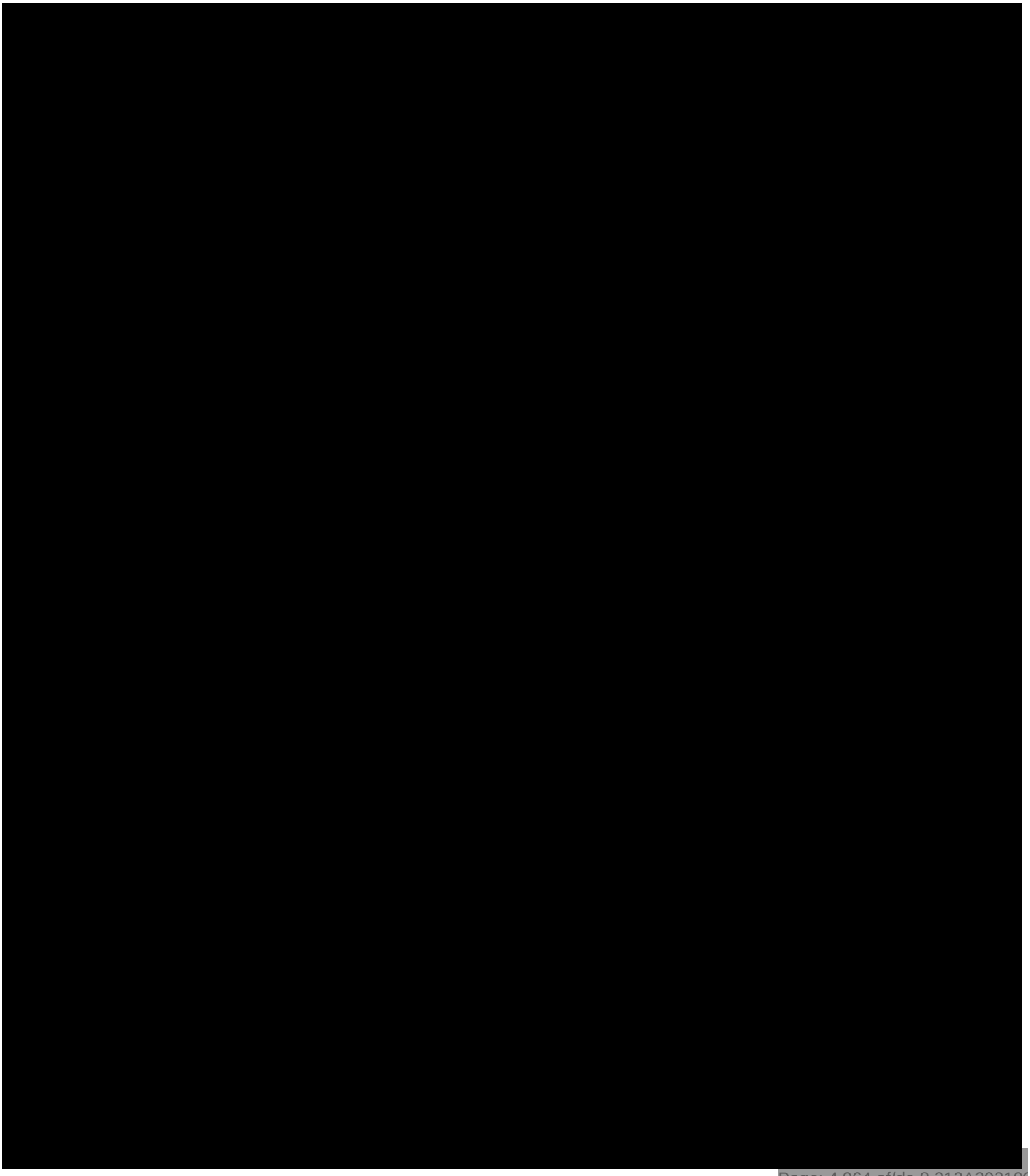

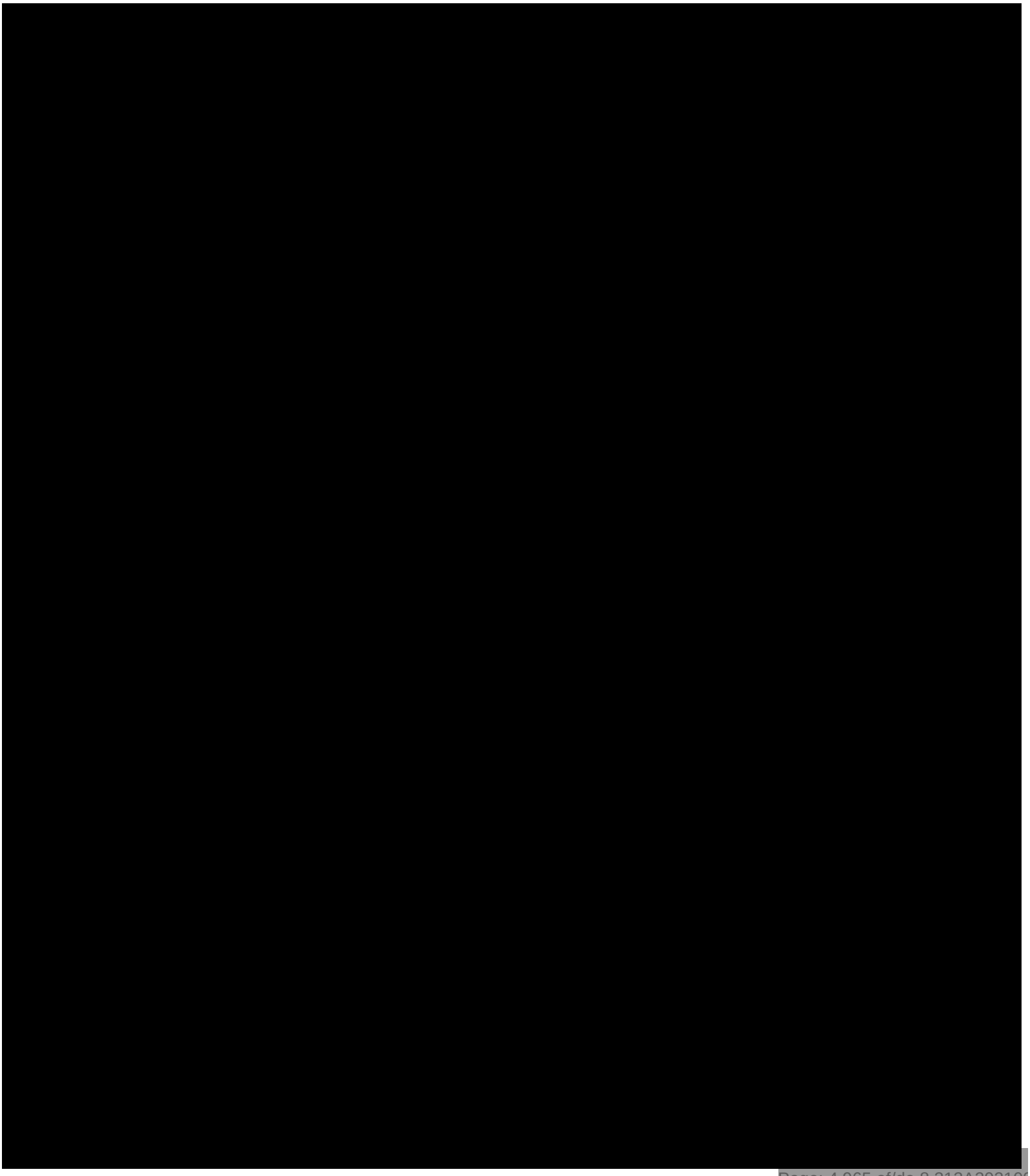

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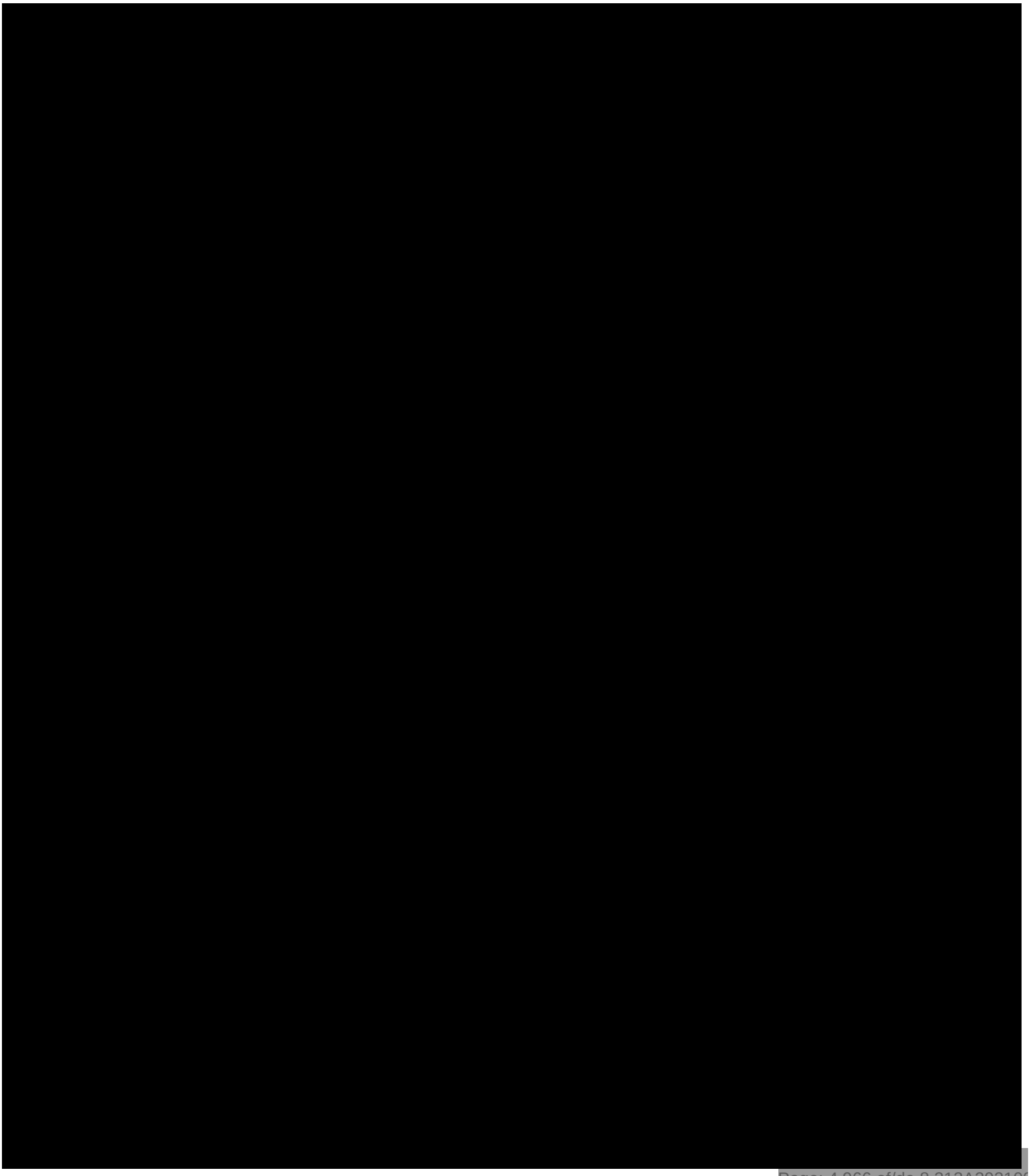

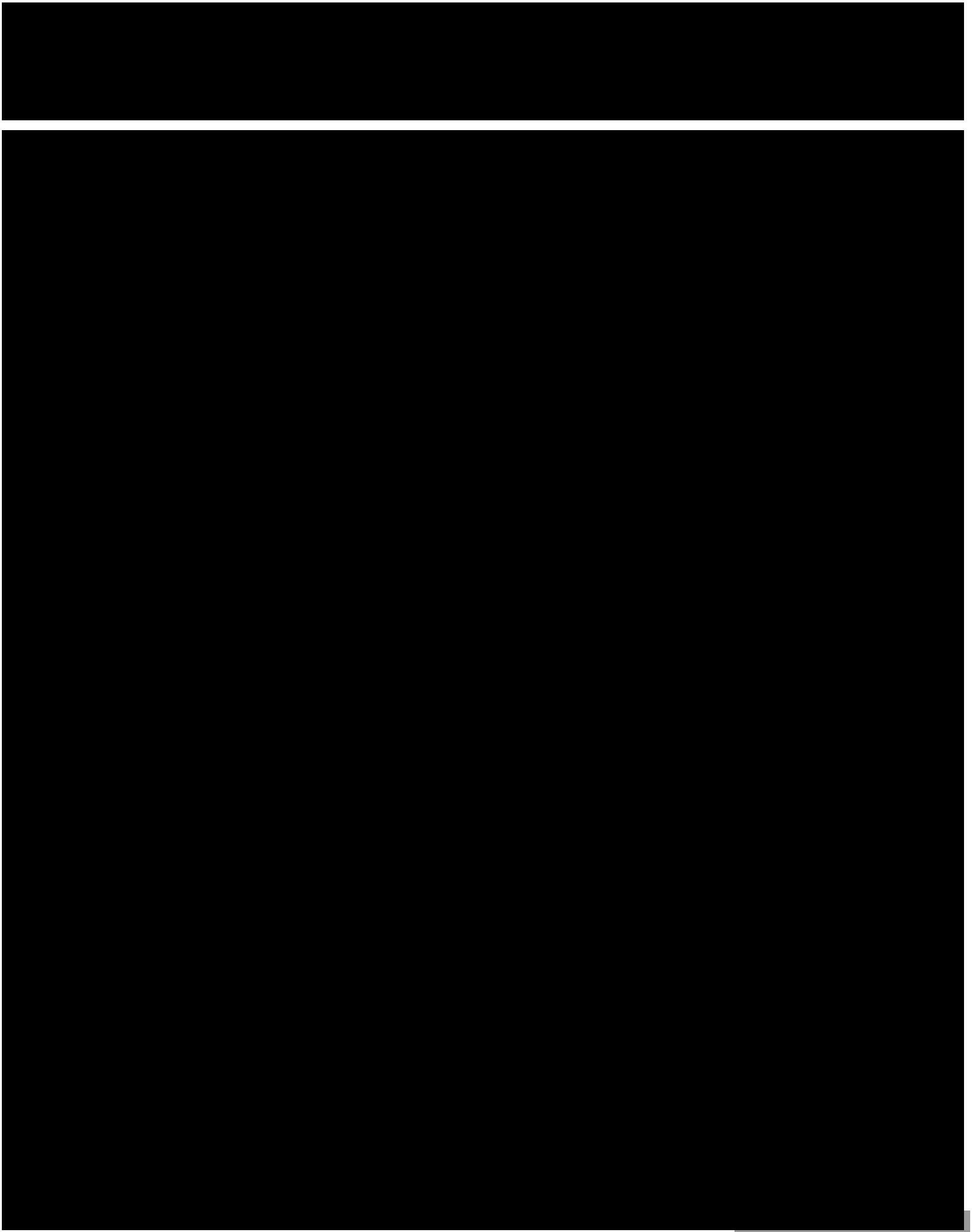

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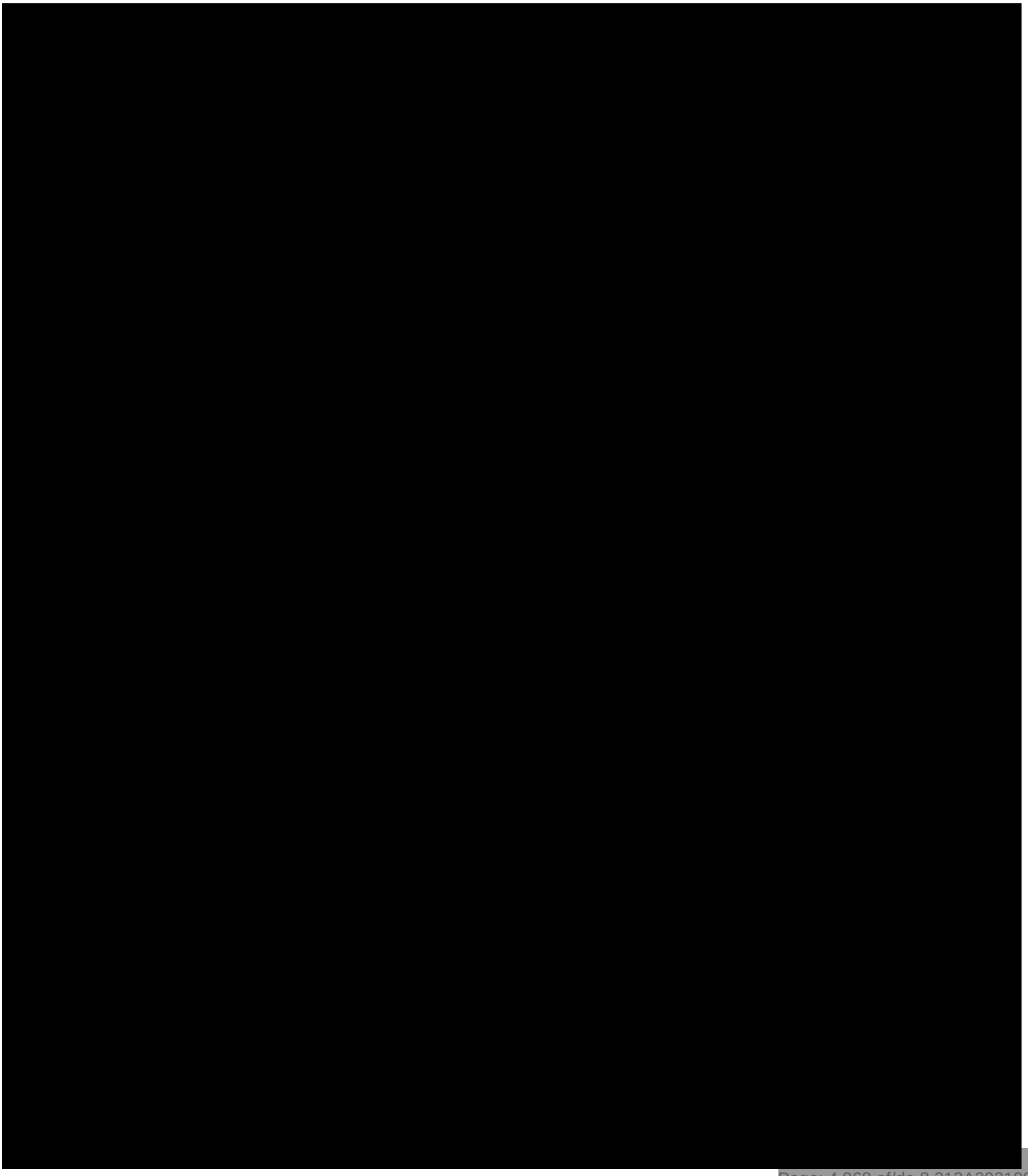

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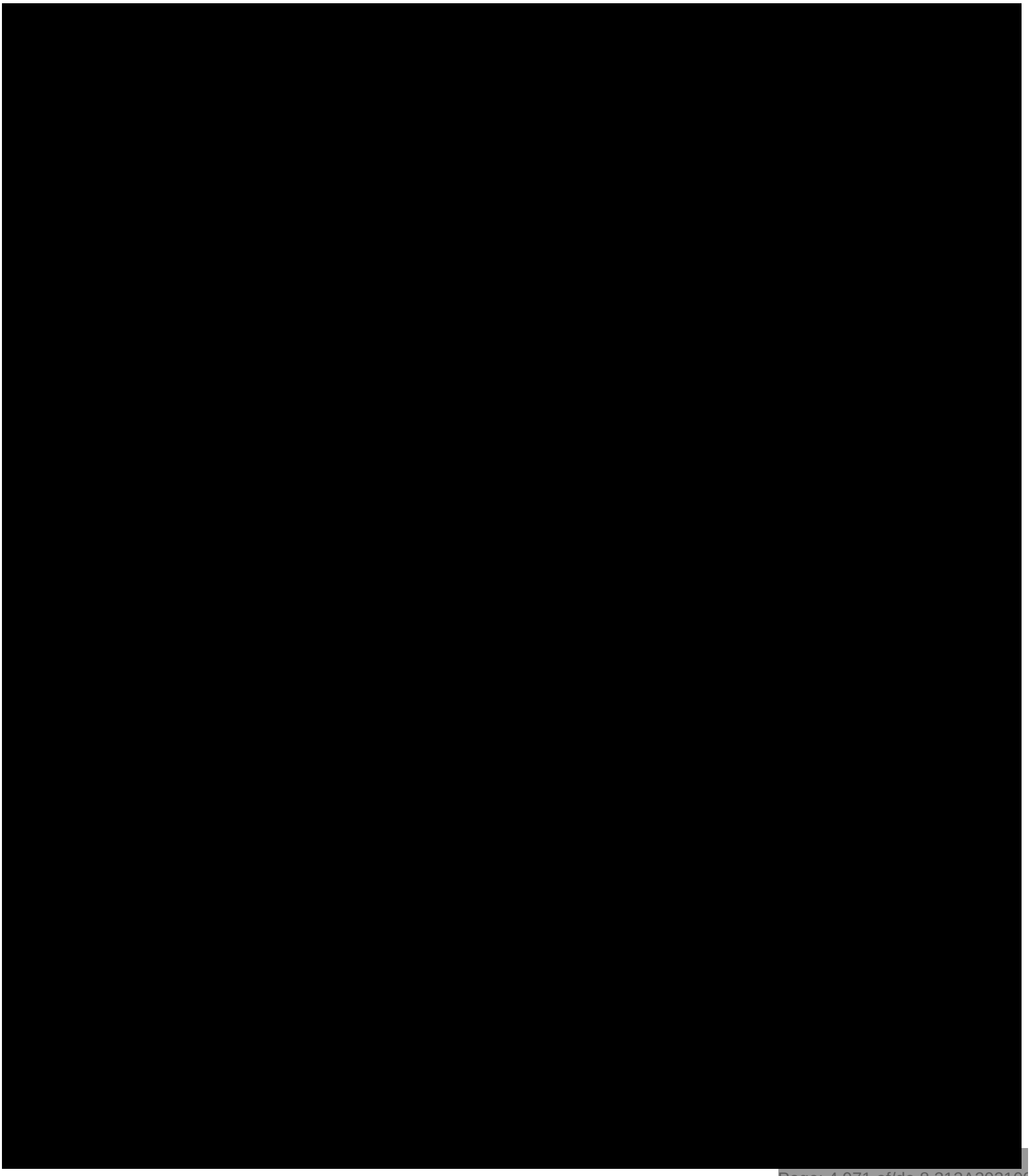

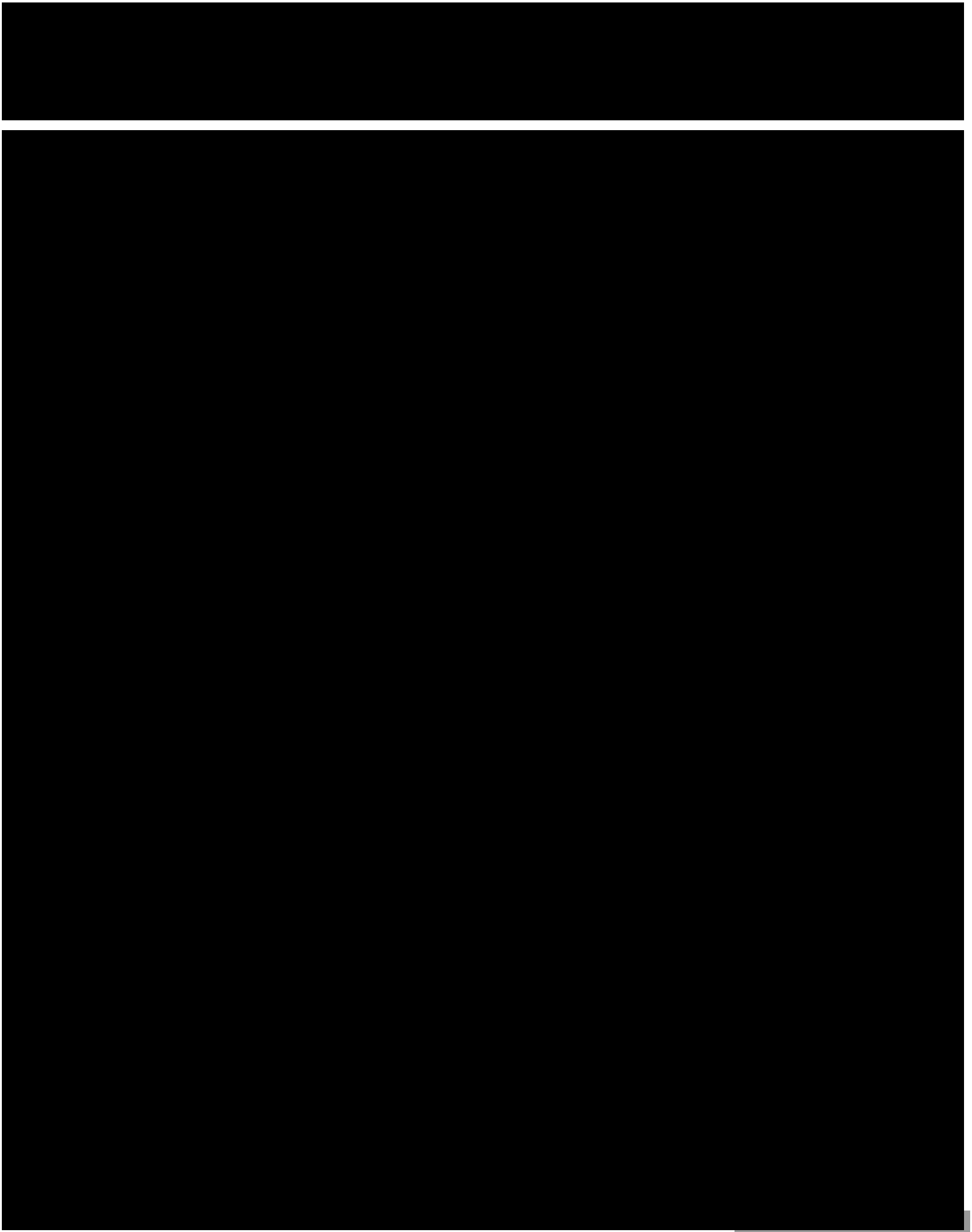

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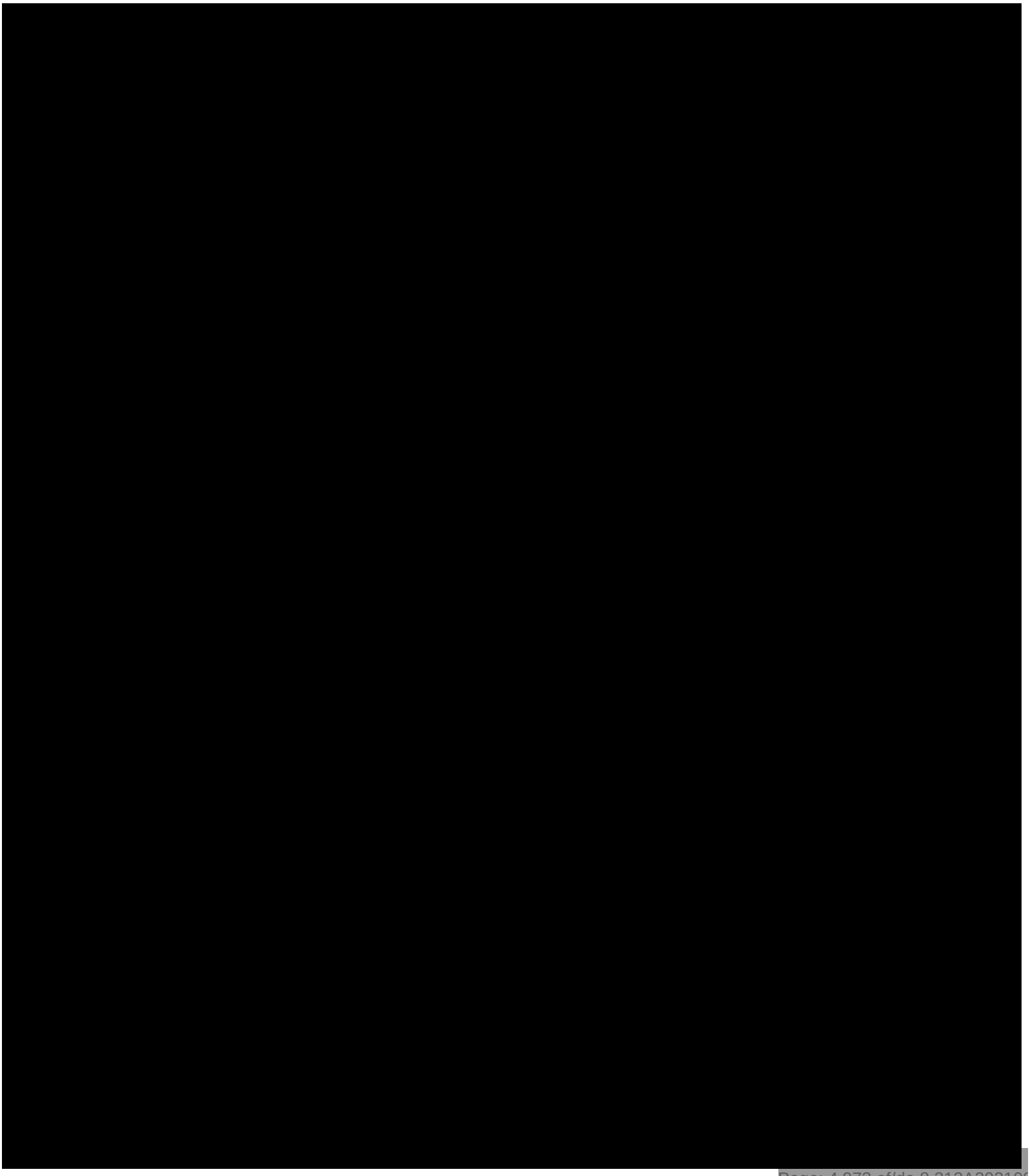

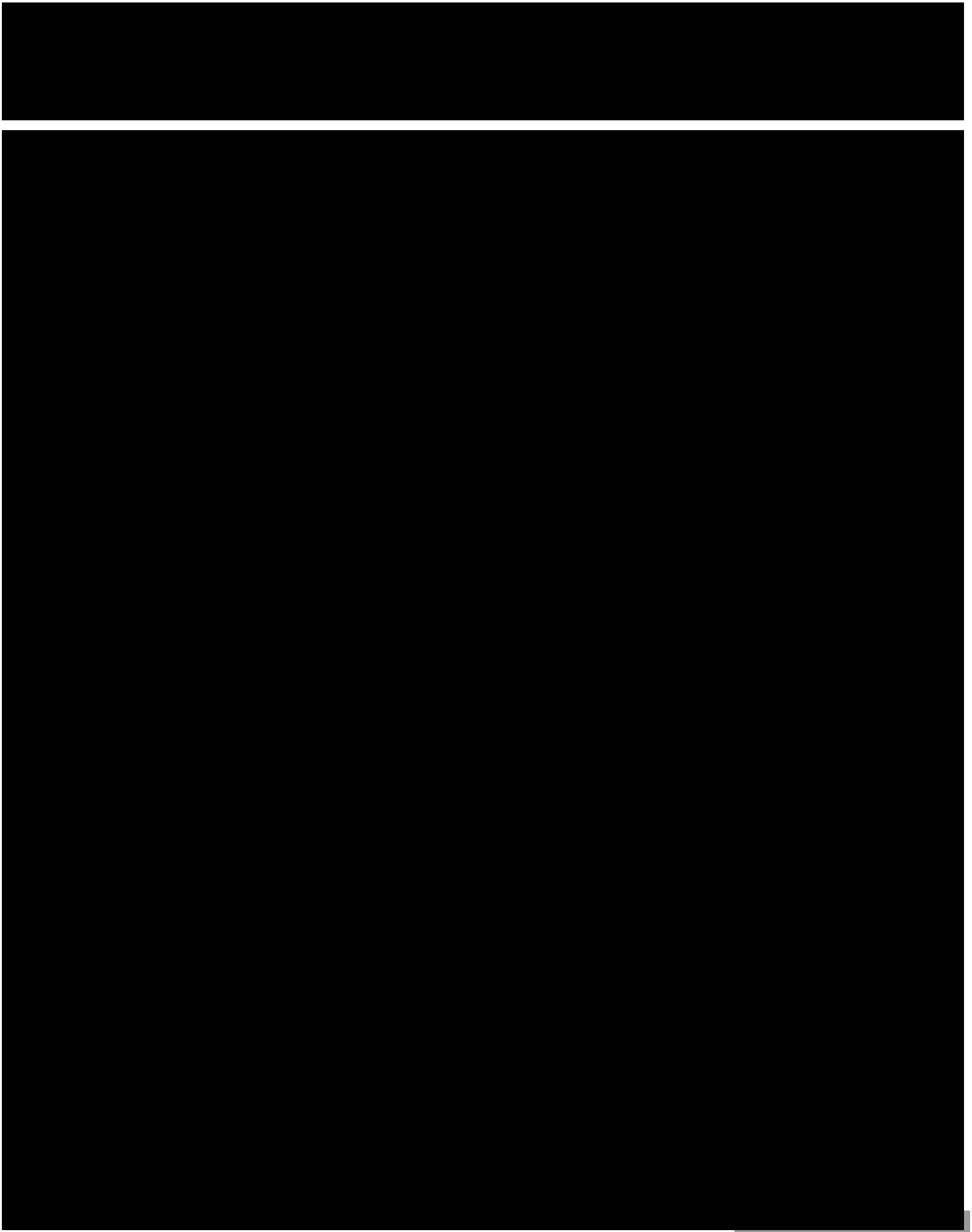

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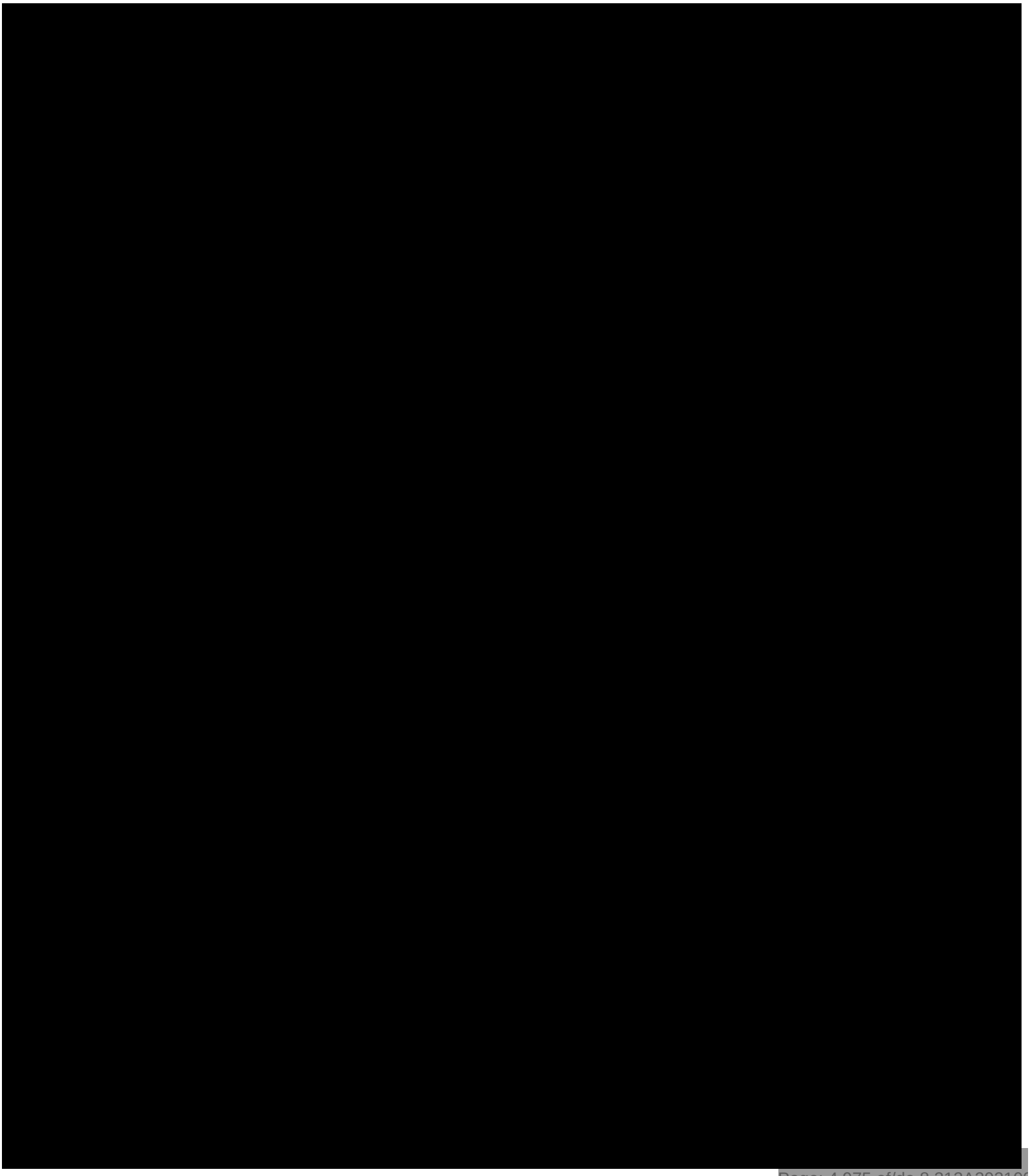

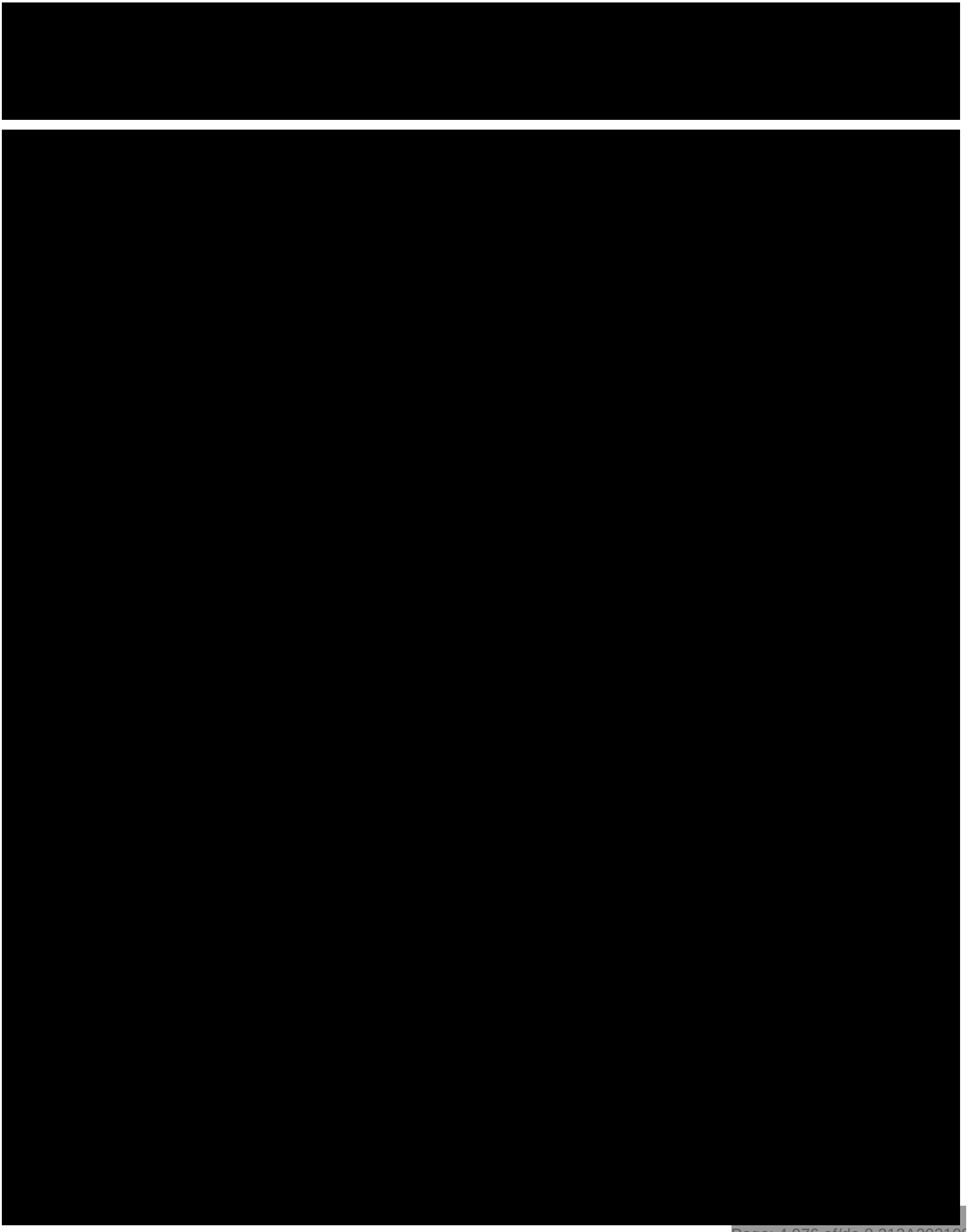

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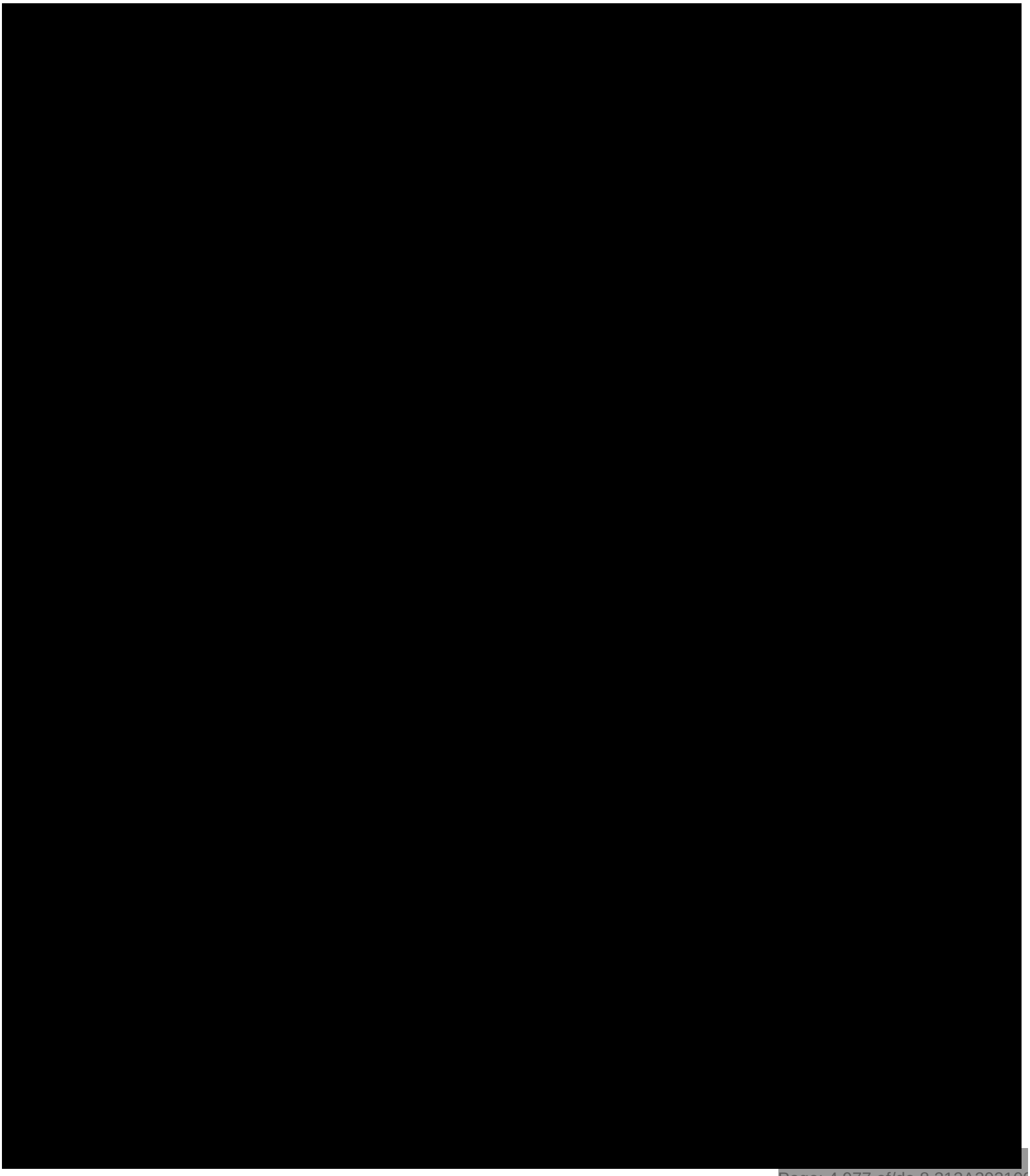

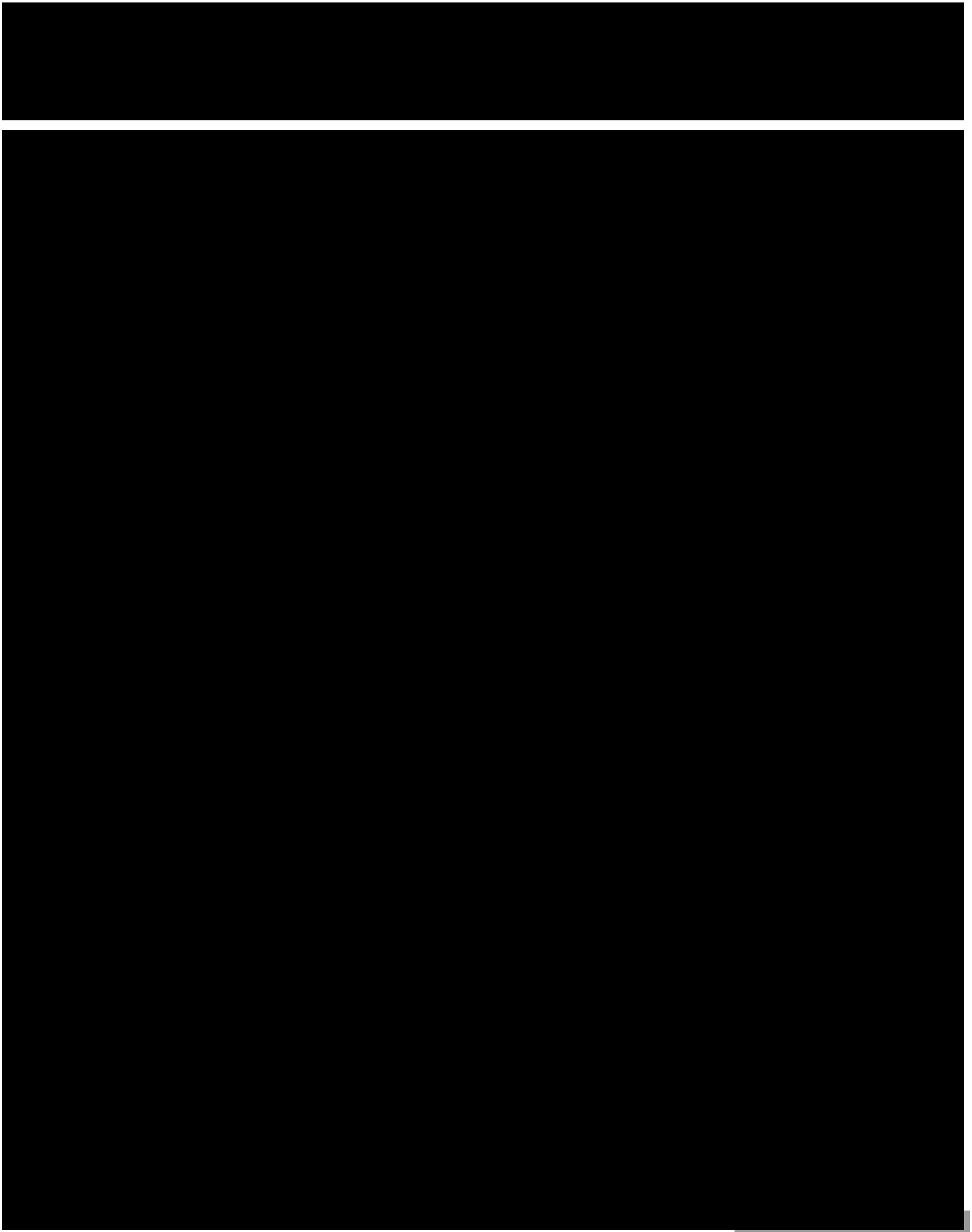

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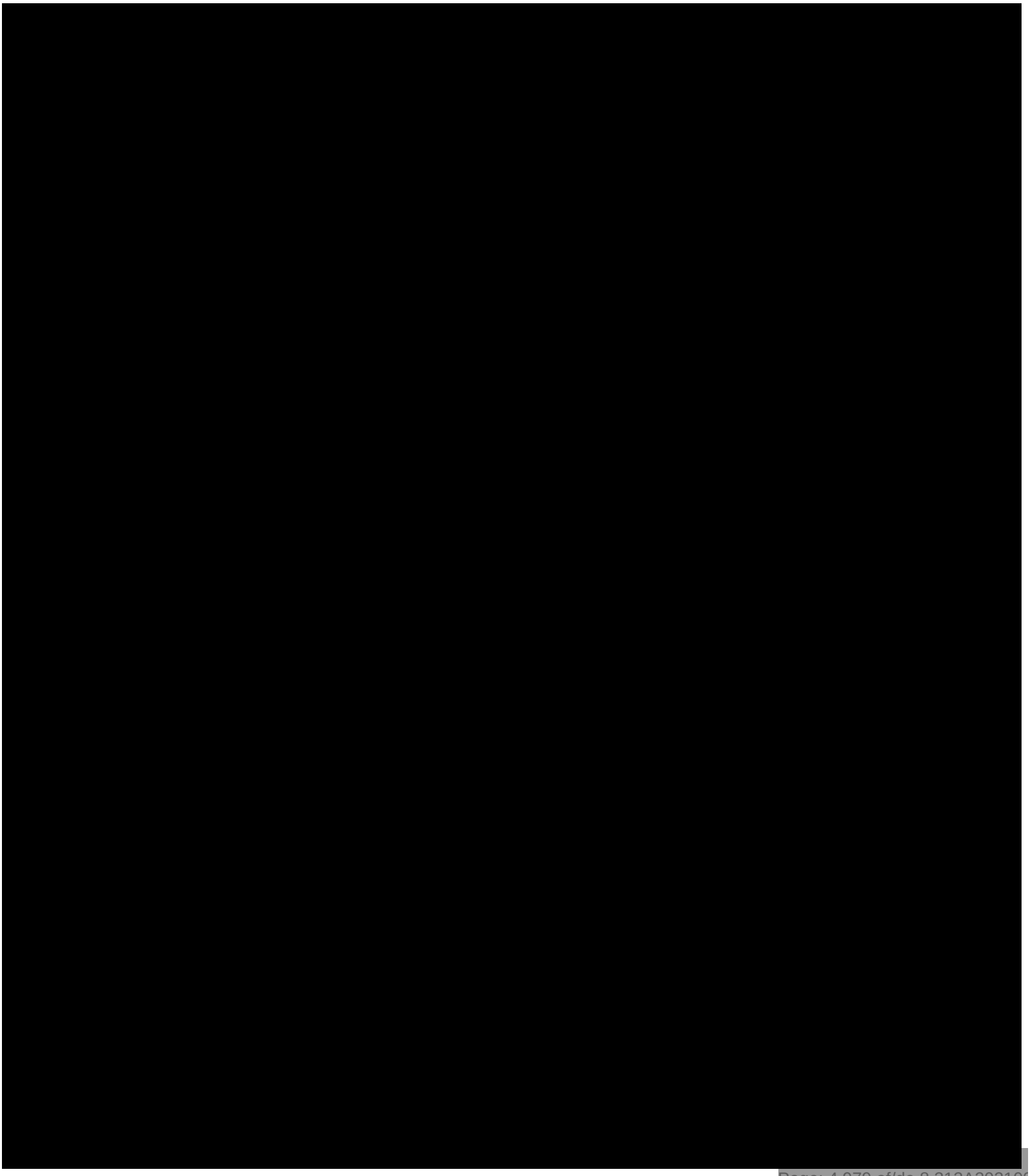

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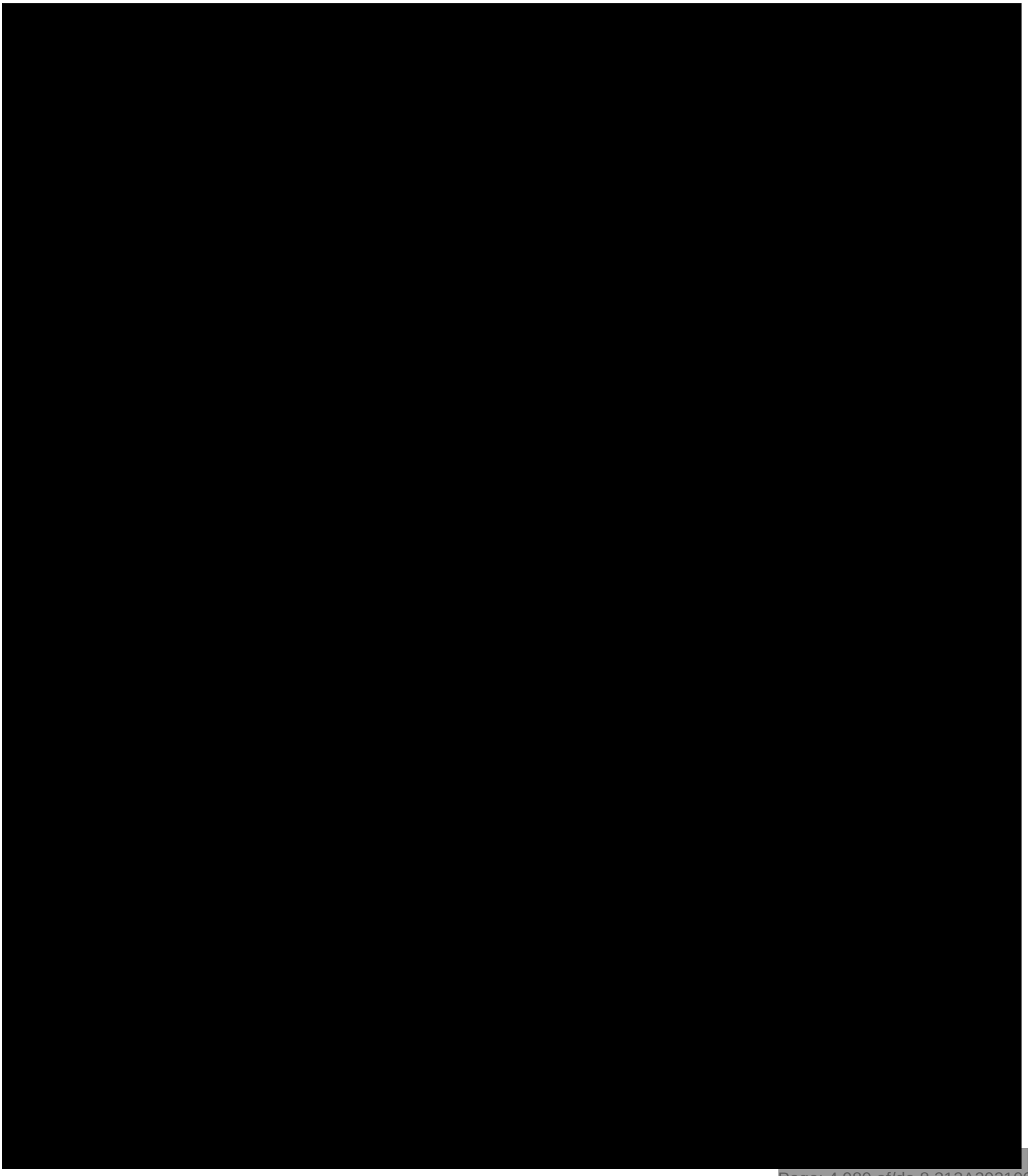

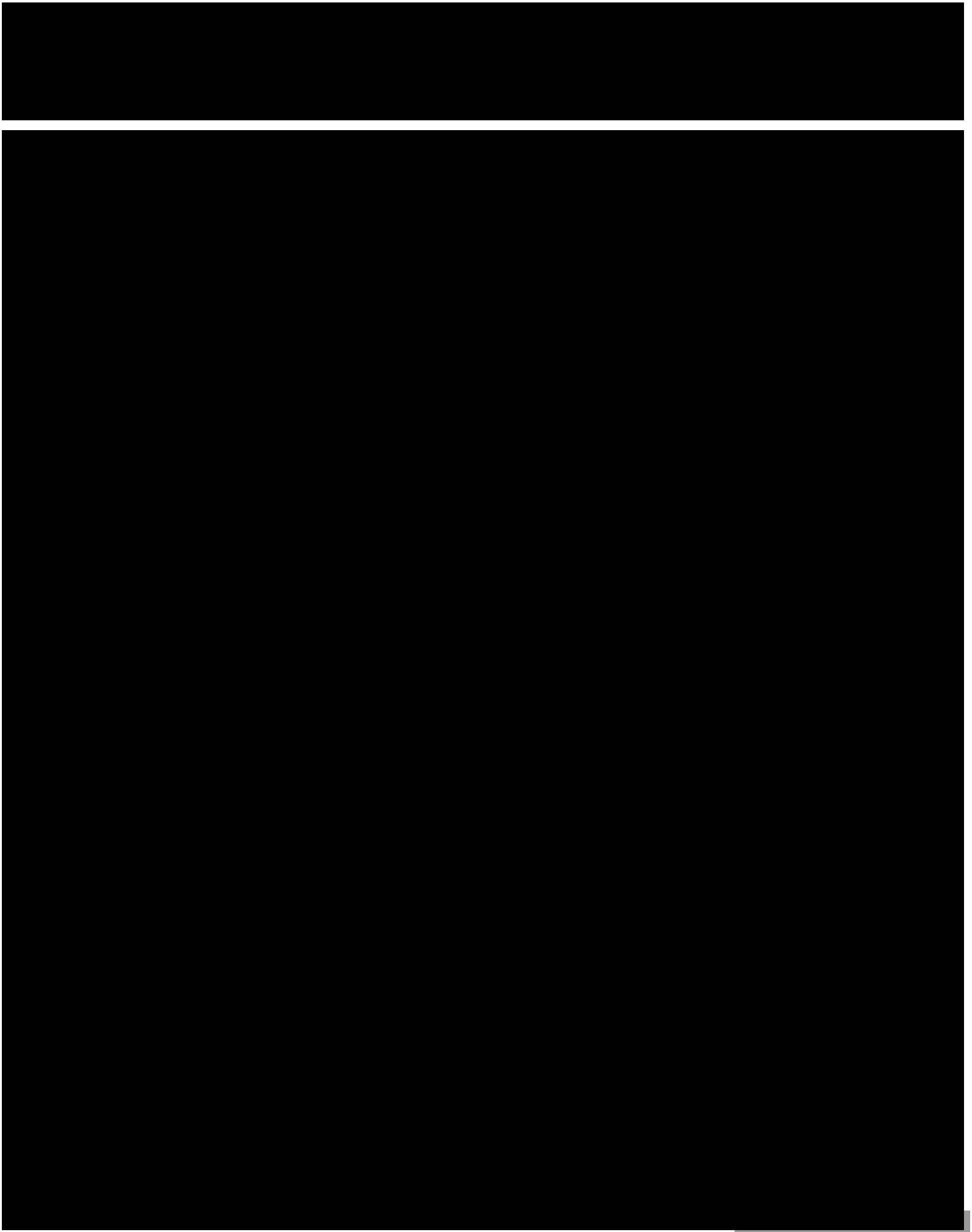

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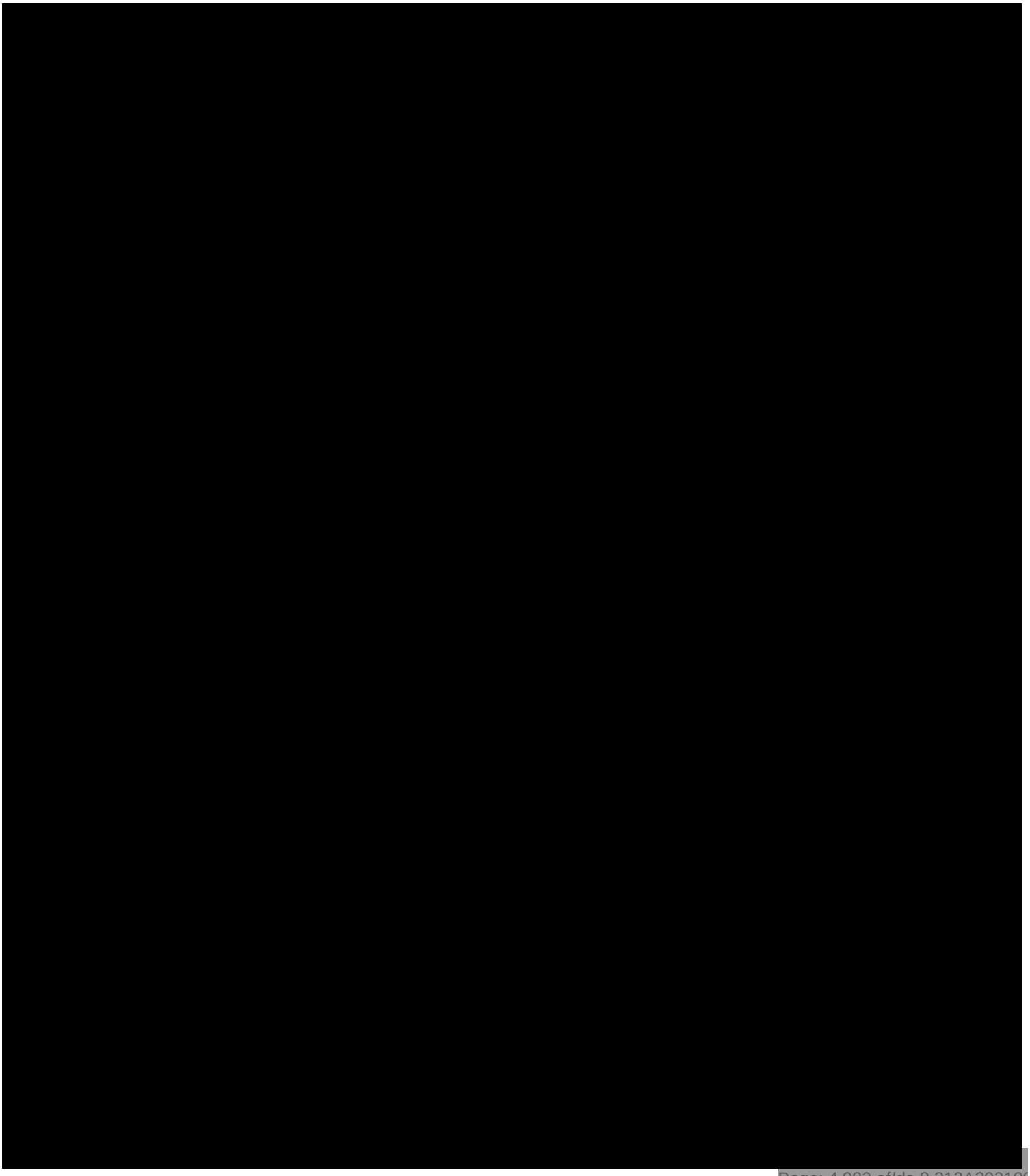

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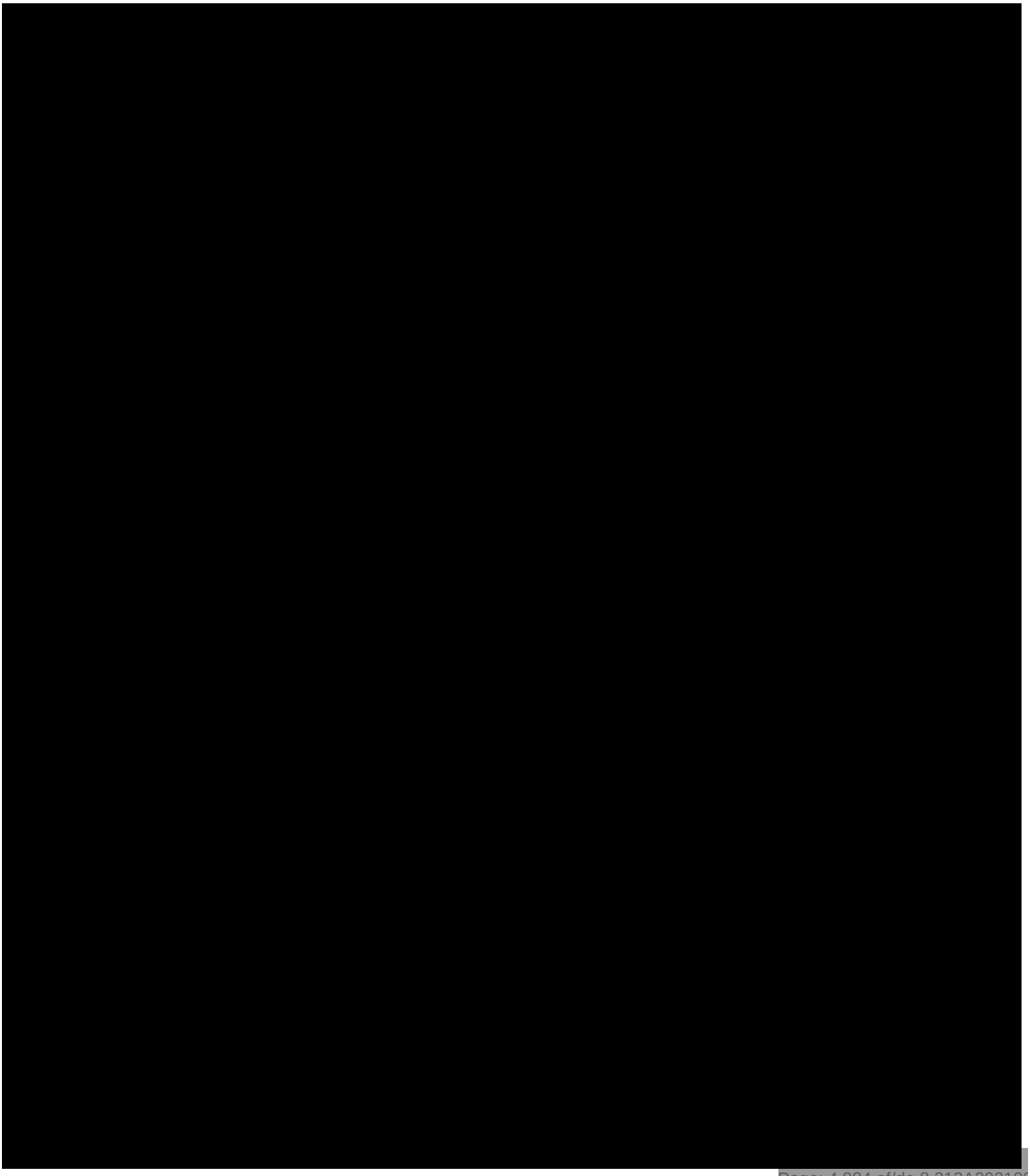

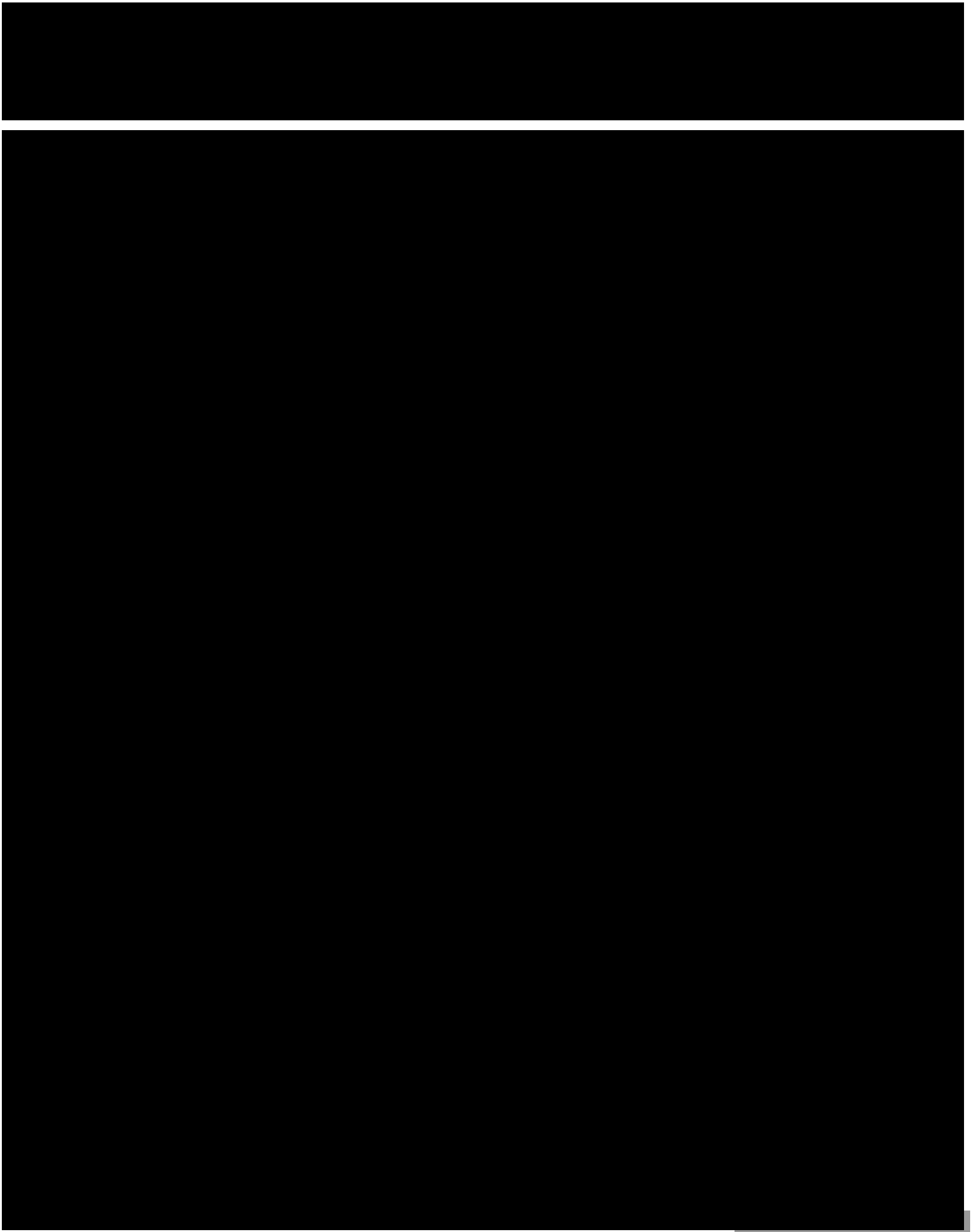

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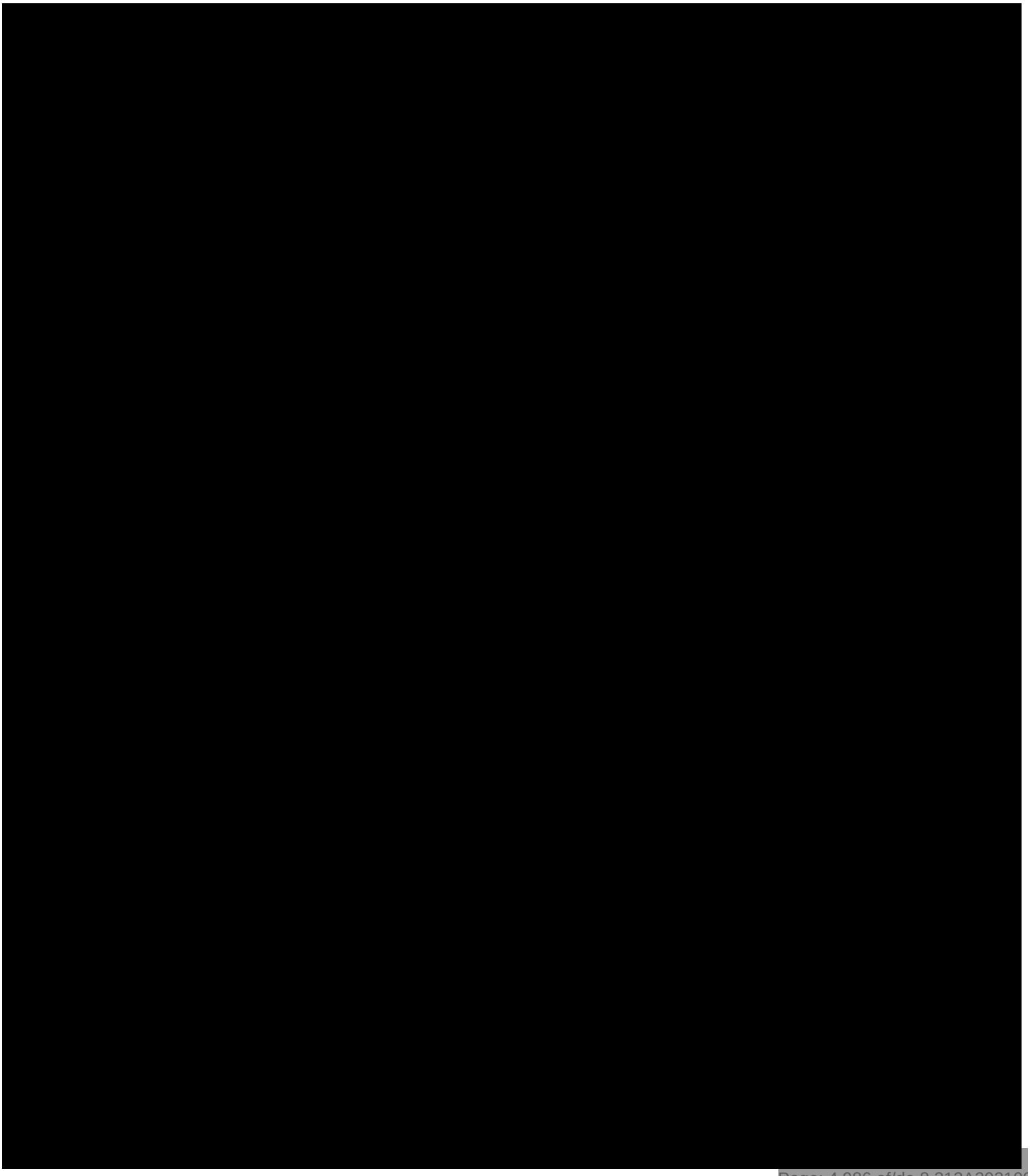

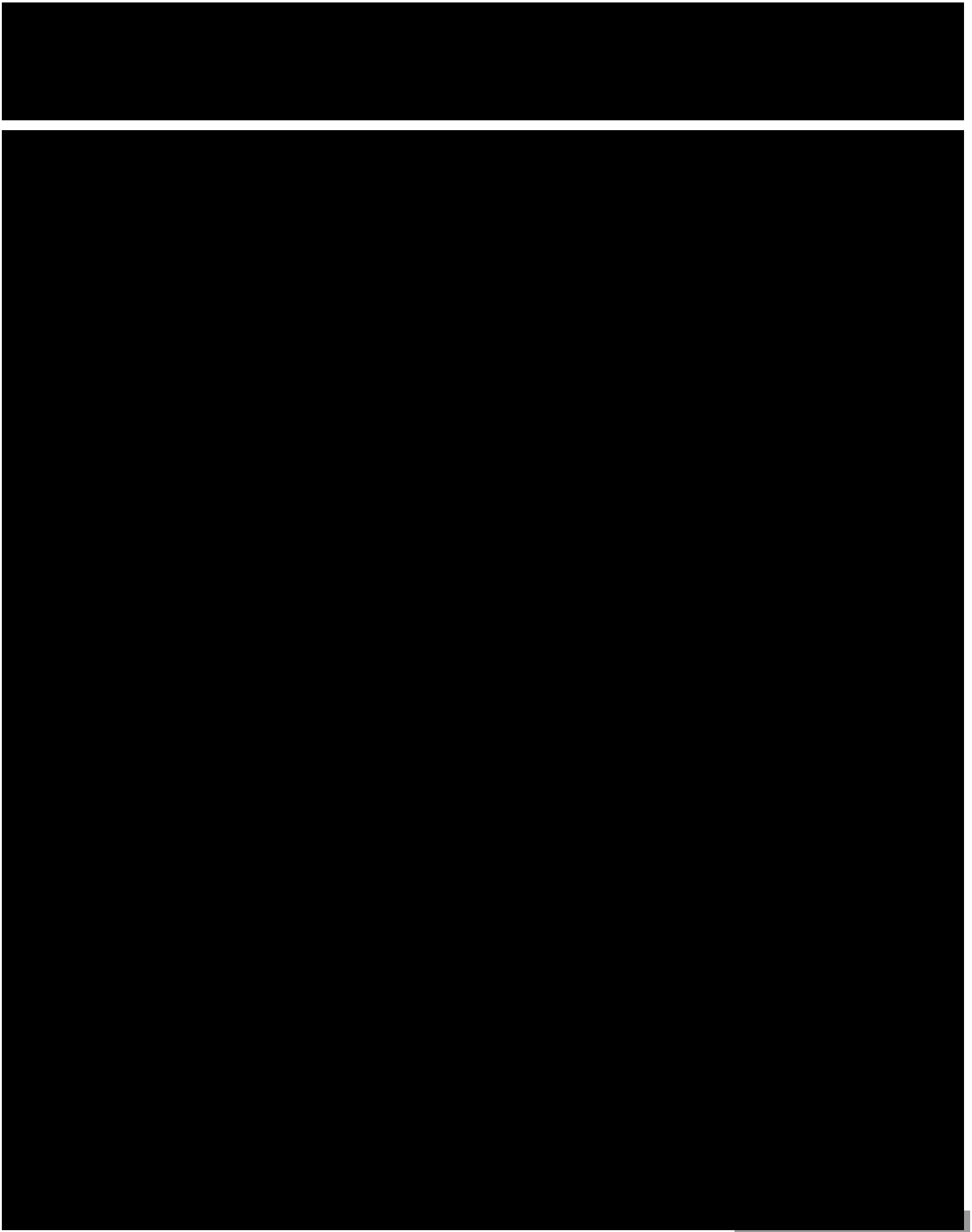

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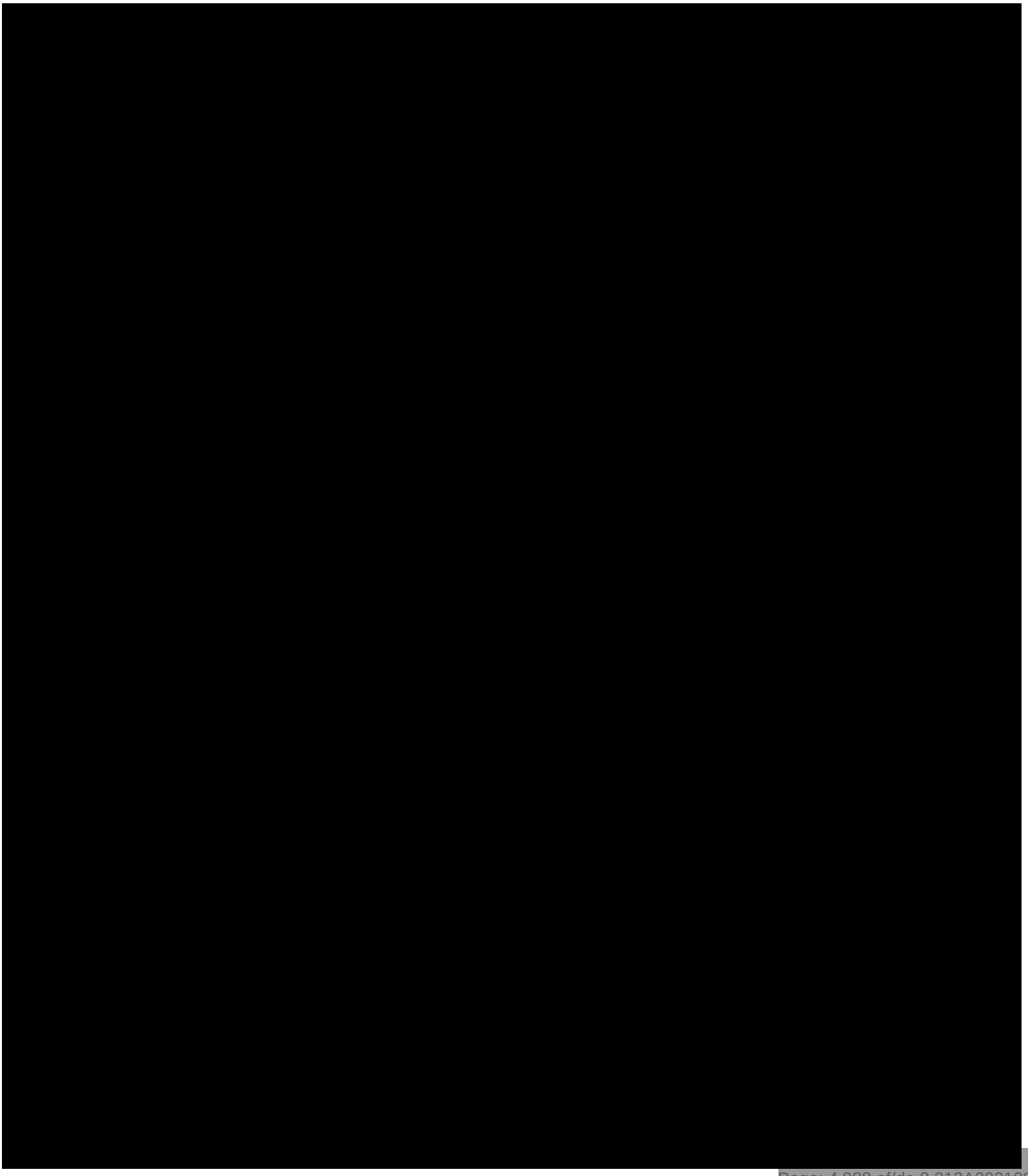

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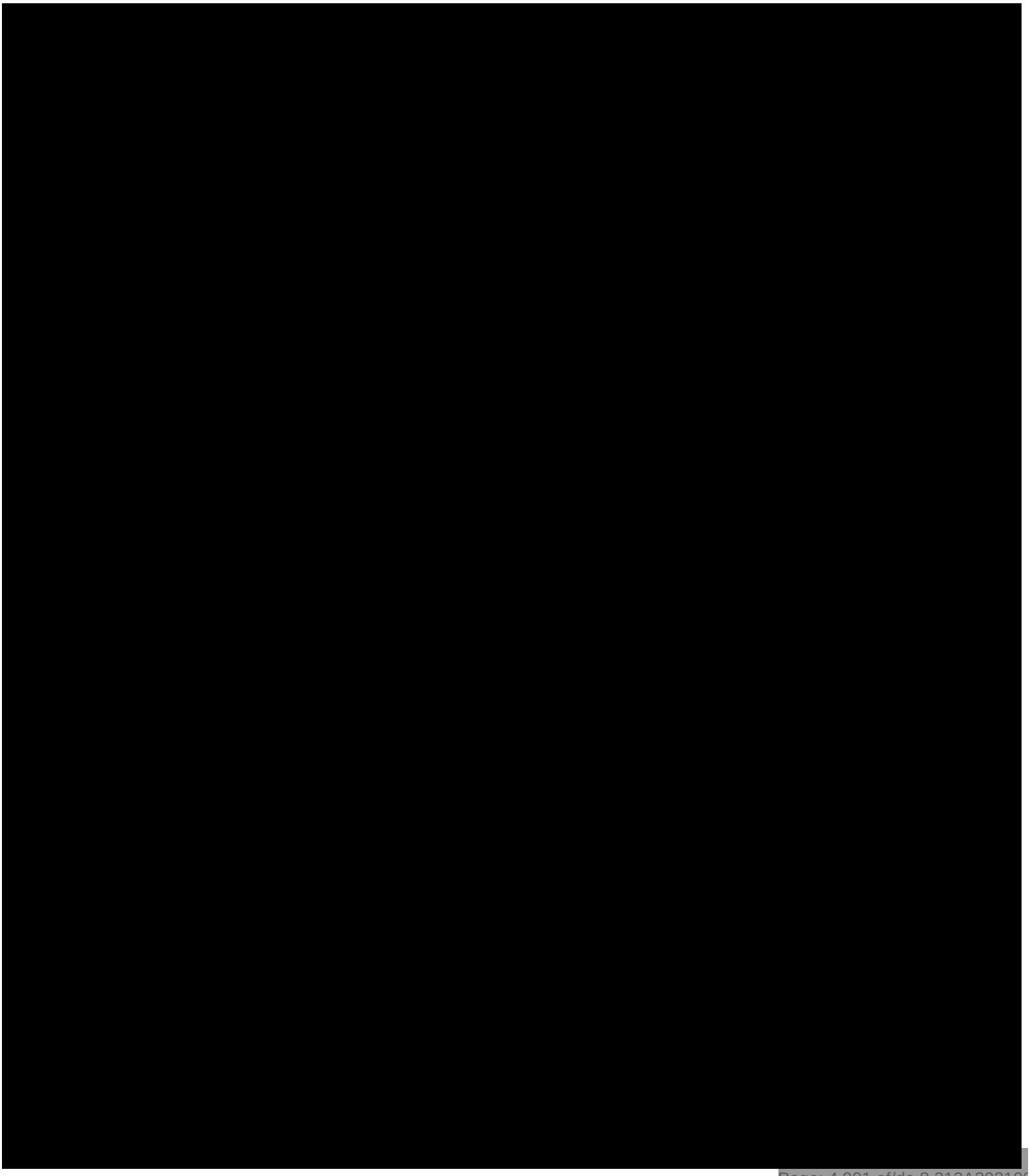

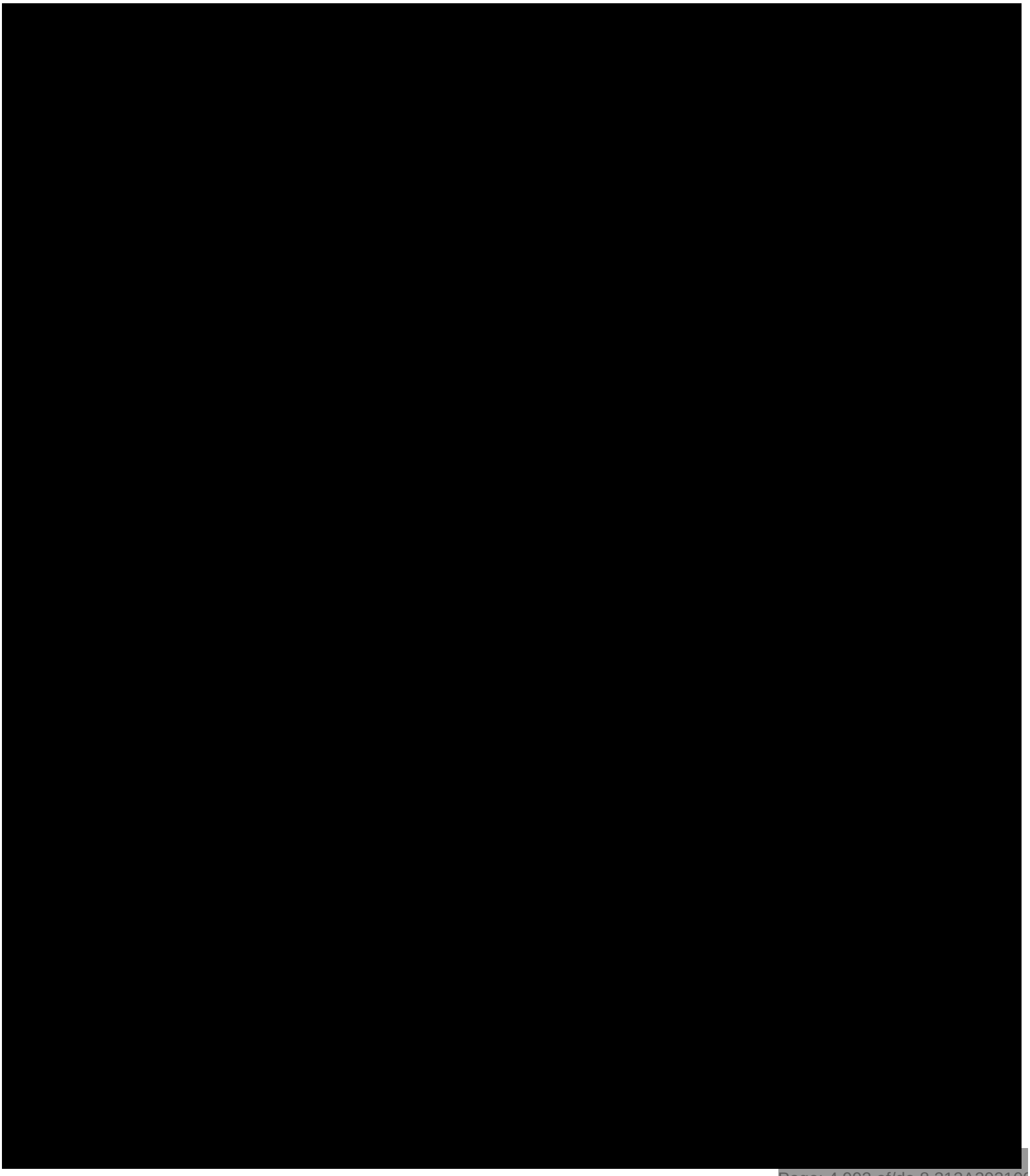

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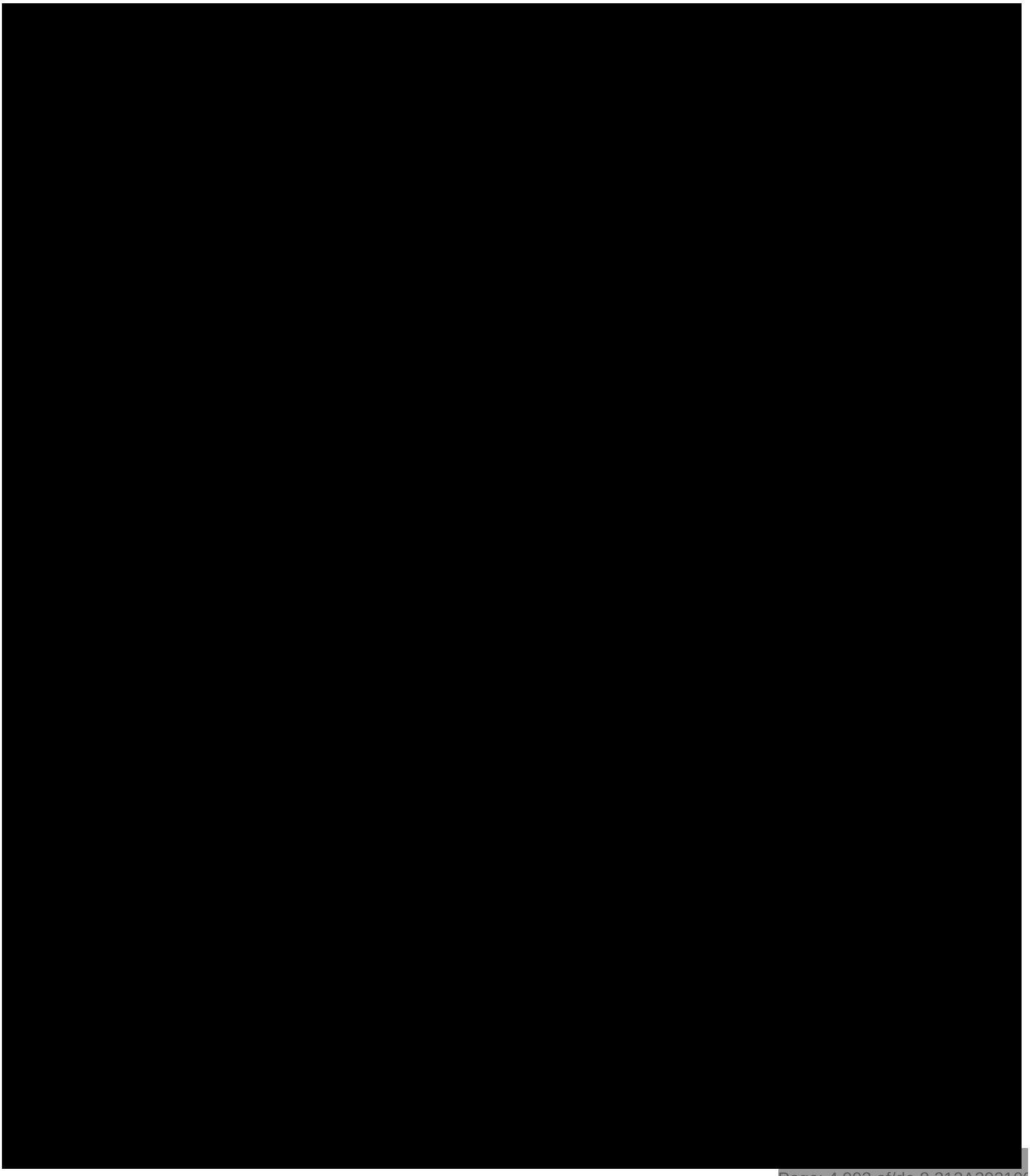

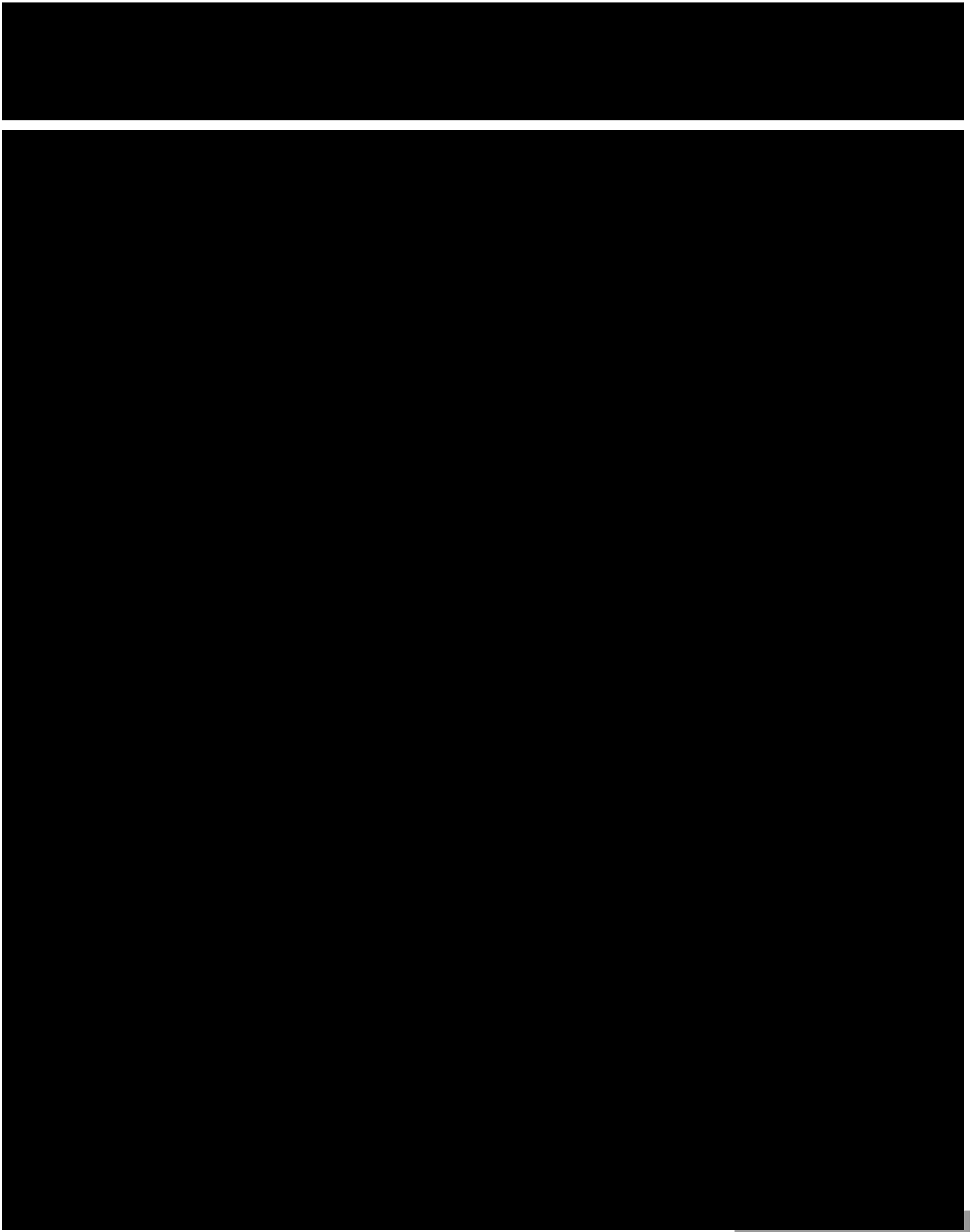

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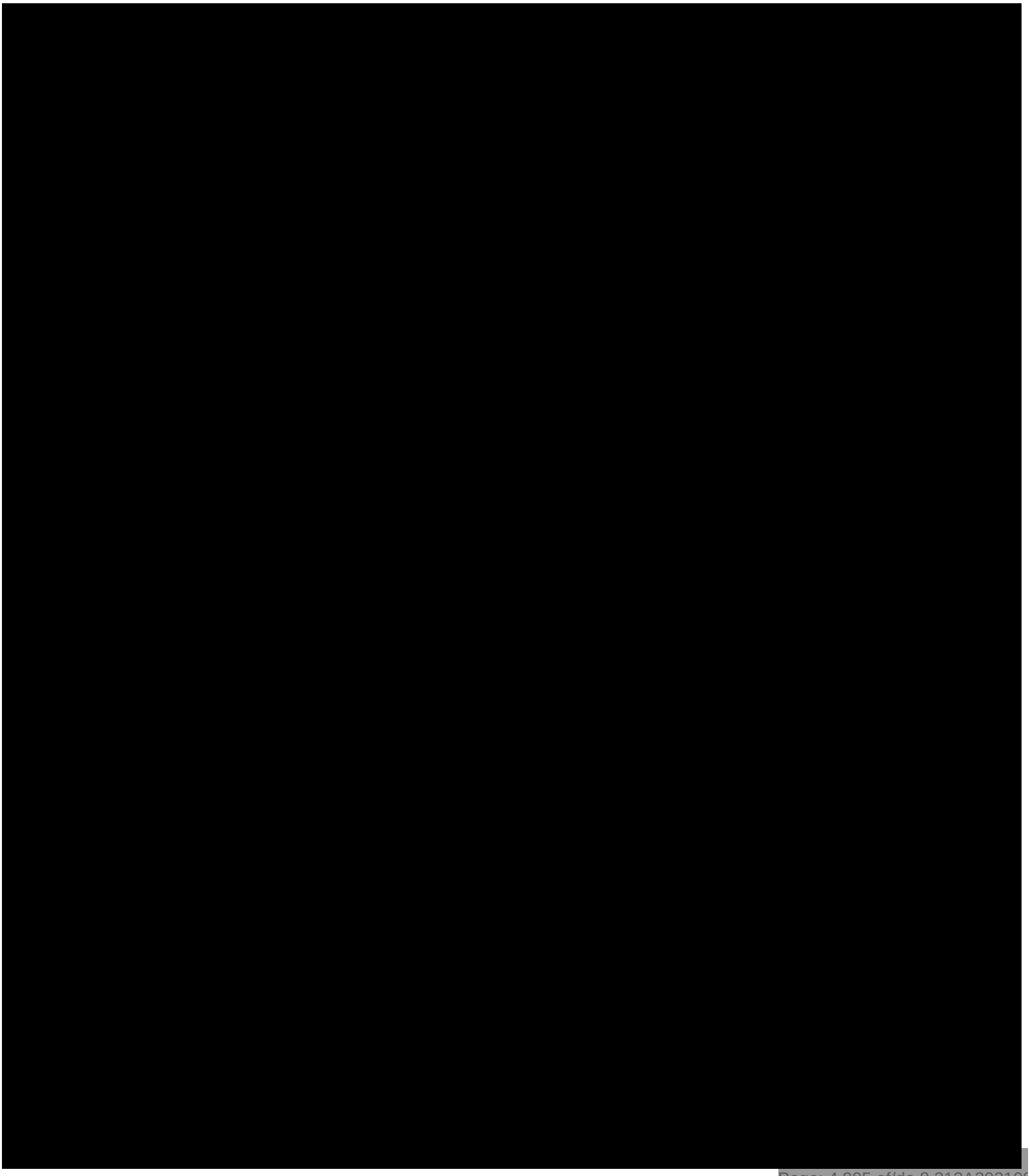

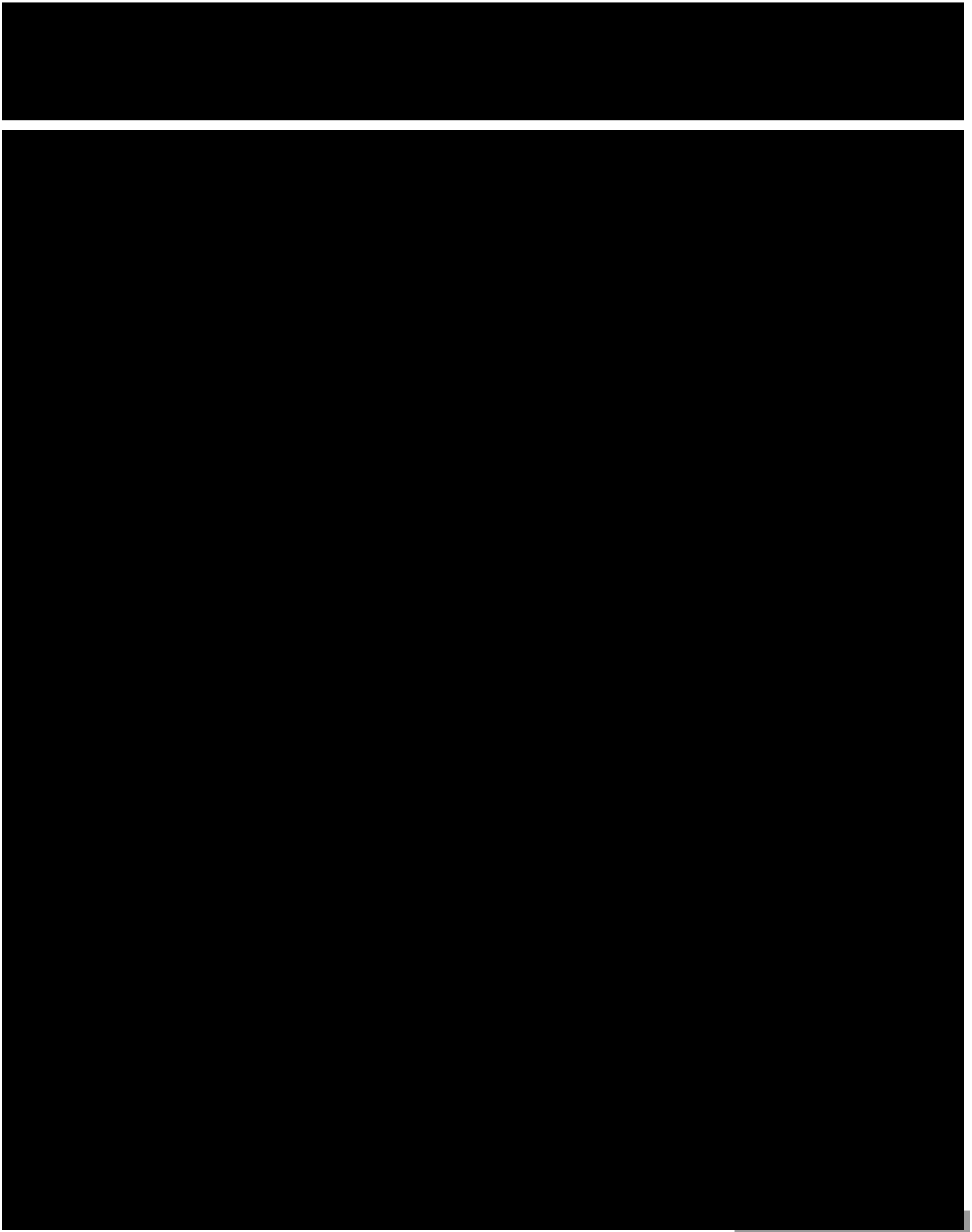

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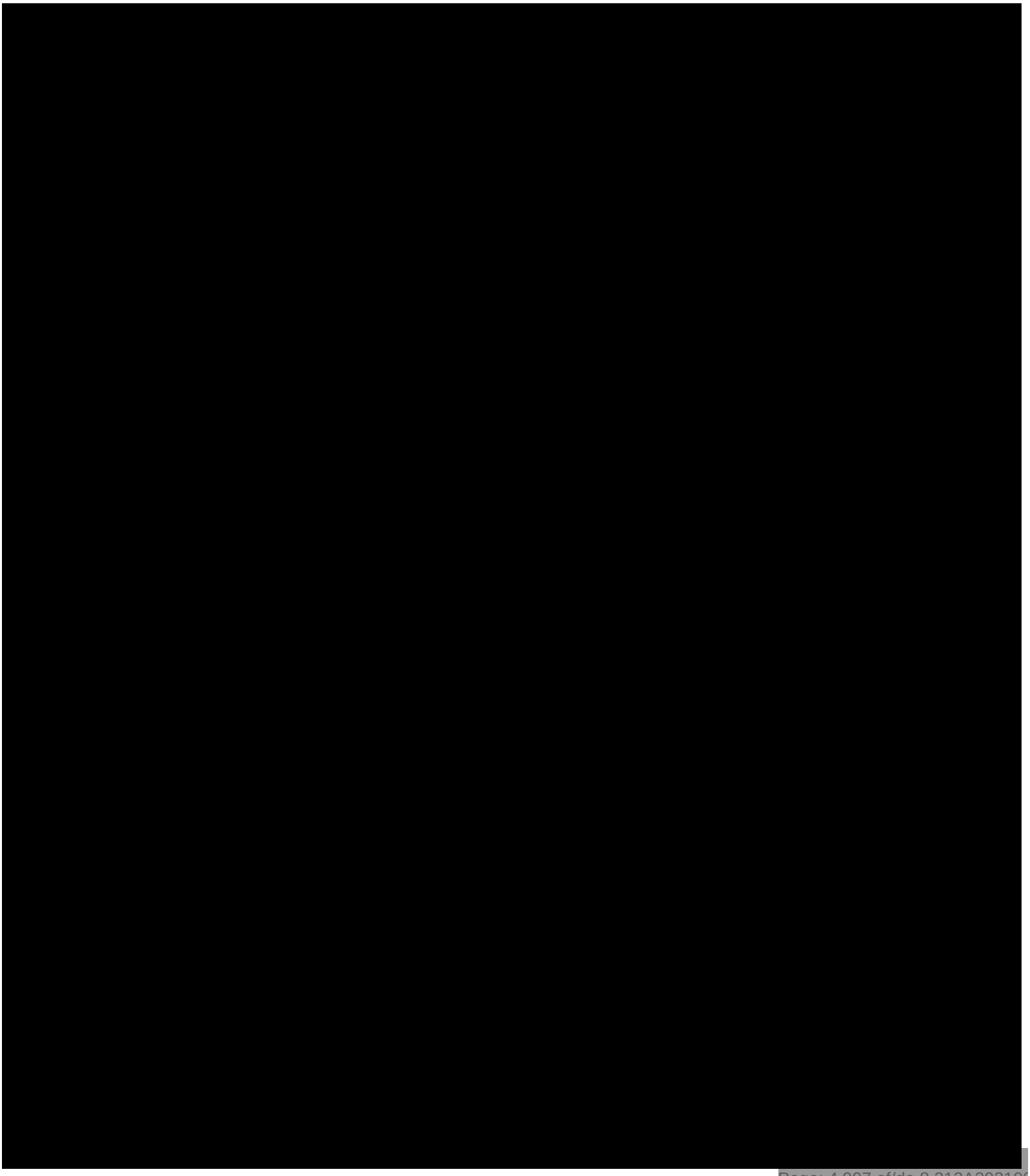

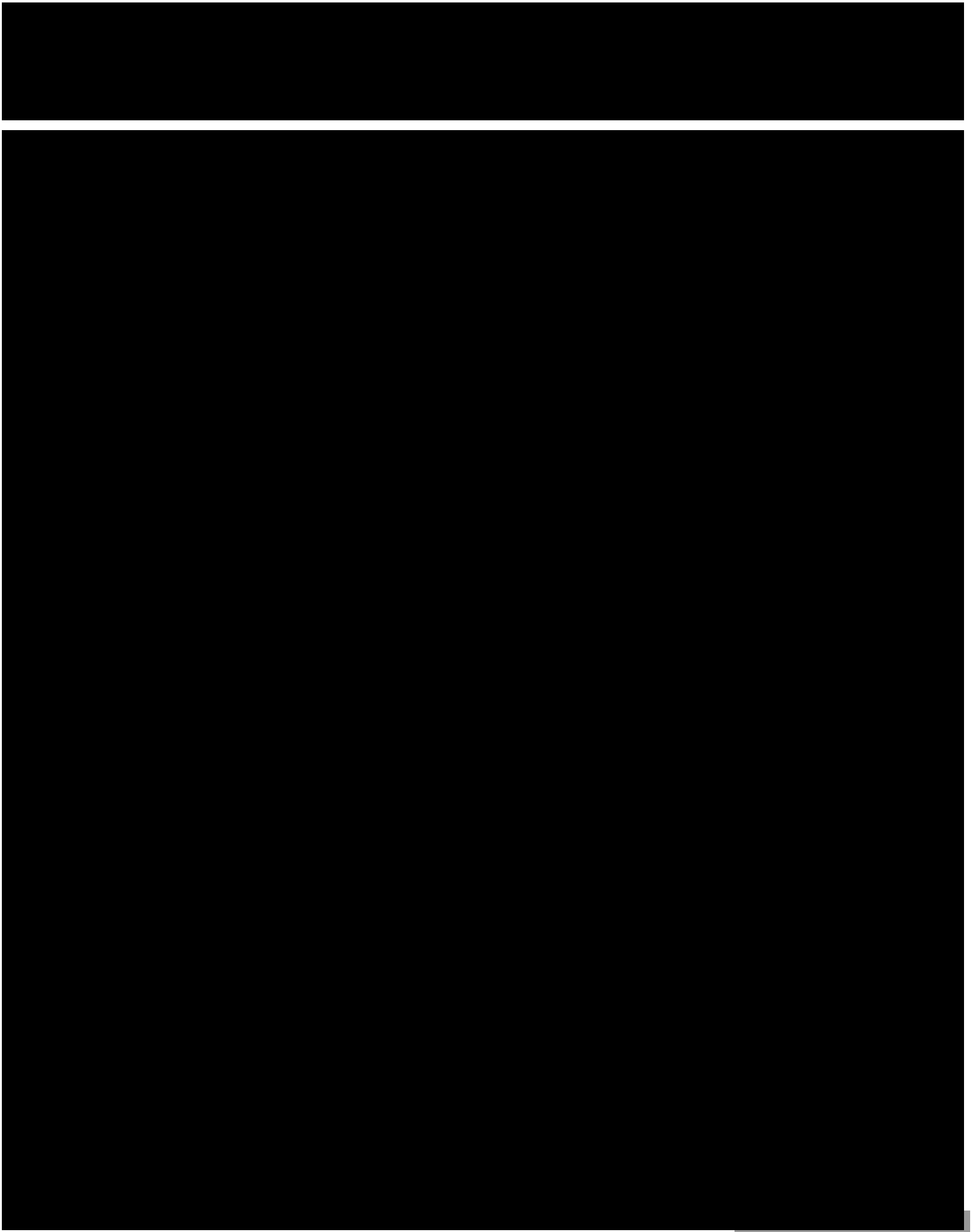

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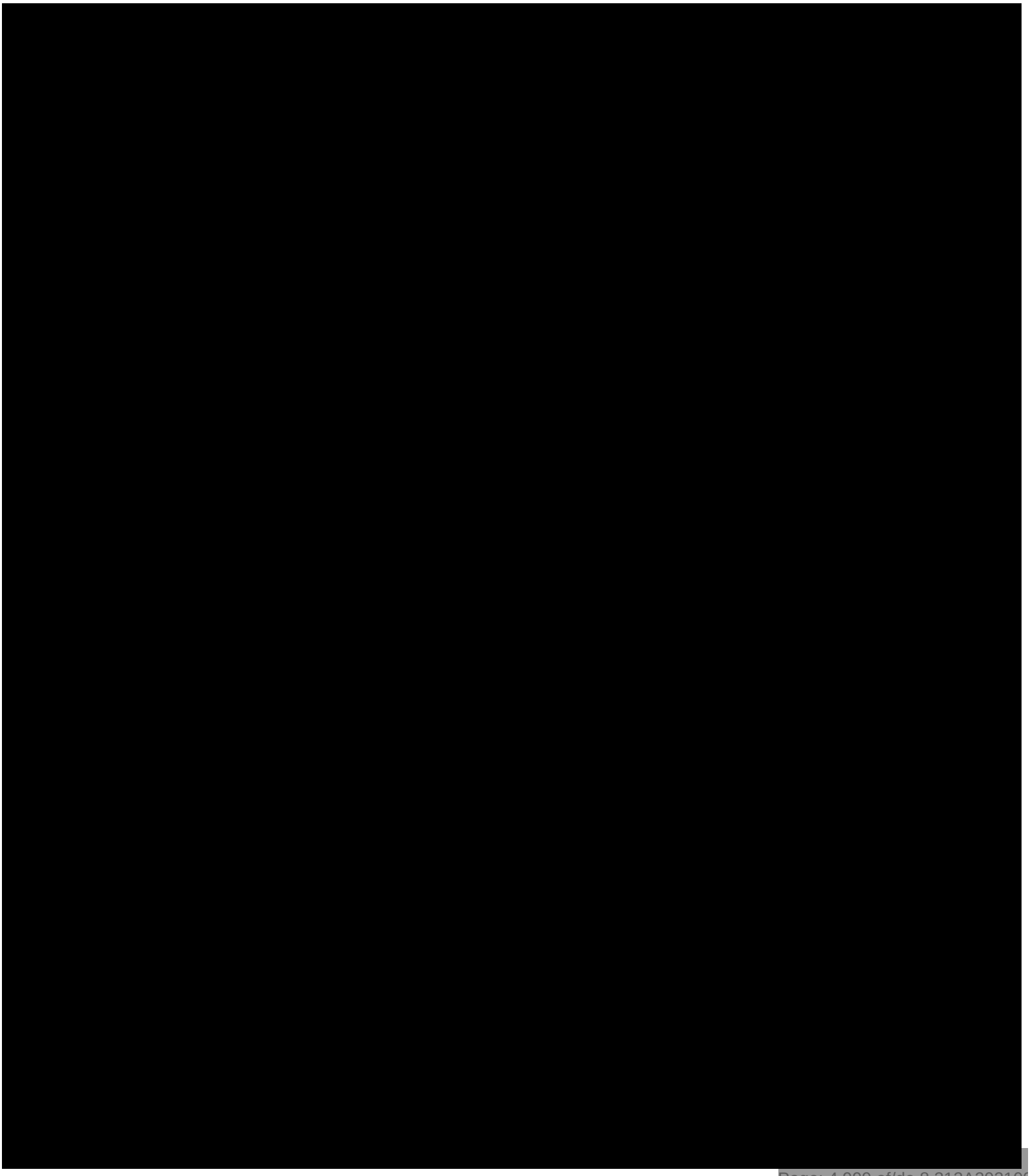

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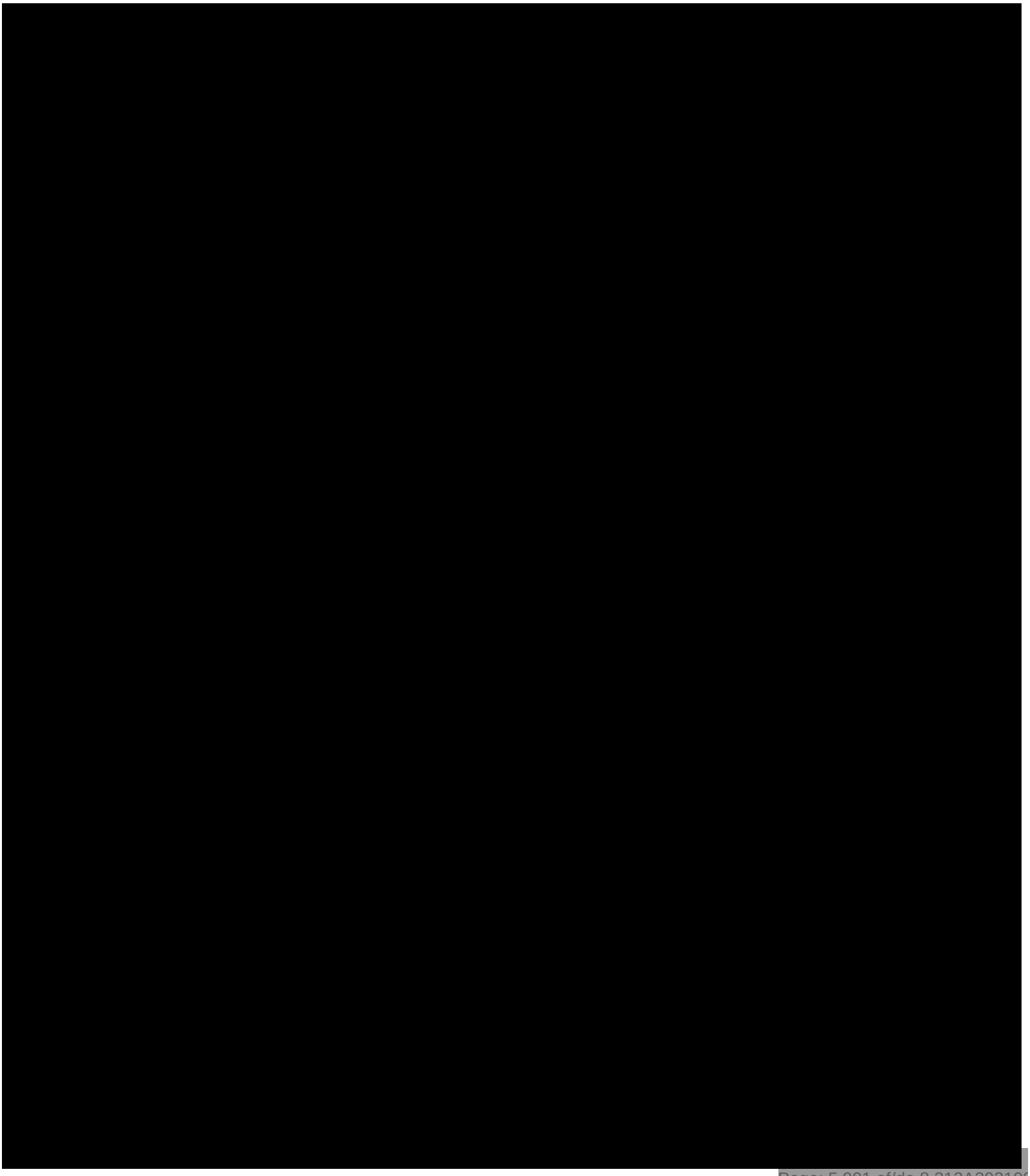

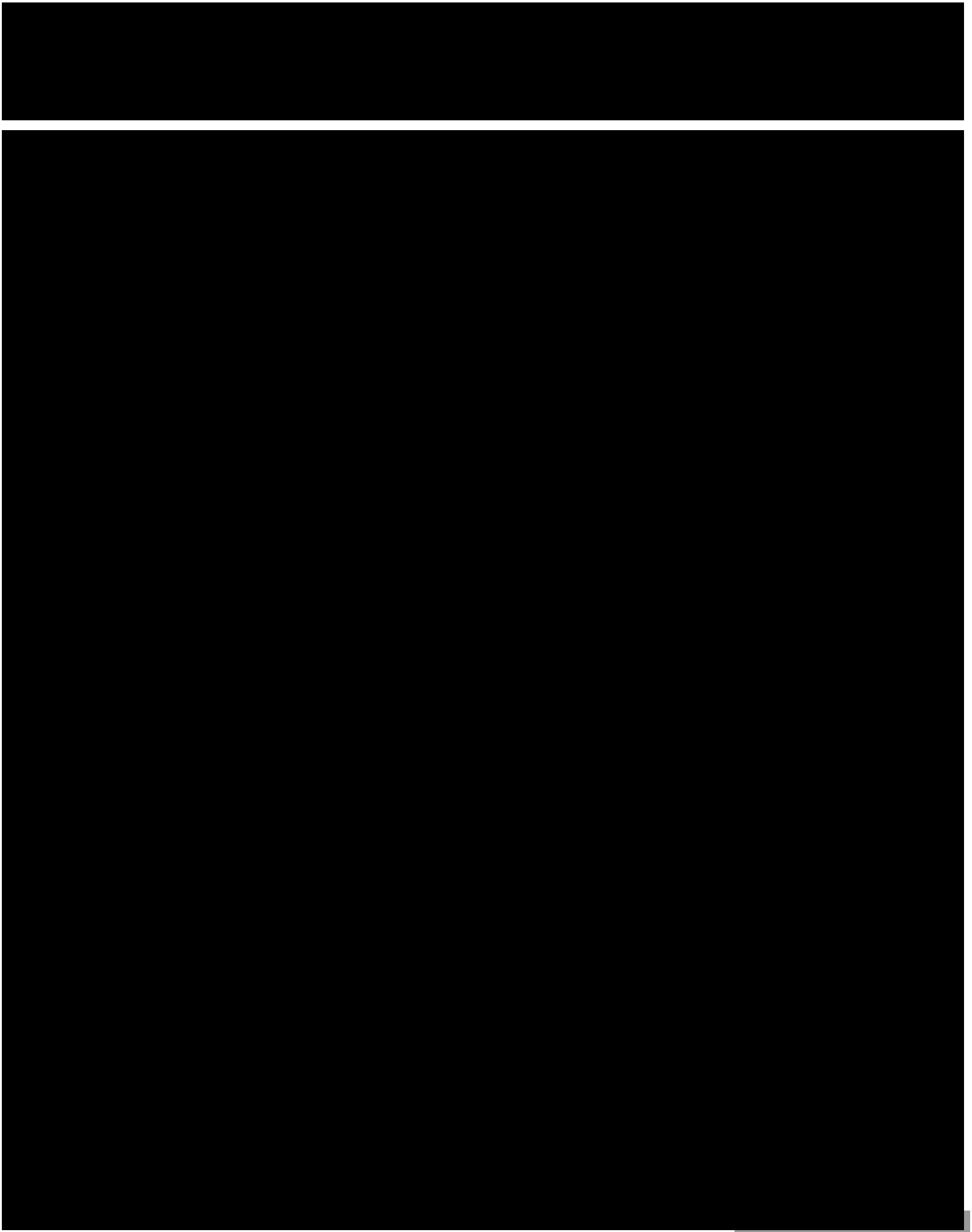

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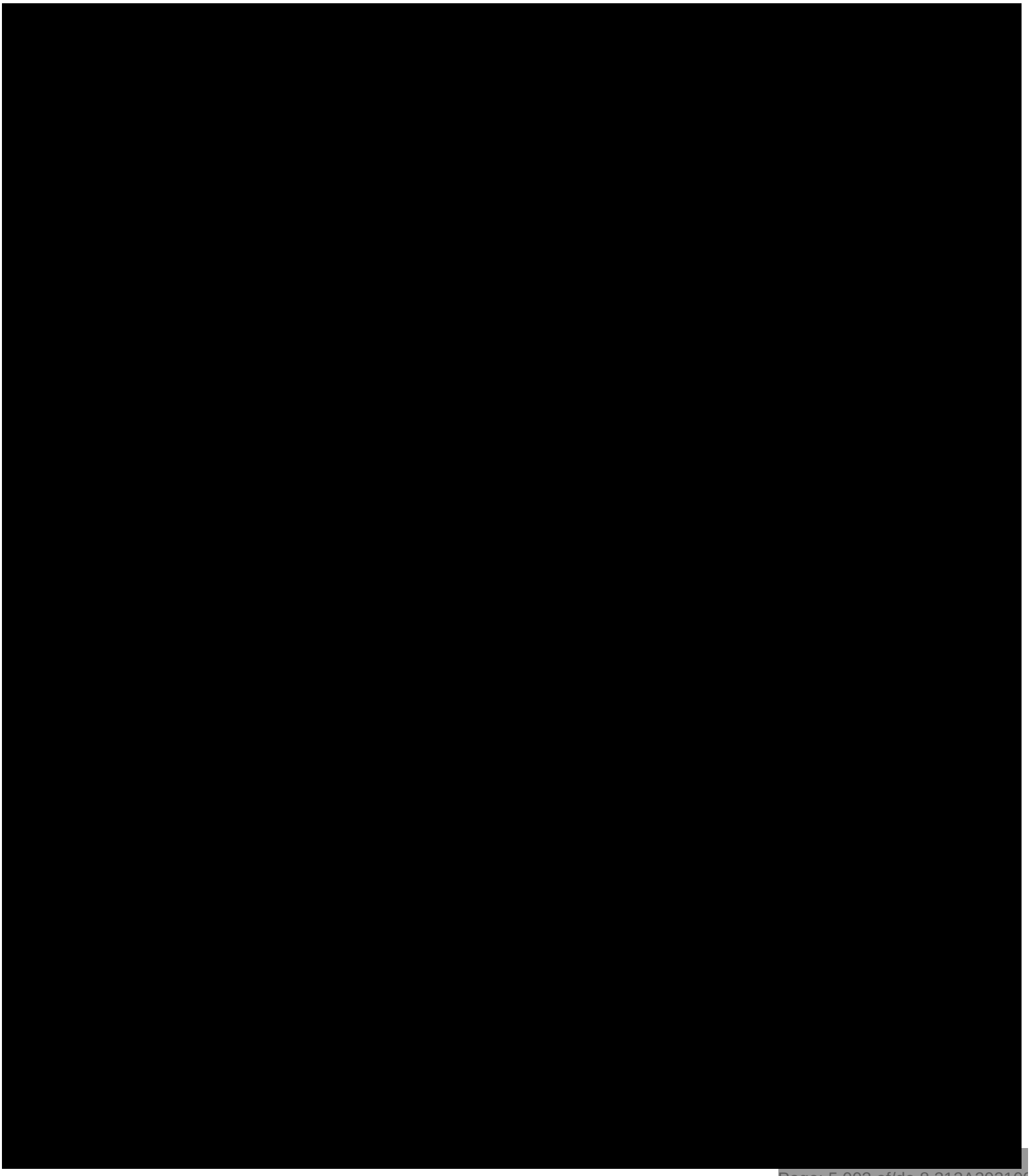

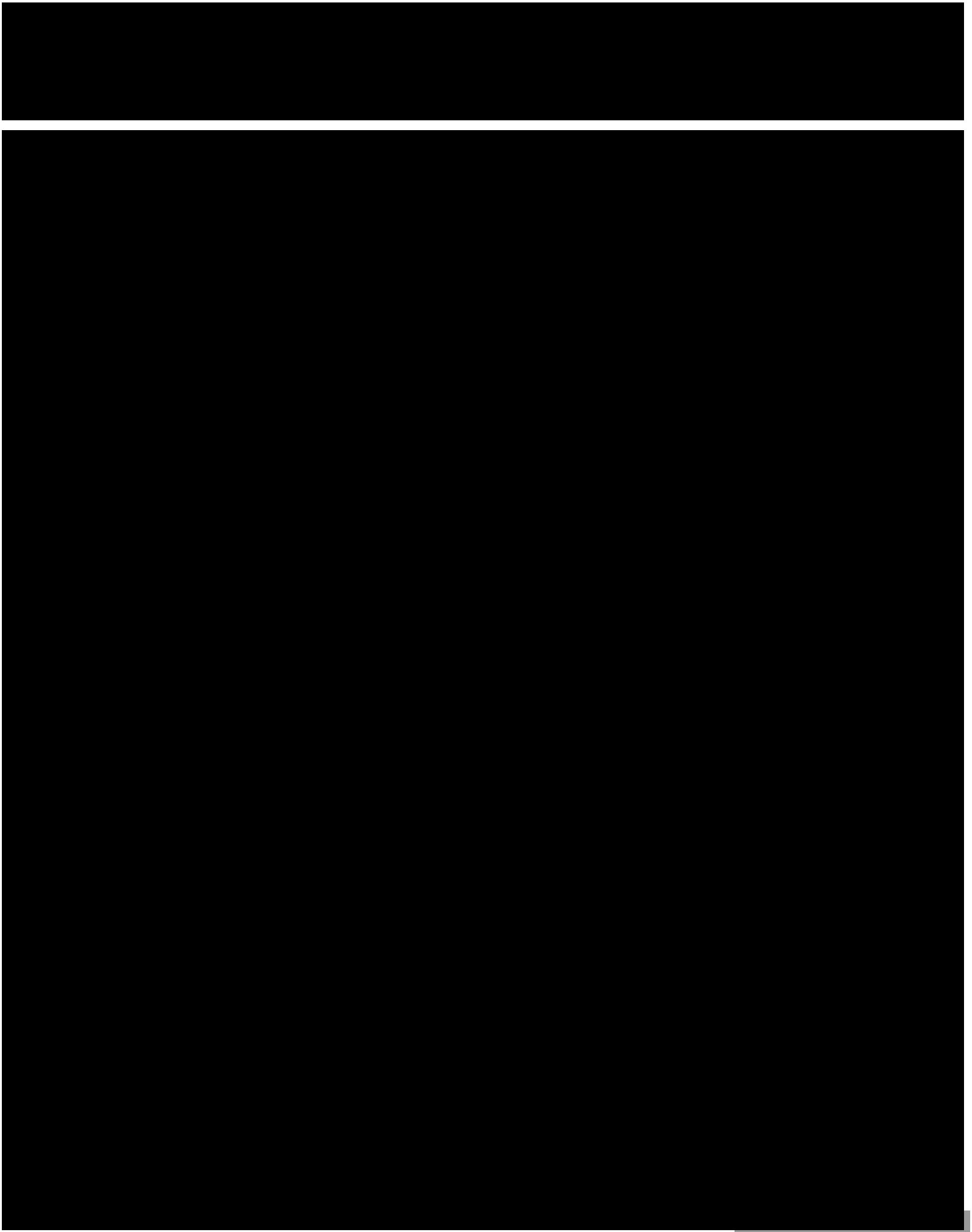

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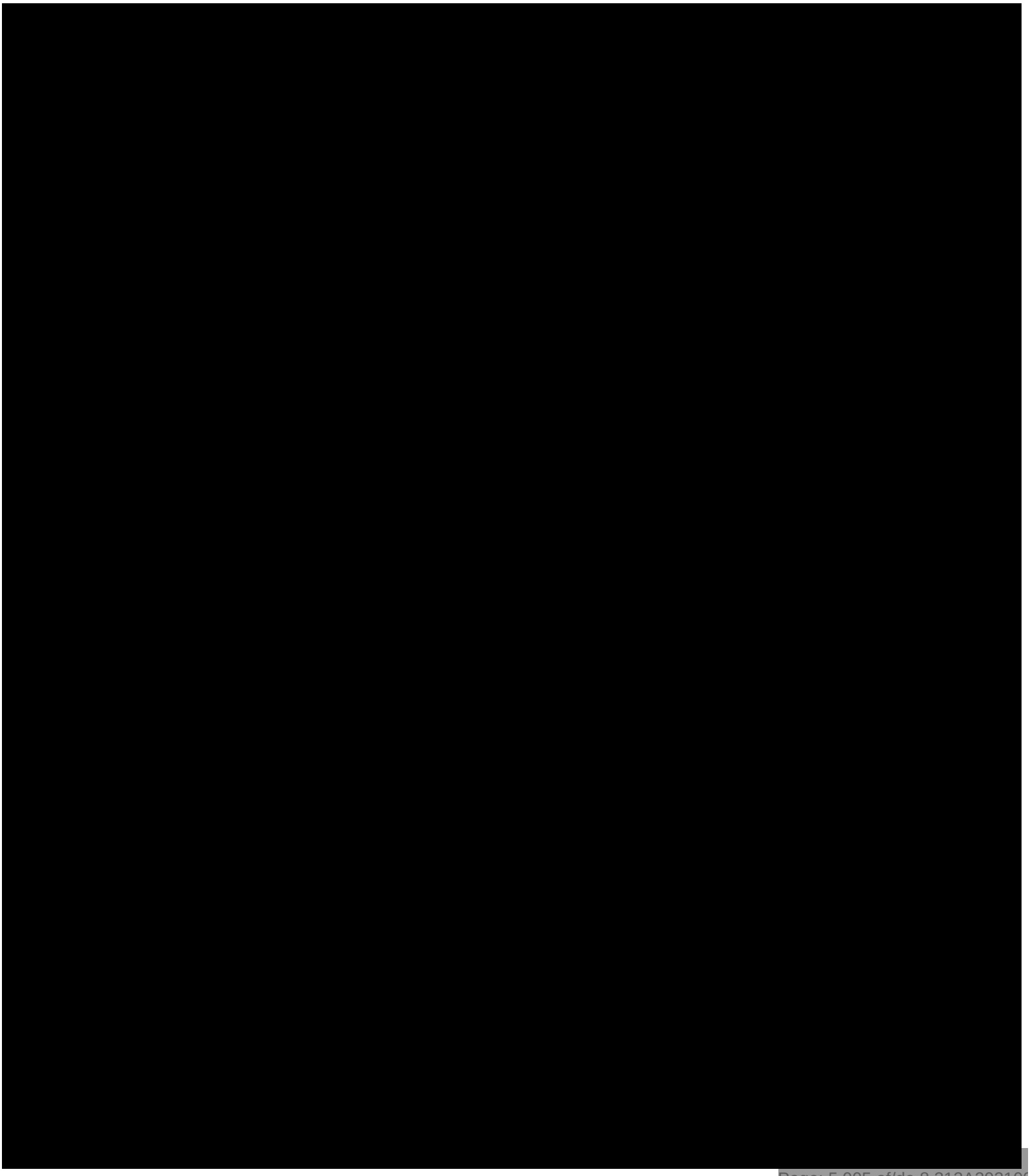

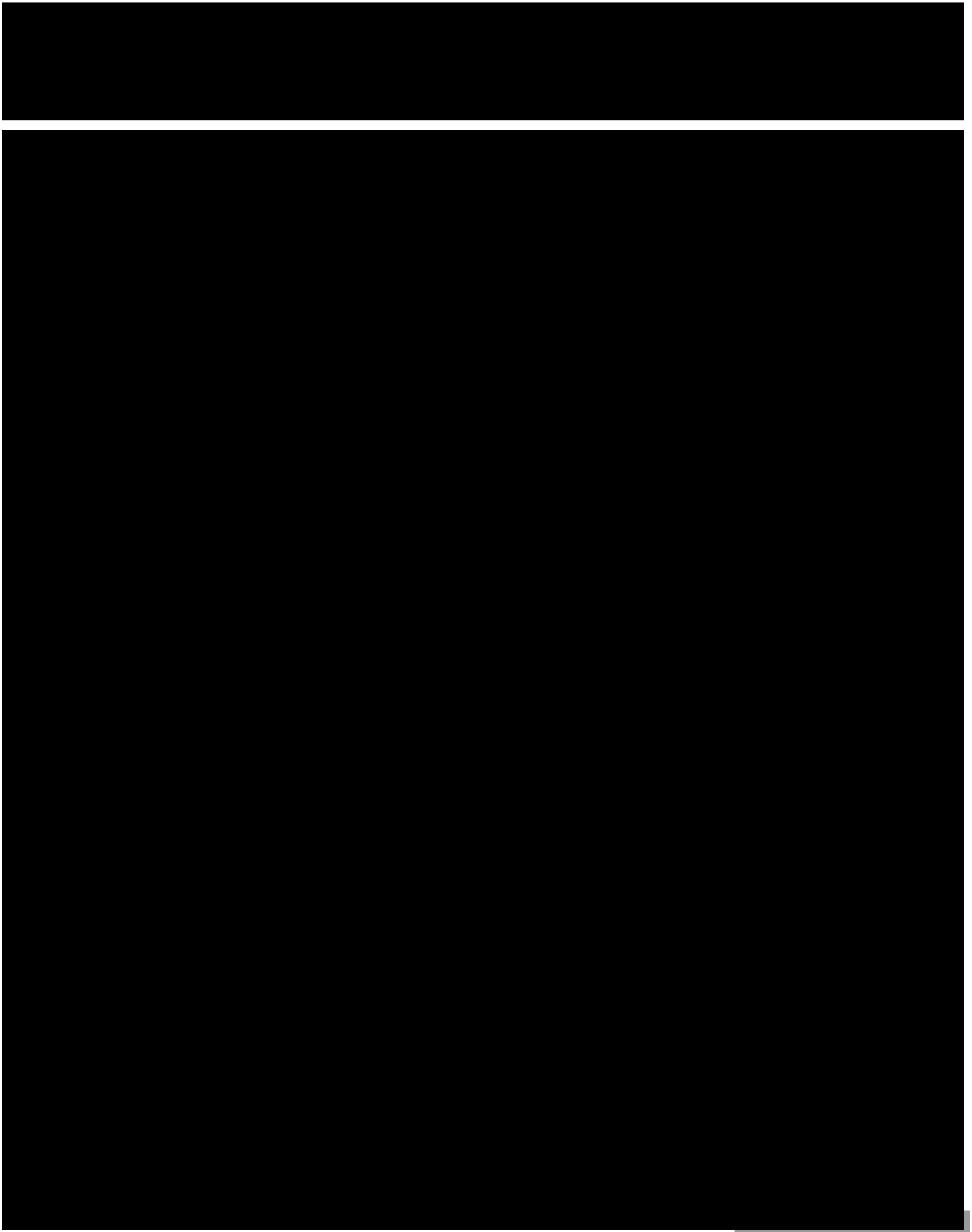

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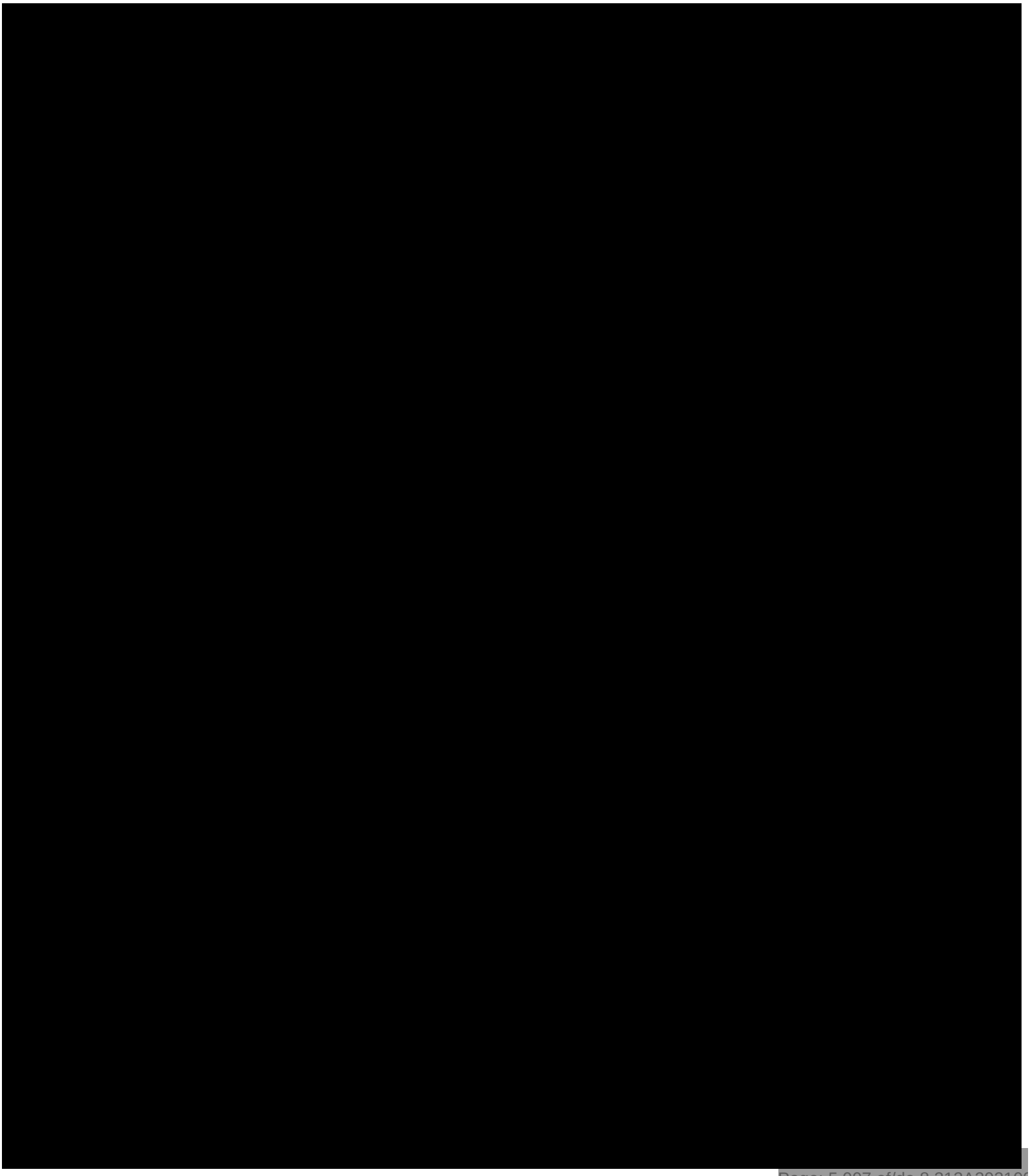

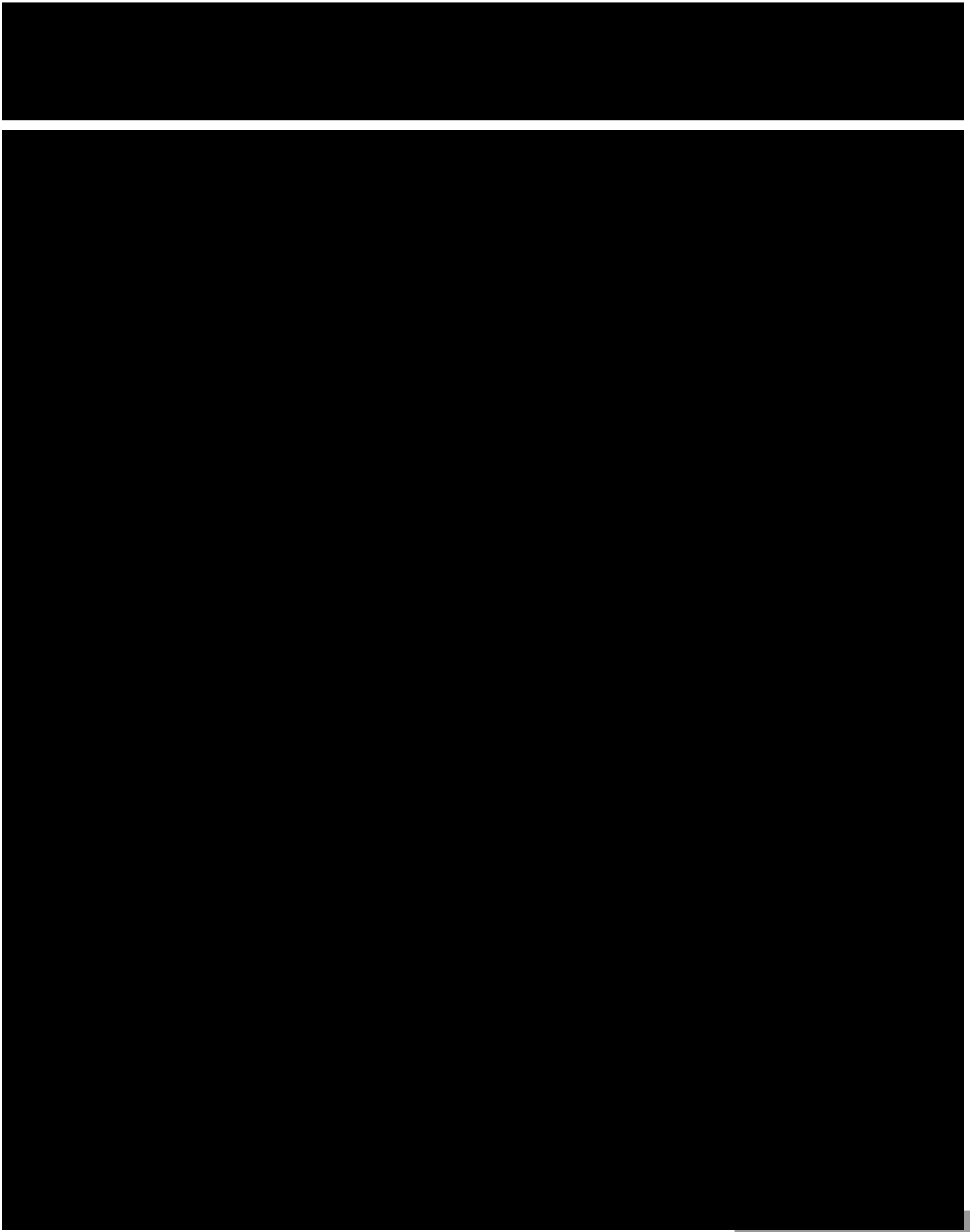

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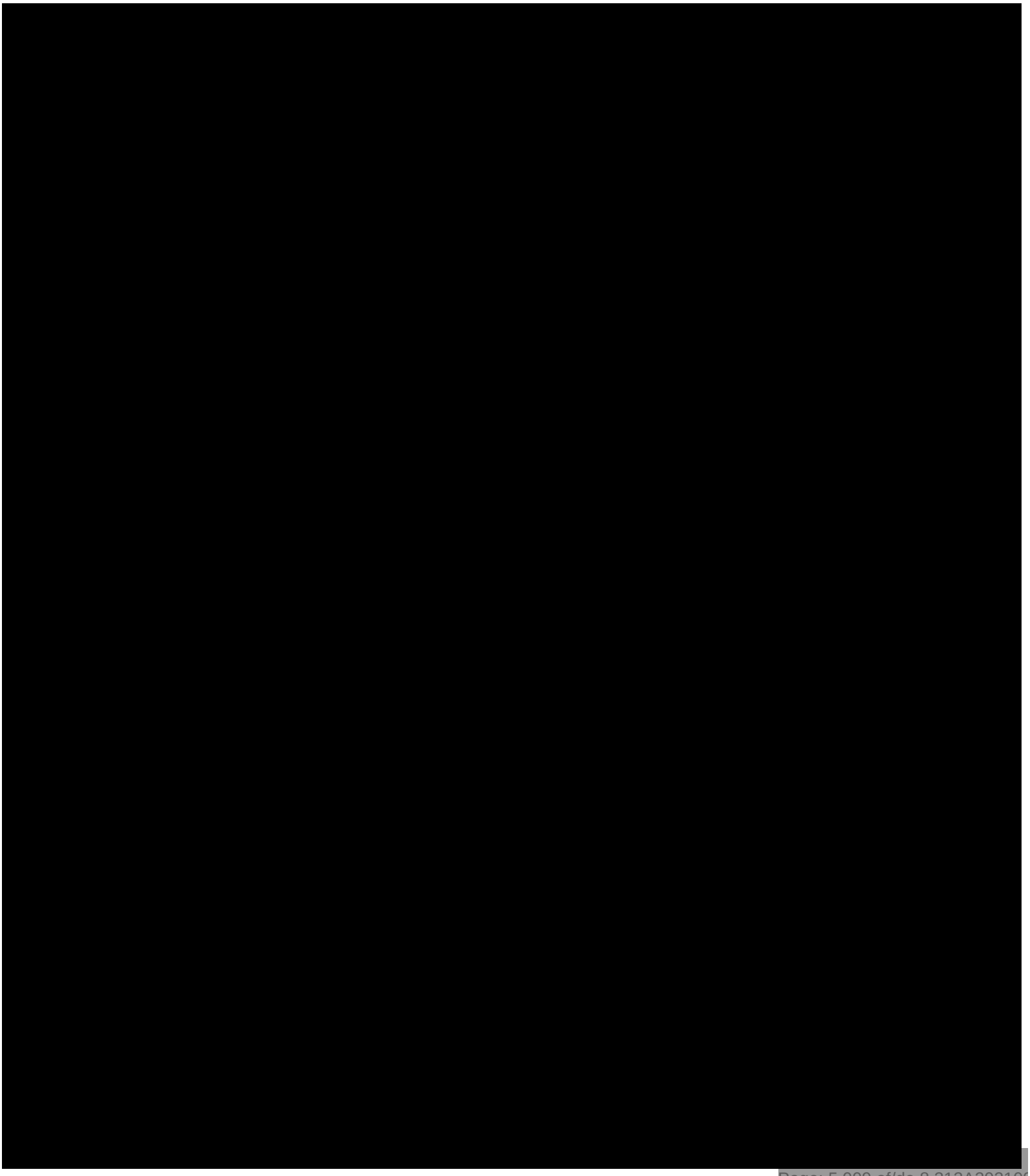

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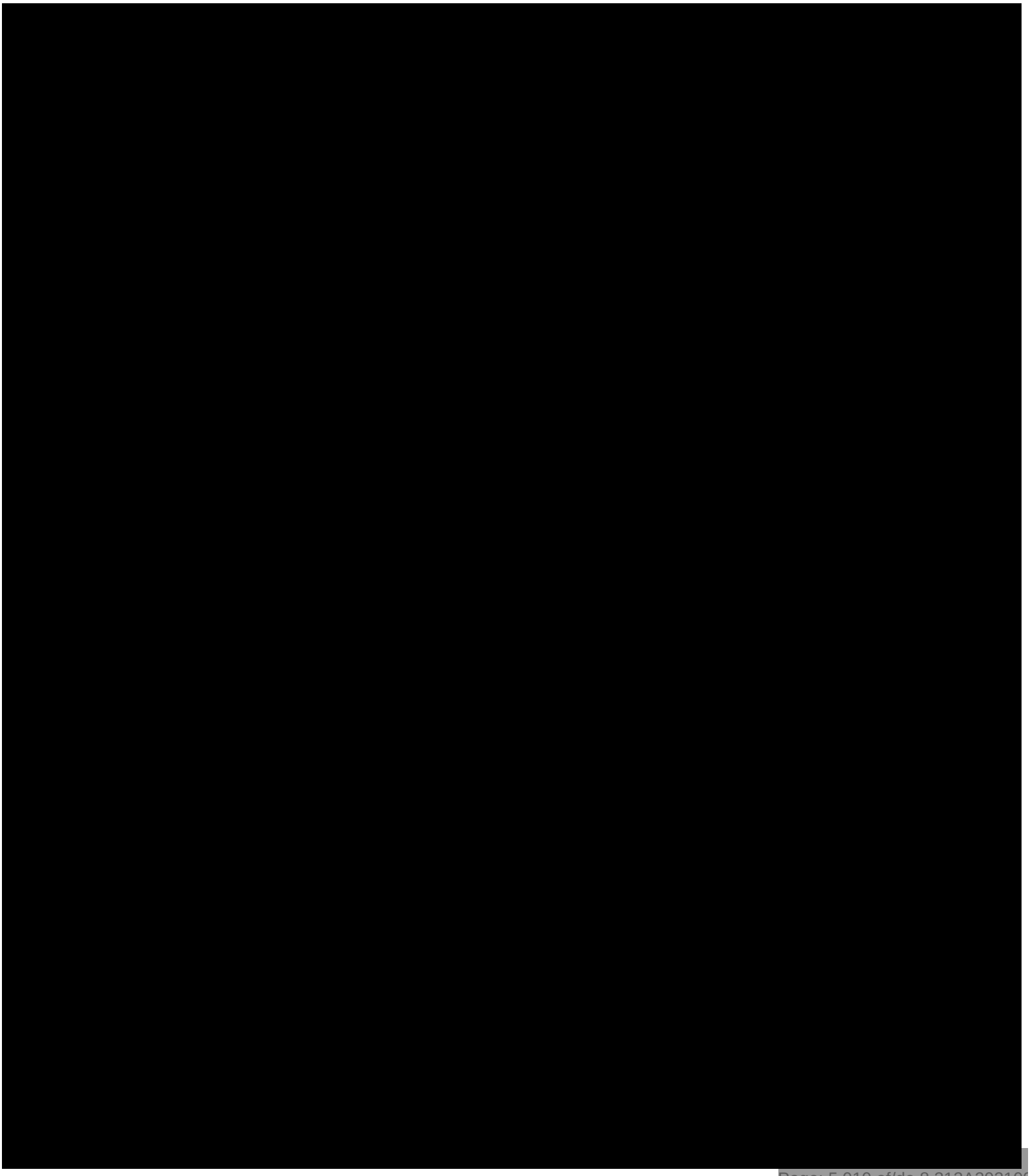

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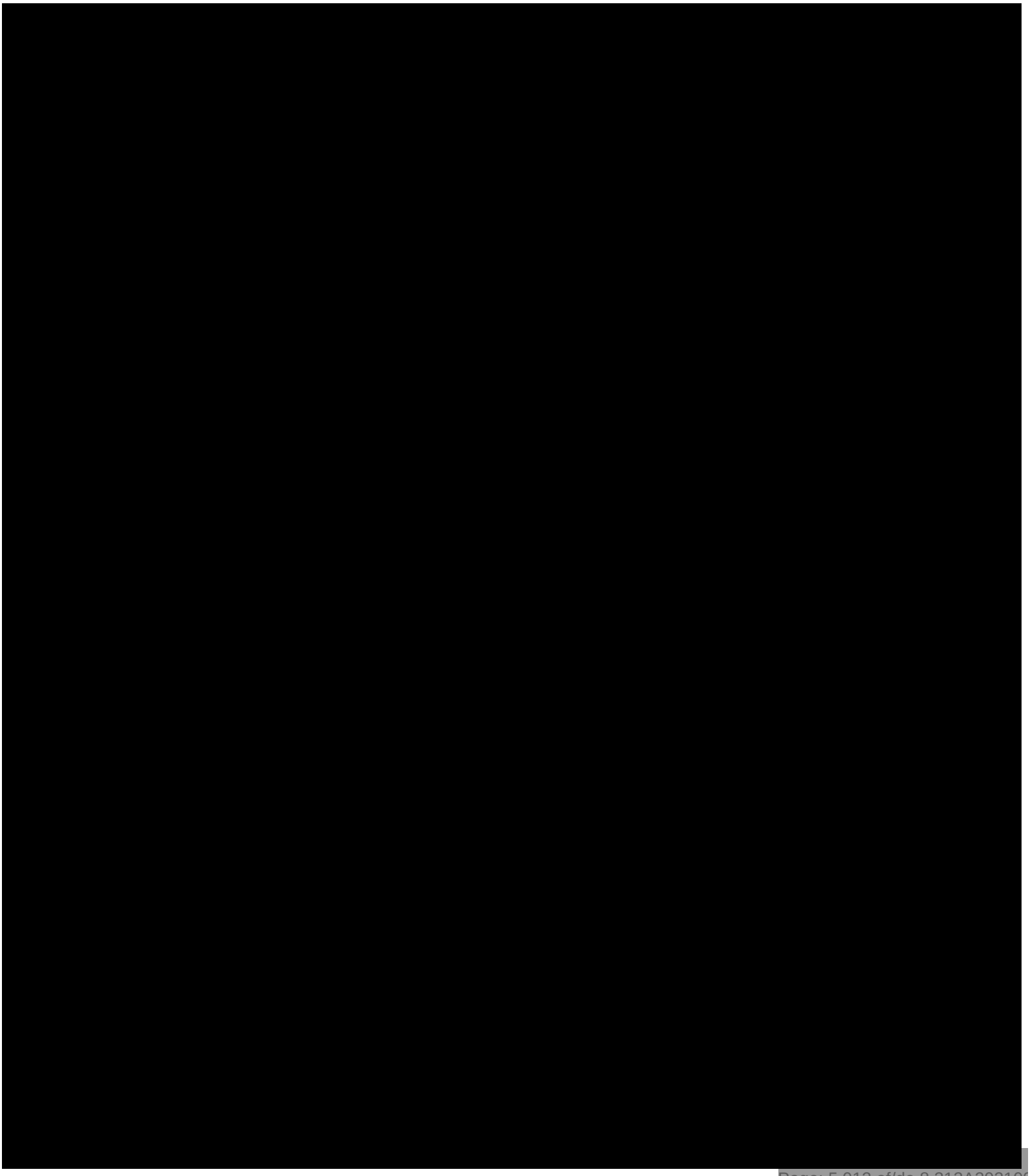

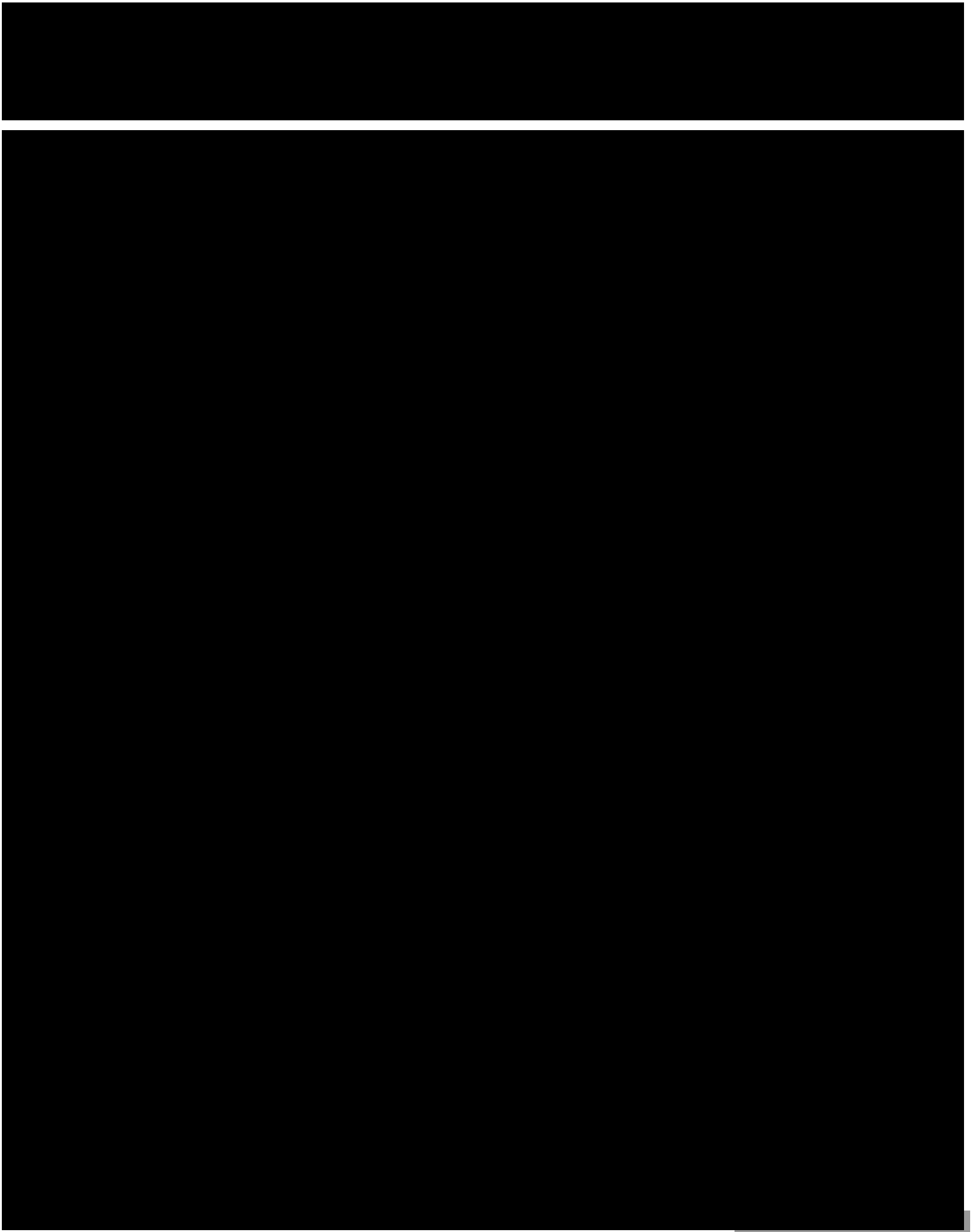

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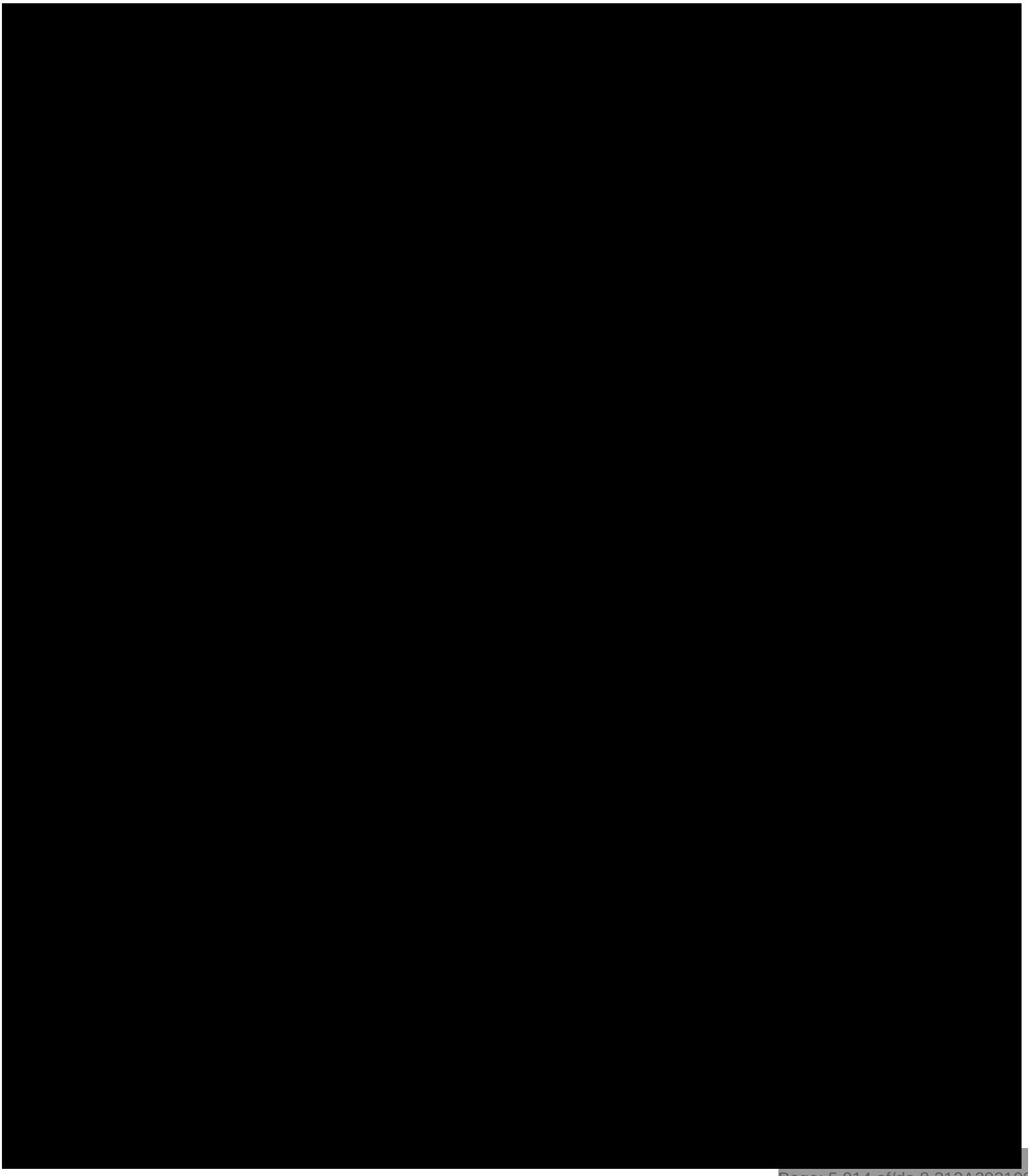

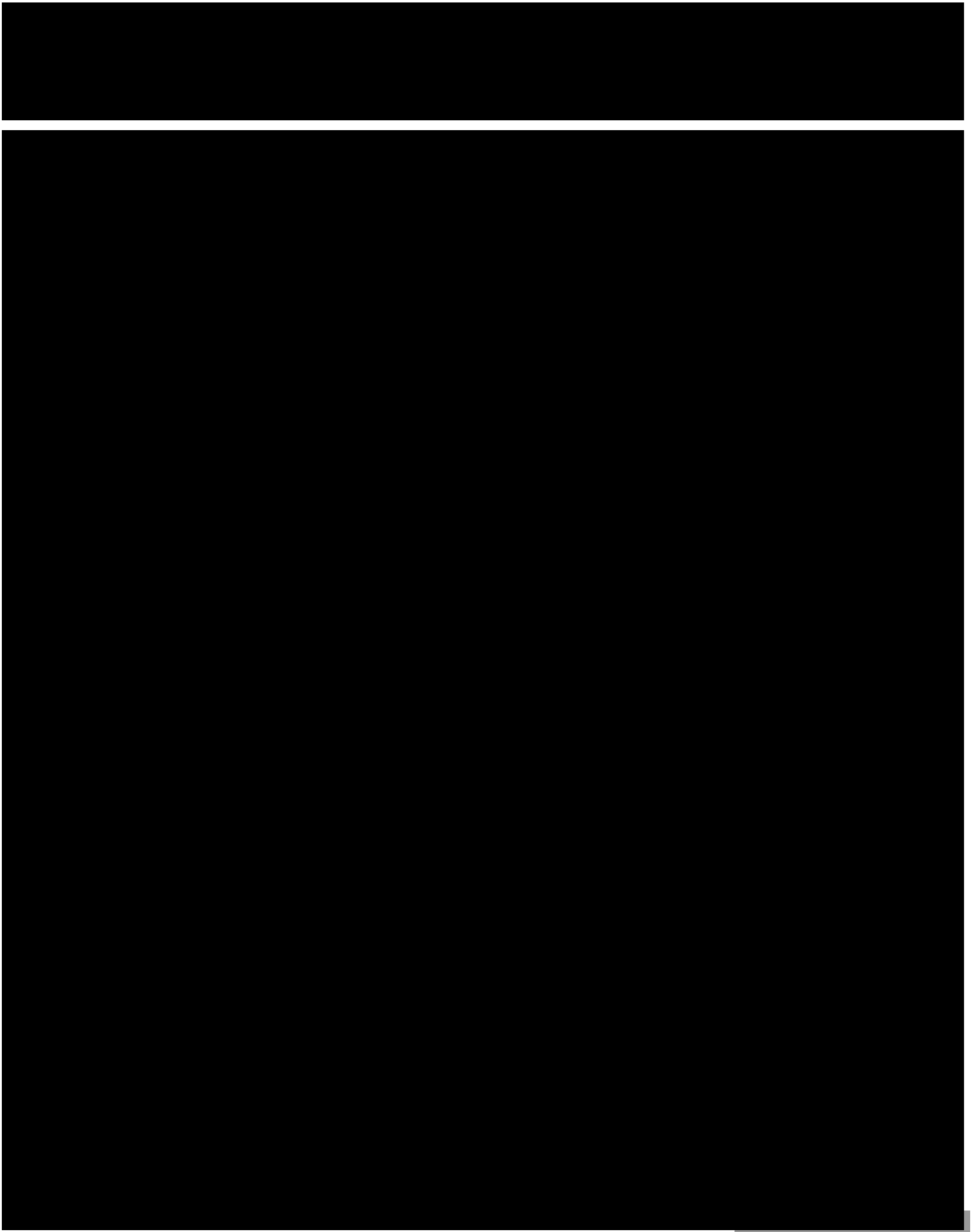

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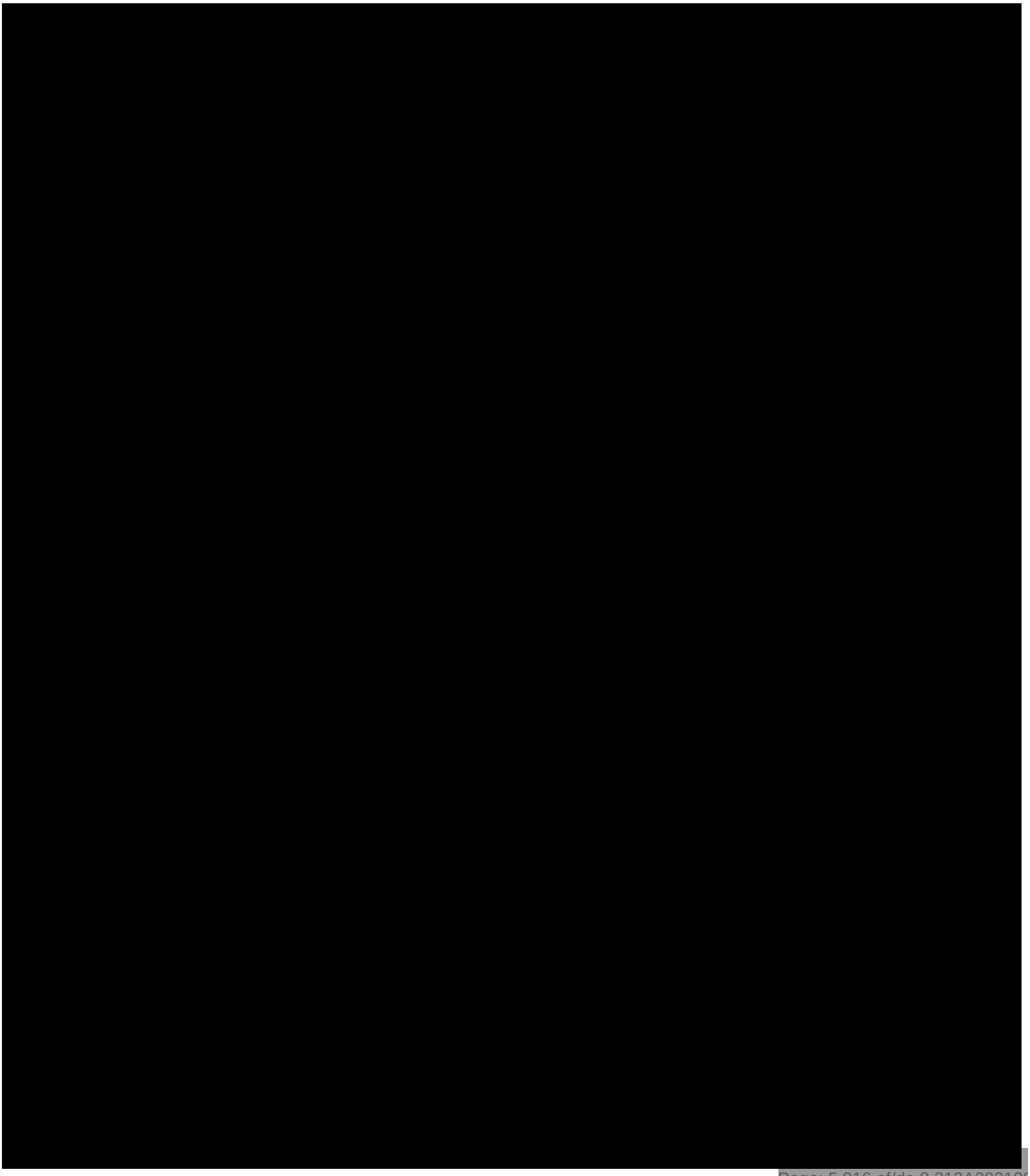

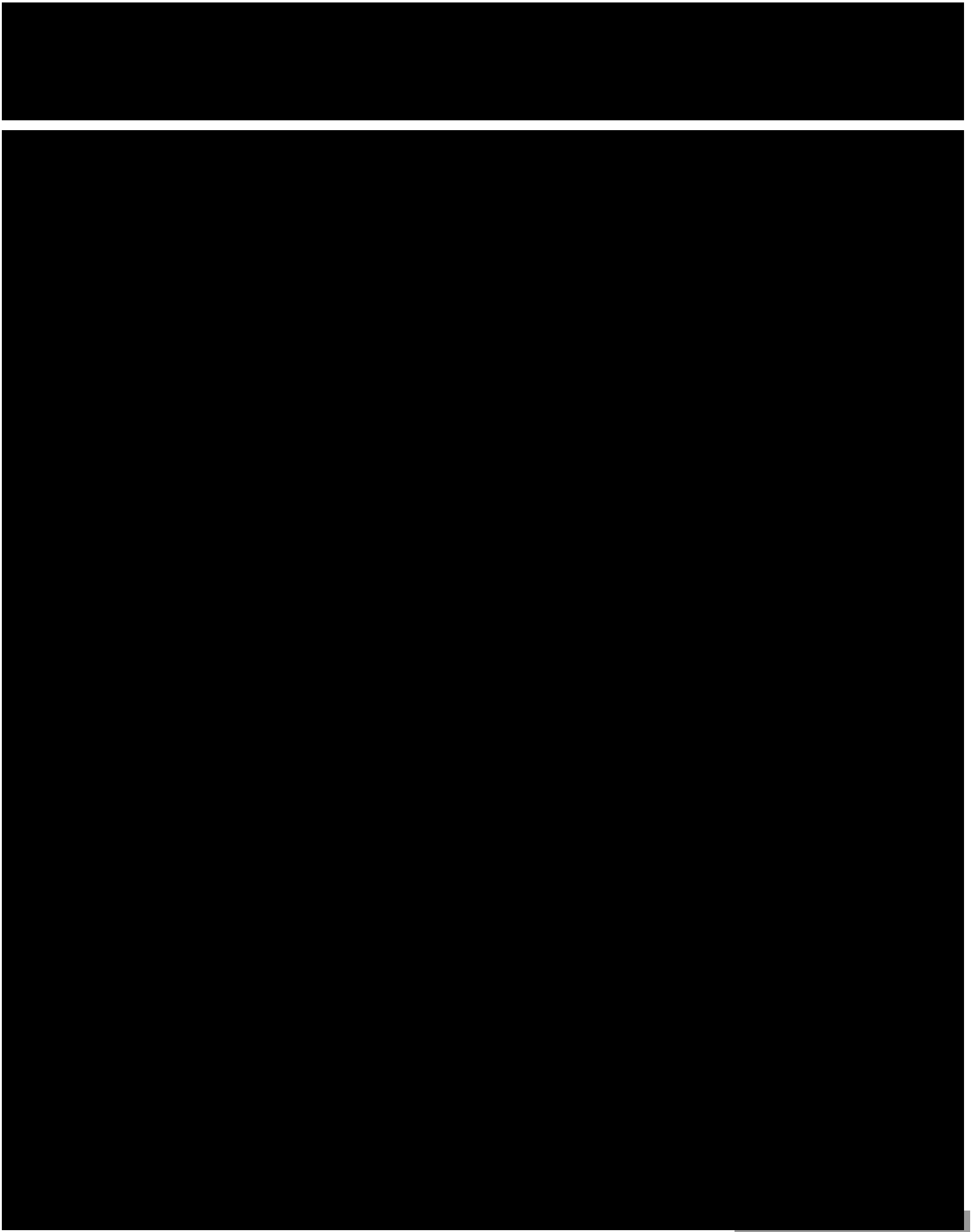

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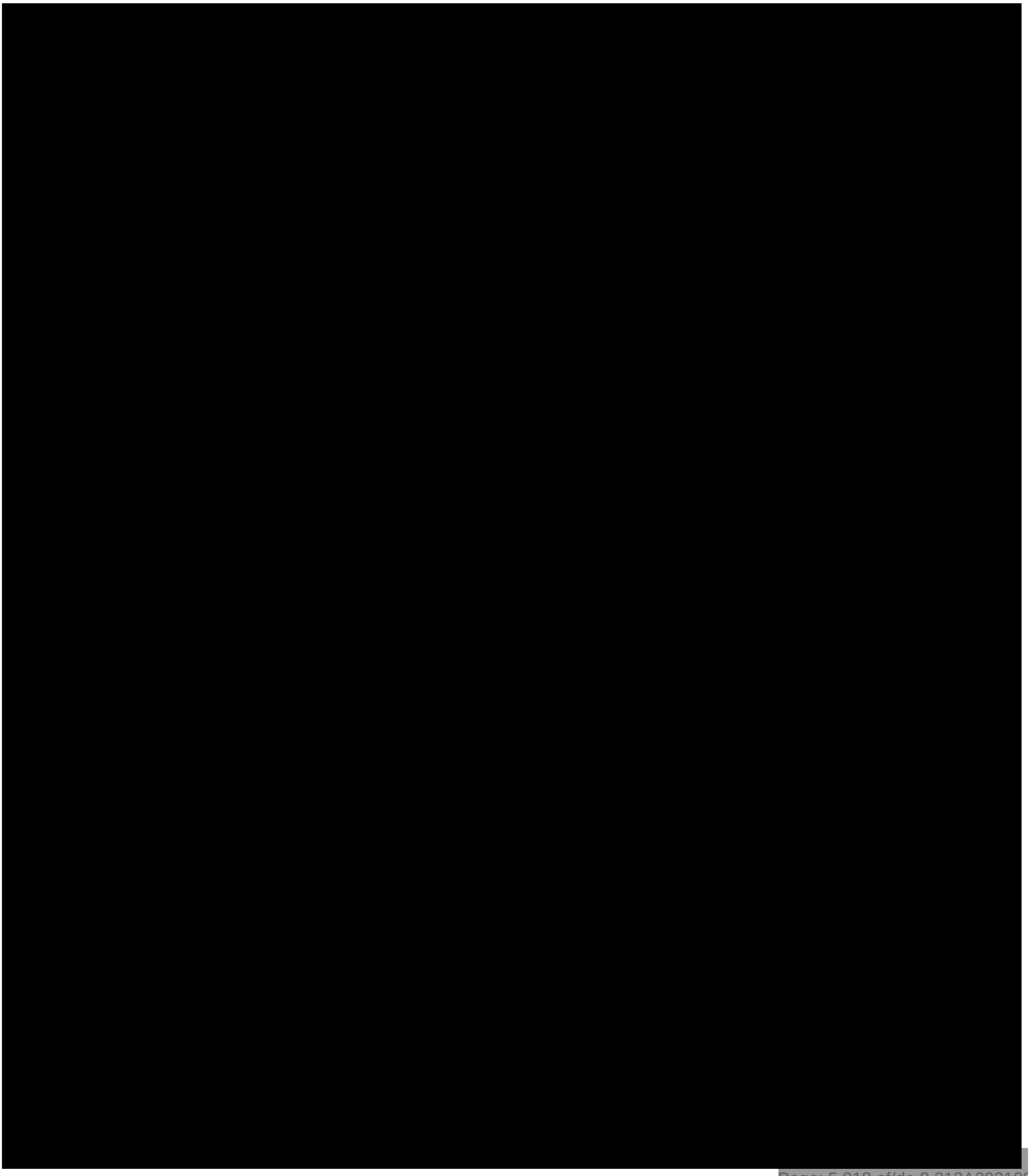

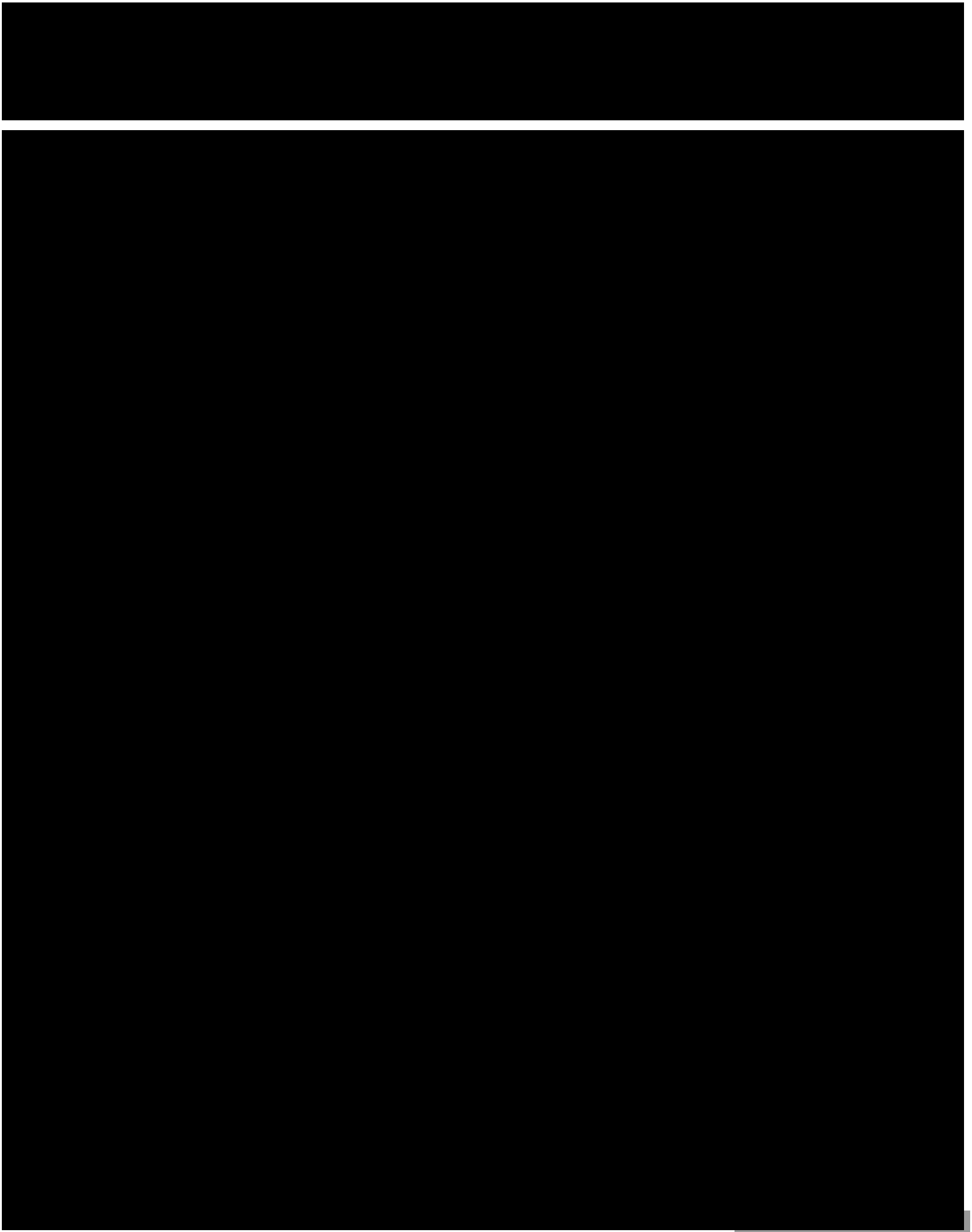

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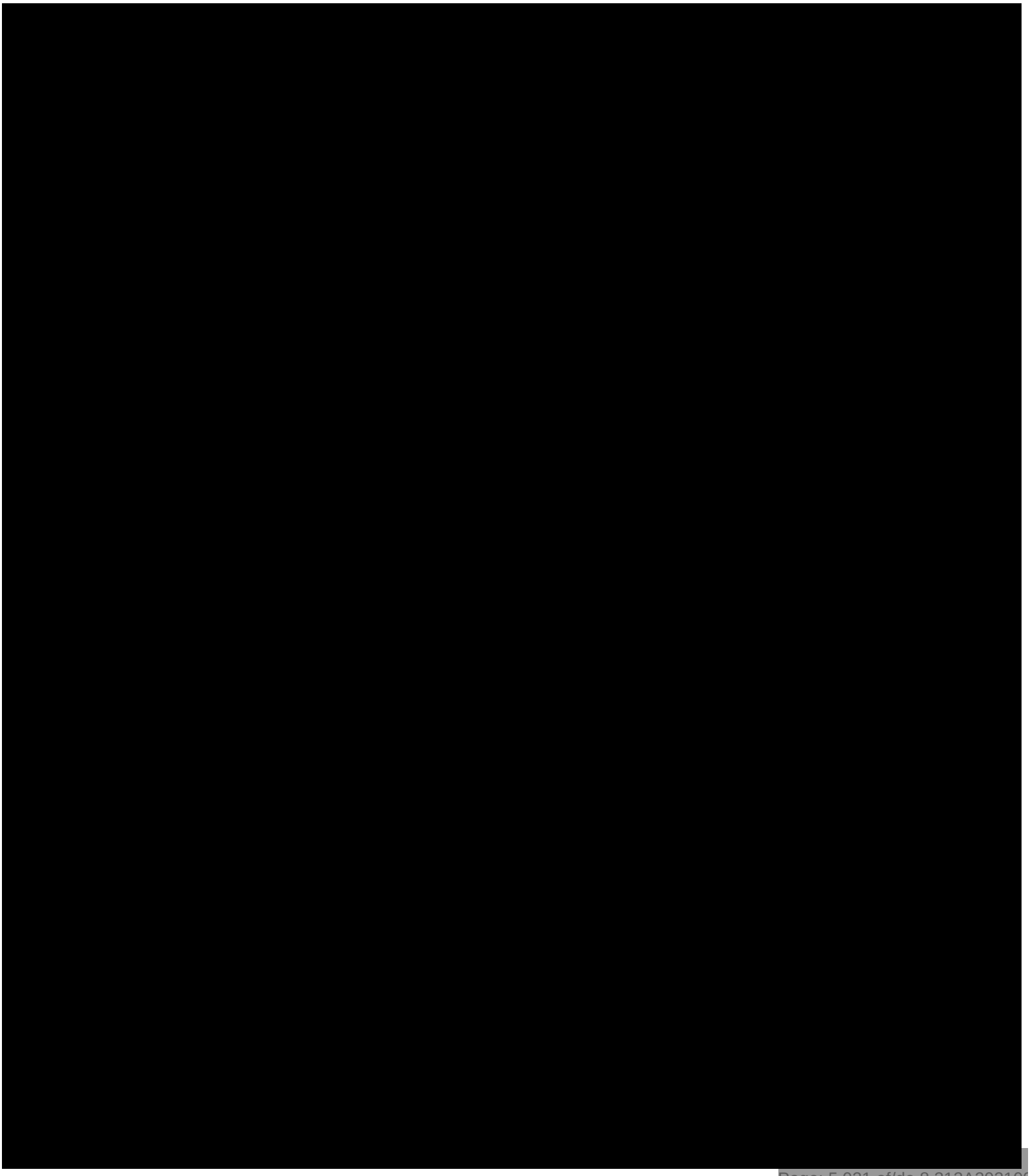

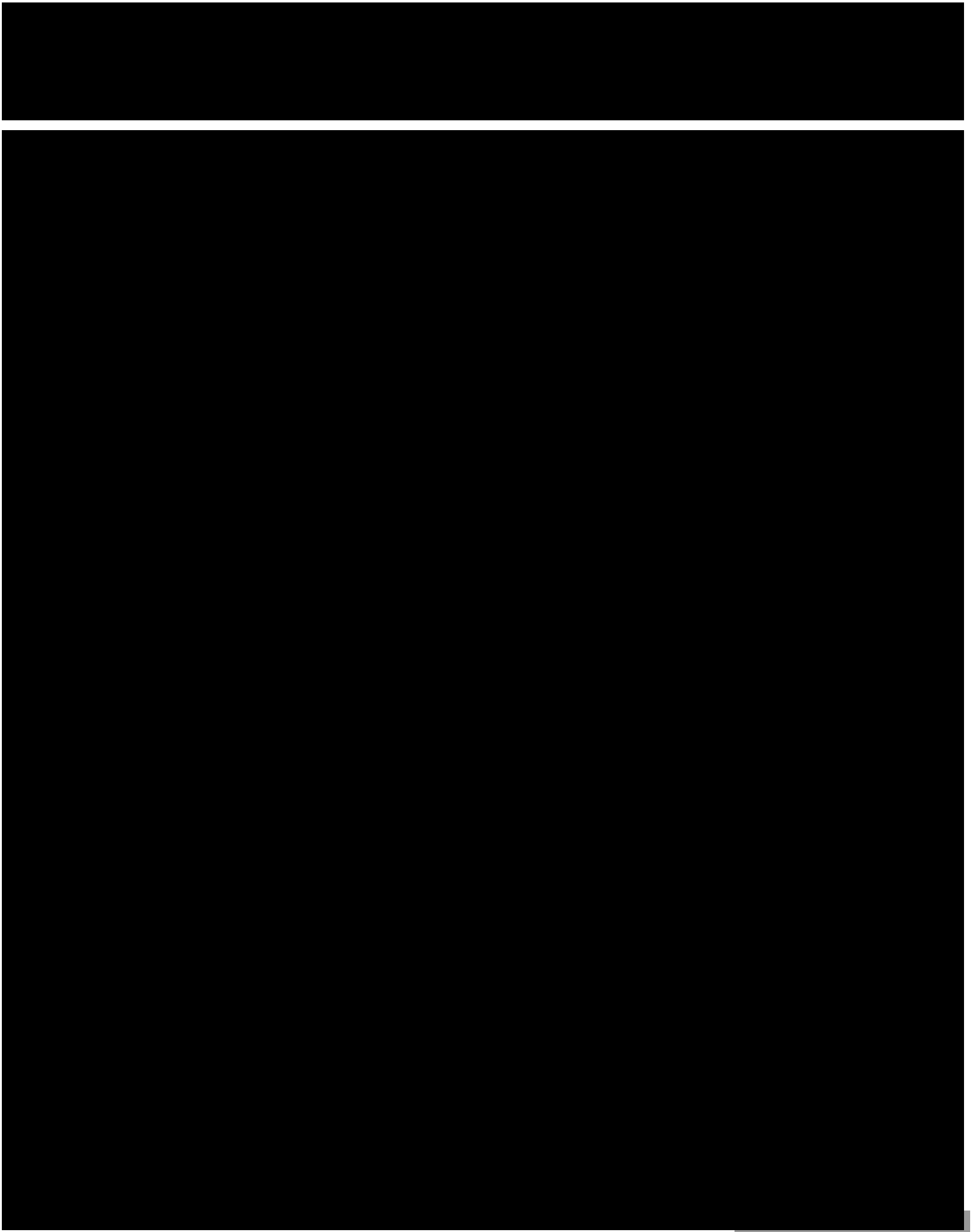

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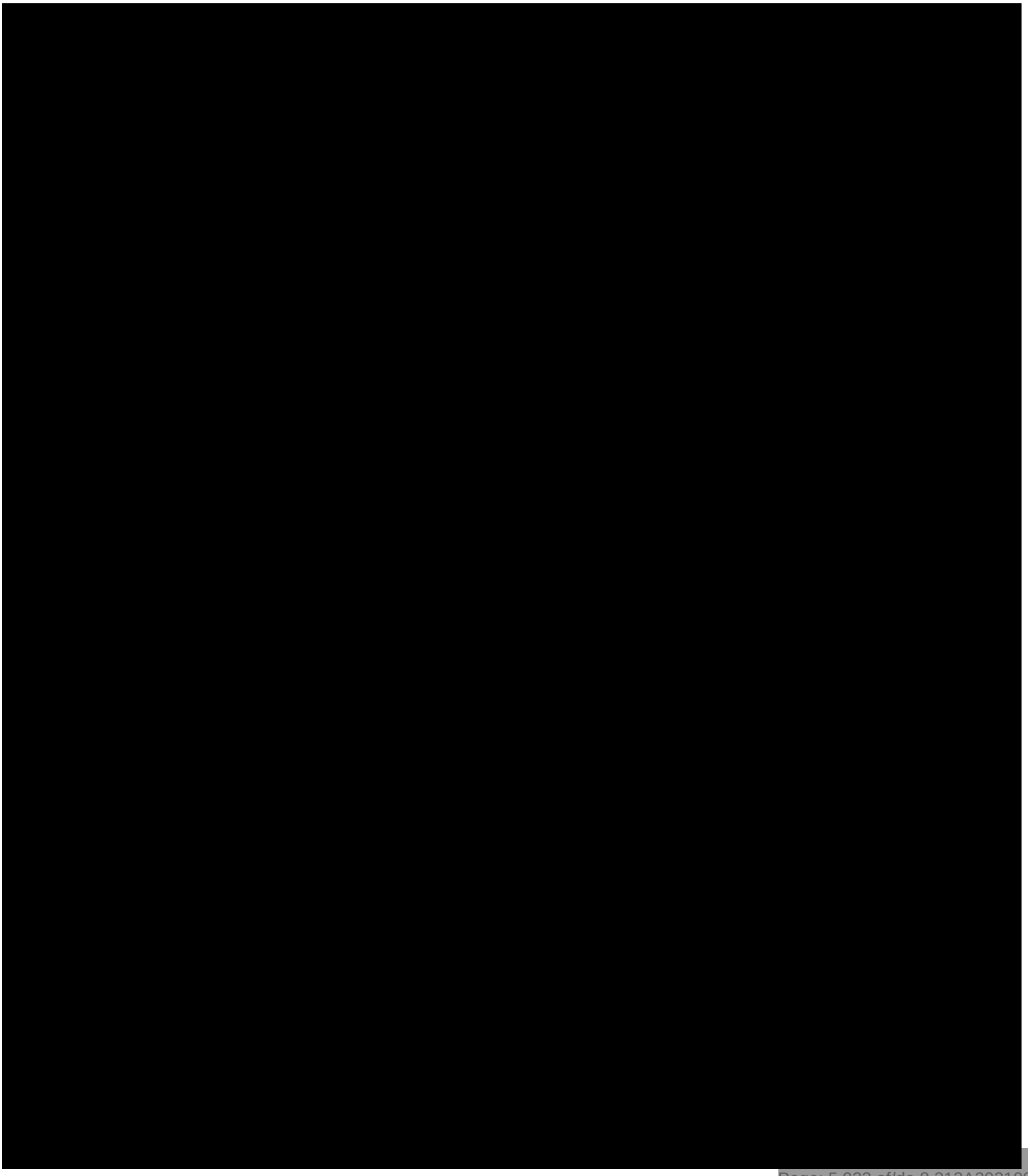

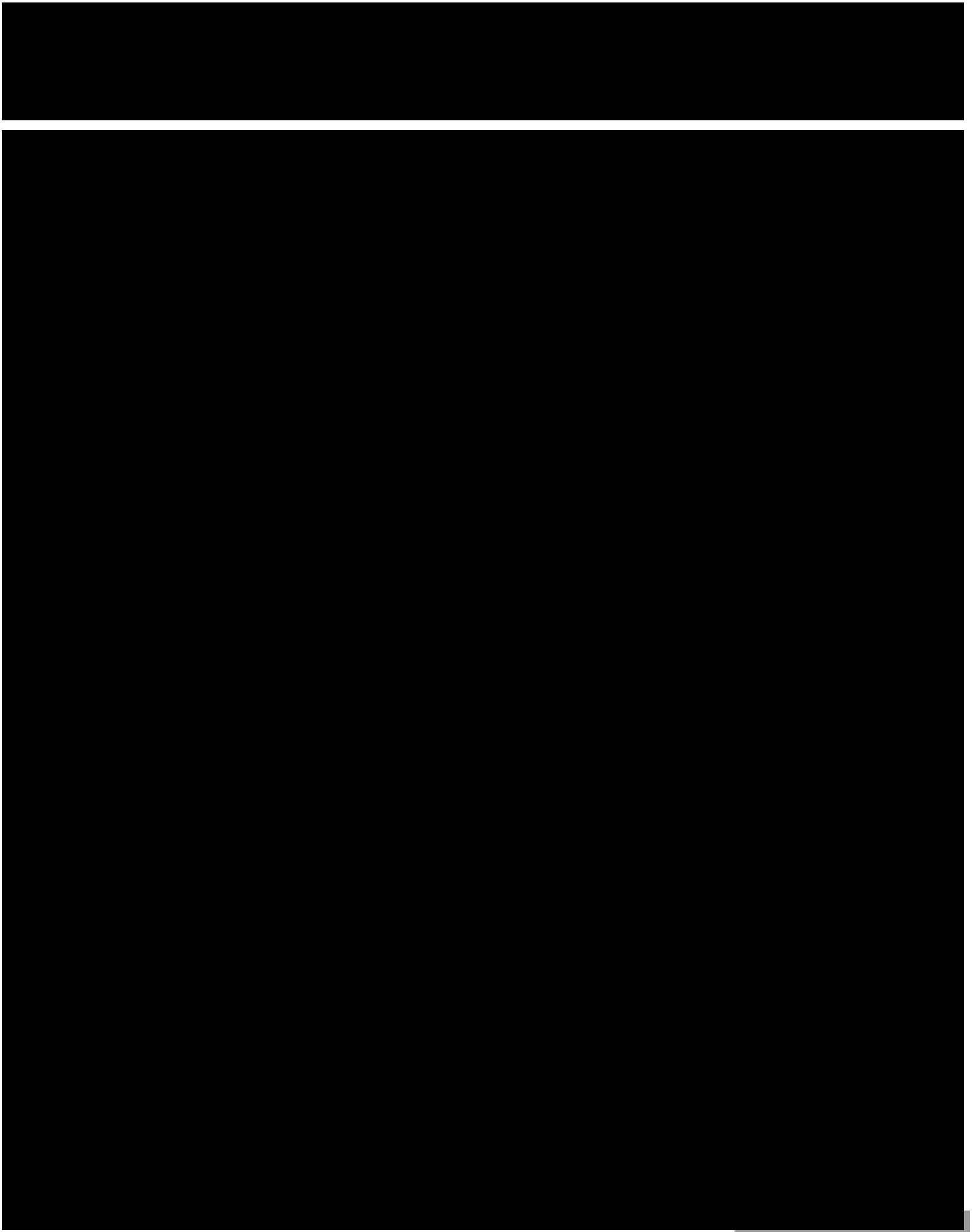

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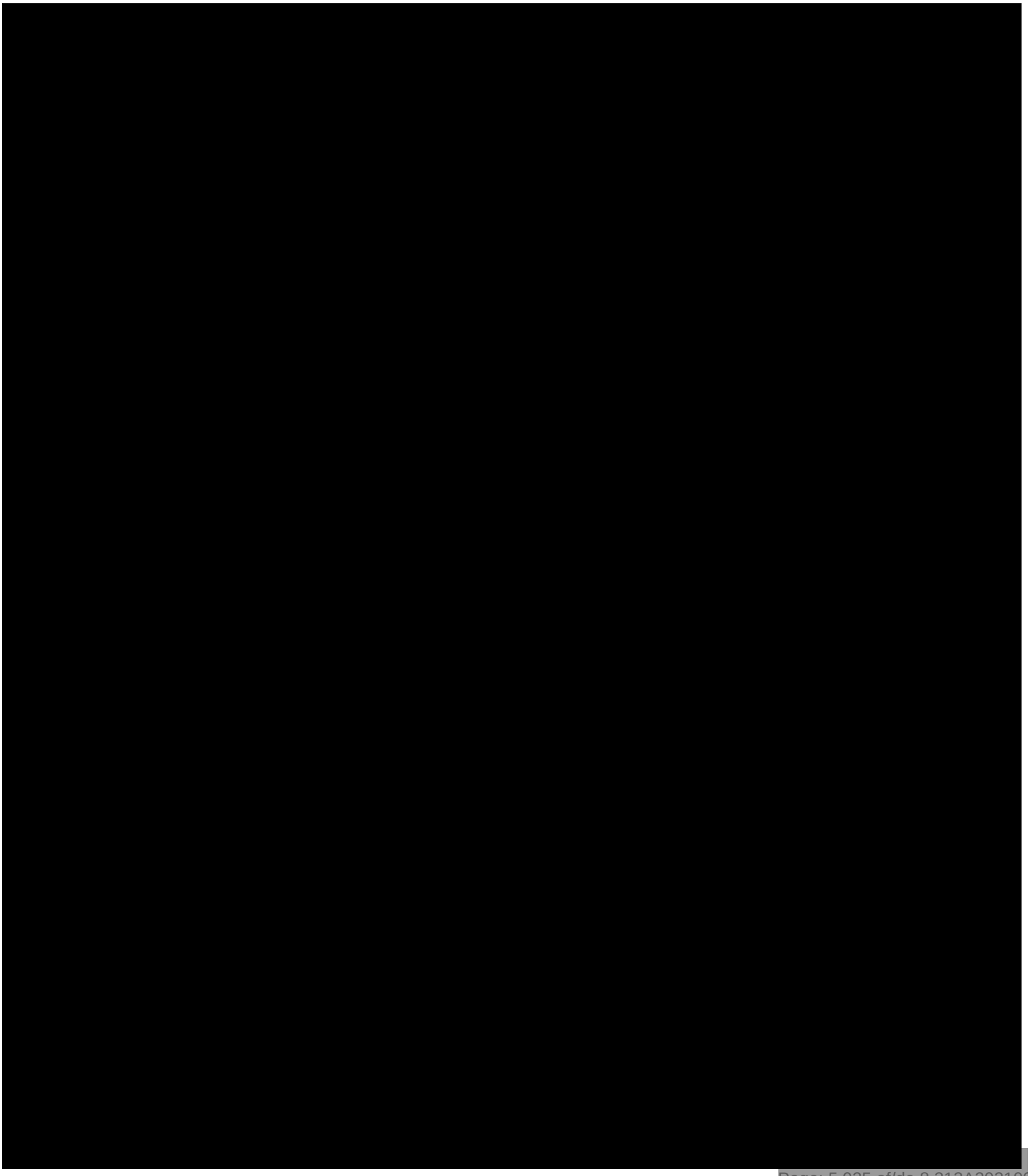

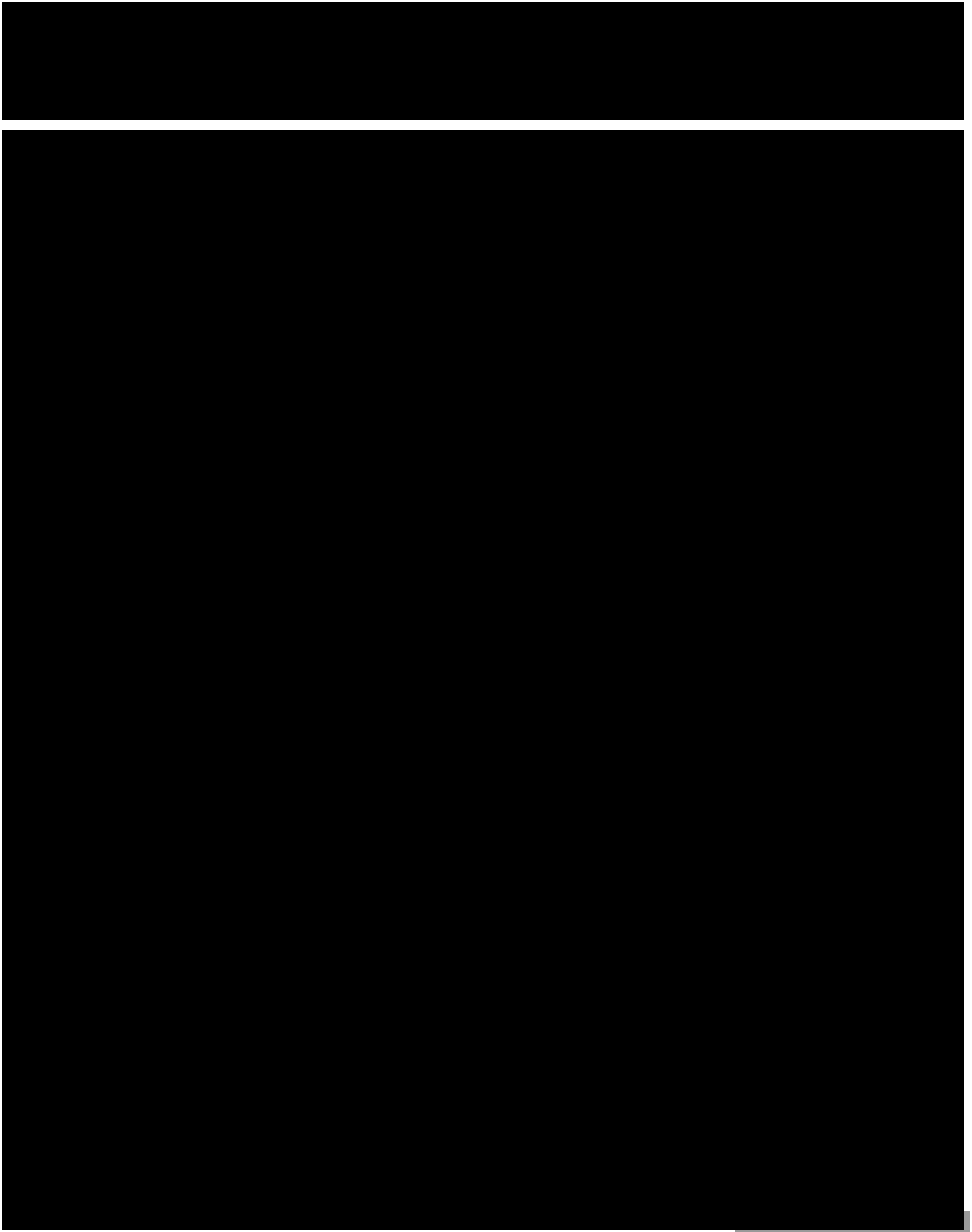

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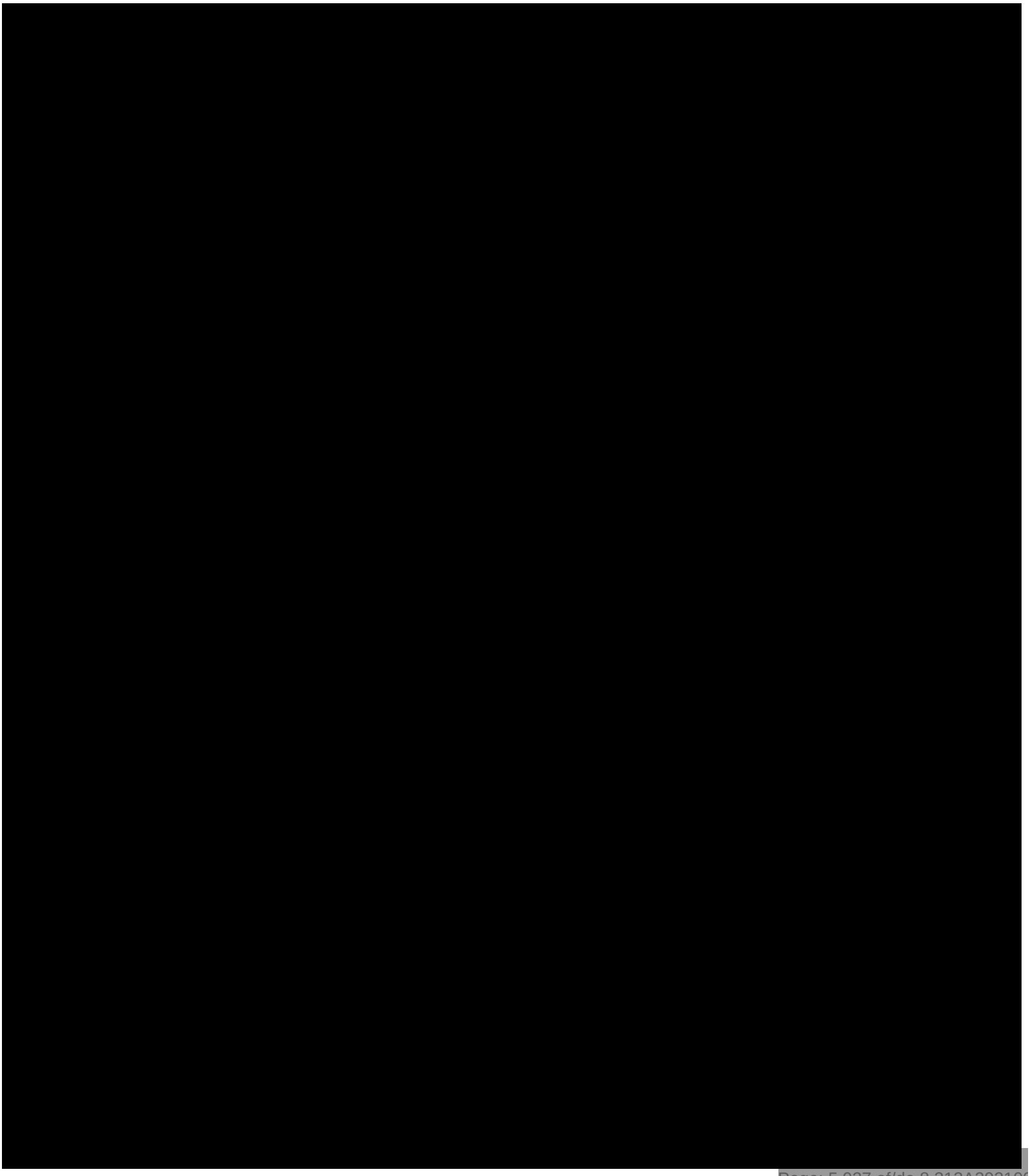

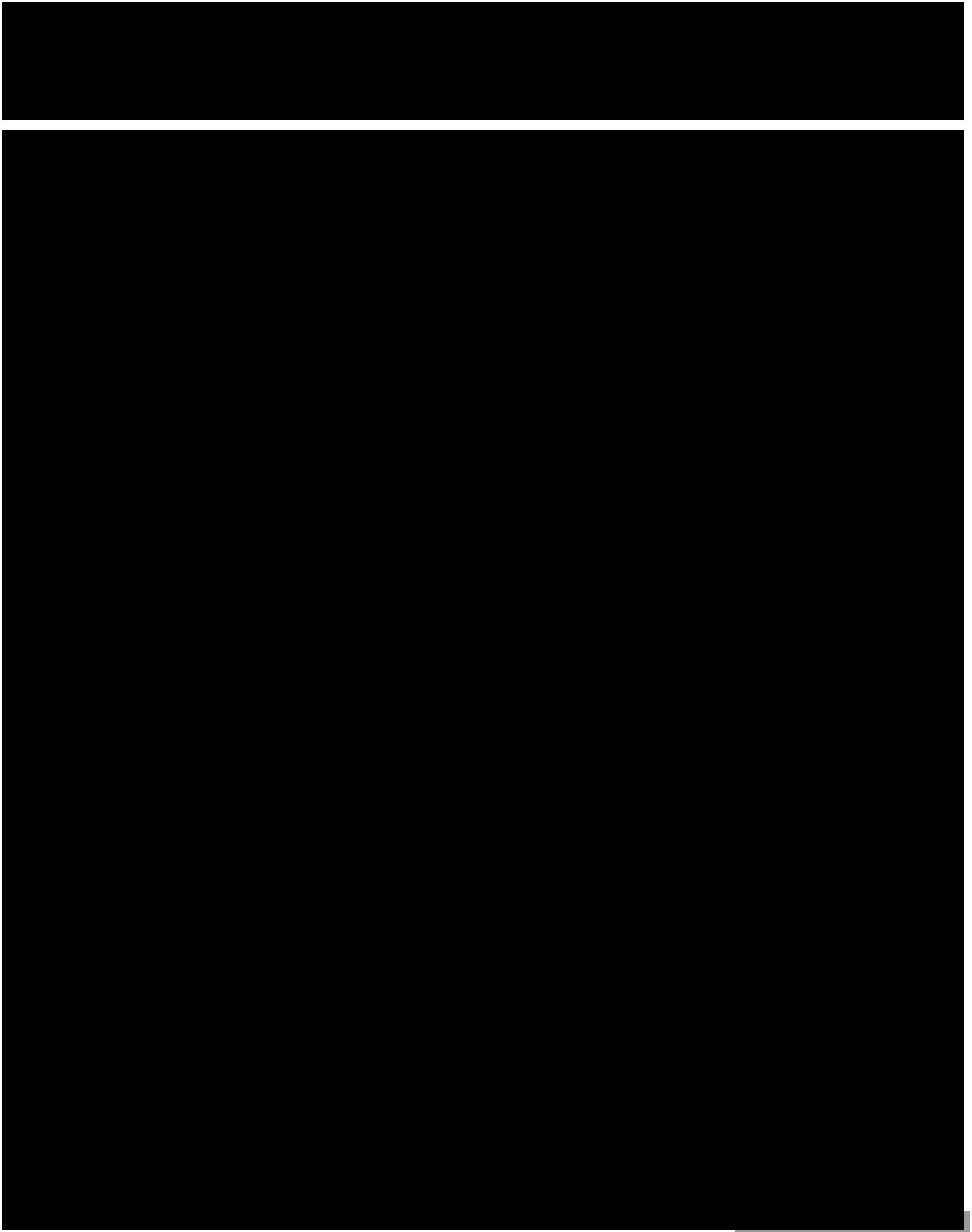

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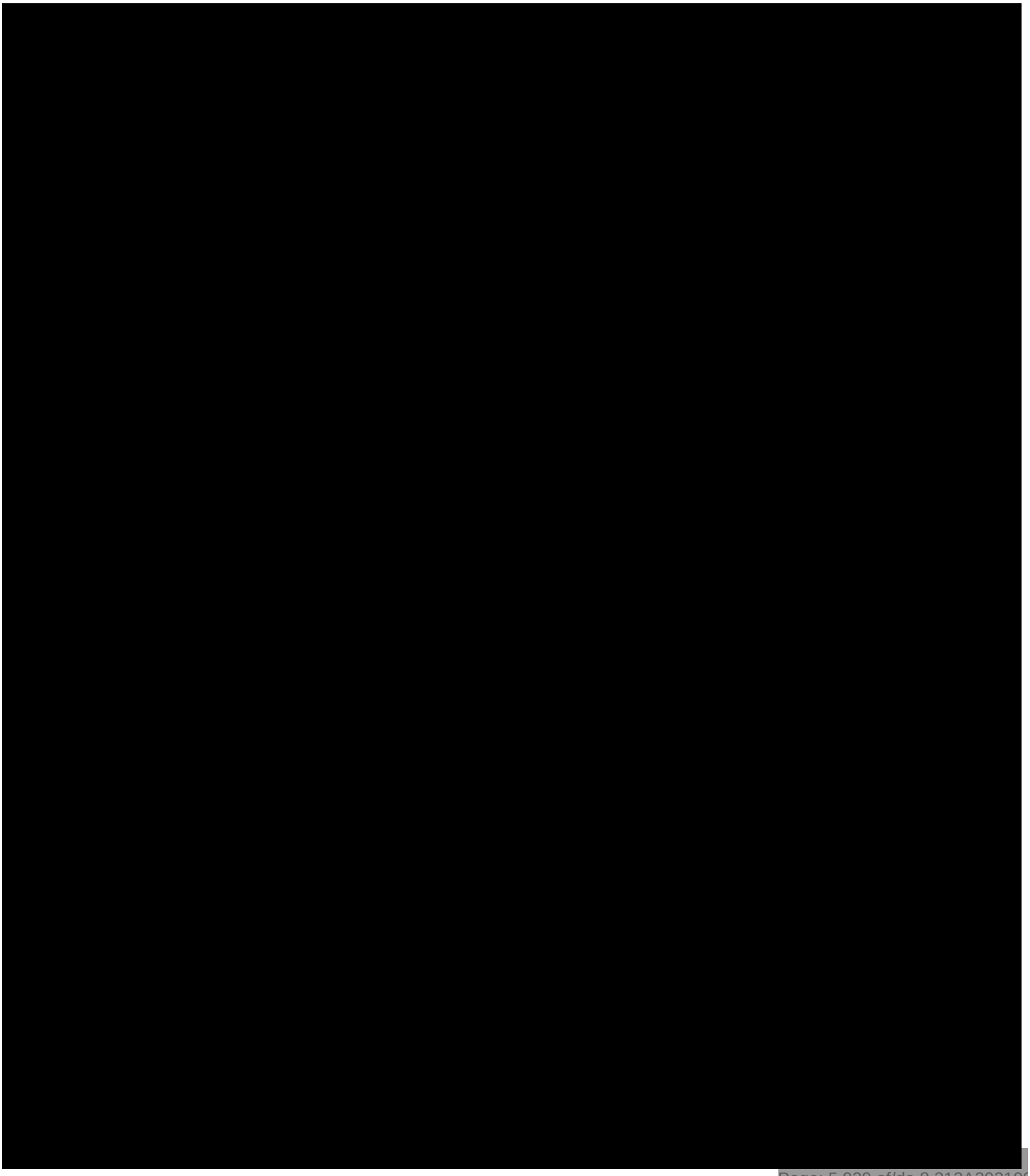

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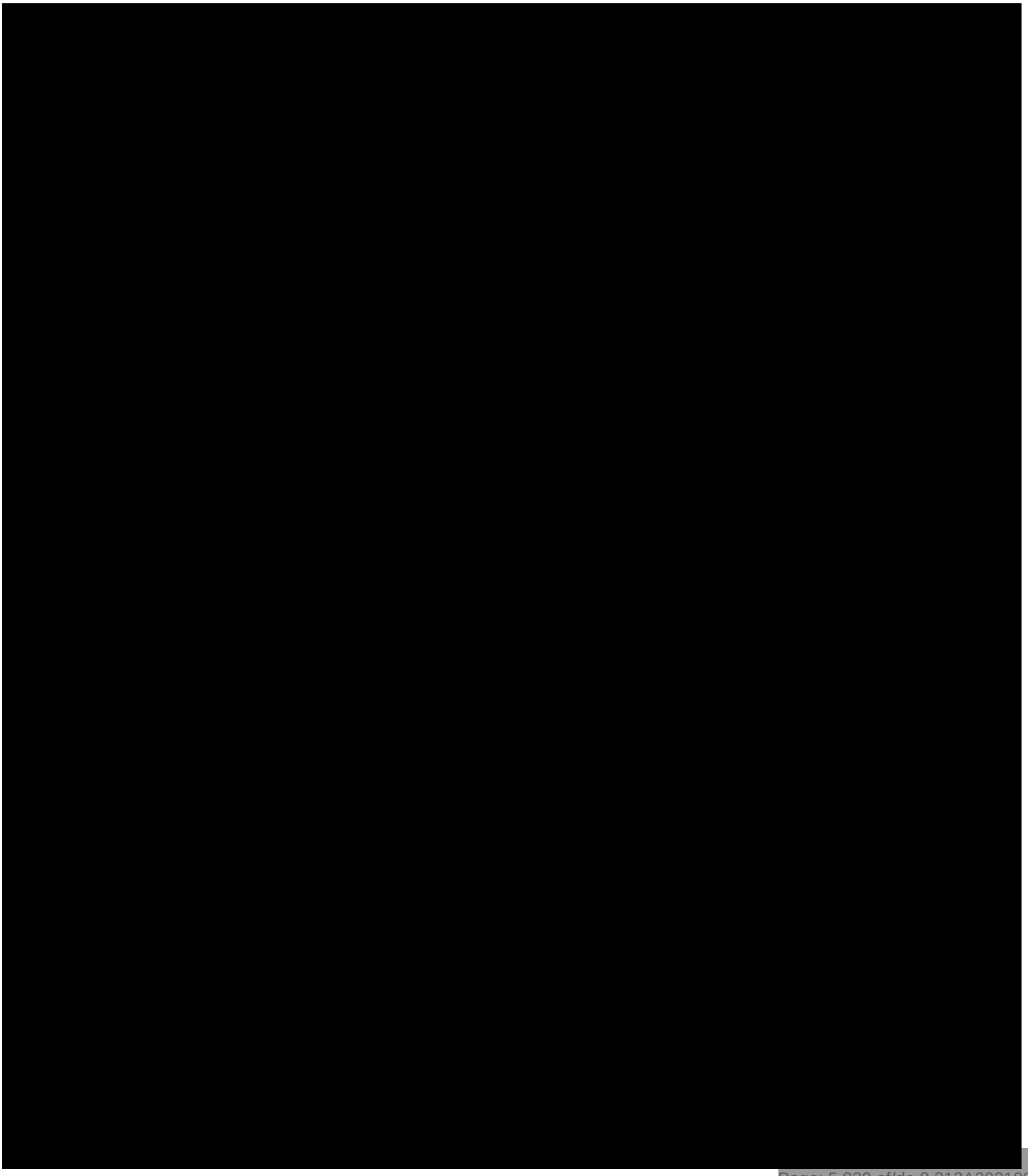

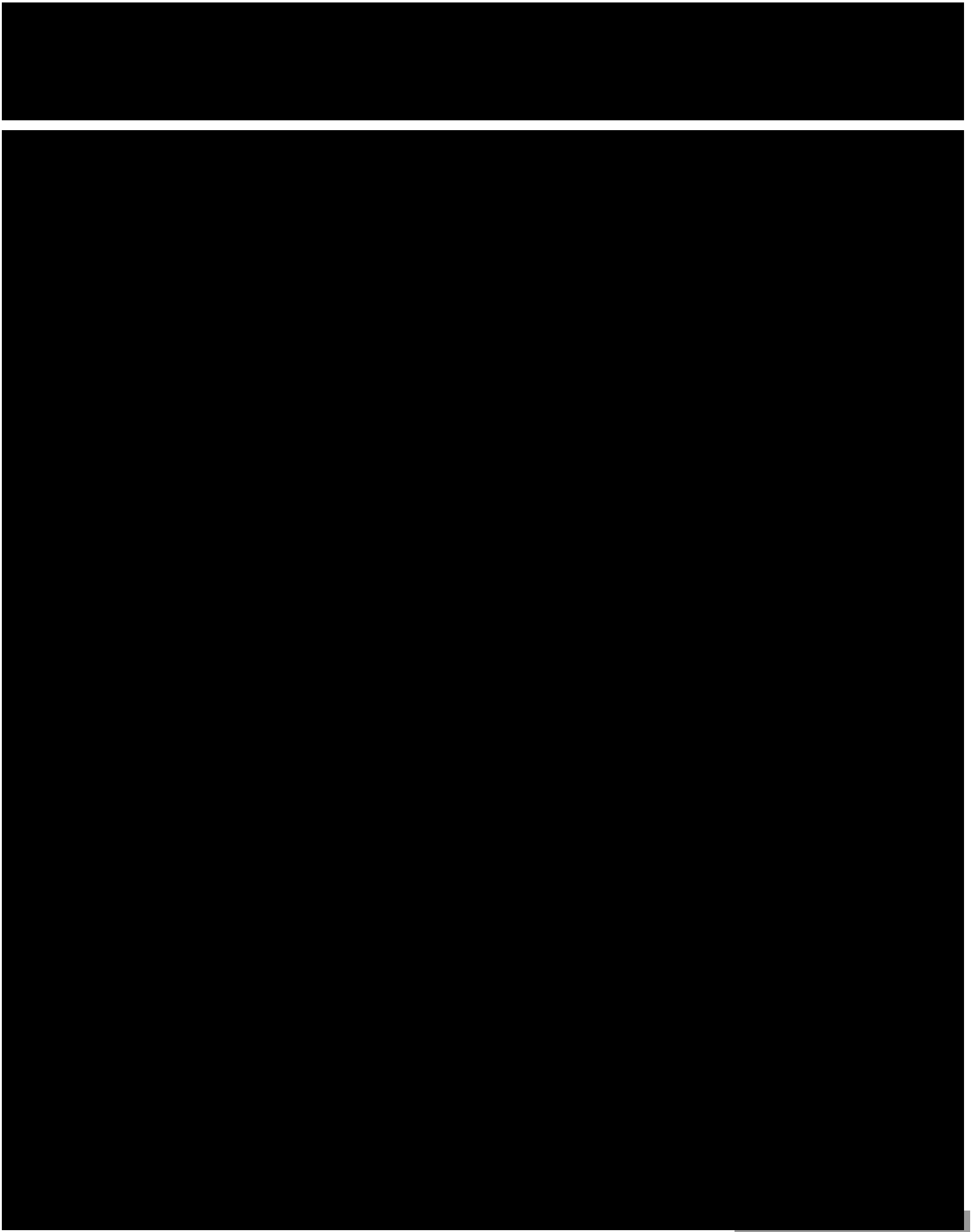

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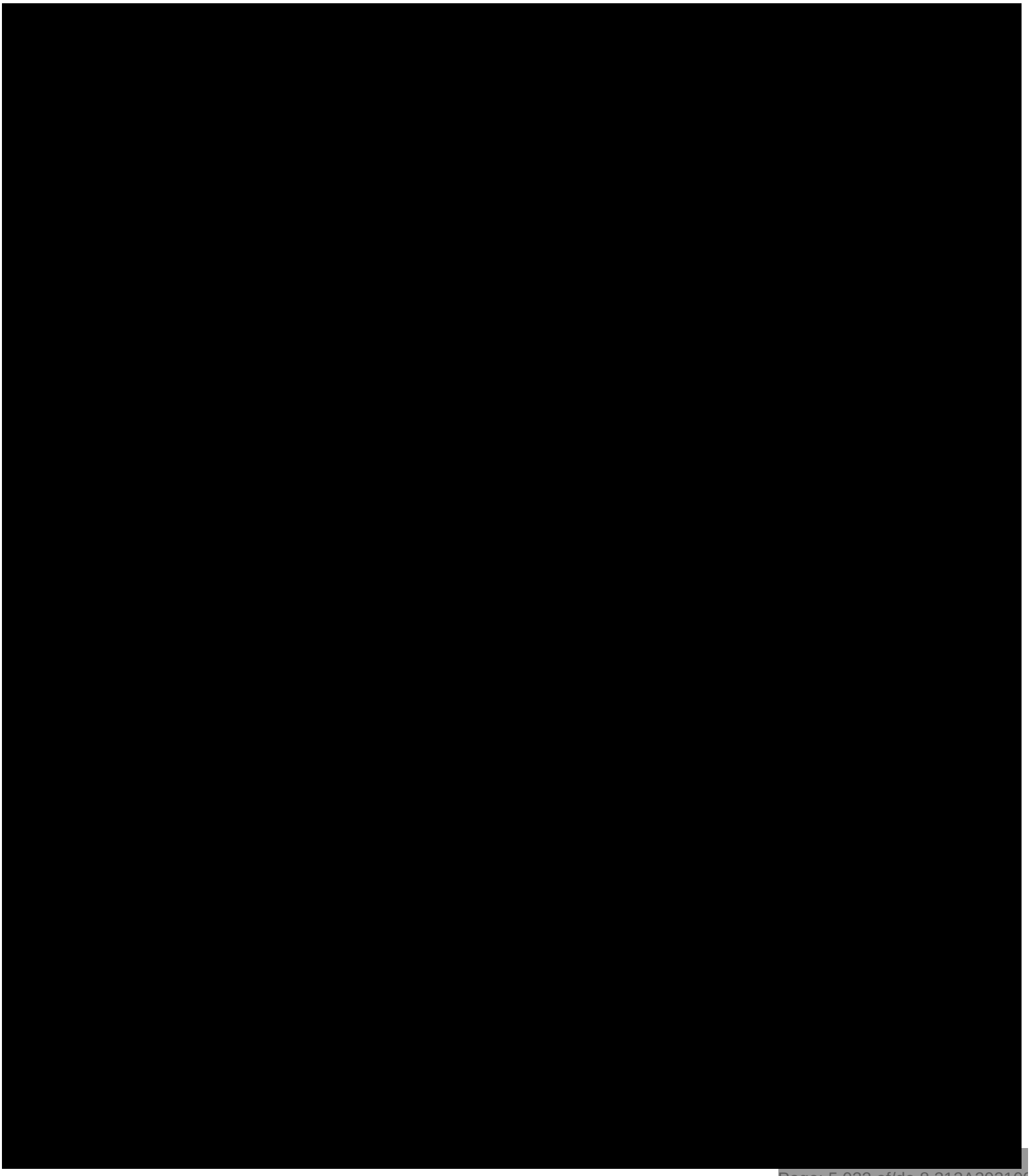

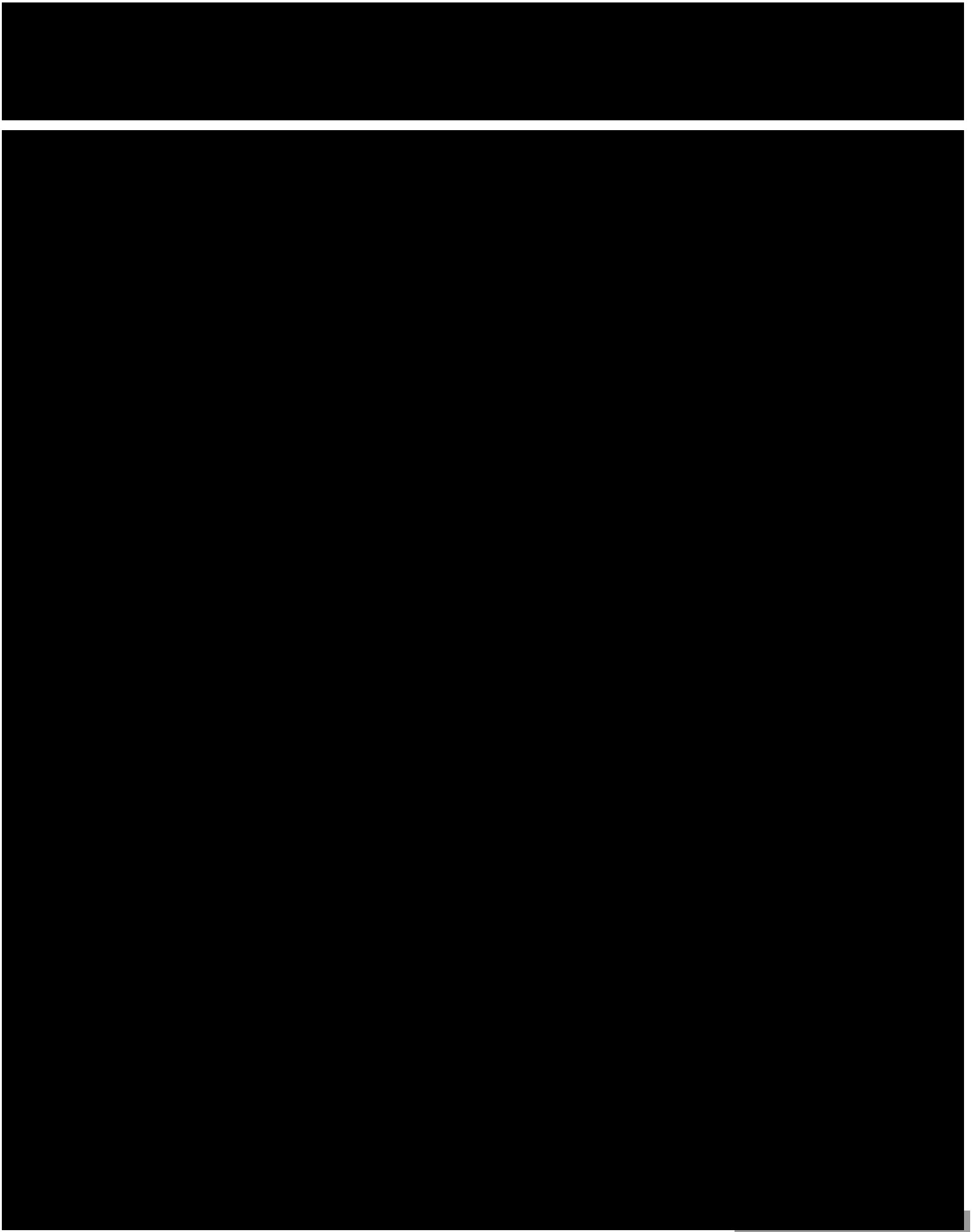

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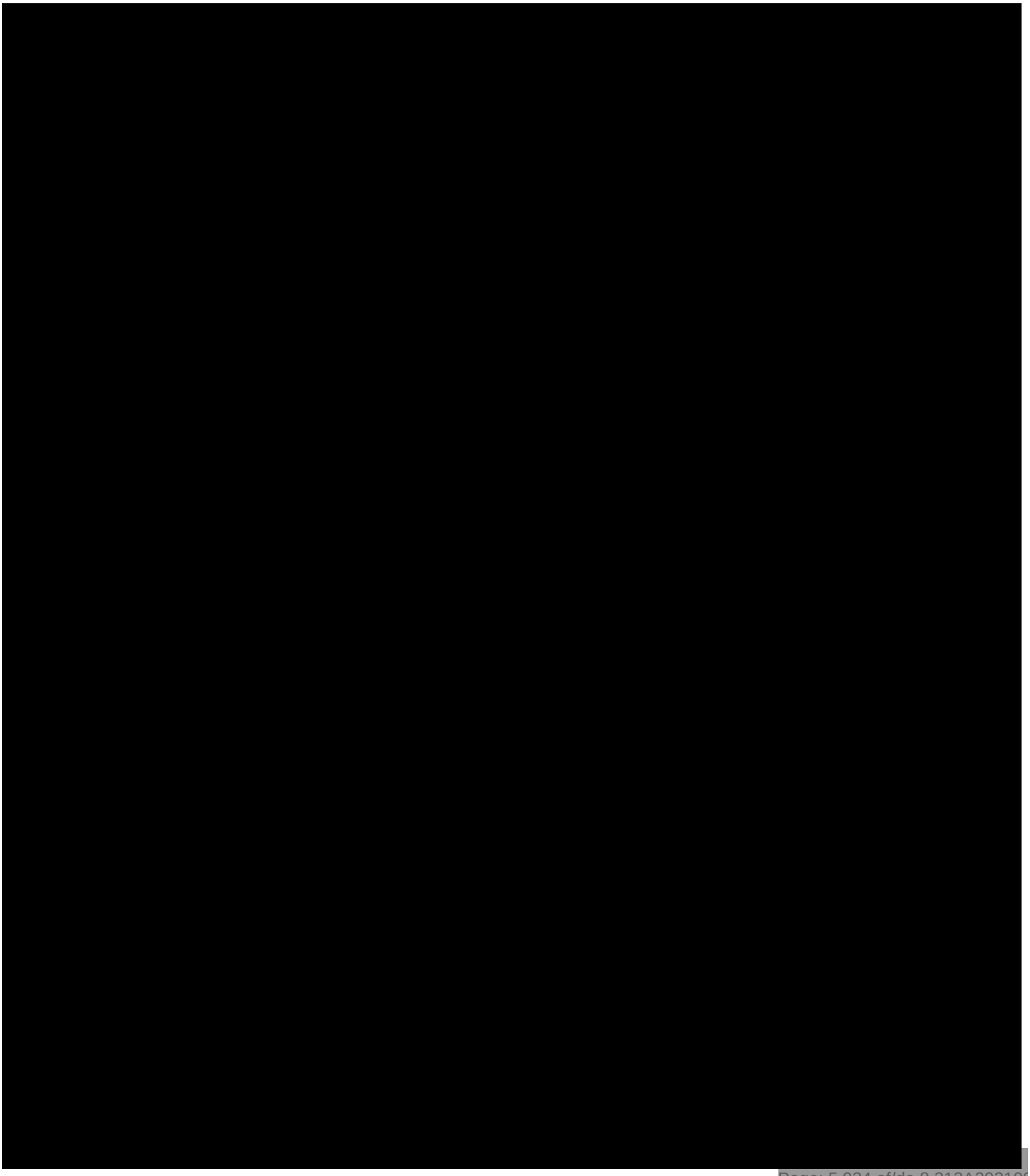

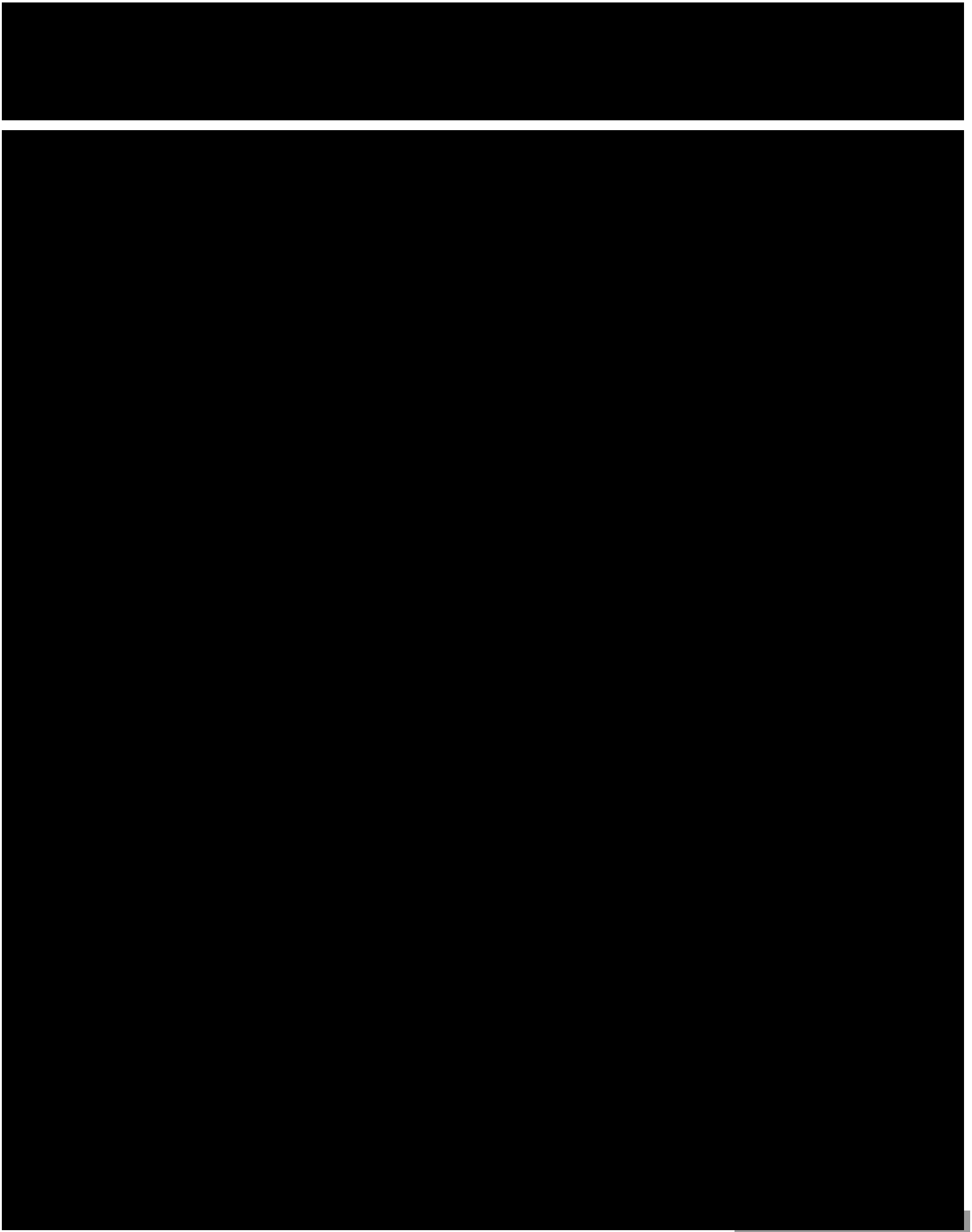

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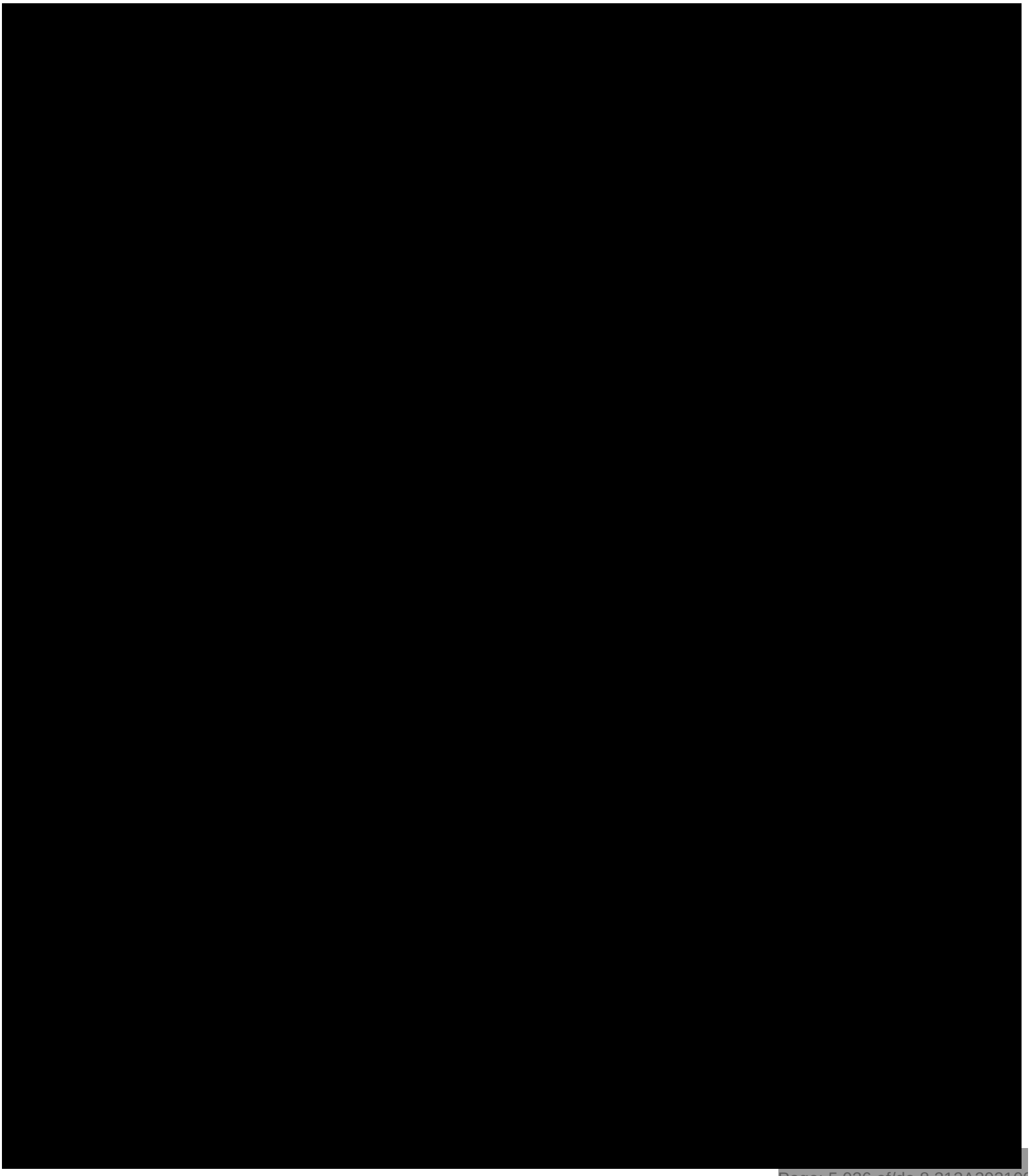

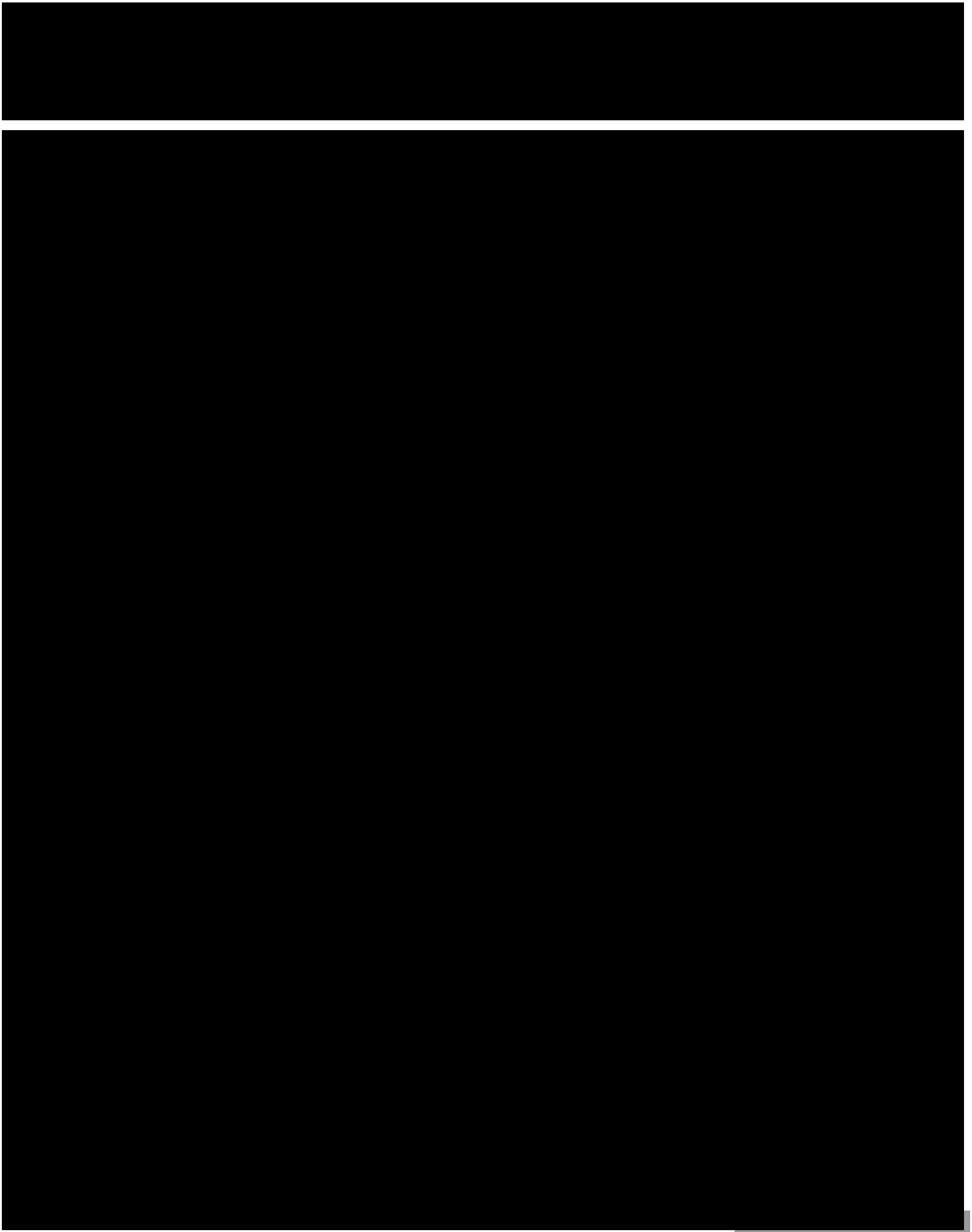

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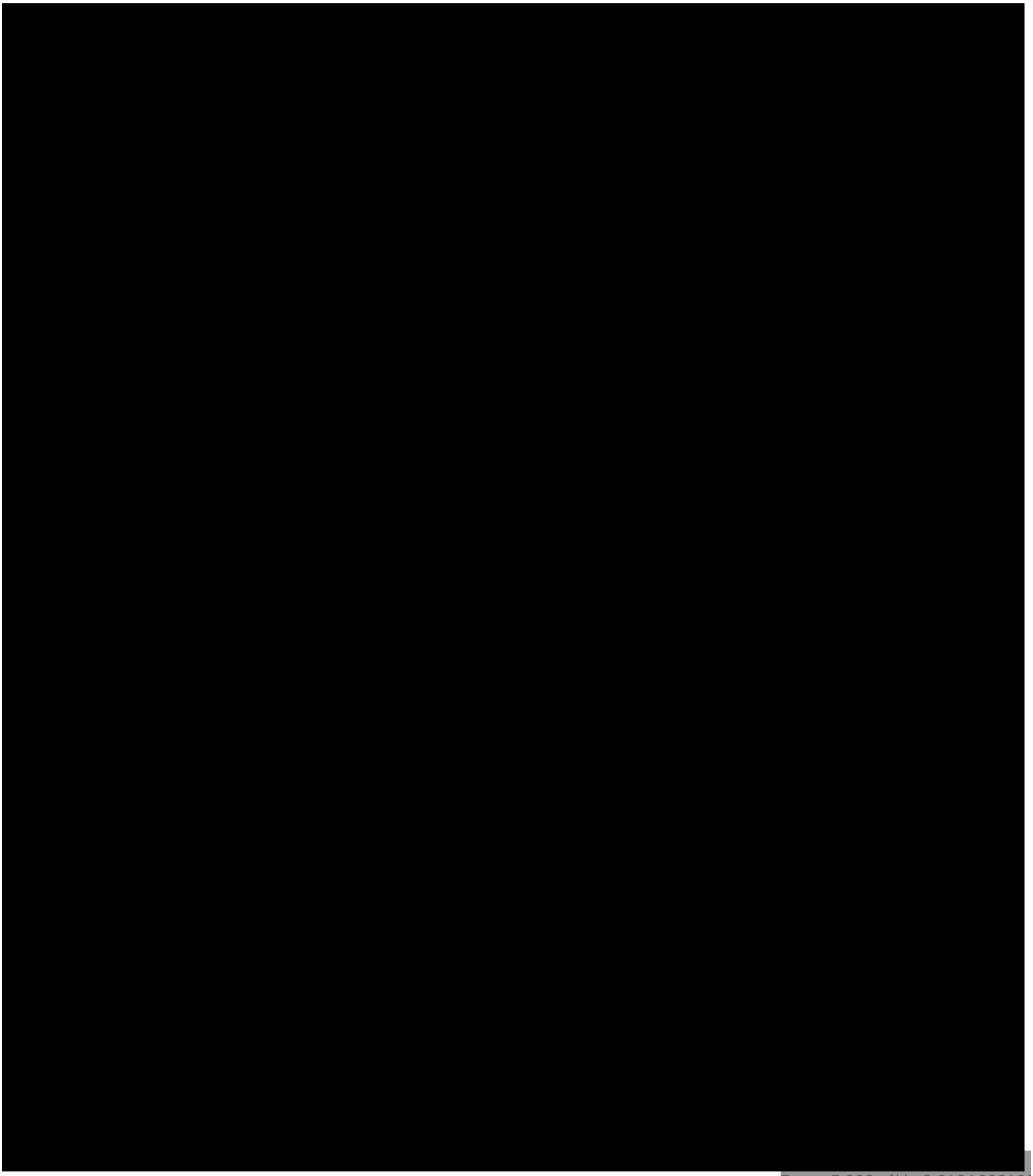

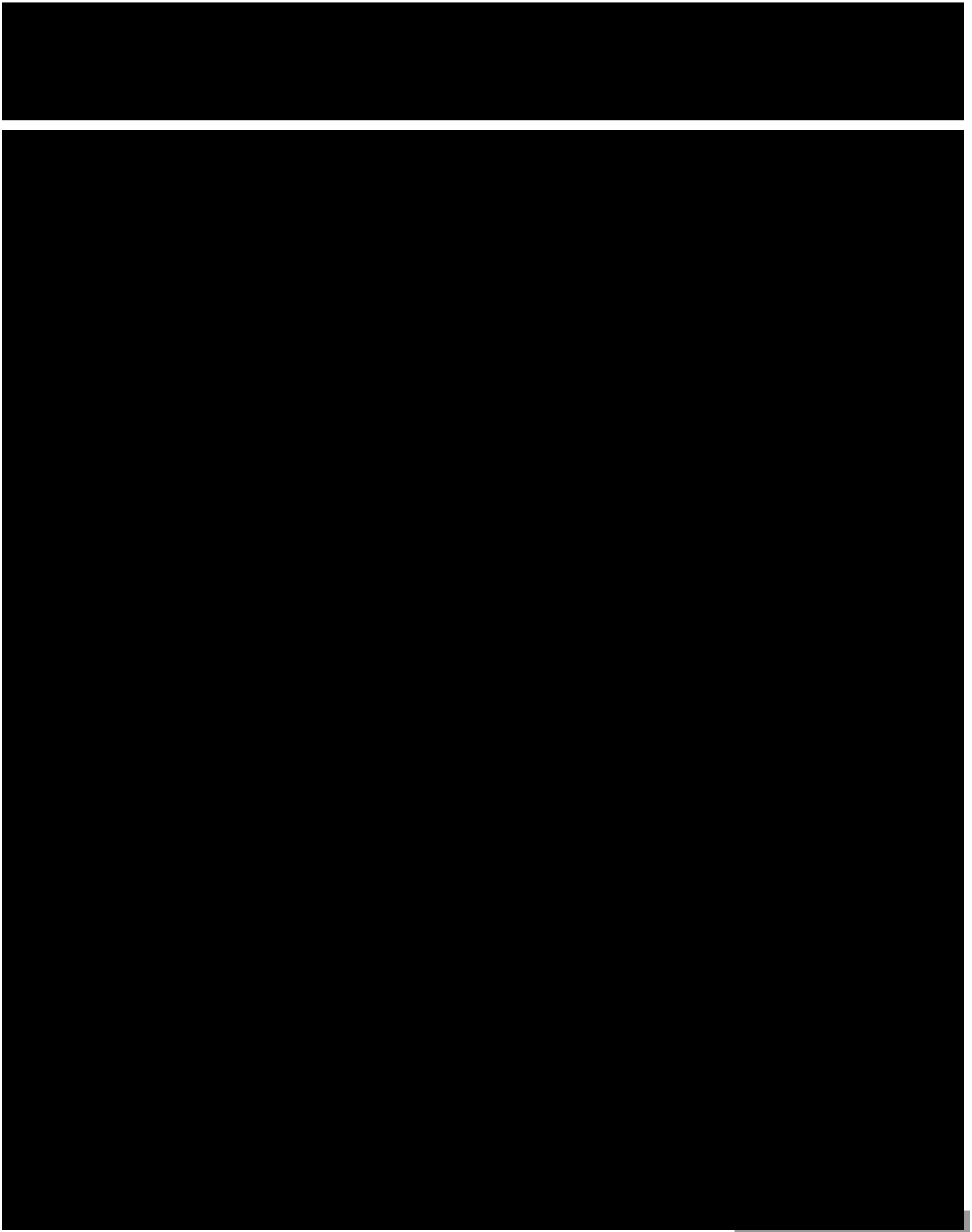

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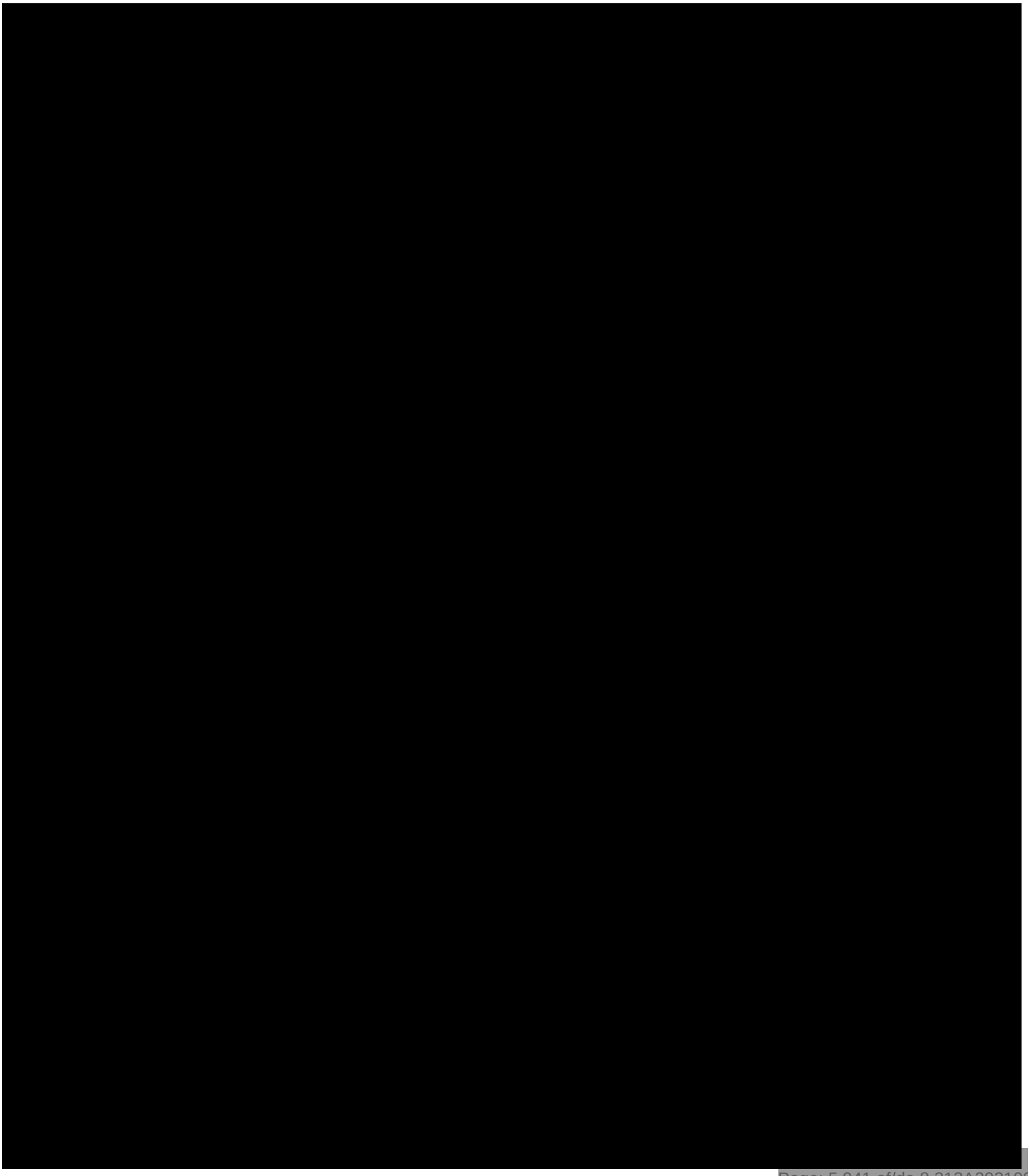

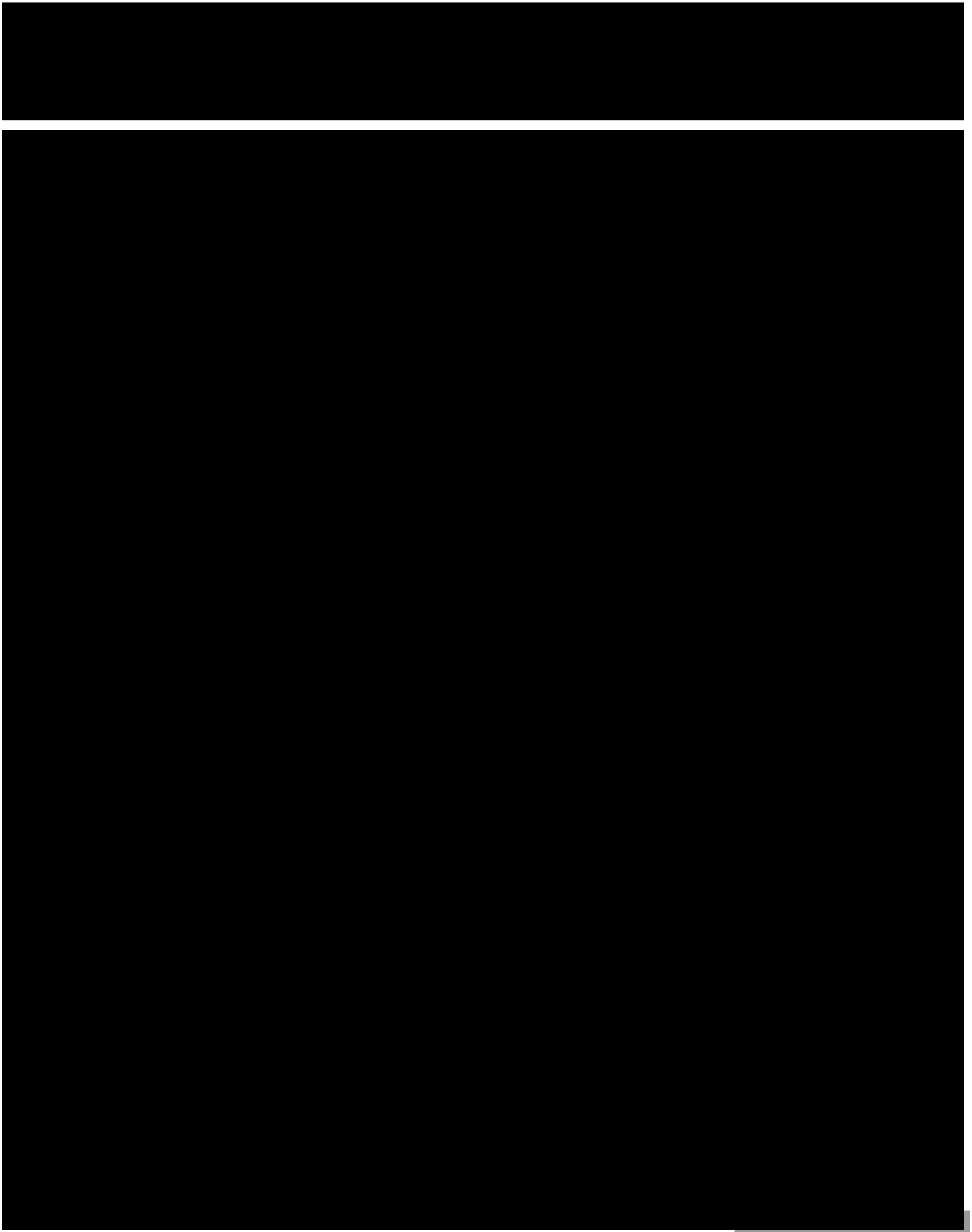

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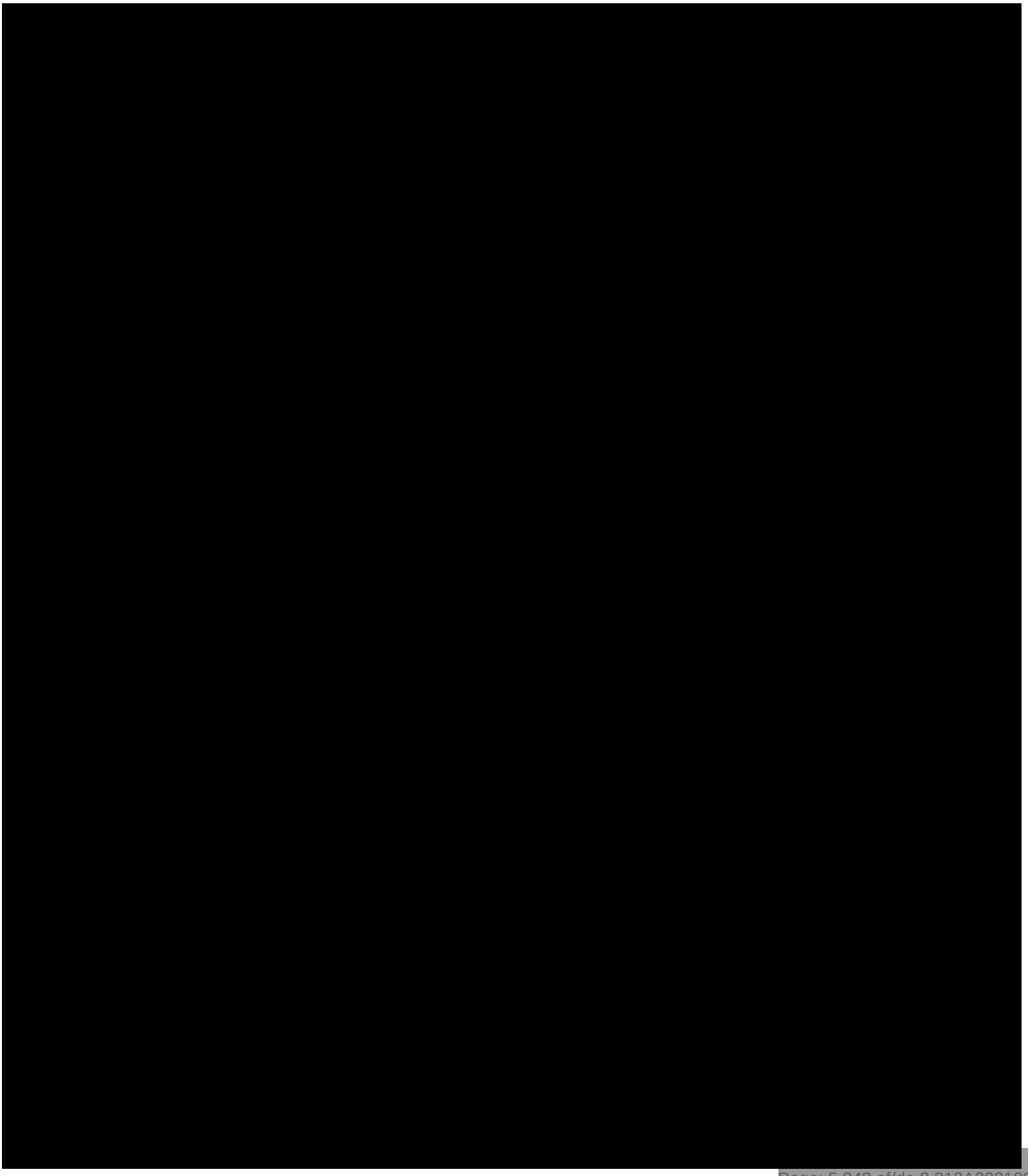

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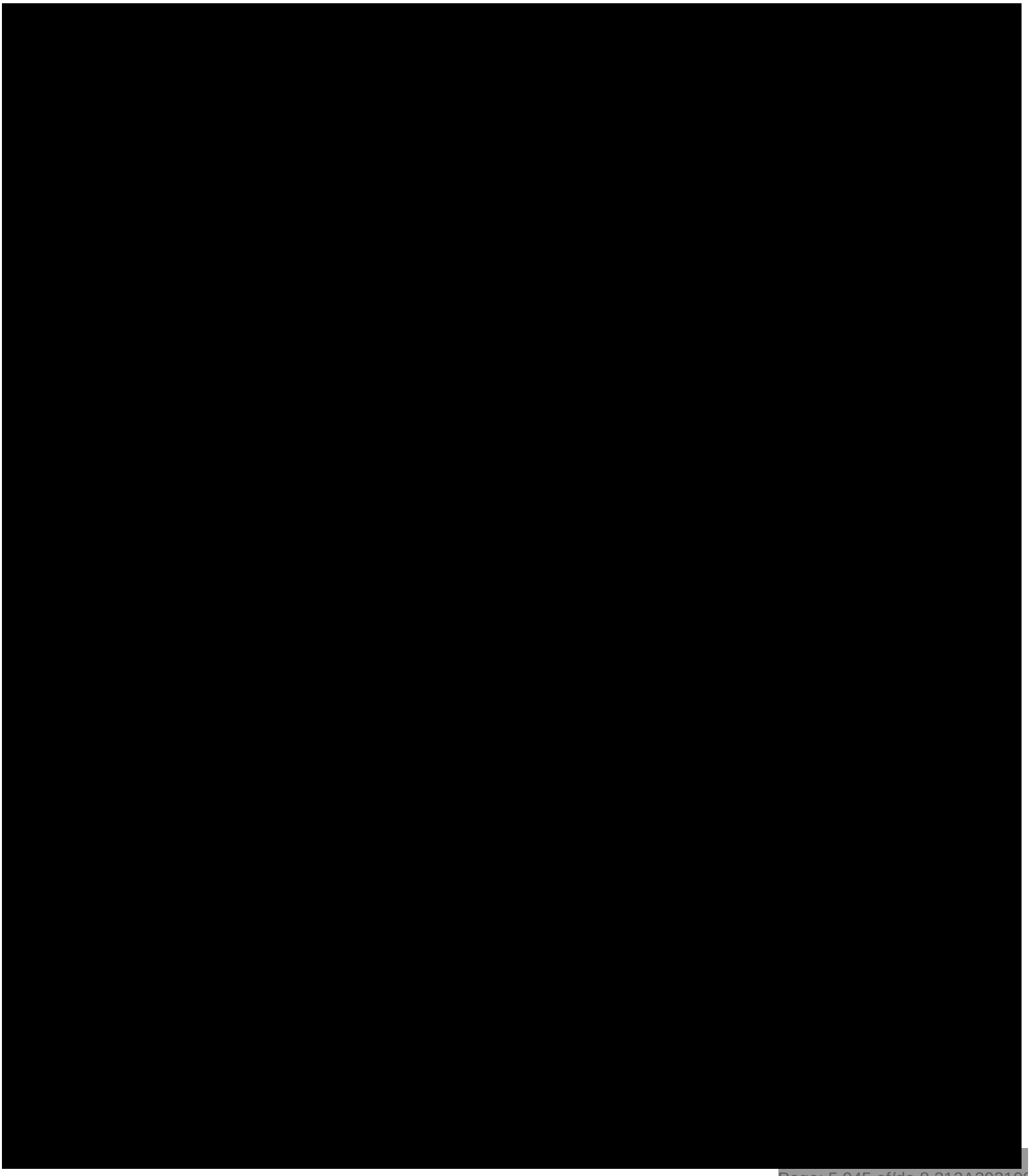

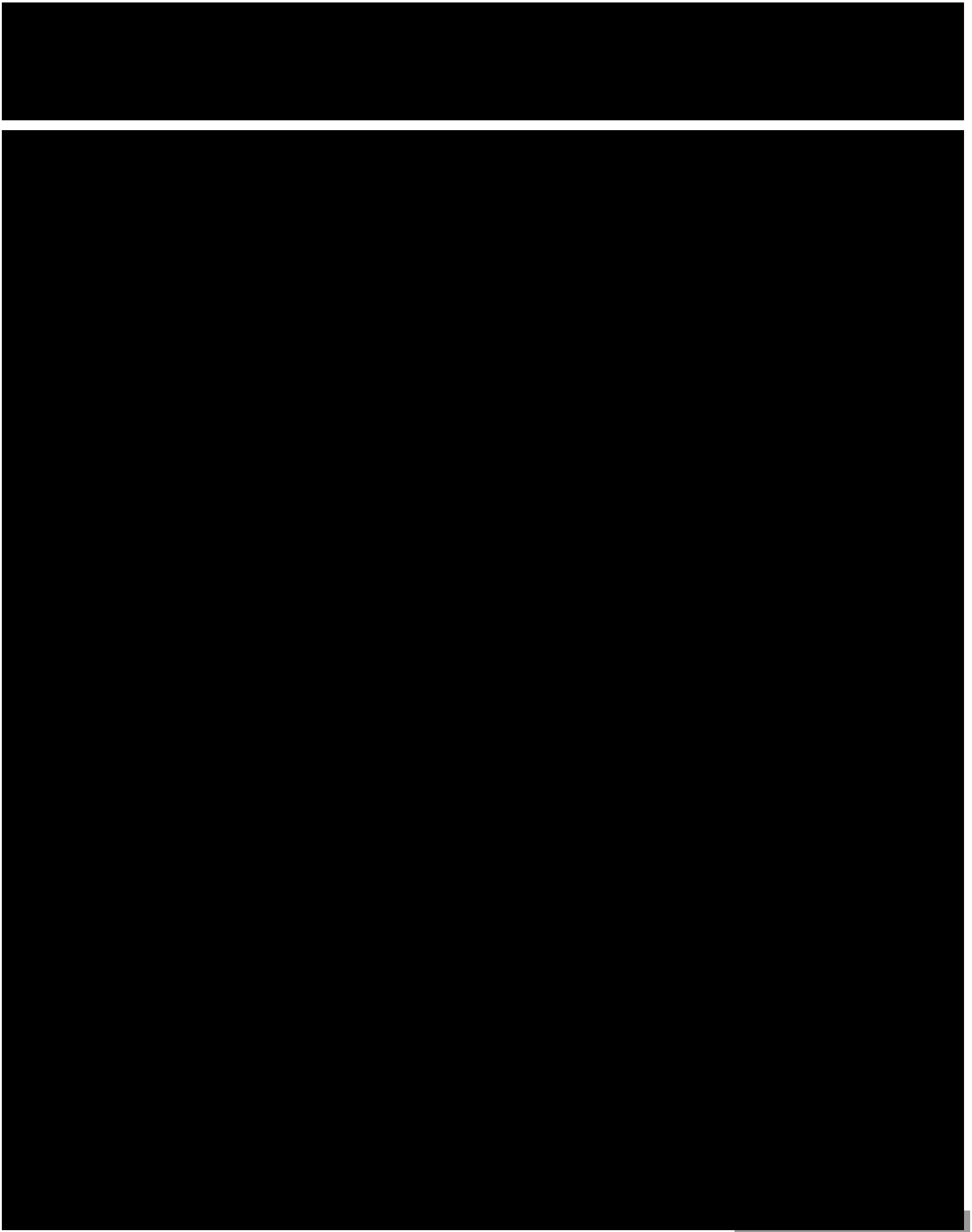

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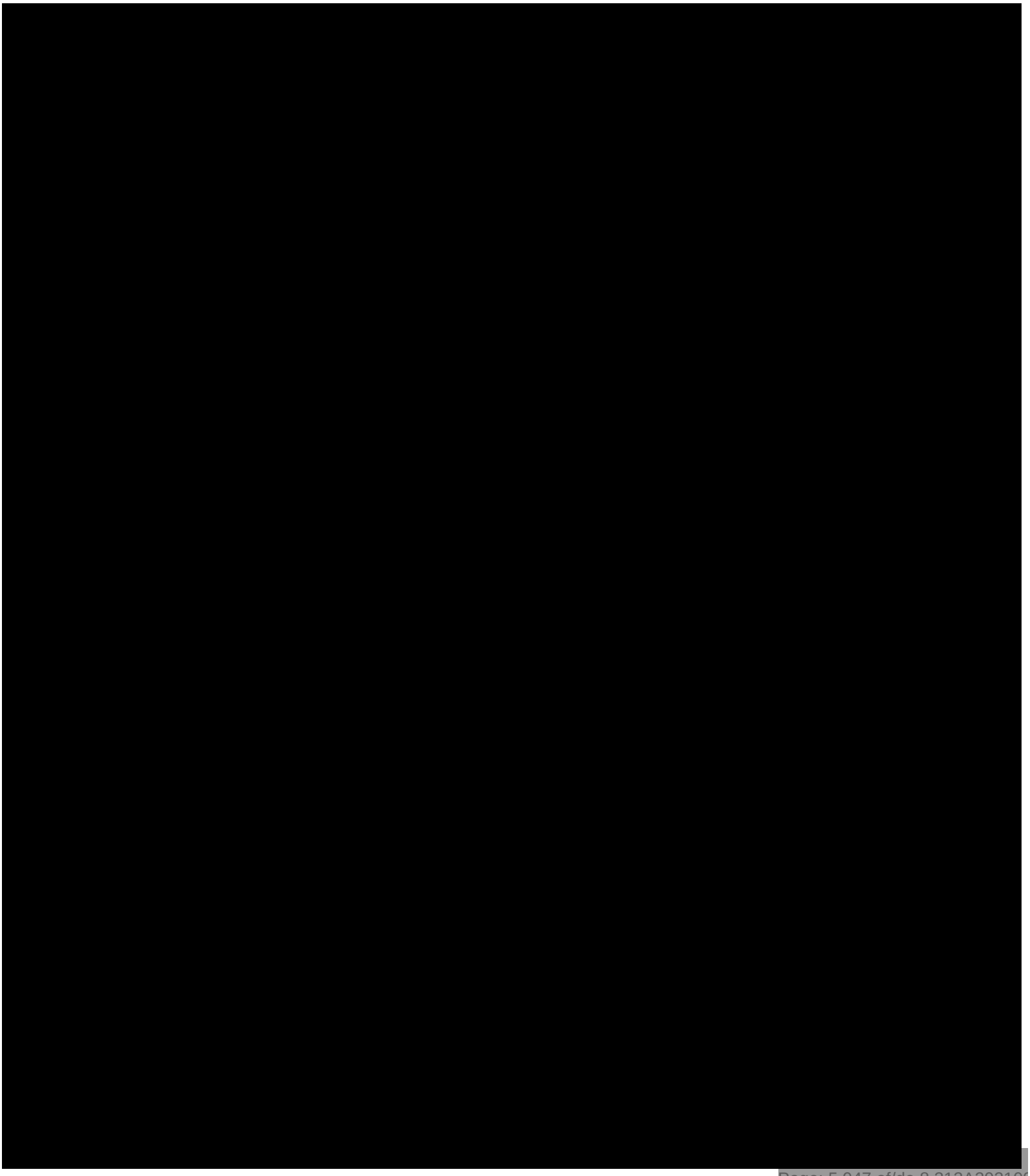

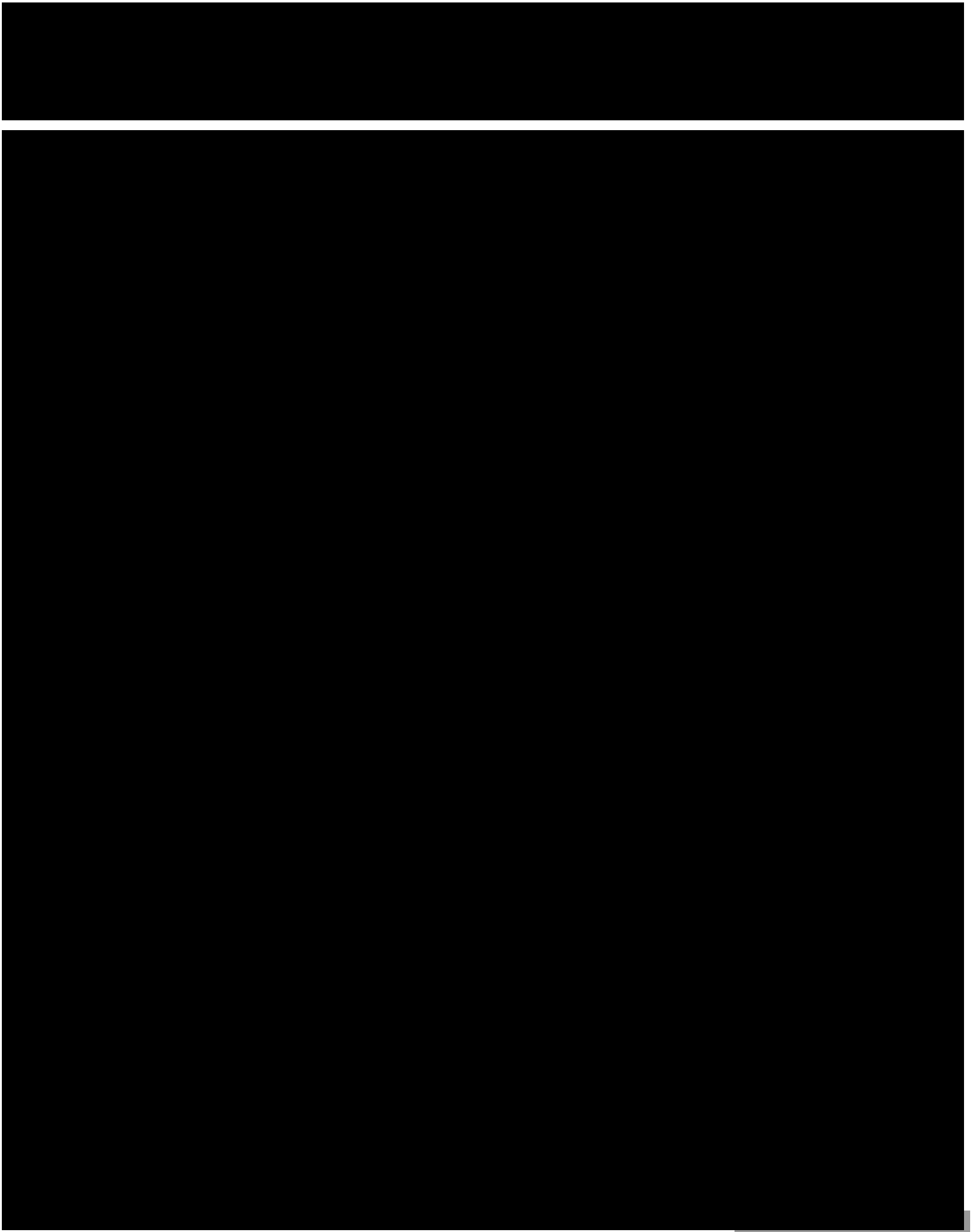

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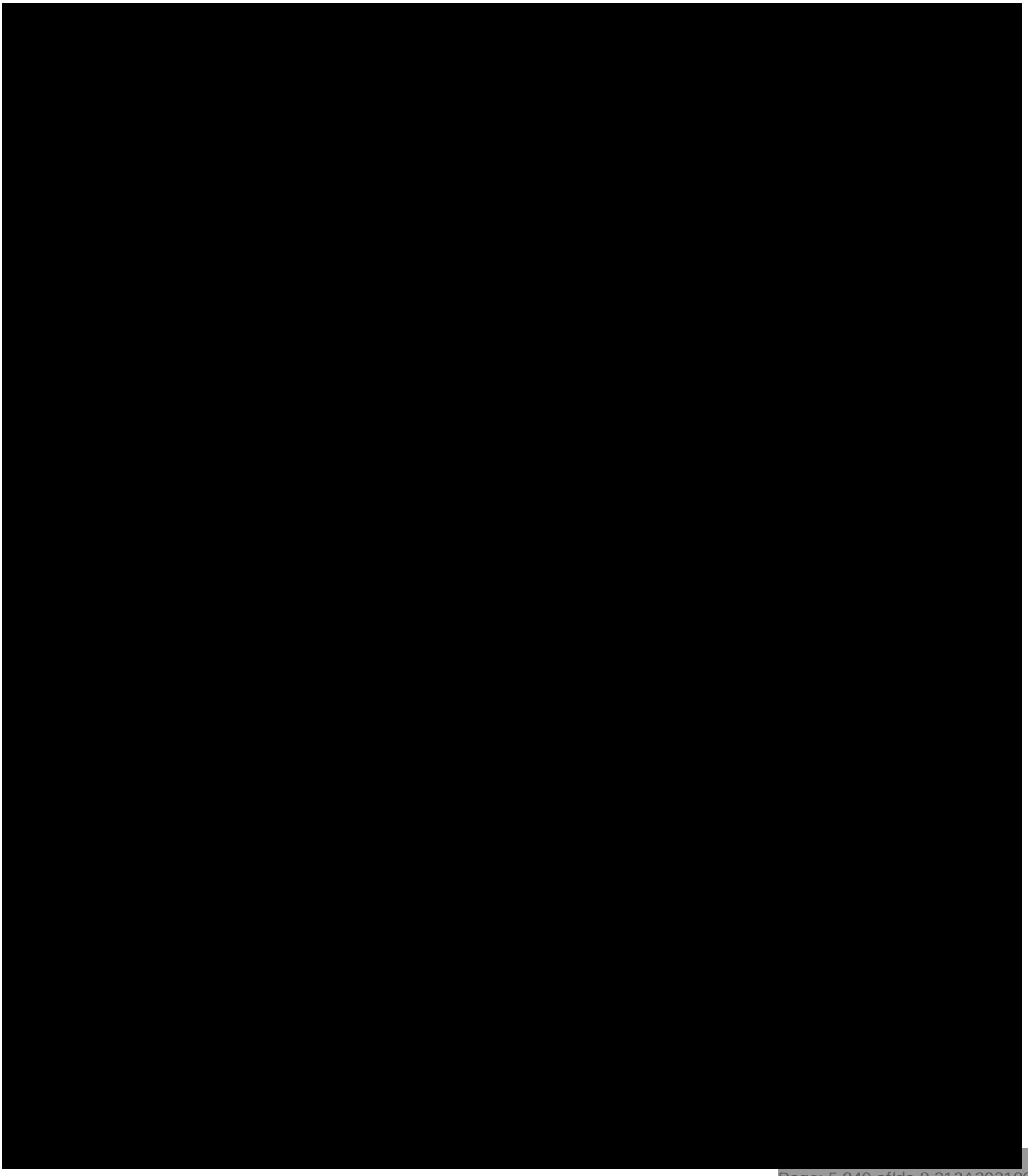

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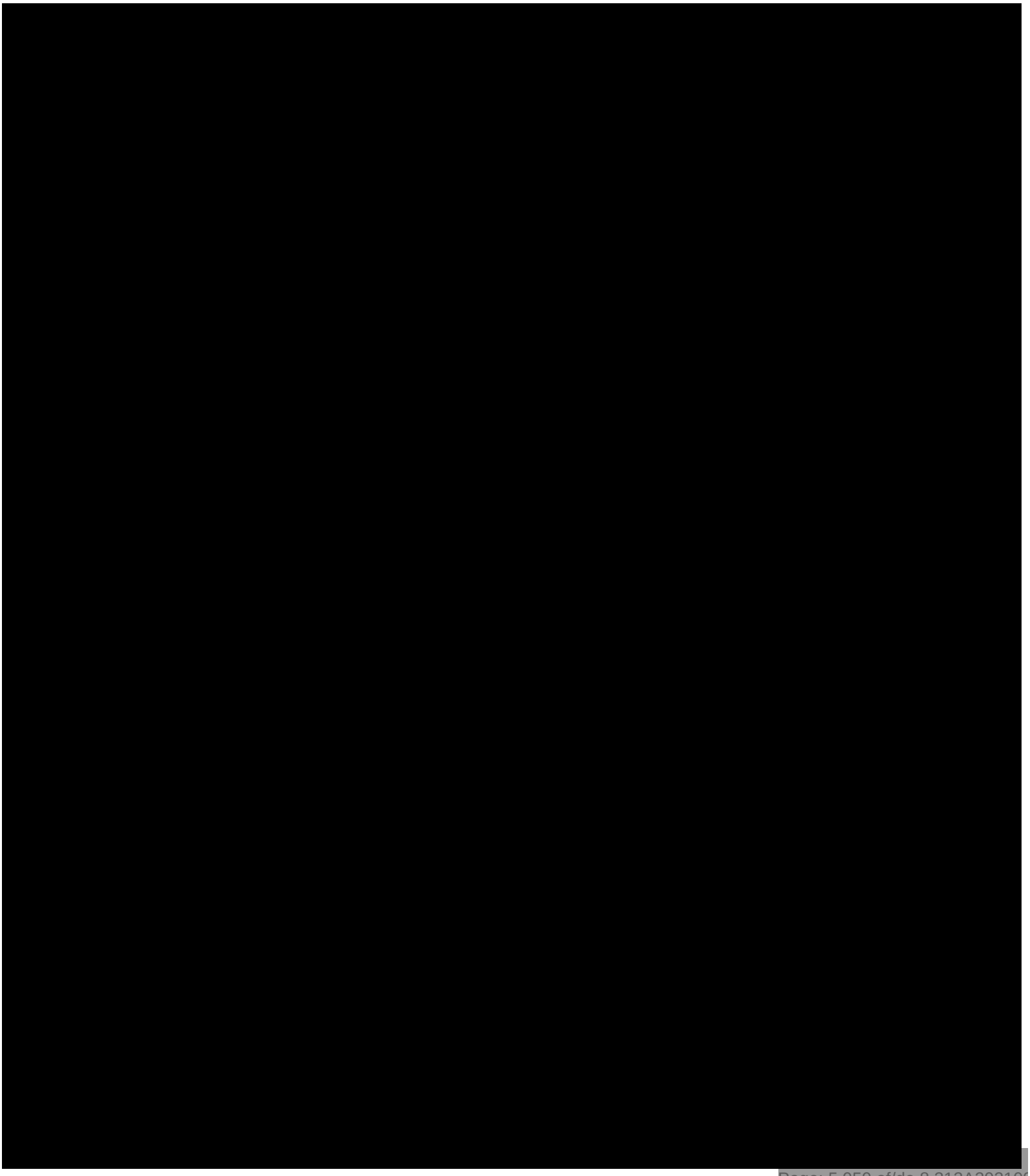

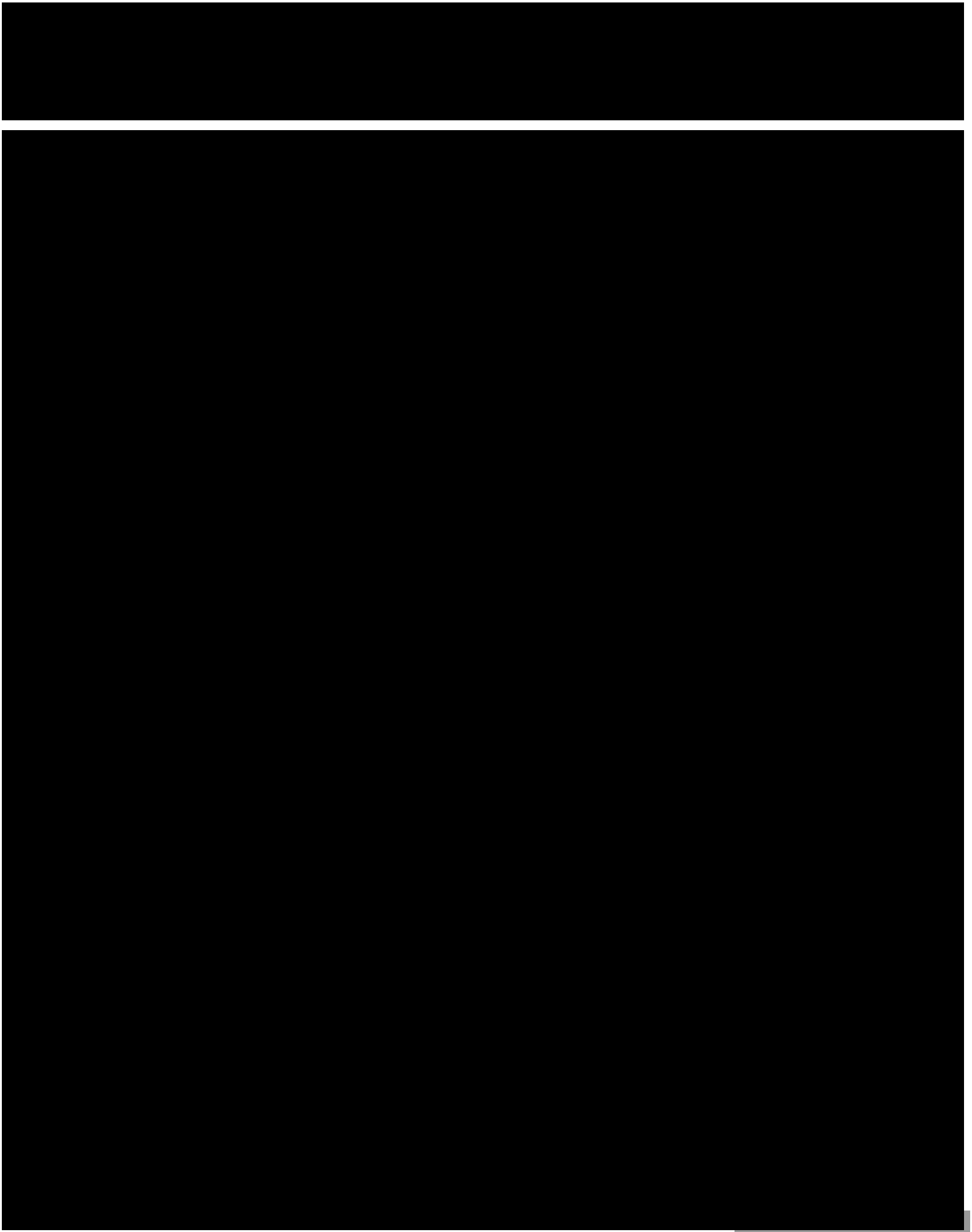

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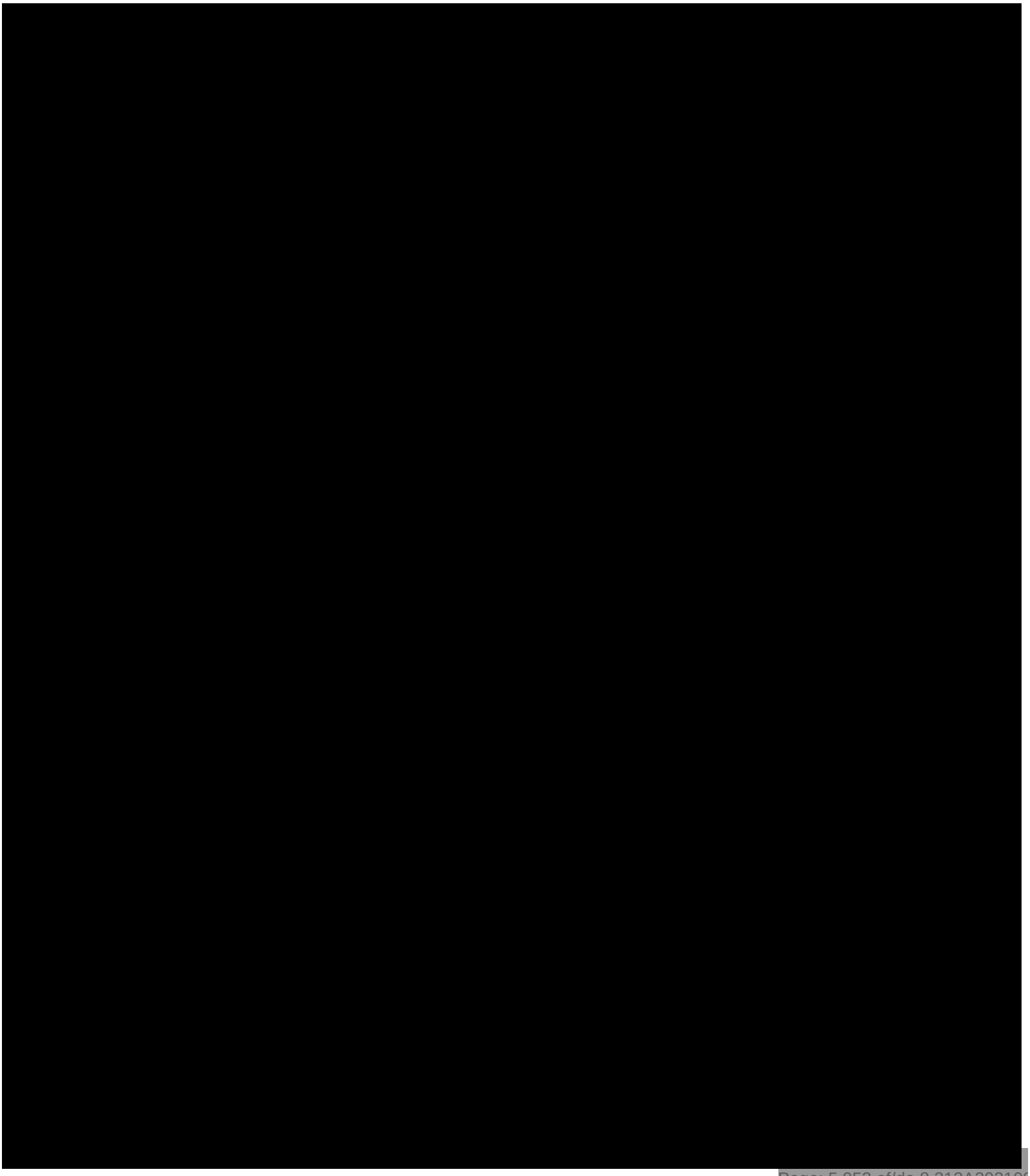

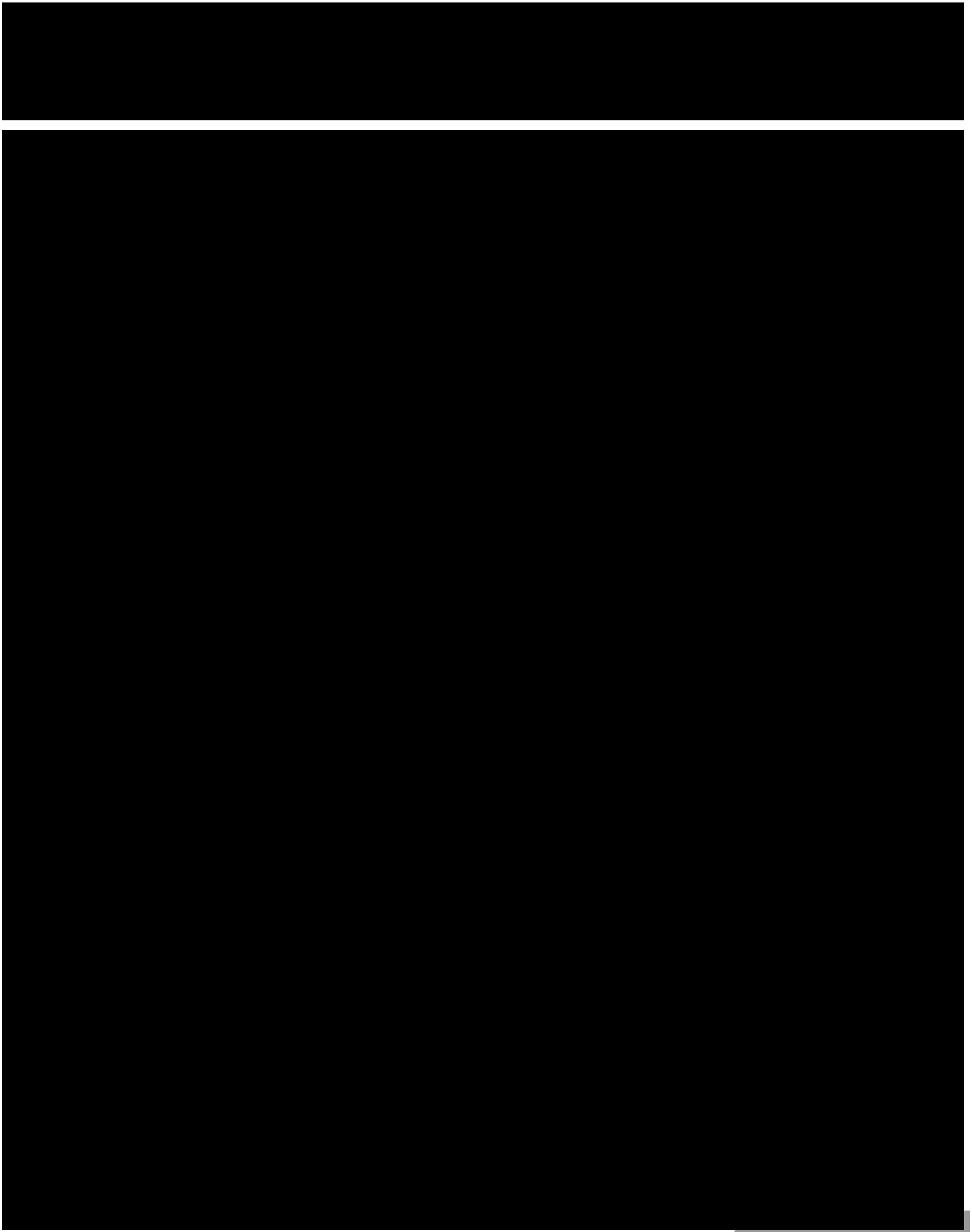

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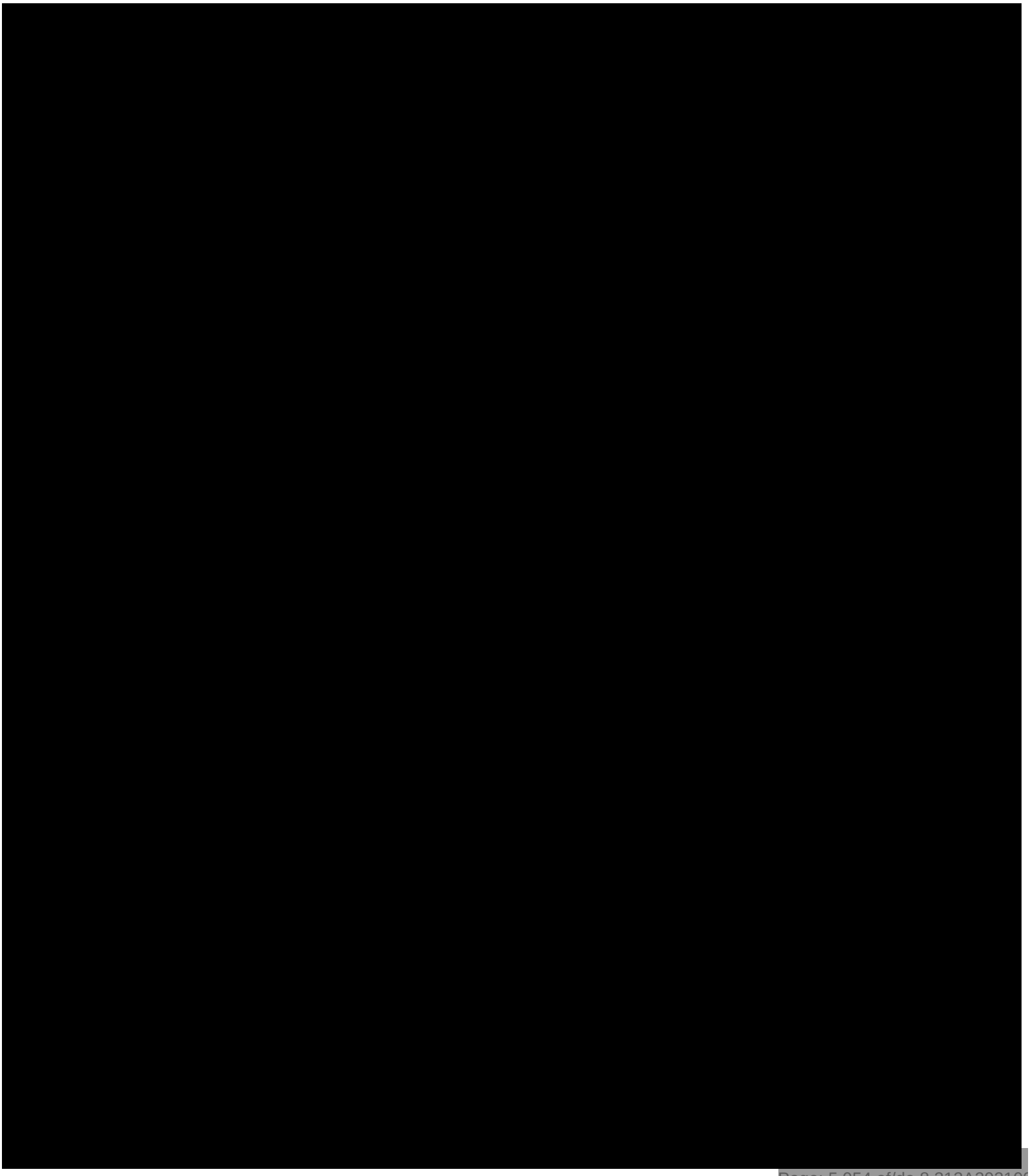

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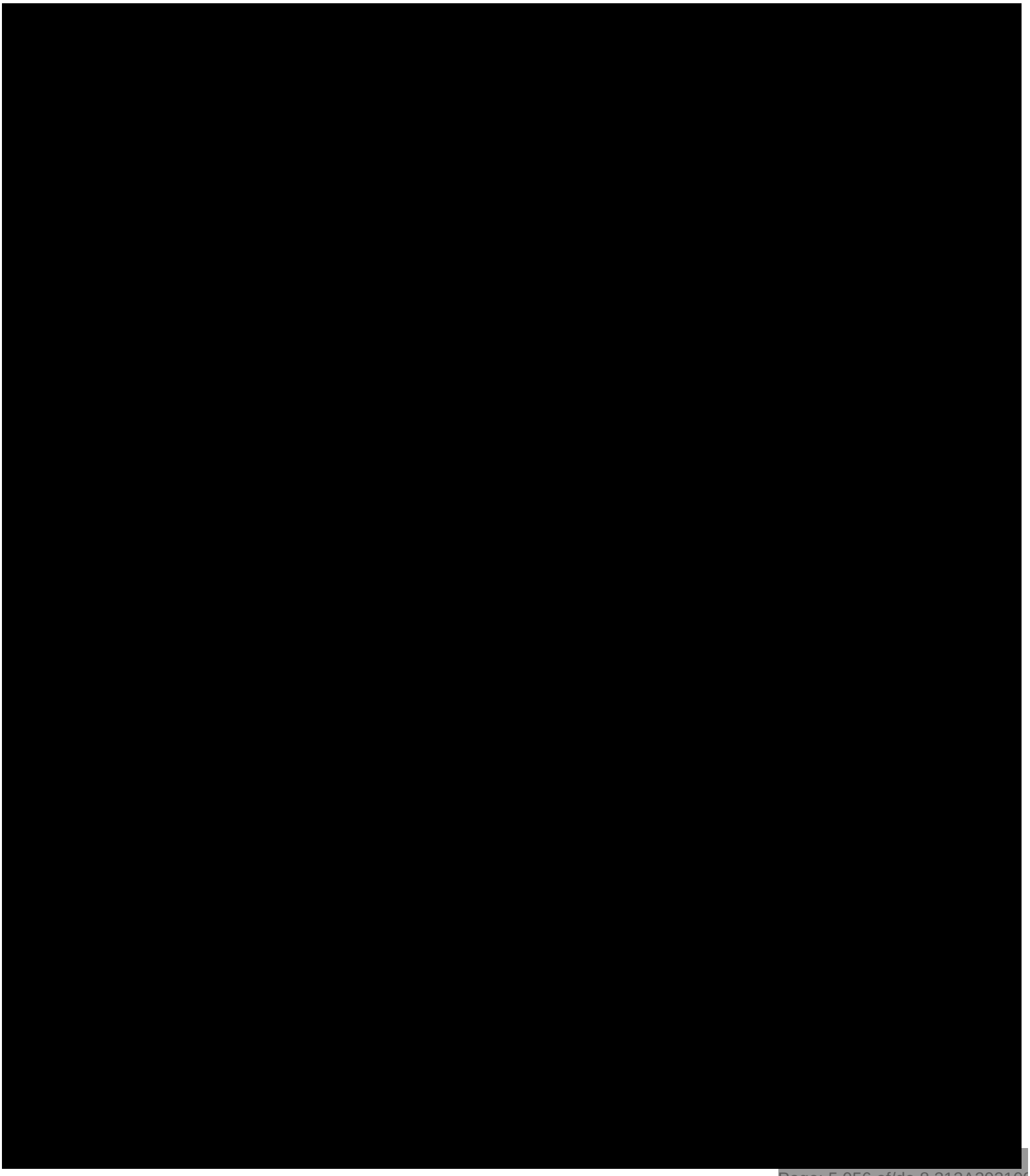

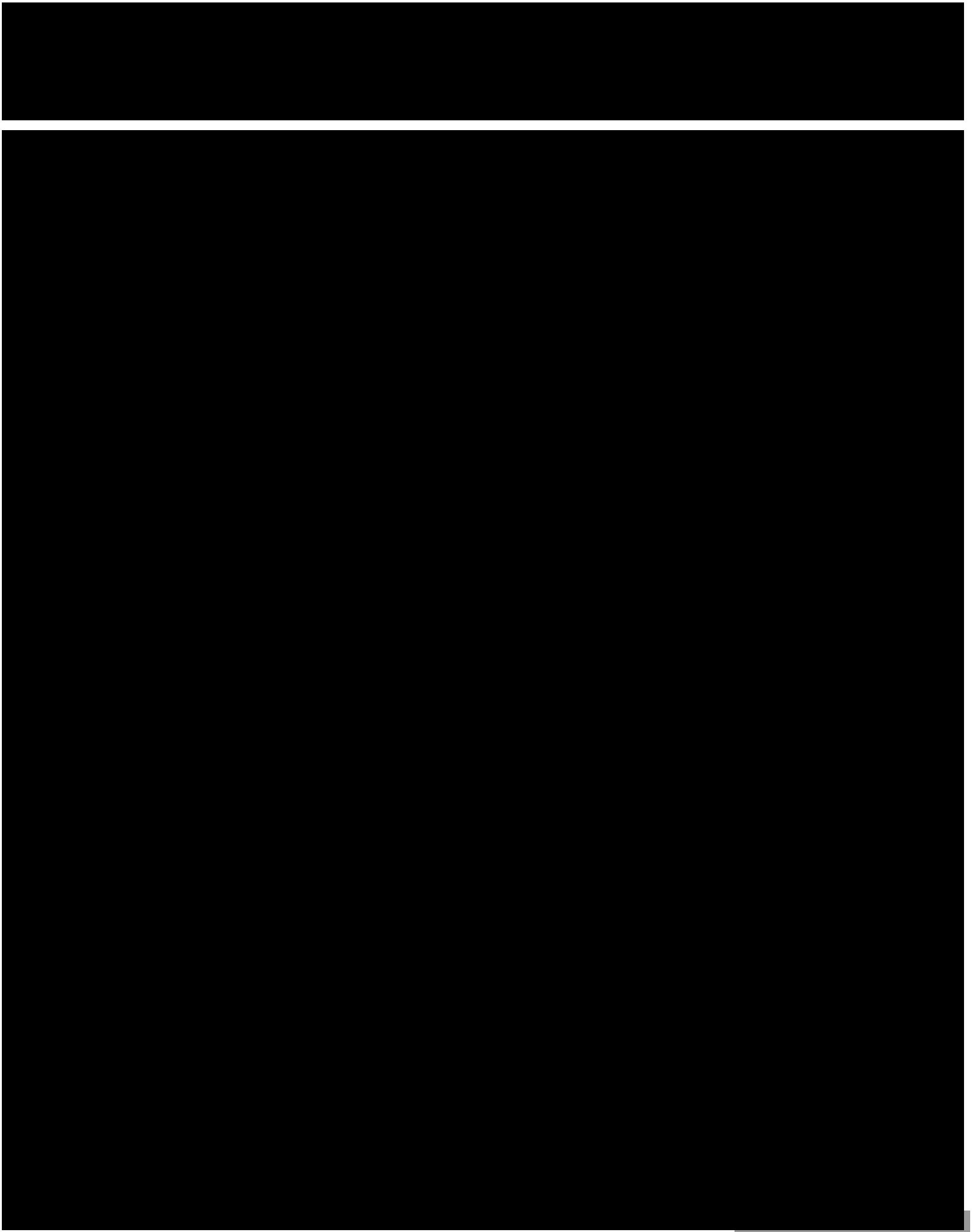

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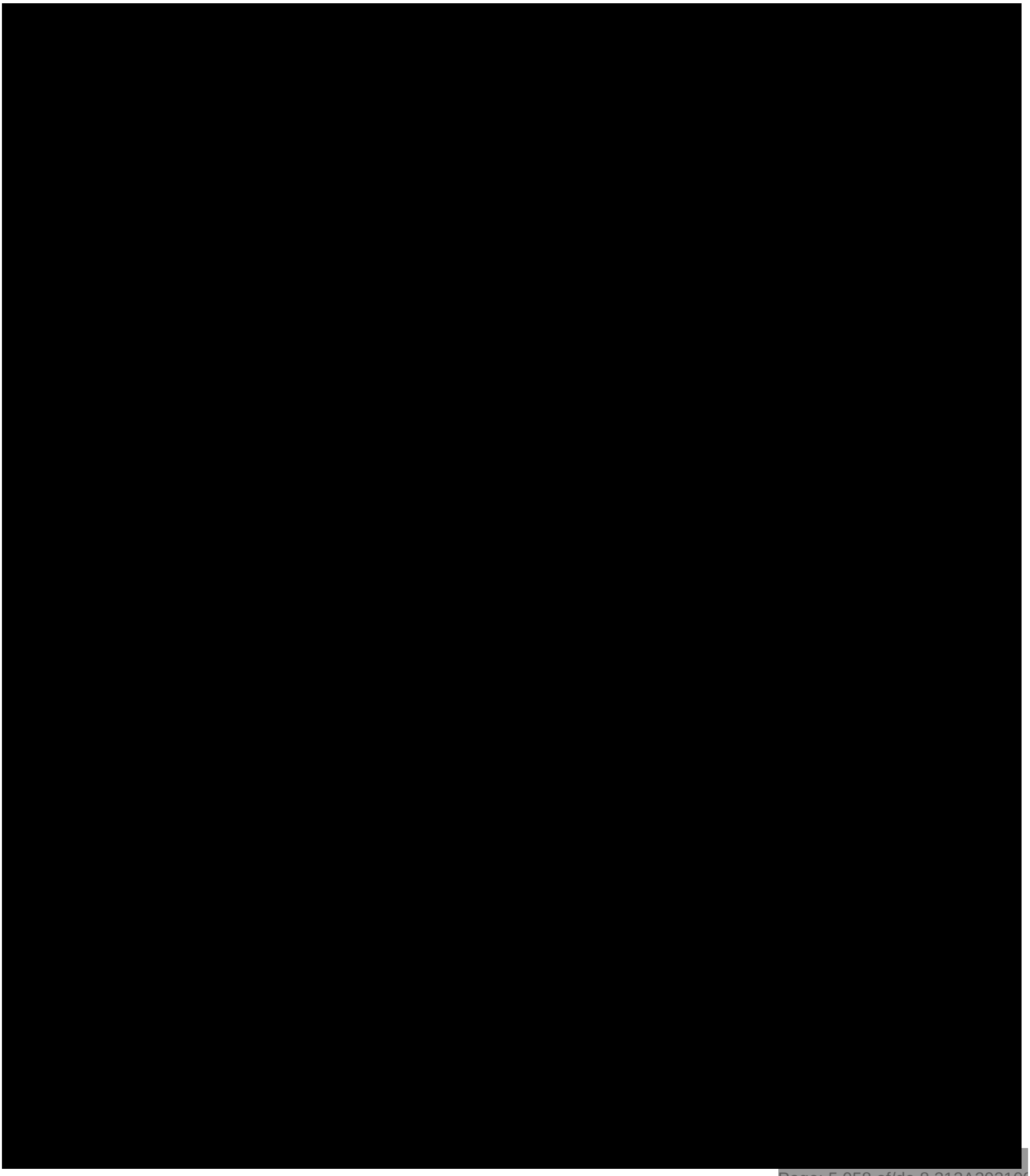

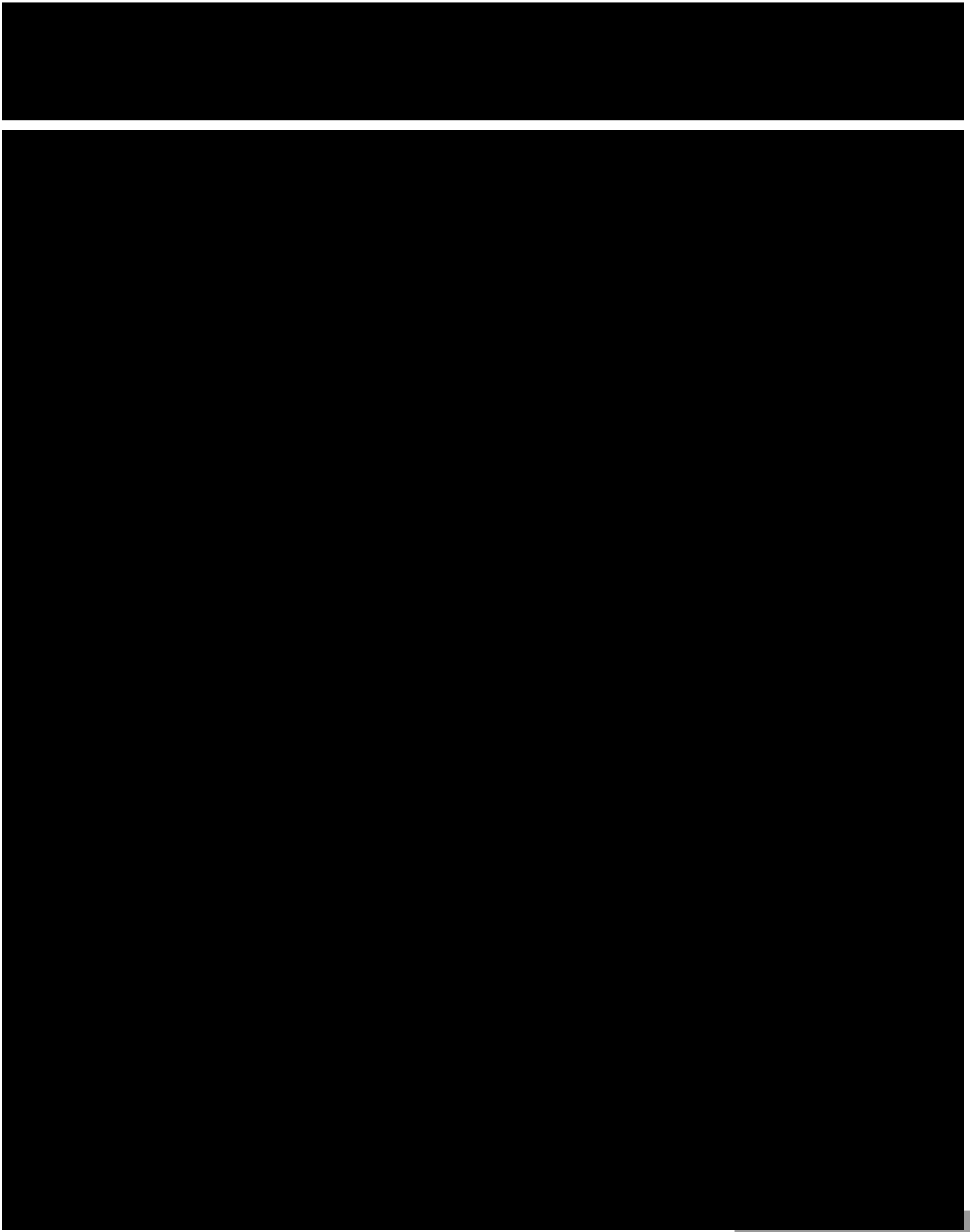

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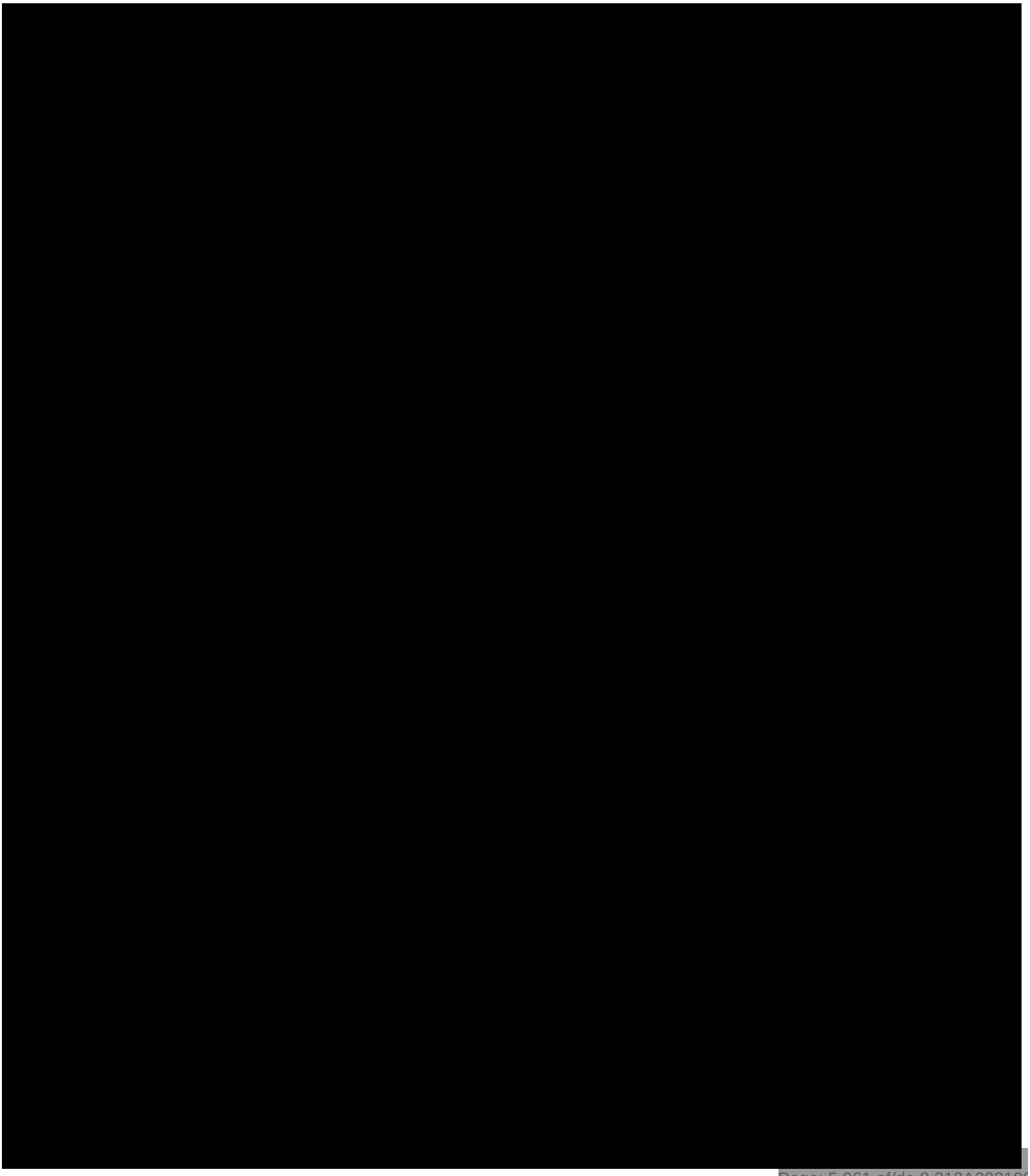

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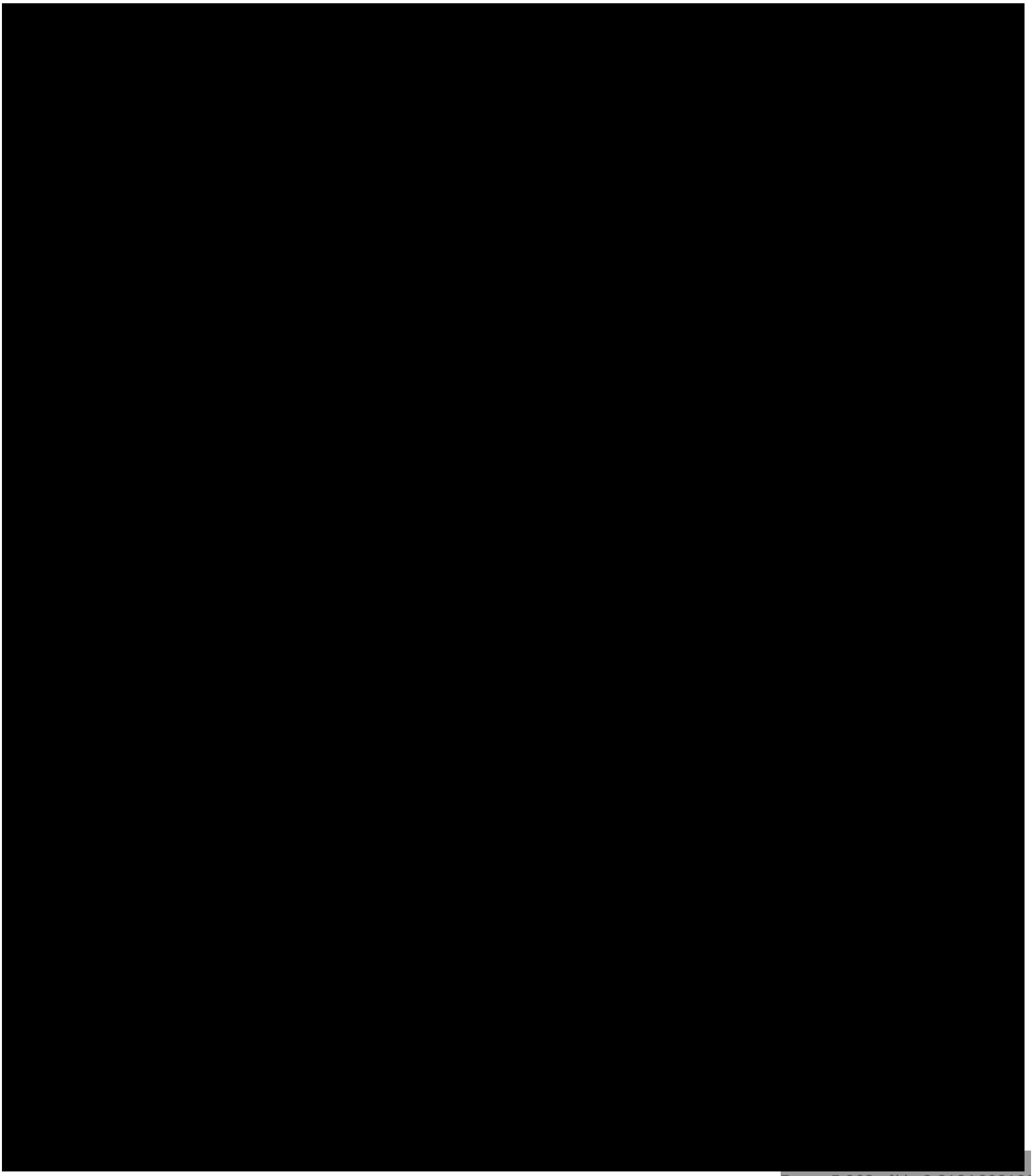

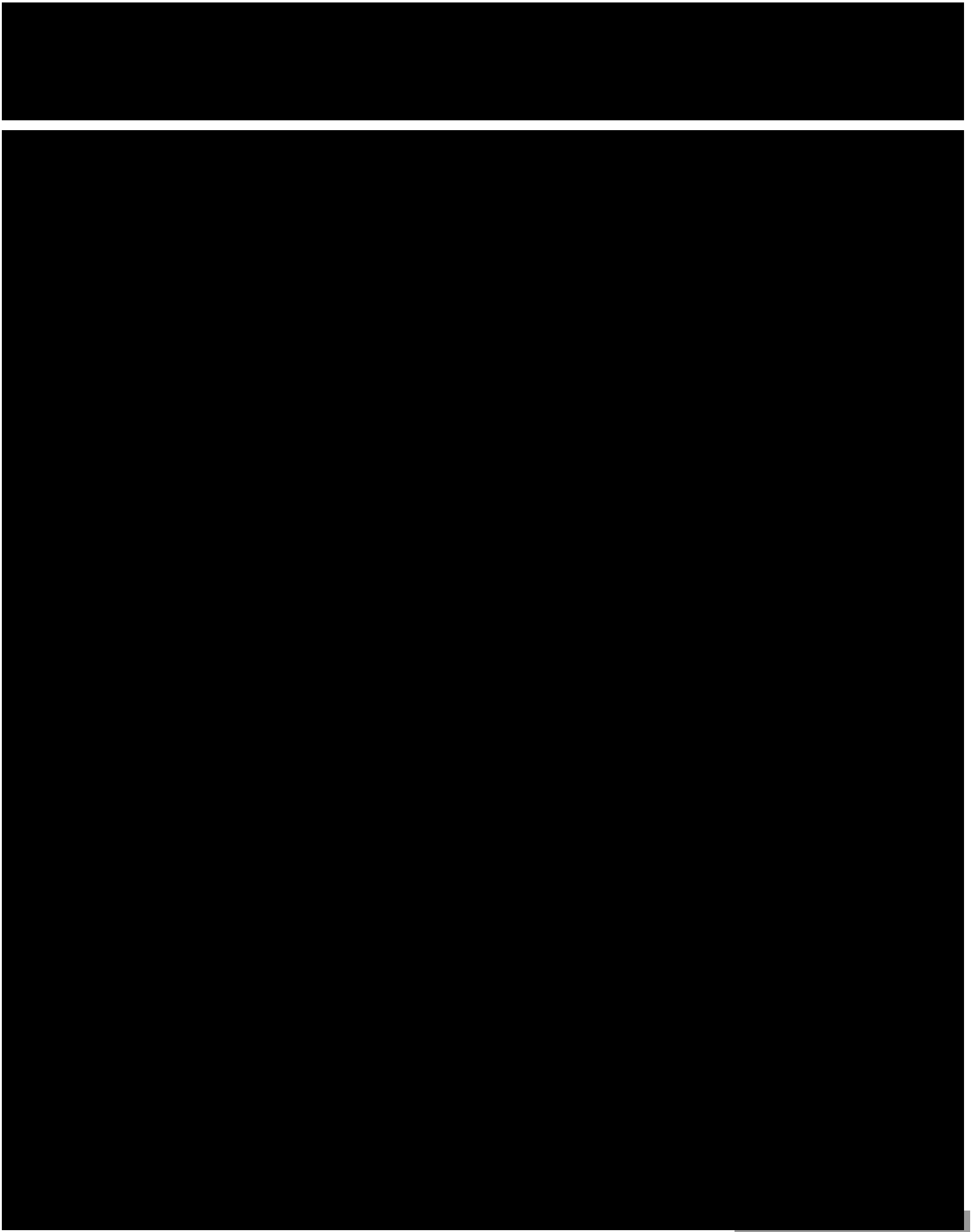

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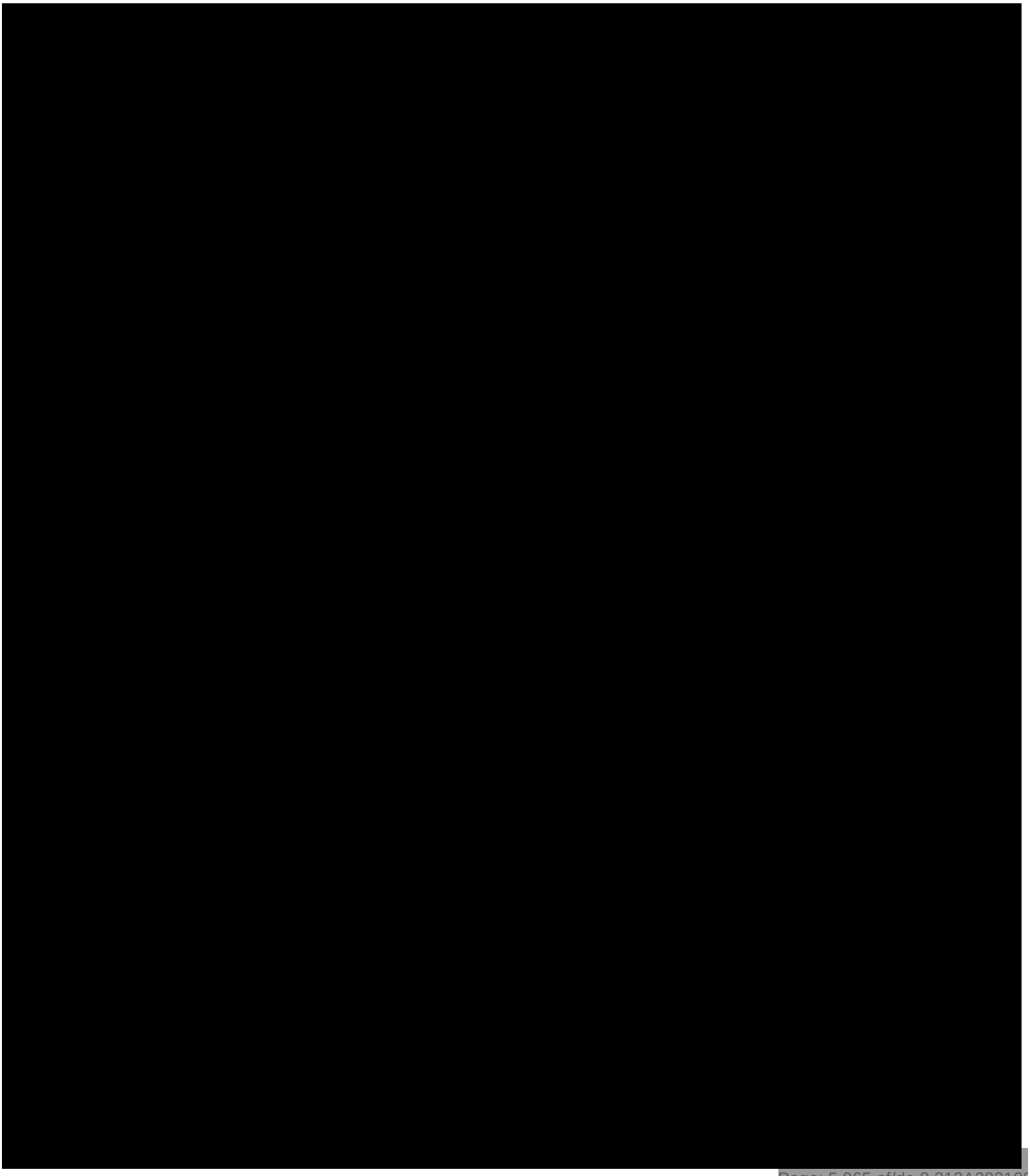

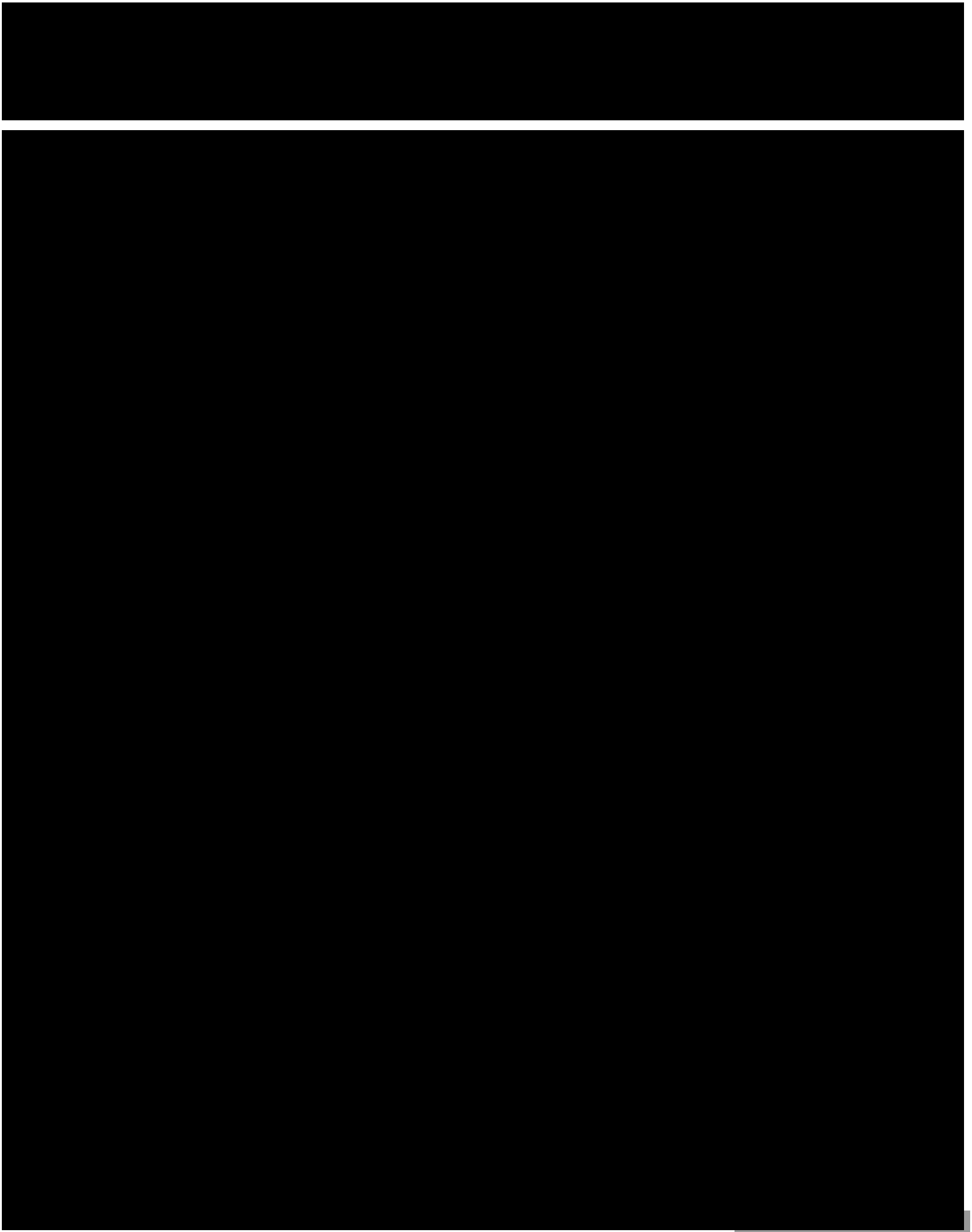

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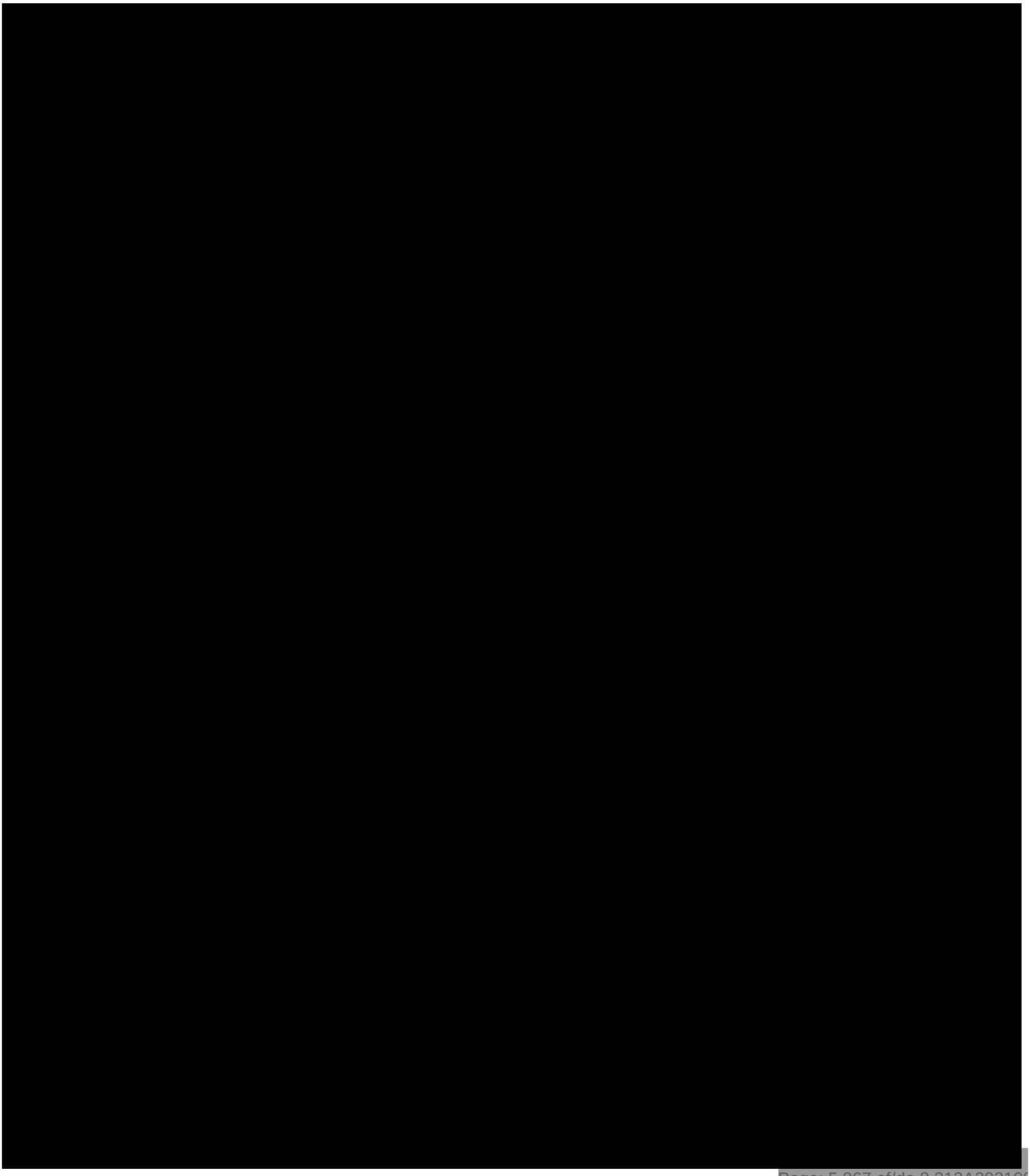

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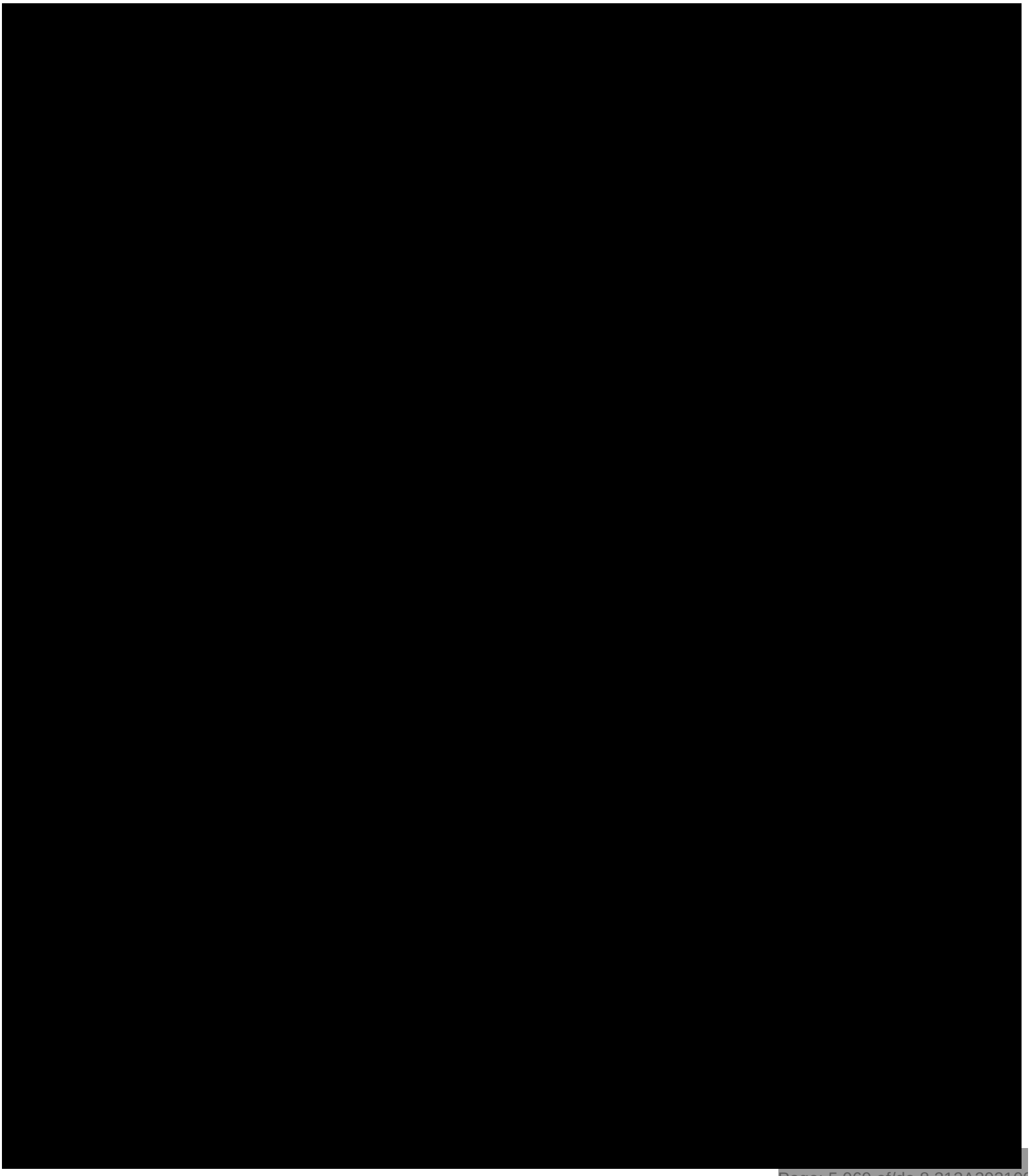

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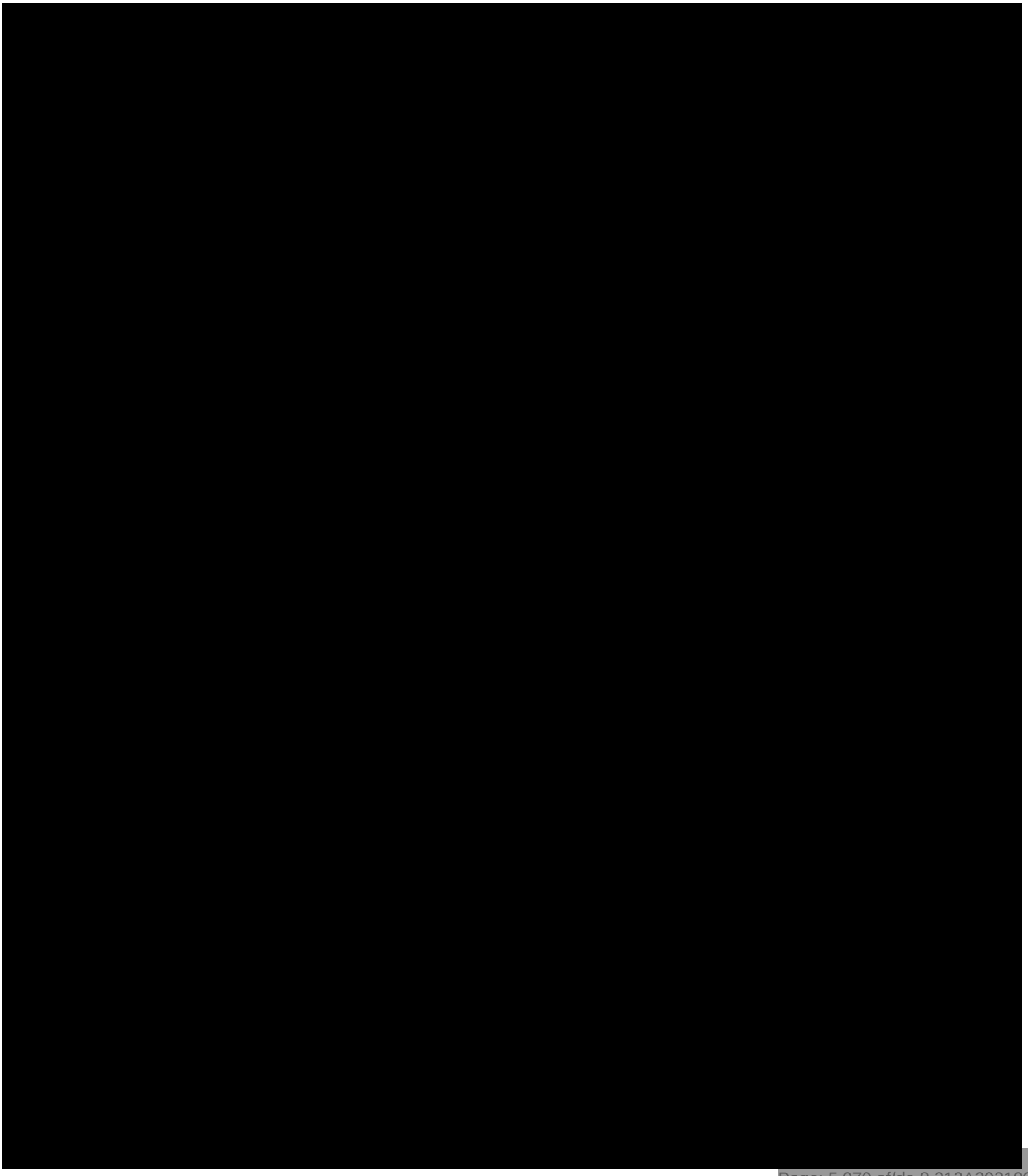

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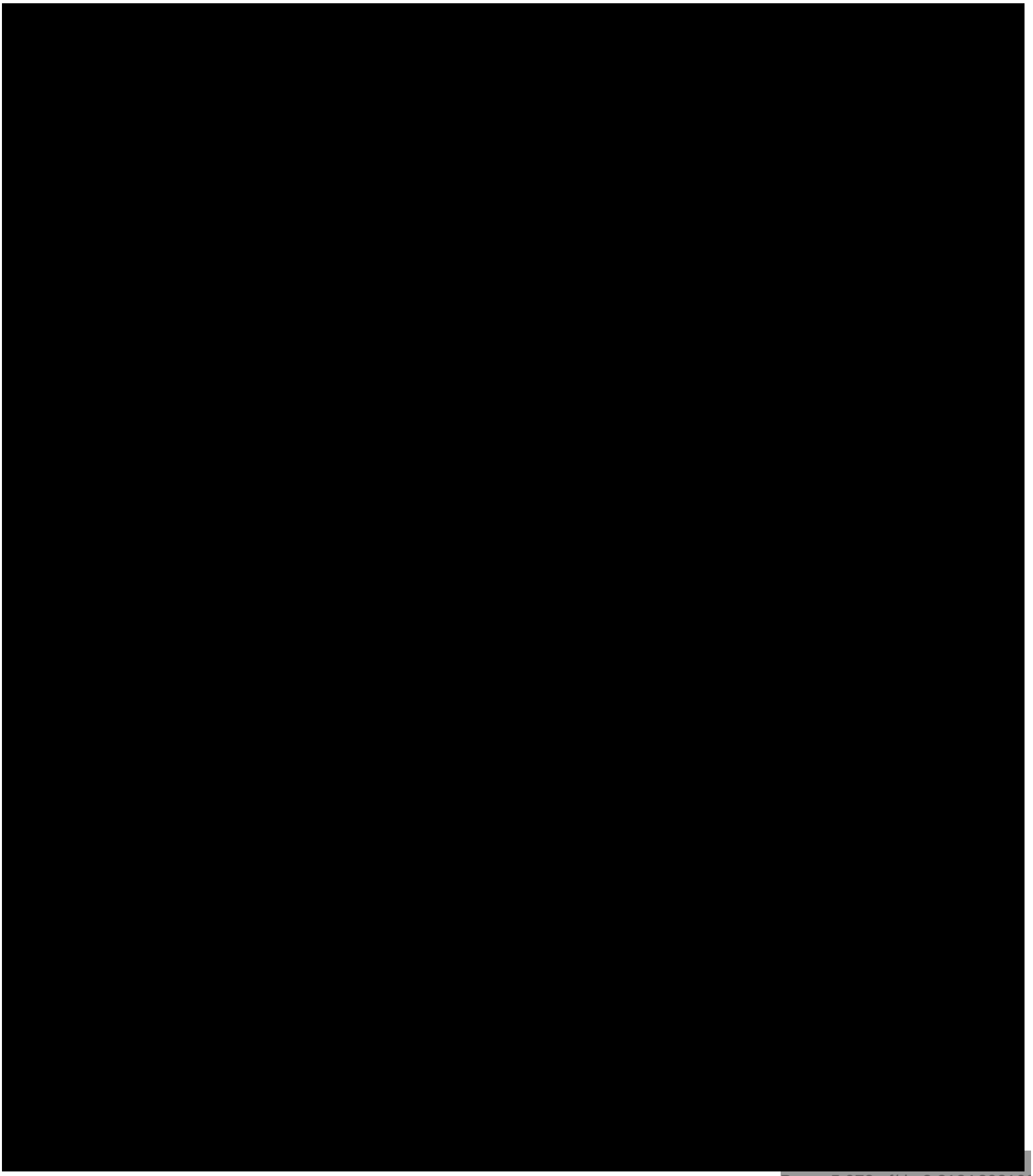

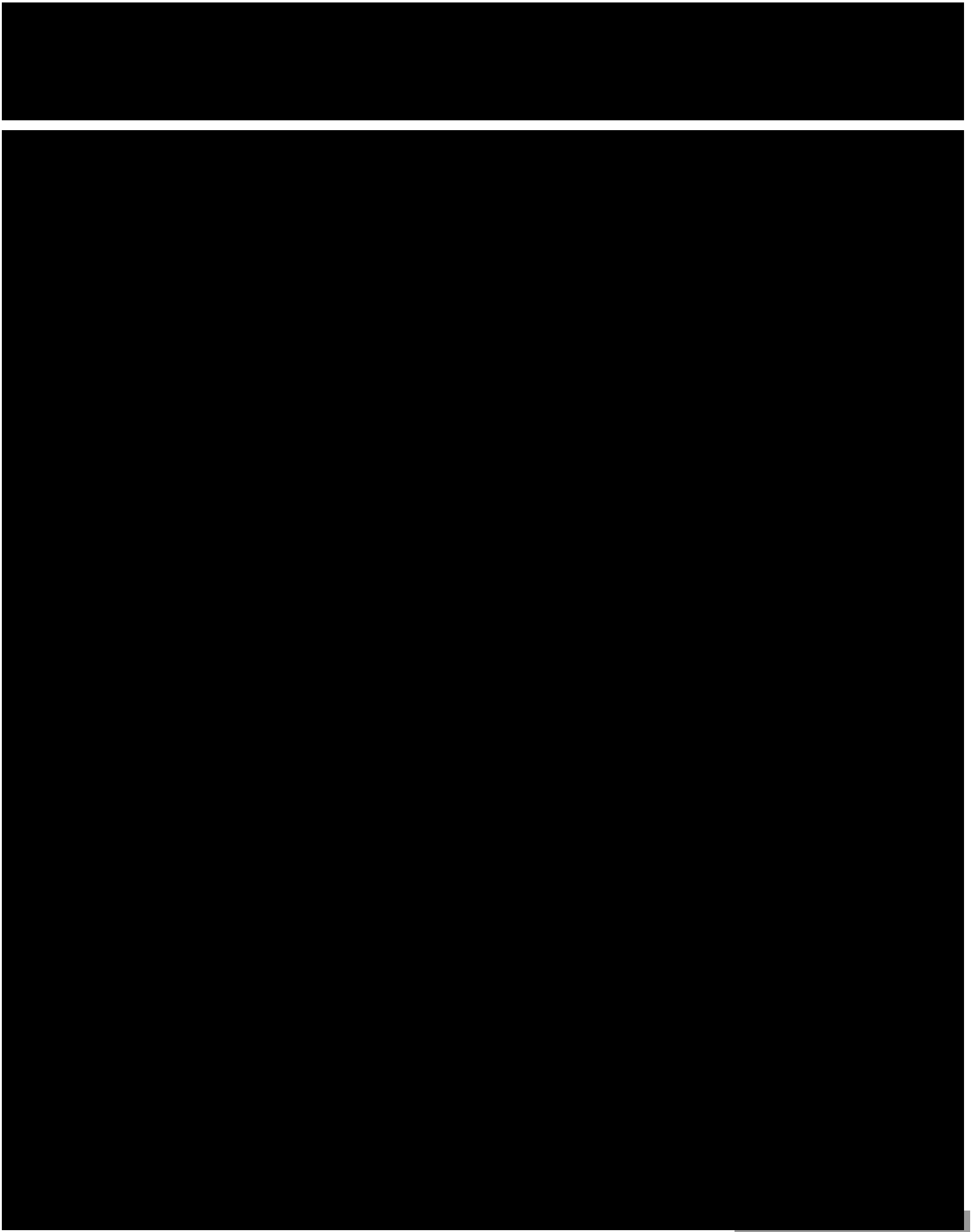

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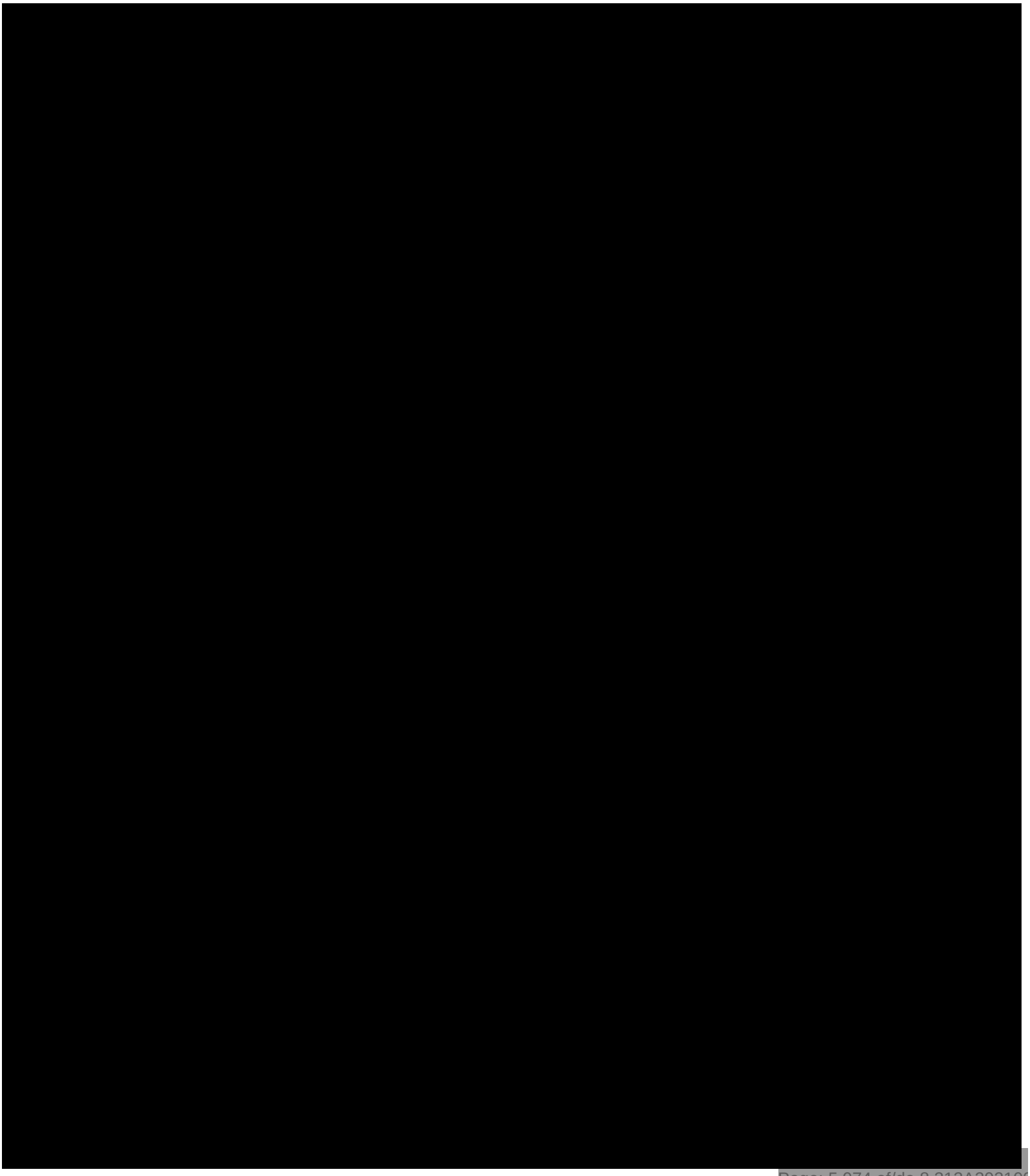

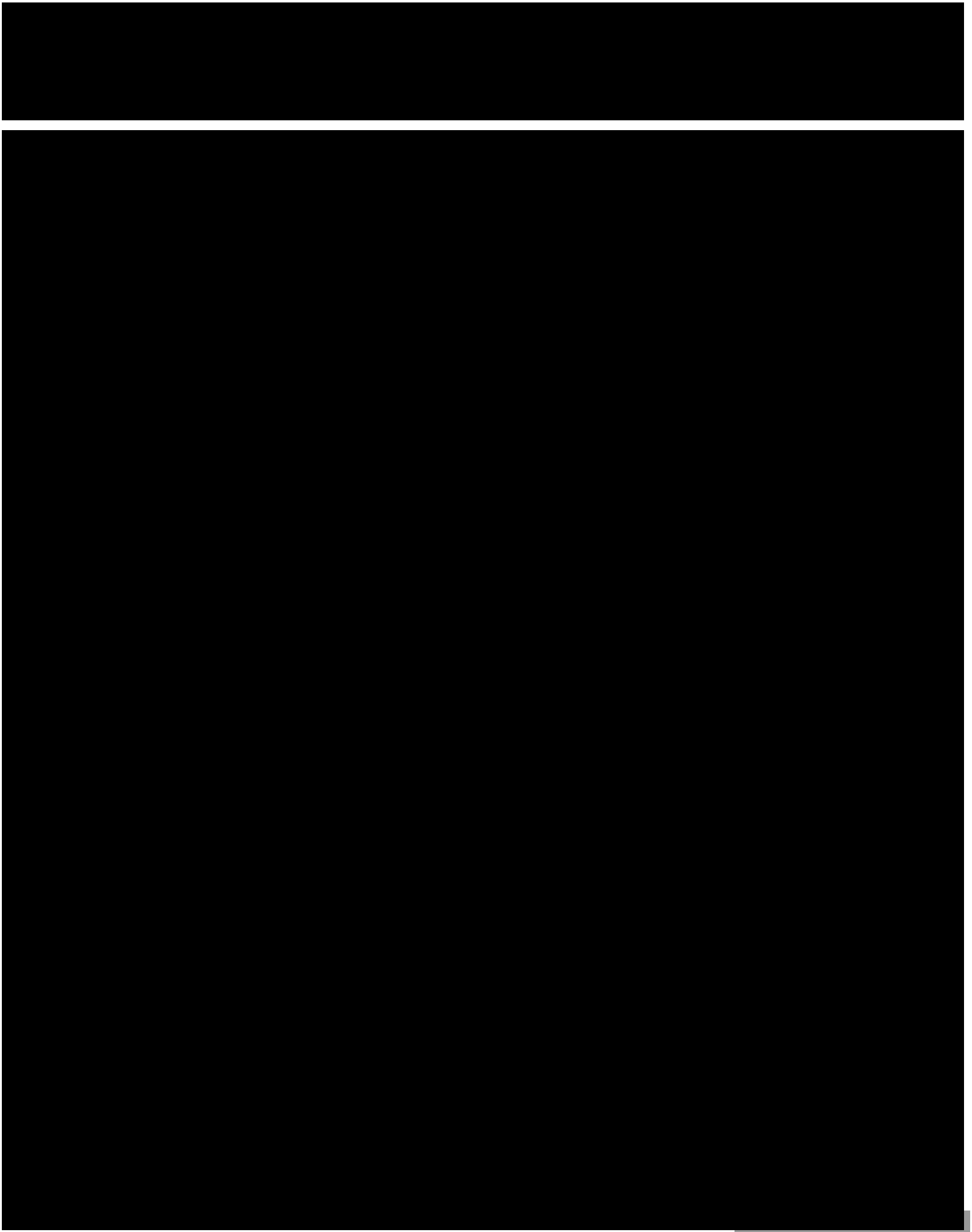

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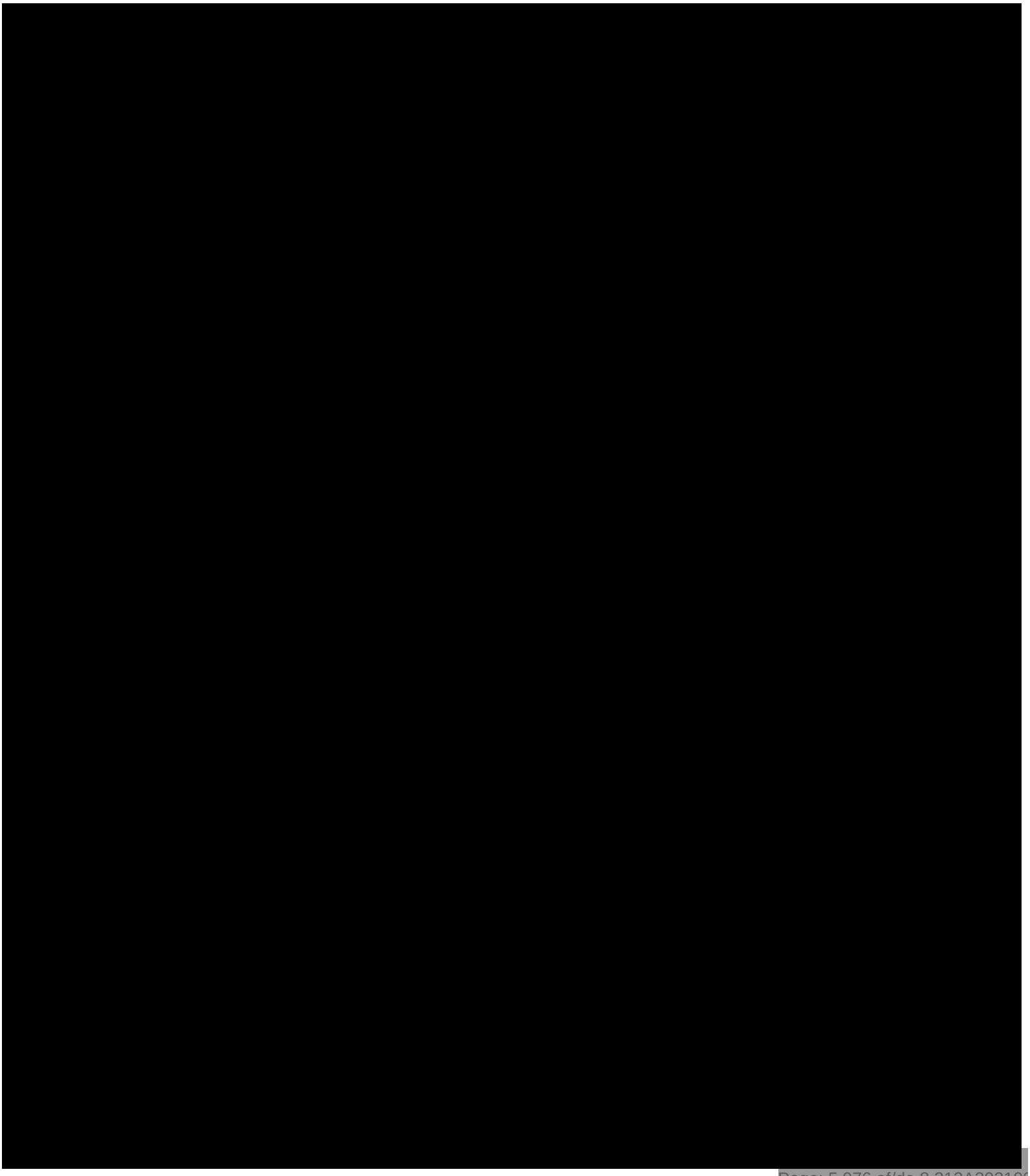

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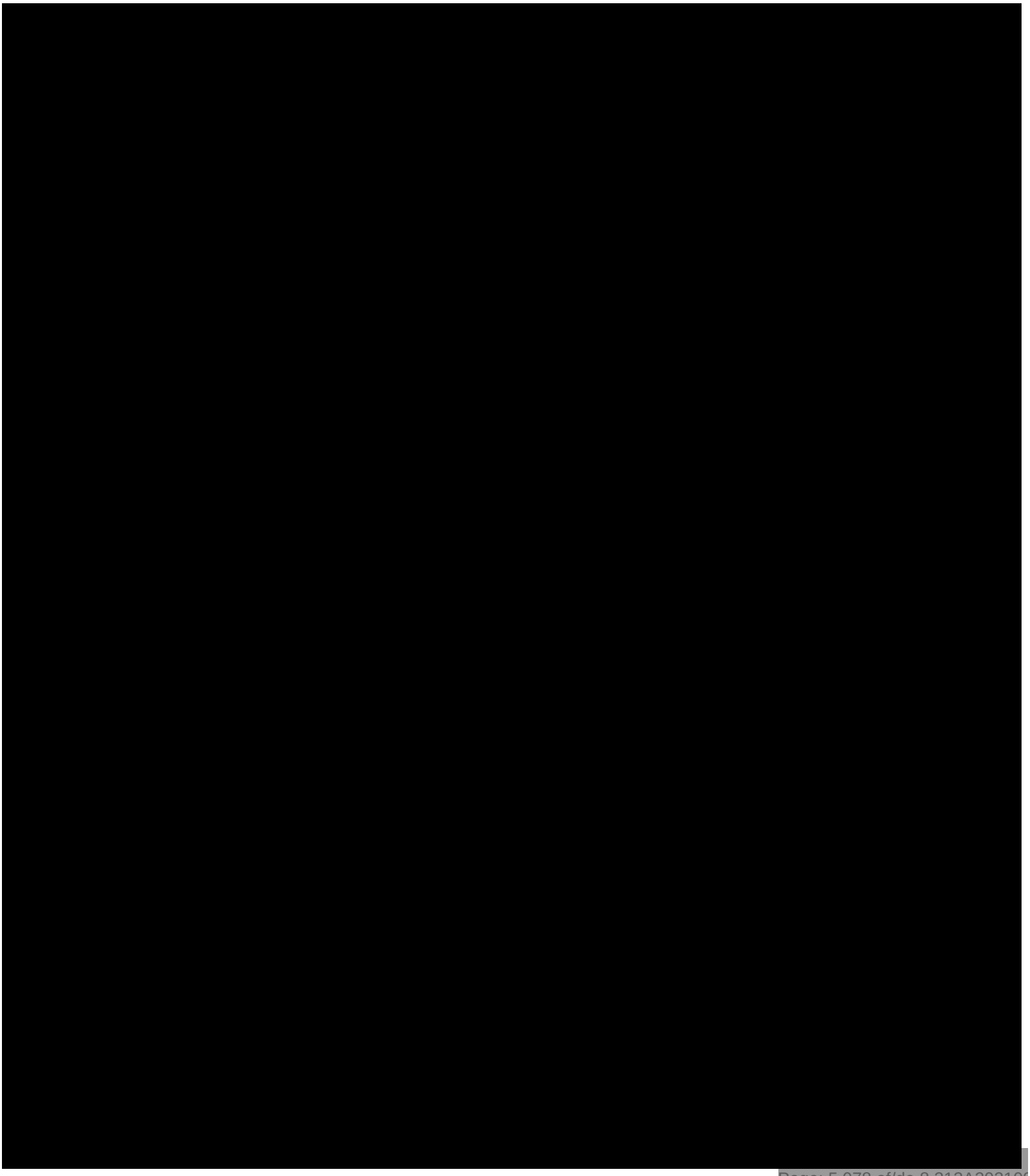

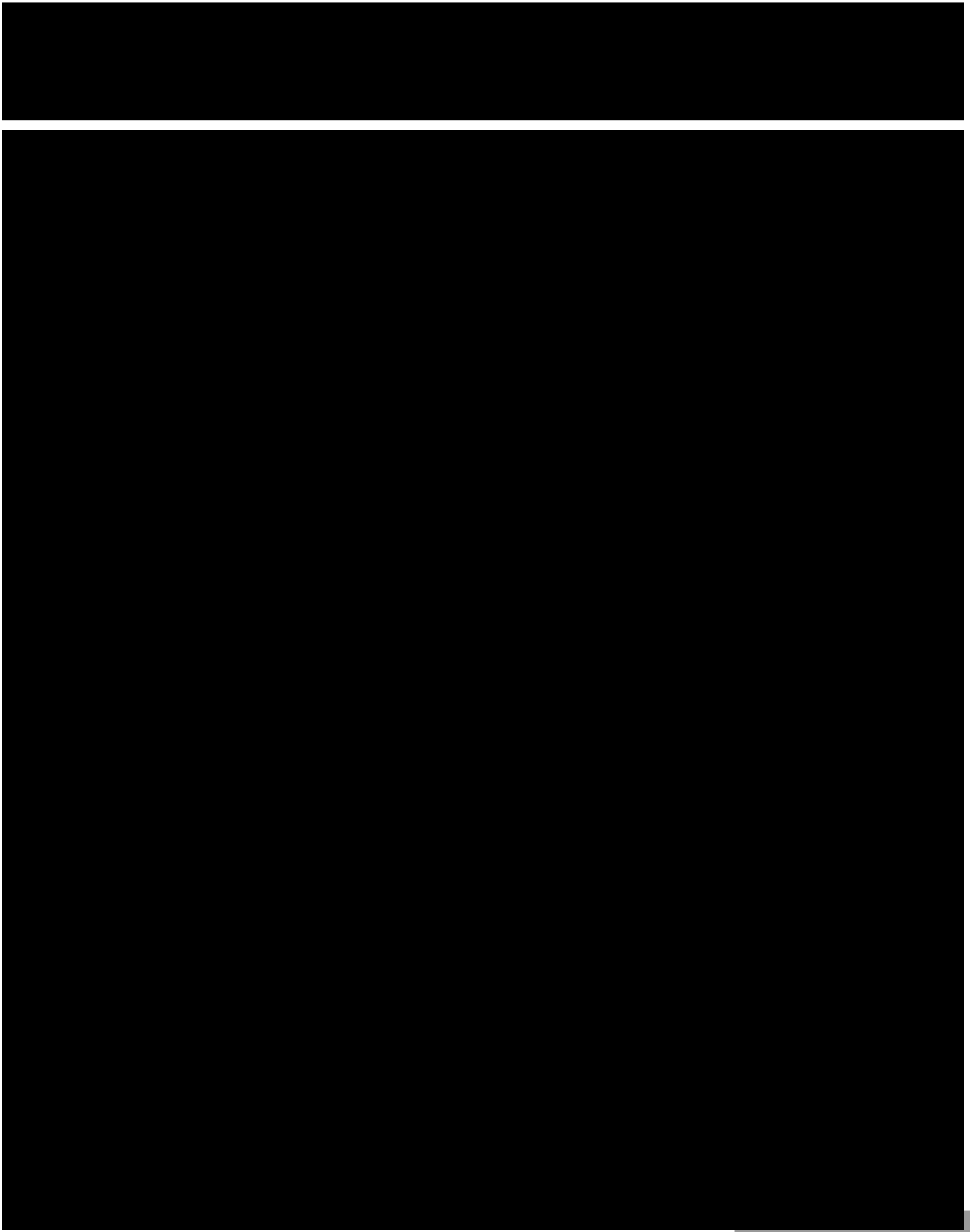

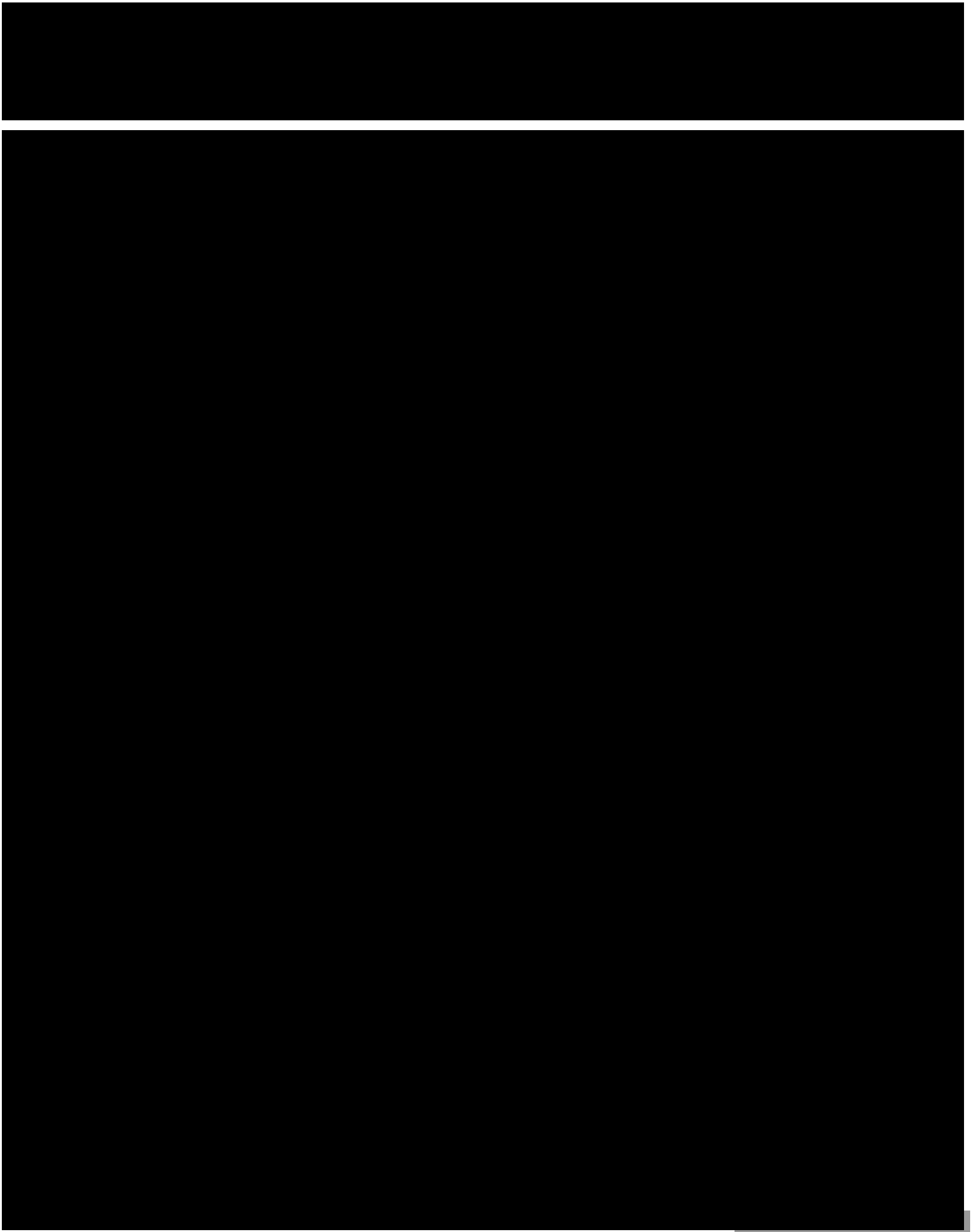

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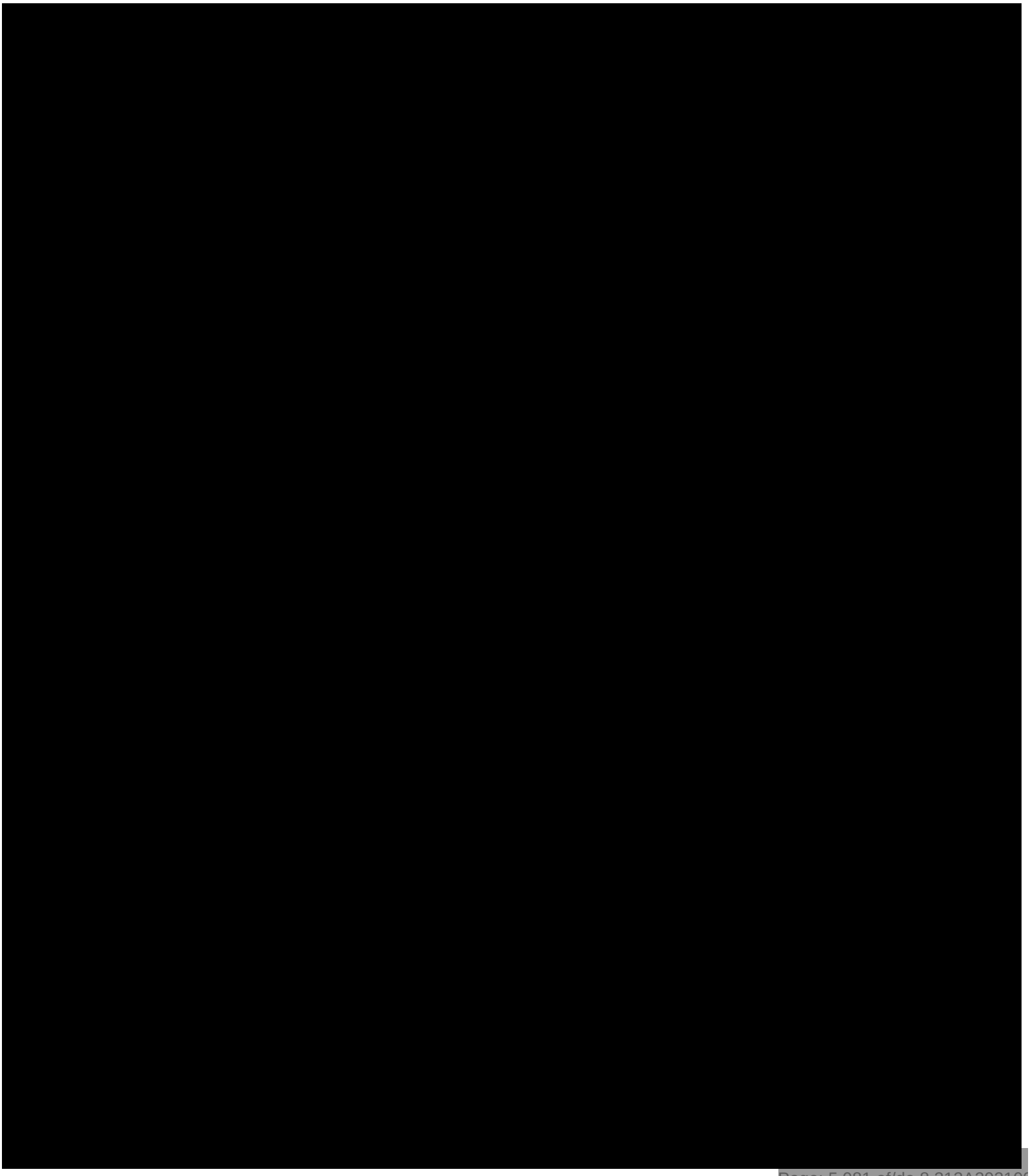

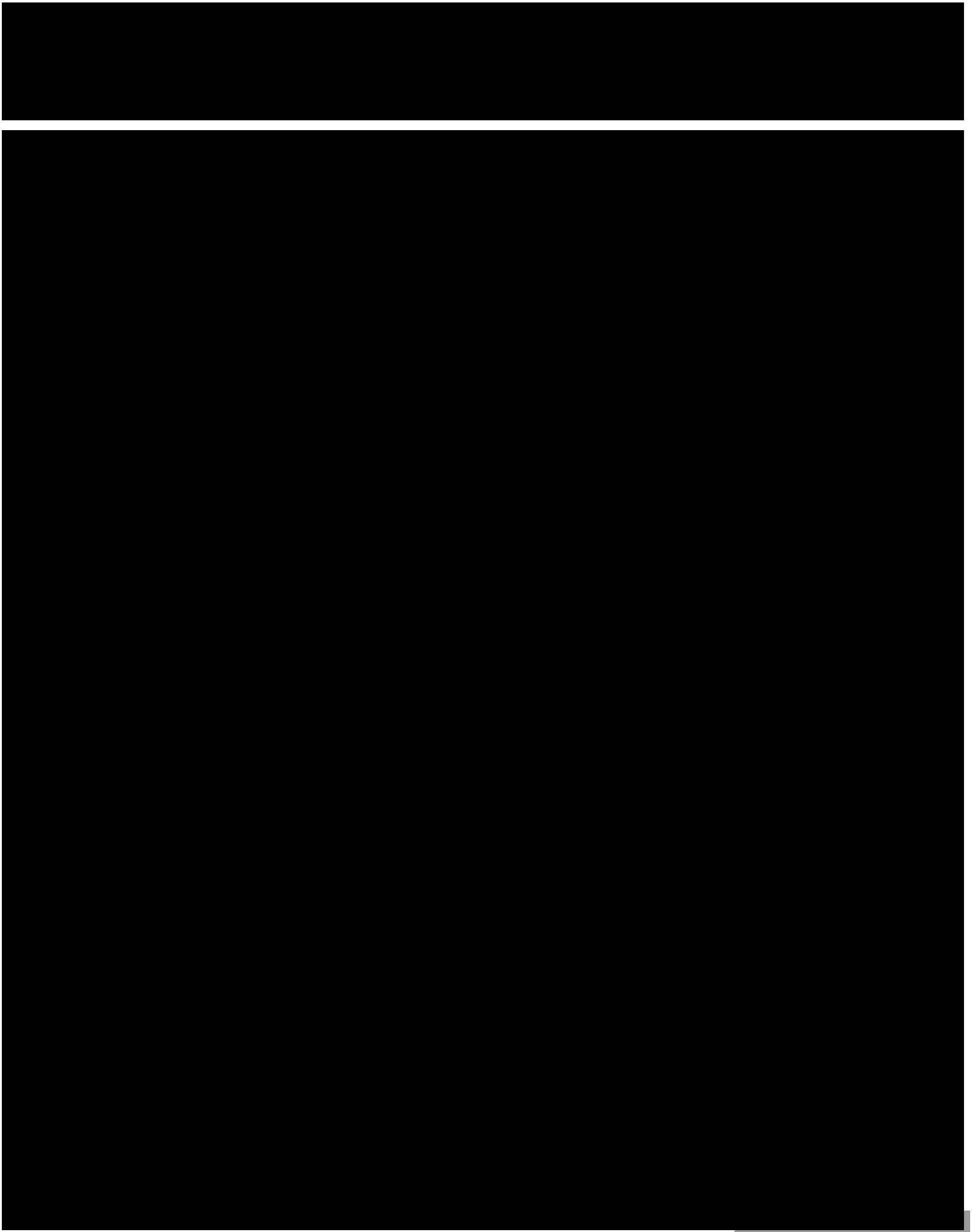

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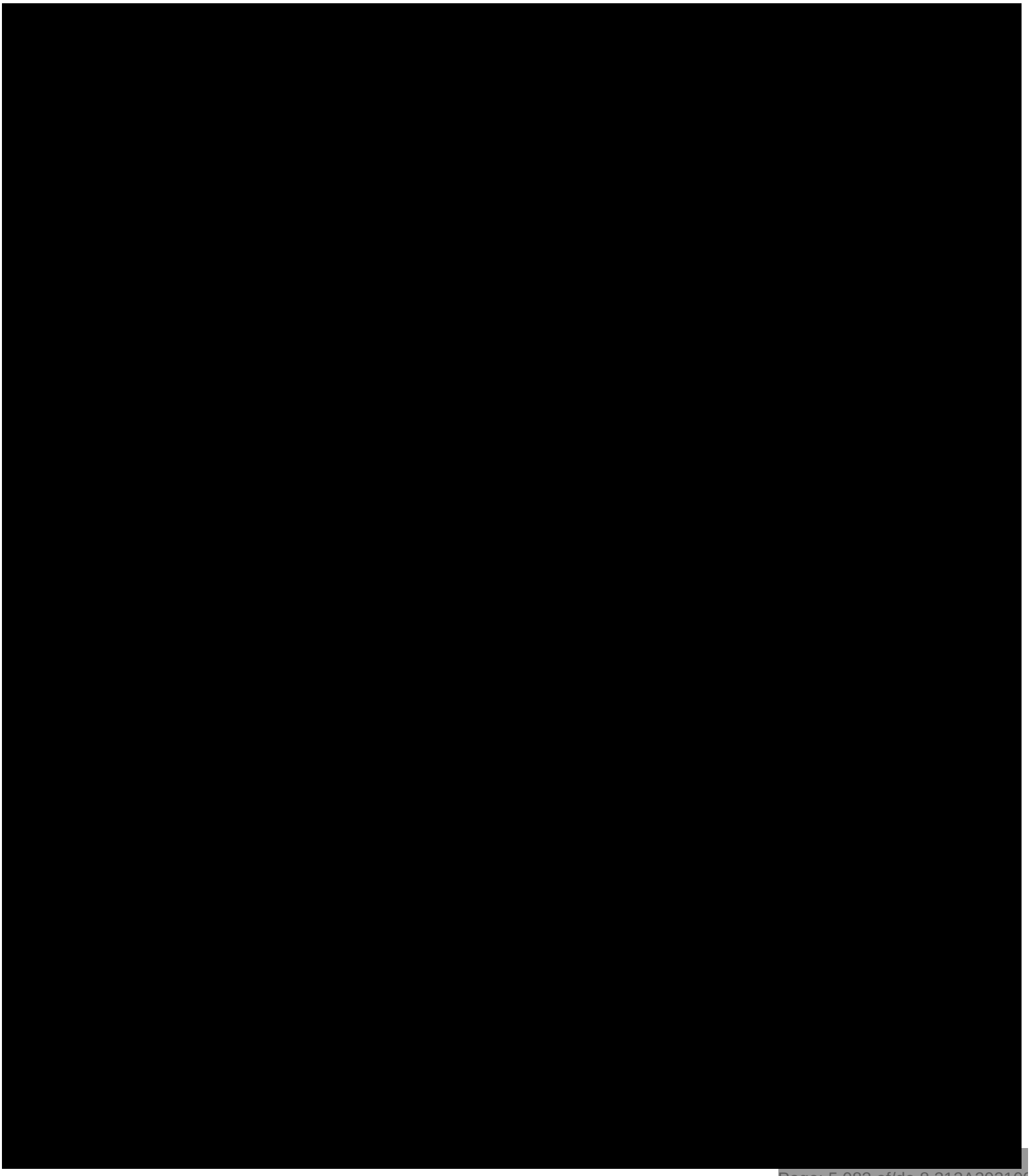

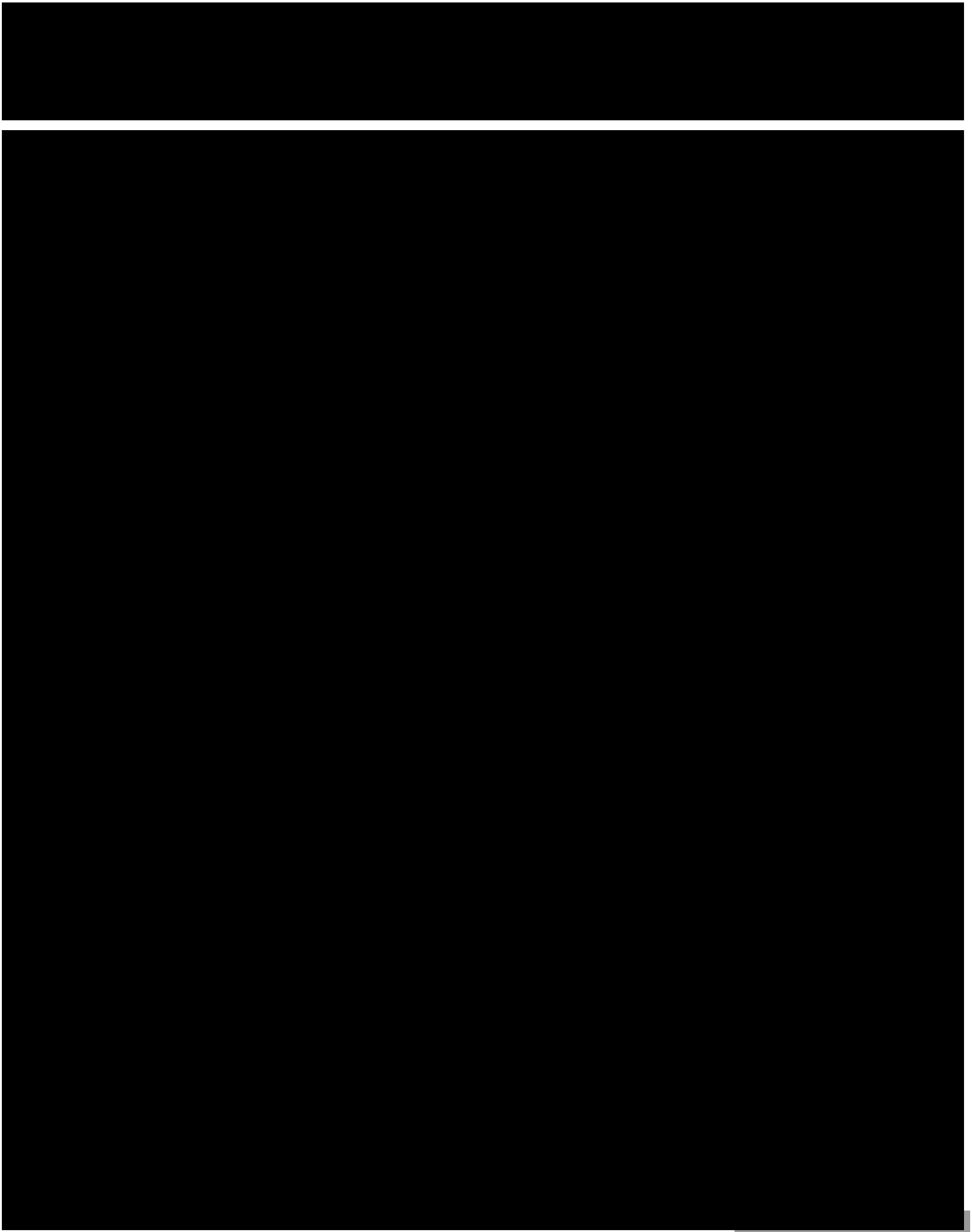

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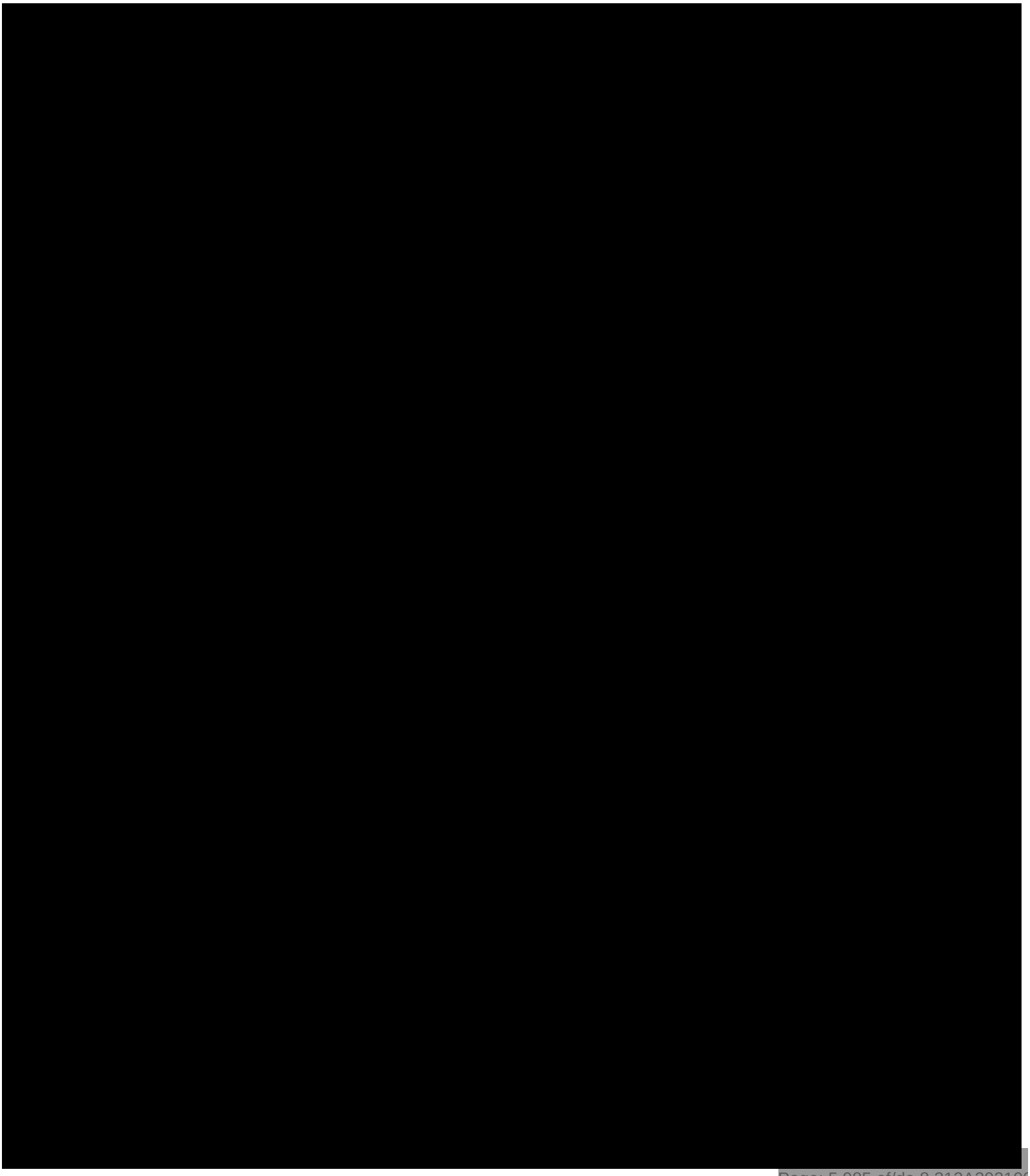

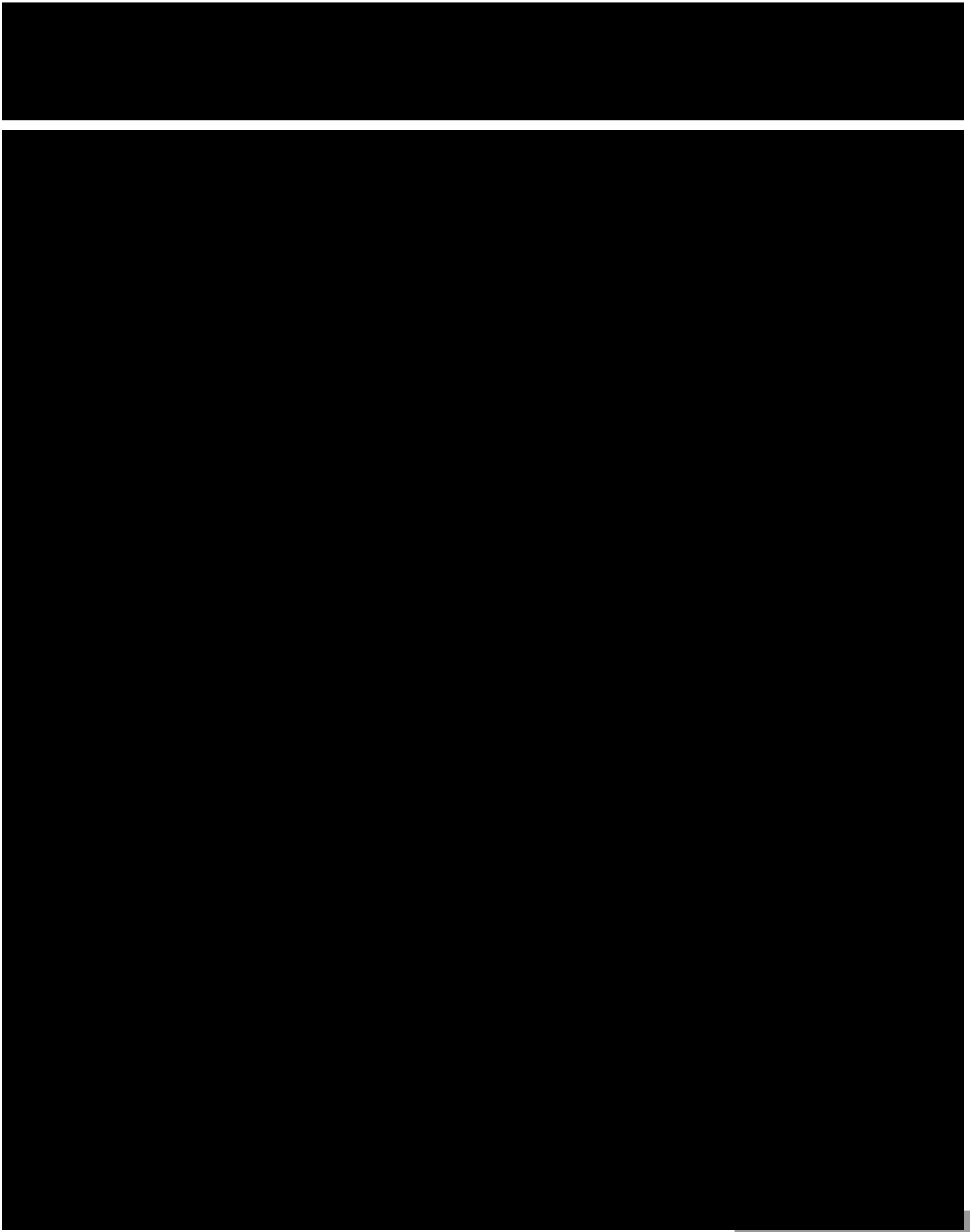

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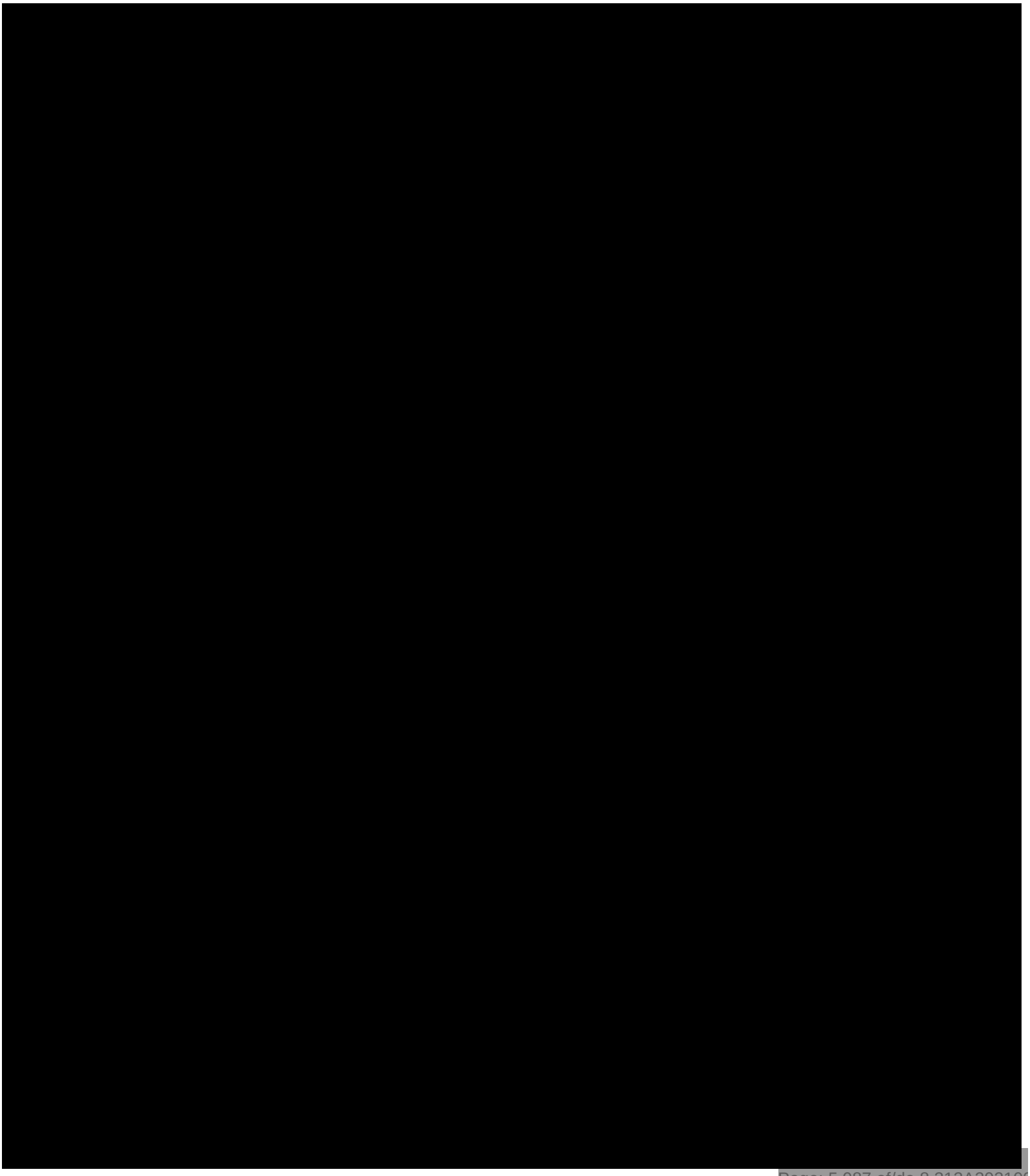

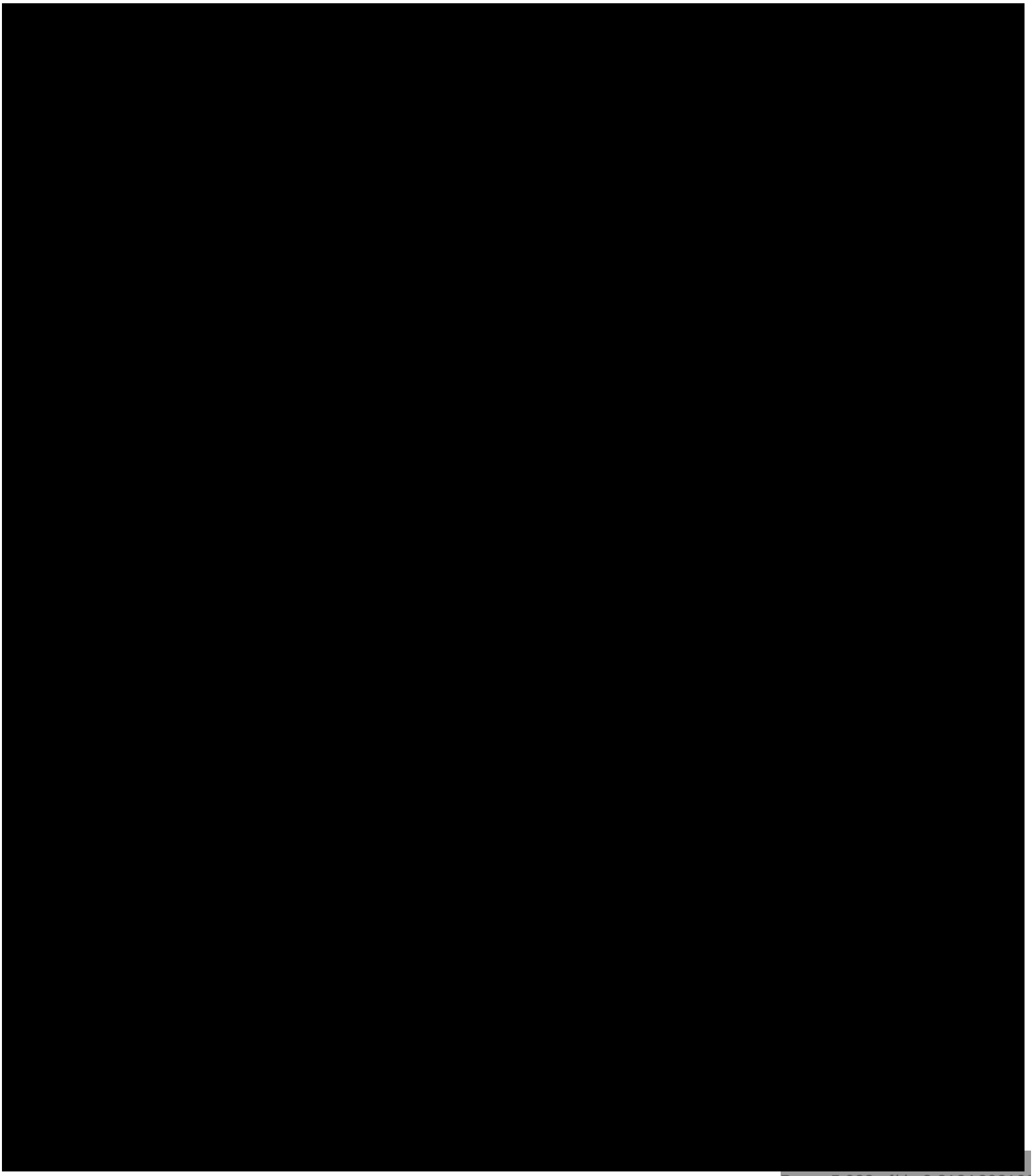

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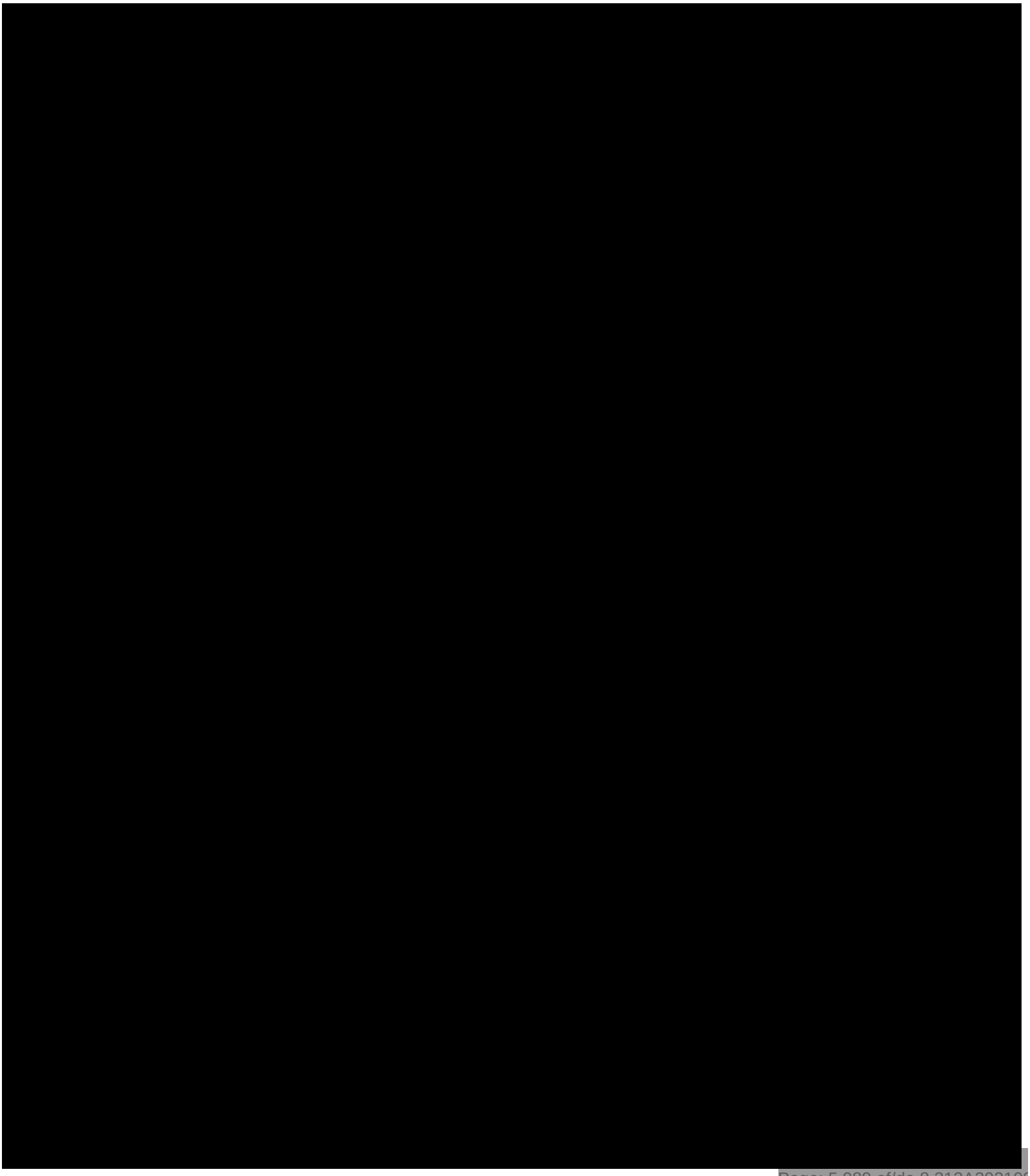

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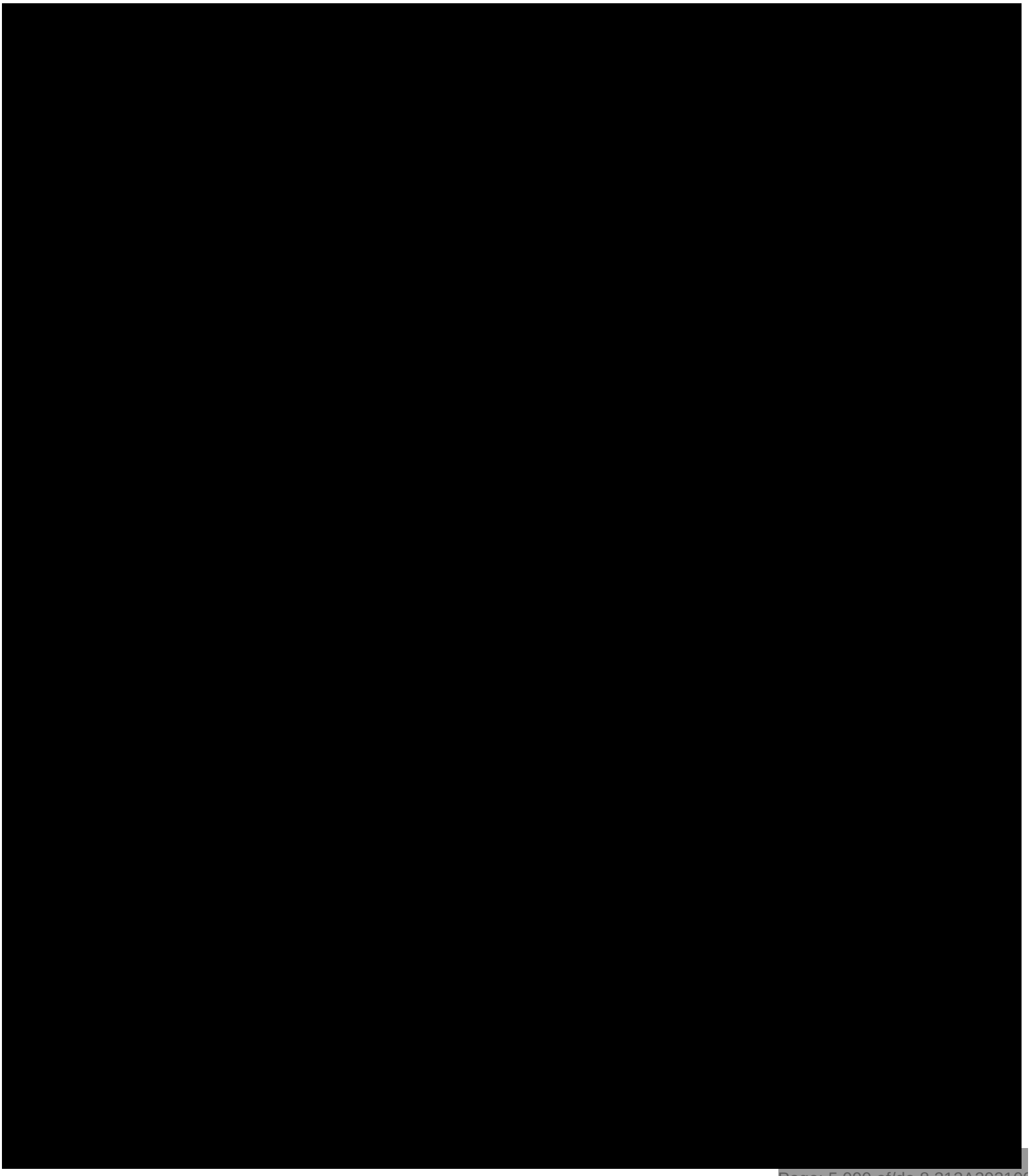

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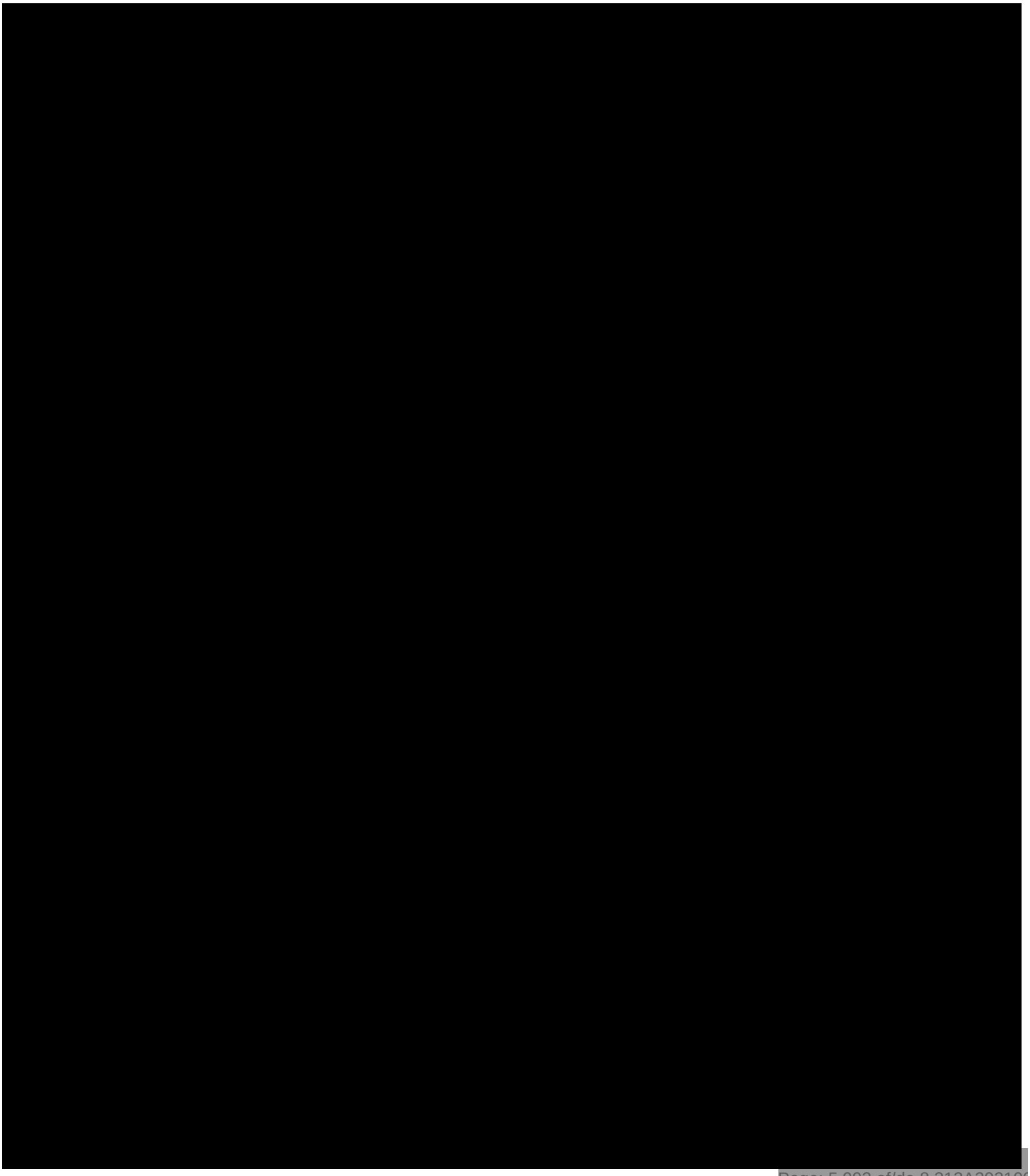

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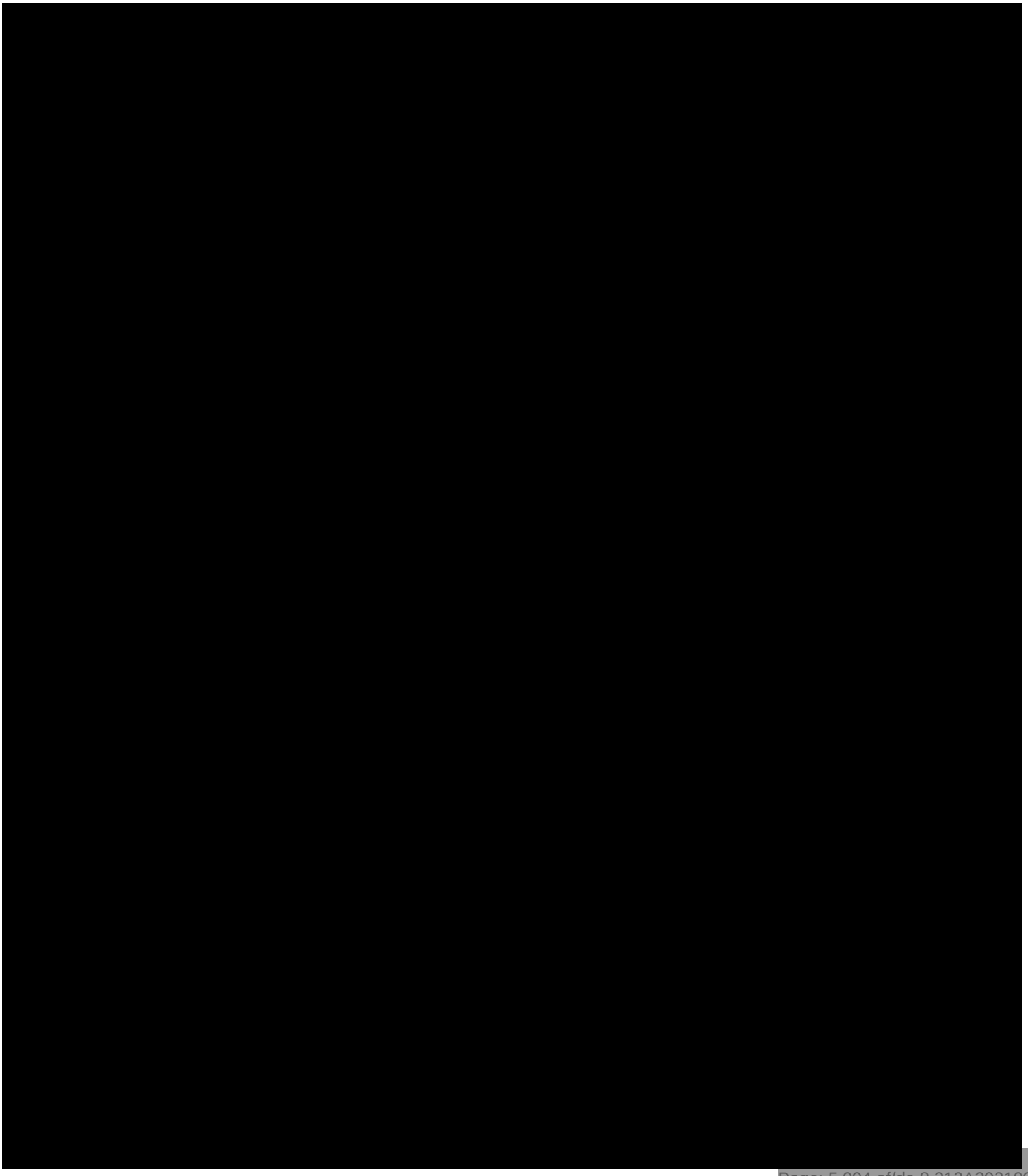

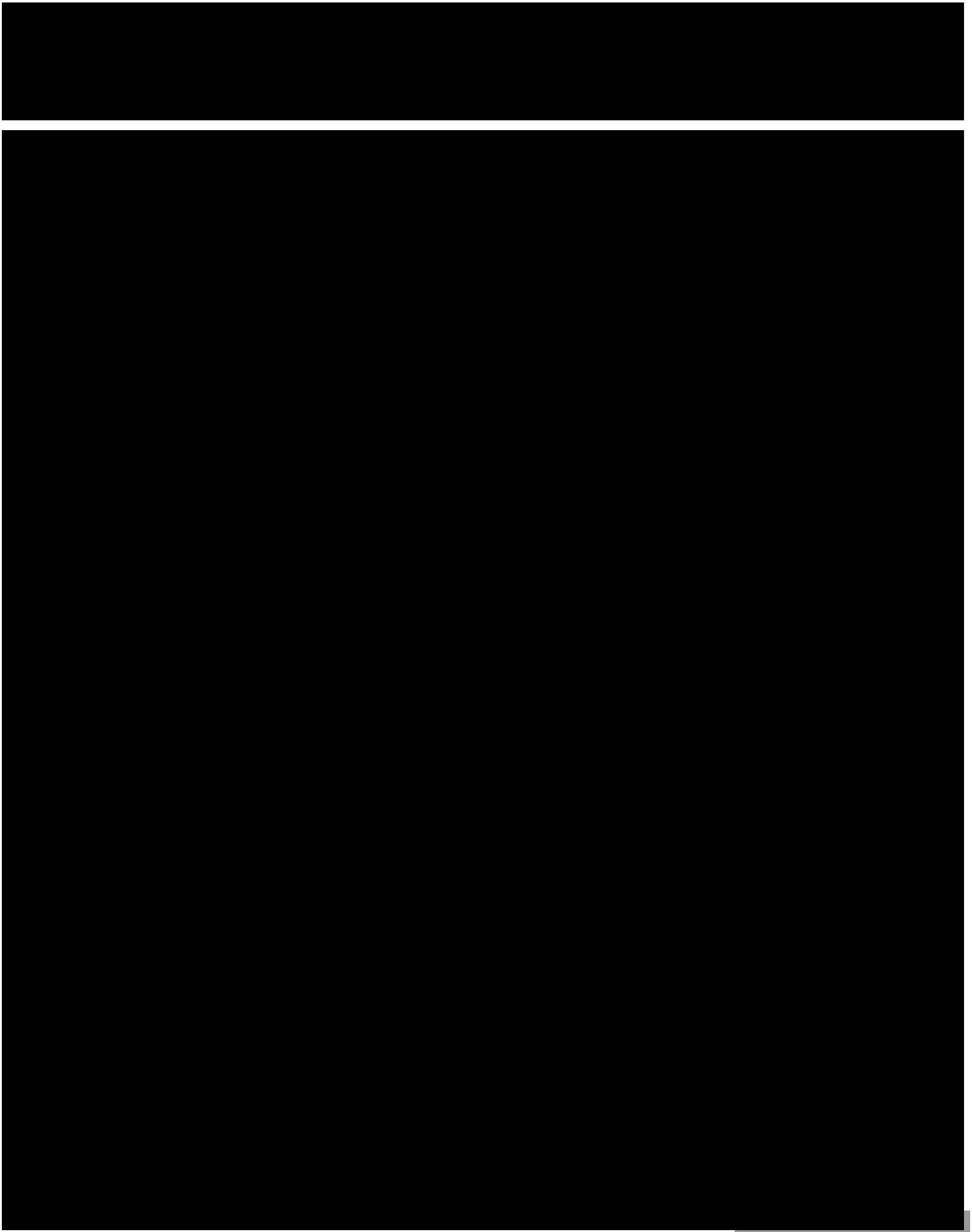

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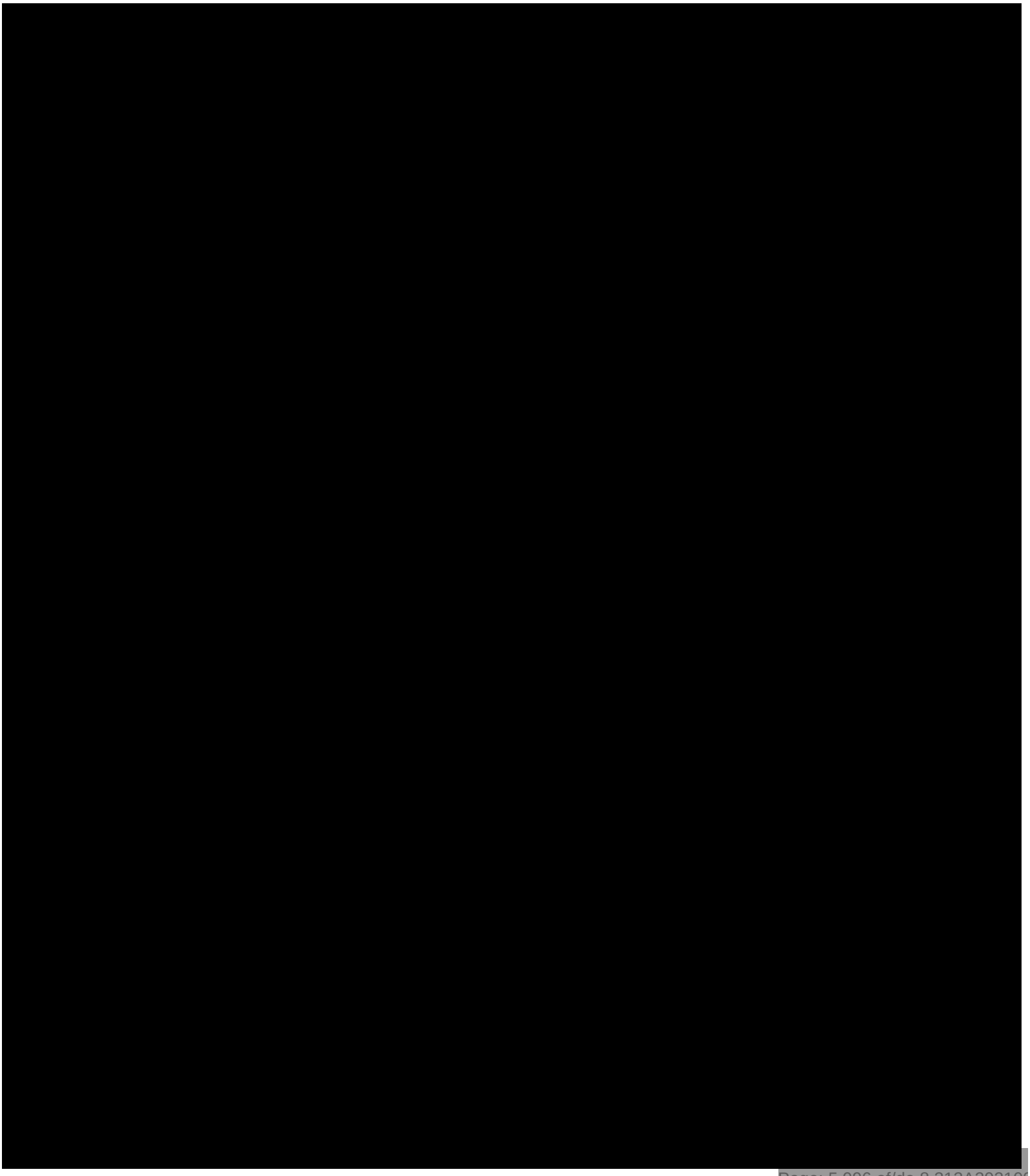

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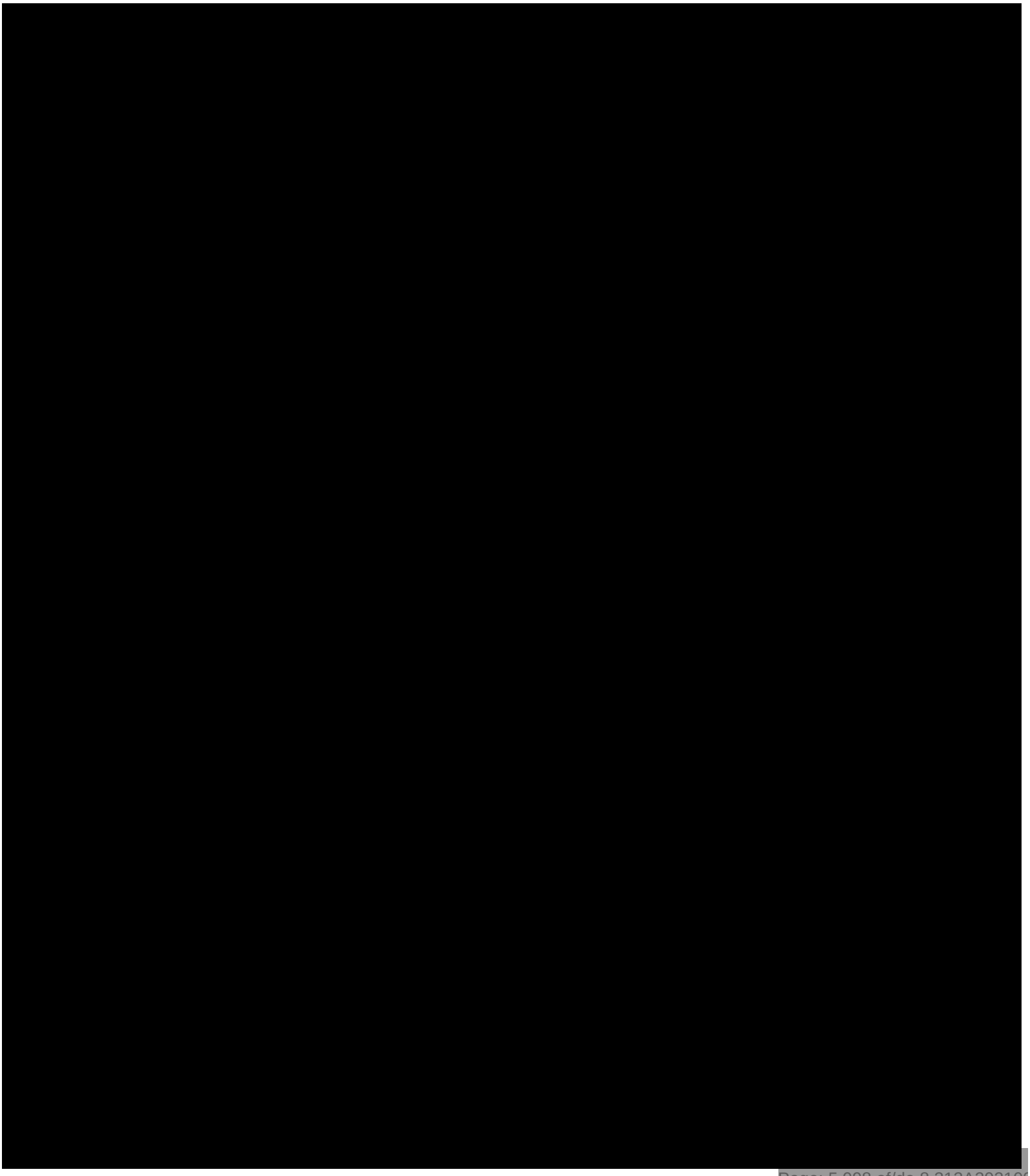

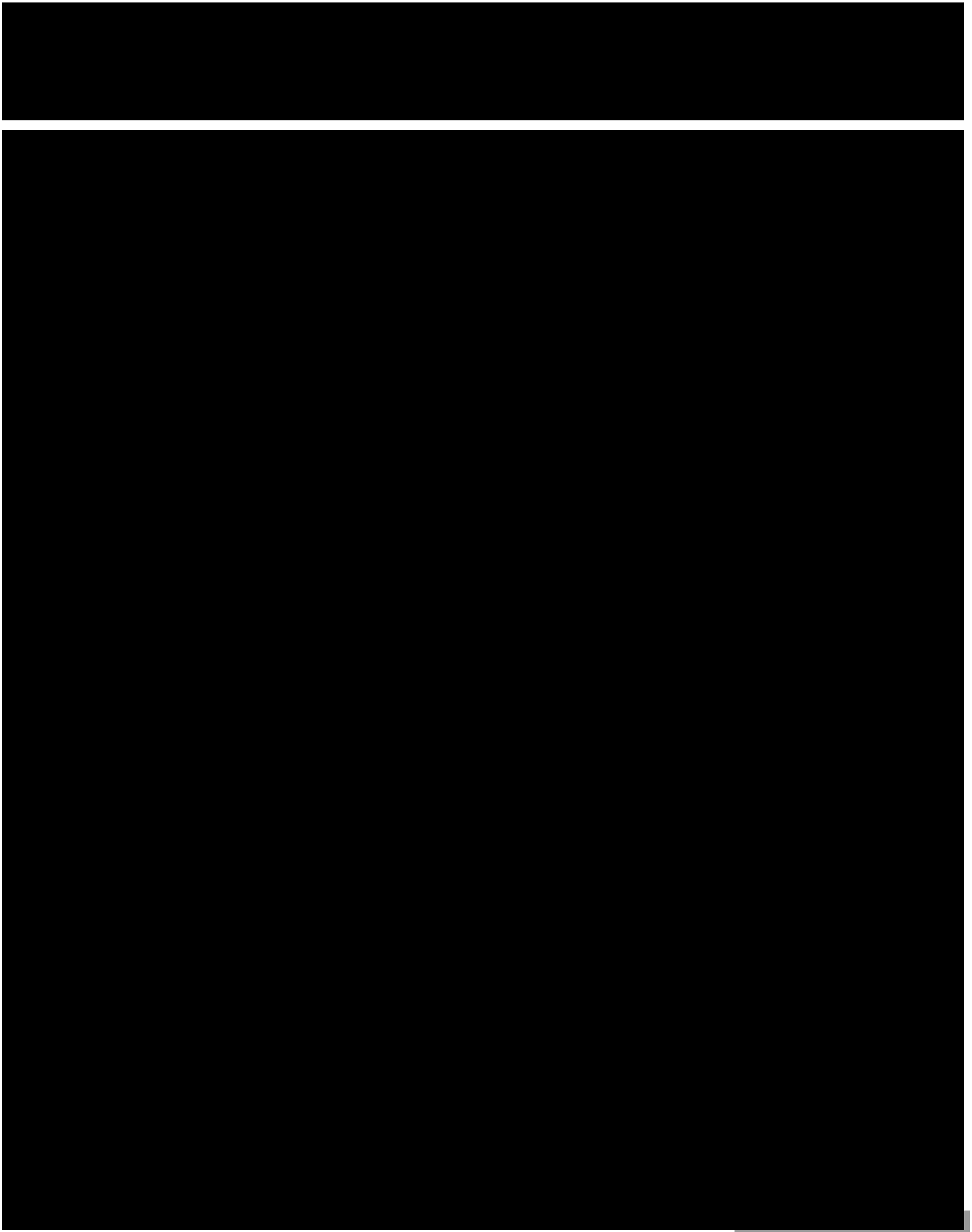

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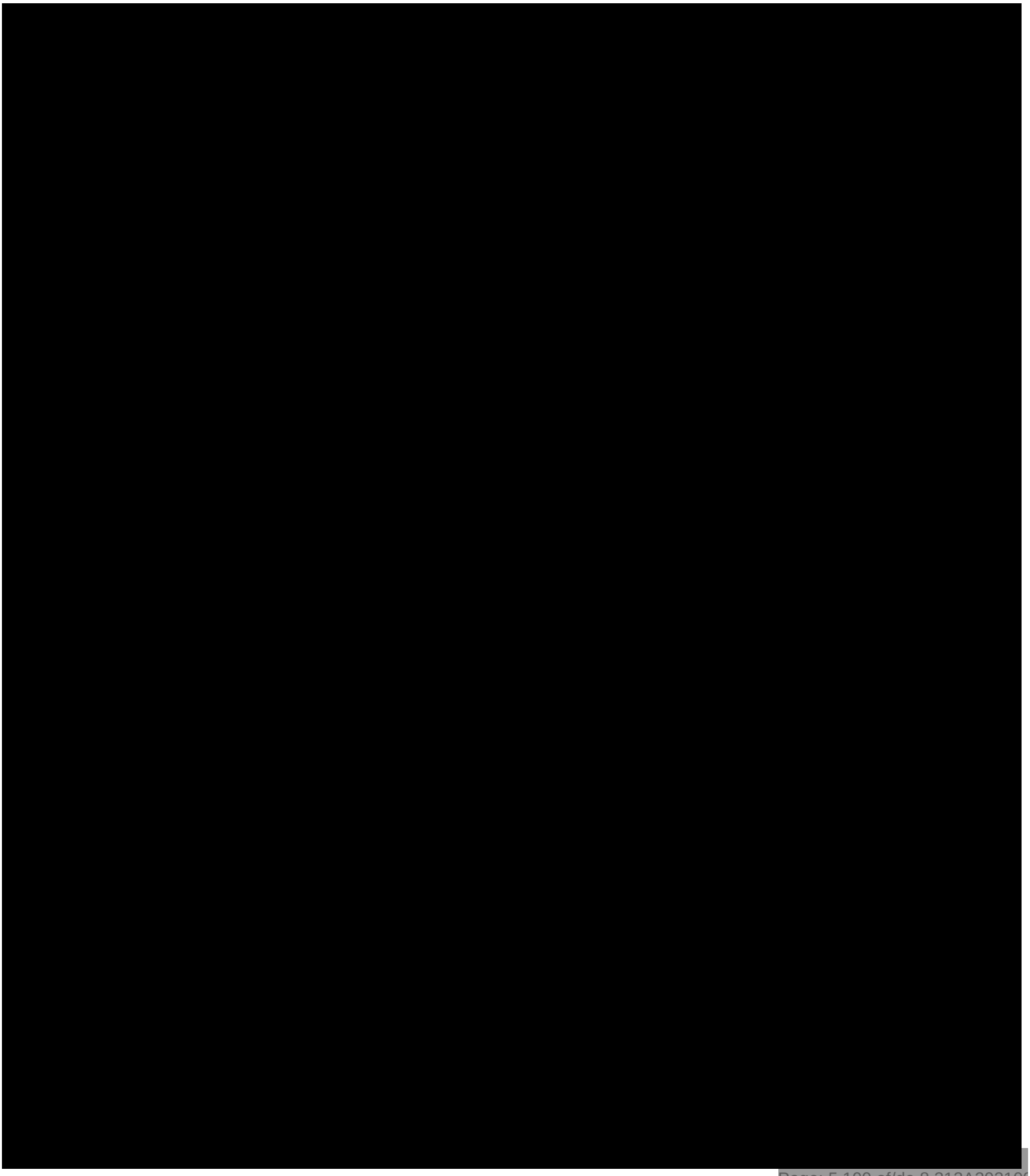

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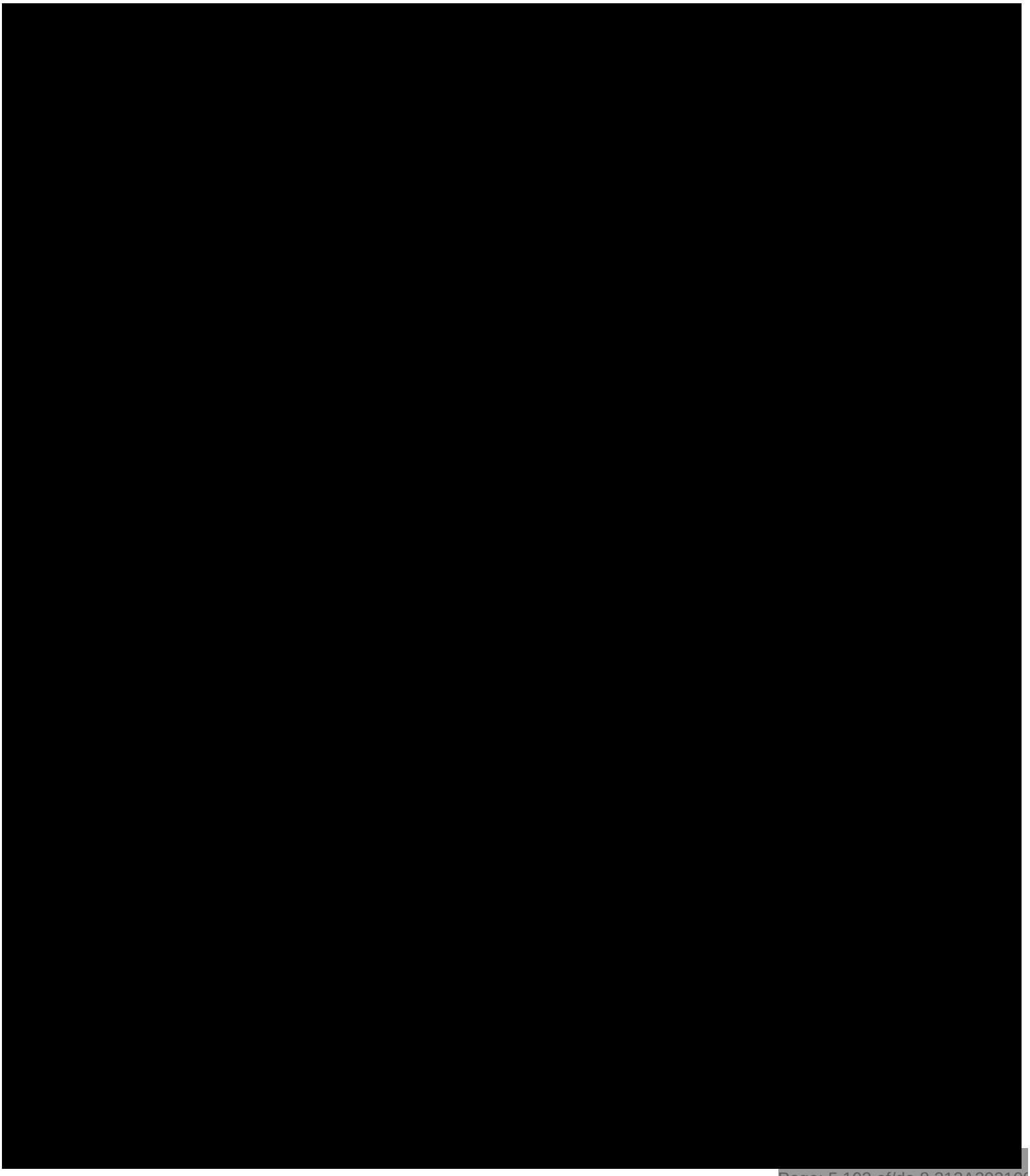

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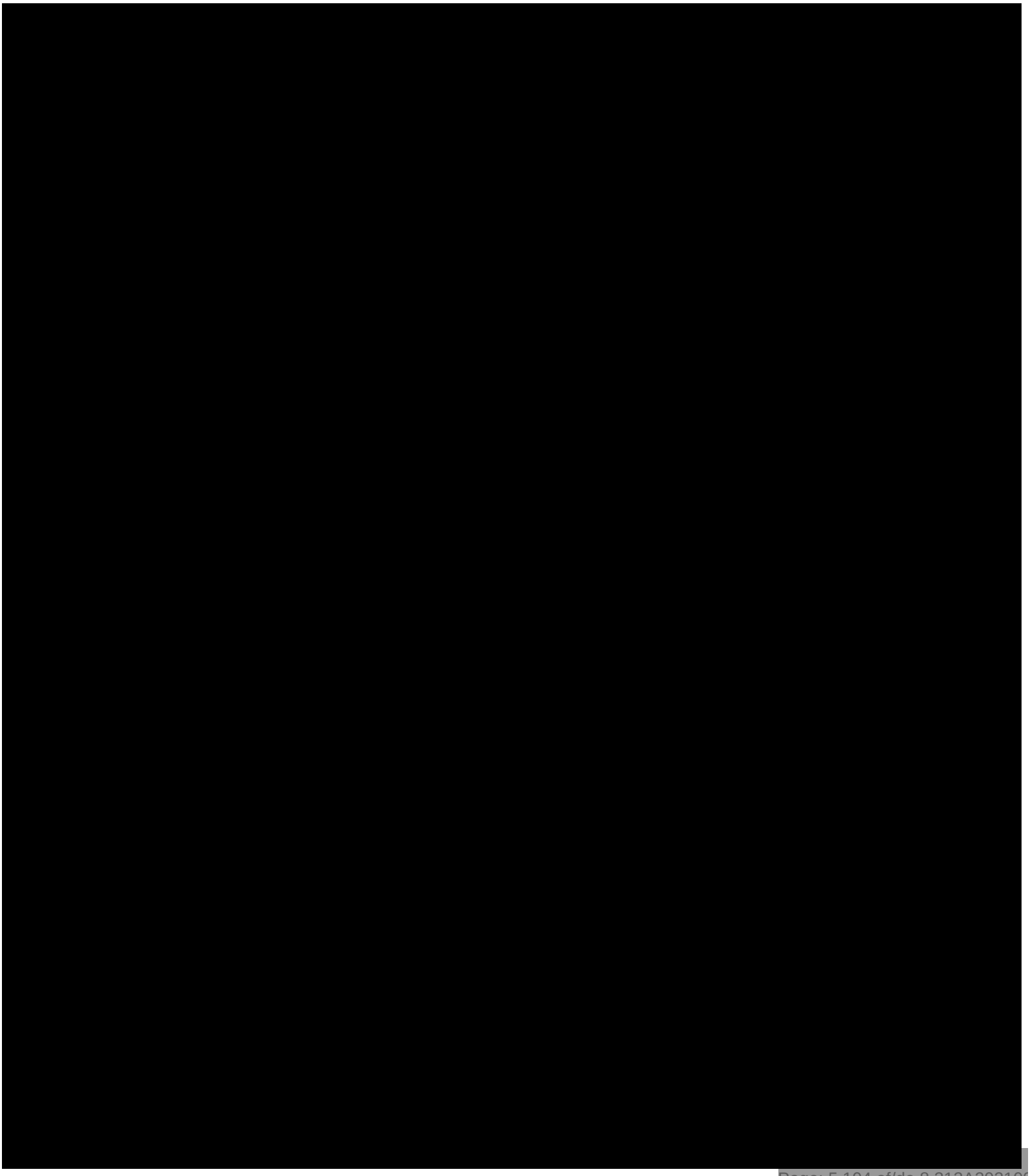

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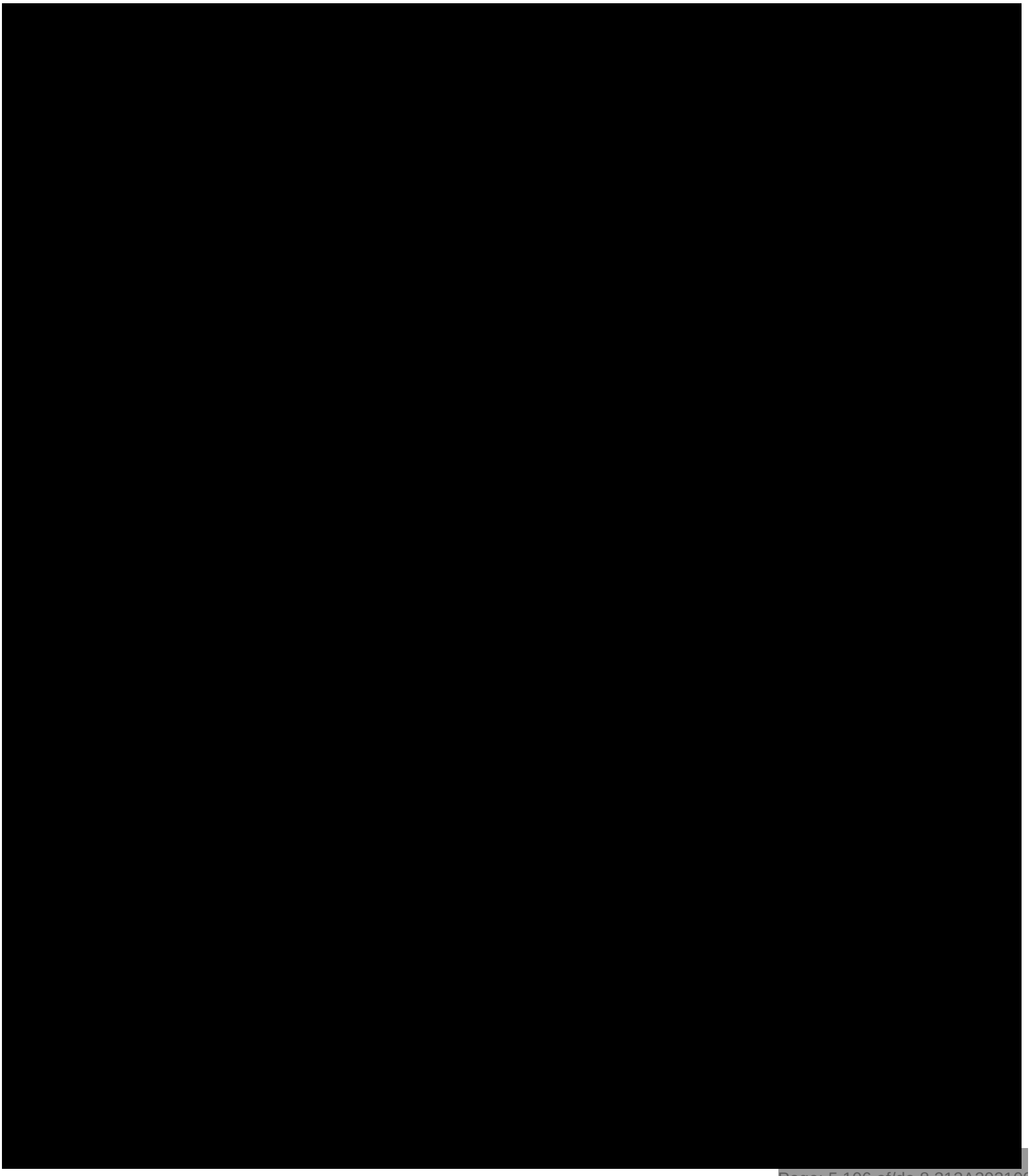

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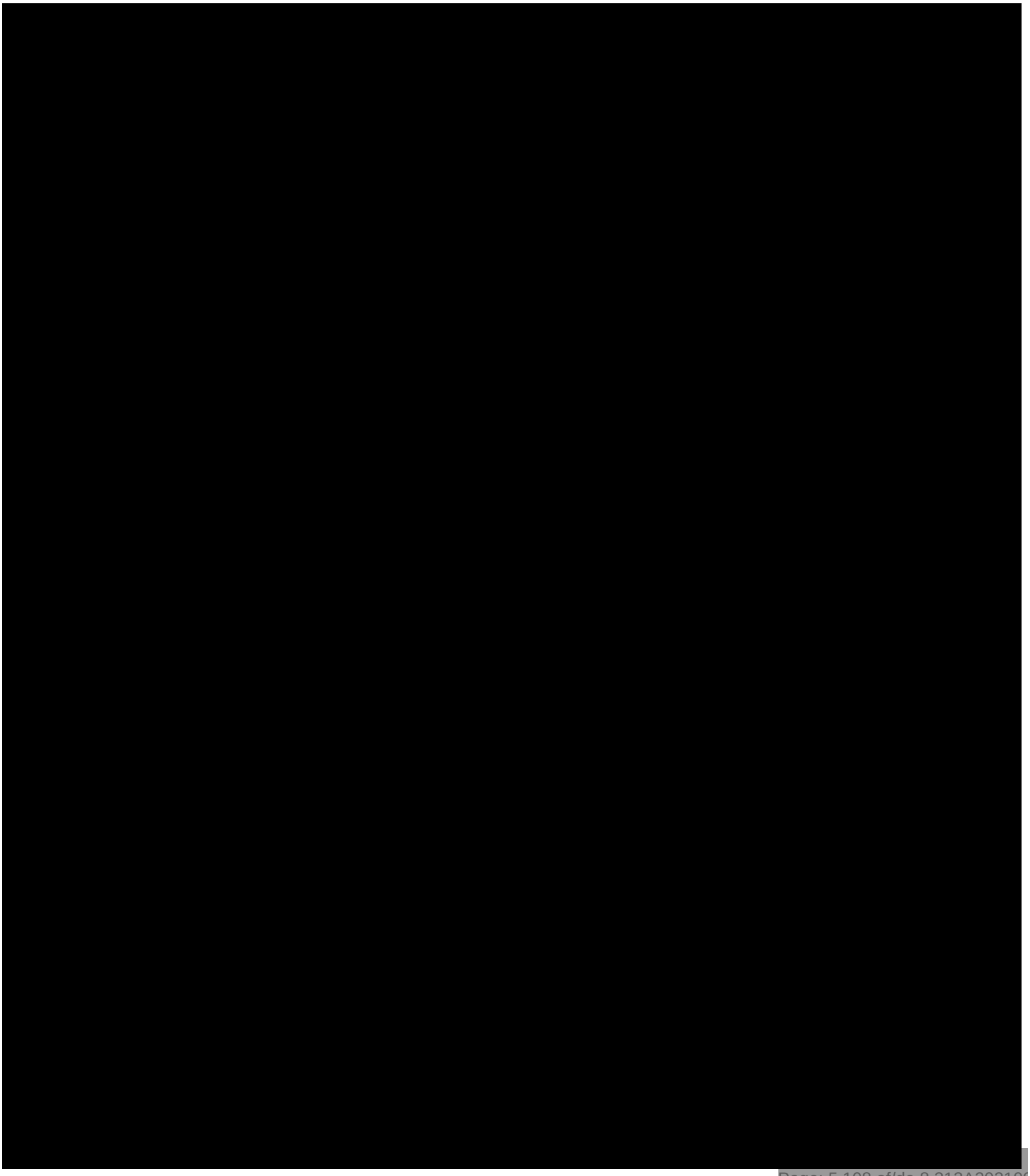

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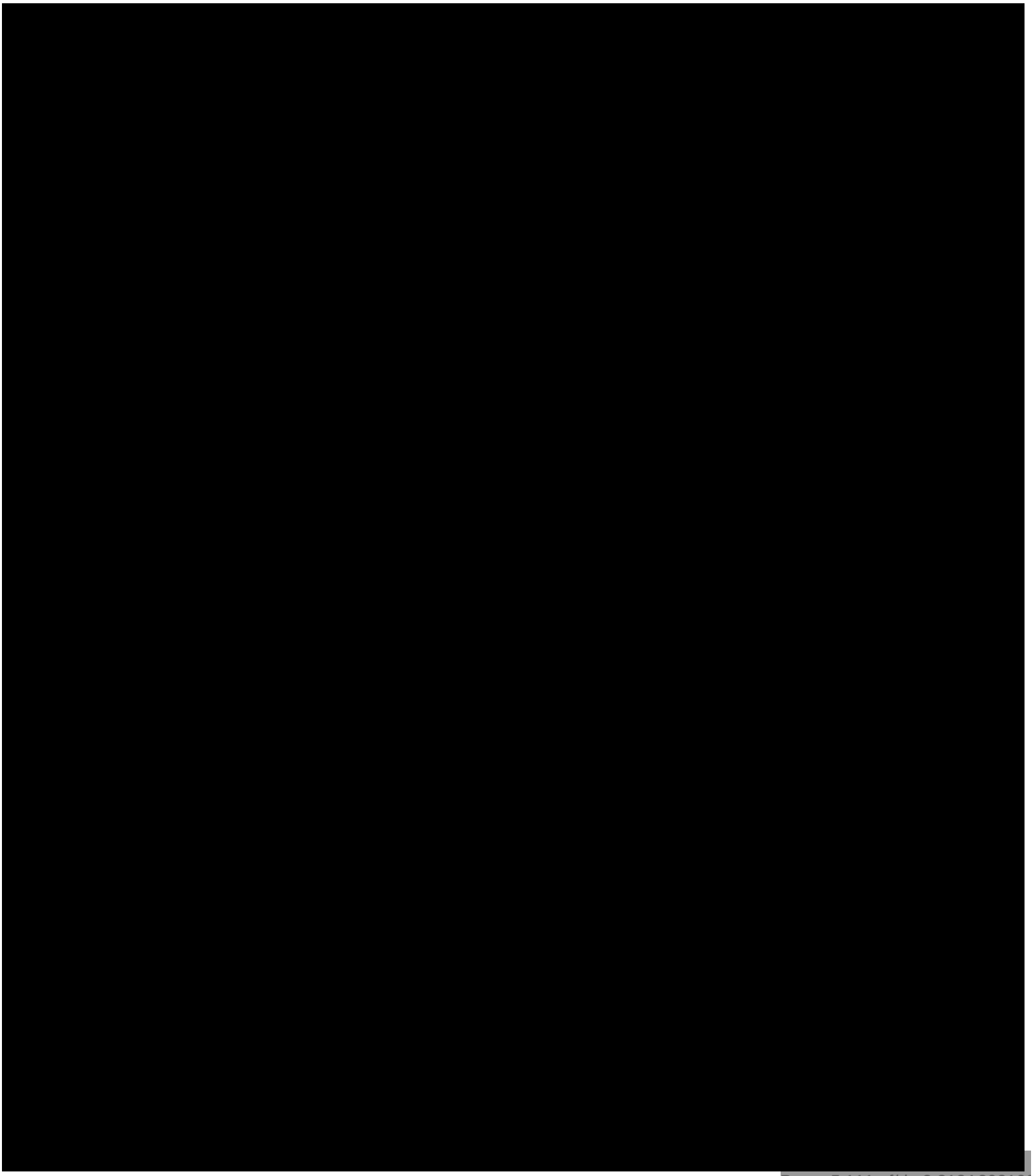

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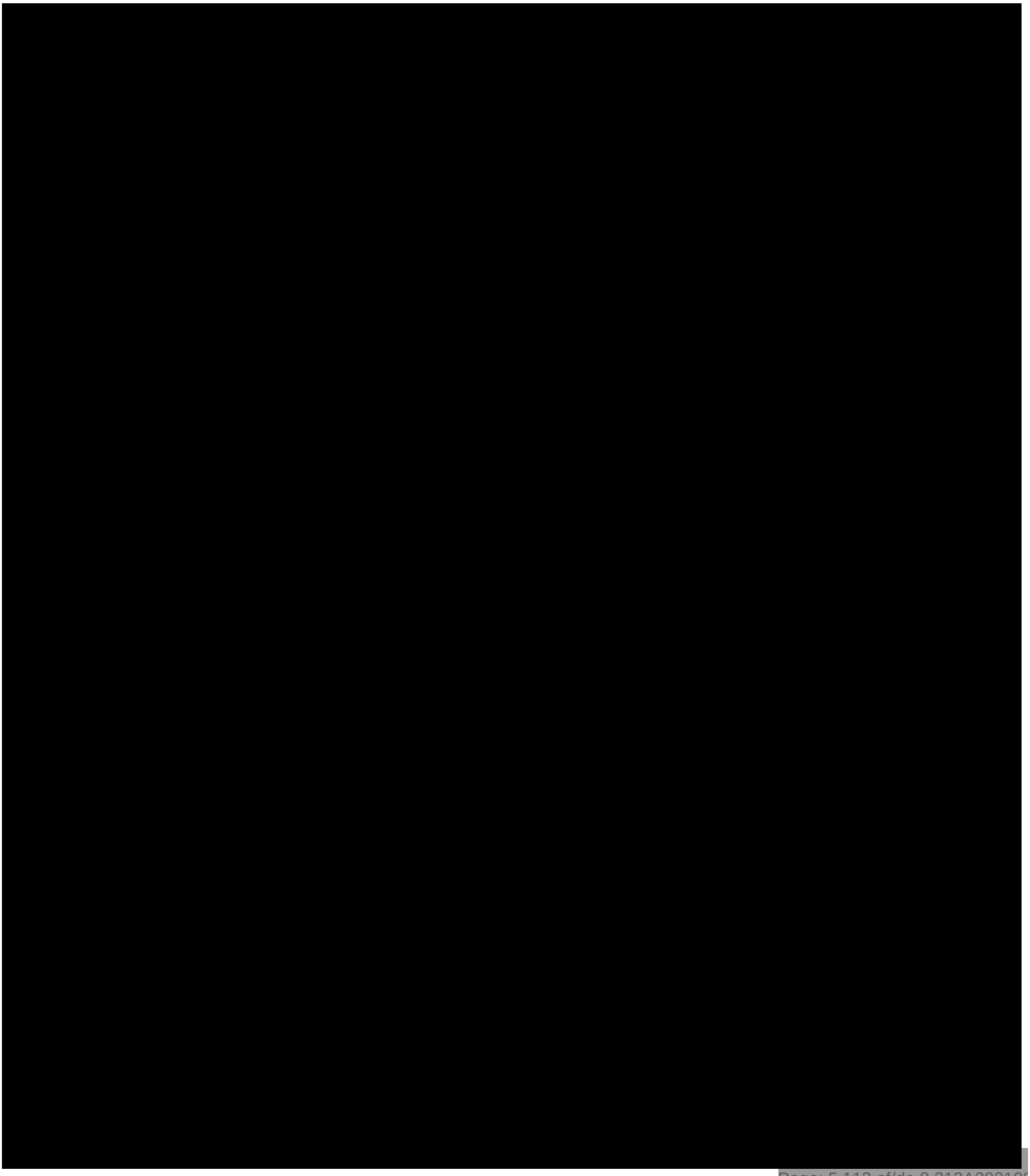

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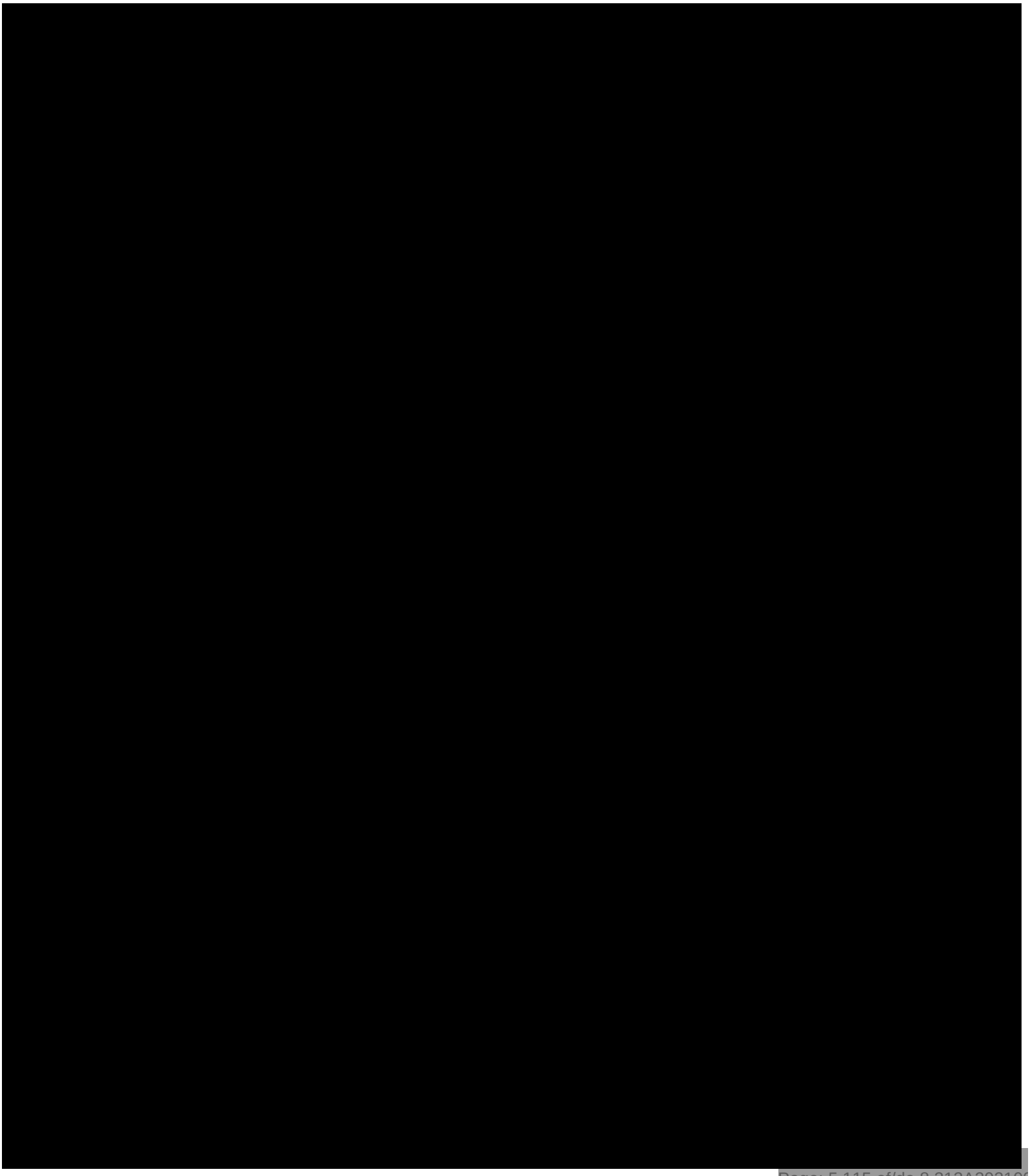

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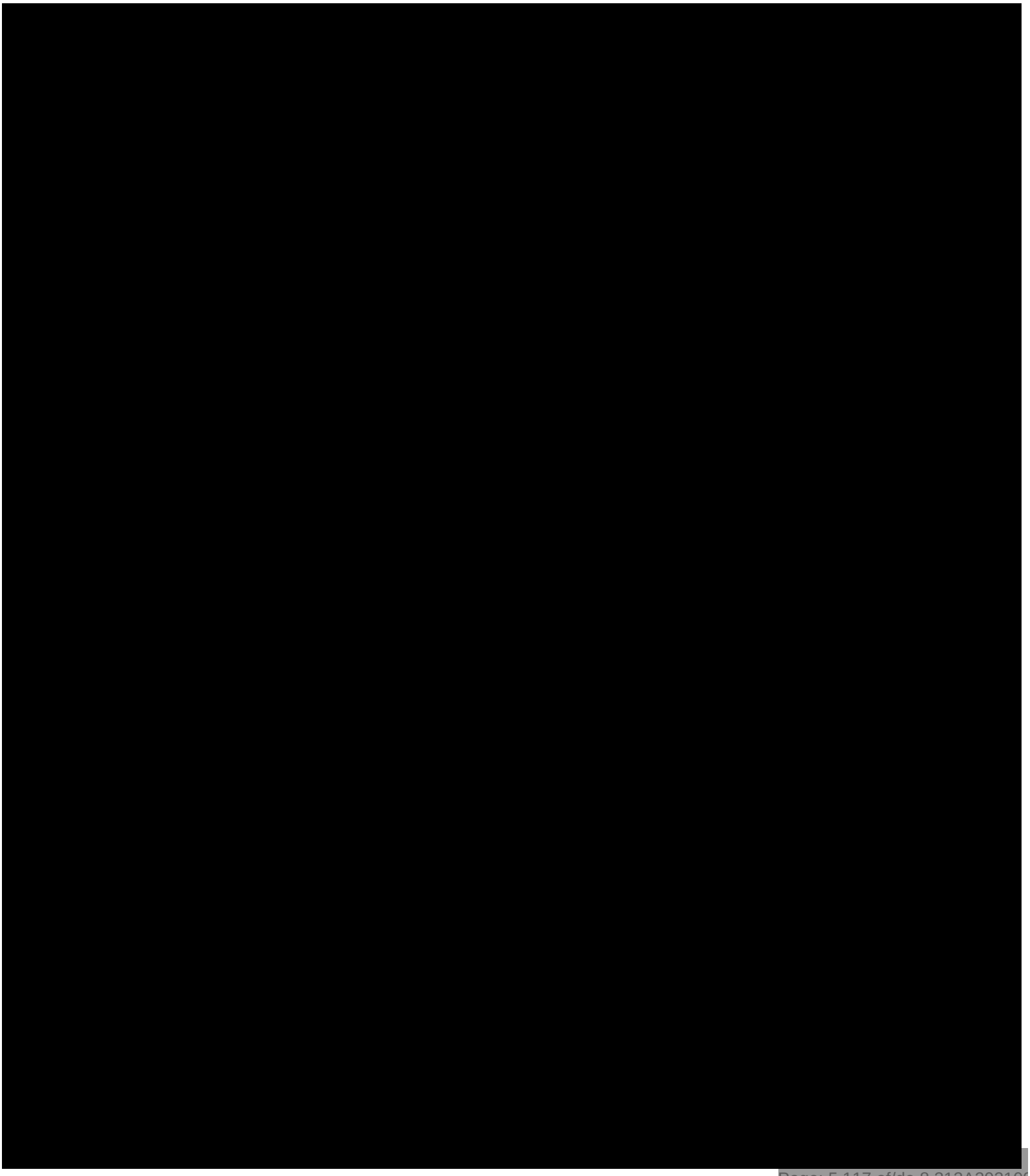

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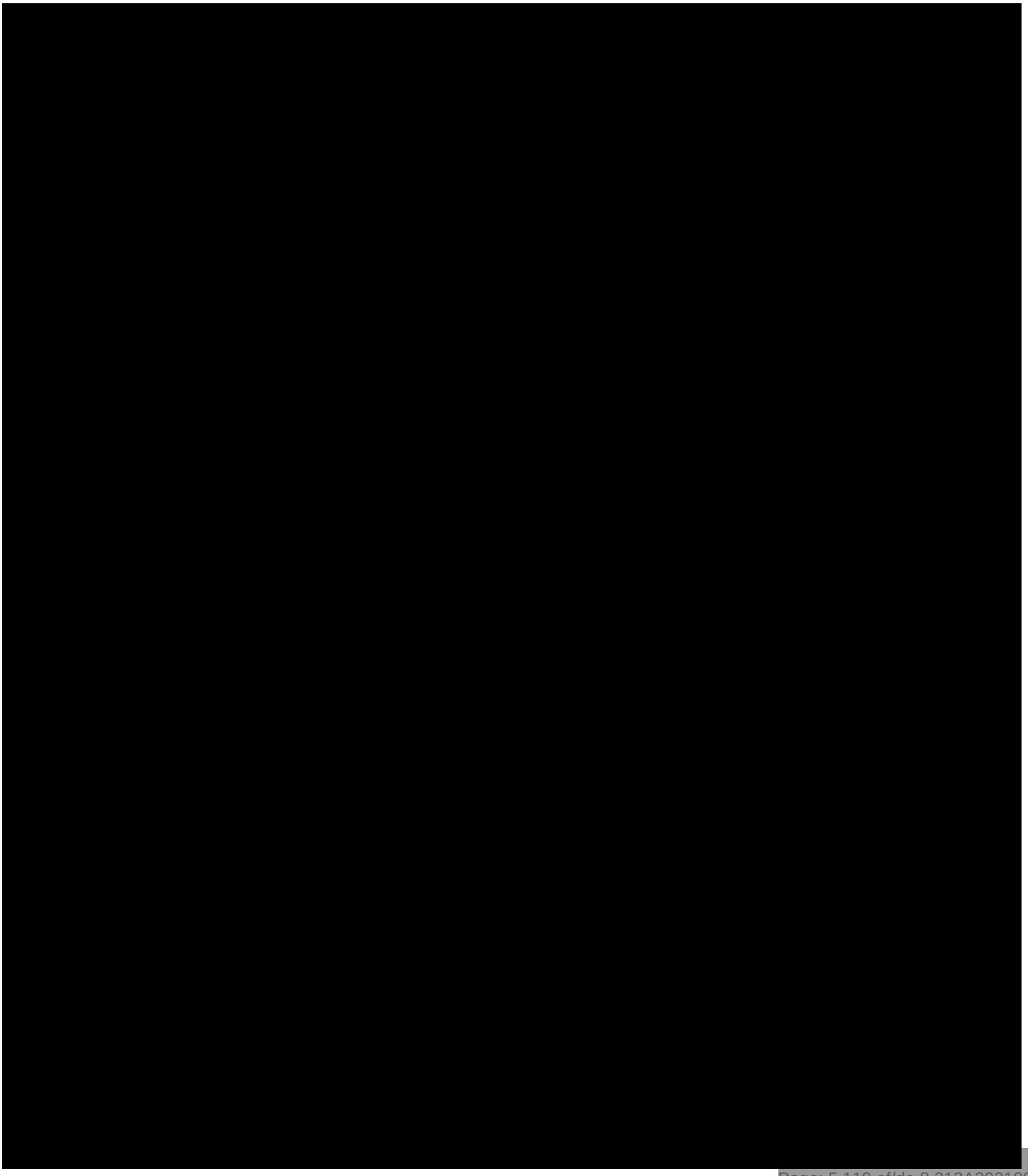

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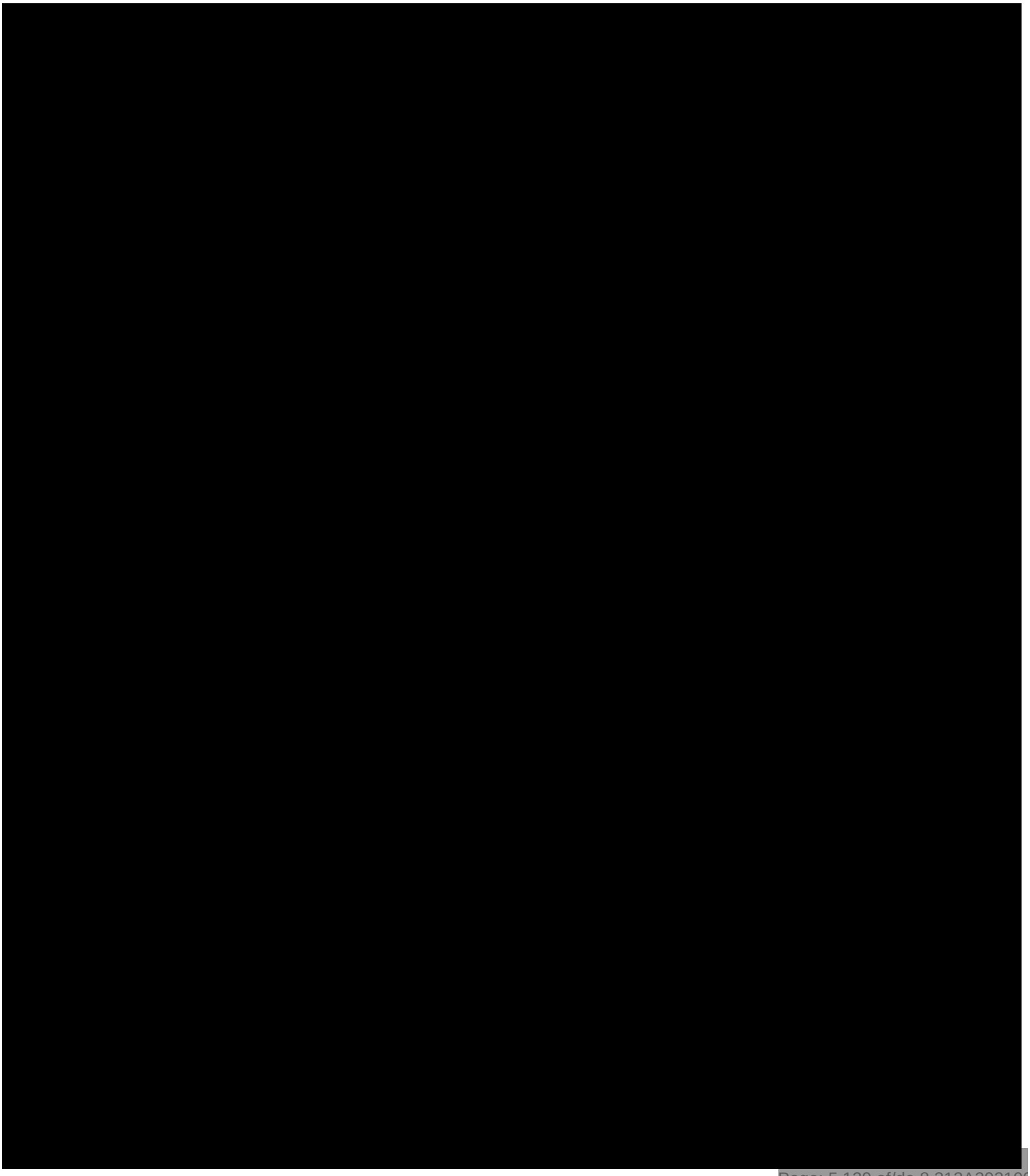

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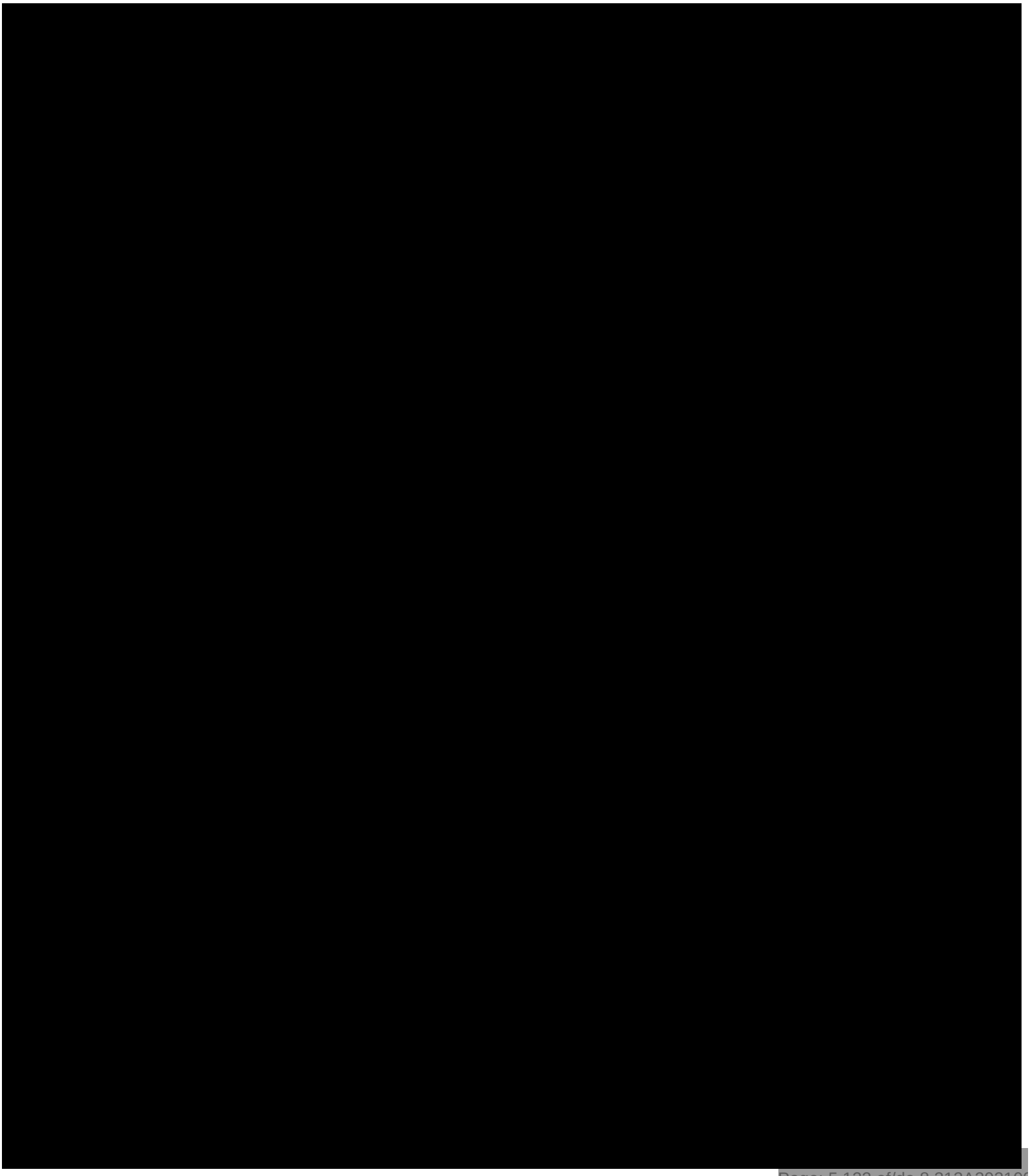

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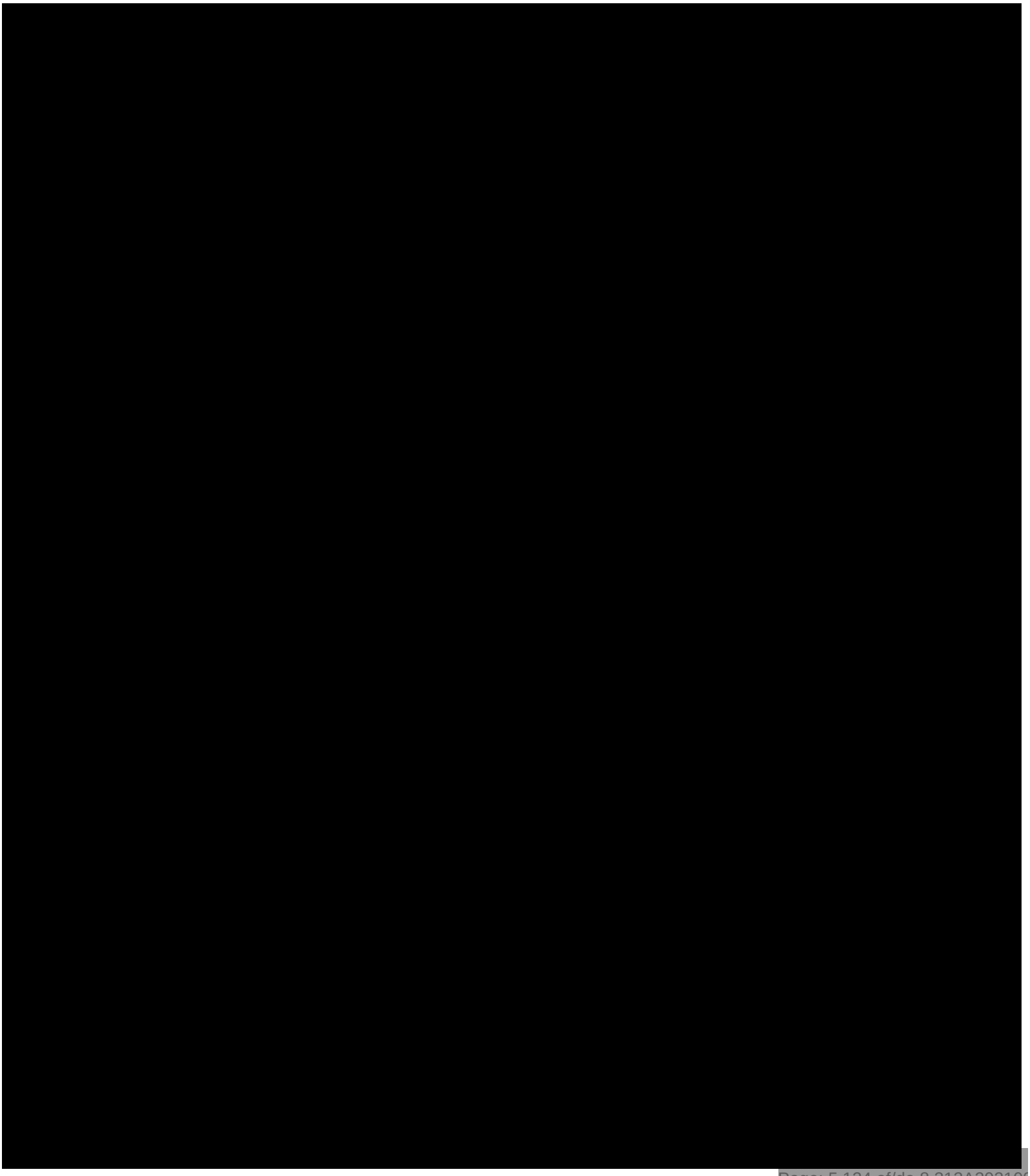

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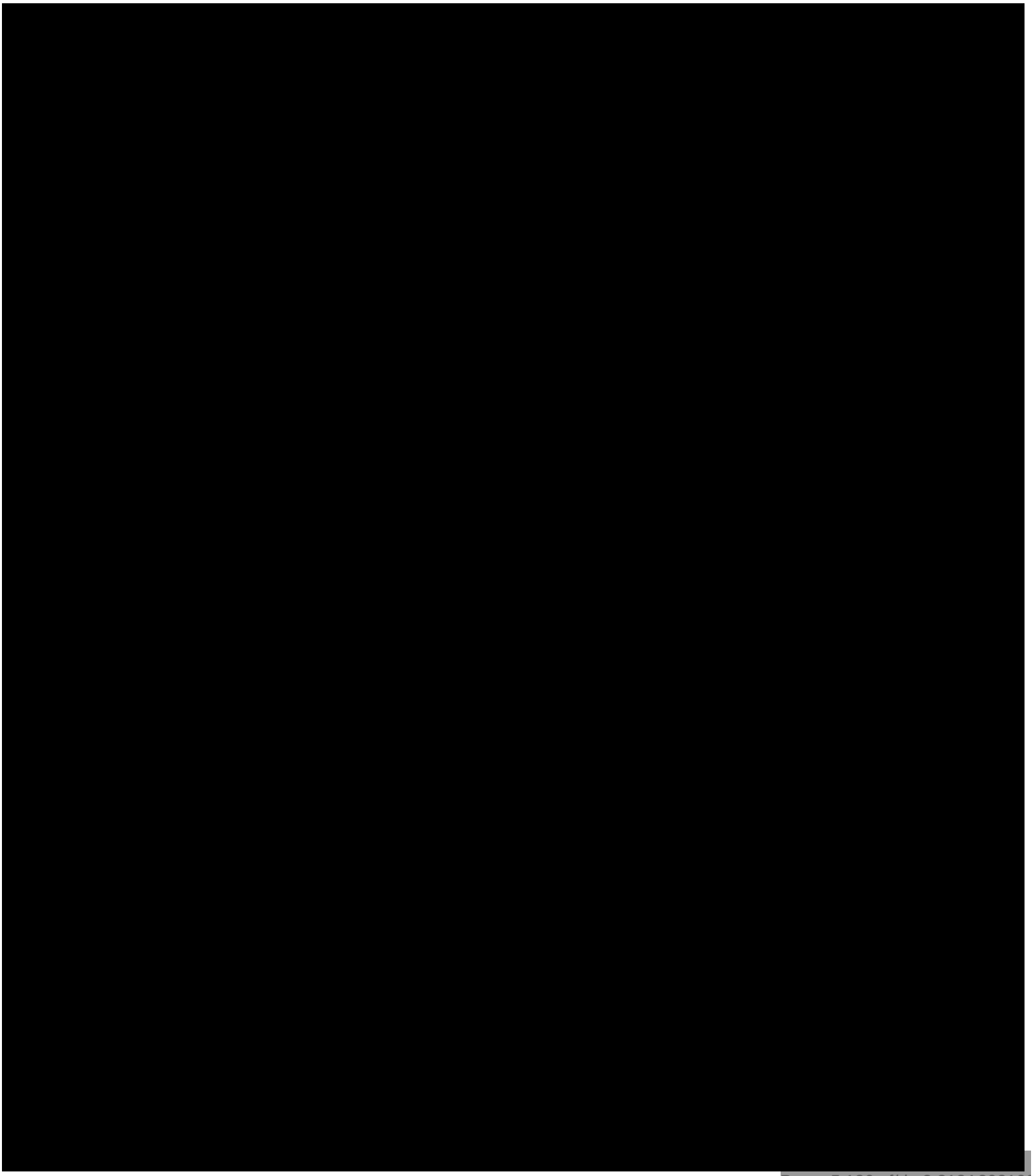

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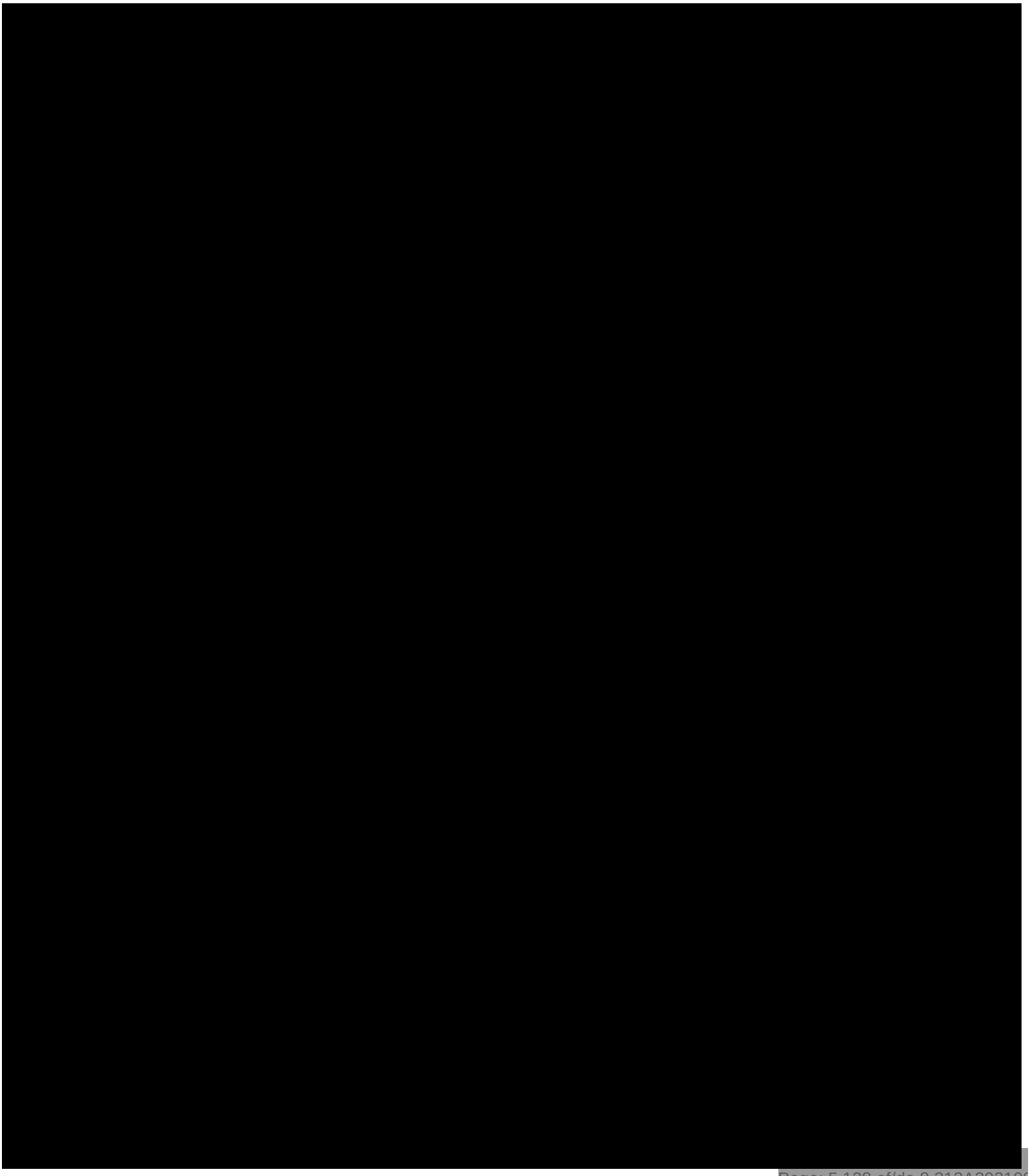

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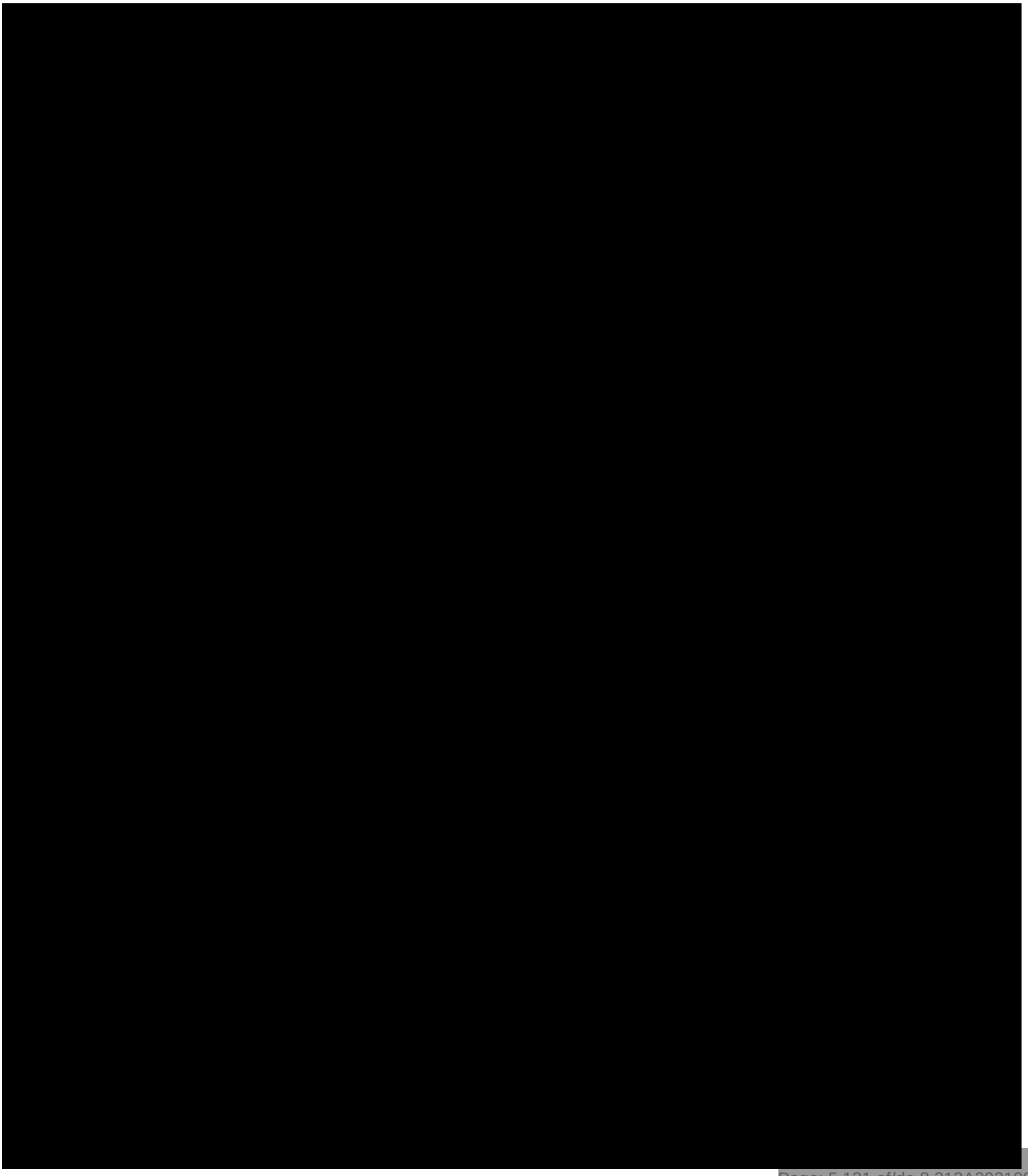

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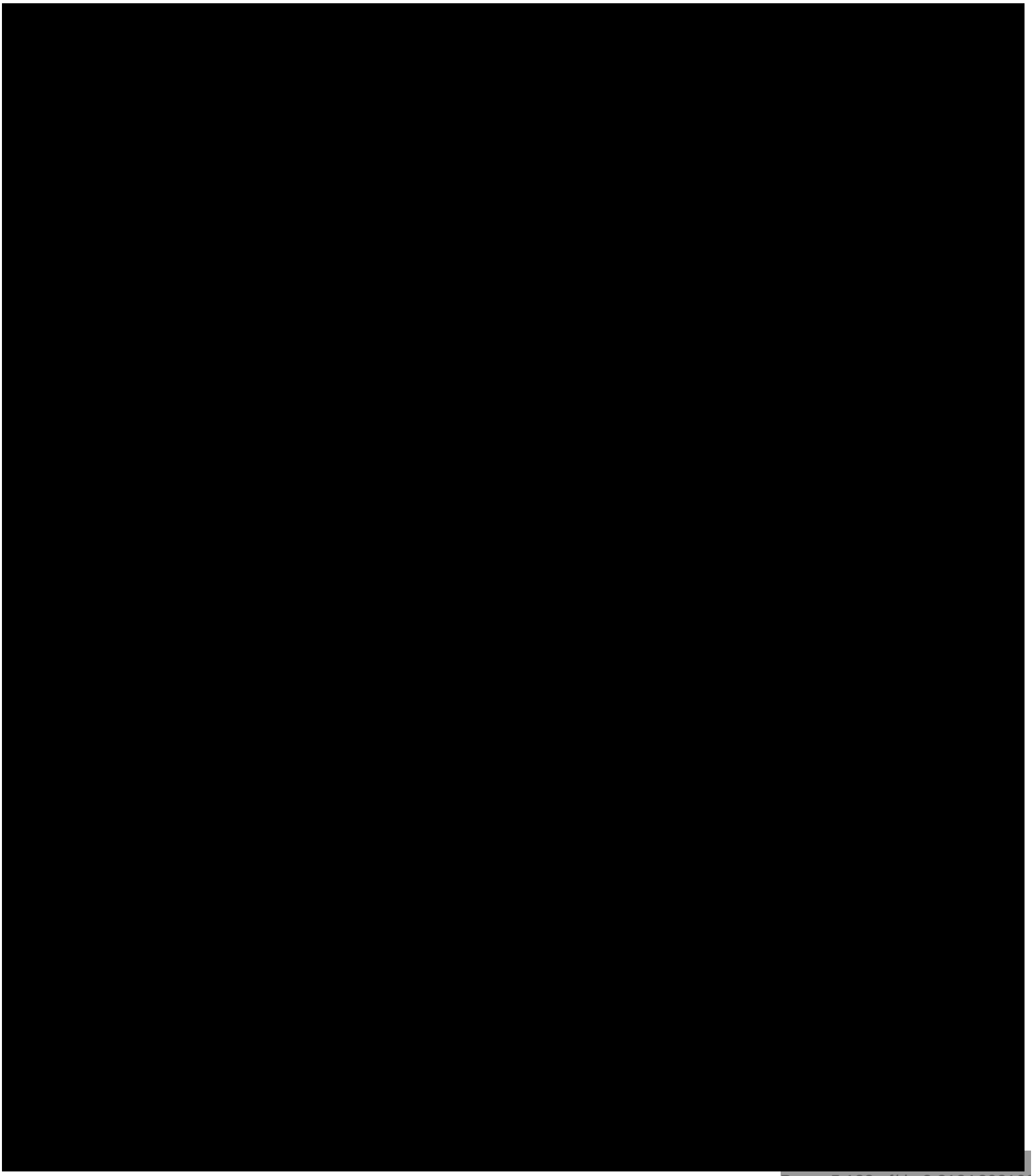

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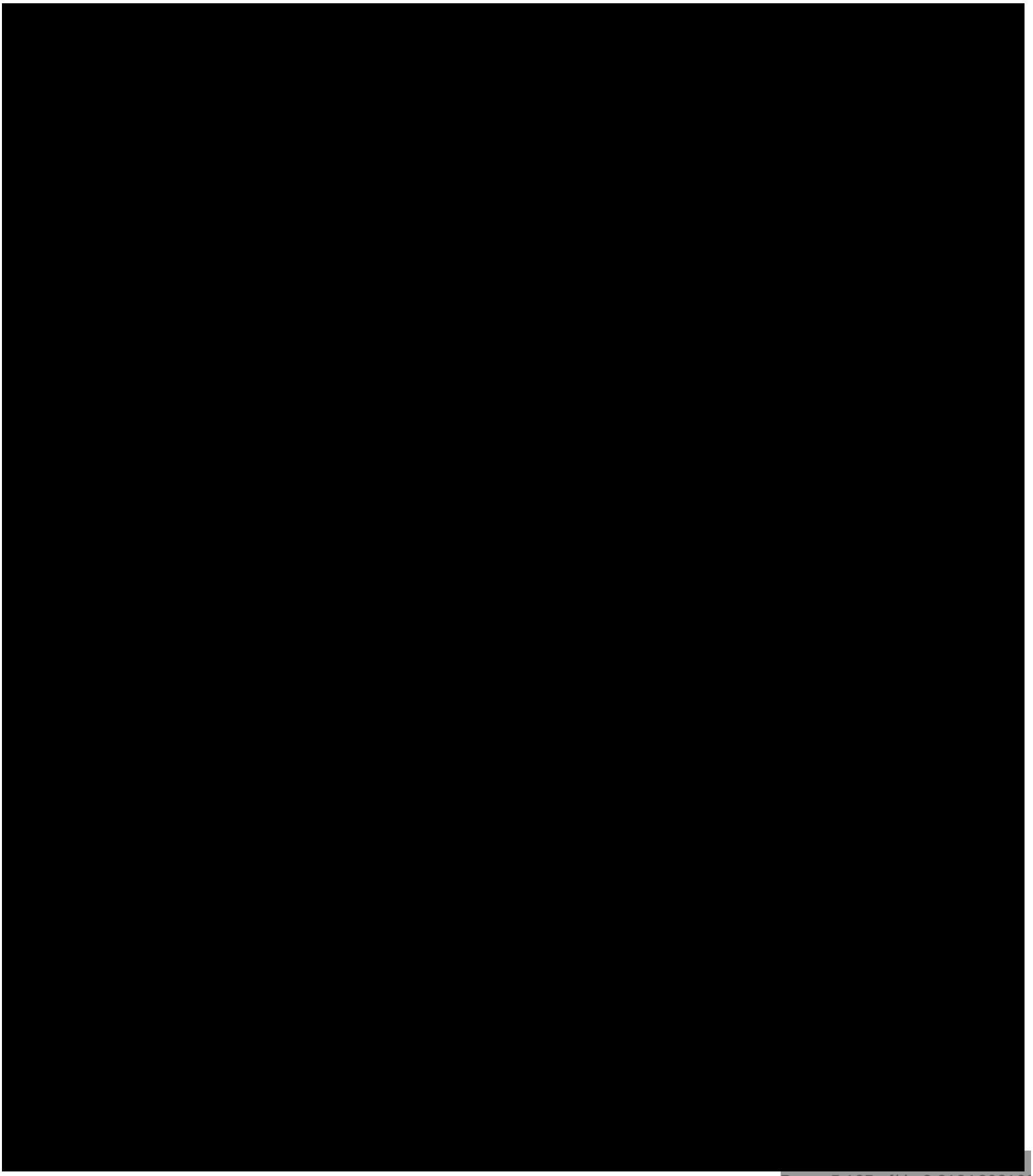

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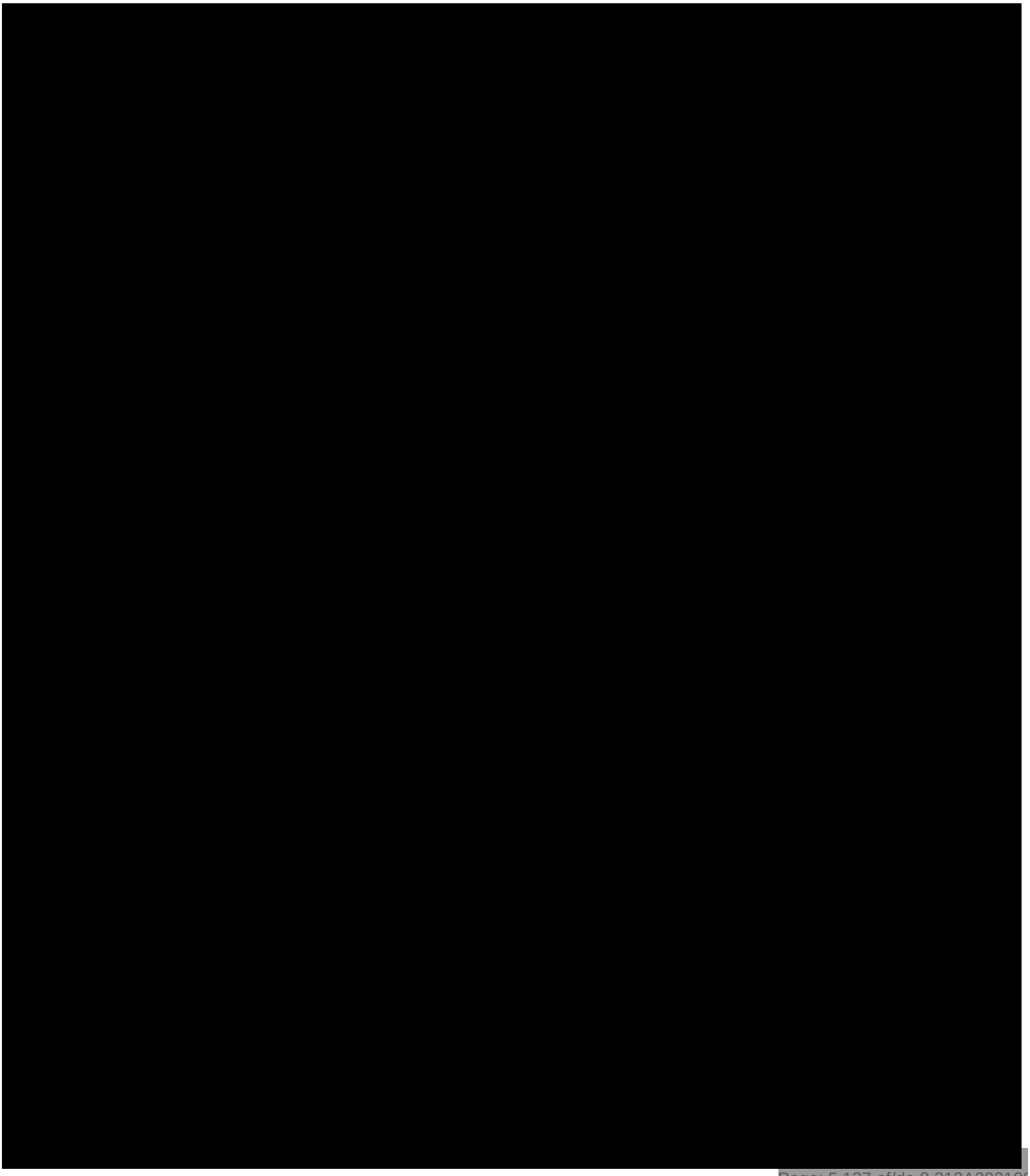

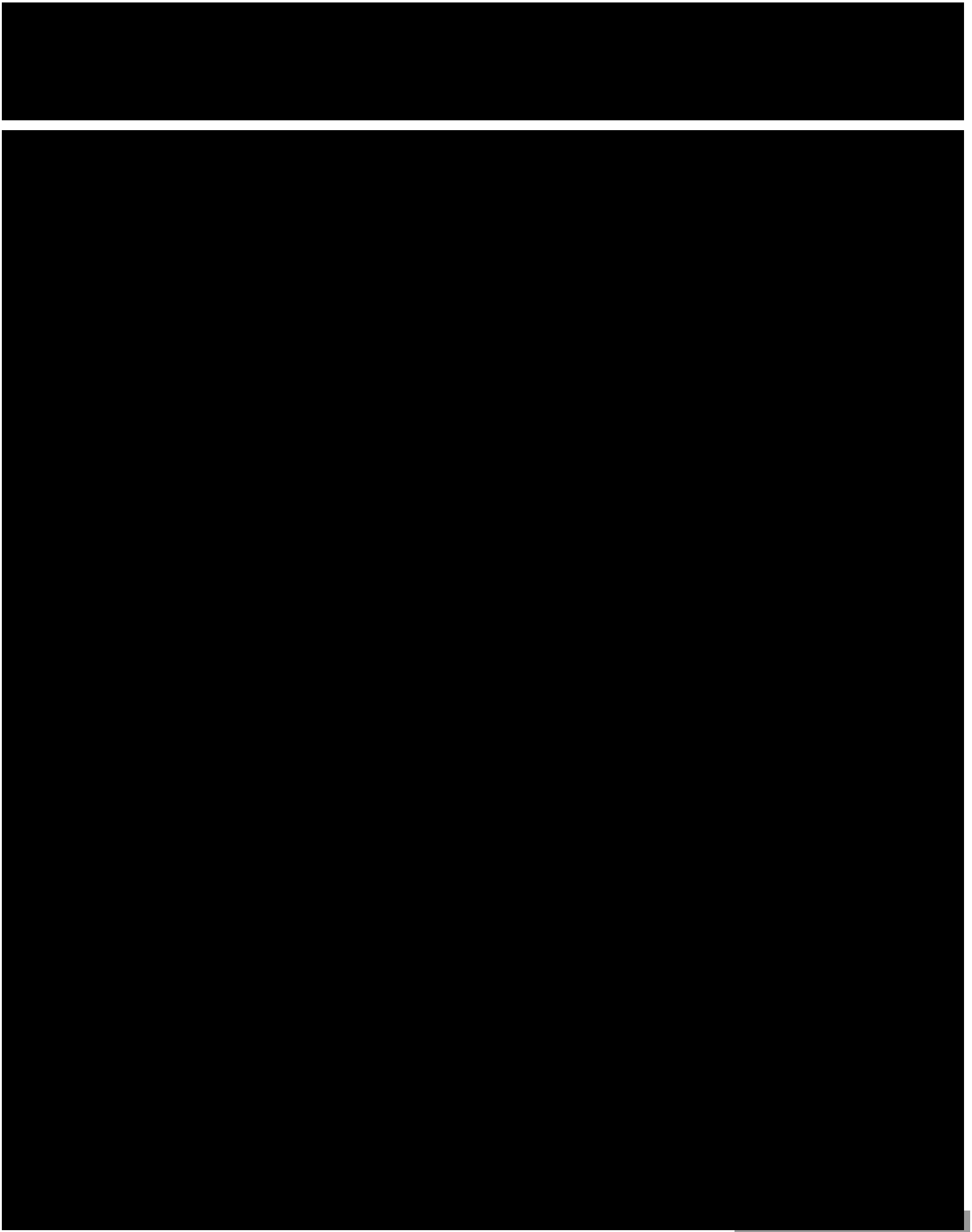

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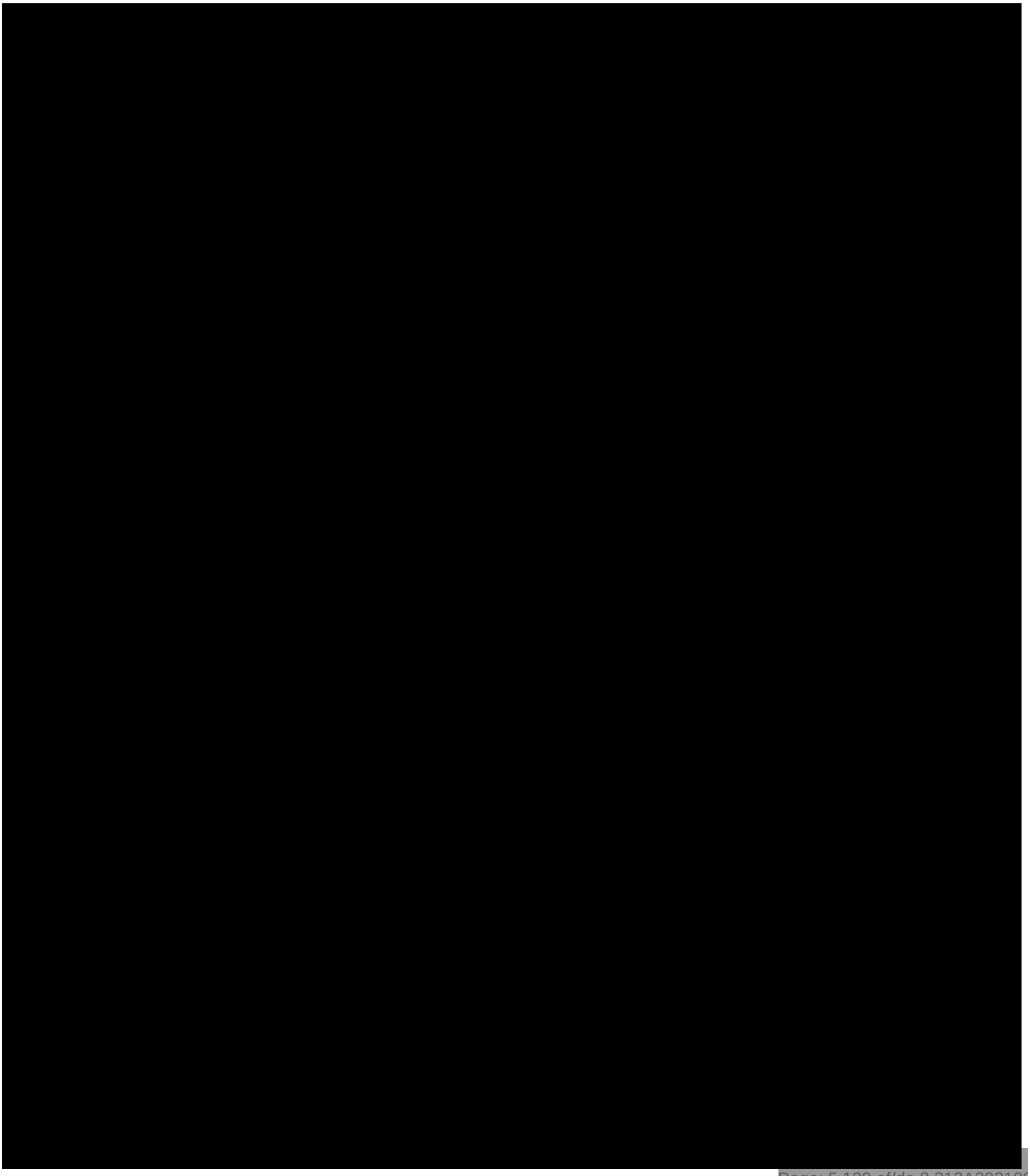

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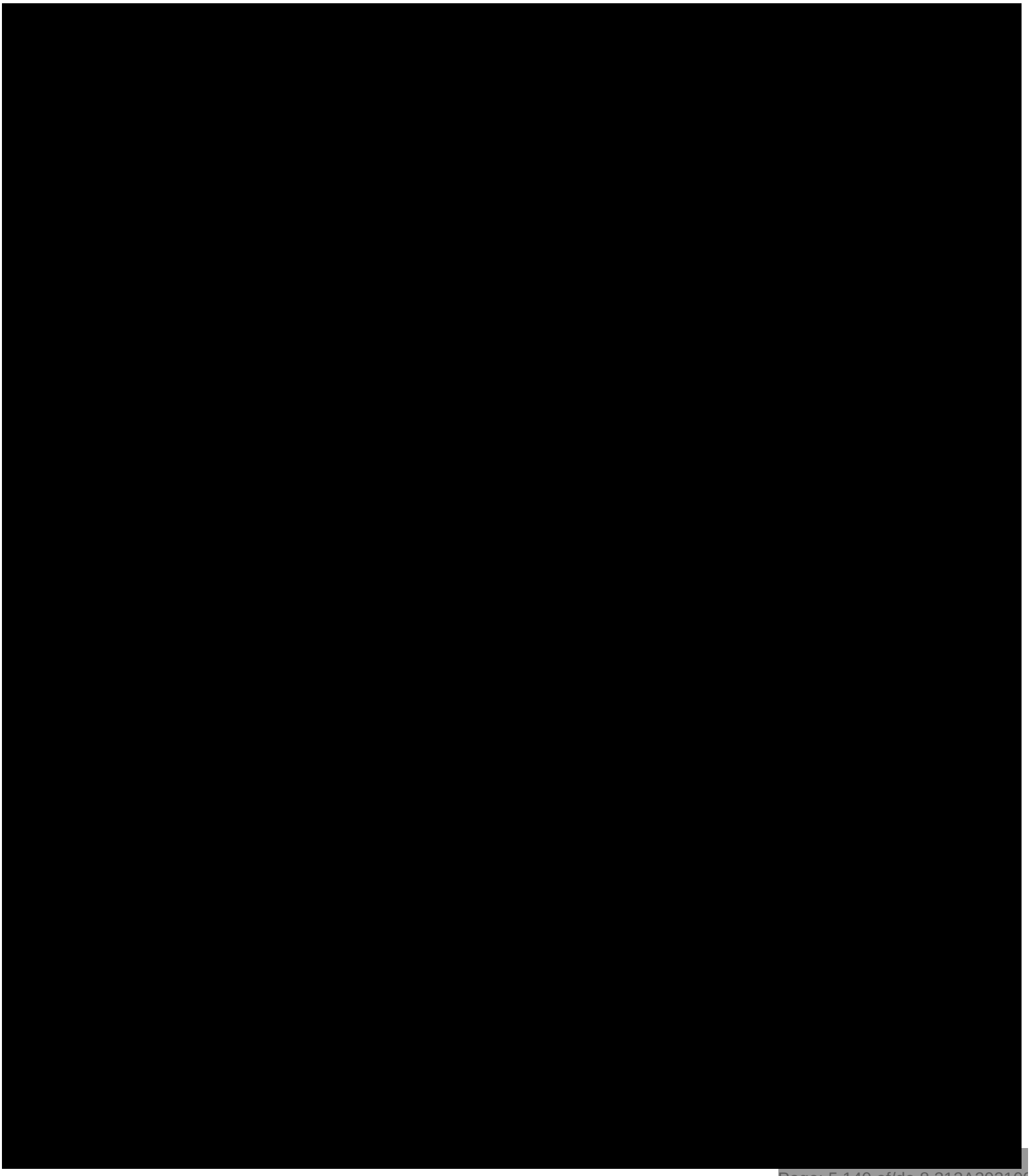

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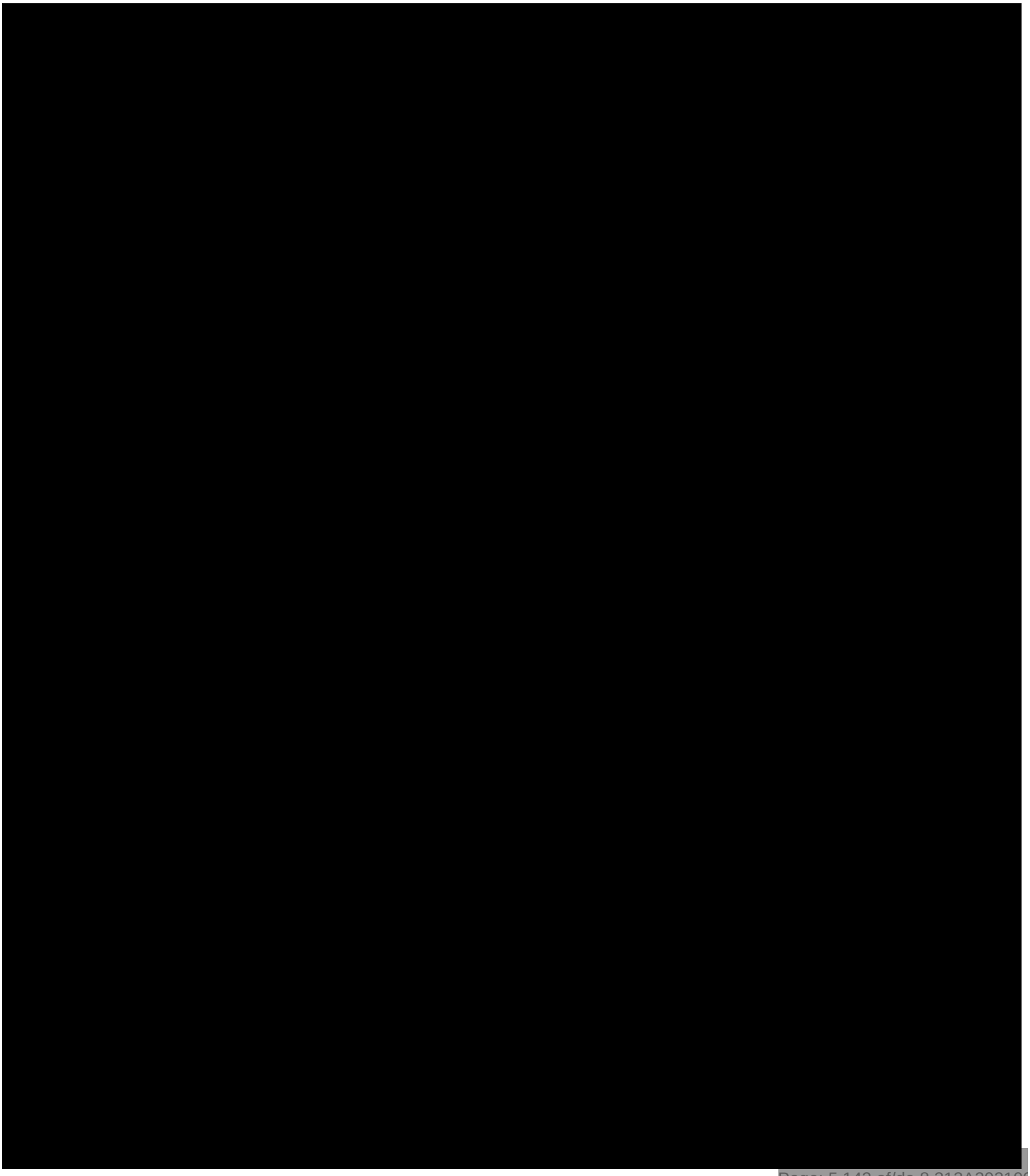

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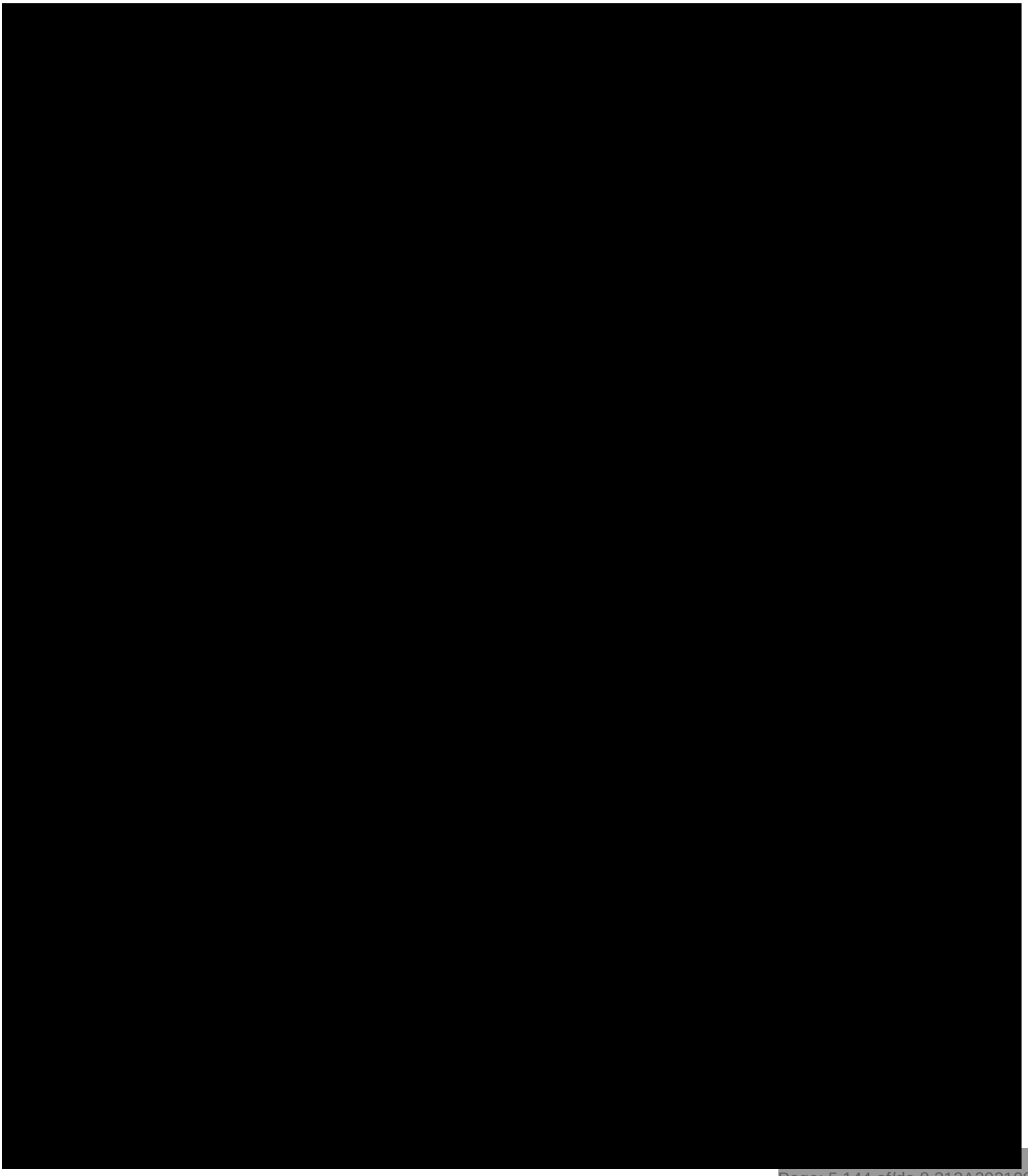

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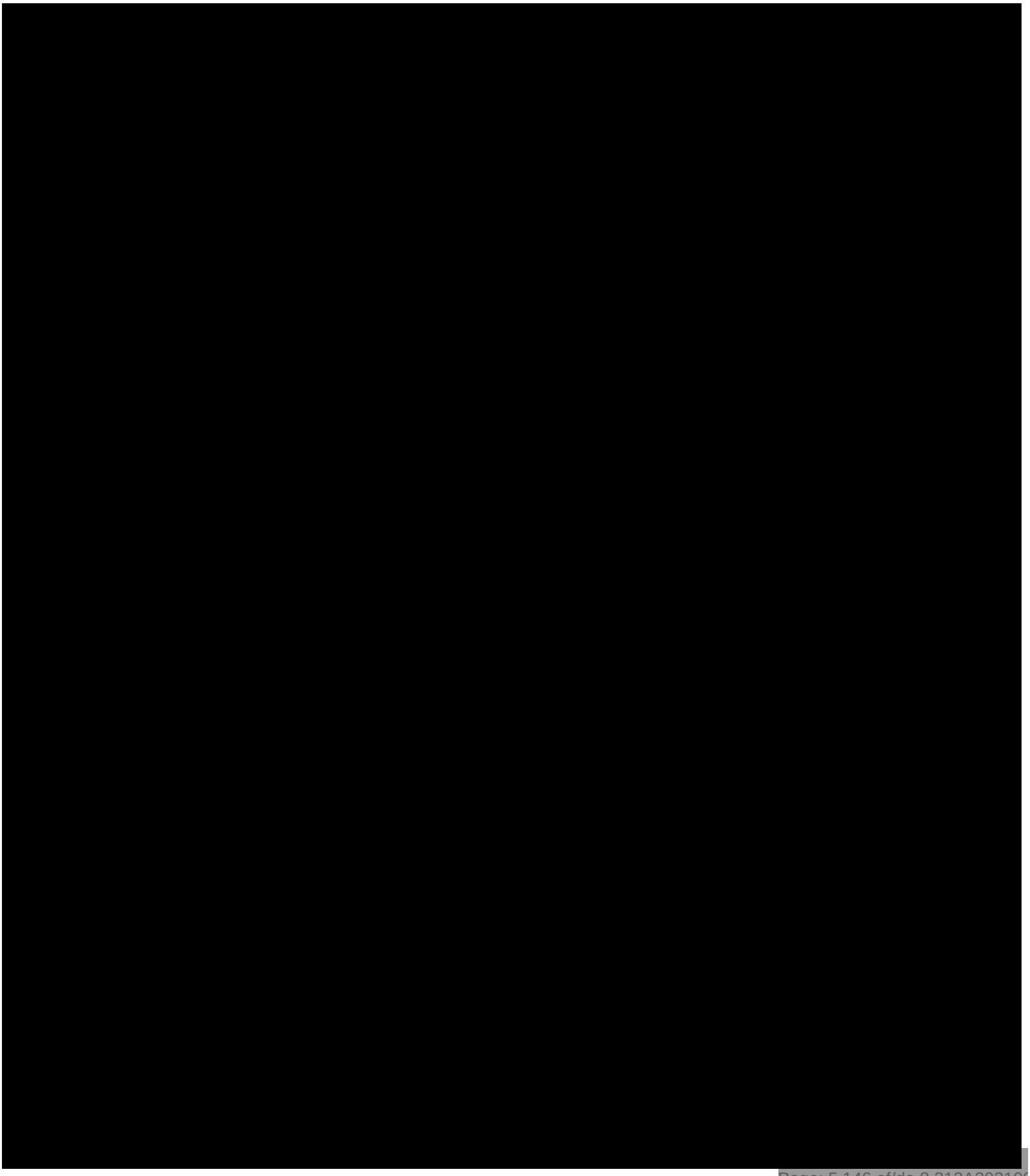

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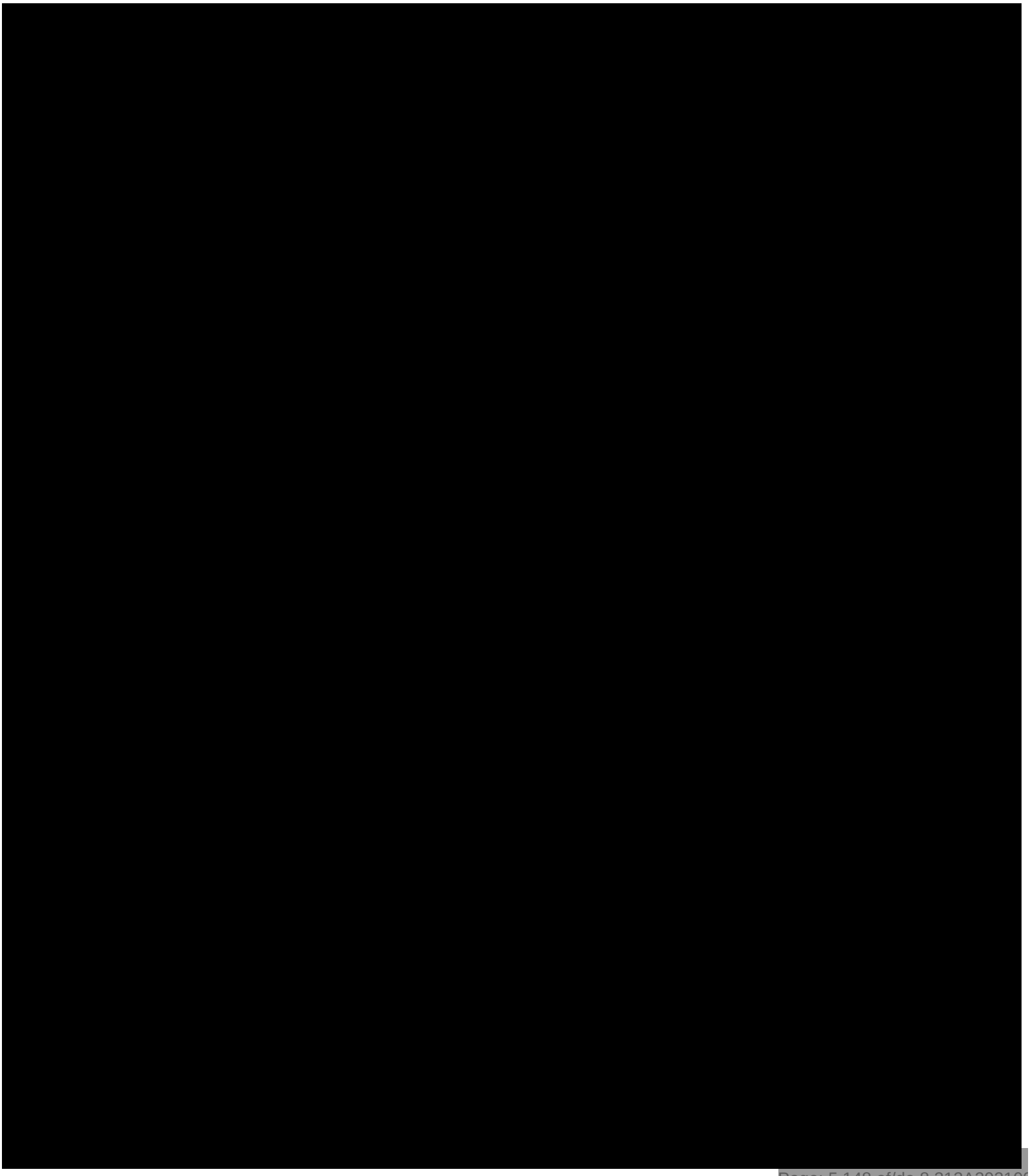

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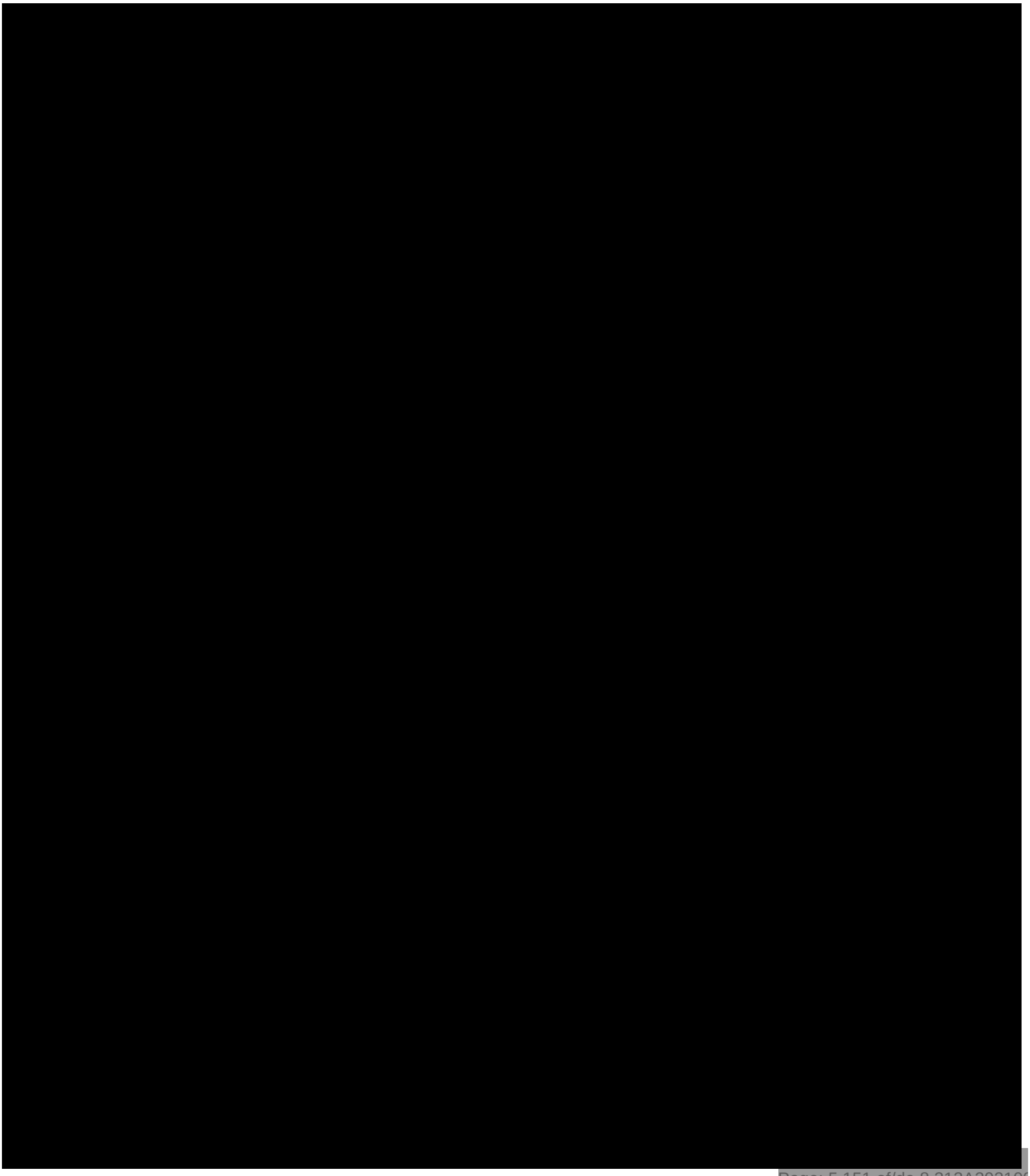

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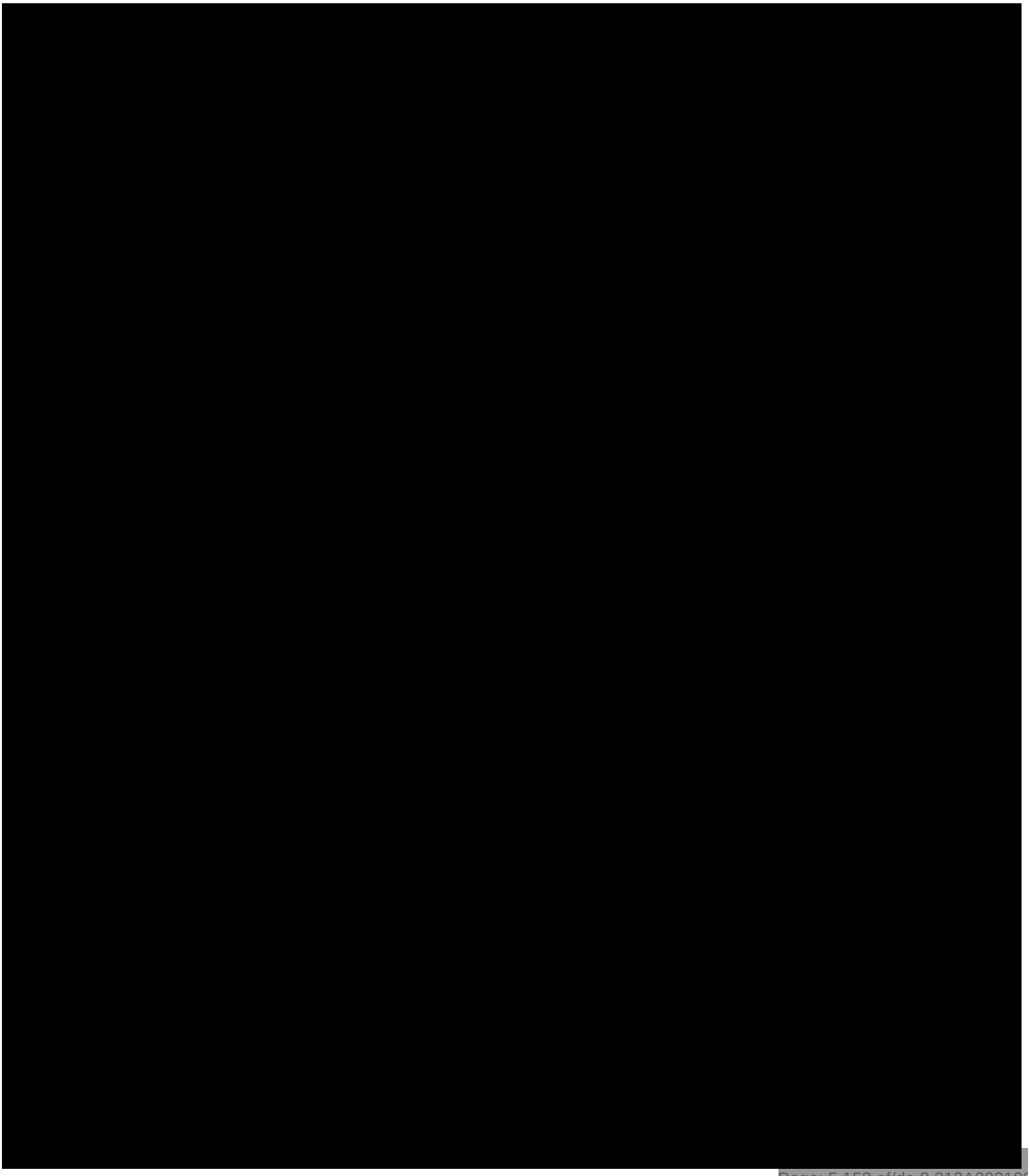

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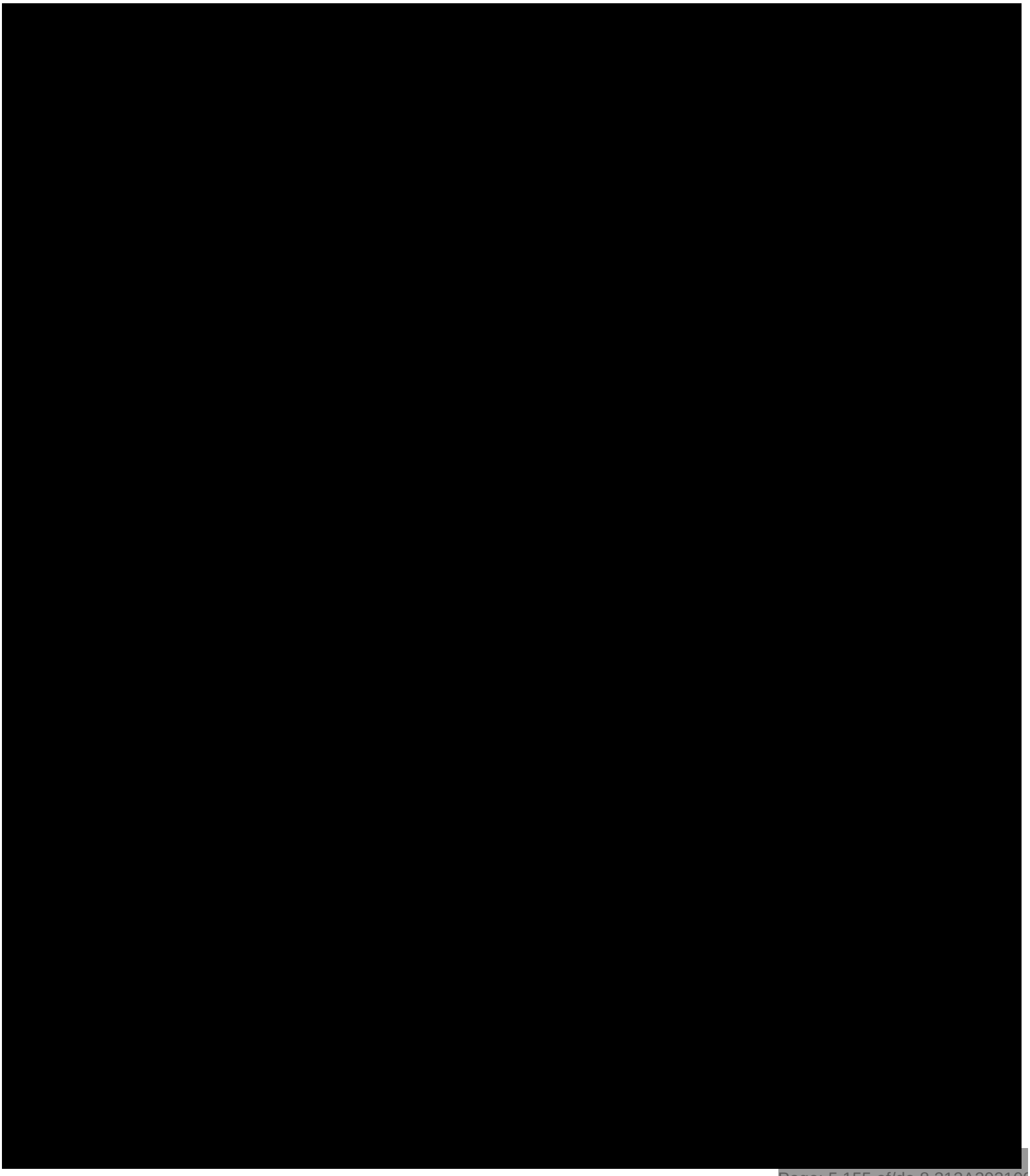

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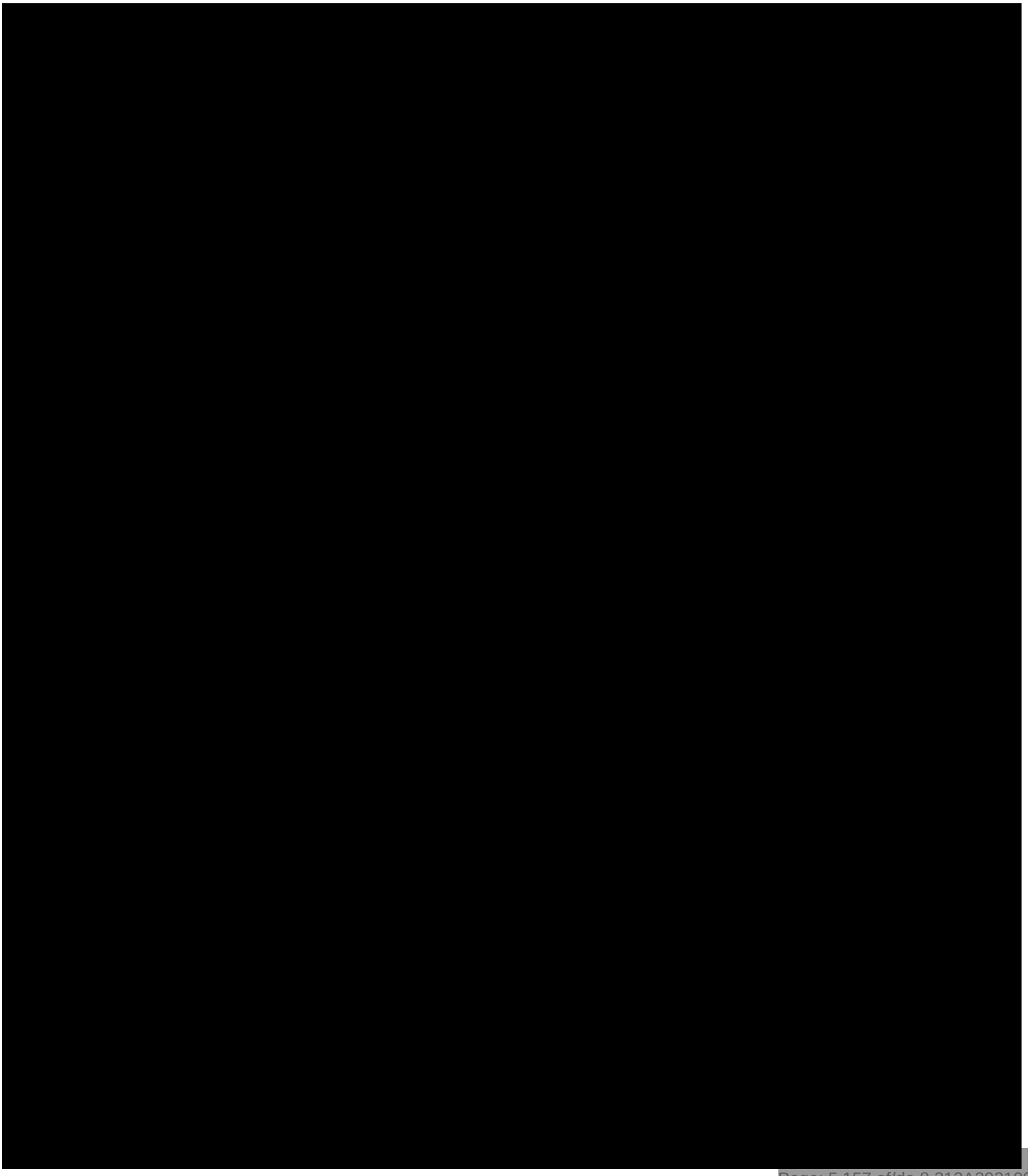

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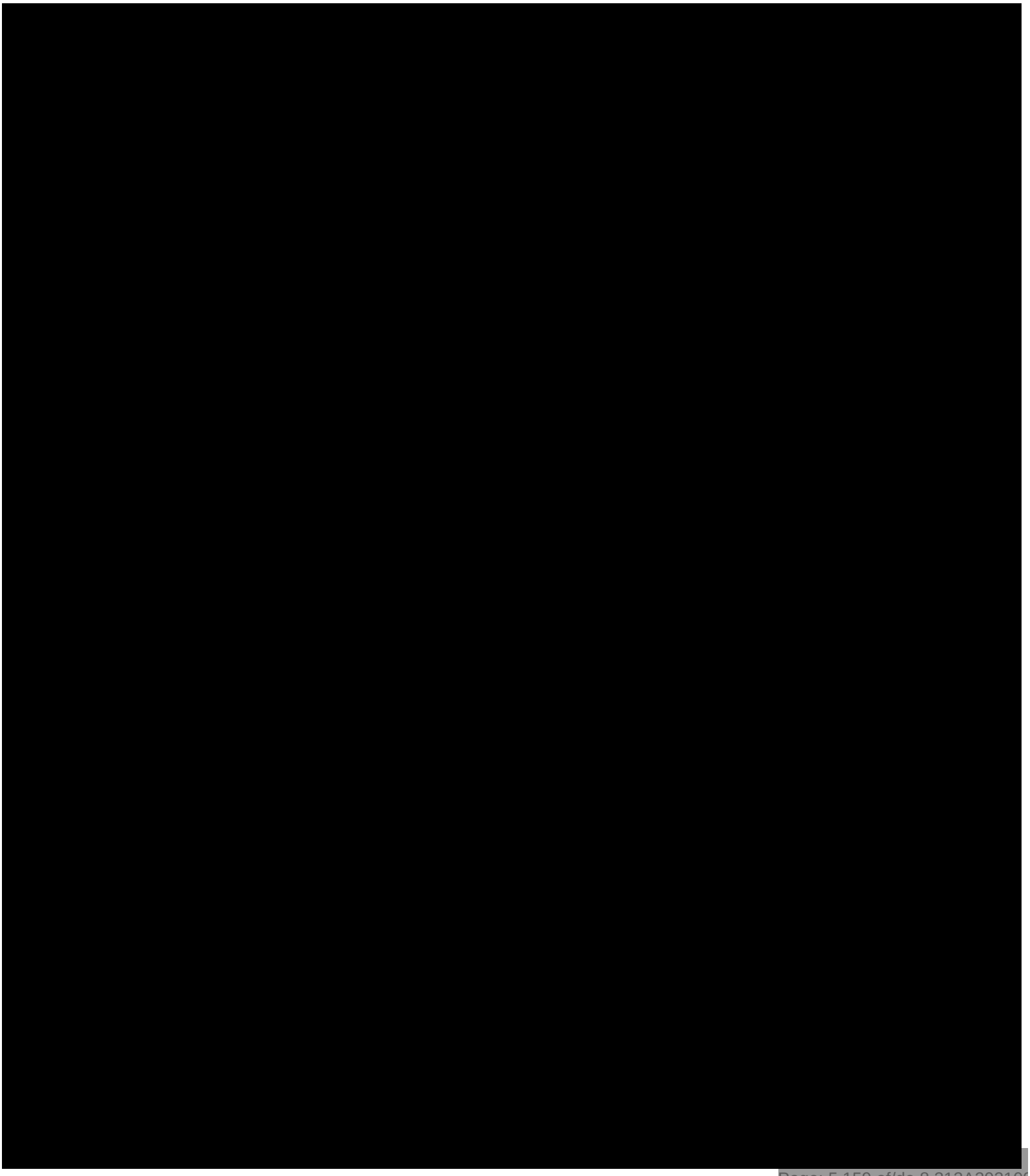

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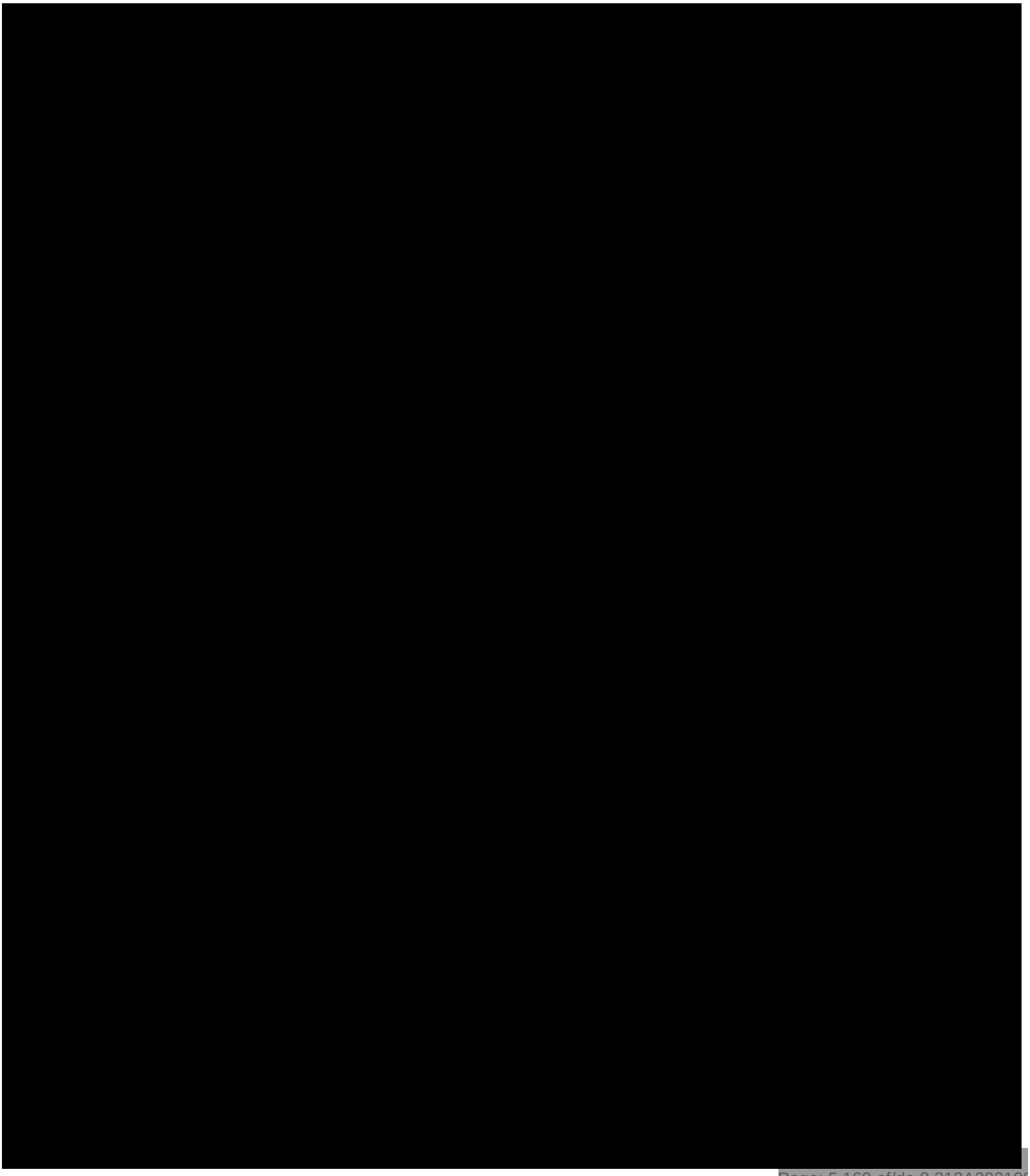

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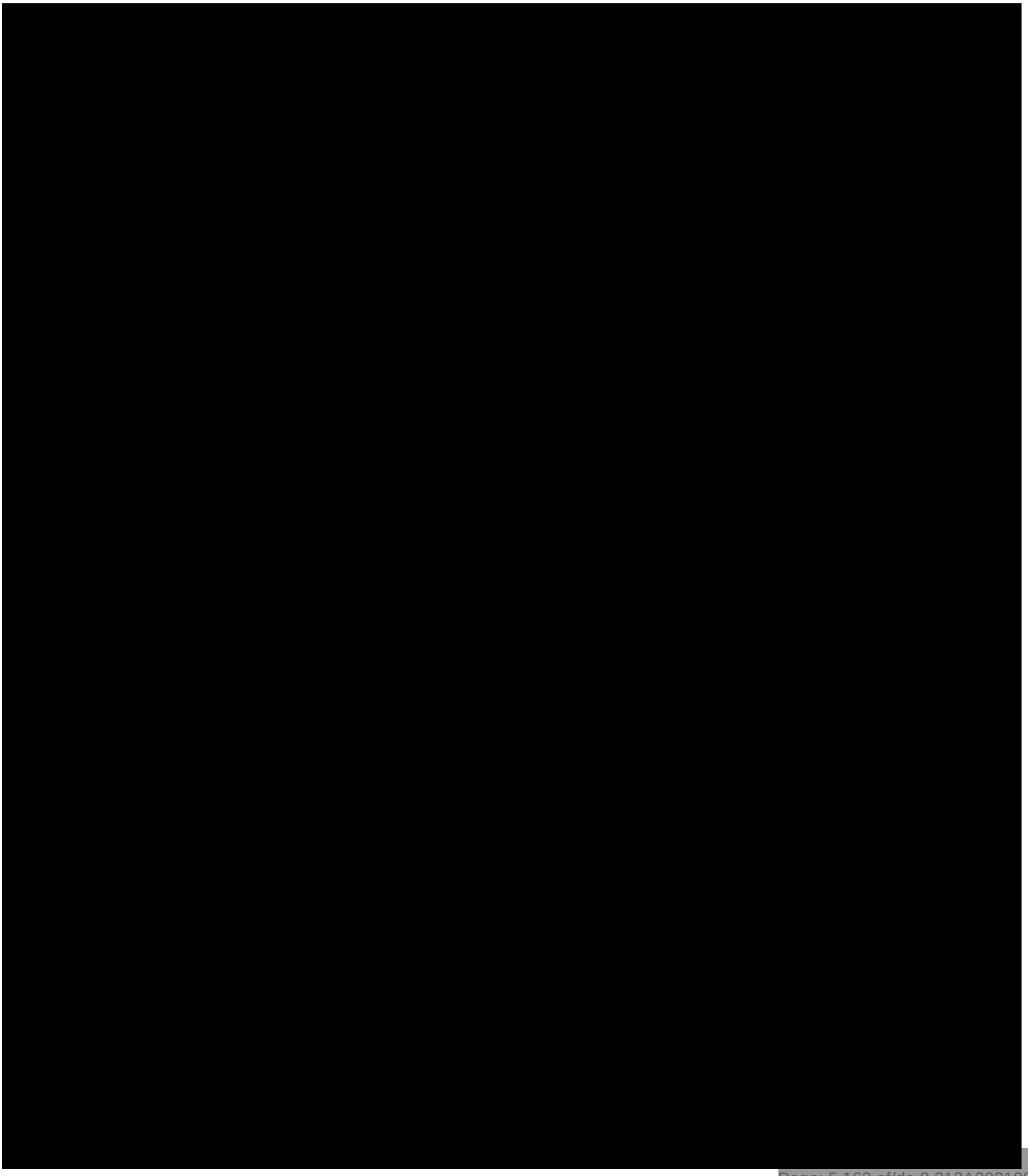

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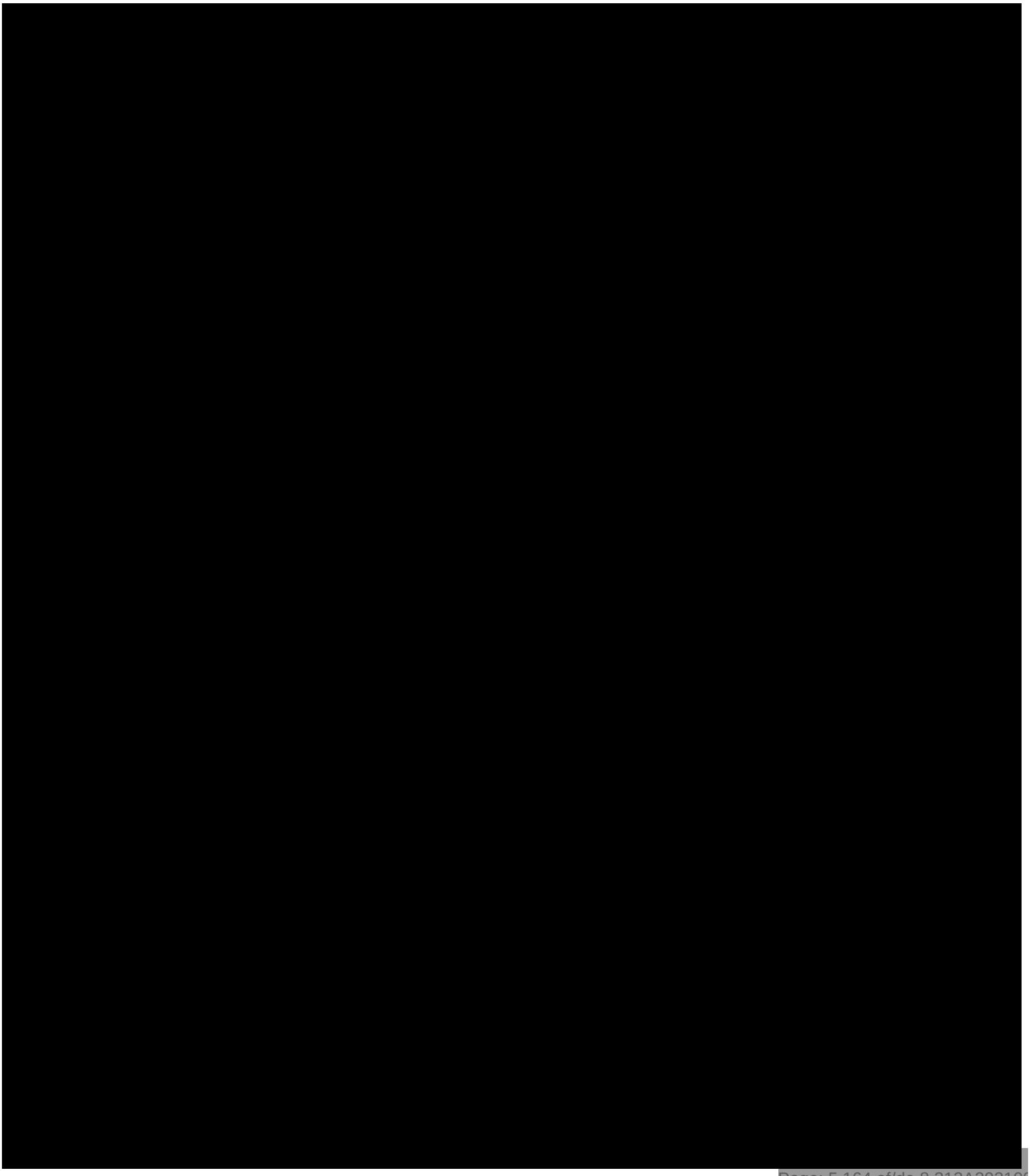

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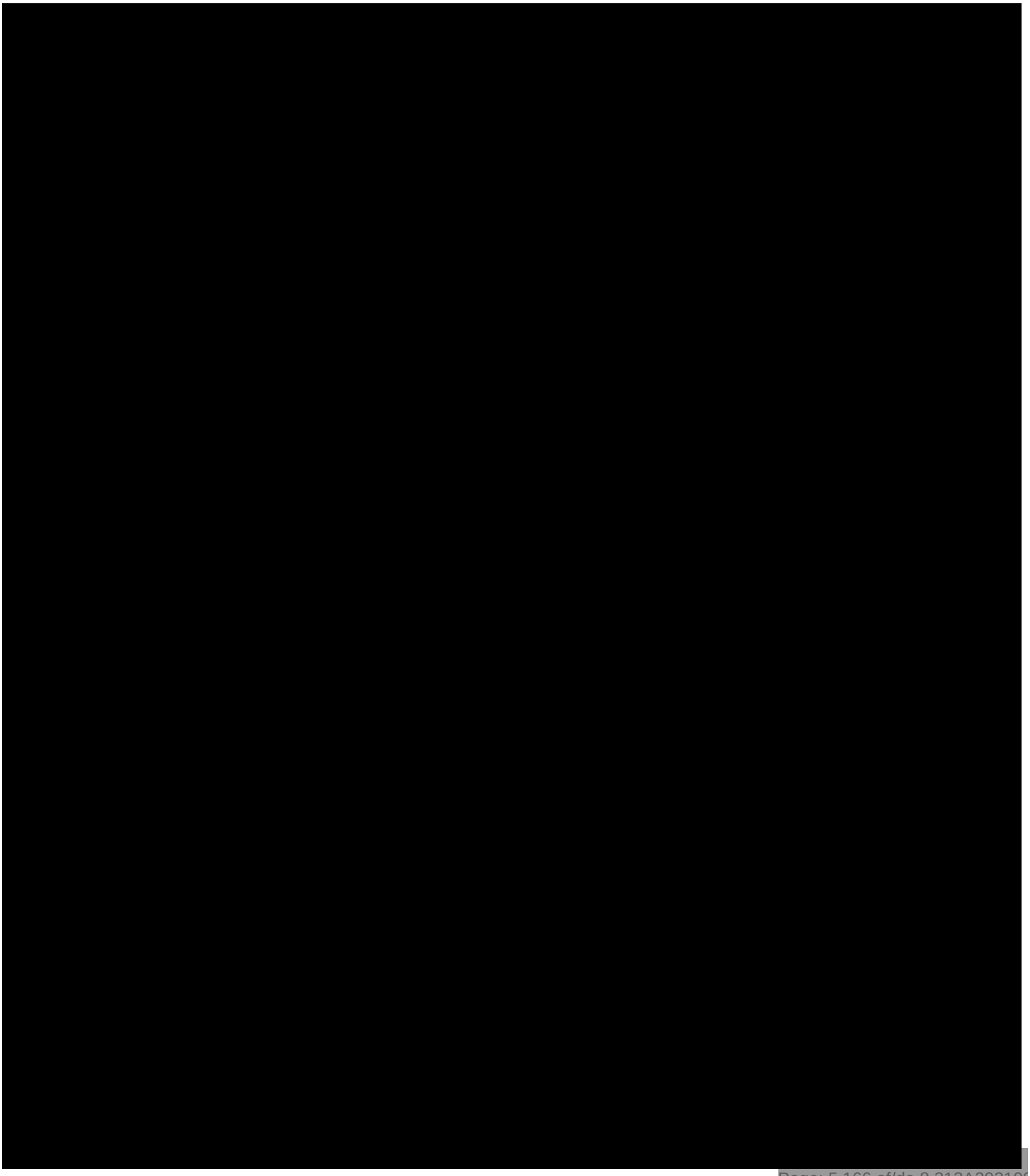

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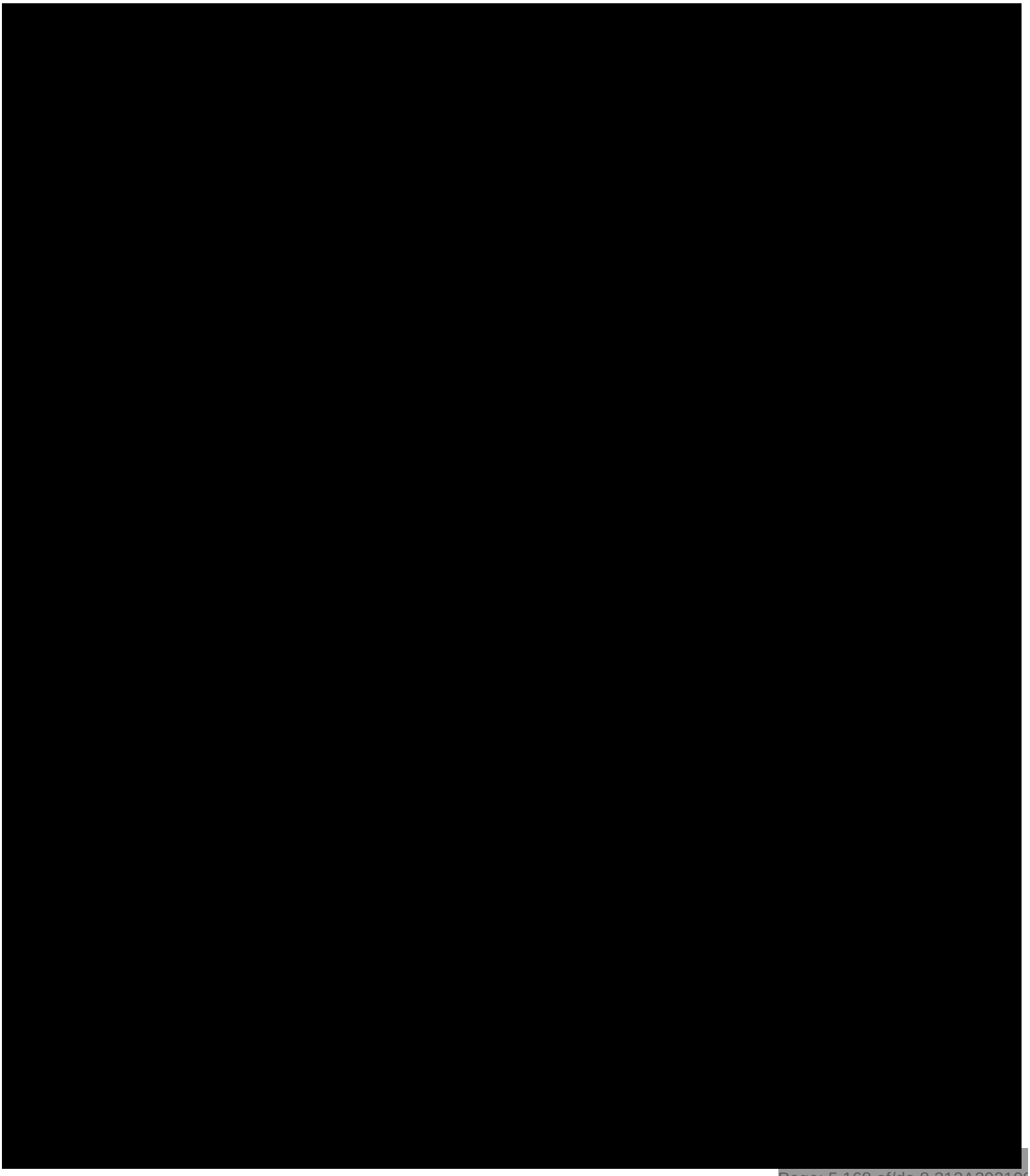

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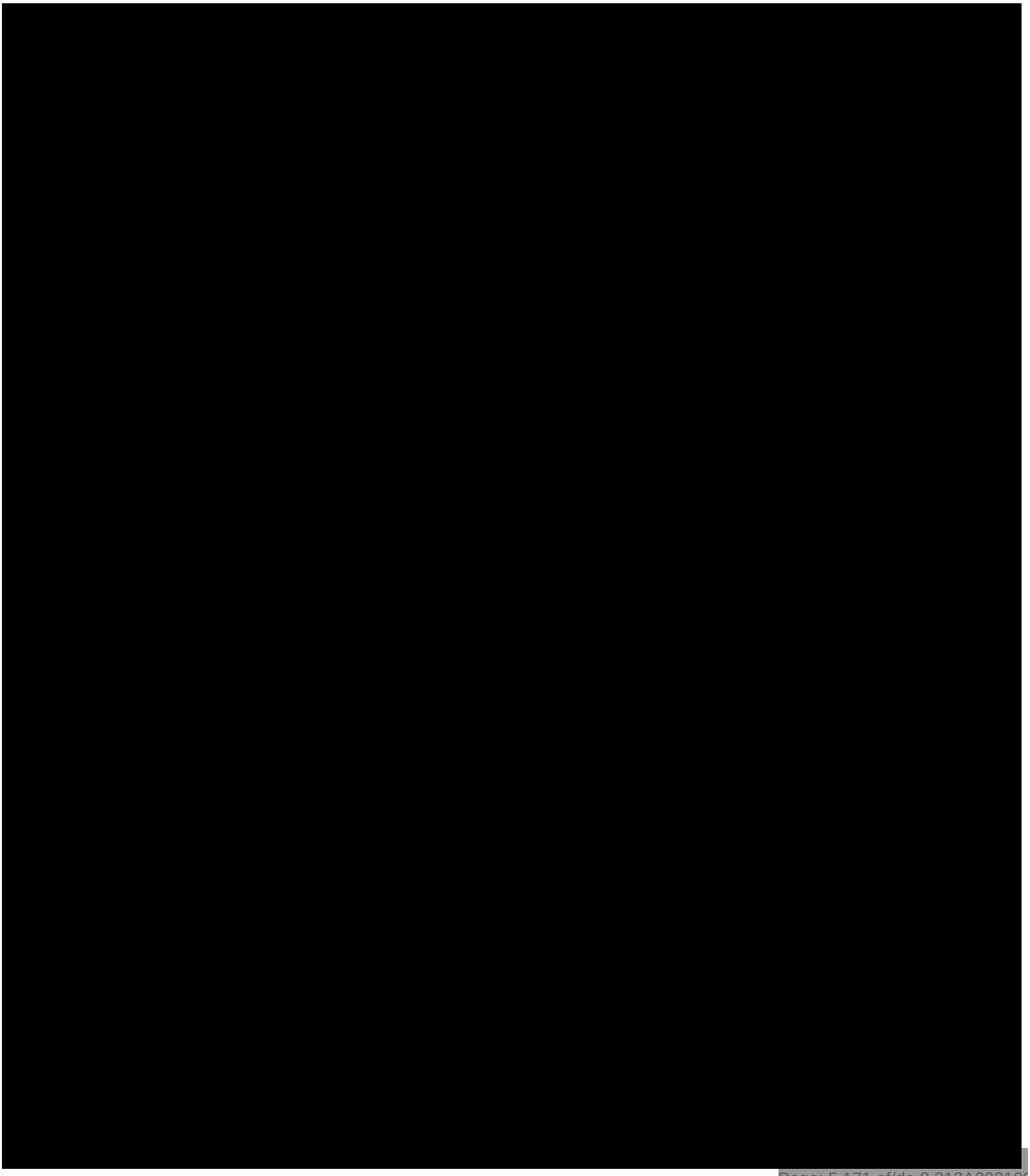

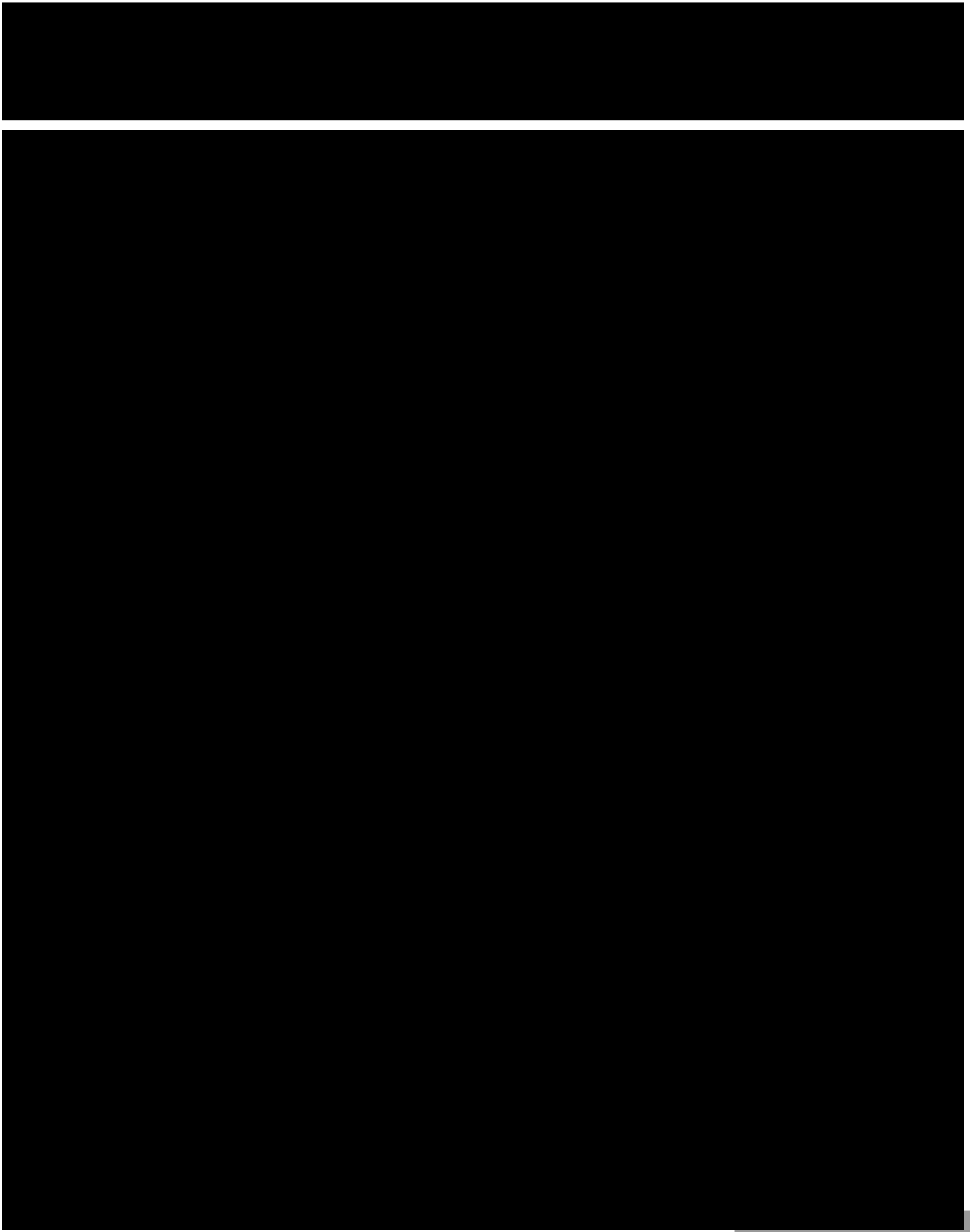

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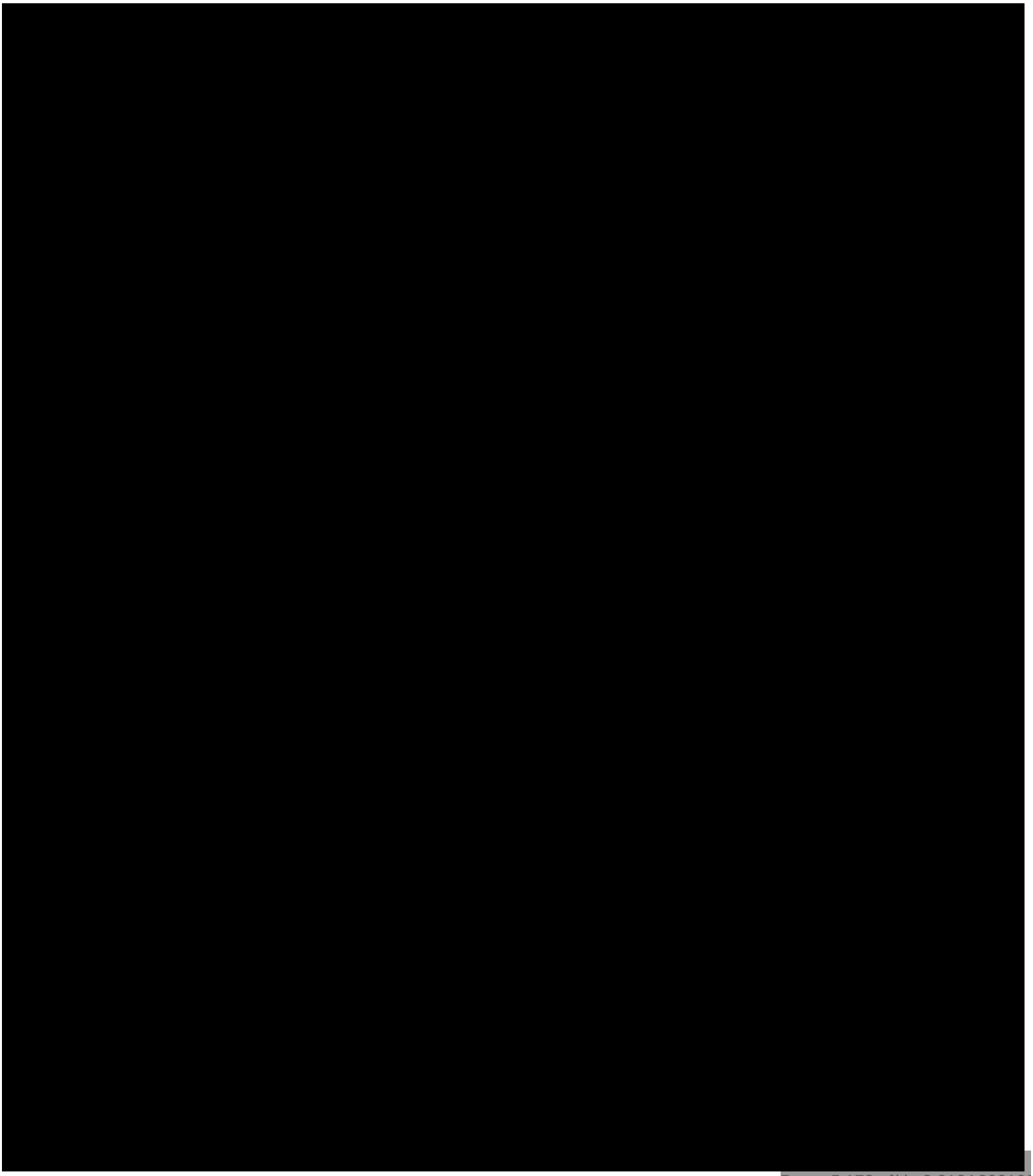

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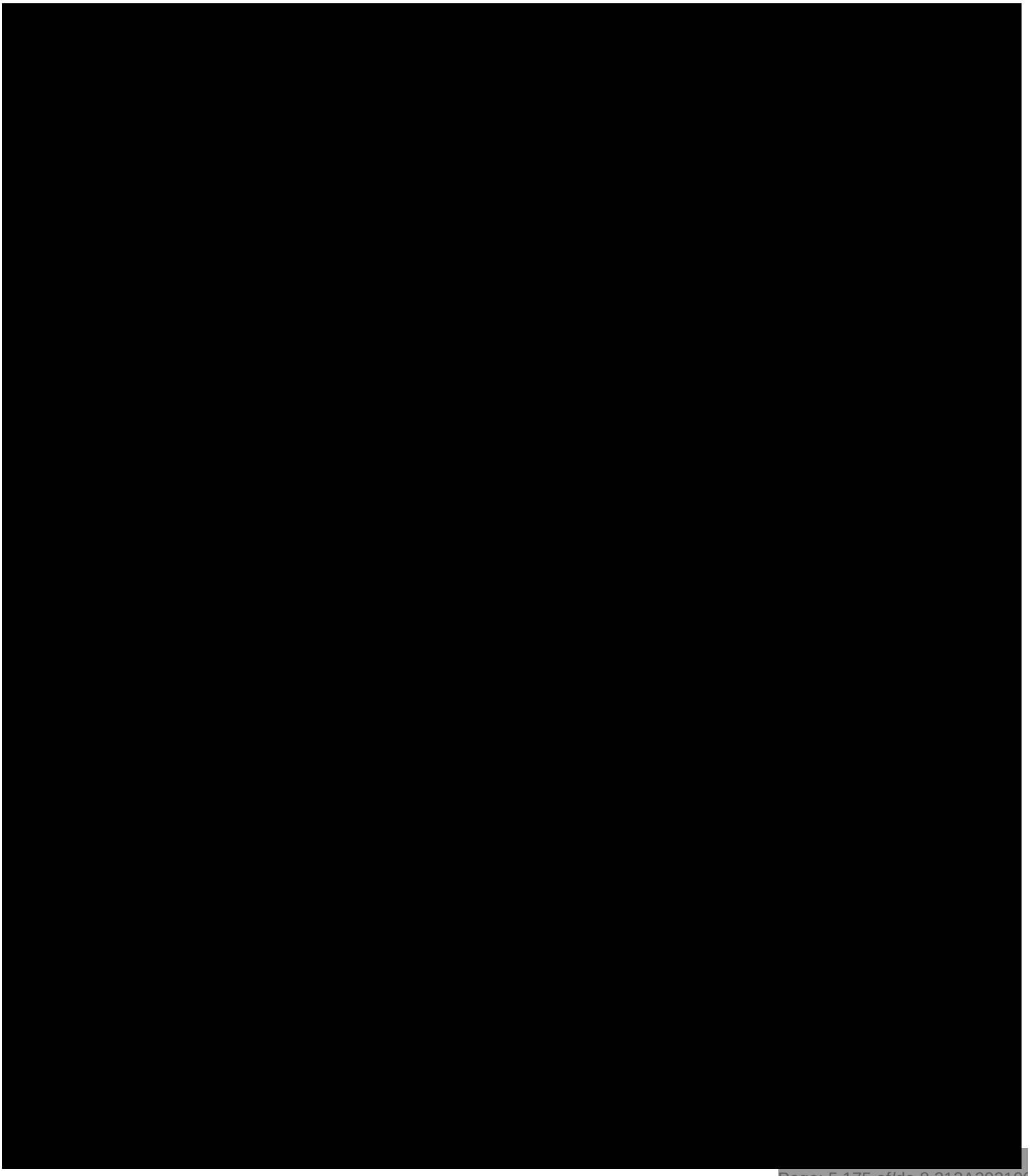

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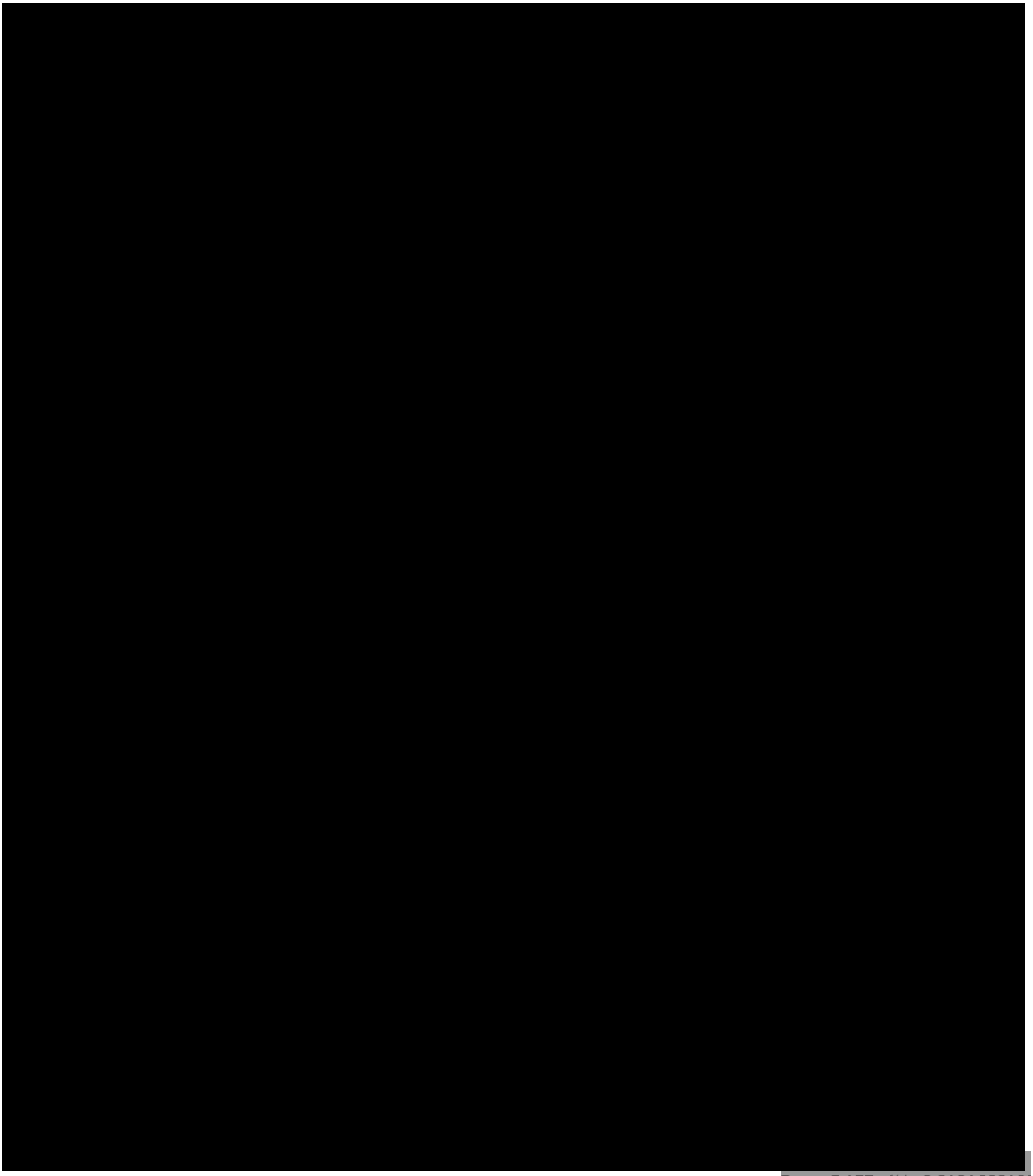

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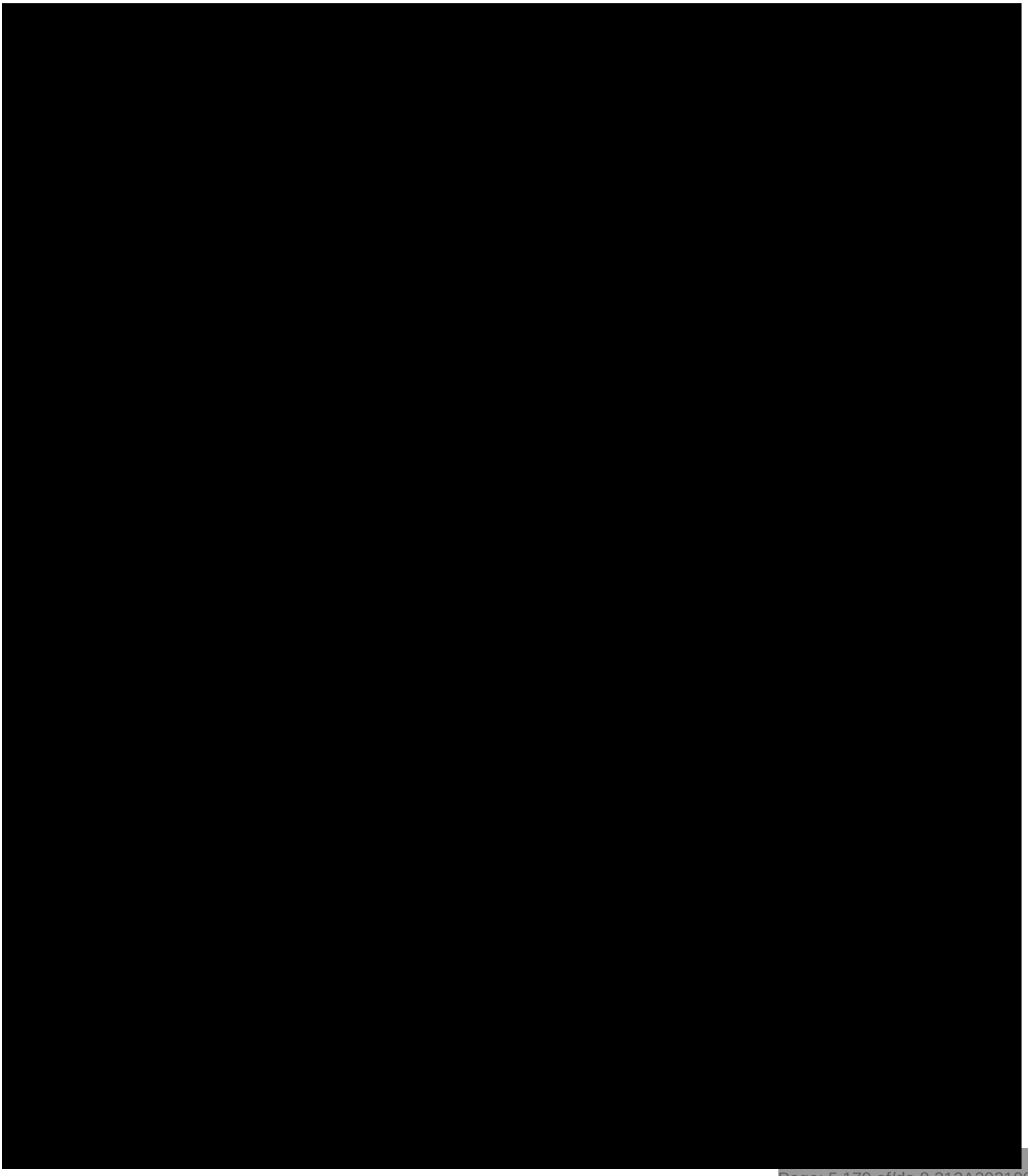

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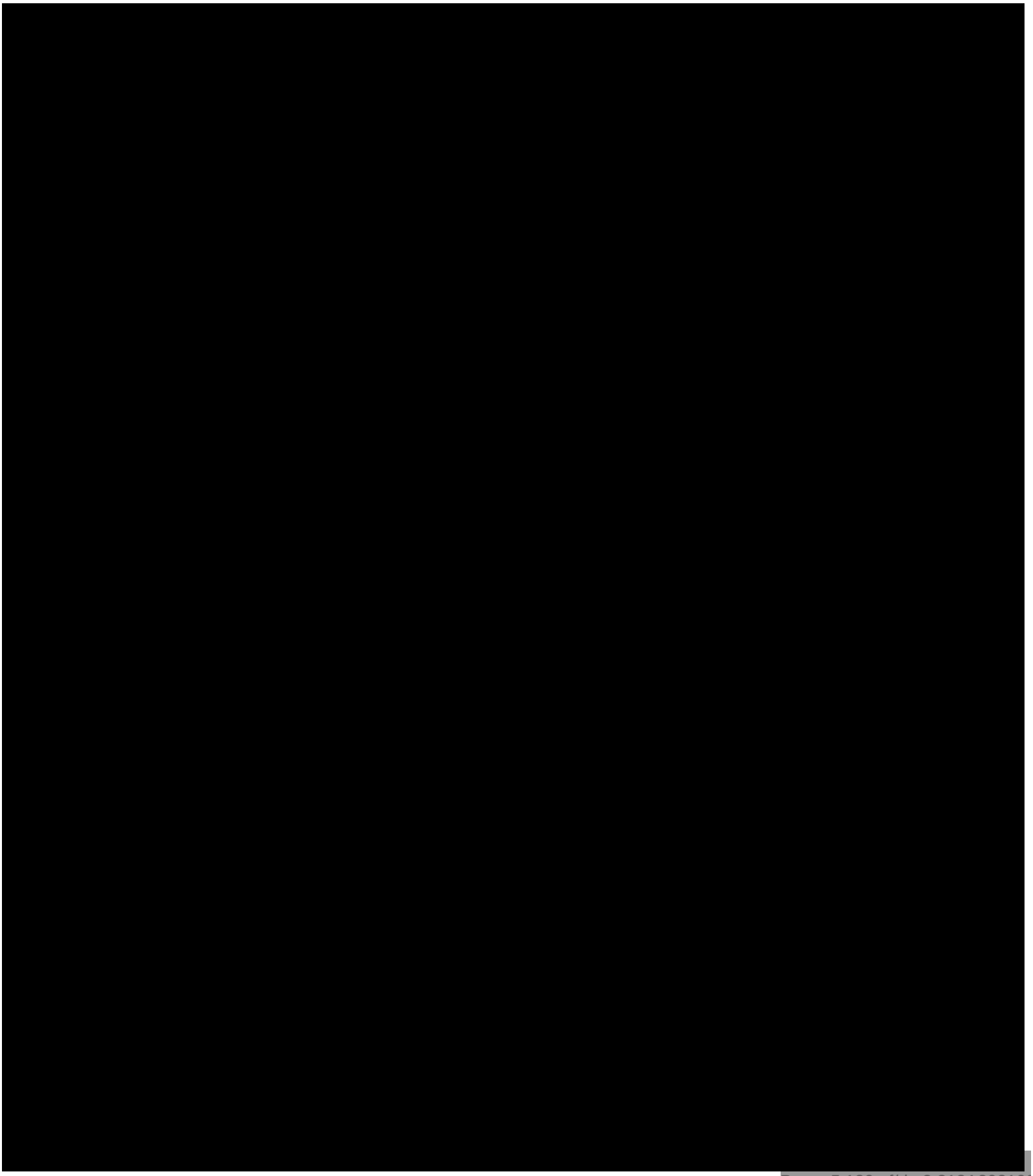

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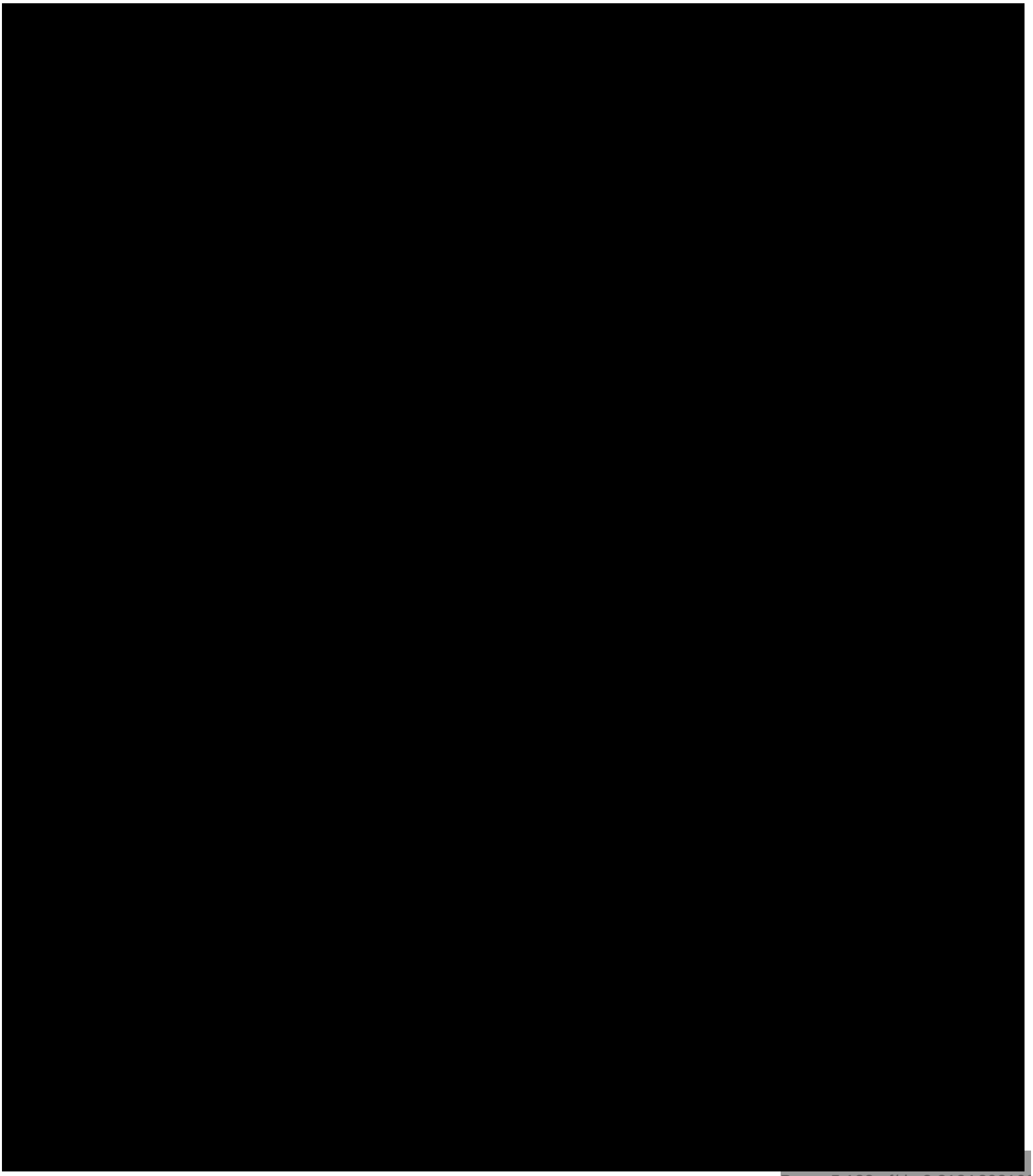

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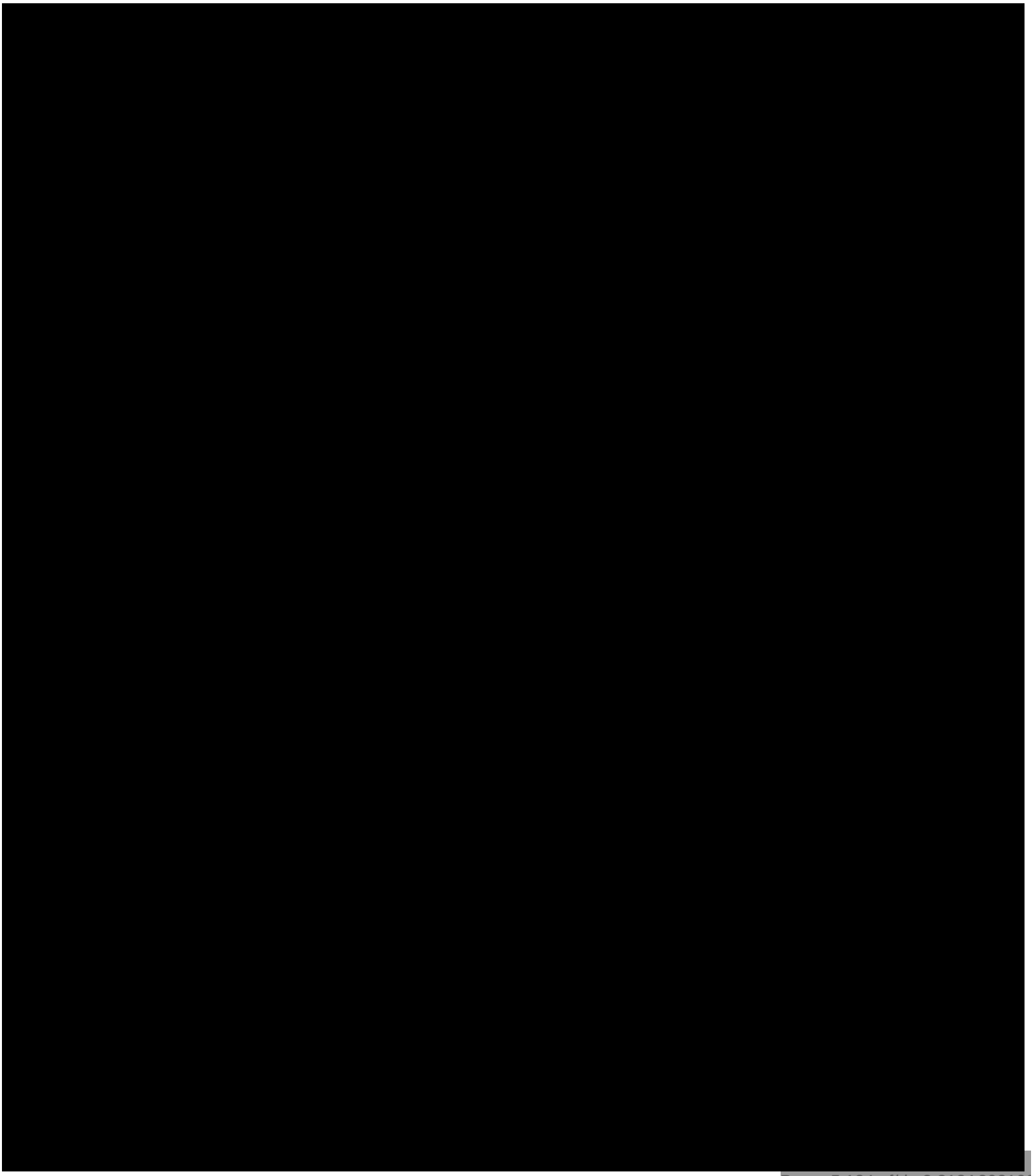

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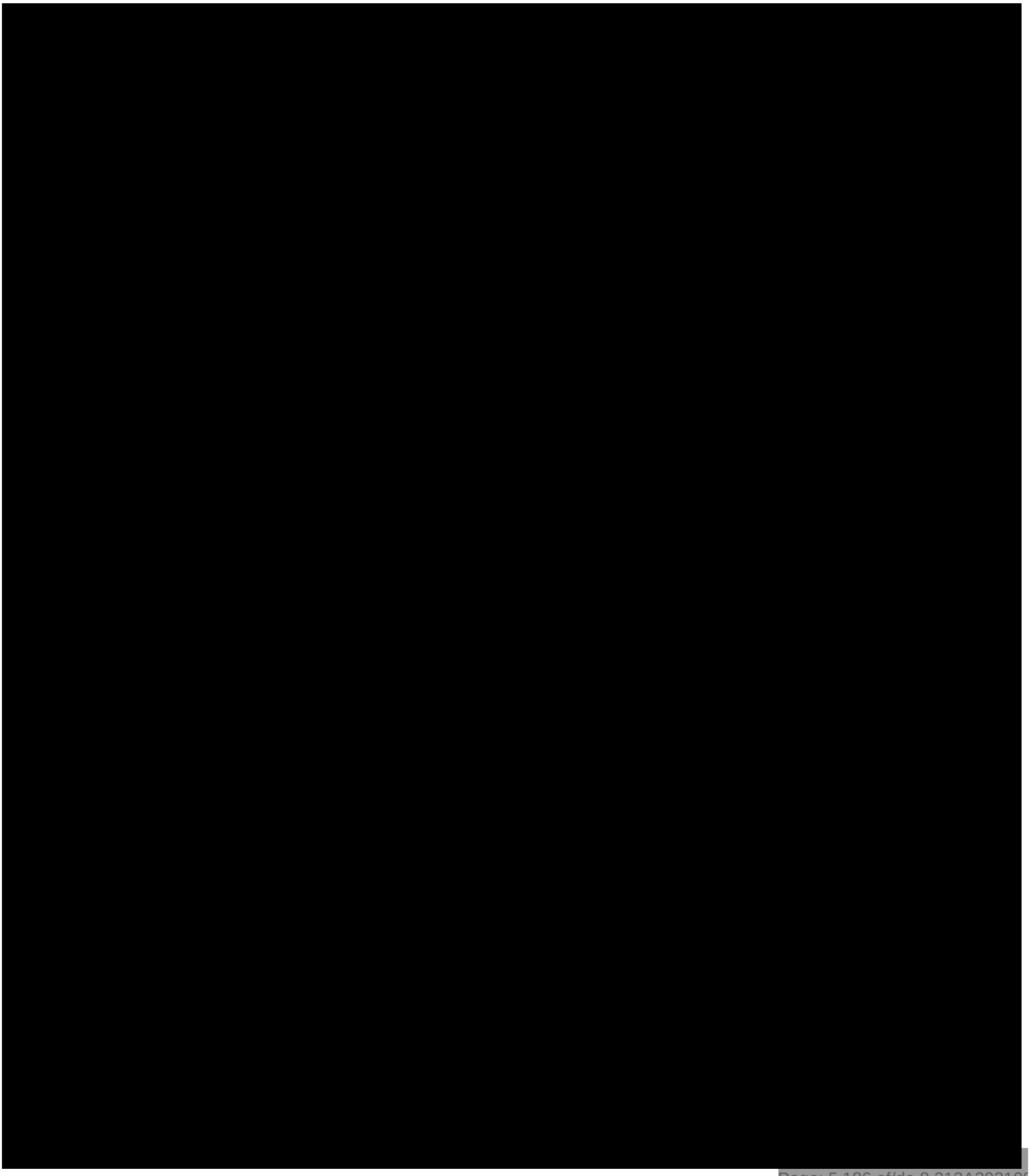

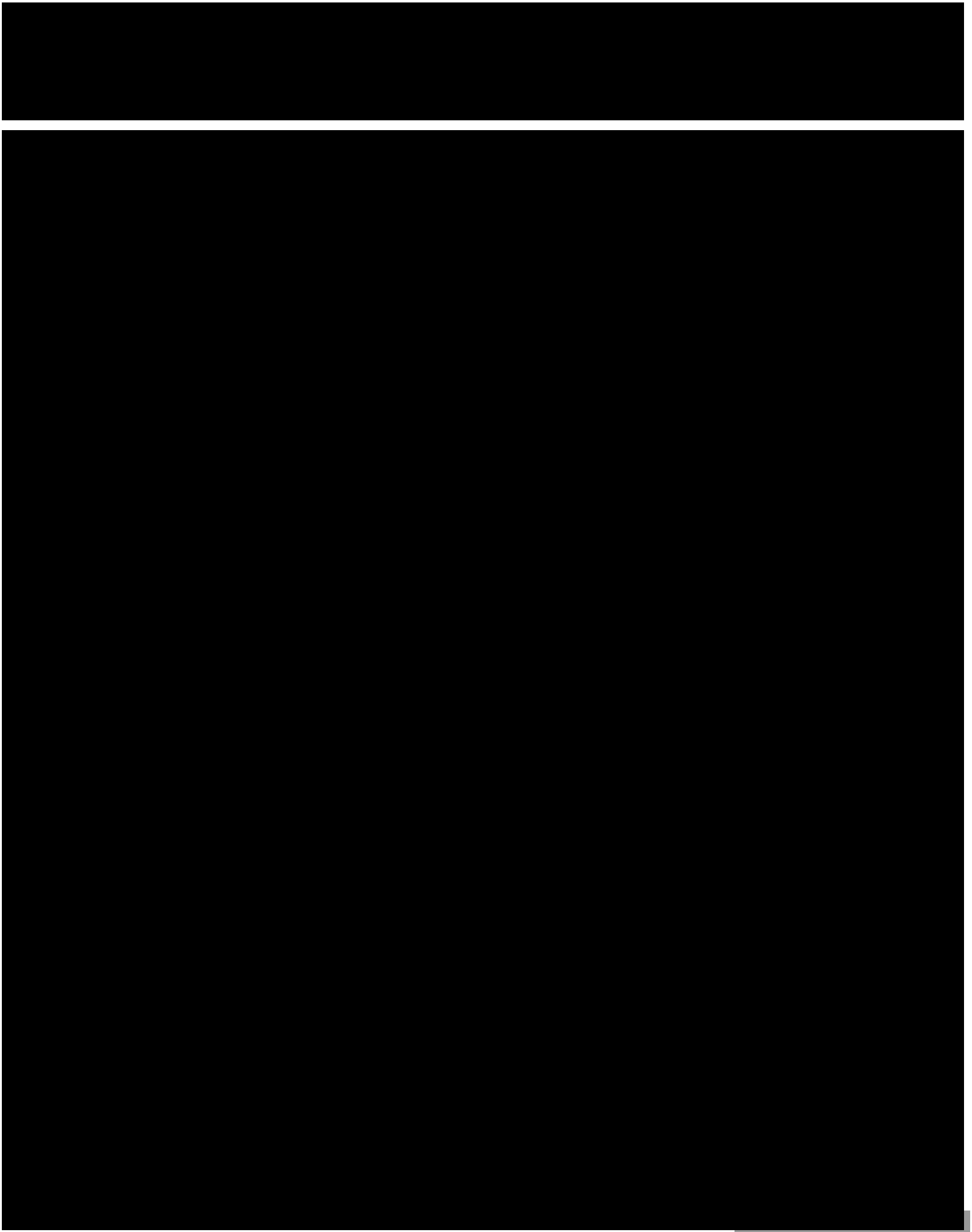

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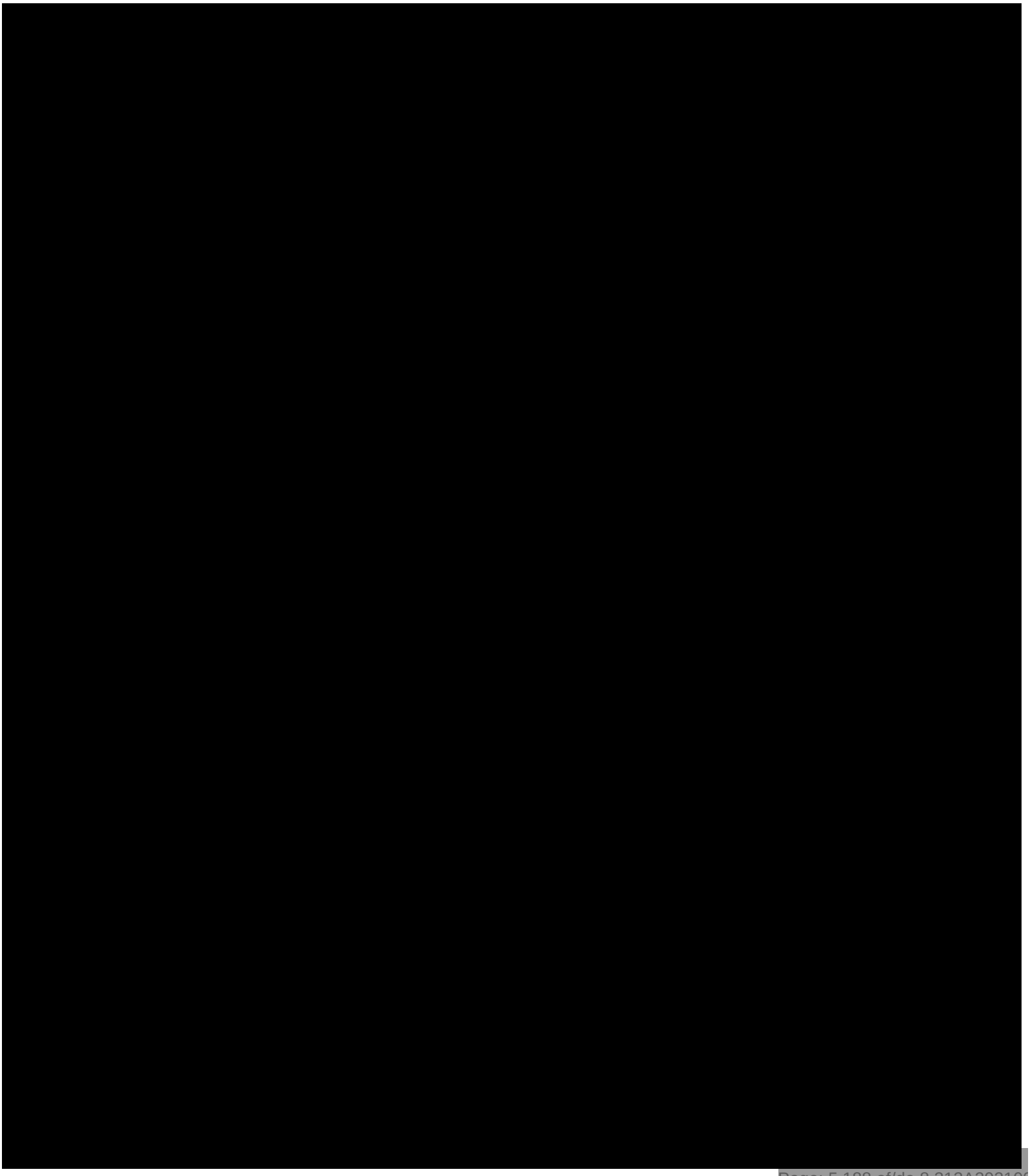

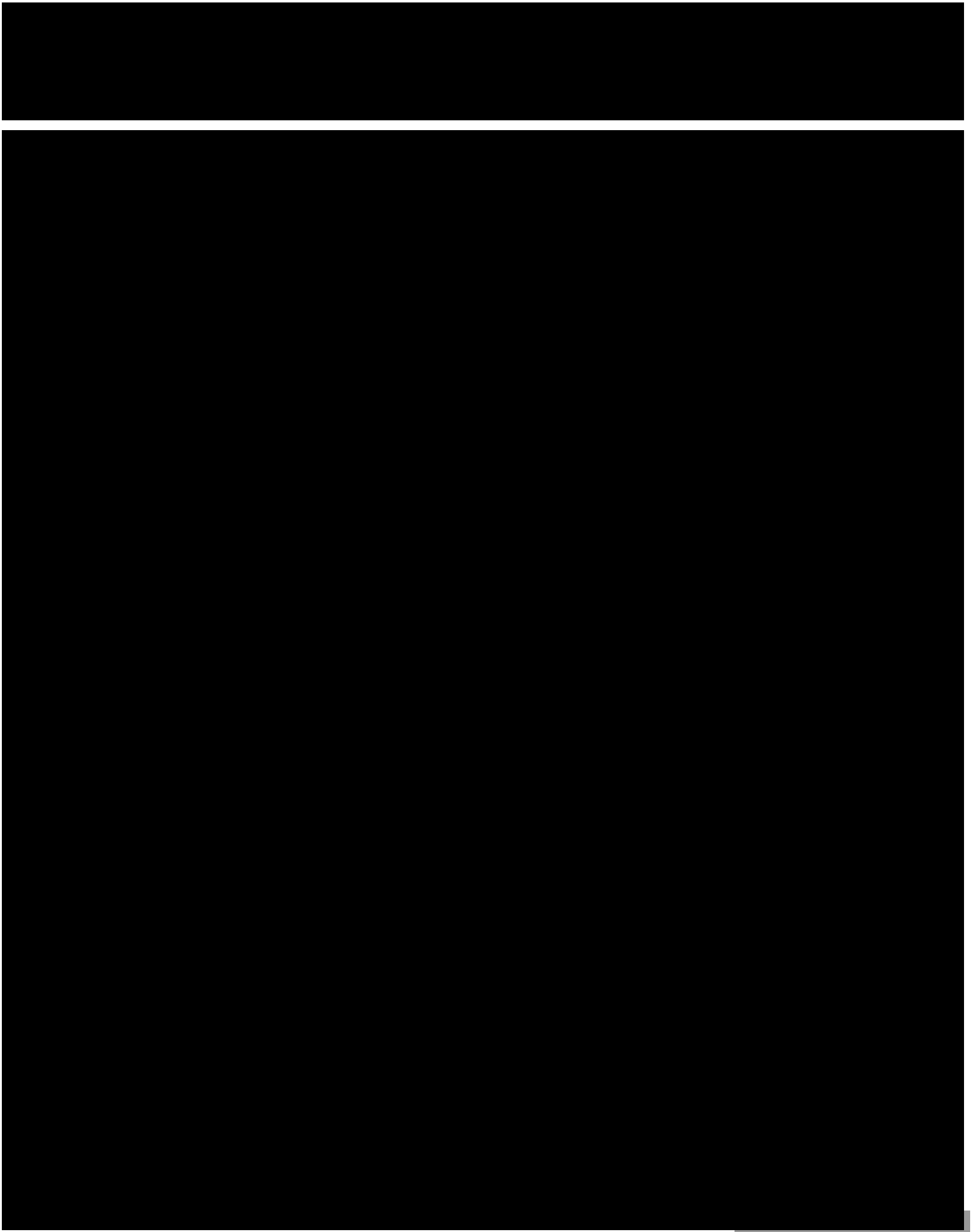

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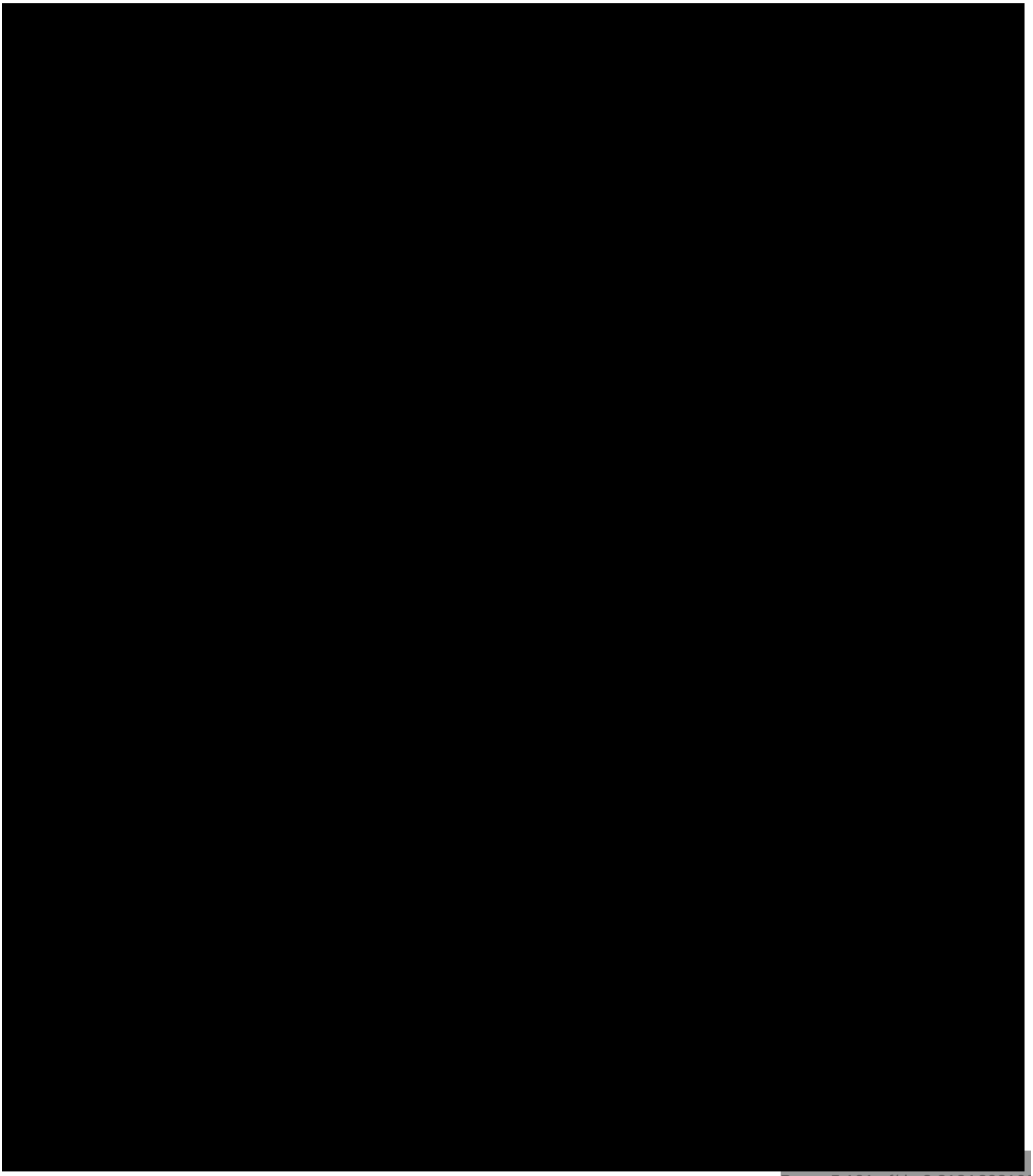

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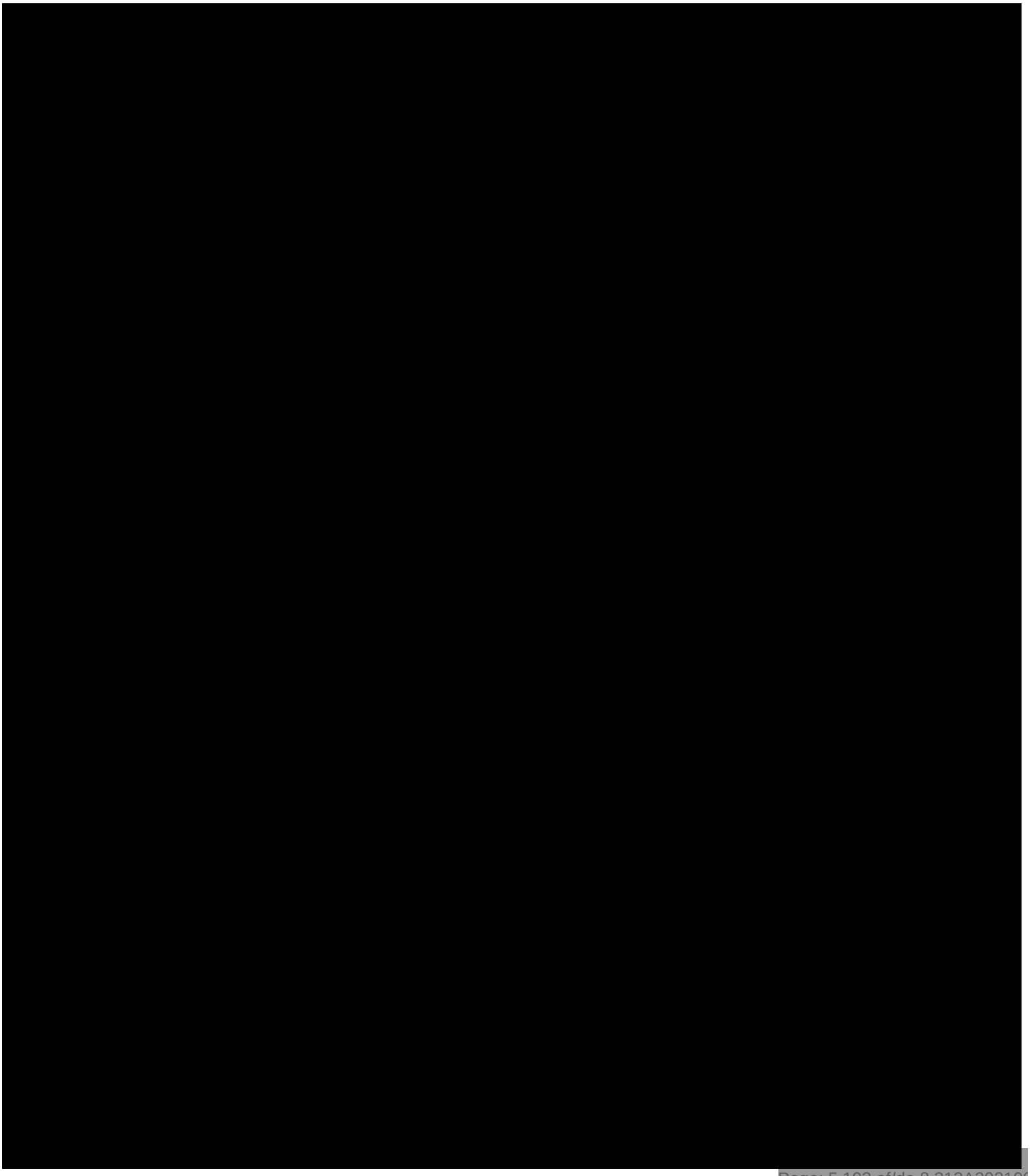

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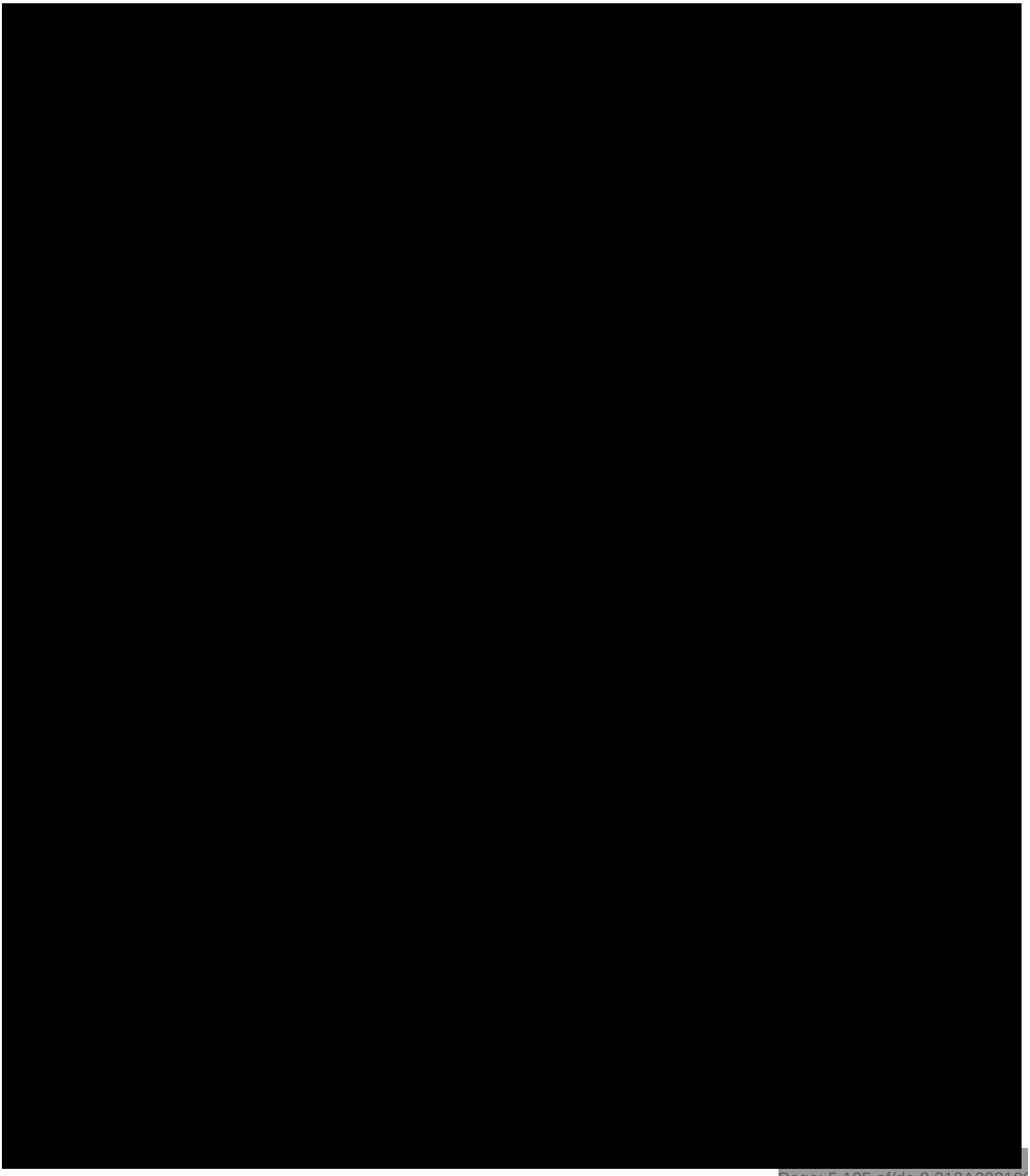

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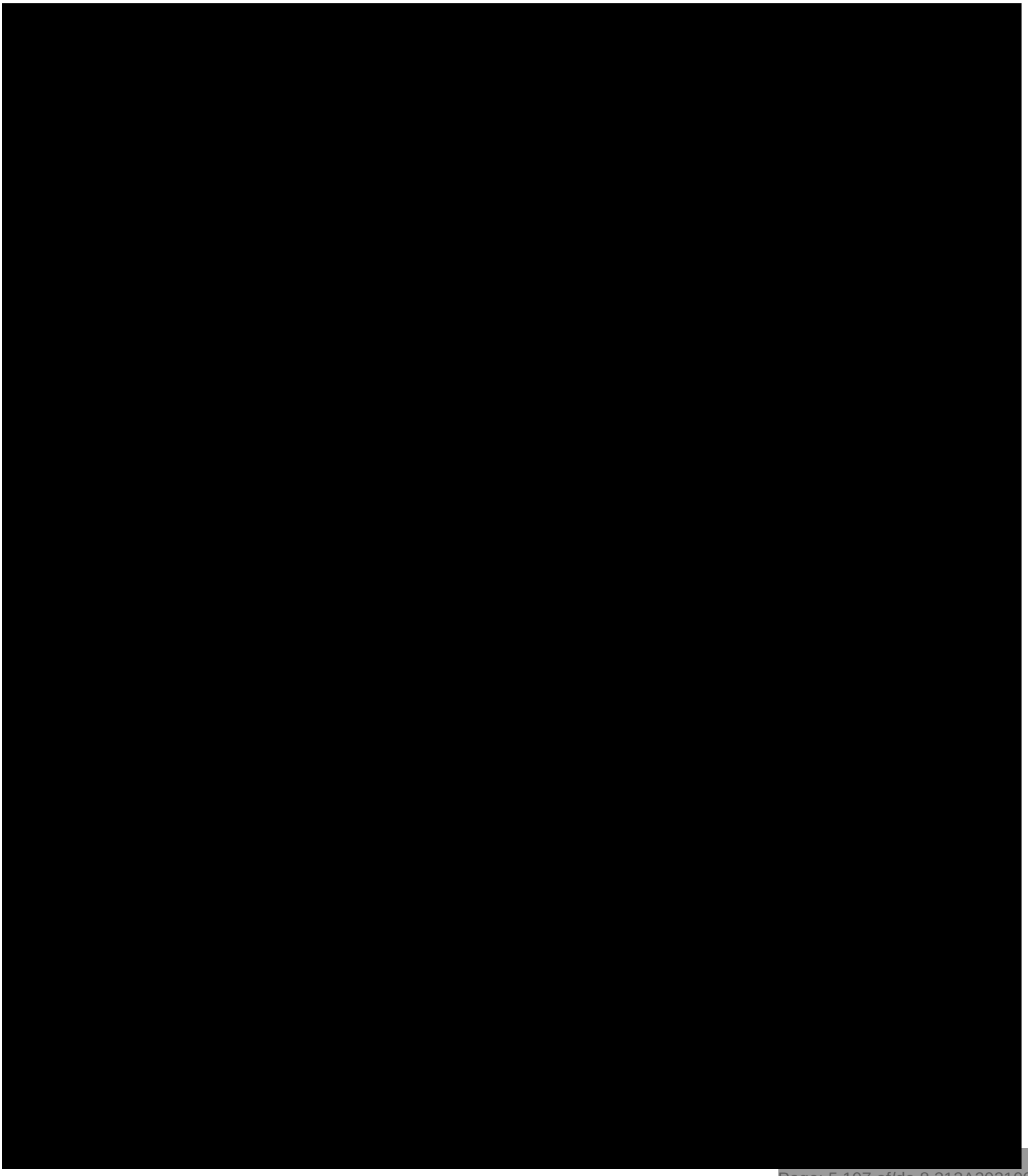

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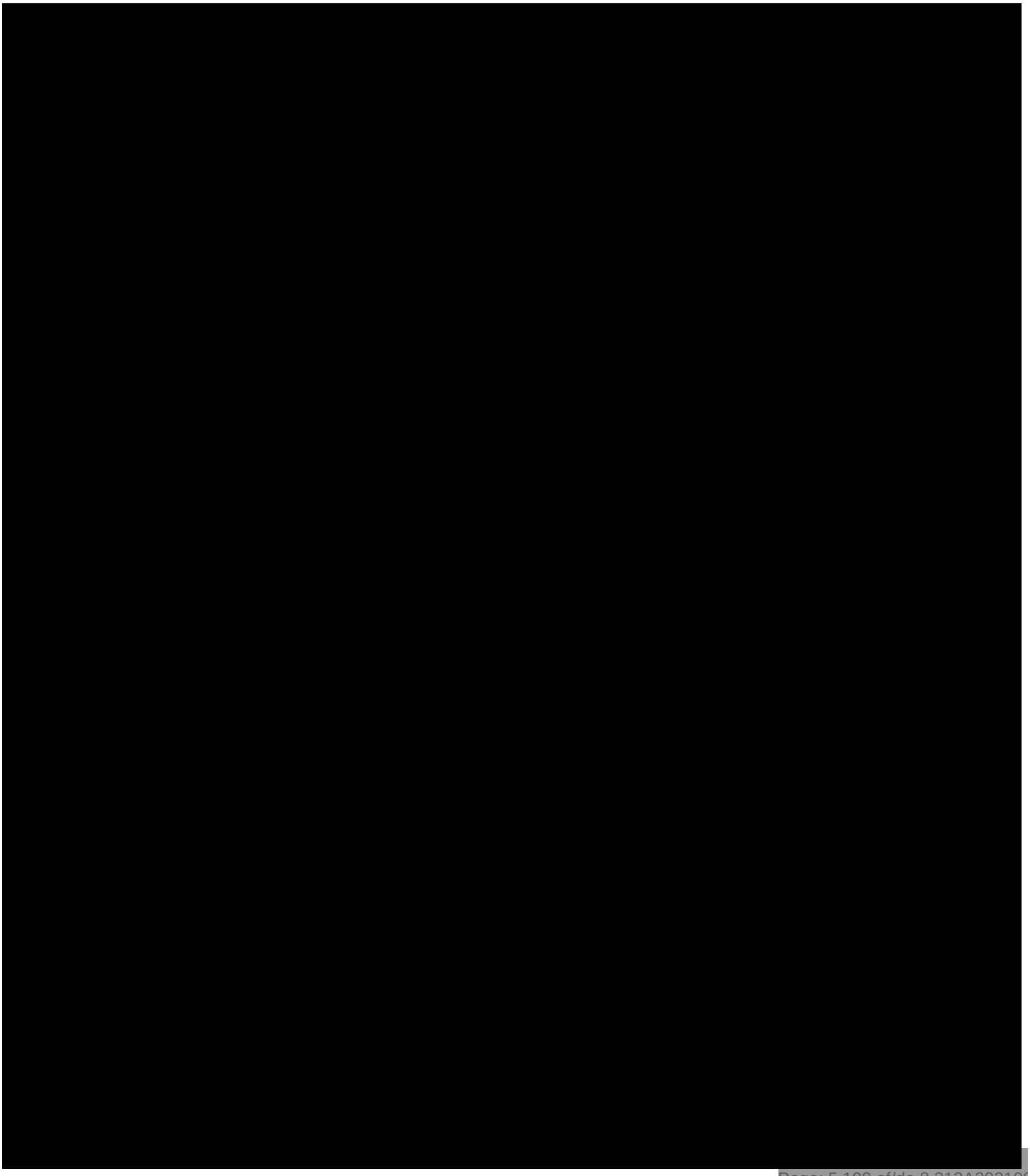

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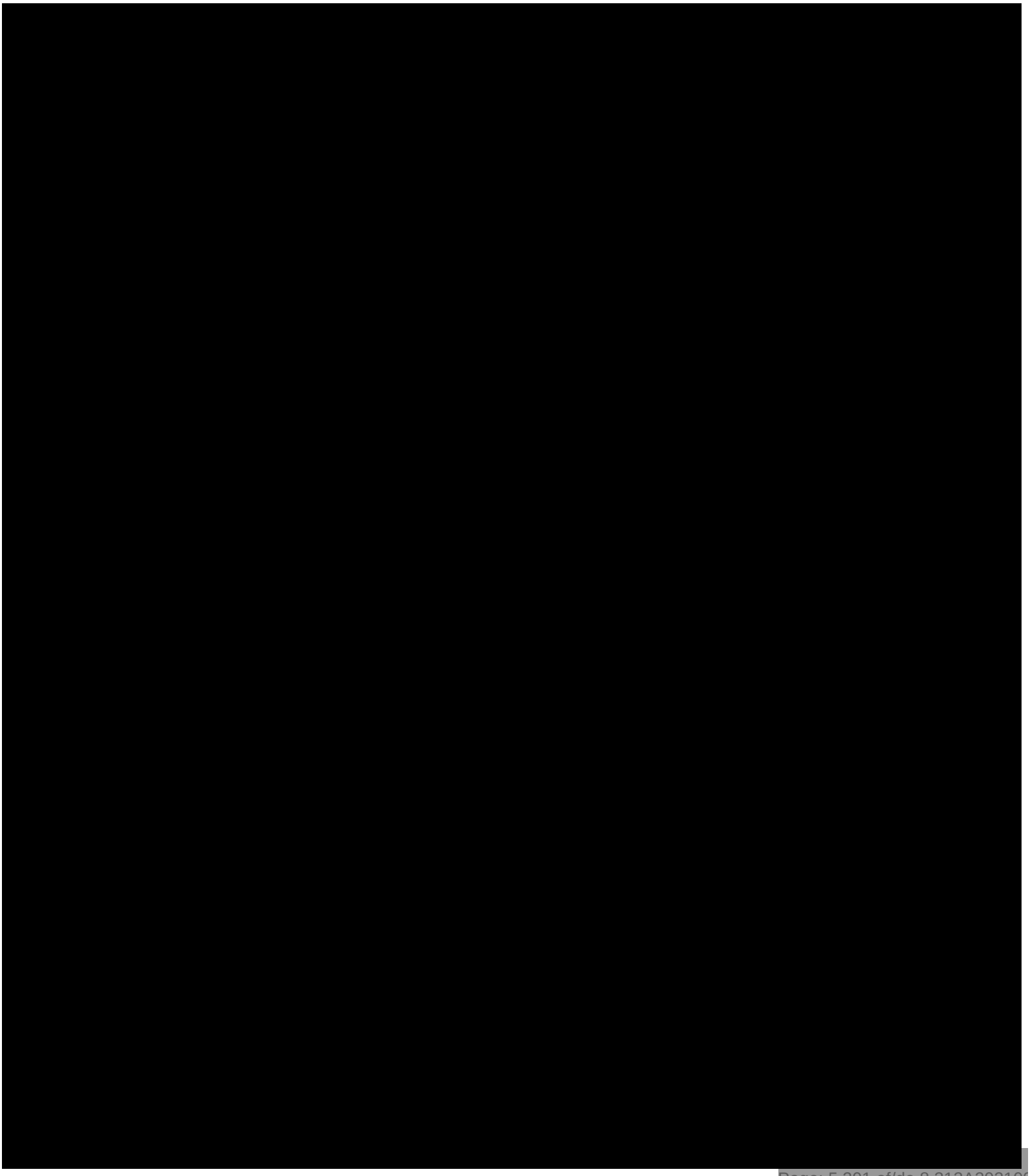

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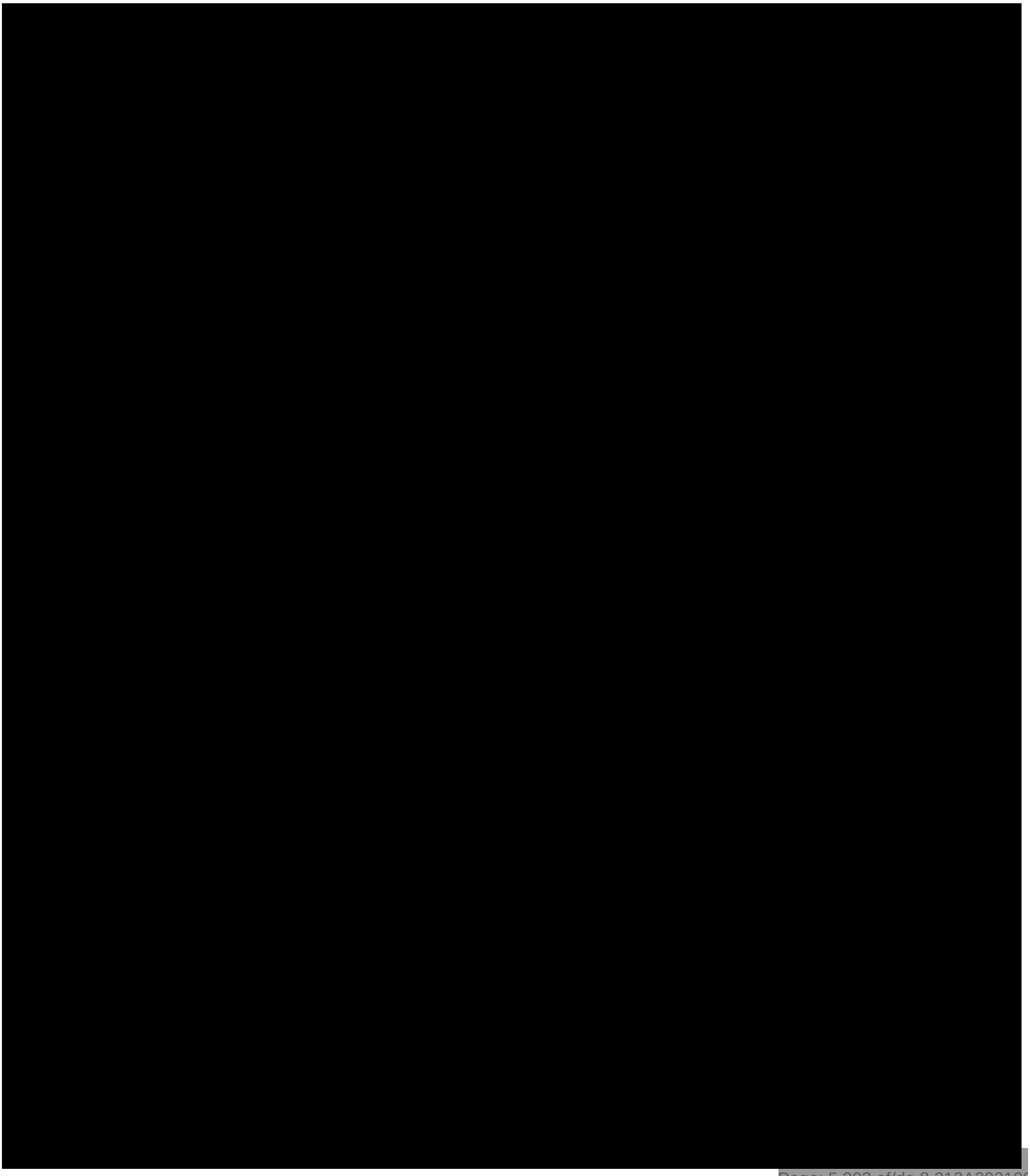

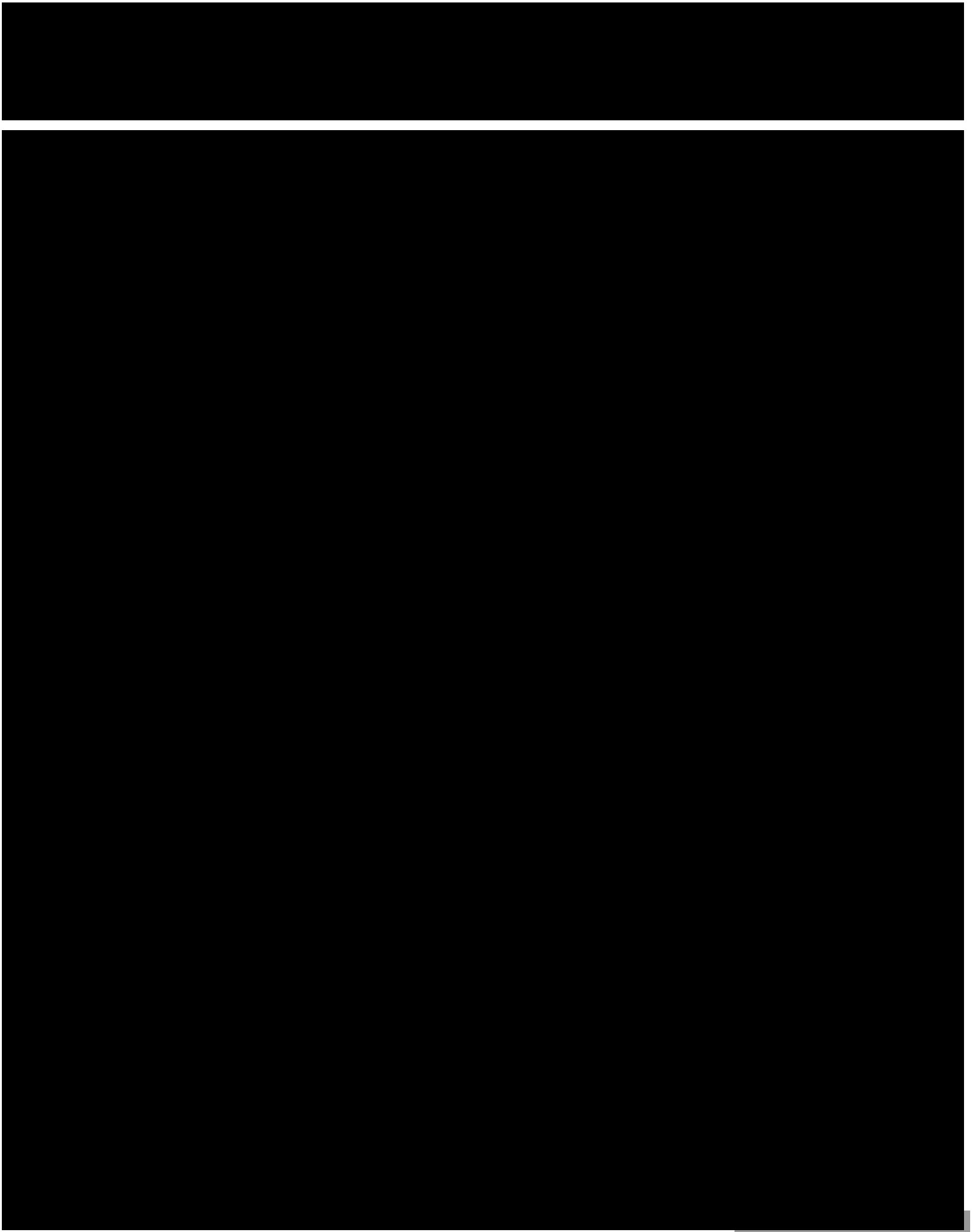

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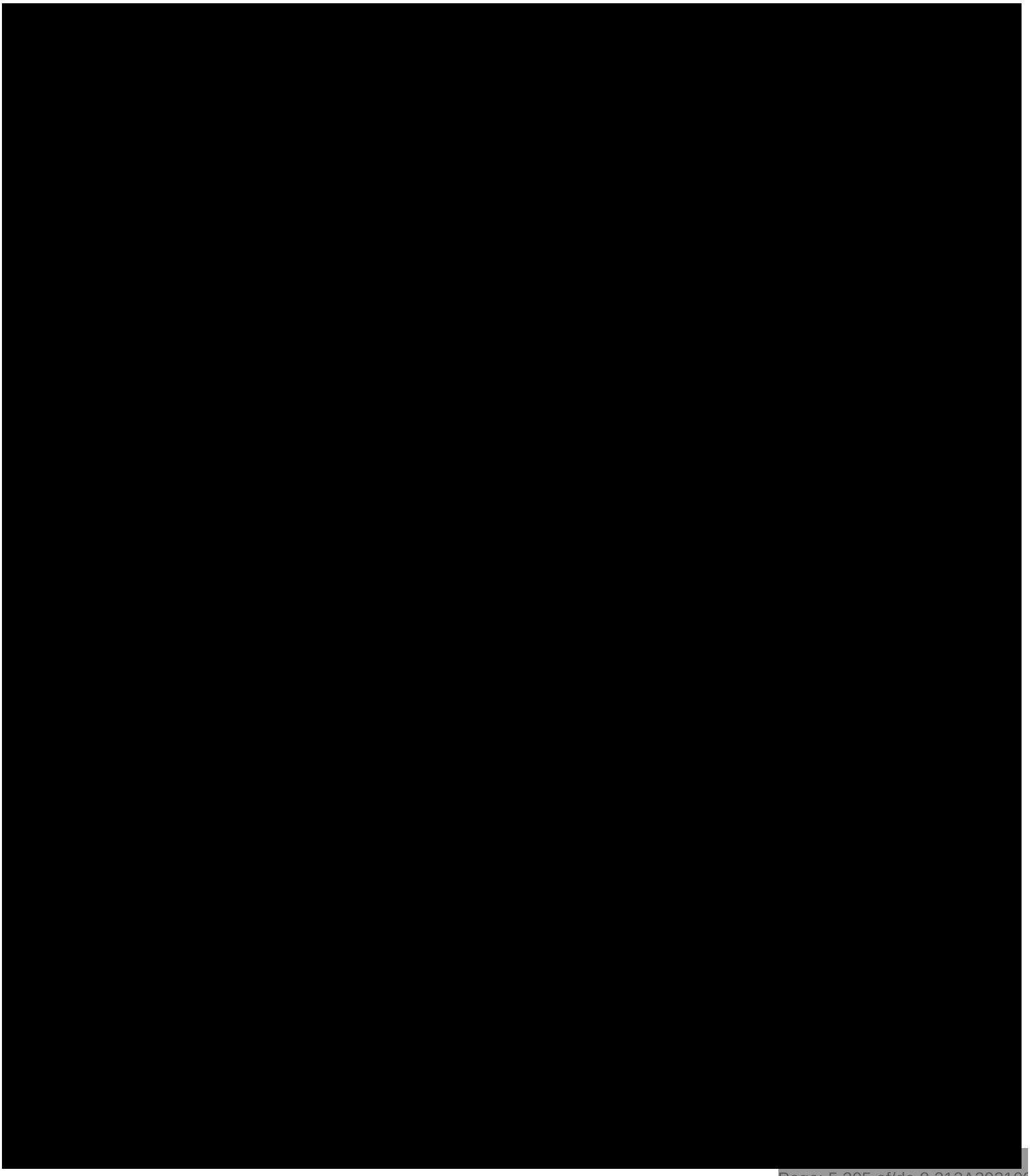

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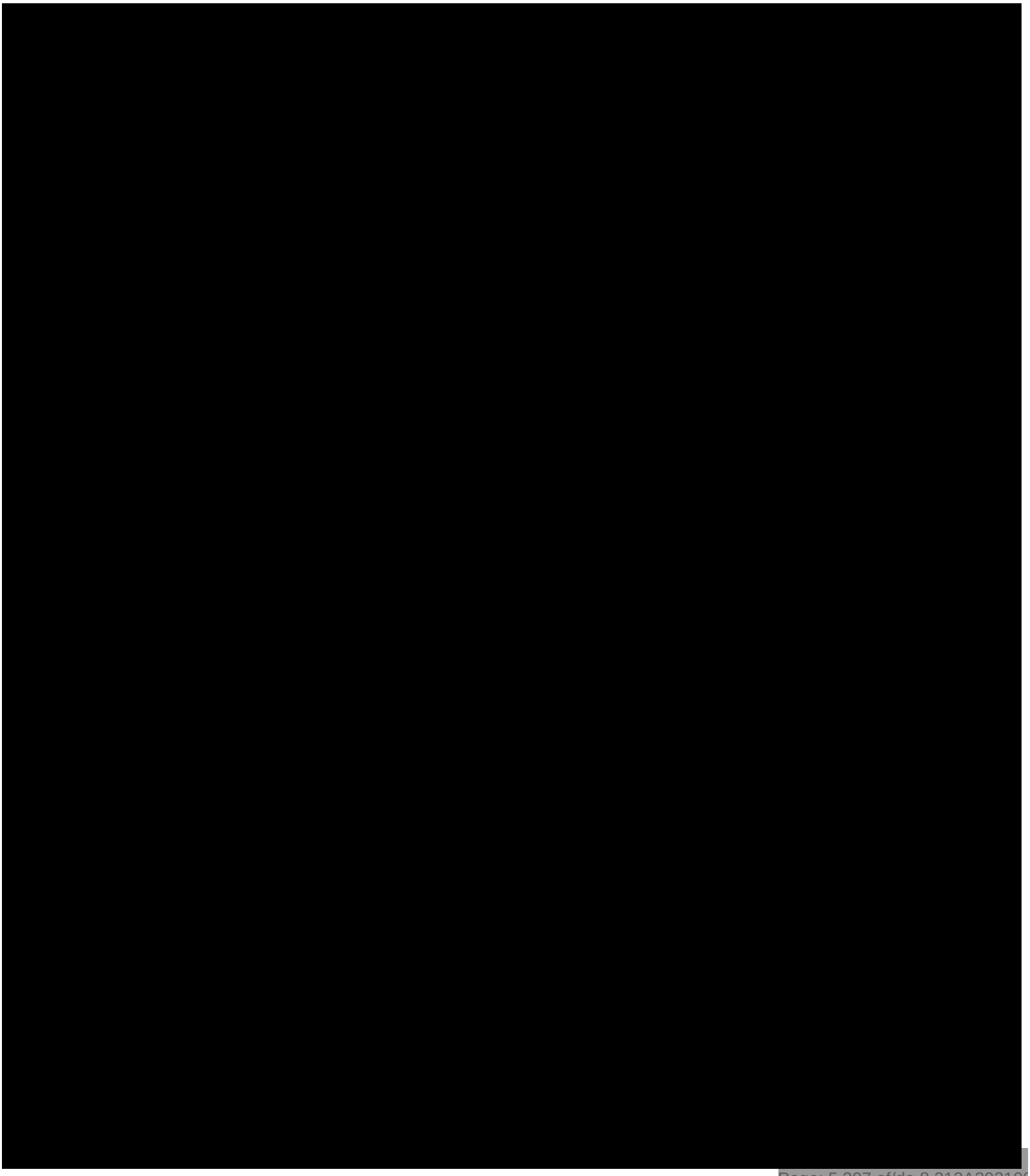

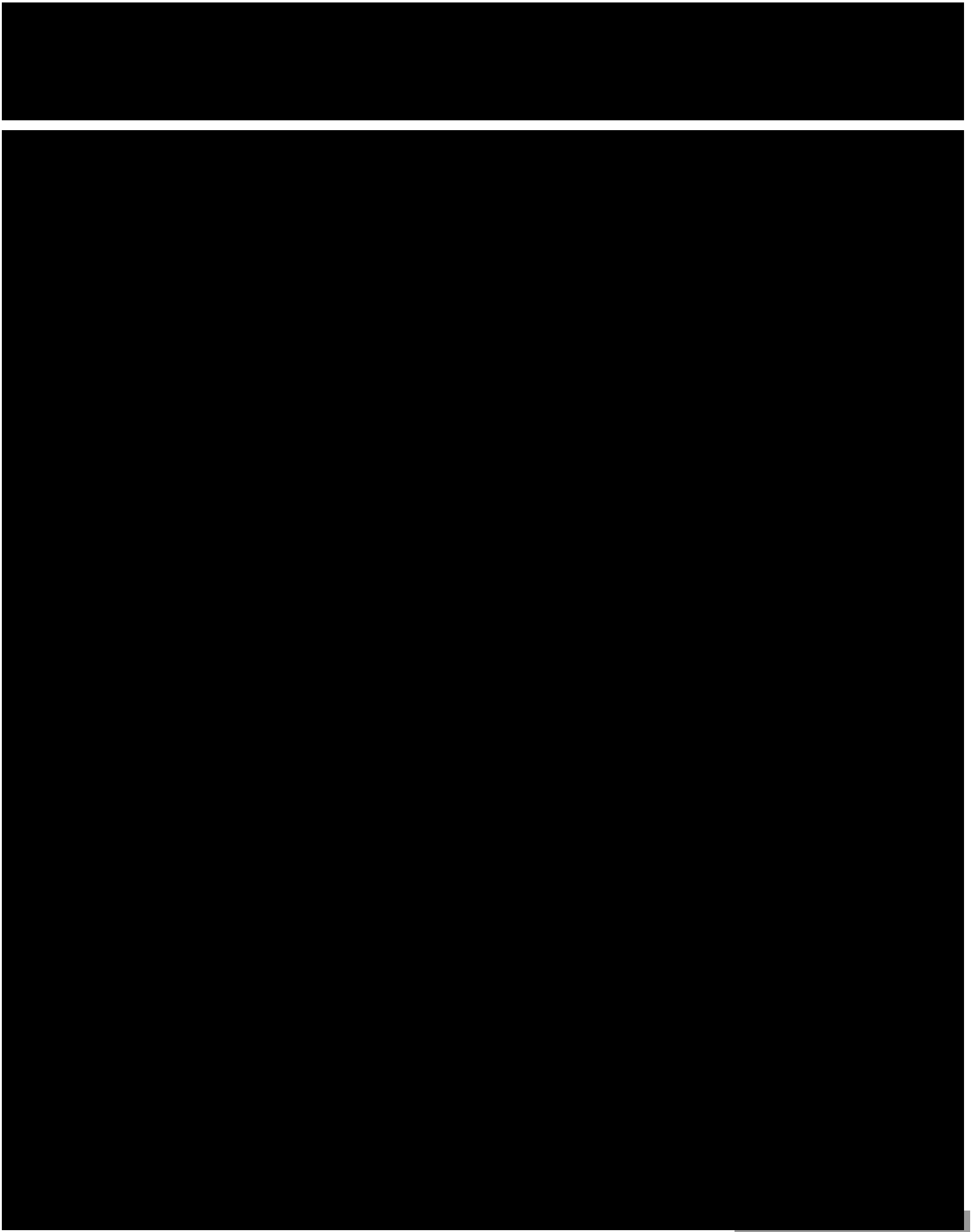

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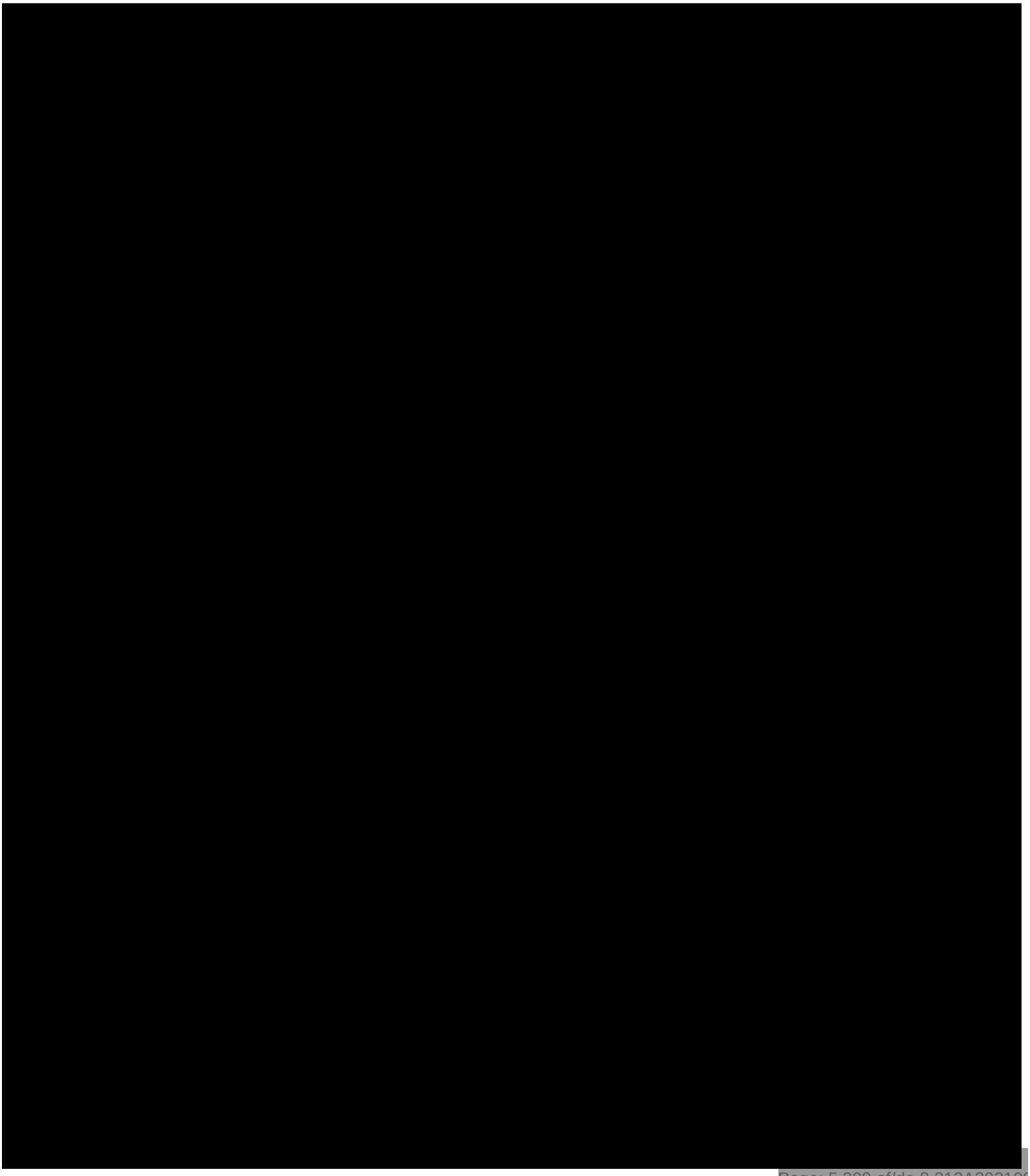

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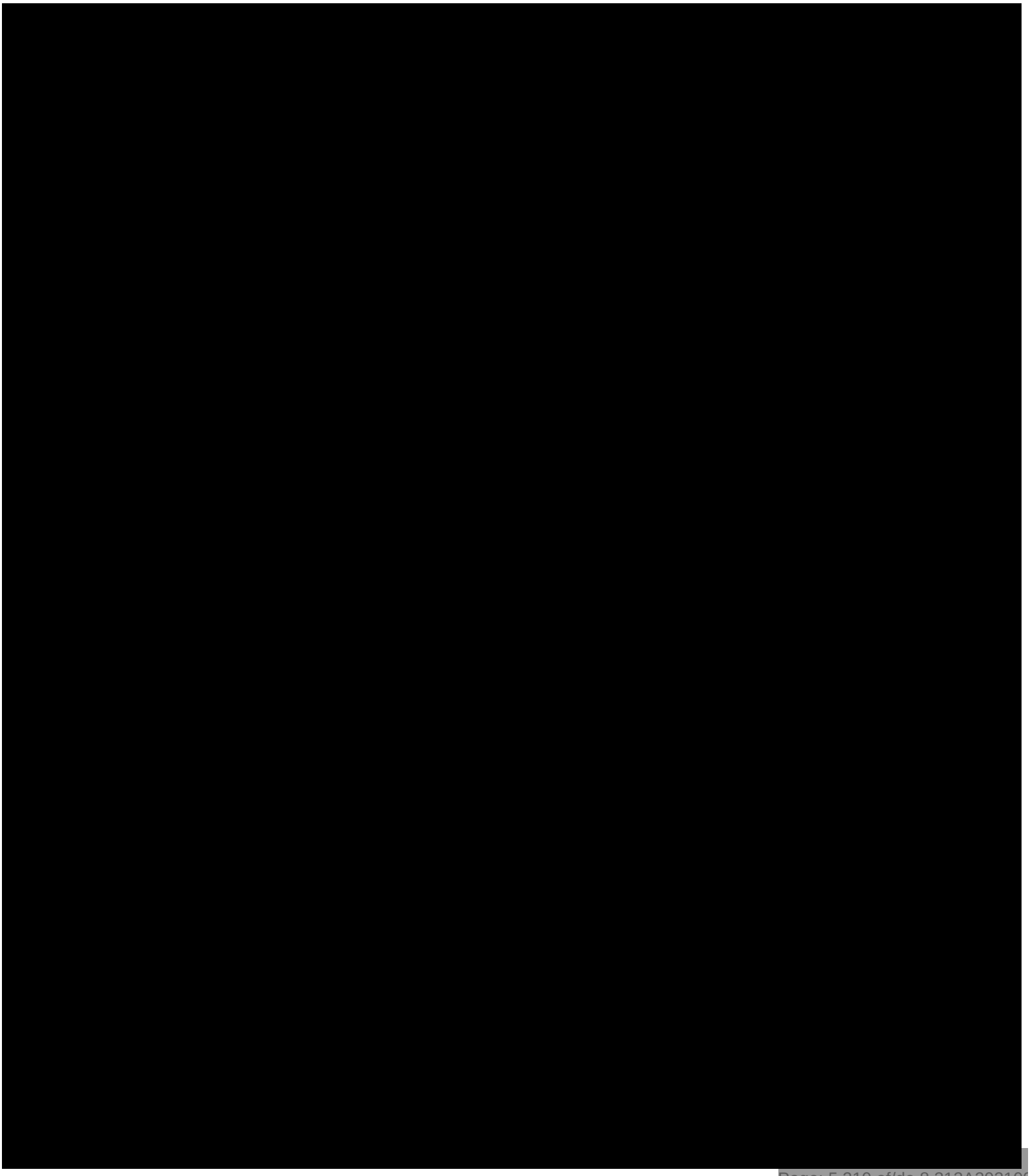

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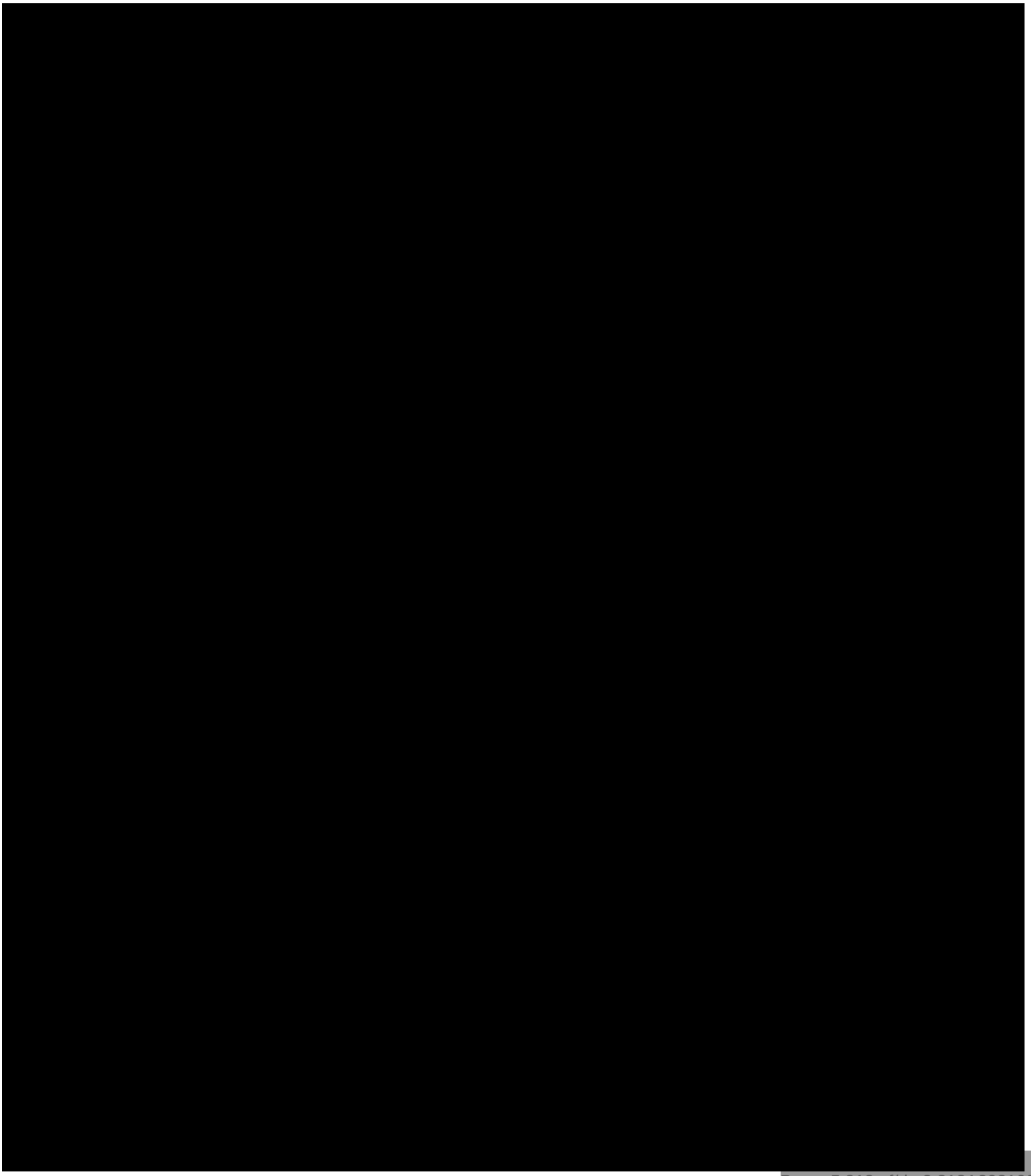

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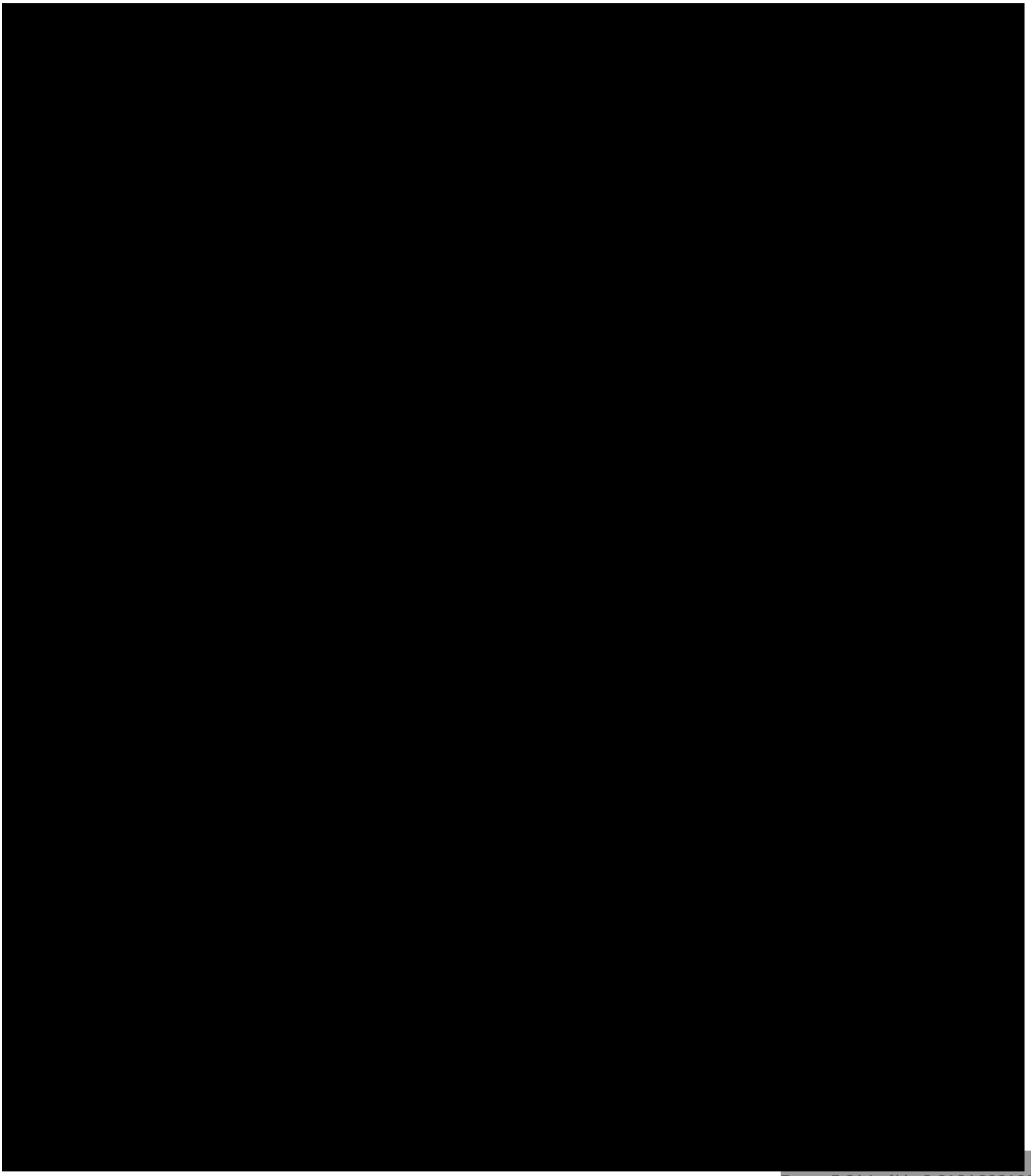

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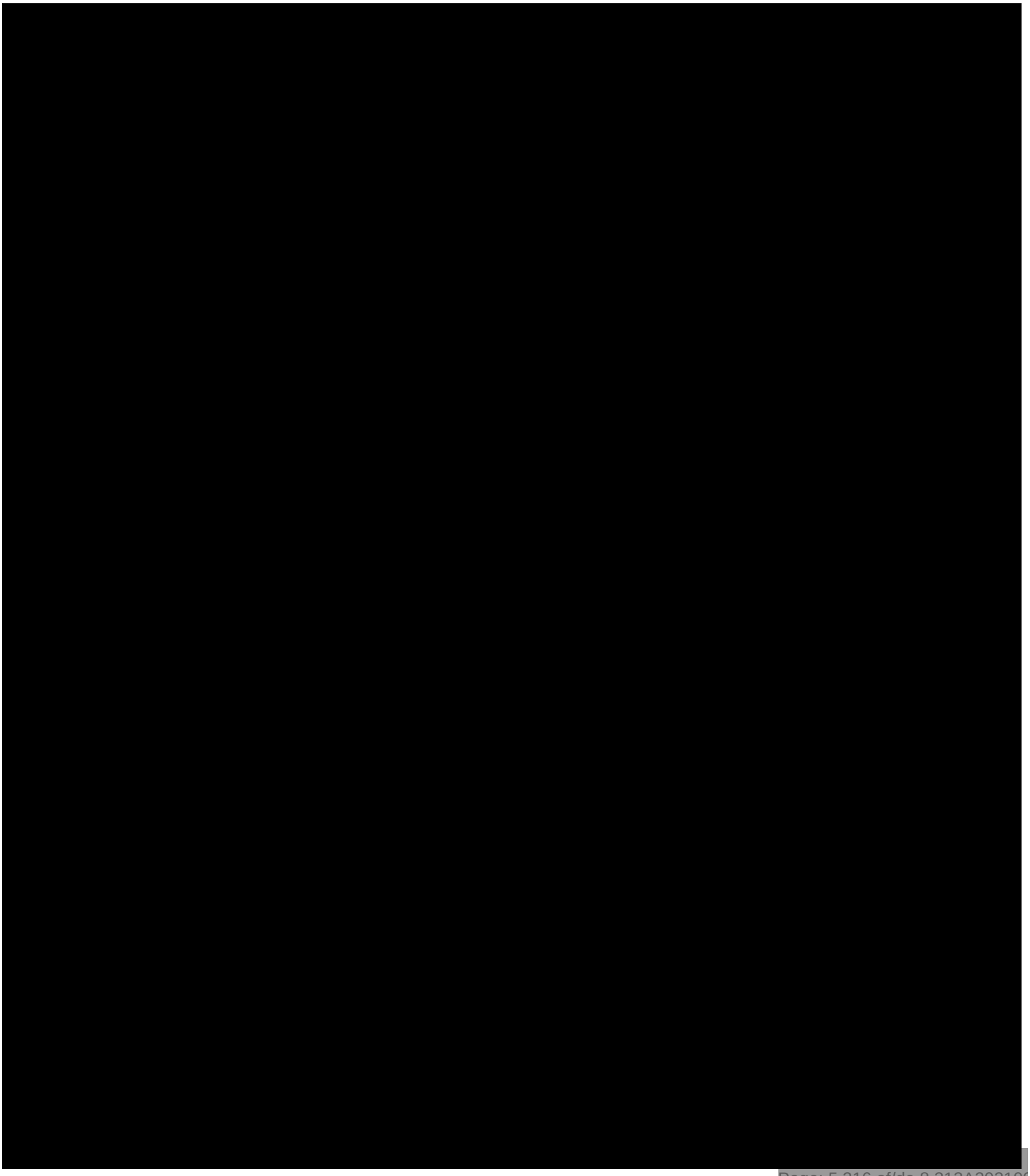

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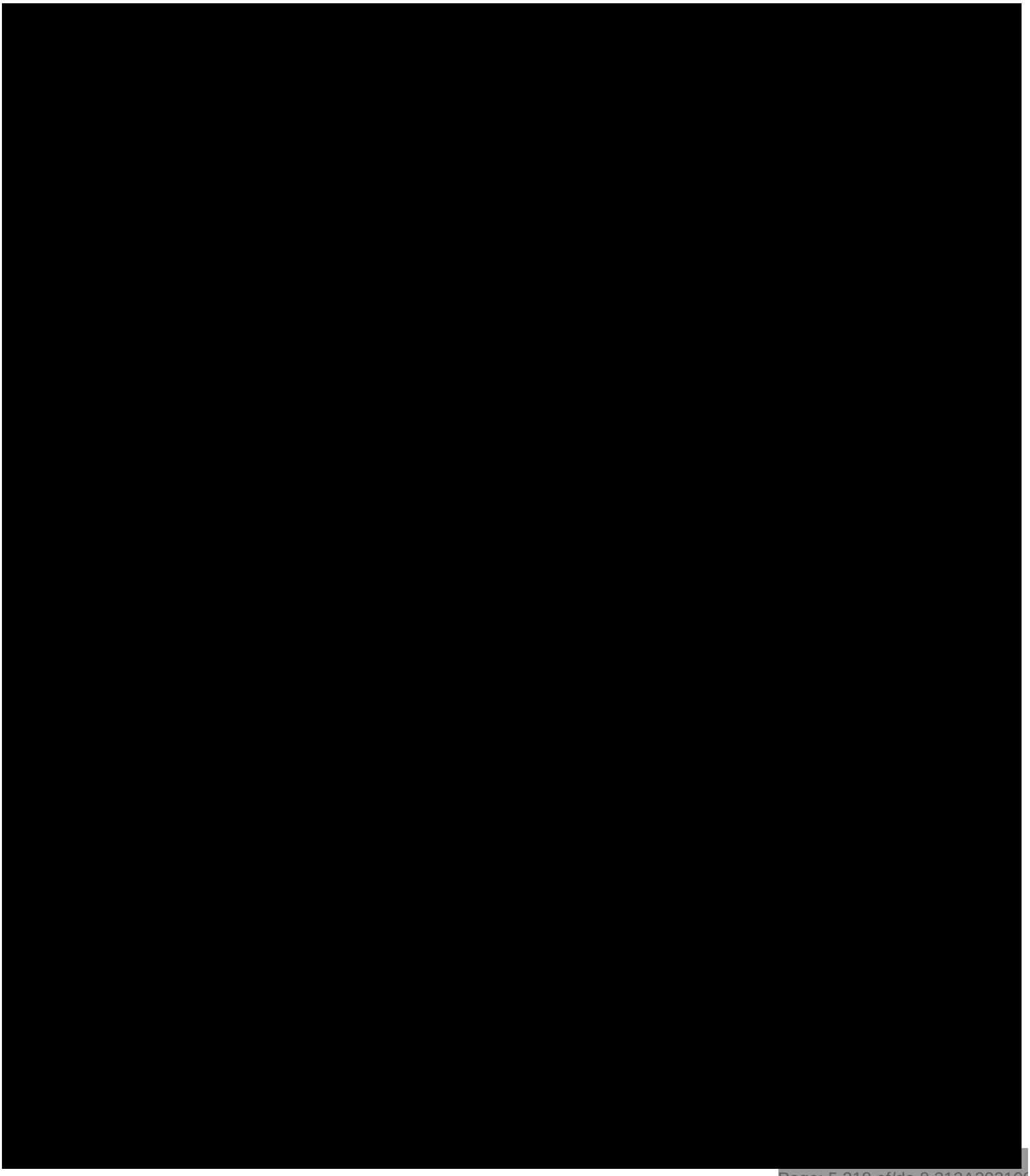

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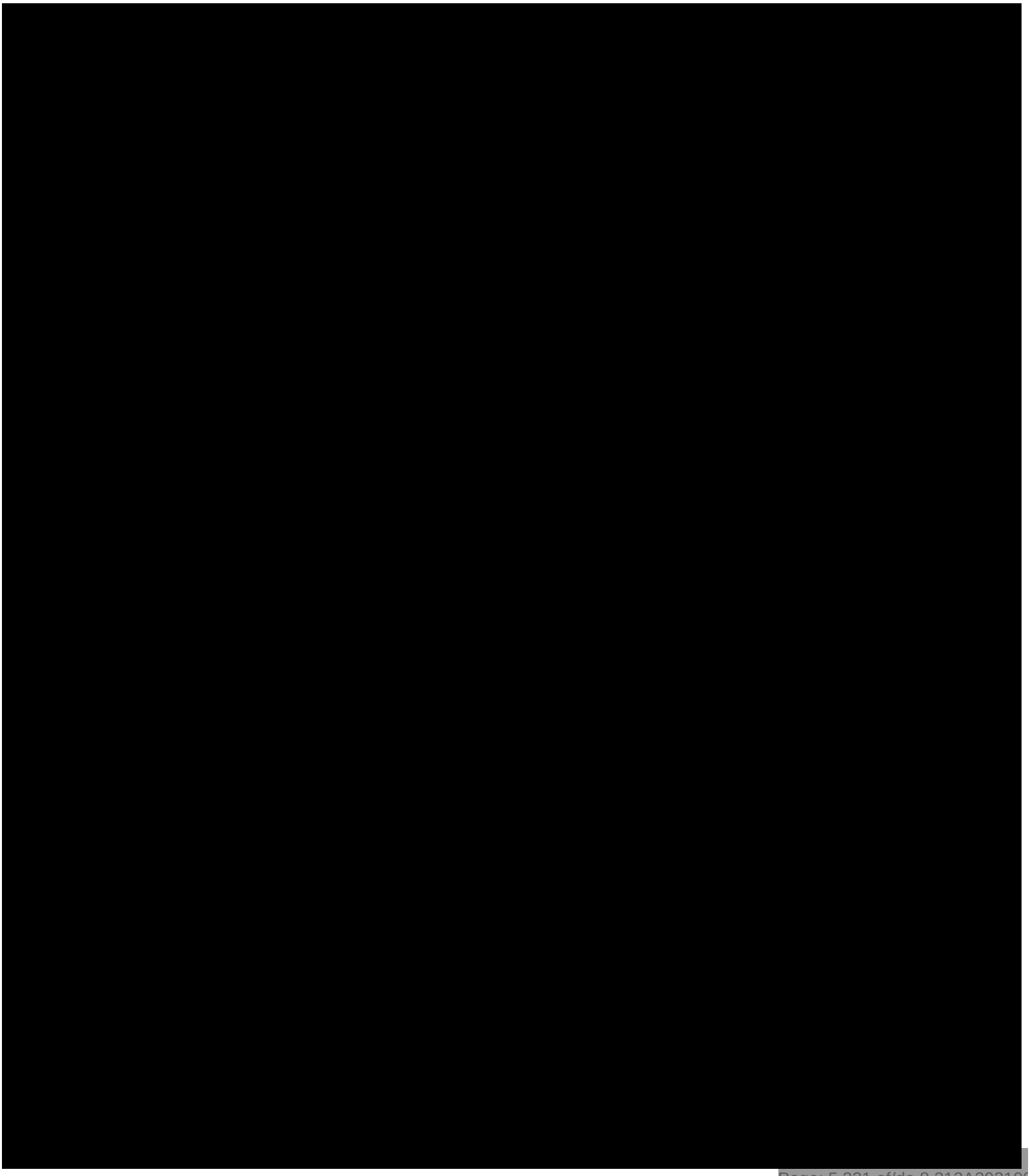

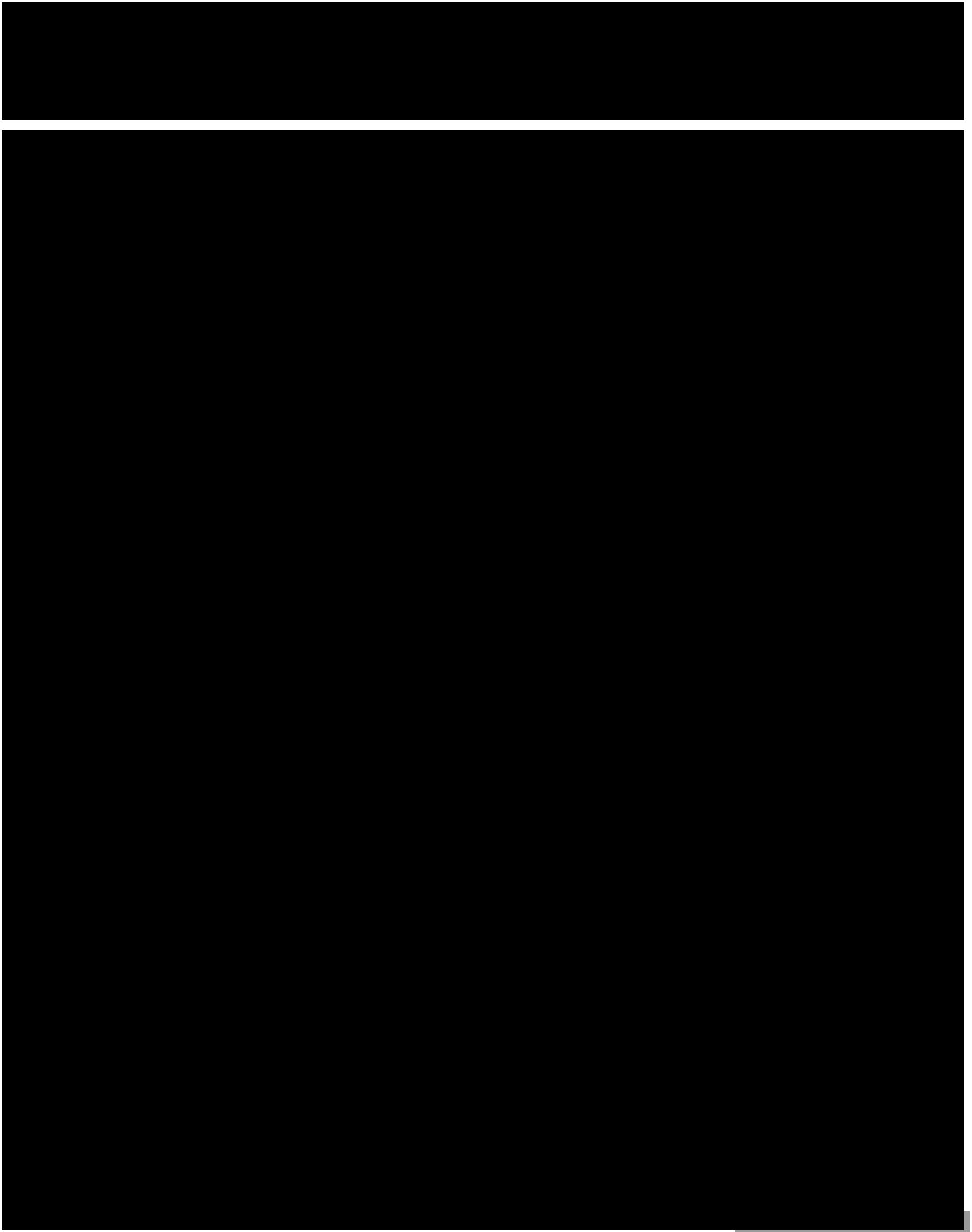

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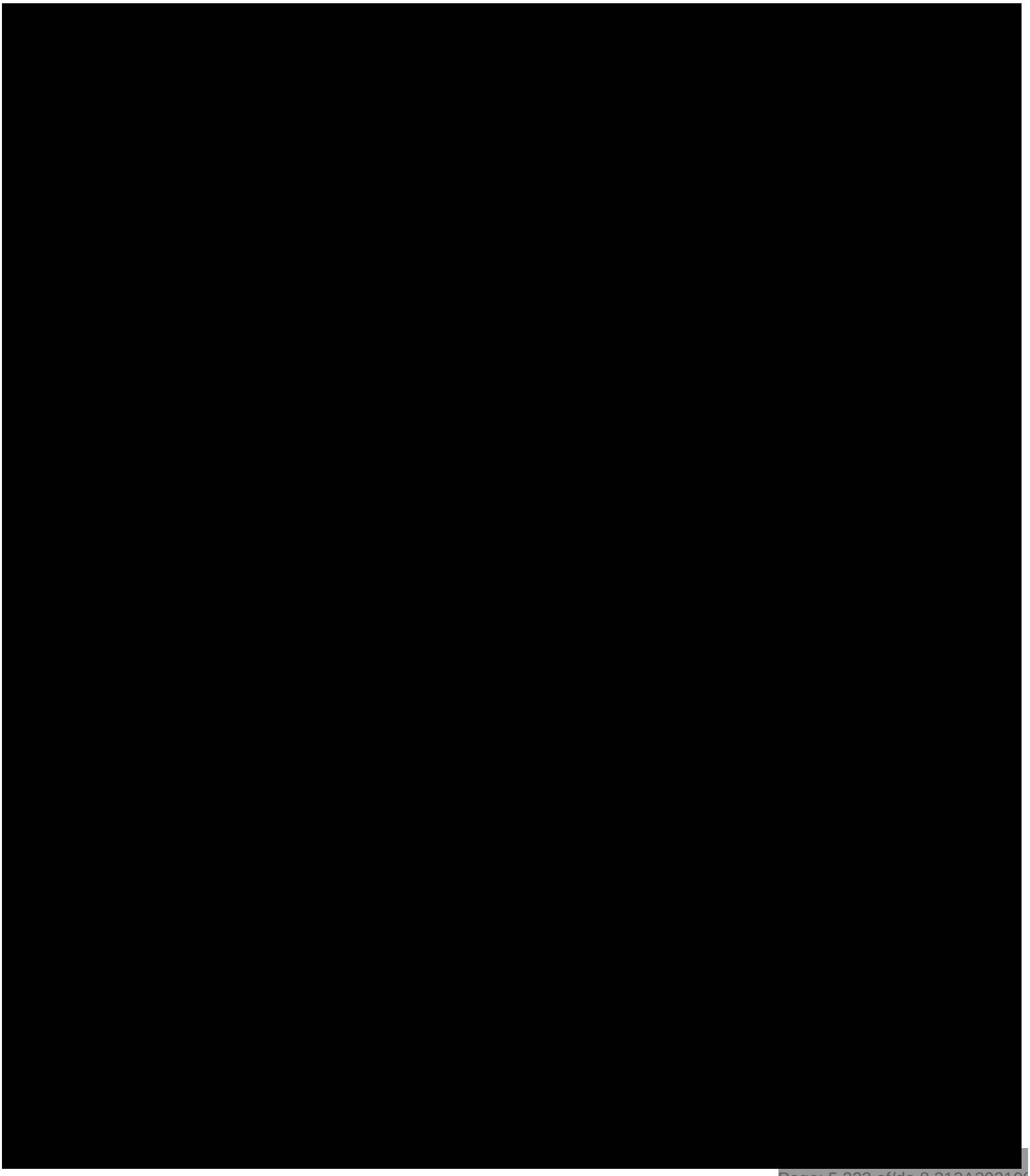

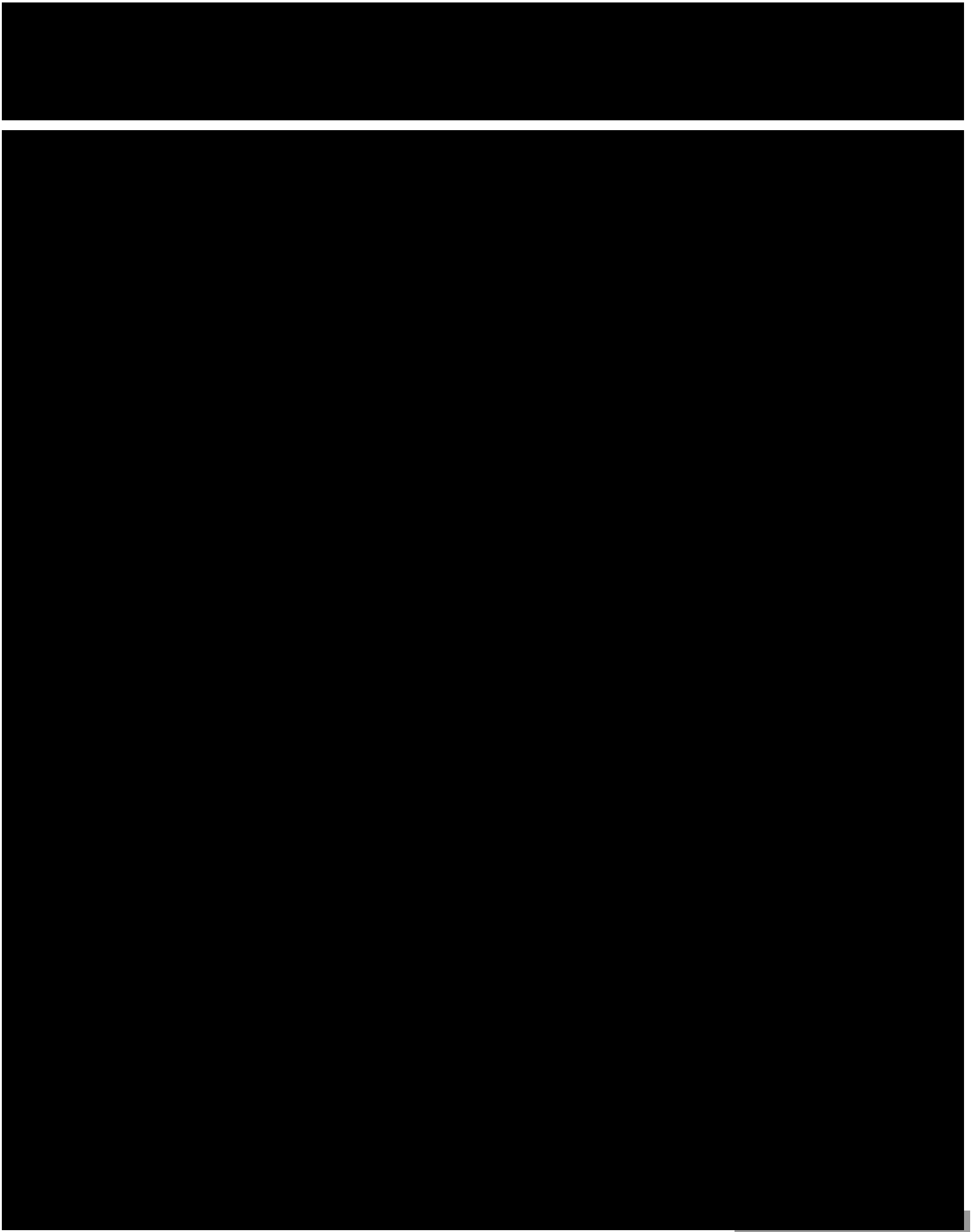

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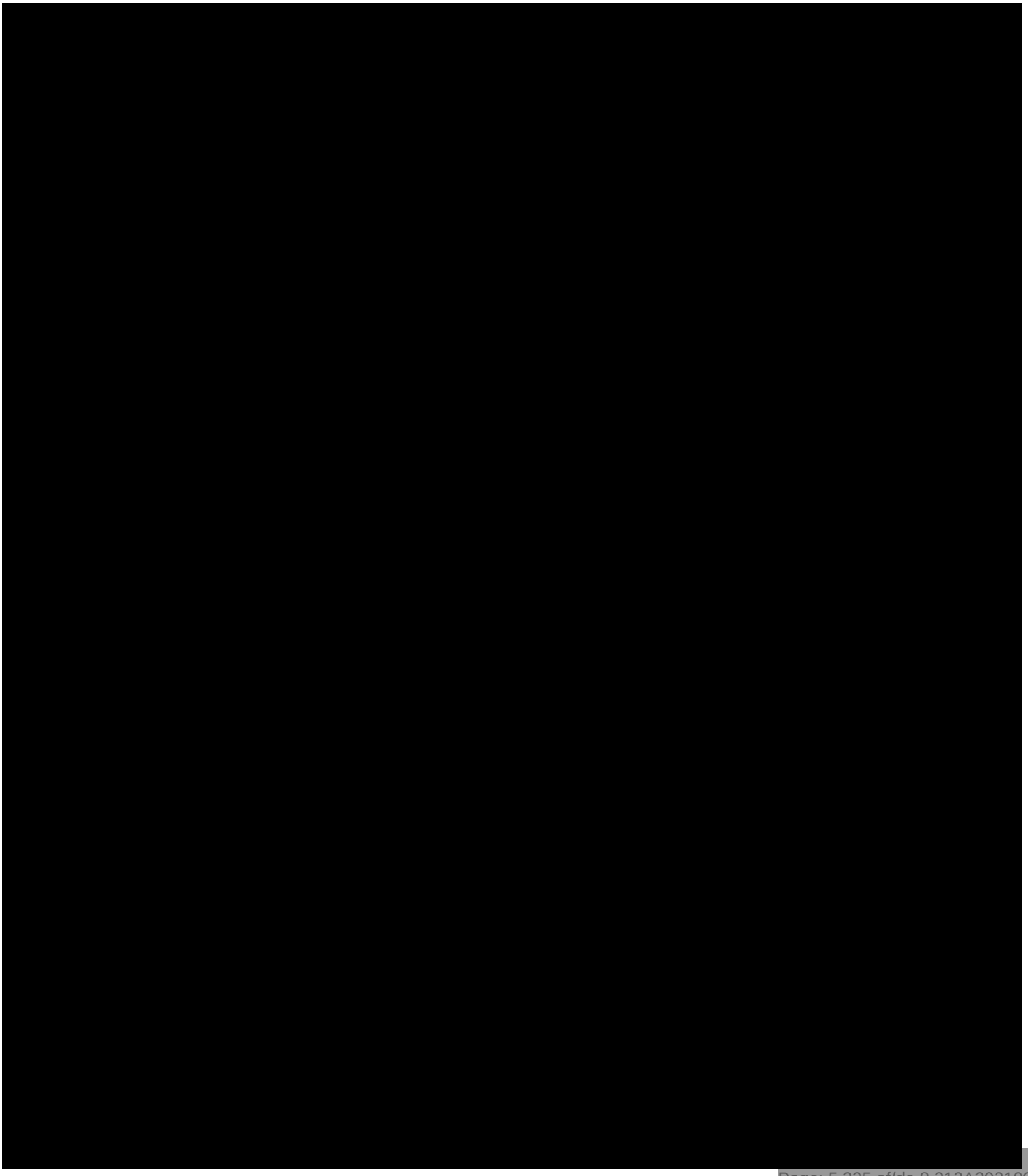

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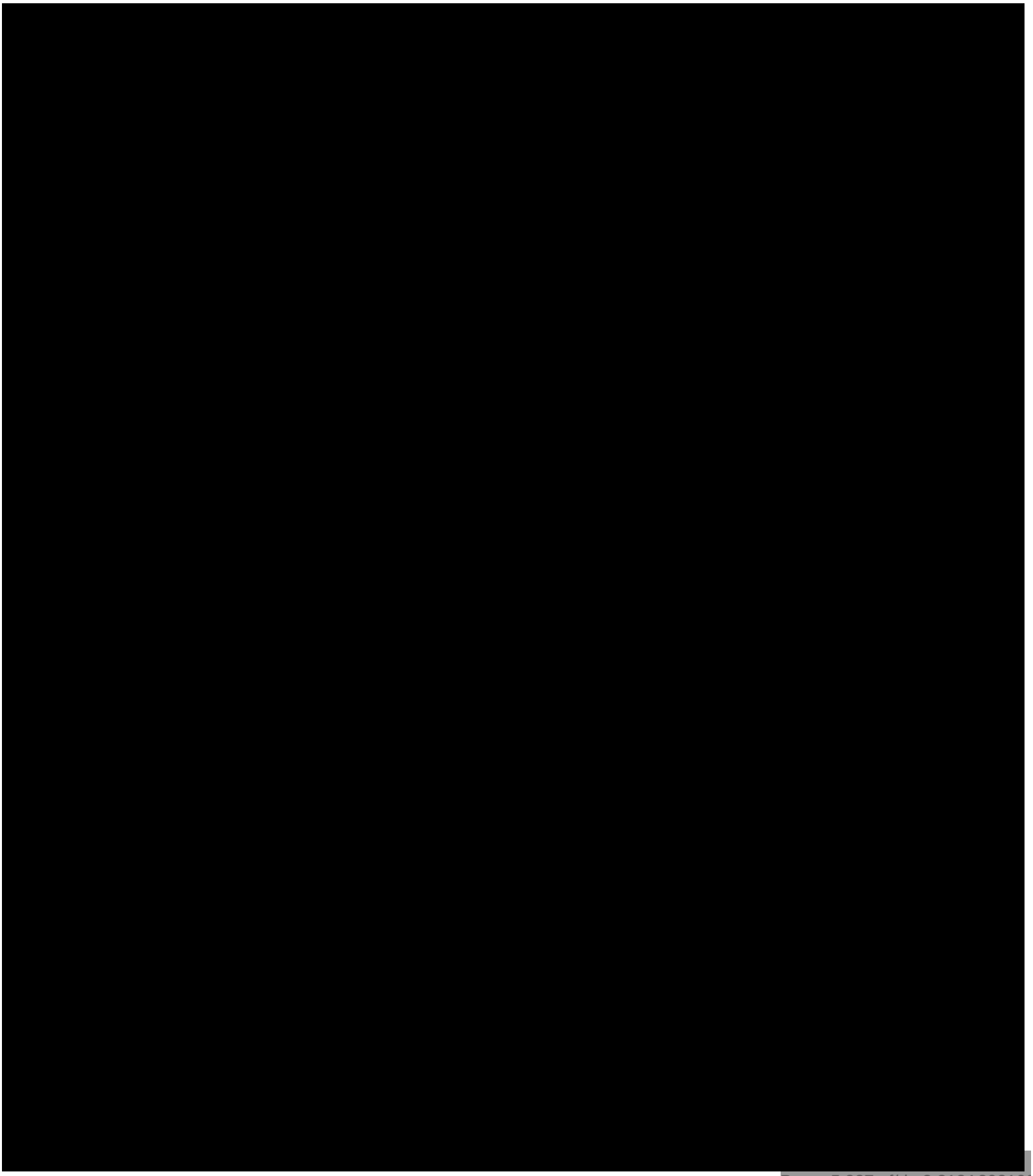

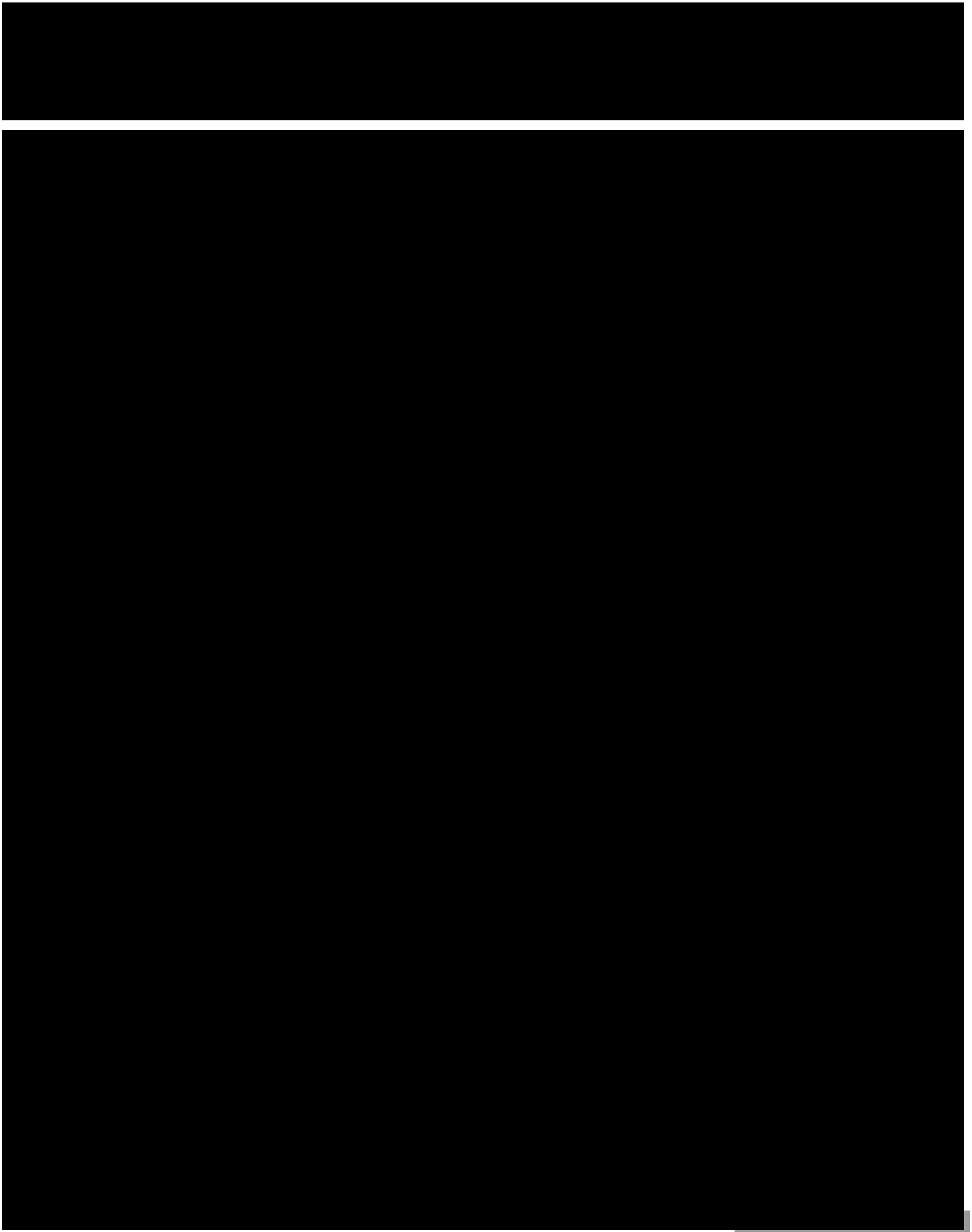

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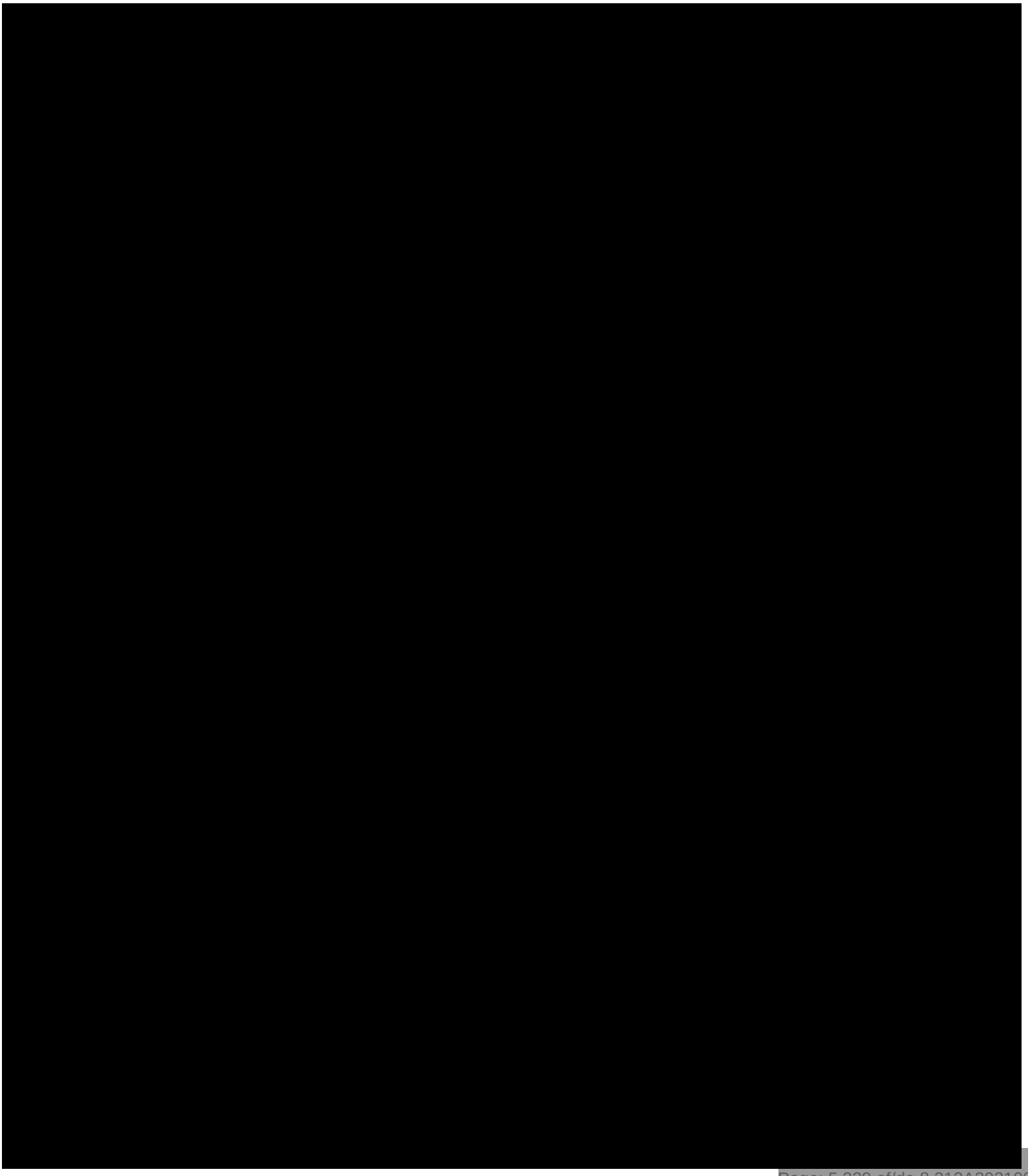

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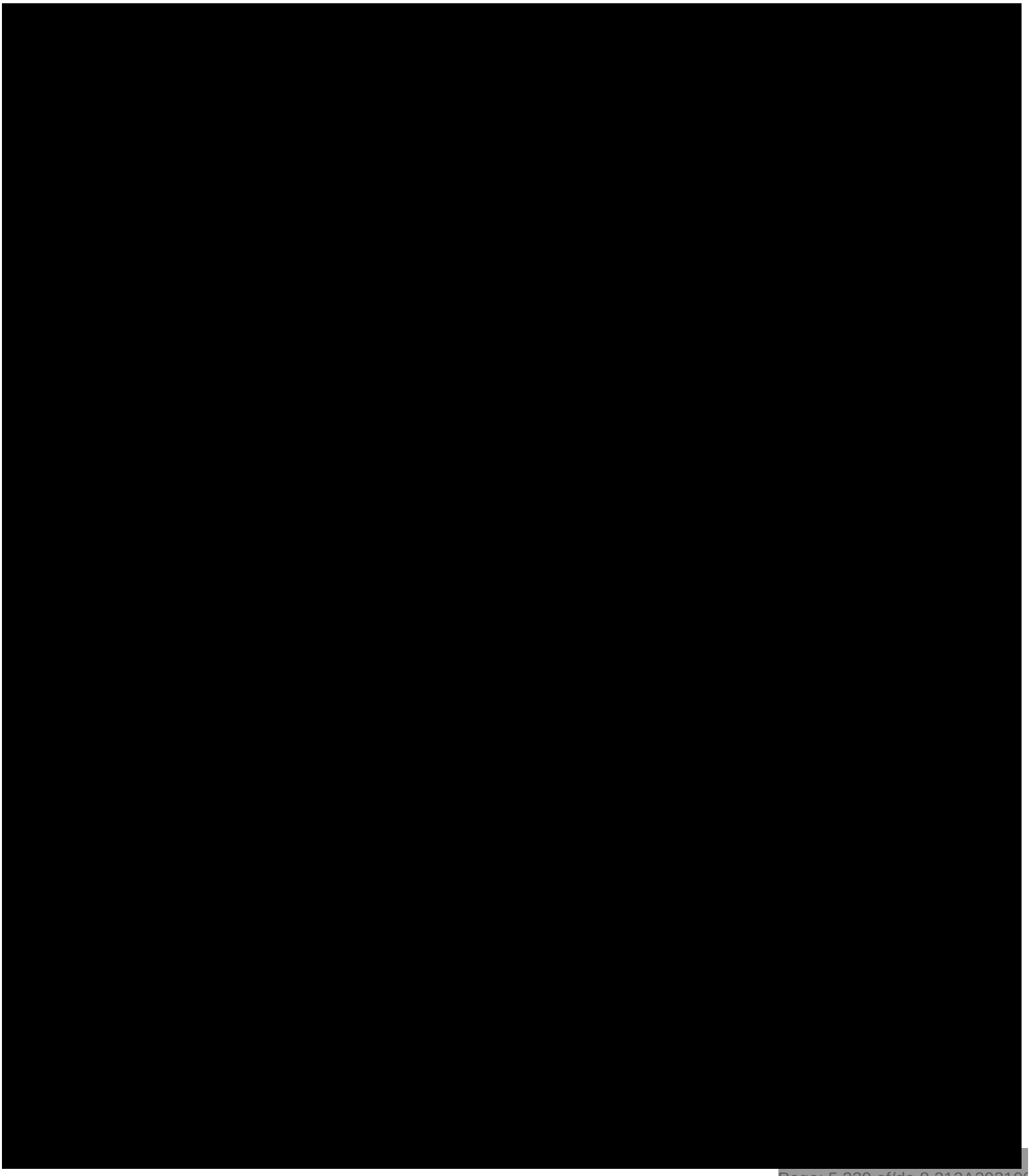

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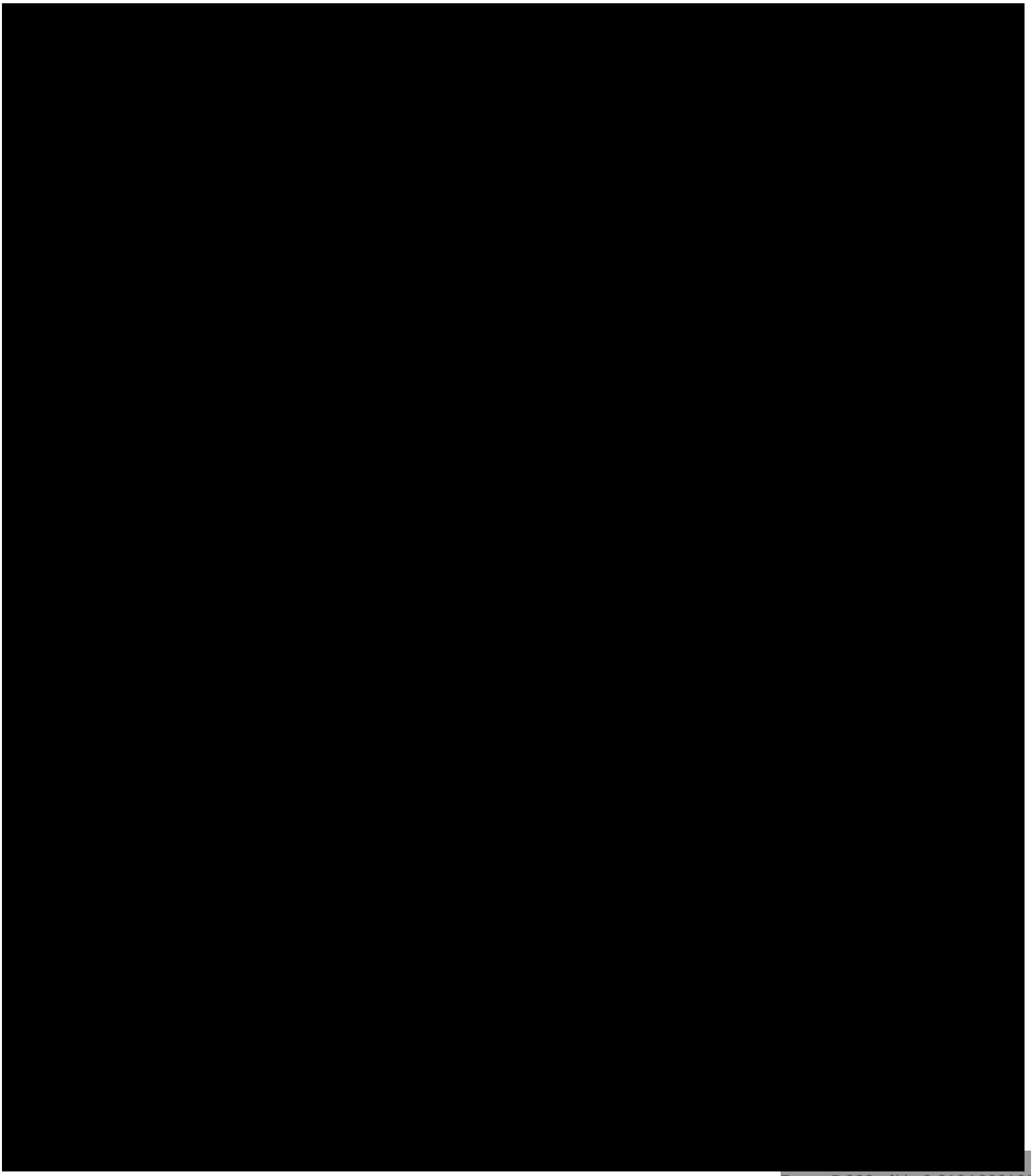

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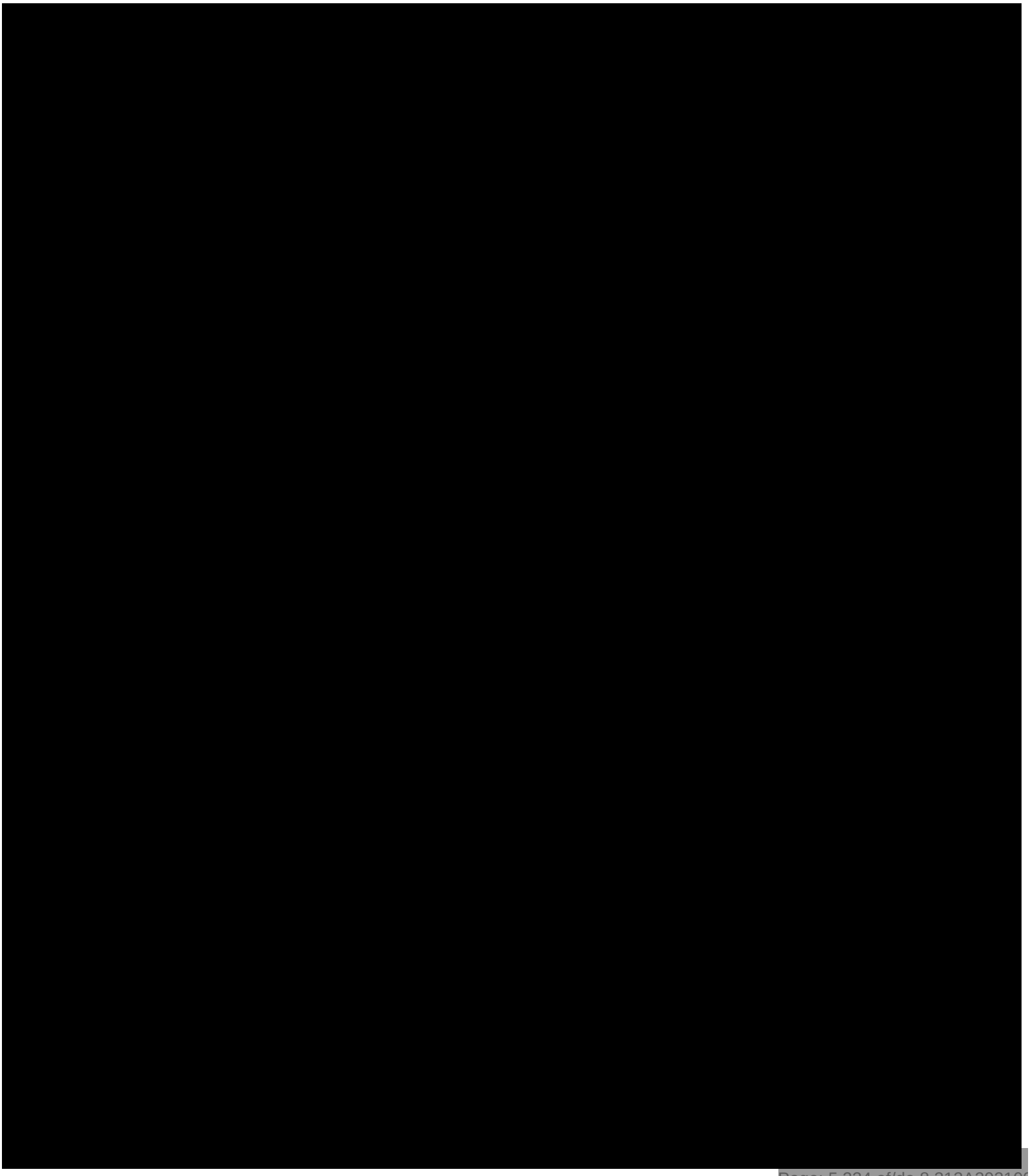

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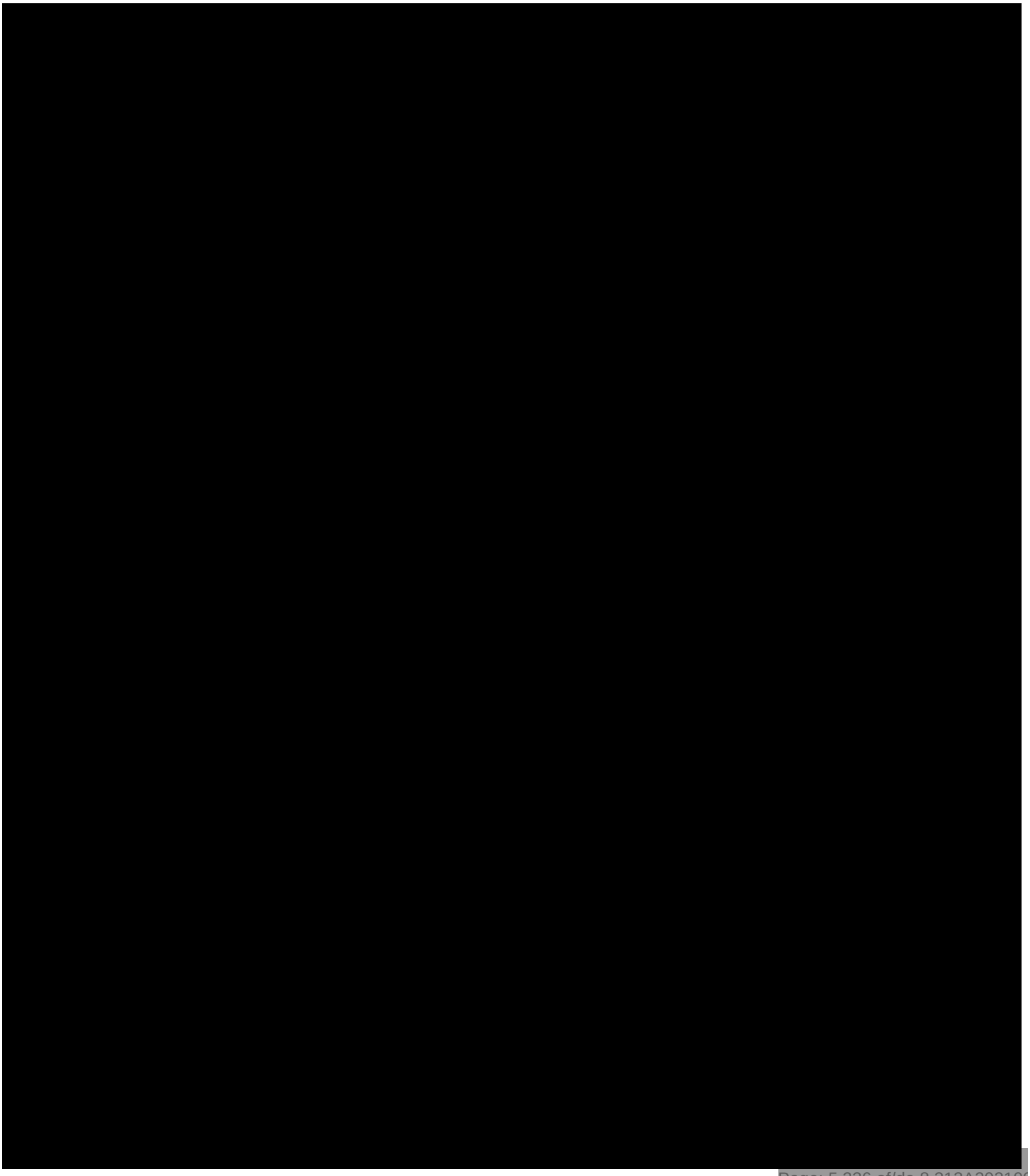

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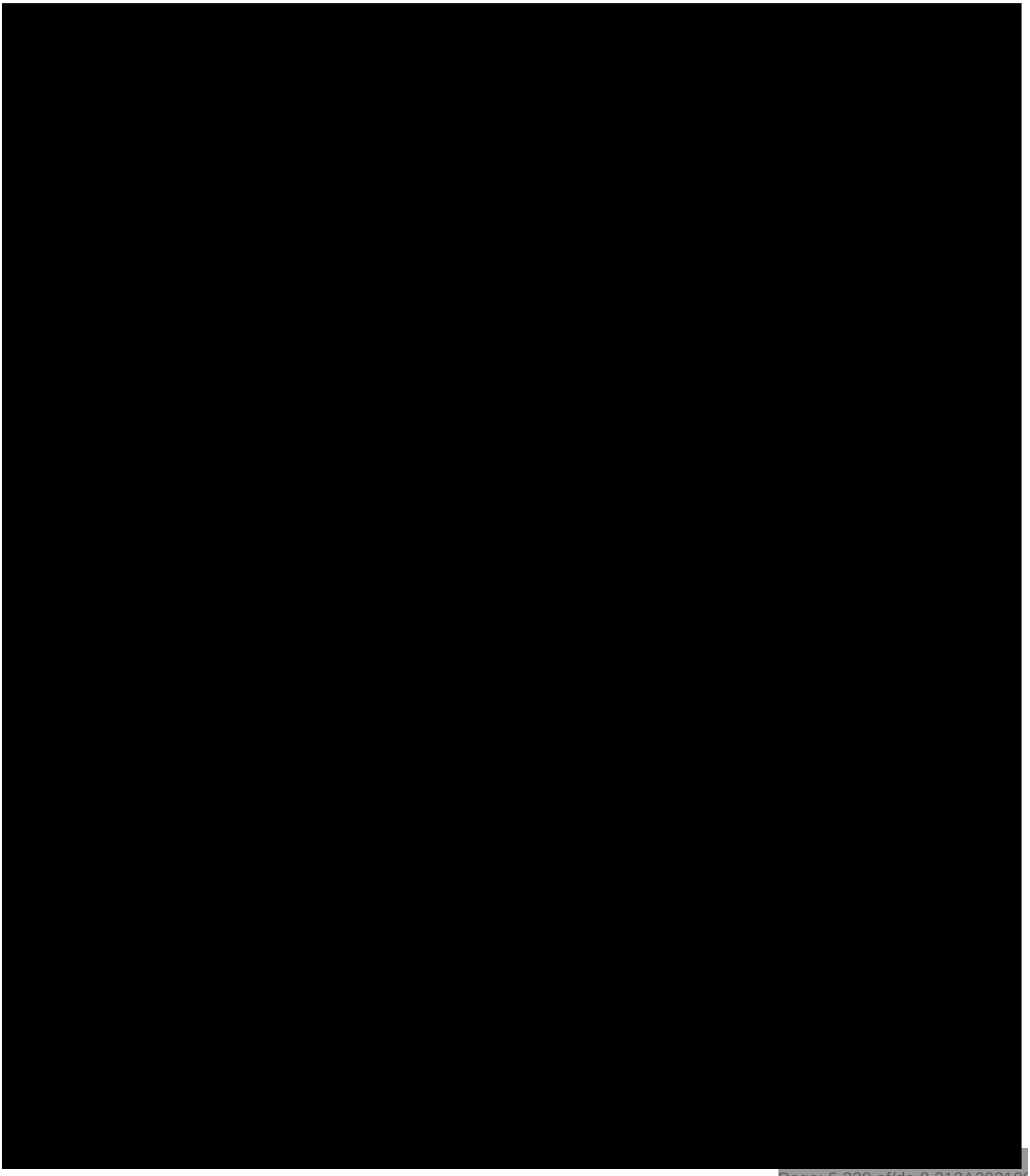

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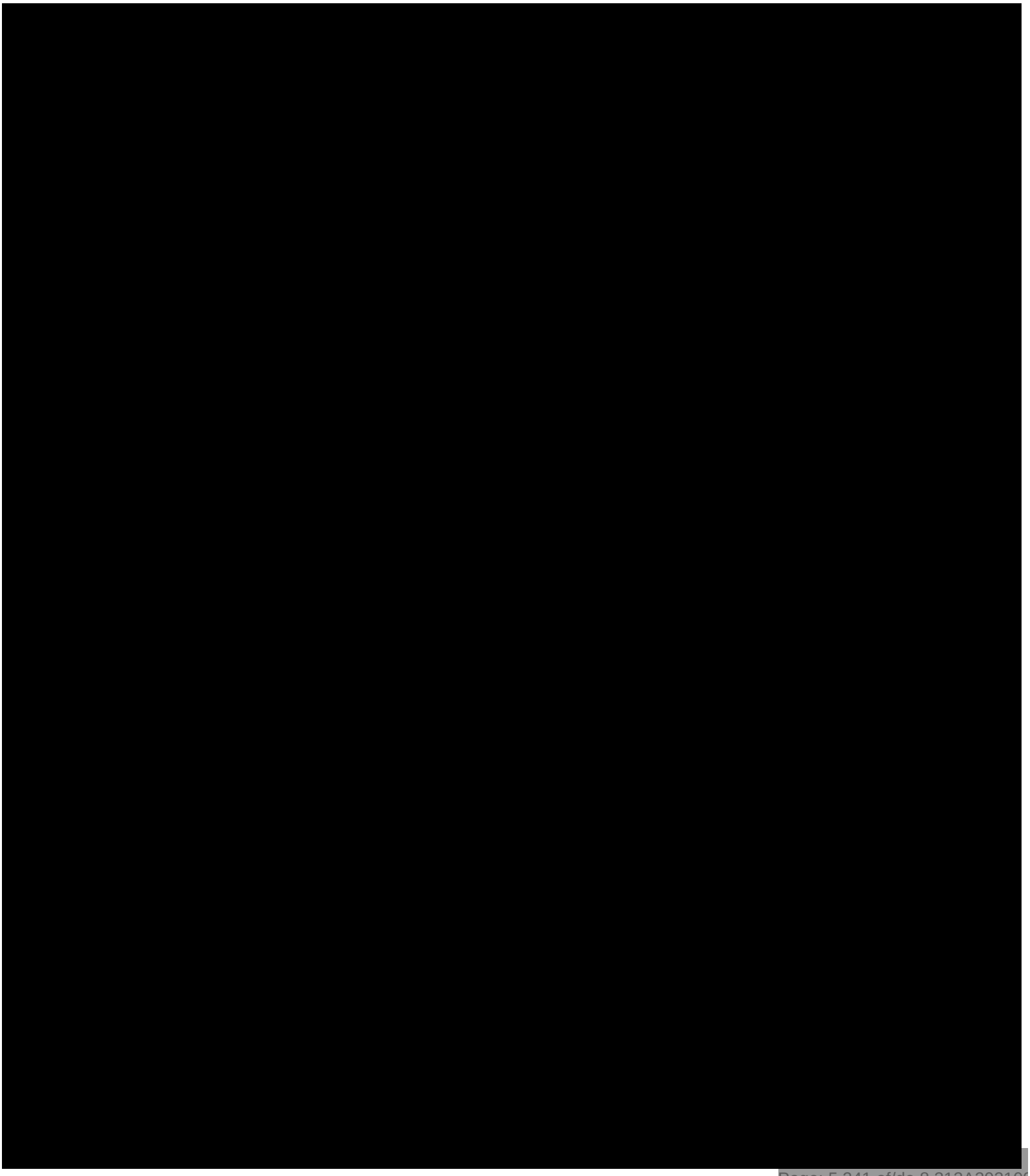

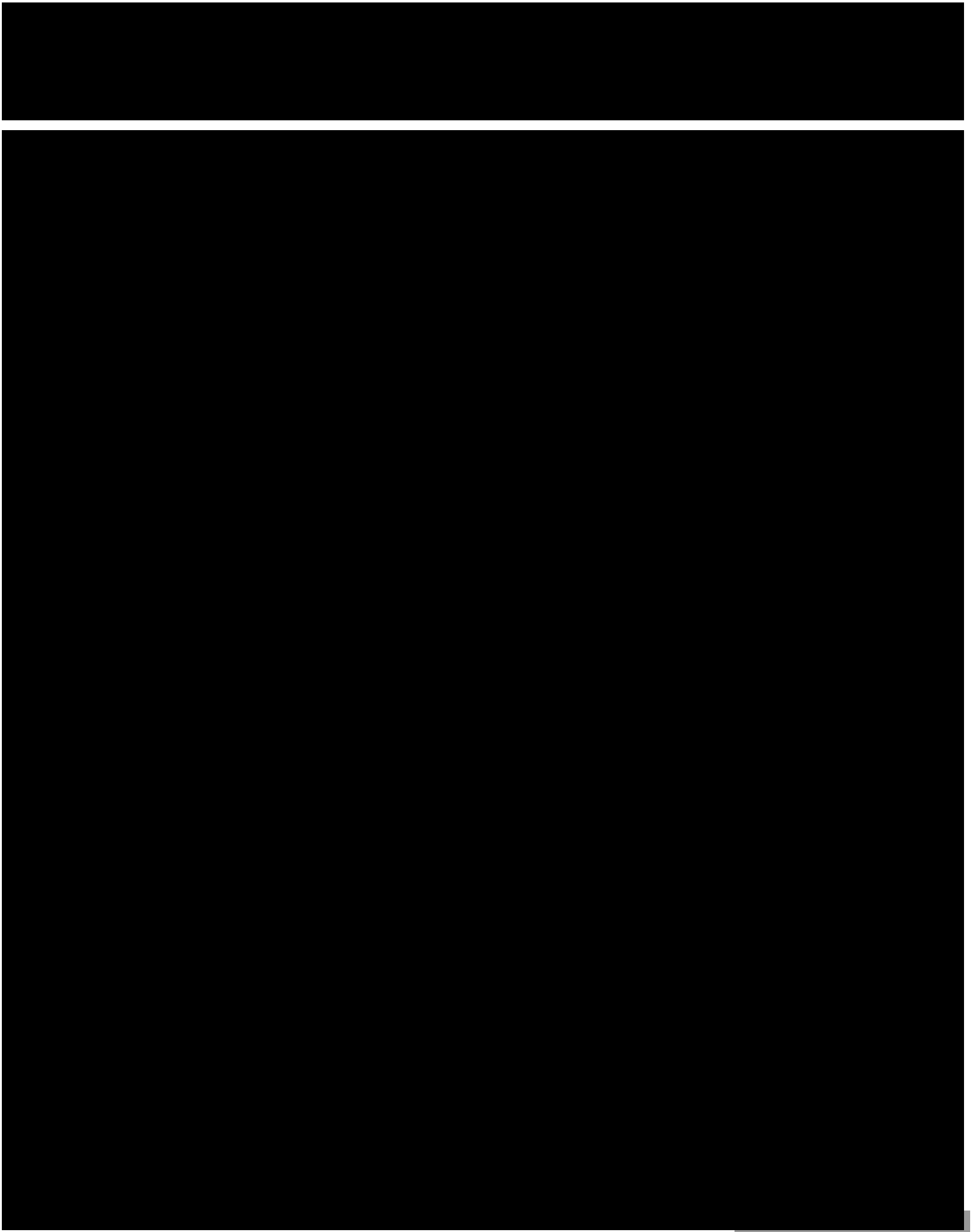

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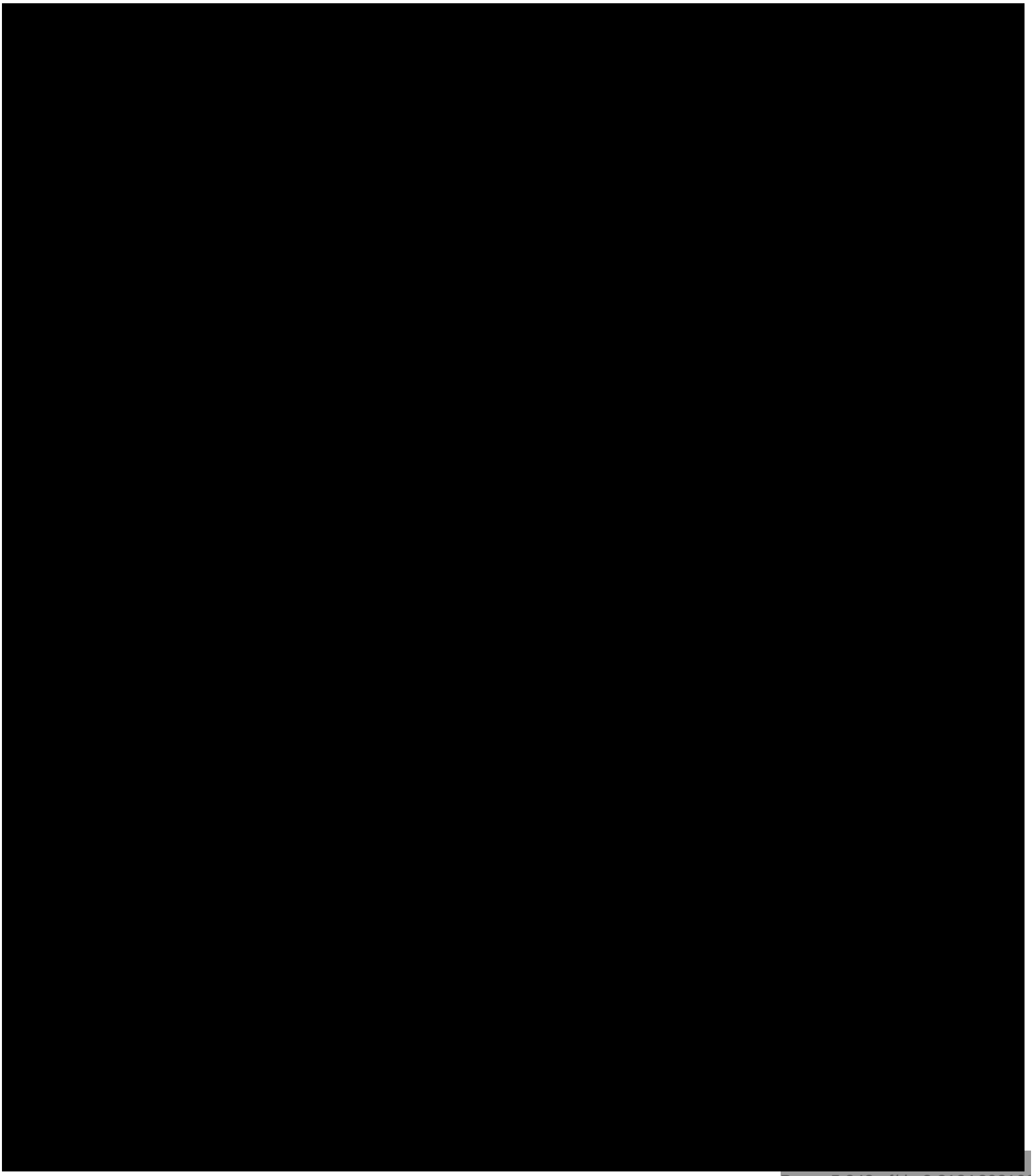

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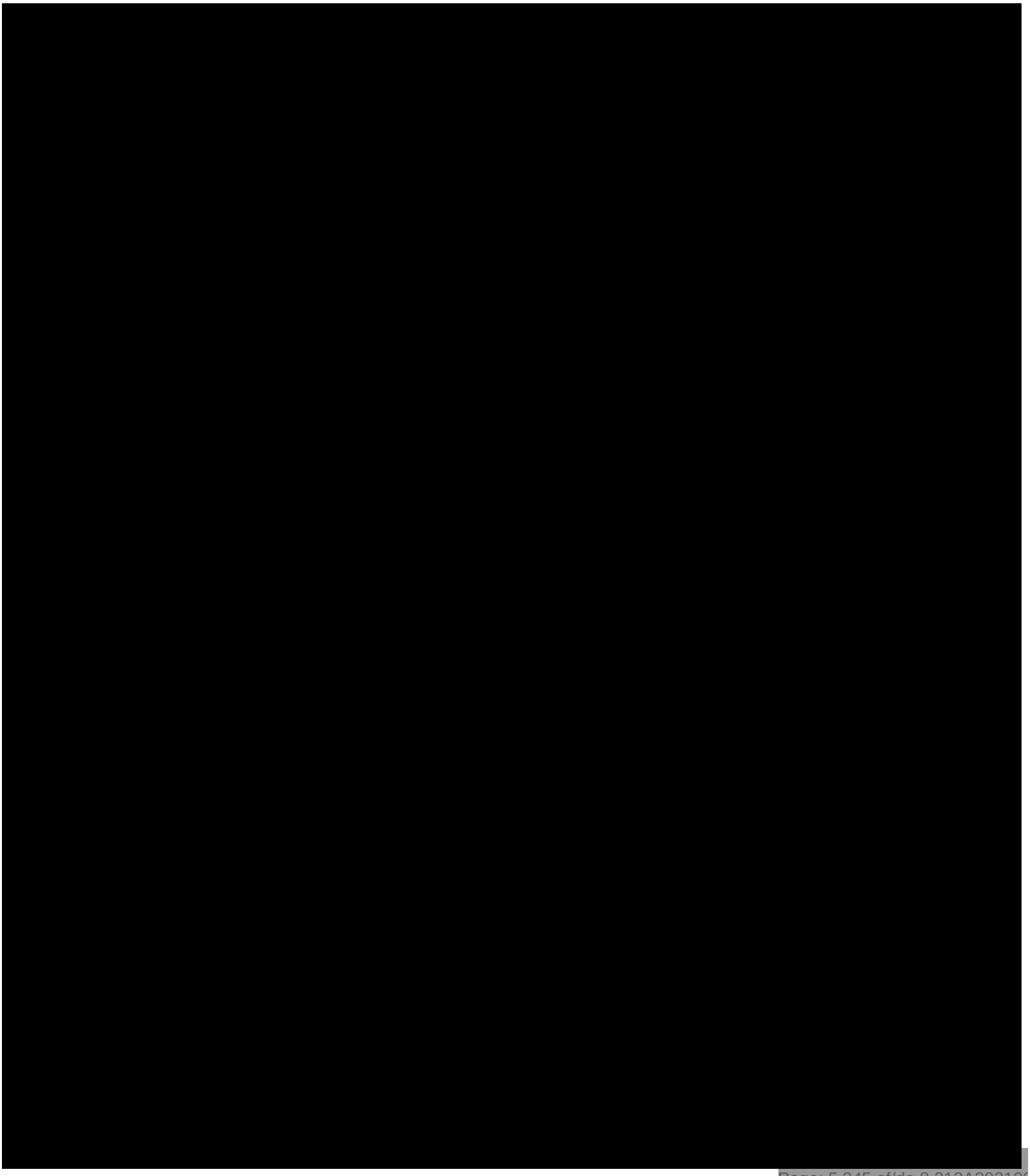

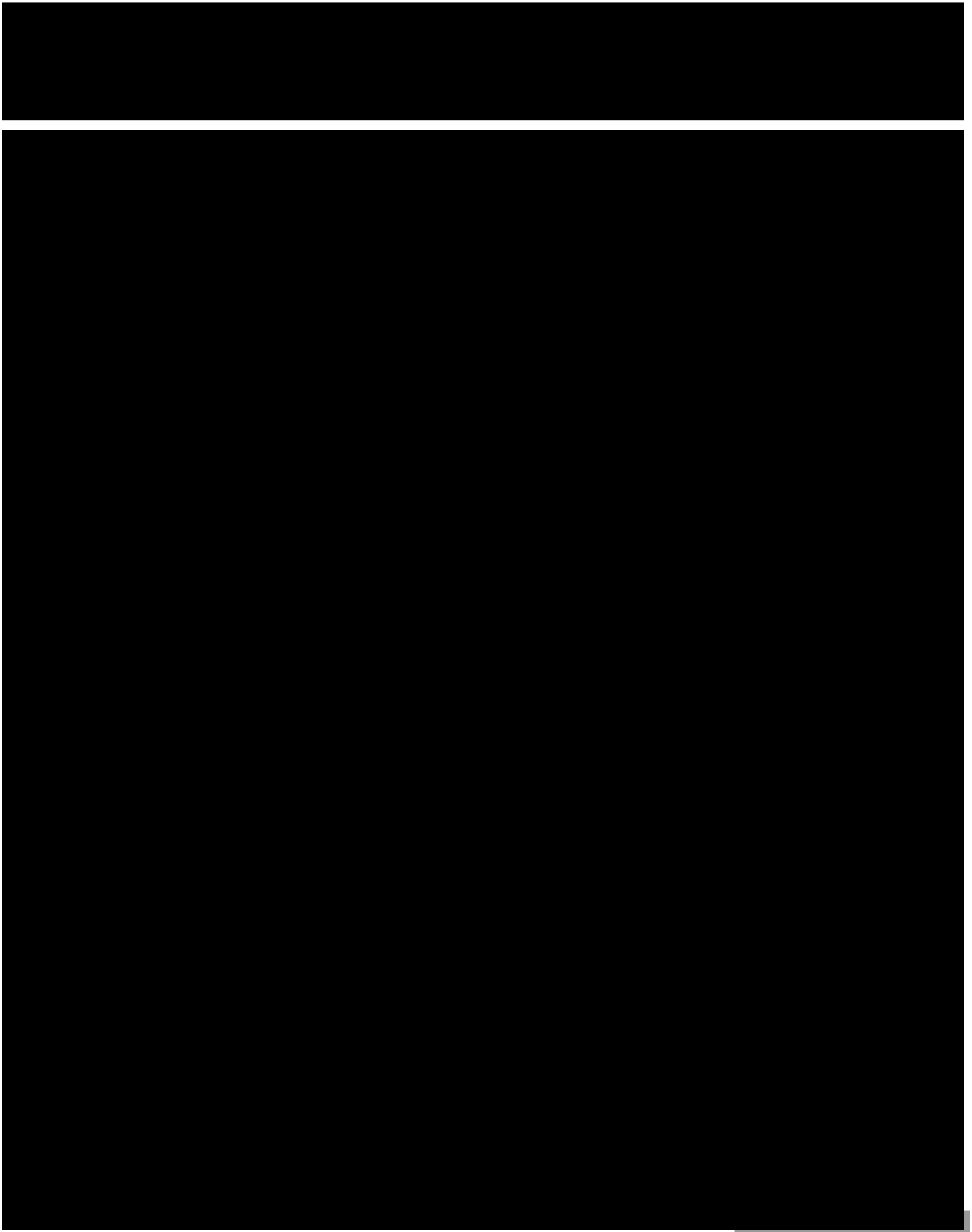

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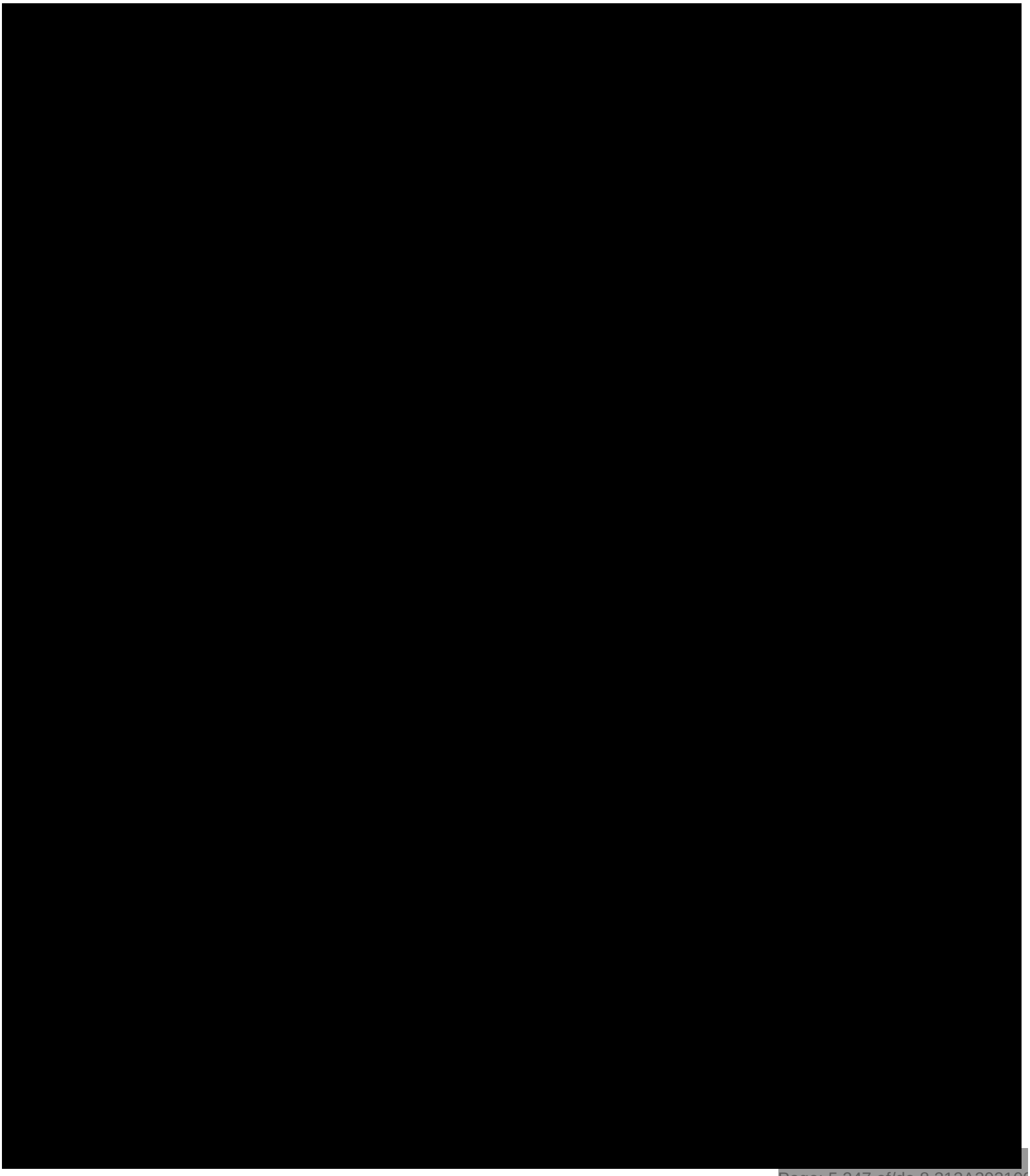

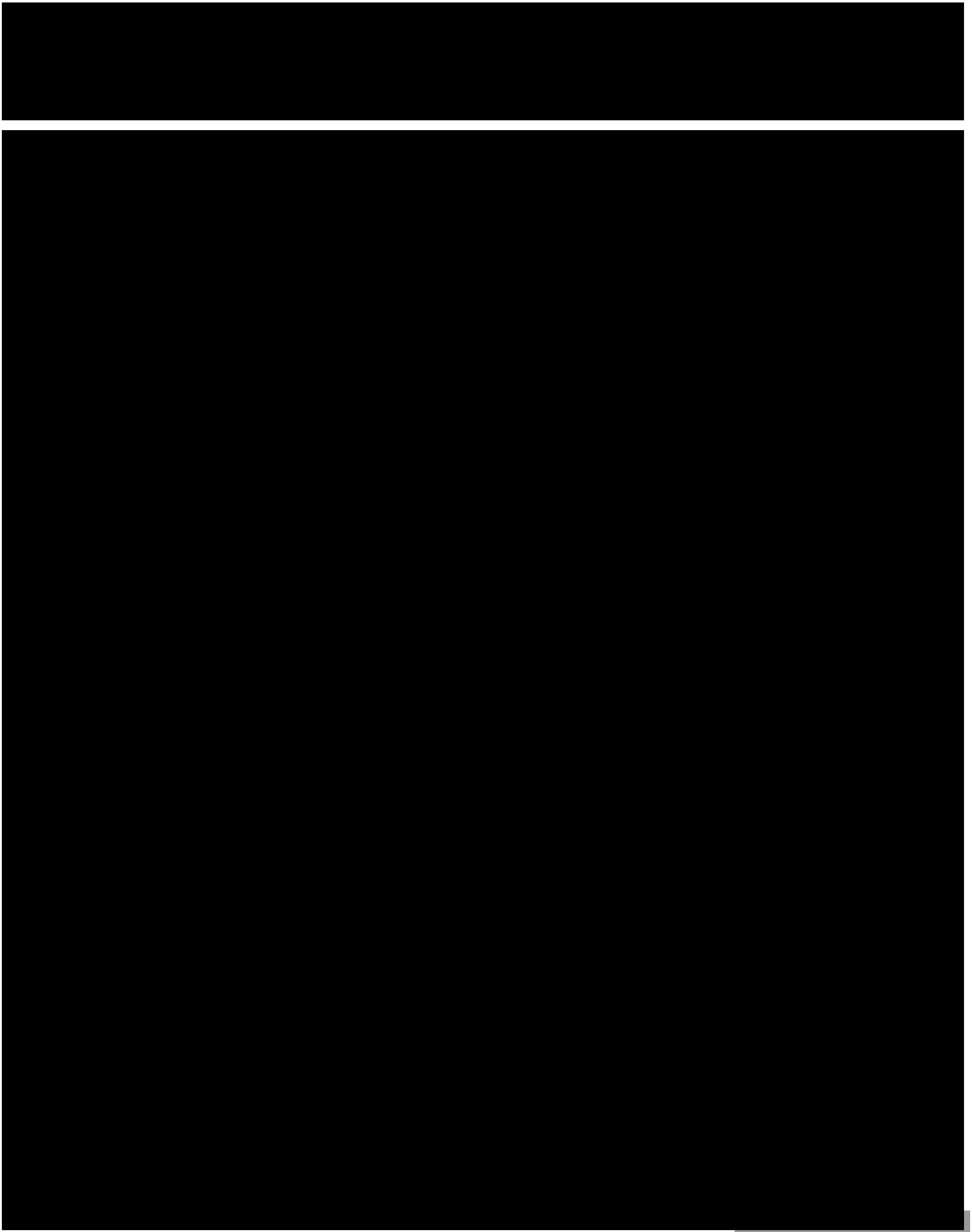

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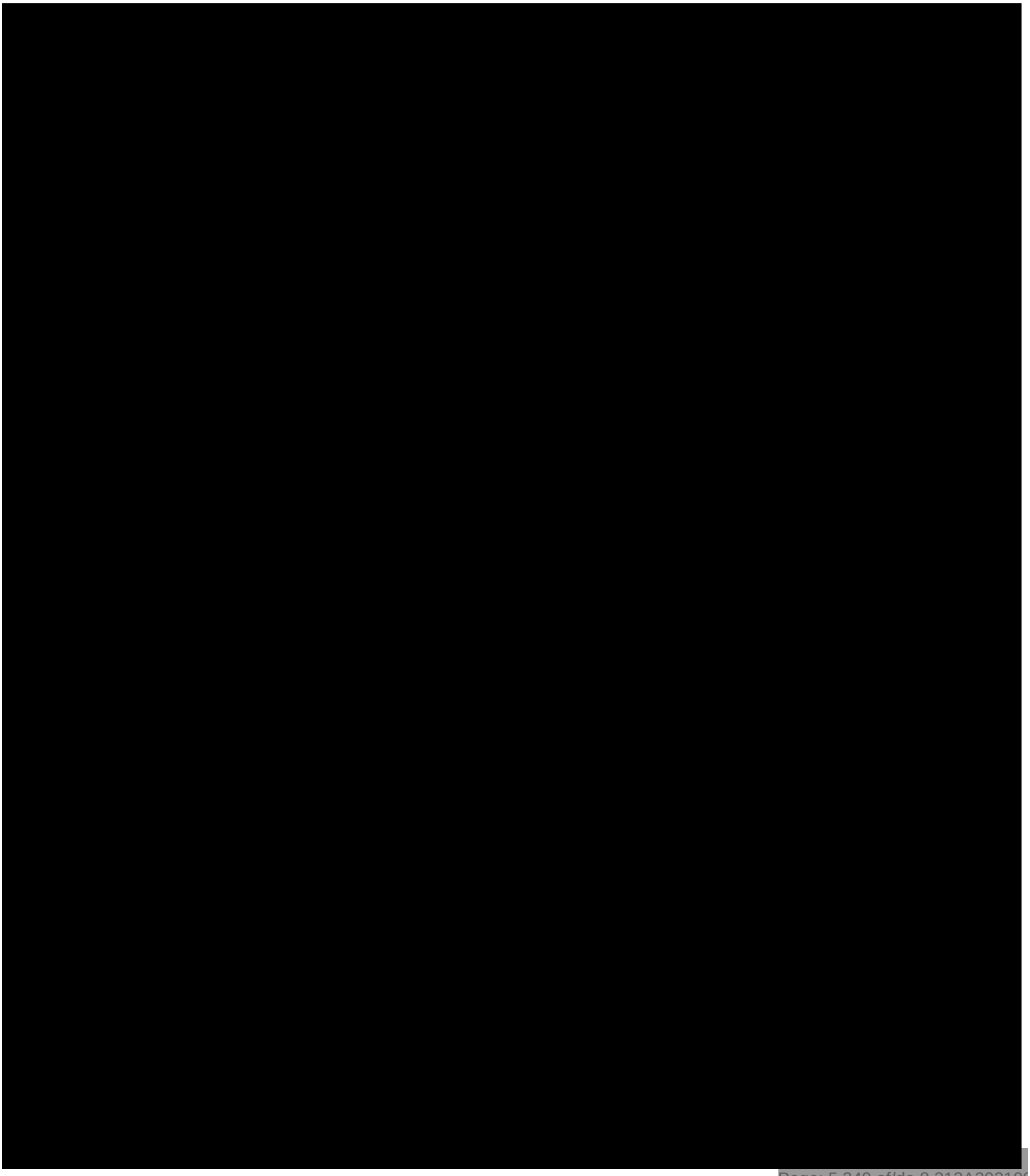

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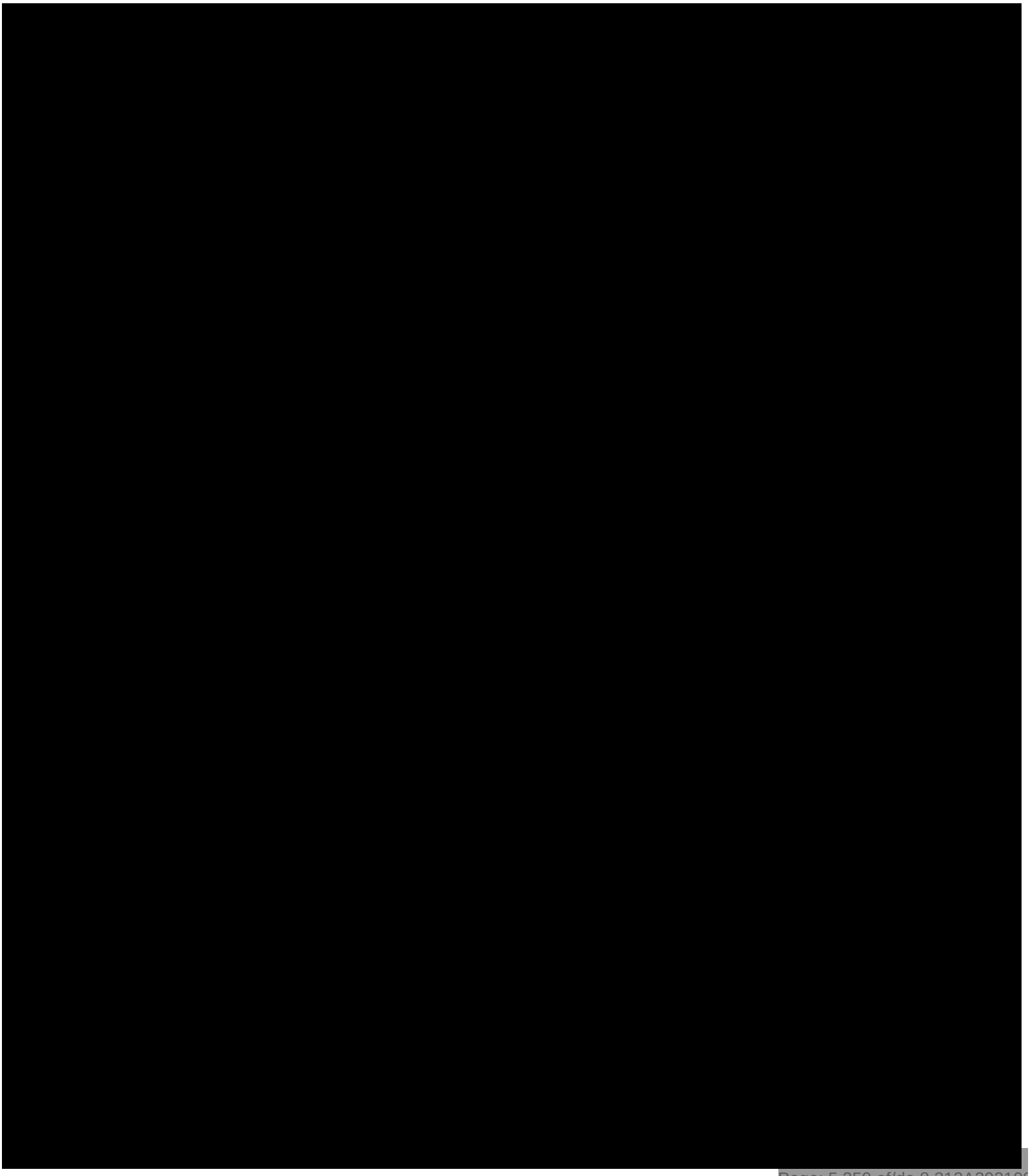

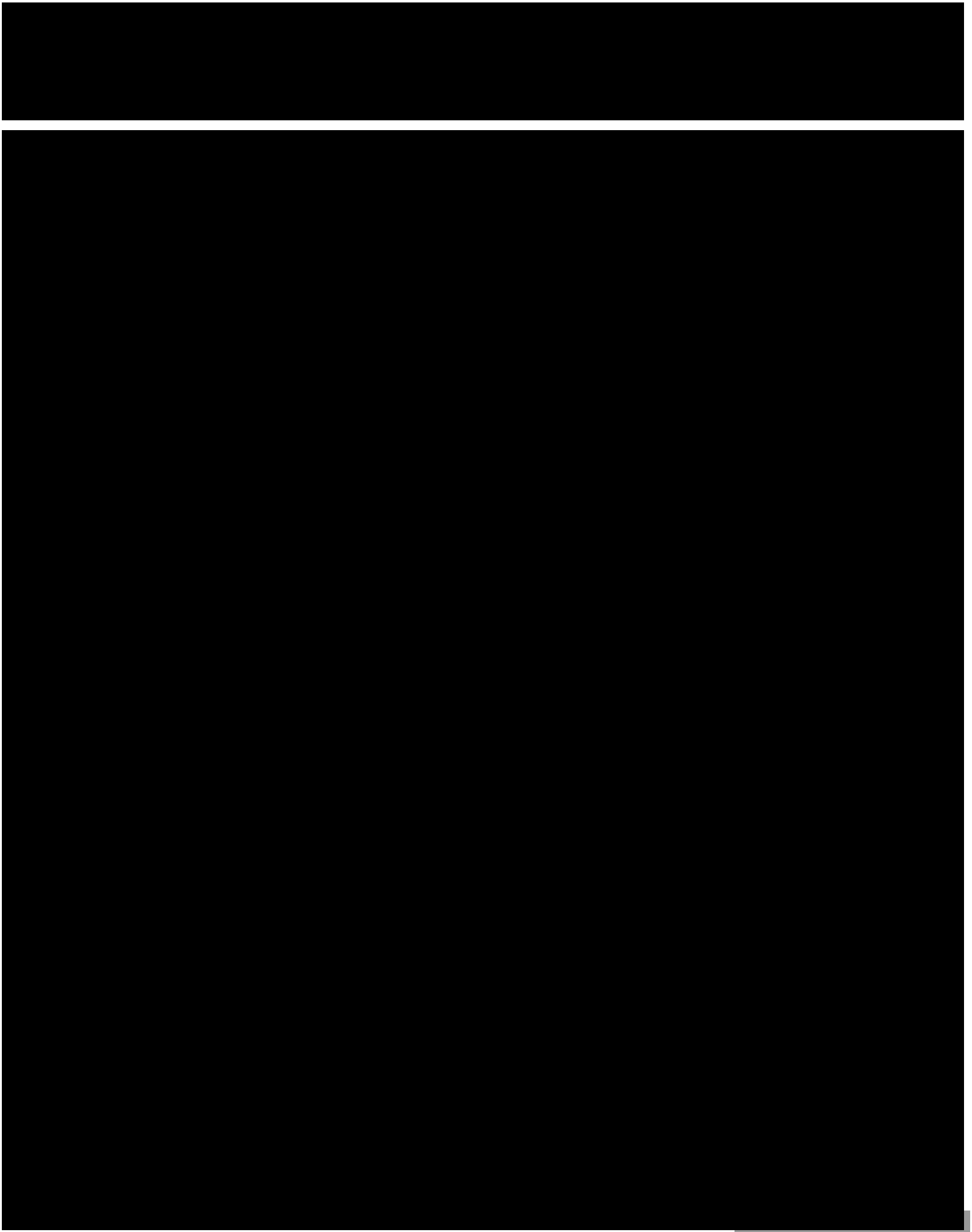

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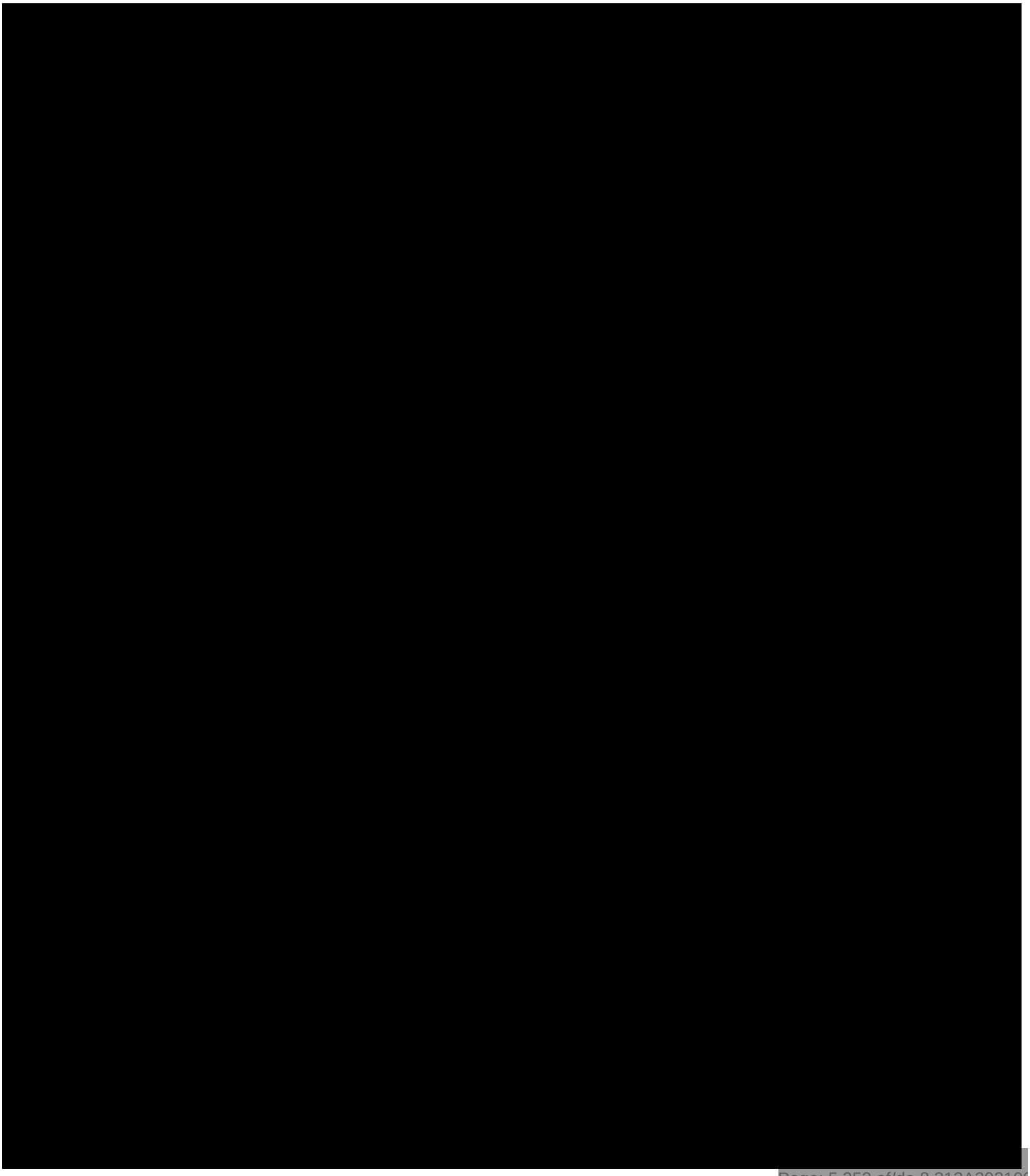

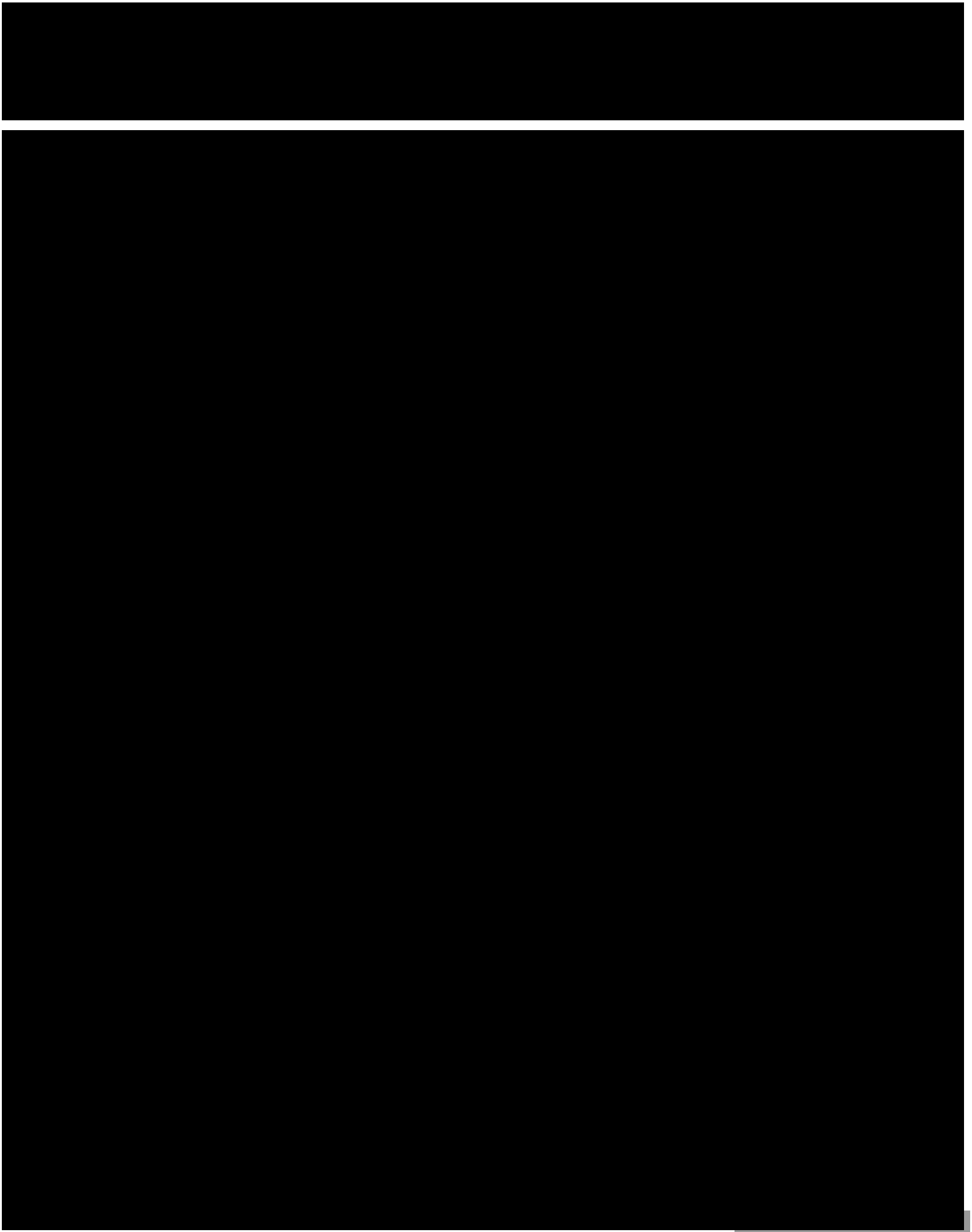

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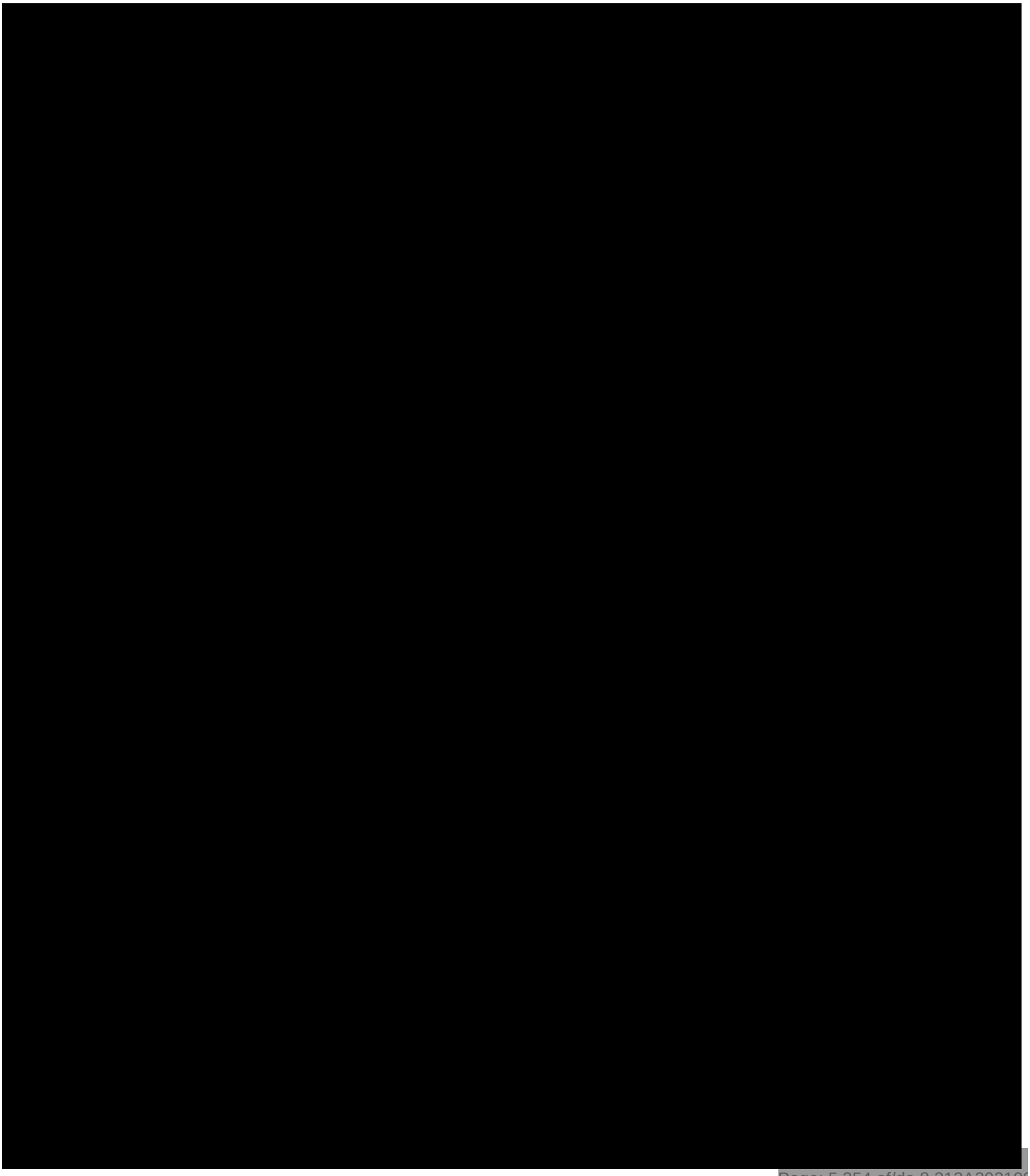

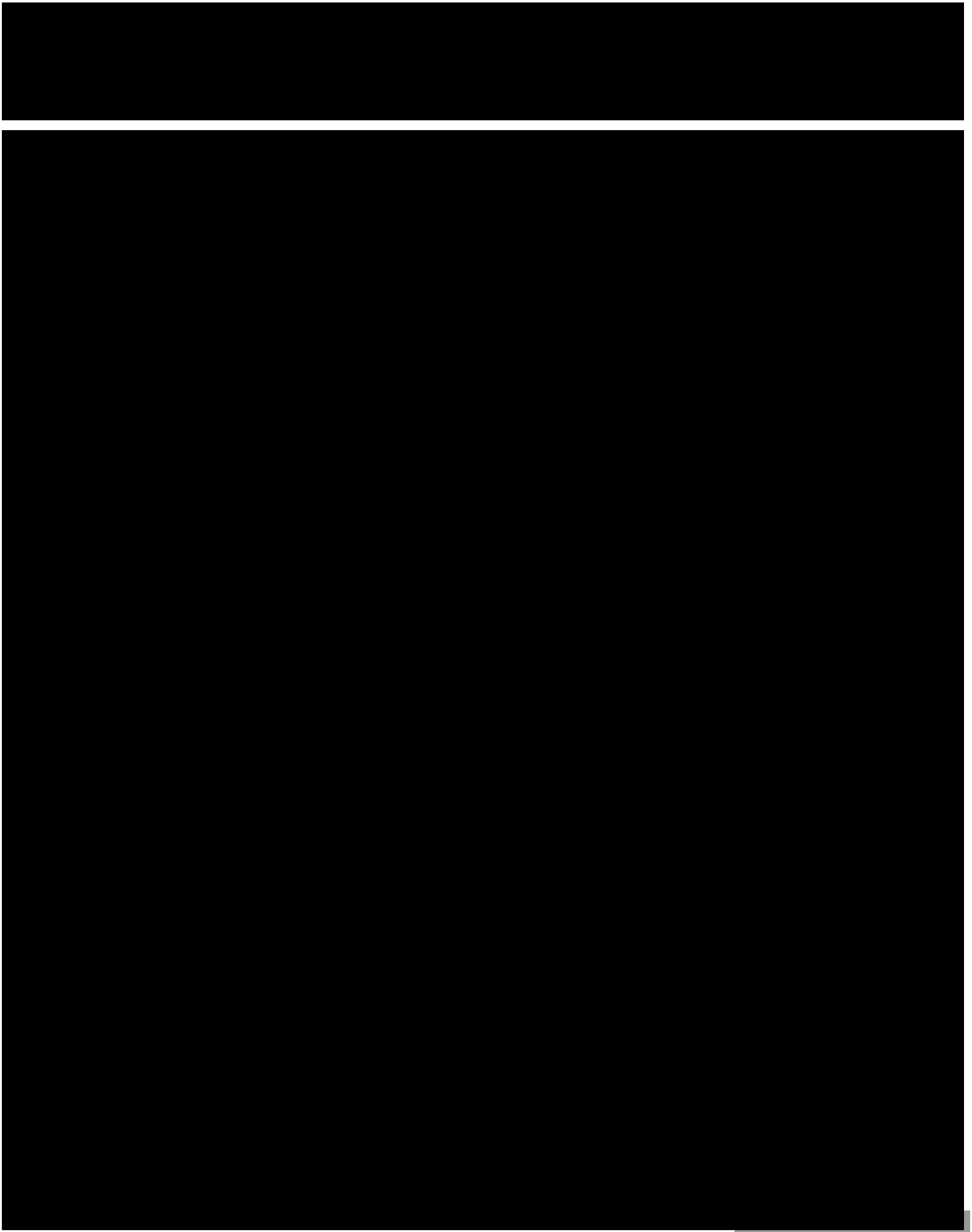

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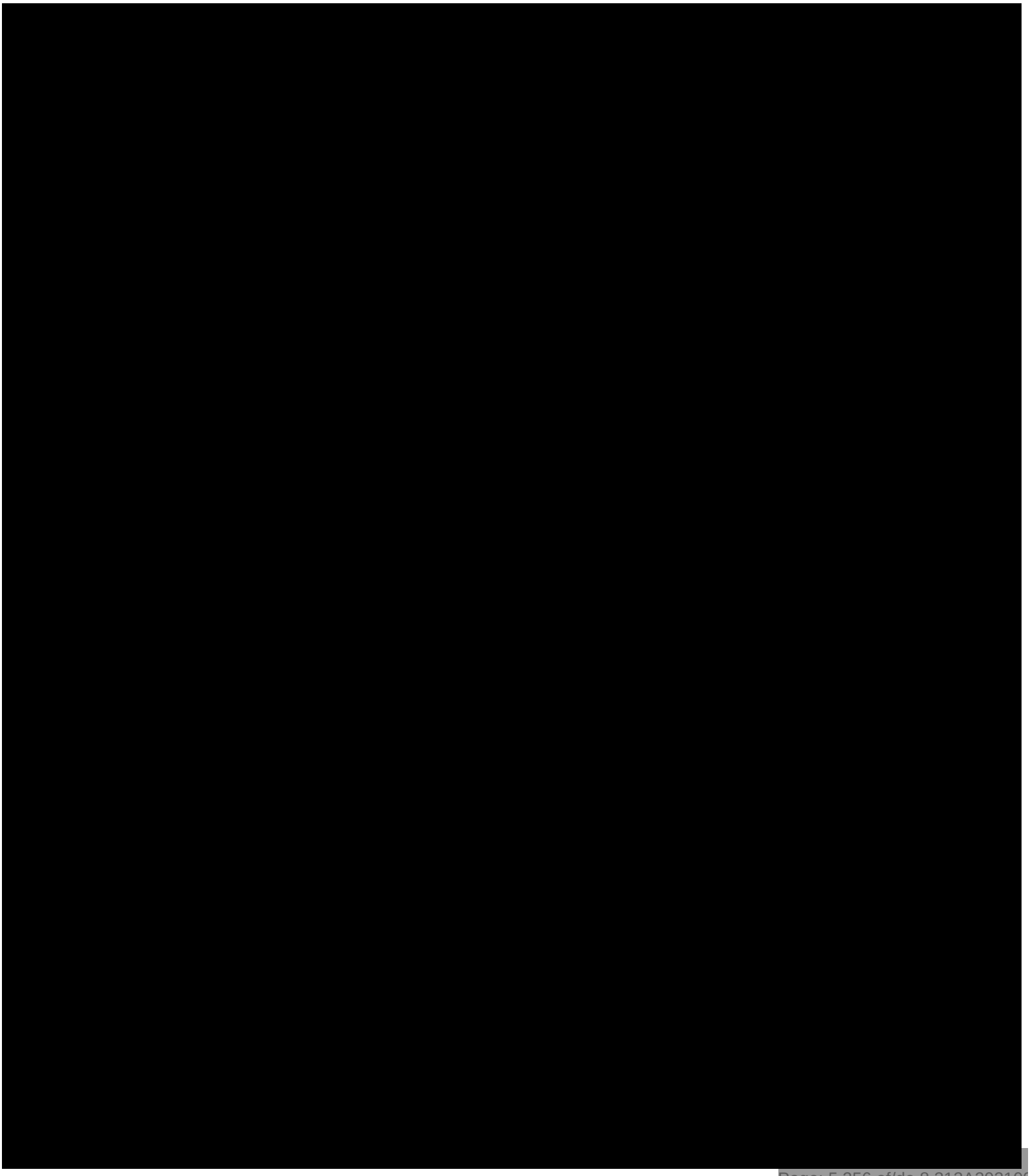

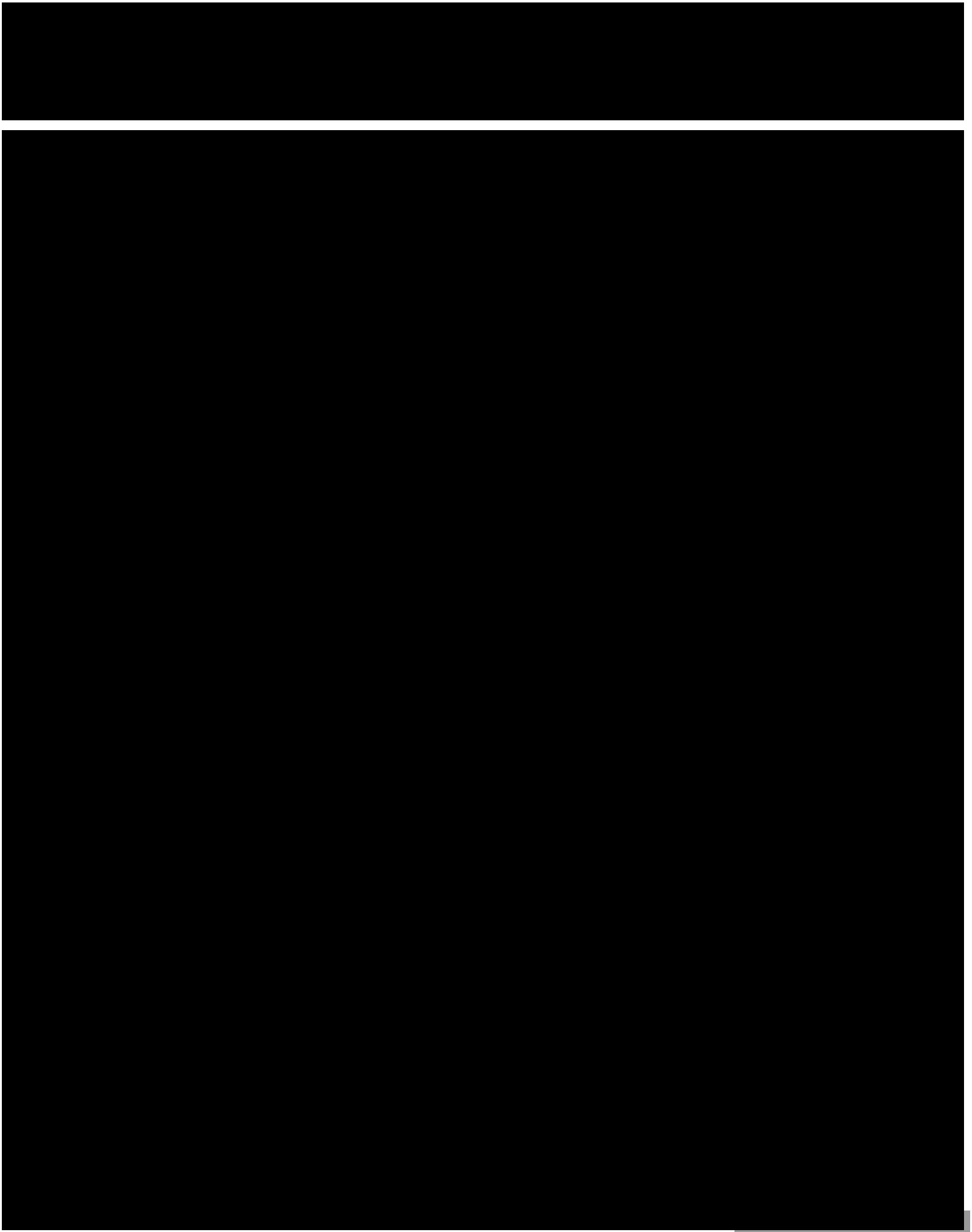

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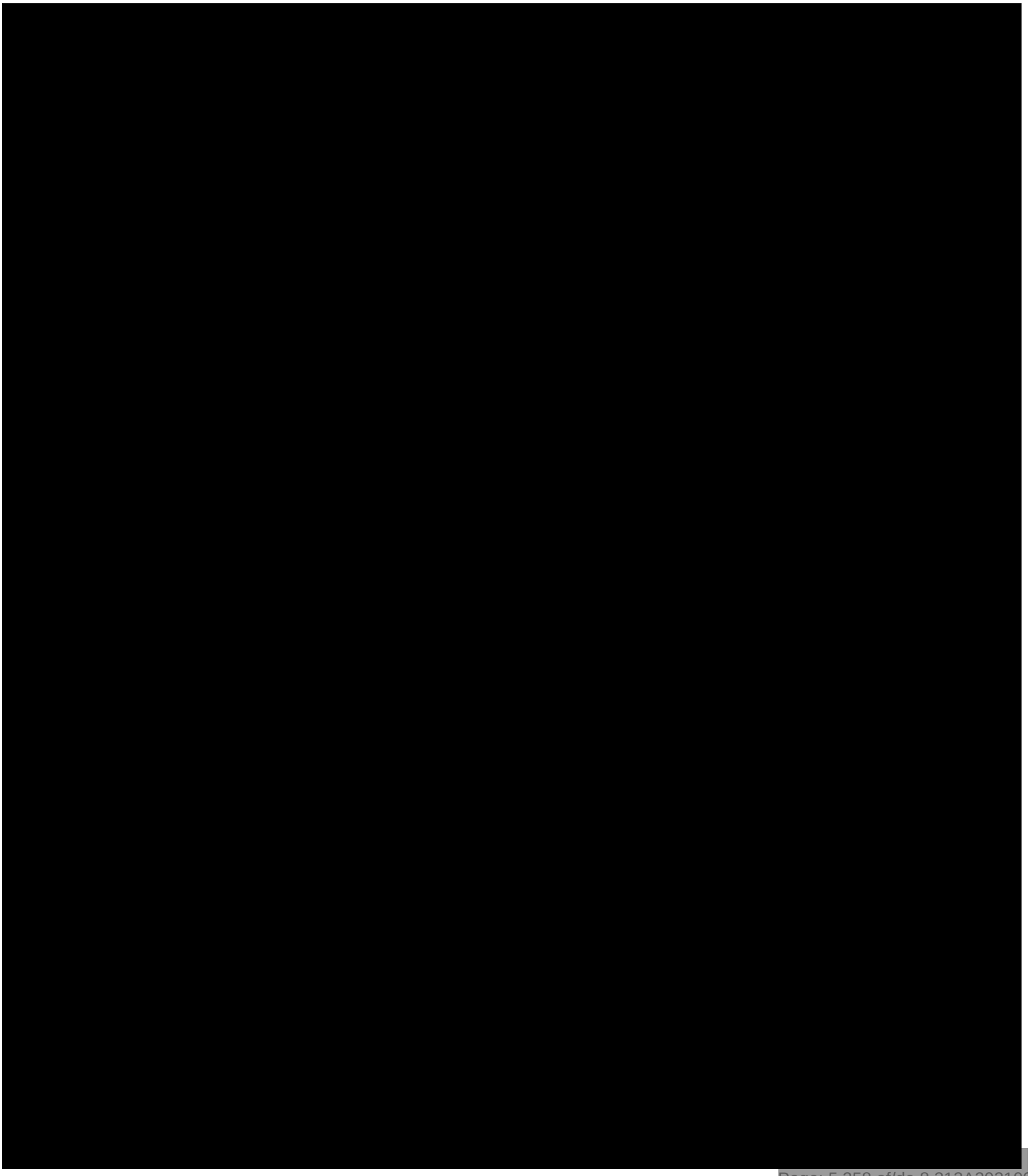

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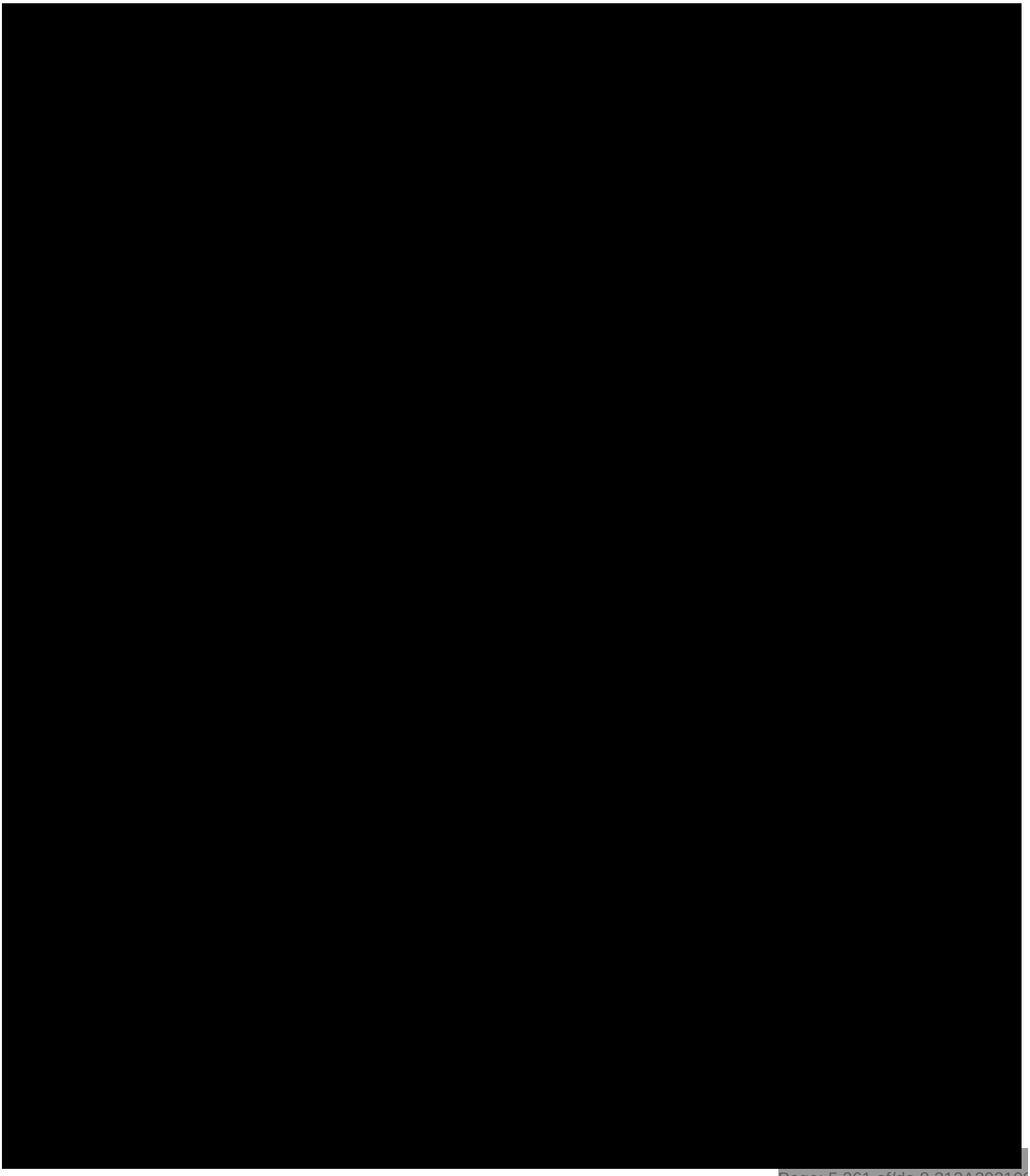

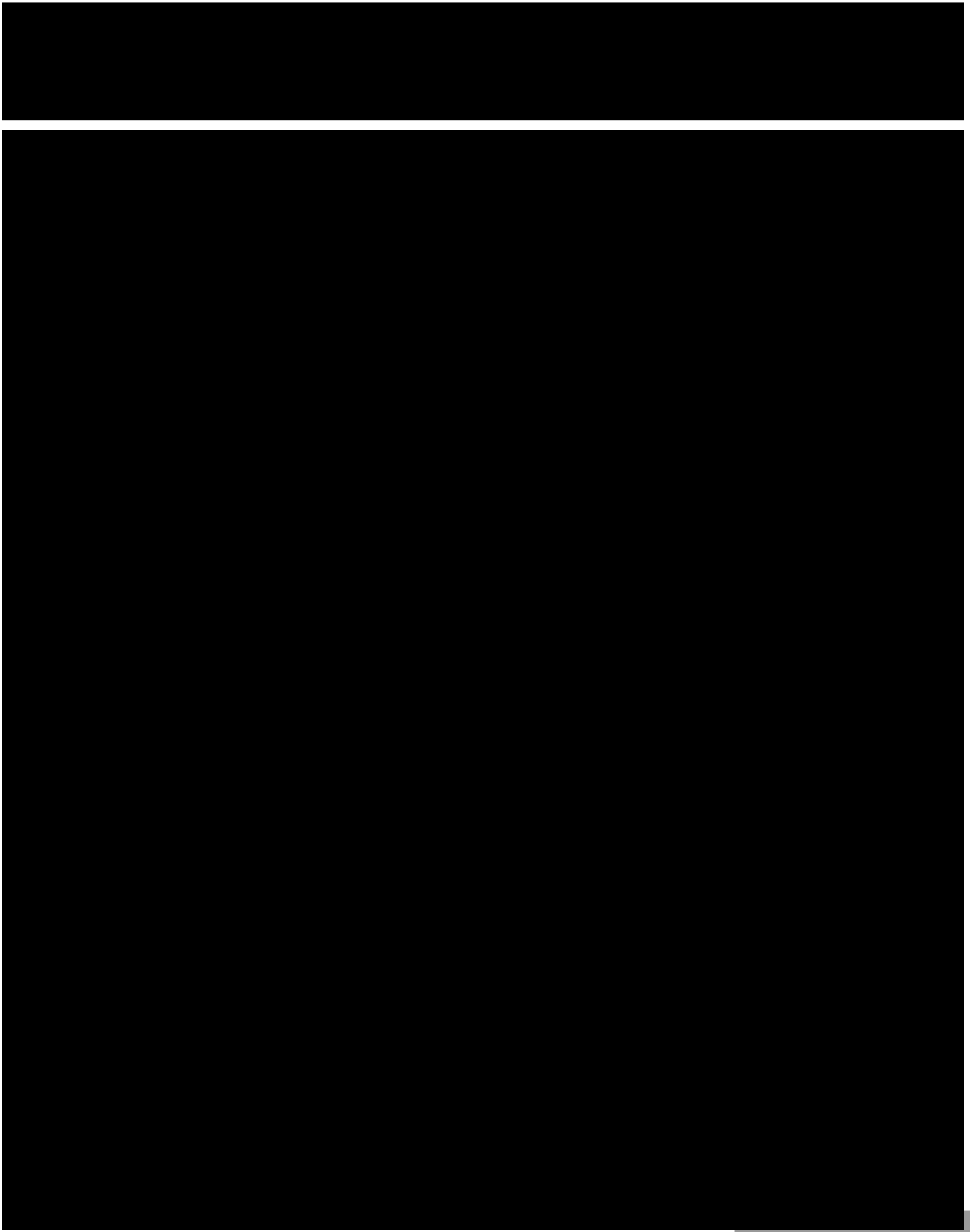

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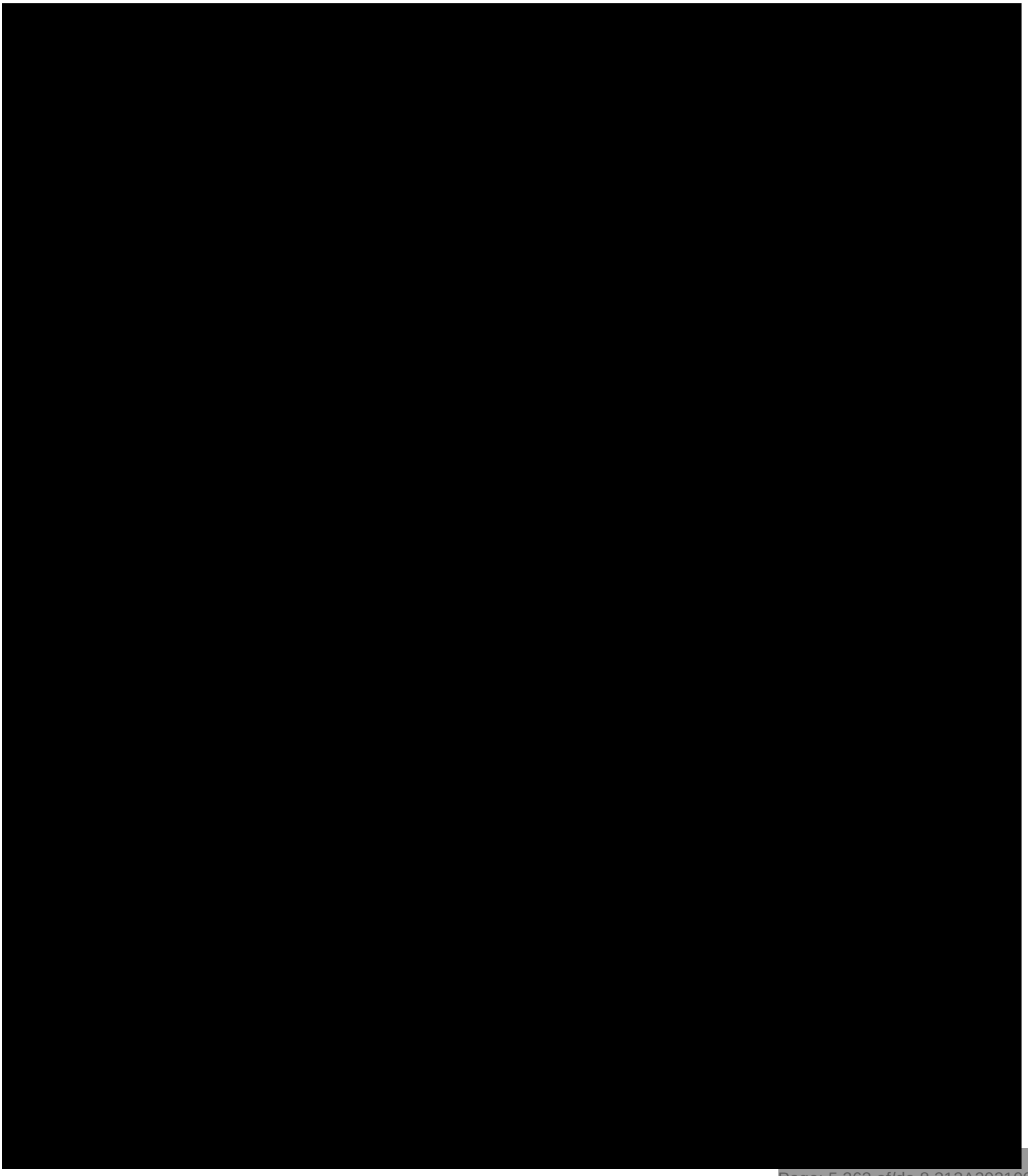

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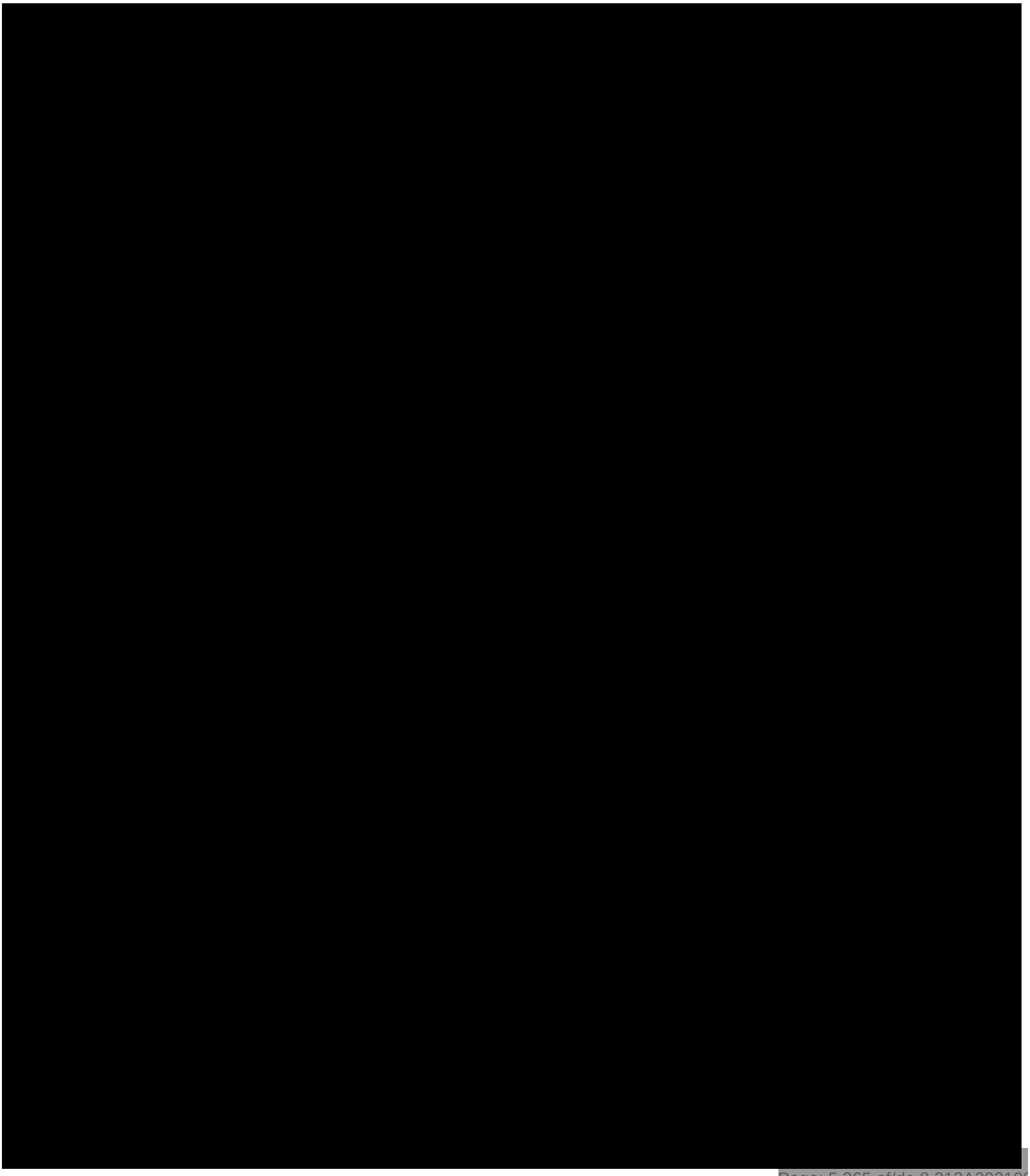

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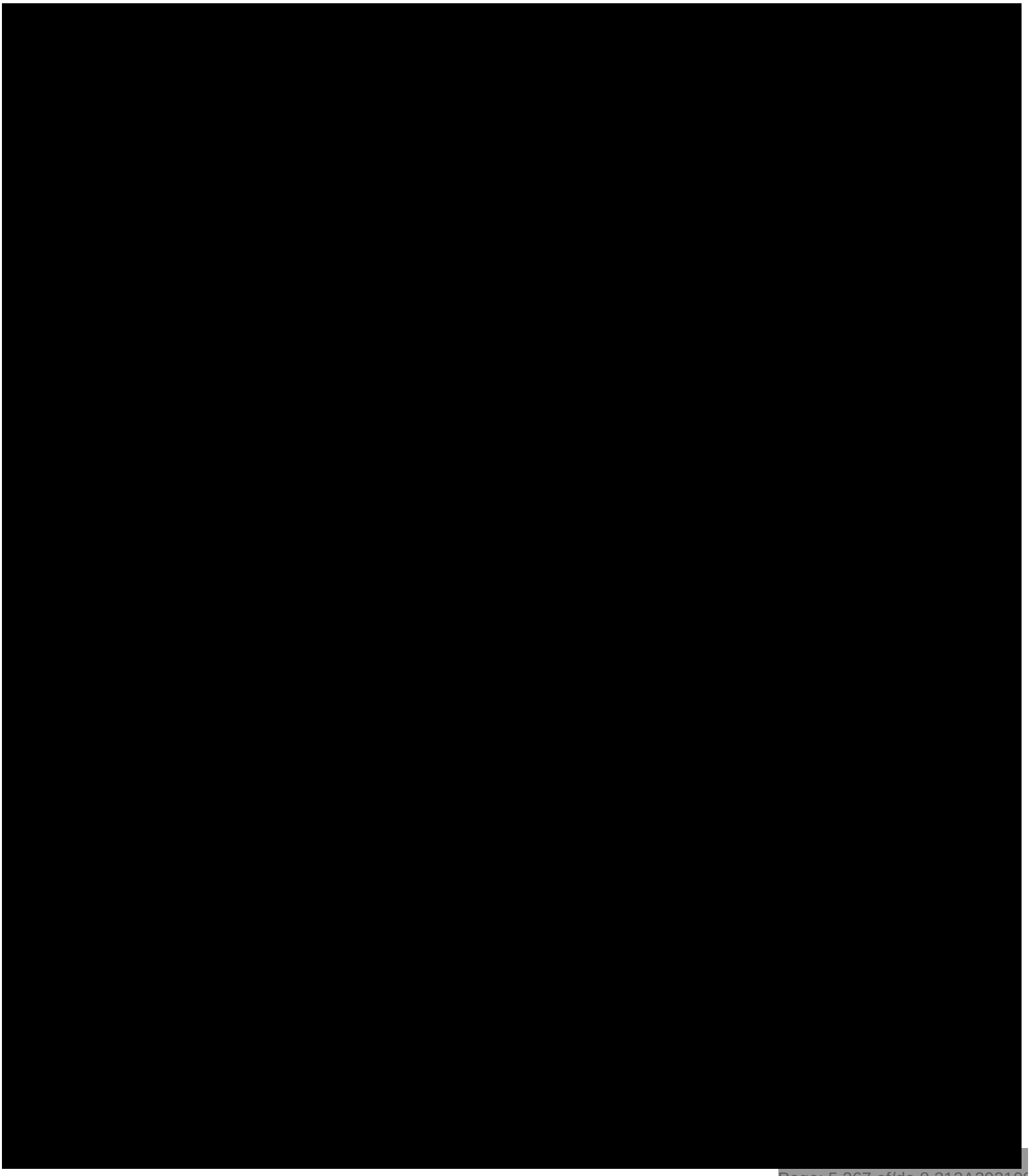

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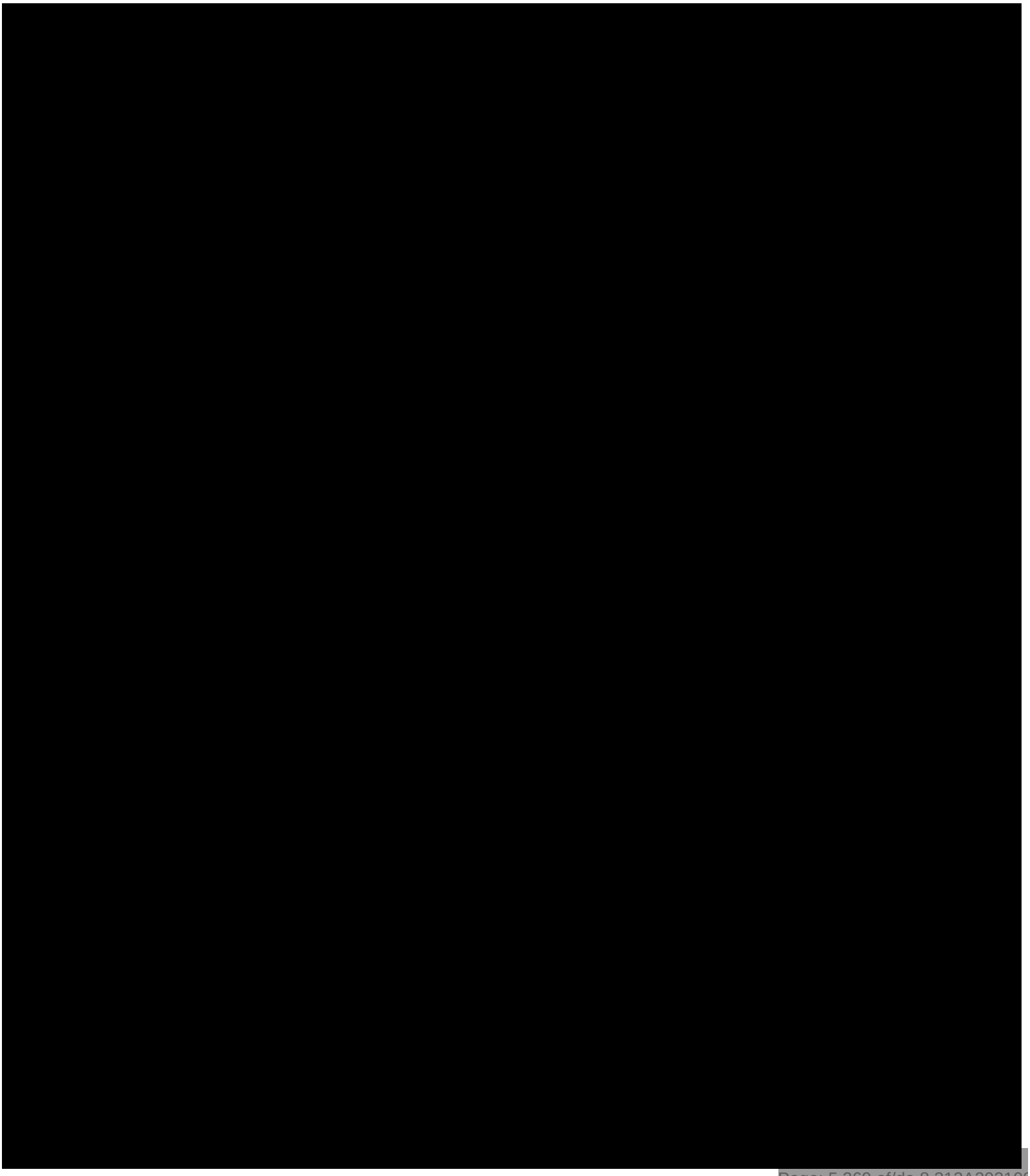

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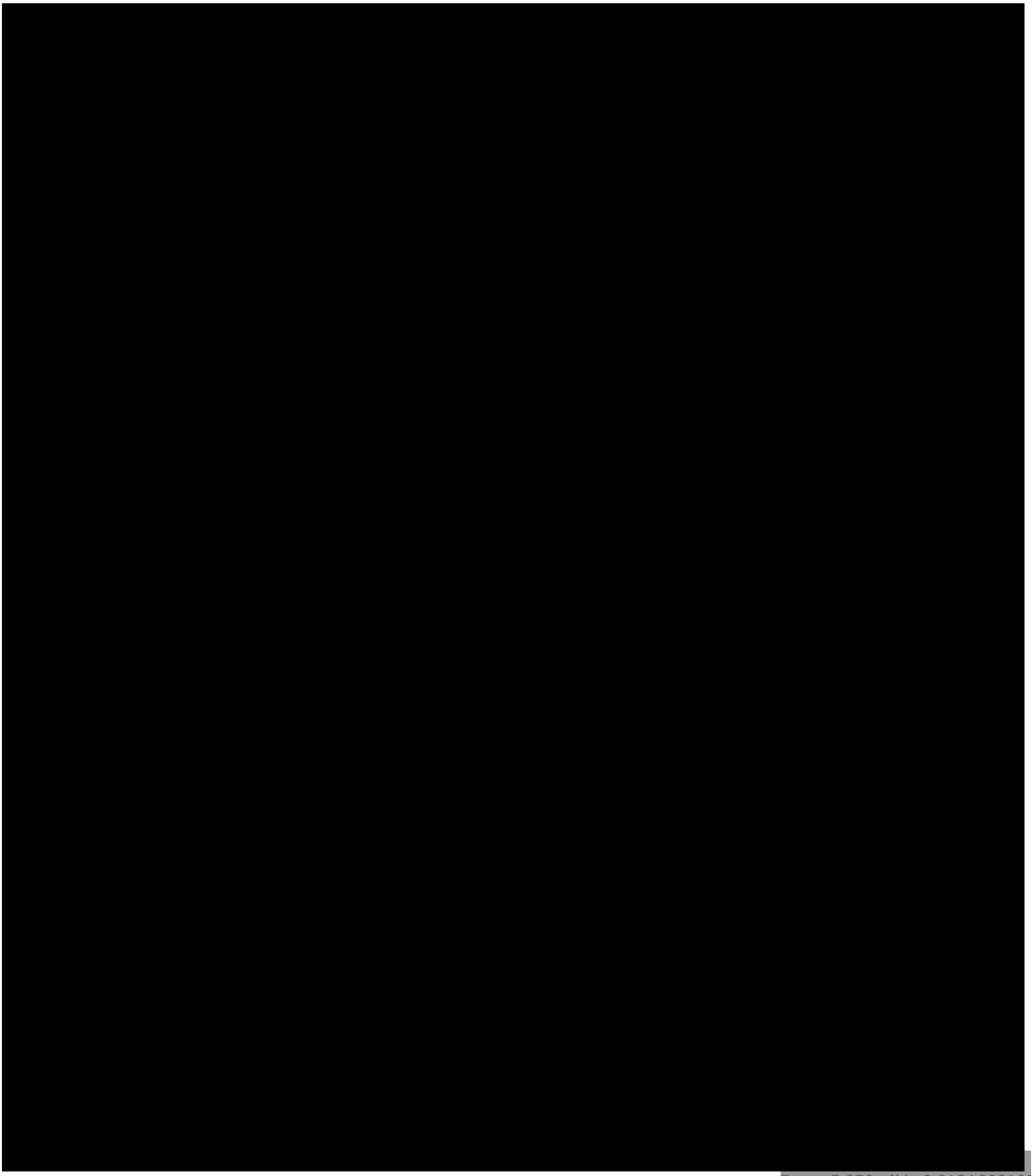

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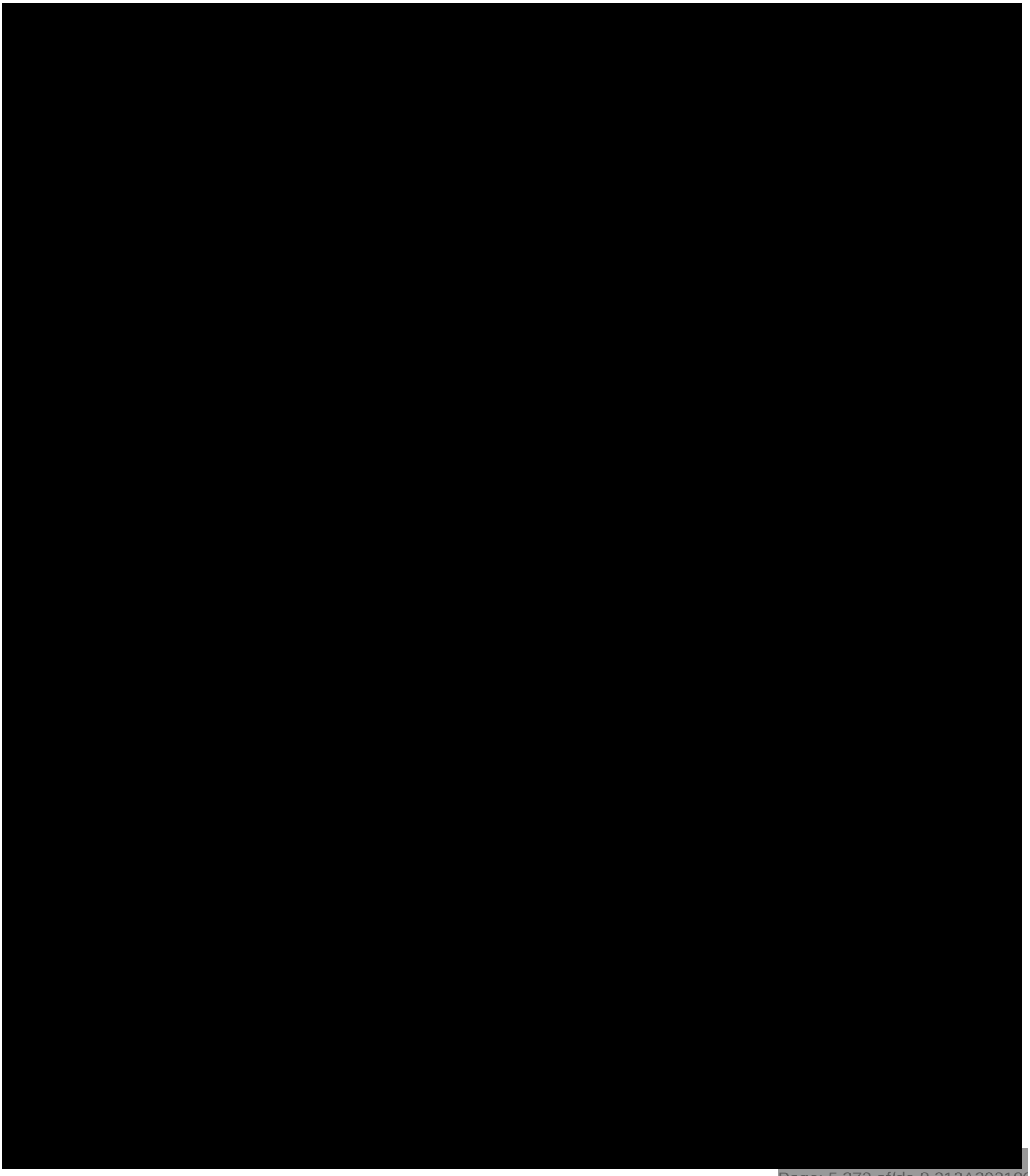

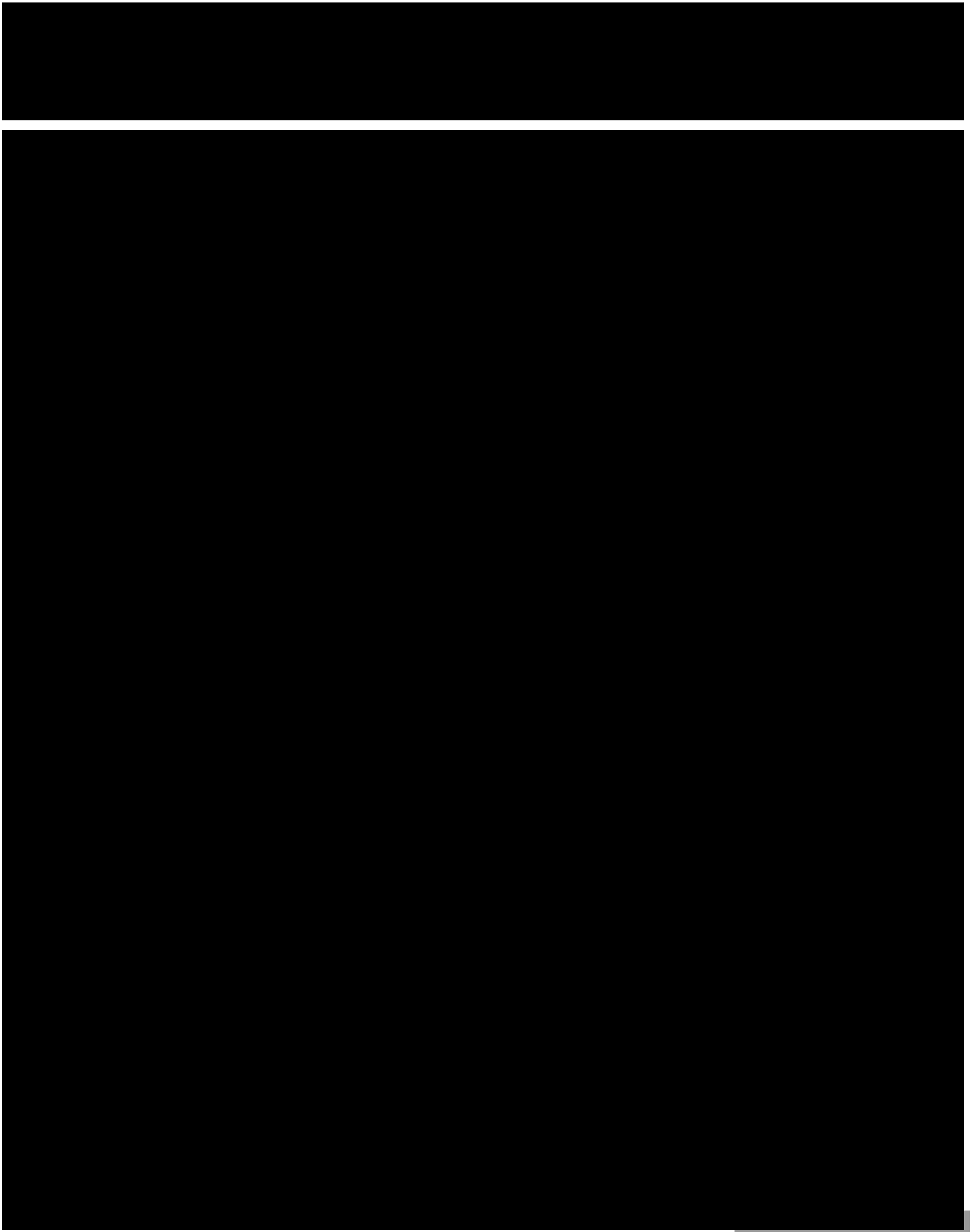

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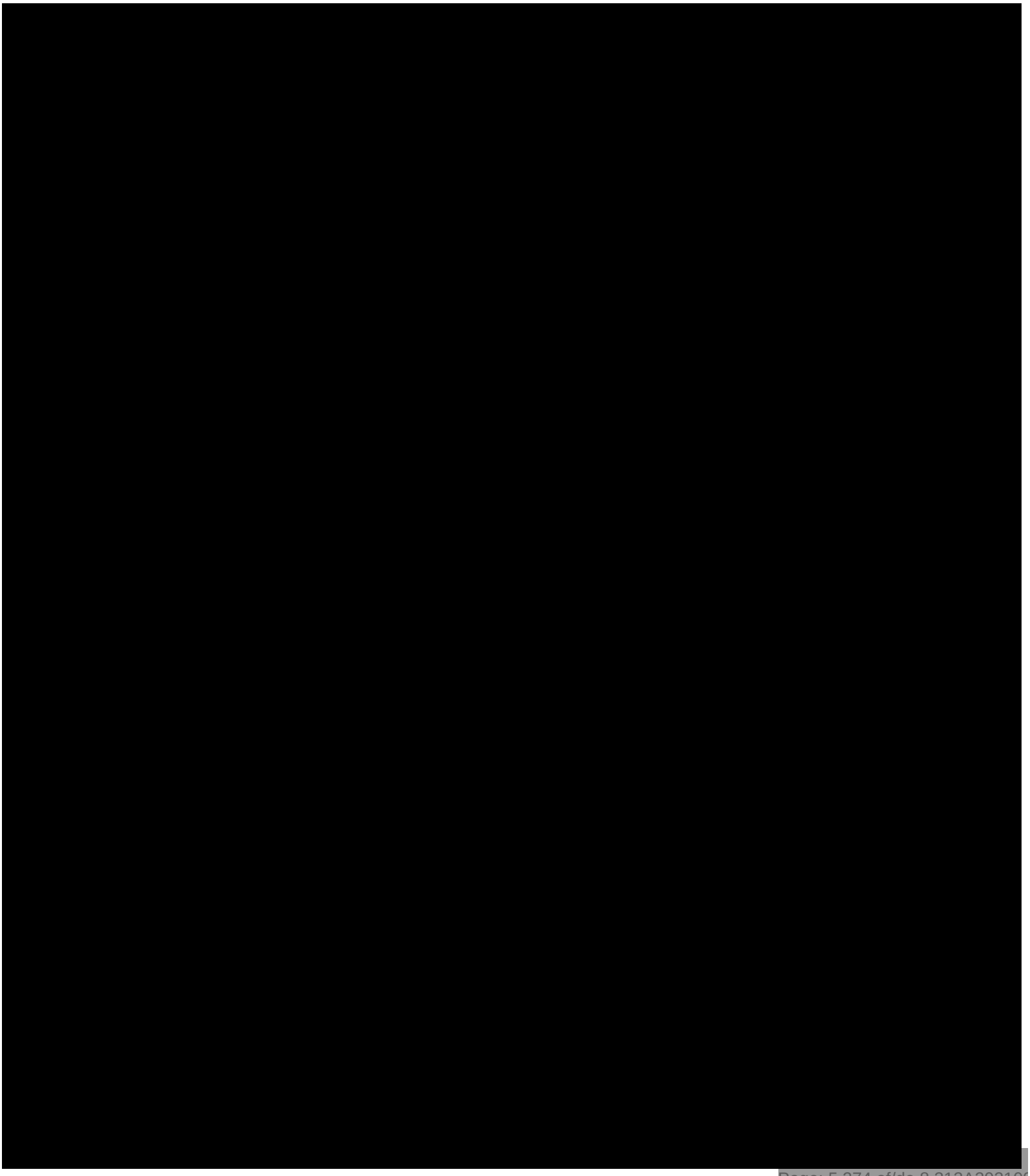

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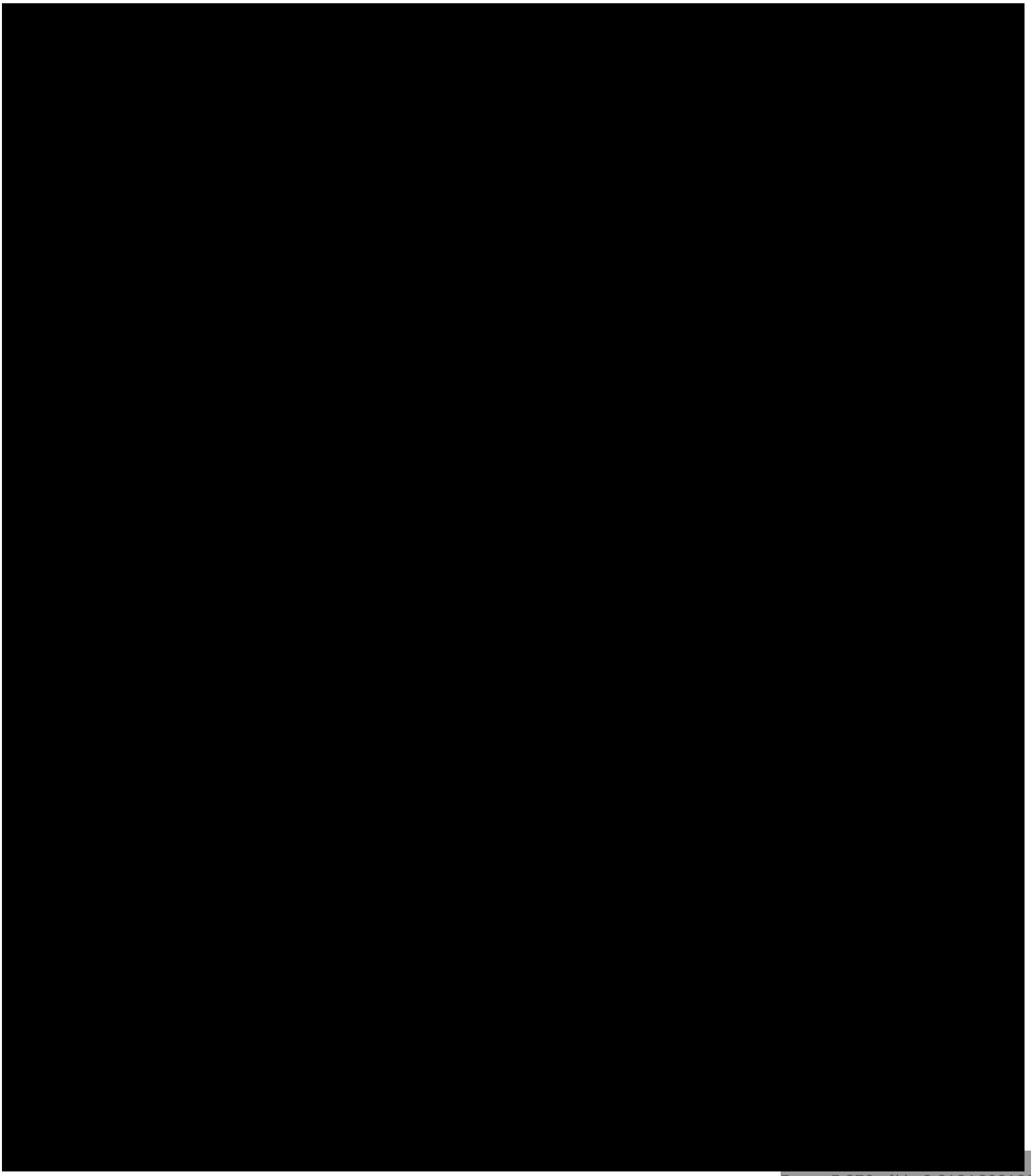

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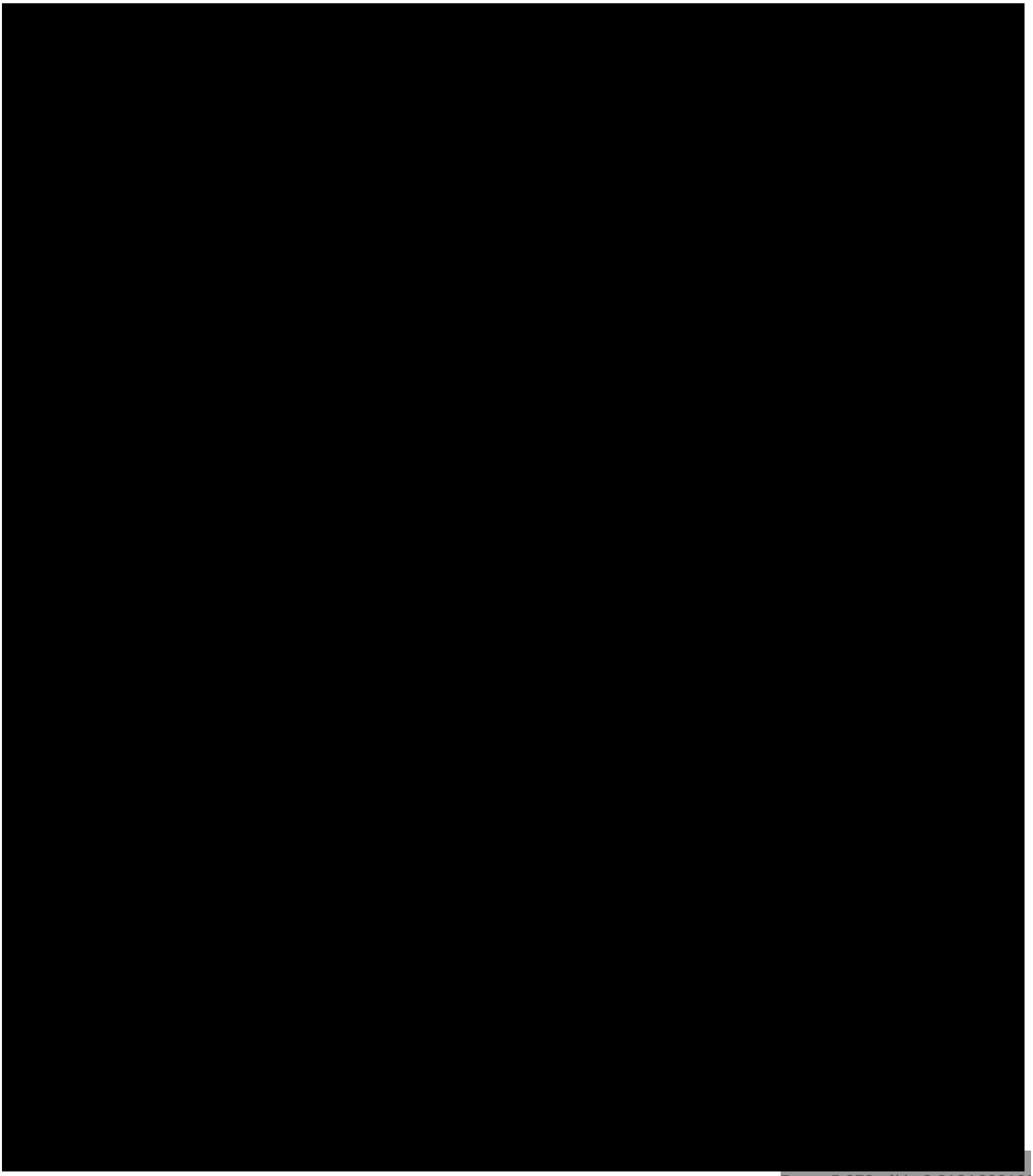

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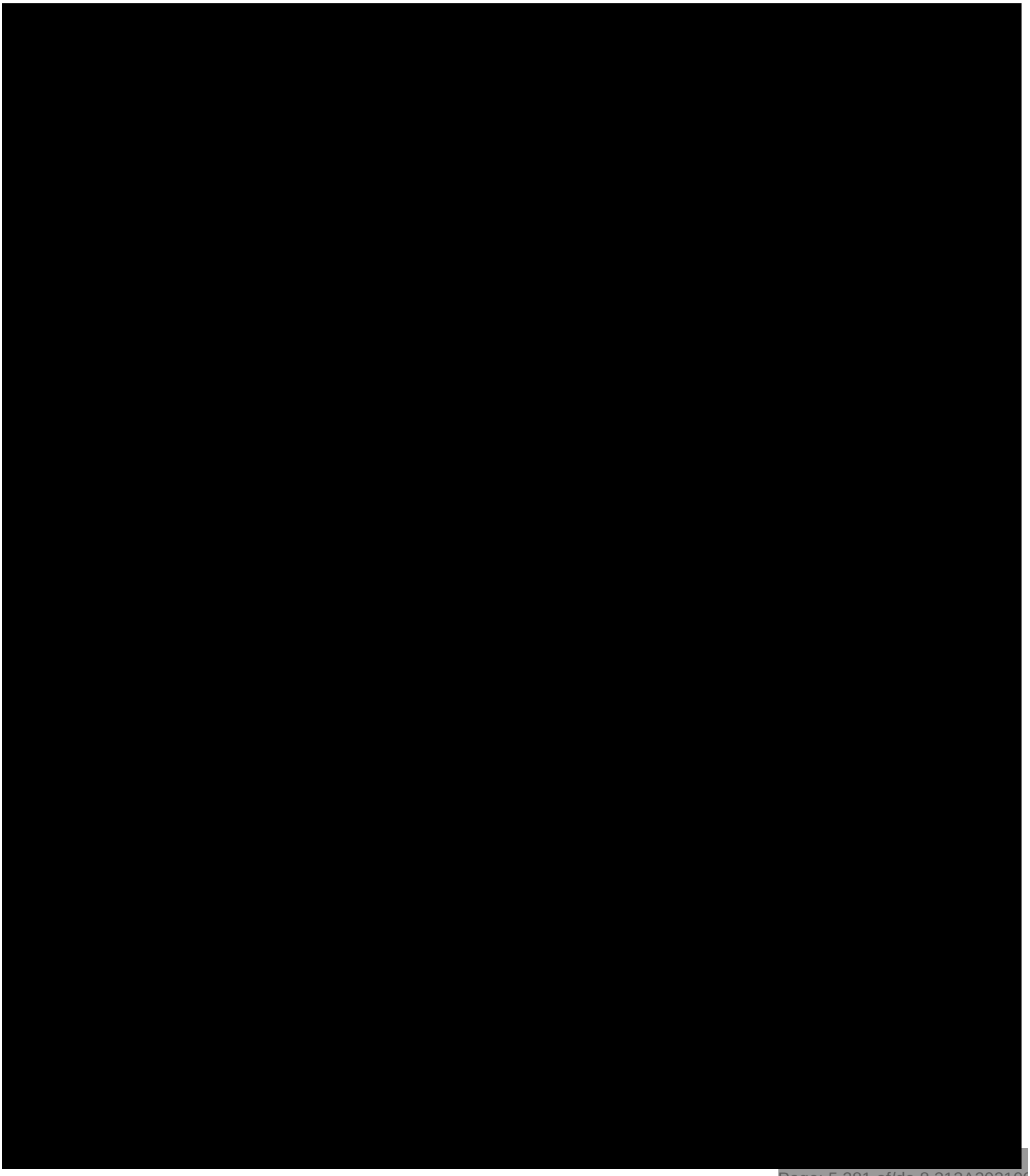

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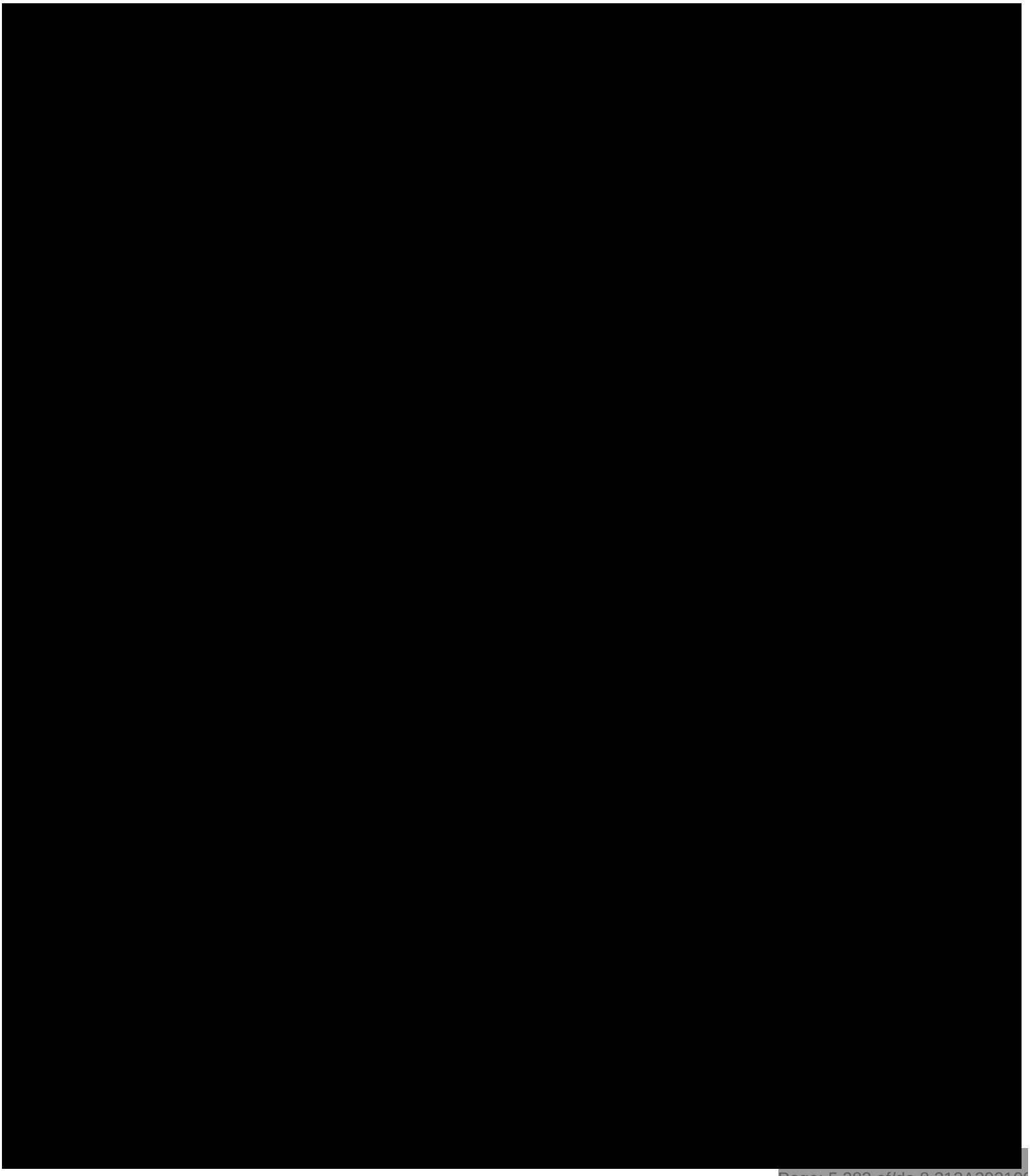

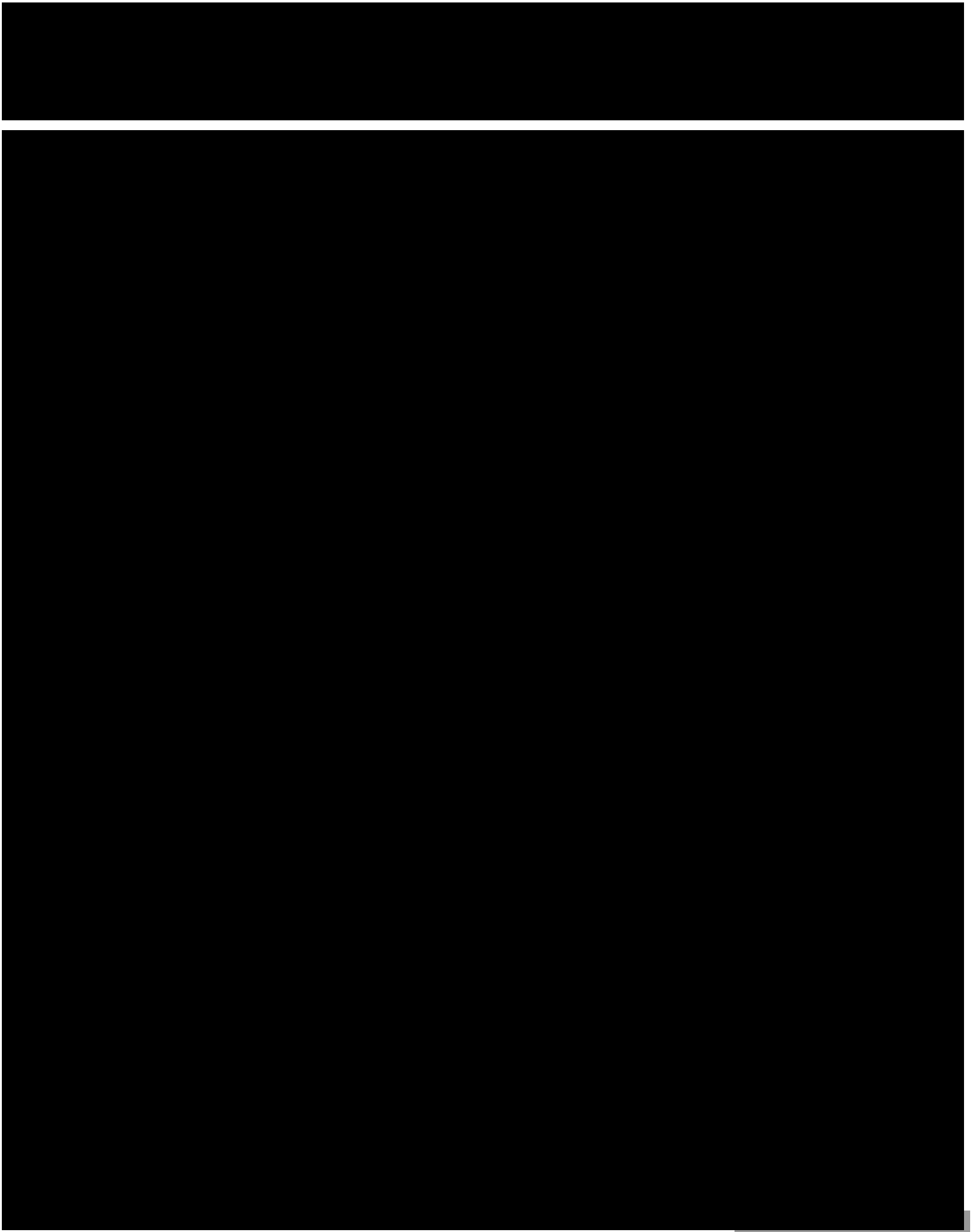

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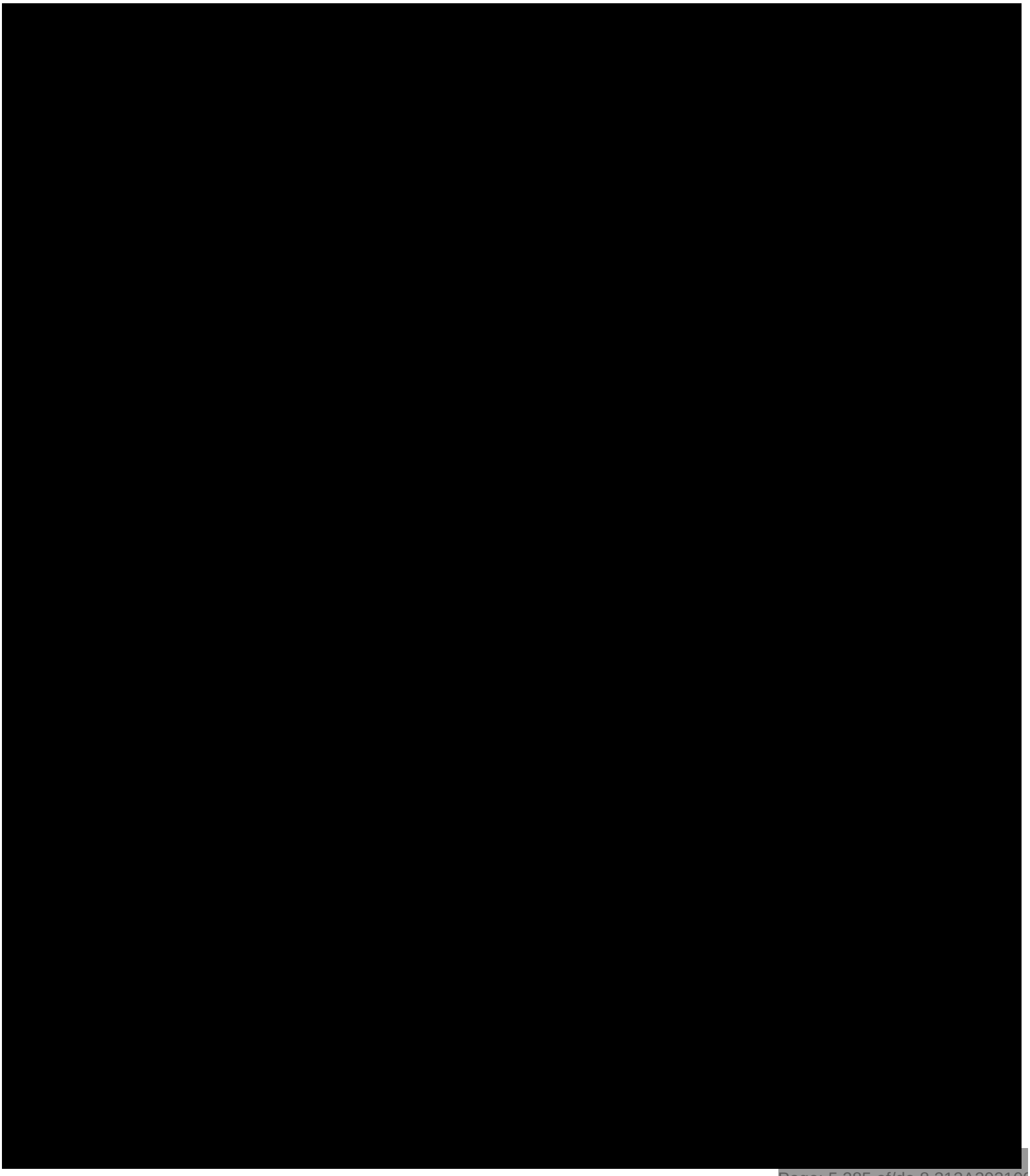

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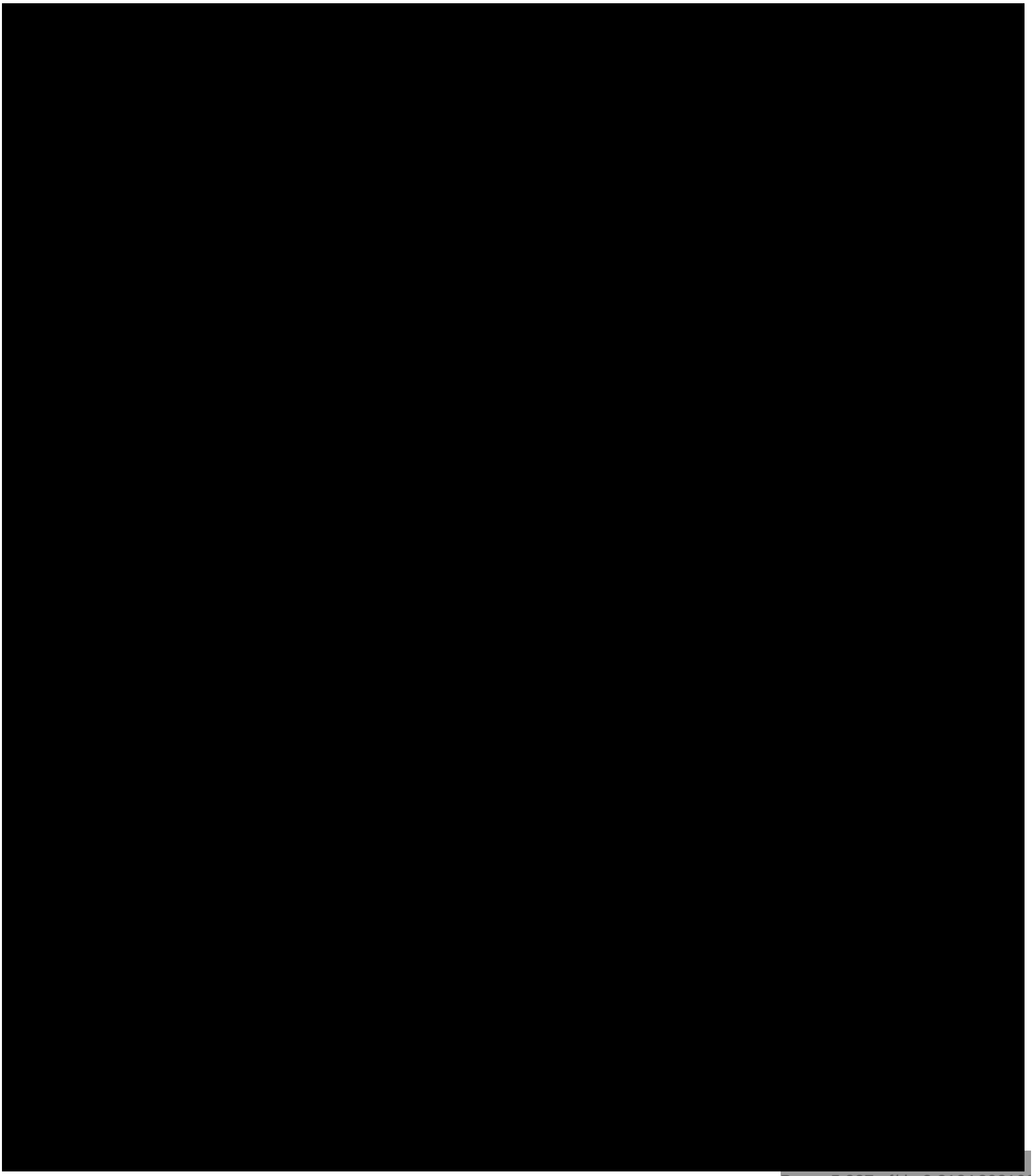

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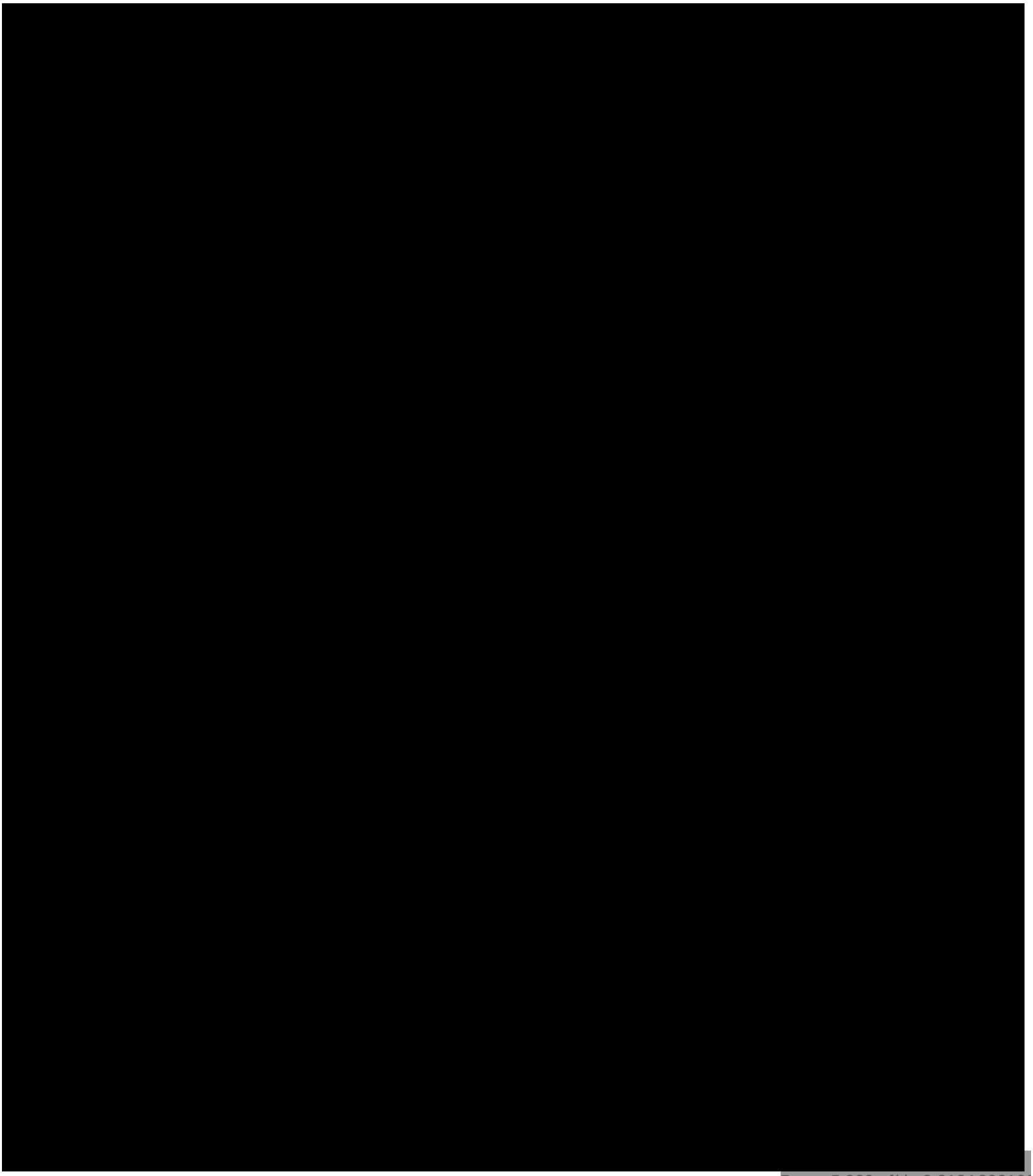

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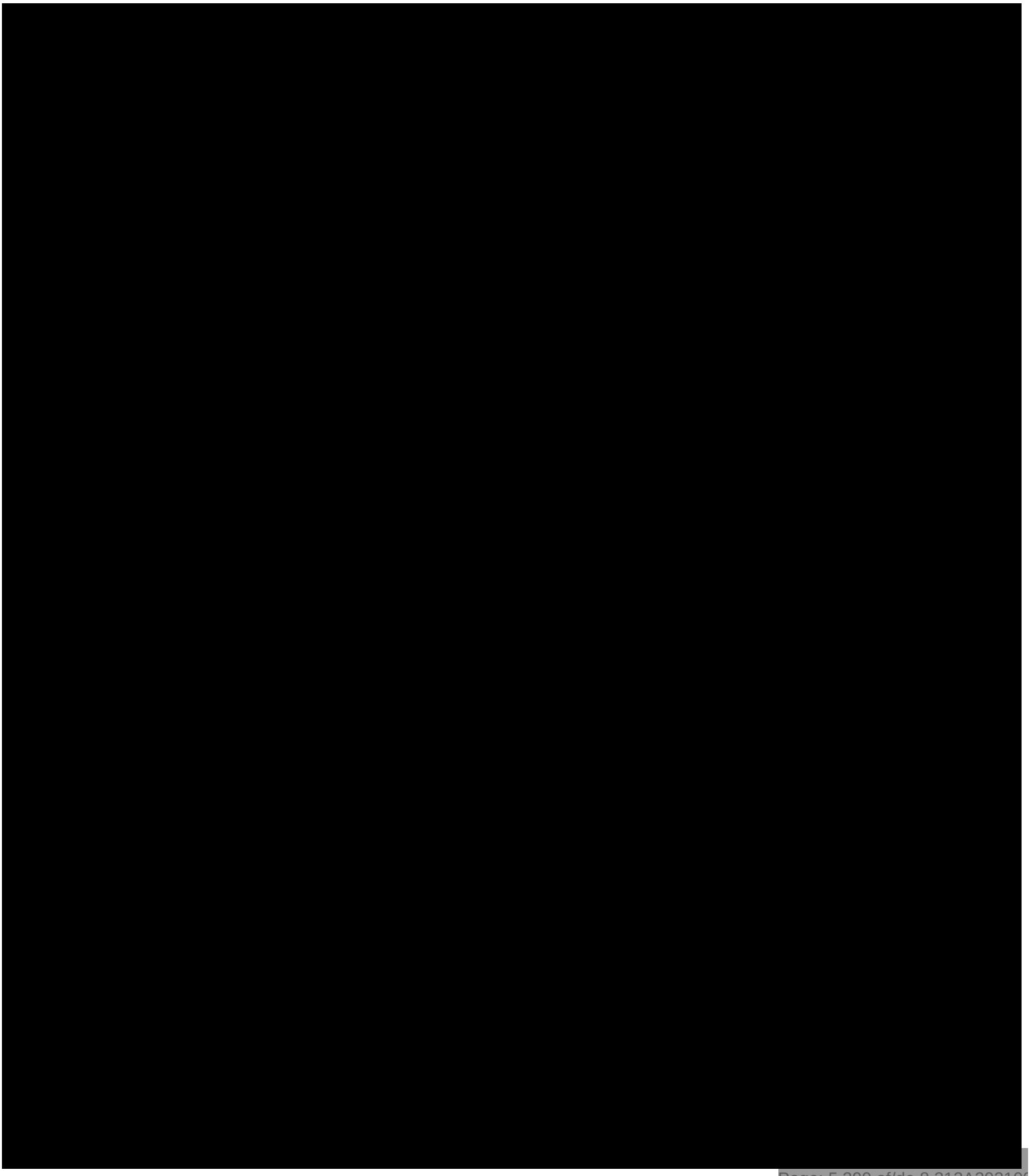

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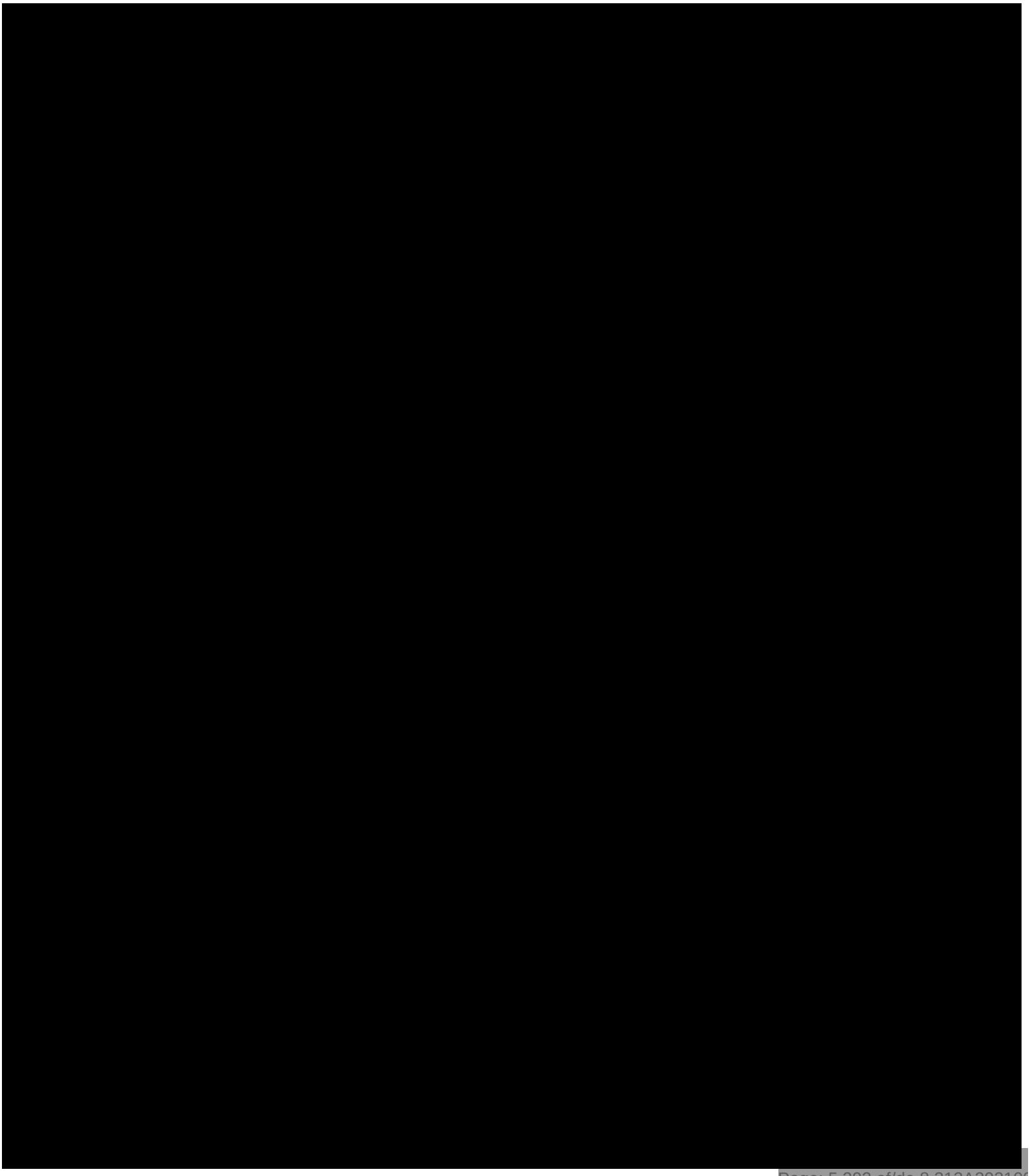

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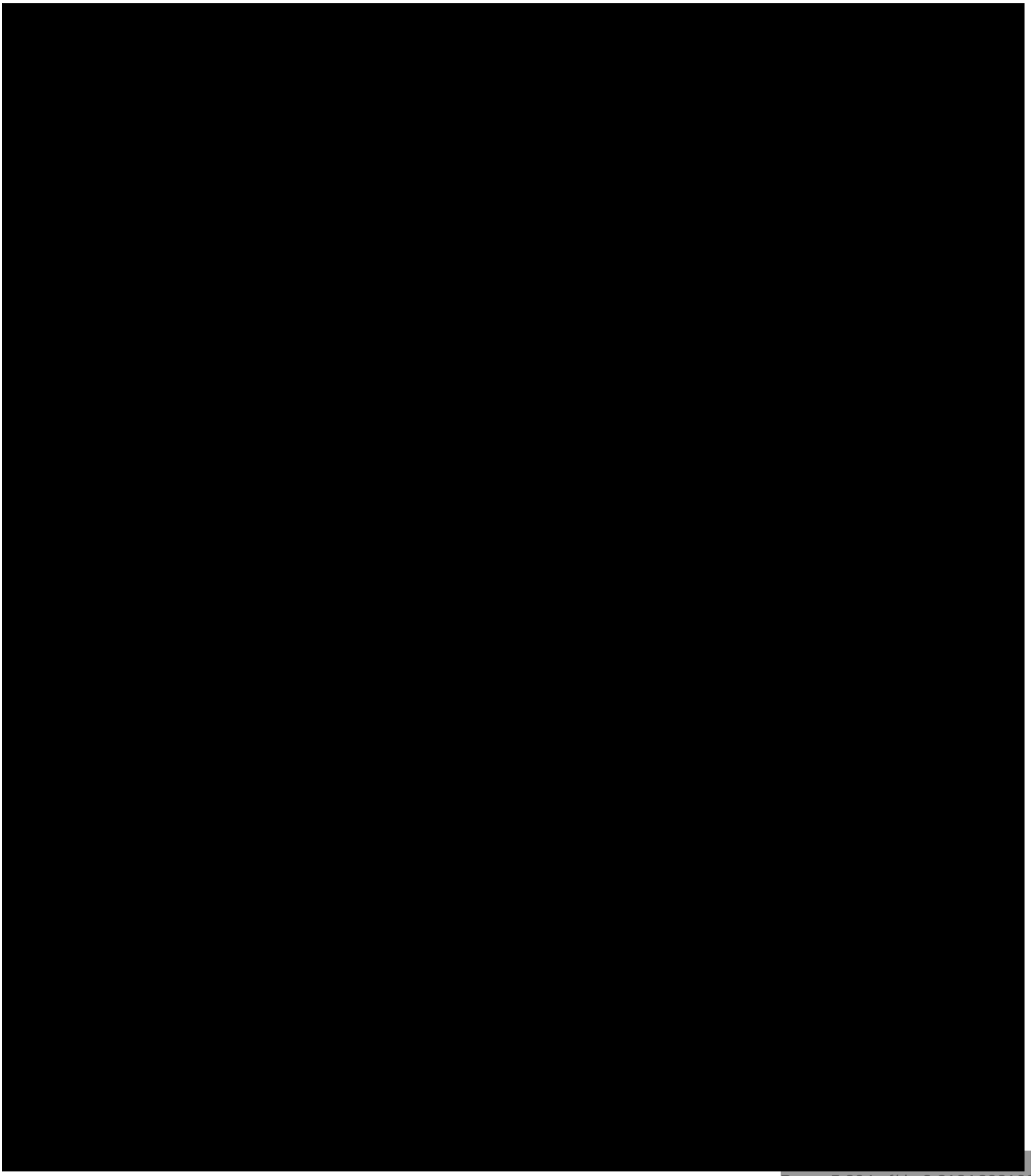

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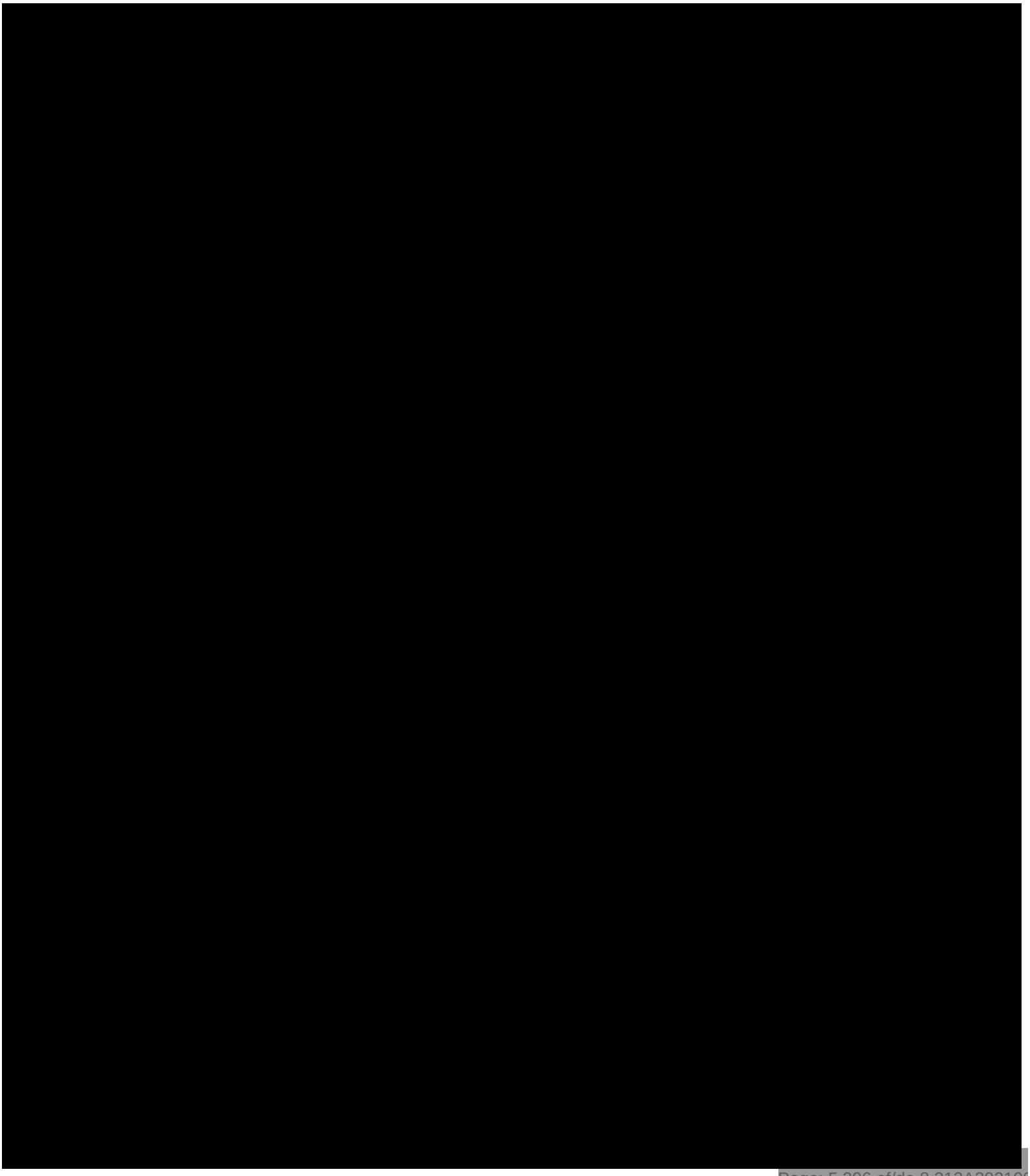

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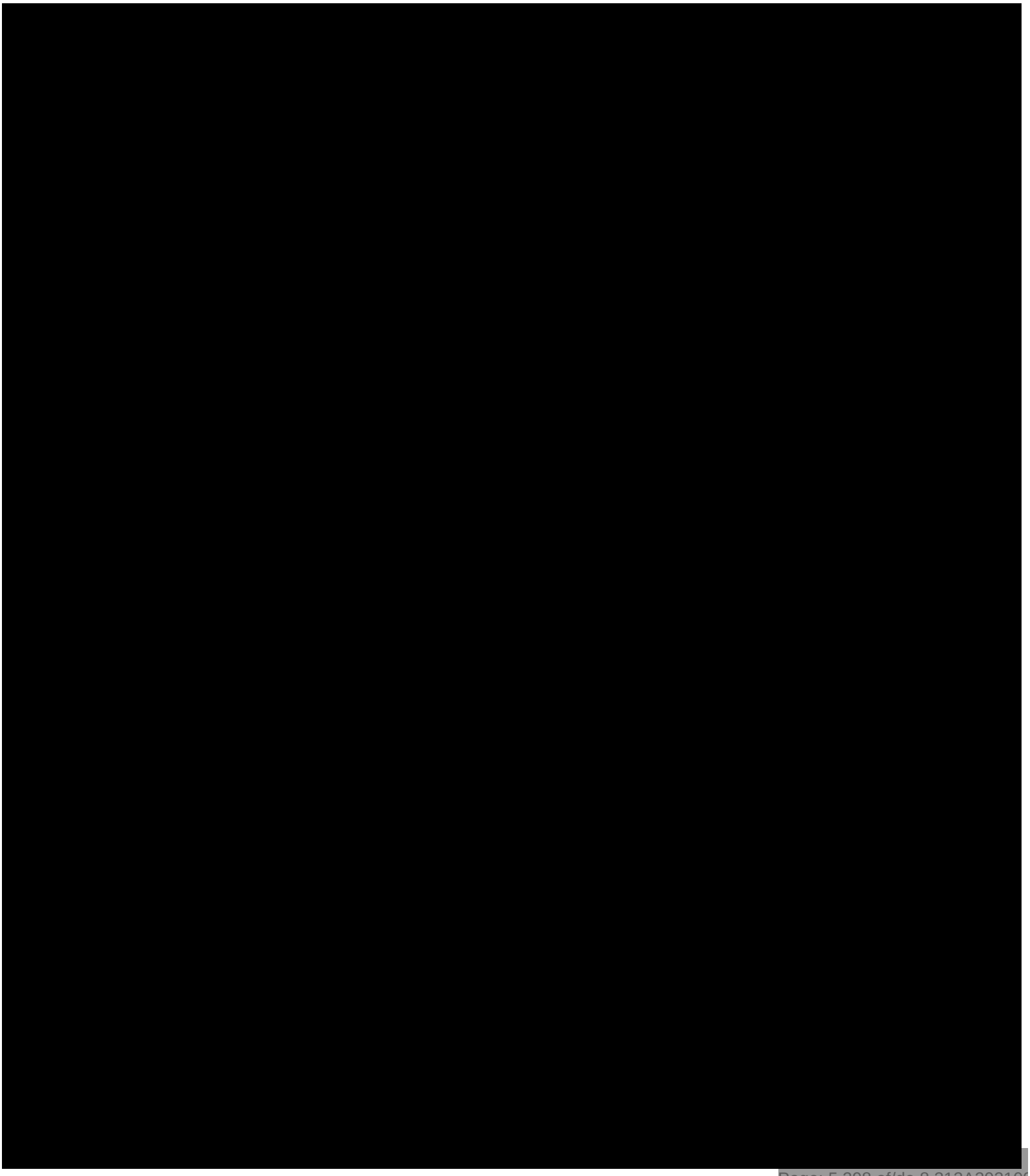

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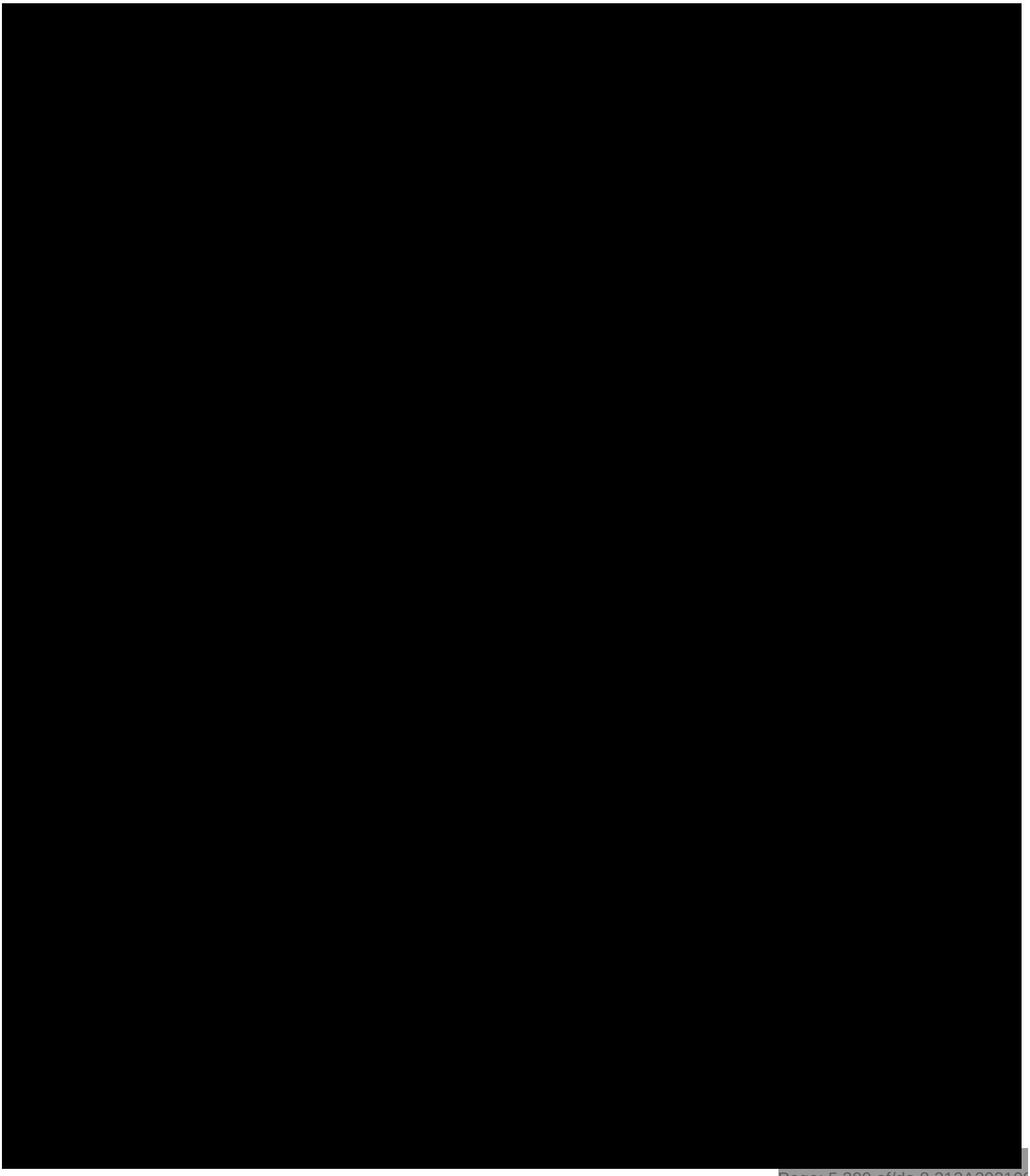

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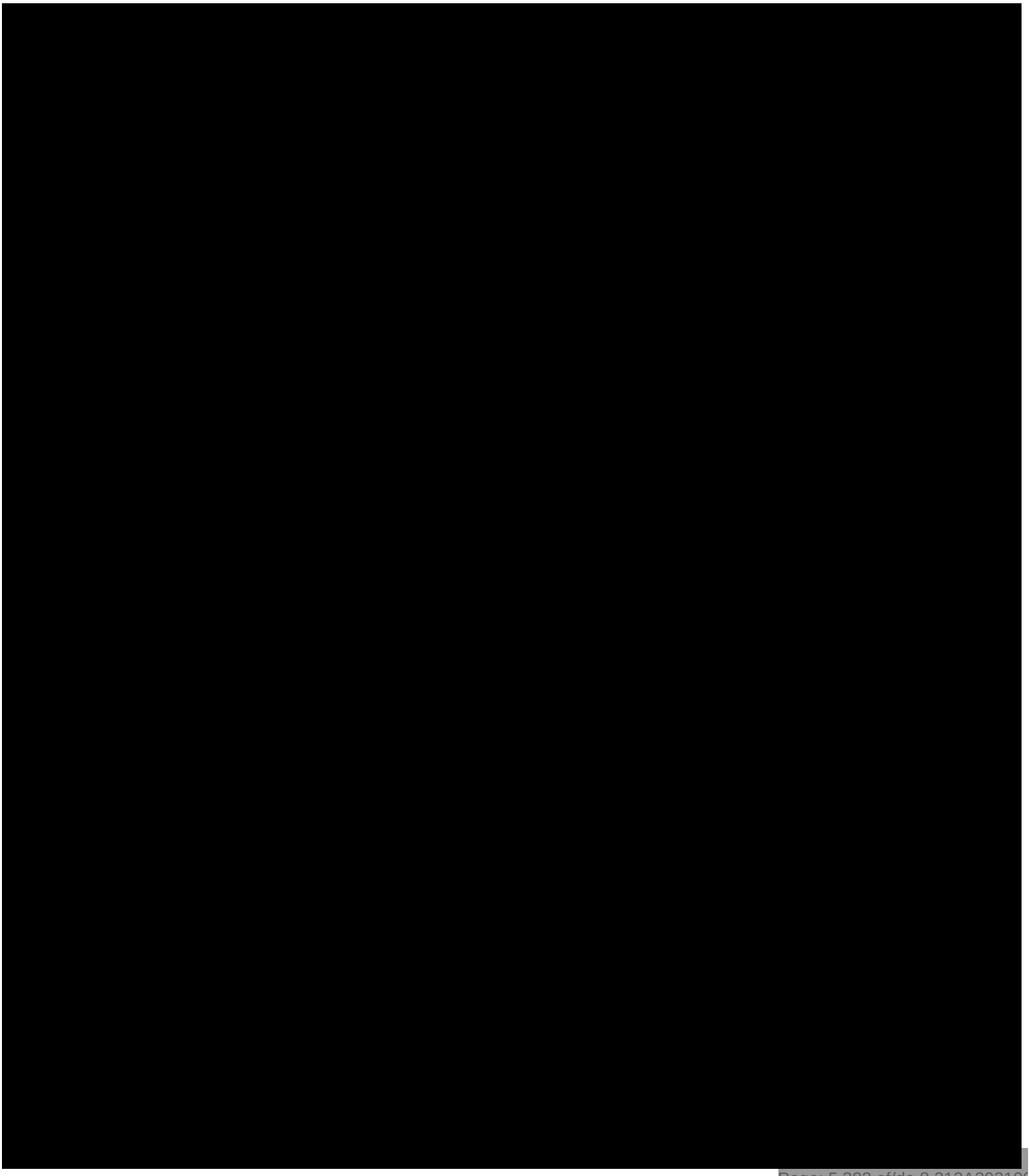

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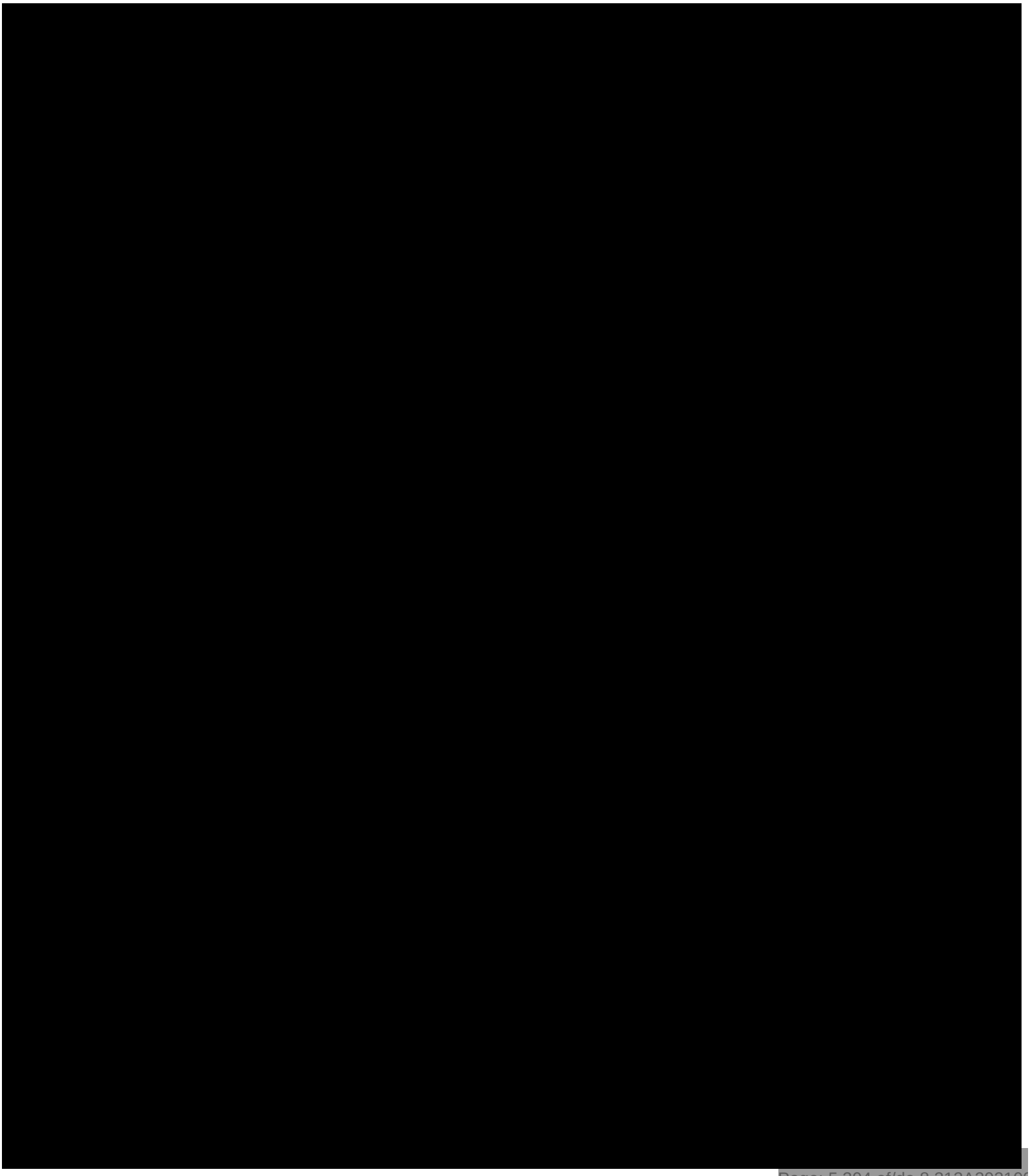

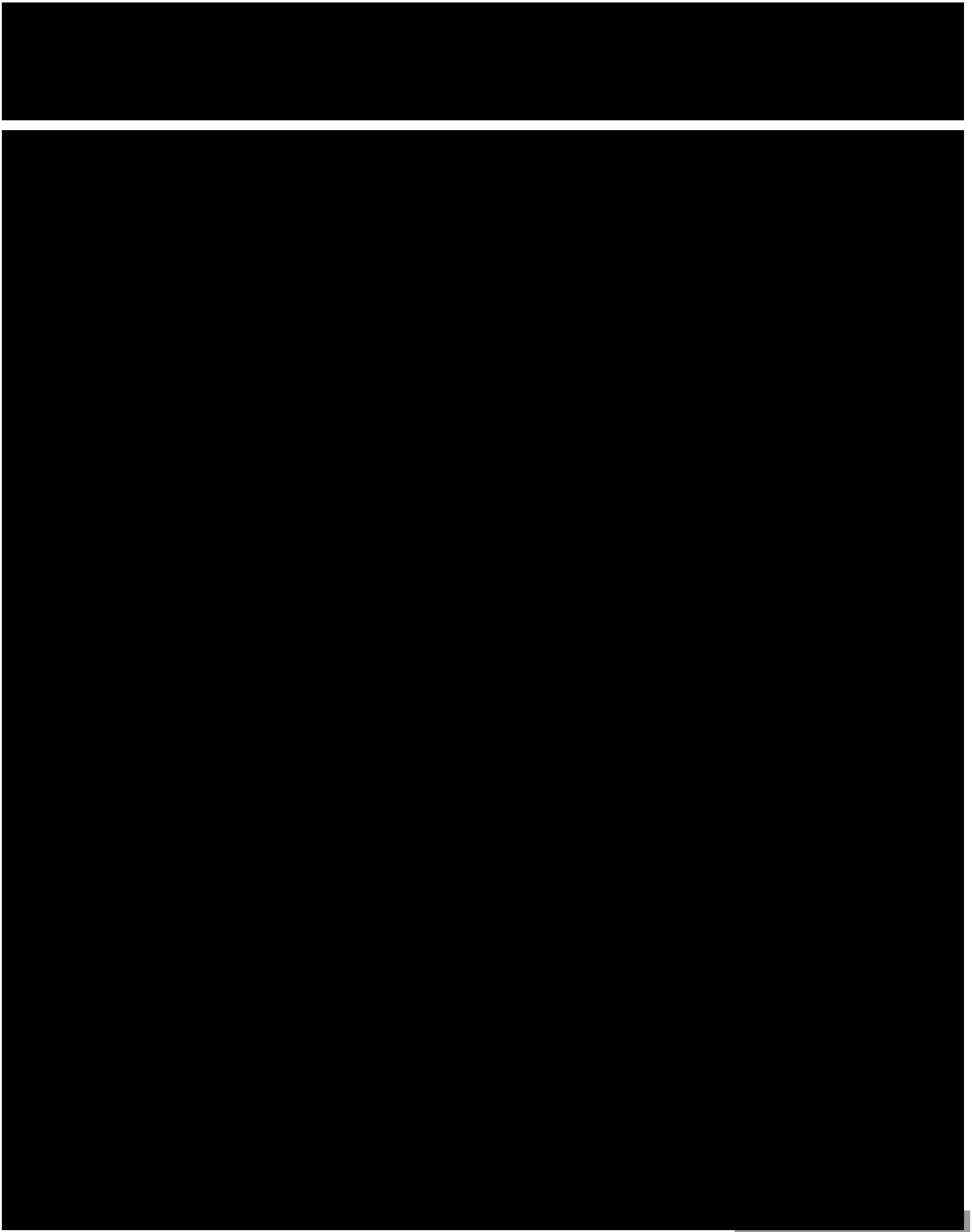

Ridgen, Patrick (HC/SC)

From: Eassa, Samar (HC/SC)
Sent: 2021-03-23 11:13 AM
To: [redacted]
Cc: Panetta, Vincent (HC/SC); Antonio, Christopher (HC/SC); Patel, Shalu (HC/SC); Akel, Sereen H (HC/SC)
Subject: COVID-19 Interim Order Application, Control # [redacted] for Novavax COVID-19 Vaccine (SARS-CoV-2 rS with Matrix-M1 Adjuvant) - Letter to stakeholders: Amending the Food and Drug Regulations

Importance: High

Dear [redacted]

Health Canada has introduced amendments to the *Food and Drug Regulations* (FDR) in order to provide a mechanism for Covid-19 products to gain a Notice of Compliance as soon as possible, and to maintain agile measures including modified data requirements, rolling reviews and Terms and Conditions (T&Cs).

We are pleased to inform you that the *Regulations Amending the Food and Drug Regulations (Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19)* were approved March 17, 2021, by the Administrator in Council and registered on March 18th, 2021 the day after Governor and Council approval. The accompanying fees order was registered on March 19th, 2021. Both packages will be published in the March 31, 2021 issue of Canada Gazette II.

The amendments to the Regulations would offer the following benefits for manufacturers who apply under the Regulations:

- enables the sale and advertising of COVID-19 drugs that were authorized under the *Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19(*ISAD IO) to continue after the IO expires
- enables new COVID-19 drugs for which authorization was not sought under the ISAD IO to seek authorization under the *Regulations* with similar flexibilities as those provided under the ISAD IO
- continues the post-market regulatory obligations placed on authorization holders, manufacturers and importers after the ISAD IO expires
- continues to allow the early importation (pre-positioning) of a promising COVID-19 drug for which a federal government contract for its procurement is in place, before that drug receives market authorization in Canada
- continues an agile approach for DELs that authorizes regulated activities for COVID-19 drugs

For COVID-19 products originally filed under the IO, amendments to the *Fees in Respect of Drugs and Medical Devices Order* were proposed and consulted on to allow products filed under the IO to transition to the FDR without paying fees. Once a product has been submitted under the FDR, then all subsequent submissions as well as any new product submissions would have the standard fees applied, including the Drug Right to Sell fee. While existing performance standards would continue to generally apply, rolling submissions would be exempt from fee penalties for missed performance standards.

The amendments will be published in Canada Gazette II with an accompanying Guidance document. Stakeholders will be able to comment on the guidance document for 30 days following its publication. We will send an advanced version of the draft Guidance soon.

We want to thank all stakeholders who contributed to the cost-benefit analysis survey and online consultation to transition drugs authorized/filed under the Interim Order for Drugs into the amended Regulations (November 30-December 23rd). We would also like to thank participants of Health Canada's interactive webinar session with innovative and generic industry as well as health system partners (December 11th). We received strong support from stakeholders on the approach described. The amended FDR to be published in CGII, are aligned with the principles described in the consultation and the What Was Heard Report, released on January 23, 2021.

As Novavax Inc., PPD Development, LP, has received an authorization or has provided a submission for Novavax COVID-19 Vaccine (SARS-CoV-2 rS with Matrix-M1 Adjuvant) under the ISAD IO, you are invited to further discuss the transition of your submission/authorization from the ISAD IO to the *Regulations*. Please contact the Office of Regulatory Affairs at your earliest convenience should you wish to schedule a meeting.

Chère [redacted]

Santé Canada a introduit des modifications au Règlement sur les aliments et drogues (RAD) afin de fournir un mécanisme permettant aux produits Covid-19 d'obtenir un avis de conformité dès que possible et de maintenir des mesures agiles, y compris des exigences de données modifiées, des examens continus et des conditions générales.

Nous avons le plaisir de vous informer que le Règlement modifiant le Règlement sur les aliments et drogues (Arrêté provisoire concernant l'importation, la vente et la publicité des médicaments à utiliser en relation avec le COVID-19) a été approuvé le 17 mars 2021 par l'administrateur en conseil et enregistré le 18 mars 2021 le lendemain de l'approbation du gouverneur et du conseil. L'ordonnance sur les droits d'accompagnement a été enregistrée le 19 mars 2021. Les deux trousses seront publiées dans le numéro du 31 mars 2021 de la Gazette du Canada II.

Les modifications apportées au règlement offriraient les avantages suivants aux fabricants qui présentent une demande en vertu du règlement:
- permet à la vente et à la publicité des médicaments COVID-19 qui ont été autorisés en vertu de l' Arrêté provisoire concernant l'importation, la vente et la publicité des médicaments à utiliser en relation avec le COVID-19 (ISAD IO) de se poursuivre après l'expiration de l'IO
- permet aux nouveaux médicaments COVID-19 pour lesquels l'autorisation n'a pas été demandée dans le cadre de l'ISAD IO de demander une autorisation en vertu du Règlement avec des flexibilités similaires à celles prévues dans l'ISAD IO
- maintient les obligations réglementaires post-commercialisation imposées aux titulaires d'autorisations, aux fabricants et aux importateurs après l'expiration de l'ISAD IO
- continue d'autoriser l'importation précoce (pré-positionnement) d'un médicament COVID-19 prometteur pour lequel un contrat du gouvernement fédéral pour son approvisionnement est en place, avant que ce médicament ne reçoive l'autorisation de mise sur le marché au Canada
- poursuit une approche agile pour les DEL qui autorise les activités réglementées pour les médicaments COVID-19

Pour les produits COVID-19 initialement déposés en vertu de l'OI, des modifications à l'arrêté sur les frais relatifs aux médicaments et instruments médicaux ont été proposées et consultées pour permettre aux produits déposés en vertu de l'OI de passer au Règlement sur les aliments et drogues sans payer de frais. Une fois qu'un produit a été soumis en vertu du RAD, toutes les présentations ultérieures ainsi que toutes les présentations de nouveaux produits seront soumises aux frais standard, y compris les frais relatifs au droit de vendre des médicaments. Alors que les normes de rendement existantes continueraient de s'appliquer généralement, il est proposé que les soumissions continues soient exemptées de pénalités de frais pour les normes de rendement manquées.

Les modifications seront publiées dans la Gazette du Canada, Partie II avec un document d'orientation. Le document d'orientation intègre pourront commenter le document d'orientation pendant 30 jours après sa publication. Nous enverrons bientôt une version avancée du document.

Nous tenons à remercier tous les intervenants qui ont contribué au sondage d'analyse coûts-avantages et à la consultation en ligne pour faire la transition des médicaments autorisés / déposés en vertu de l'ordonnance provisoire pour les médicaments dans le règlement modifié (30 novembre-23 décembre). Nous tenons également à remercier les participants à la session de webinaire interactif de Santé Canada avec l'industrie novatrice et générique ainsi que les partenaires du système de santé (11 décembre). Nous avons reçu un fort soutien des parties prenantes sur l'approche décrite. Le RAD modifié qui sera publié dans la CGII est conforme aux principes décrits dans la consultation et dans le rapport Ce qui a été entendu, publié le 23 janvier 2021.

Comme Novavax Inc., PPD Development, LP, a reçu une autorisation ou a fourni une soumission pour Novavax COVID-19 Vaccine (SARS-CoV-2 rS with Matrix-M1 Adjuvant) dans le cadre de l'ISAD IO, vous êtes invité à discuter davantage de la transition de votre soumission / autorisation de l'ISAD IO vers le Règlement. Veuillez contacter le bureau des affaires réglementaires si vous souhaitez planifier une réunion.

Thank you / Merci,

On behalf of Ms. Shalu Patel,

Best regards,
Samar Eassa, B. Pharm,
Senior Regulatory Affairs Officer / Agente Principale des Affaires Réglementaires
Office of Regulatory Affairs / Bureau des Affaires Réglementaires
Centre for Regulatory Excellence, Statistics and Trials / Centre d'Excellence Règlementaire, Statistiques et Essais
Biologic and Radiopharmaceutical Drugs Directorate / Direction des Médicaments Biologiques et Radiopharmaceutiques
Health Products and Food Branch / Direction Générale des Produits de Santé et des Aliments
Health Canada / Santé Canada
Tel. (613) 447- 8661
TTY: 613-946-9520
samar.eassa@canada.ca
Health Canada Santé Canada

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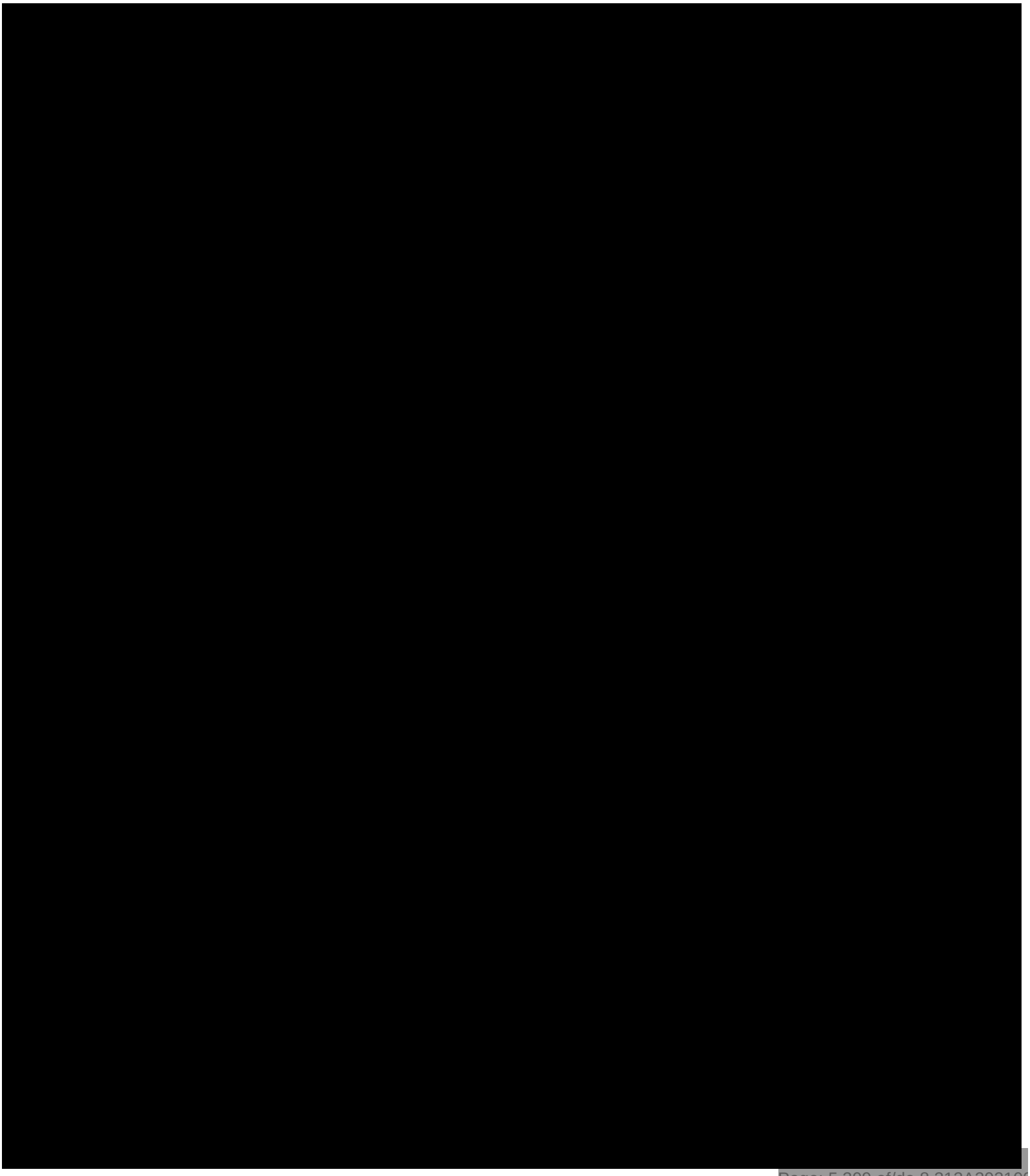

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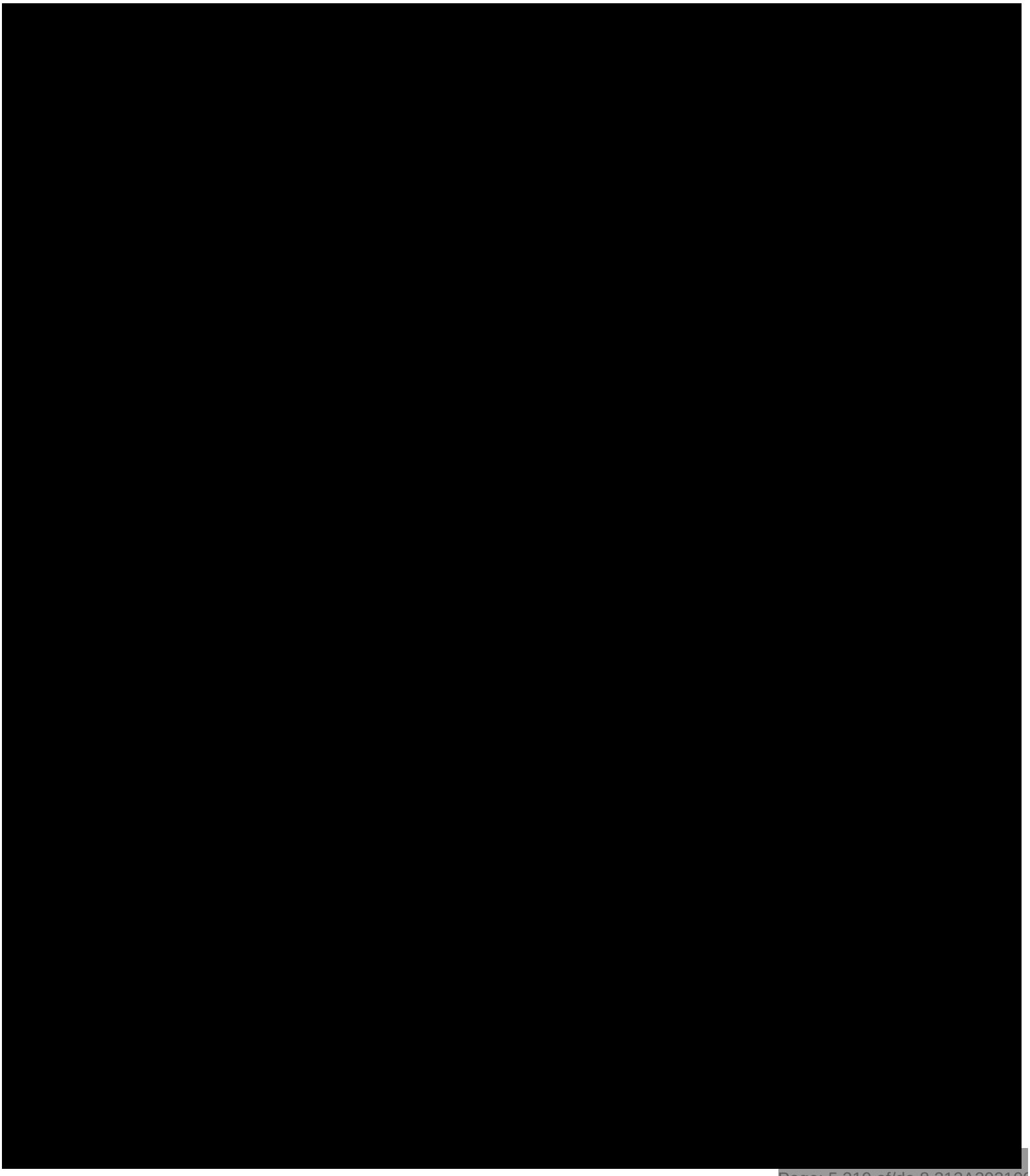

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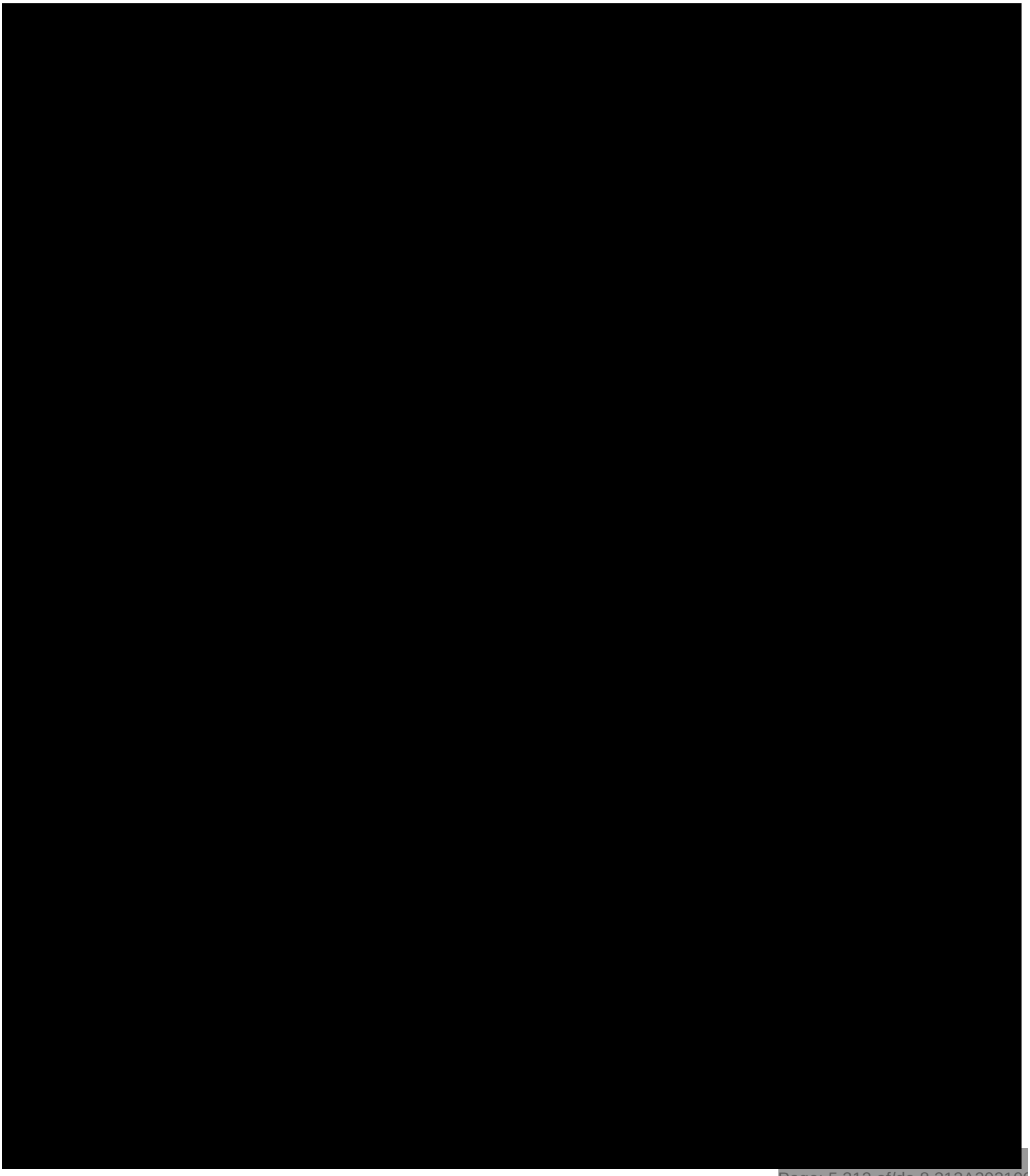

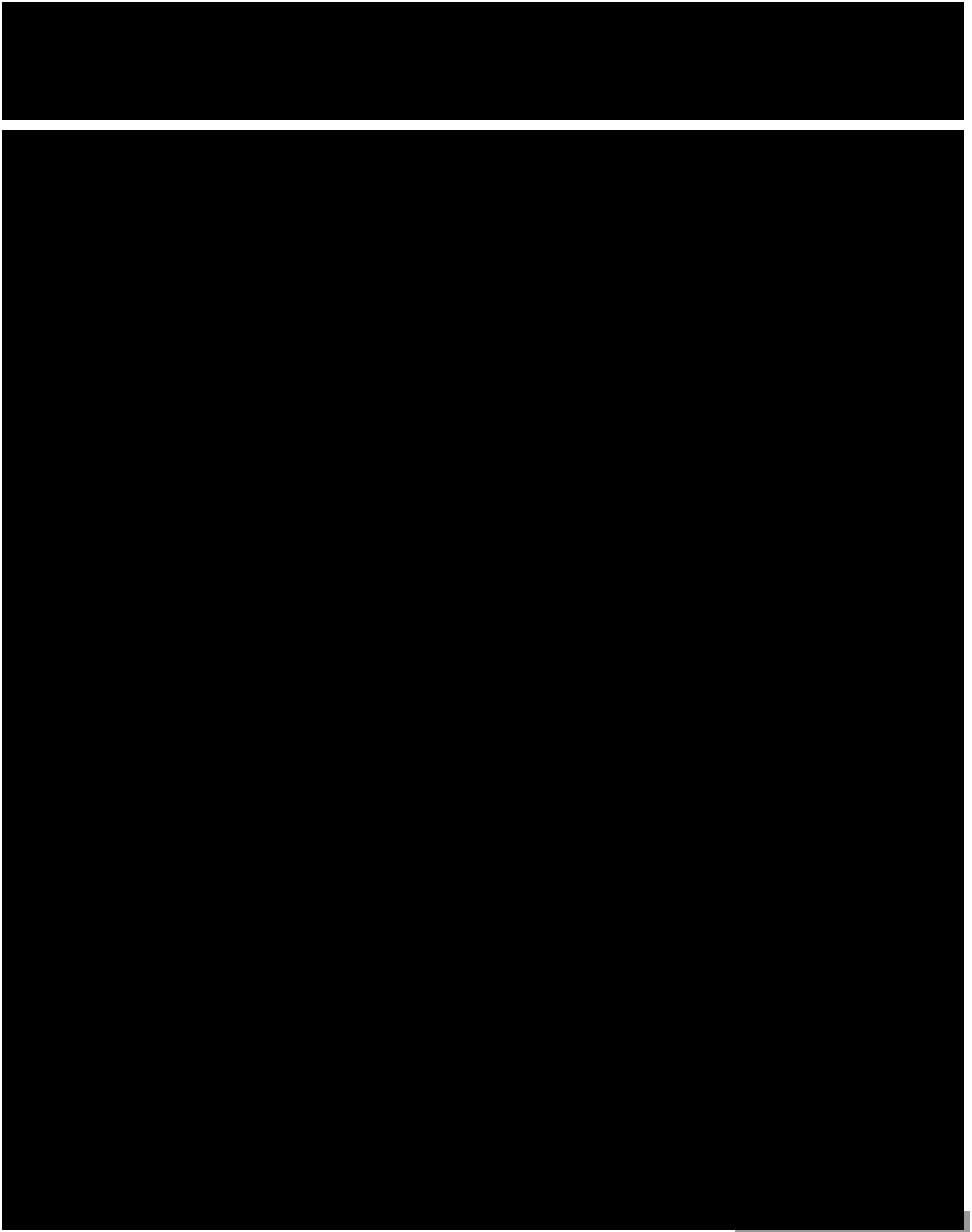

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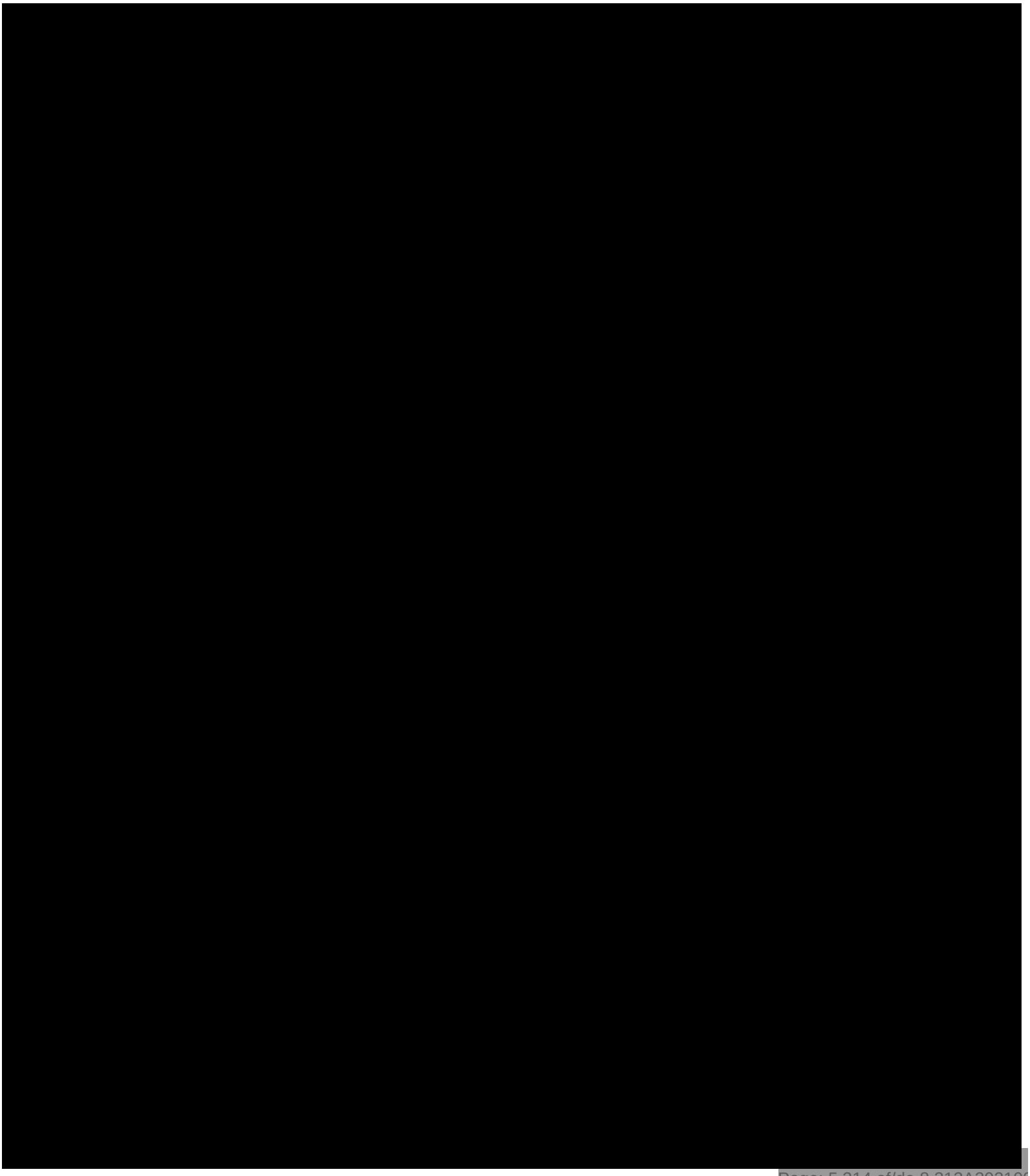

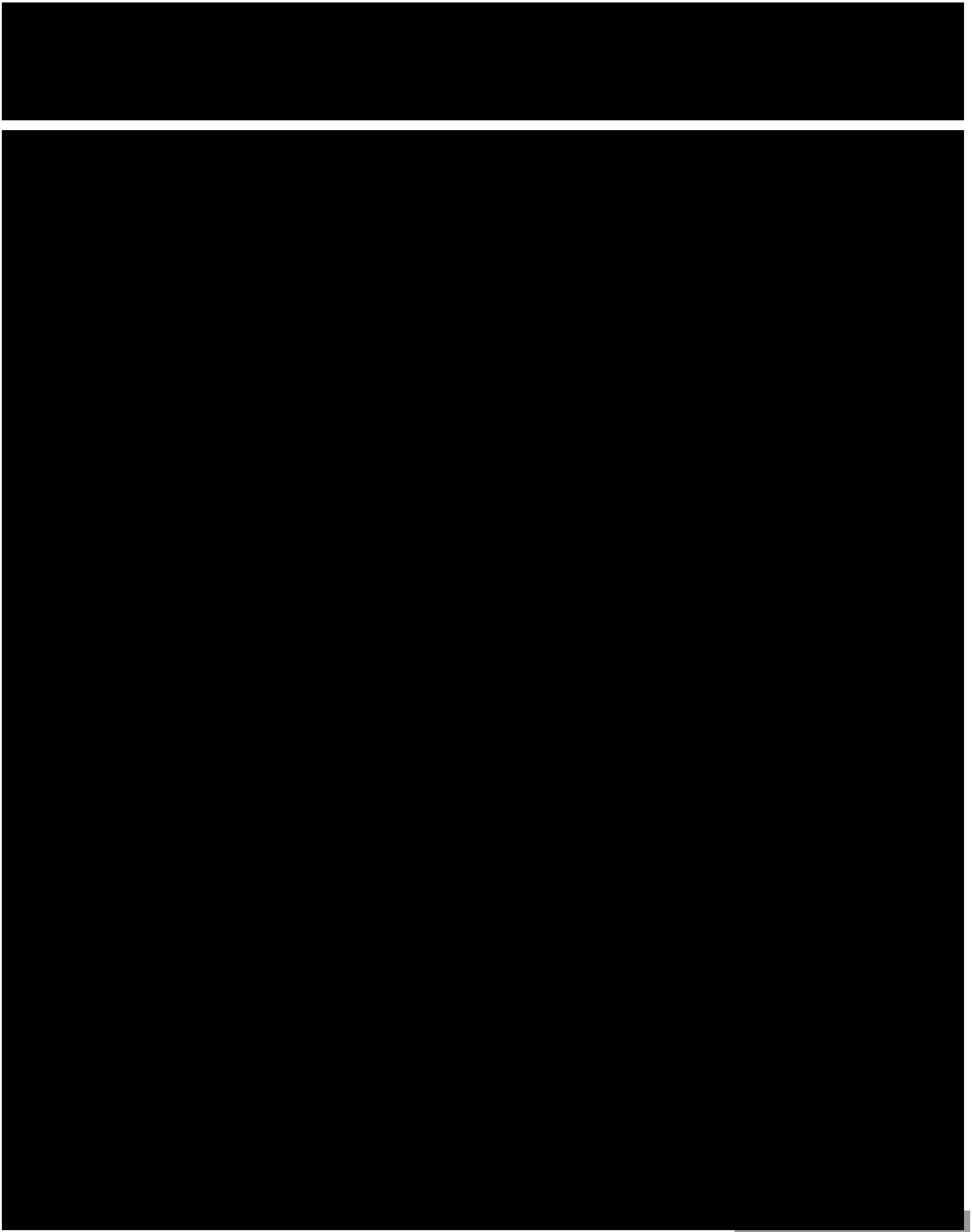

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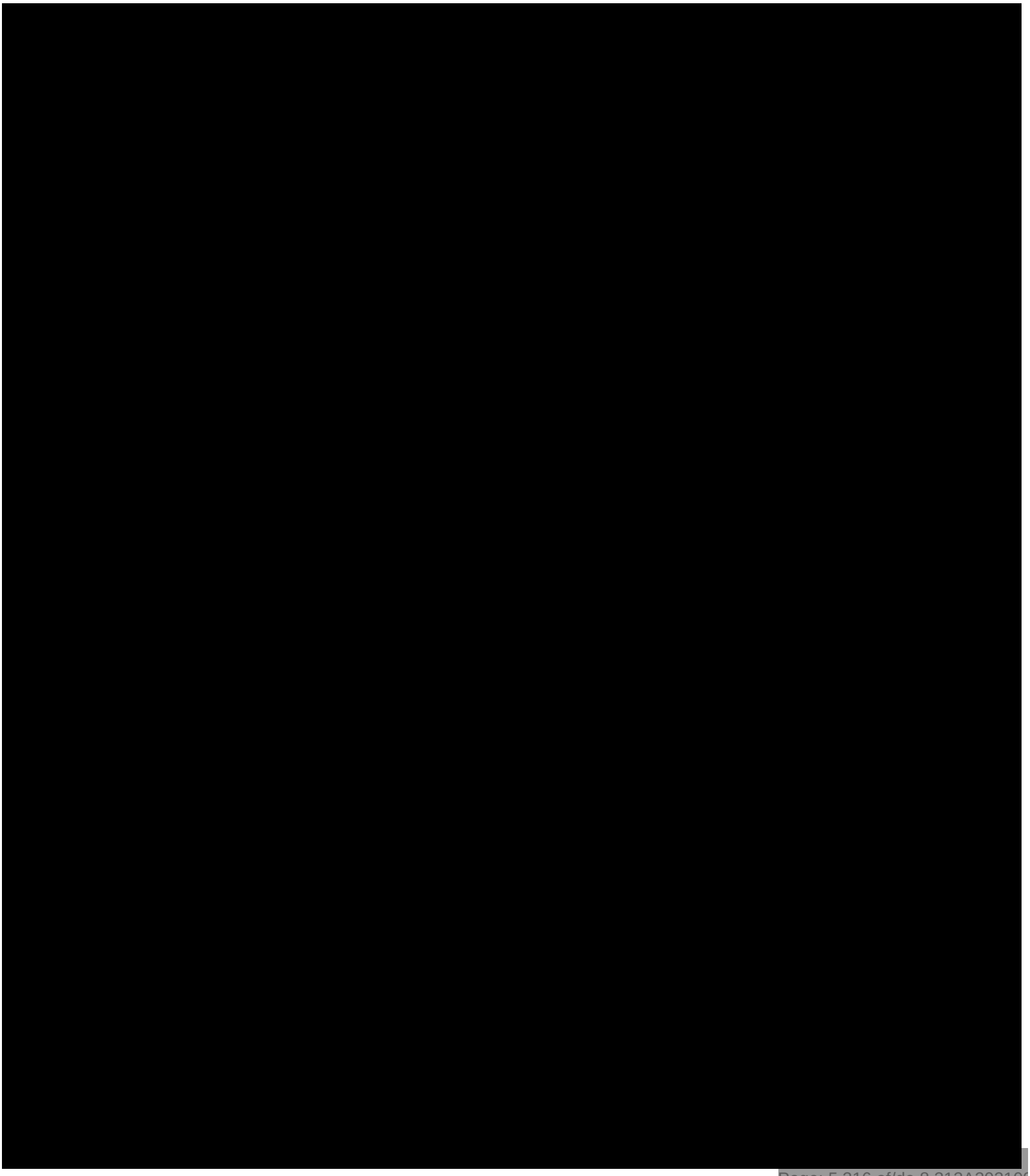

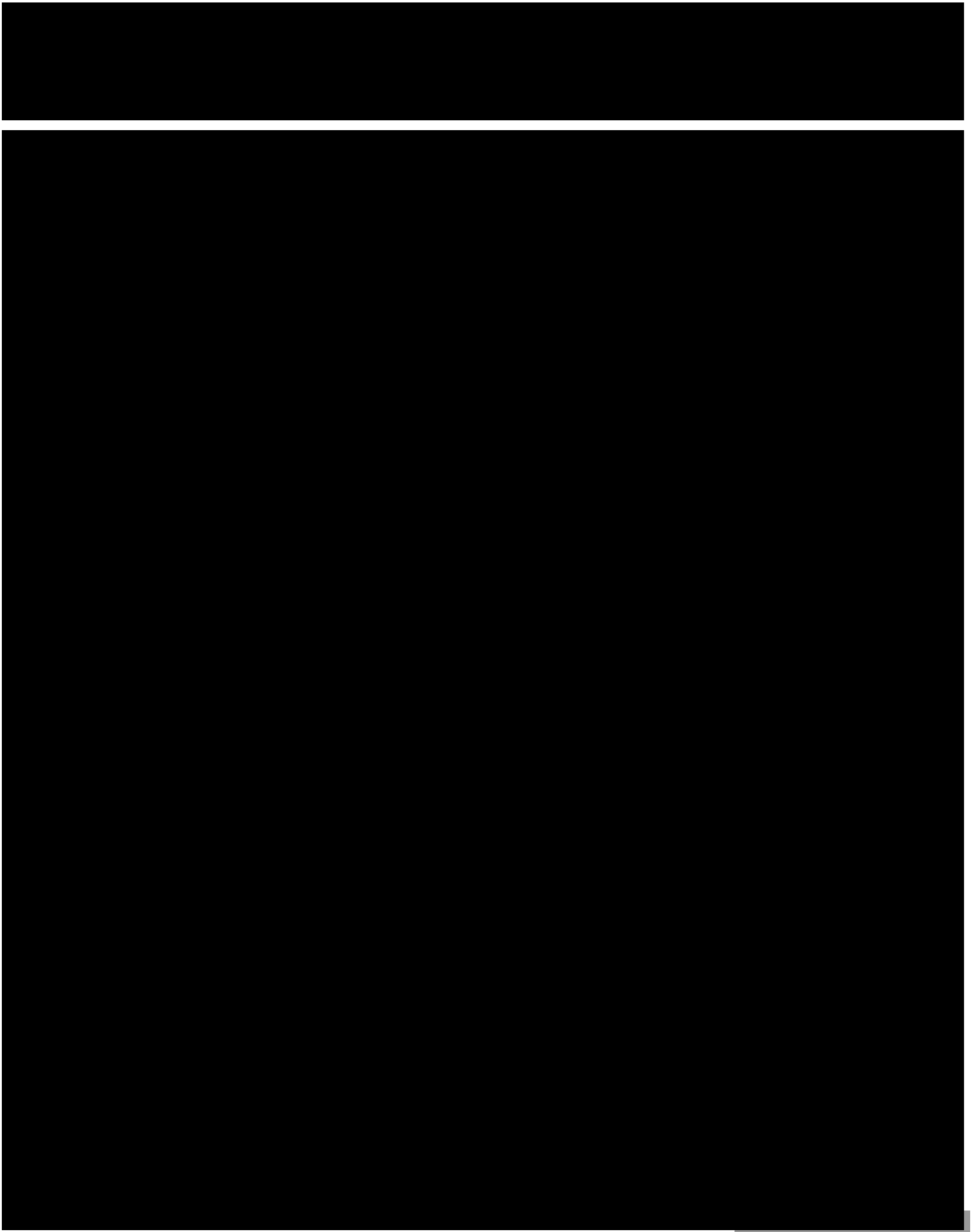

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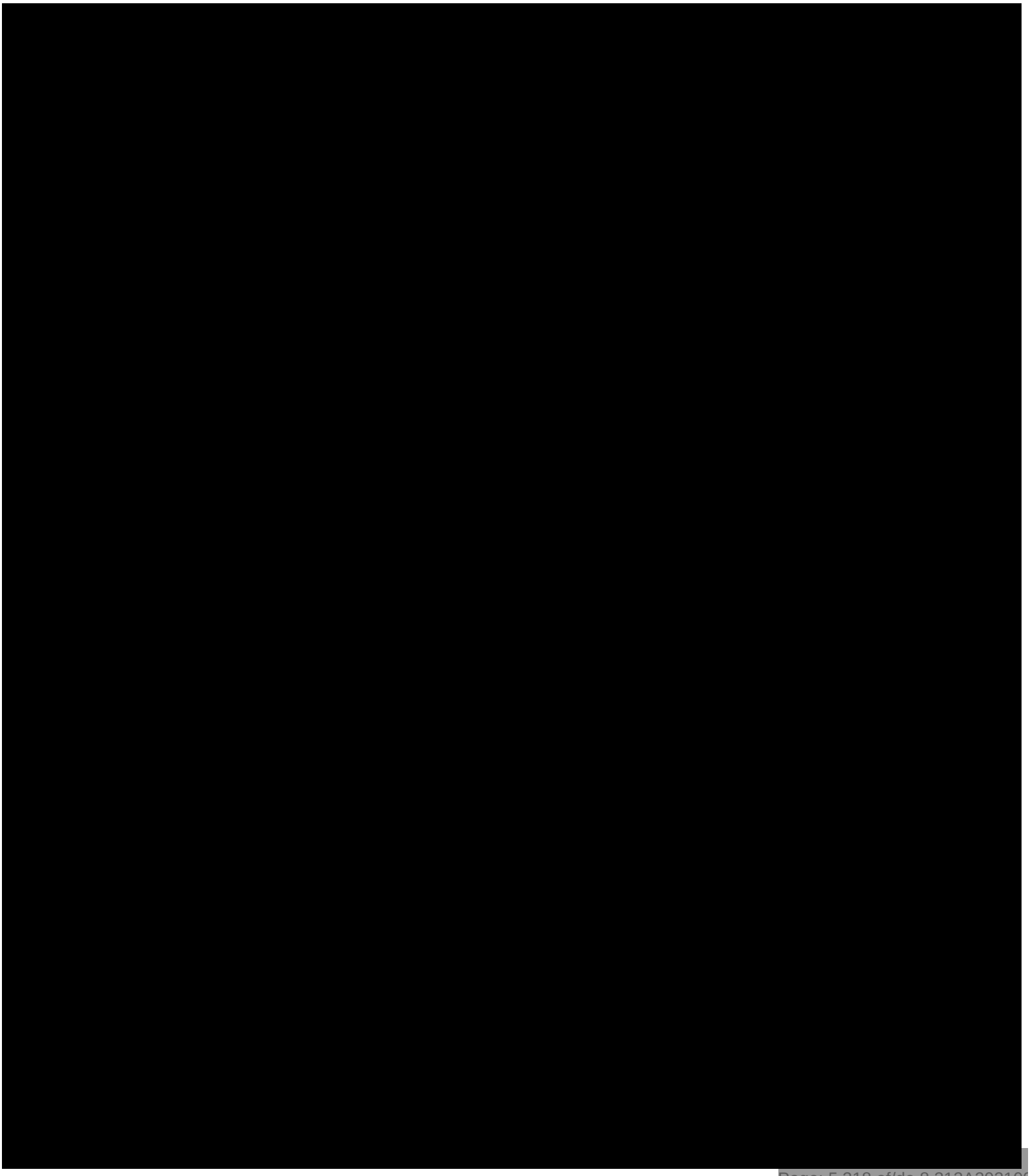

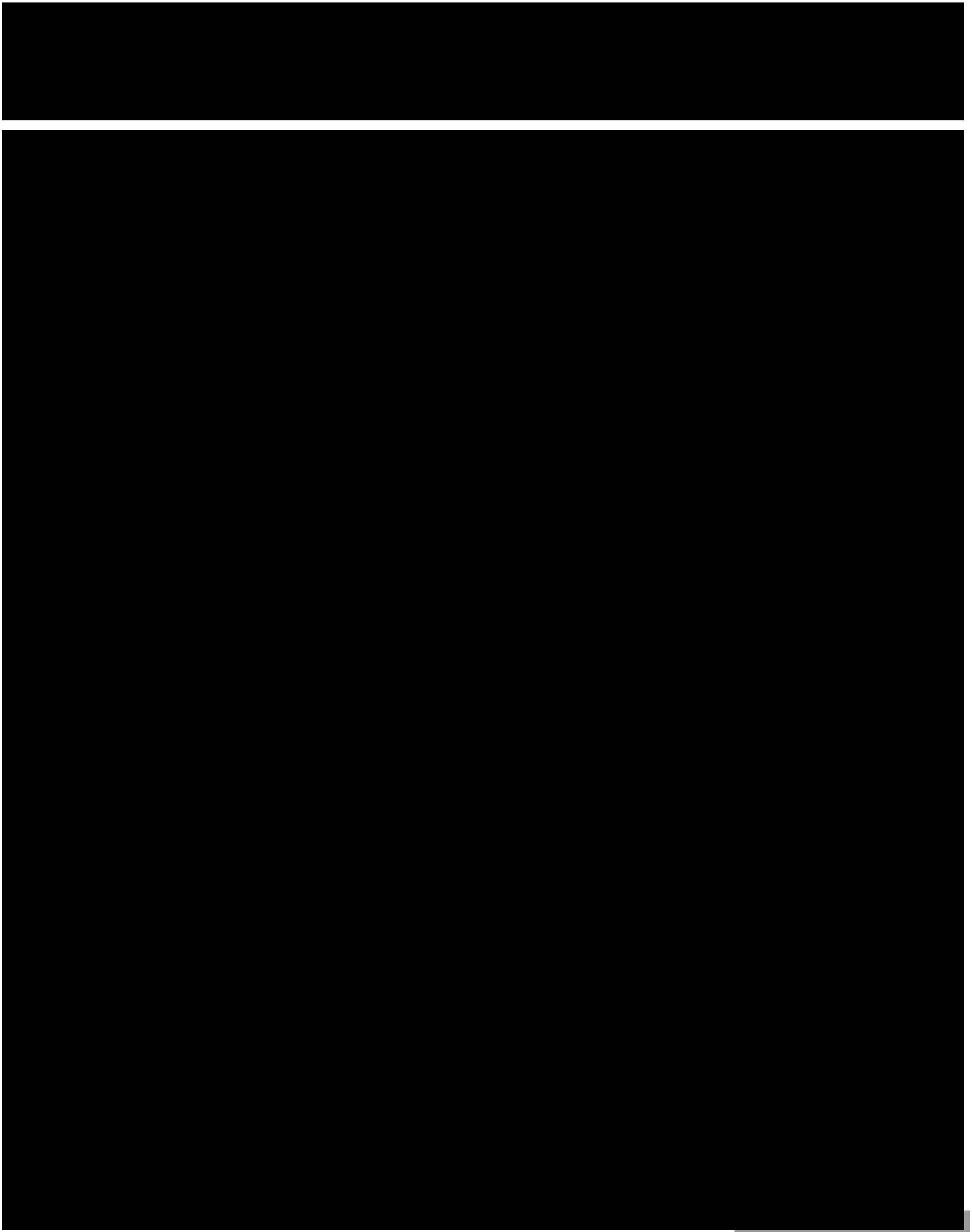

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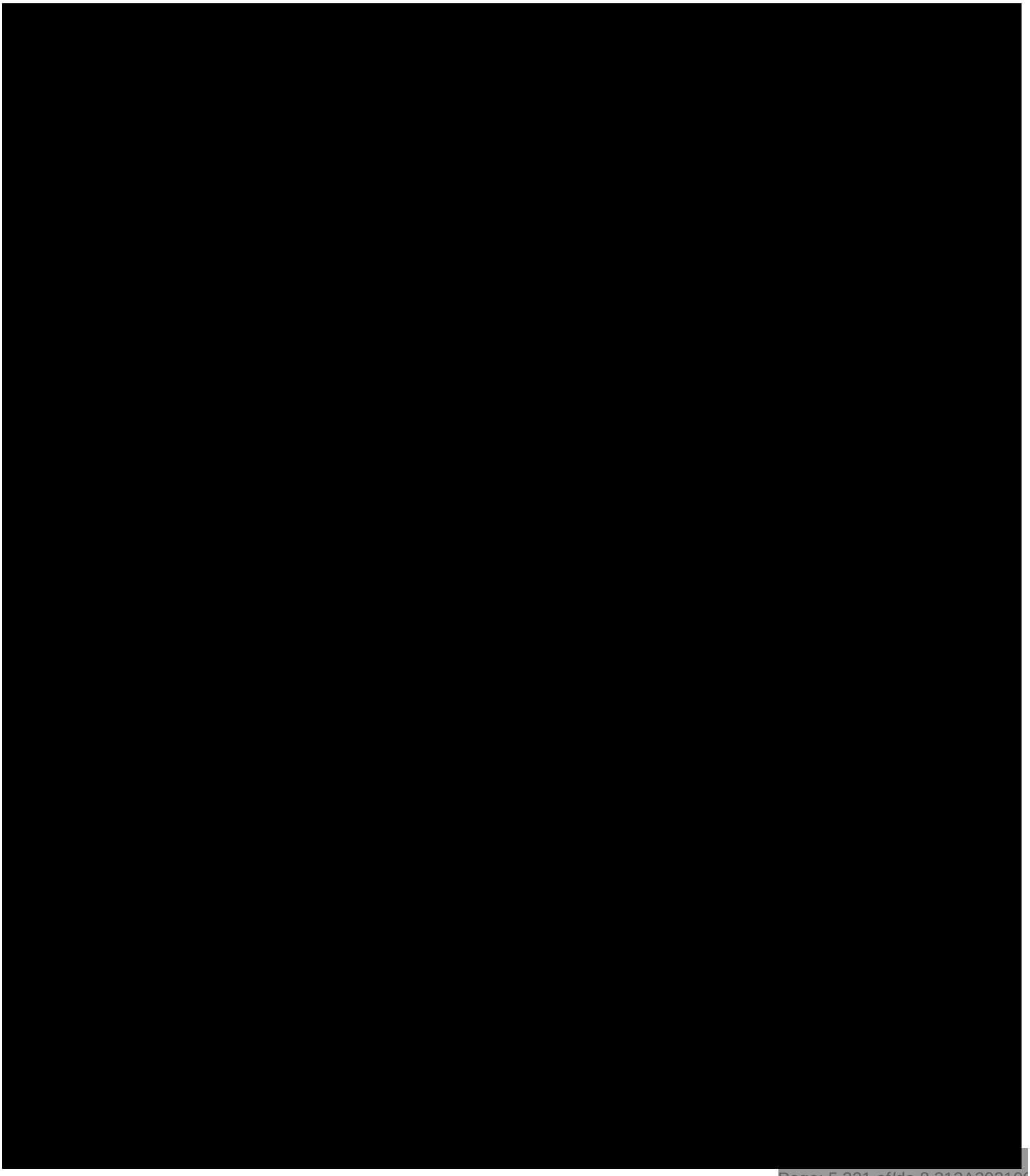

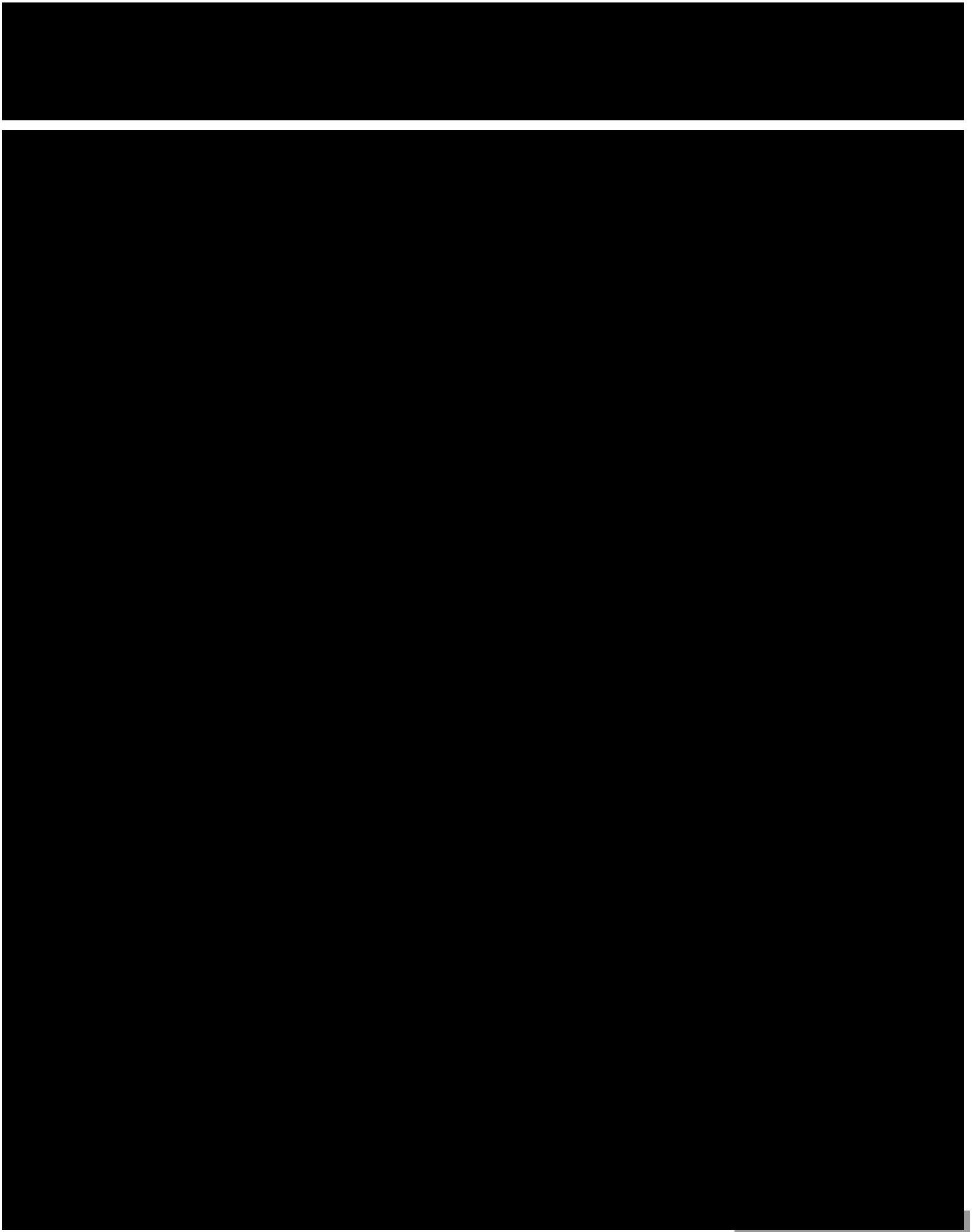

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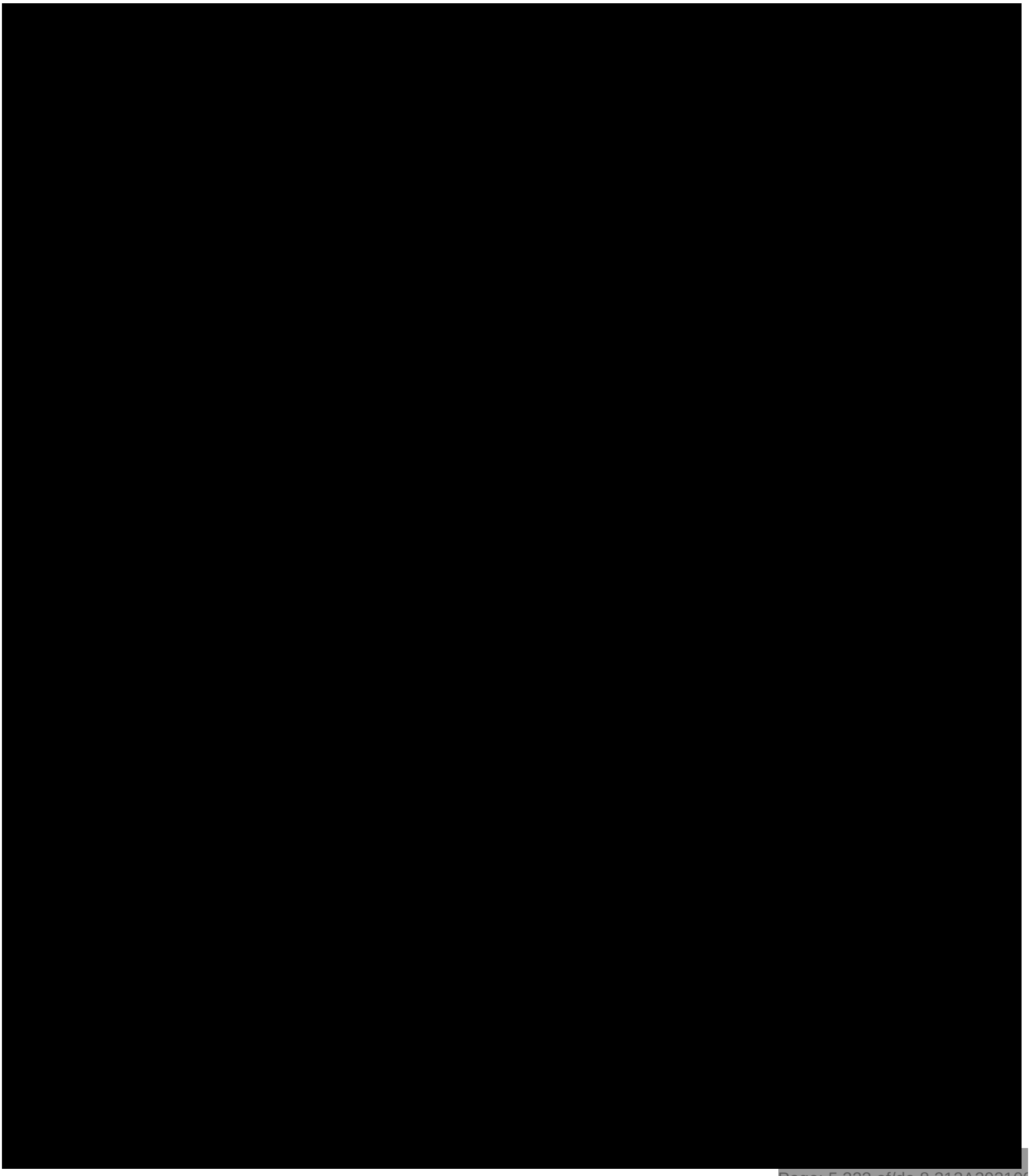

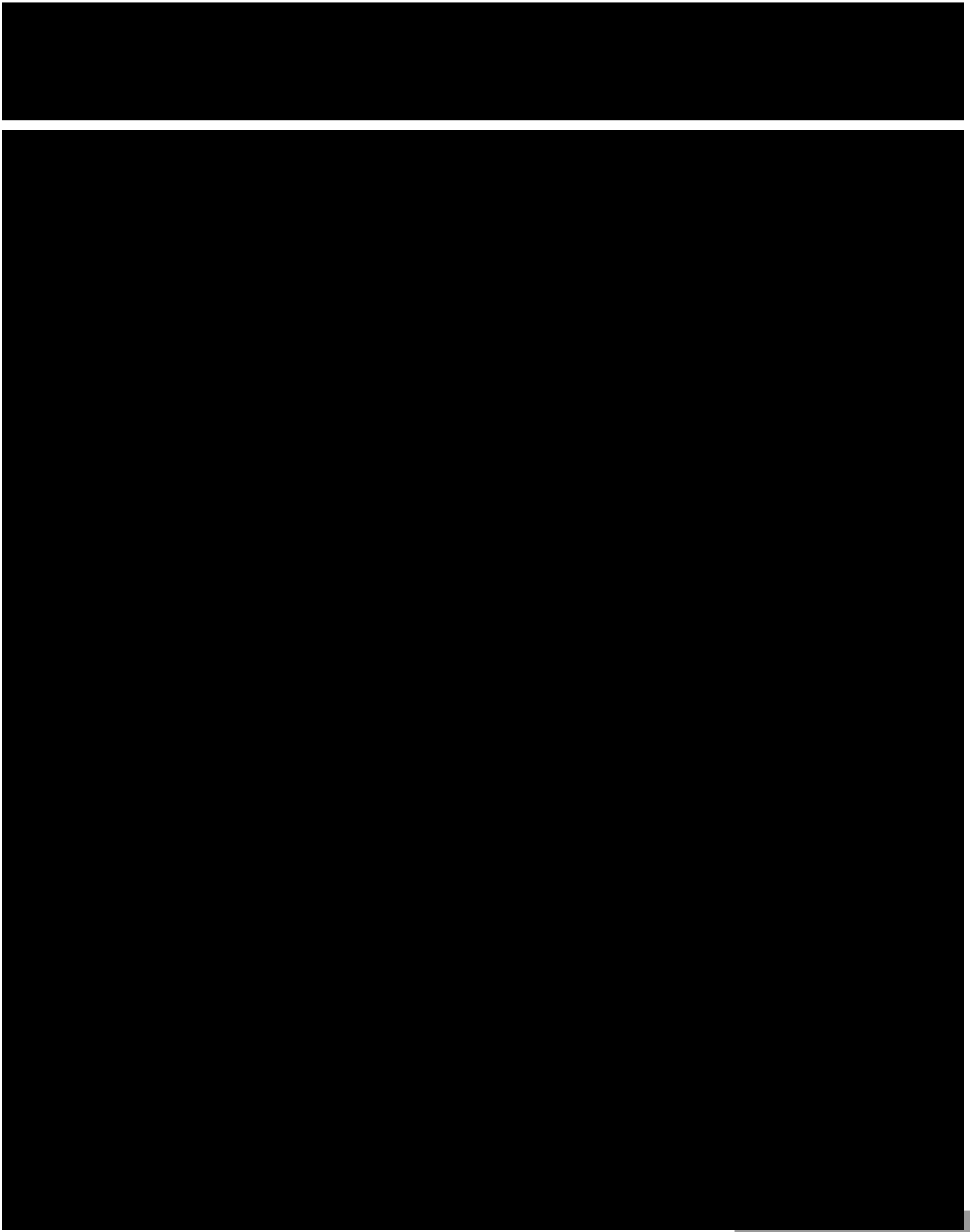

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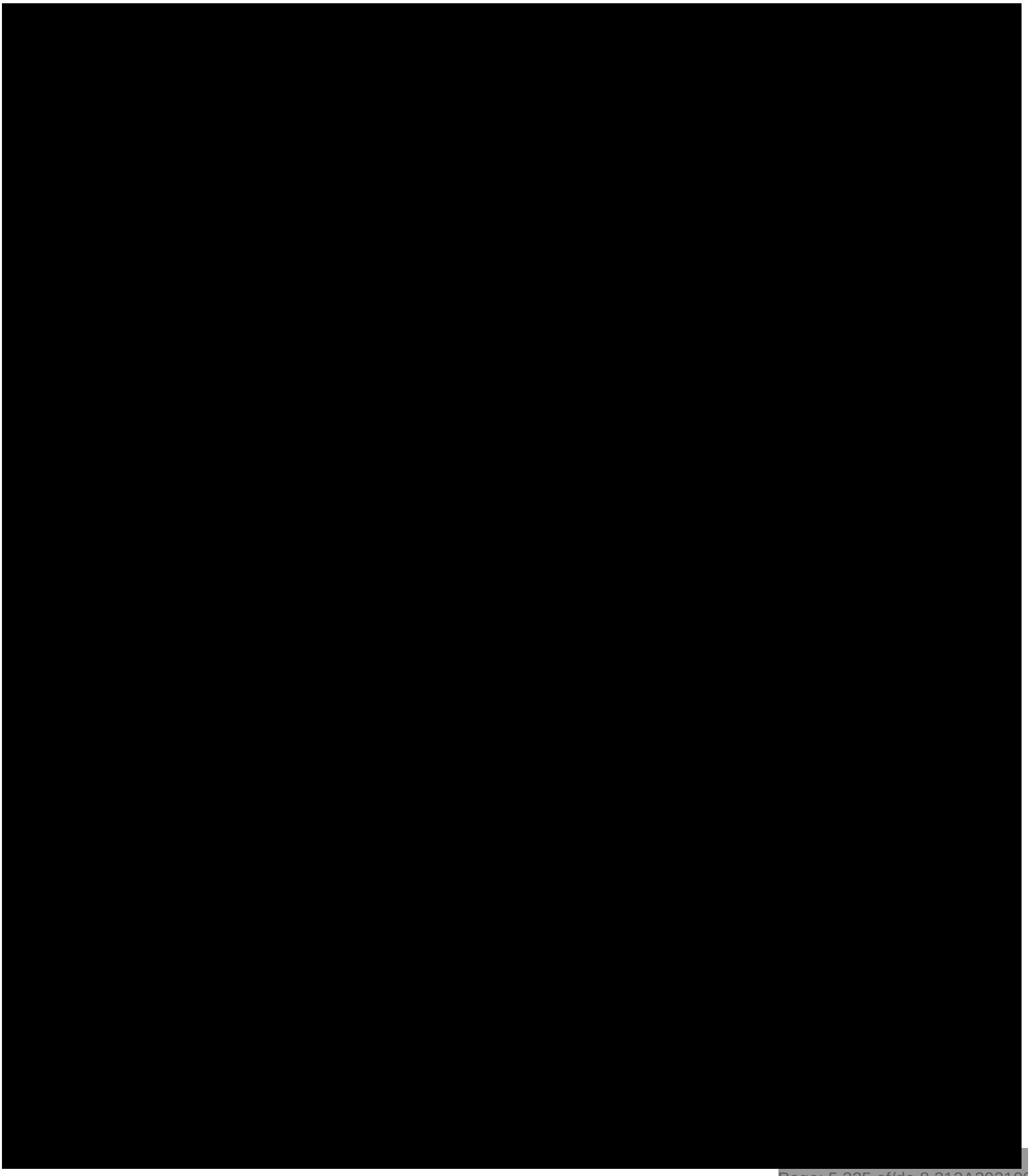

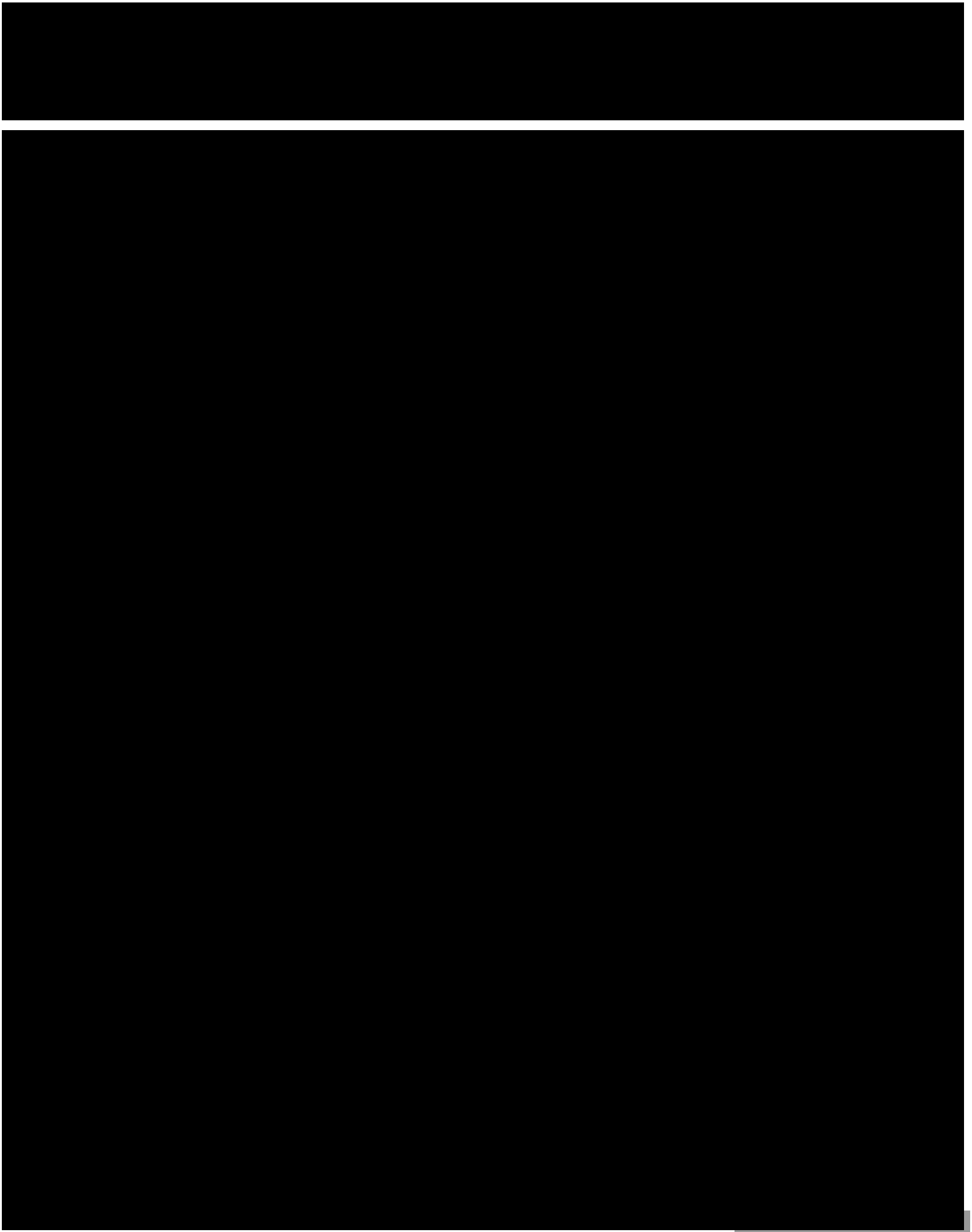

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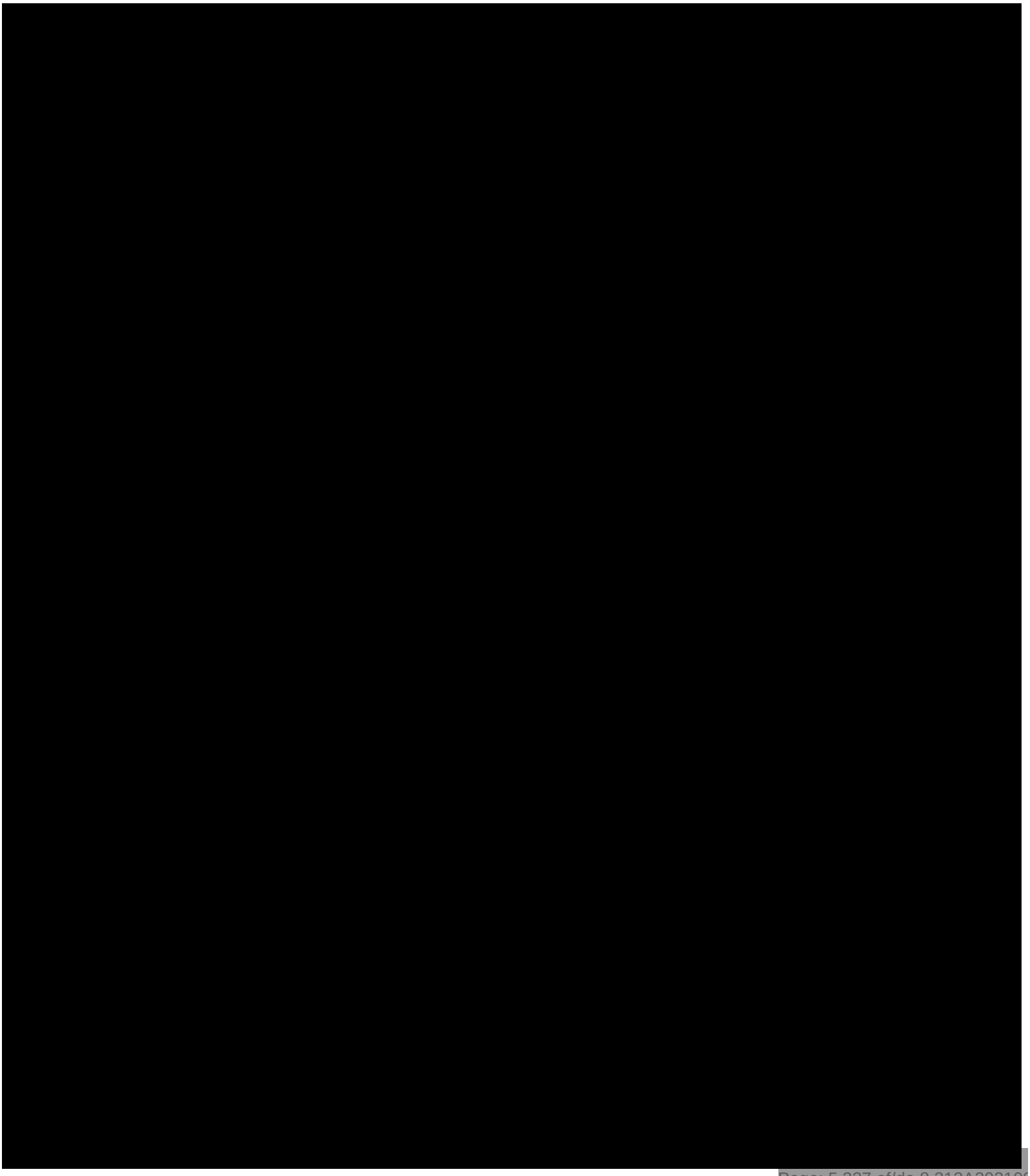

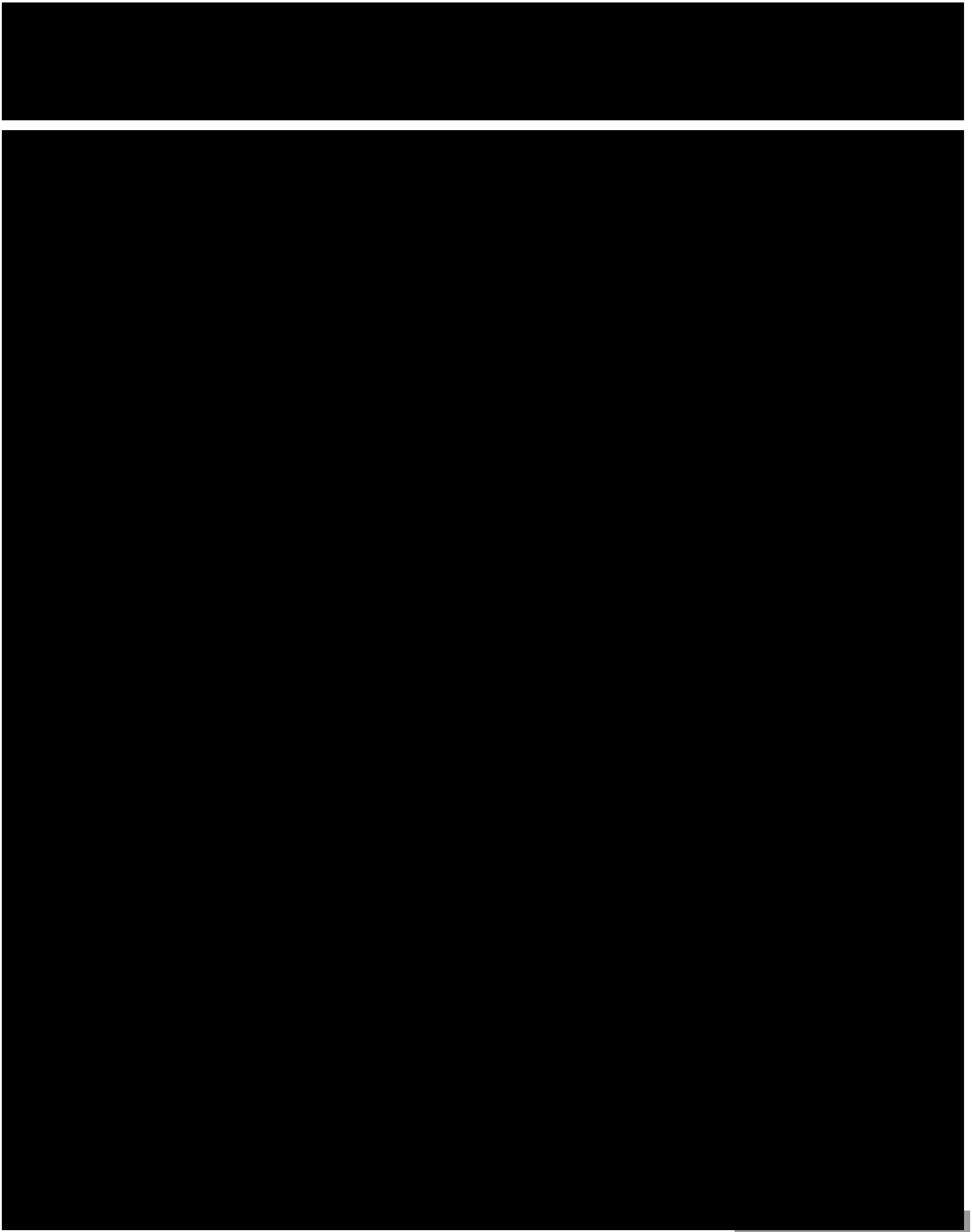

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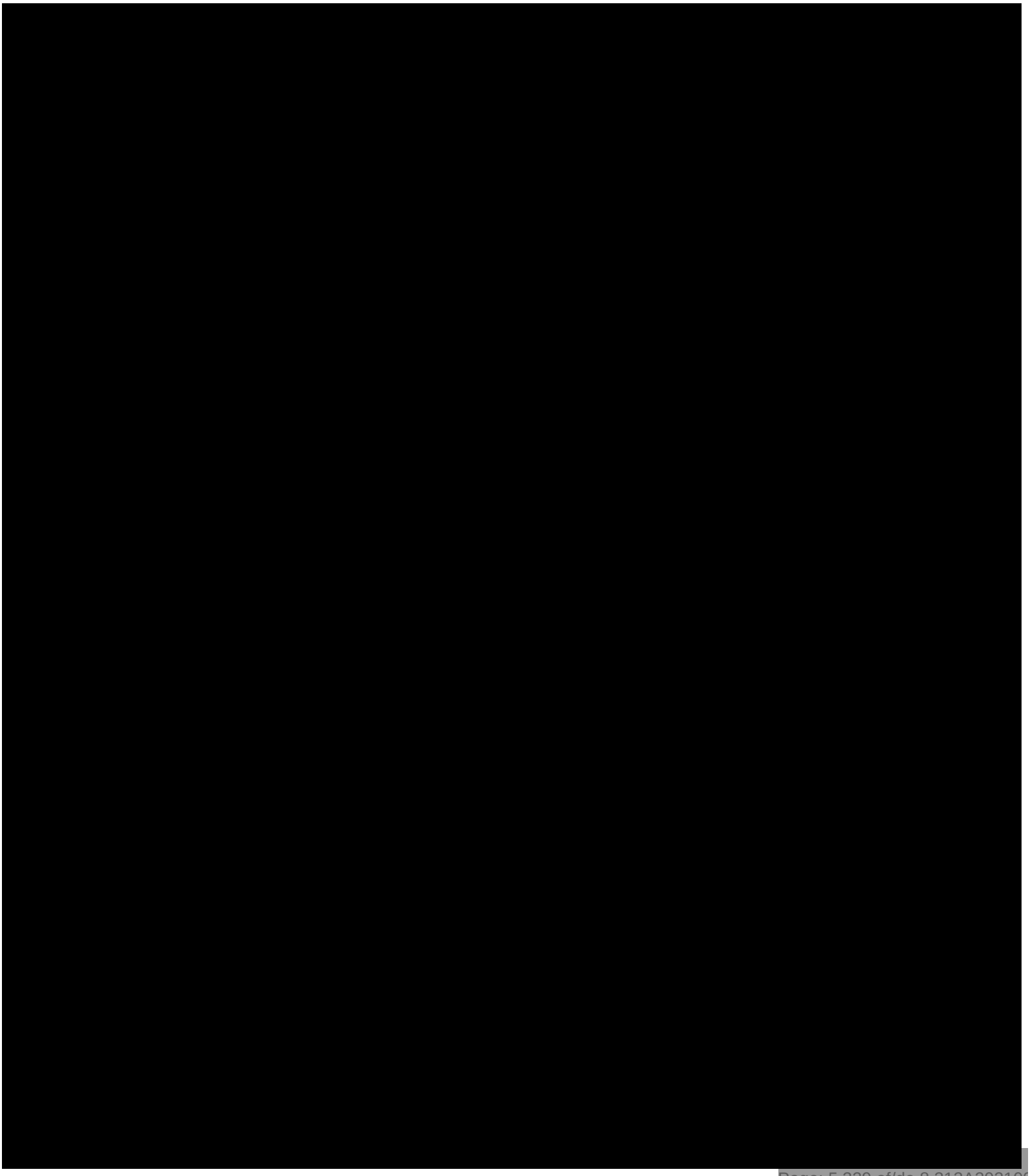

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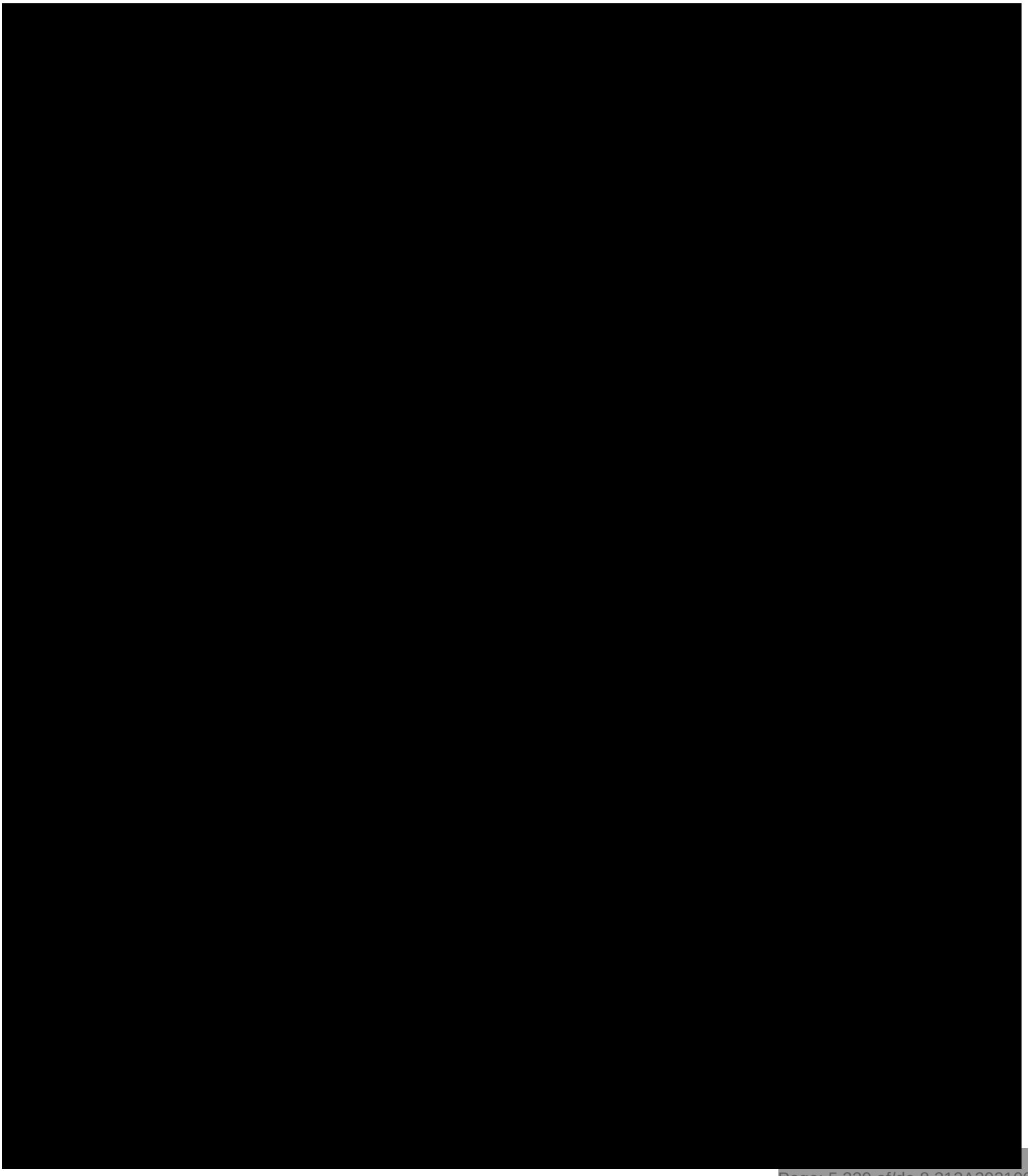

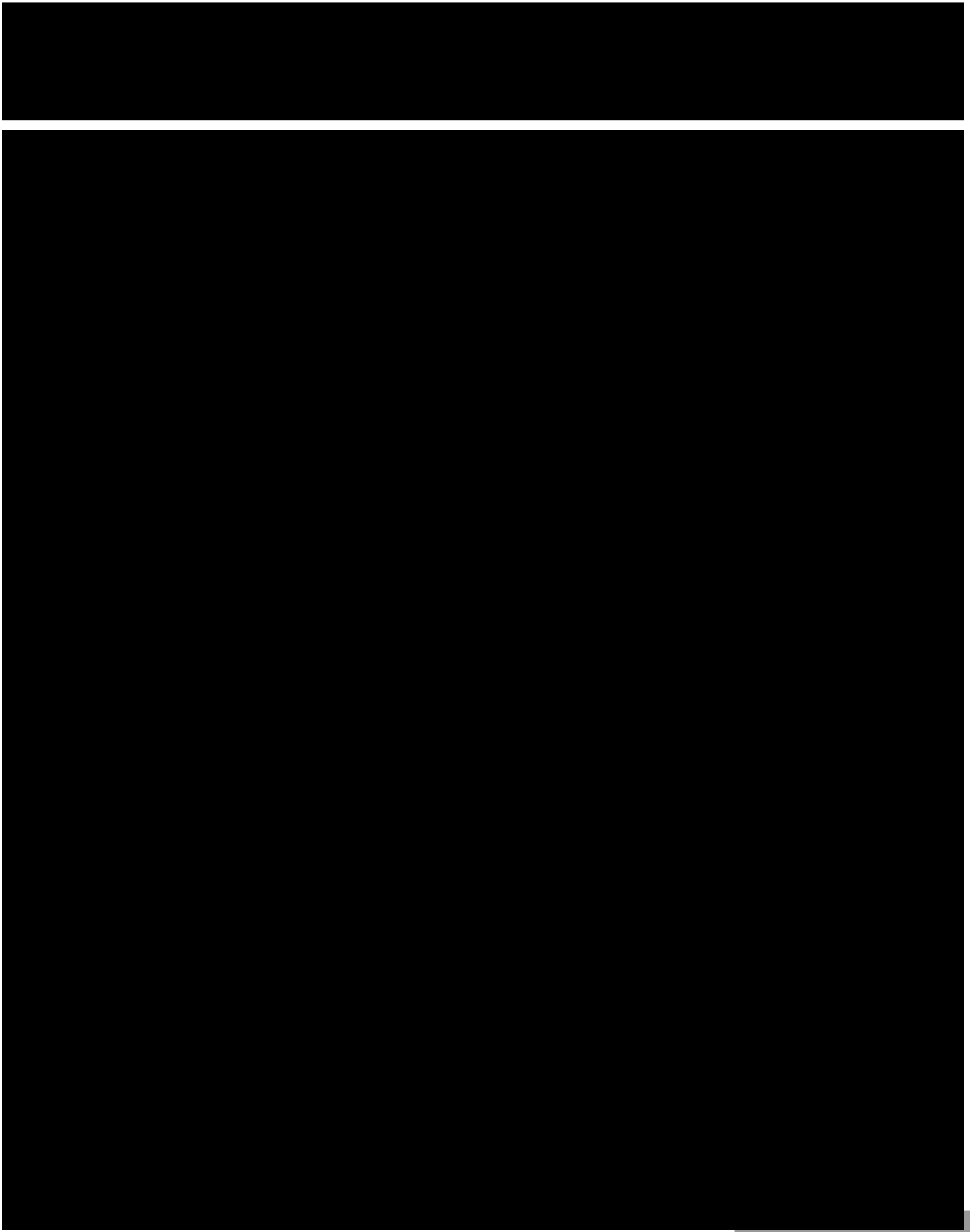

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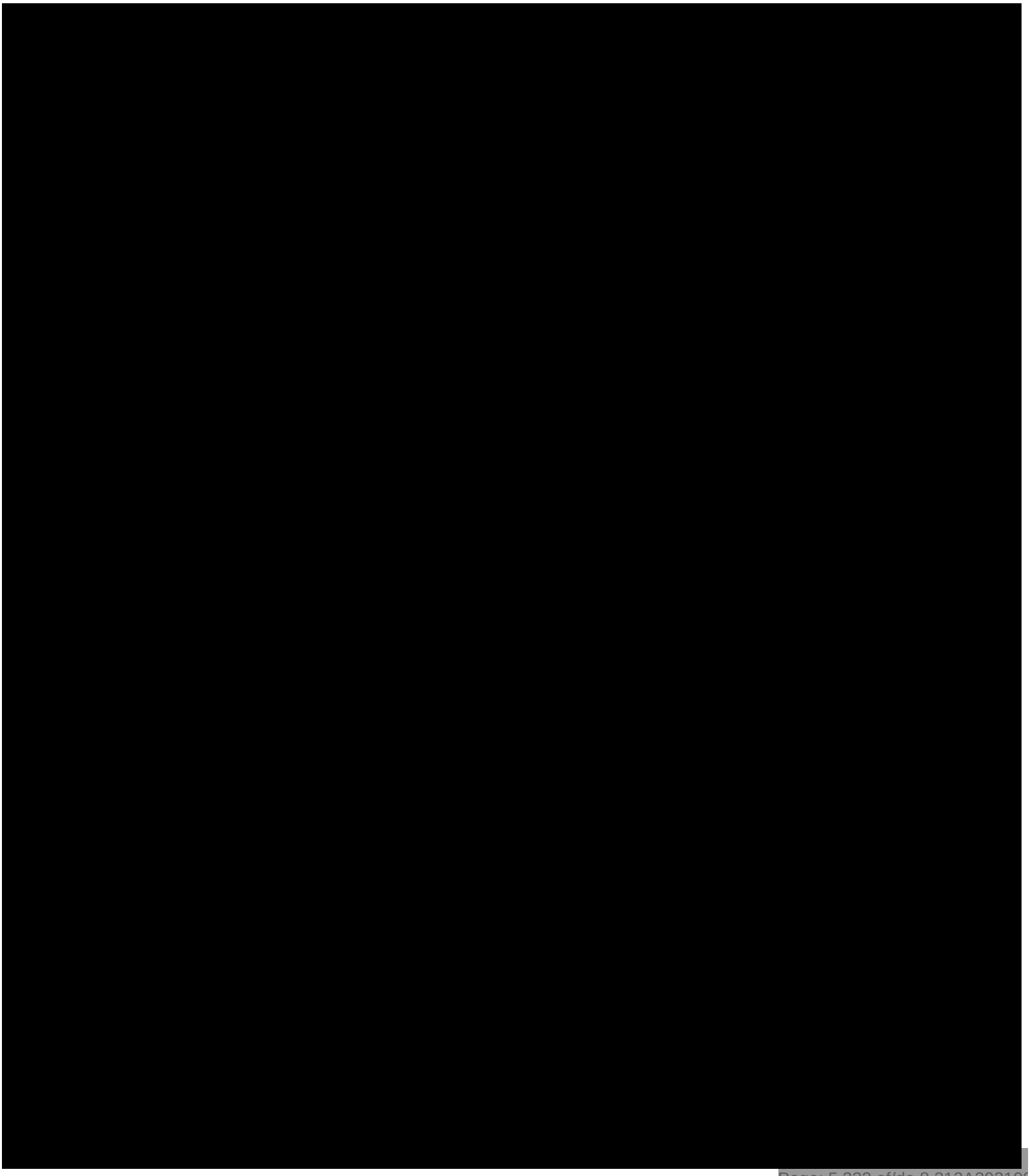

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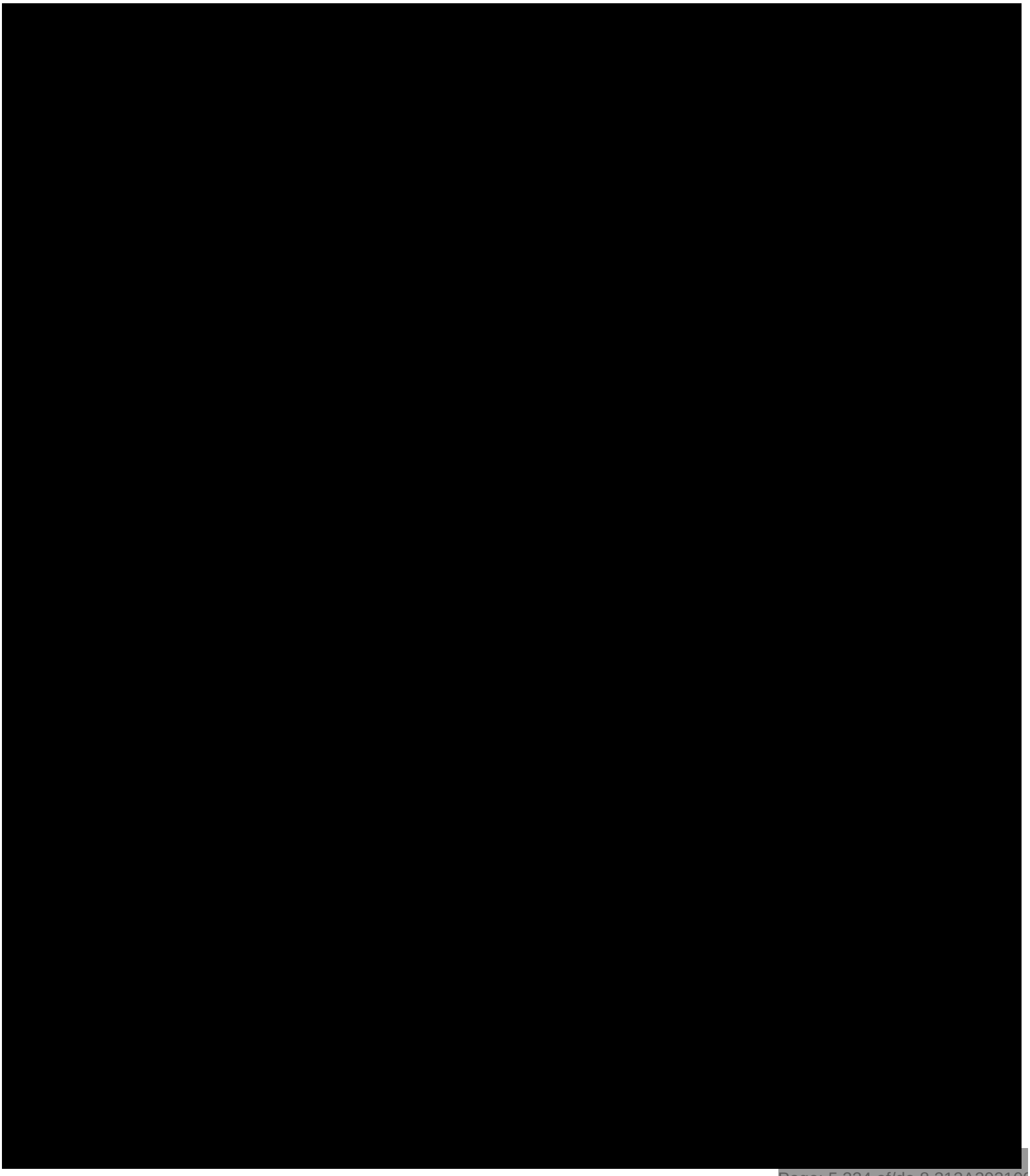

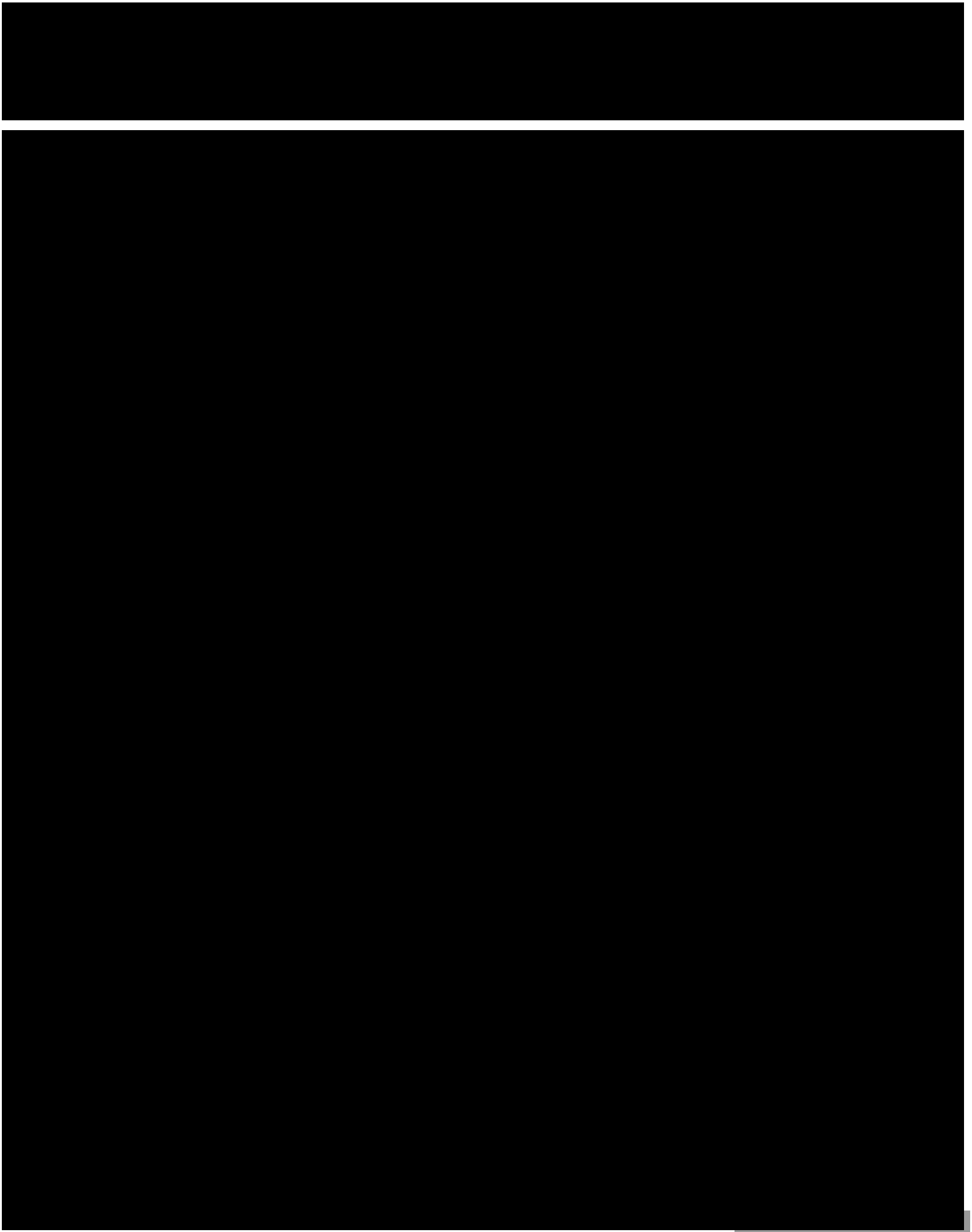

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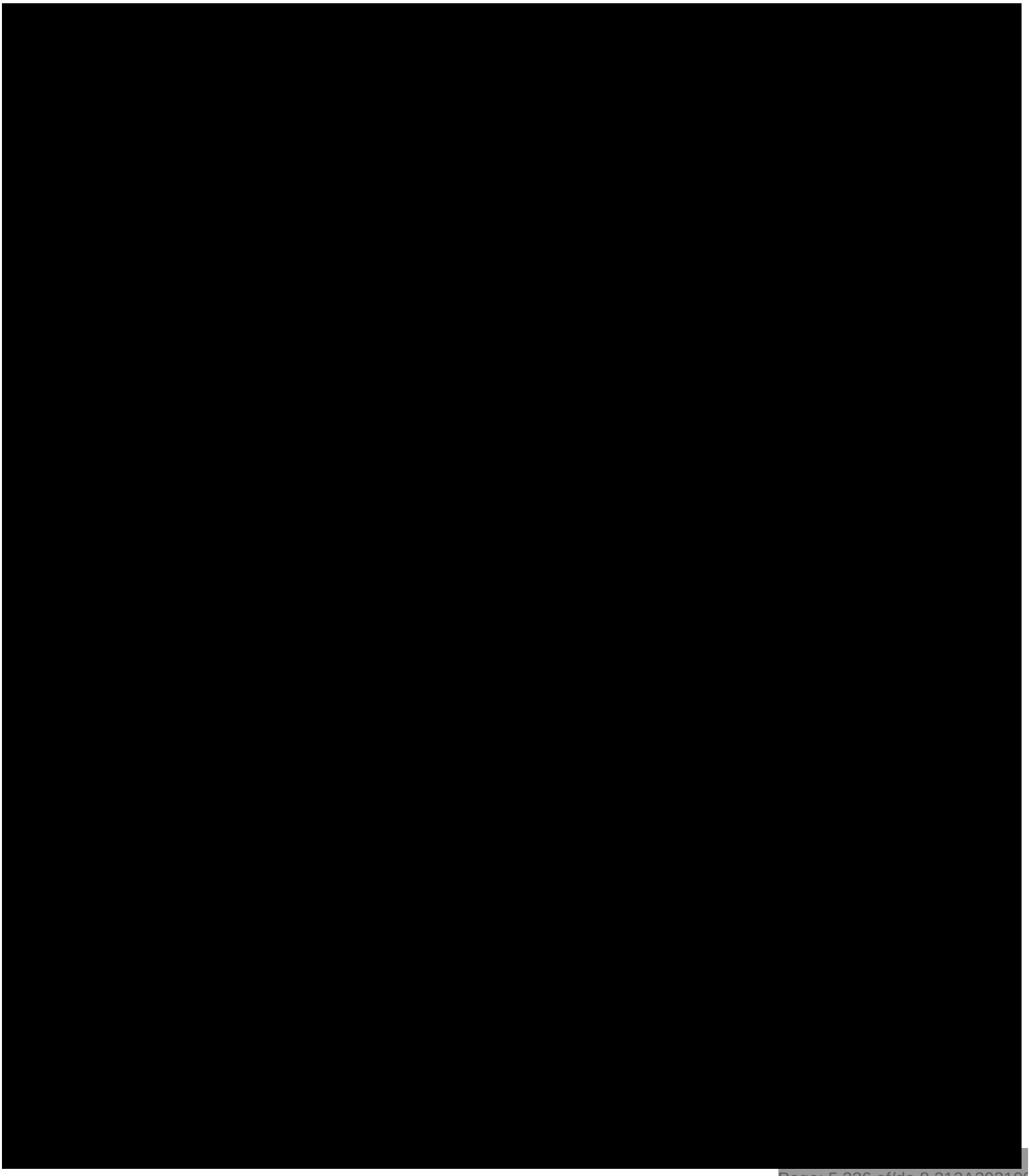

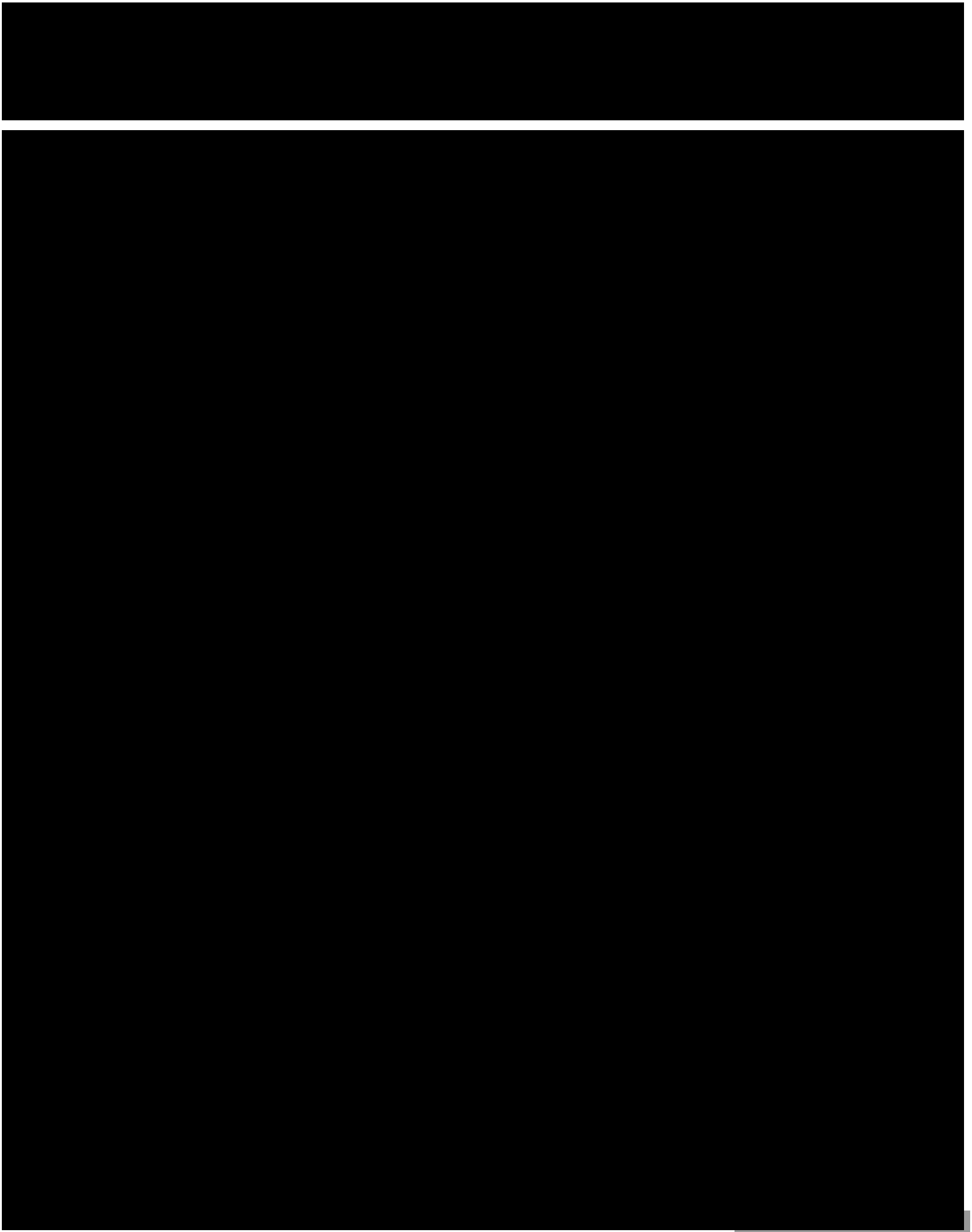

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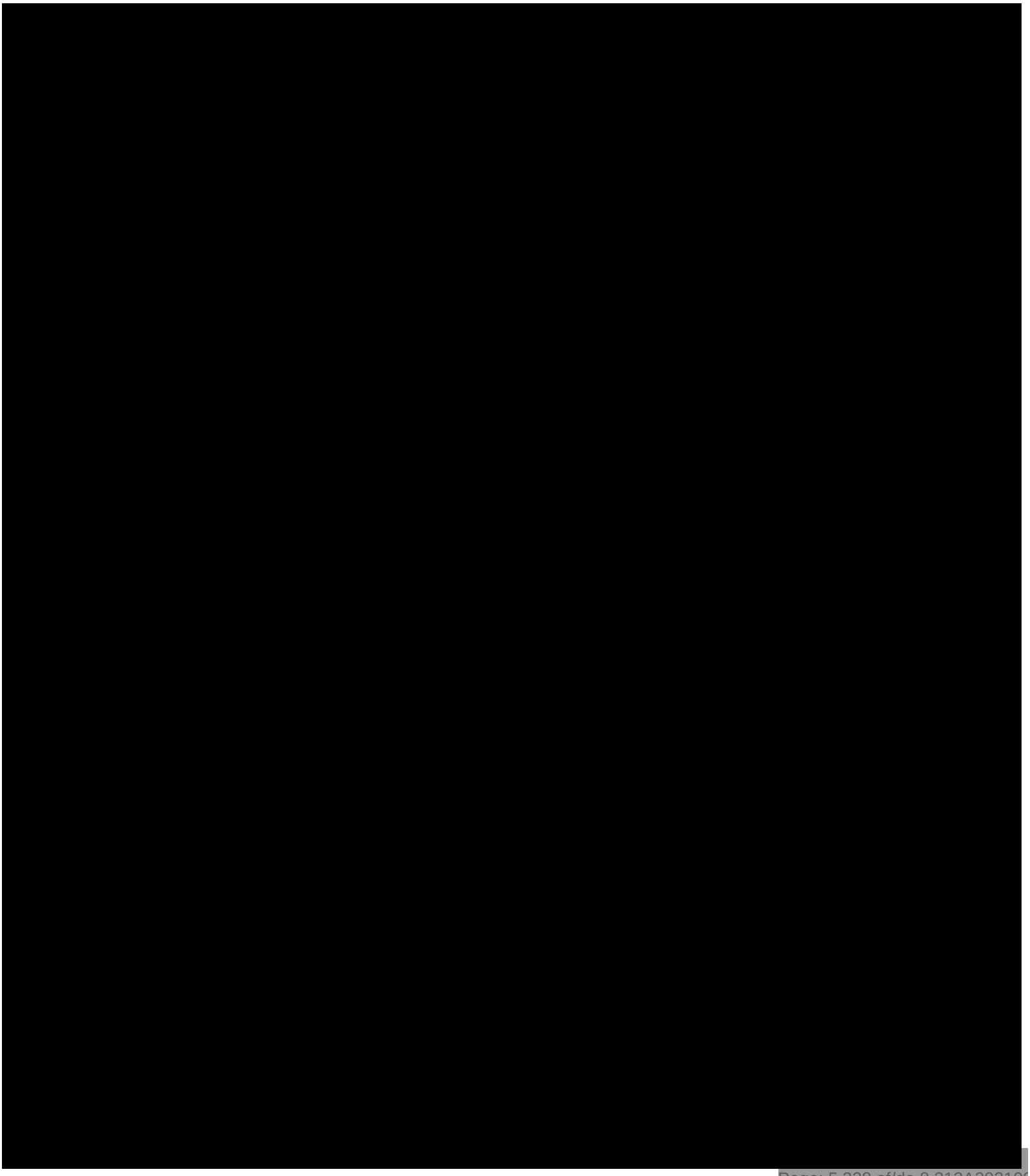

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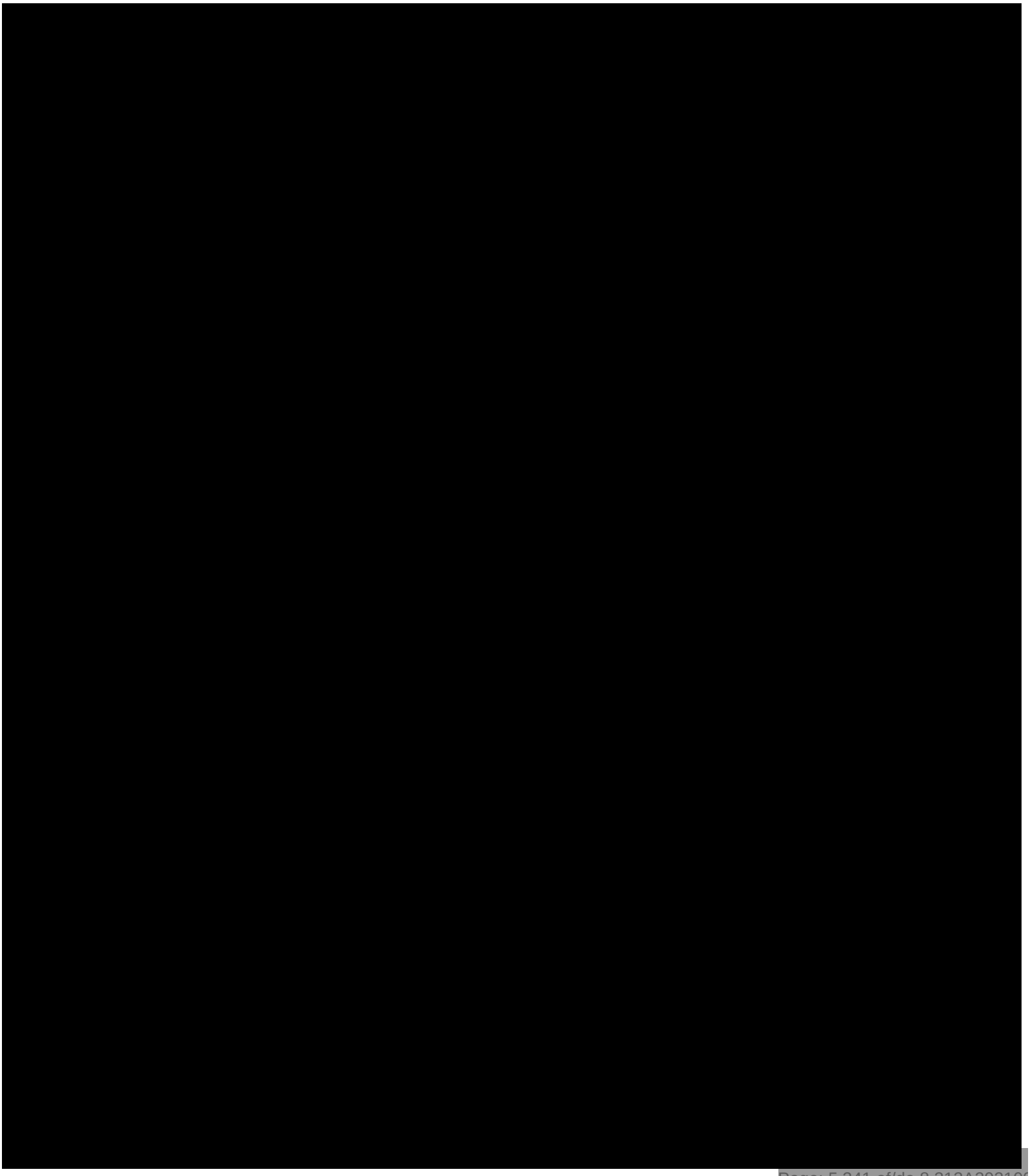

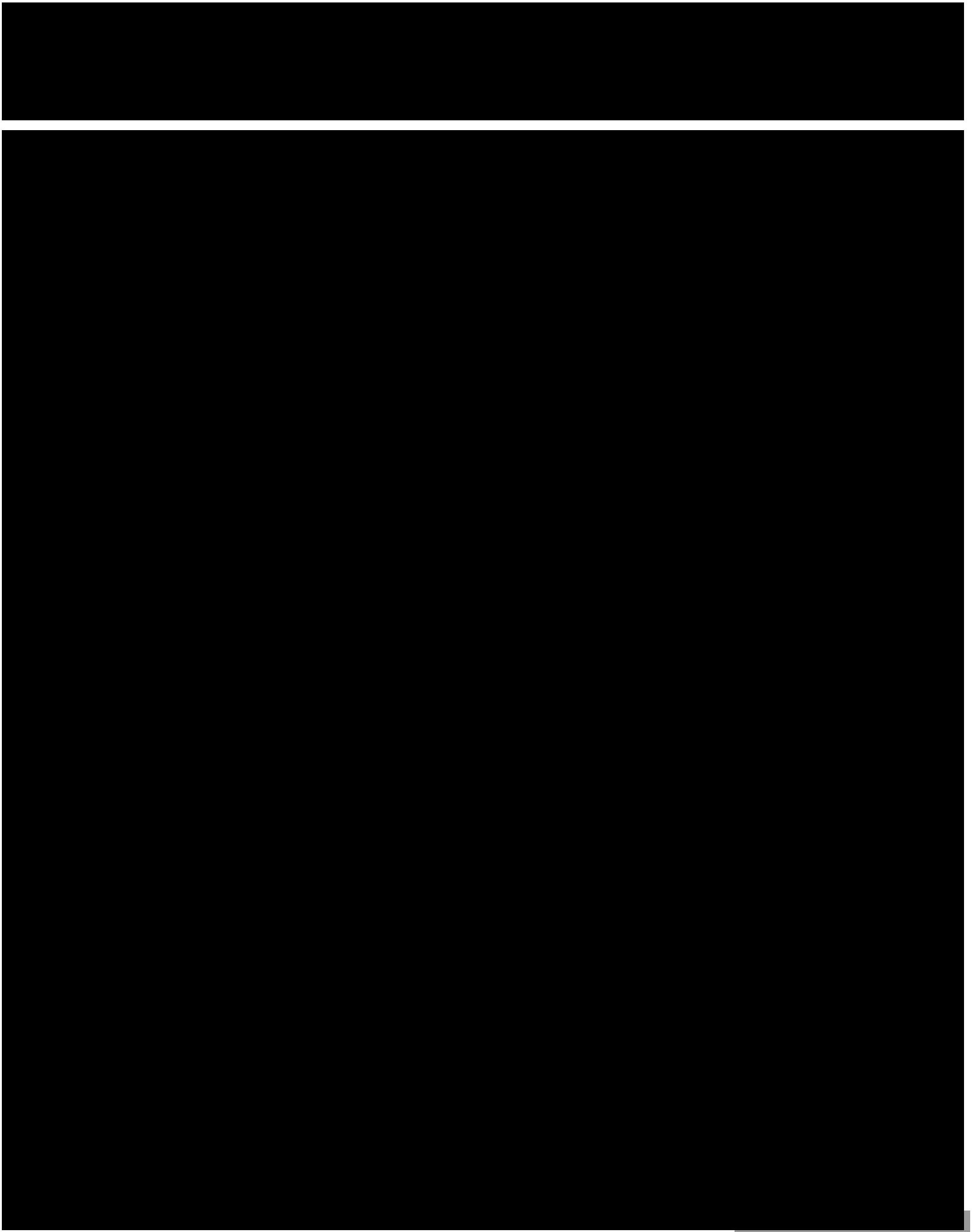

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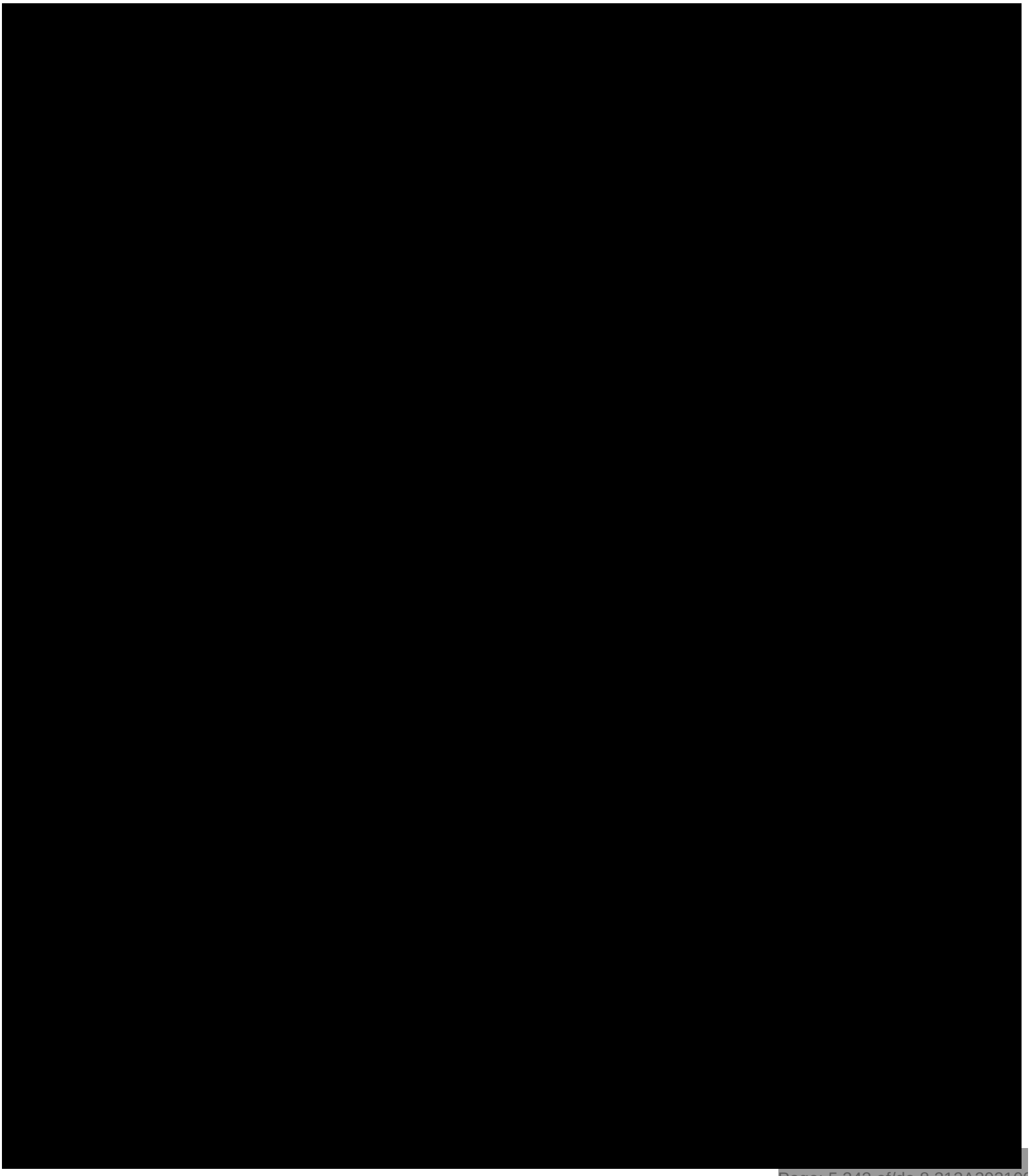

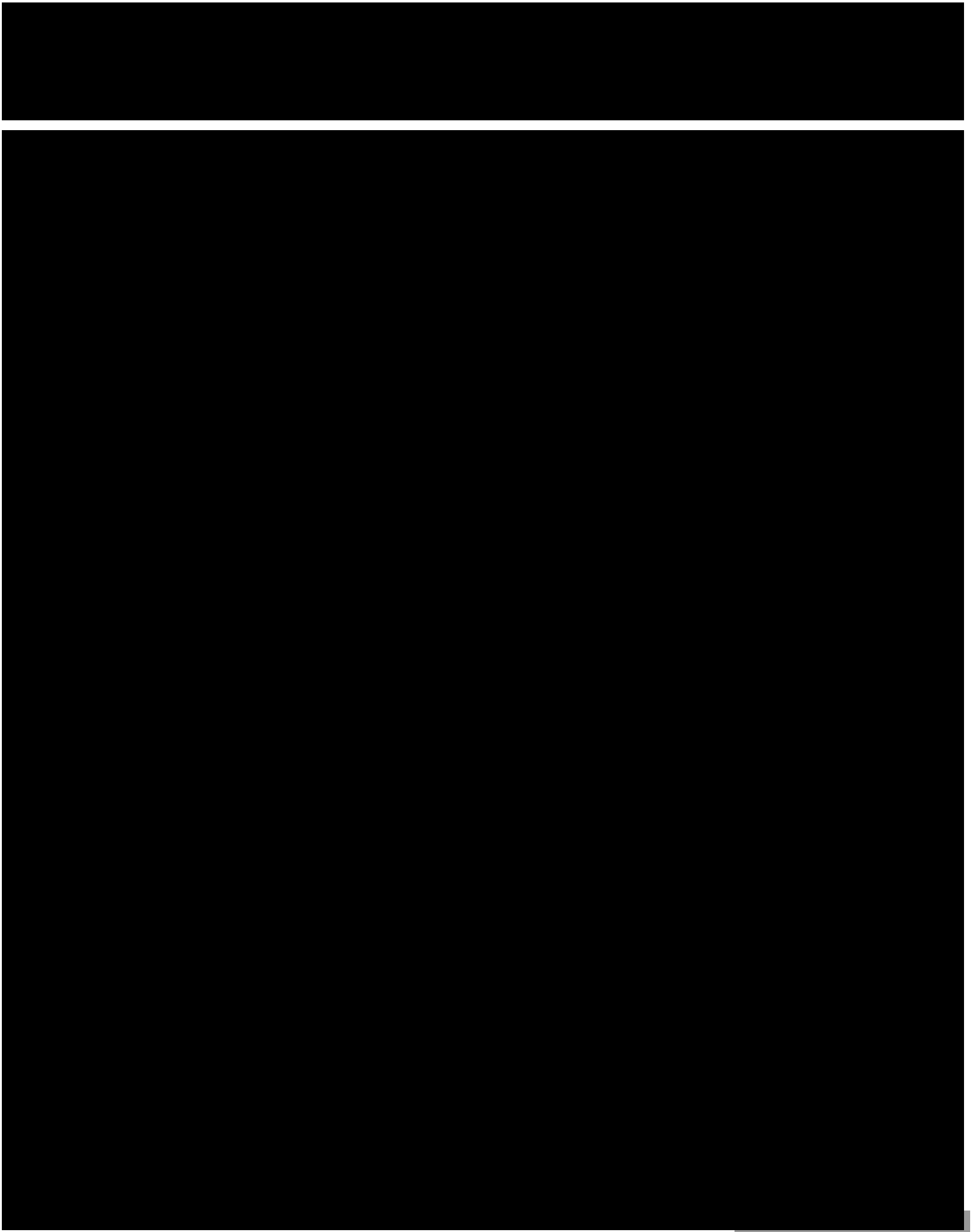

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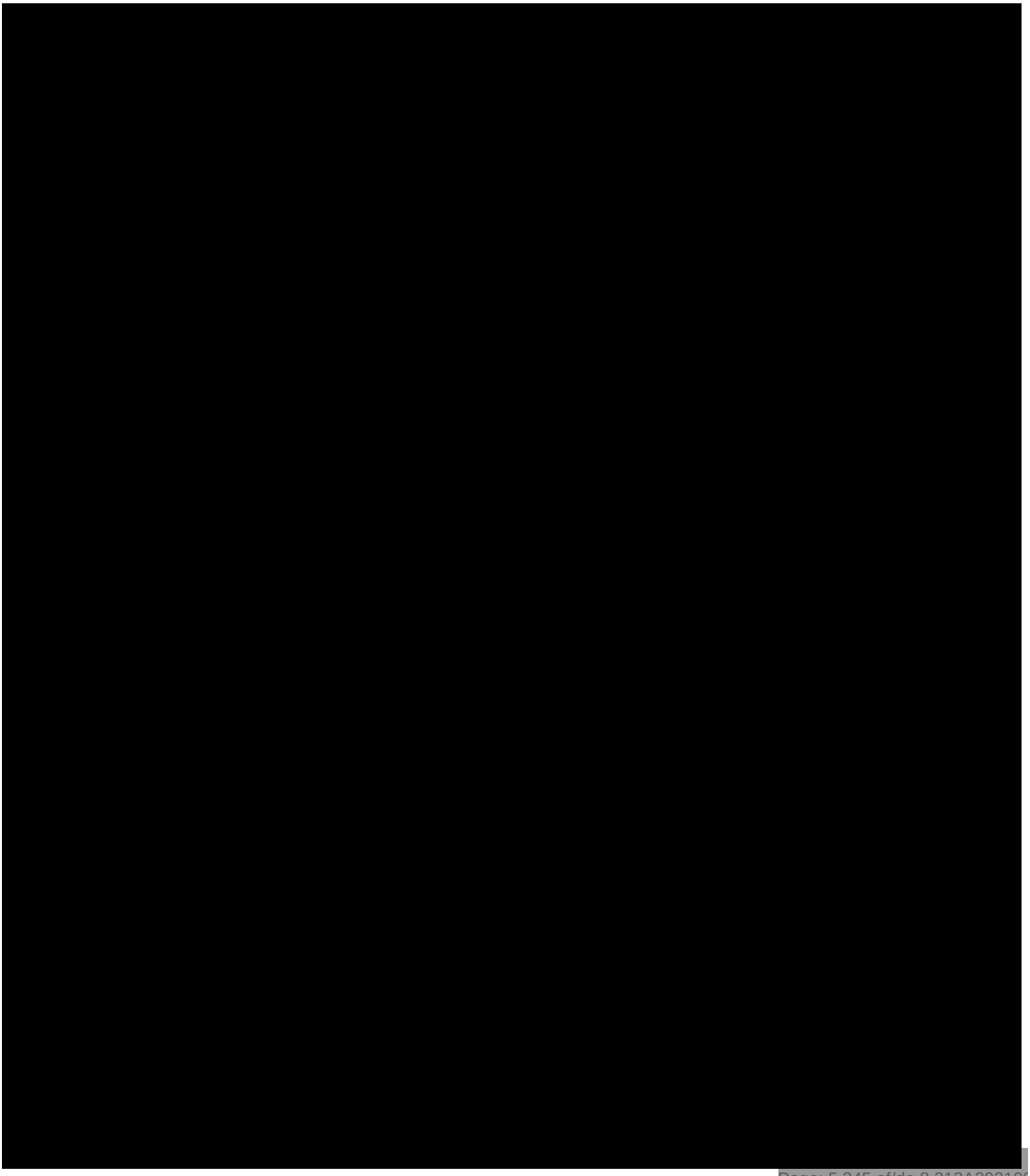

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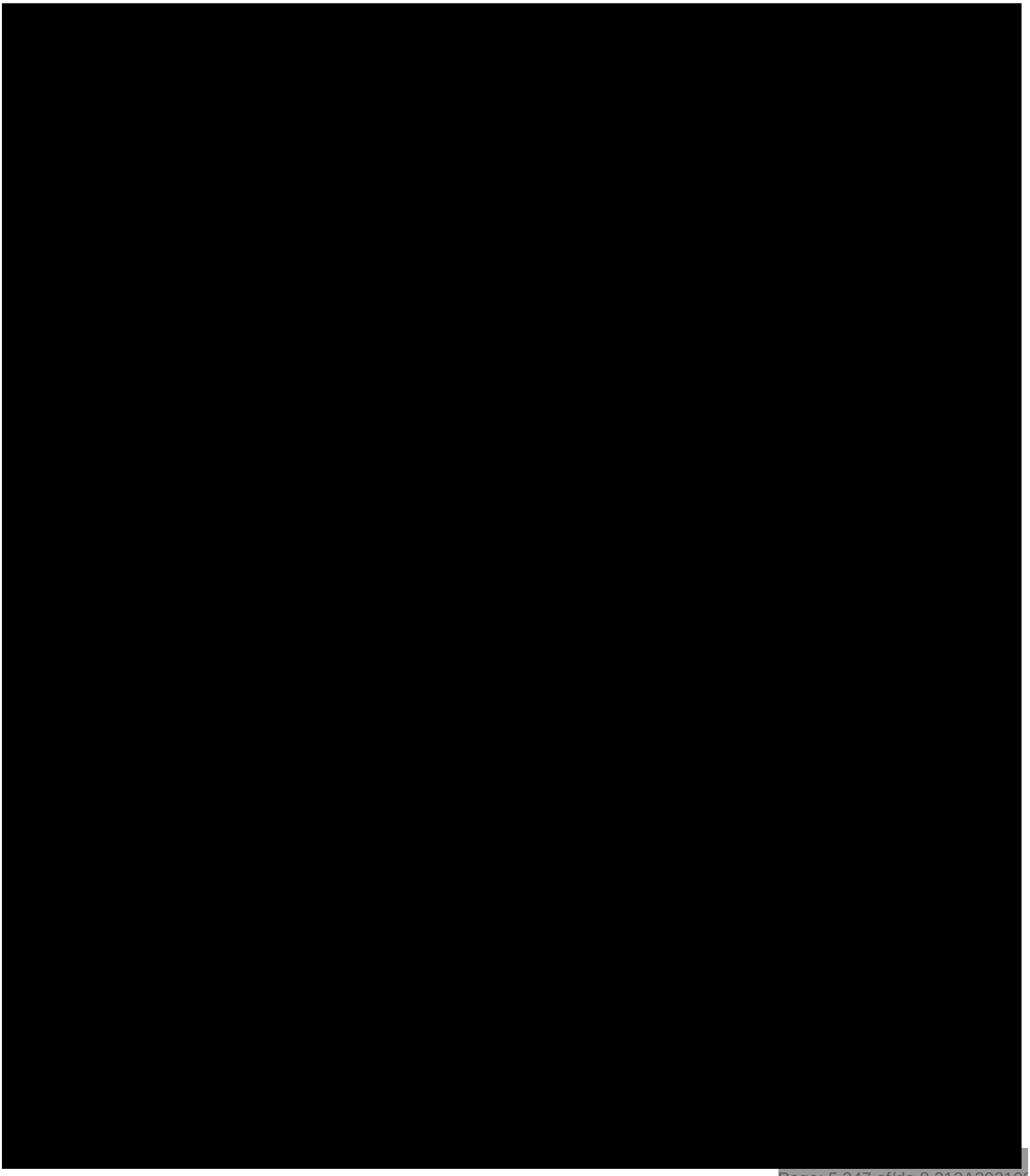

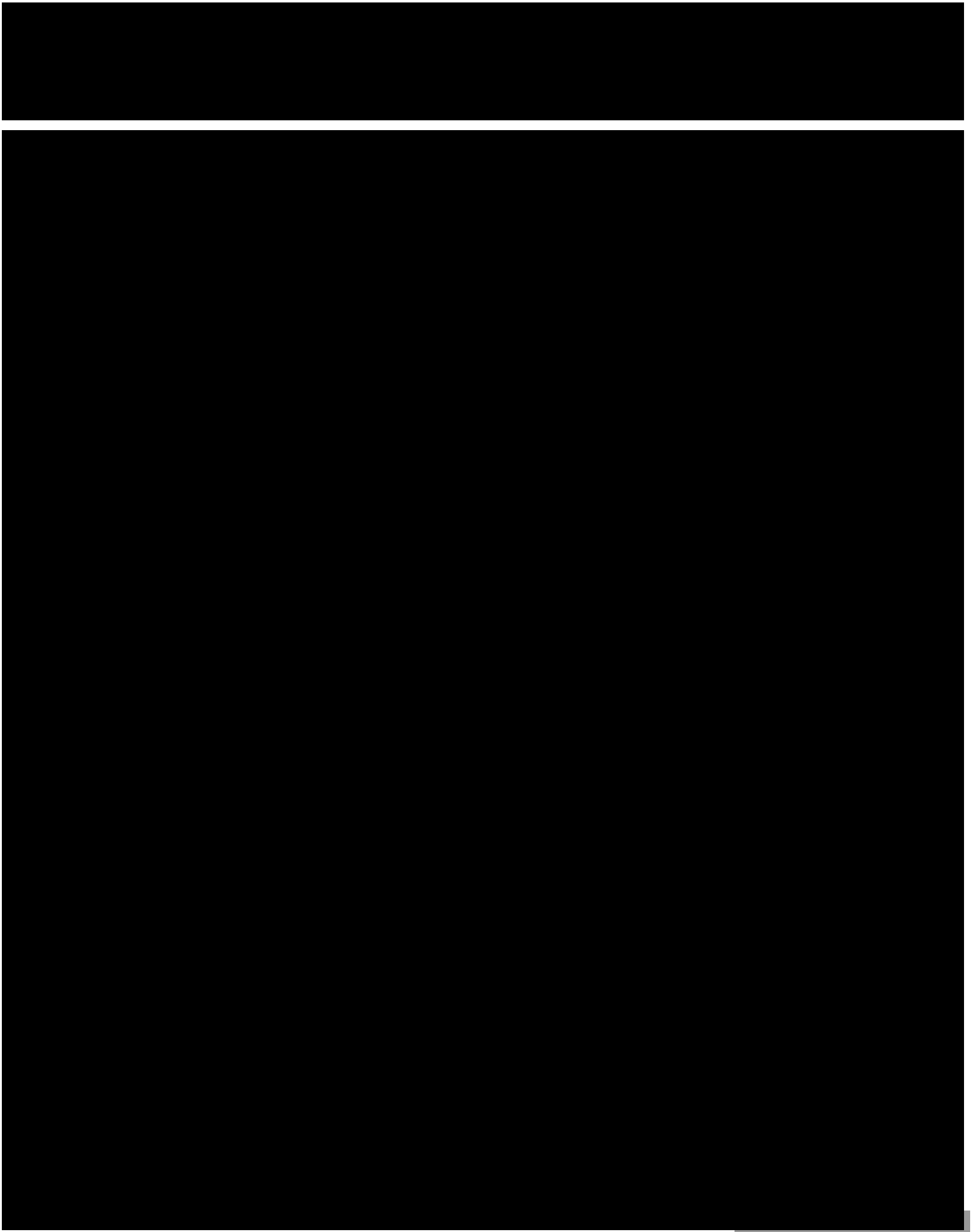

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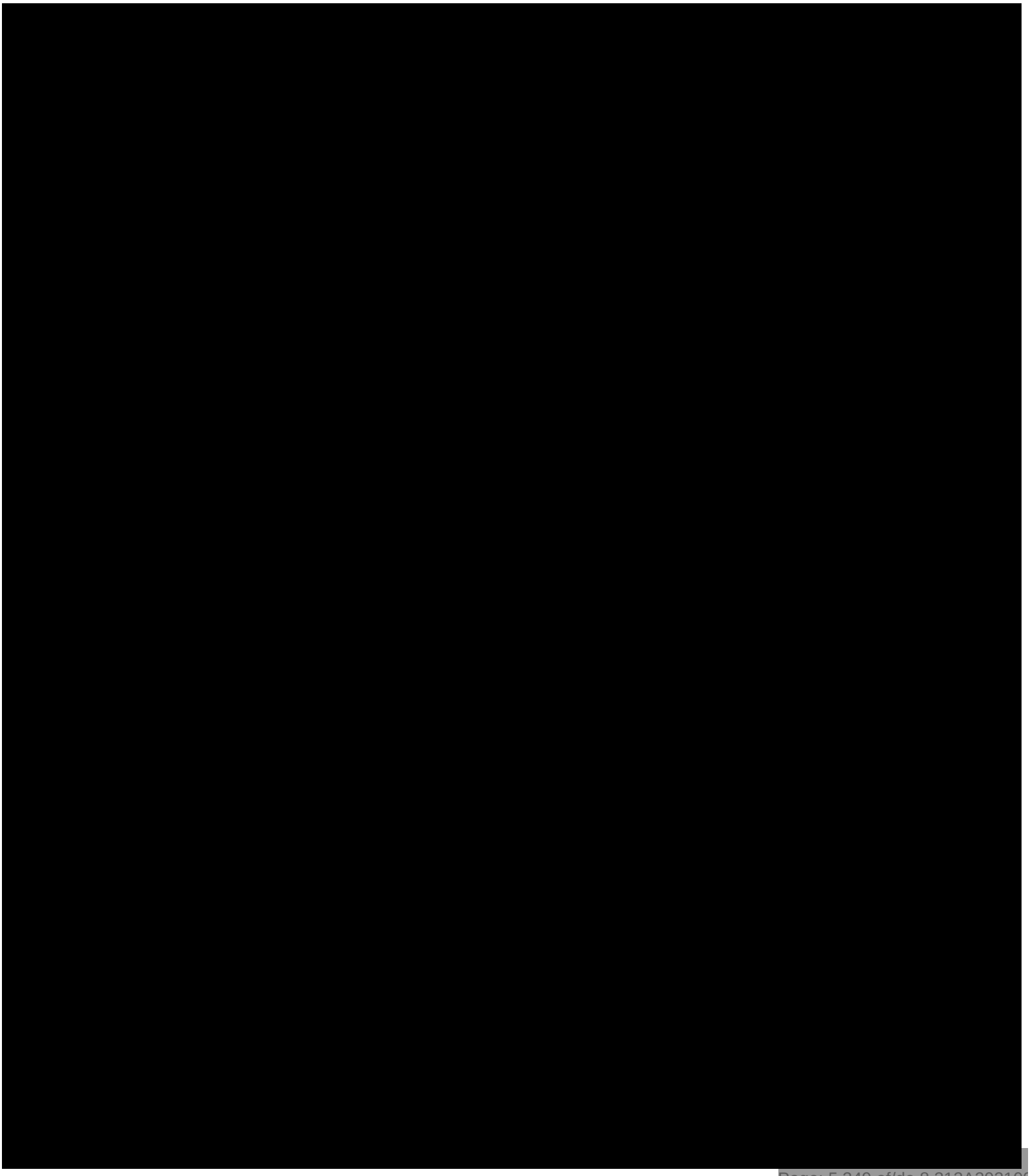

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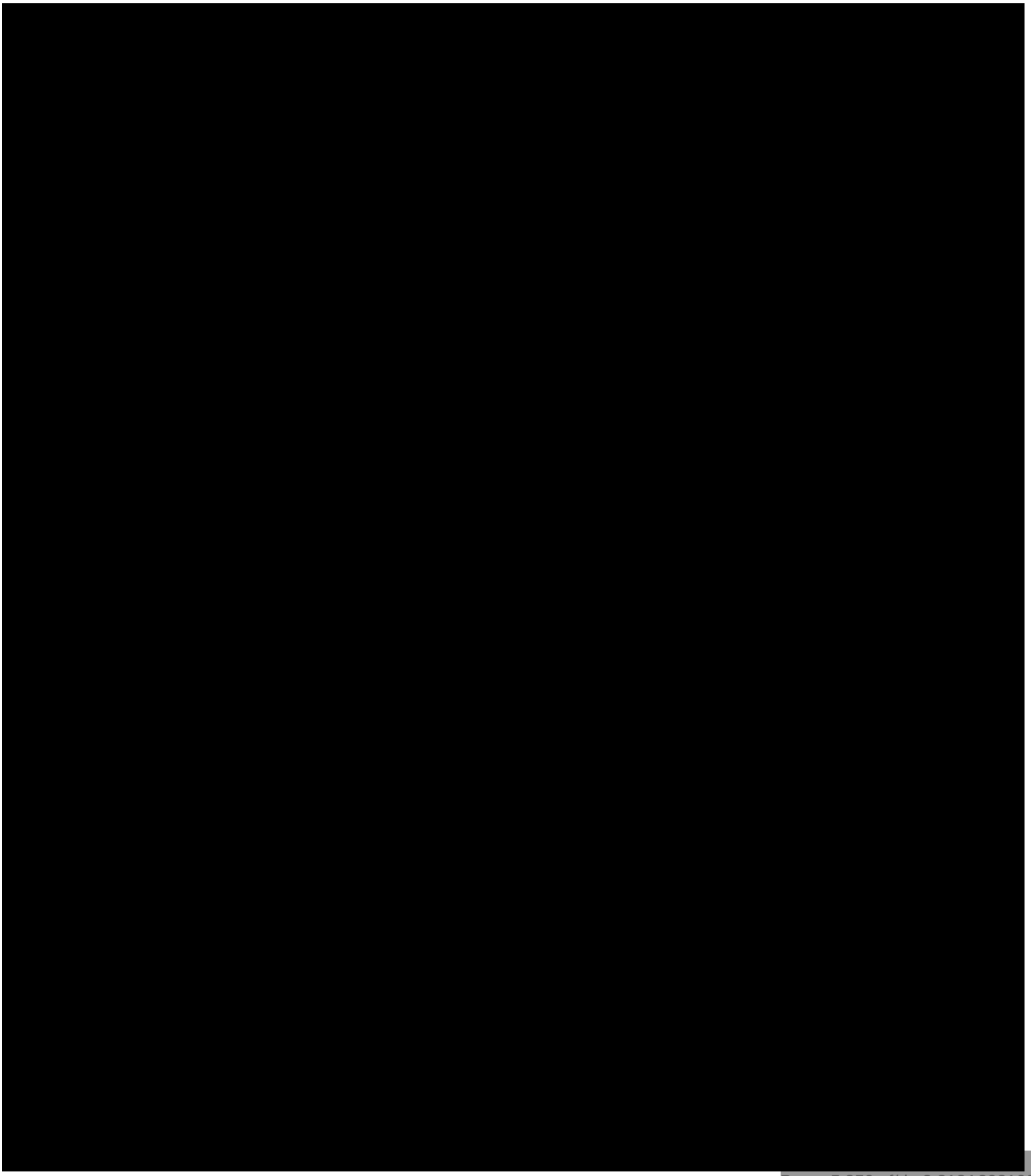

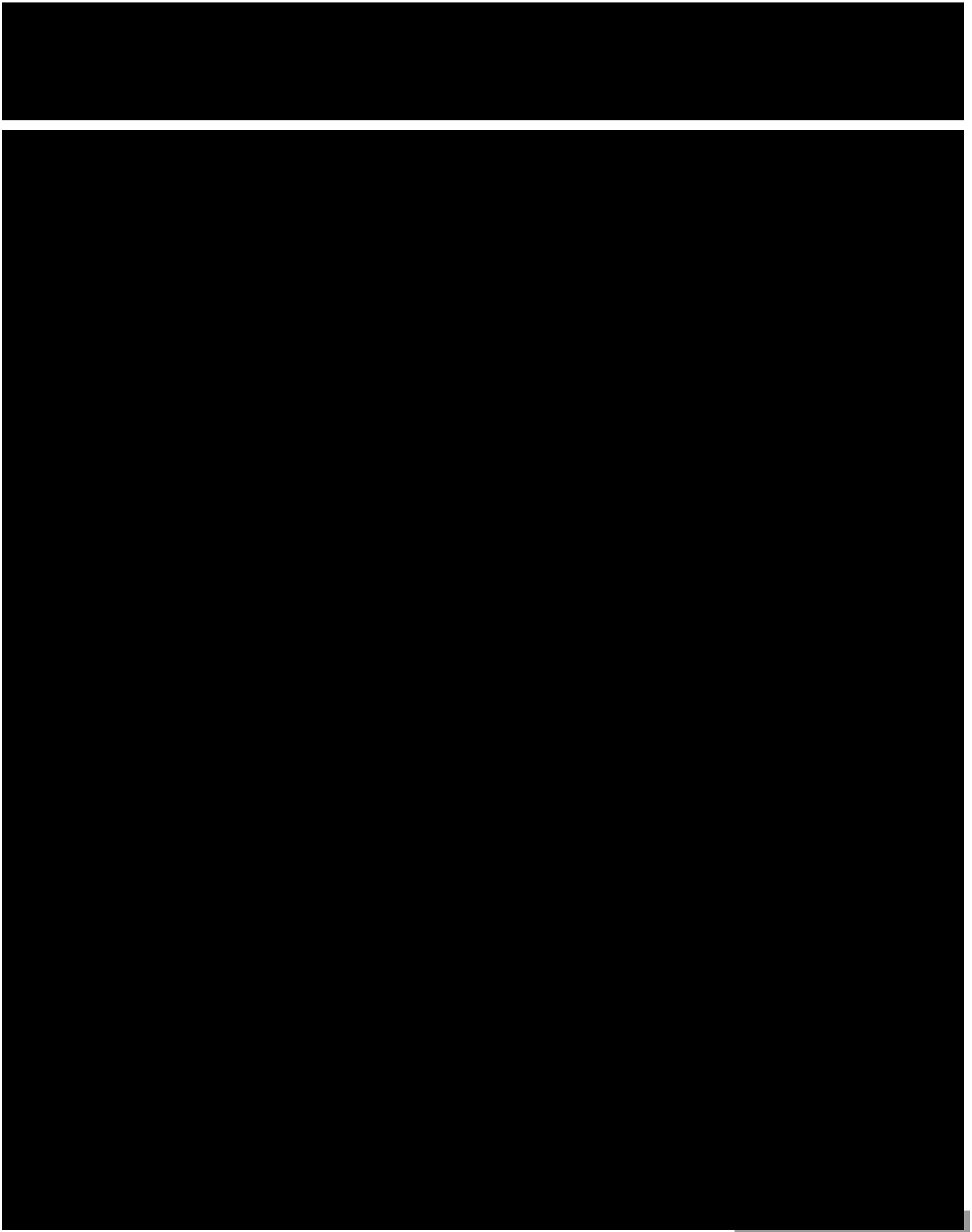

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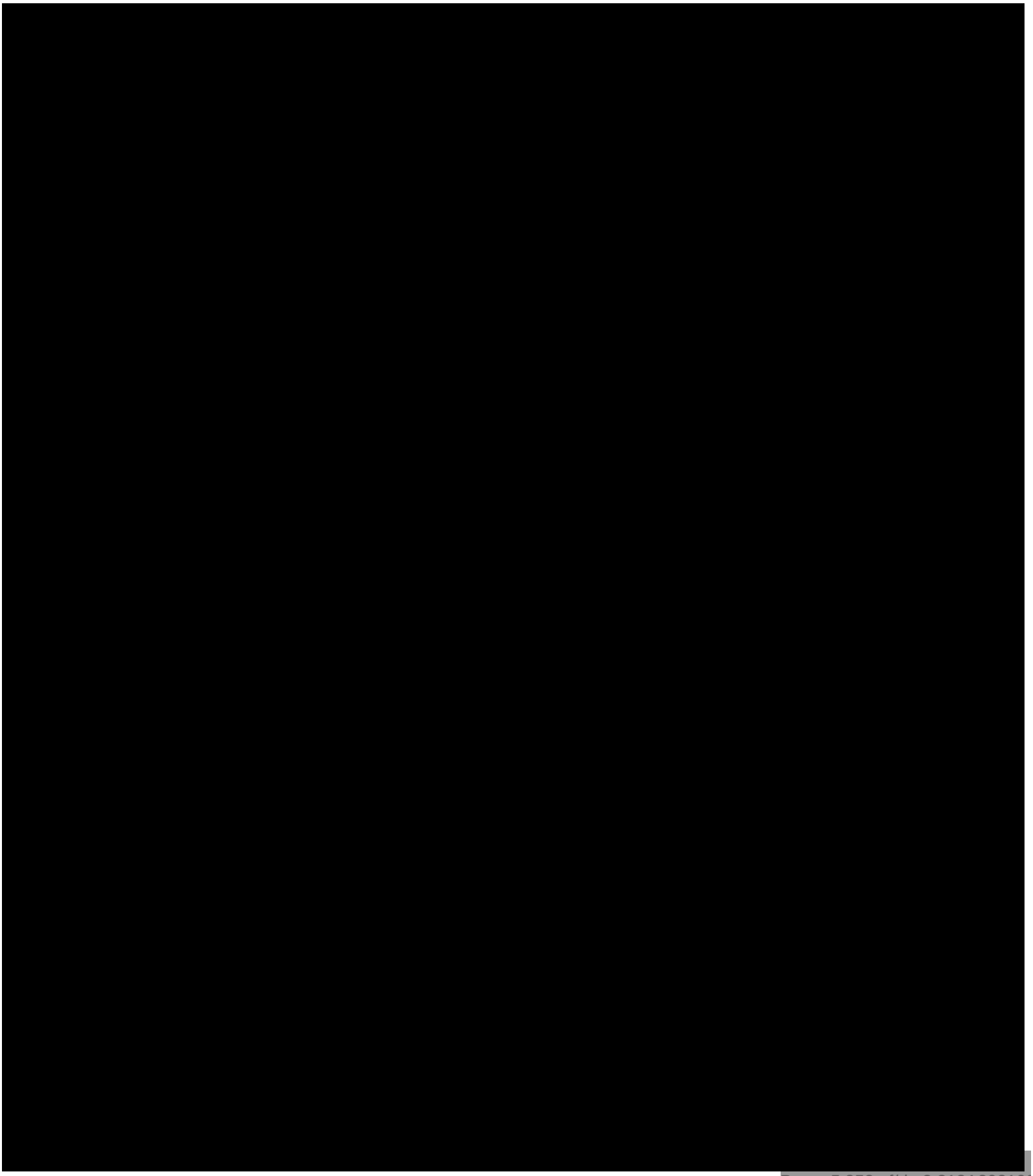

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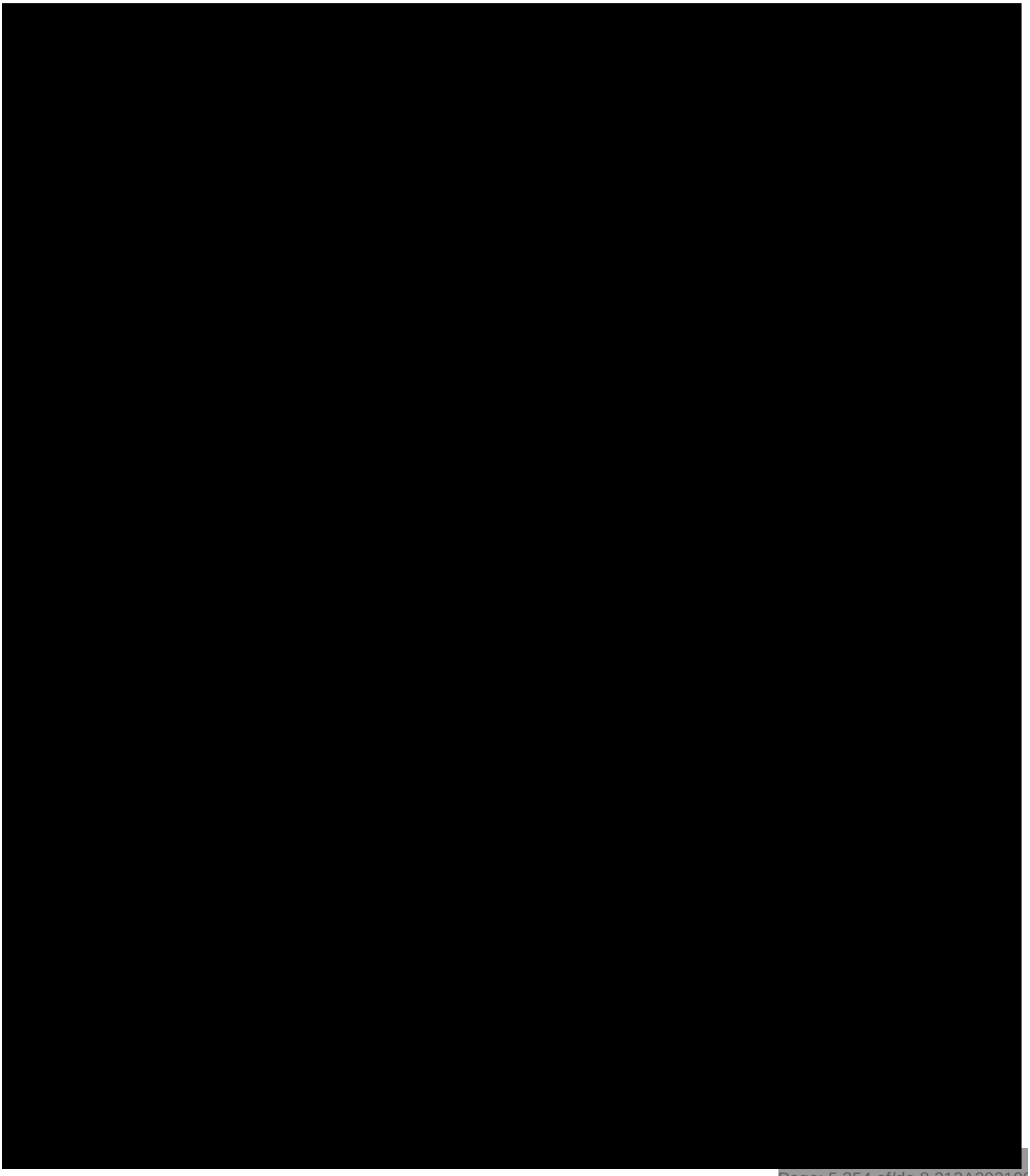

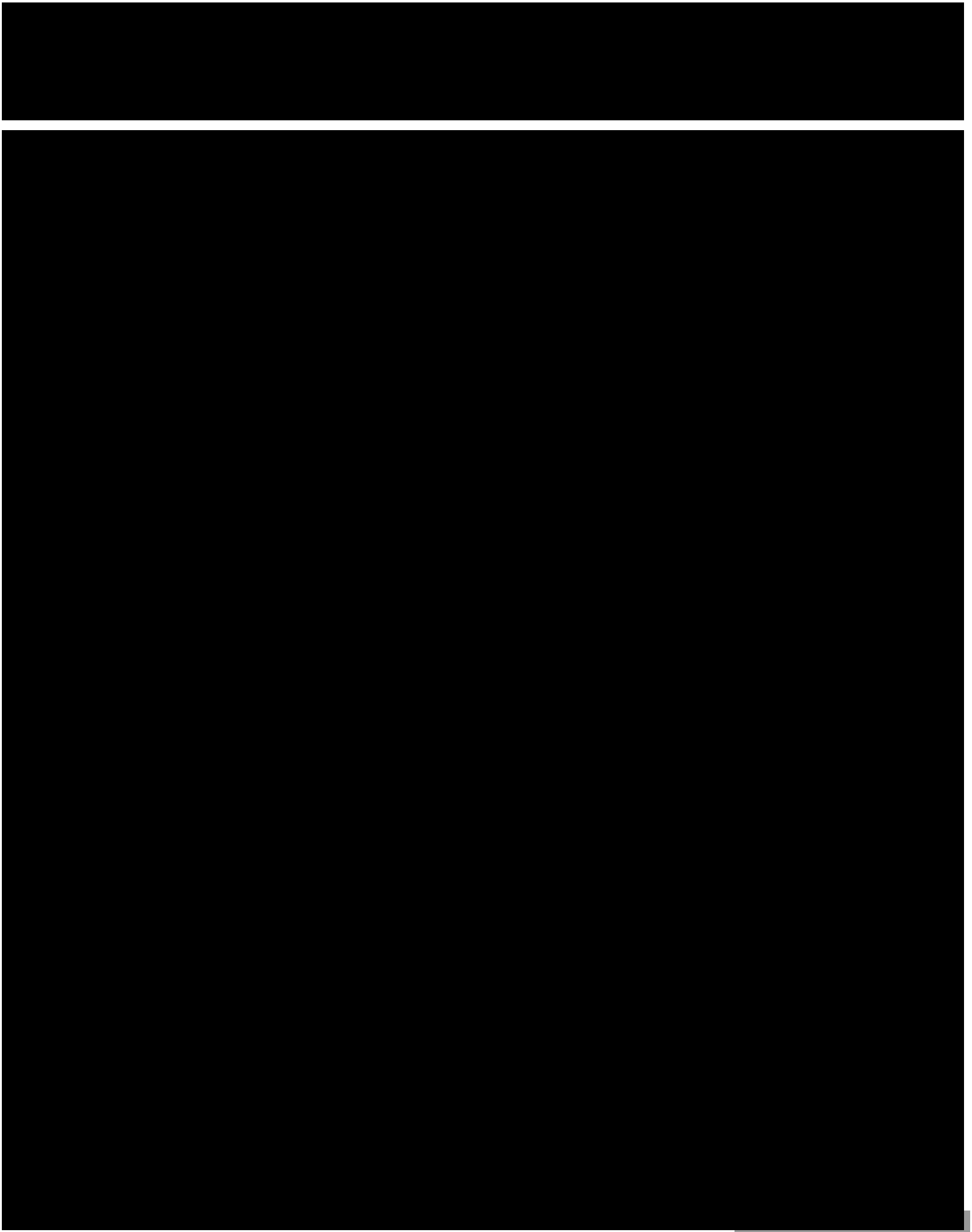

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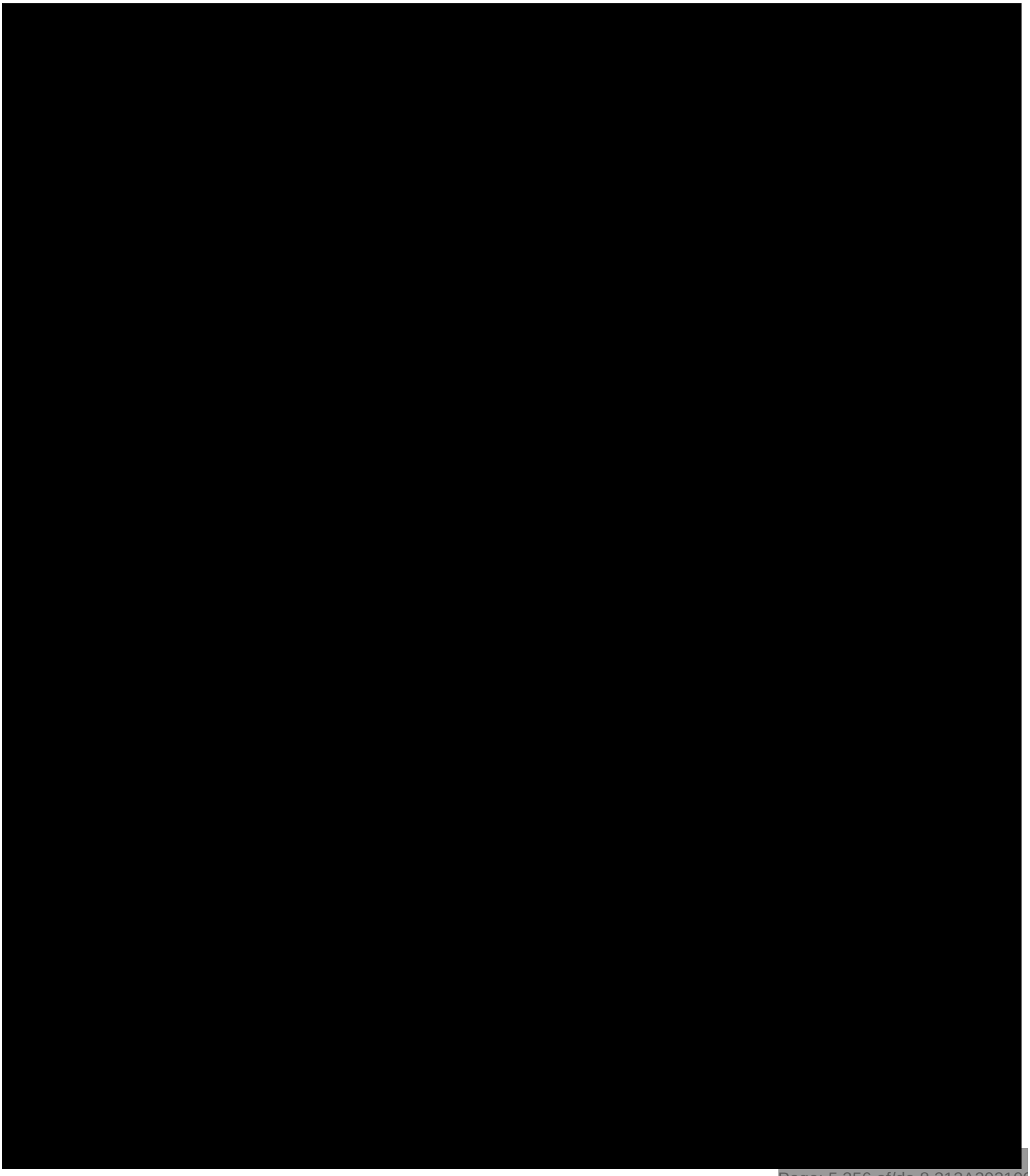

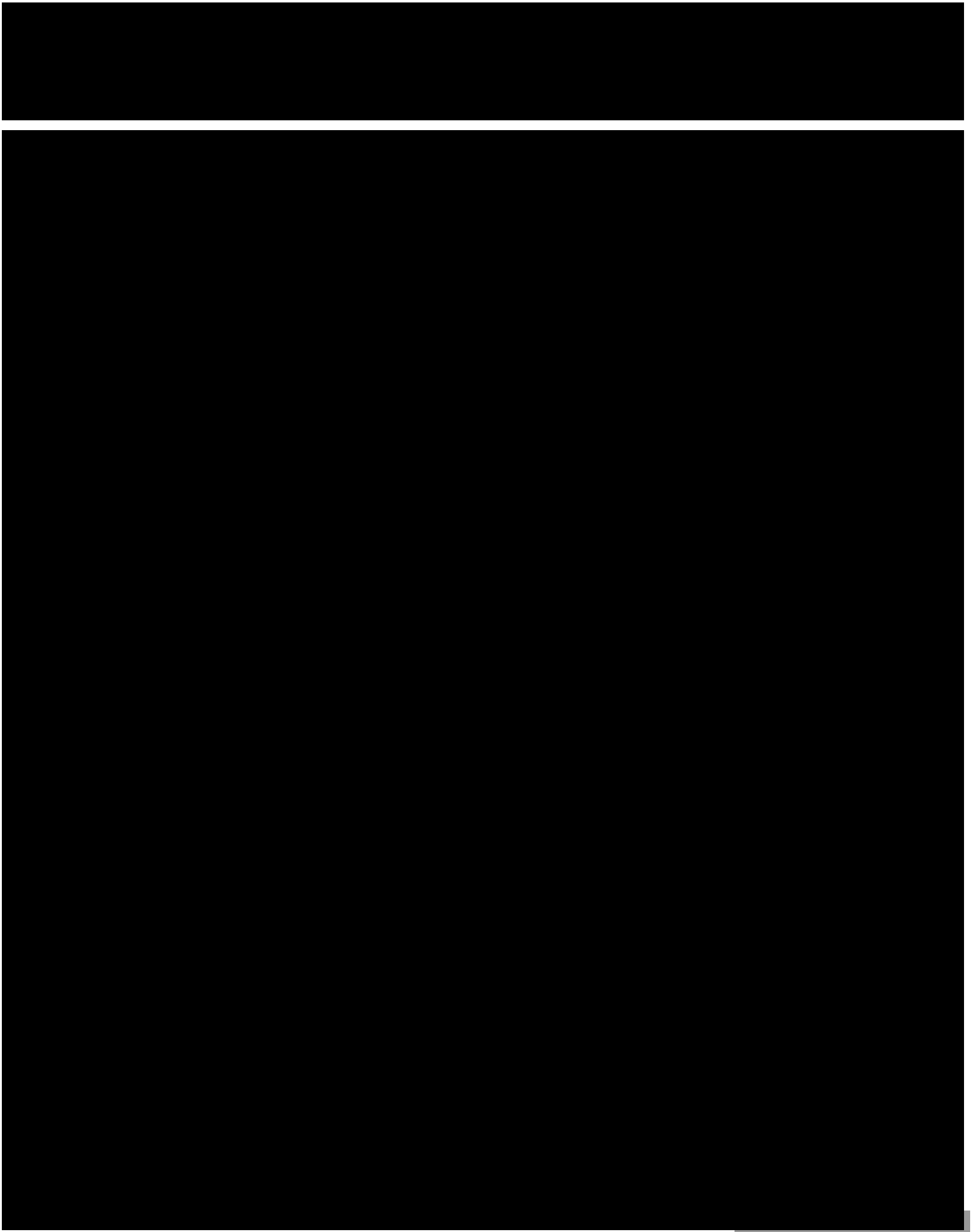

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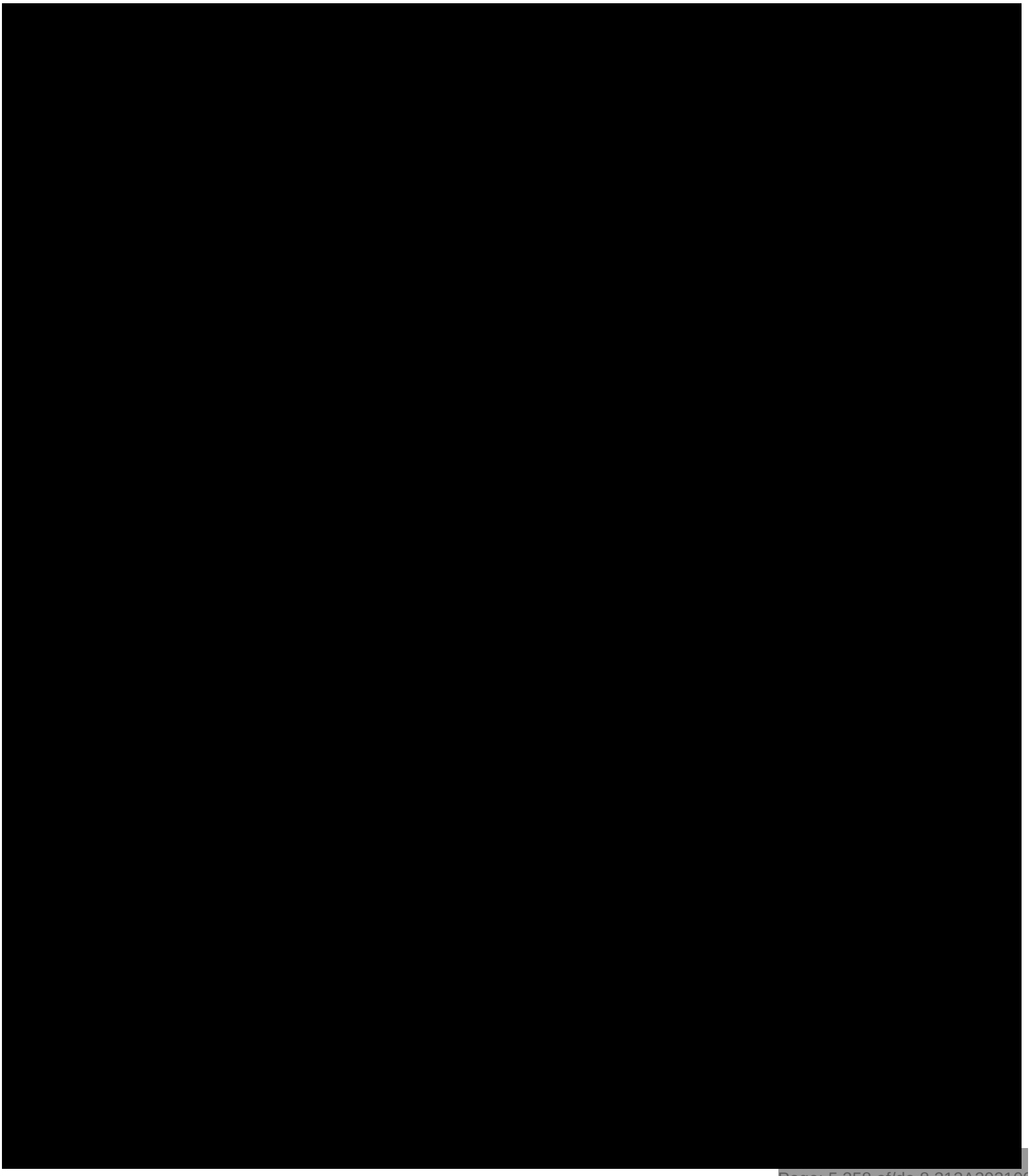

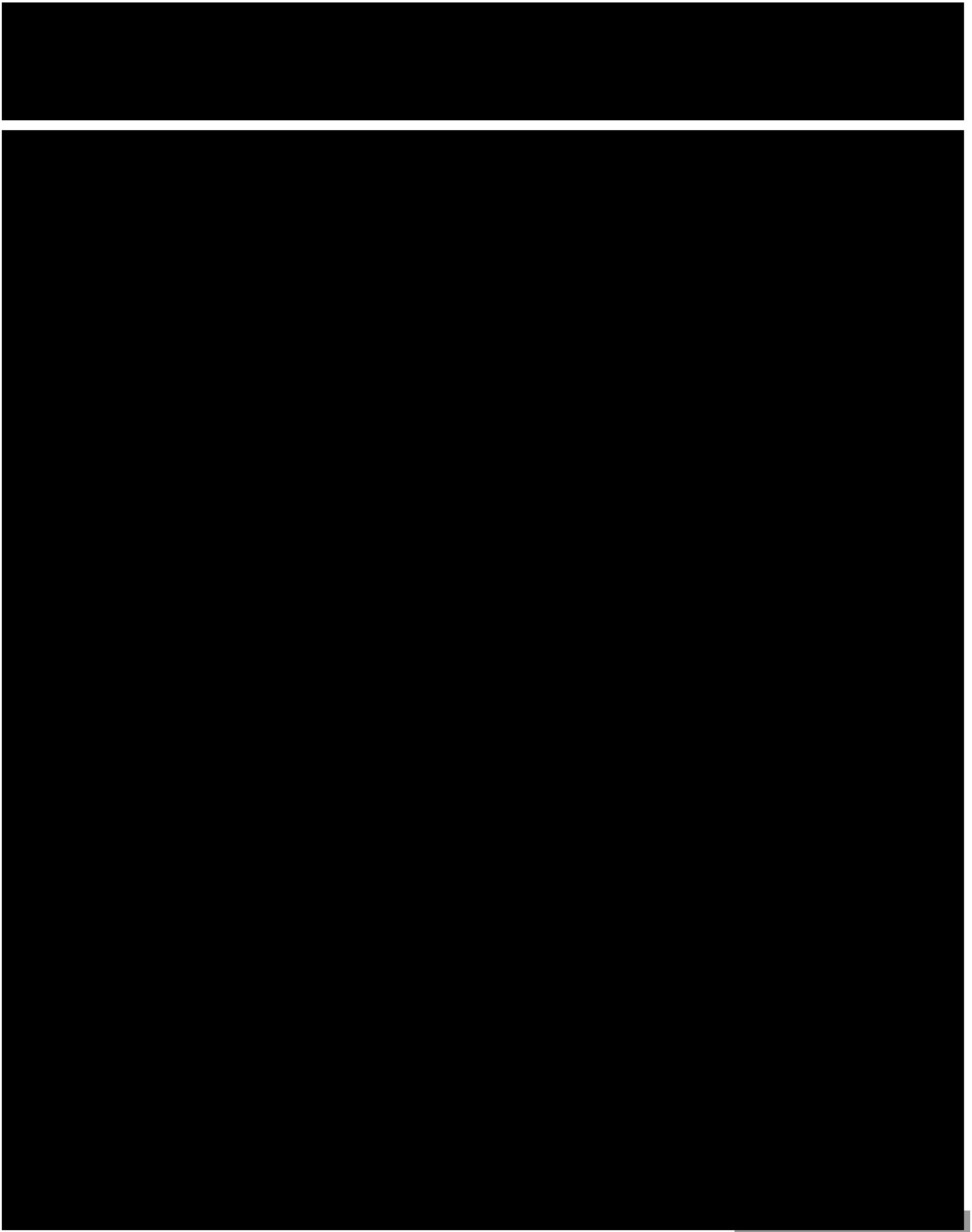

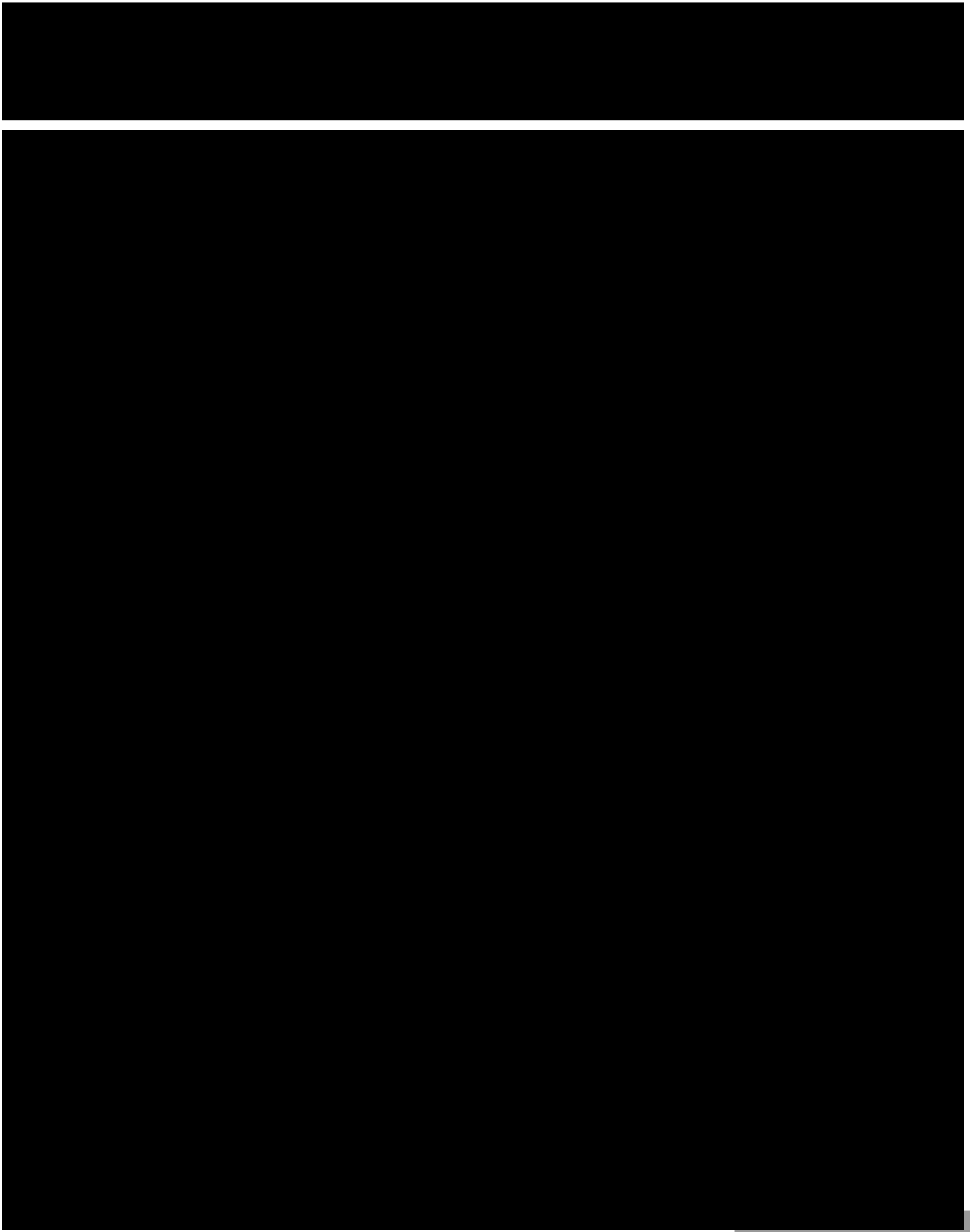

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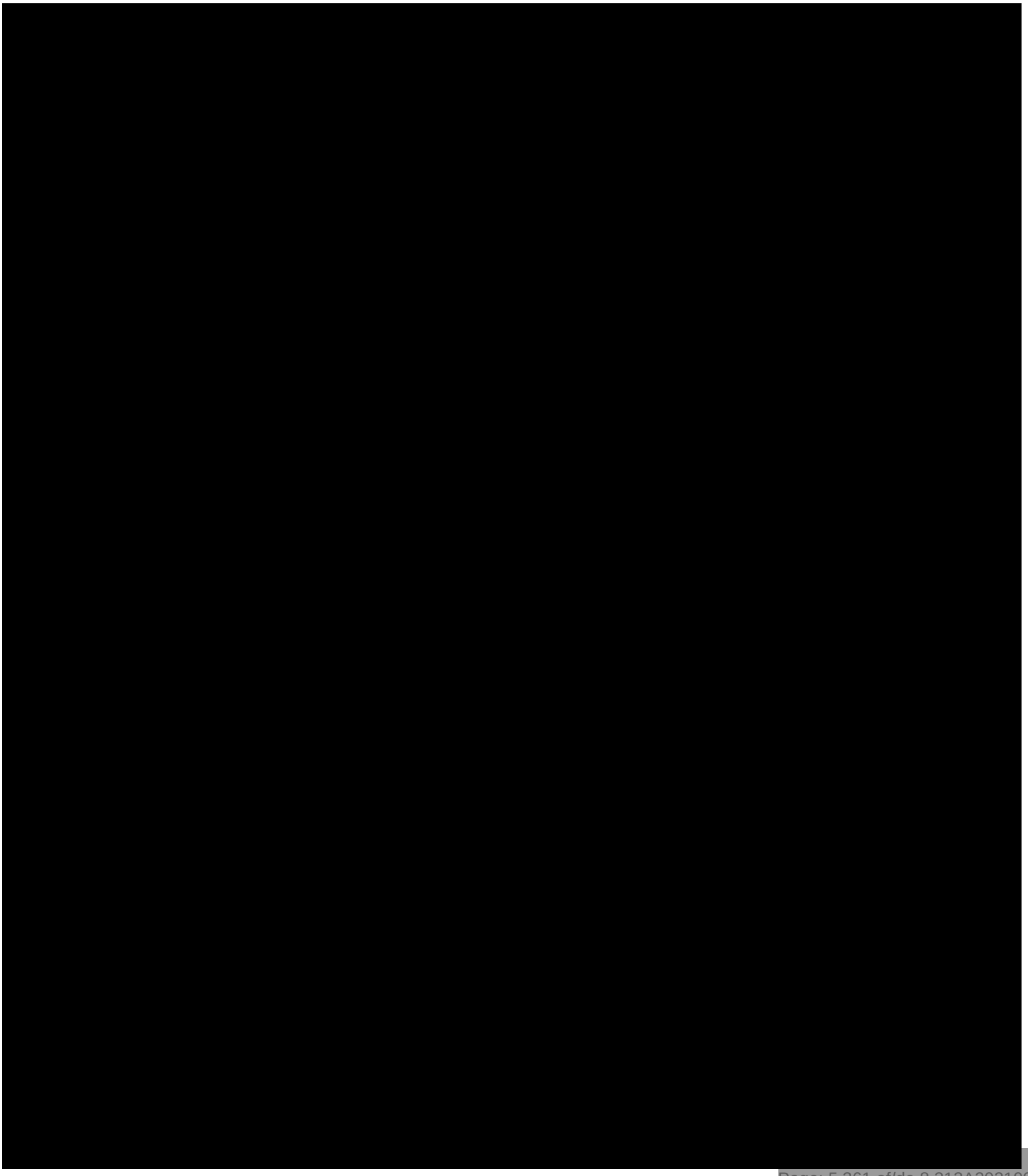

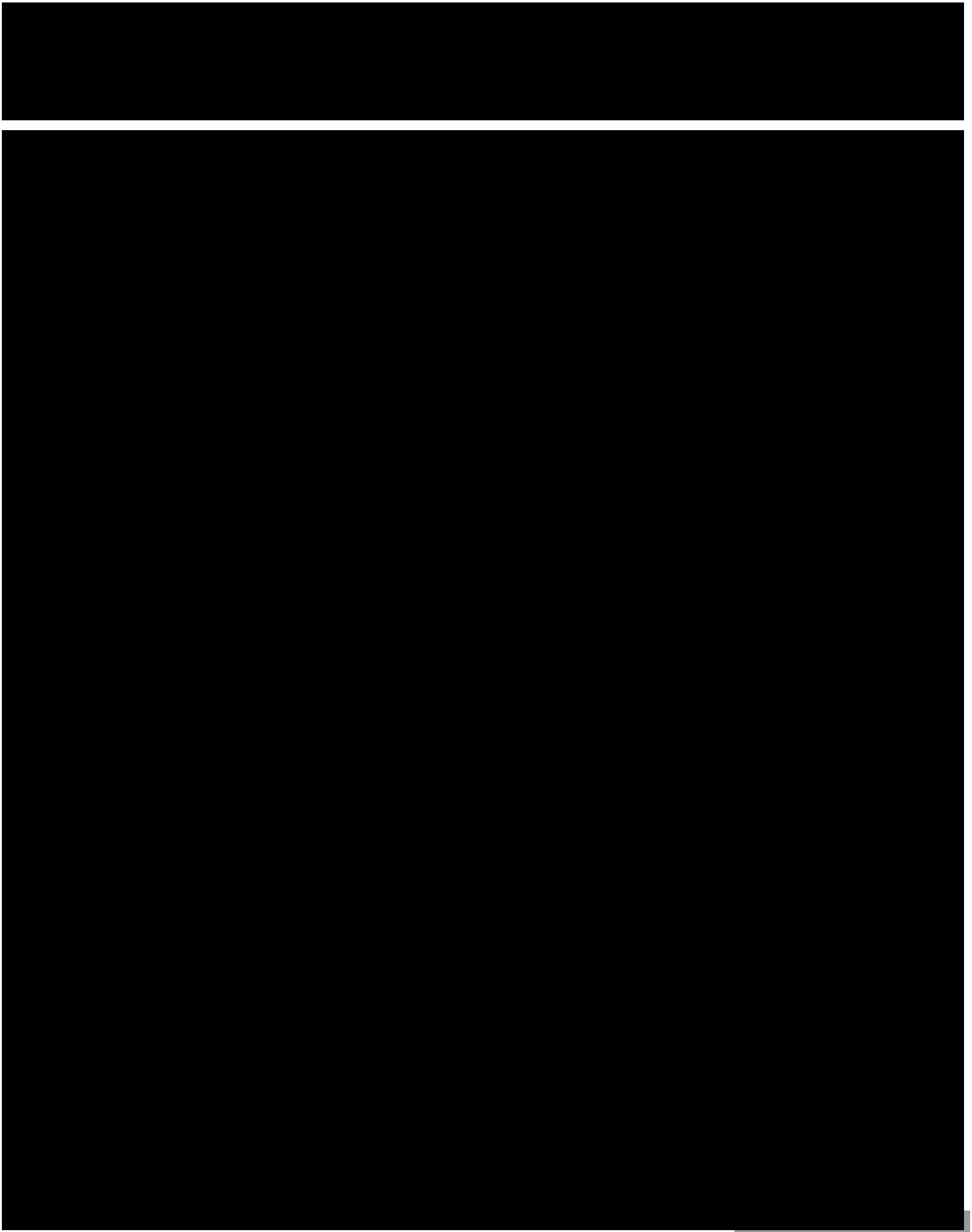

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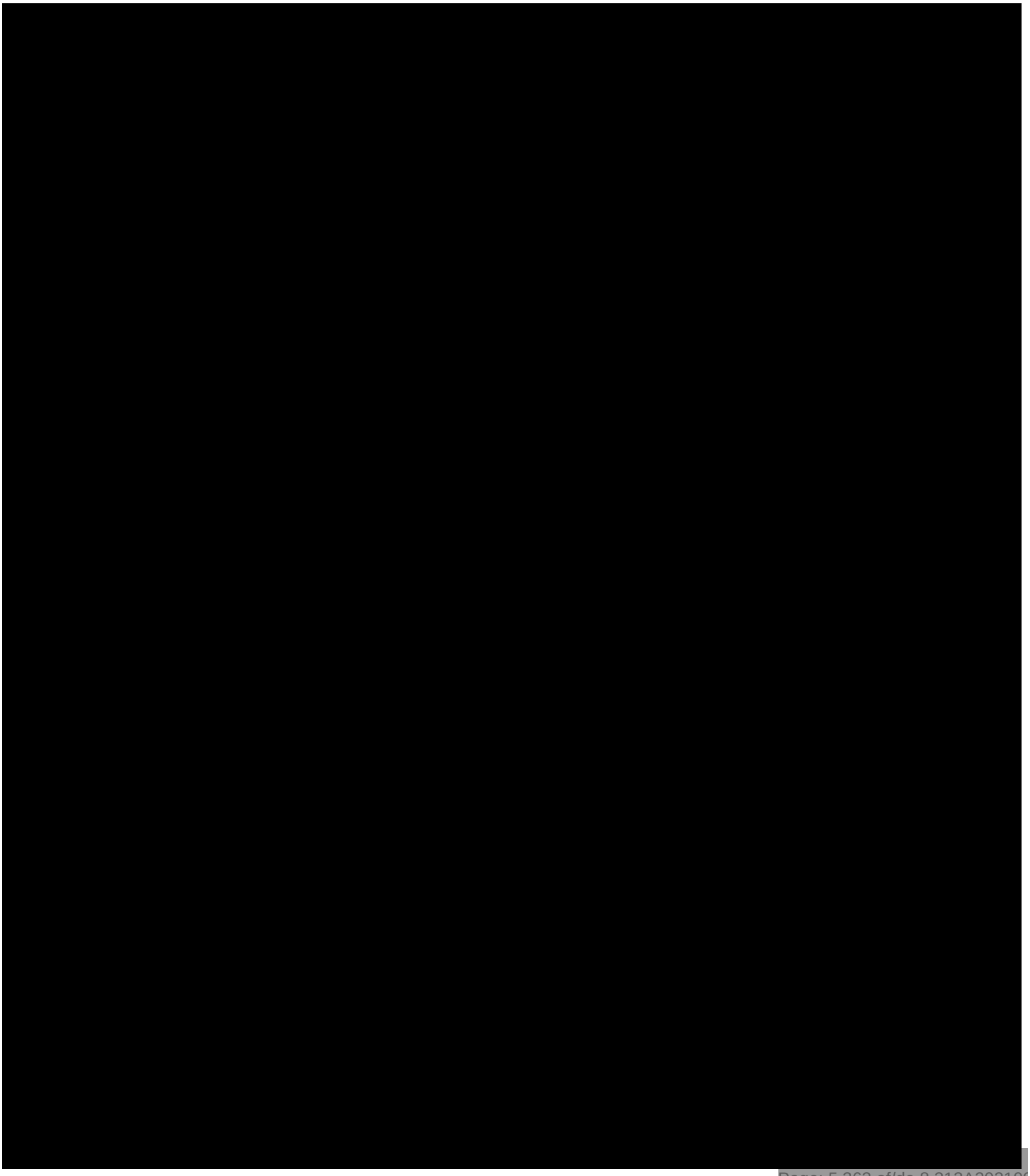

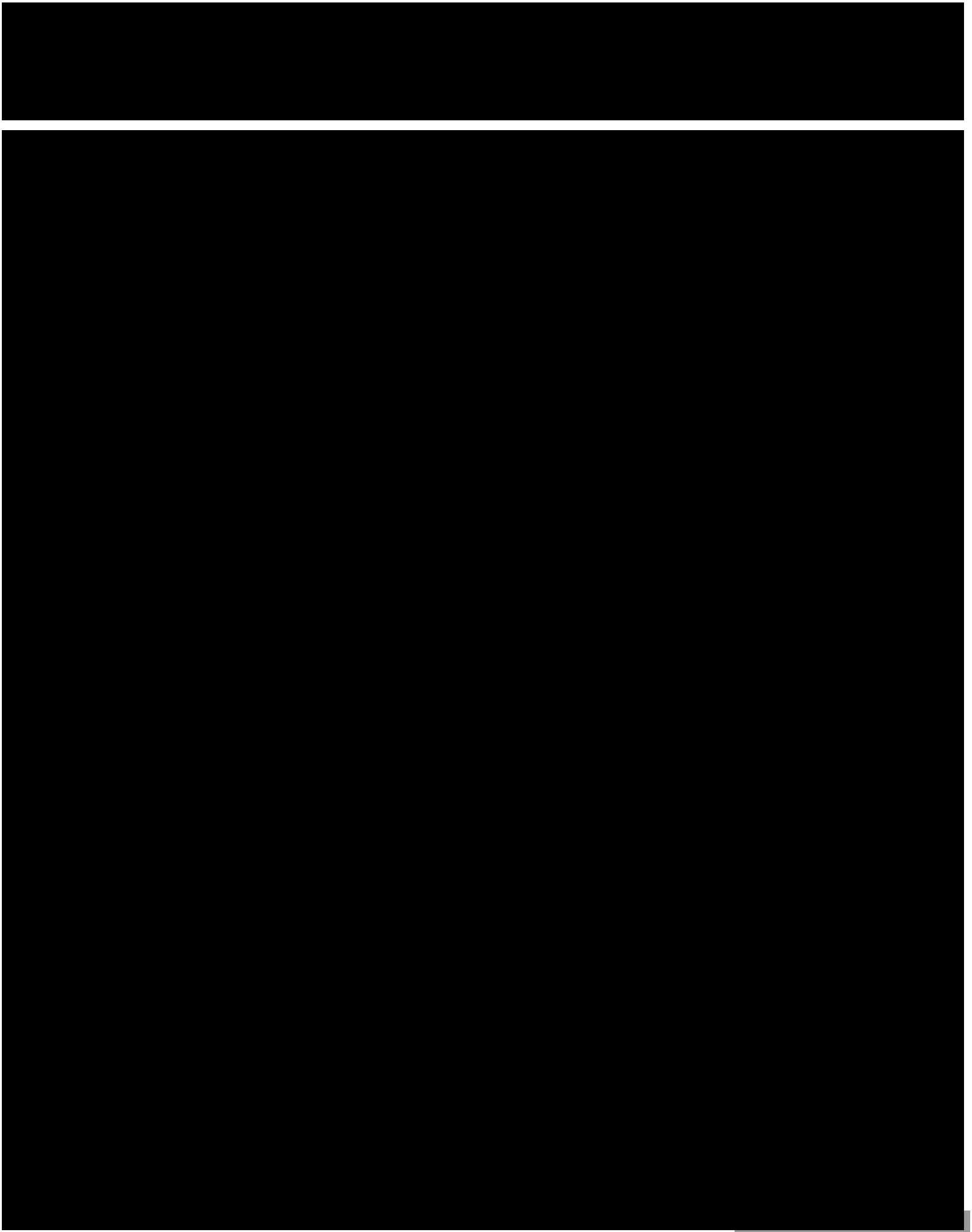

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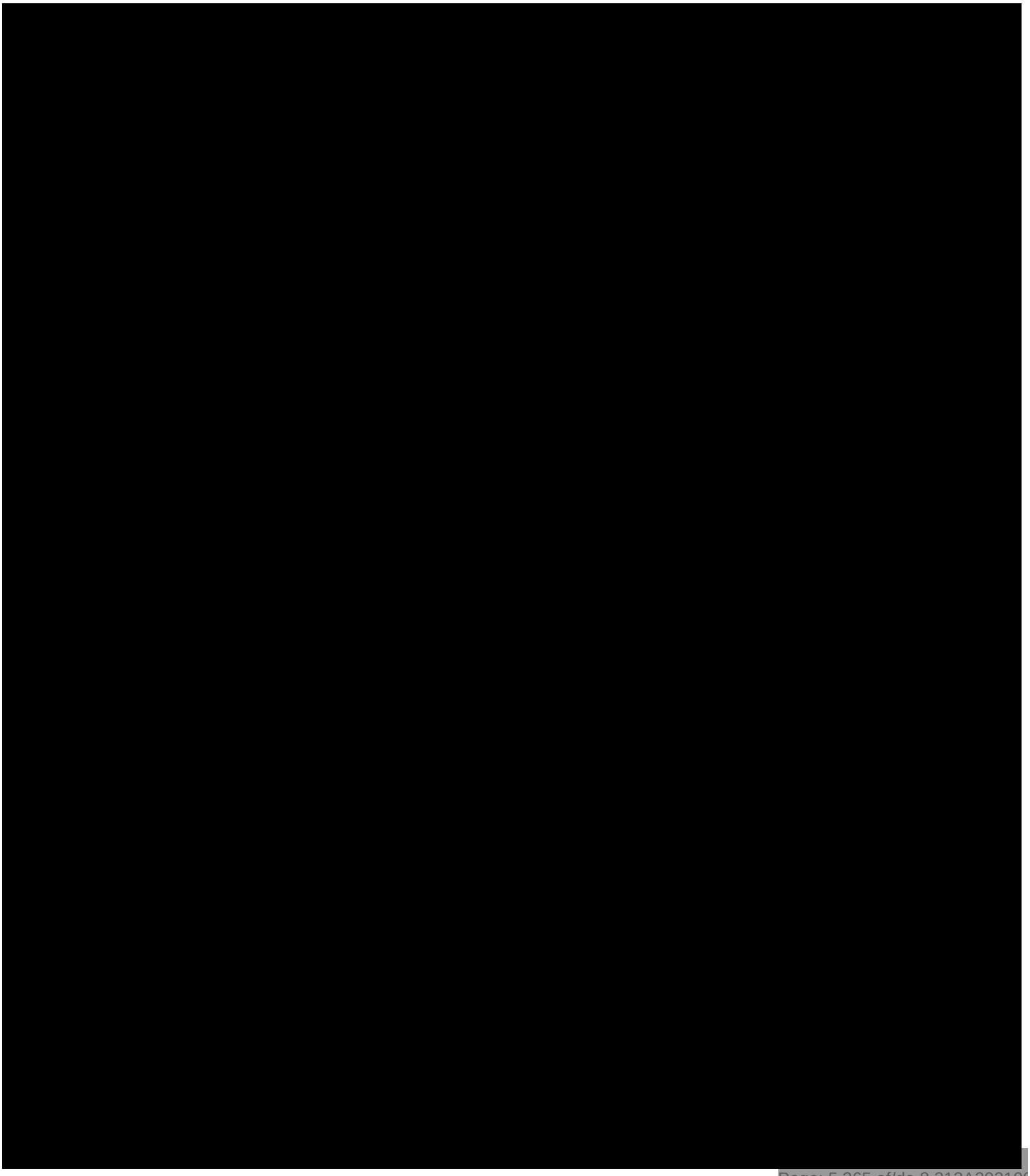

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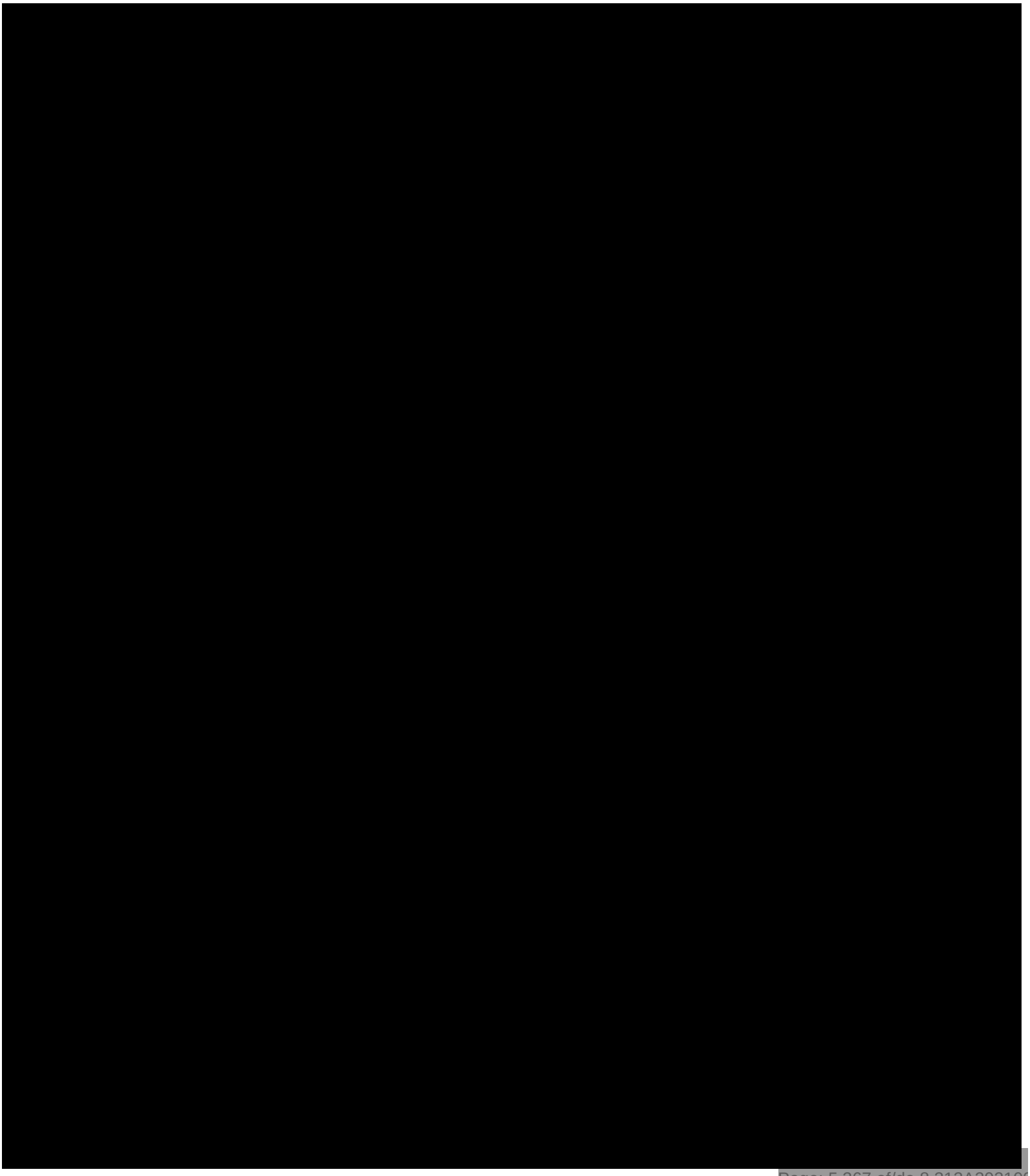

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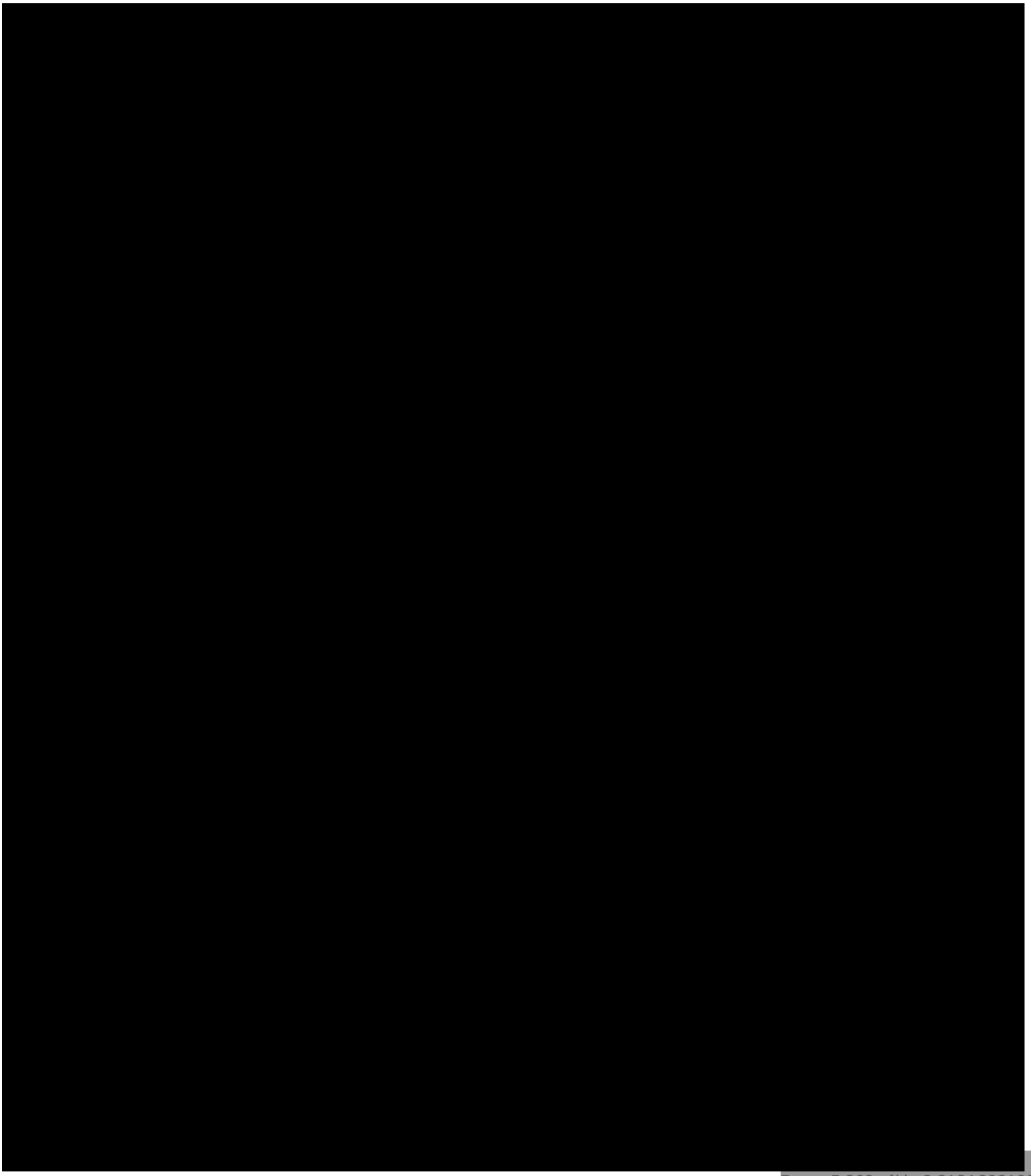

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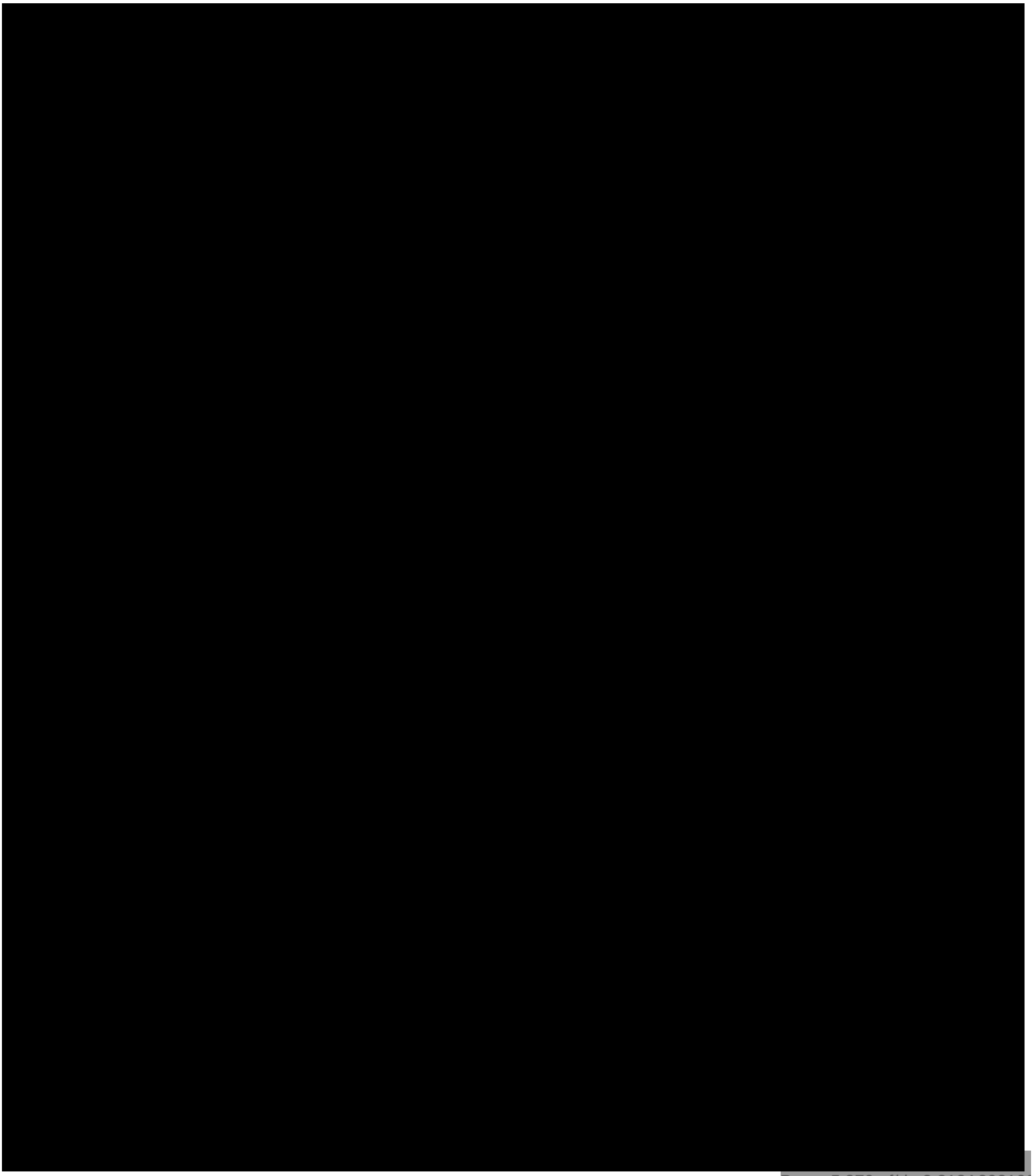

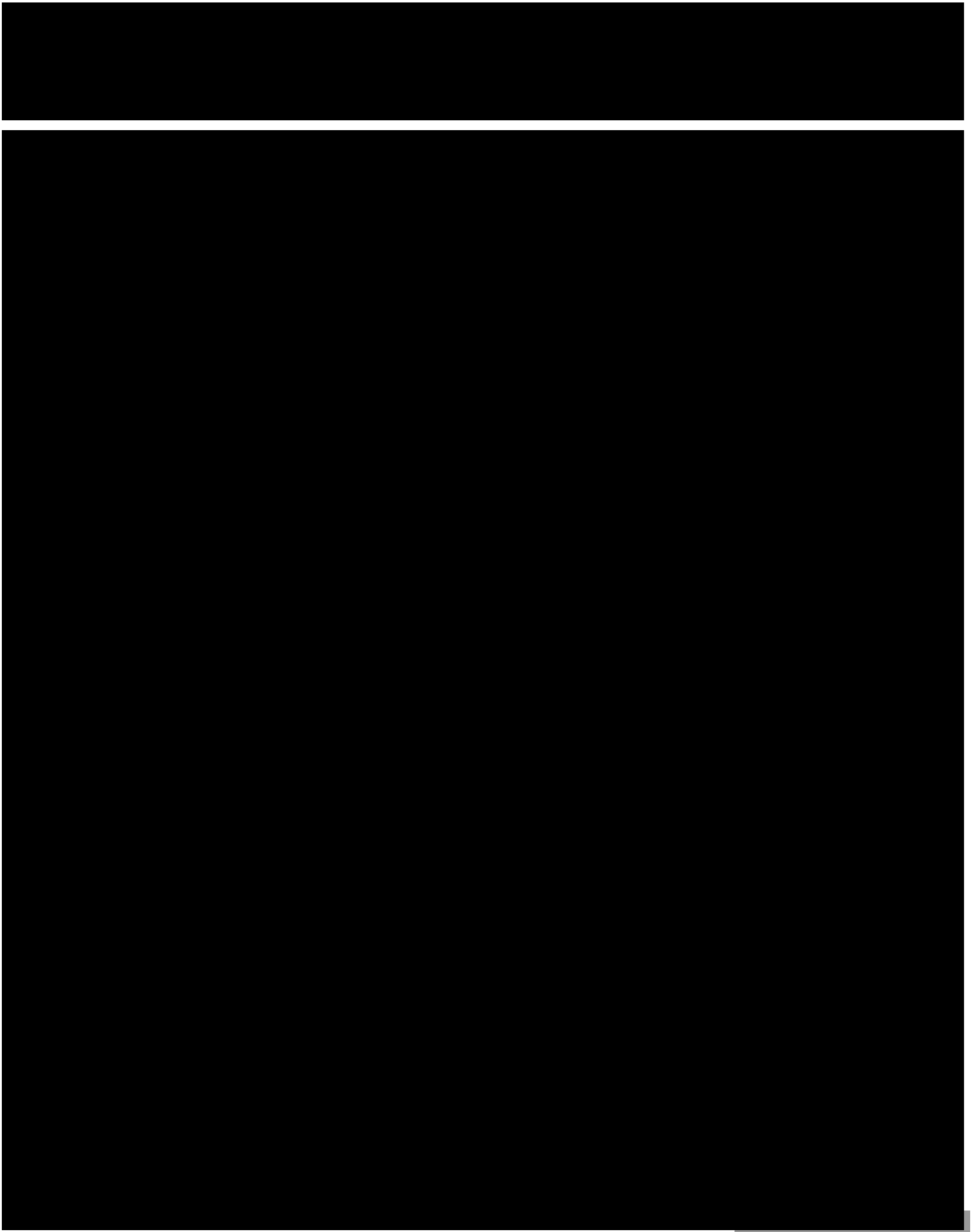

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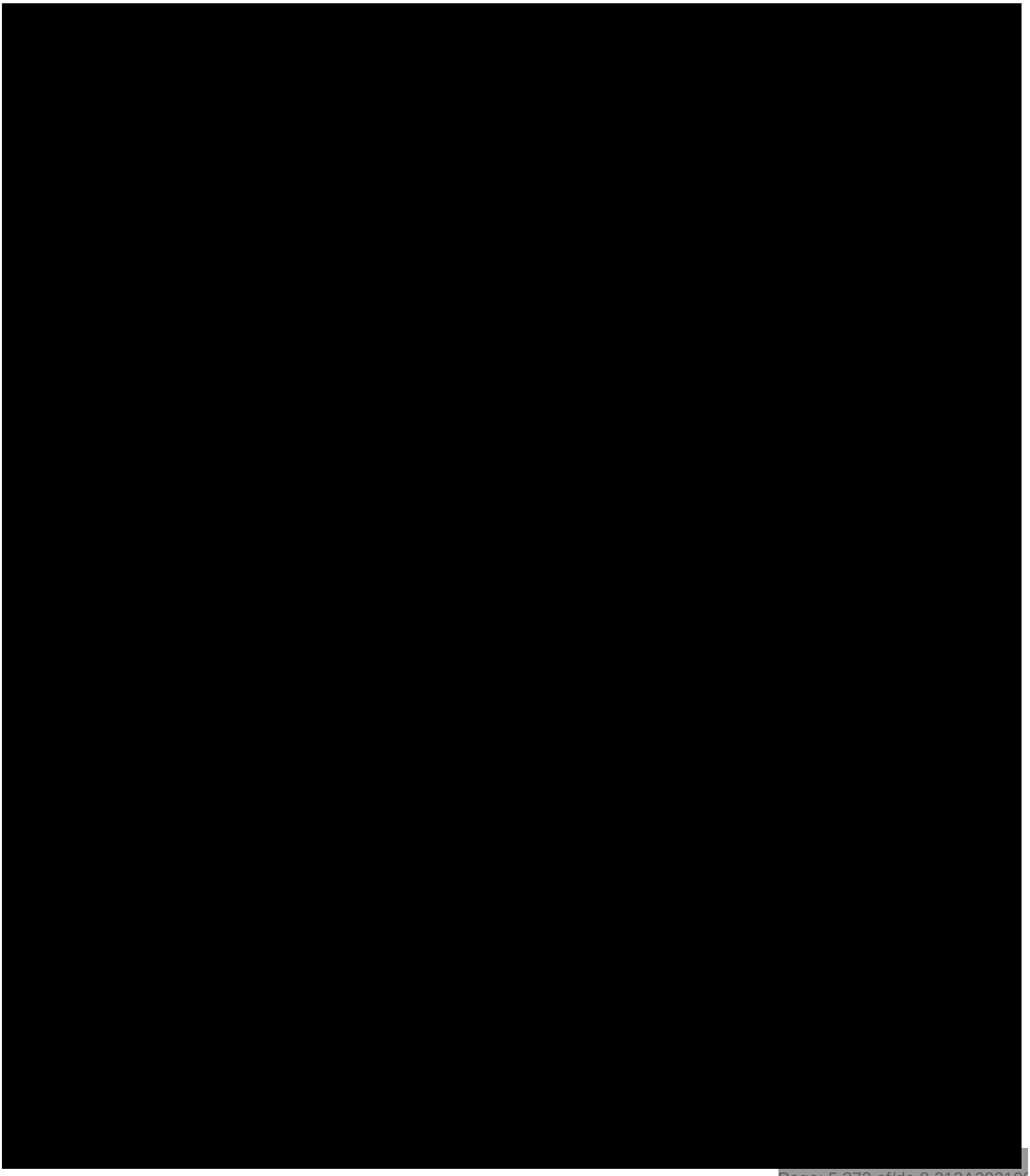

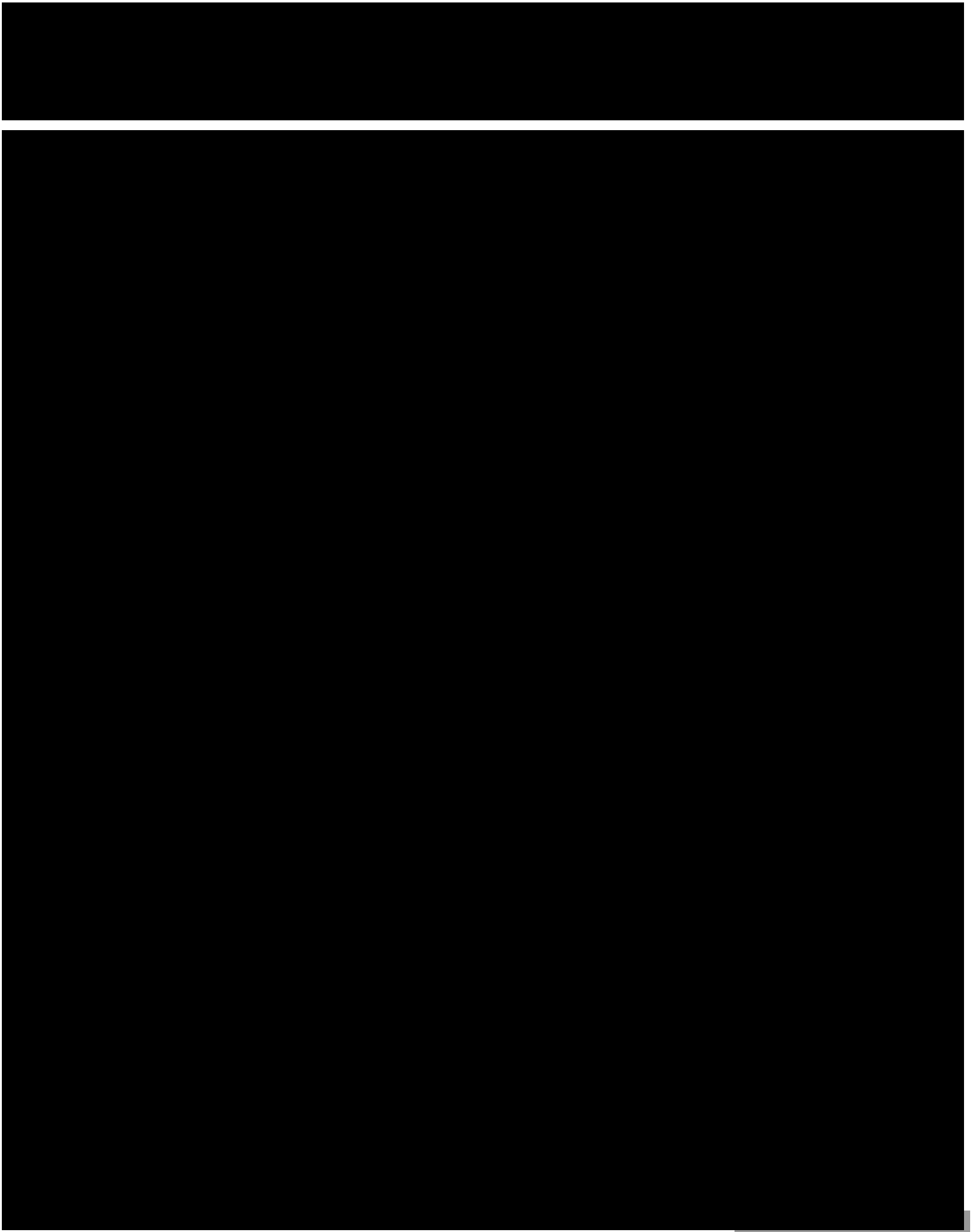

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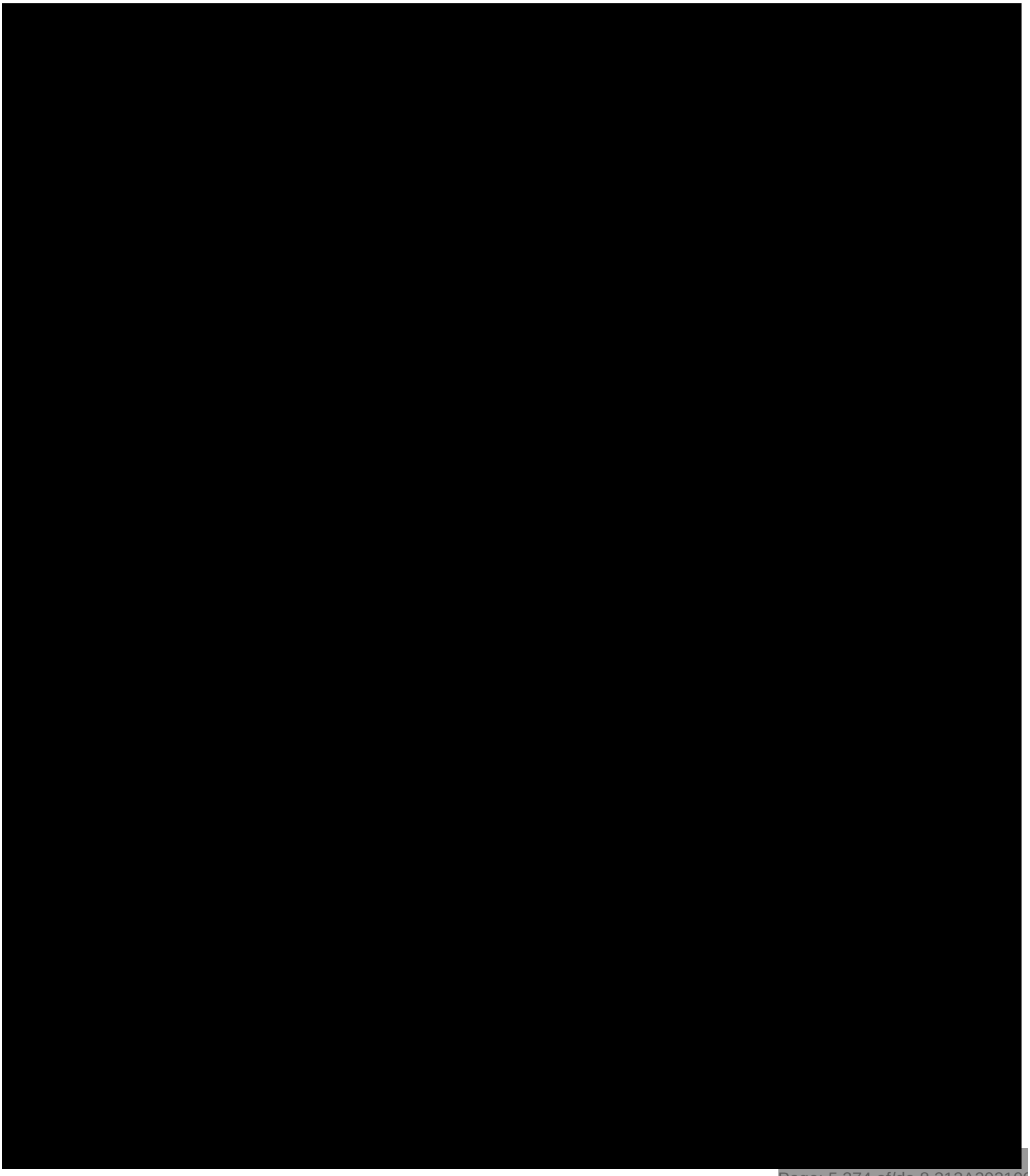

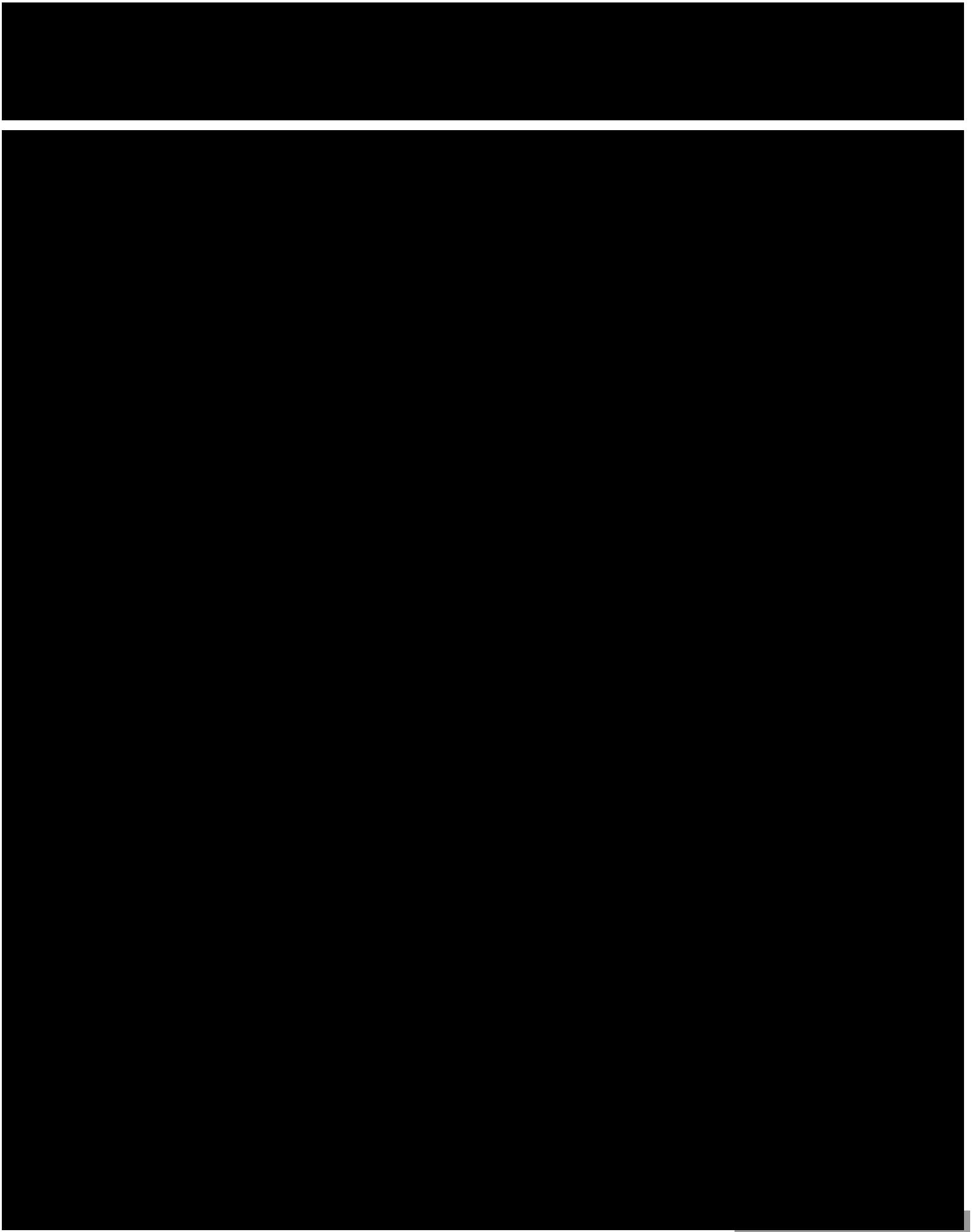

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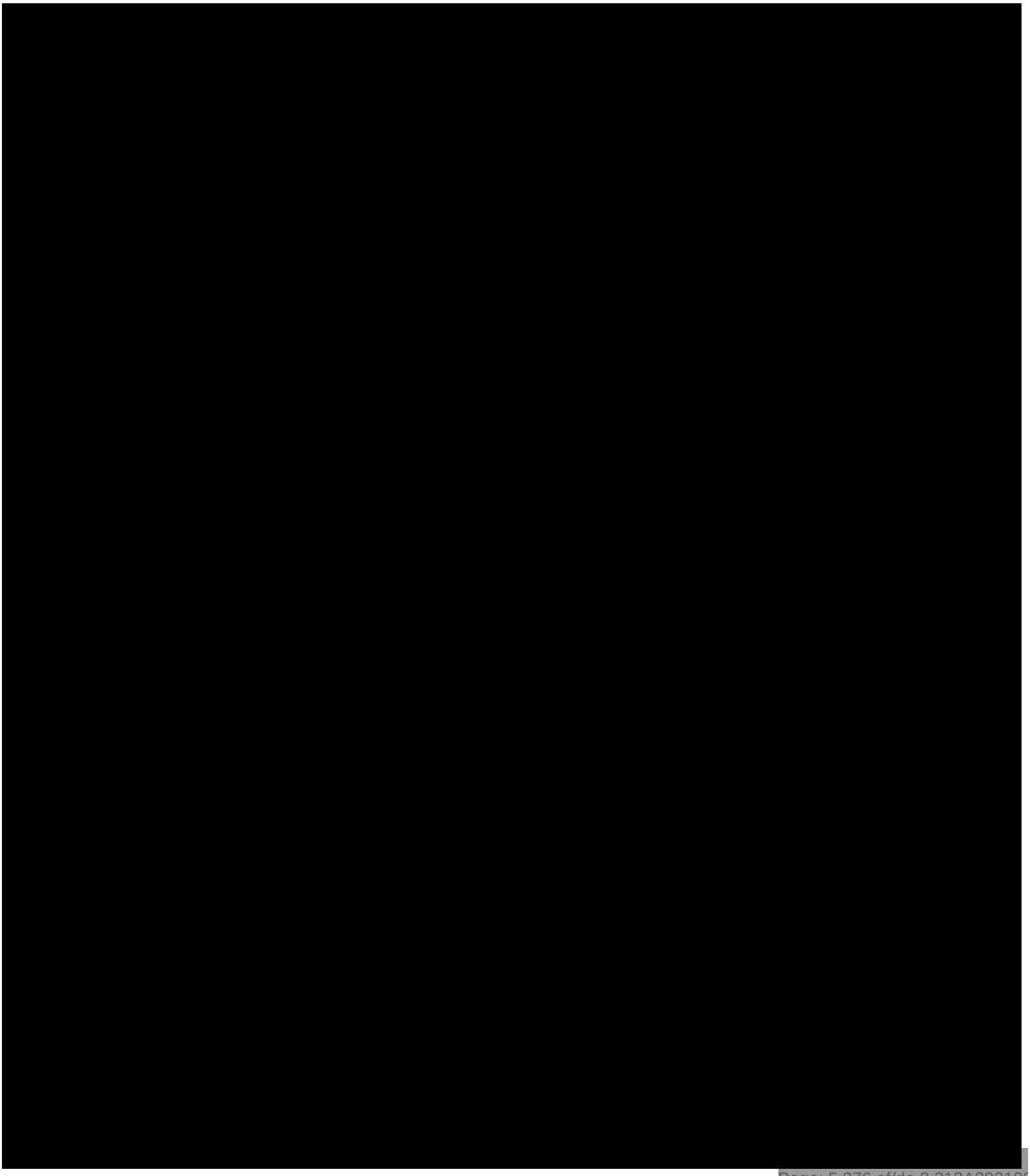

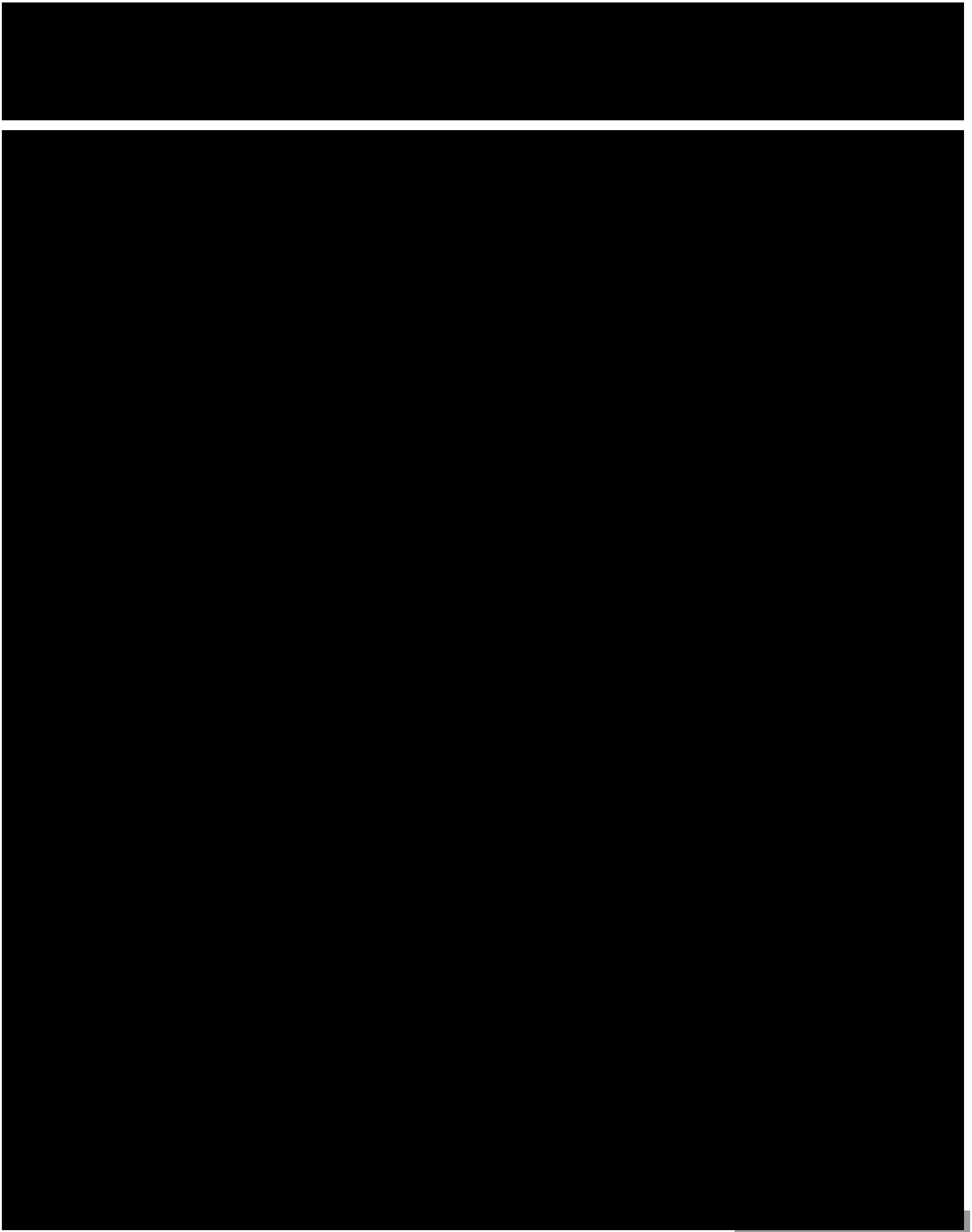

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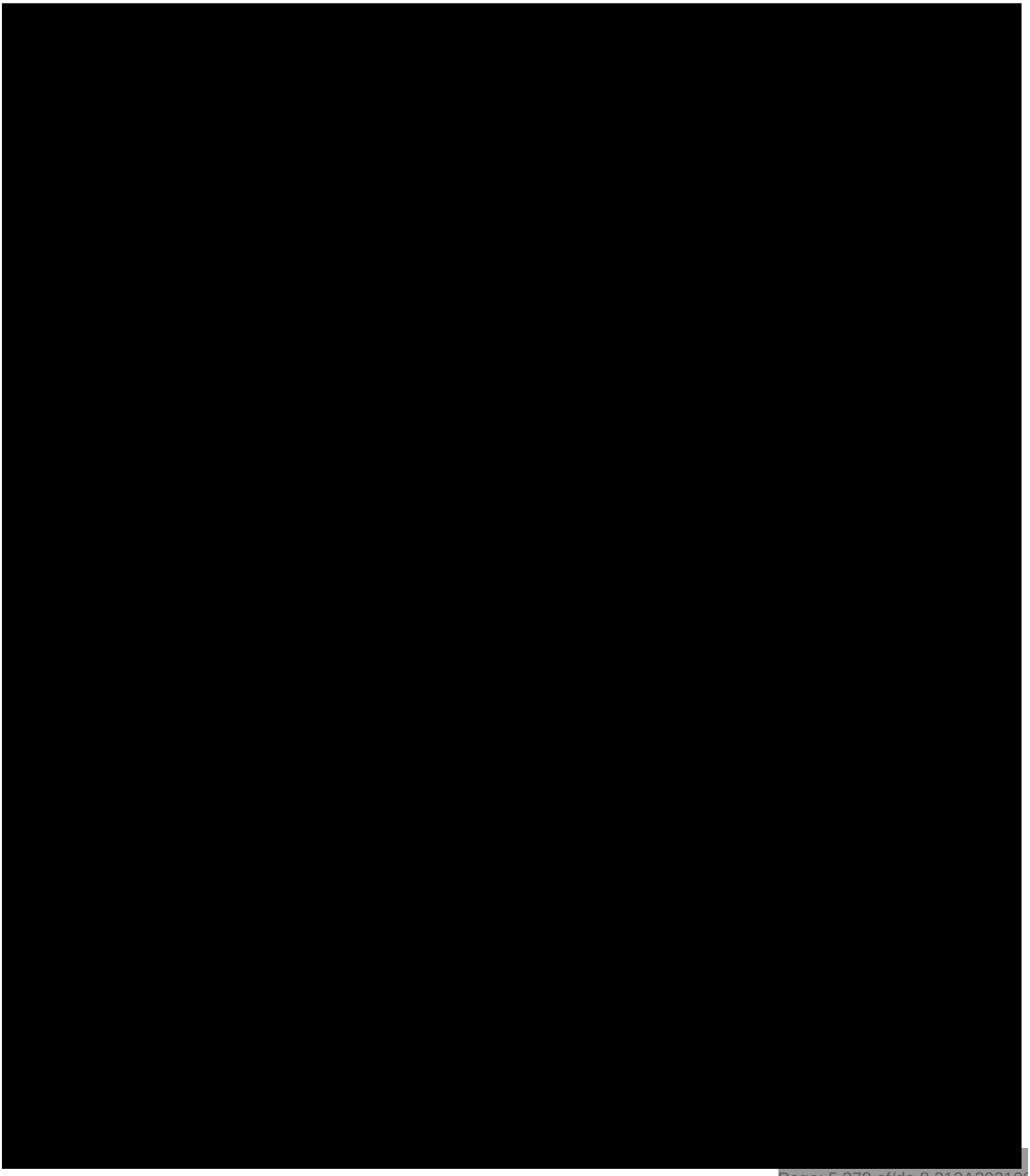

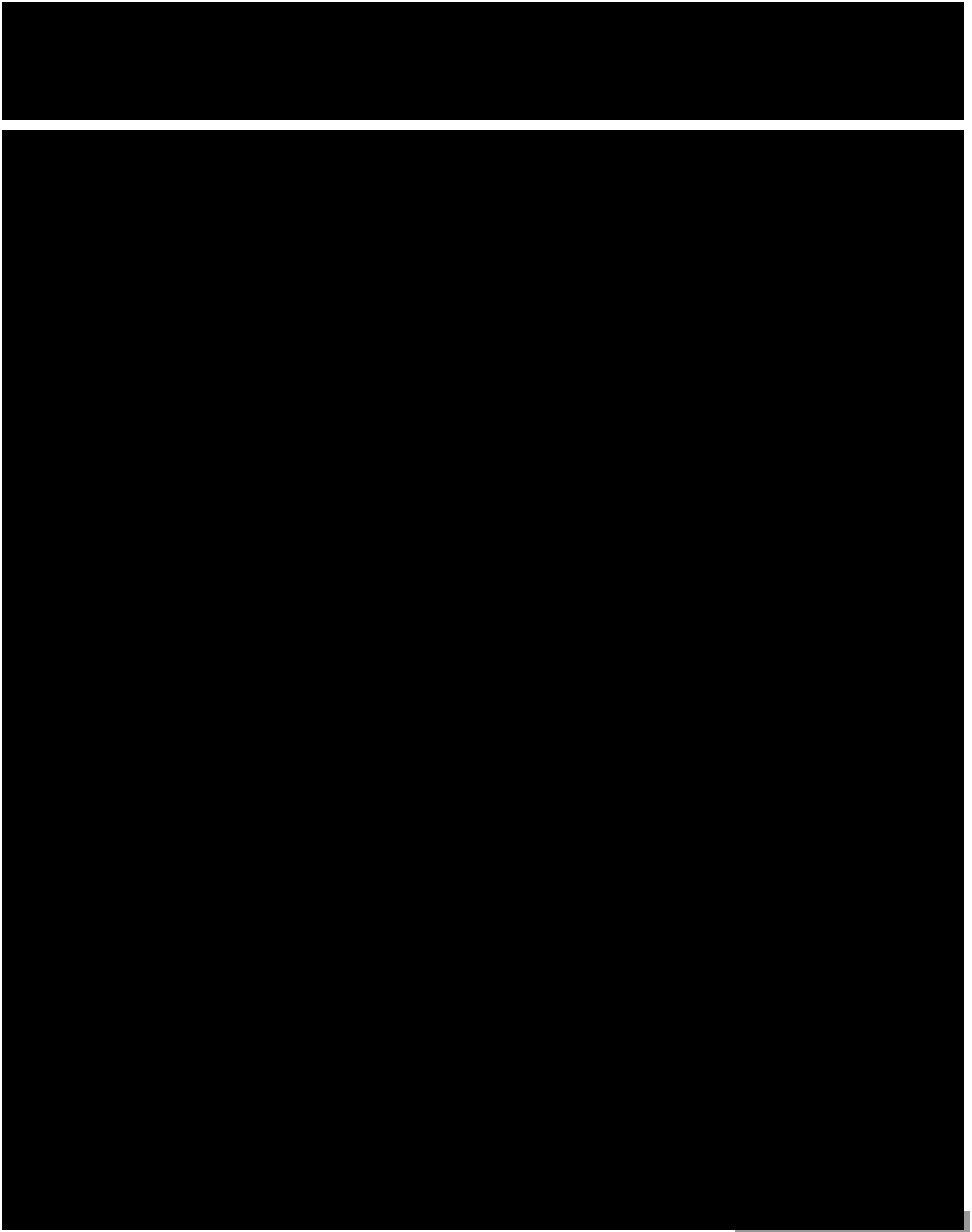

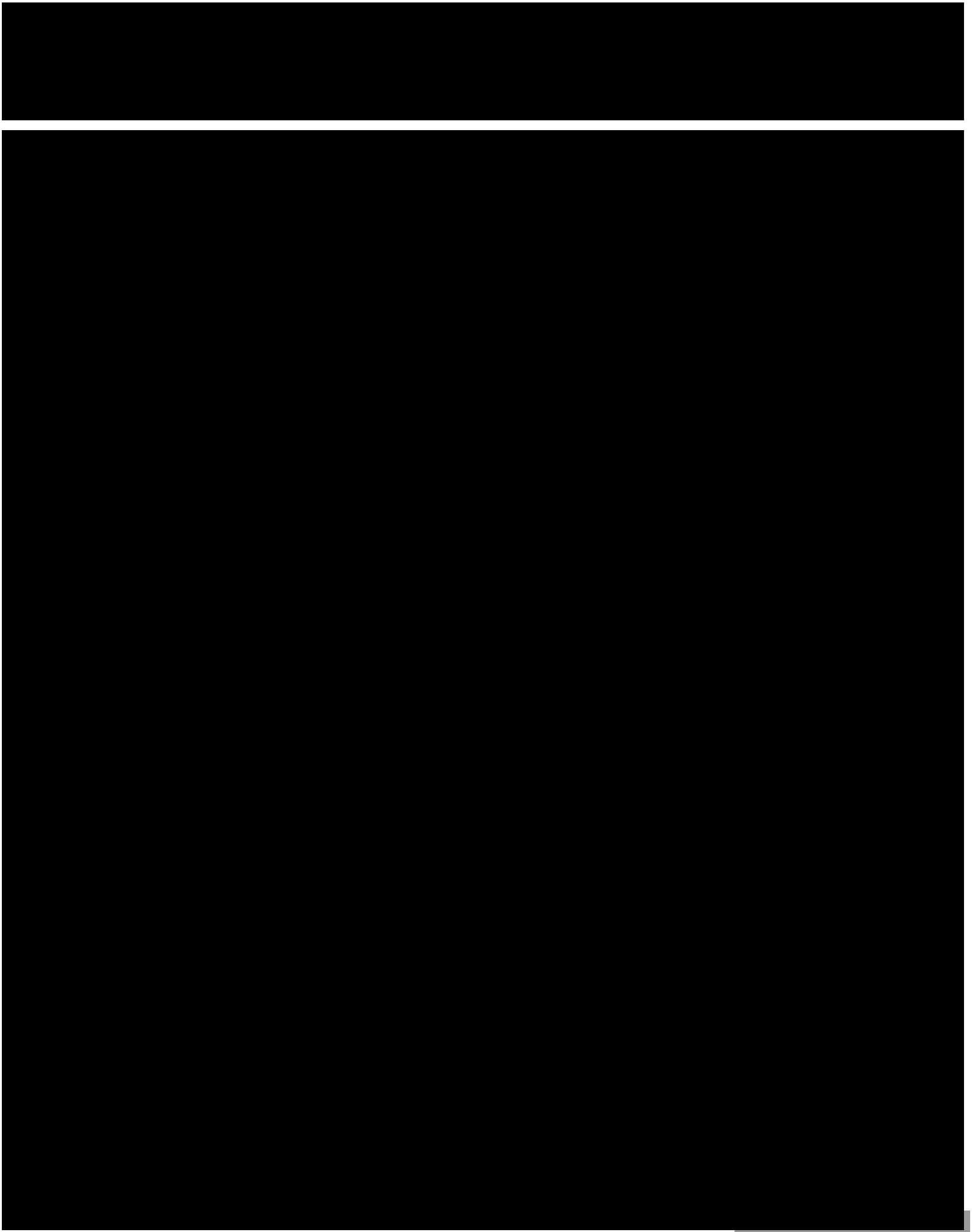

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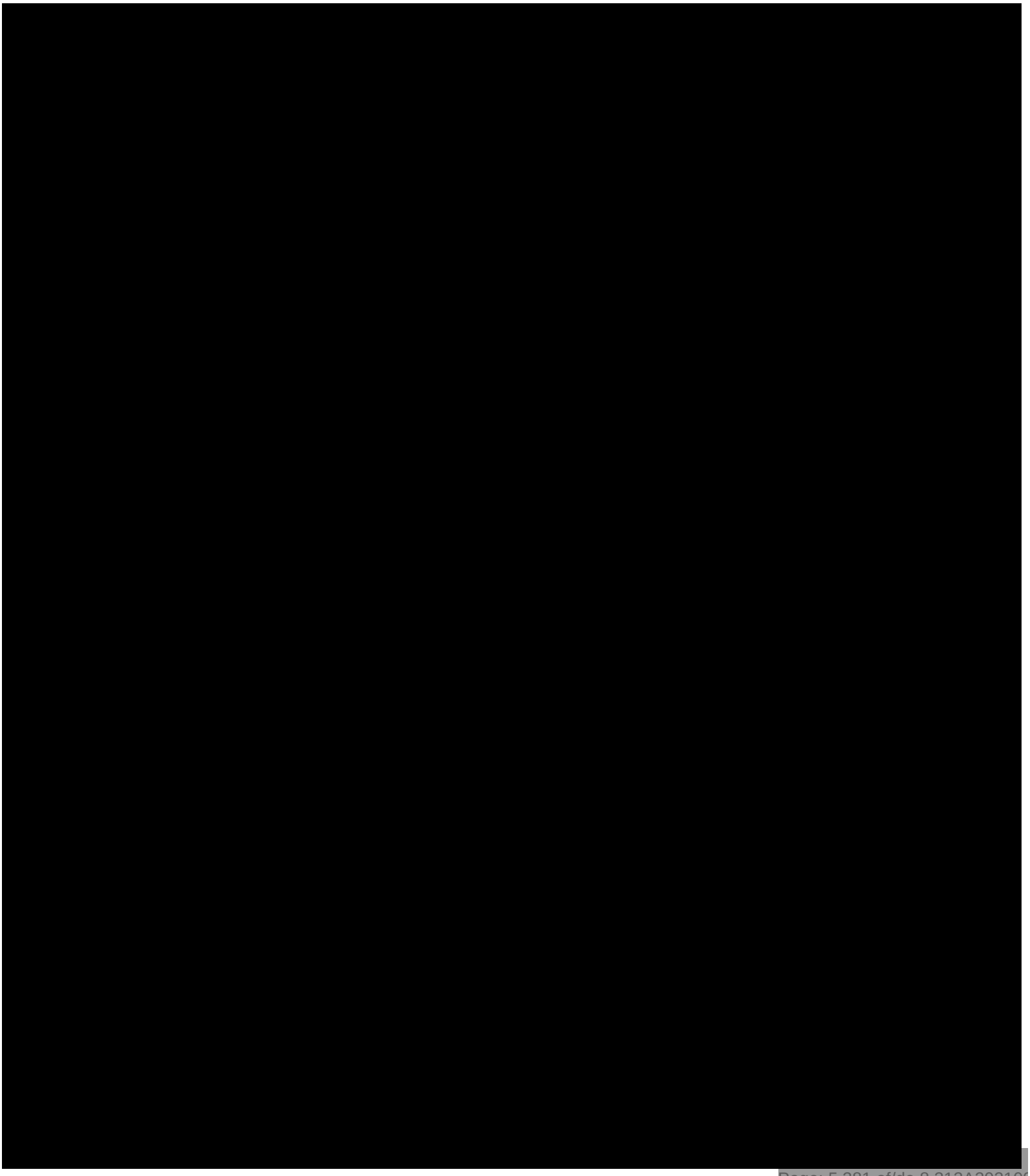

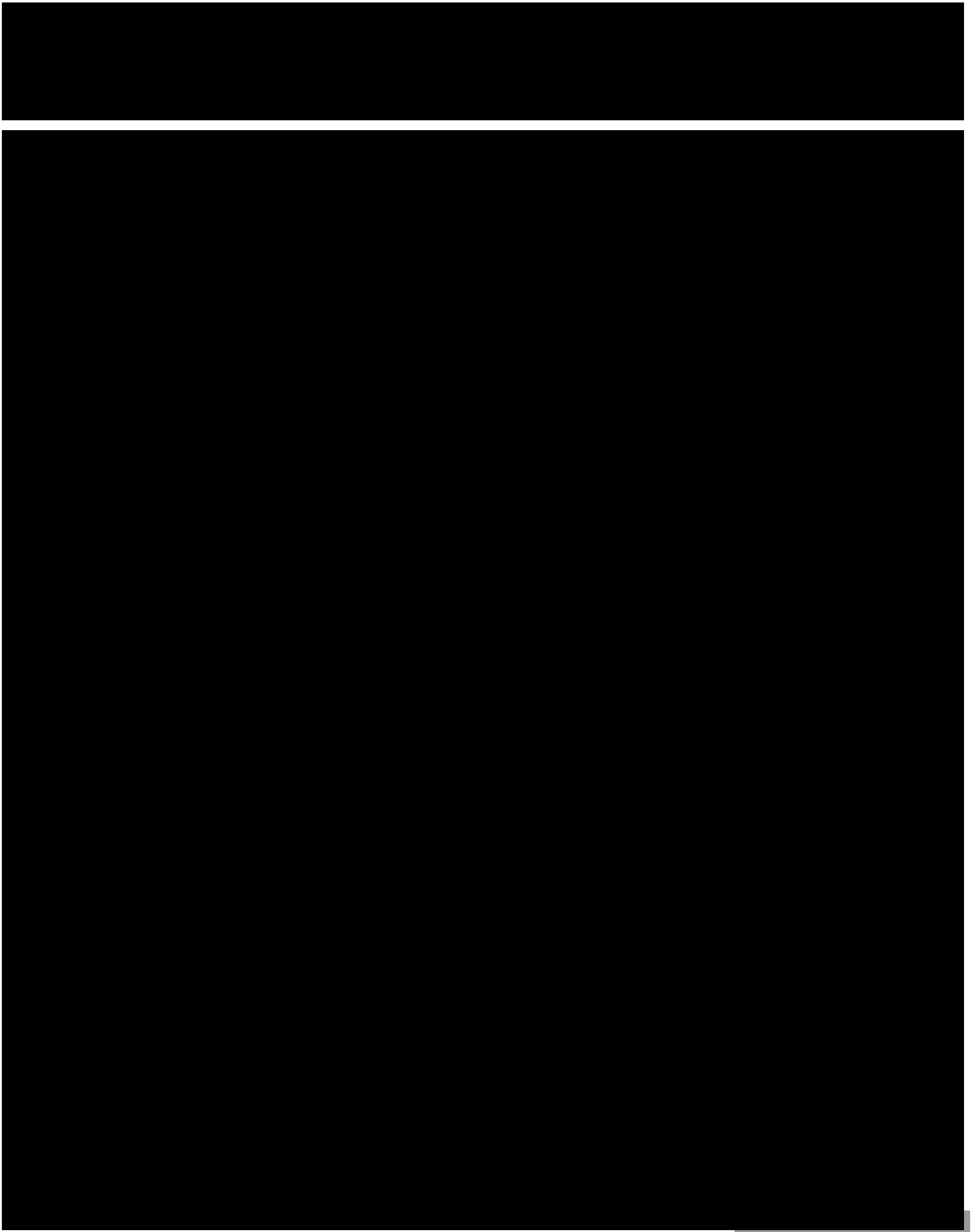

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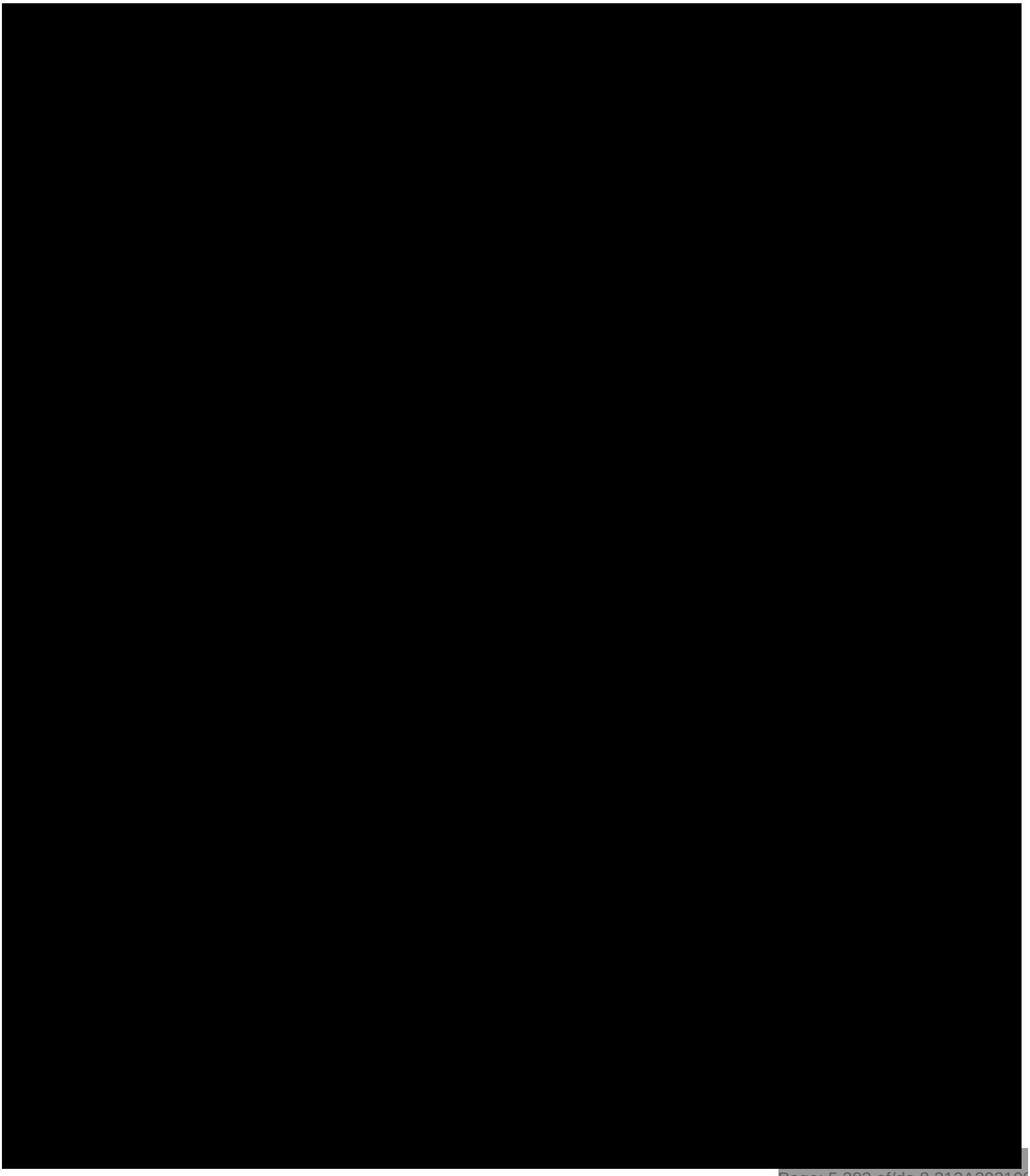

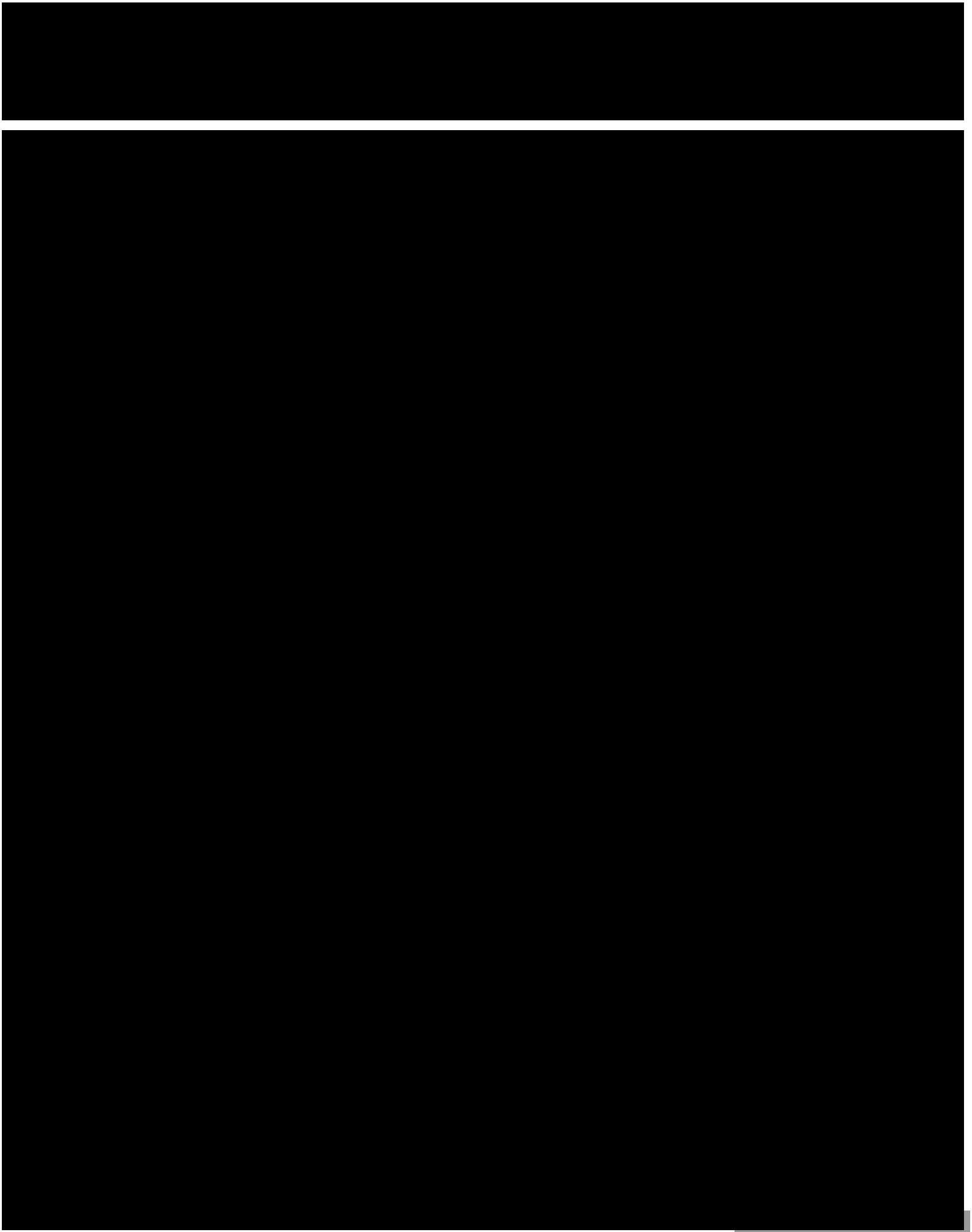

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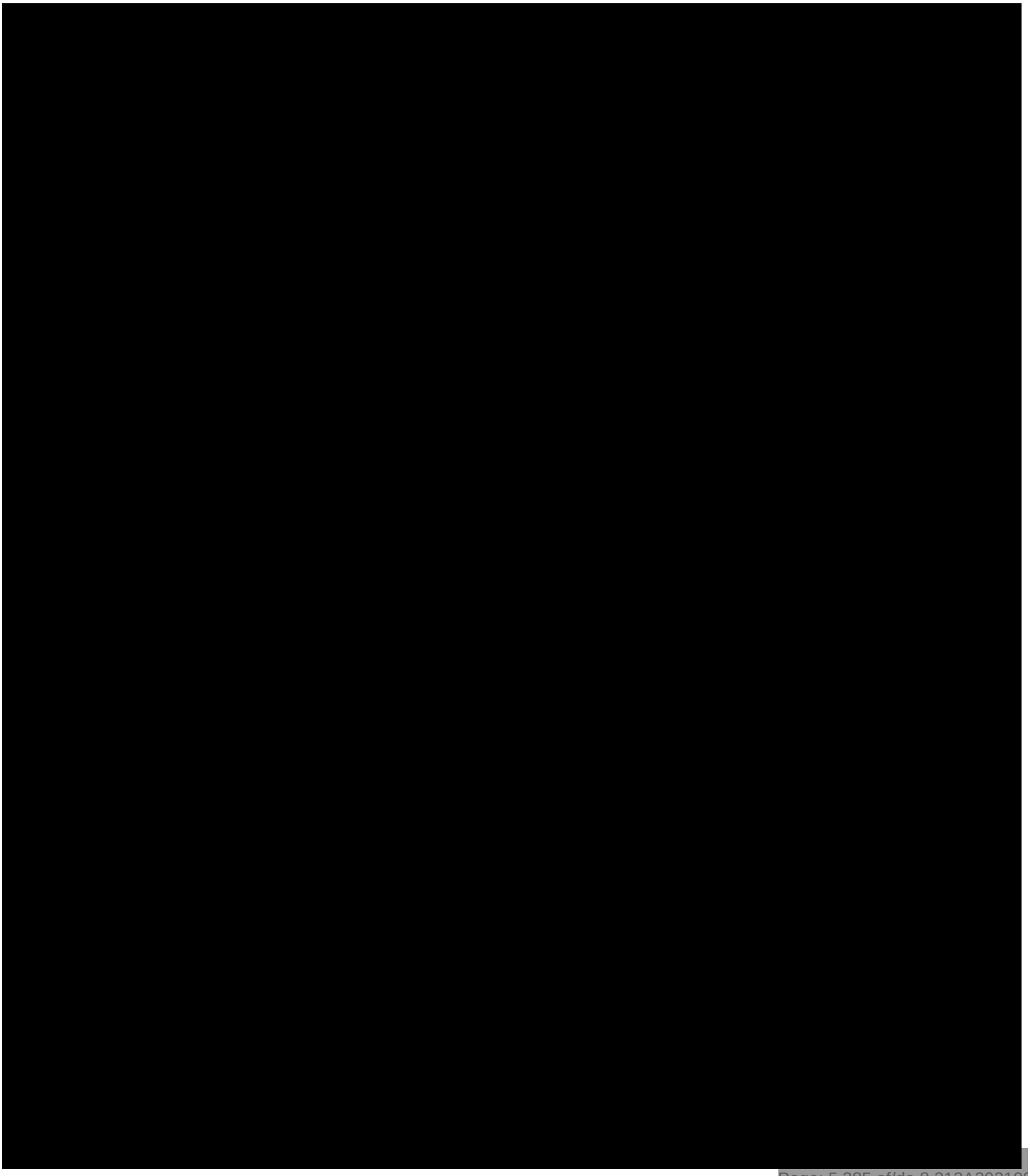

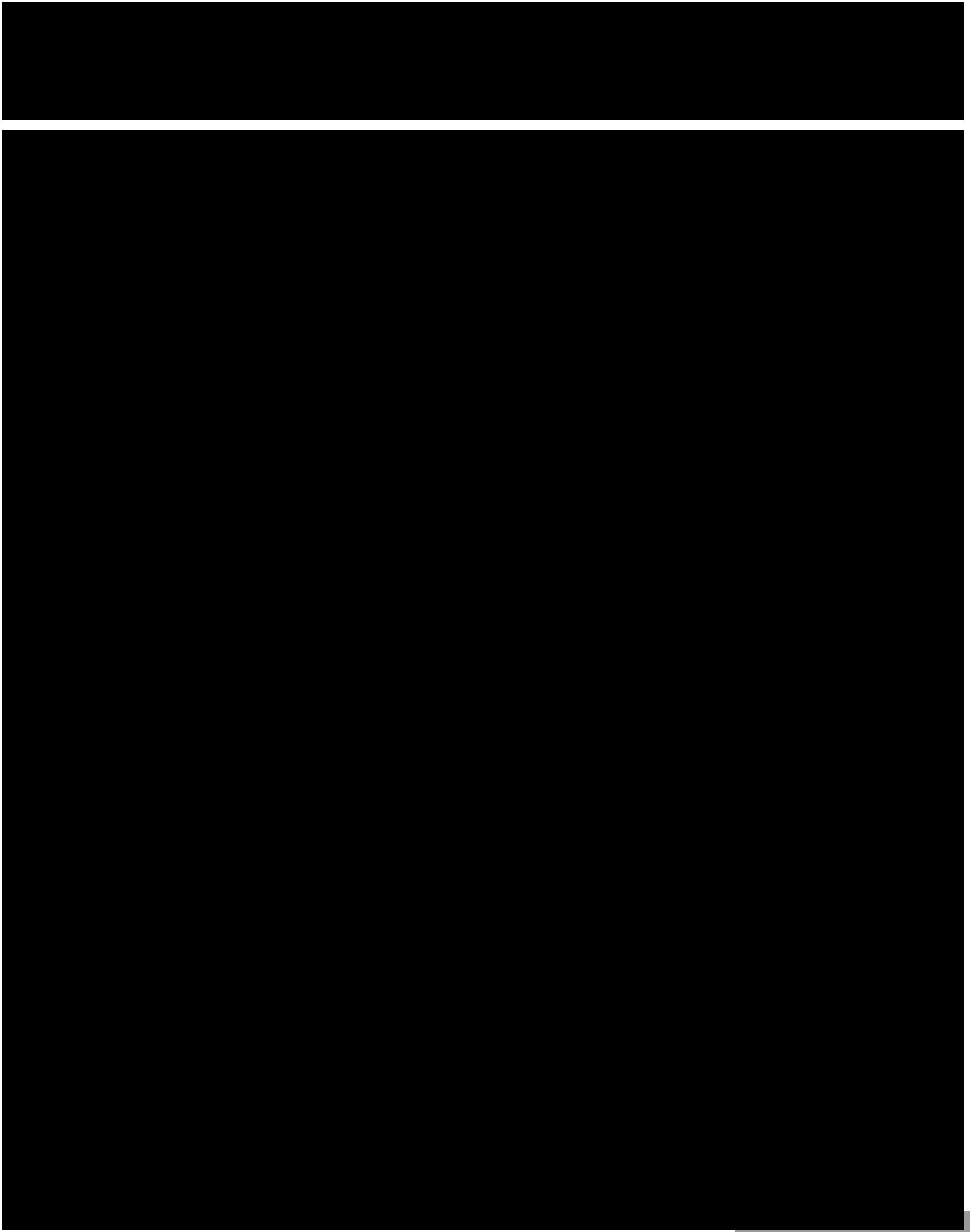

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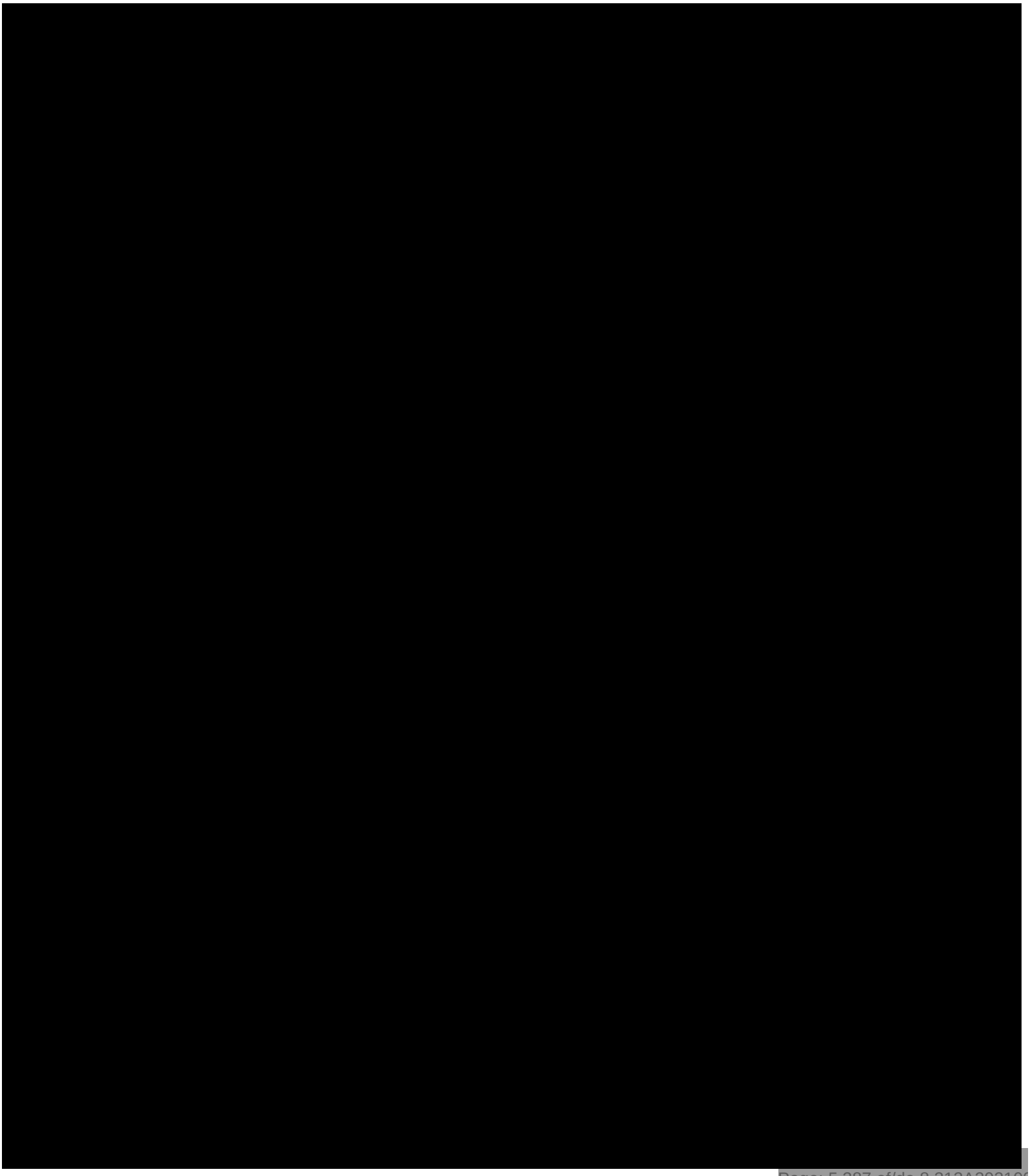

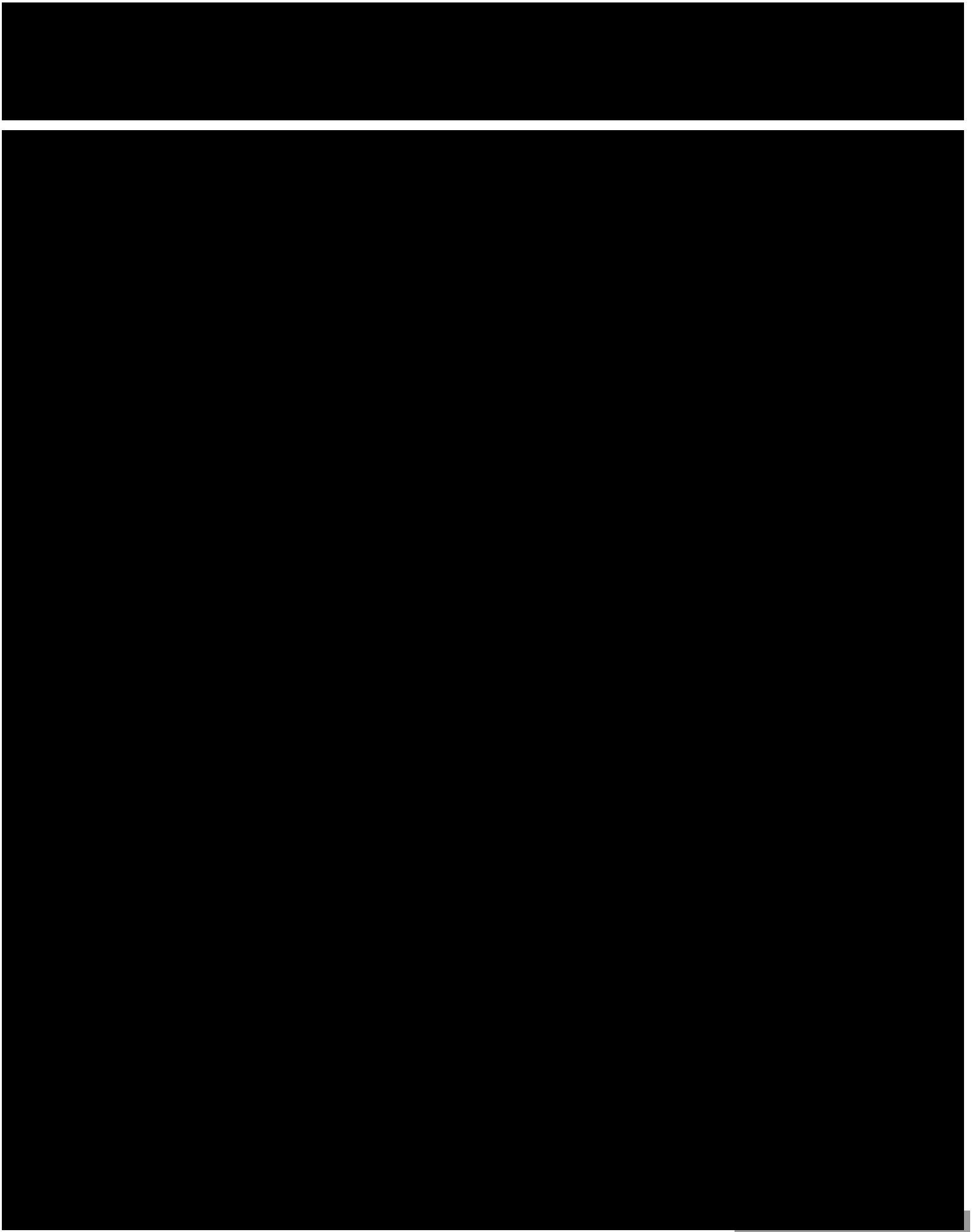

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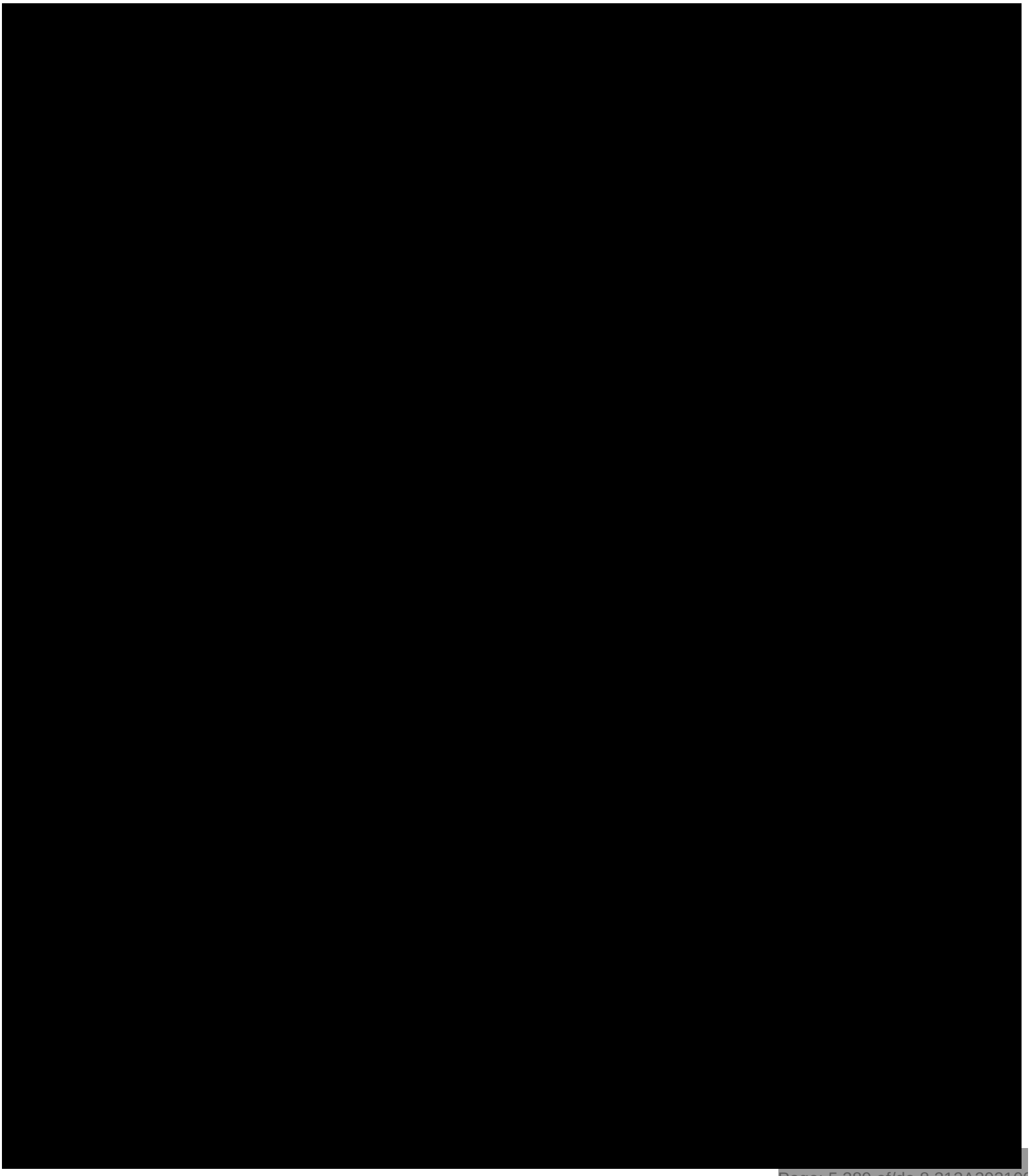

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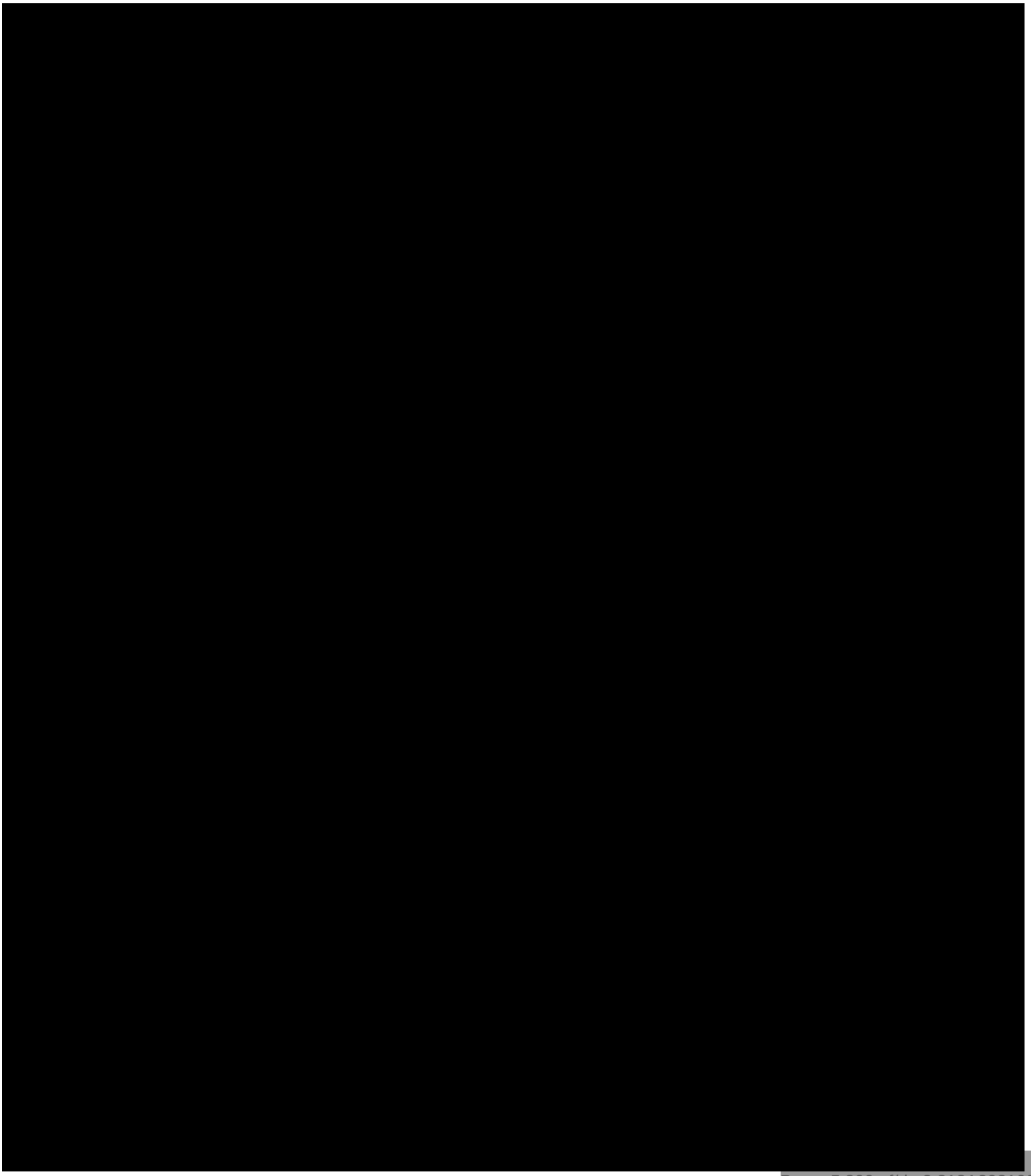

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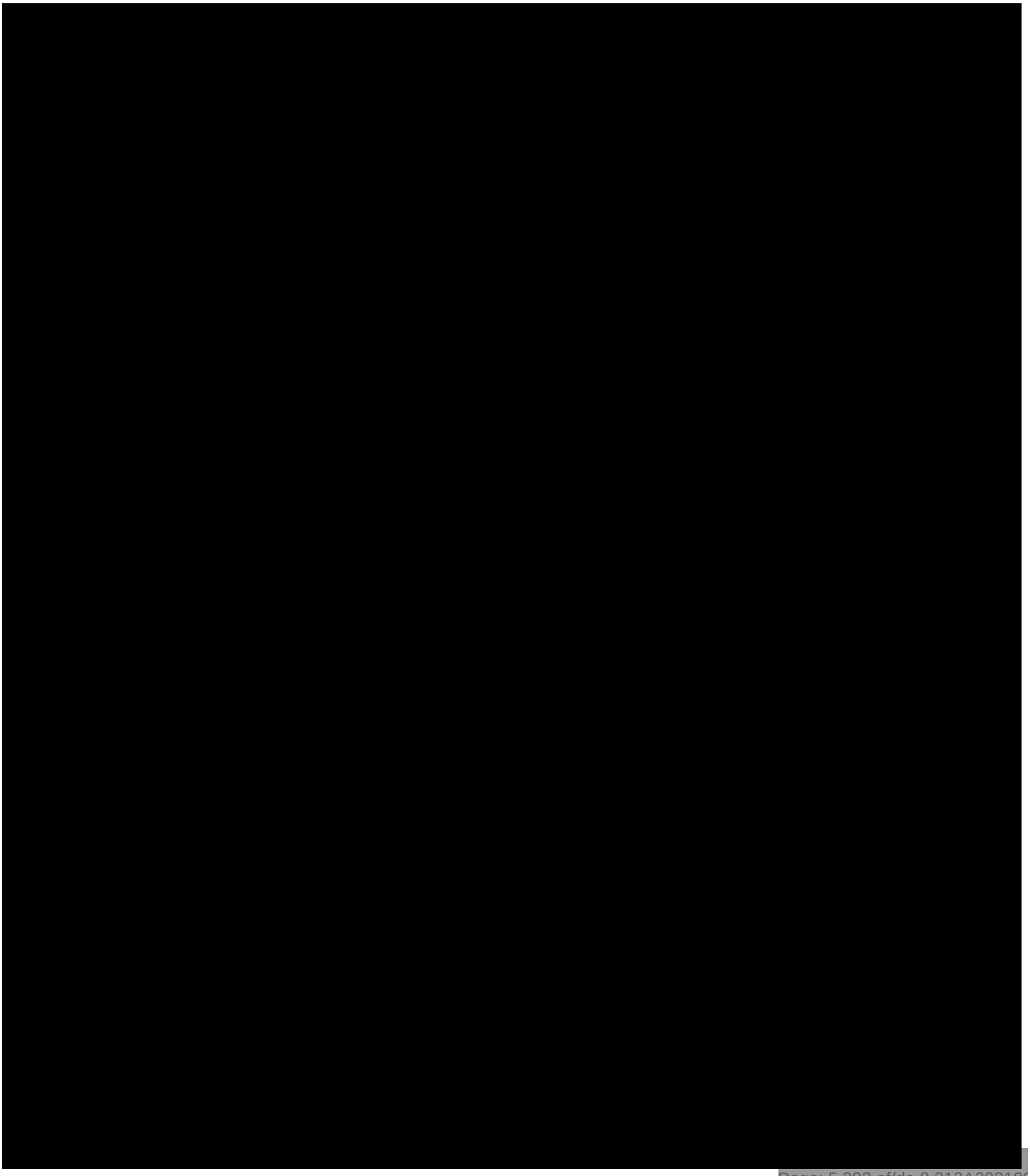

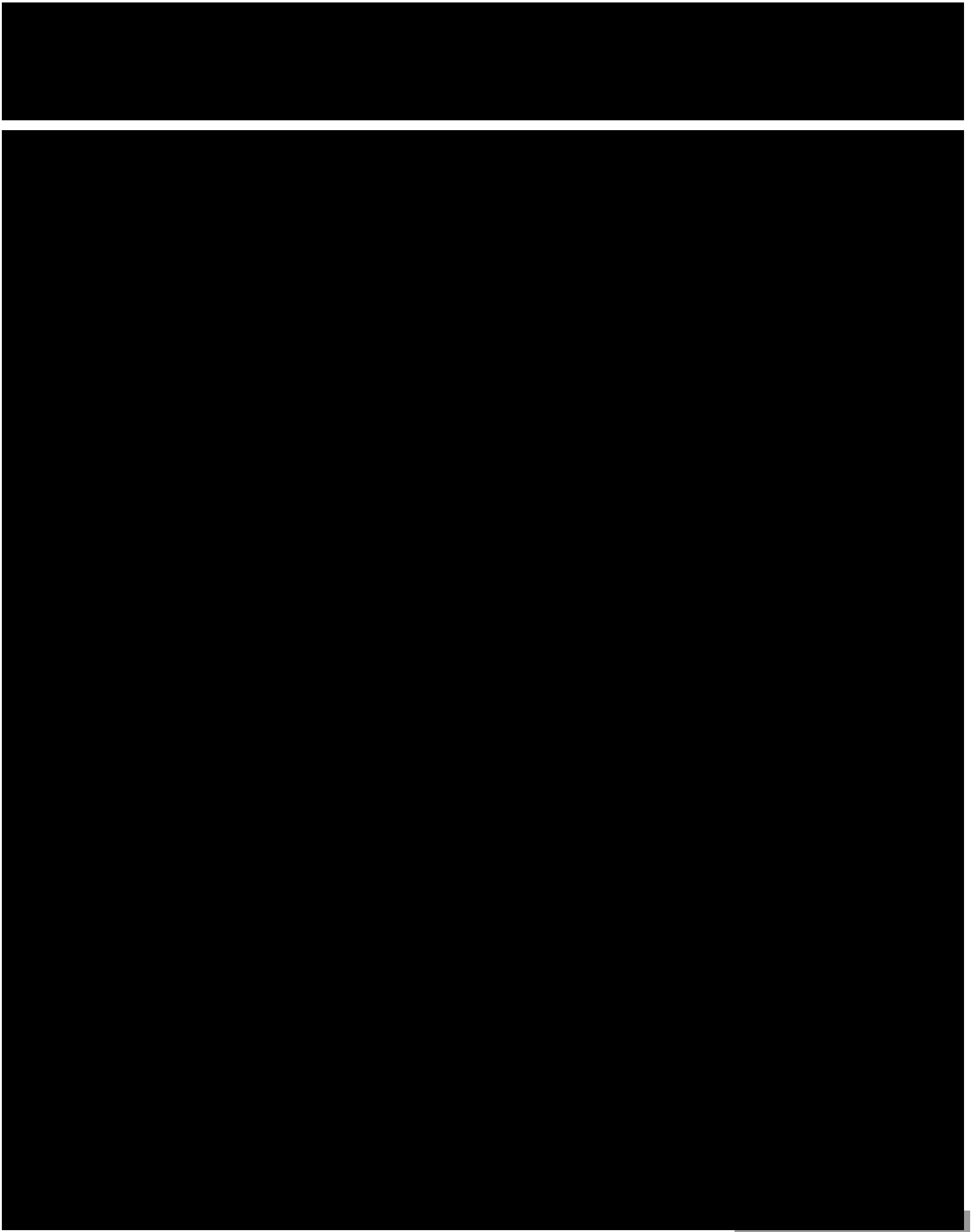

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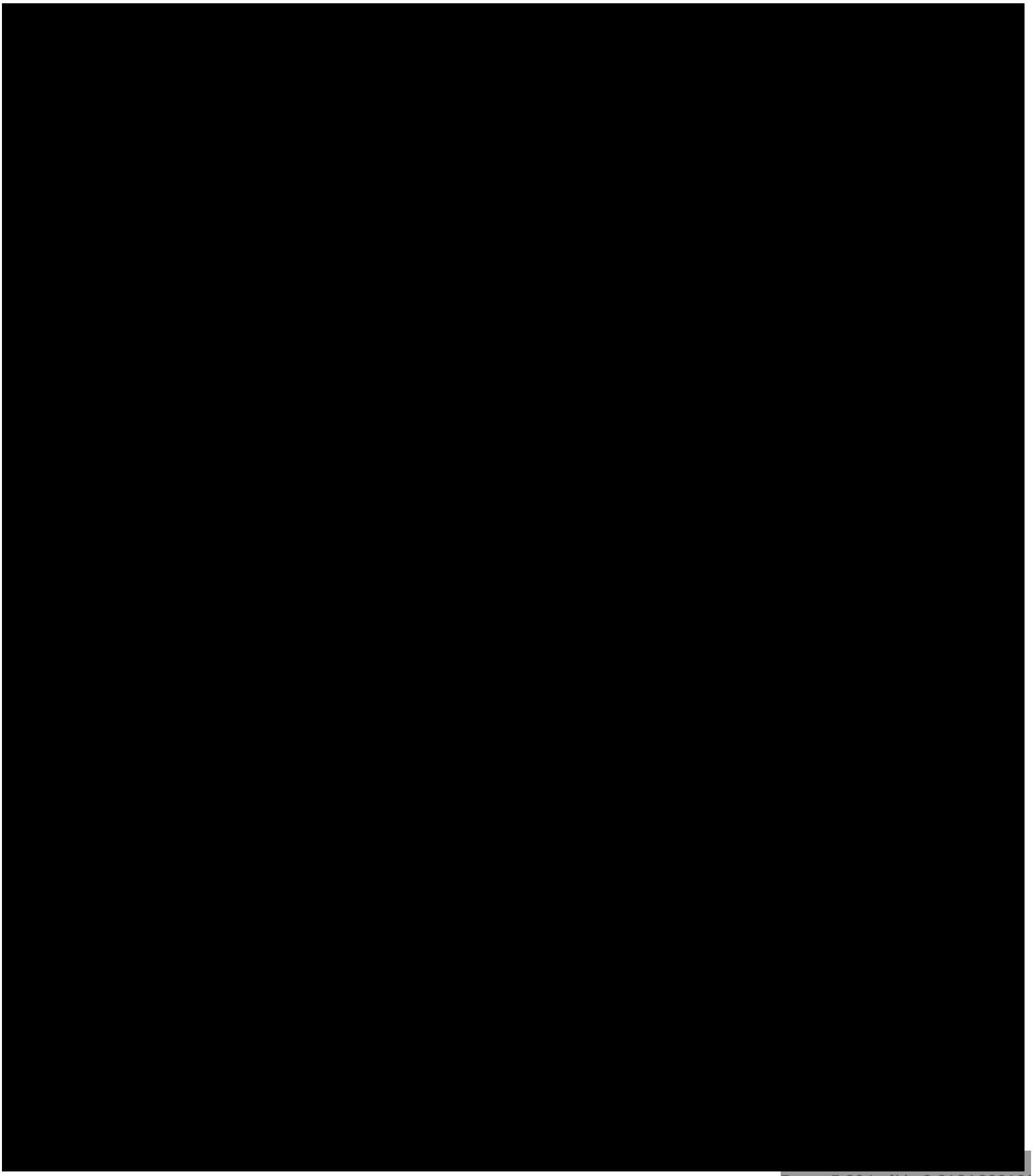

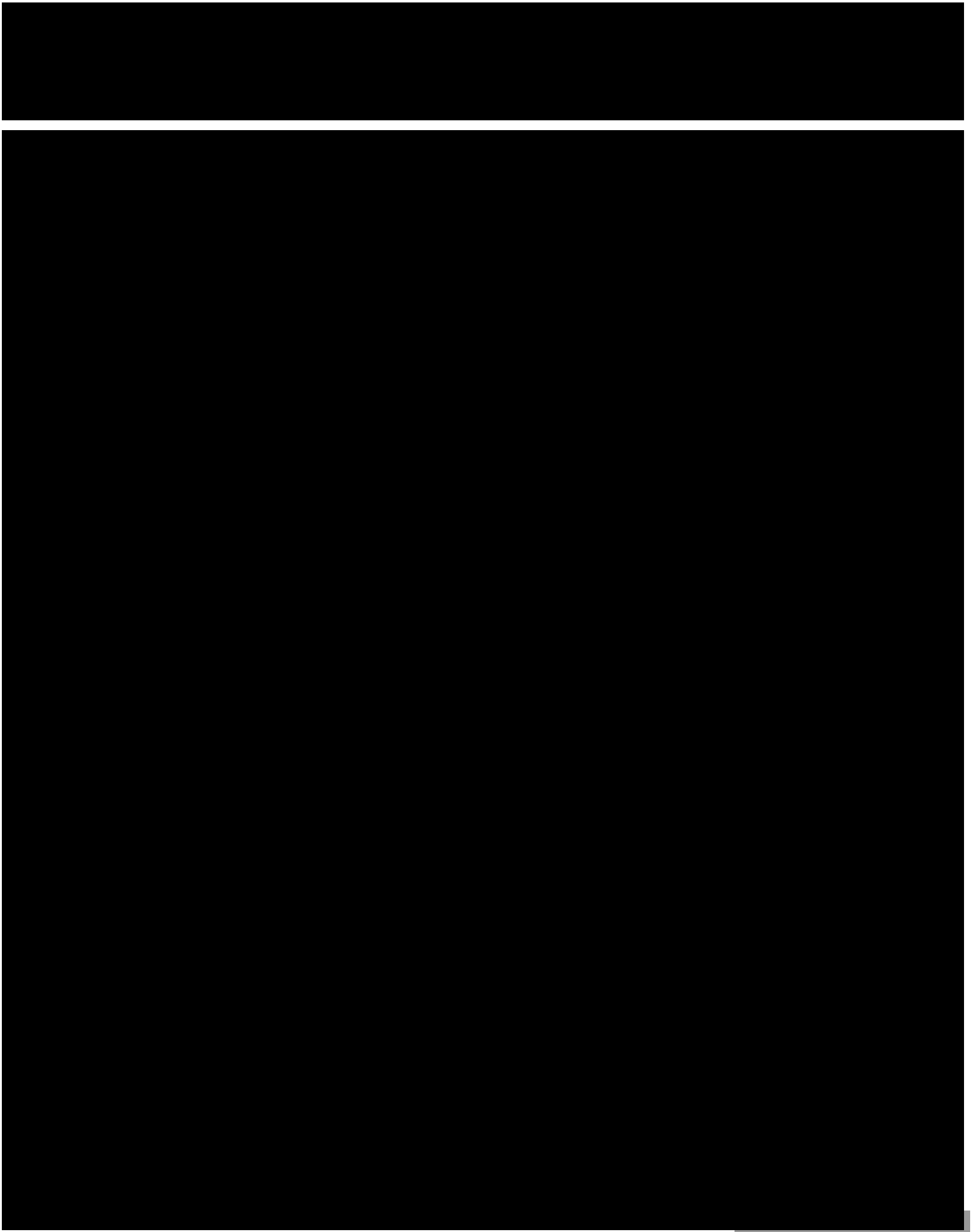

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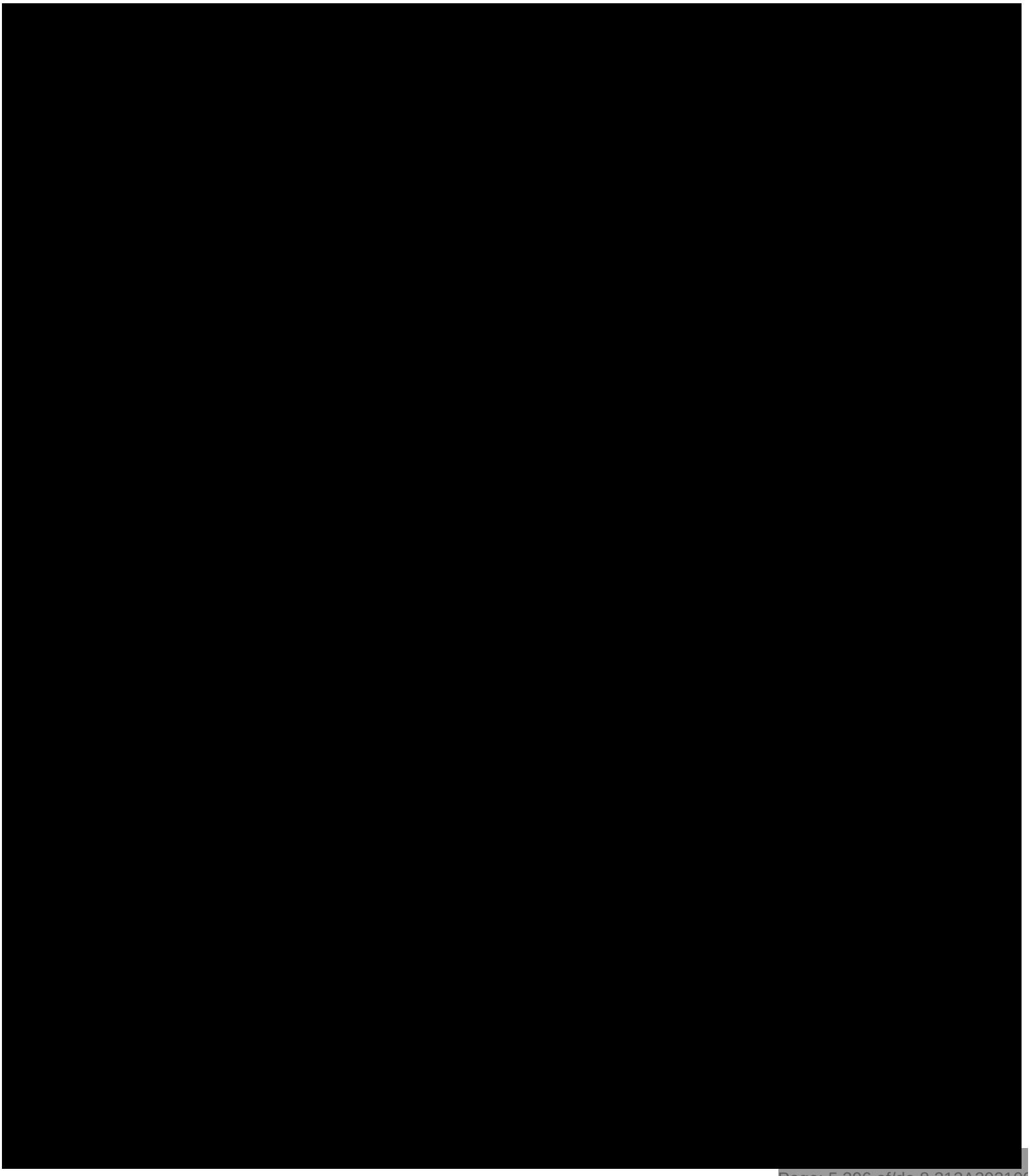

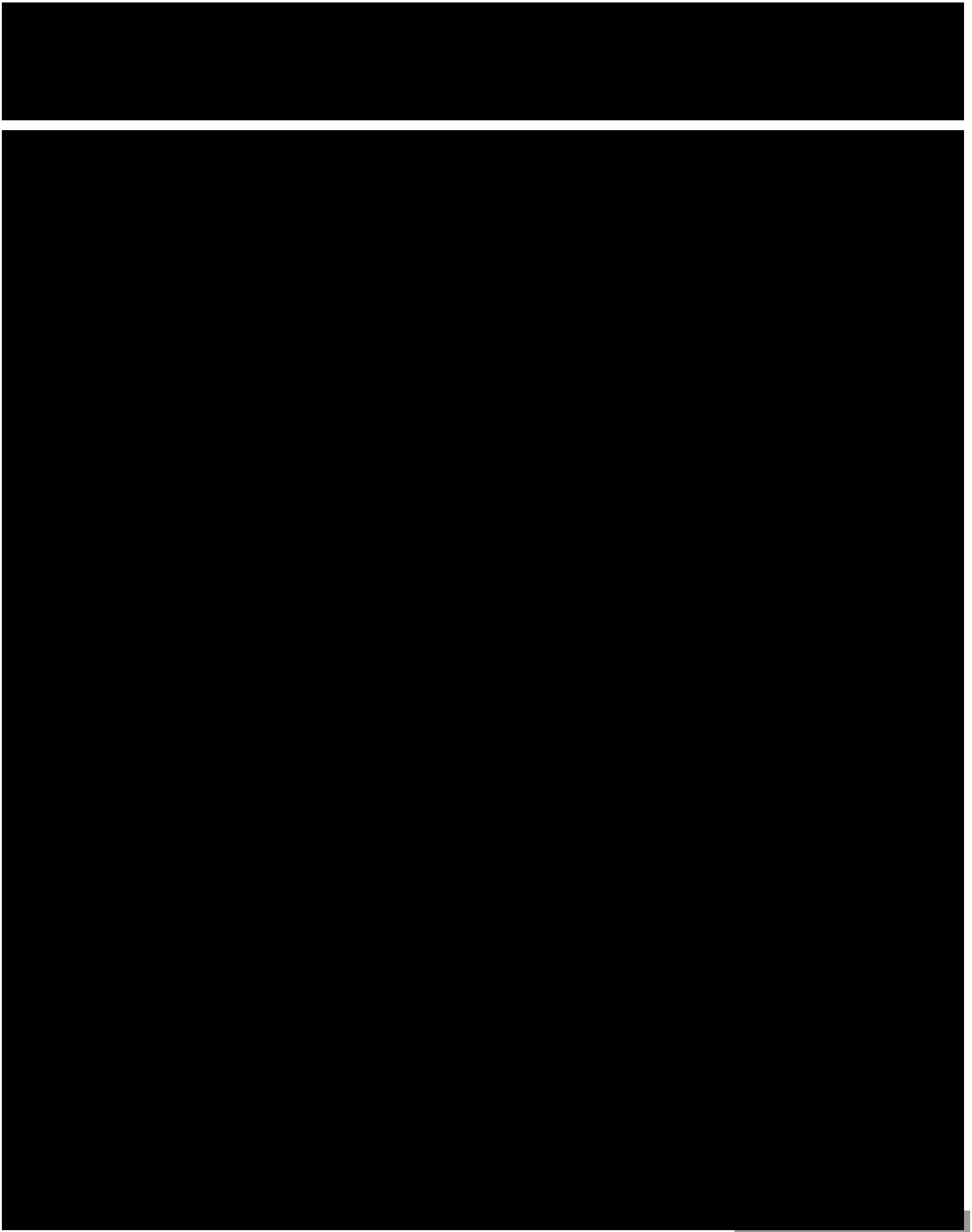

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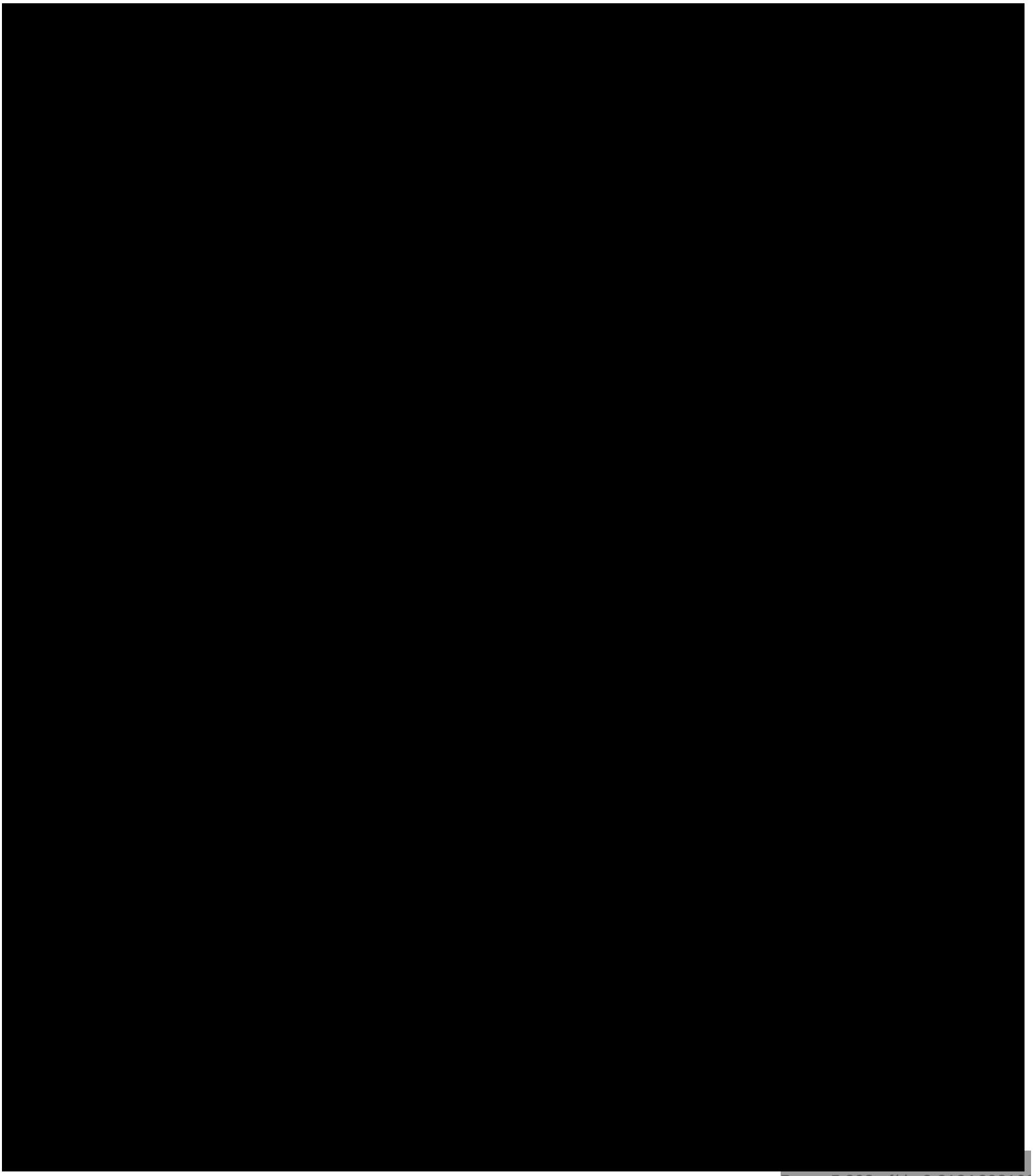

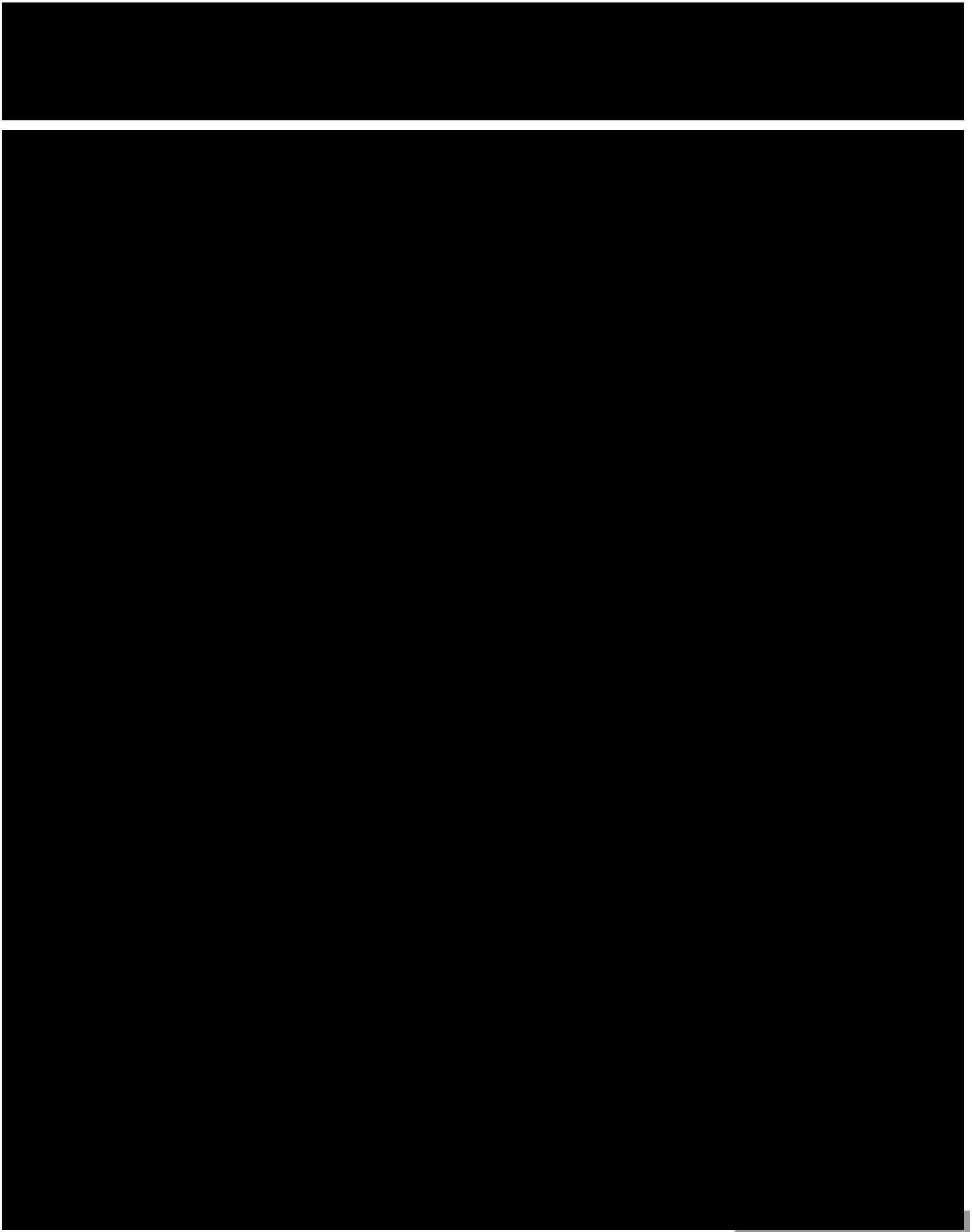

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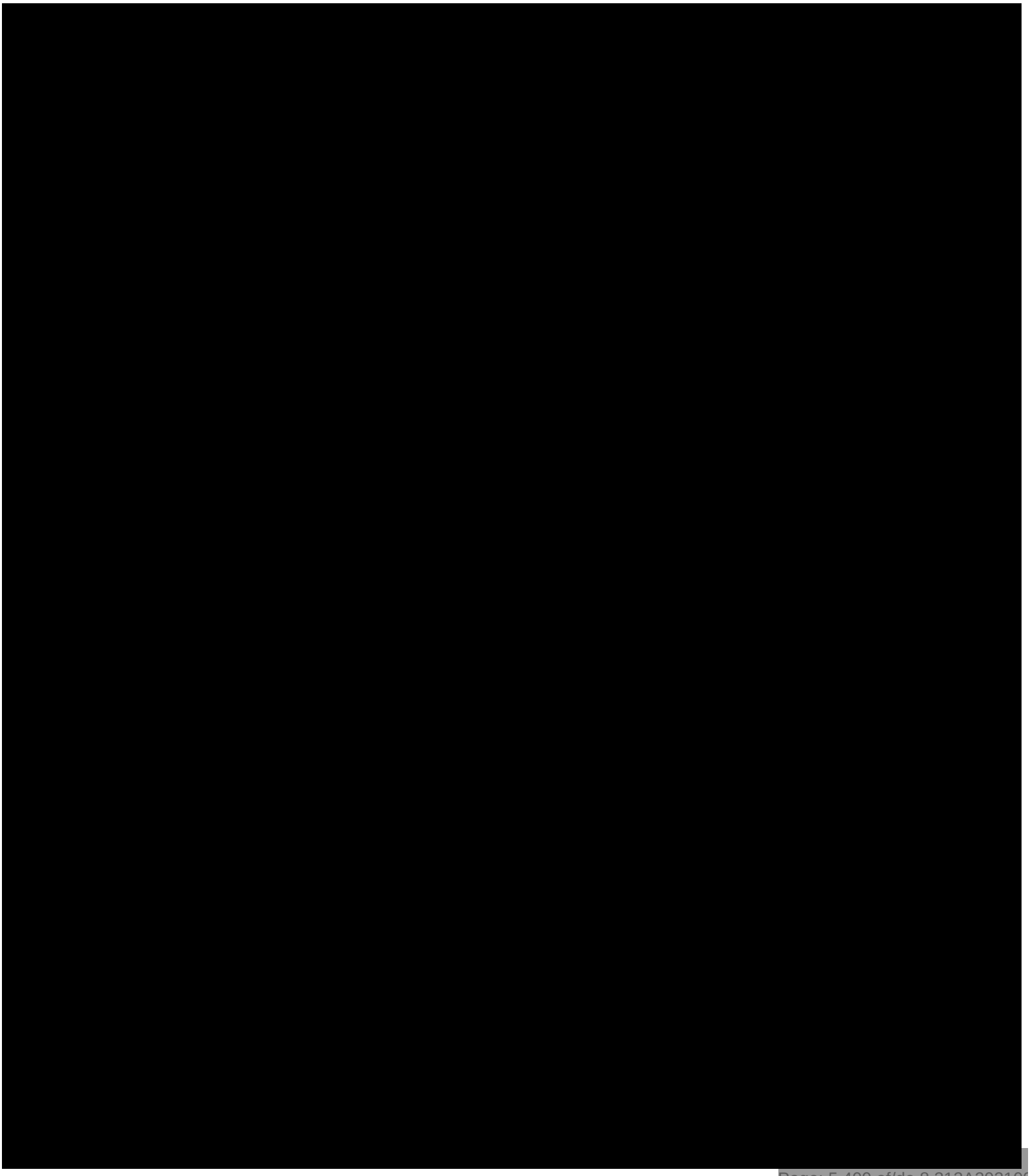

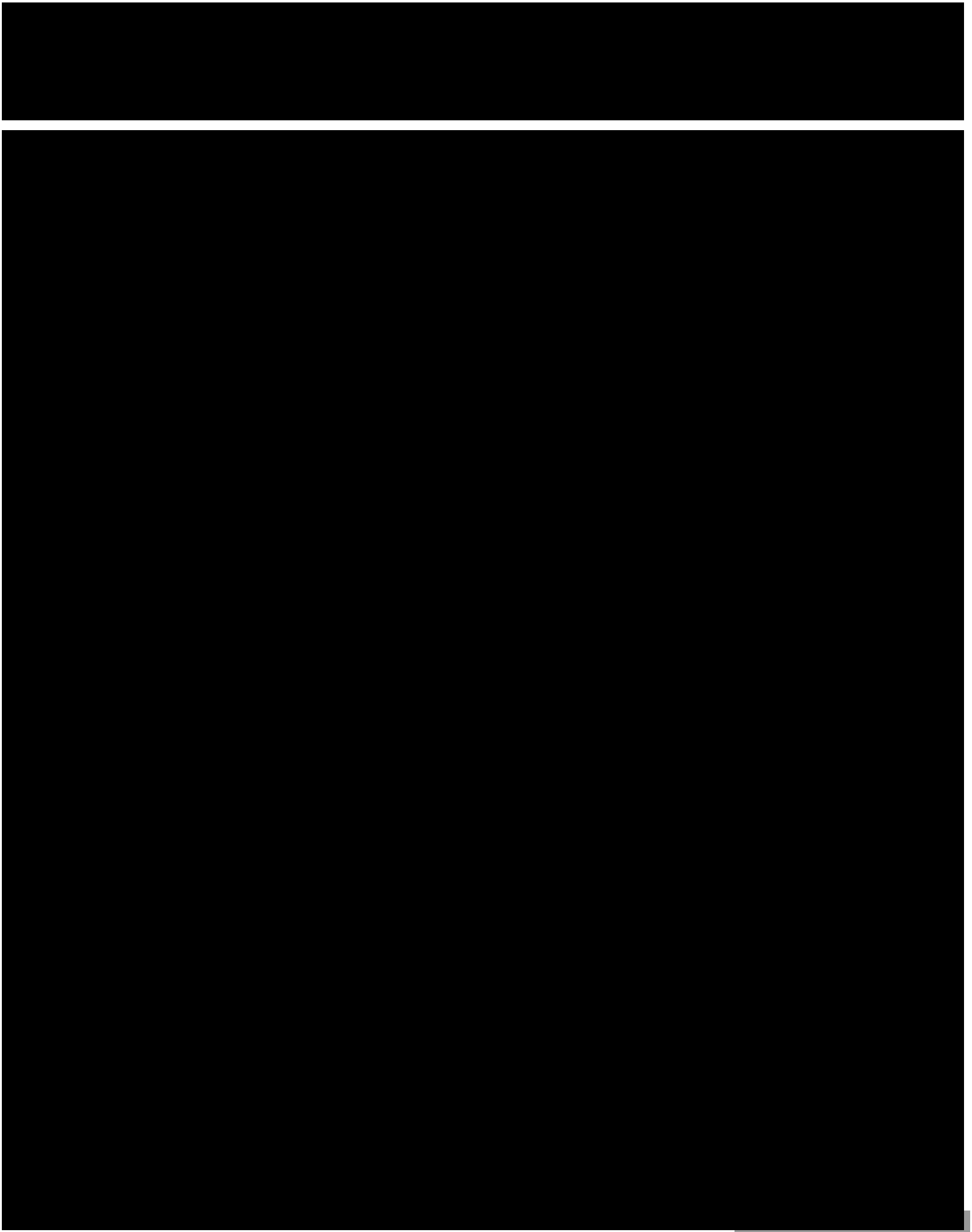

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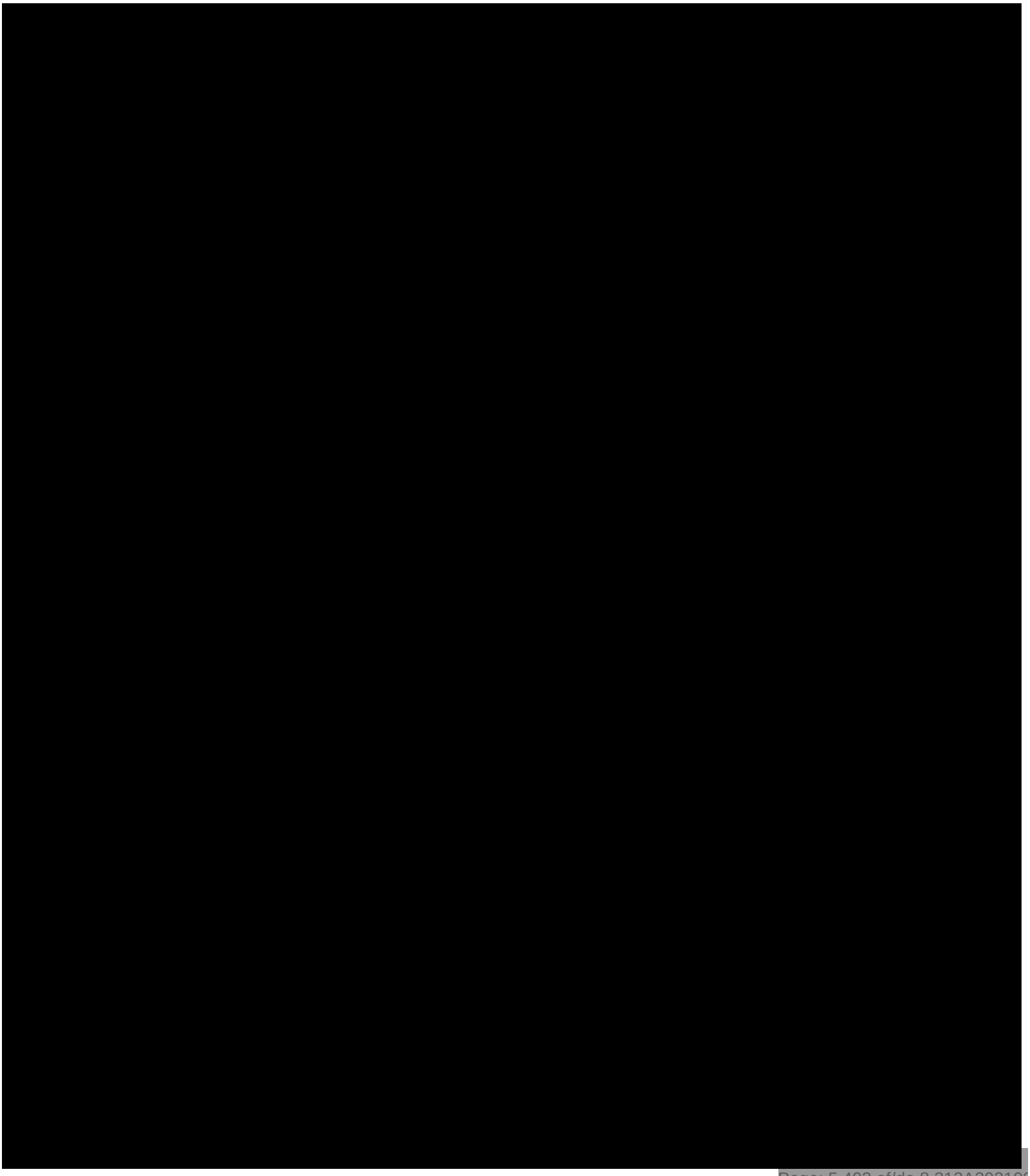

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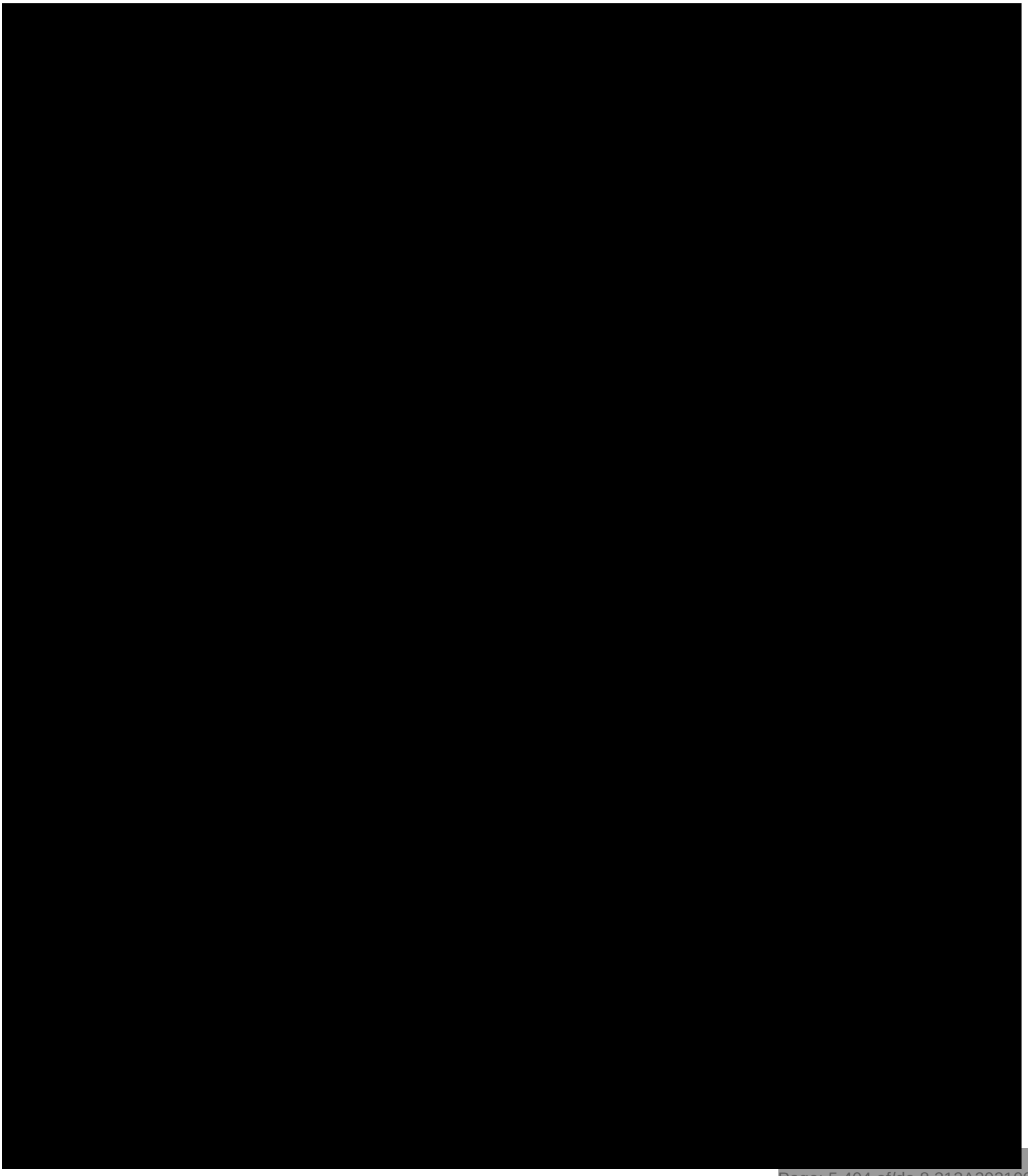

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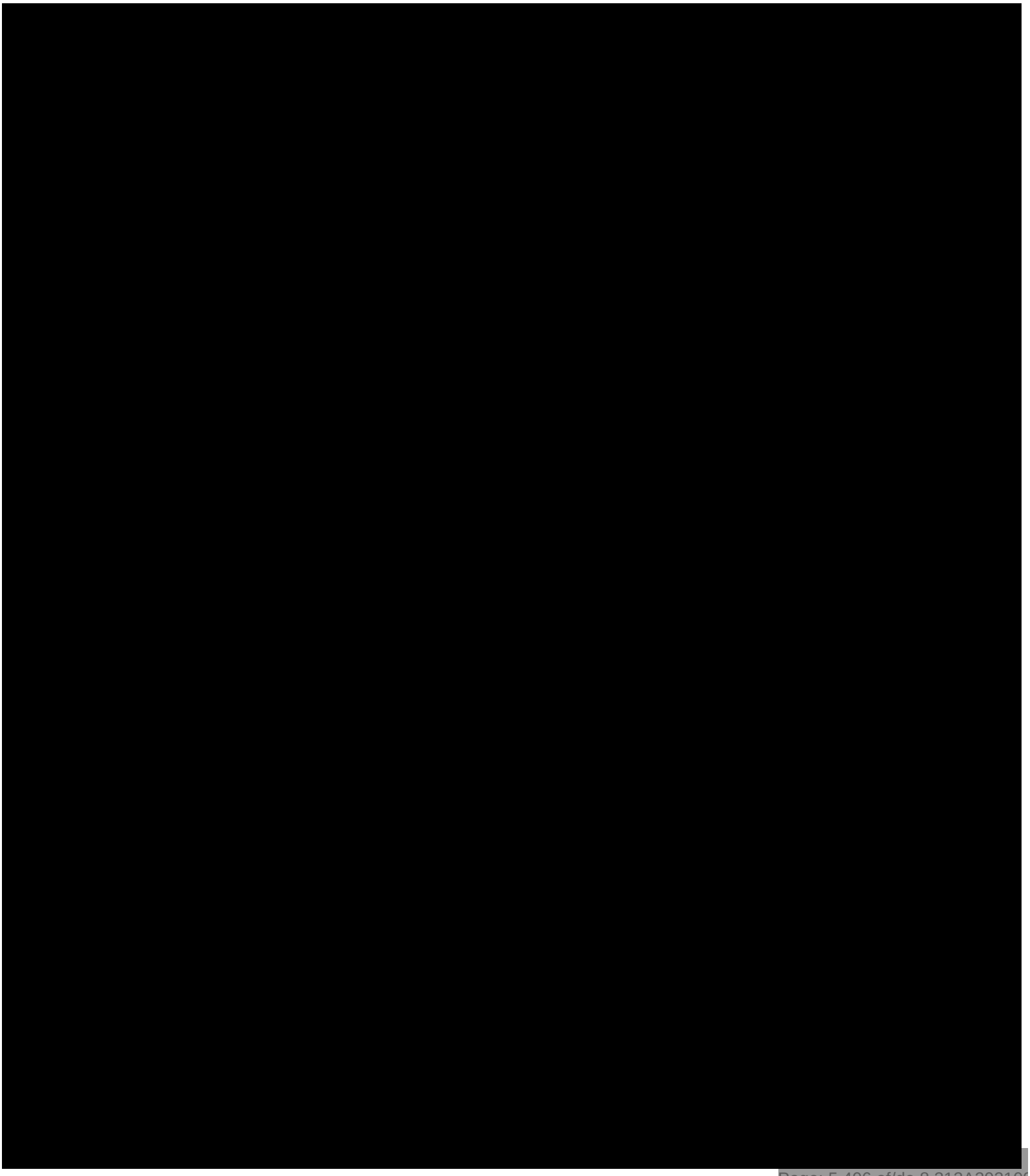

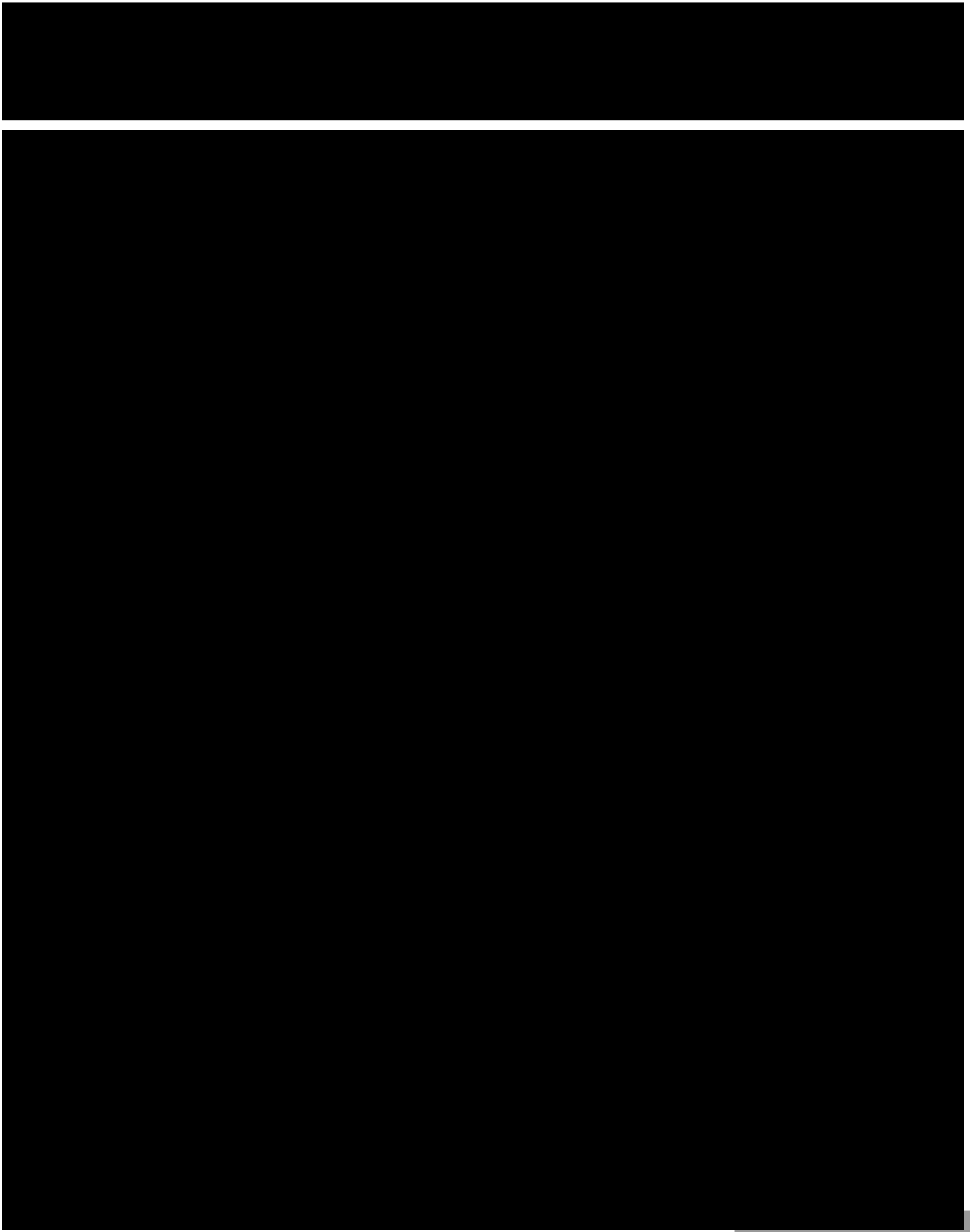

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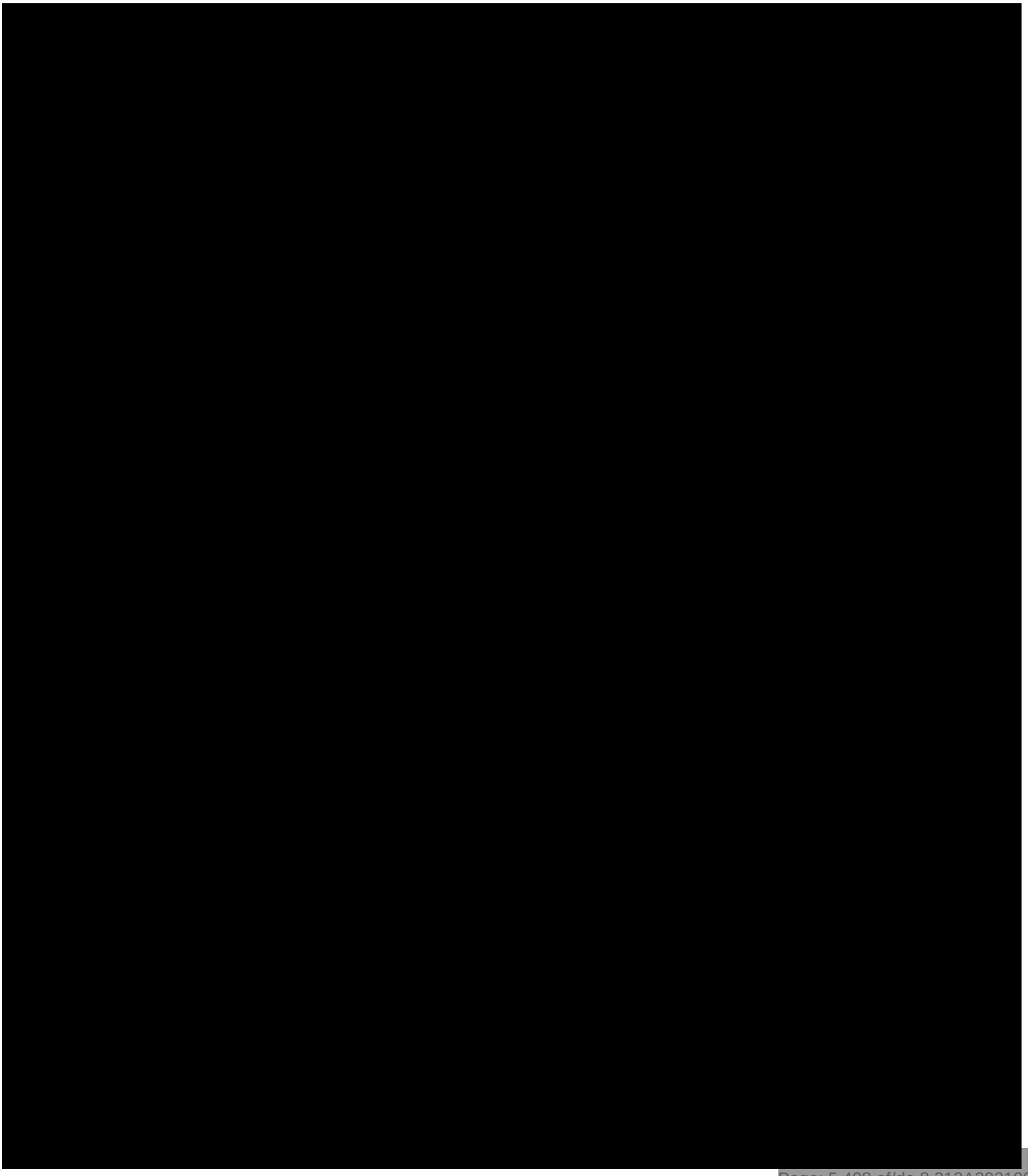

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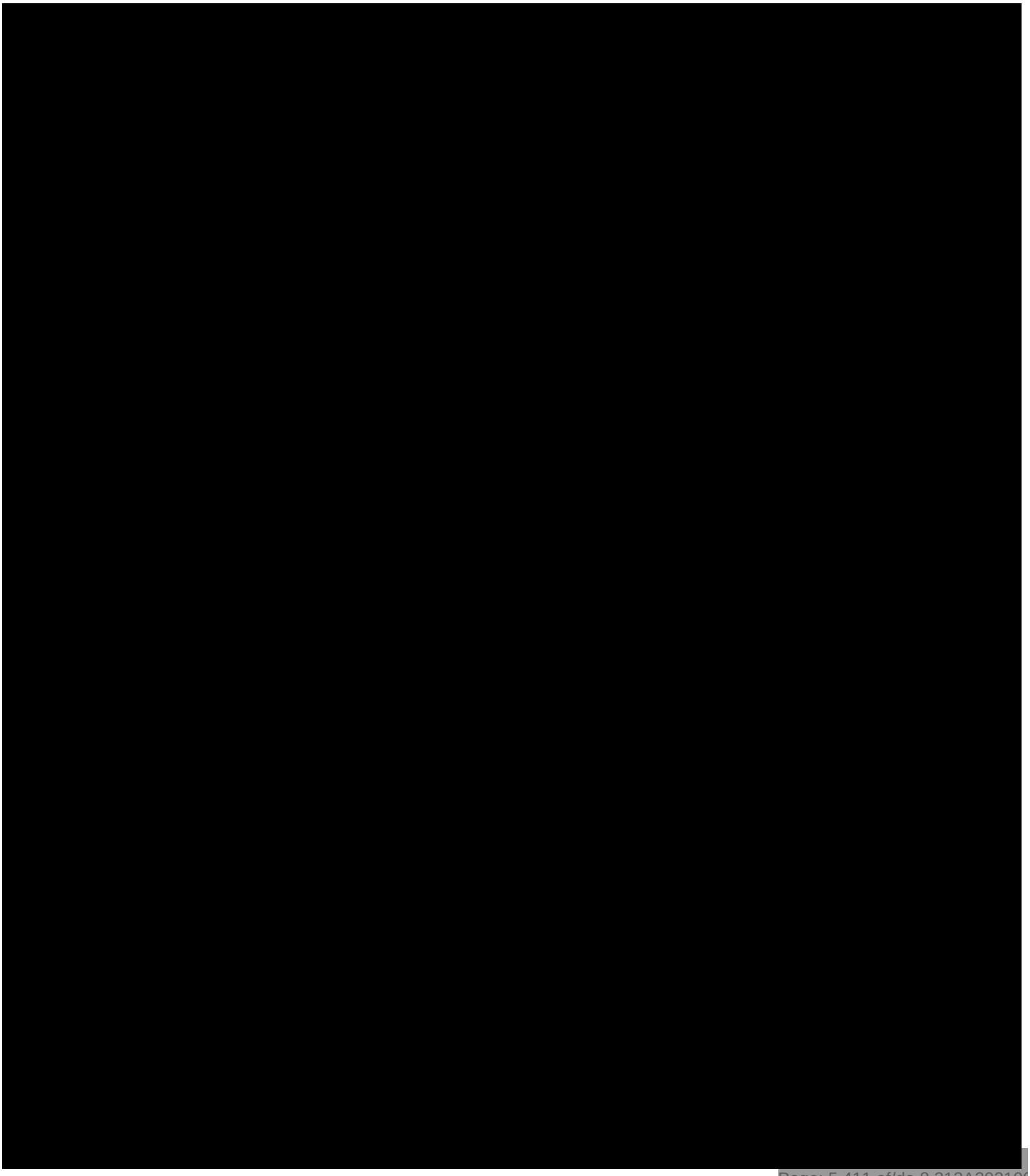

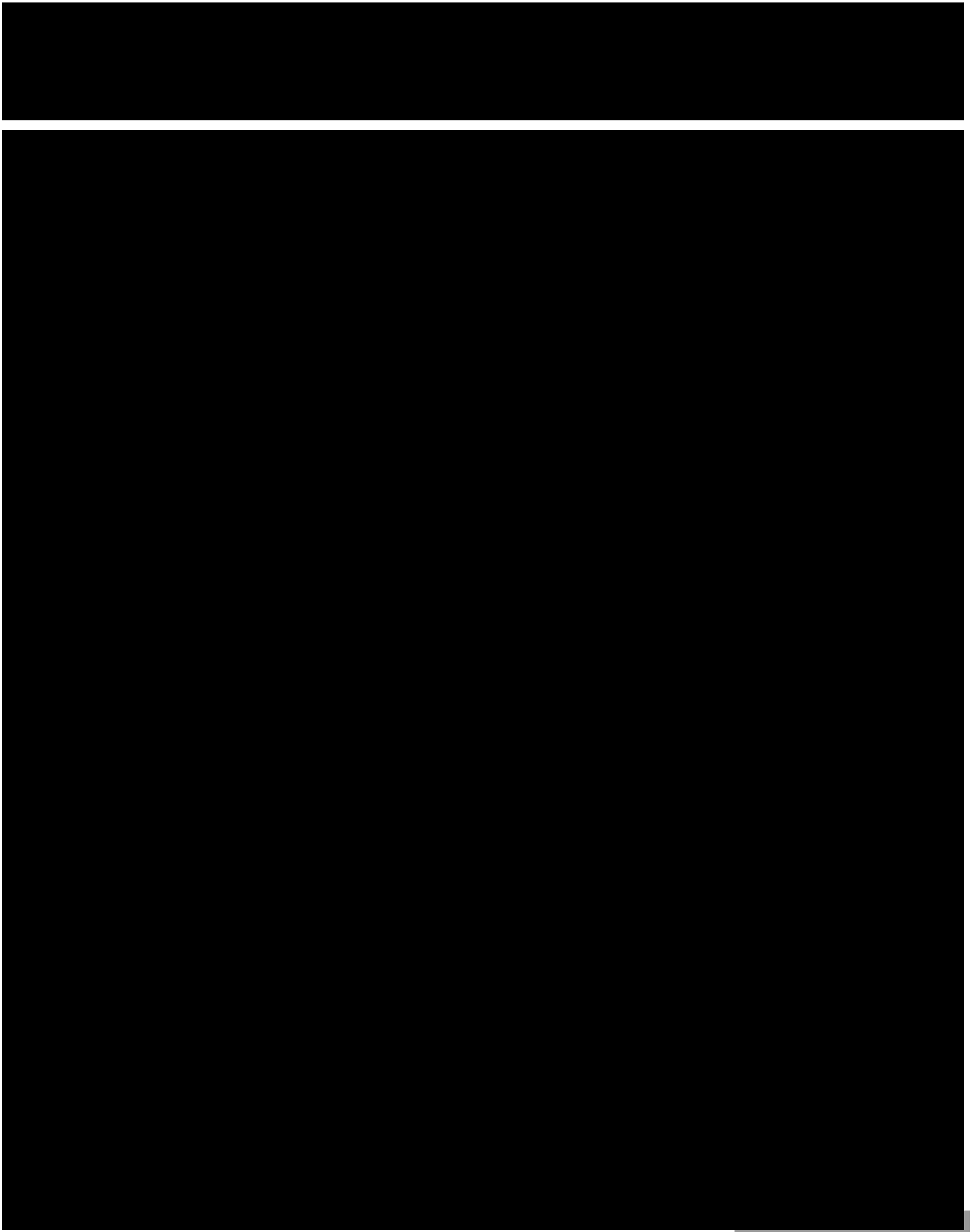

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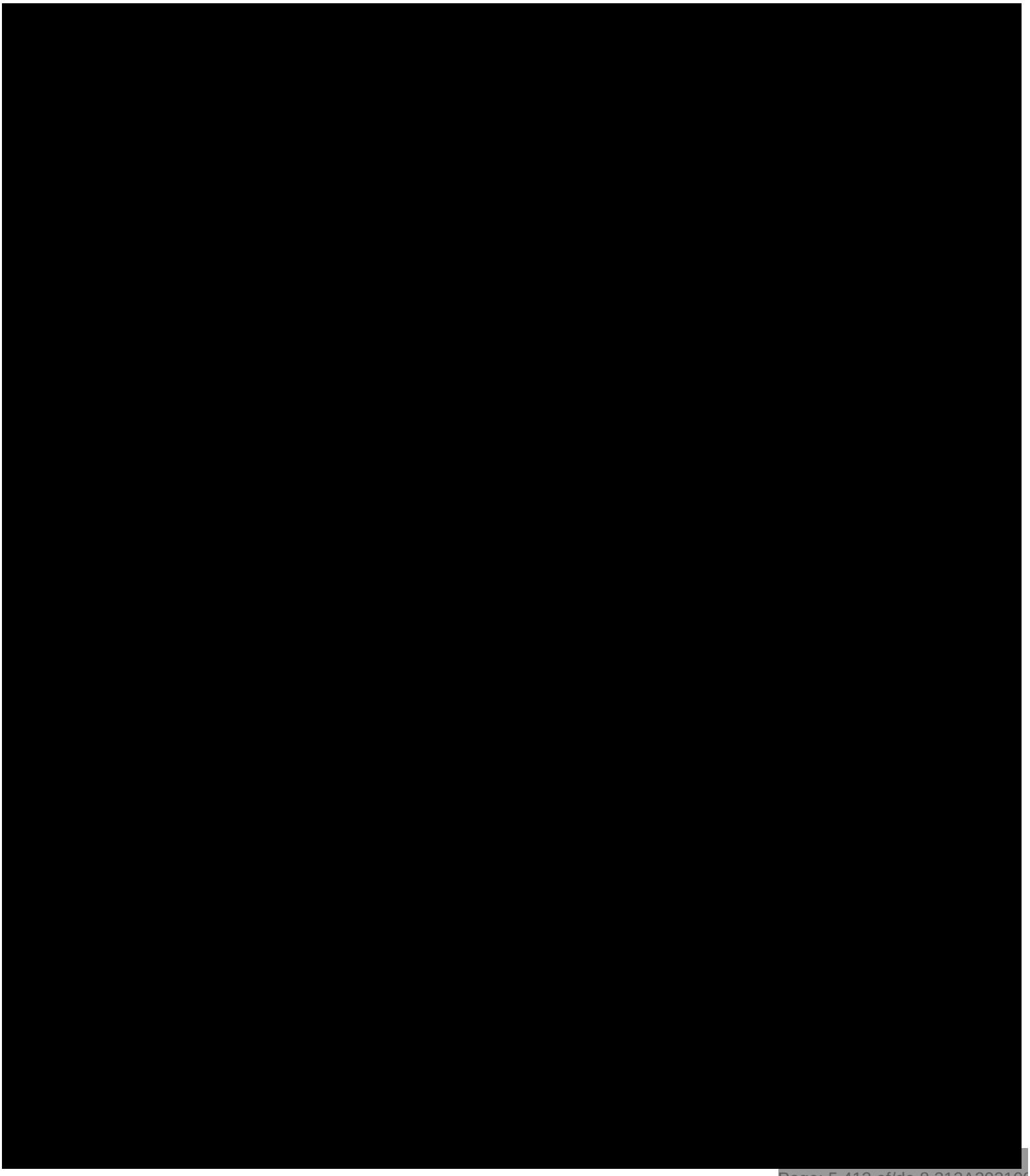

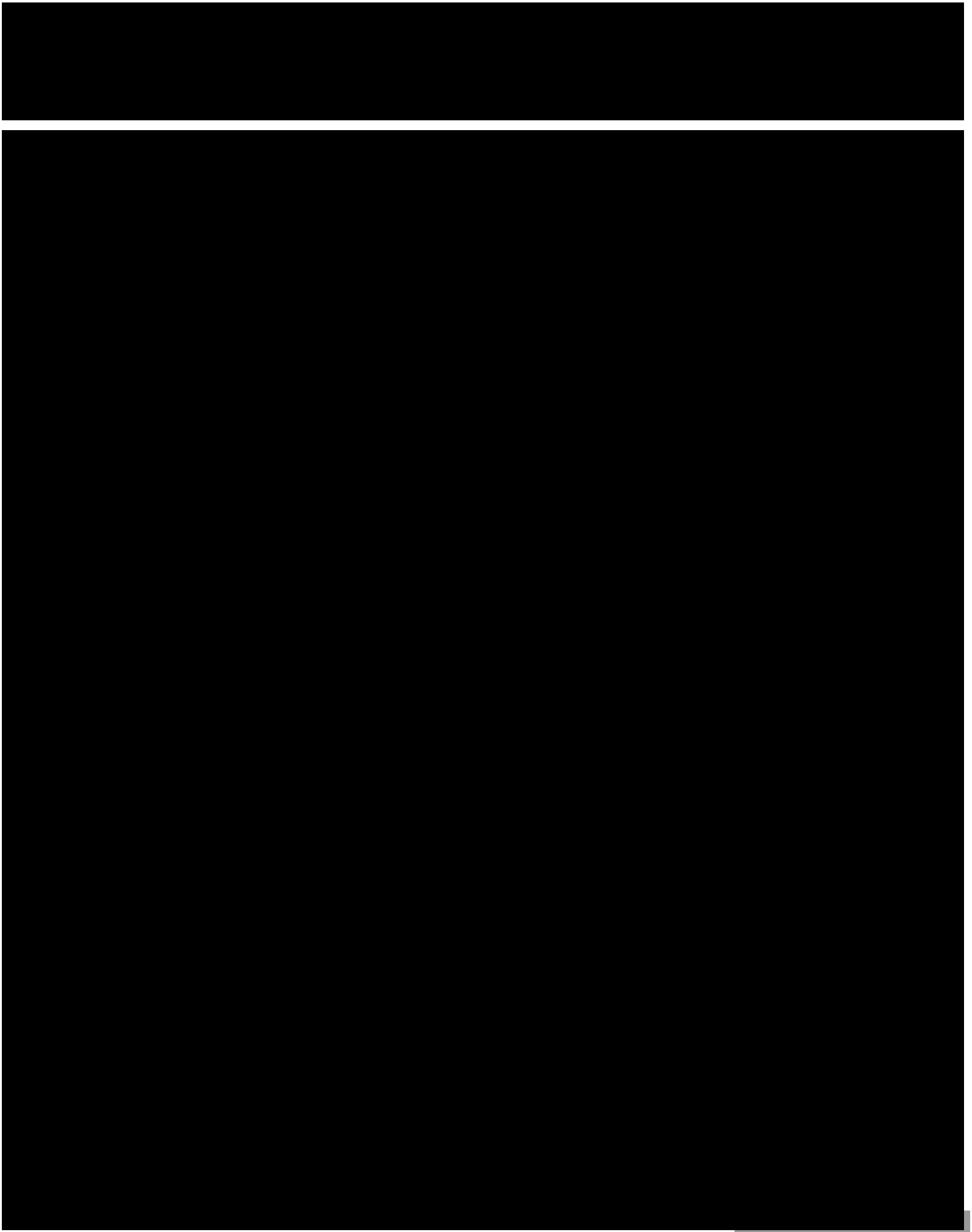

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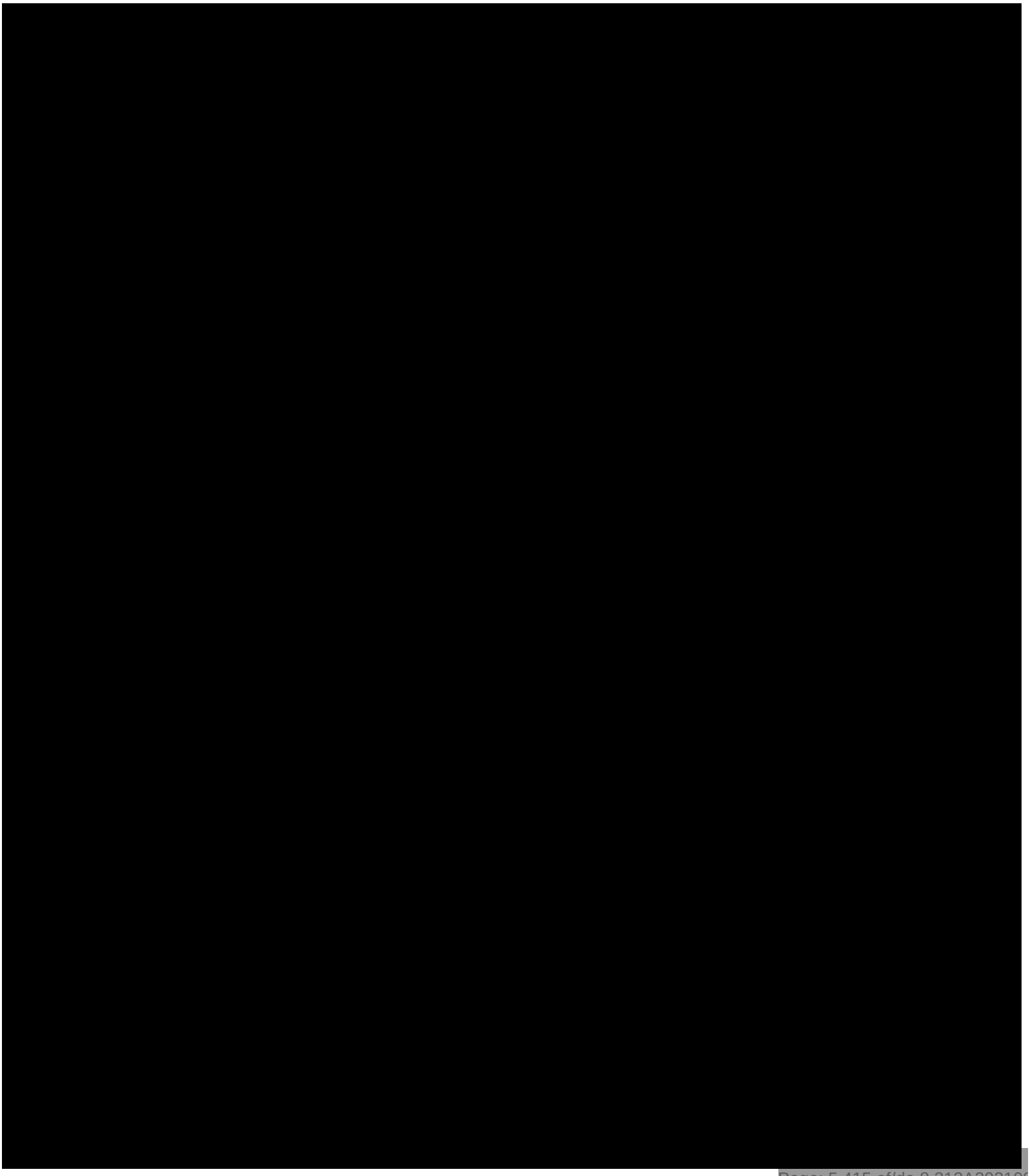

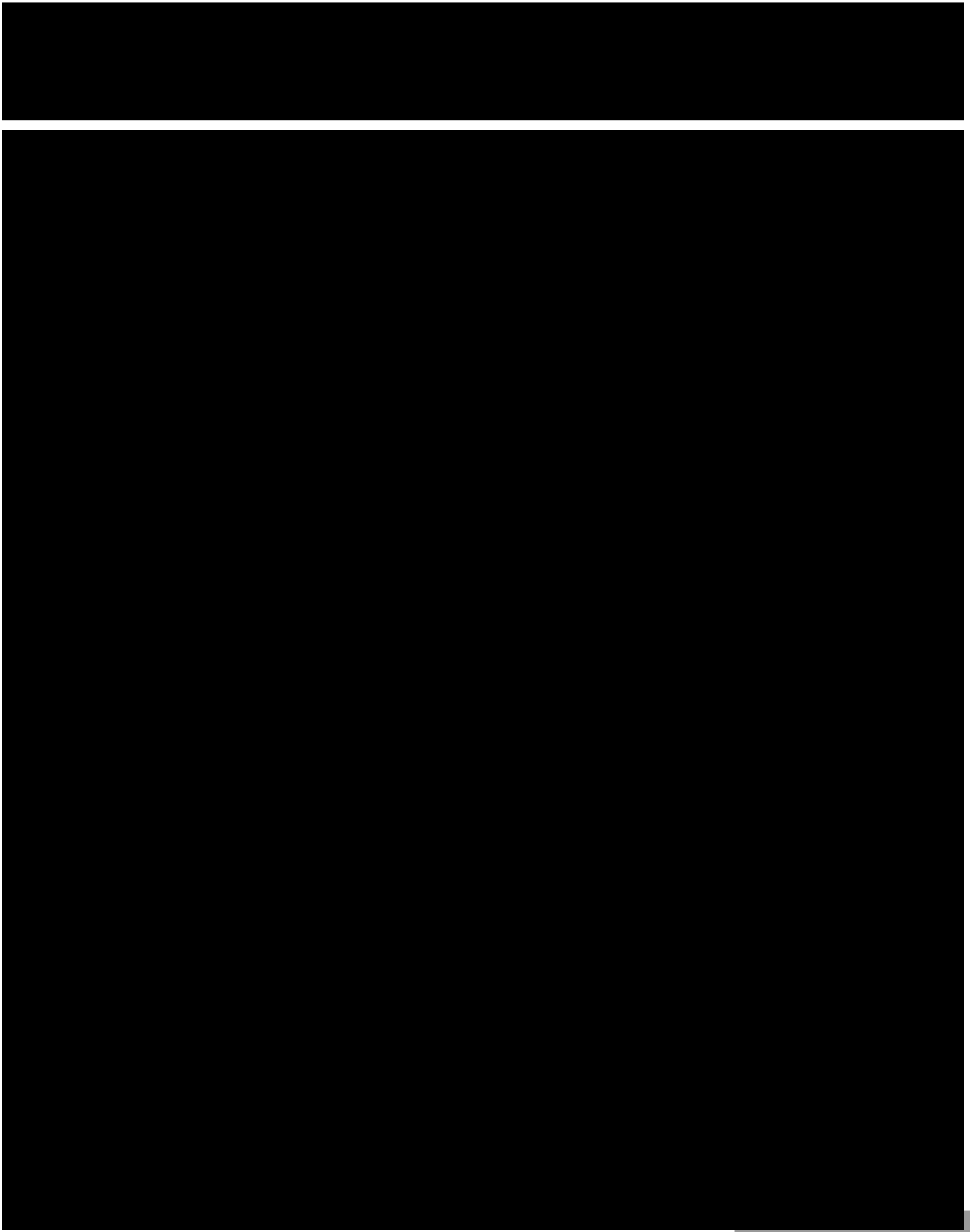

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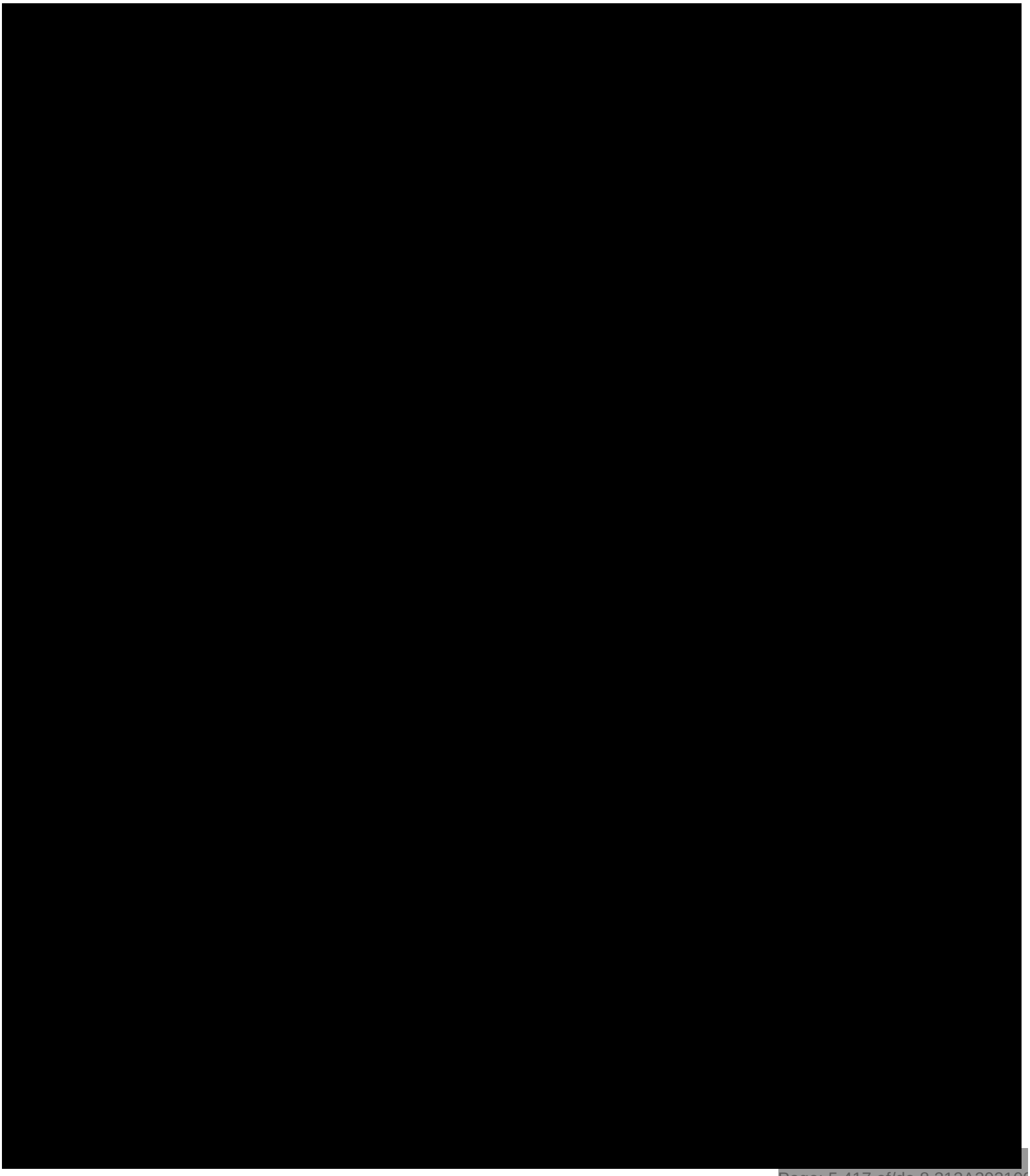

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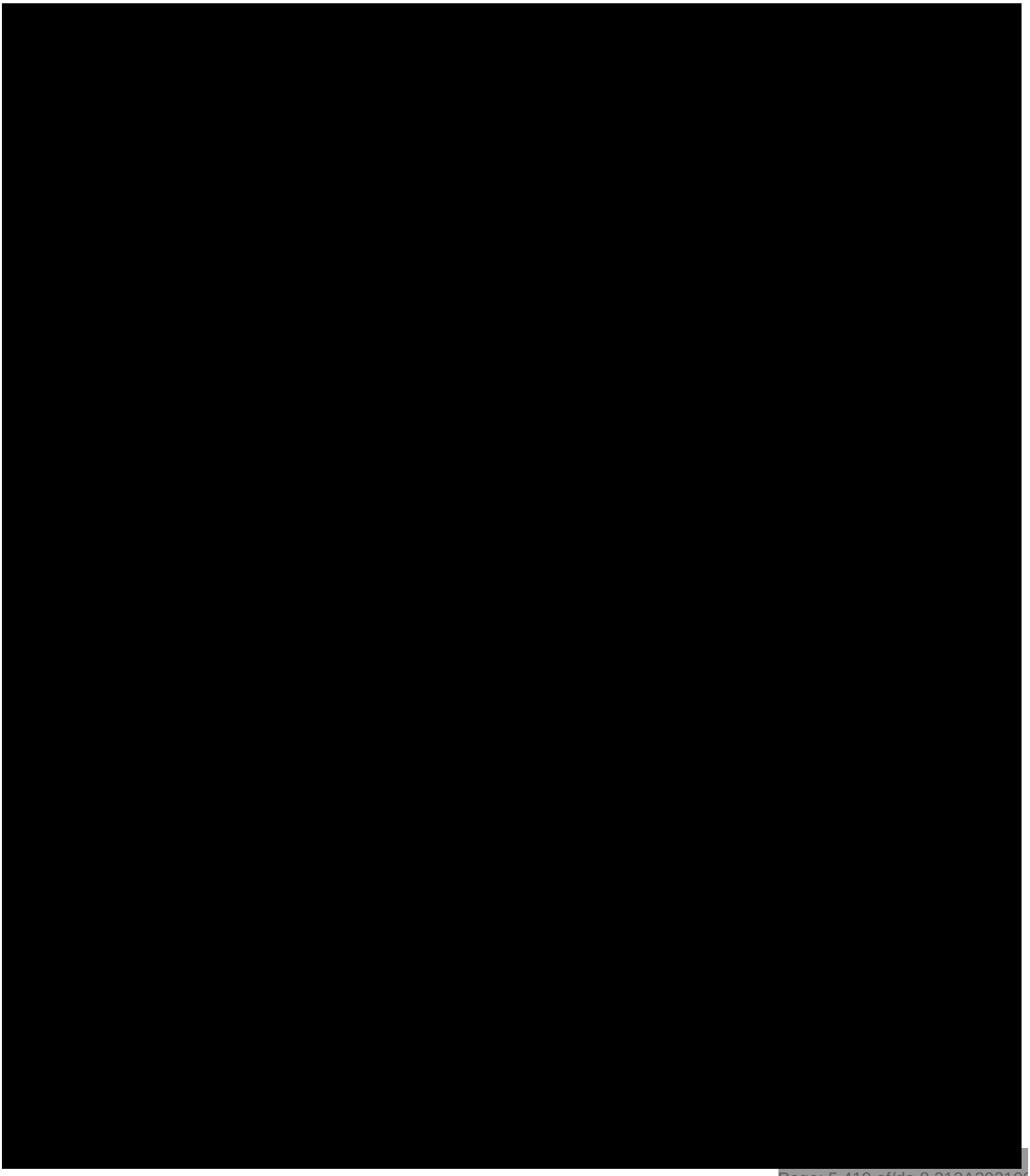

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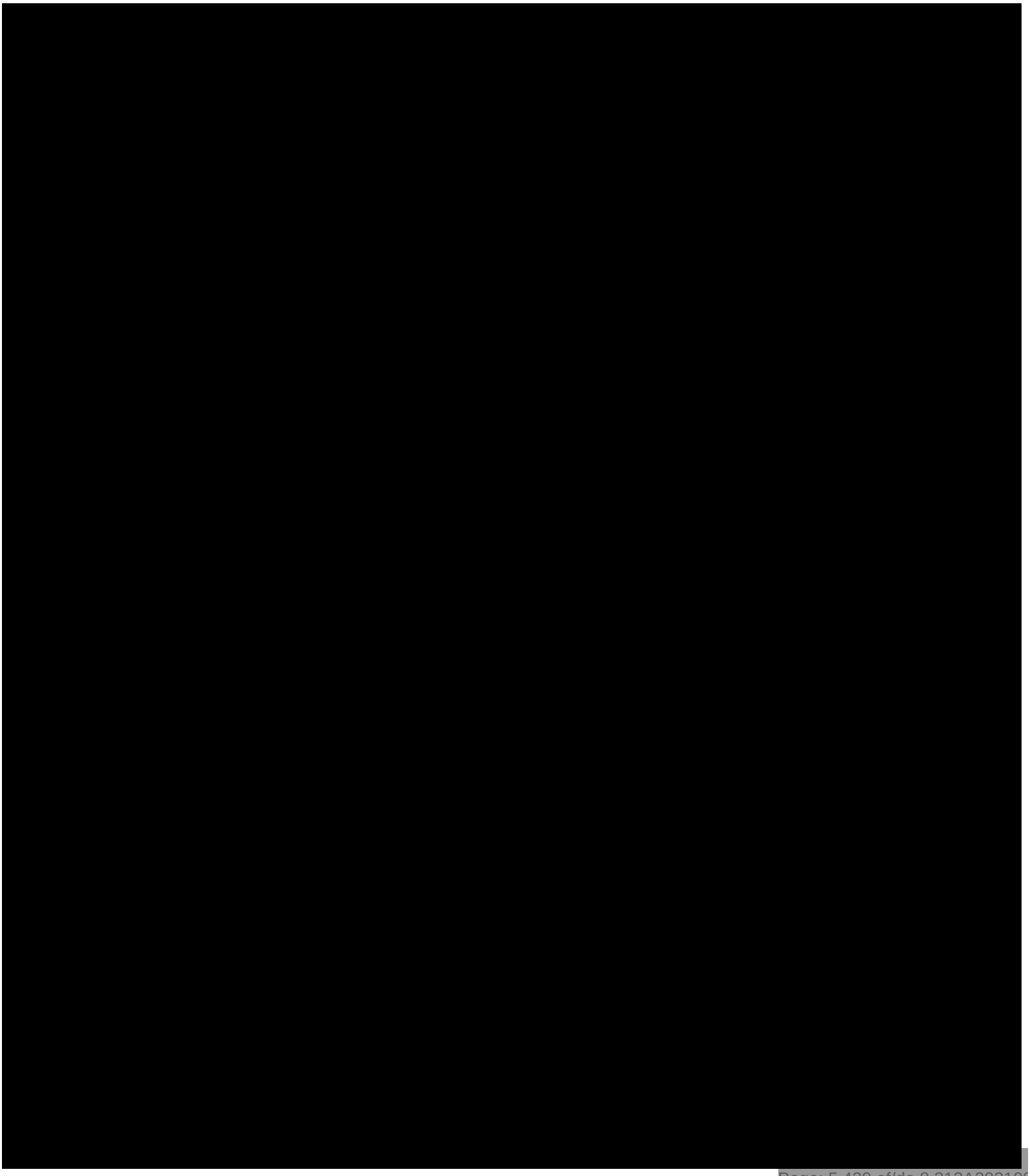

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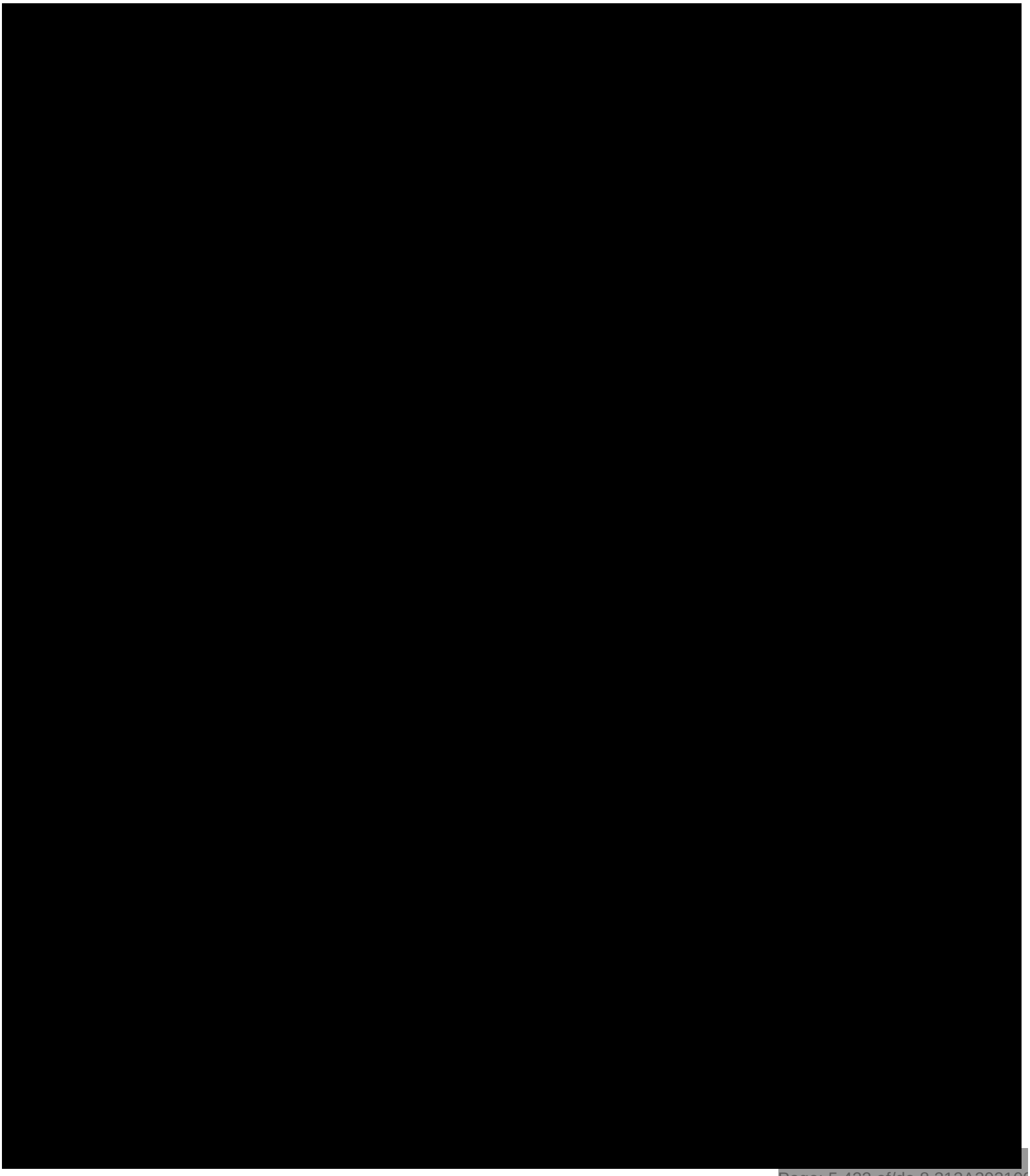

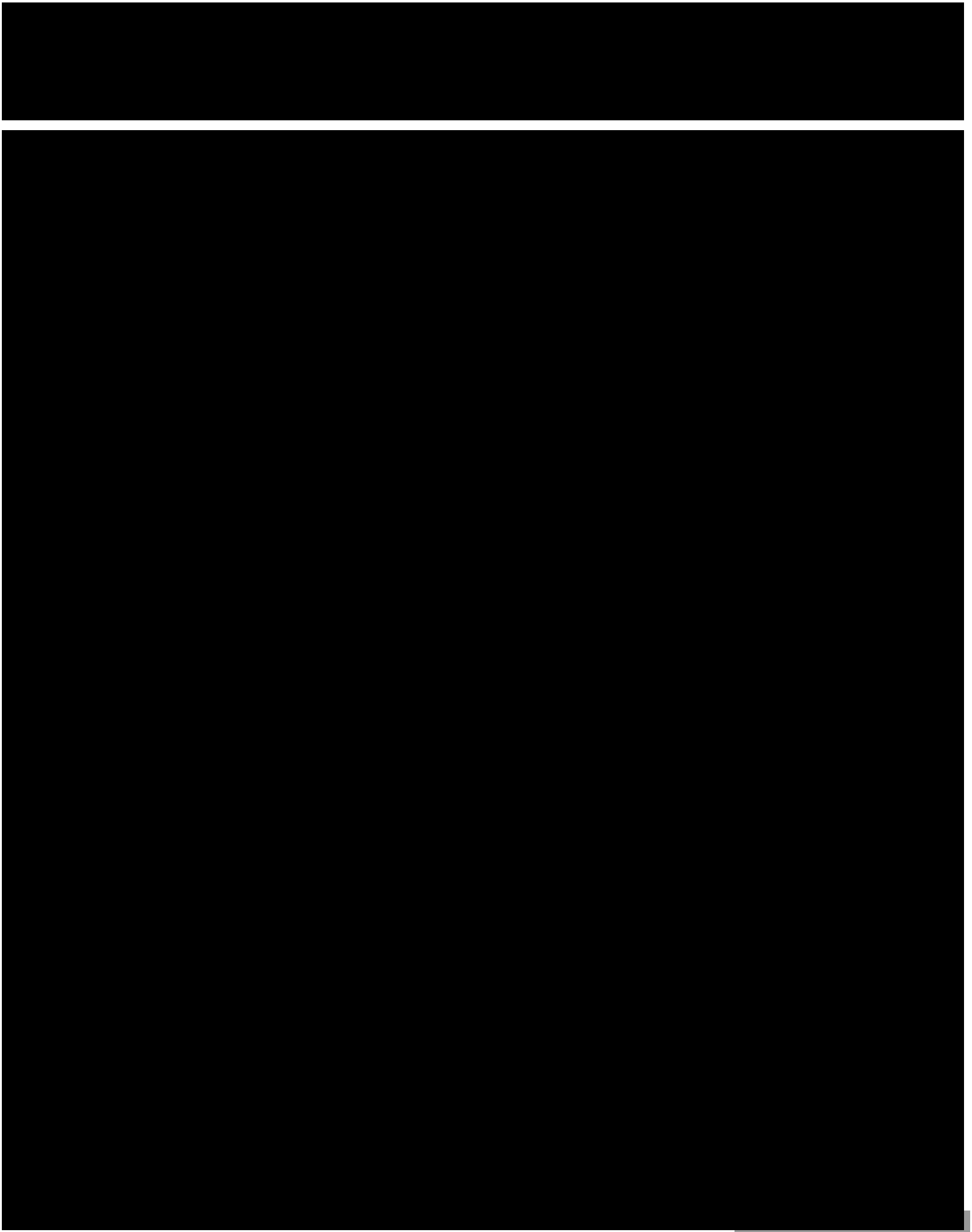

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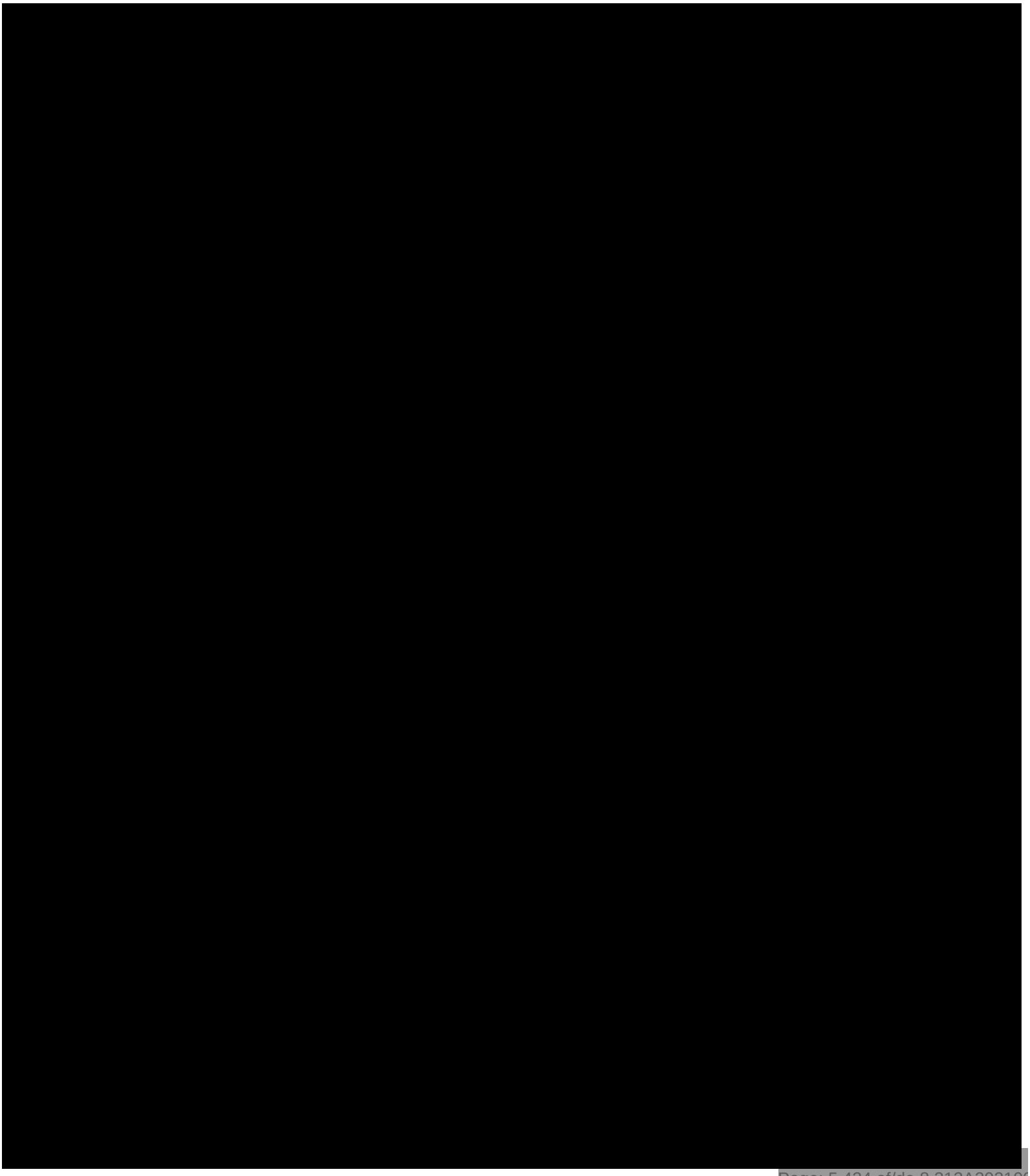

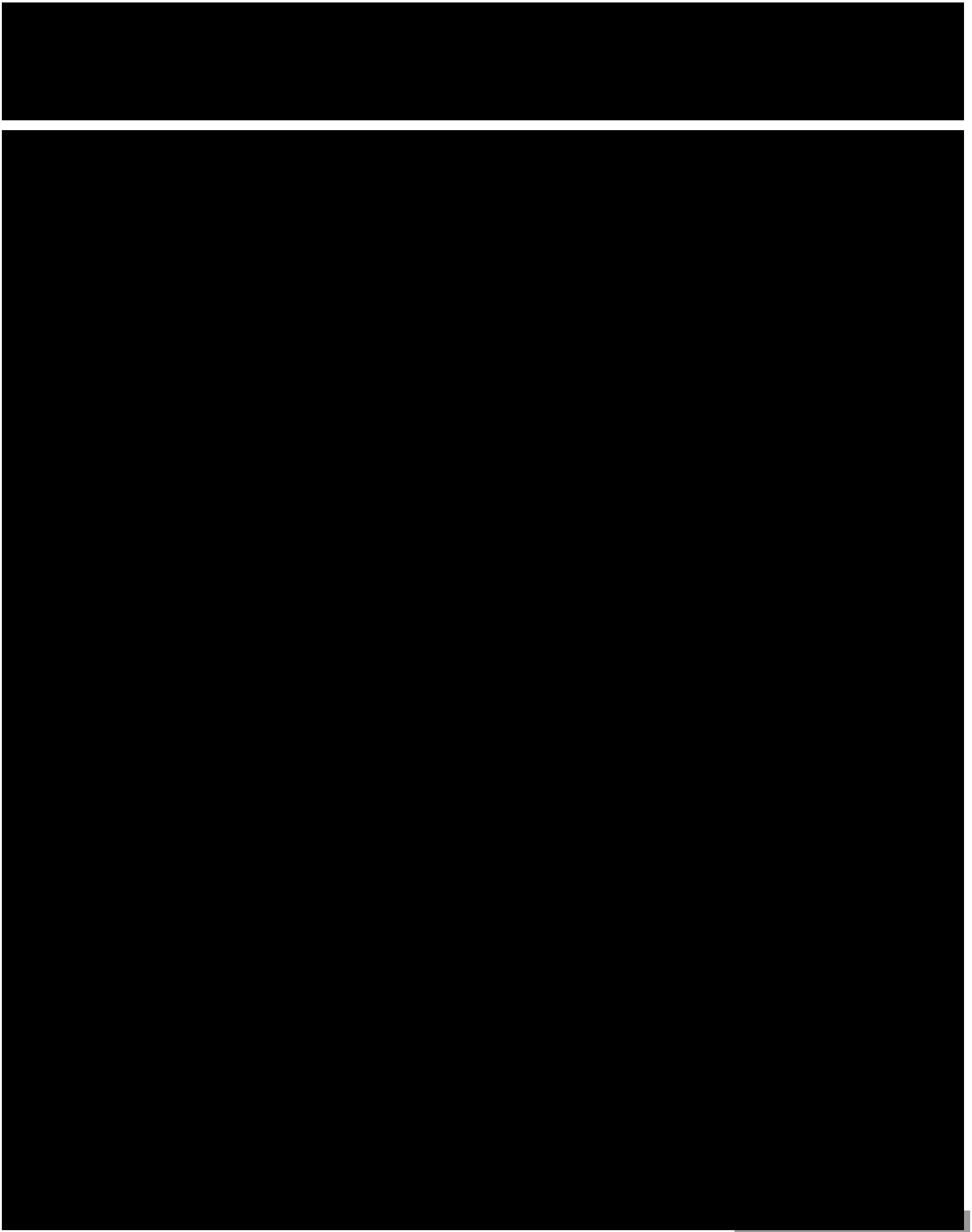

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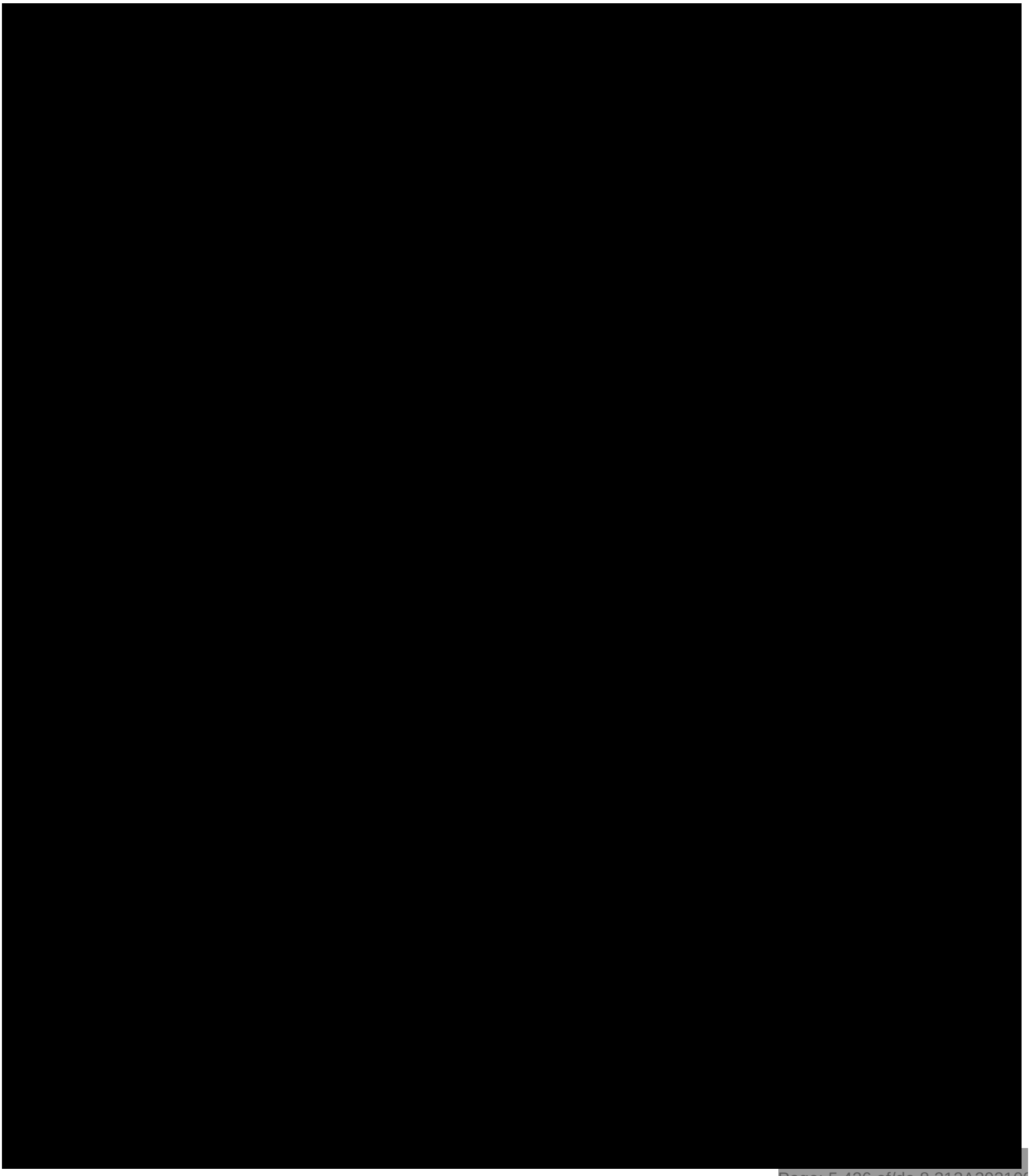

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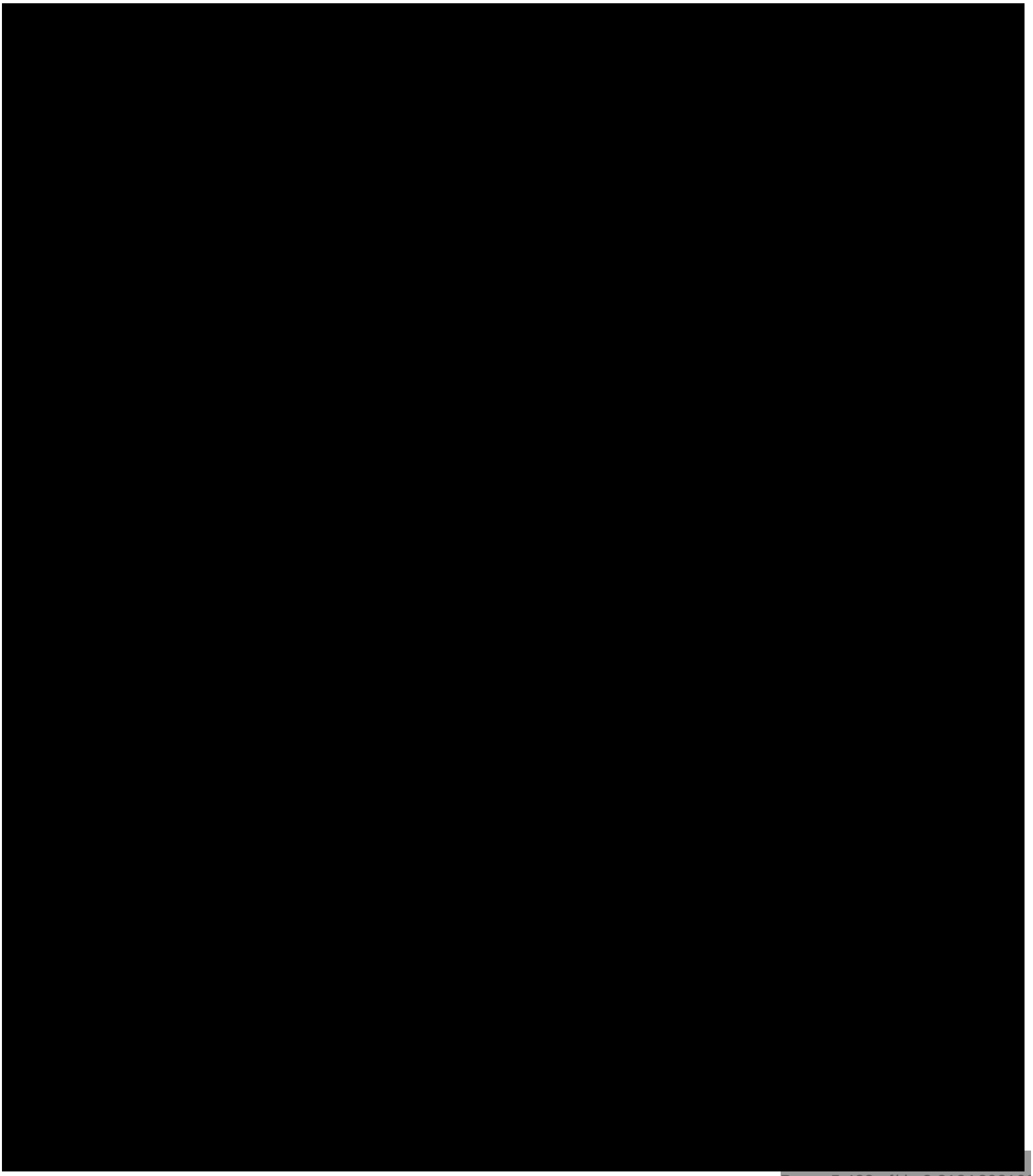

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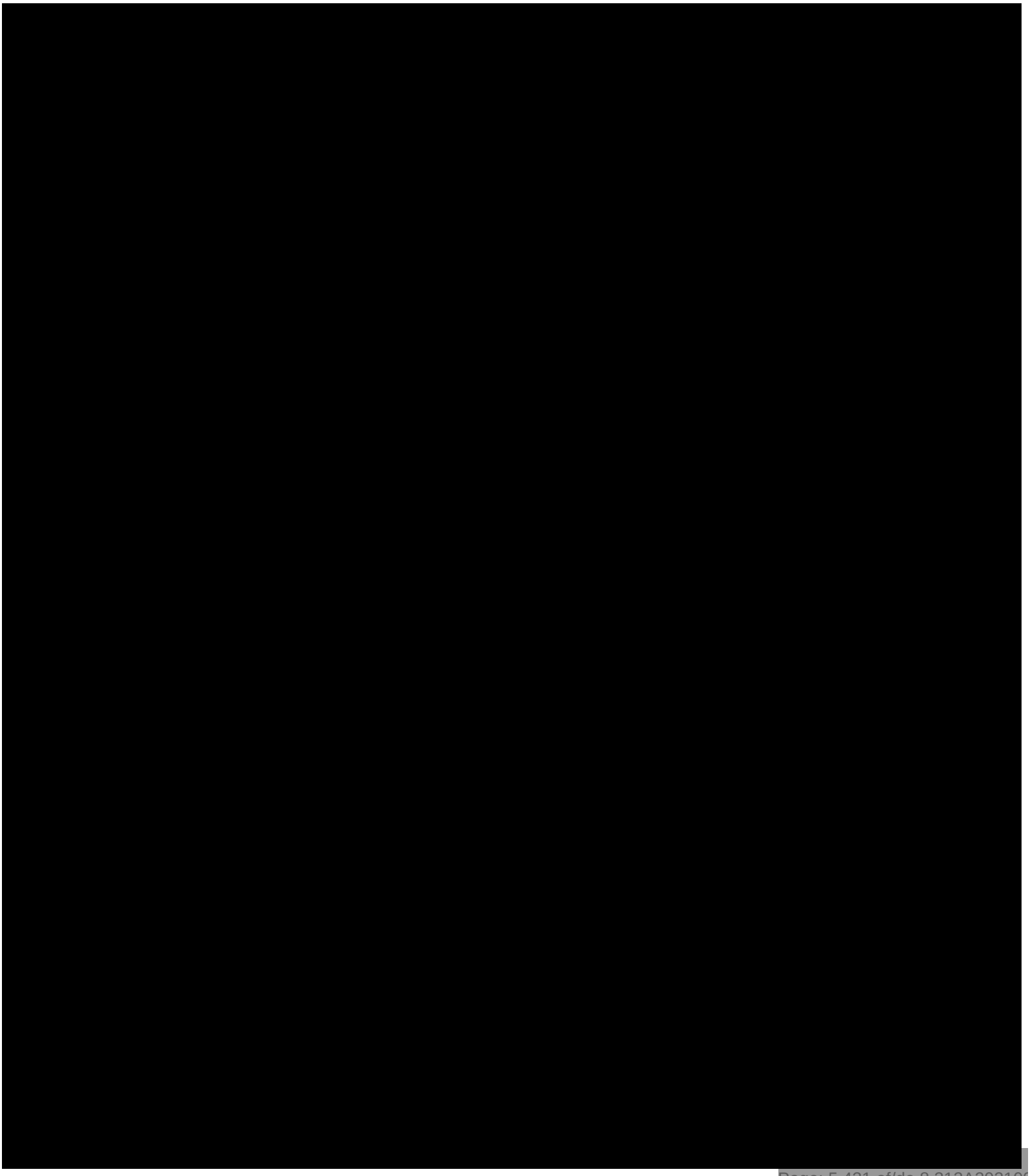

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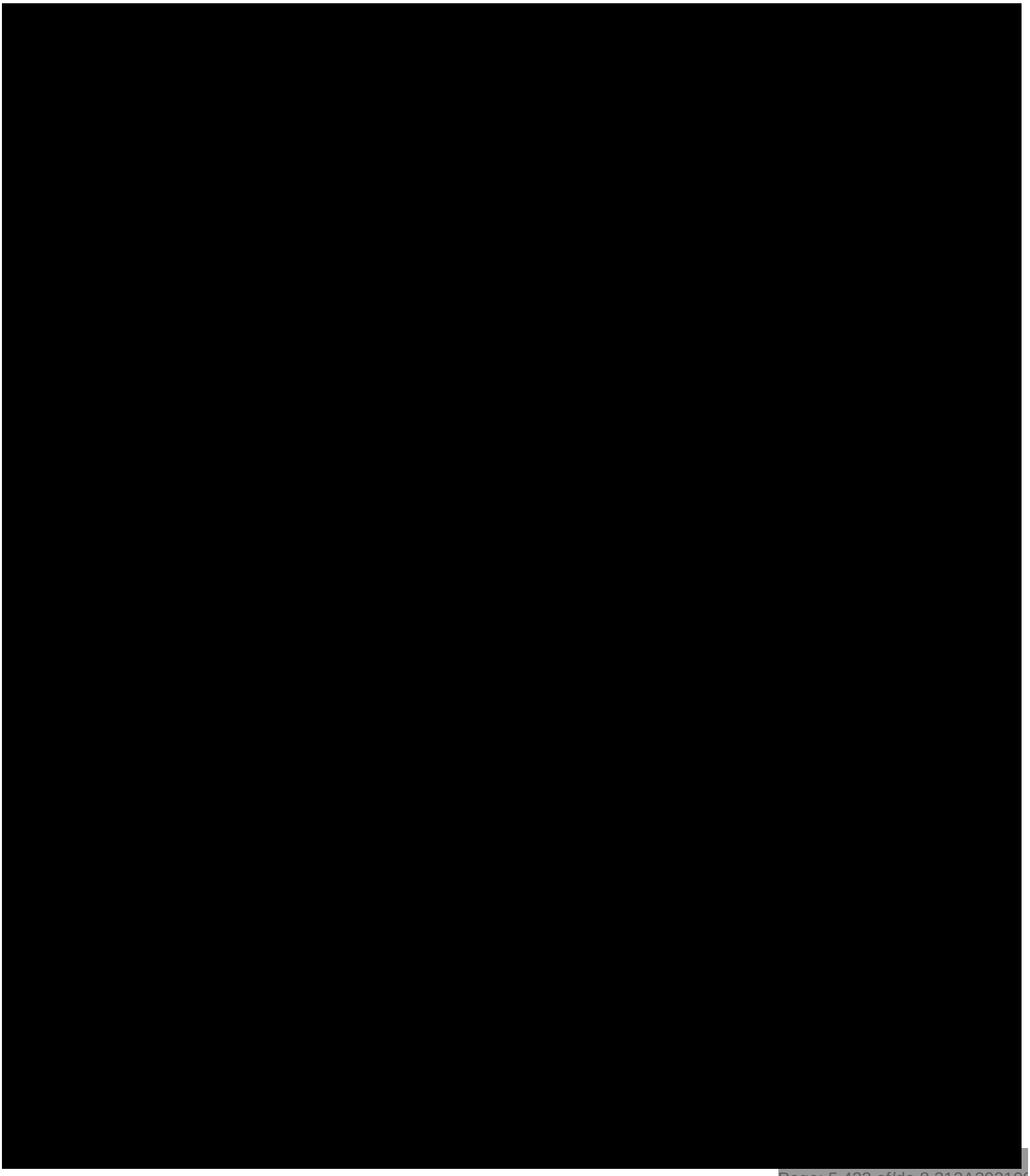

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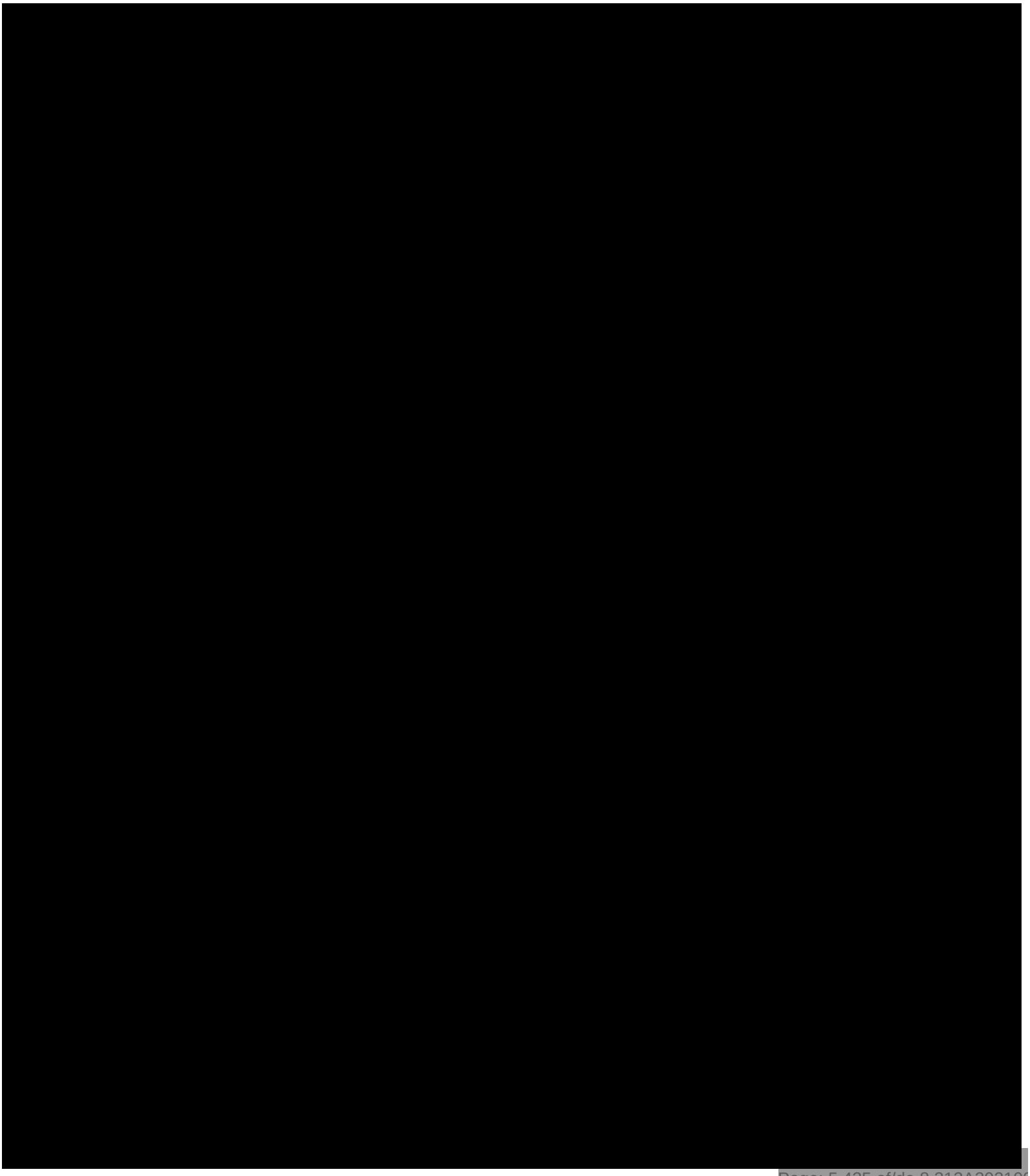

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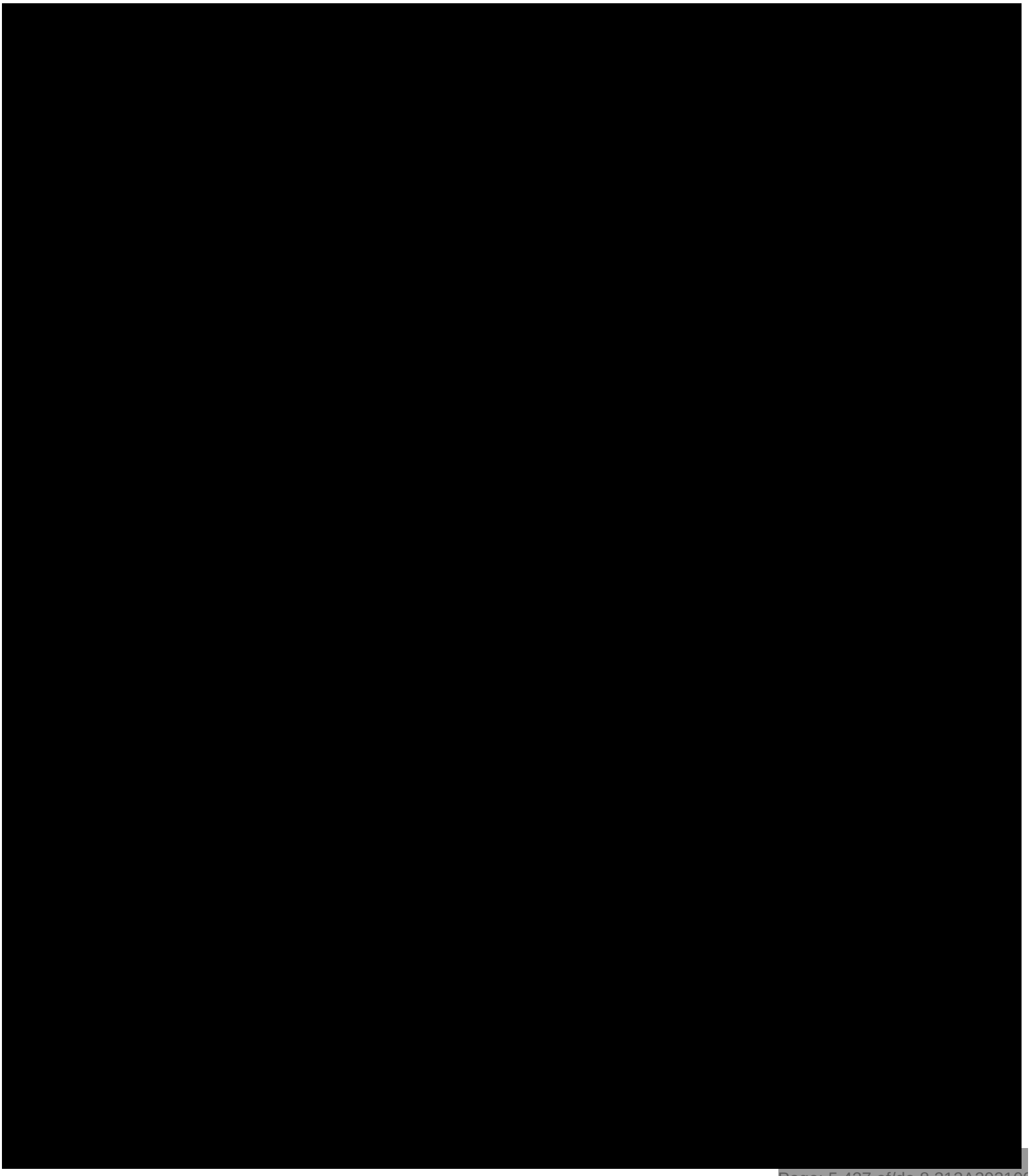

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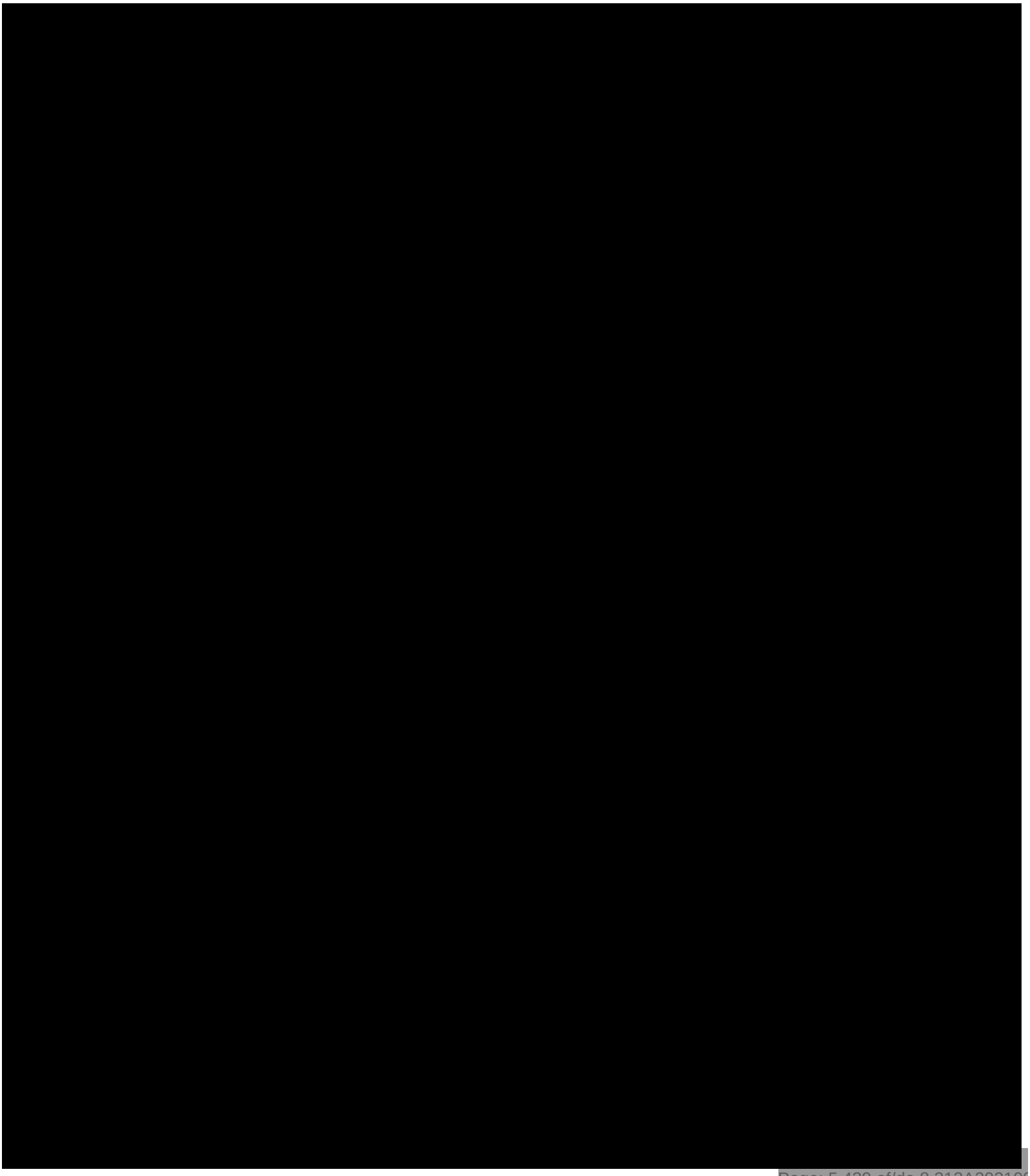

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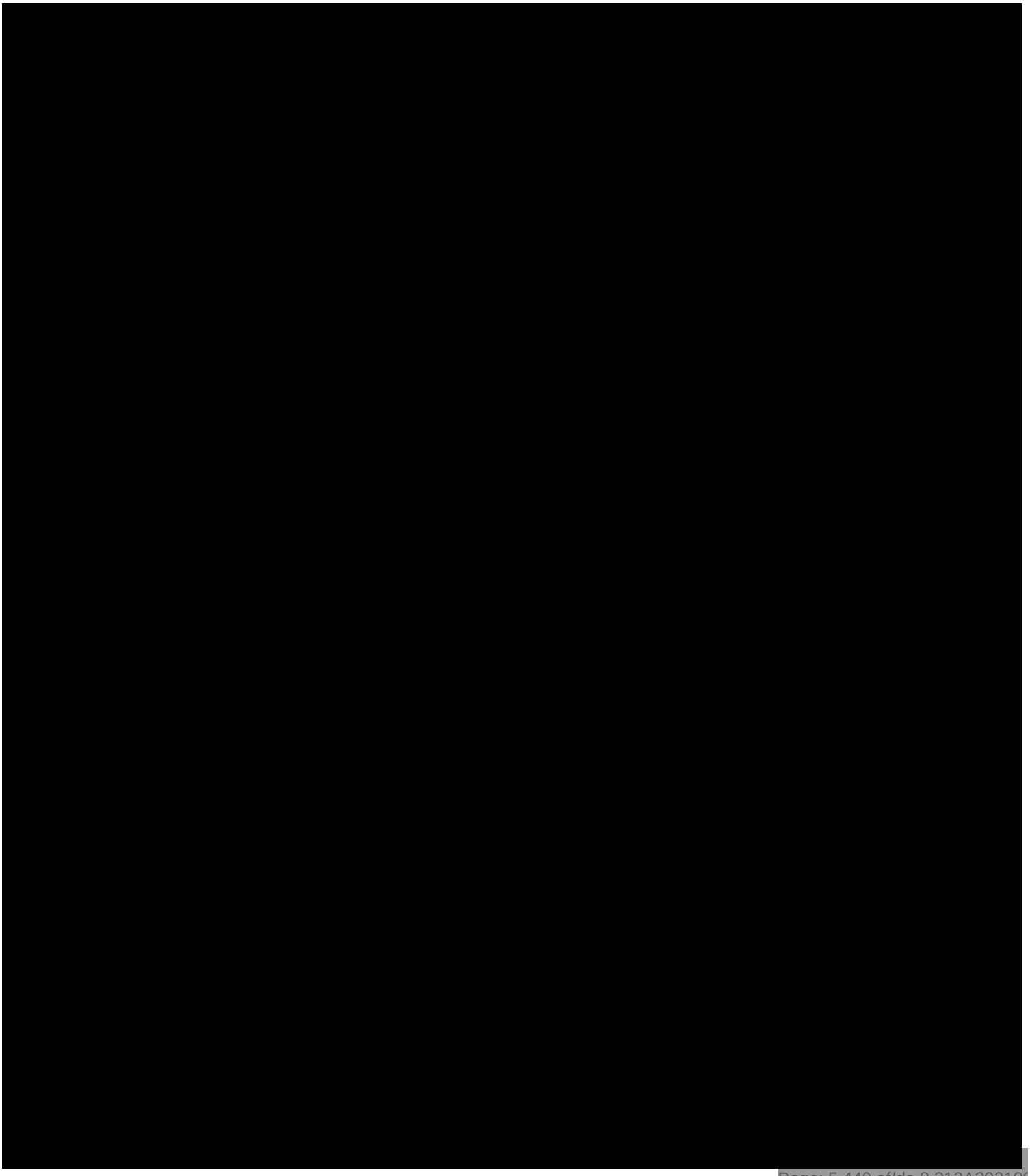

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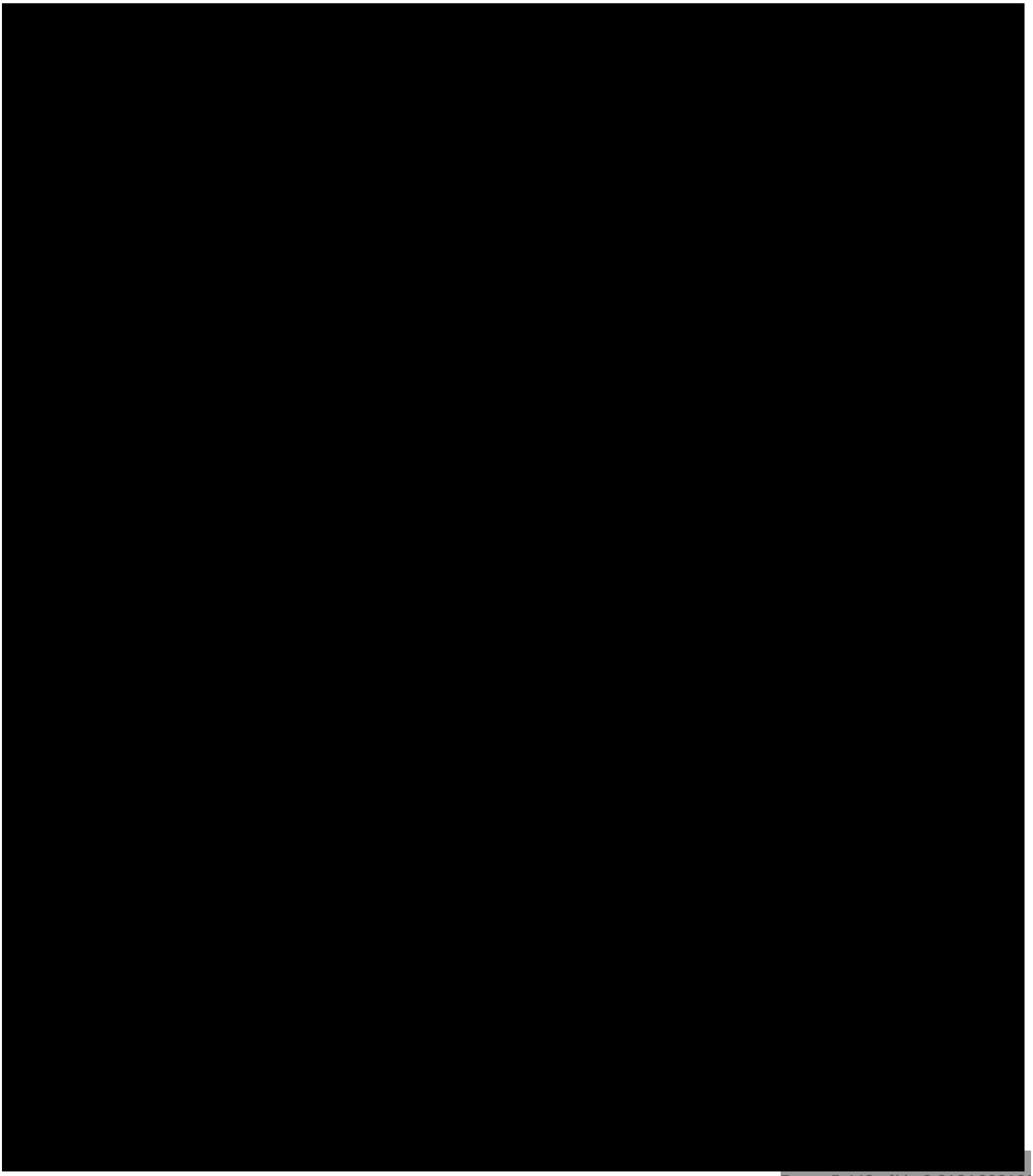

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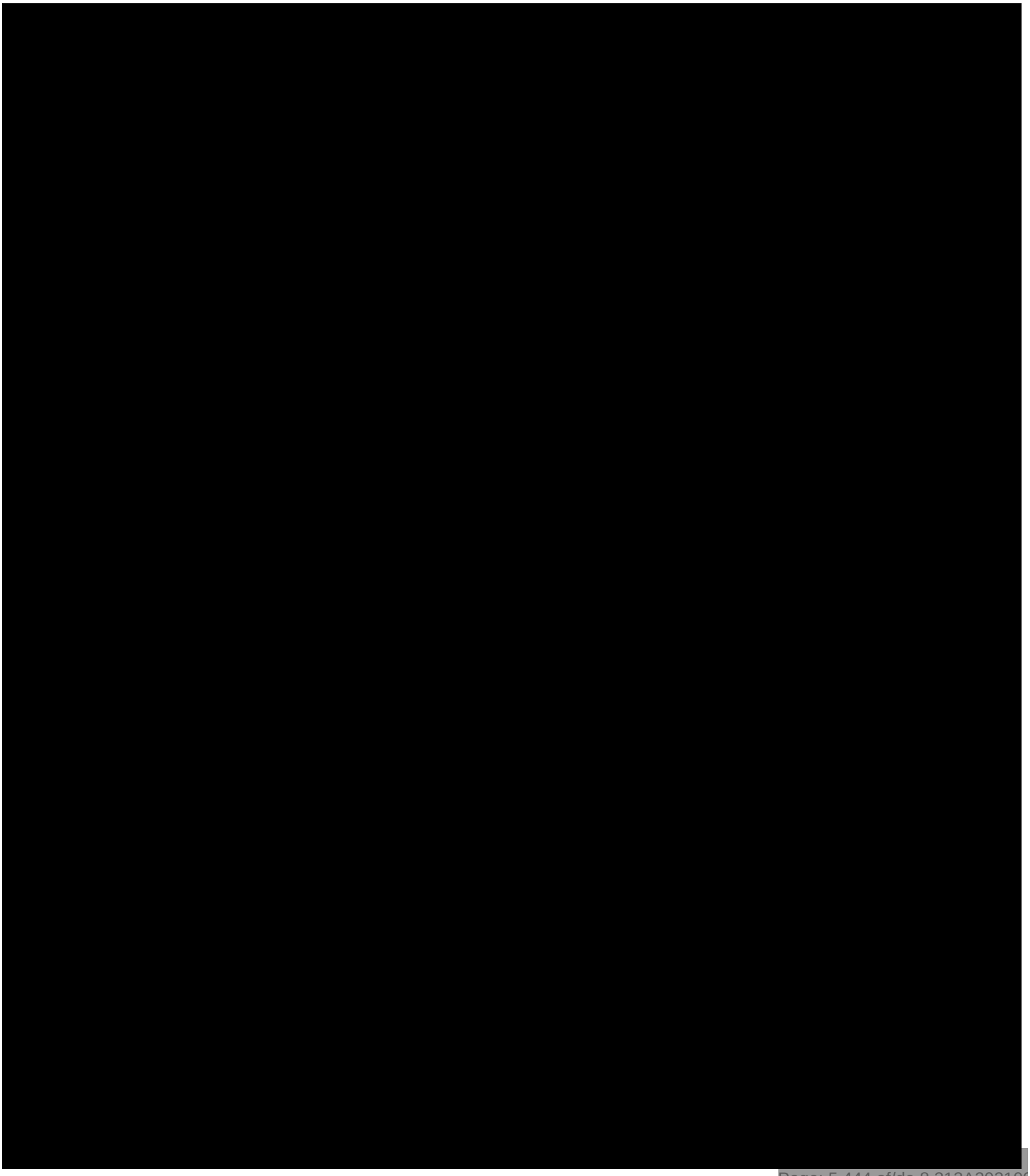

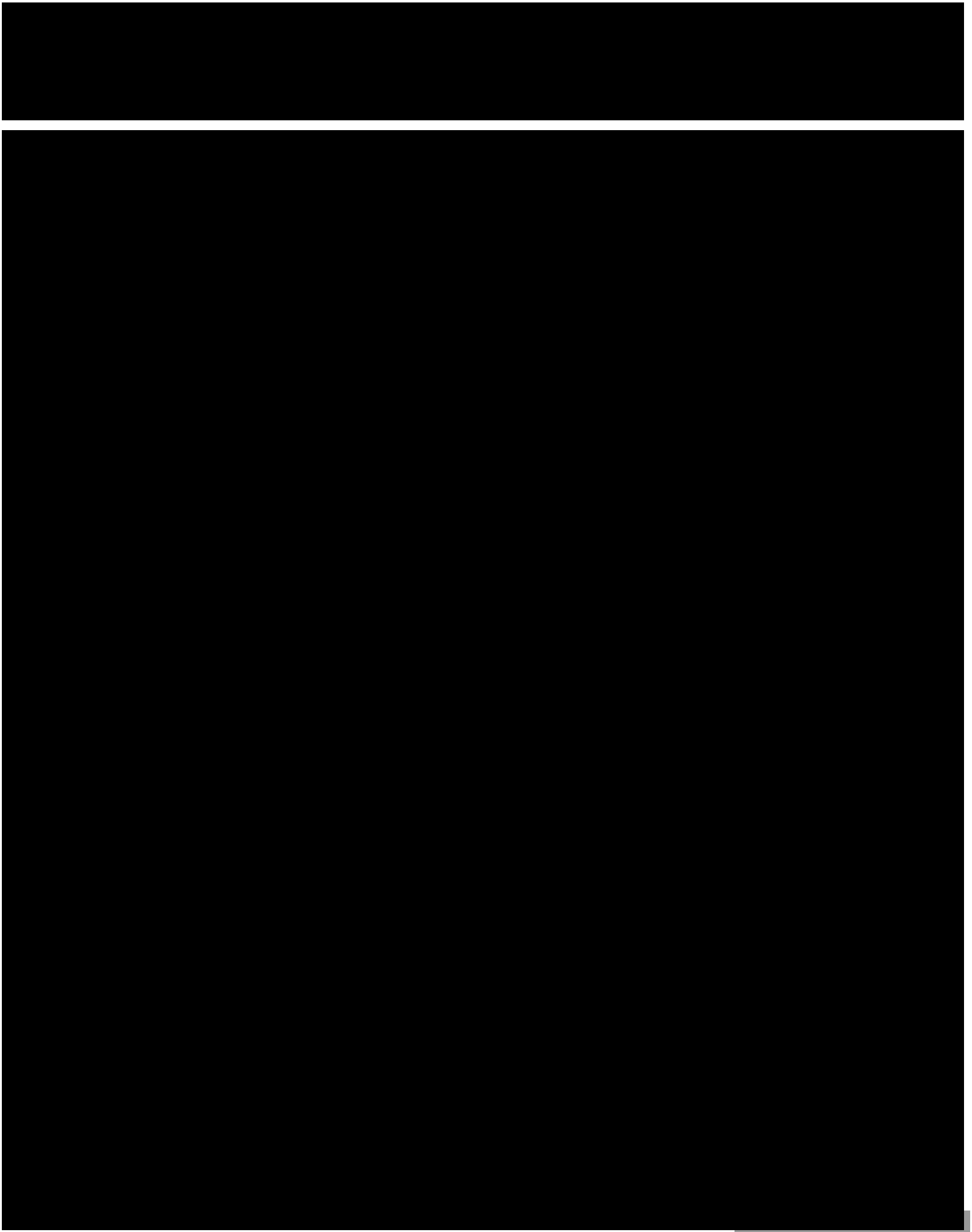

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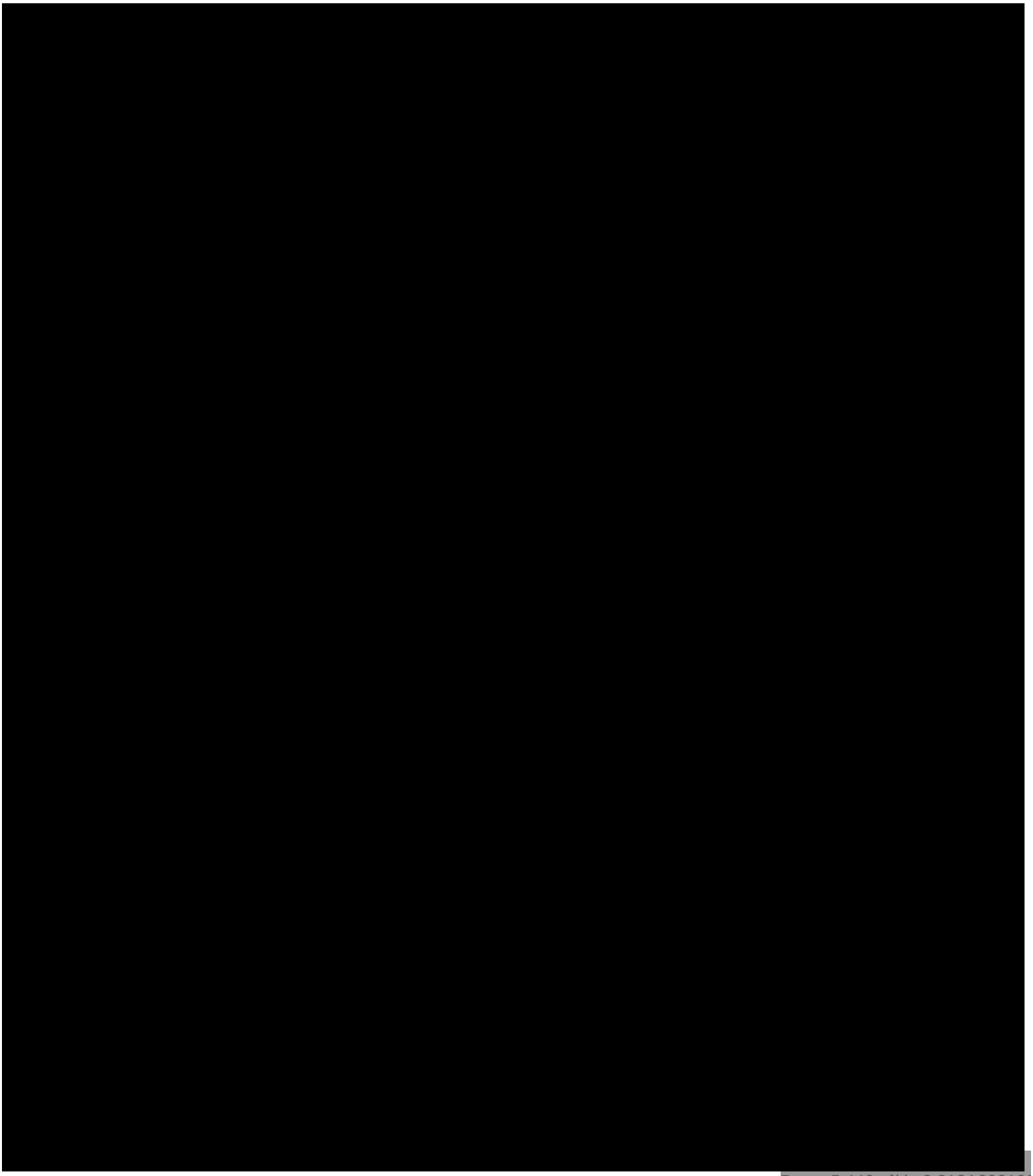

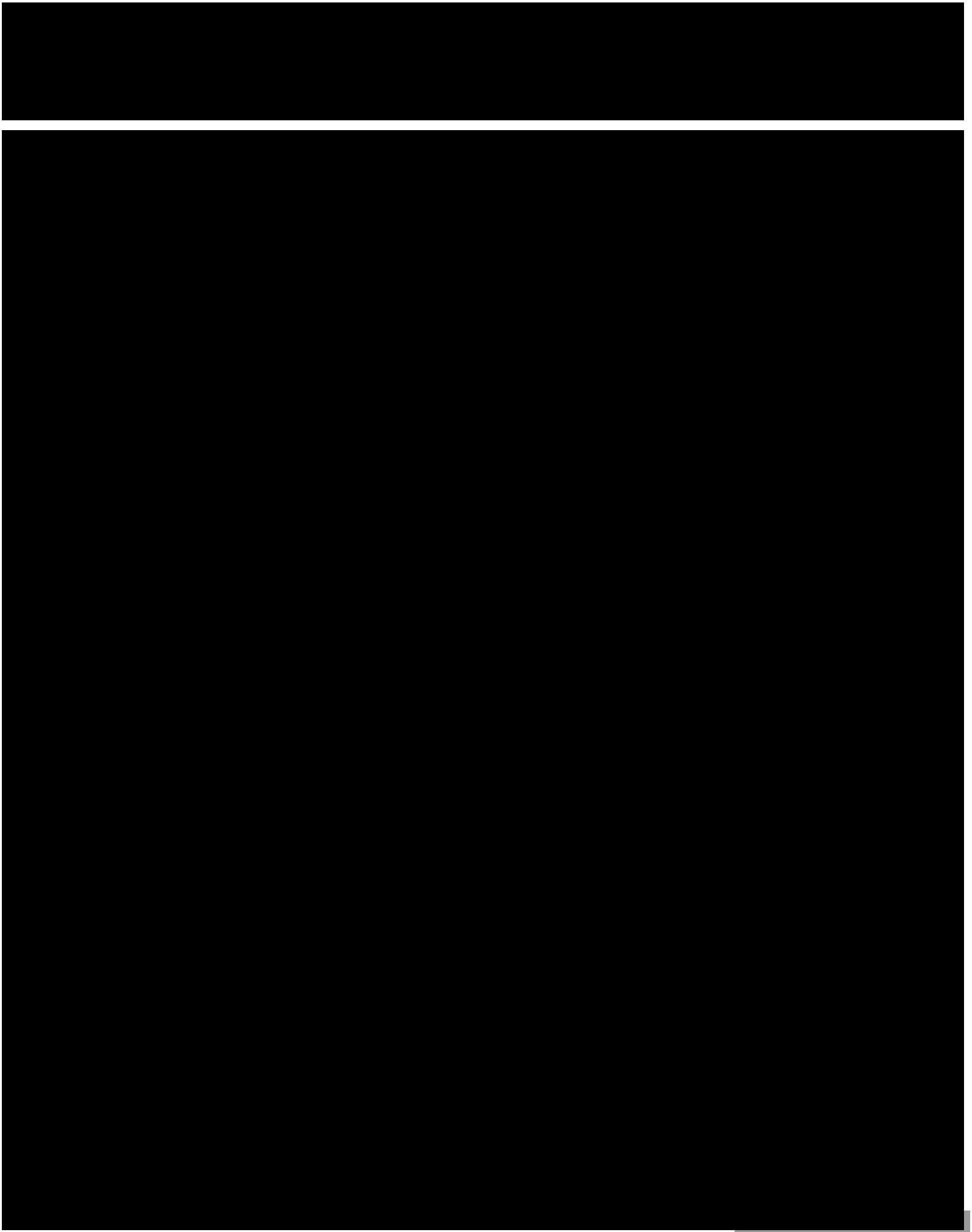

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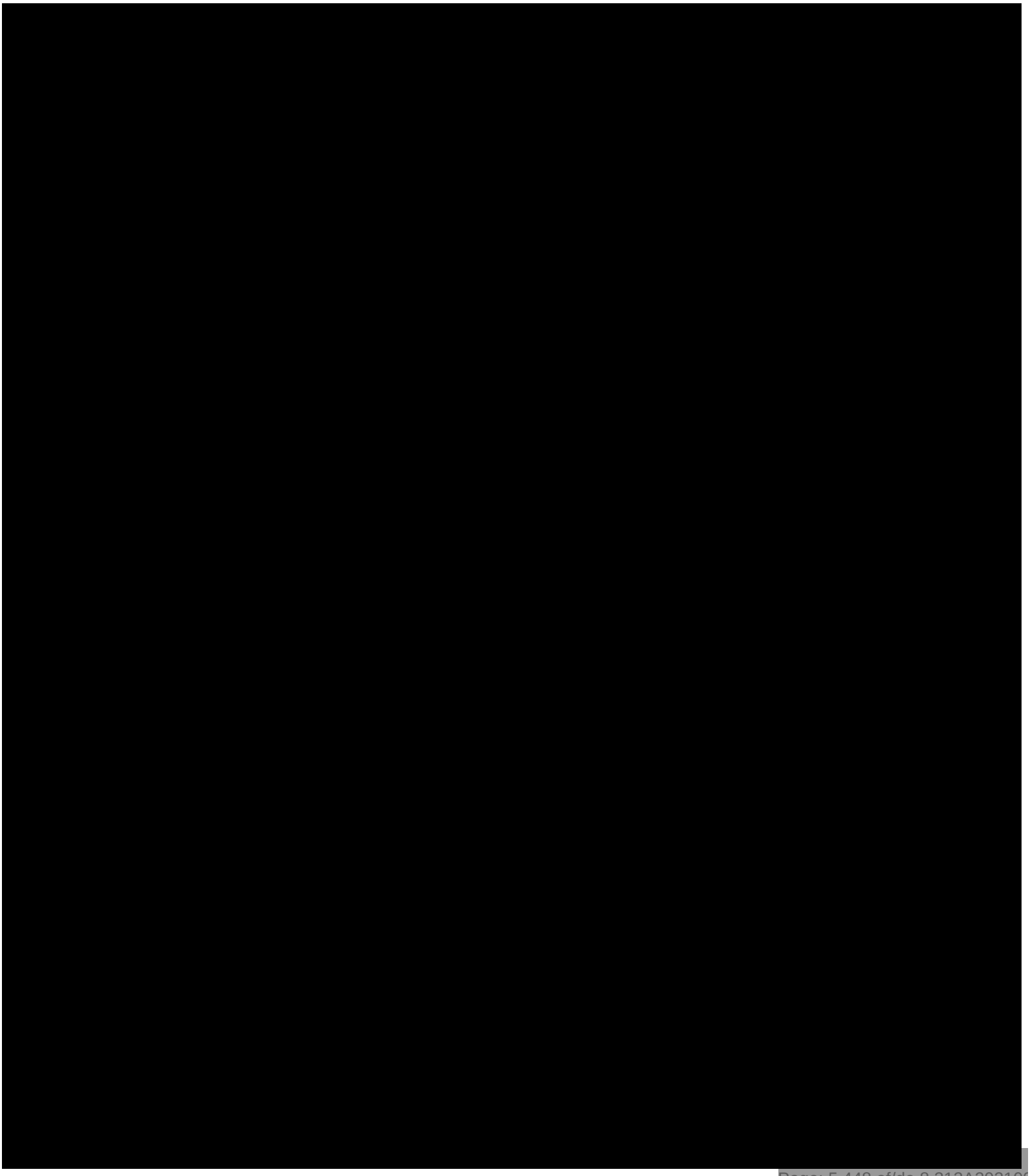

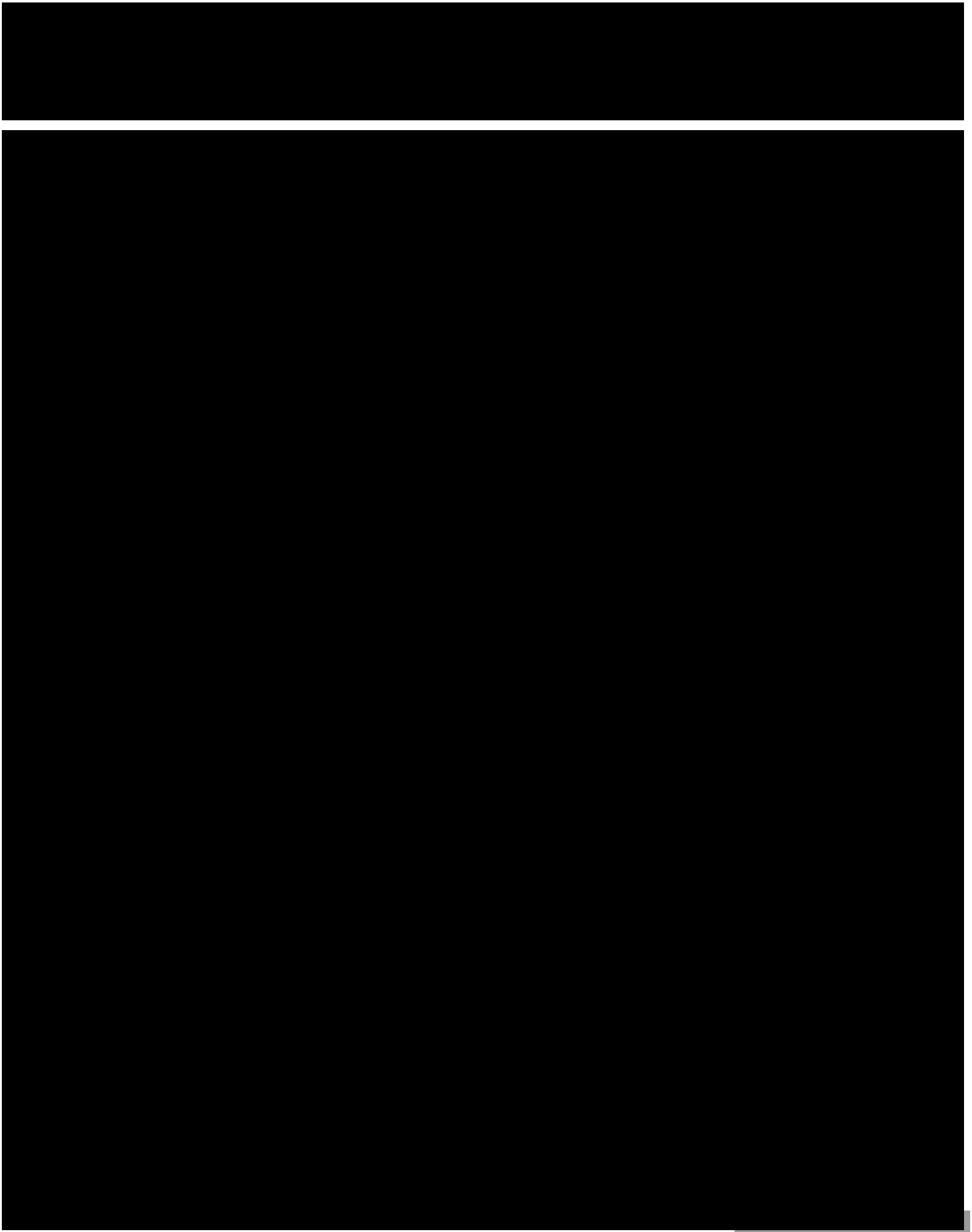

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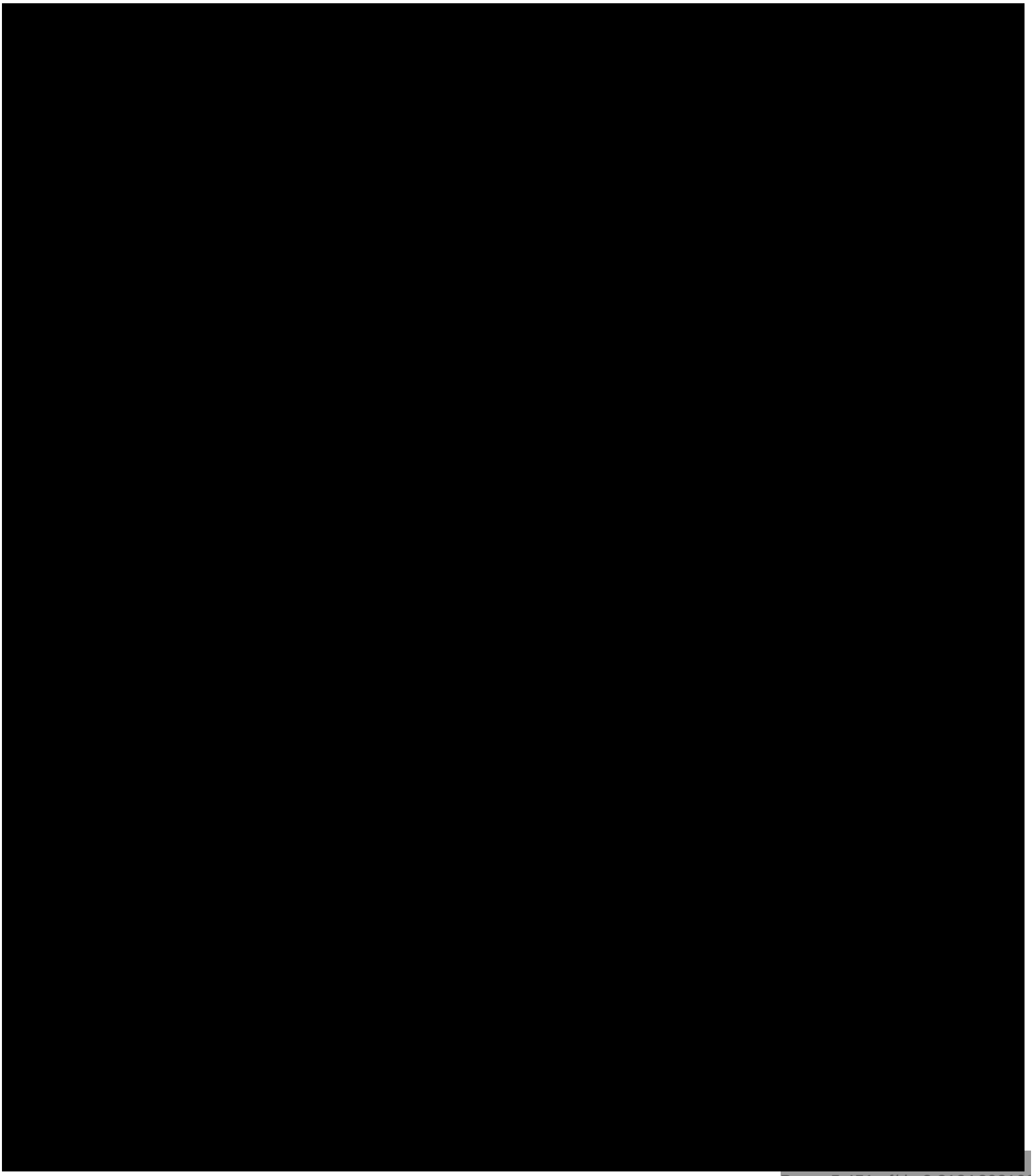

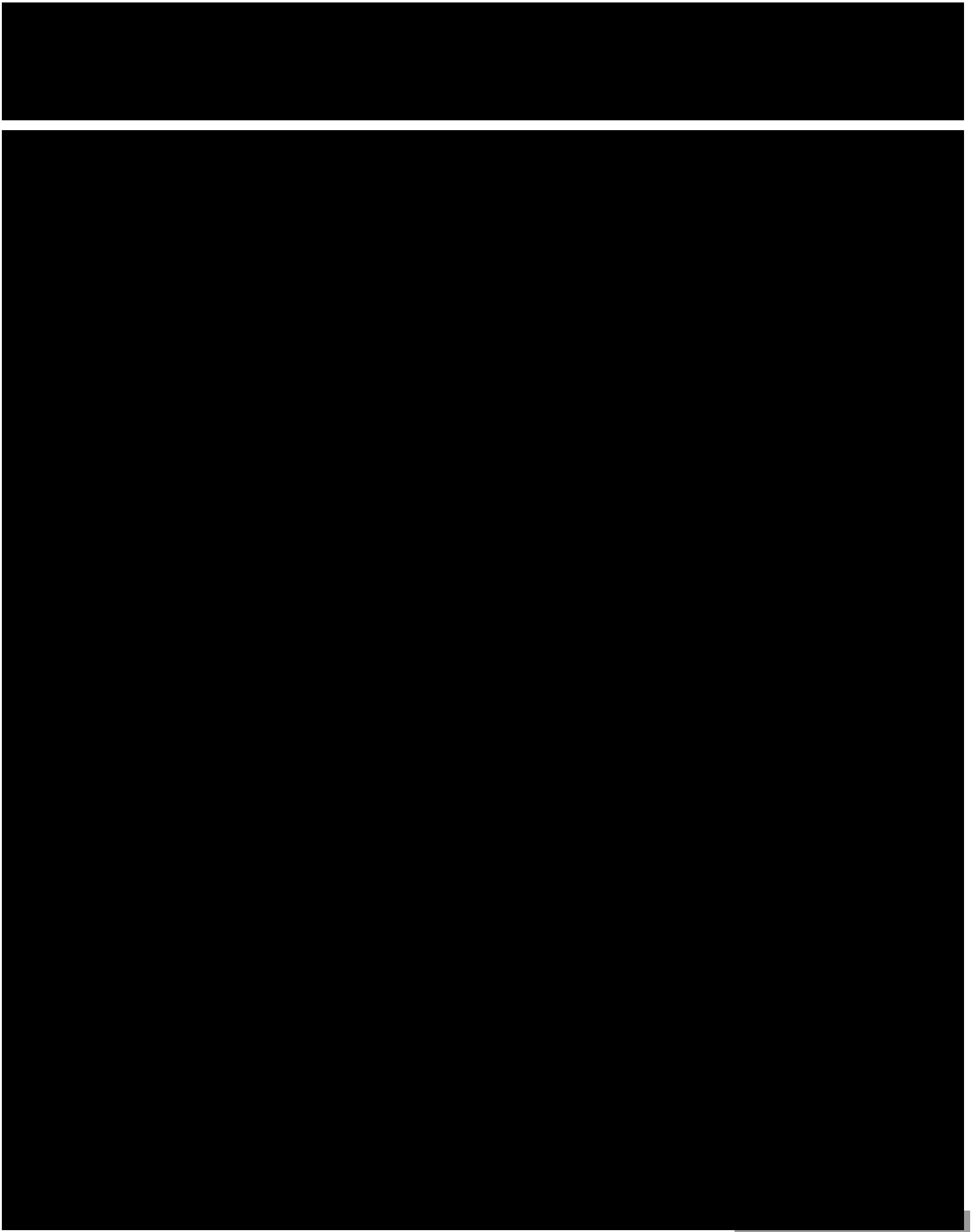

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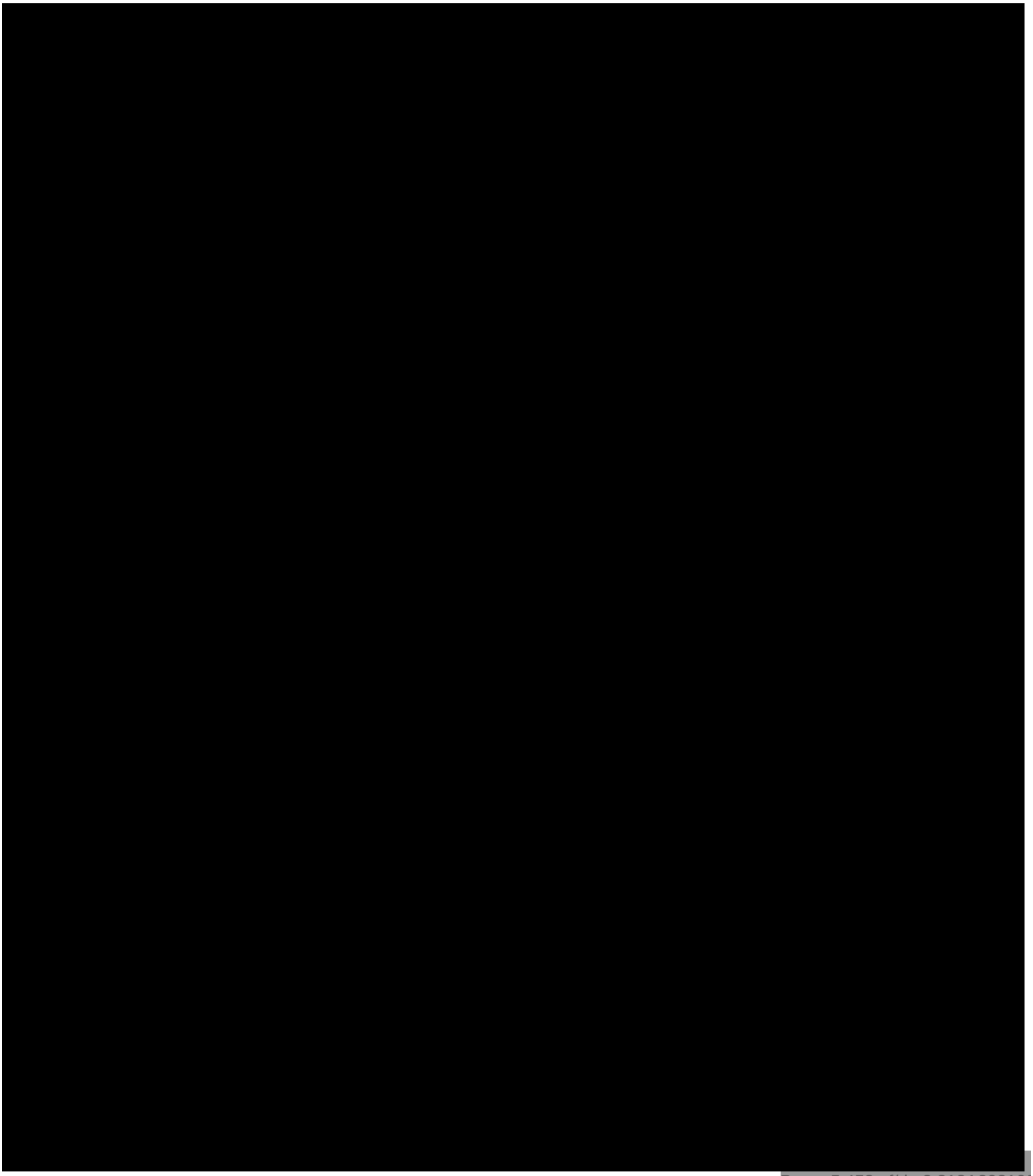

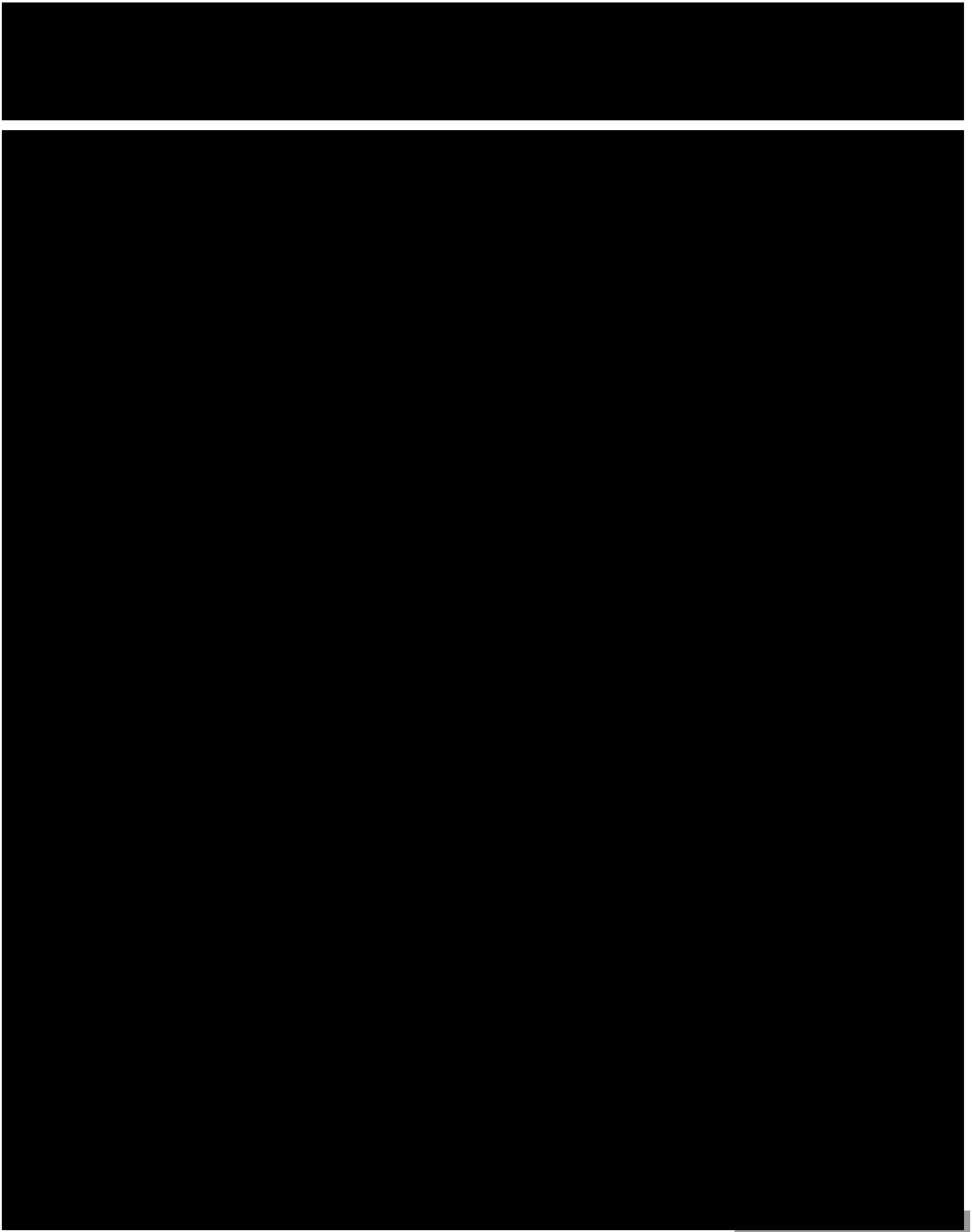

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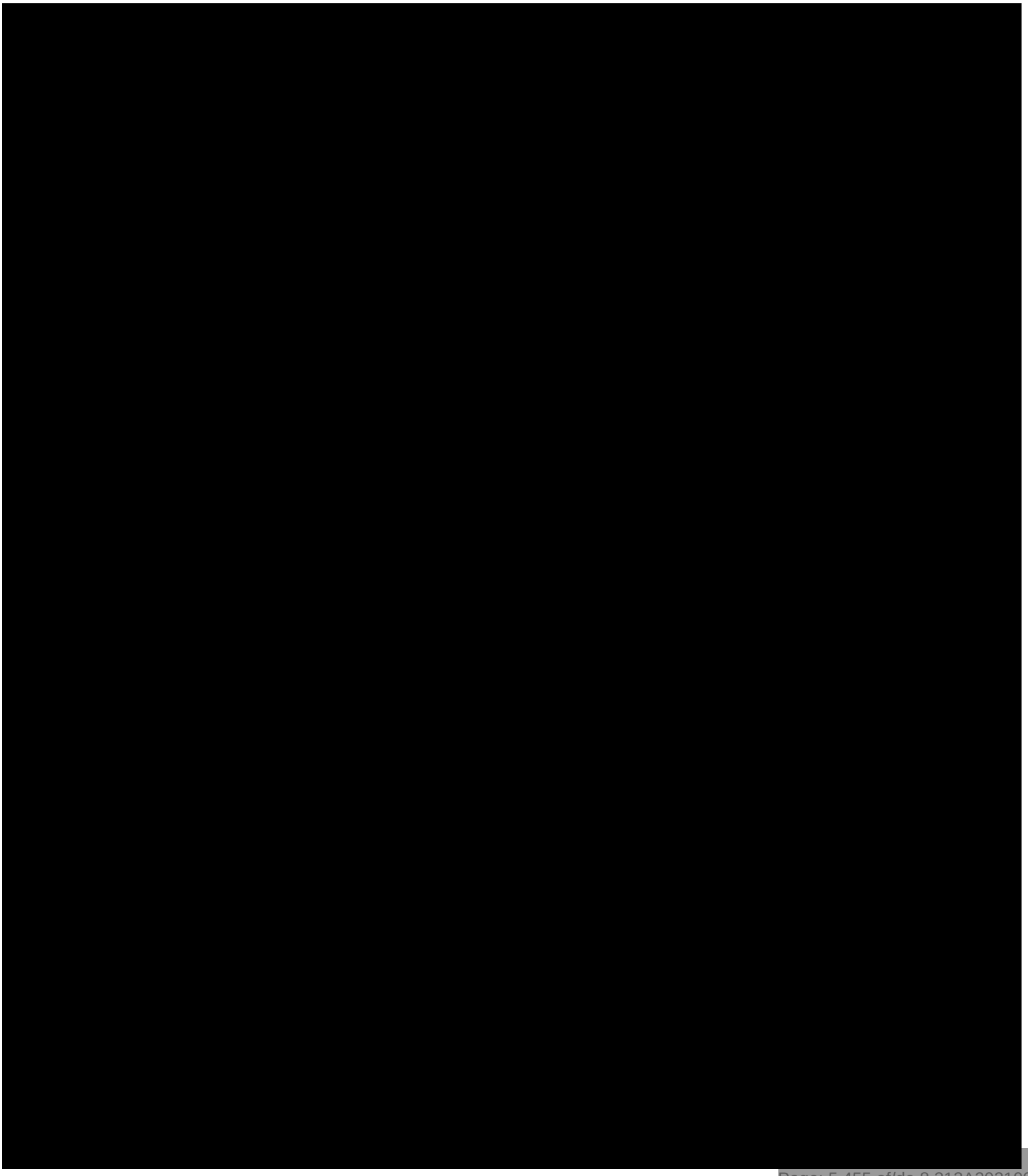

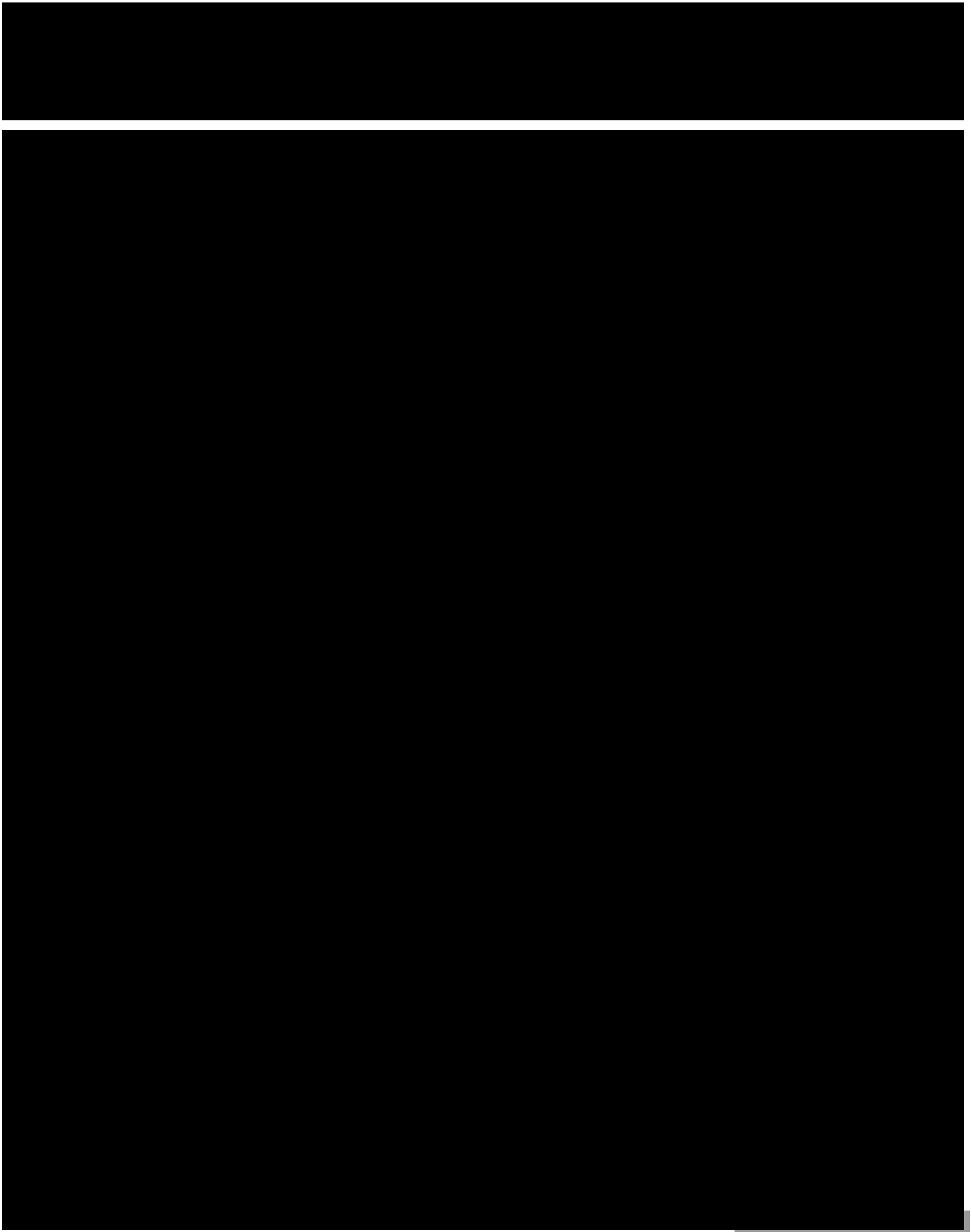

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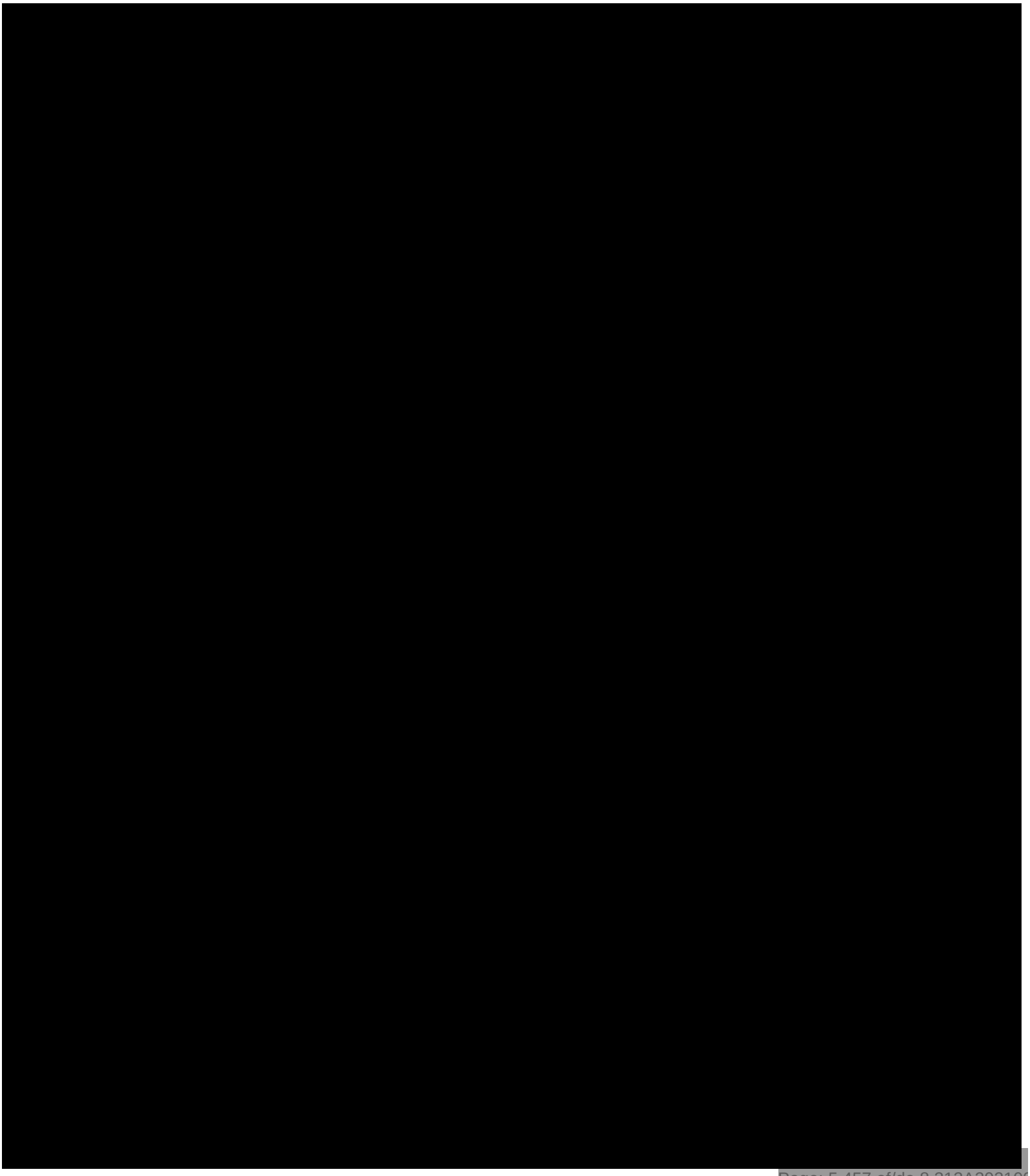

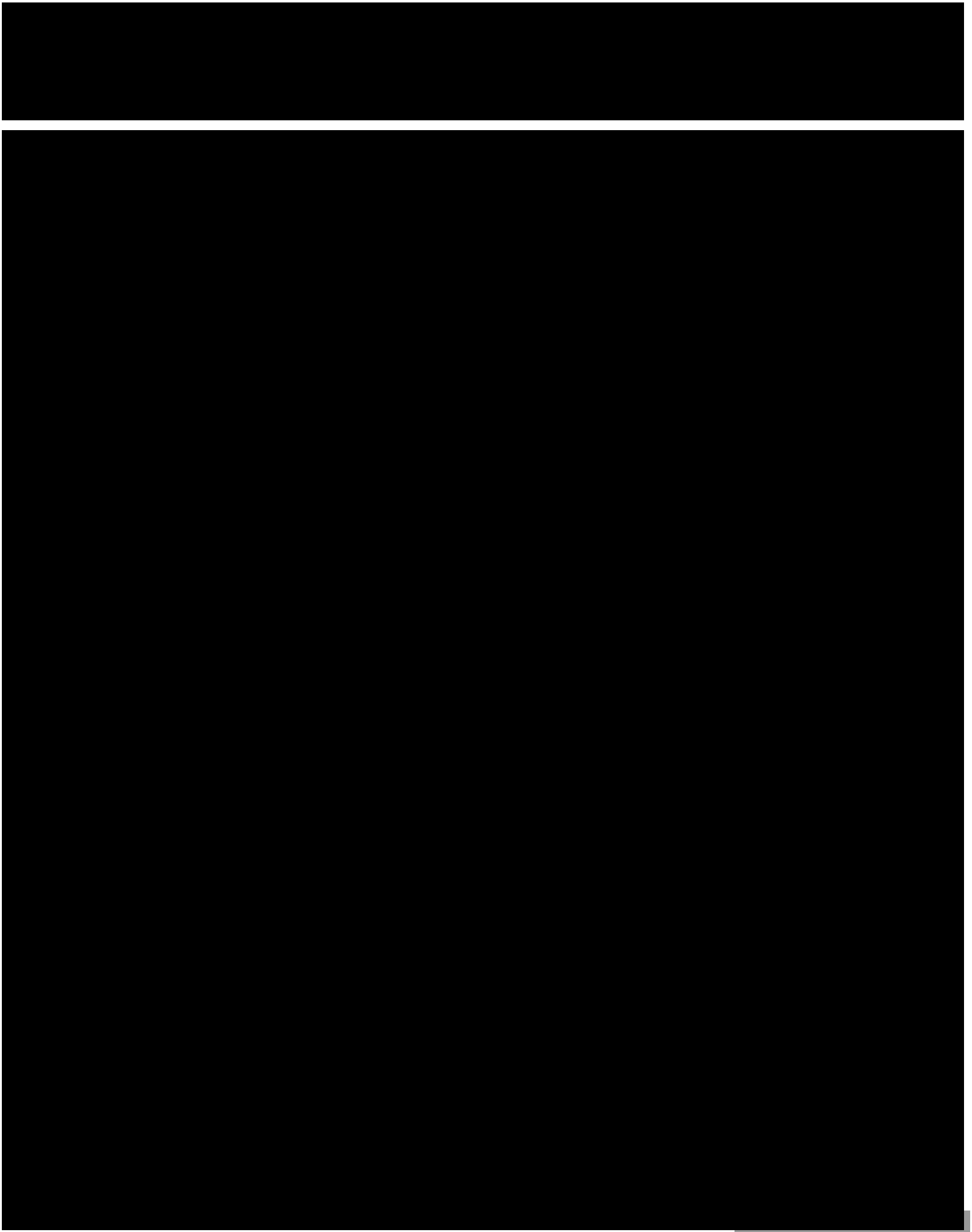

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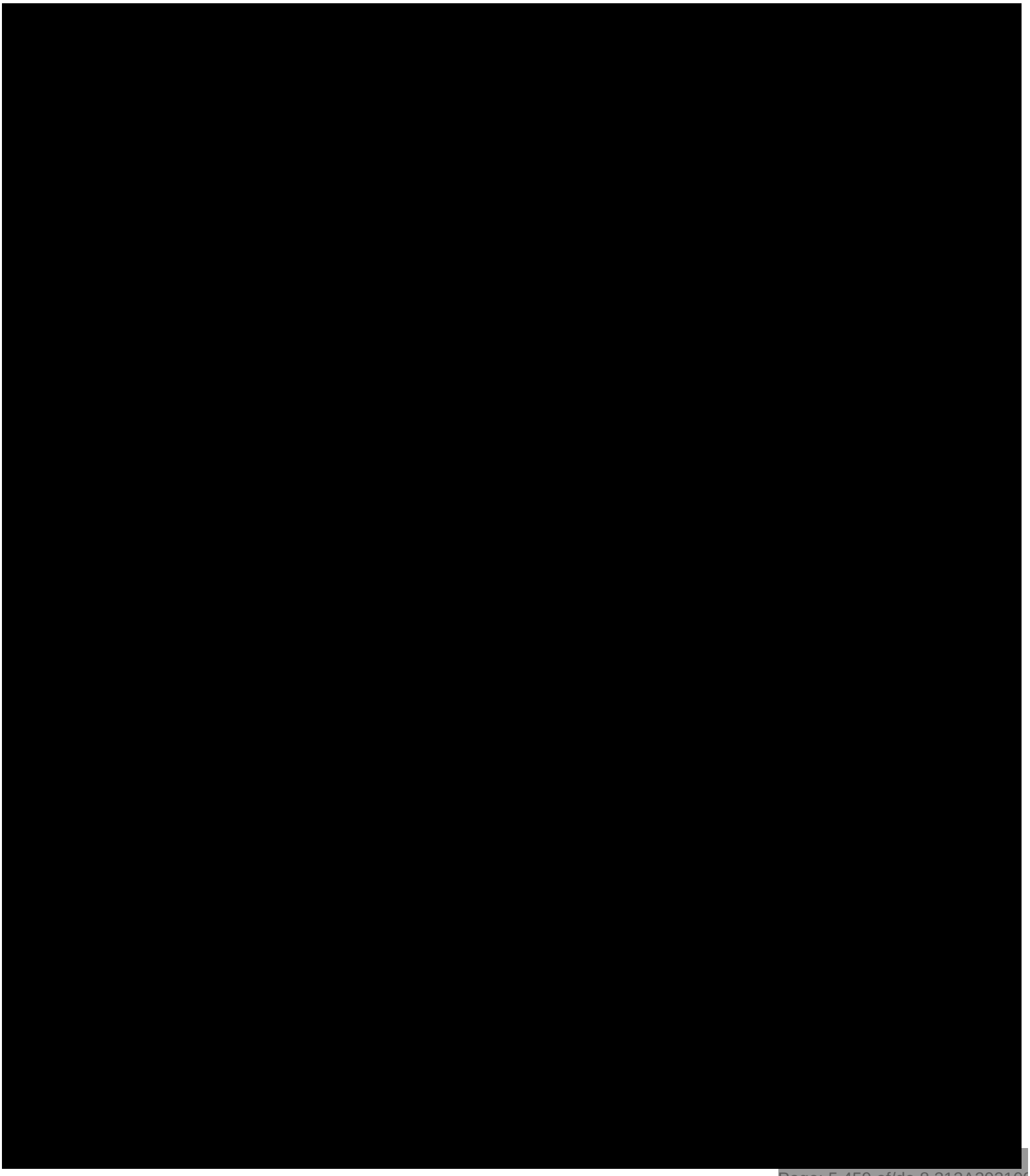

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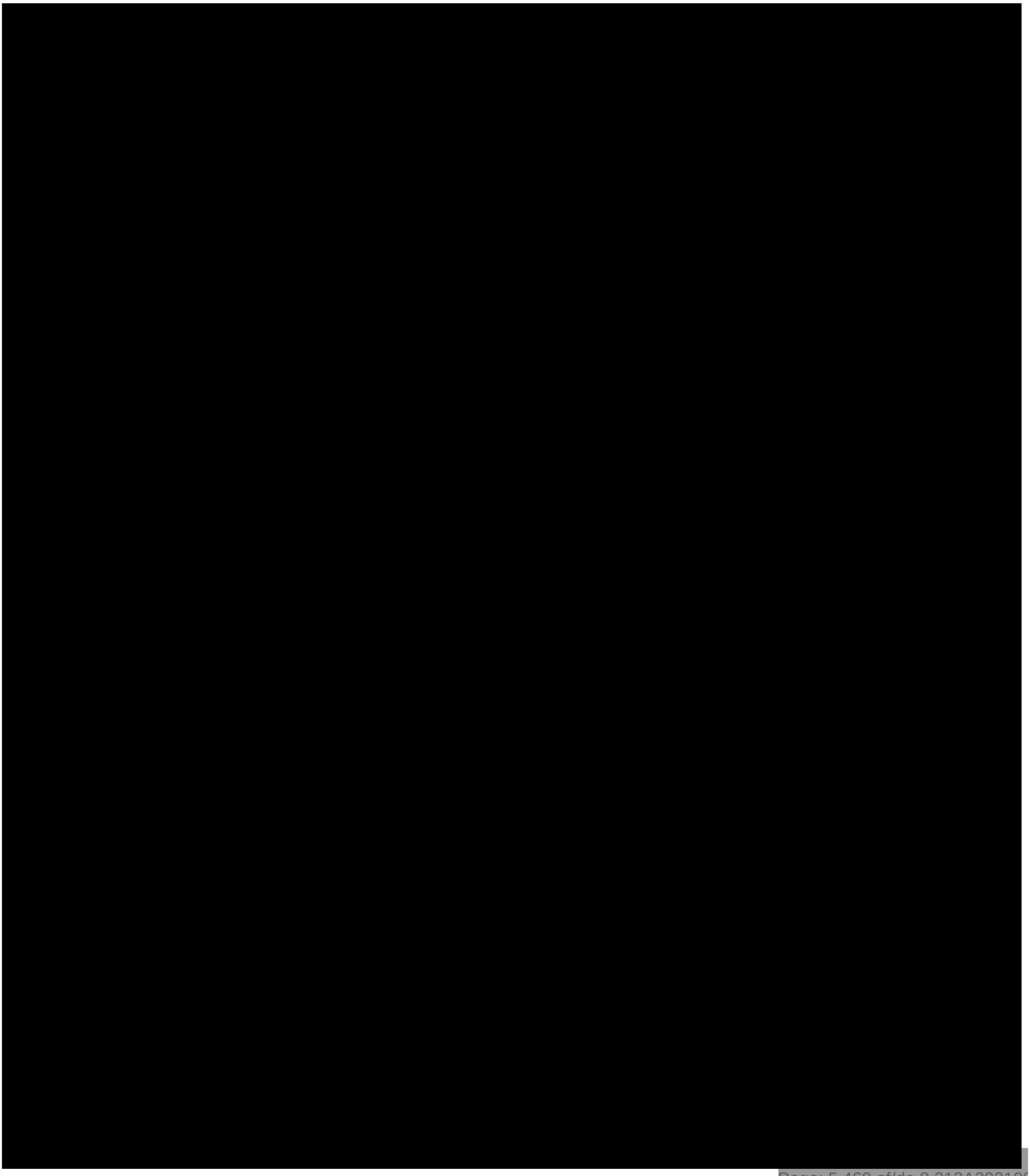

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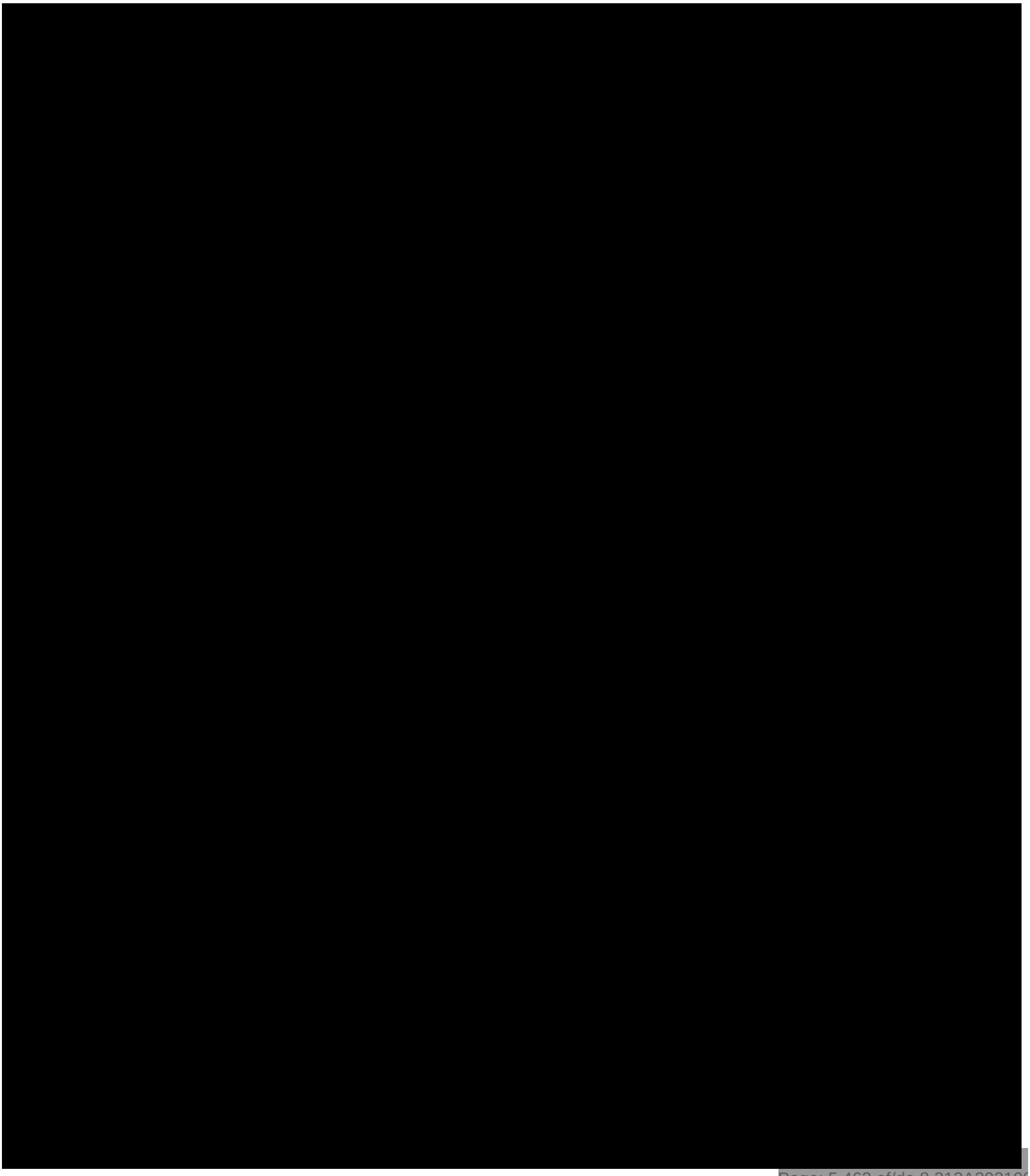

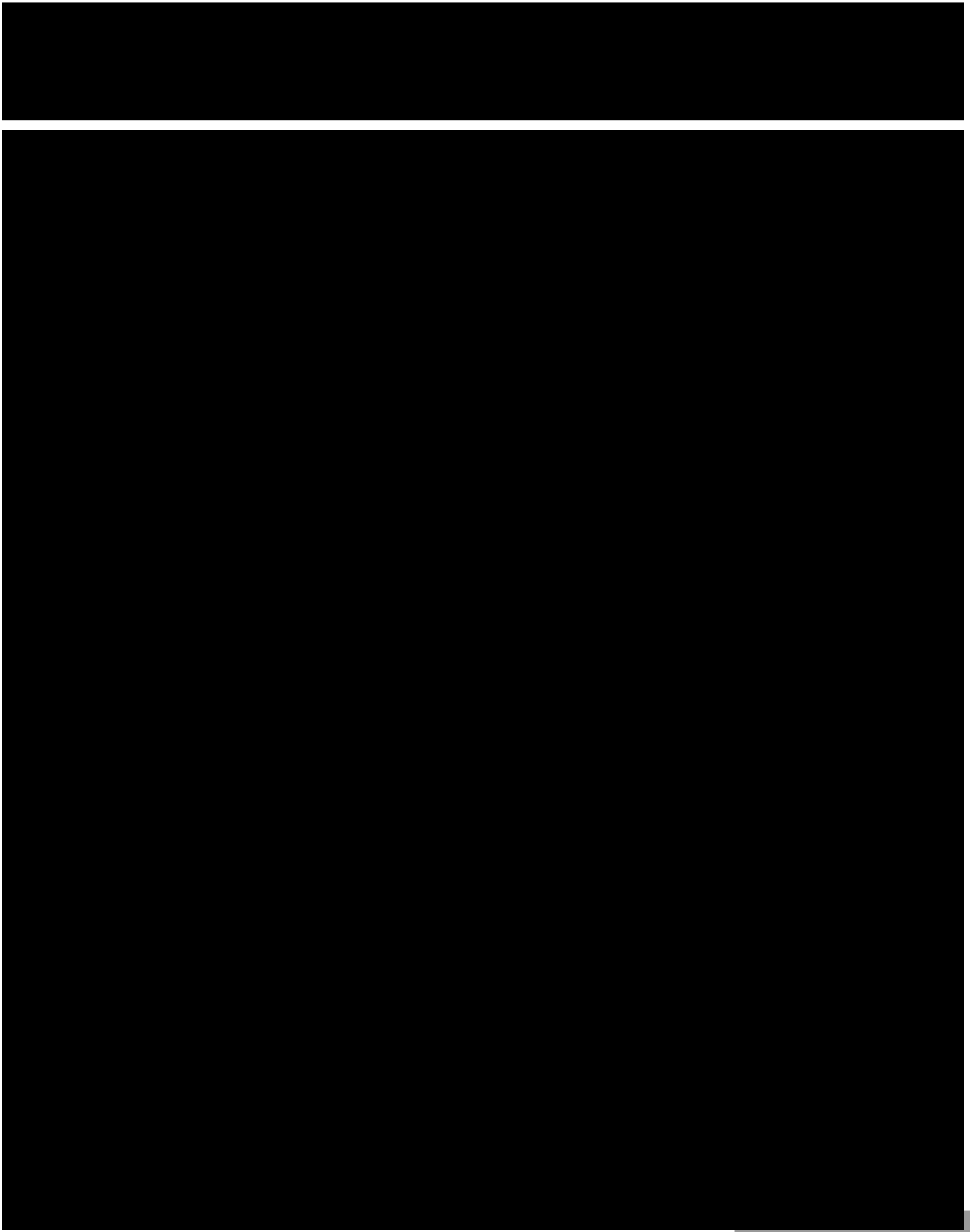

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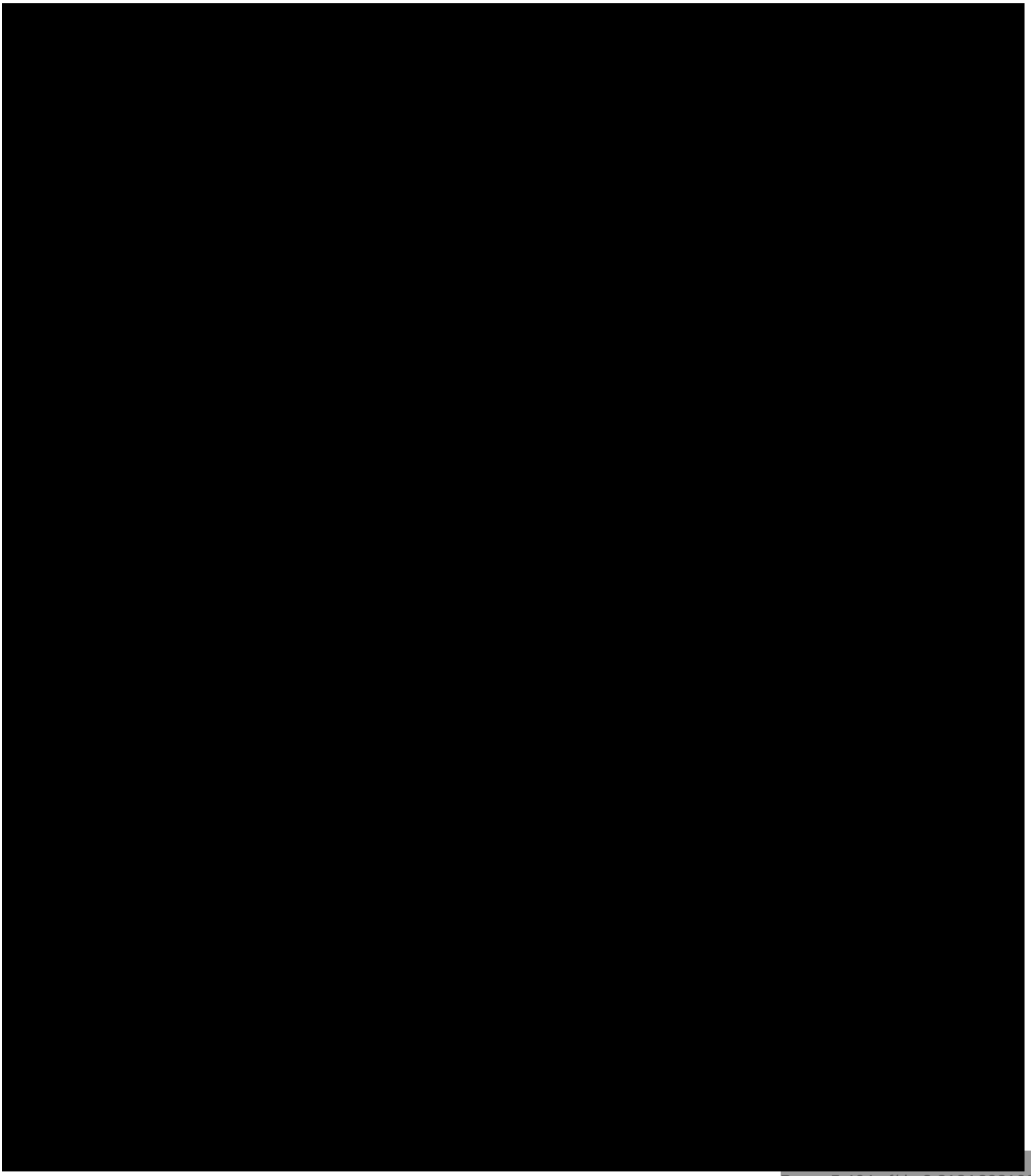

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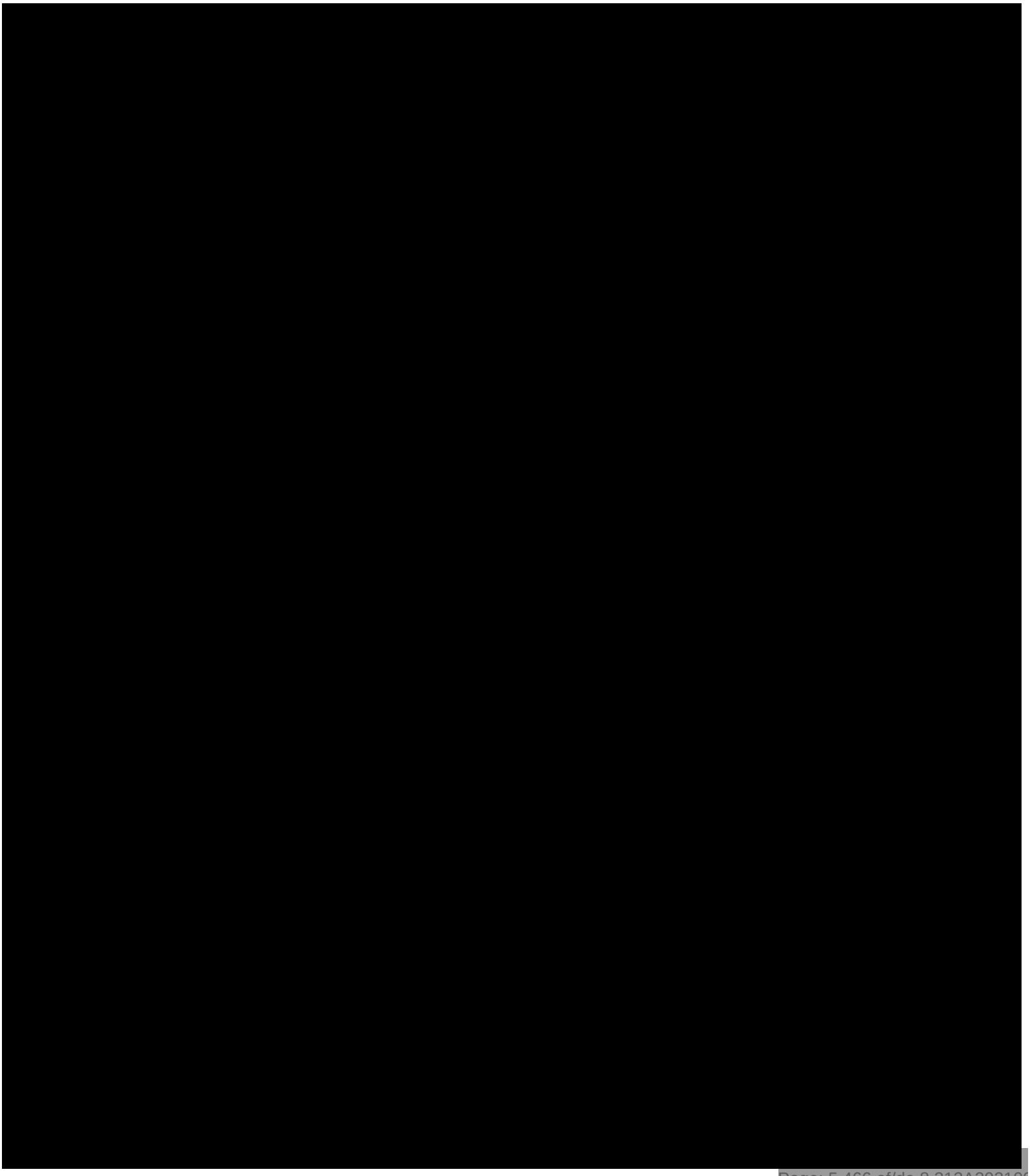

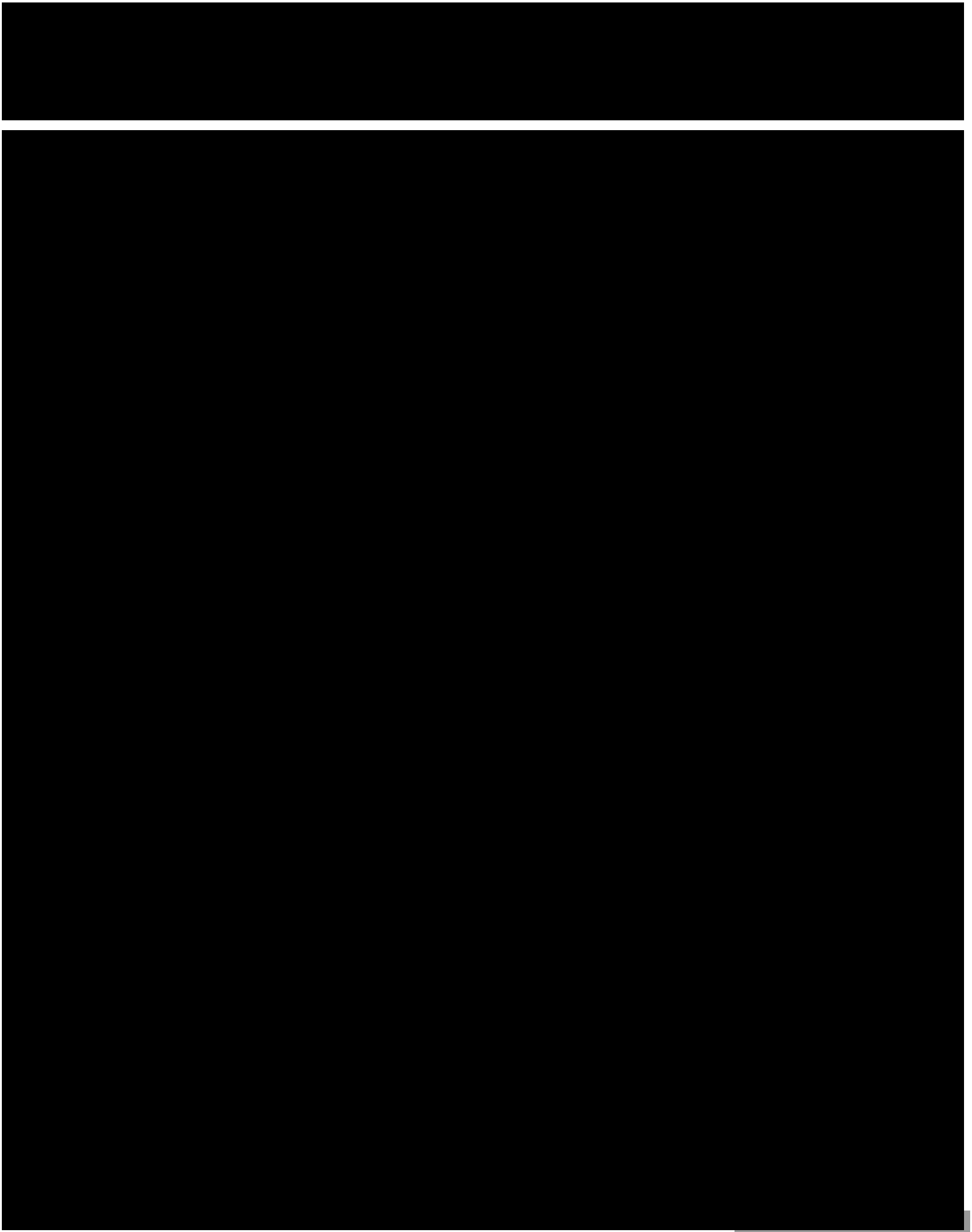

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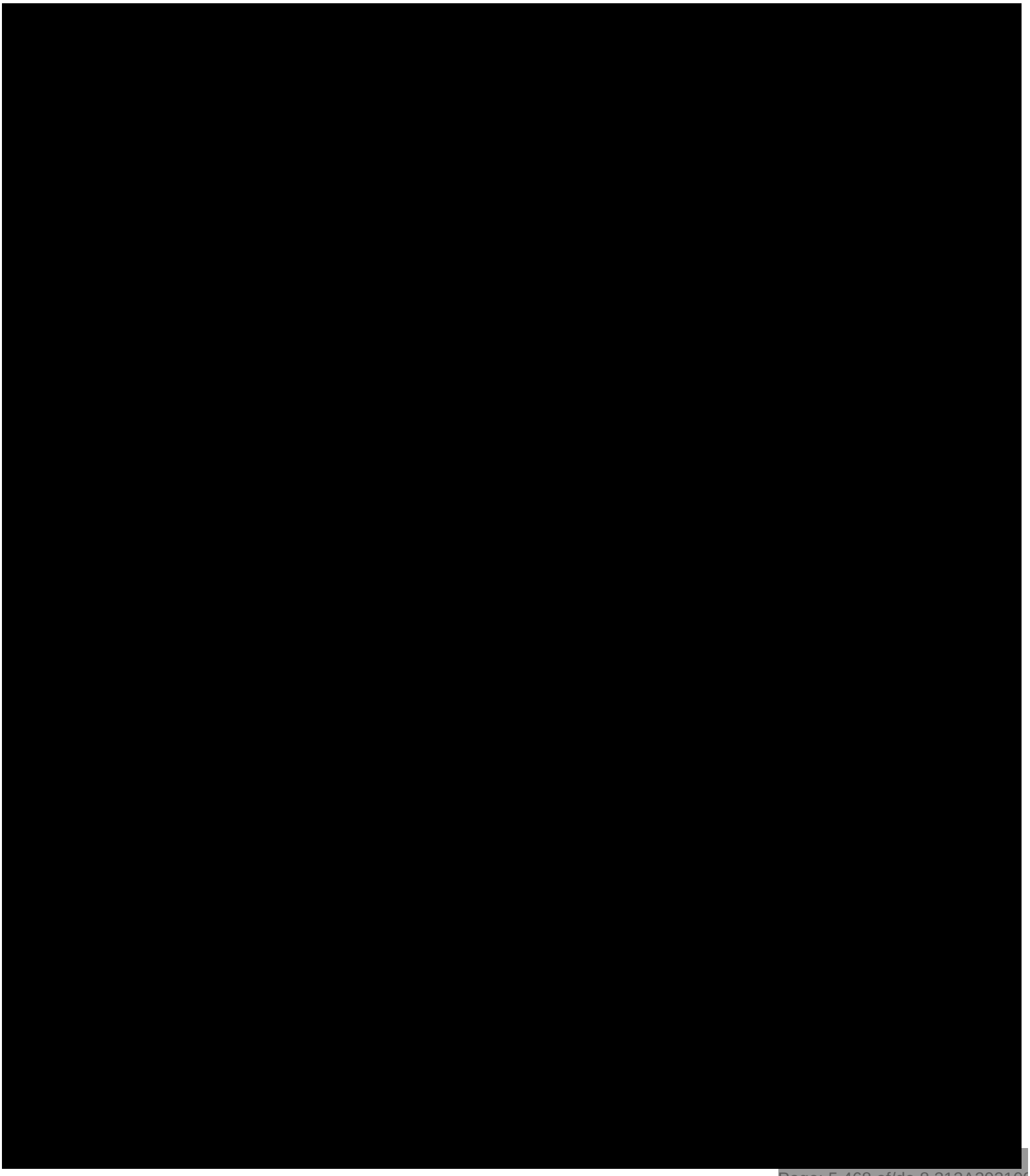

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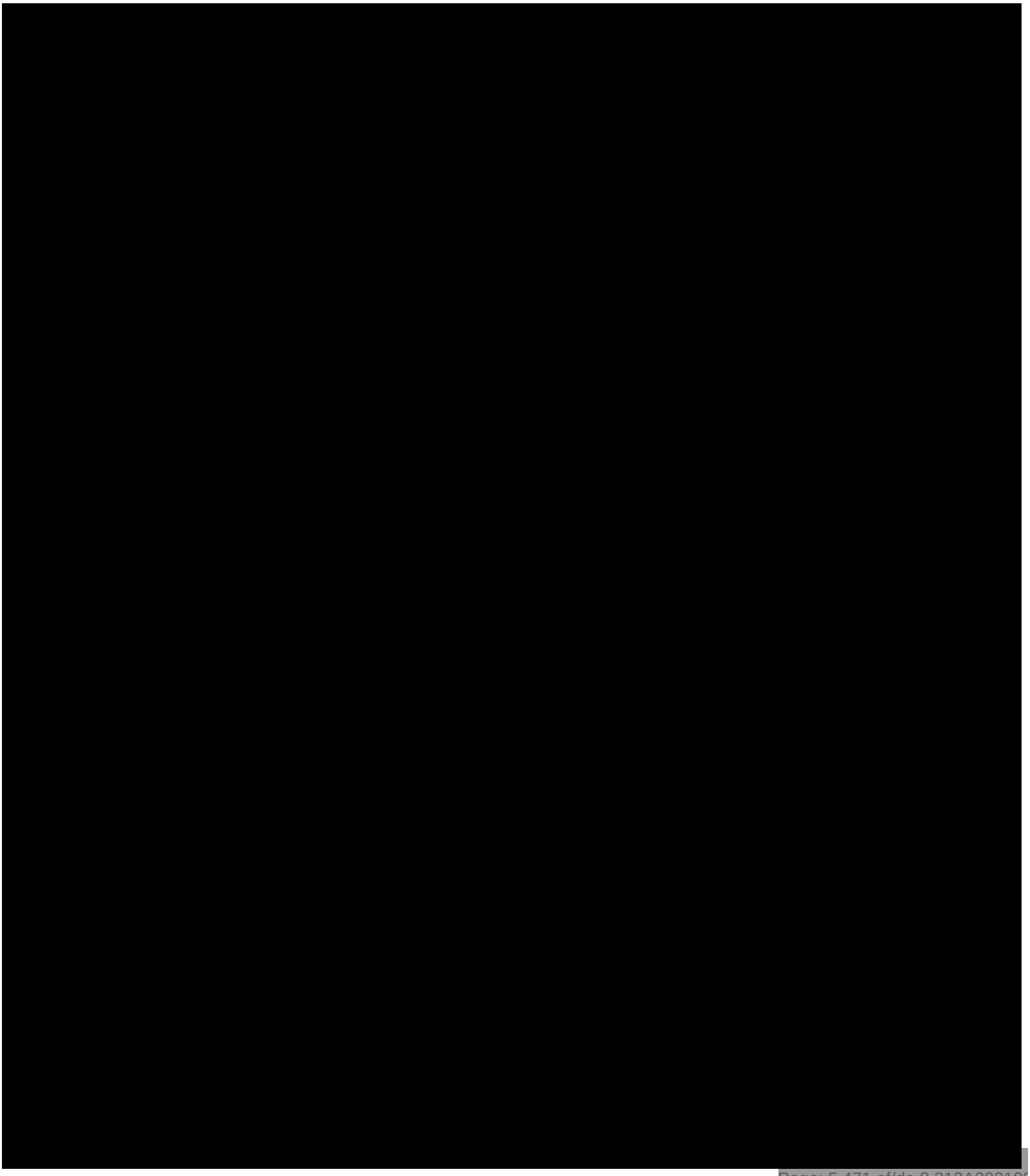

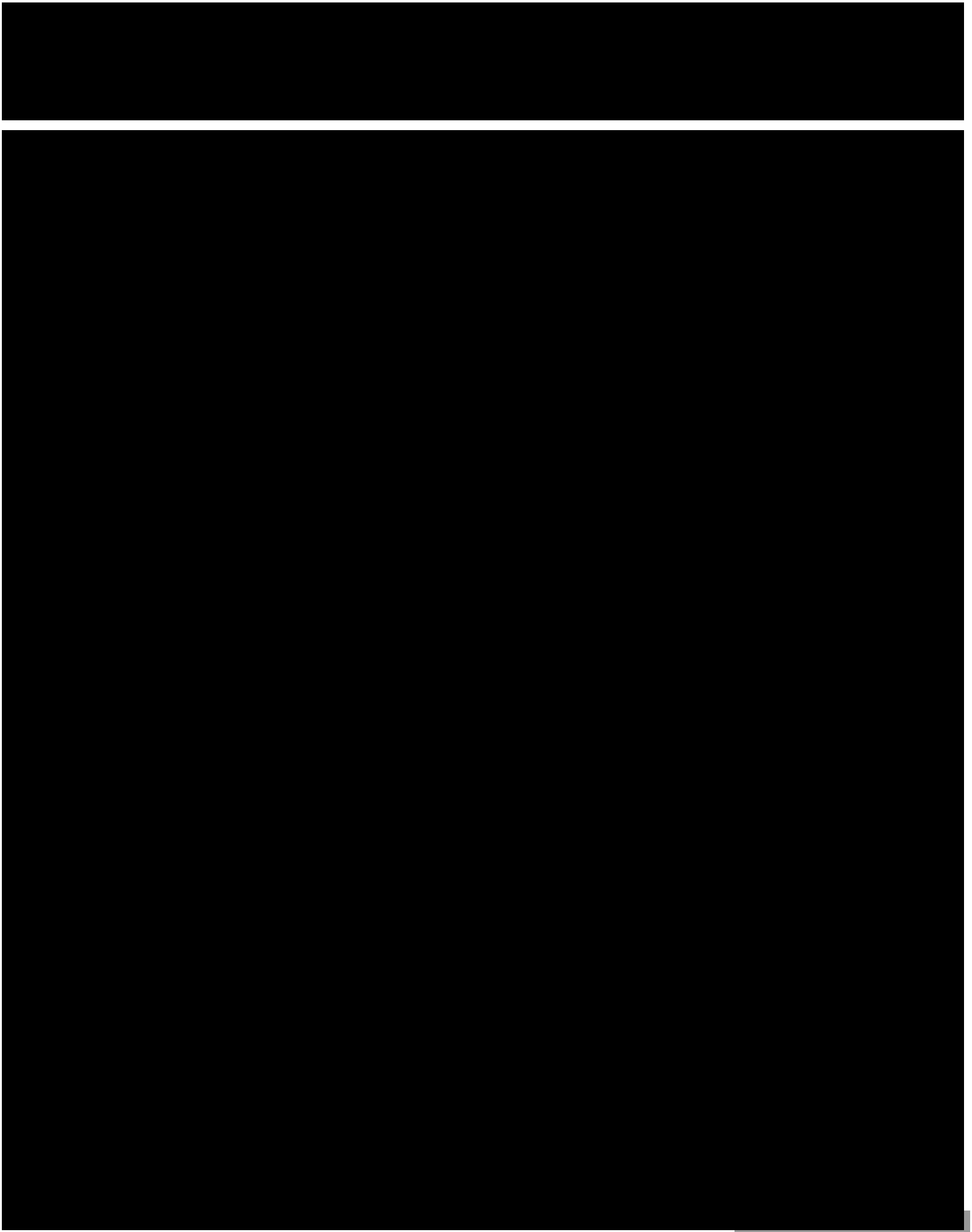

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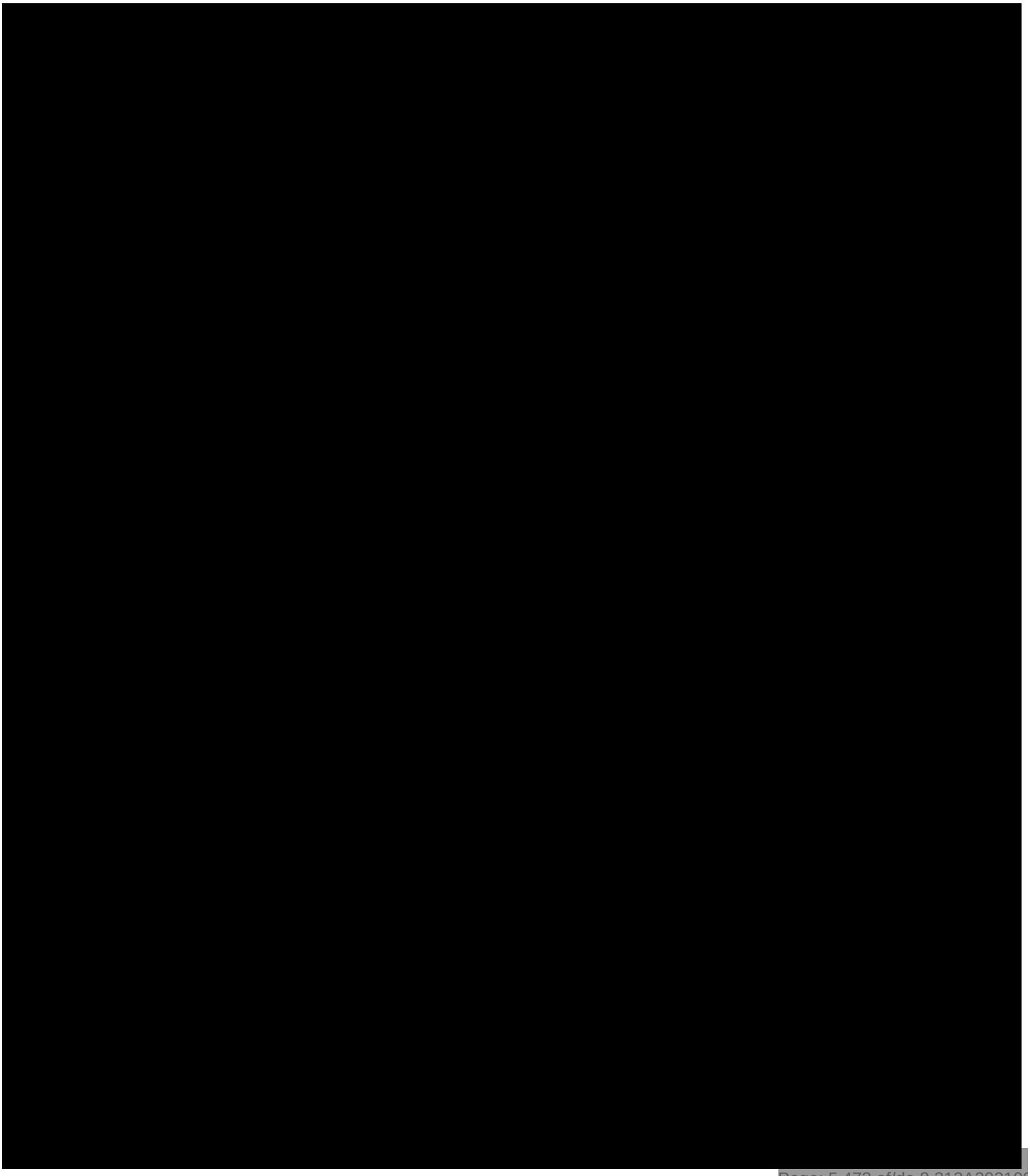

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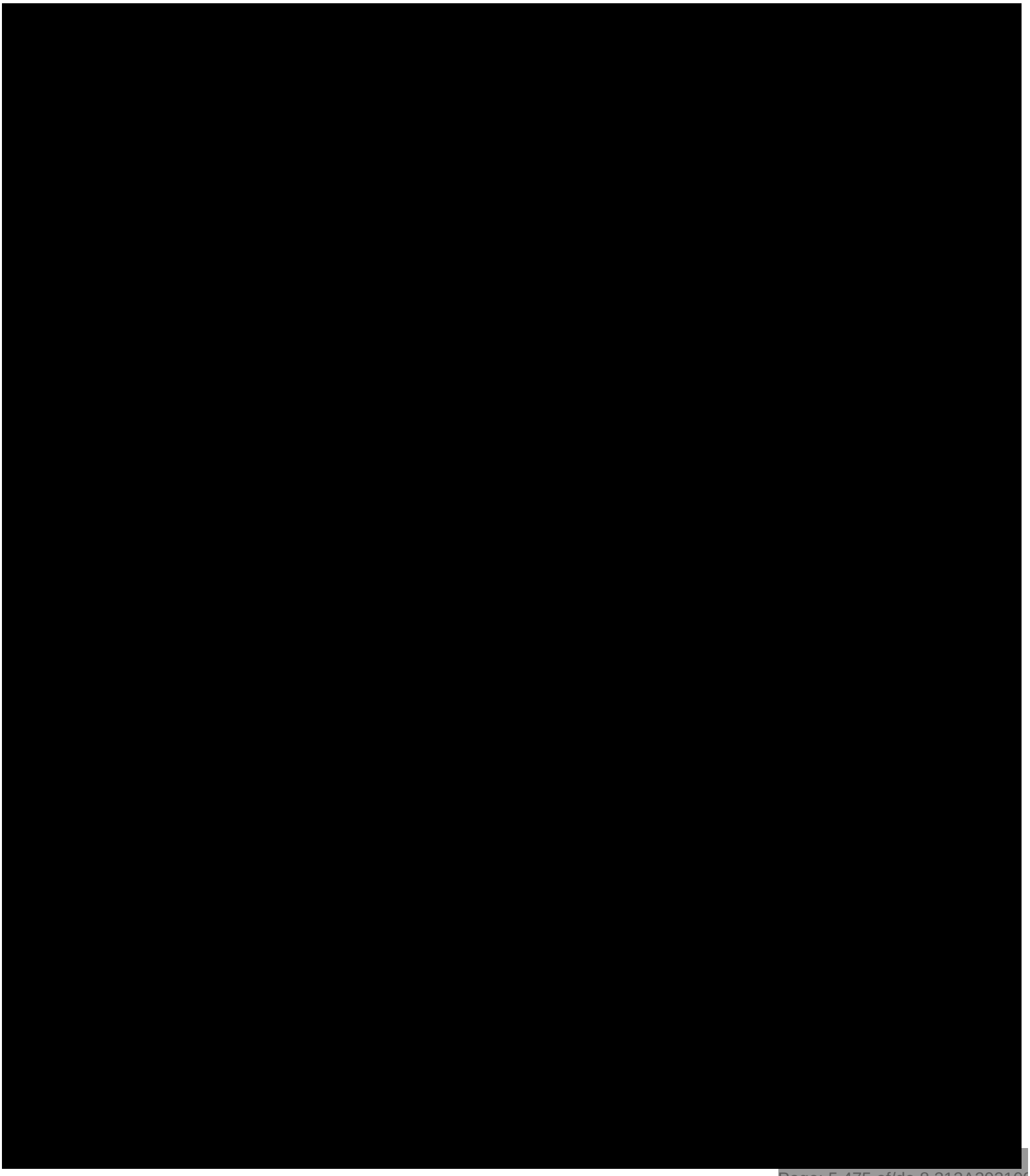

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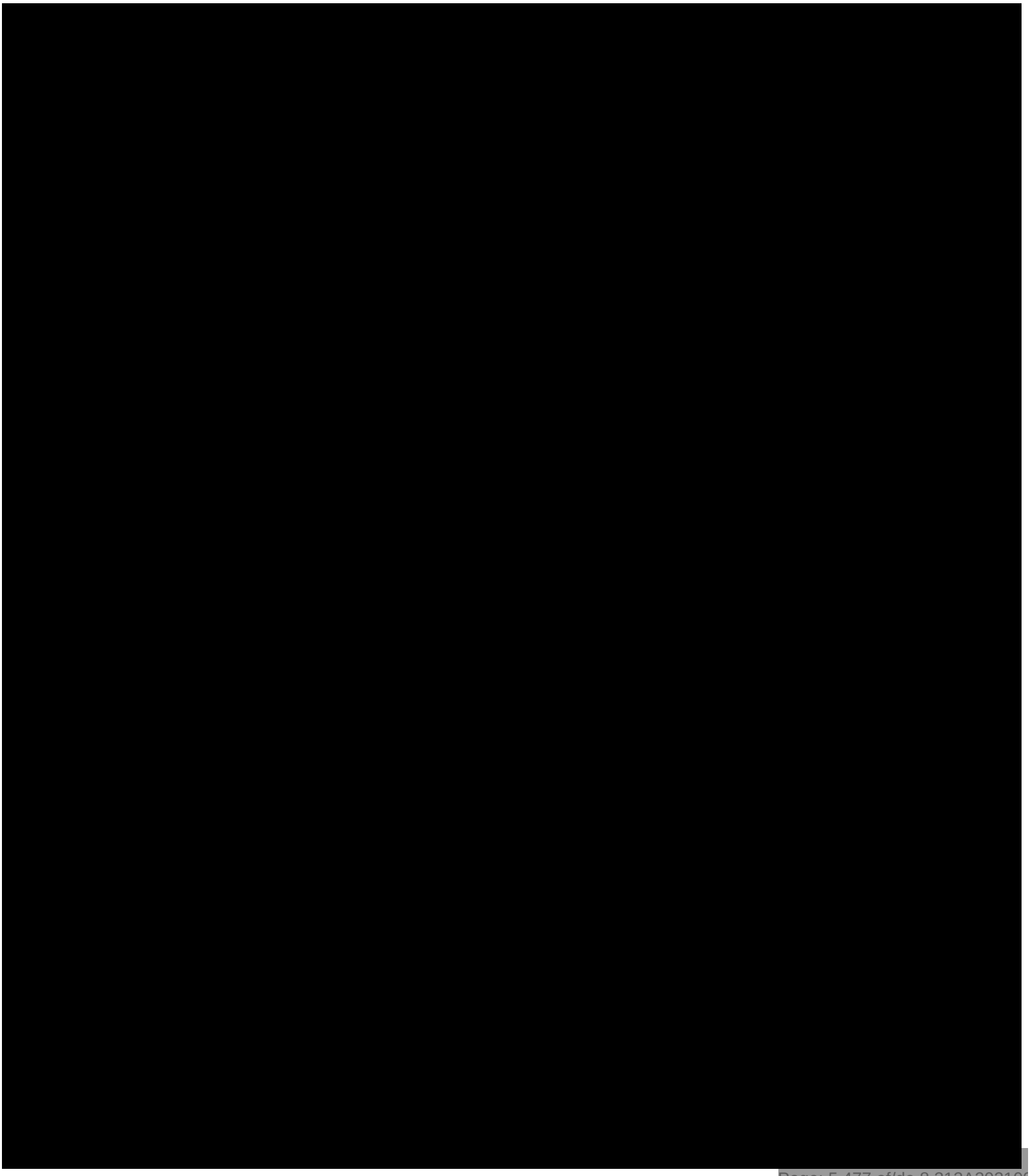

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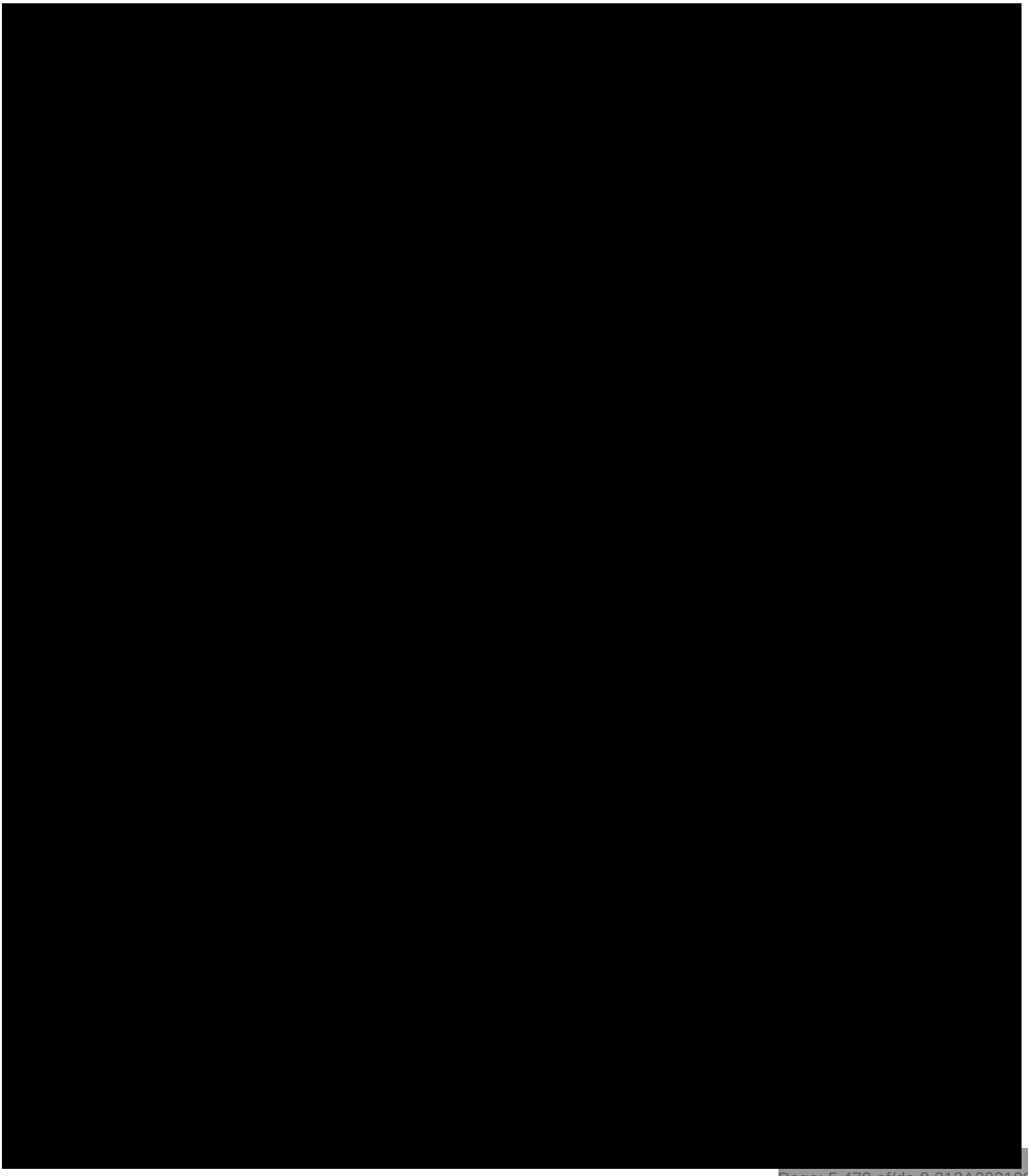

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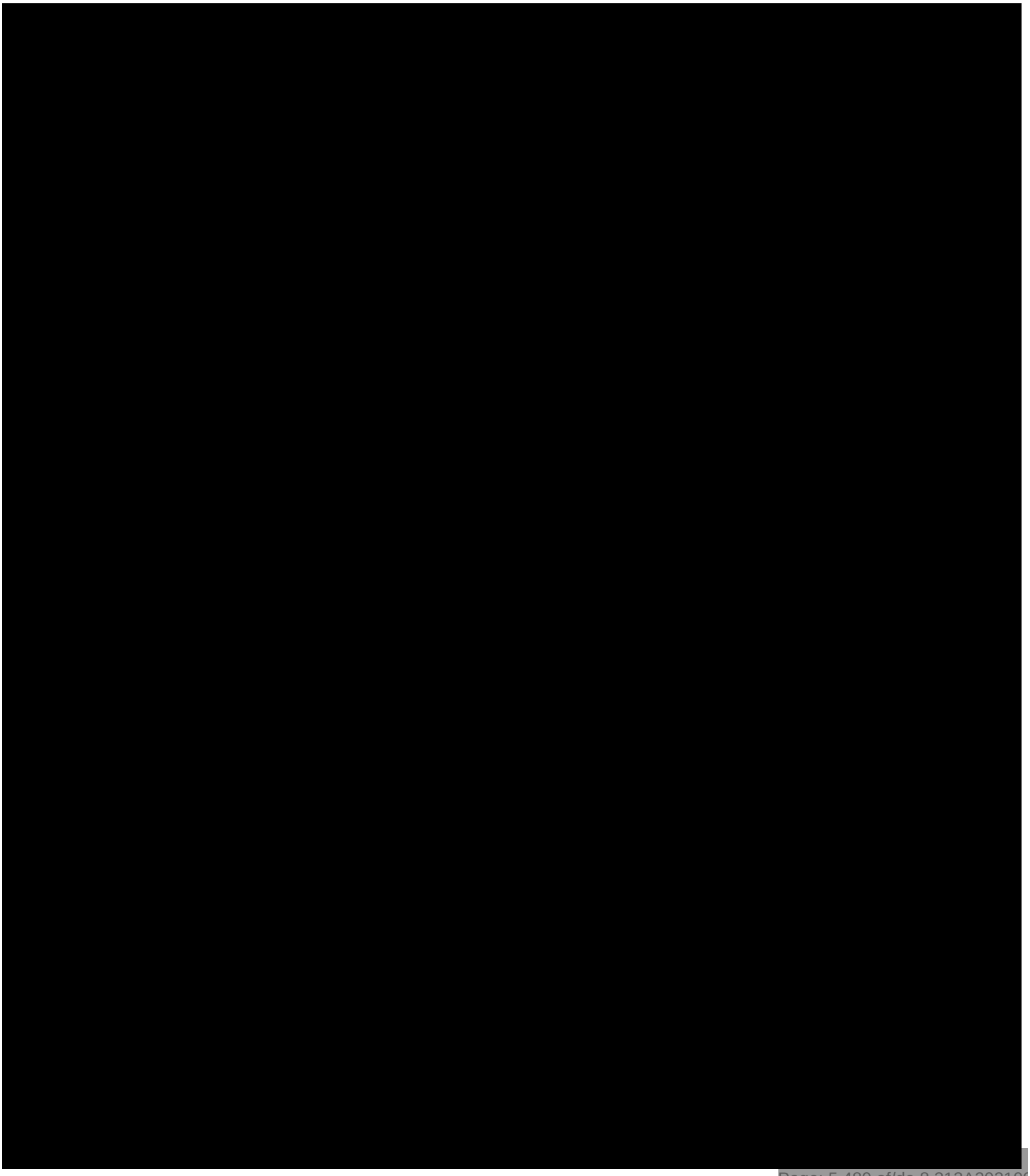

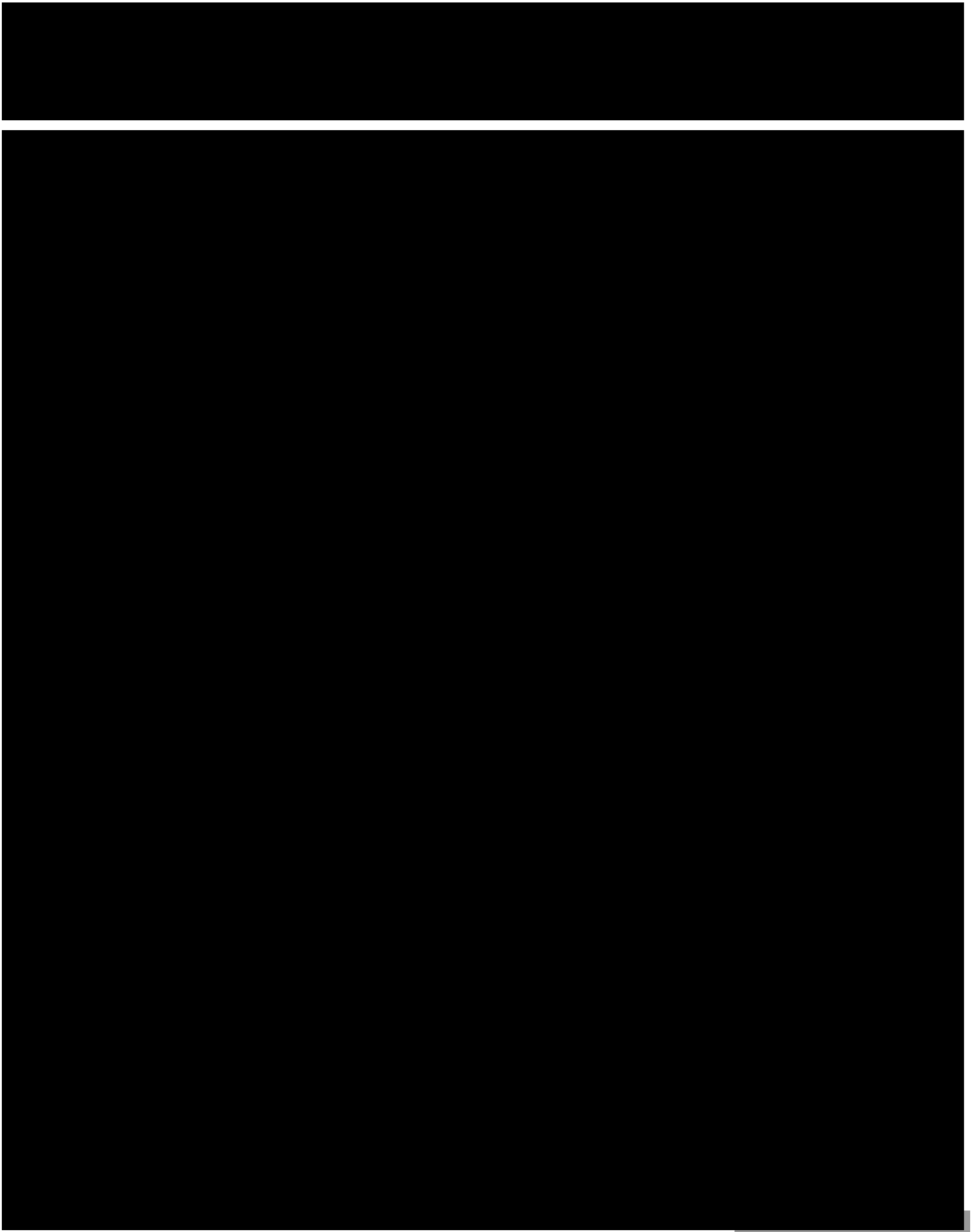

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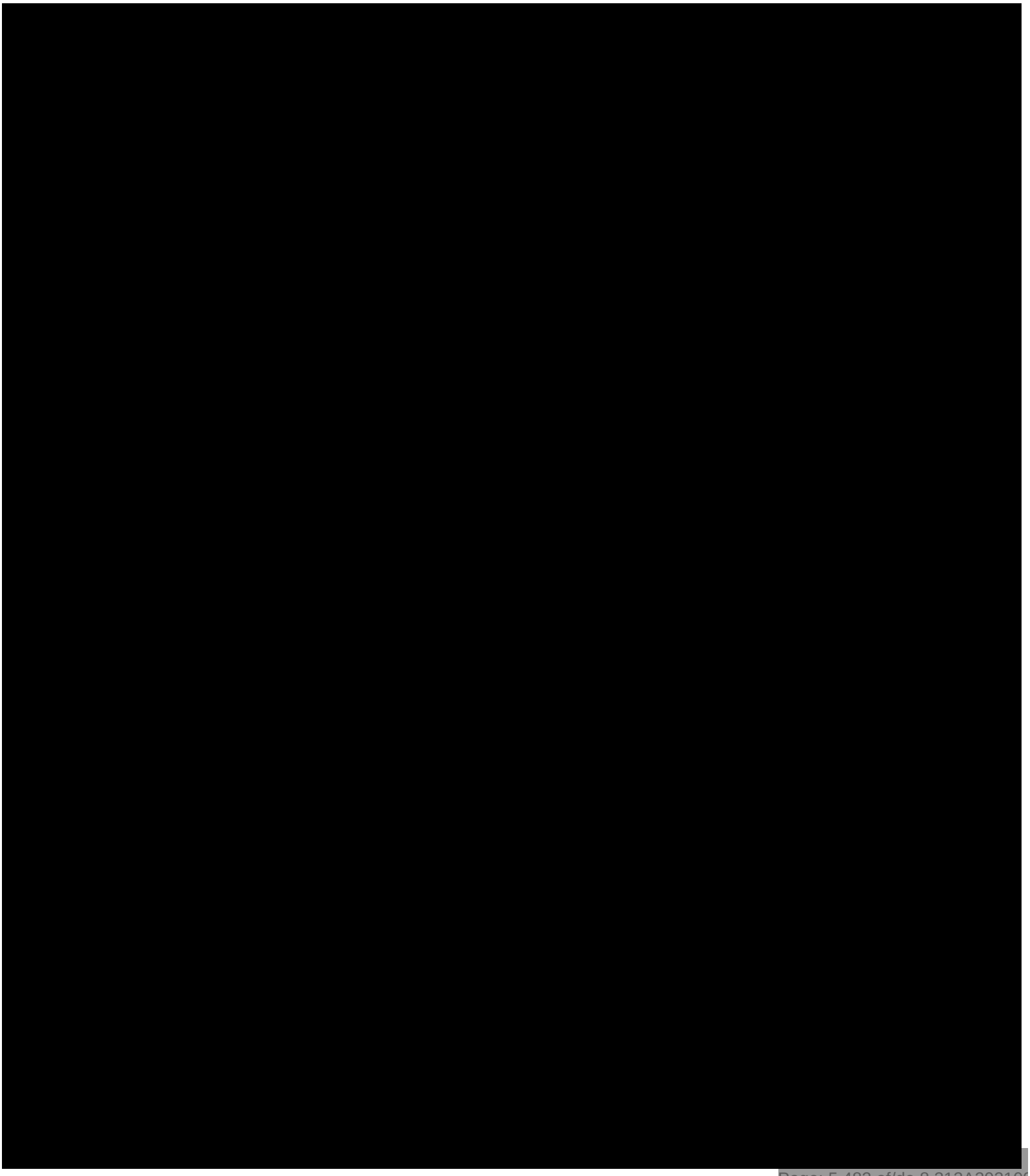

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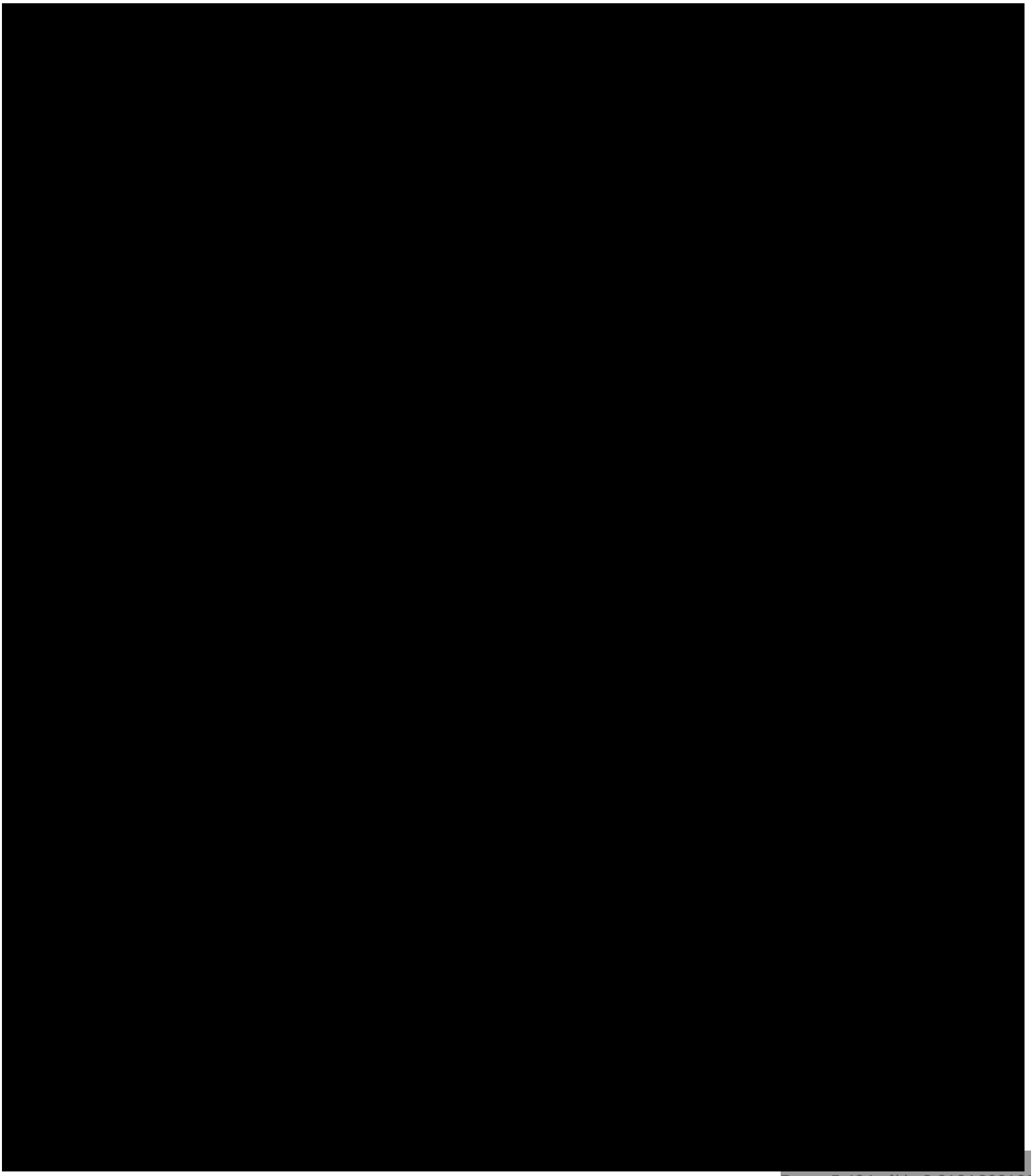

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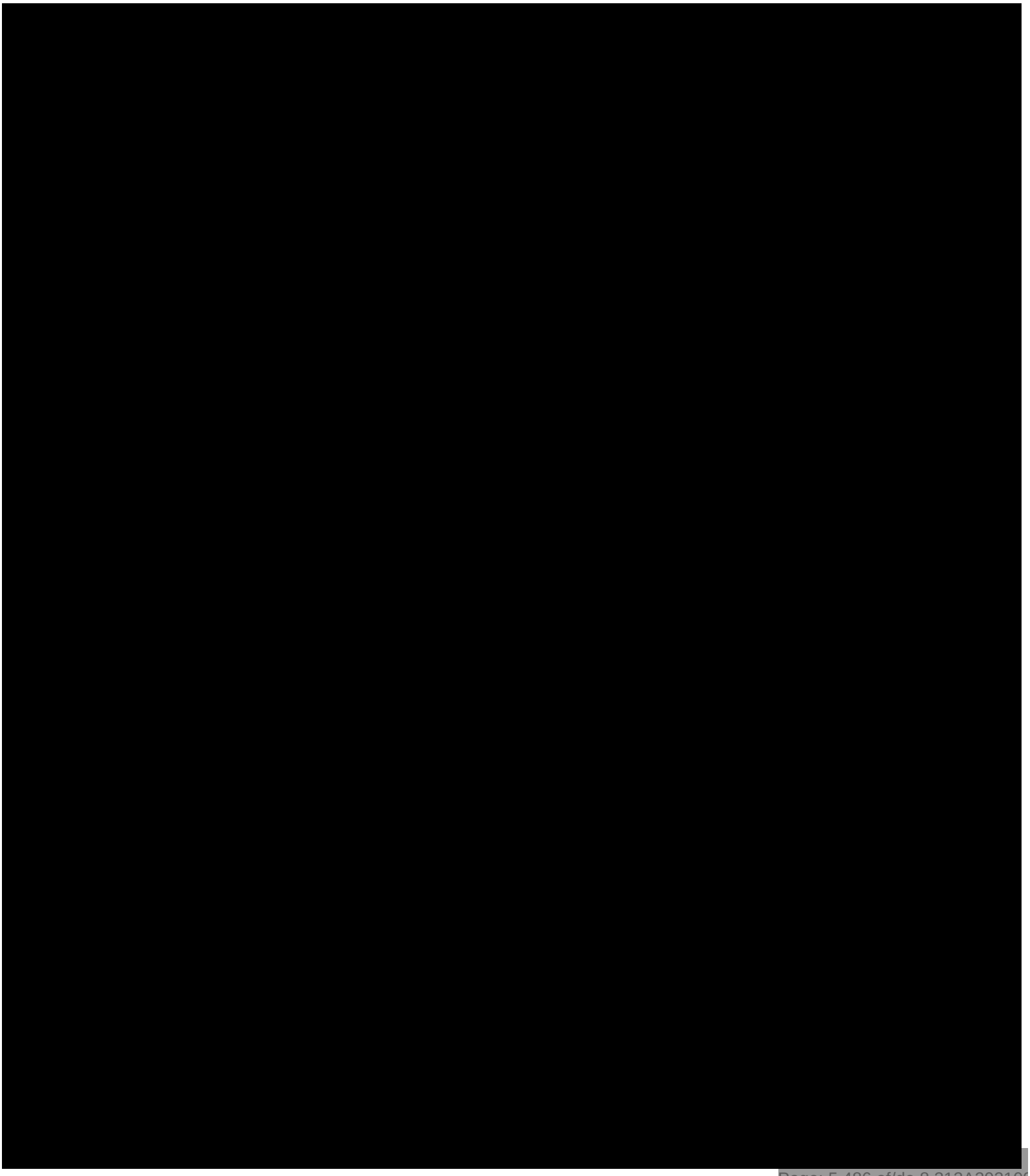

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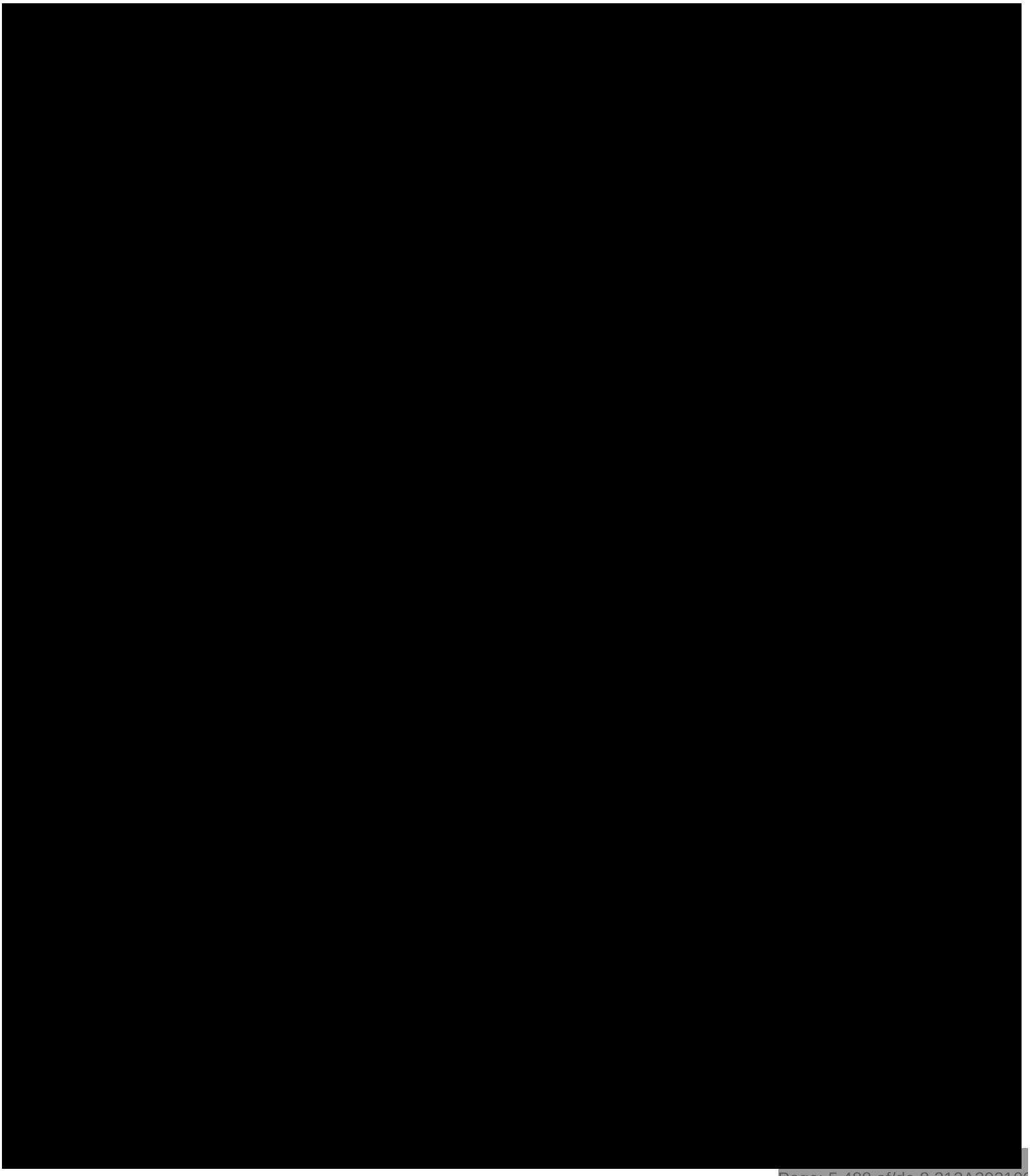

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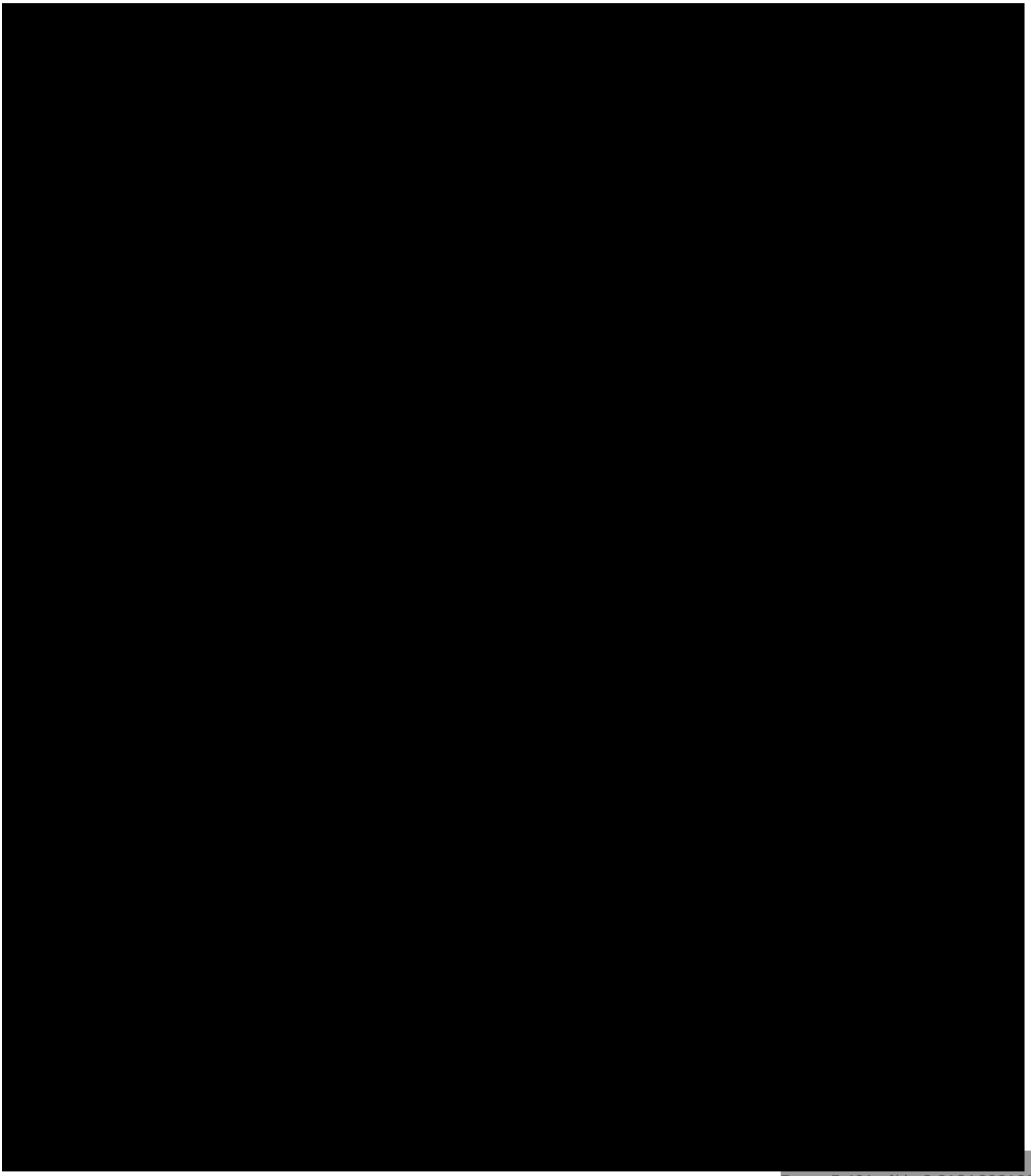

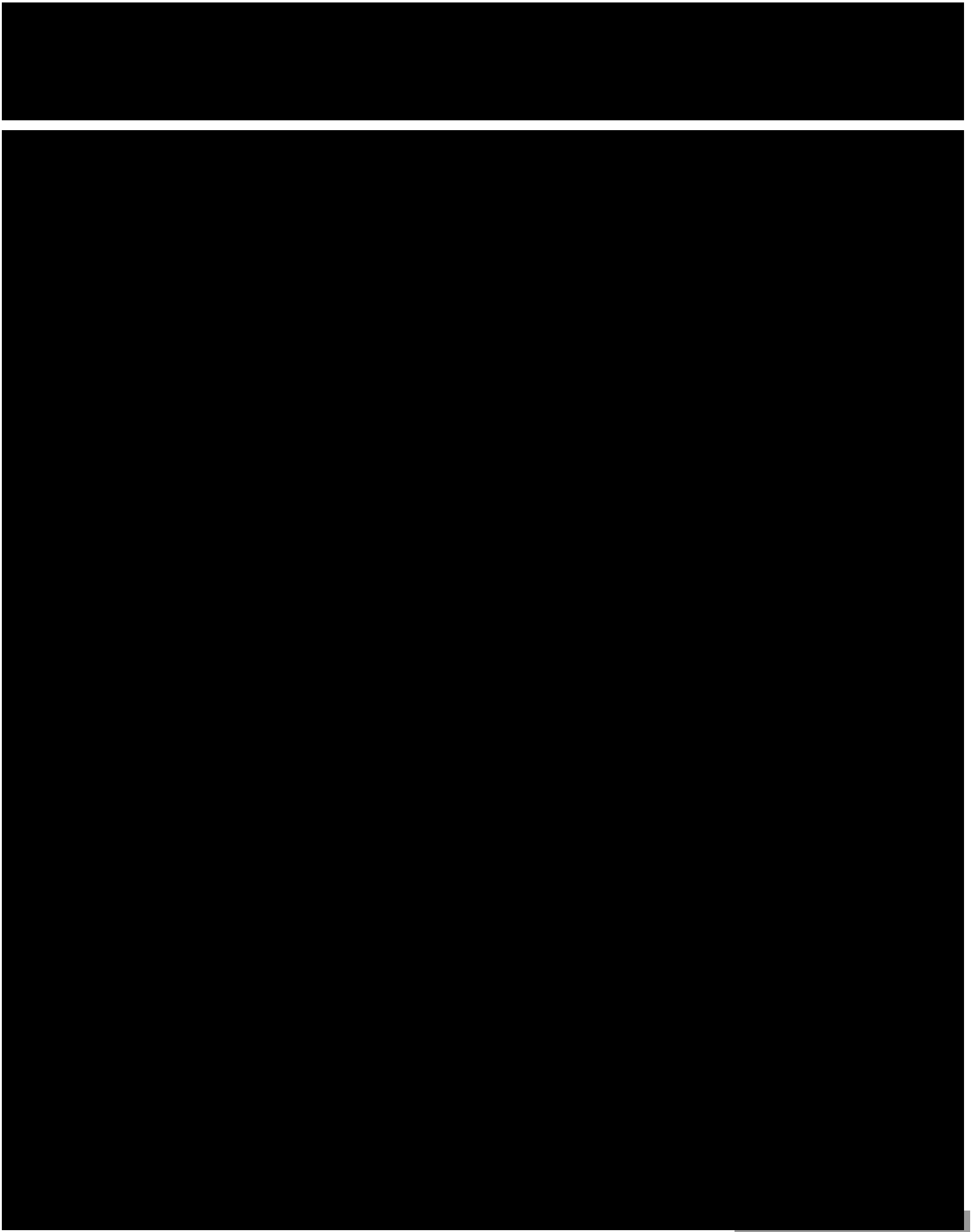

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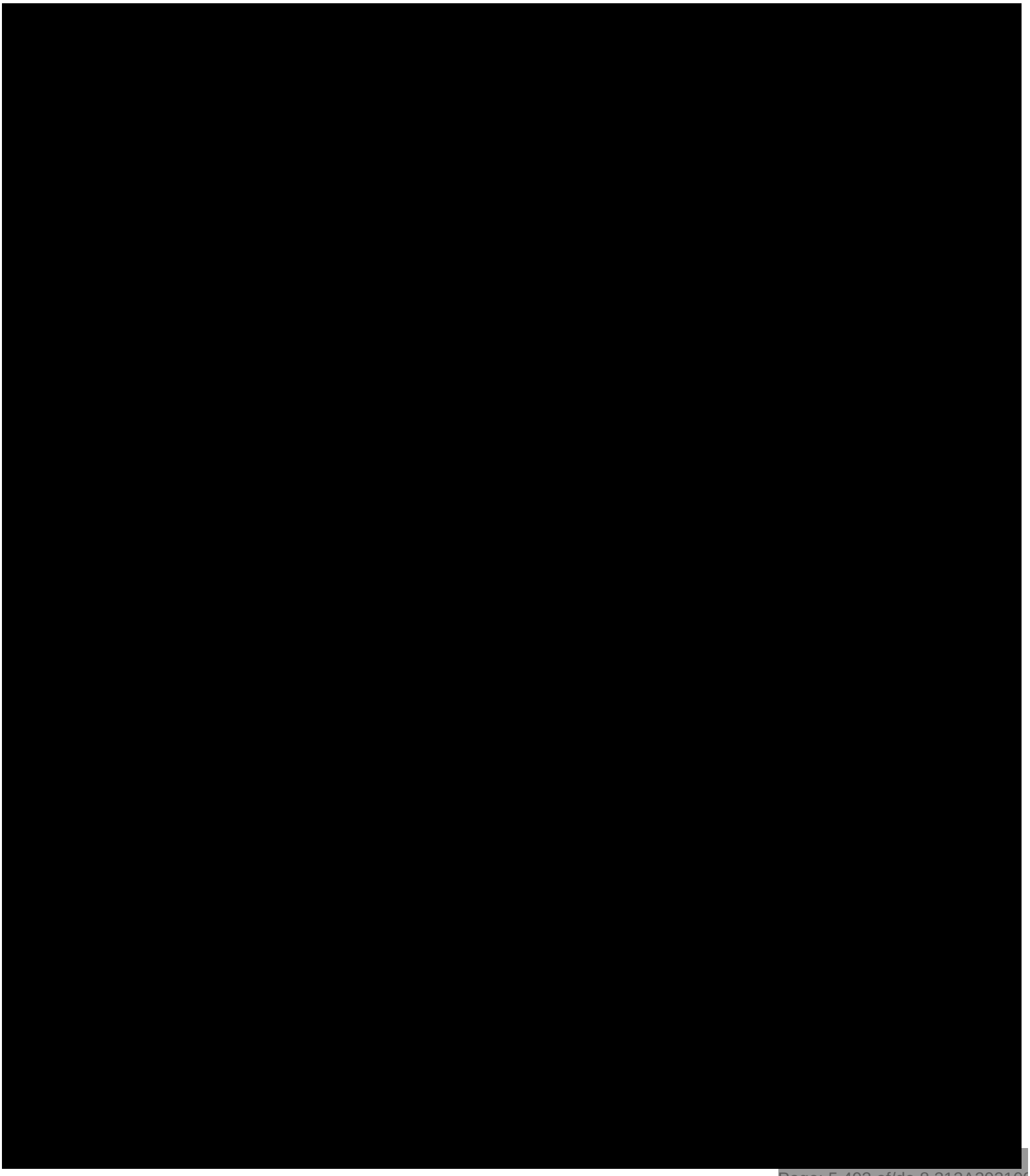

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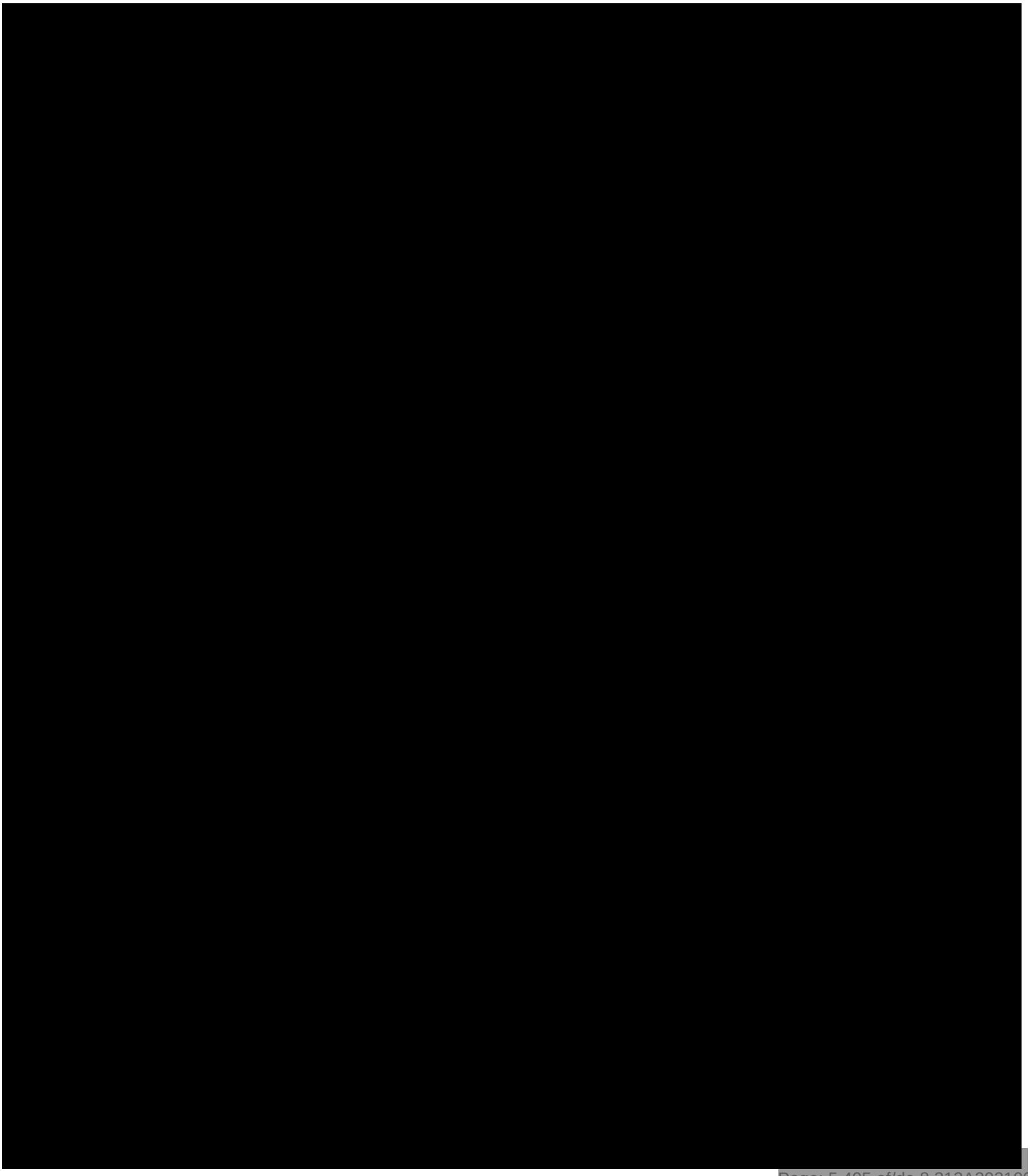

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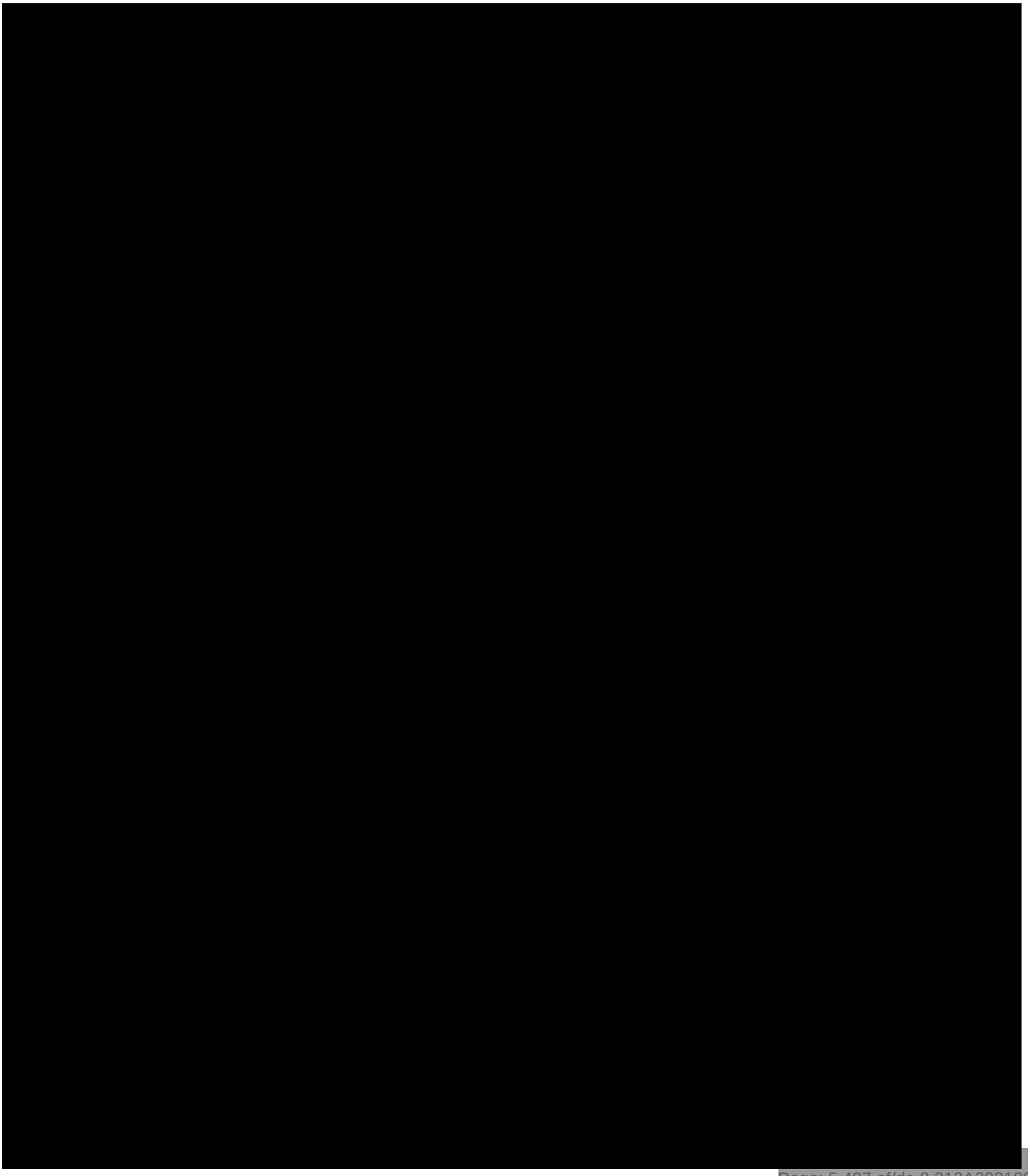

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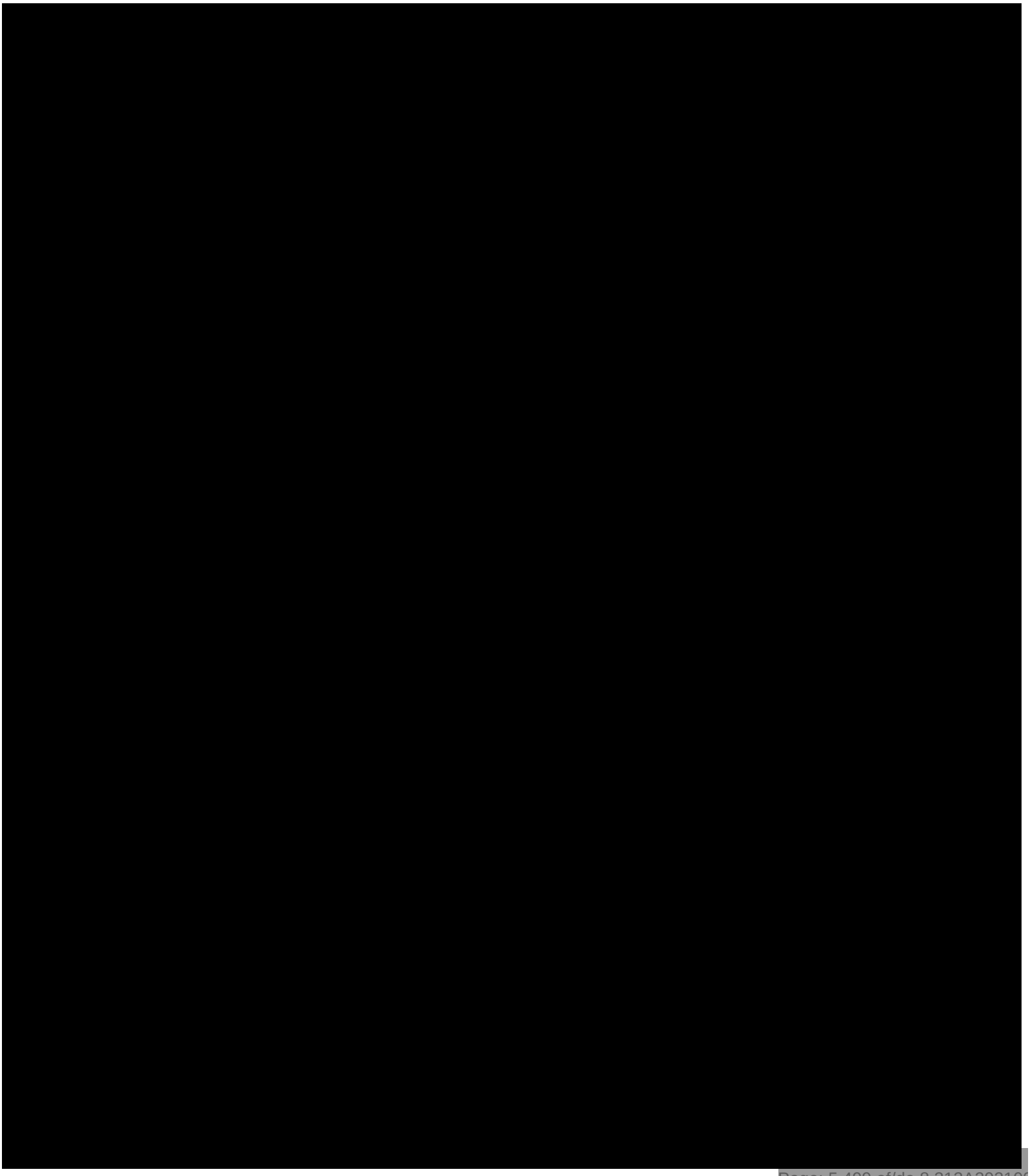

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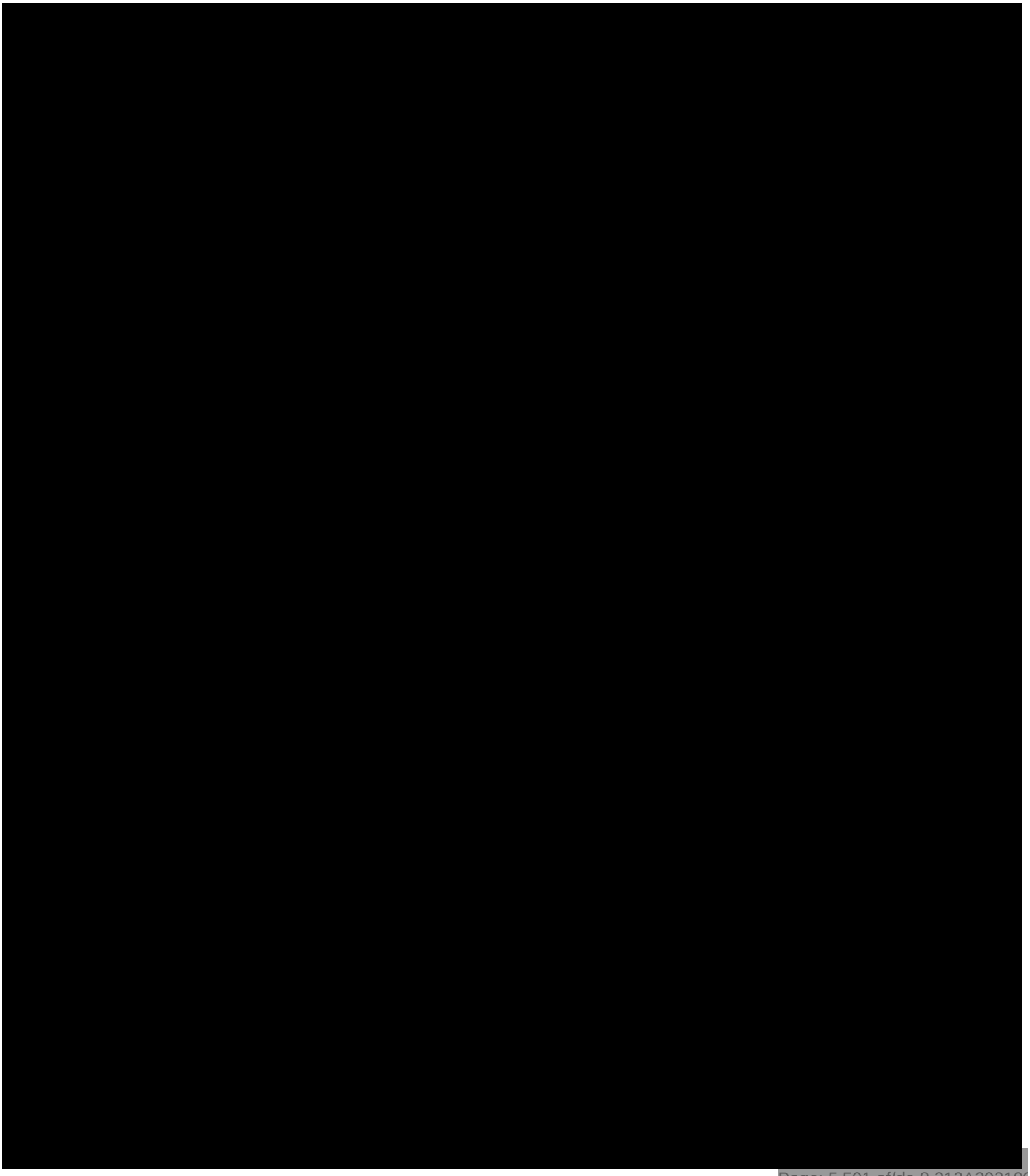

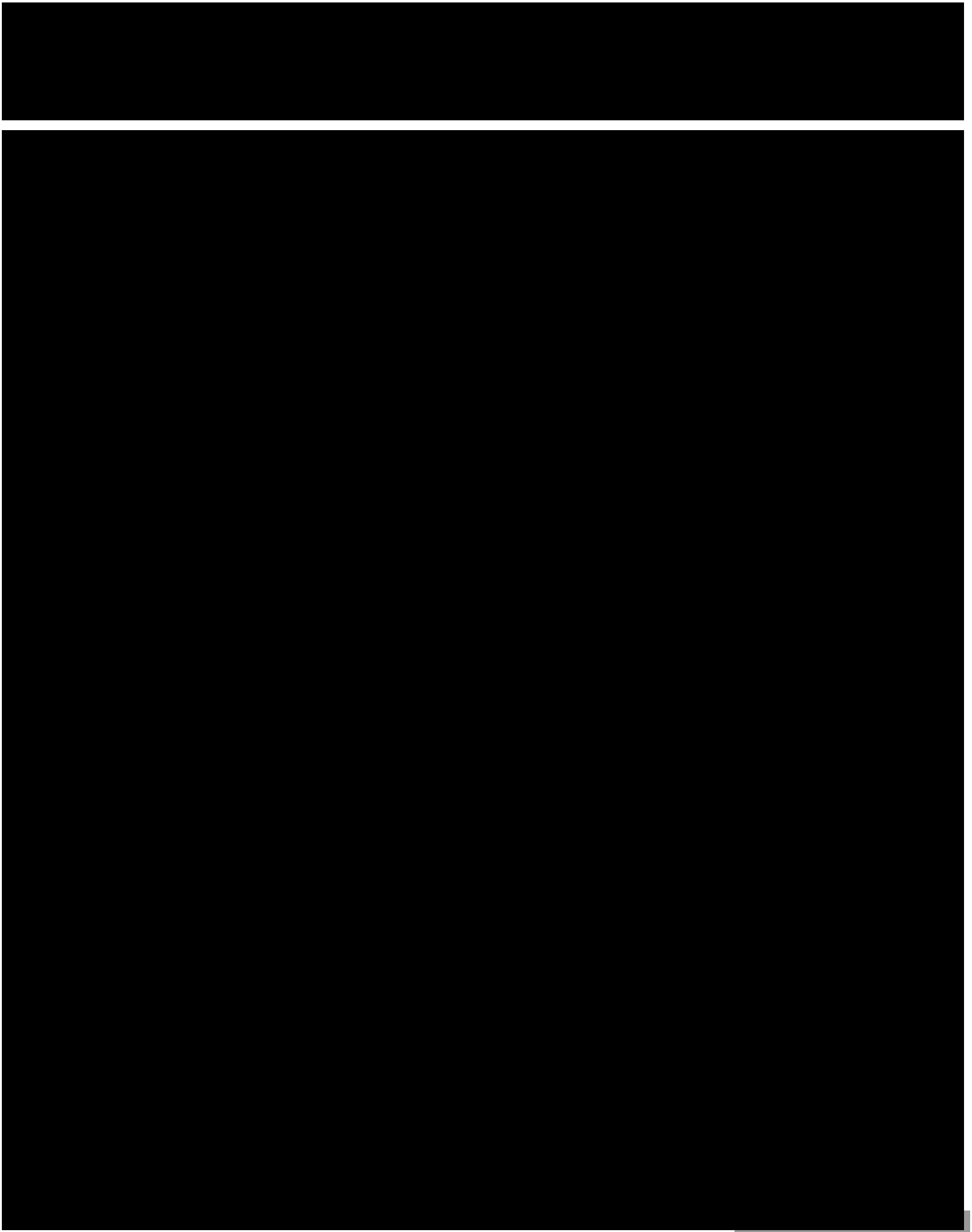

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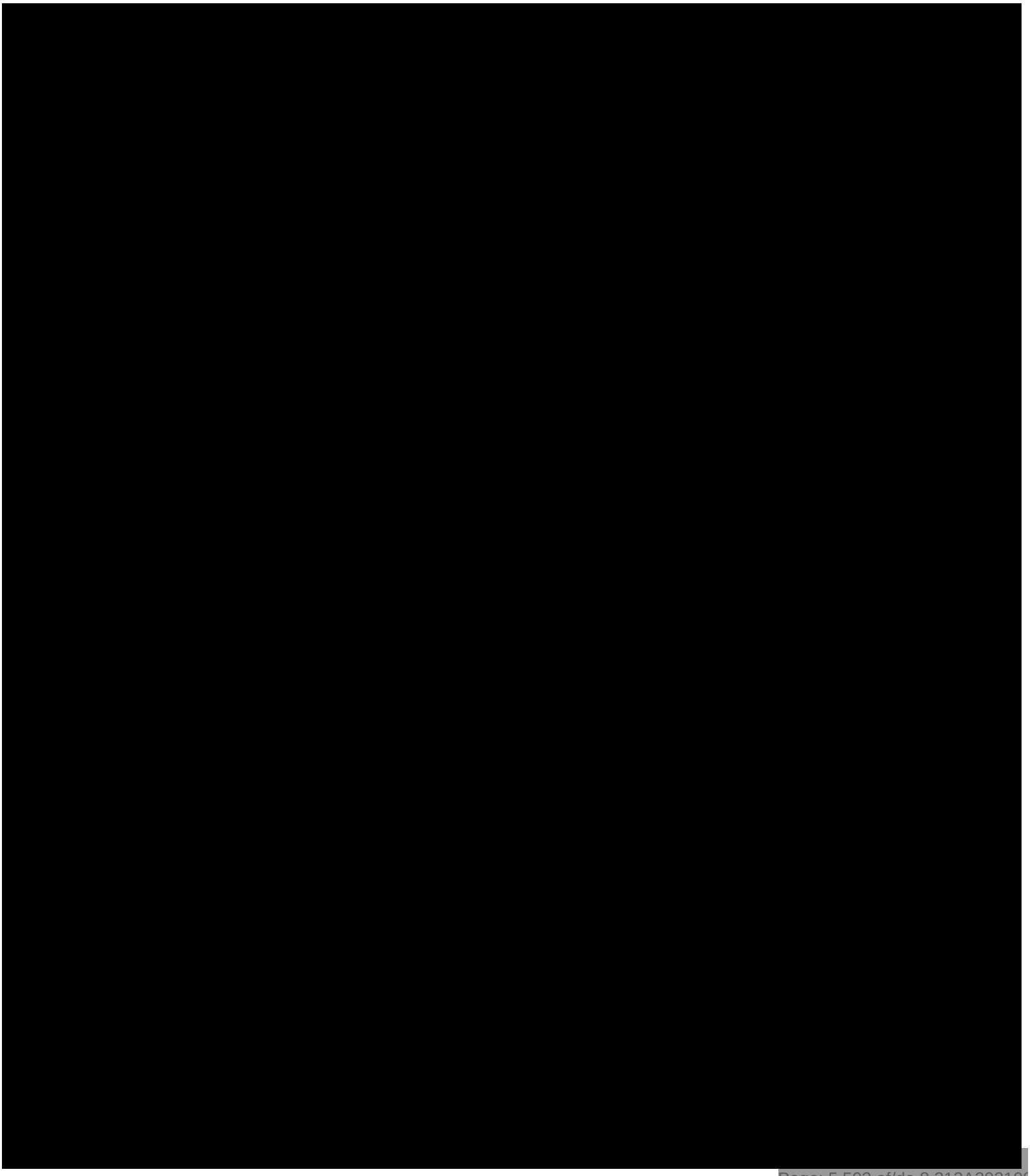

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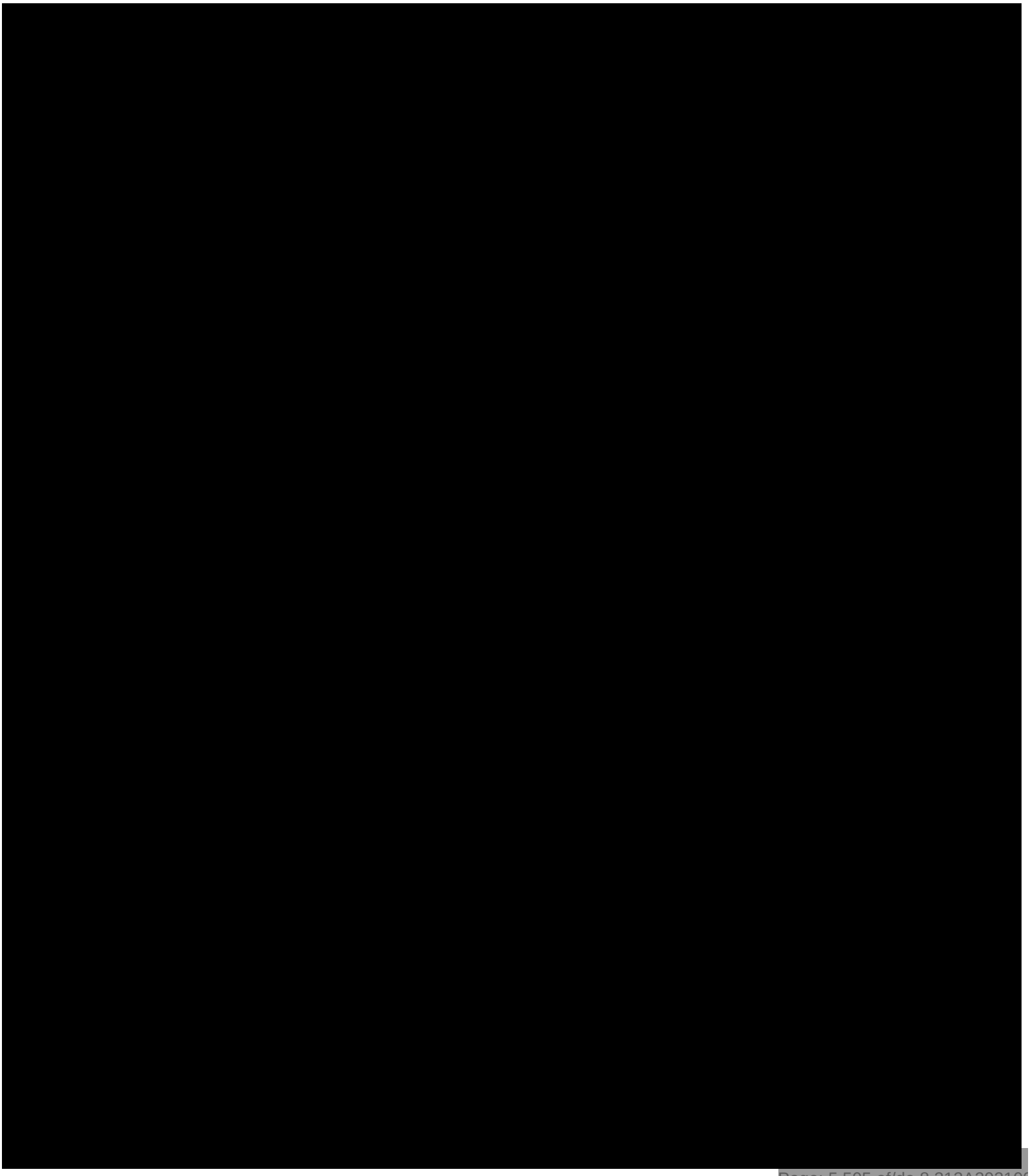

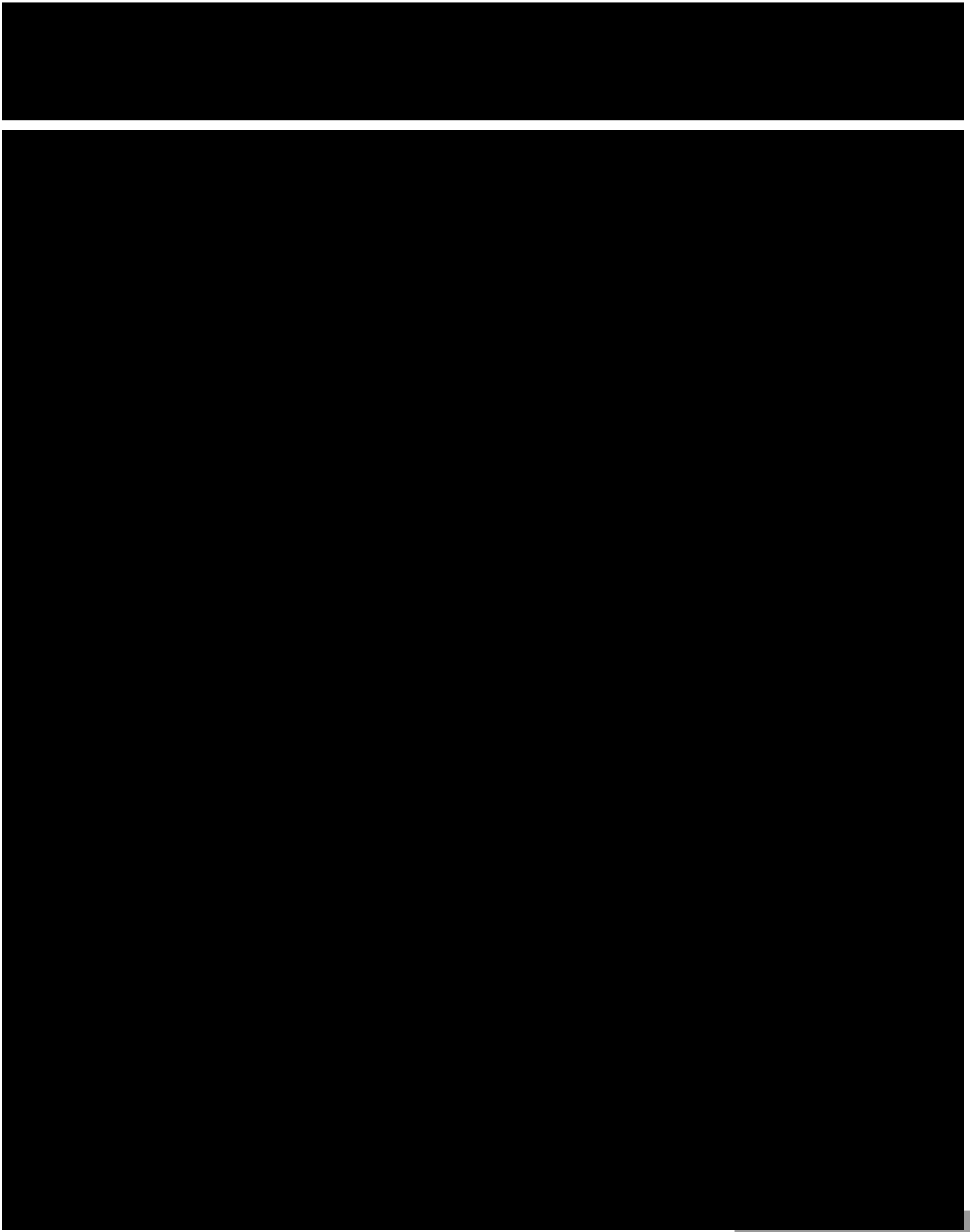

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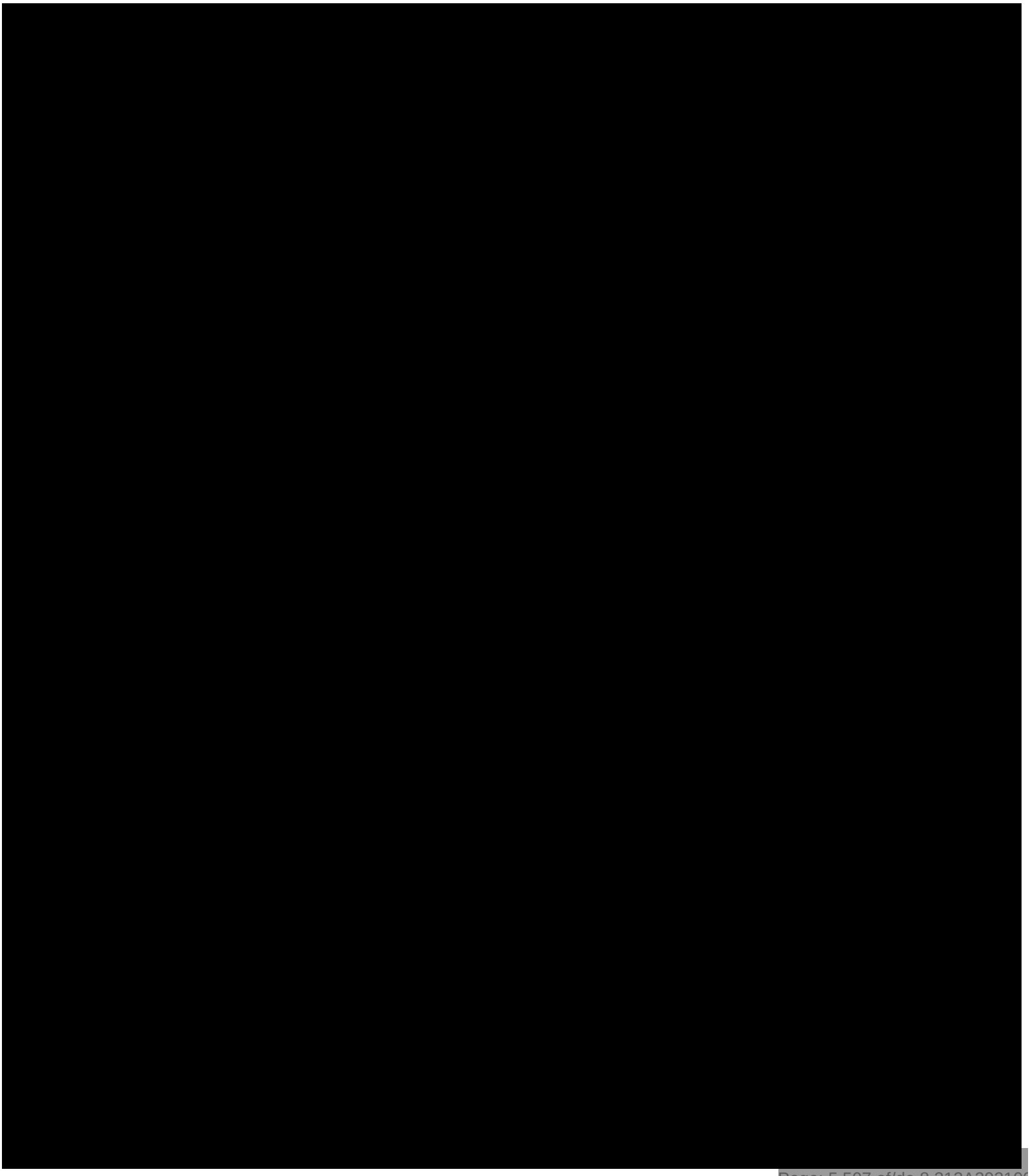

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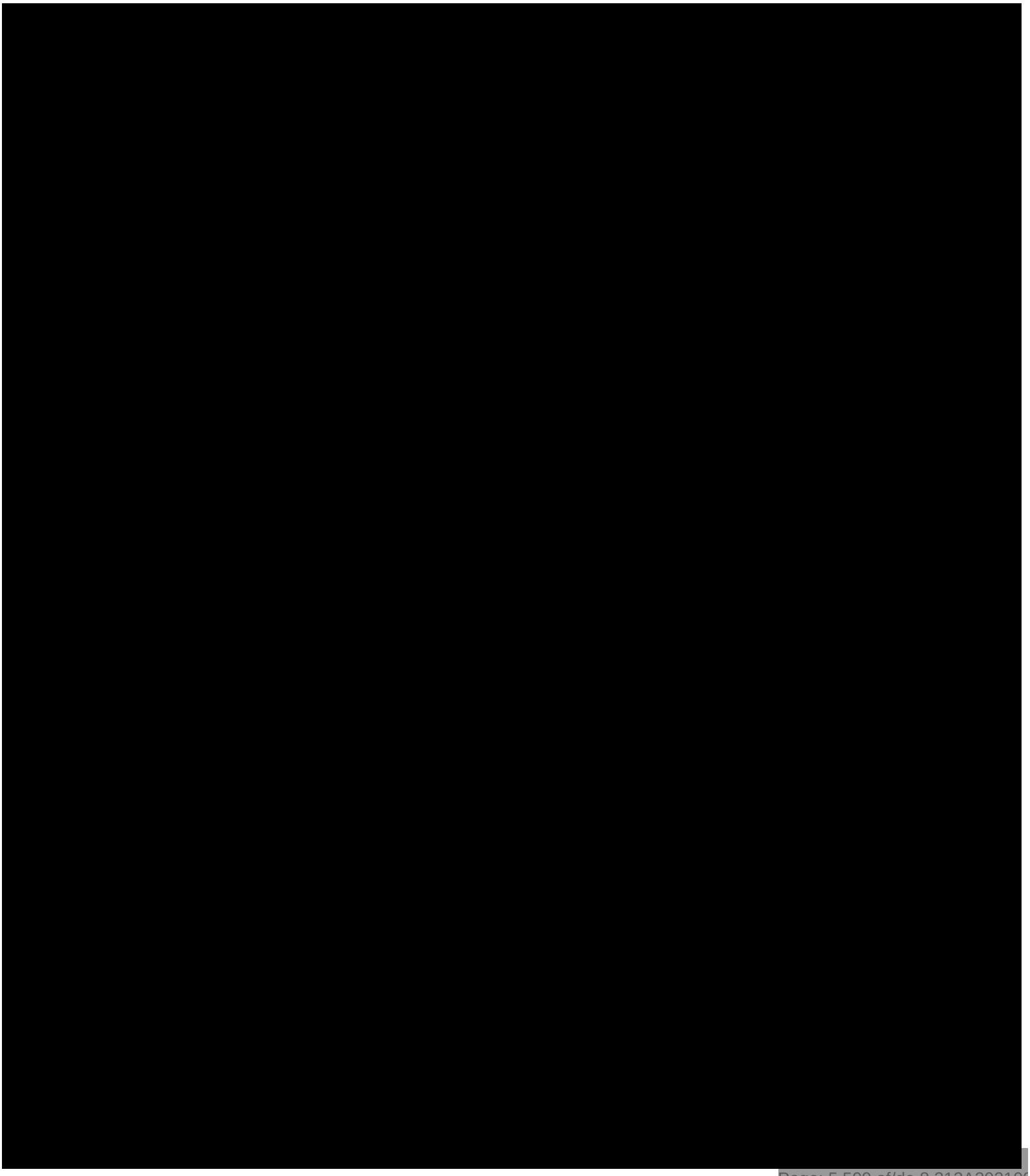

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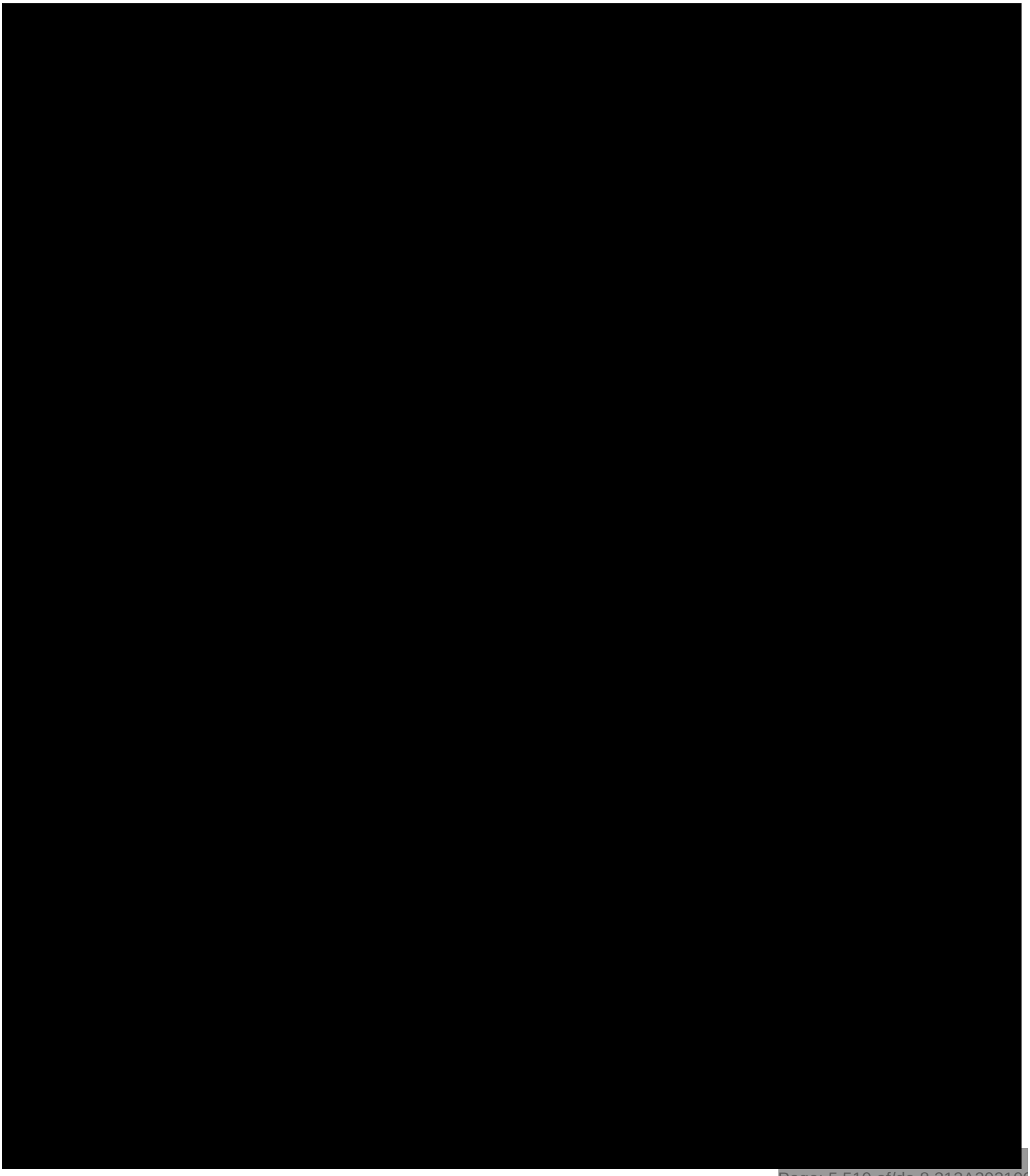

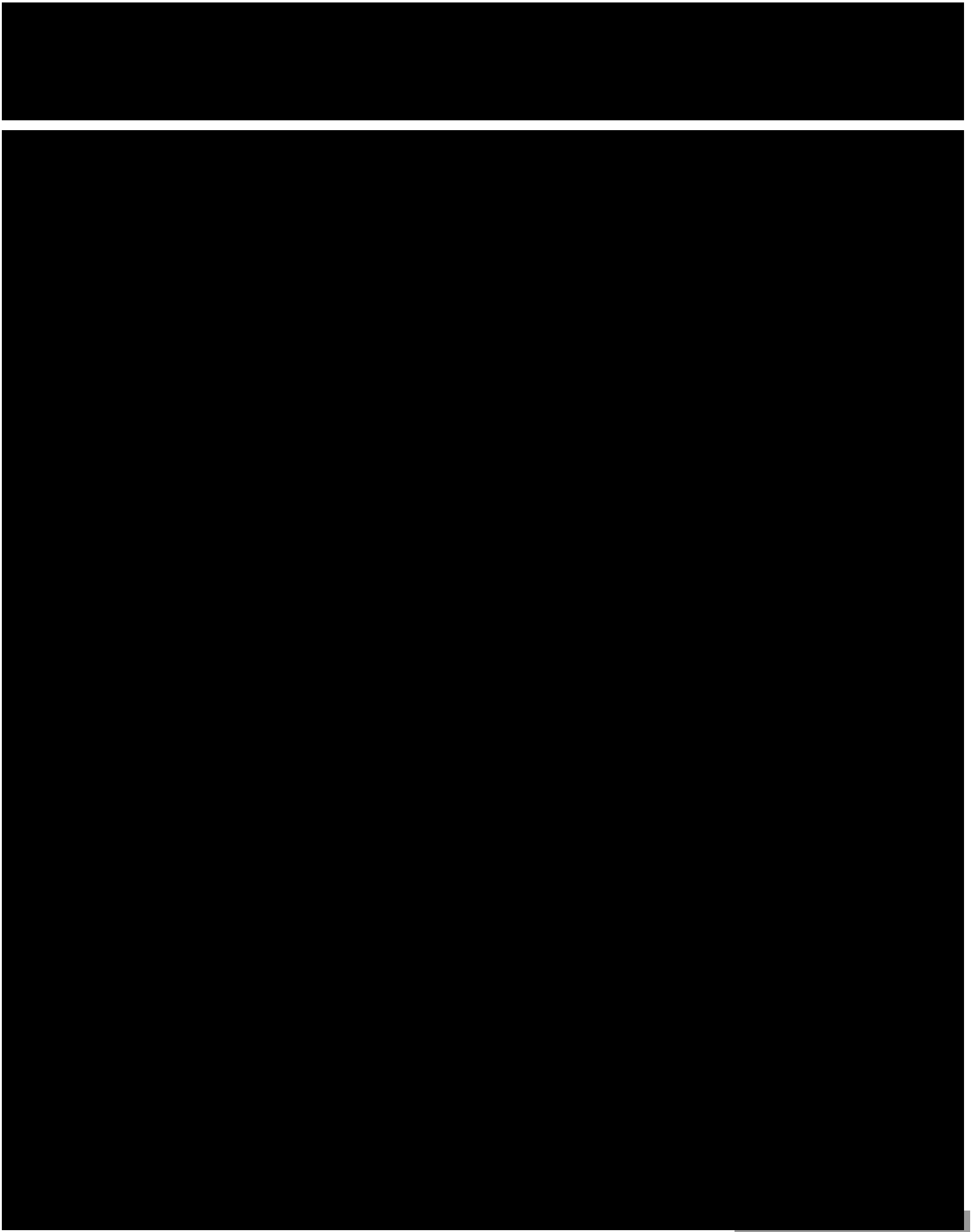

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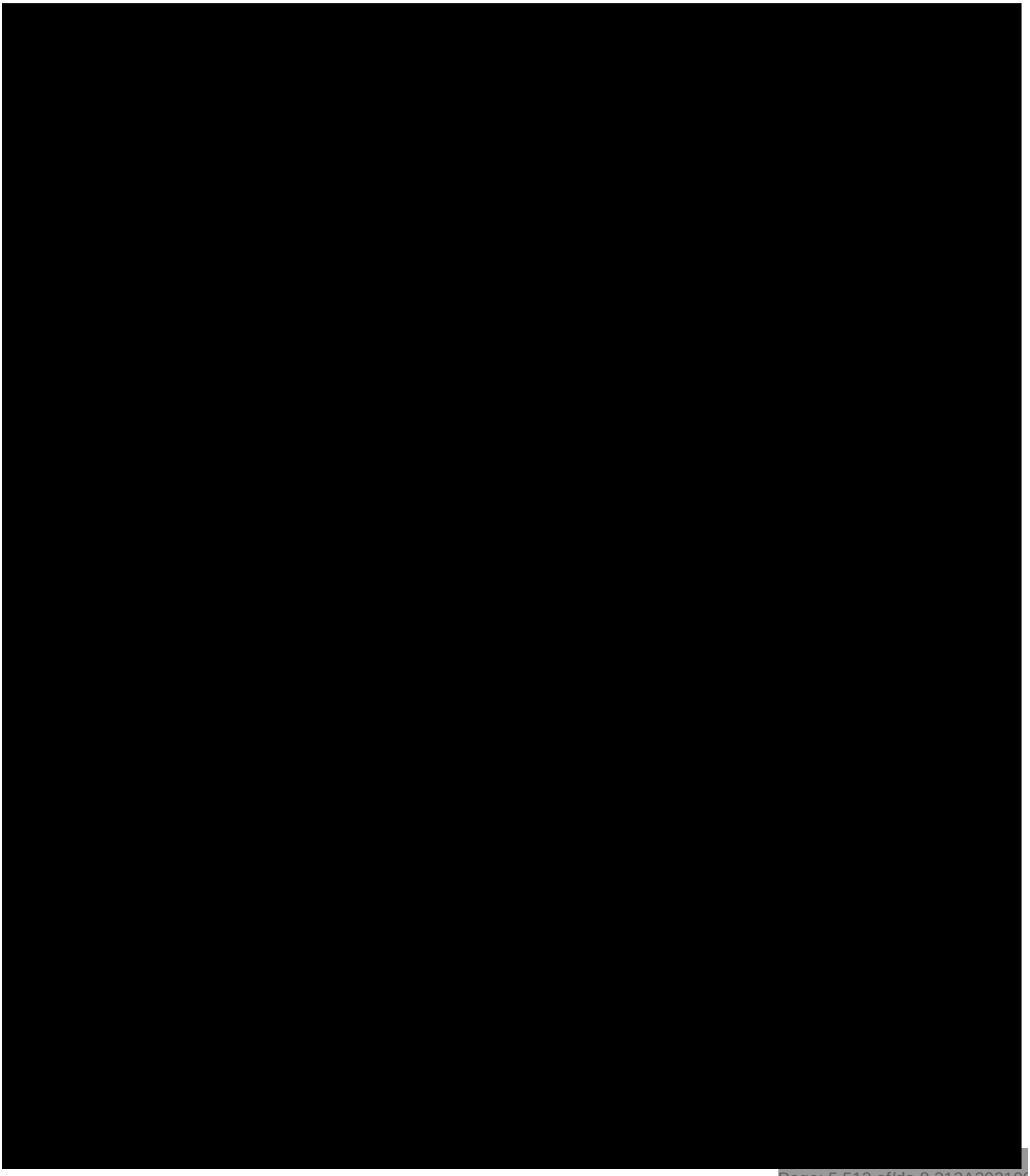

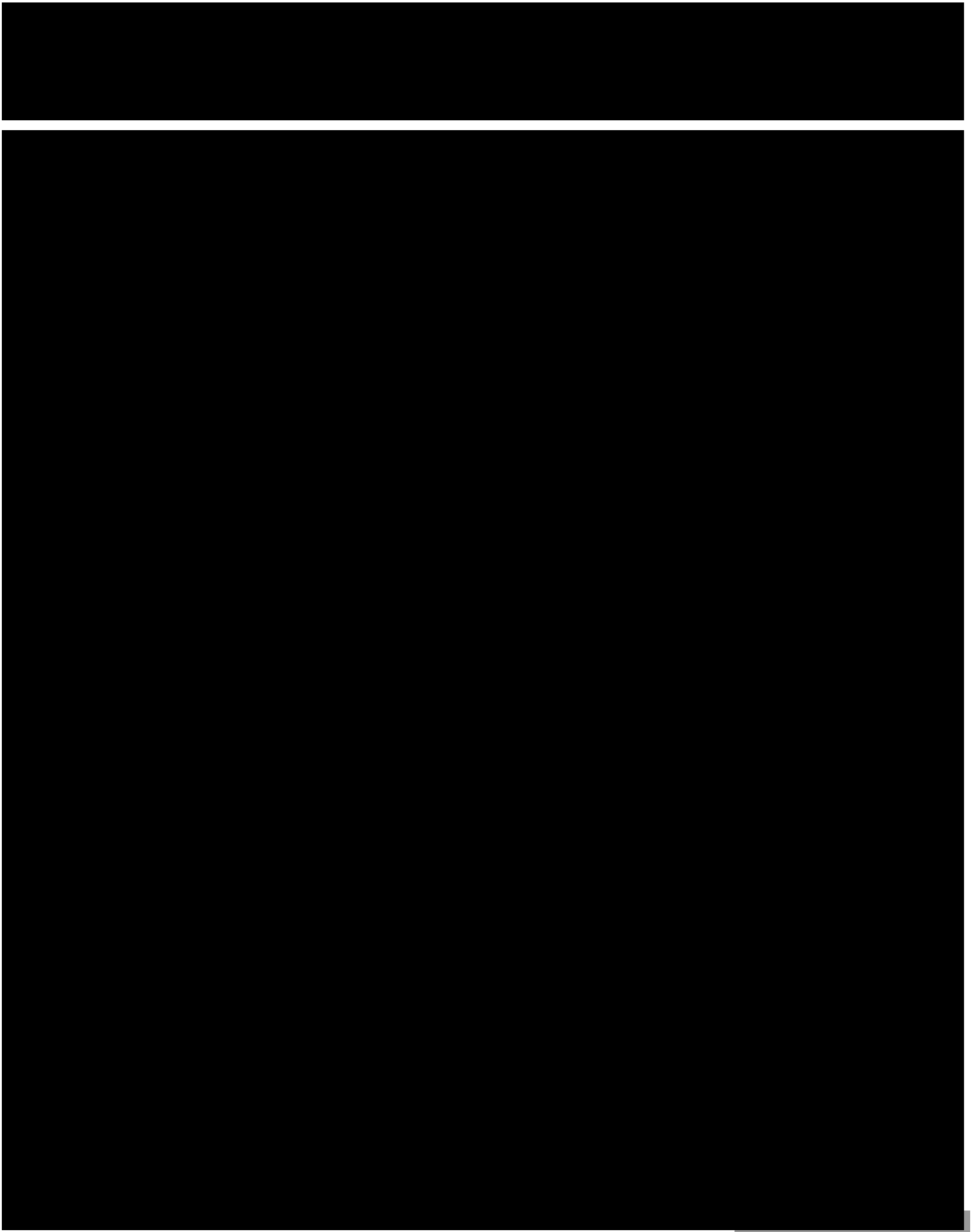

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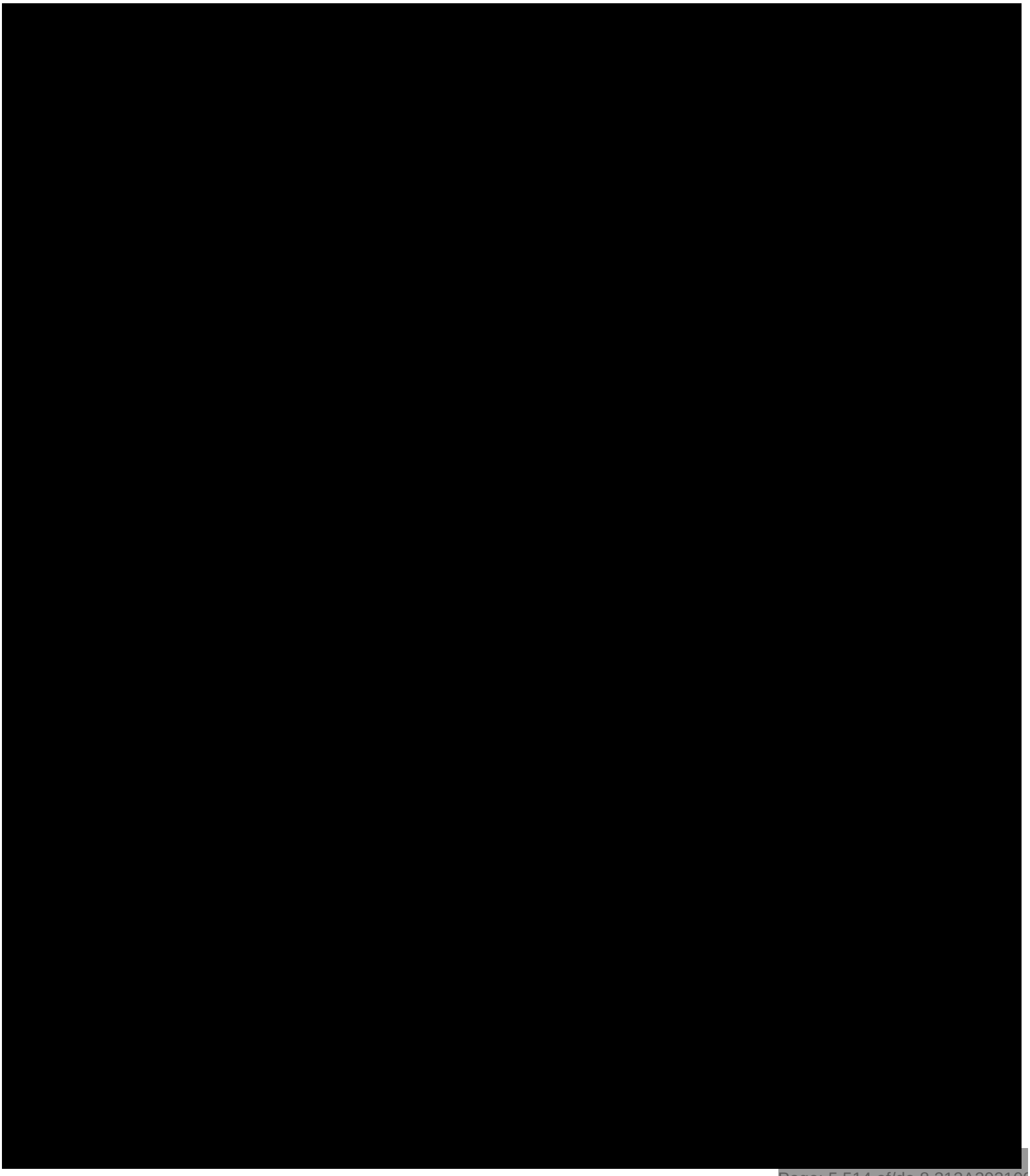

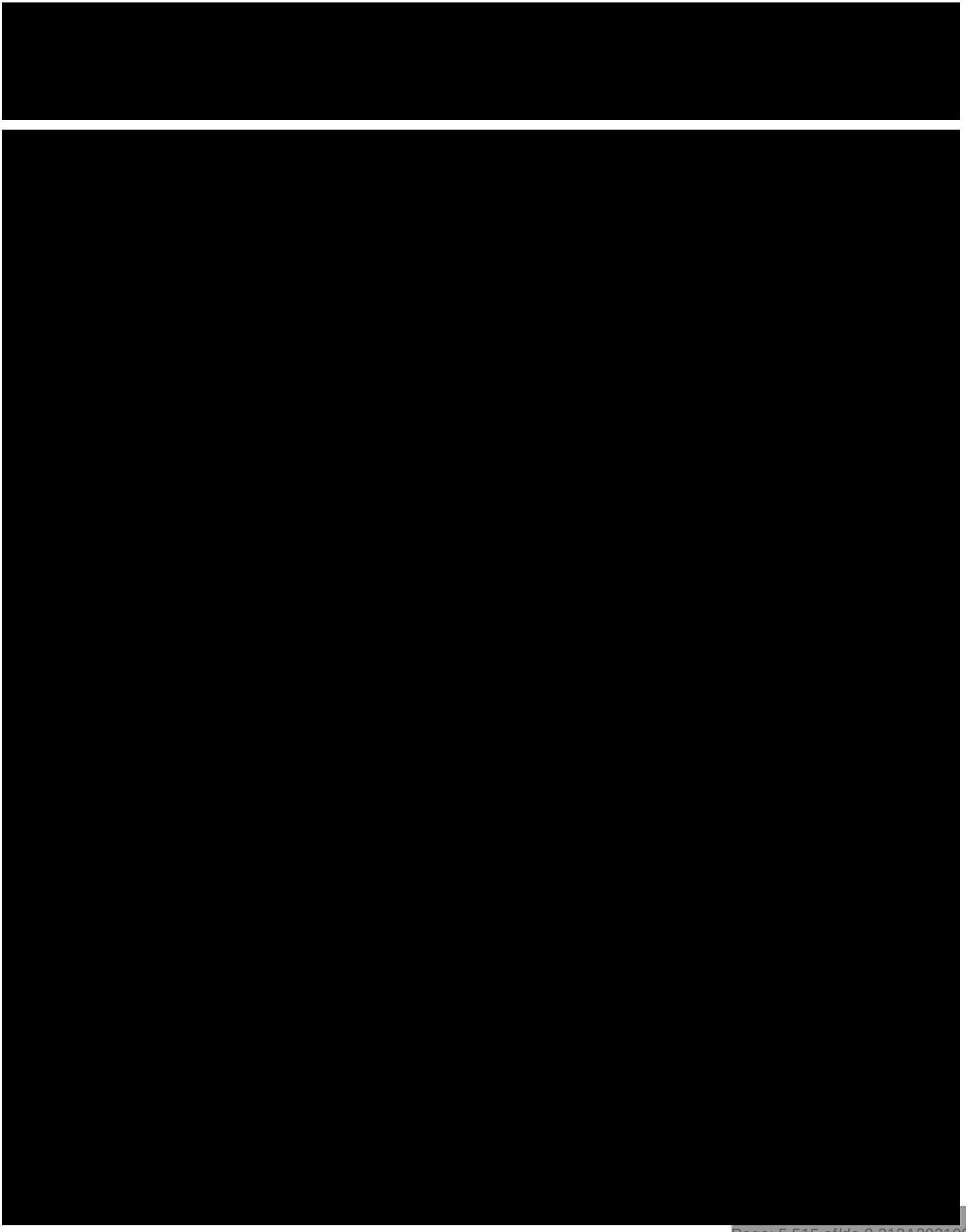

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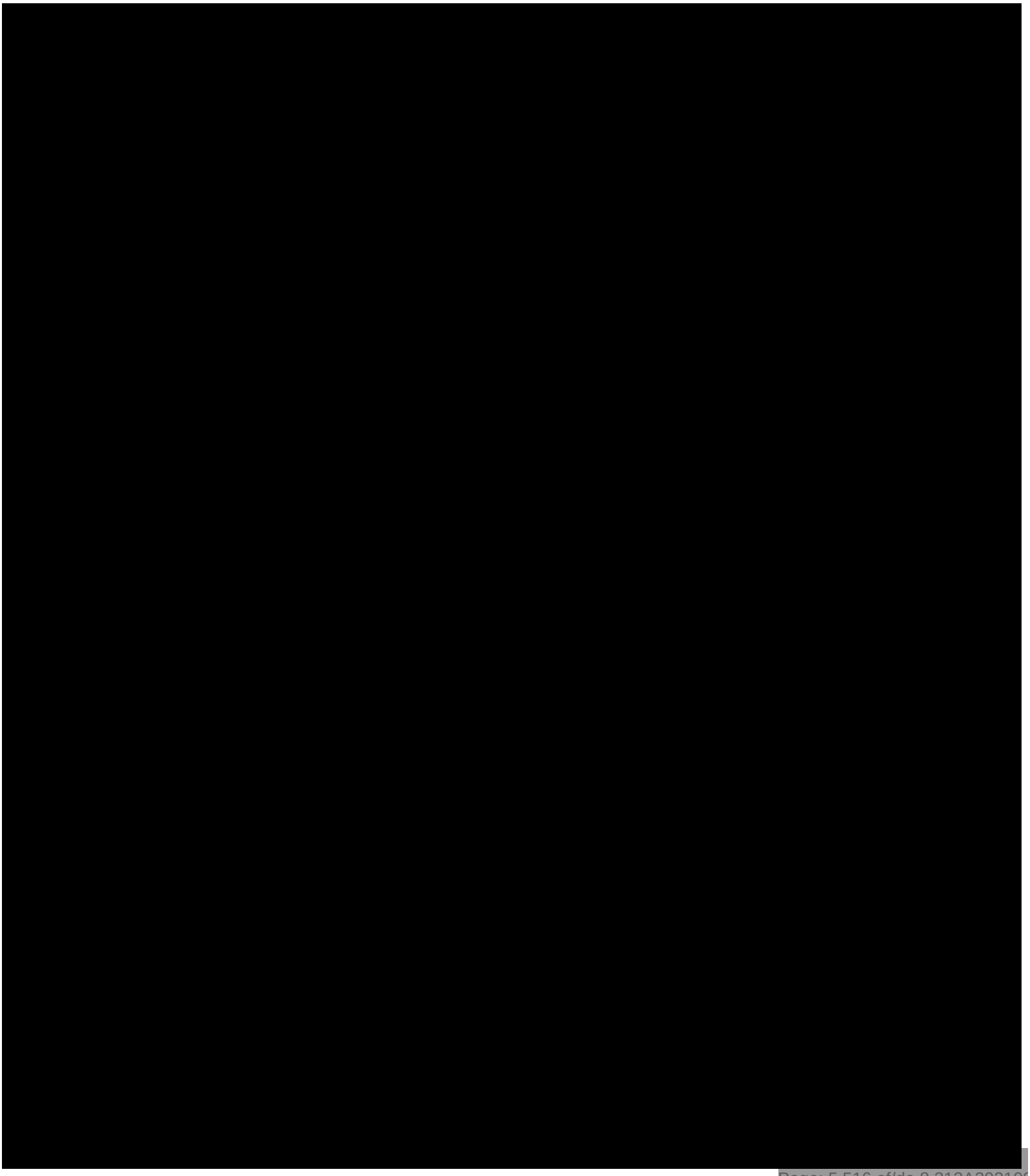

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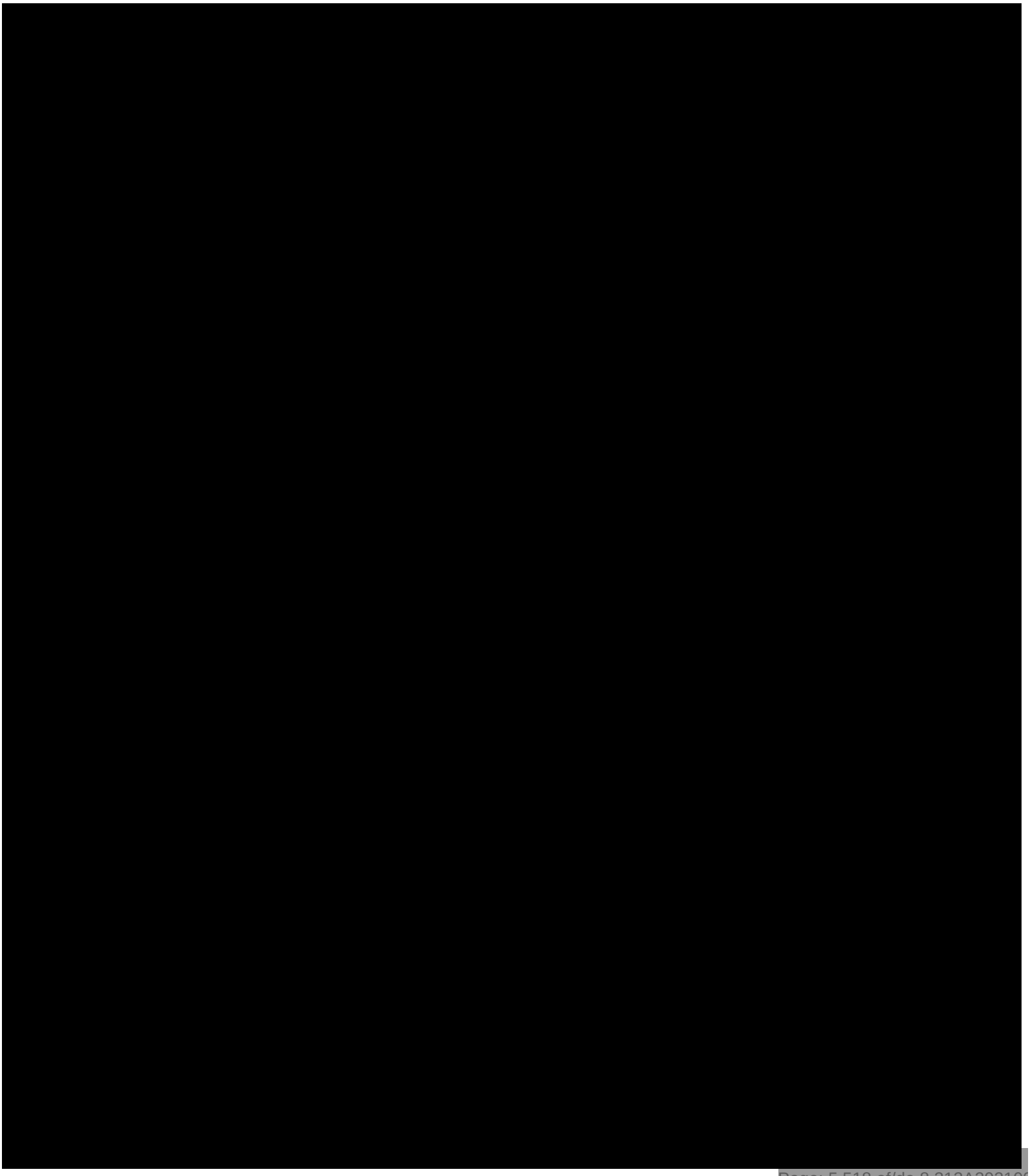

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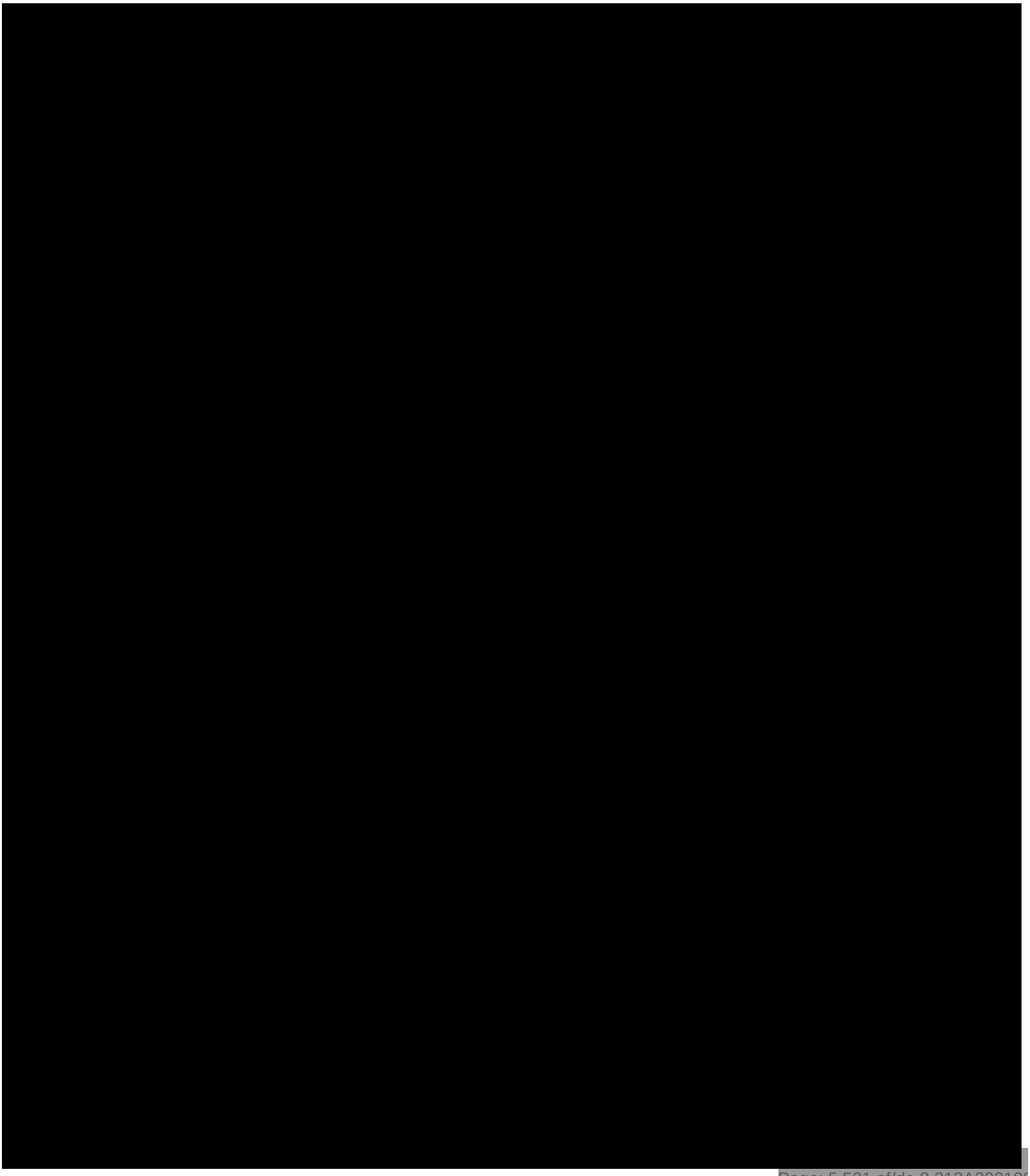

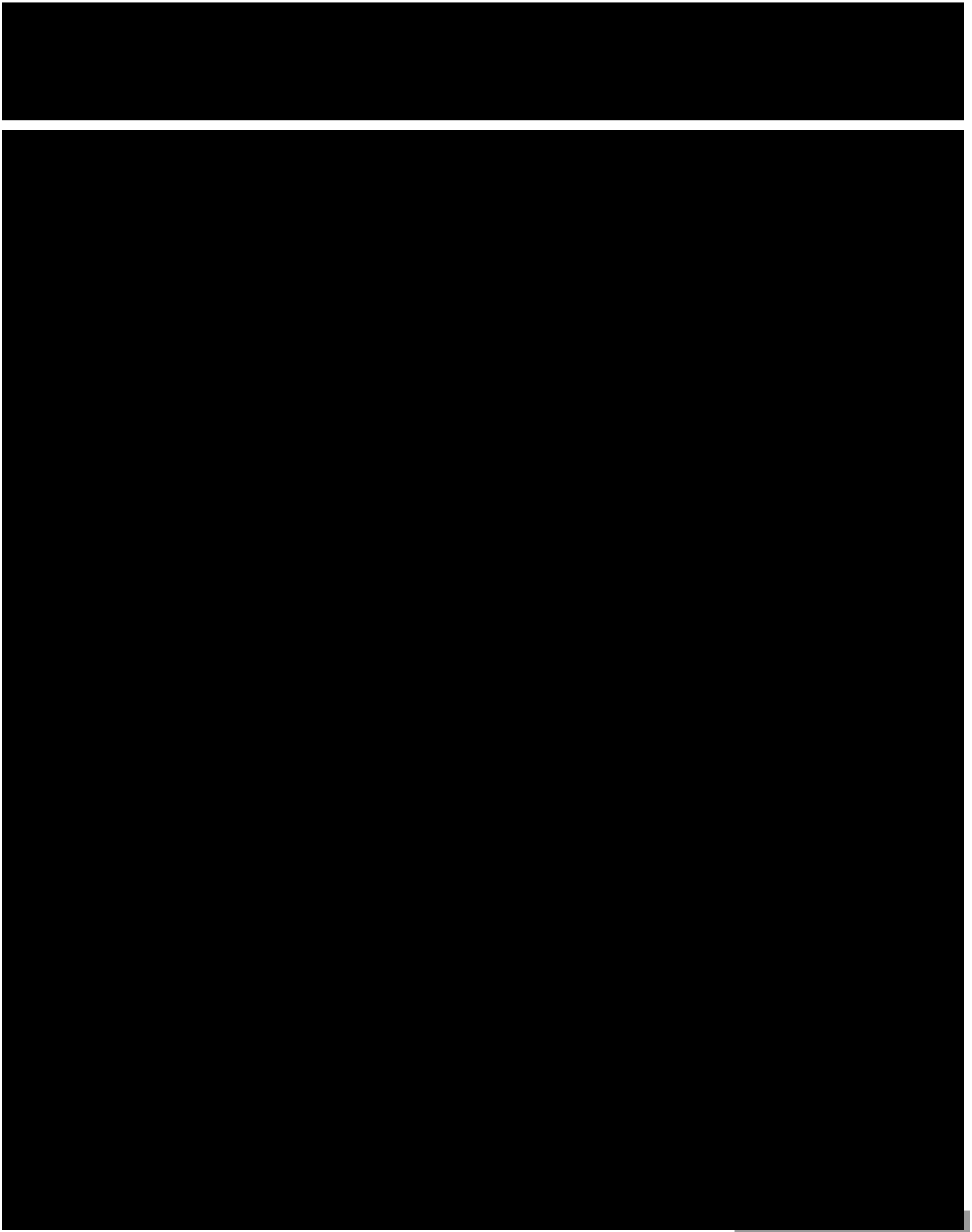

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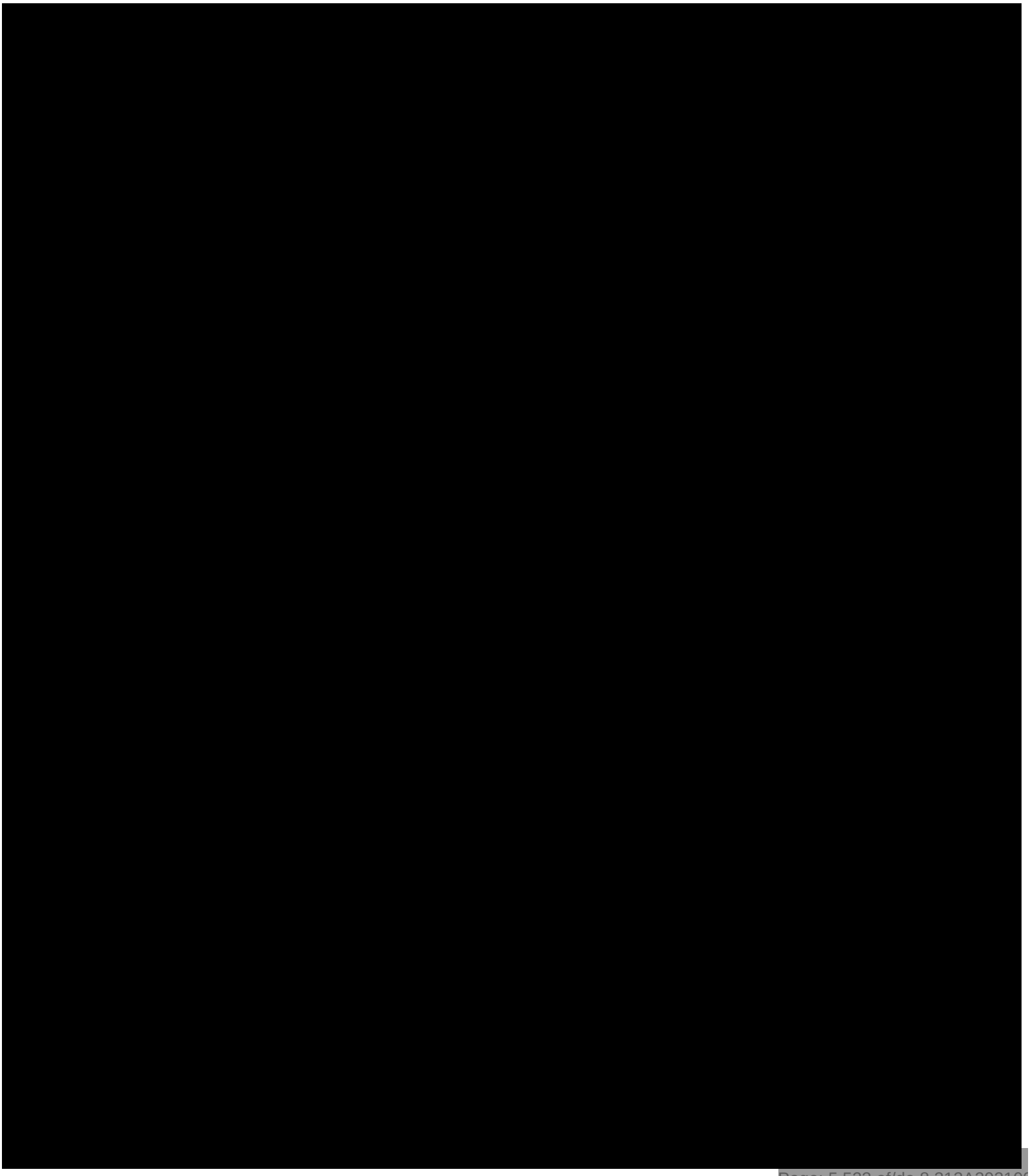

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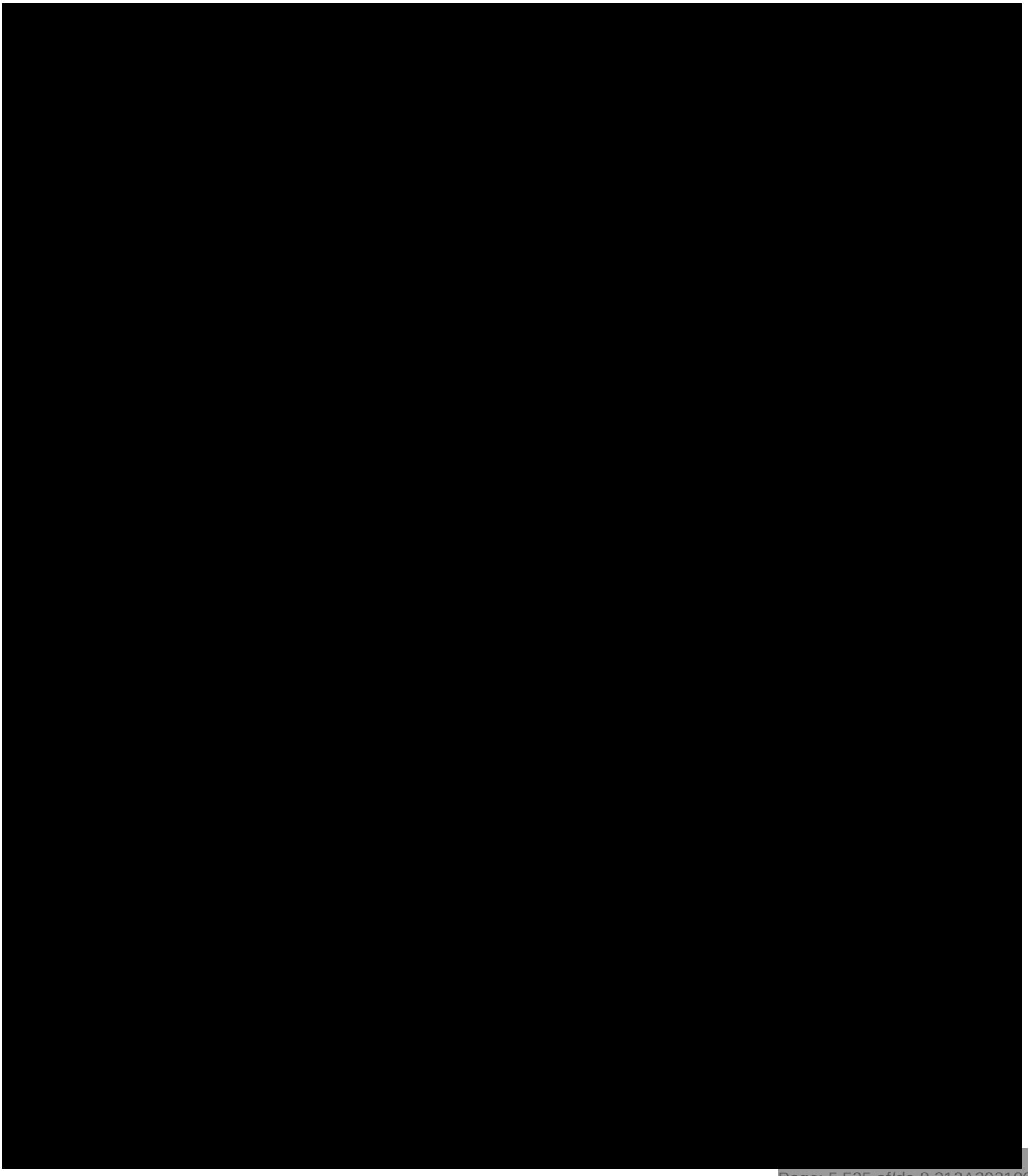

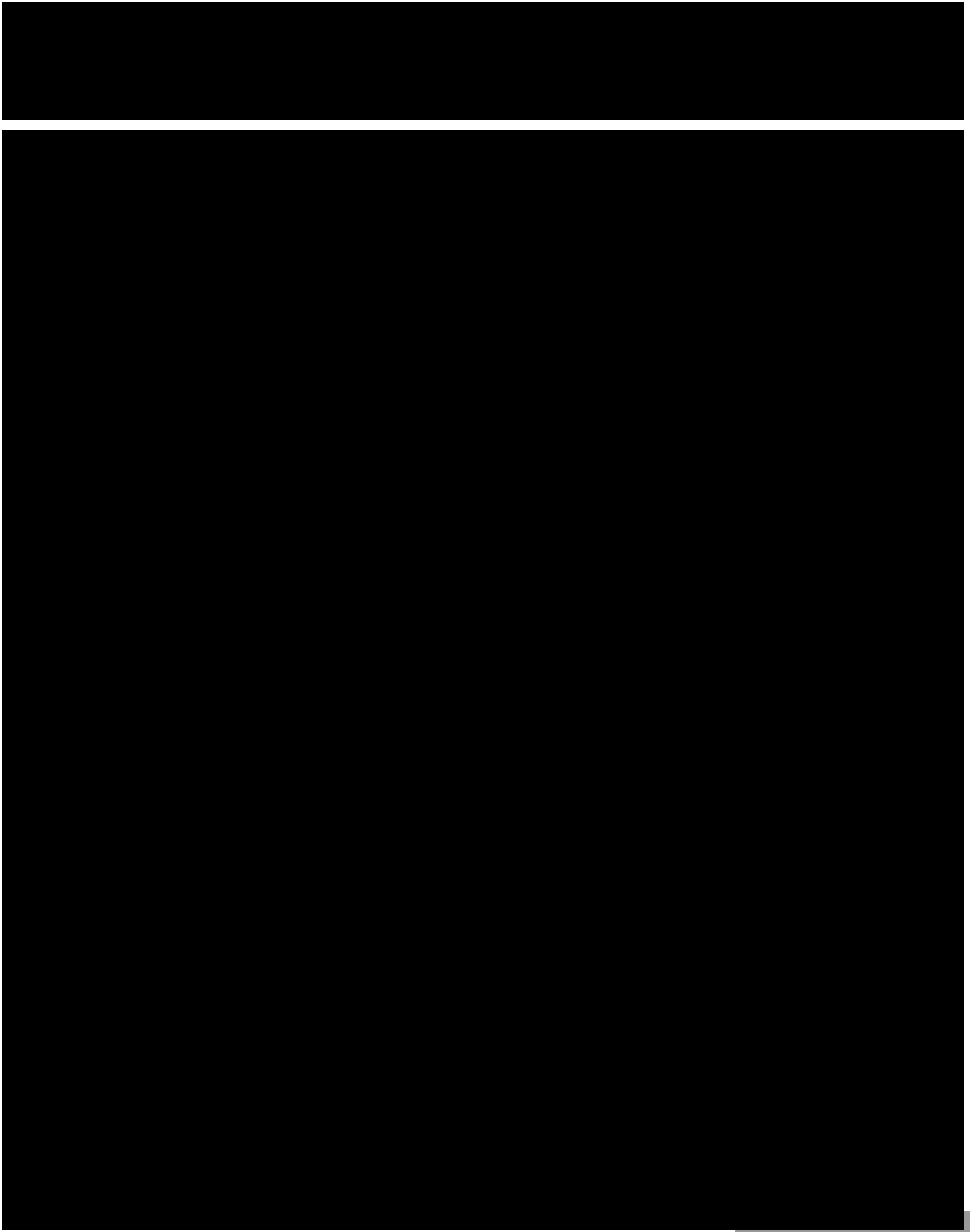

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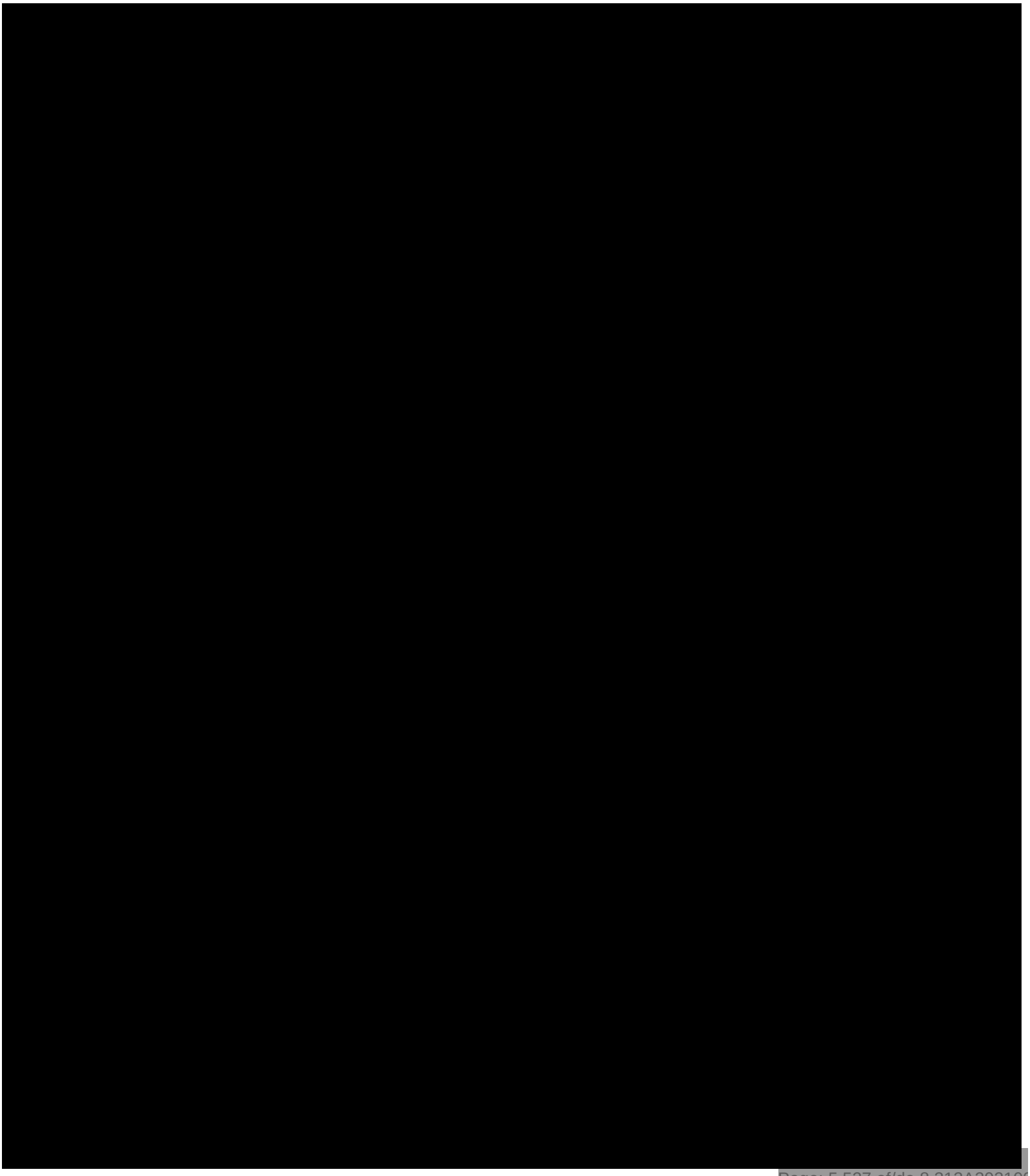

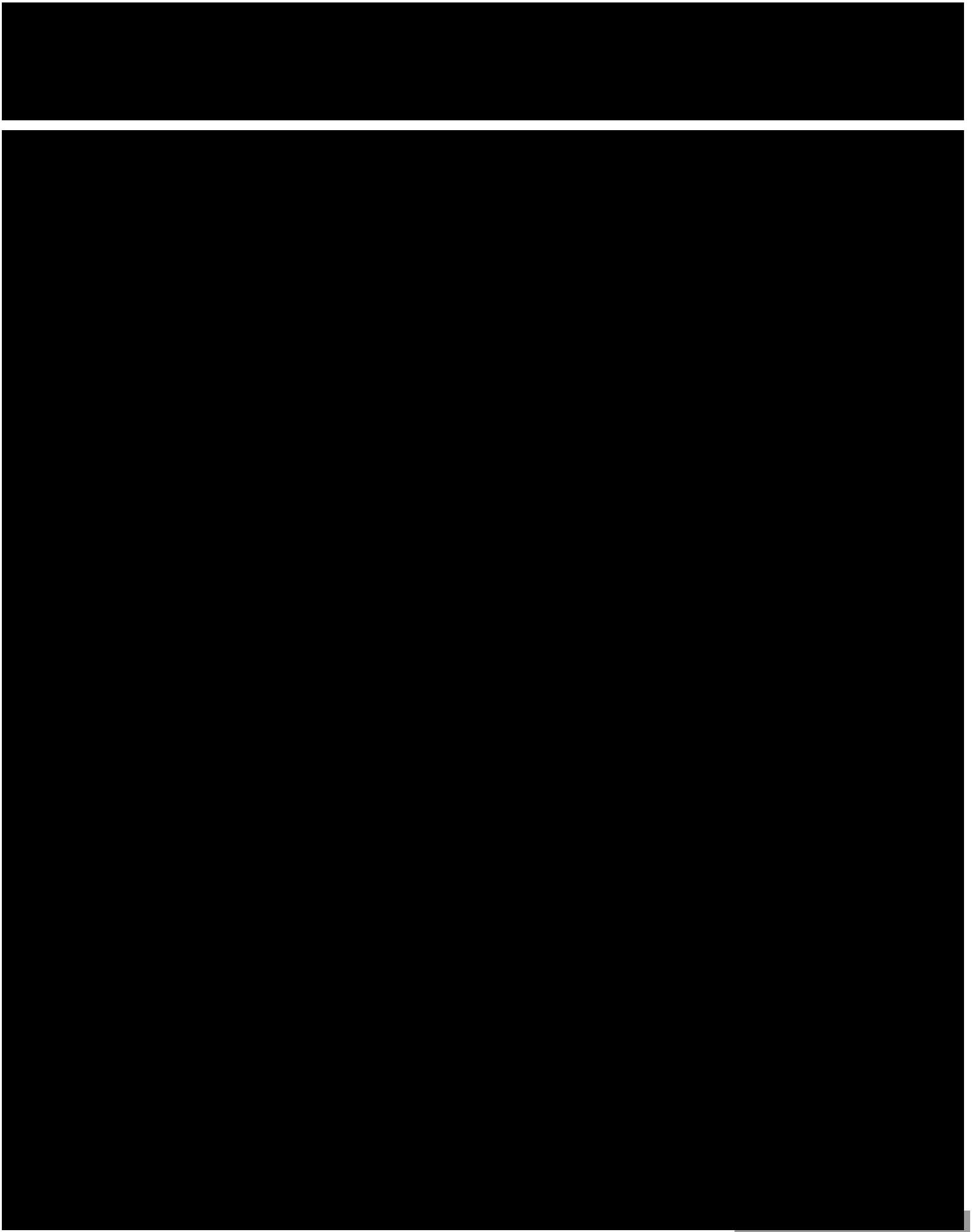

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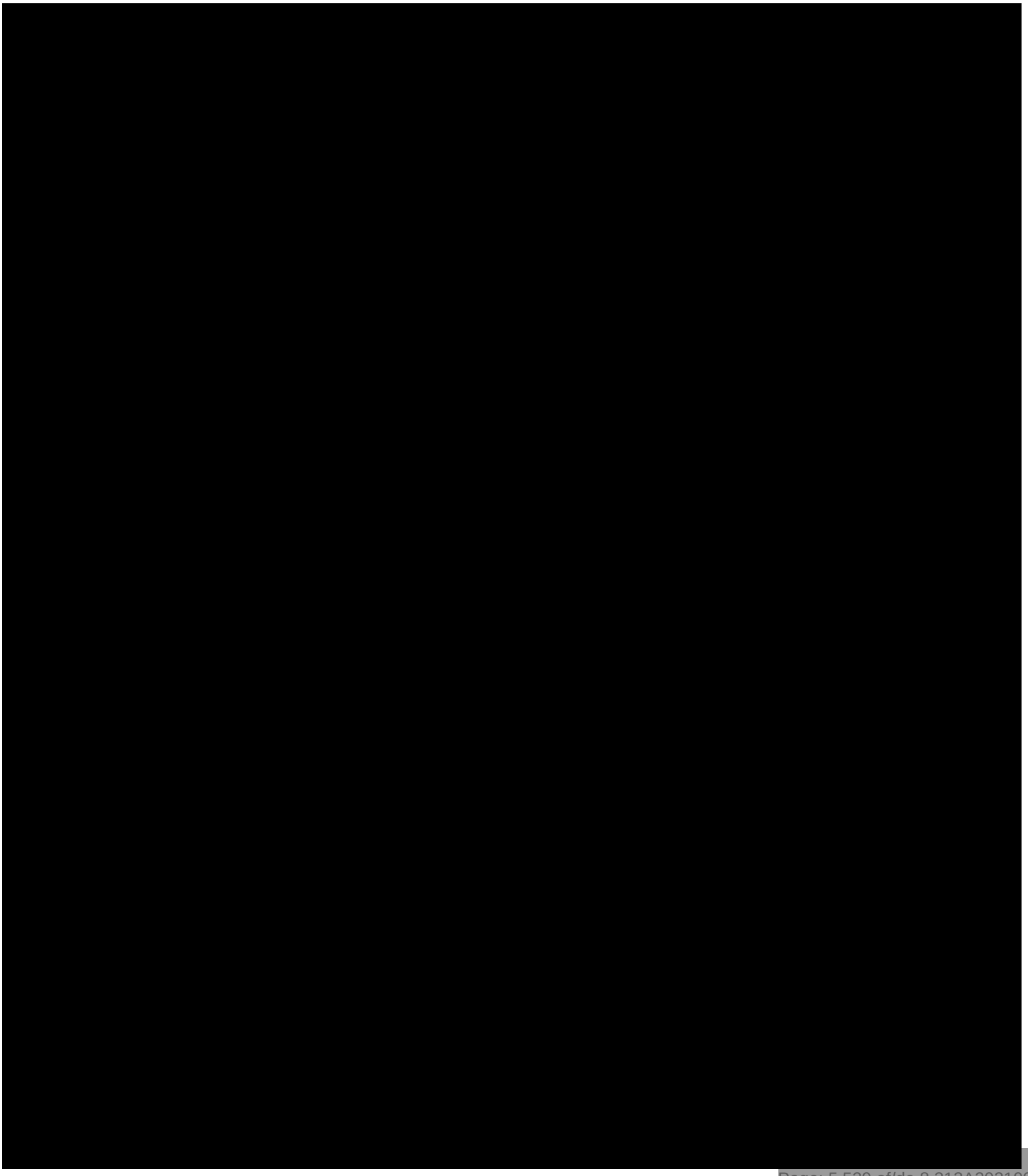

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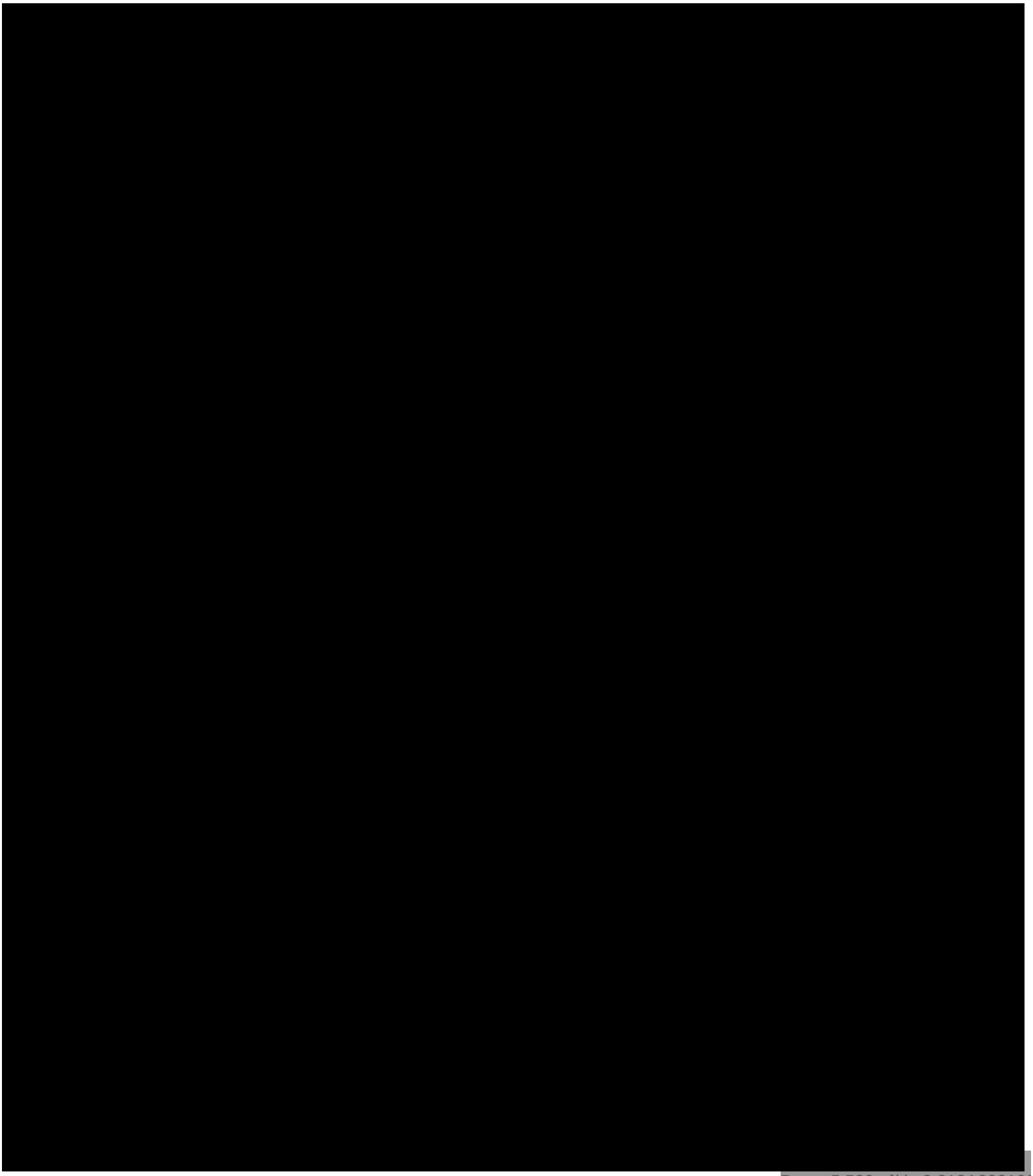

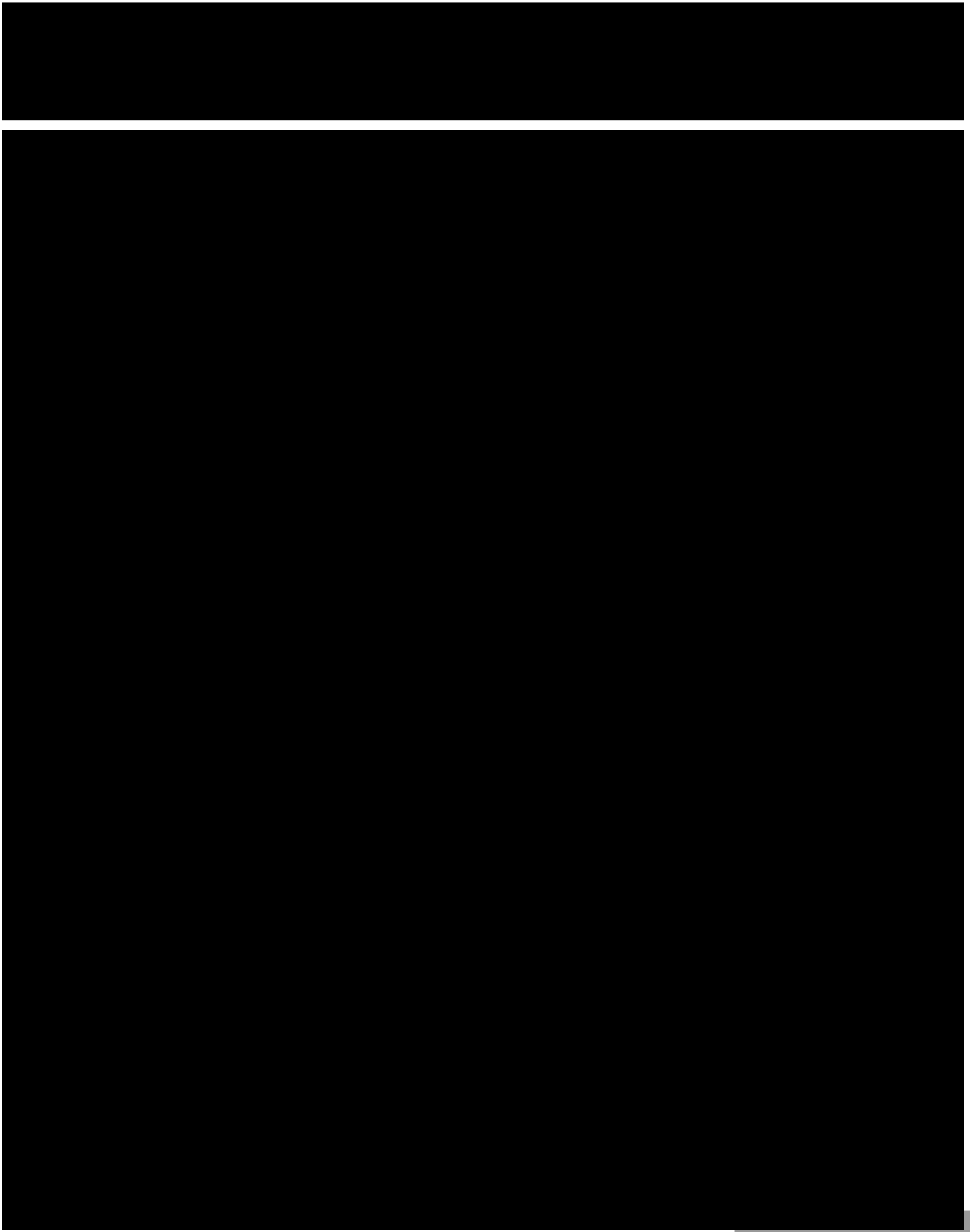

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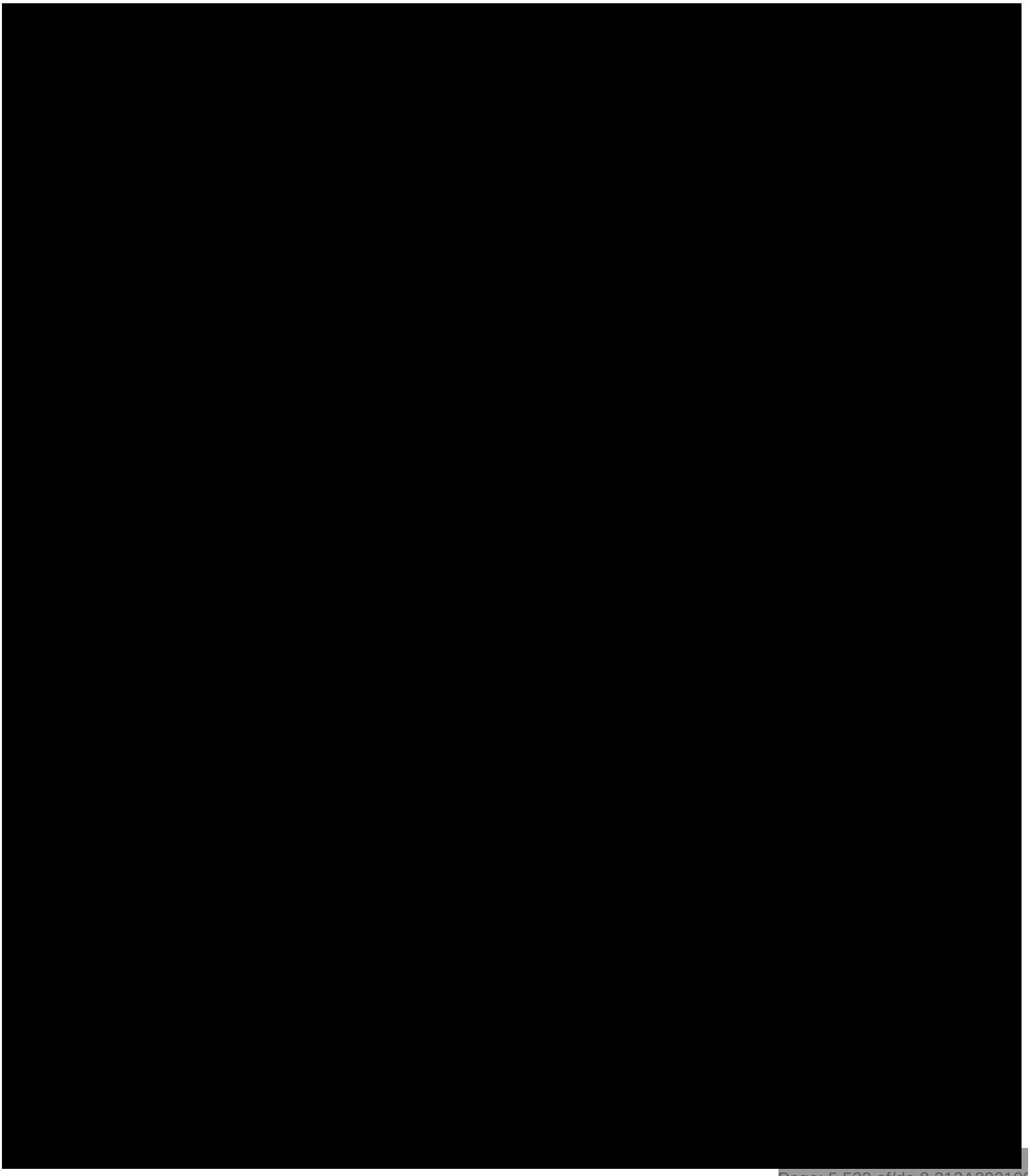

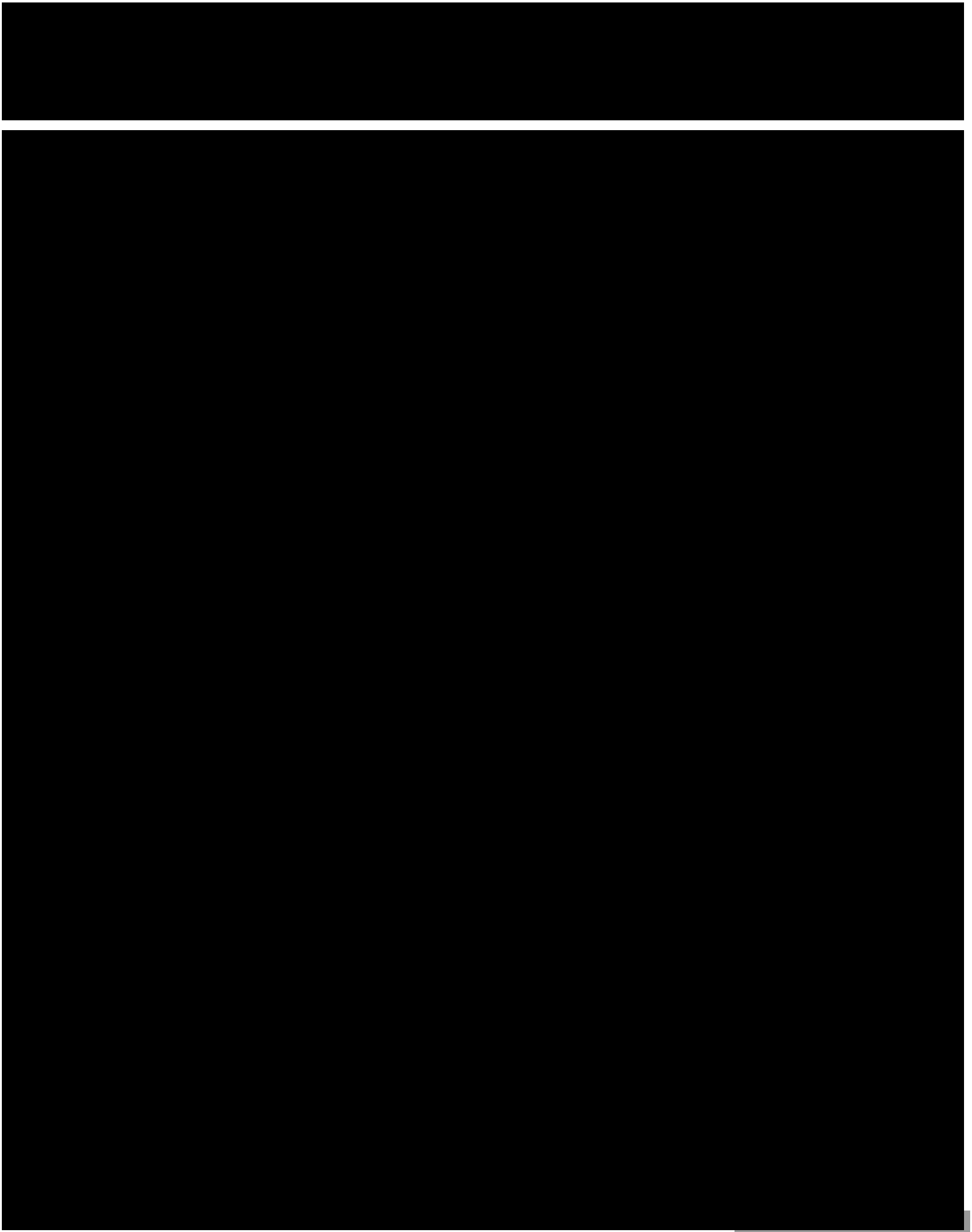

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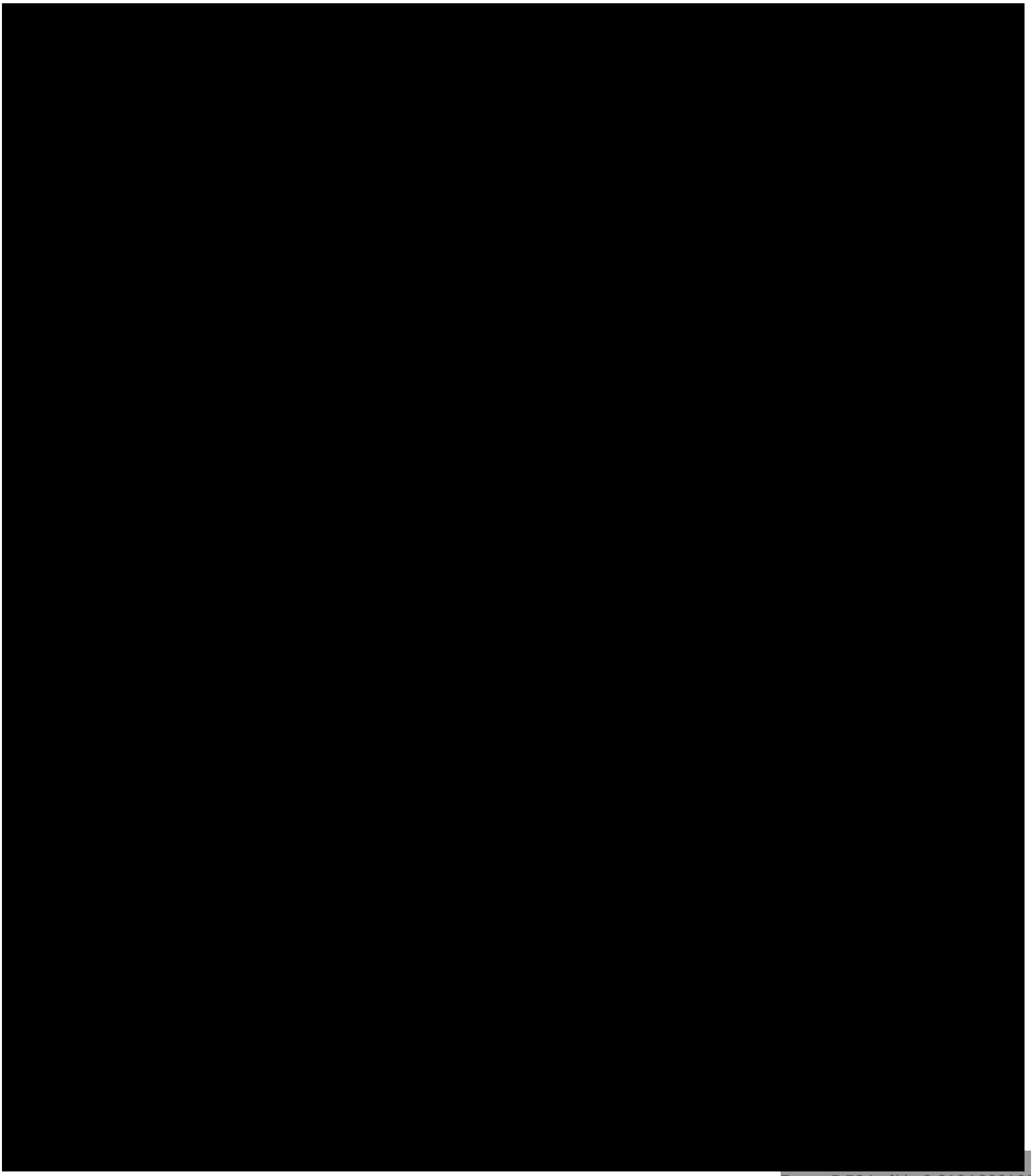

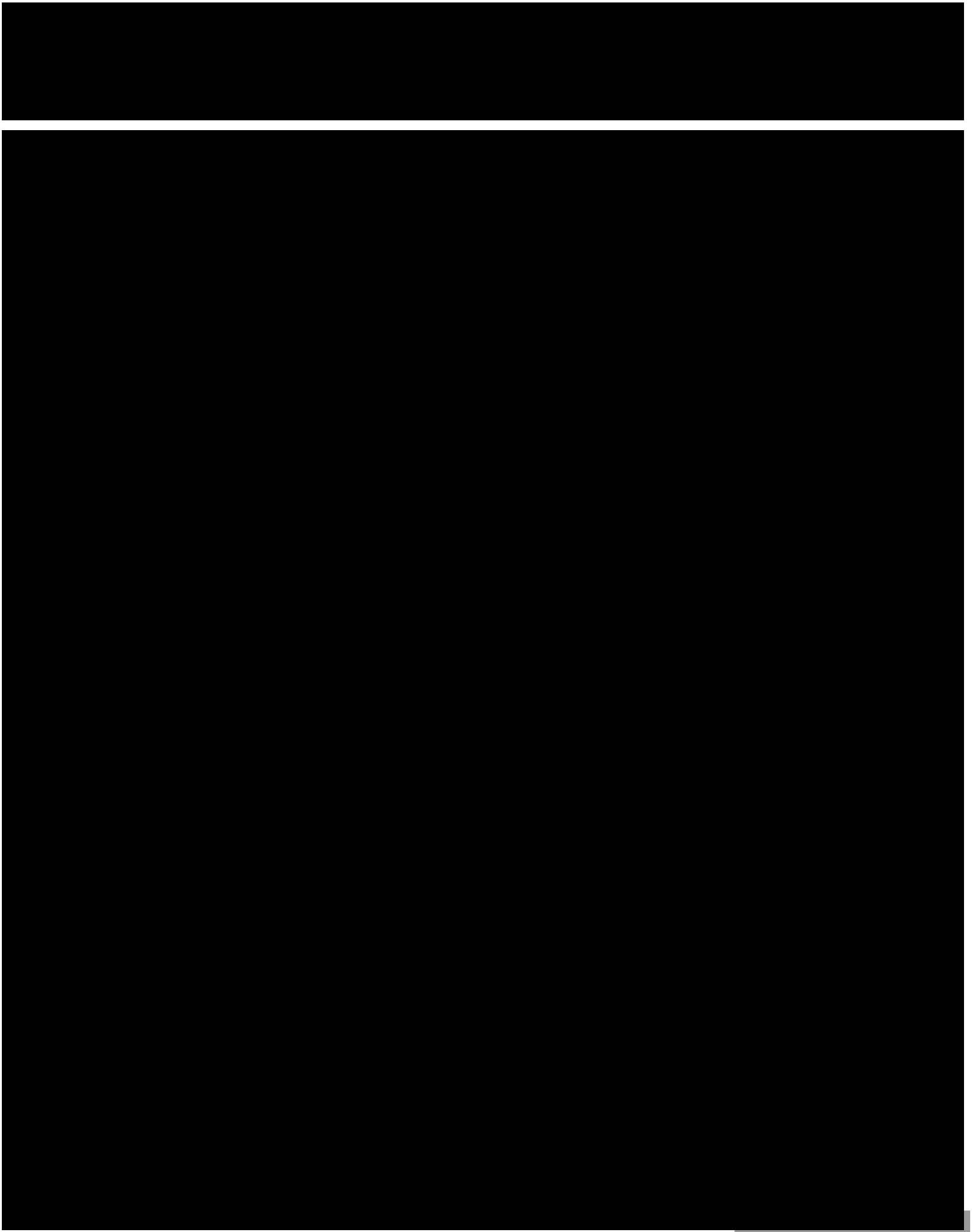

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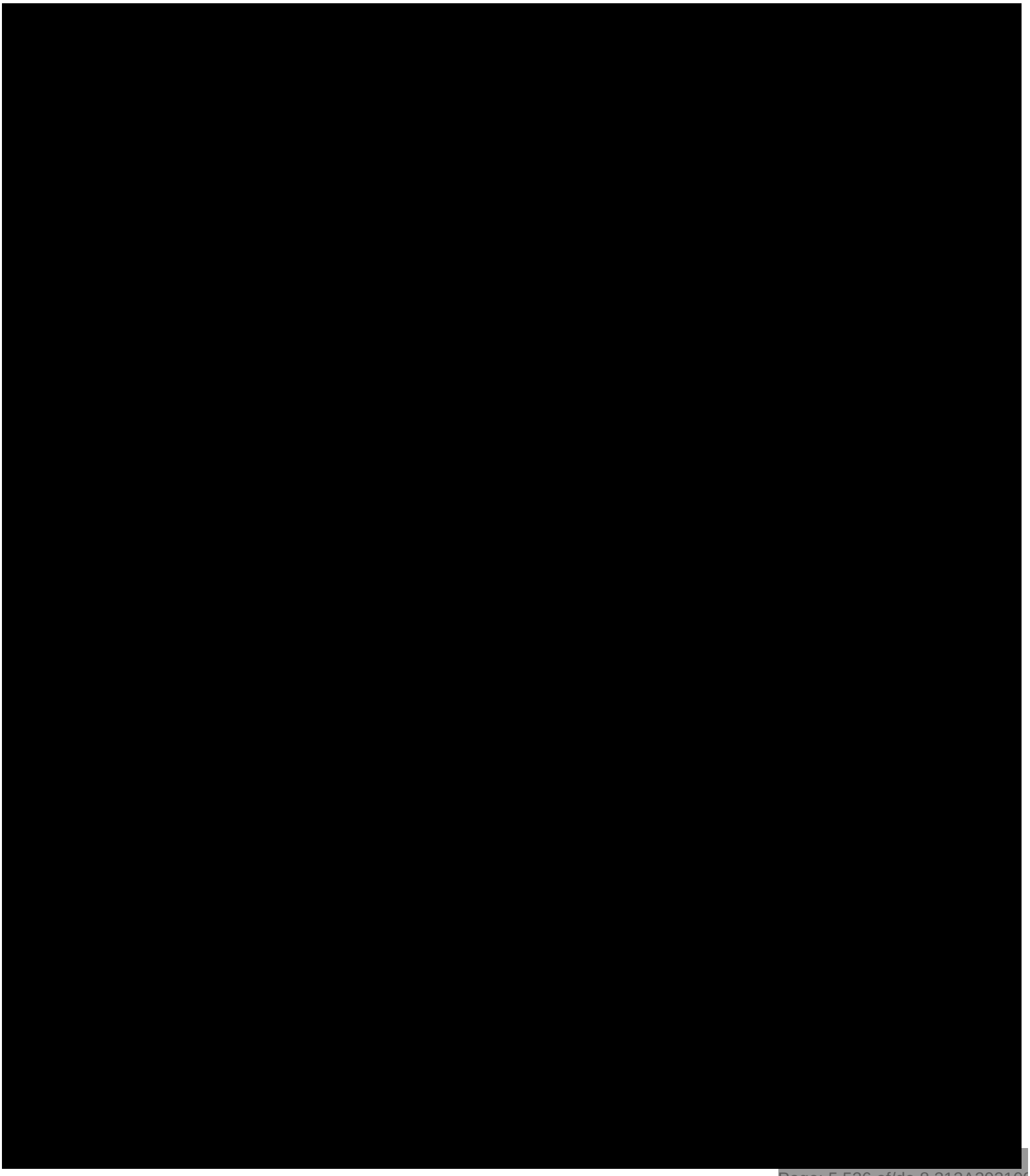

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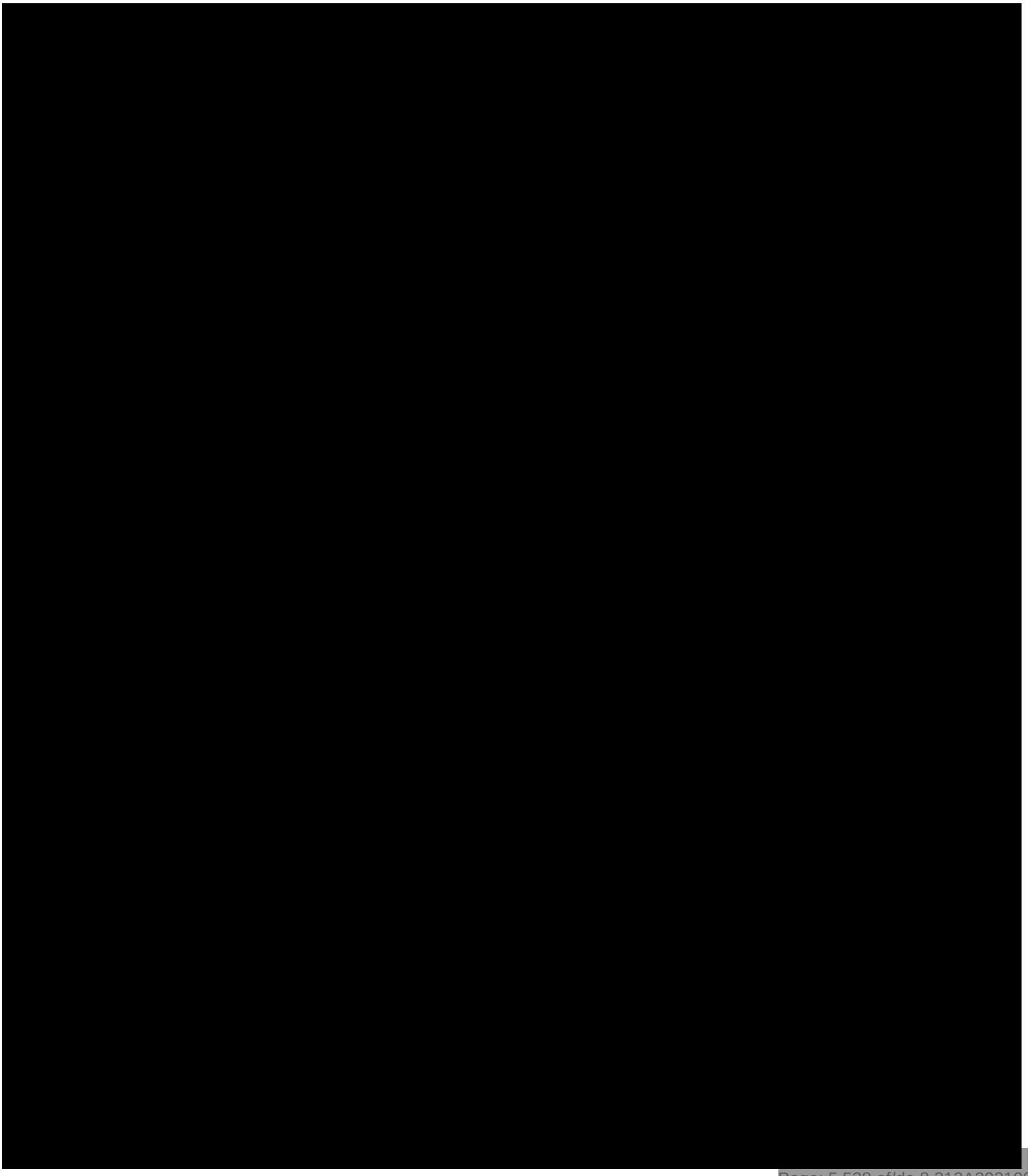

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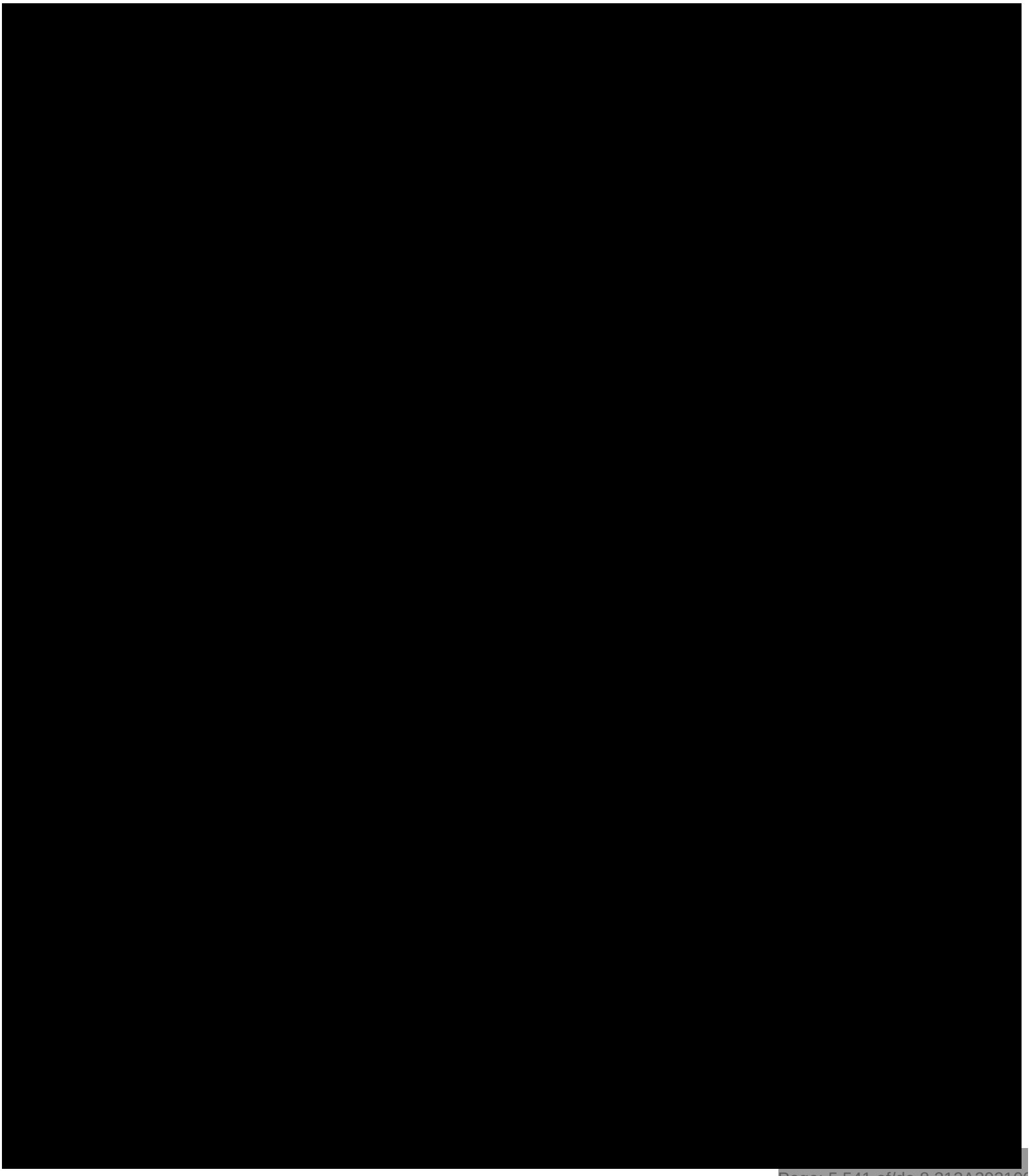

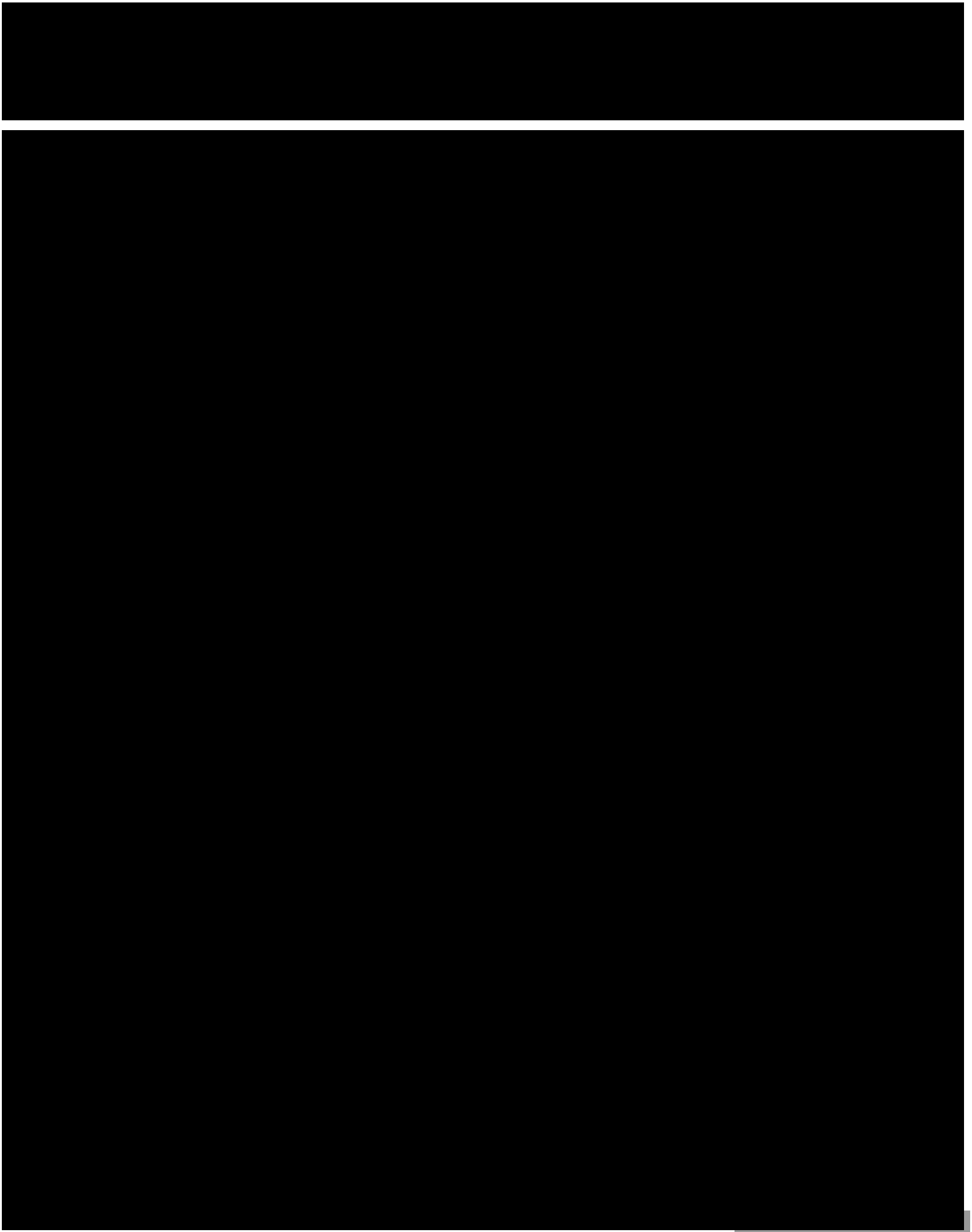

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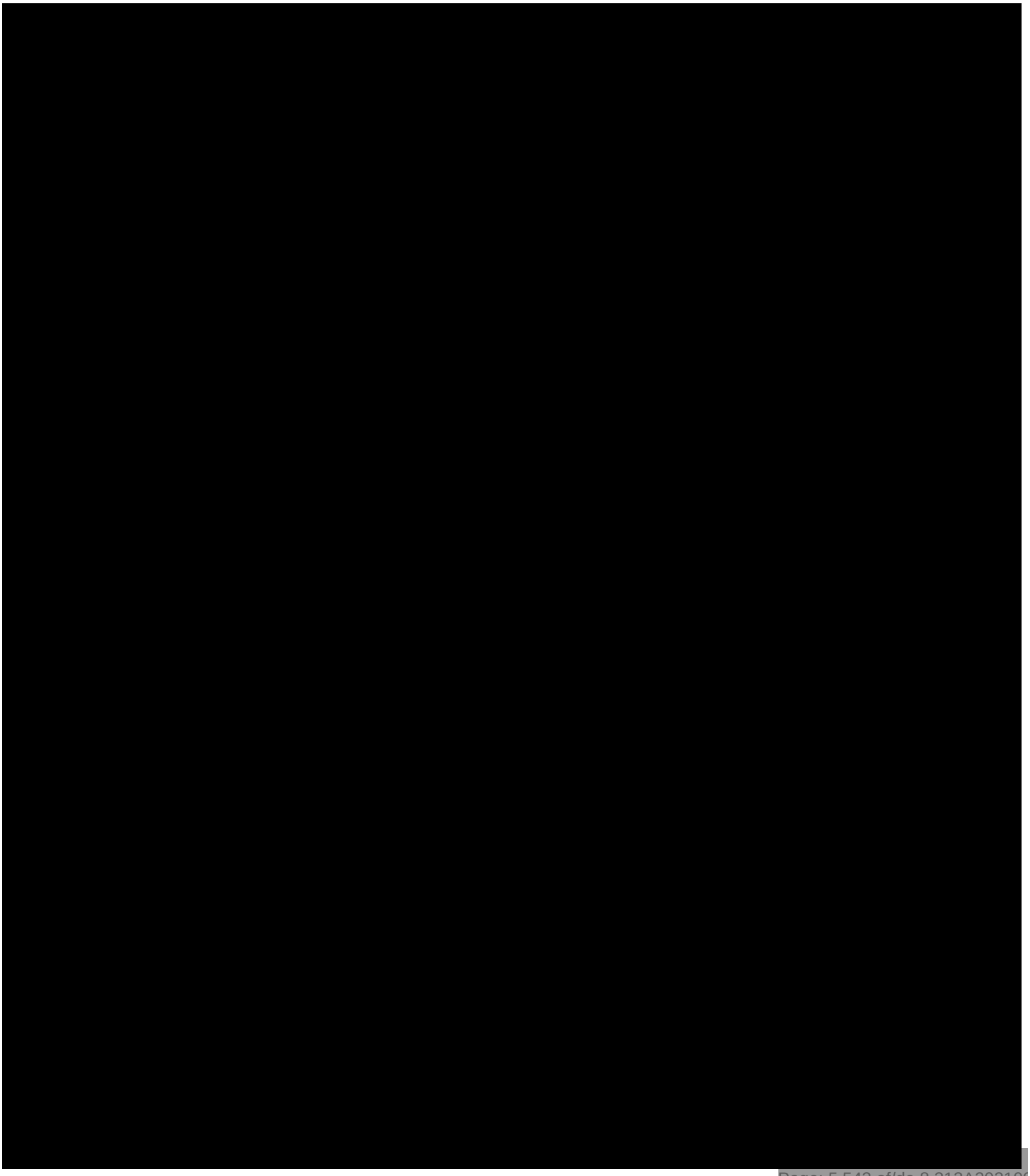

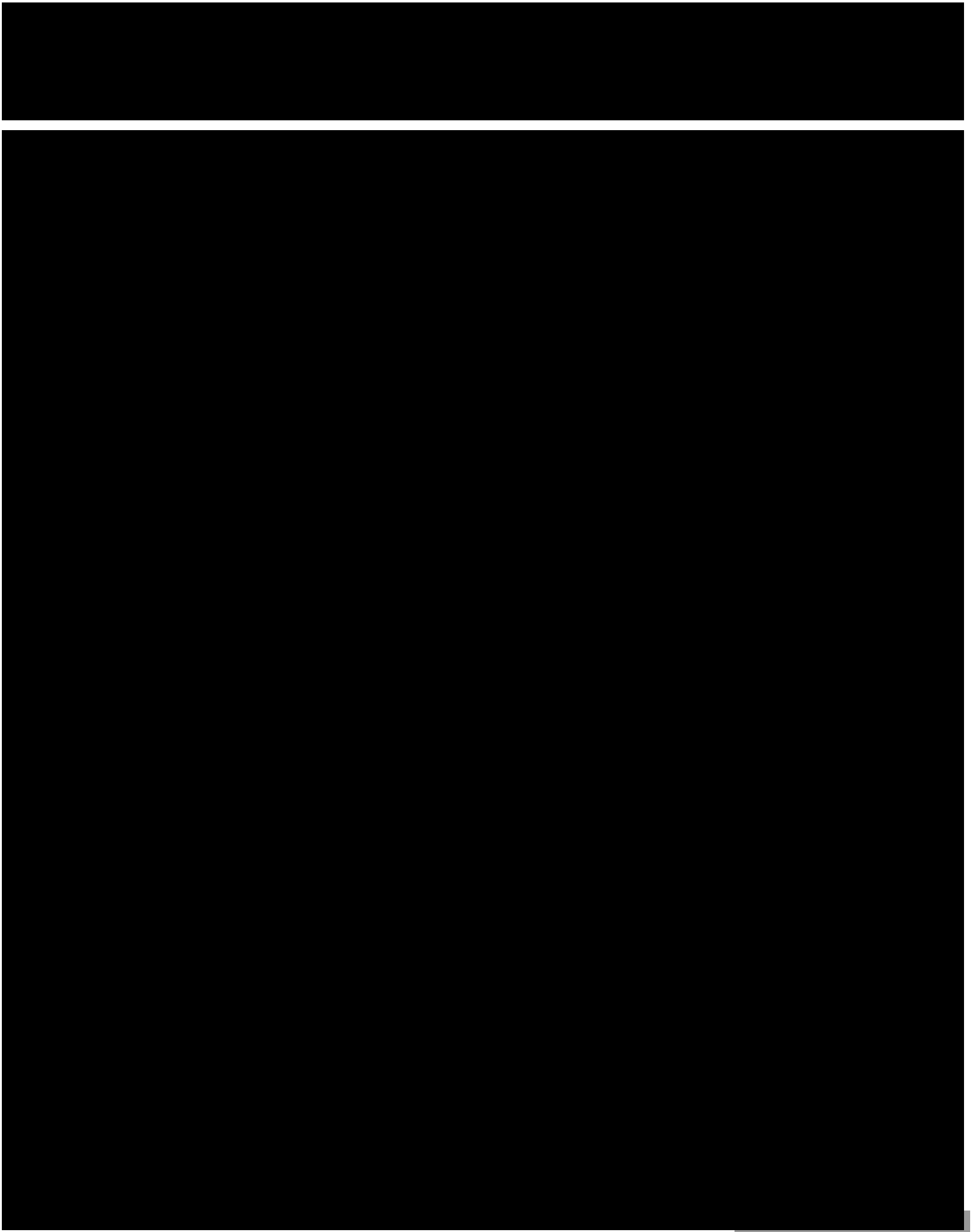

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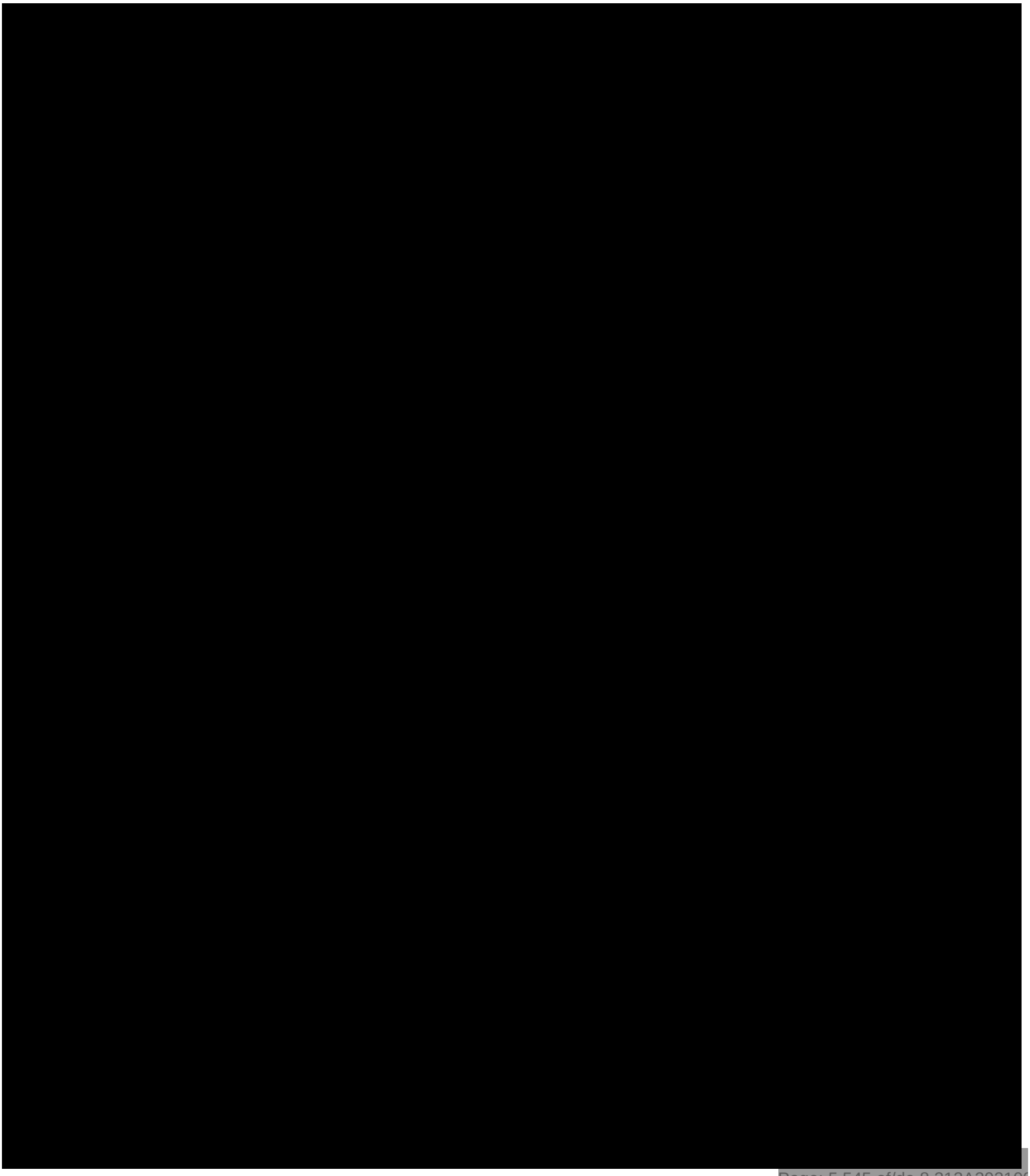

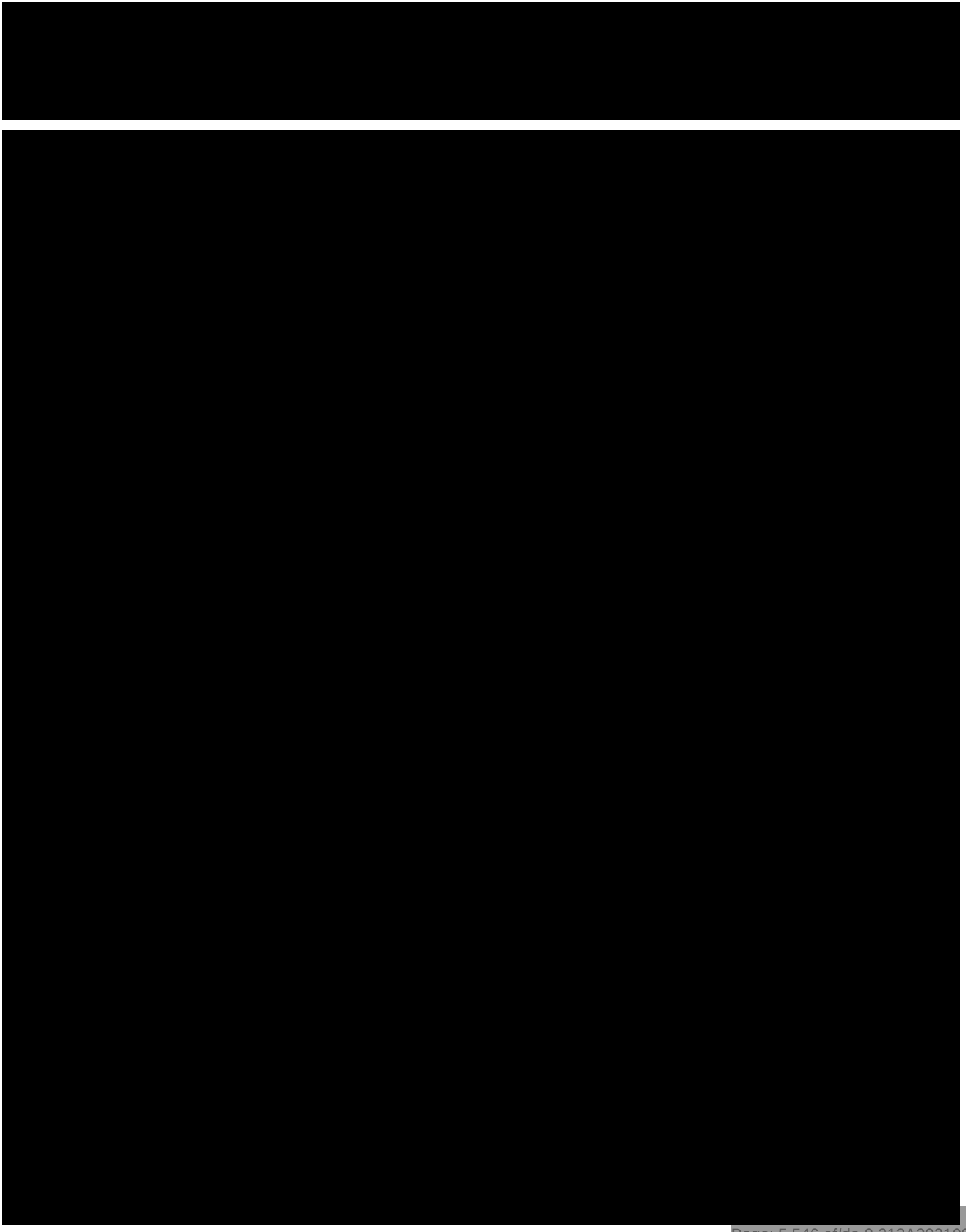

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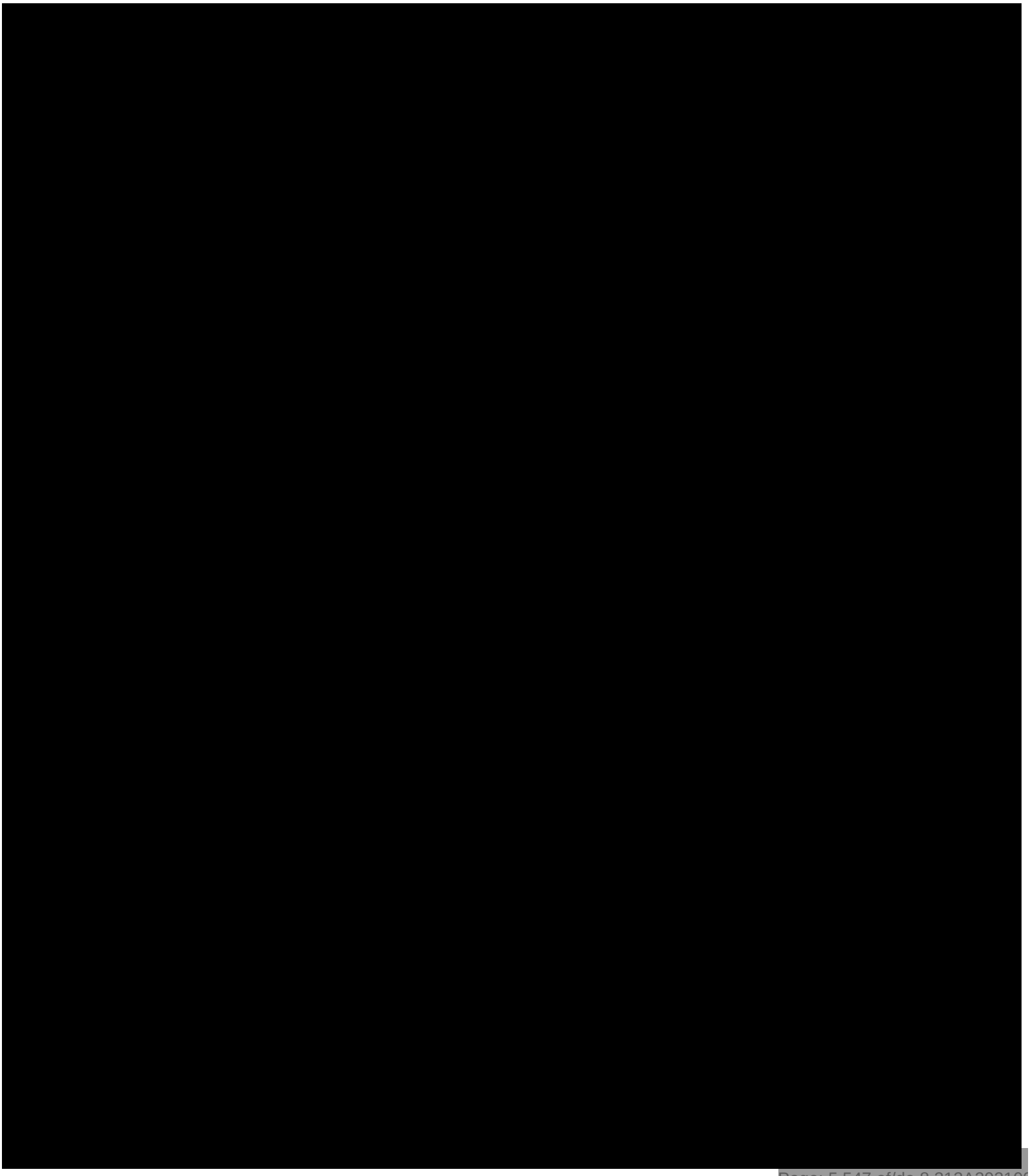

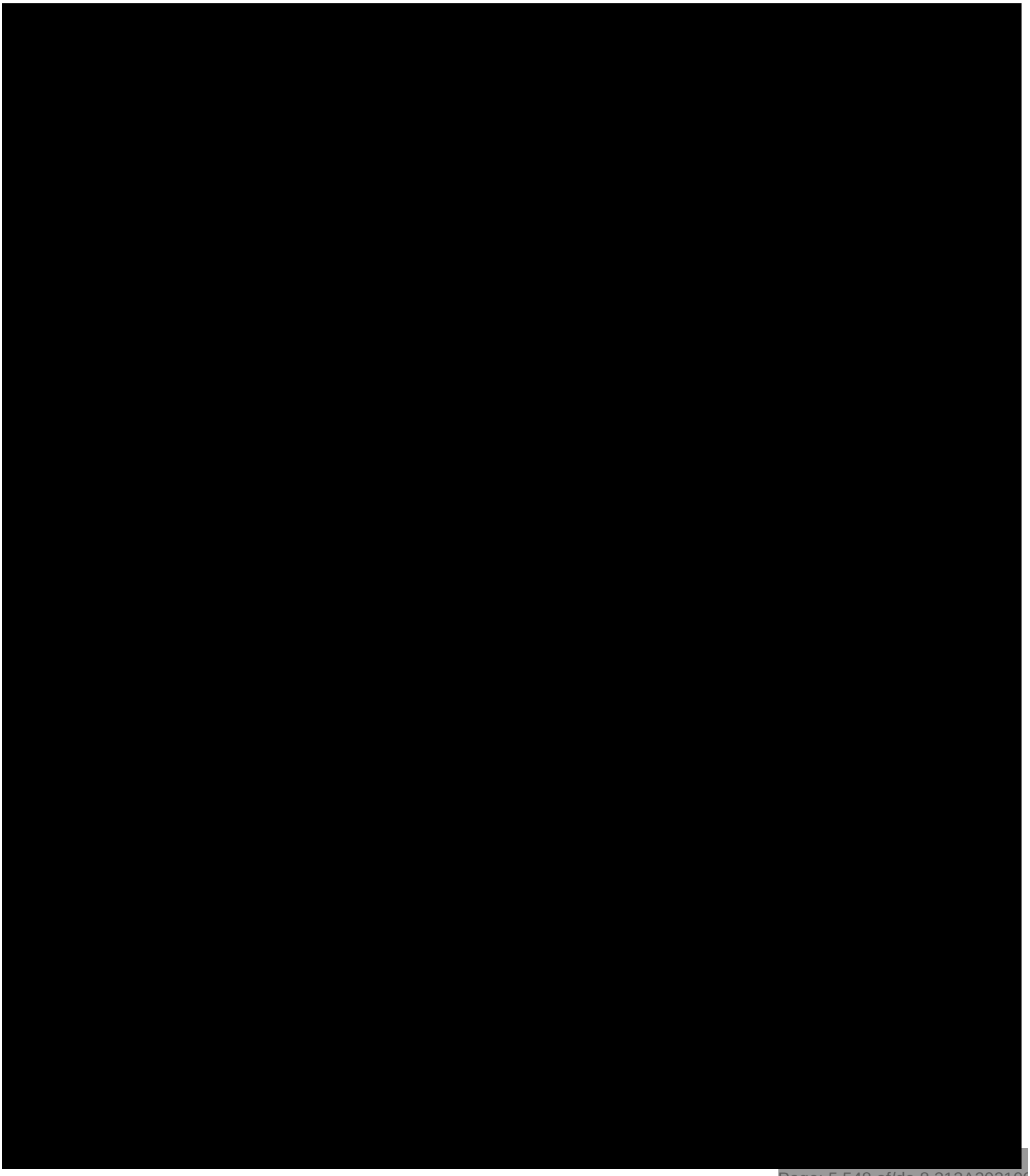

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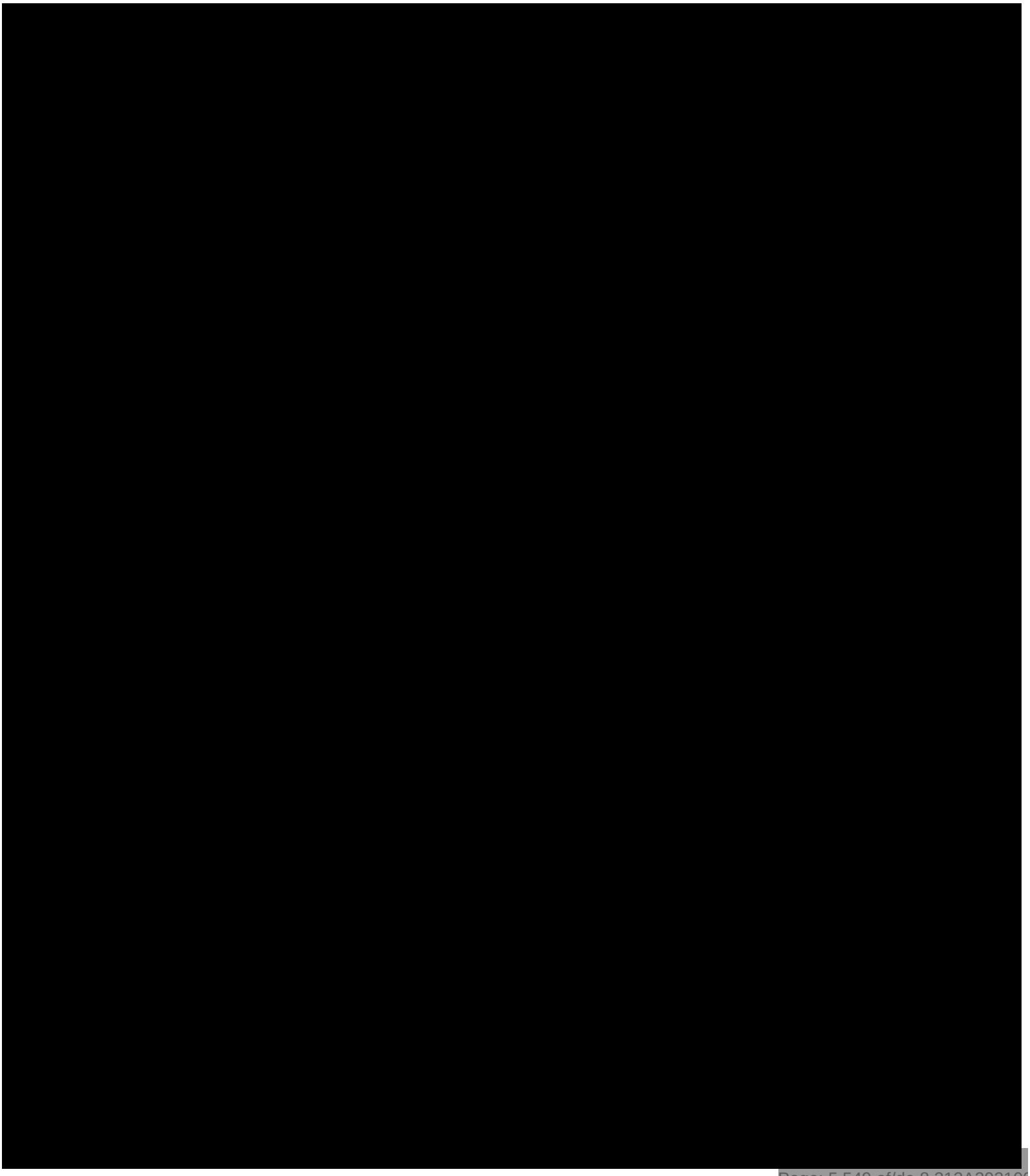

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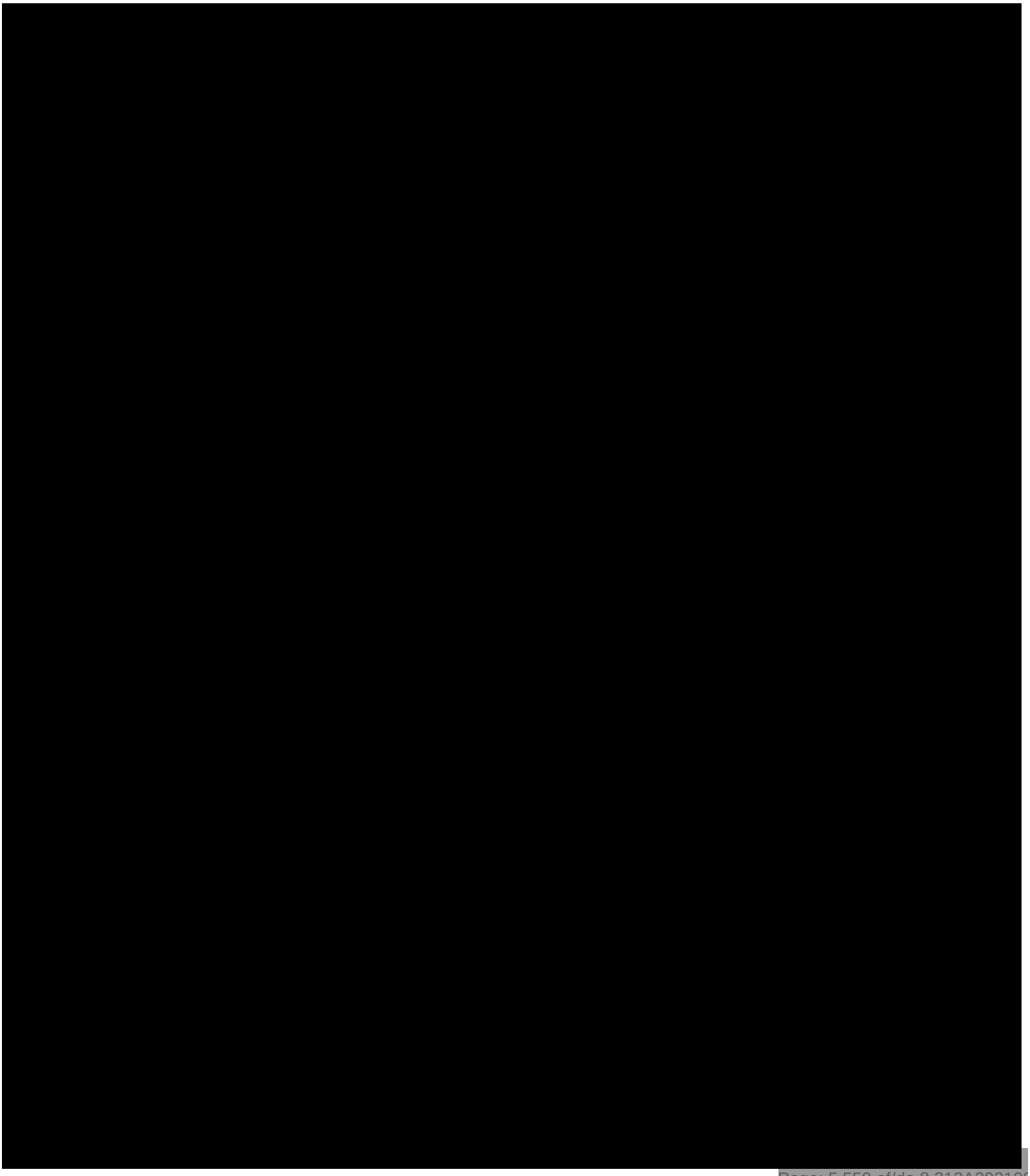

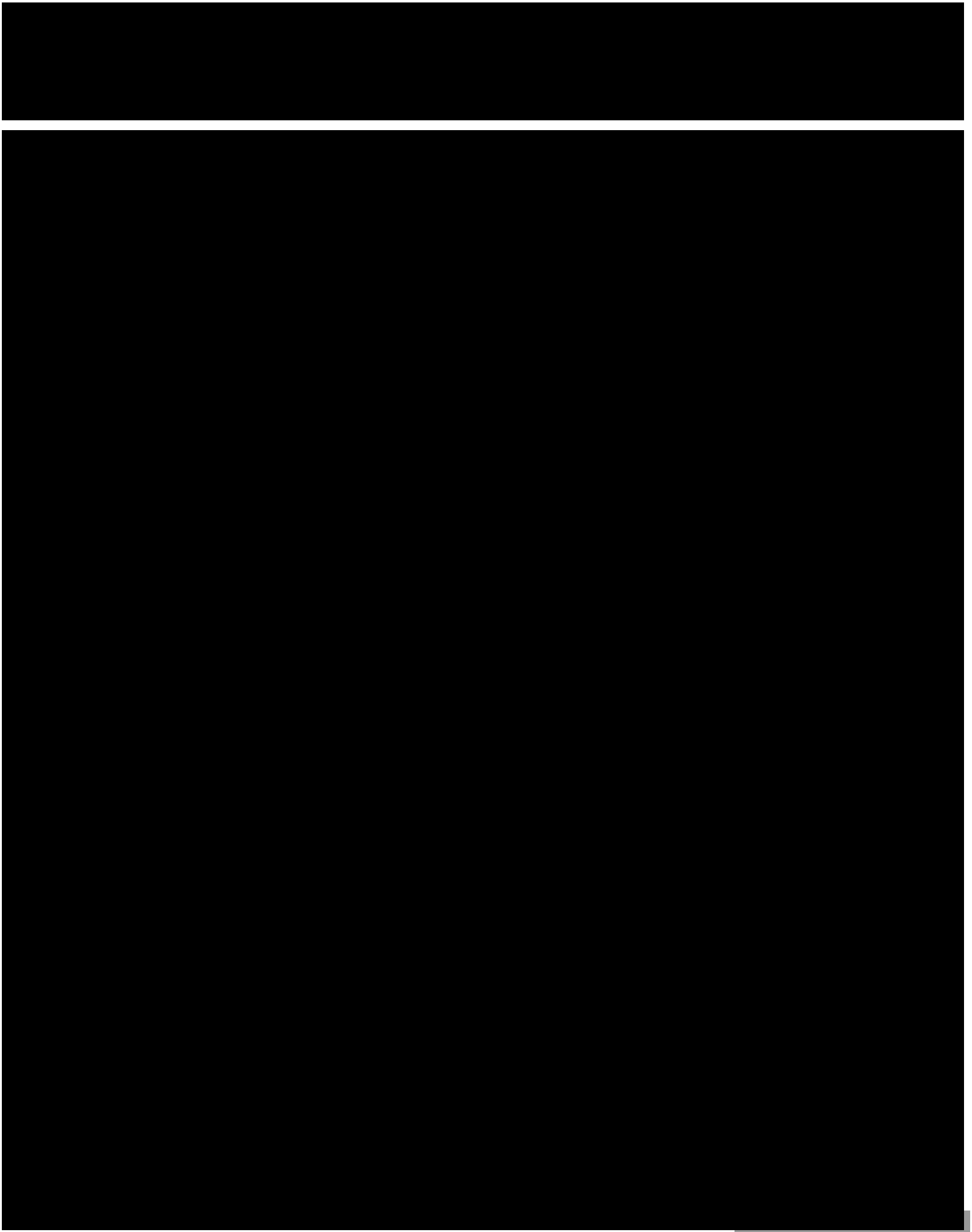

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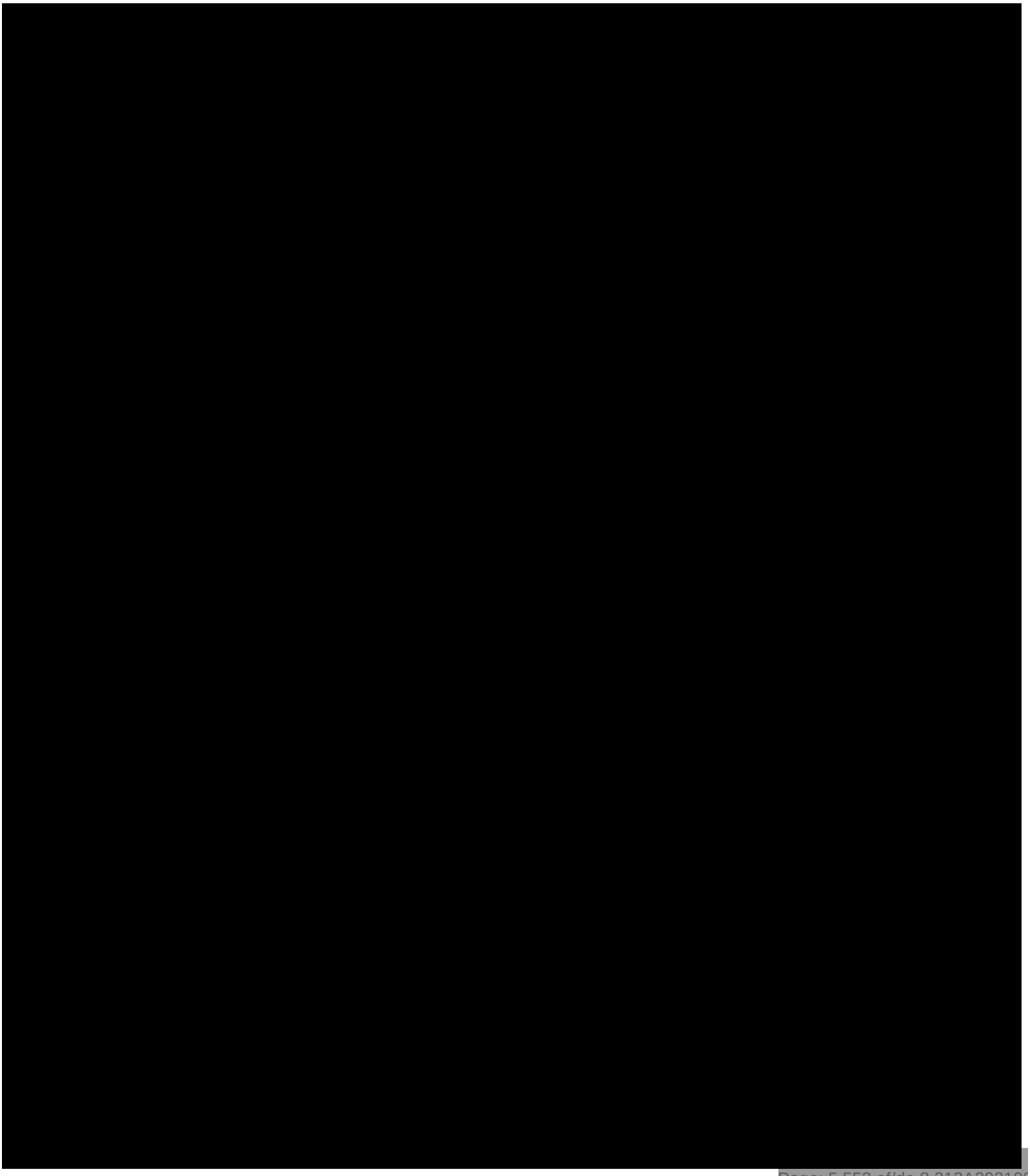

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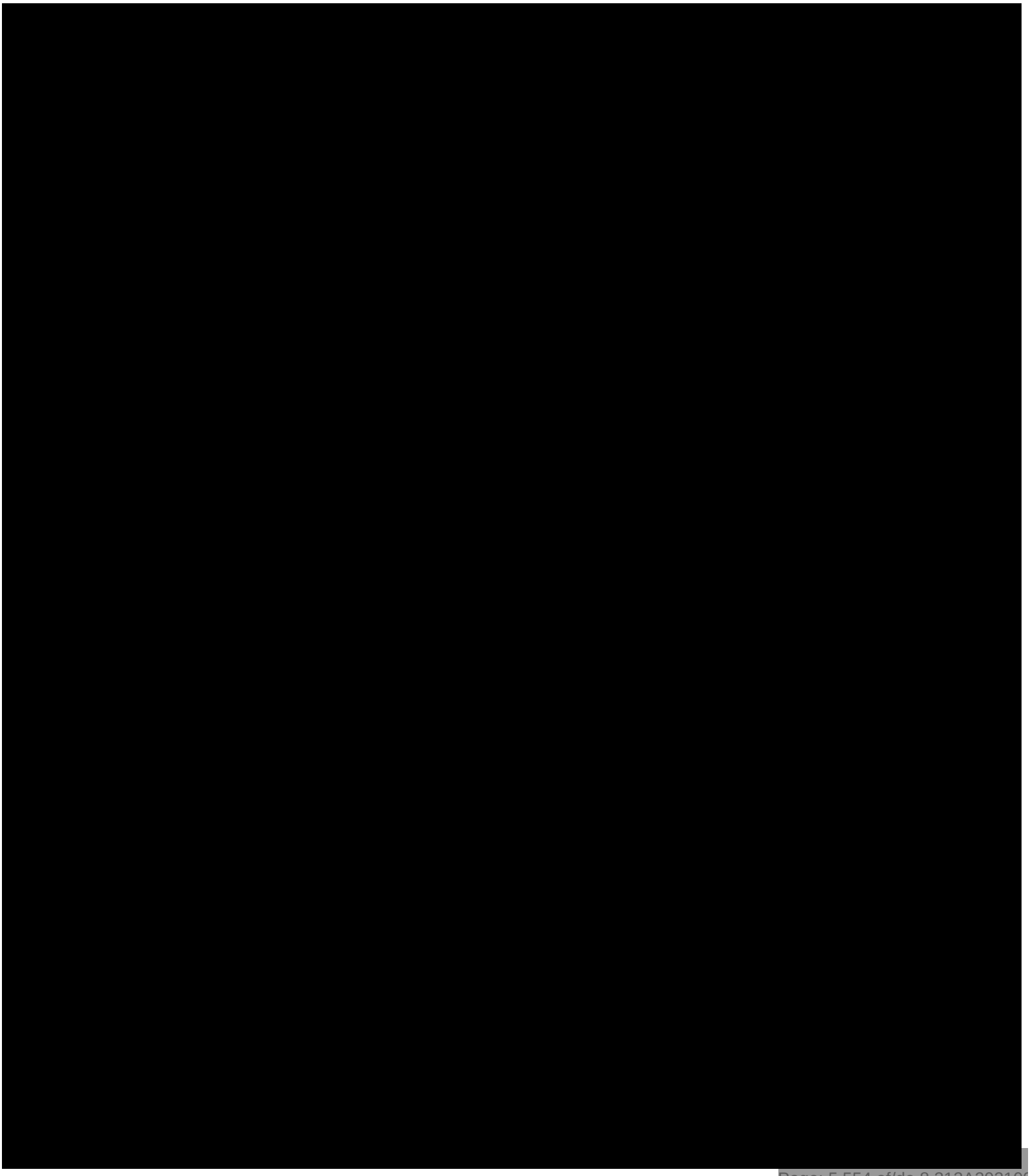

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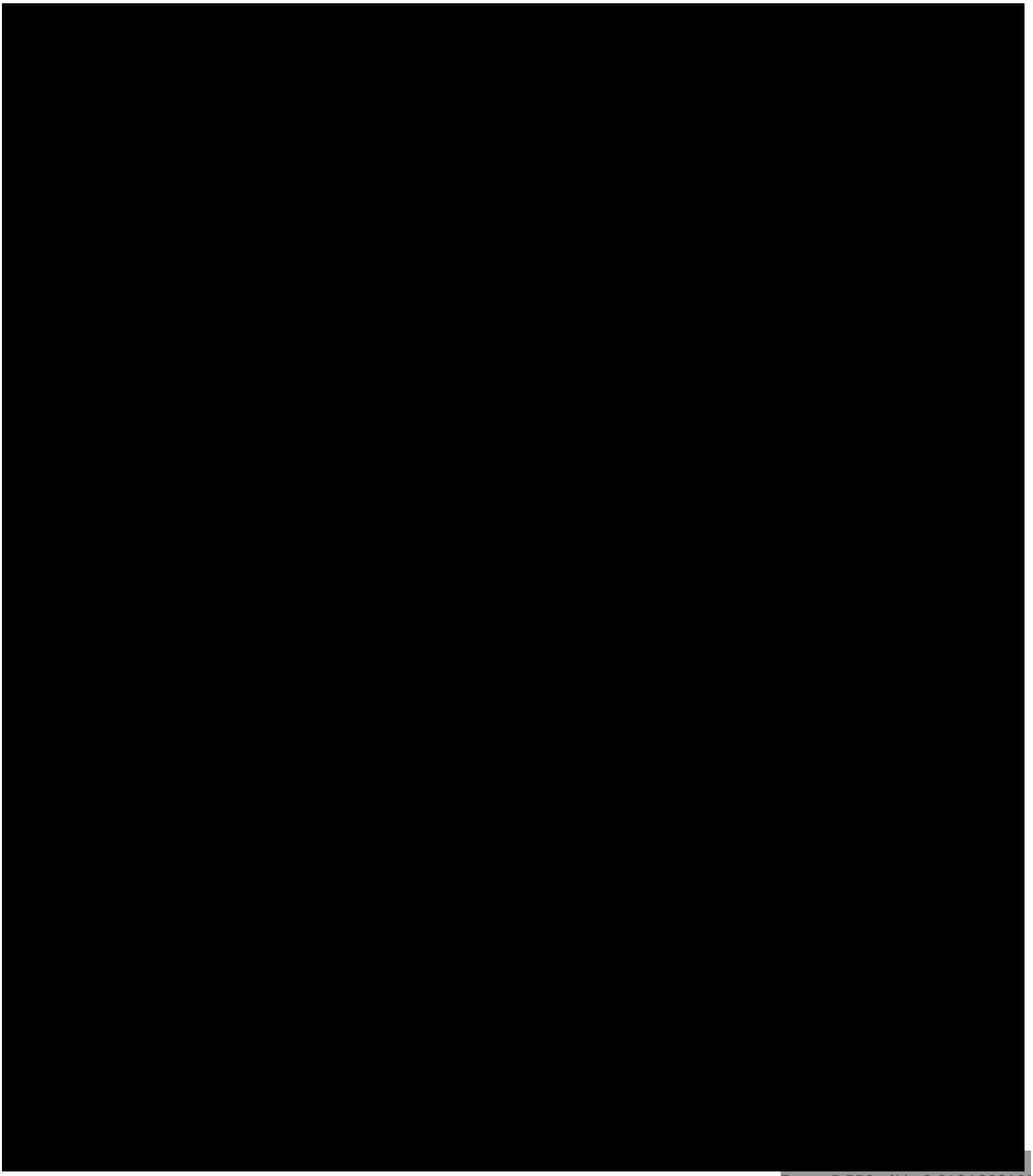

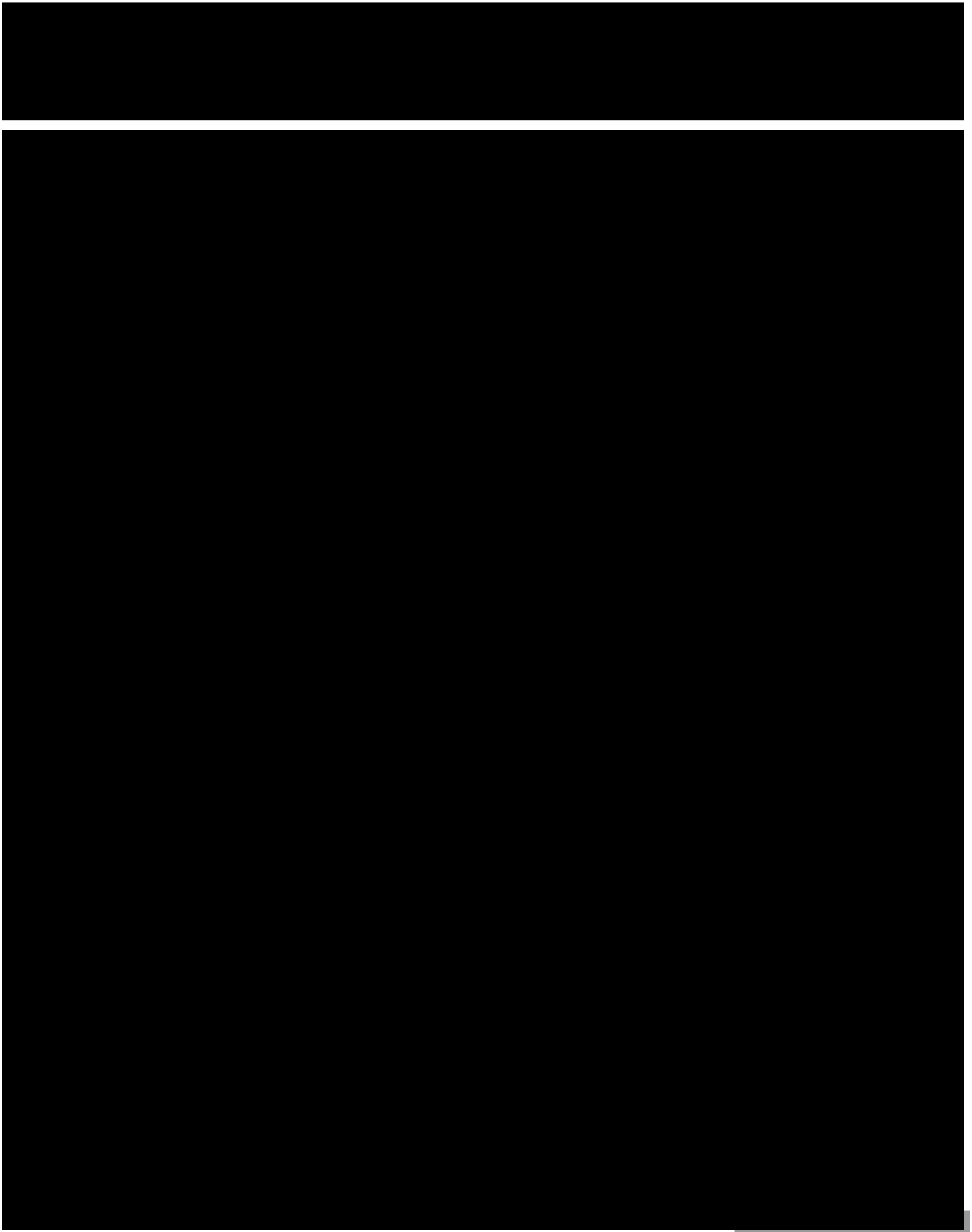

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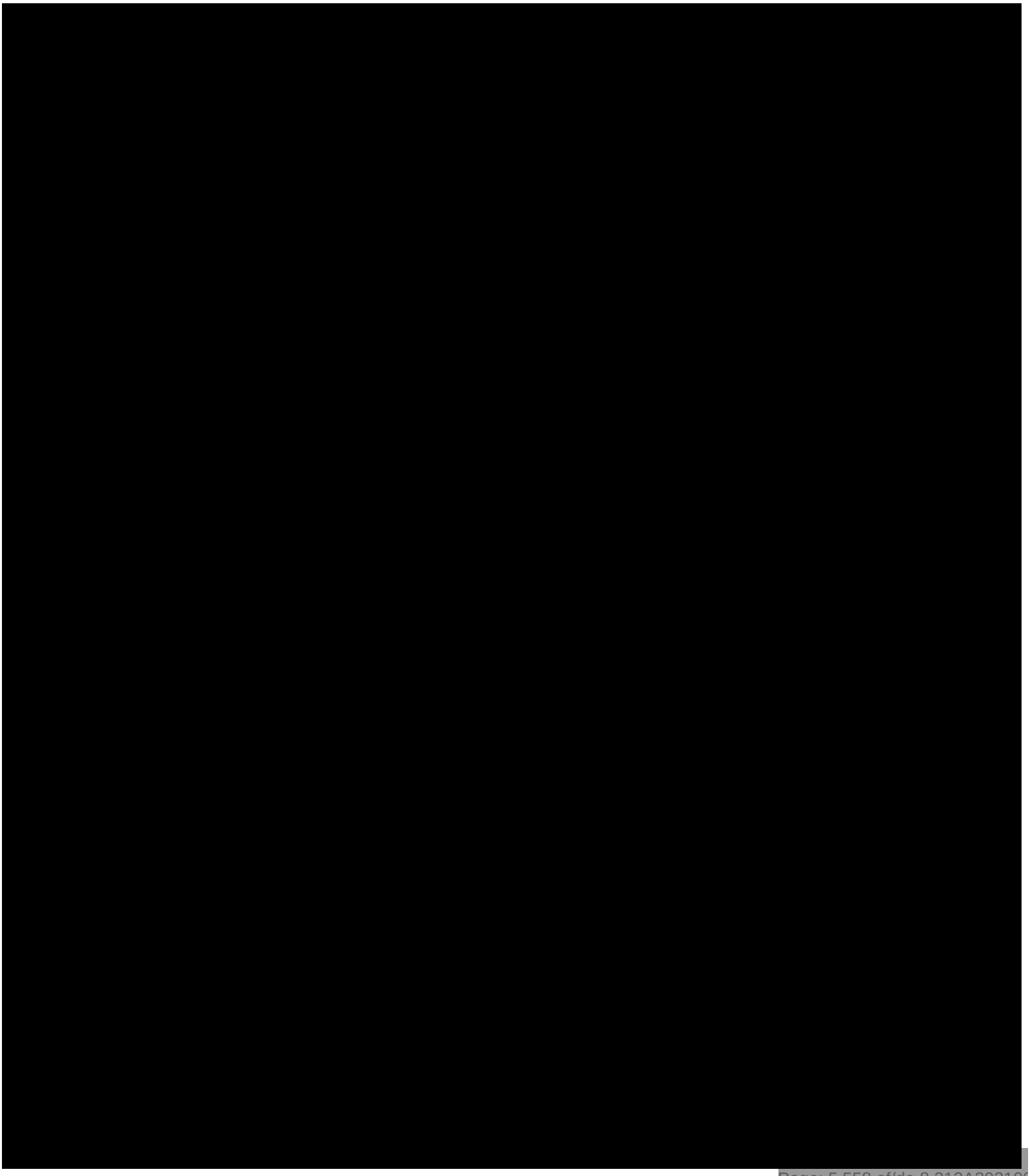

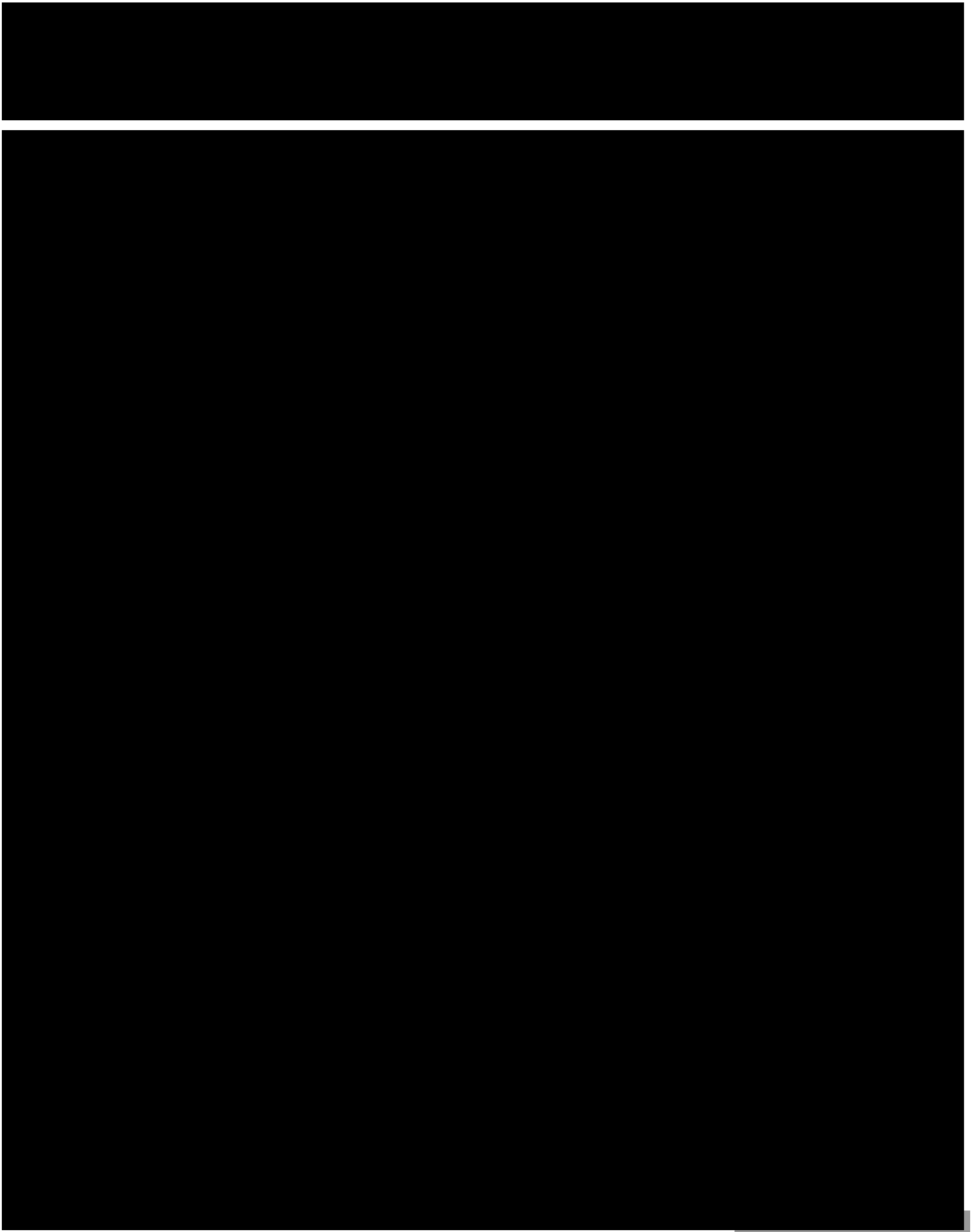

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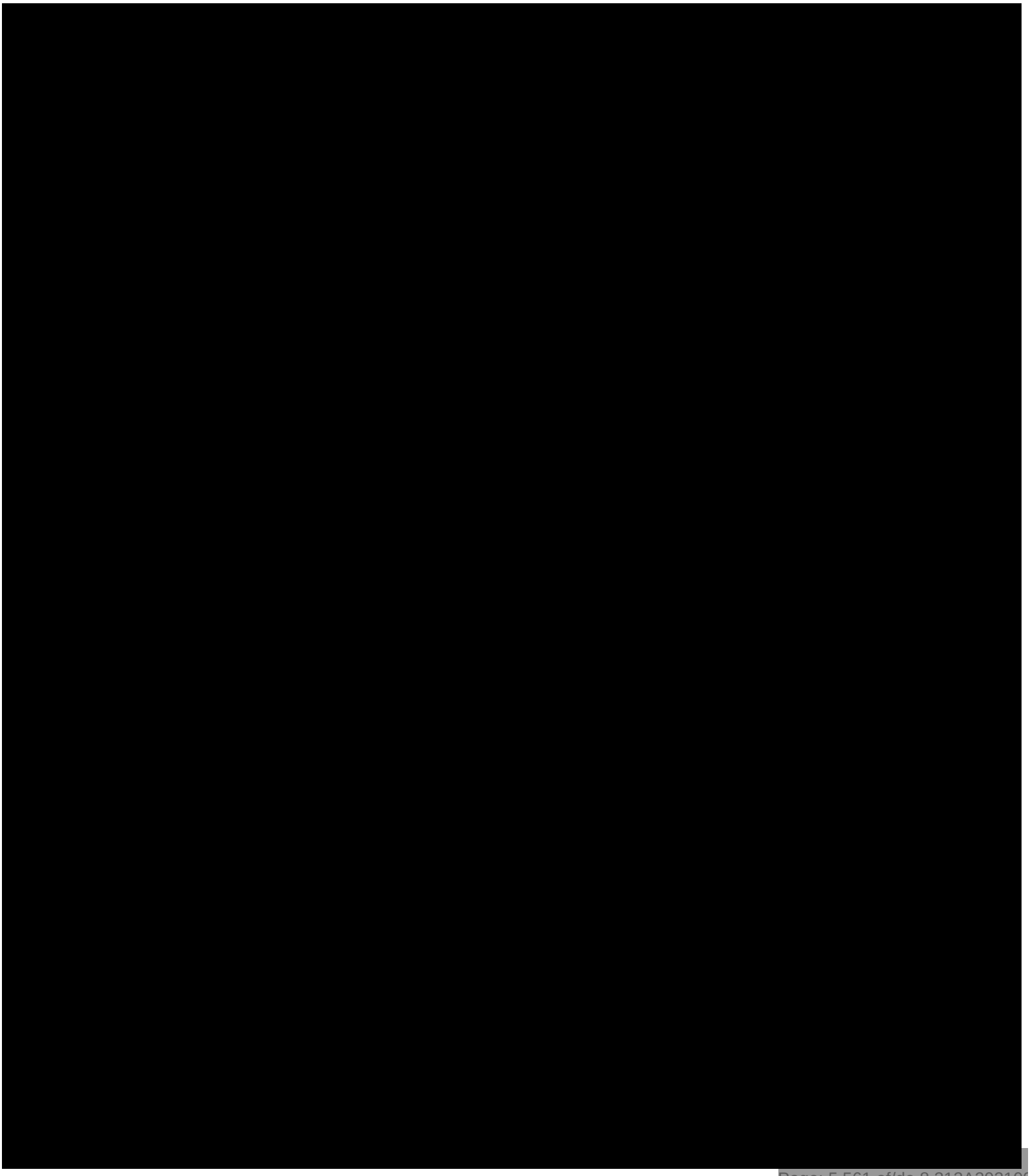

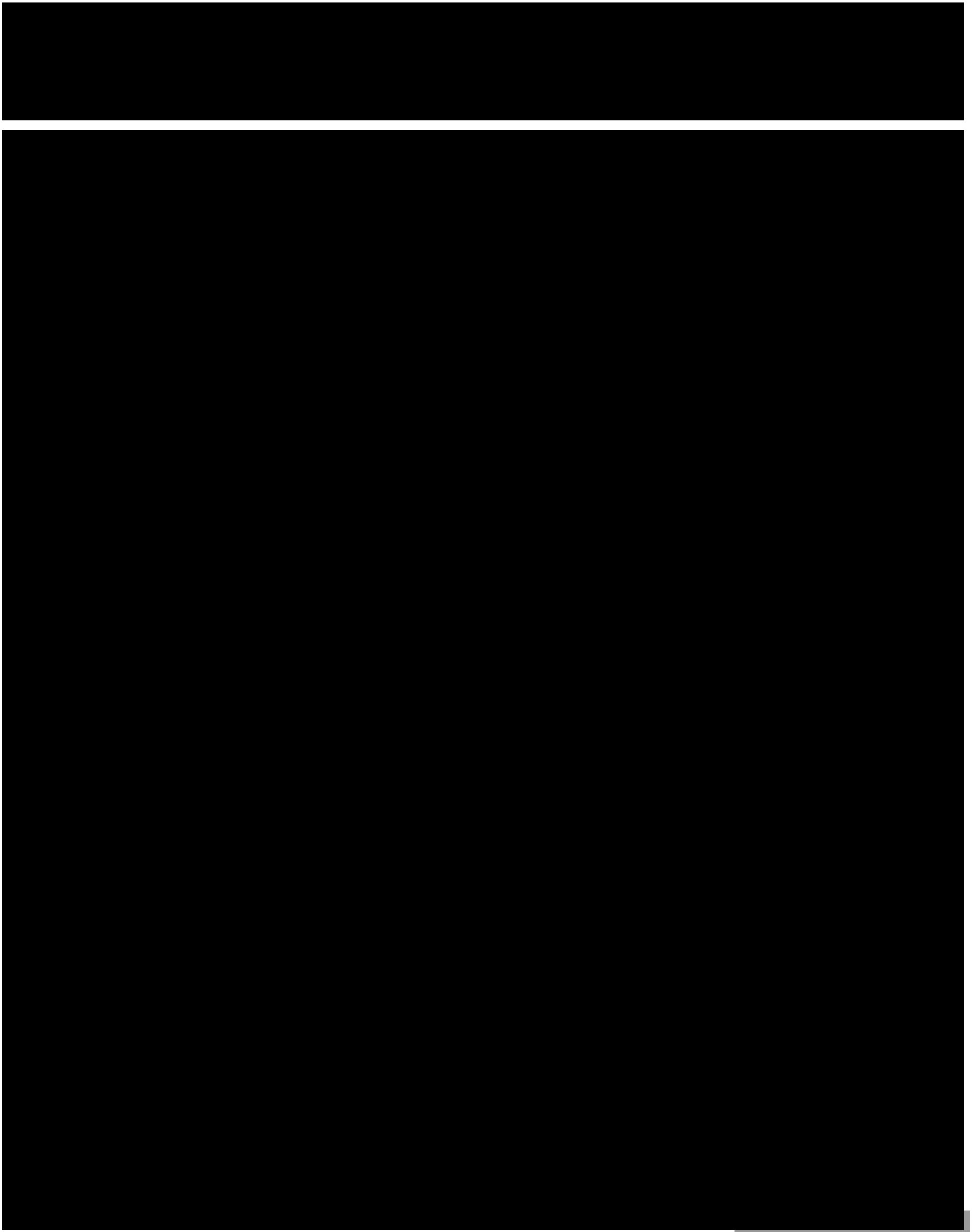

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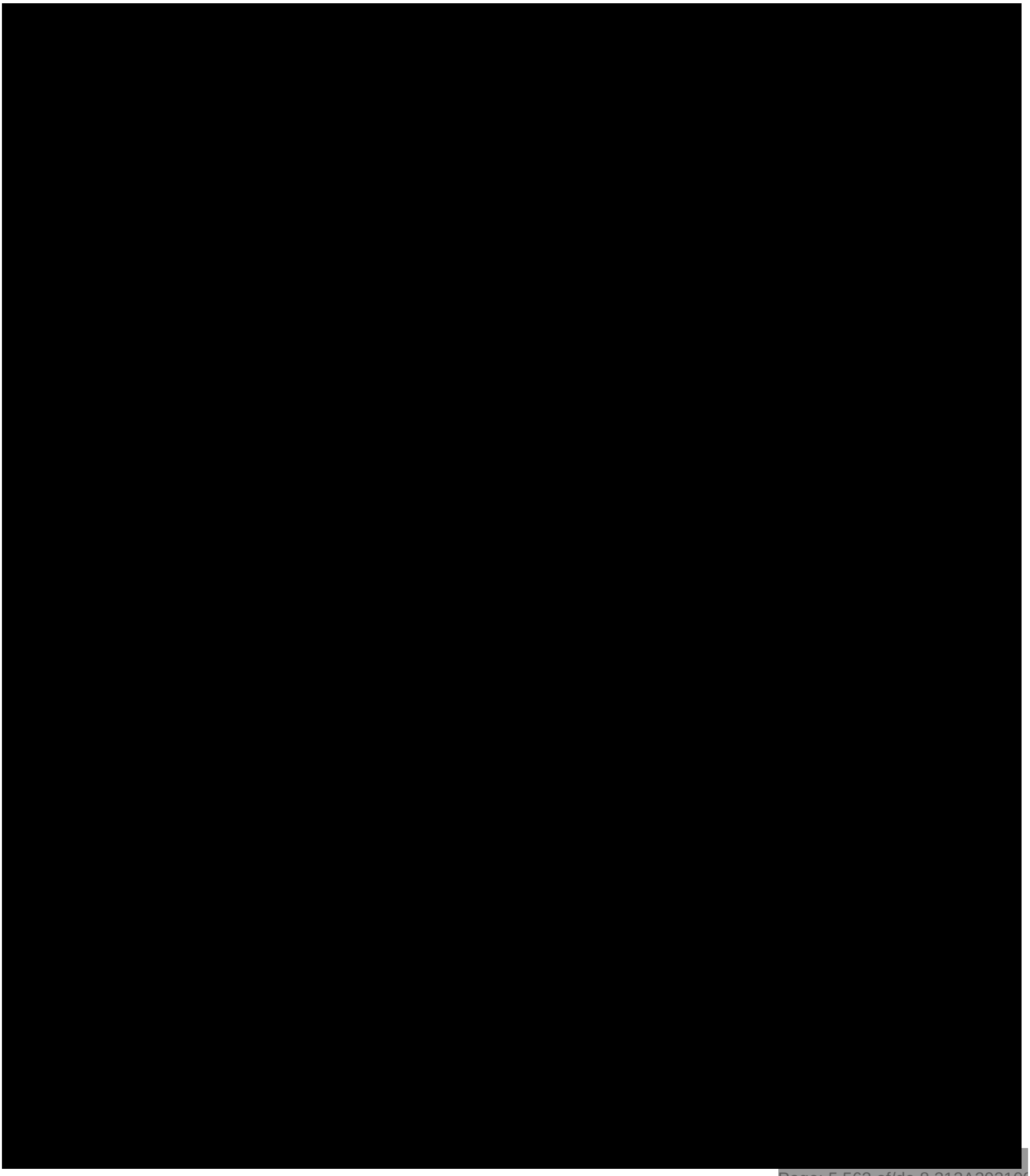

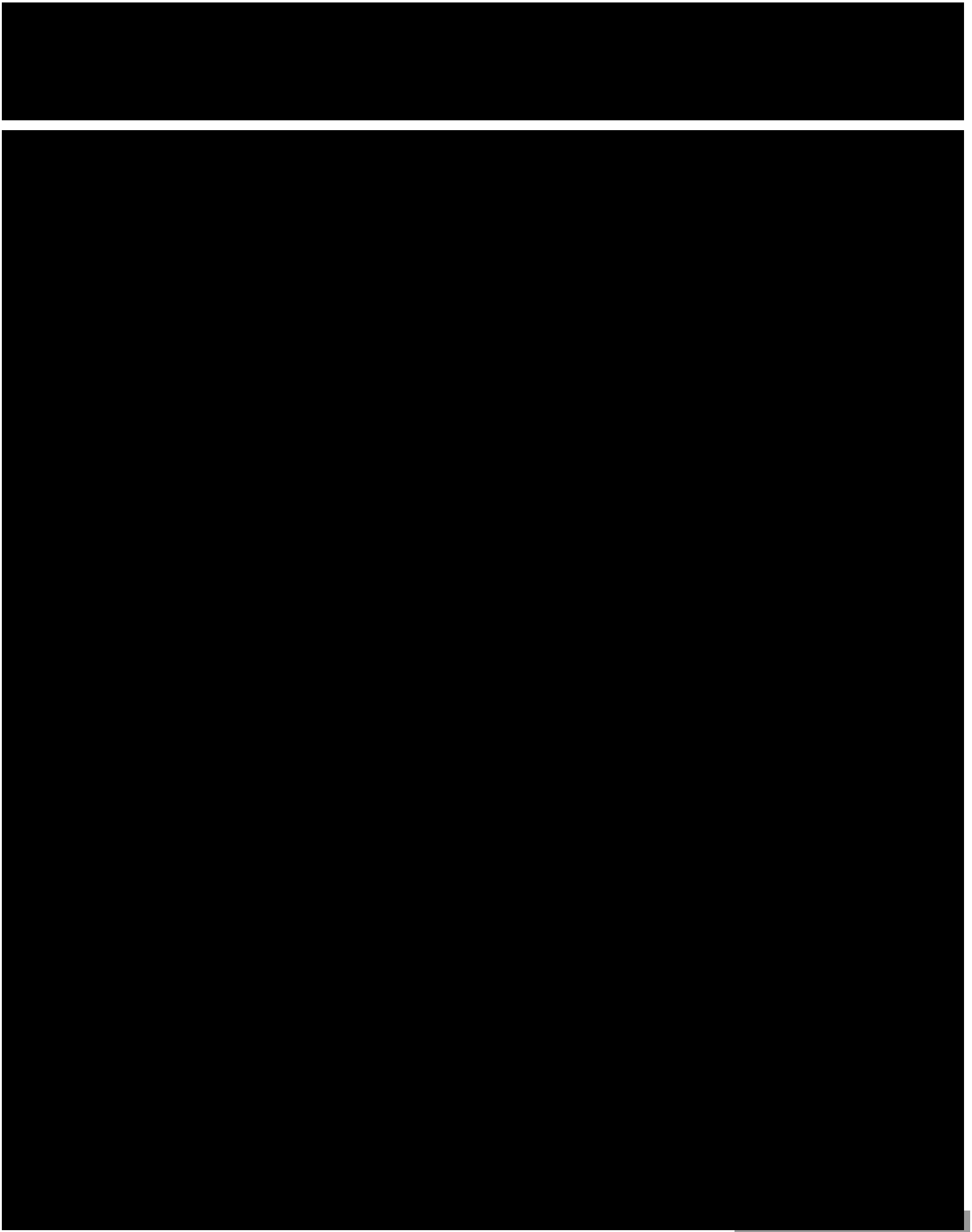

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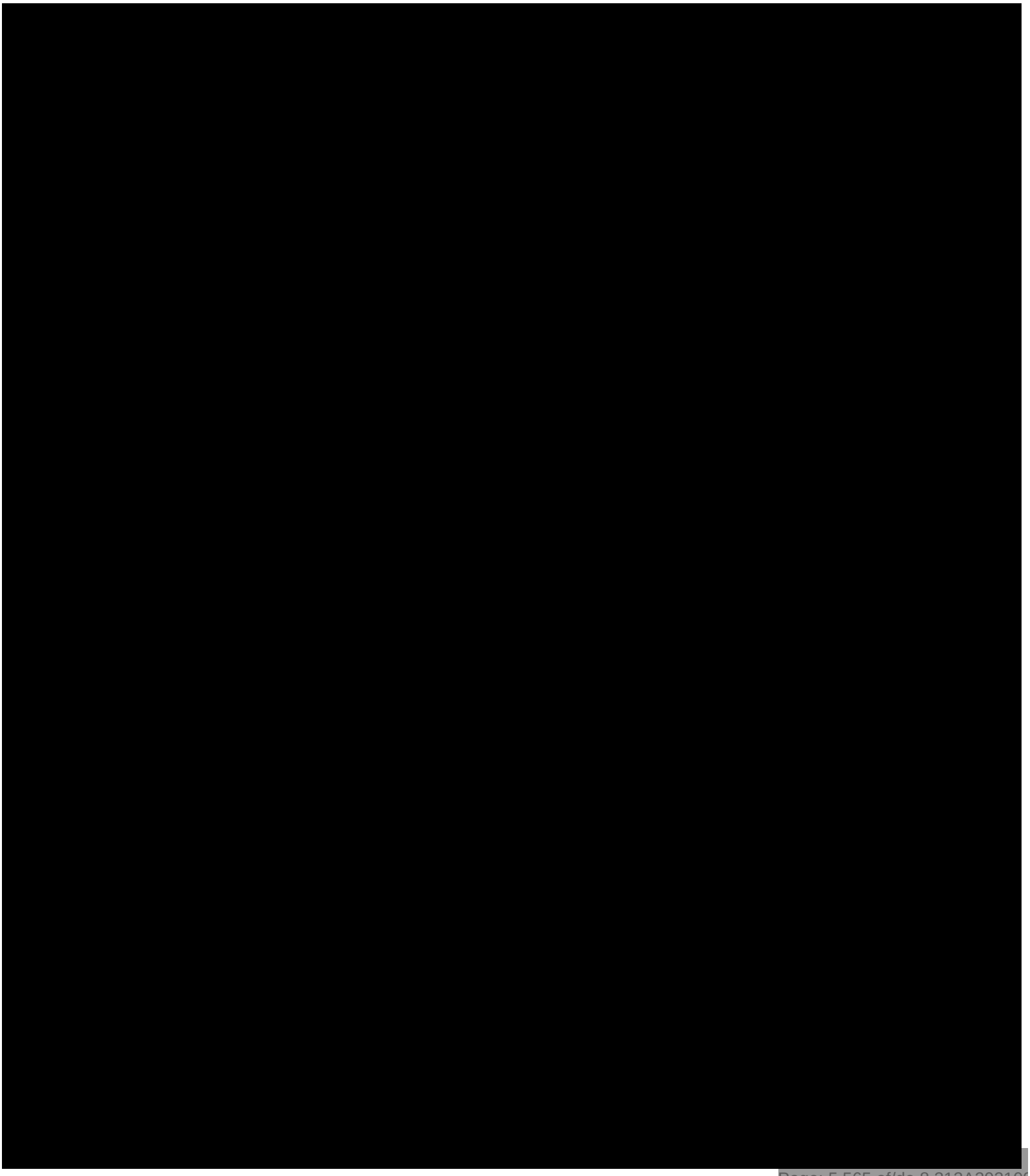

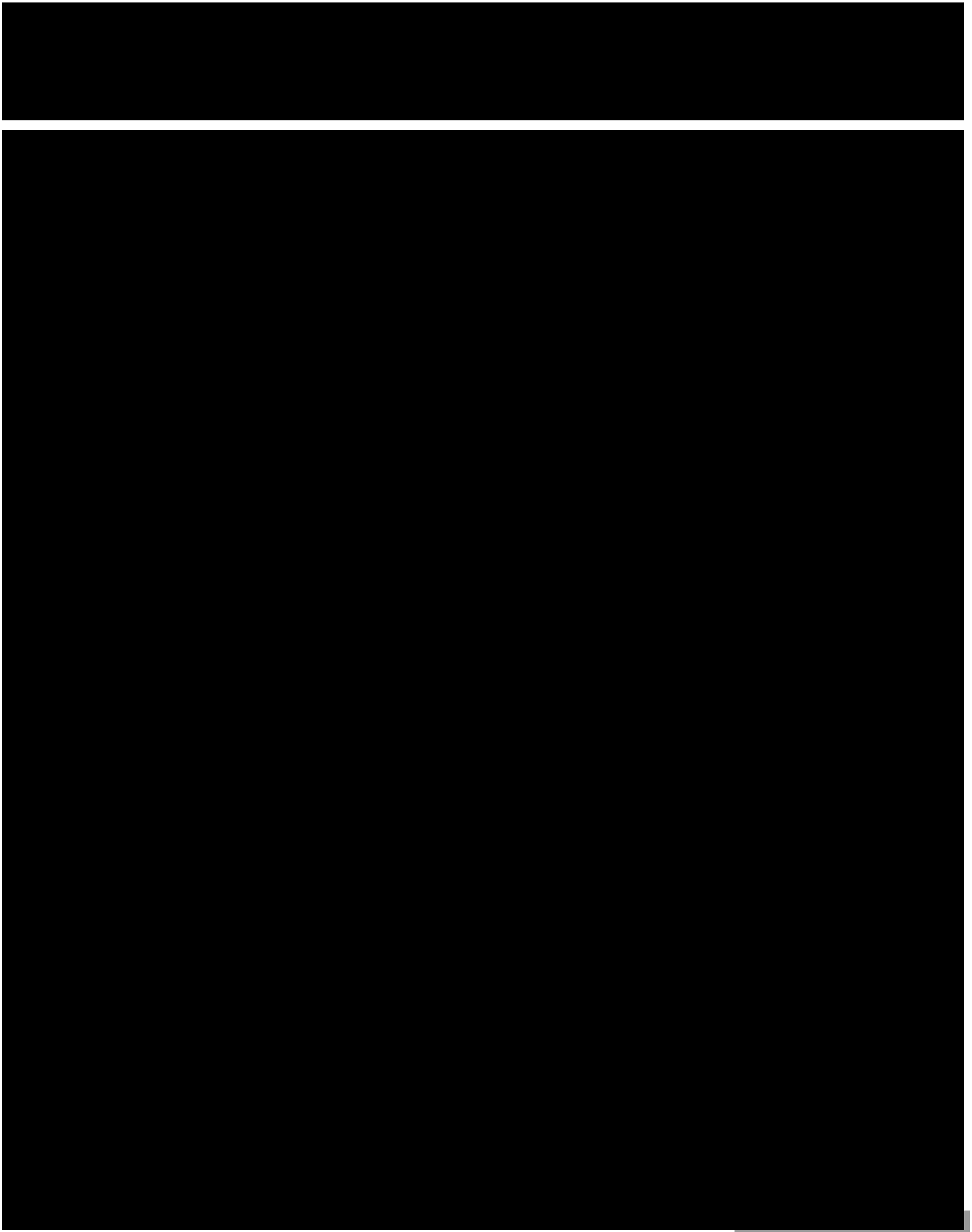

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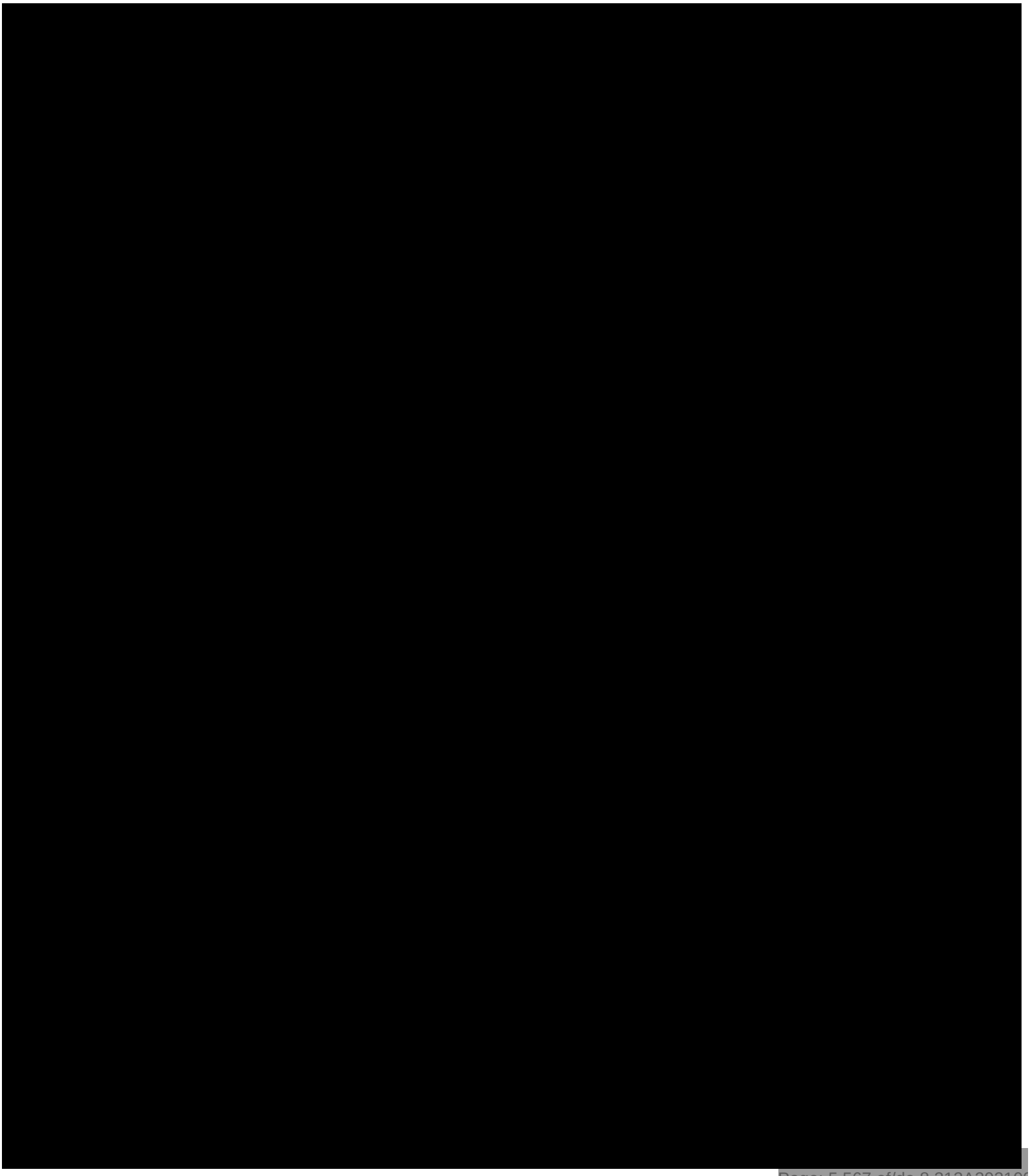

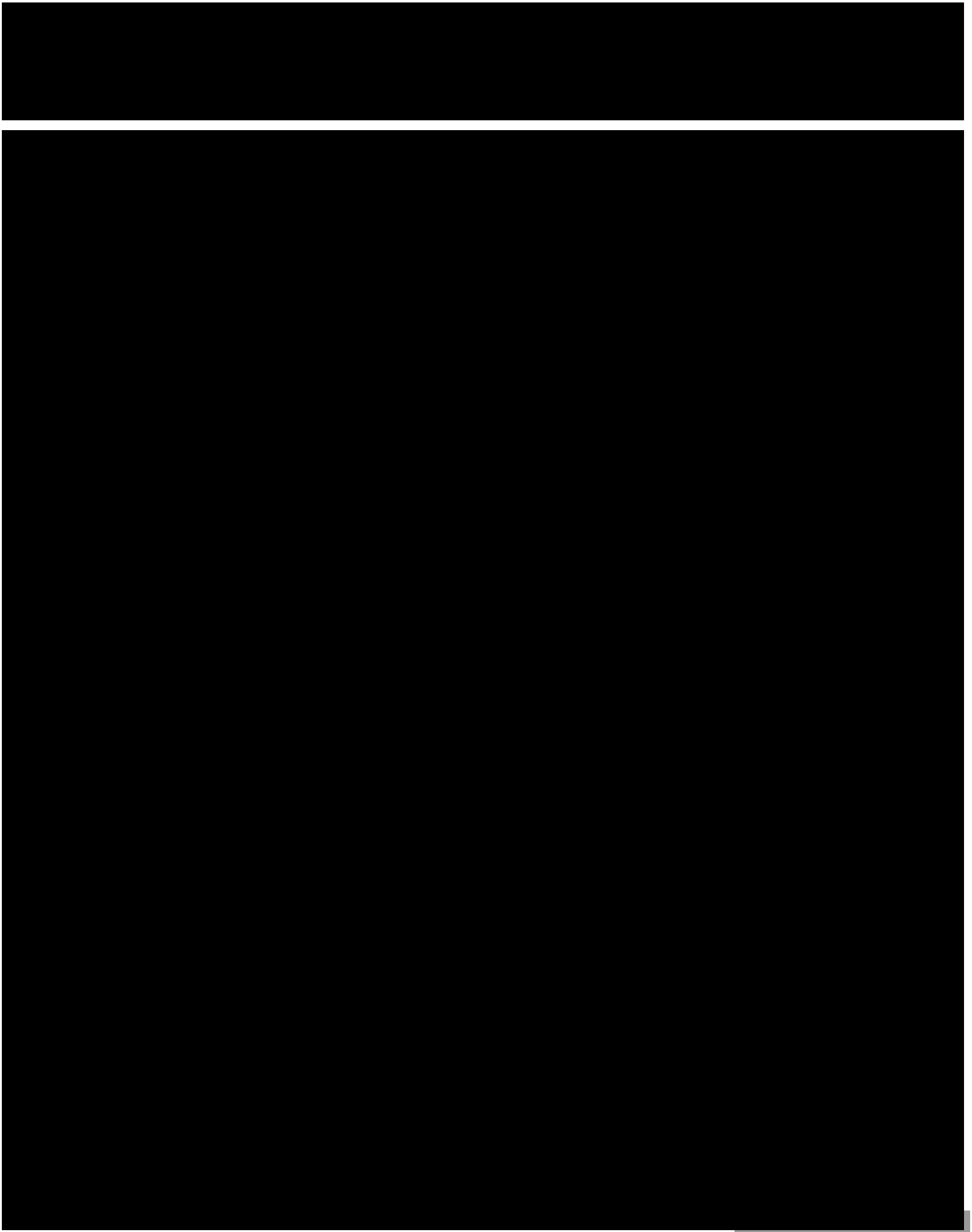

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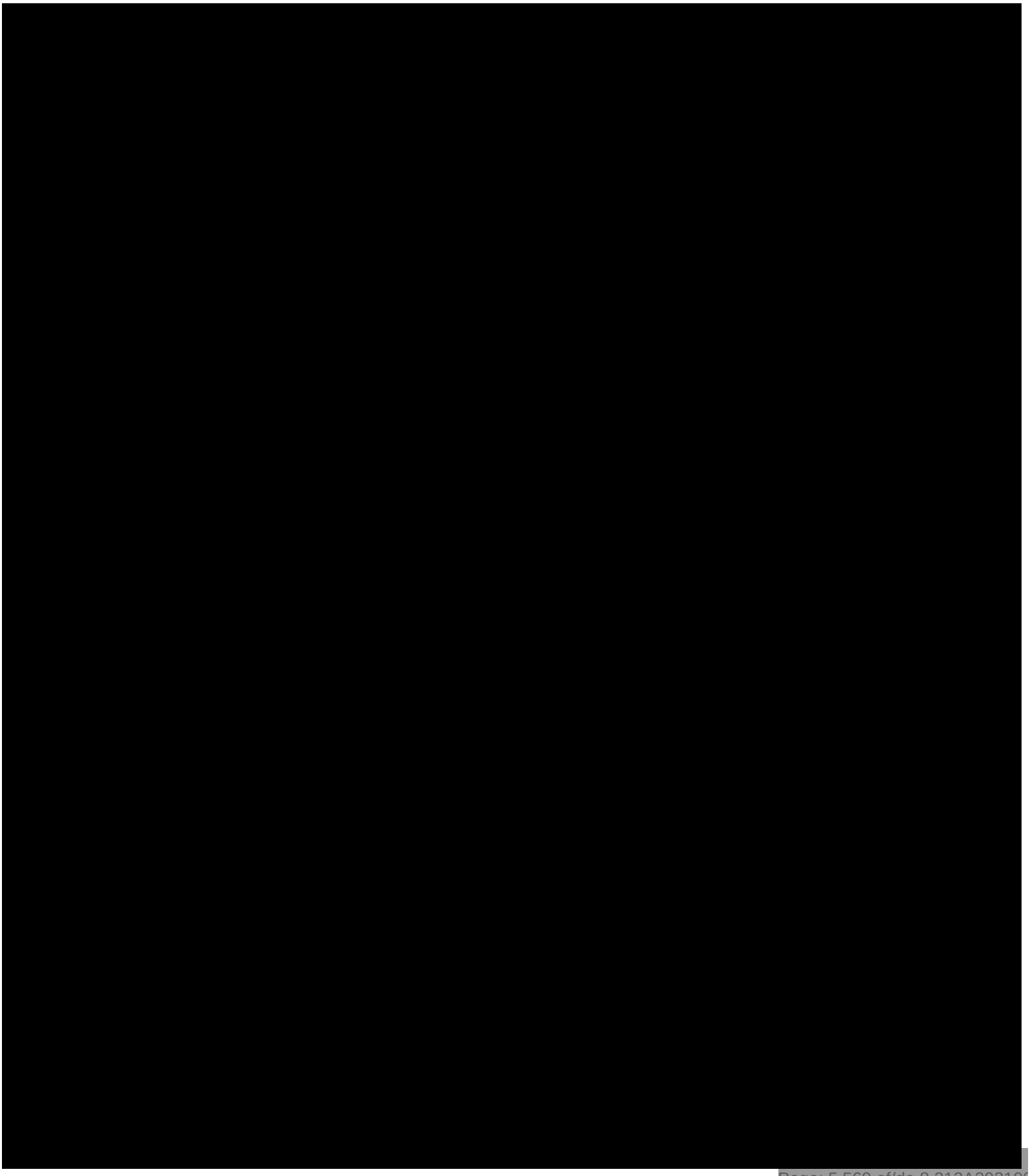

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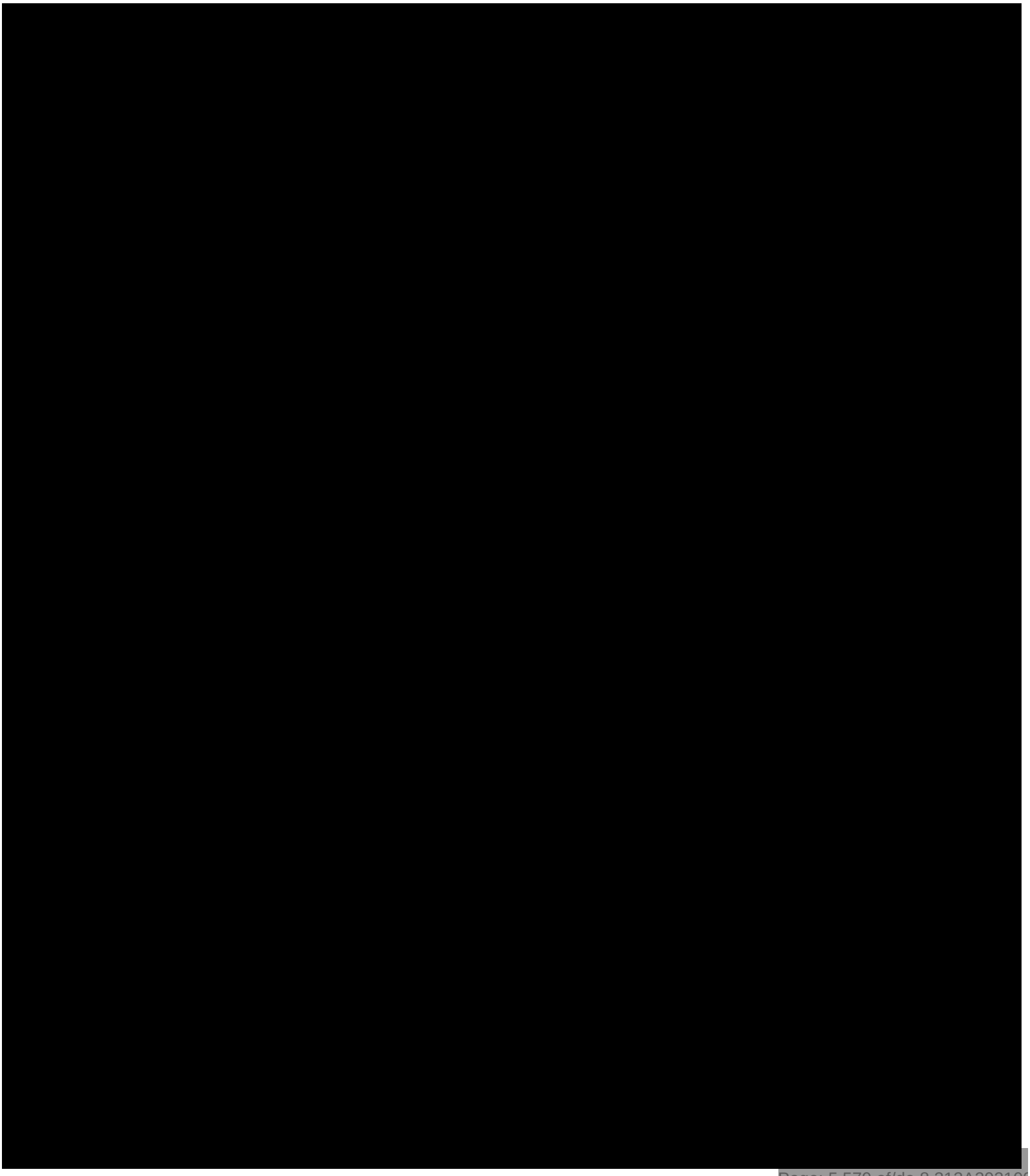

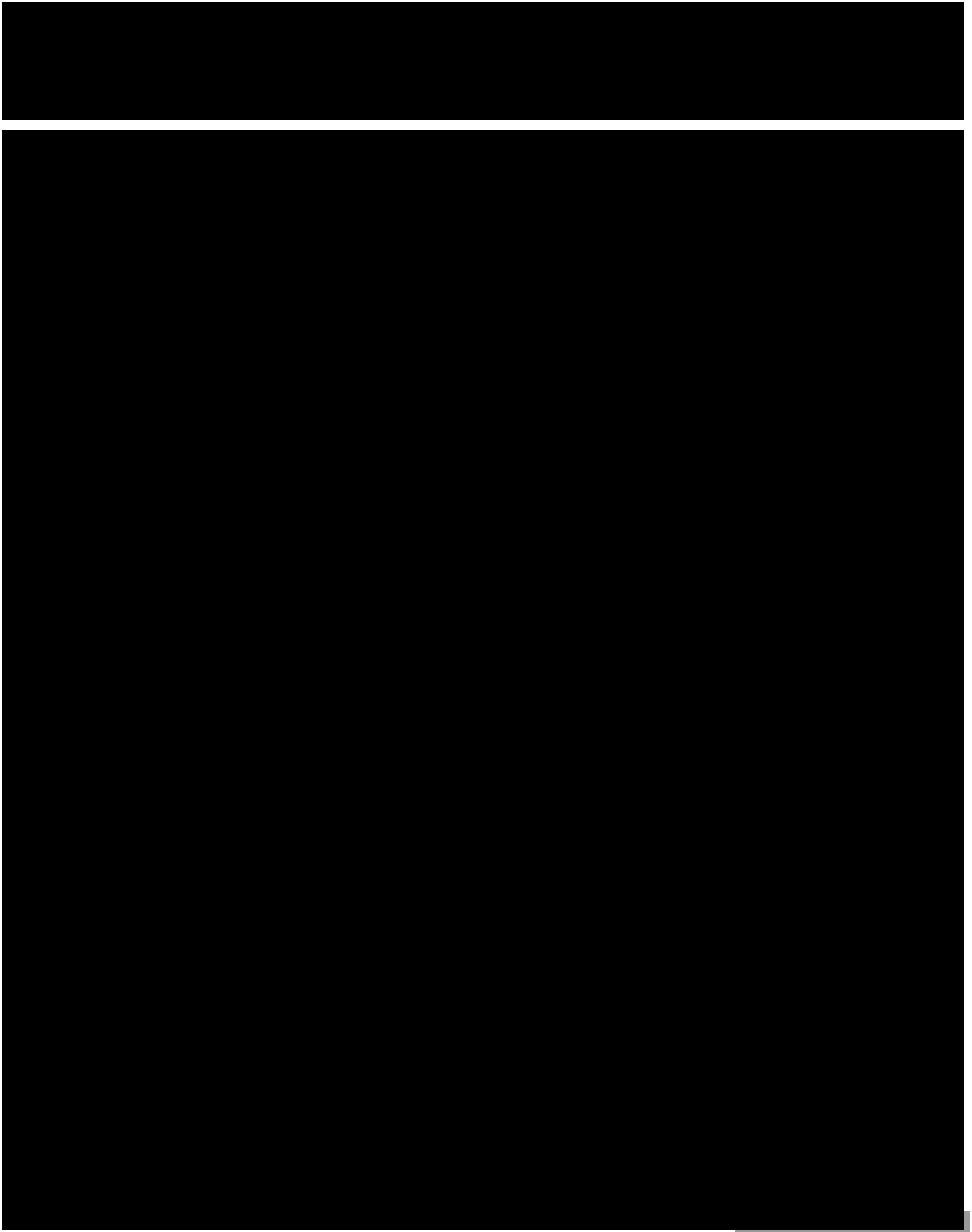

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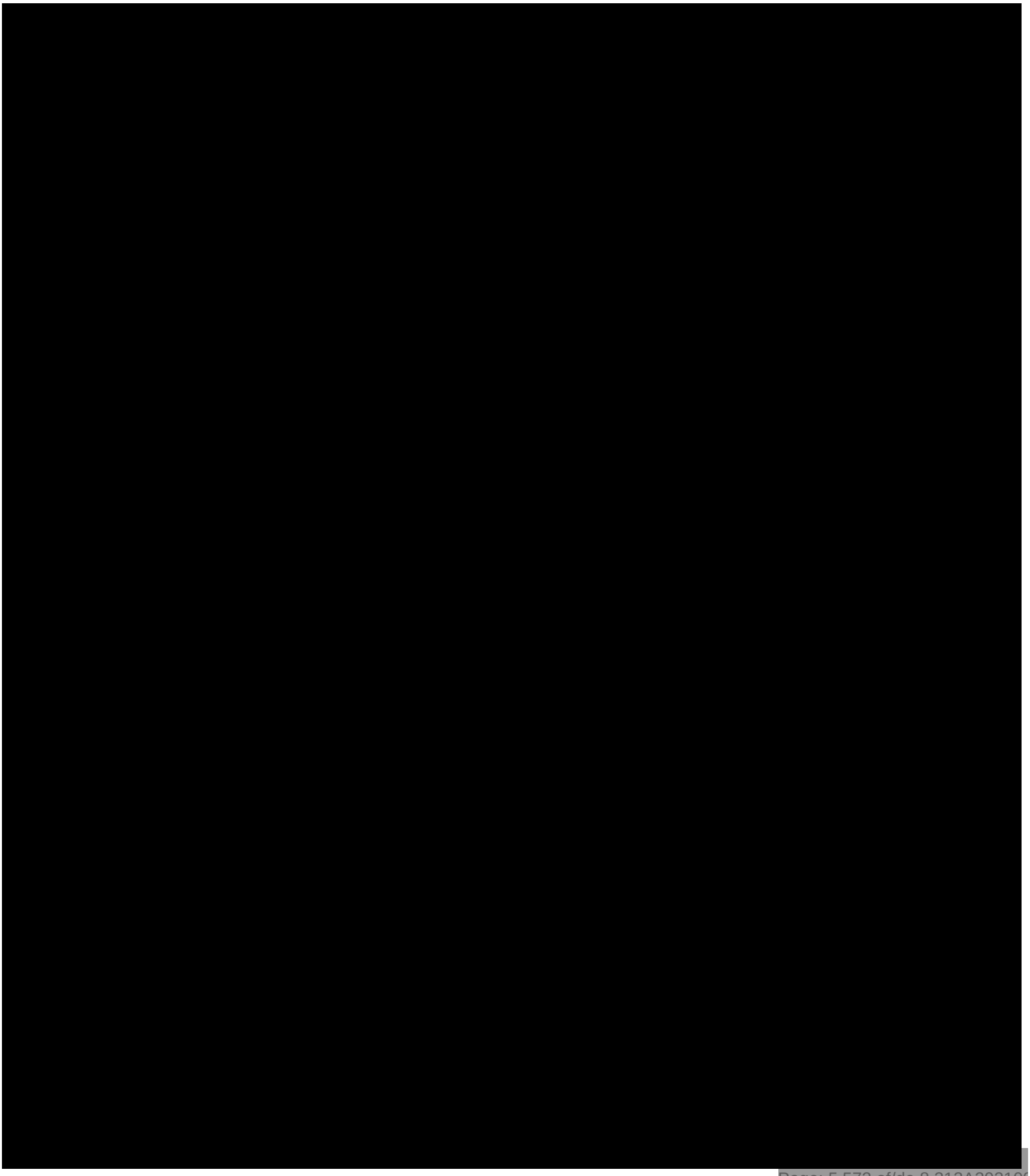

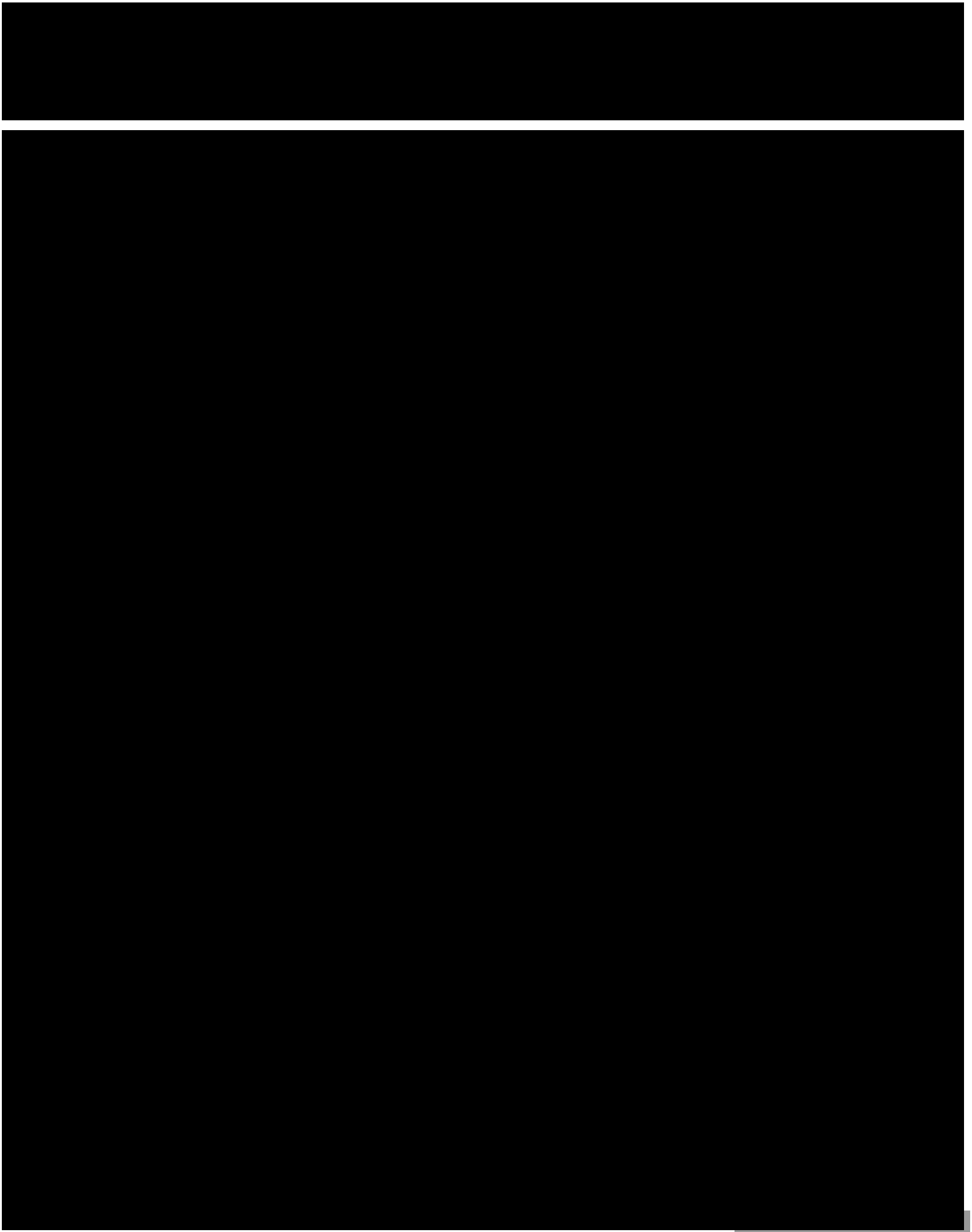

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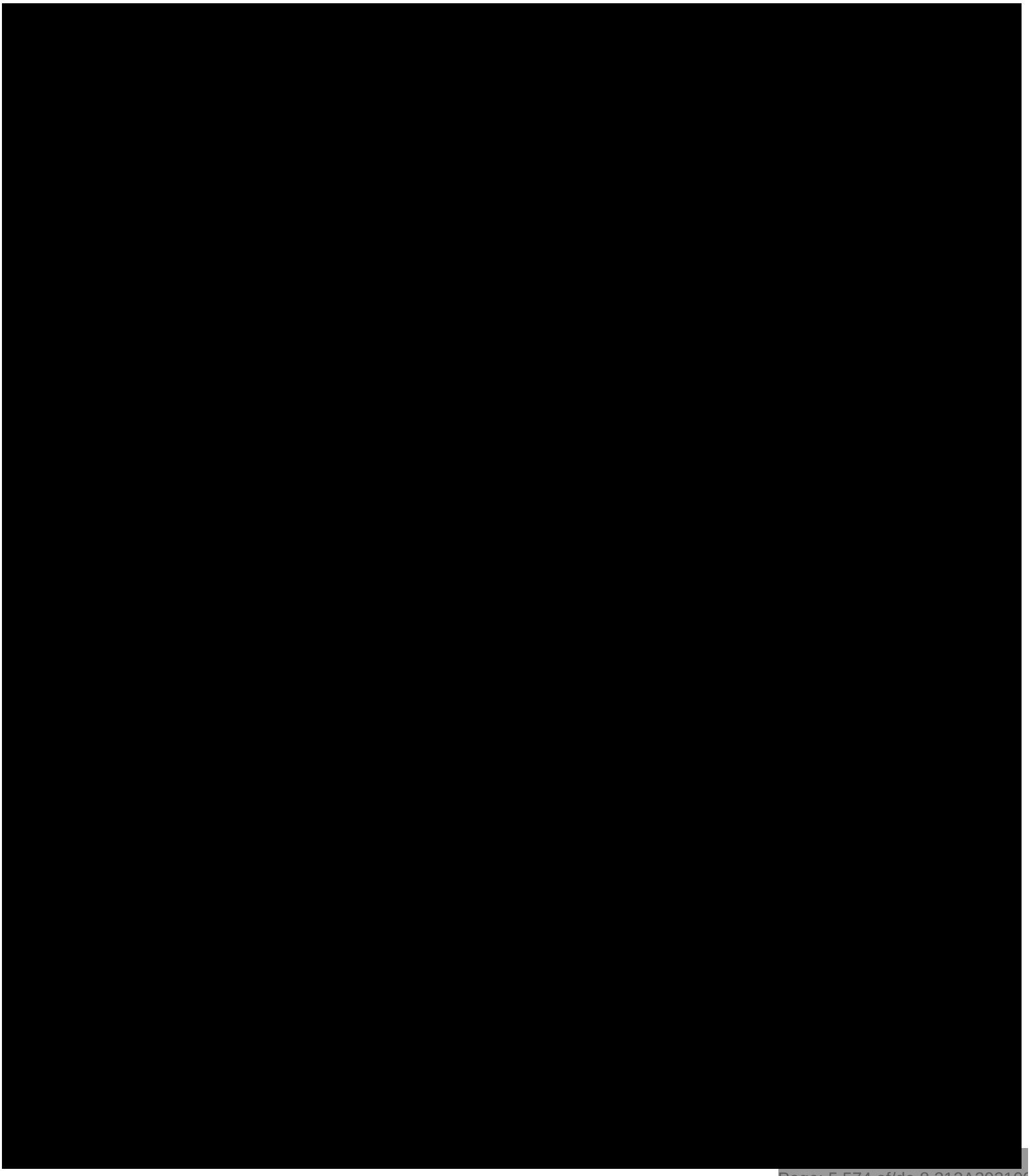

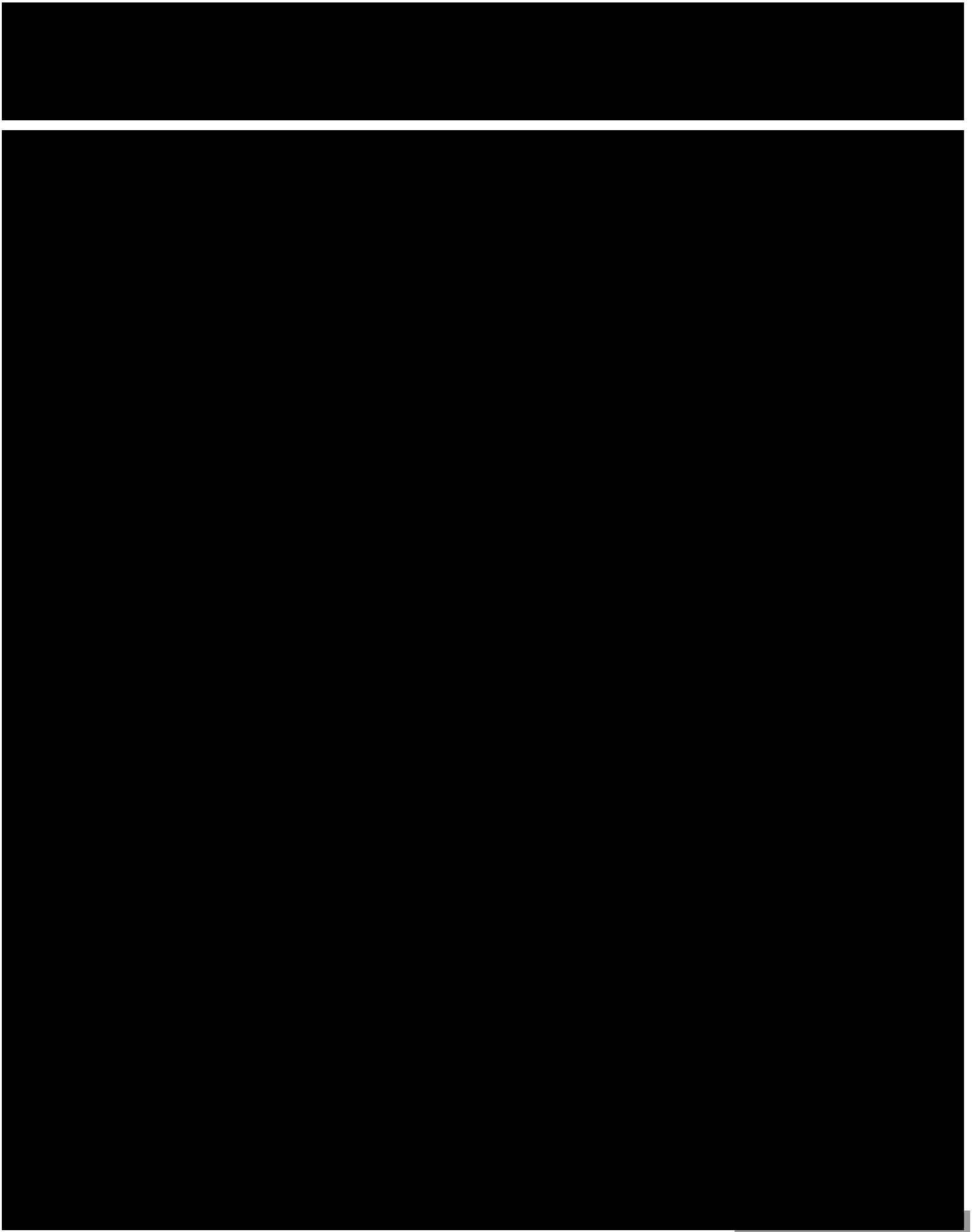

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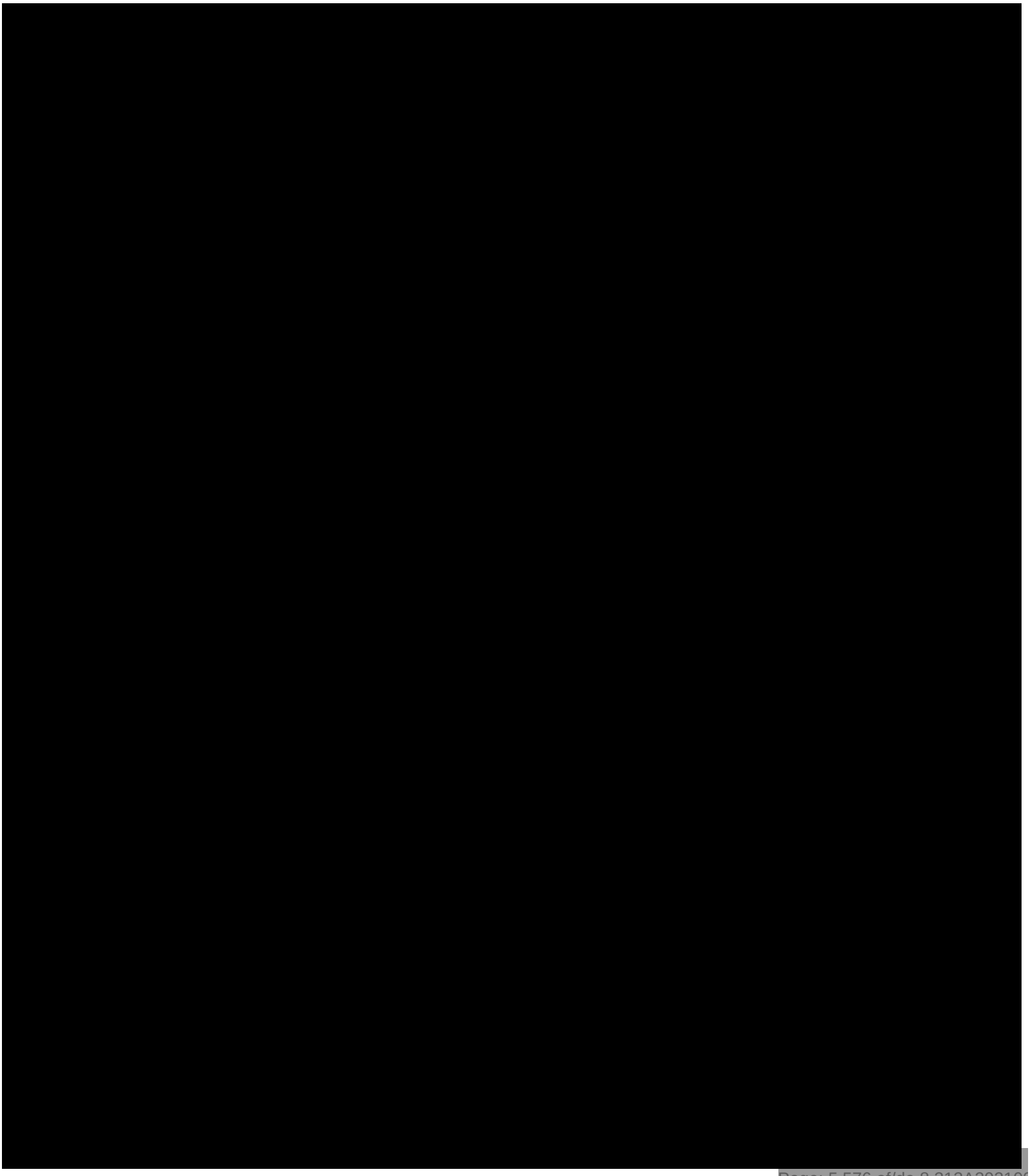

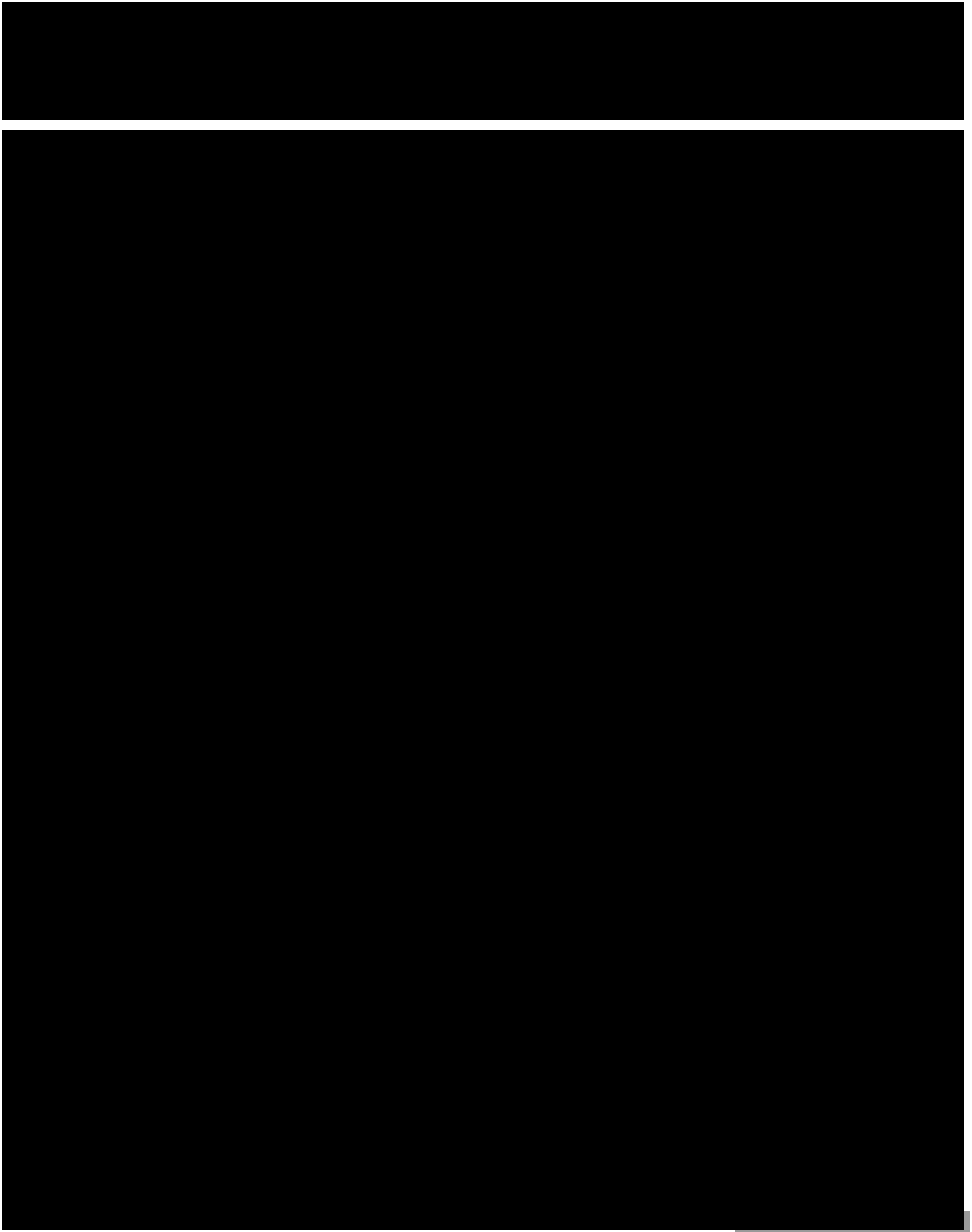

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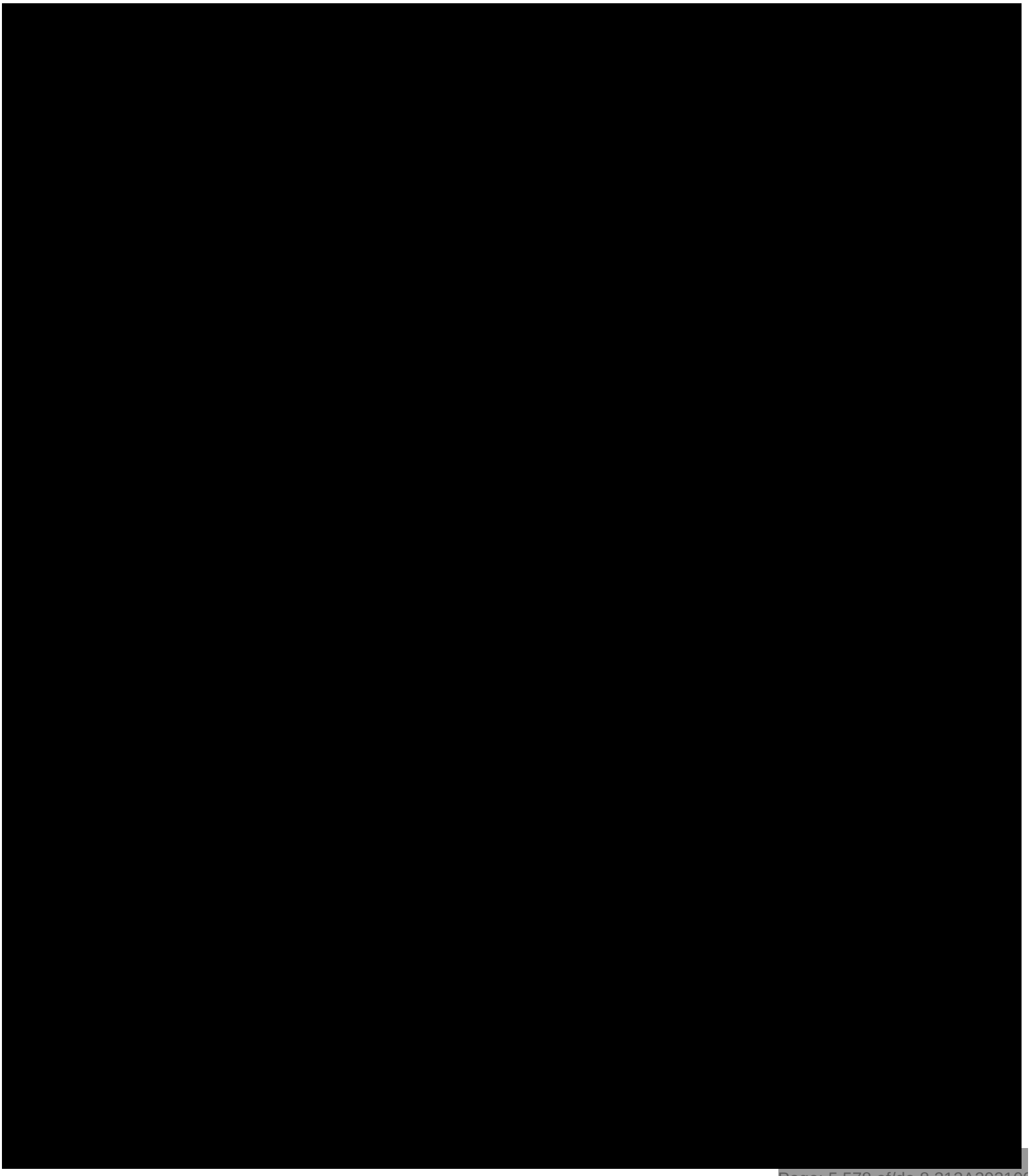

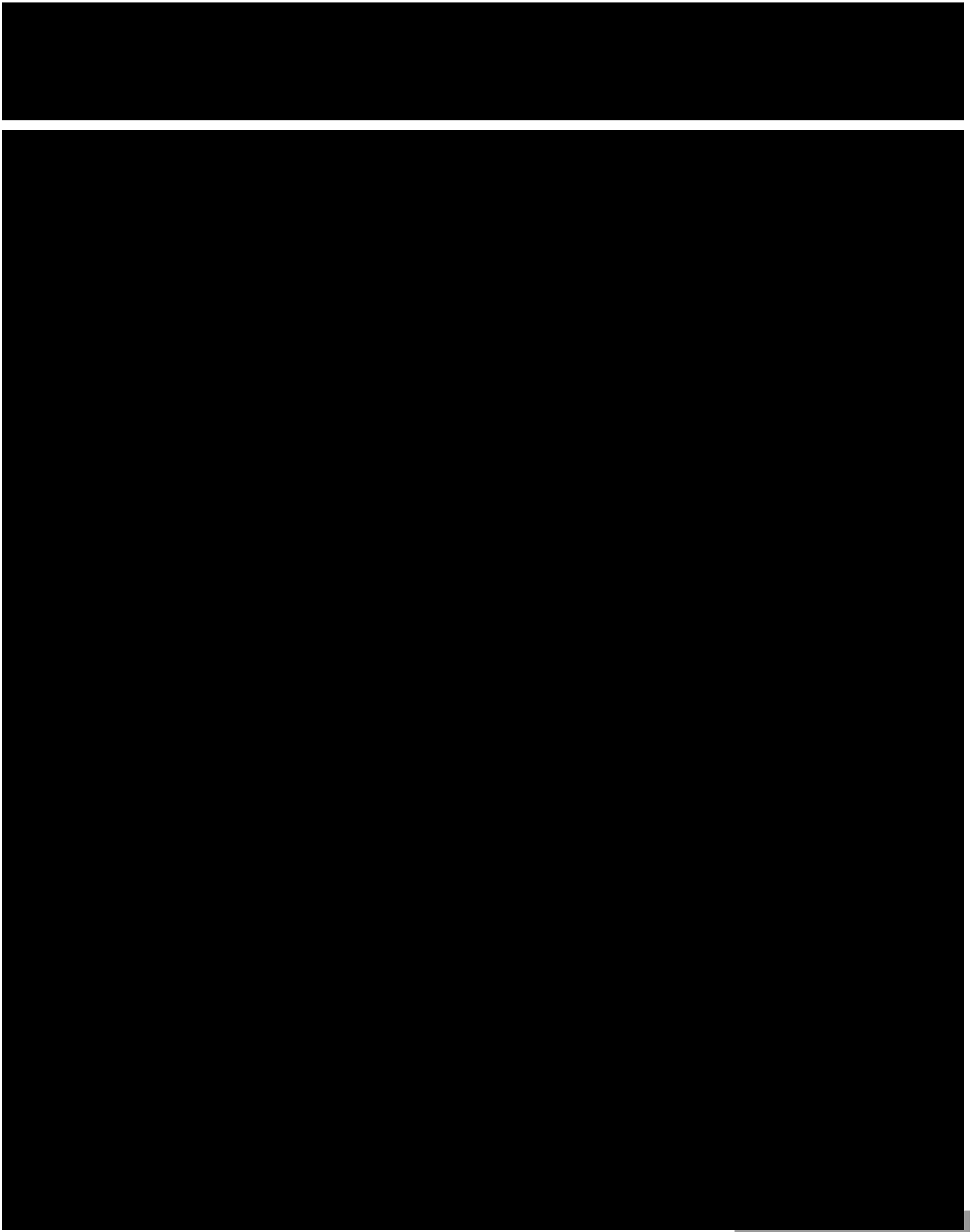

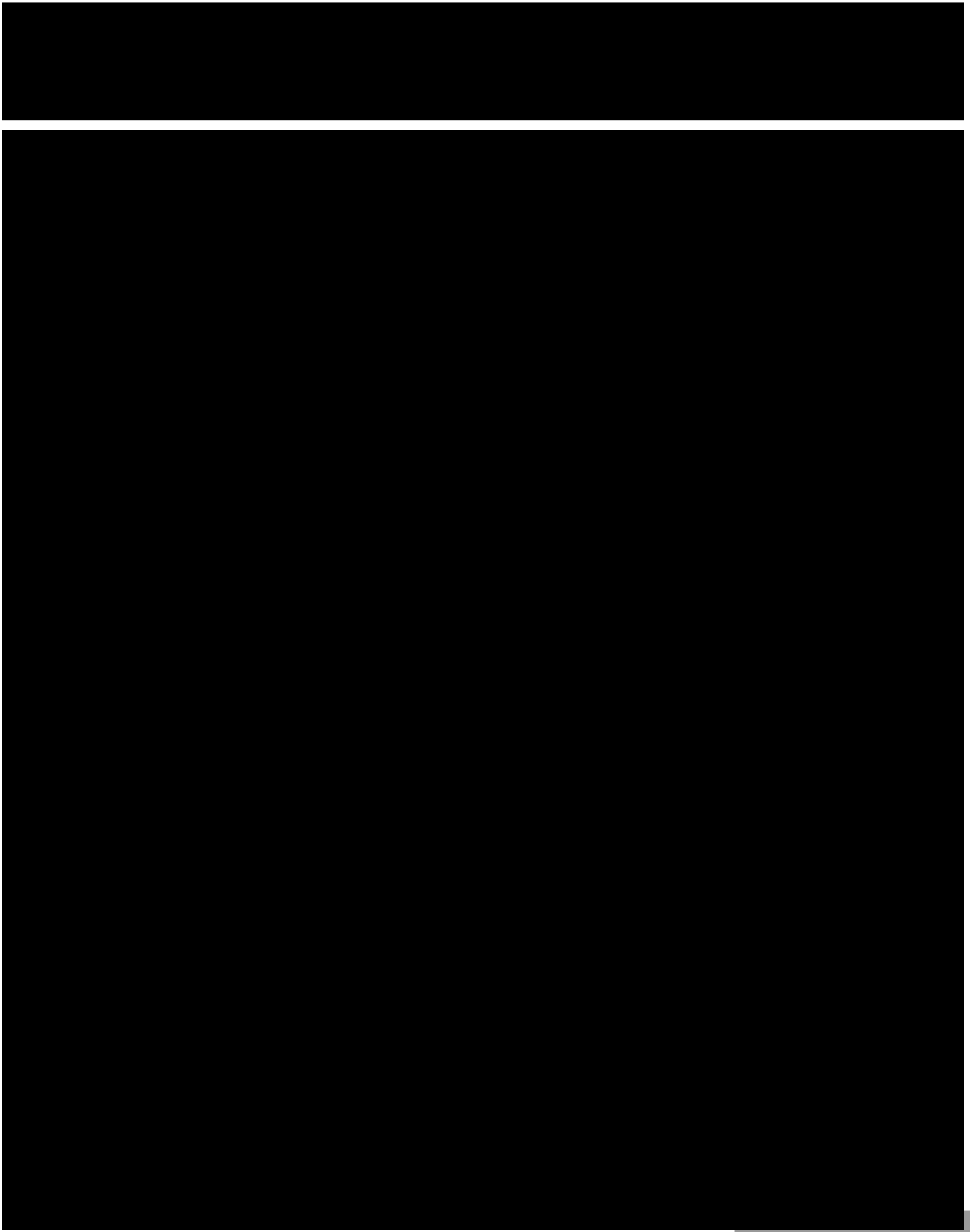

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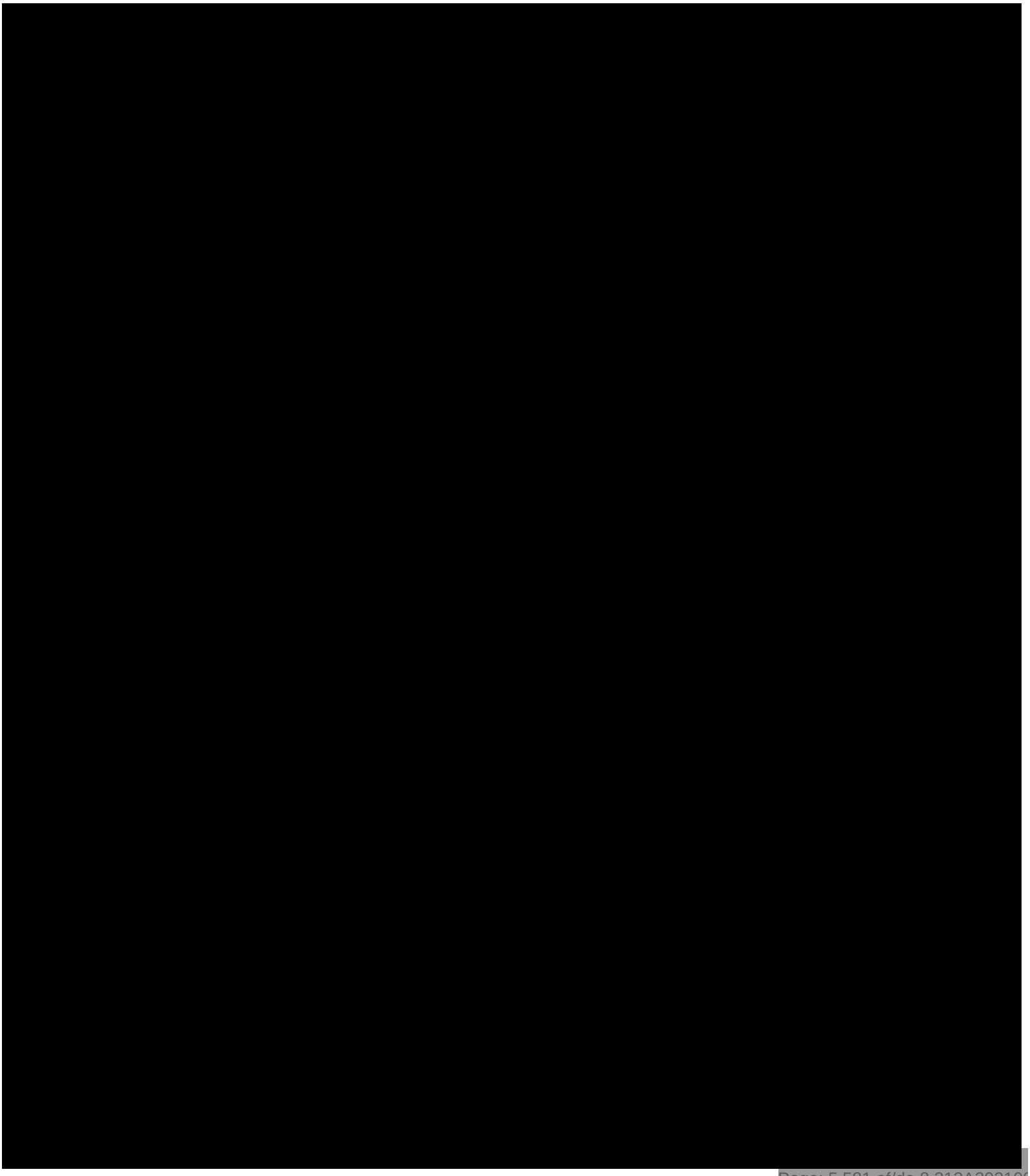

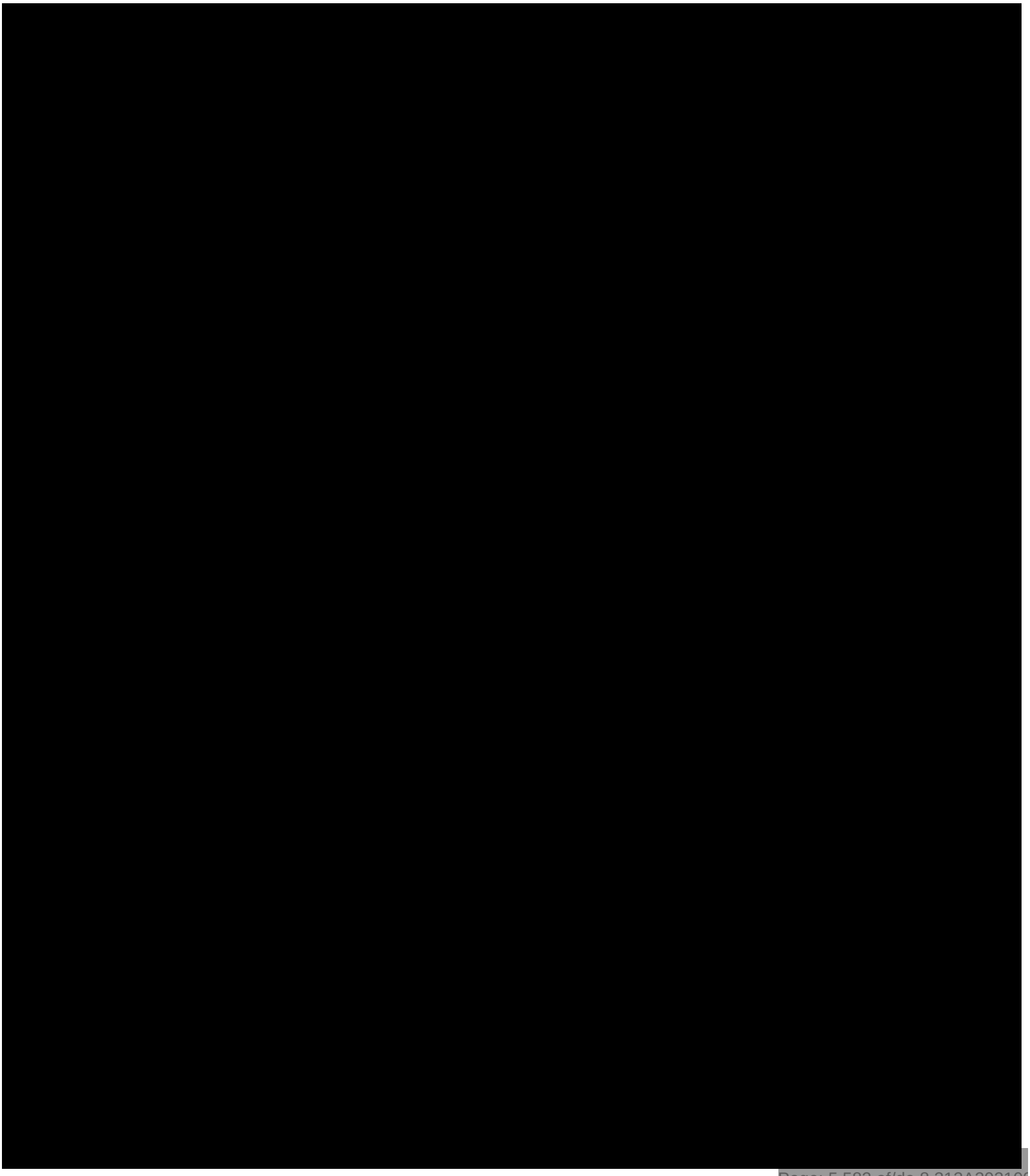

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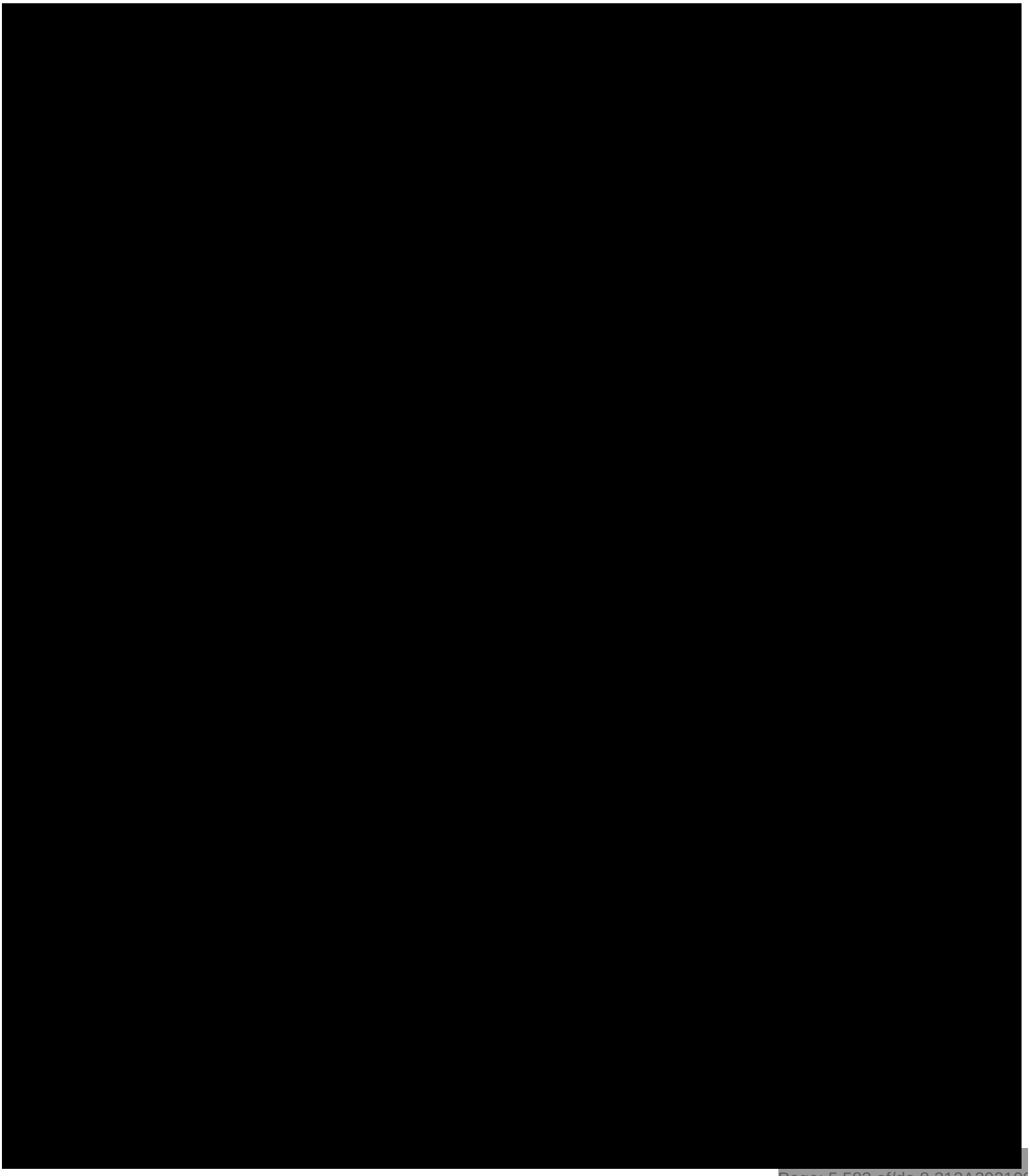

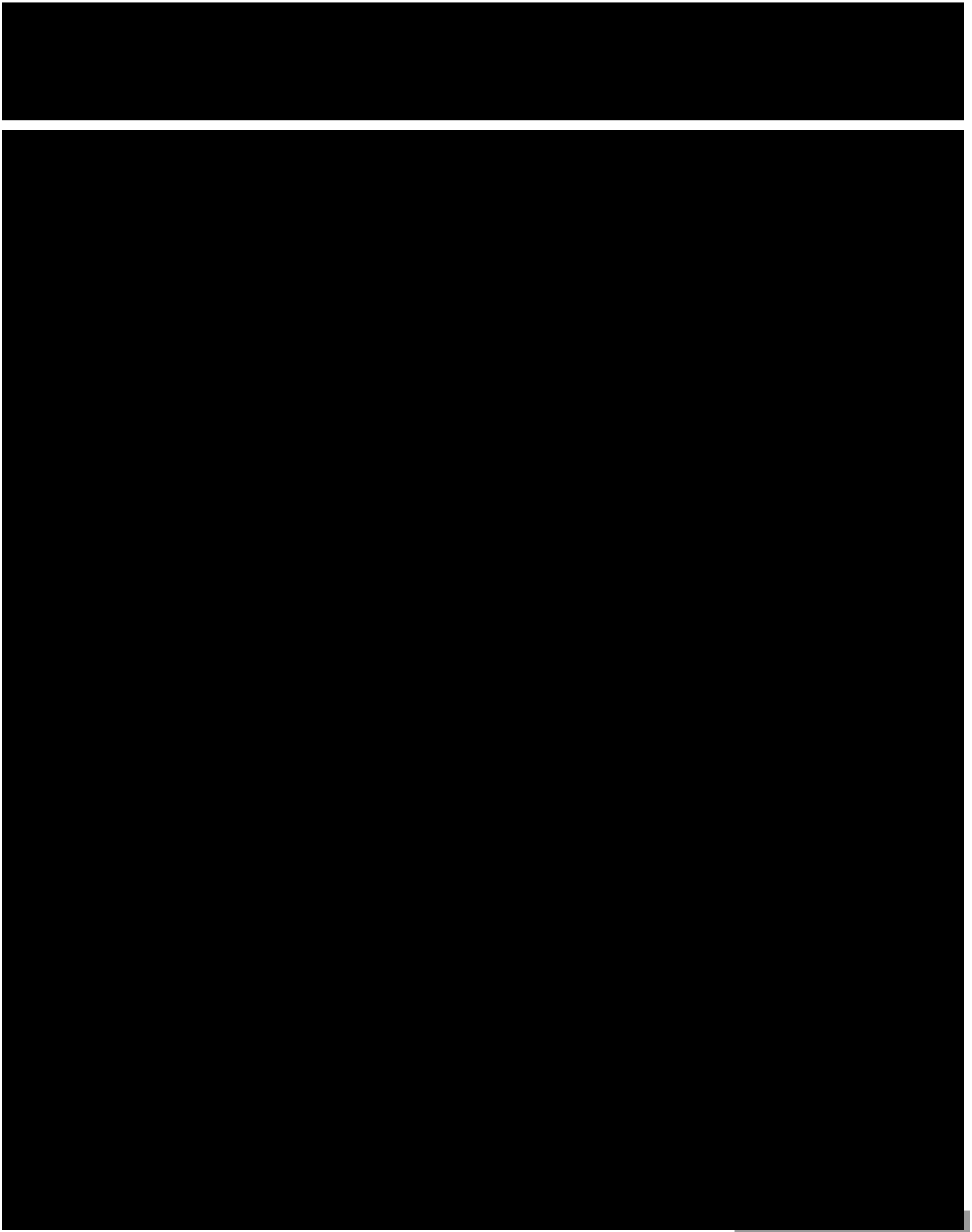

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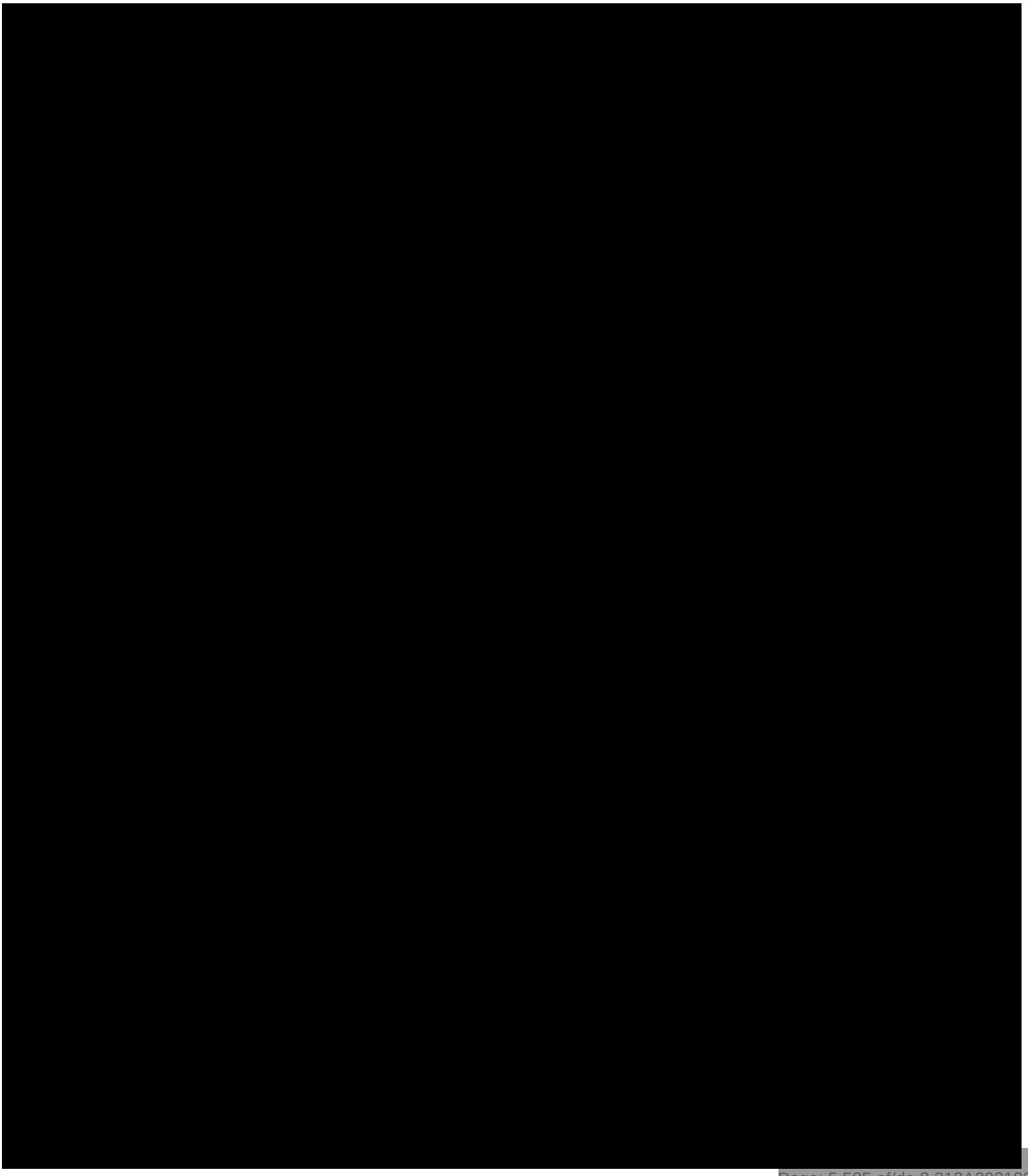

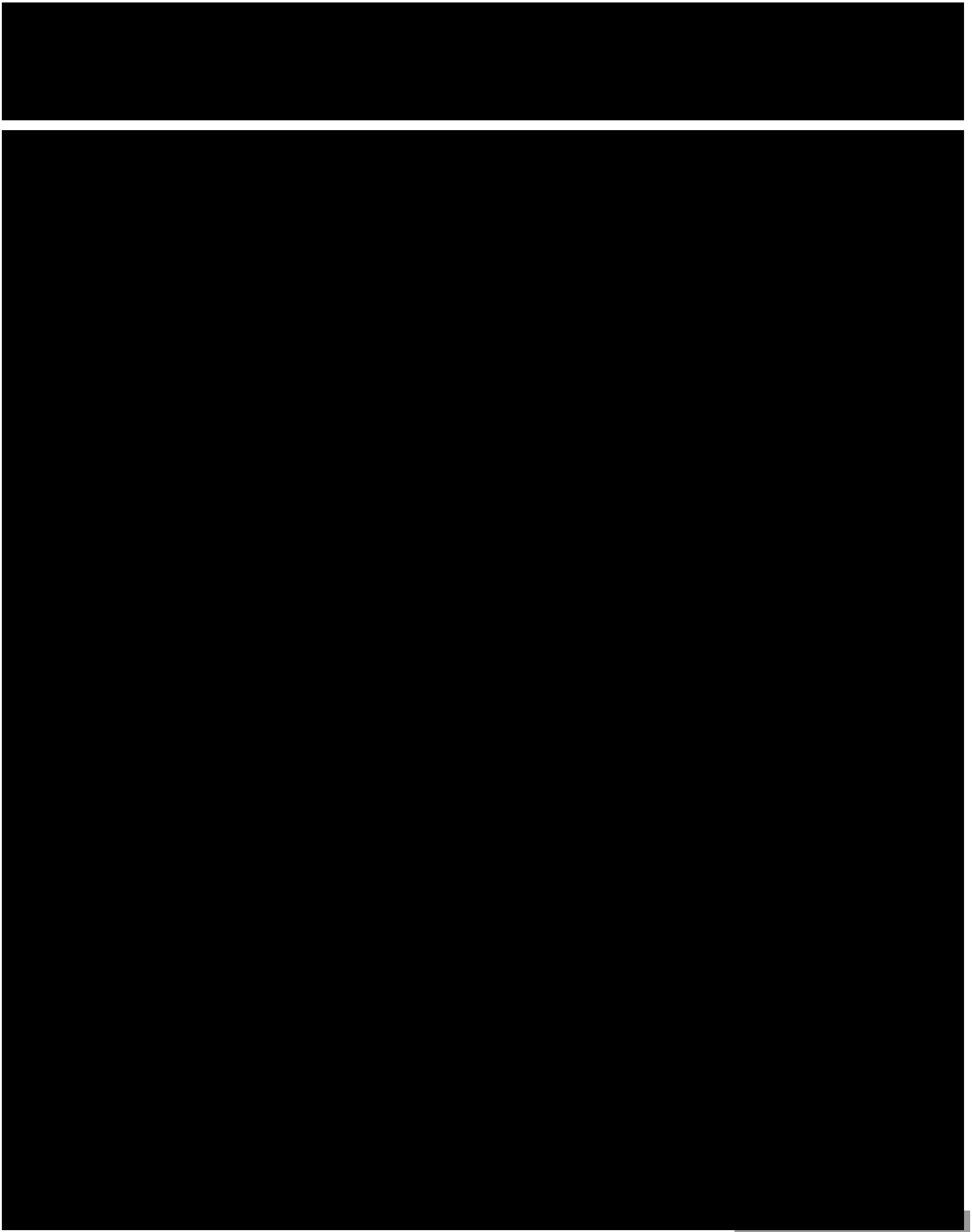

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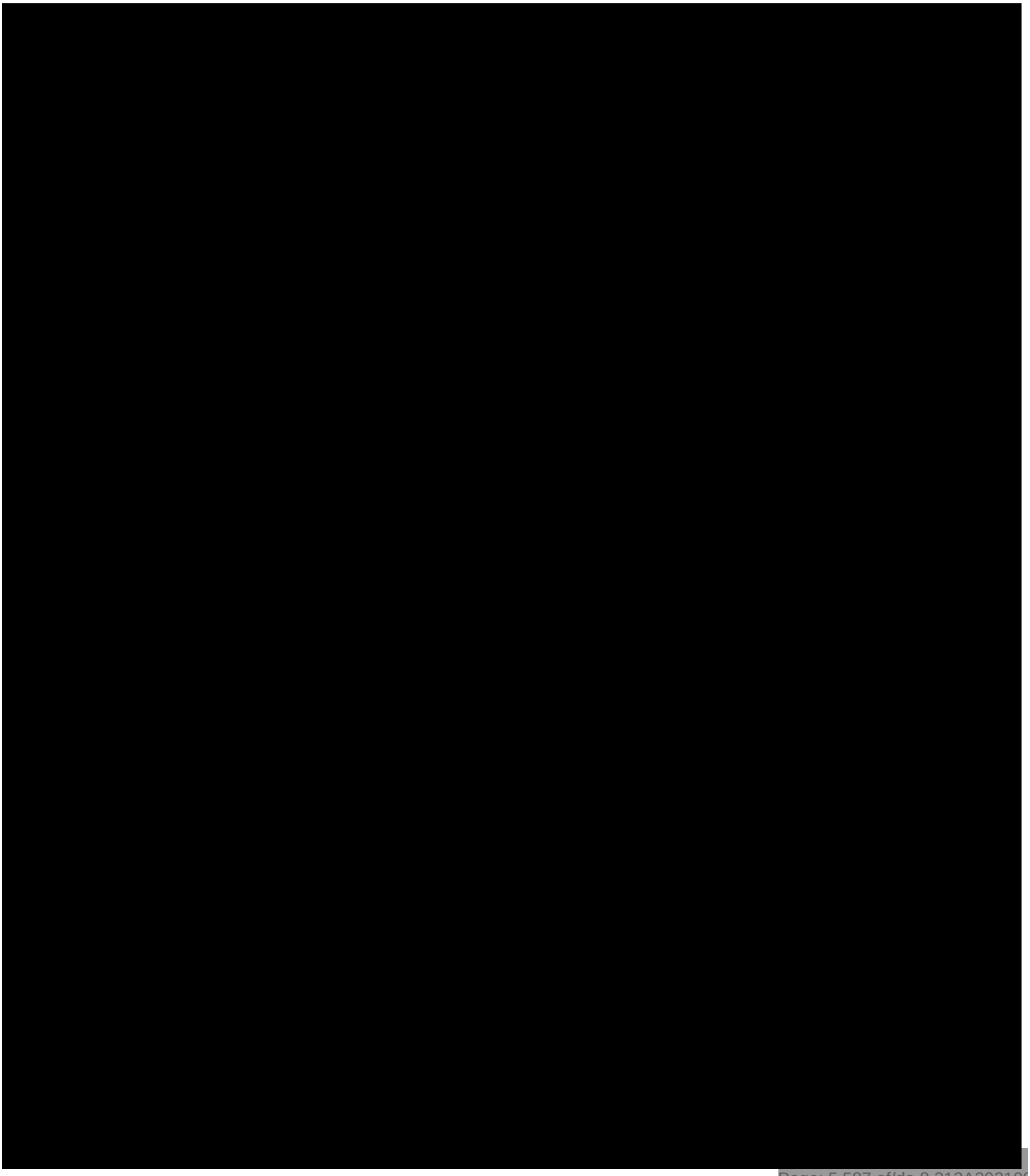

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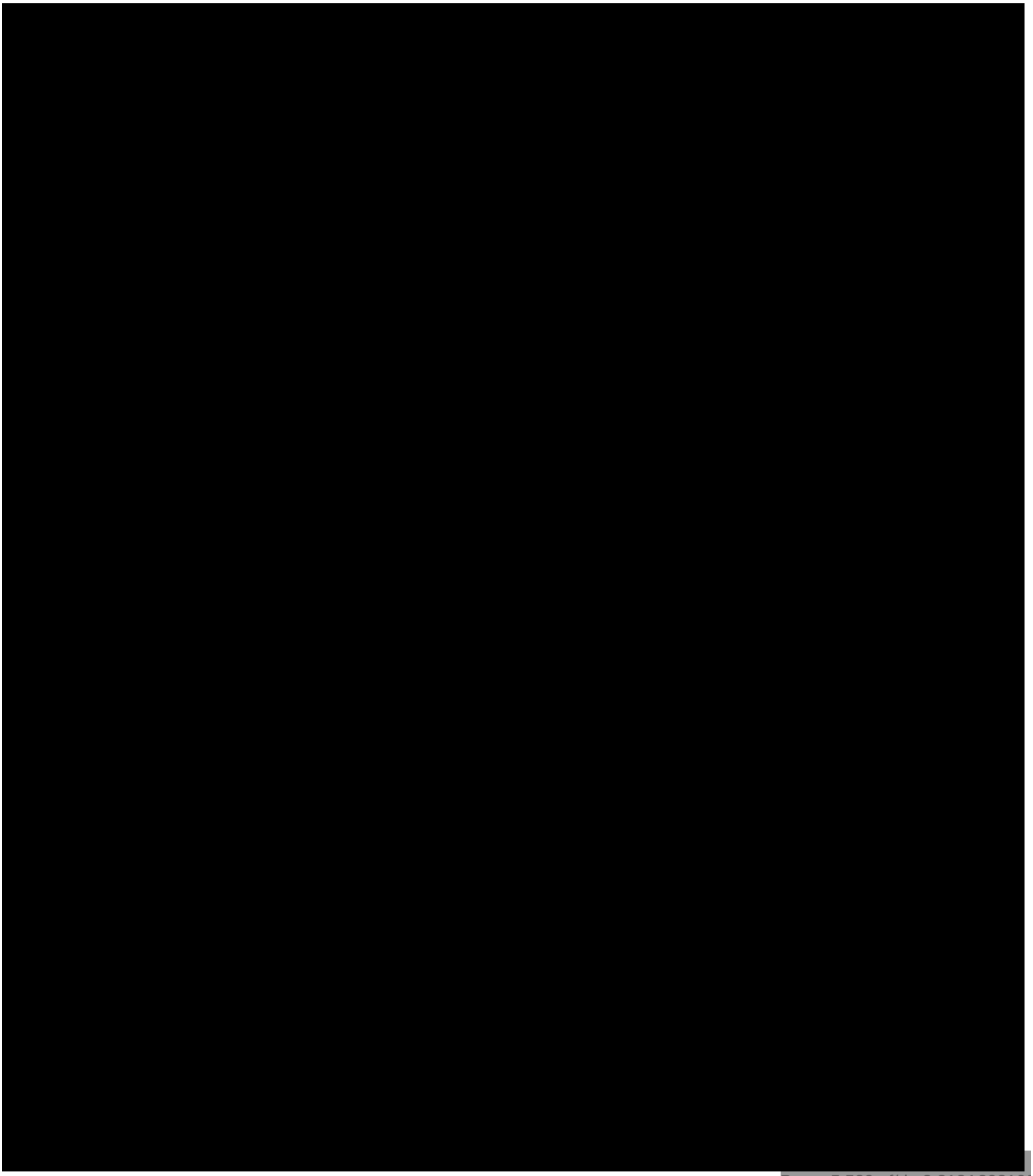

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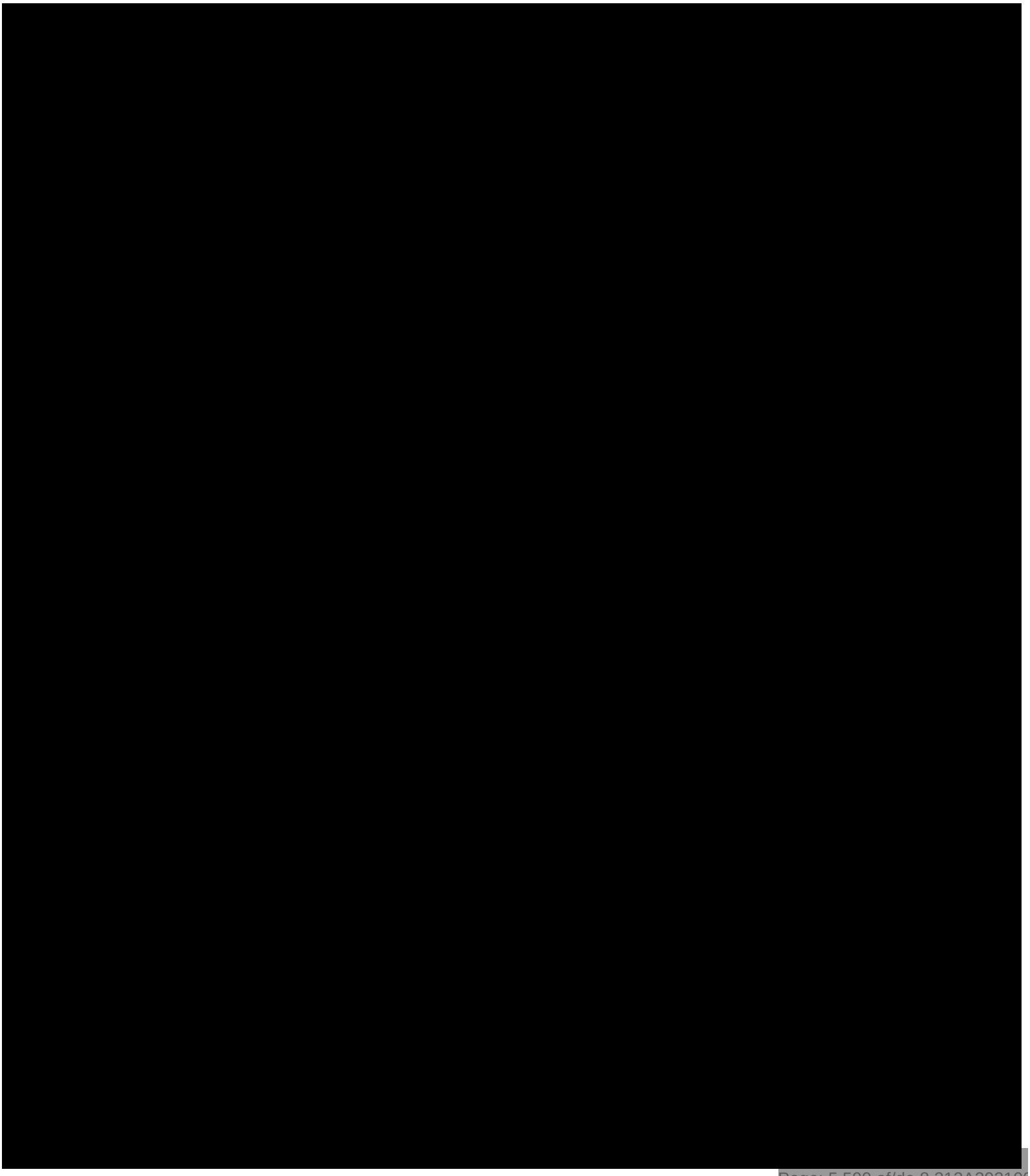

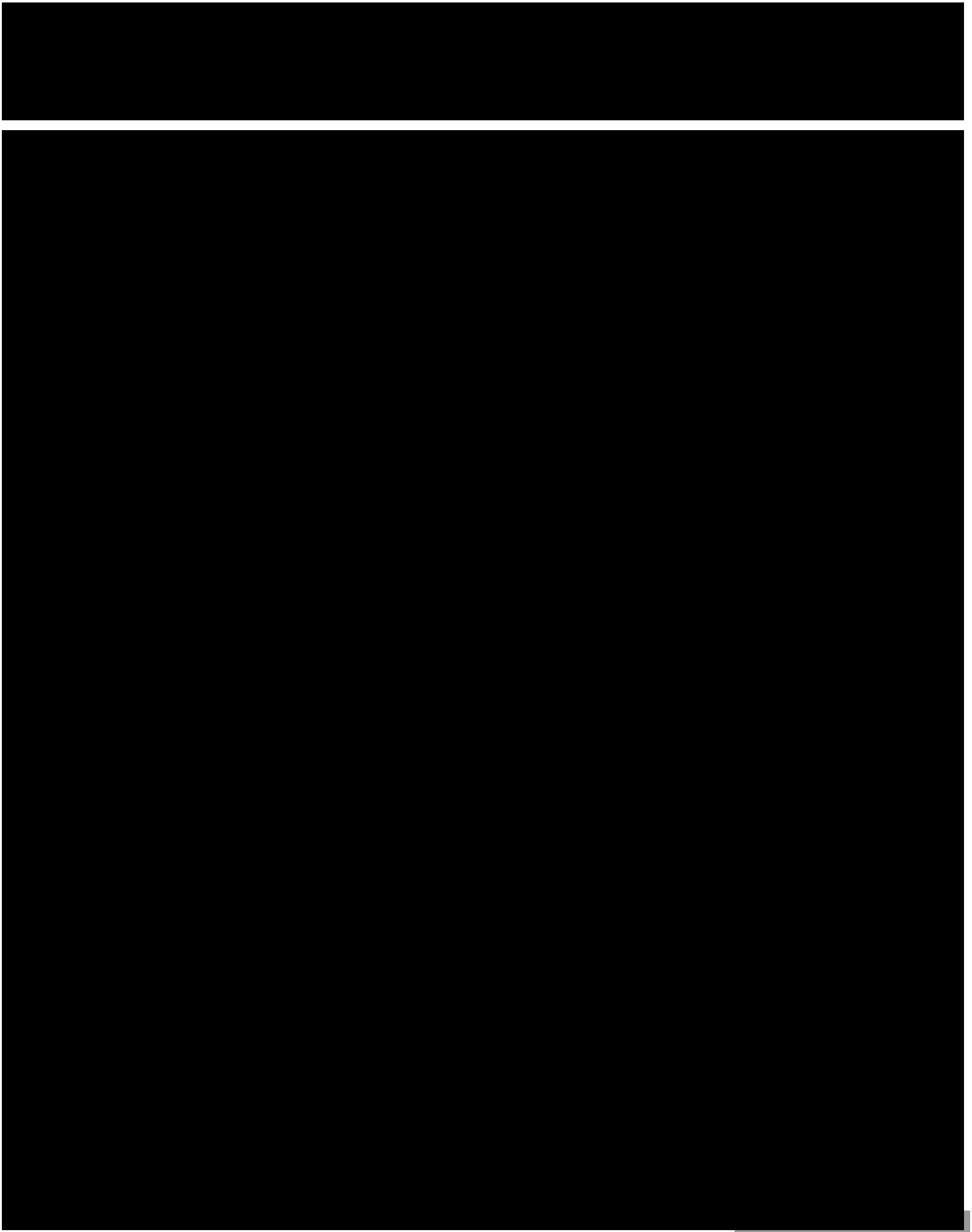

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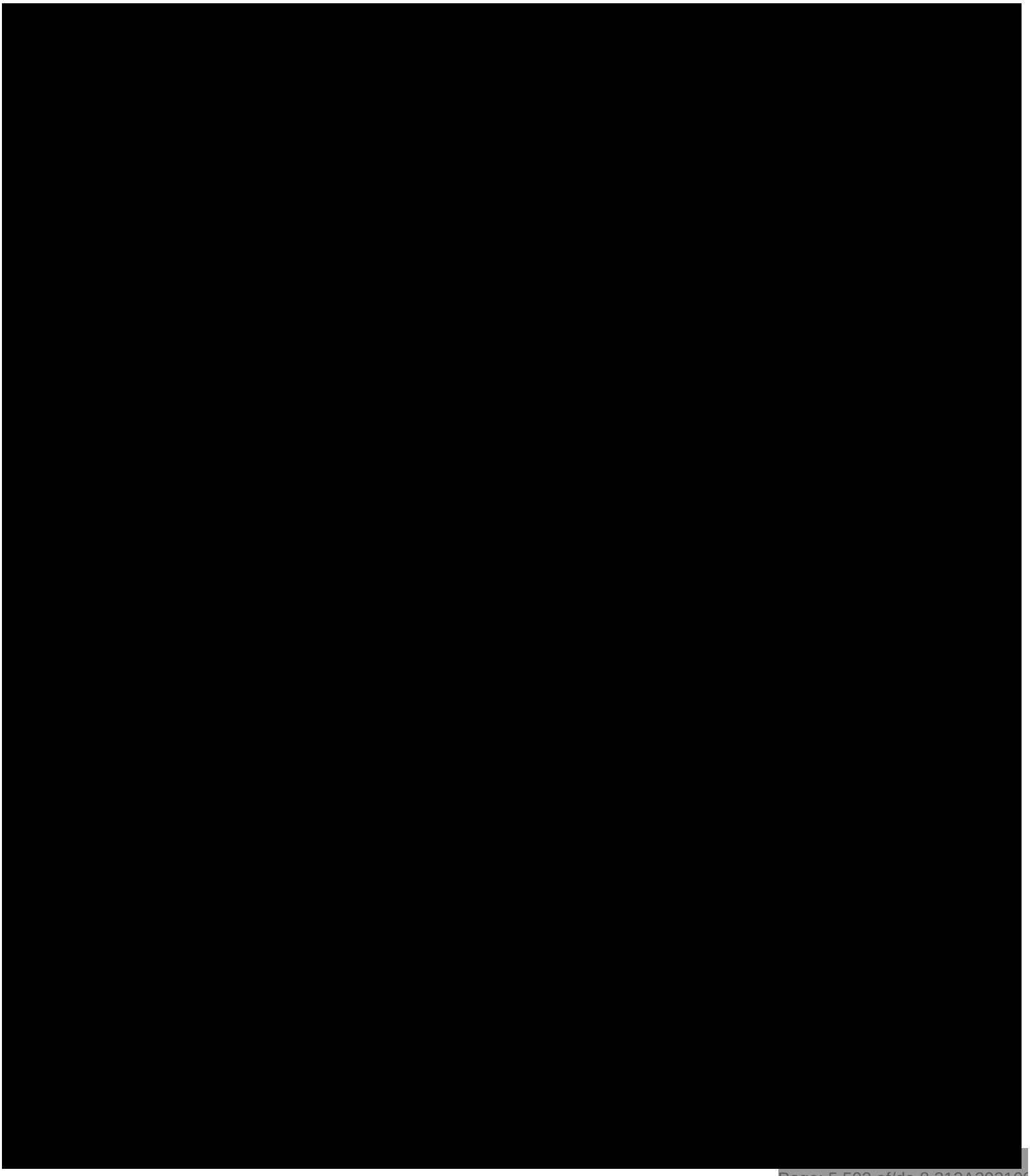

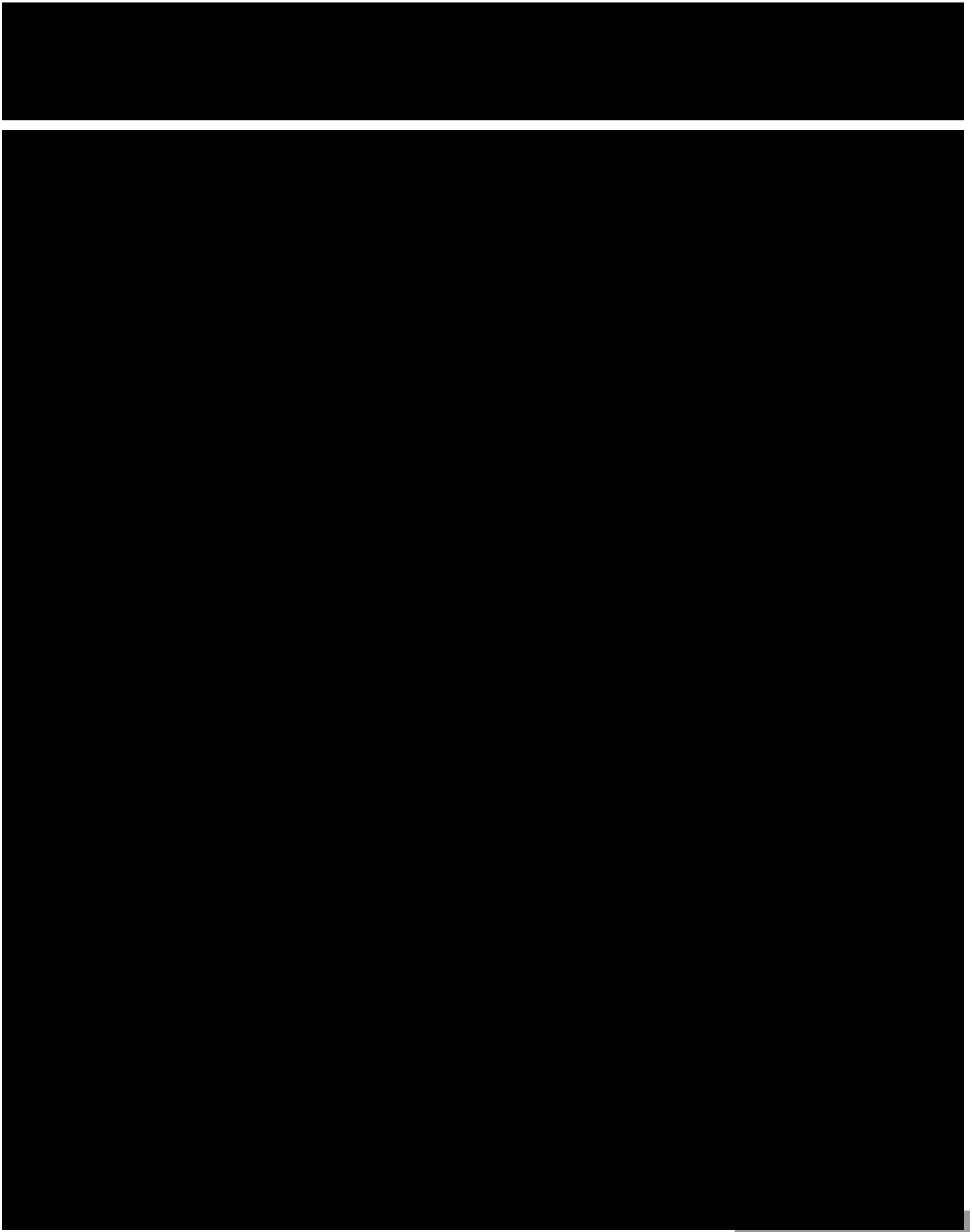

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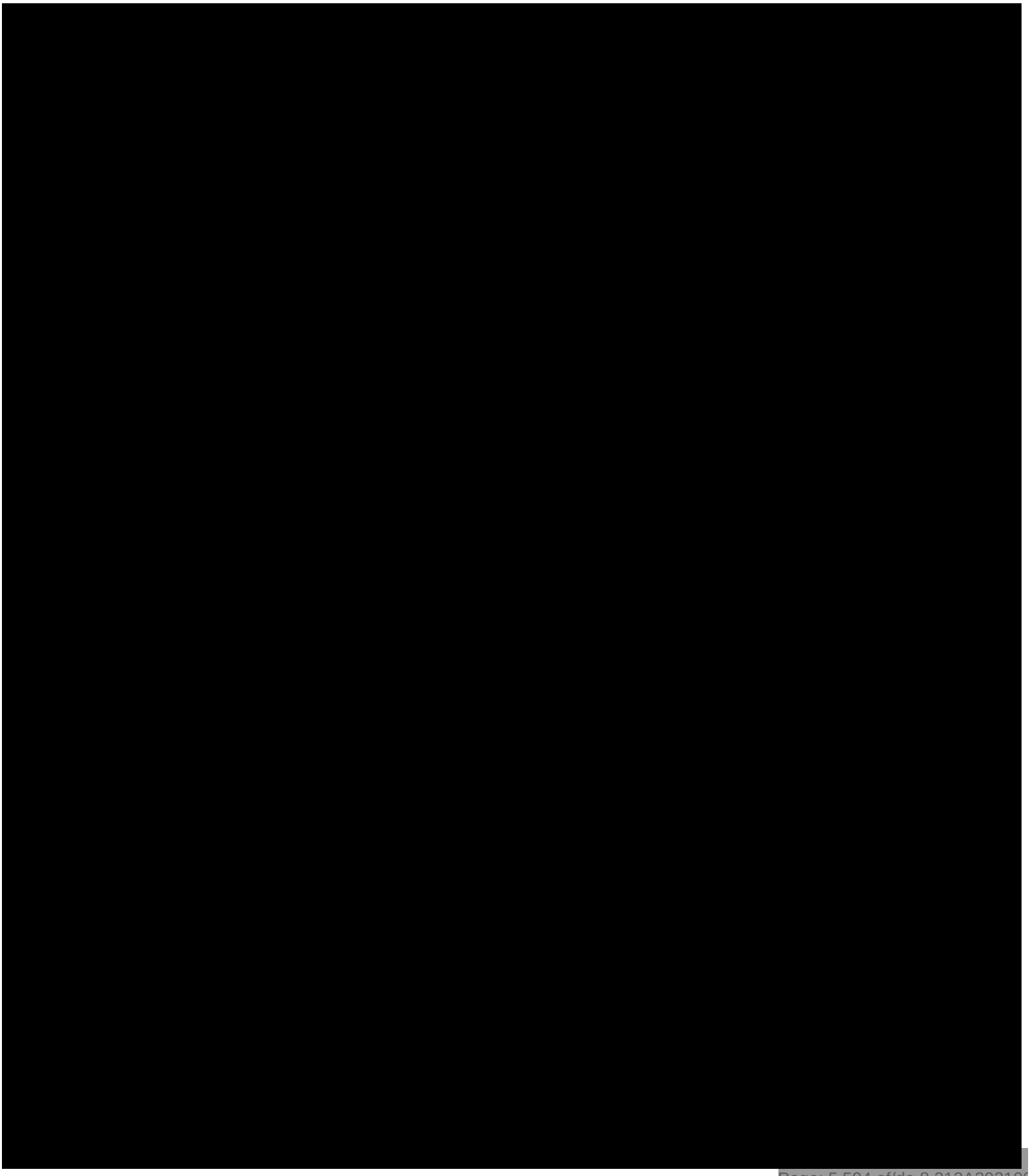

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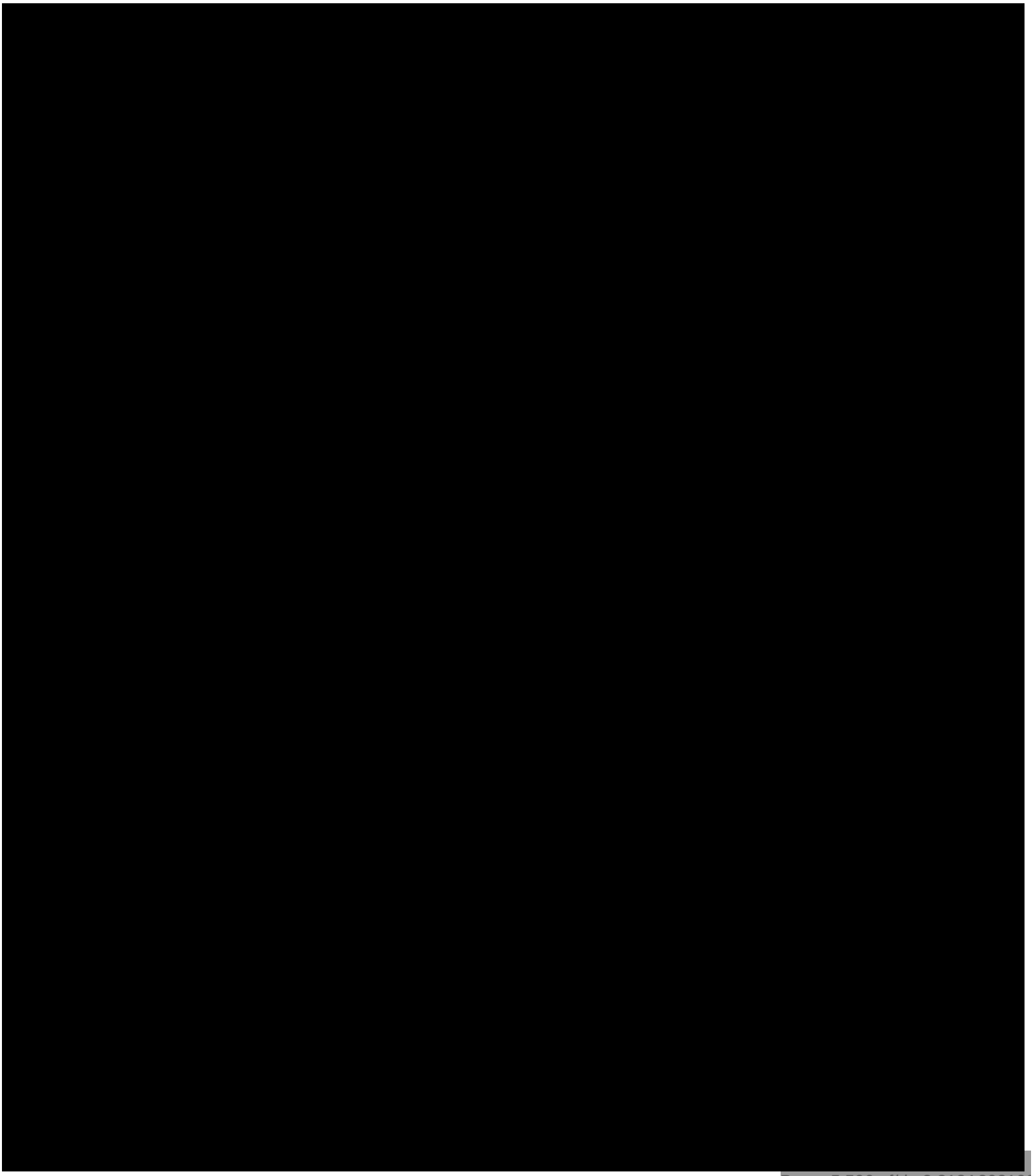

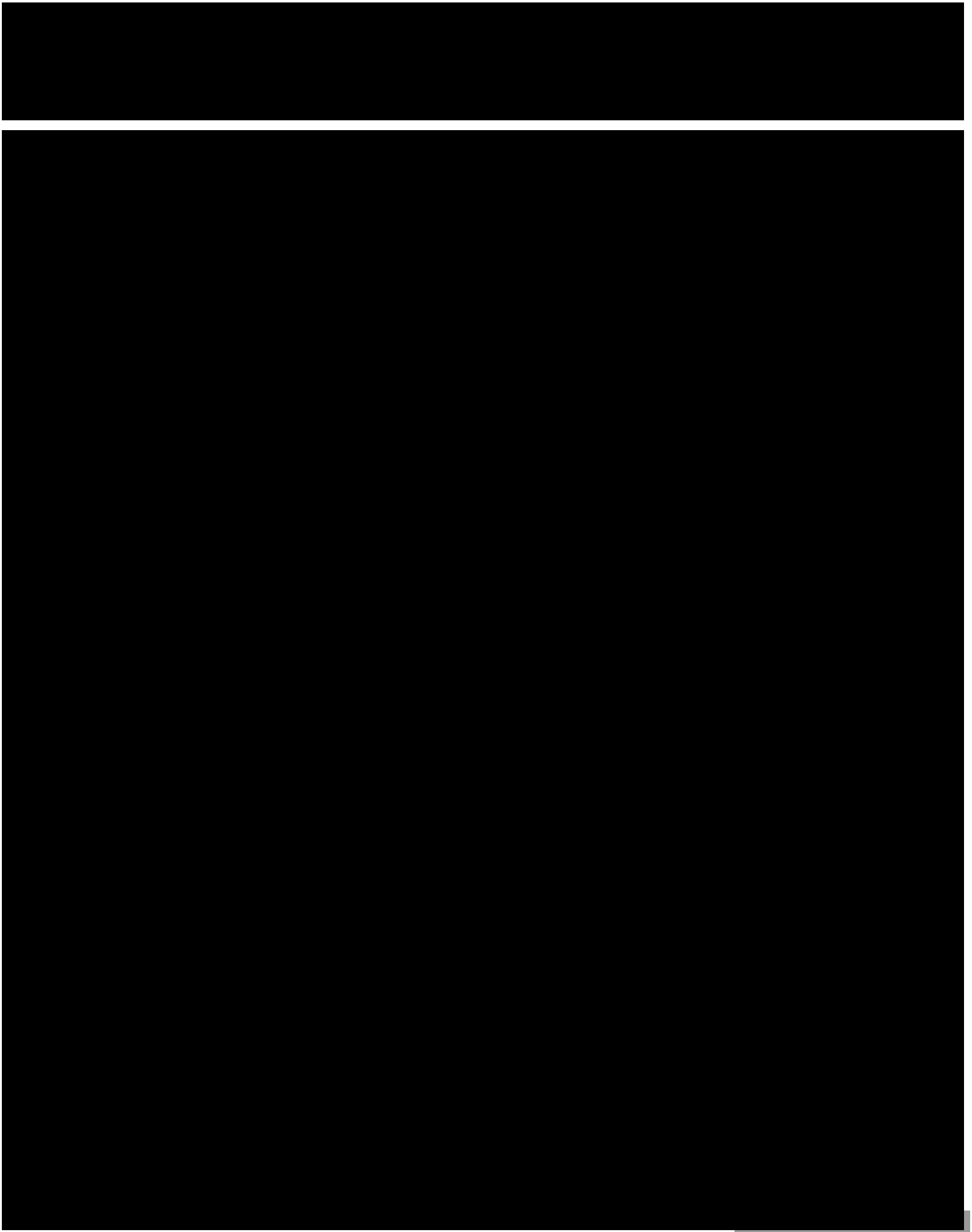

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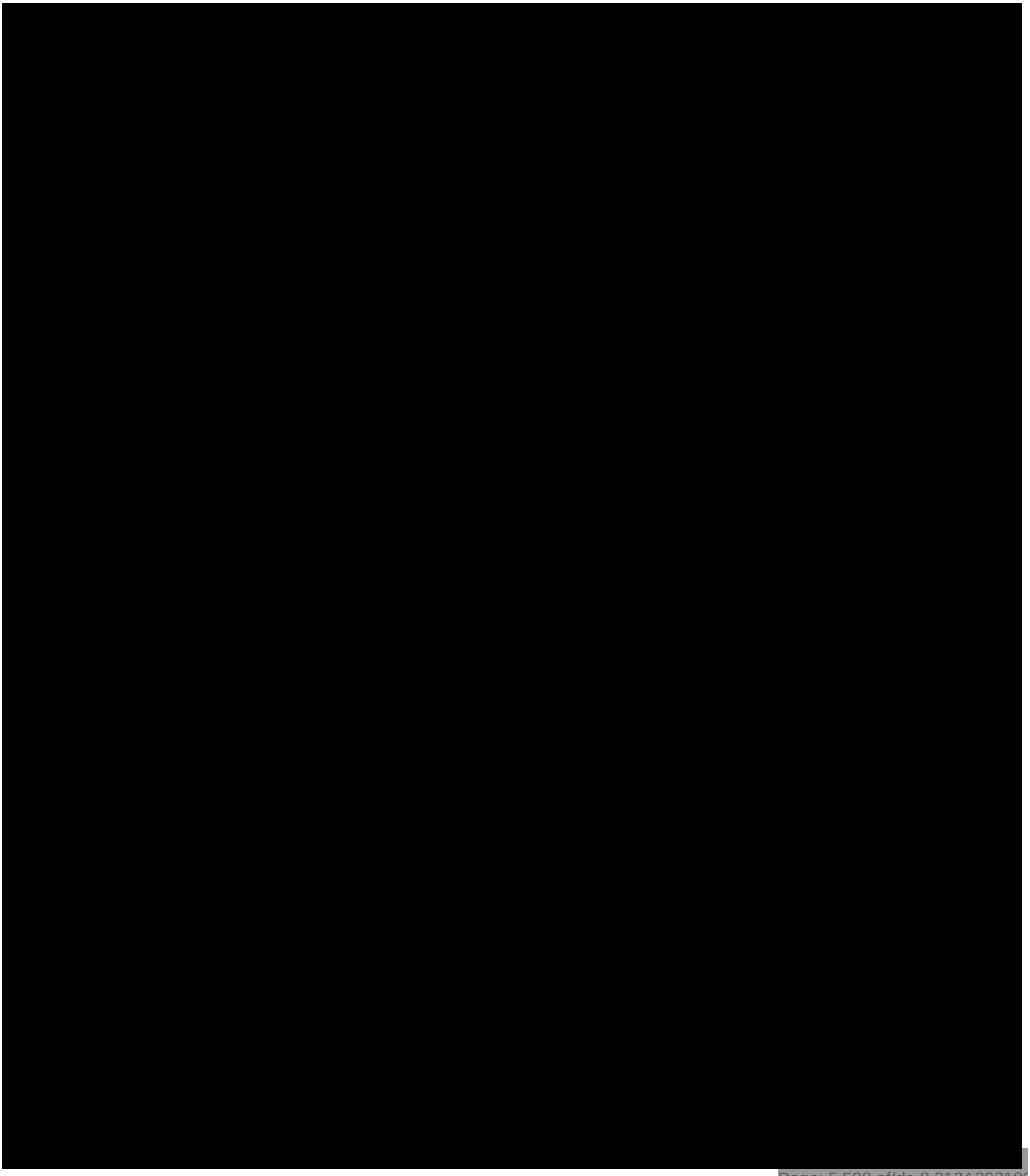

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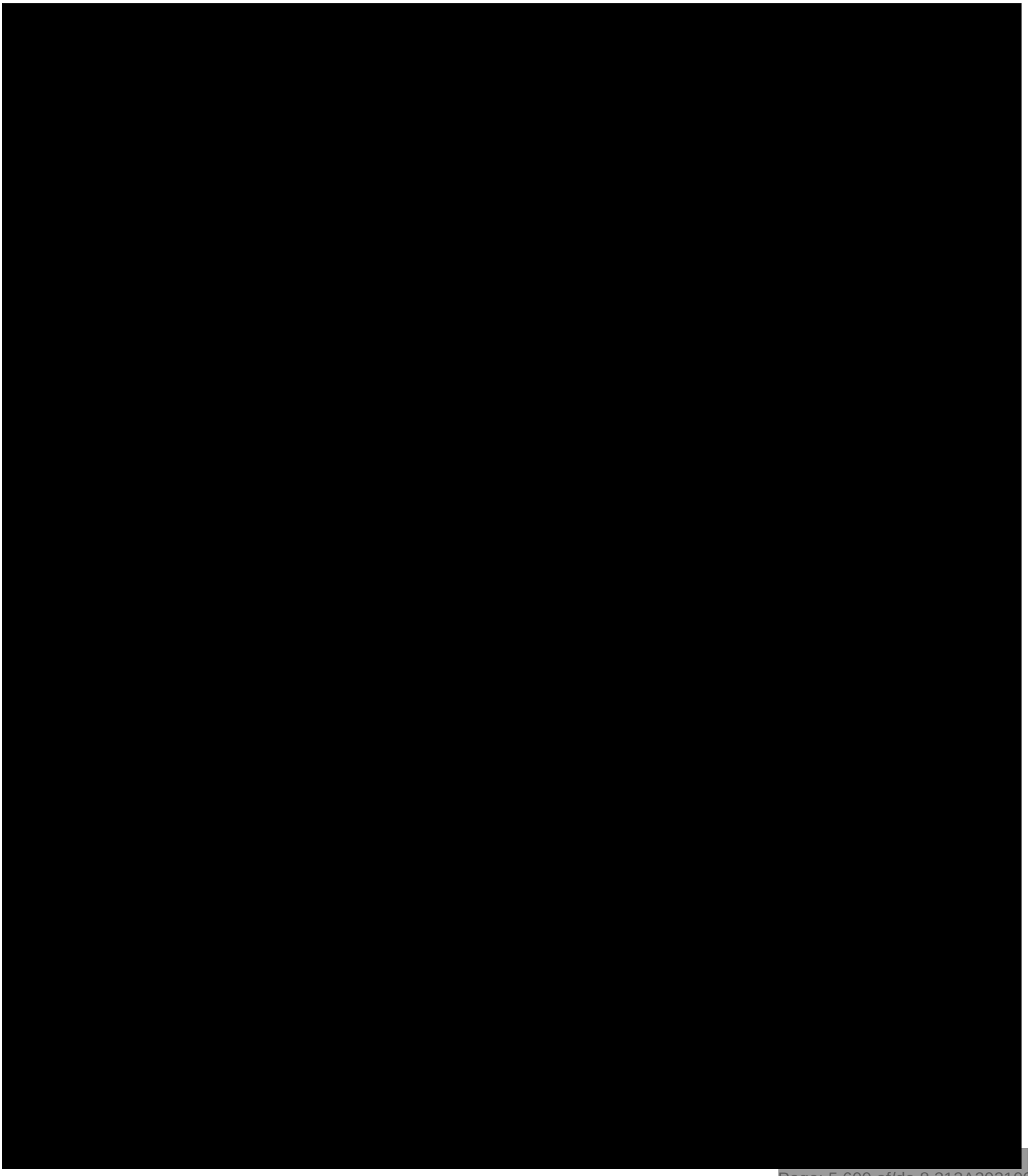

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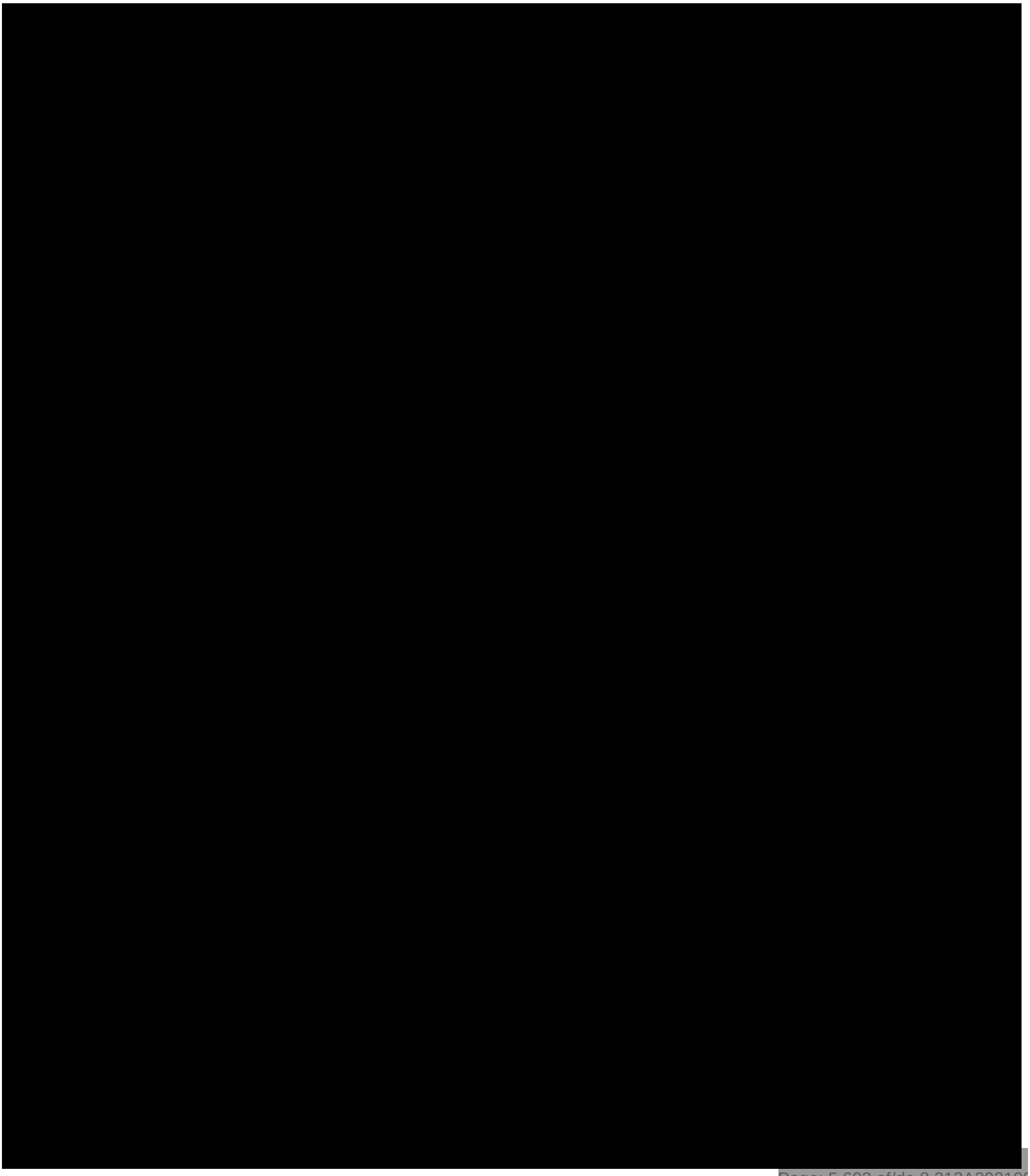

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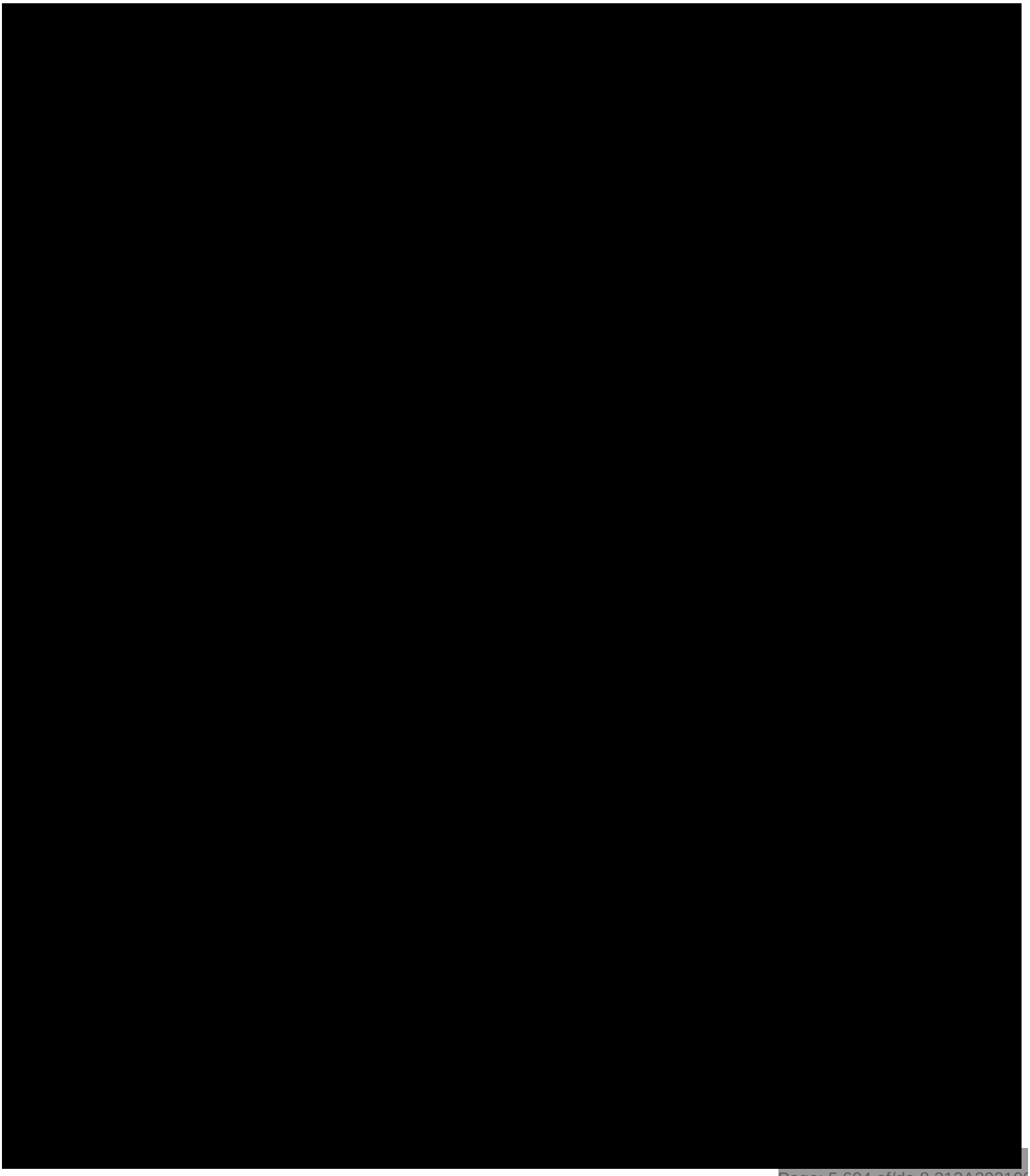

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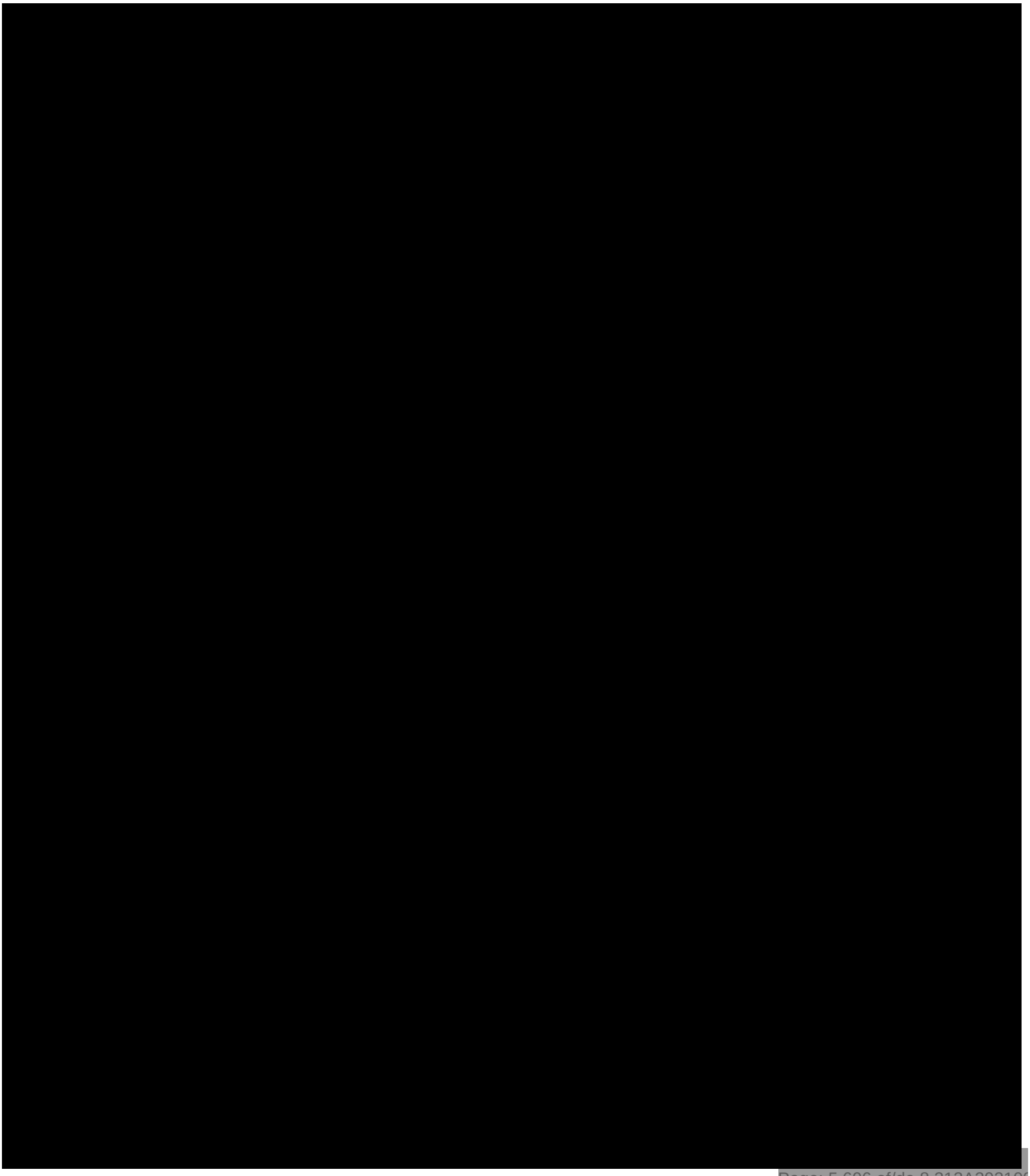

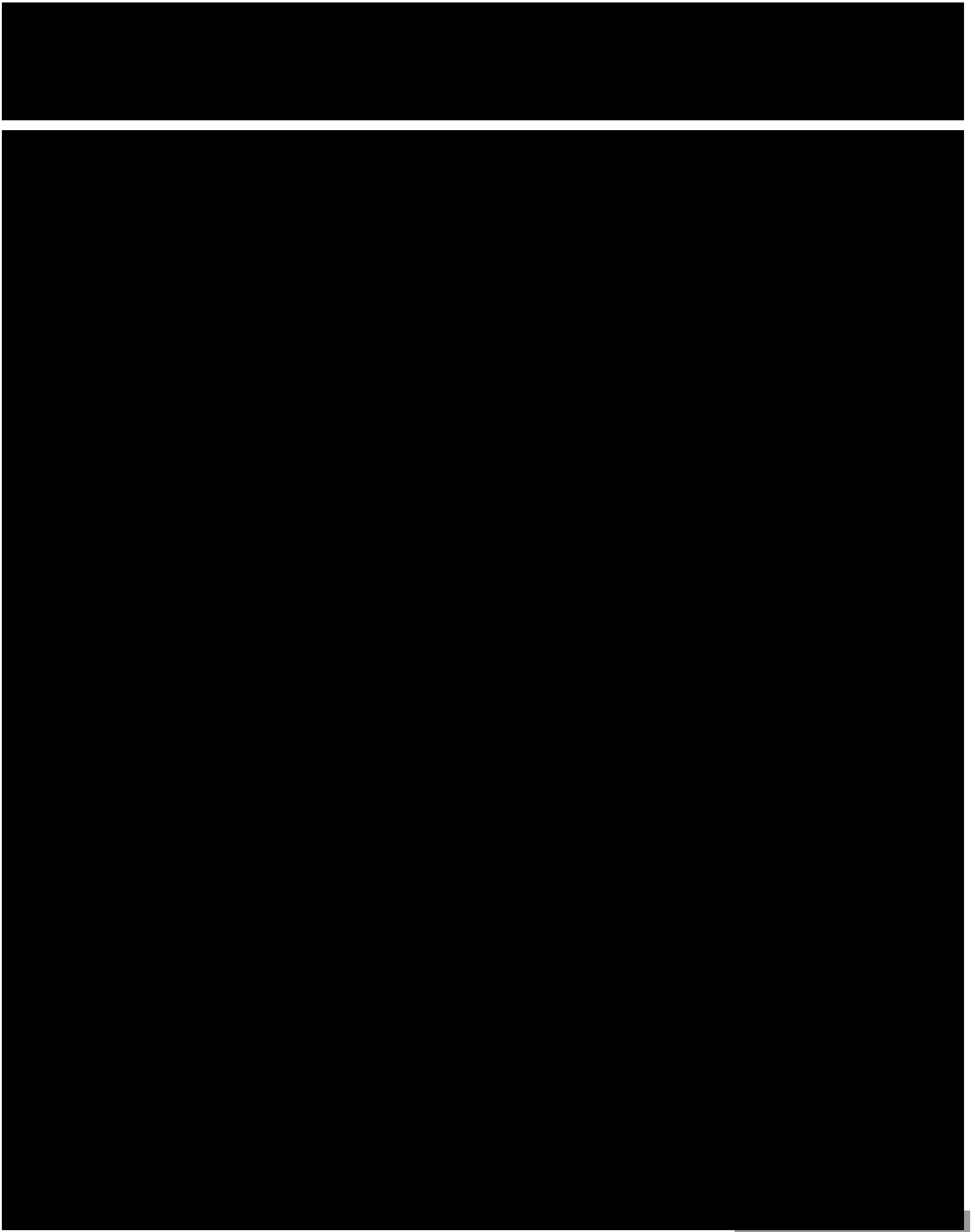

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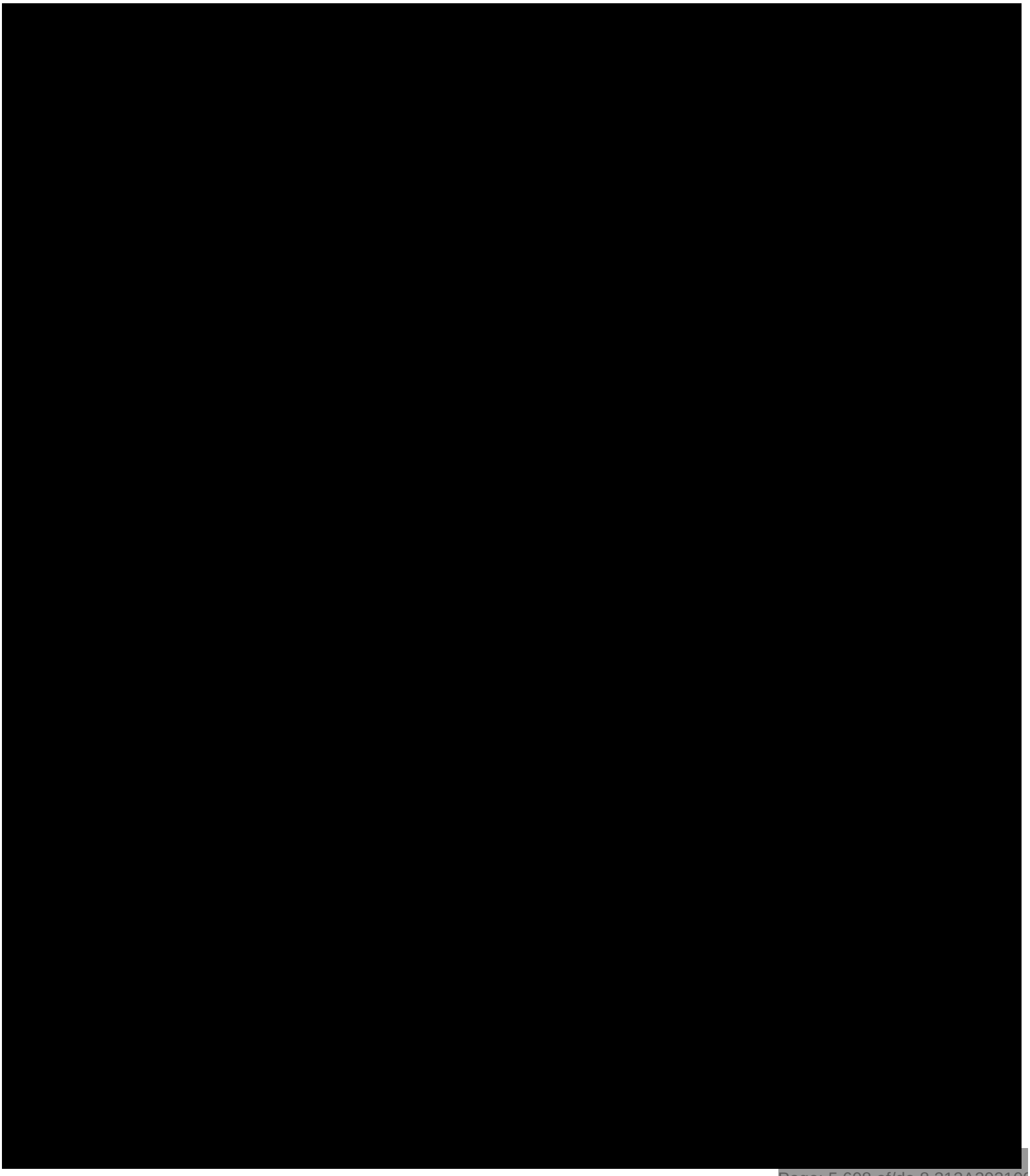

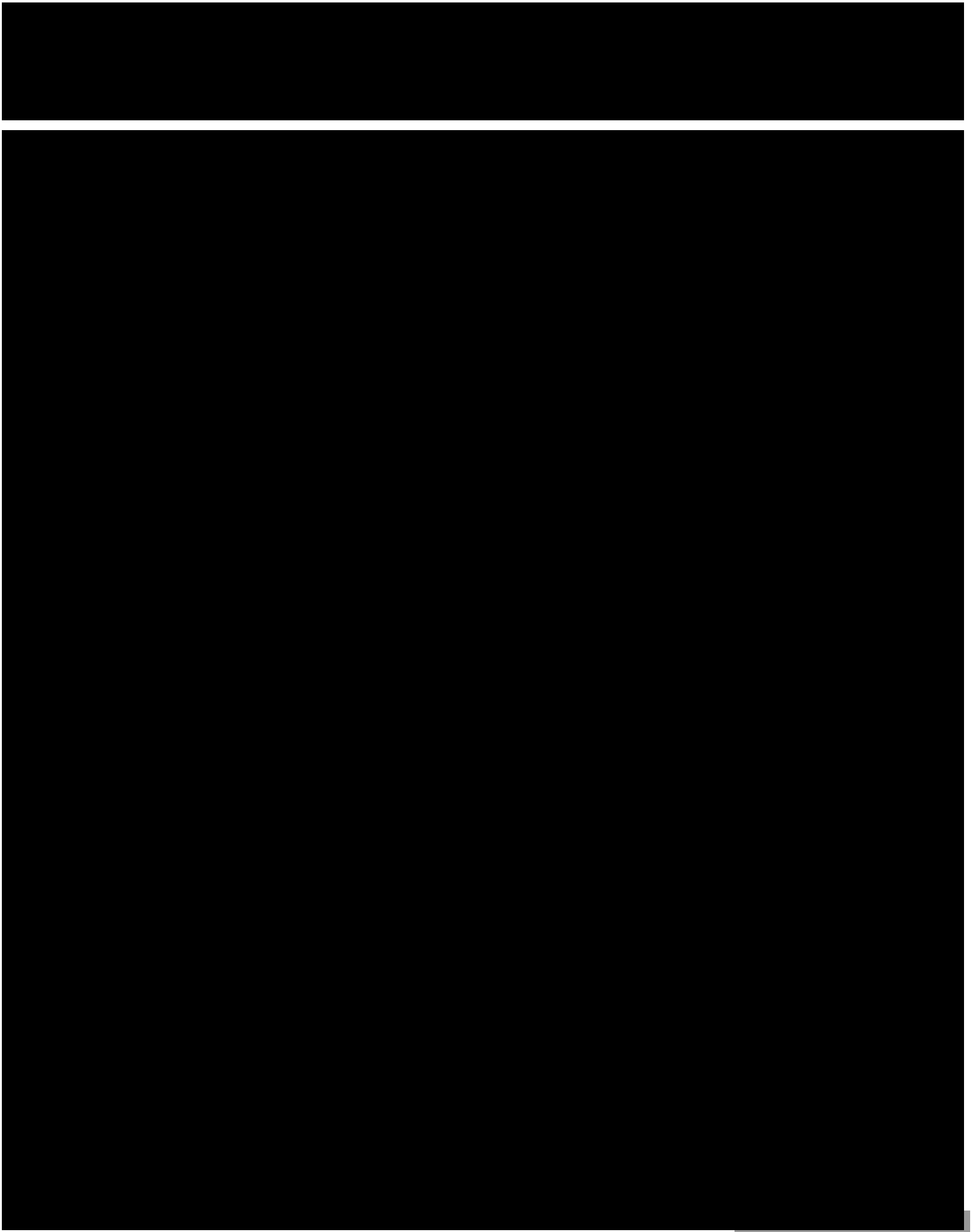

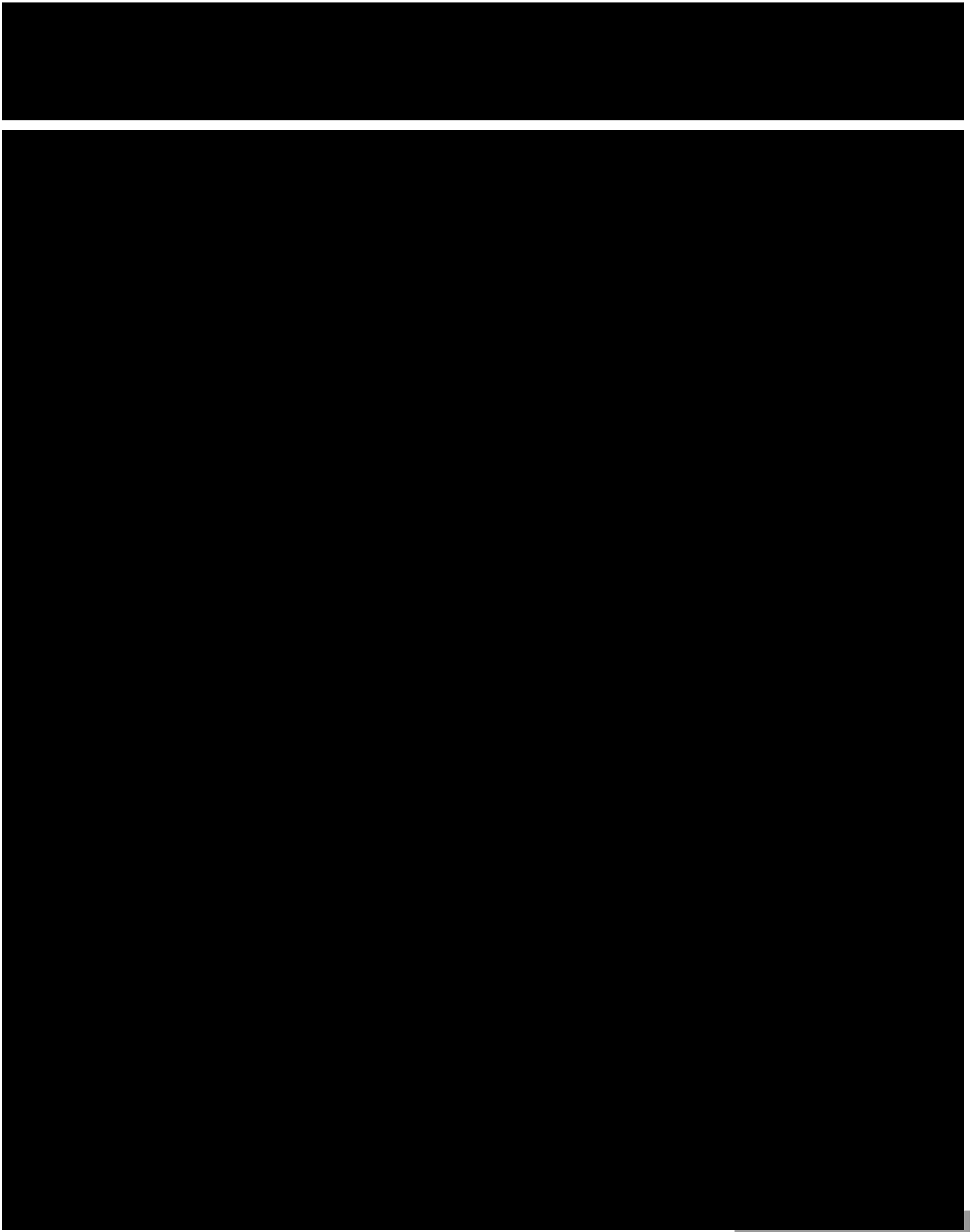

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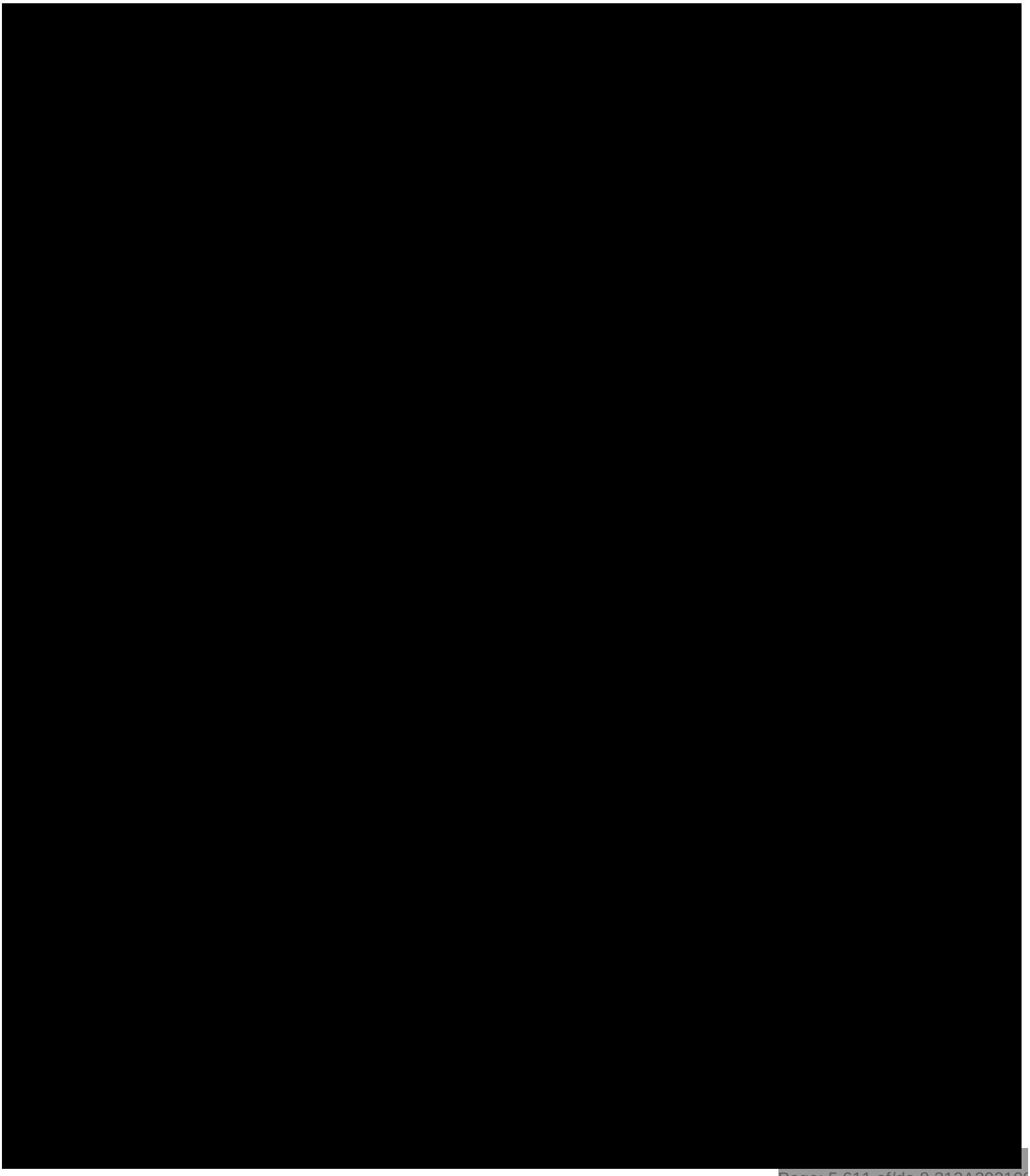

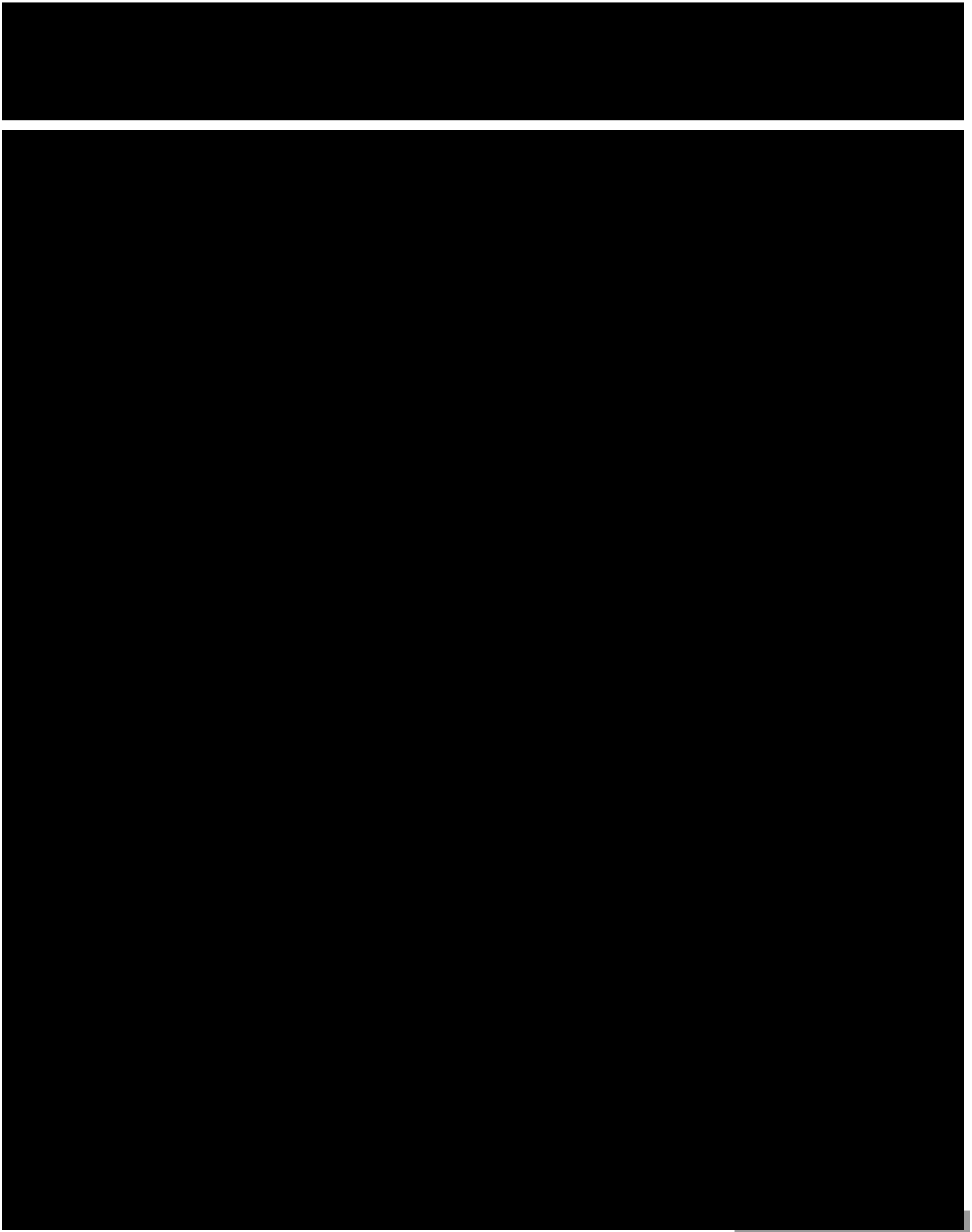

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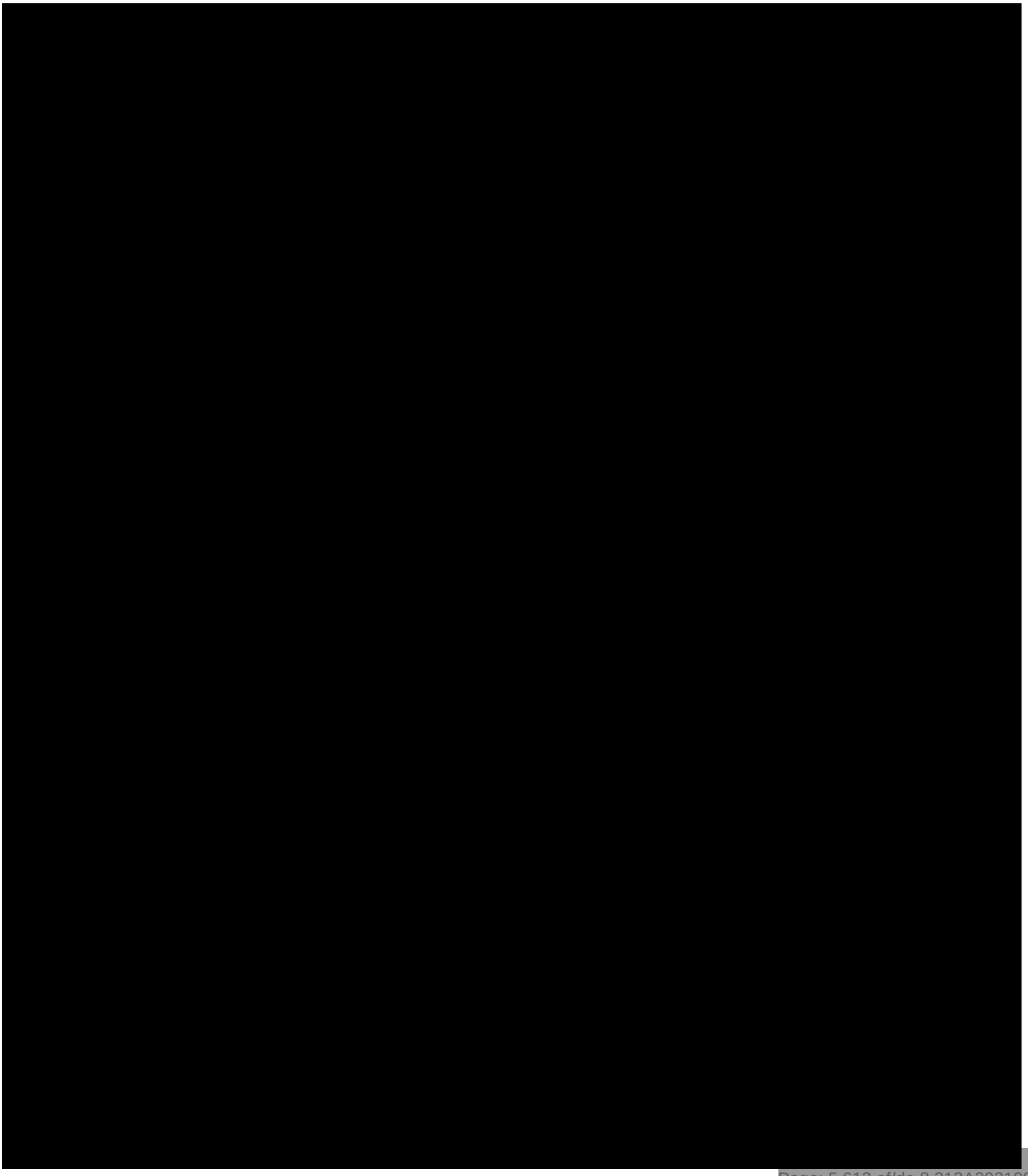

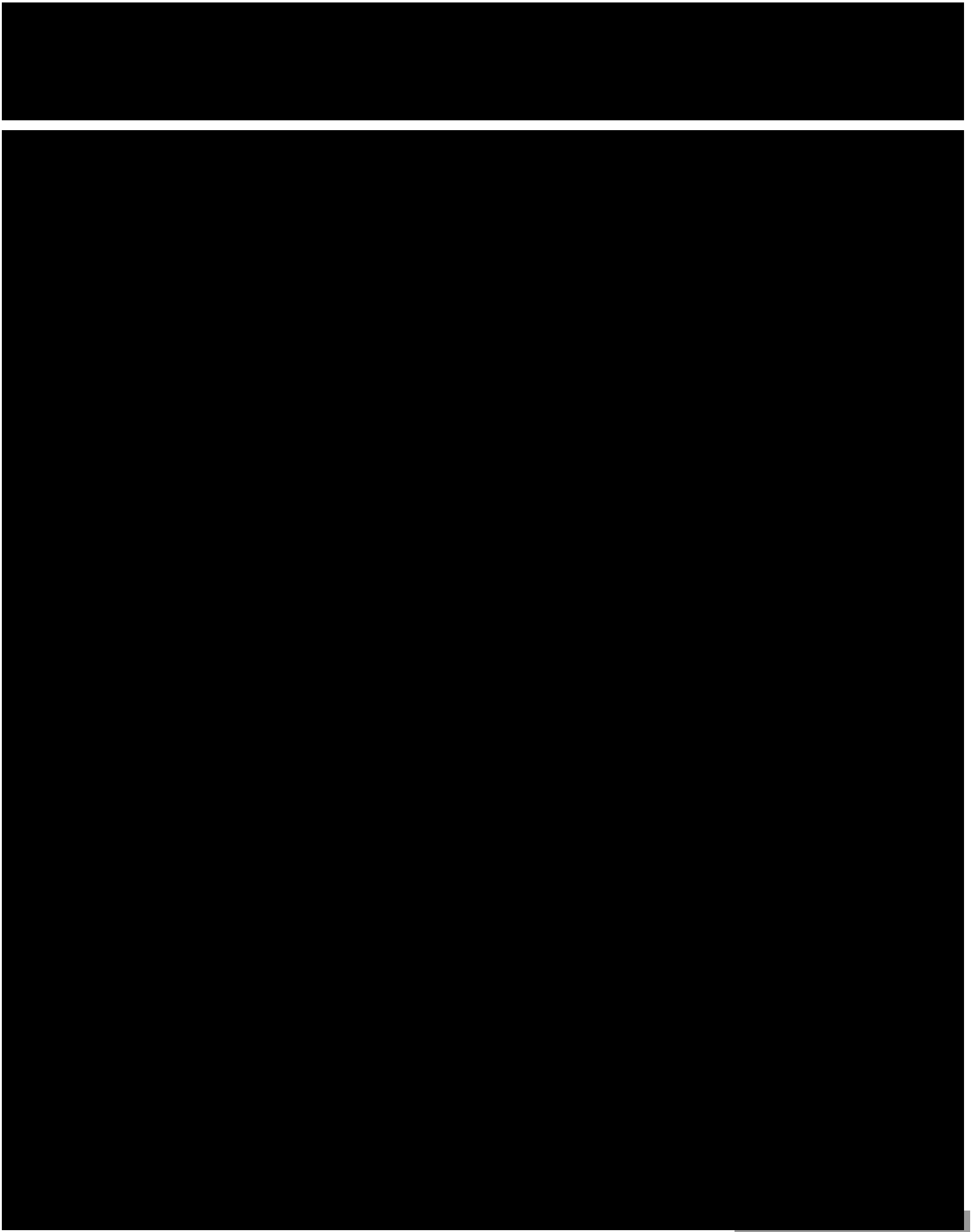

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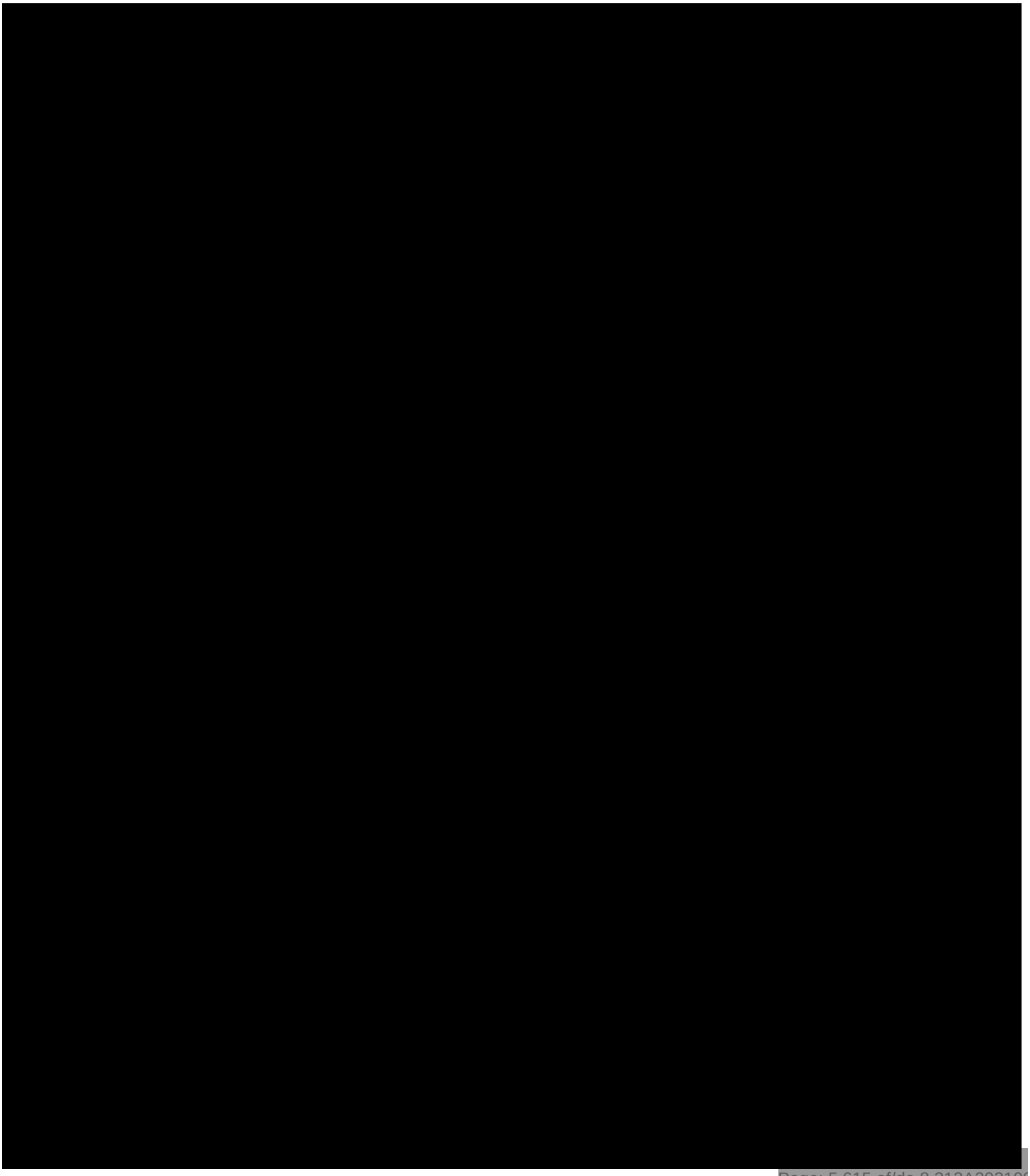

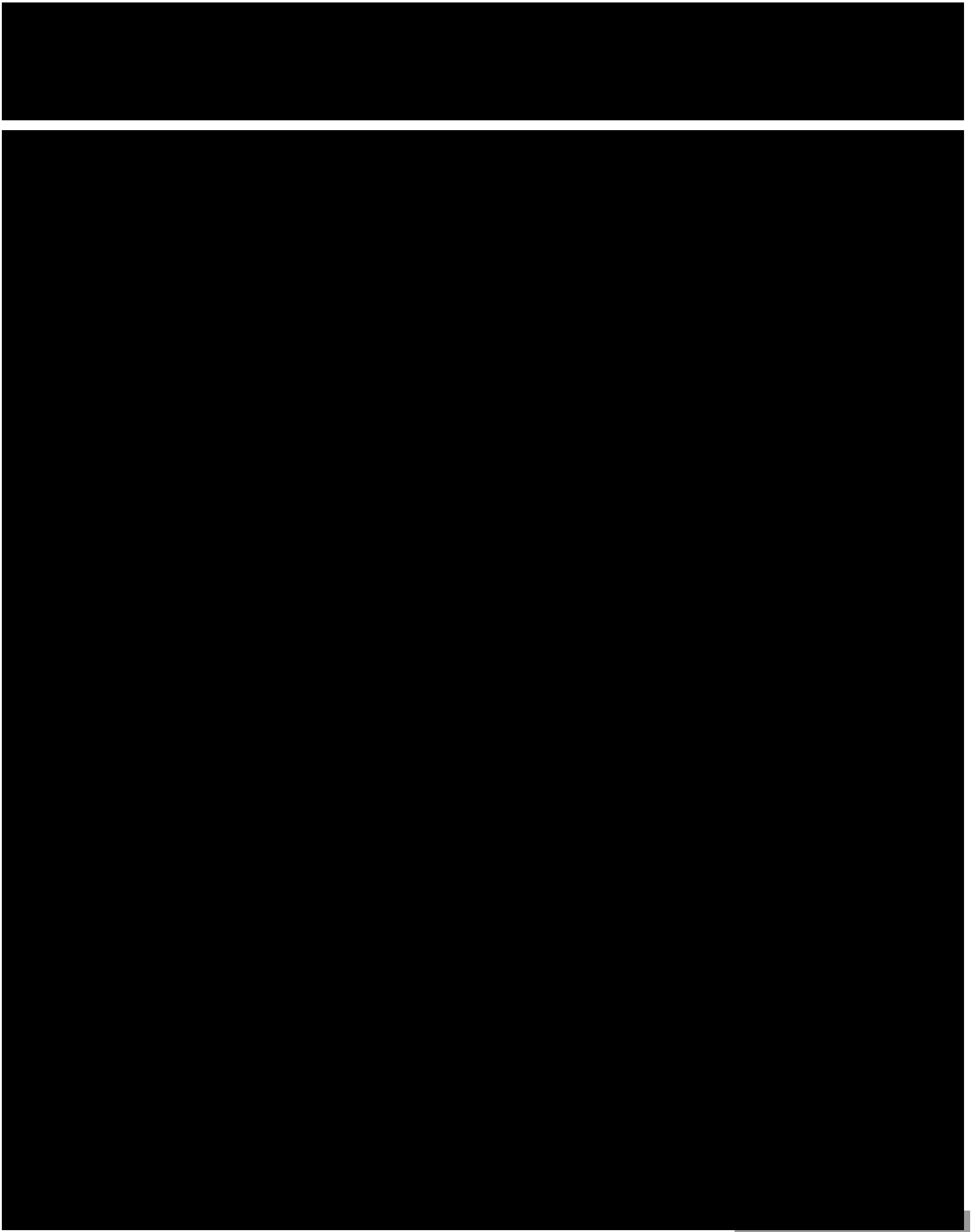

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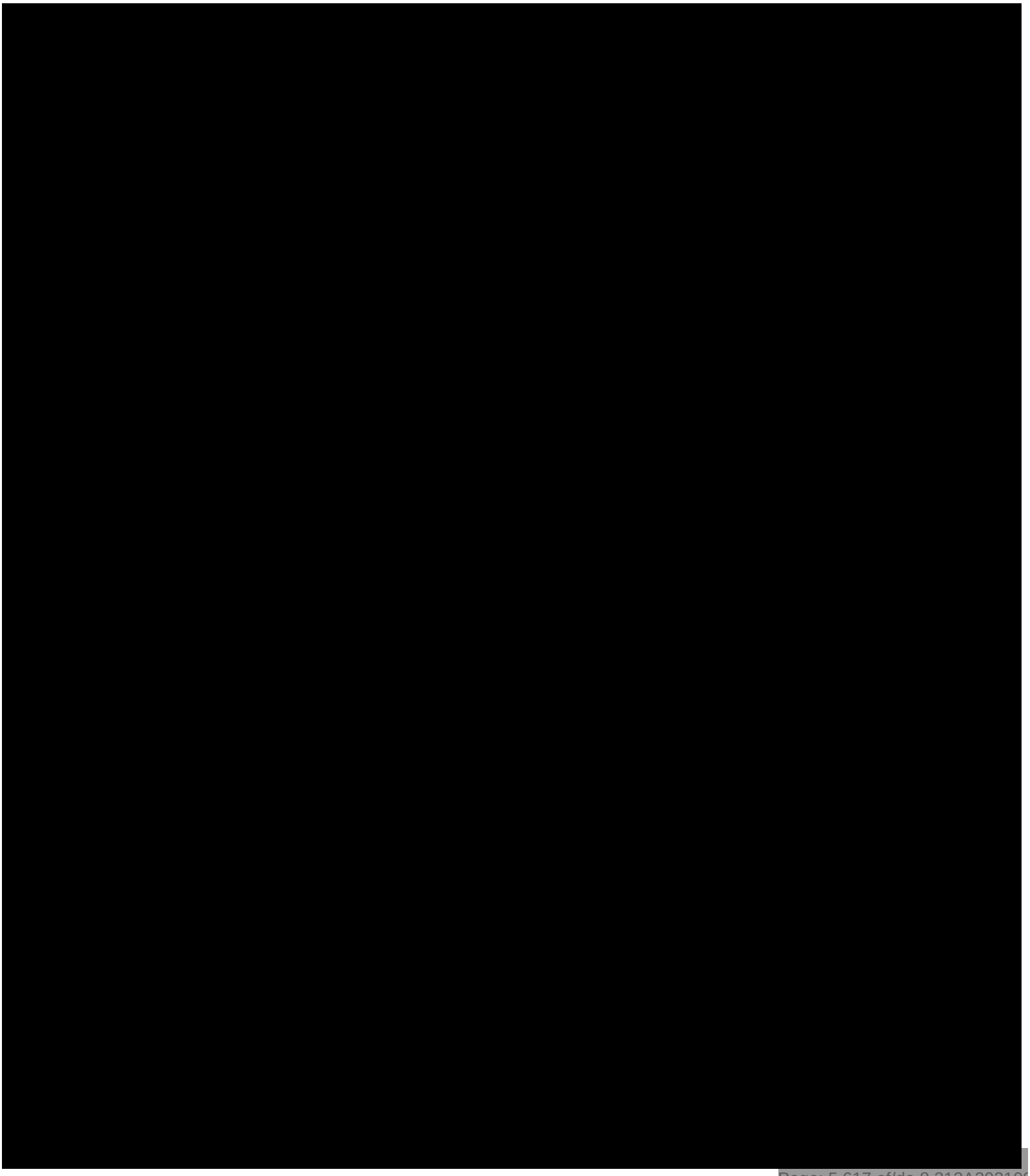

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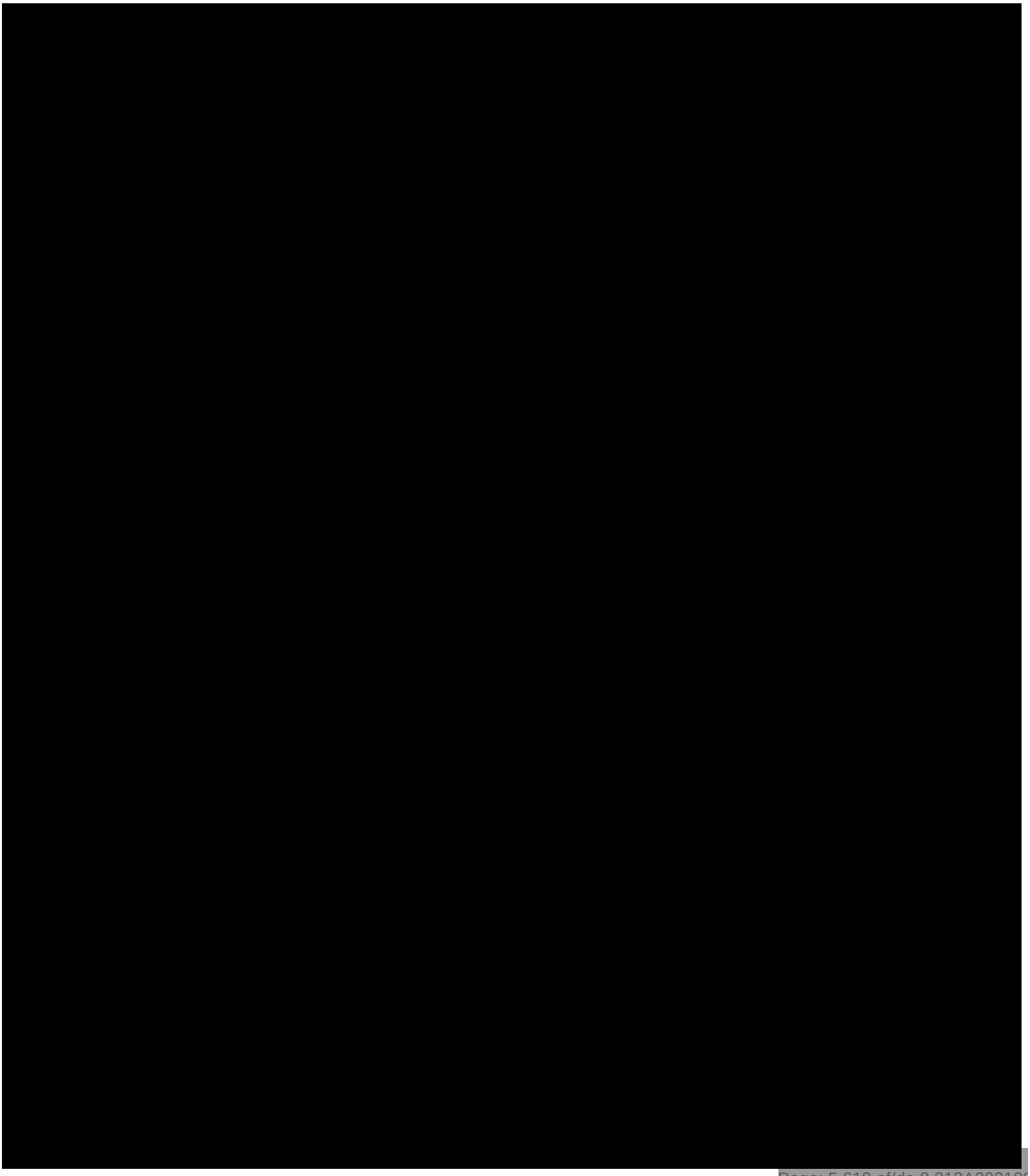

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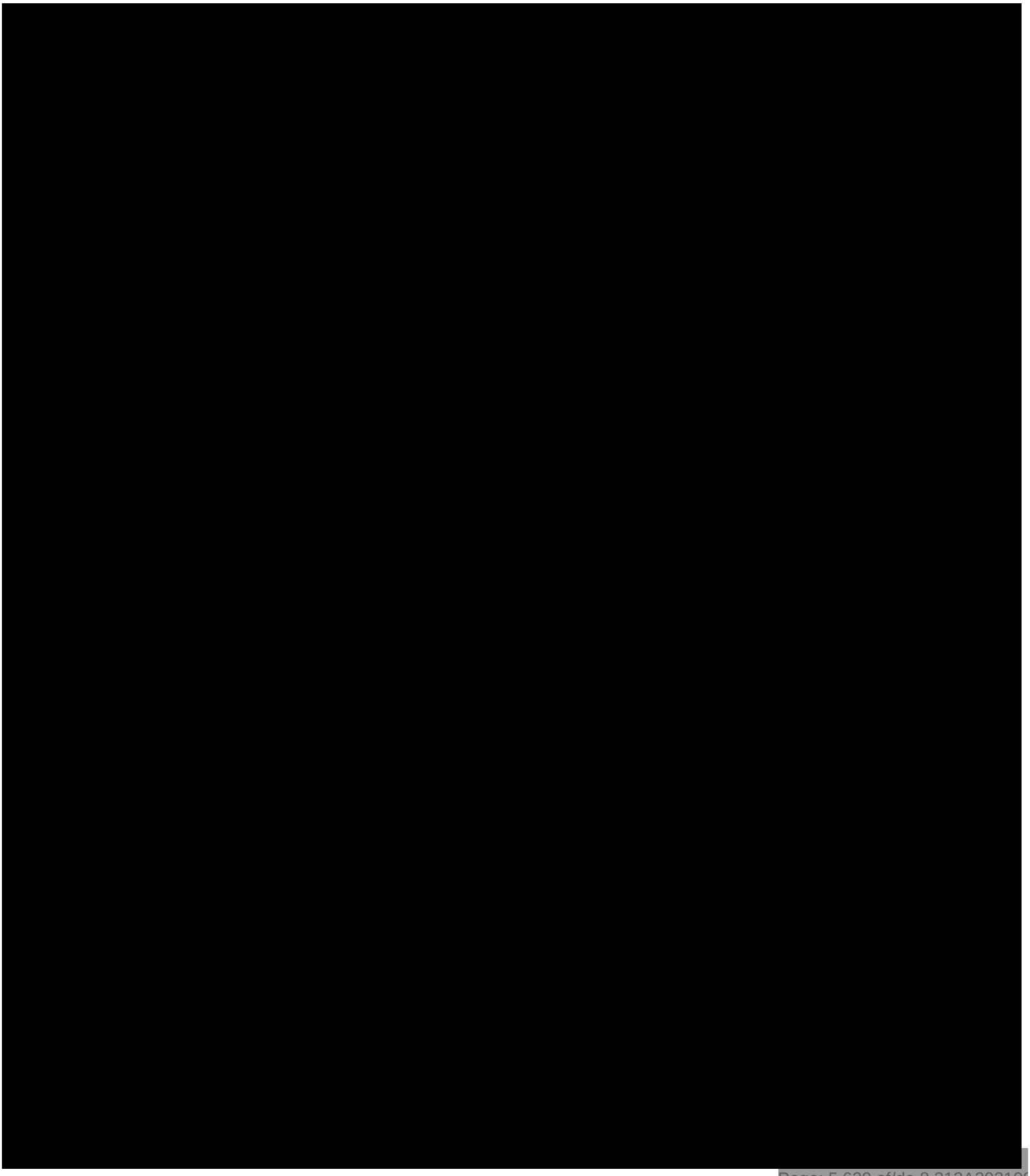

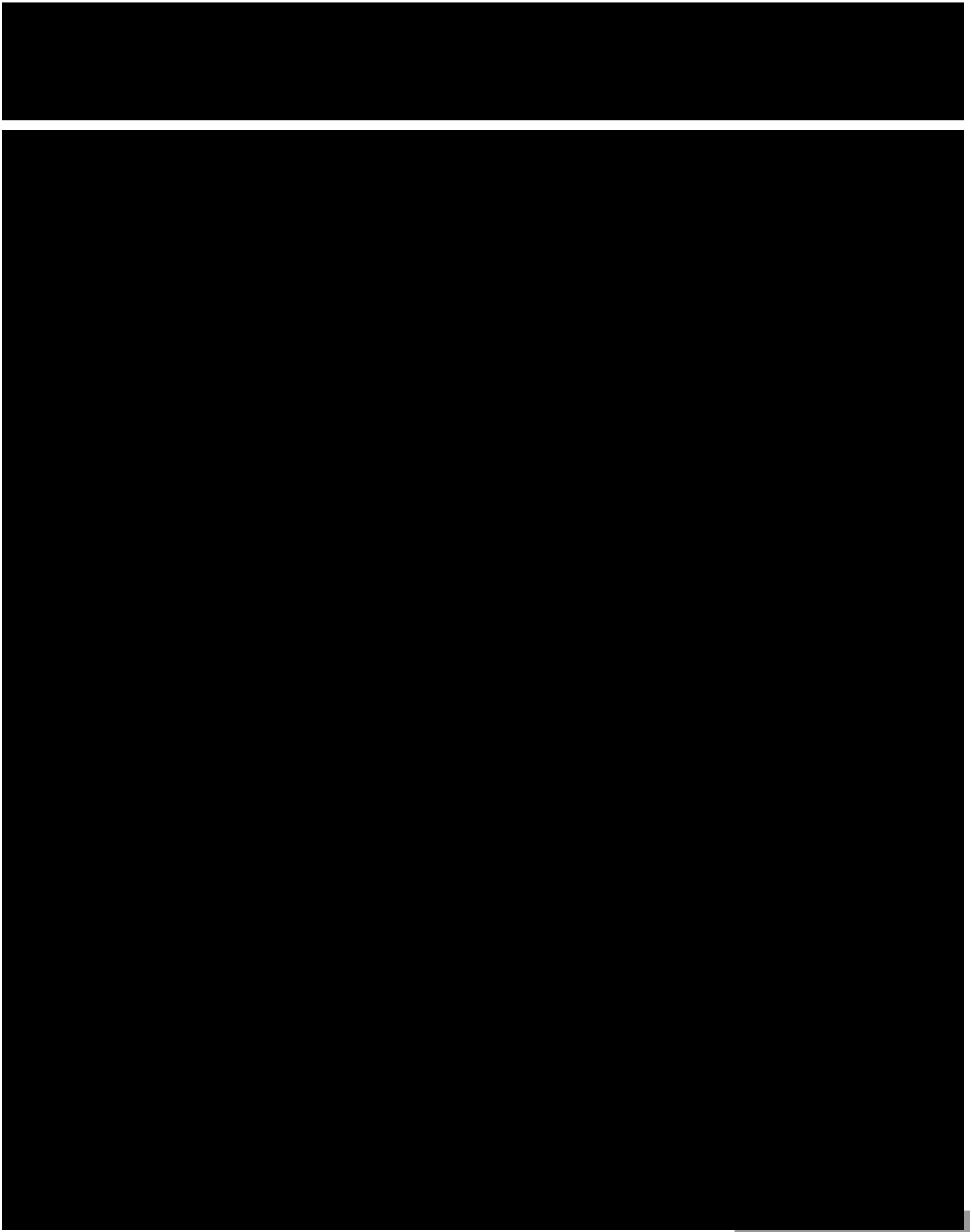

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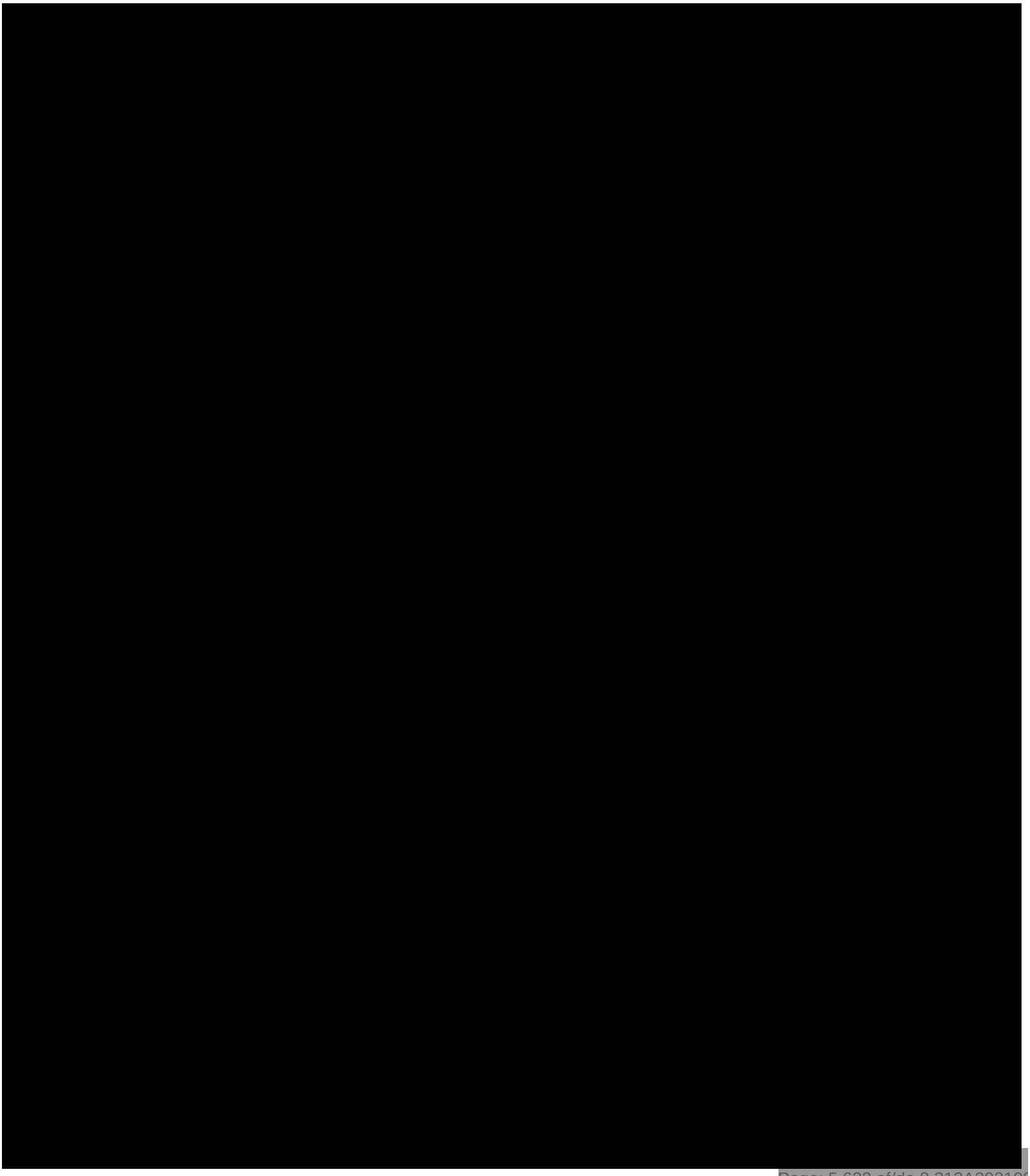

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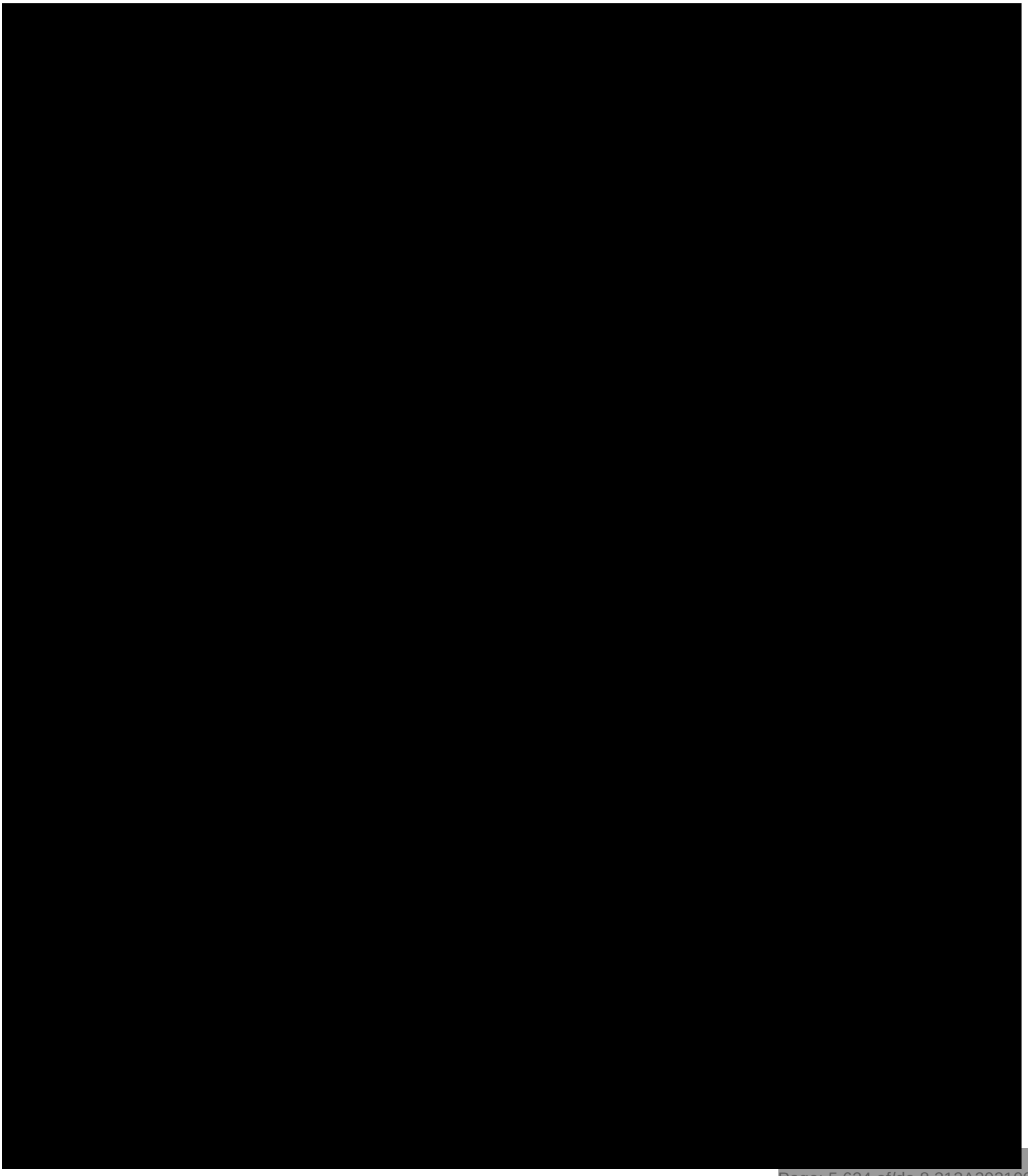

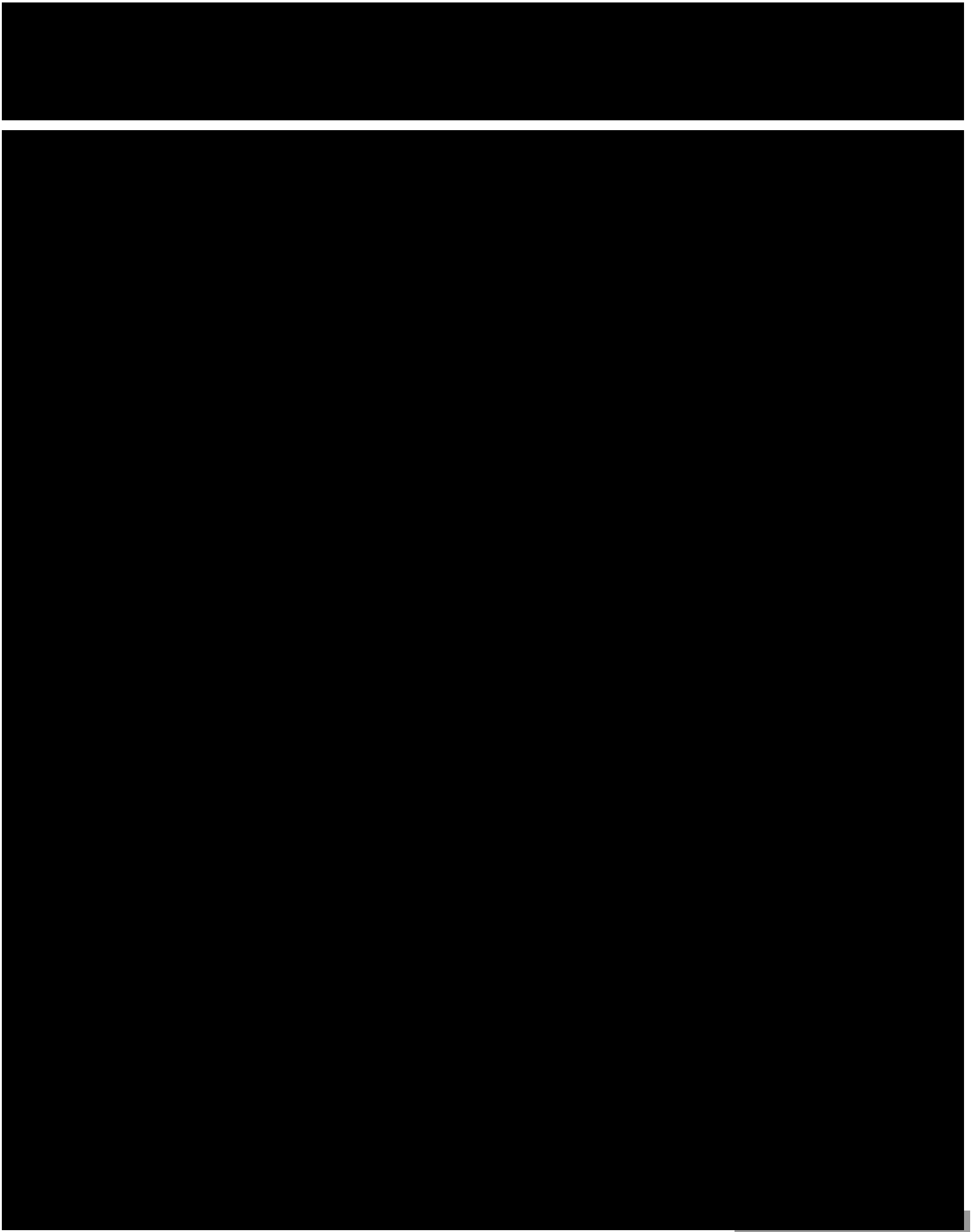

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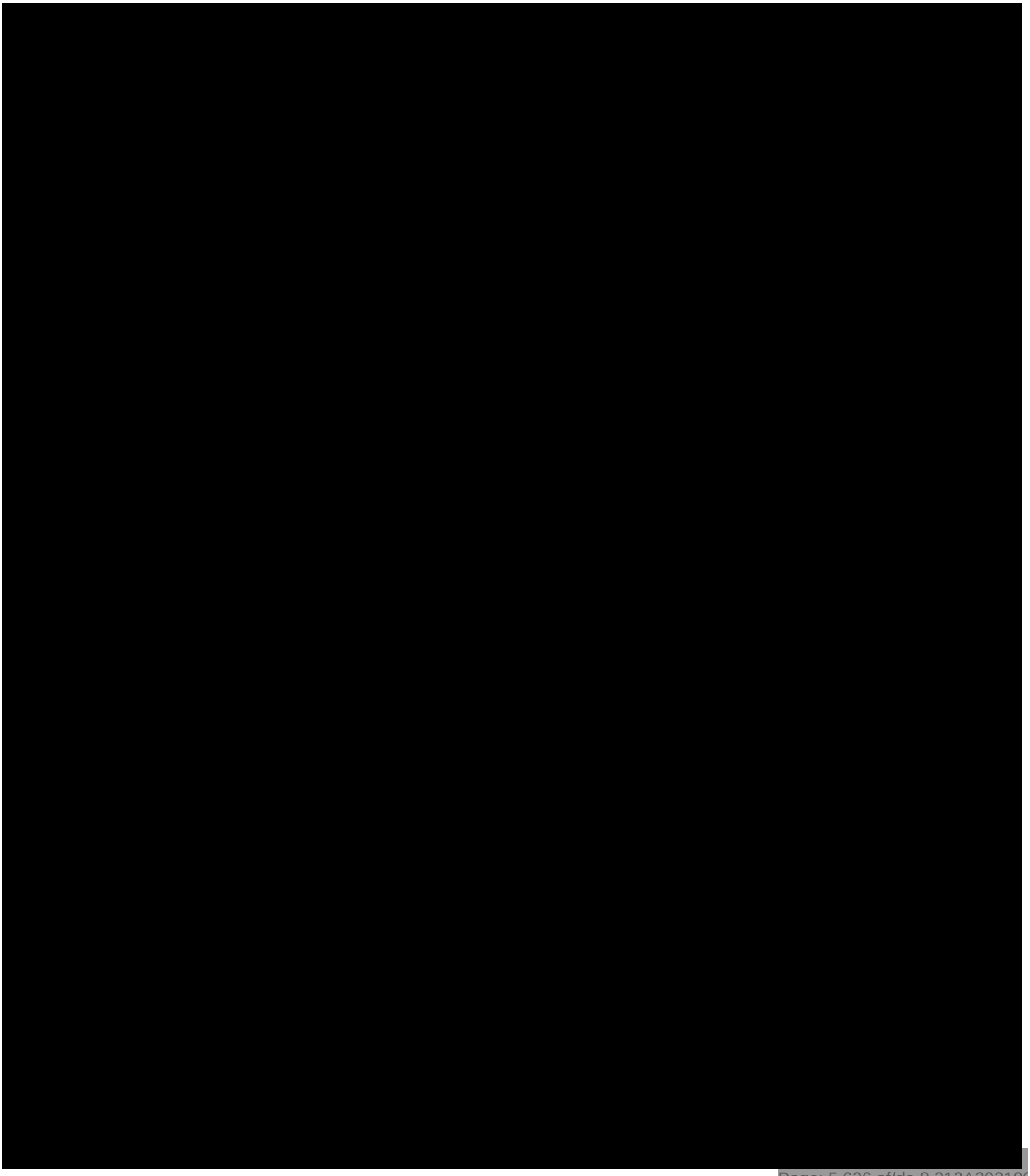

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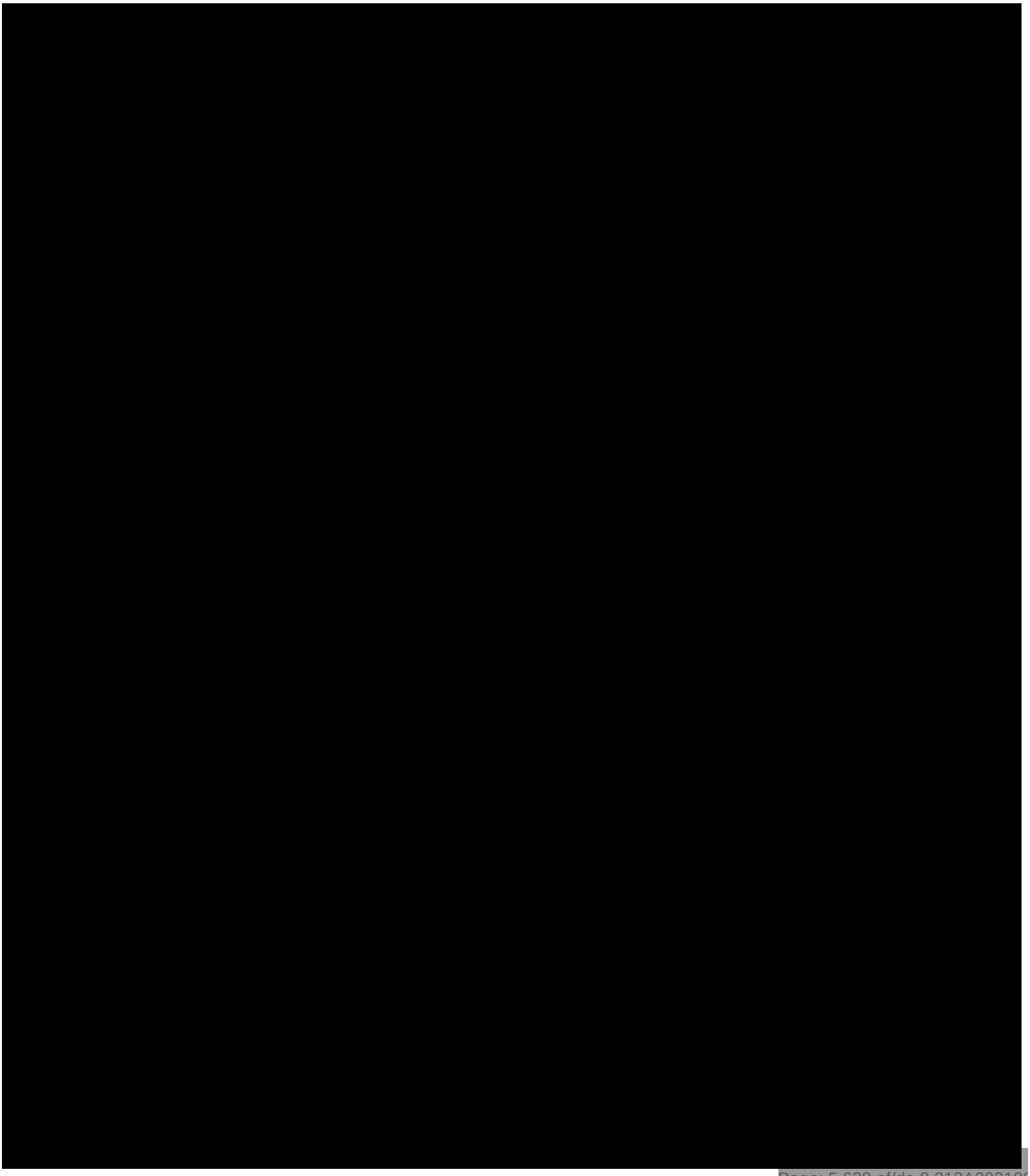

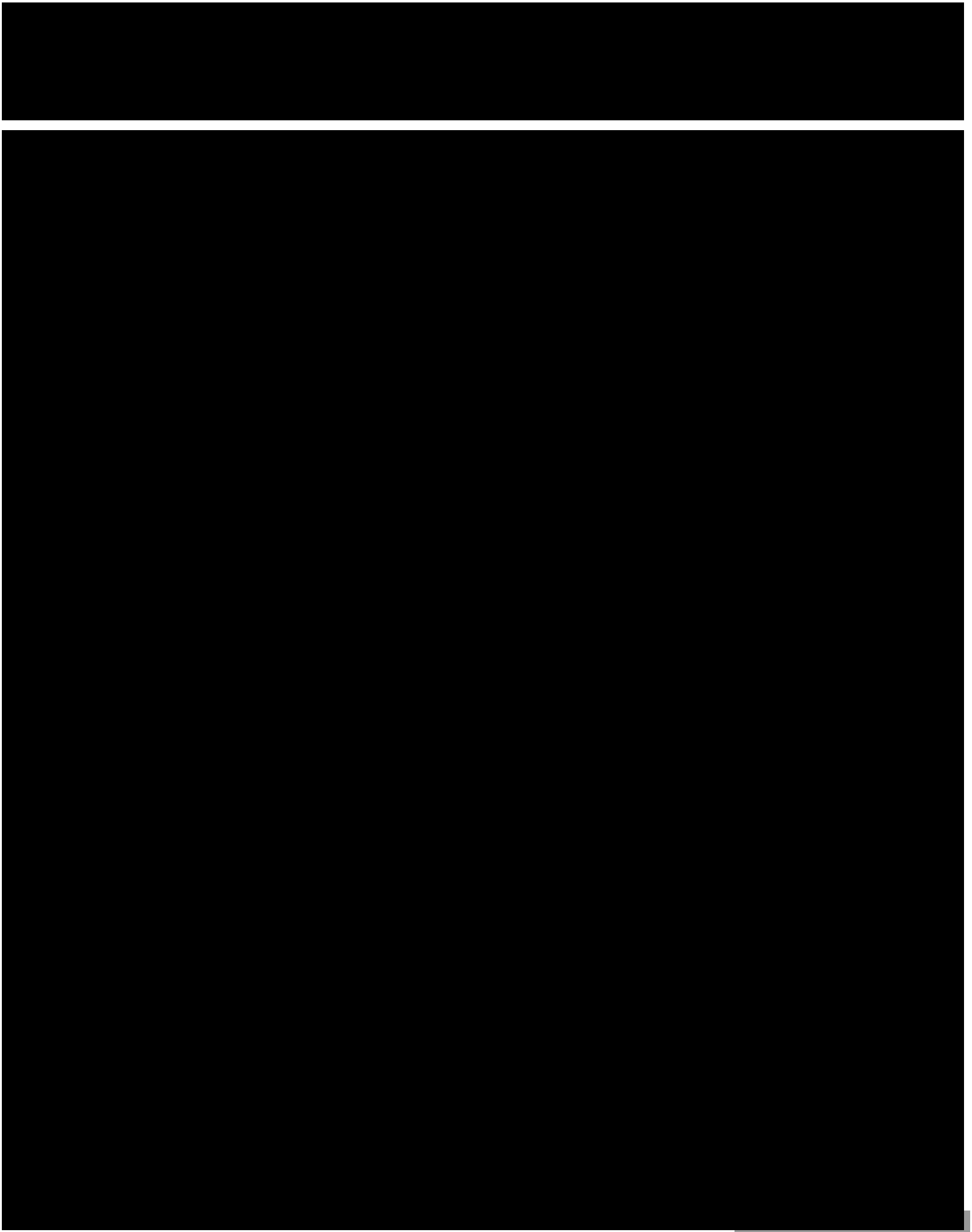

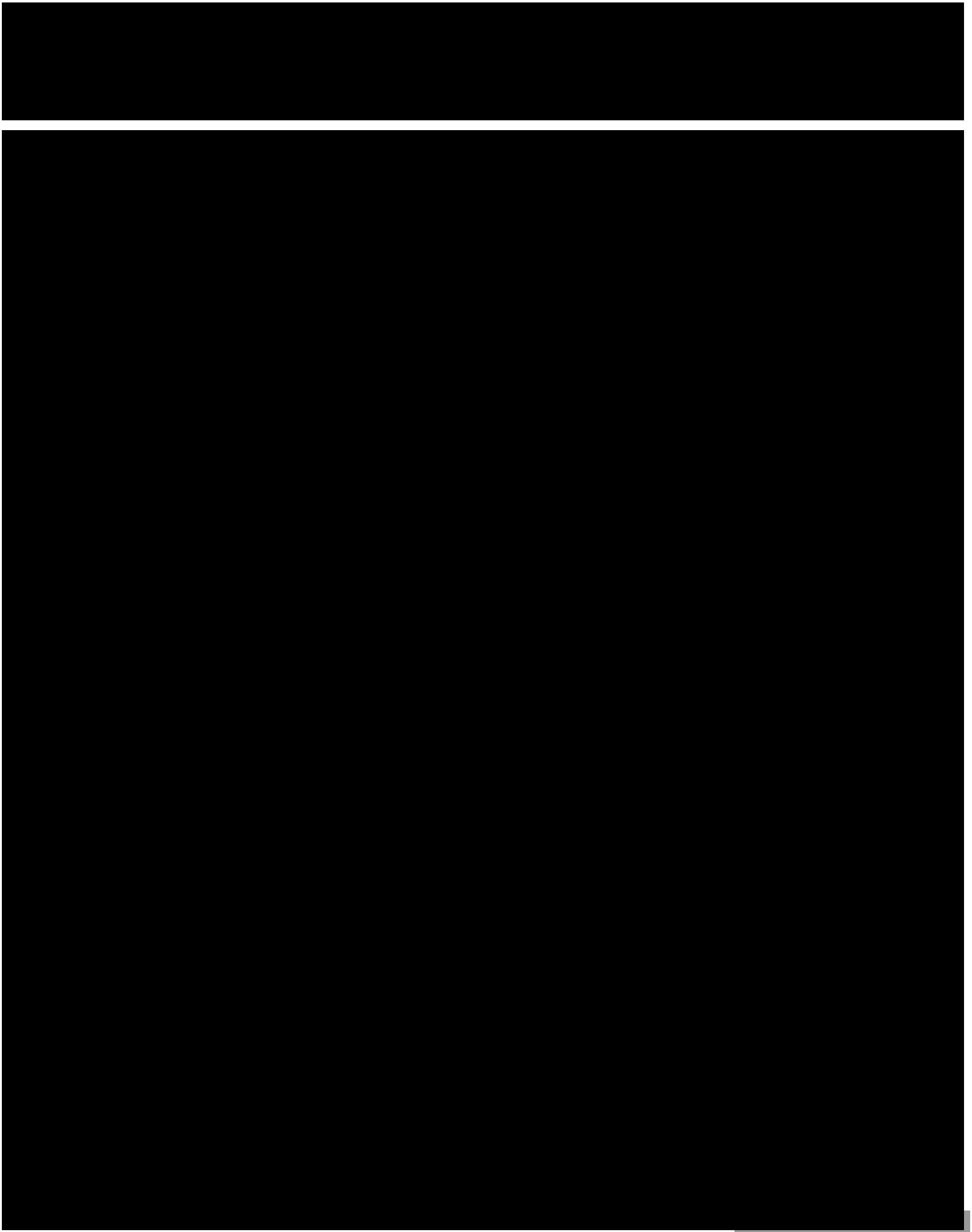

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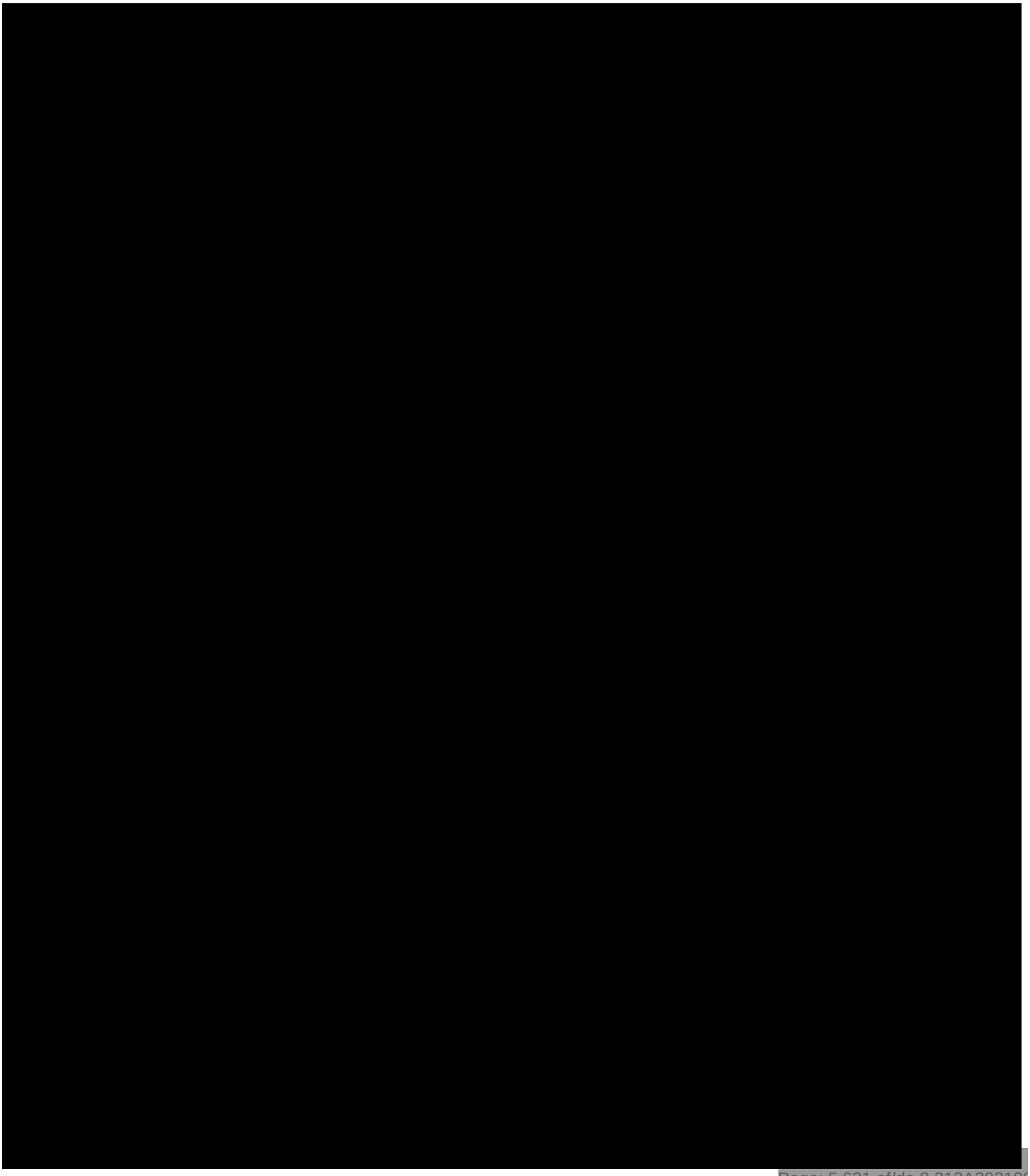

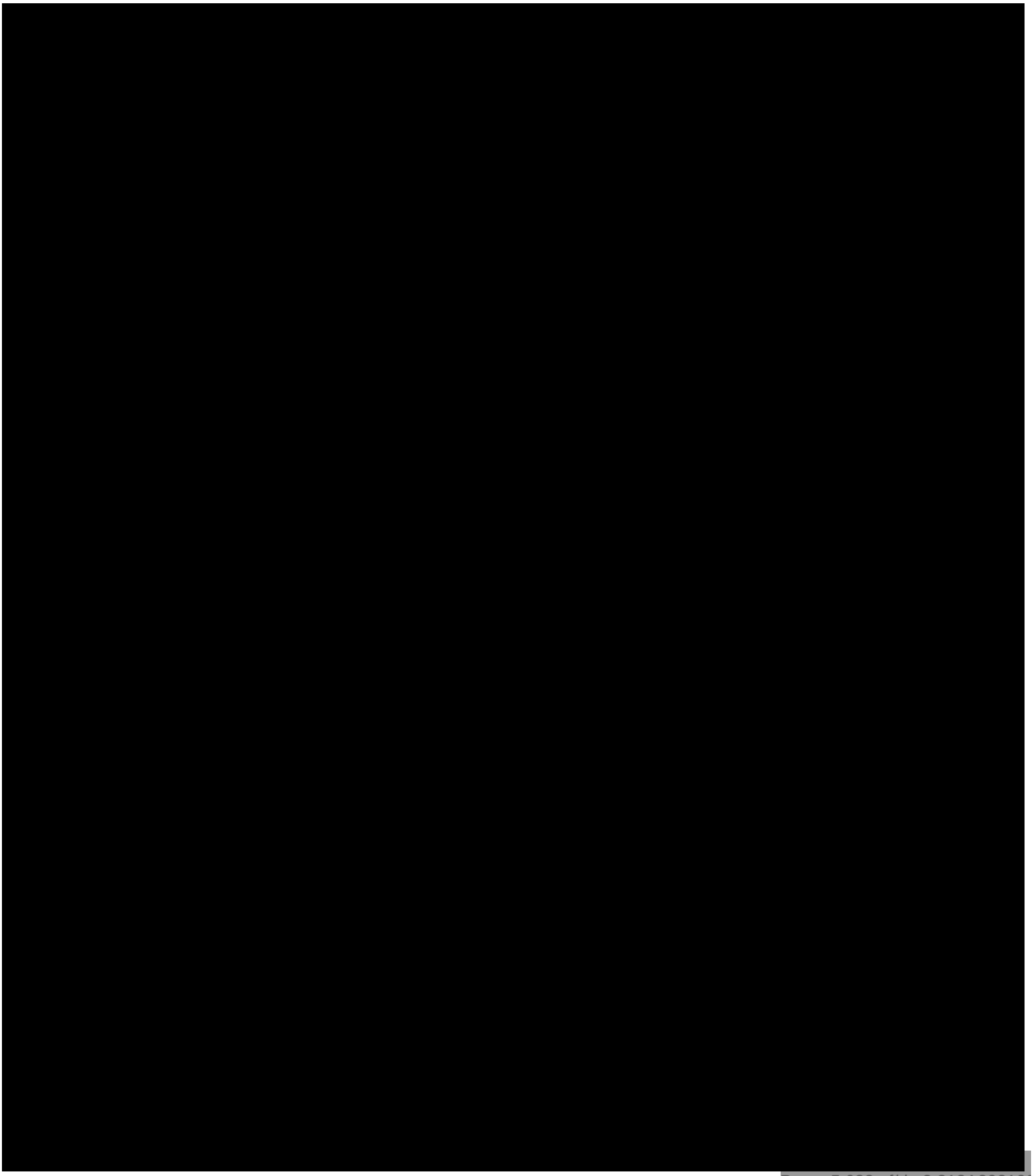

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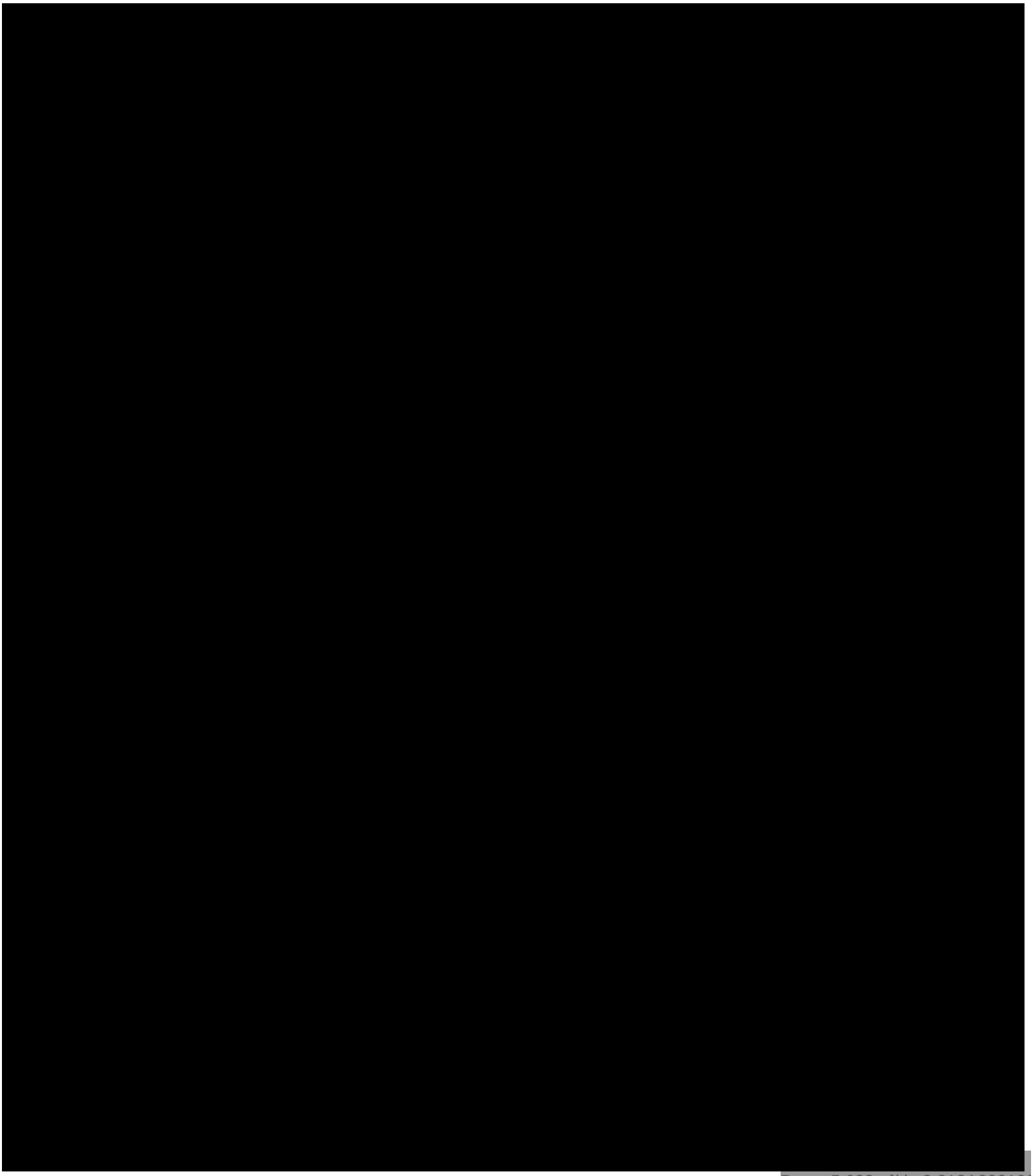

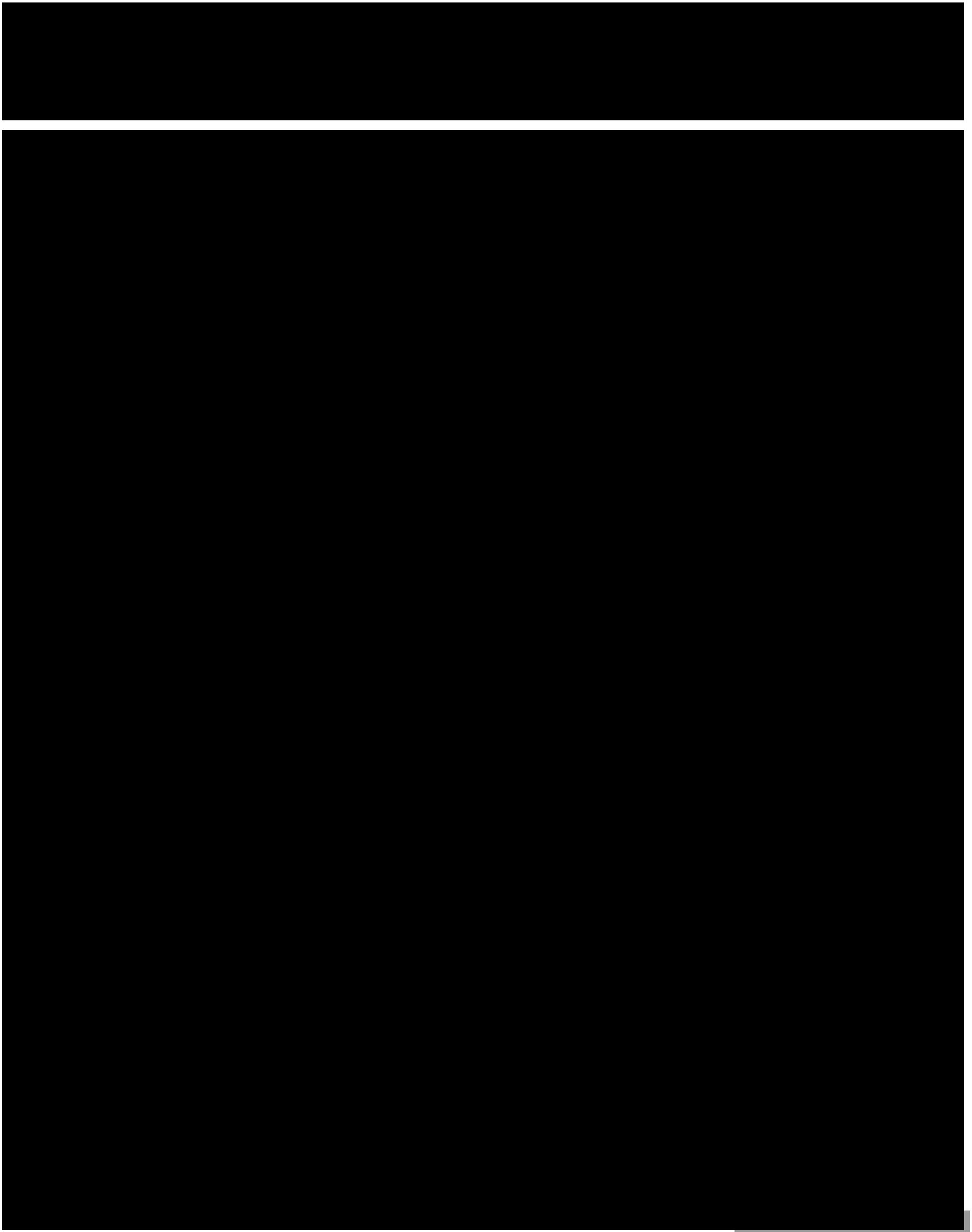

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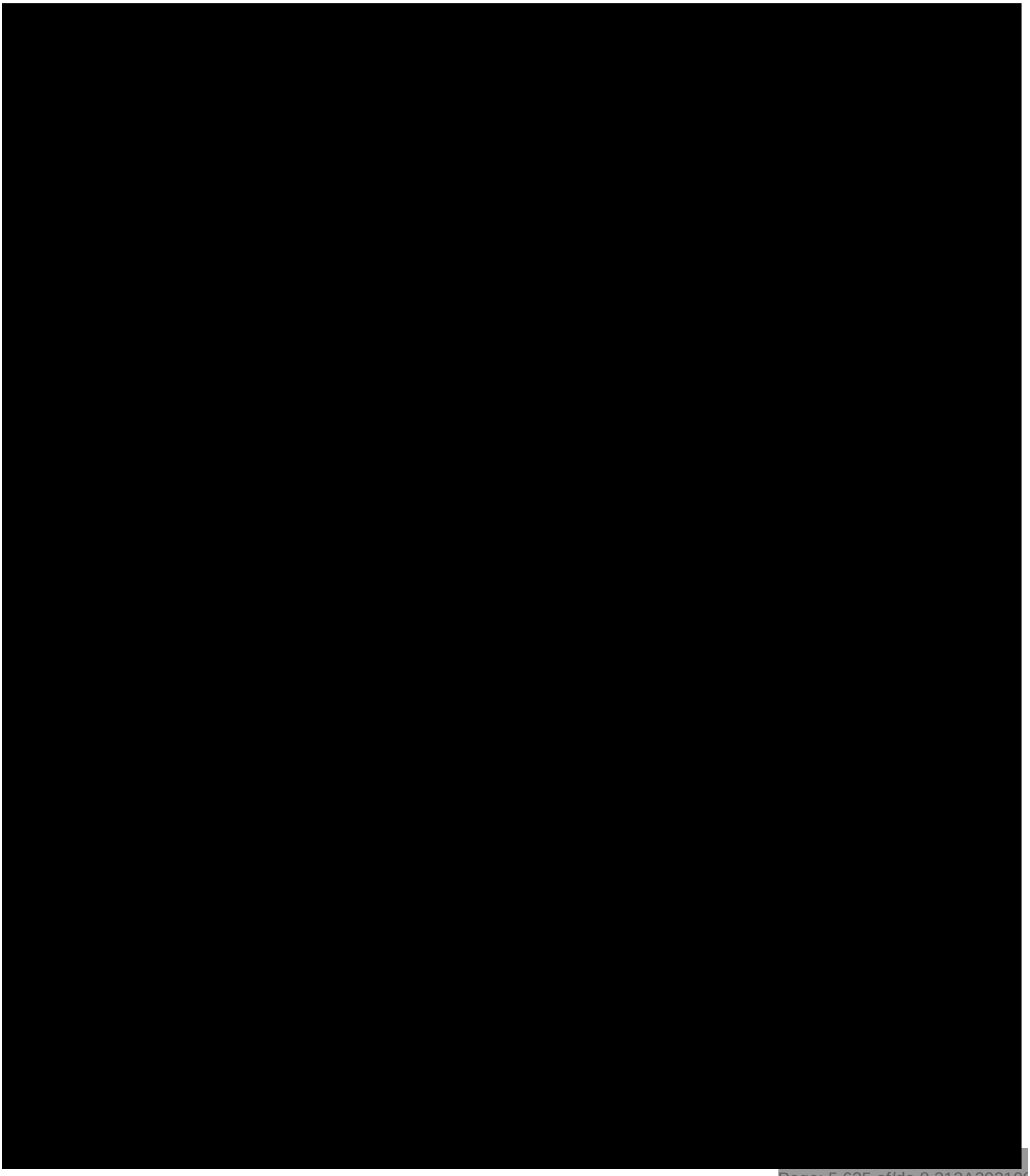

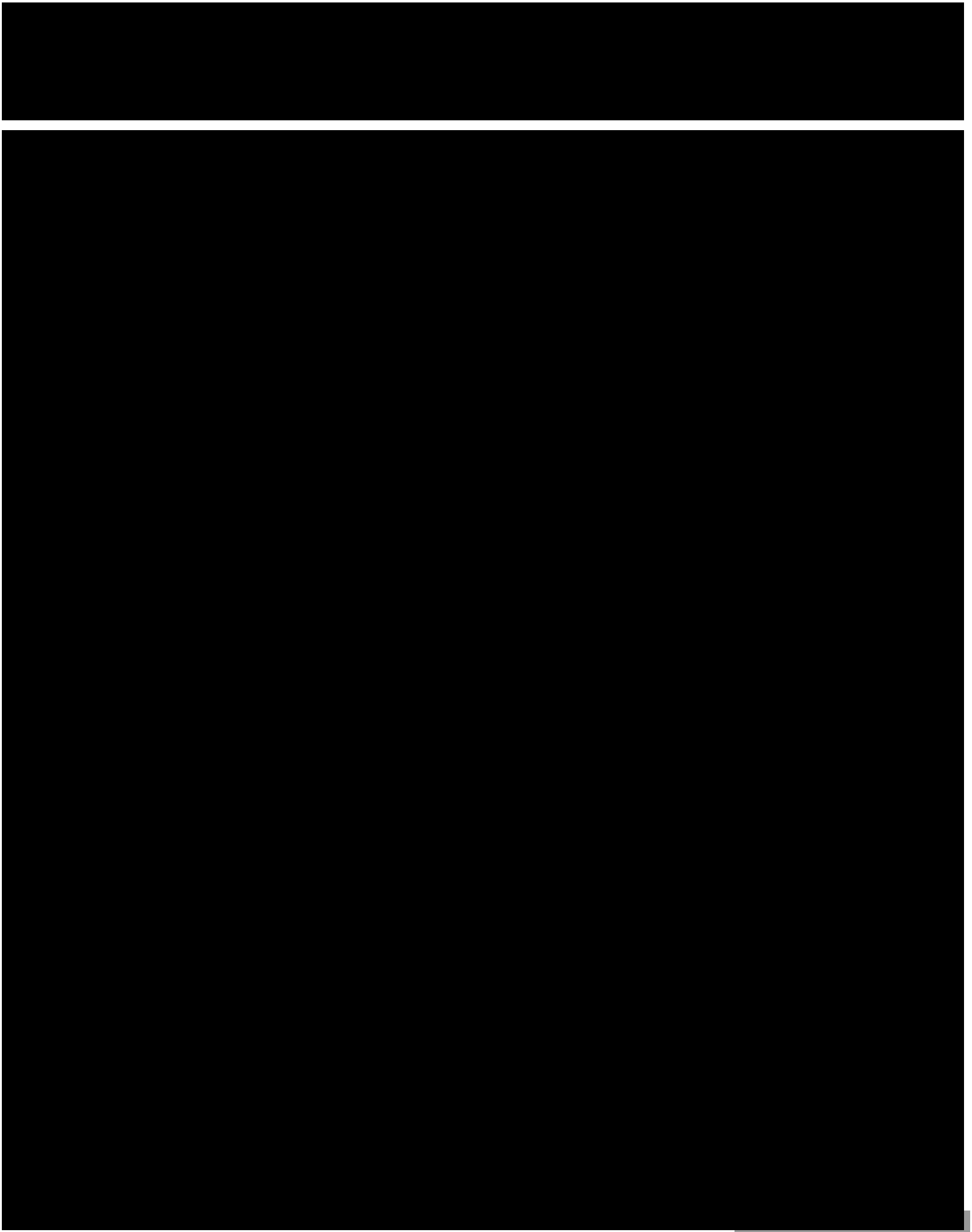

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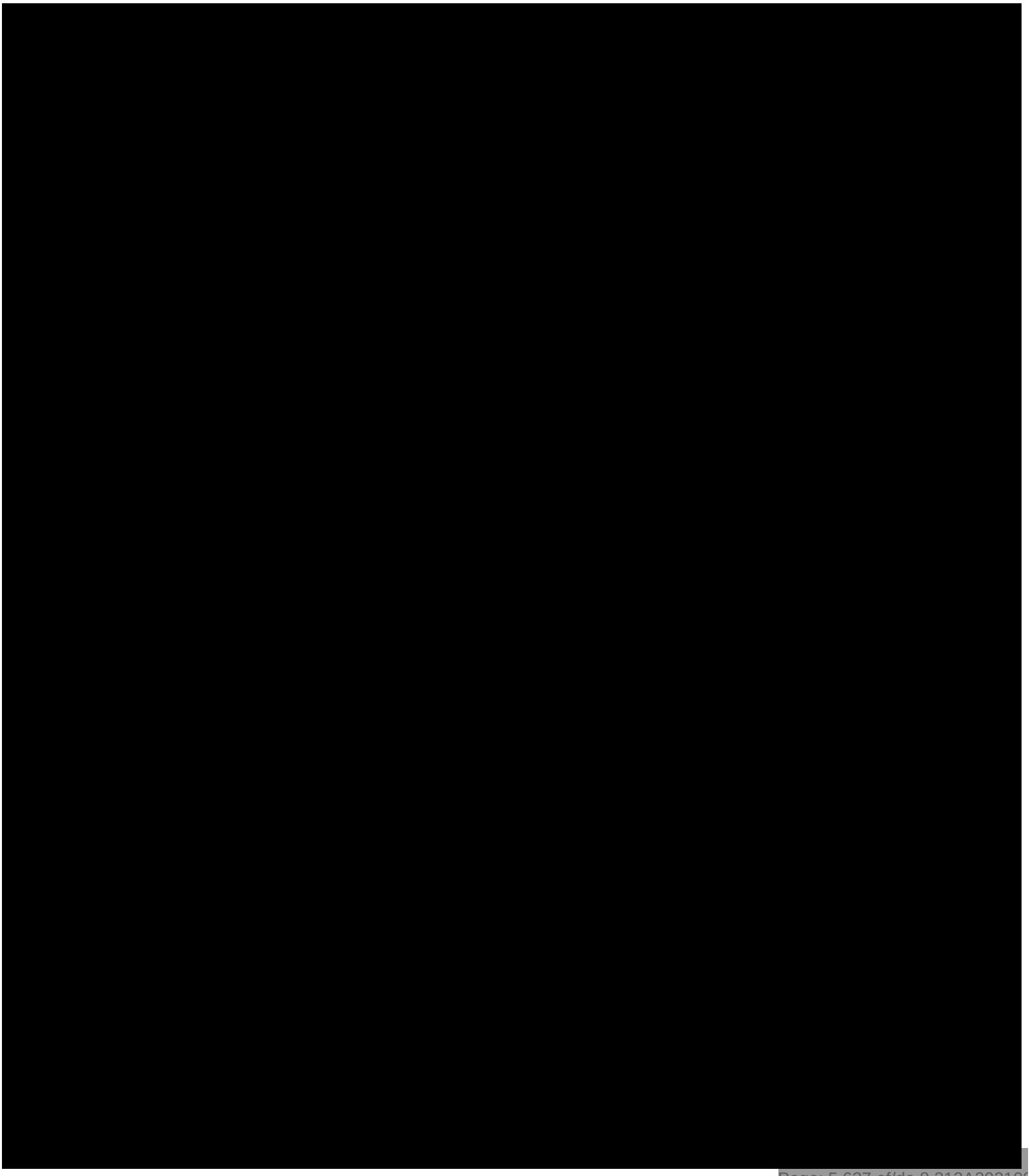

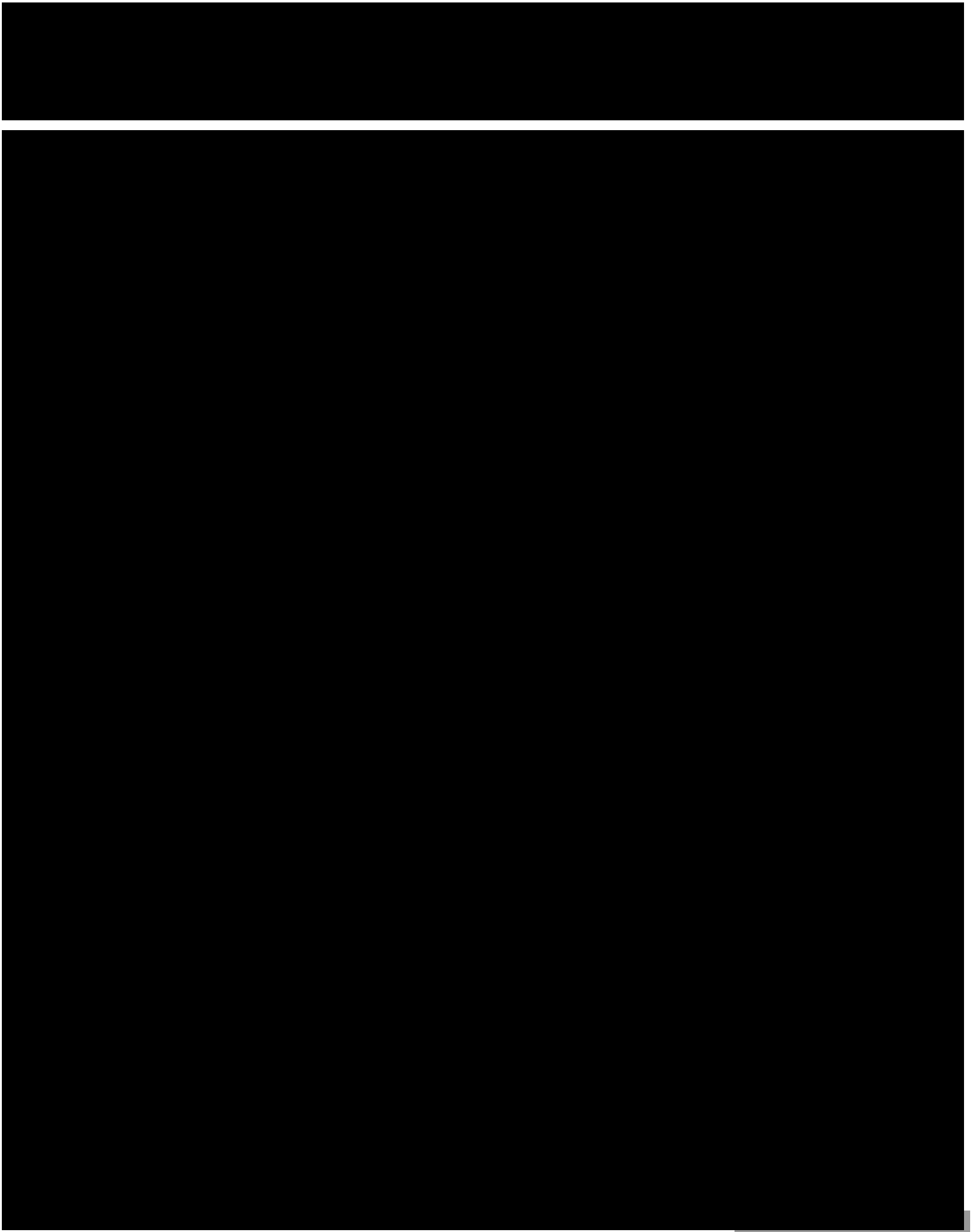

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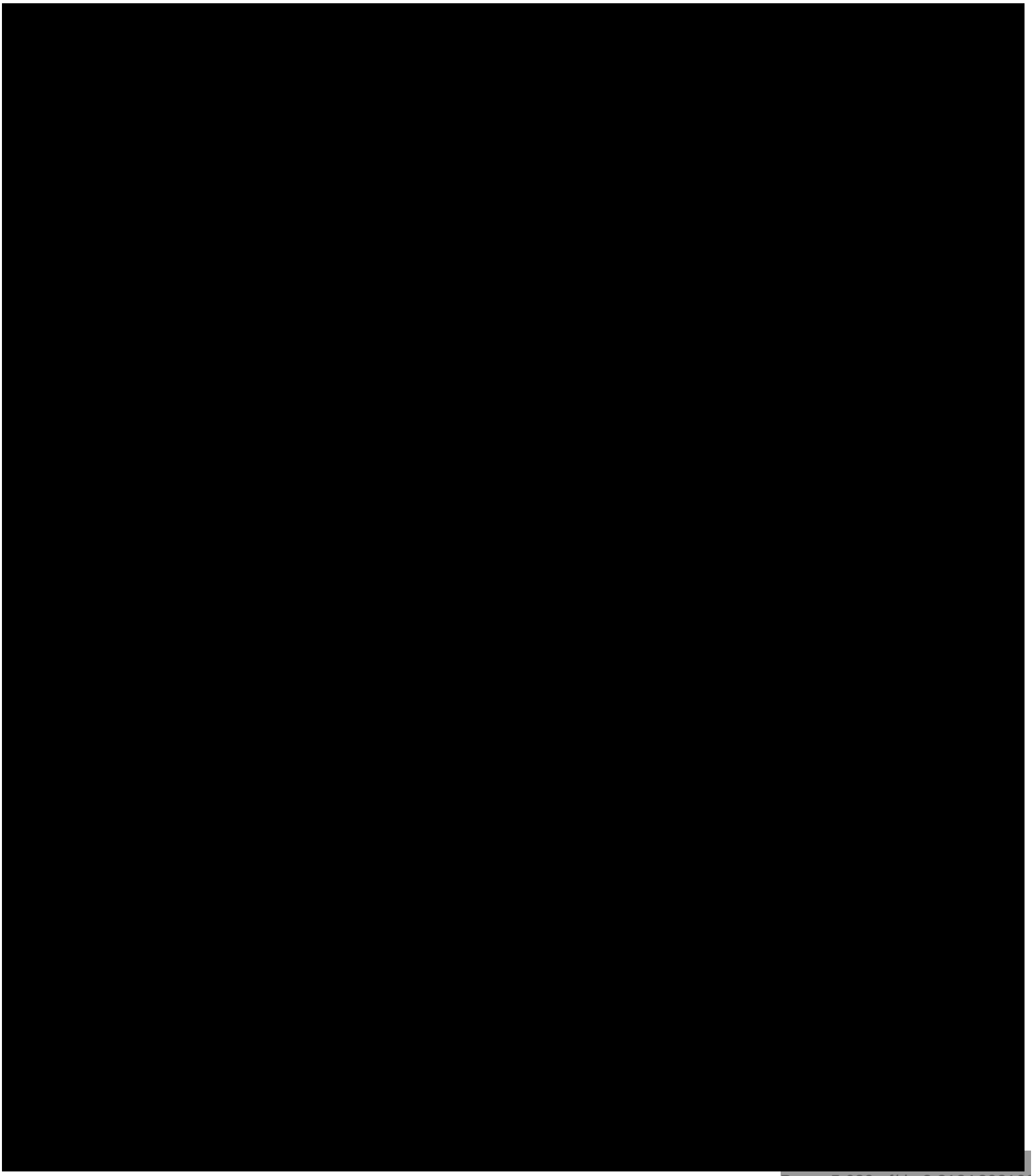

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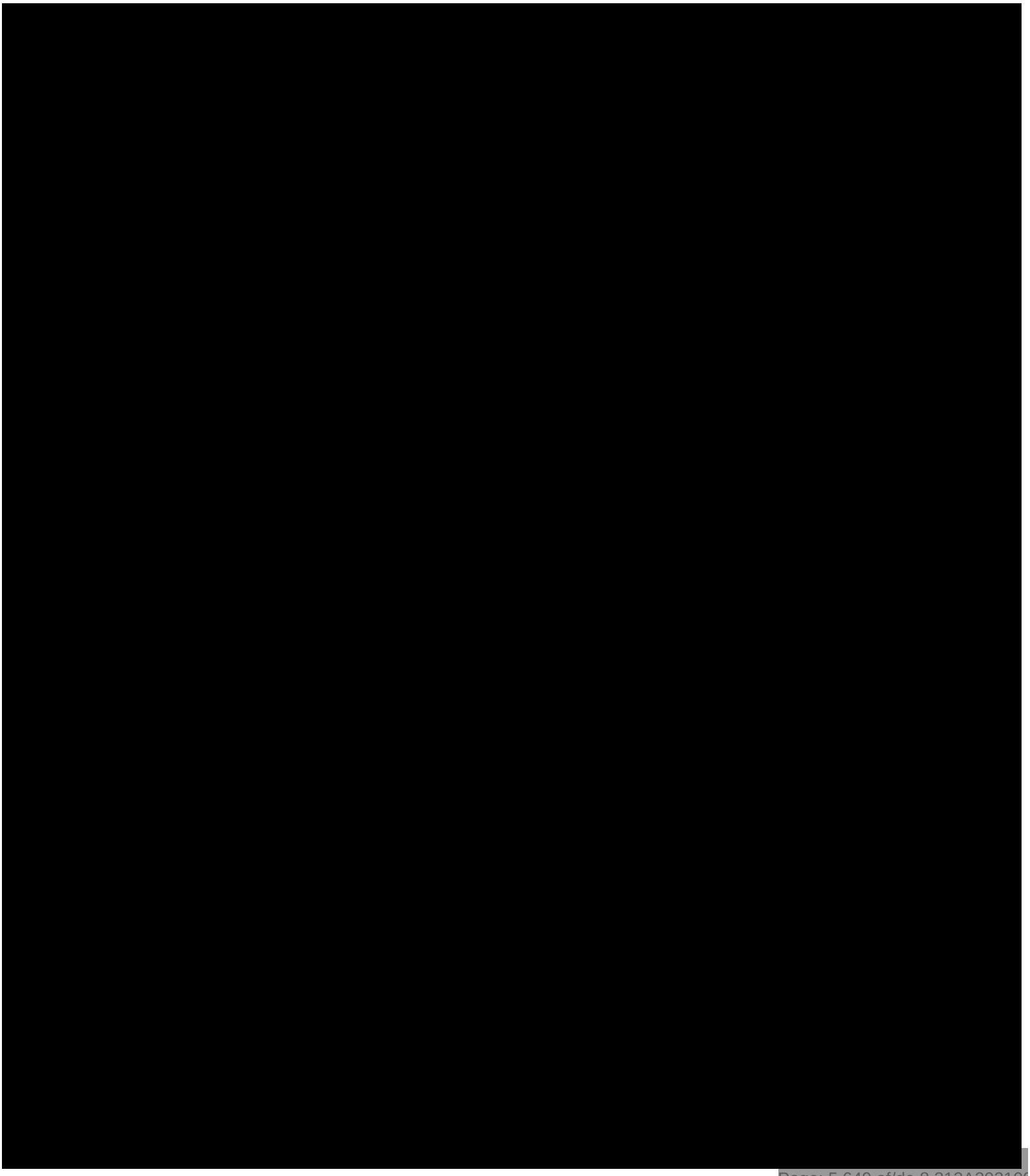

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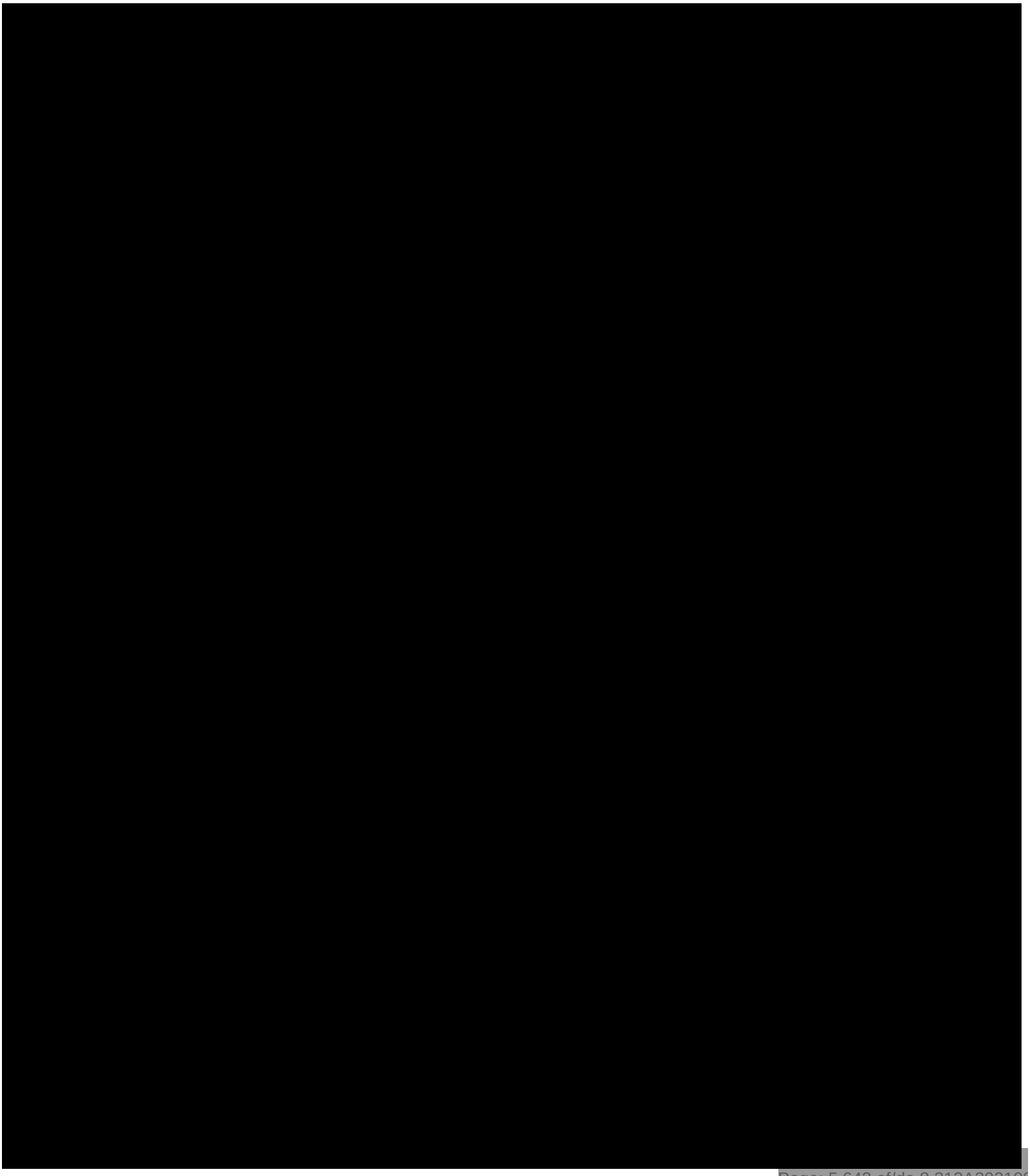

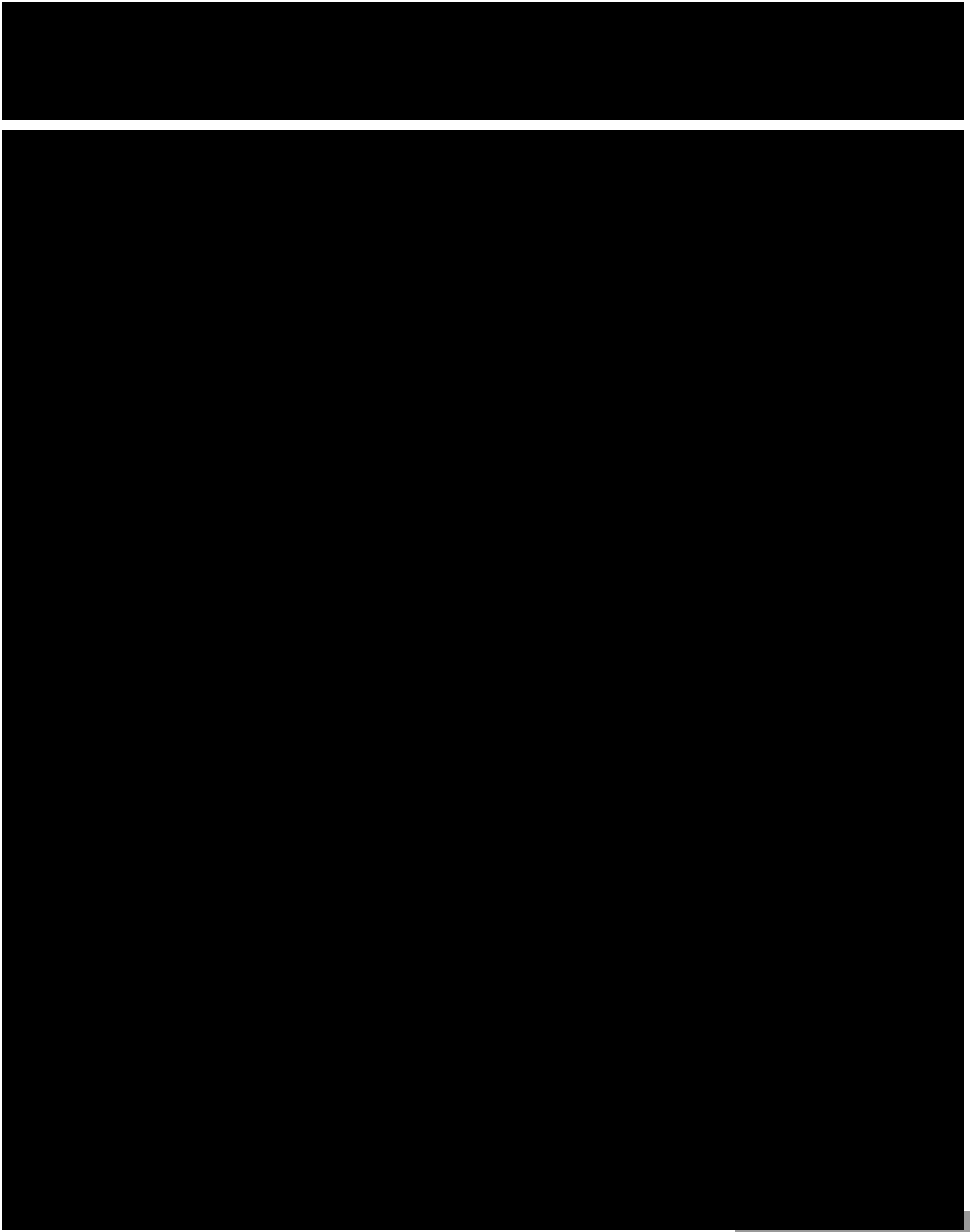

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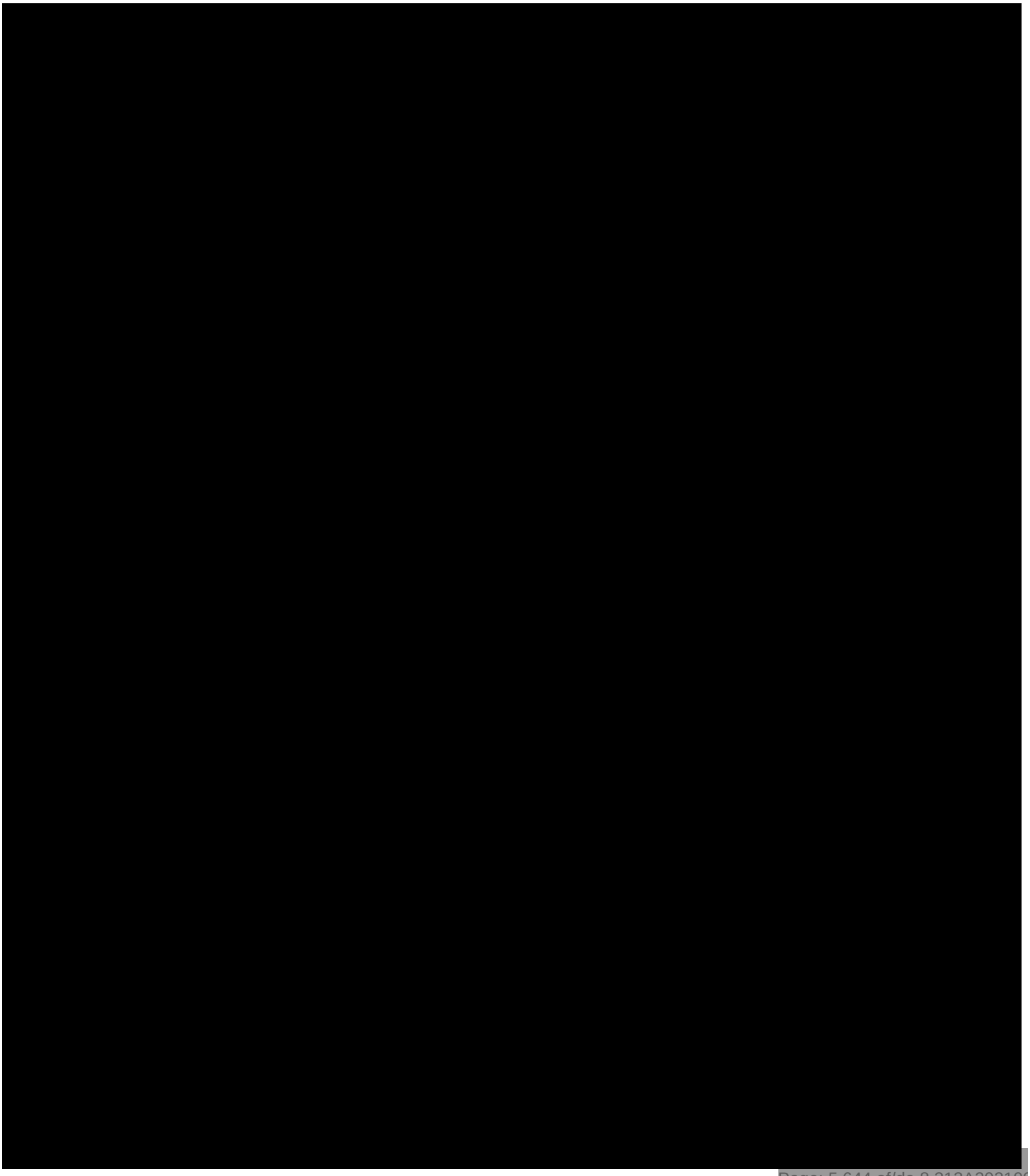

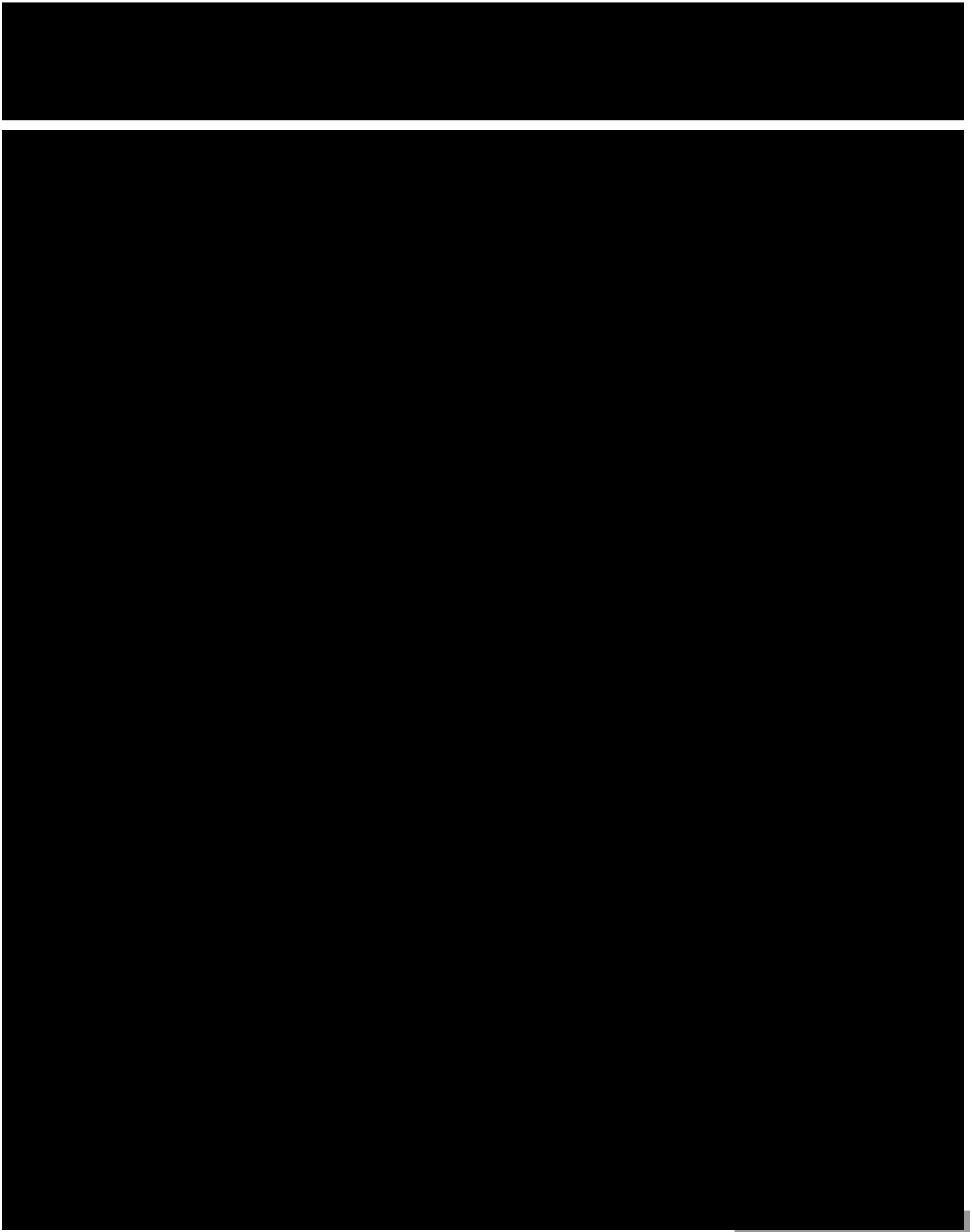

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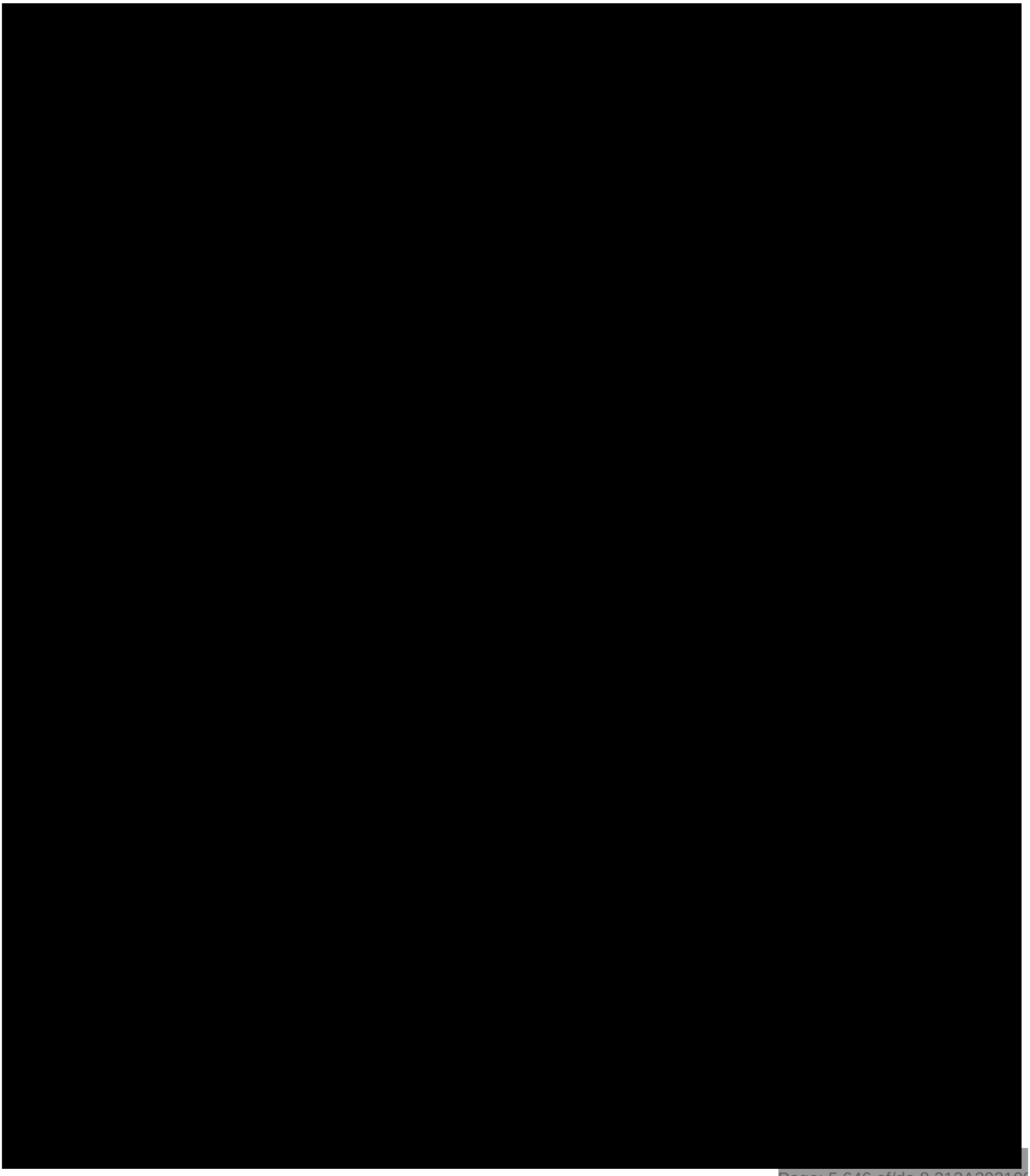

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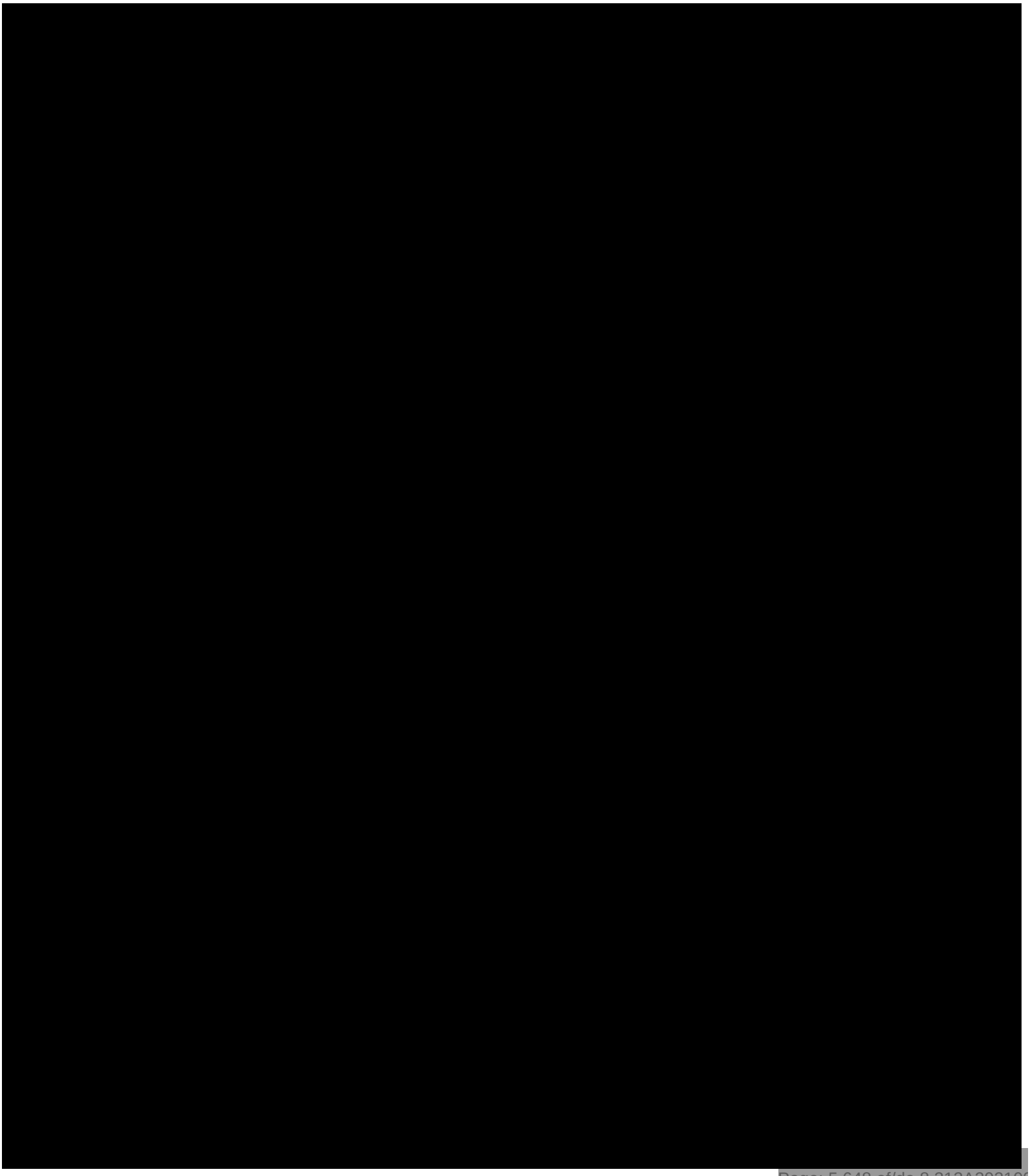

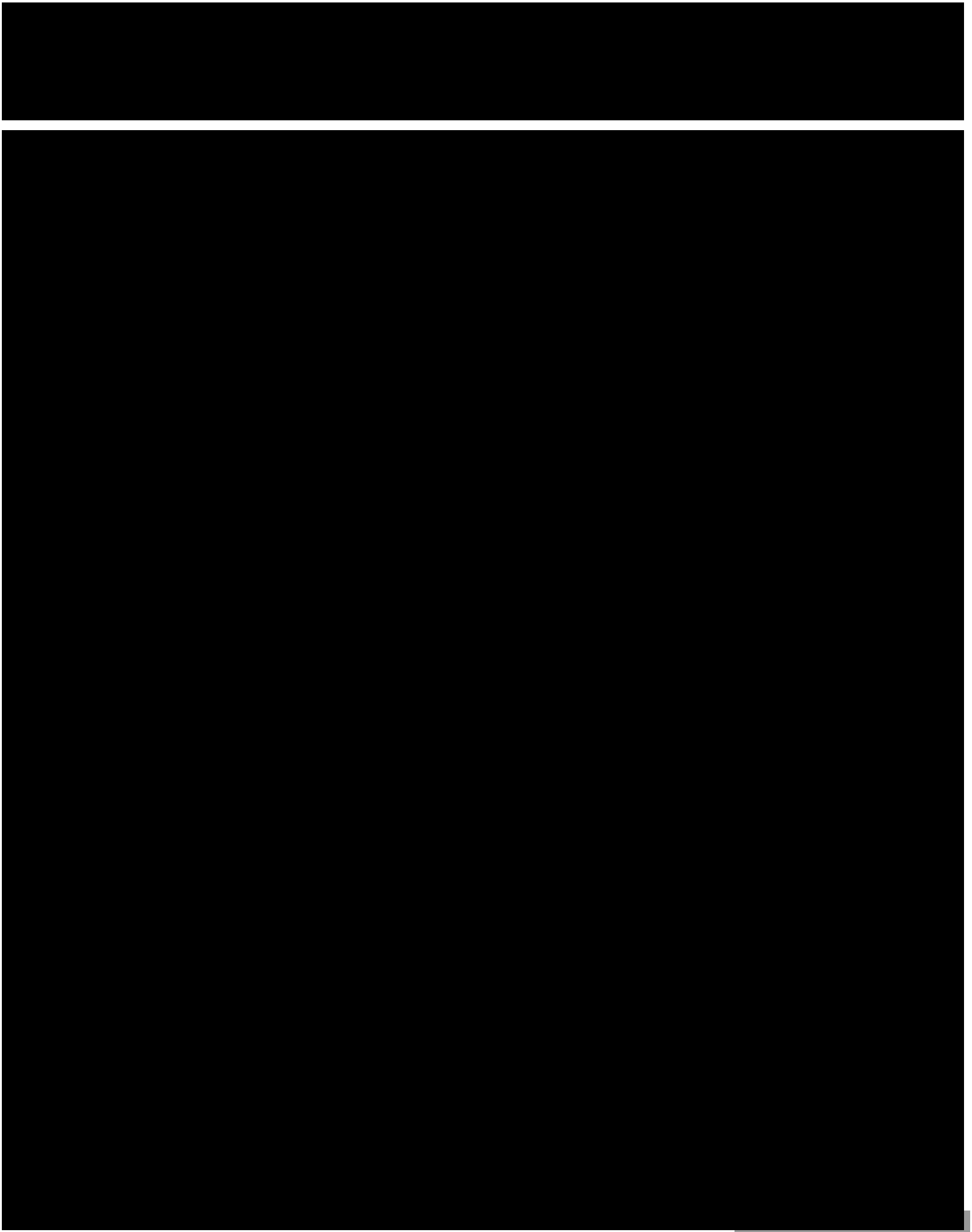

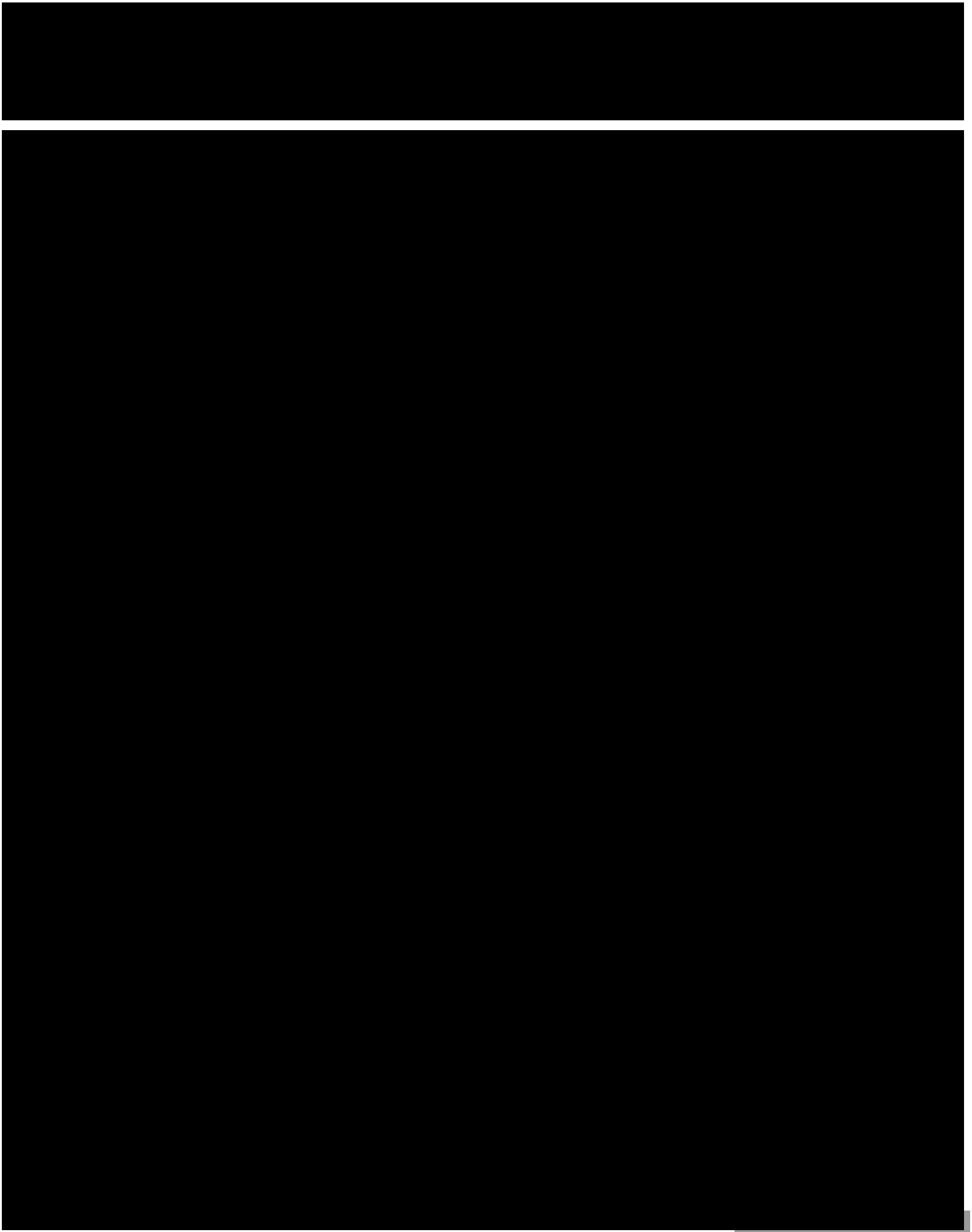

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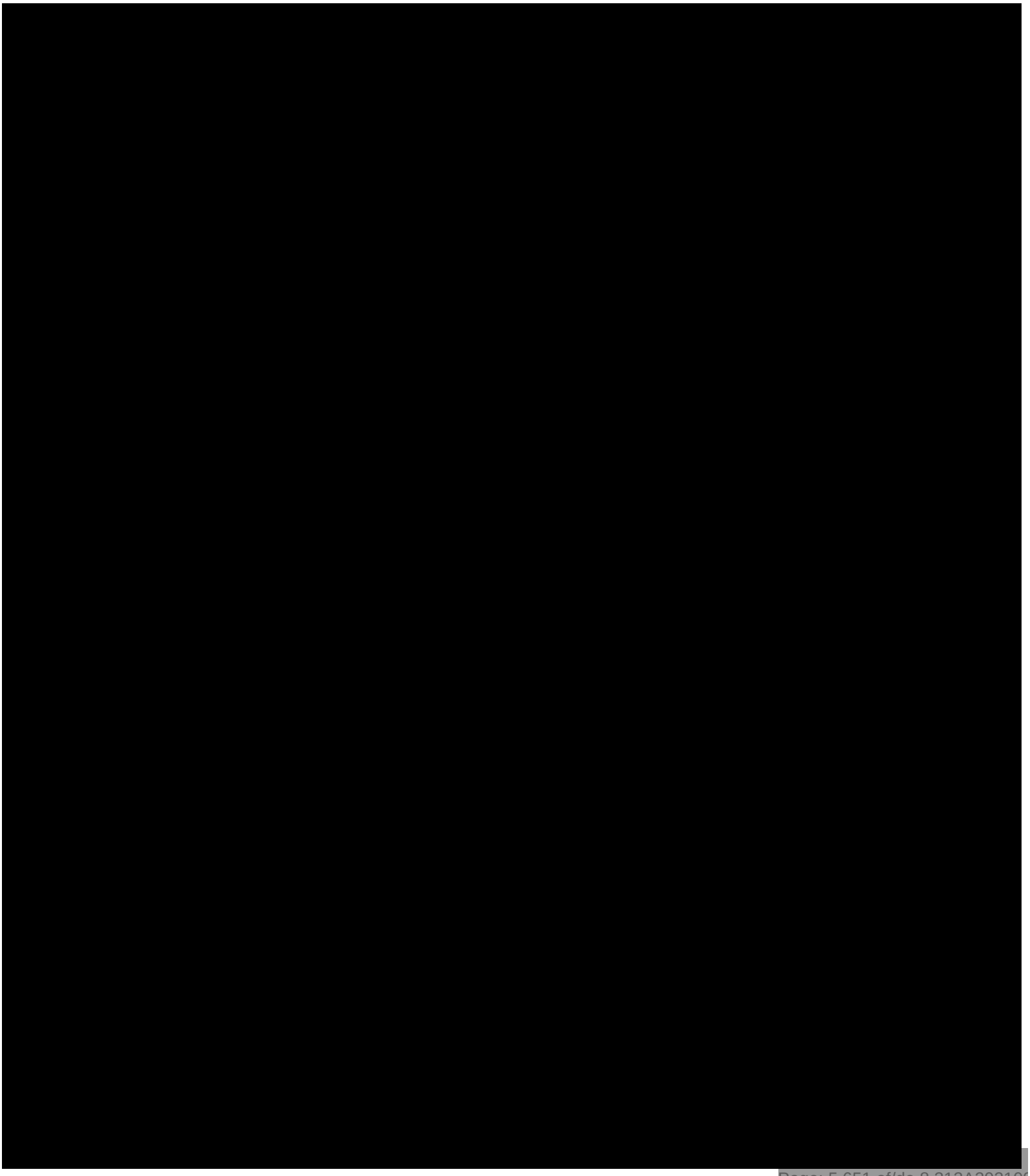

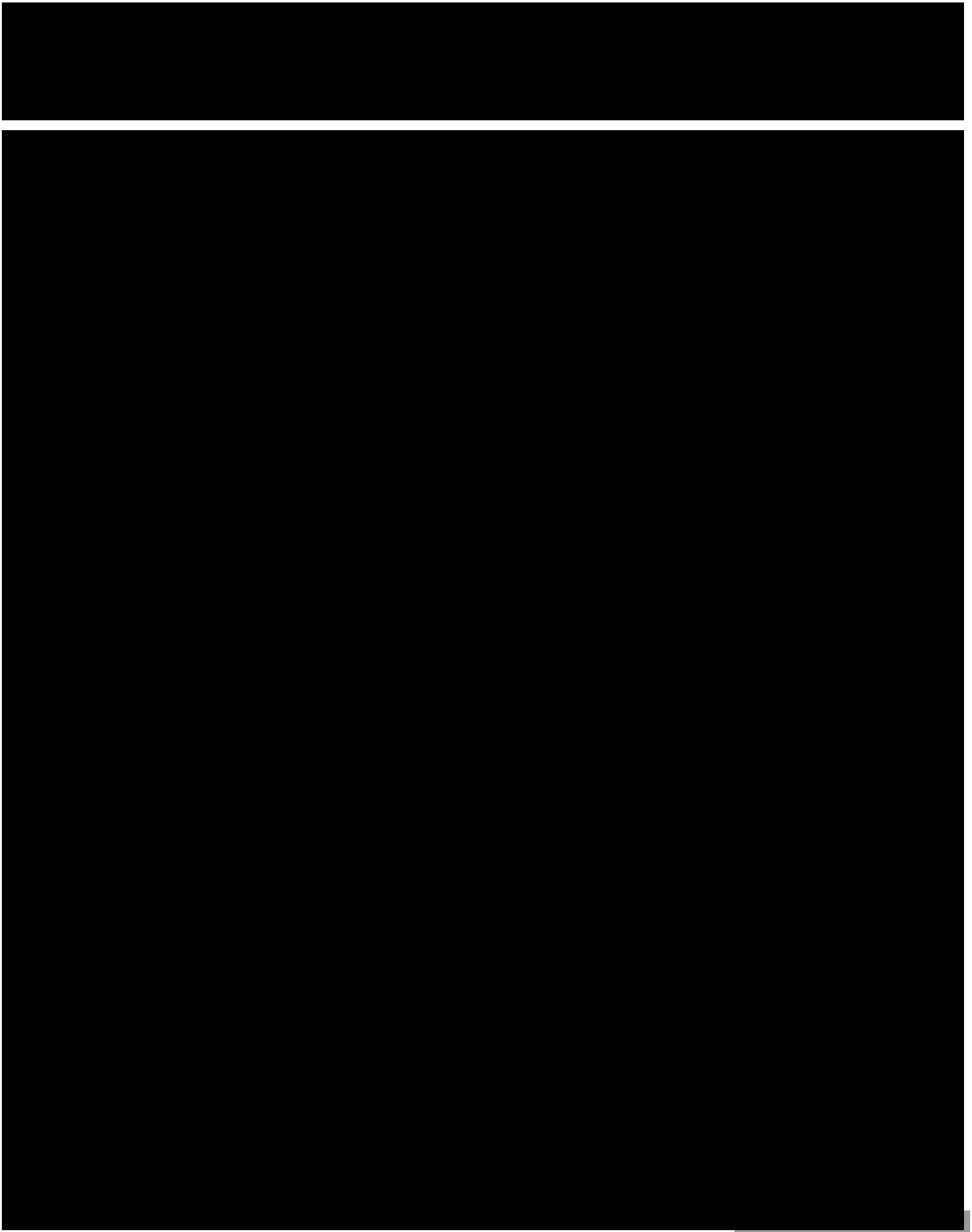

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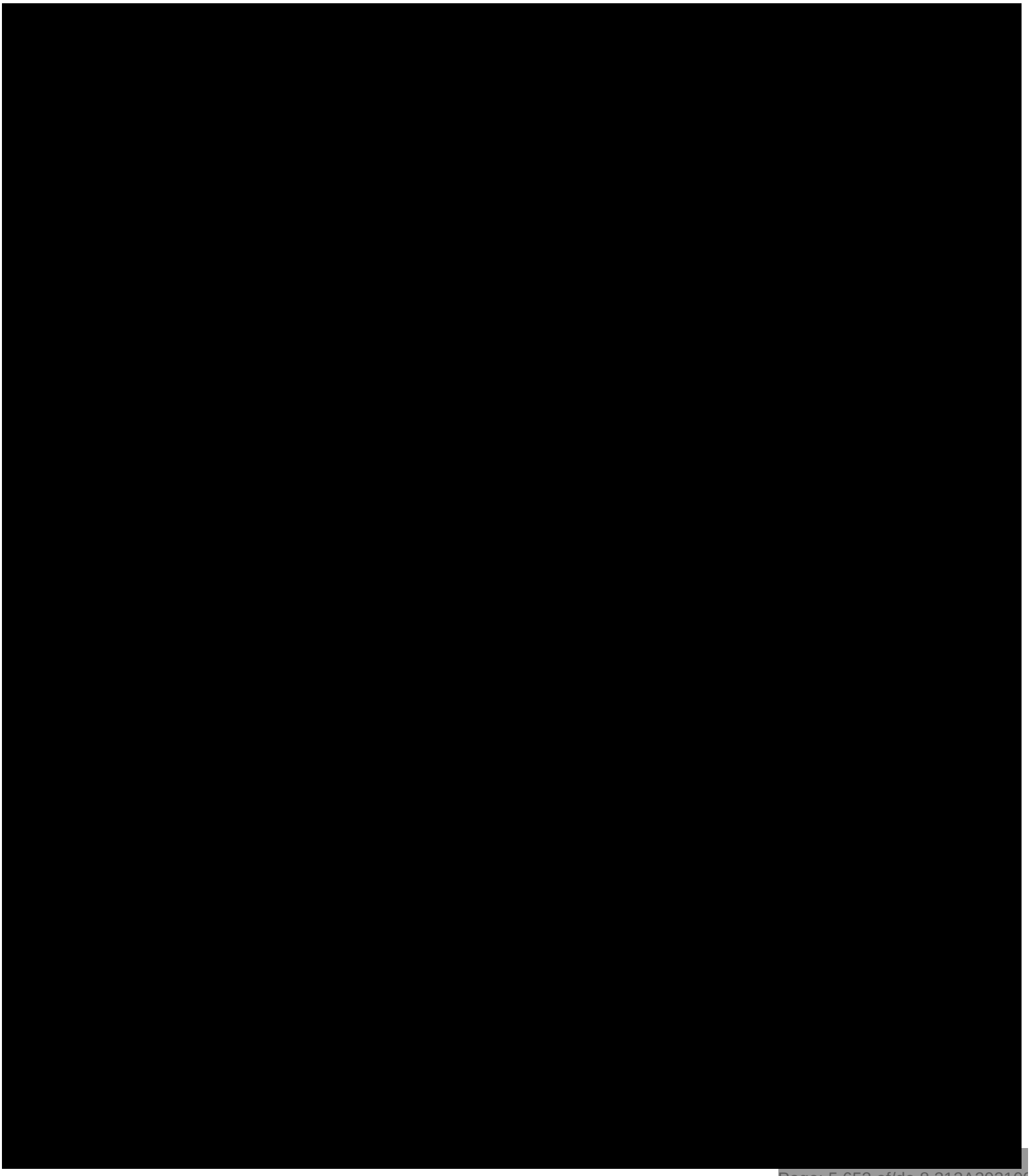

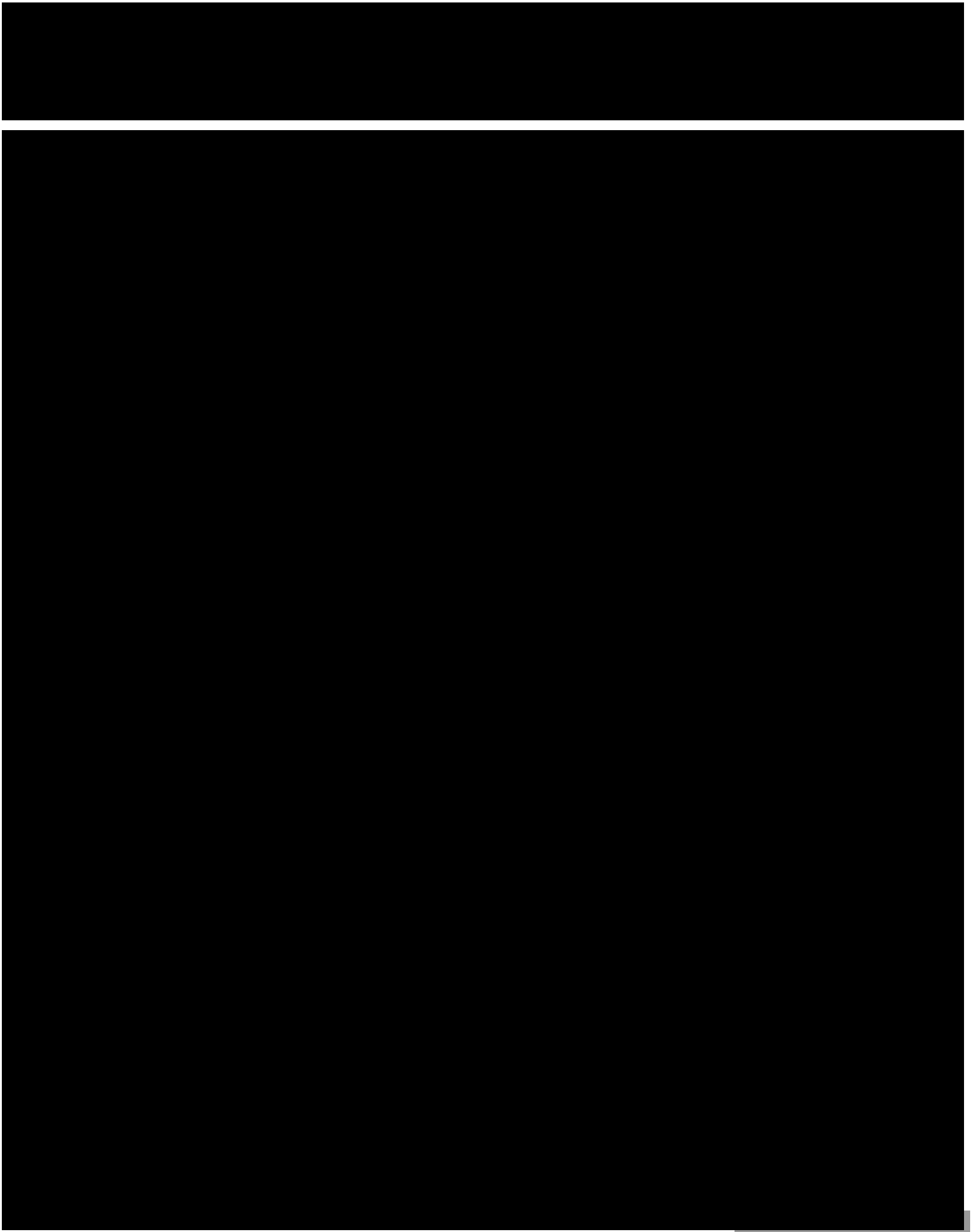

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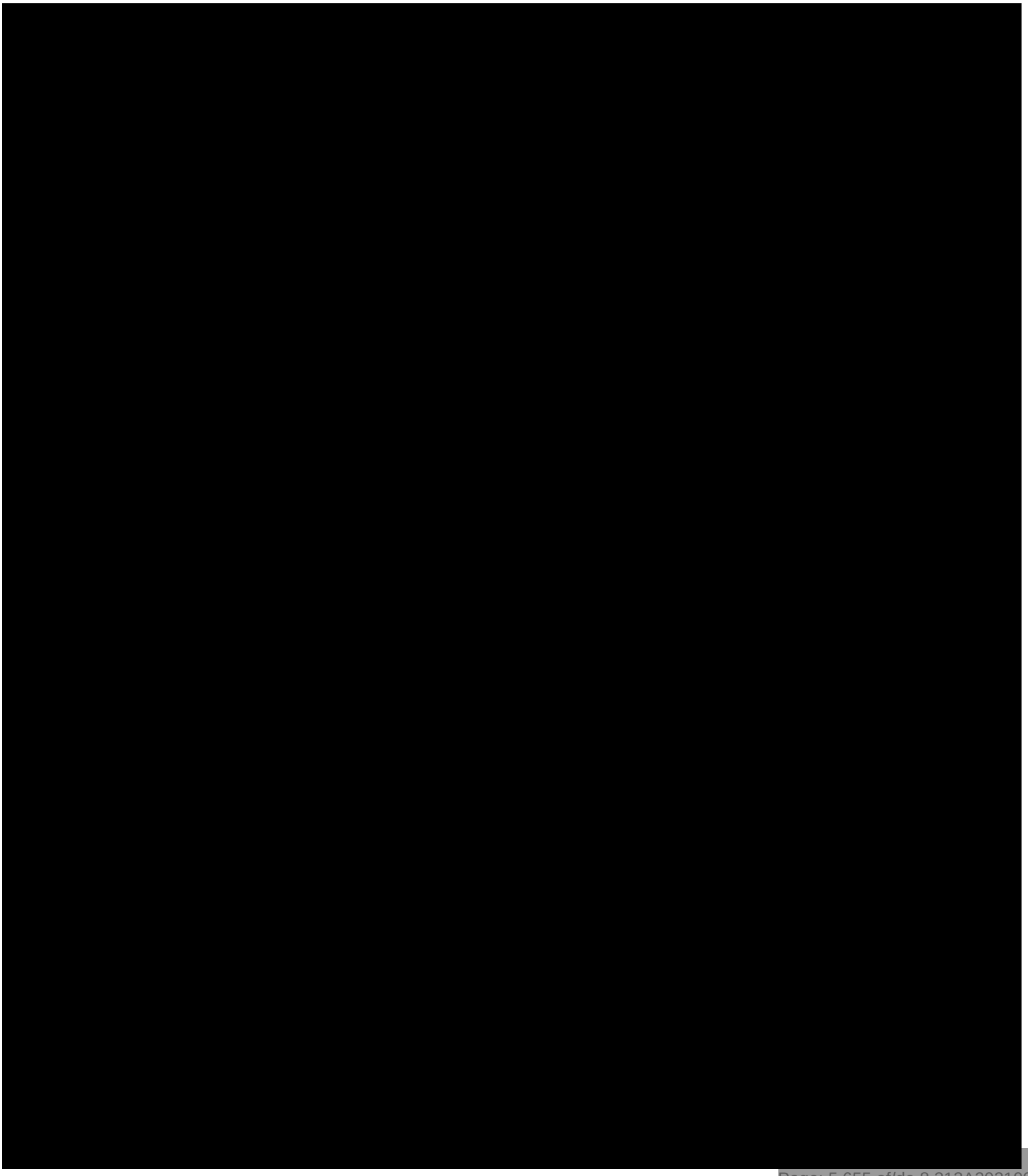

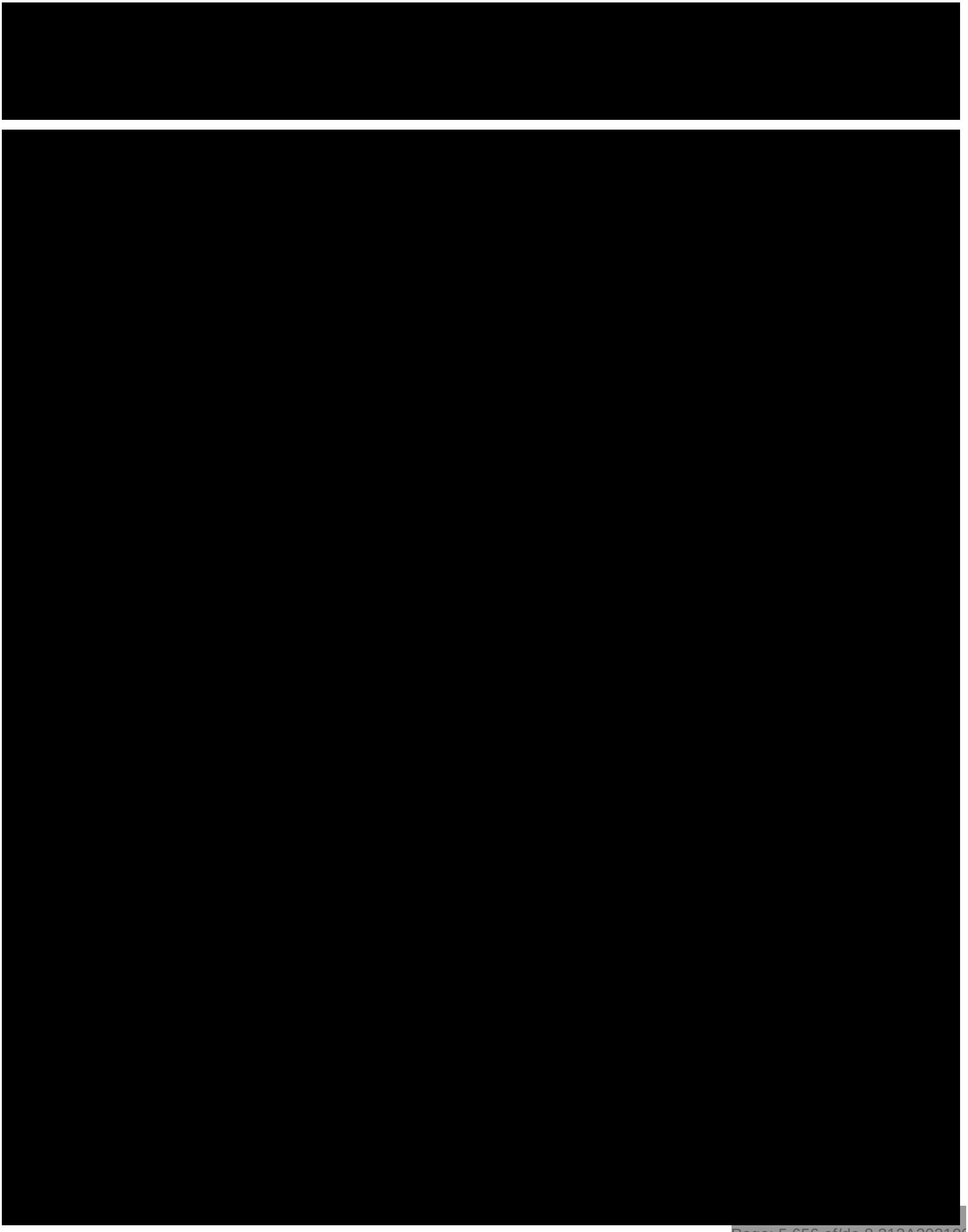

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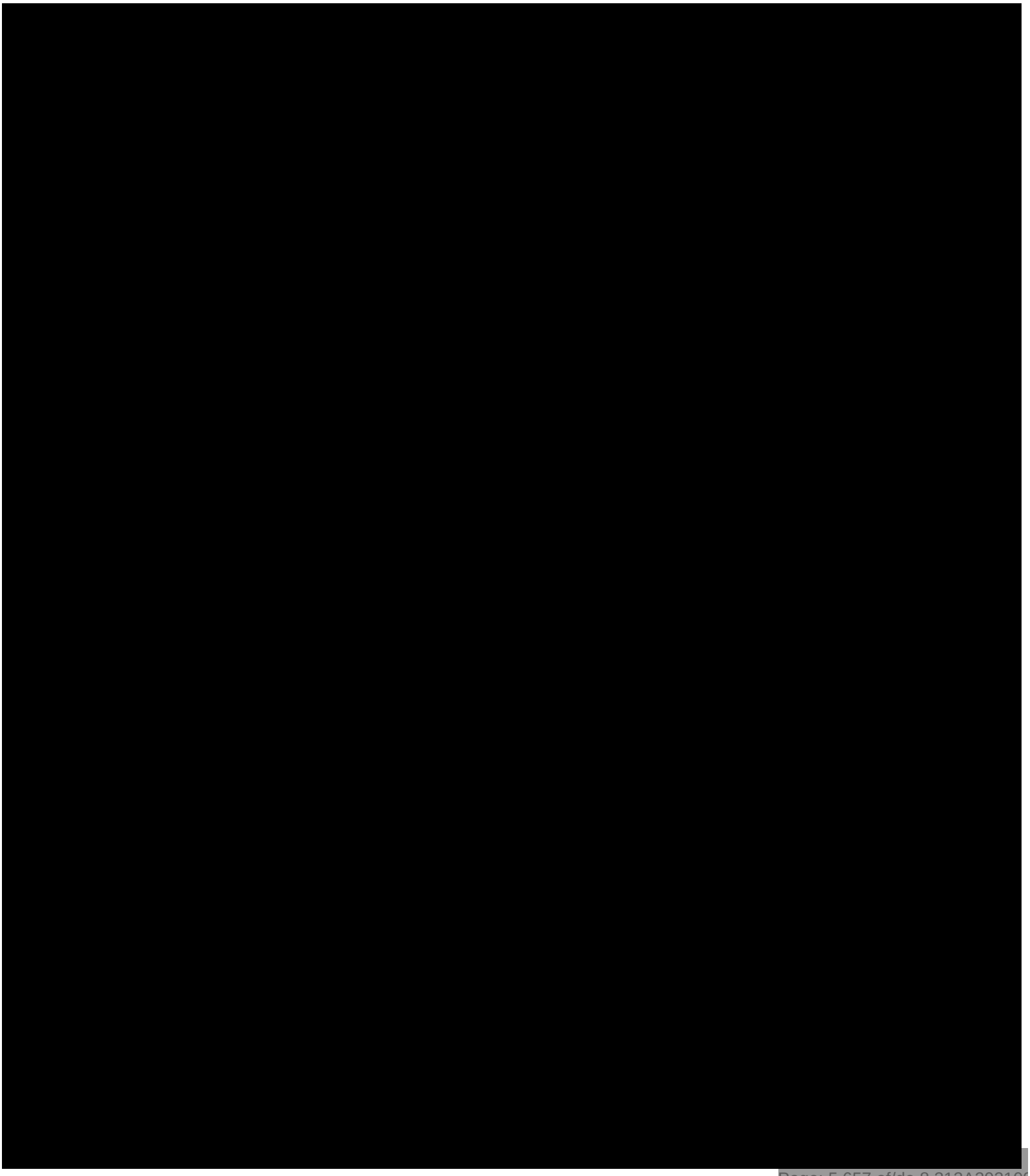

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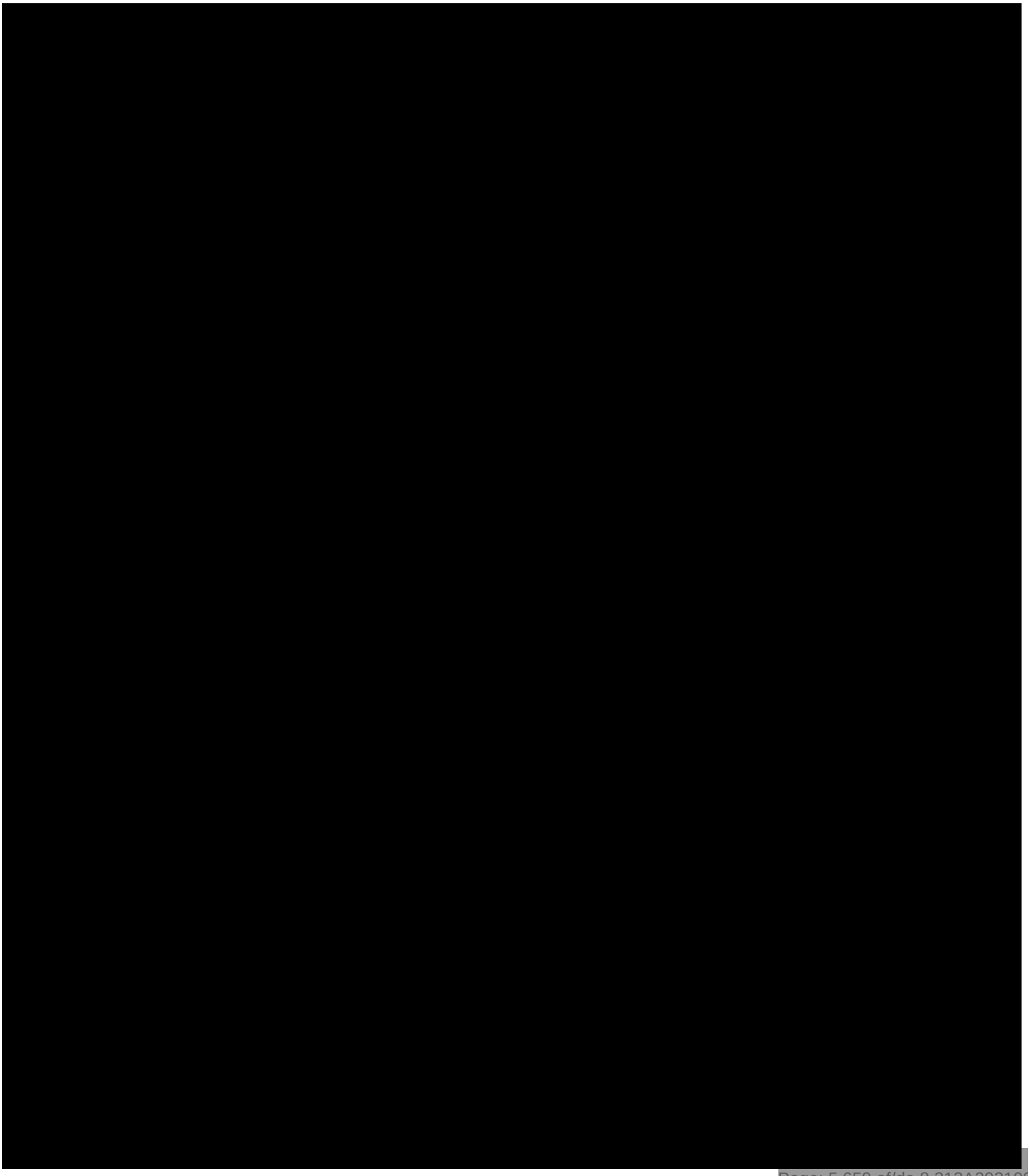

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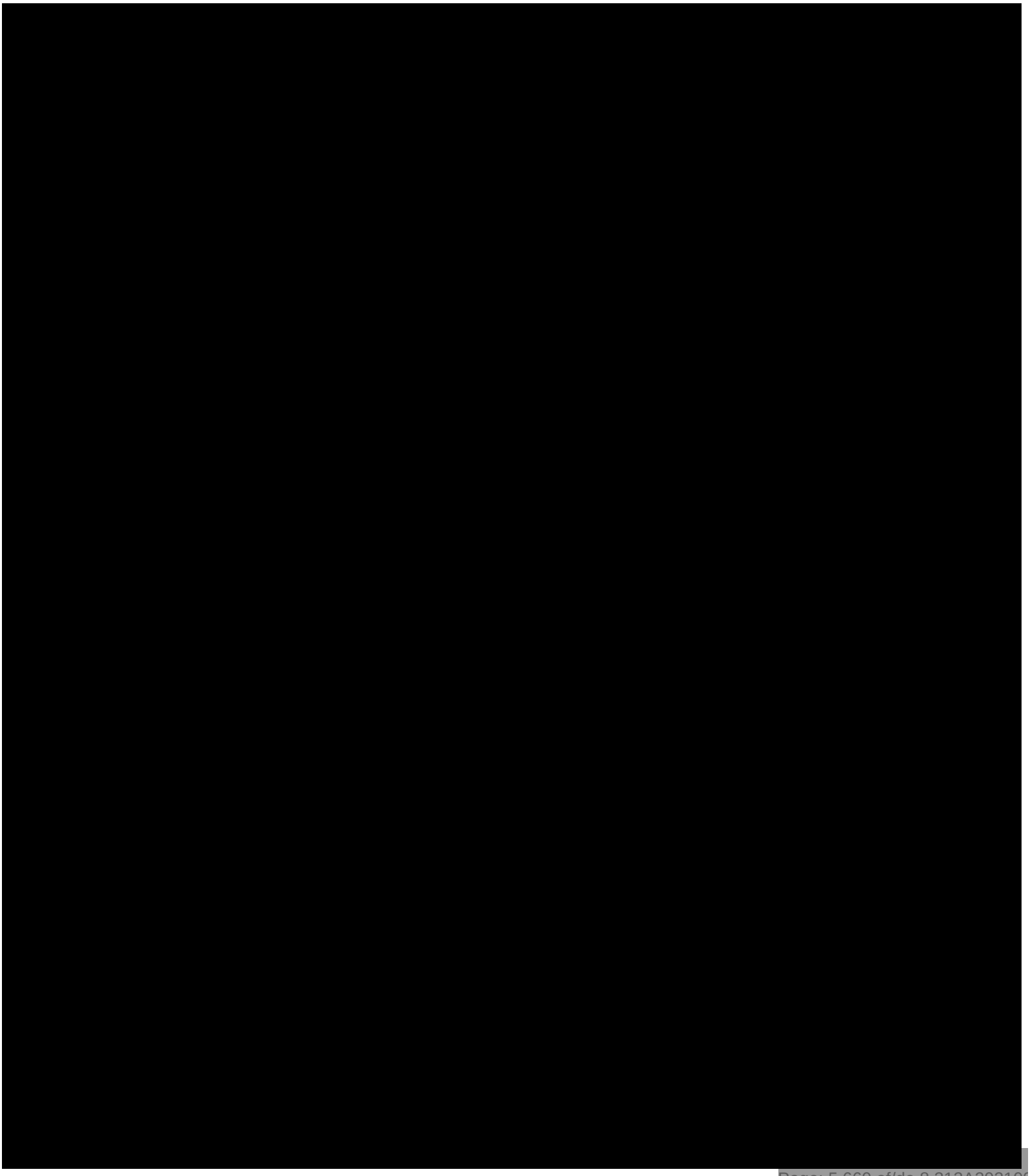

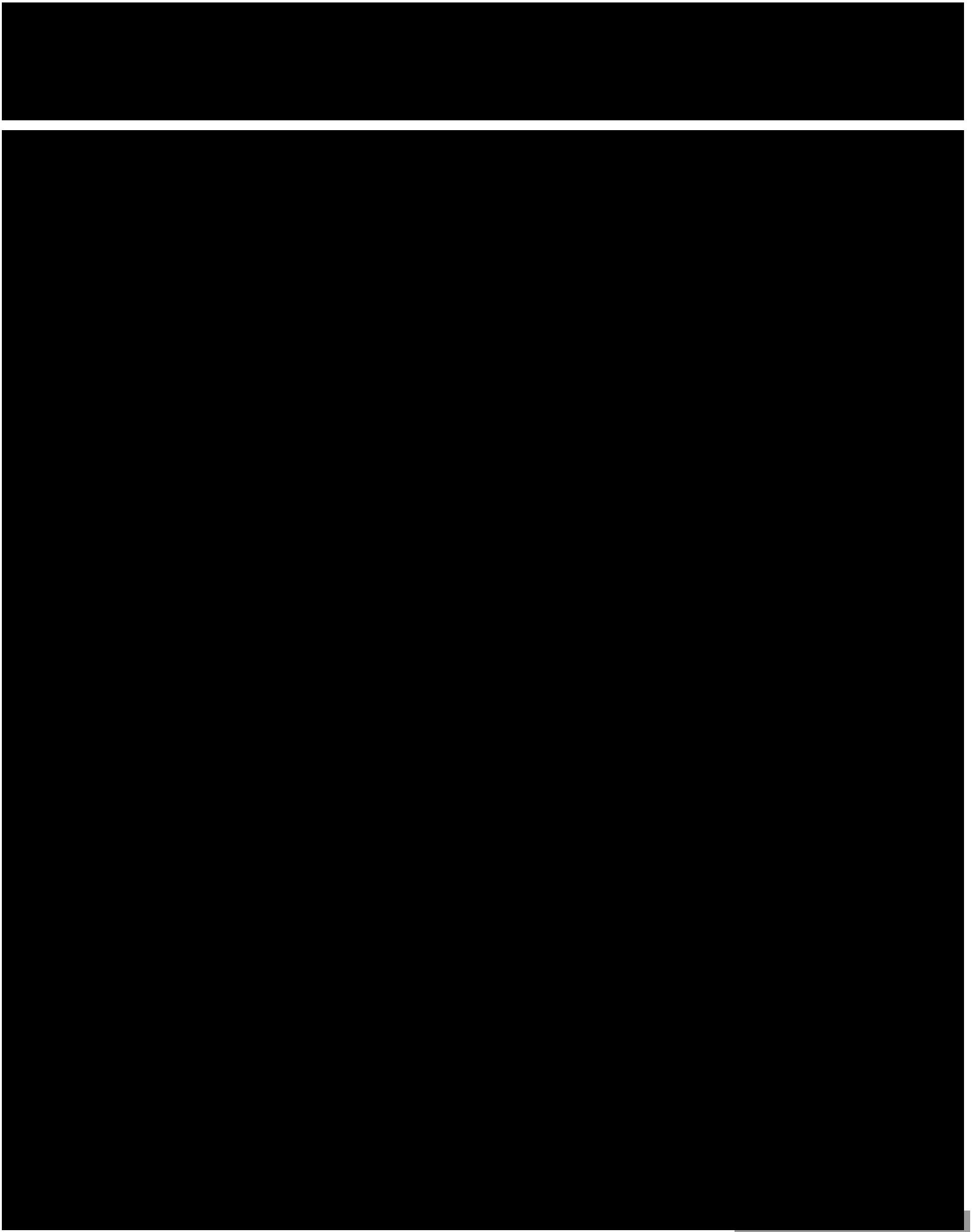

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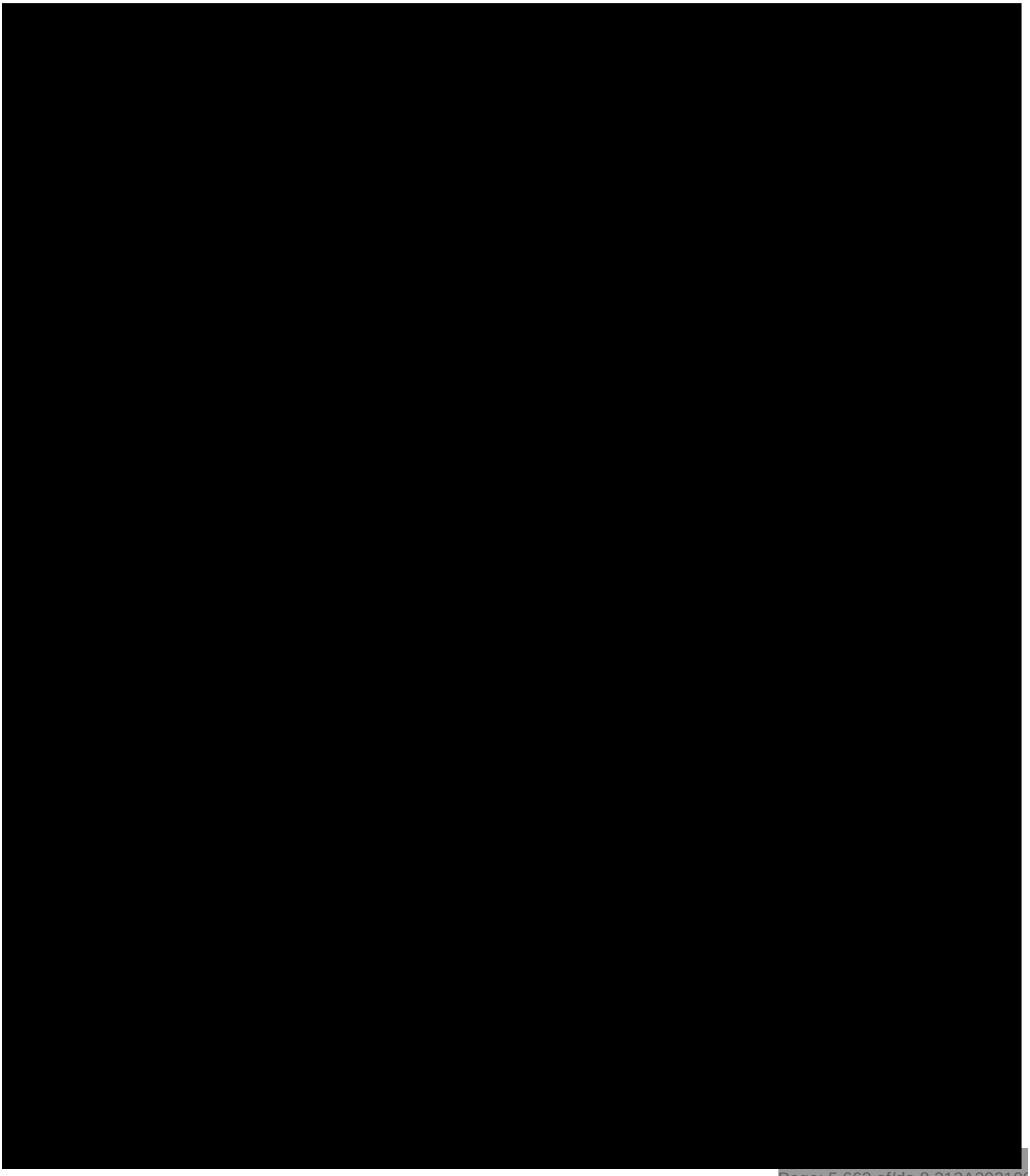

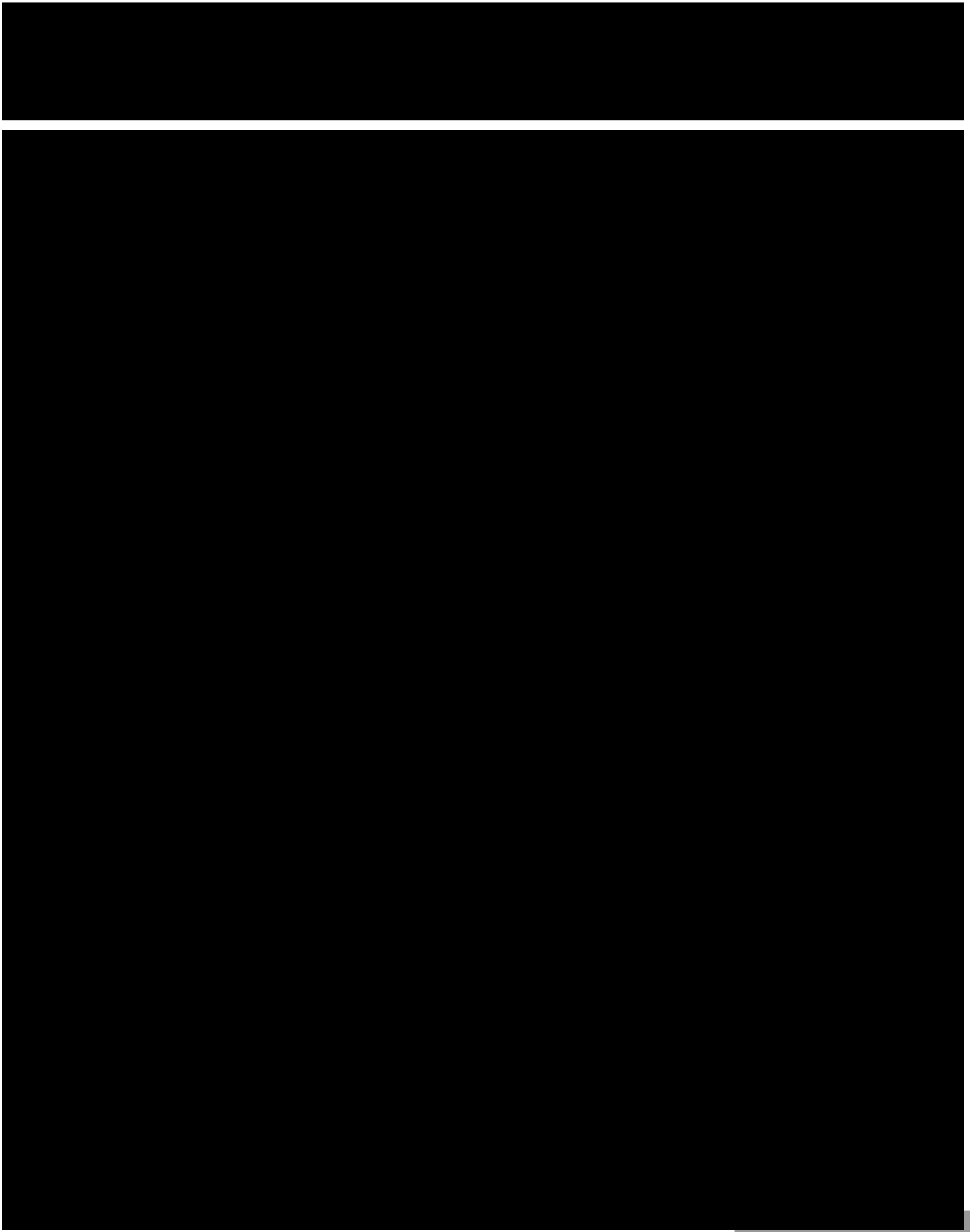

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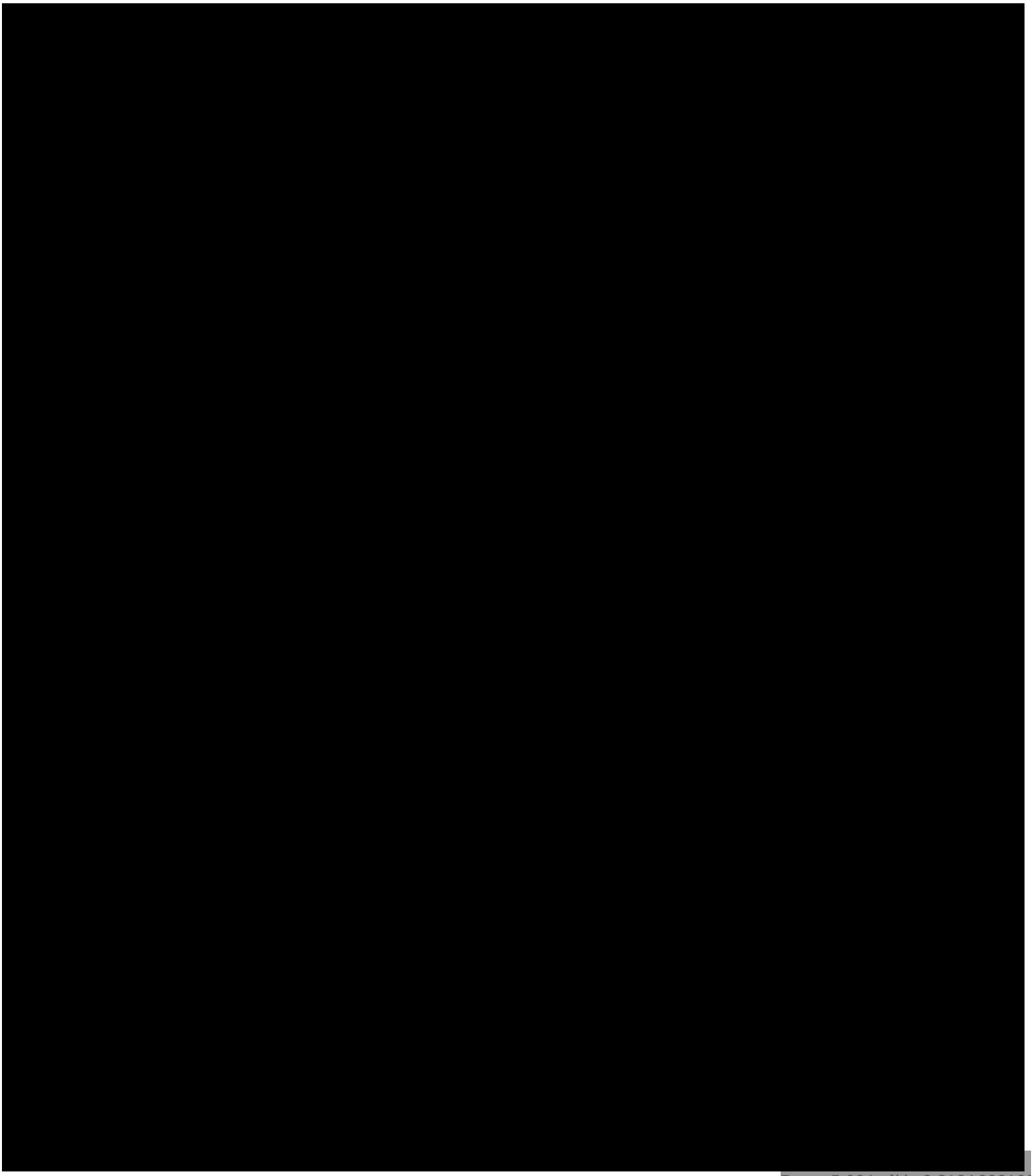

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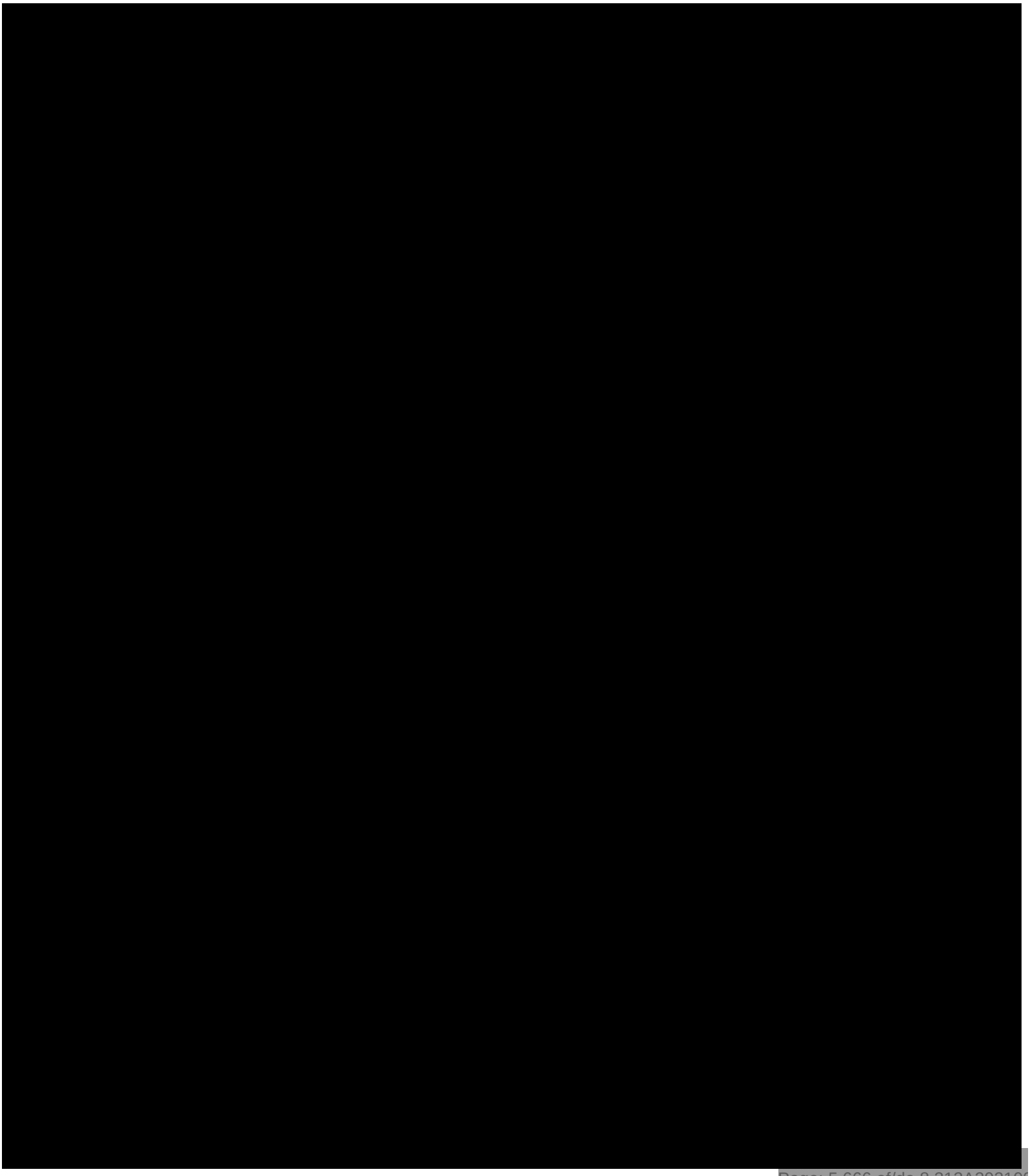

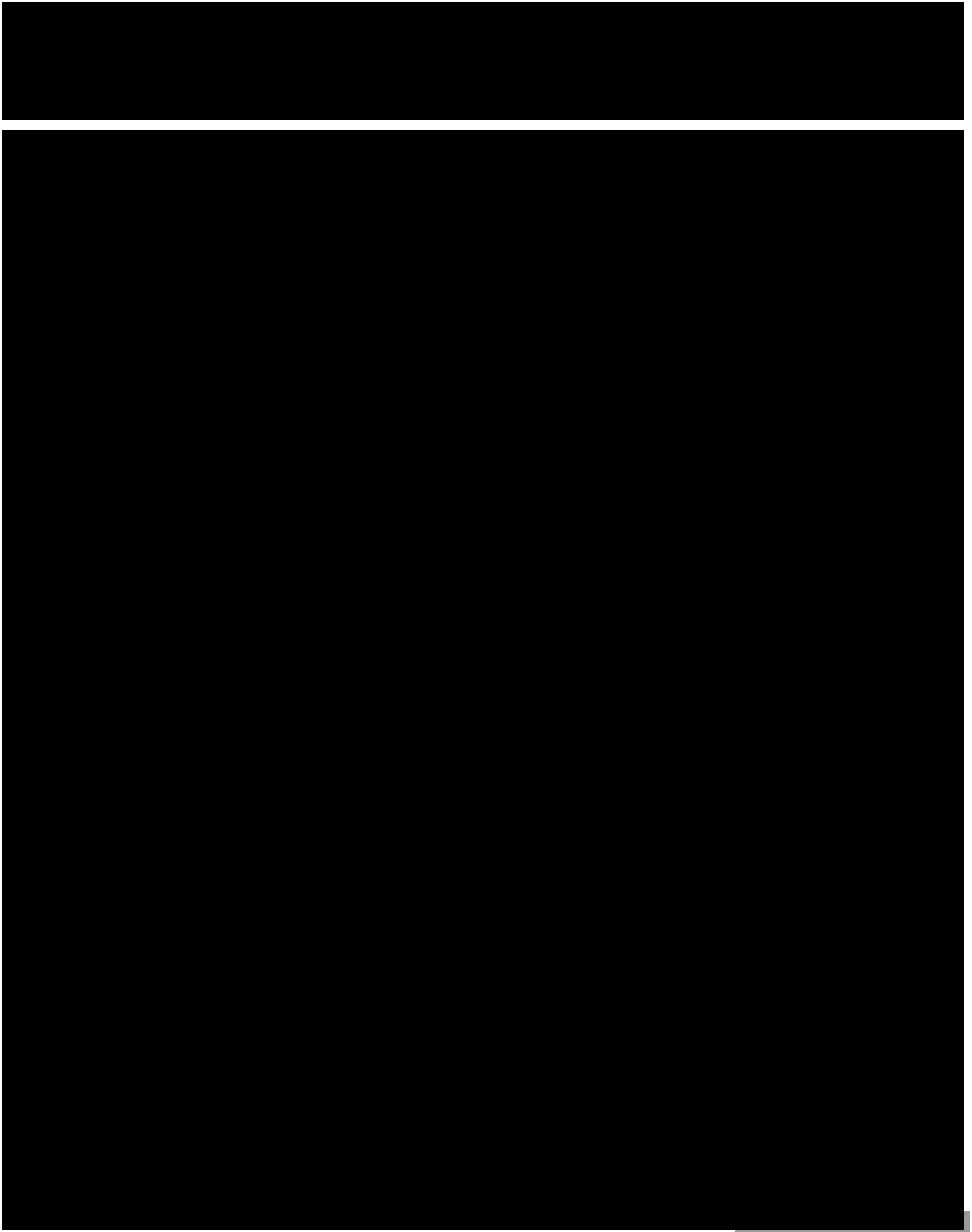

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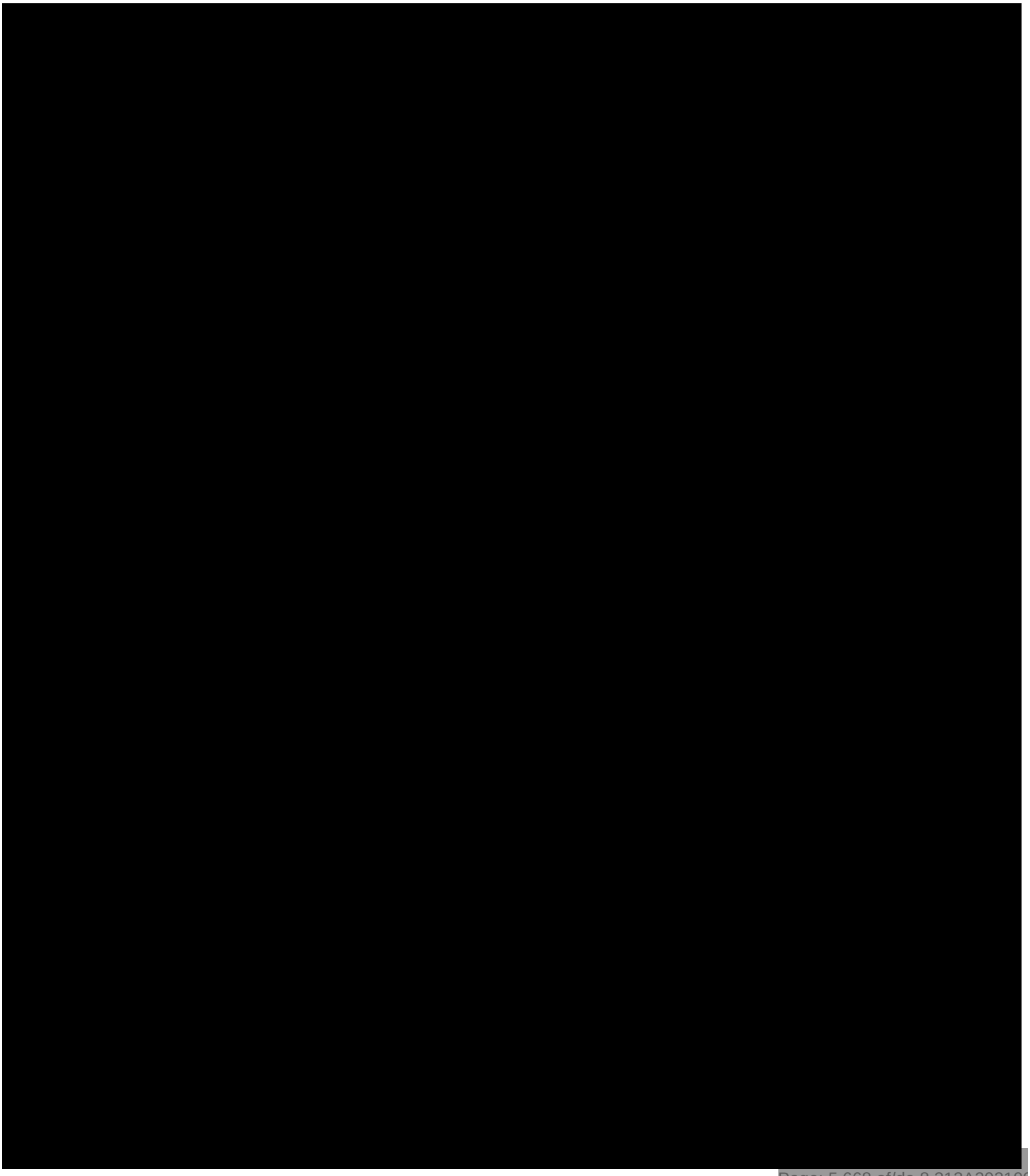

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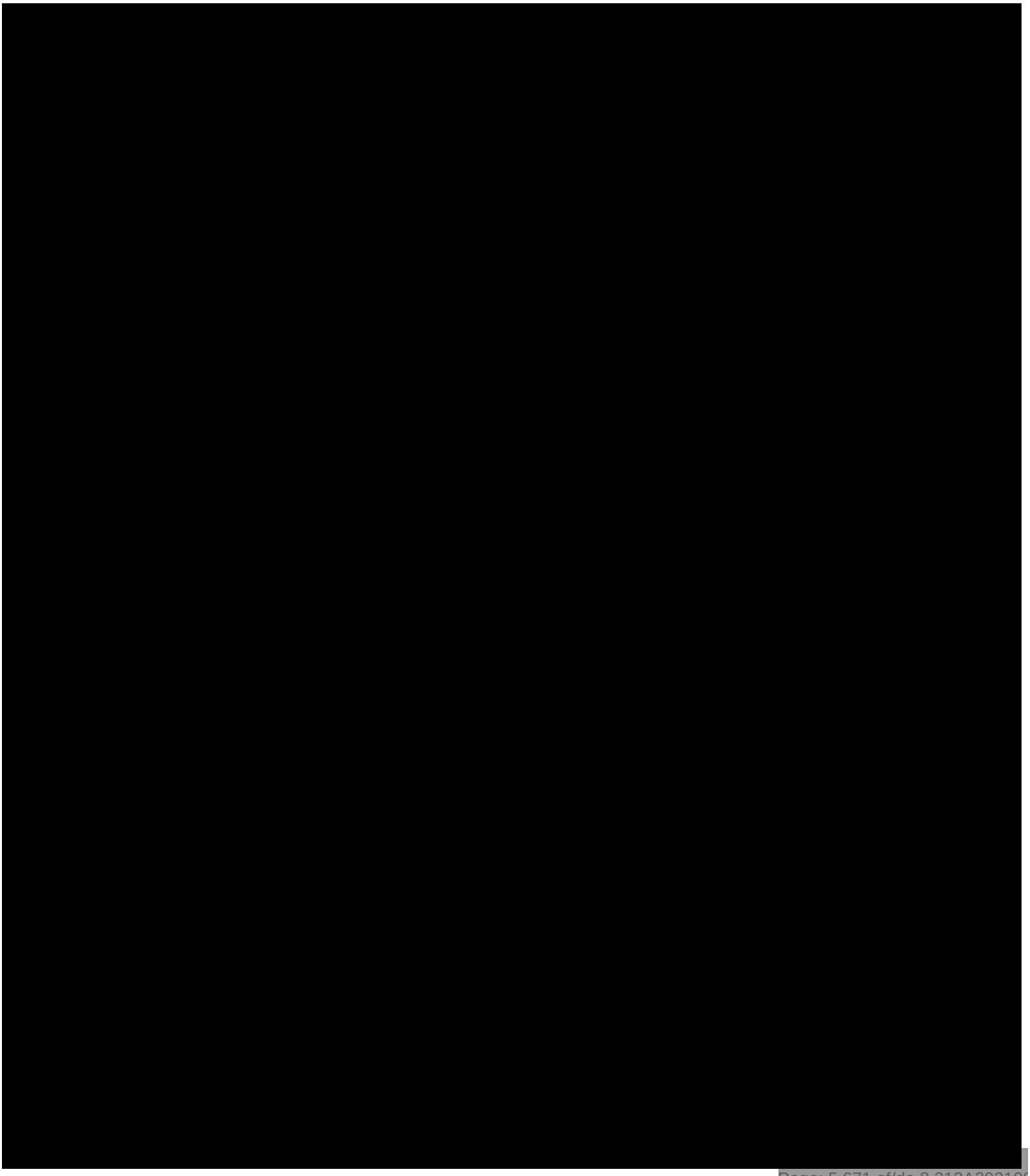

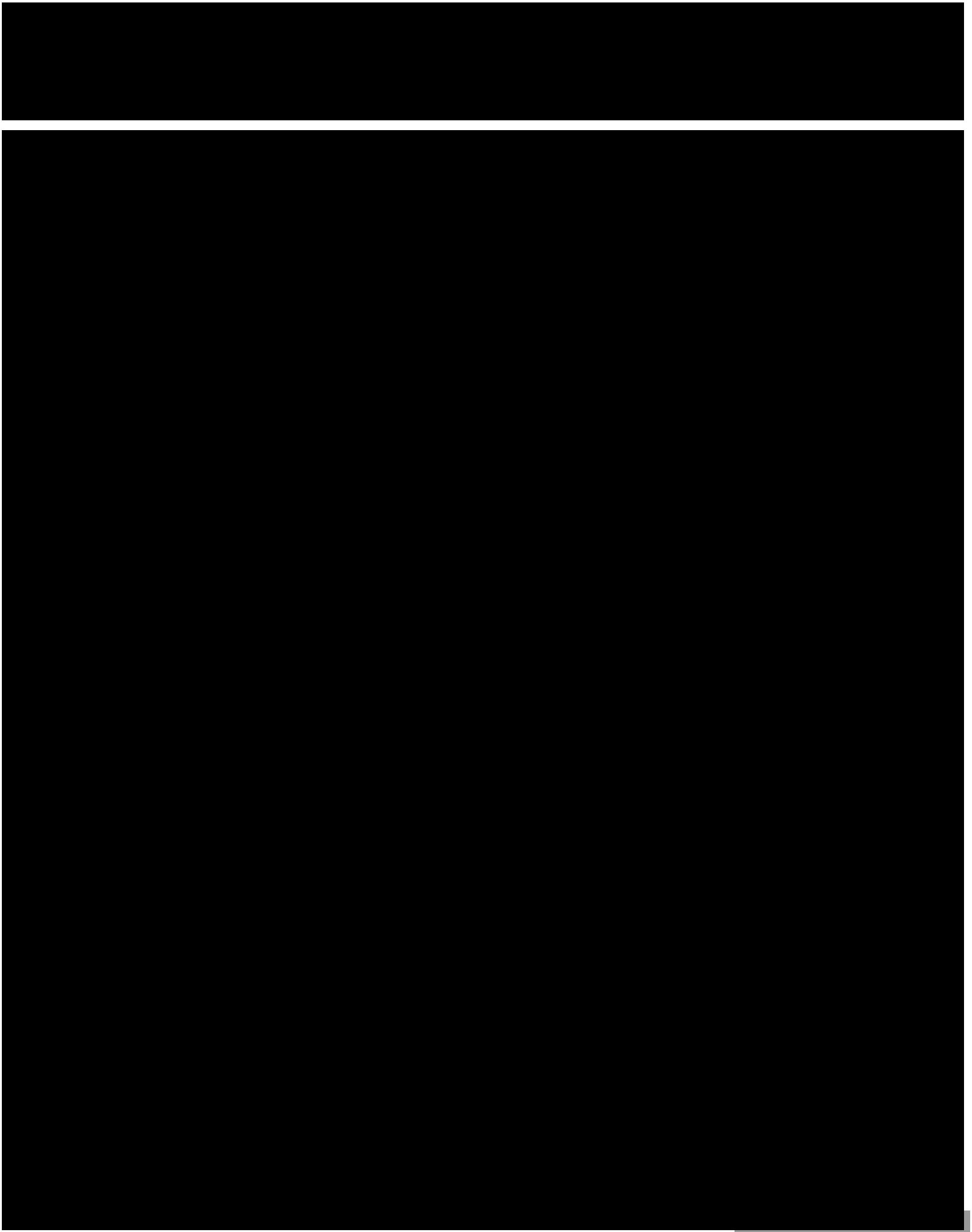

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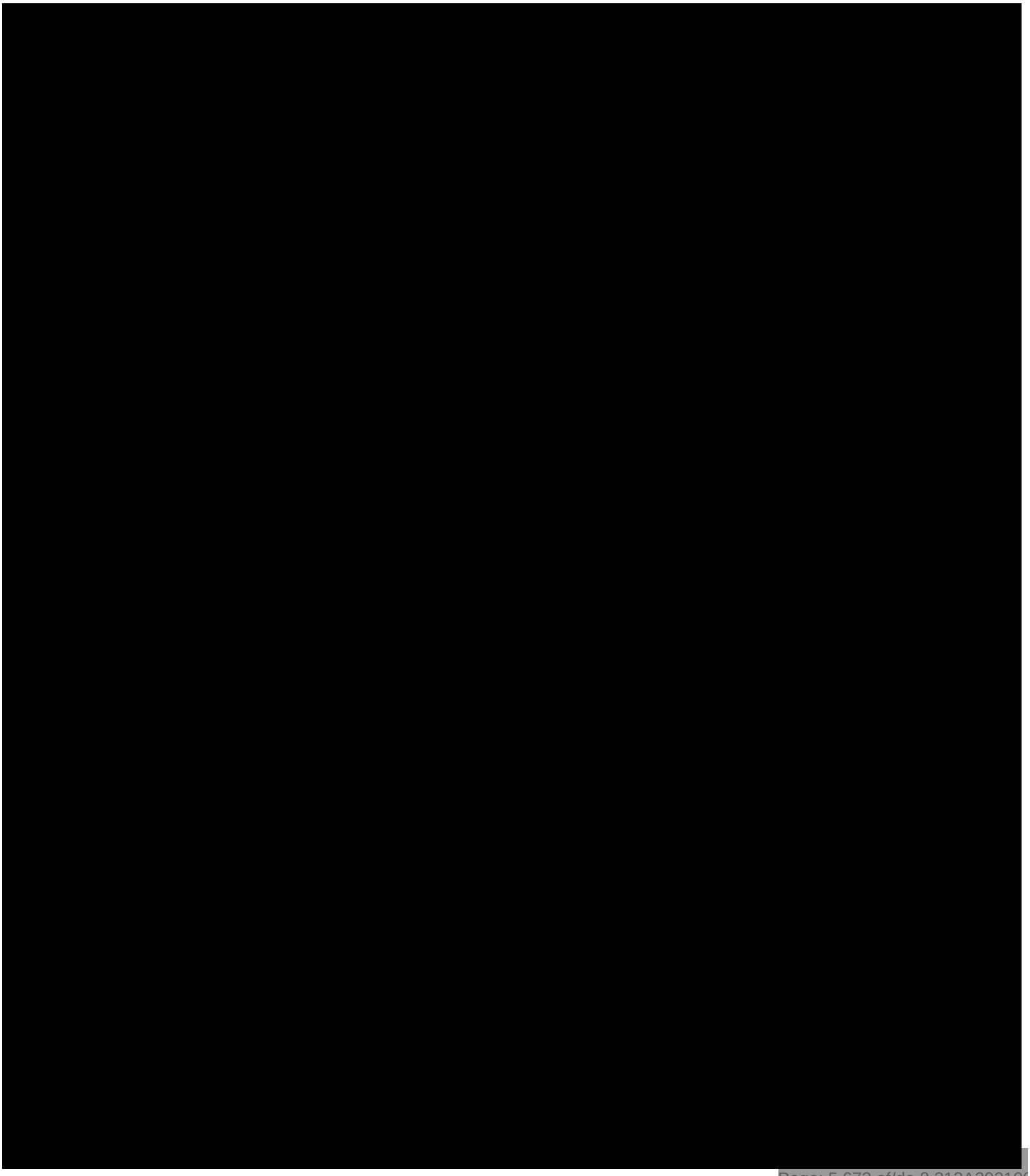

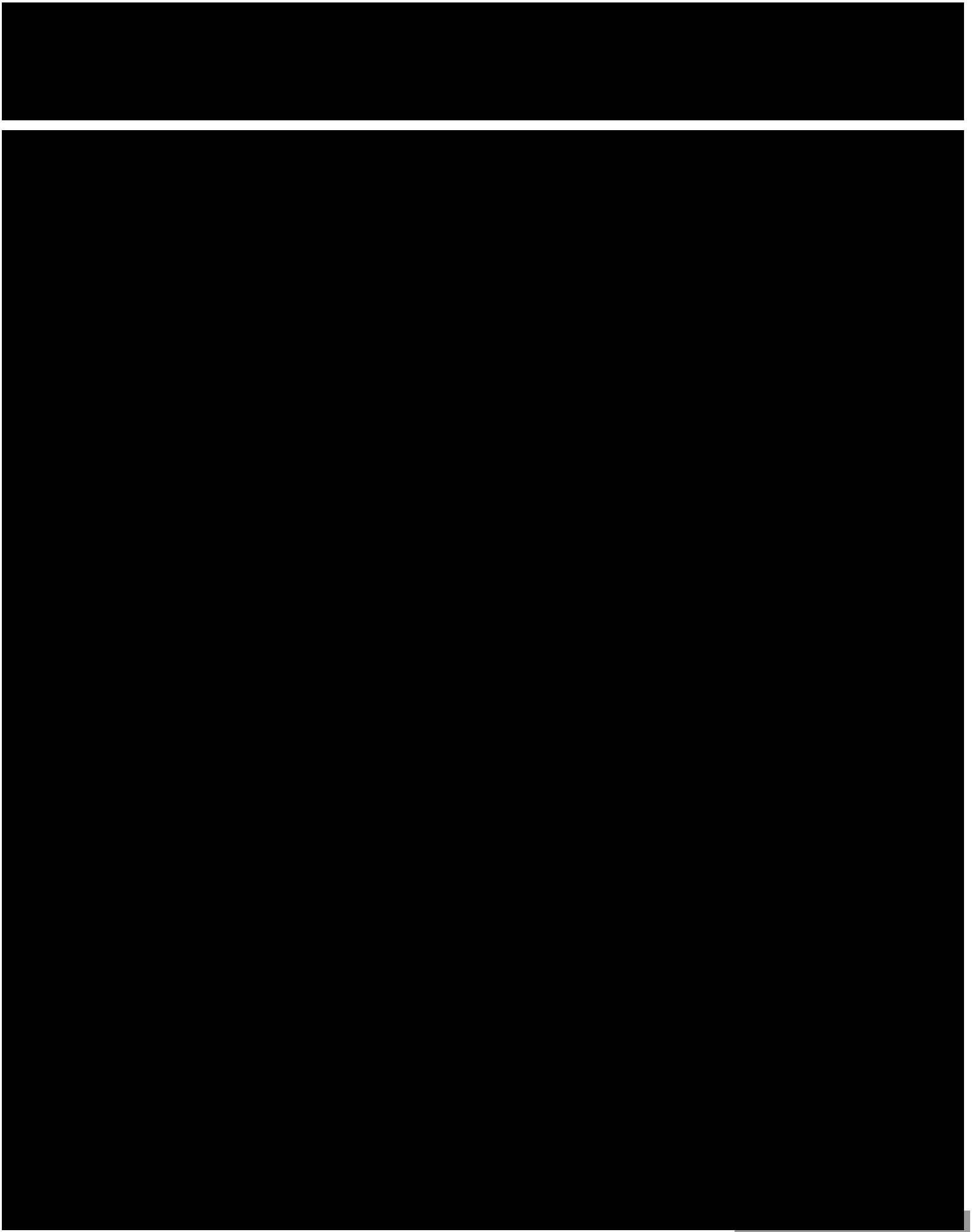

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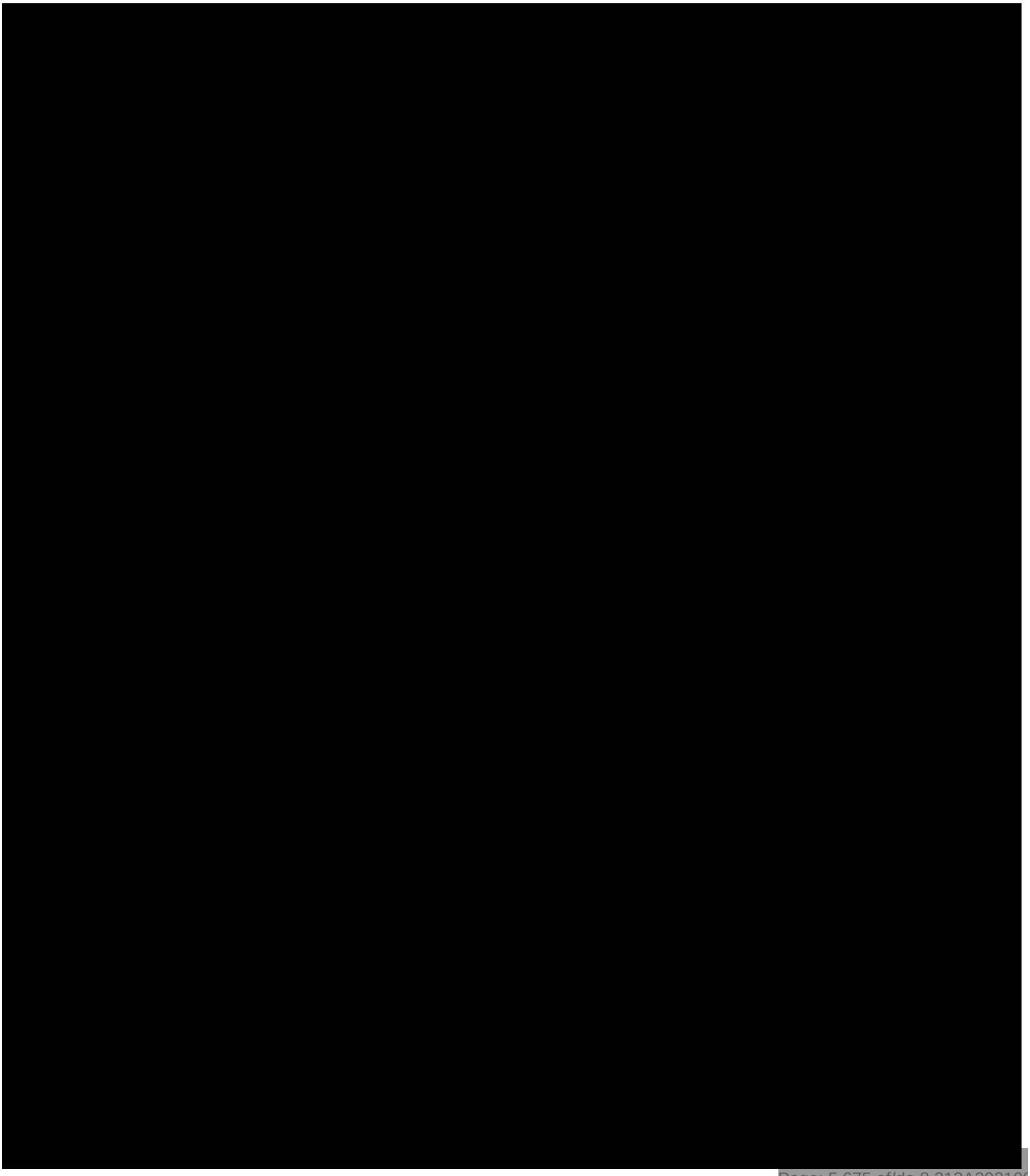

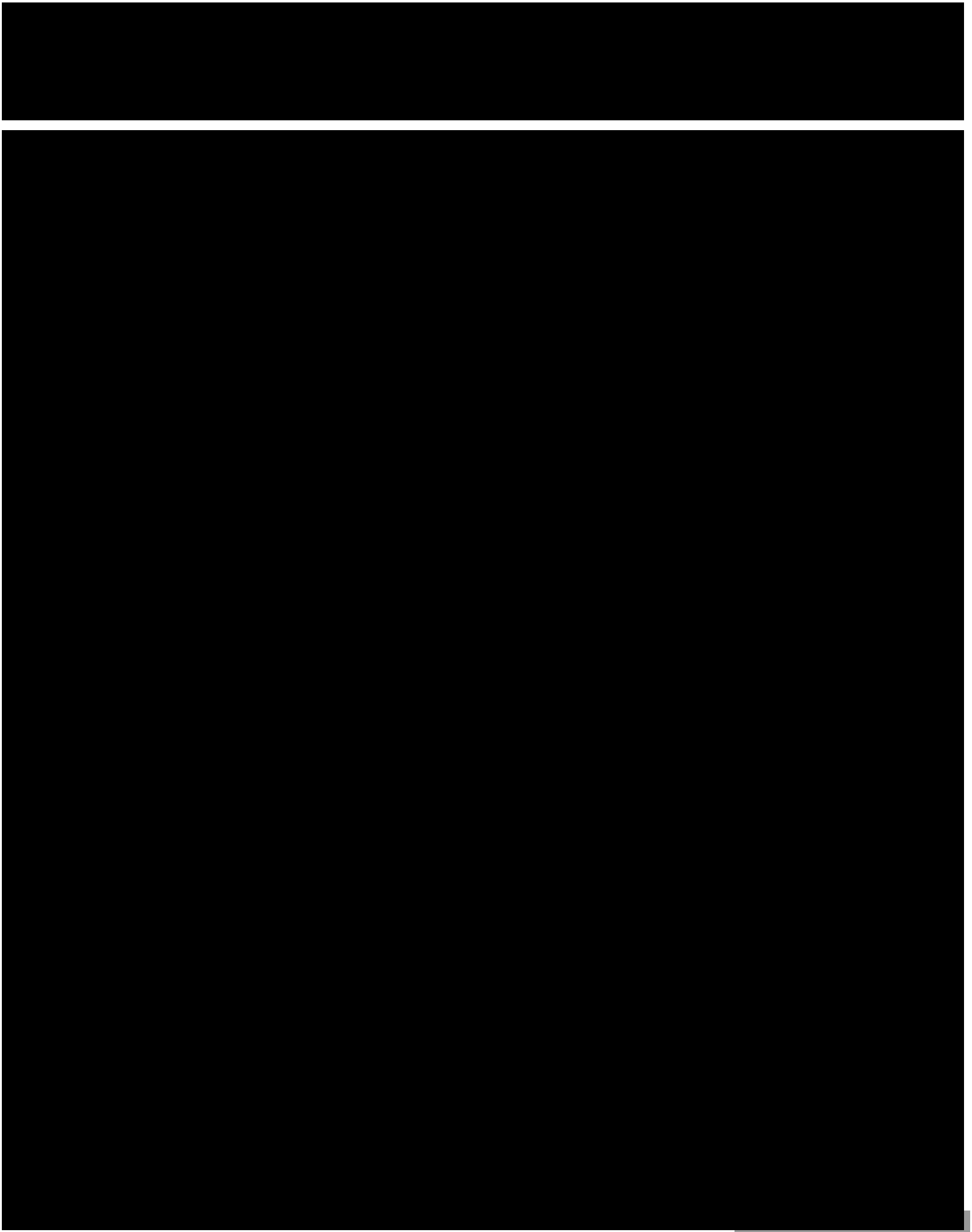

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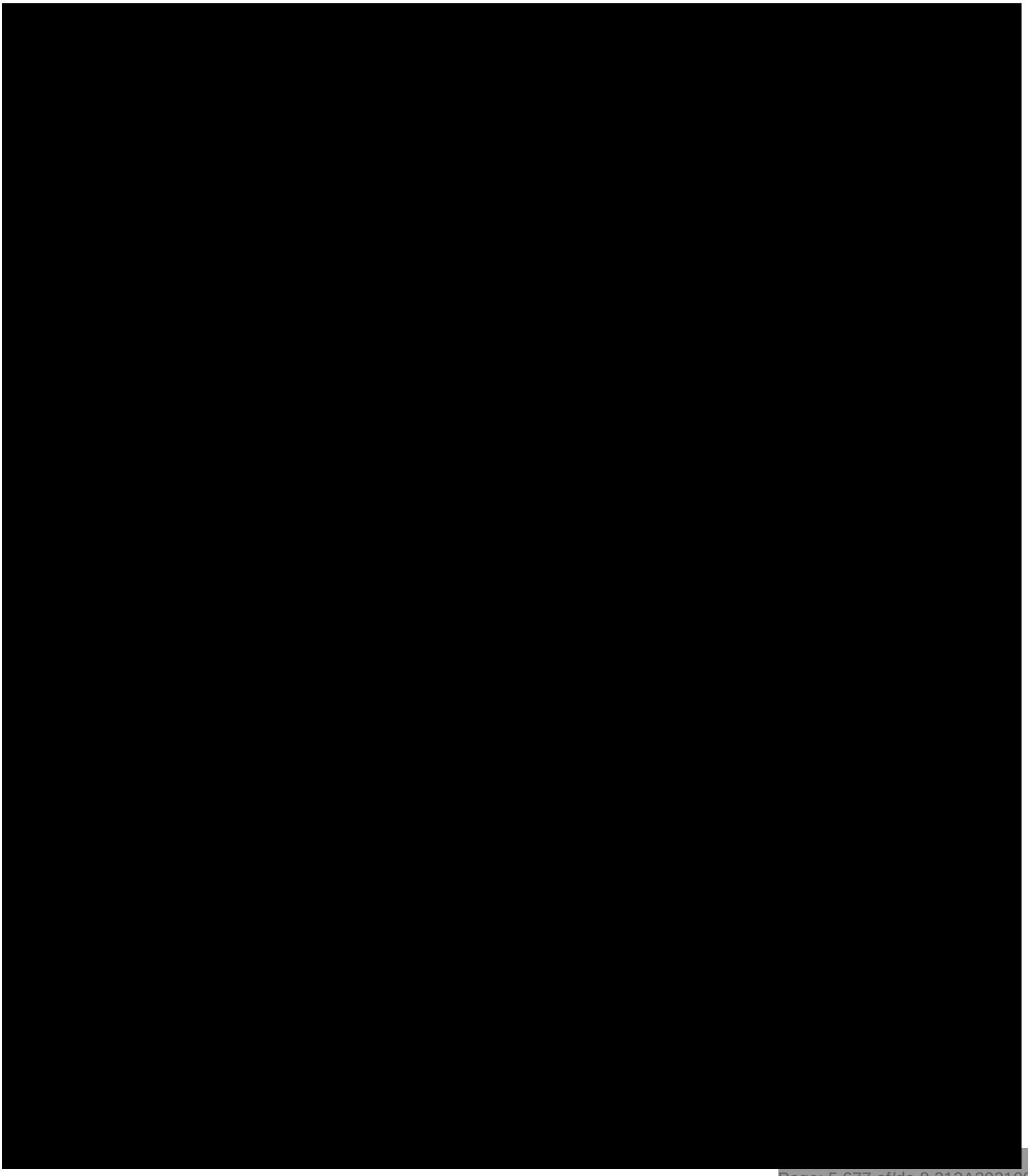

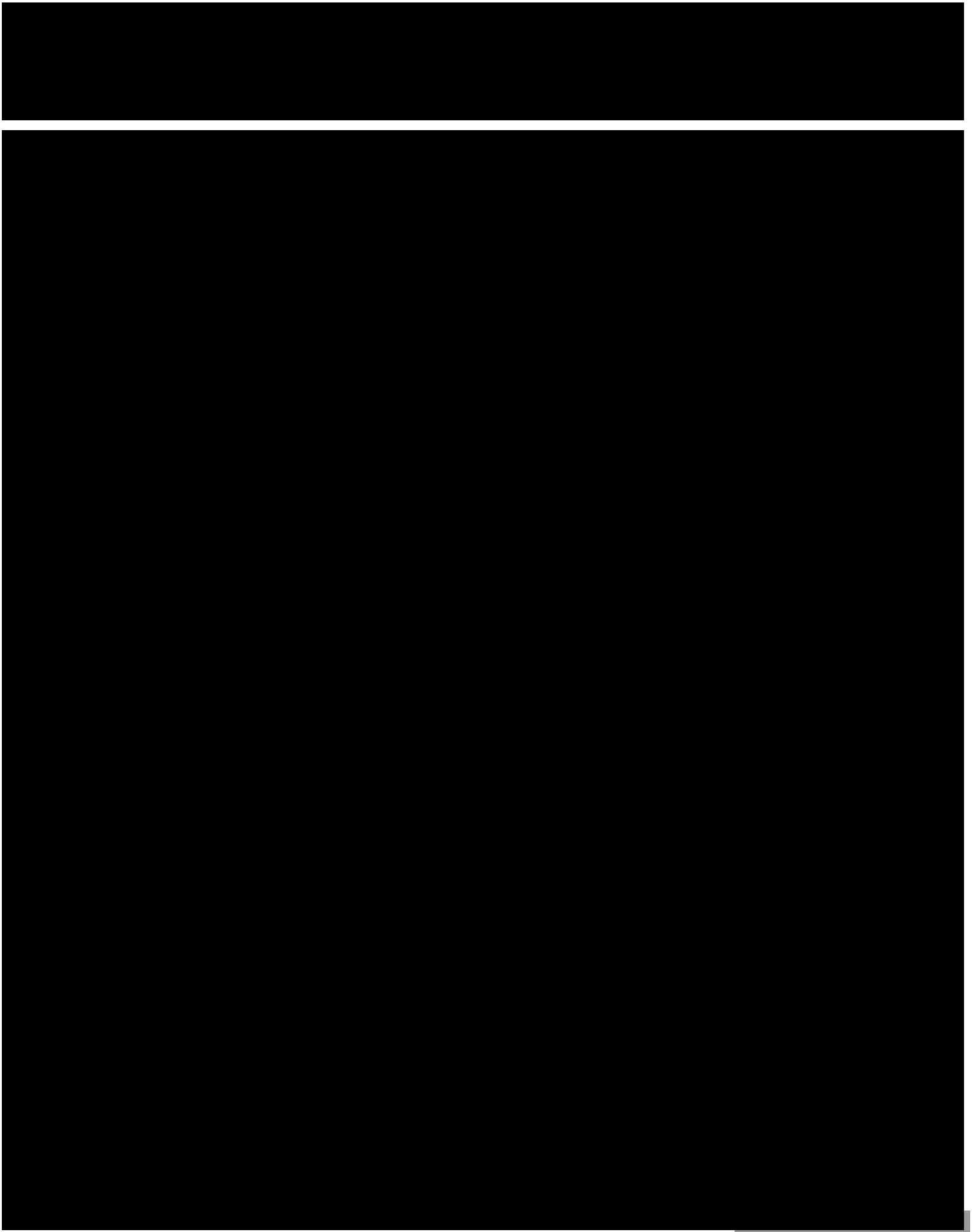

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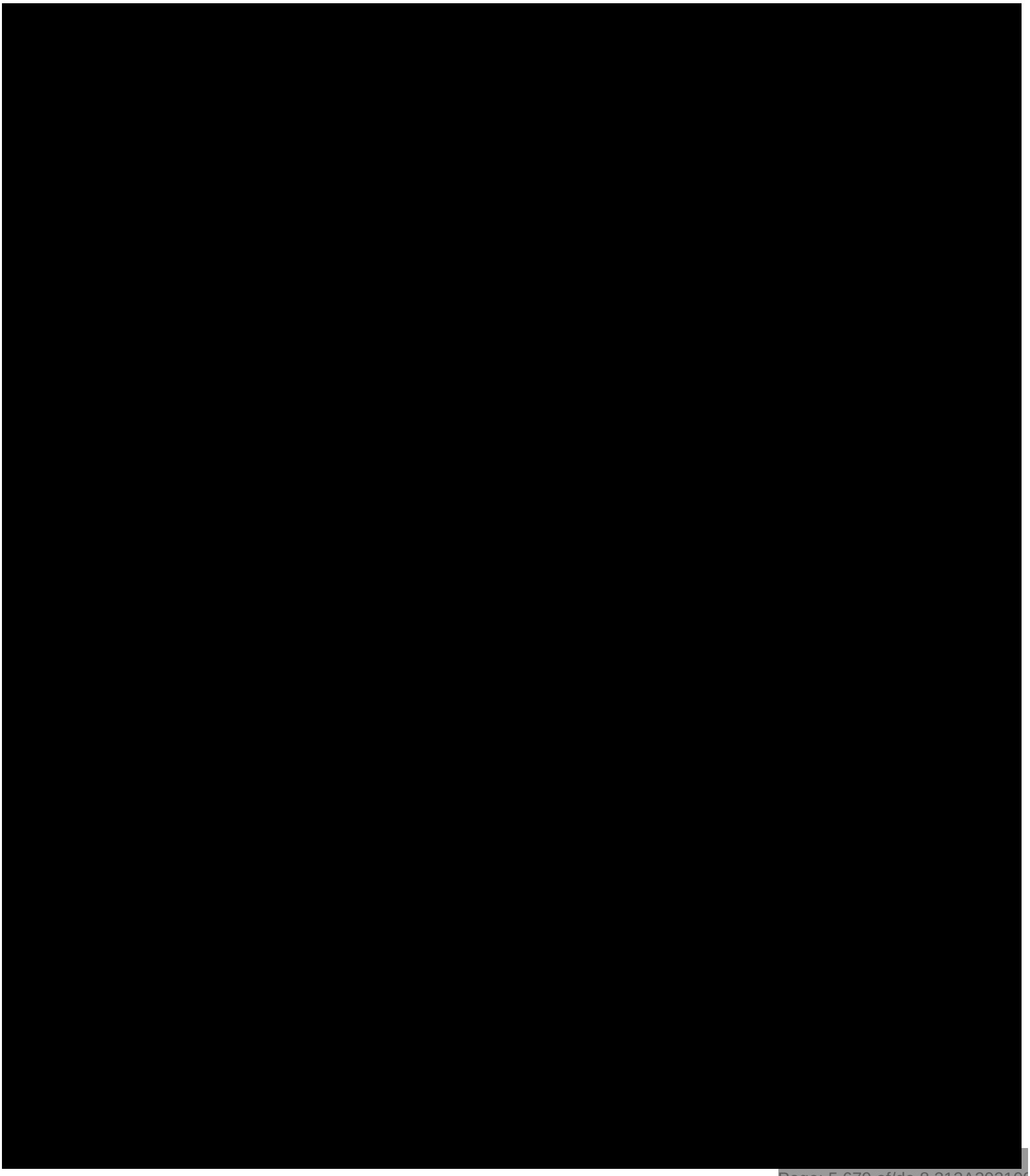

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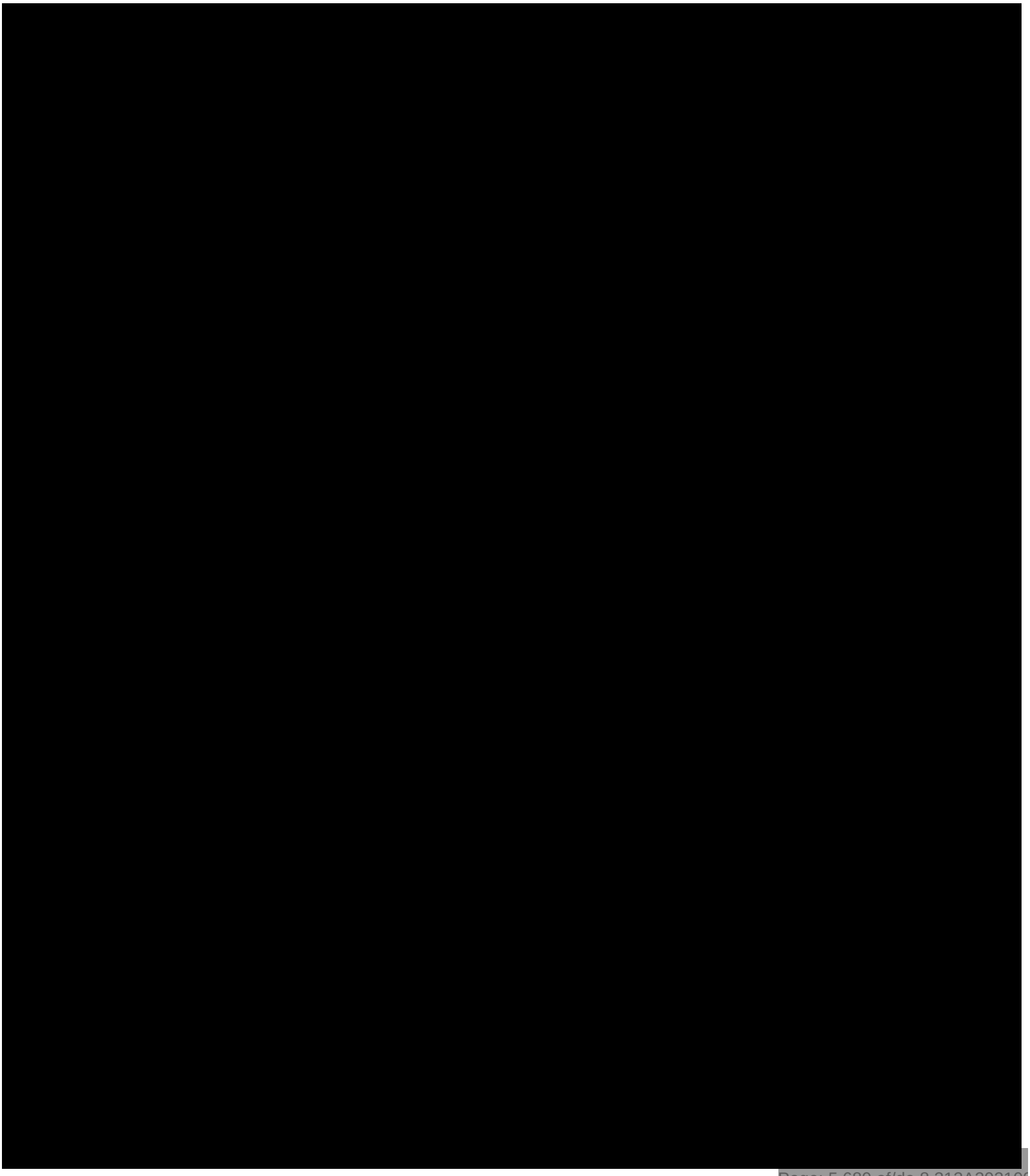

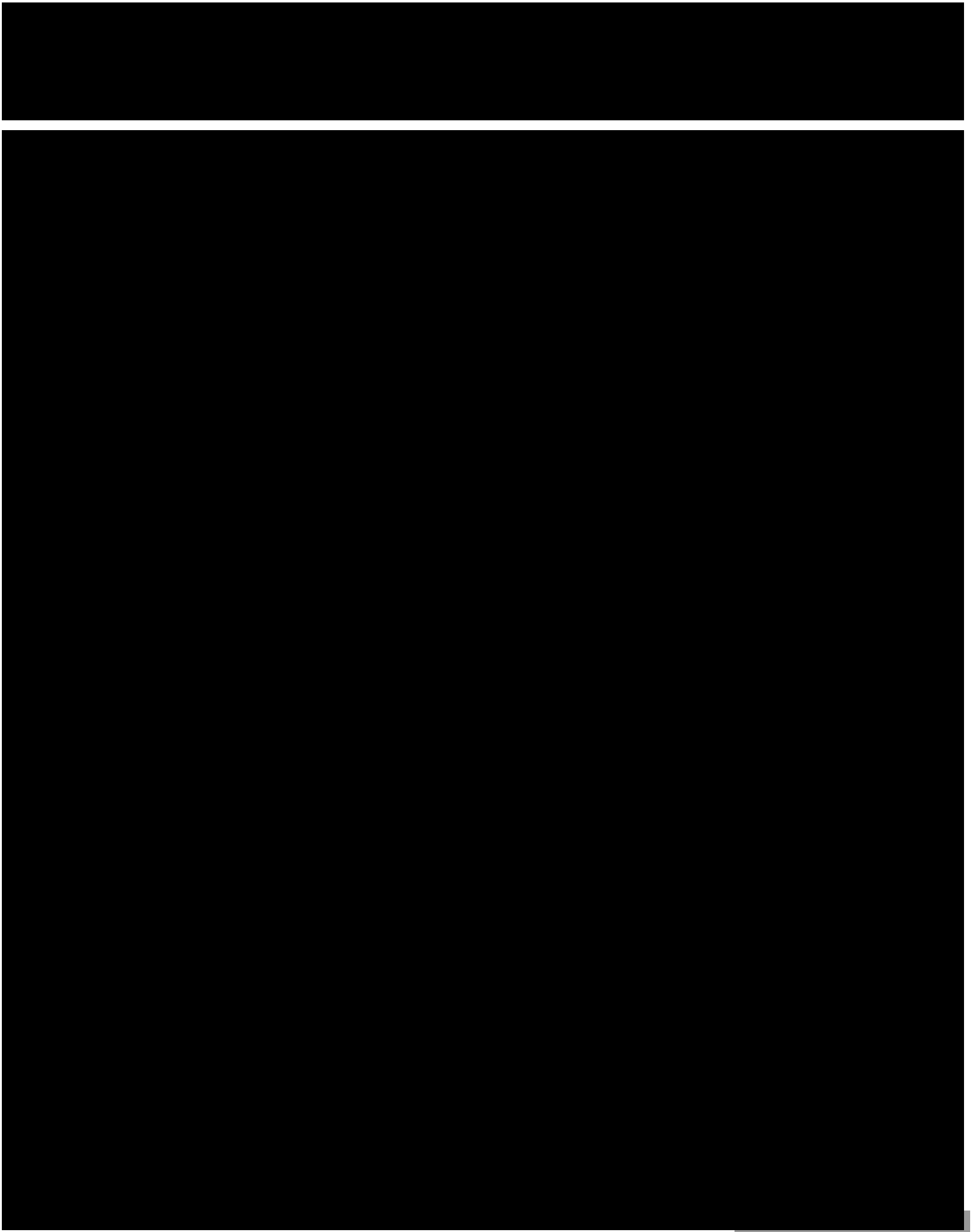

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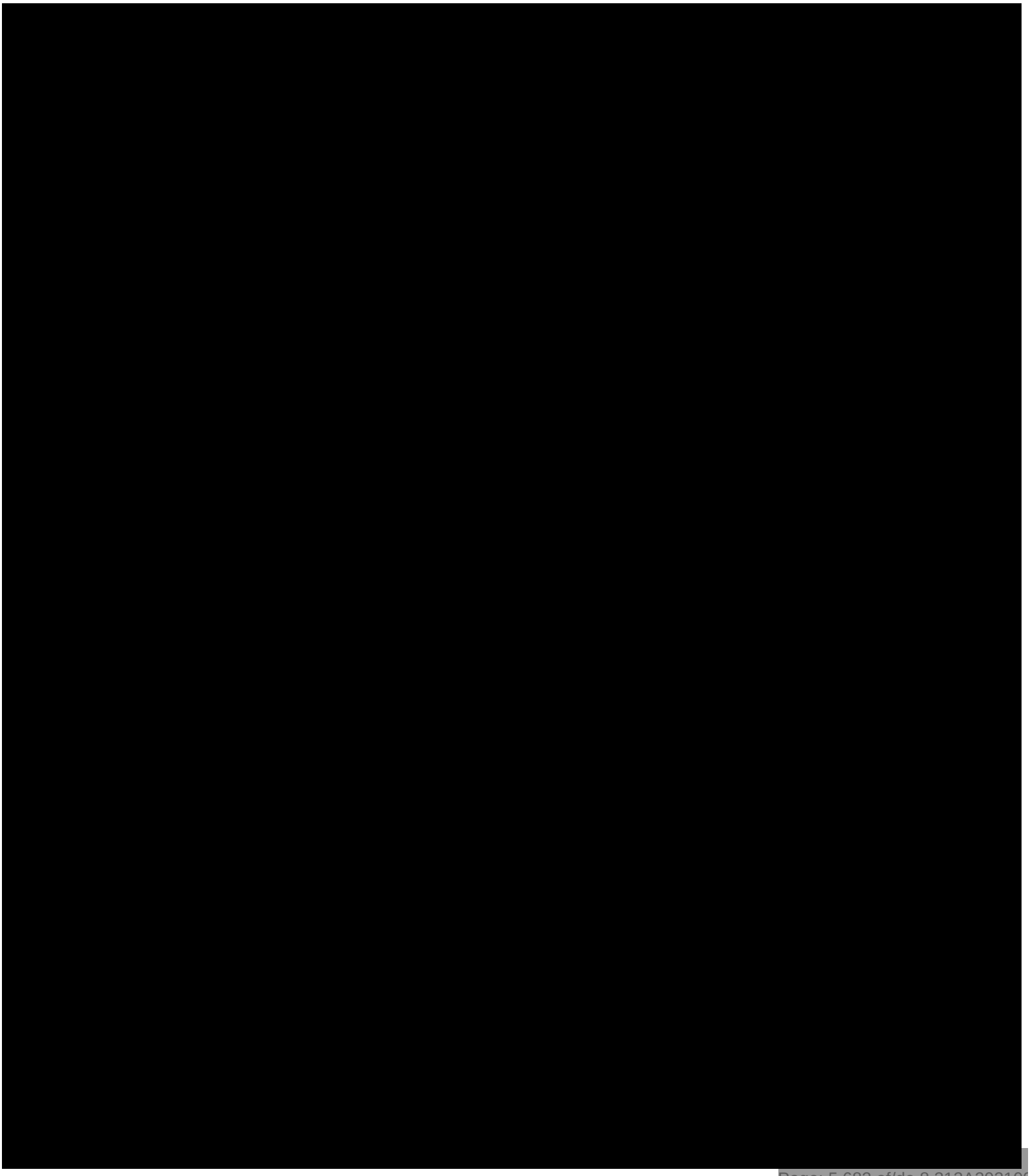

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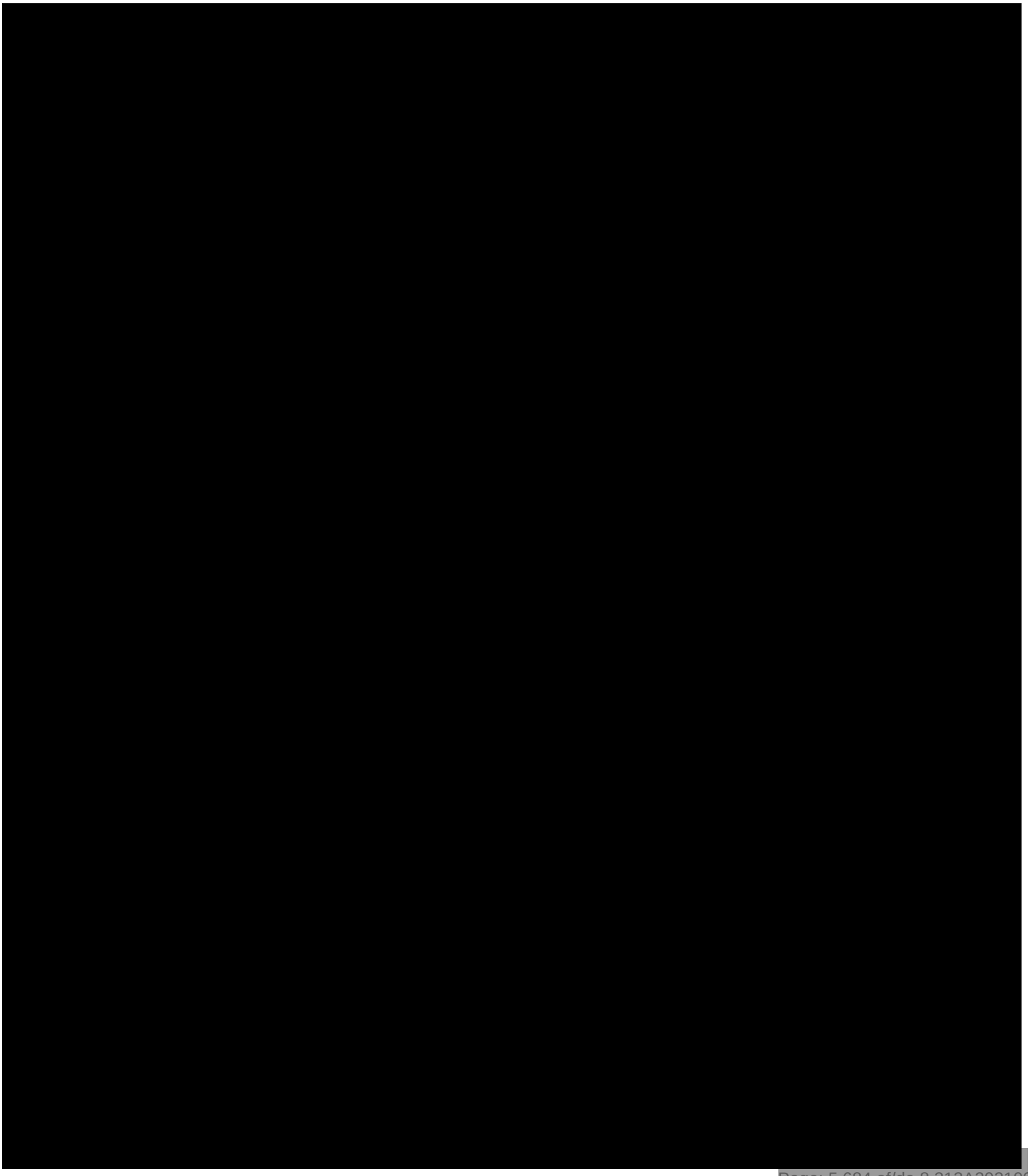

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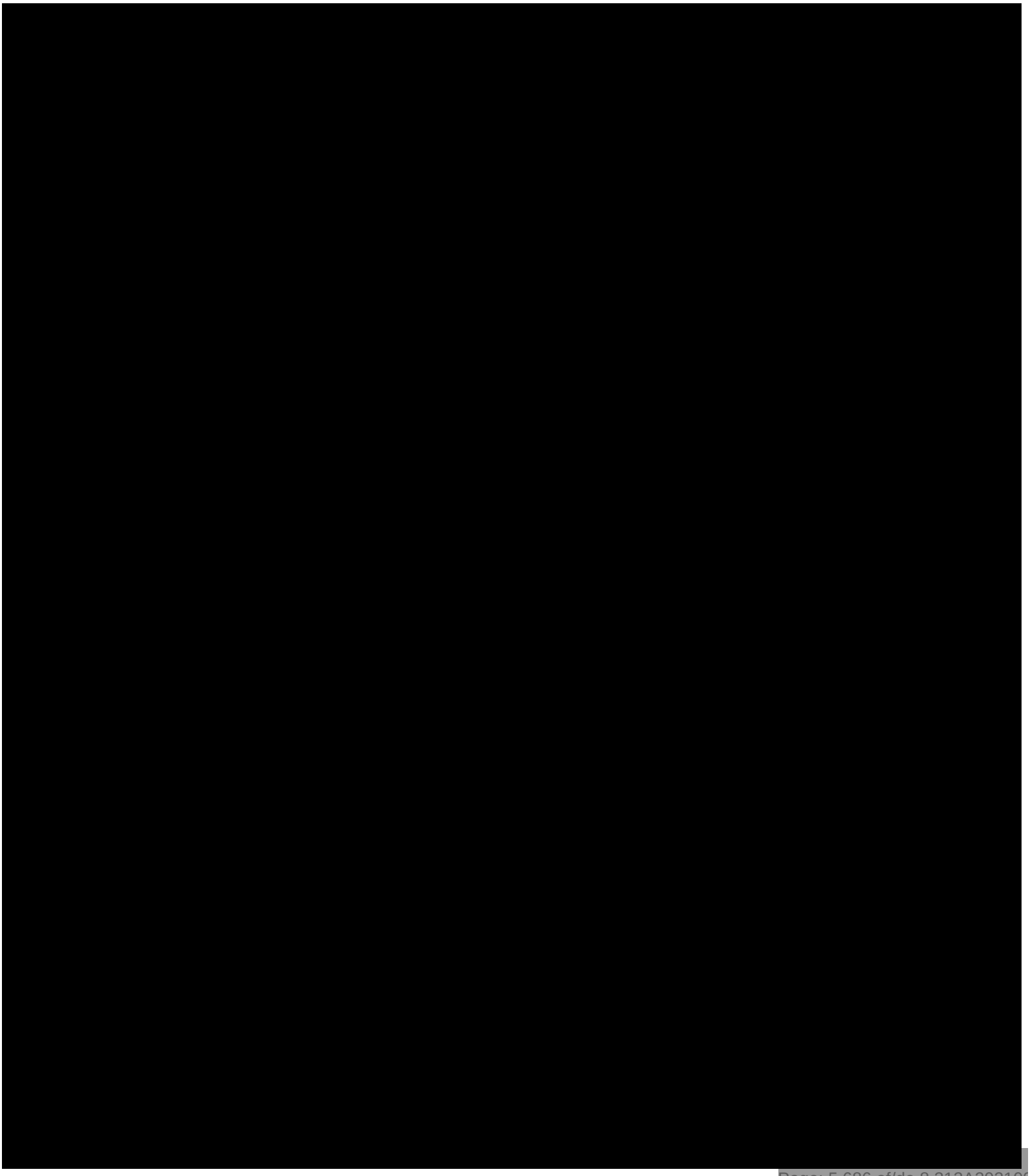

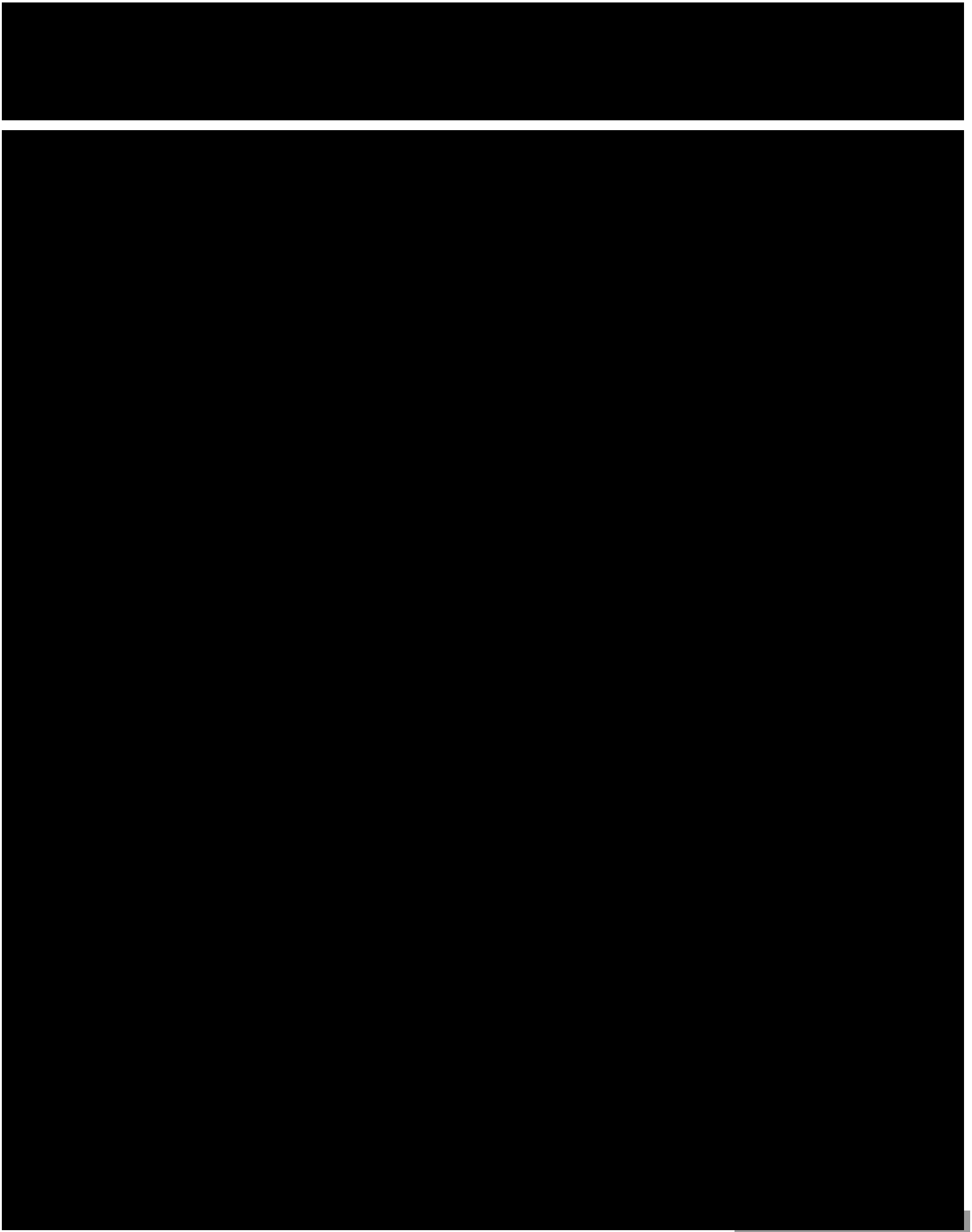

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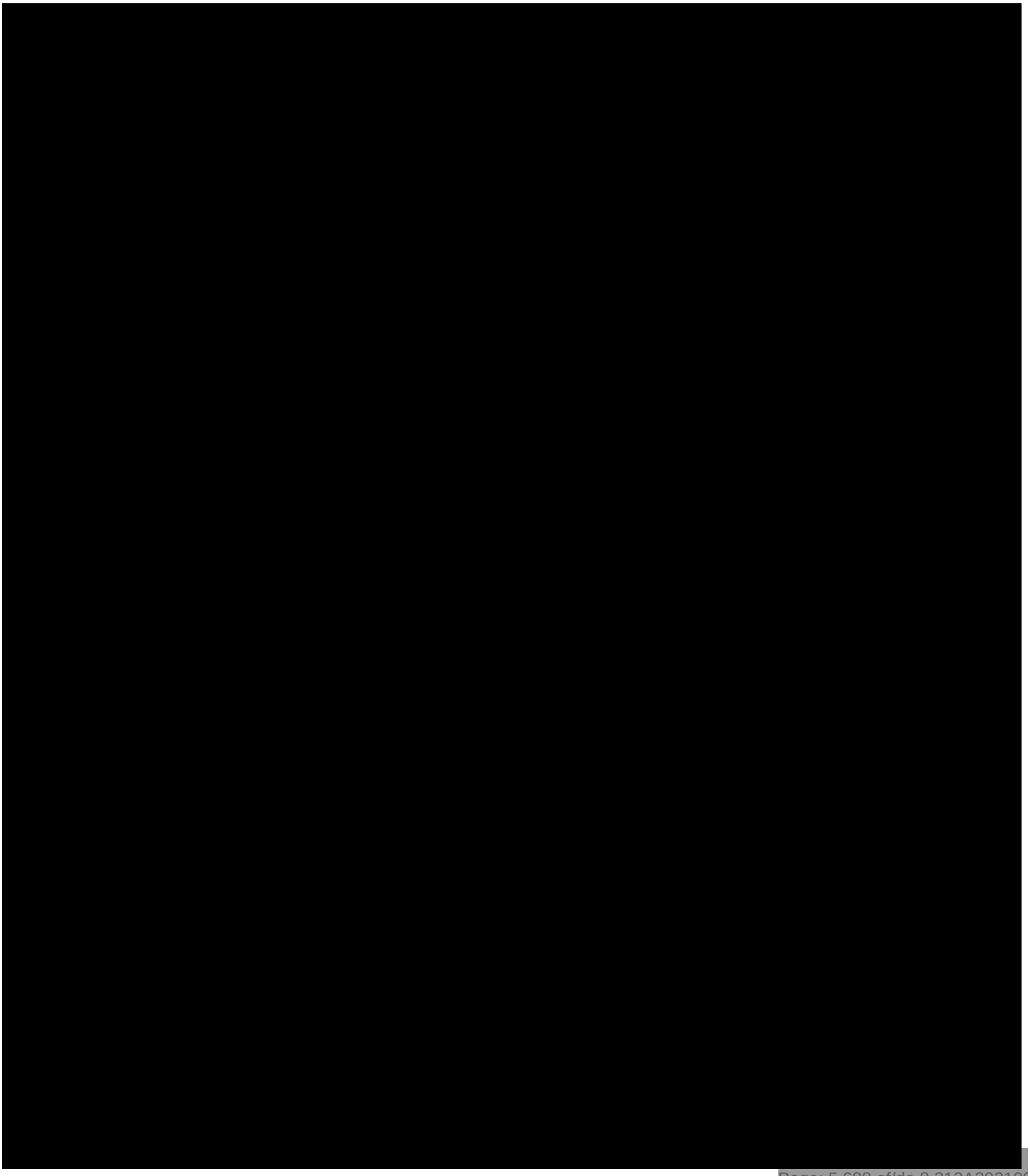

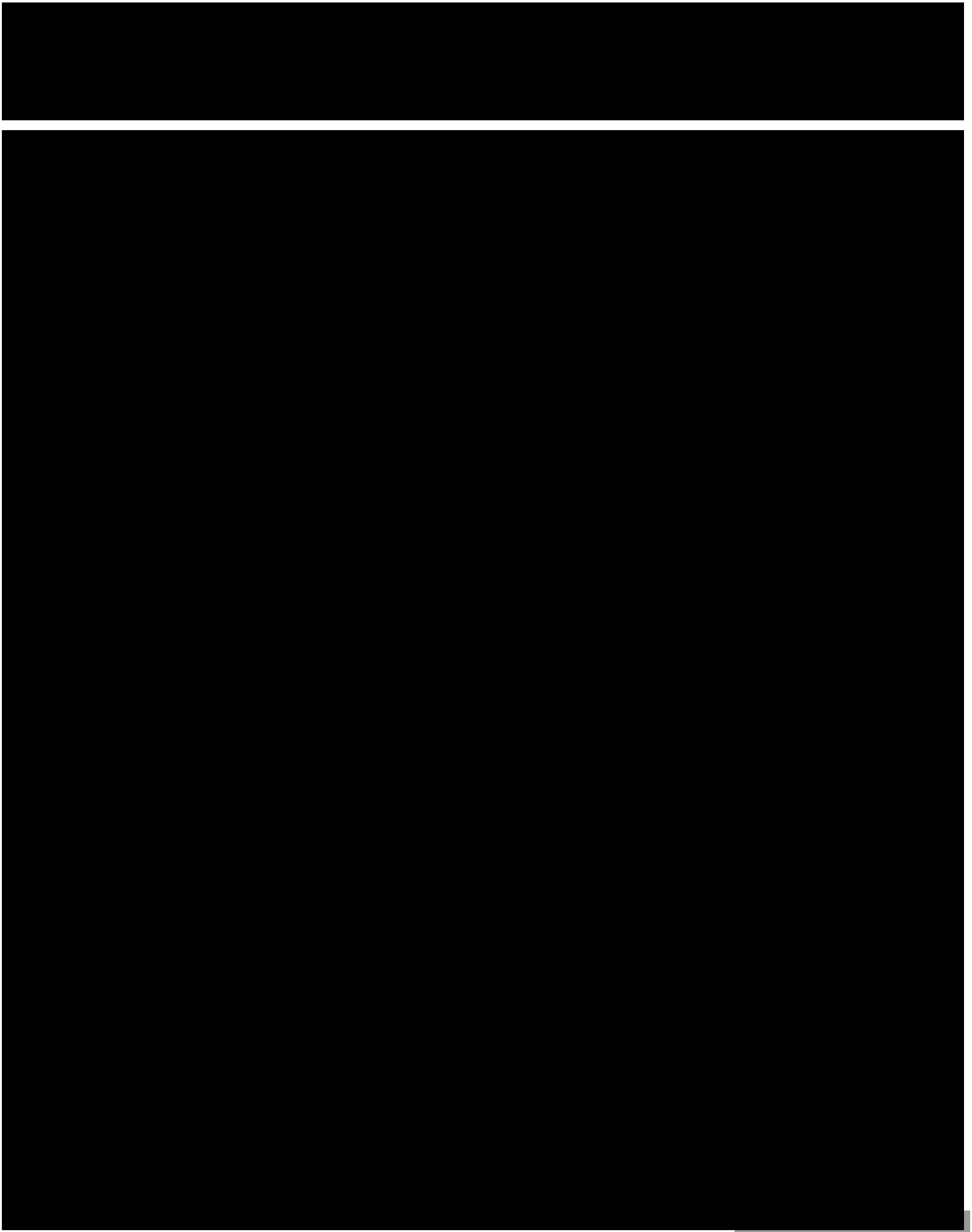

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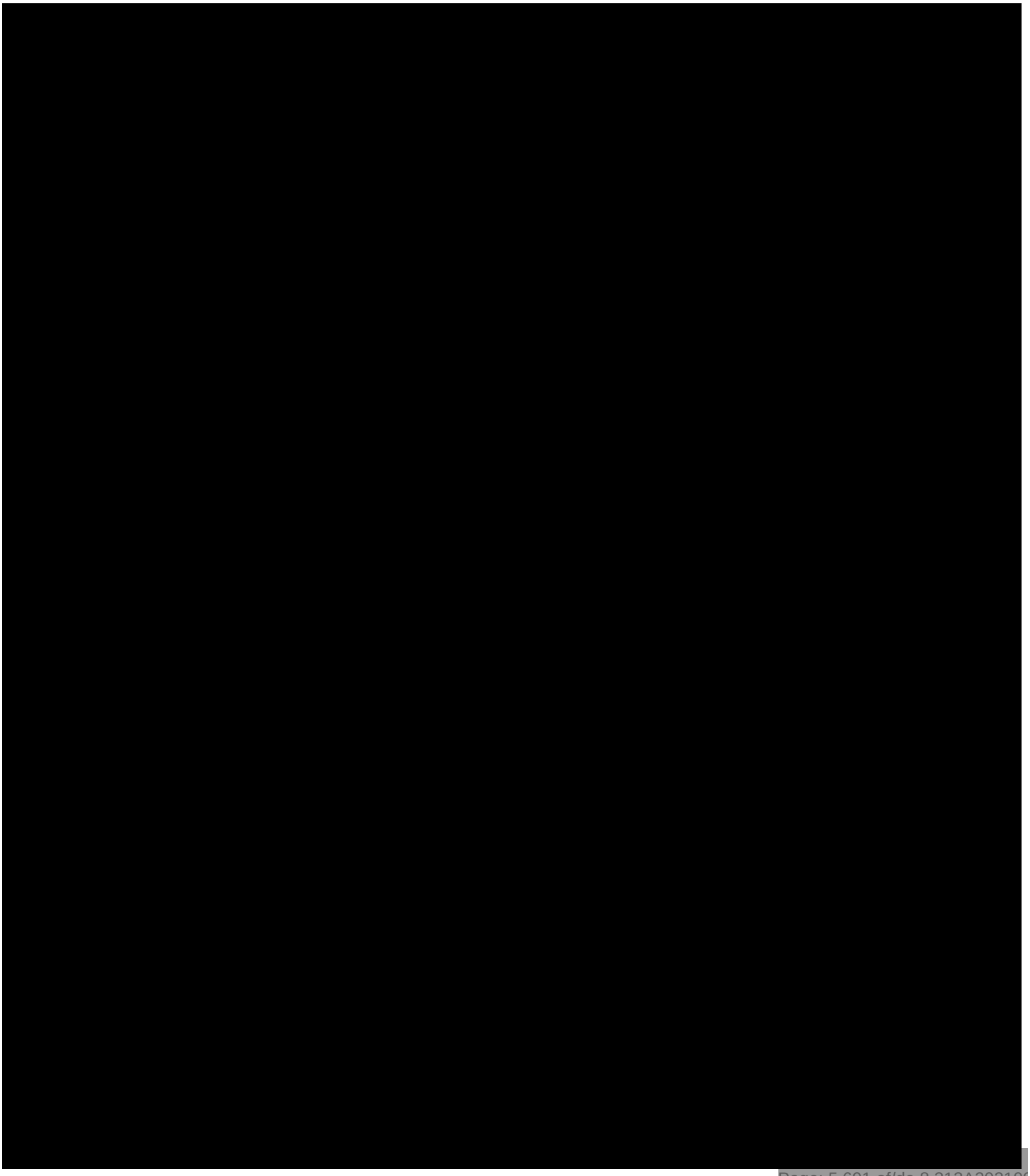

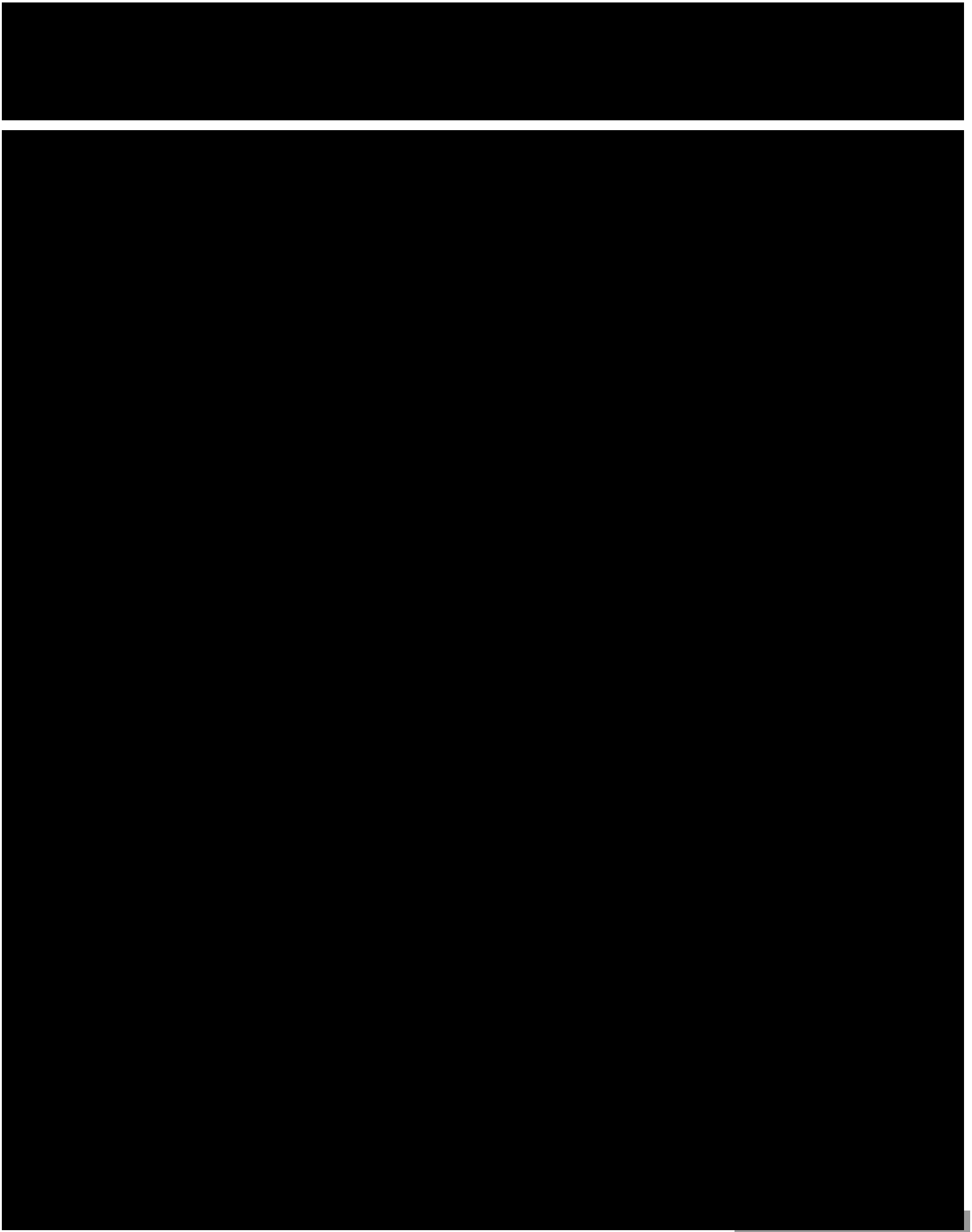

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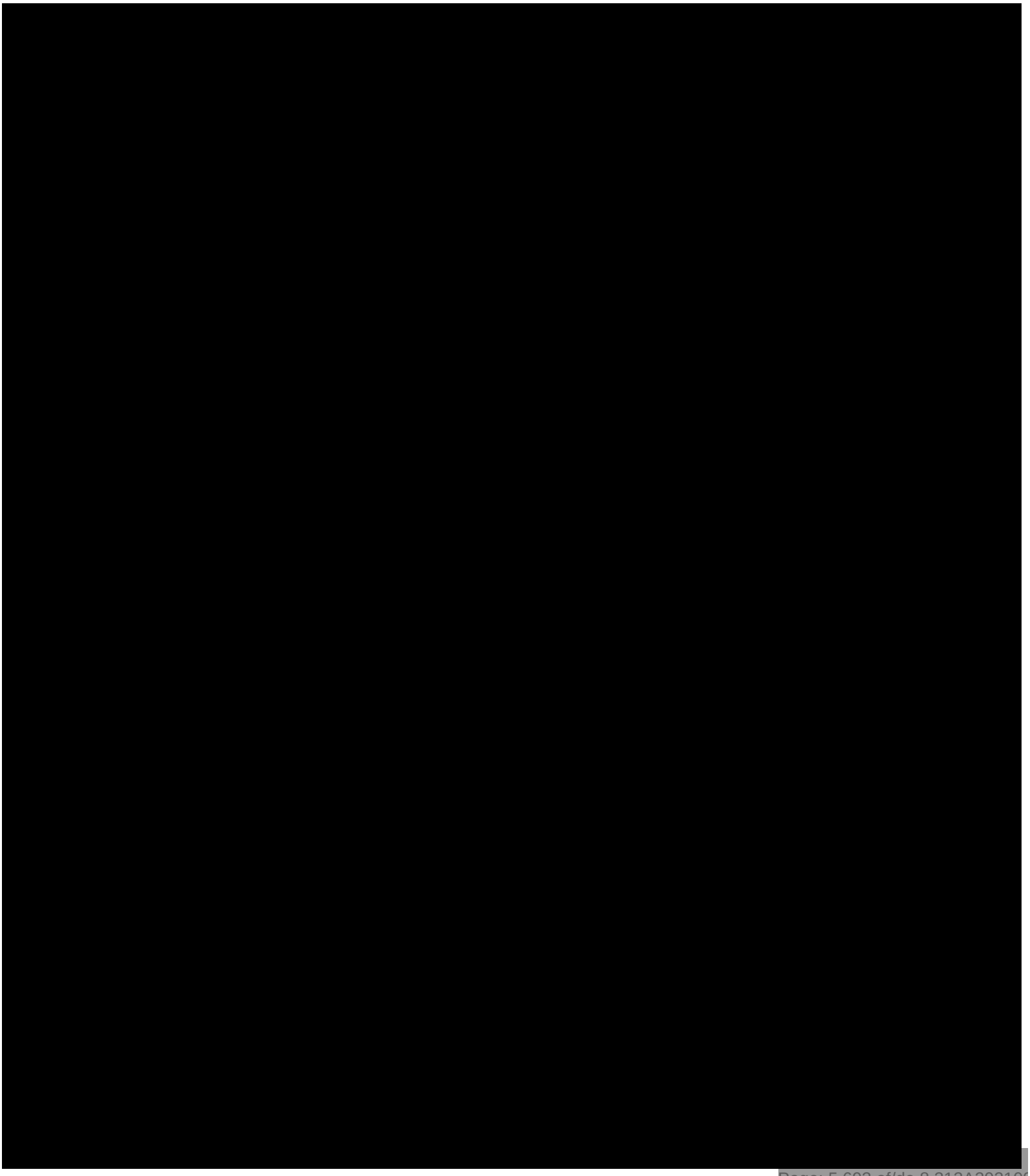

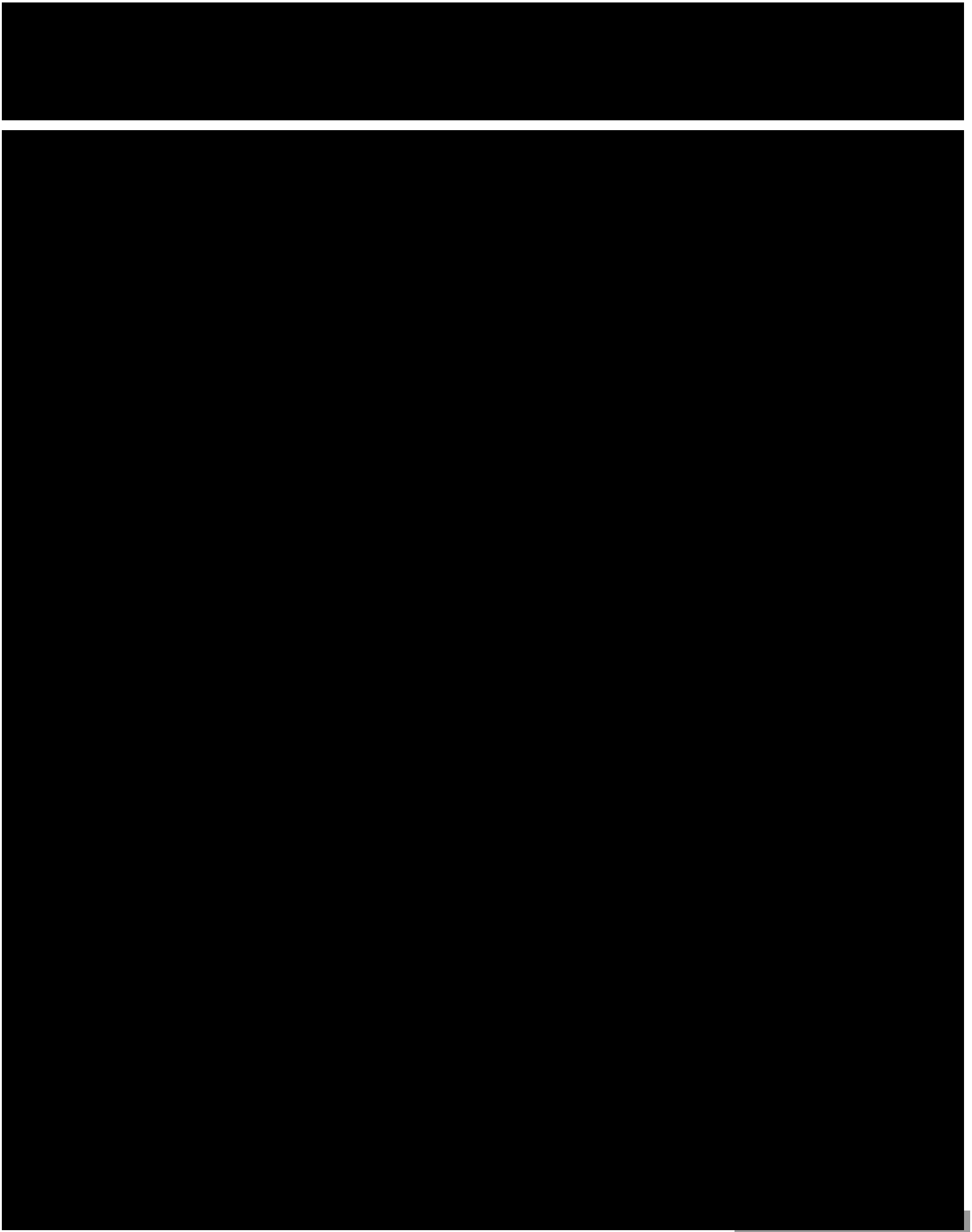

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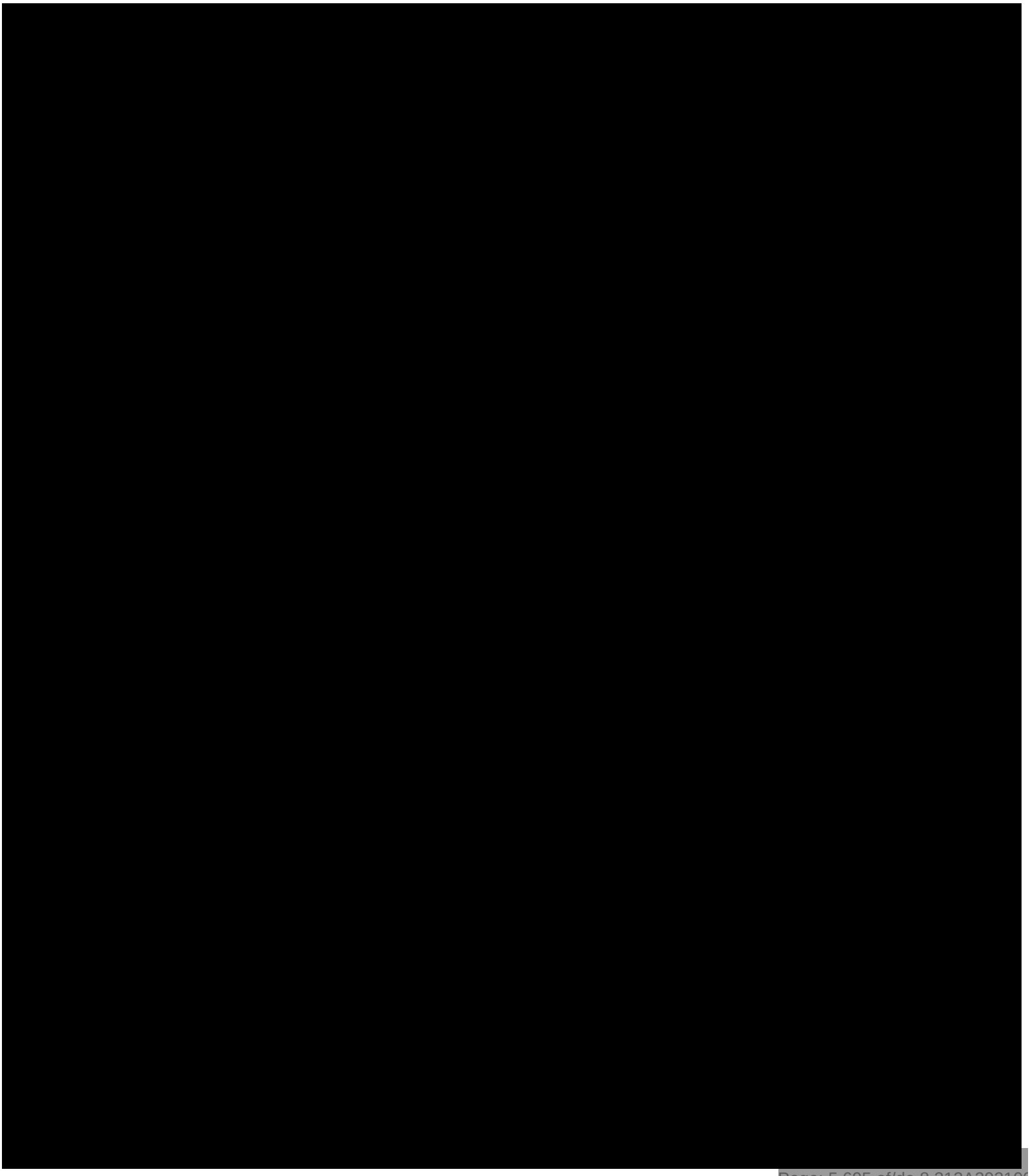

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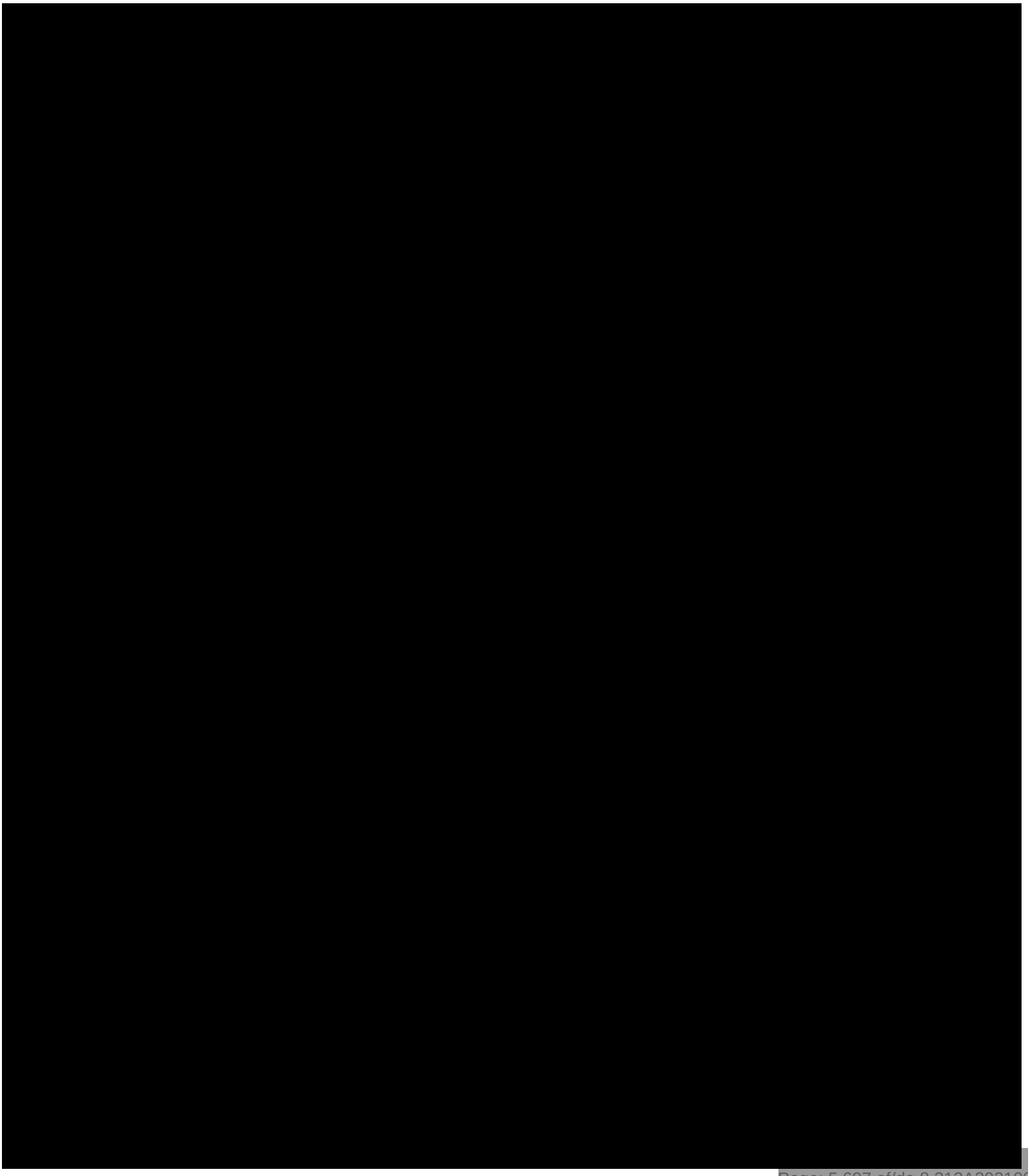

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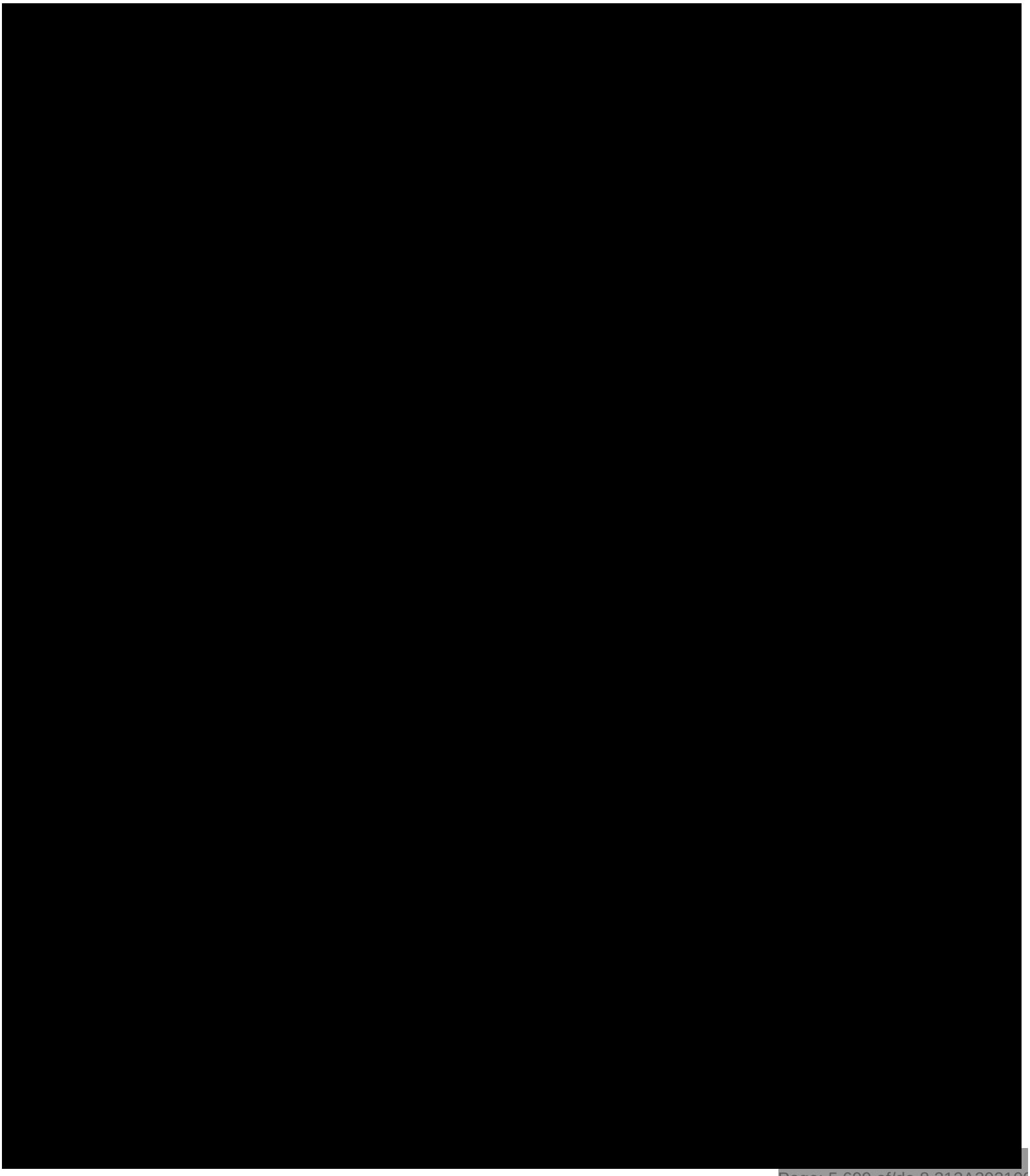

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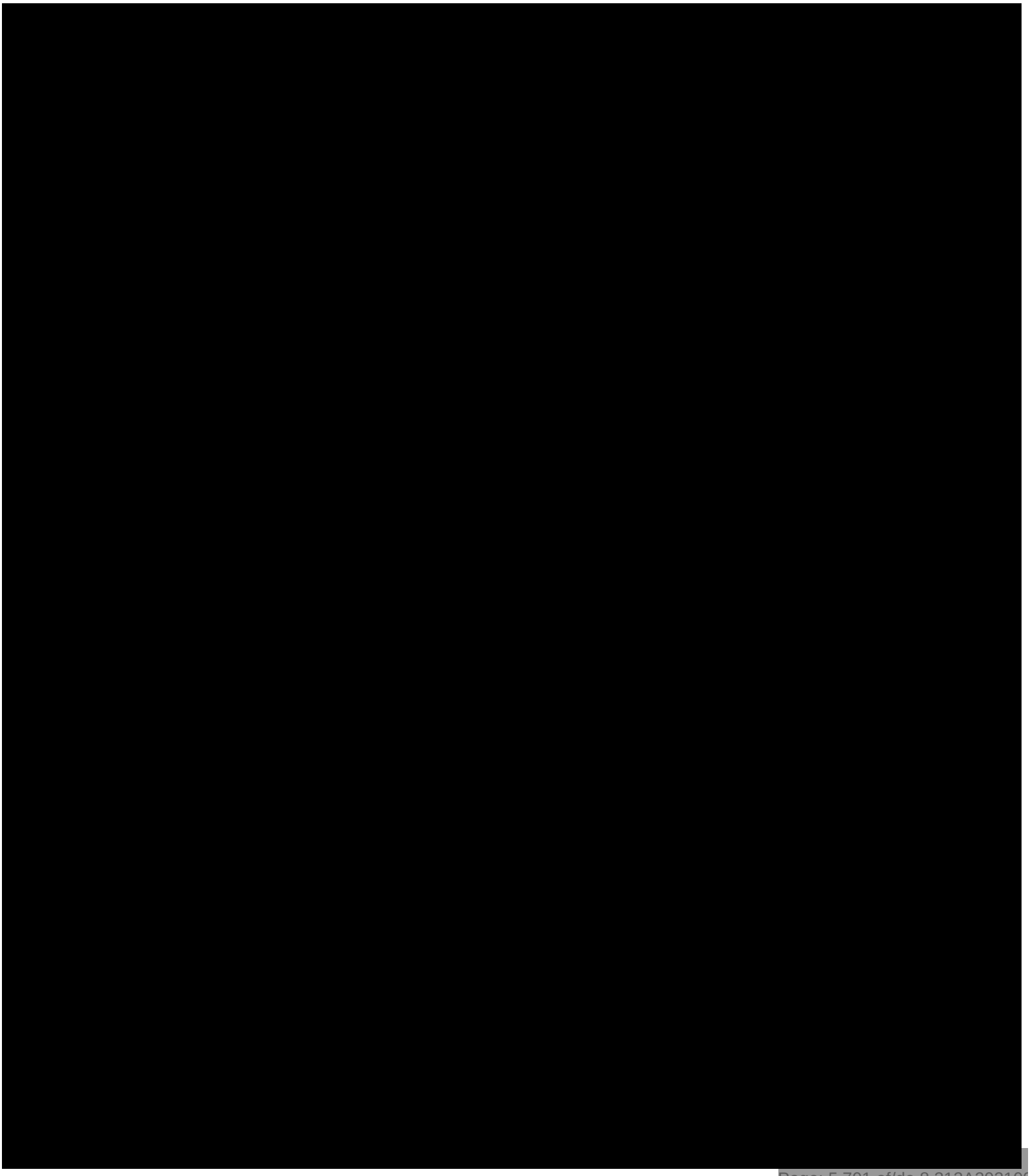

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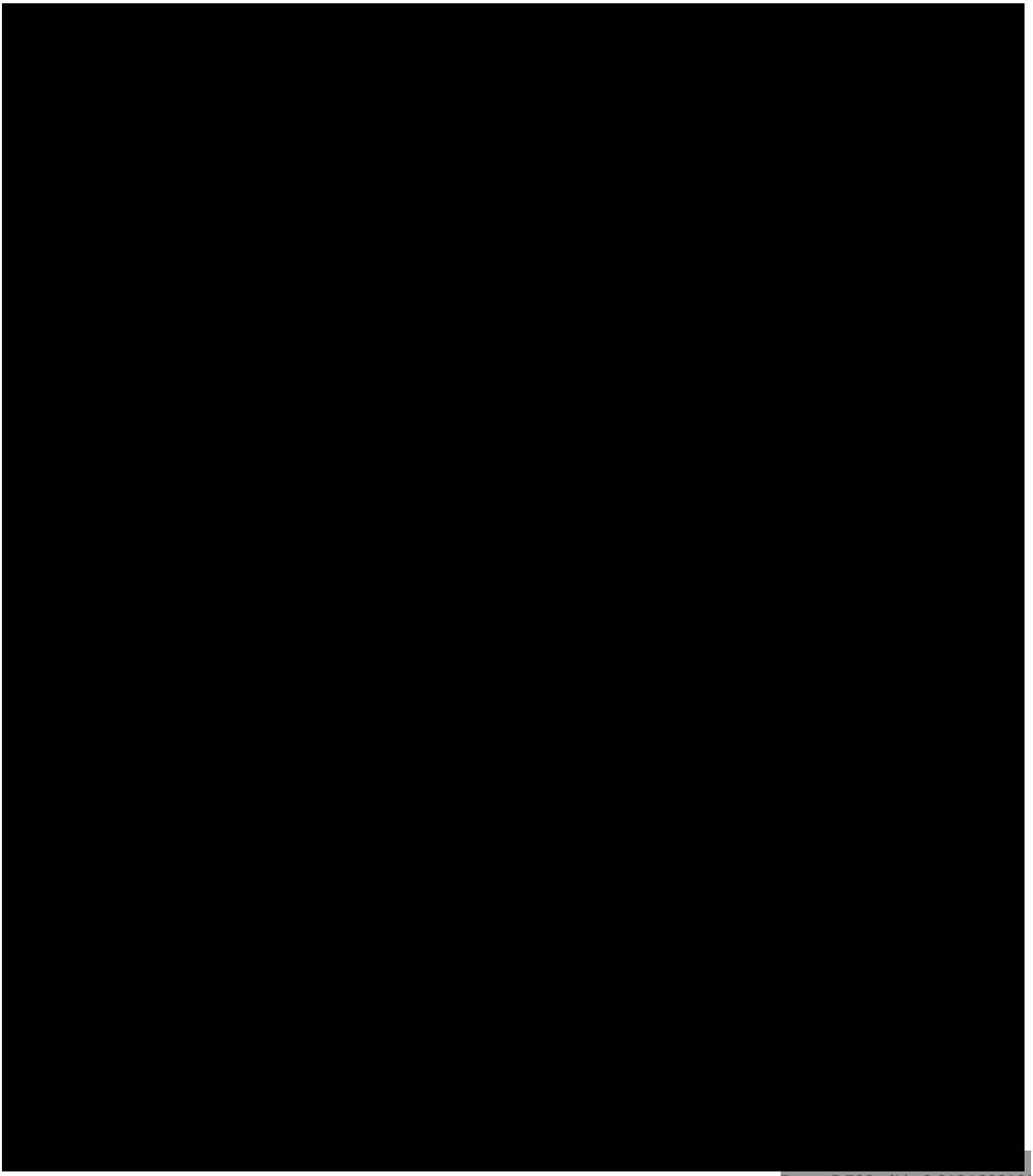

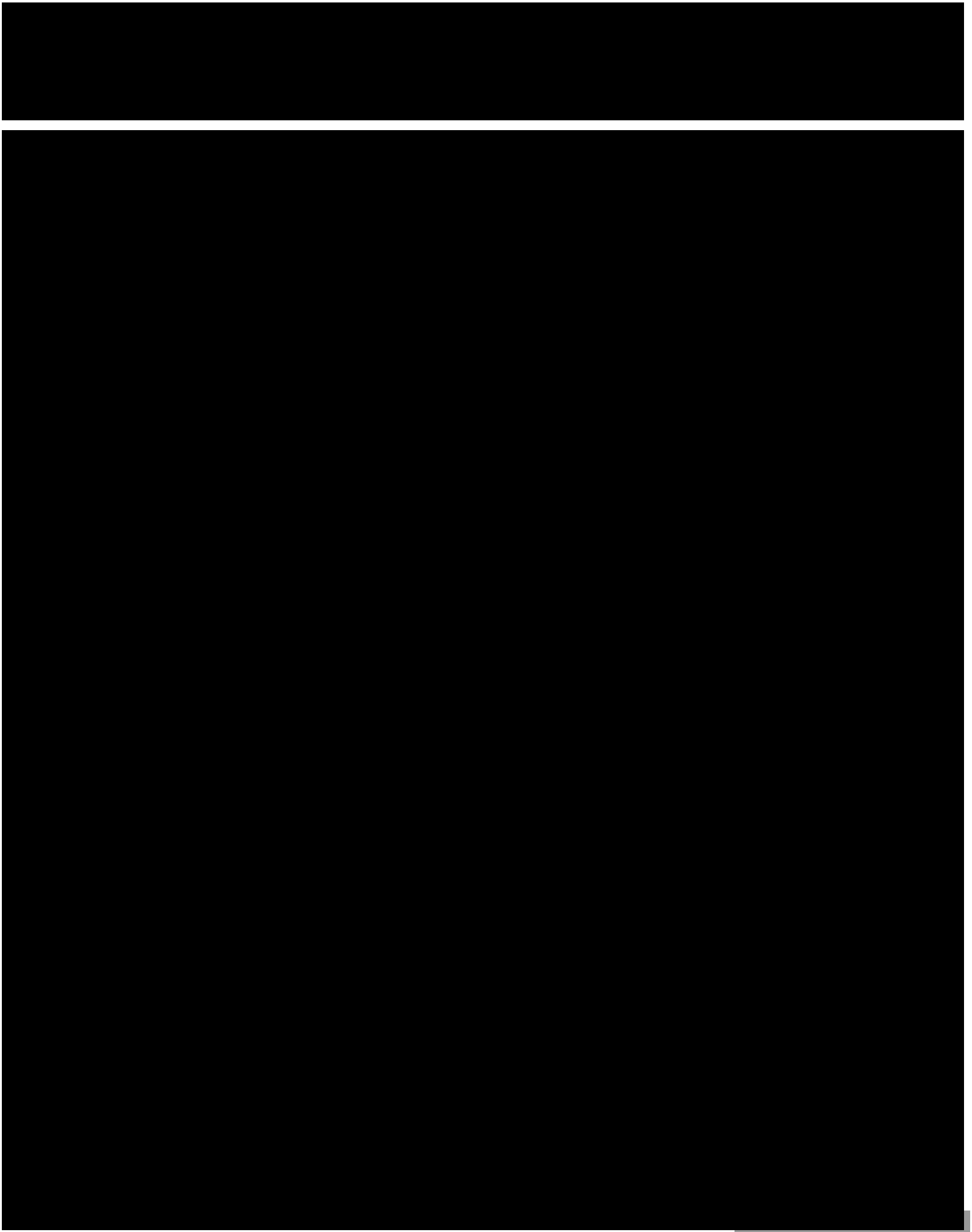

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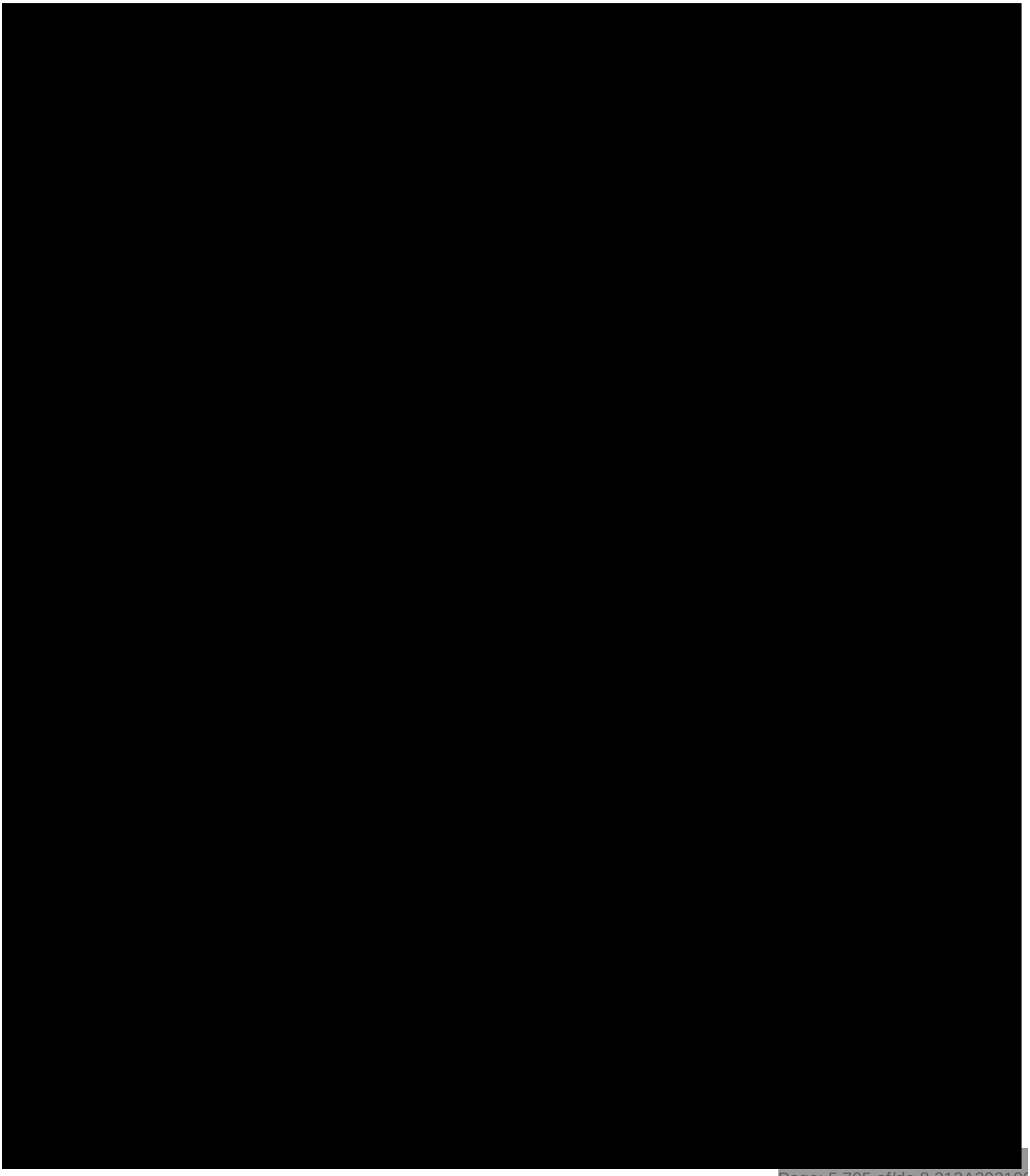

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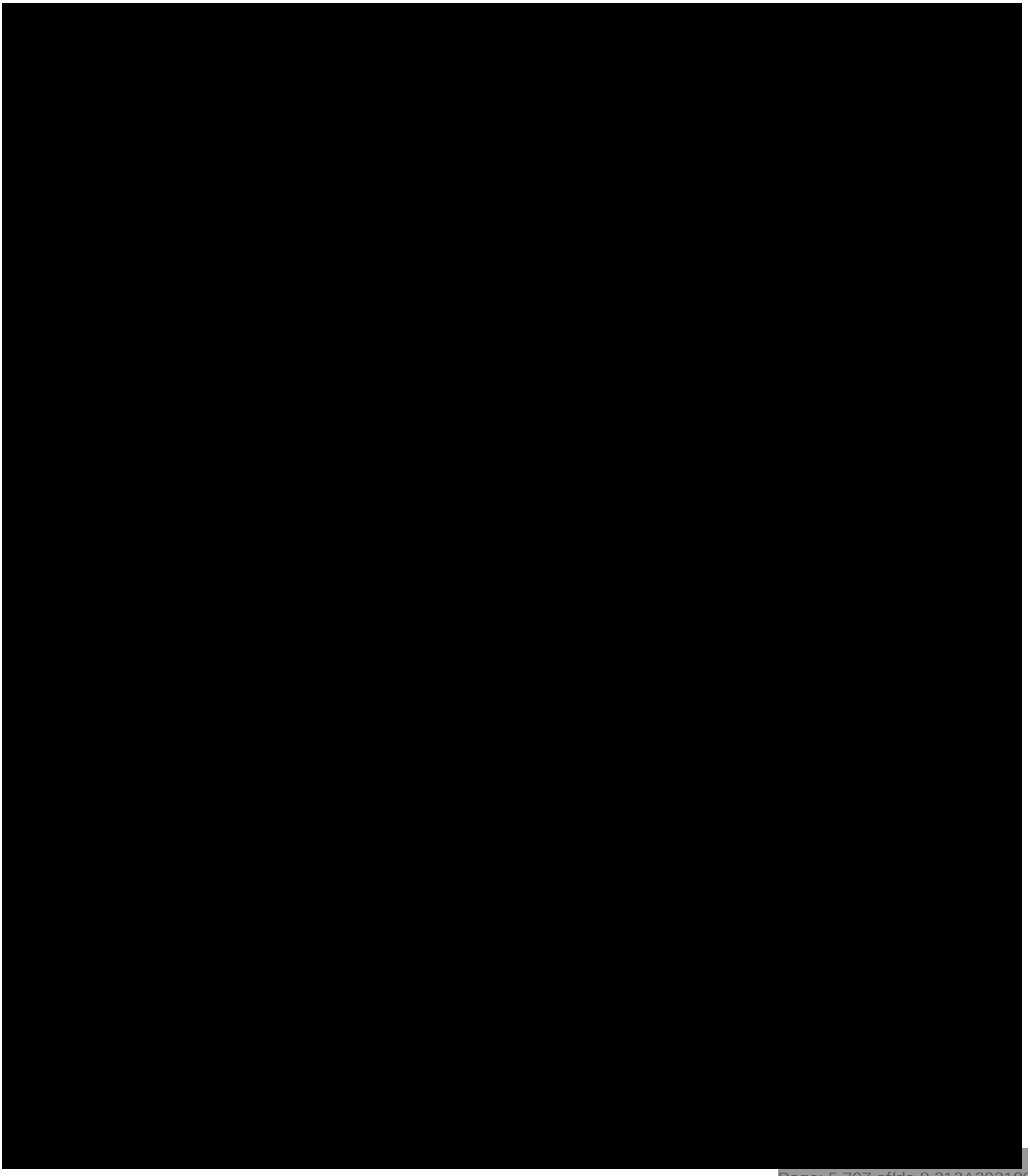

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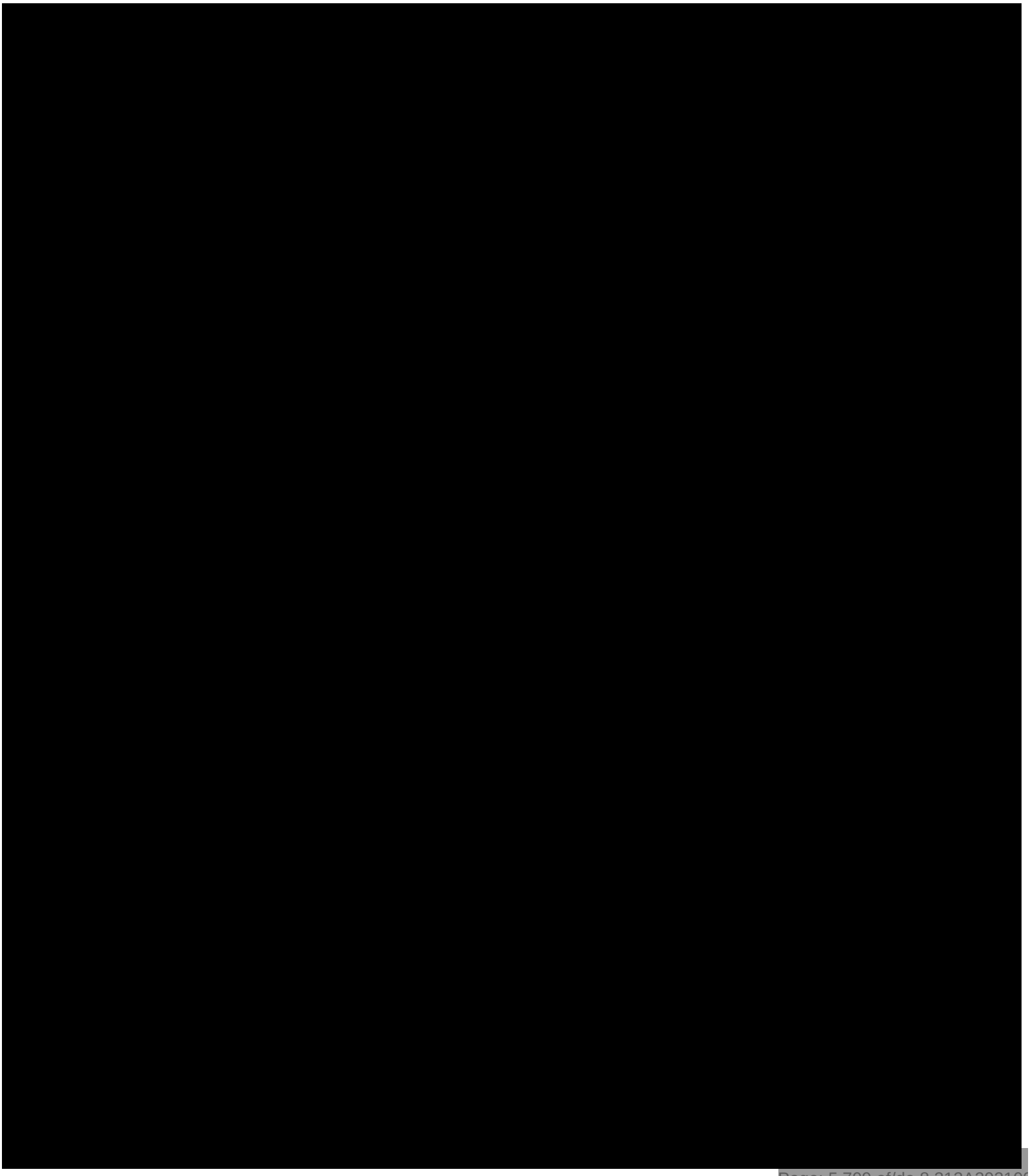

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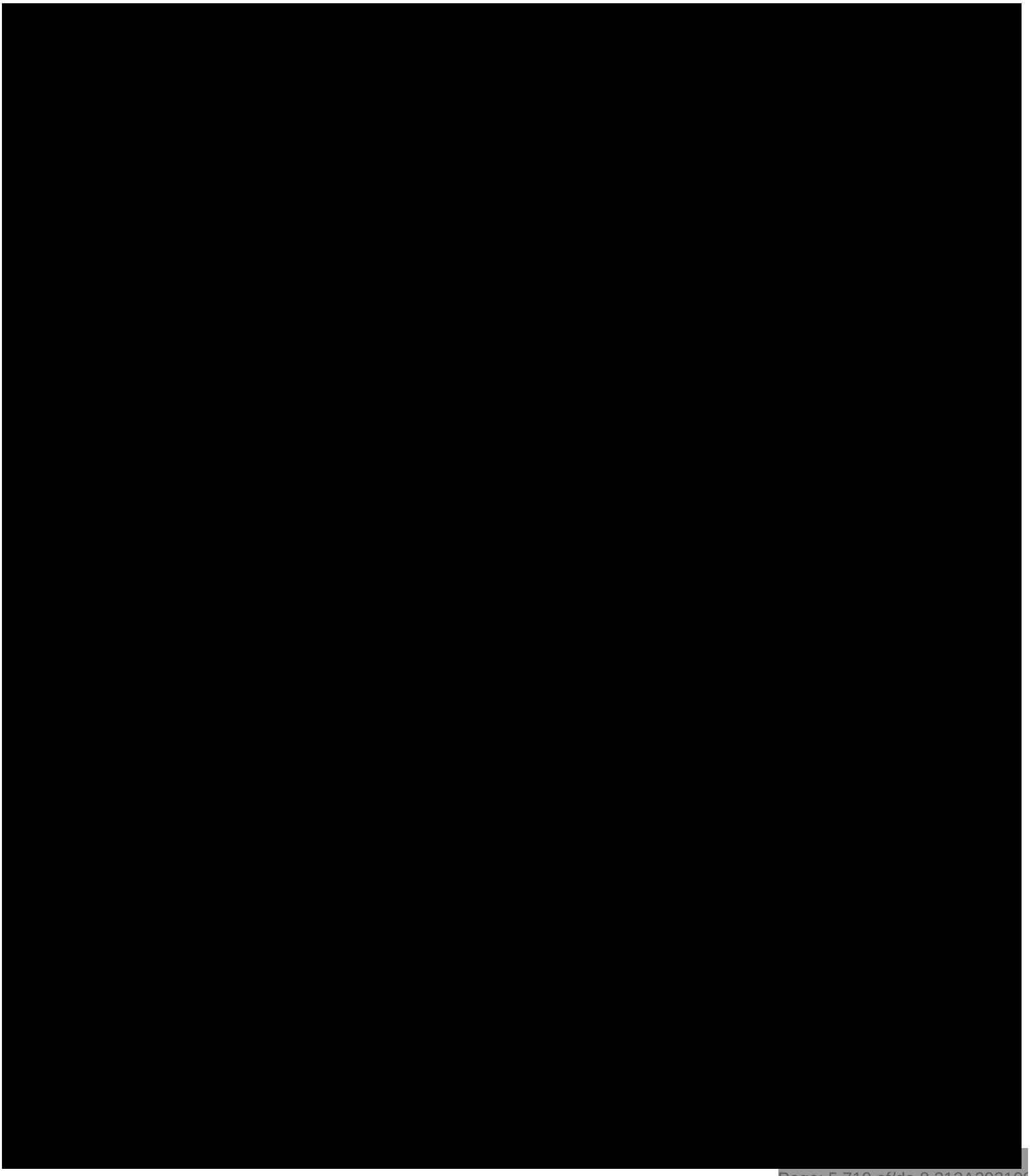

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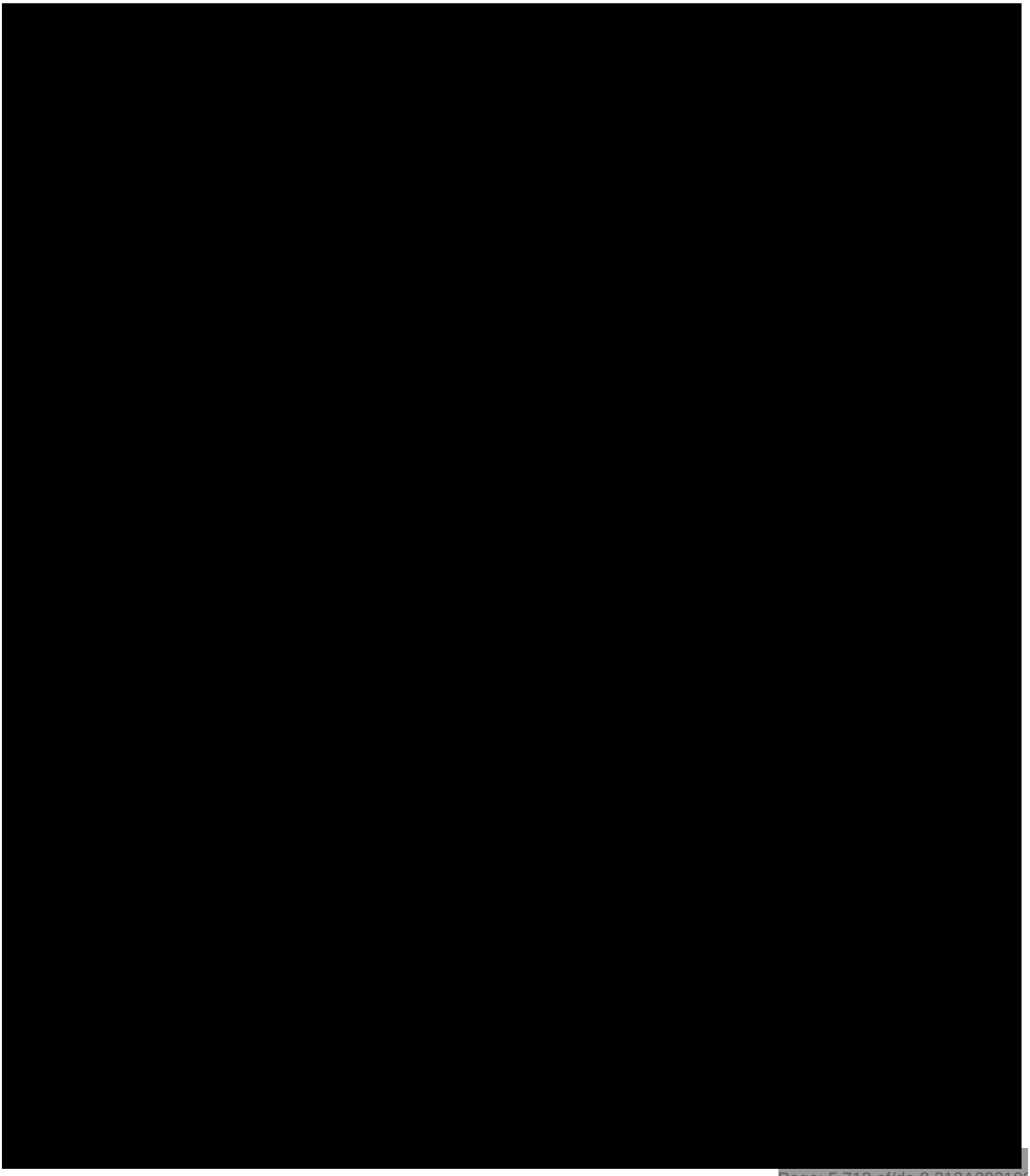

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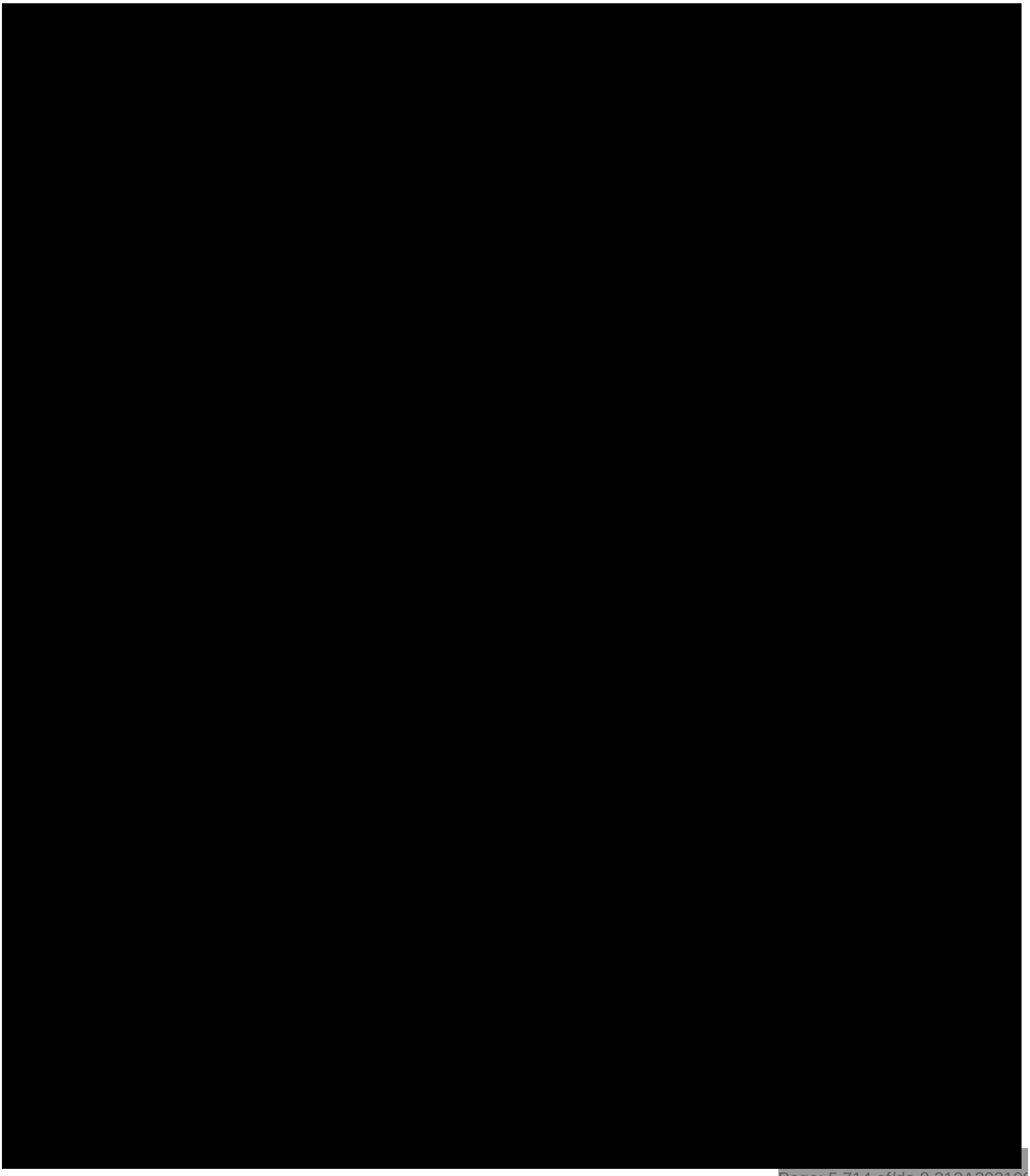

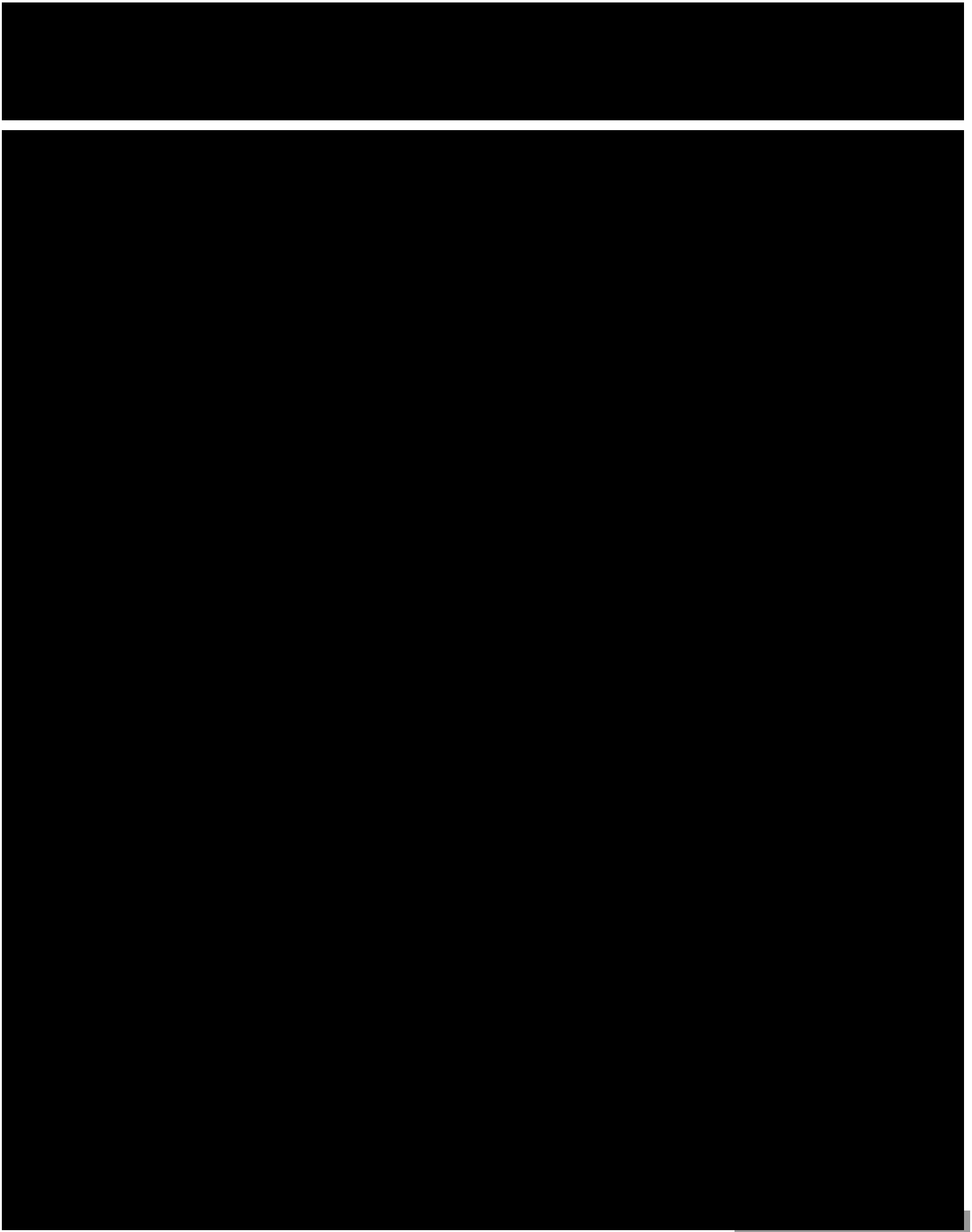

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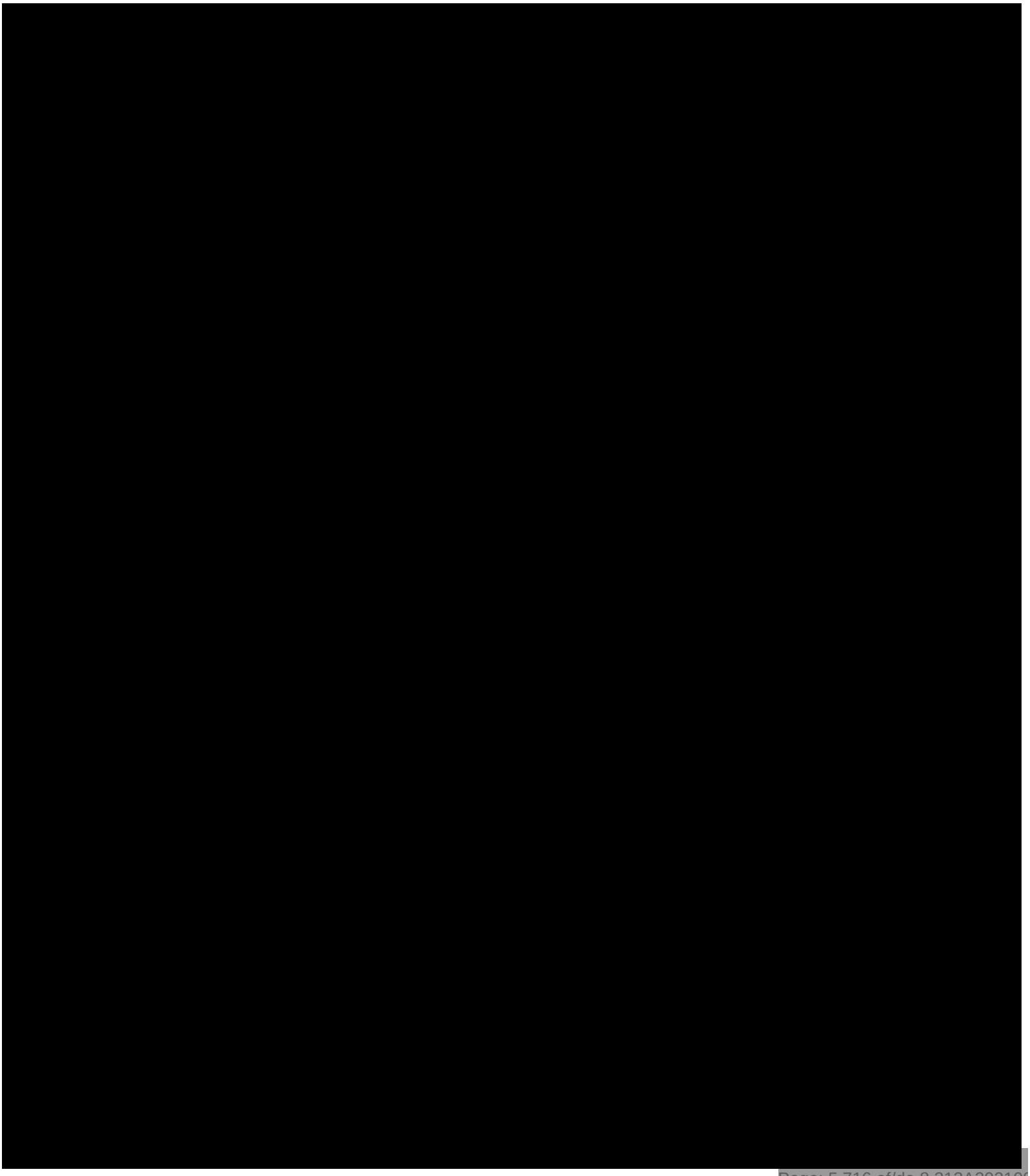

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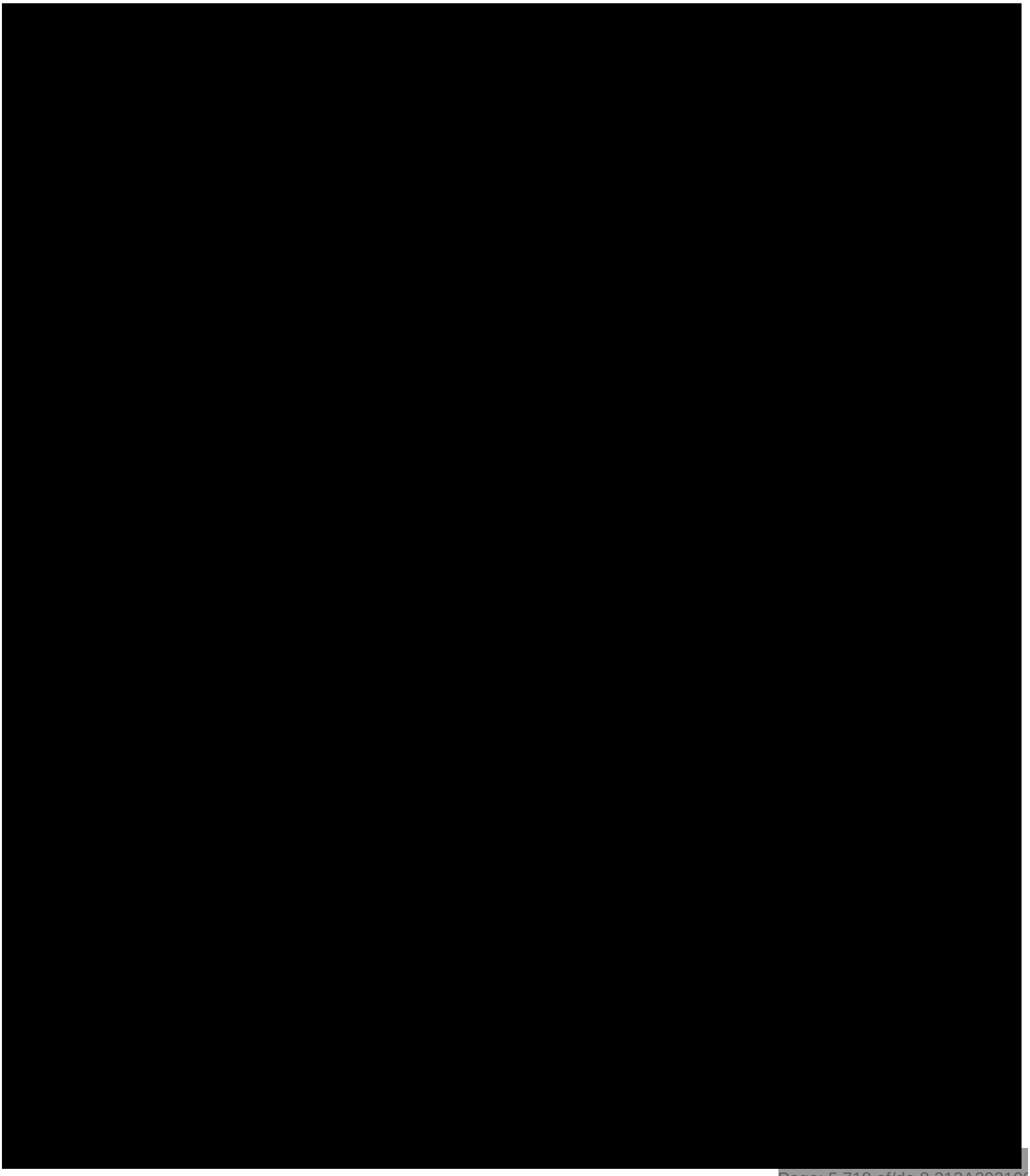

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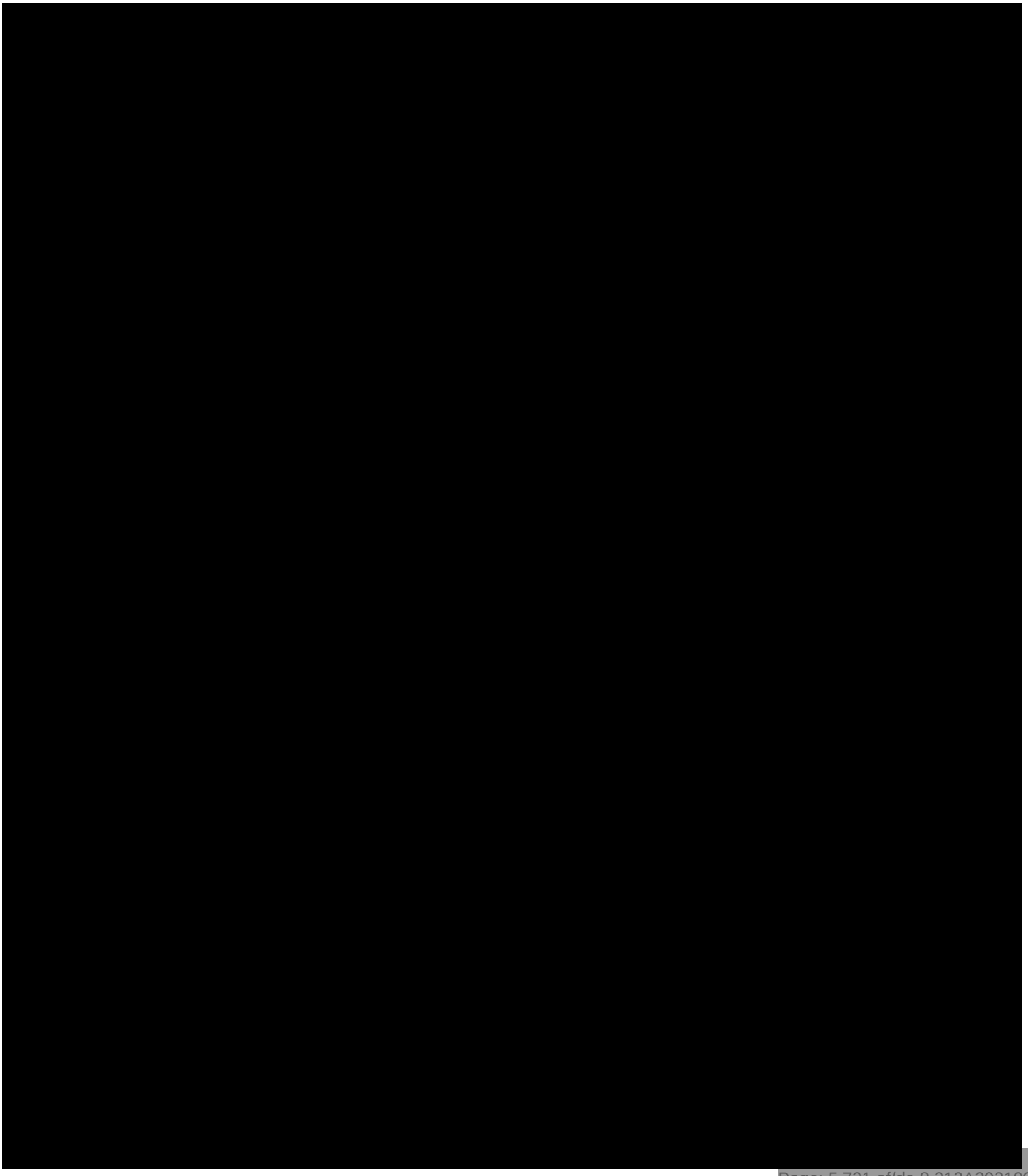

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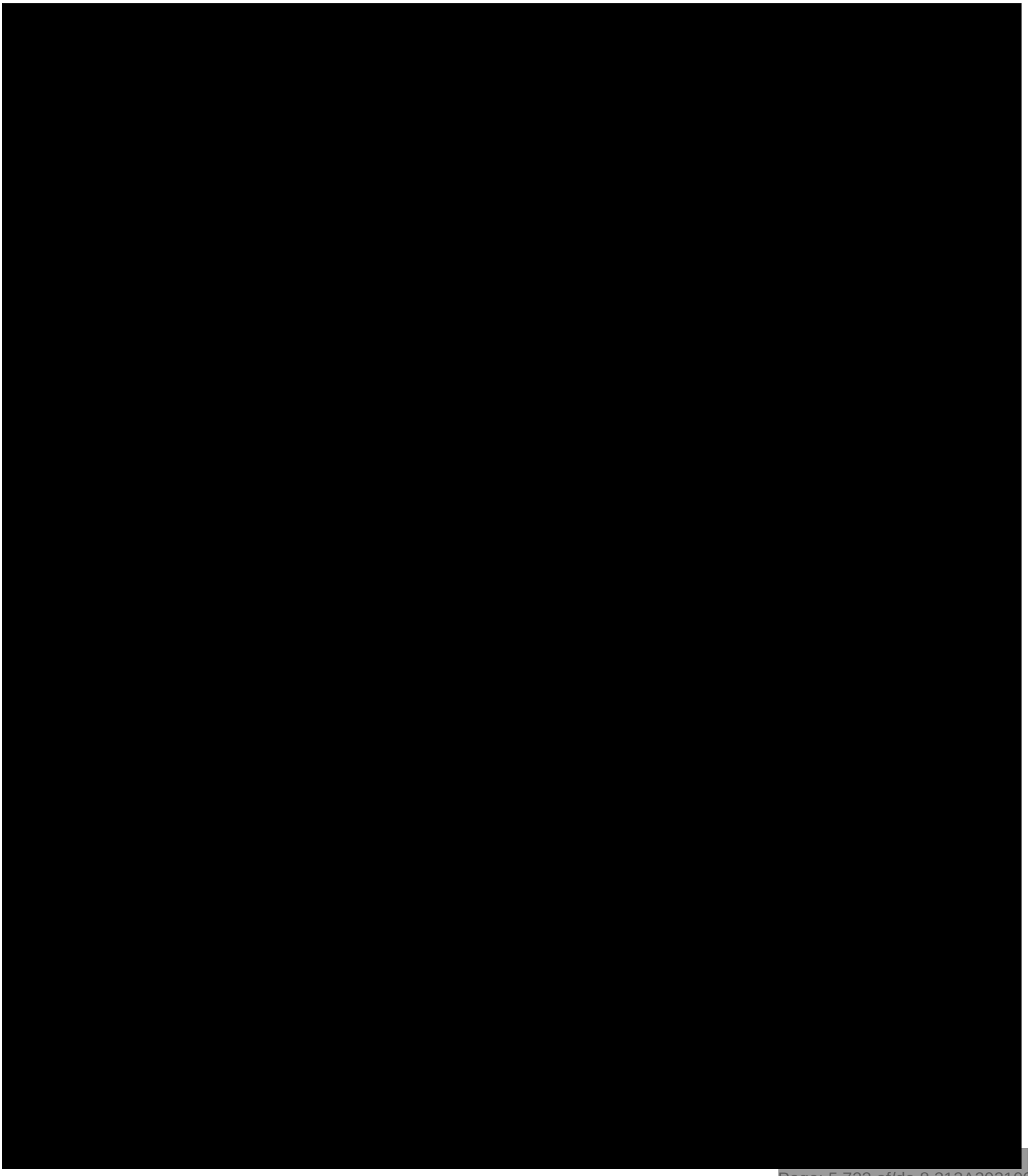

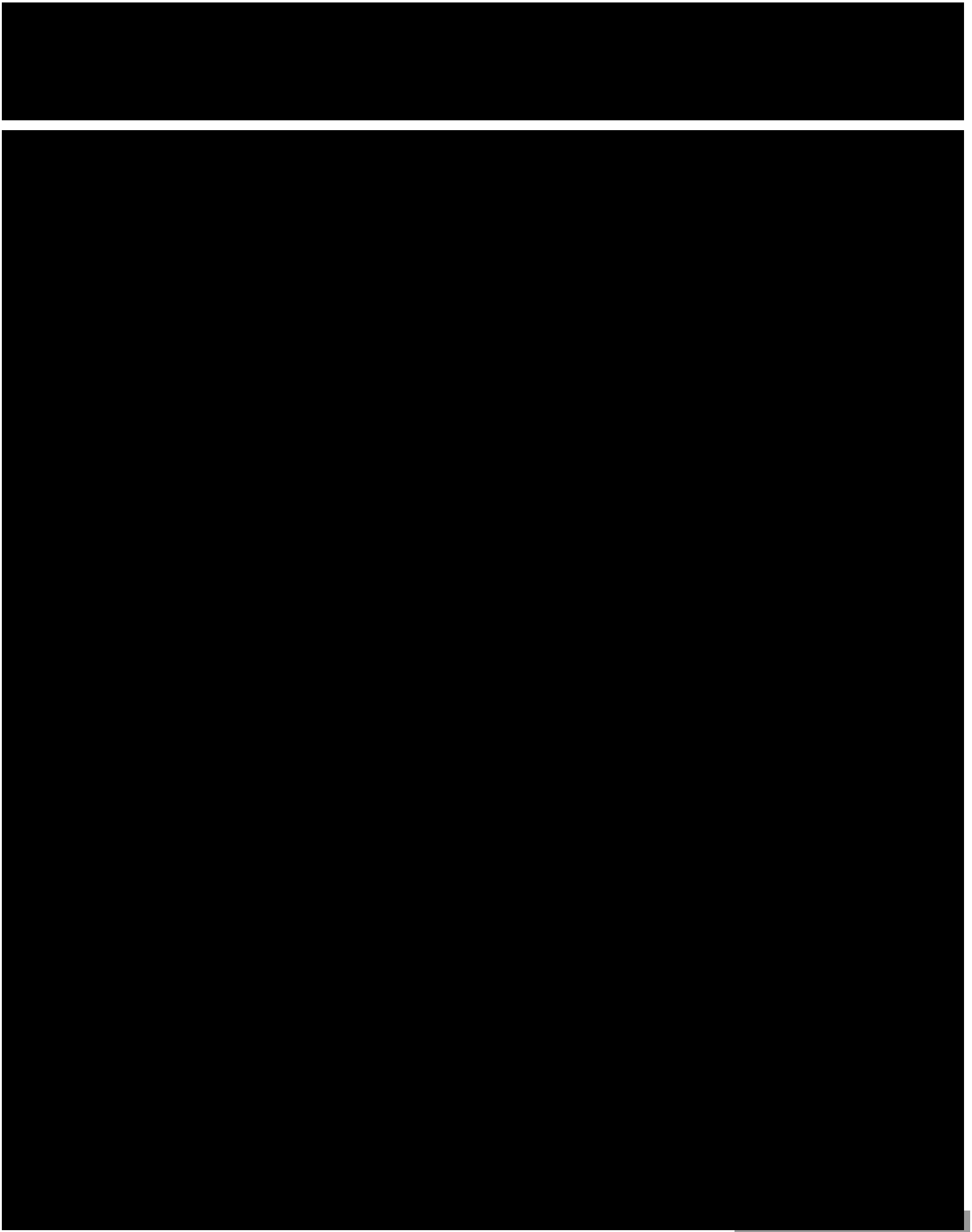

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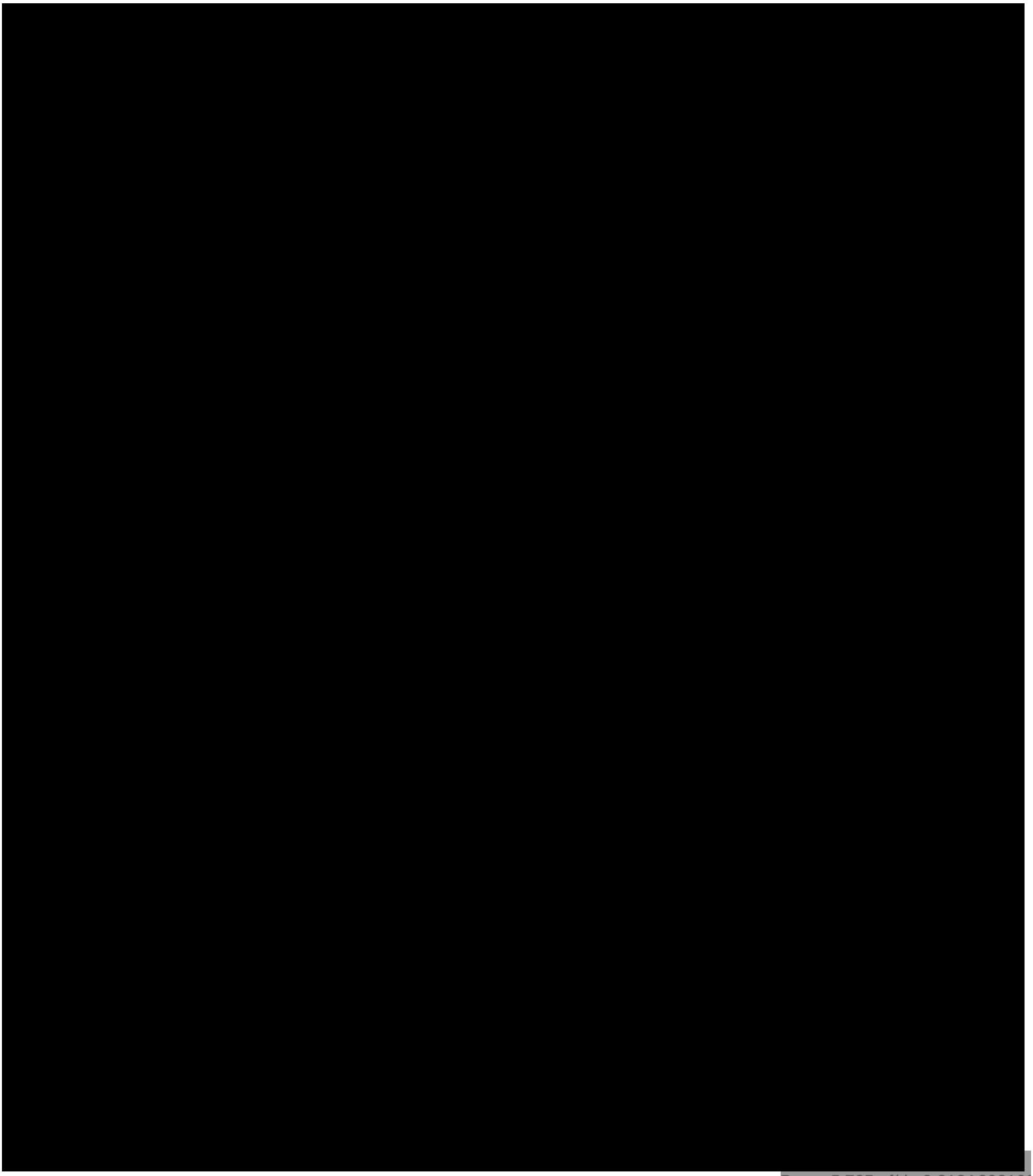

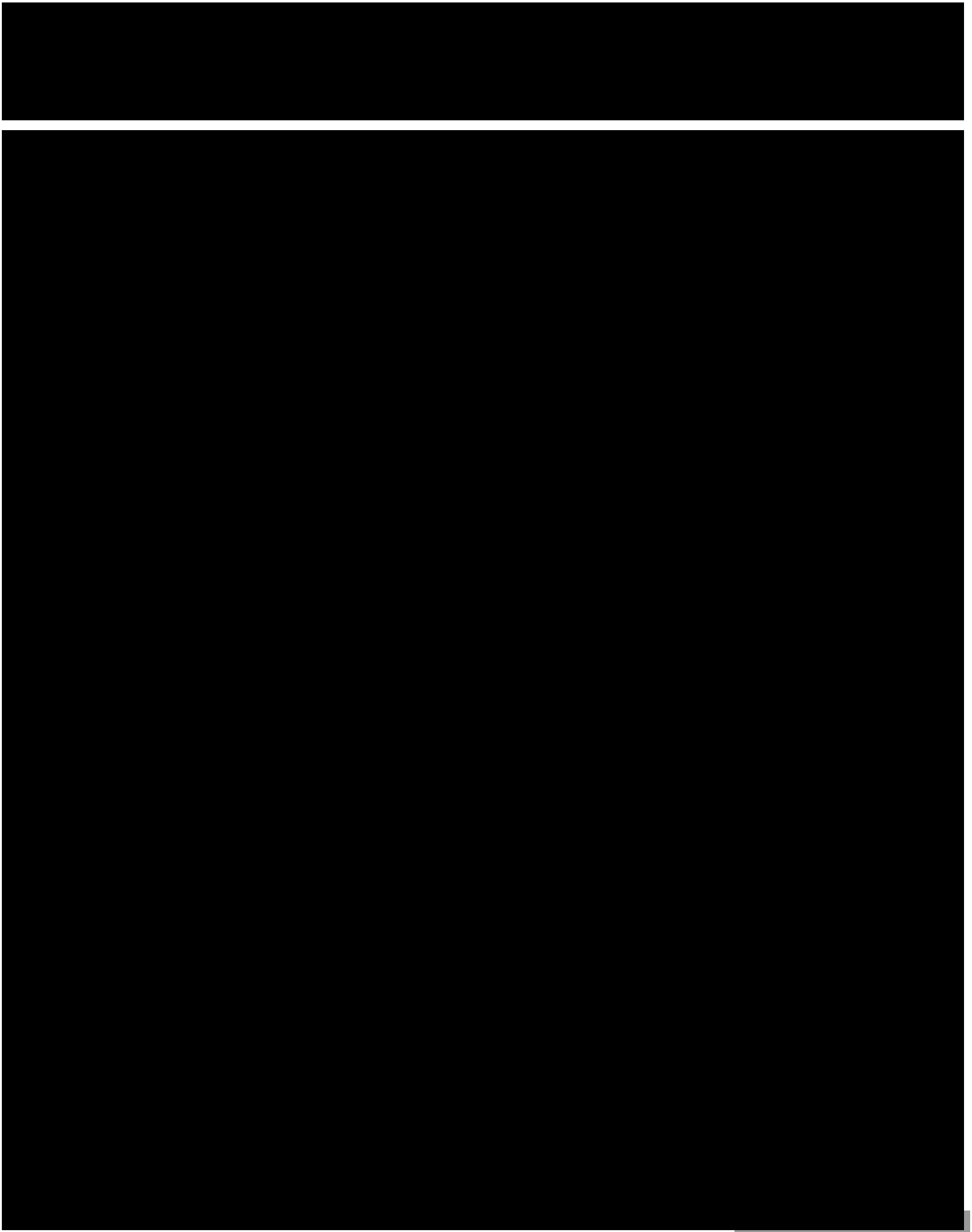

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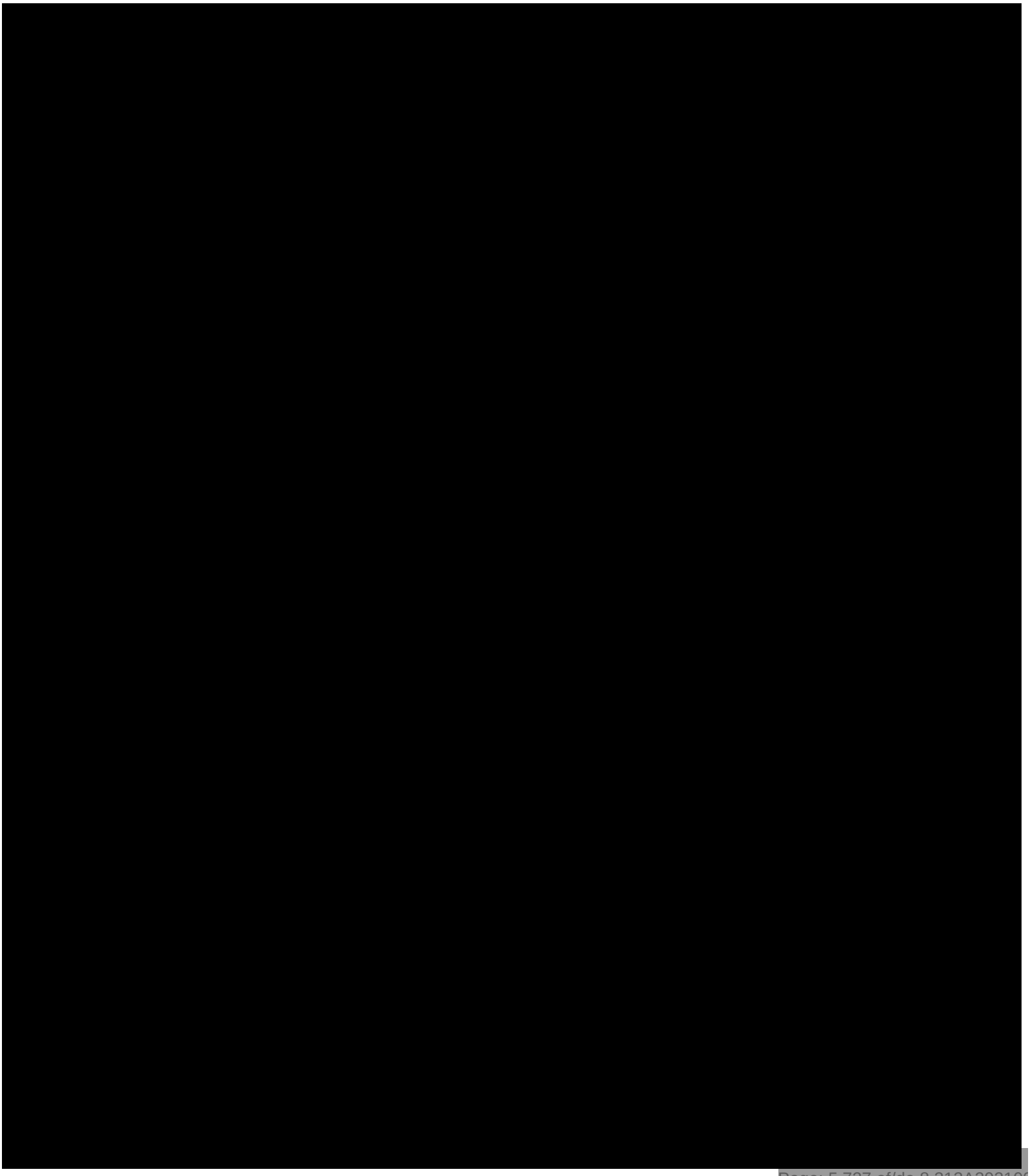

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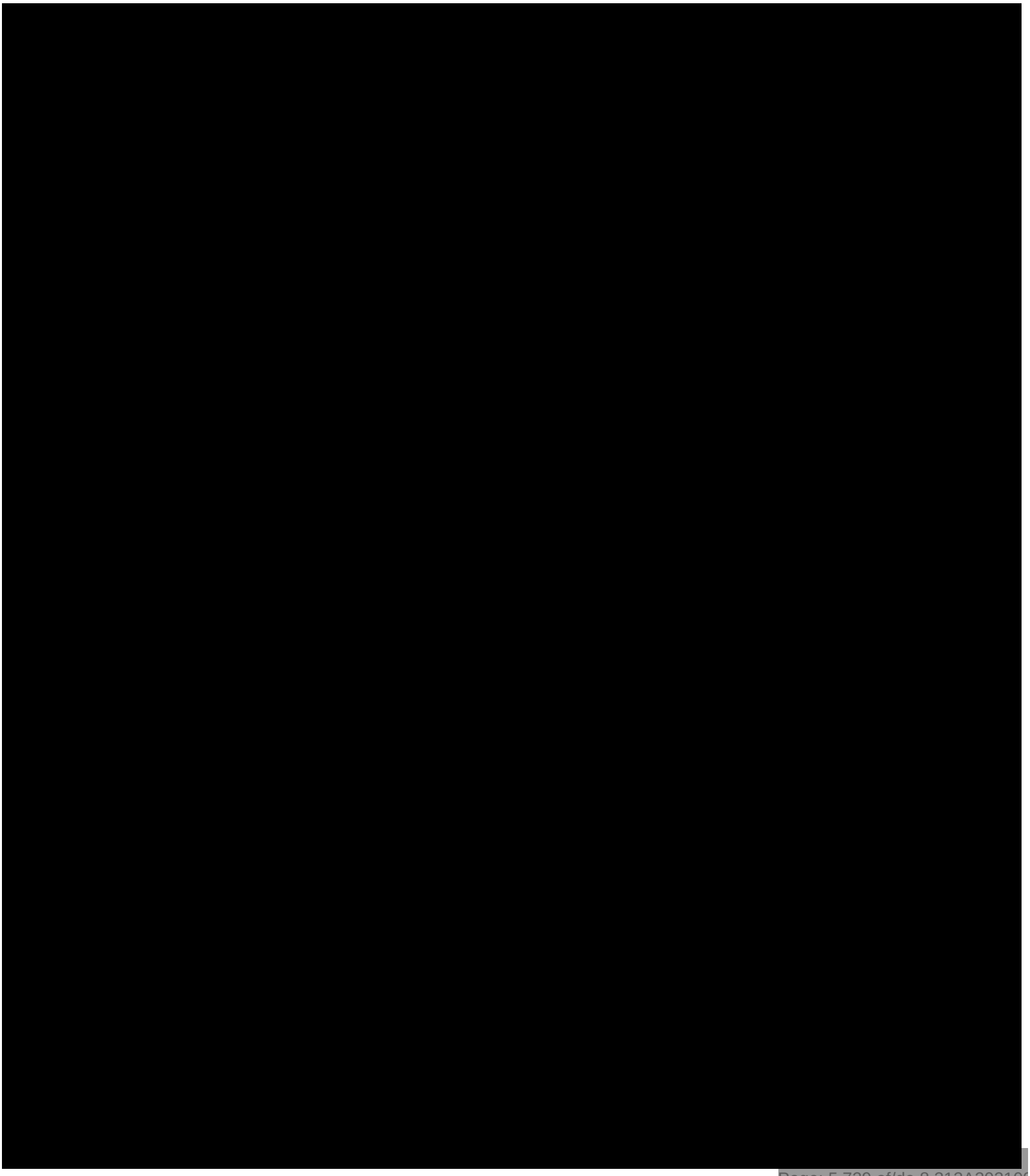

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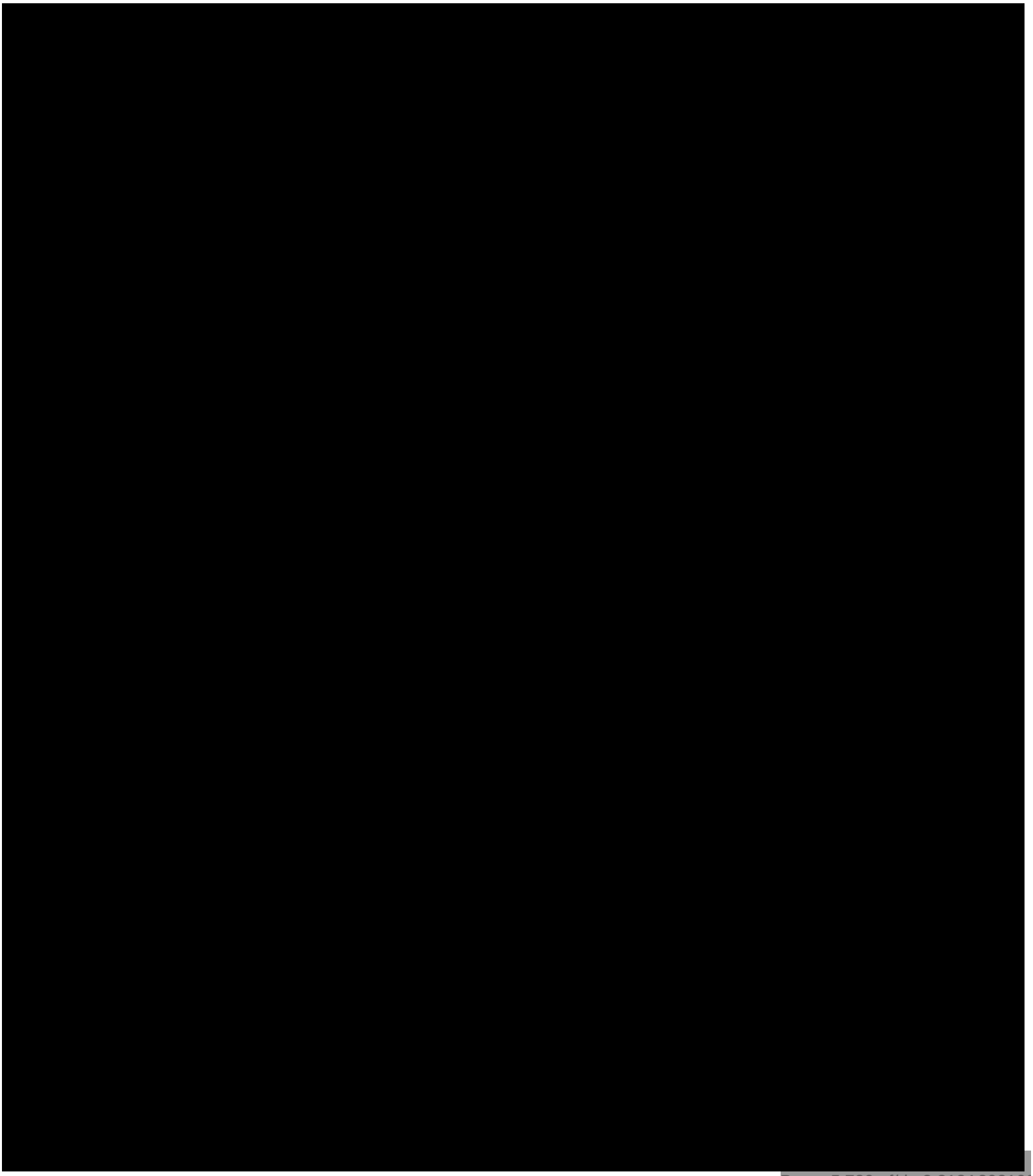

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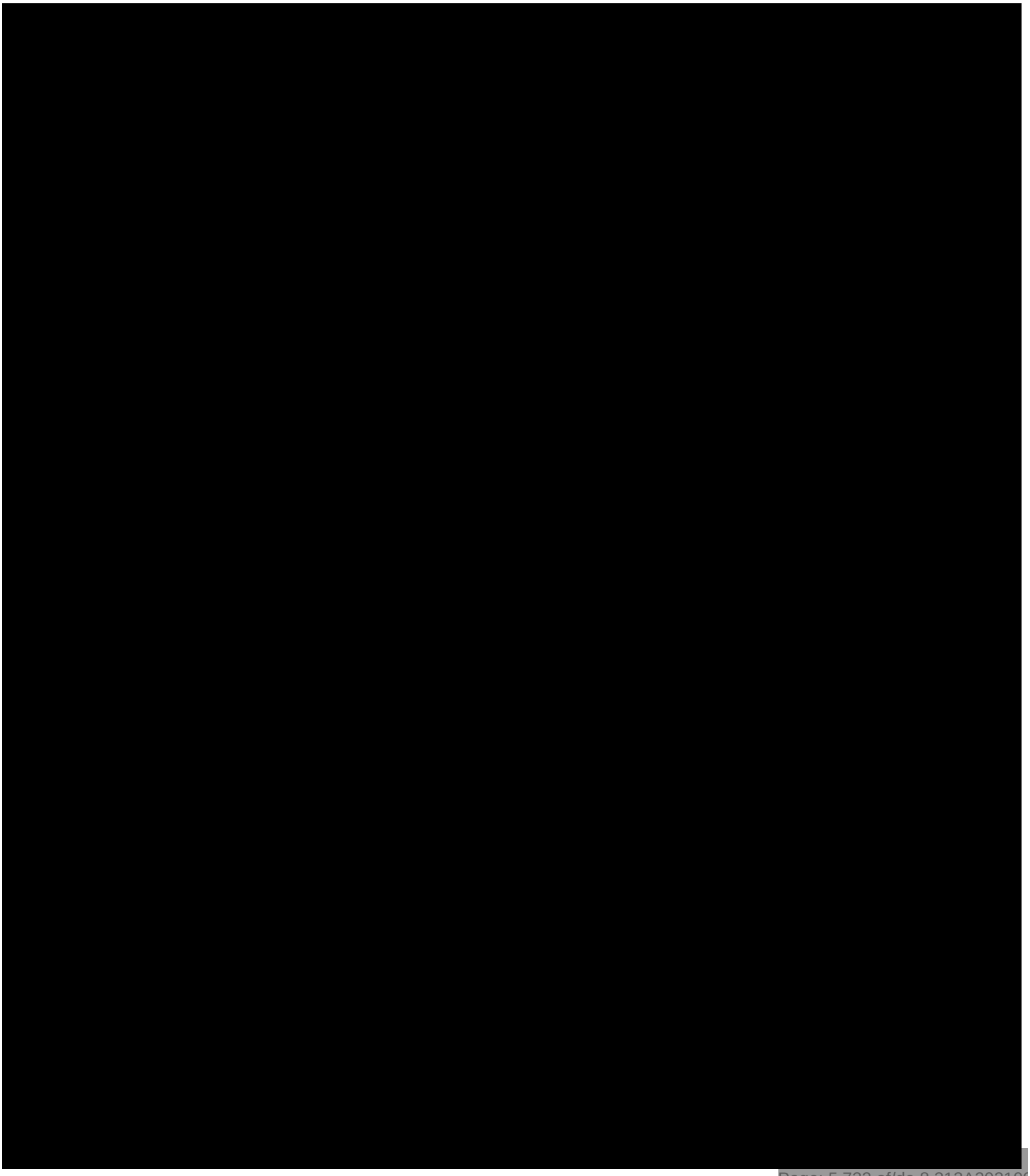

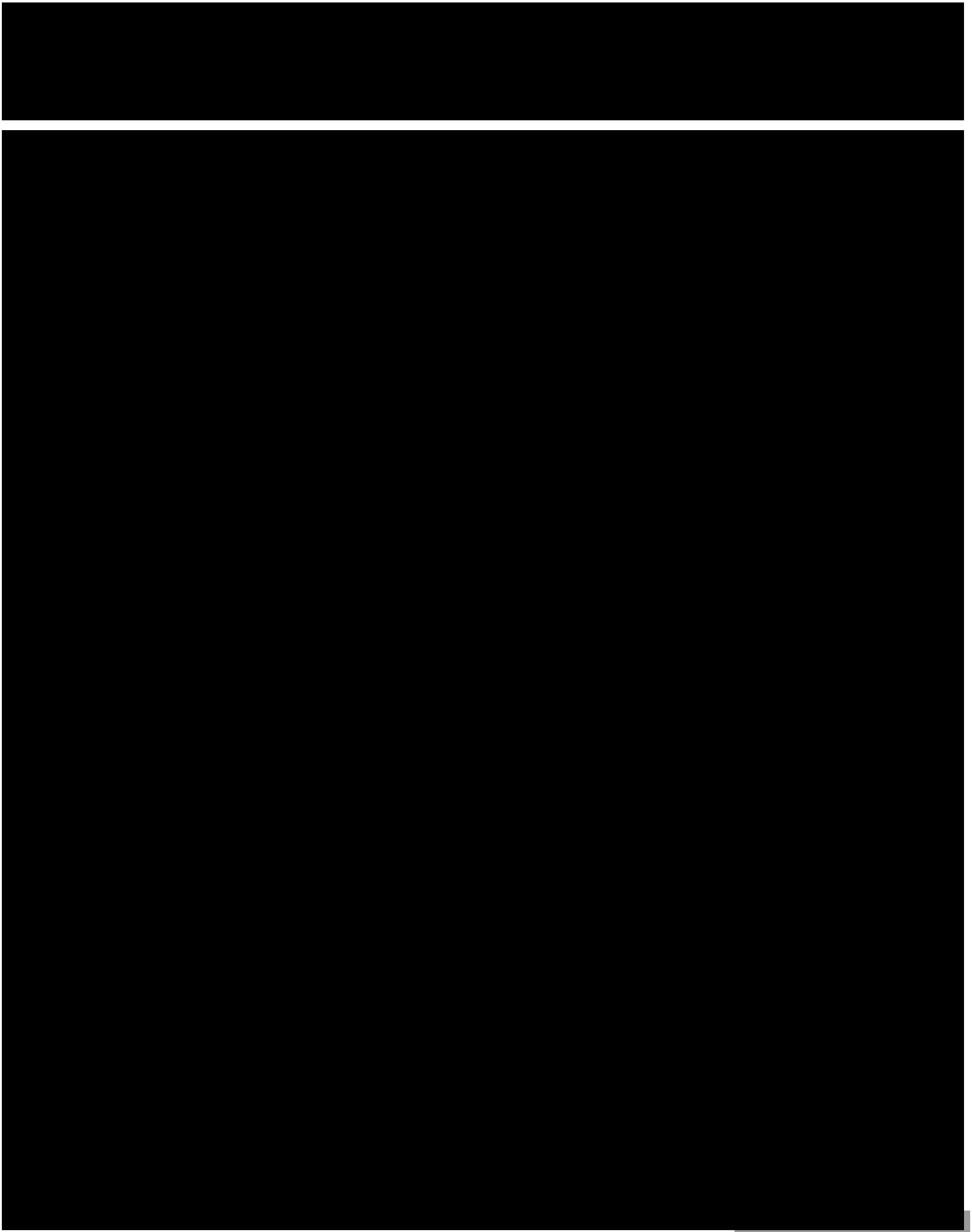

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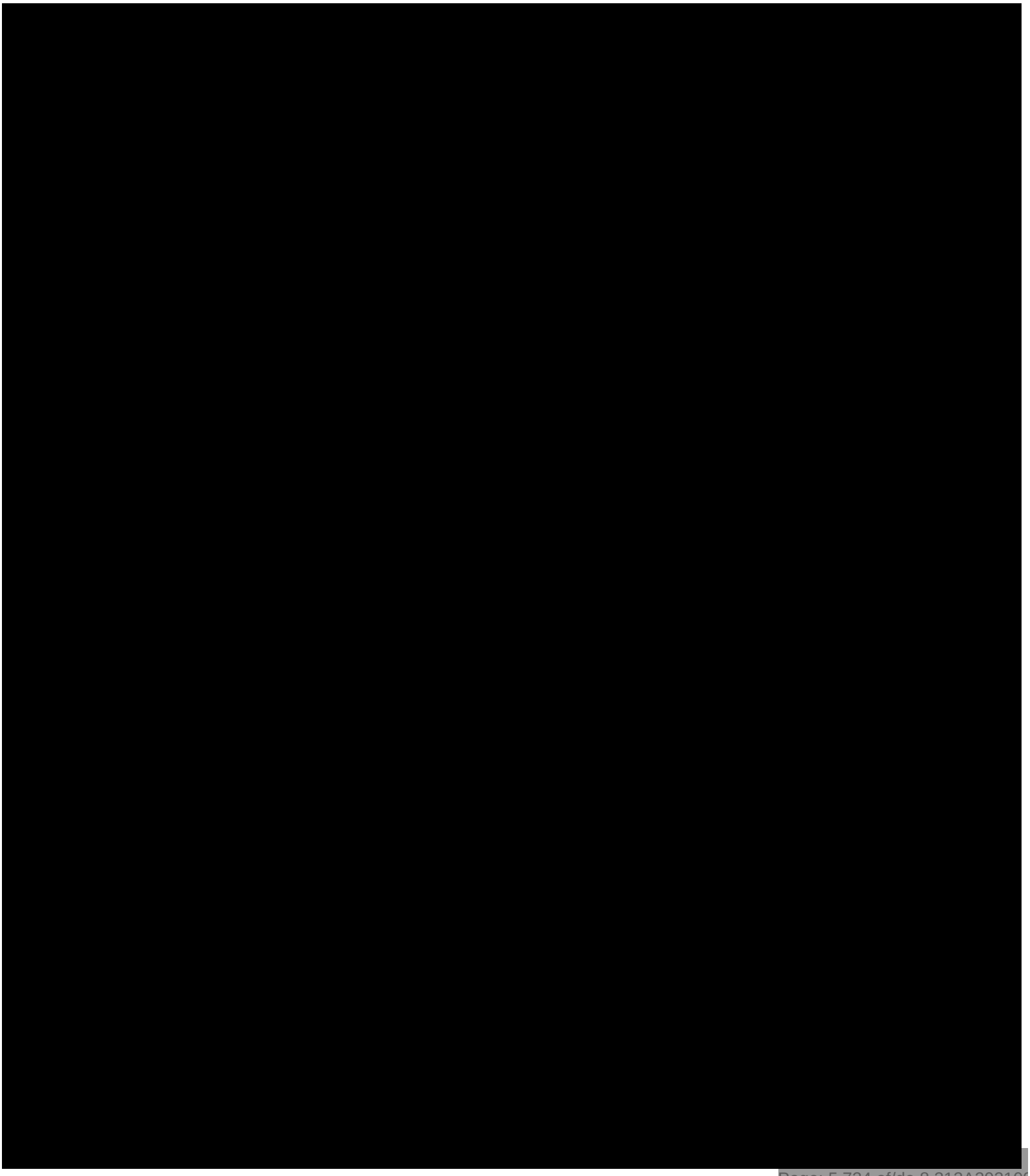

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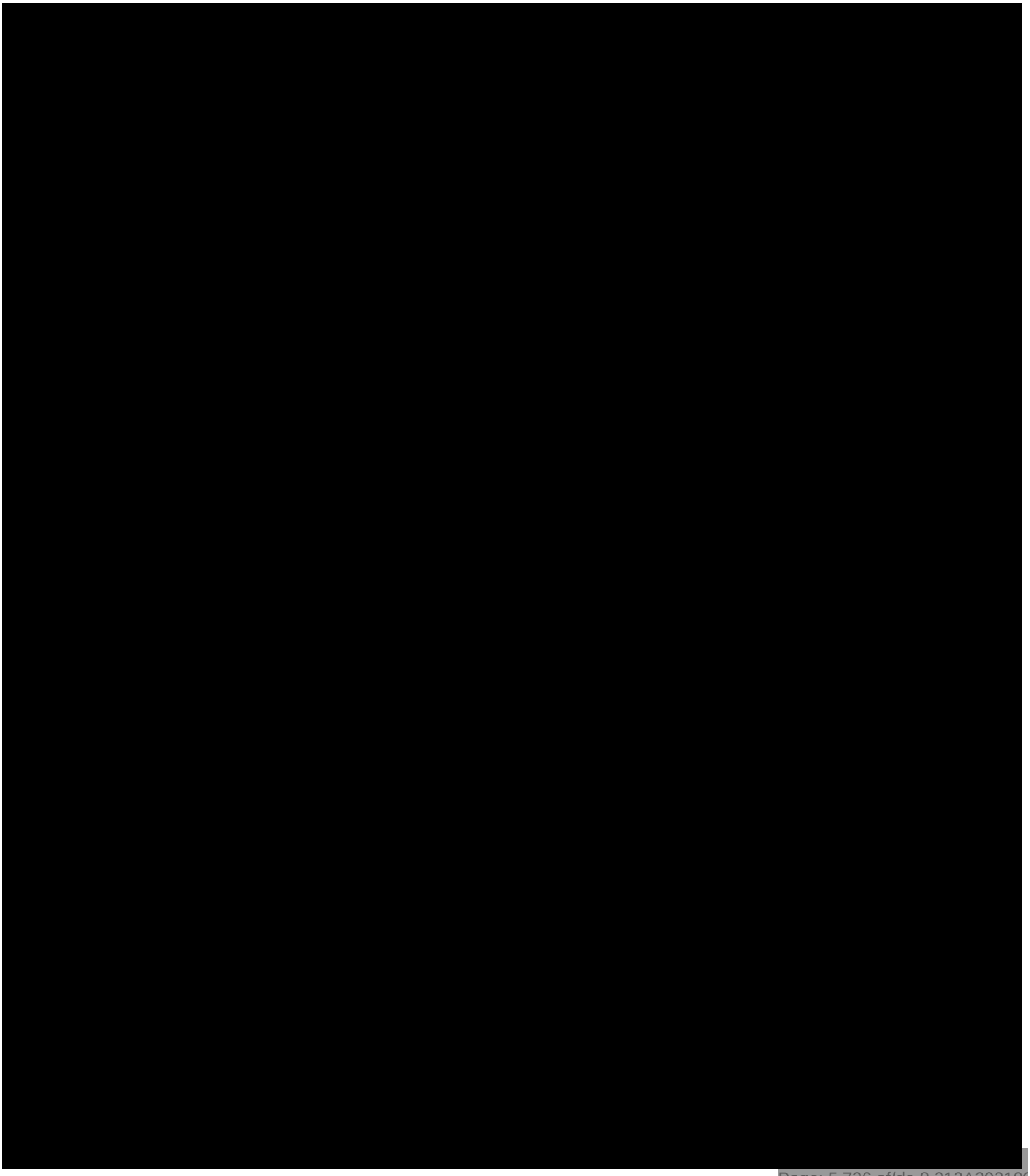

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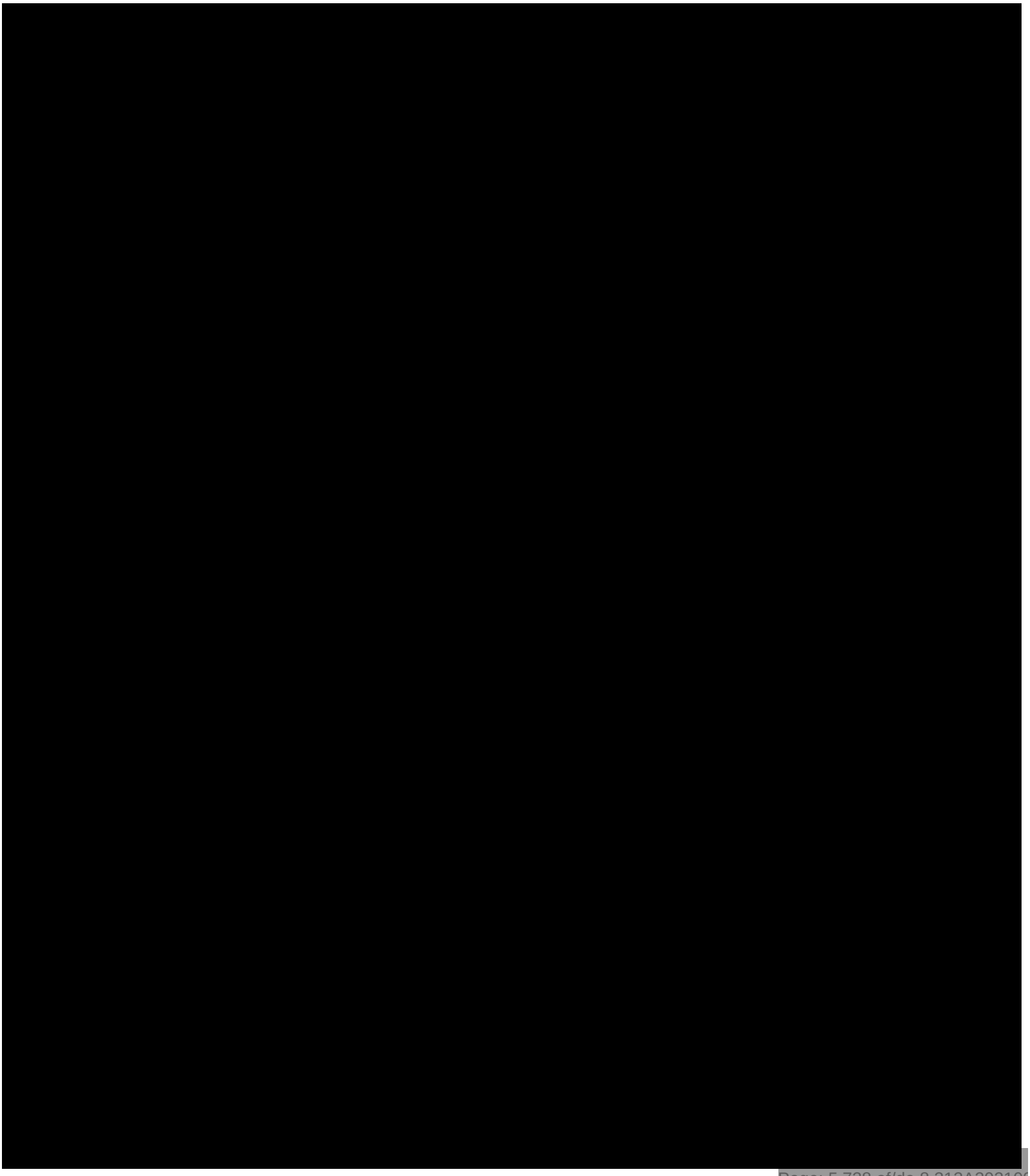

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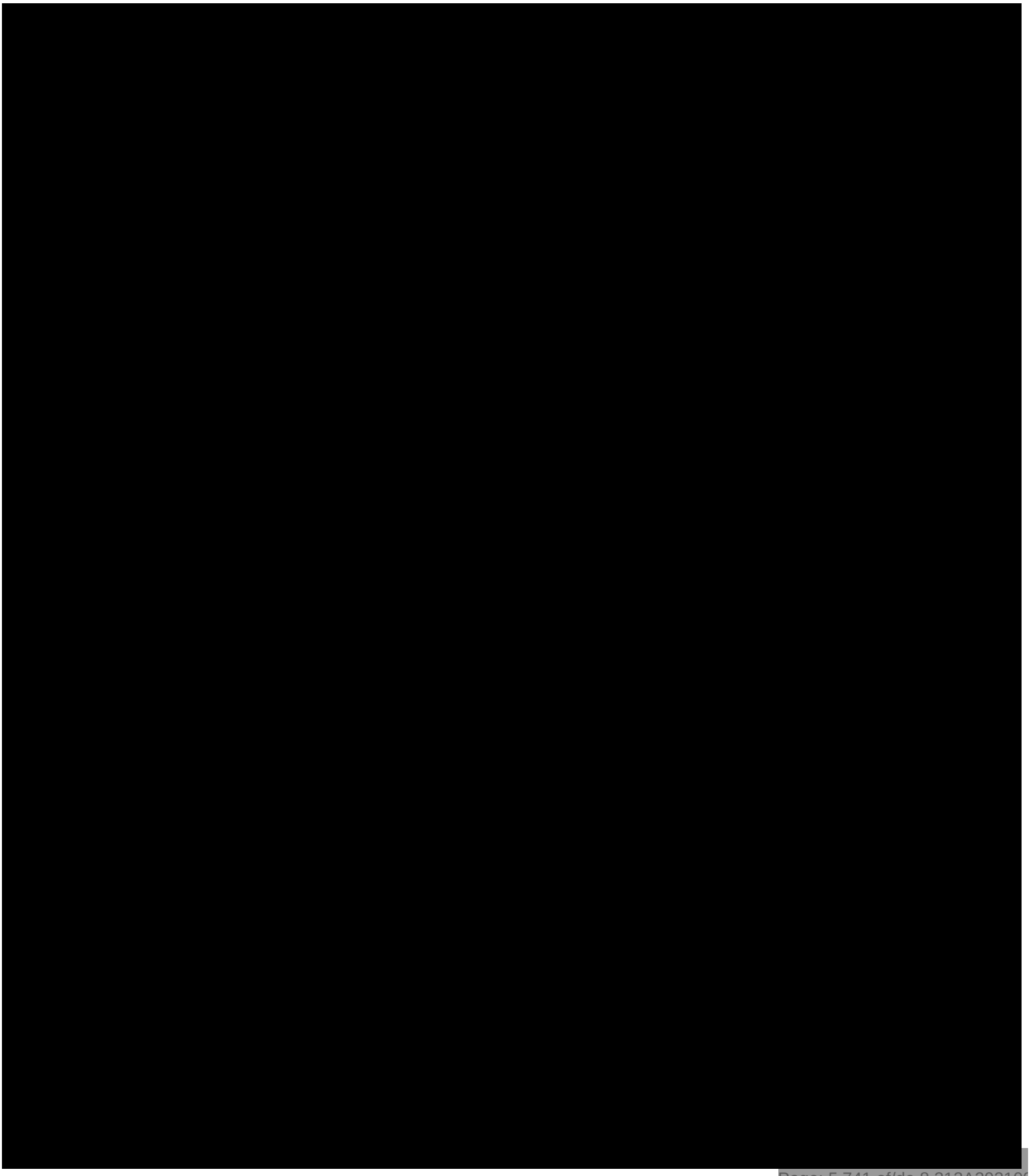

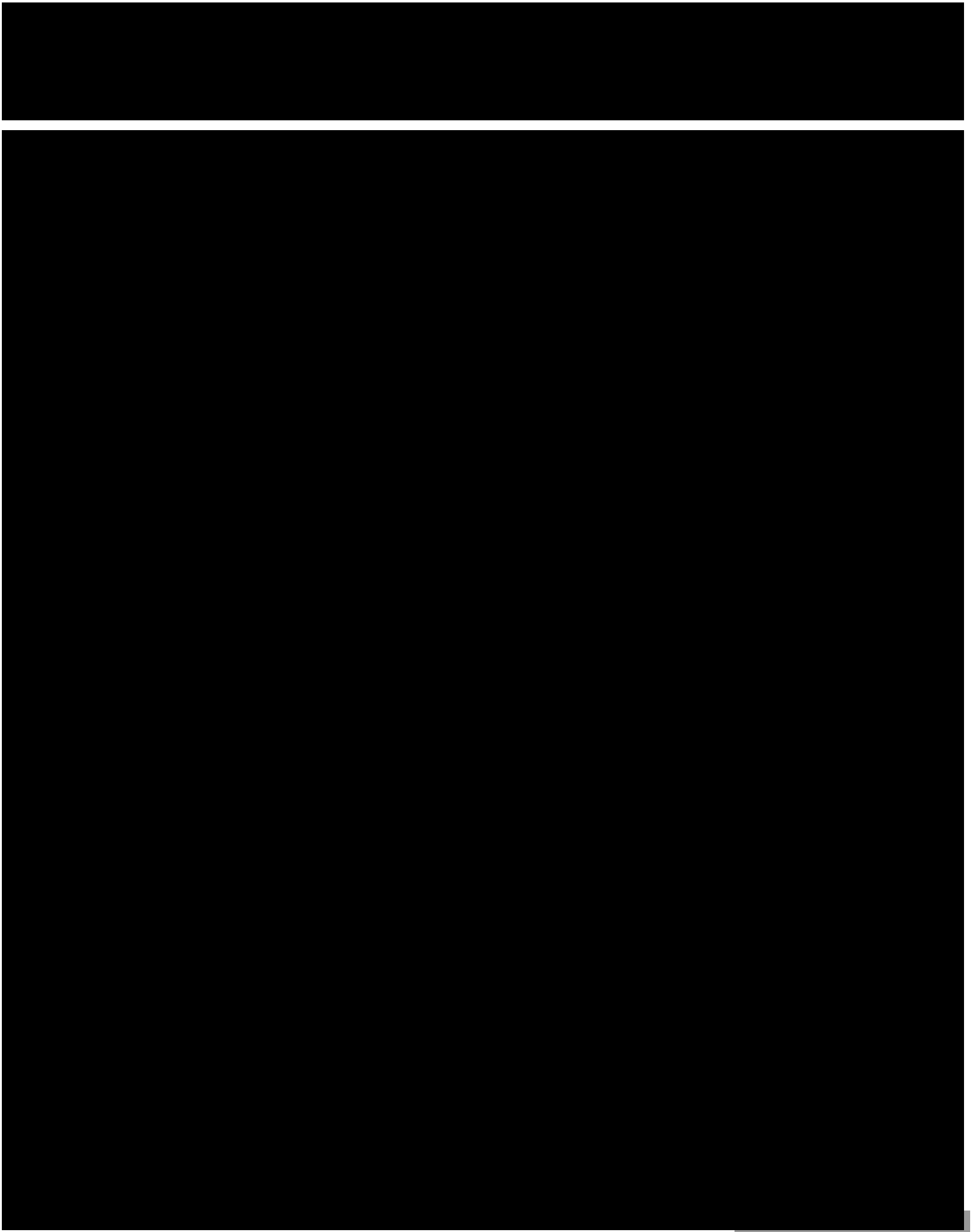

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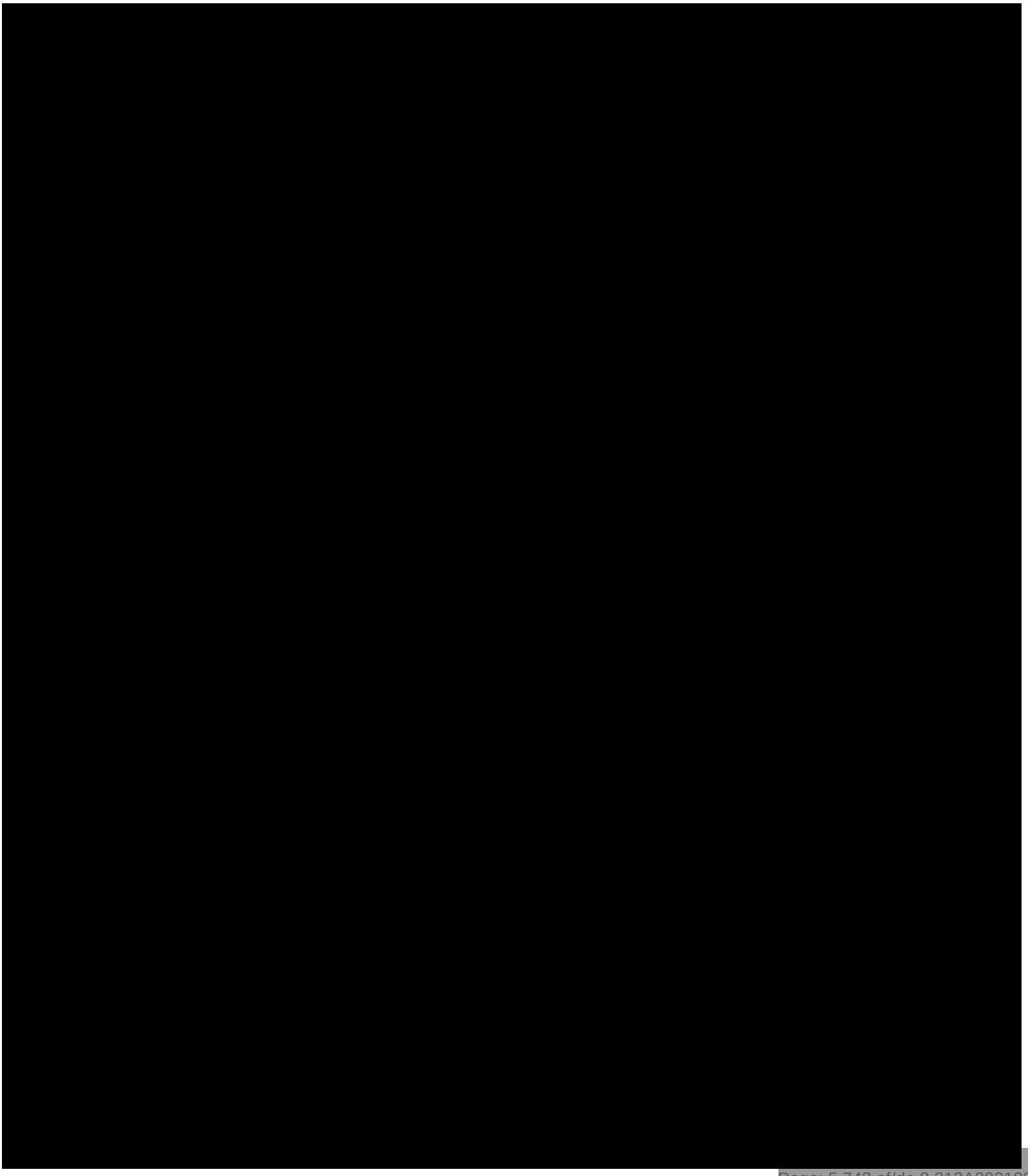

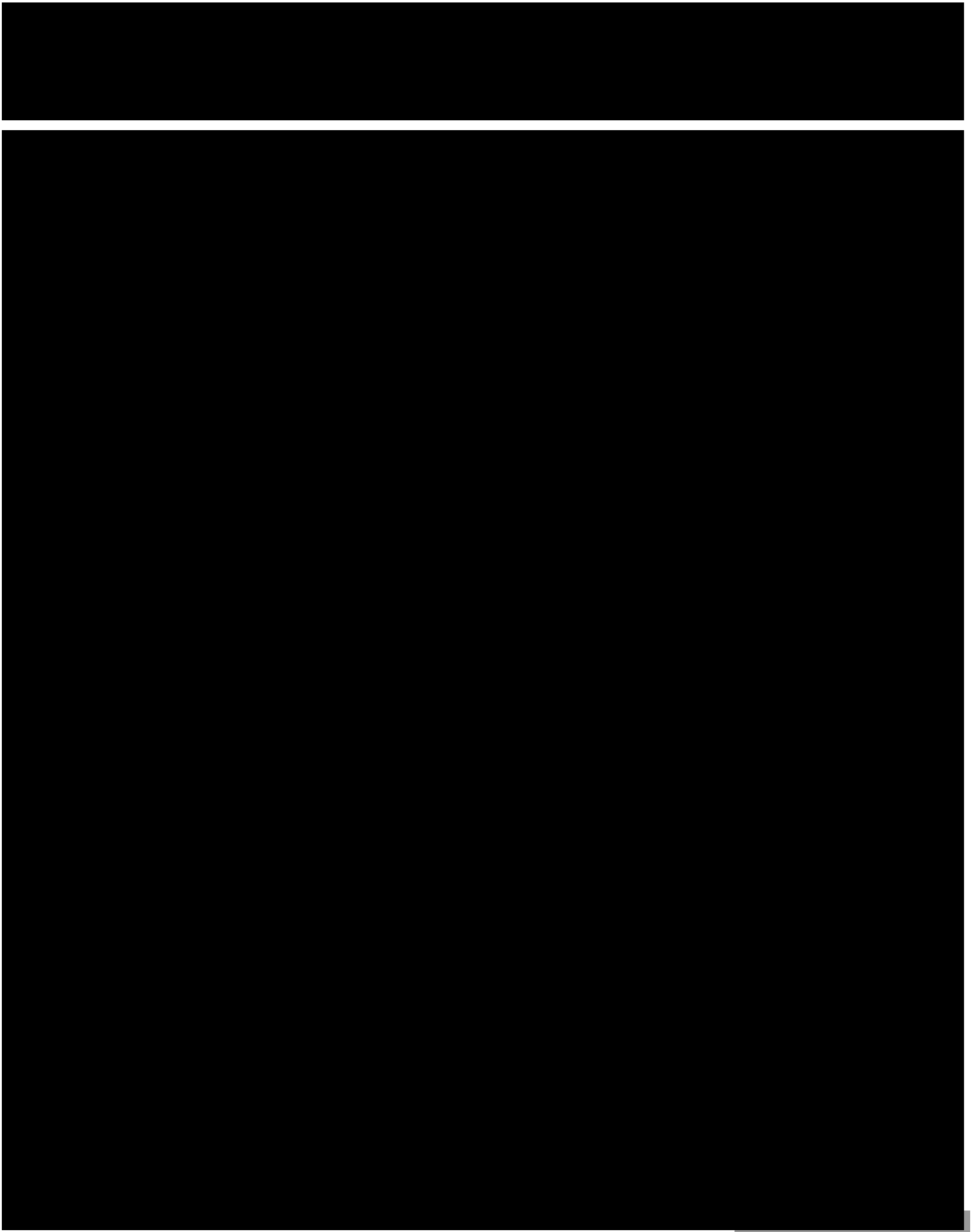

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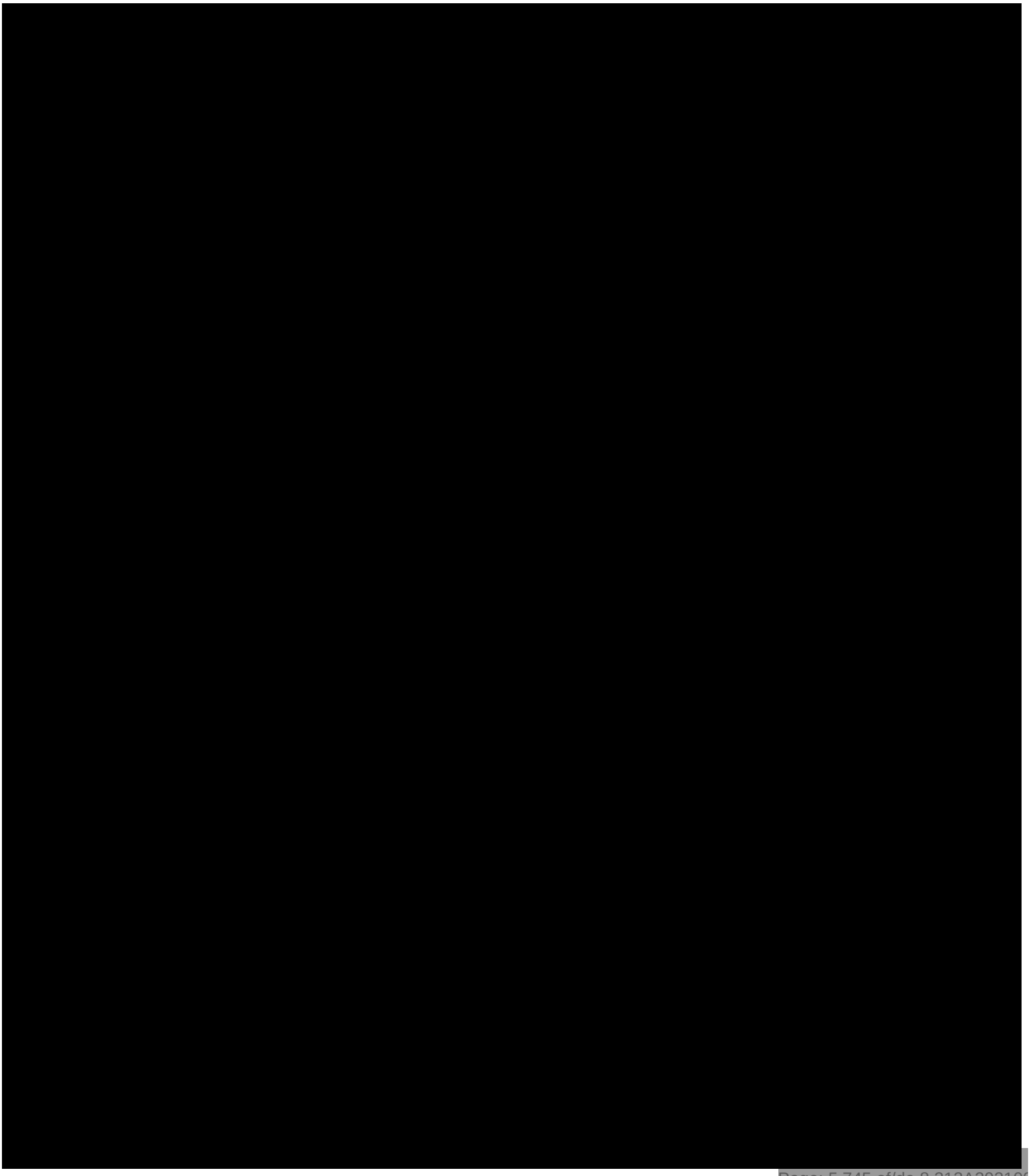

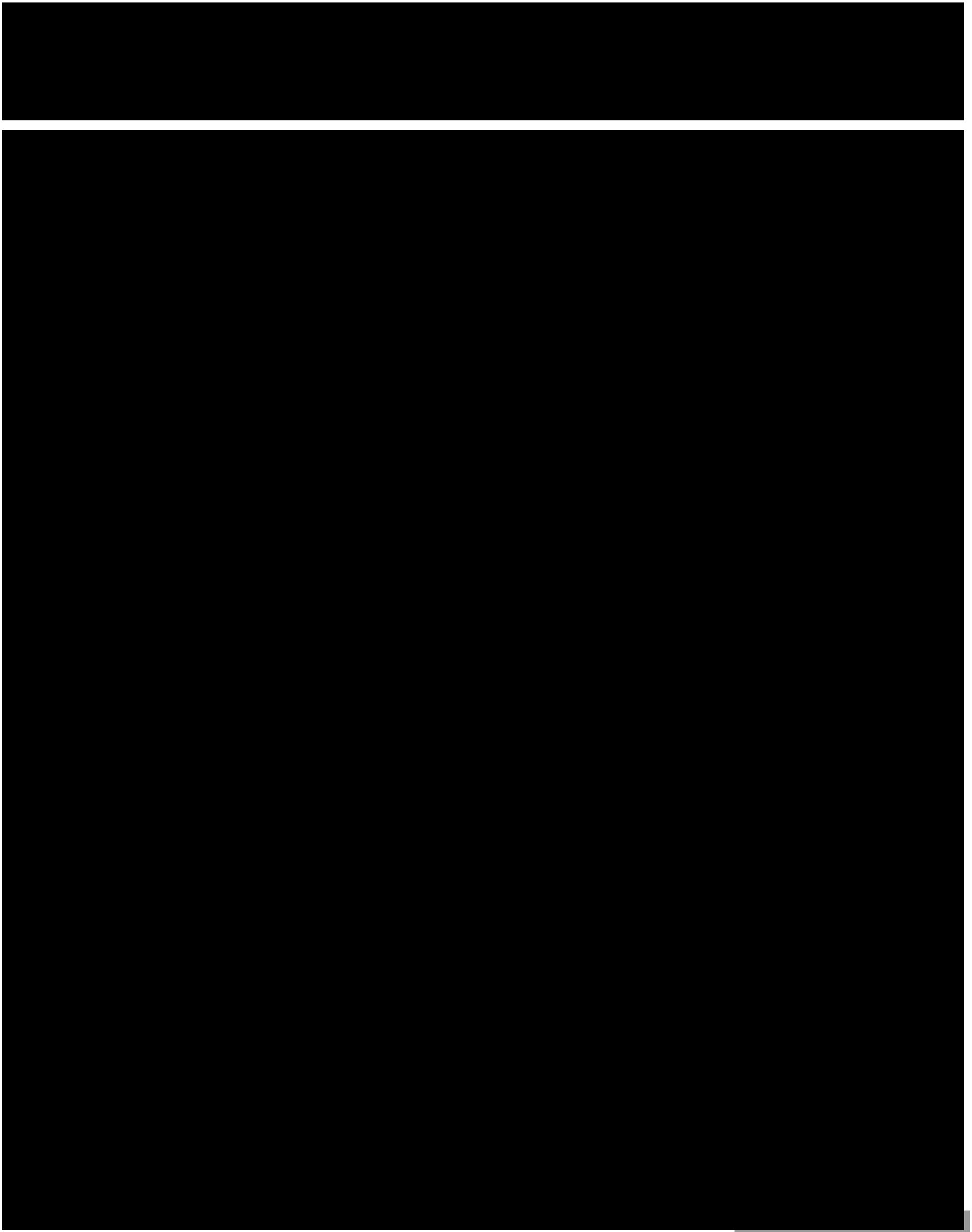

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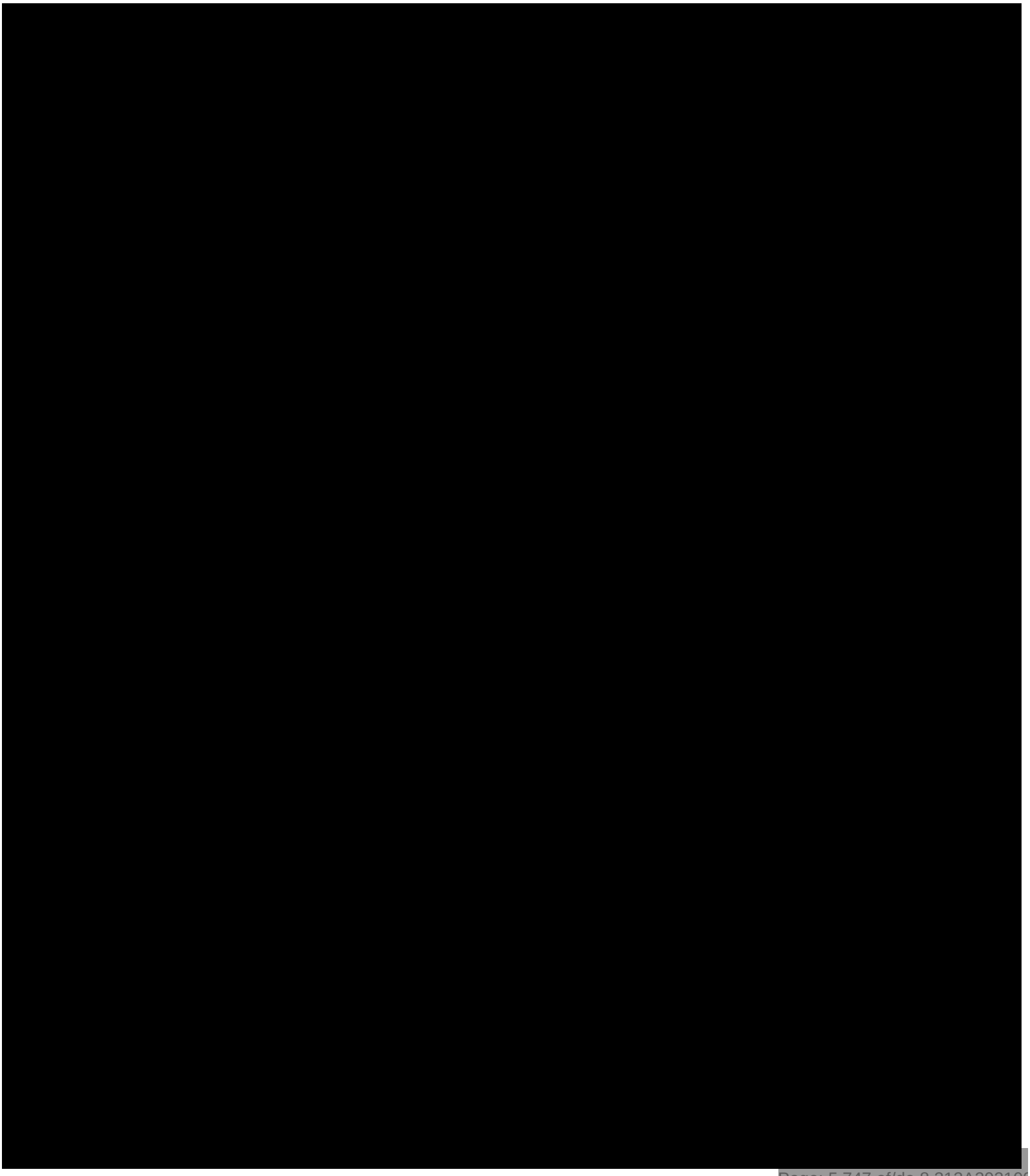

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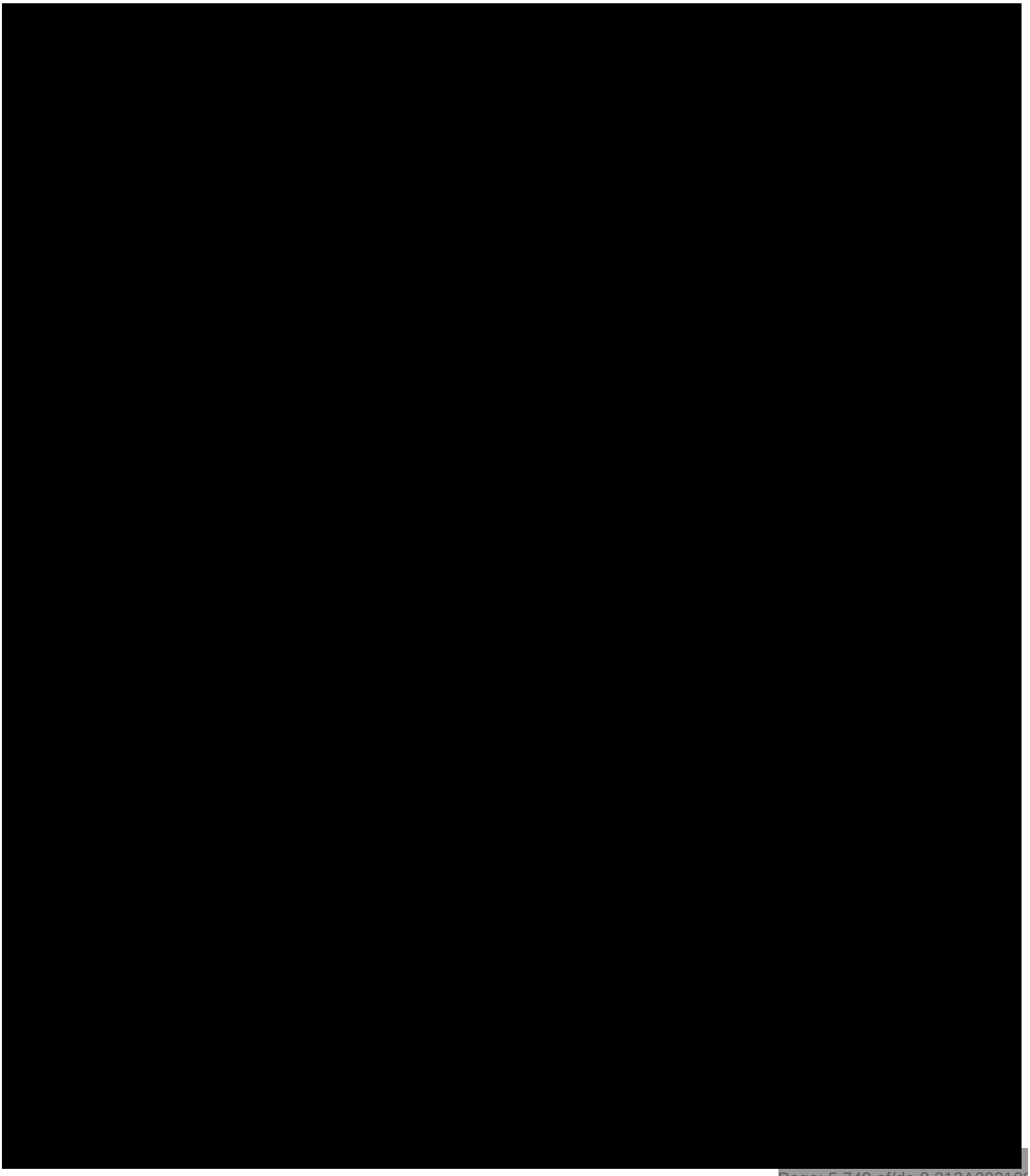

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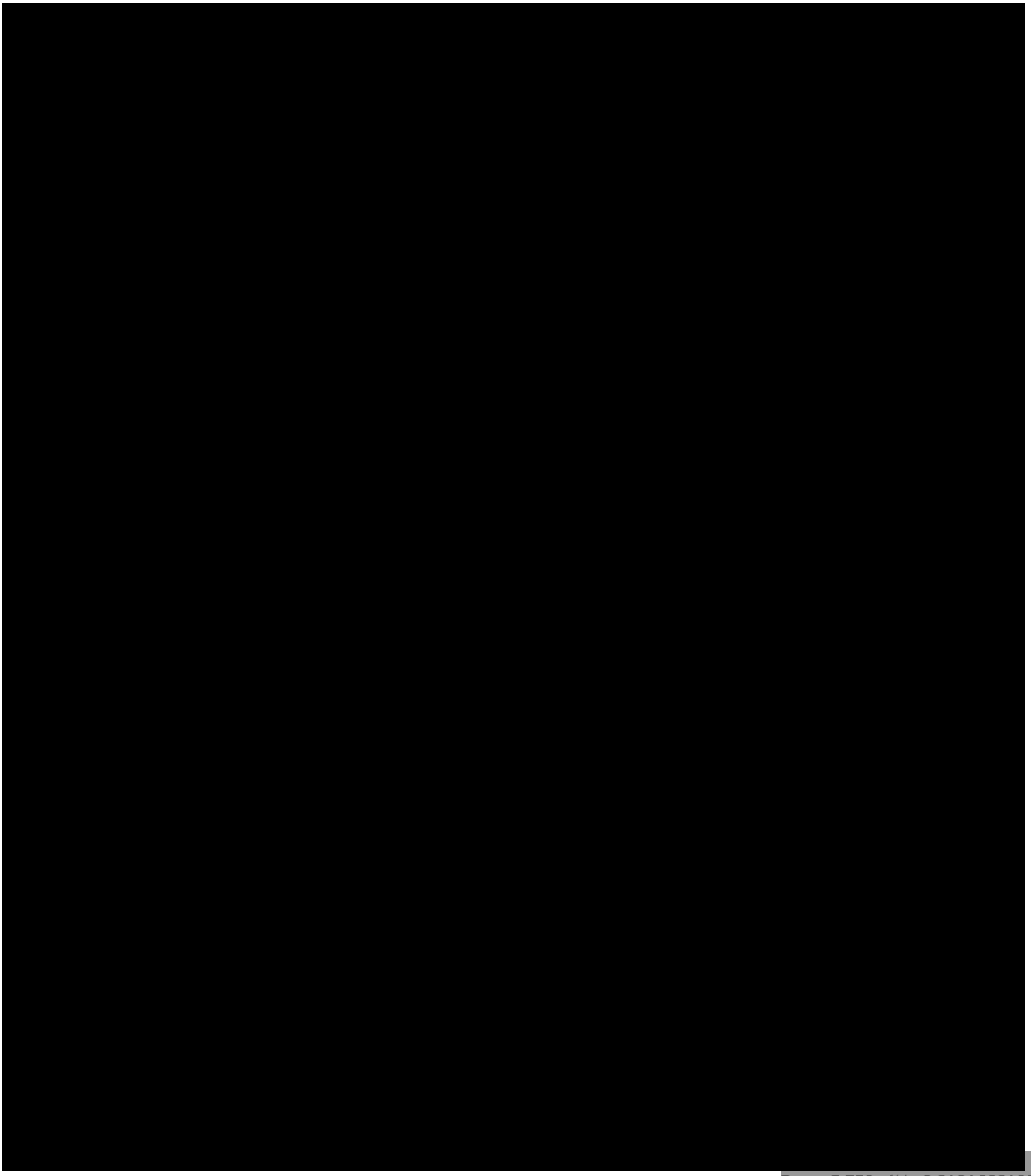

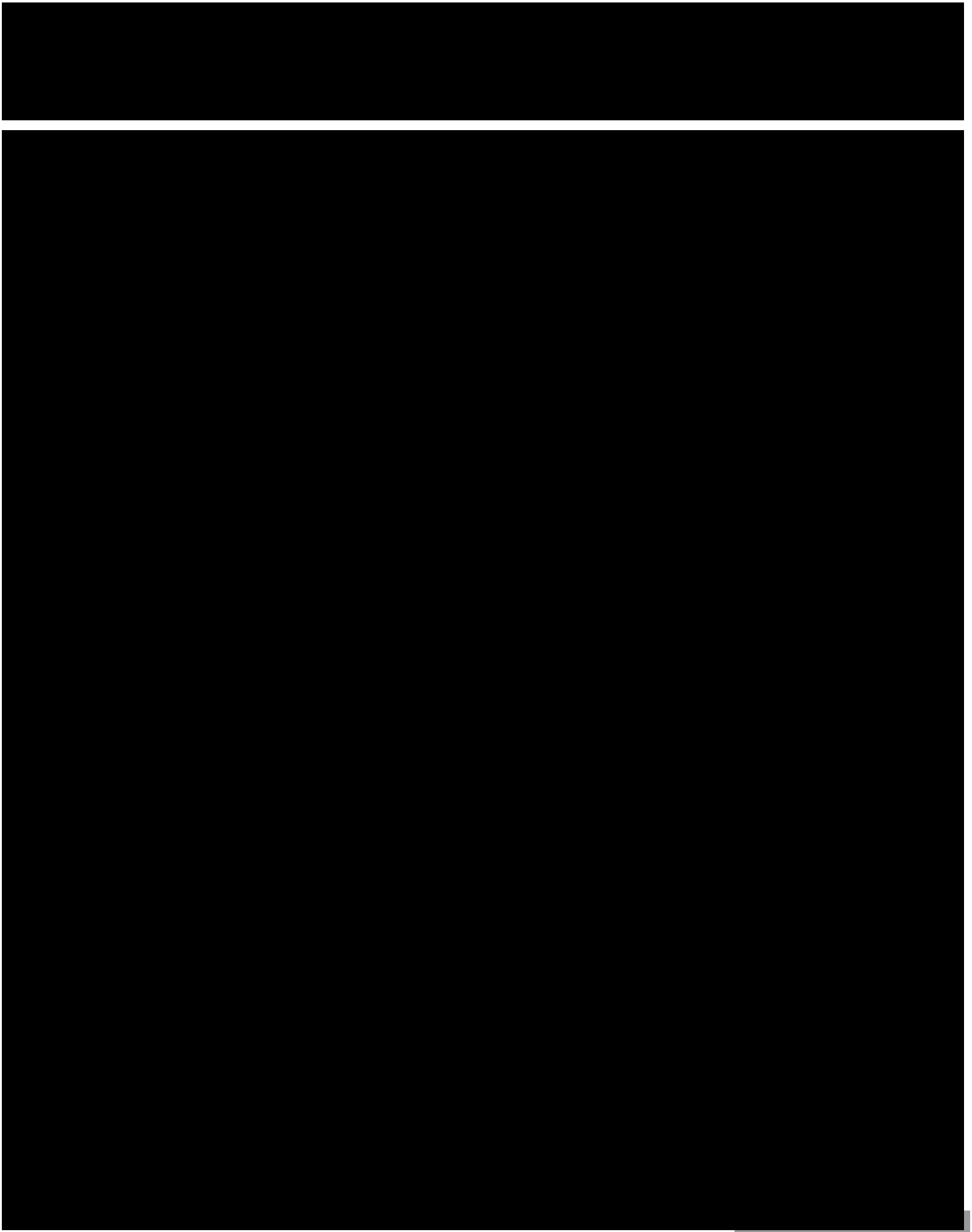

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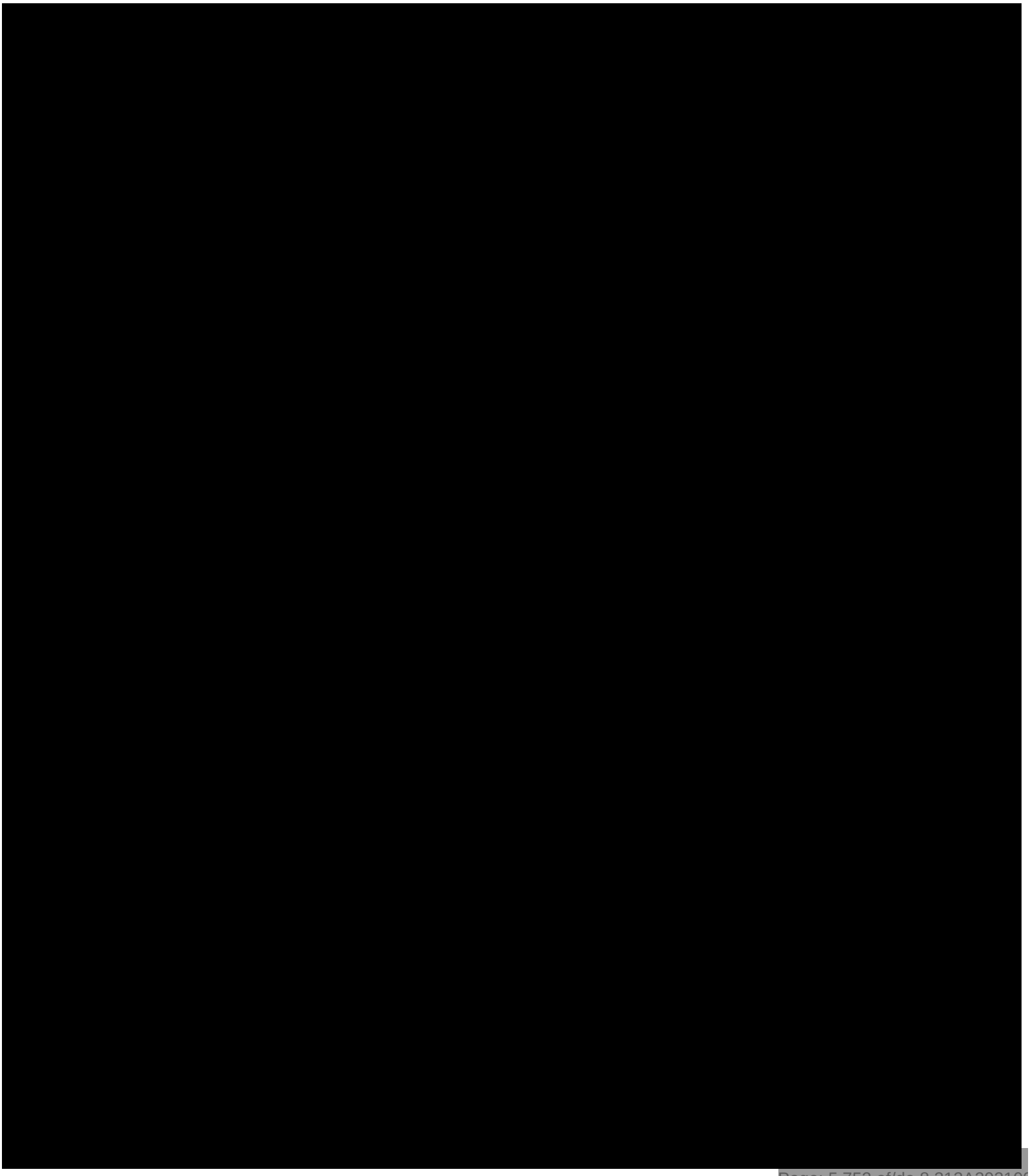

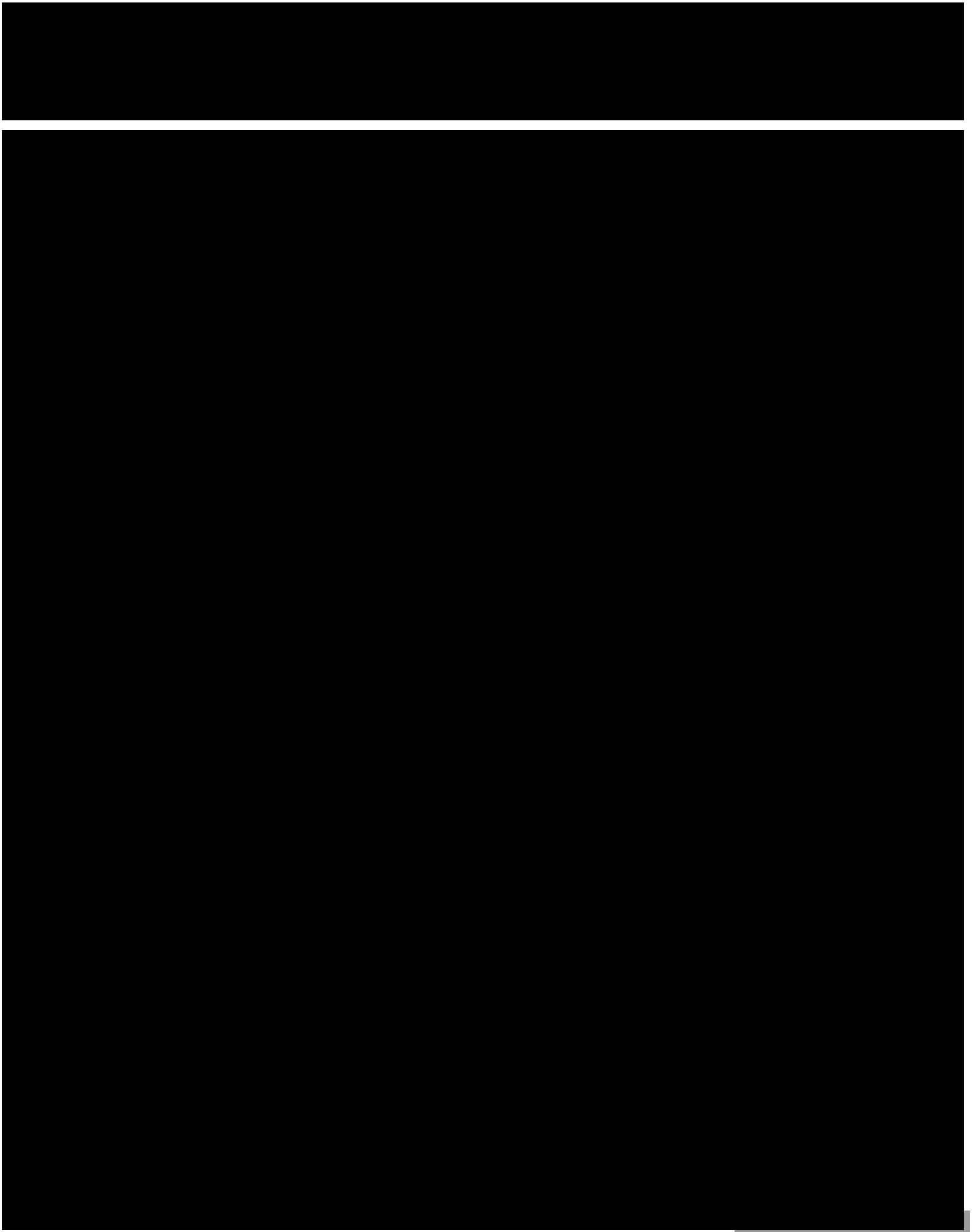

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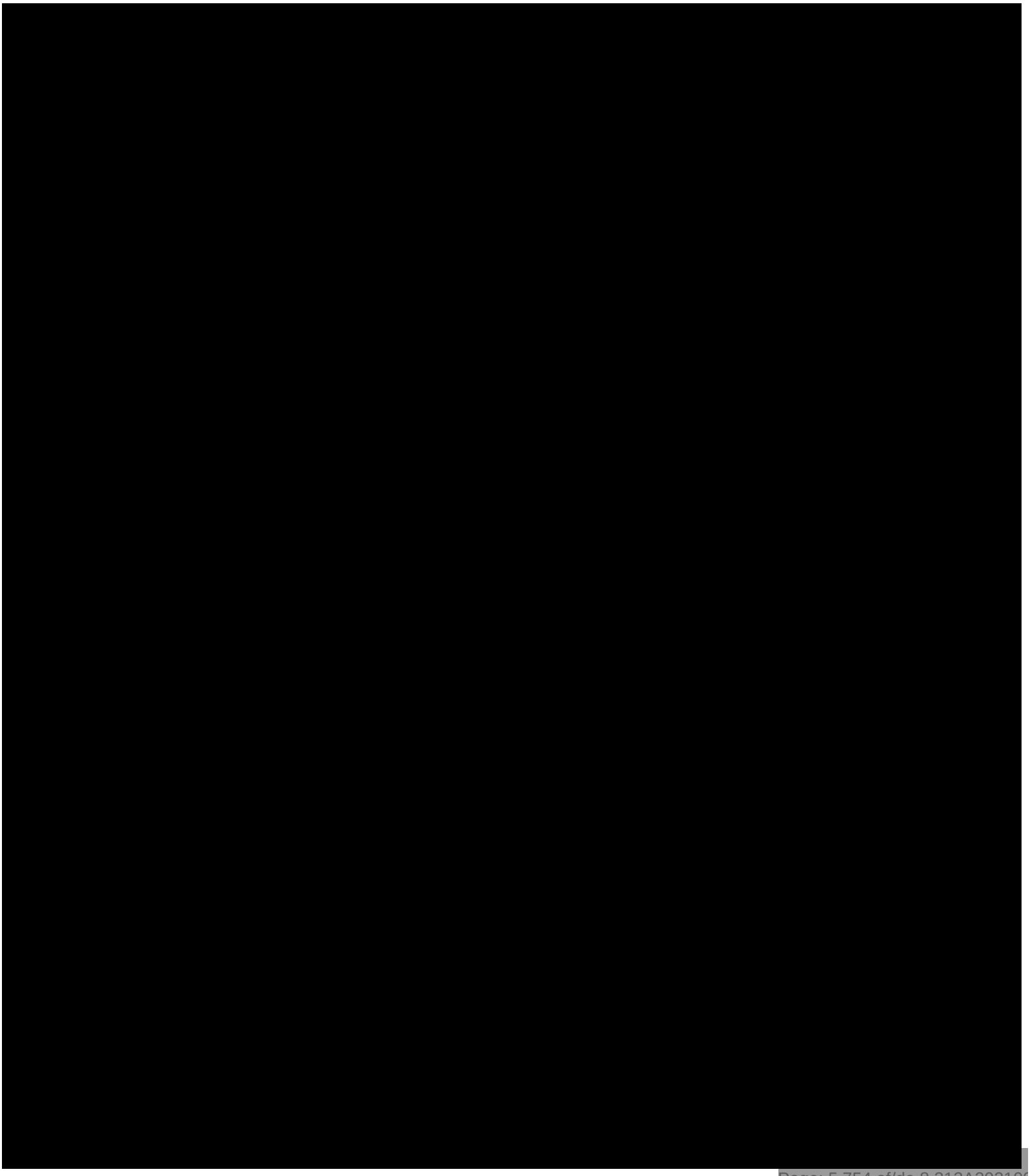

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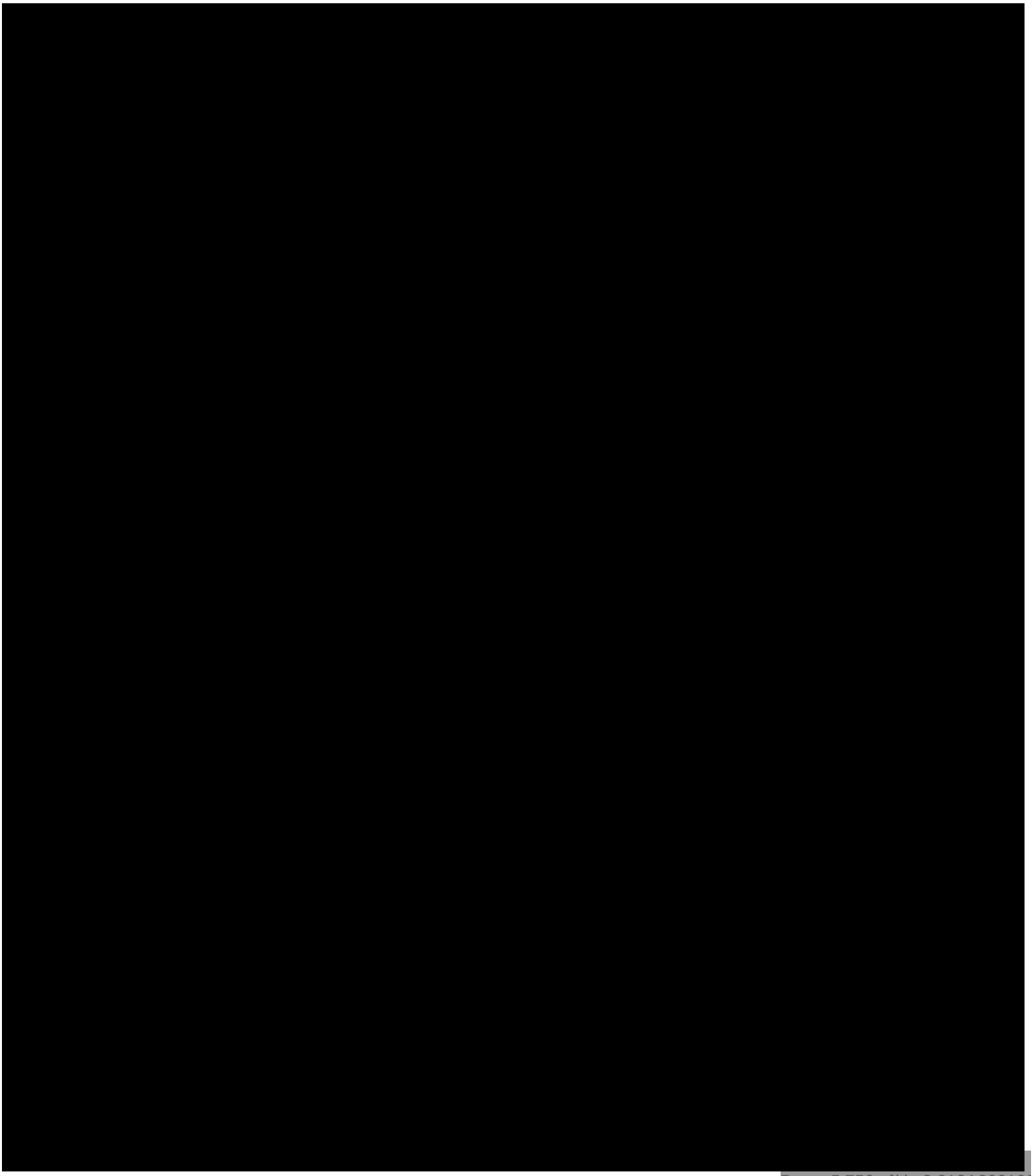

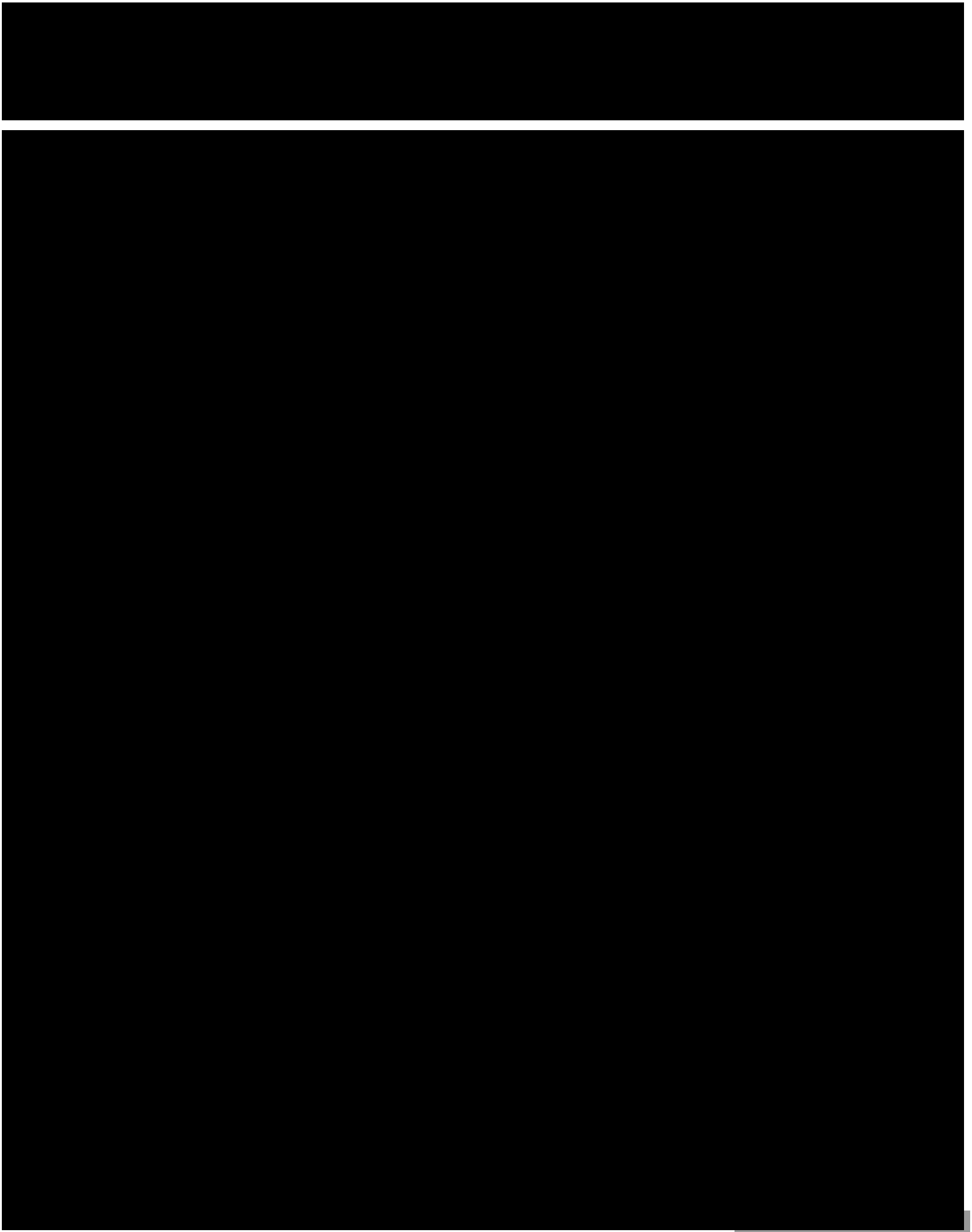

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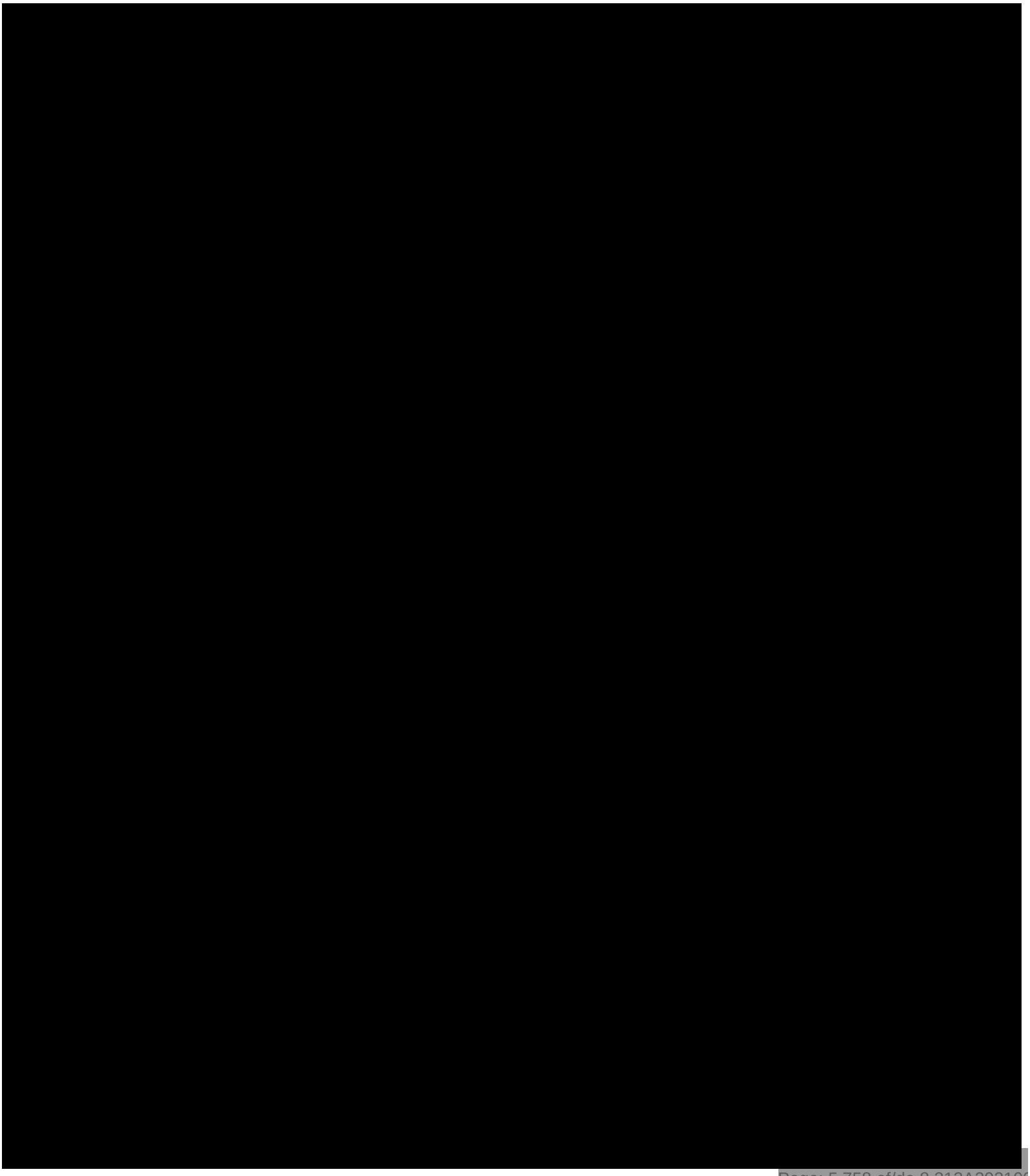

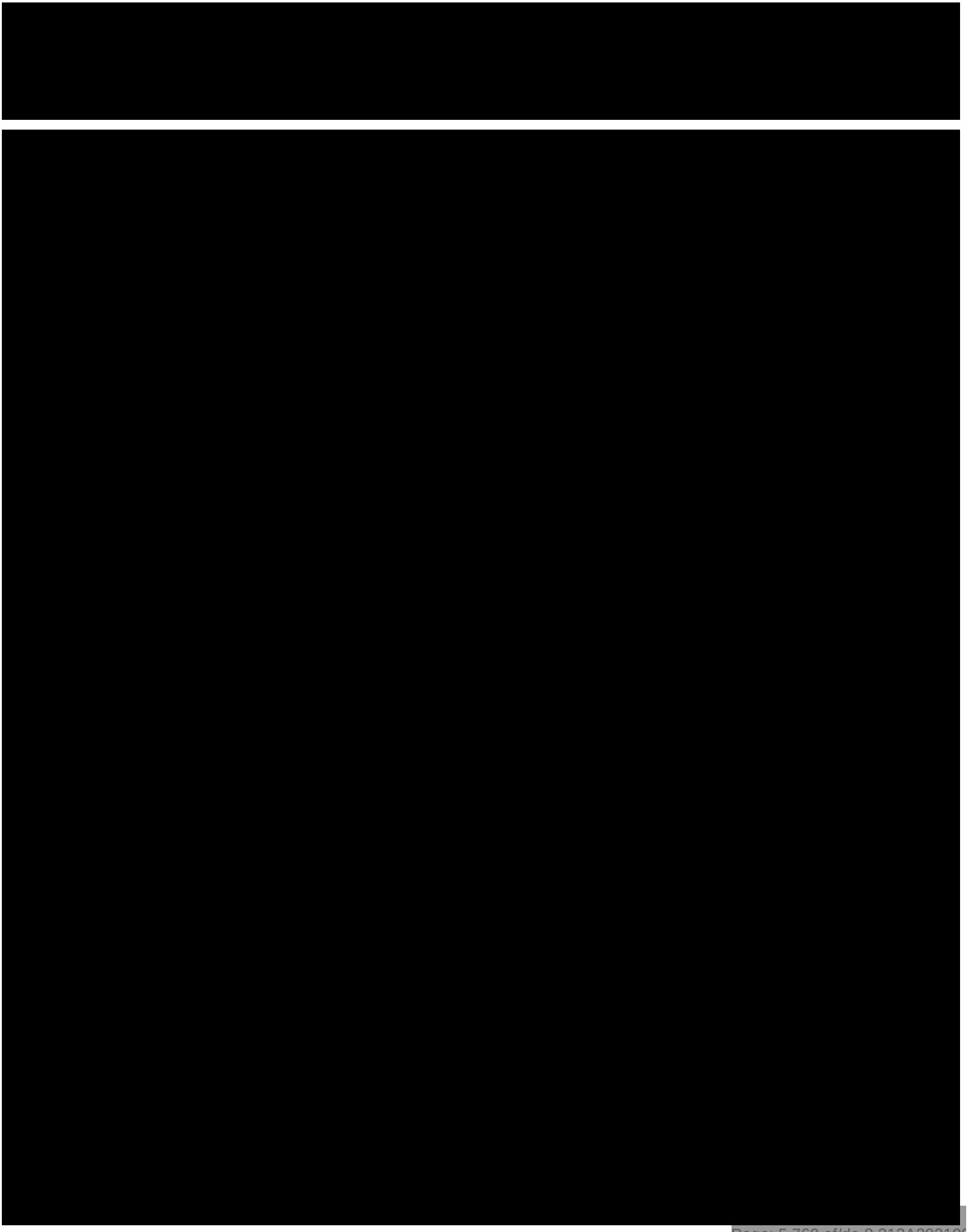

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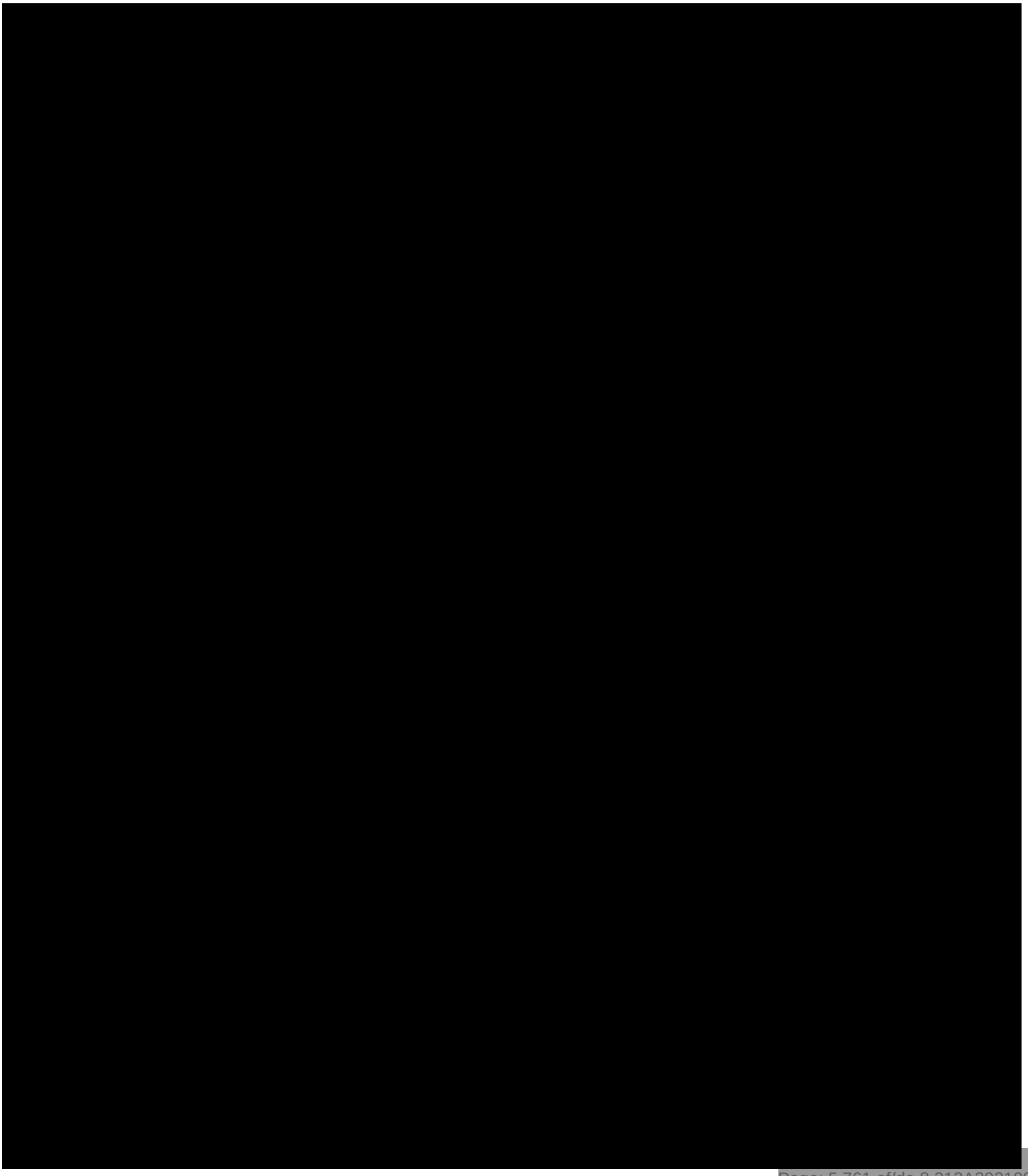

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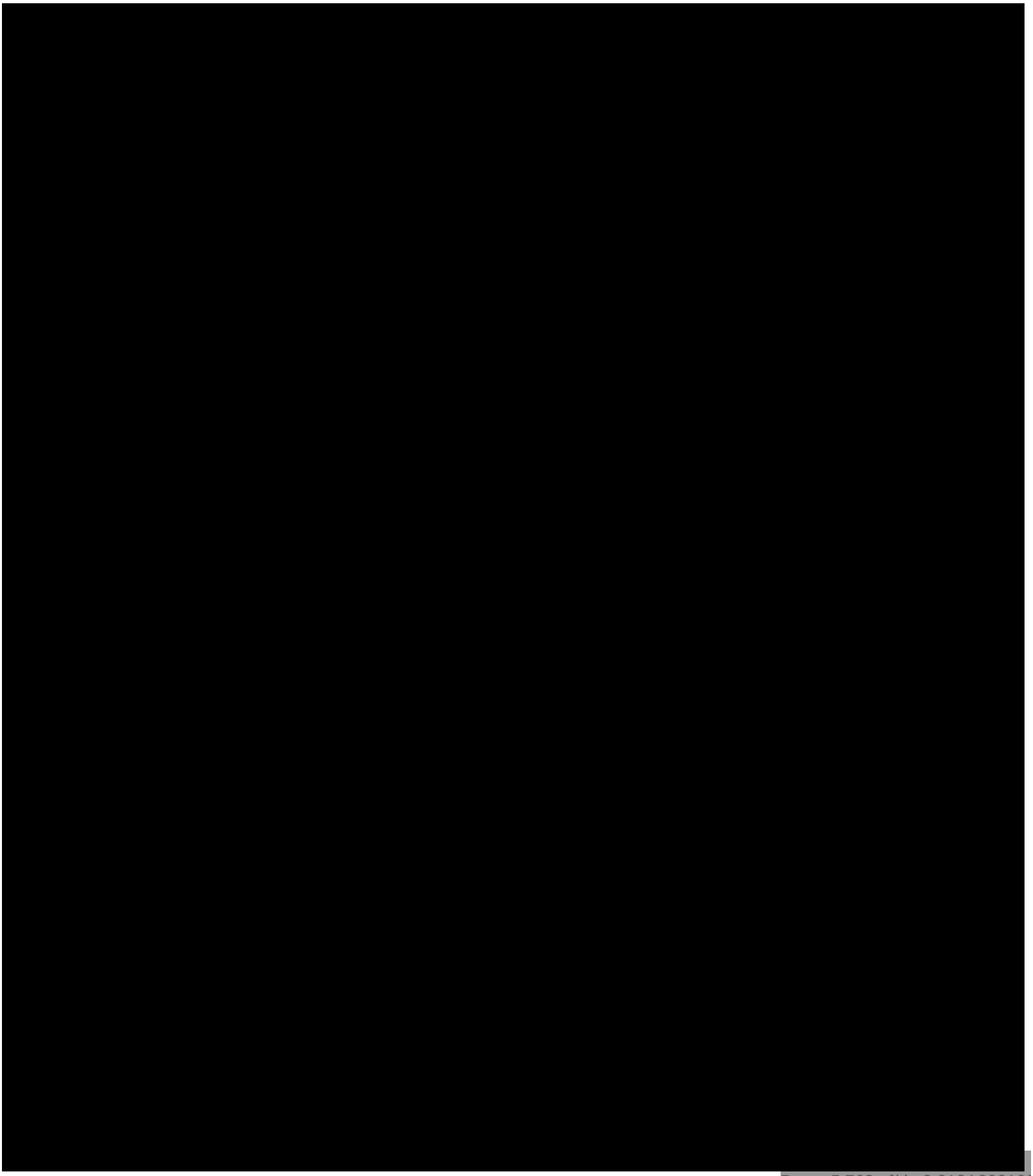

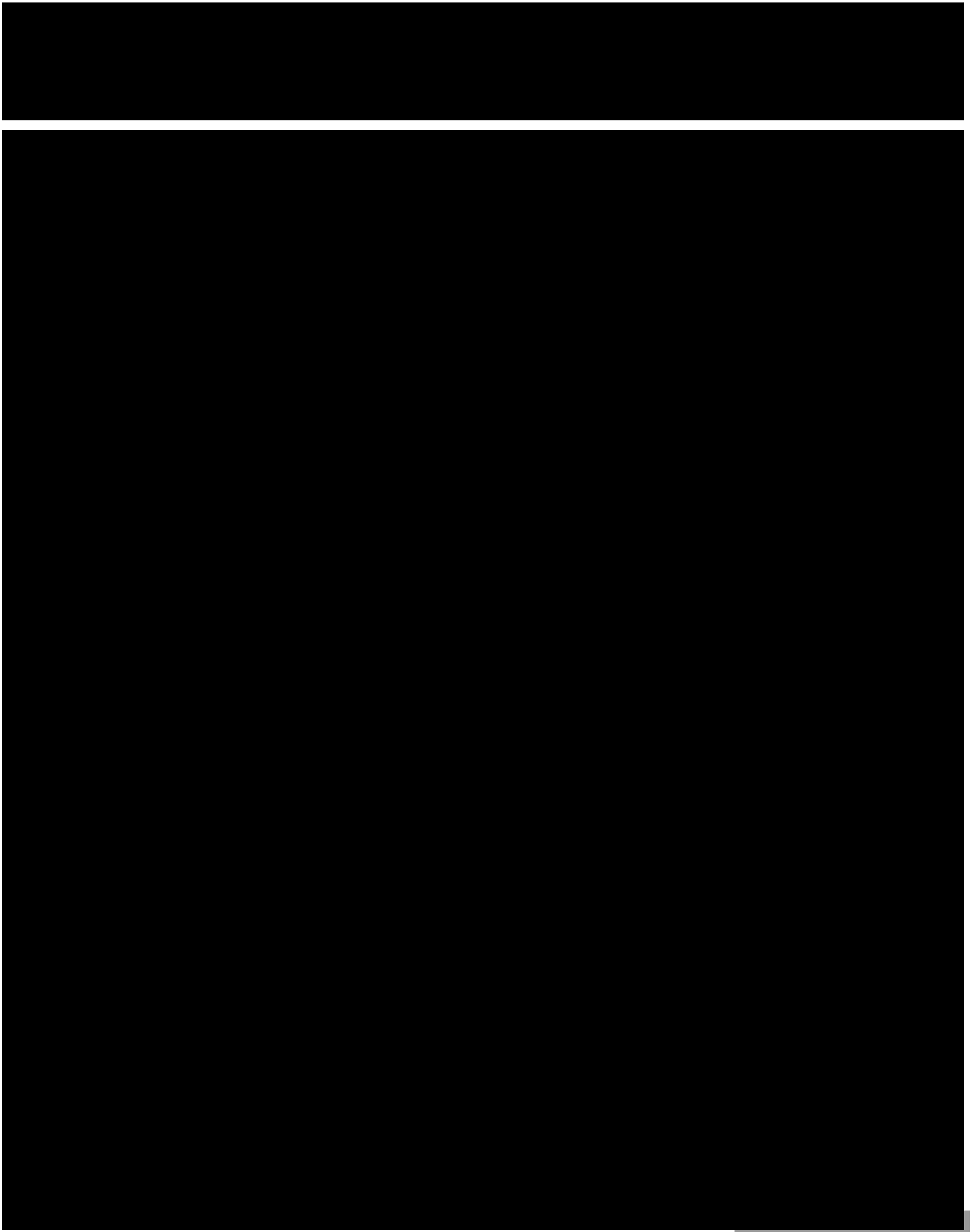

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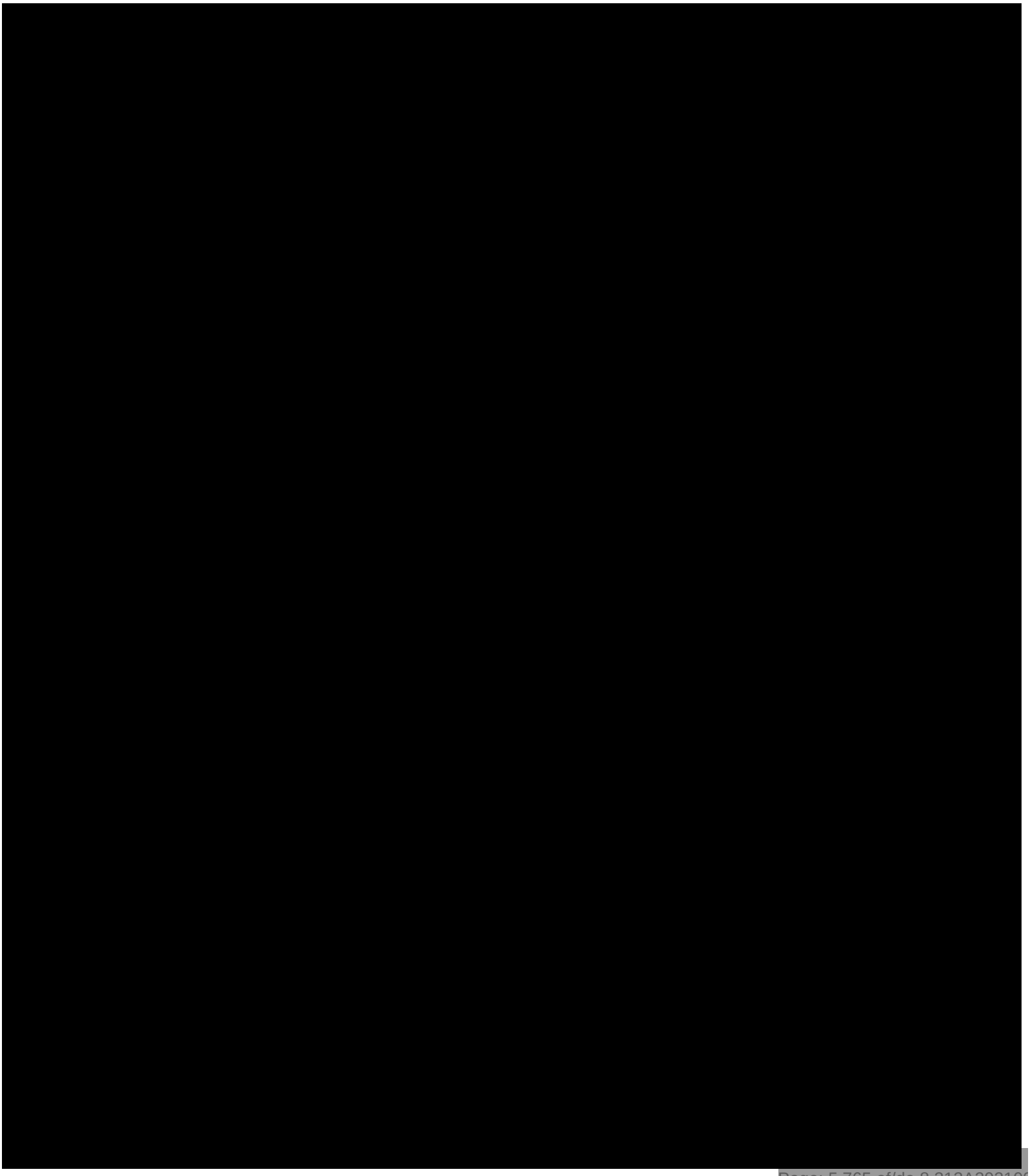

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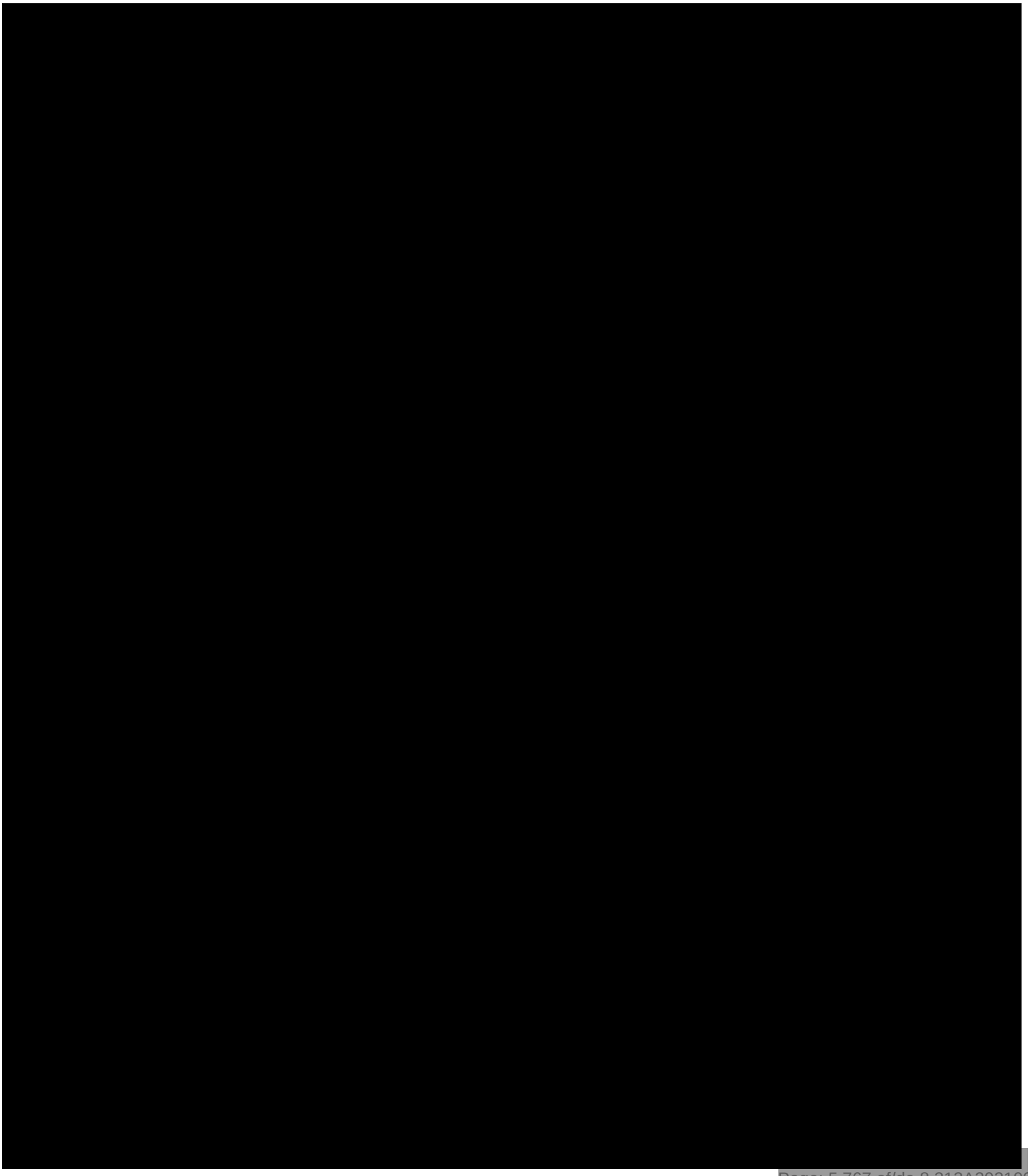

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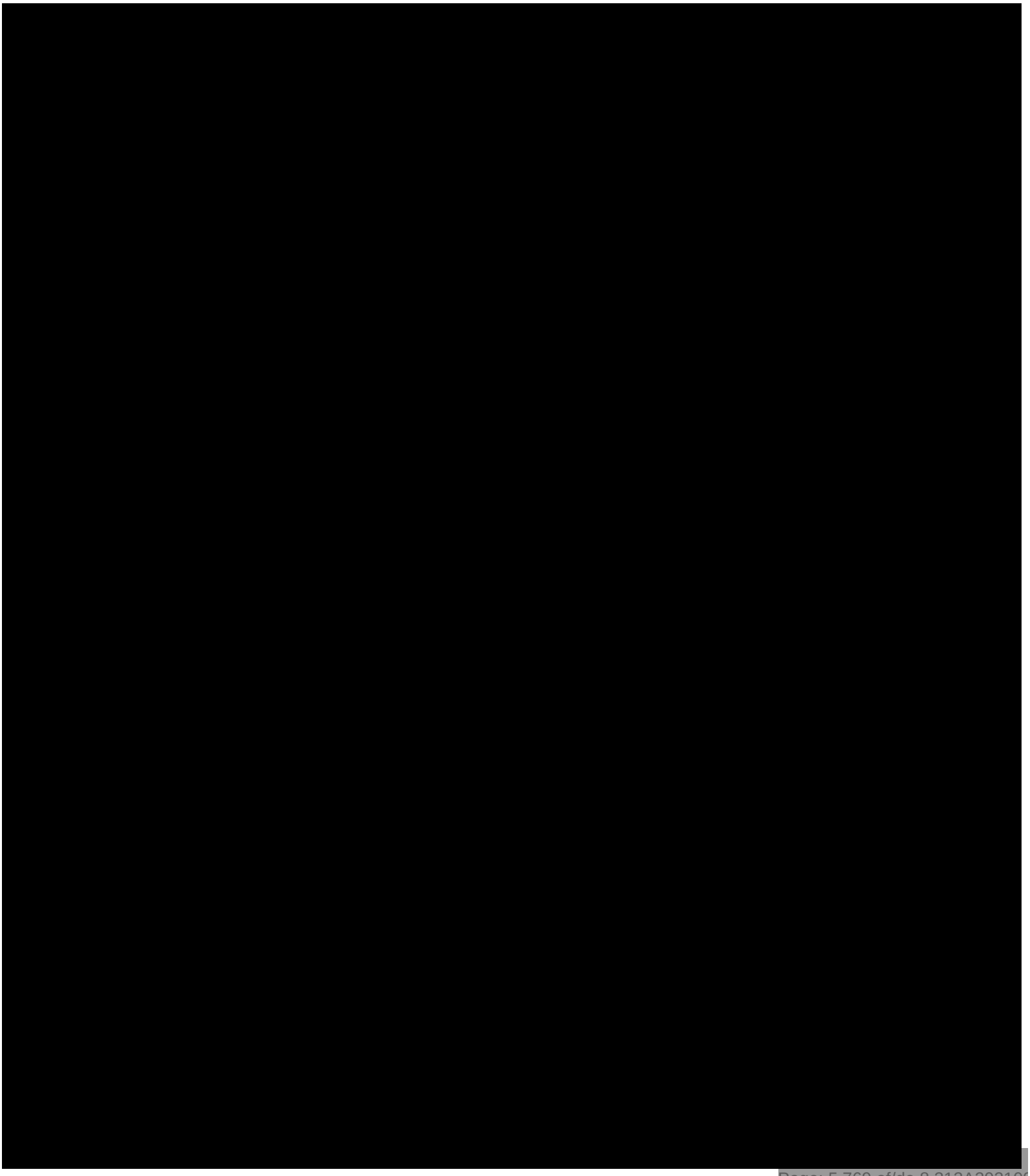

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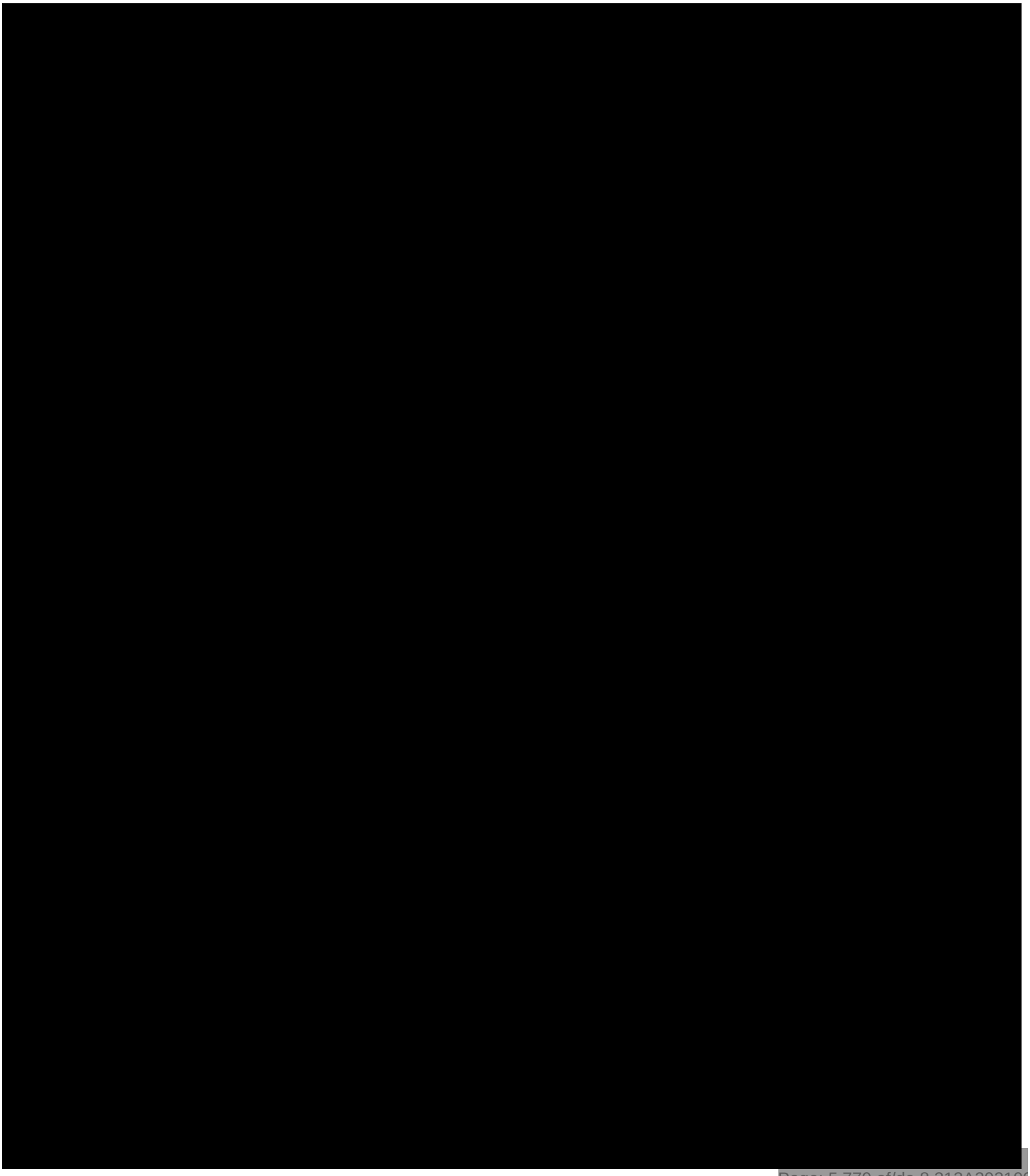

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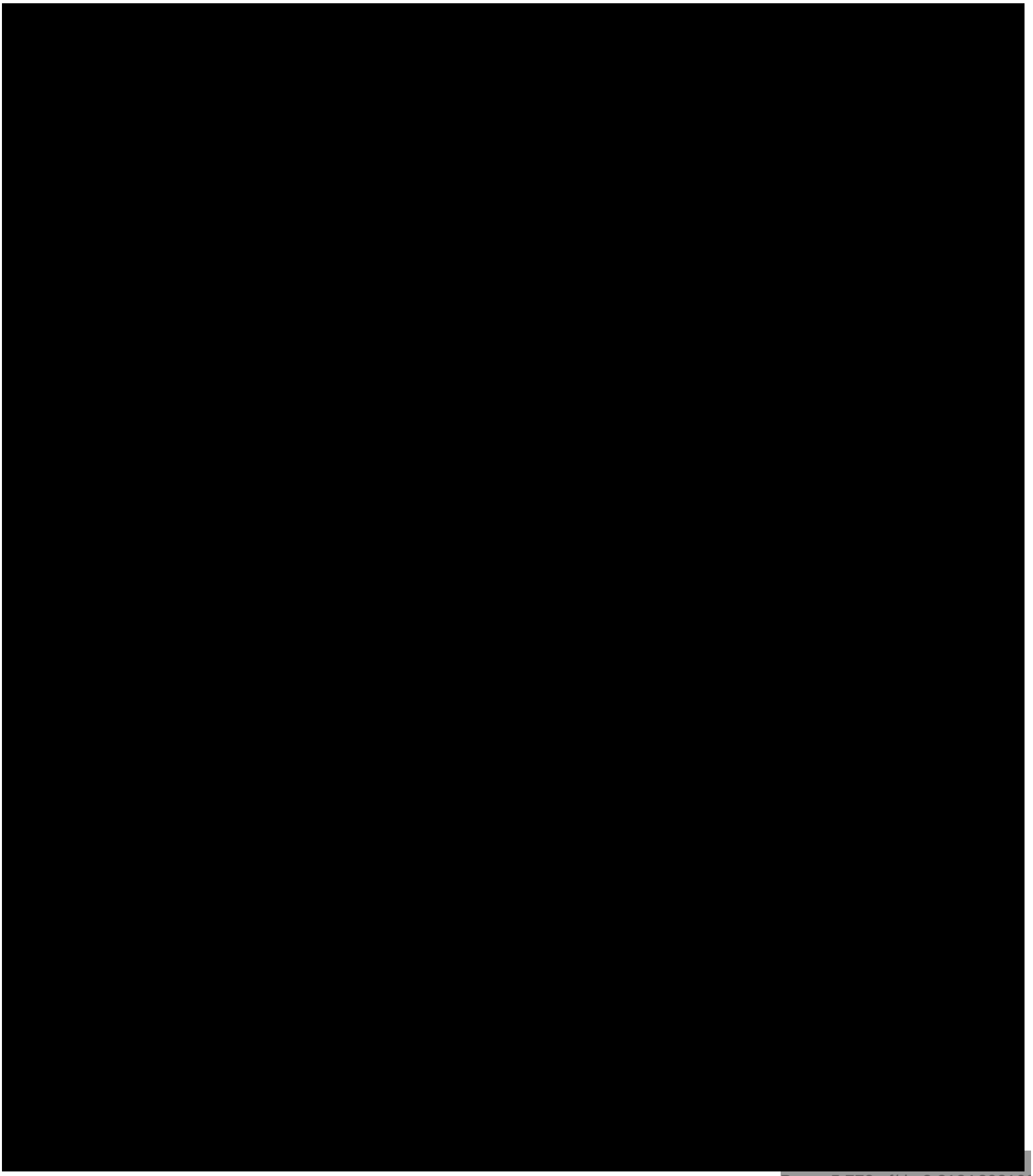

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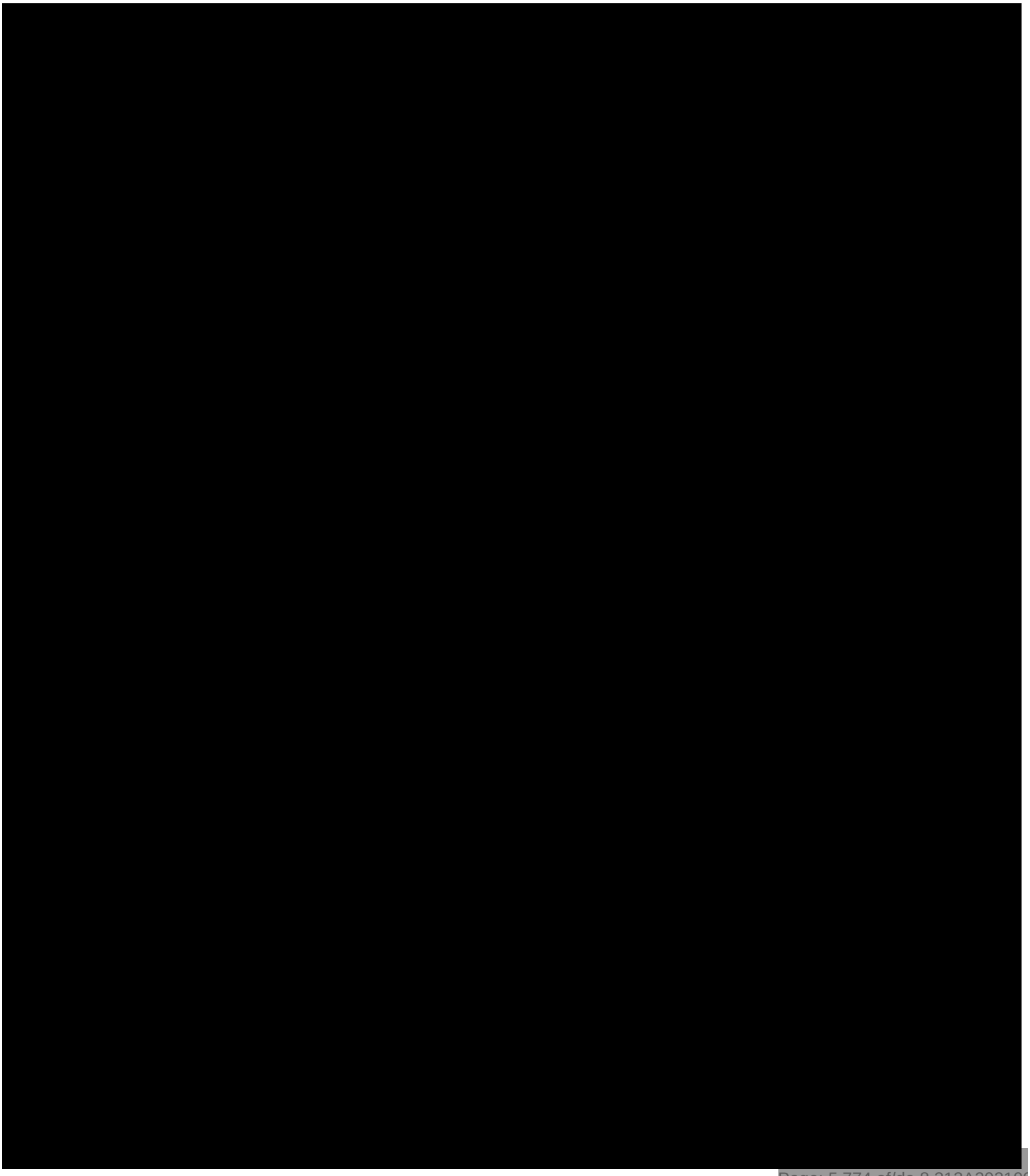

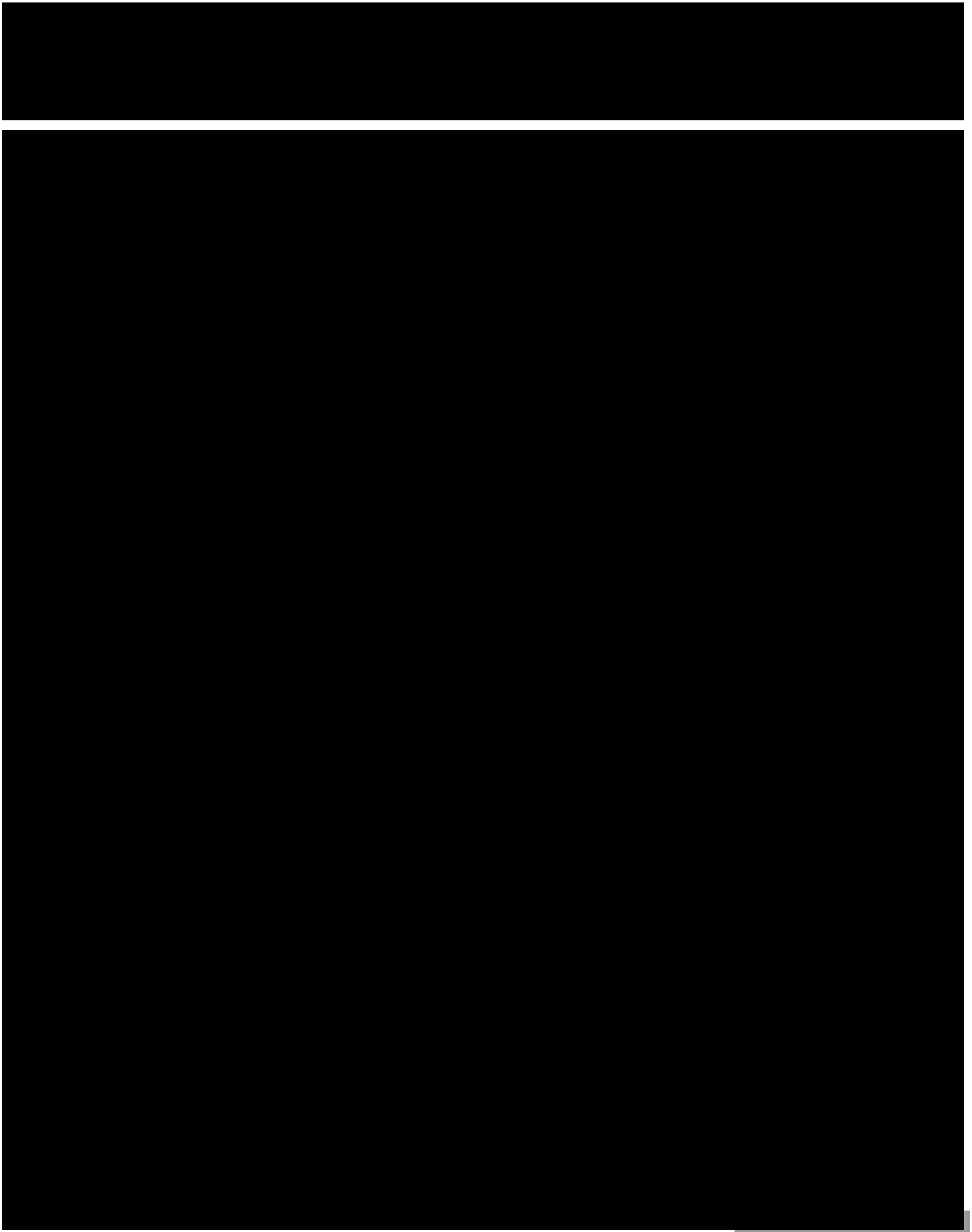

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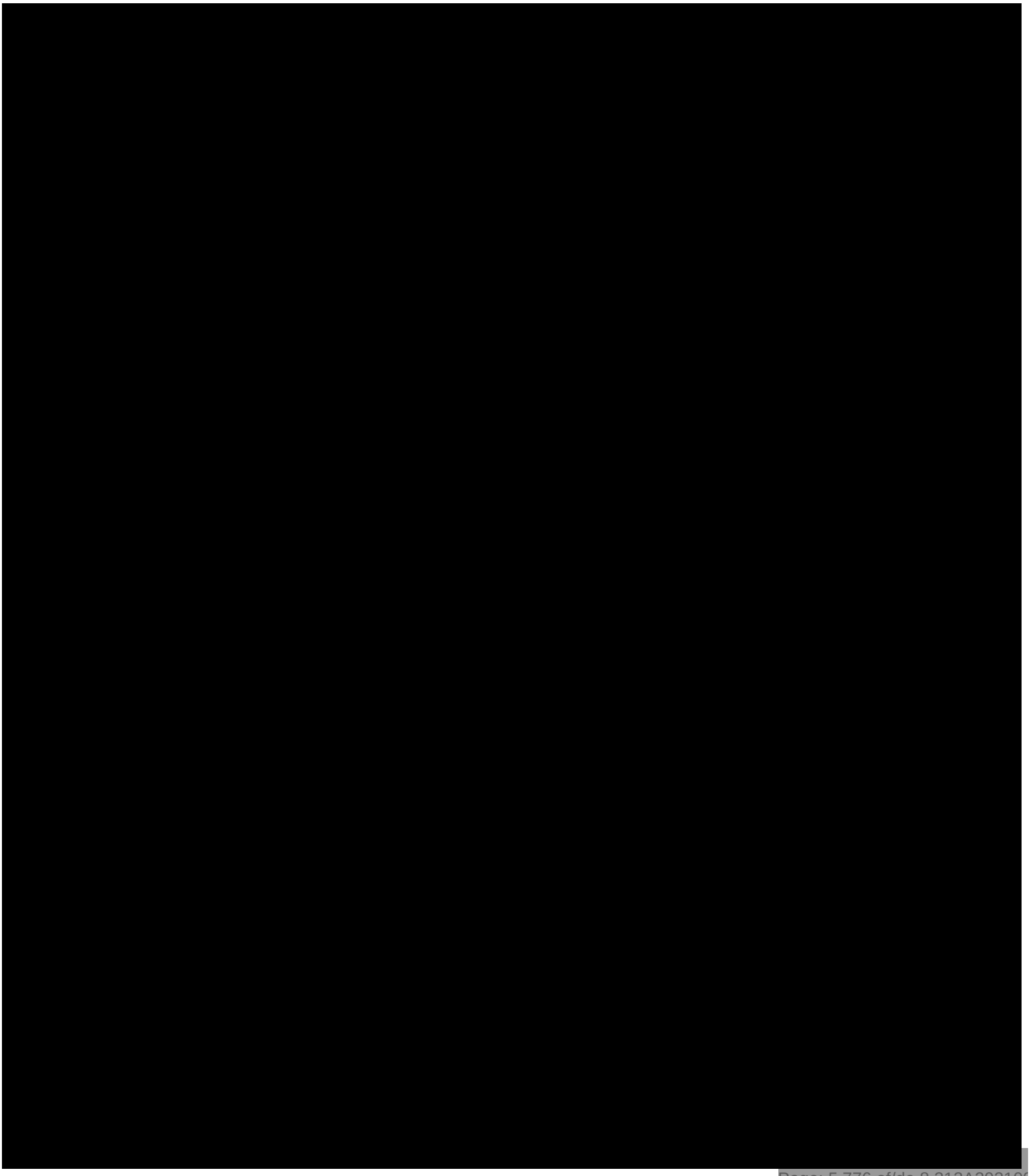

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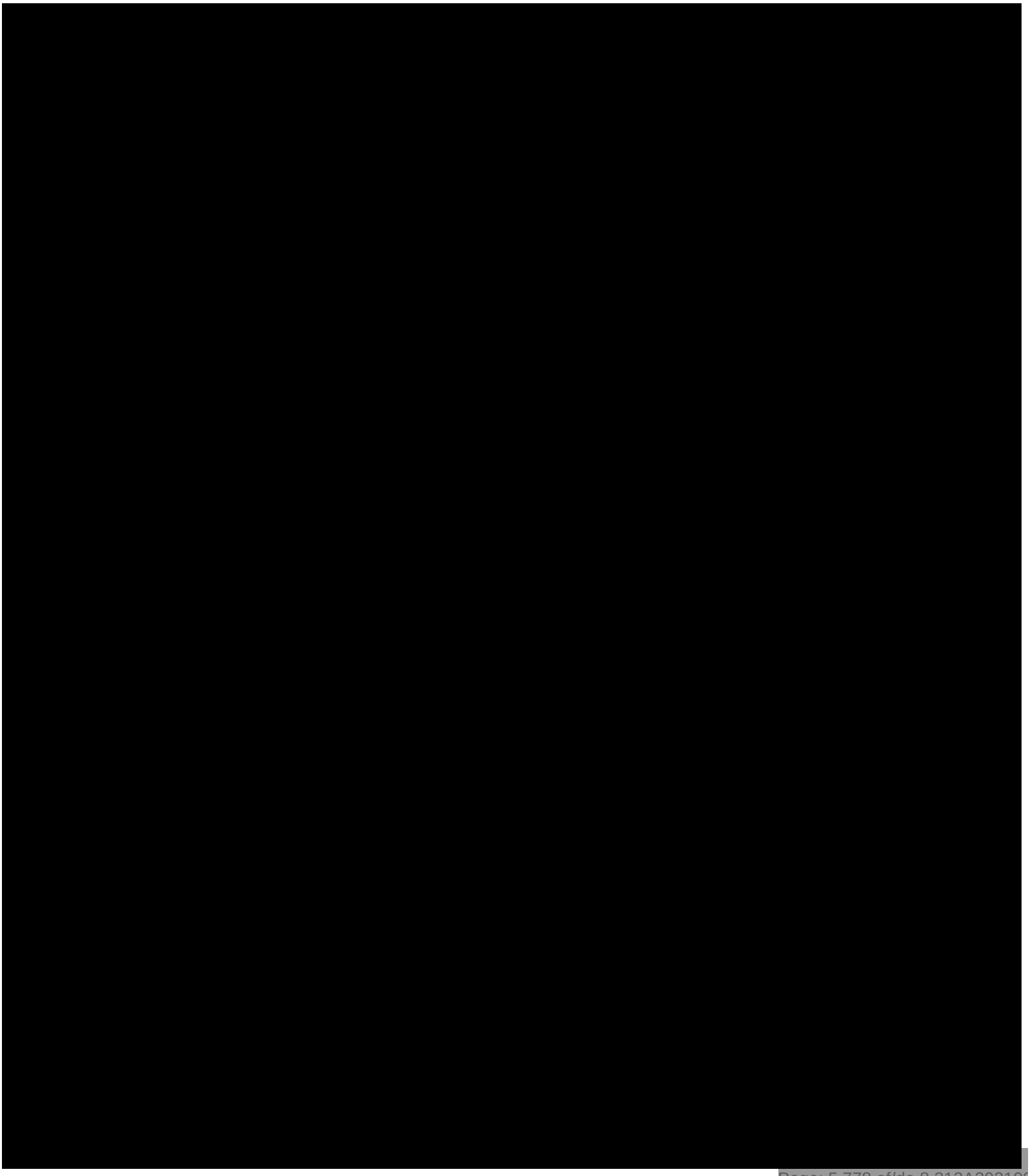

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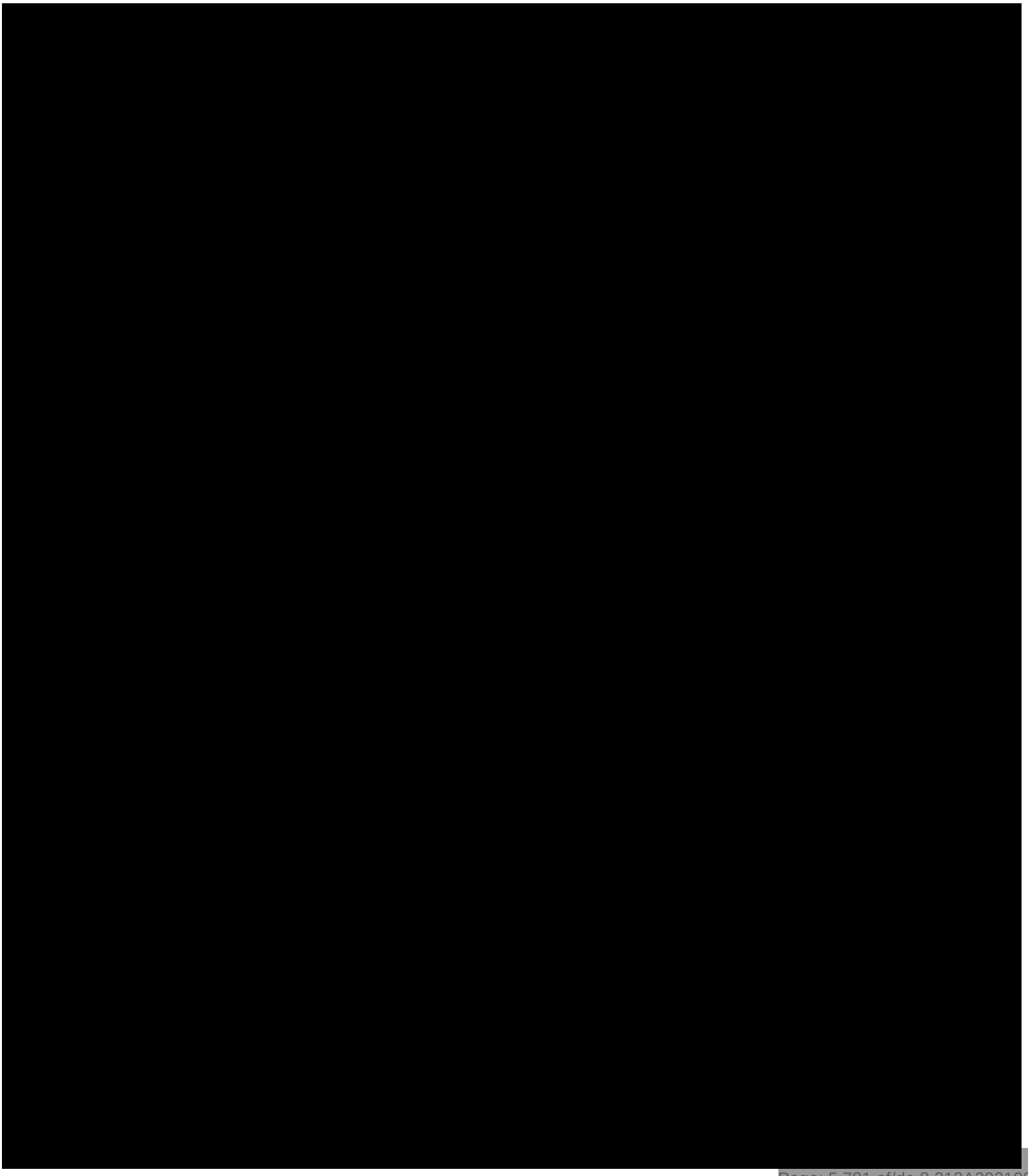

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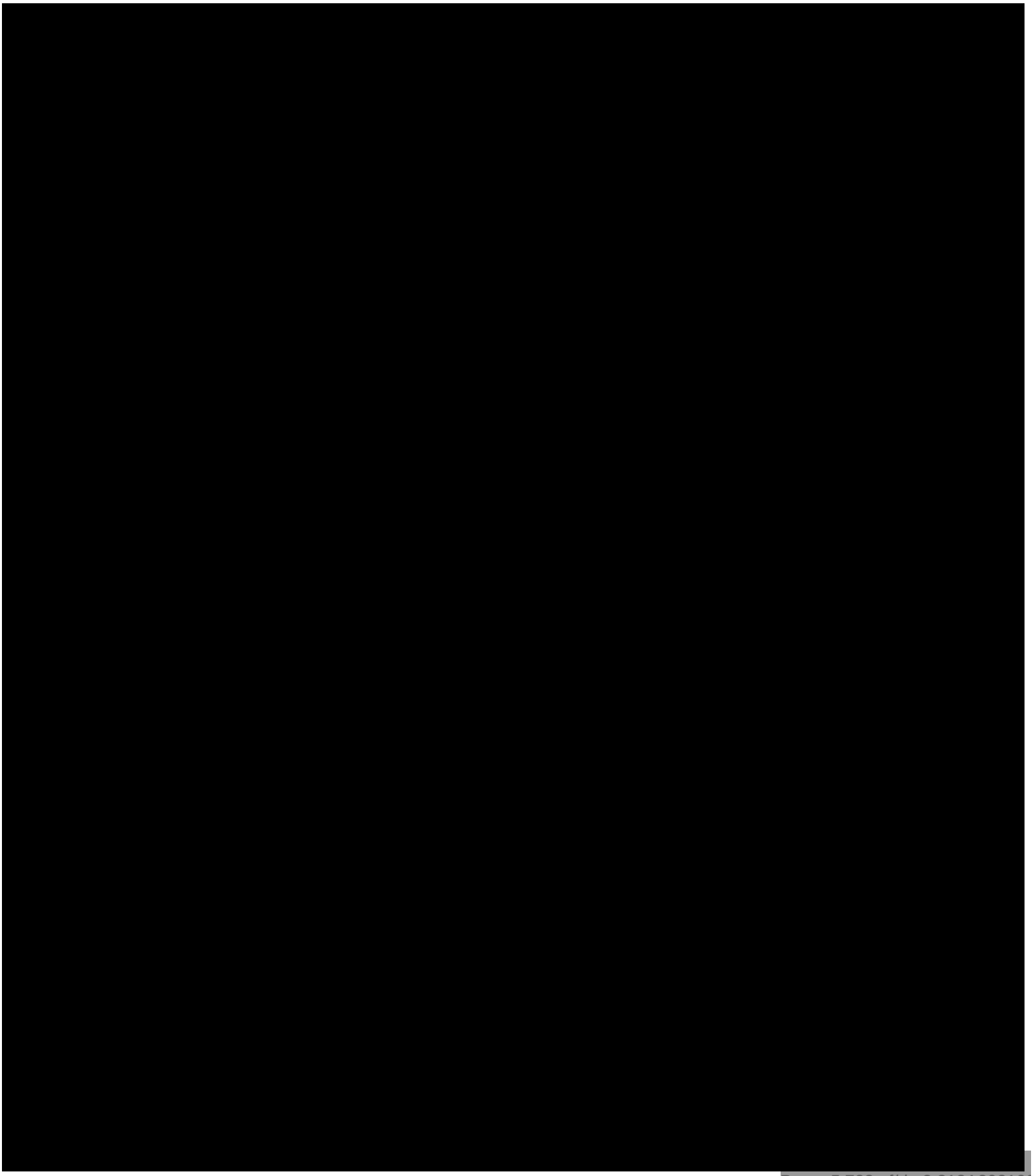

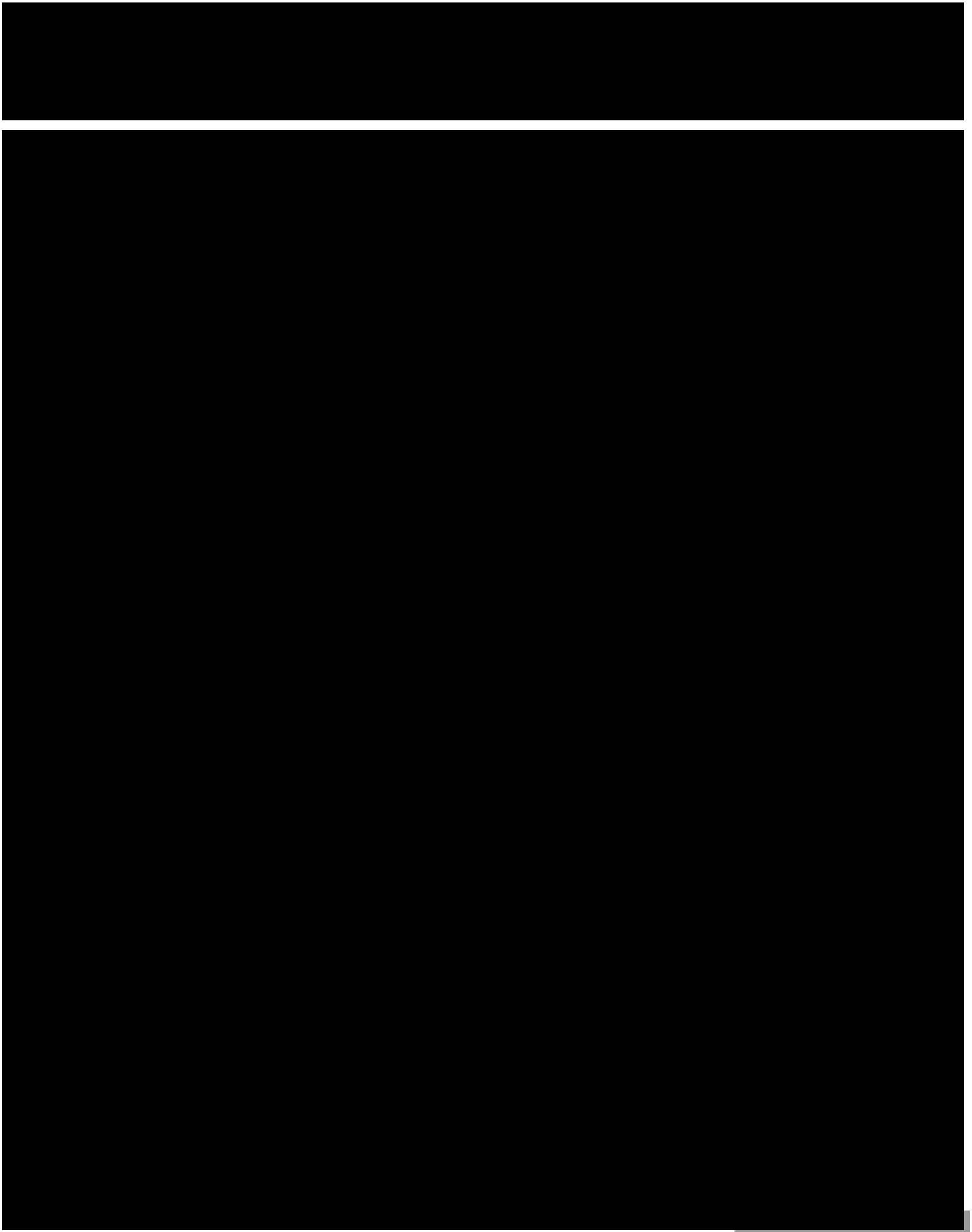

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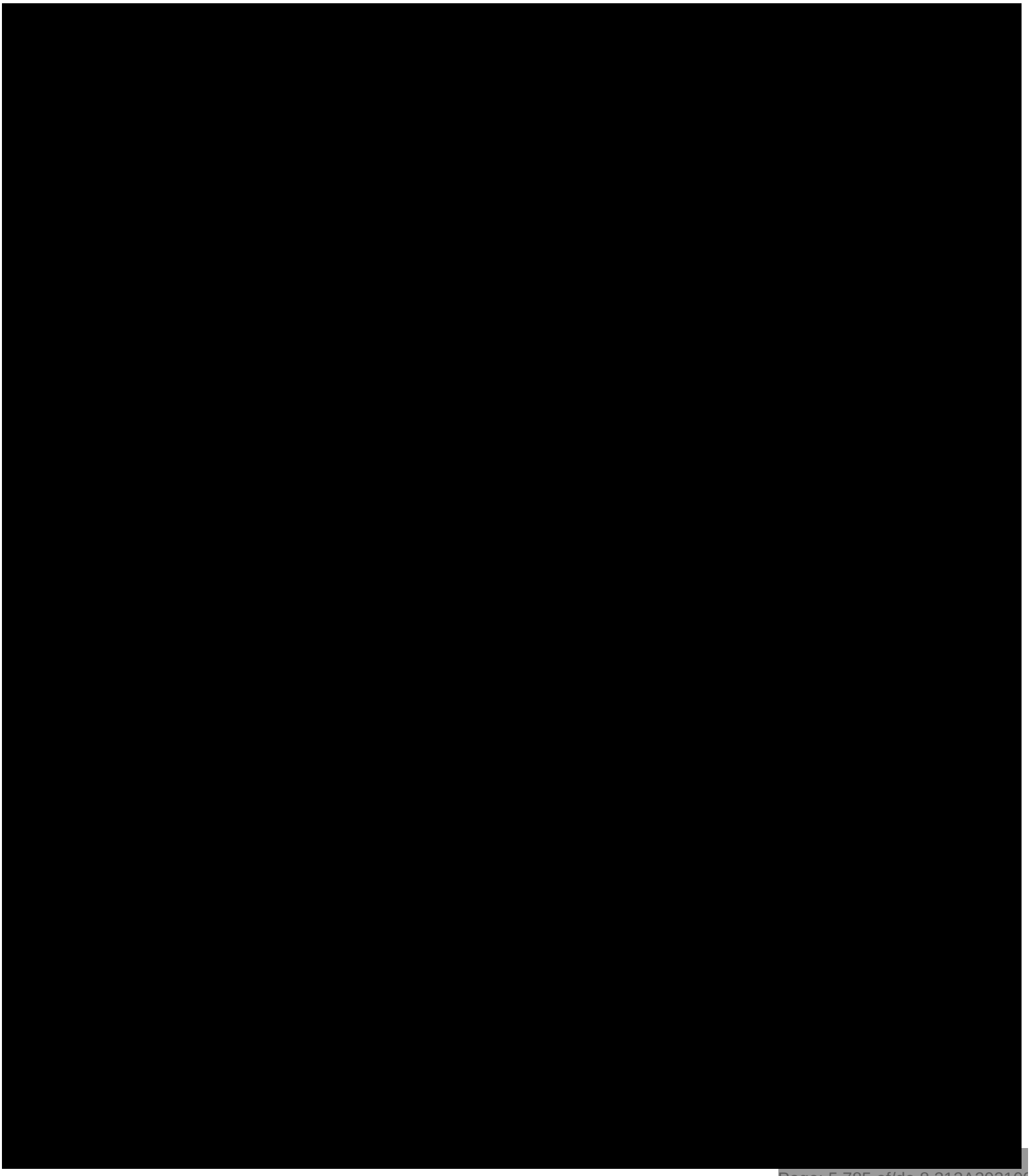

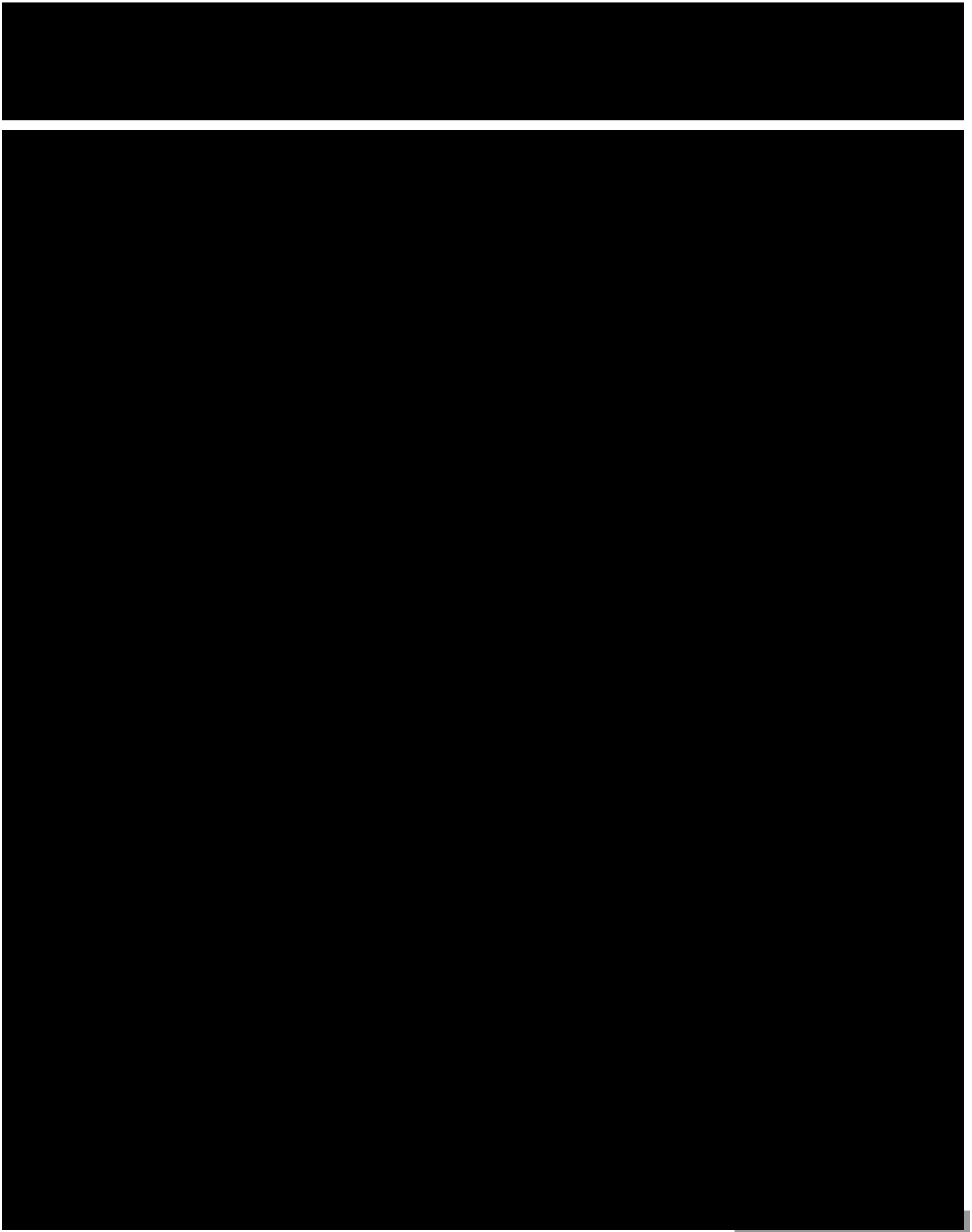

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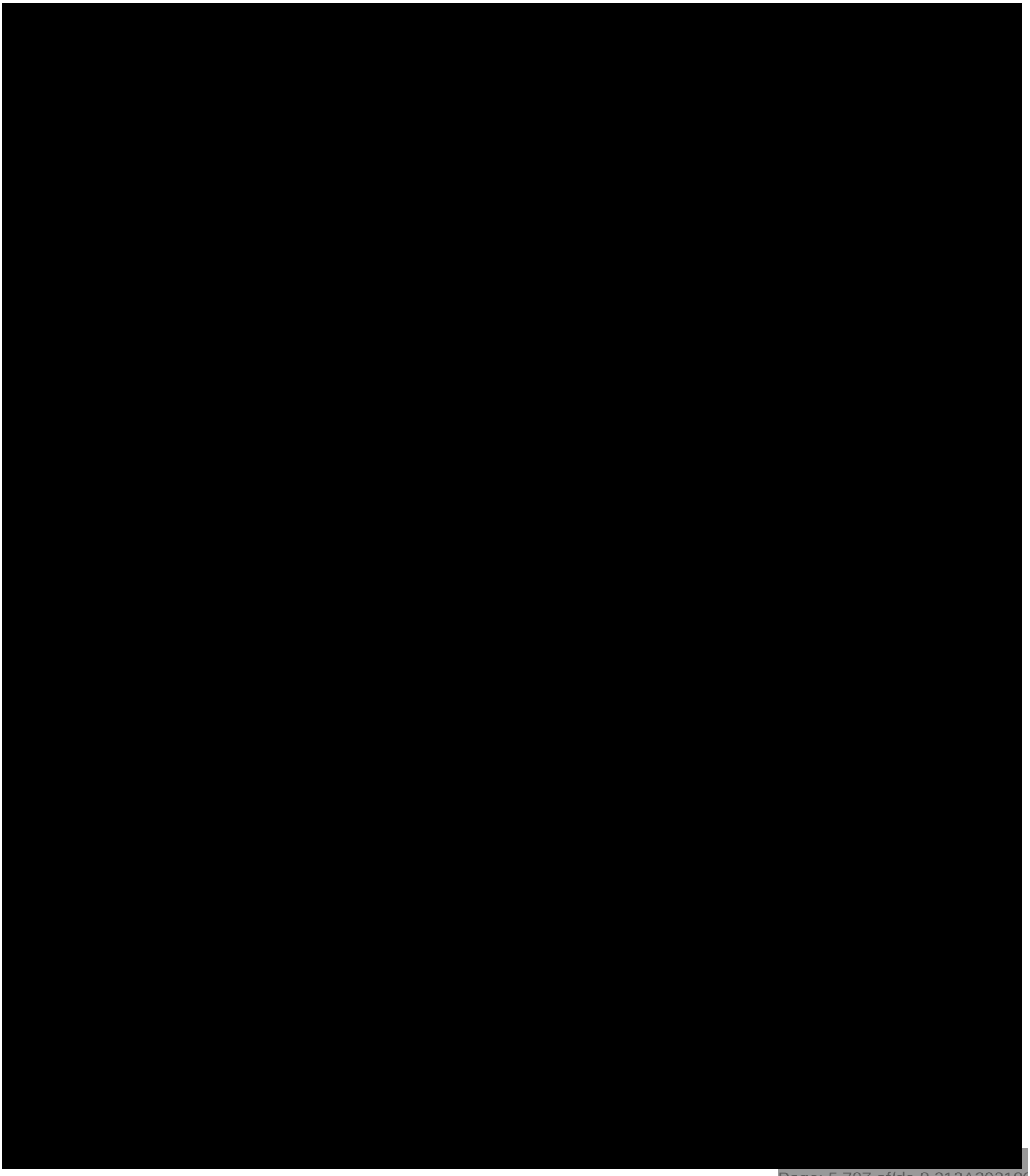

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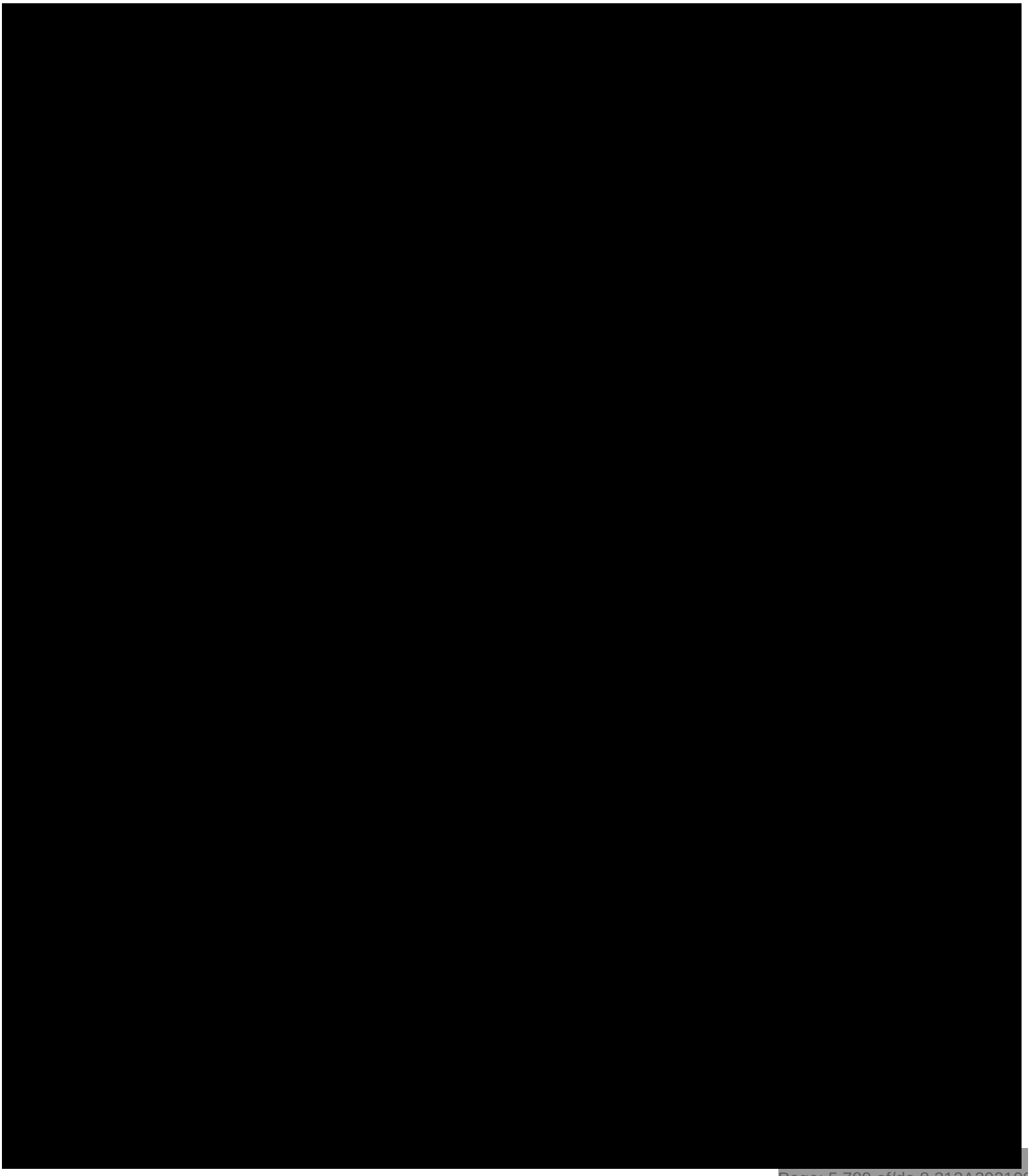

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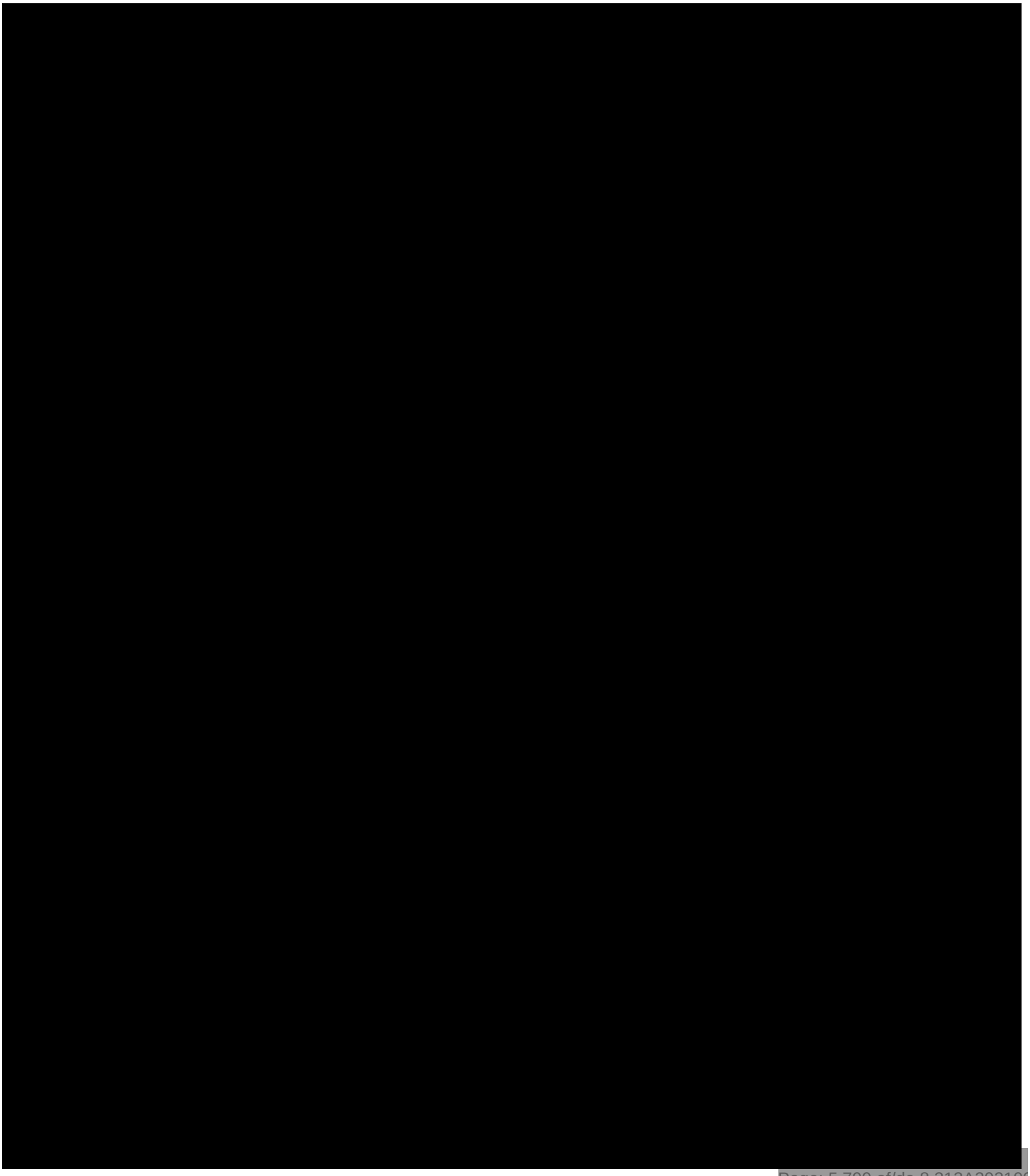

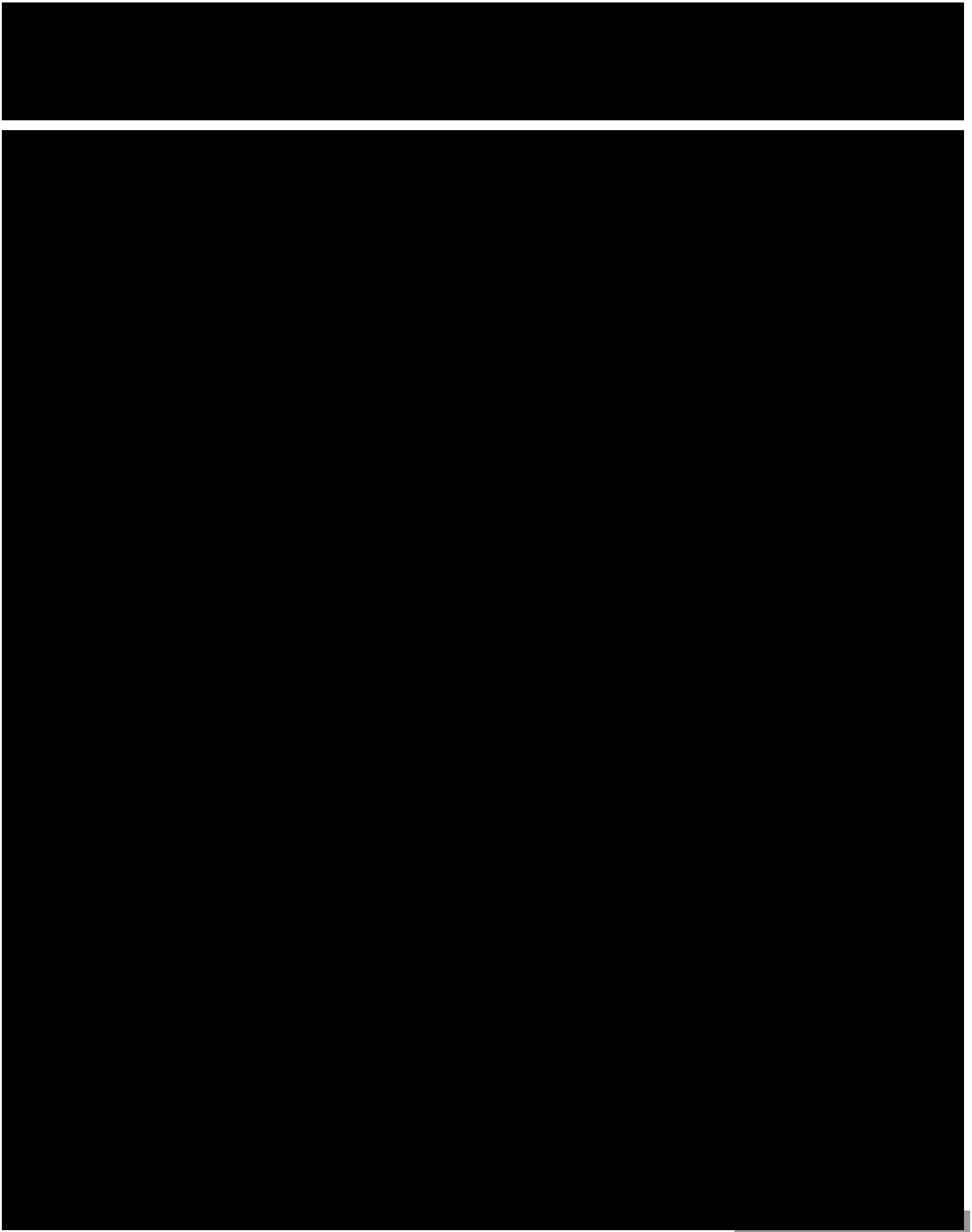

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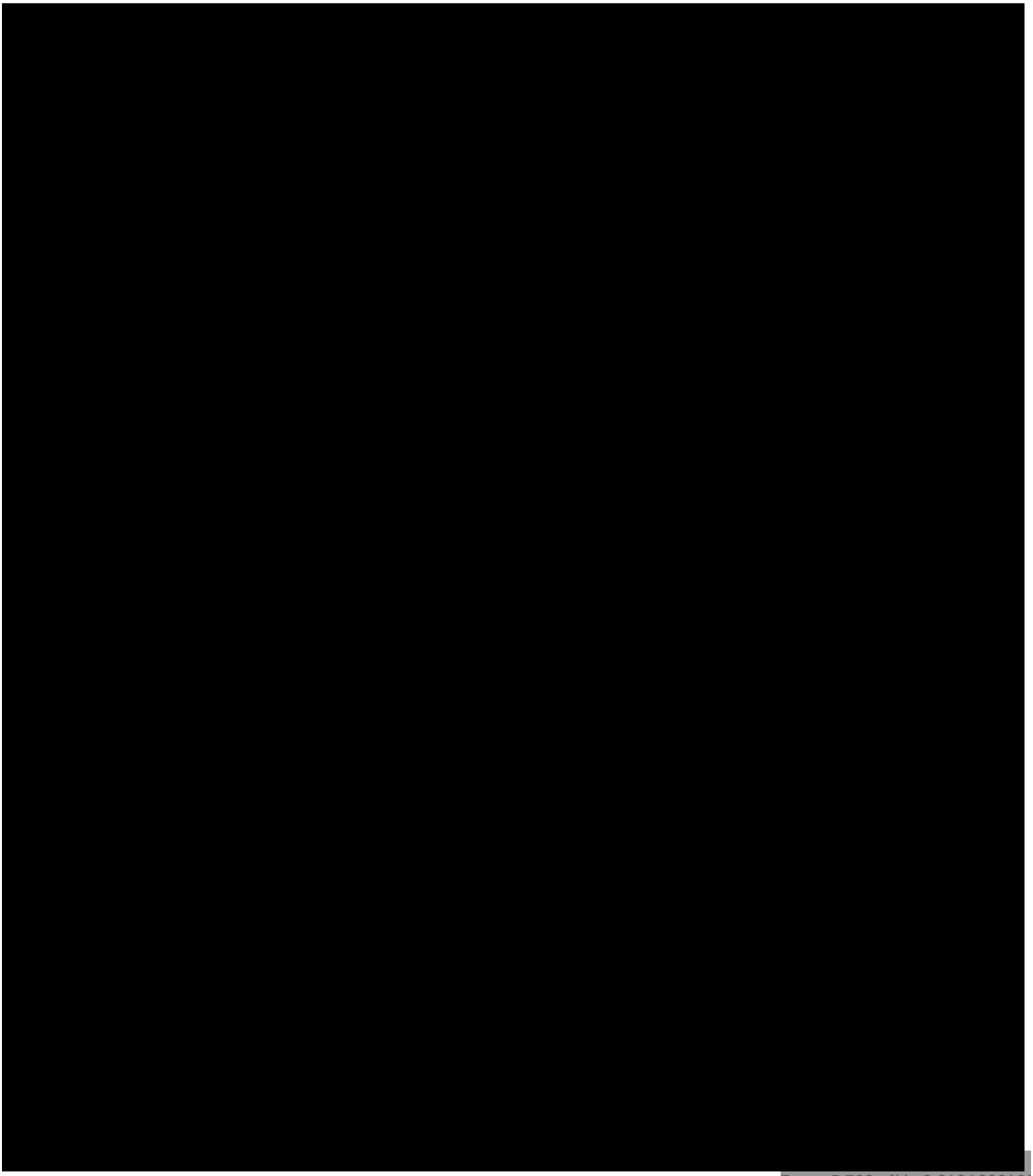

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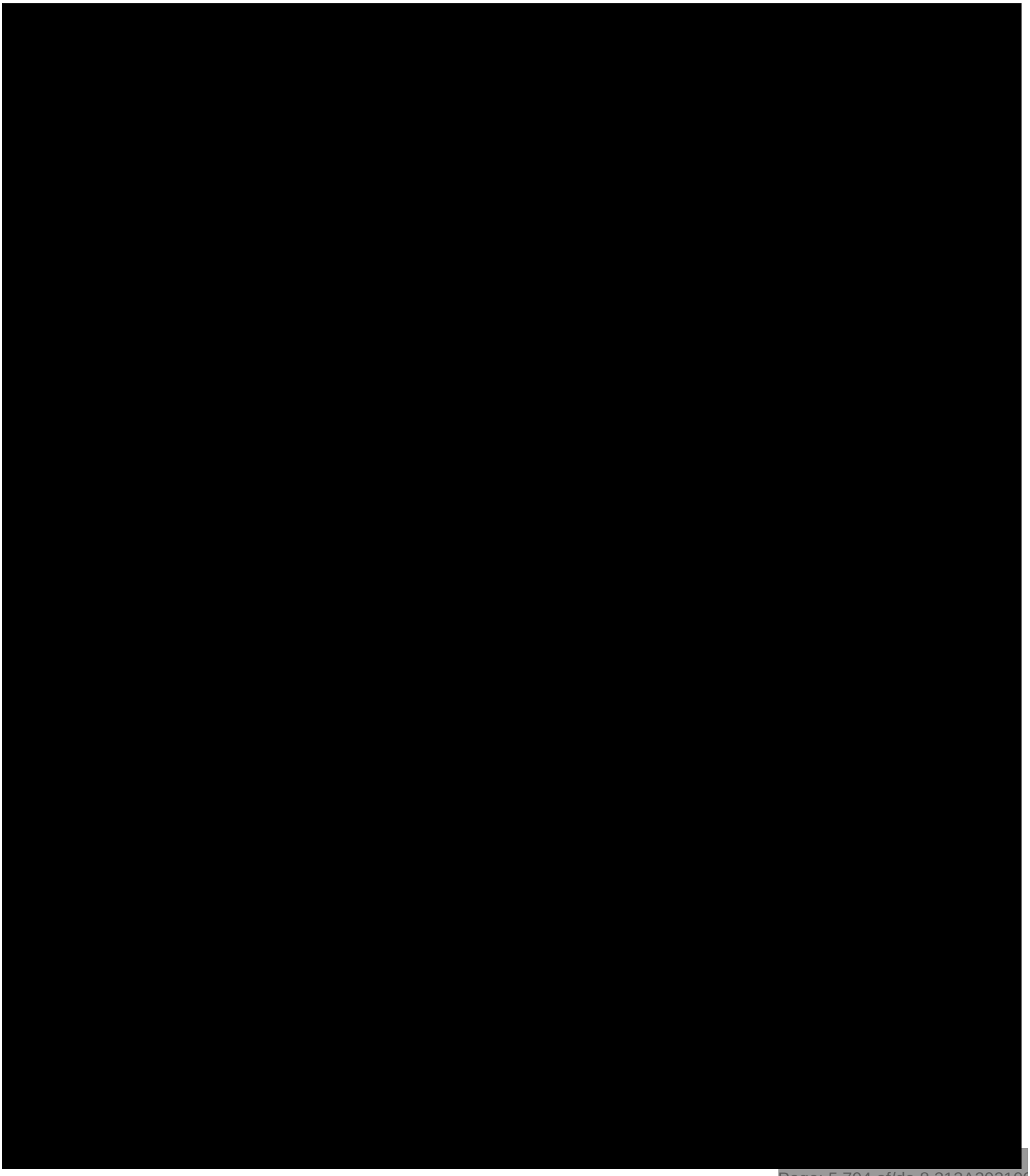

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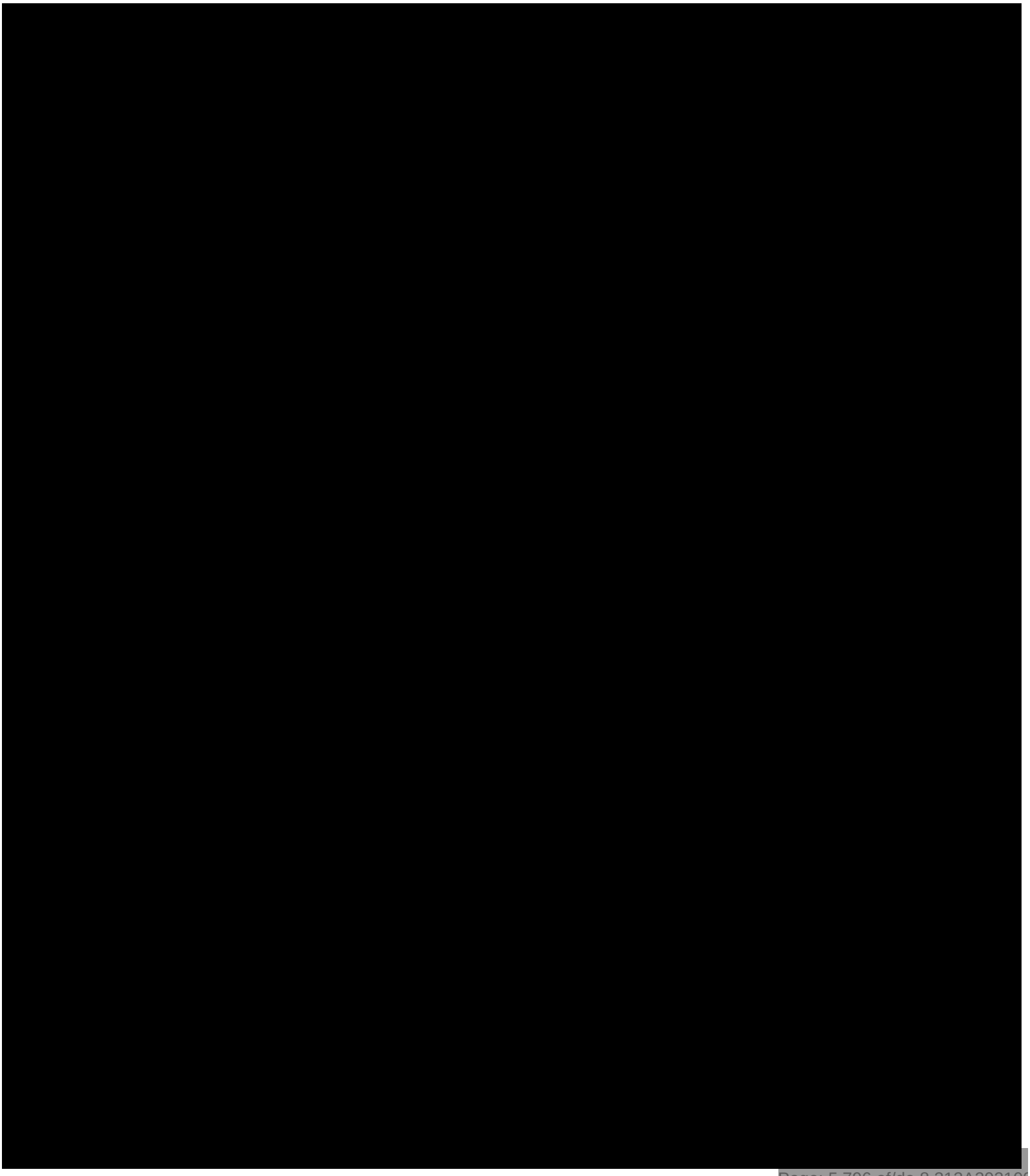

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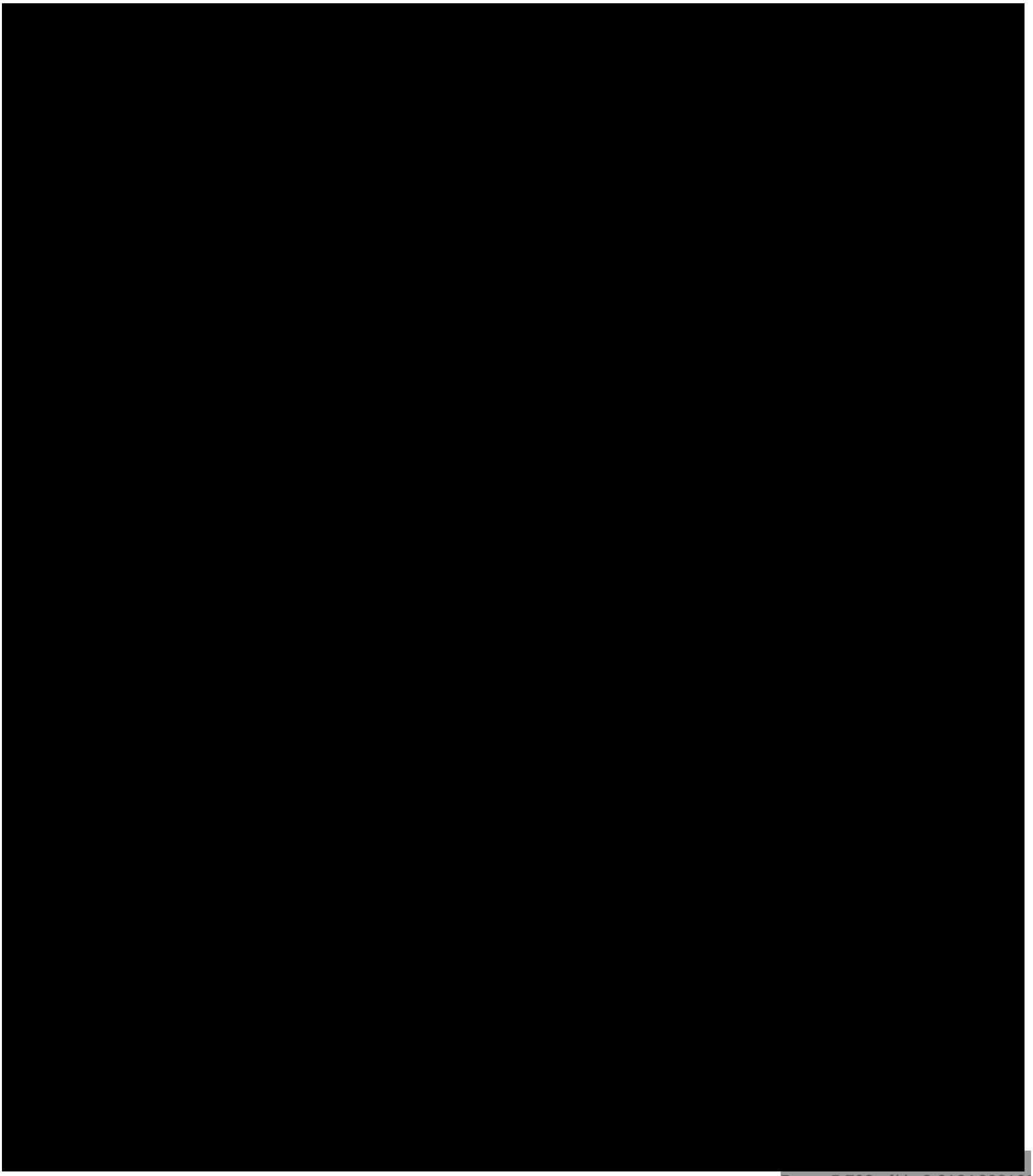

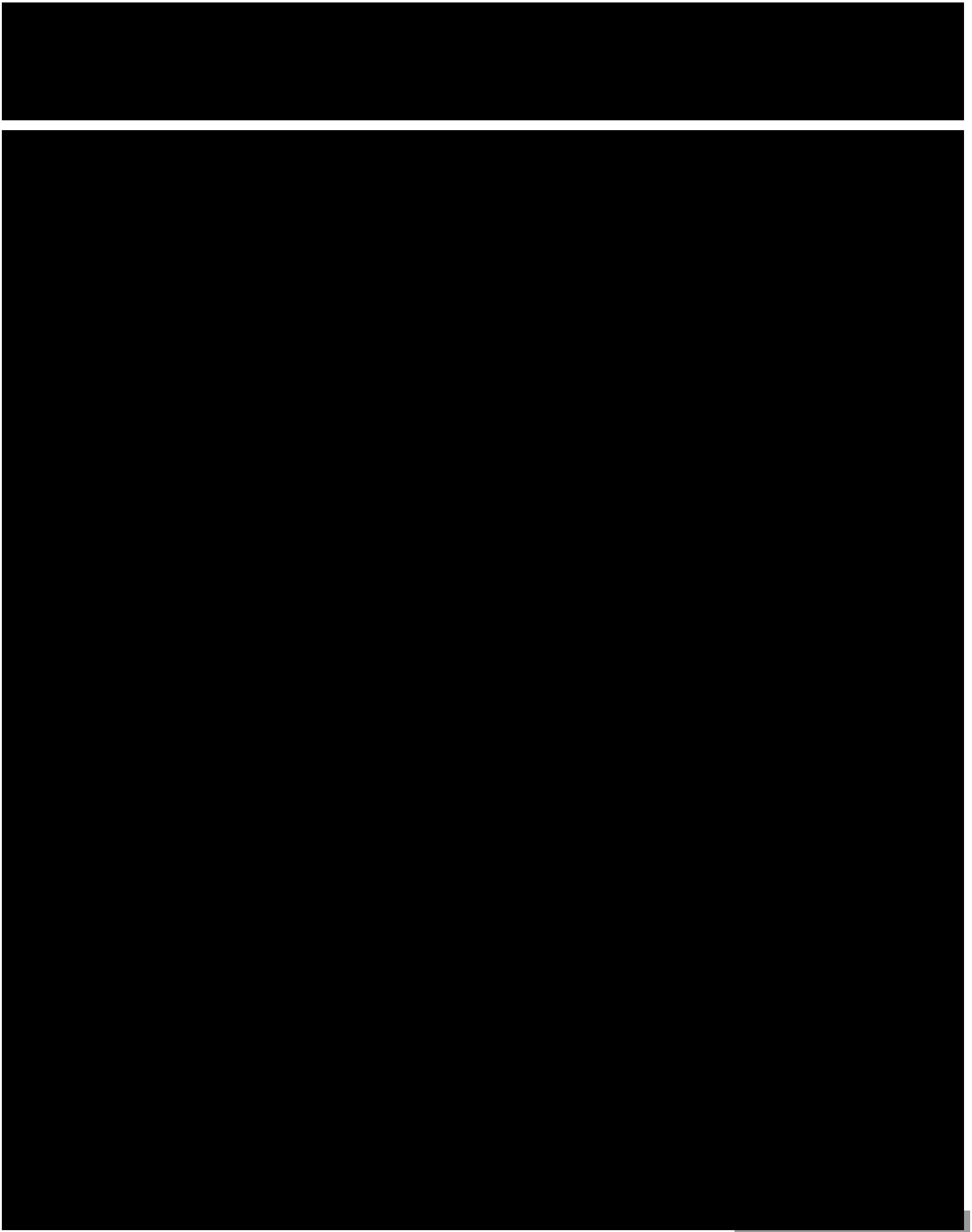

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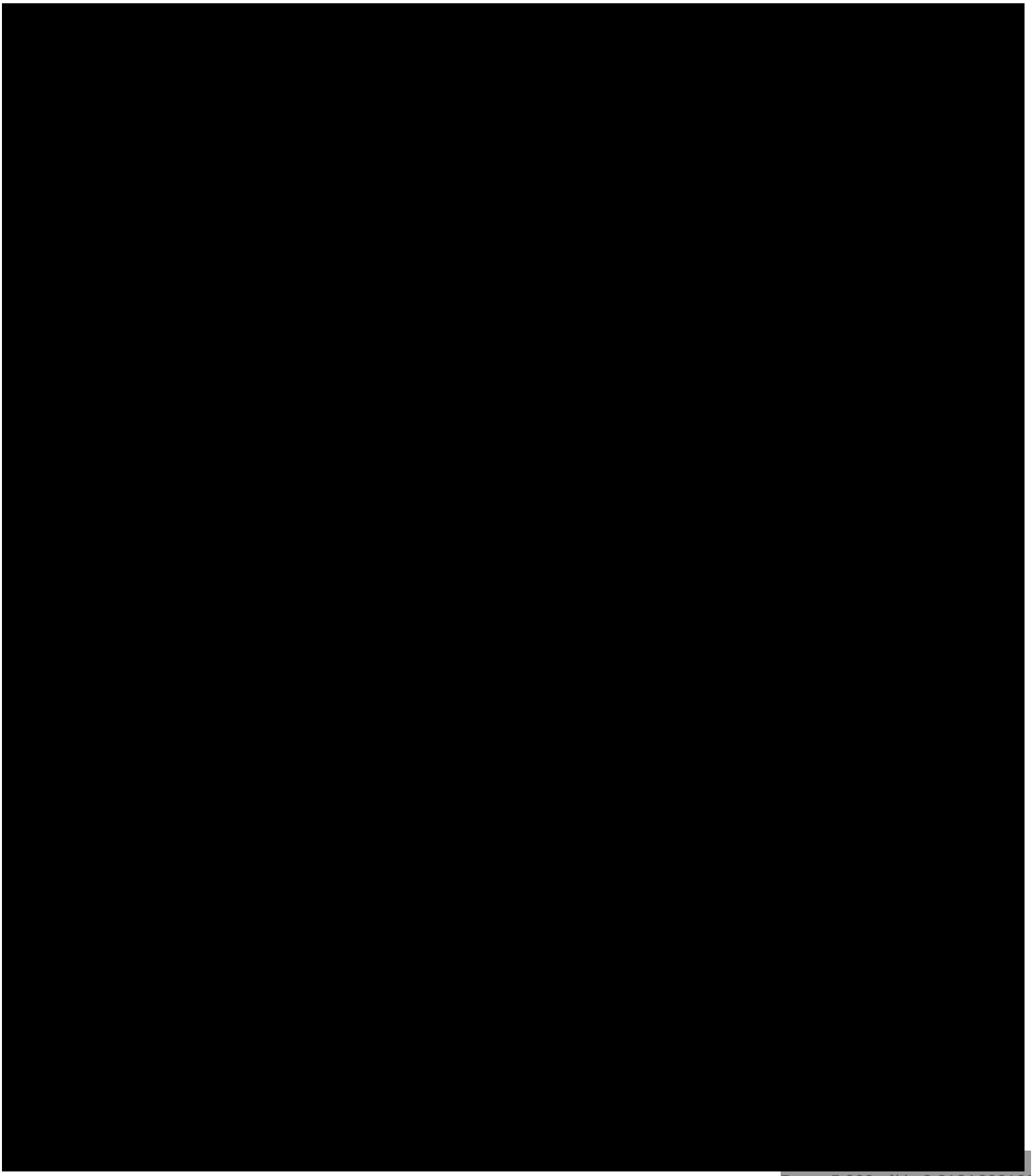

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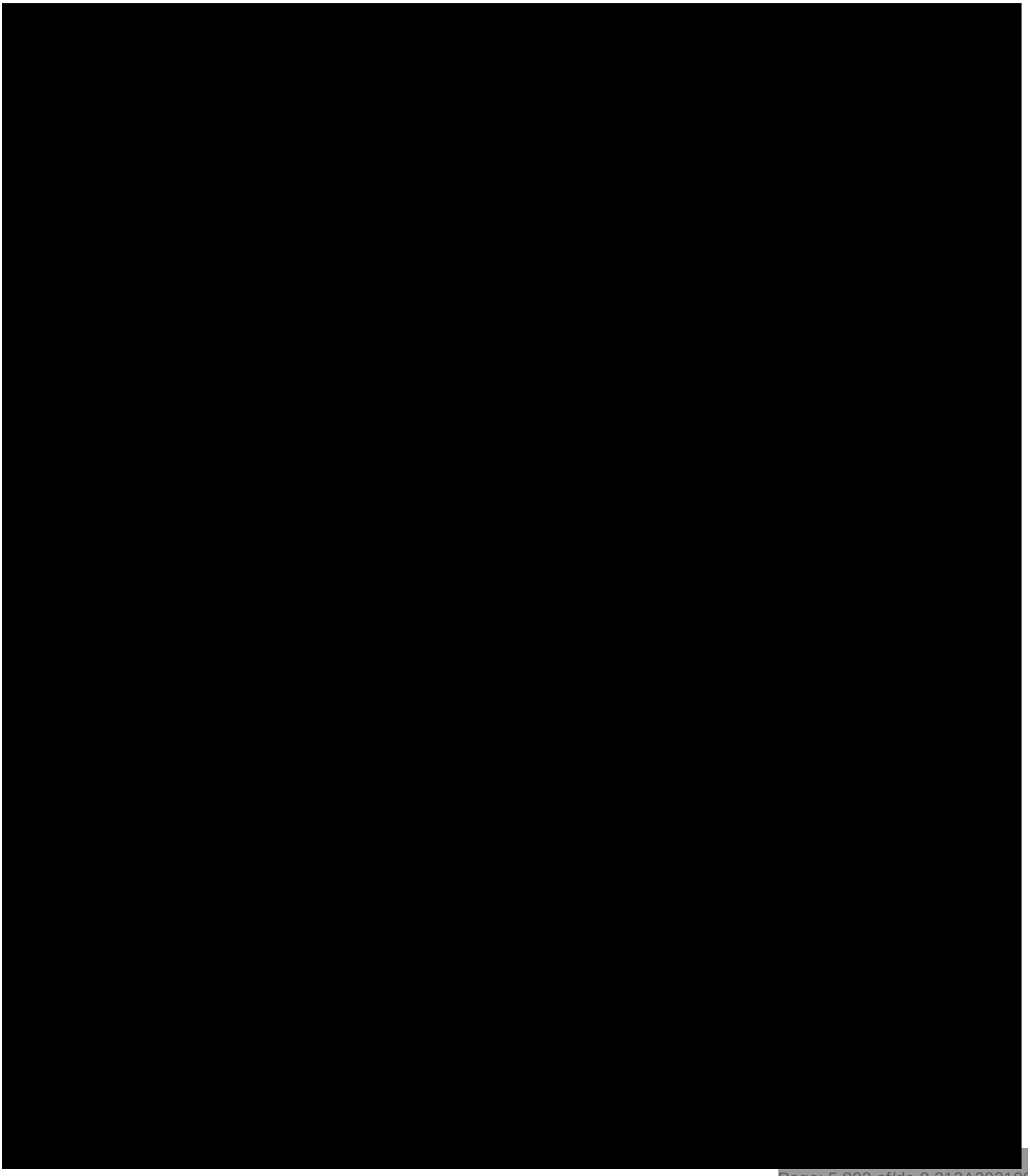

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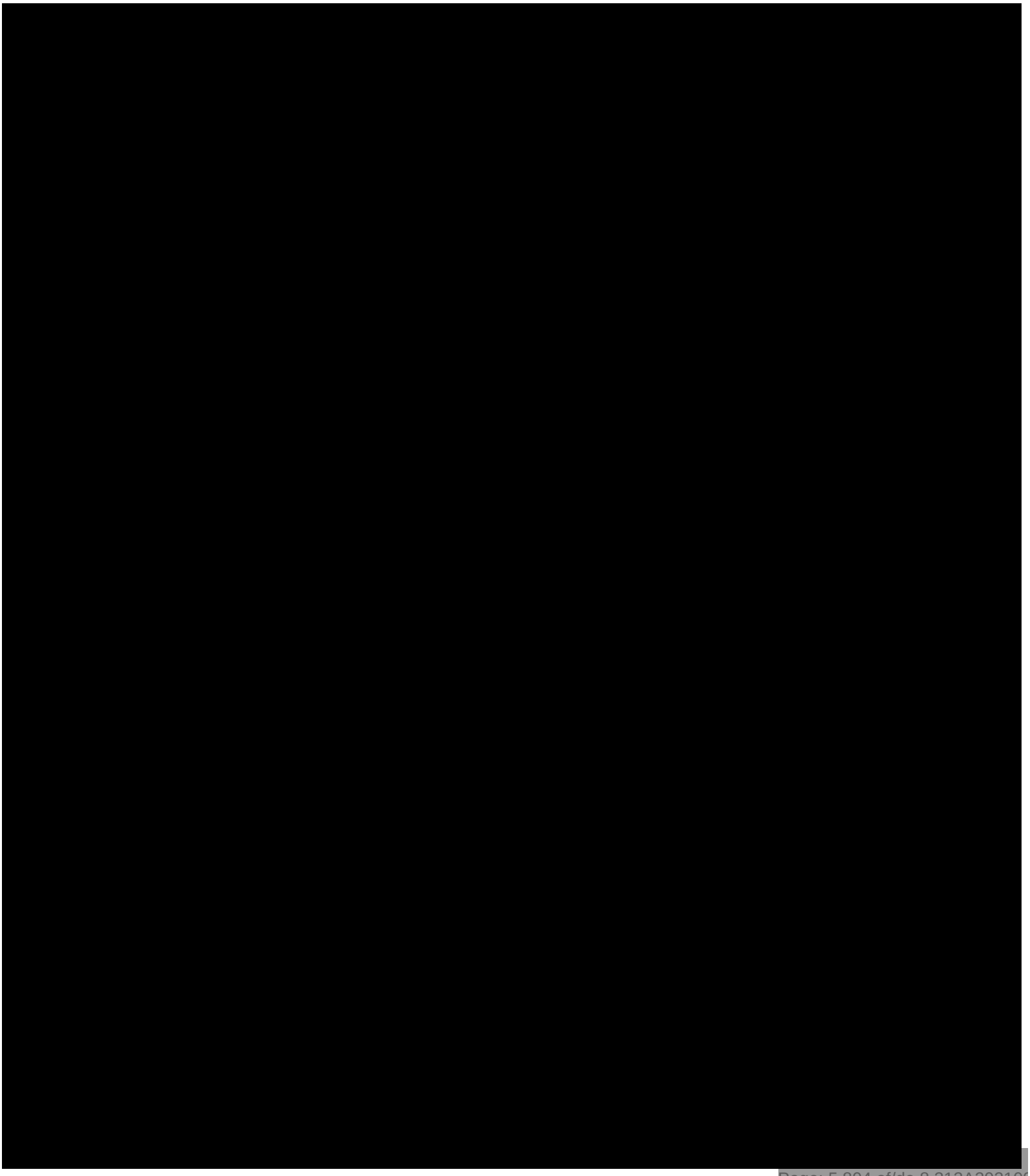

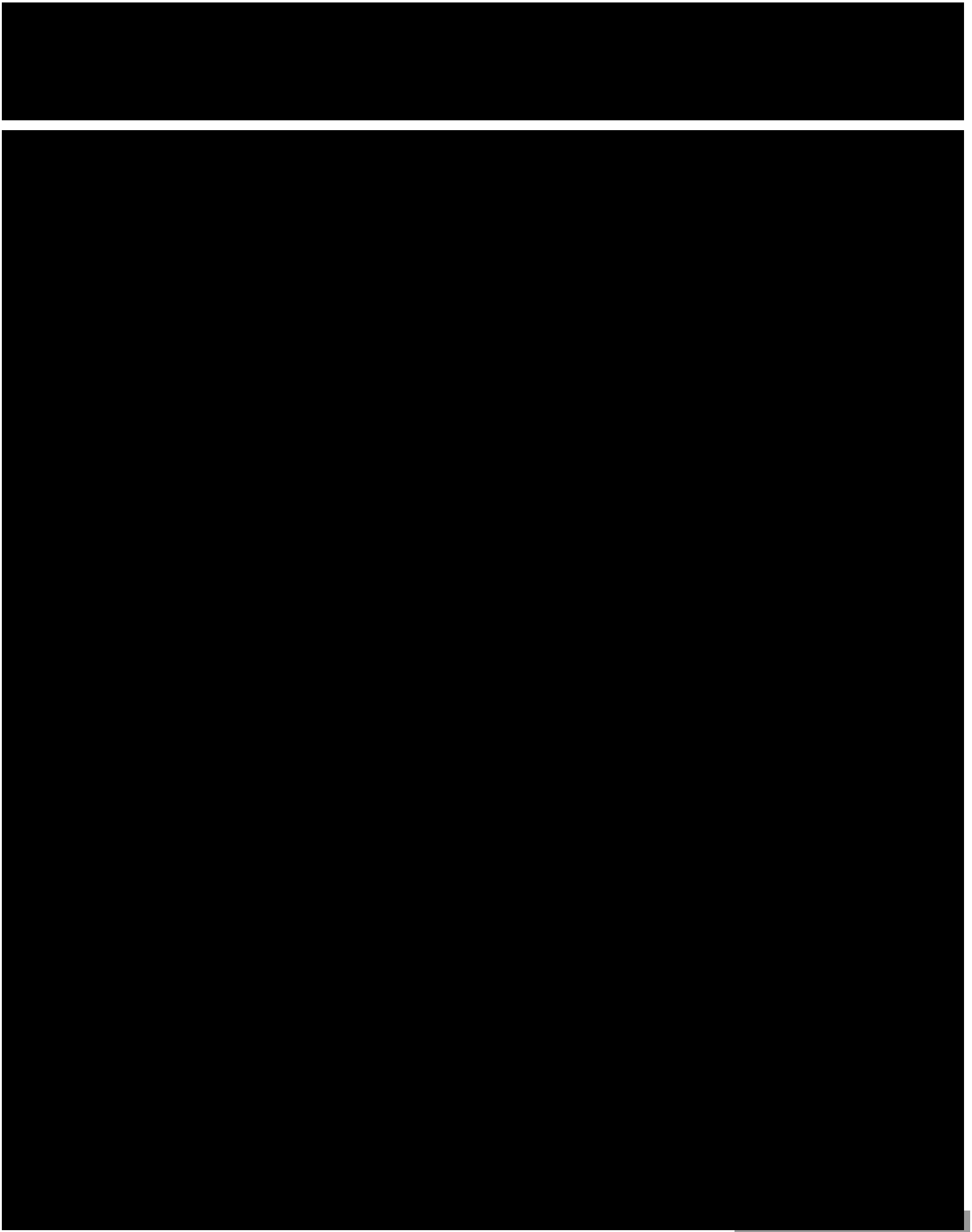

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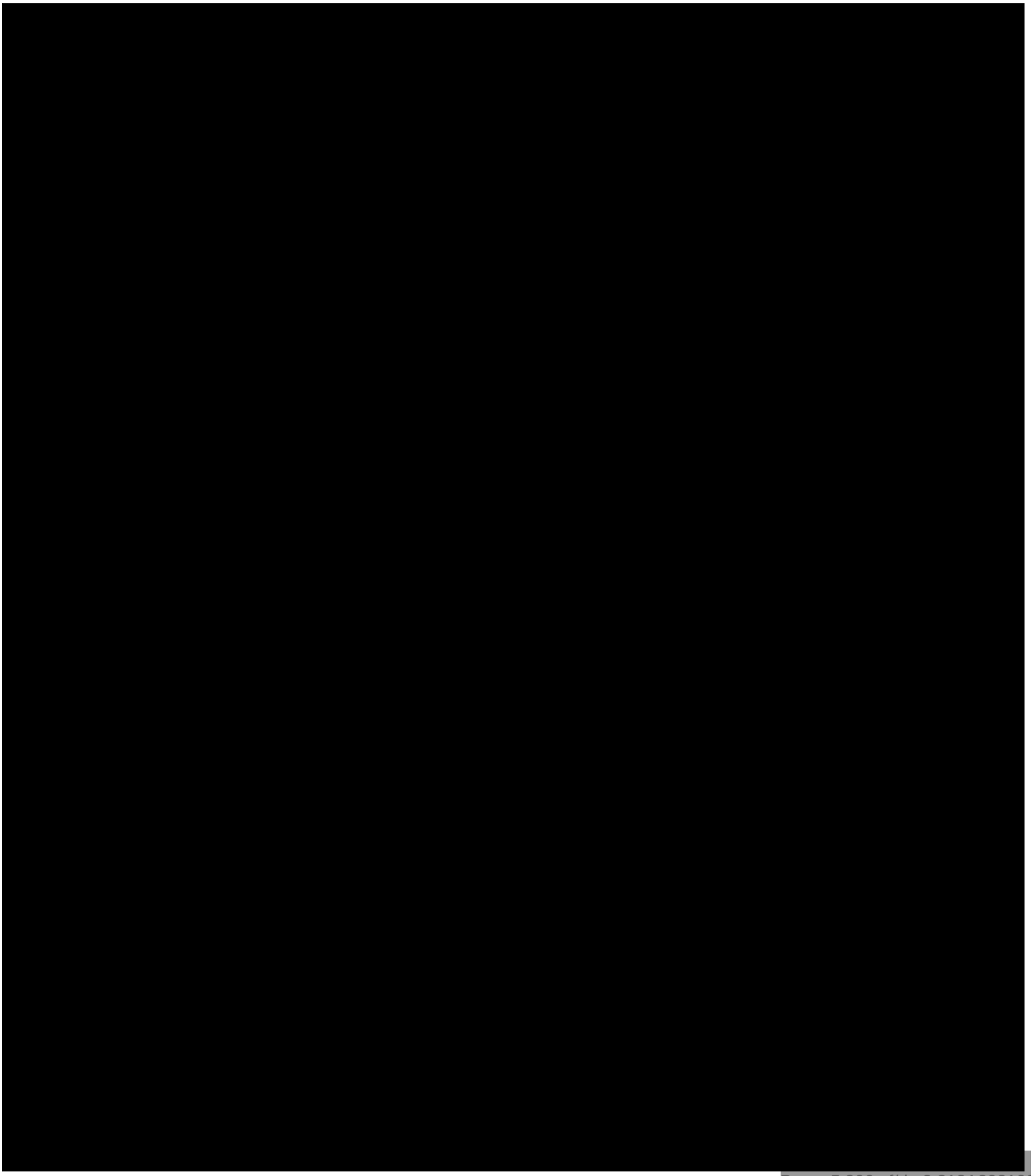

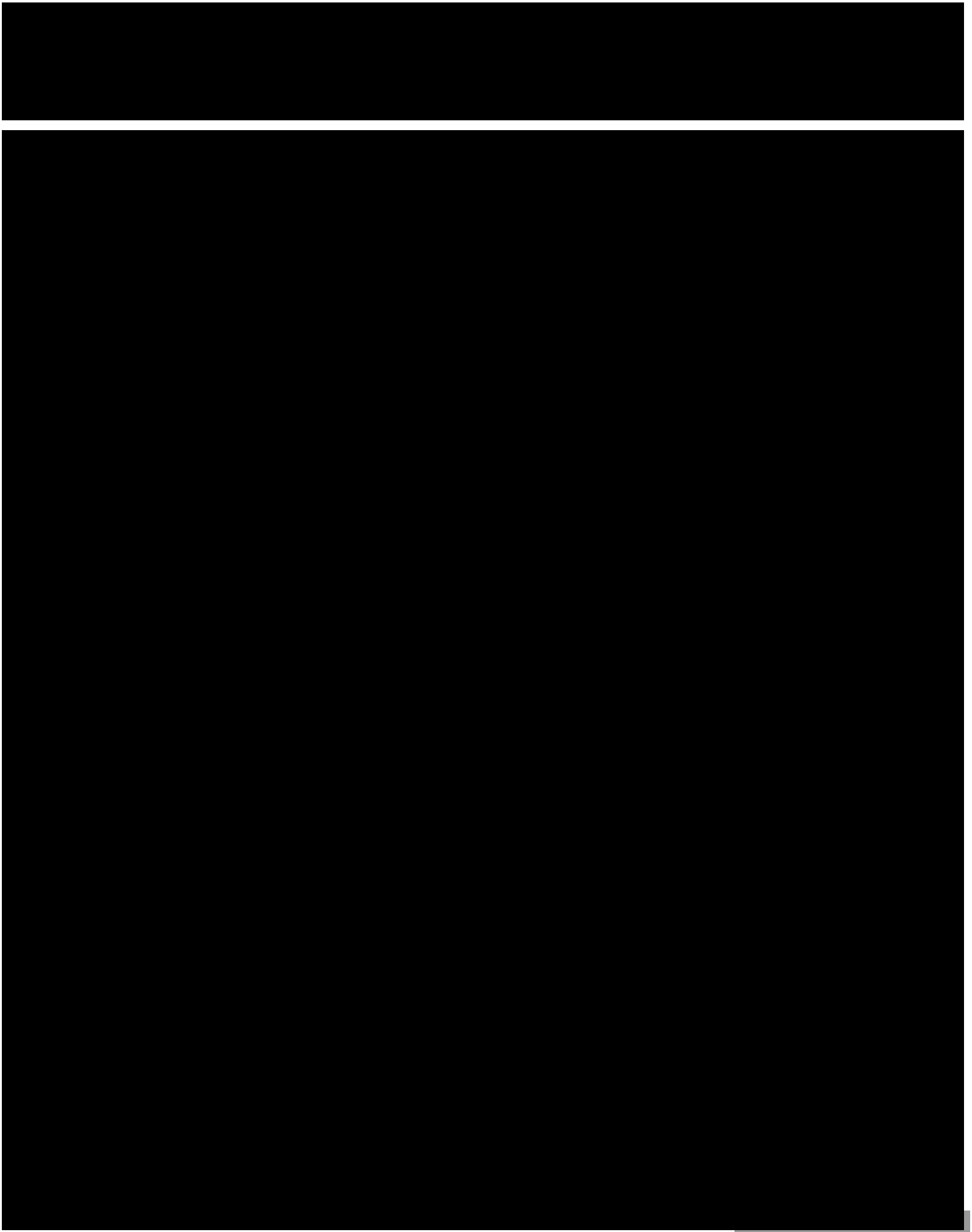

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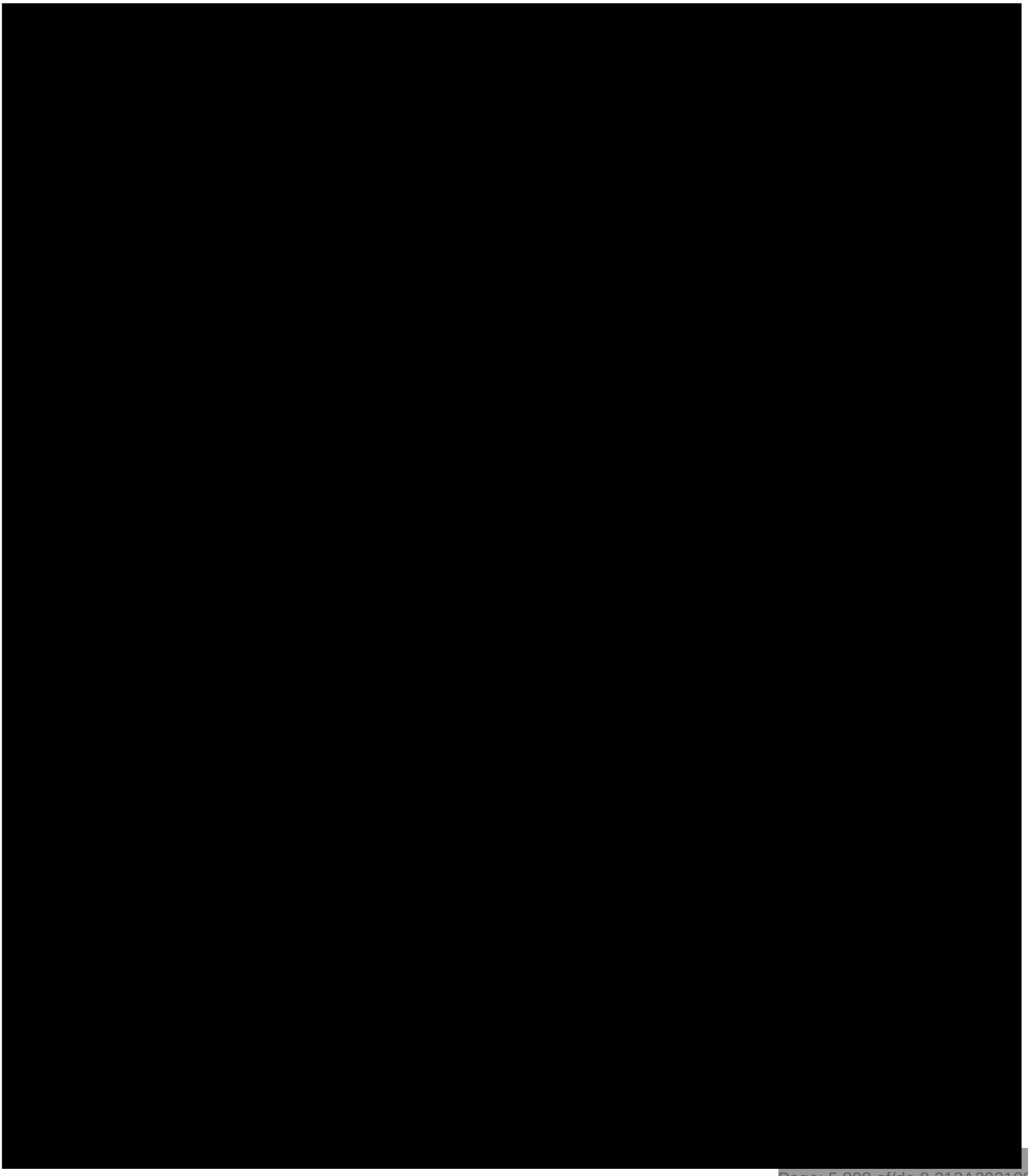

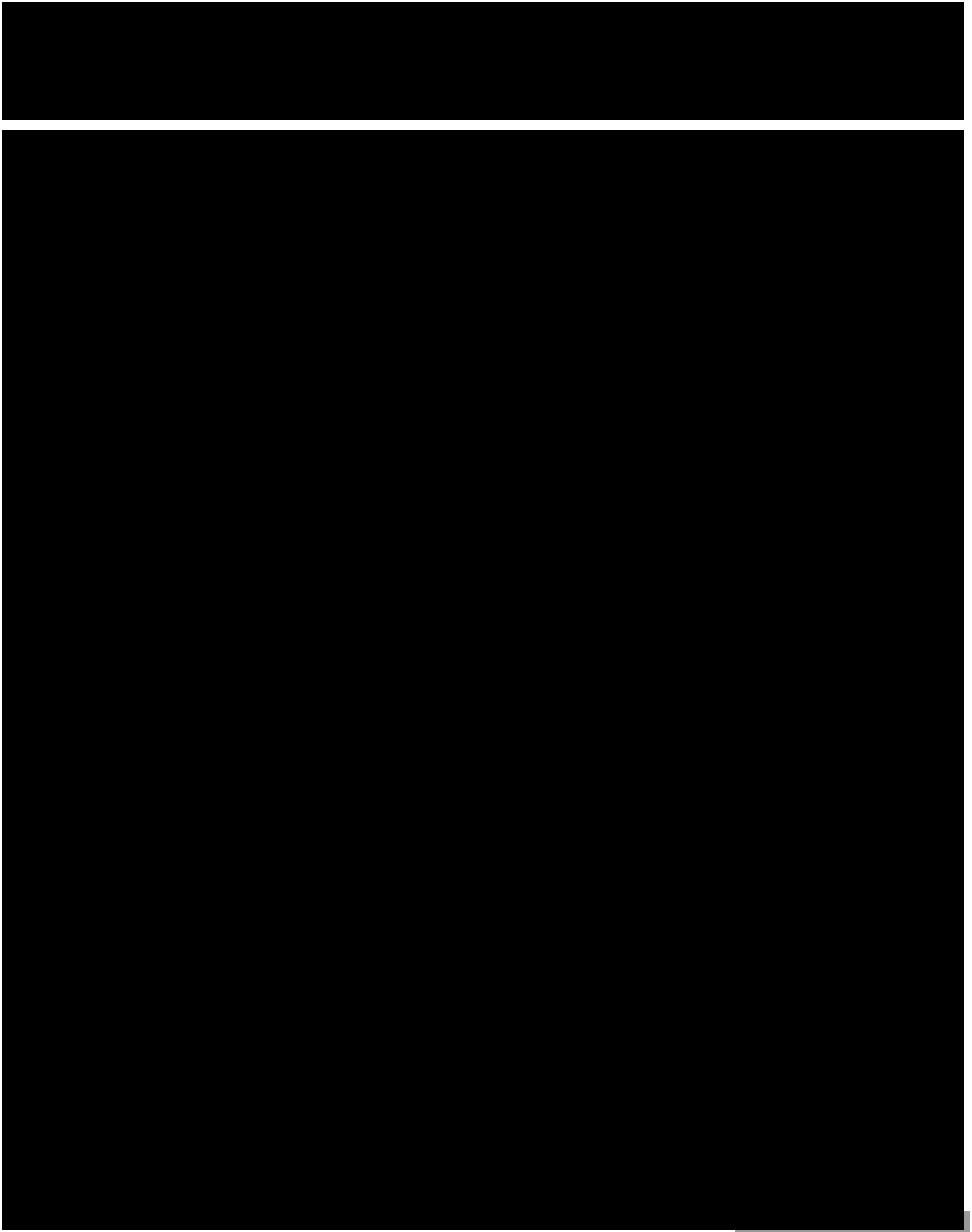

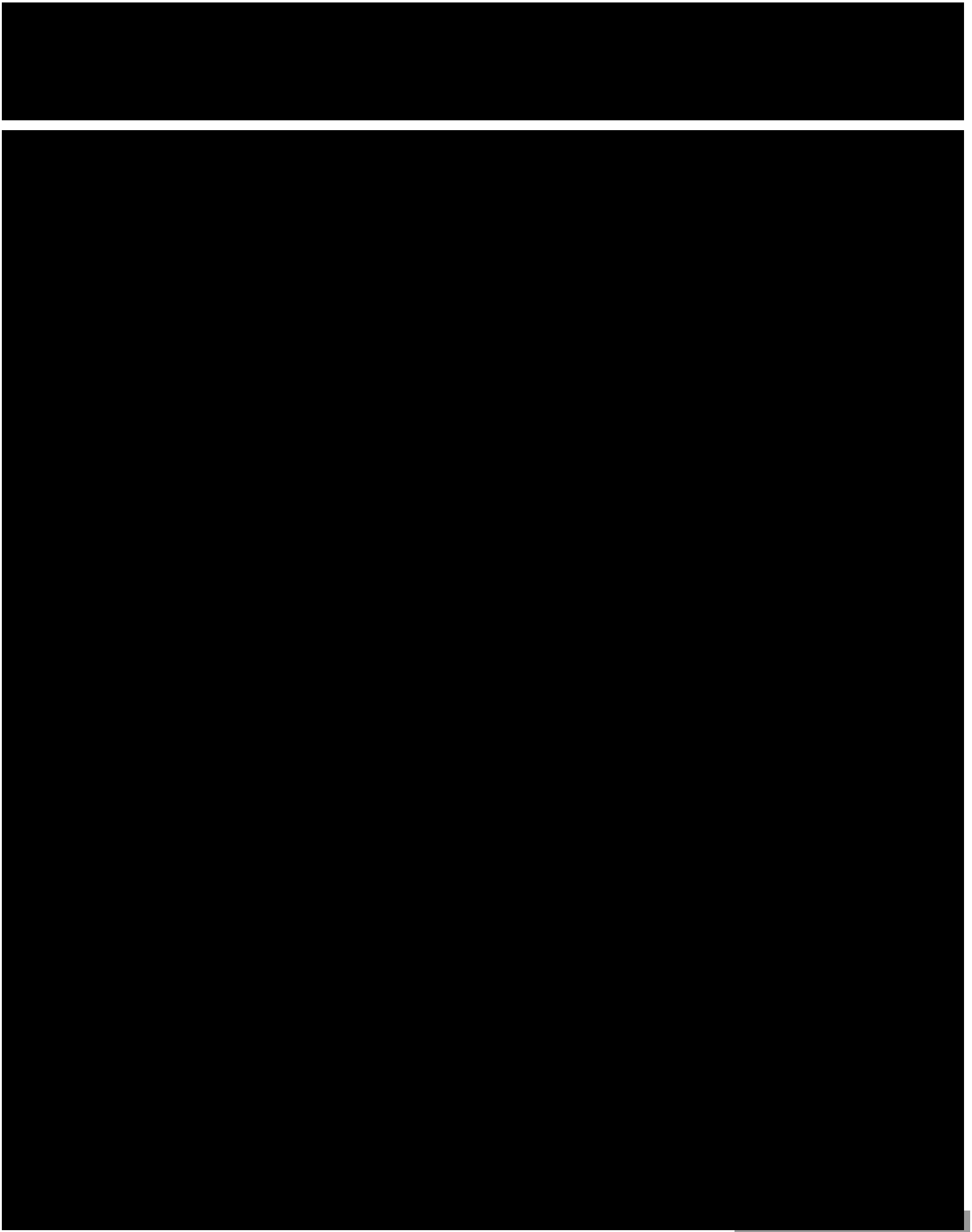

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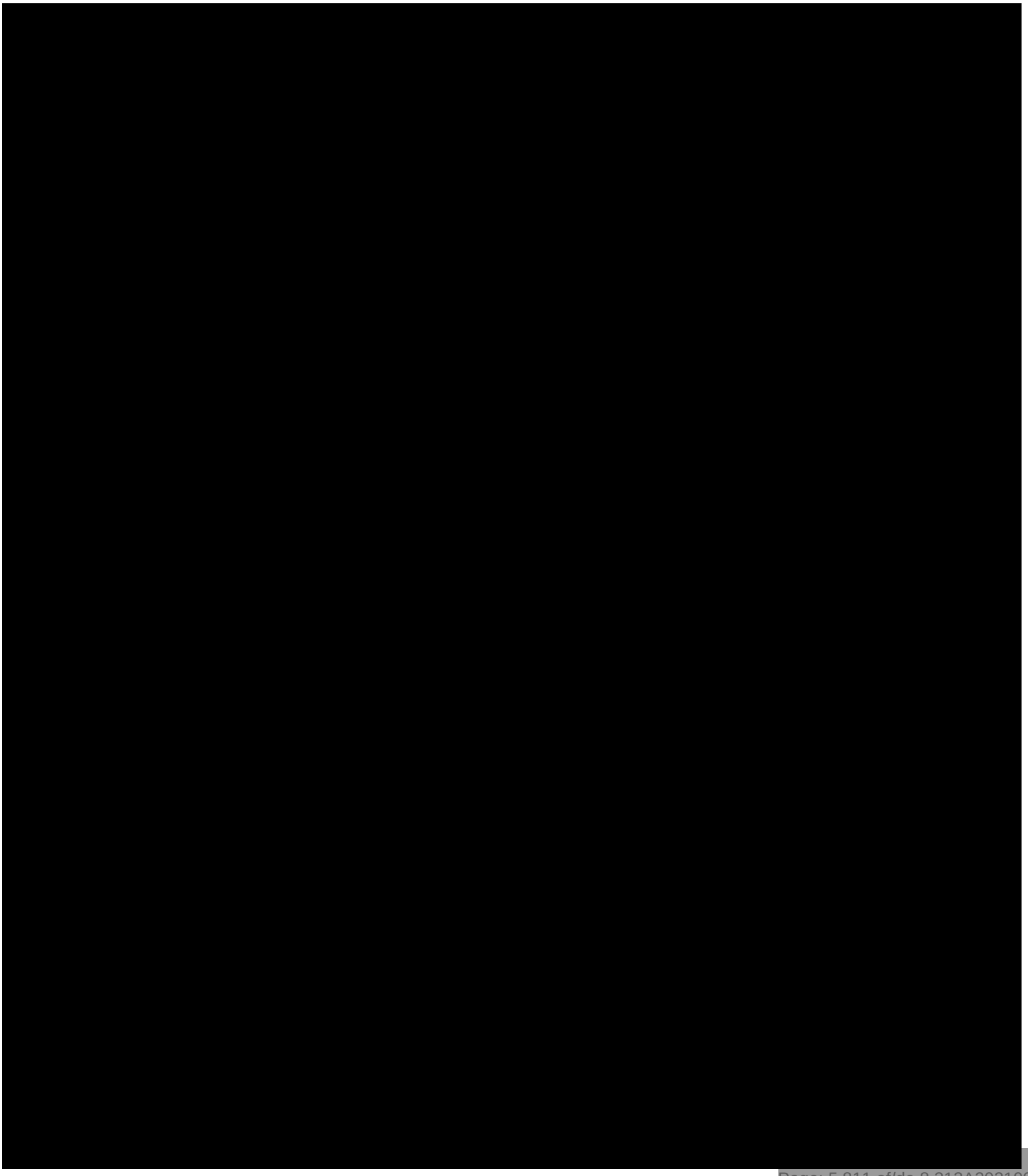

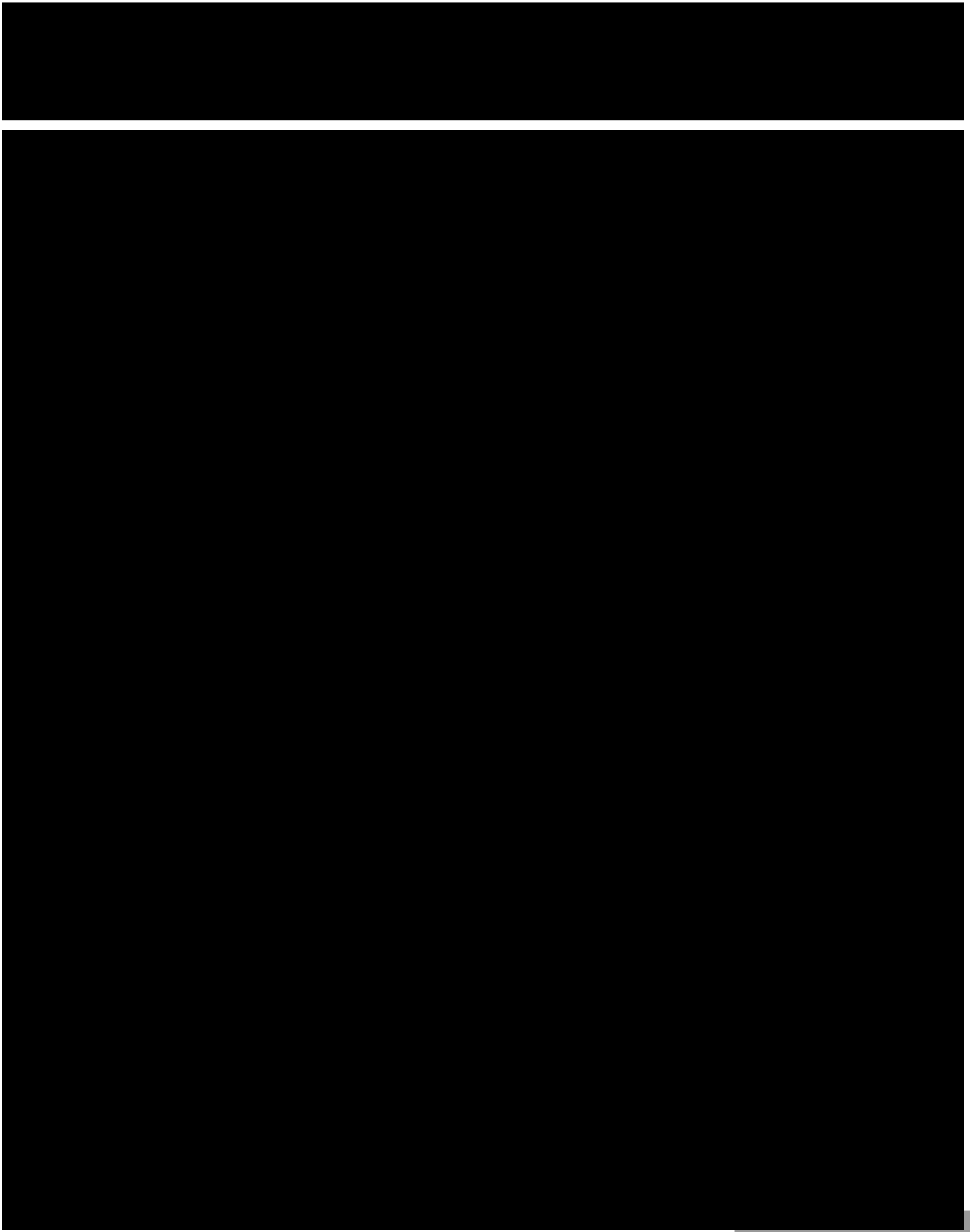

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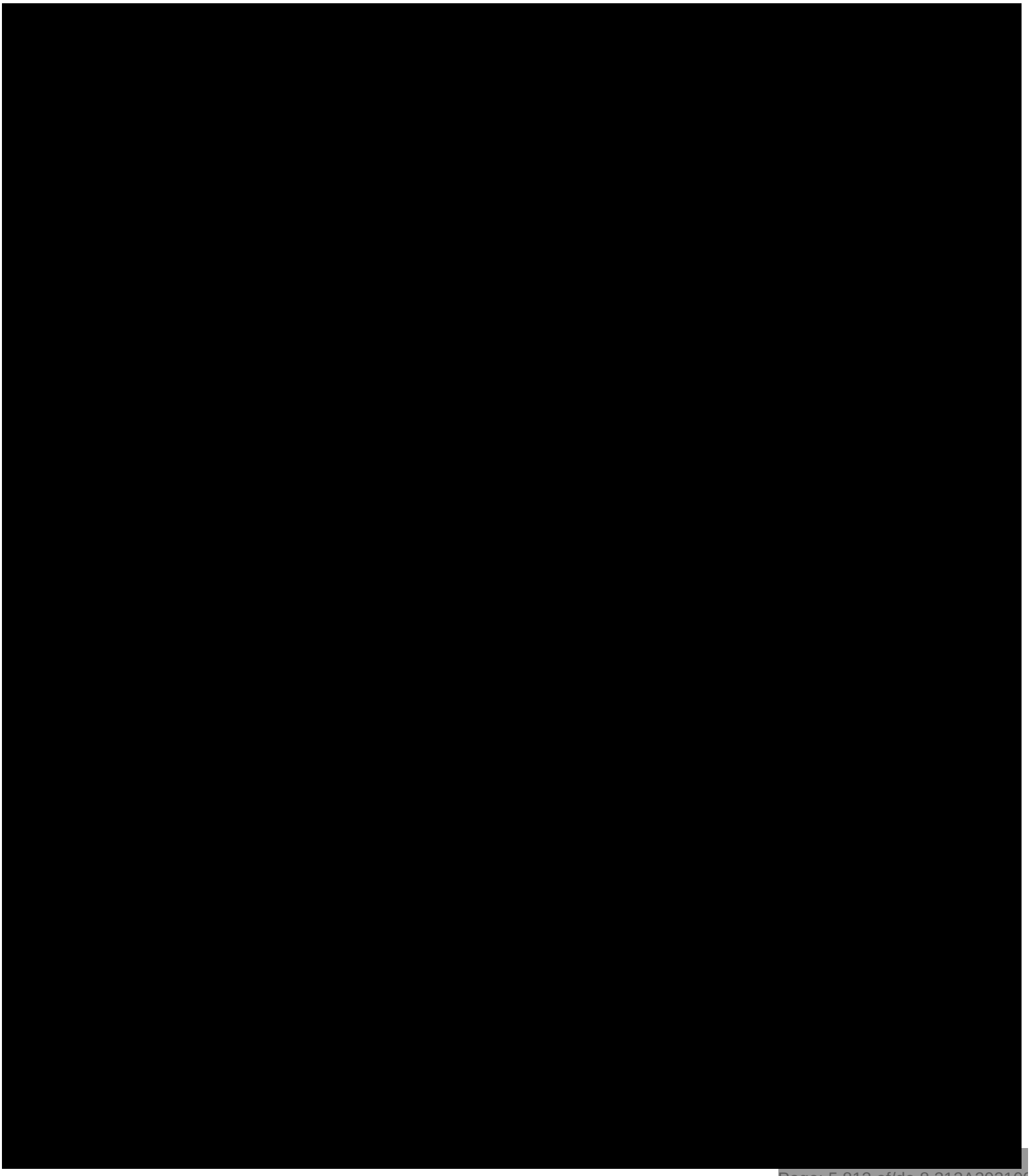

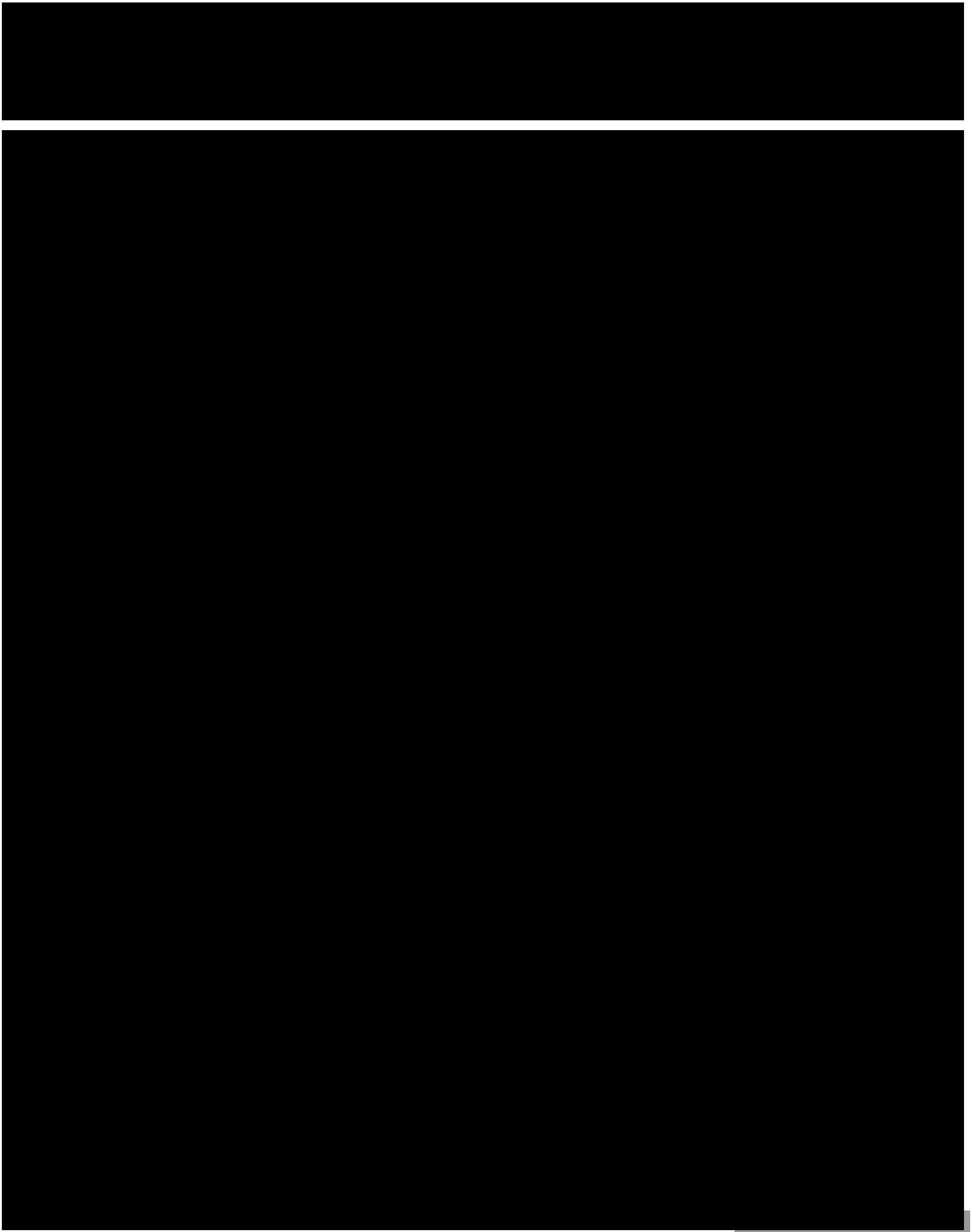

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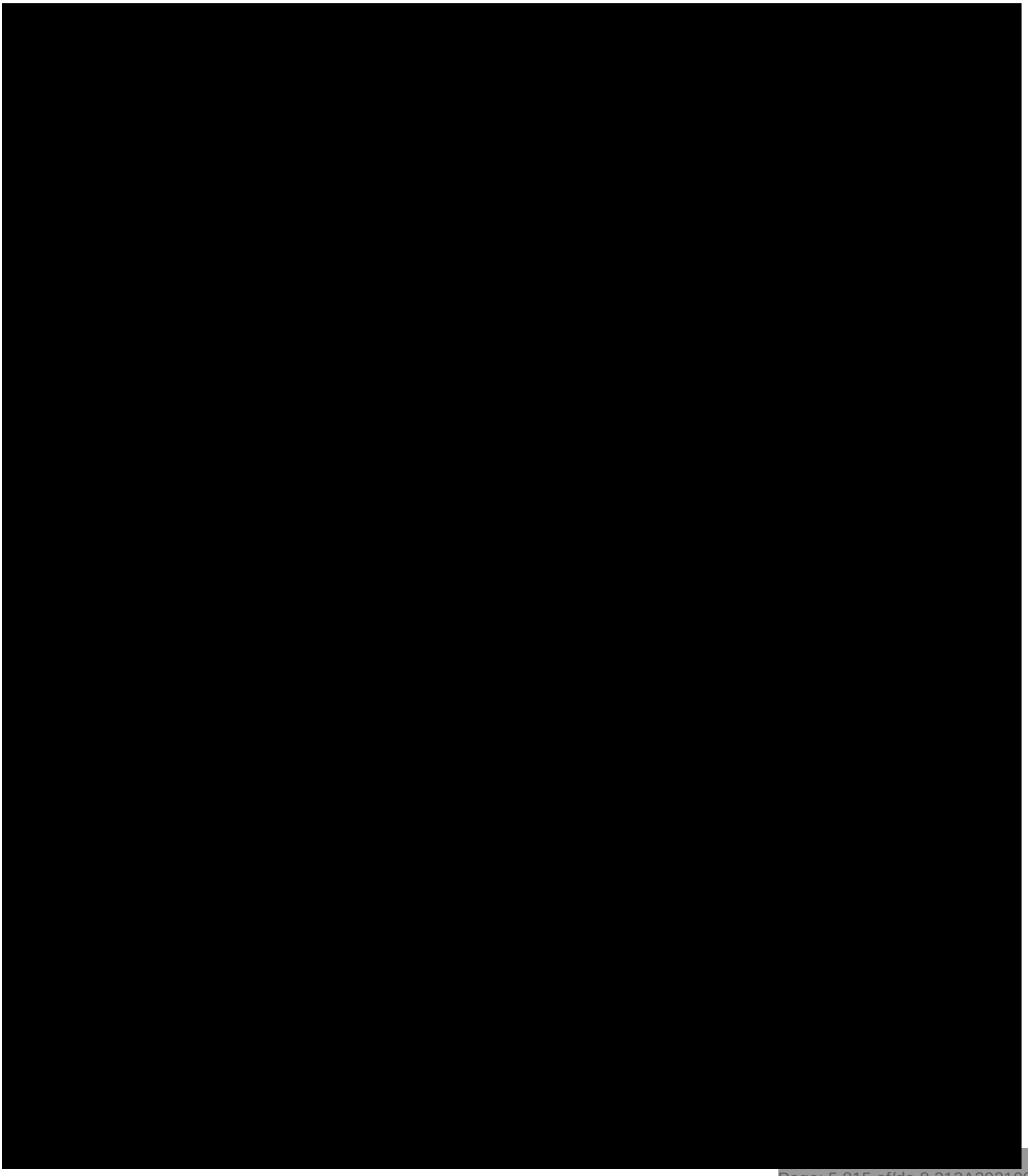

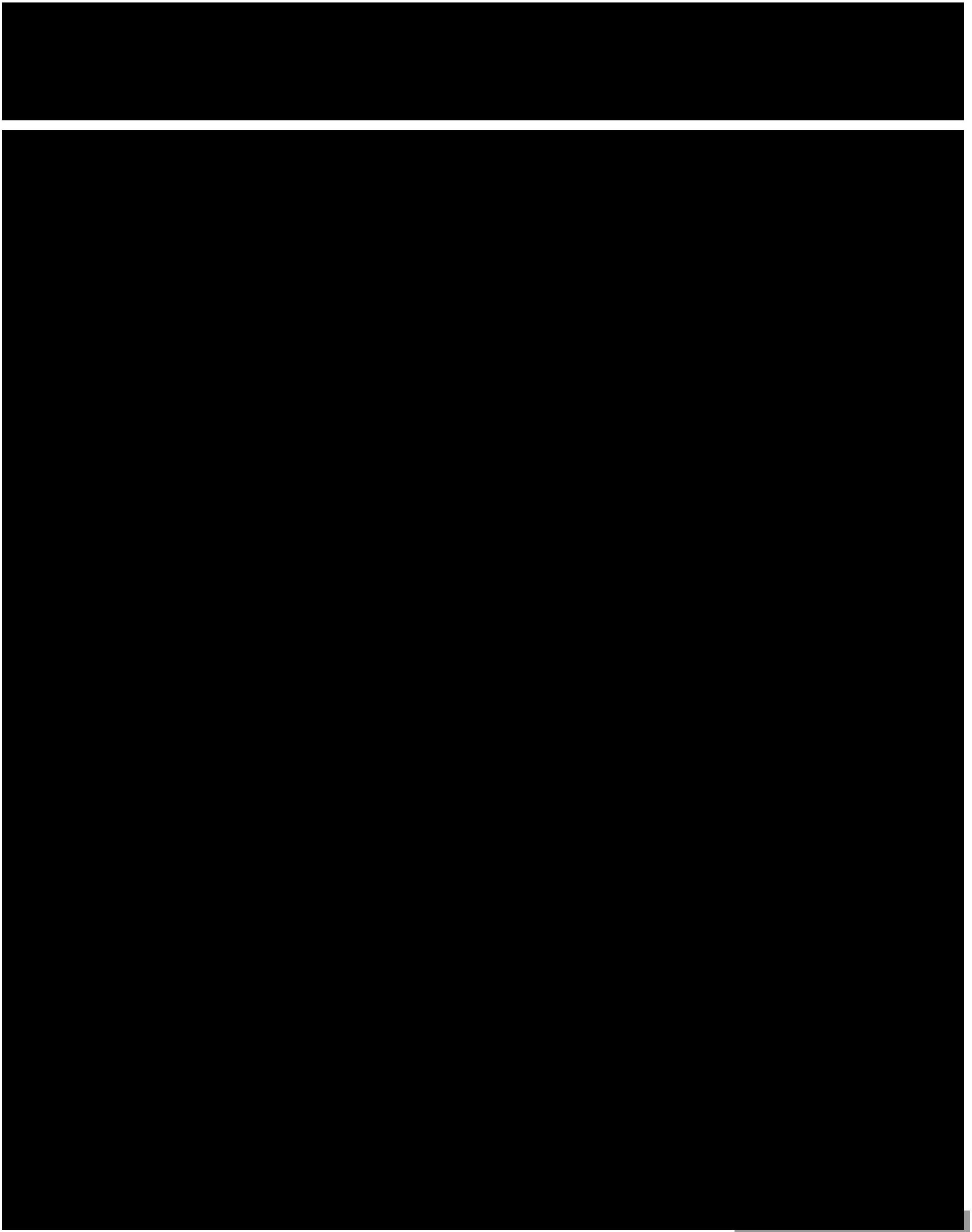

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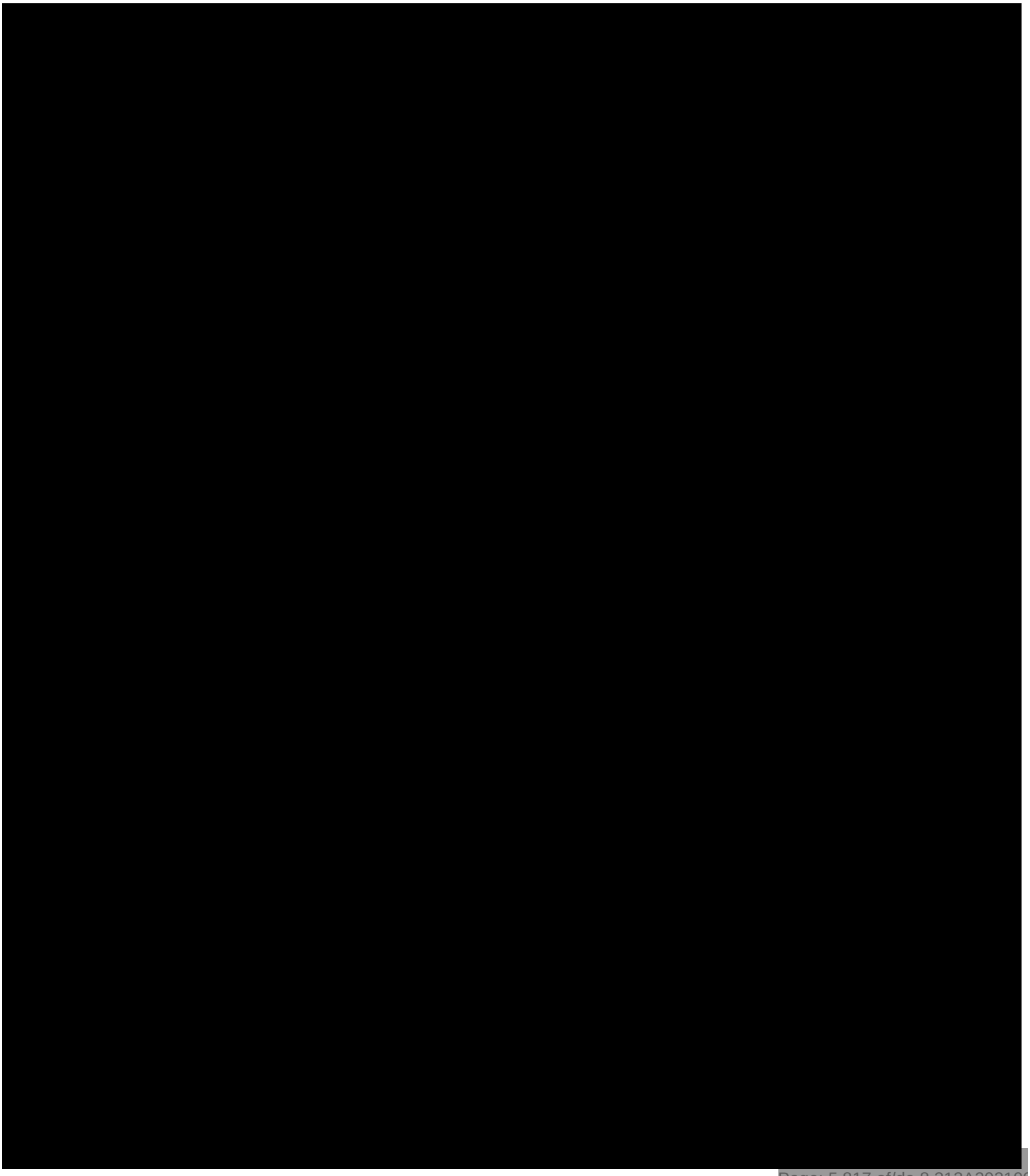

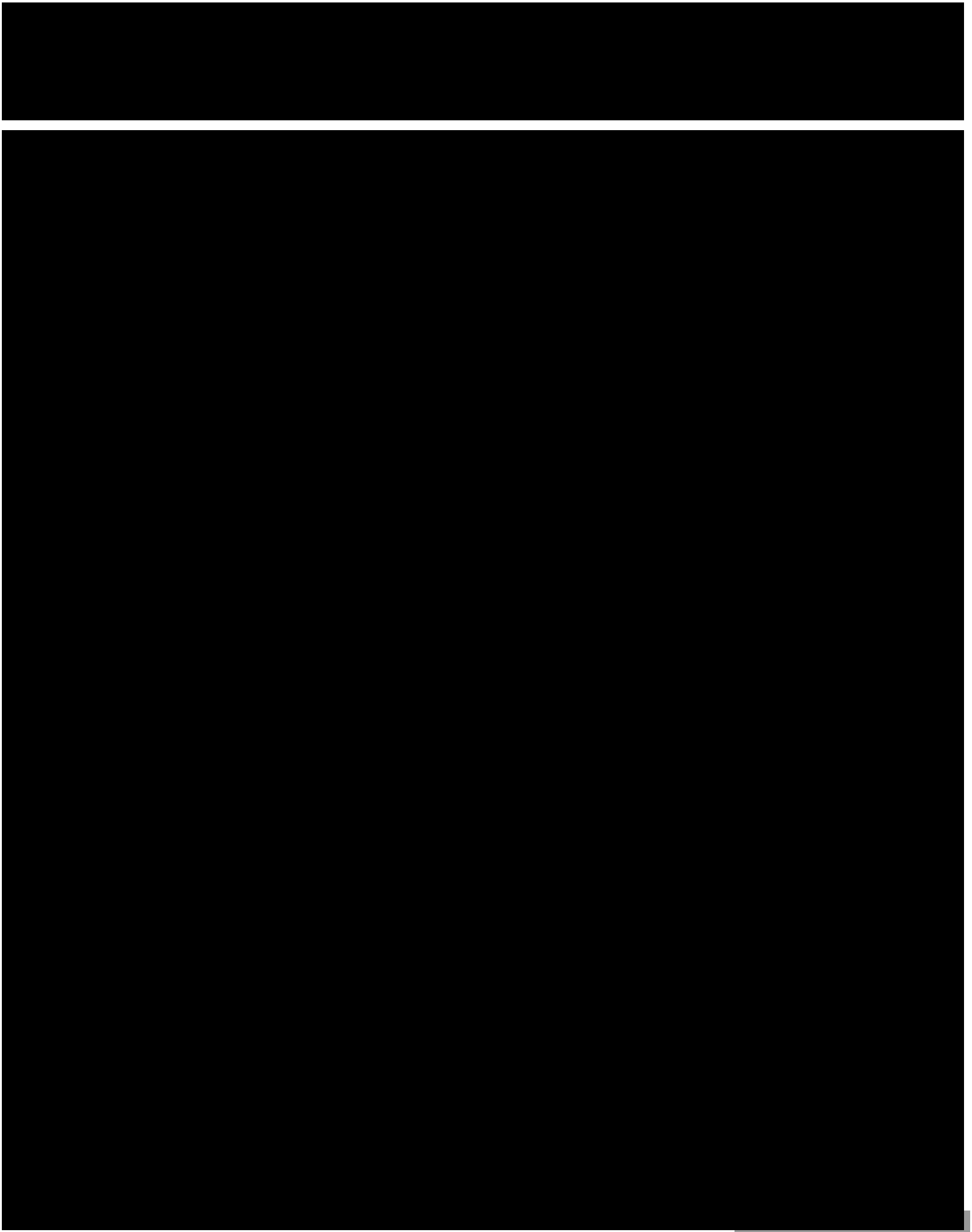

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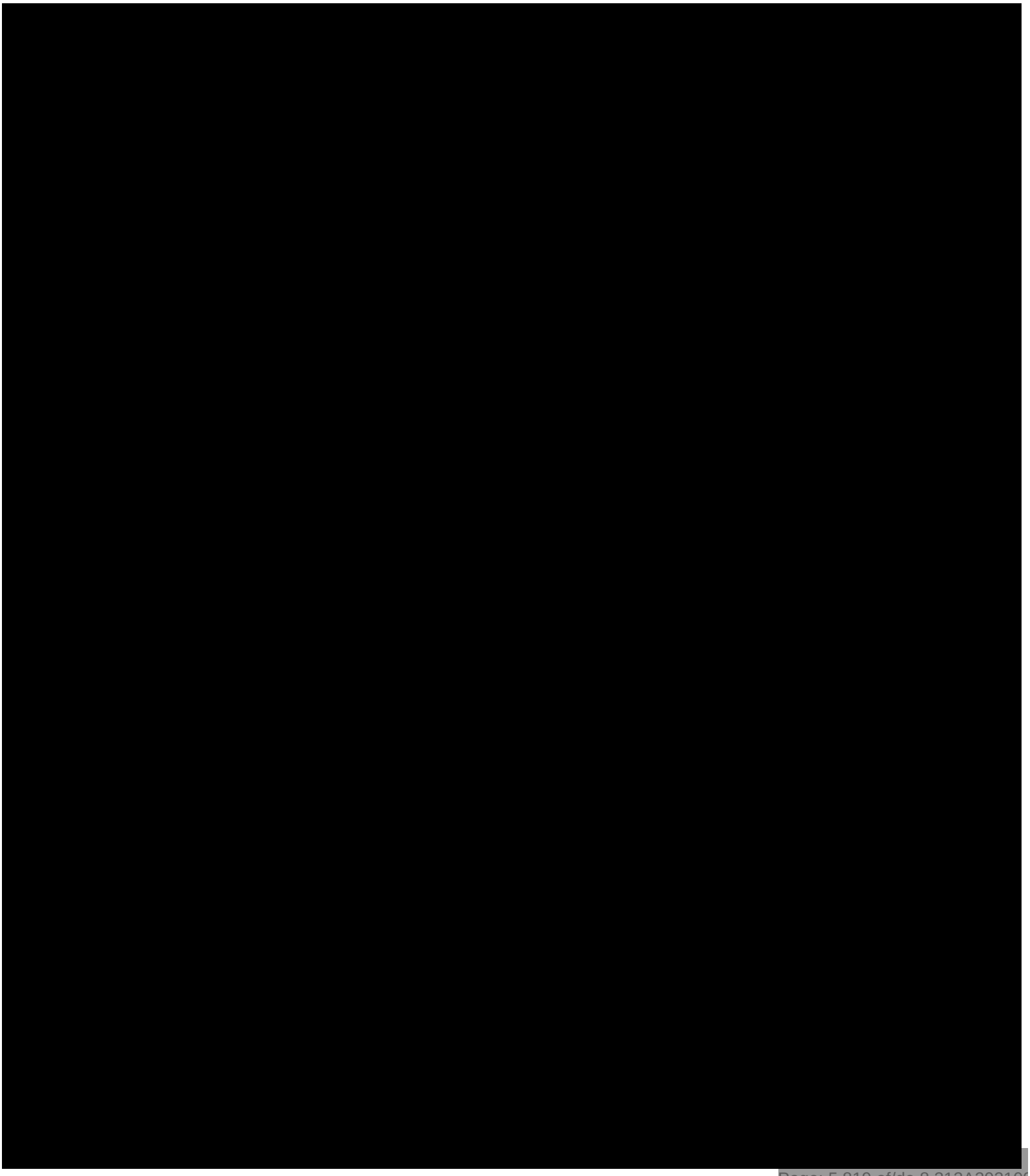

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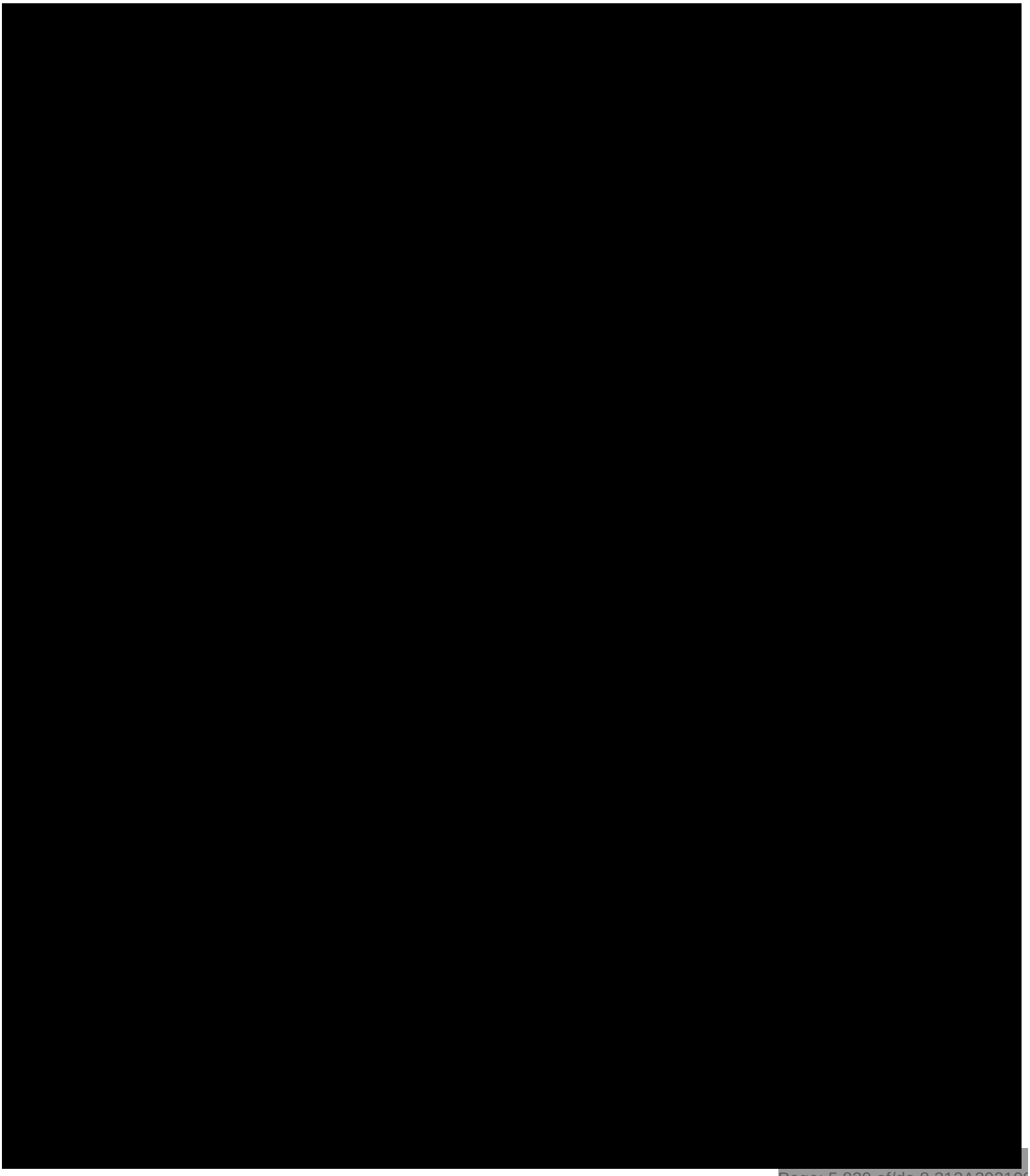

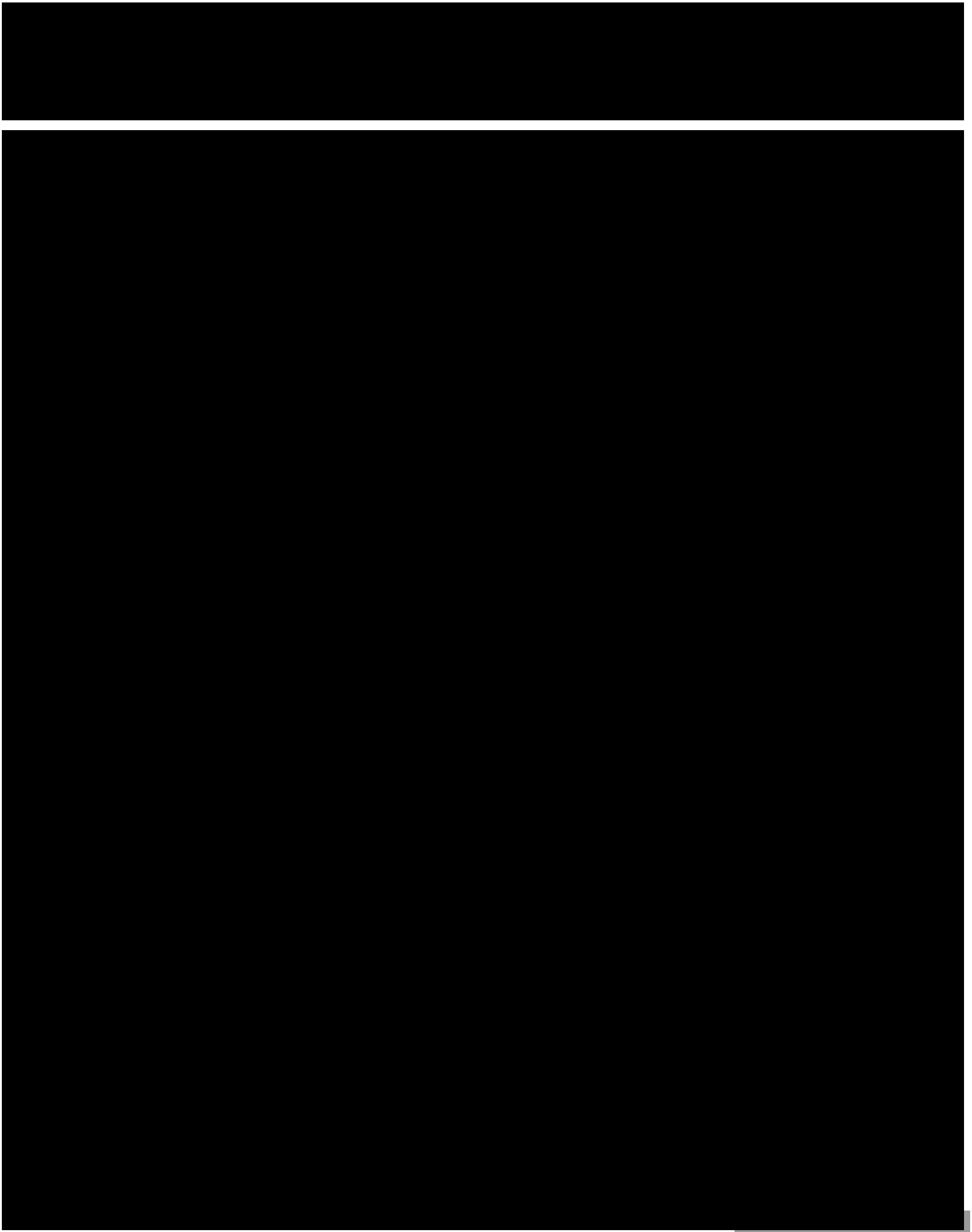

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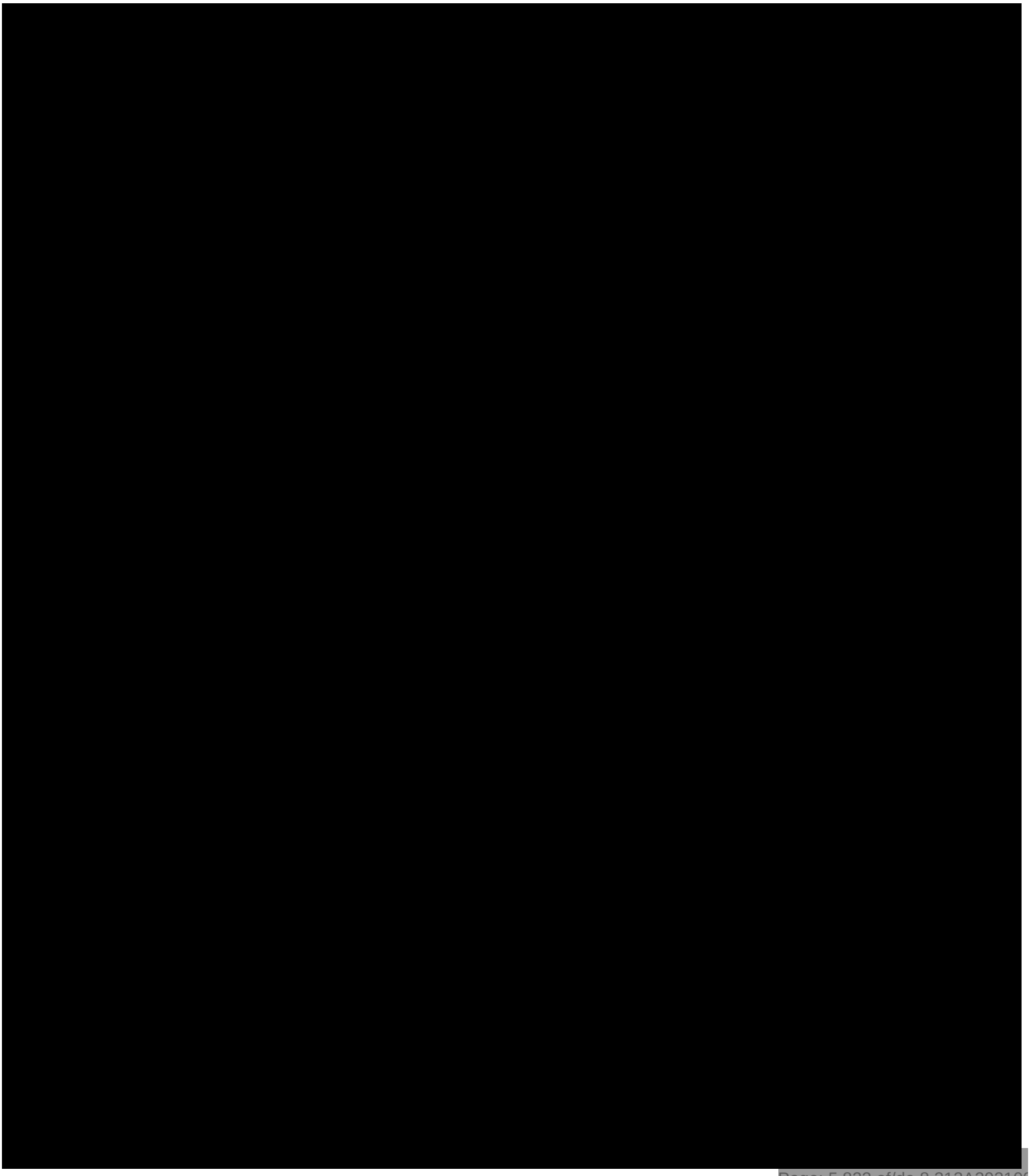

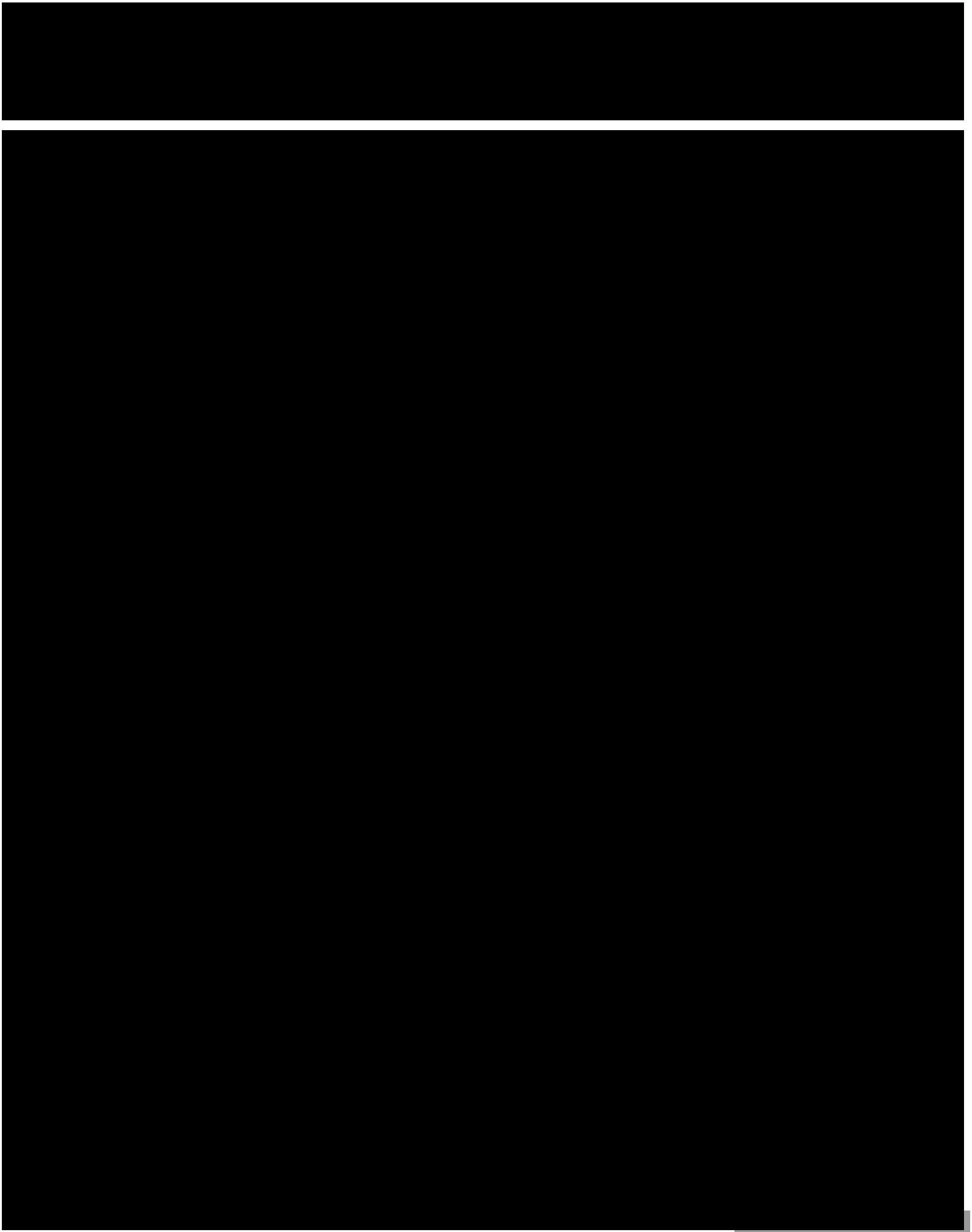

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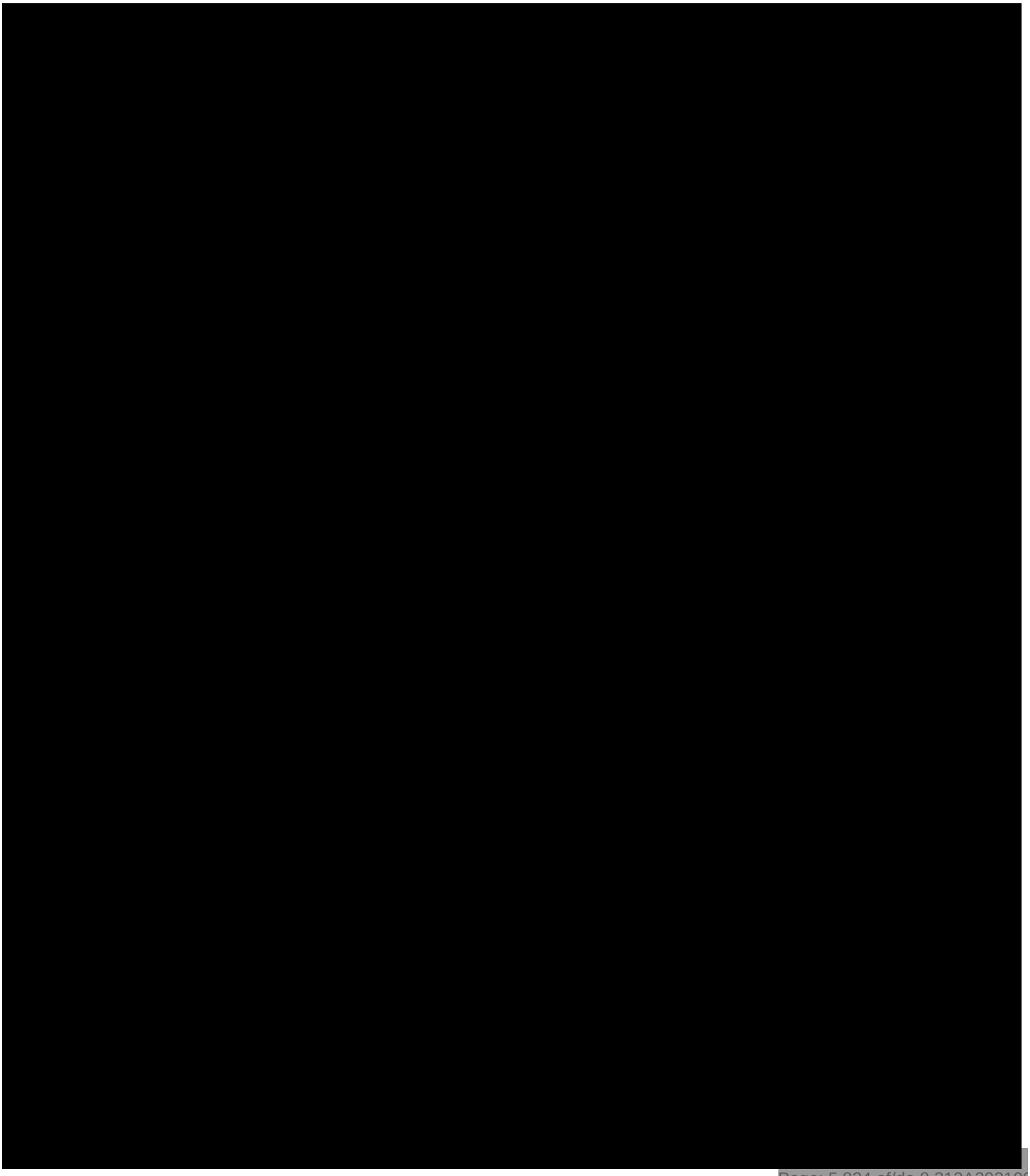

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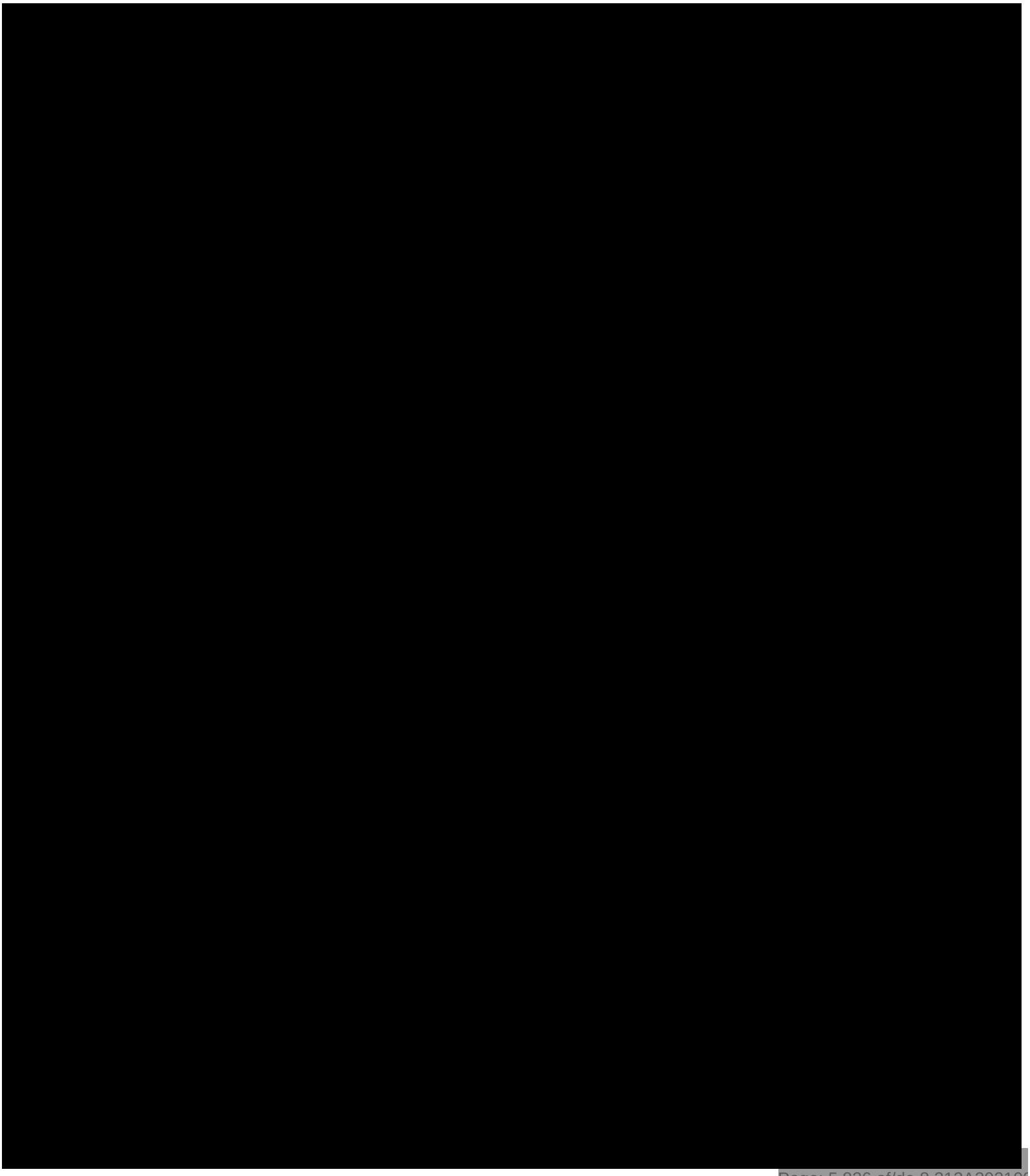

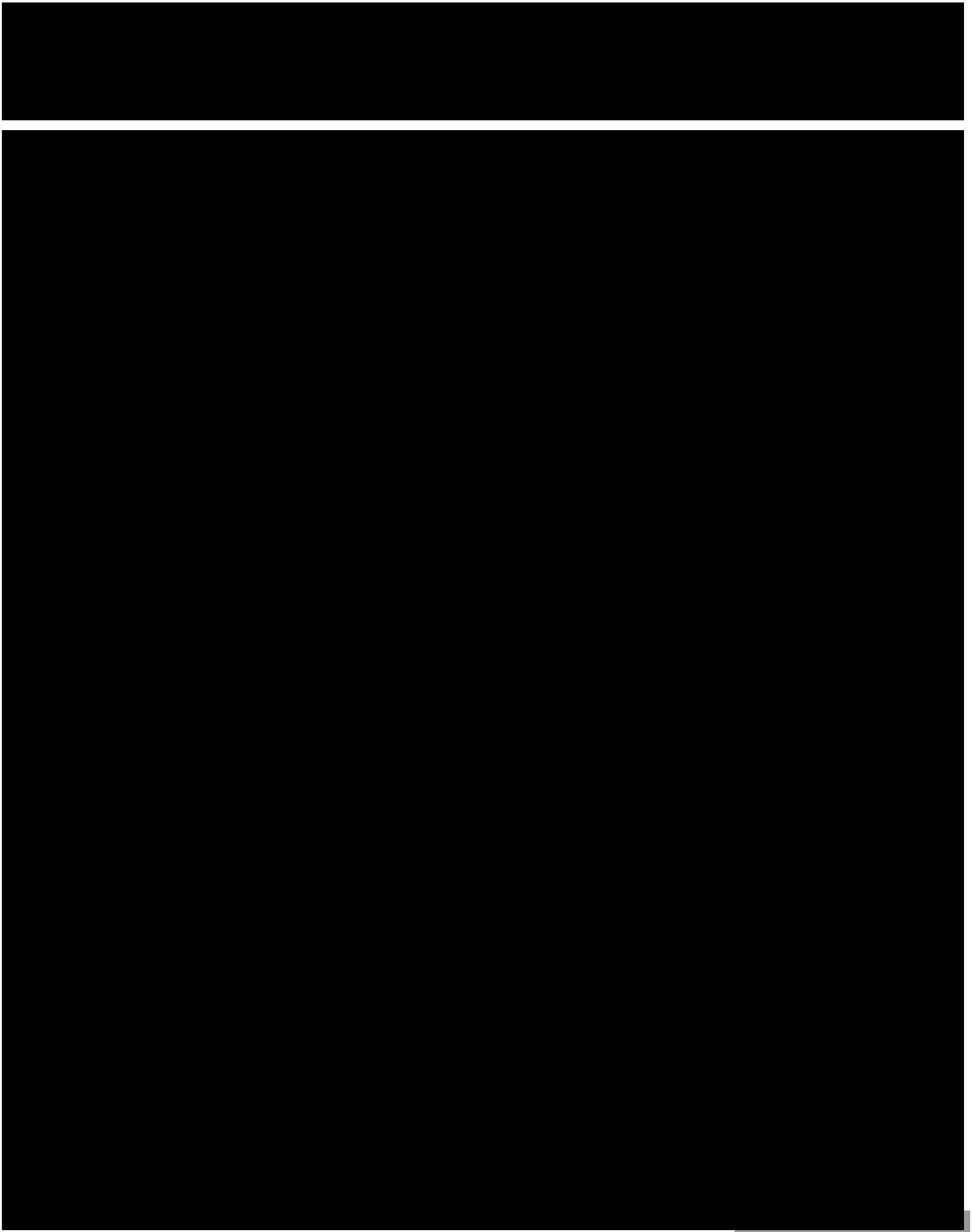

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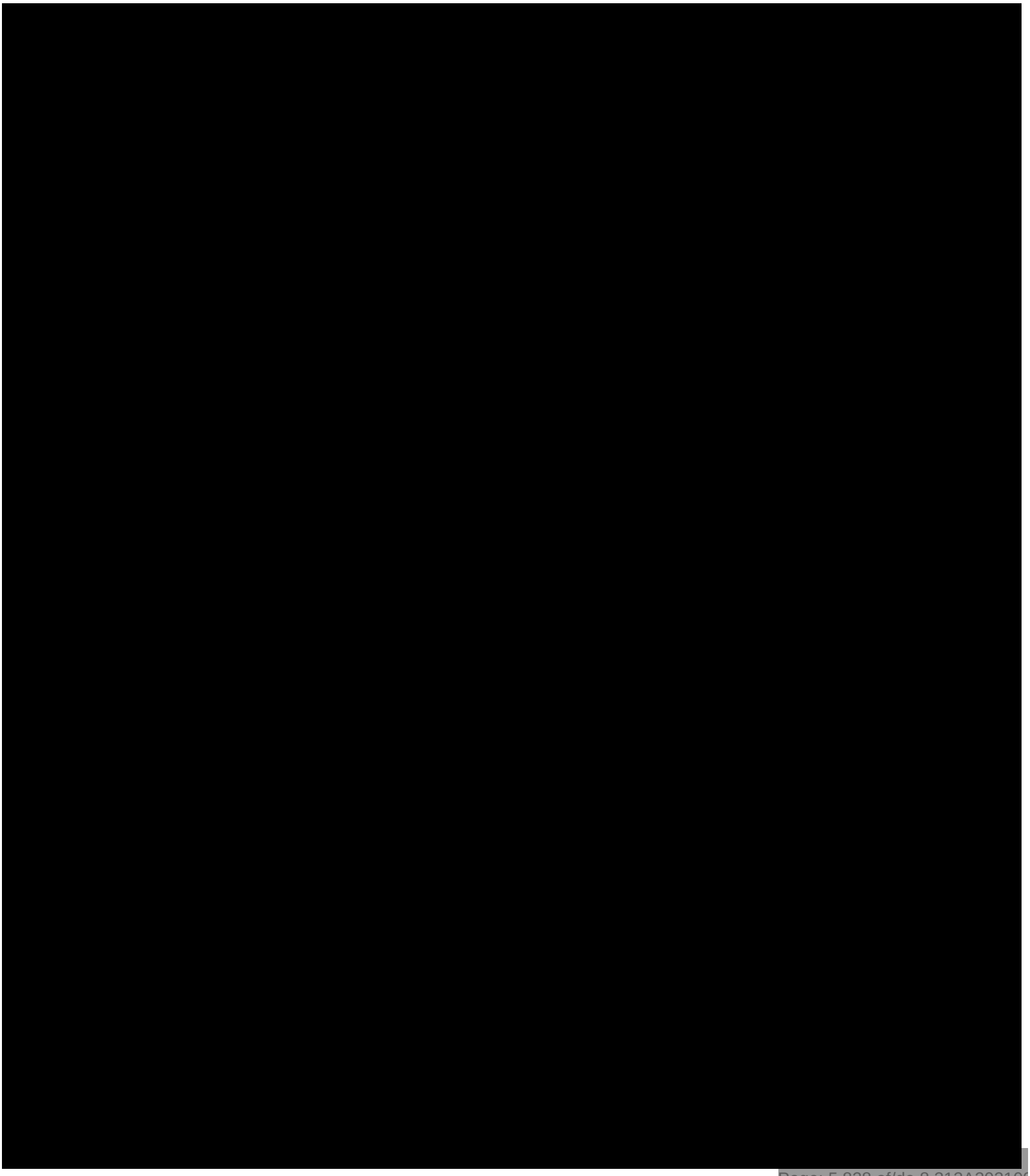

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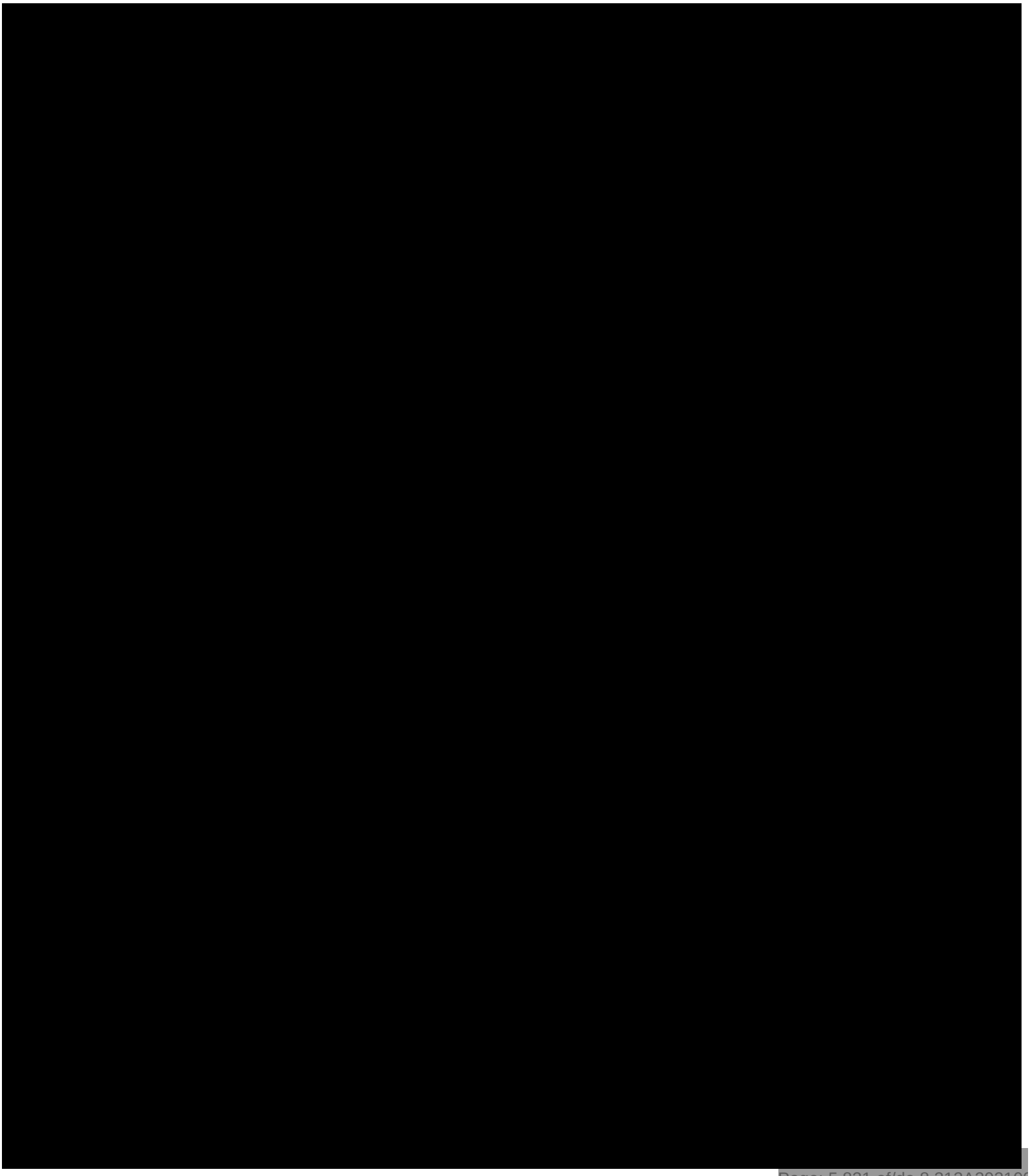

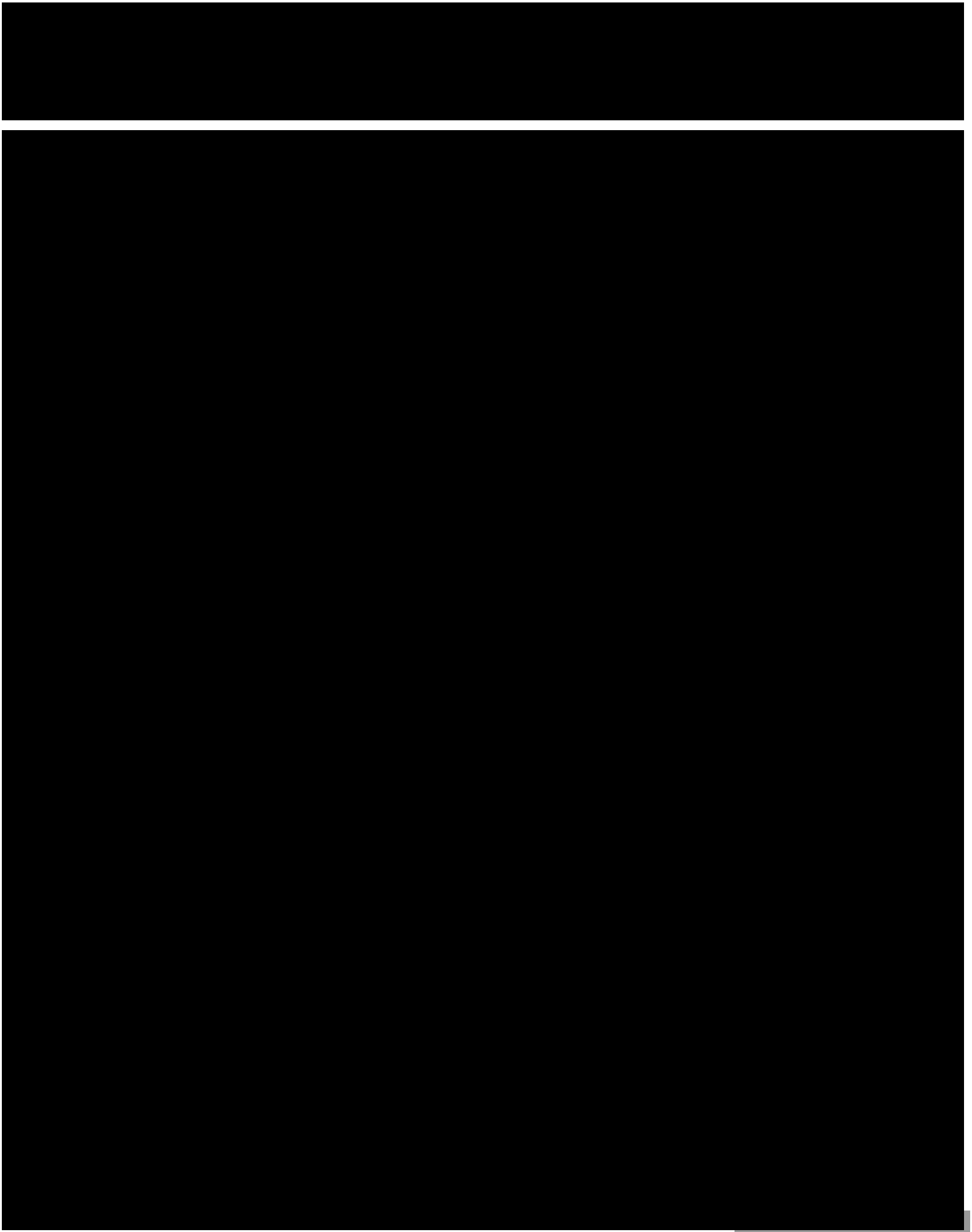

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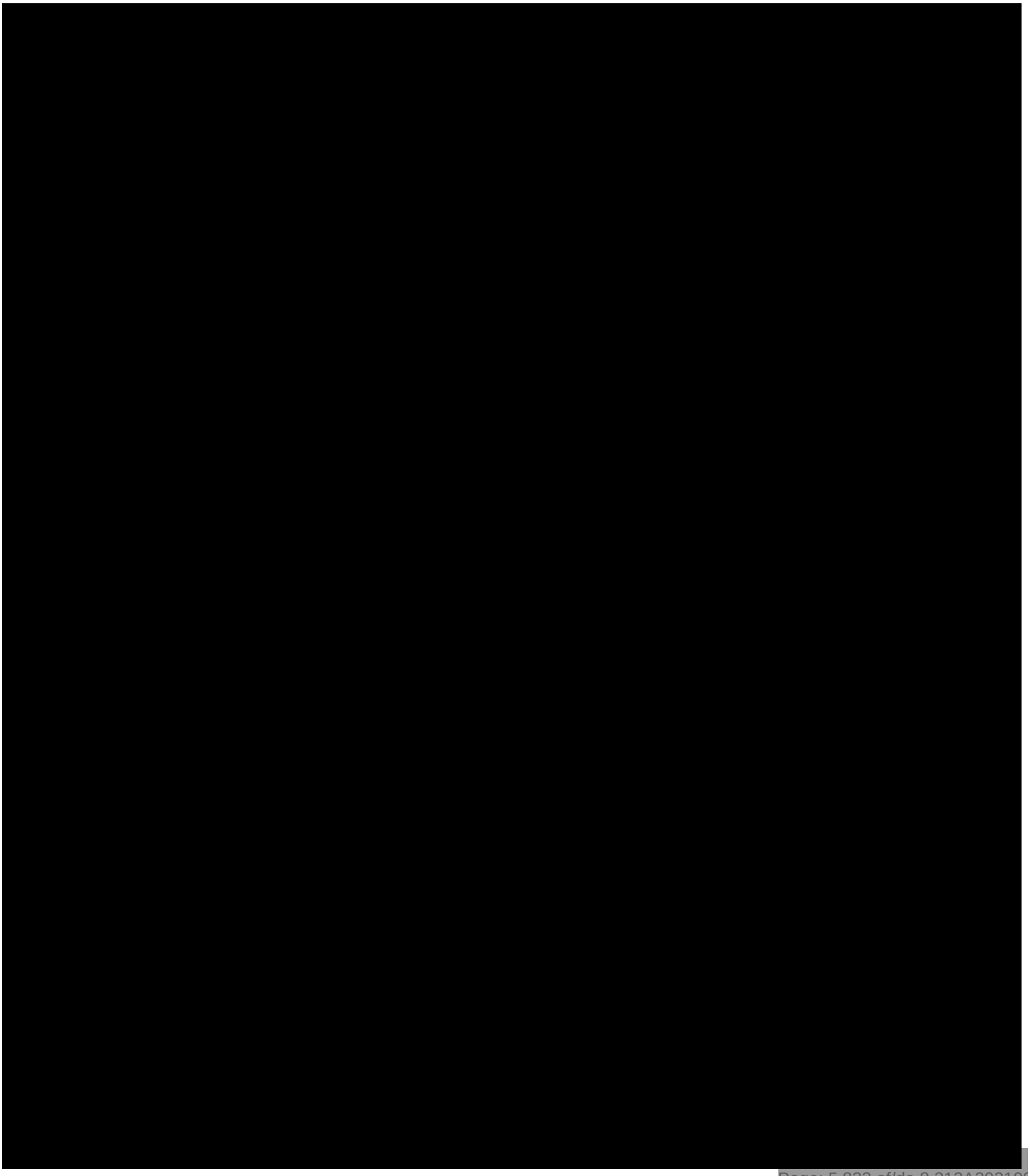

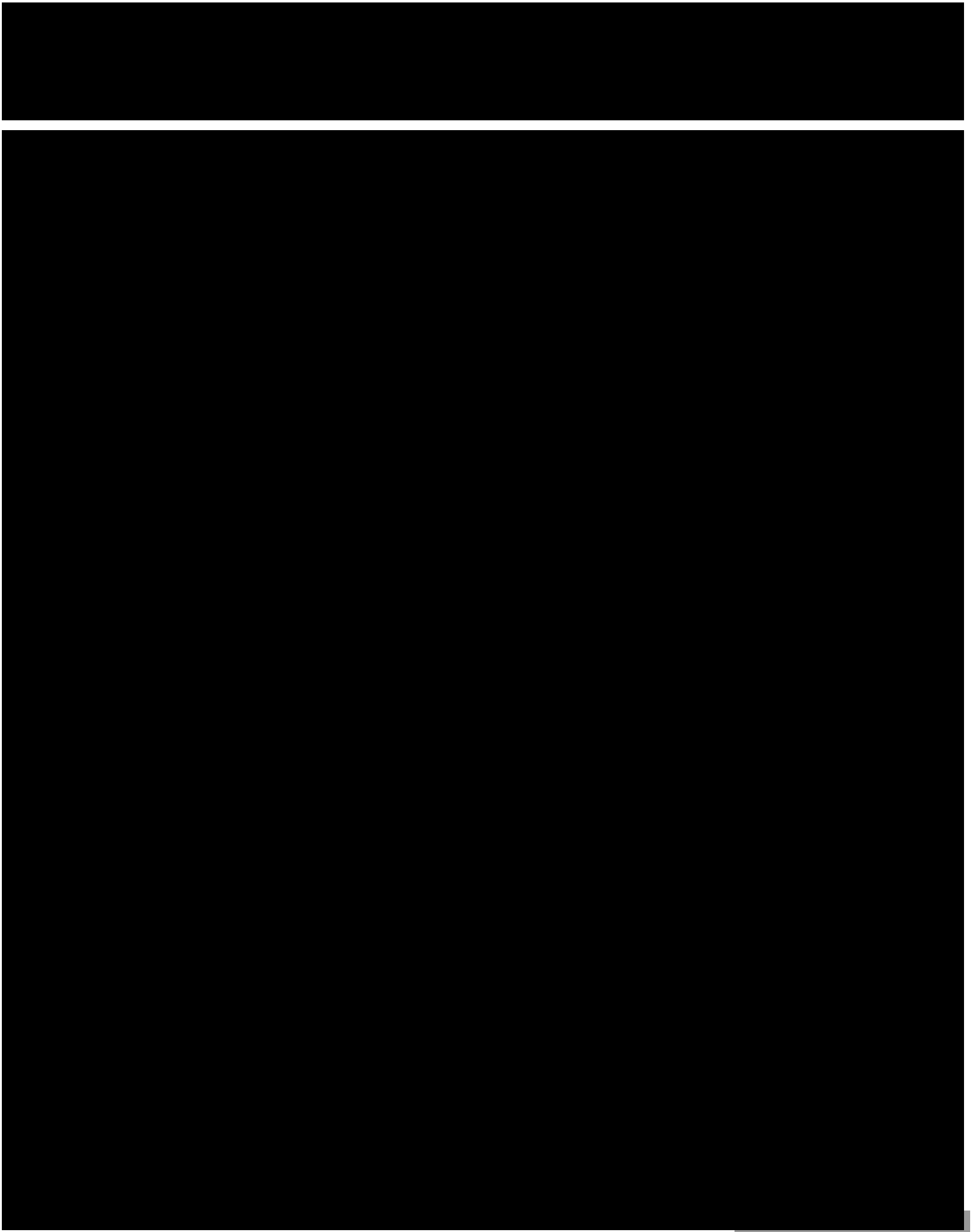

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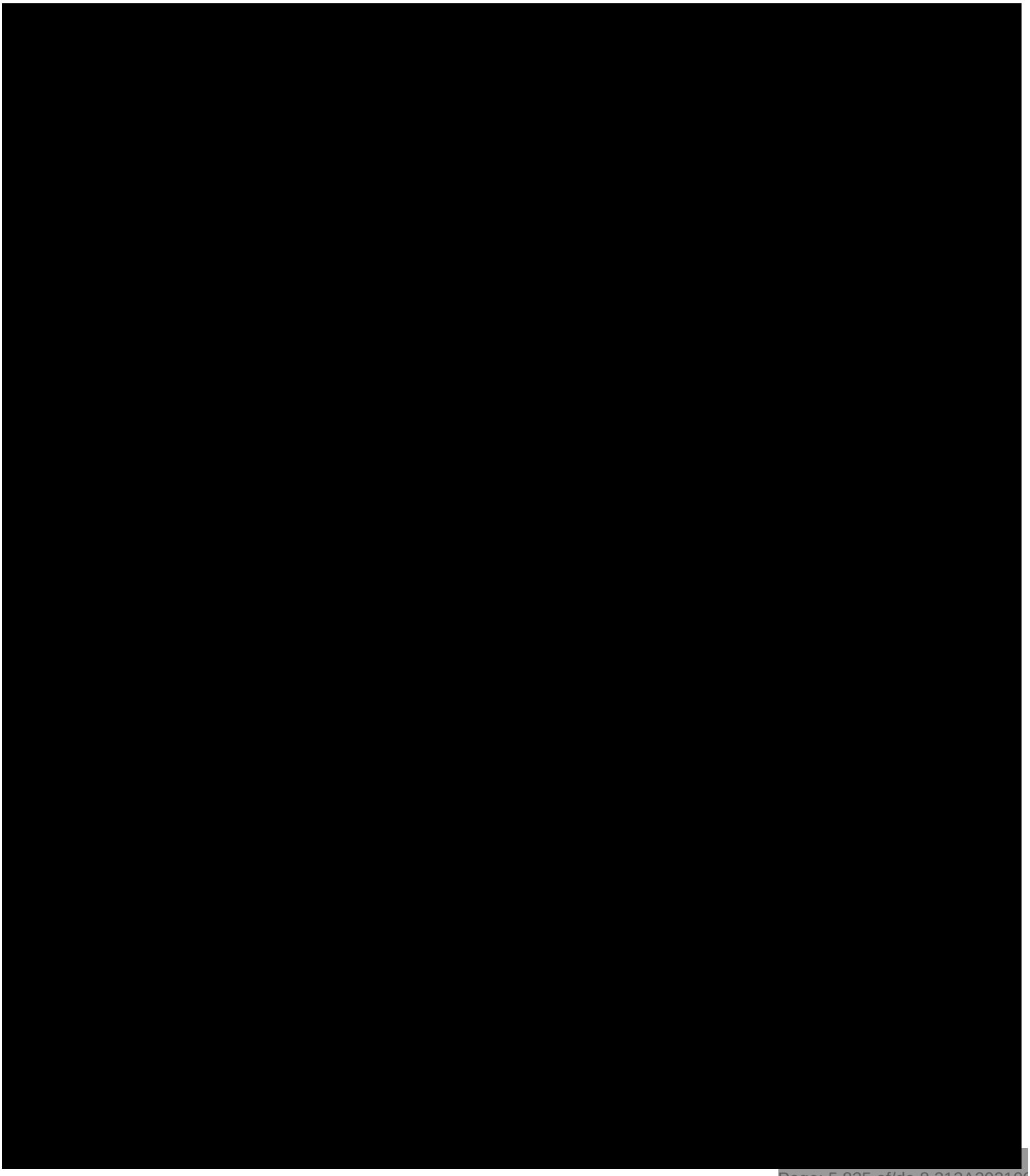

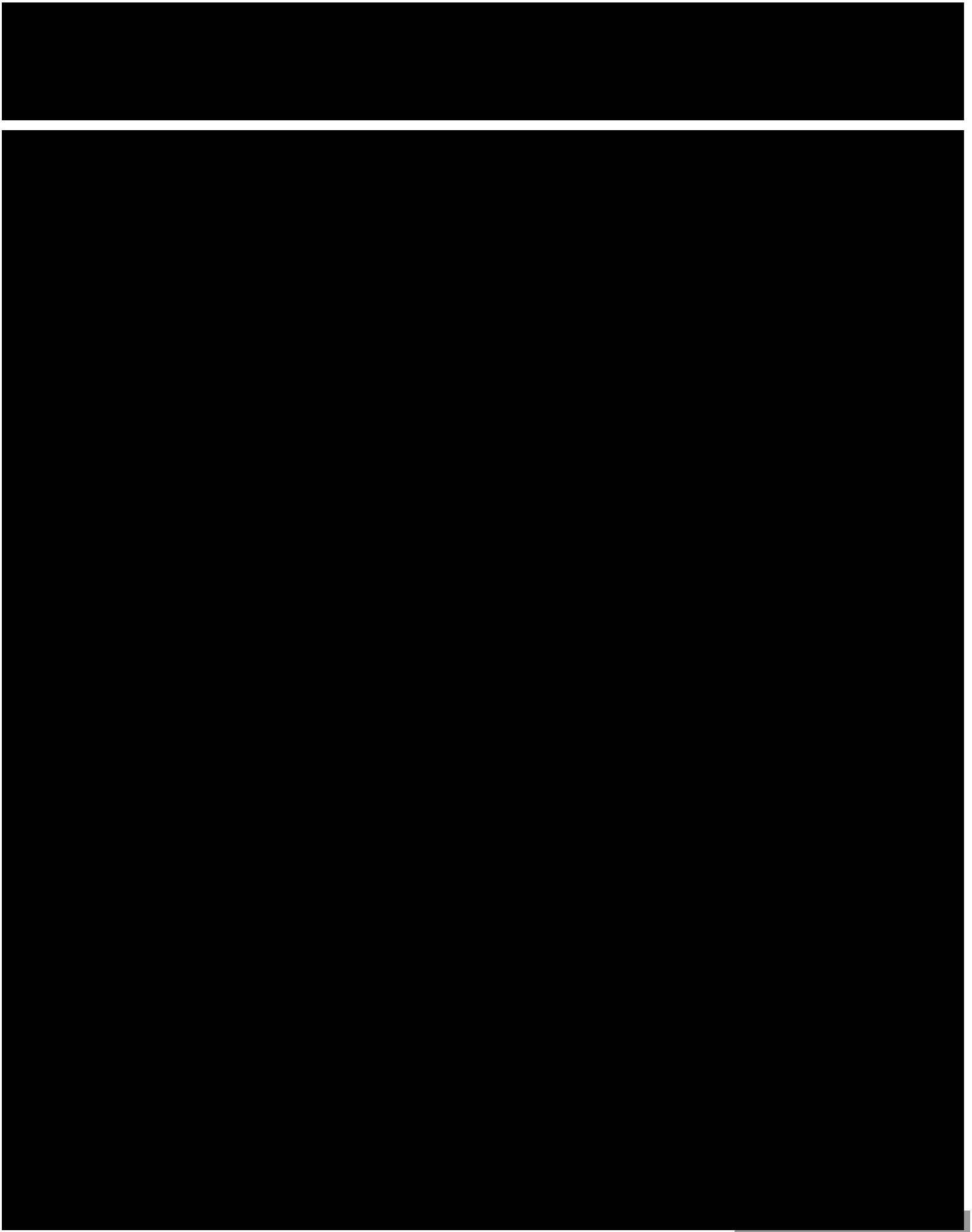

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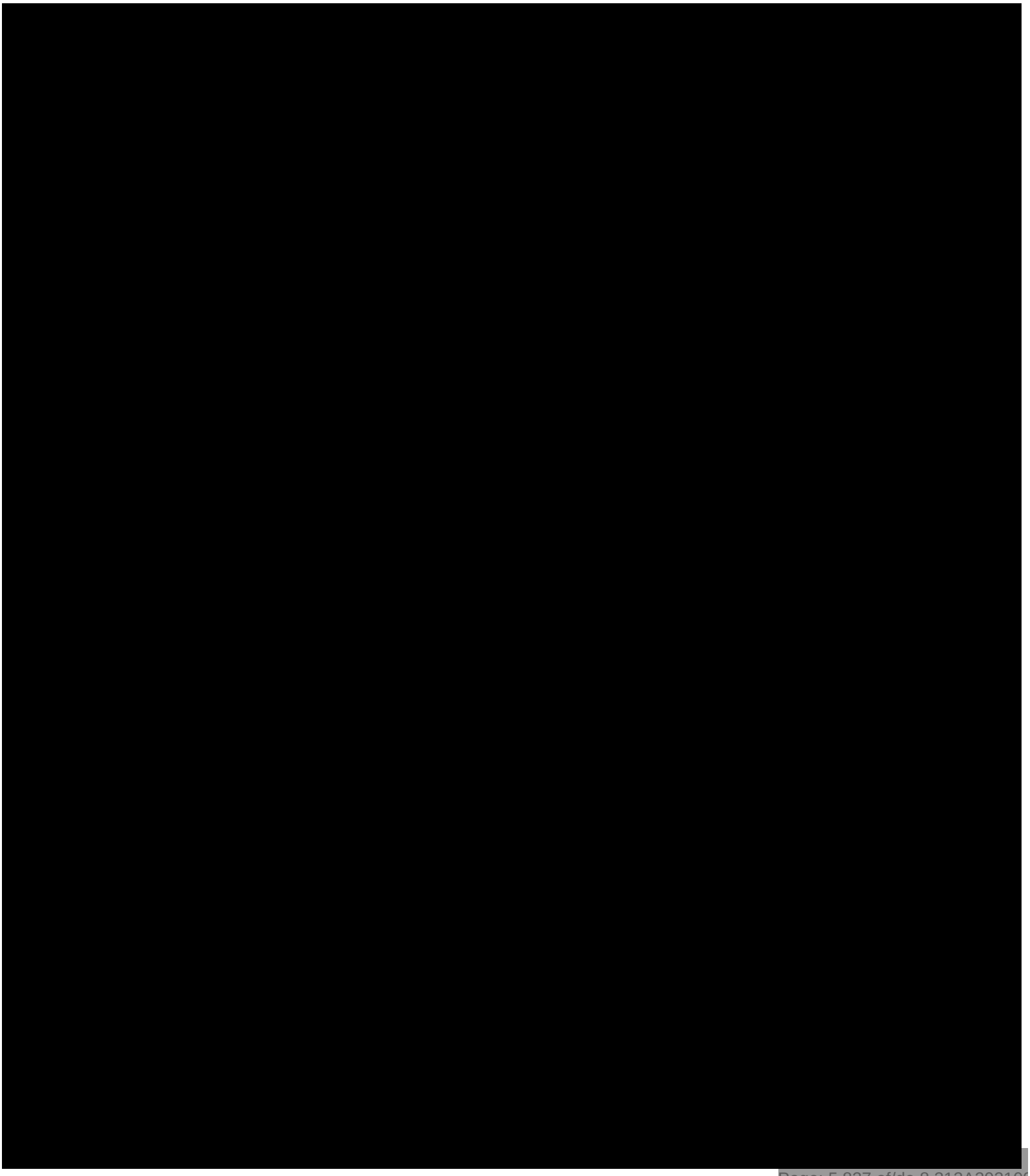

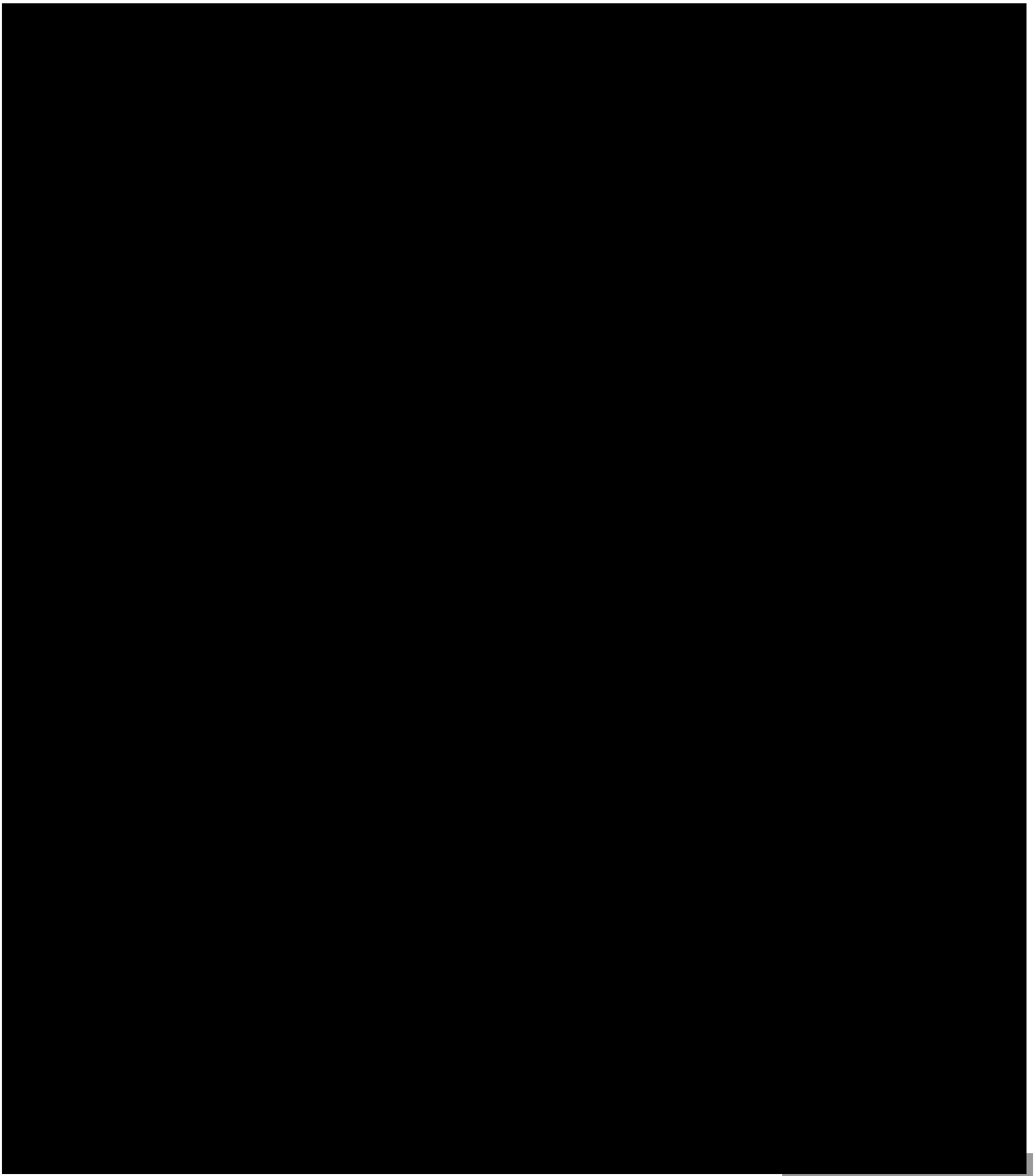

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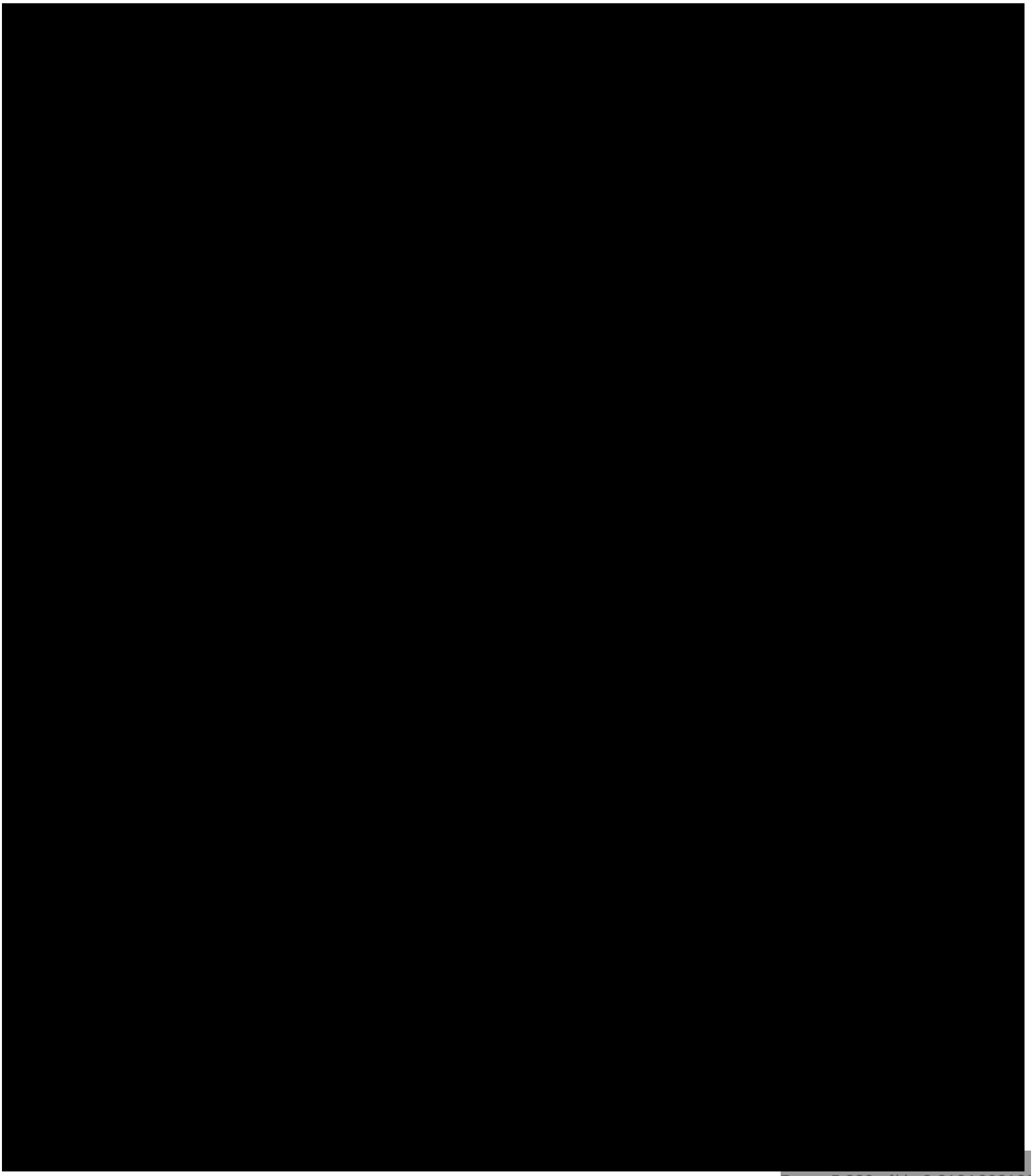

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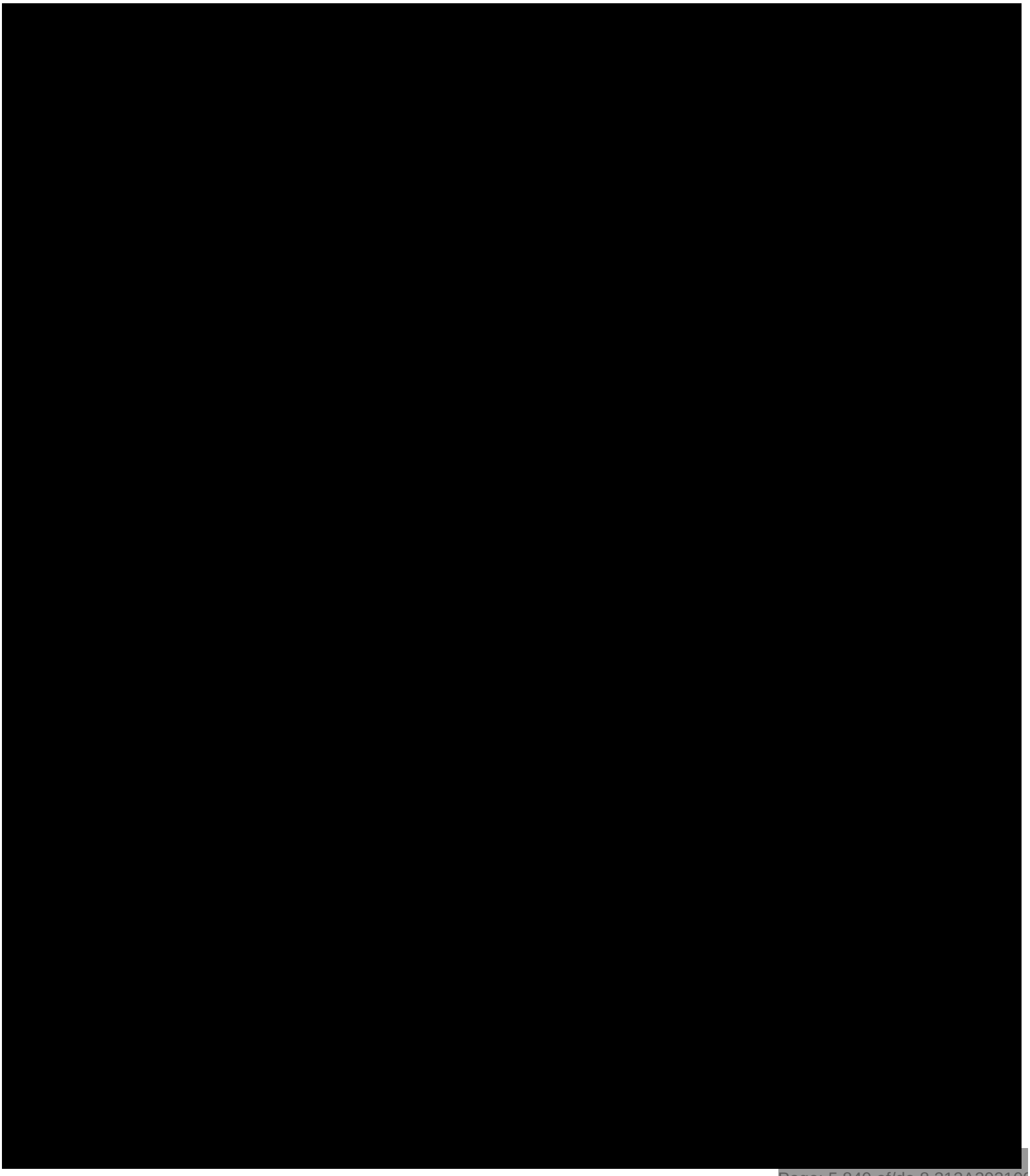

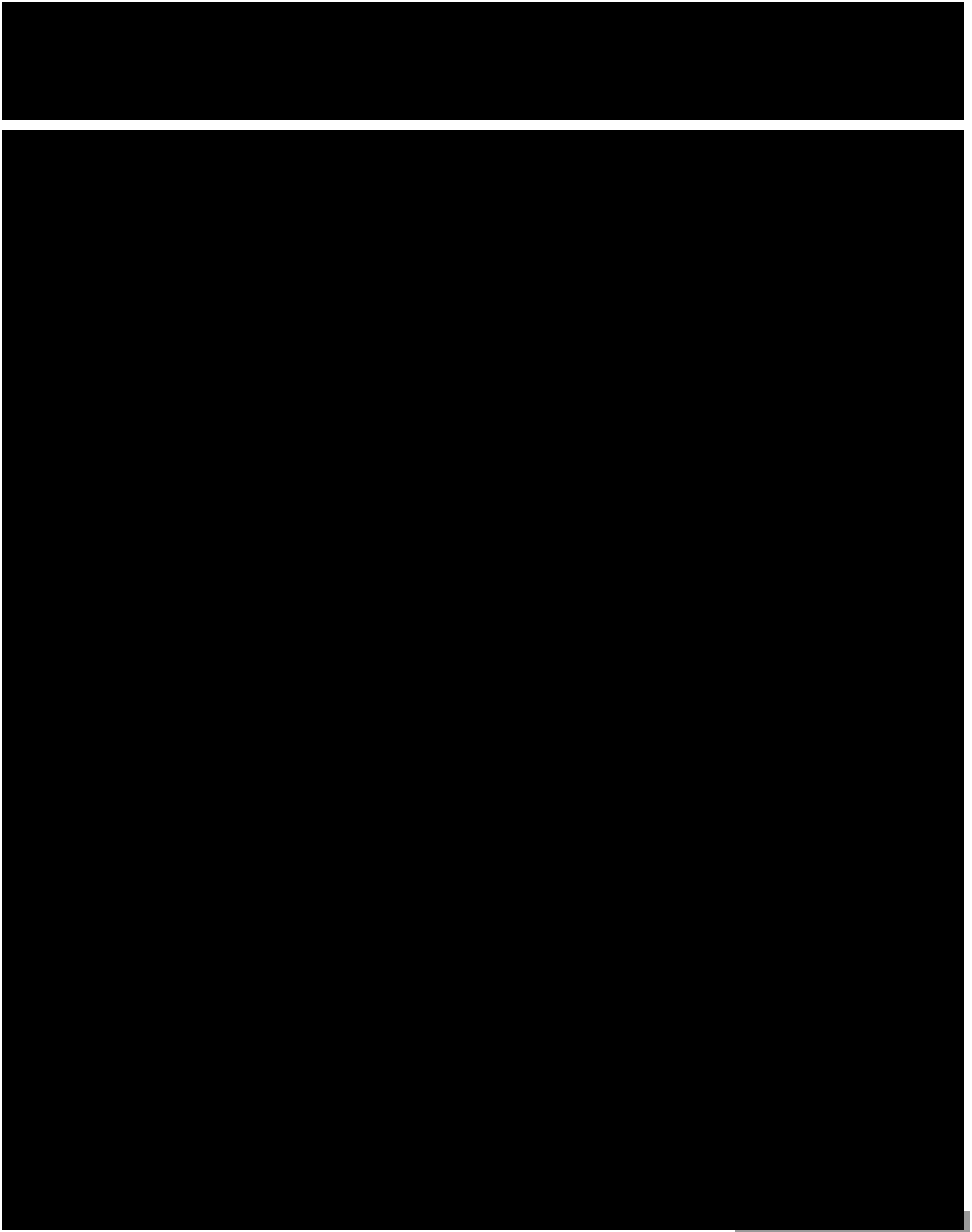

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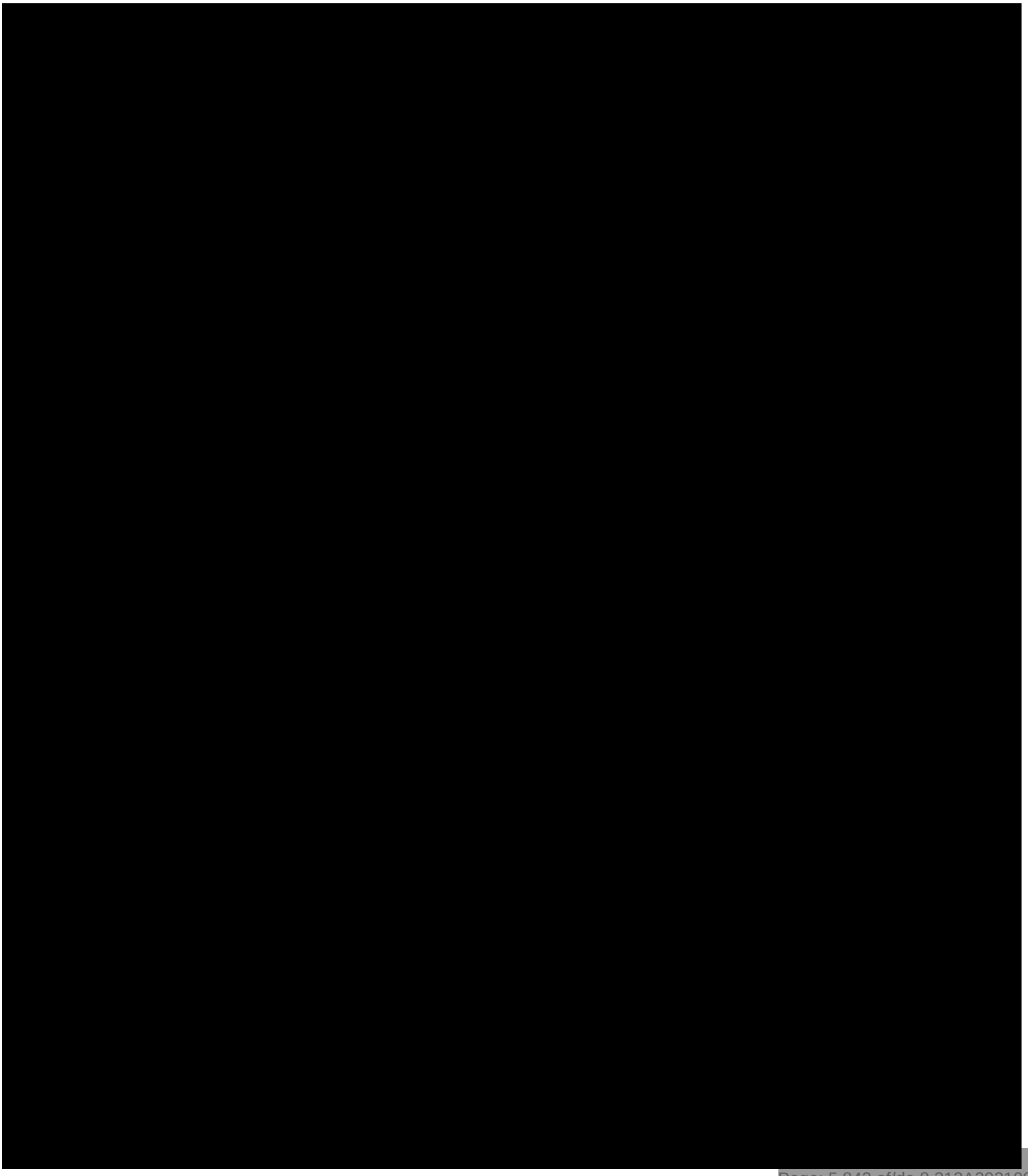

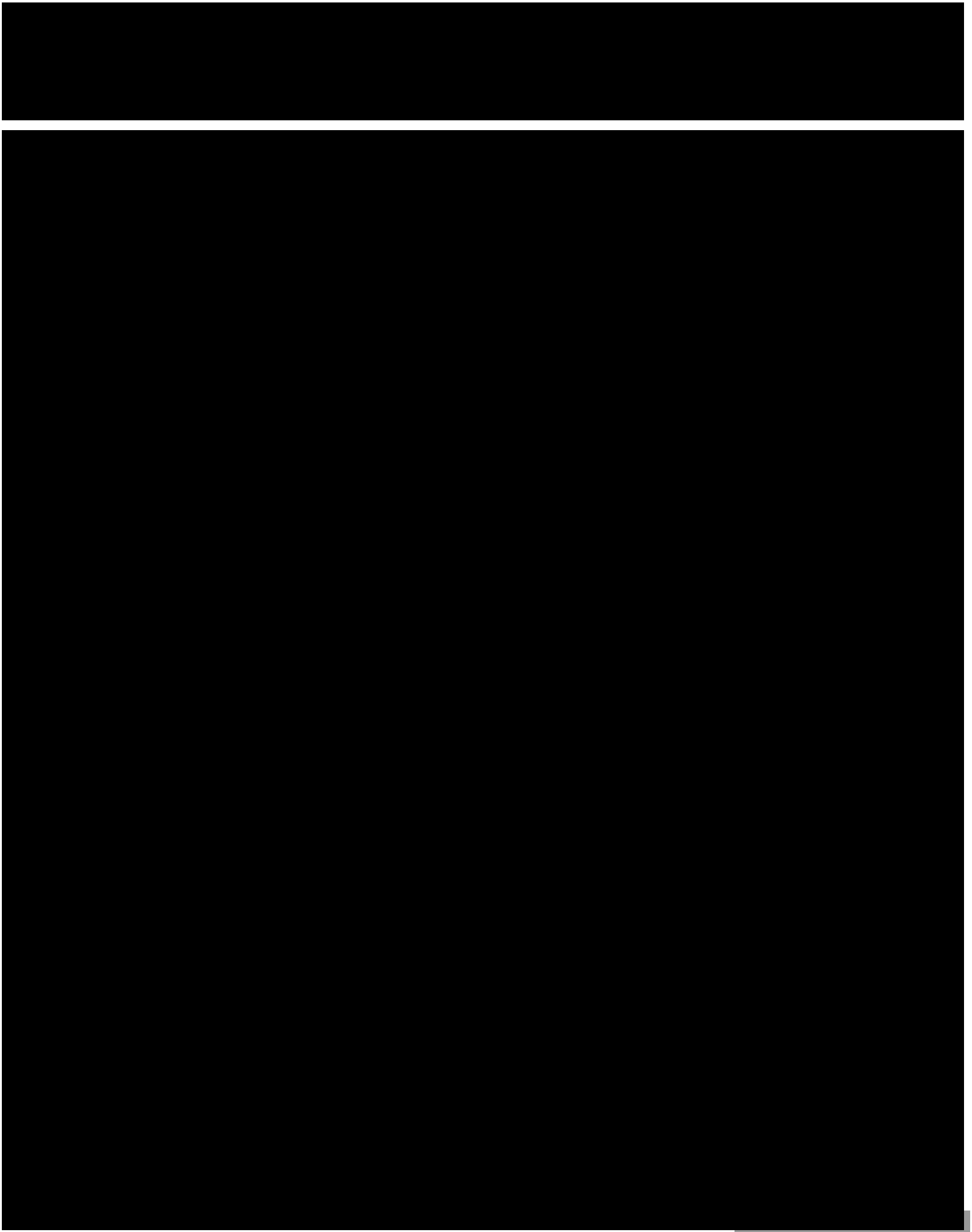

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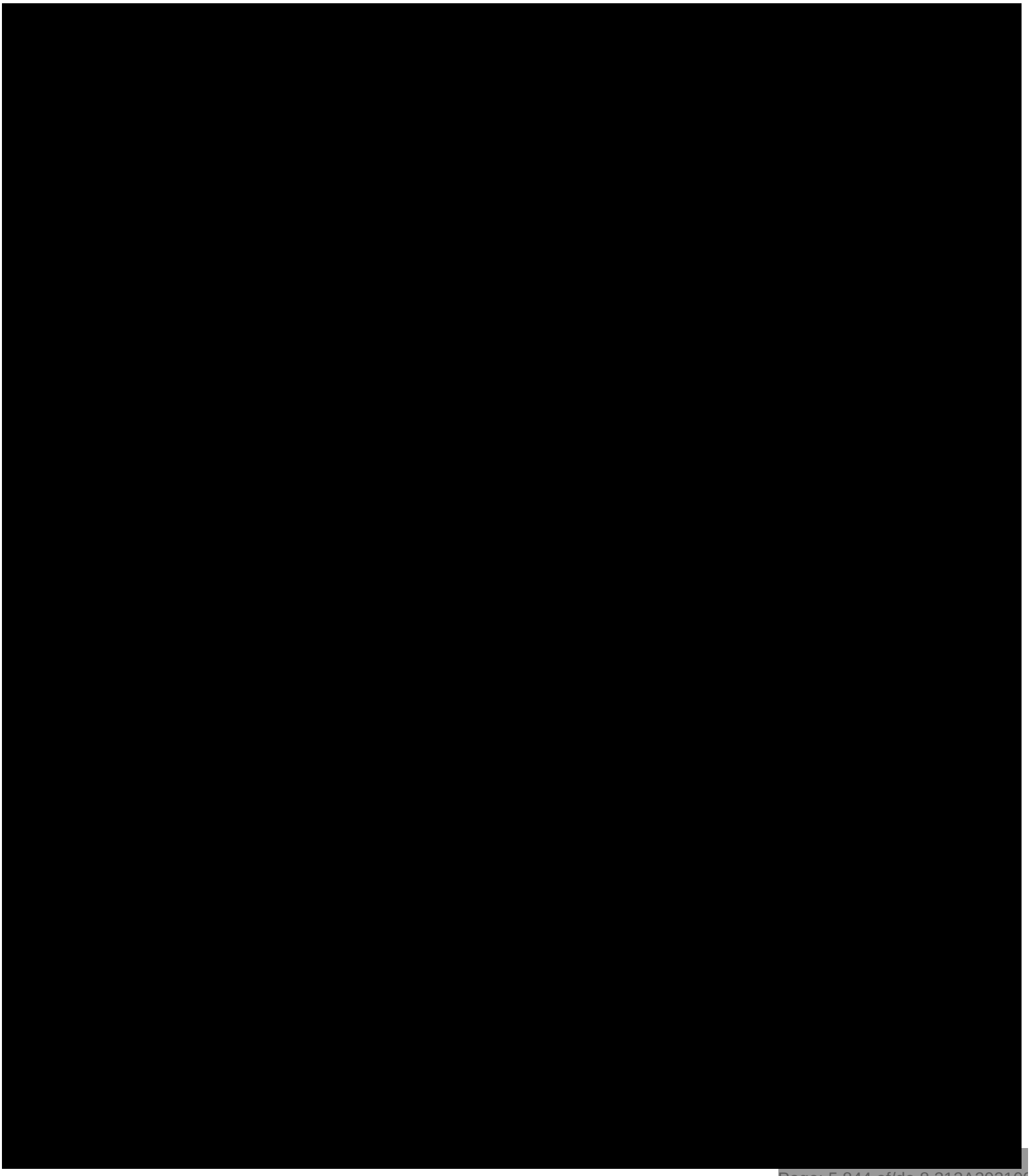

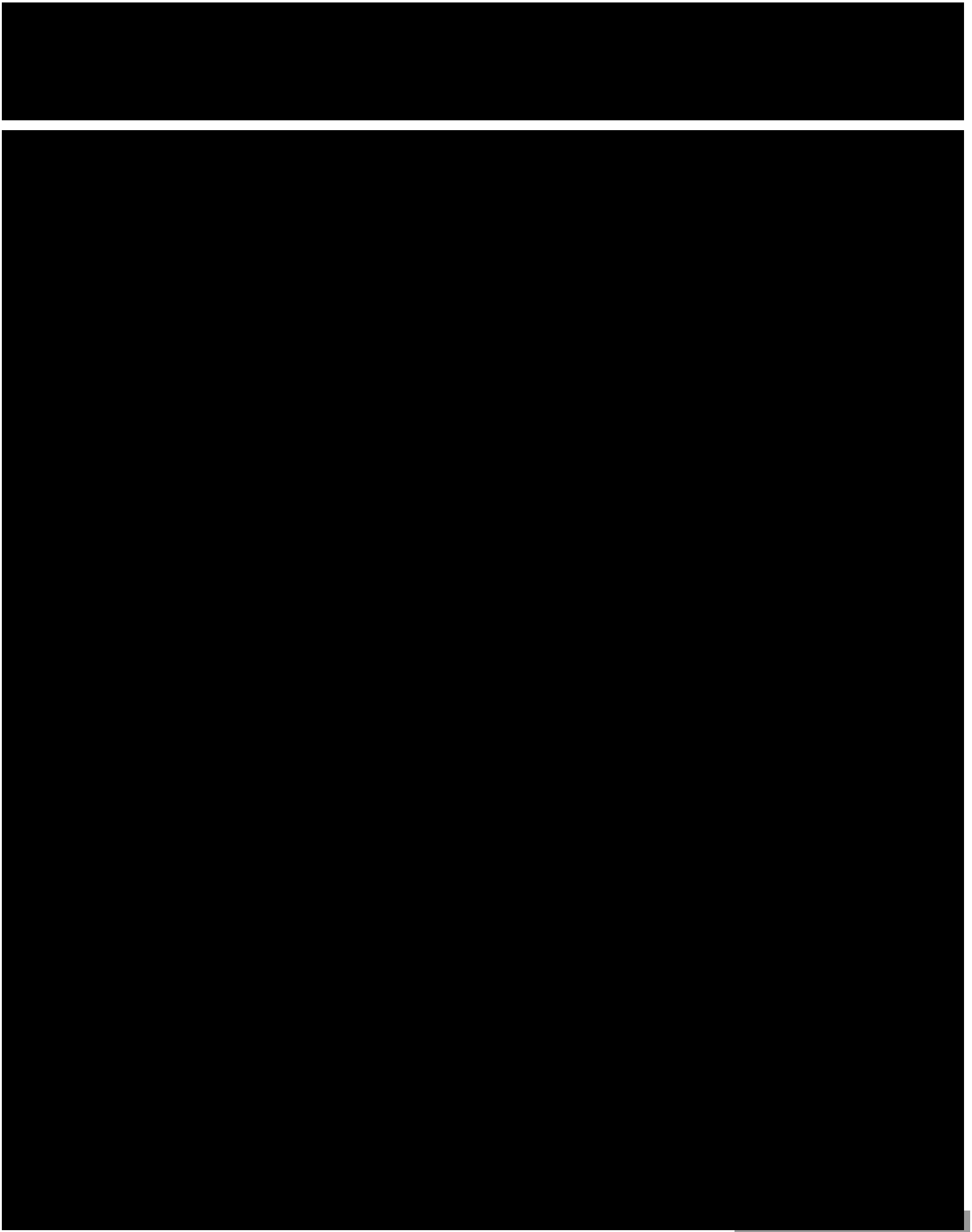

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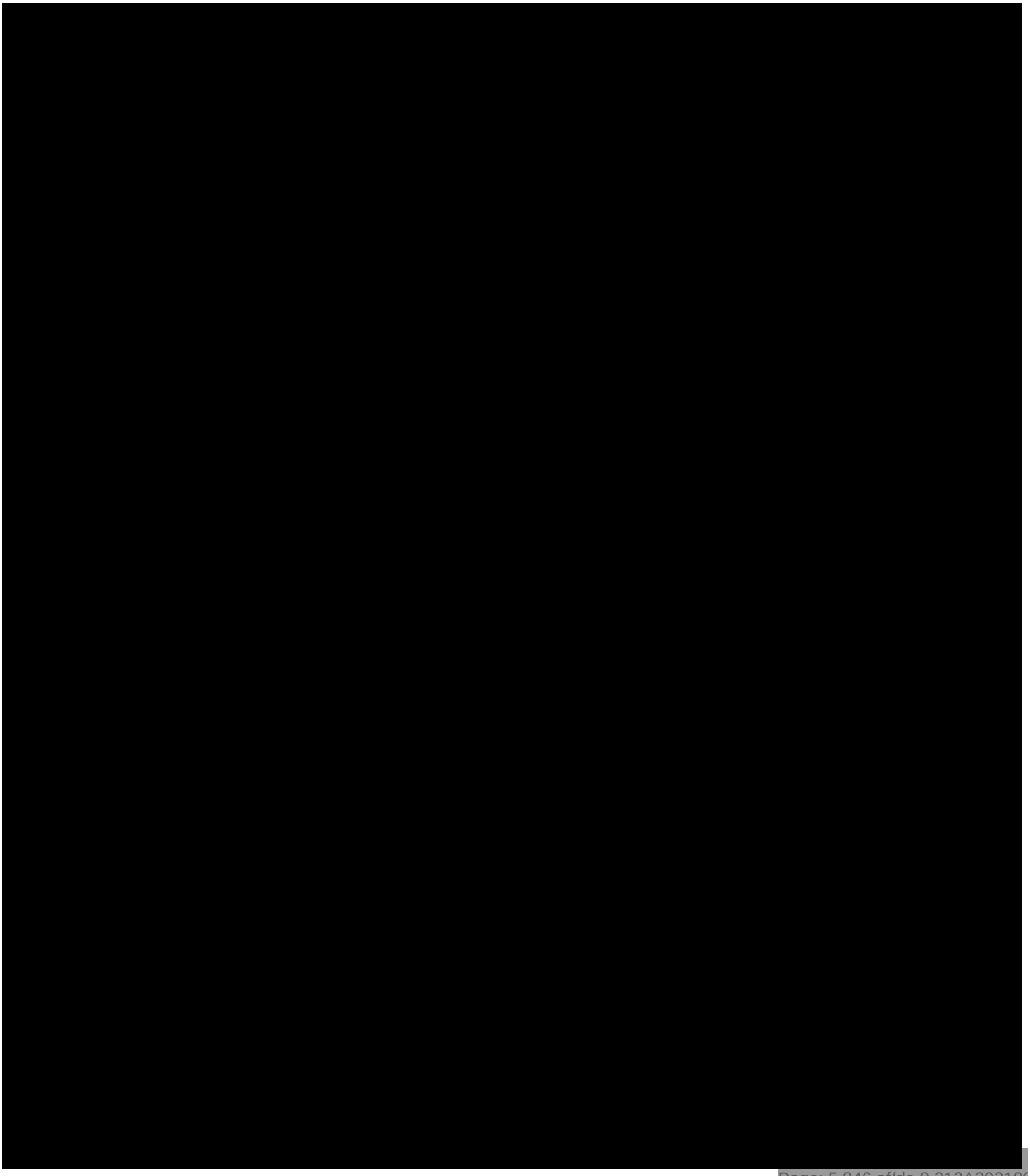

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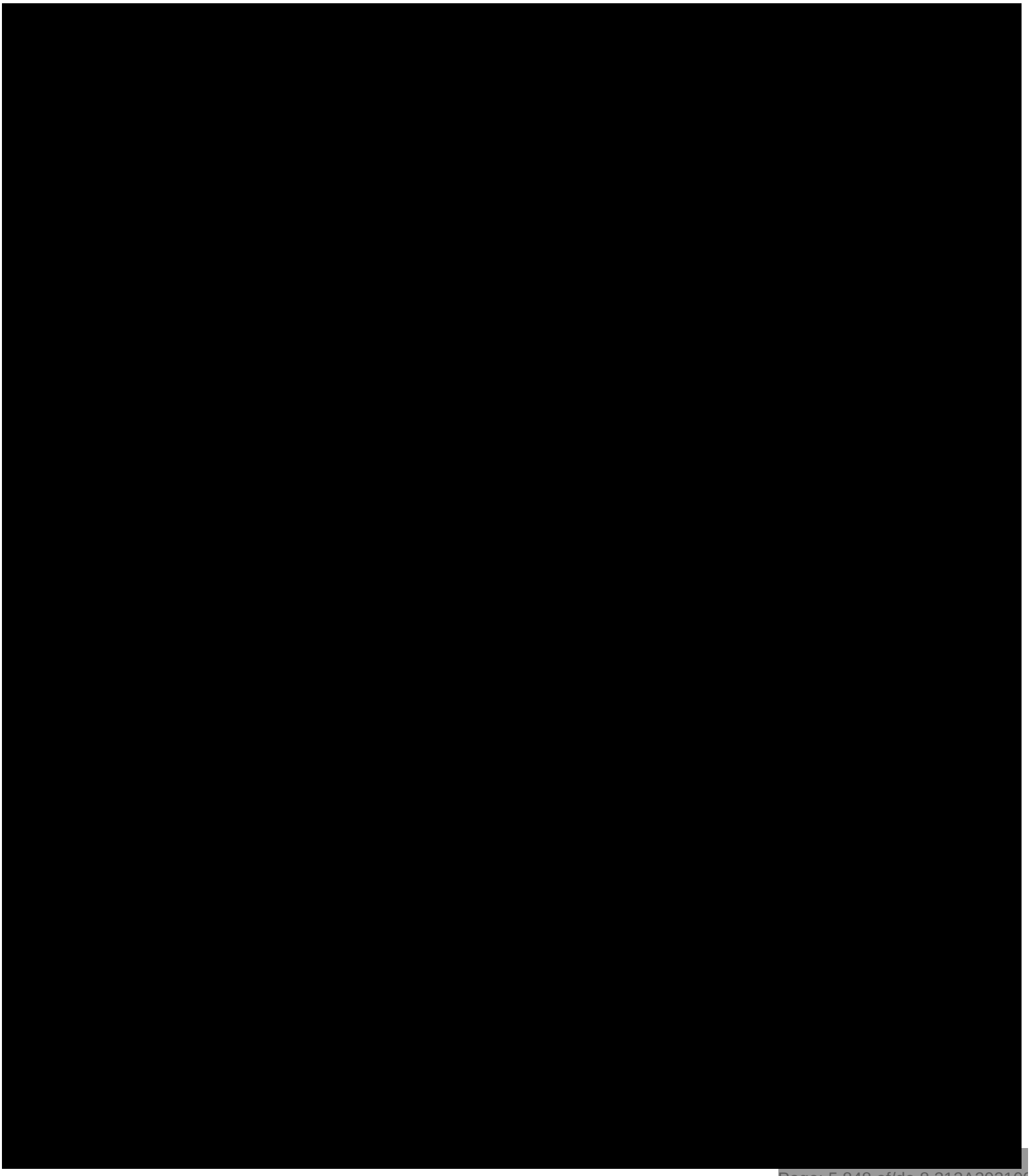

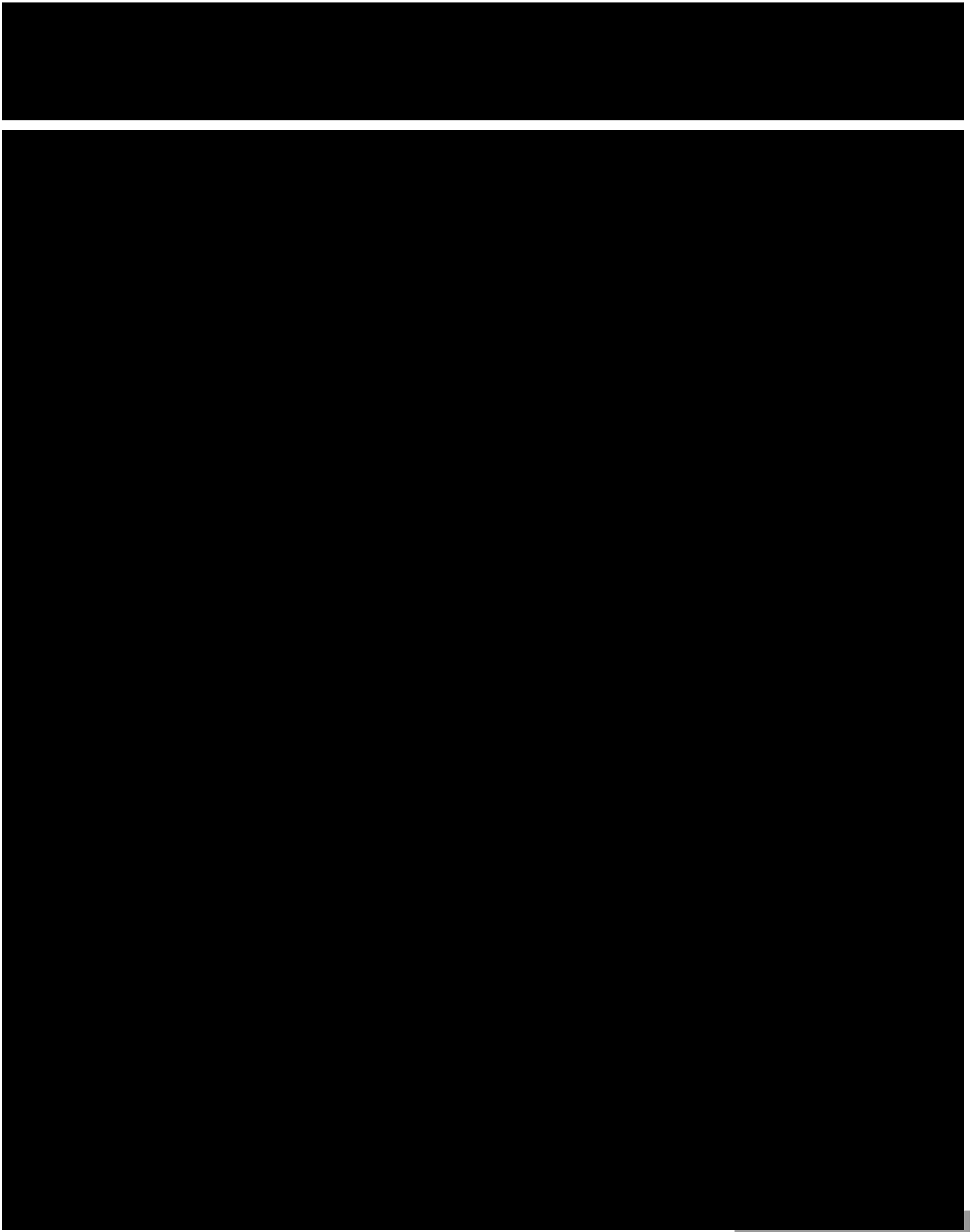

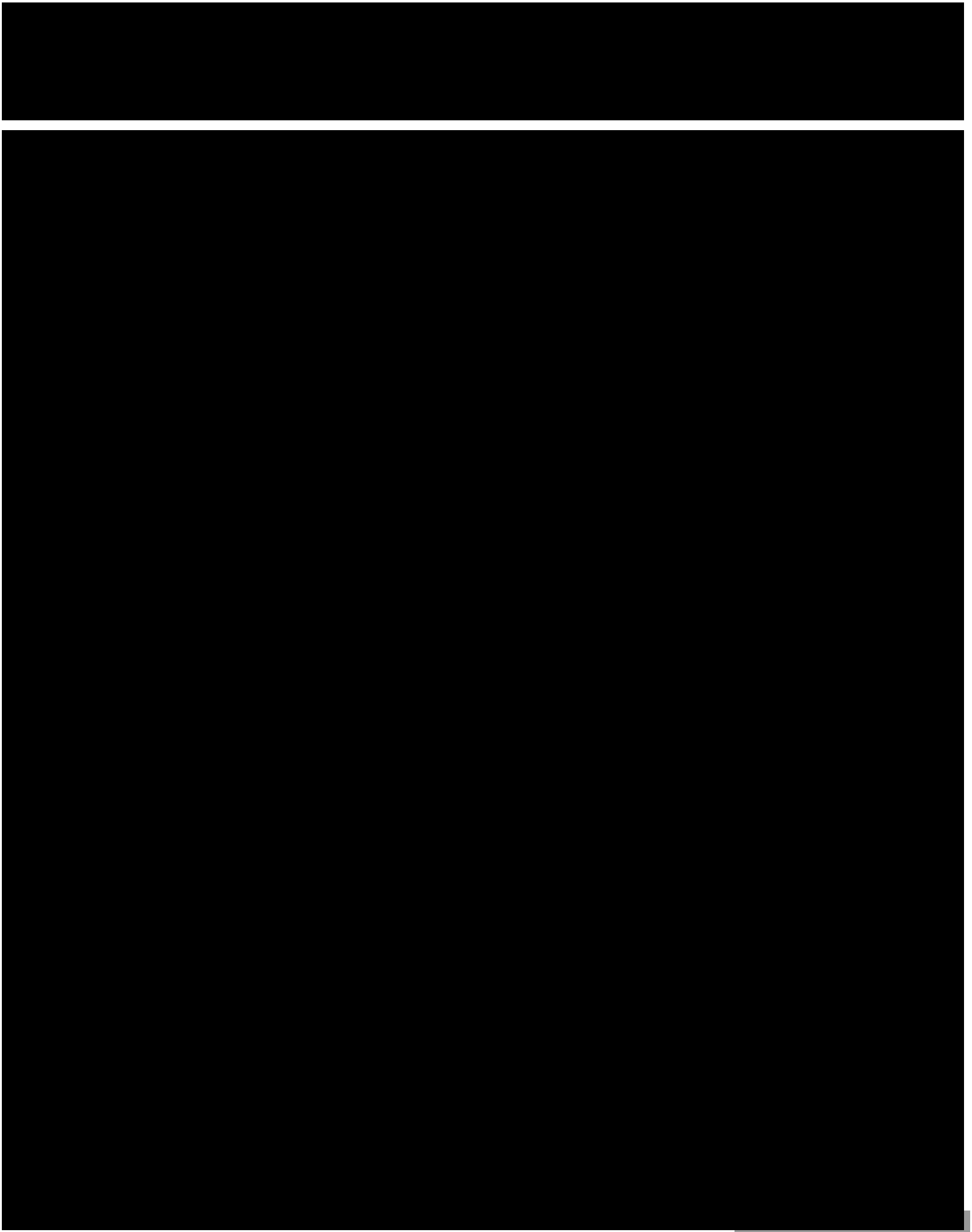

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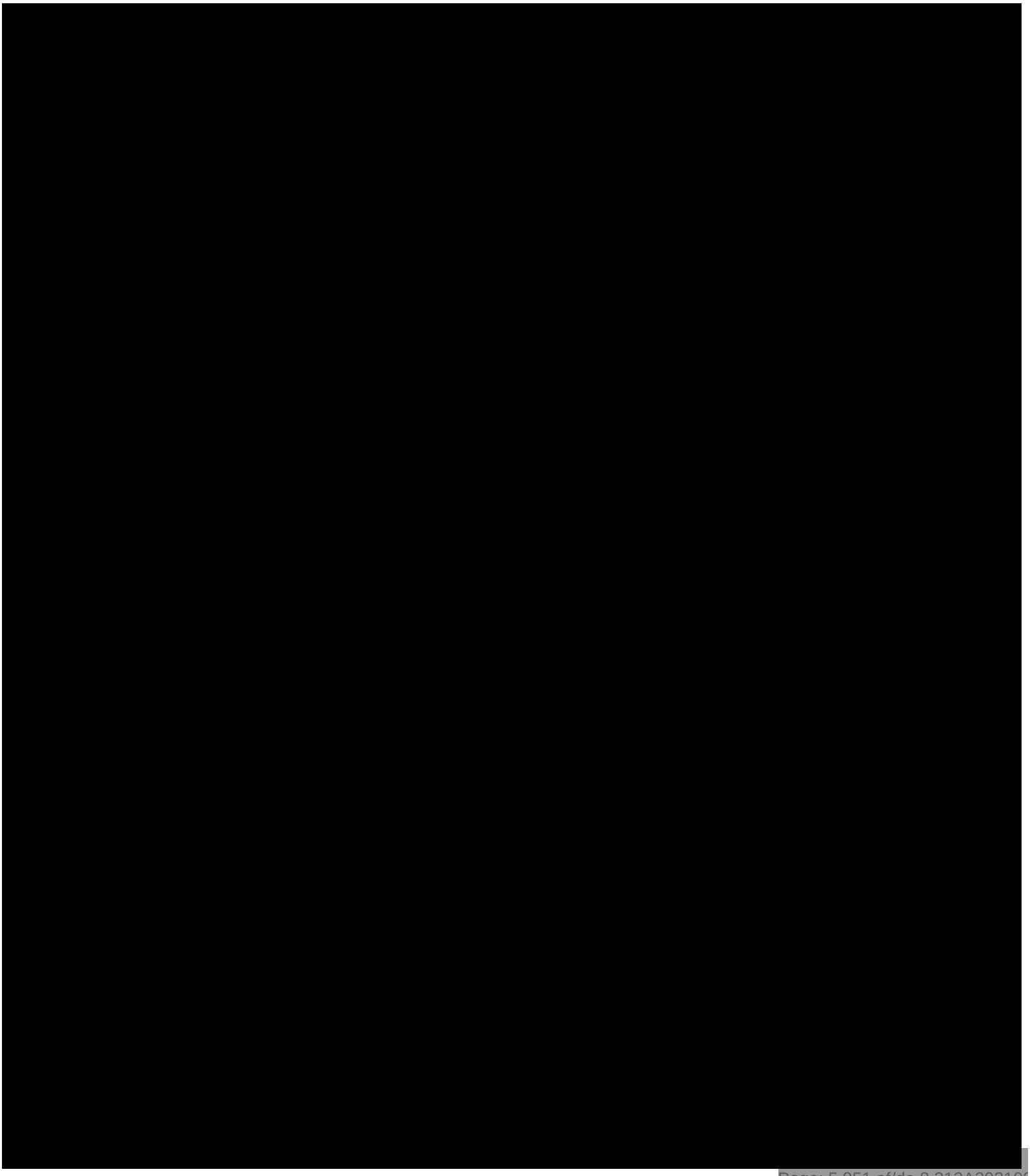

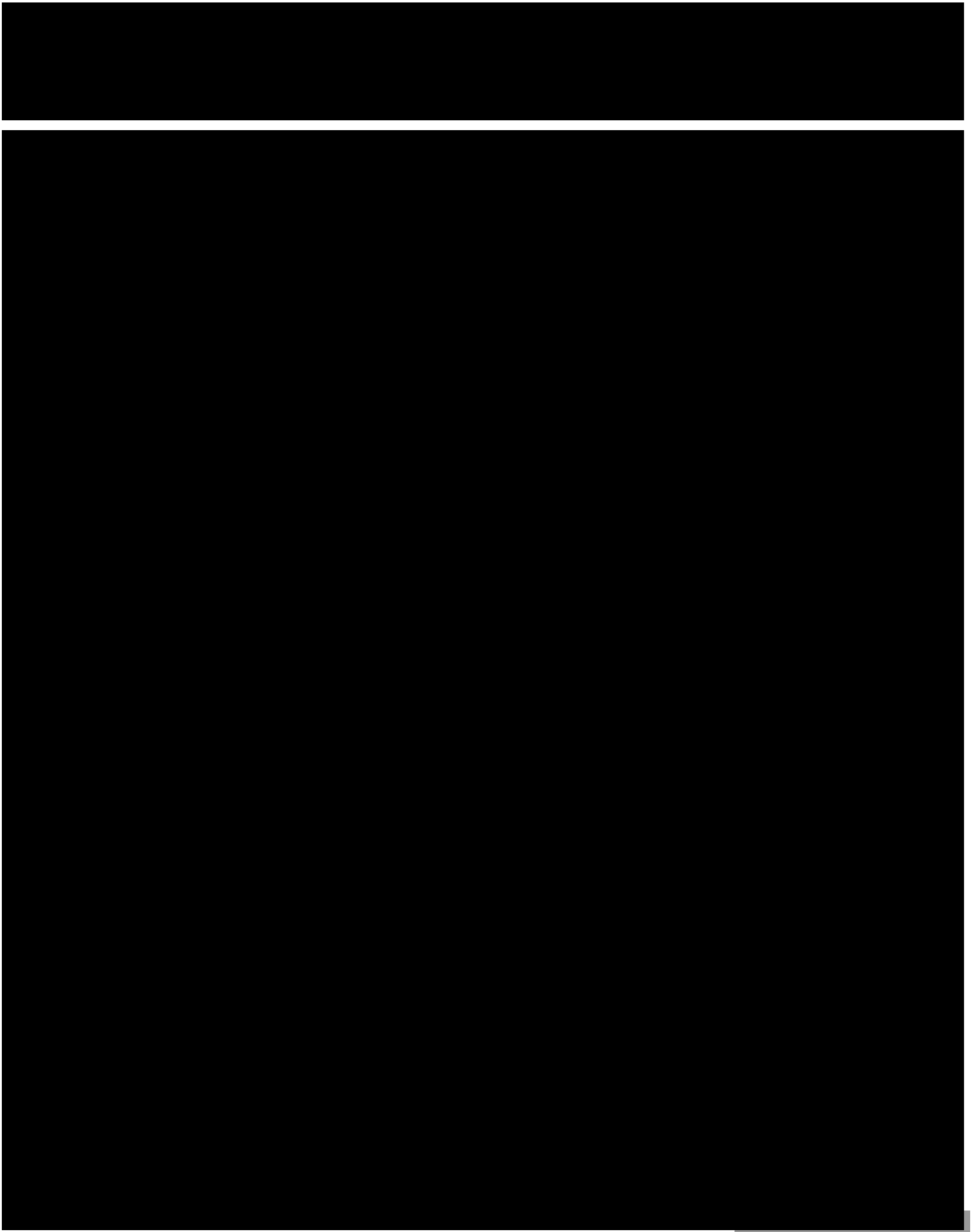

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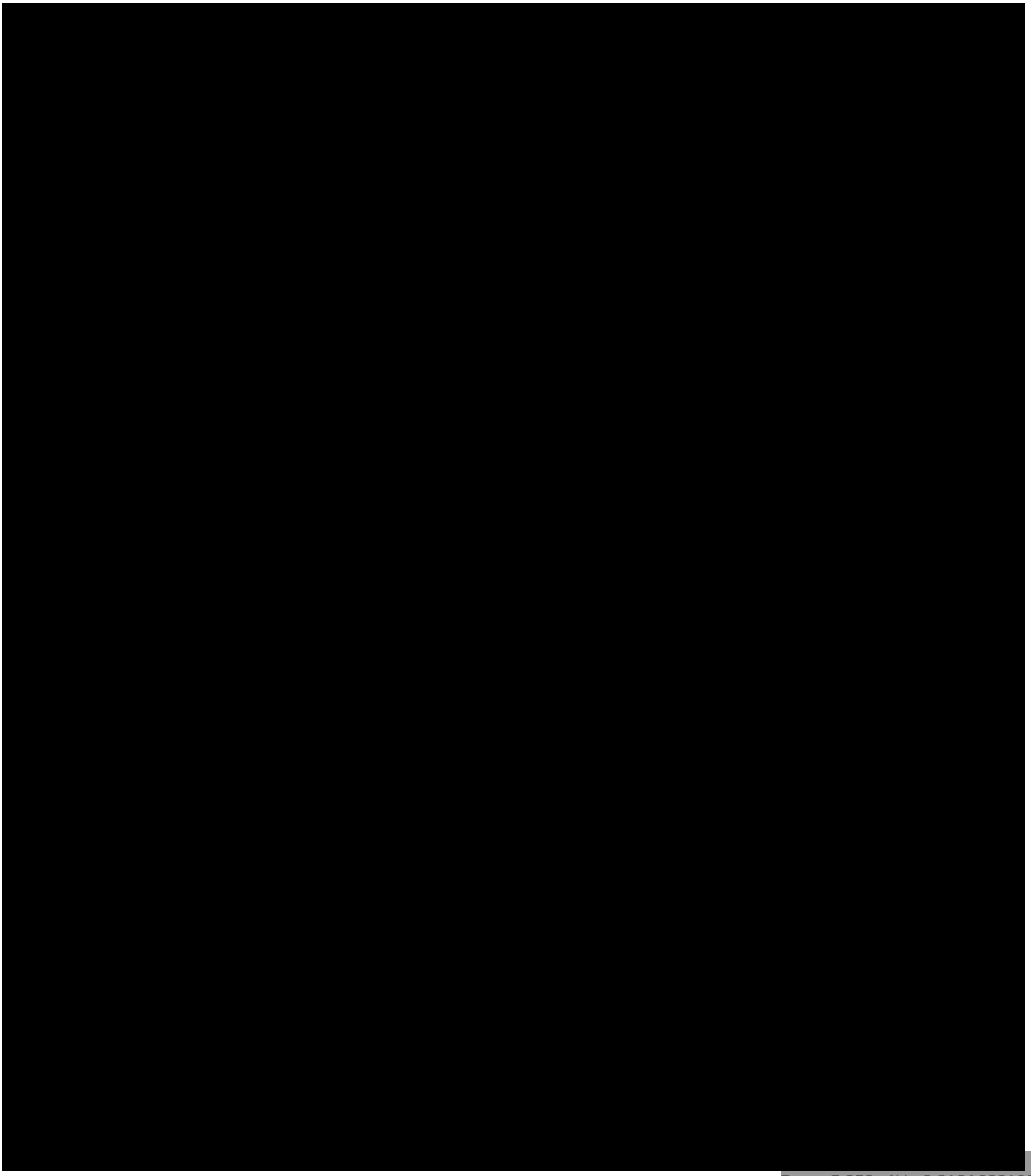

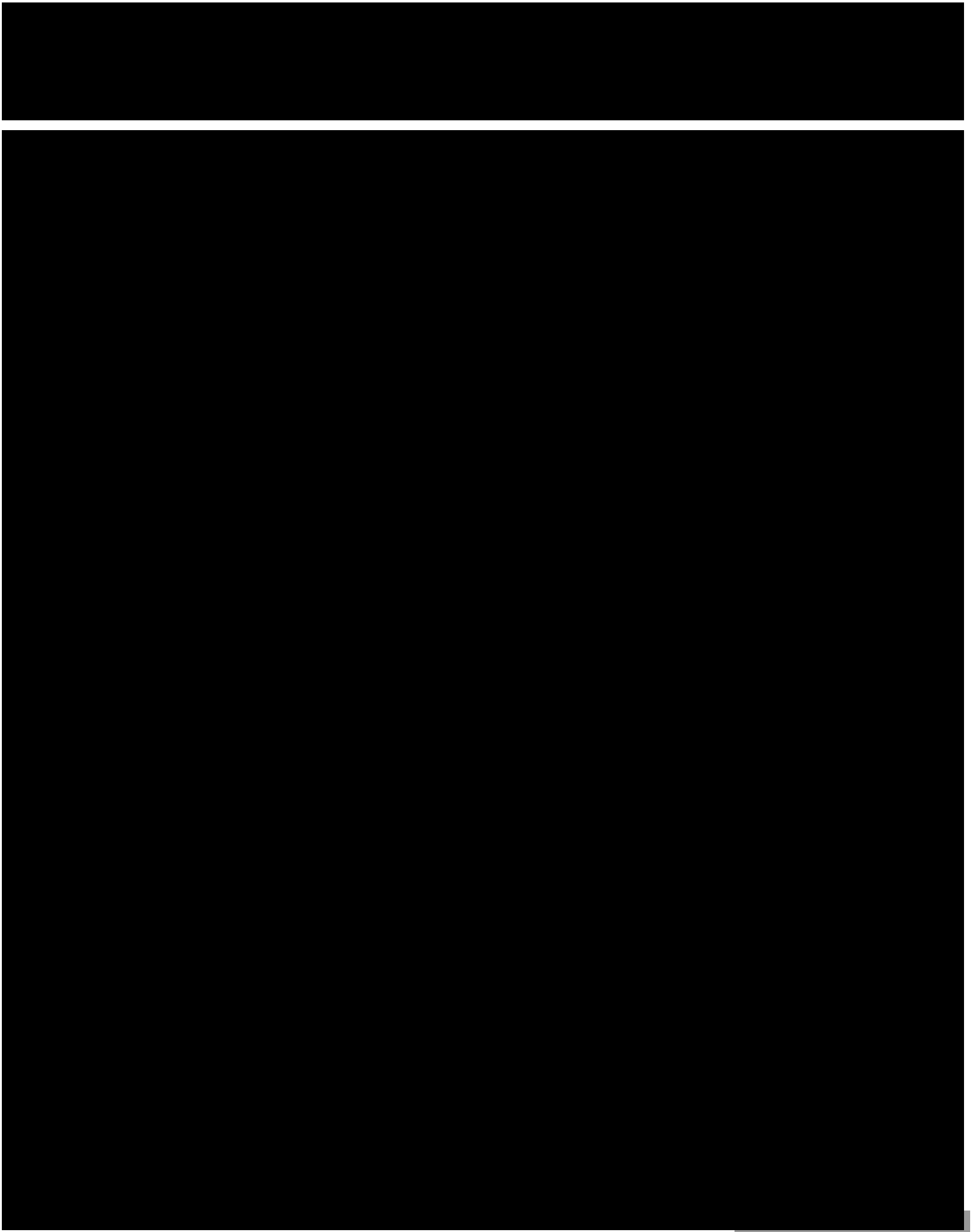

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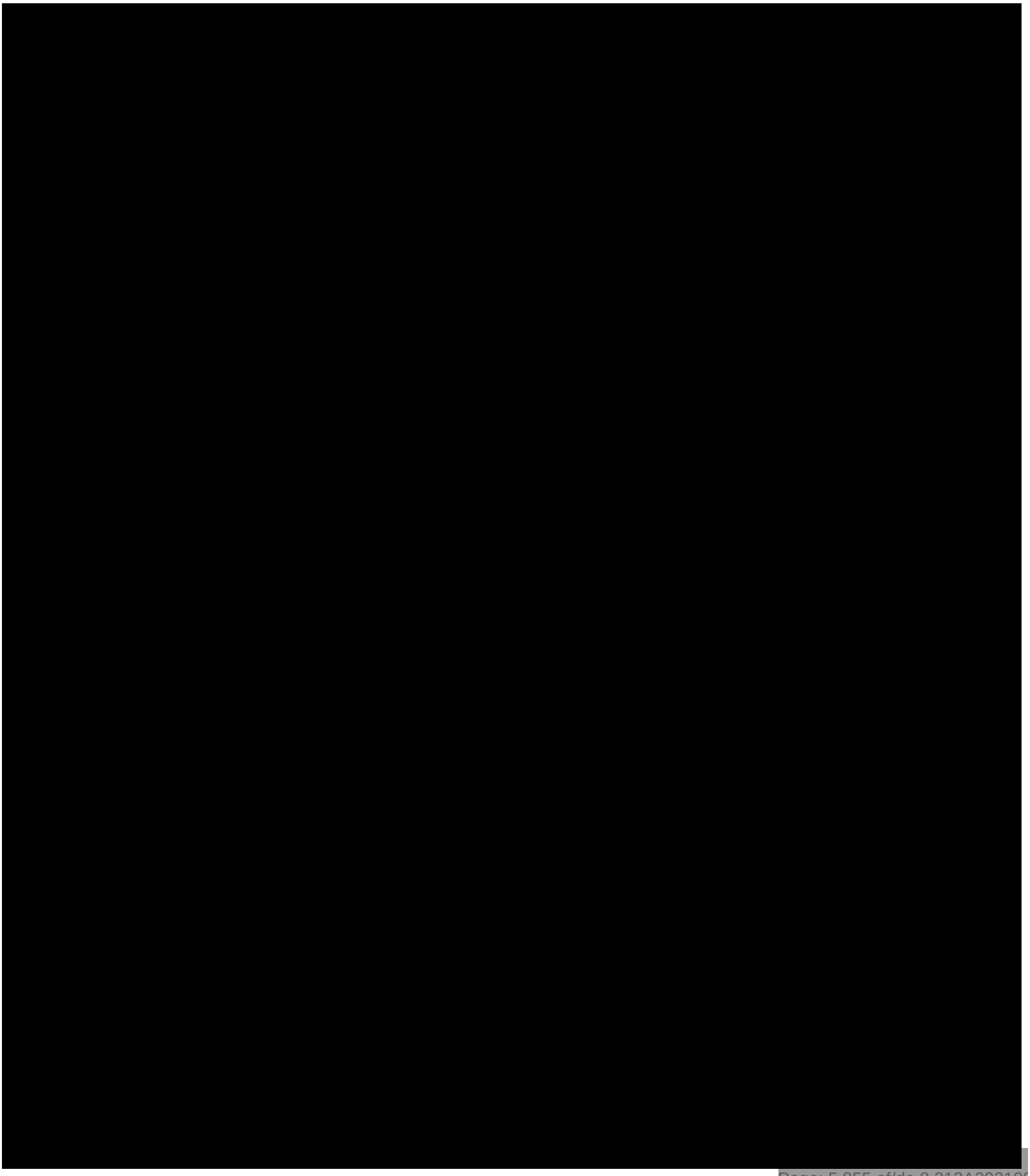

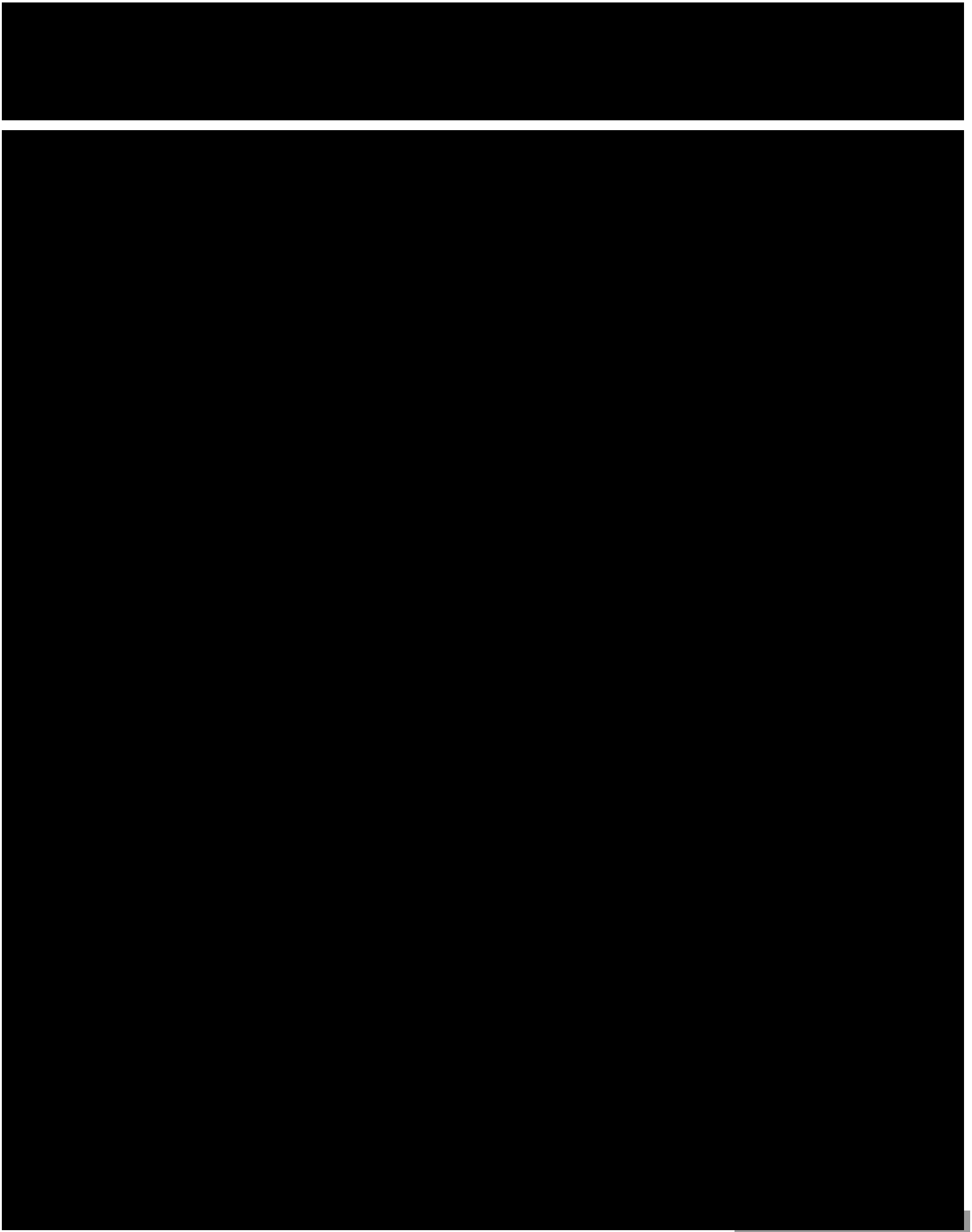

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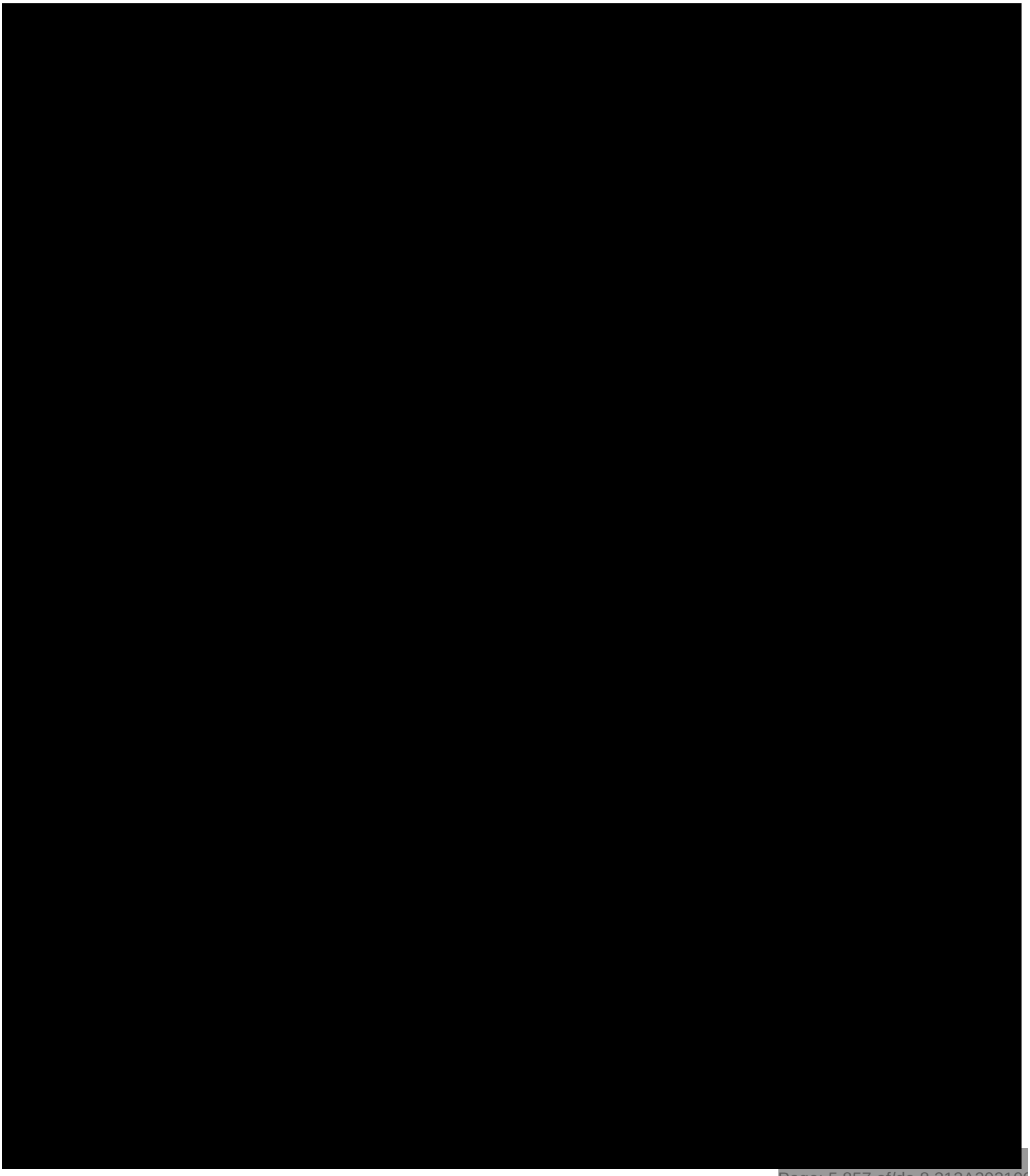

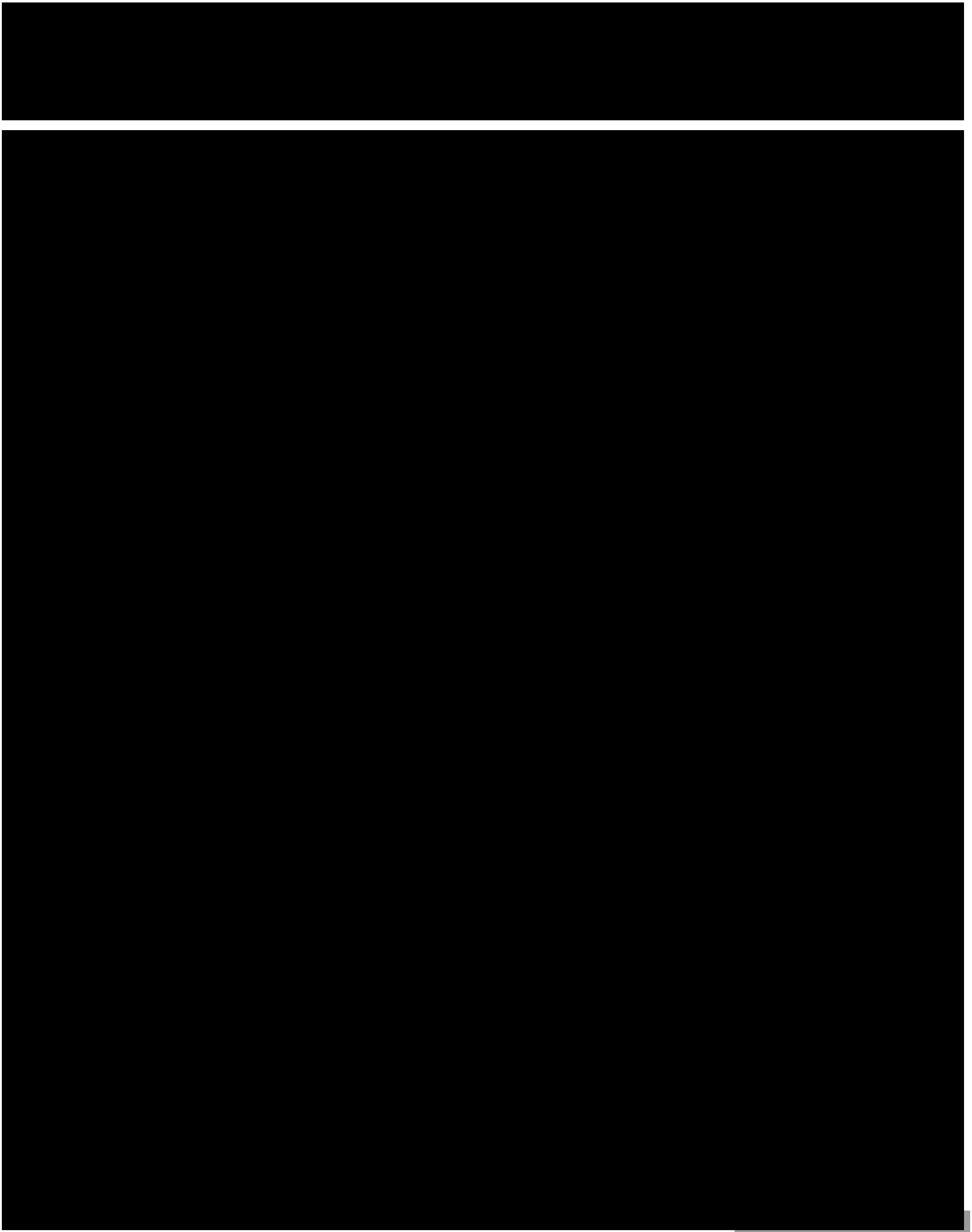

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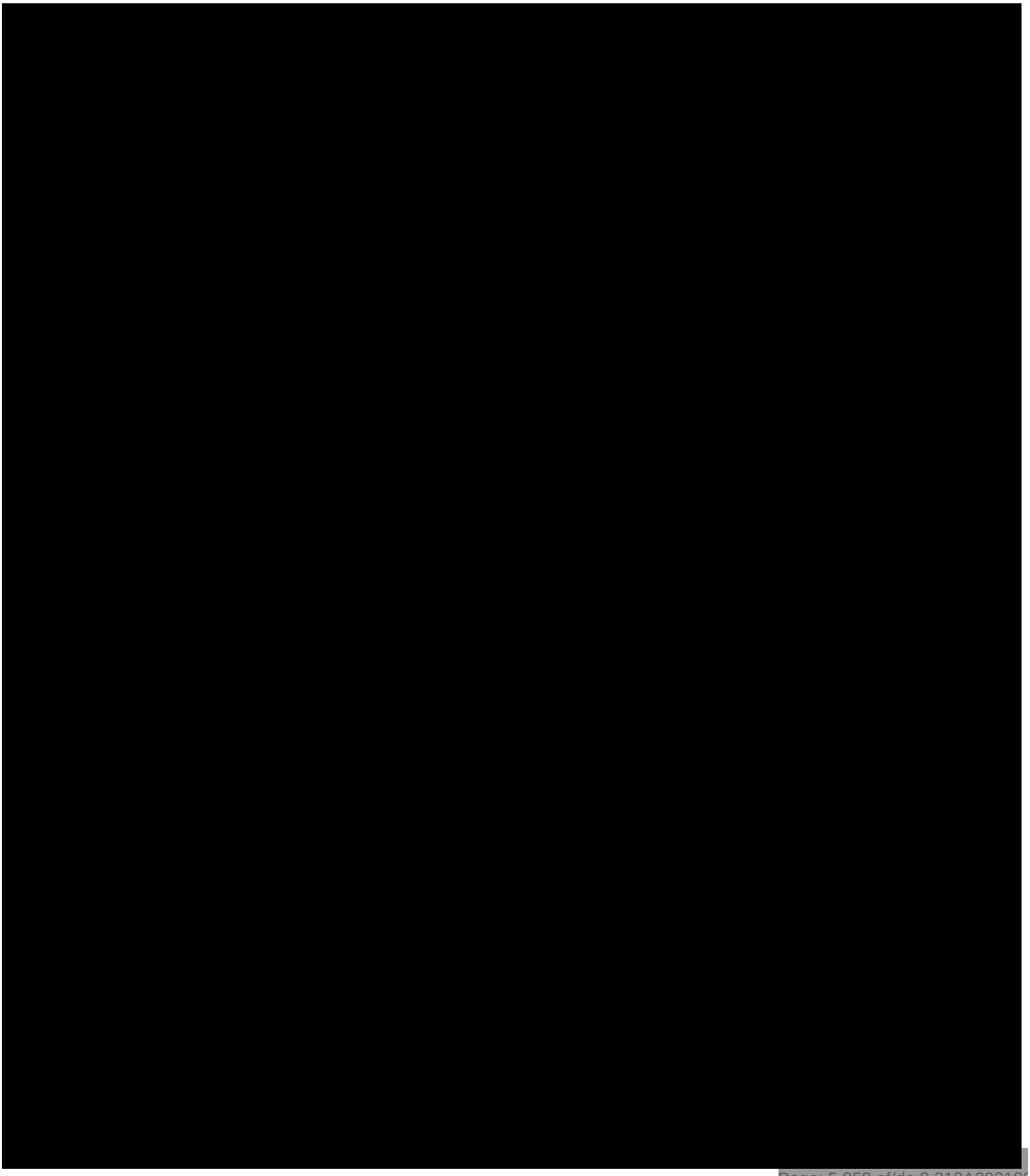

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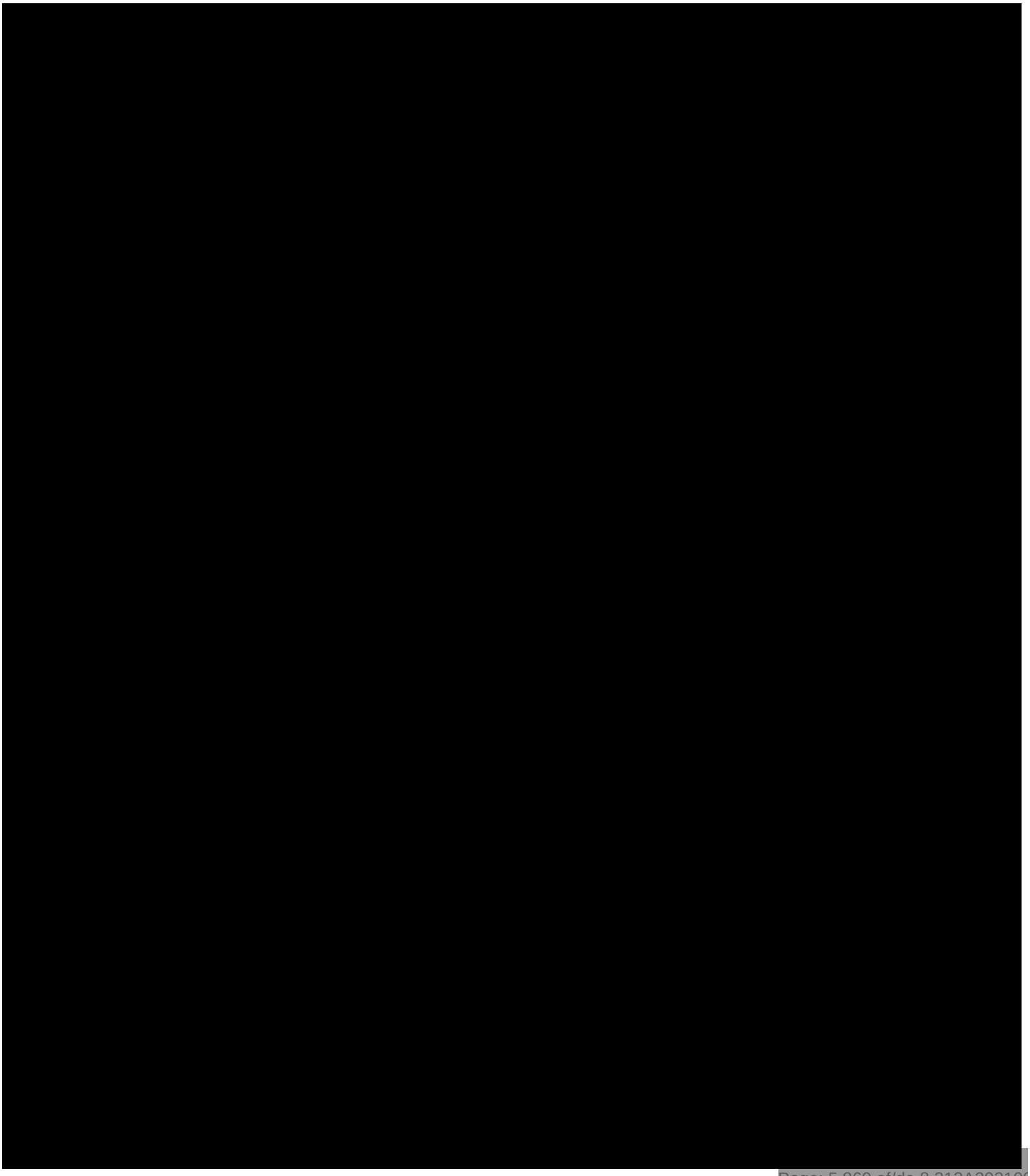

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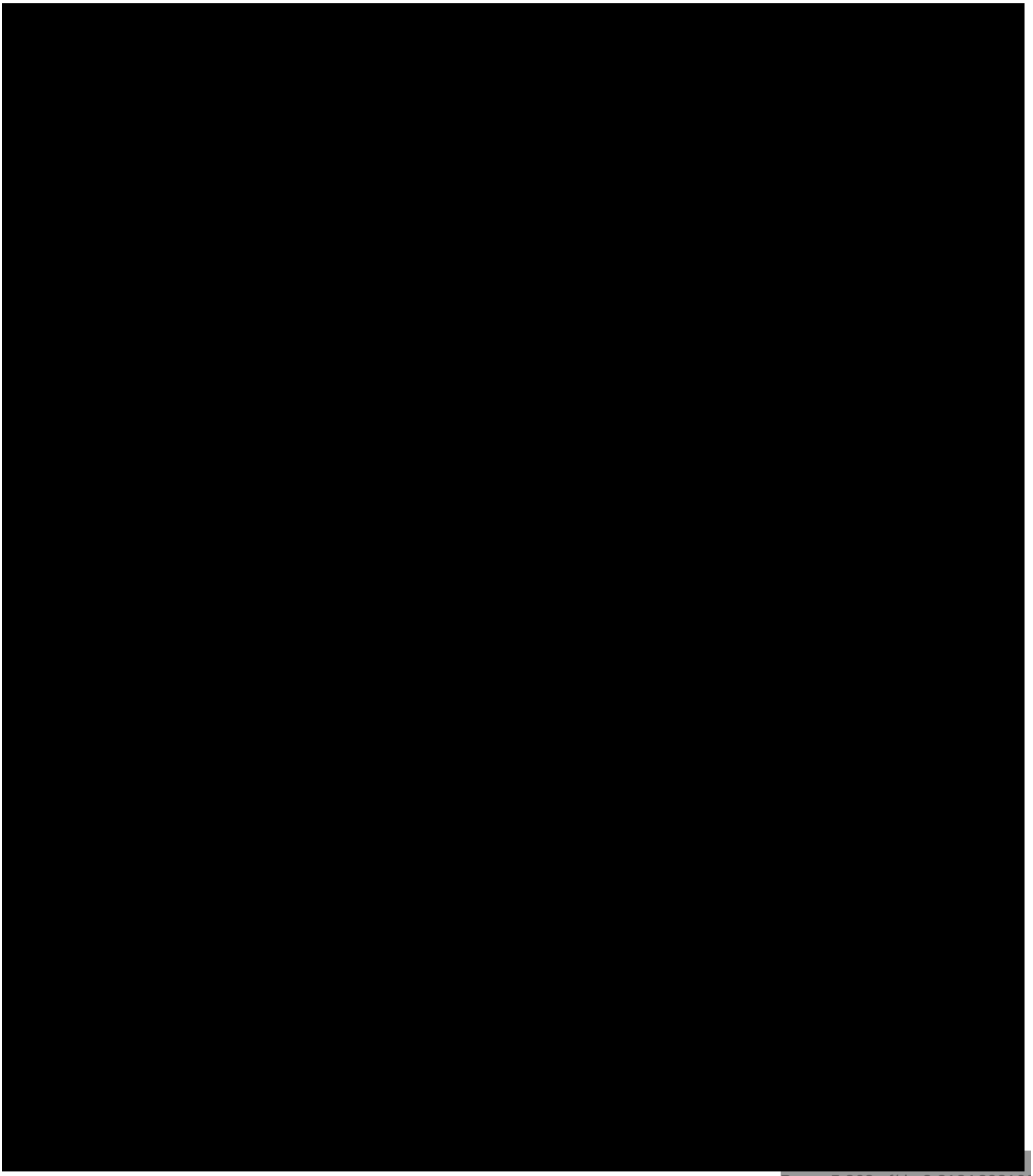

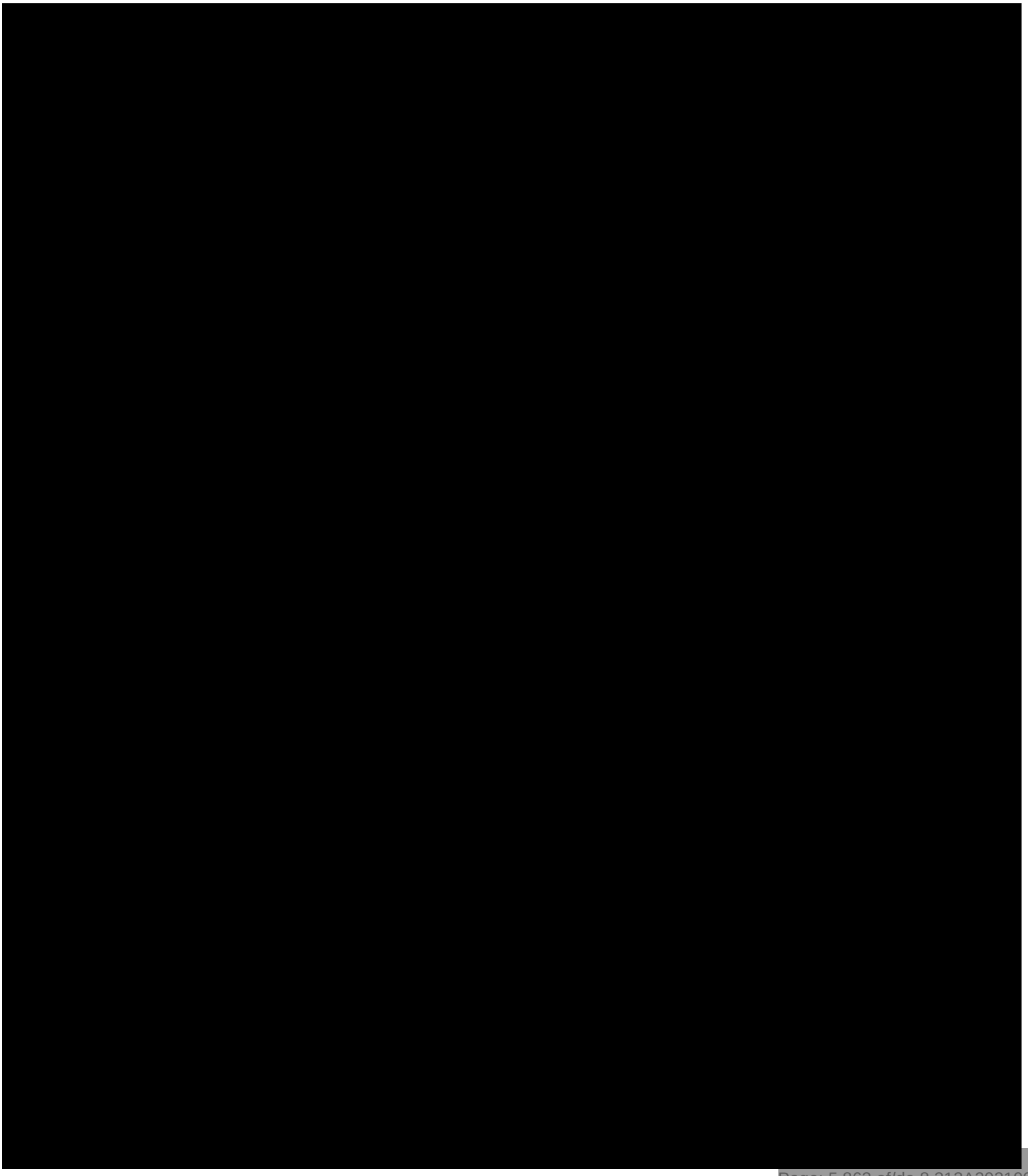

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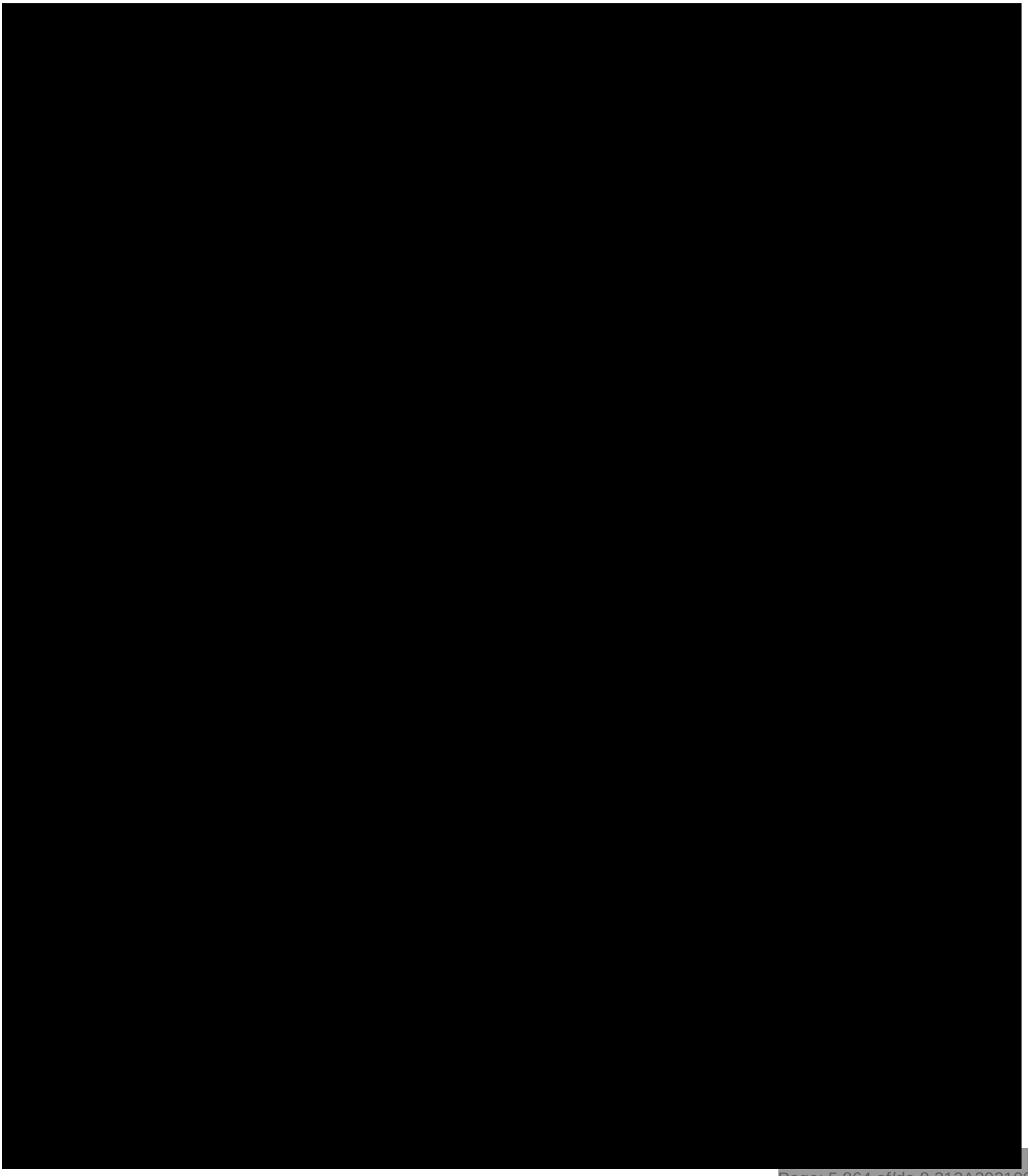

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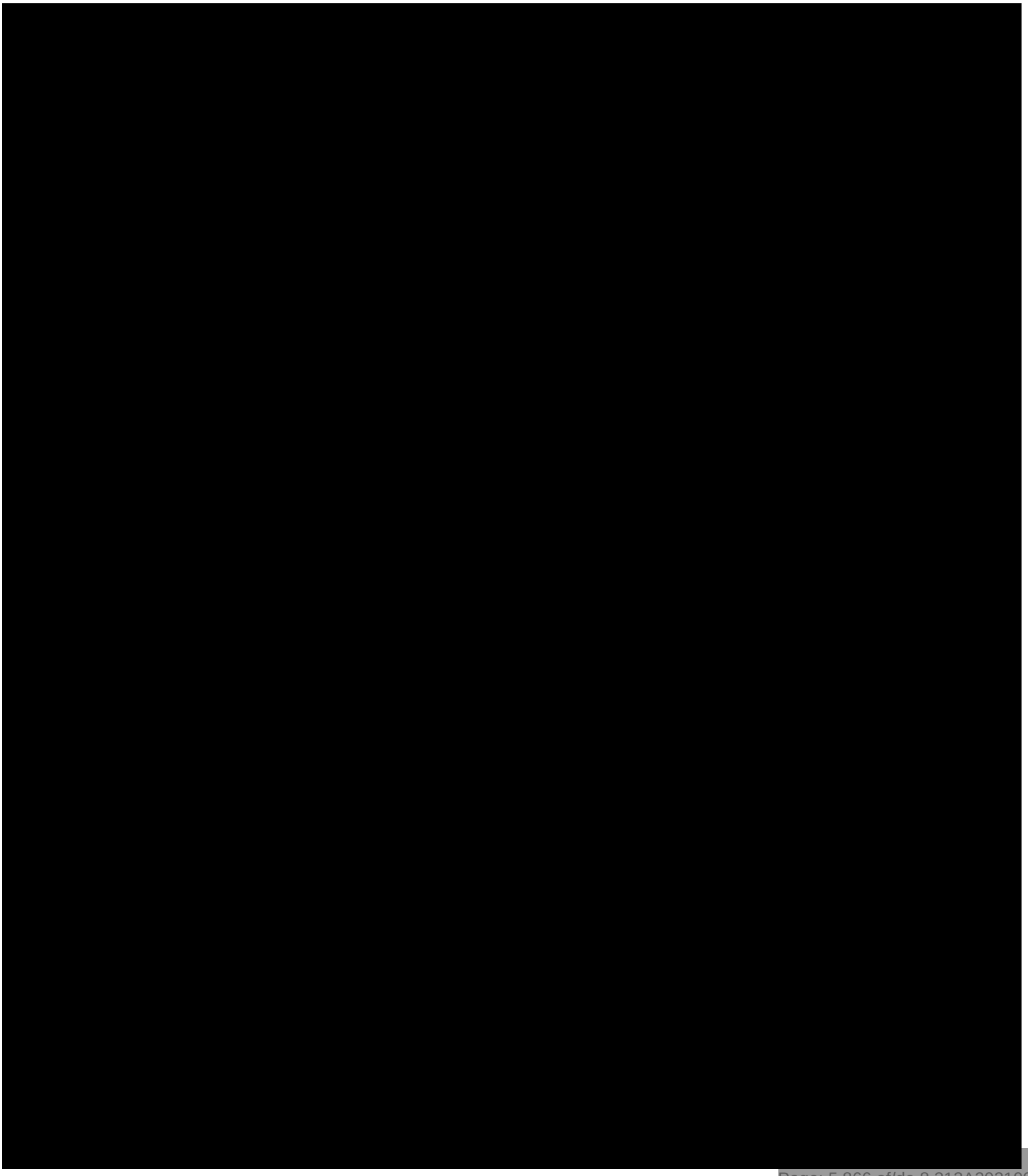

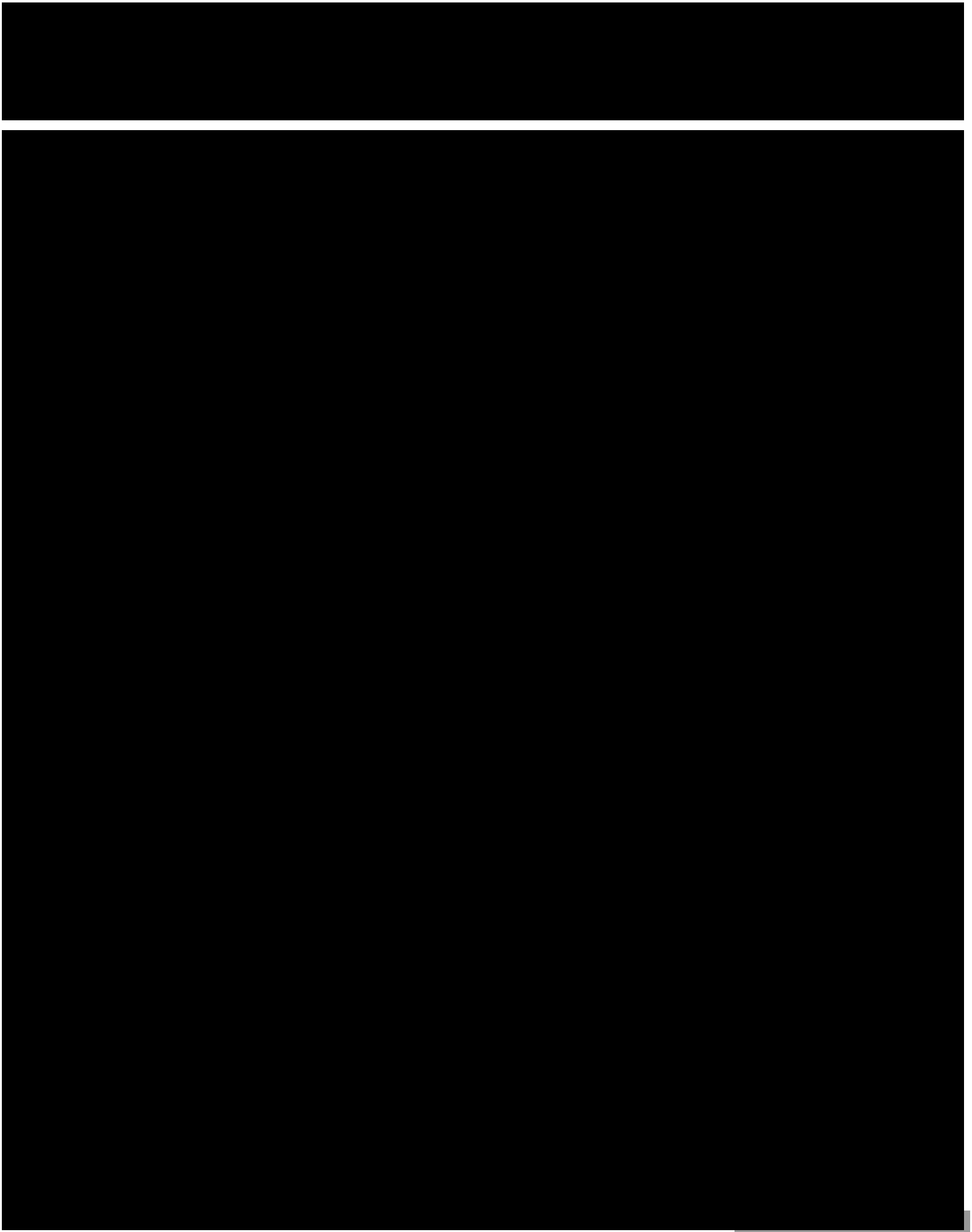

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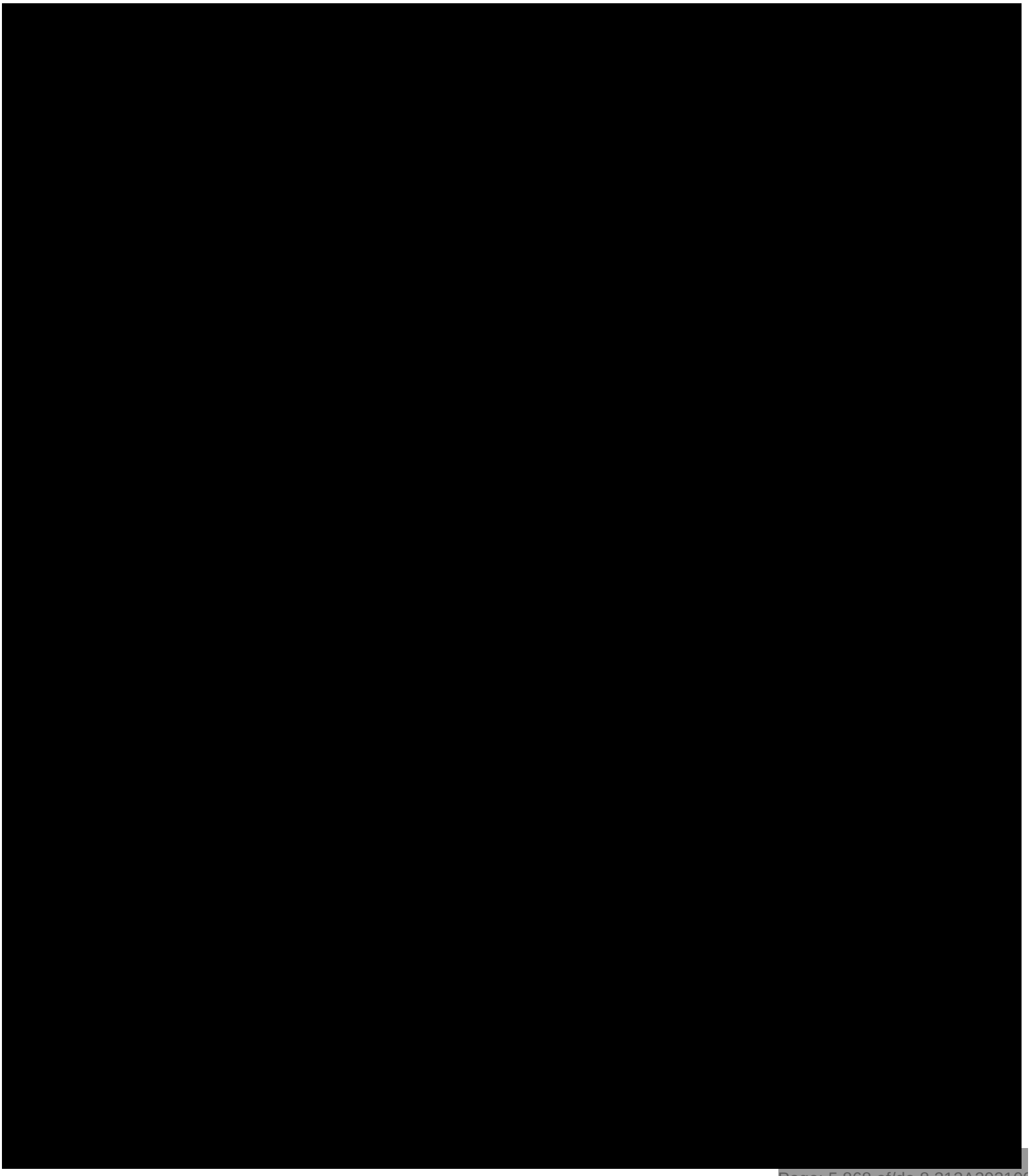

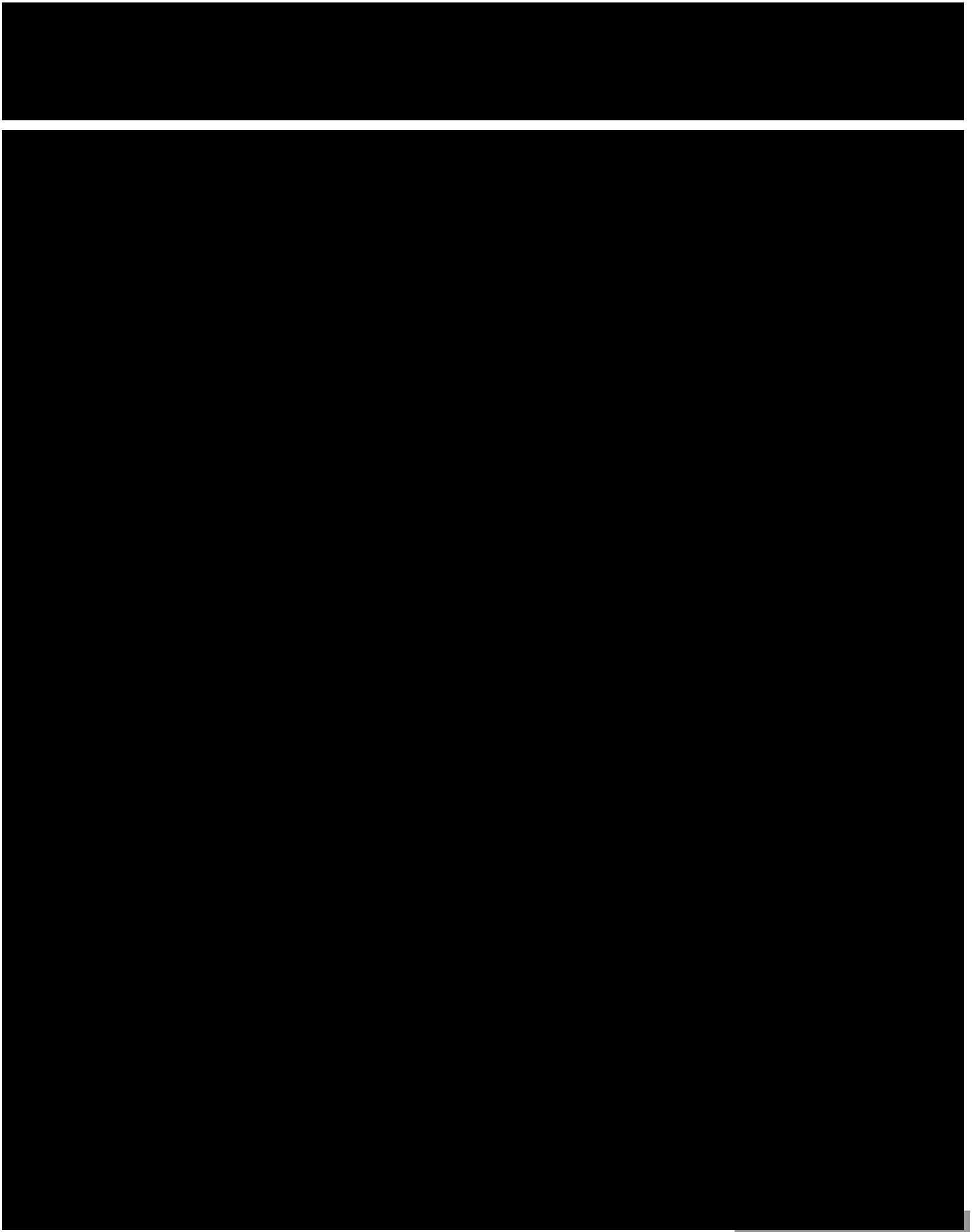

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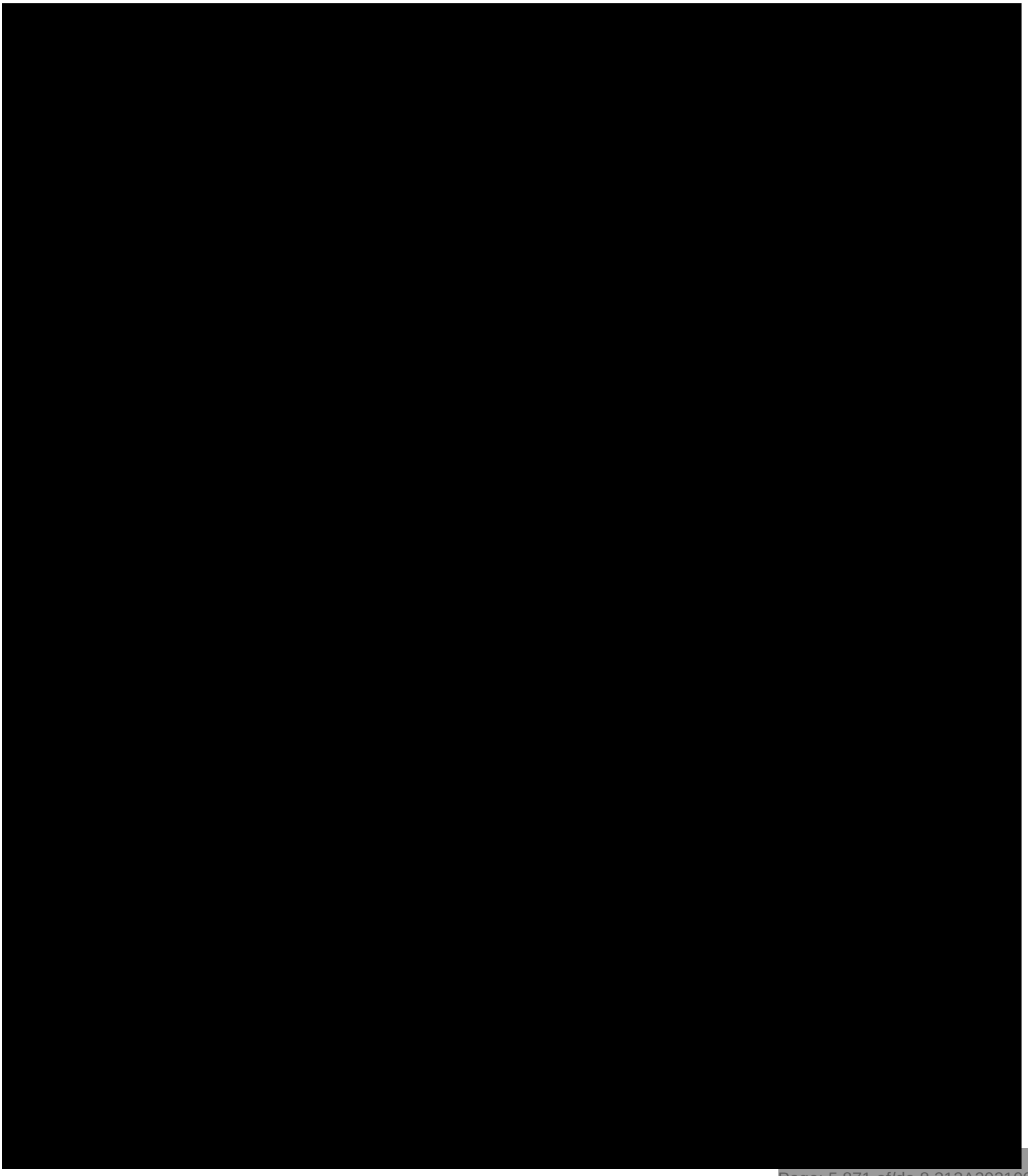

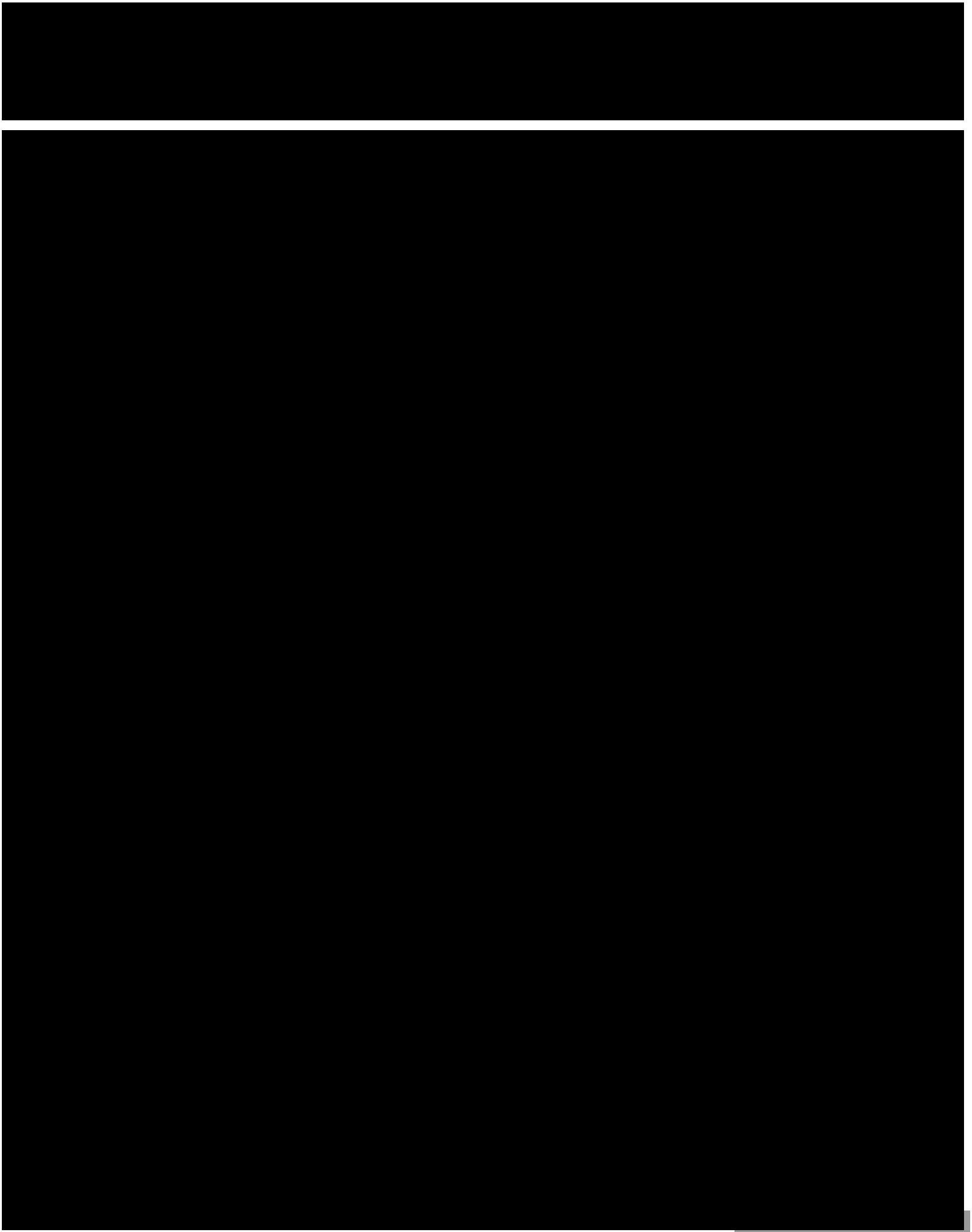

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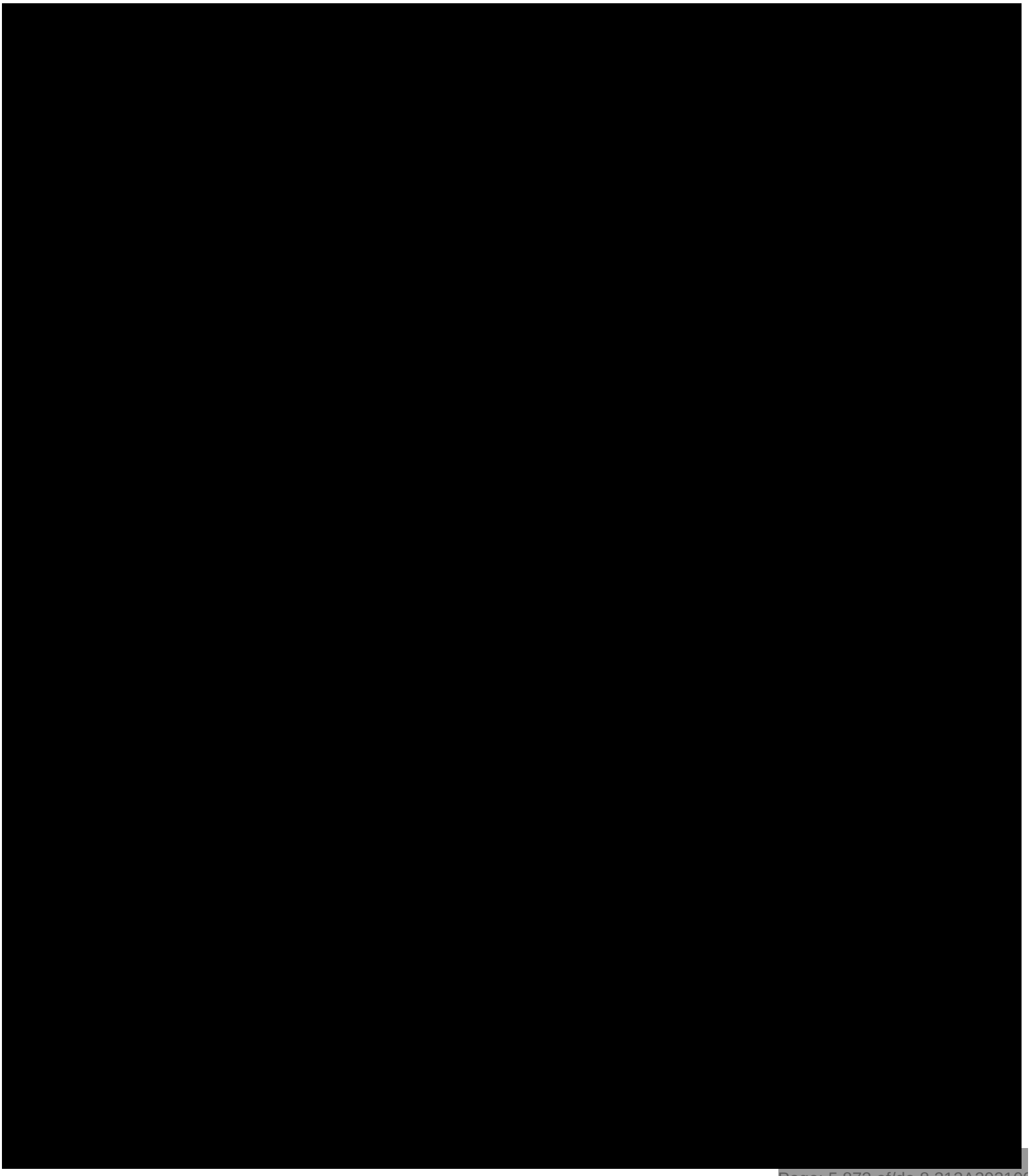

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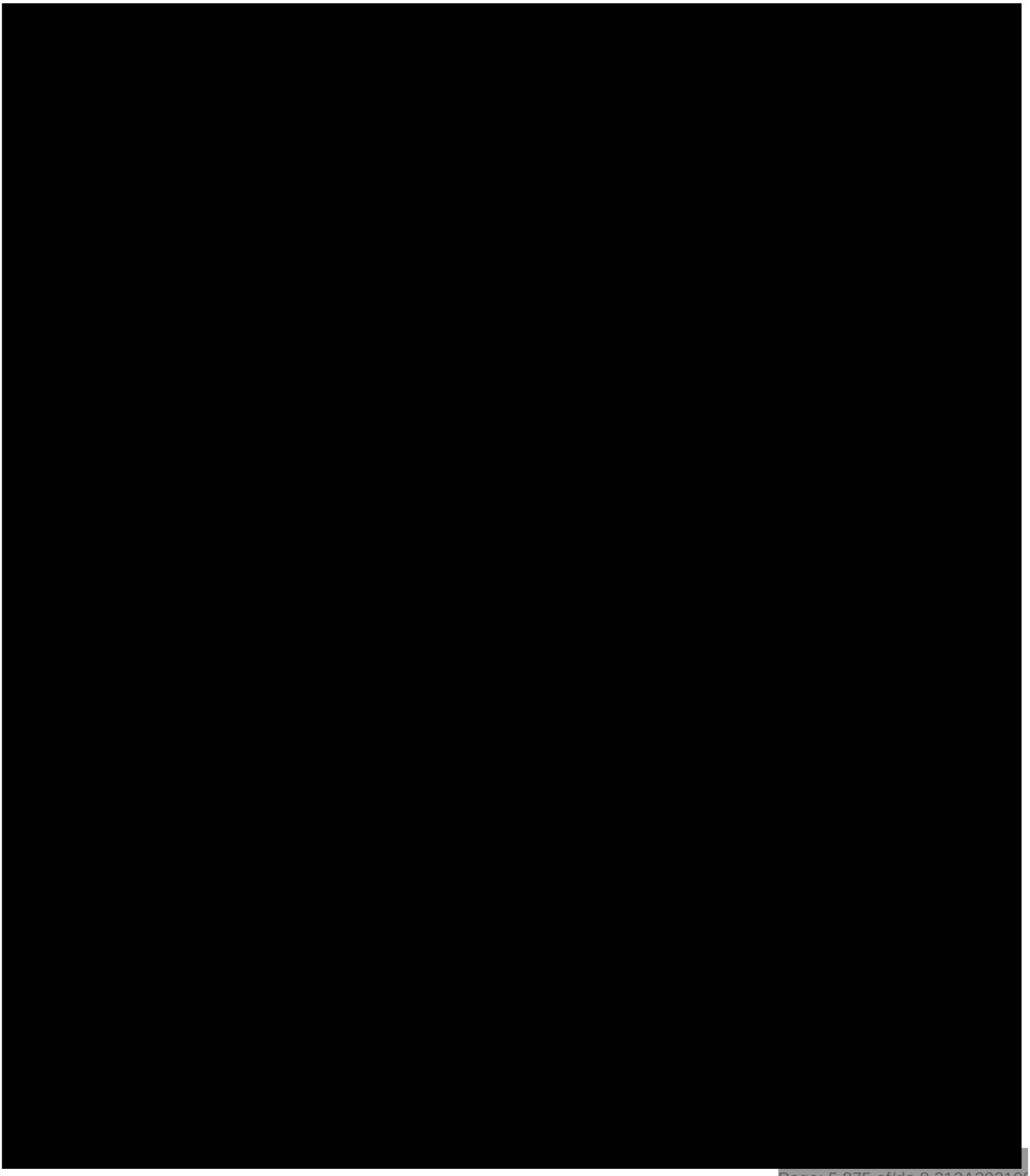

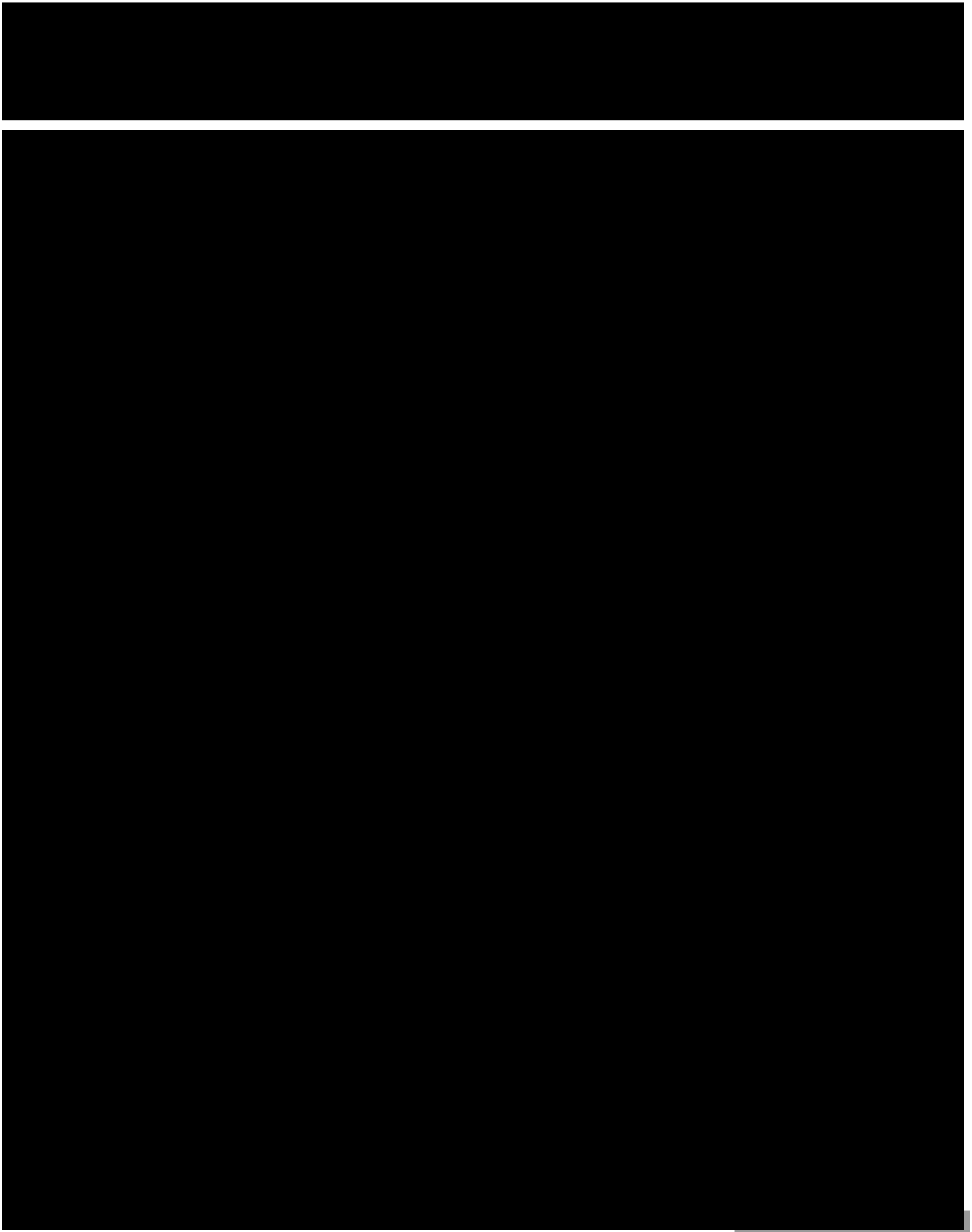

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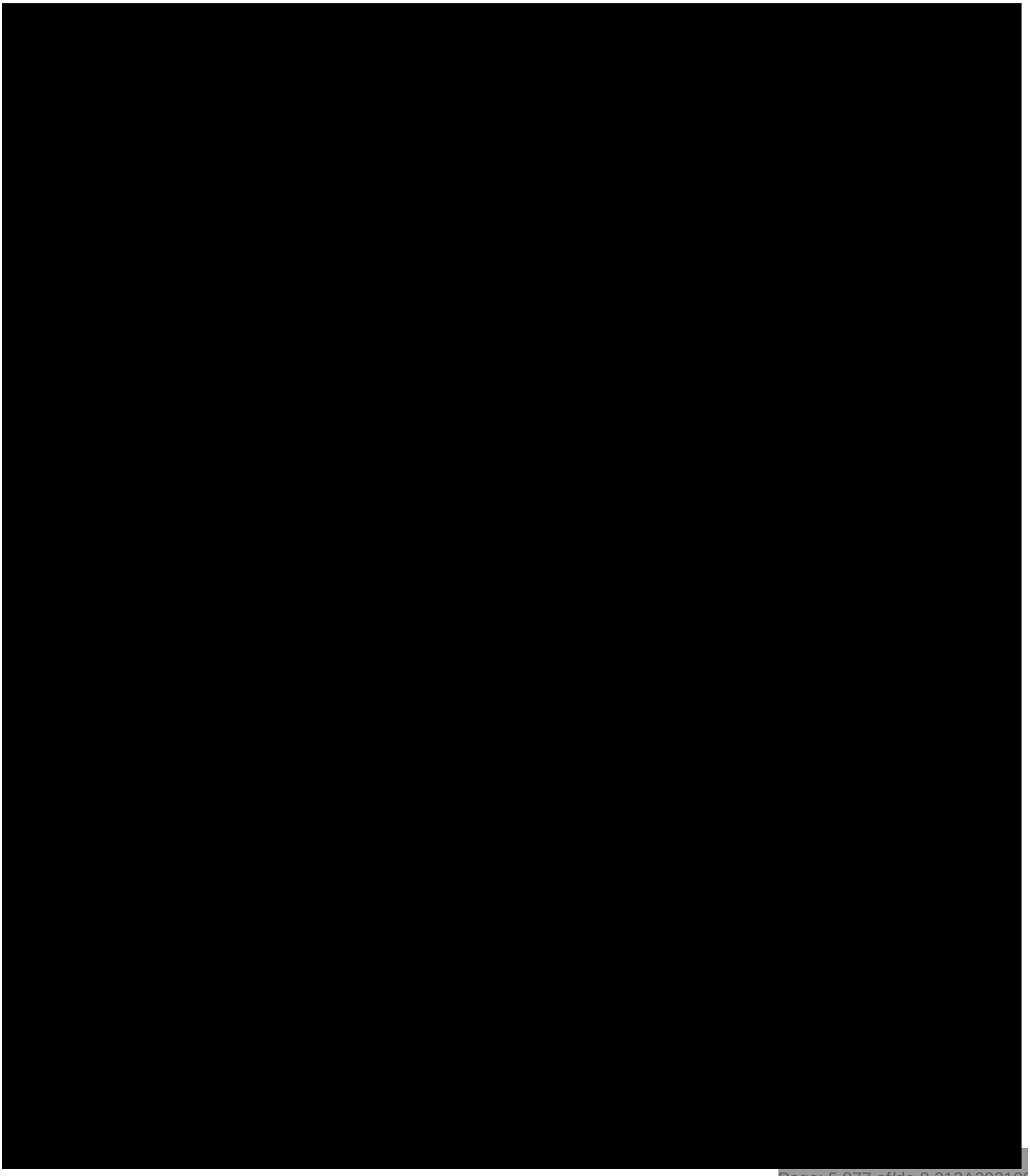

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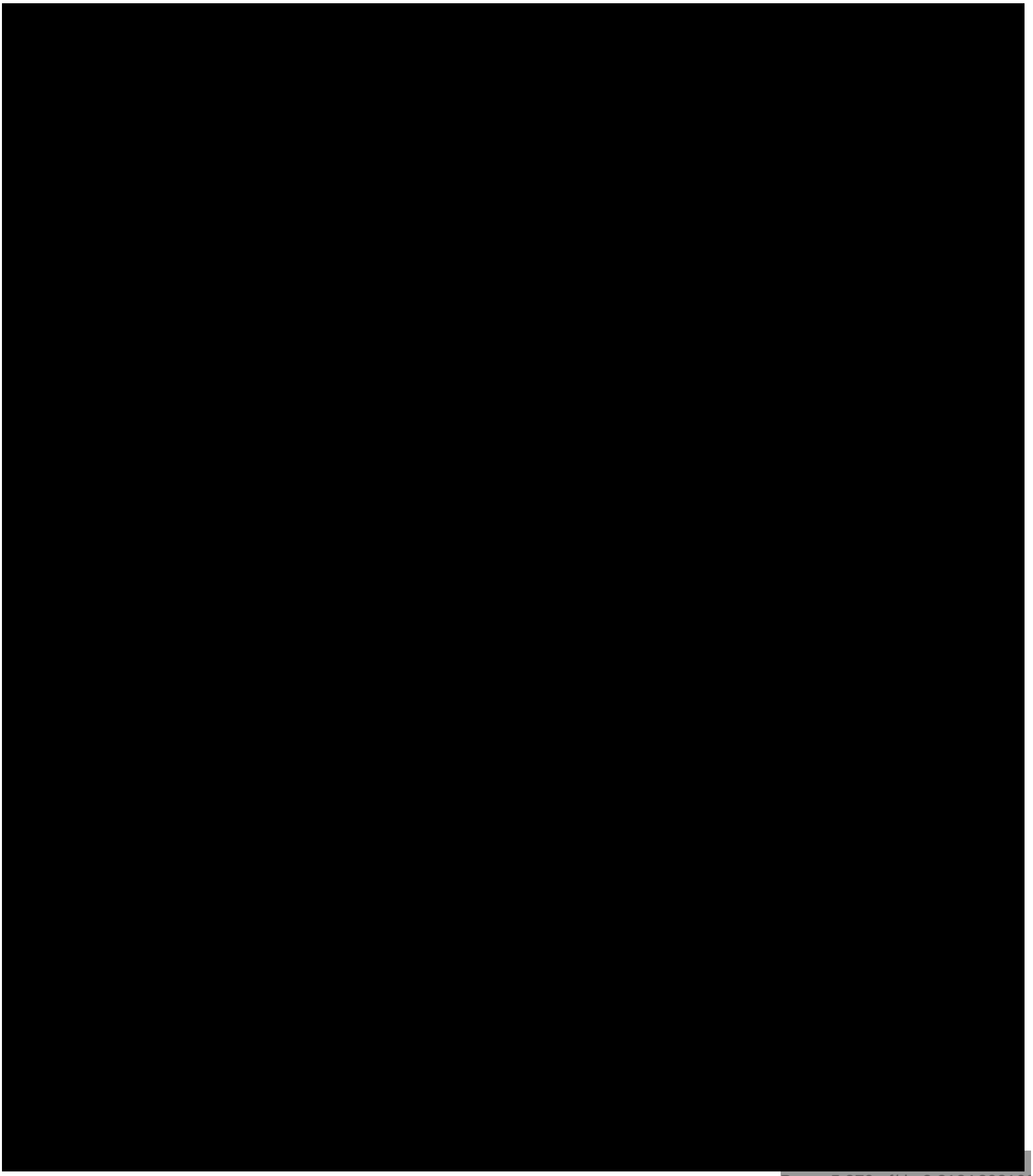

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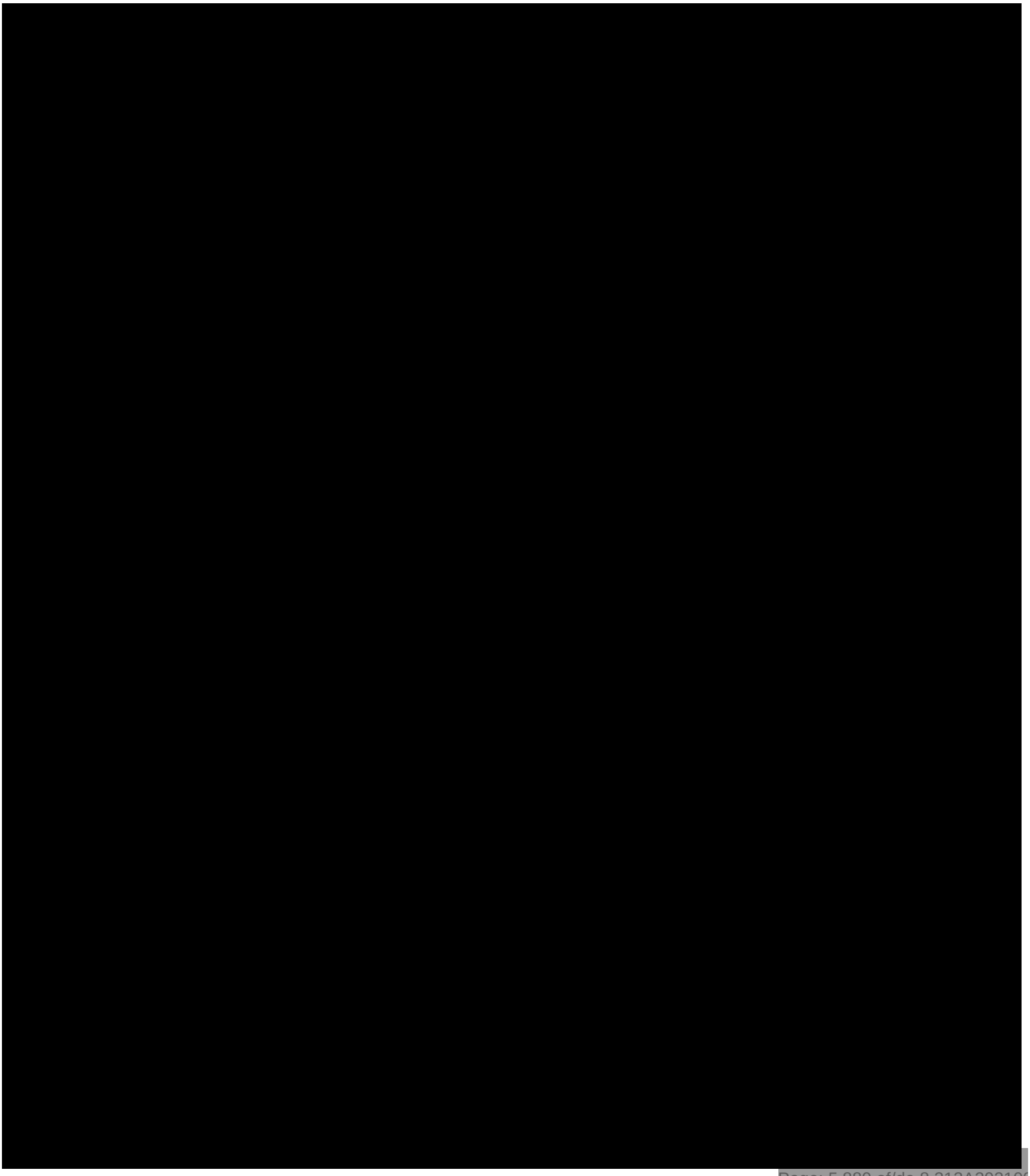

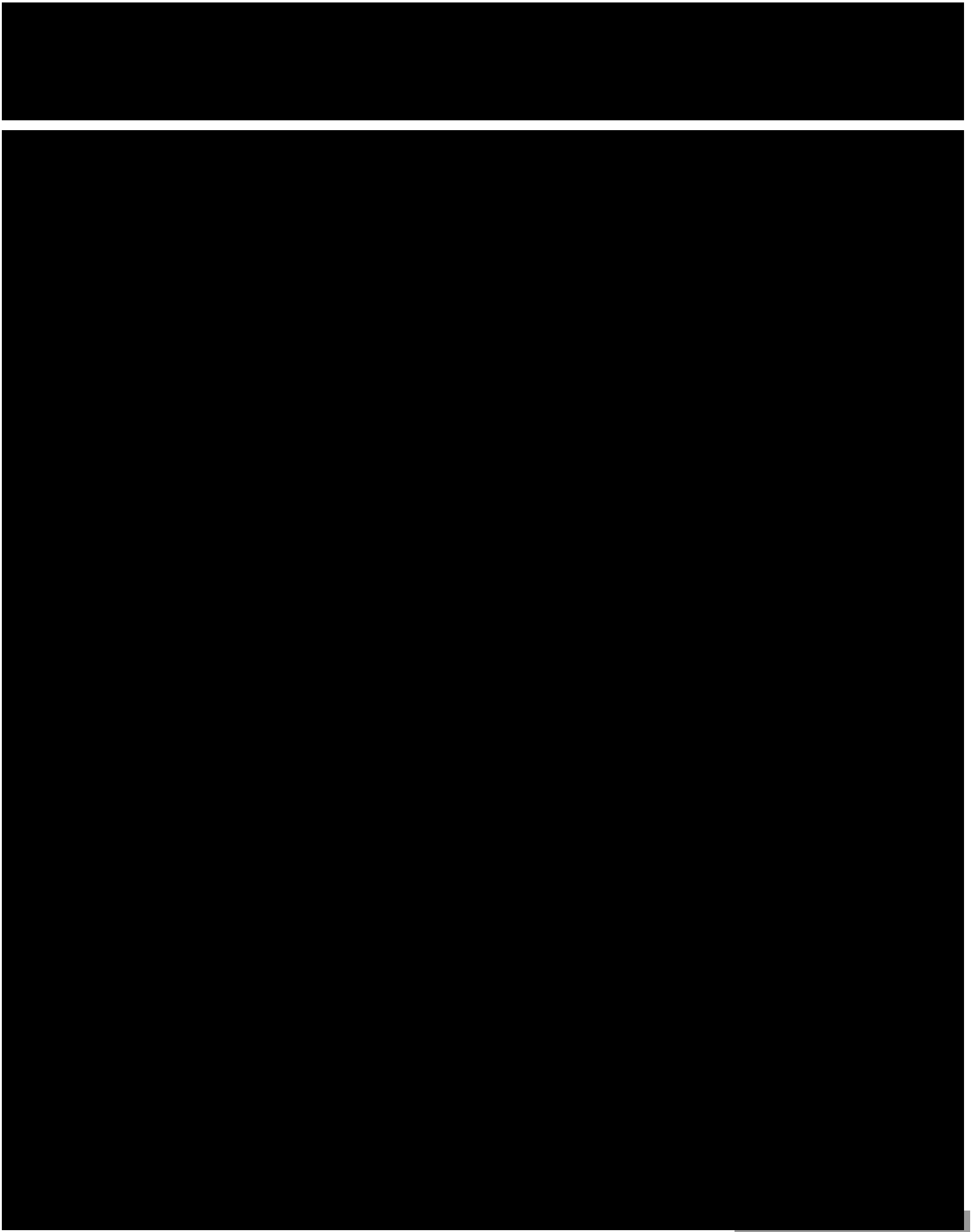

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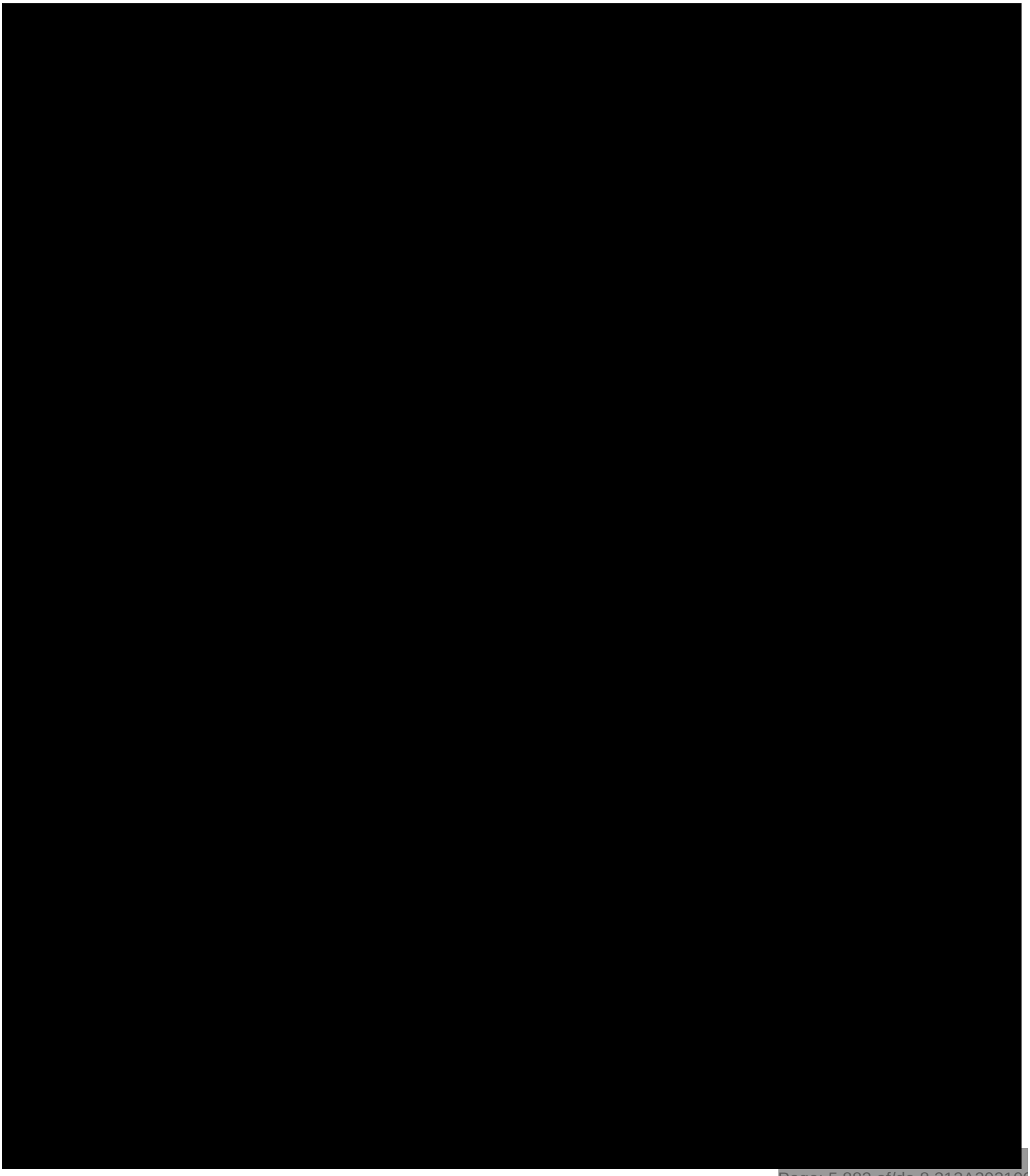

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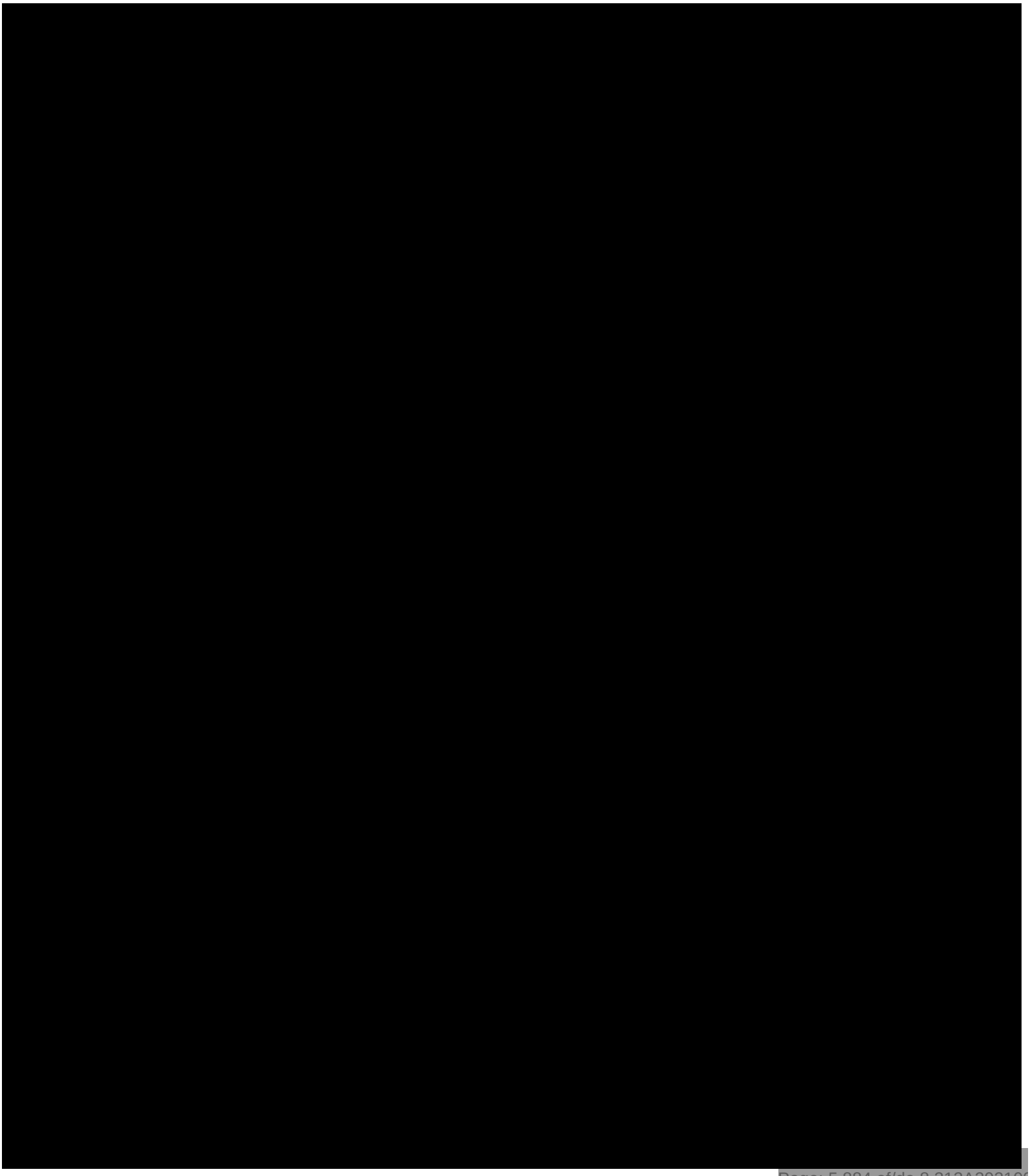

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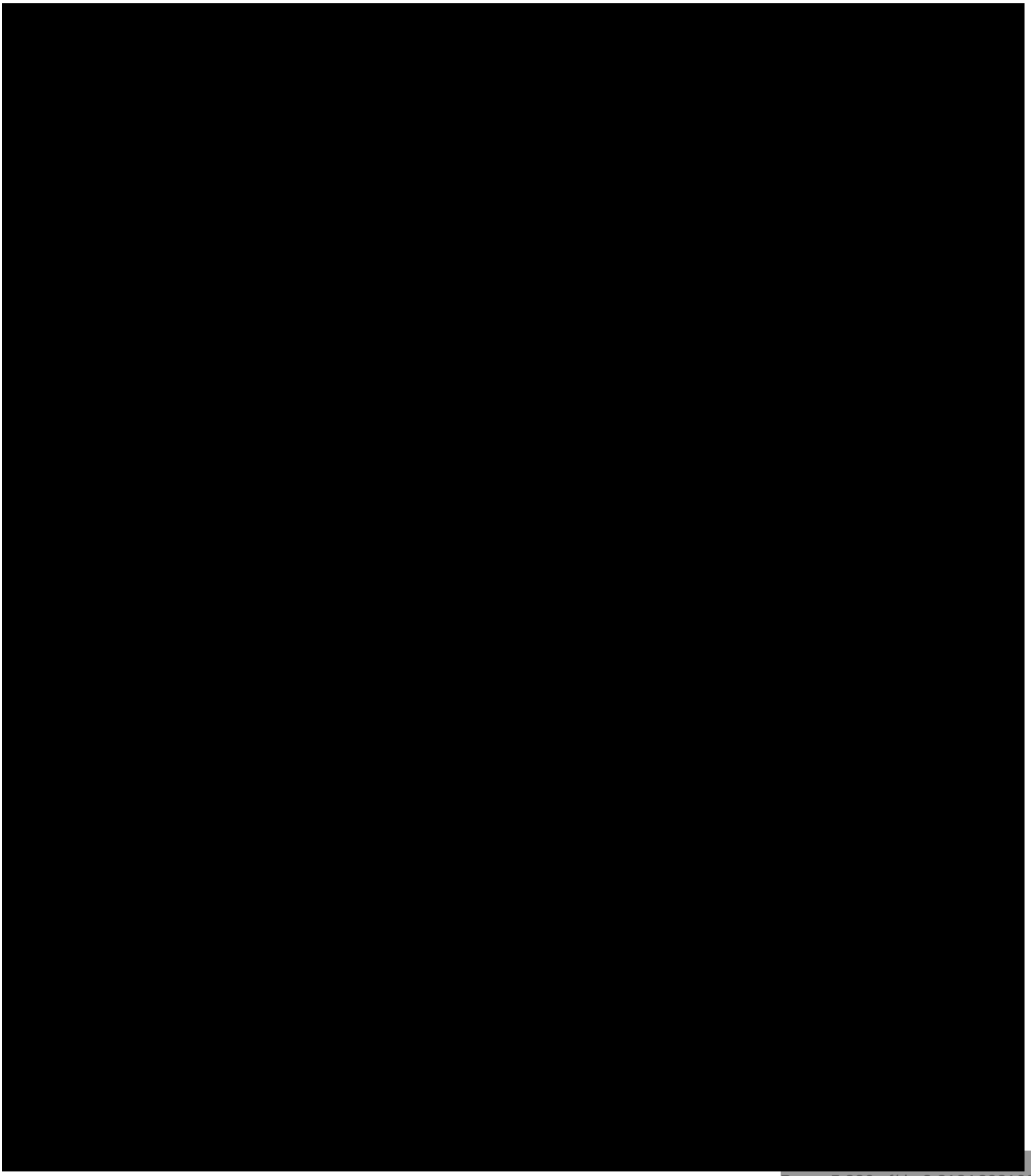

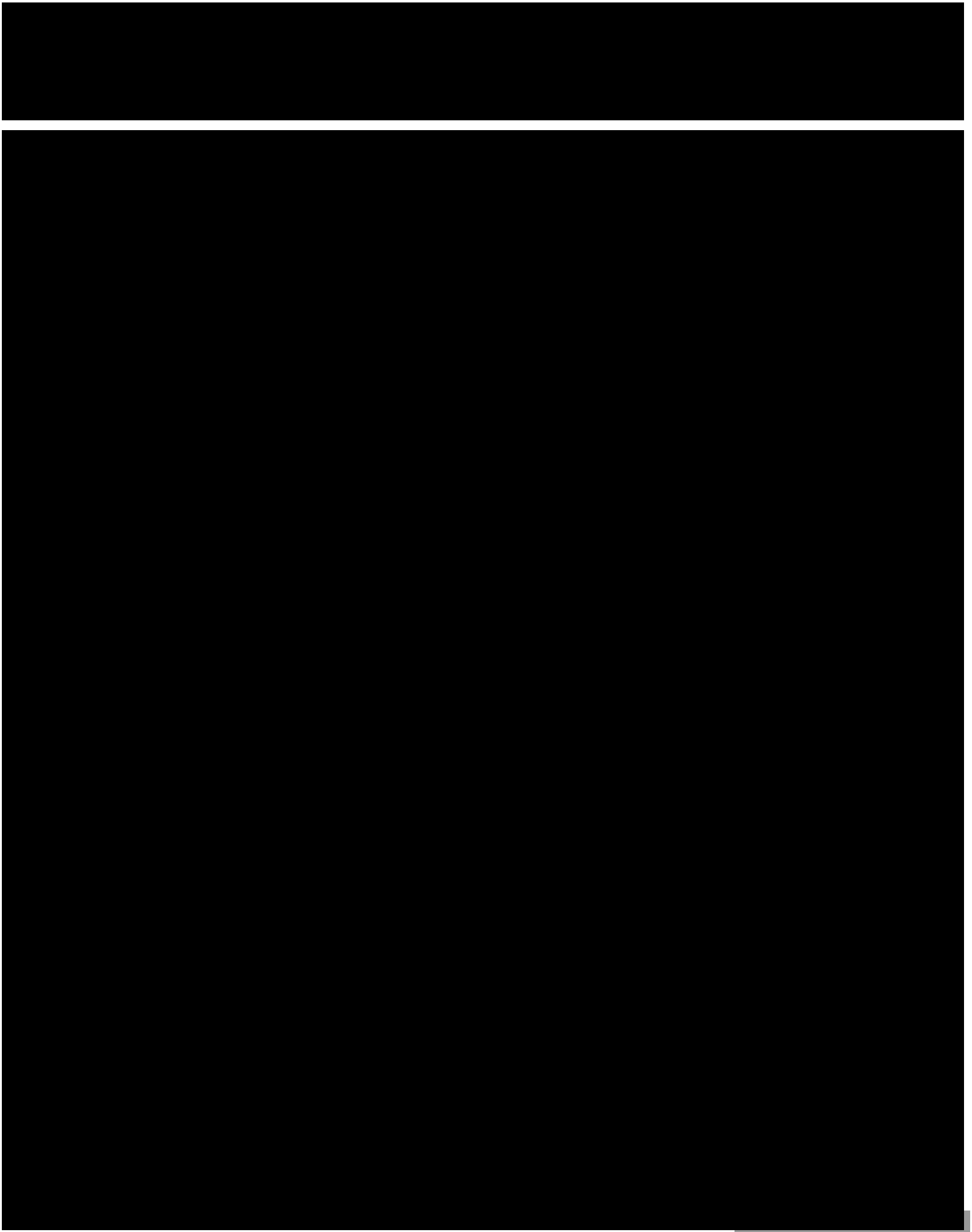

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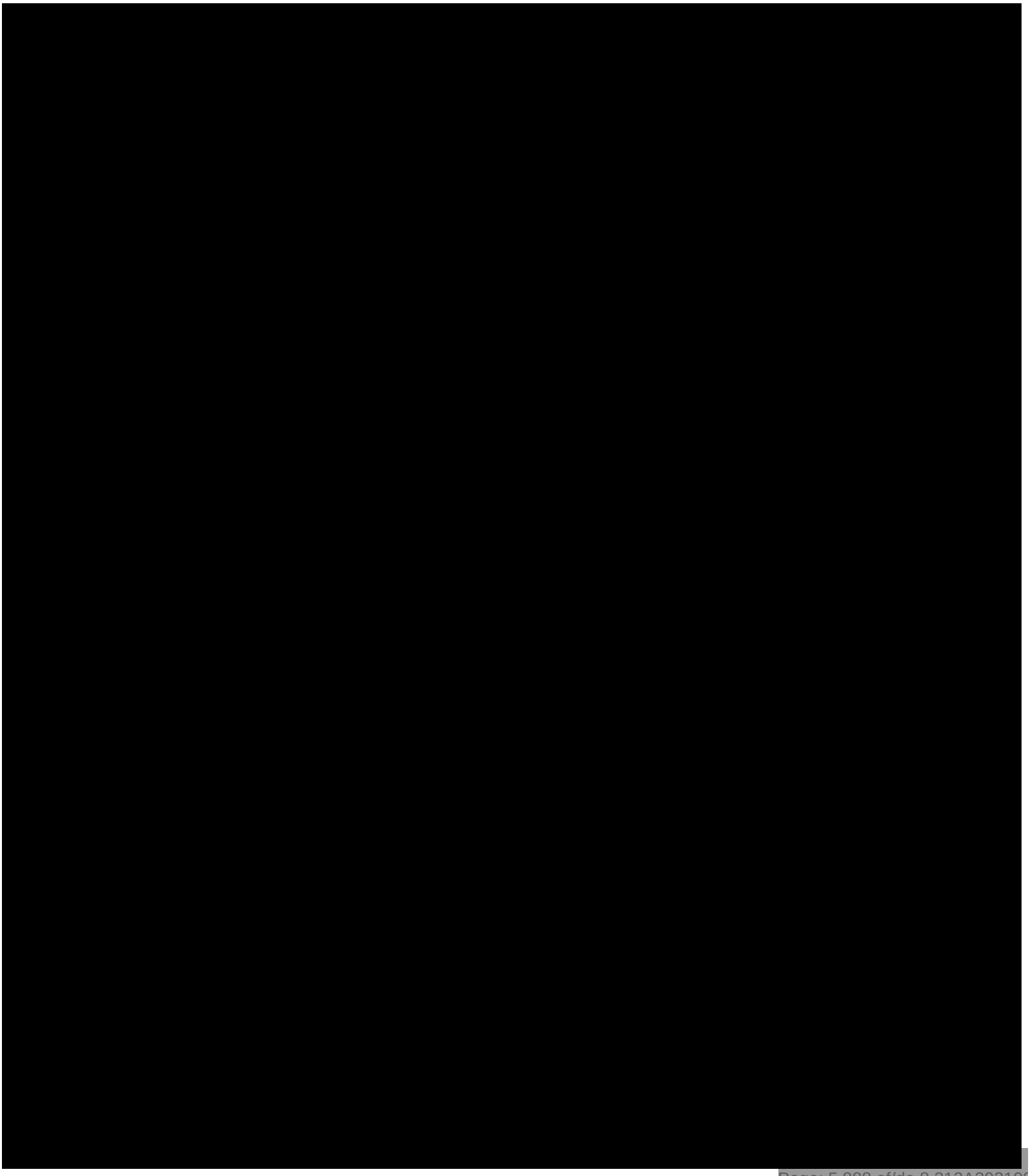

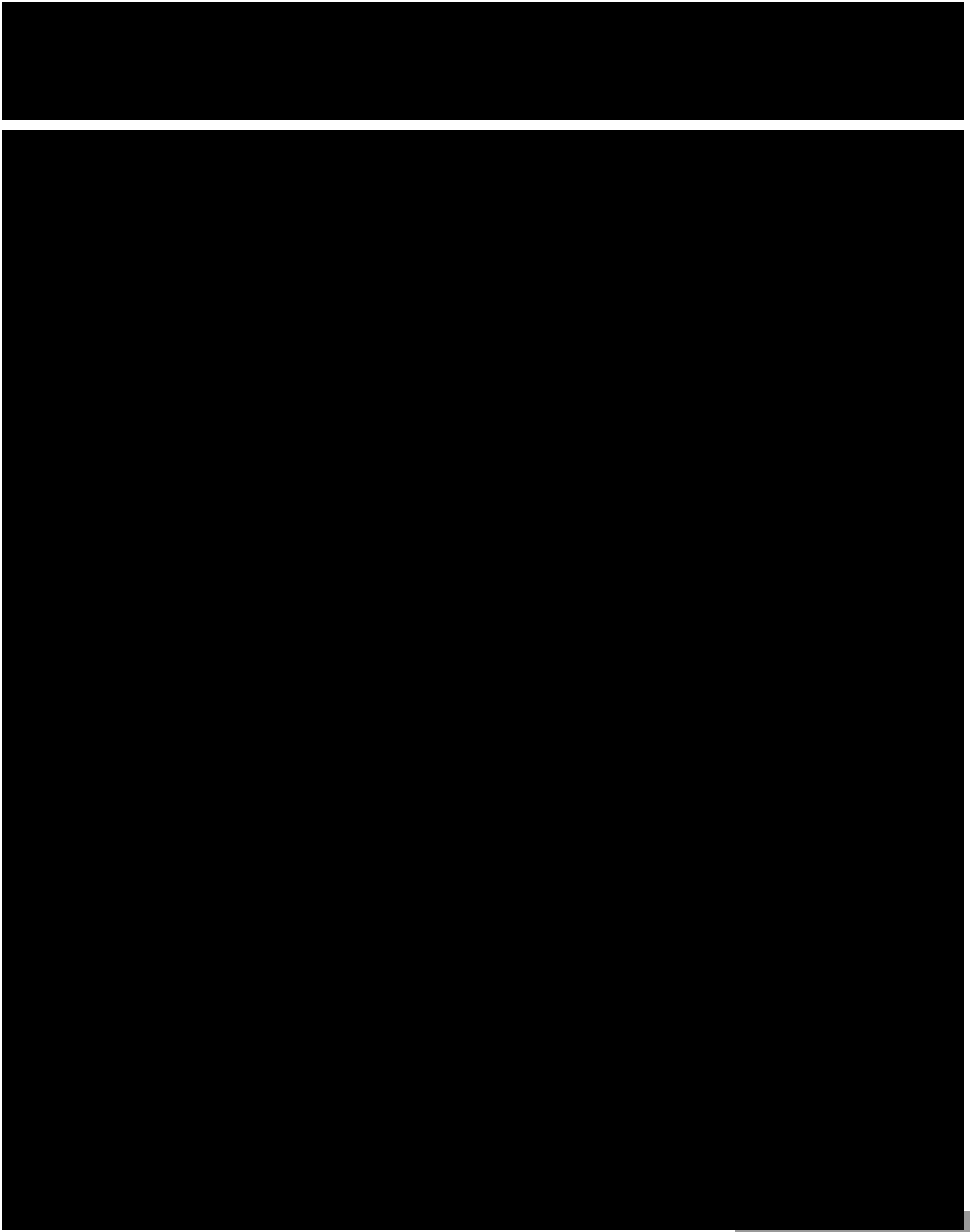

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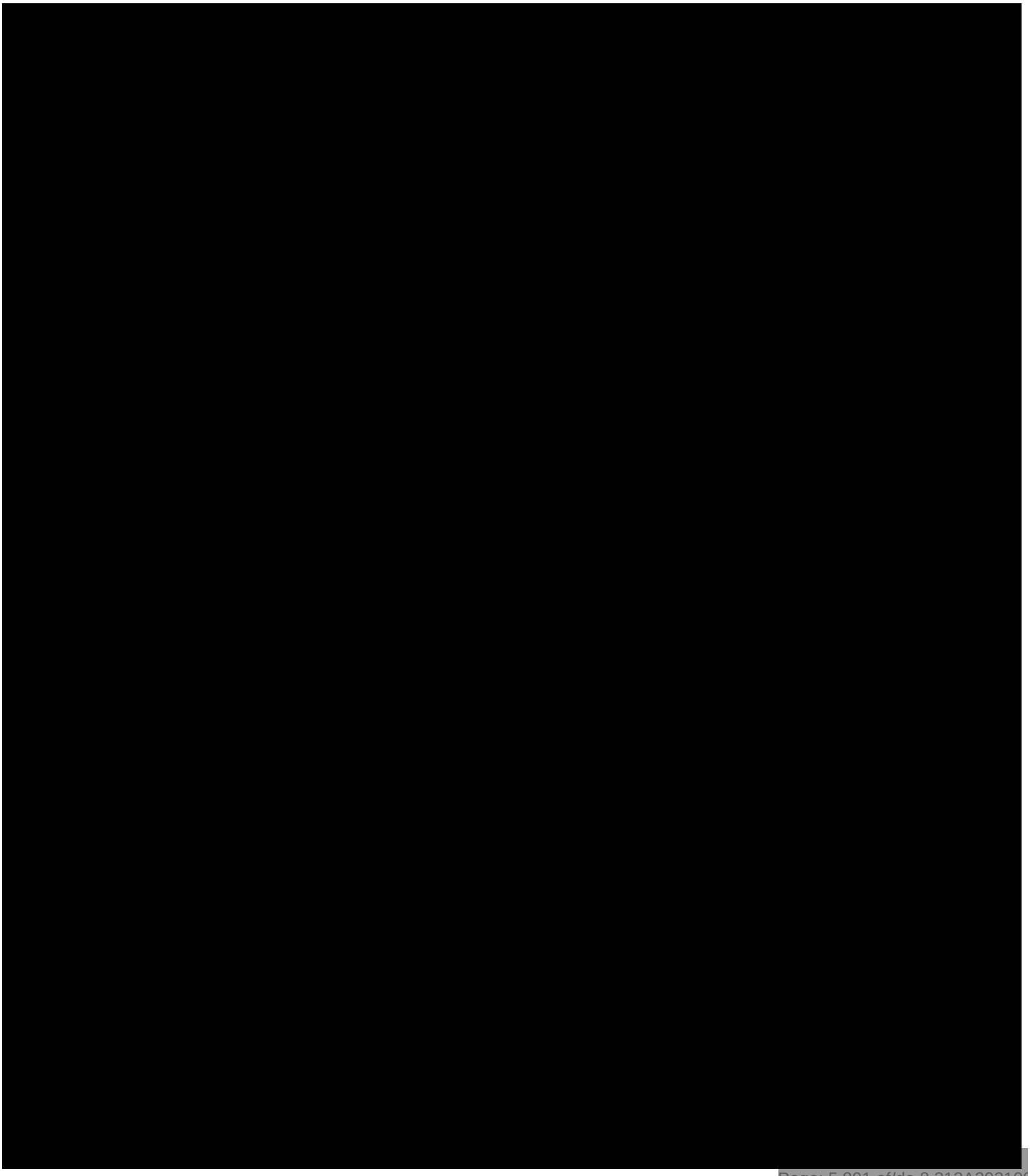

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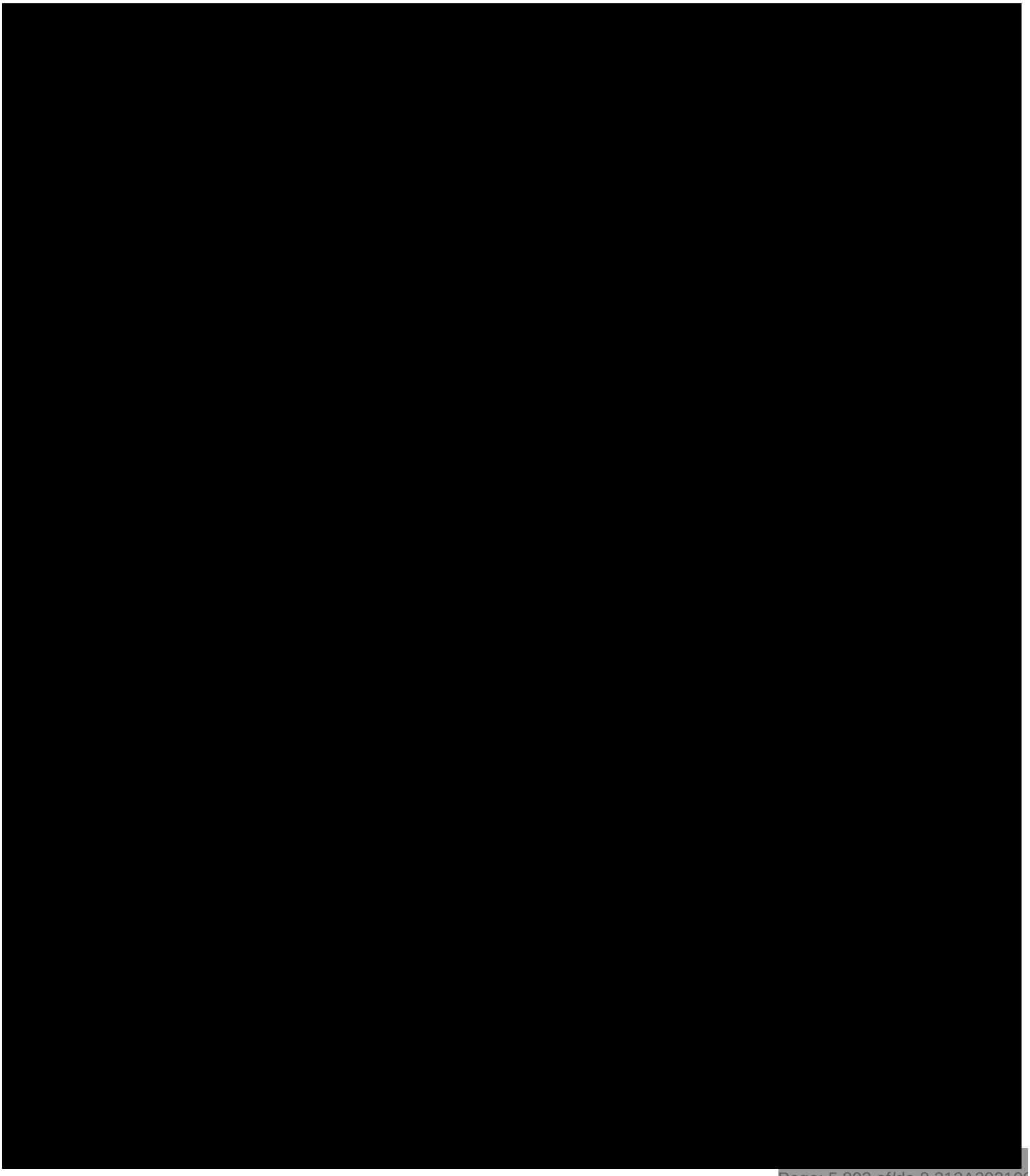

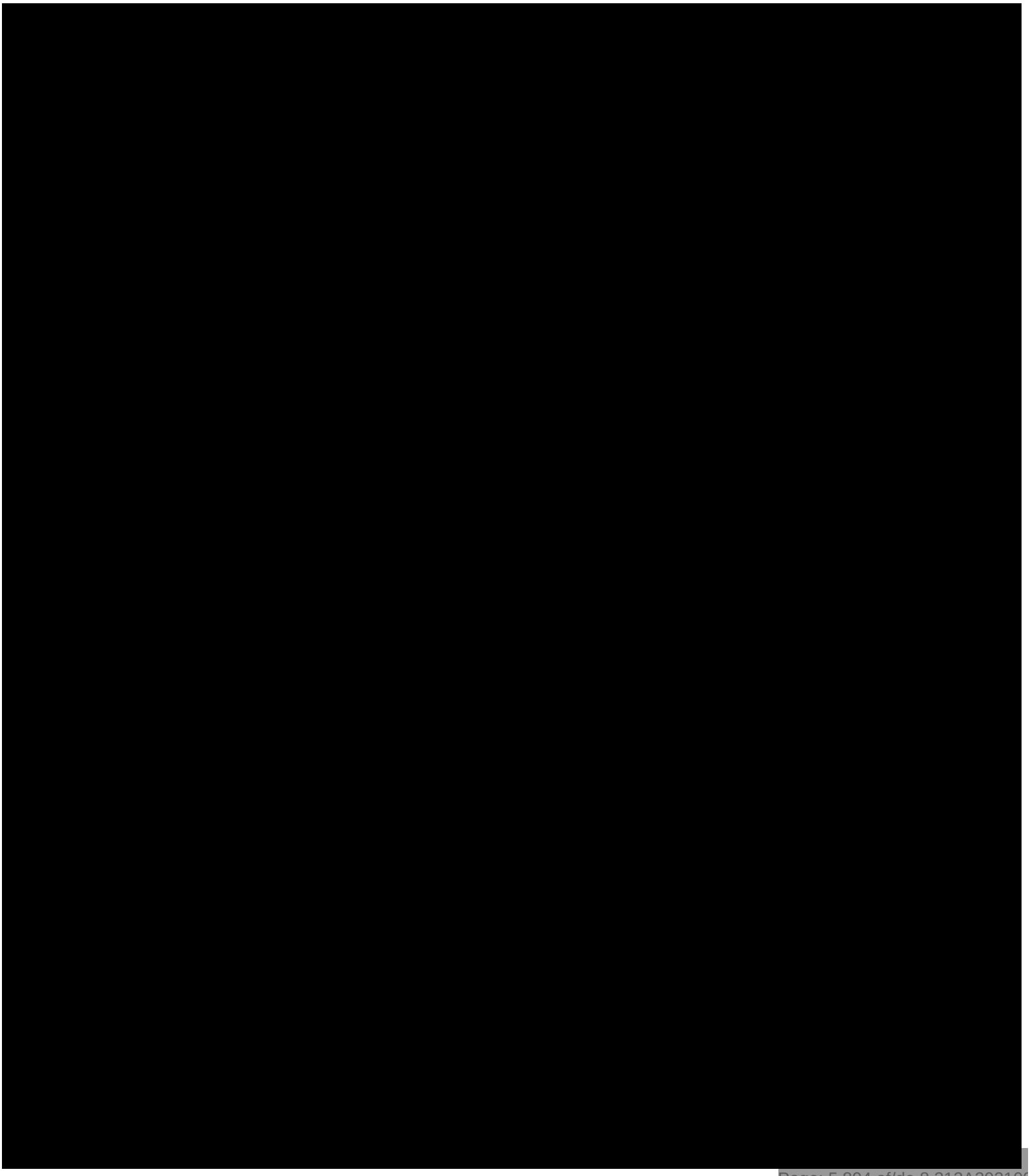

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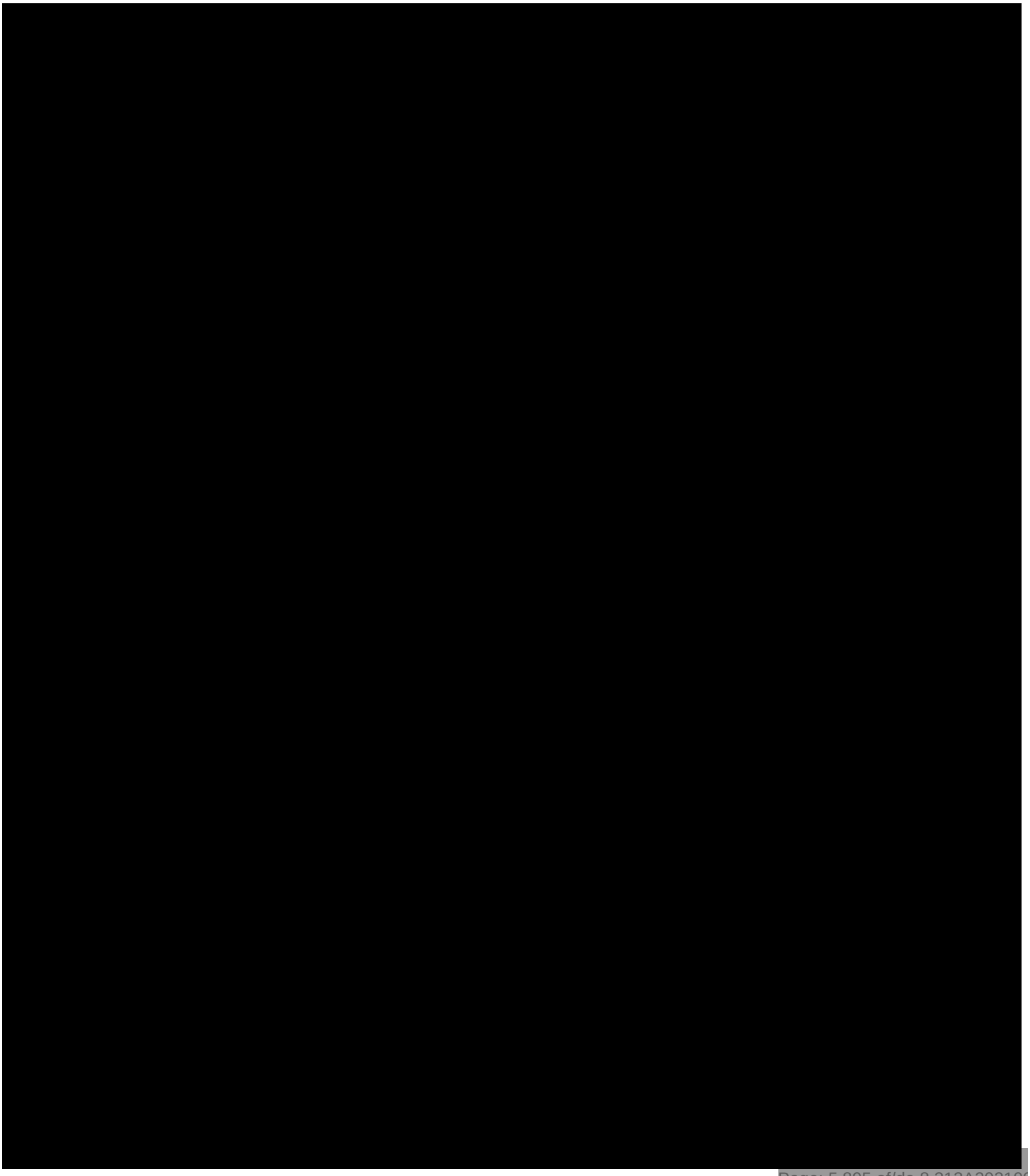

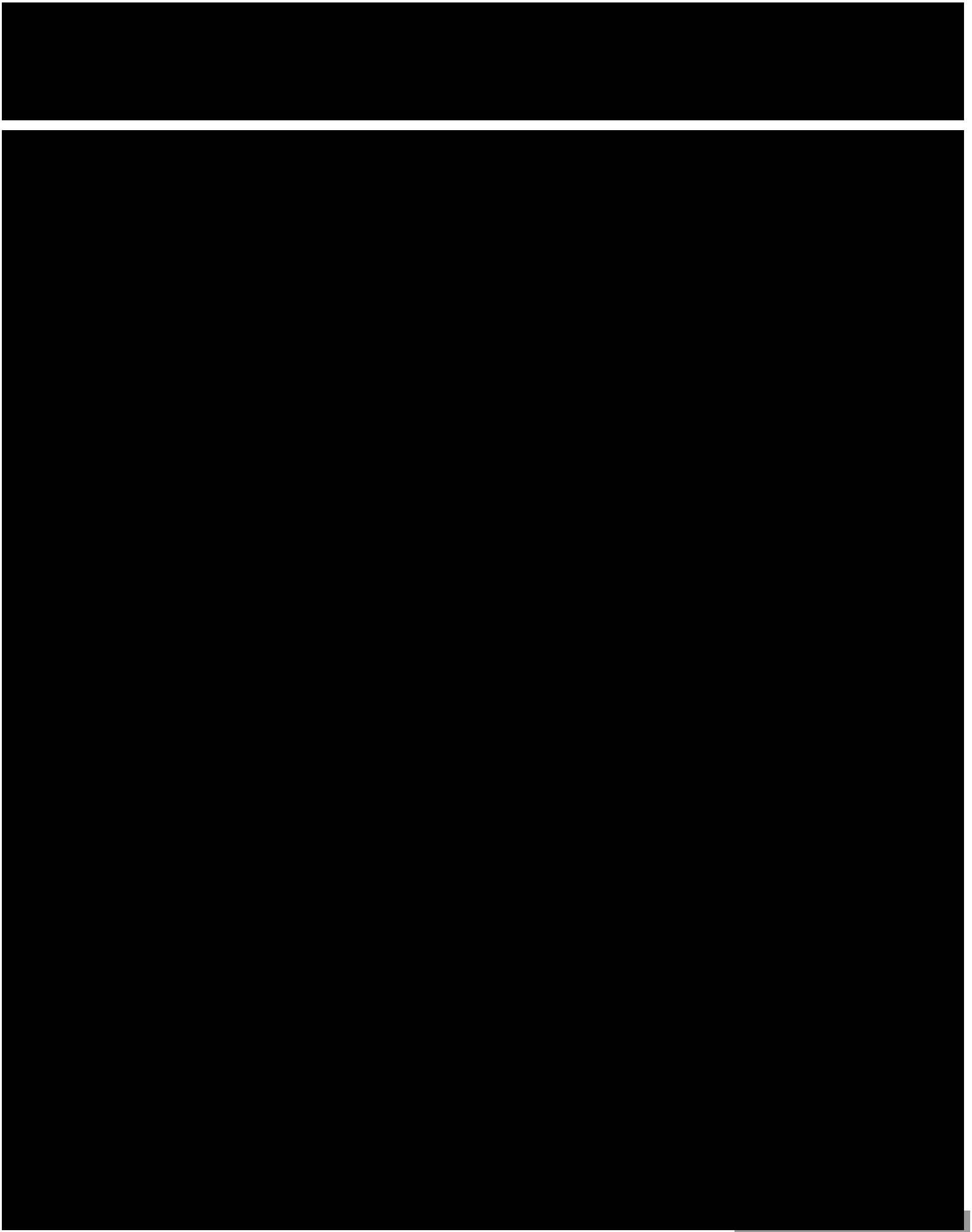

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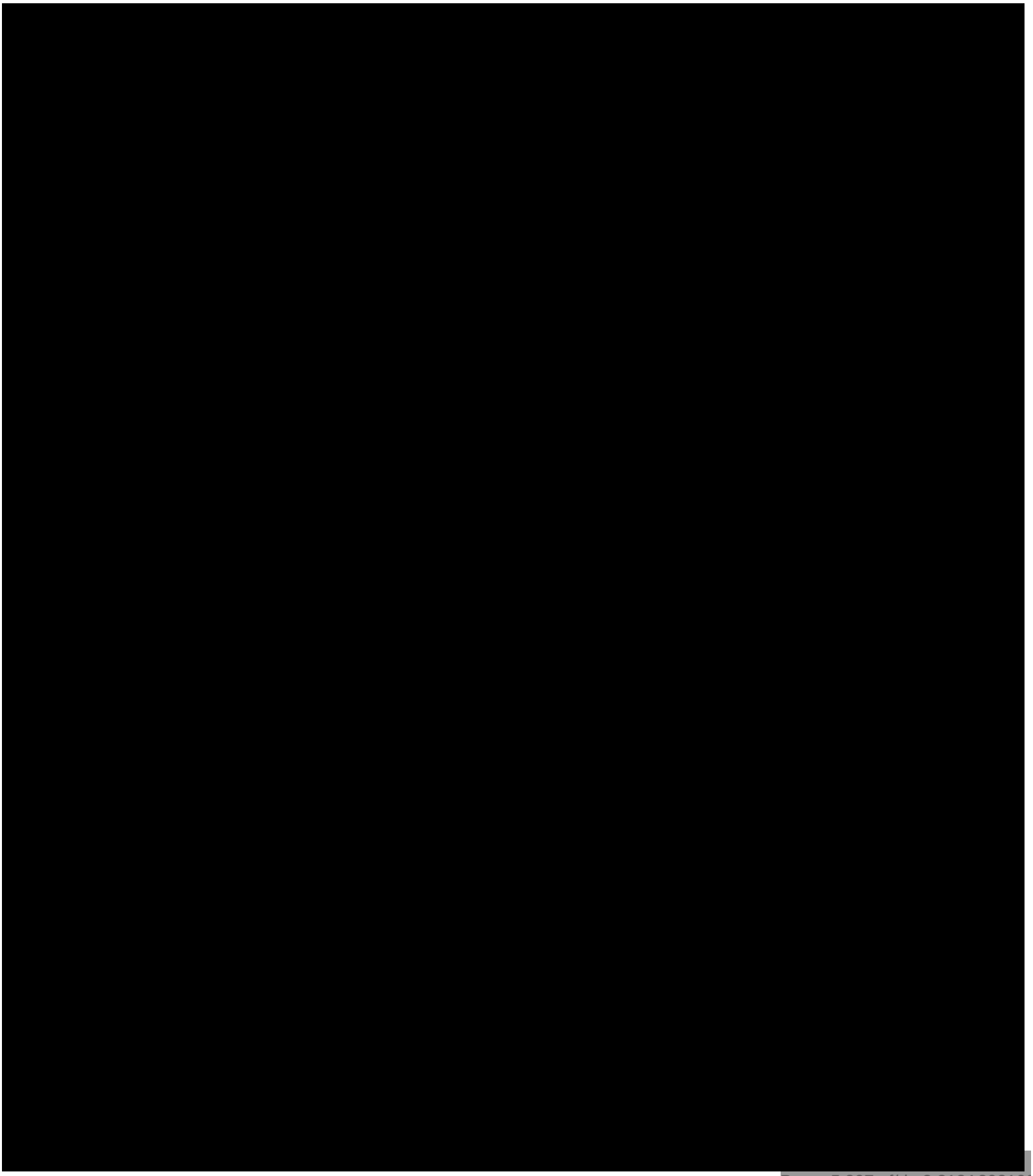

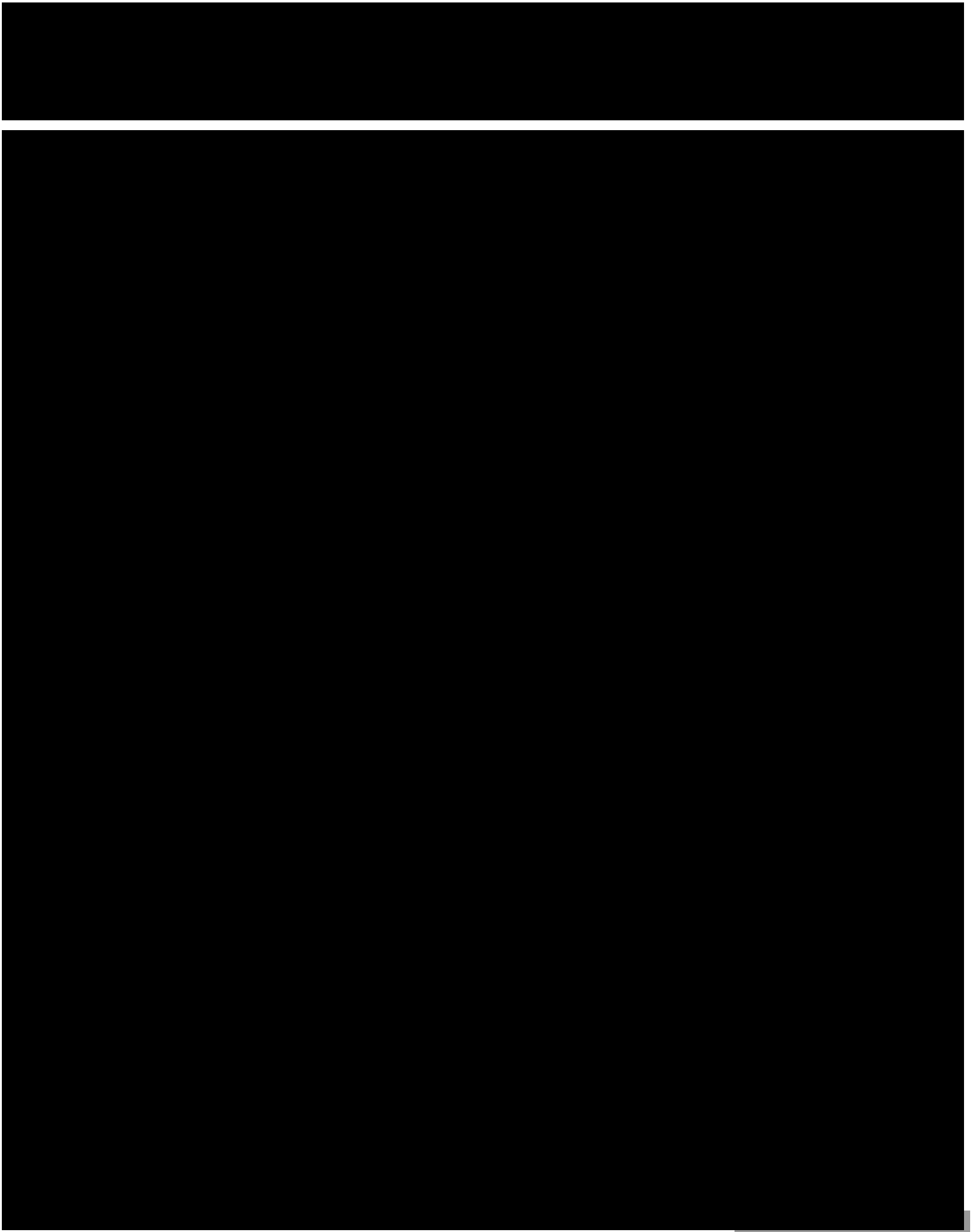

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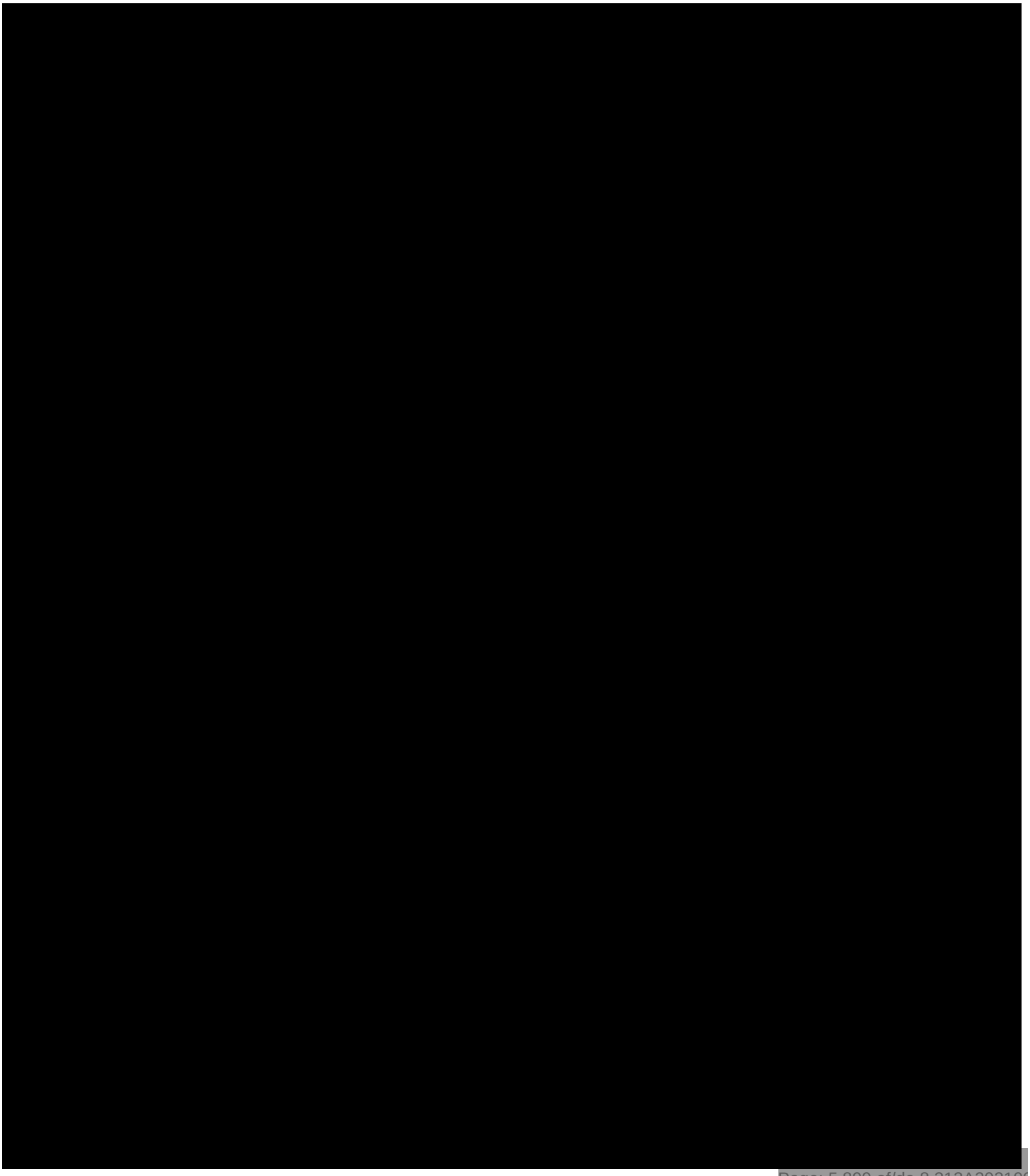

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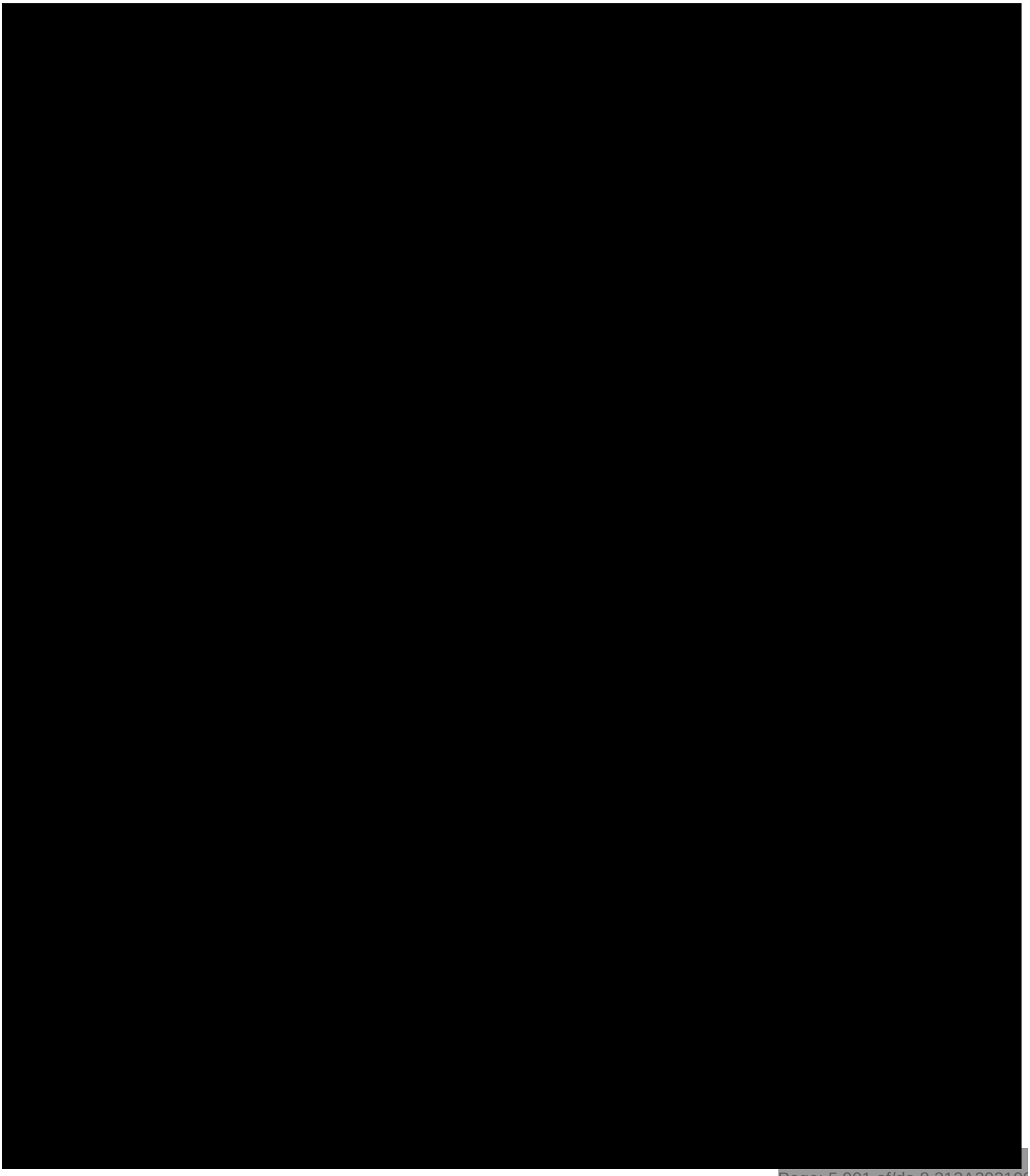

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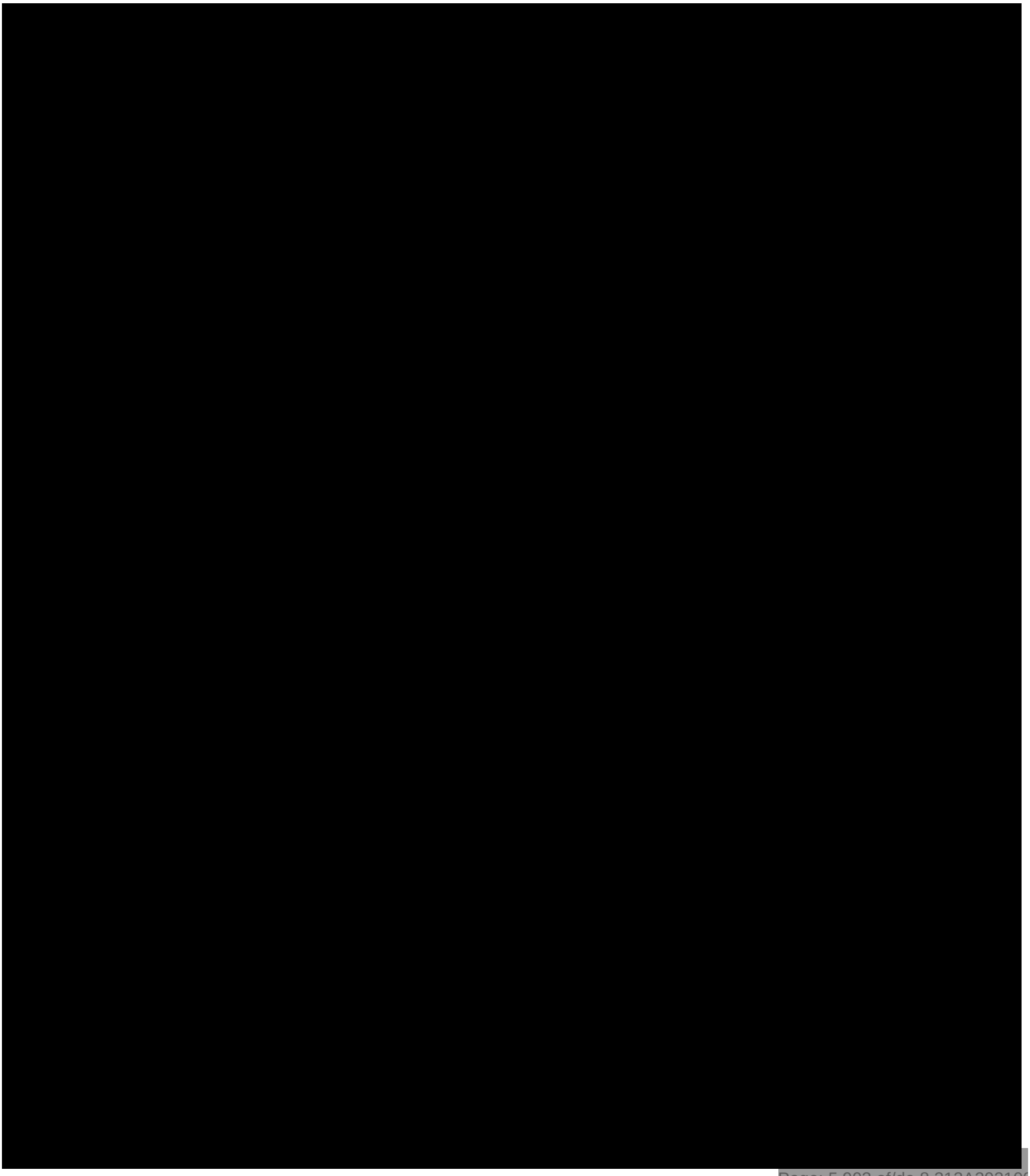

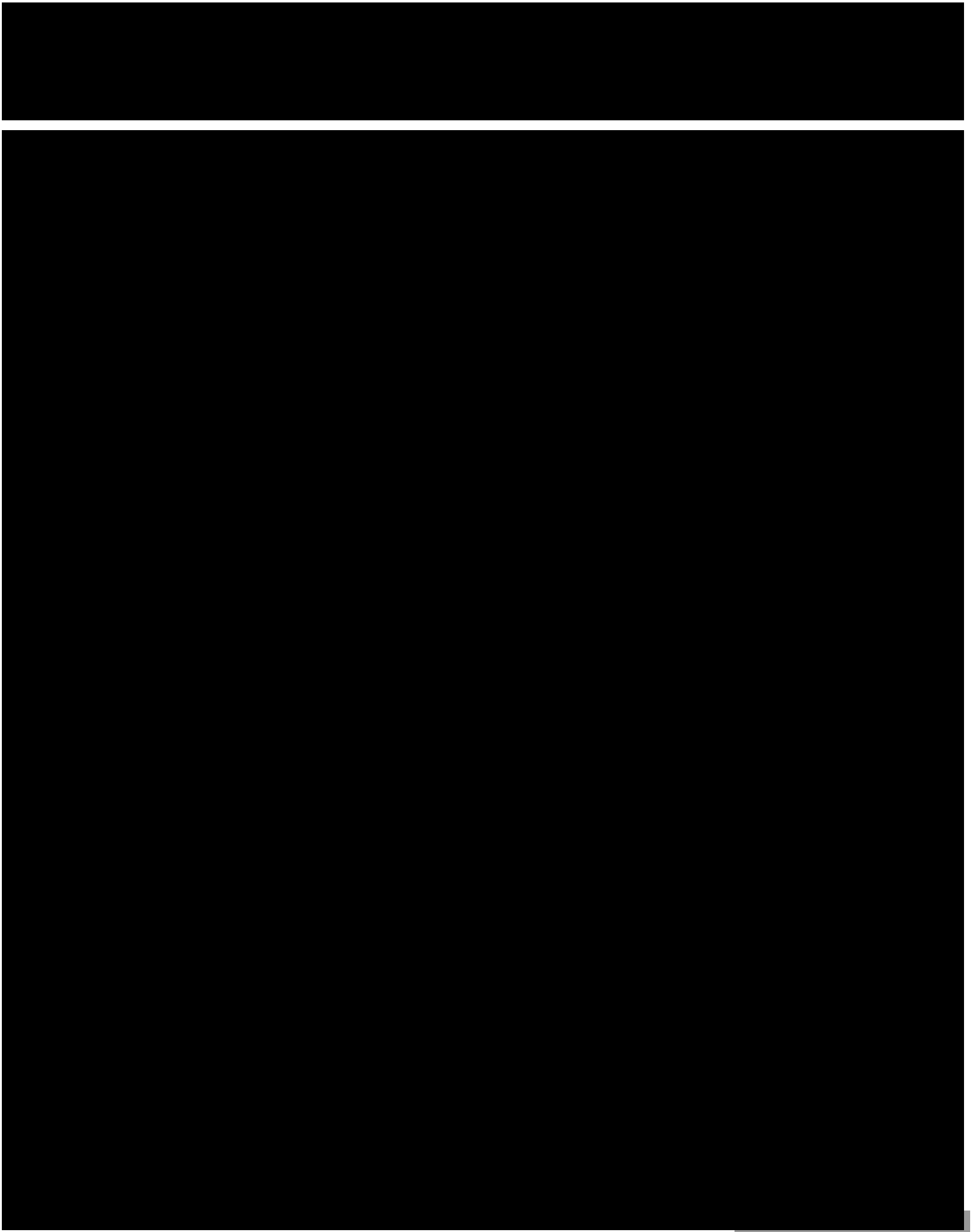

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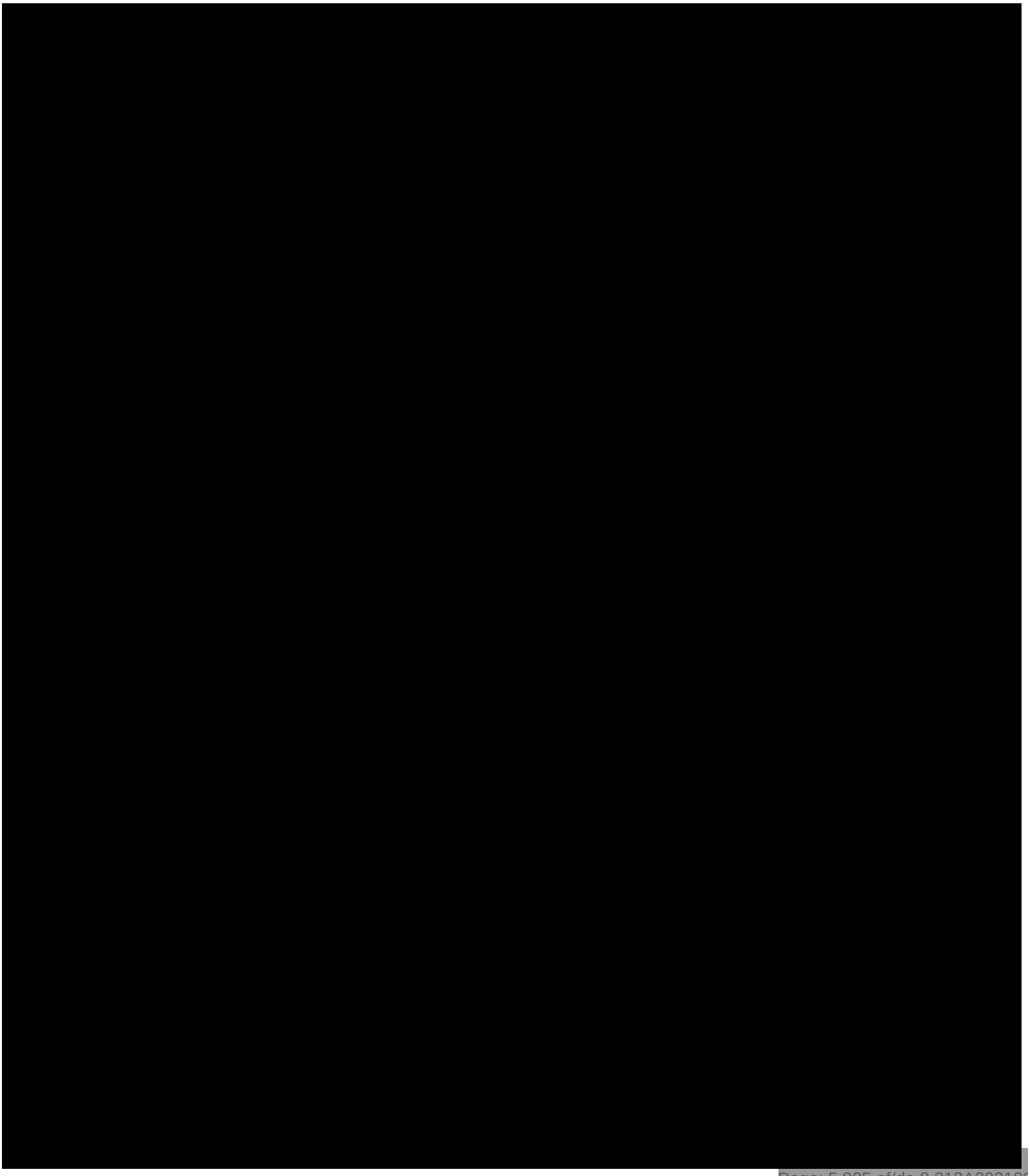

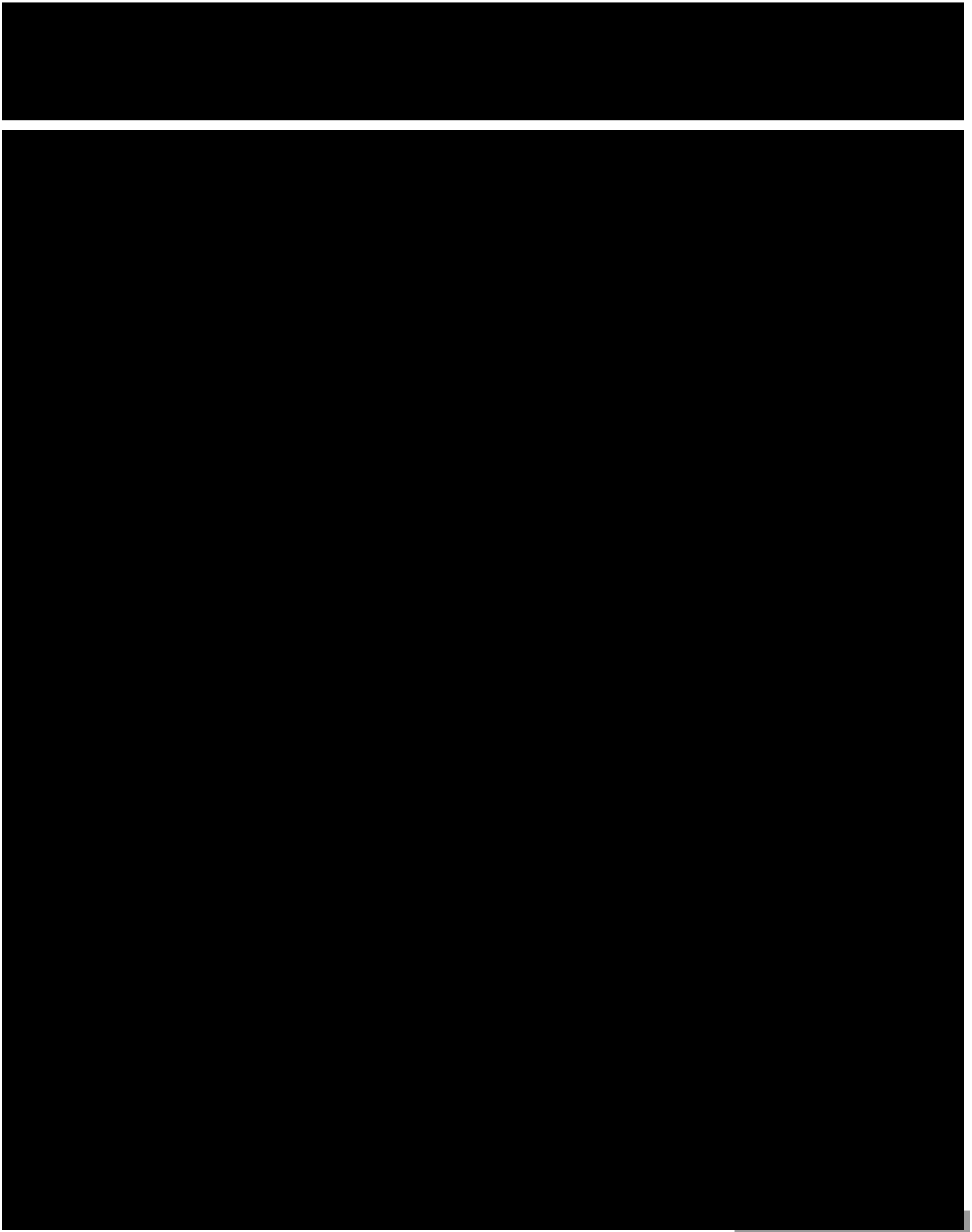

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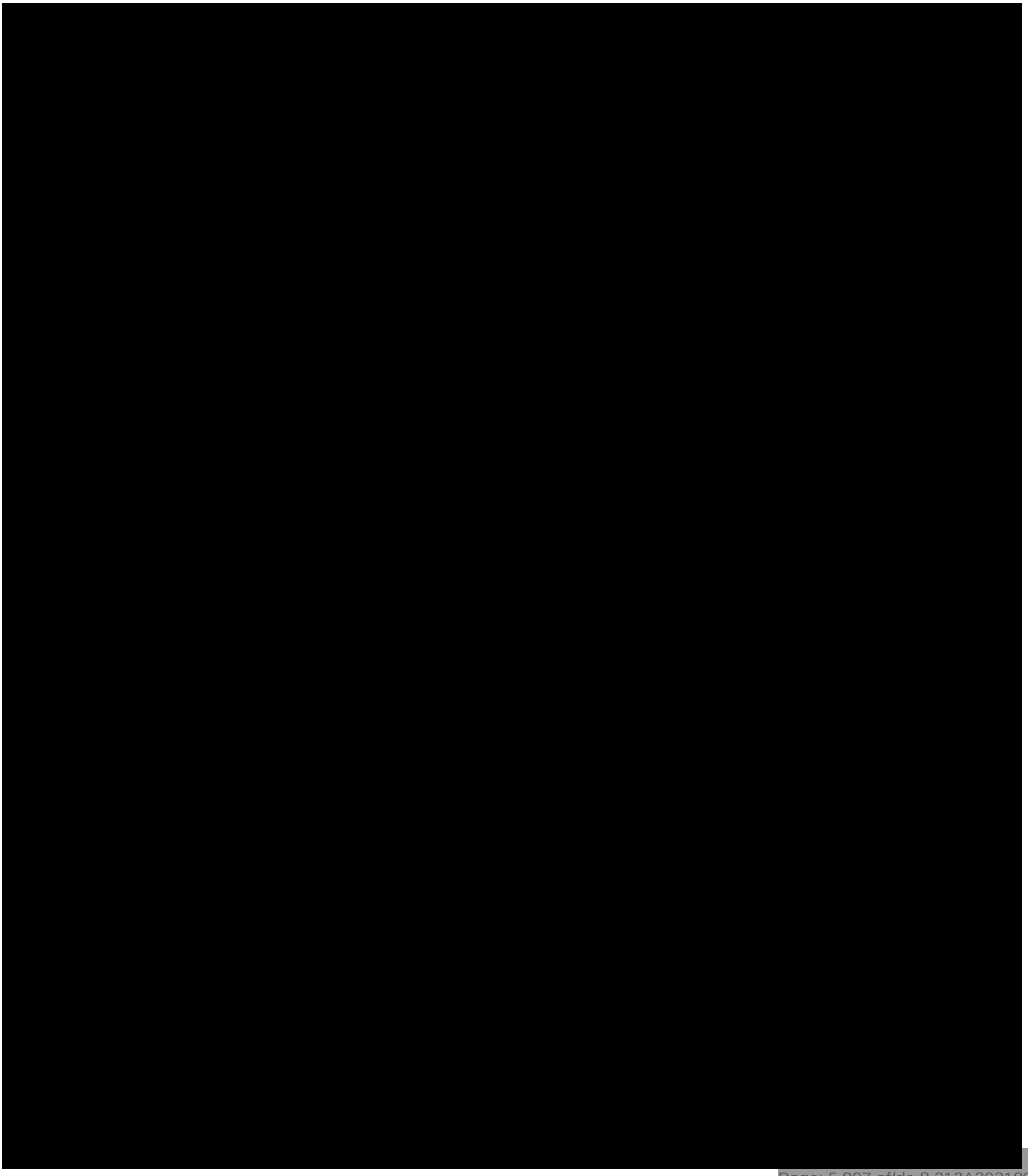

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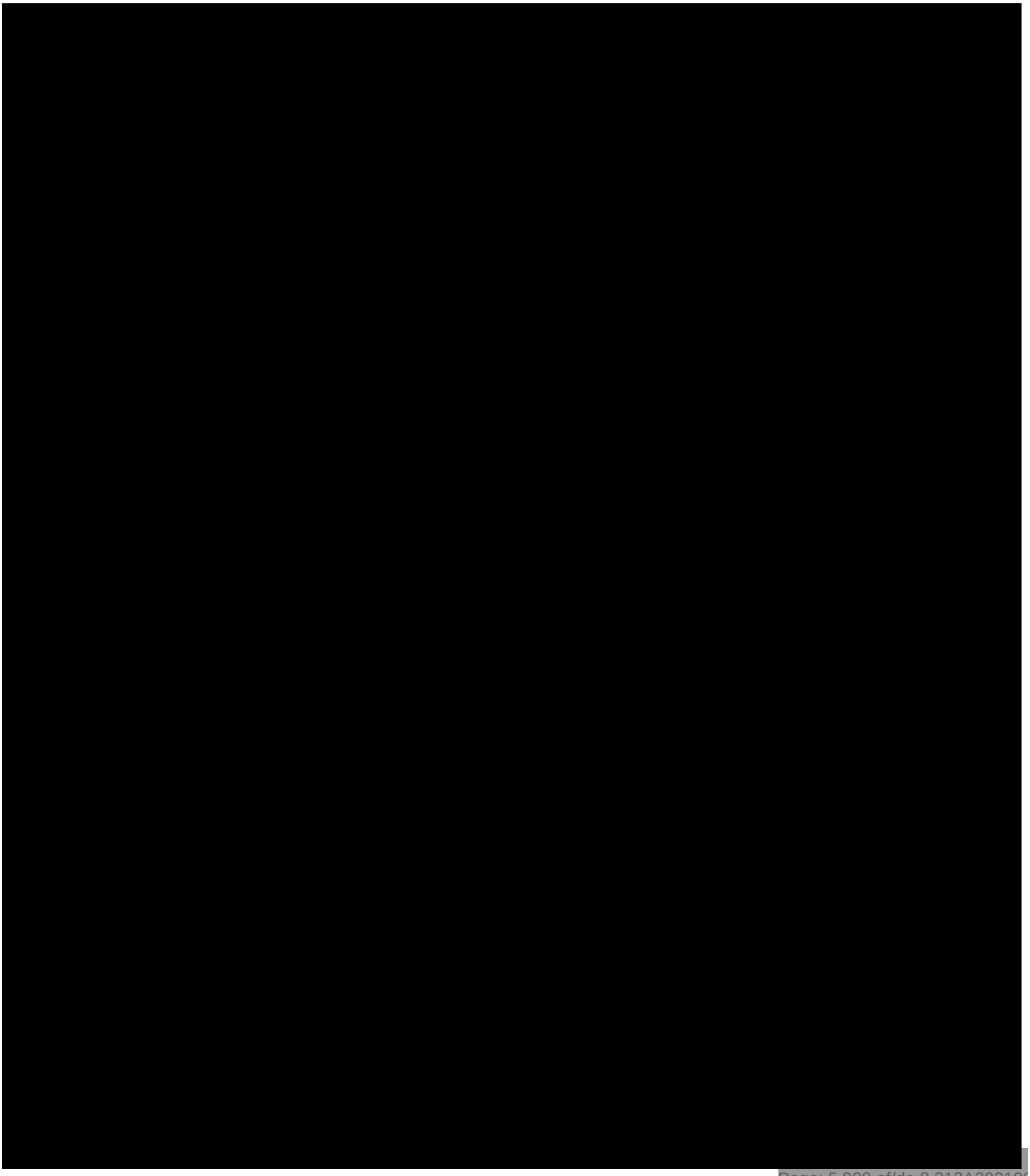

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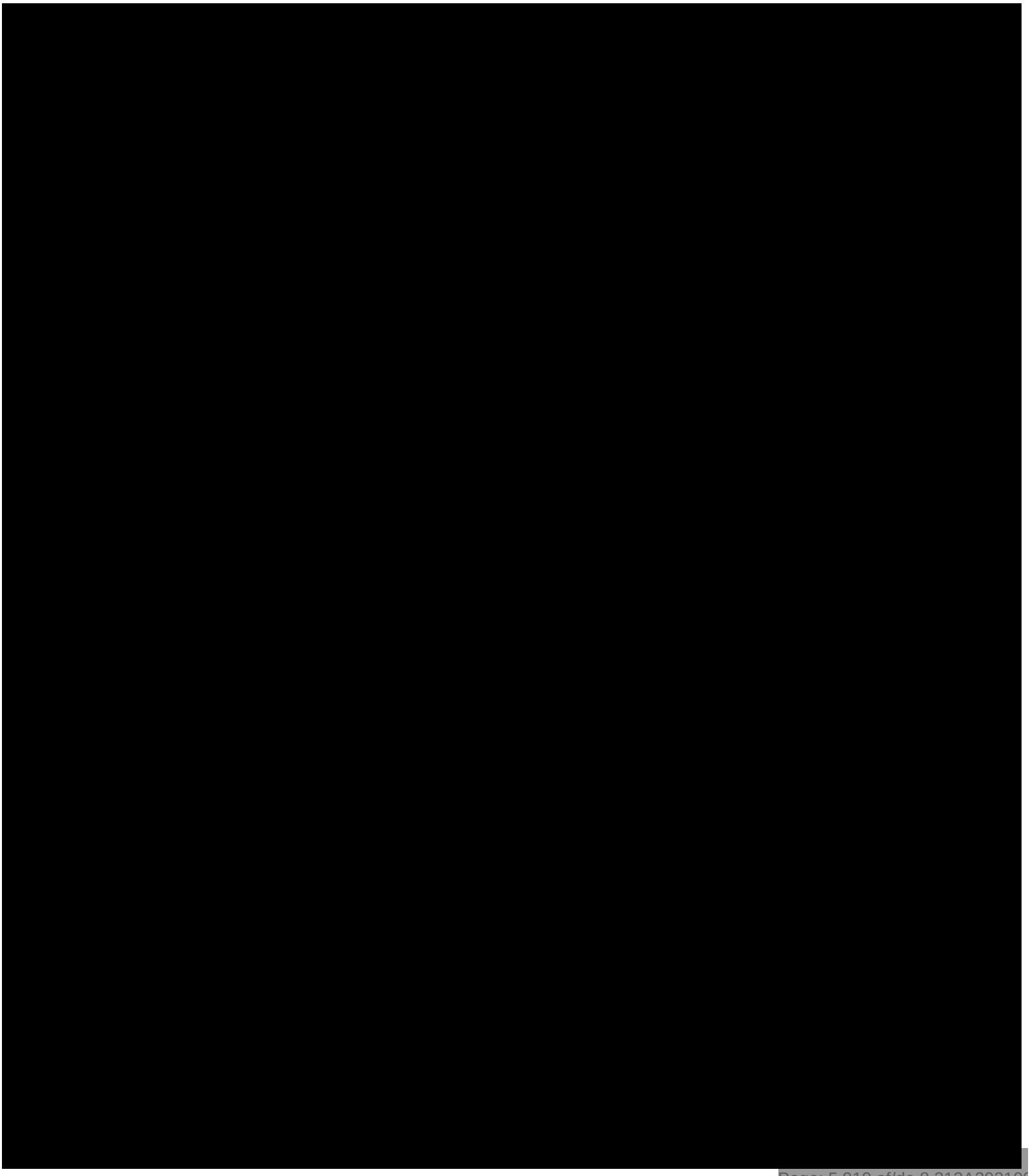

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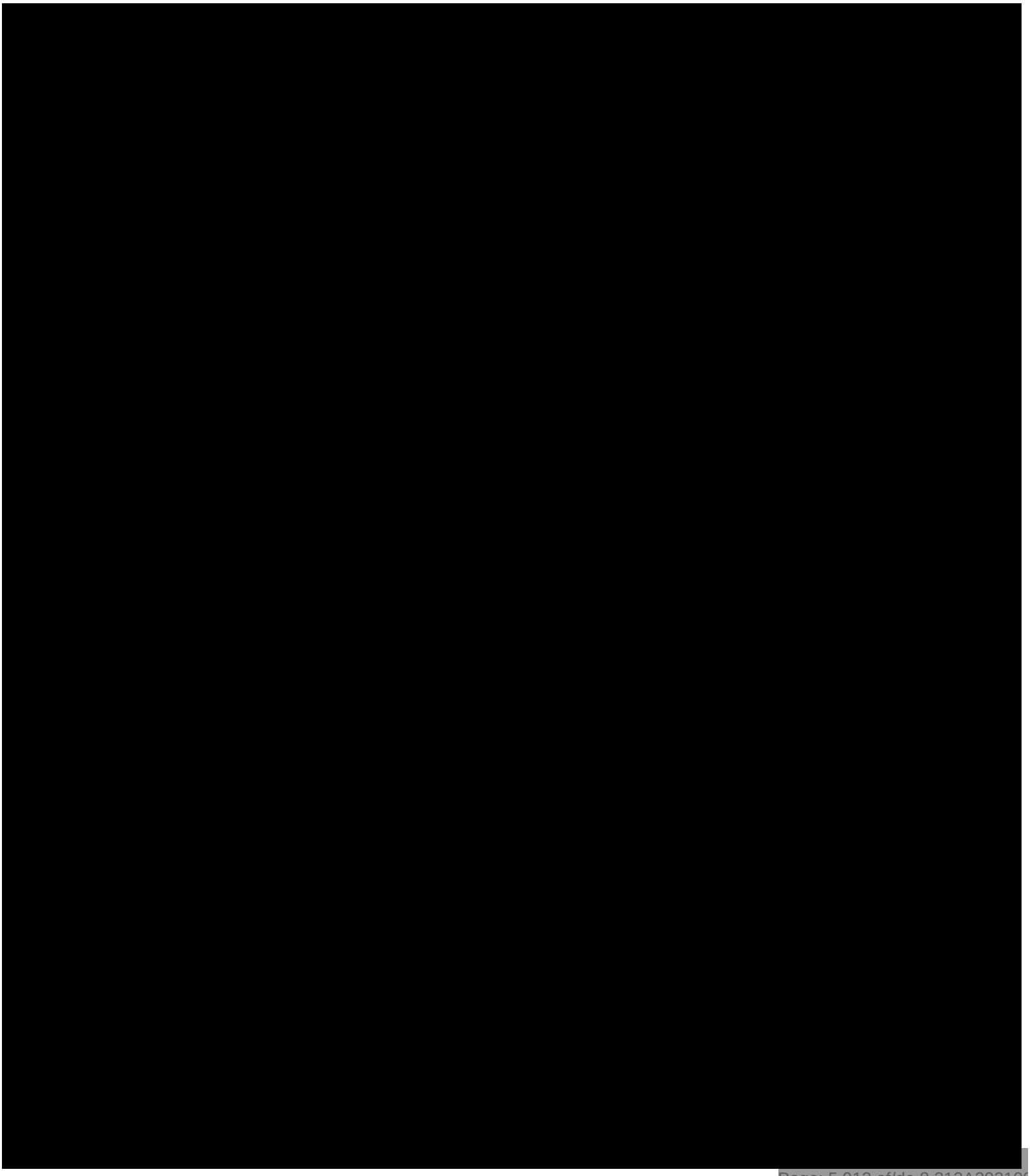

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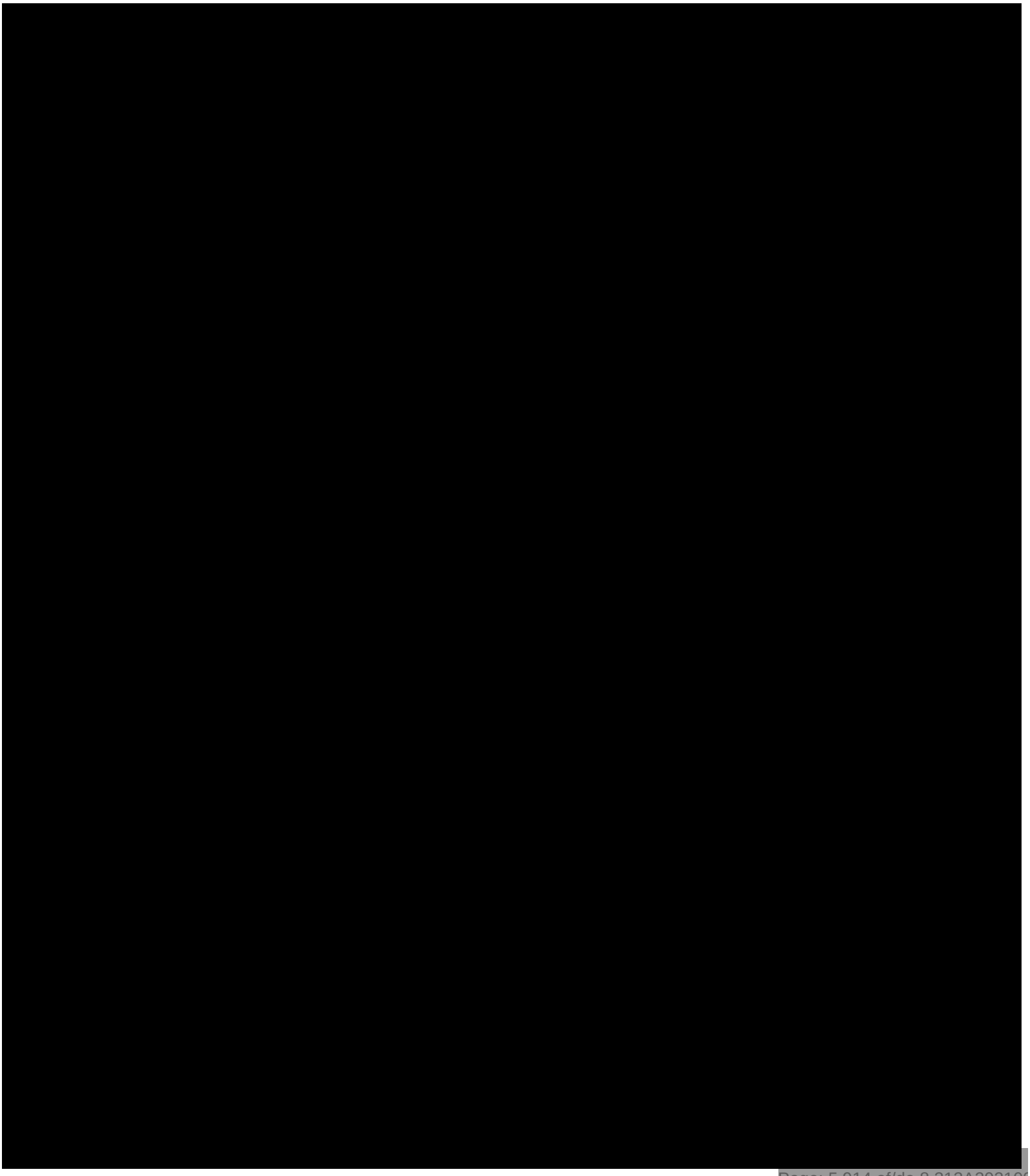

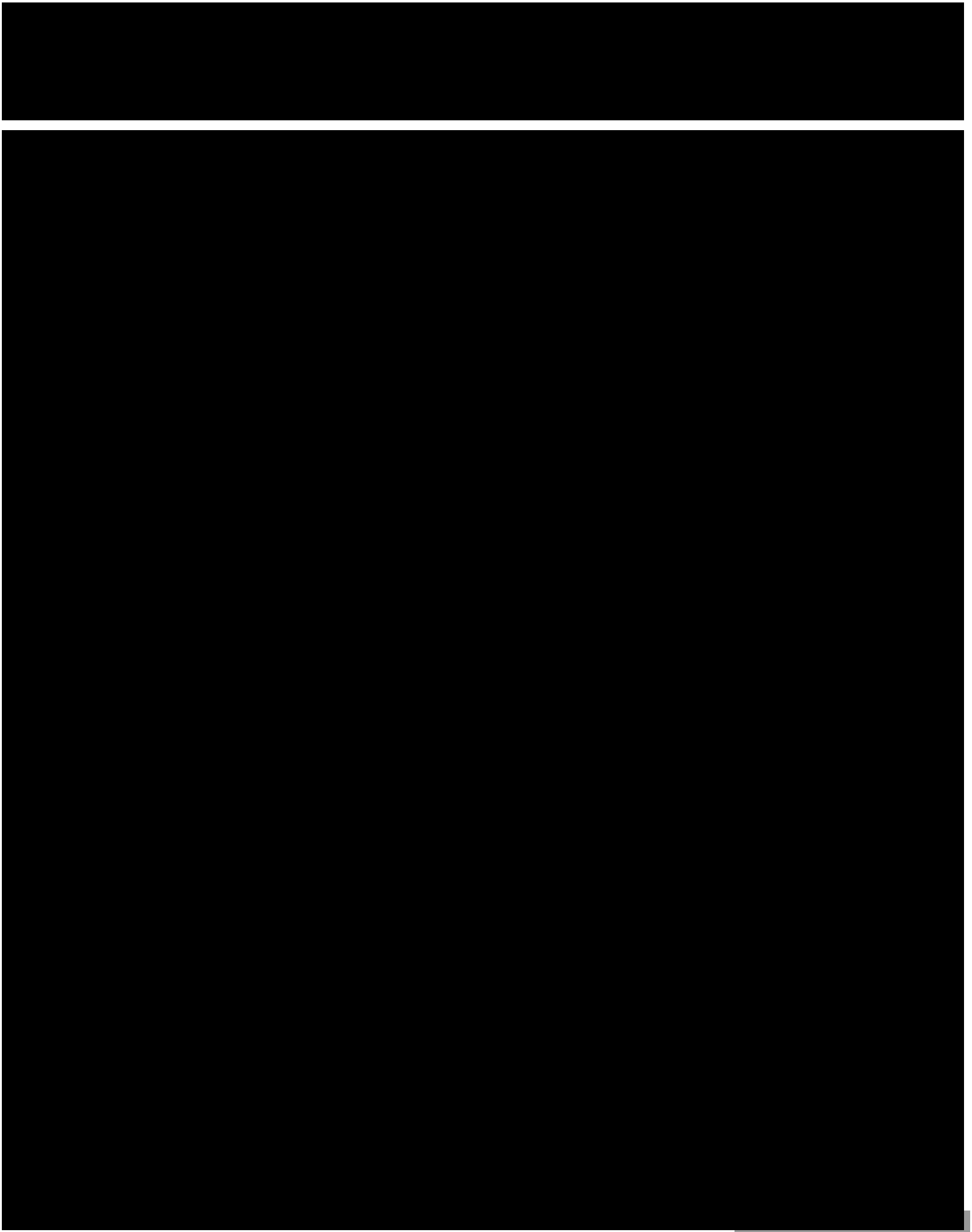

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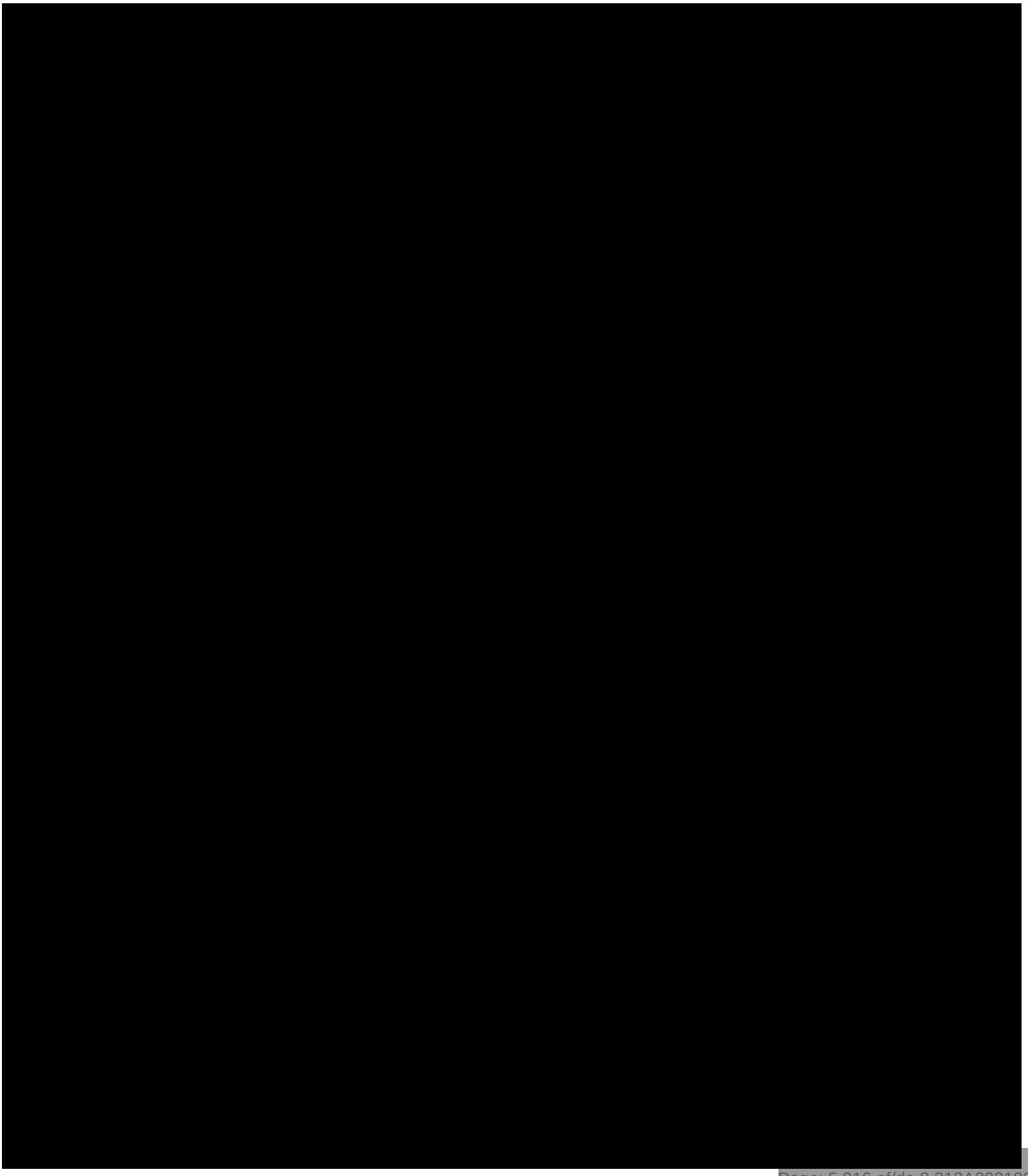

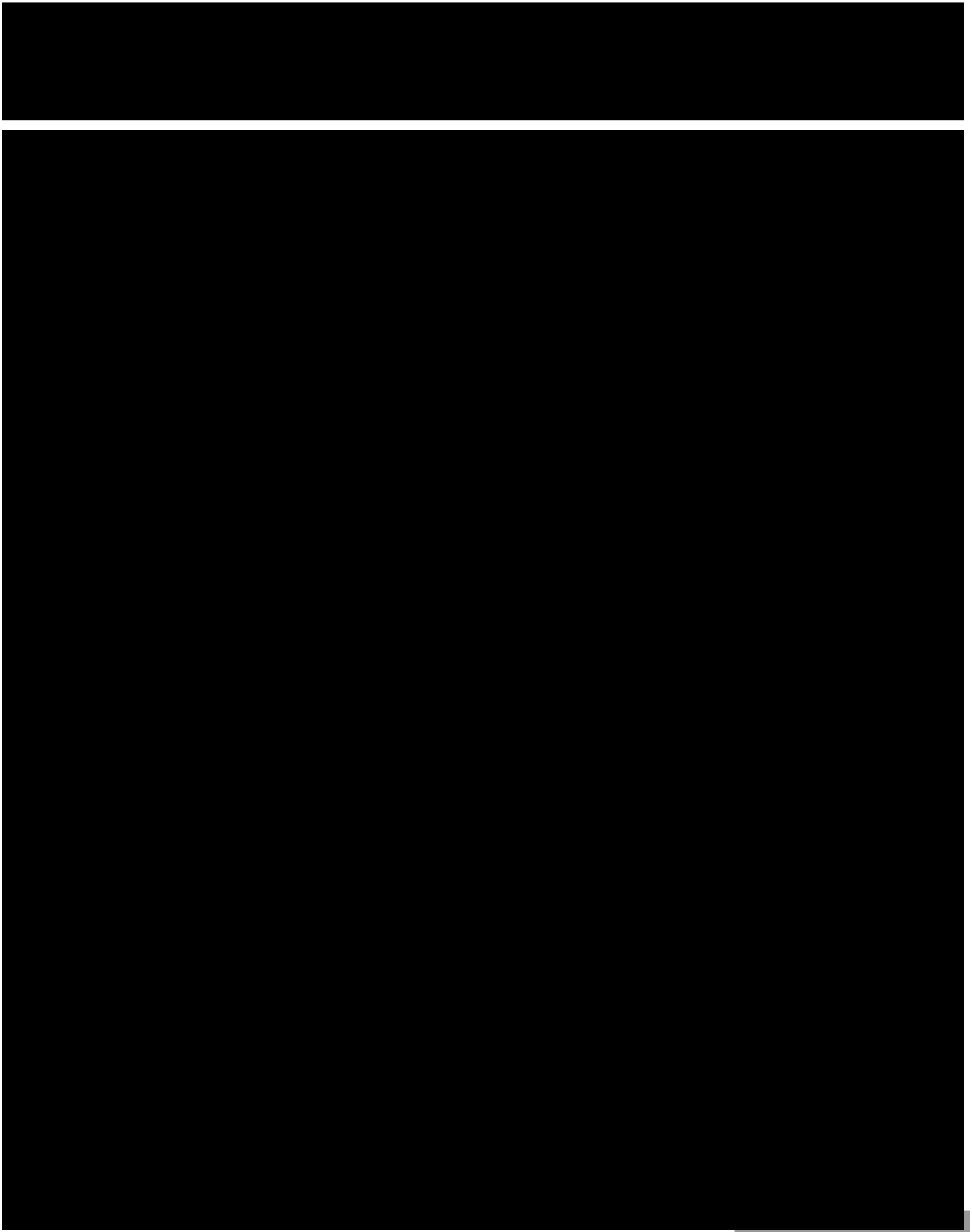

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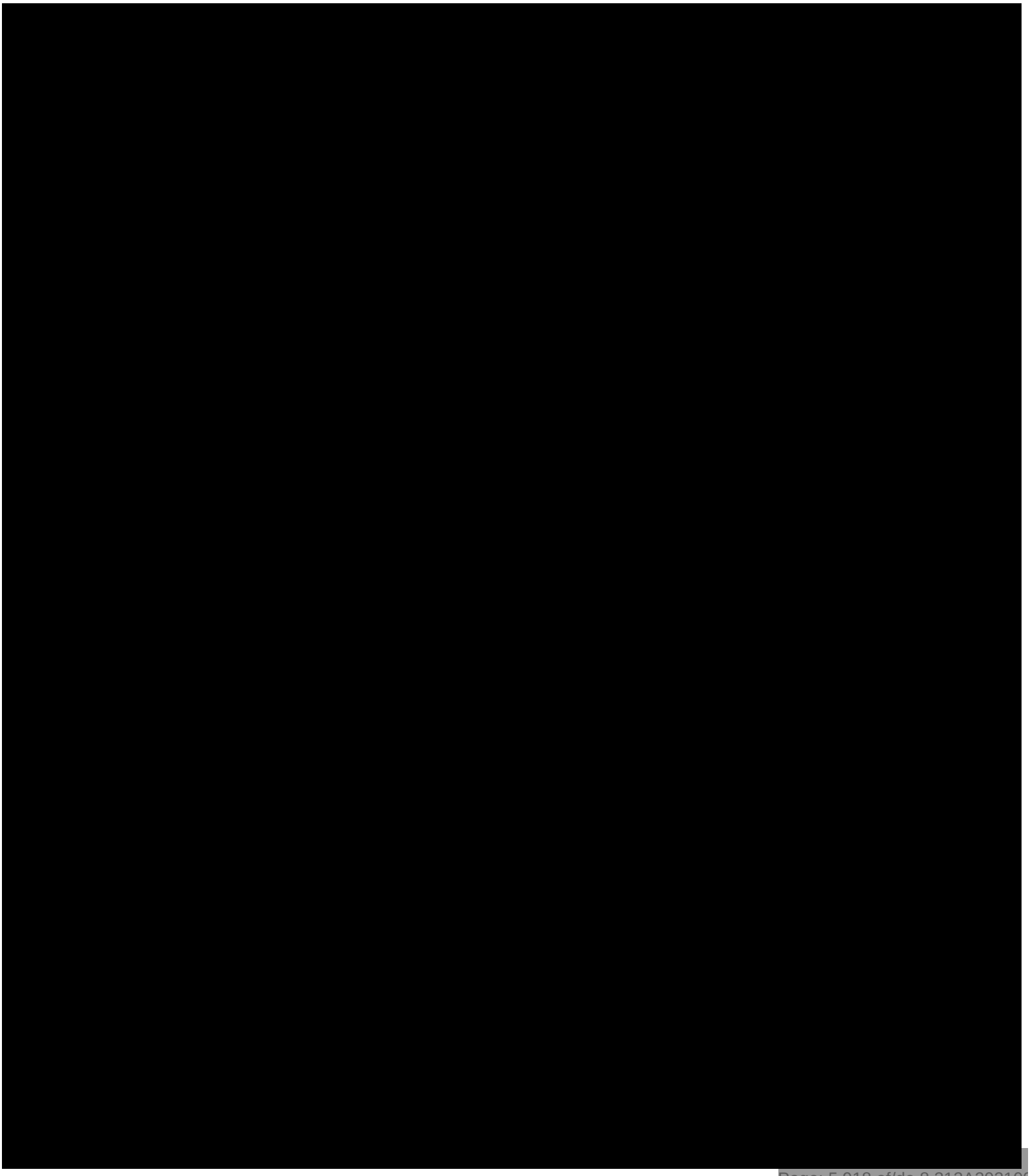

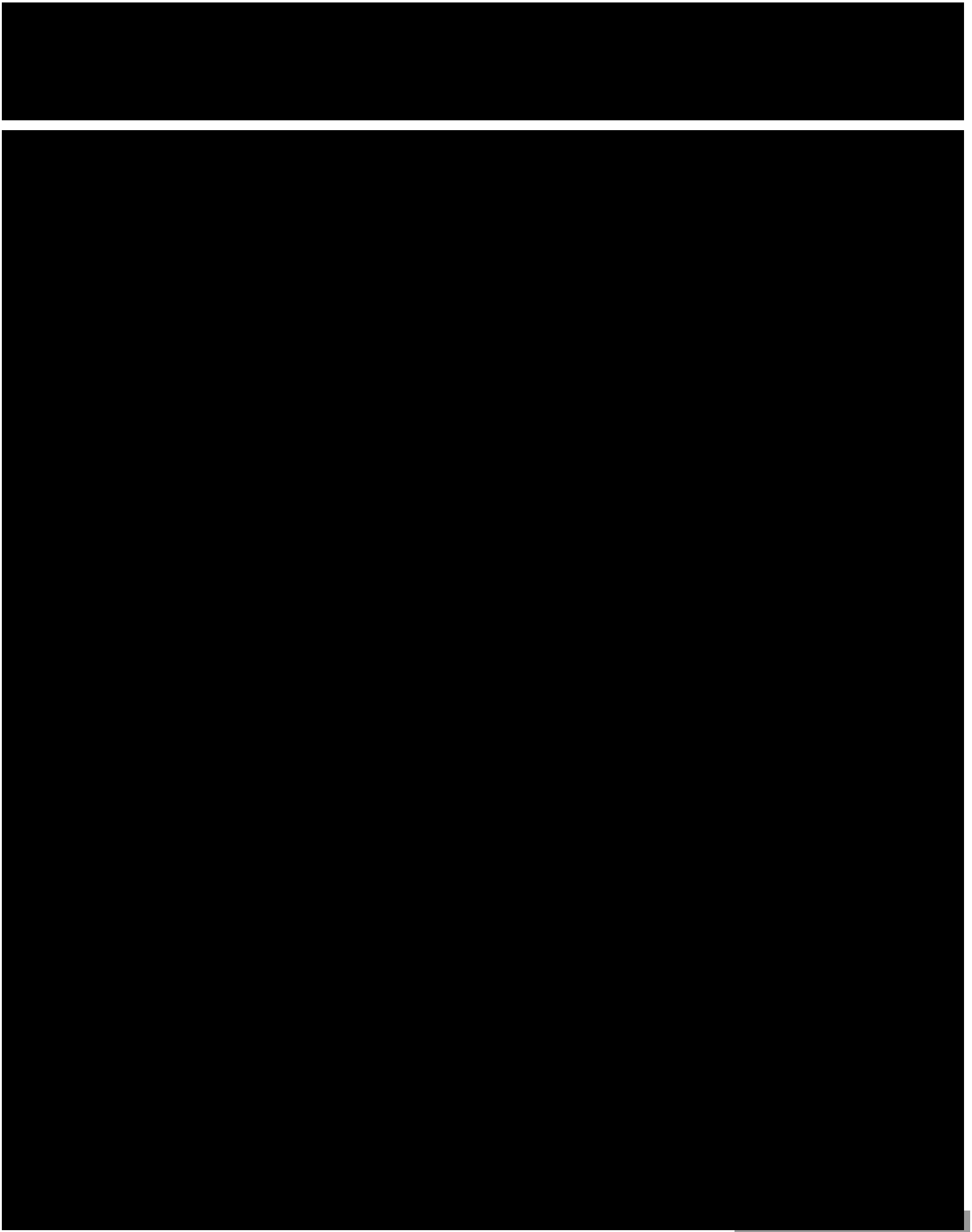

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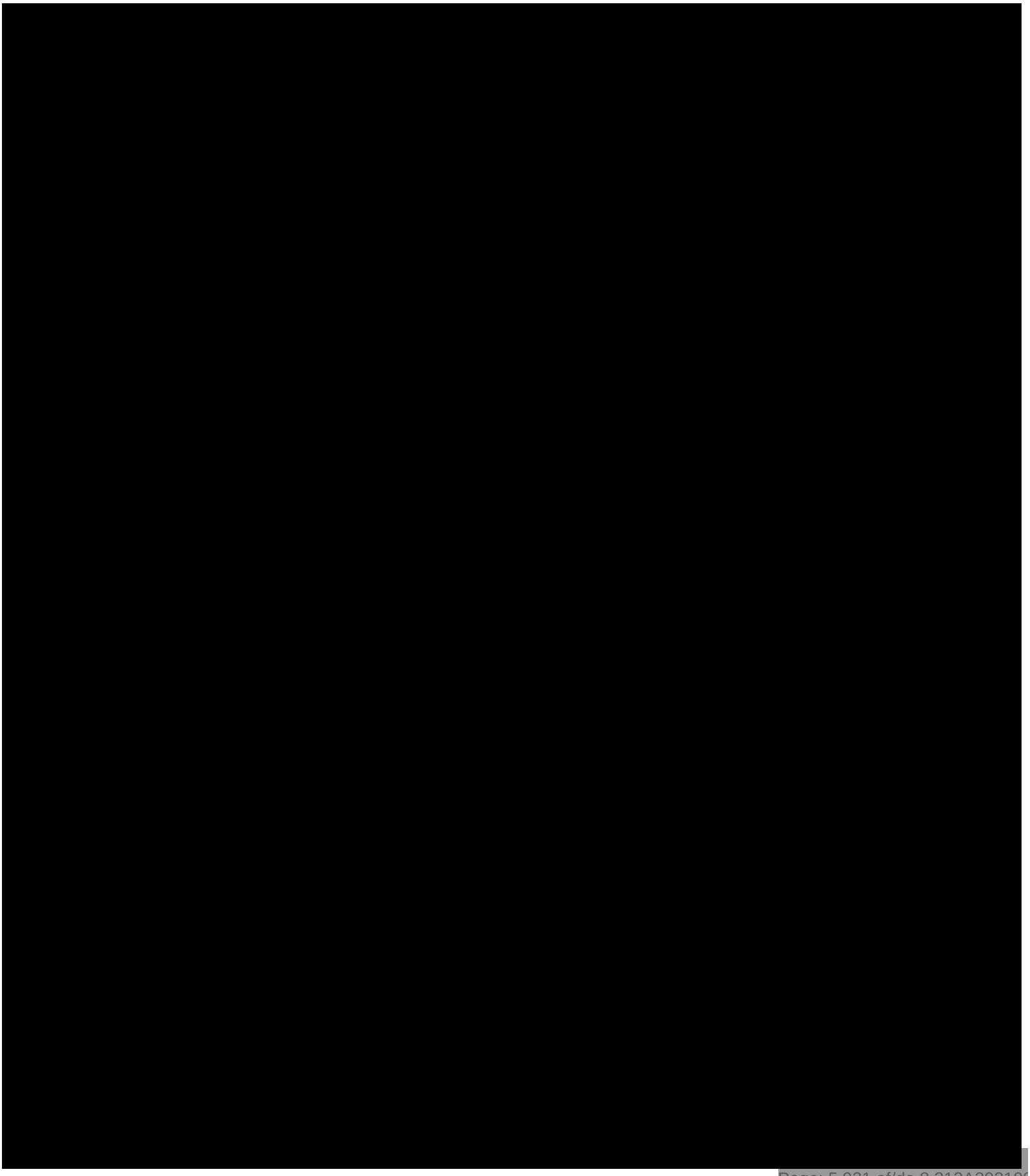

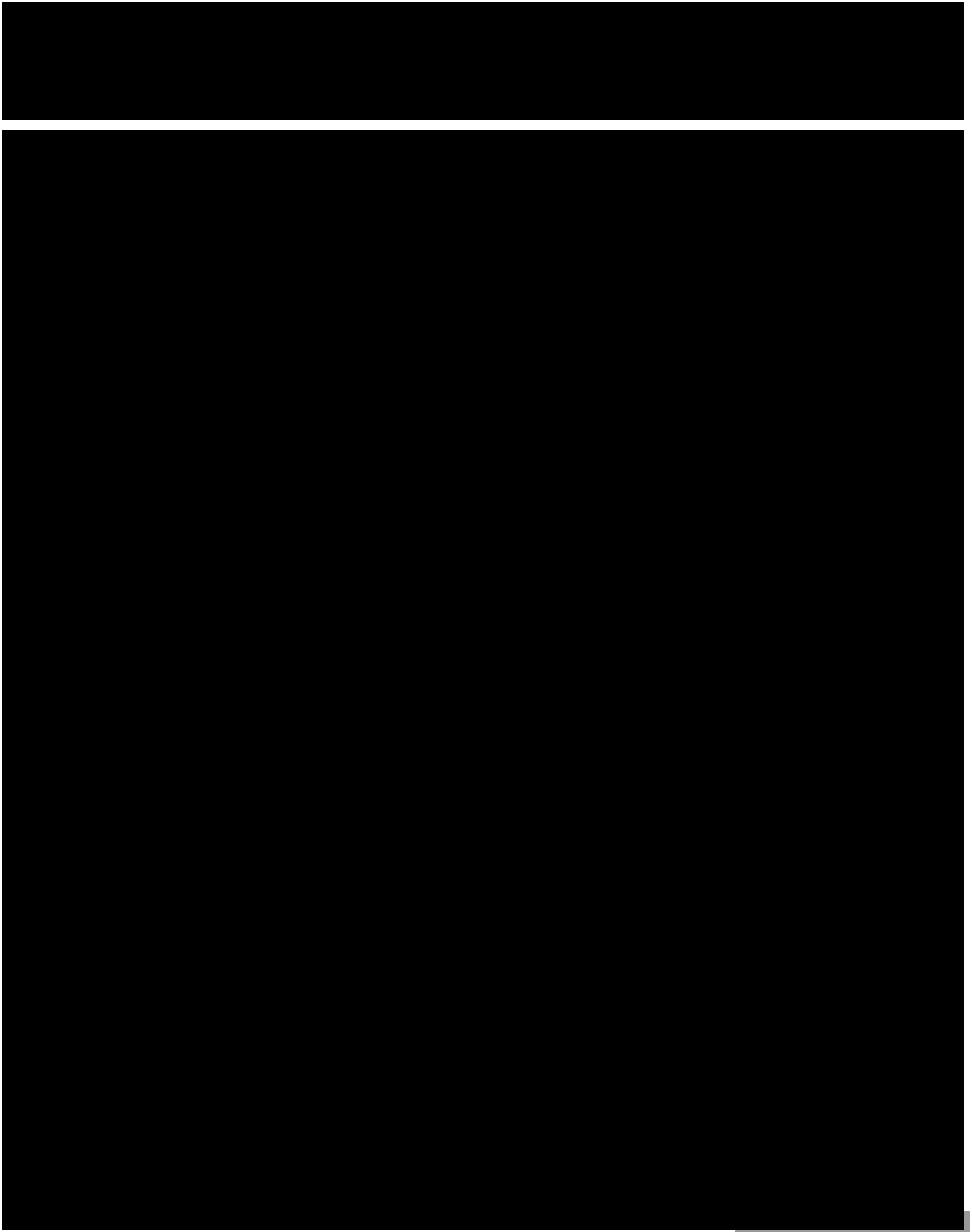

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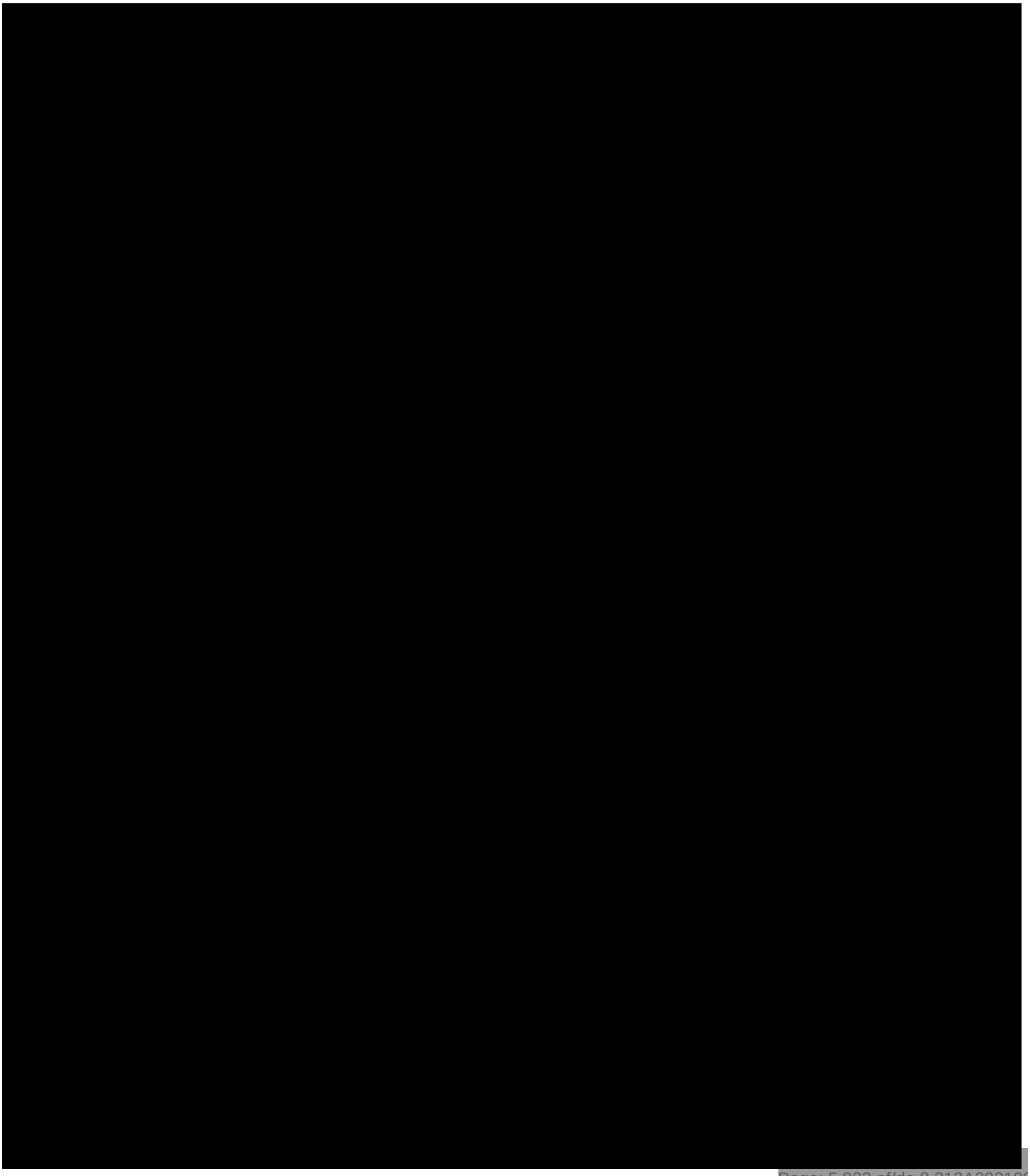

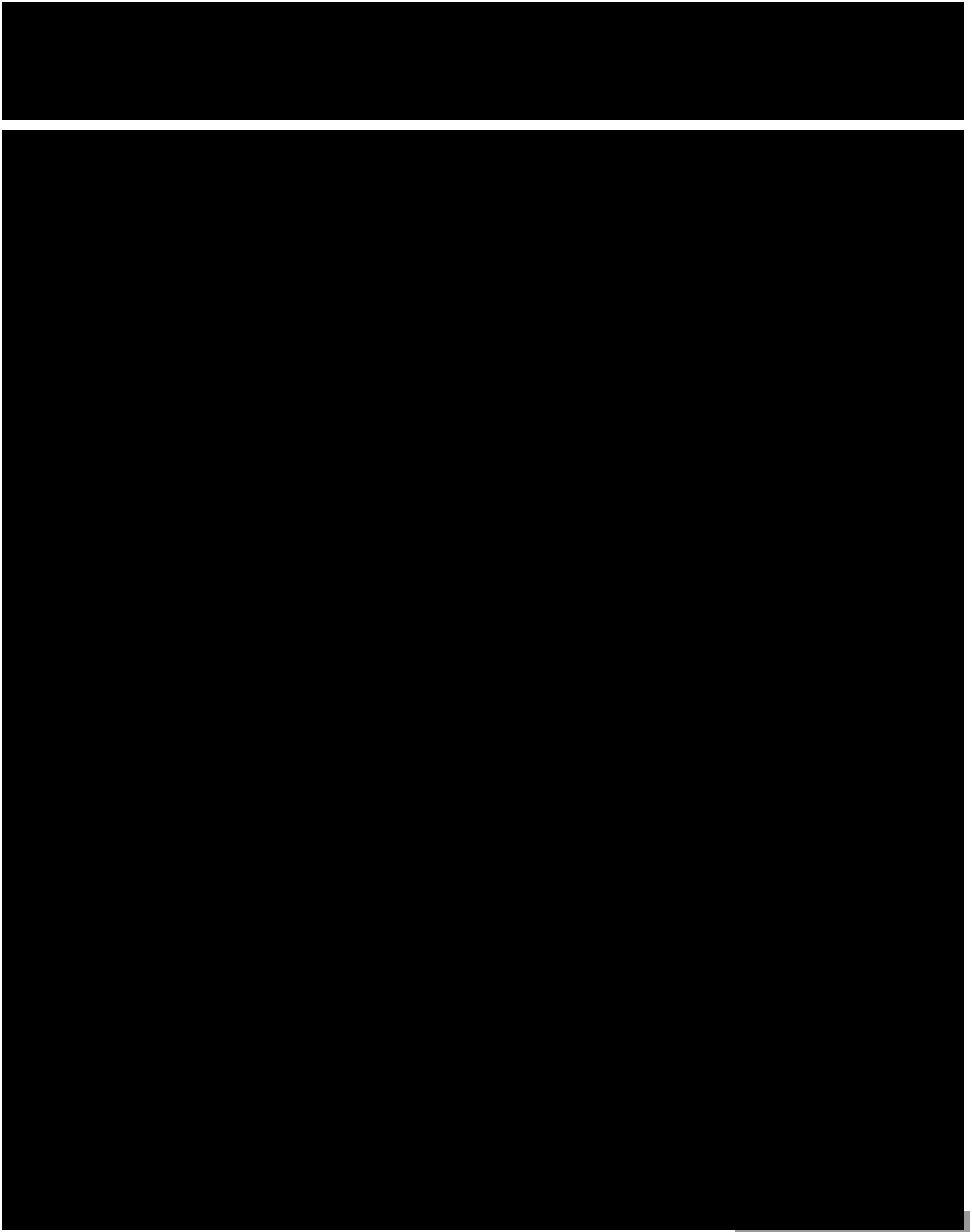

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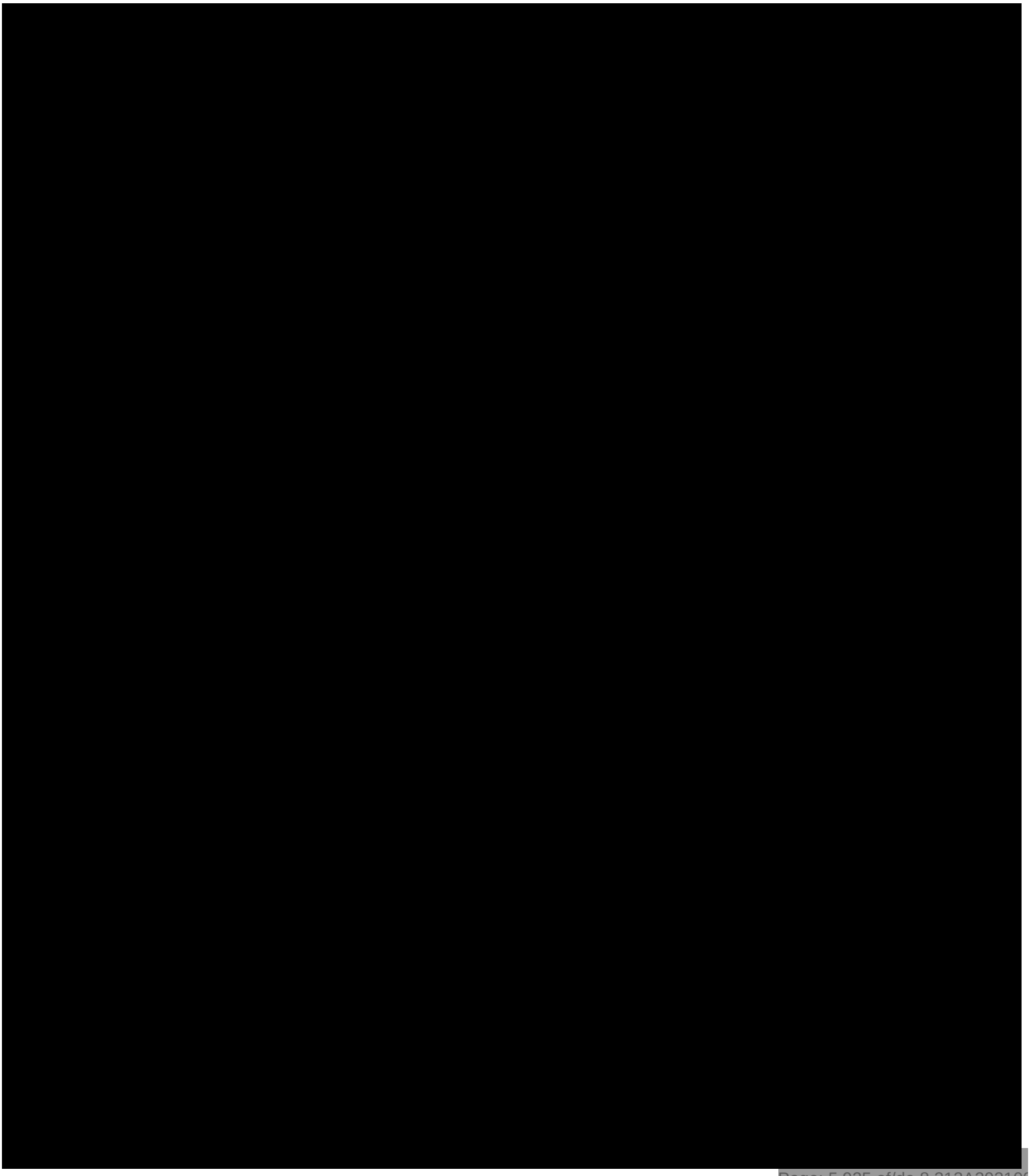

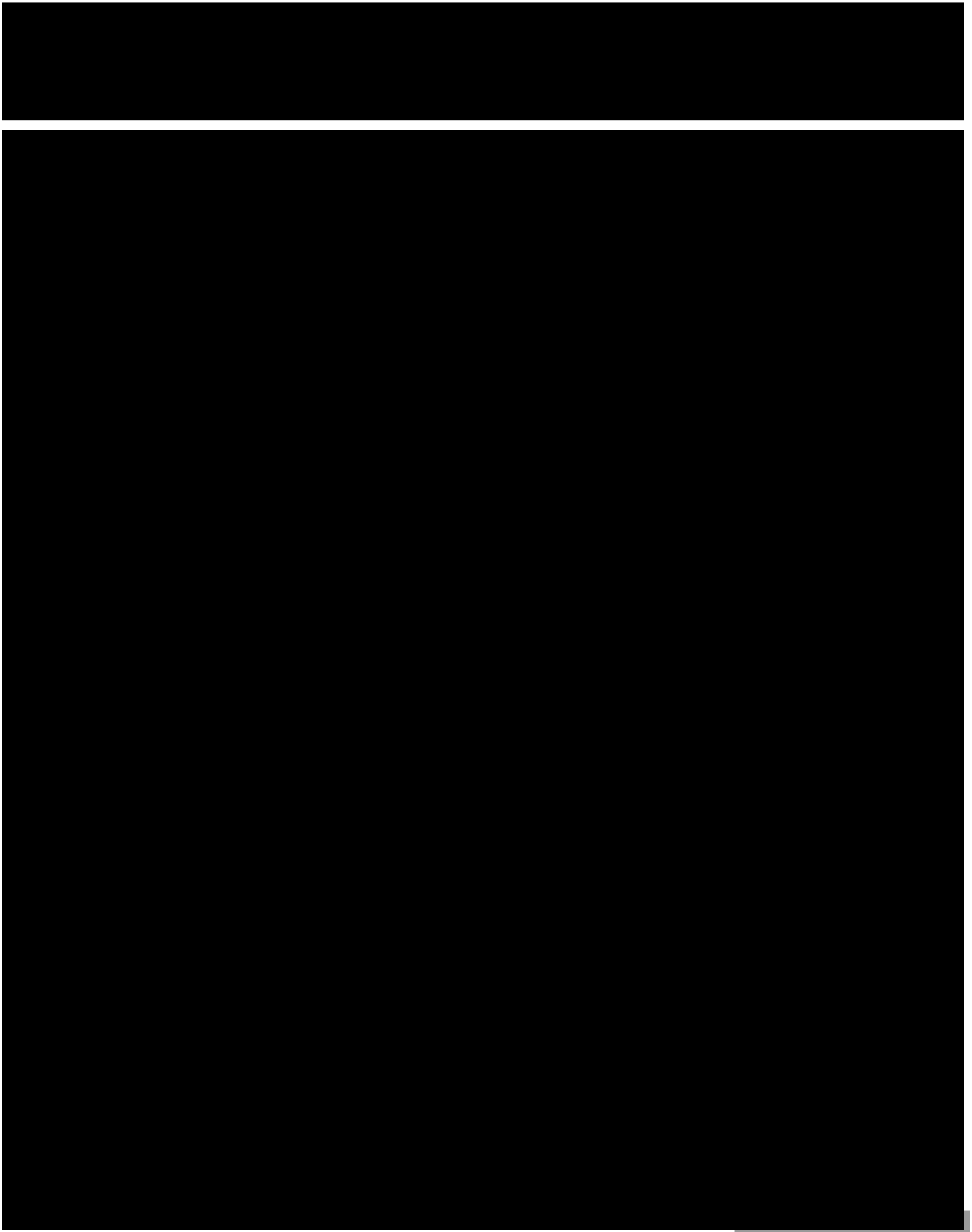

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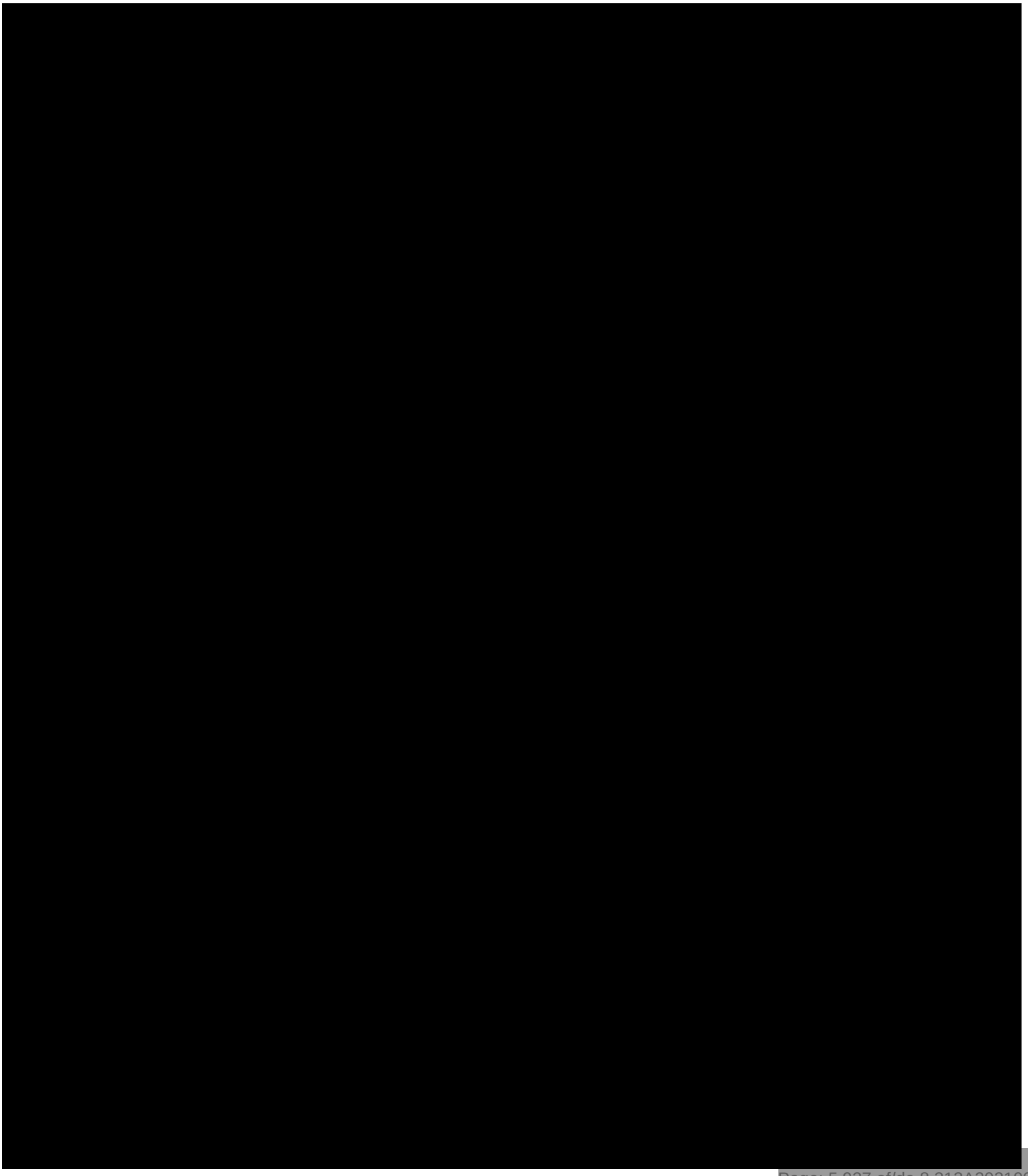

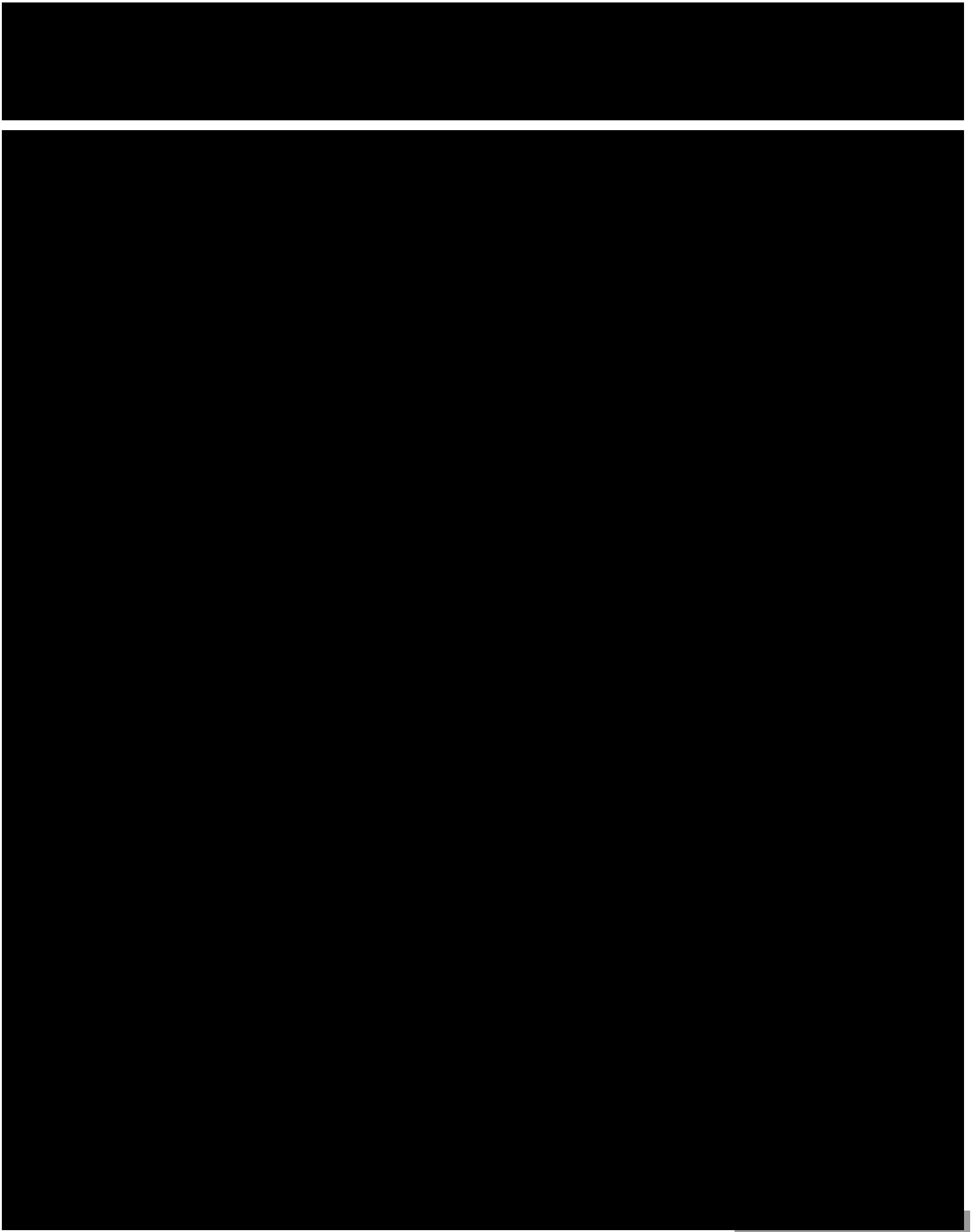

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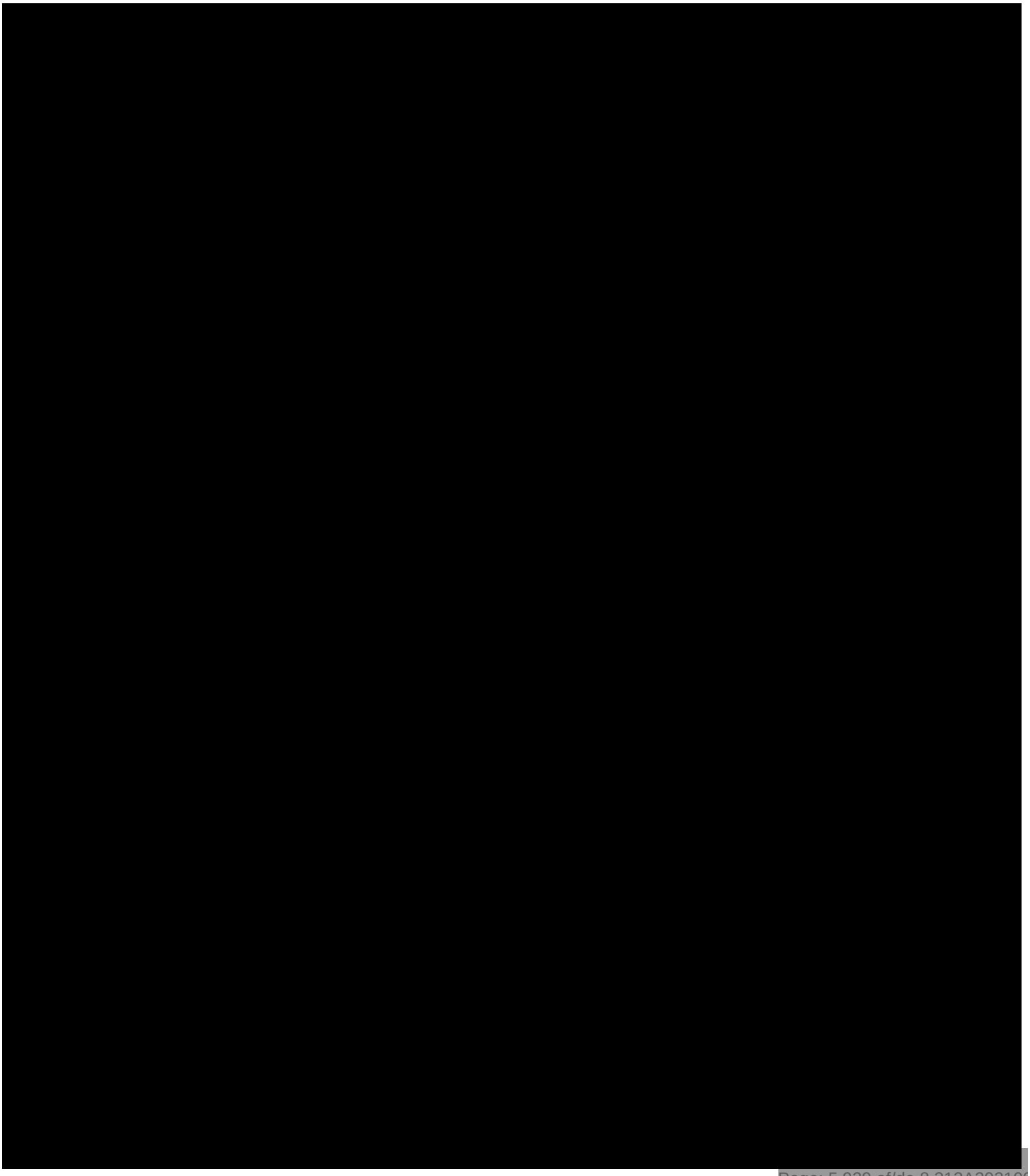

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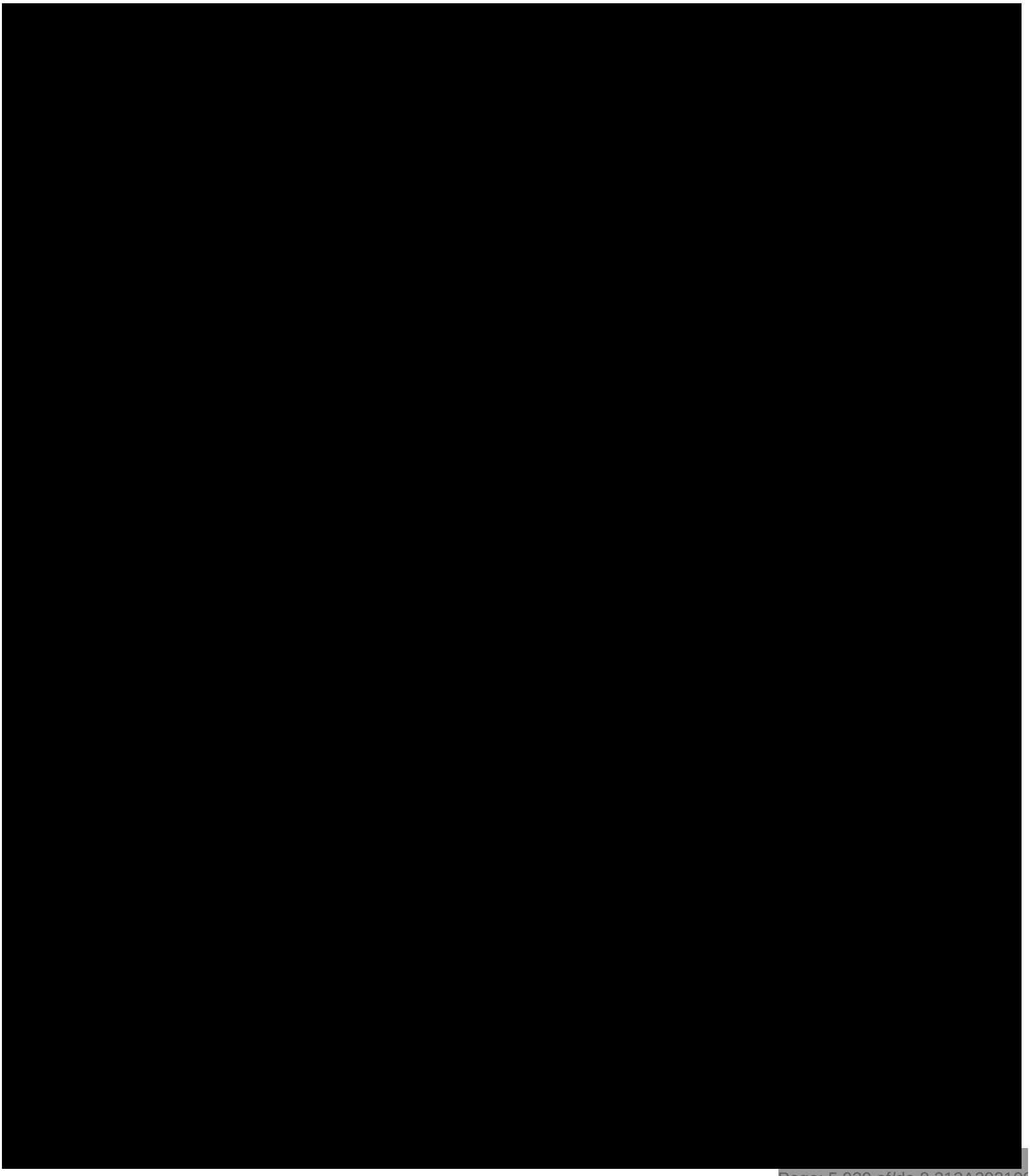

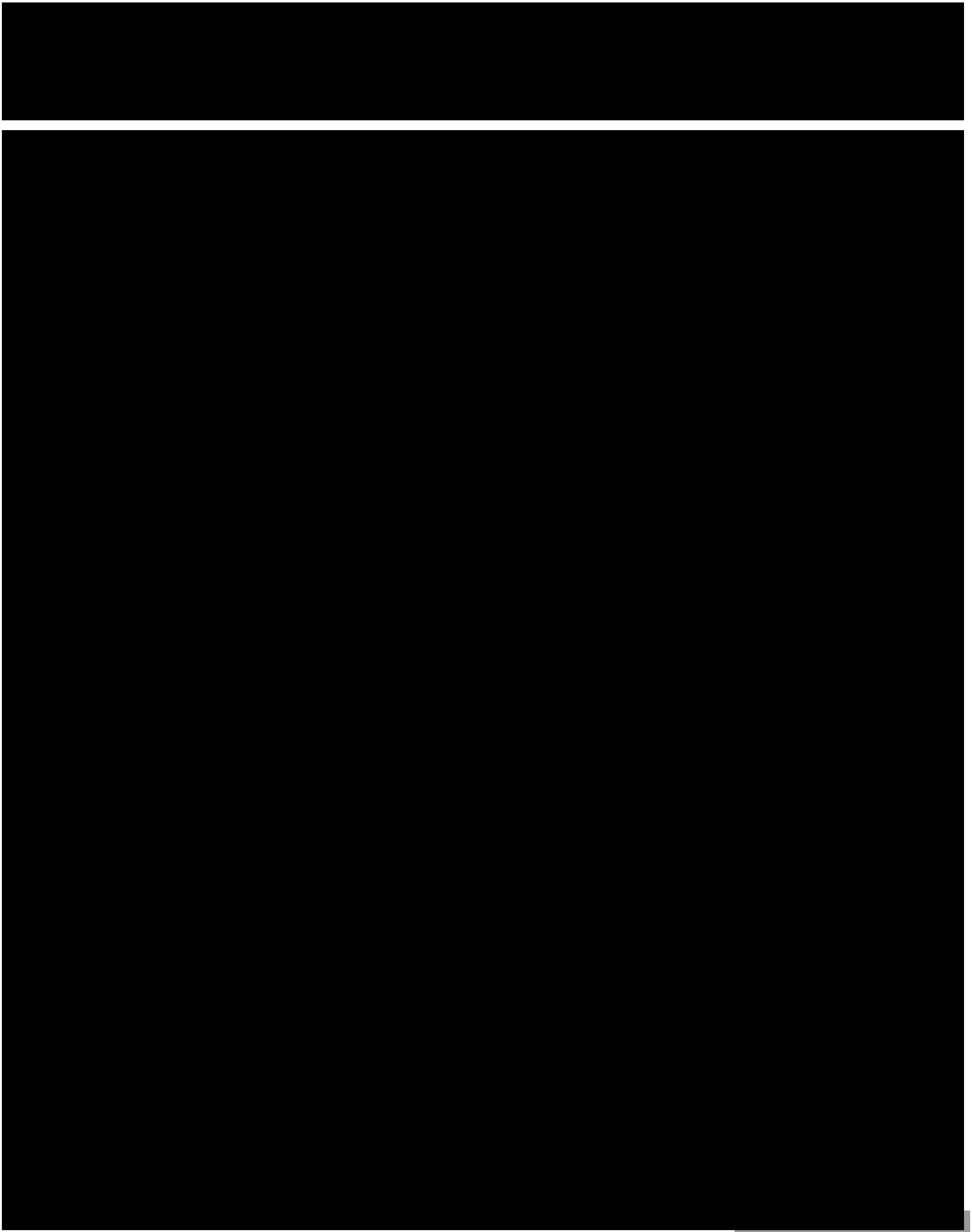

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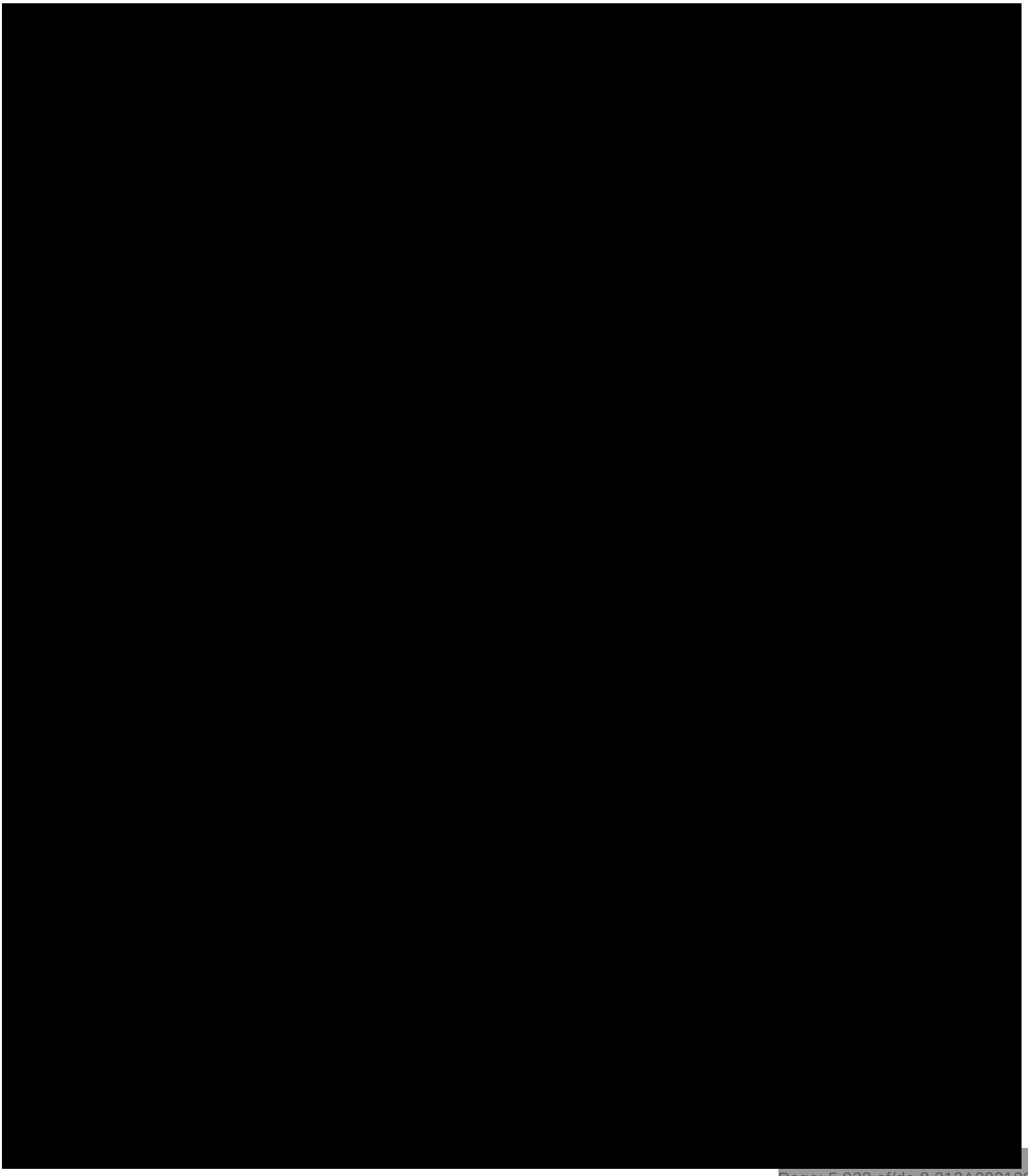

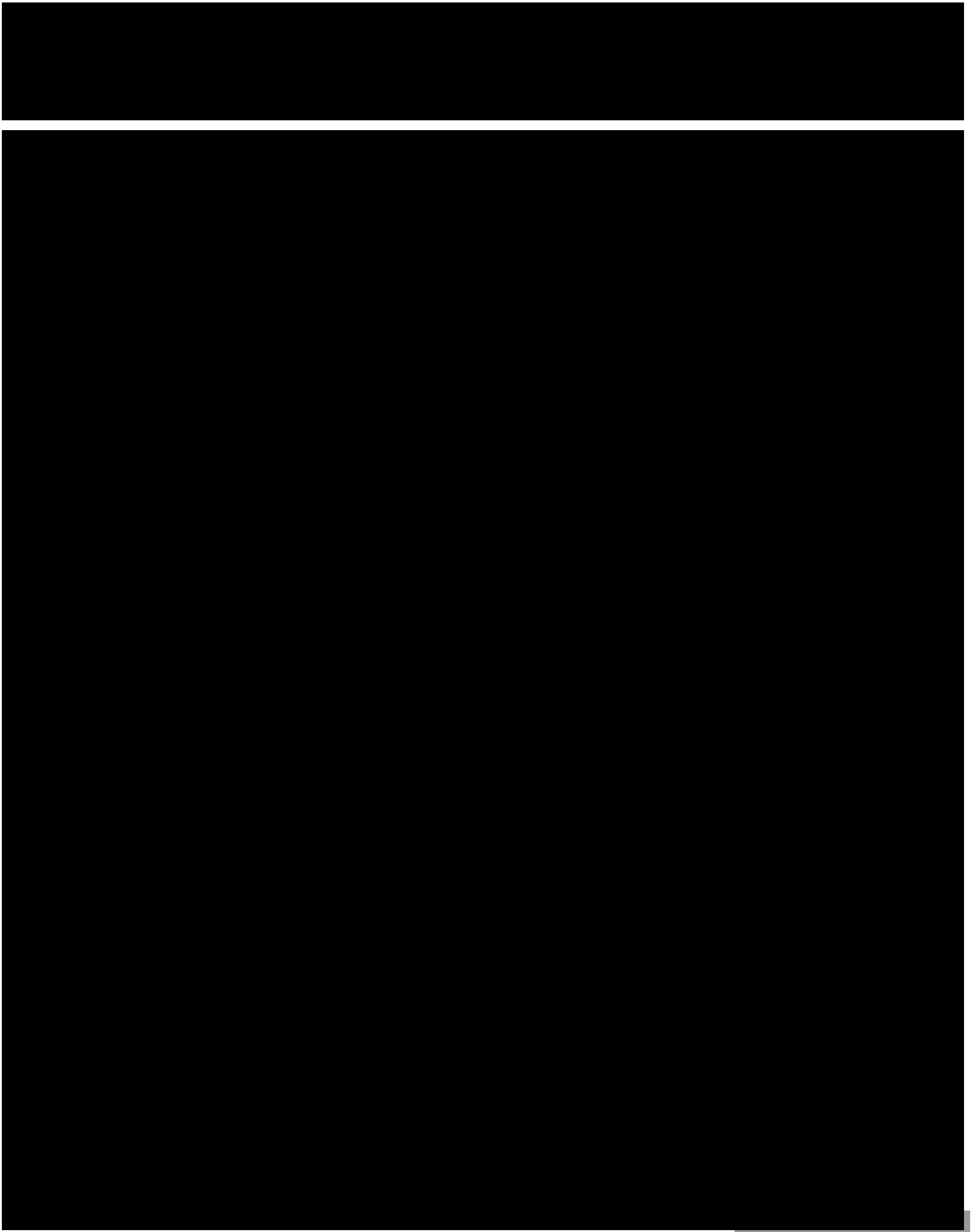

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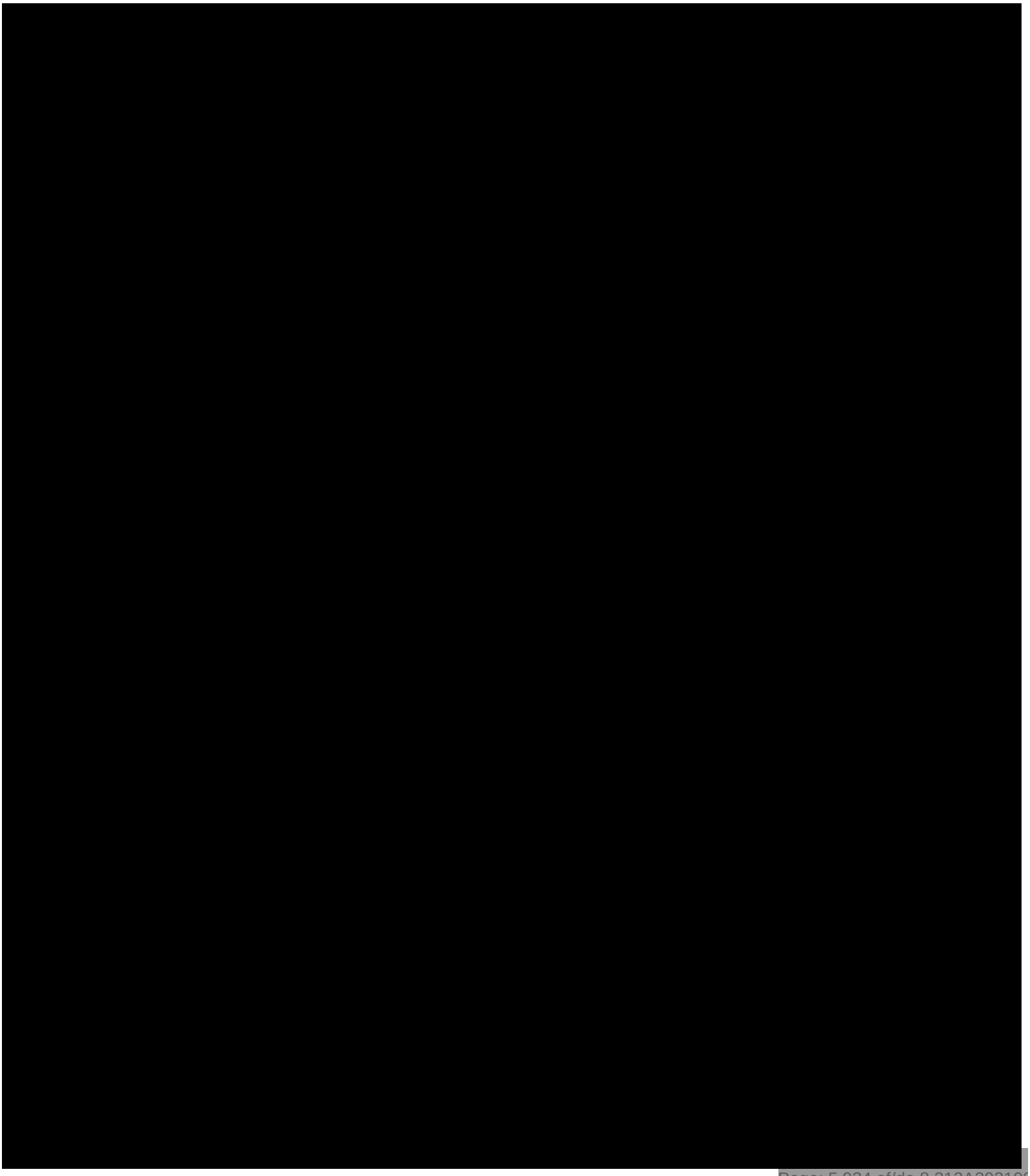

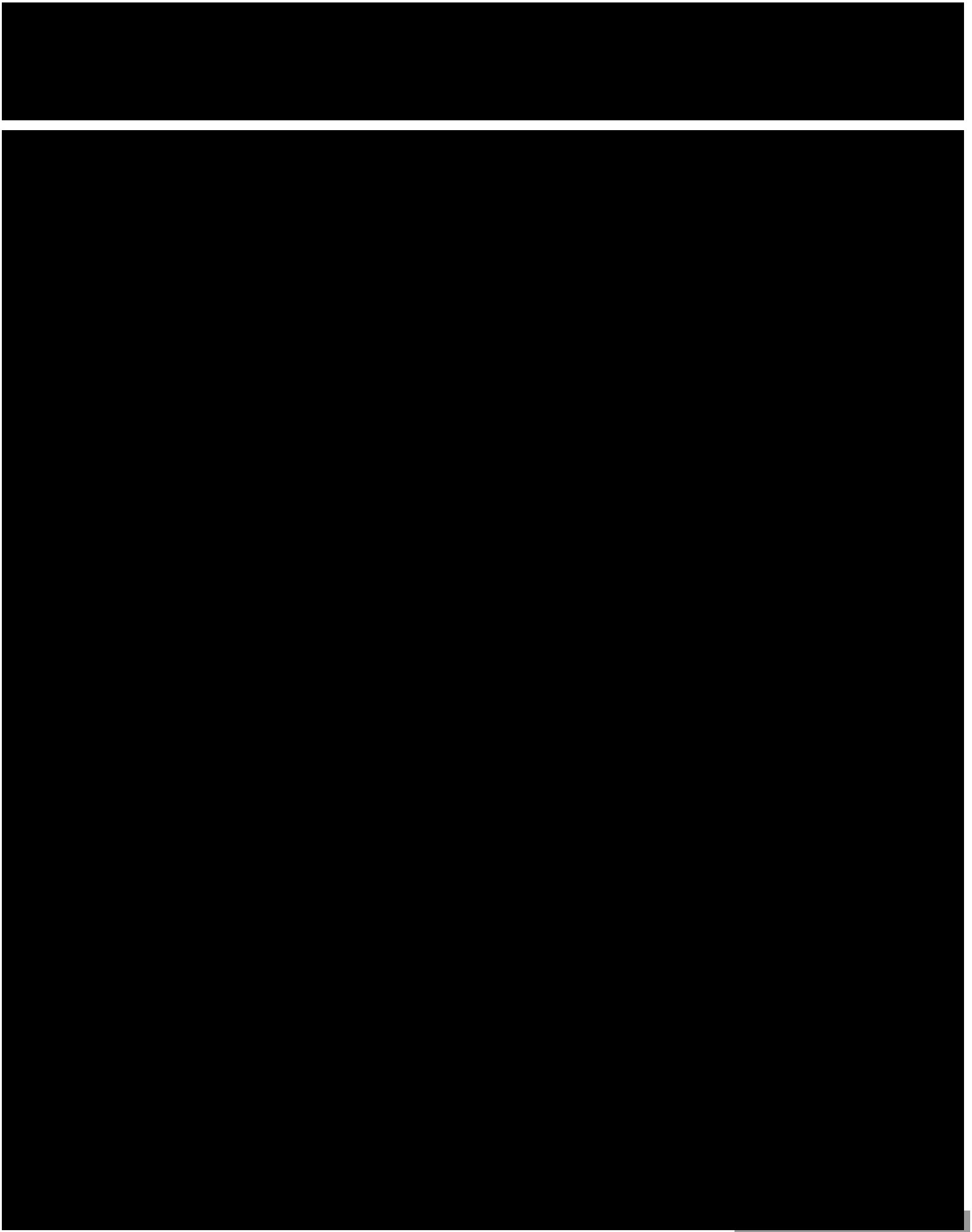

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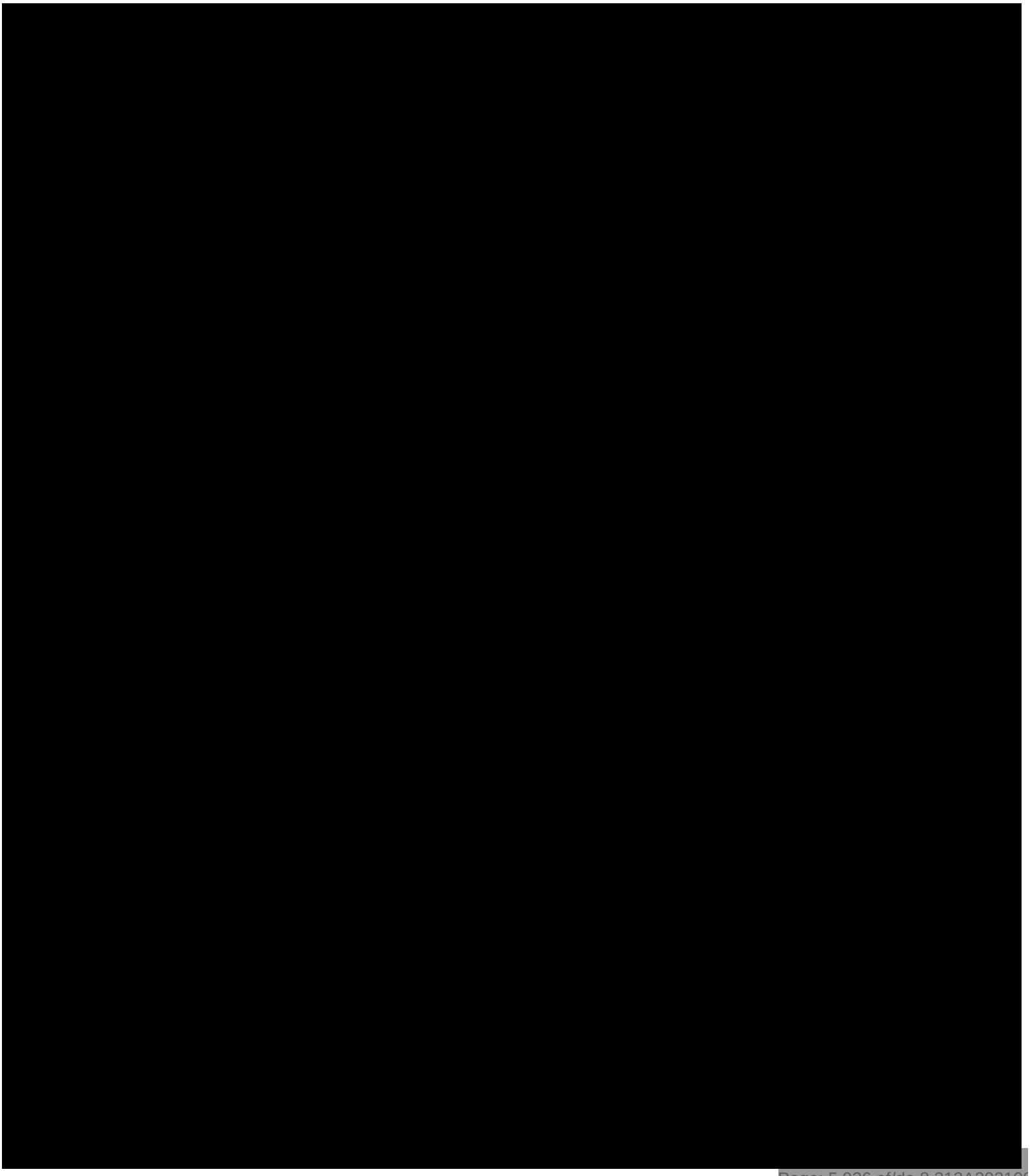

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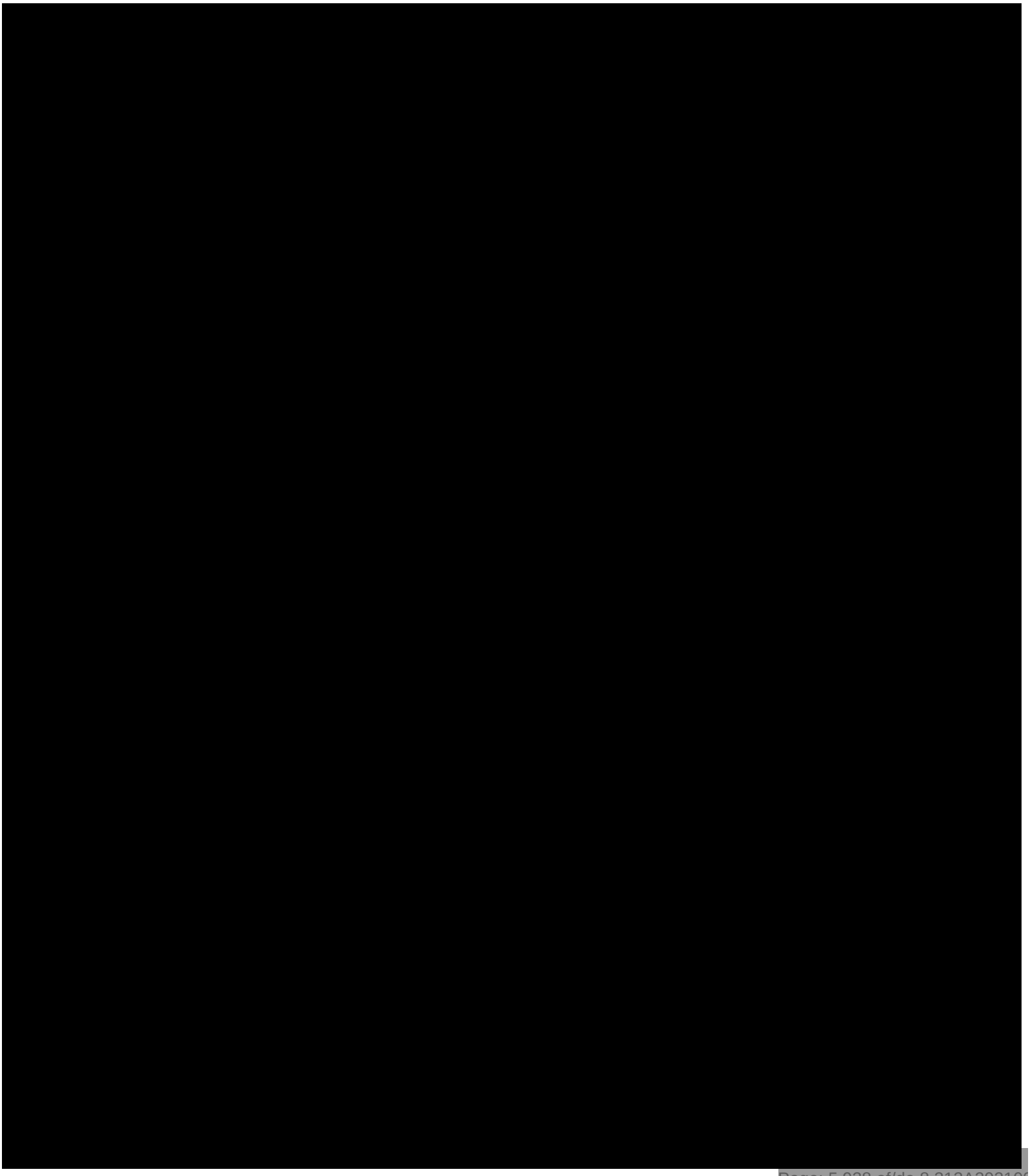

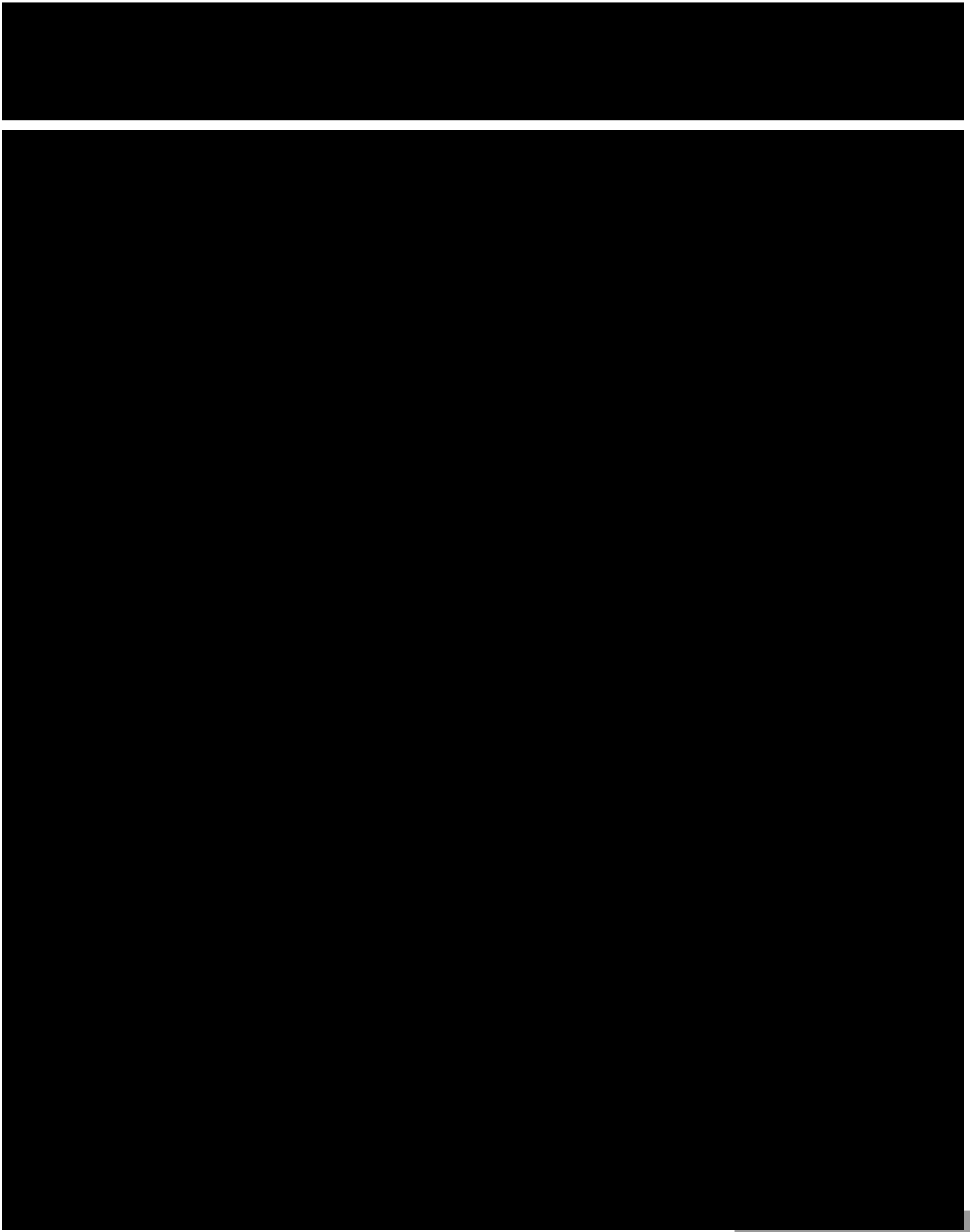

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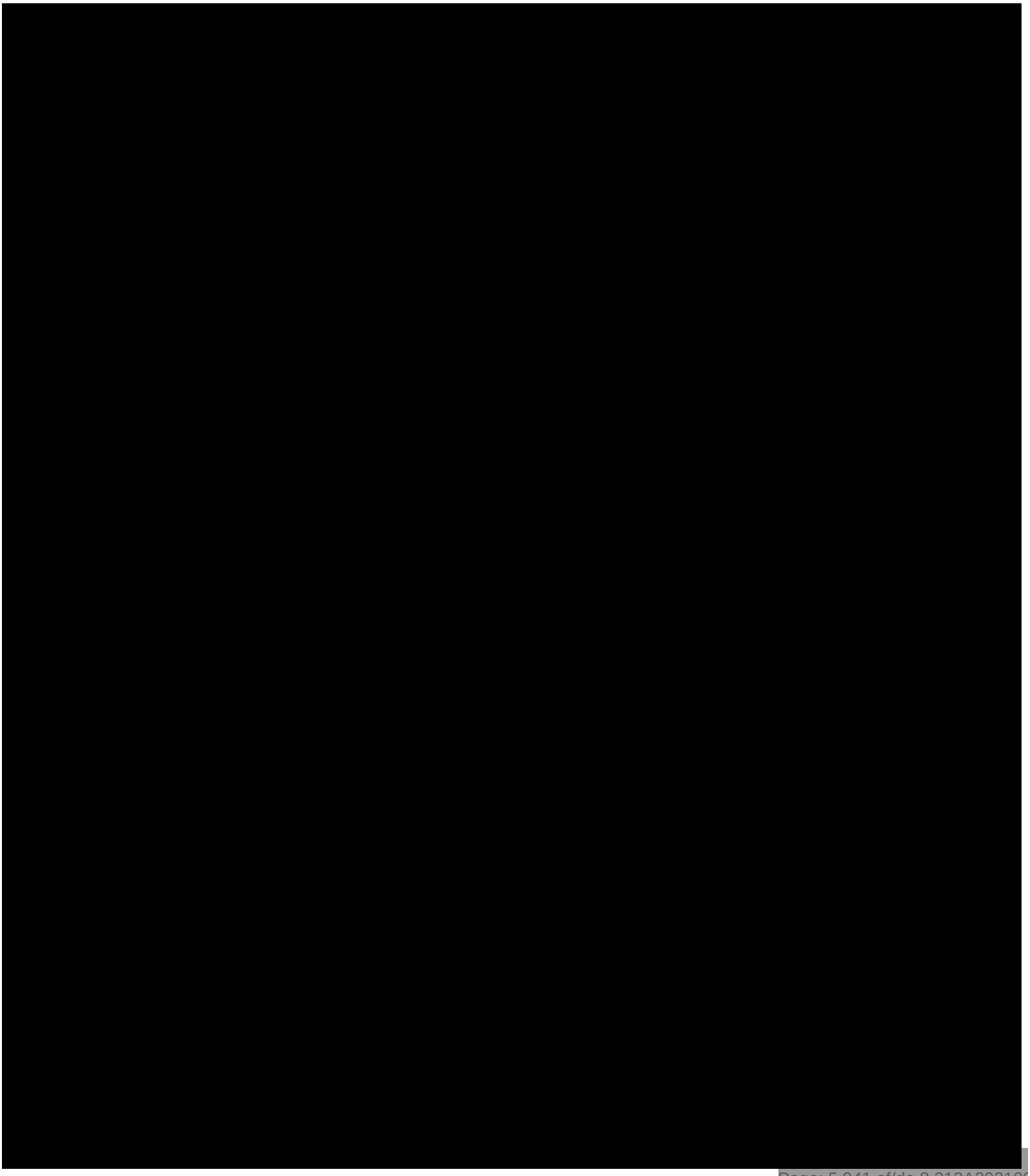

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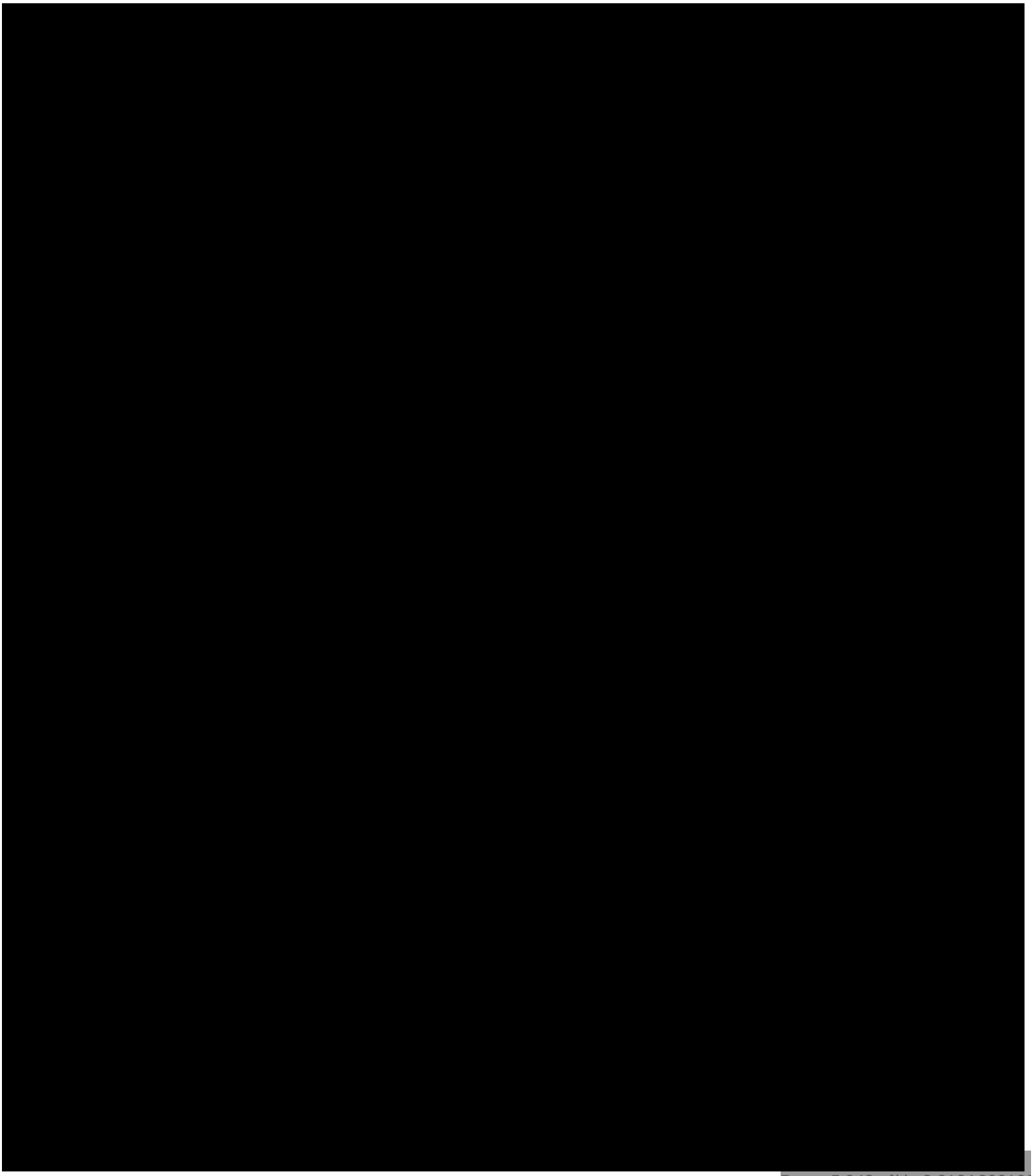

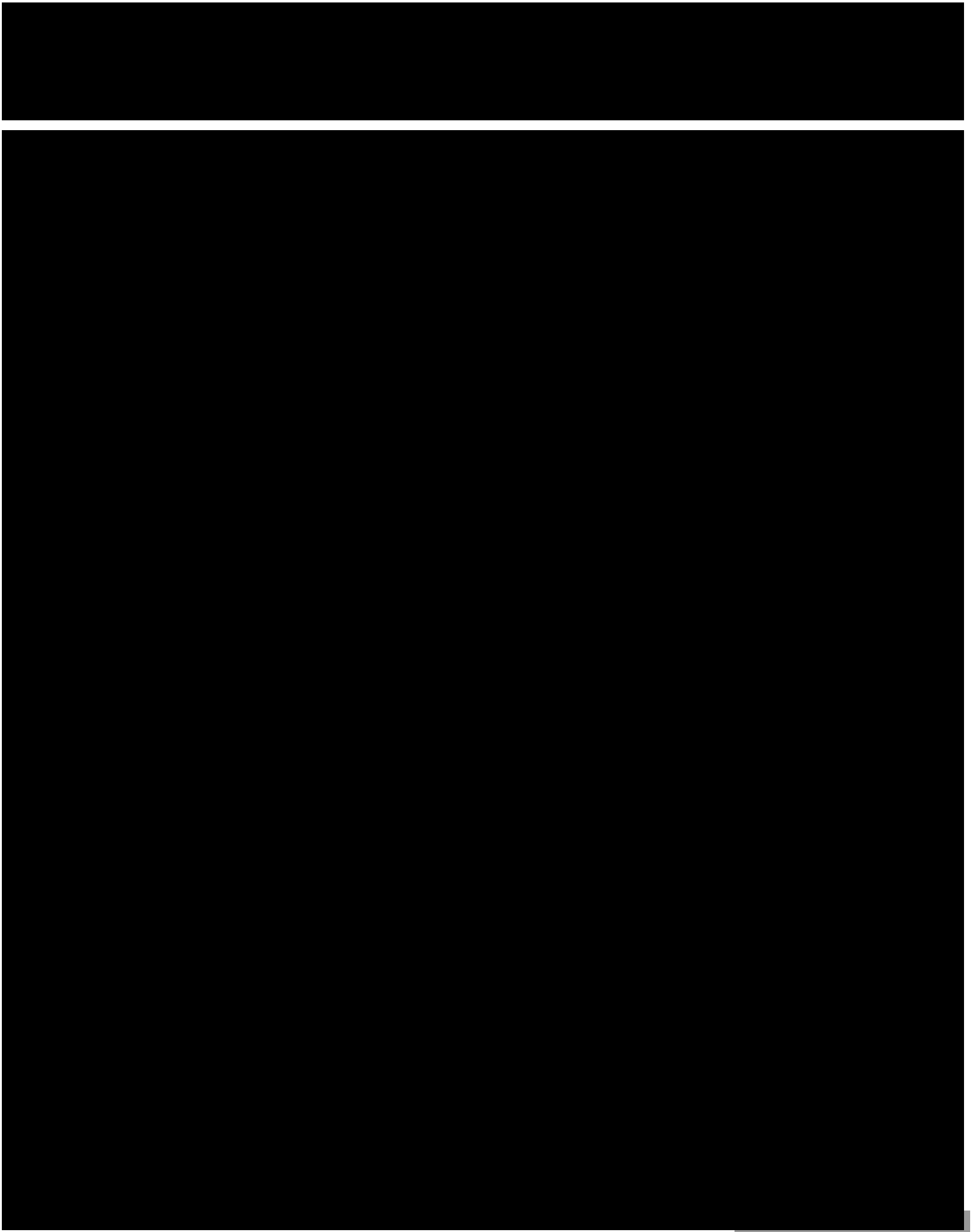

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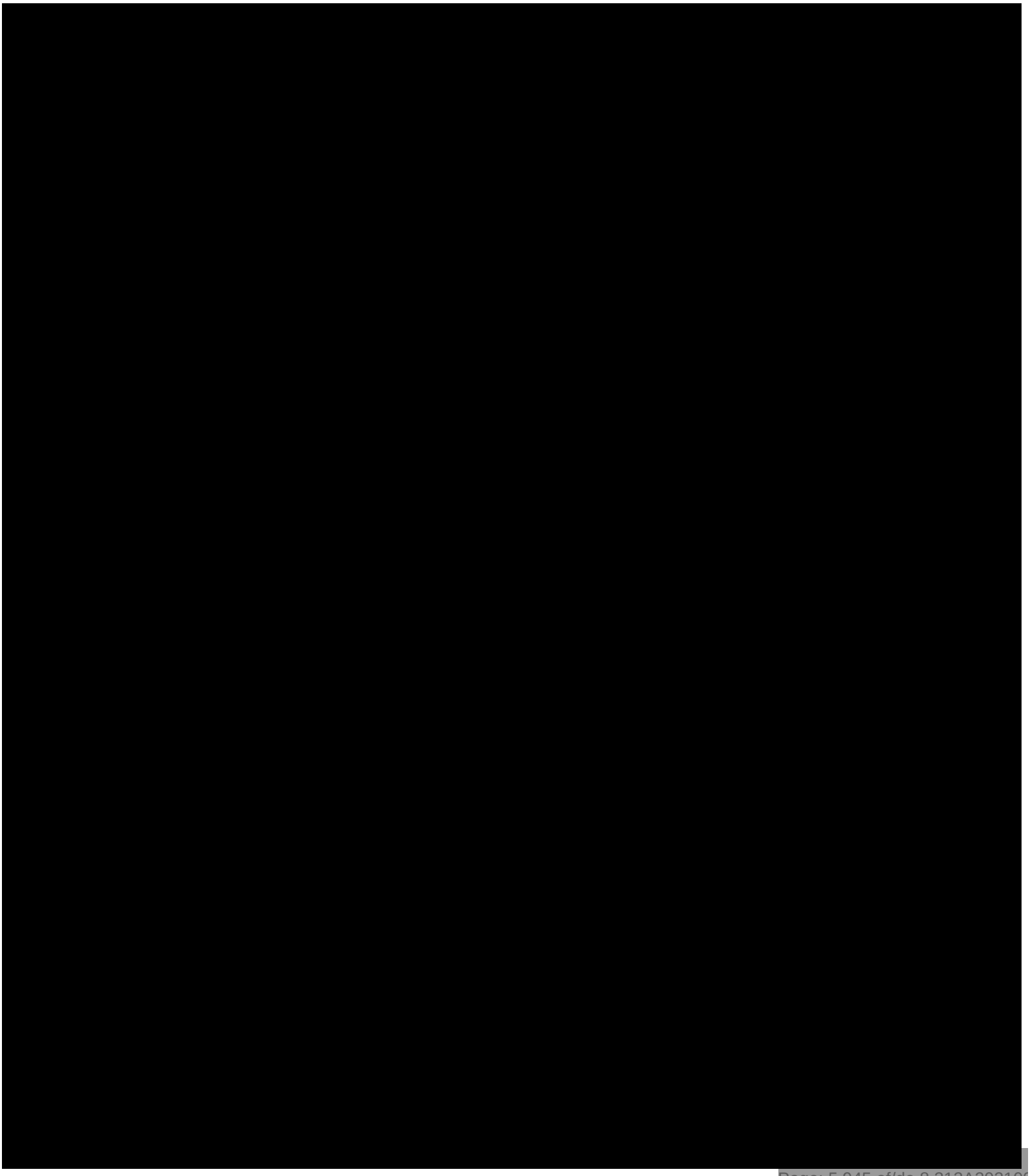

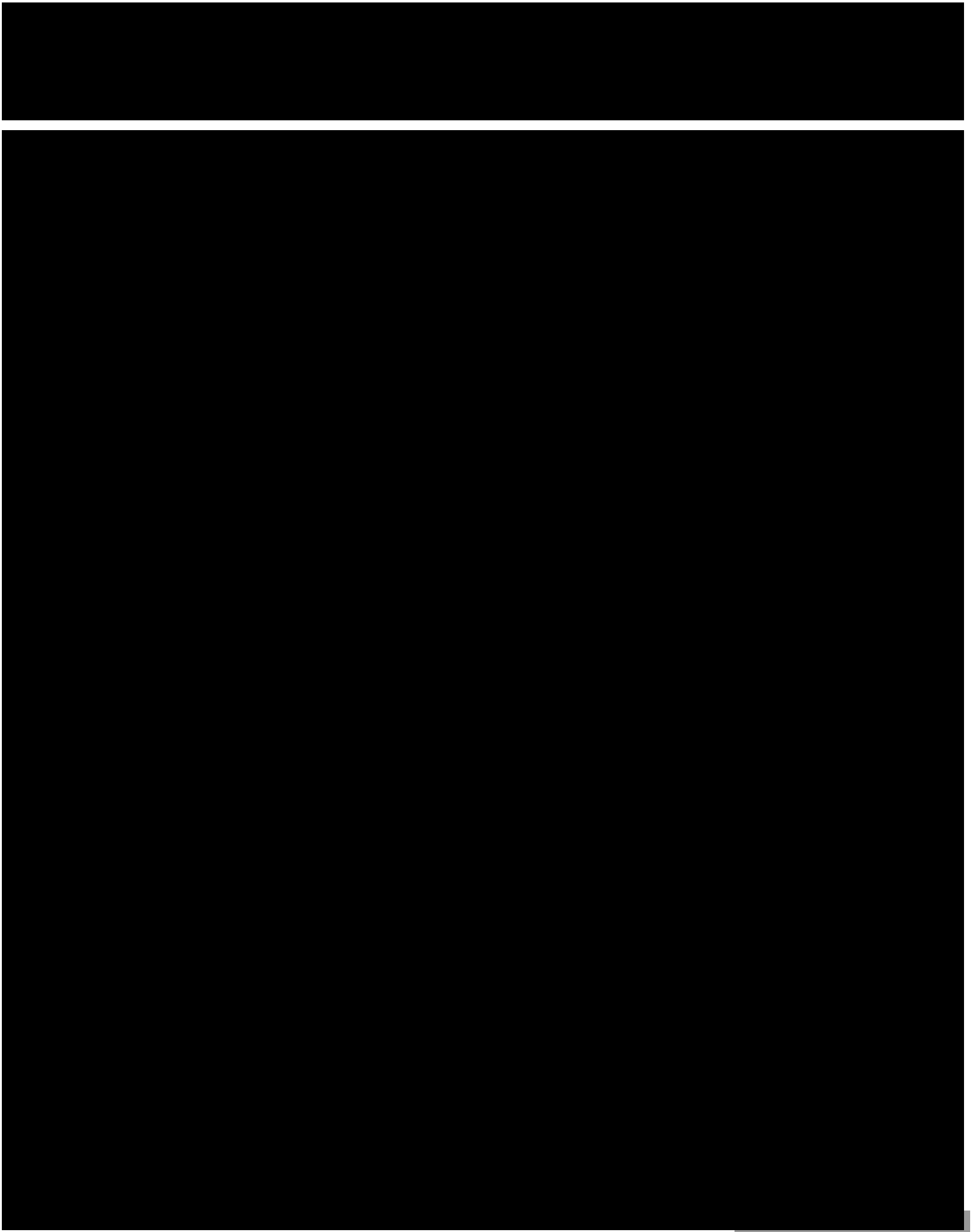

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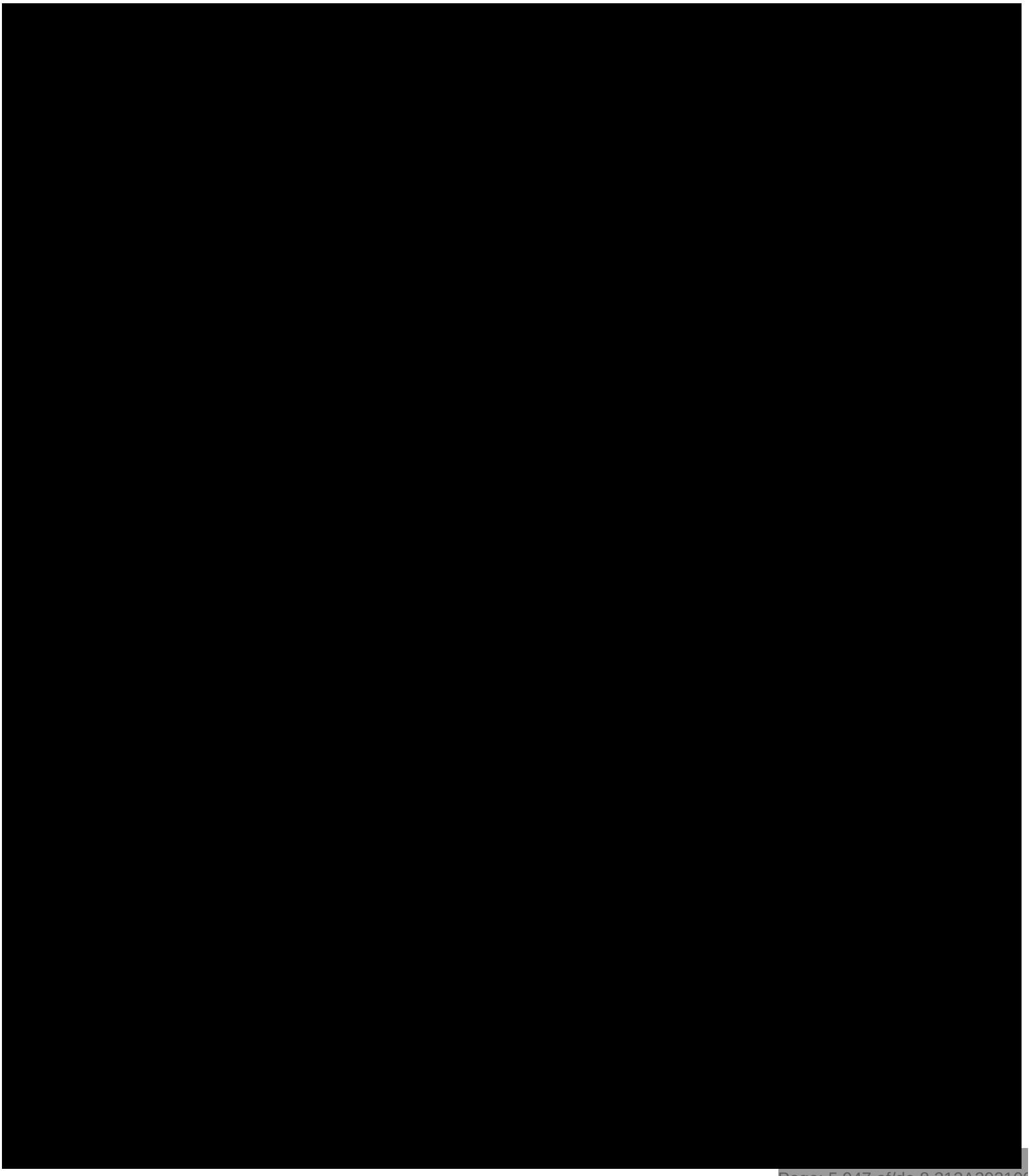

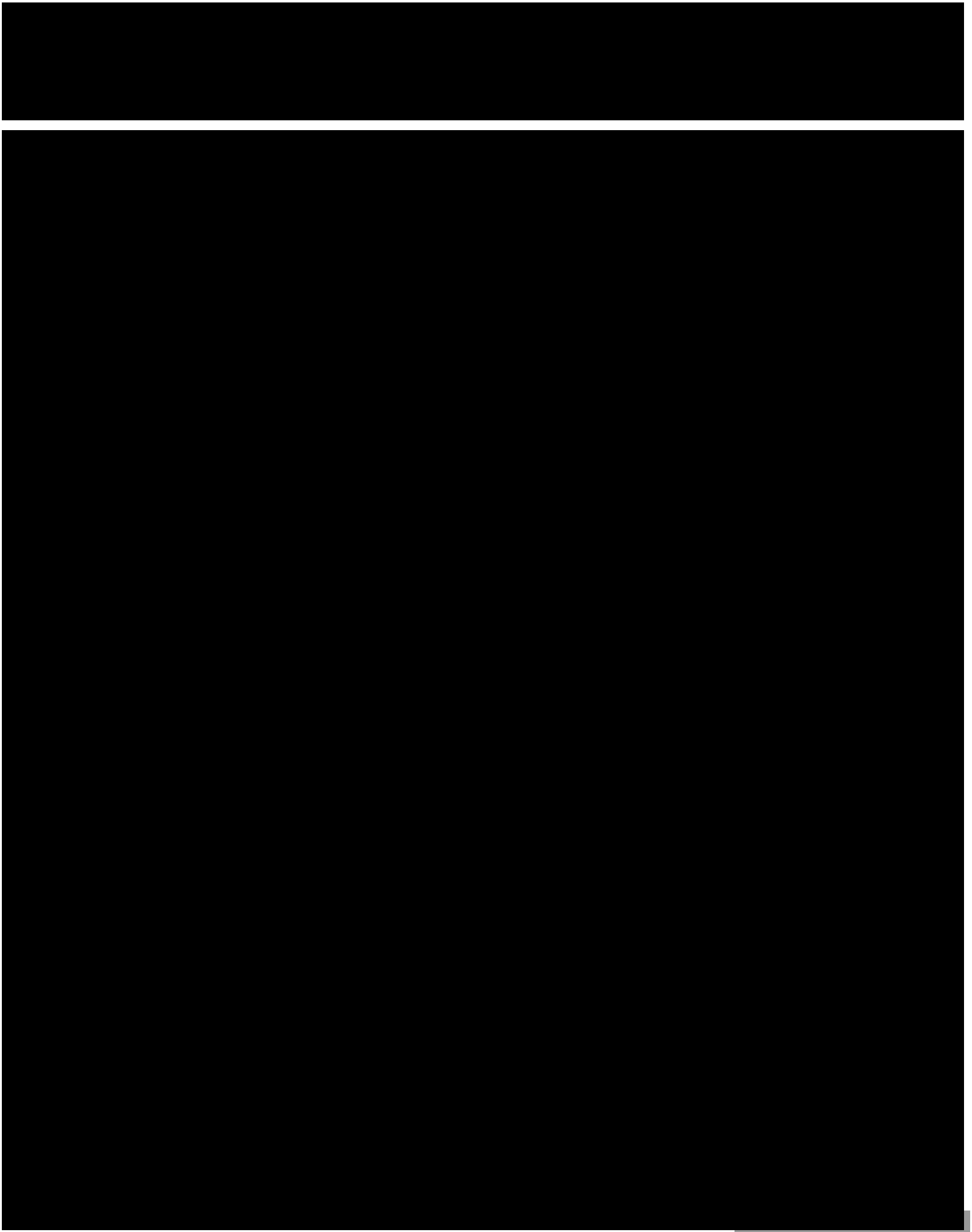

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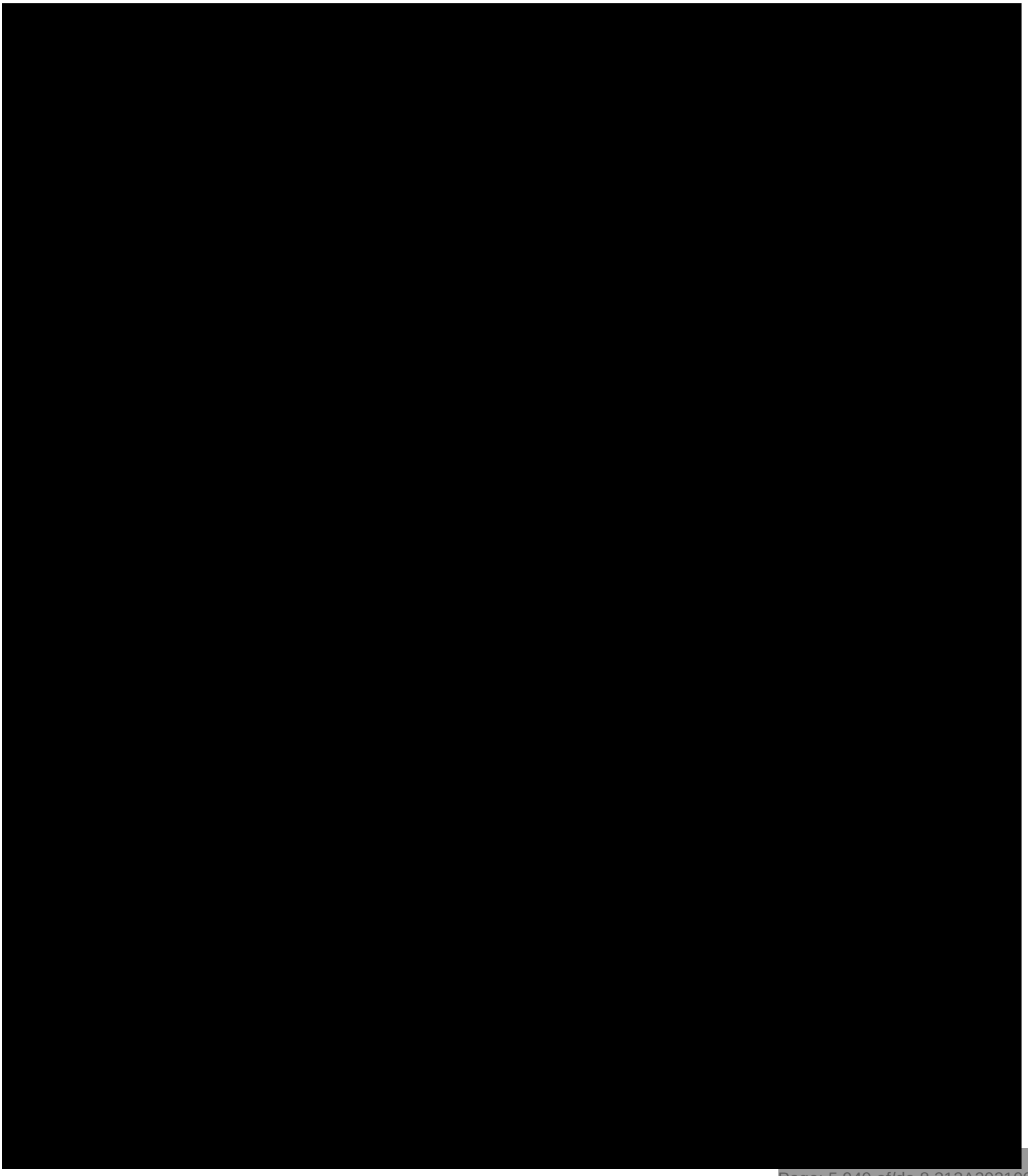

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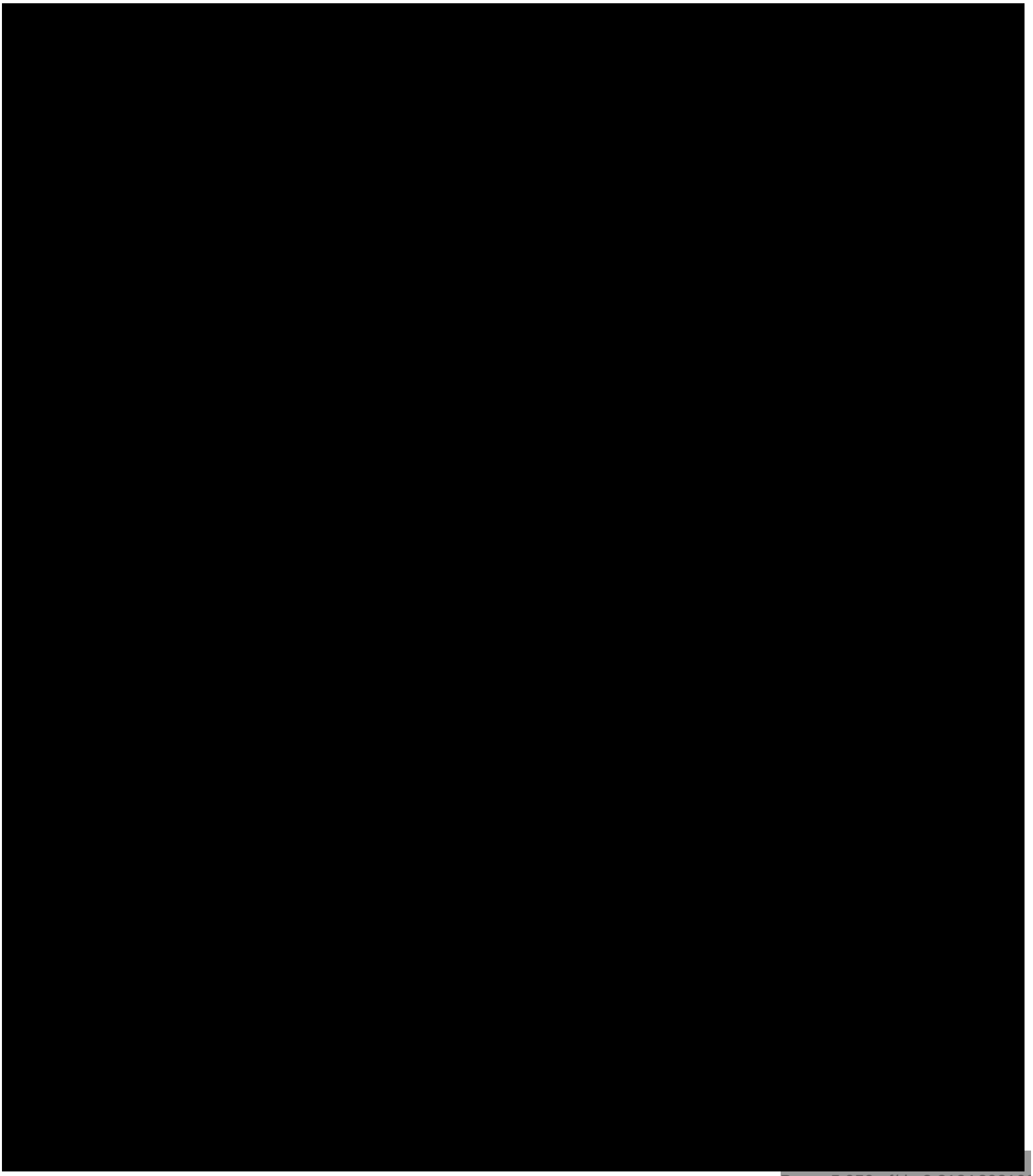

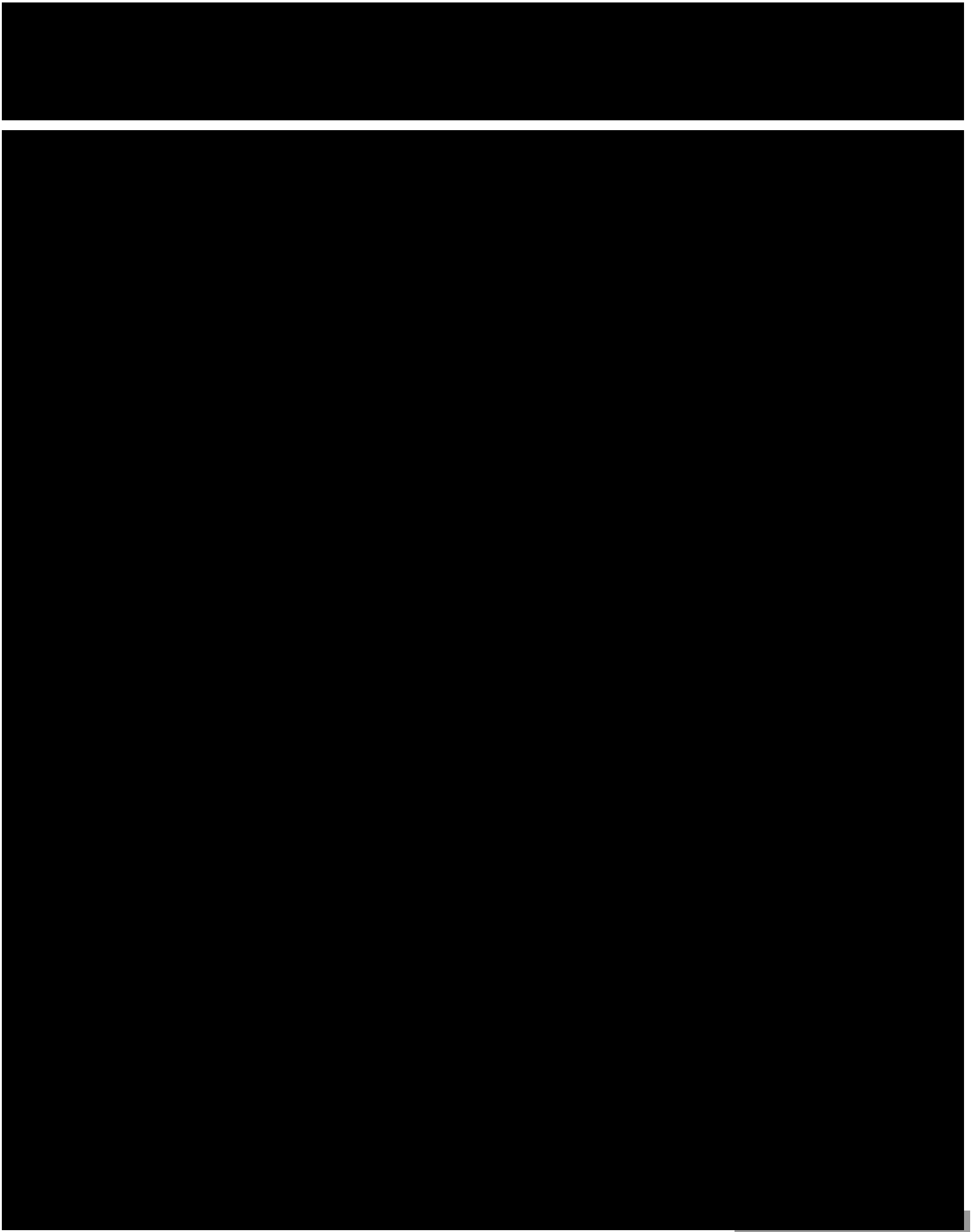

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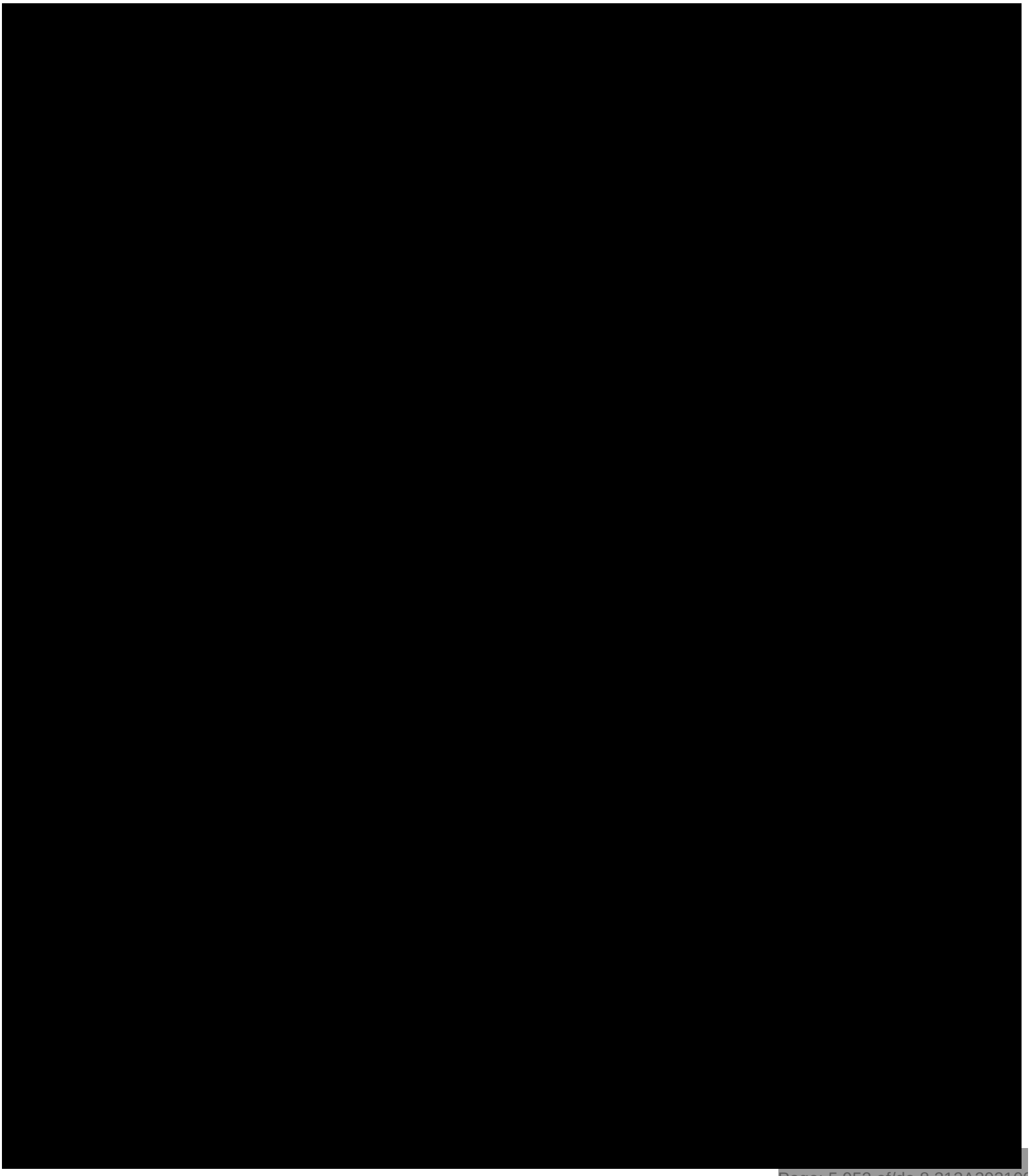

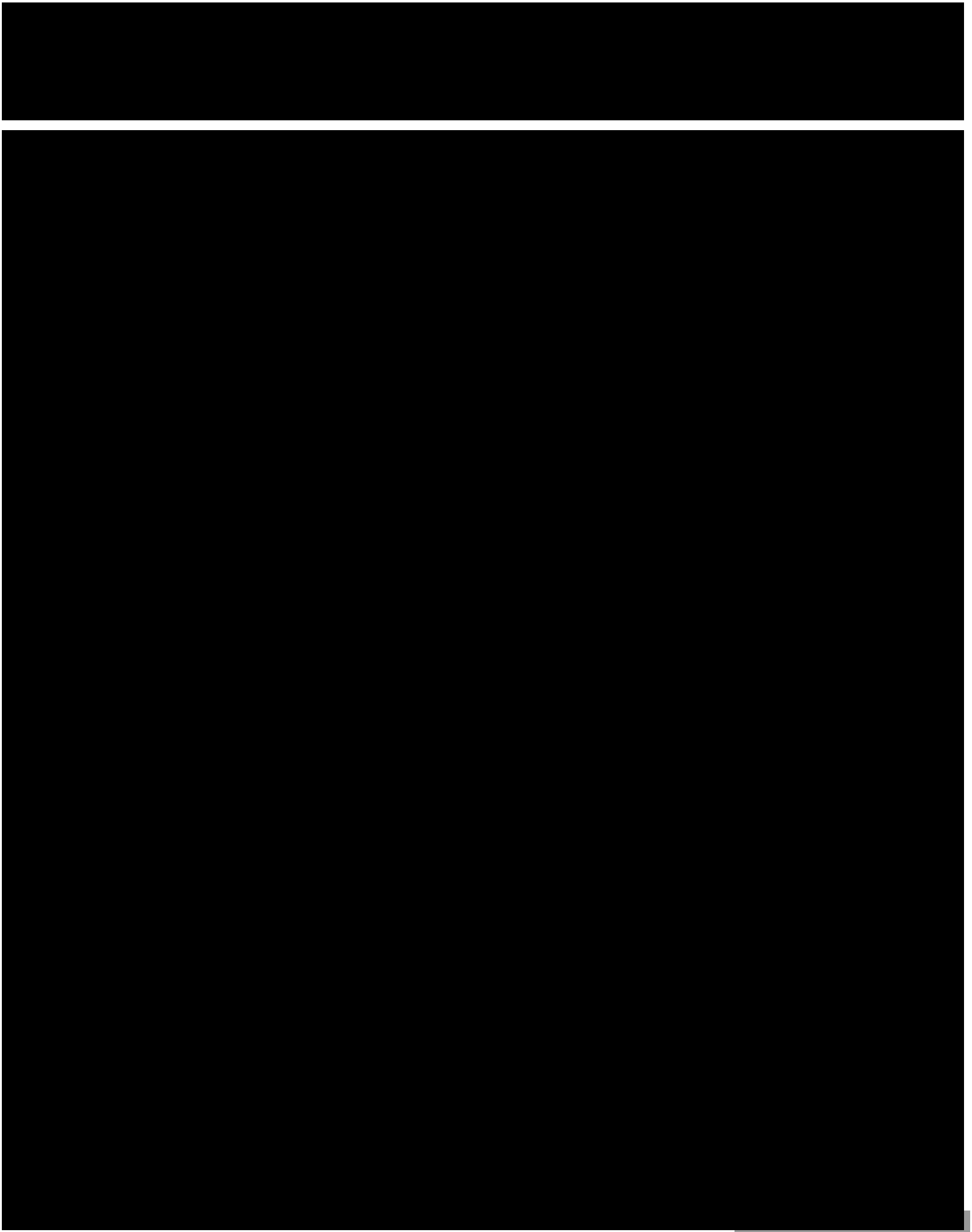

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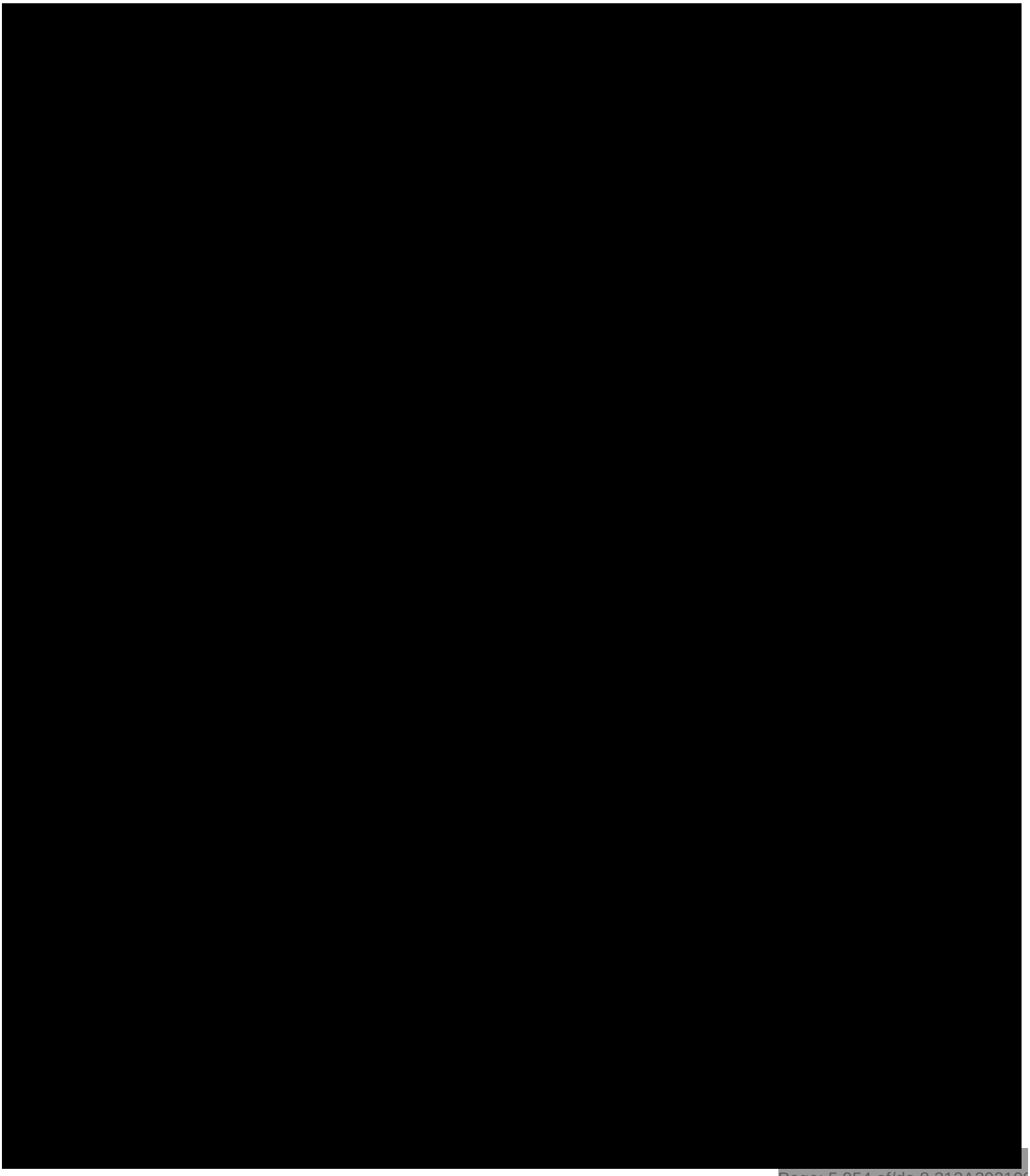

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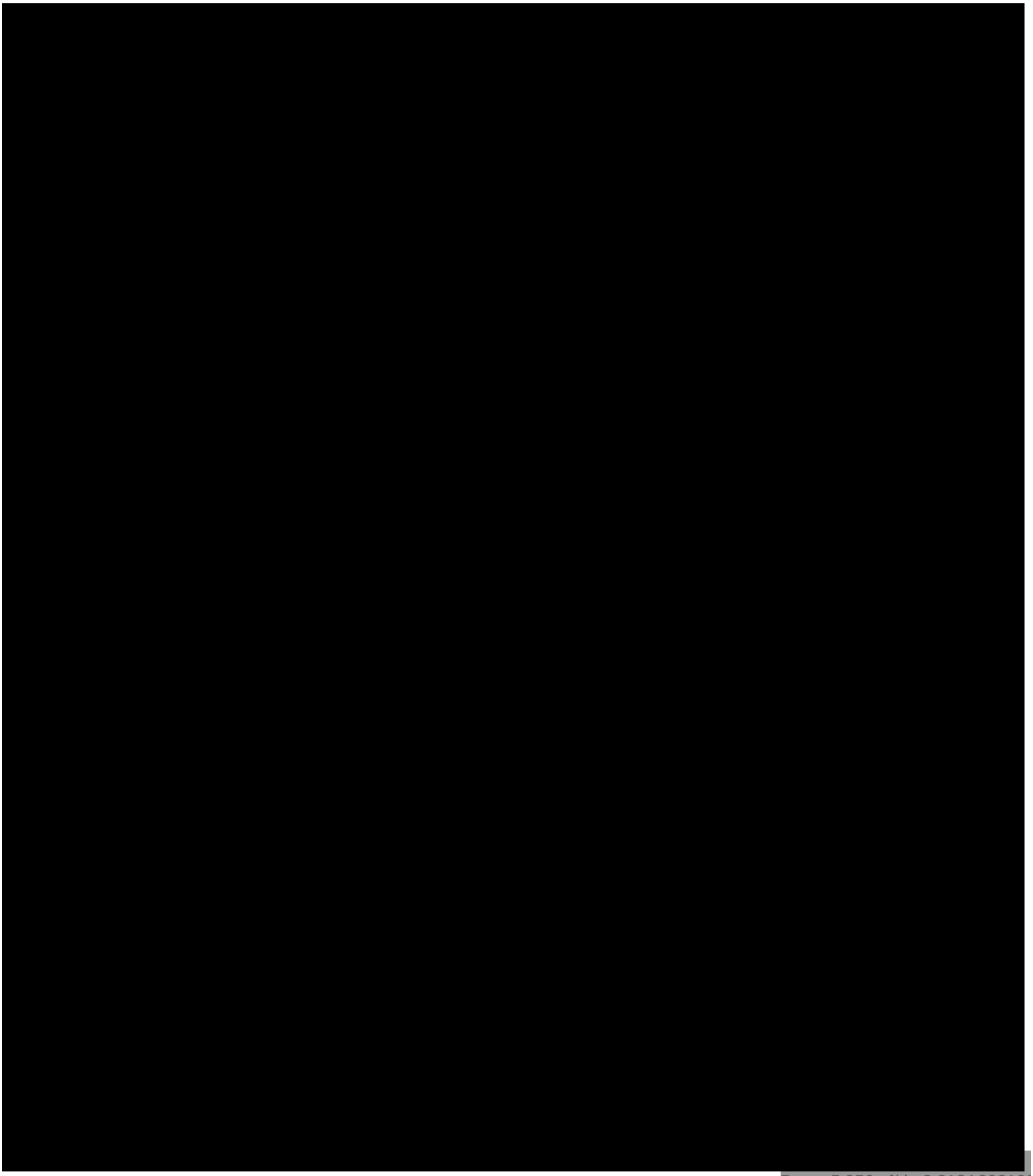

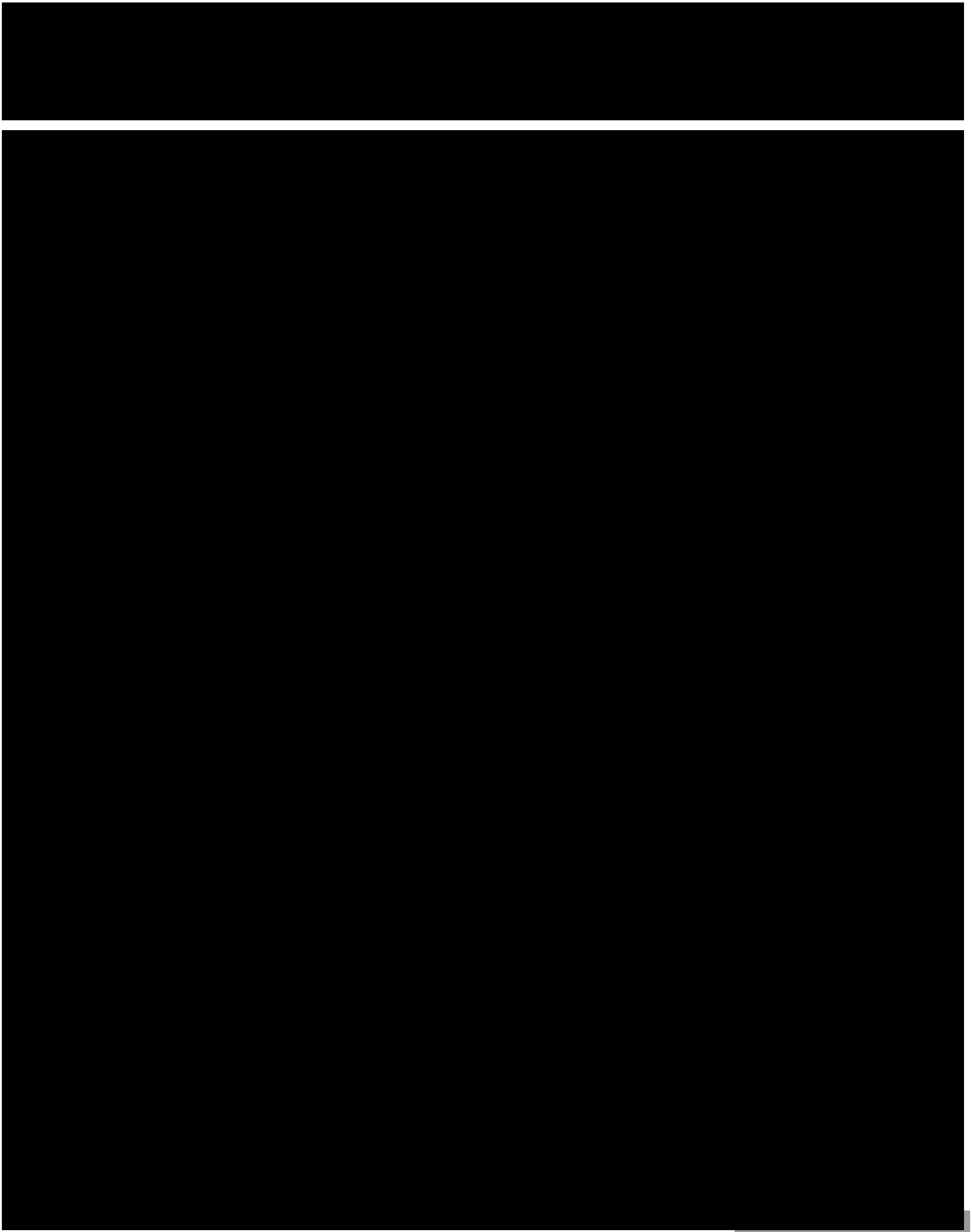

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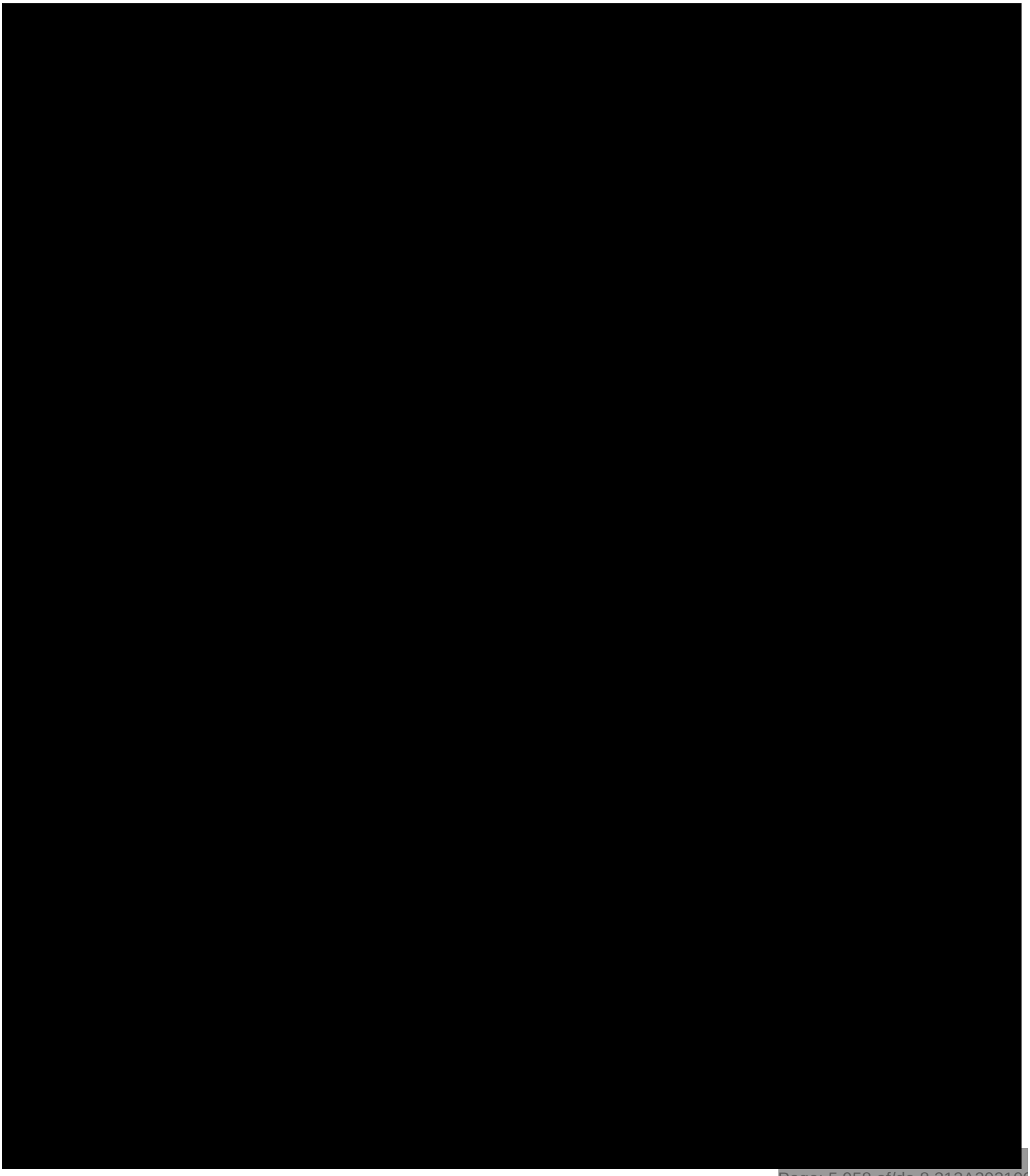

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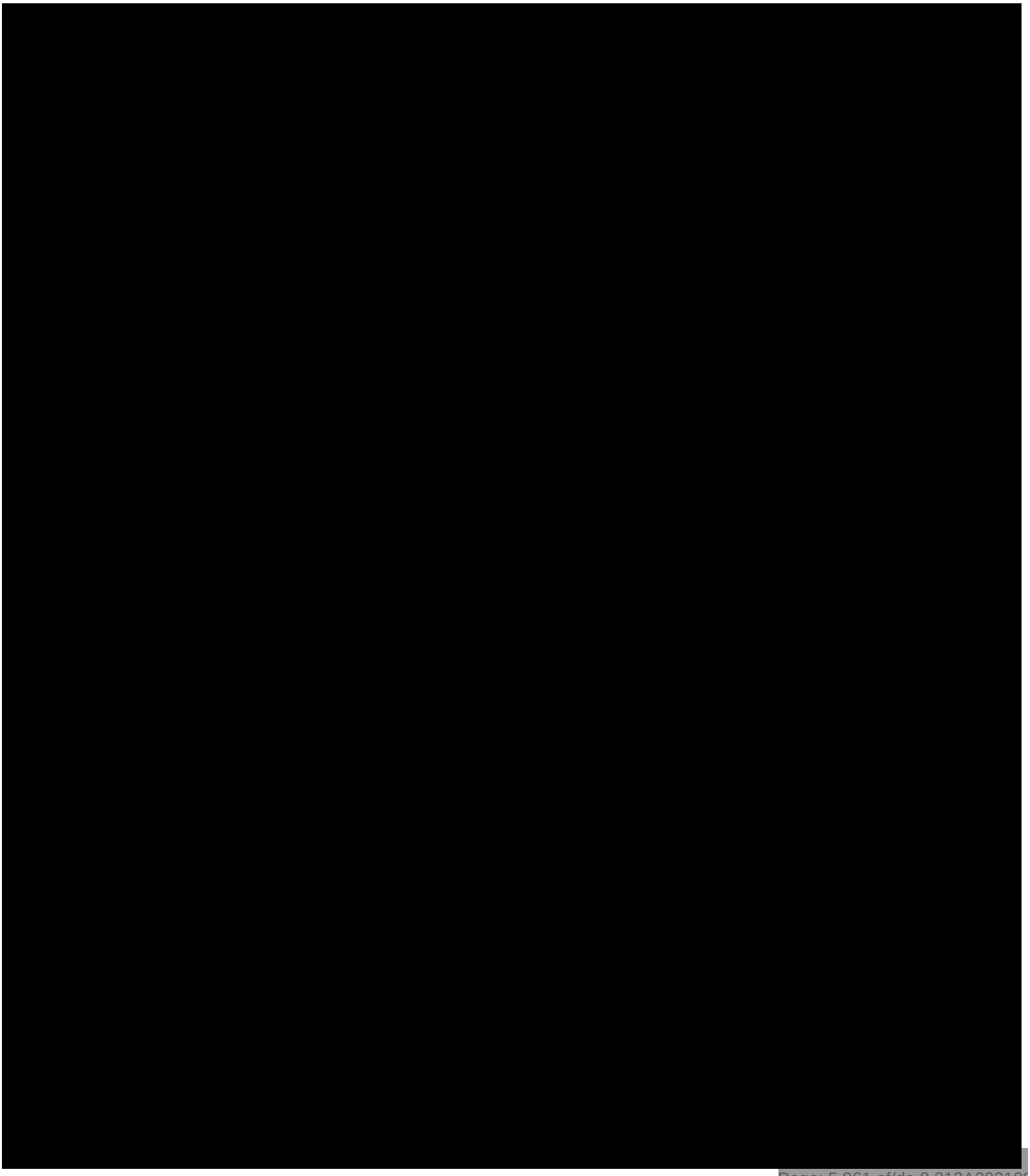

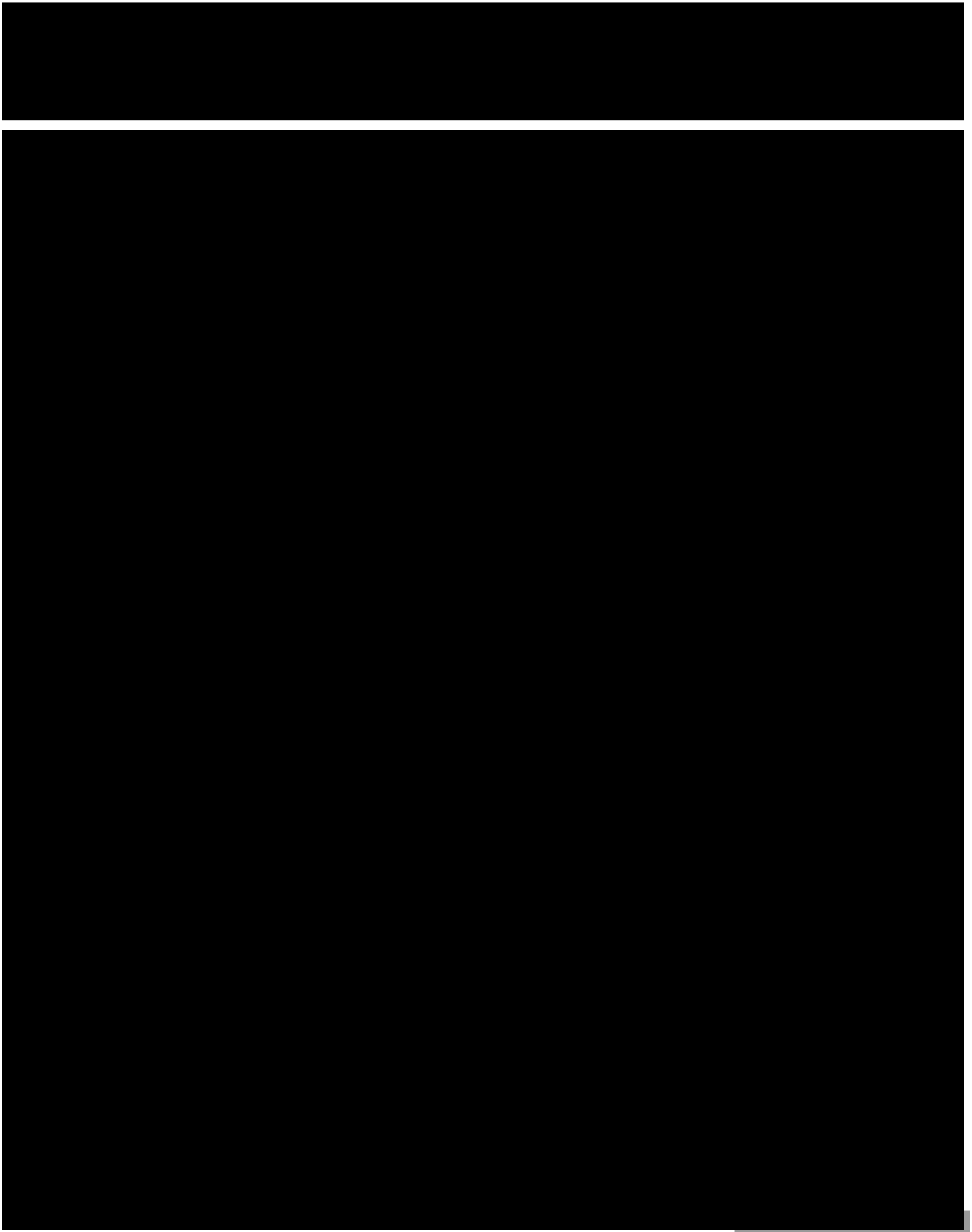

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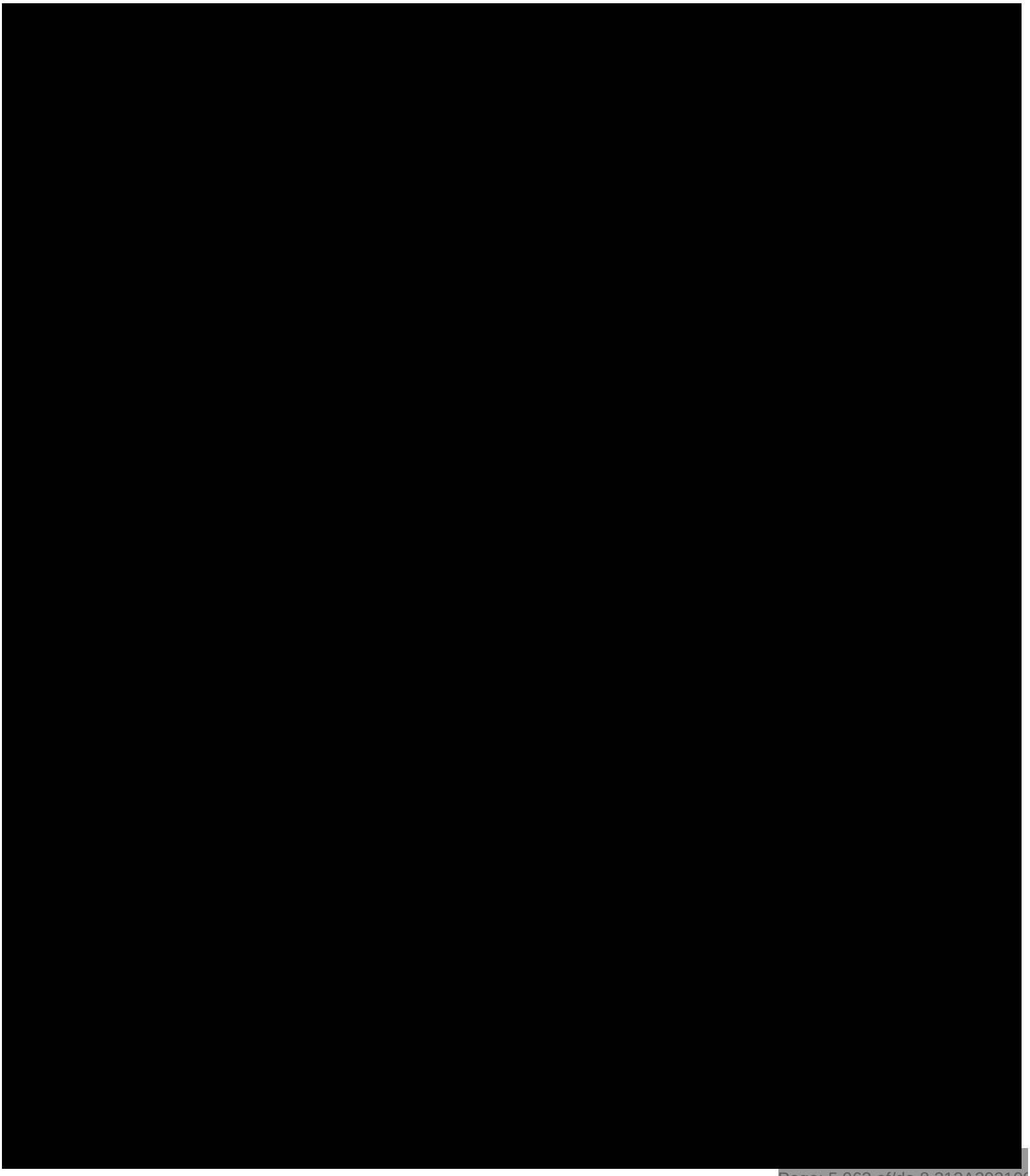

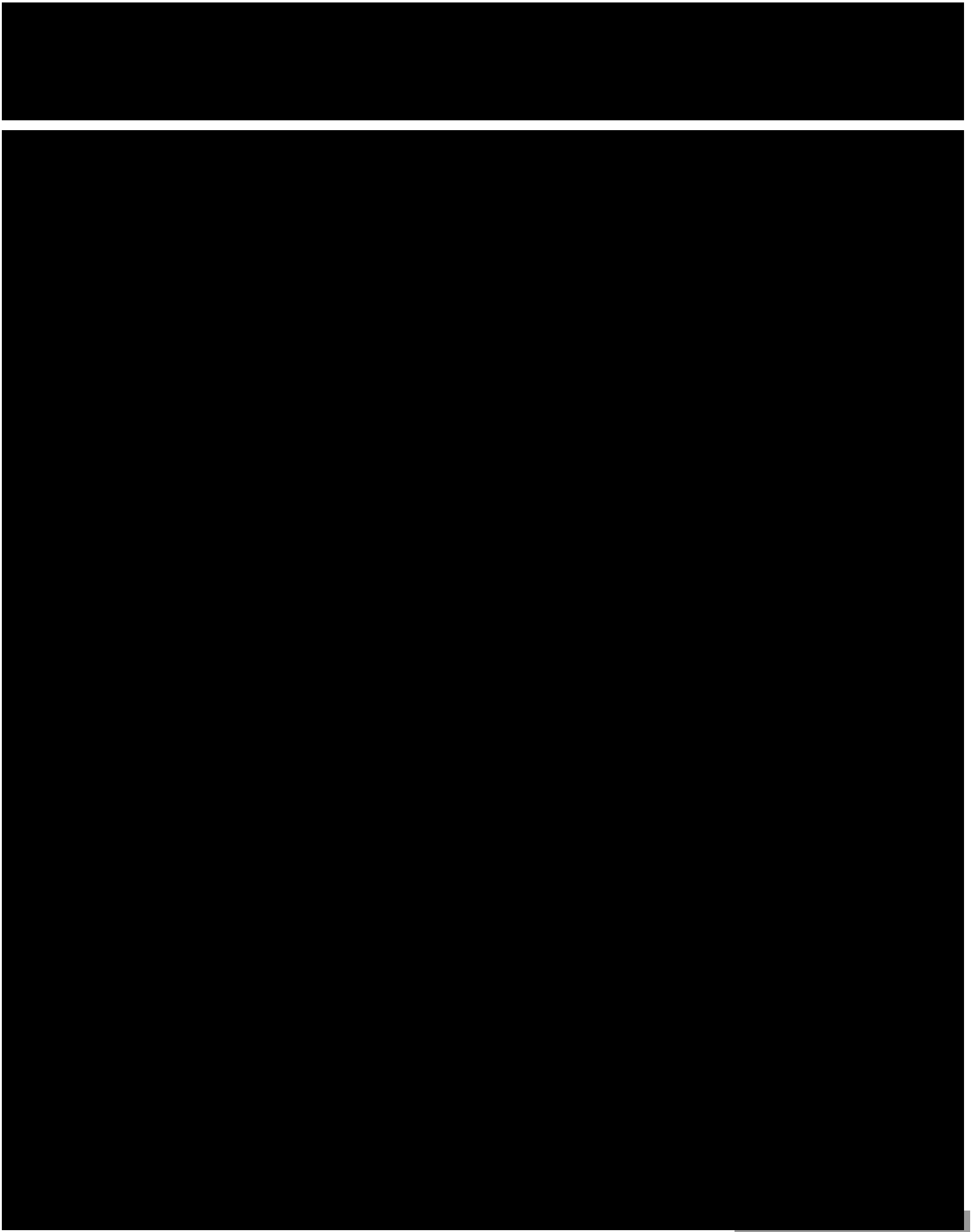

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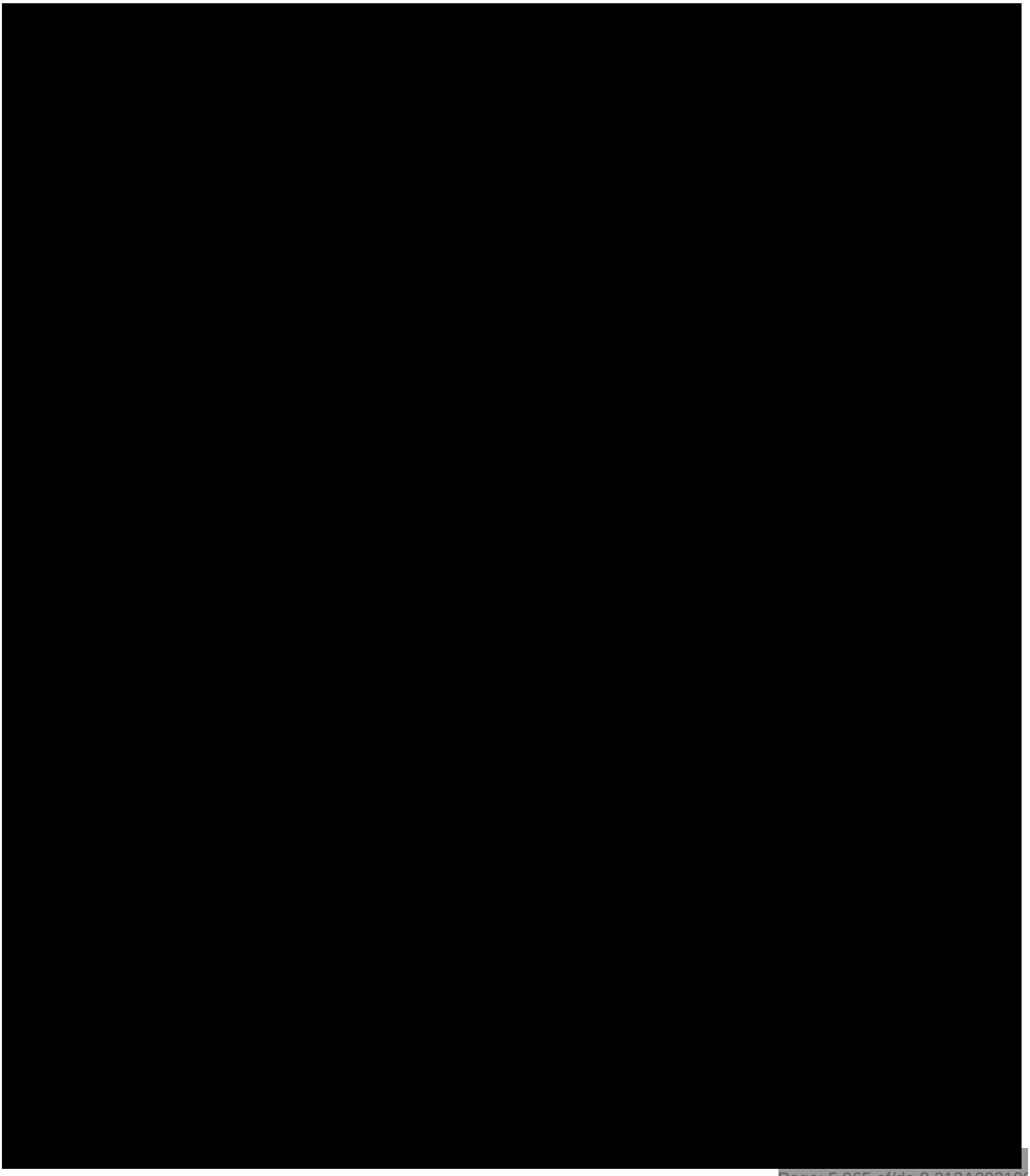

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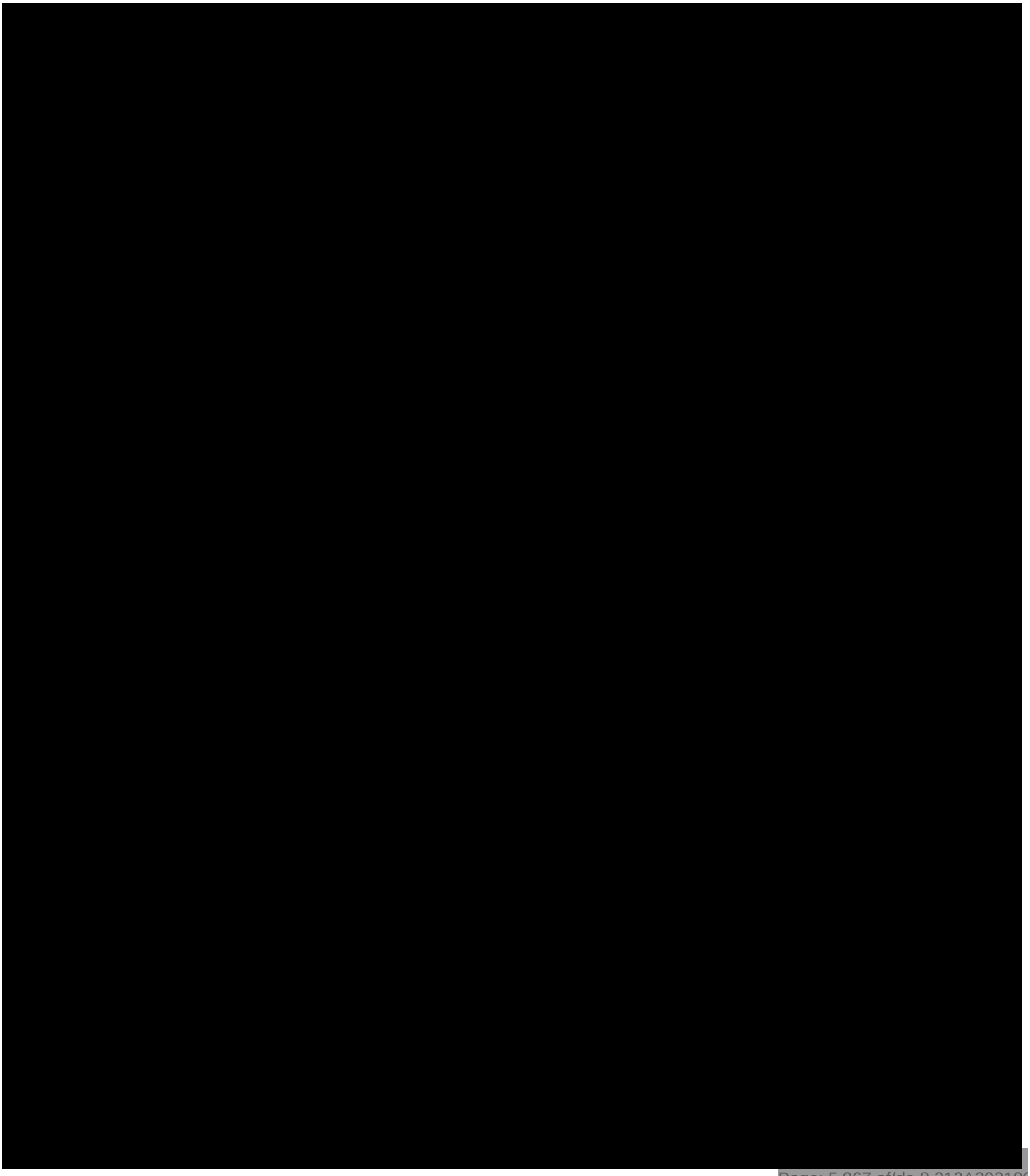

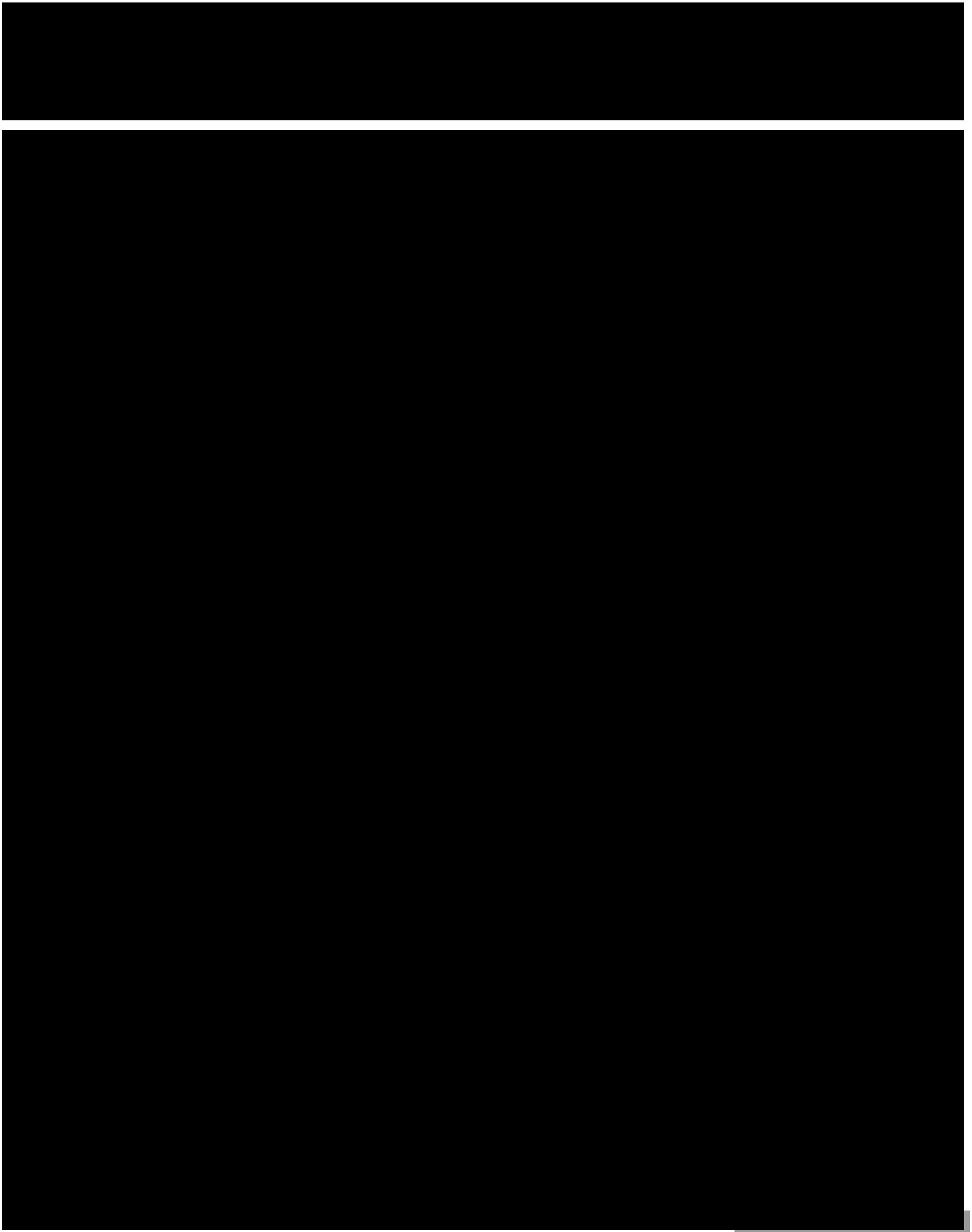

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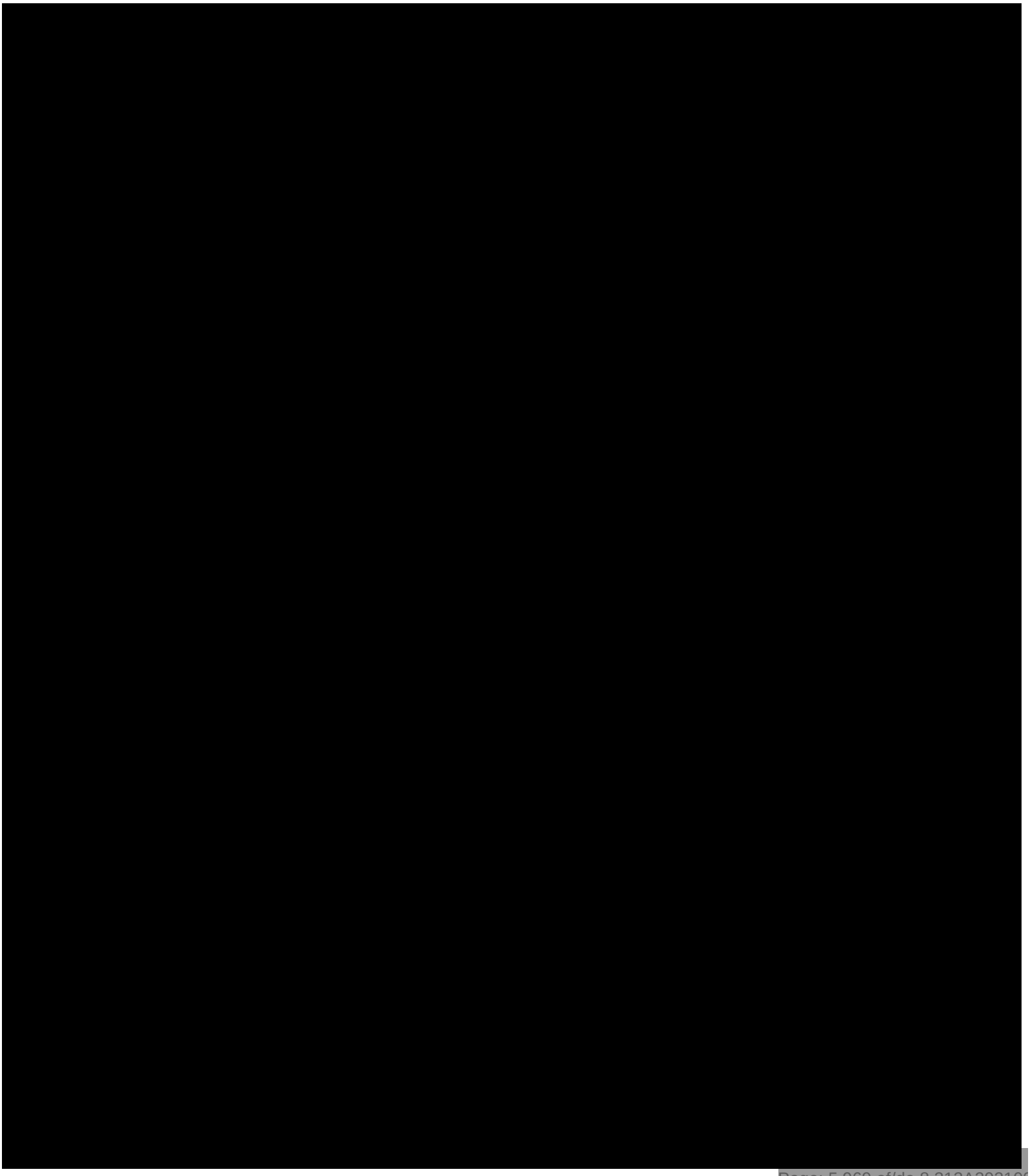

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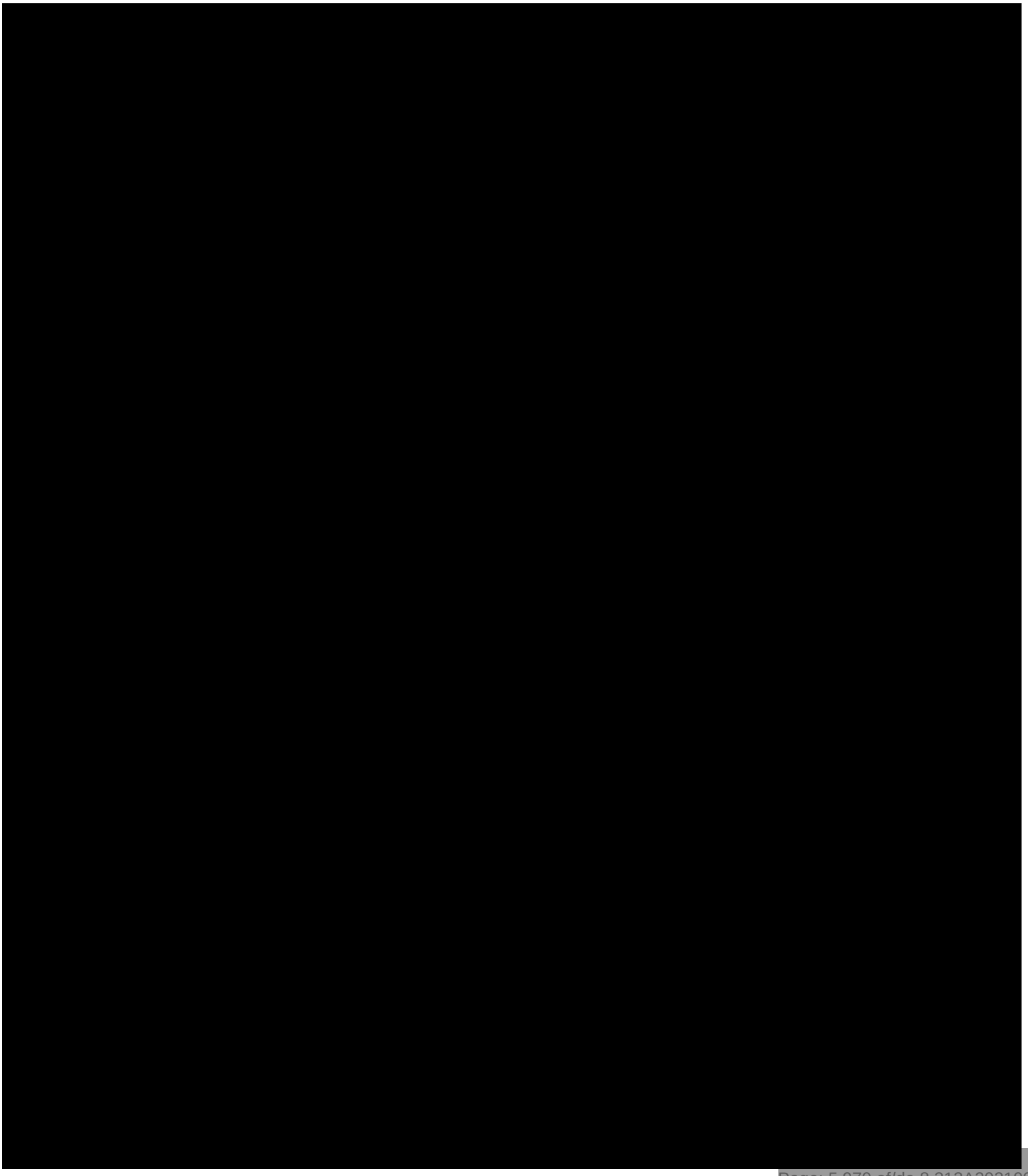

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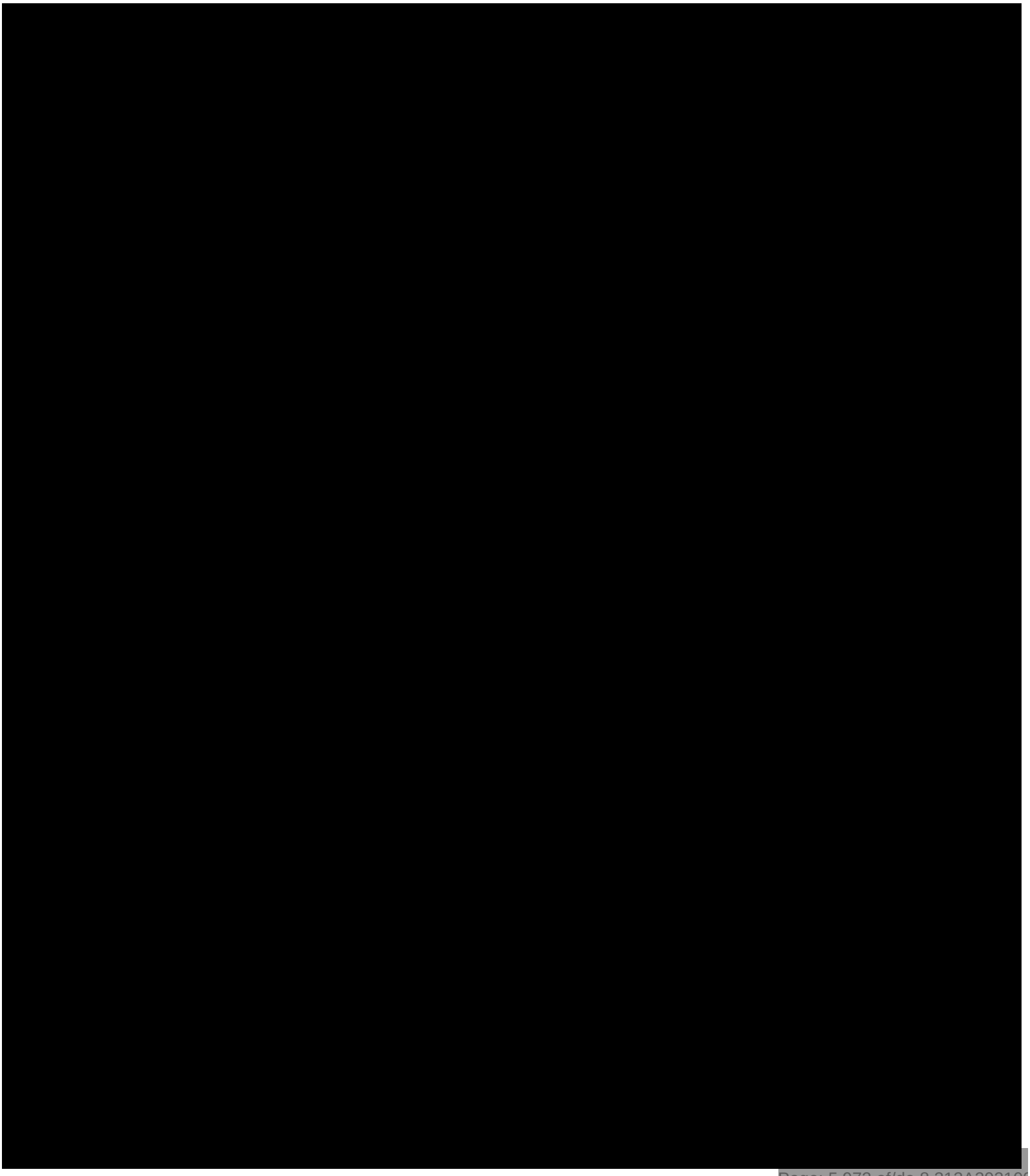

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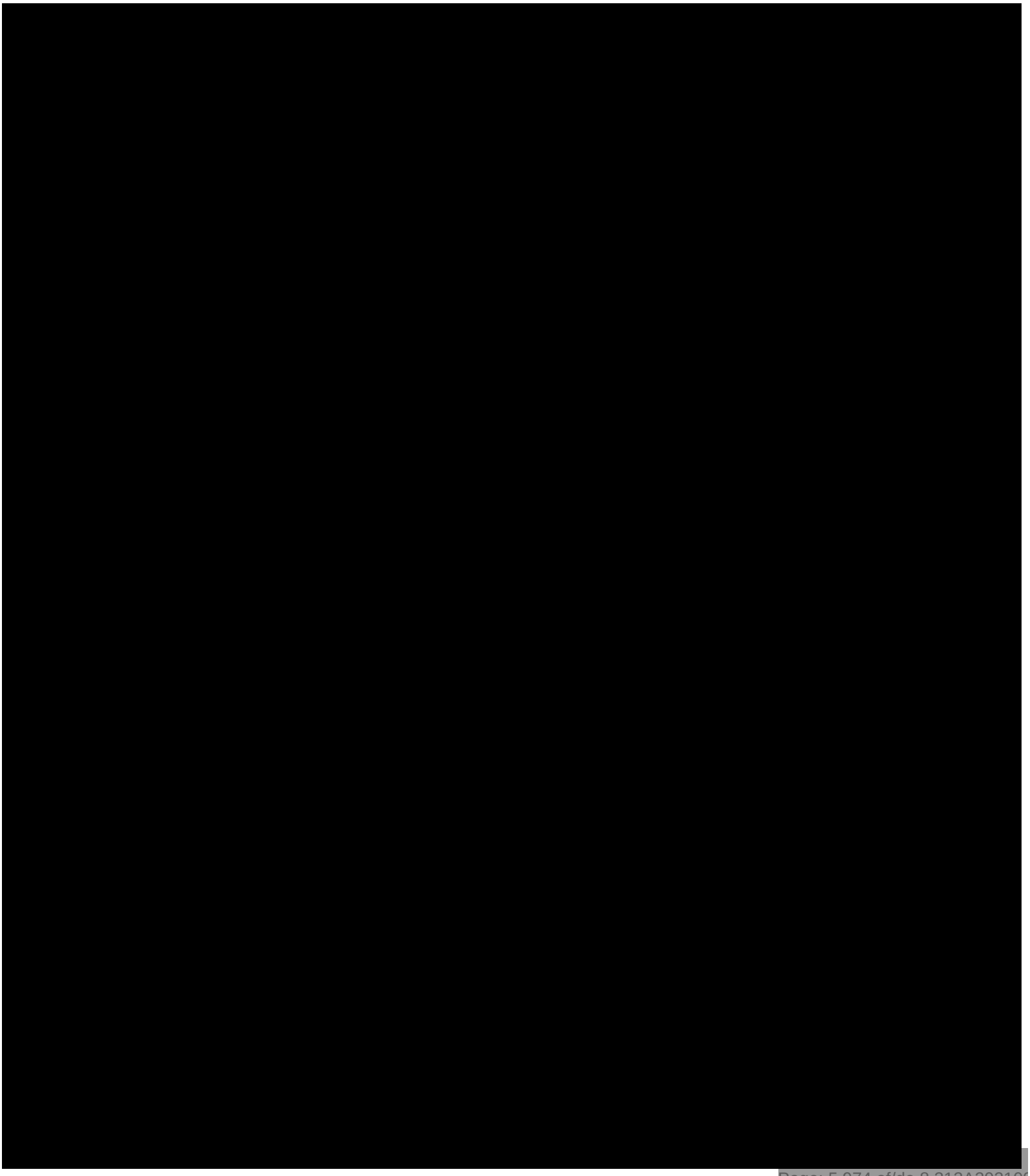

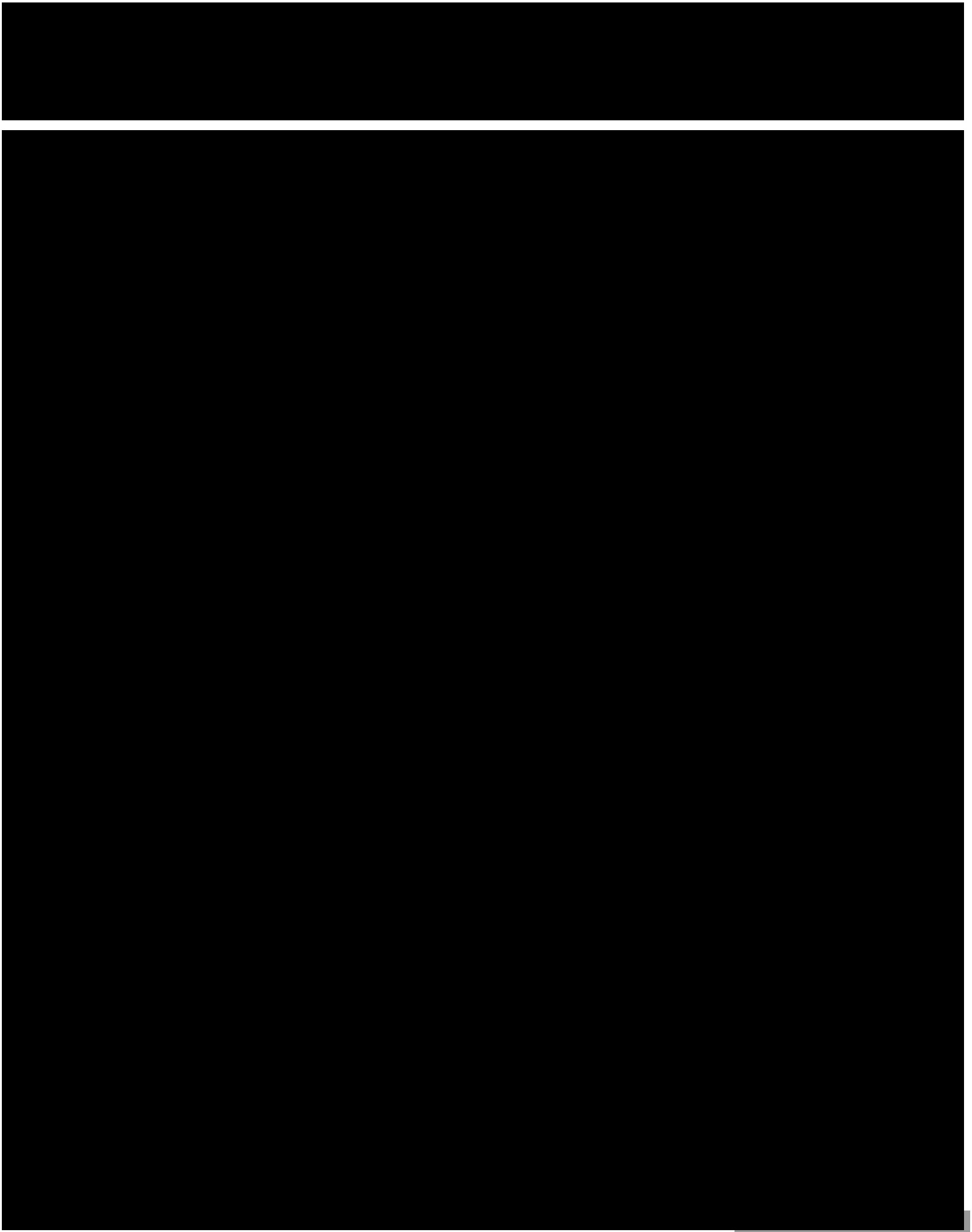

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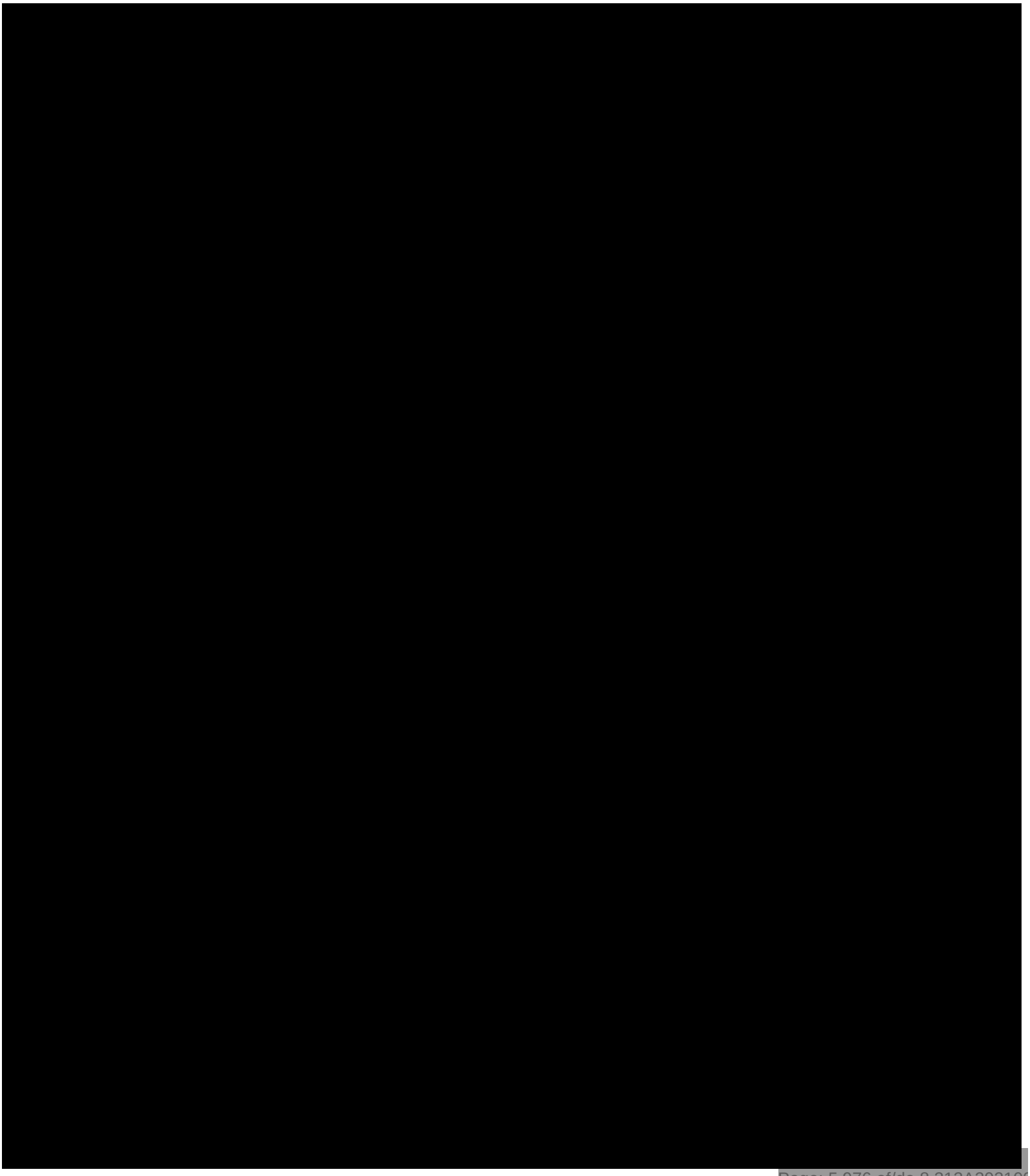

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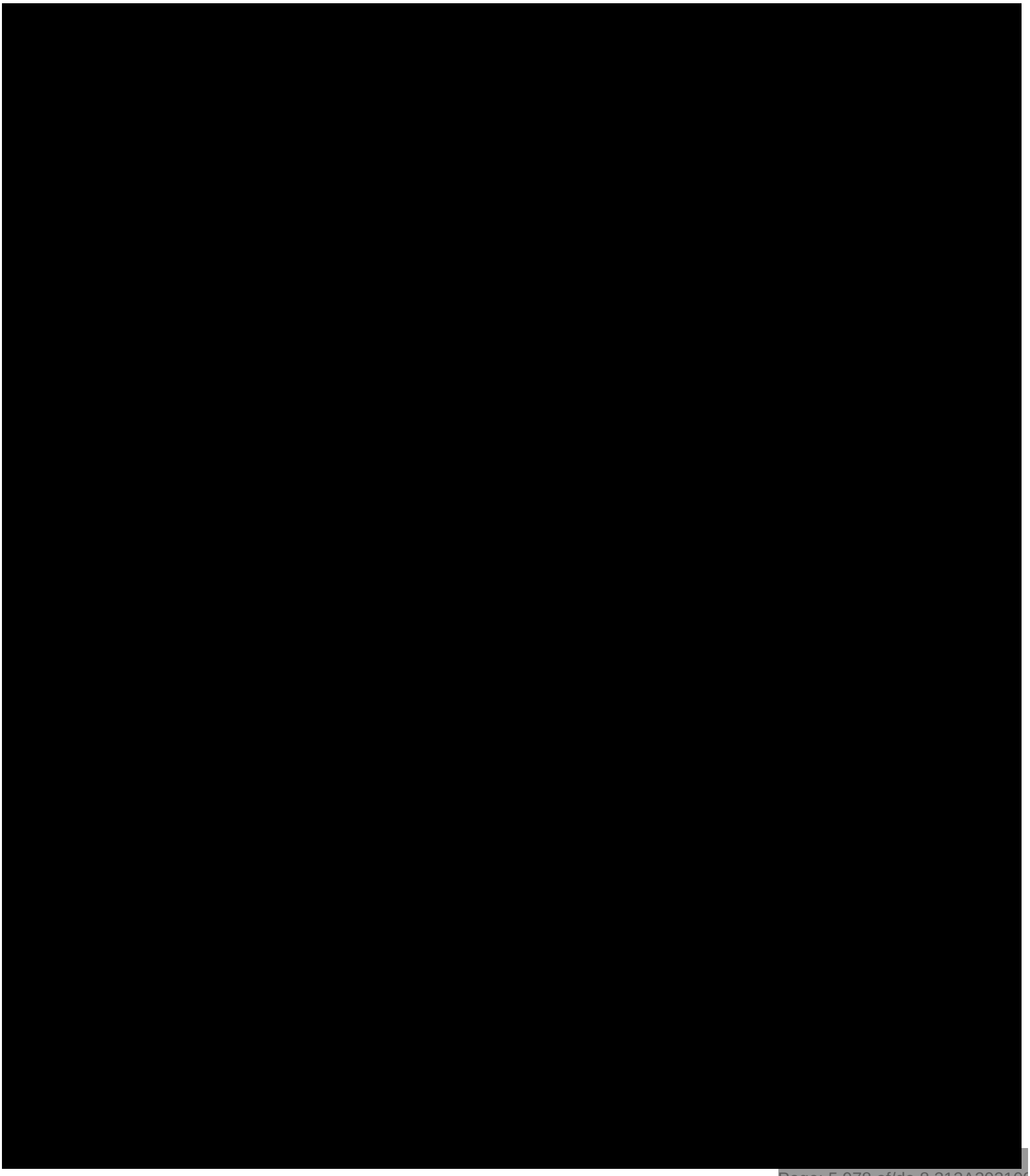

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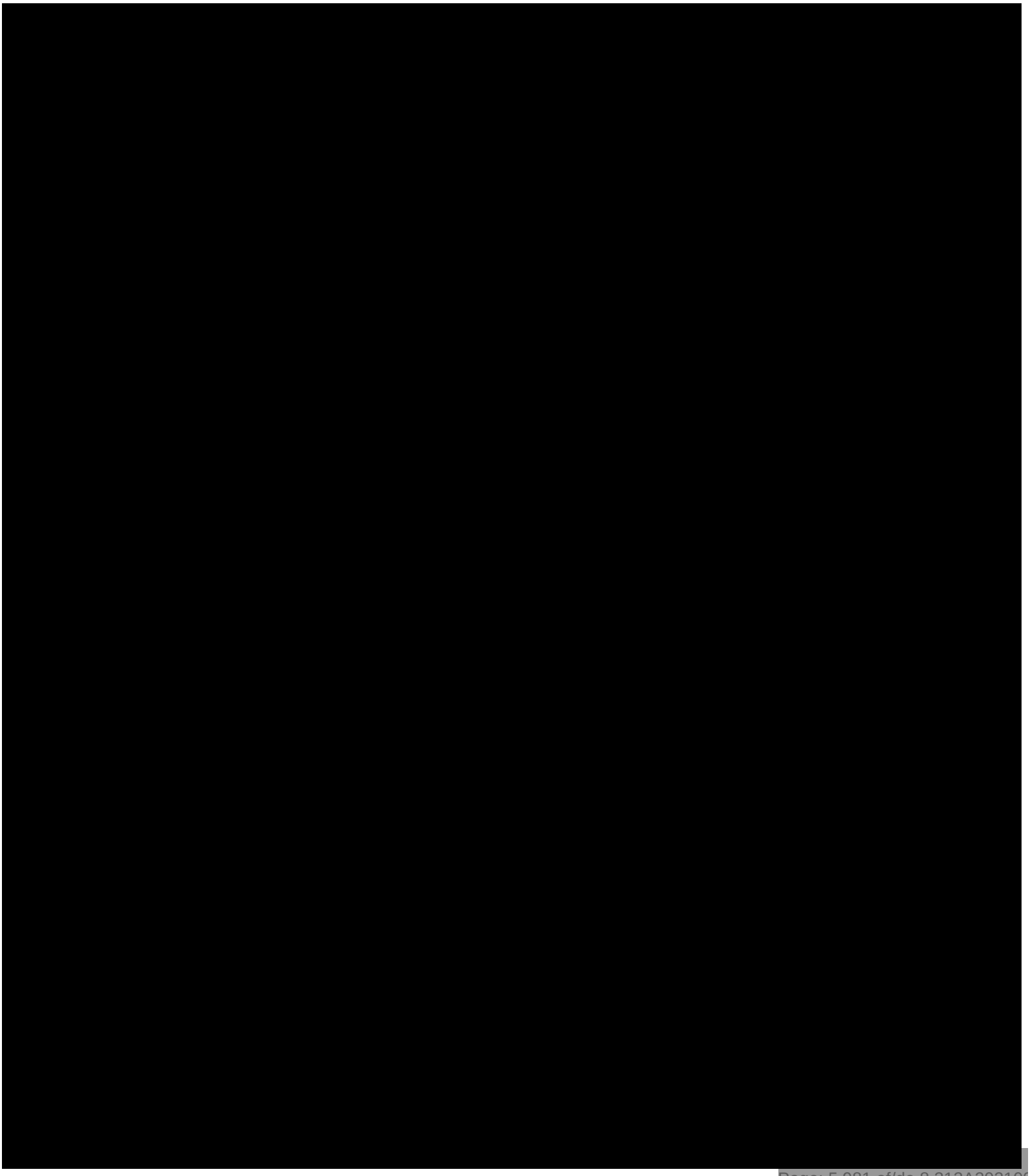

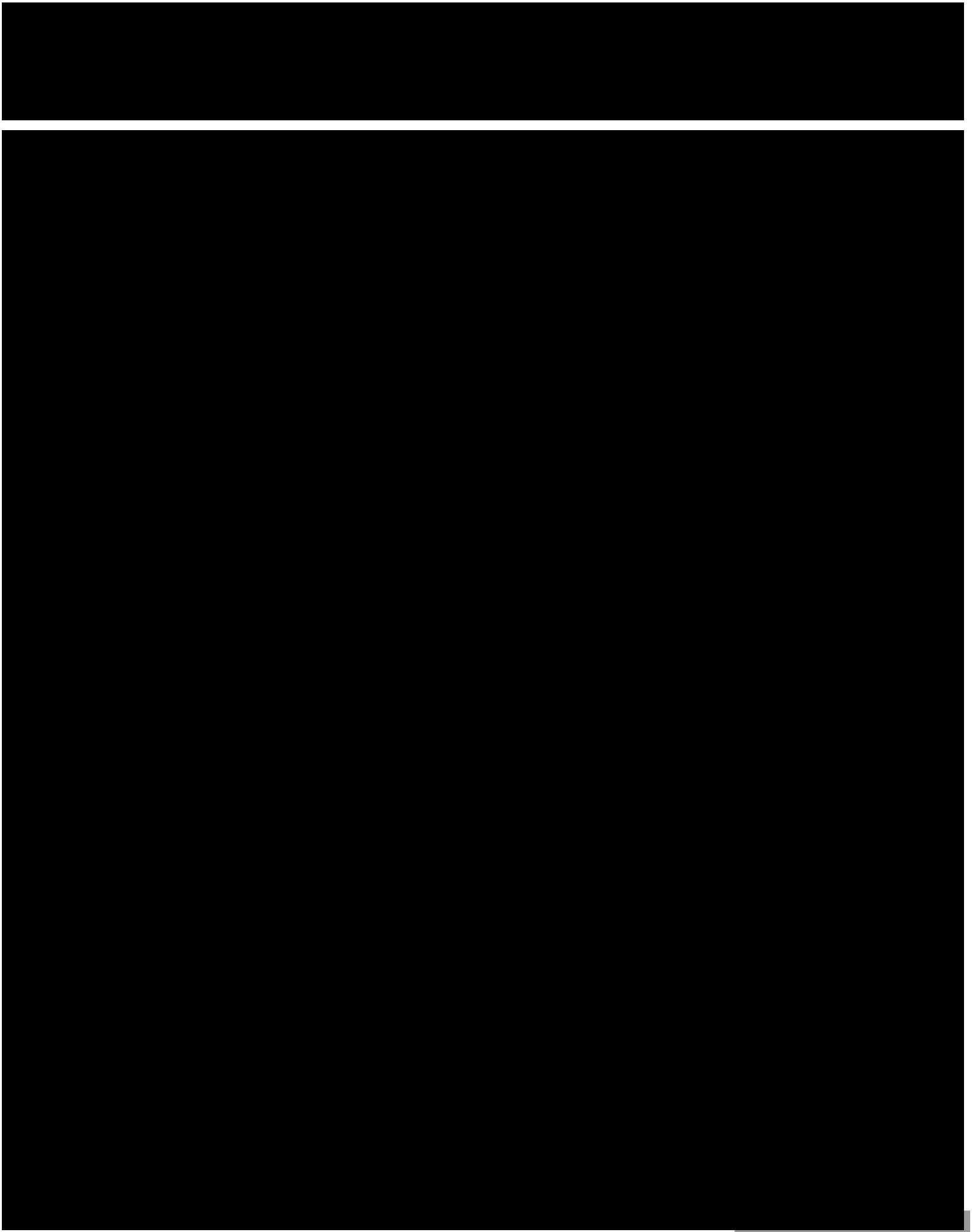

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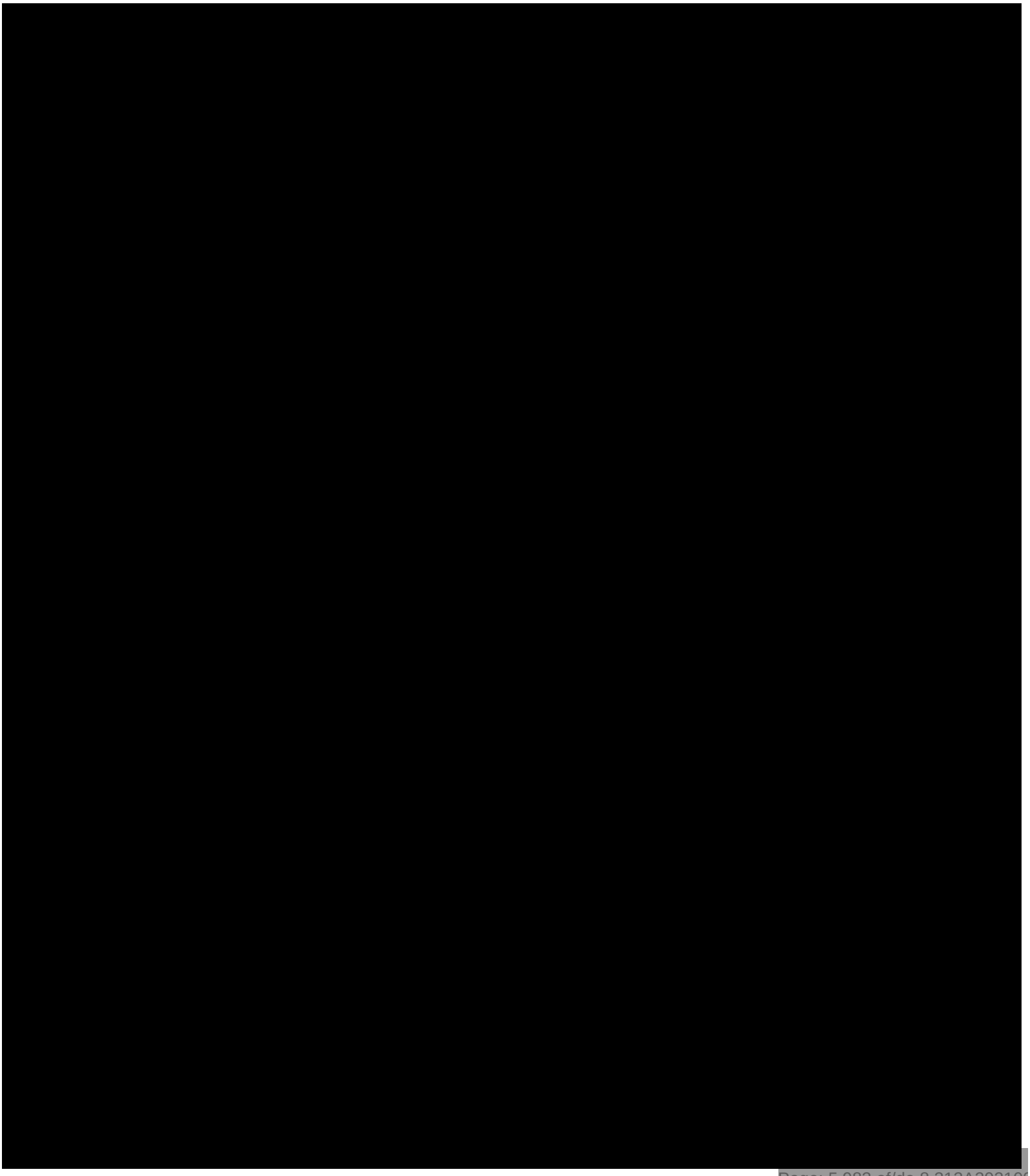

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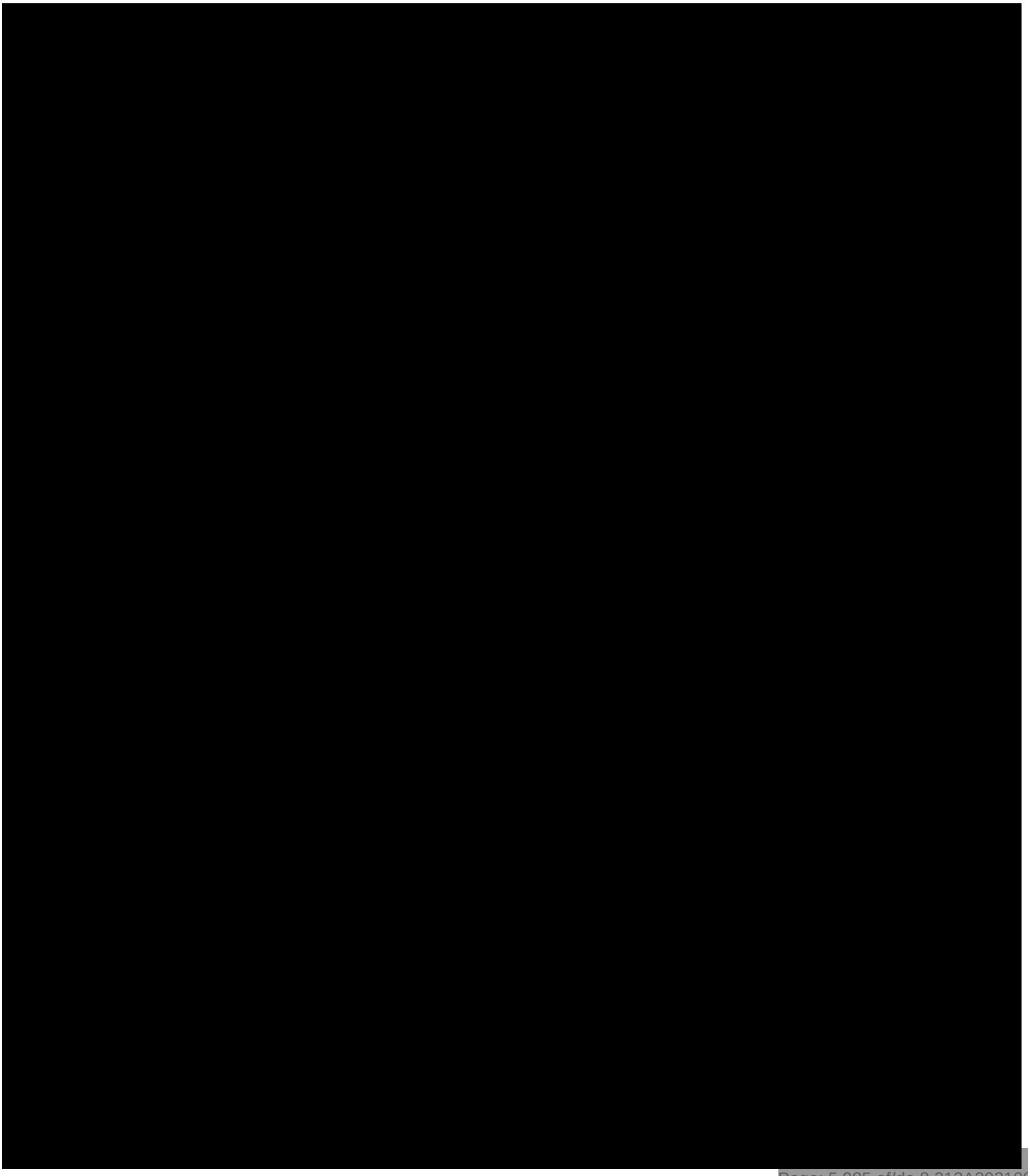

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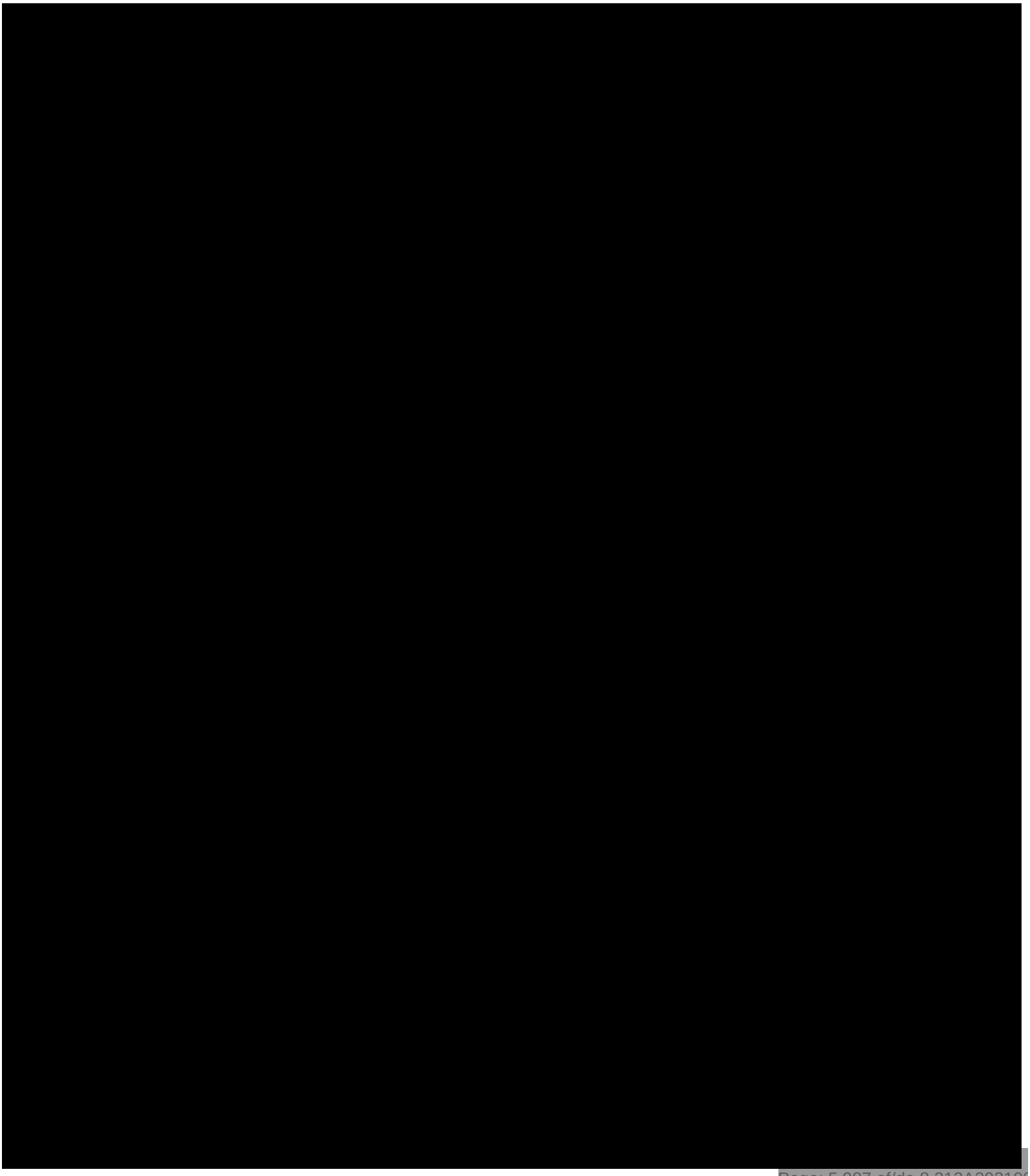

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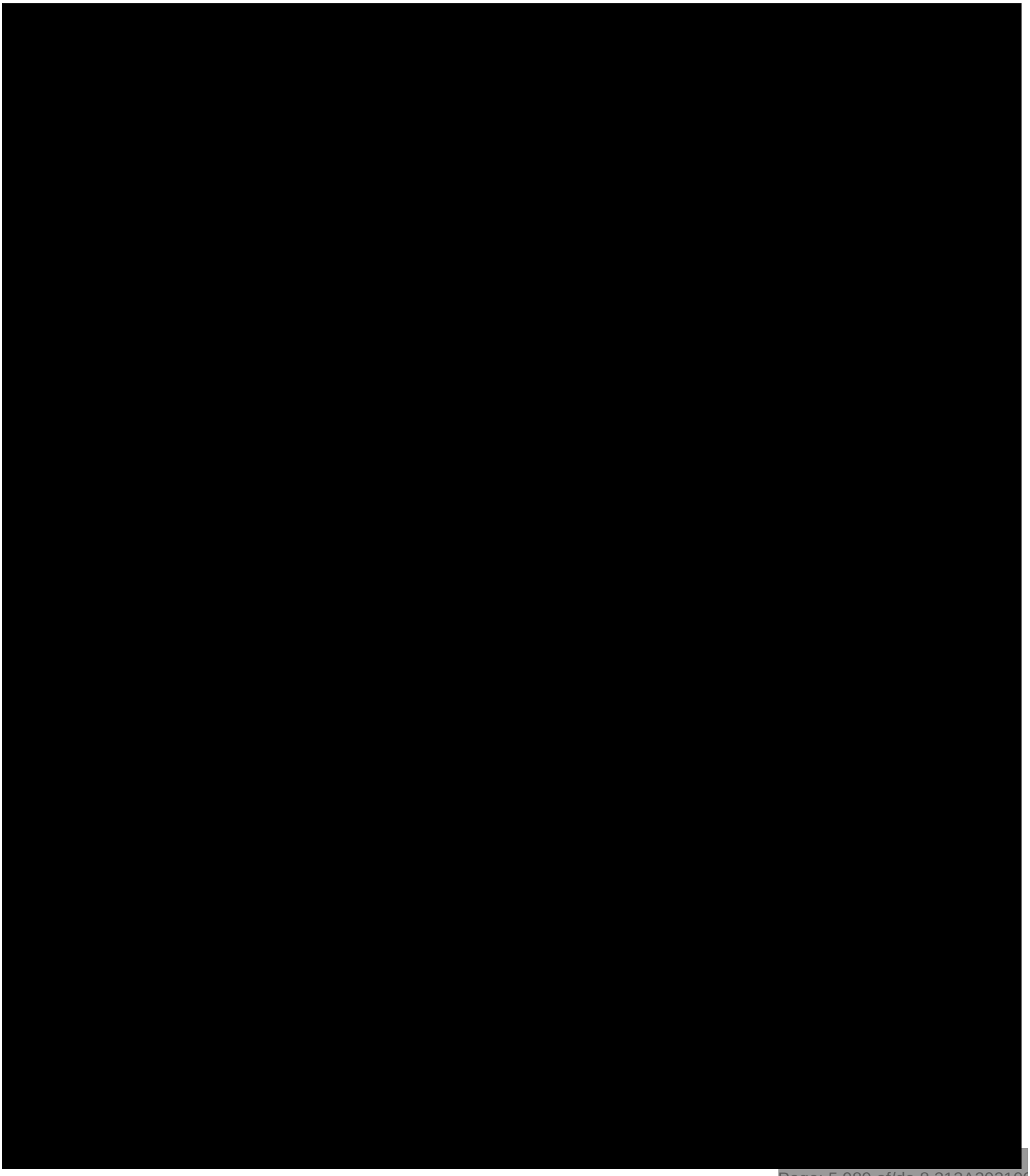

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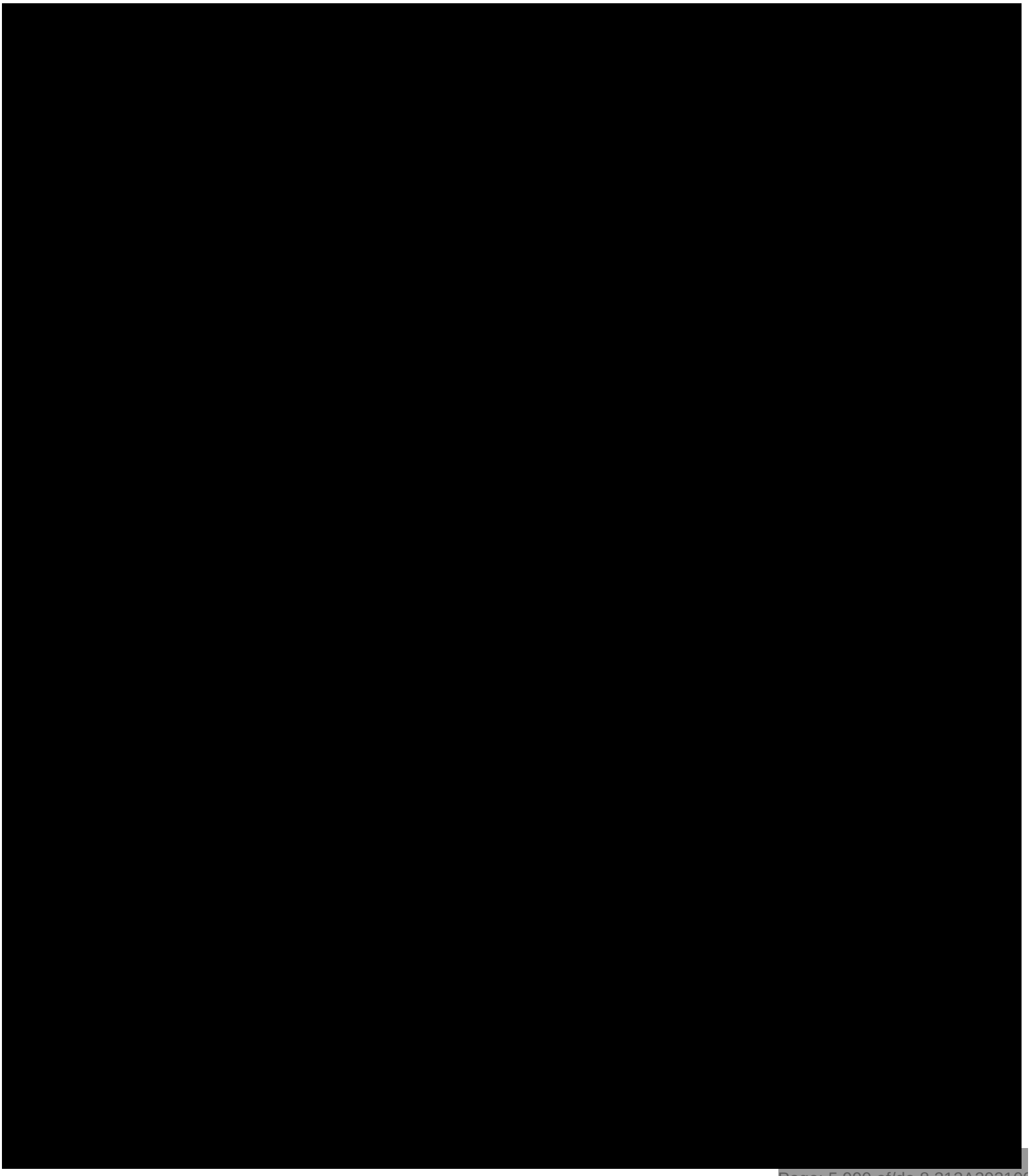

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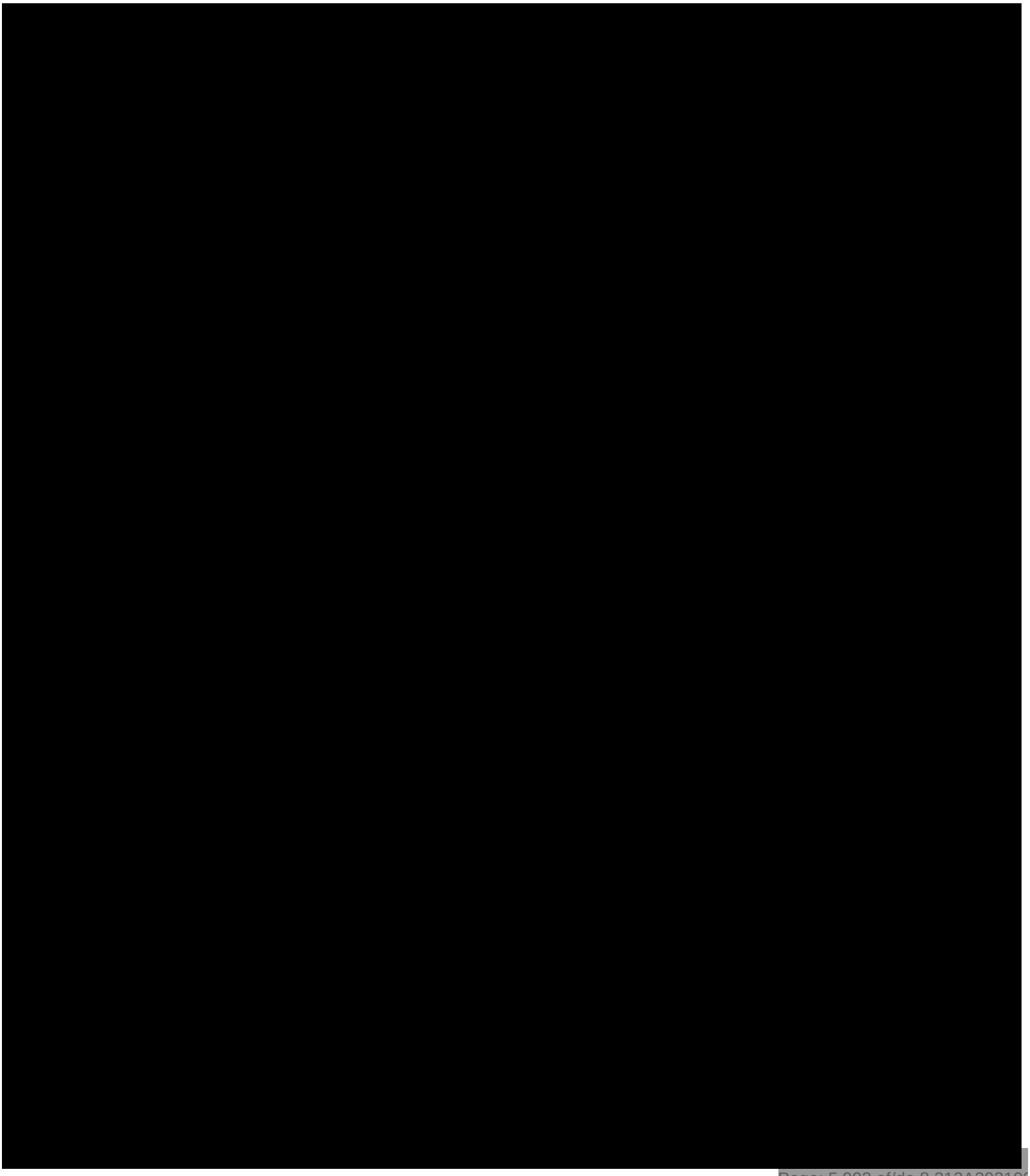

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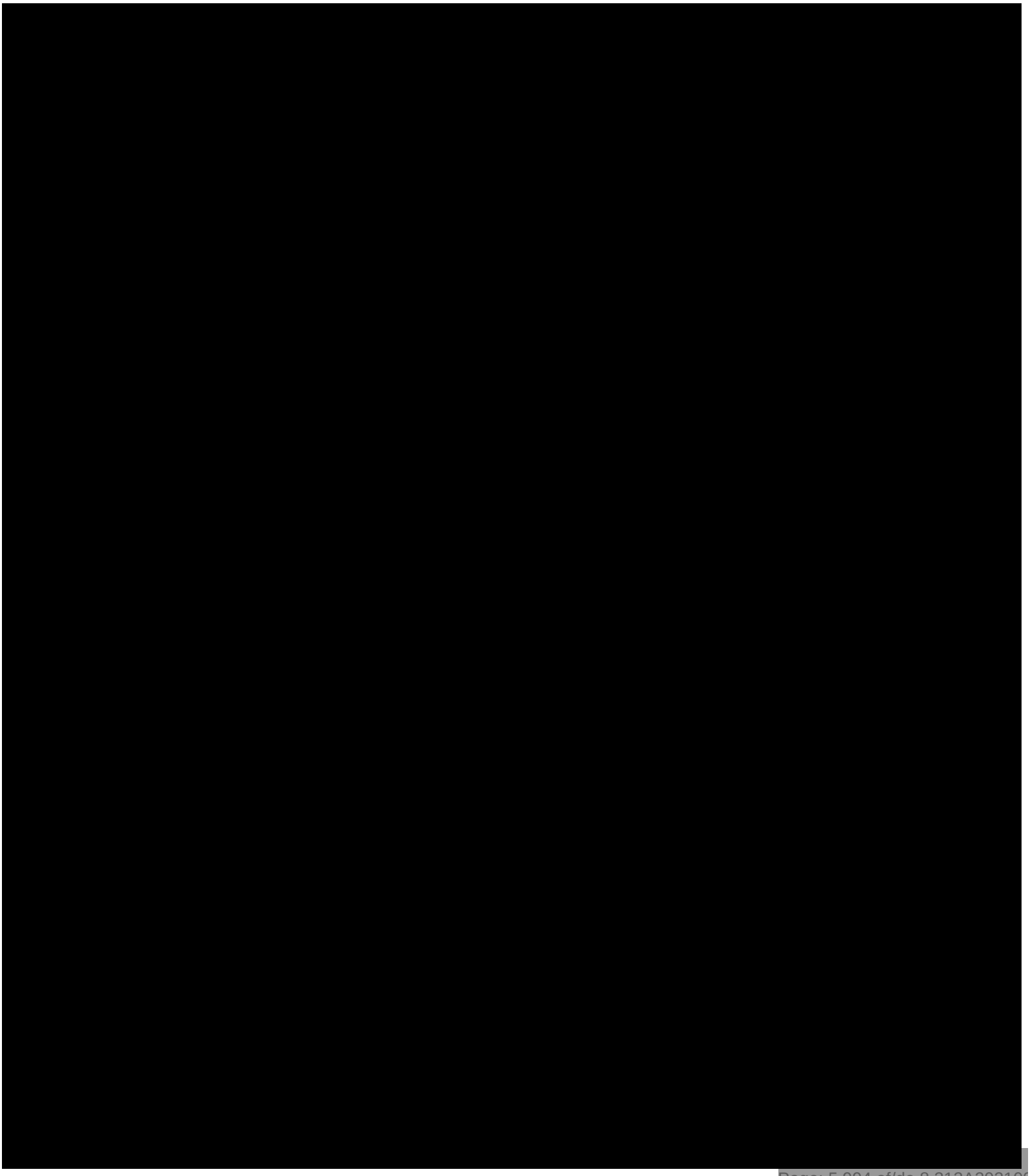

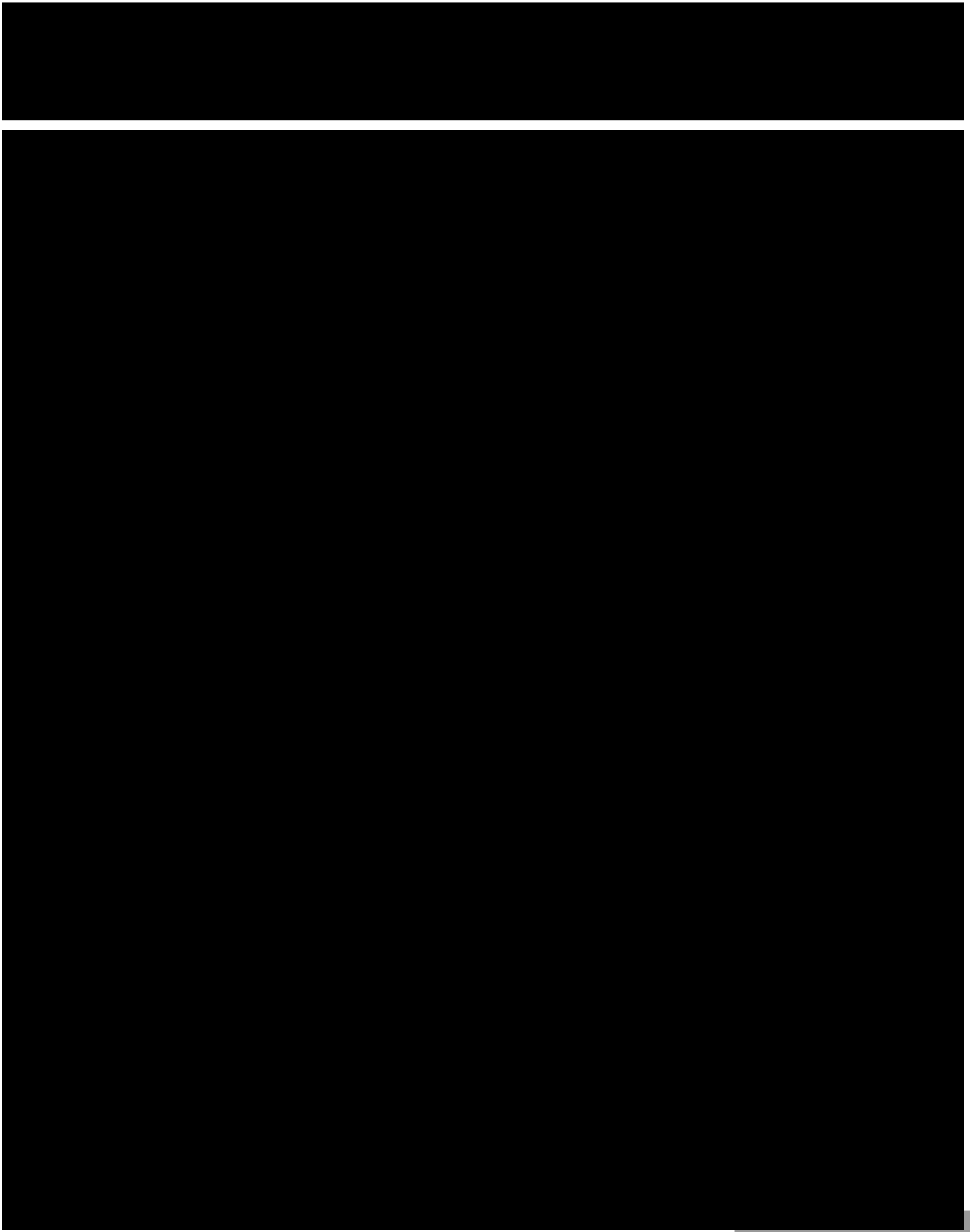

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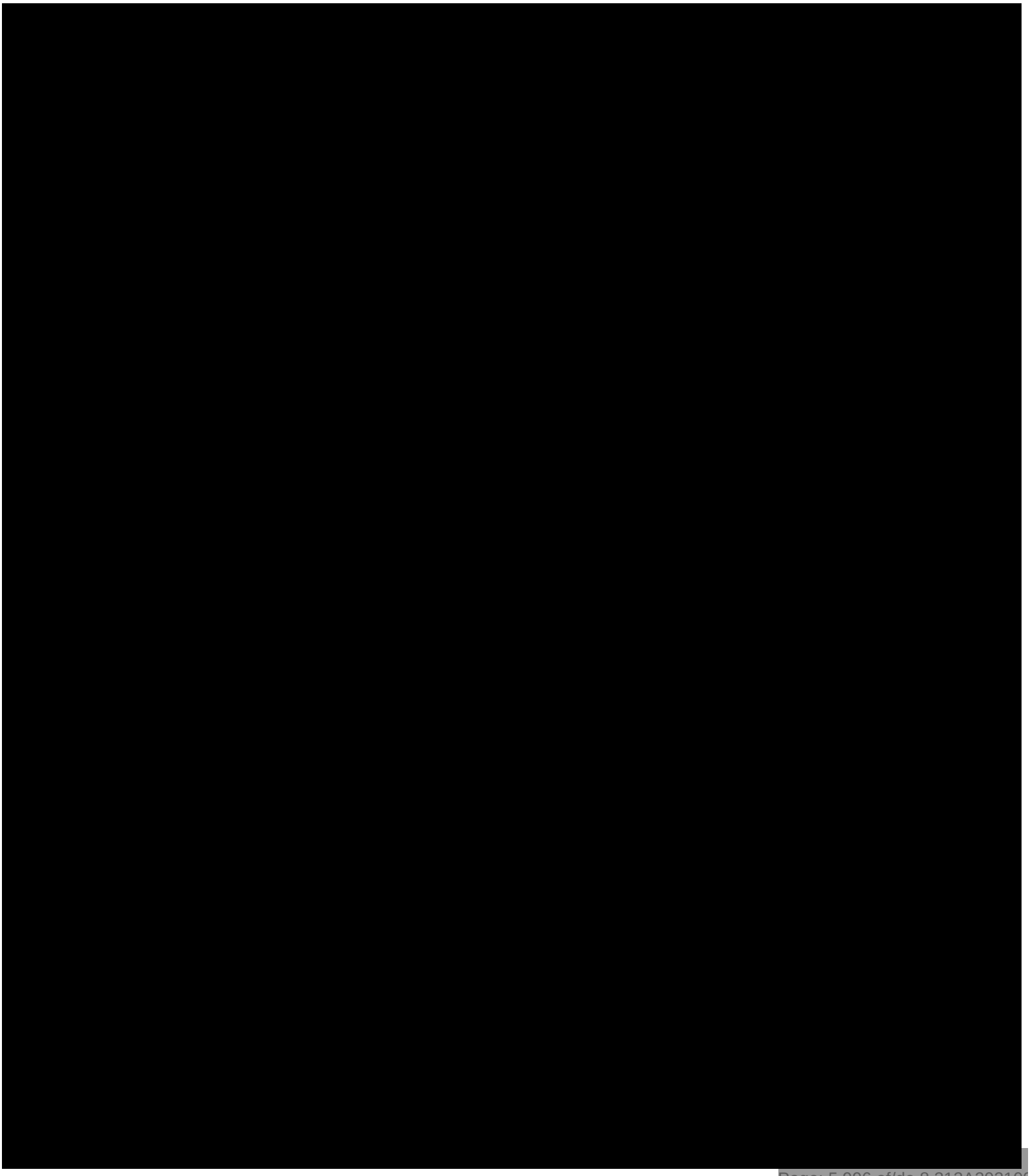

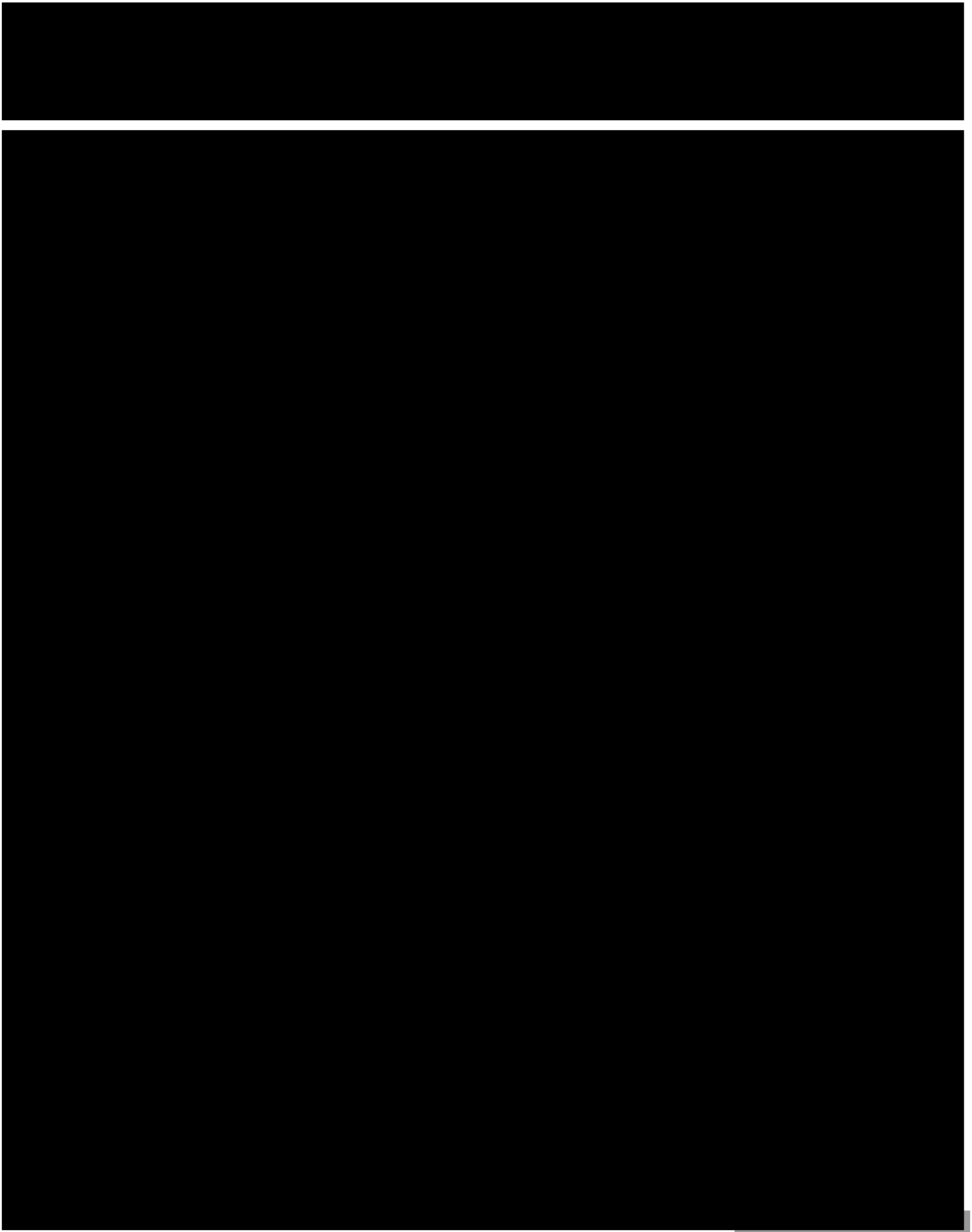

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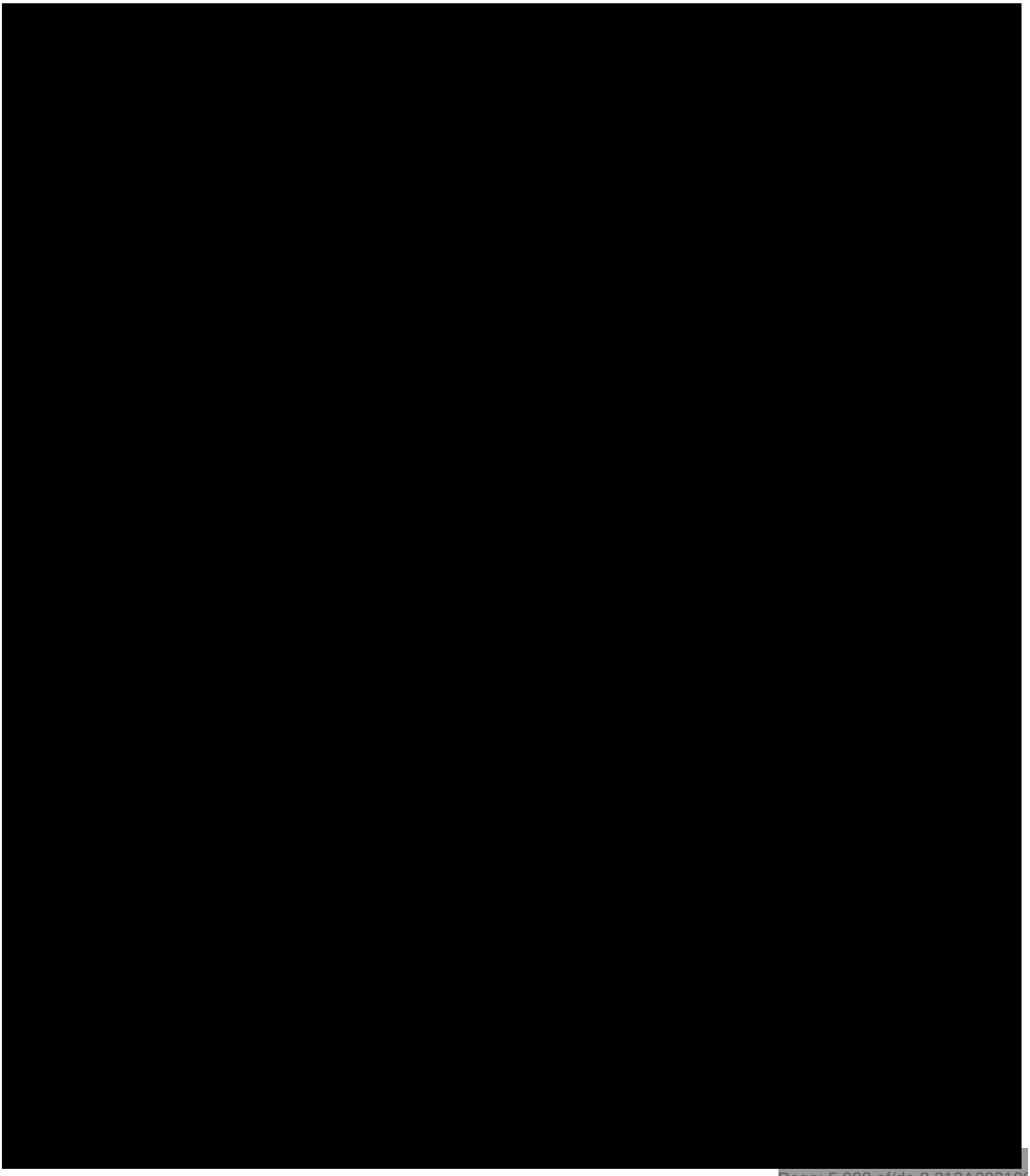

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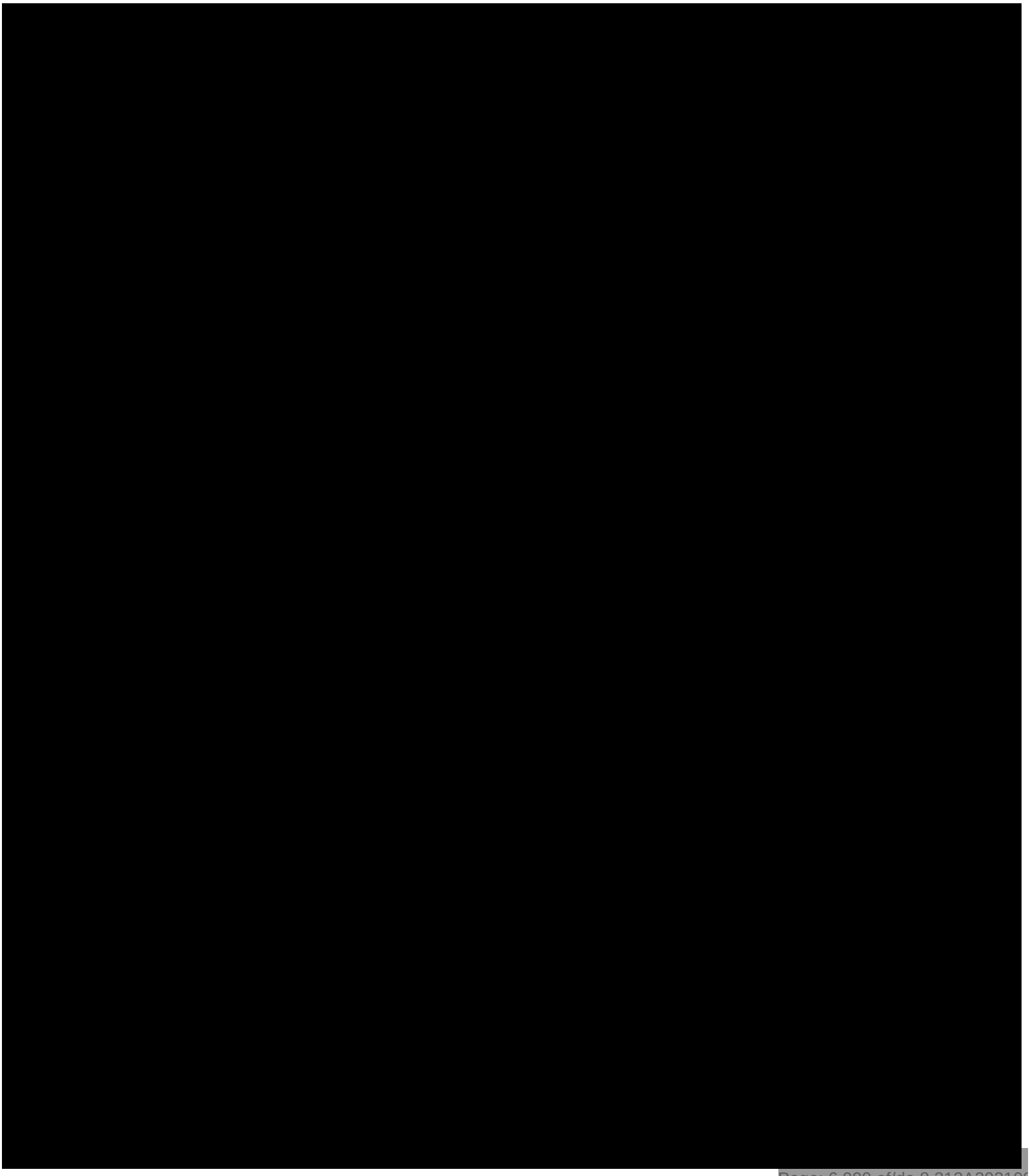

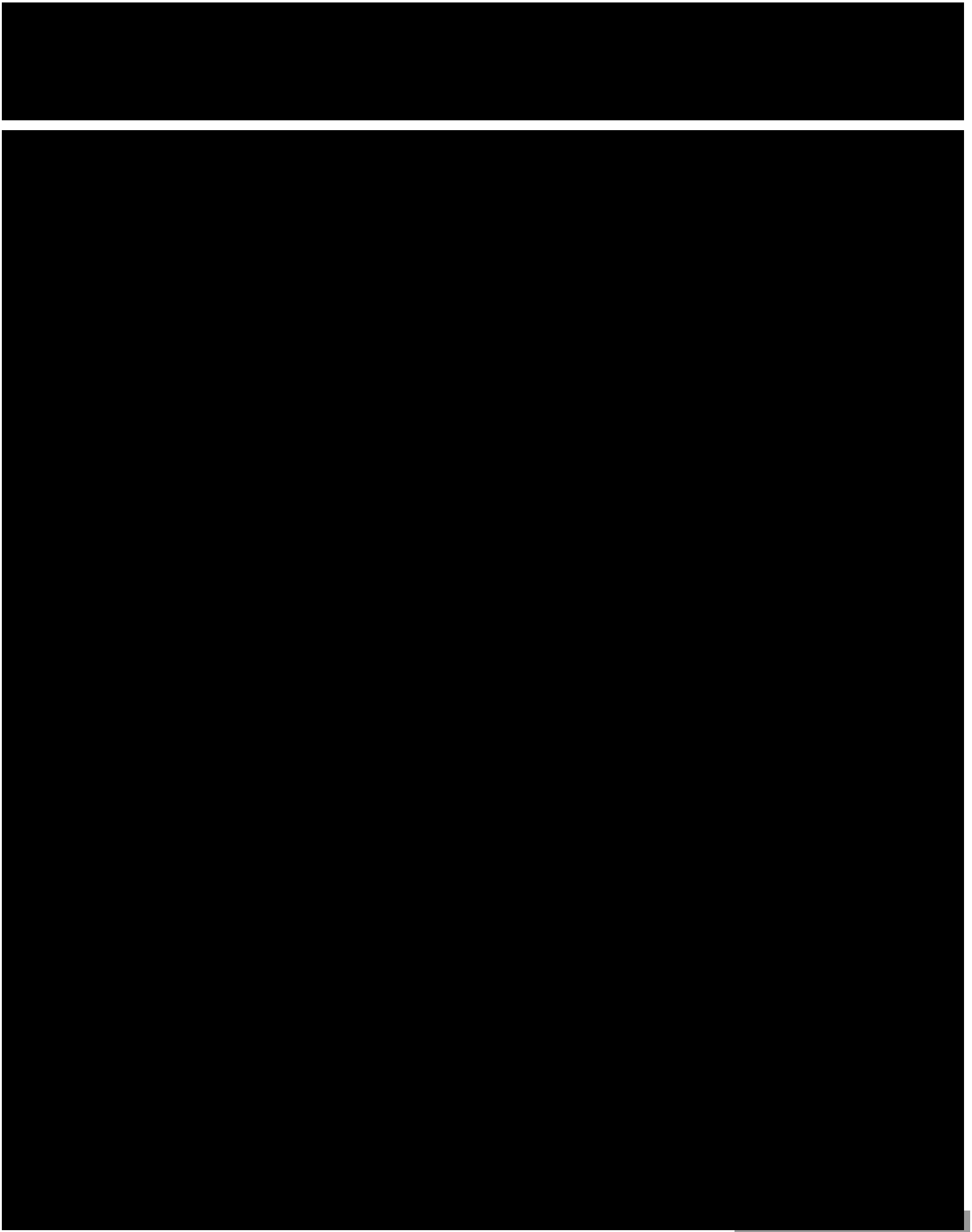

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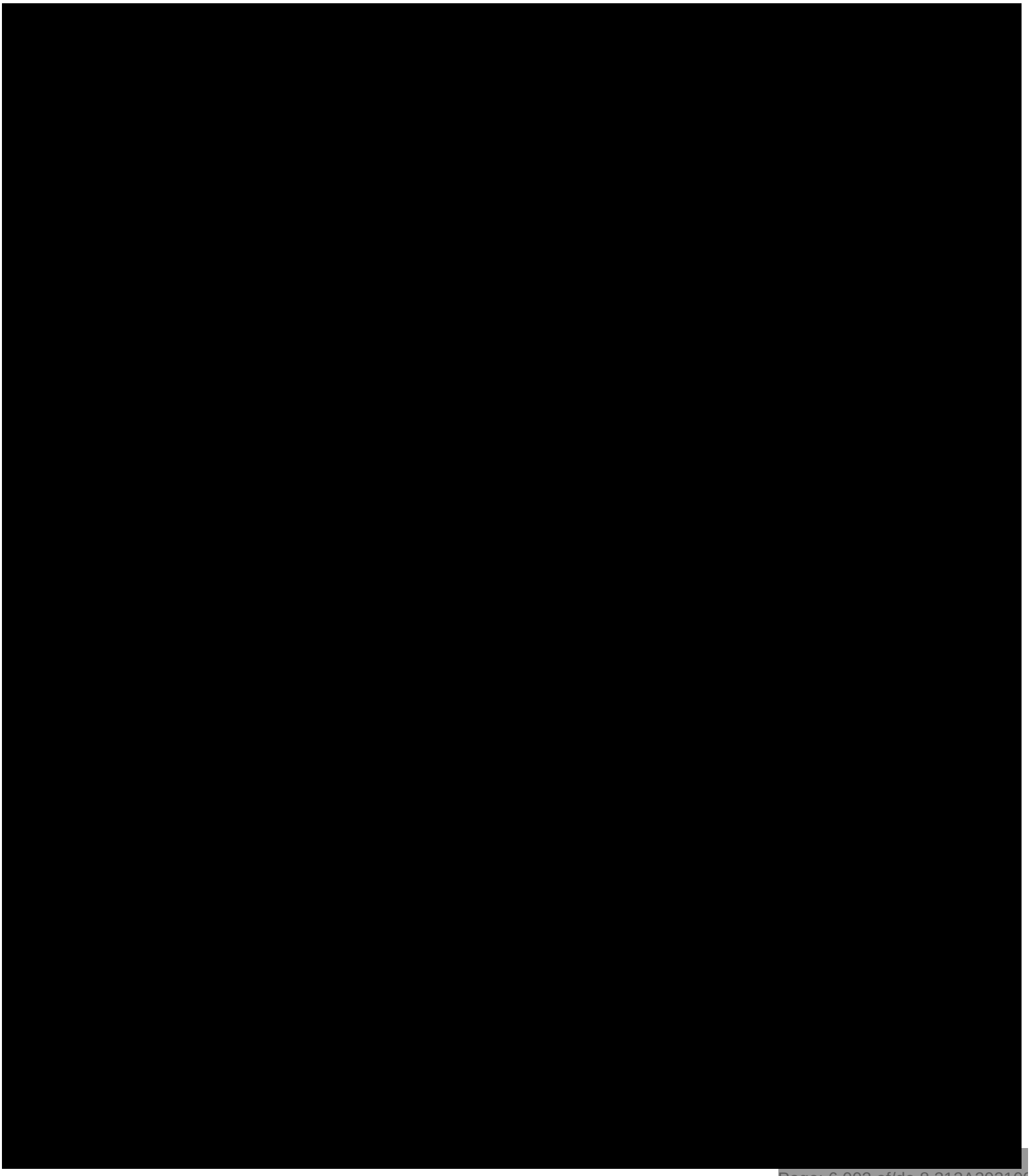

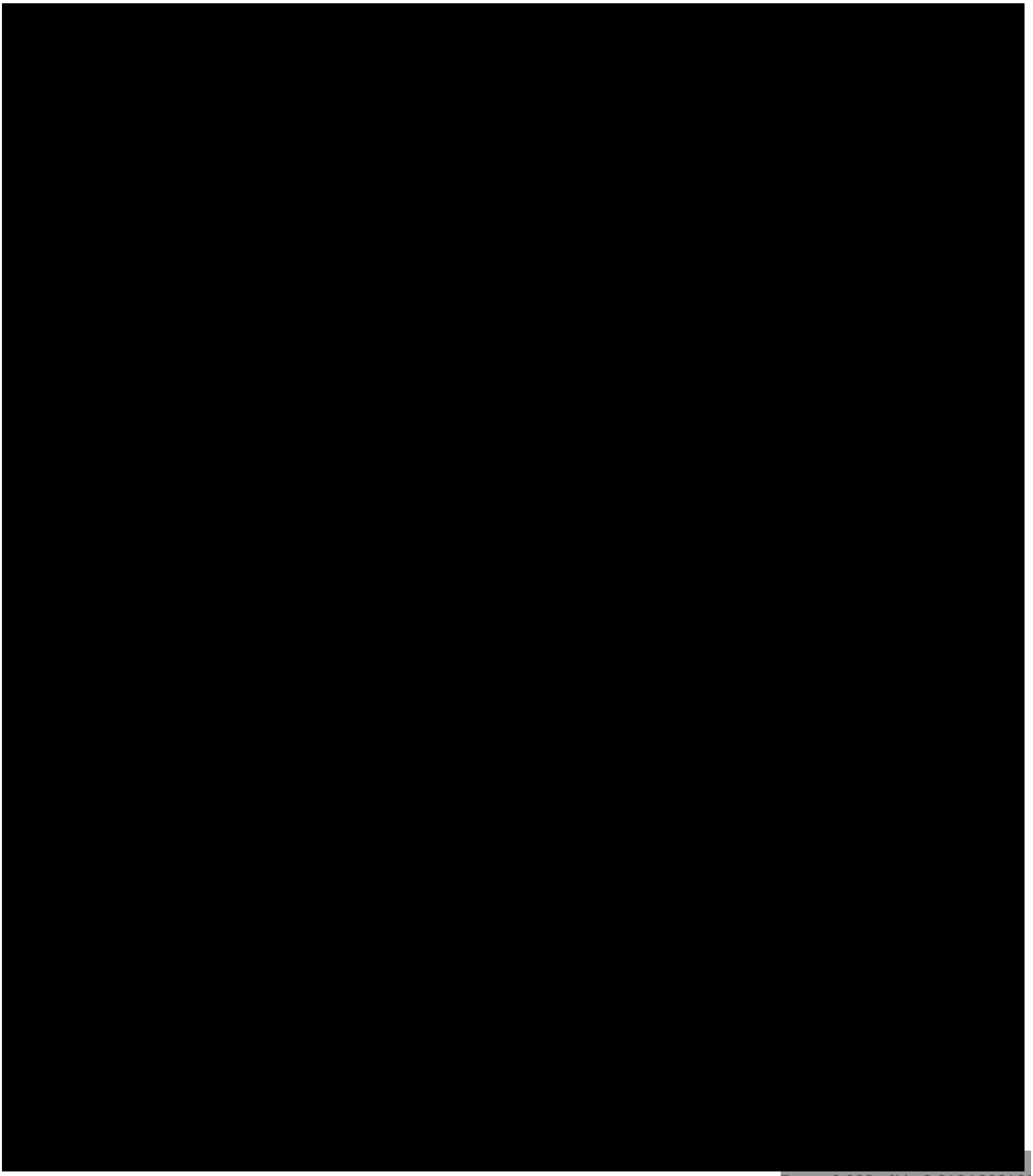

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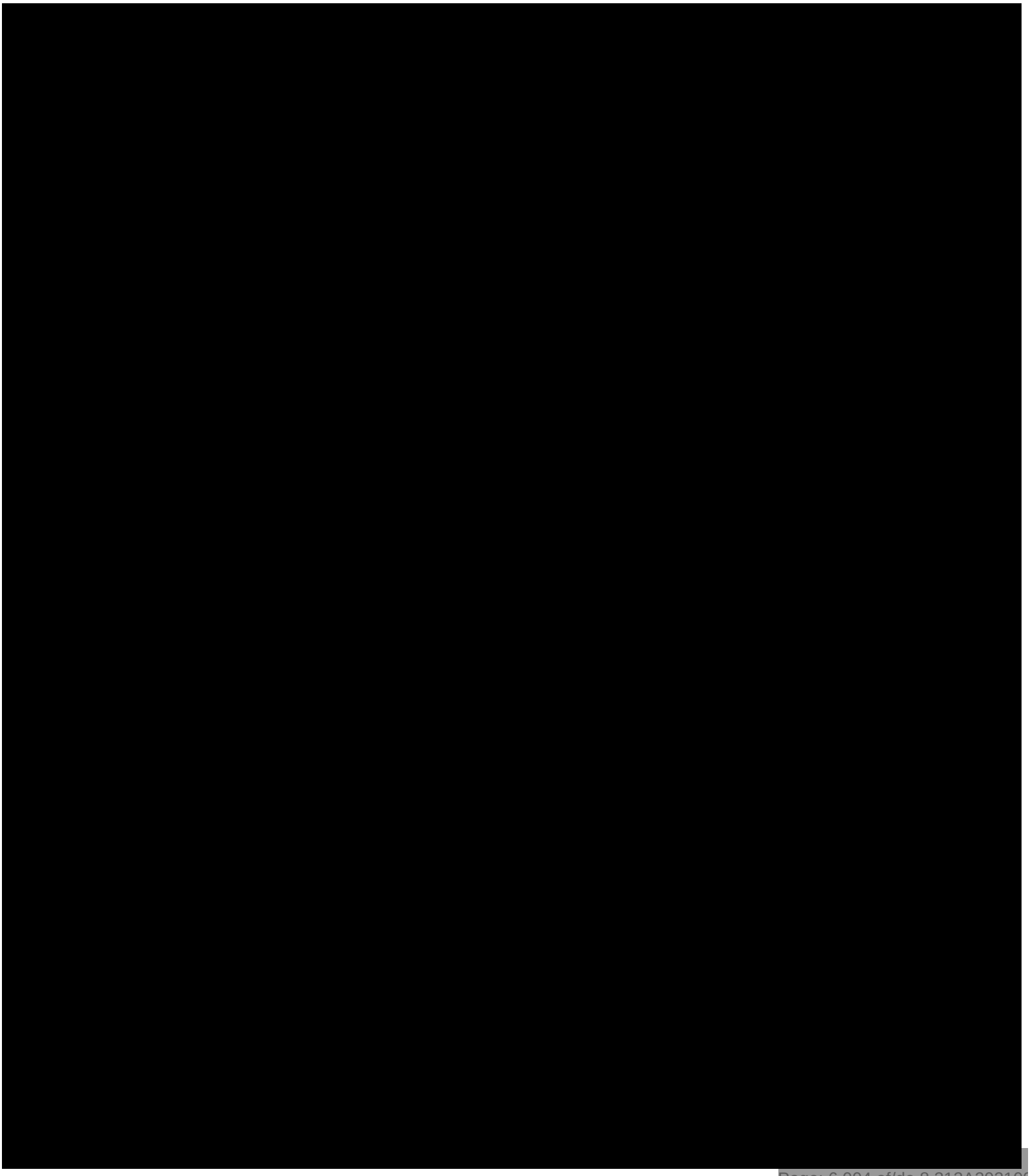

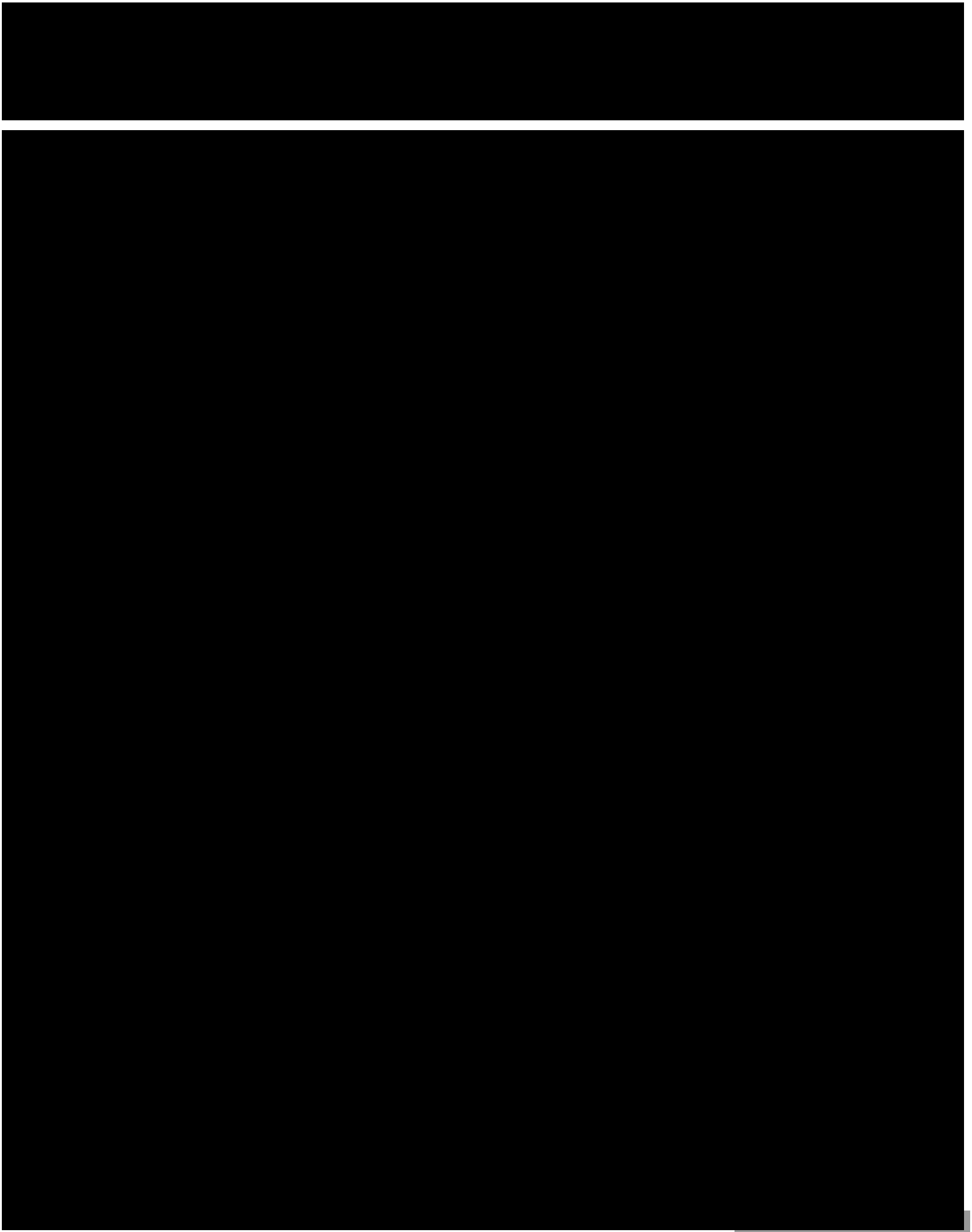

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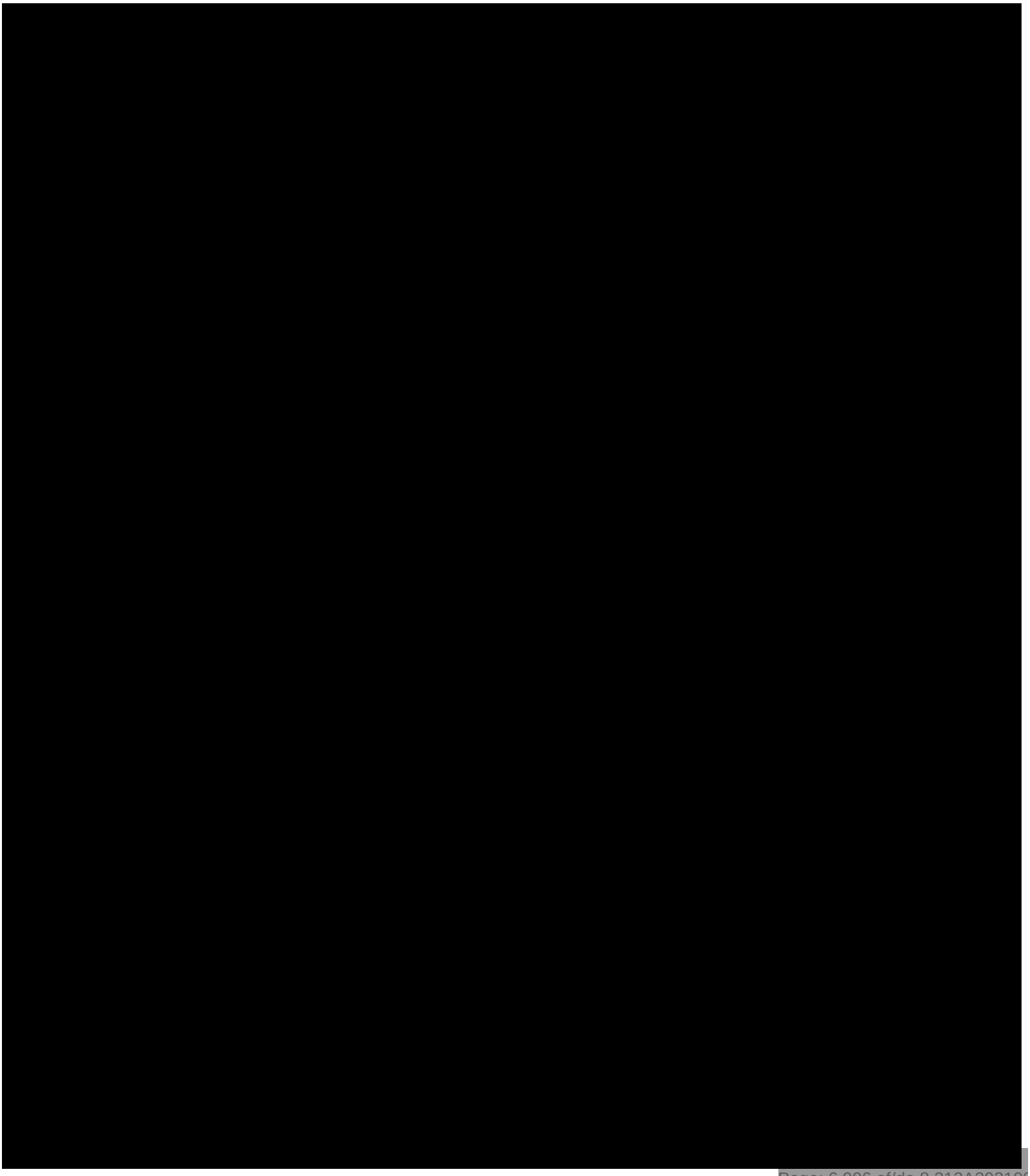

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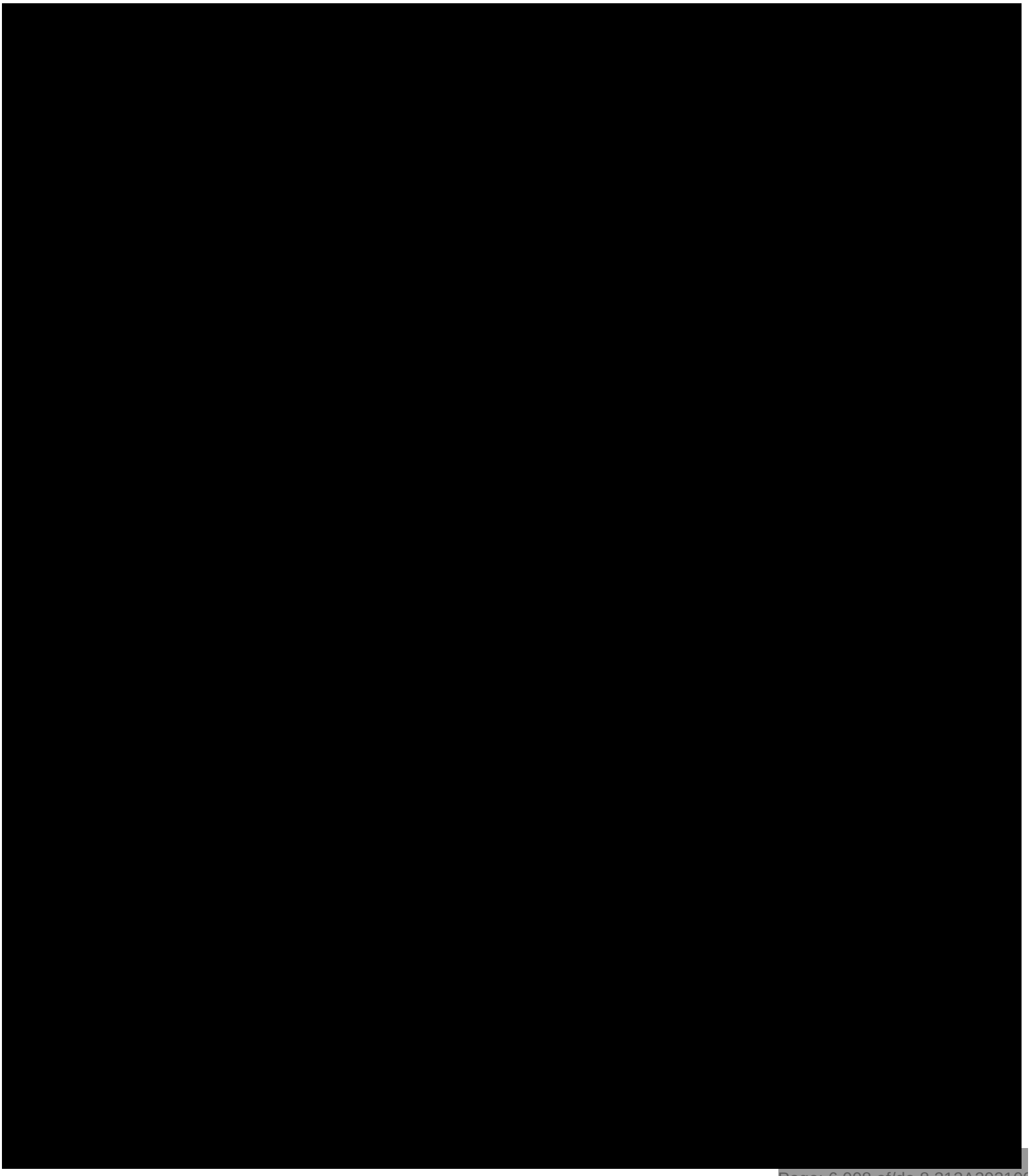

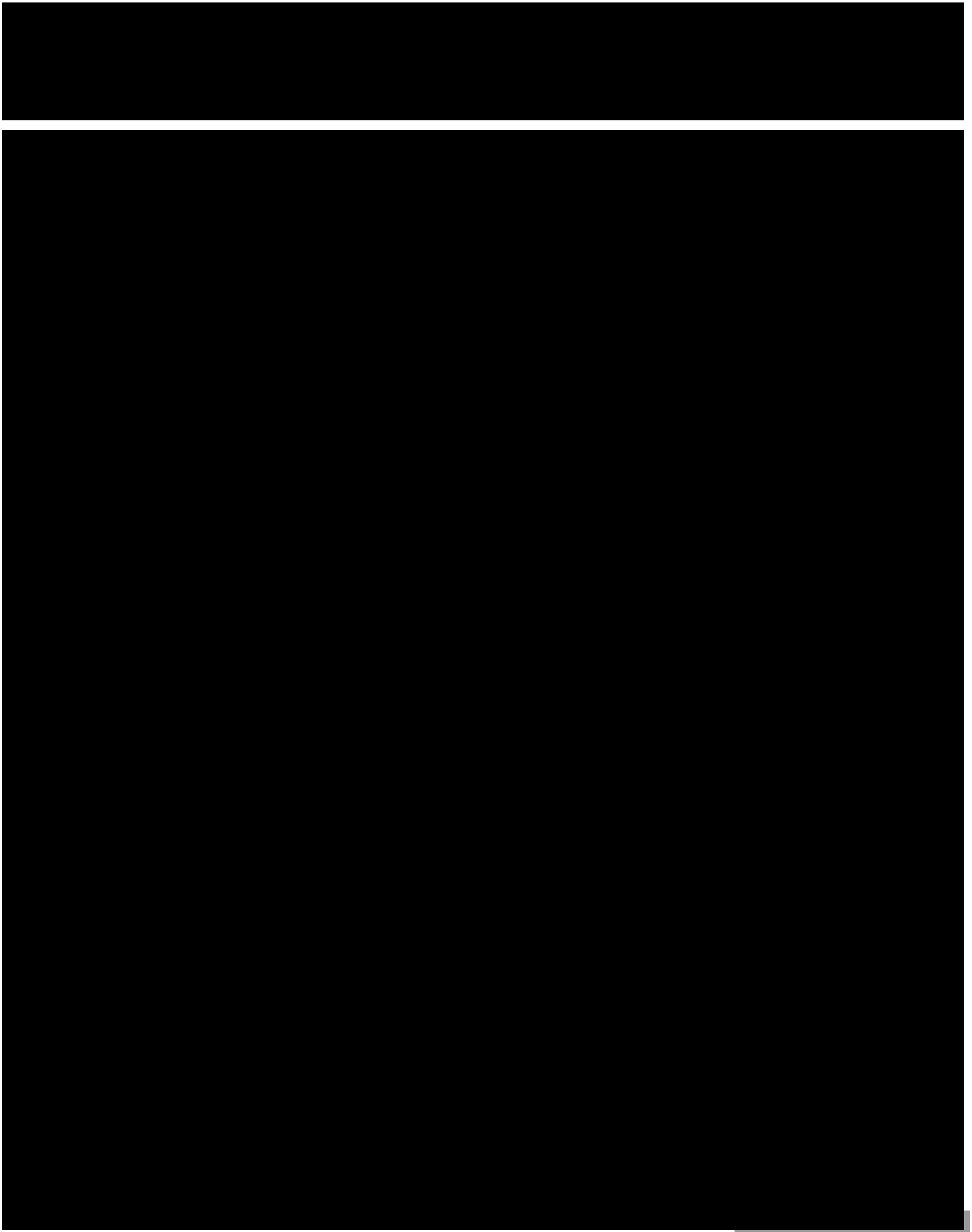

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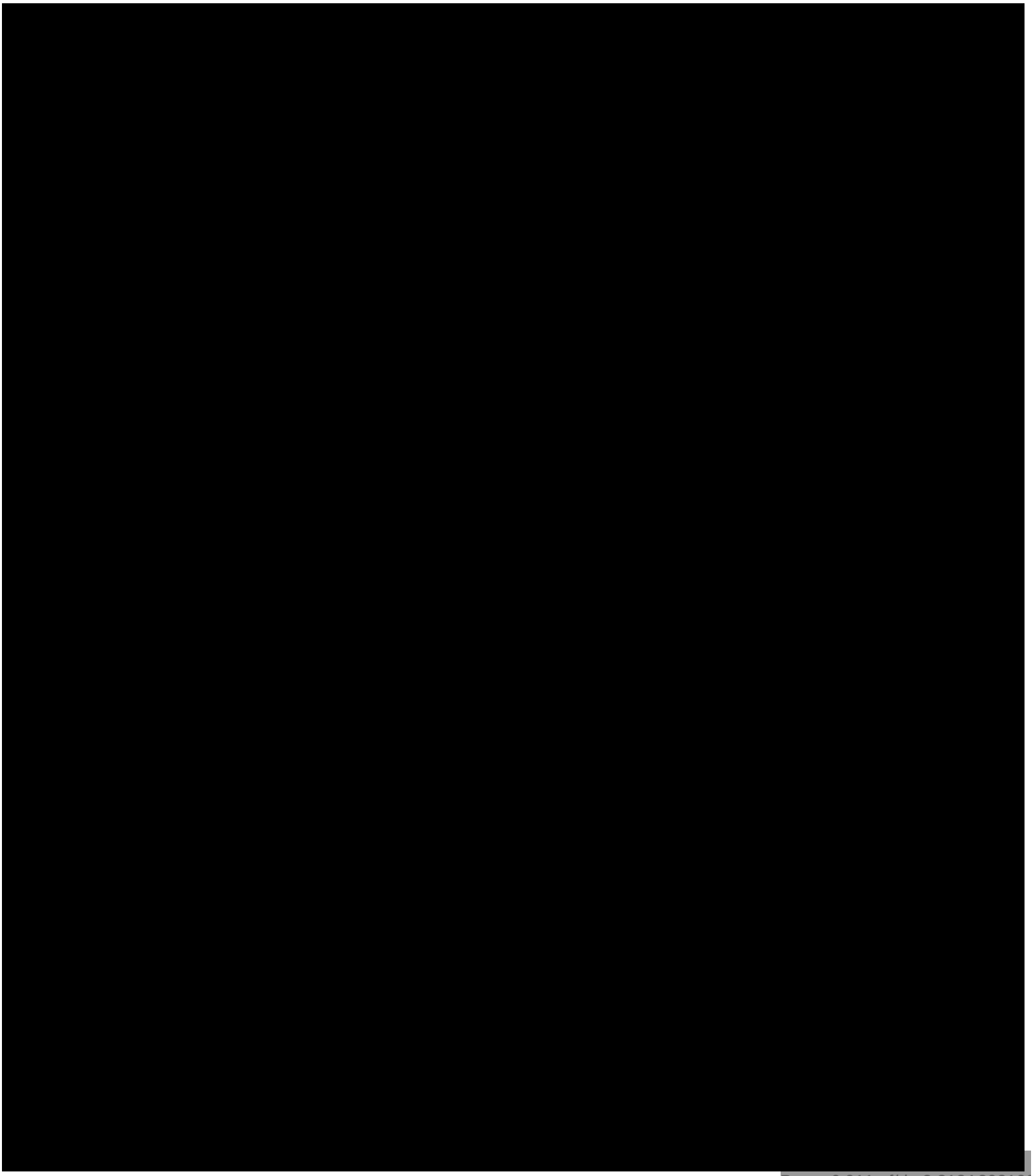

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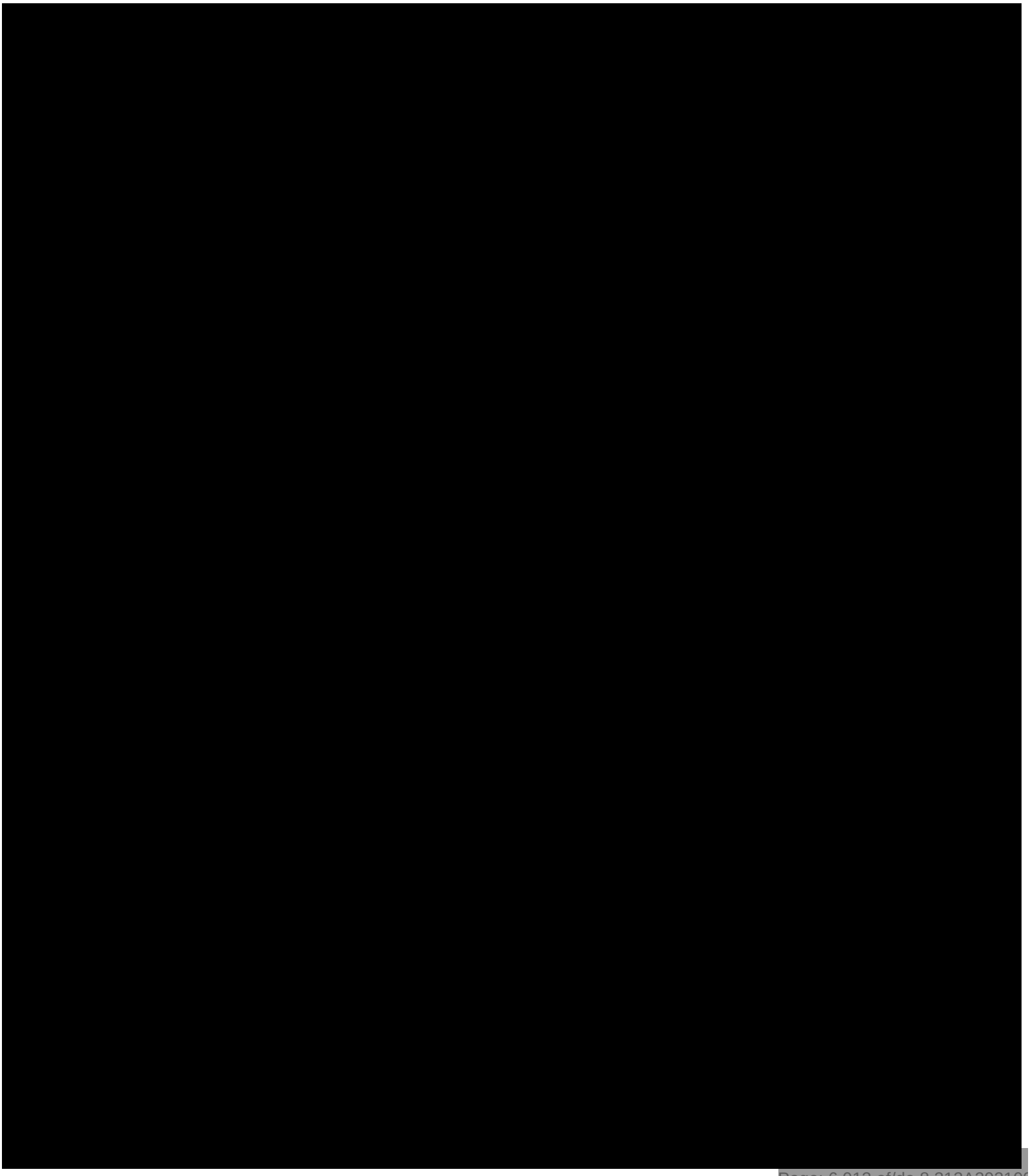

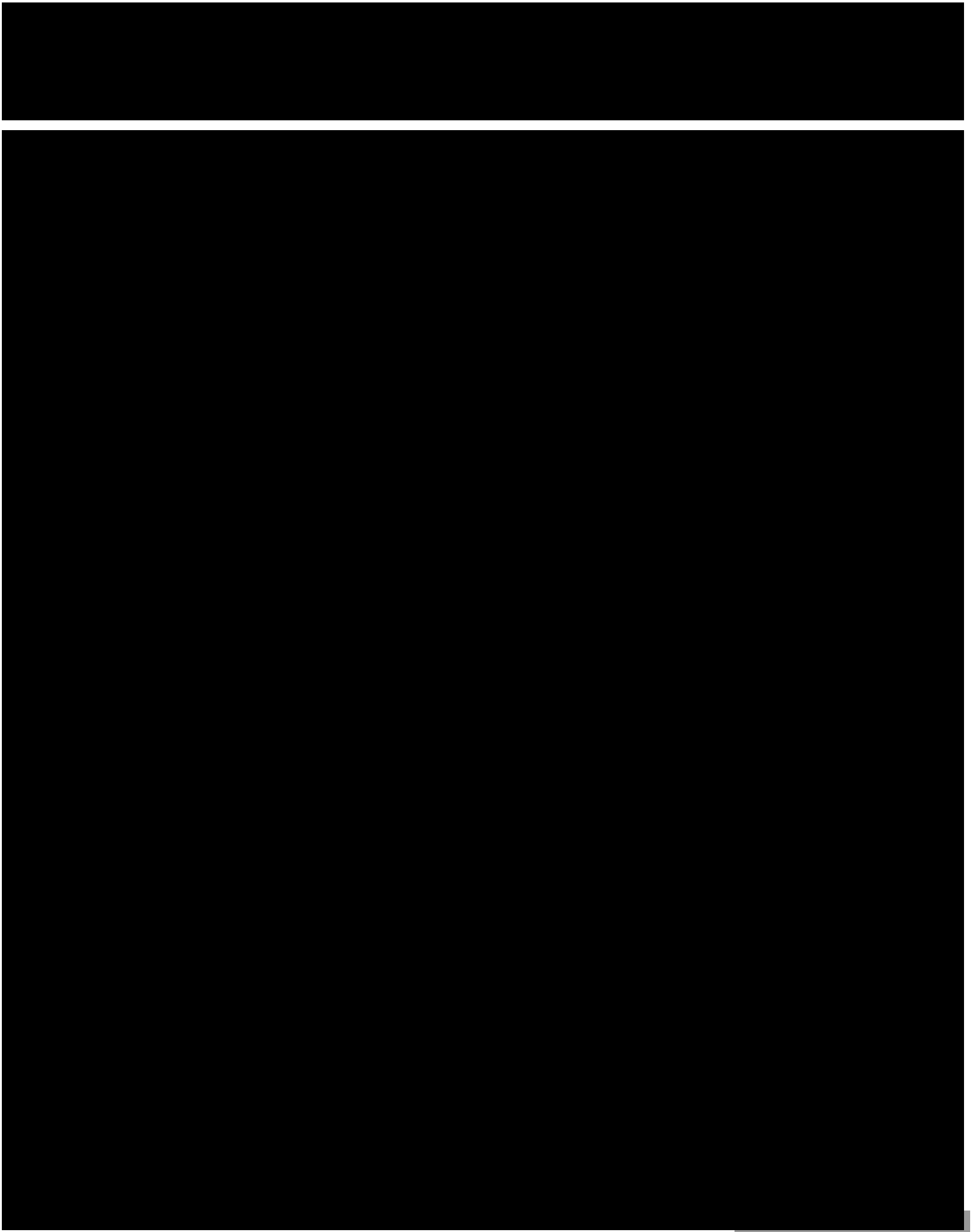

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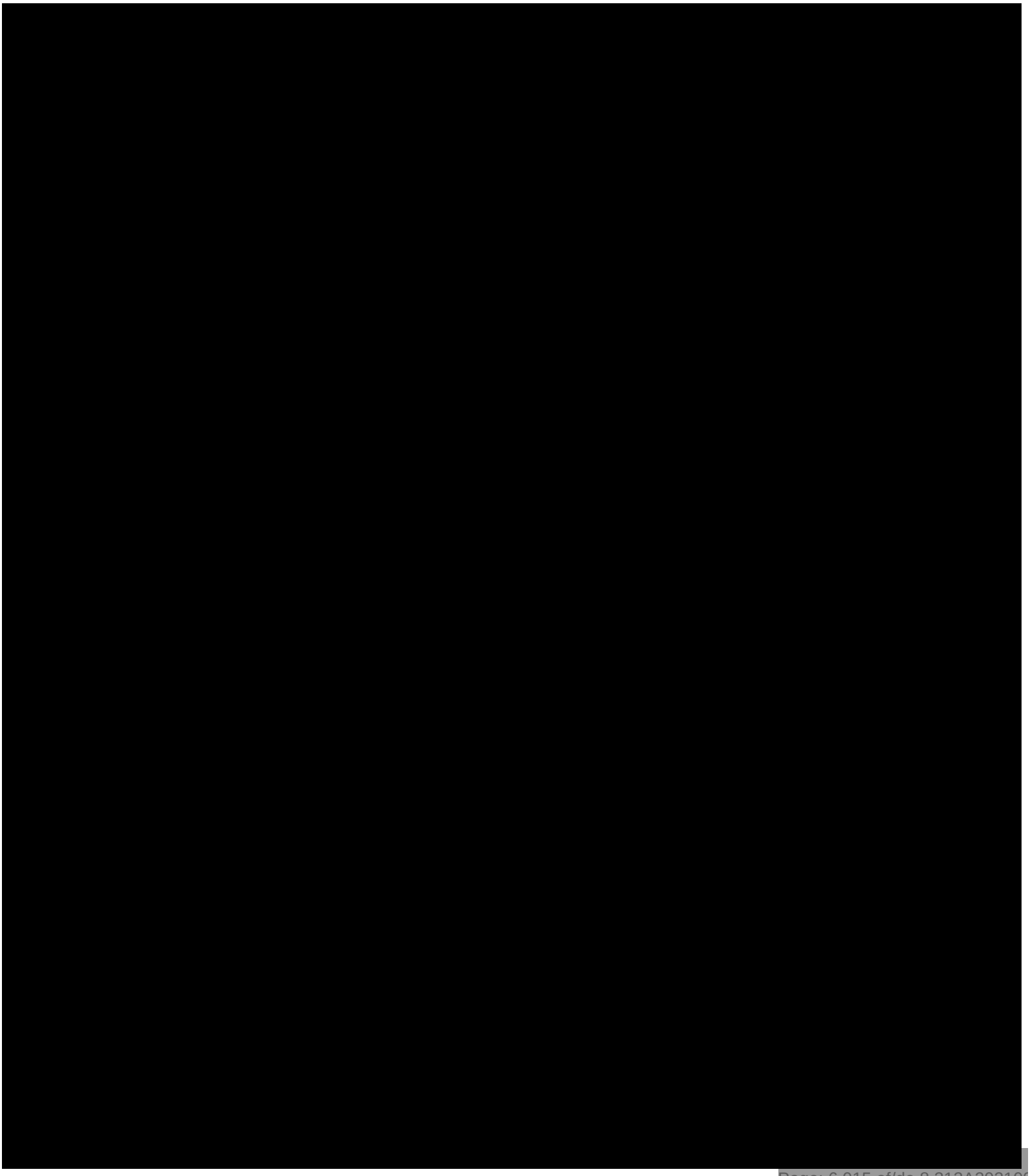

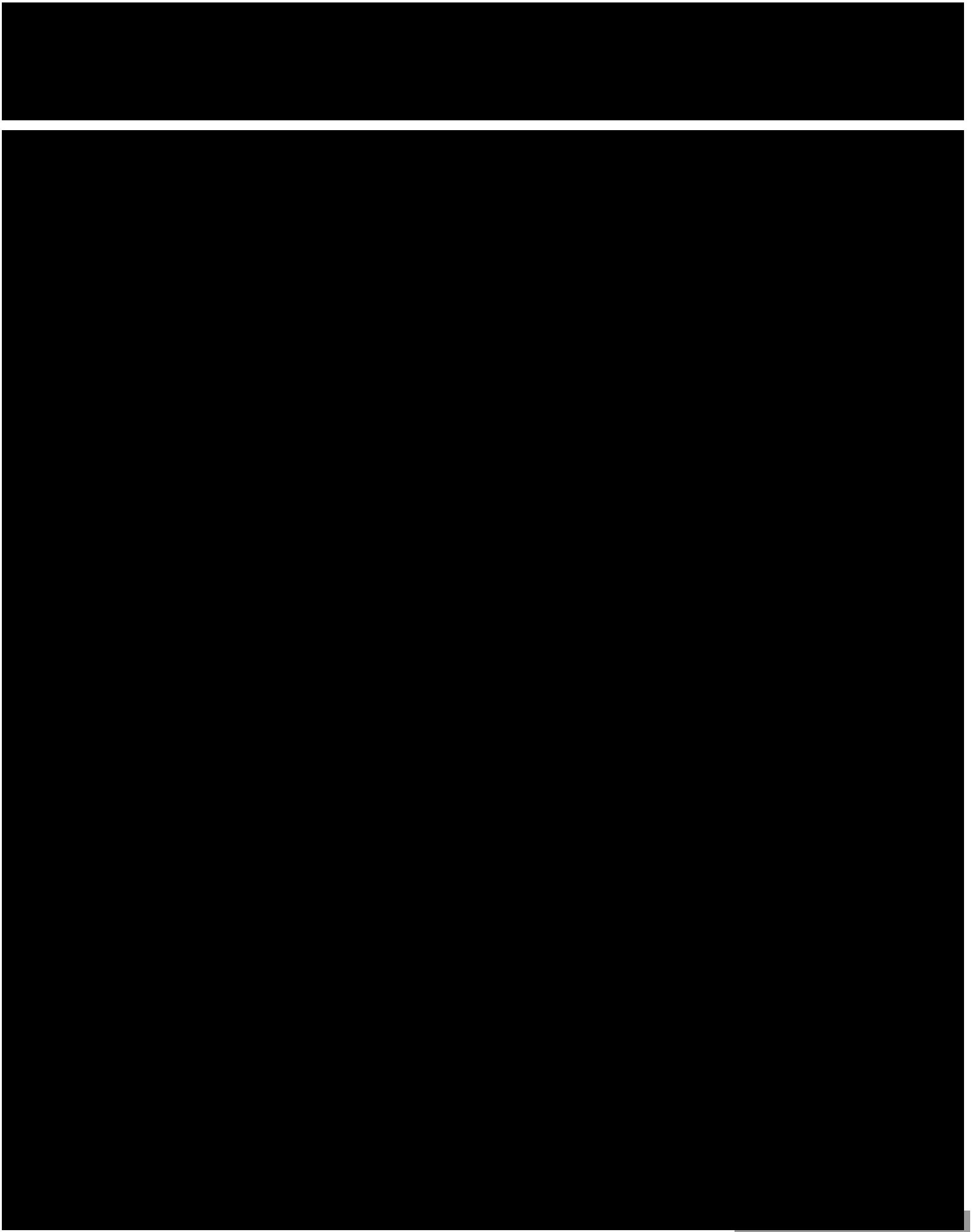

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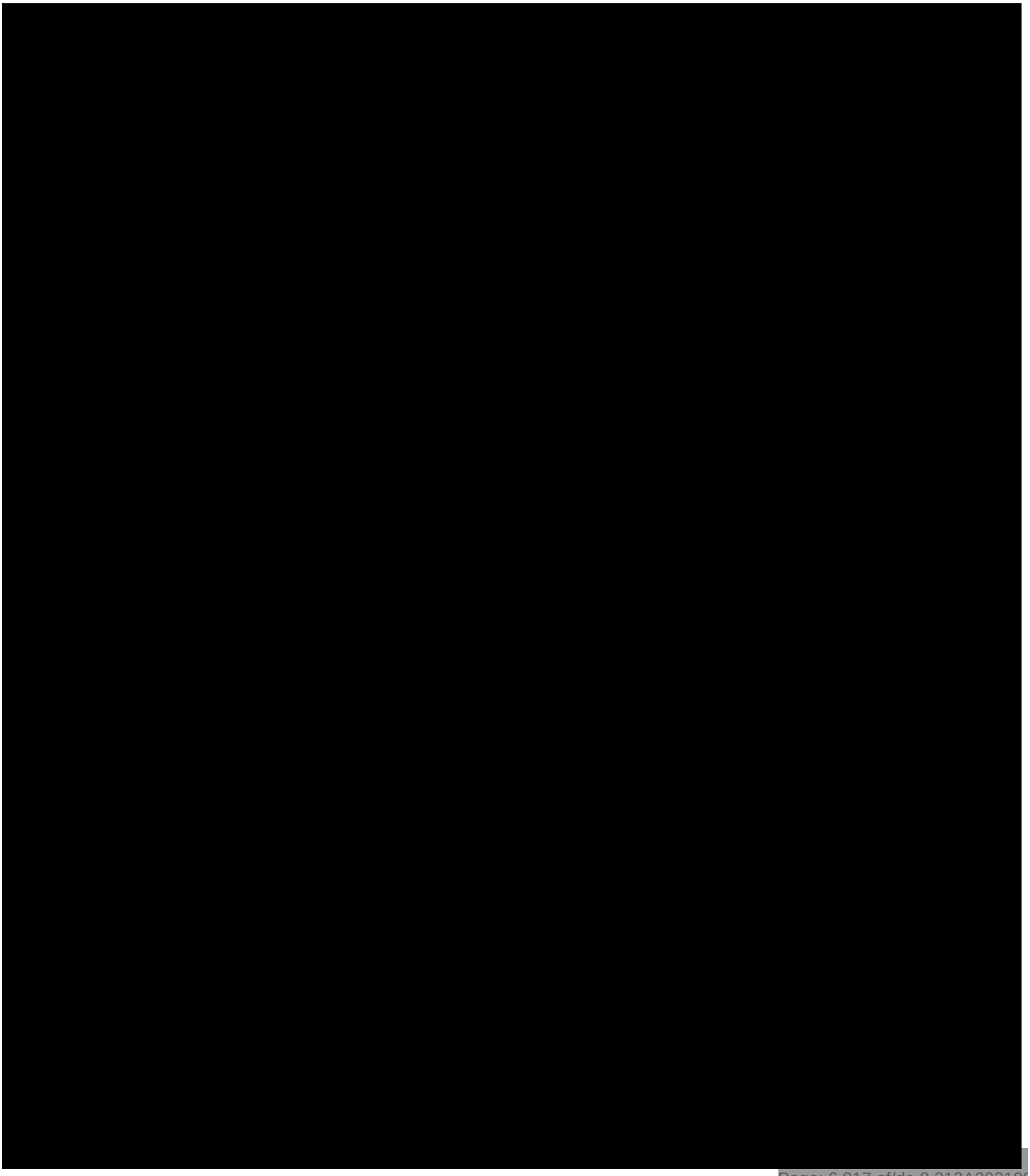

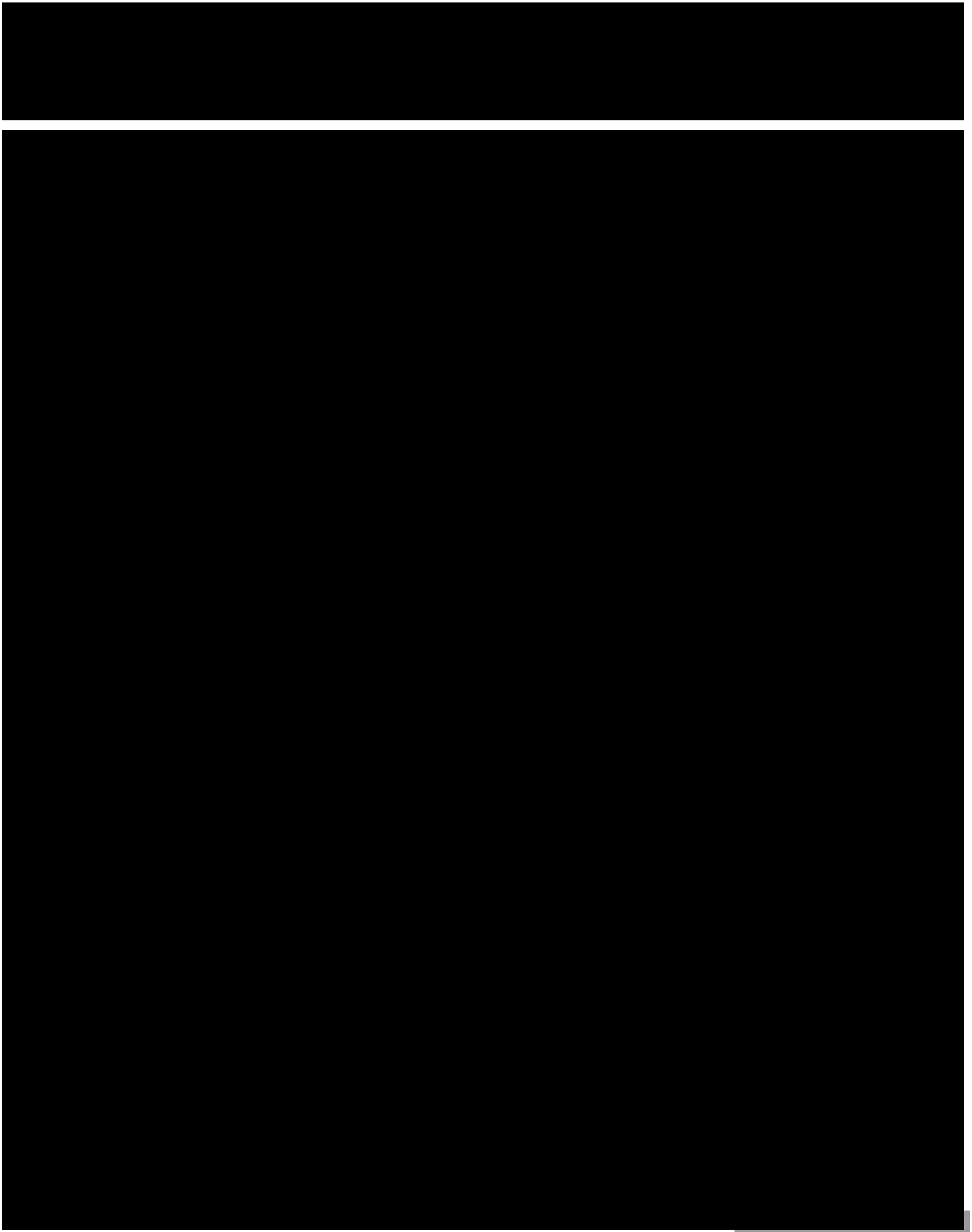

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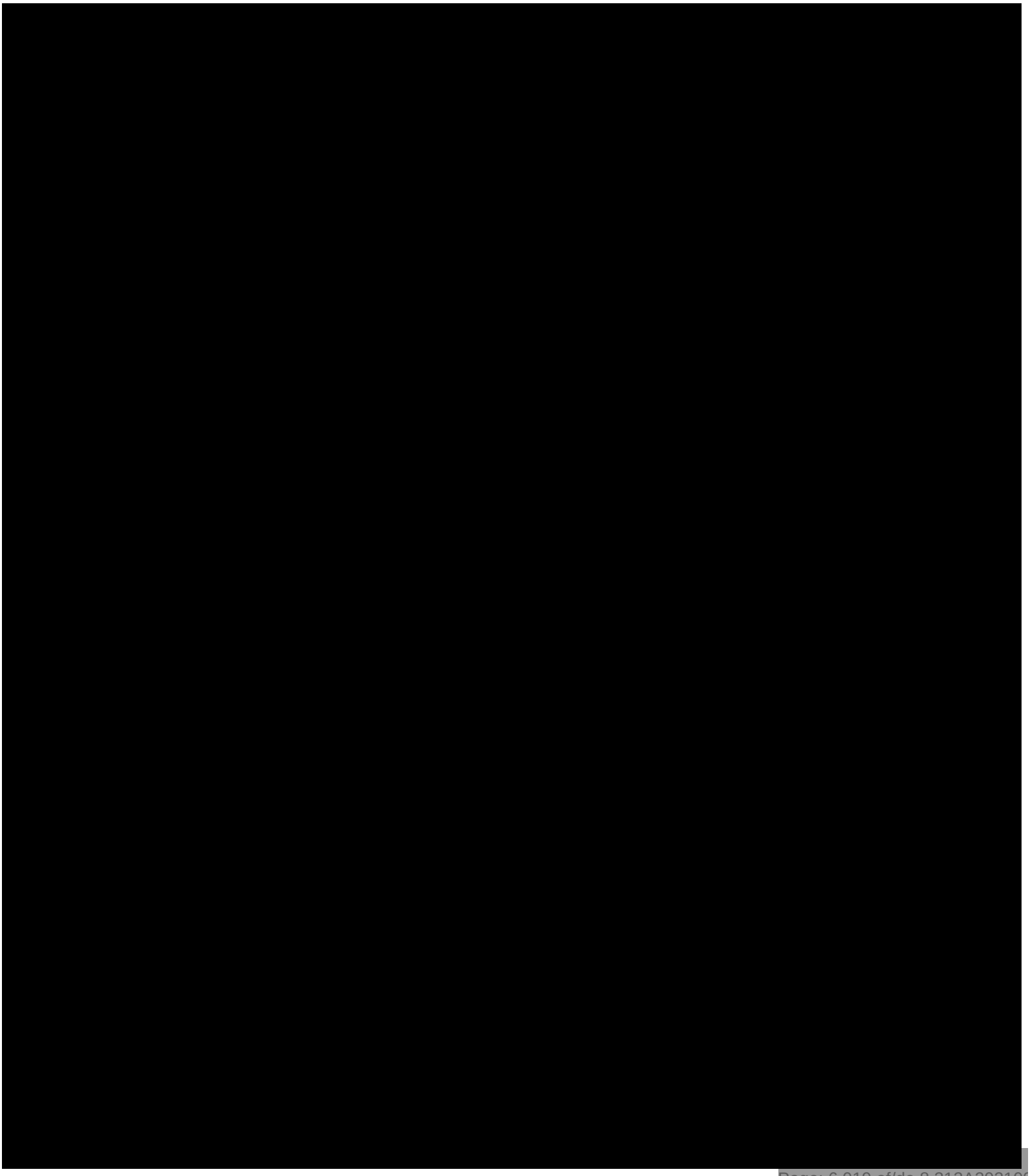

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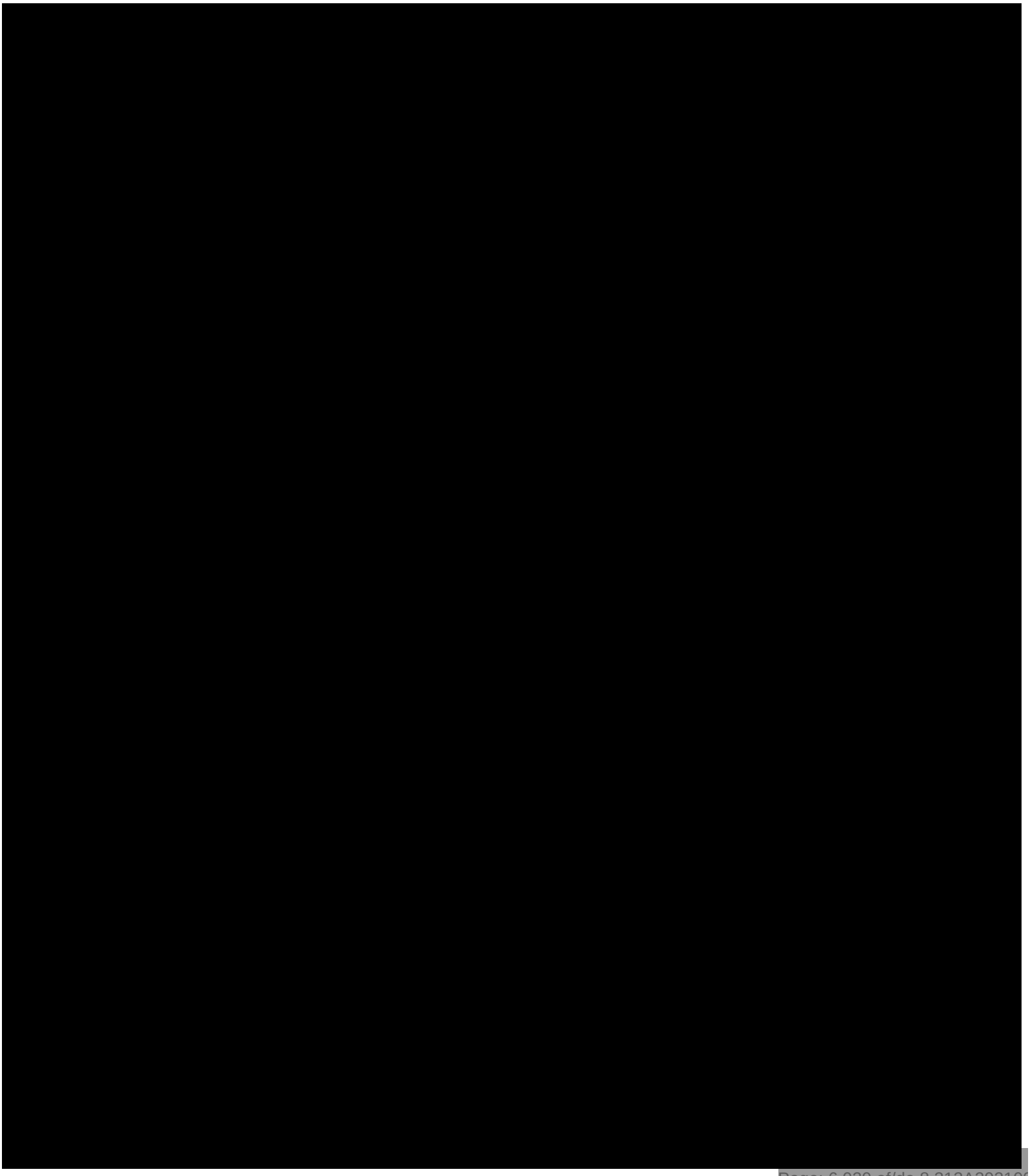

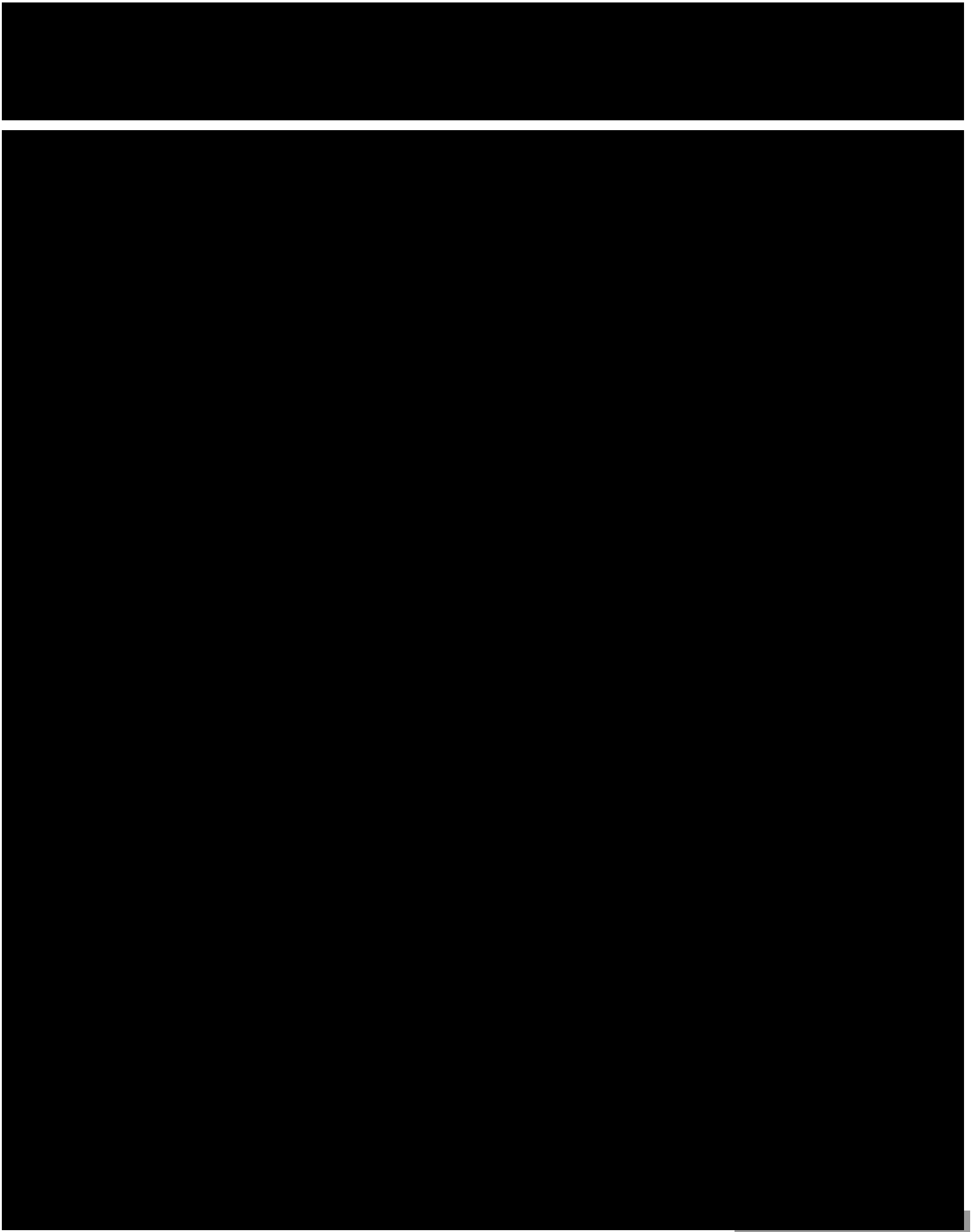

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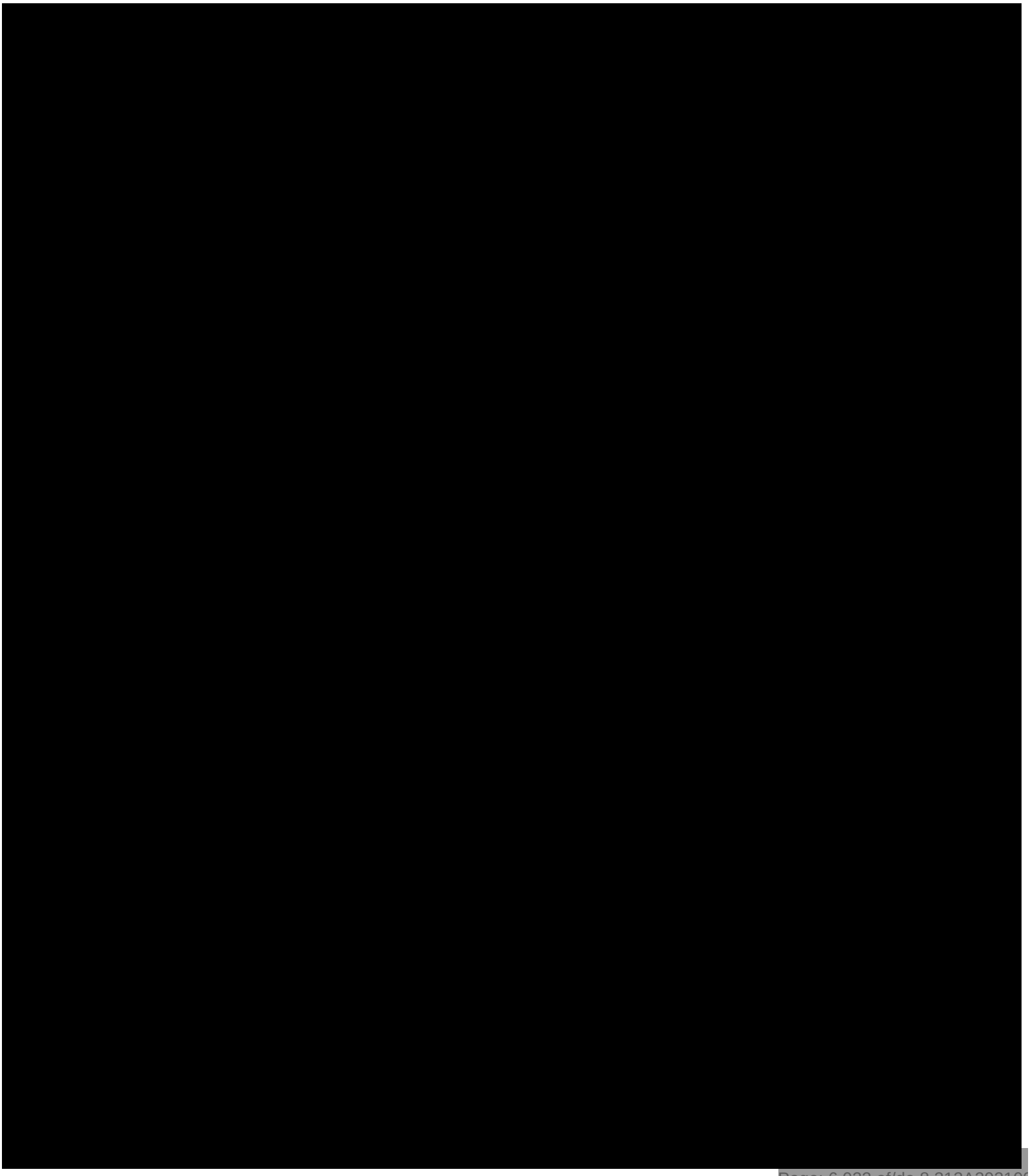

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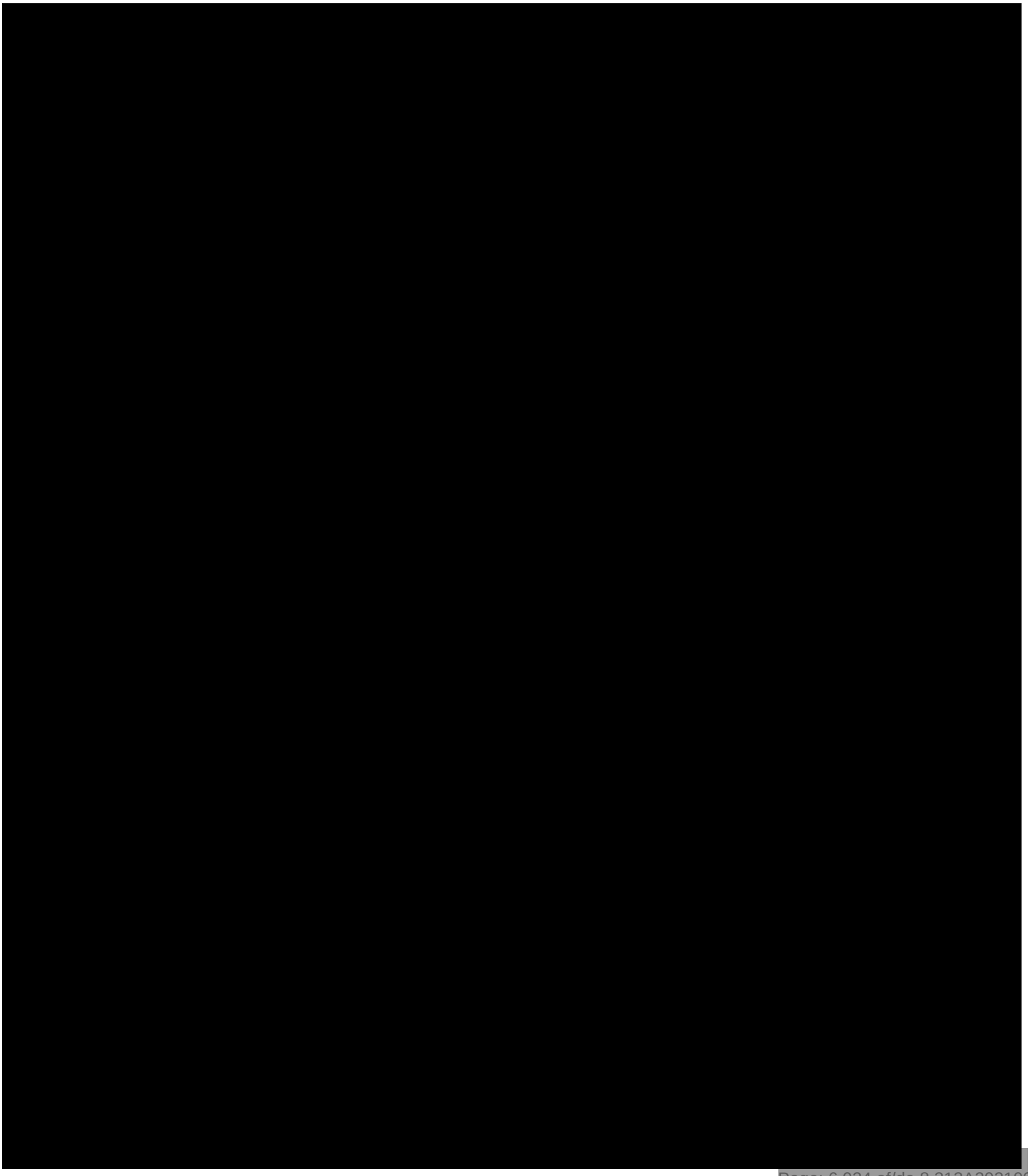

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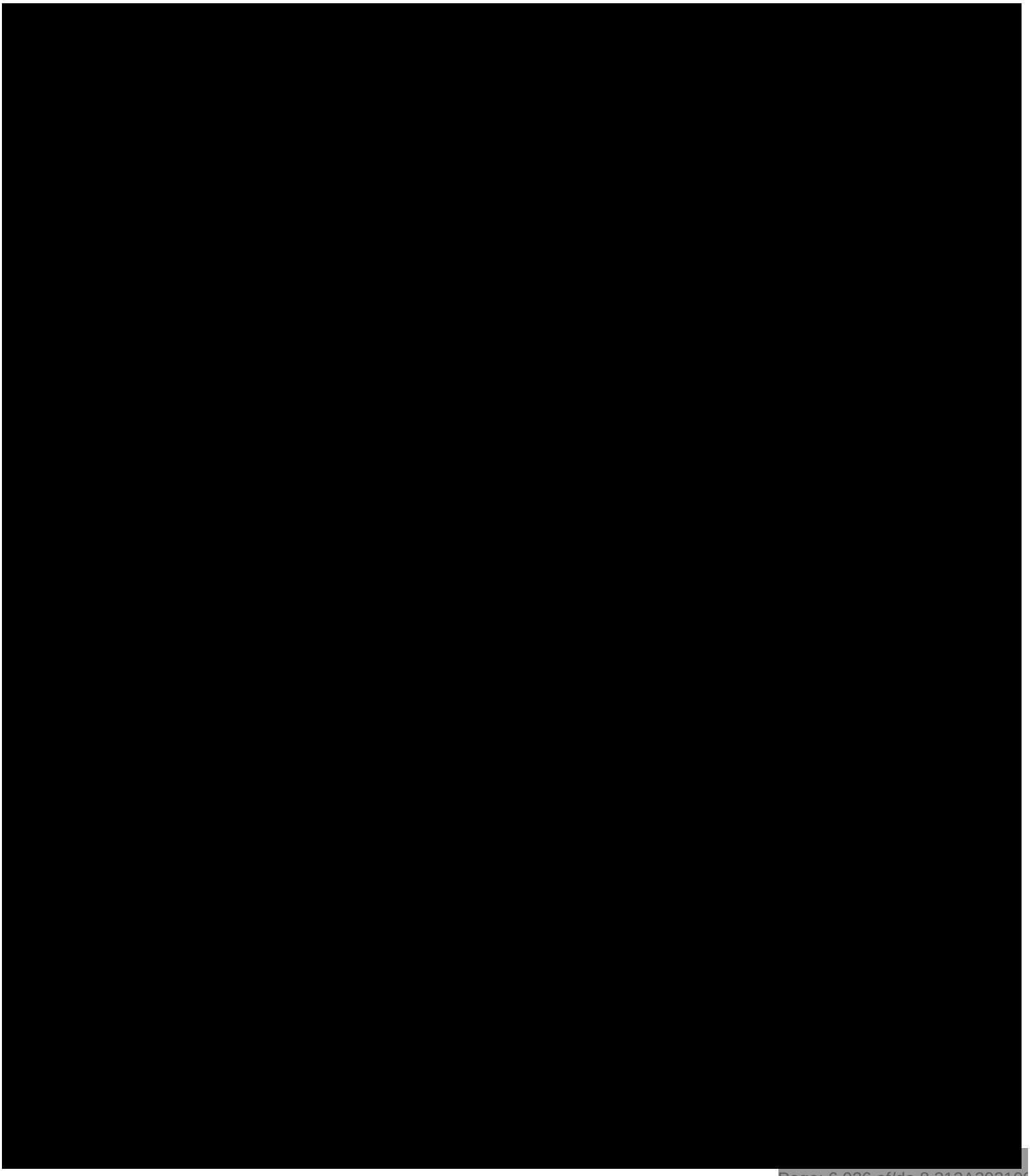

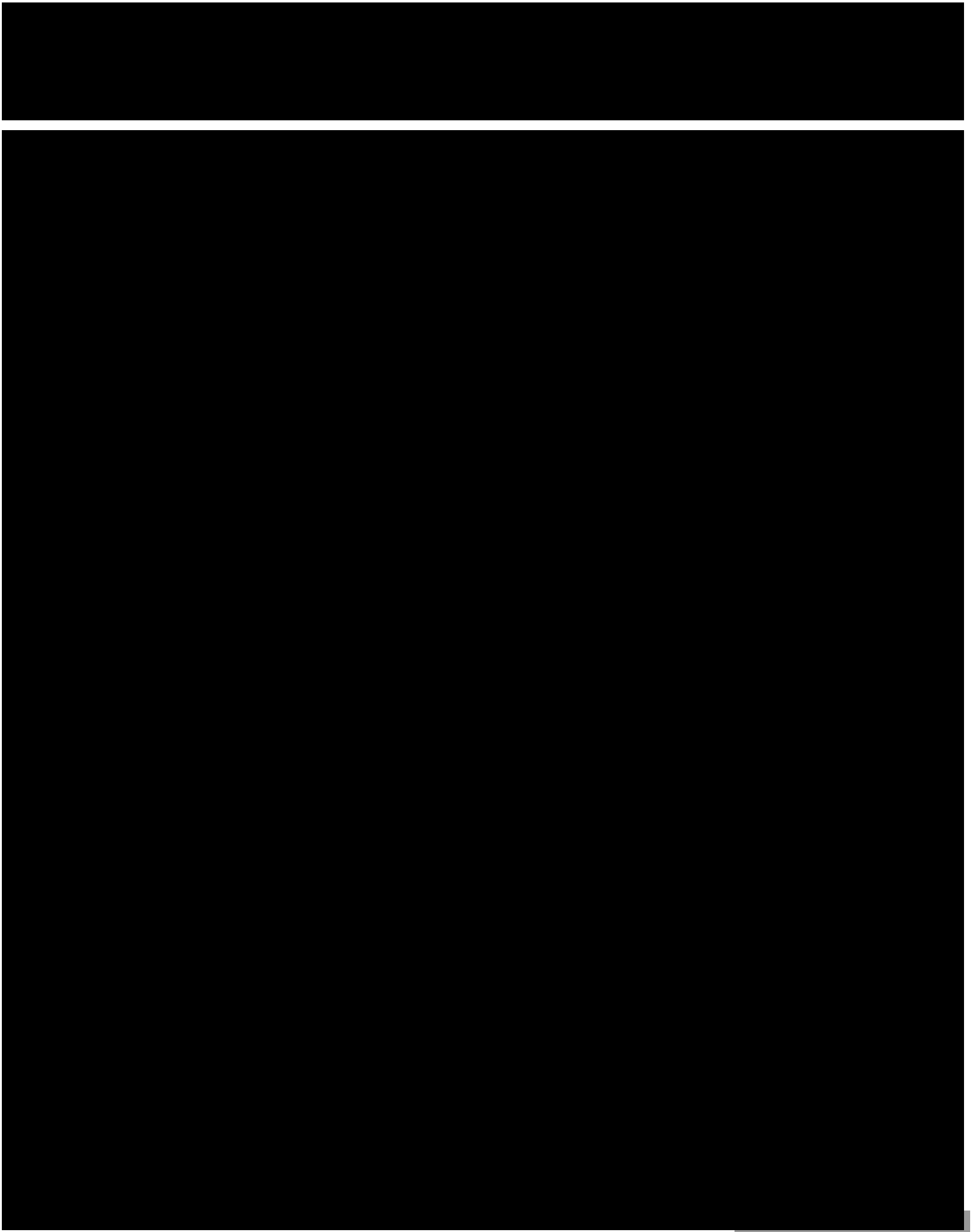

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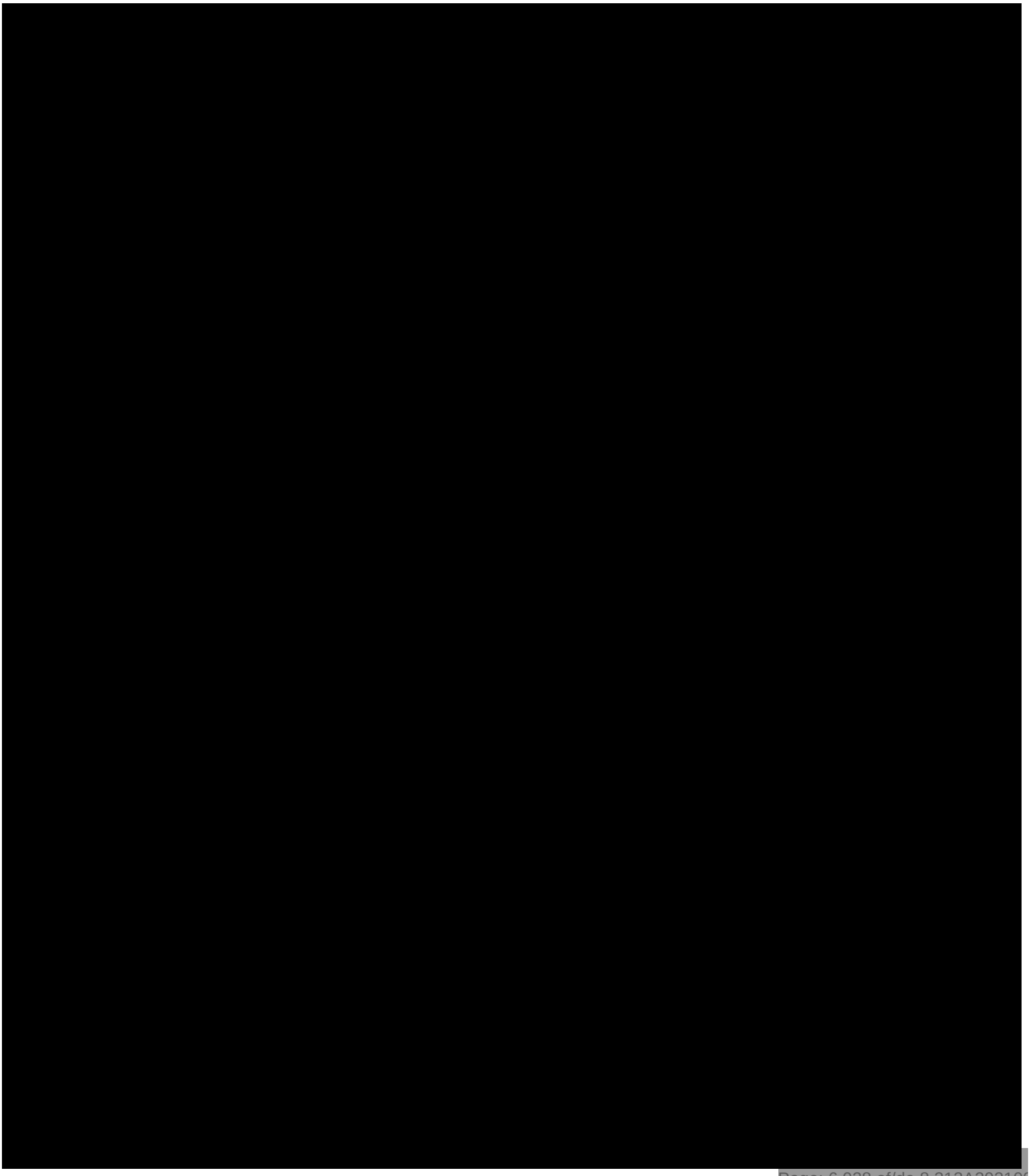

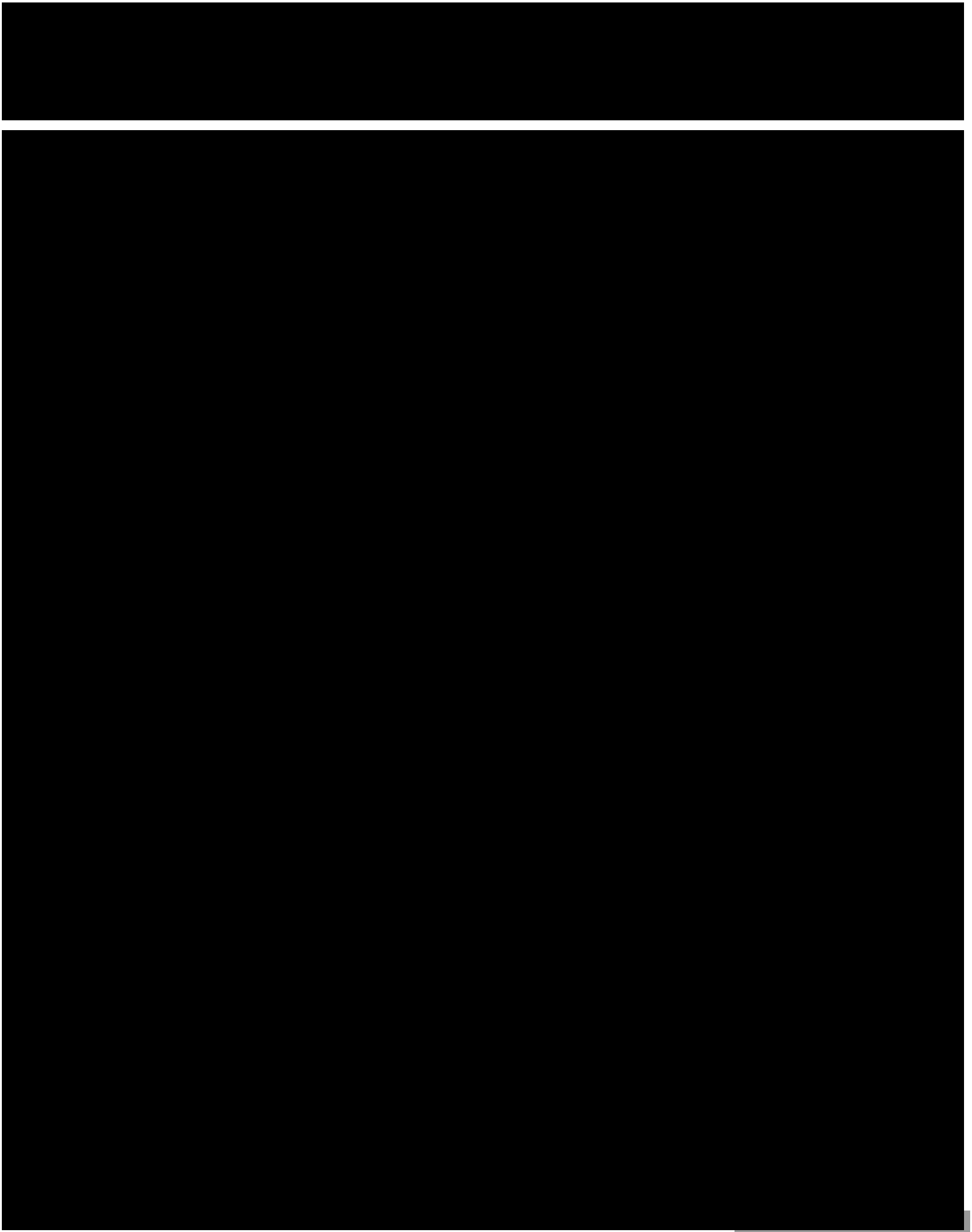

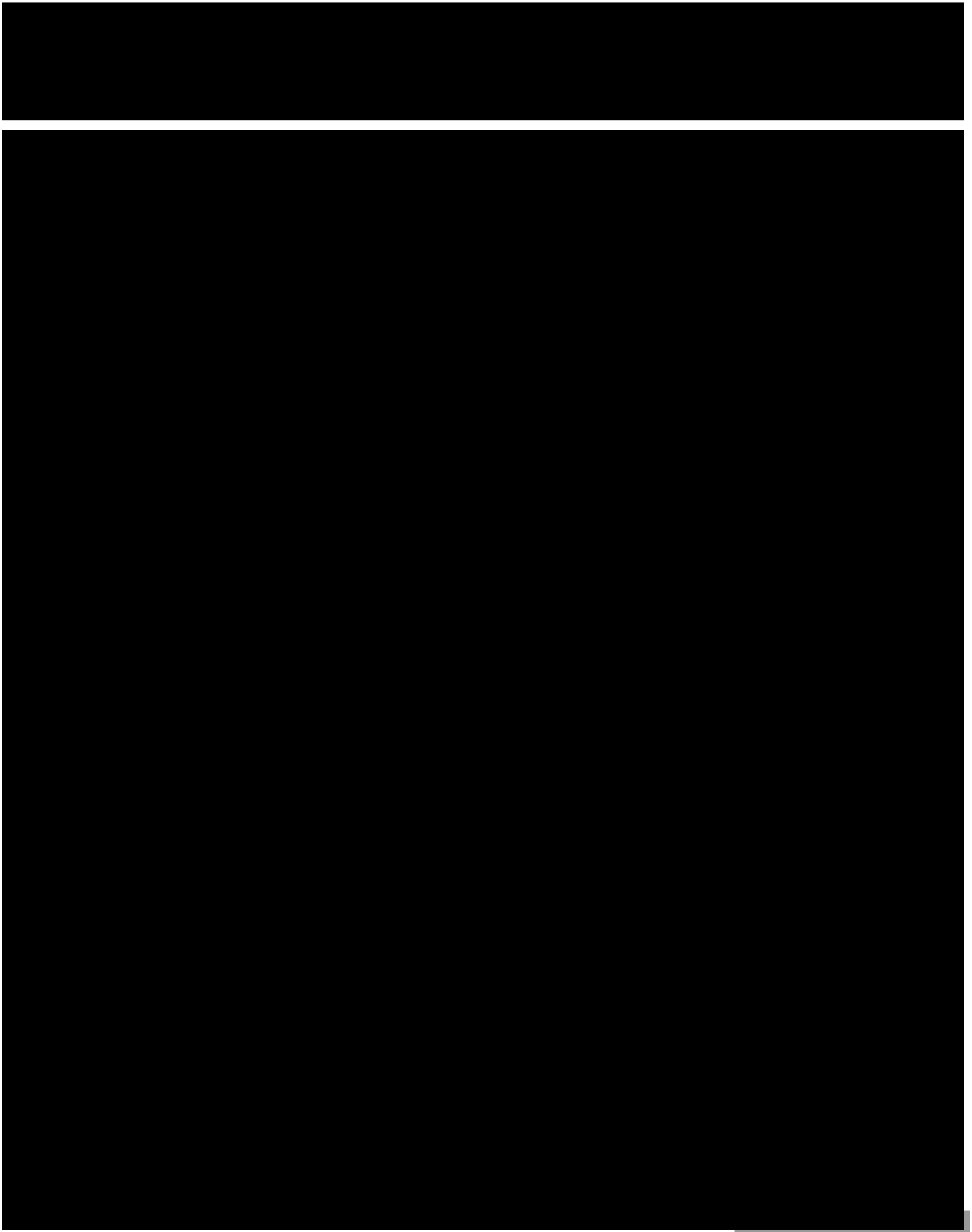

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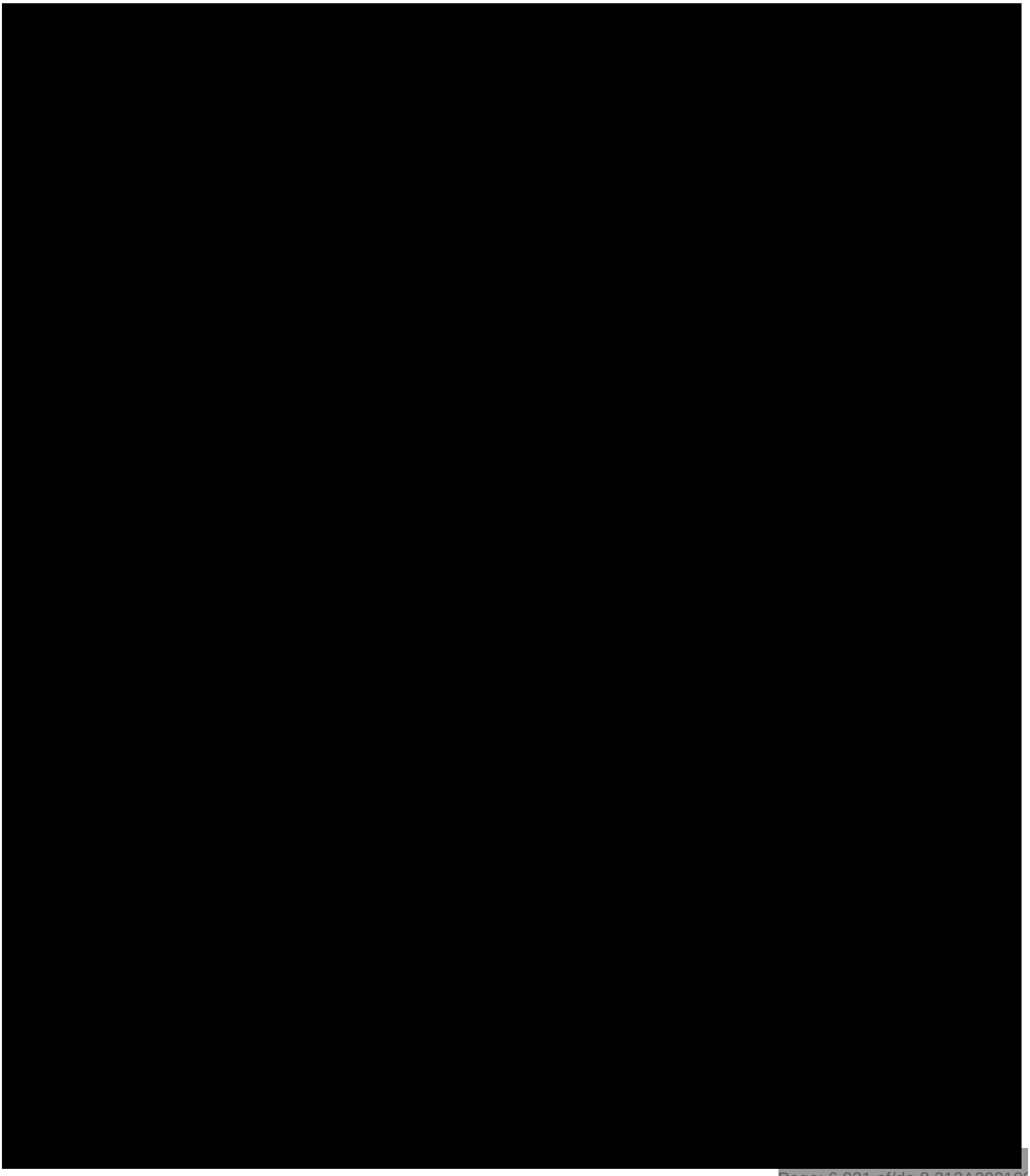

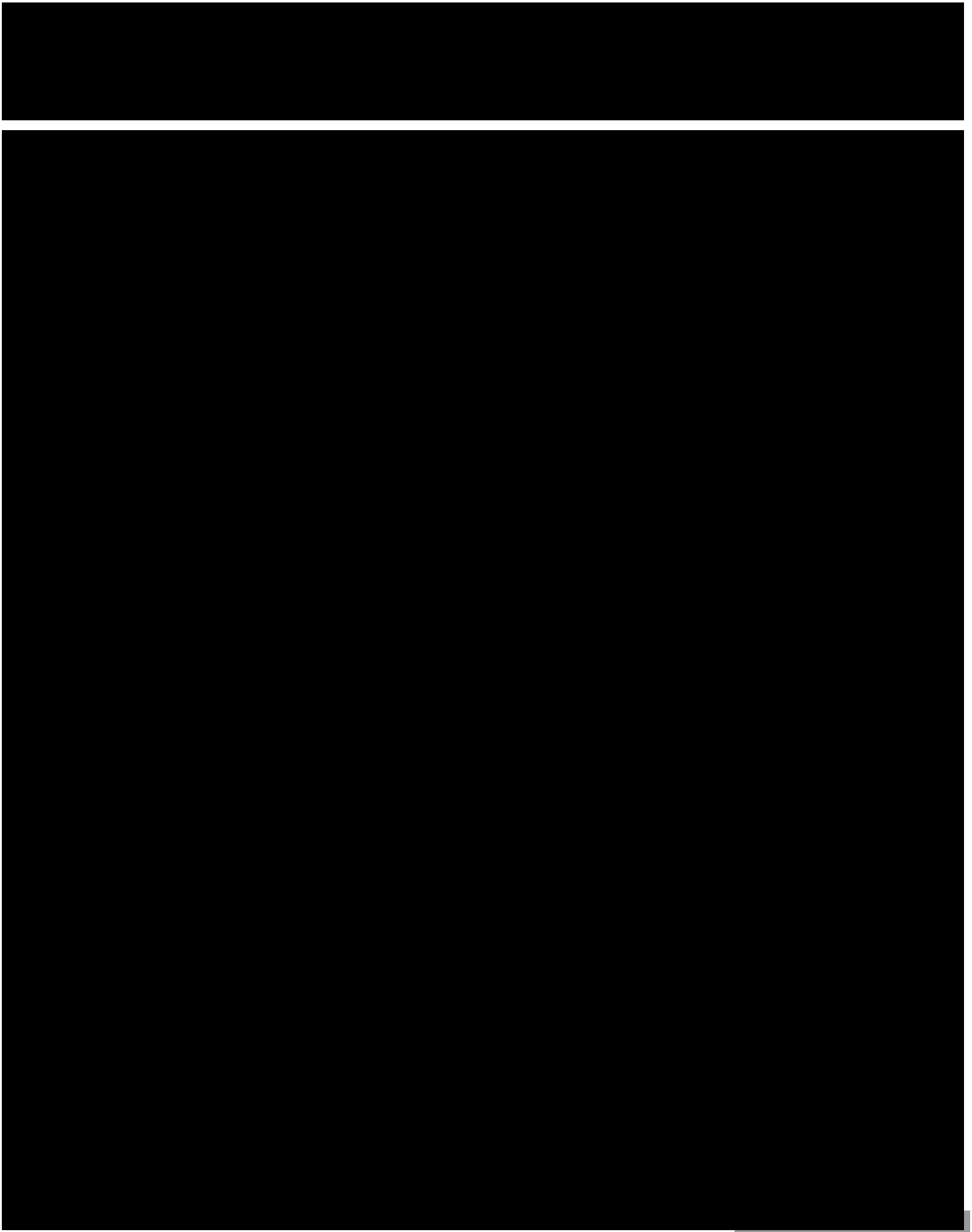

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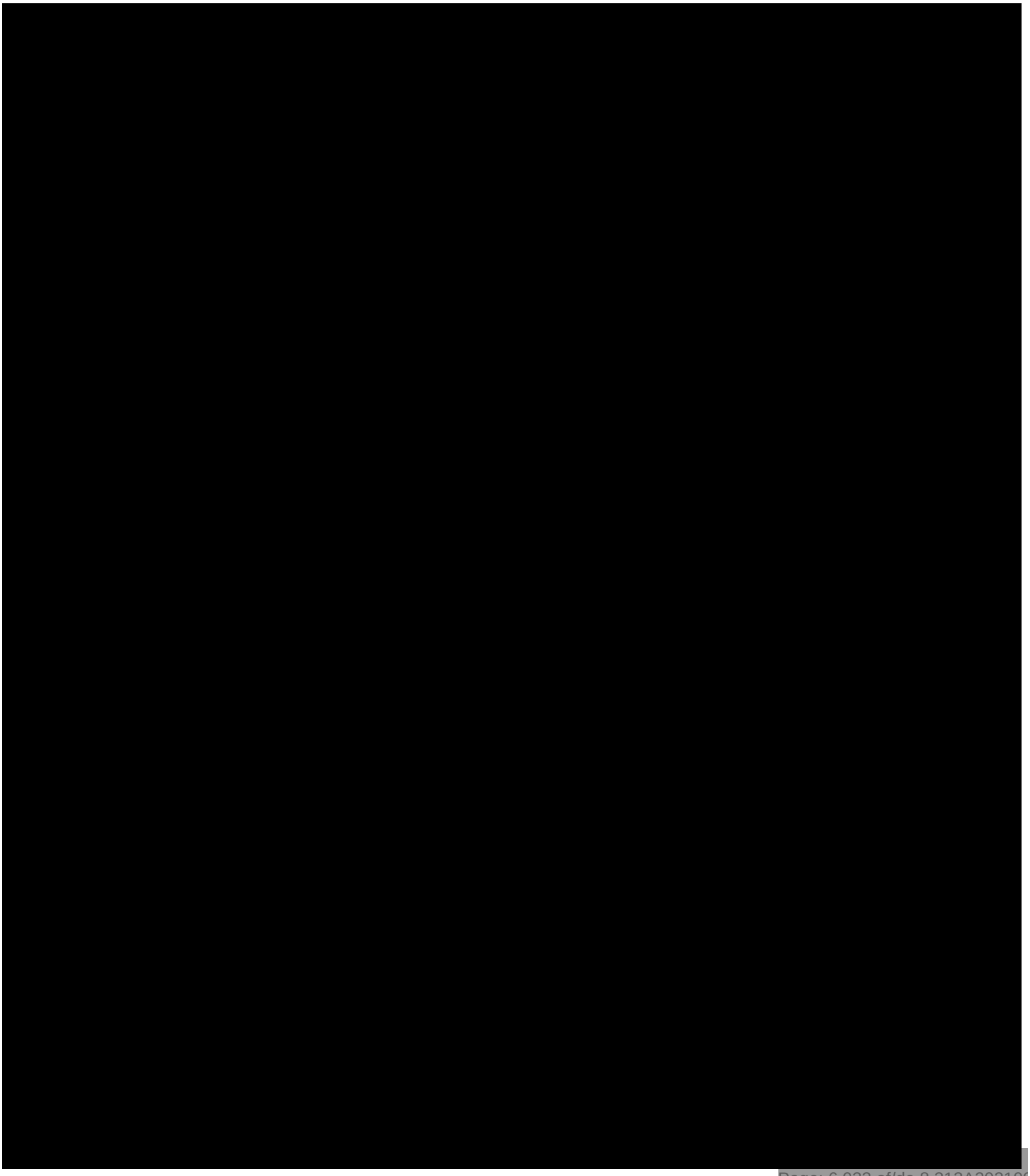

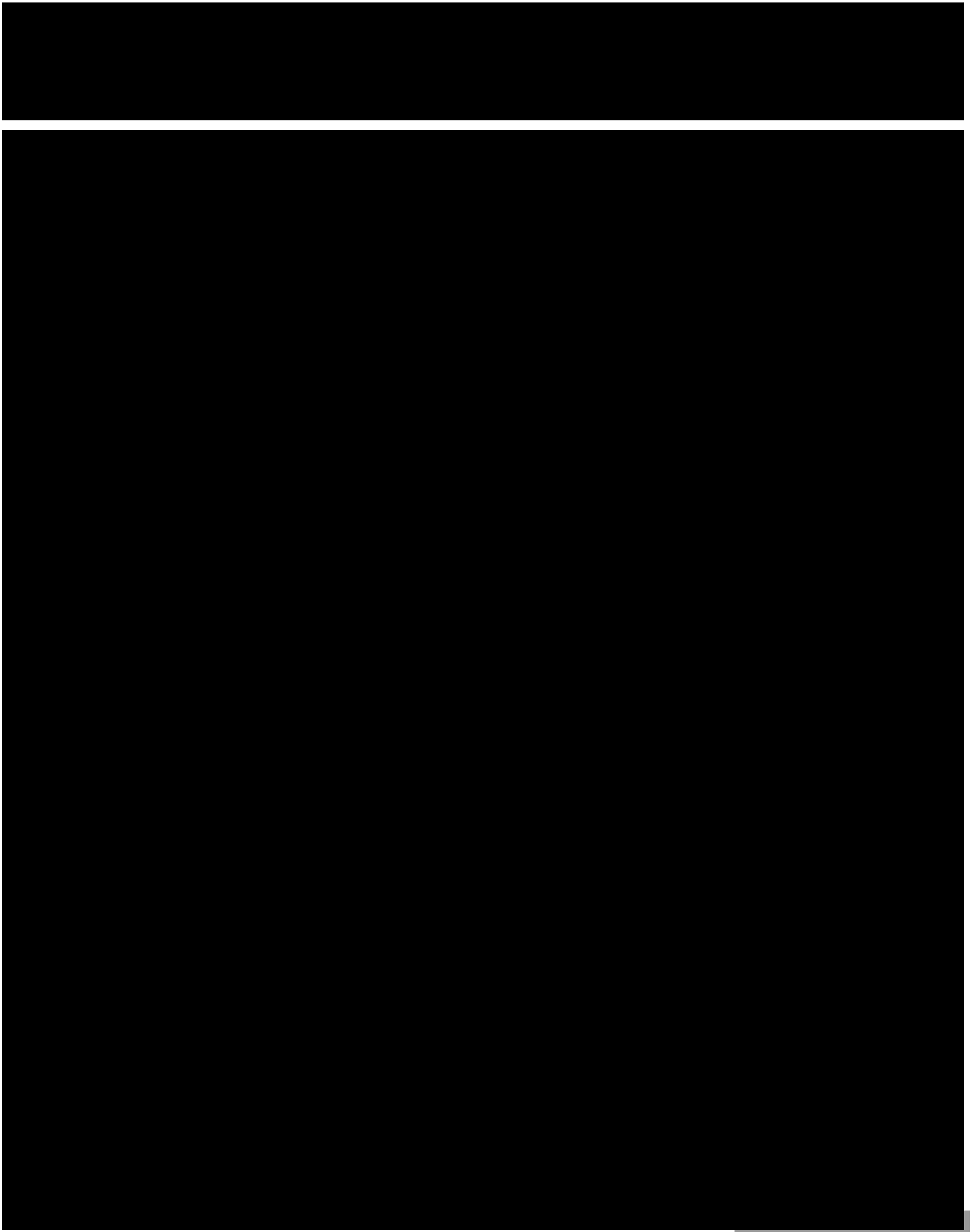

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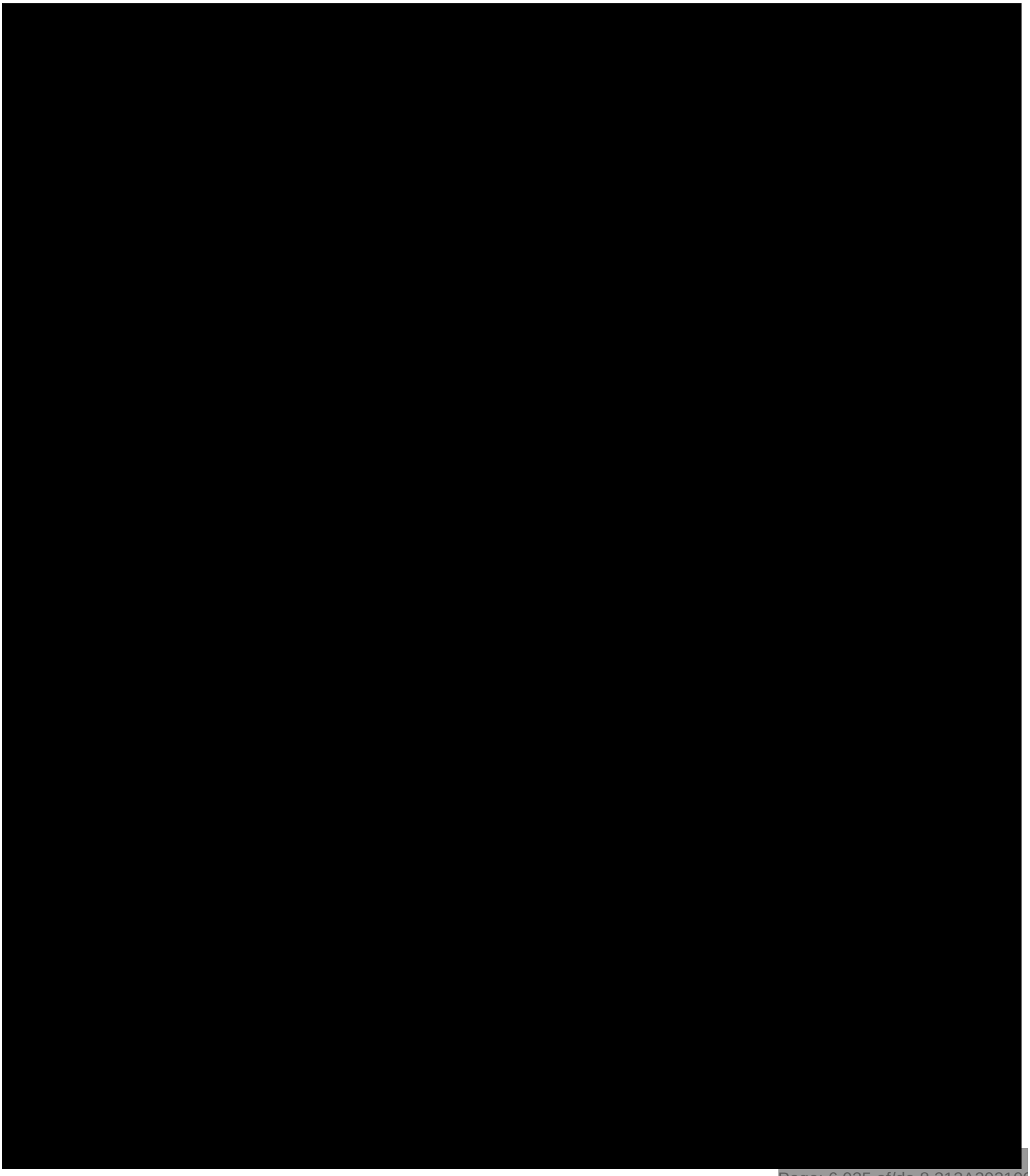

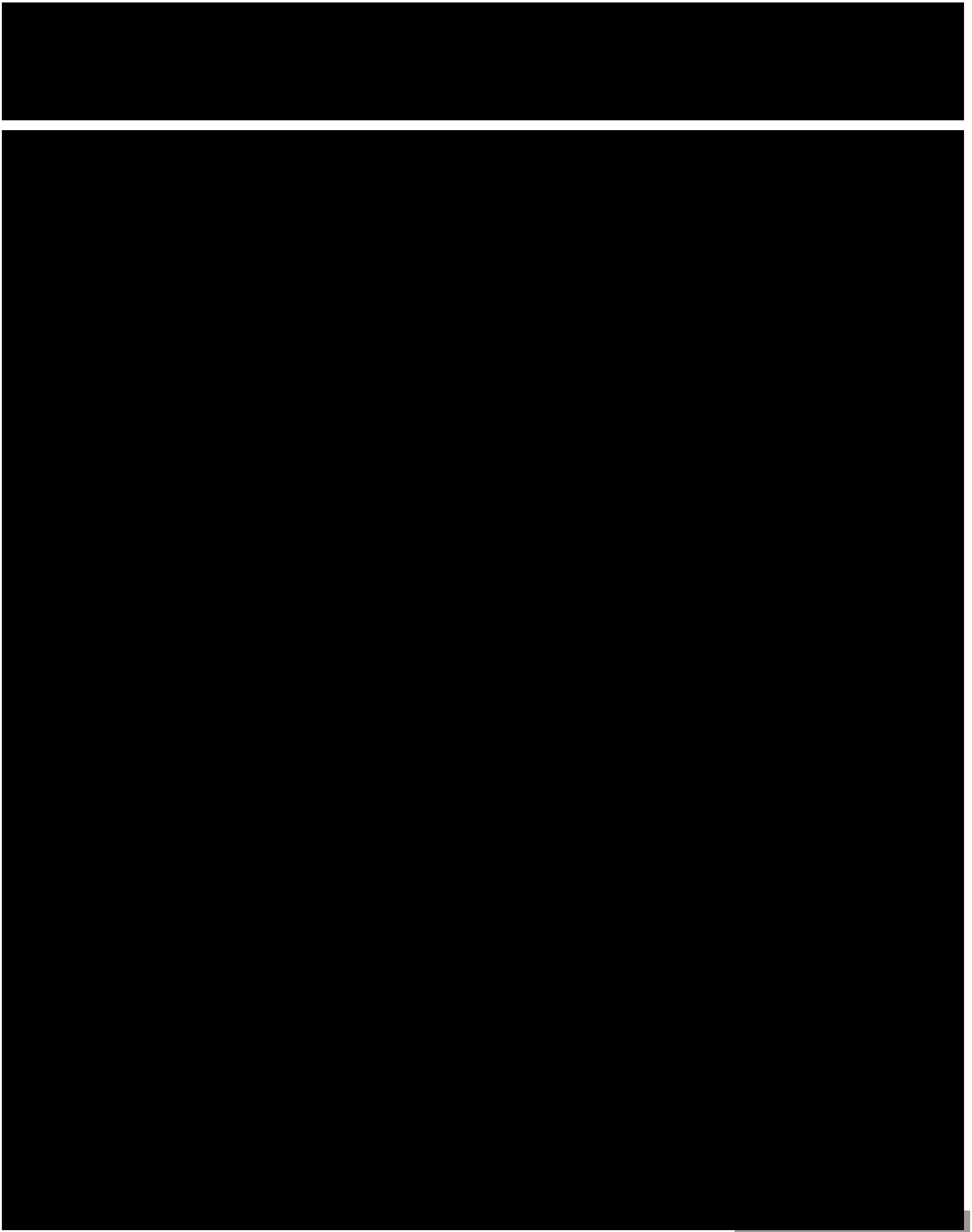

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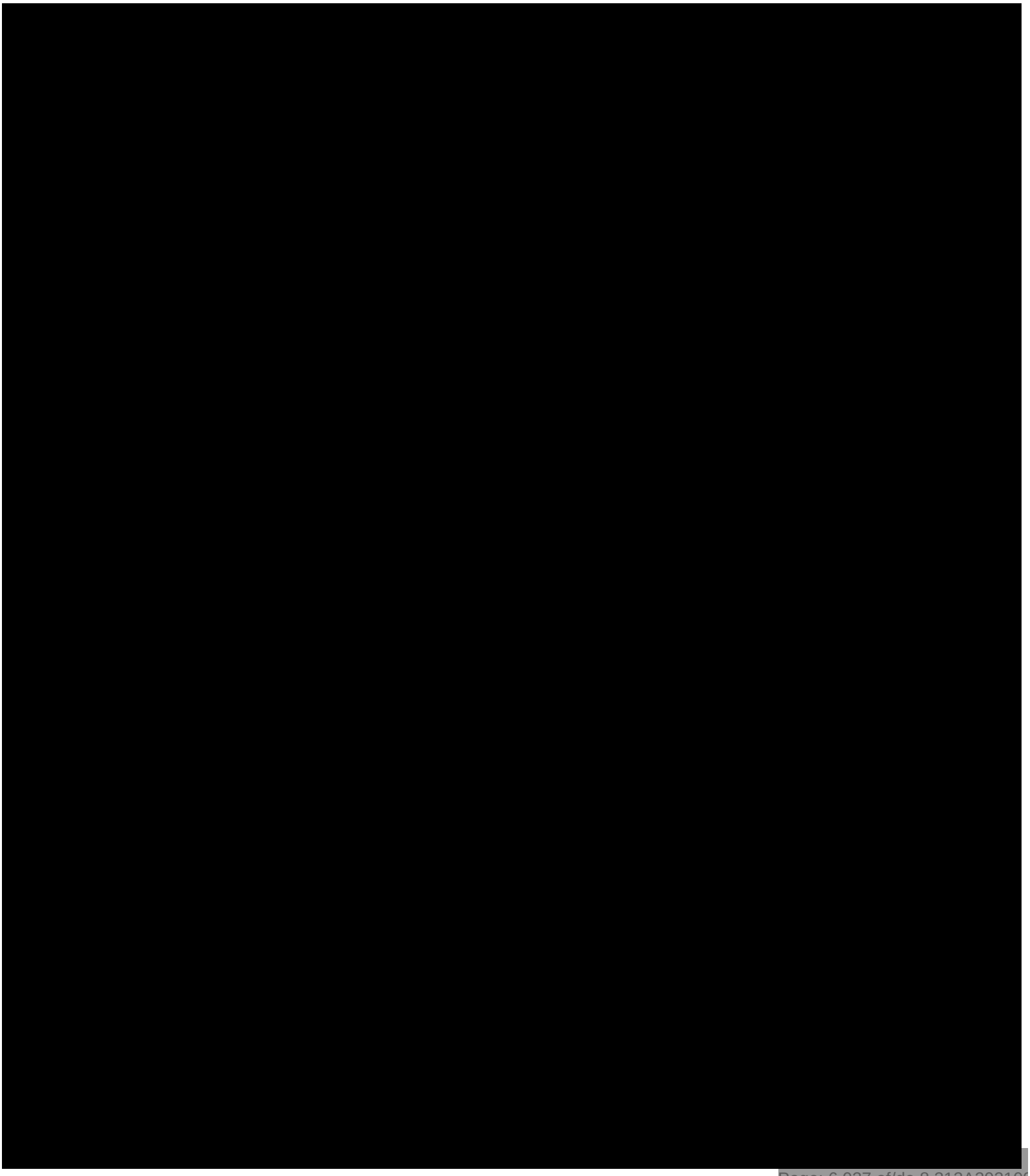

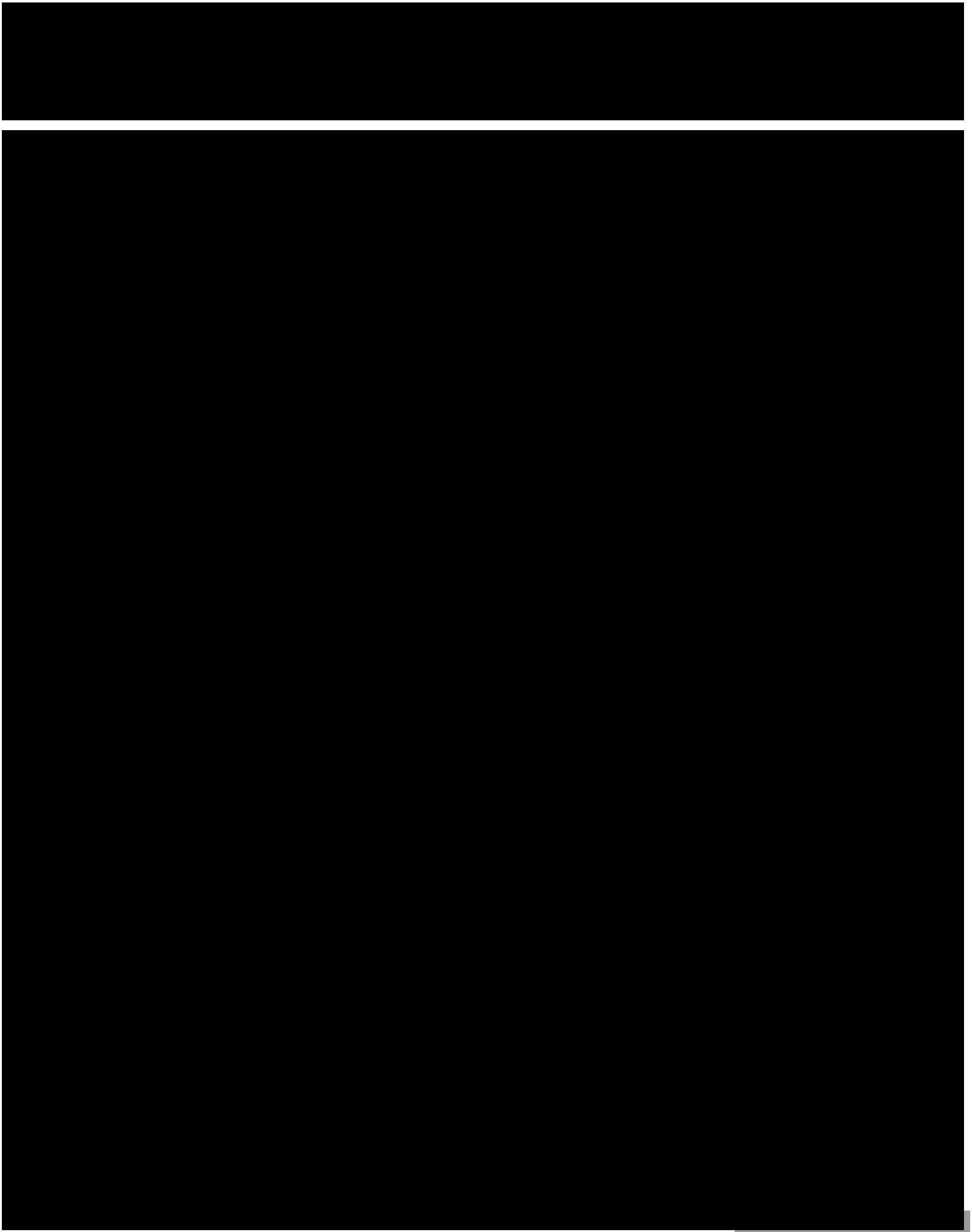

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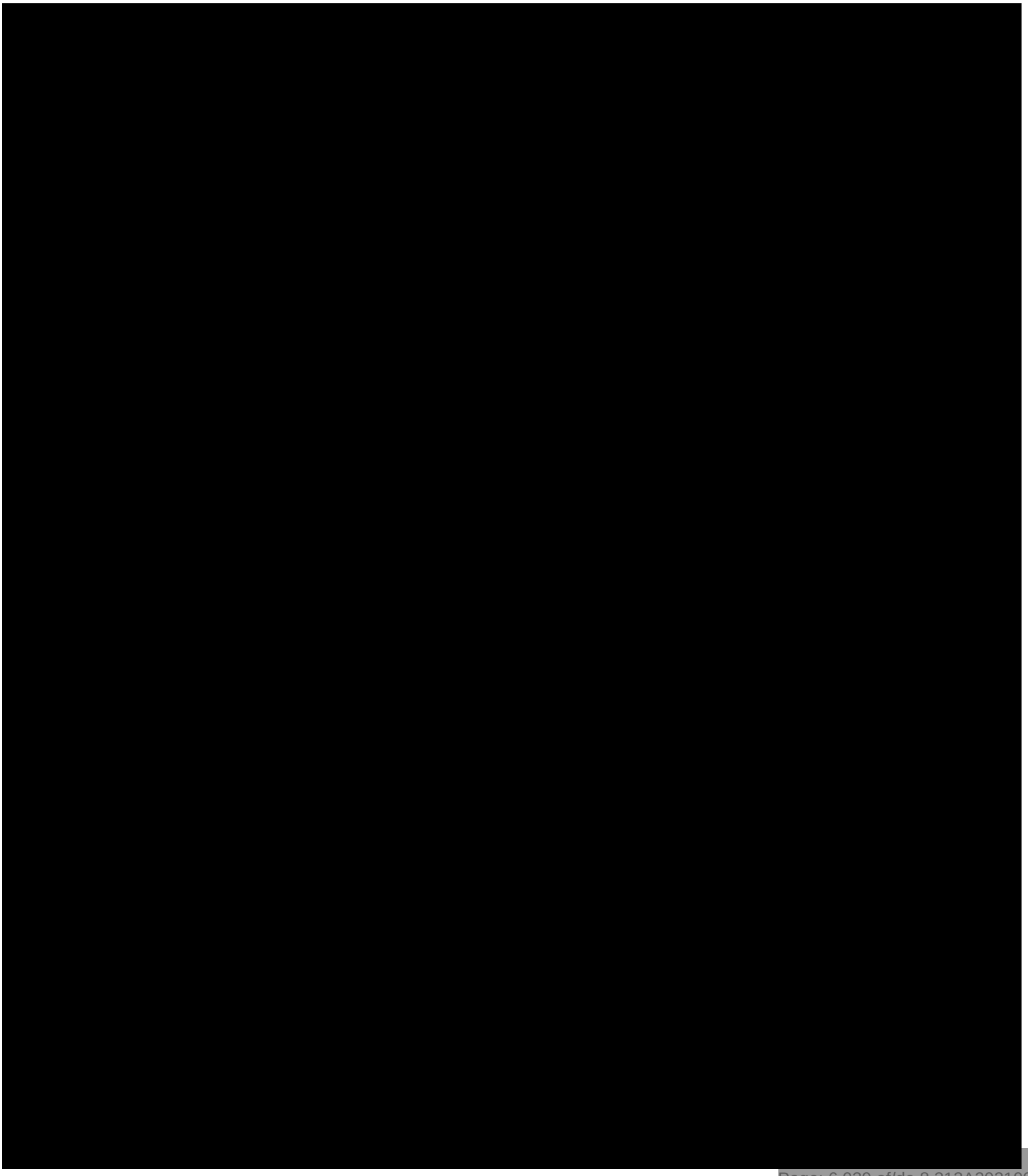

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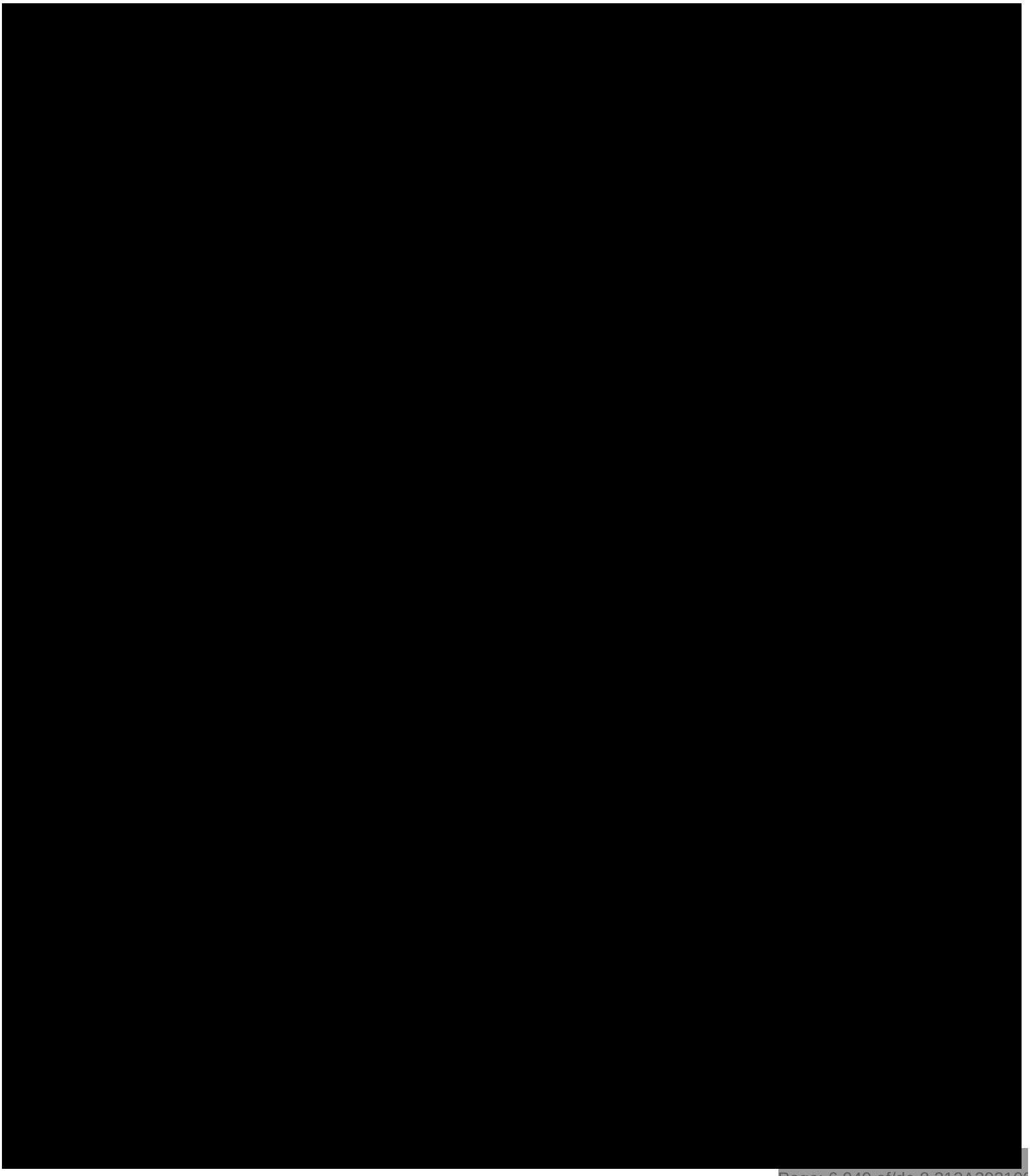

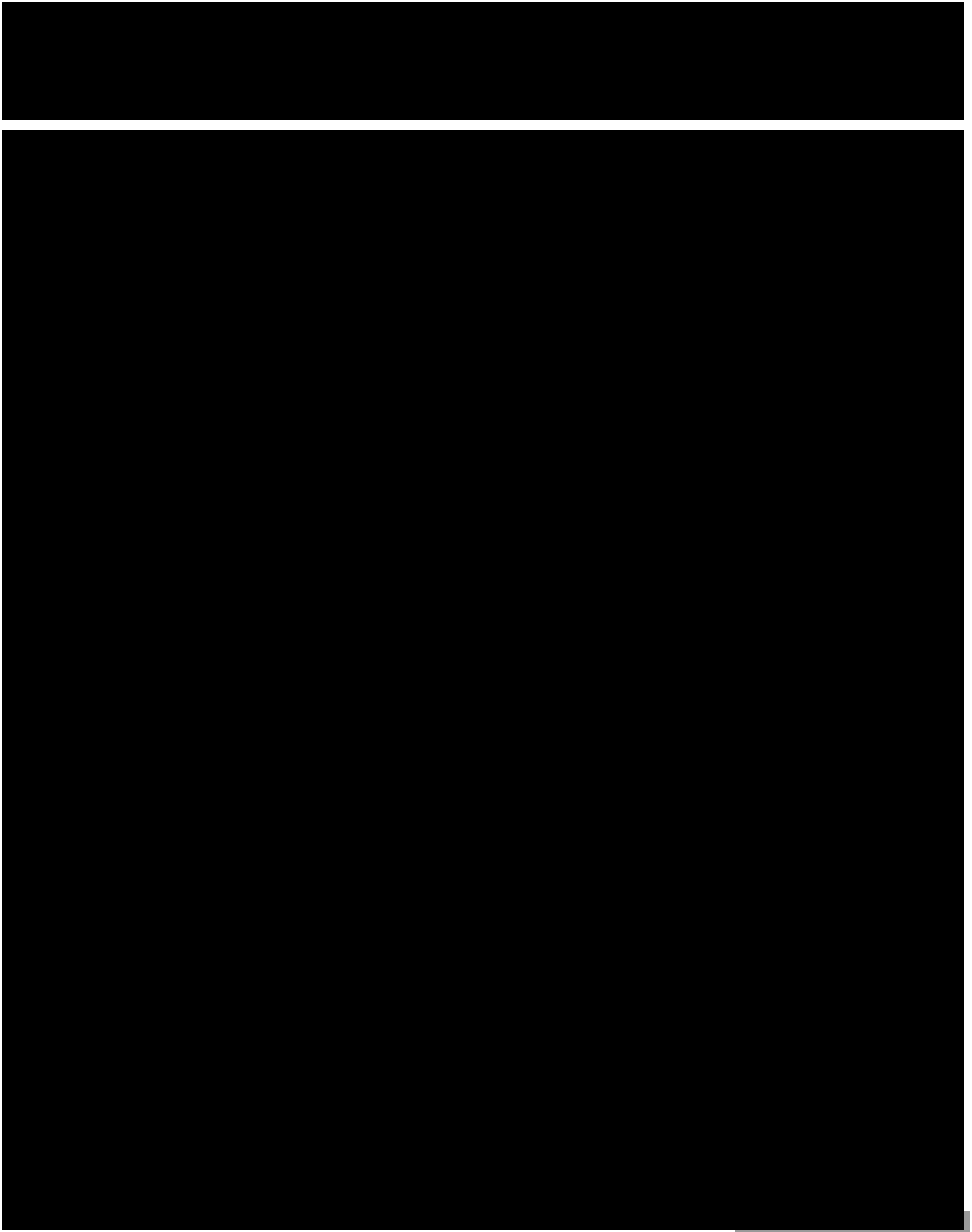

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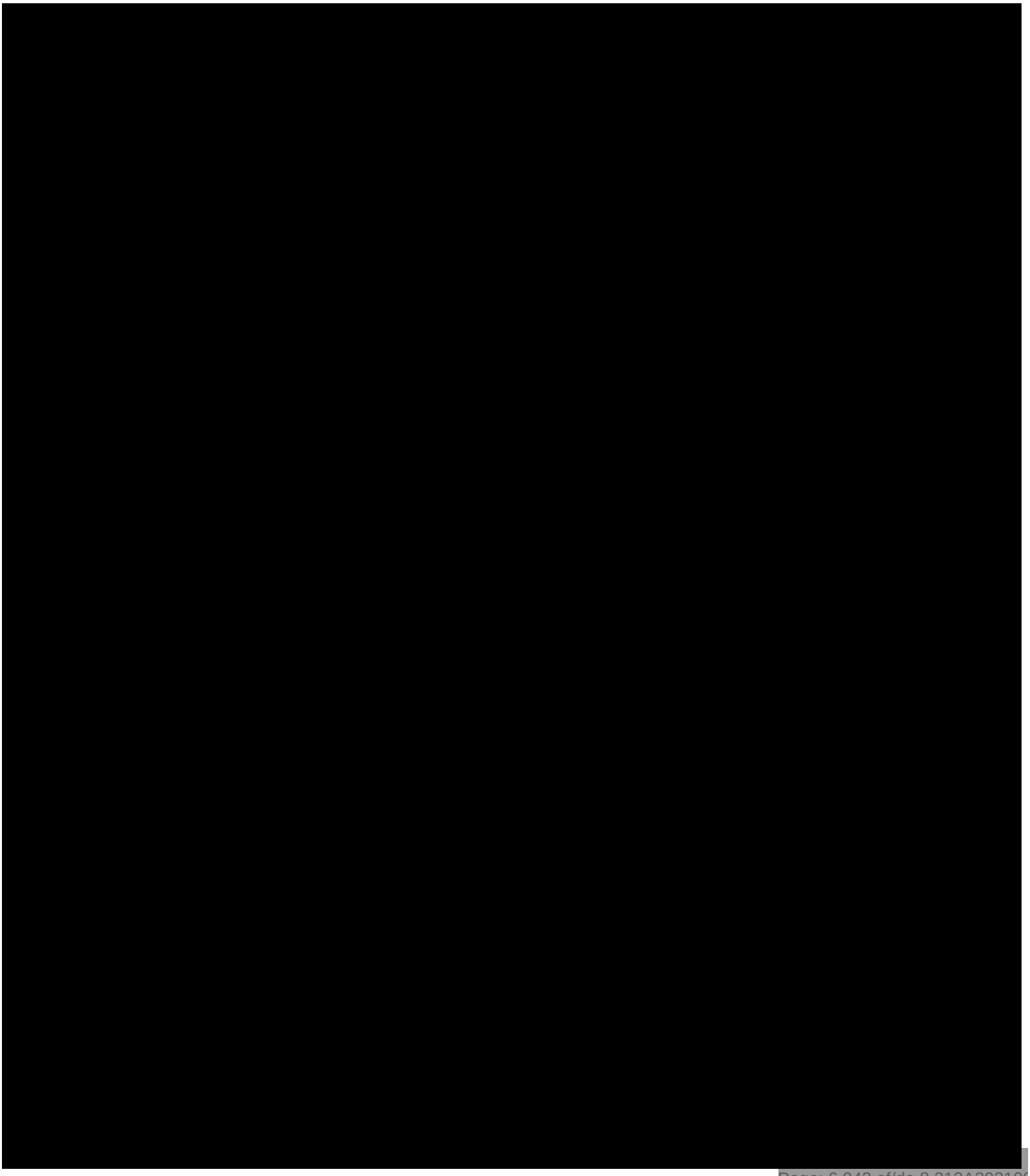

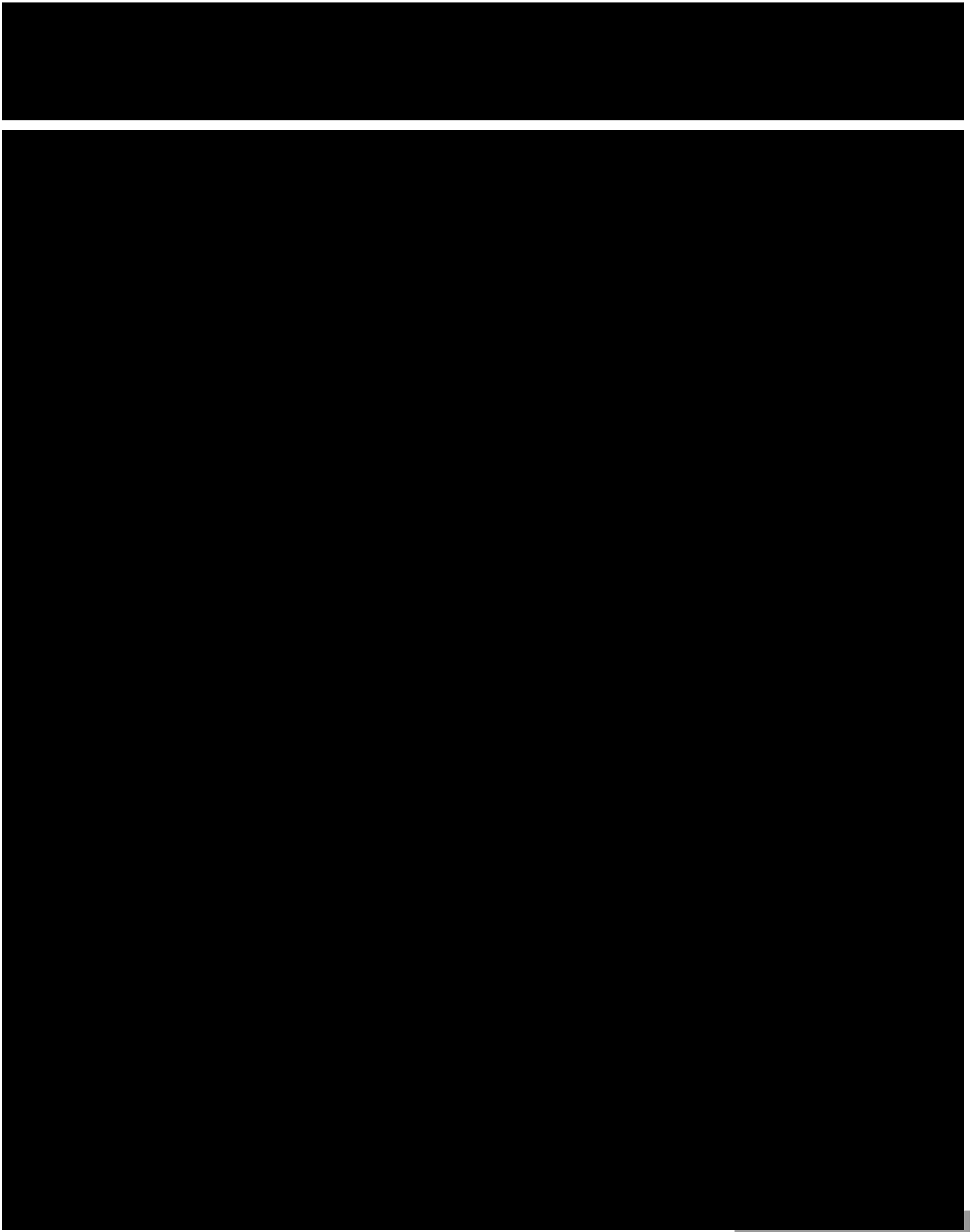

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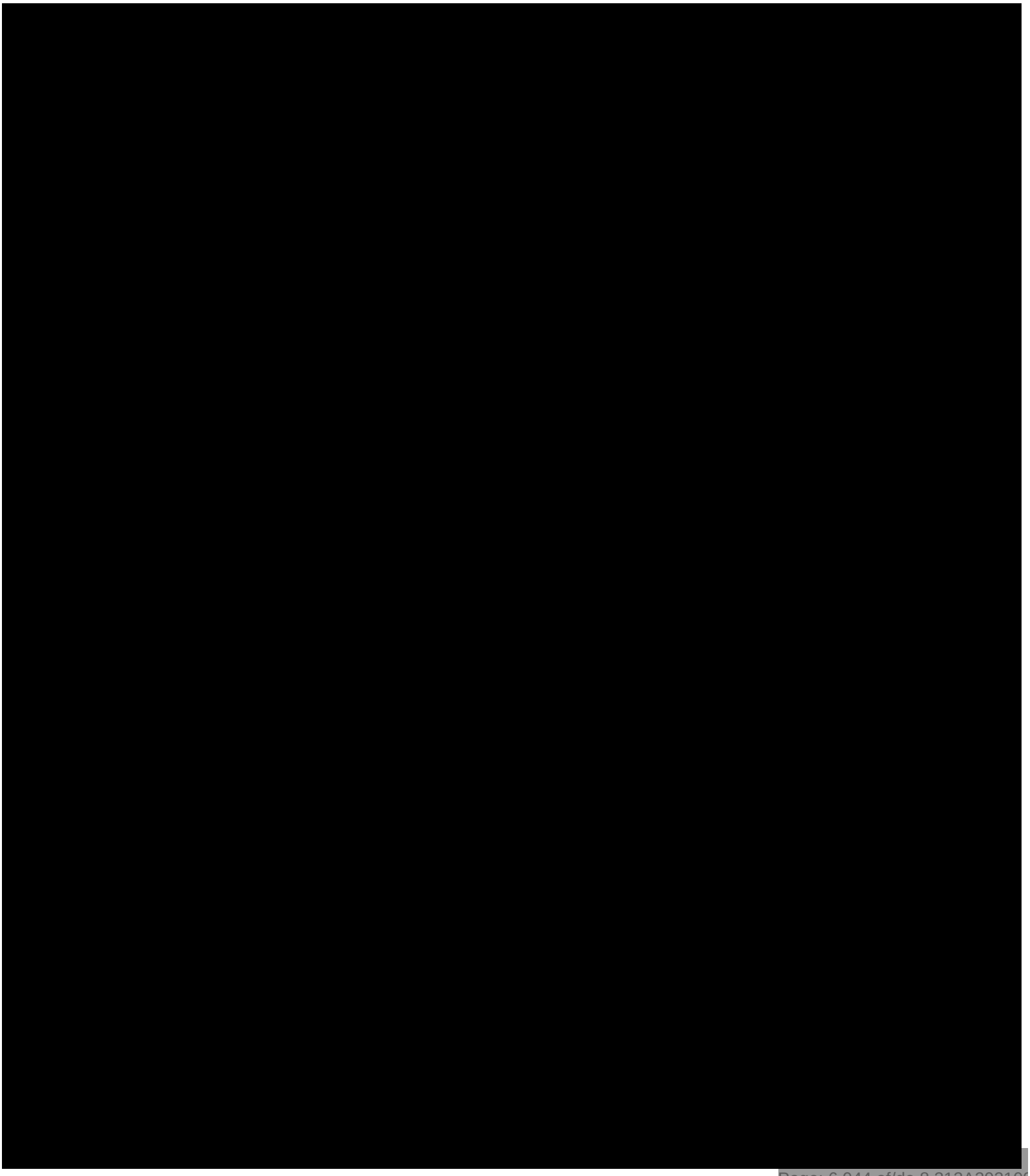

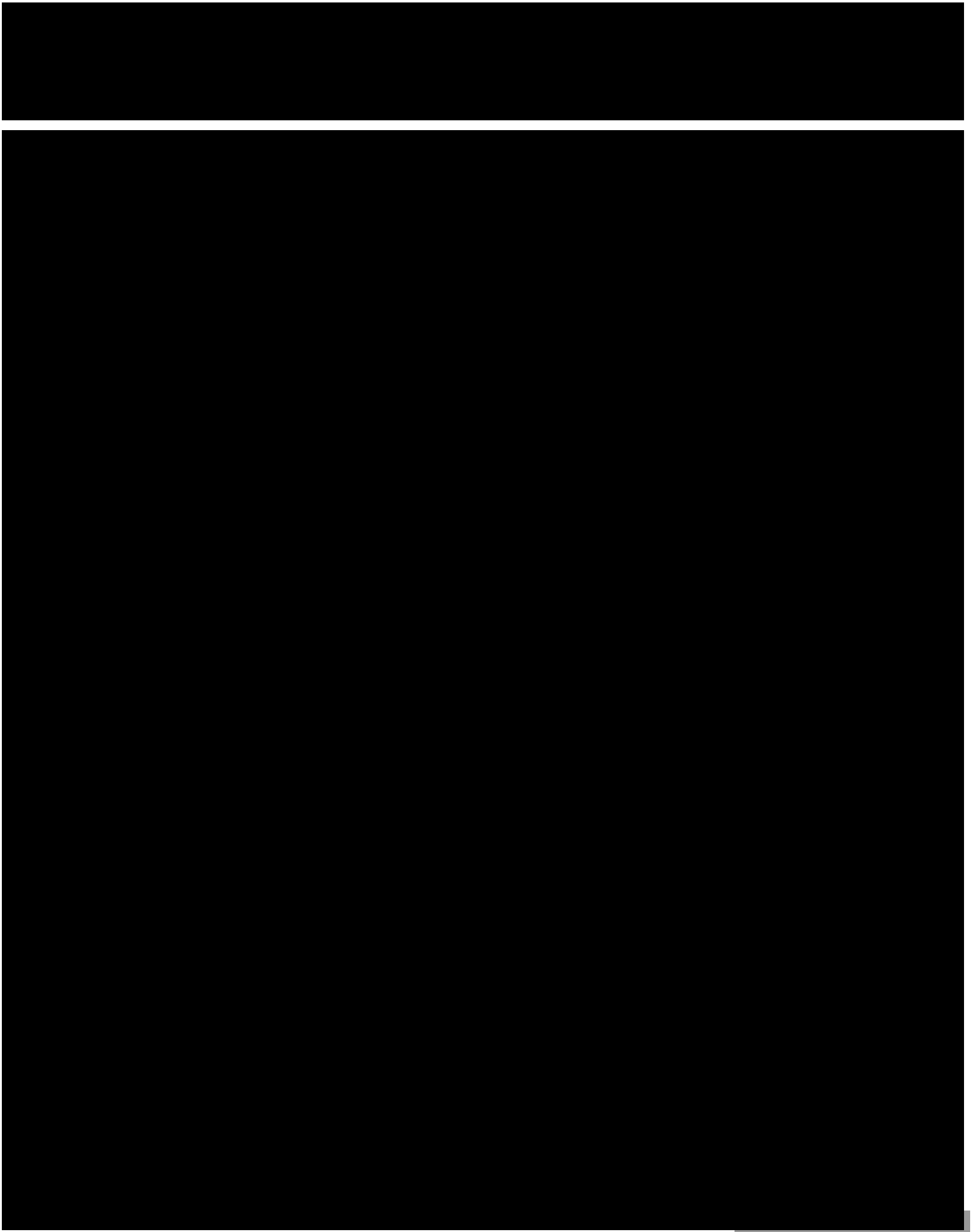

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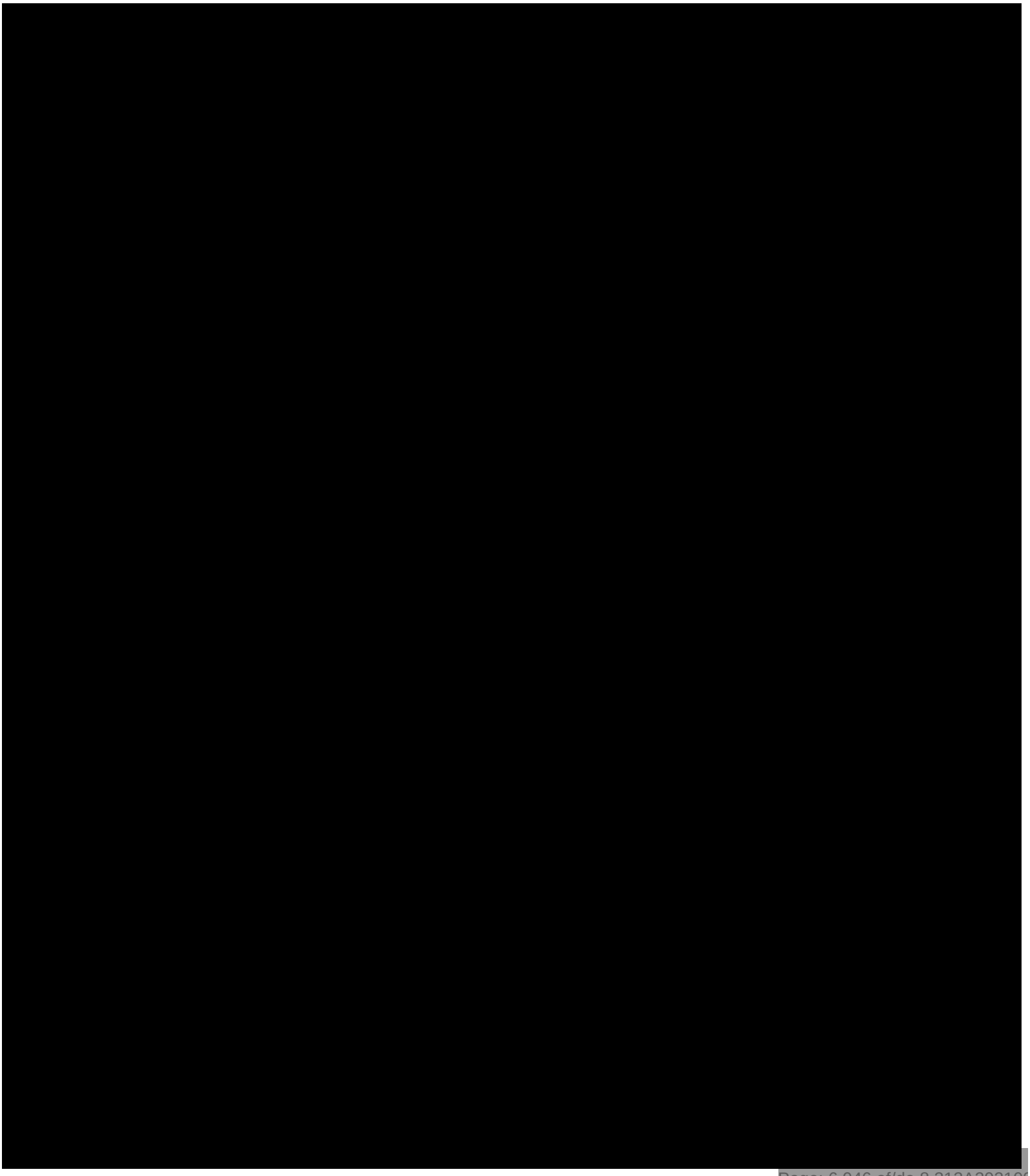

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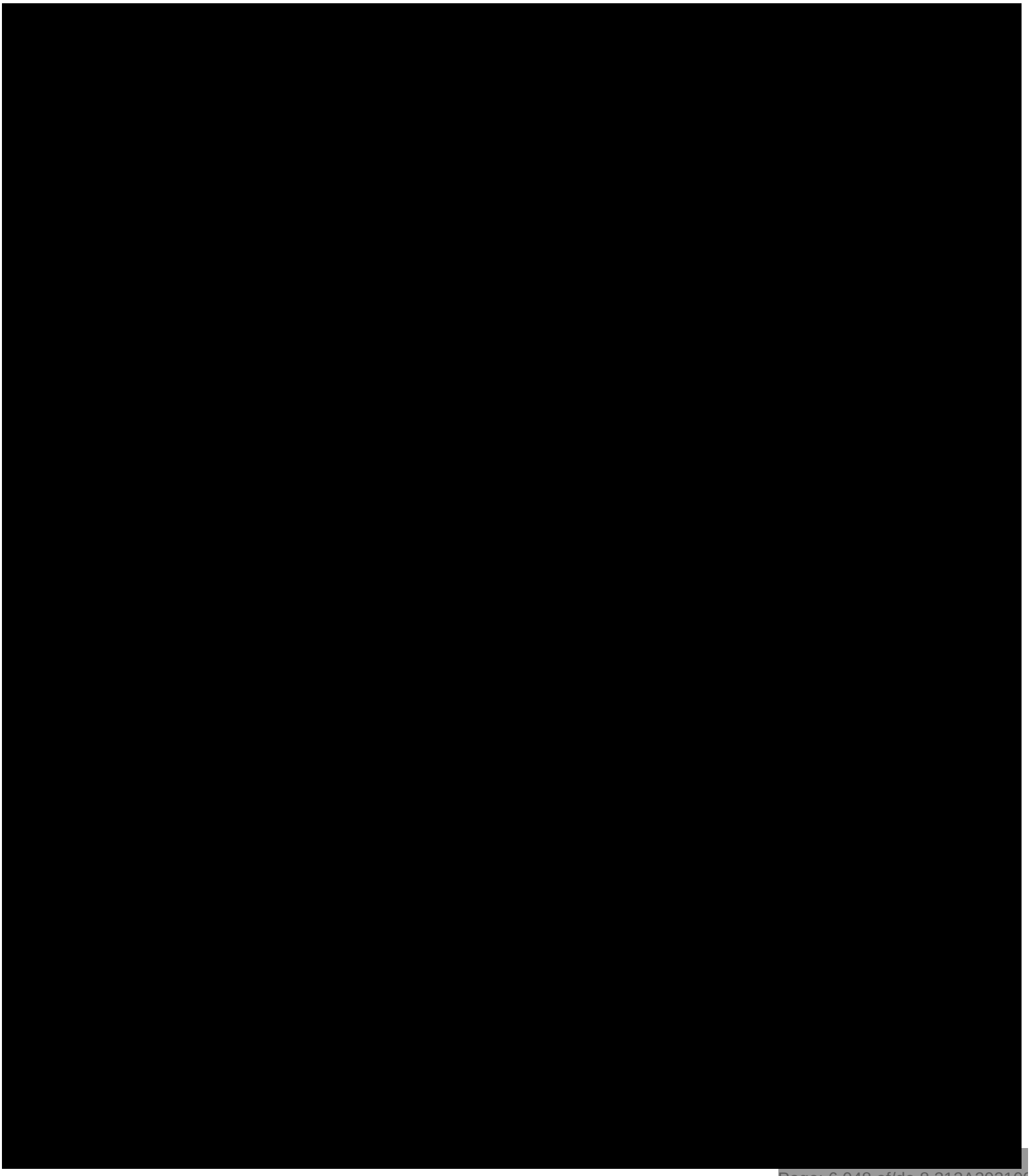

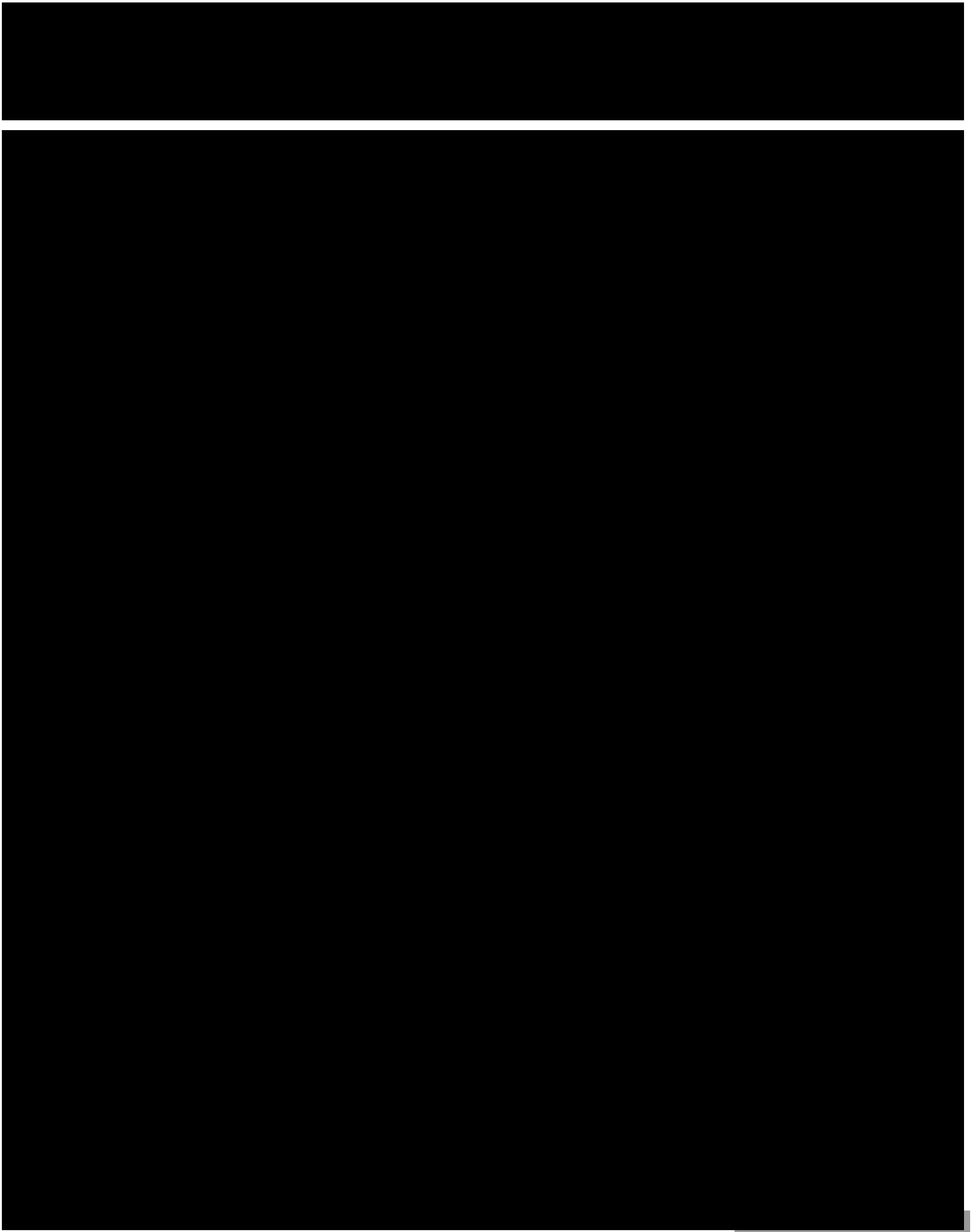

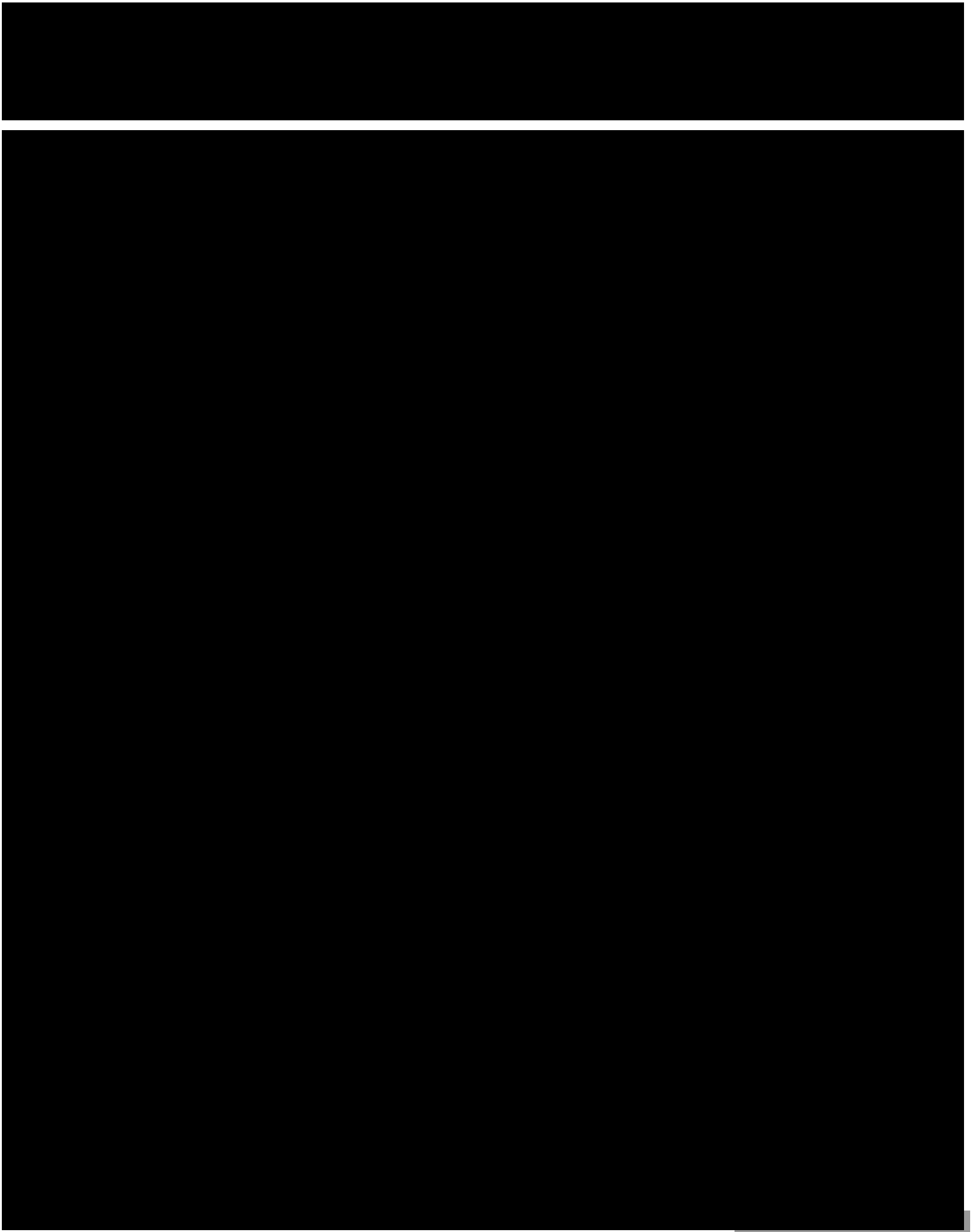

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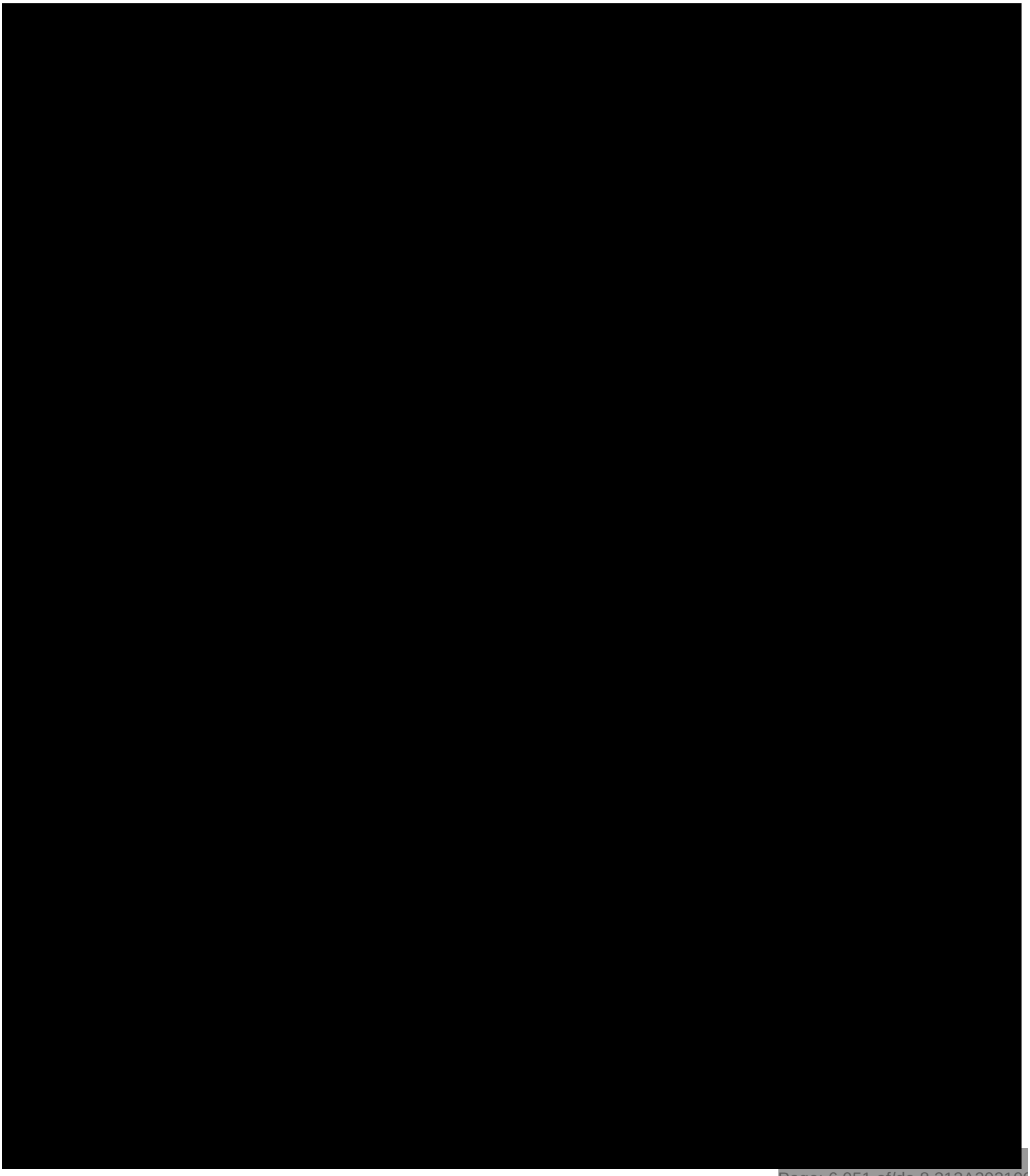

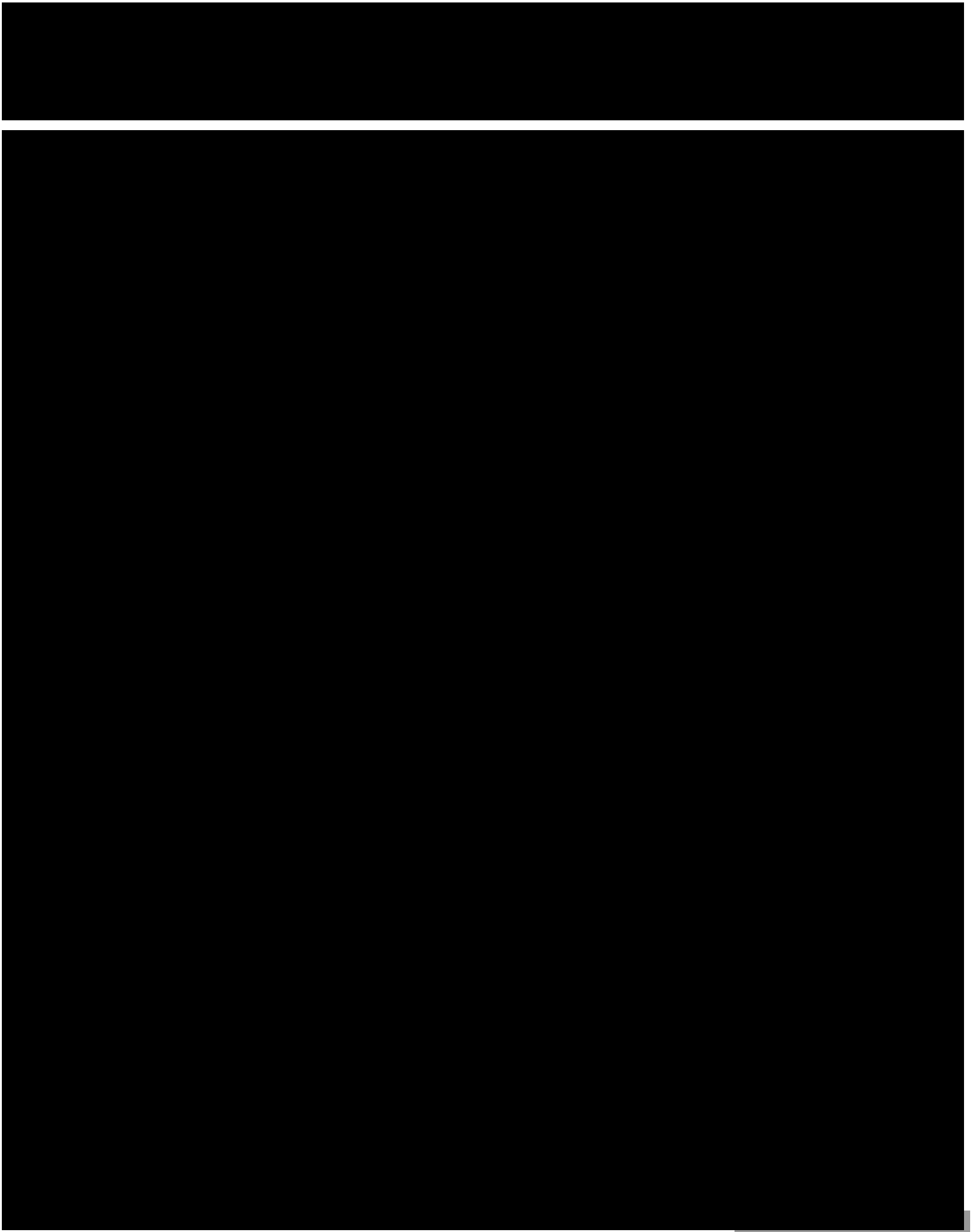

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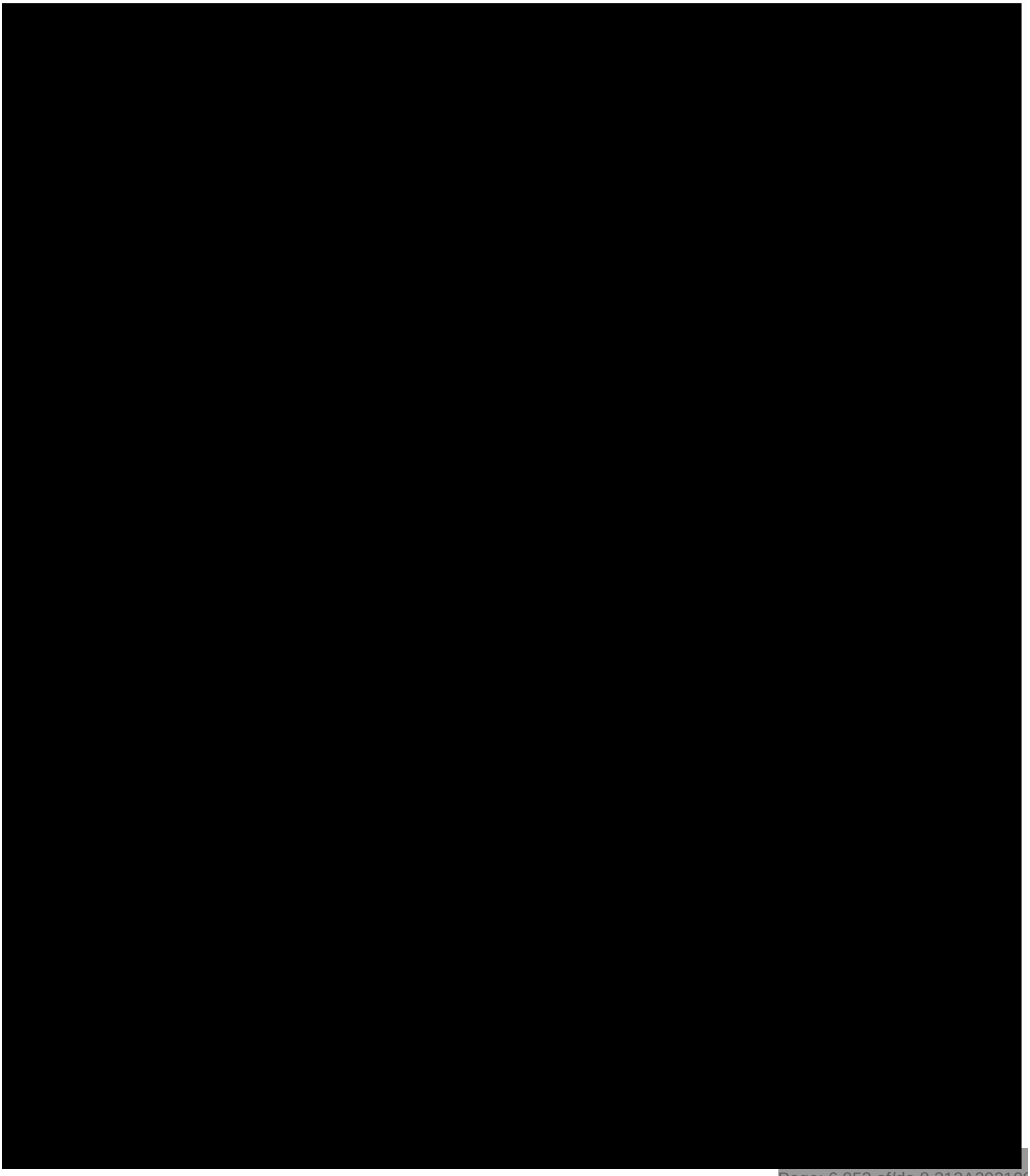

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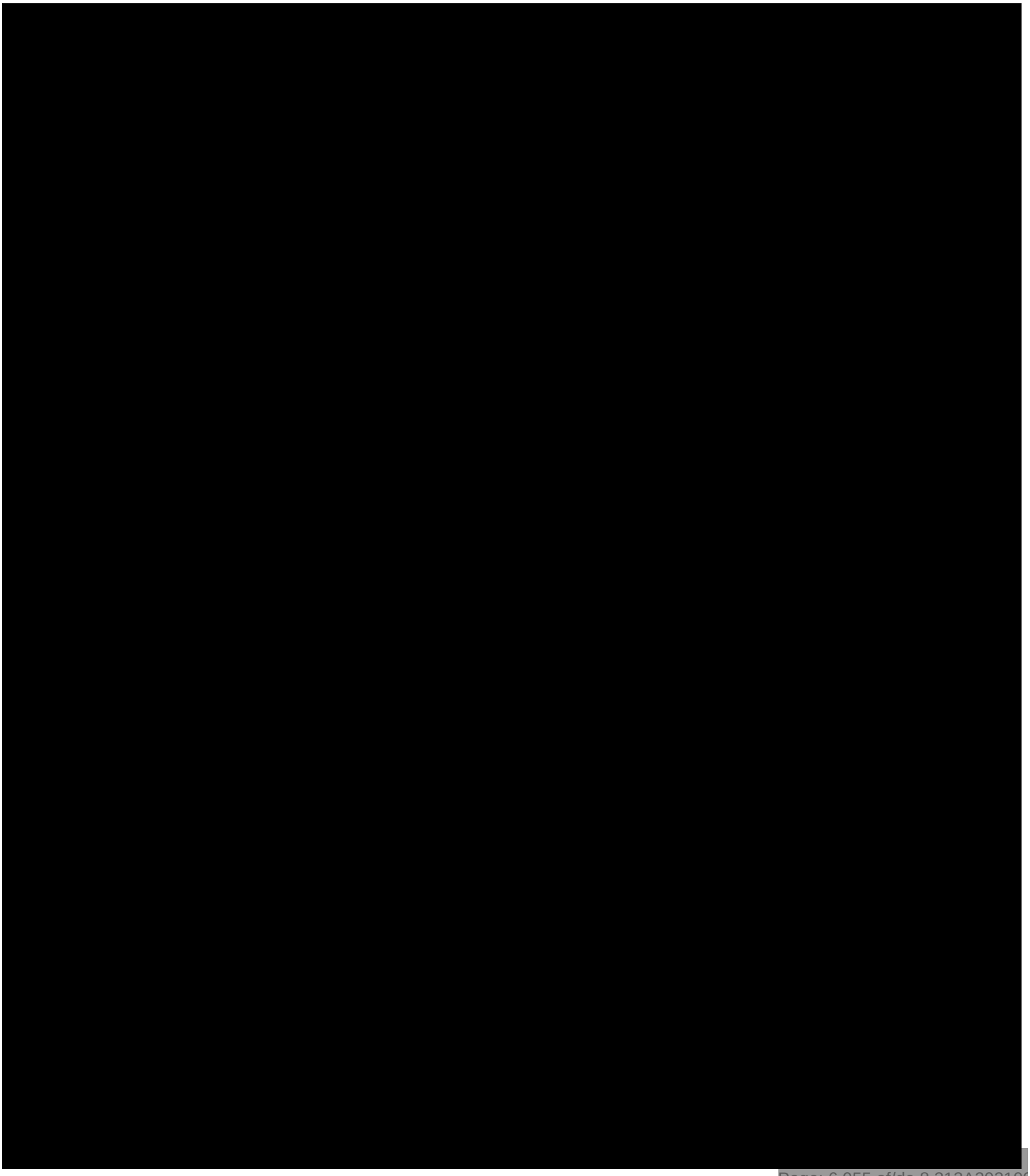

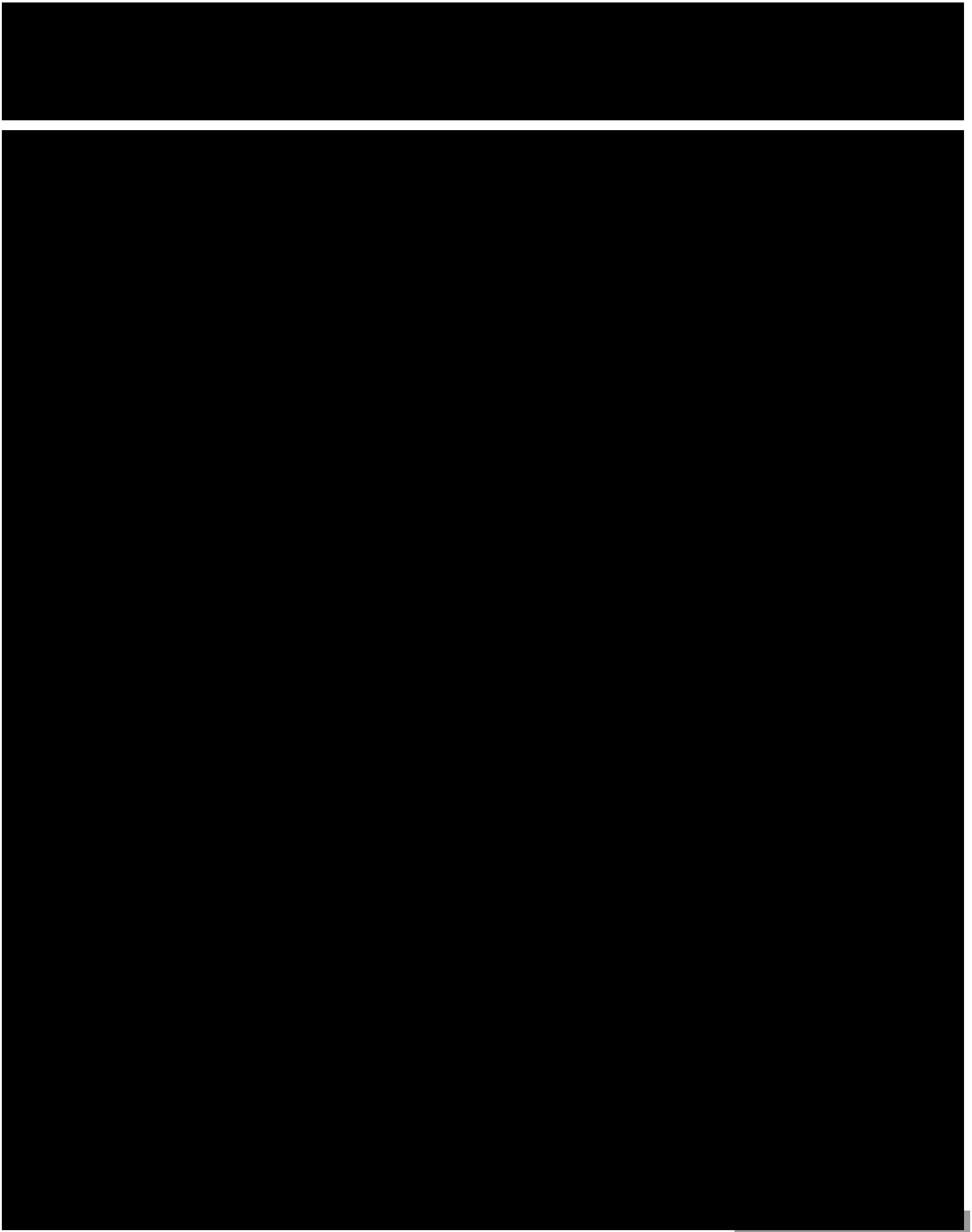

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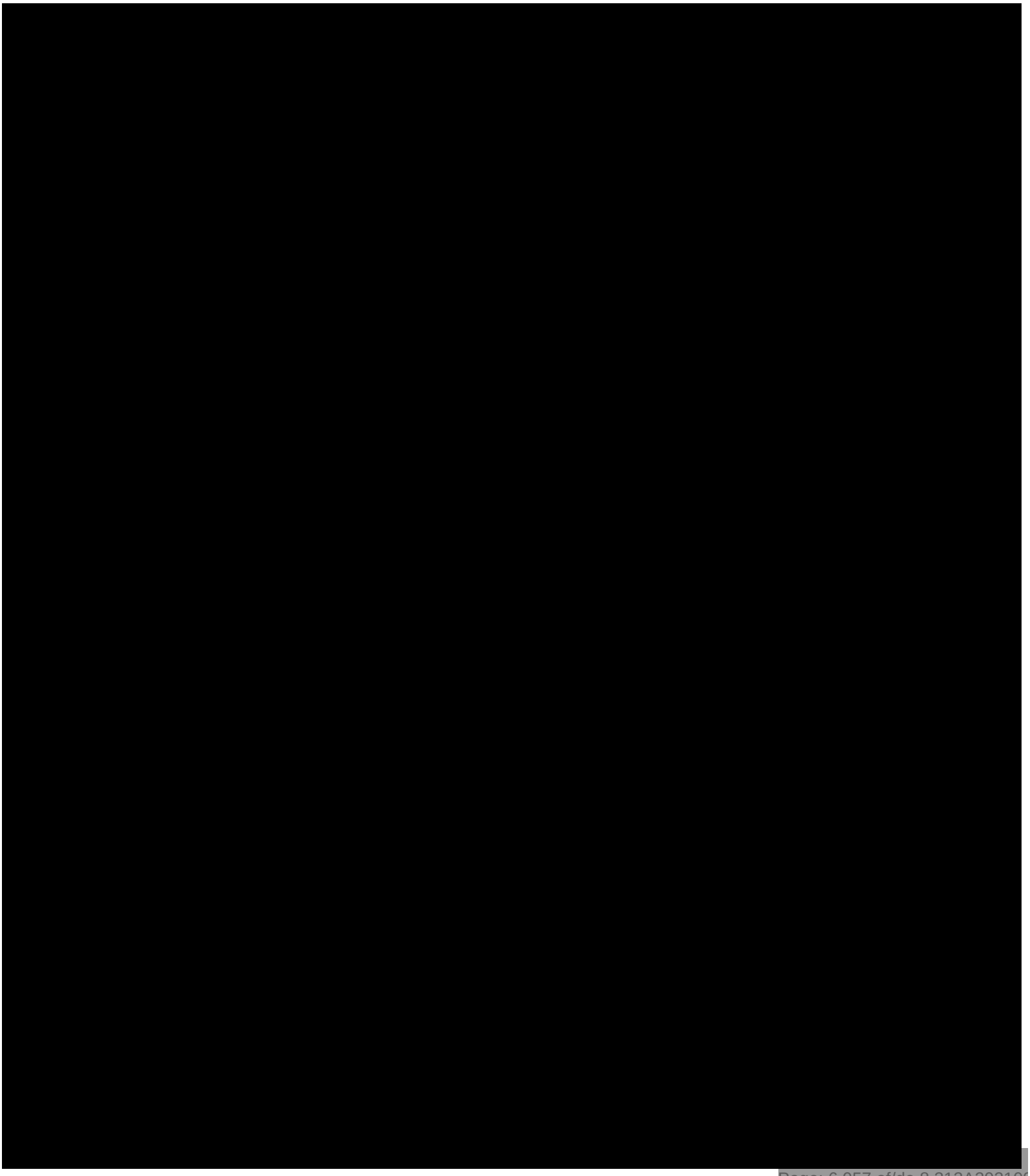

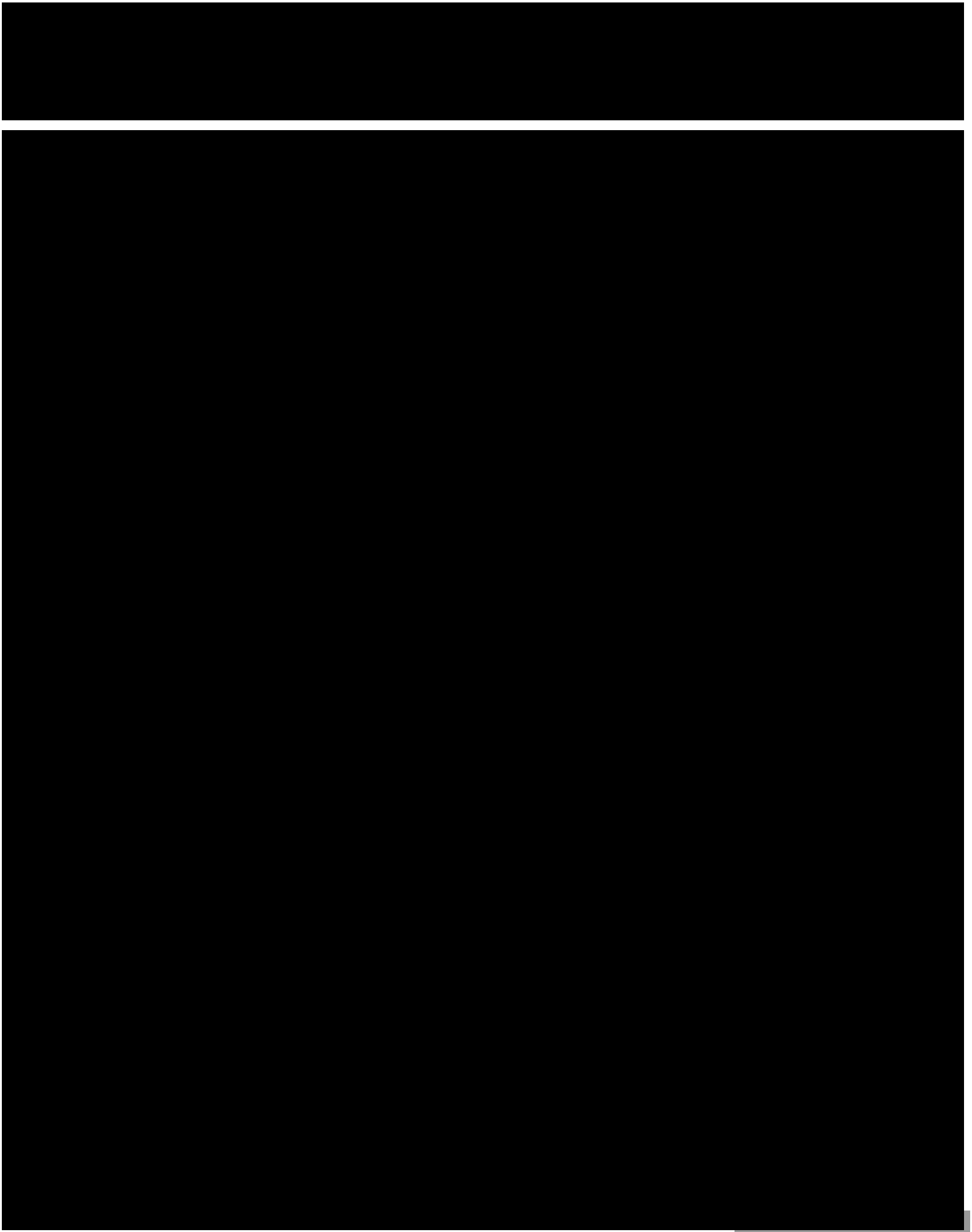

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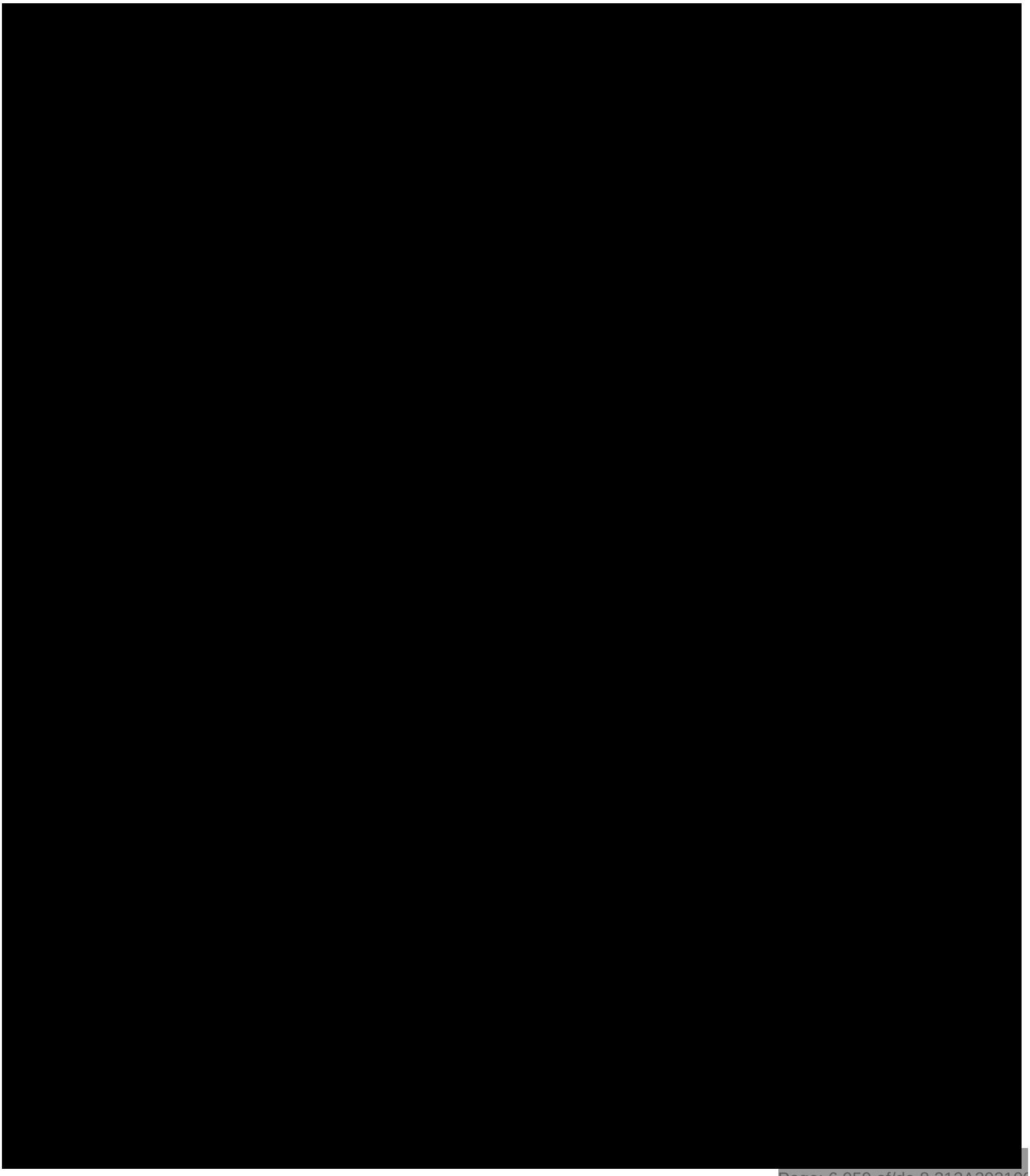

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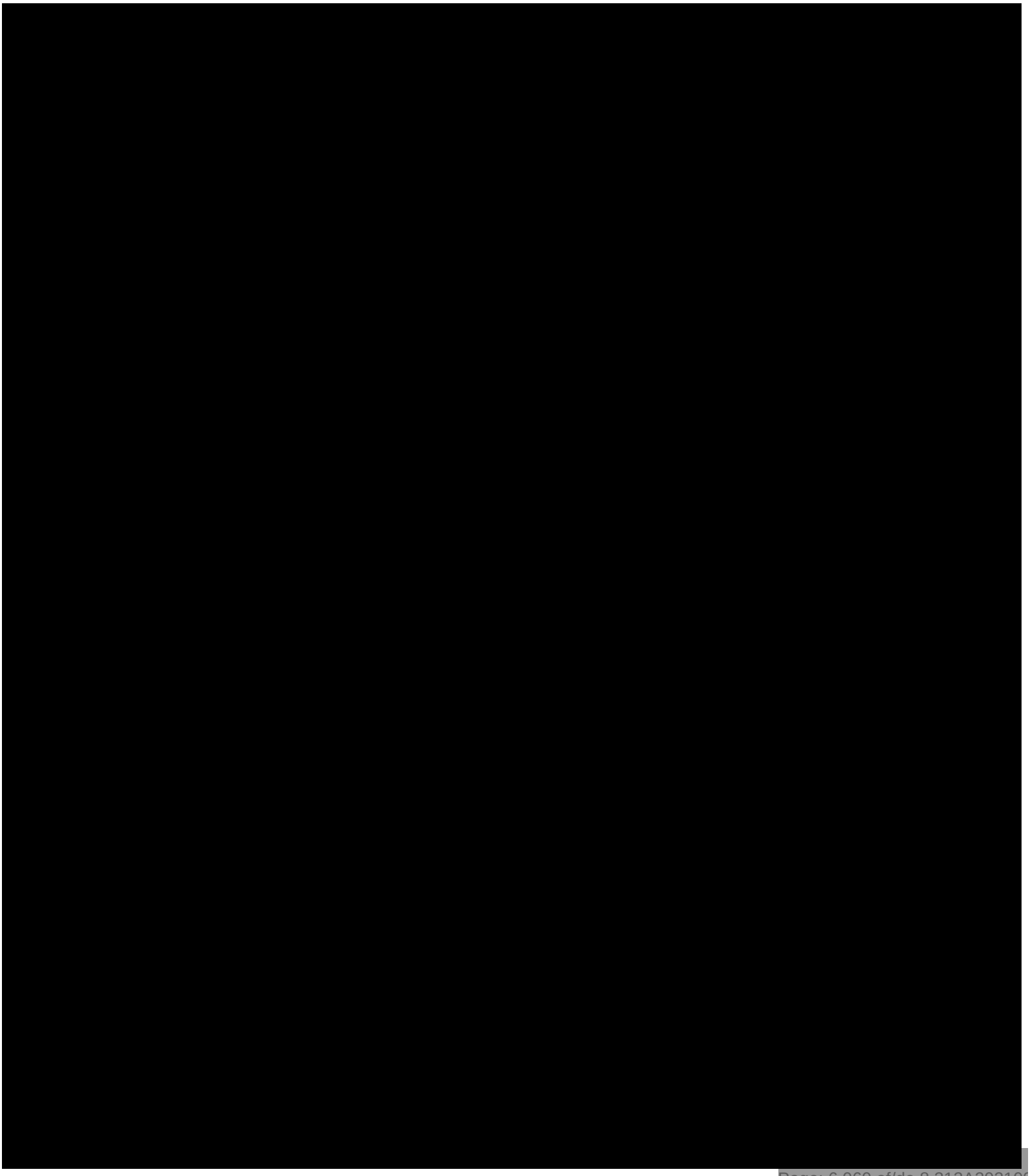

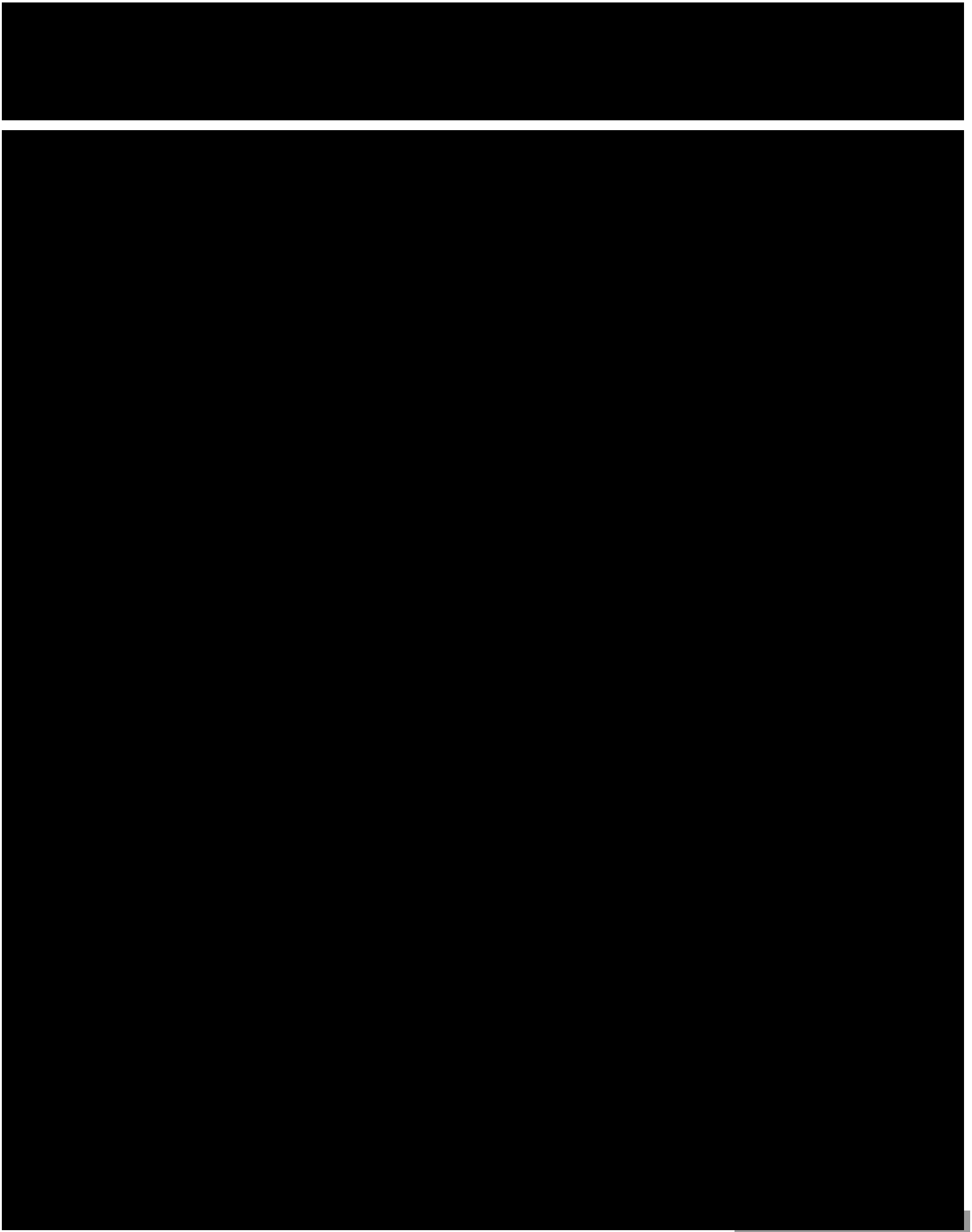

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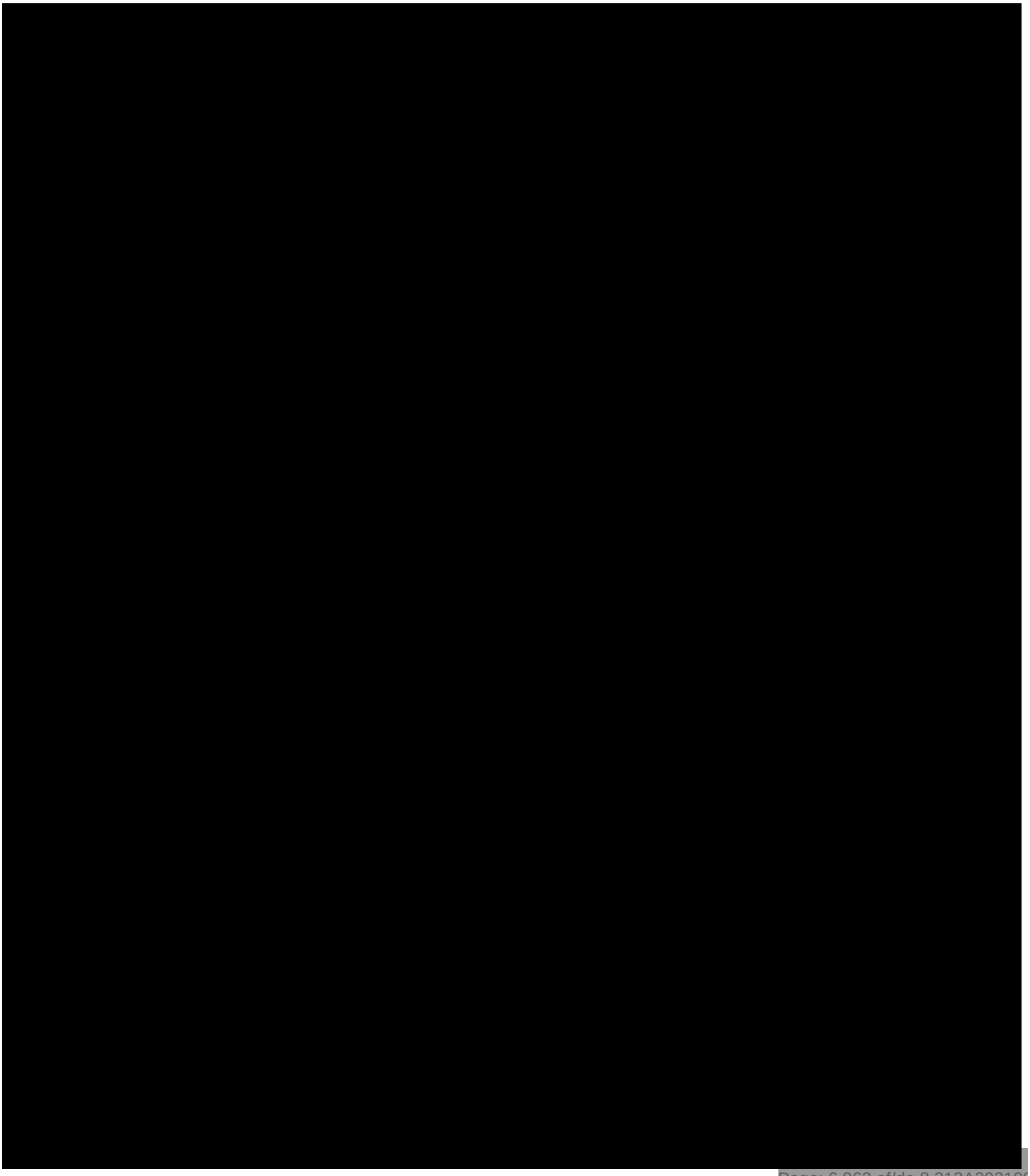

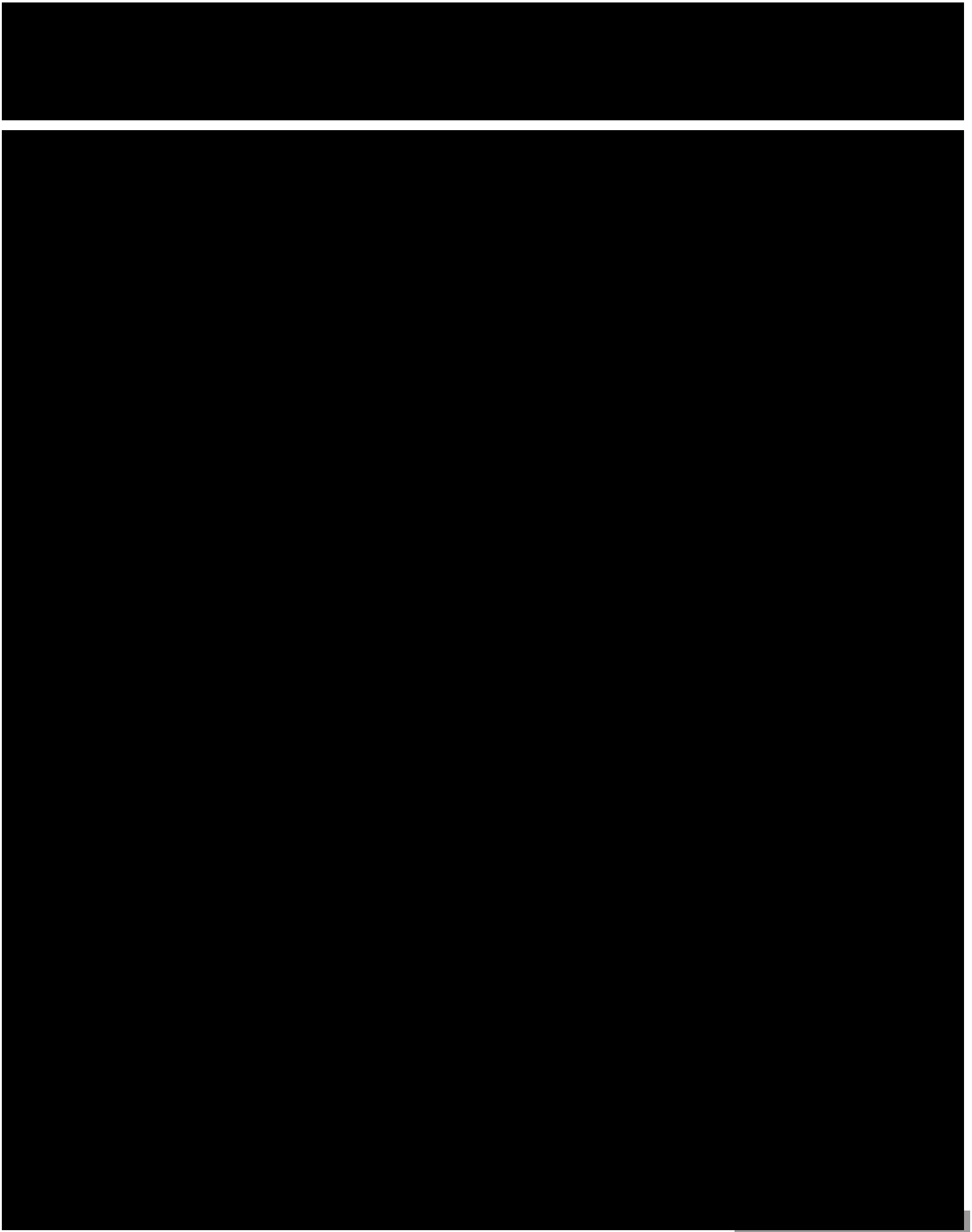

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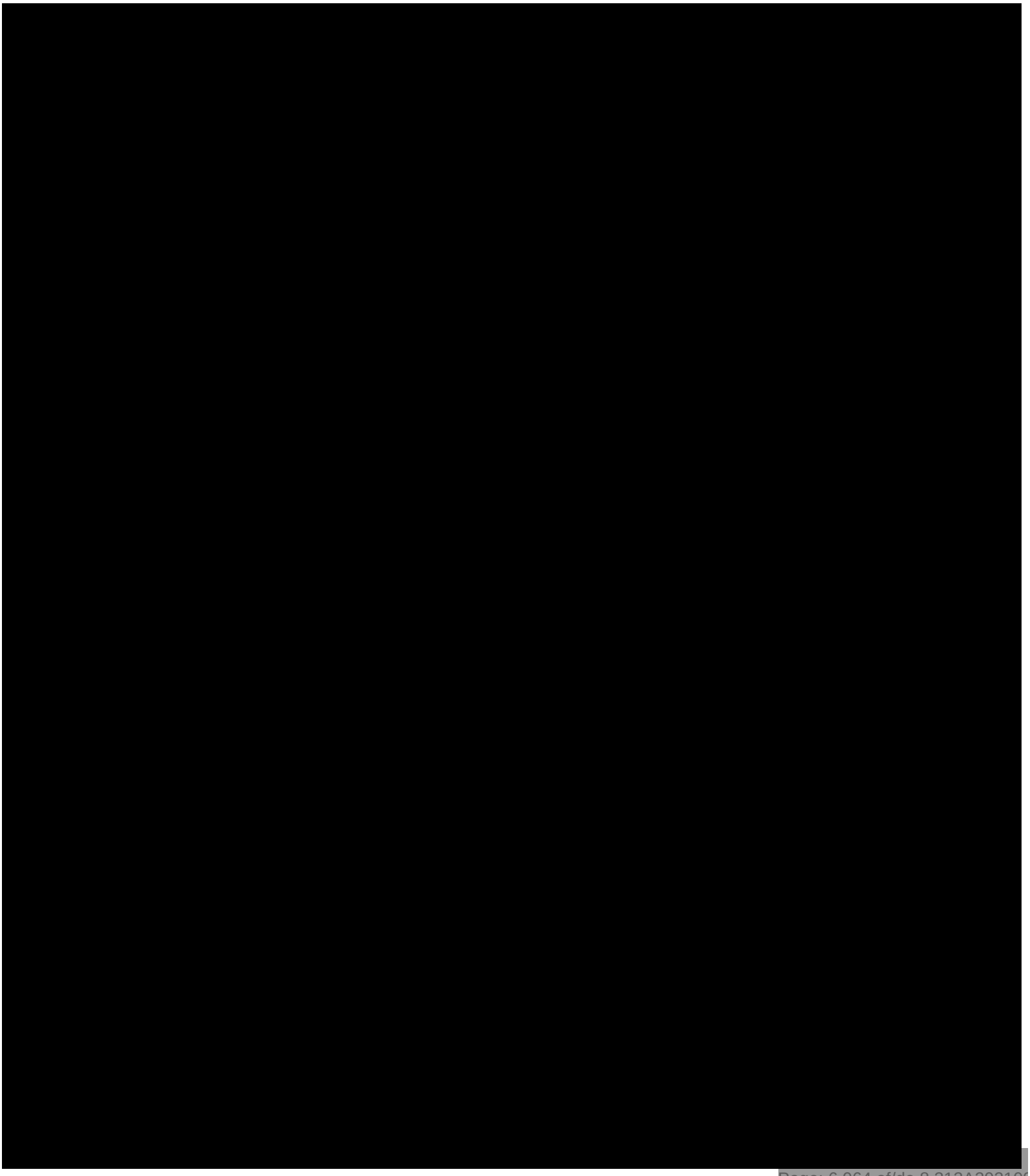

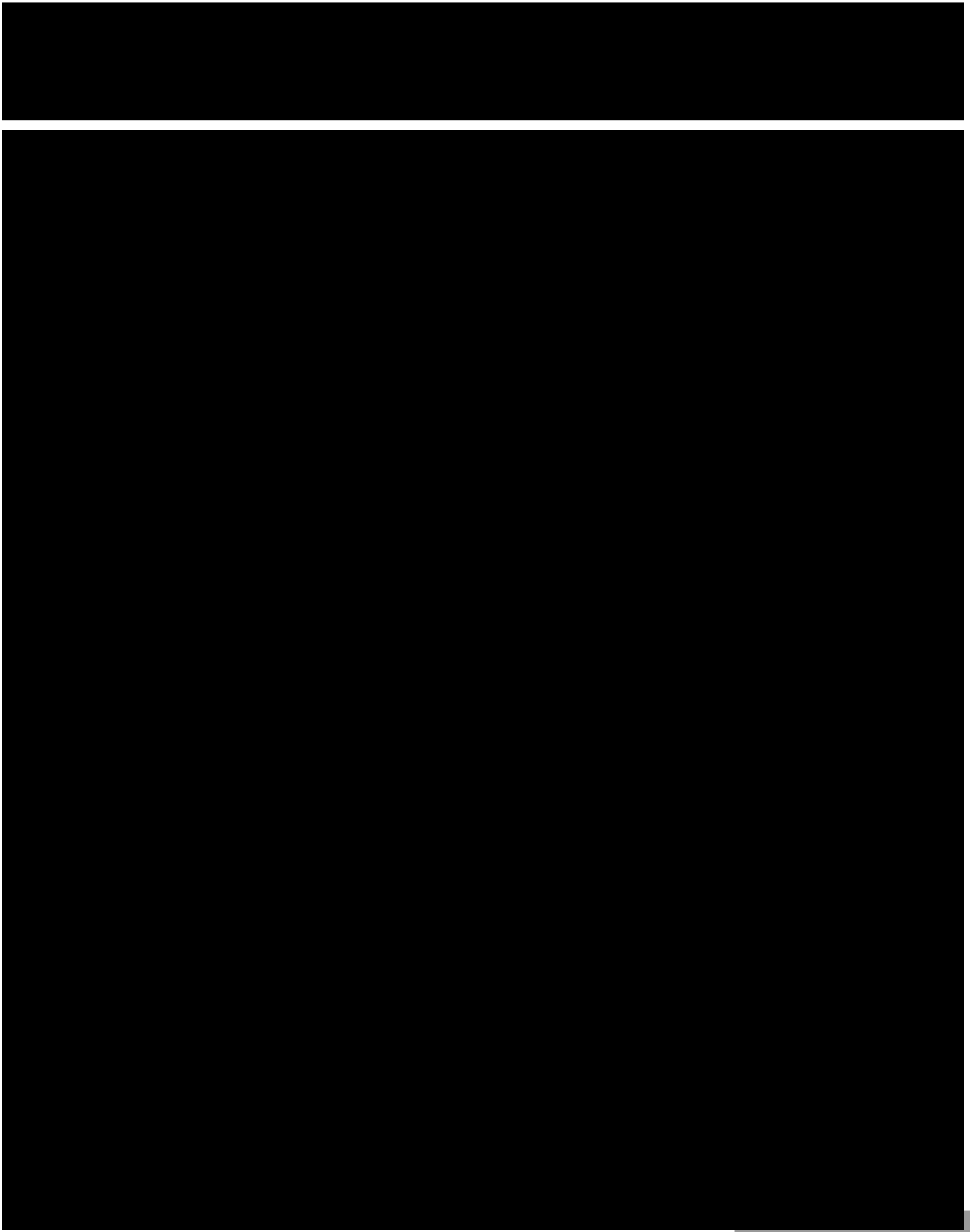

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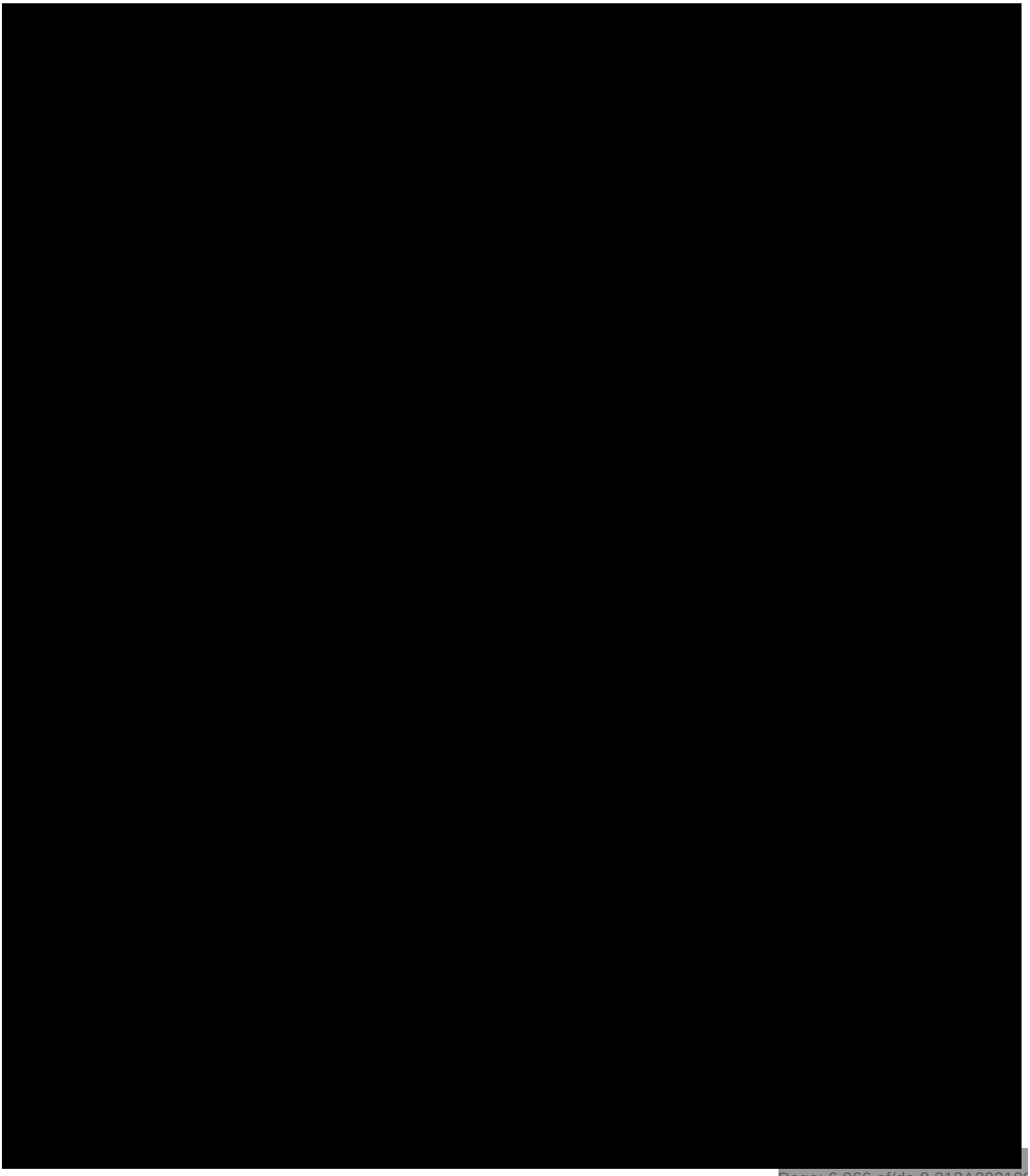

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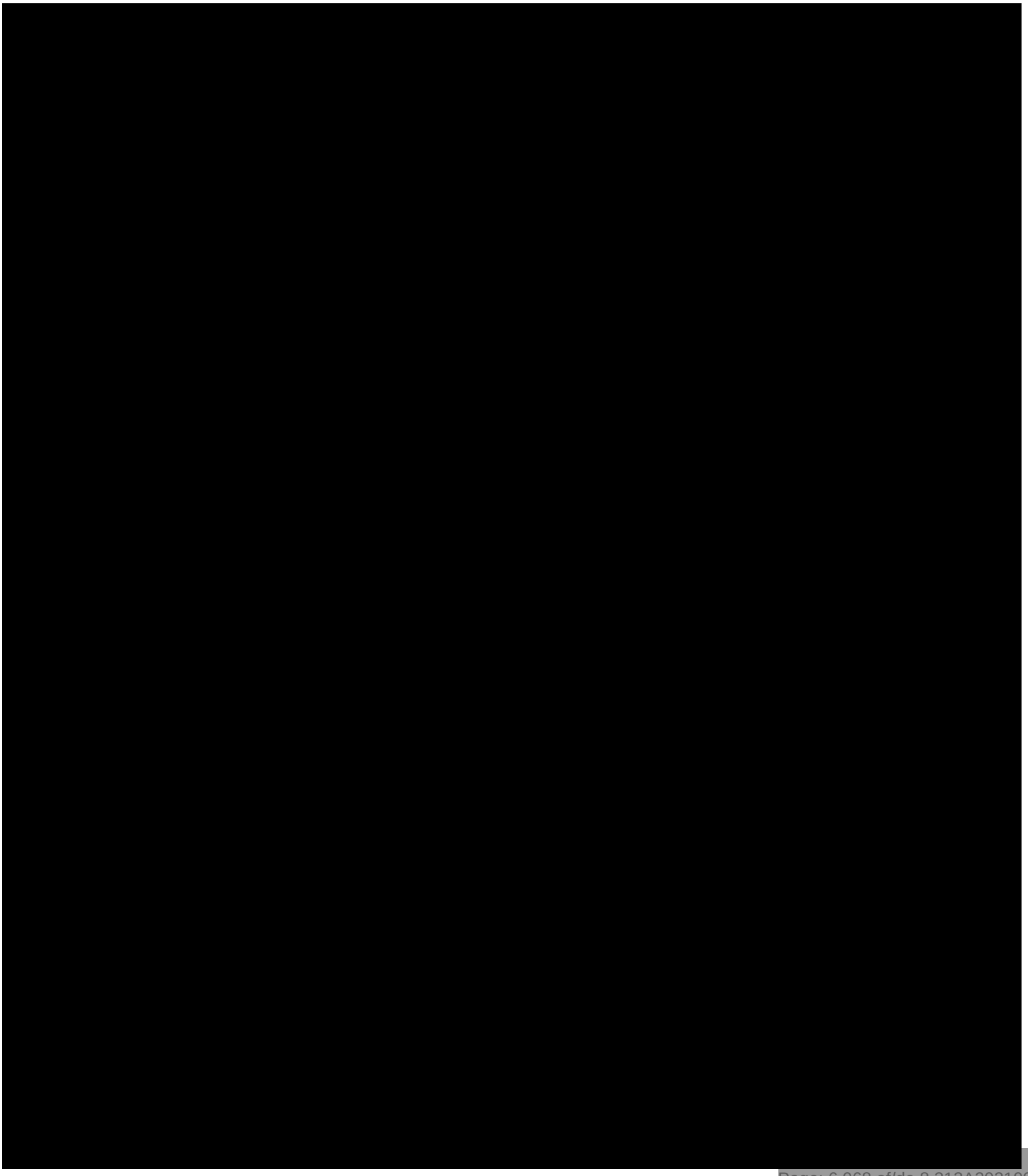

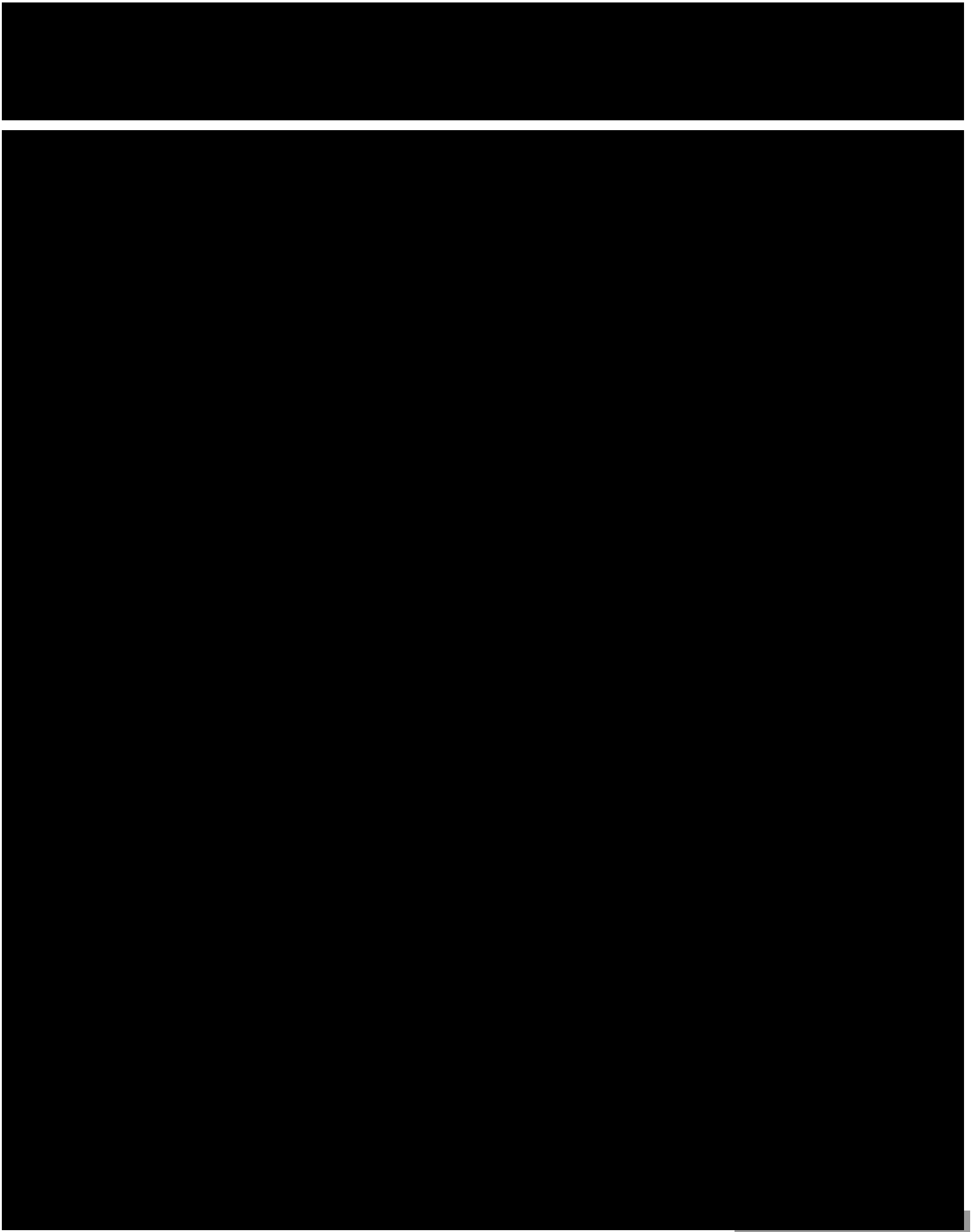

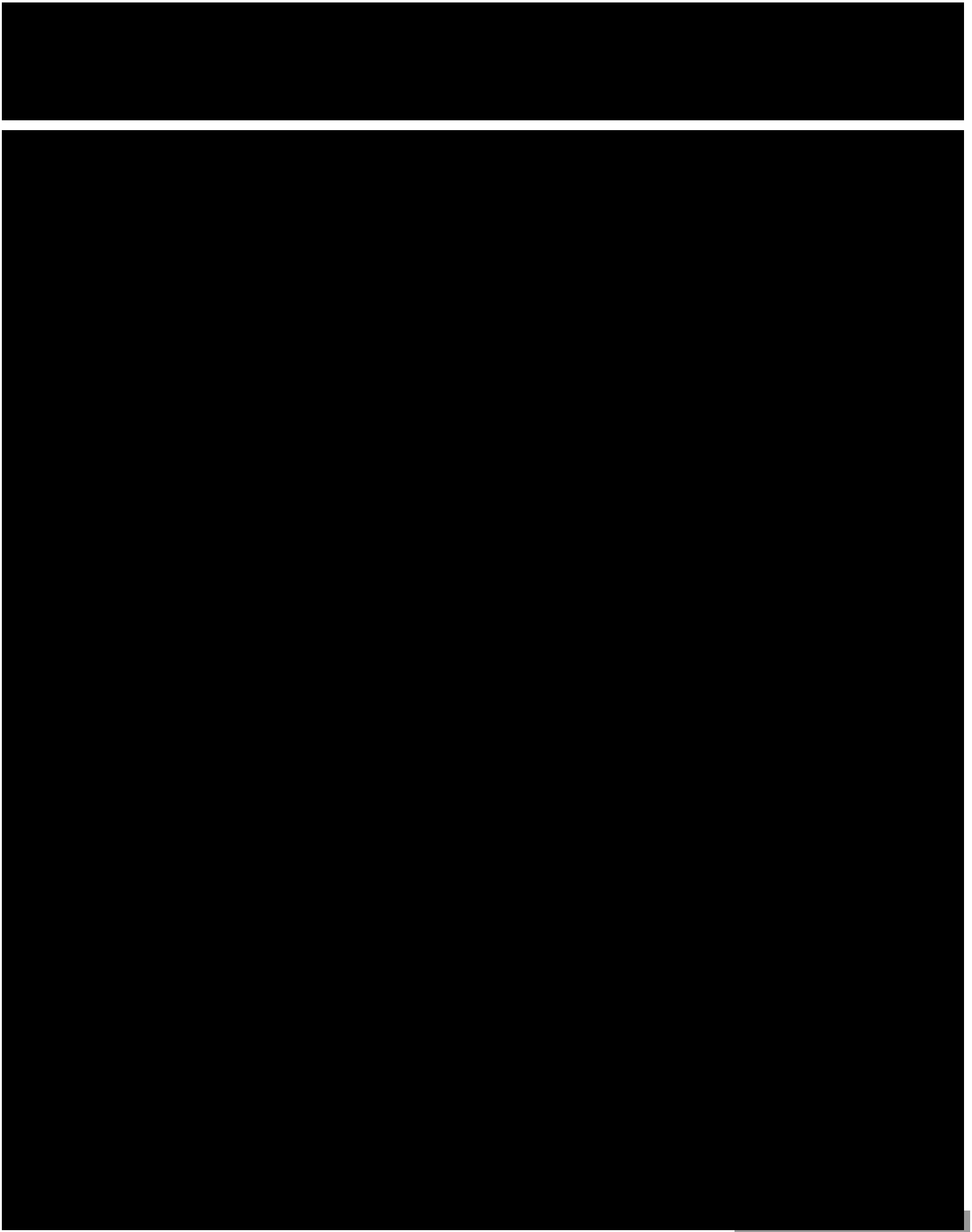

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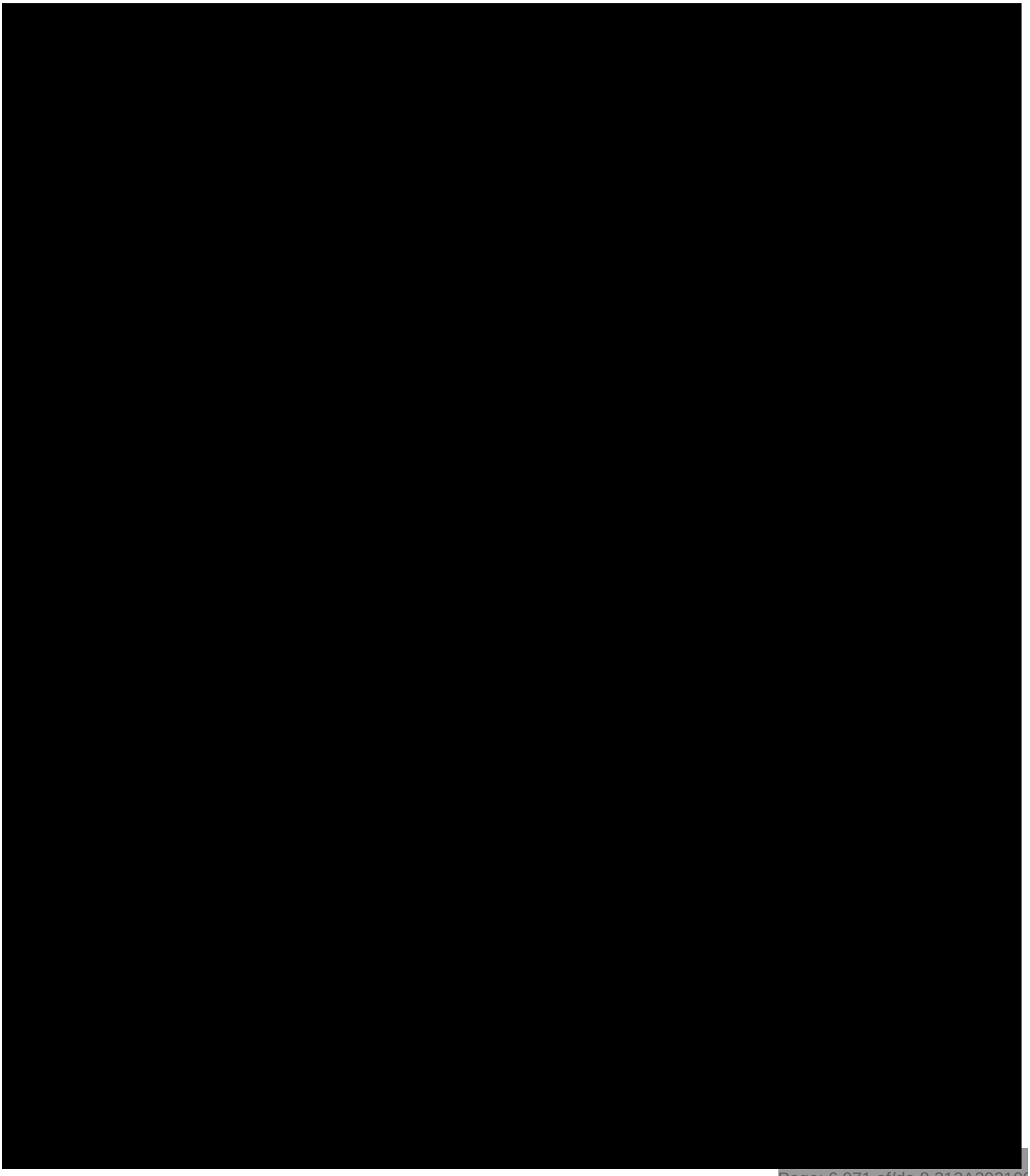

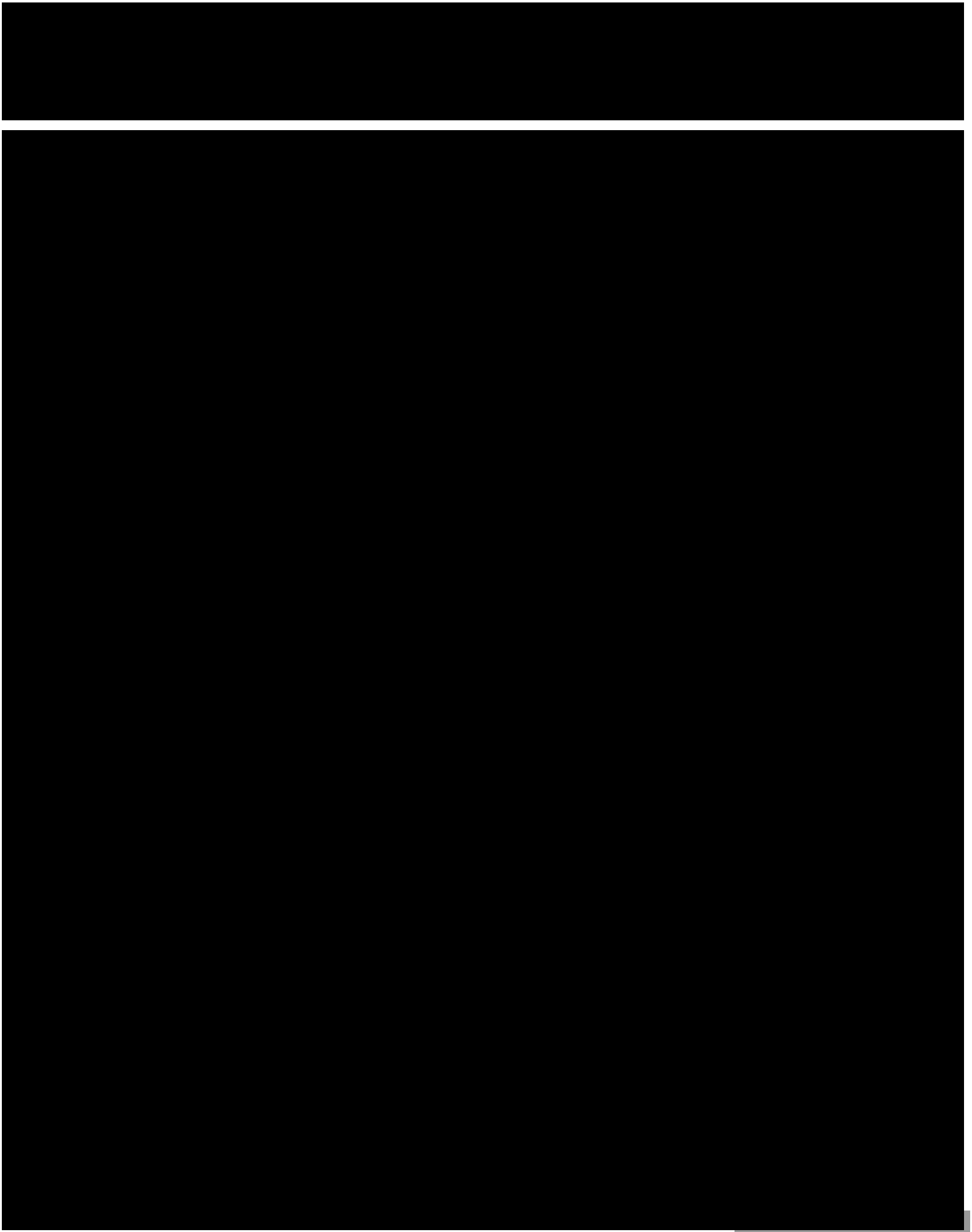

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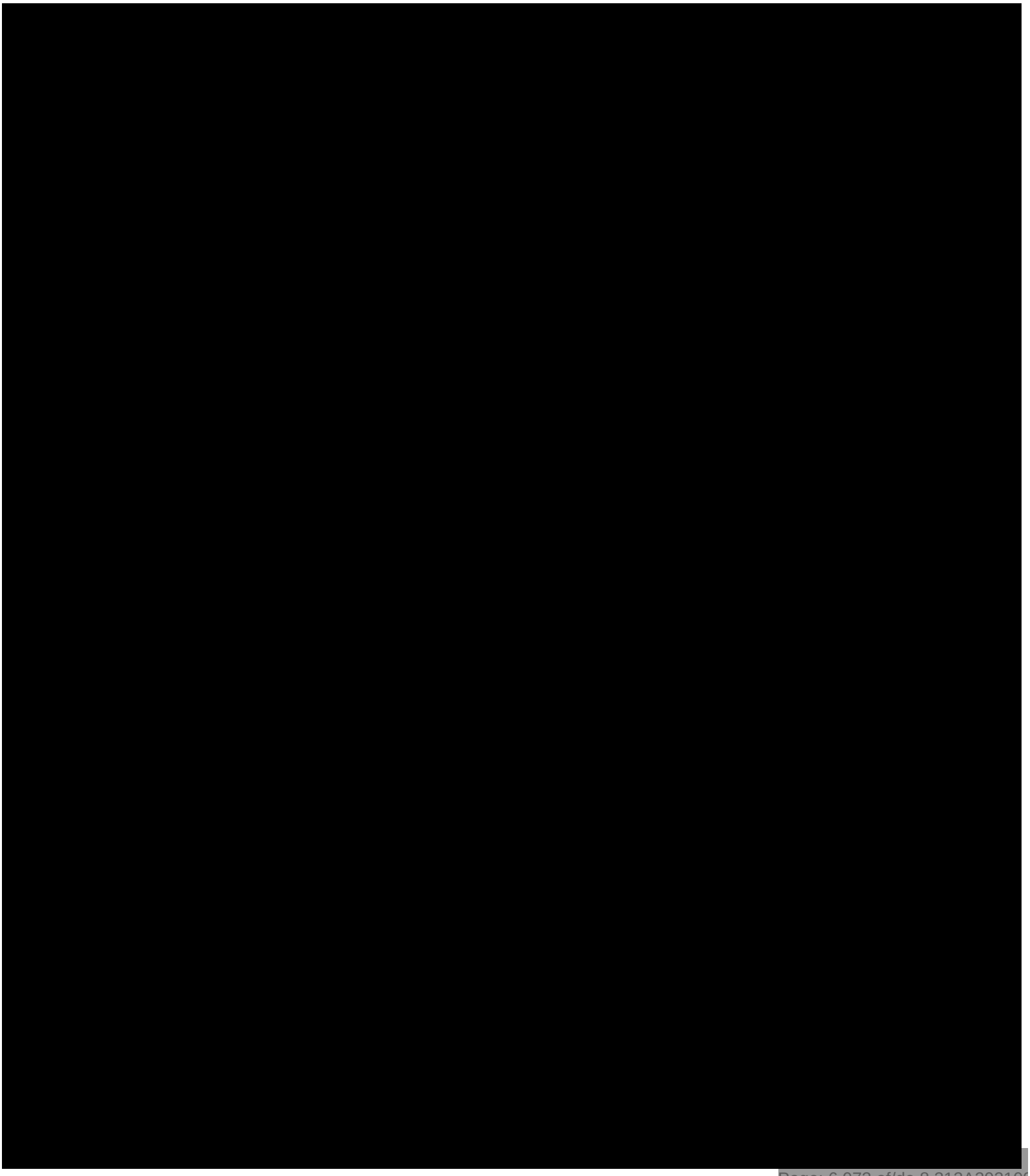

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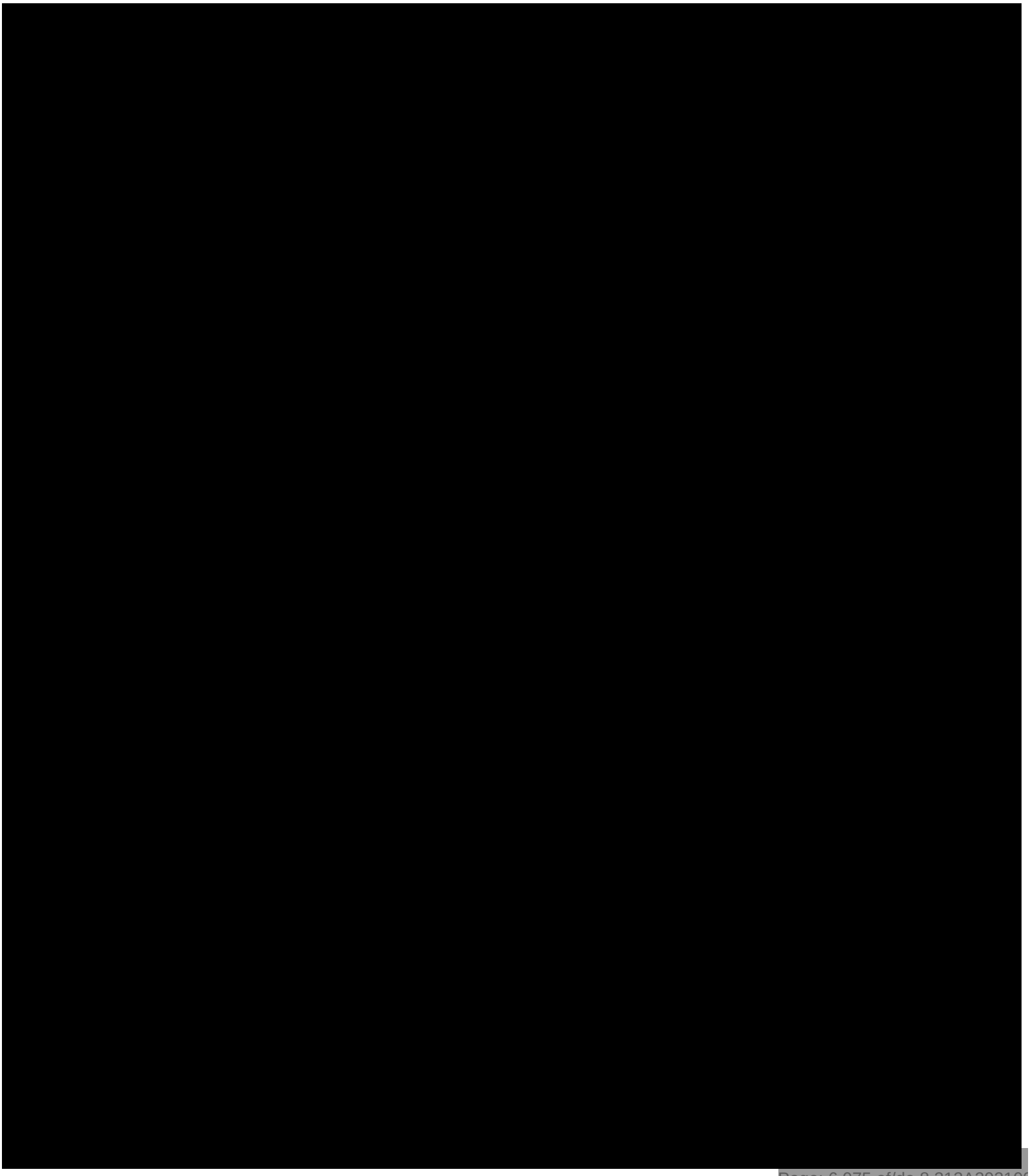

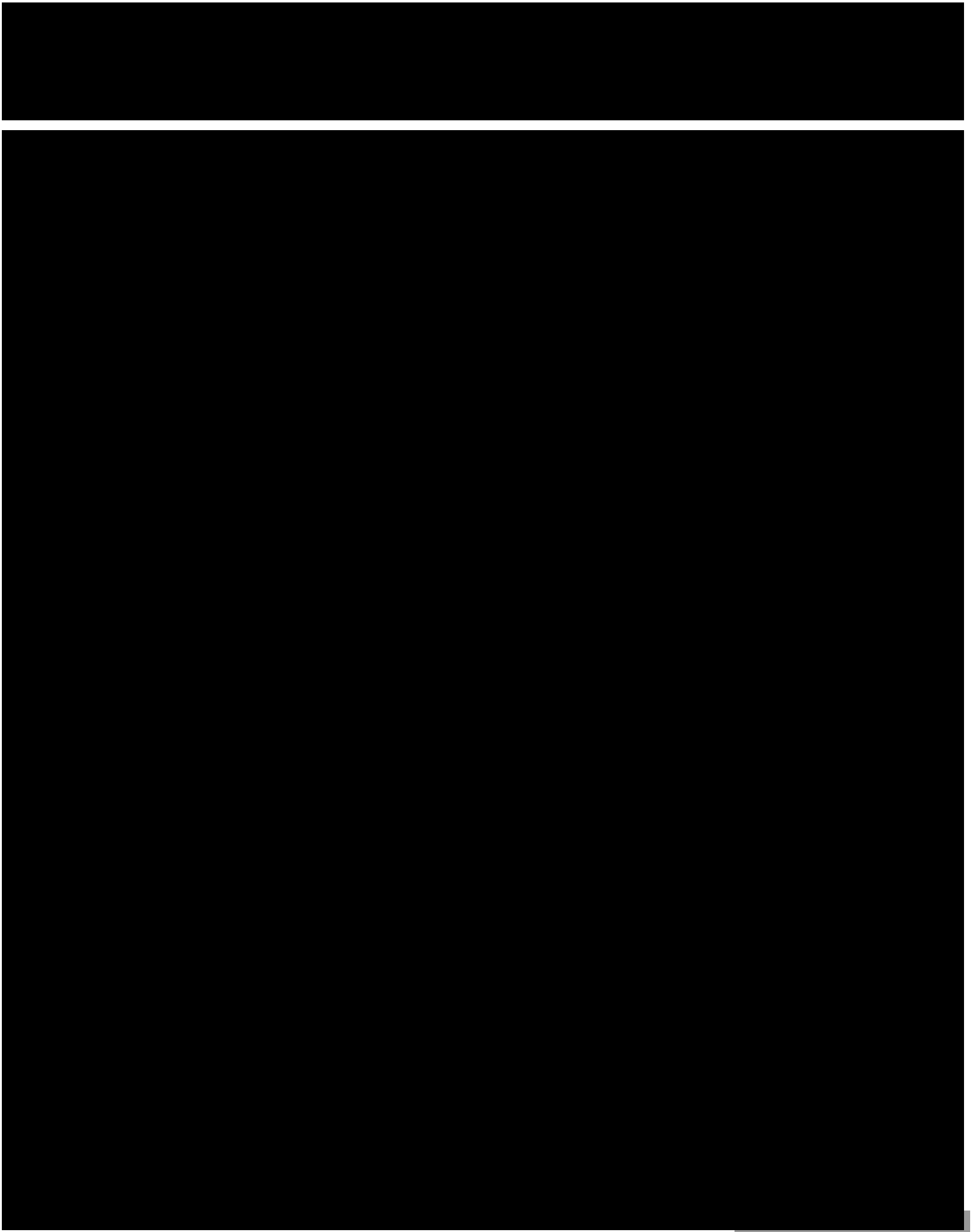

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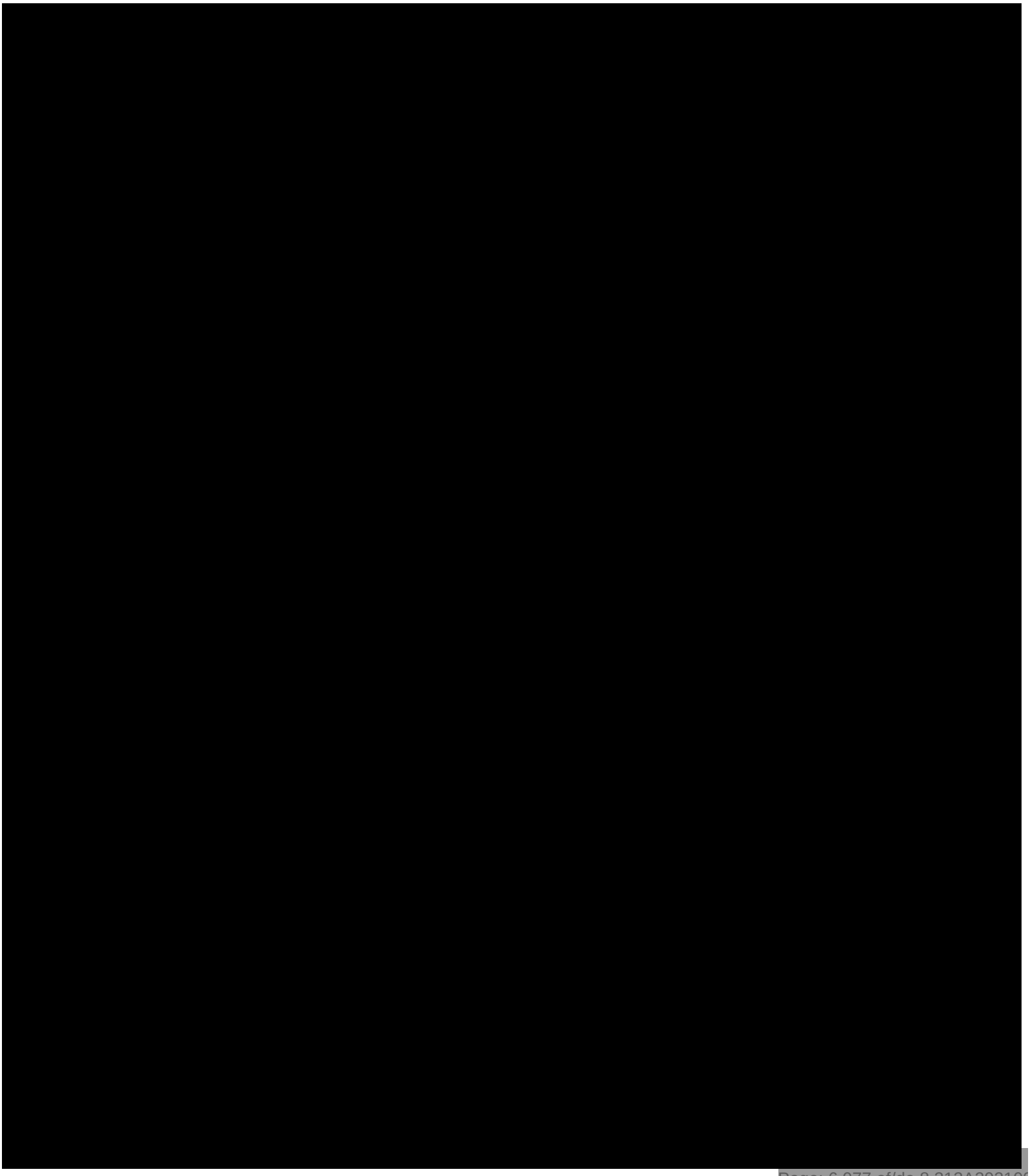

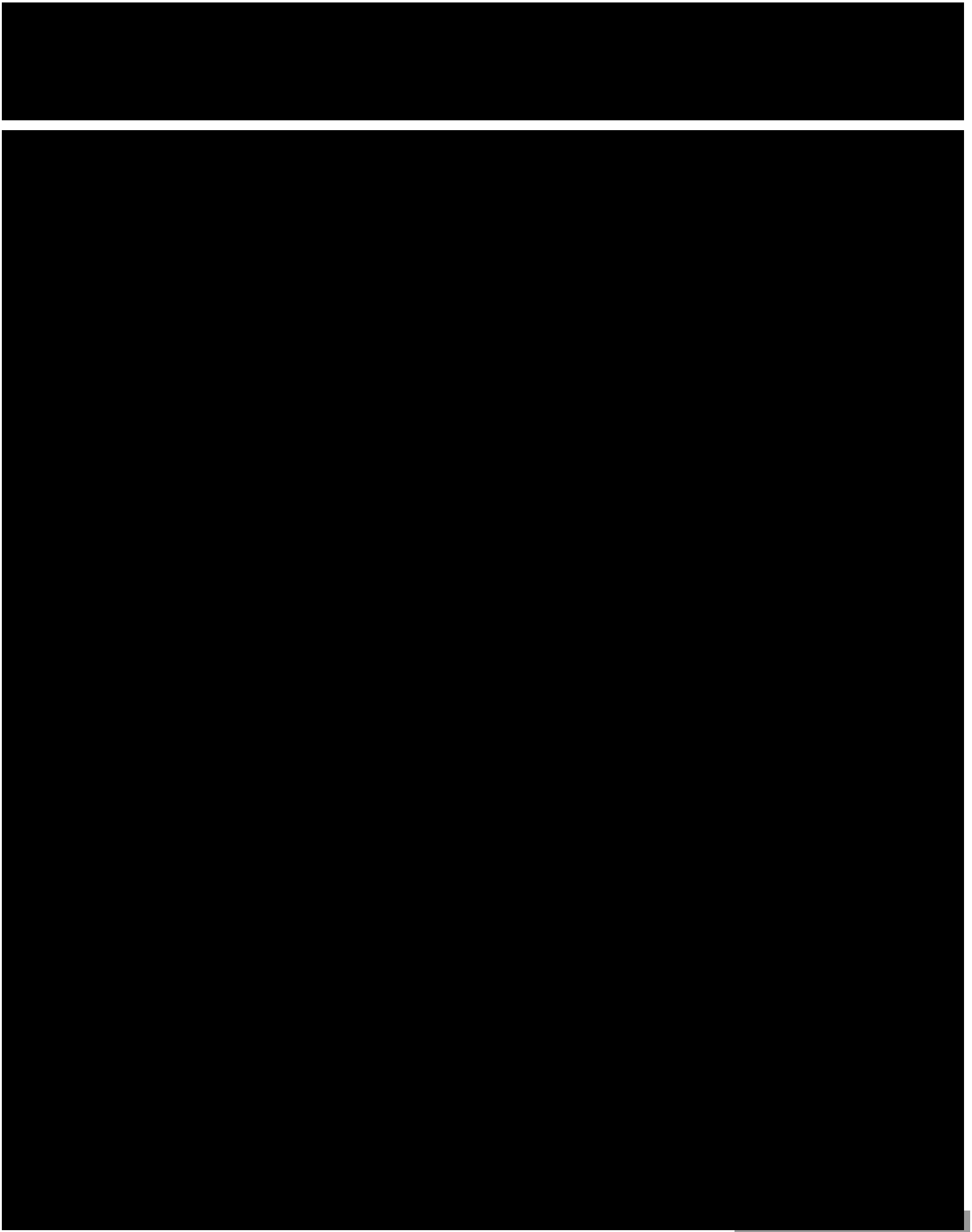

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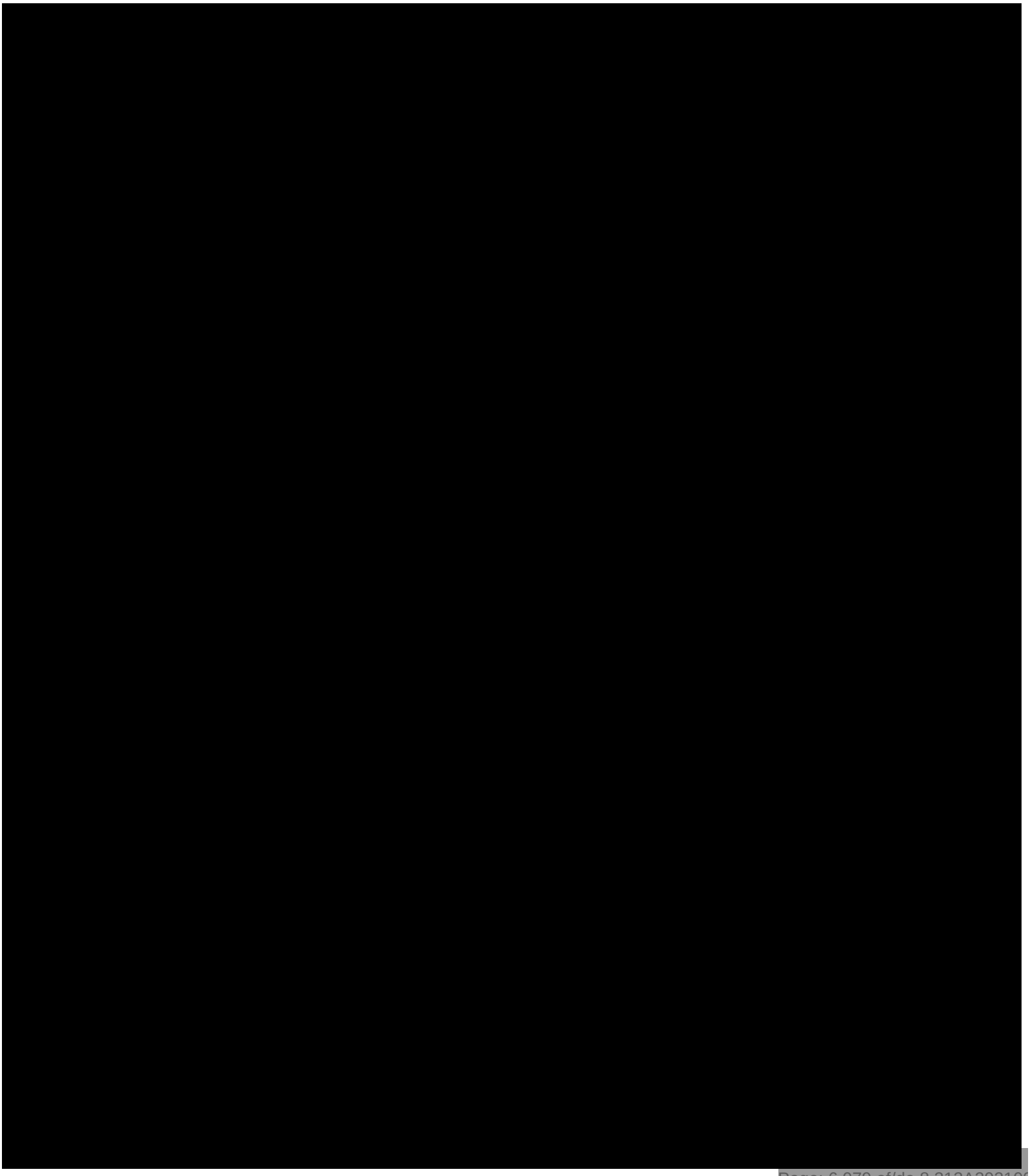

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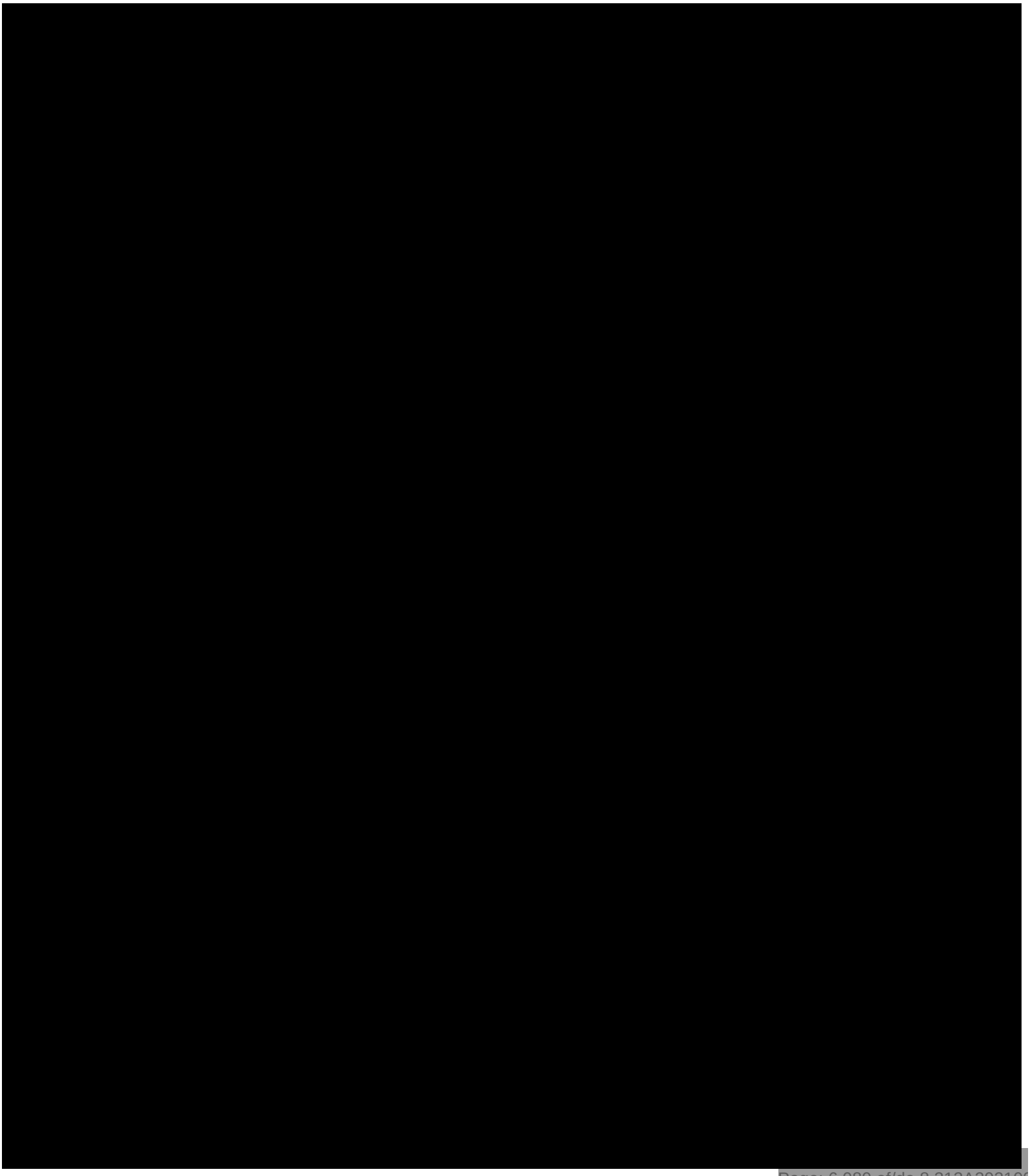

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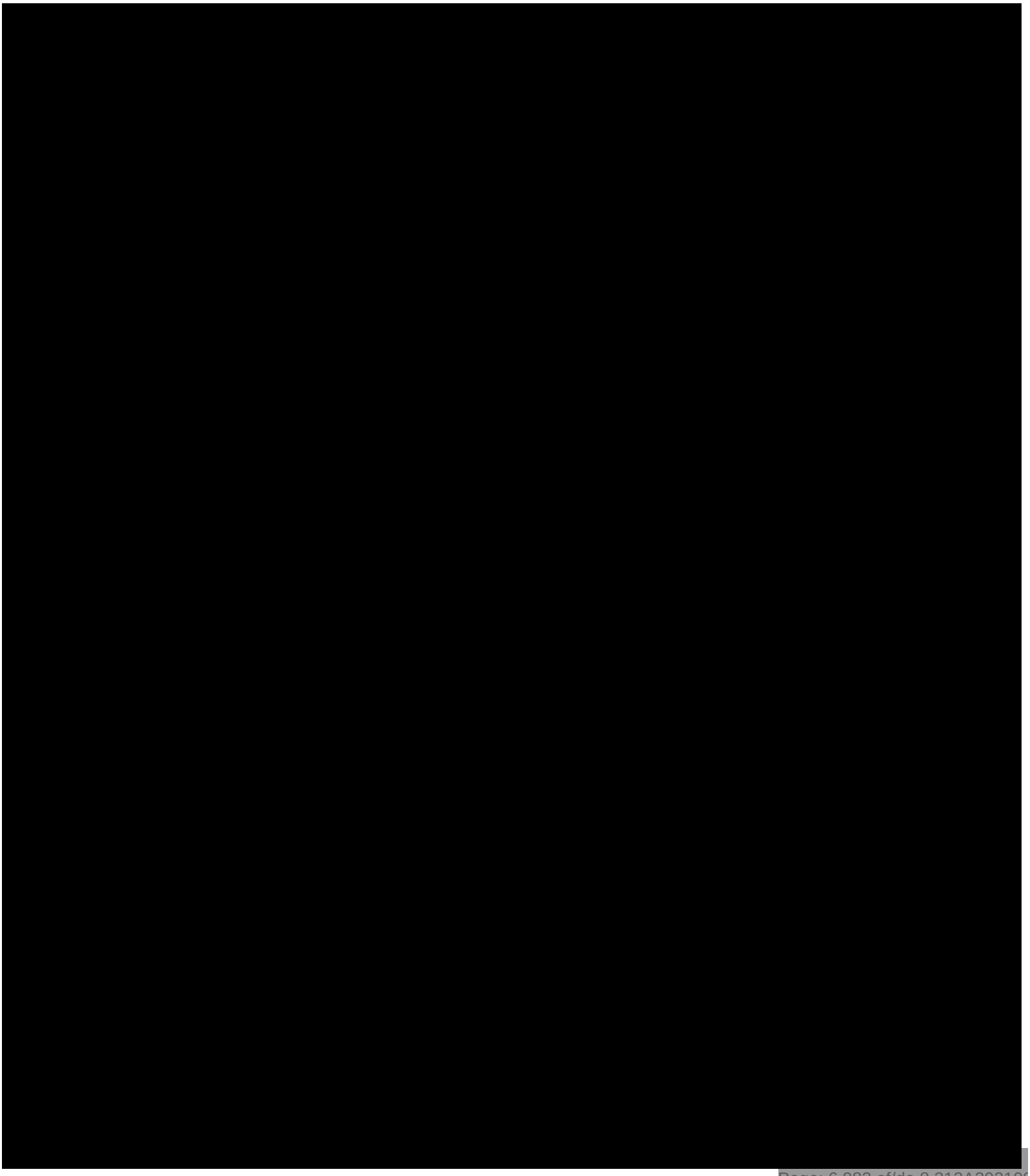

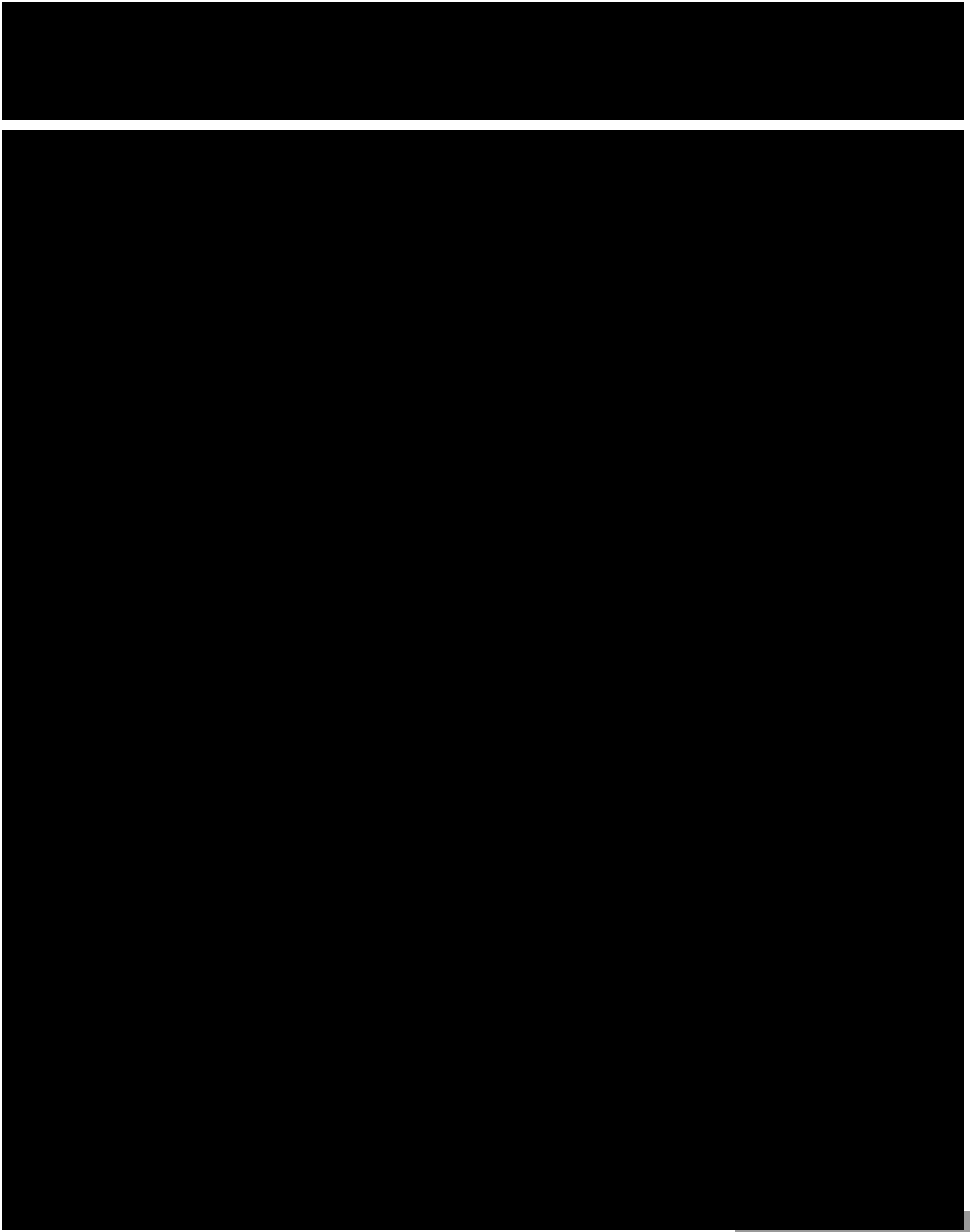

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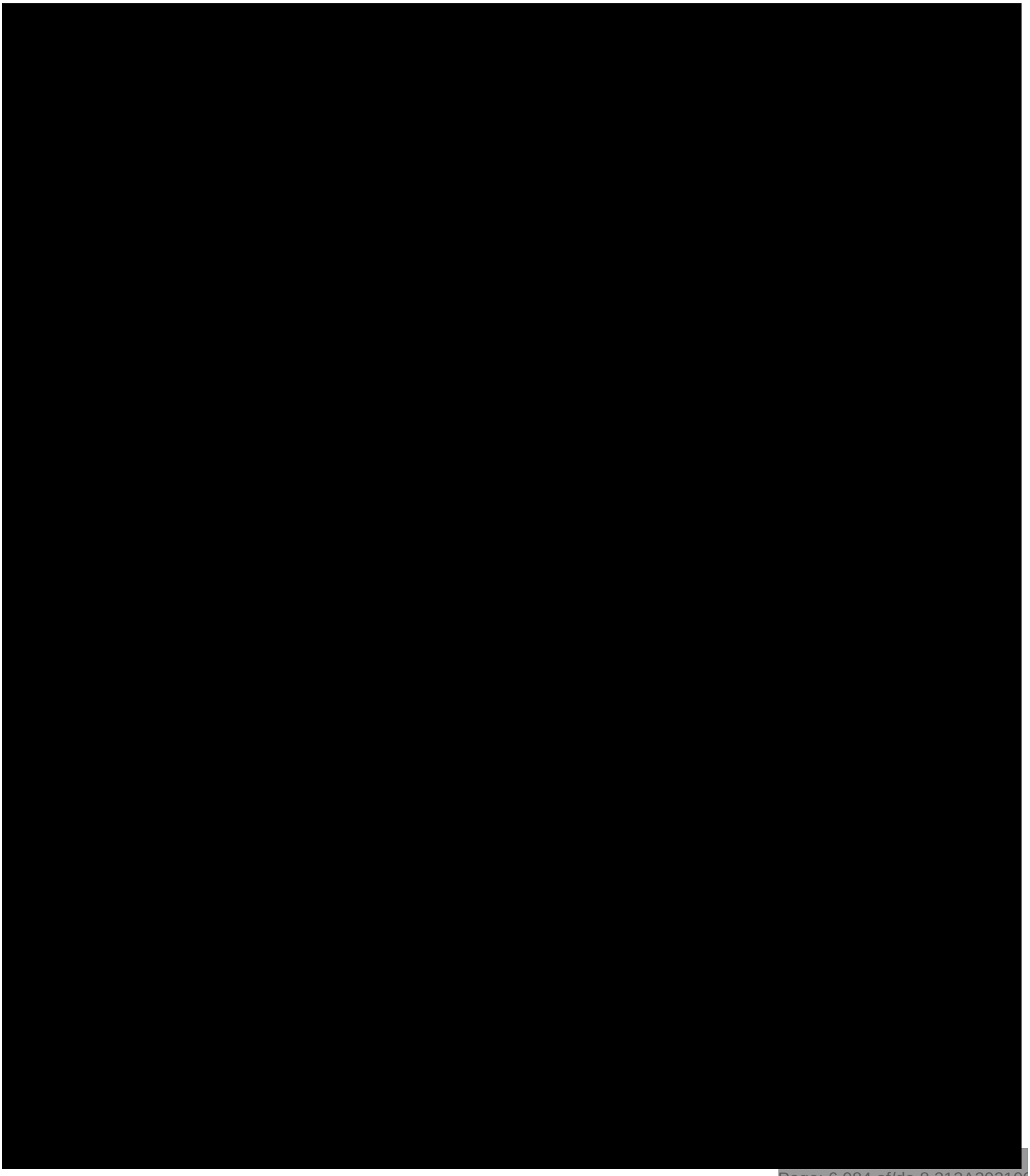

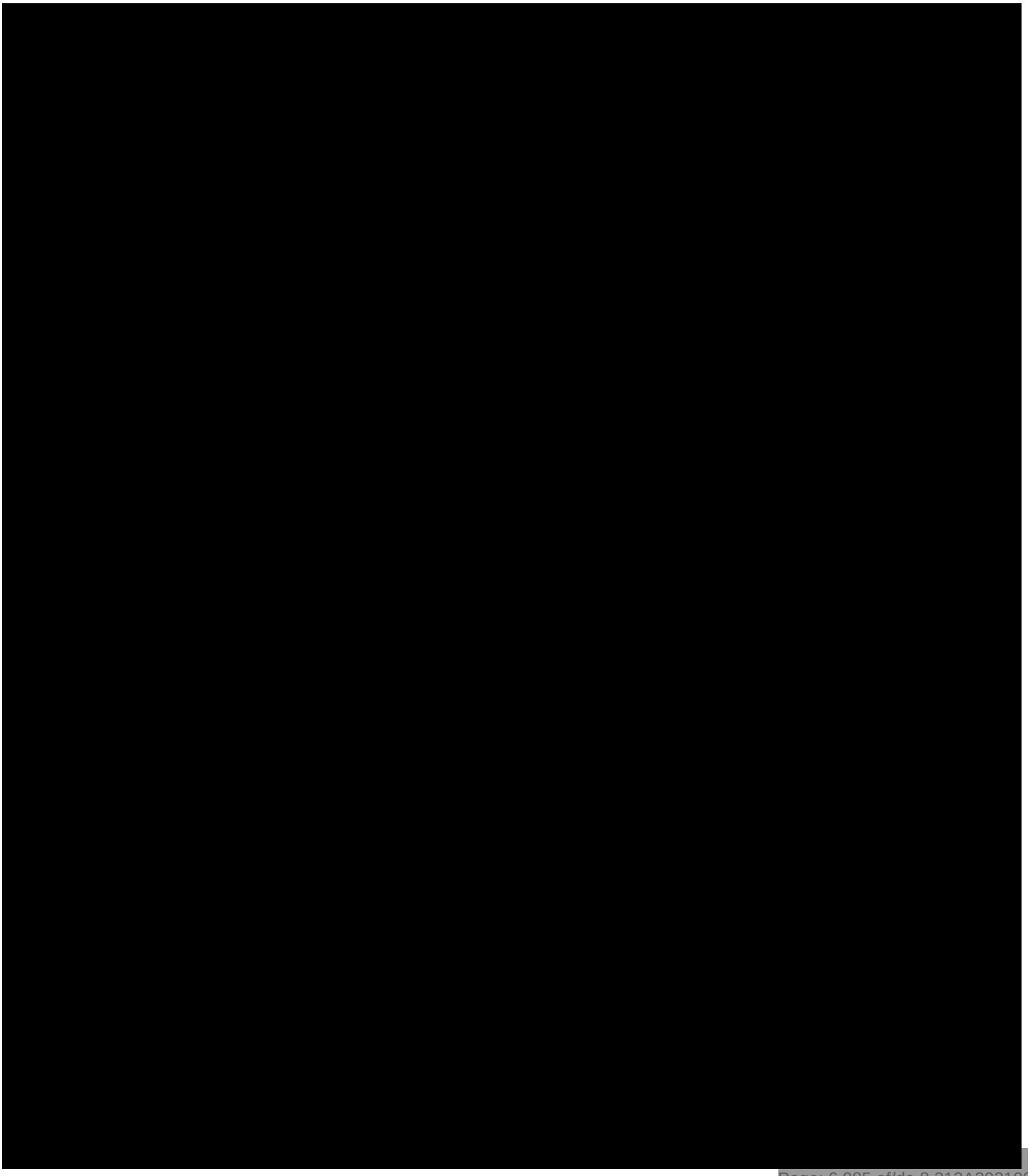

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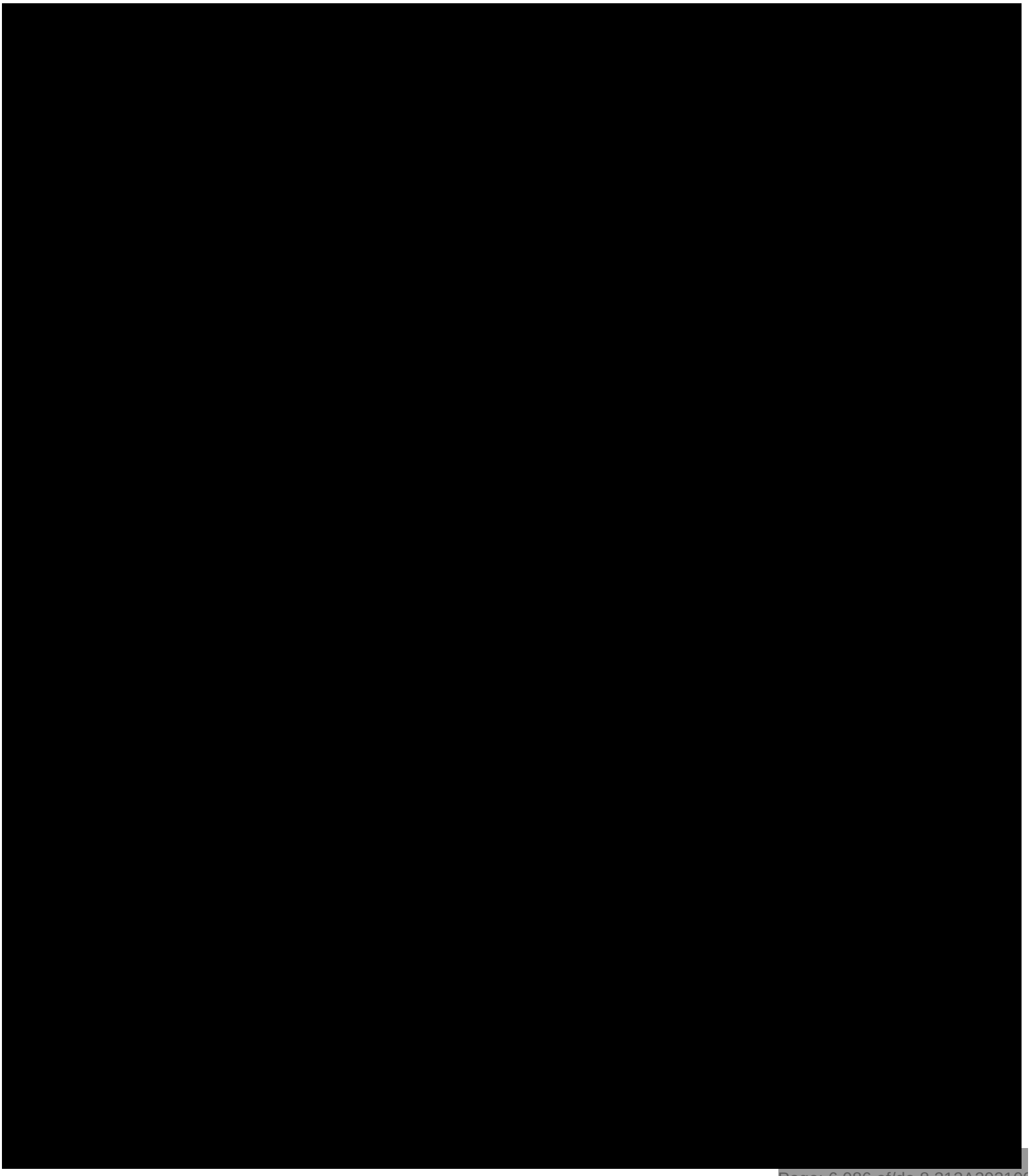

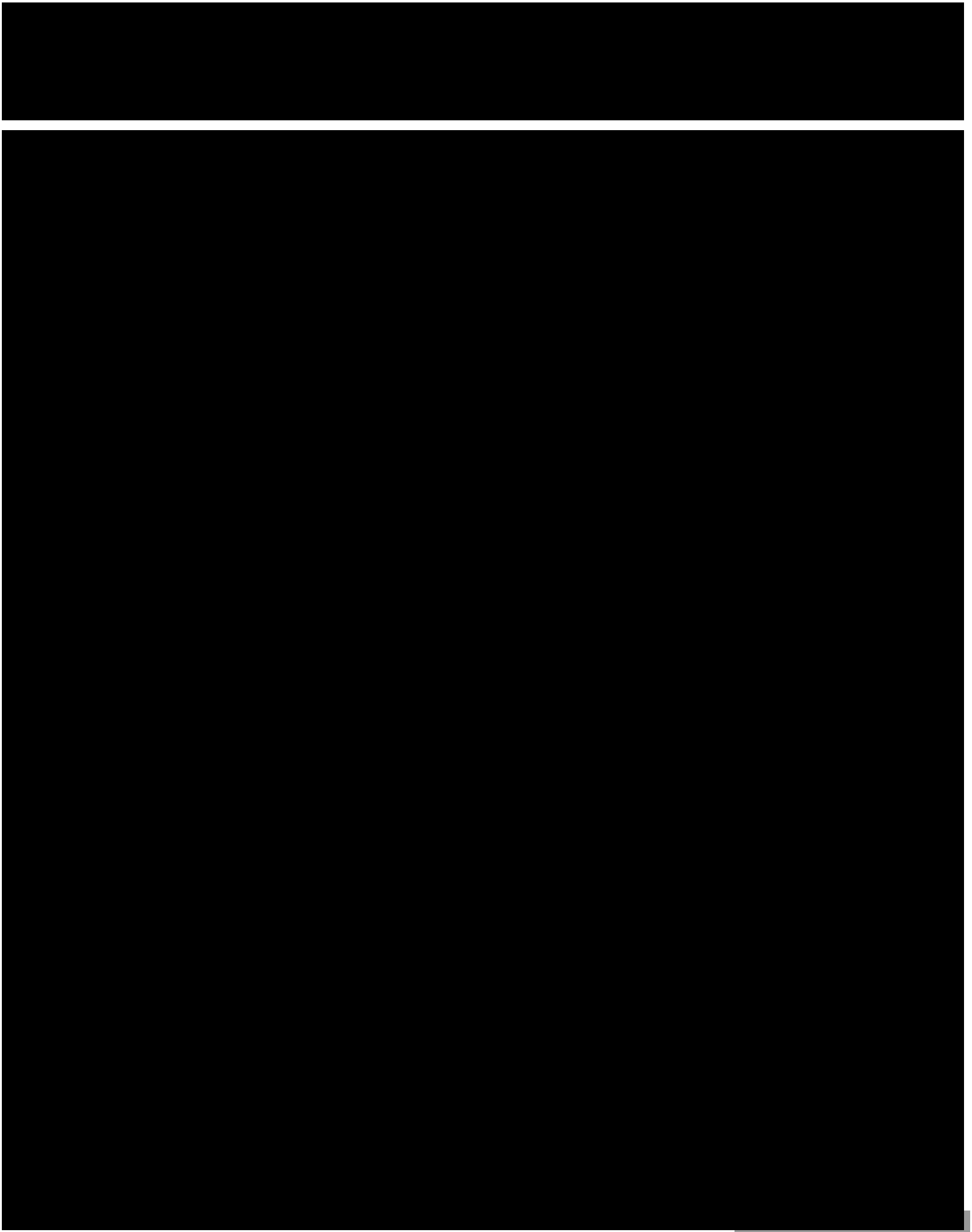

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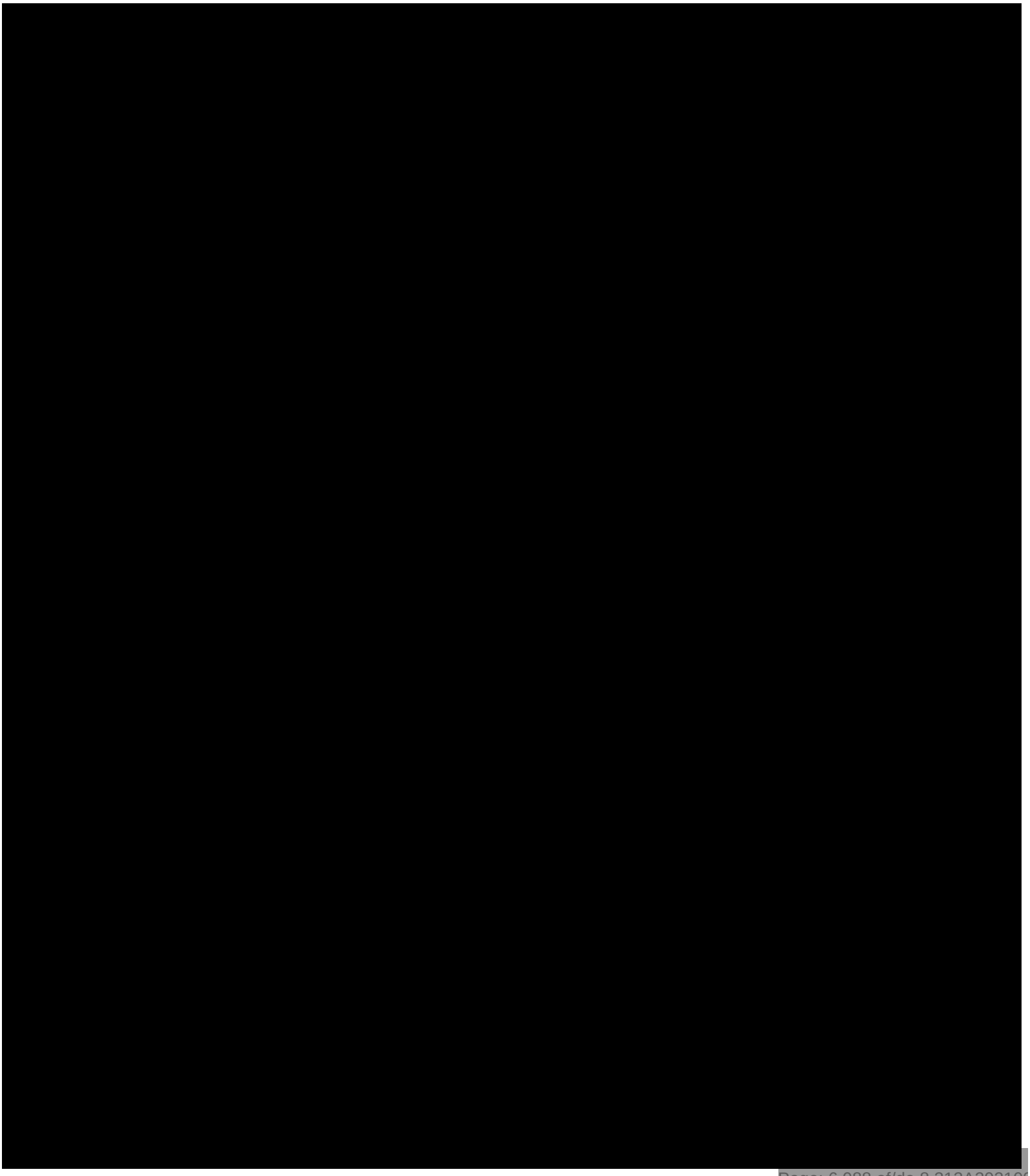

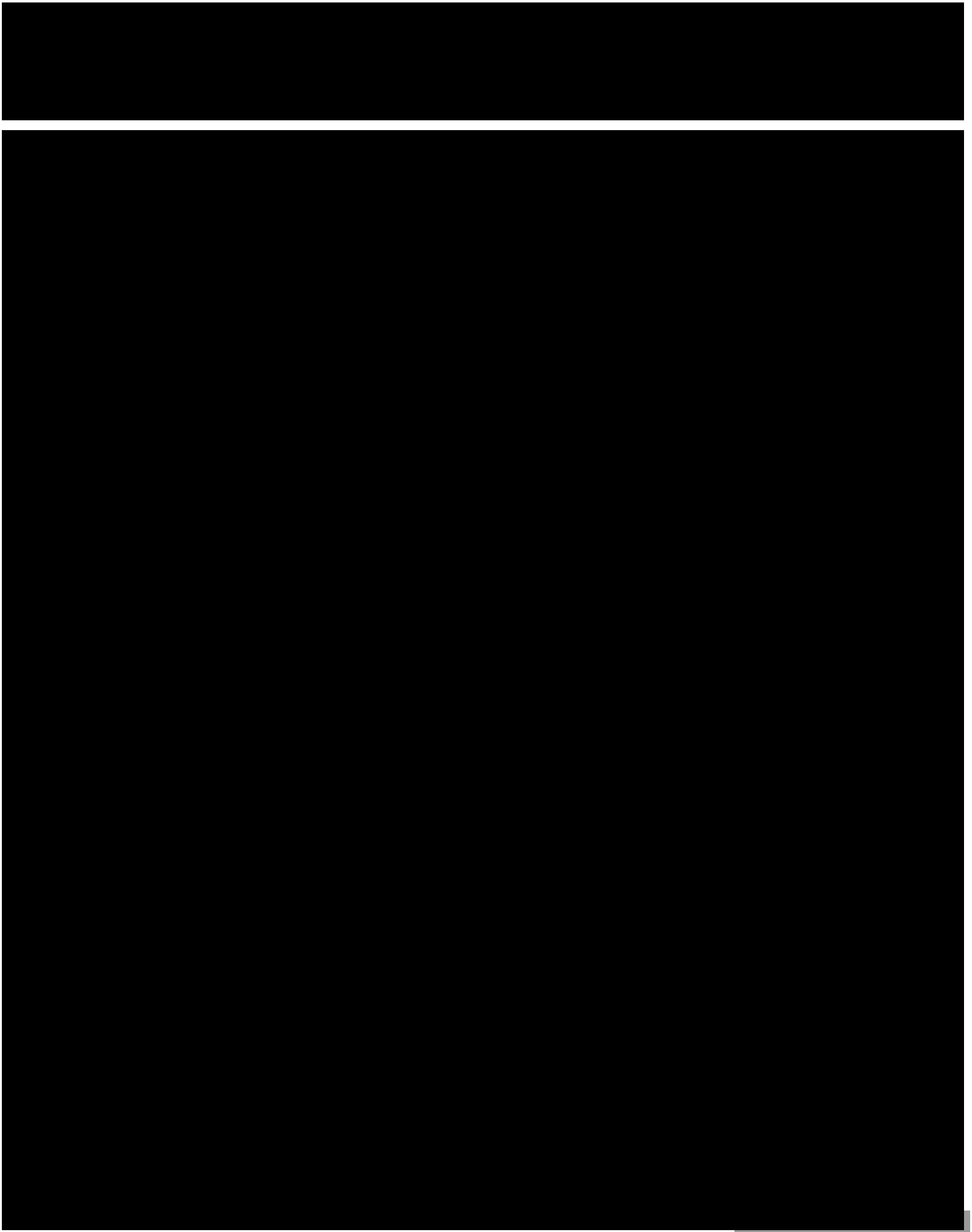

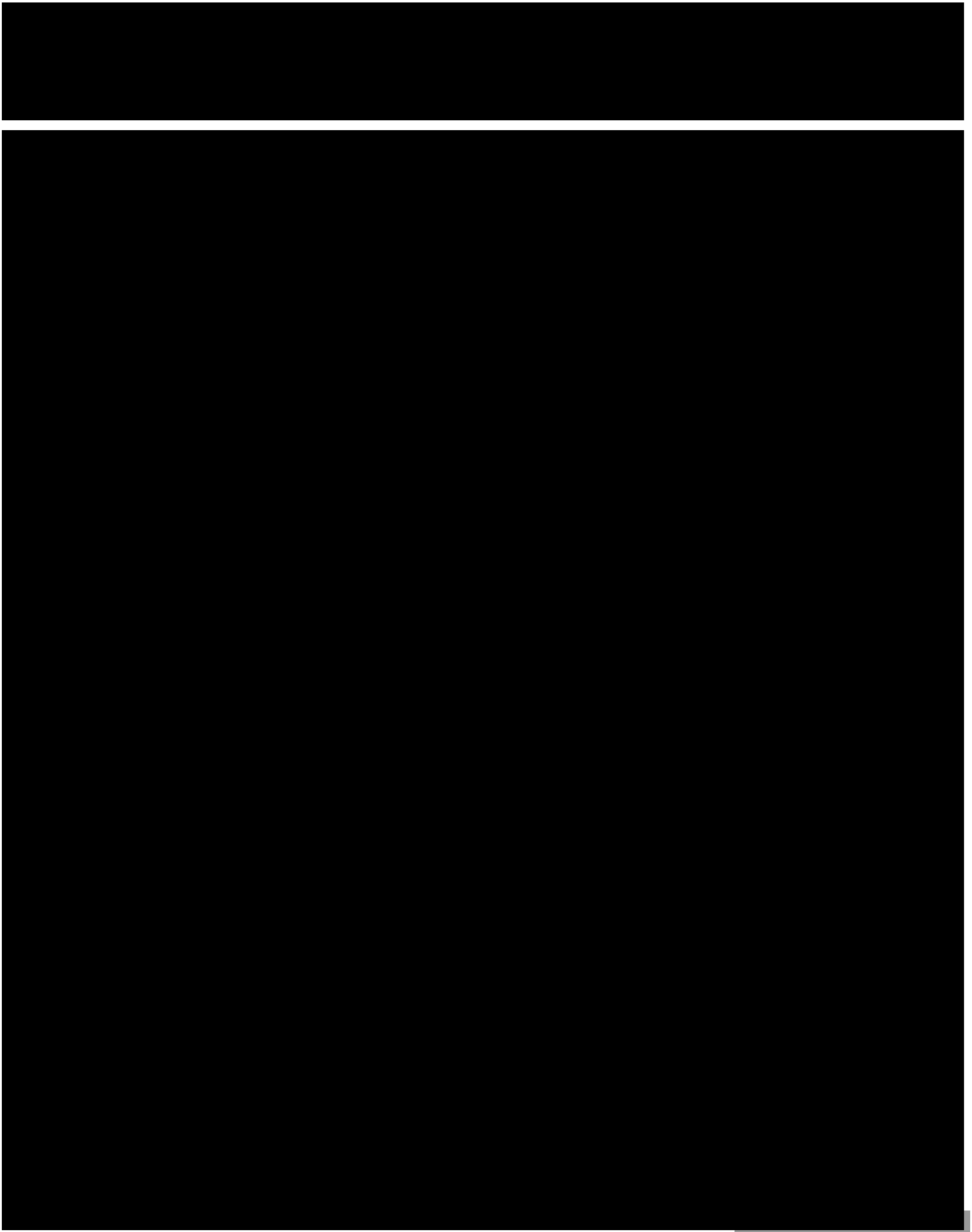

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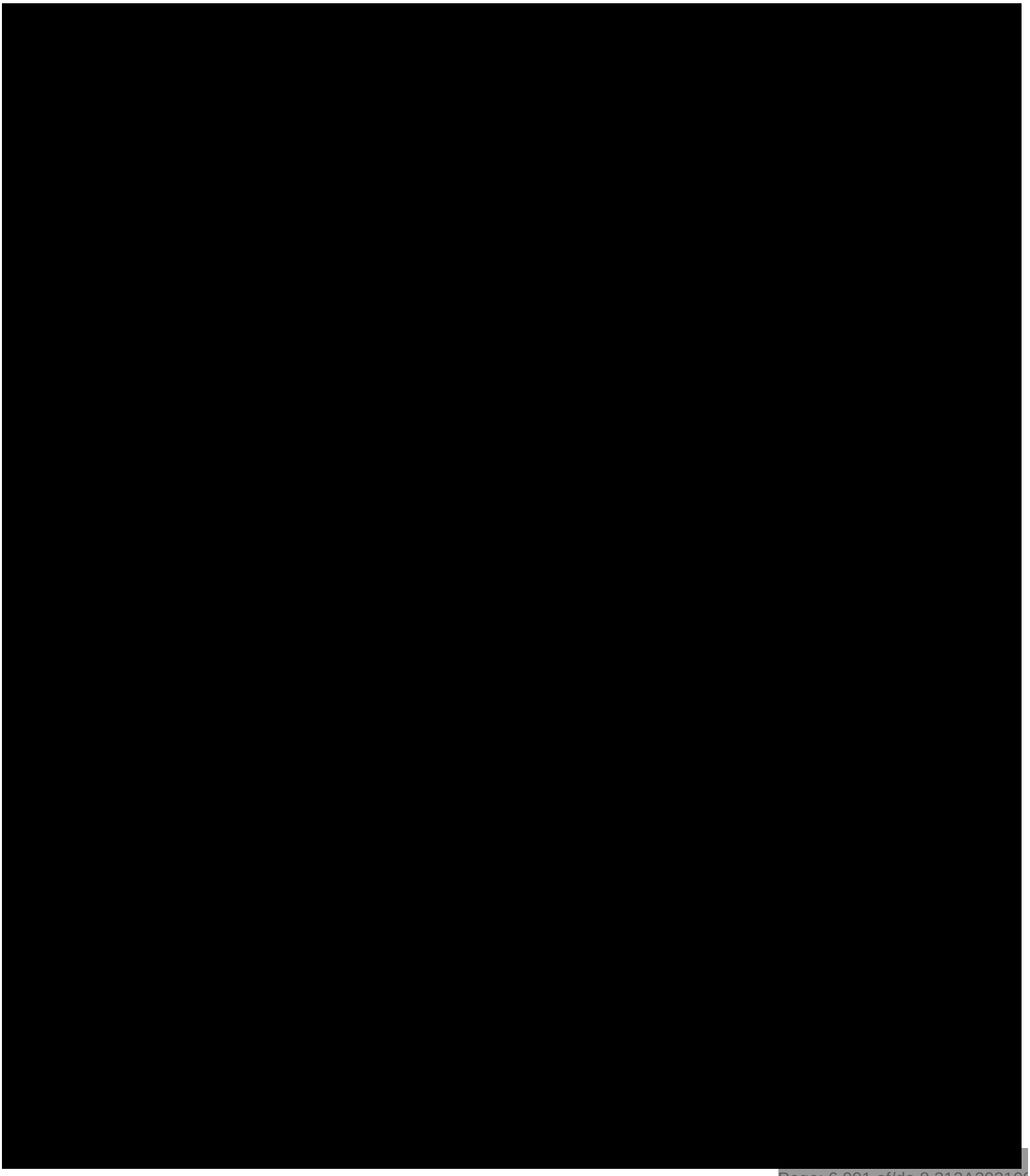

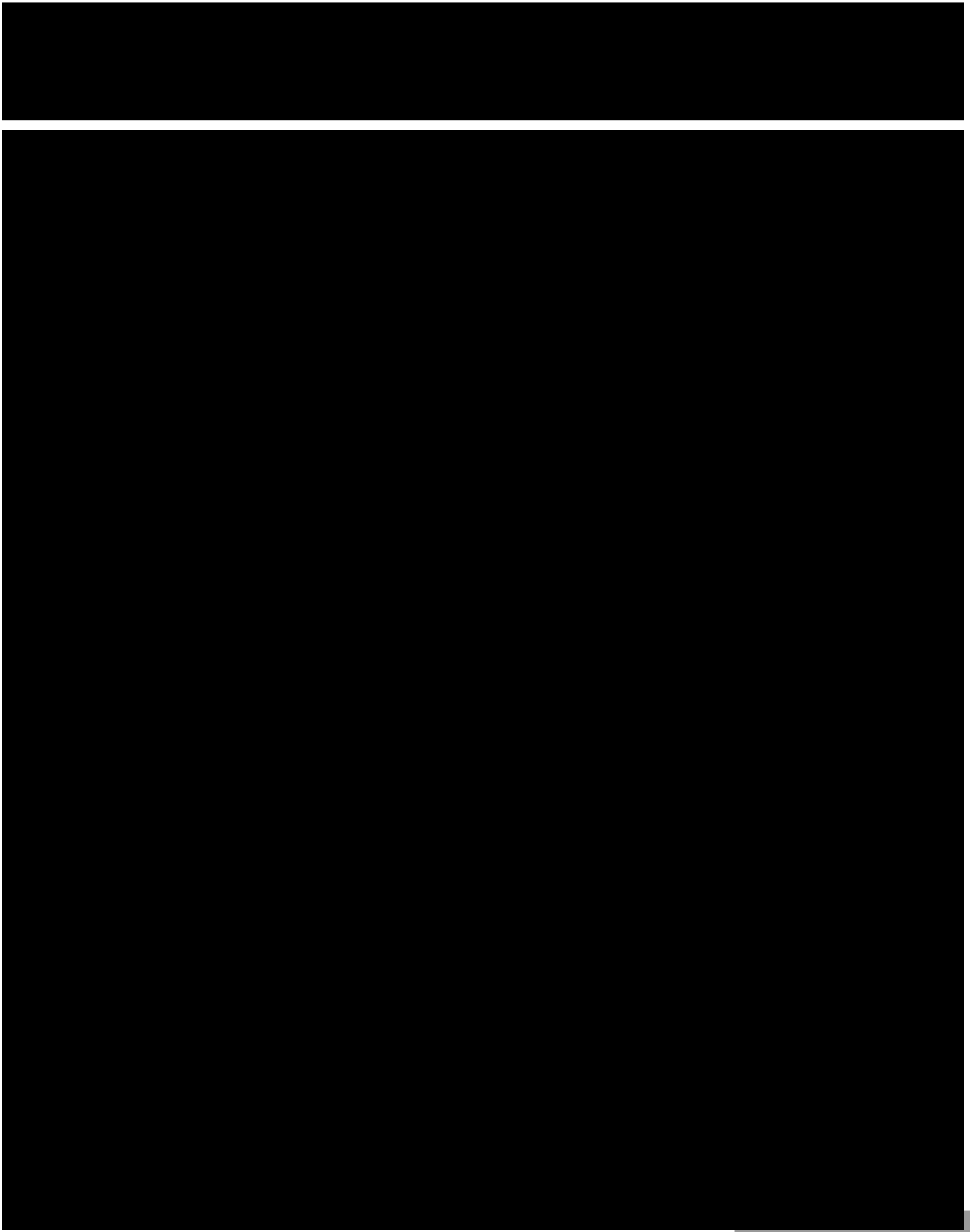

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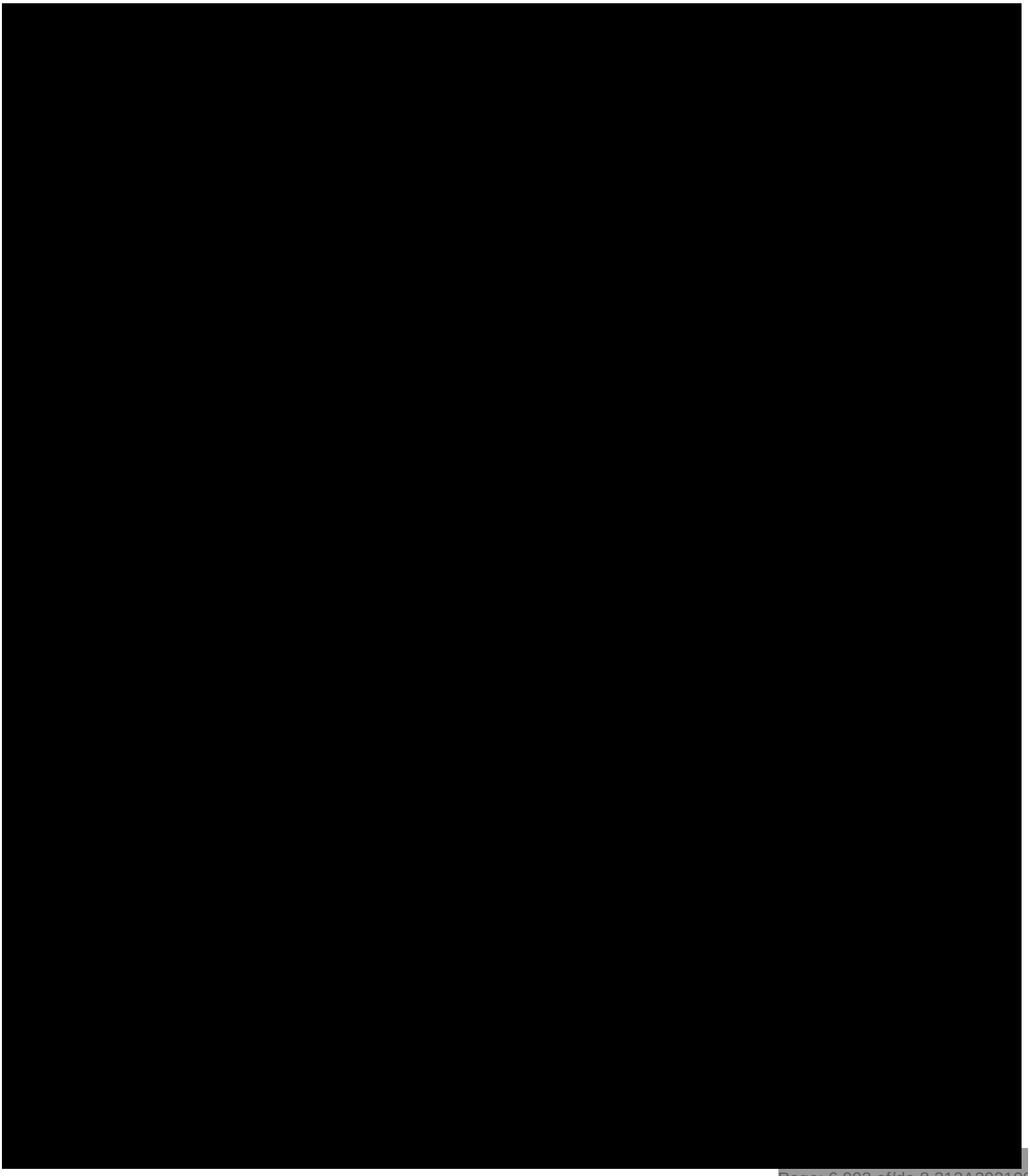

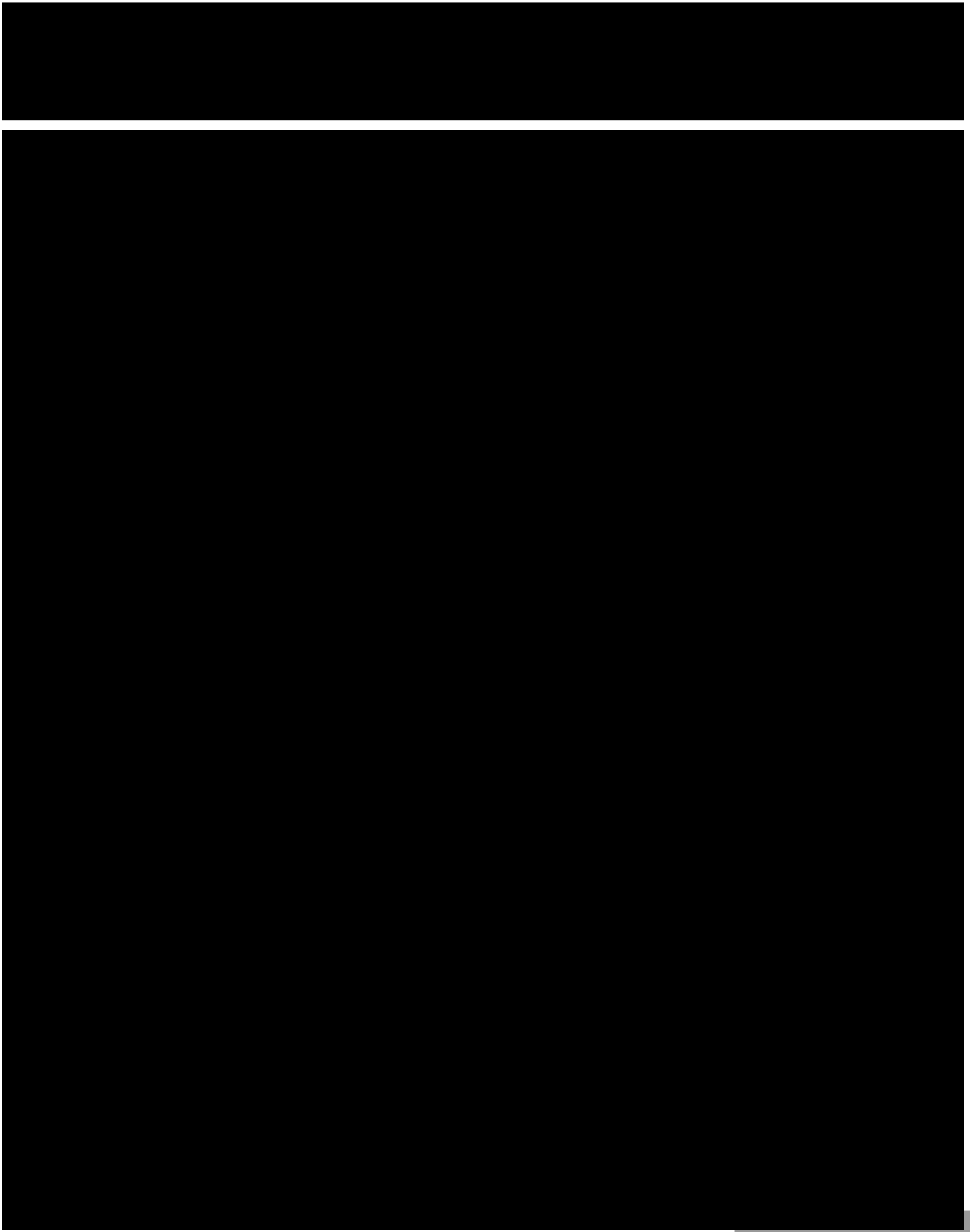

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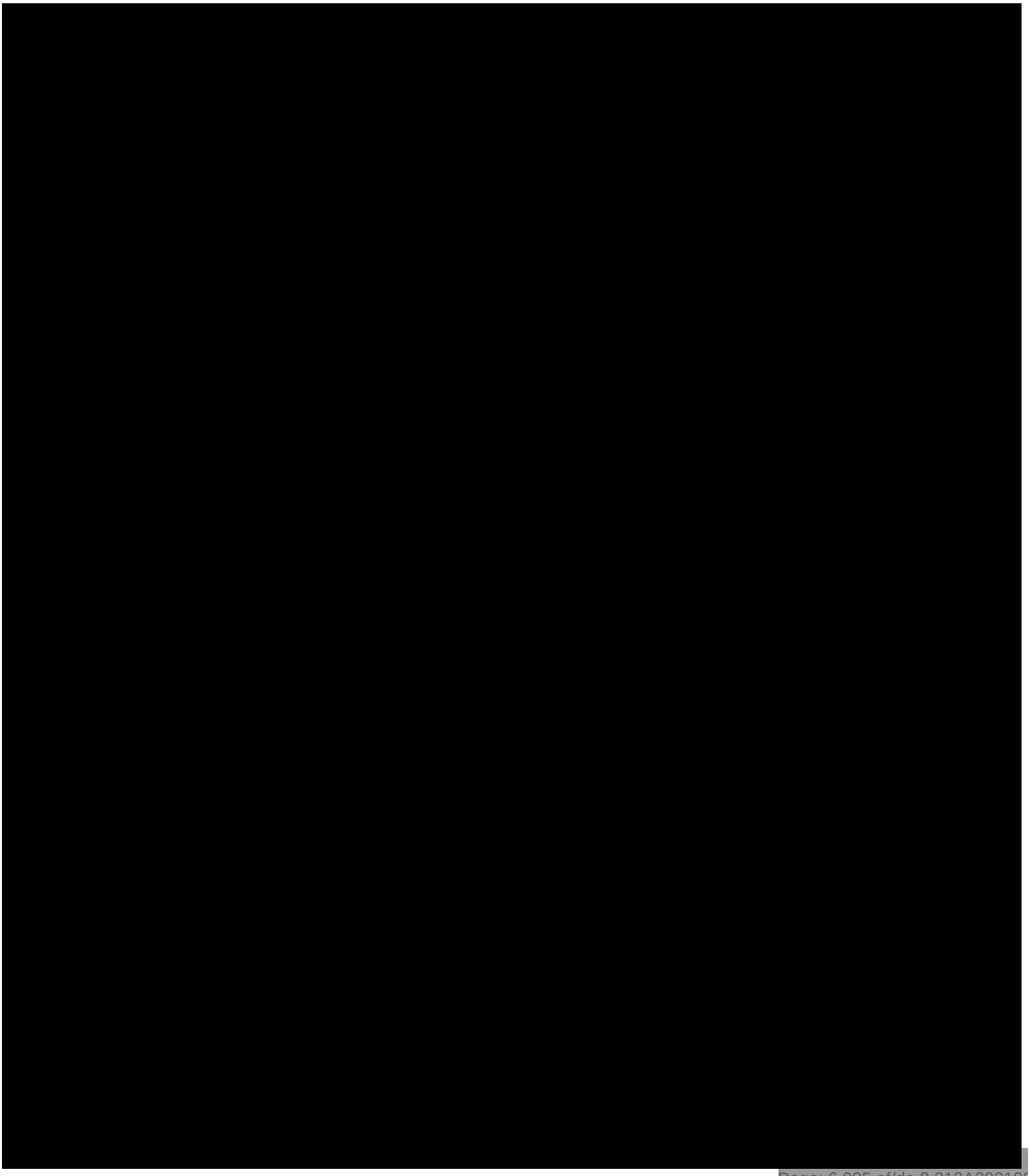

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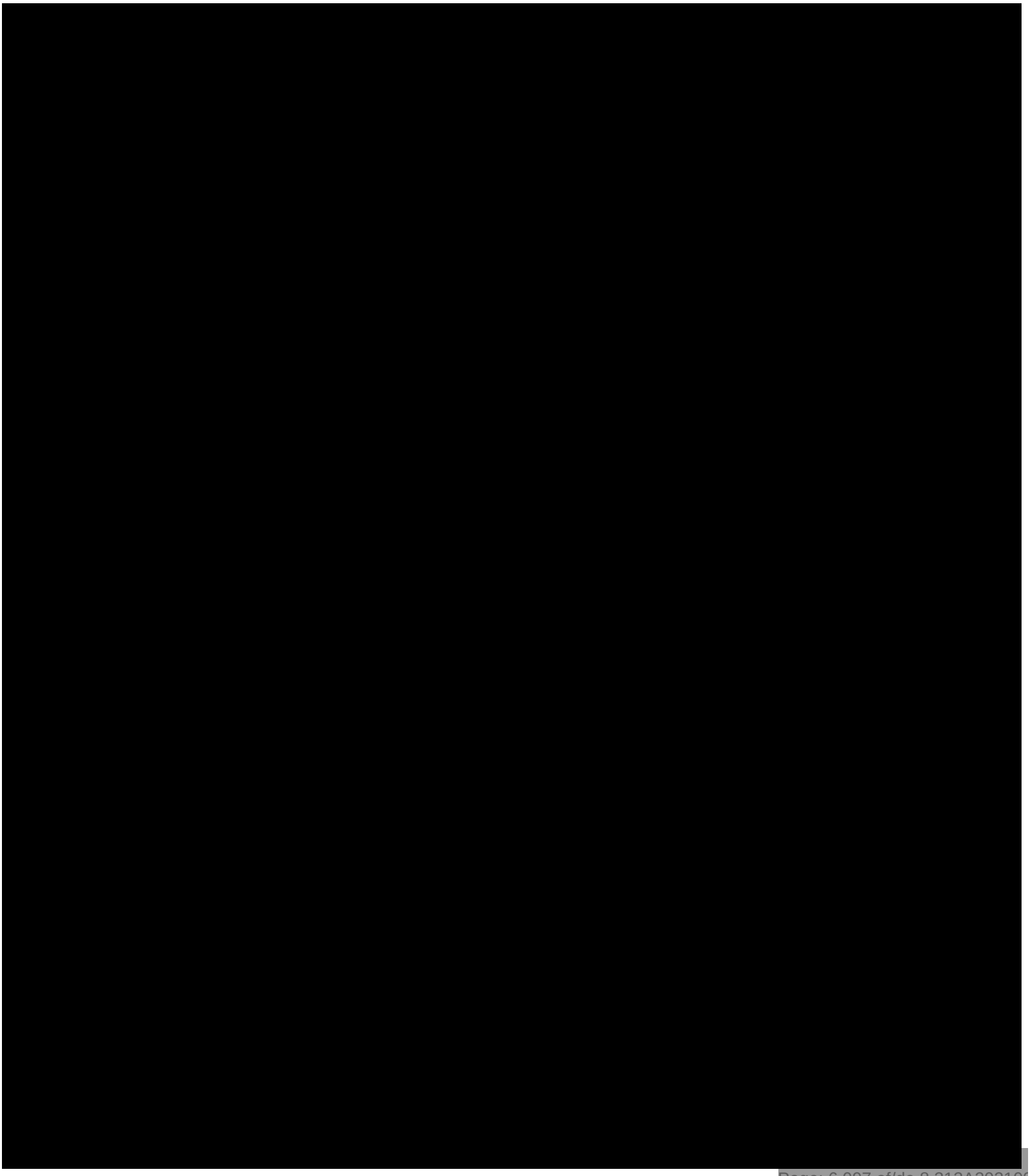

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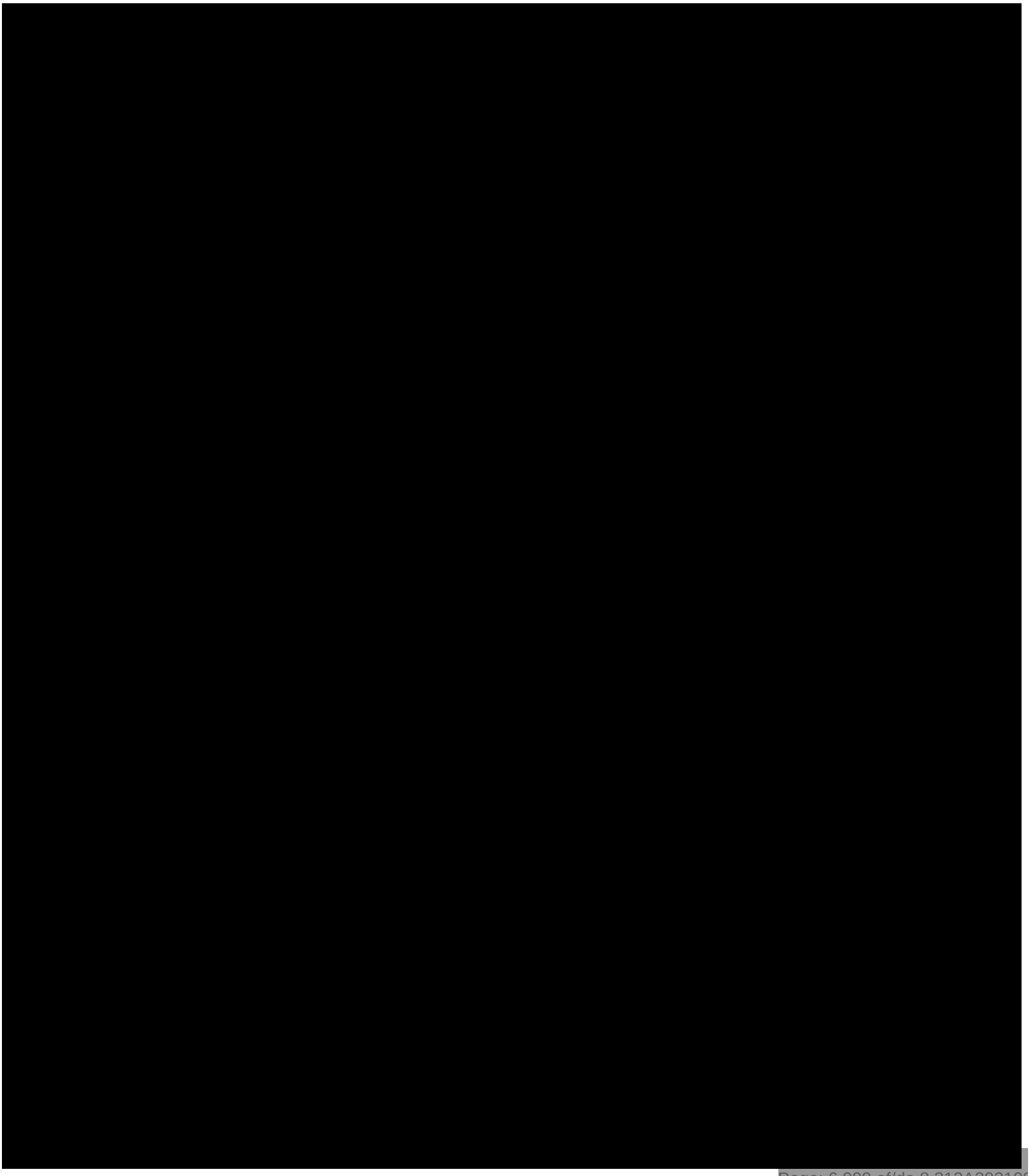

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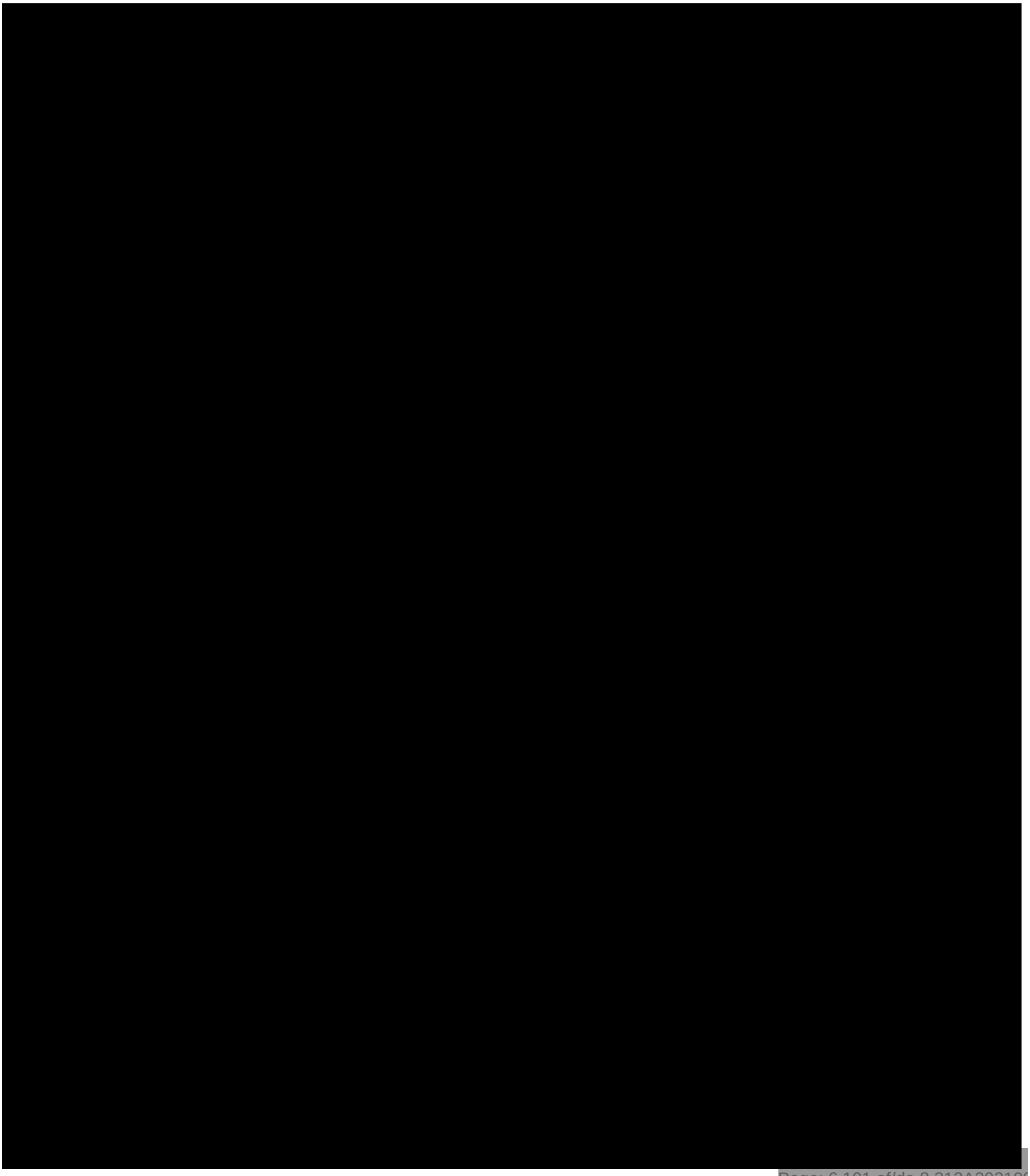

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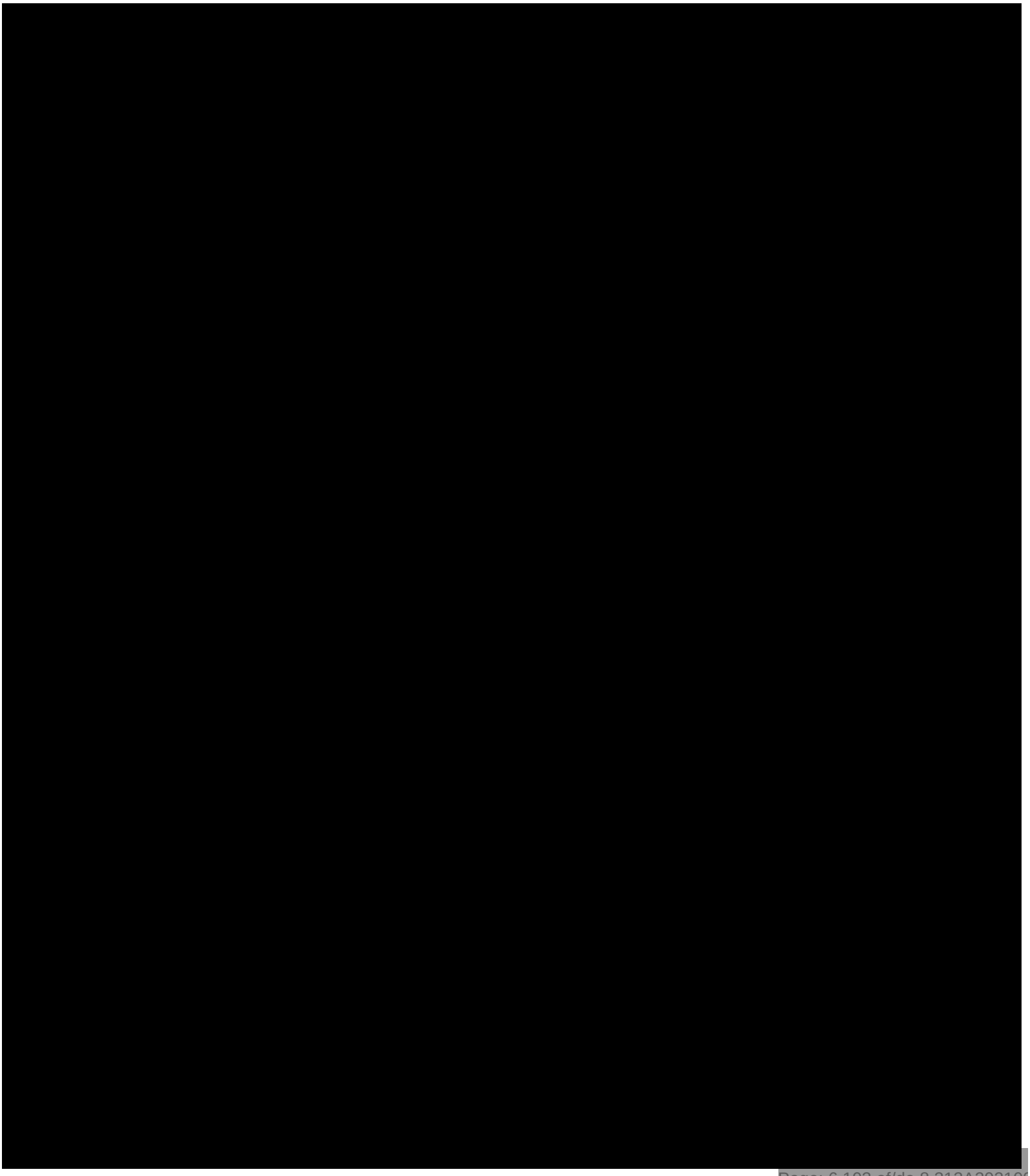

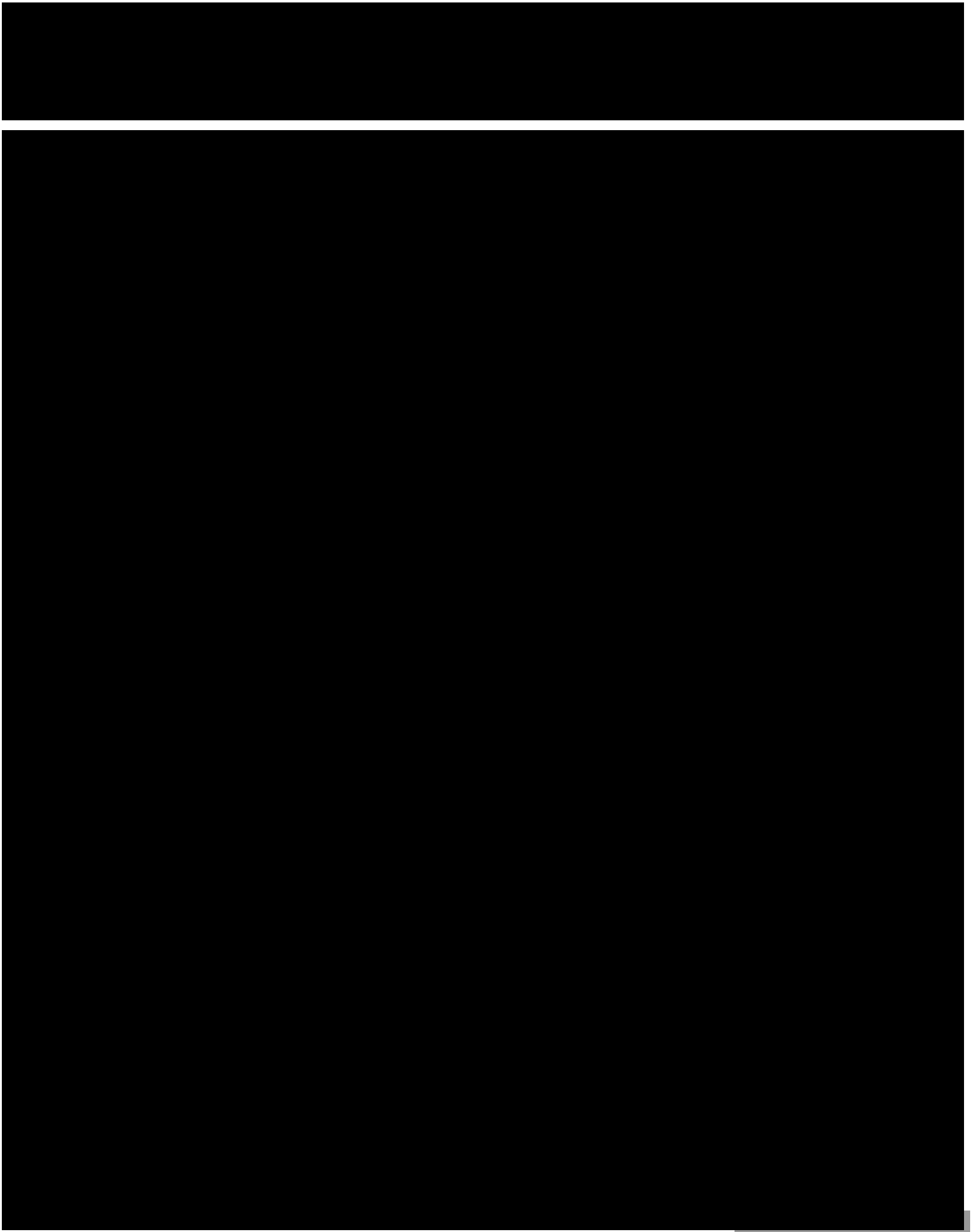

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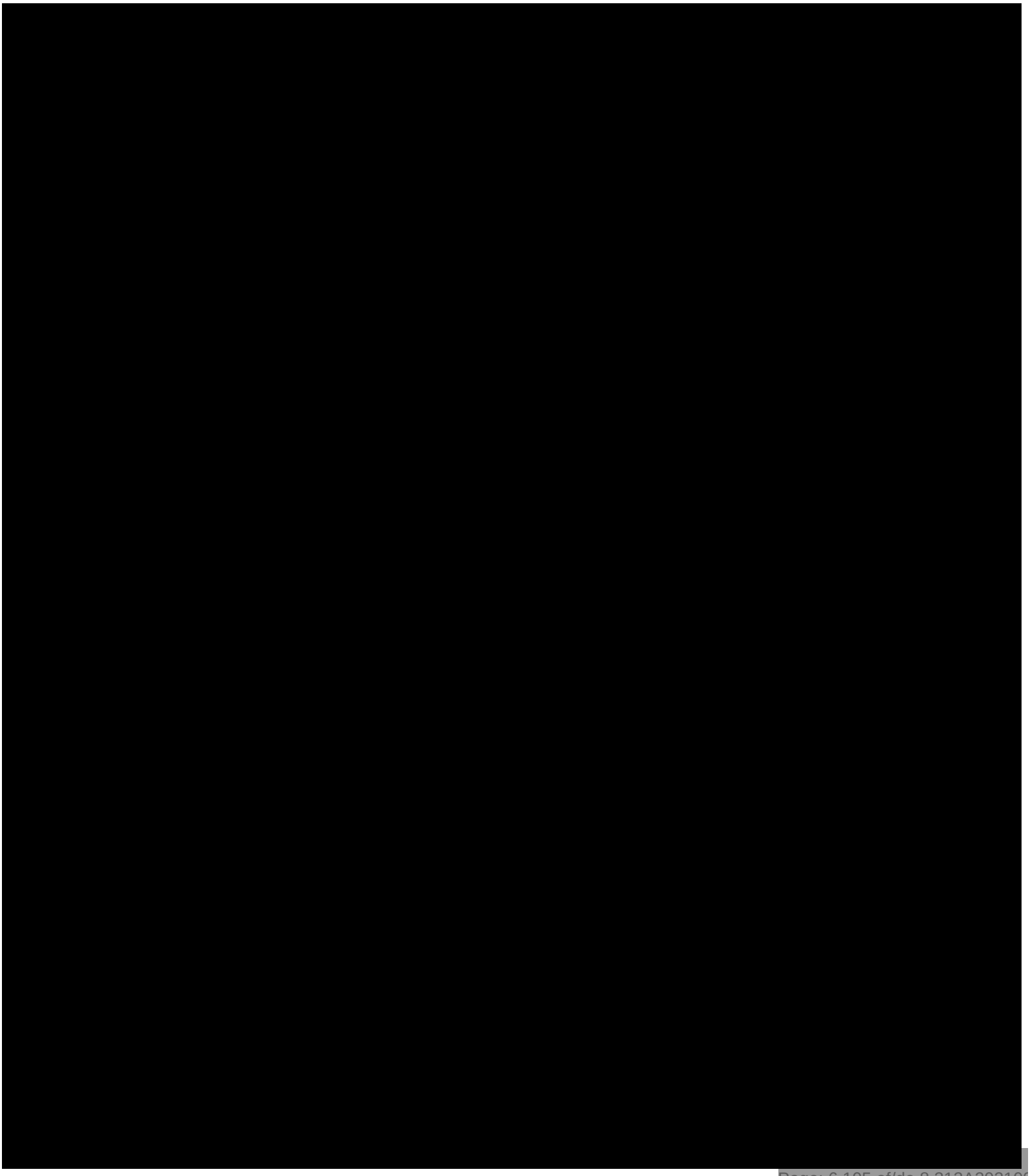

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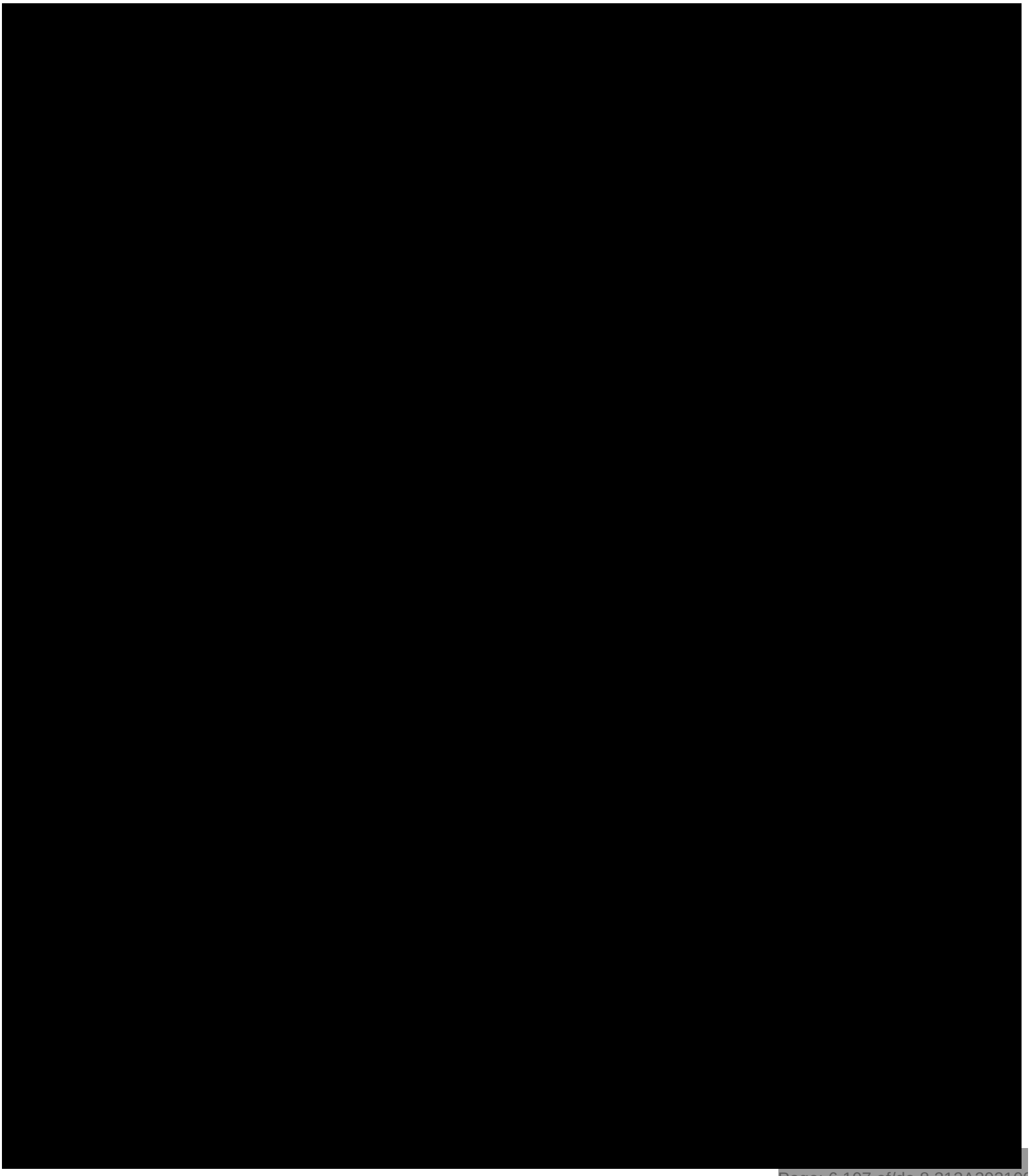

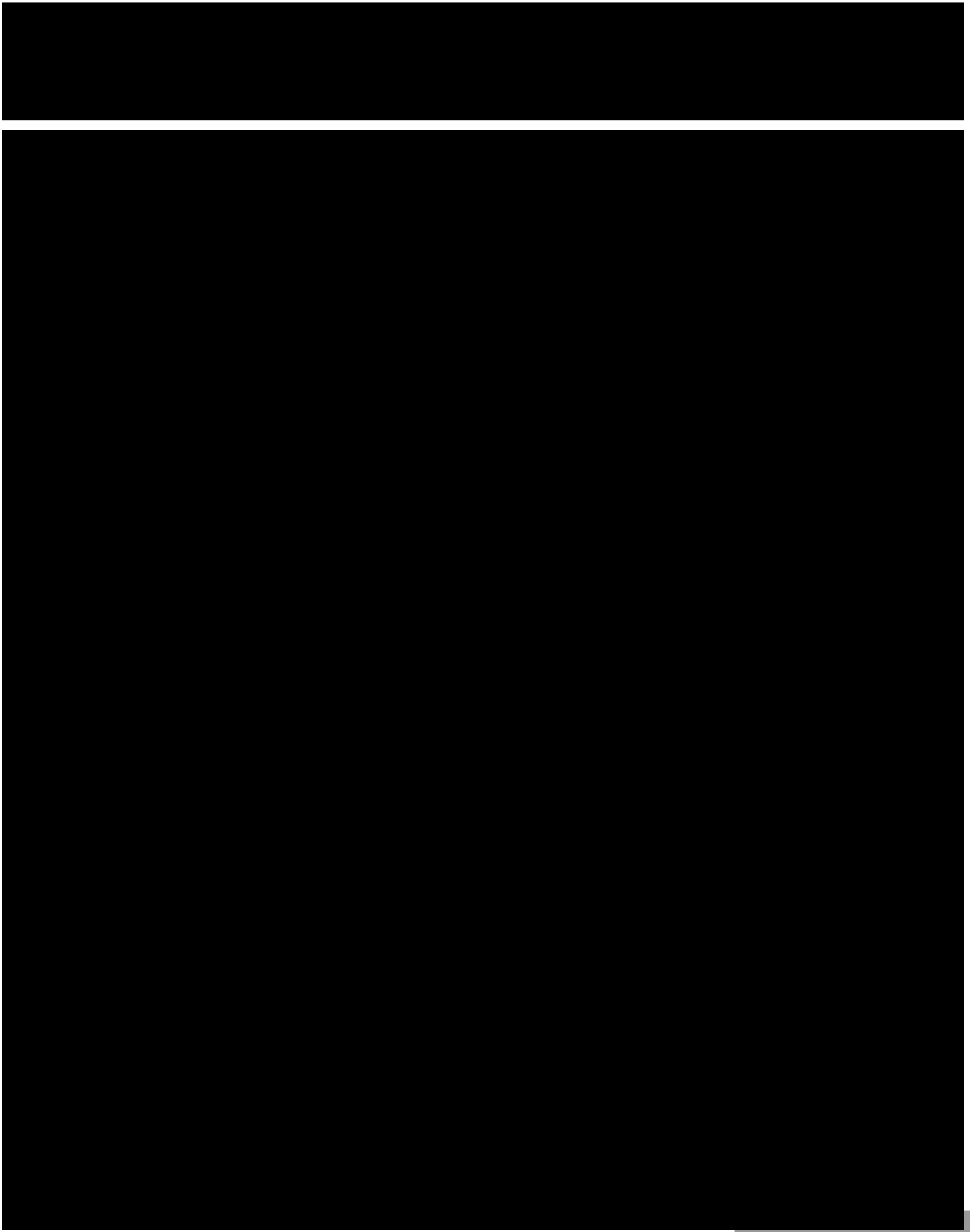

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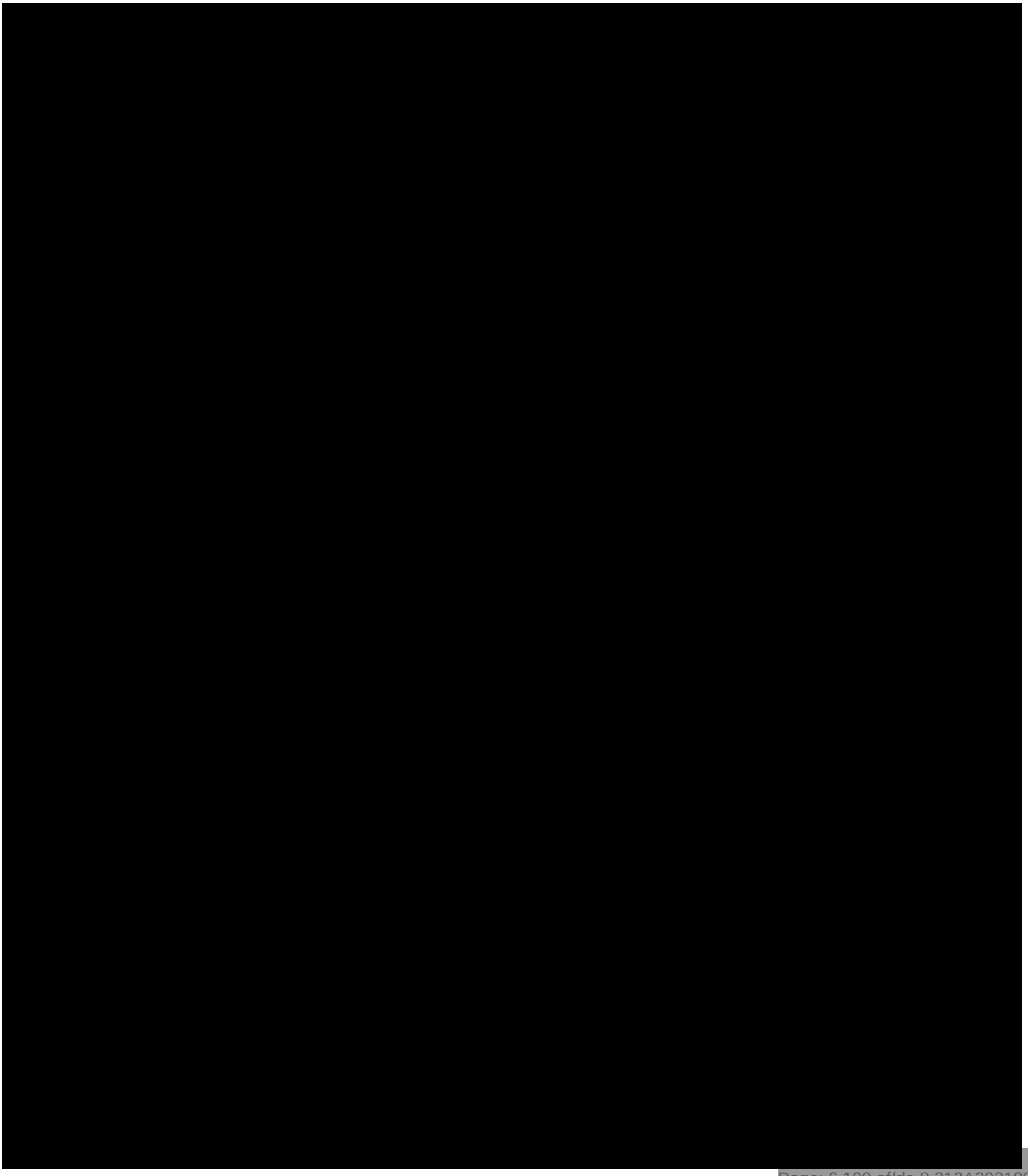

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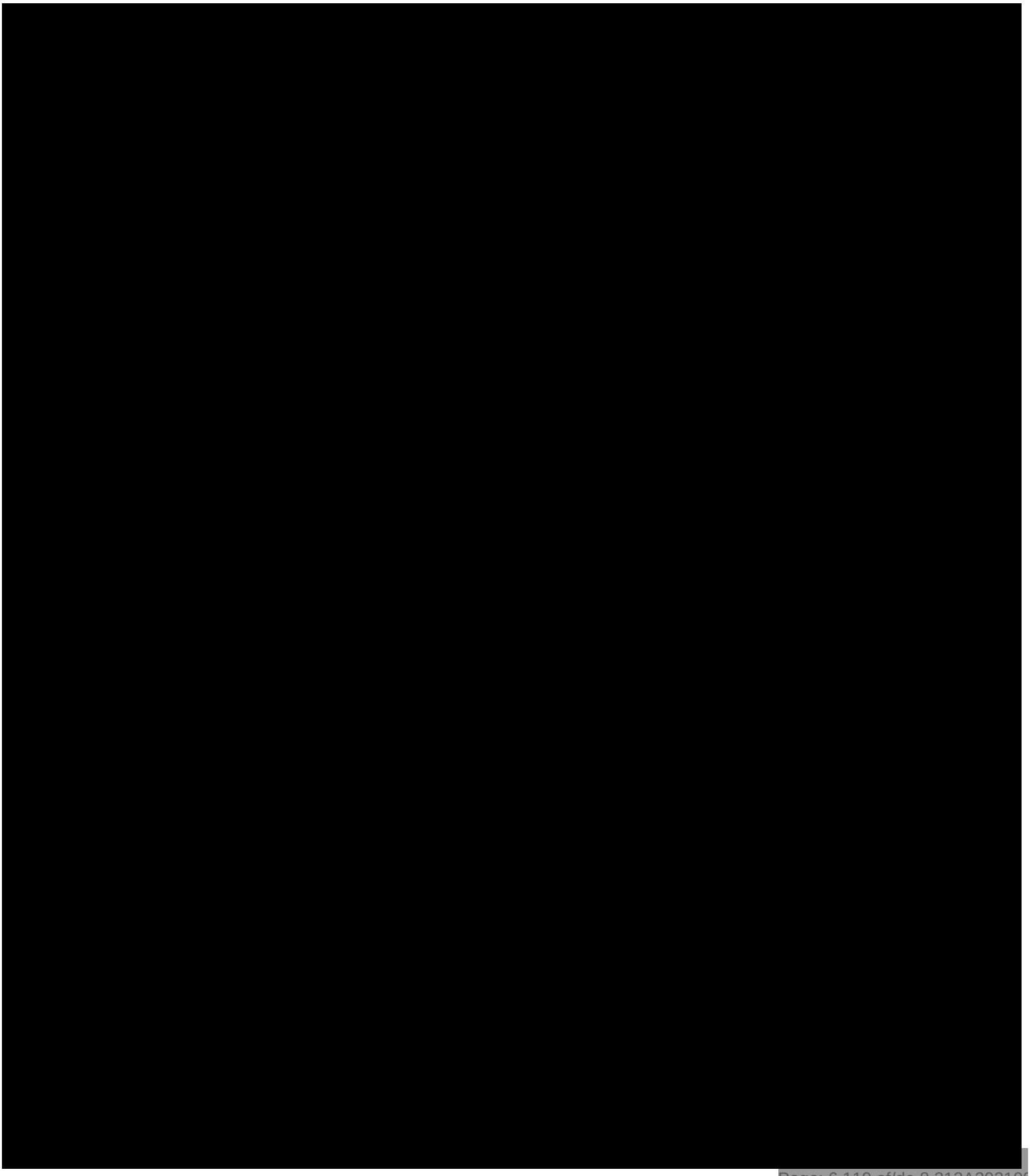

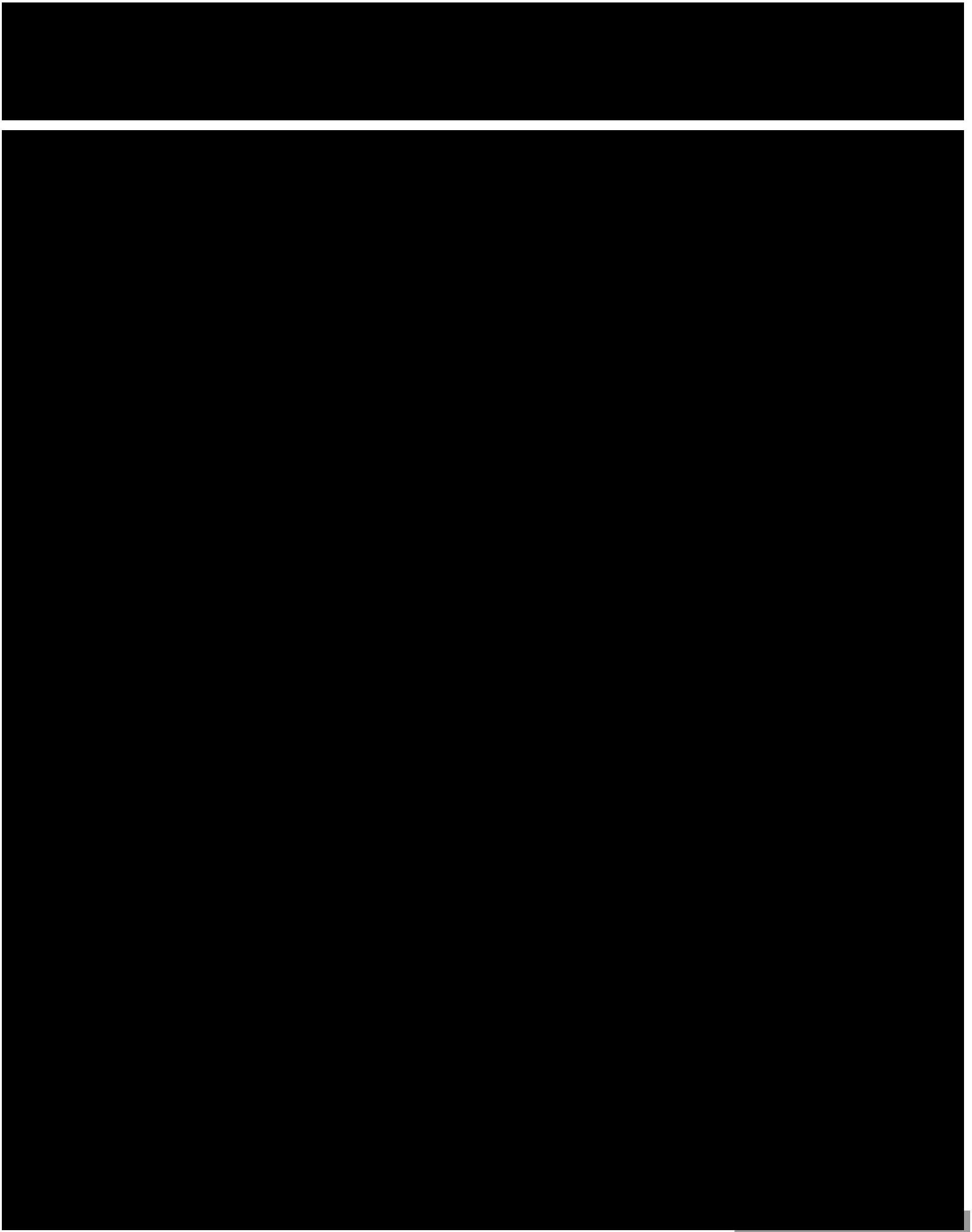

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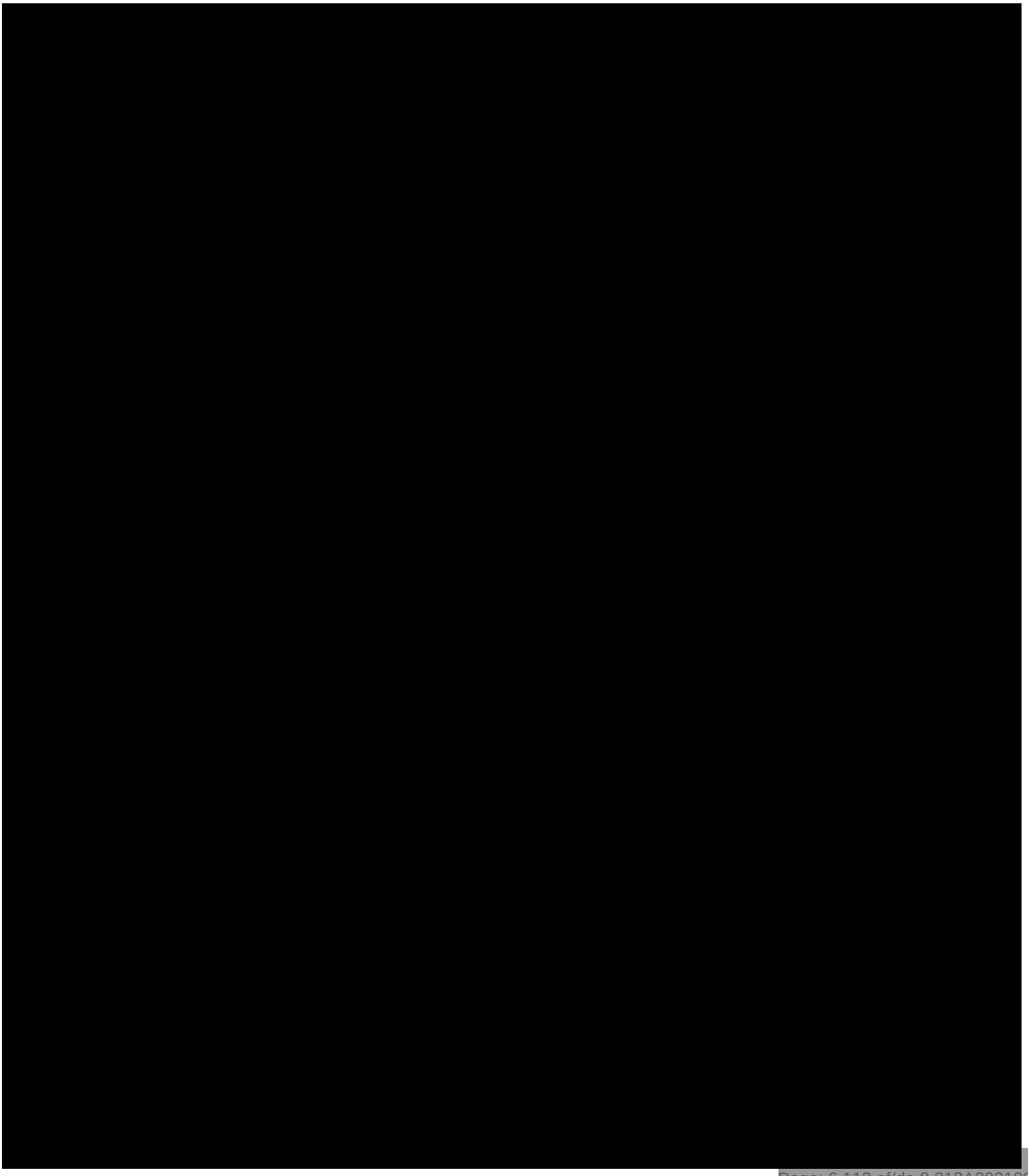

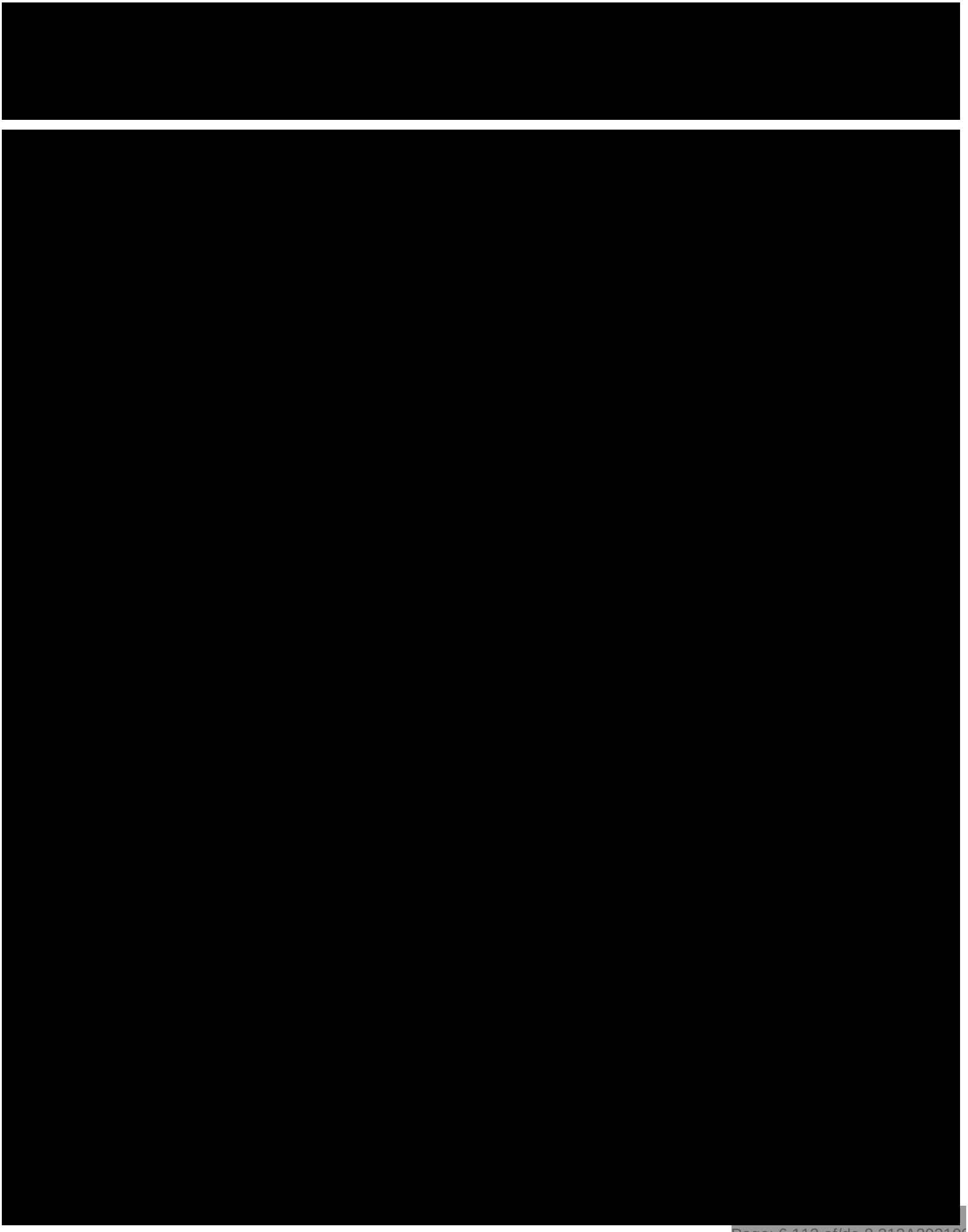

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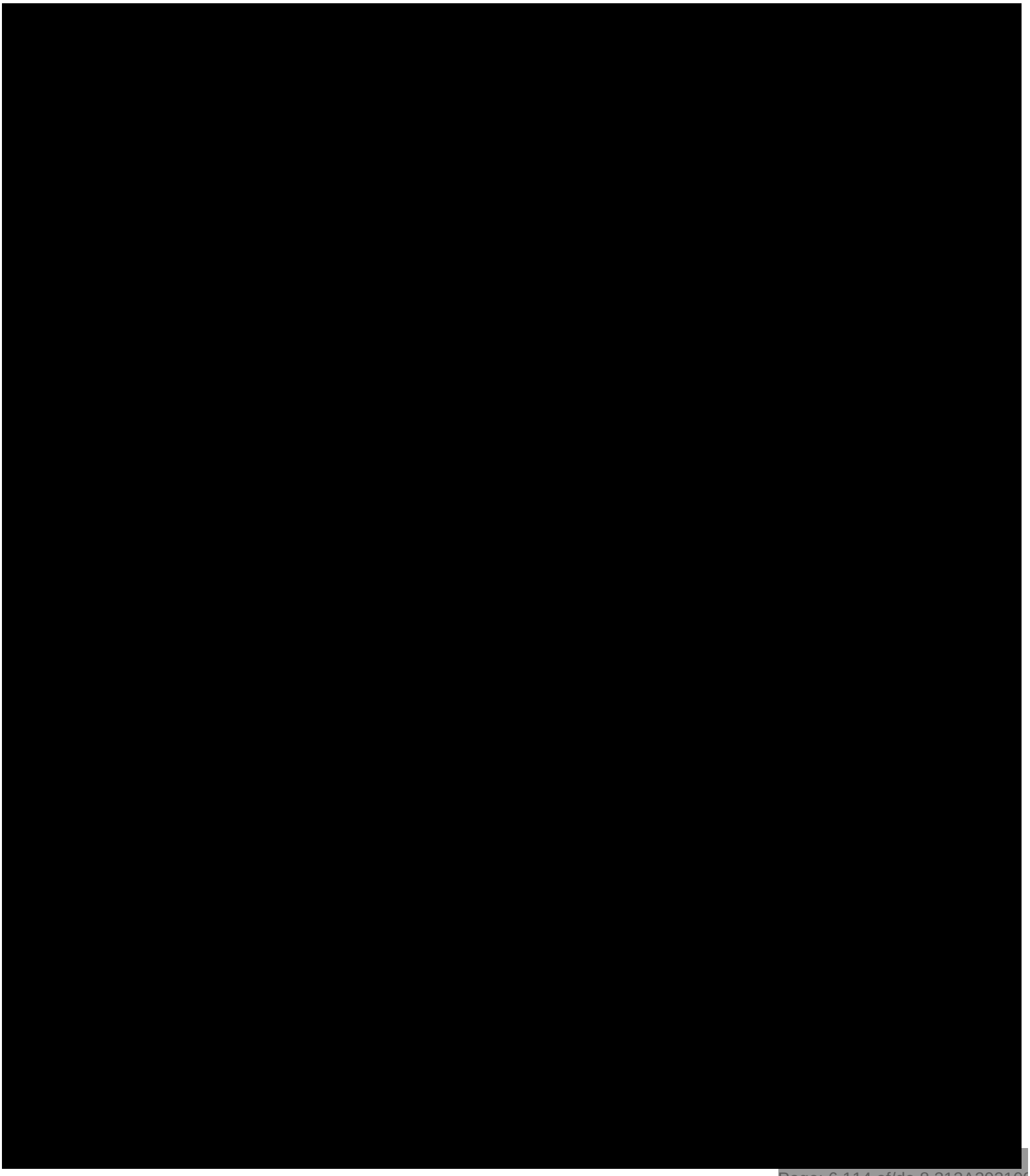

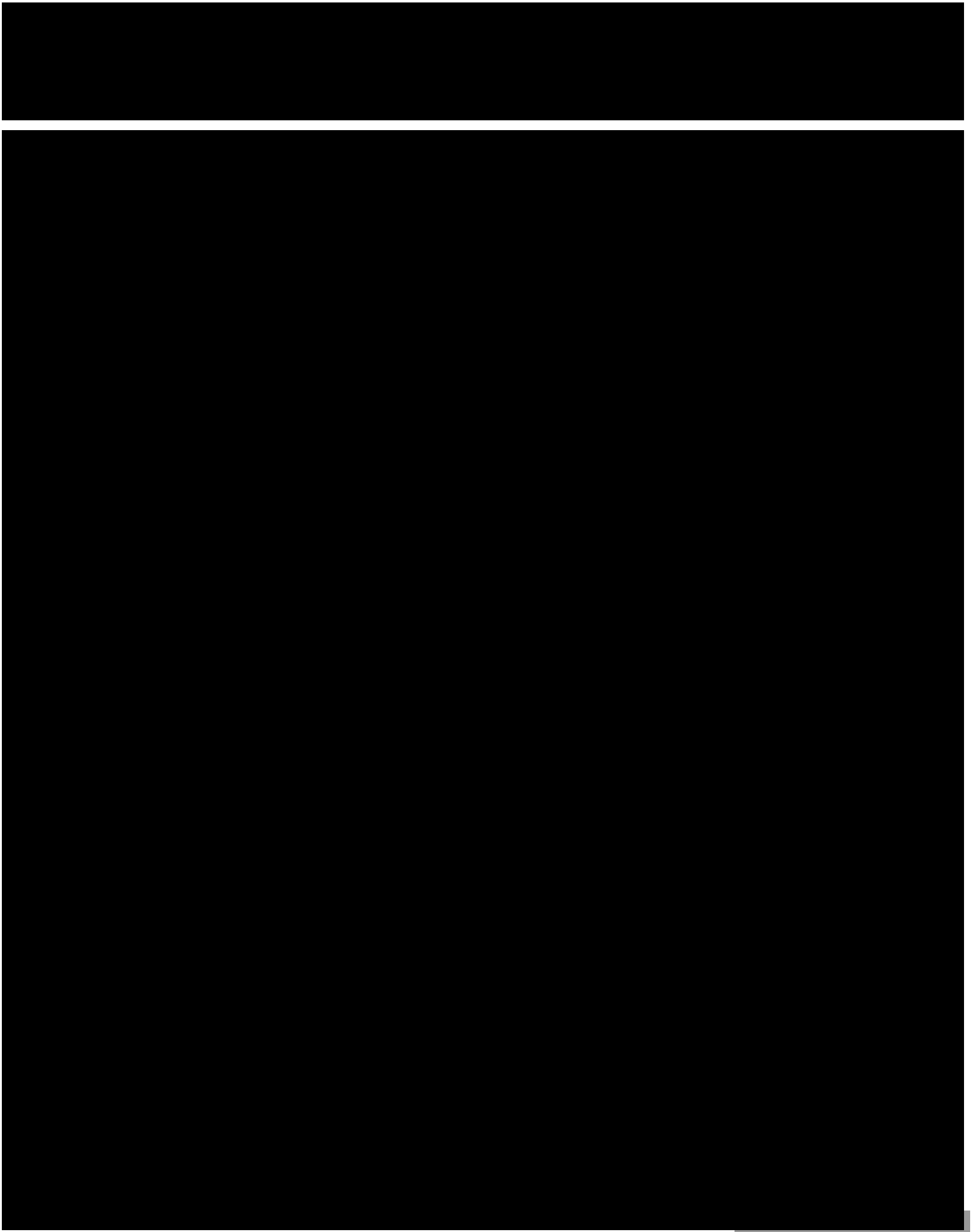

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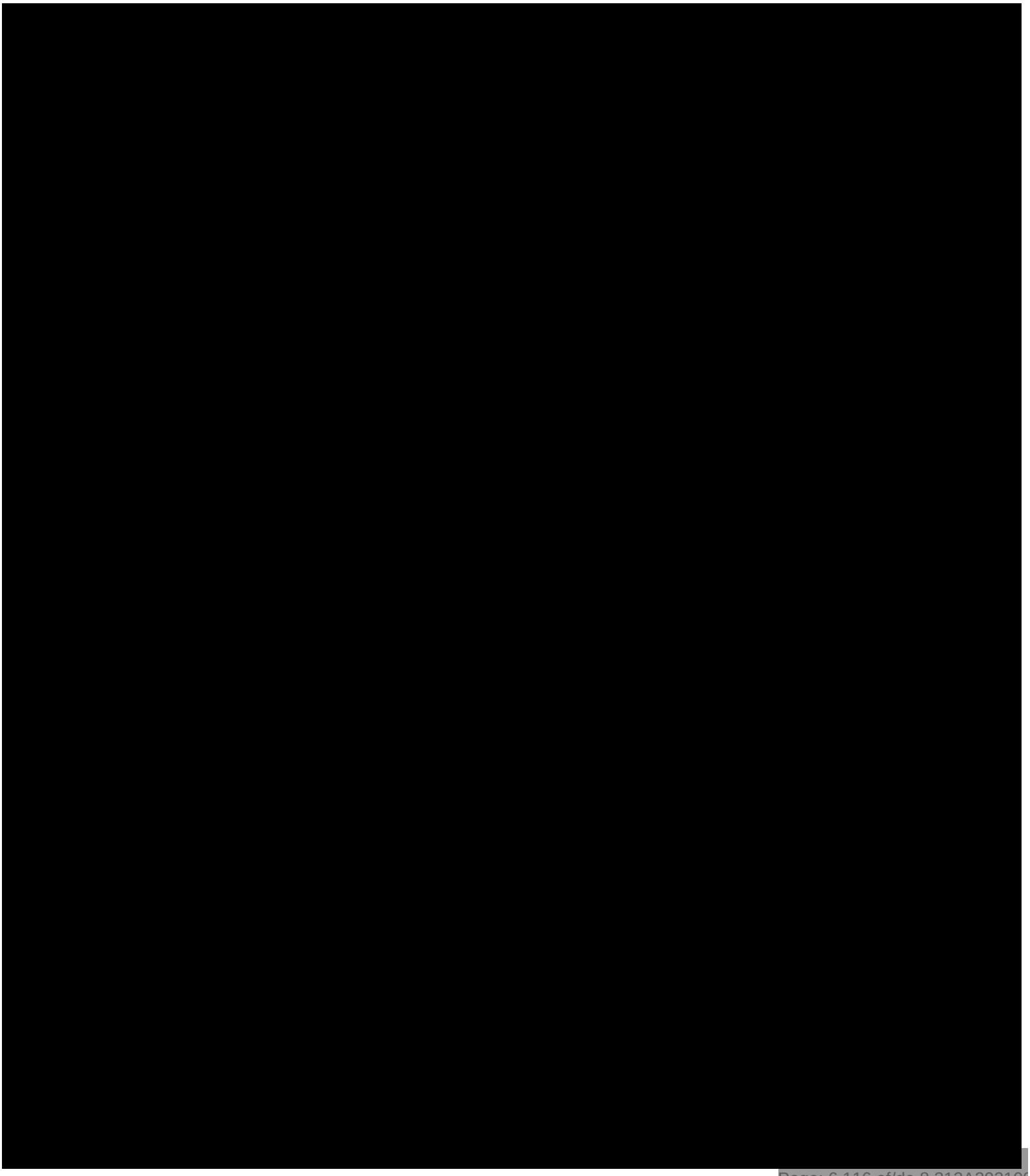

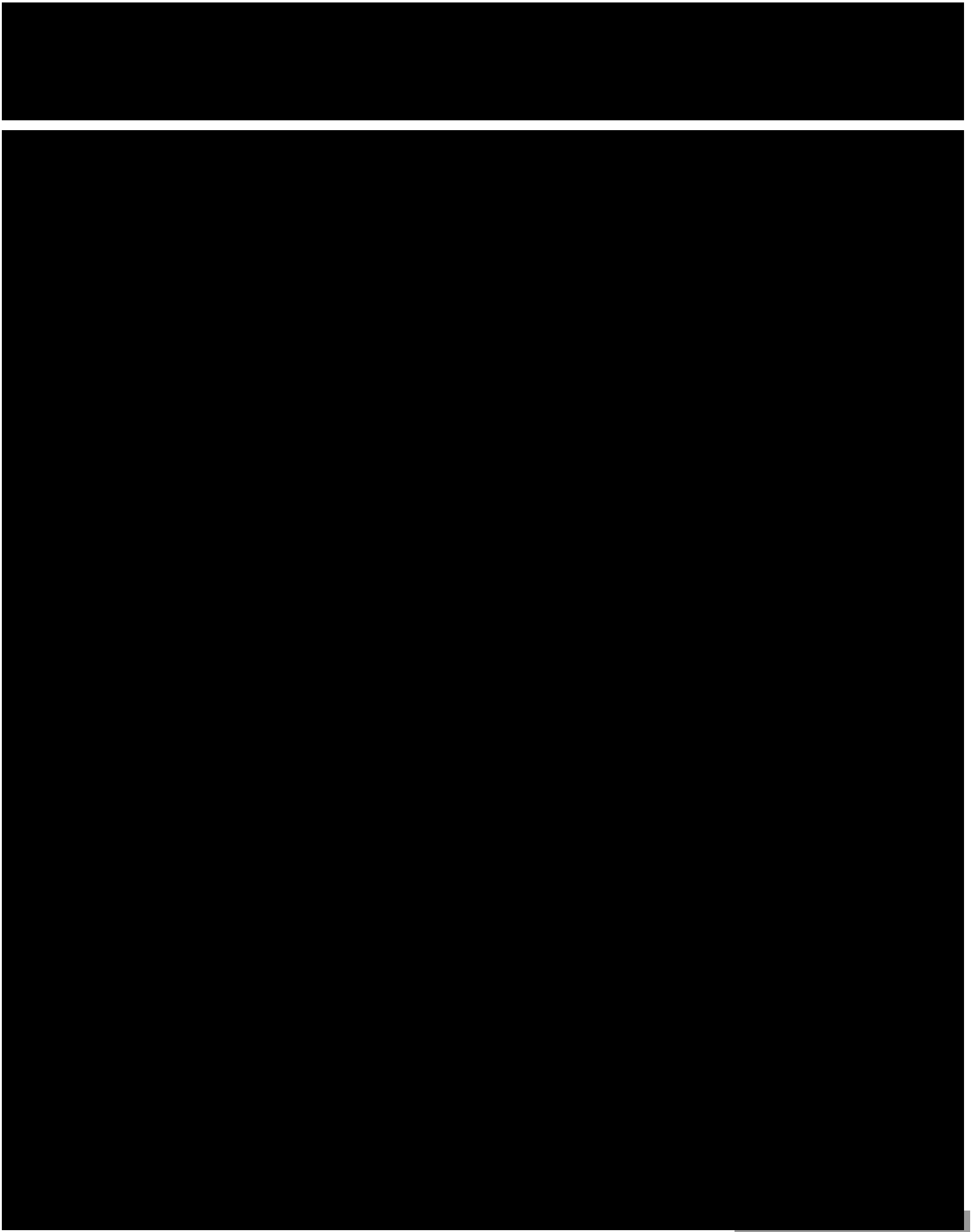

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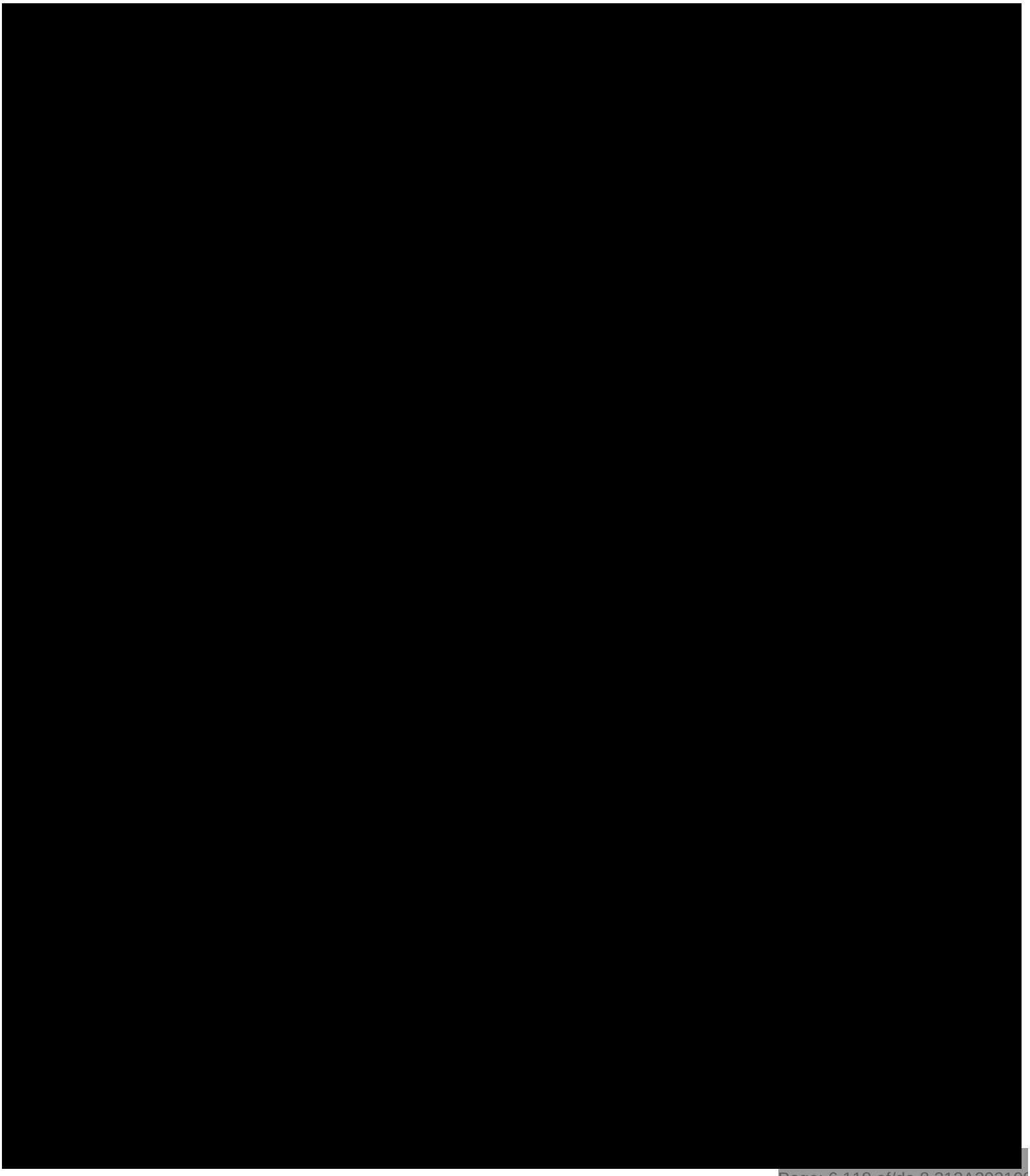

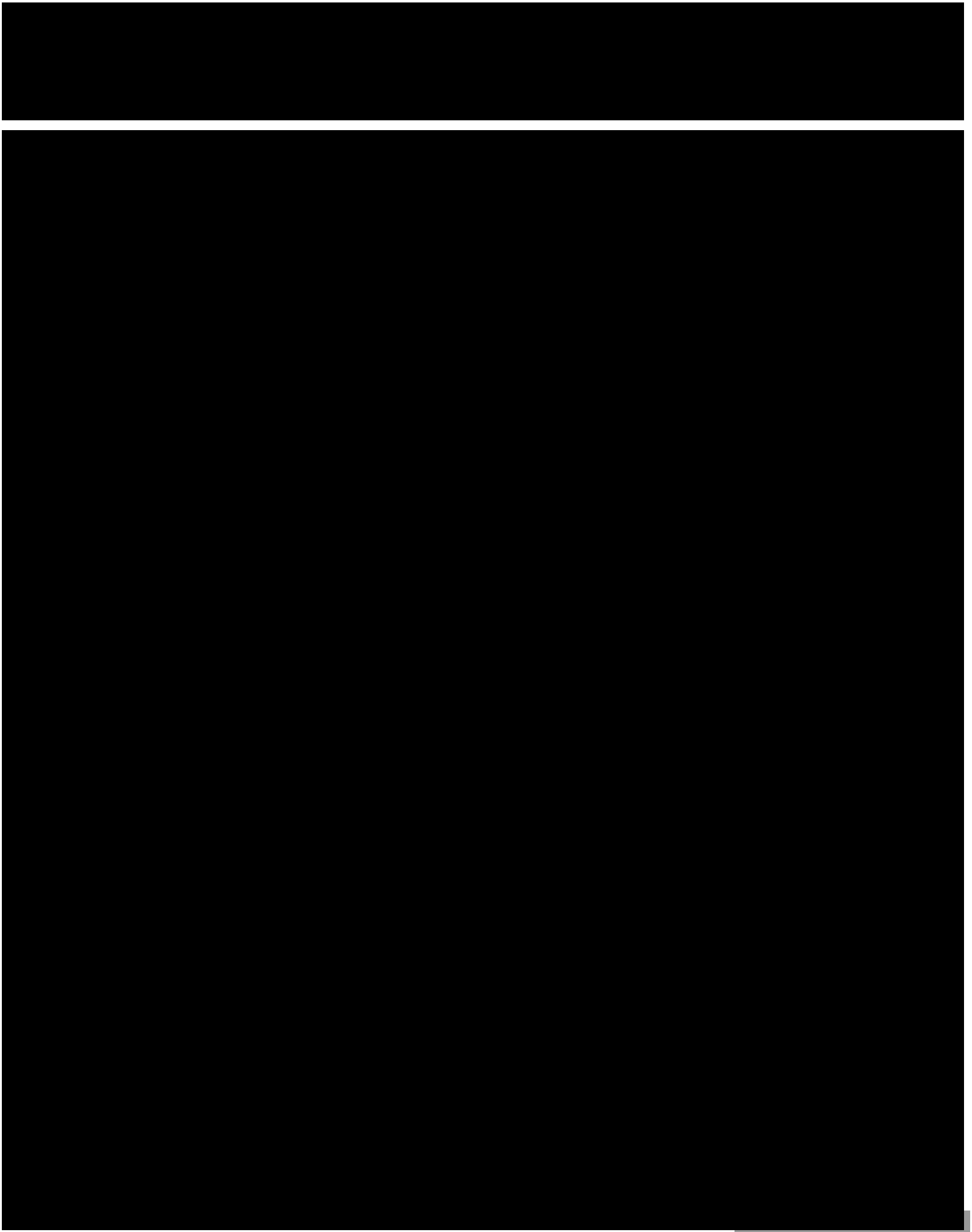

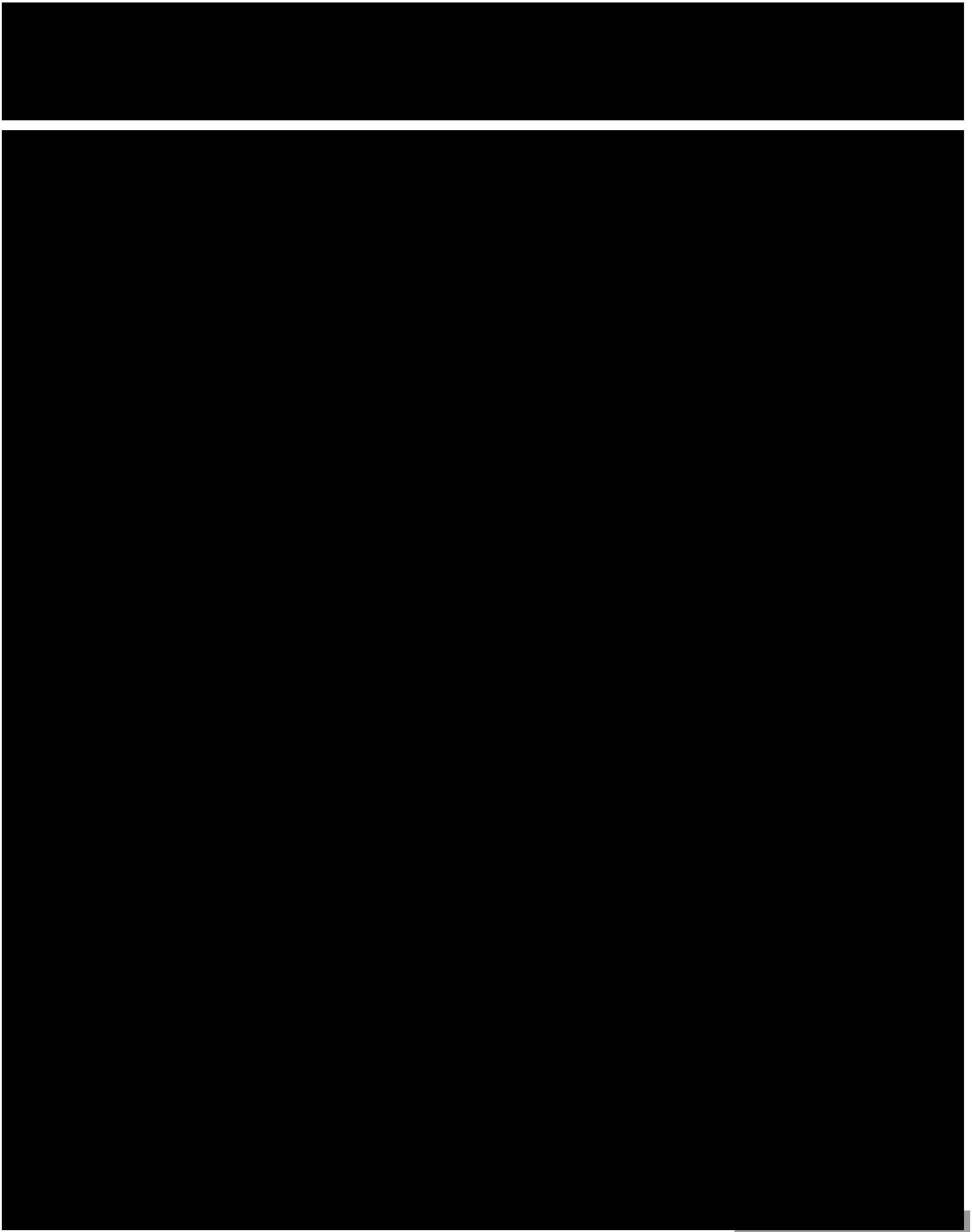

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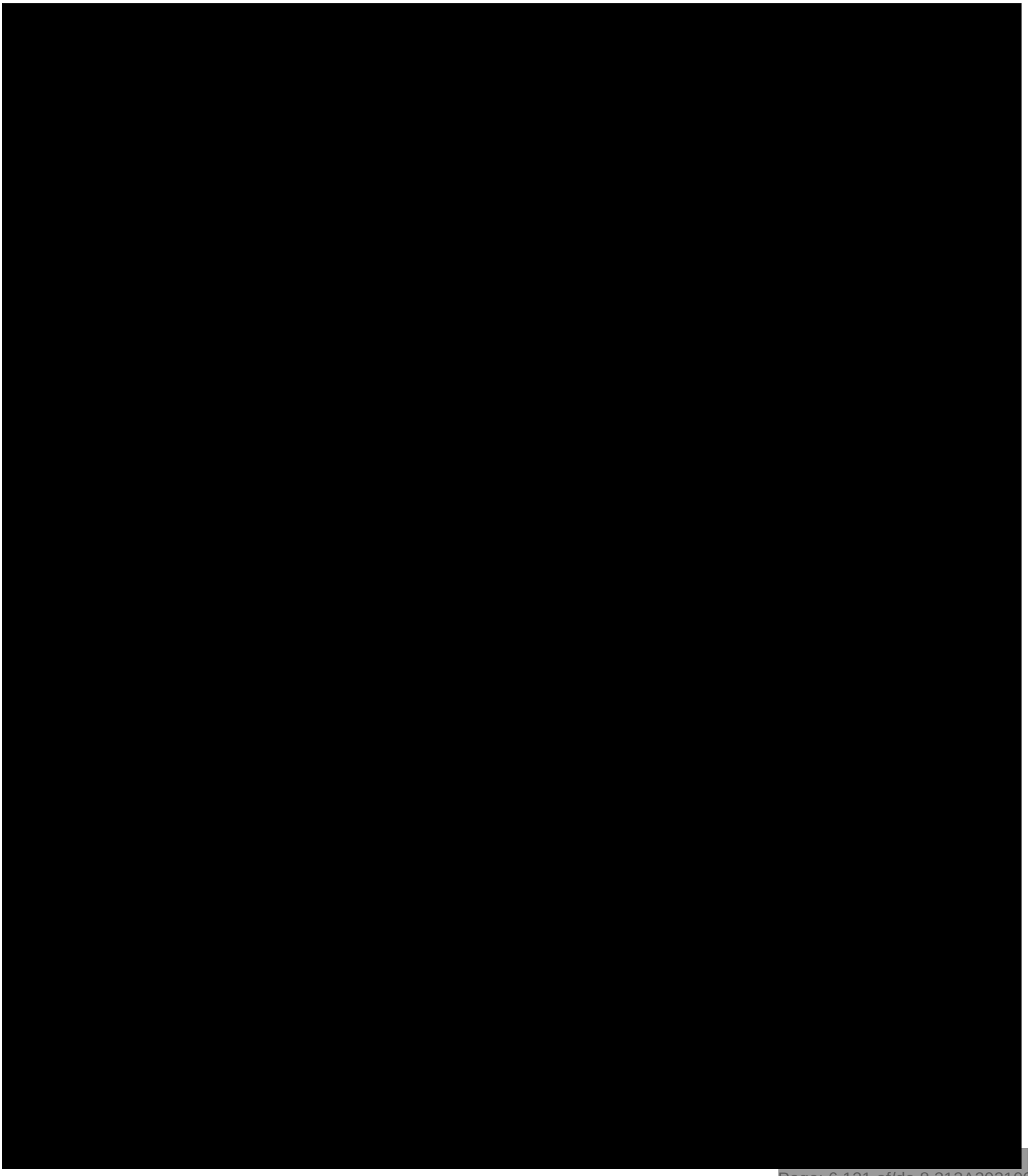

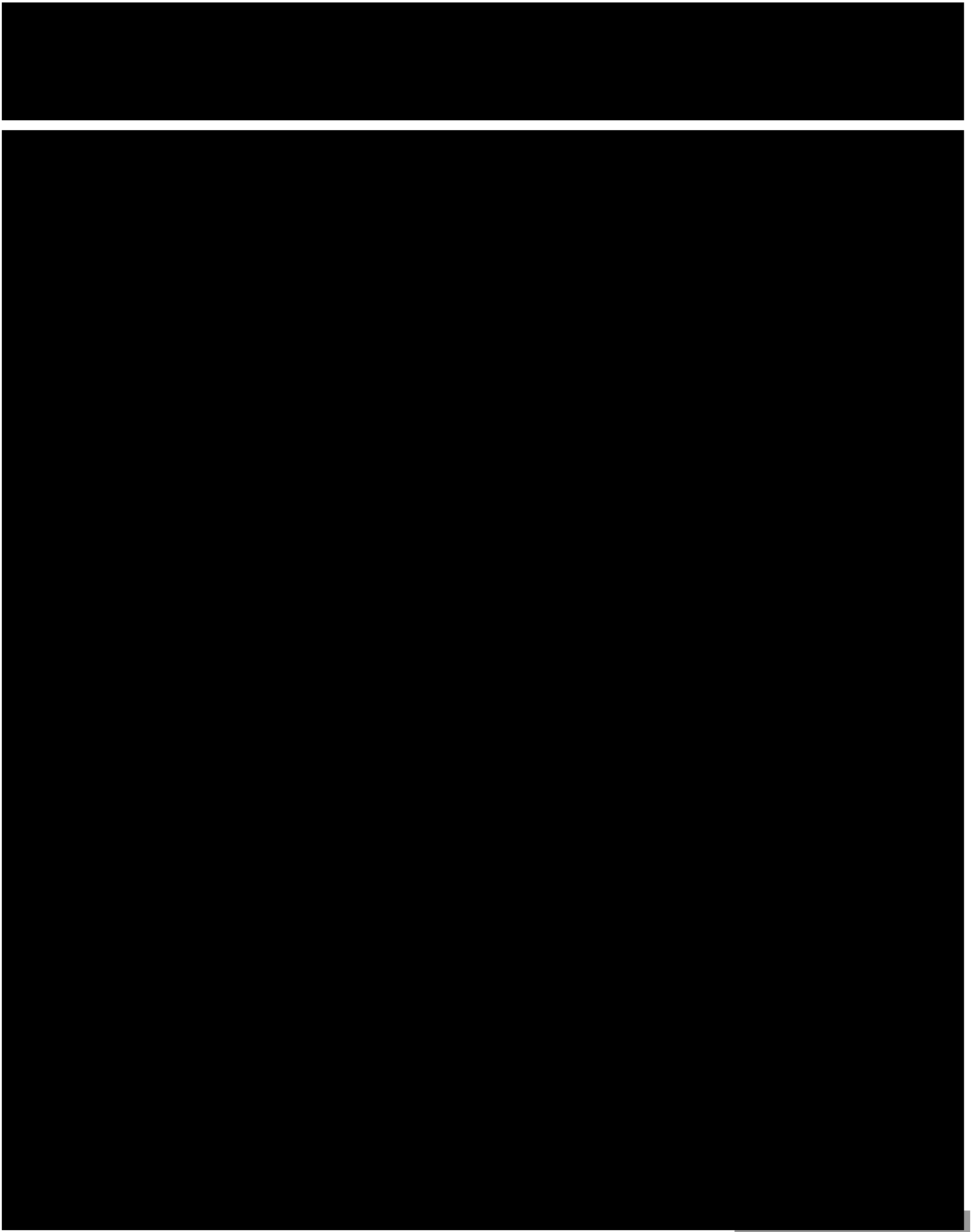

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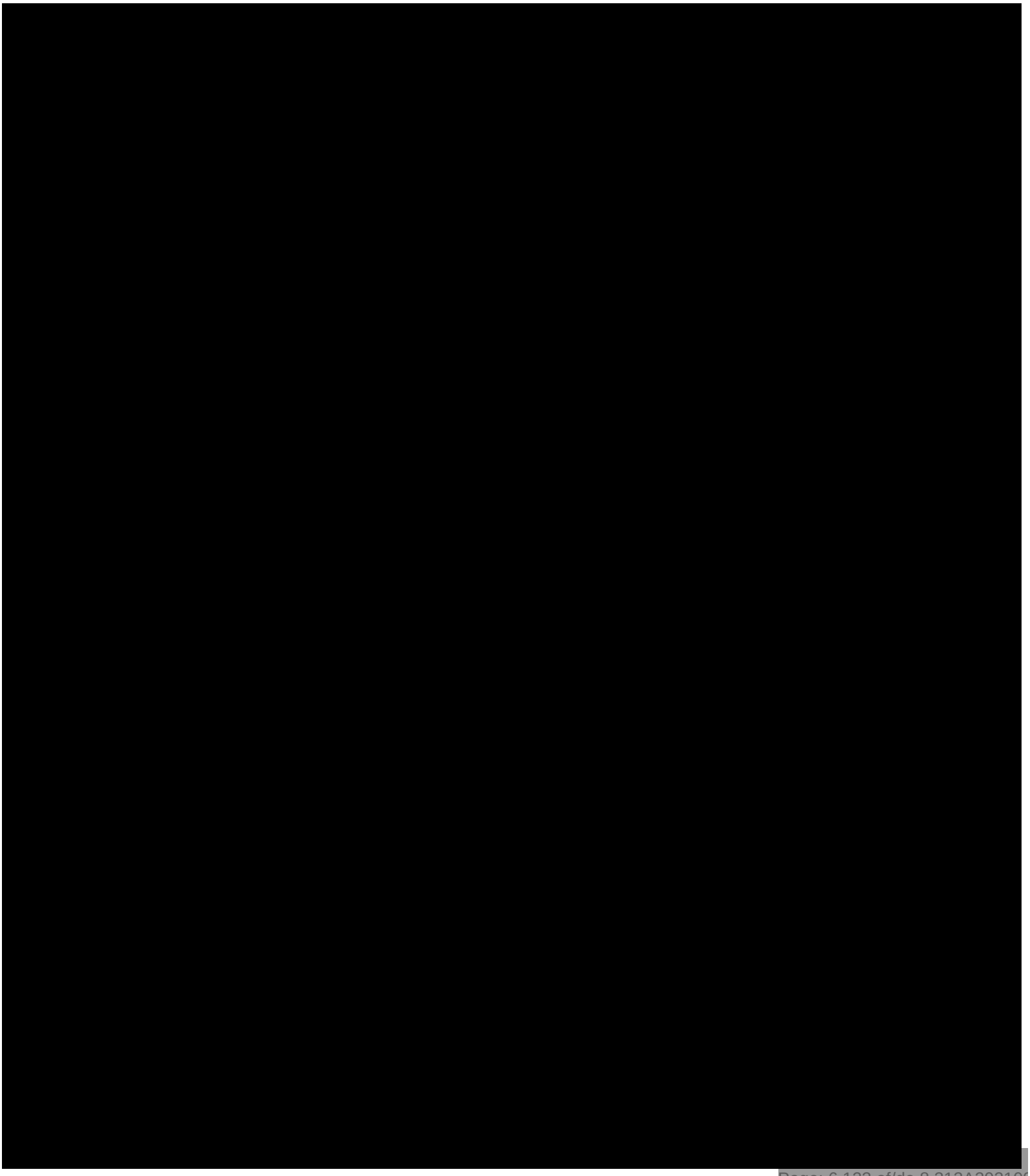

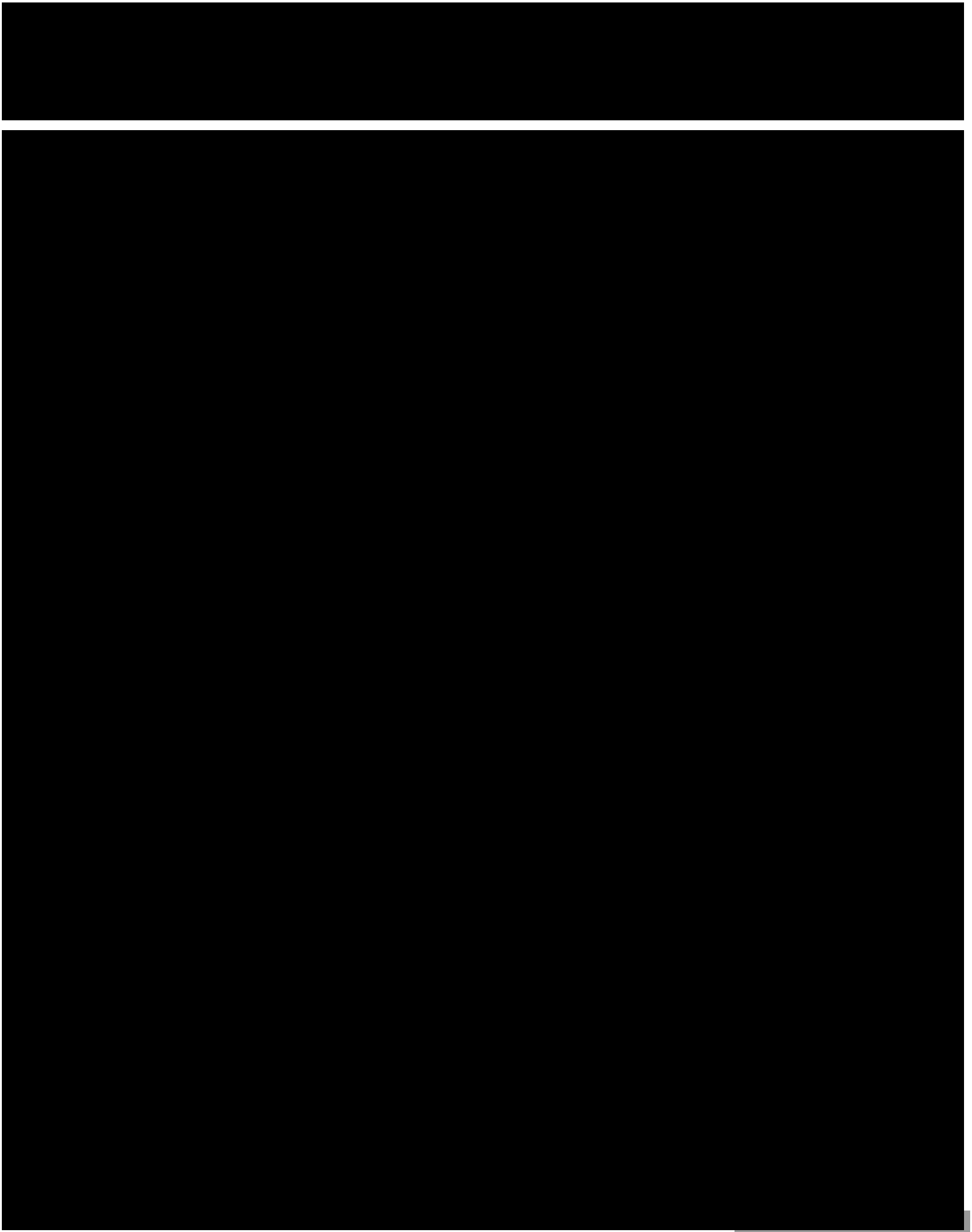

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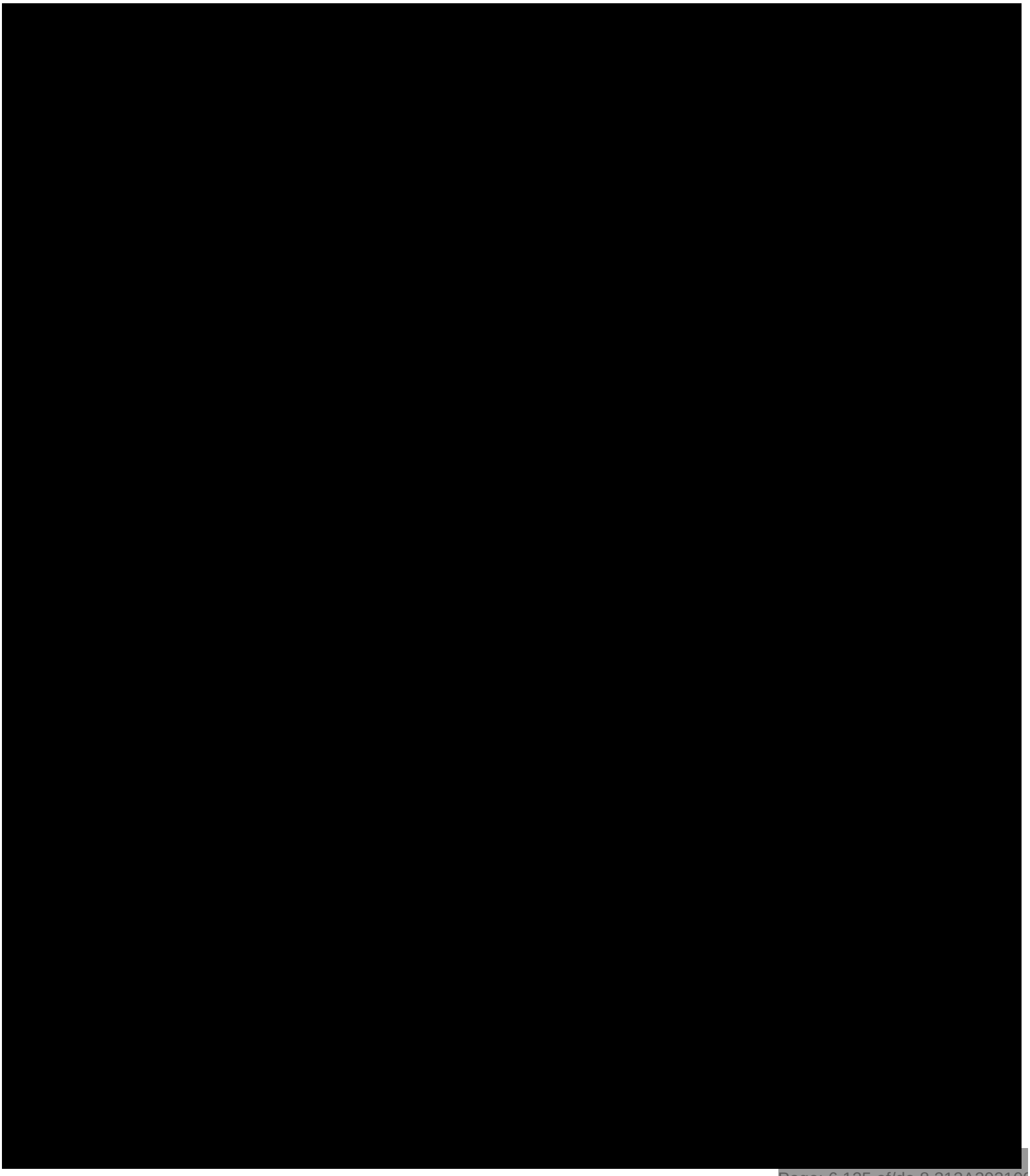

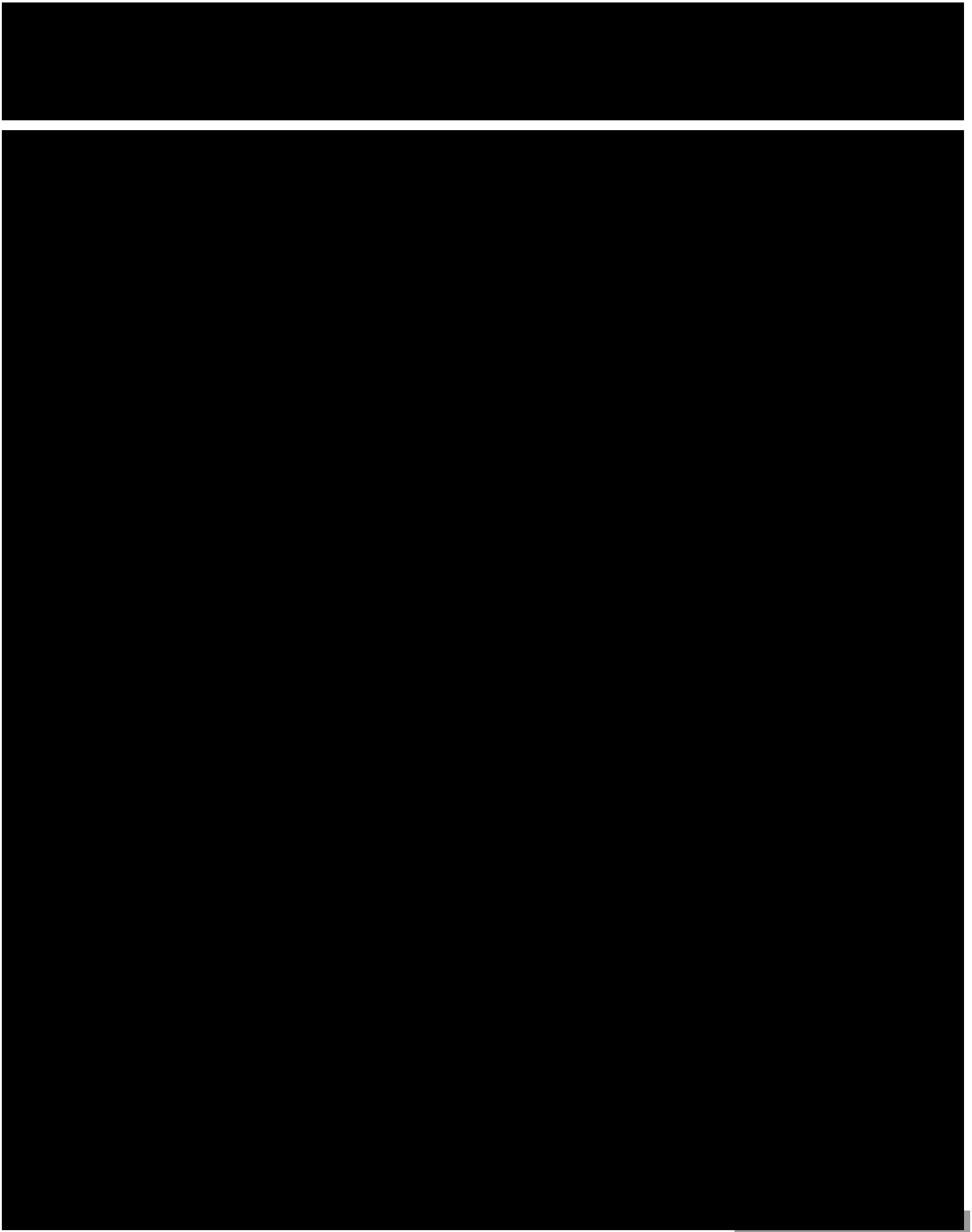

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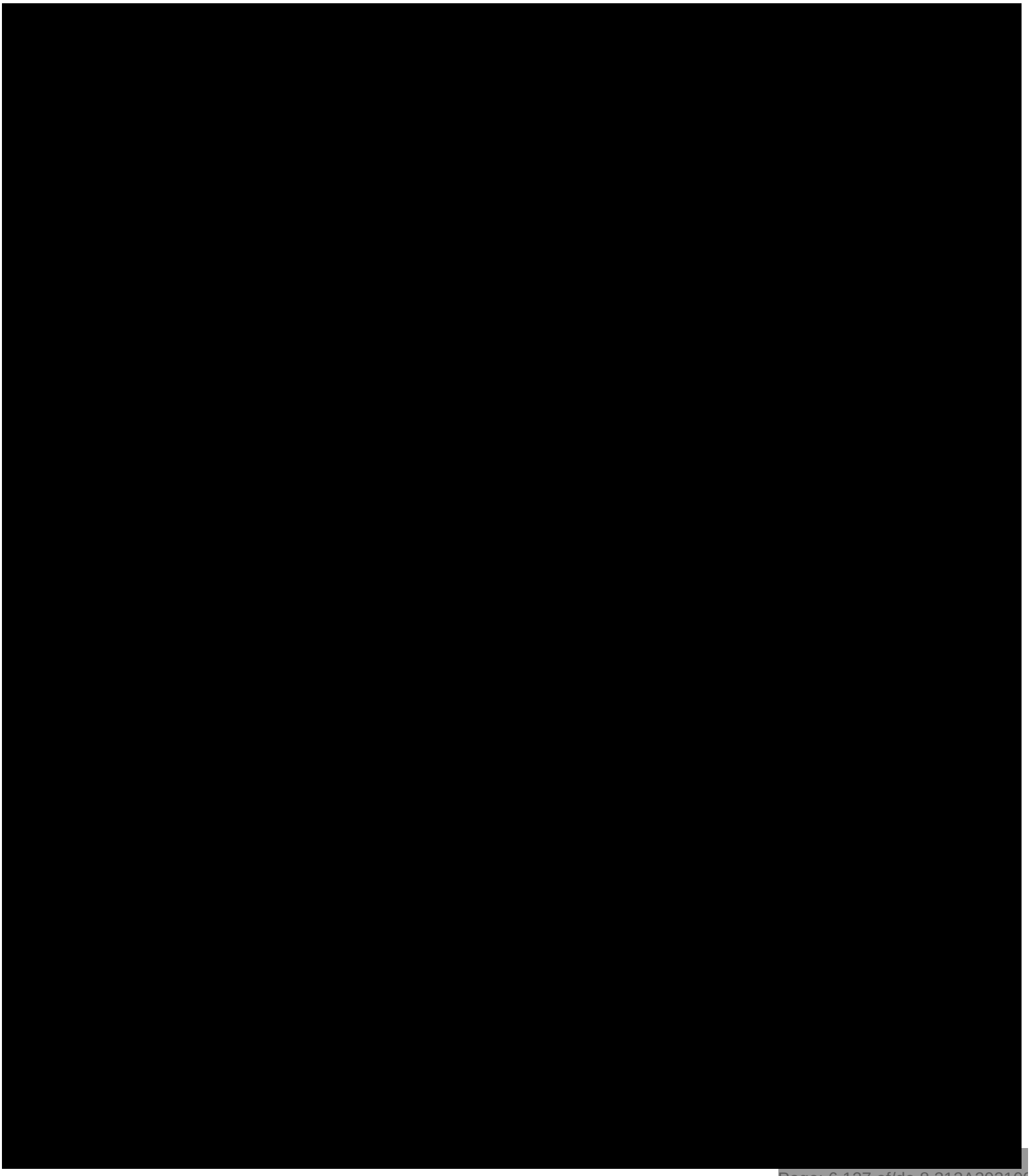

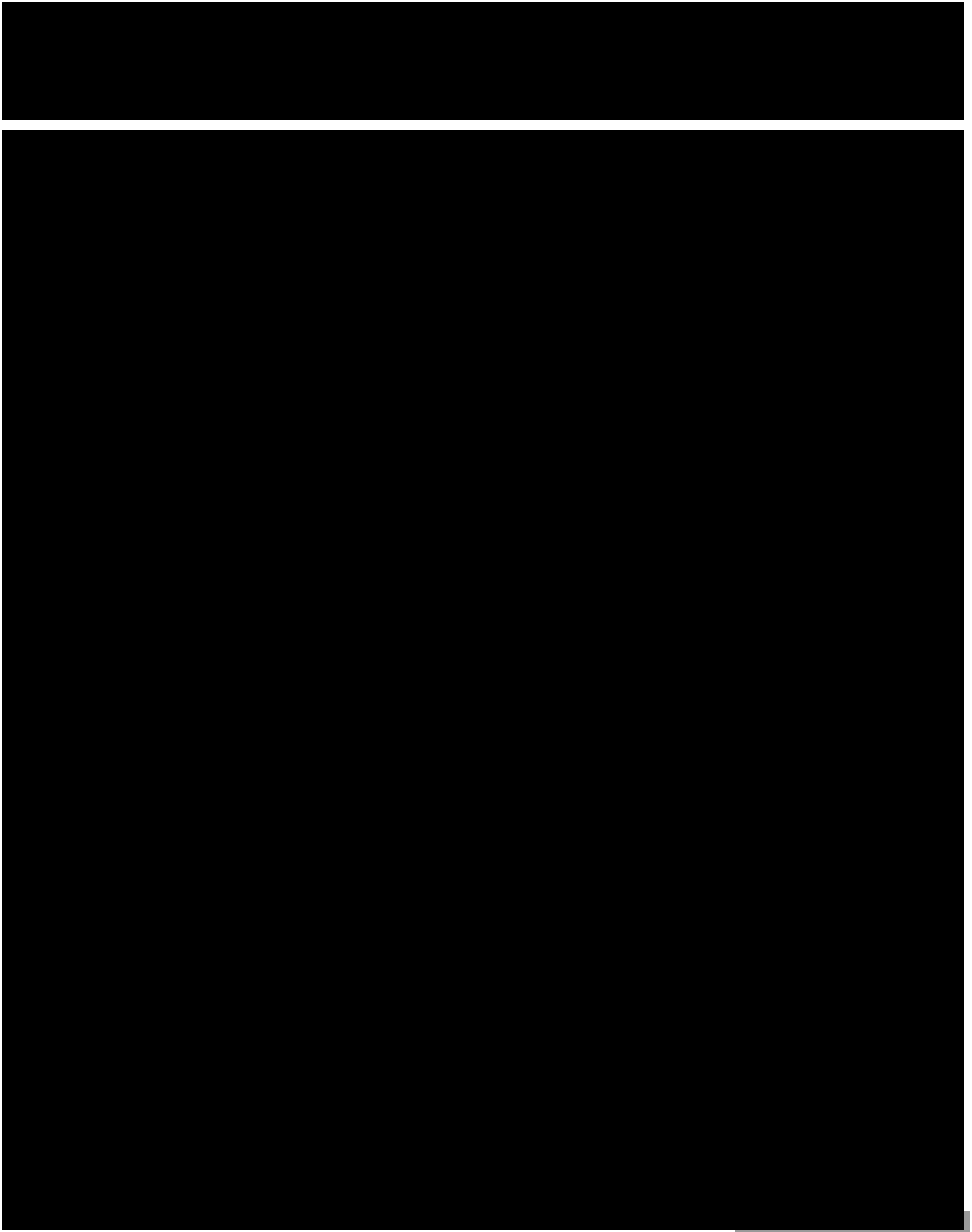

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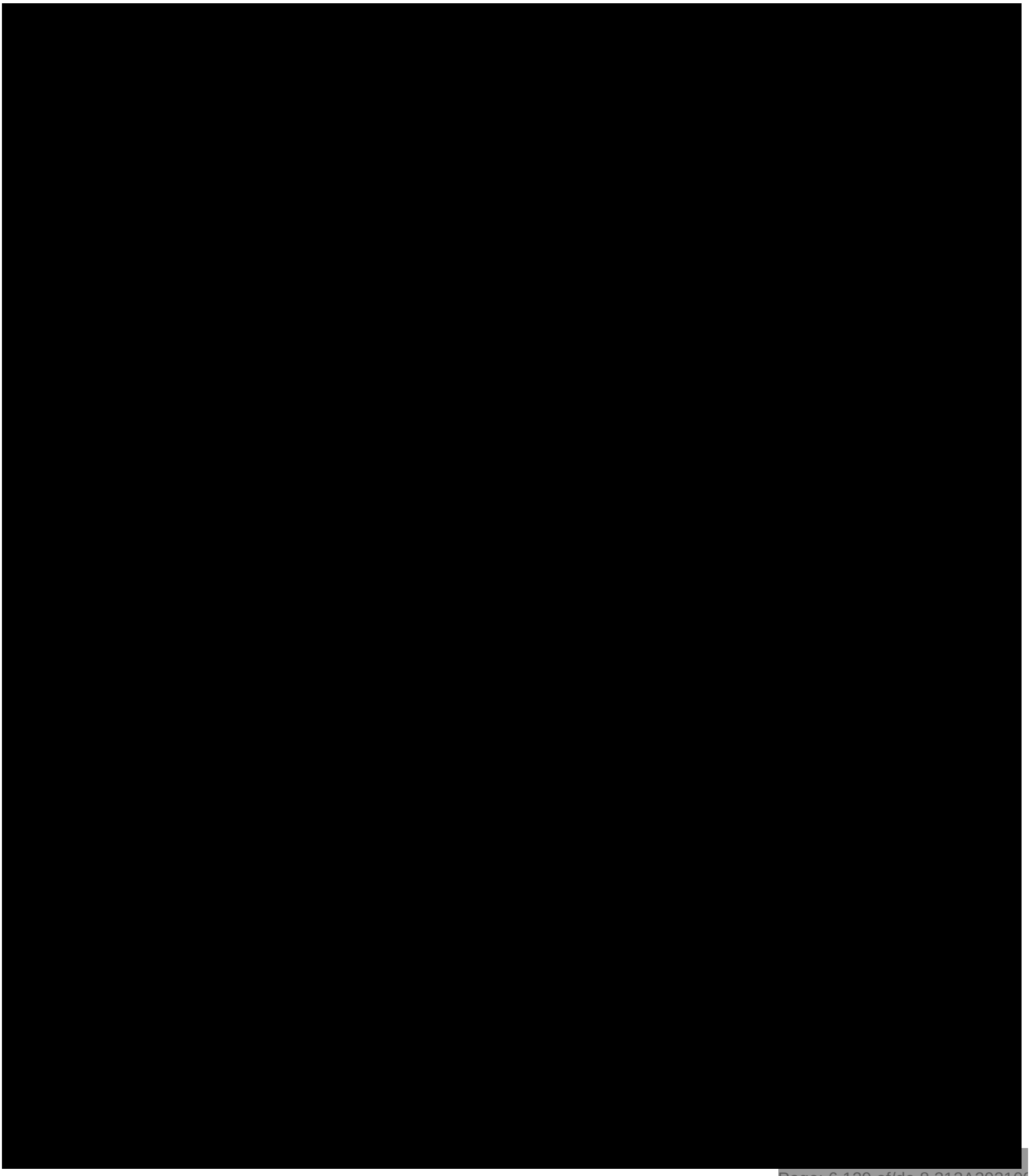

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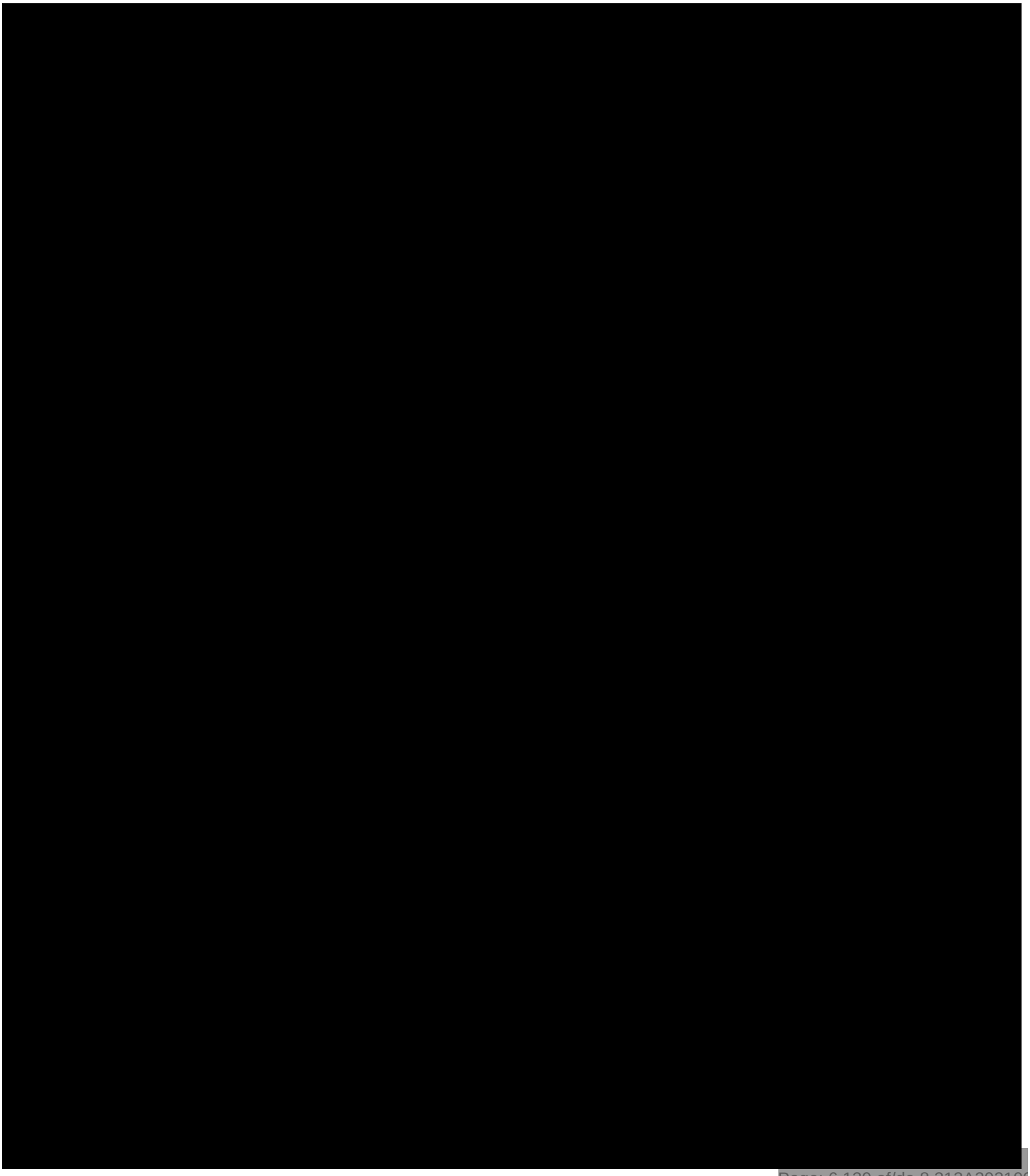

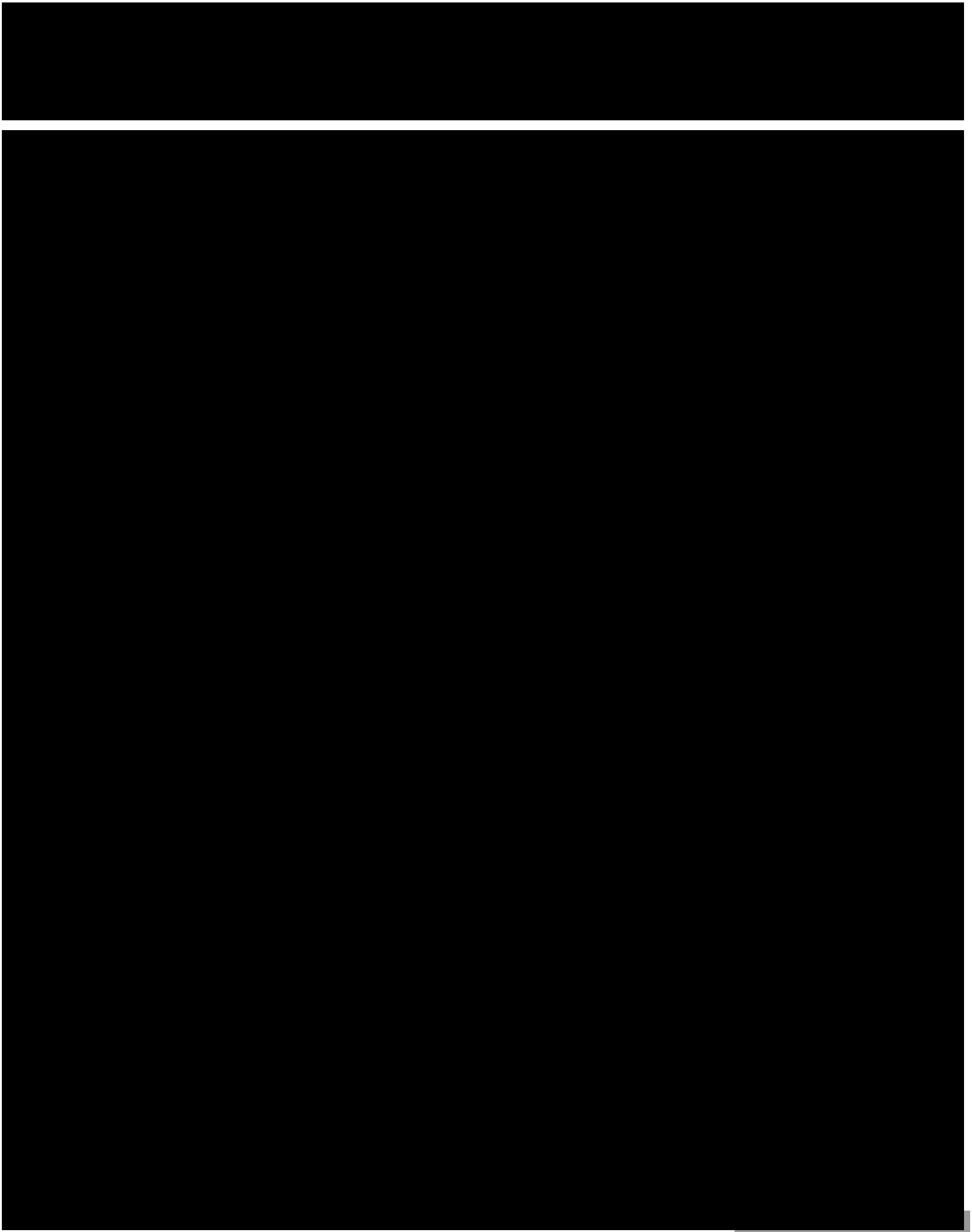

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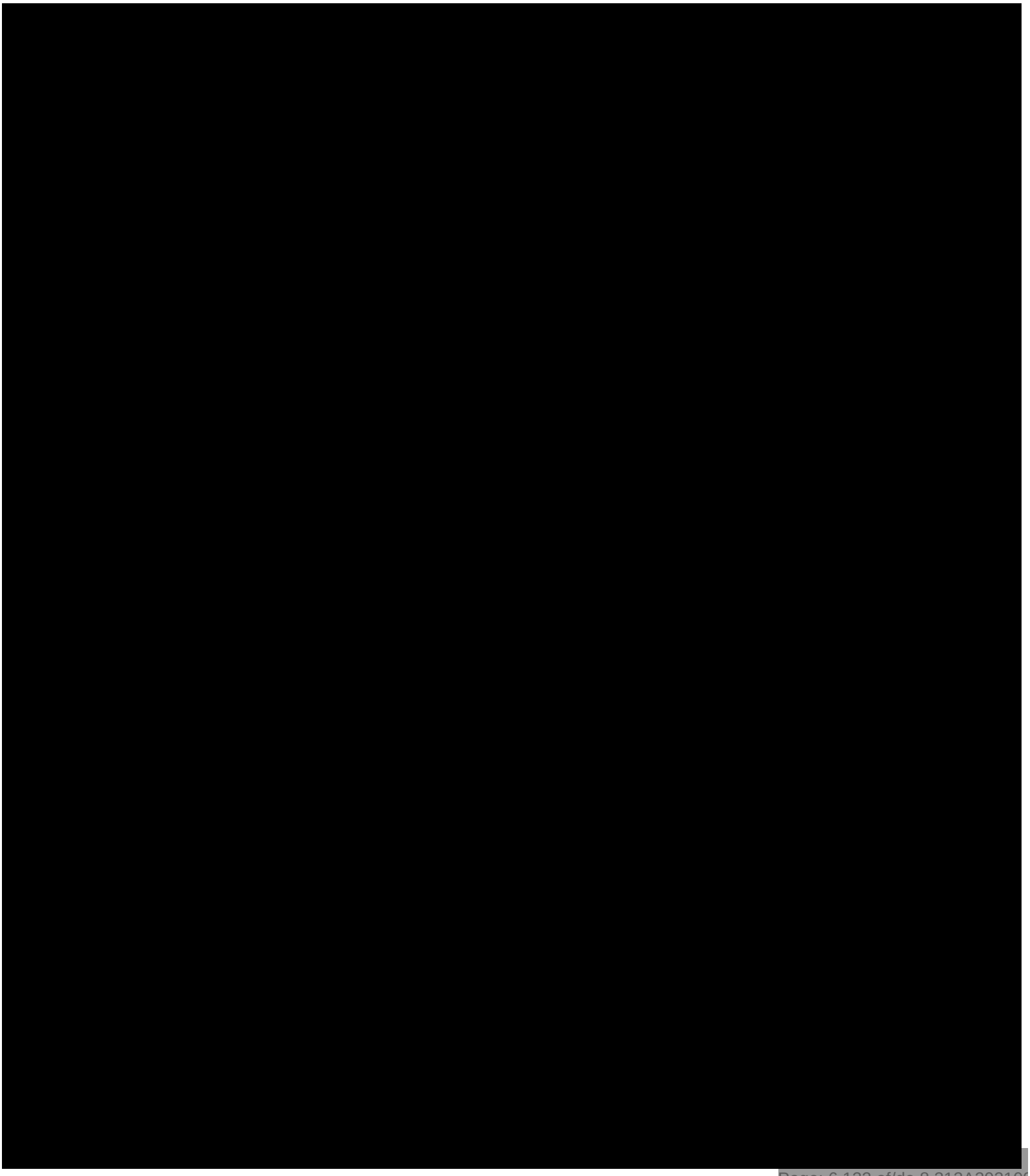

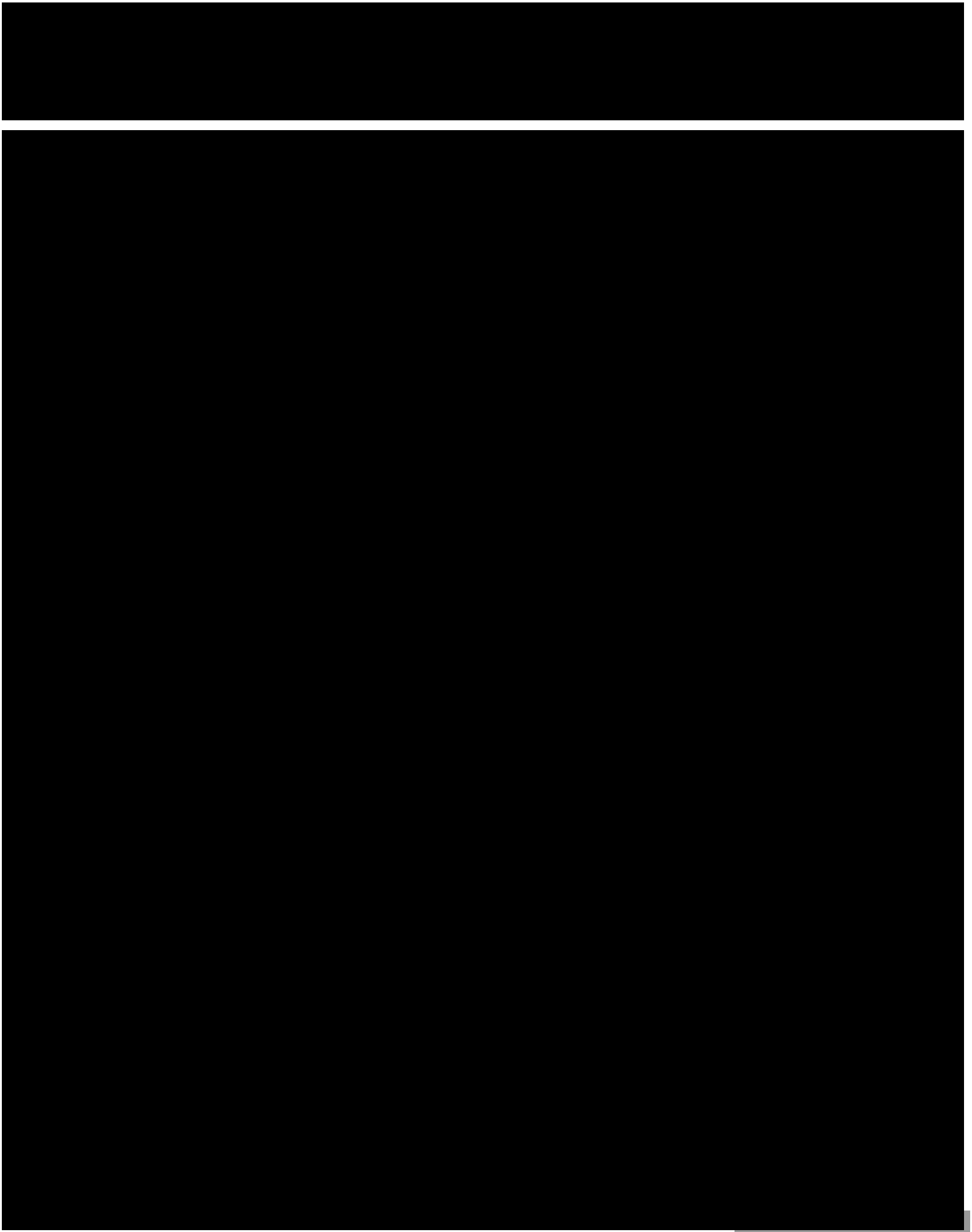

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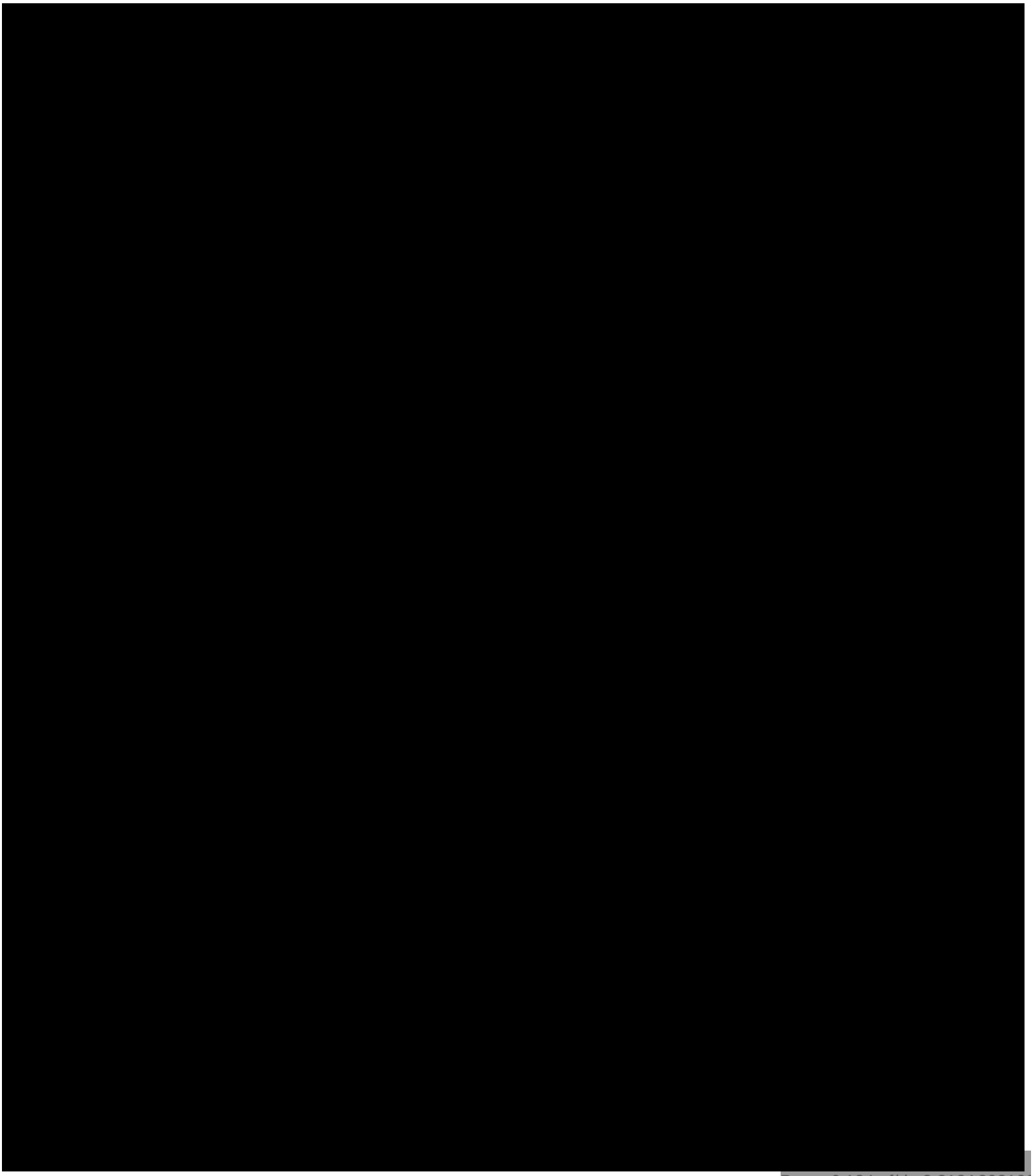

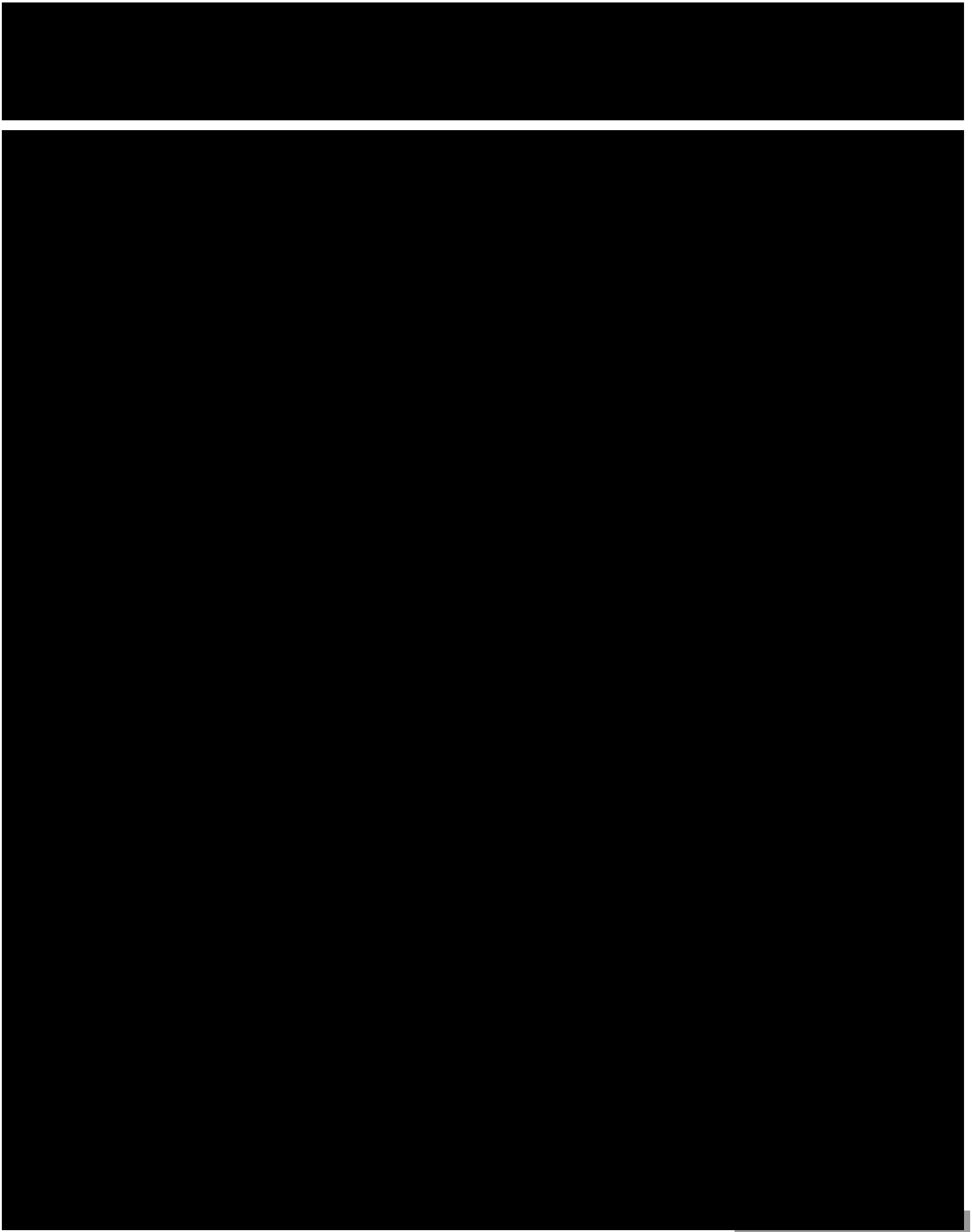

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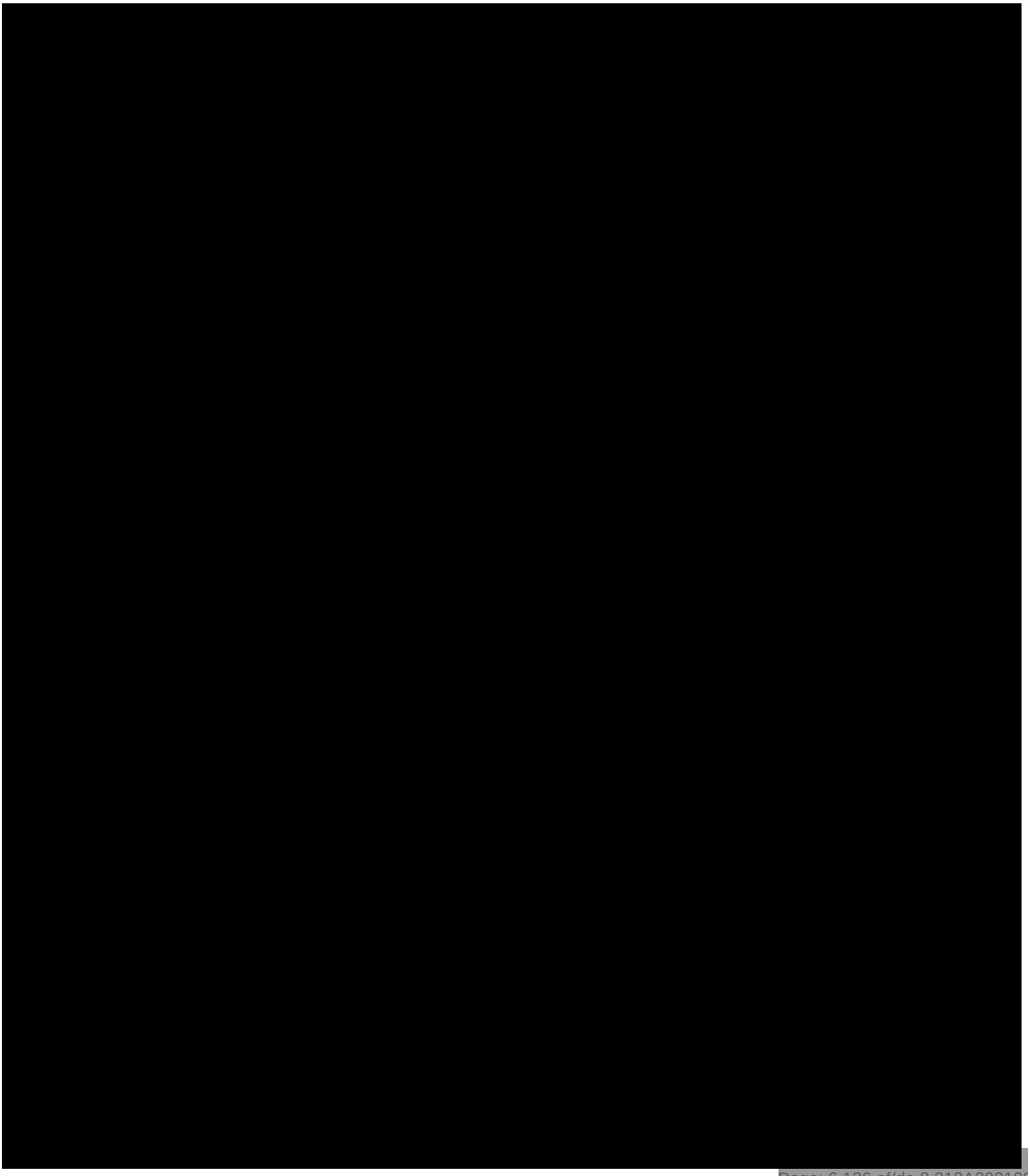

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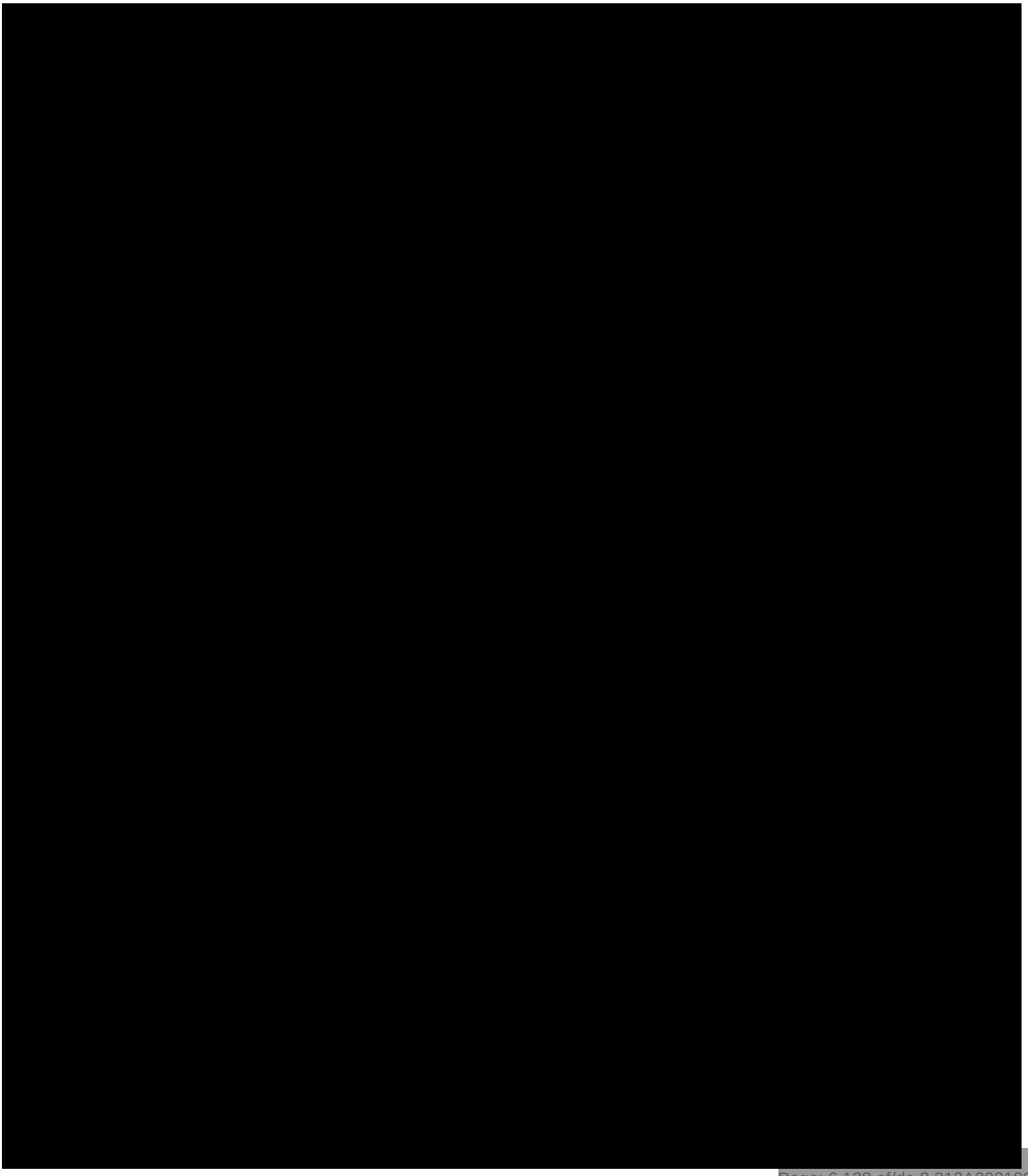

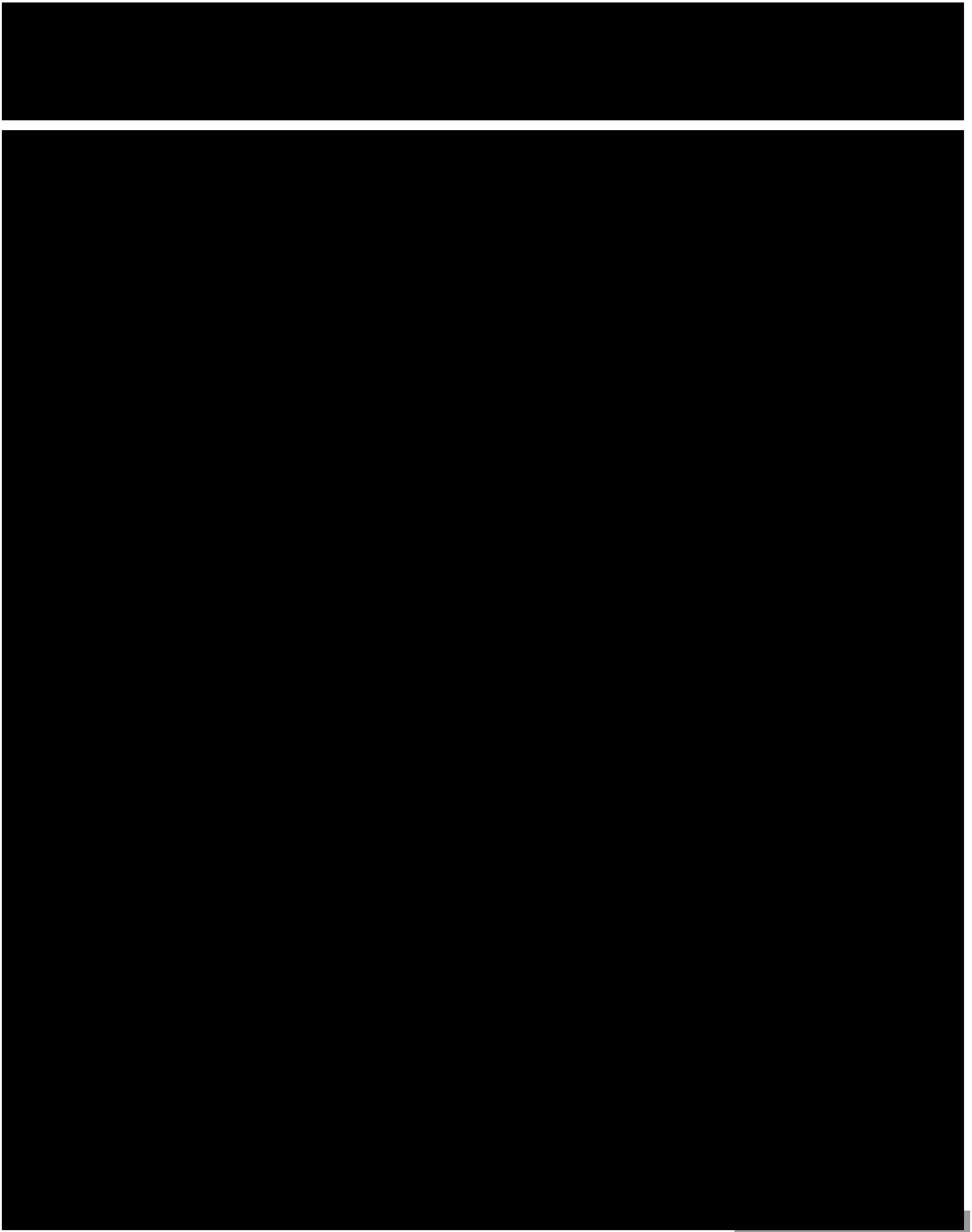

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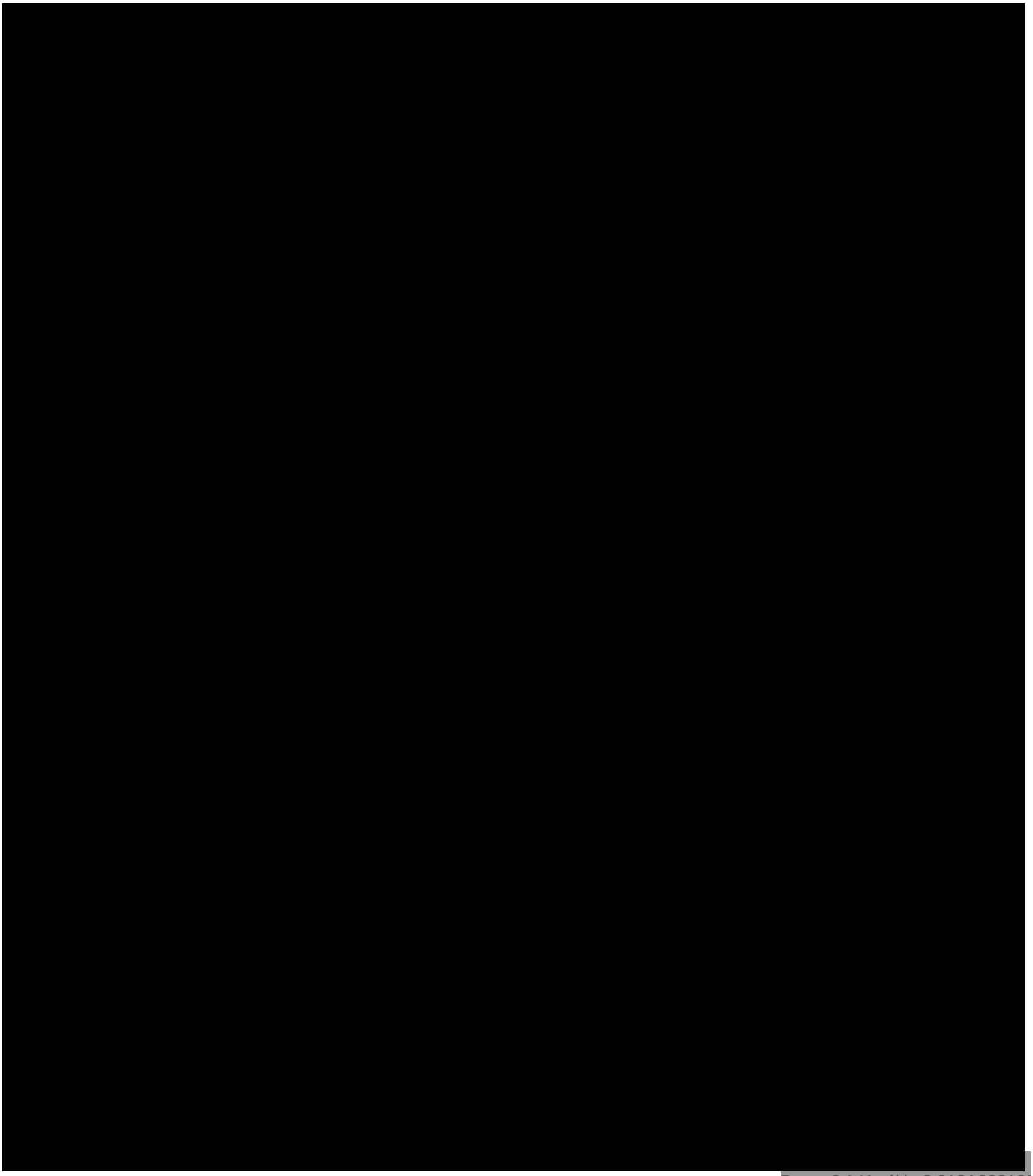

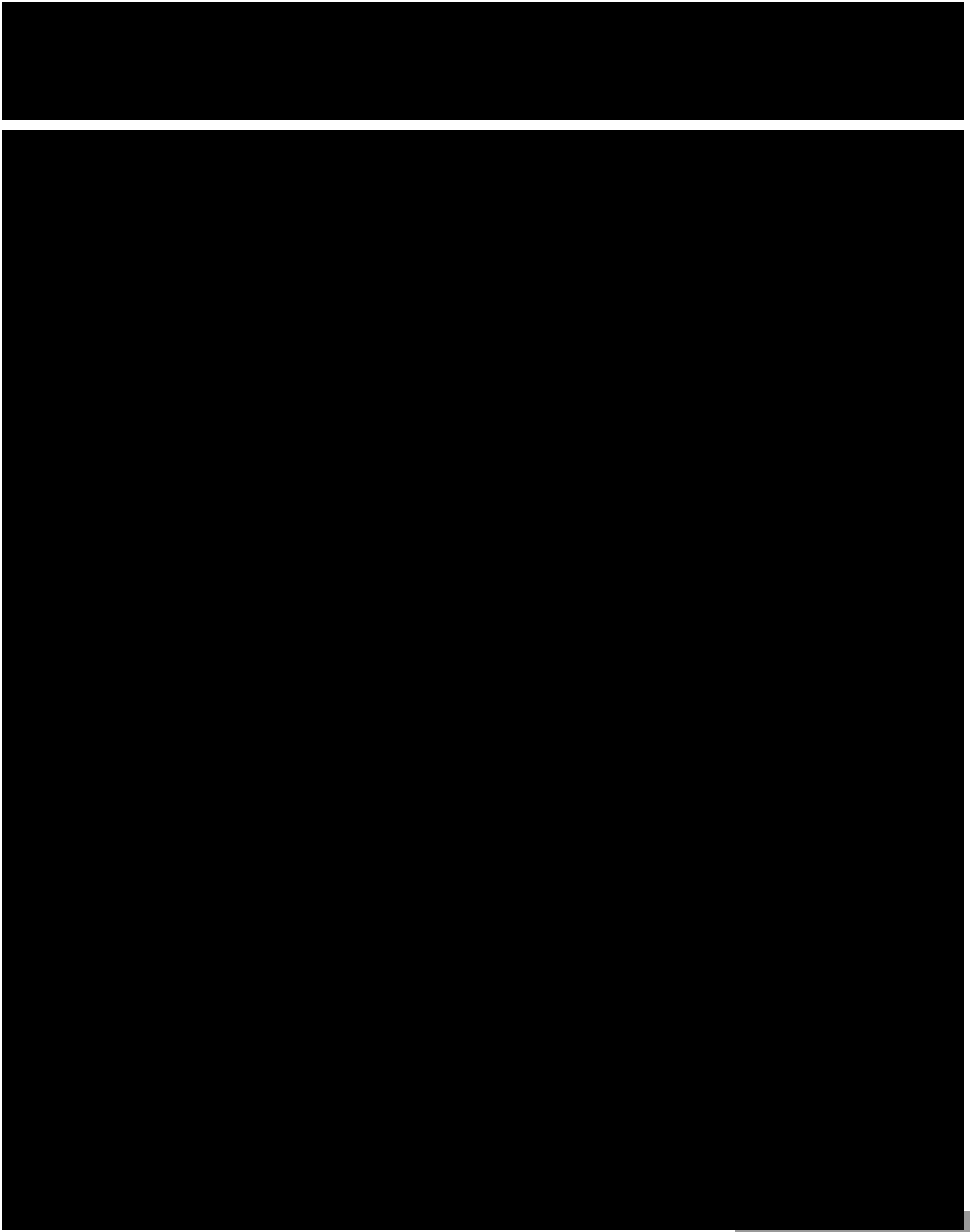

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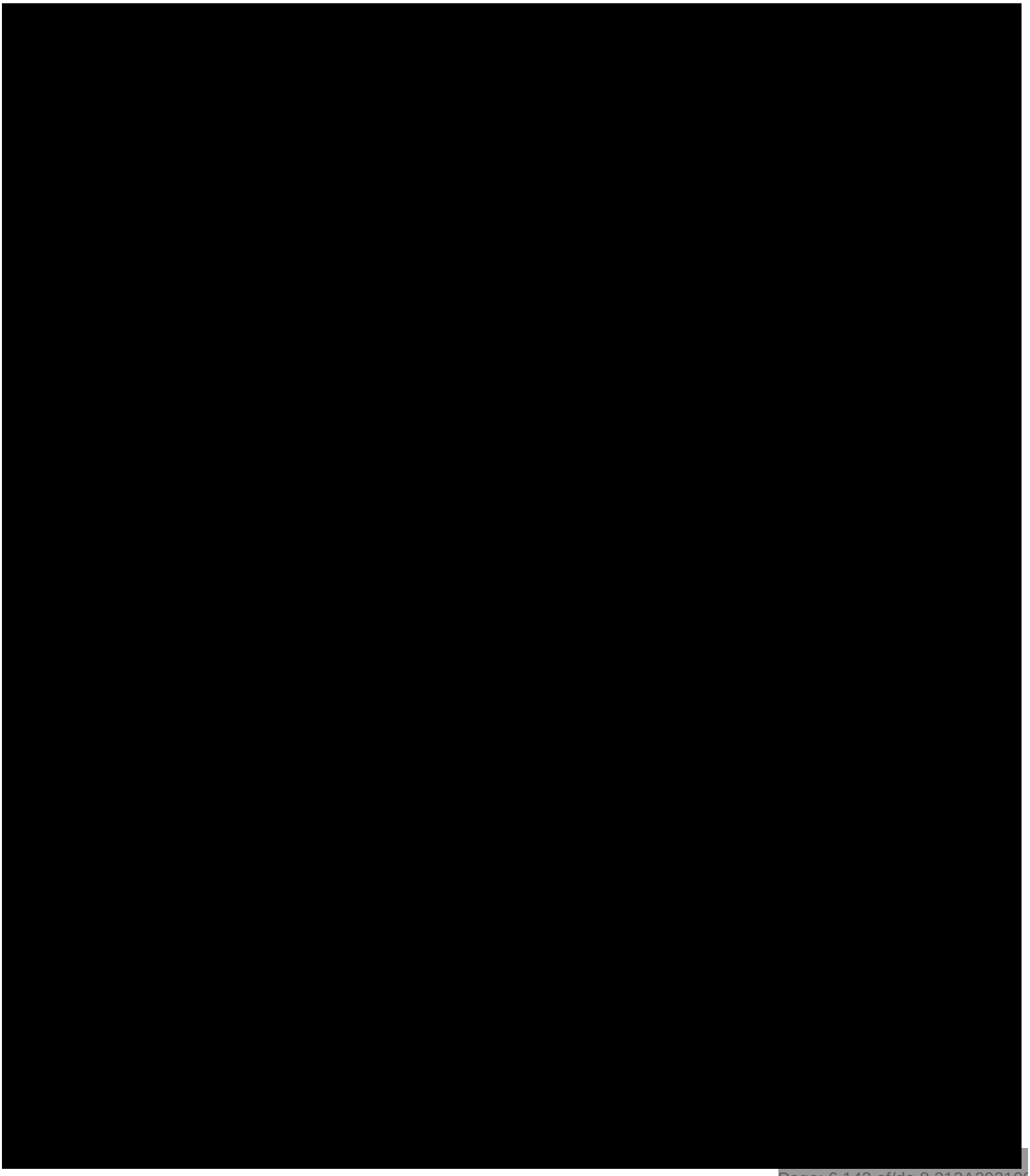

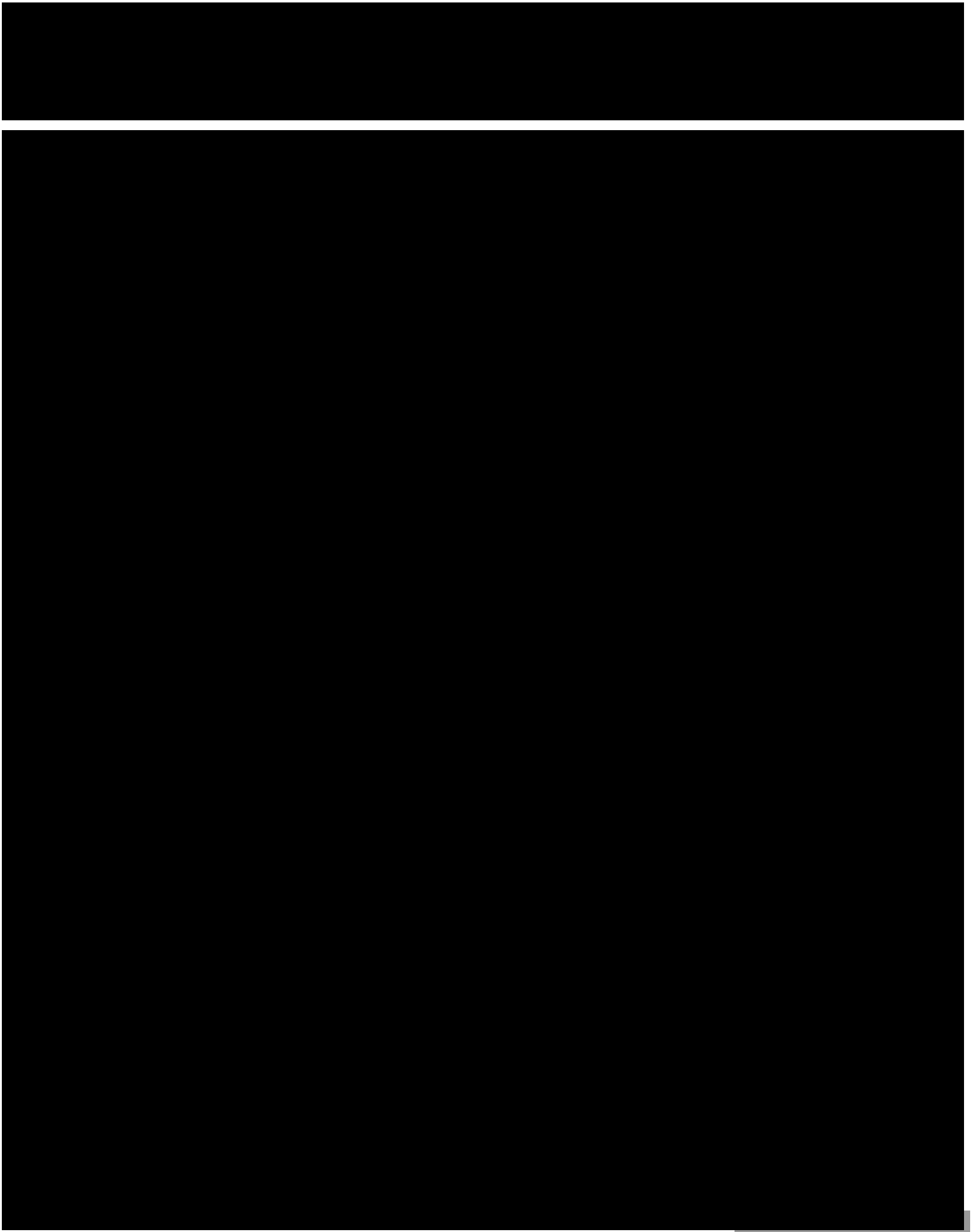

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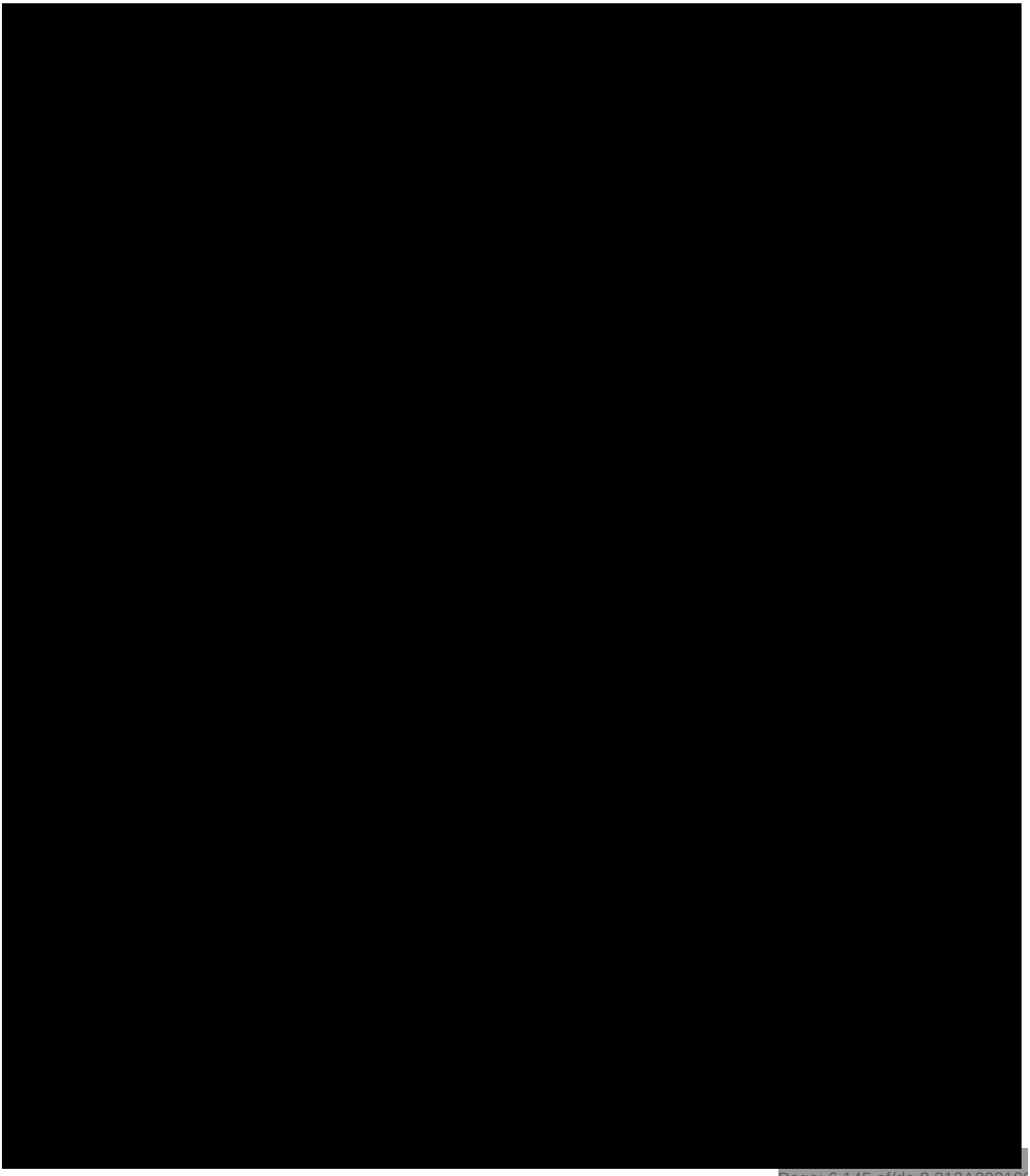

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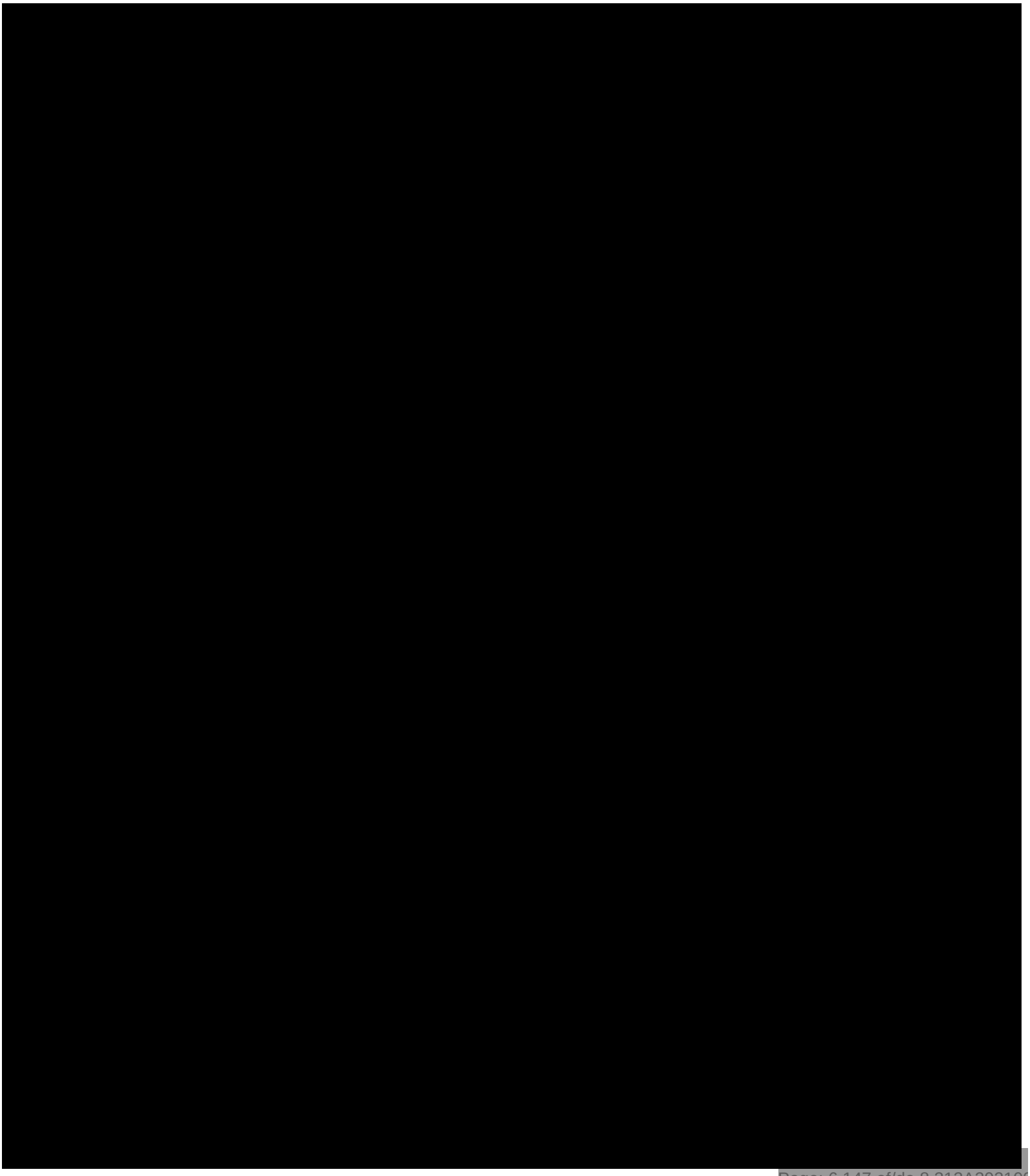

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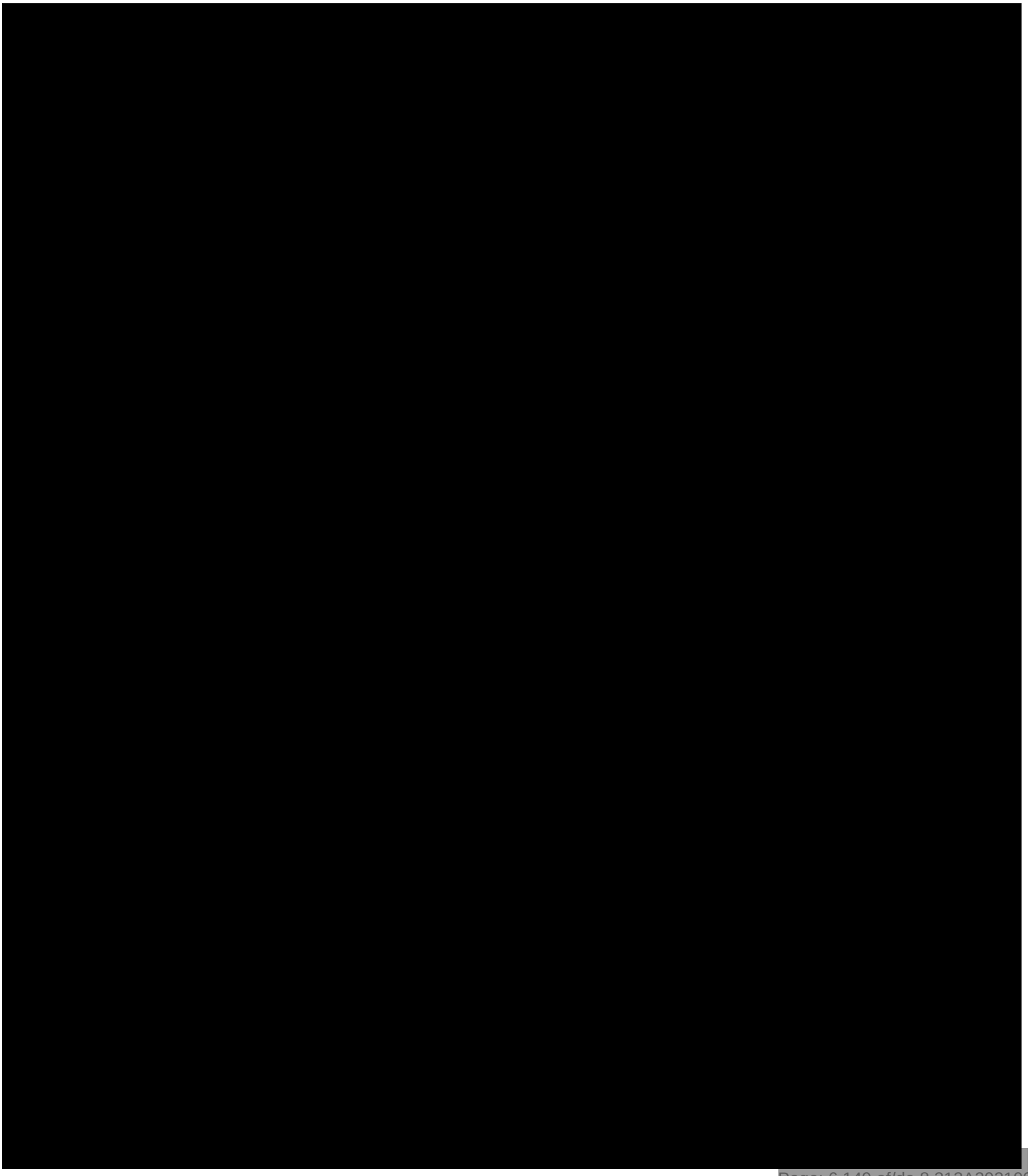

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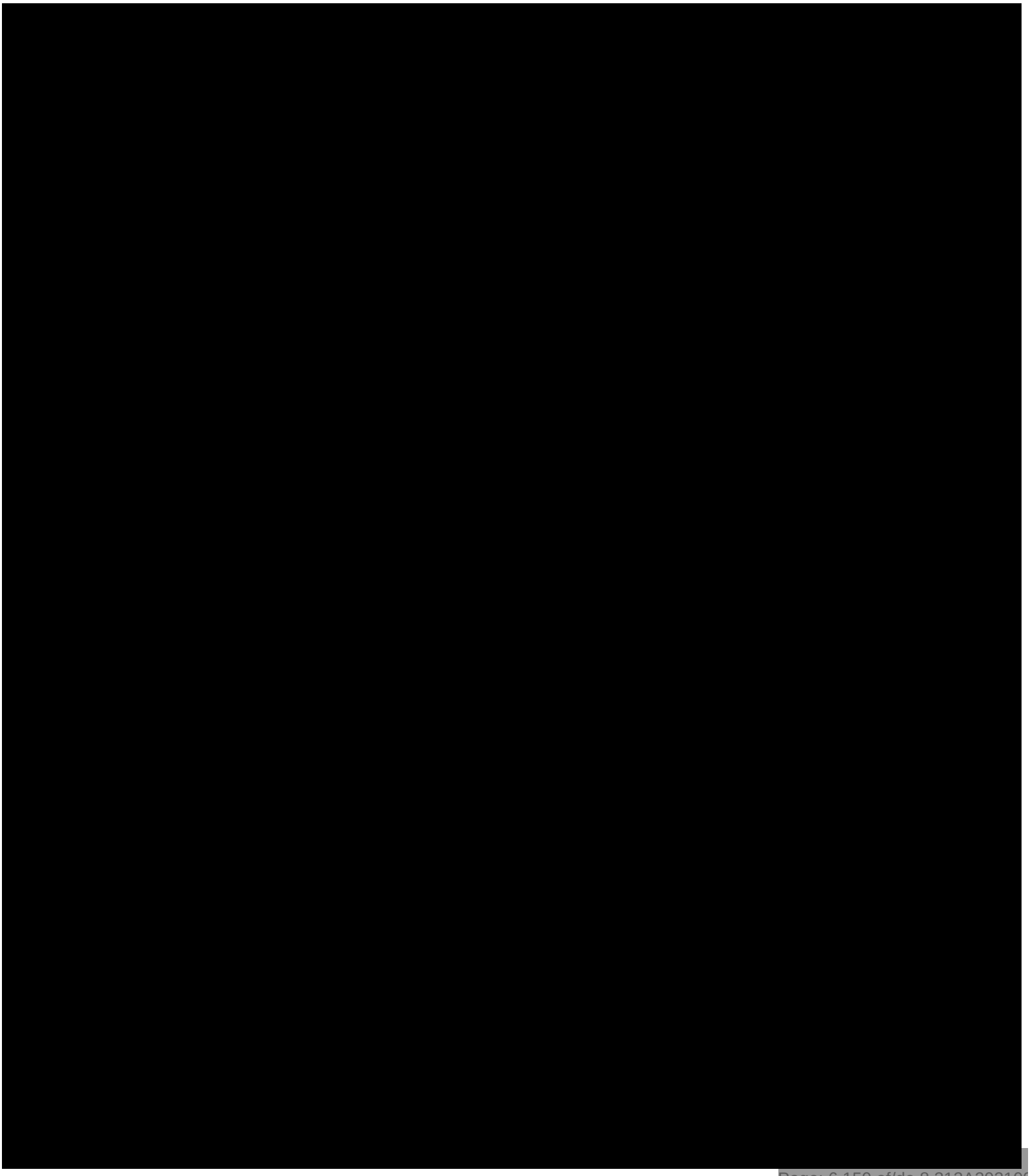

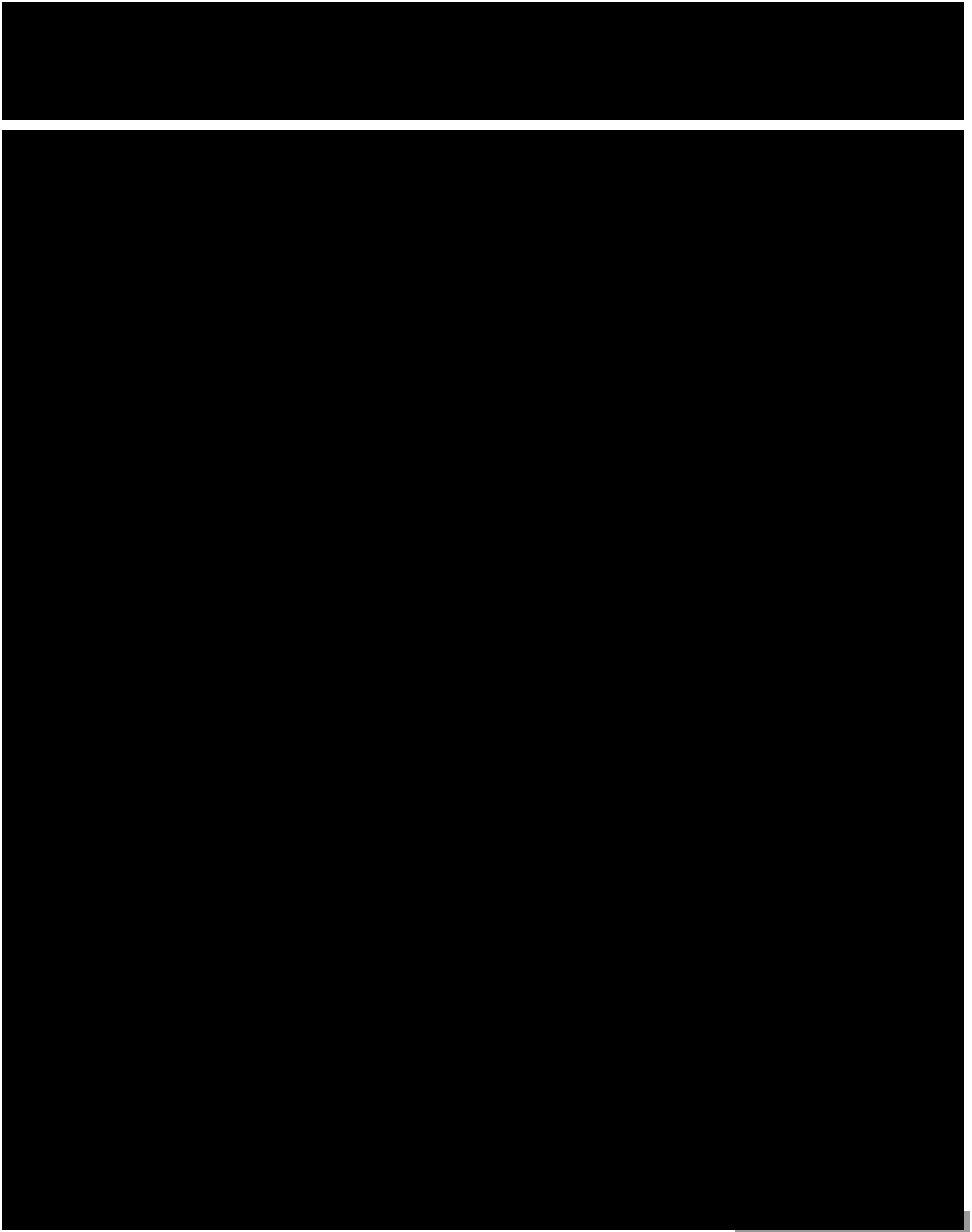

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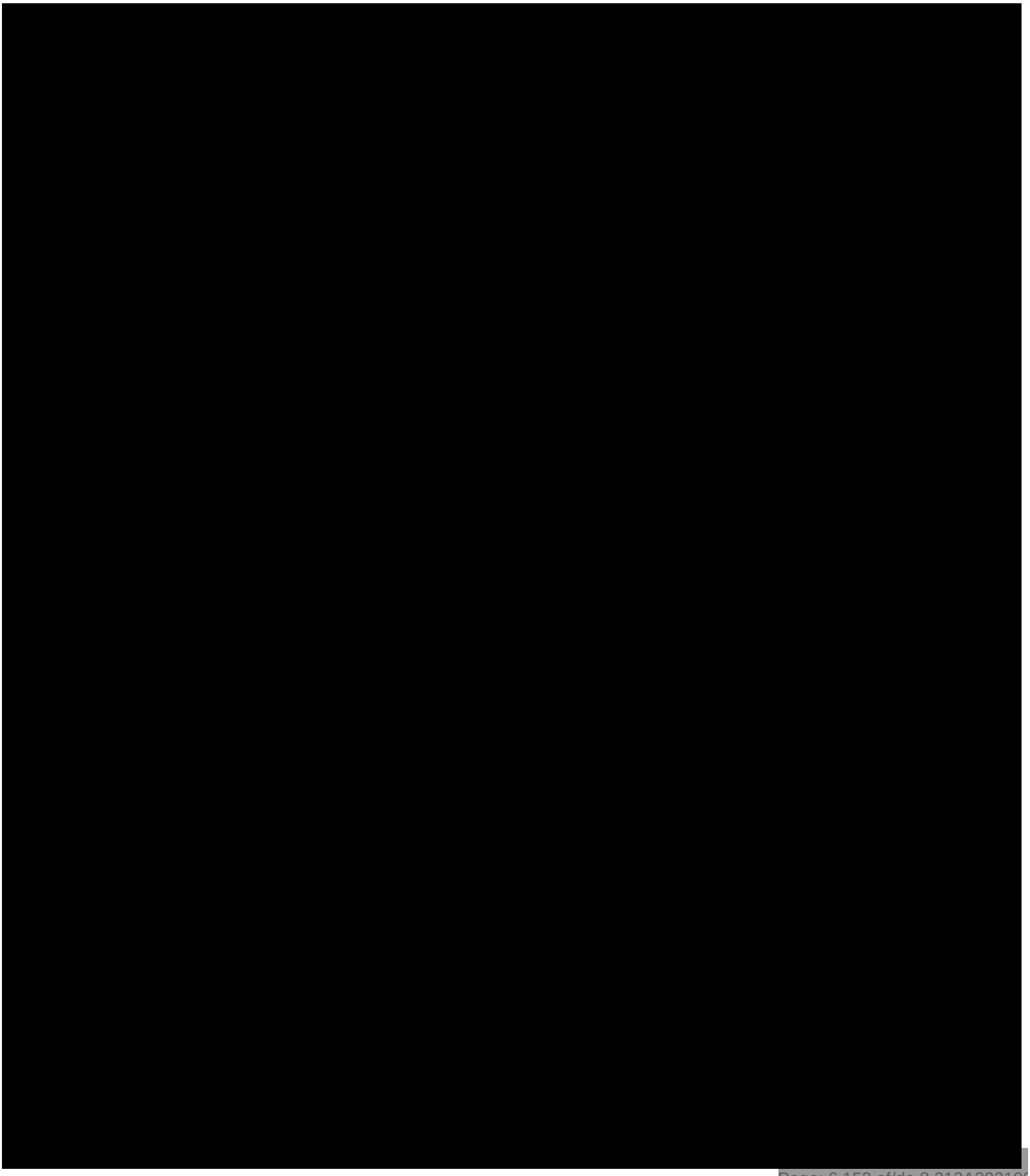

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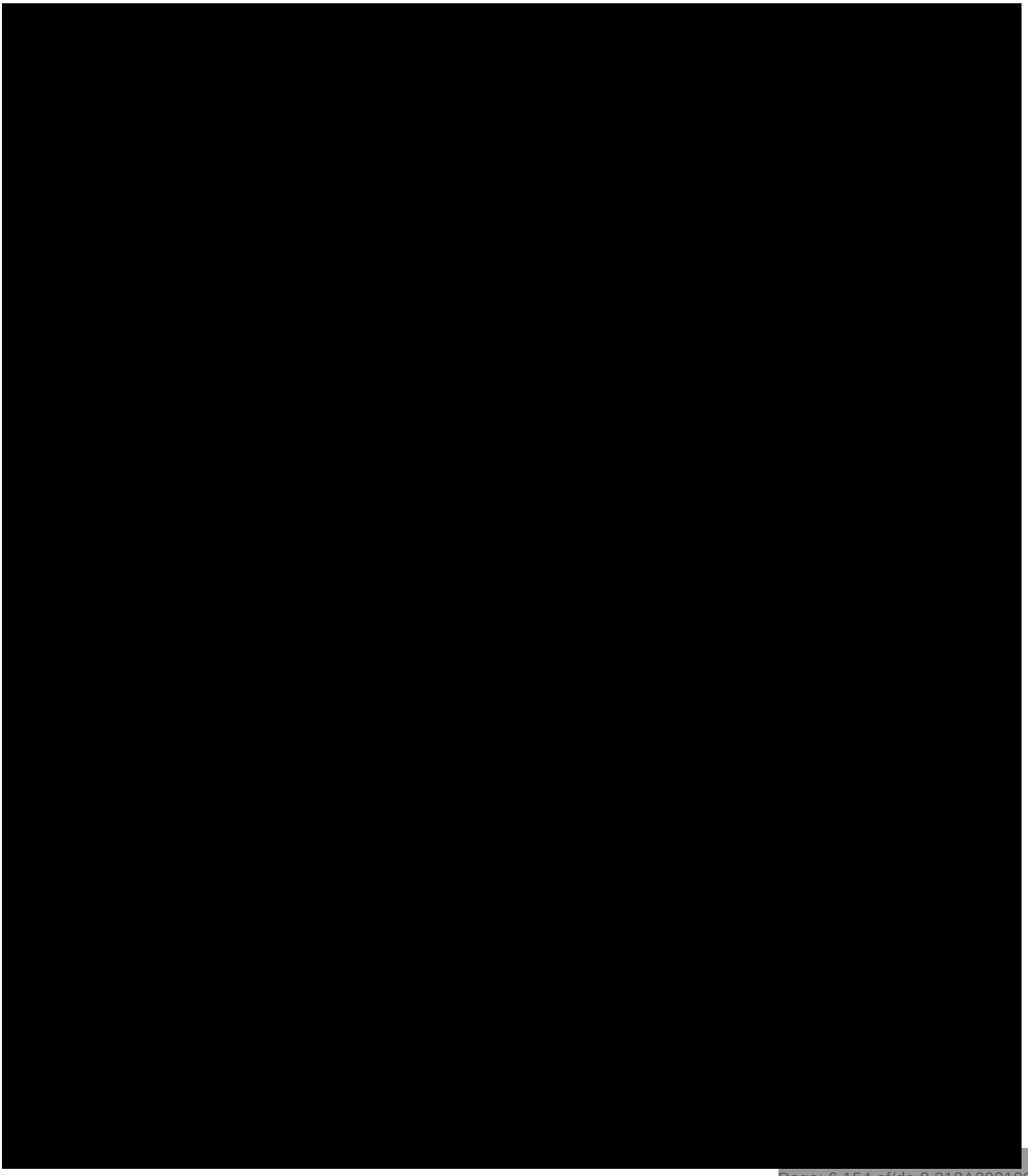

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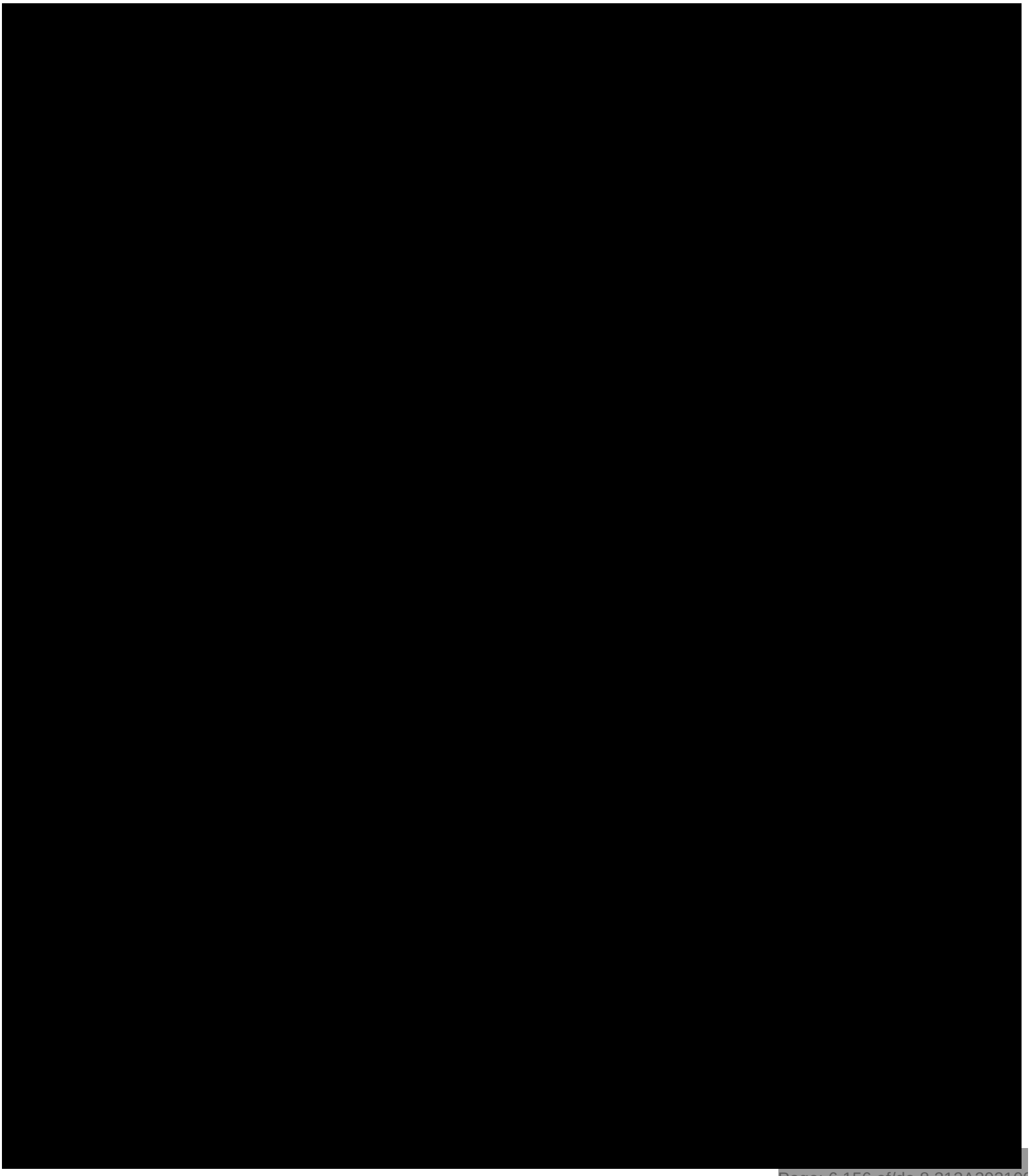

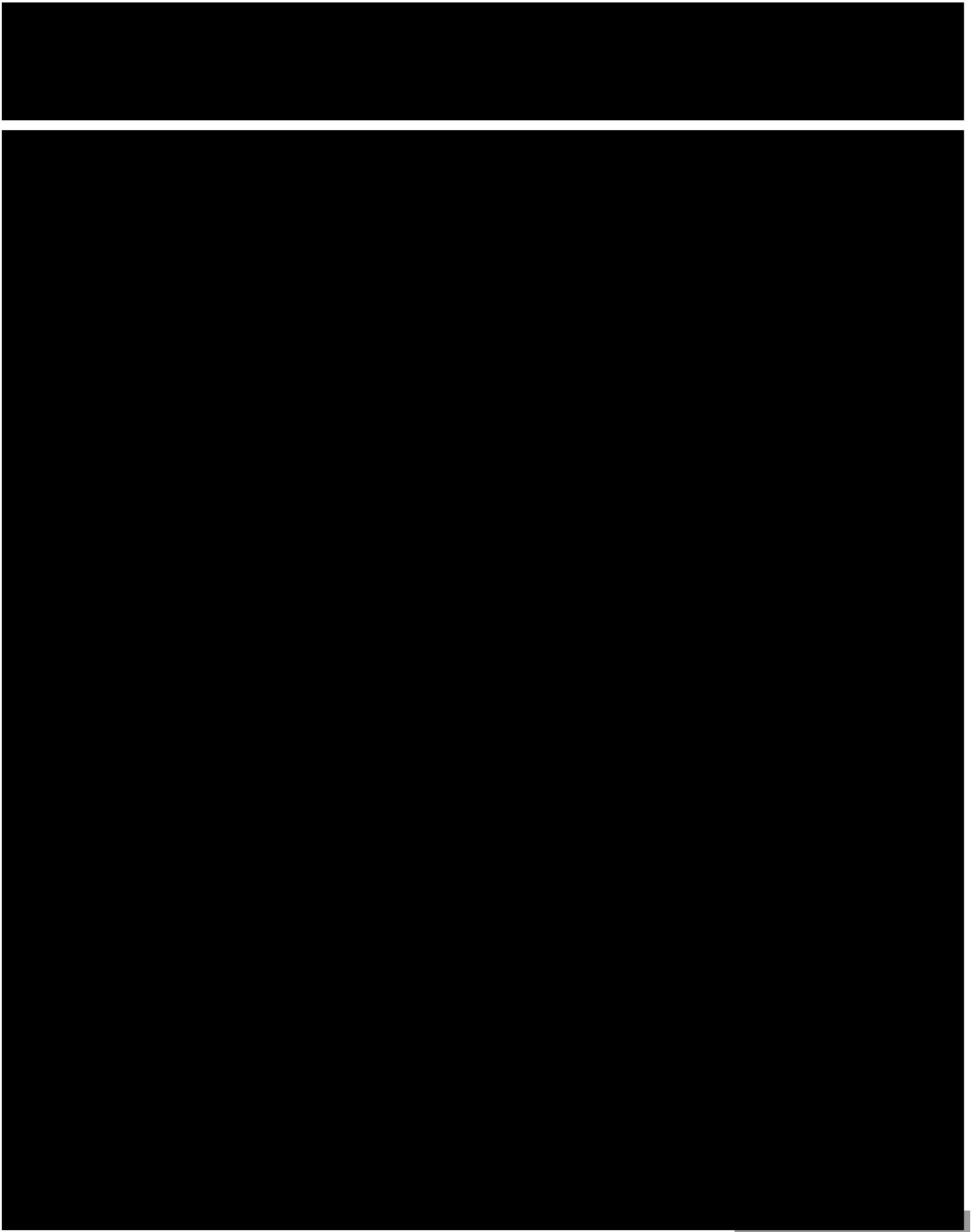

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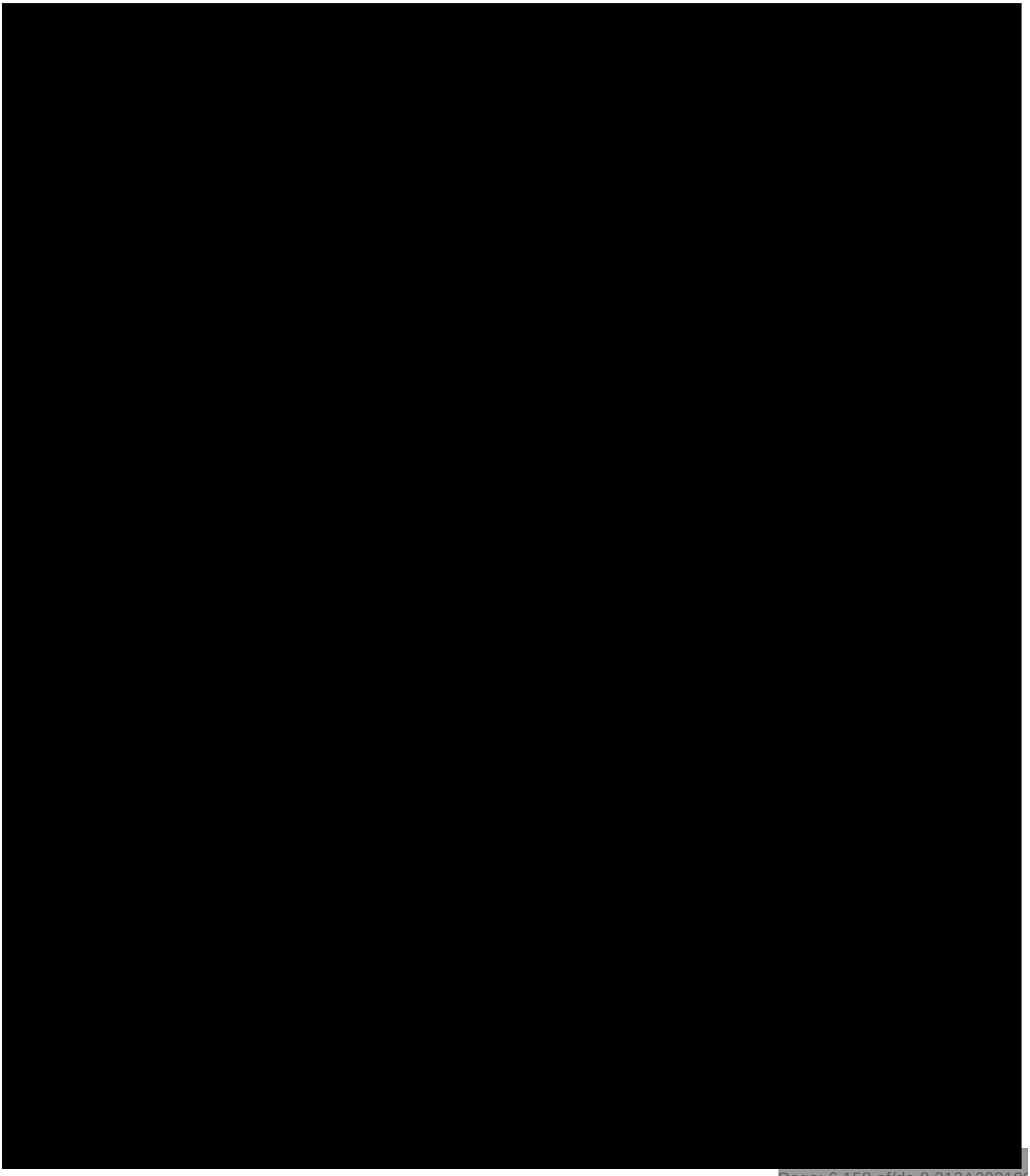

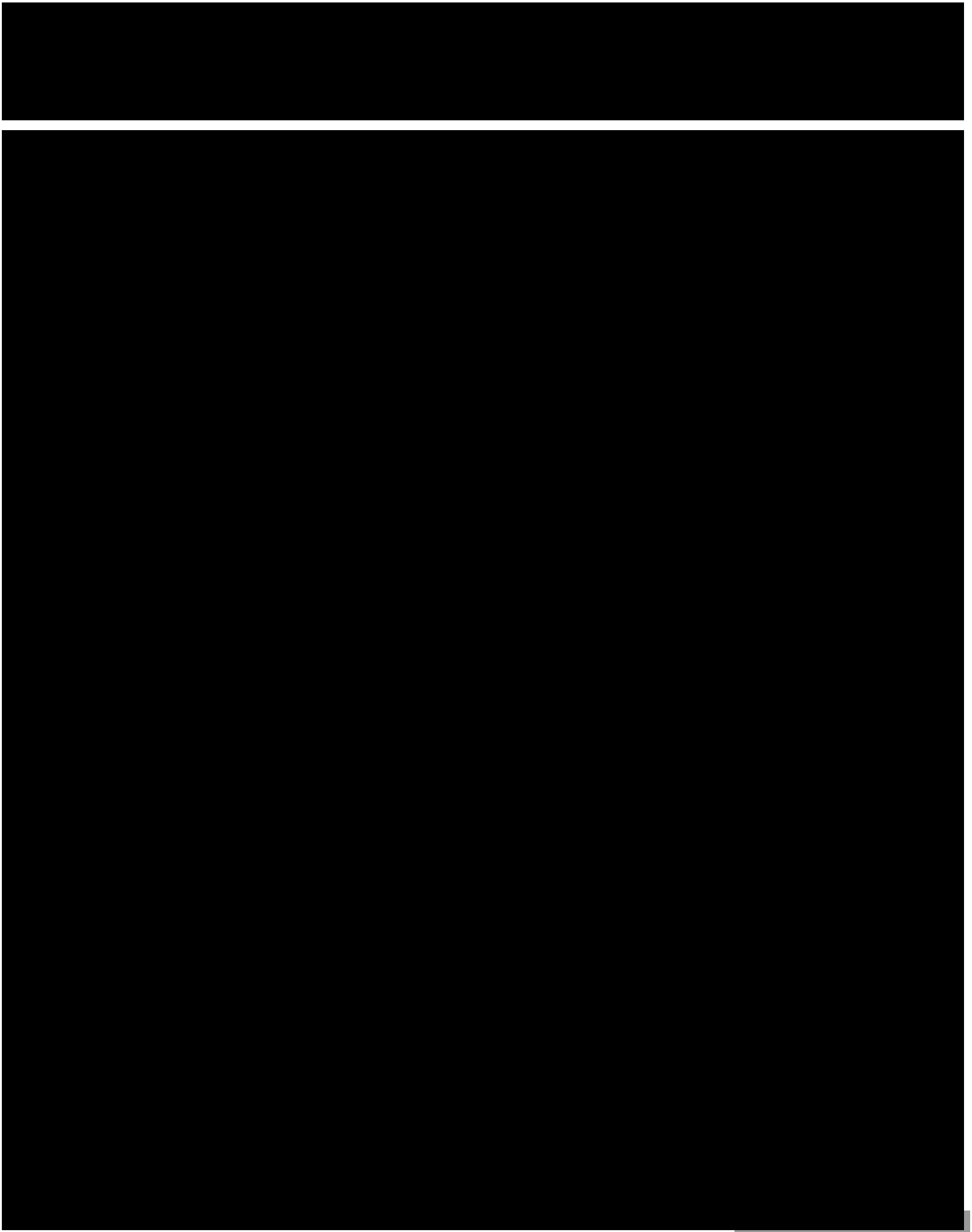

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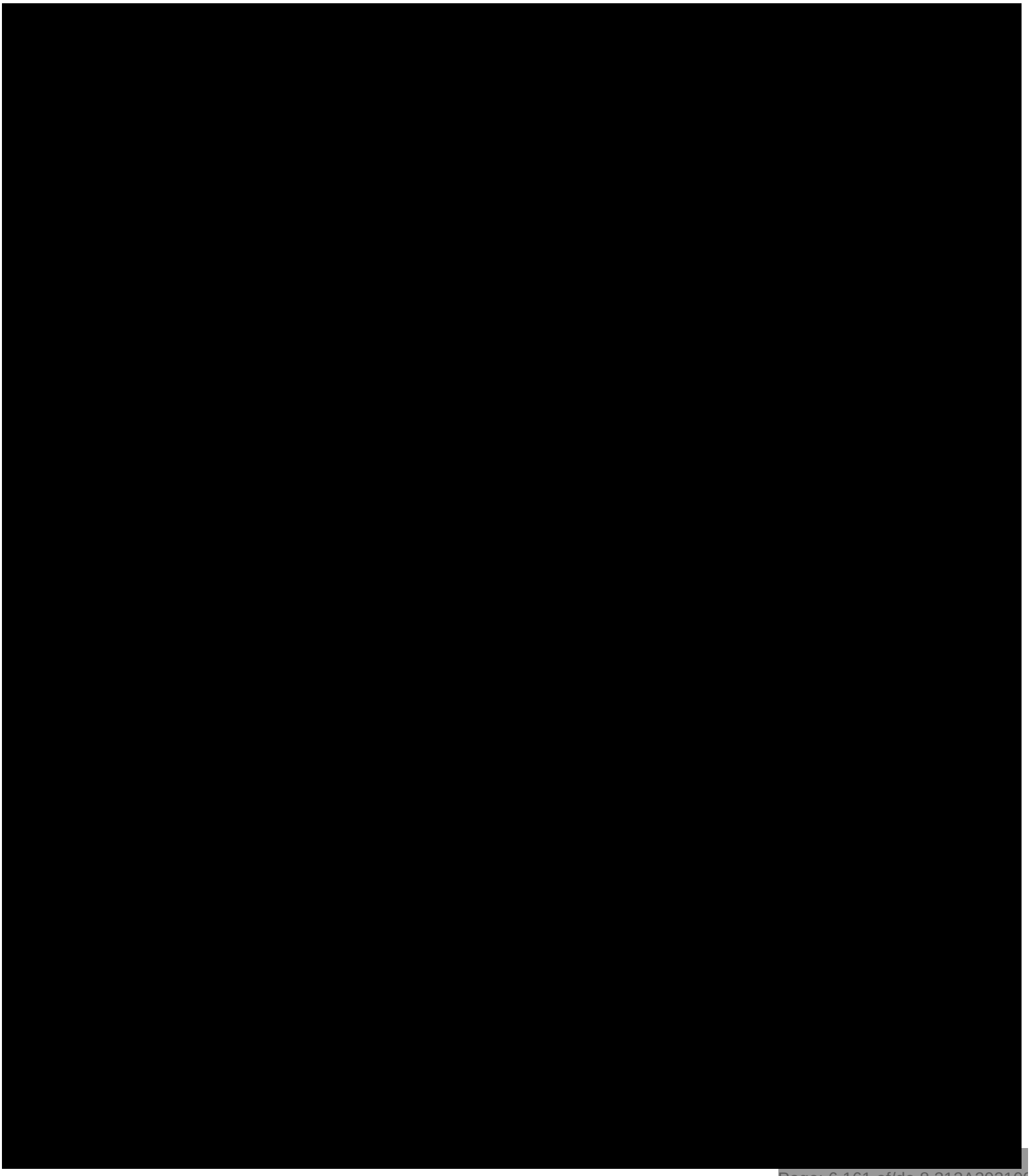

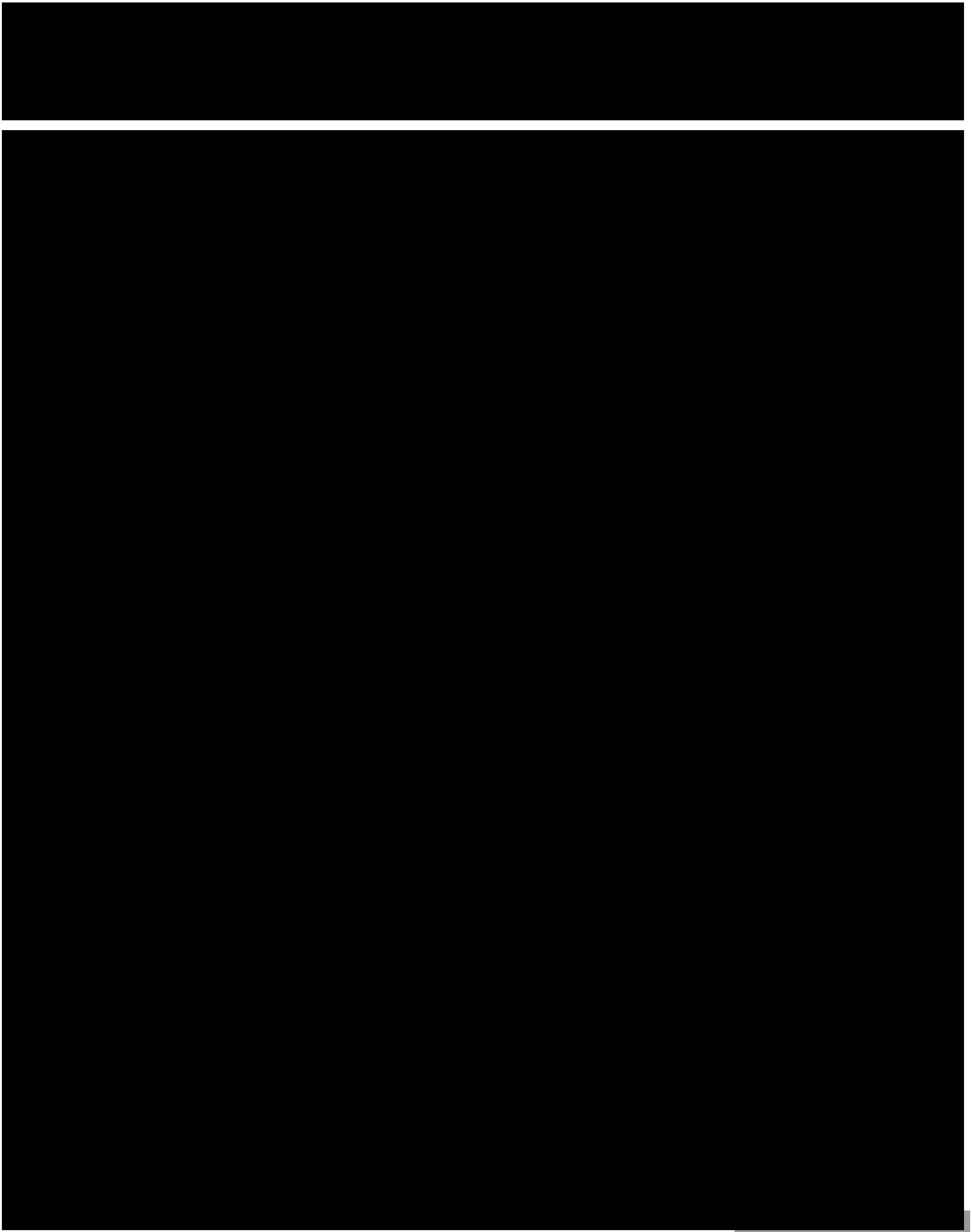

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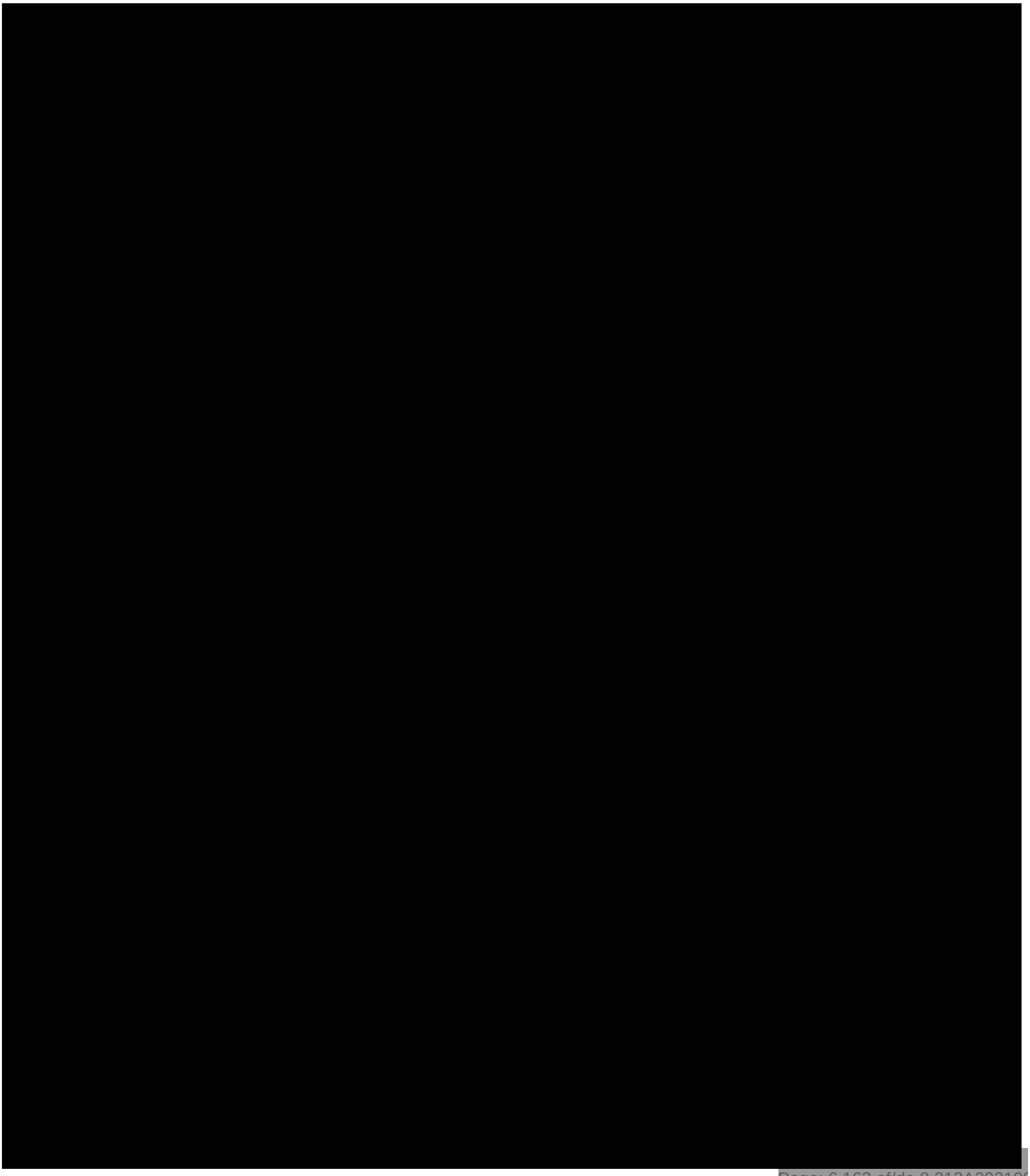

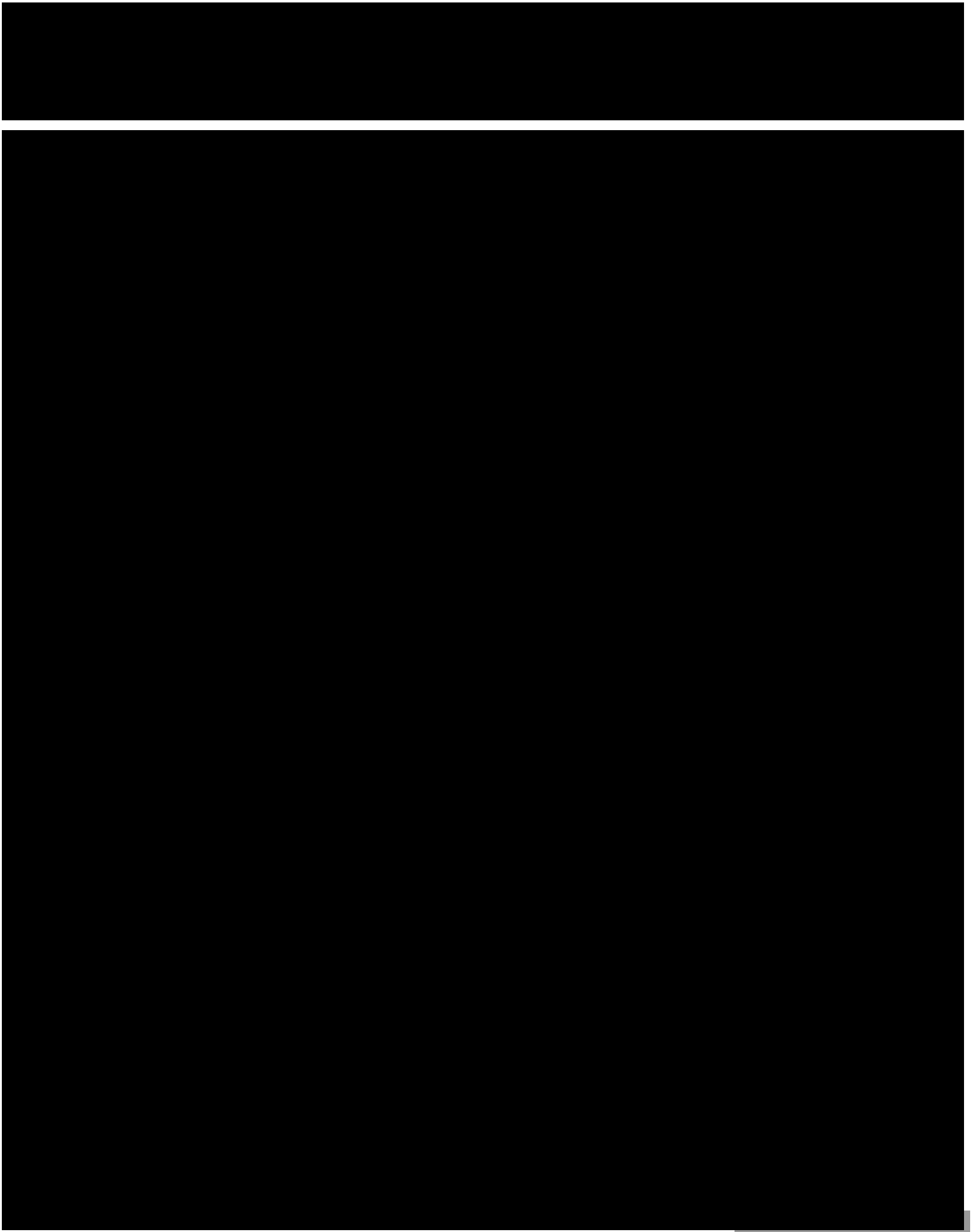

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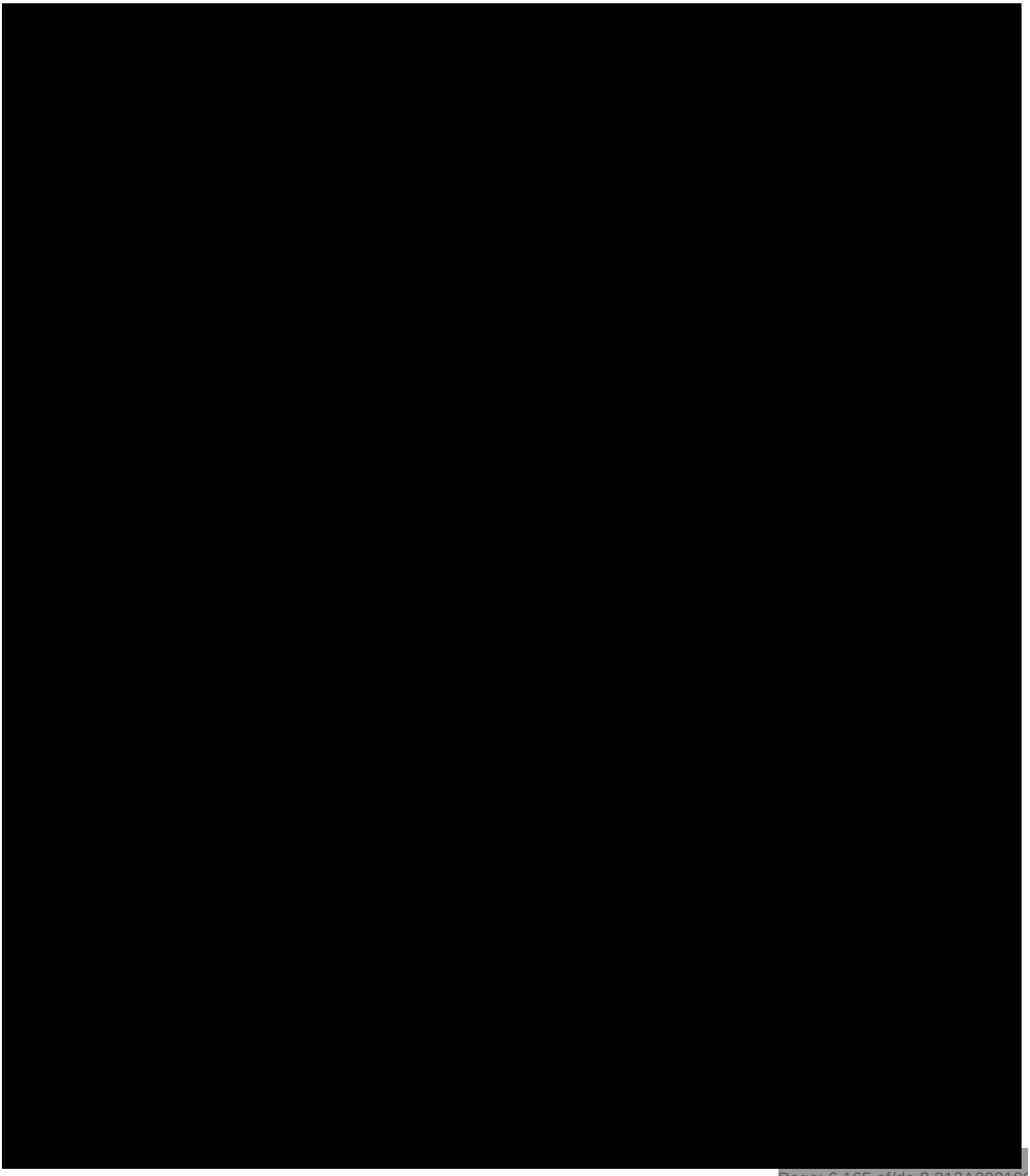

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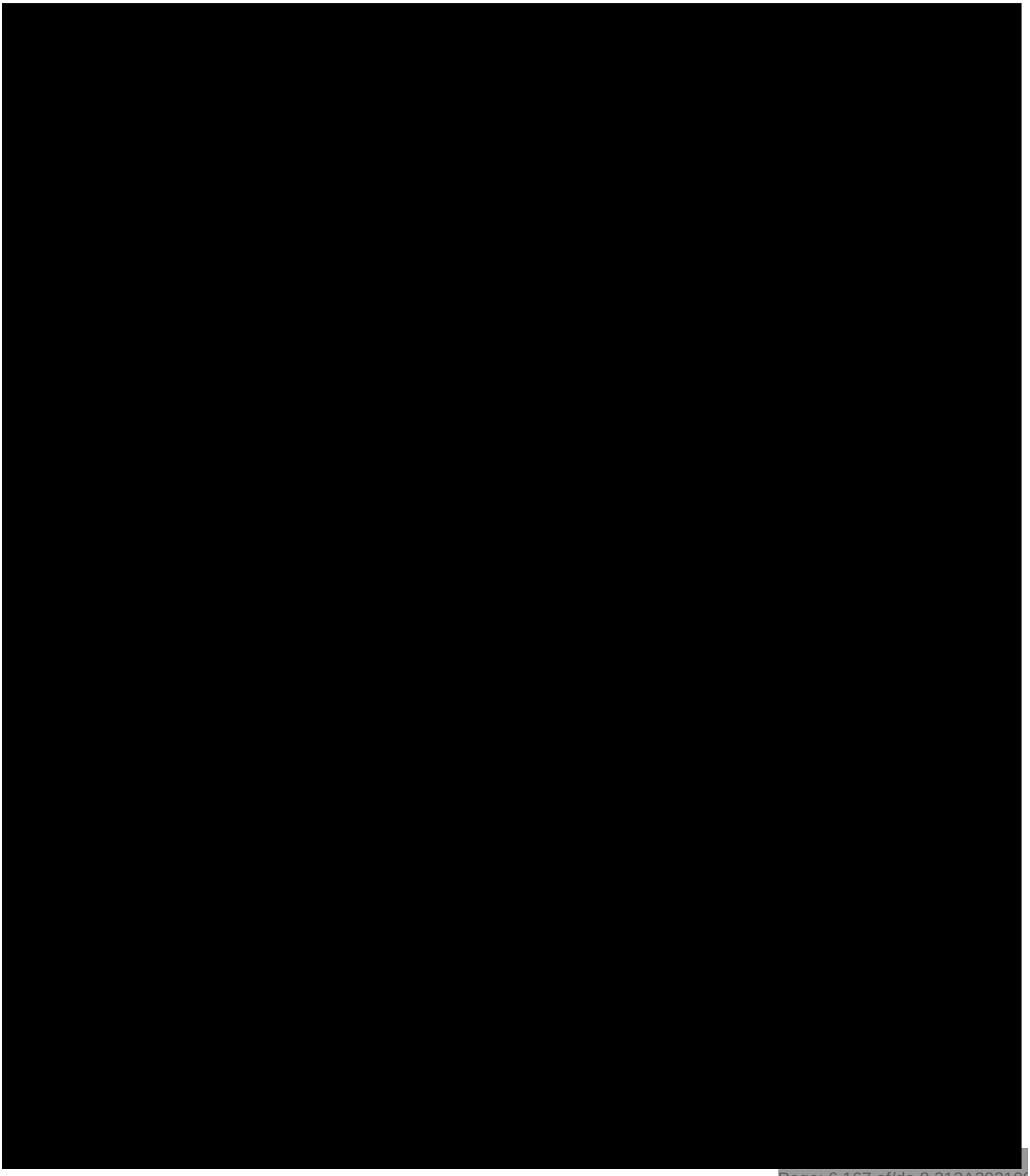

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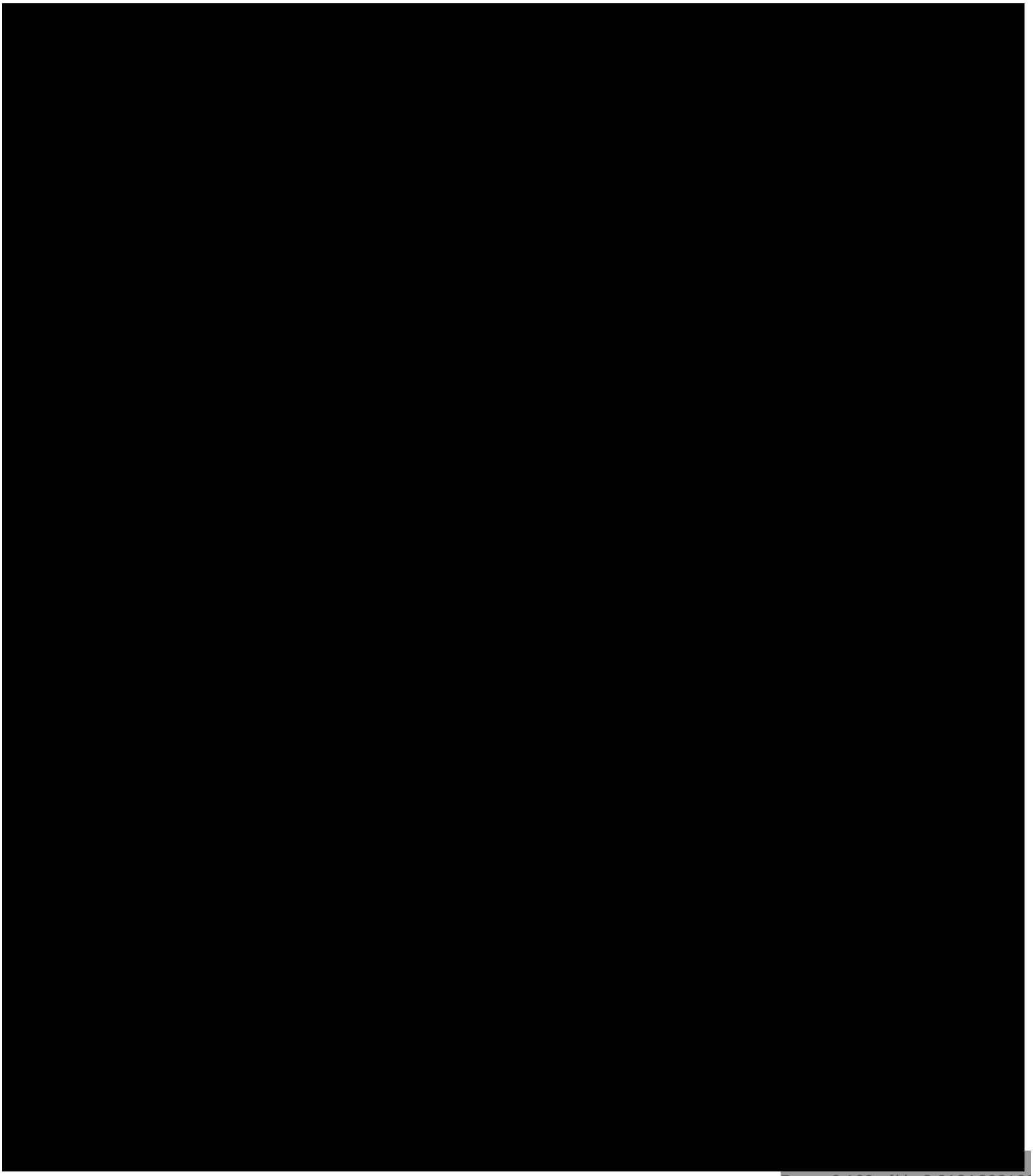

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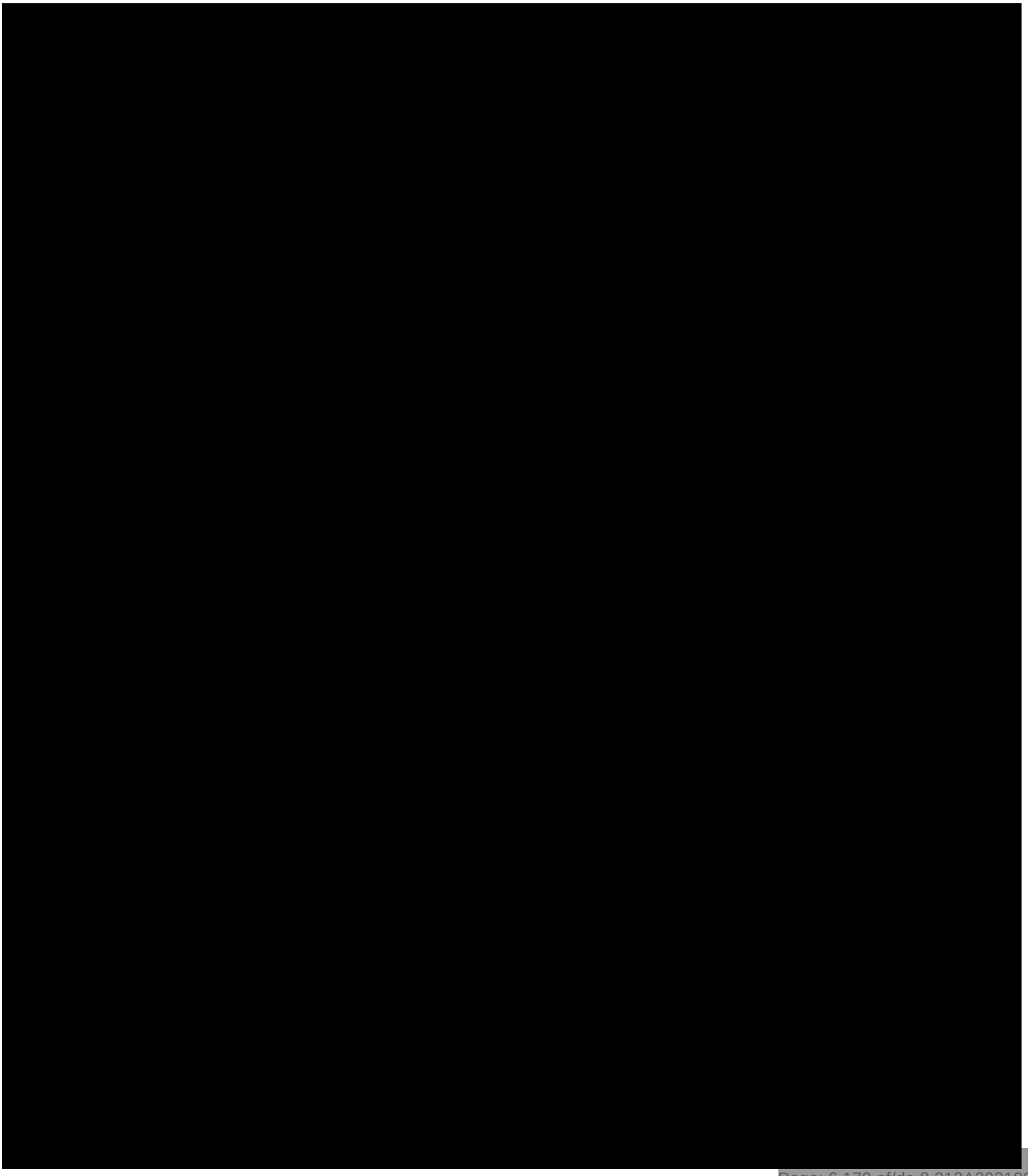

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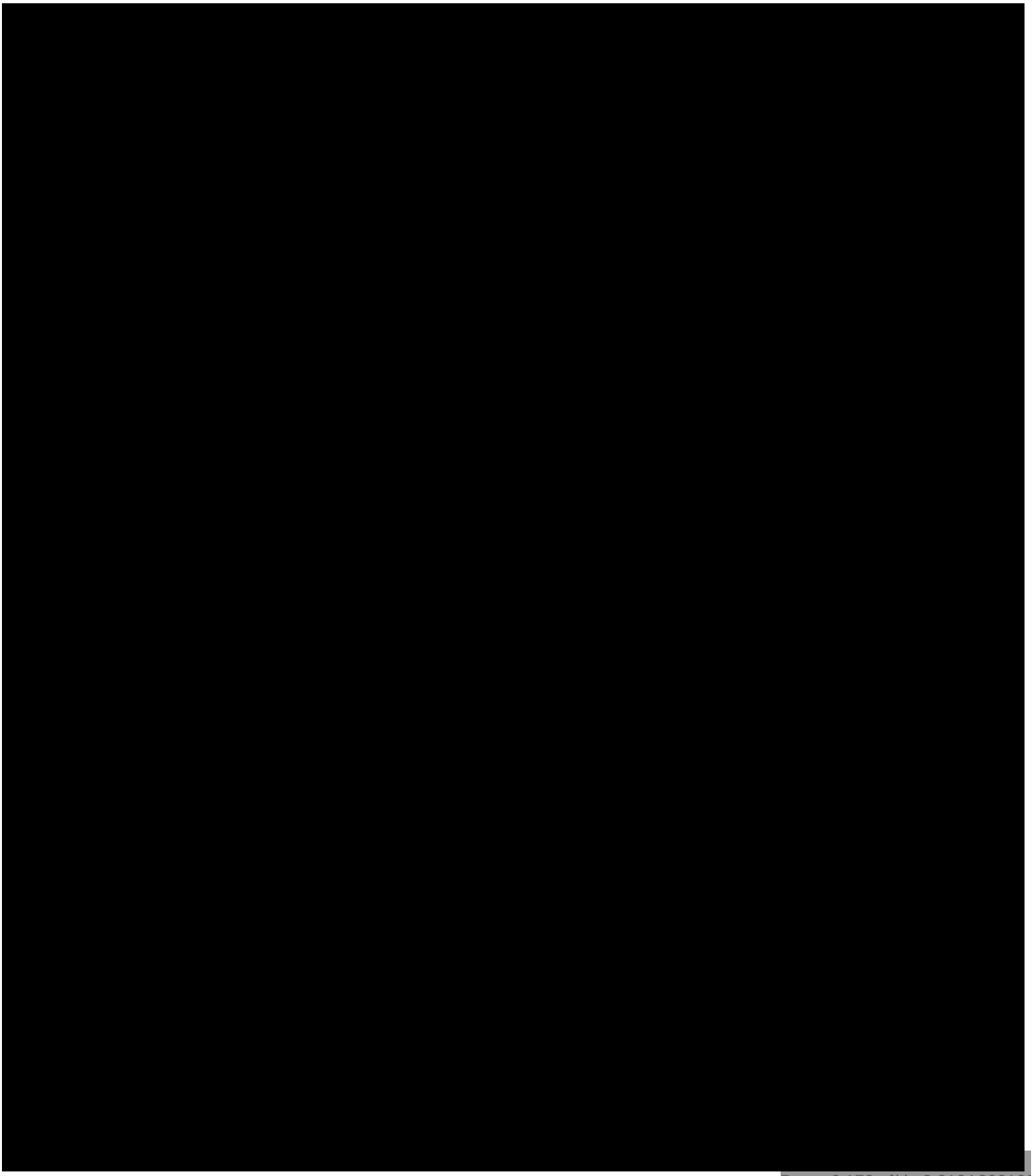

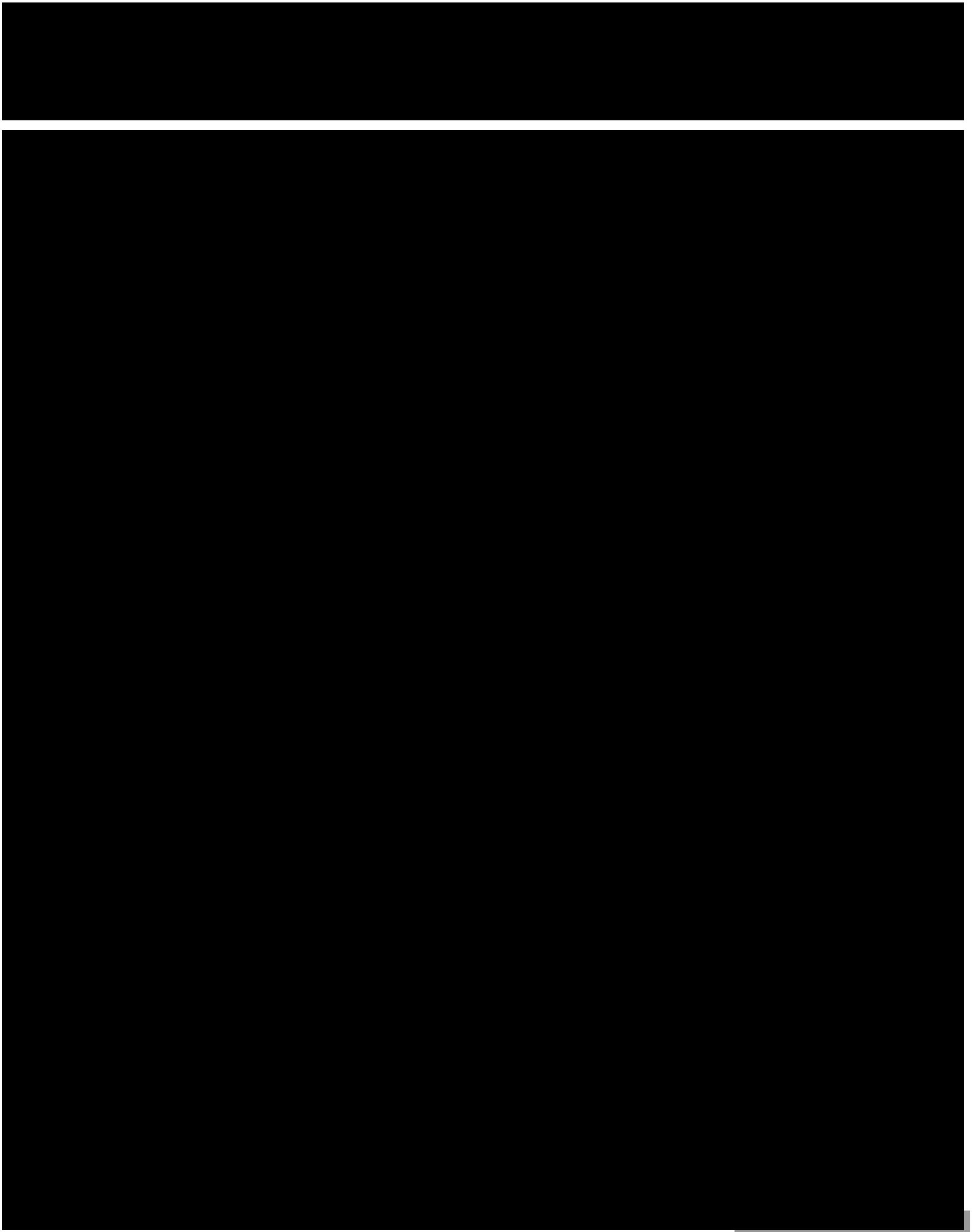

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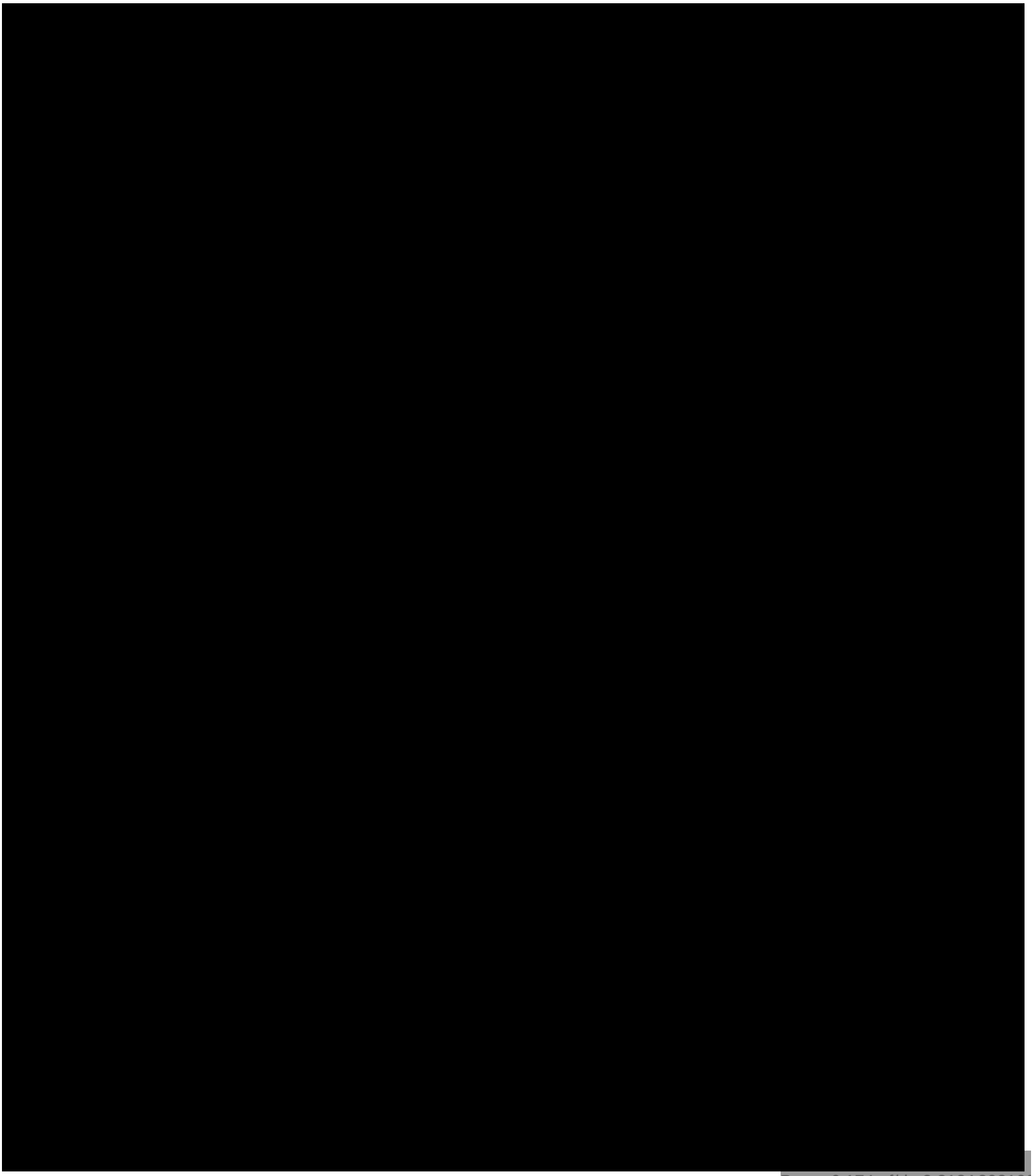

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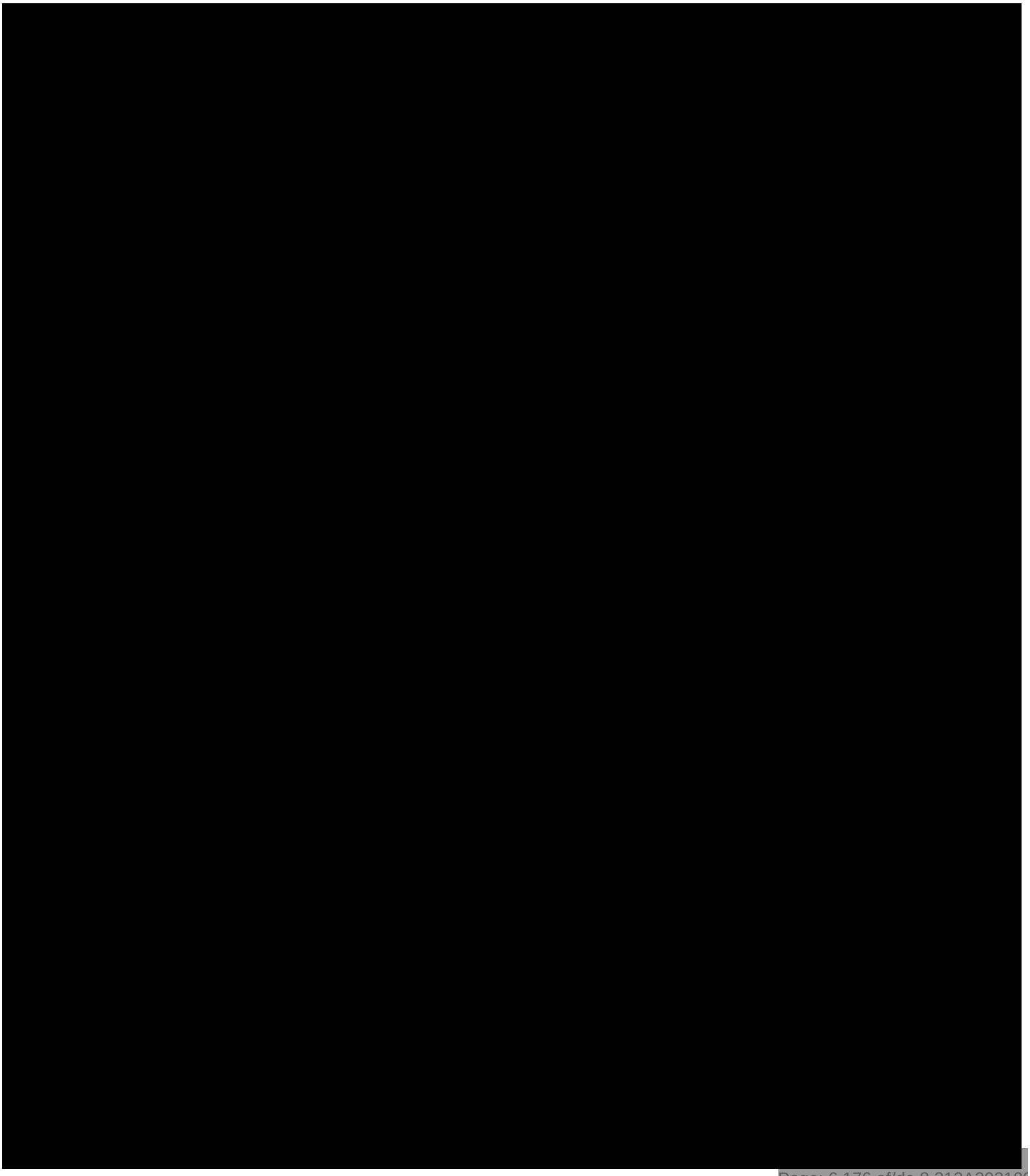

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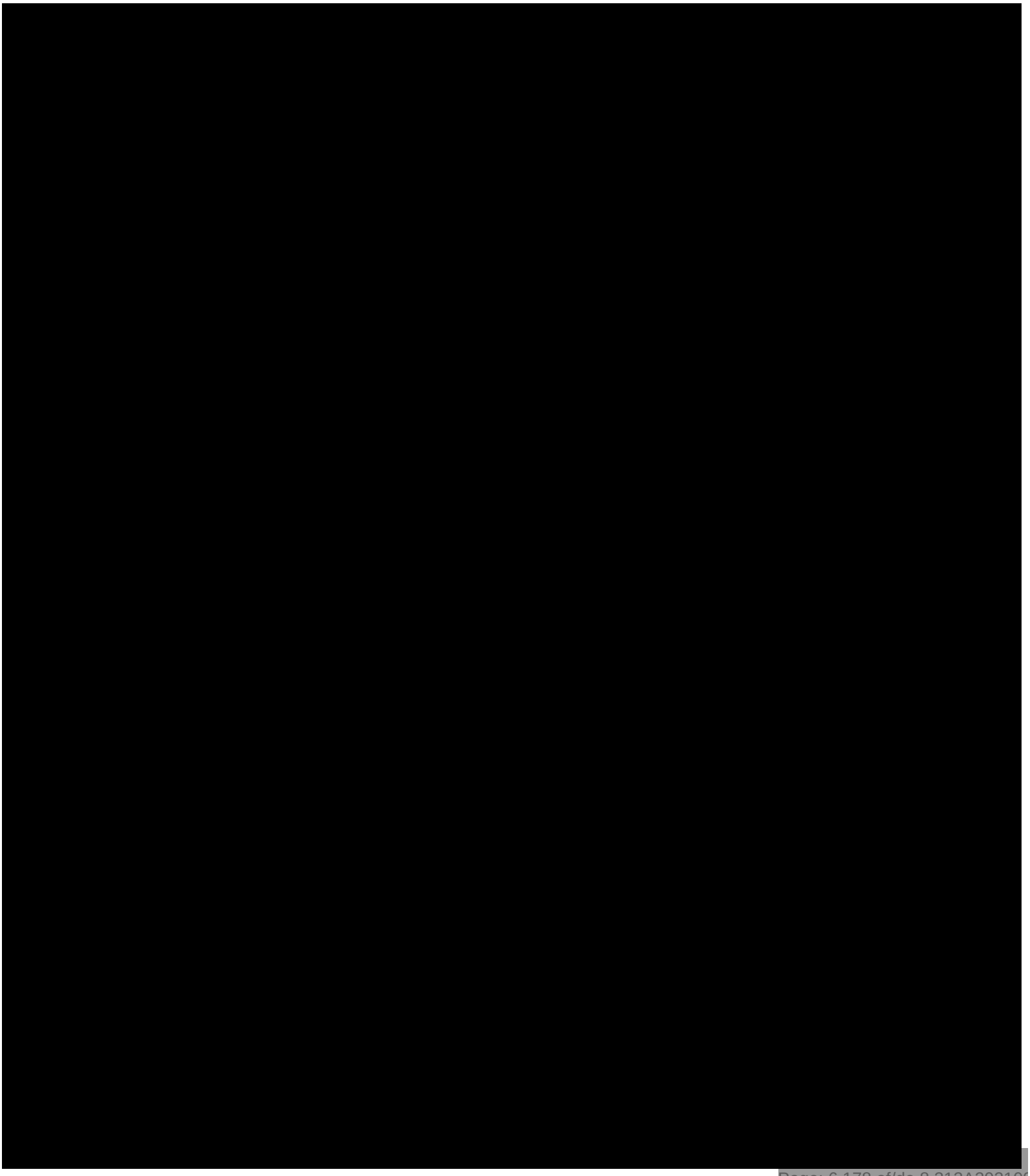

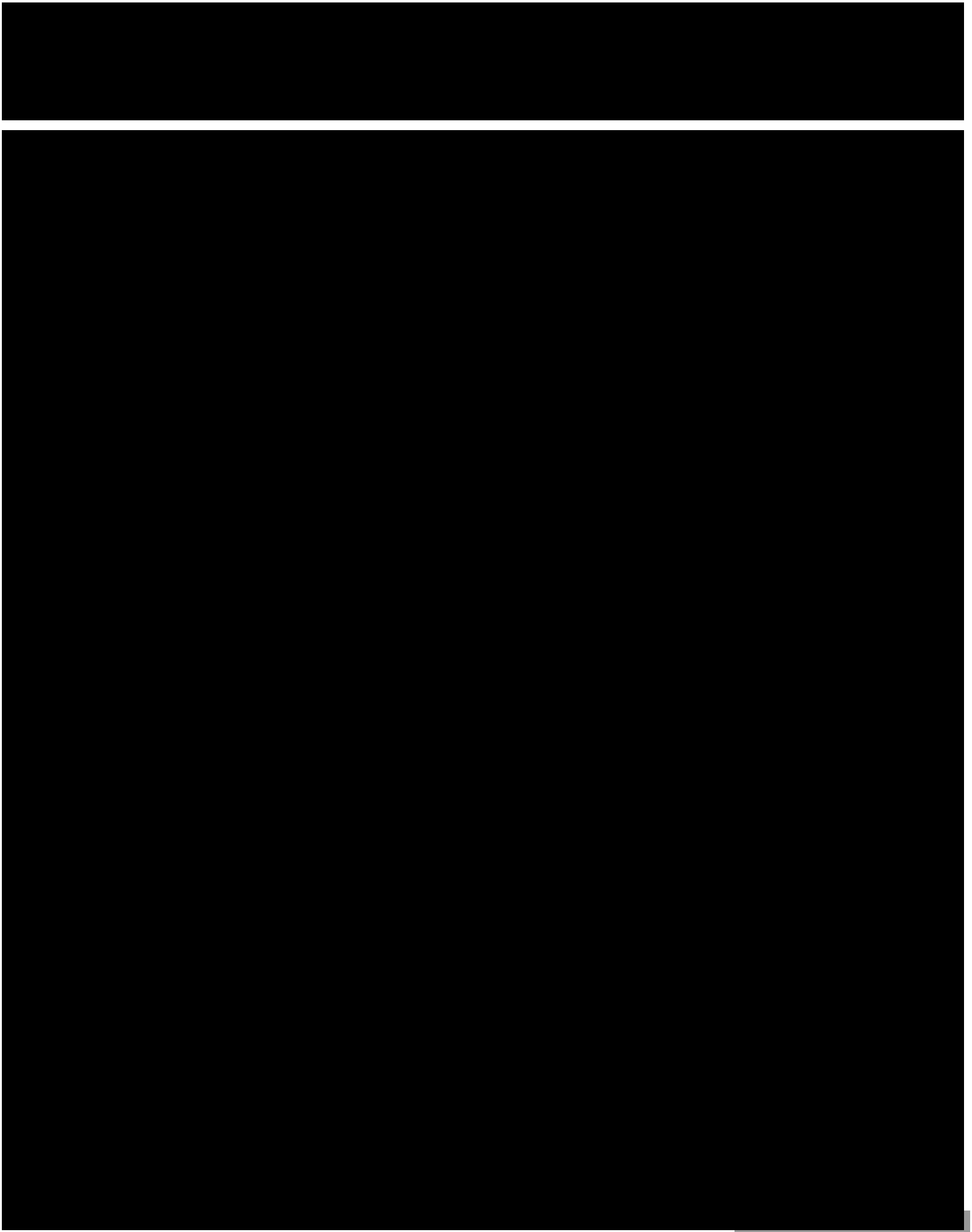

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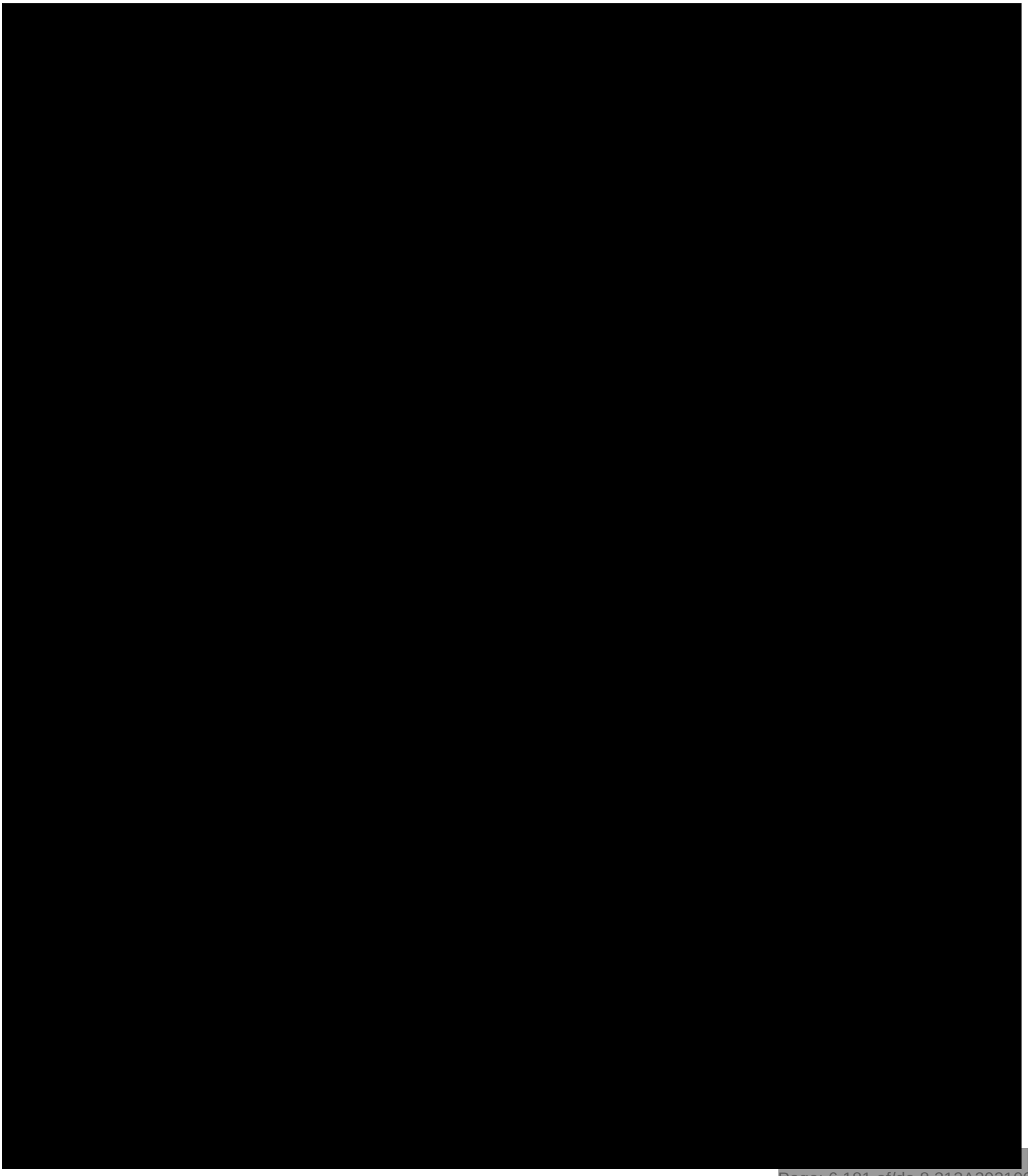

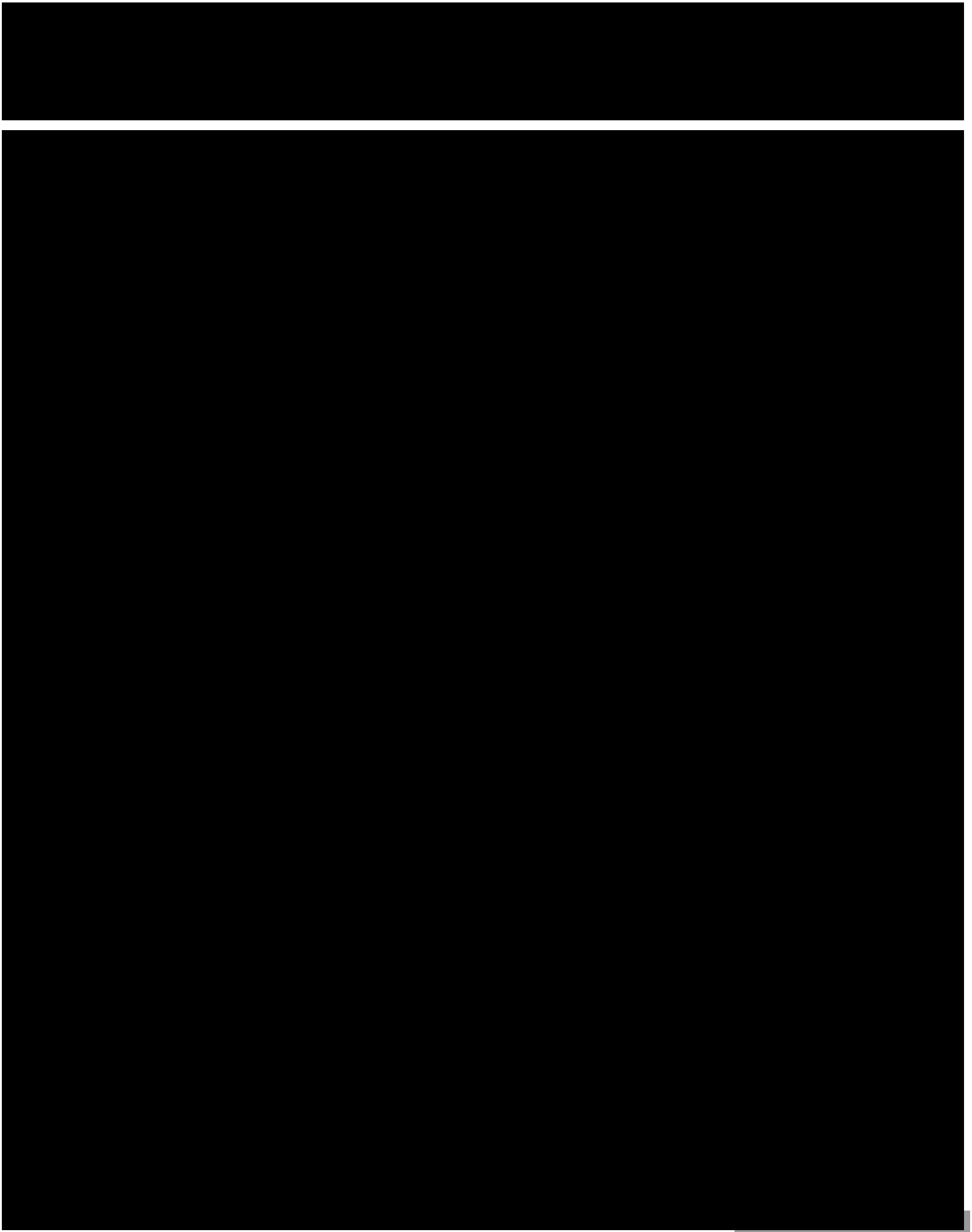

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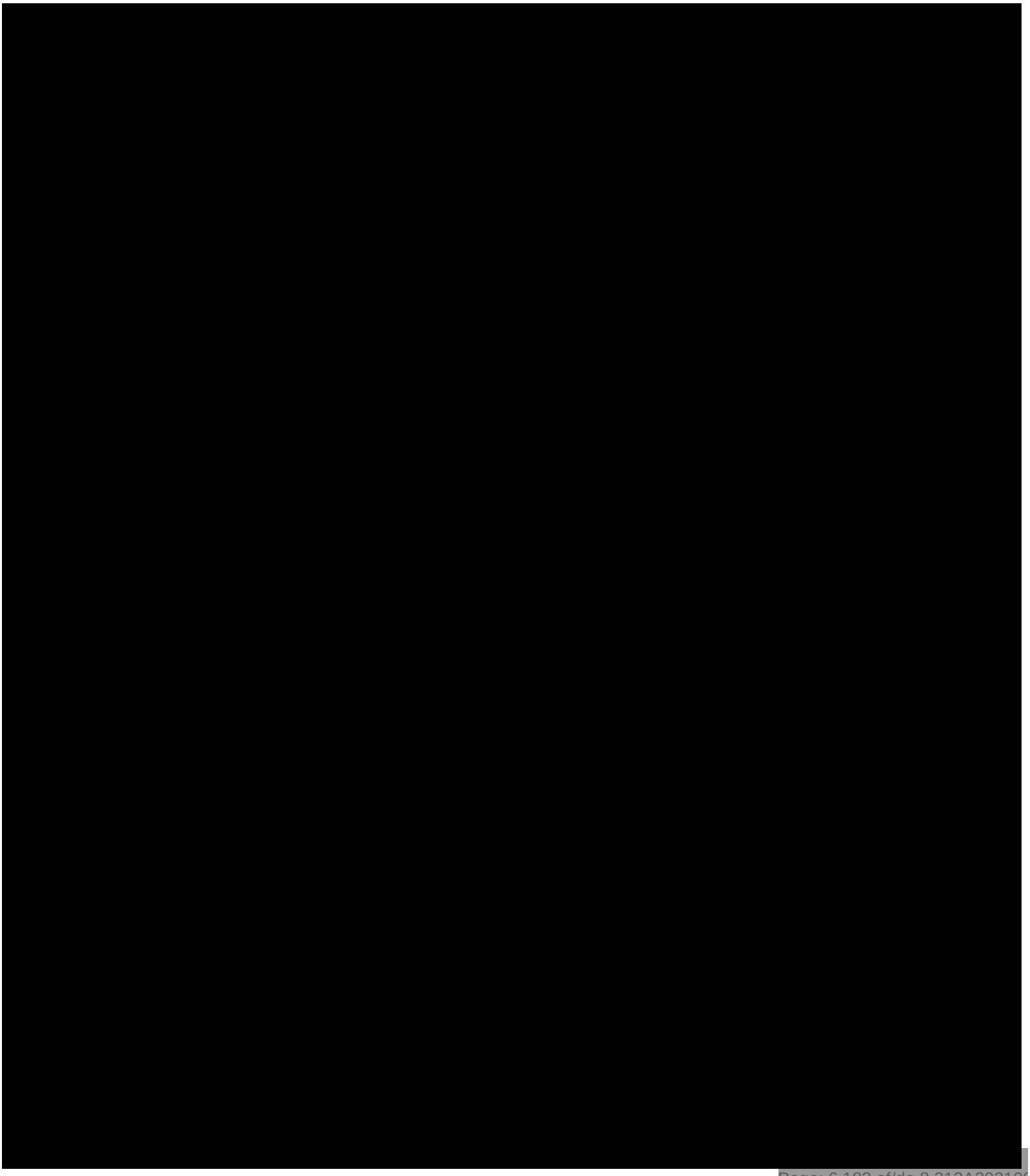

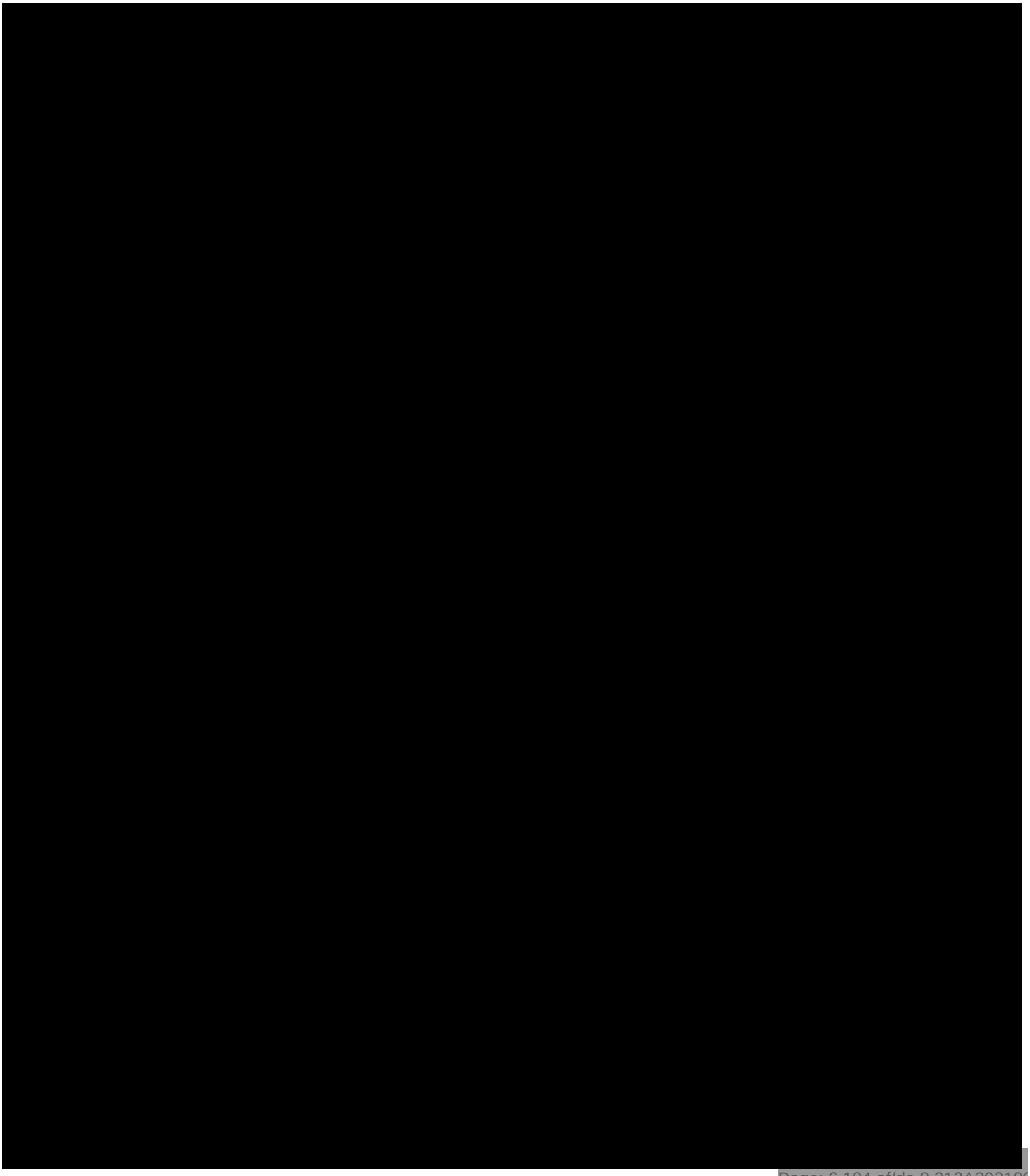

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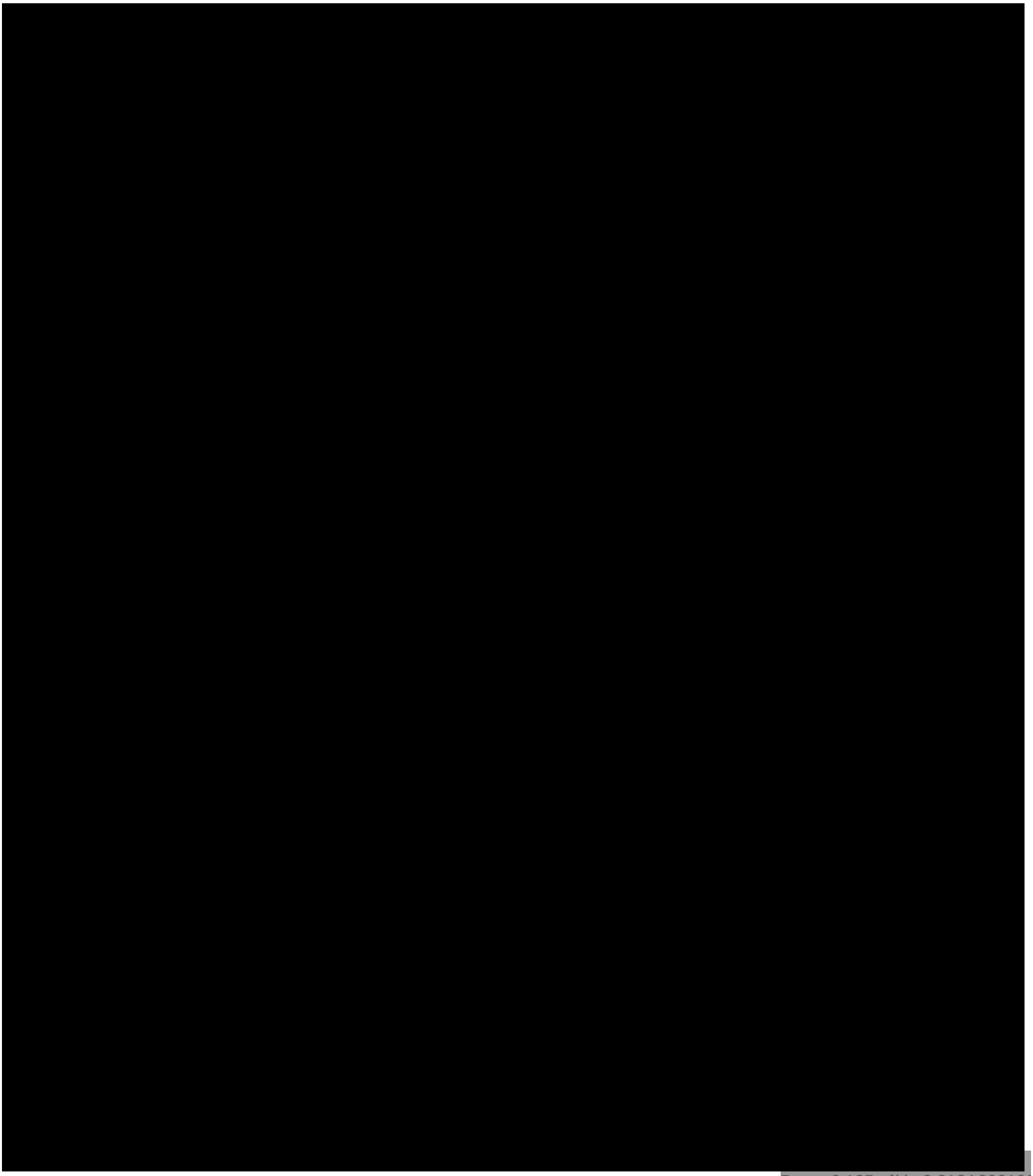

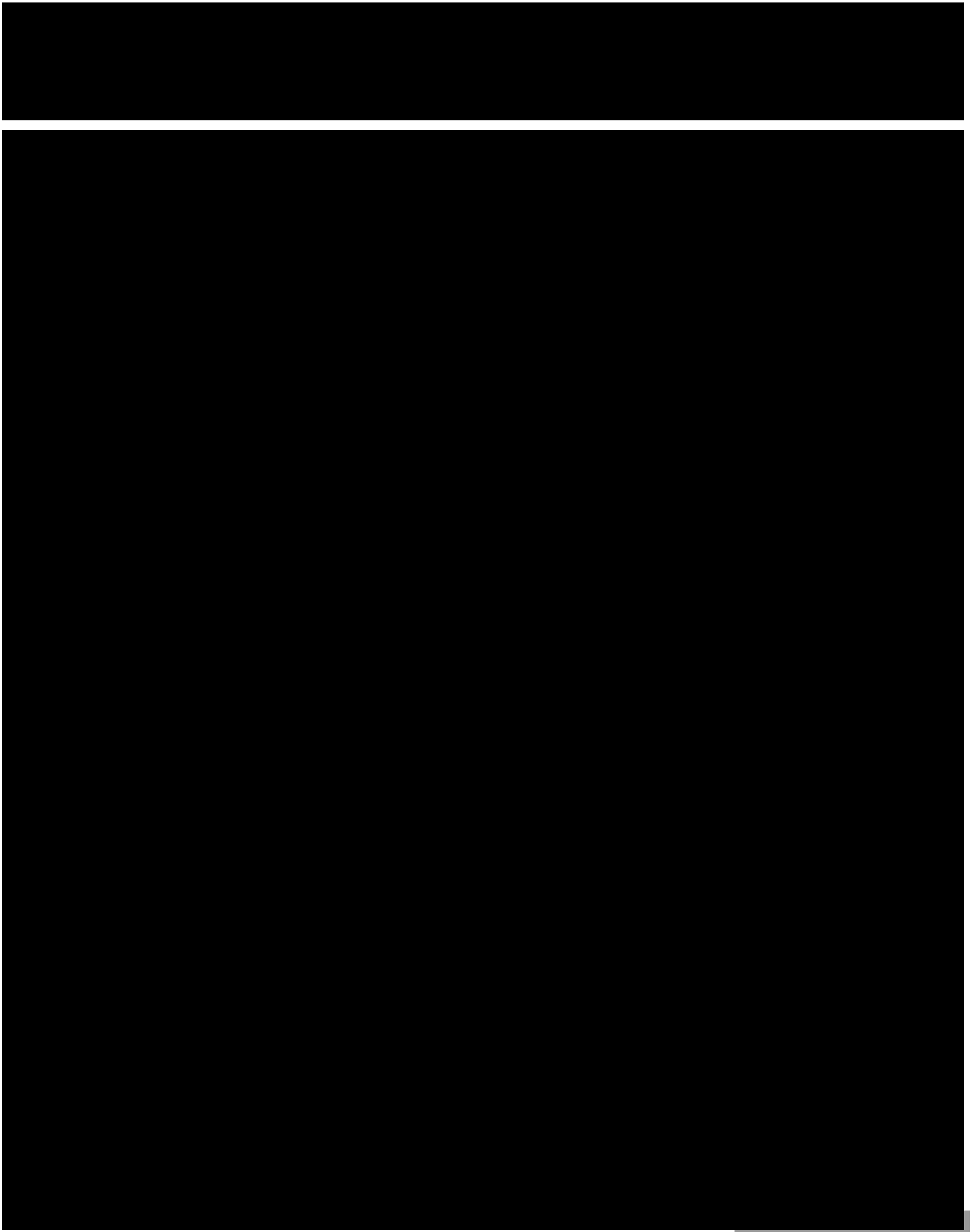

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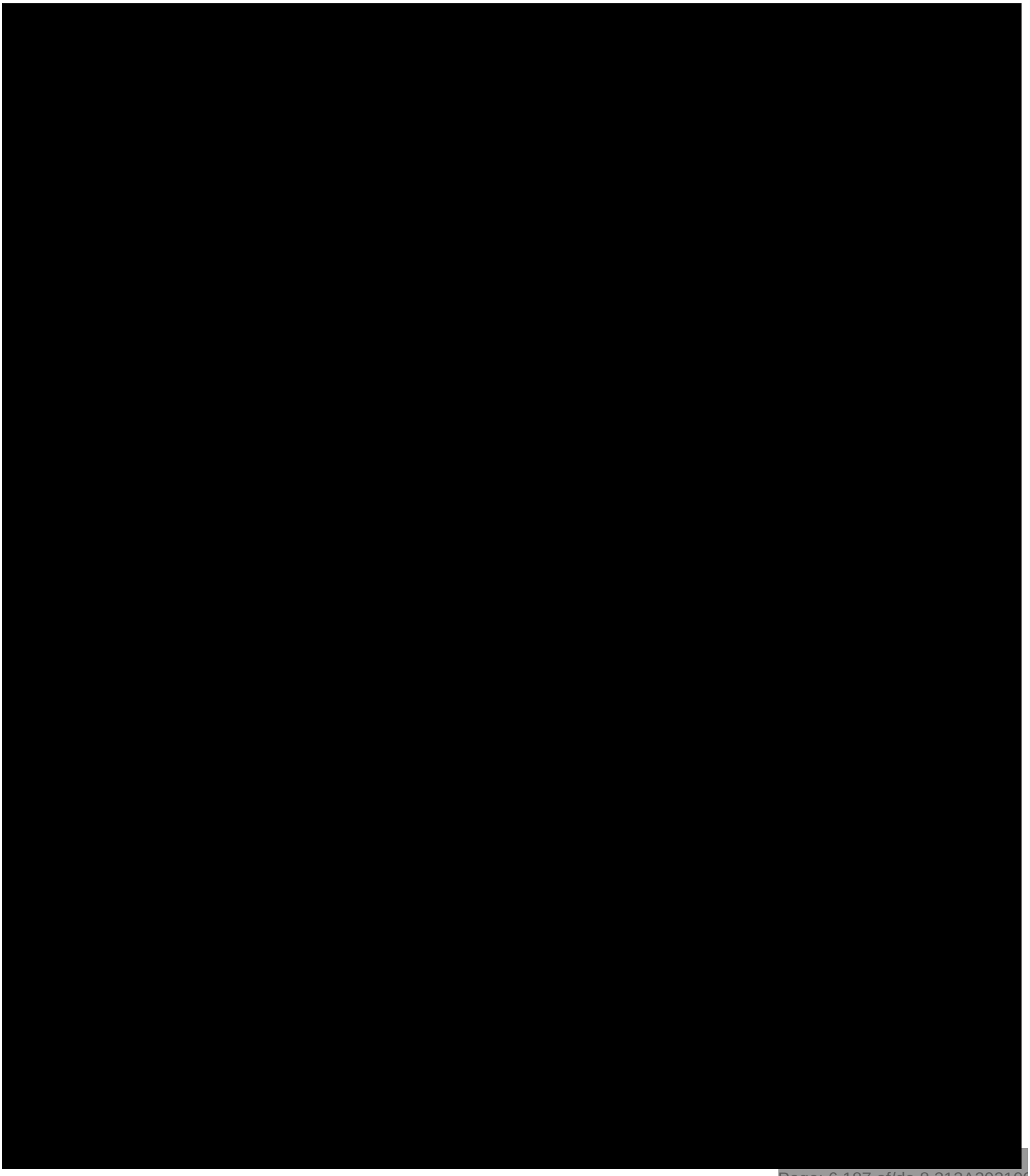

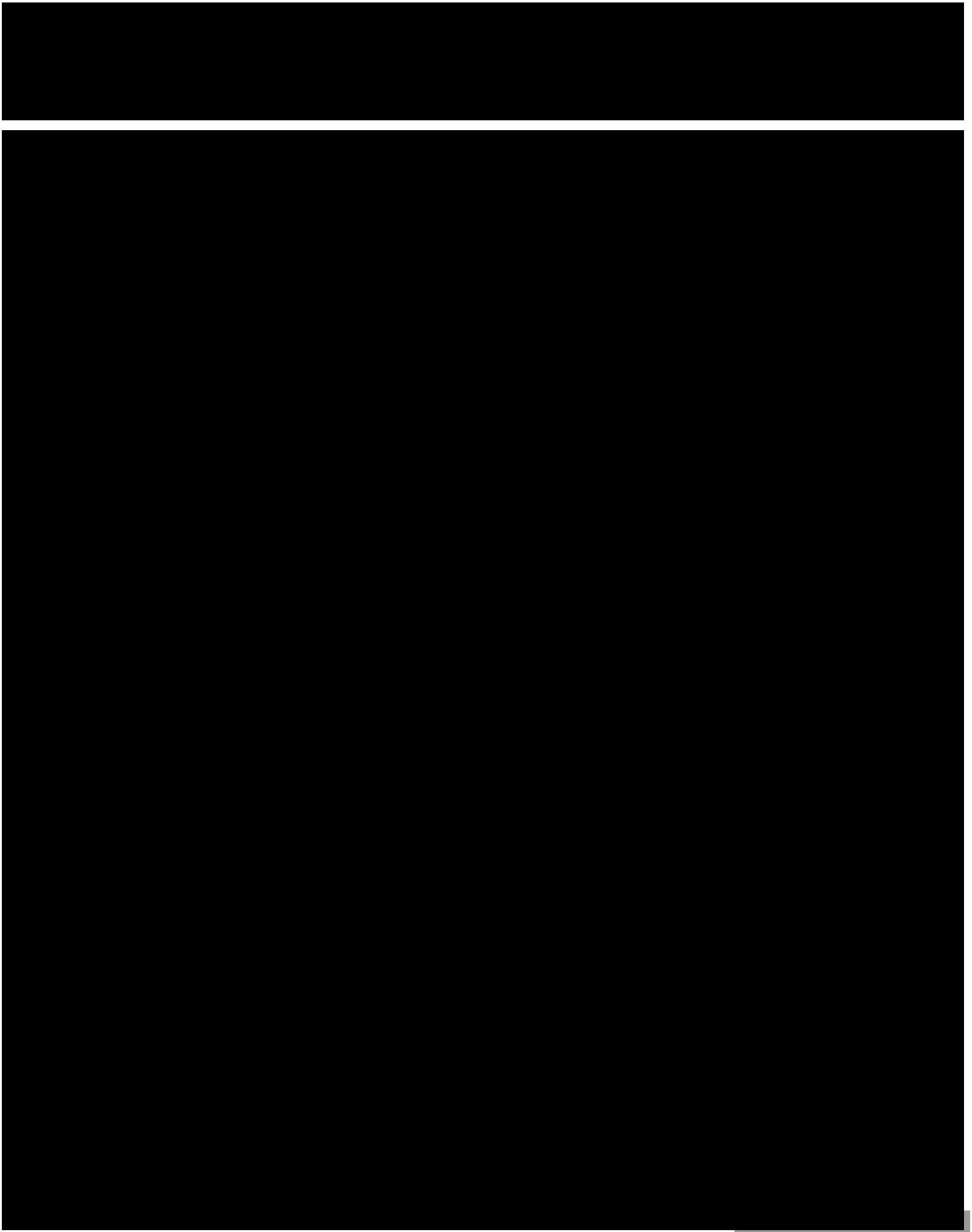

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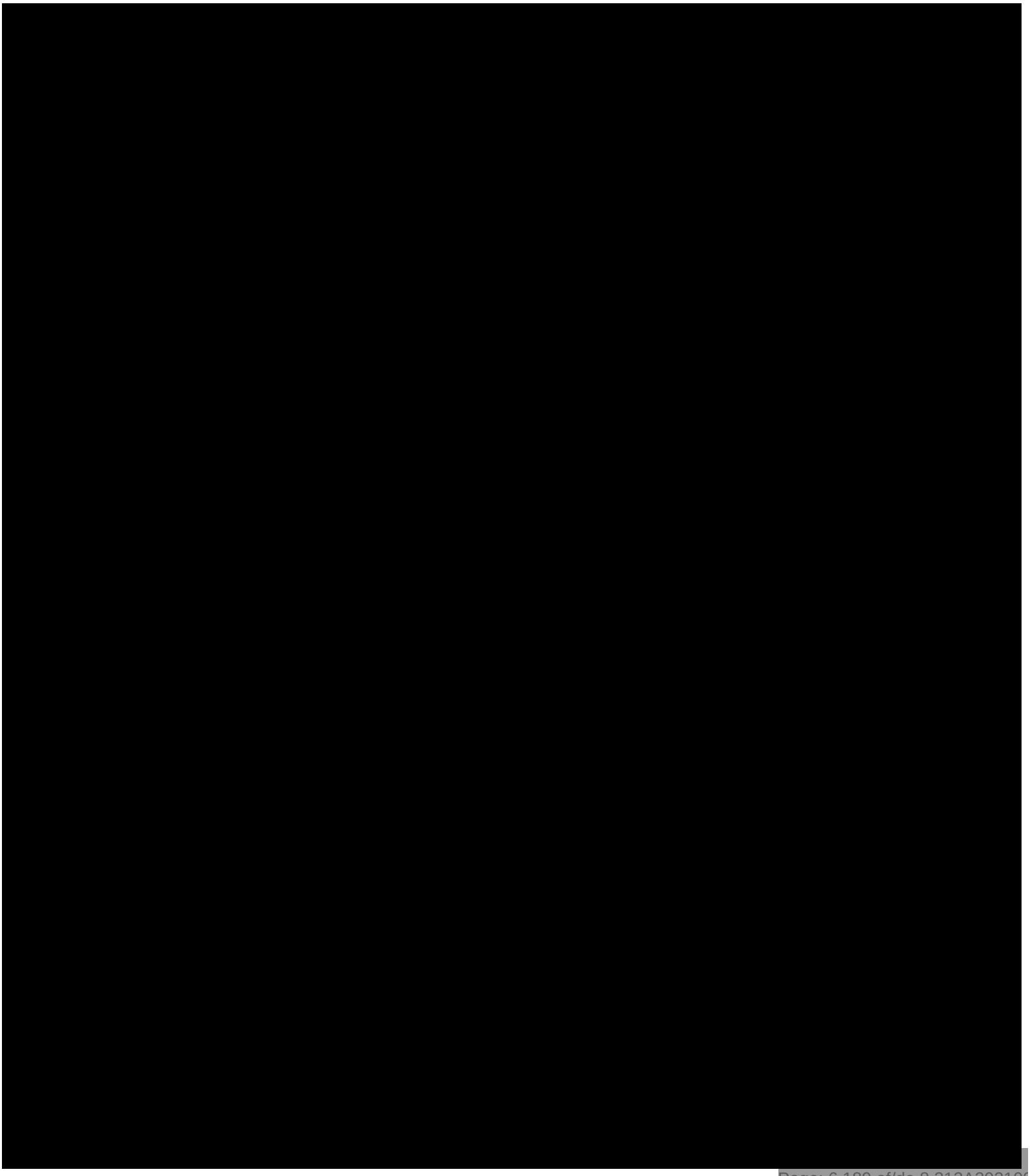

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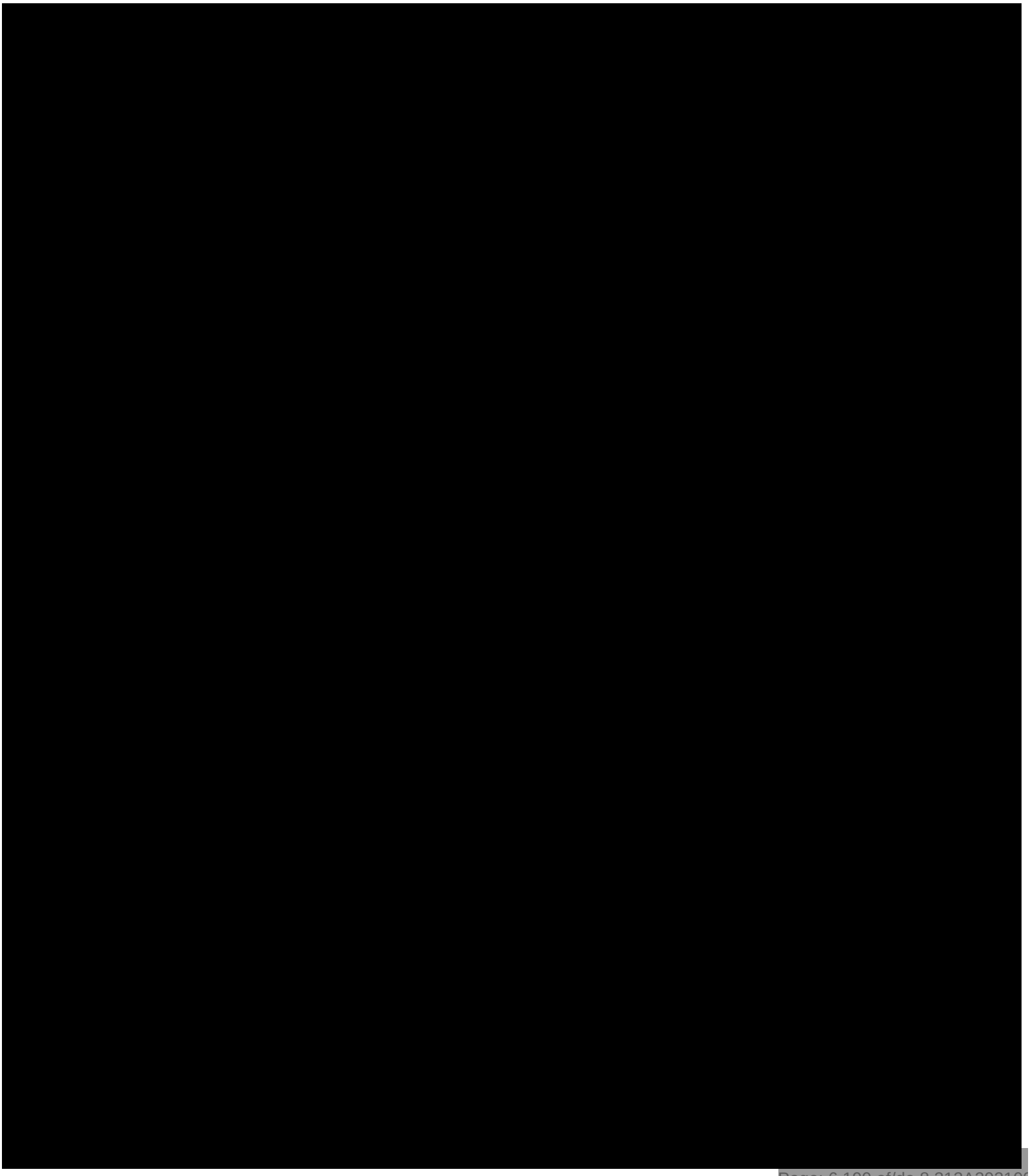

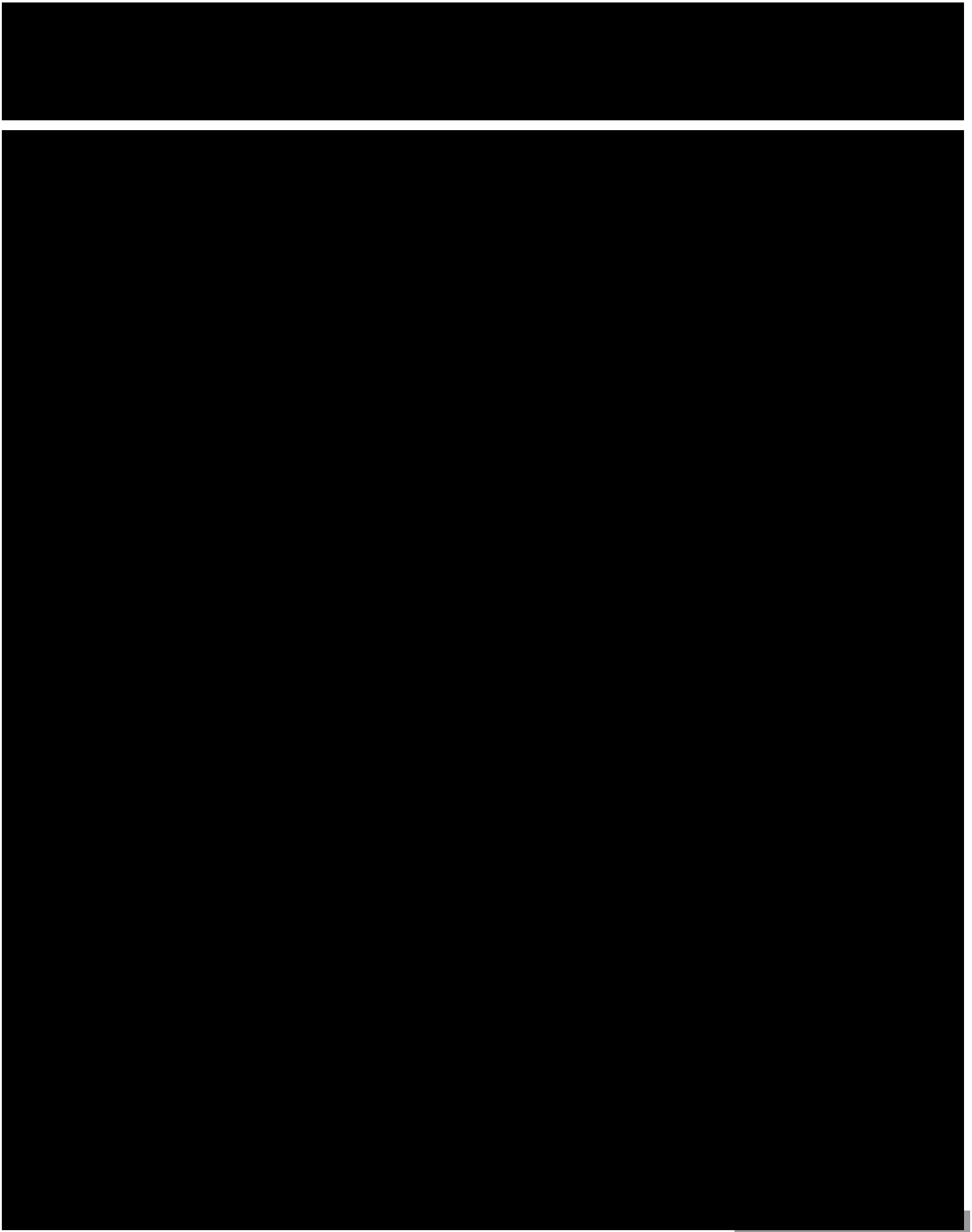

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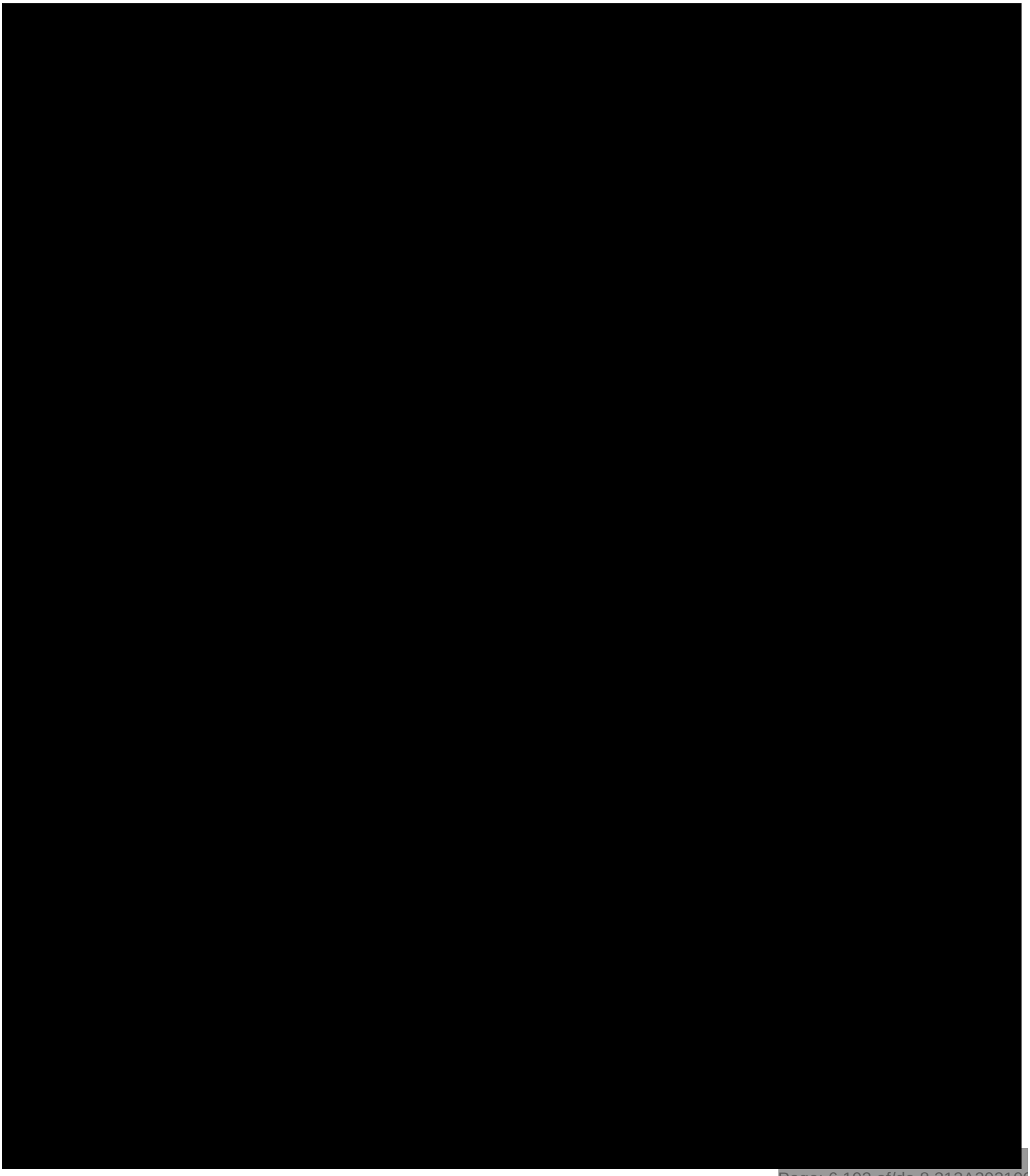

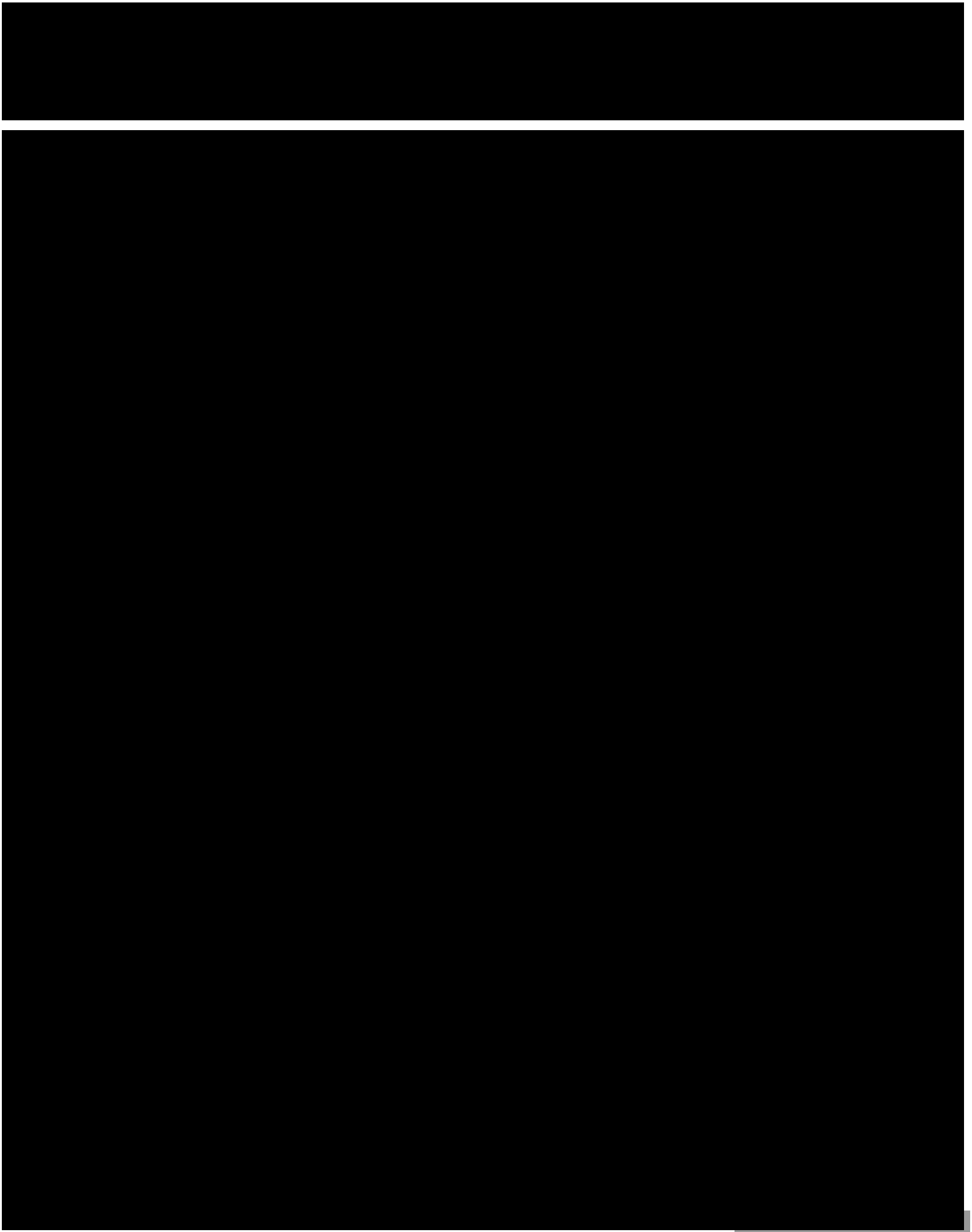

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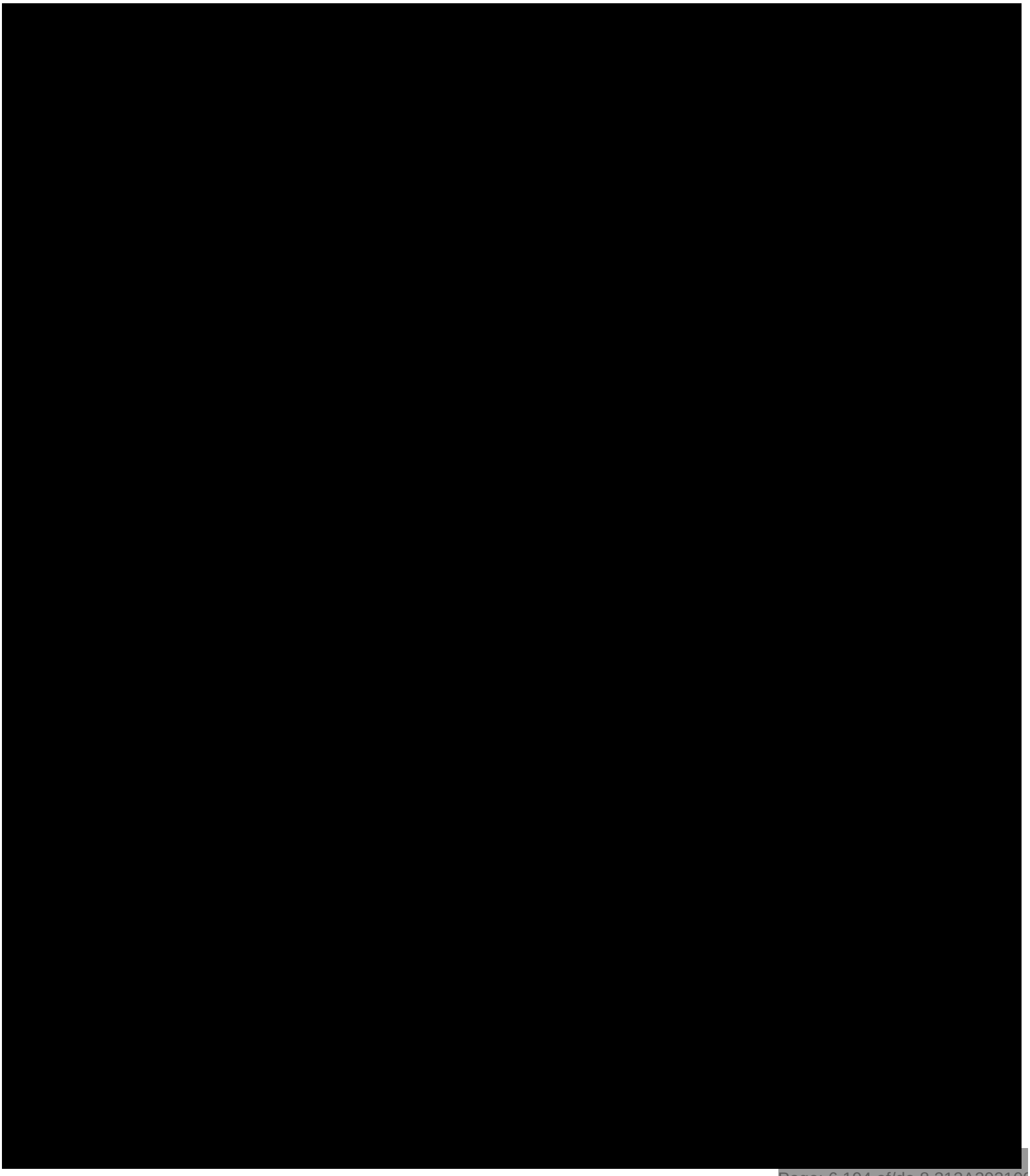

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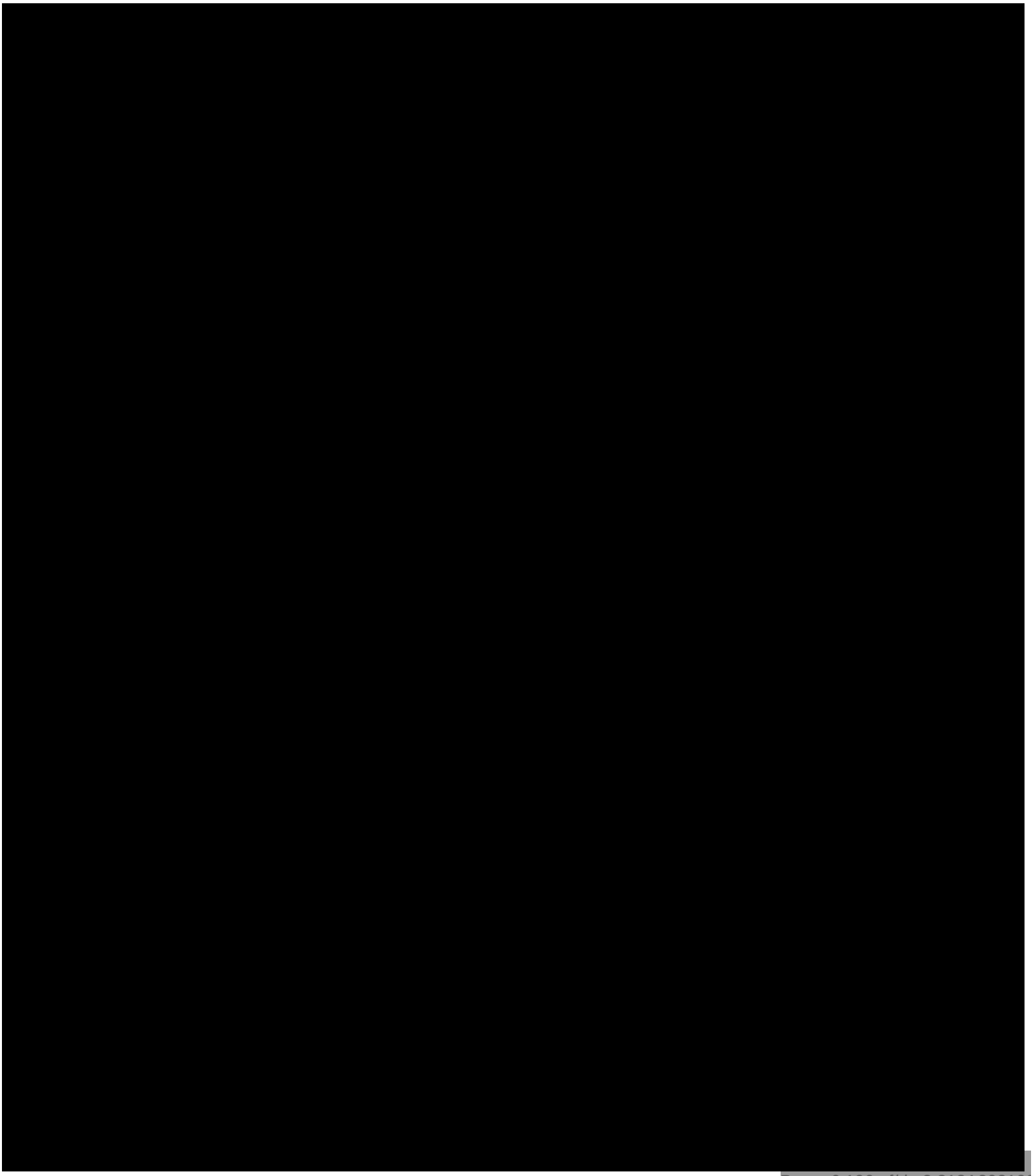

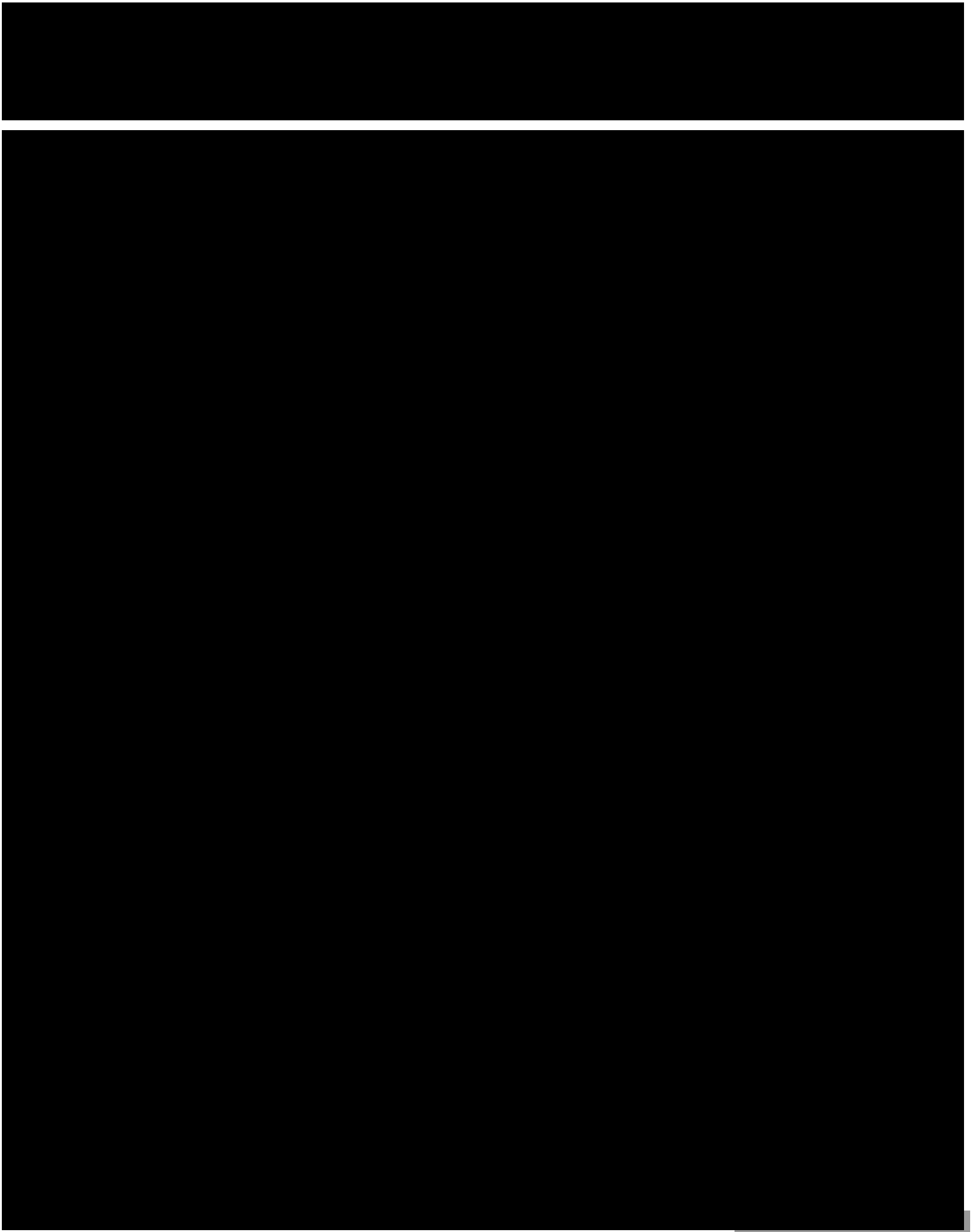

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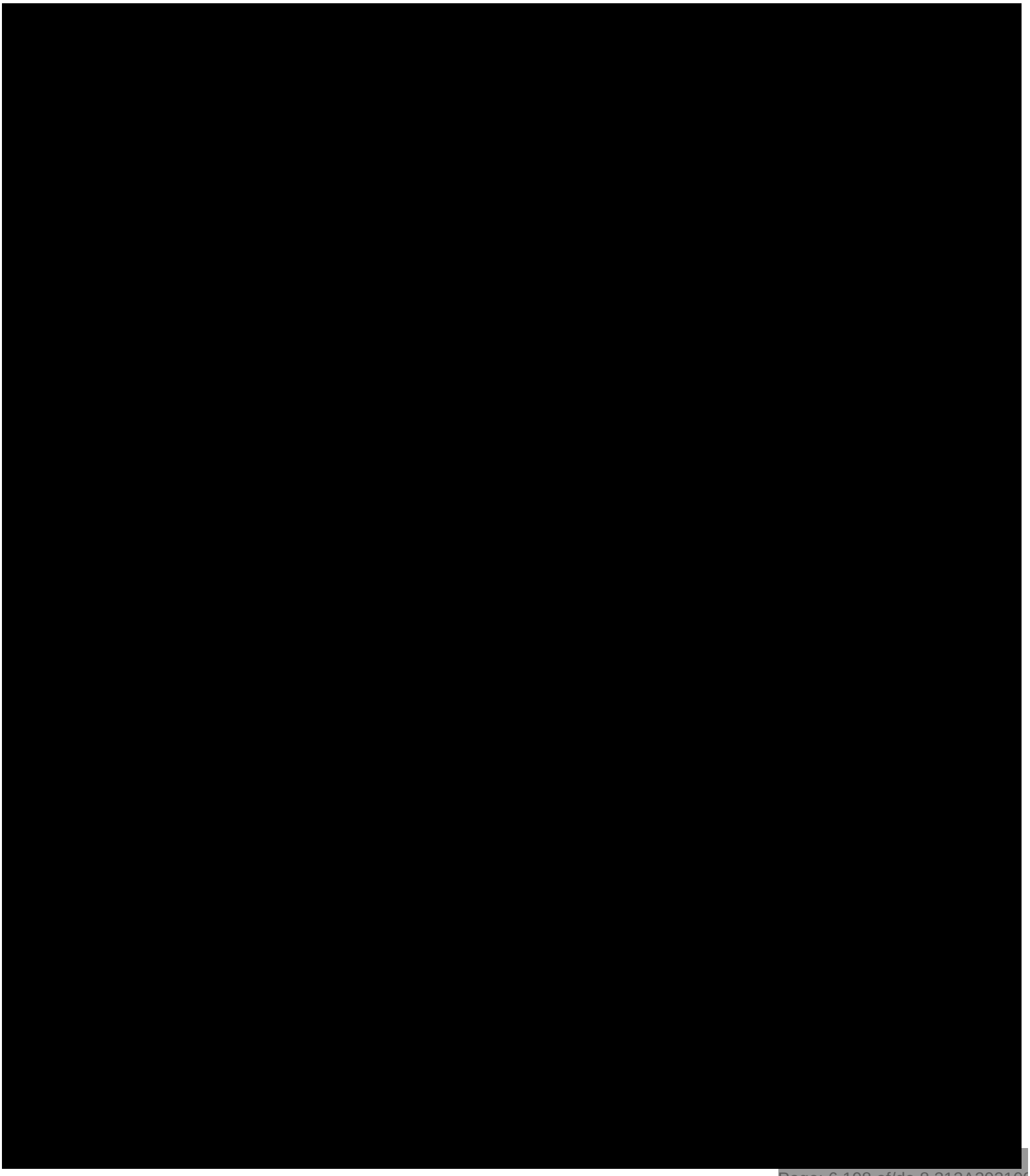

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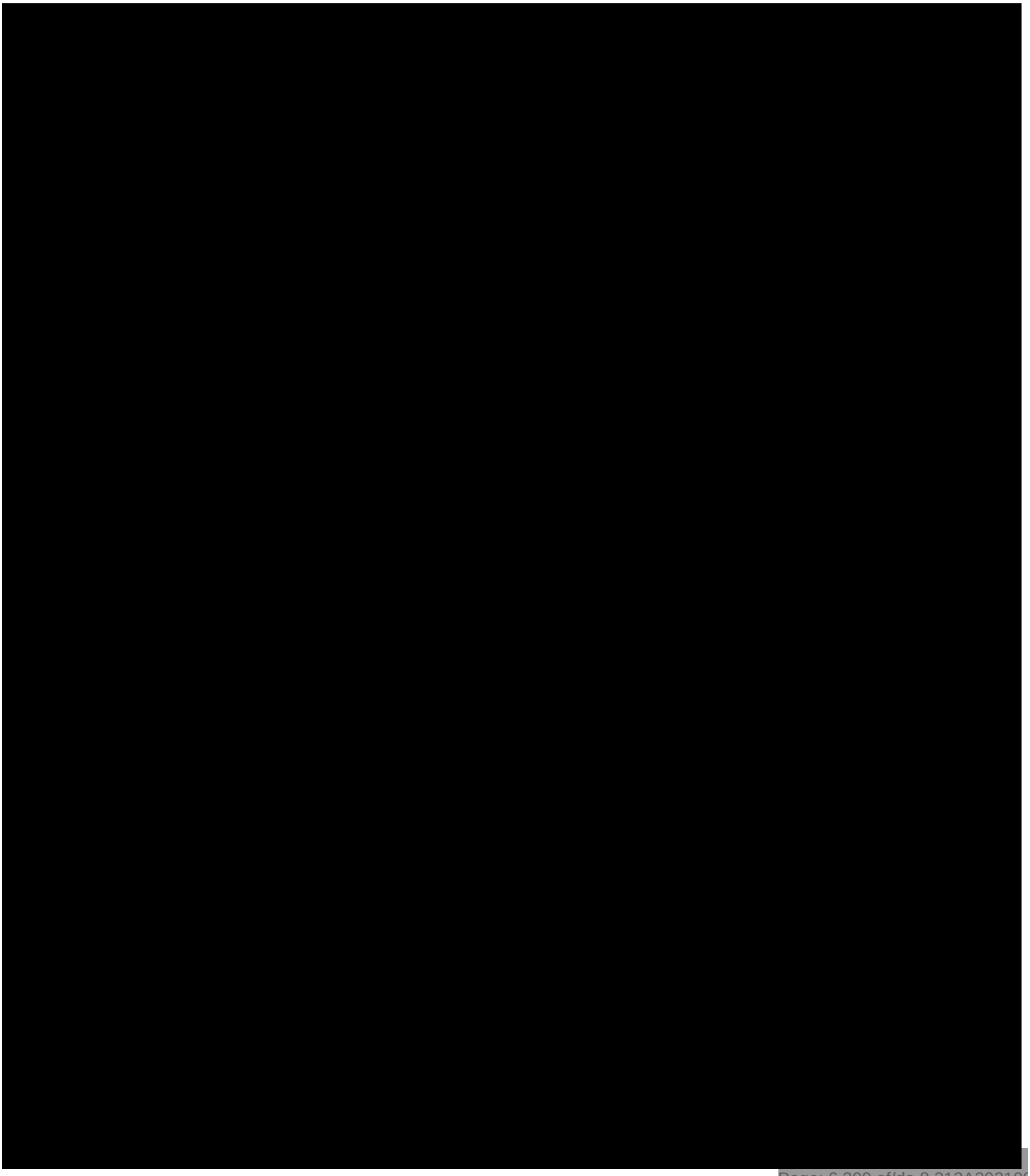

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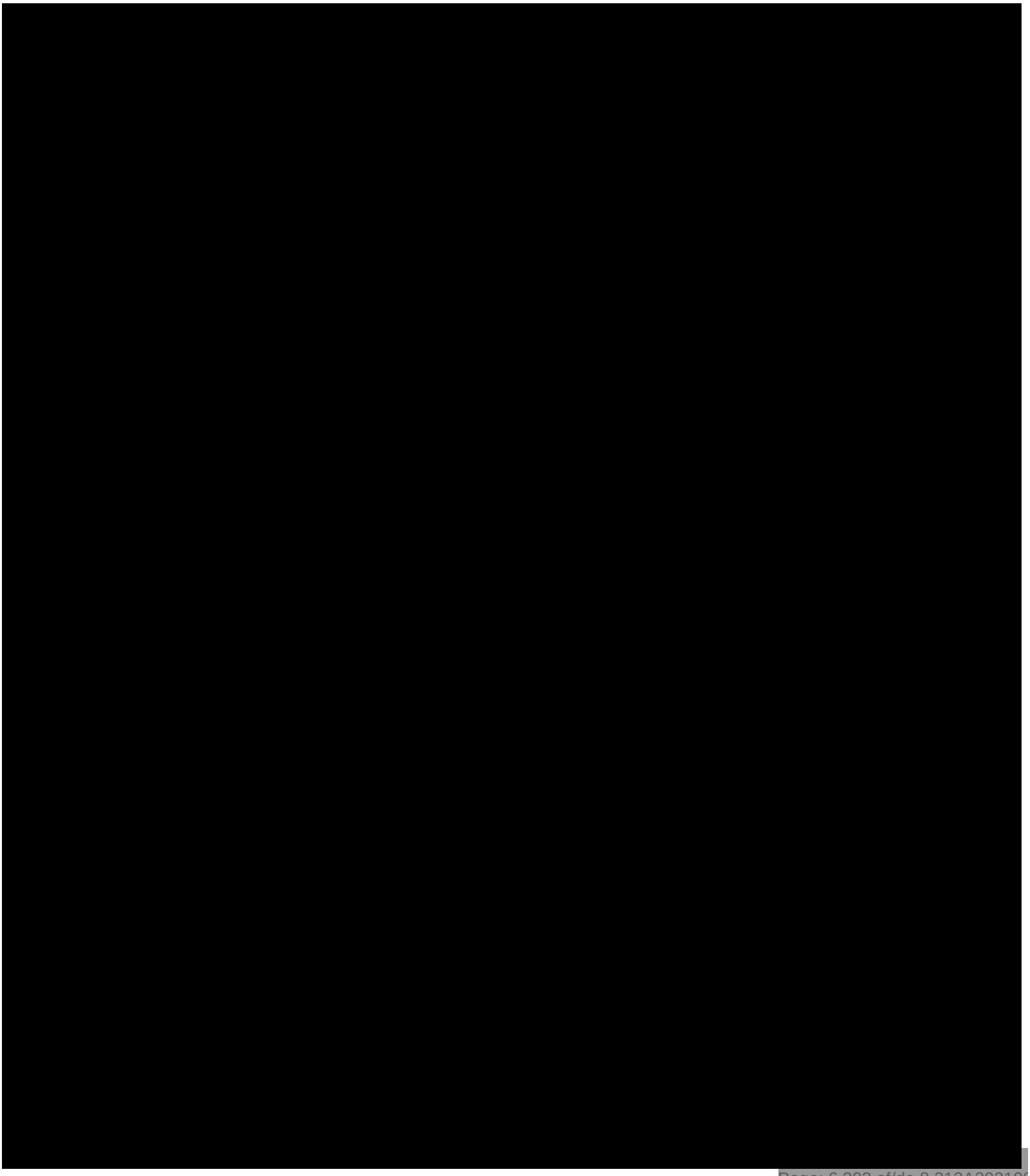

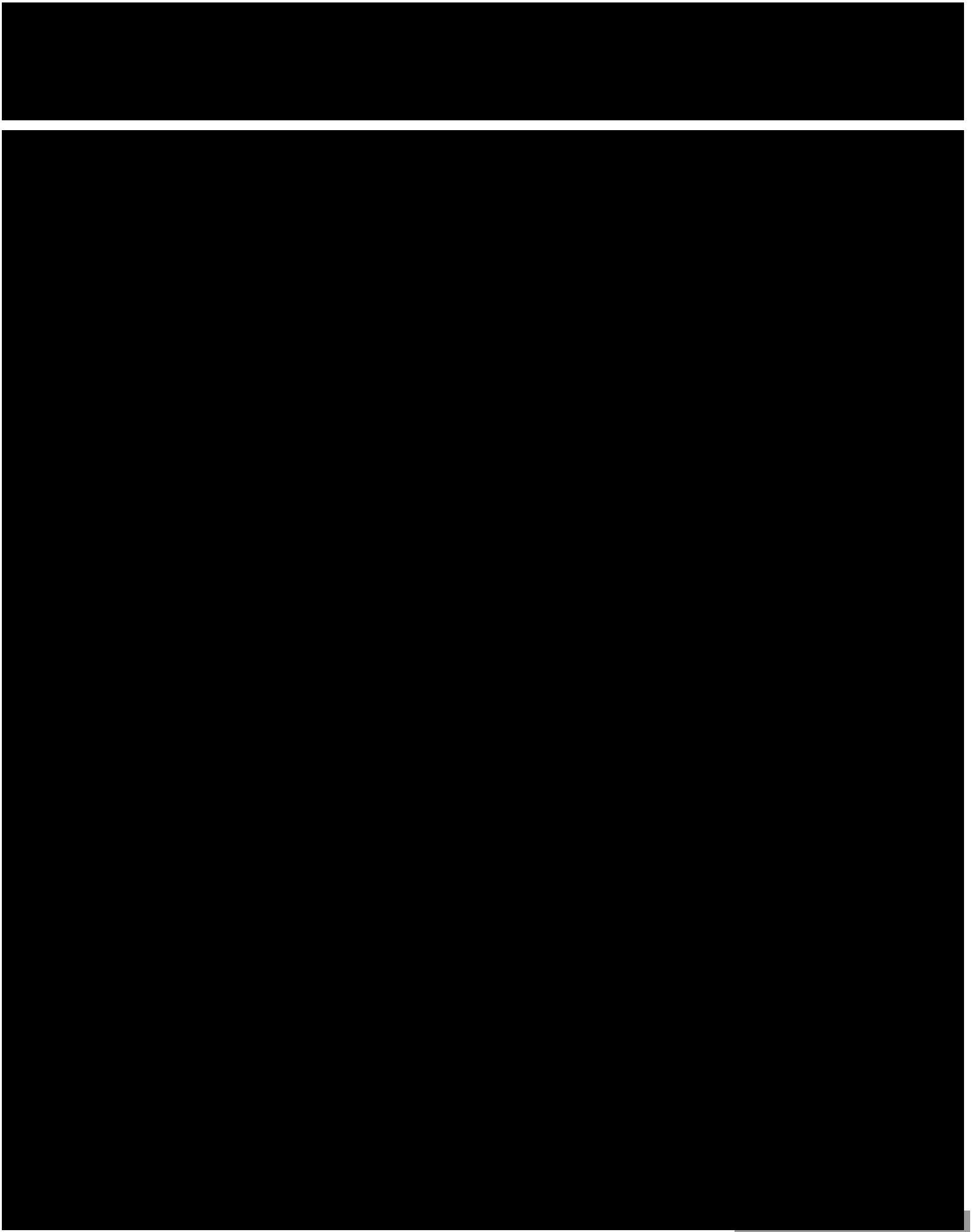

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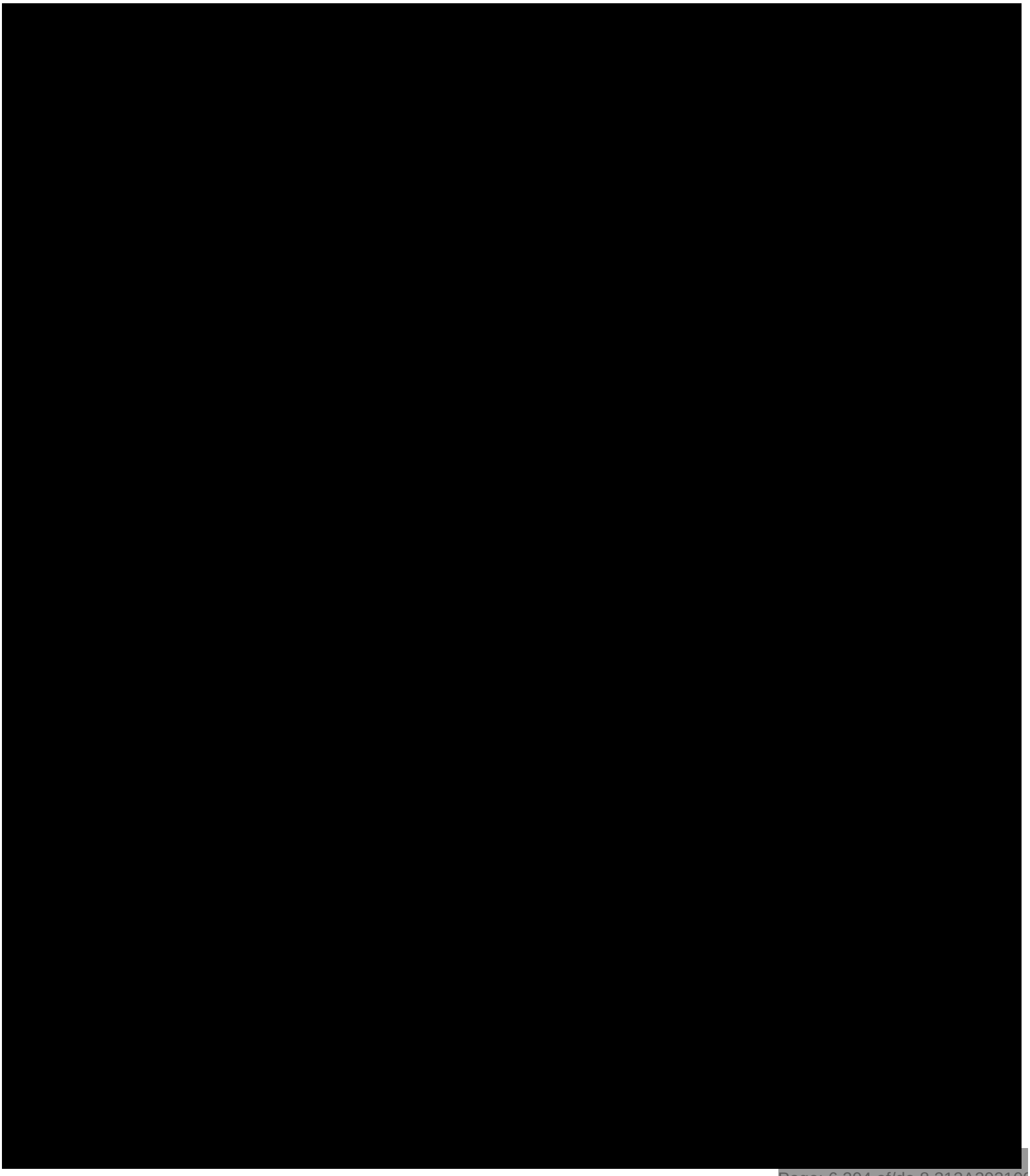

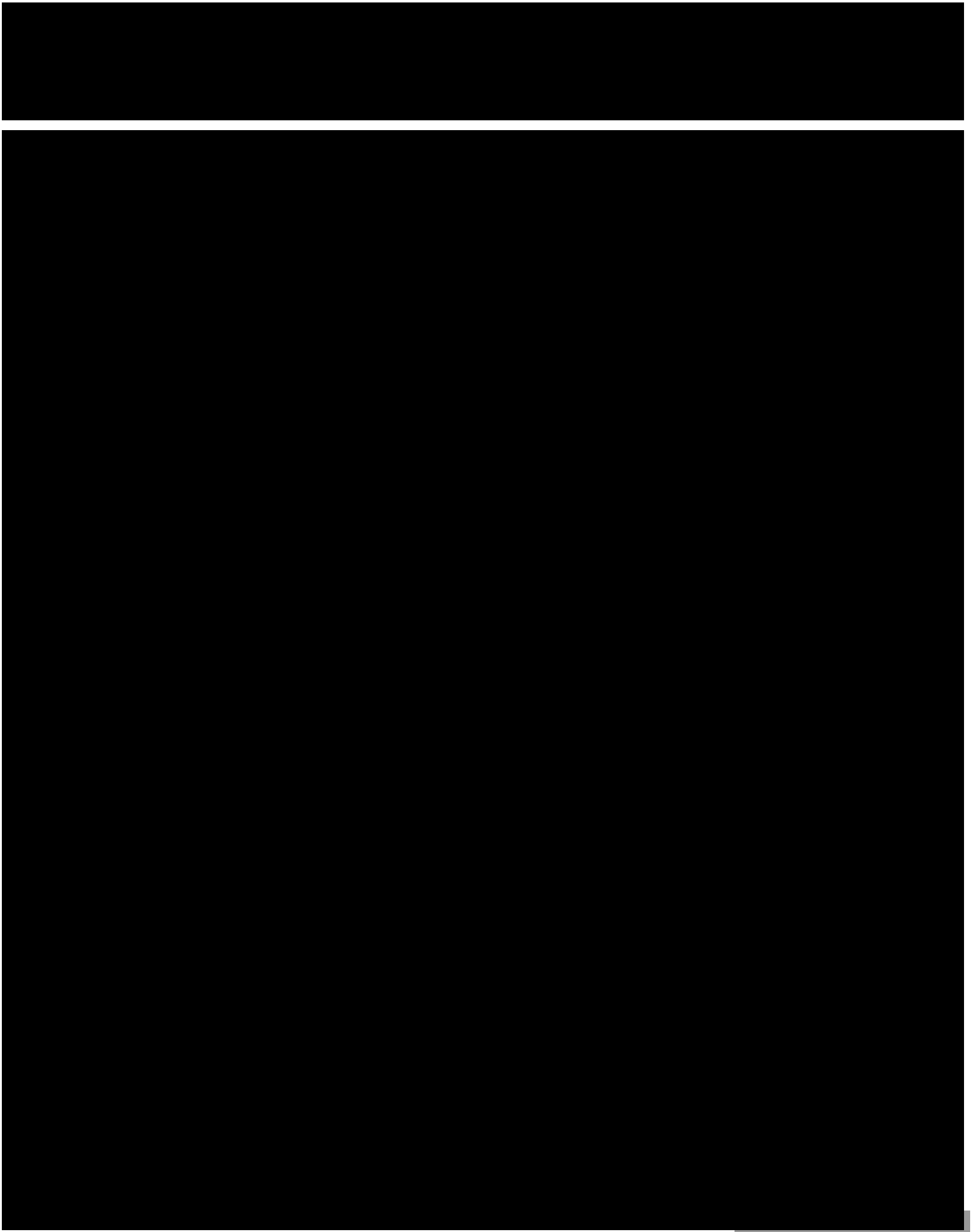

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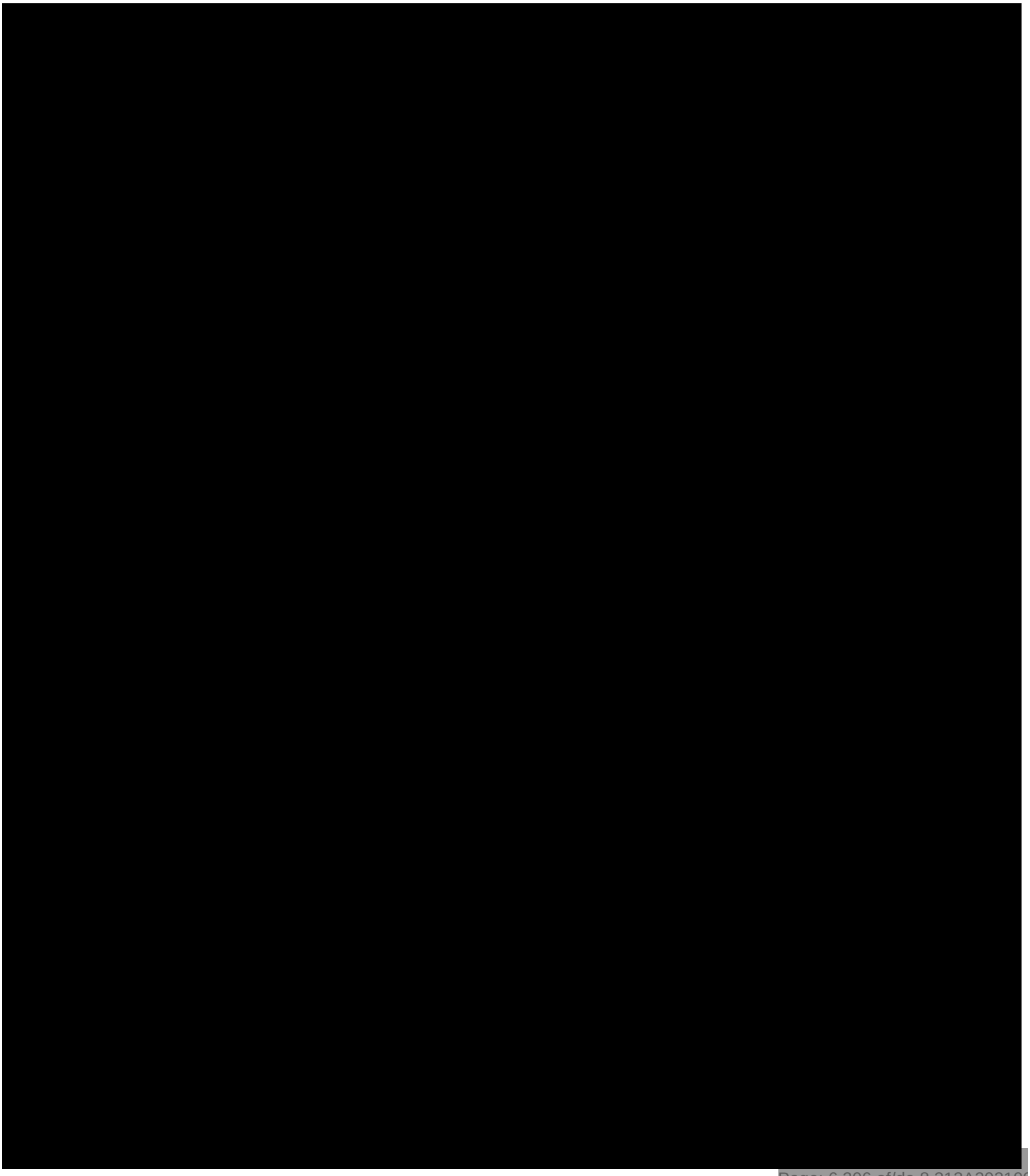

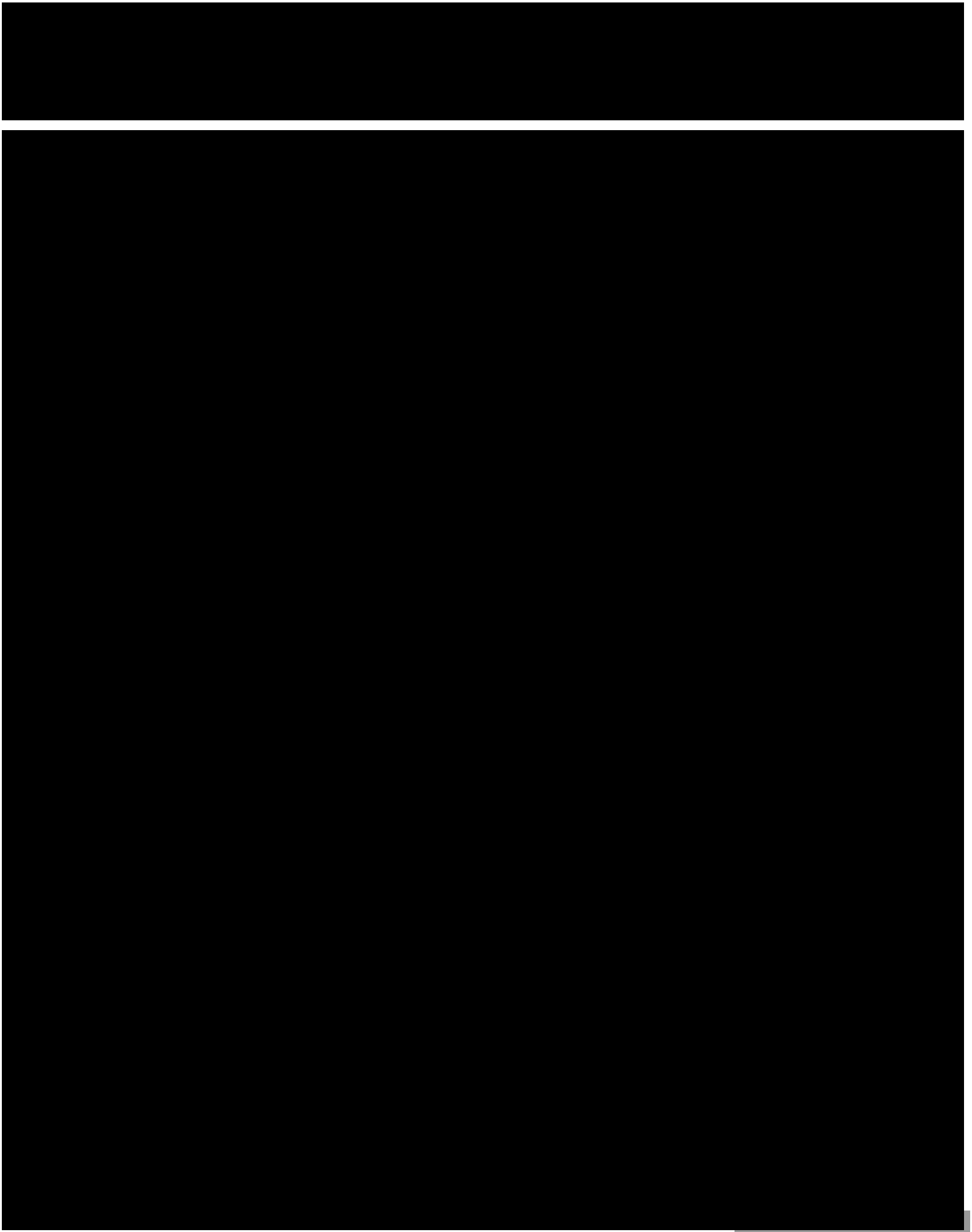

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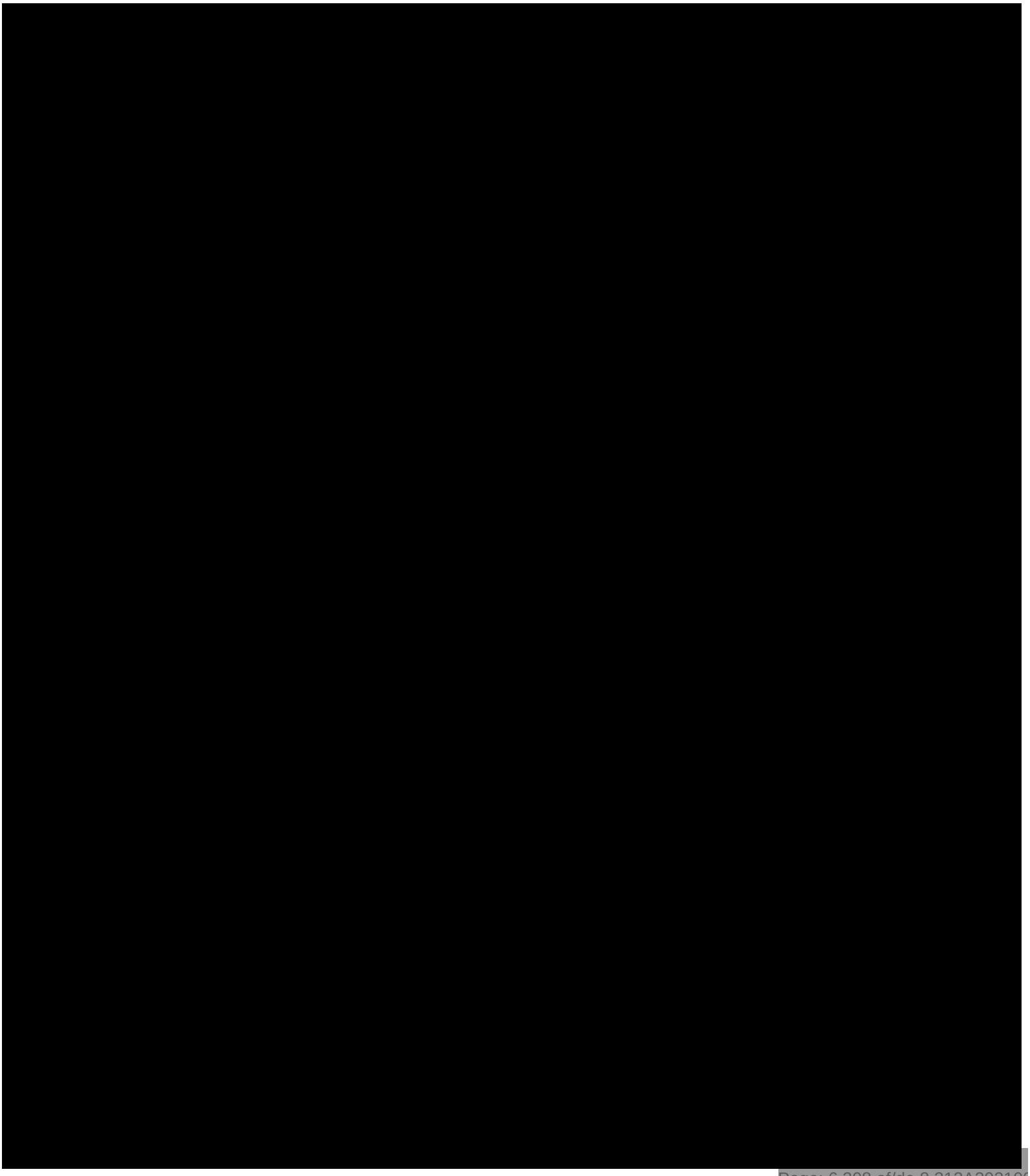

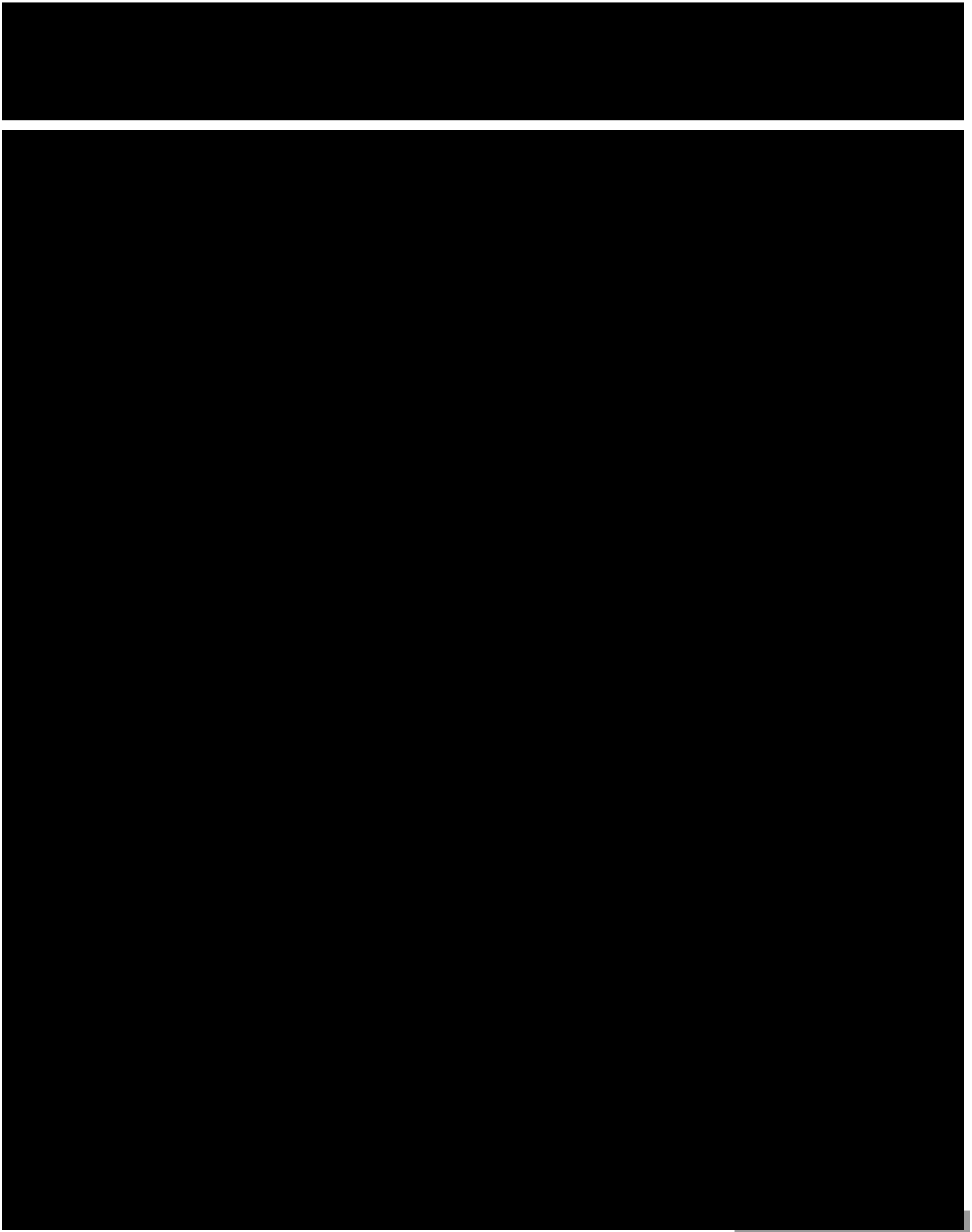

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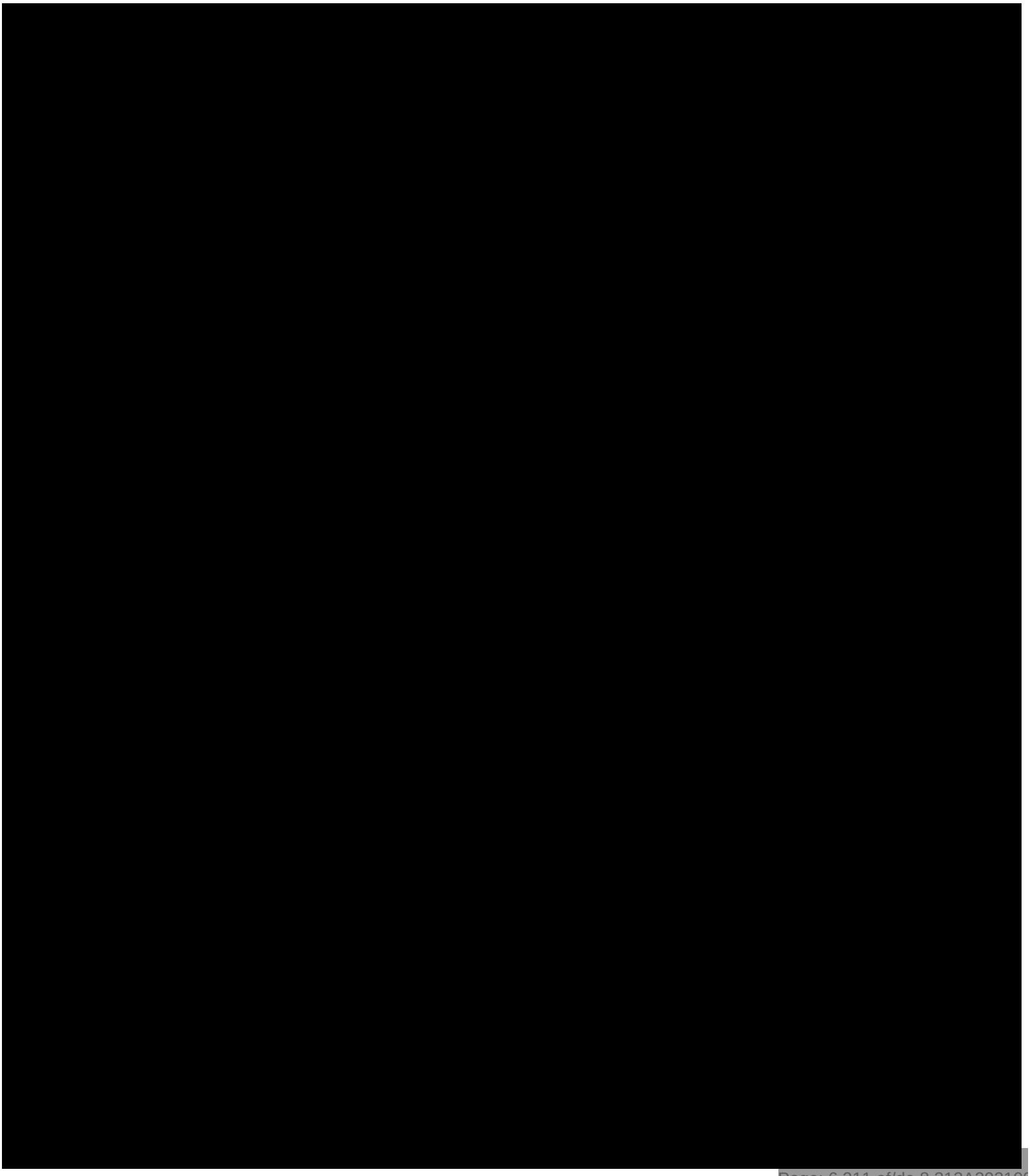

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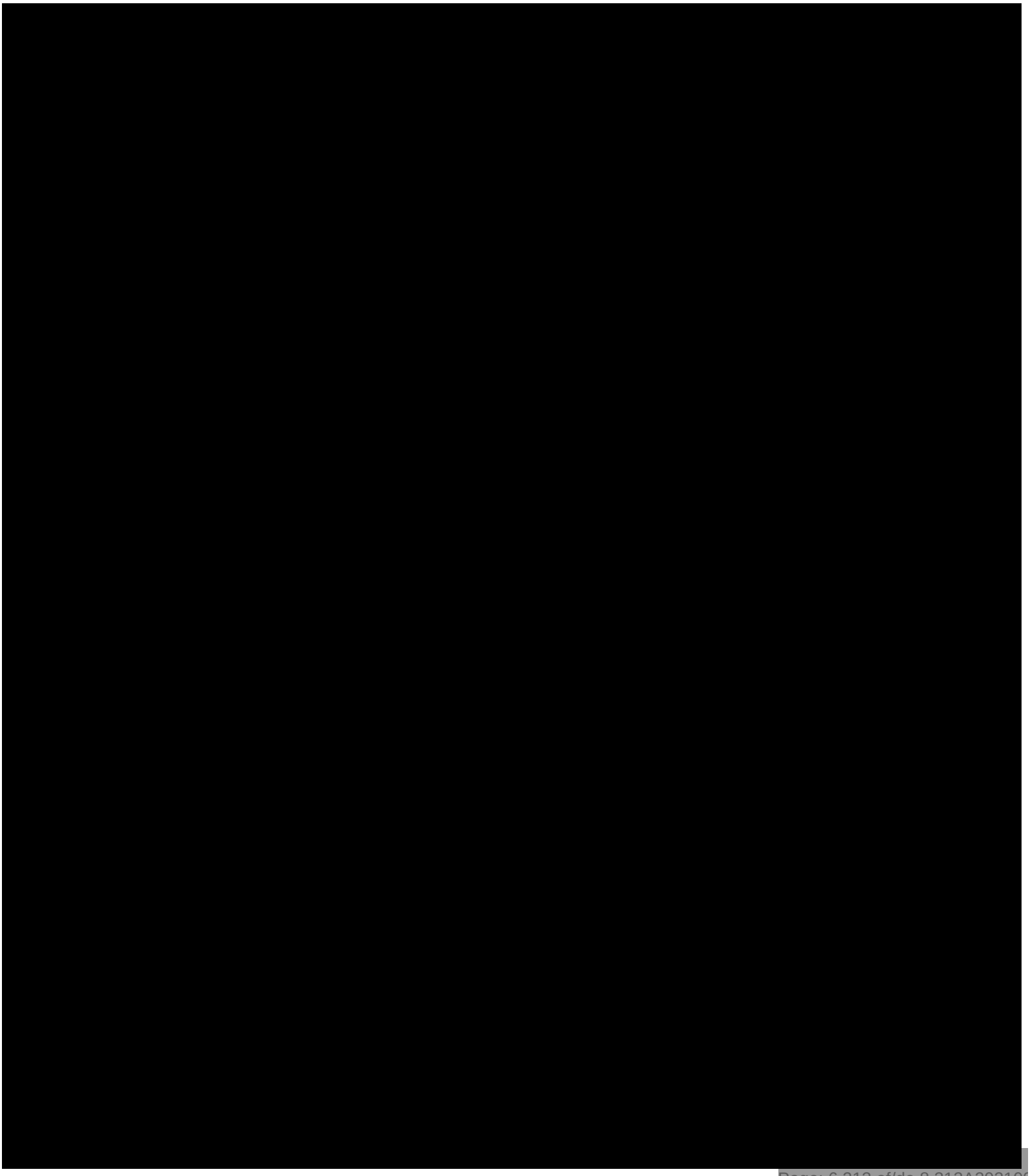

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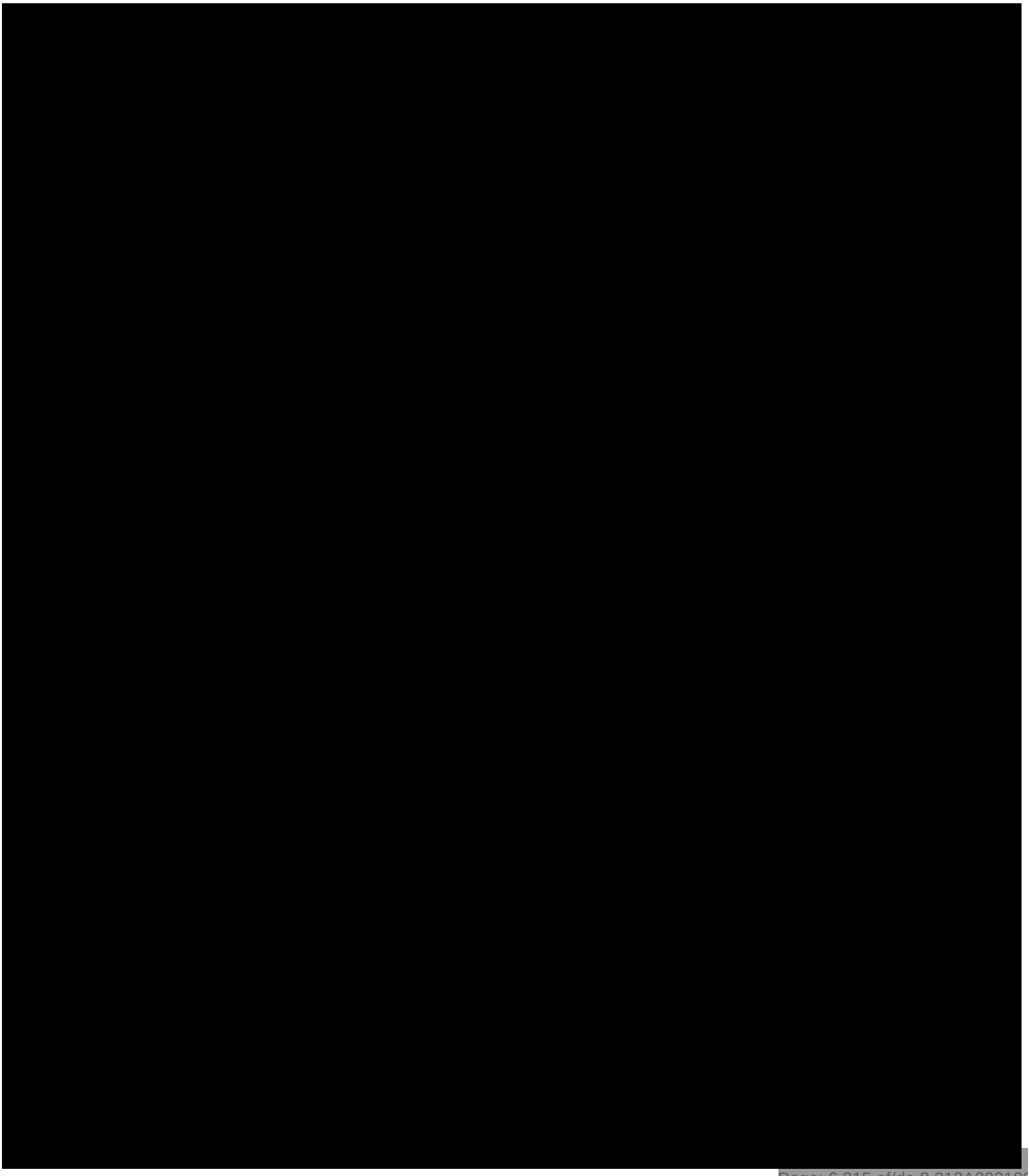

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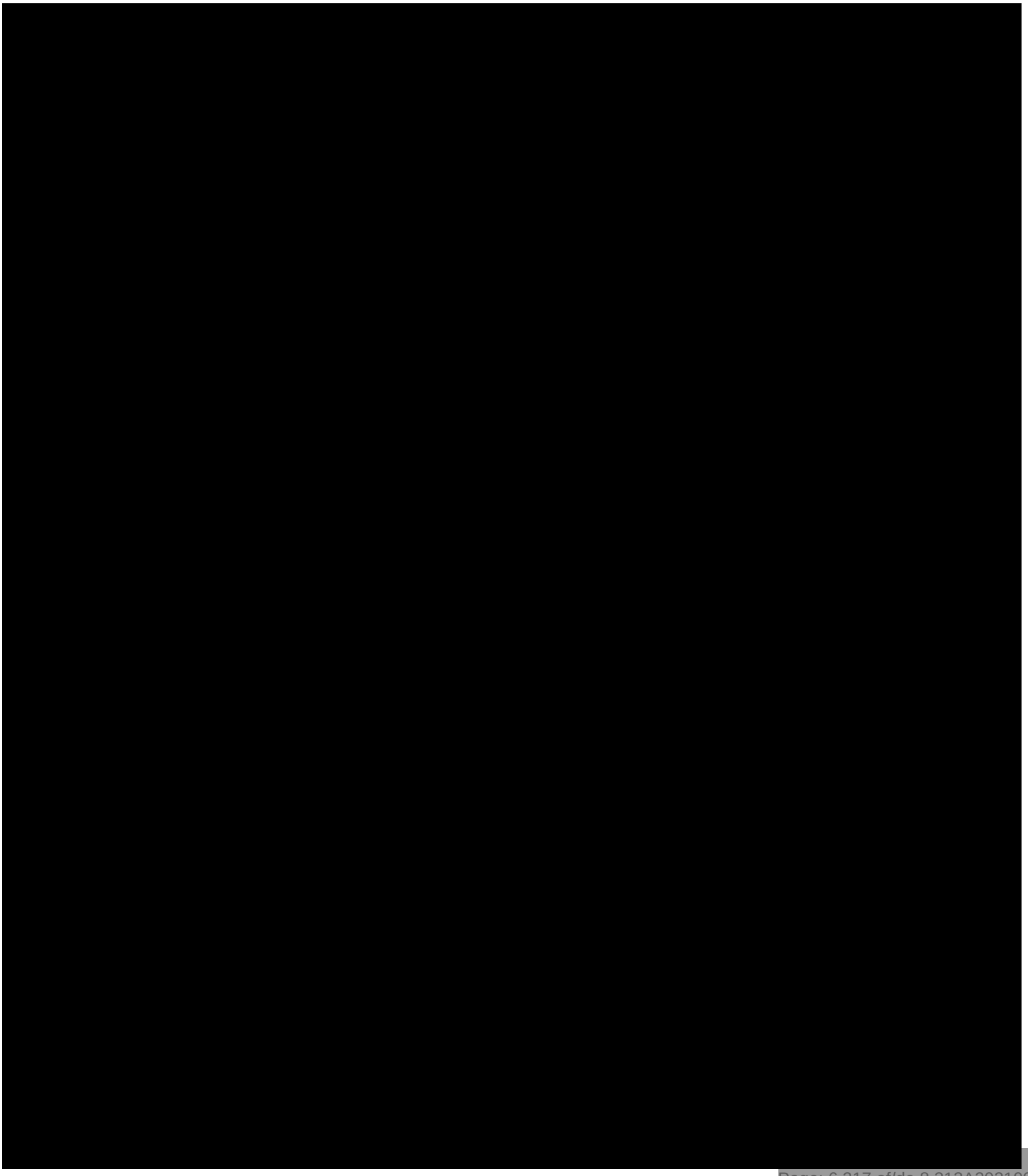

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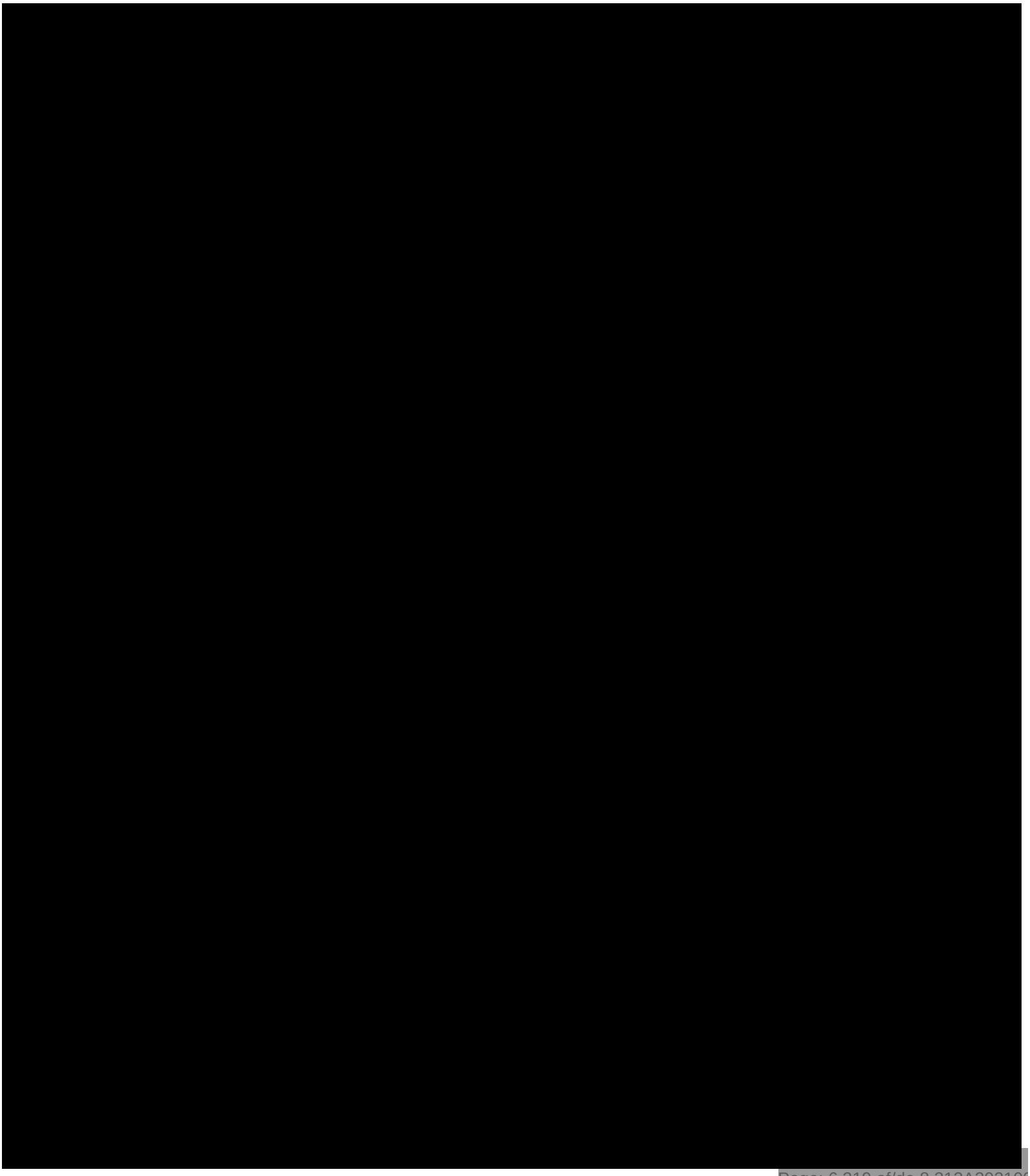

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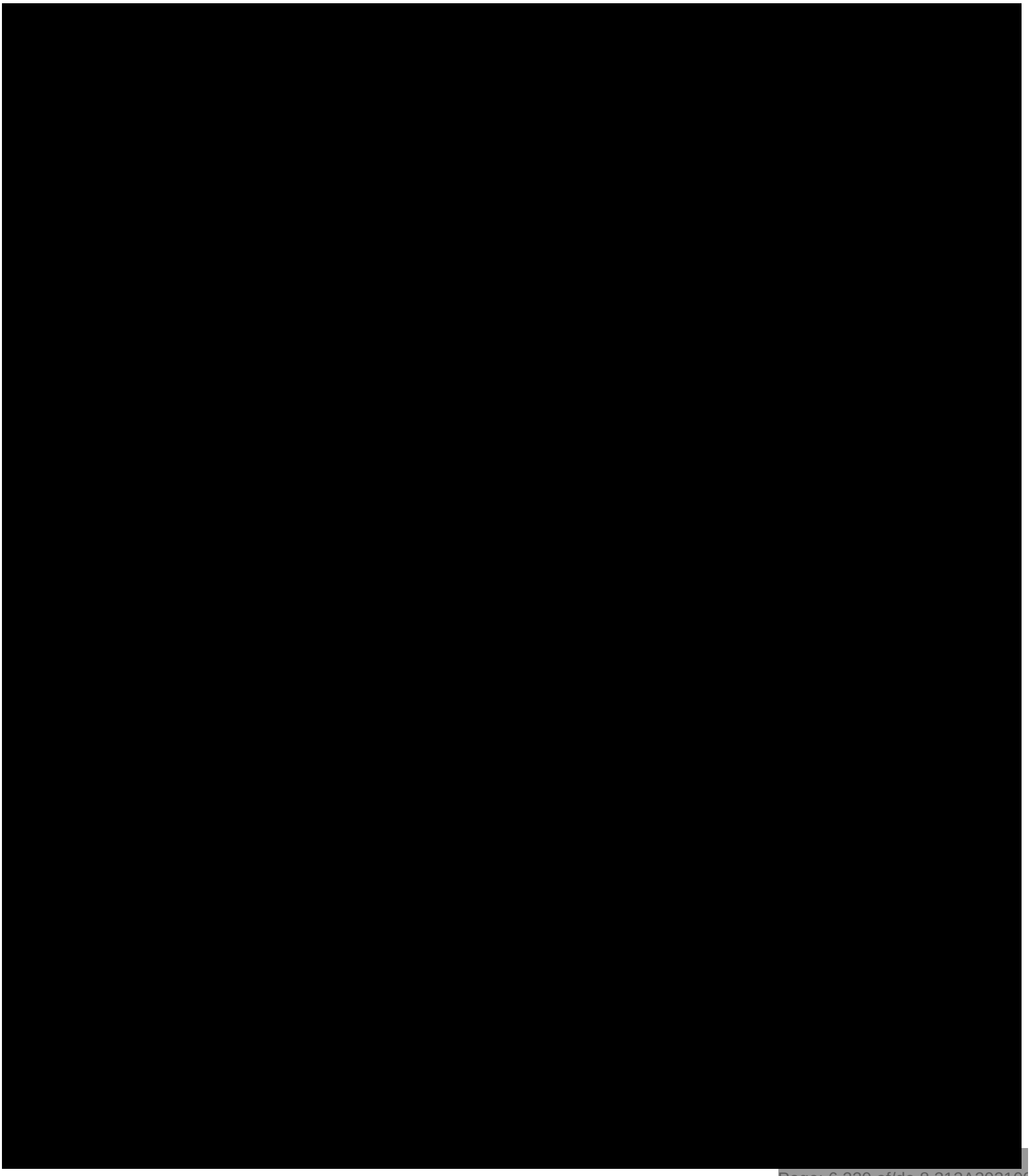

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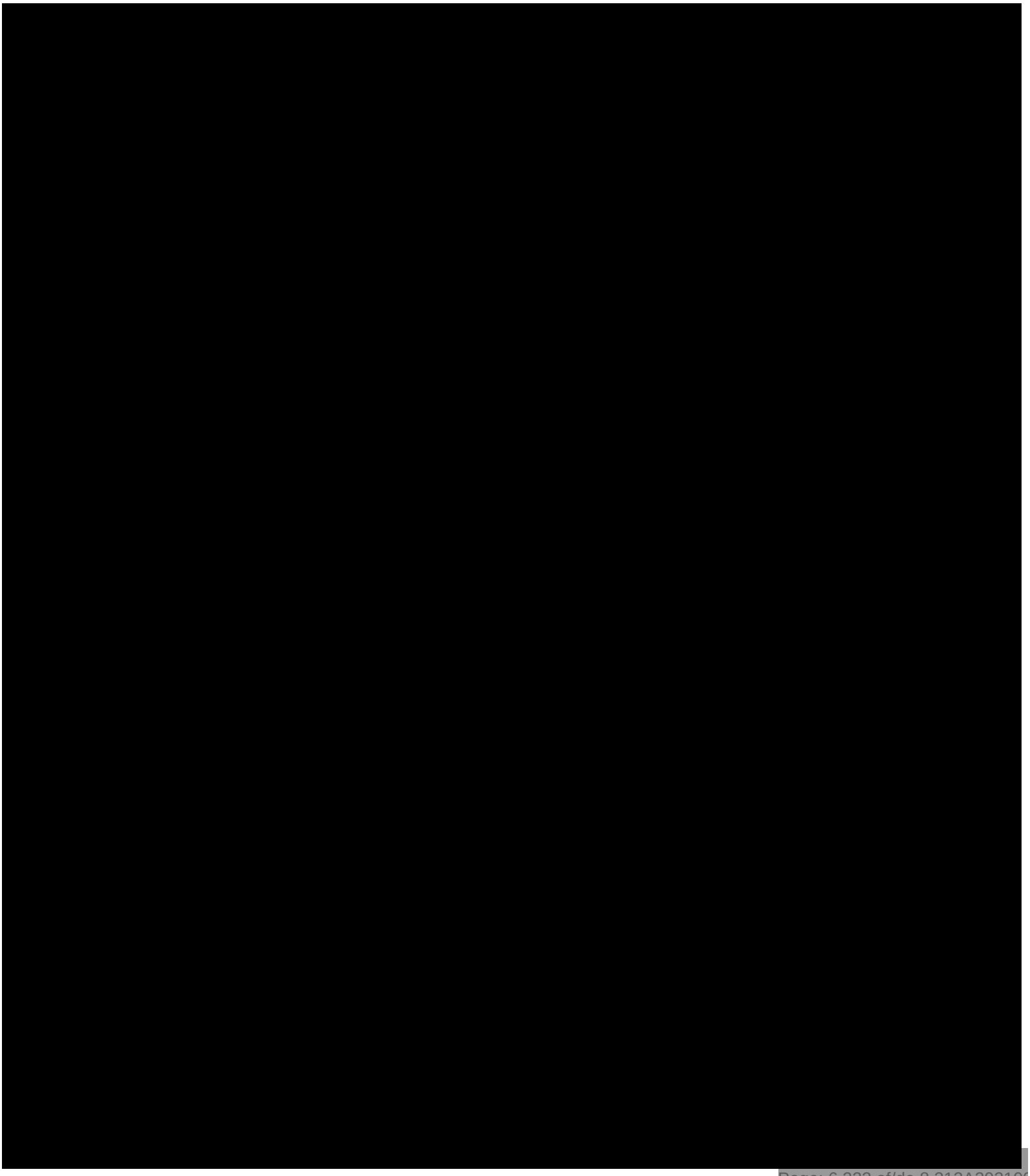

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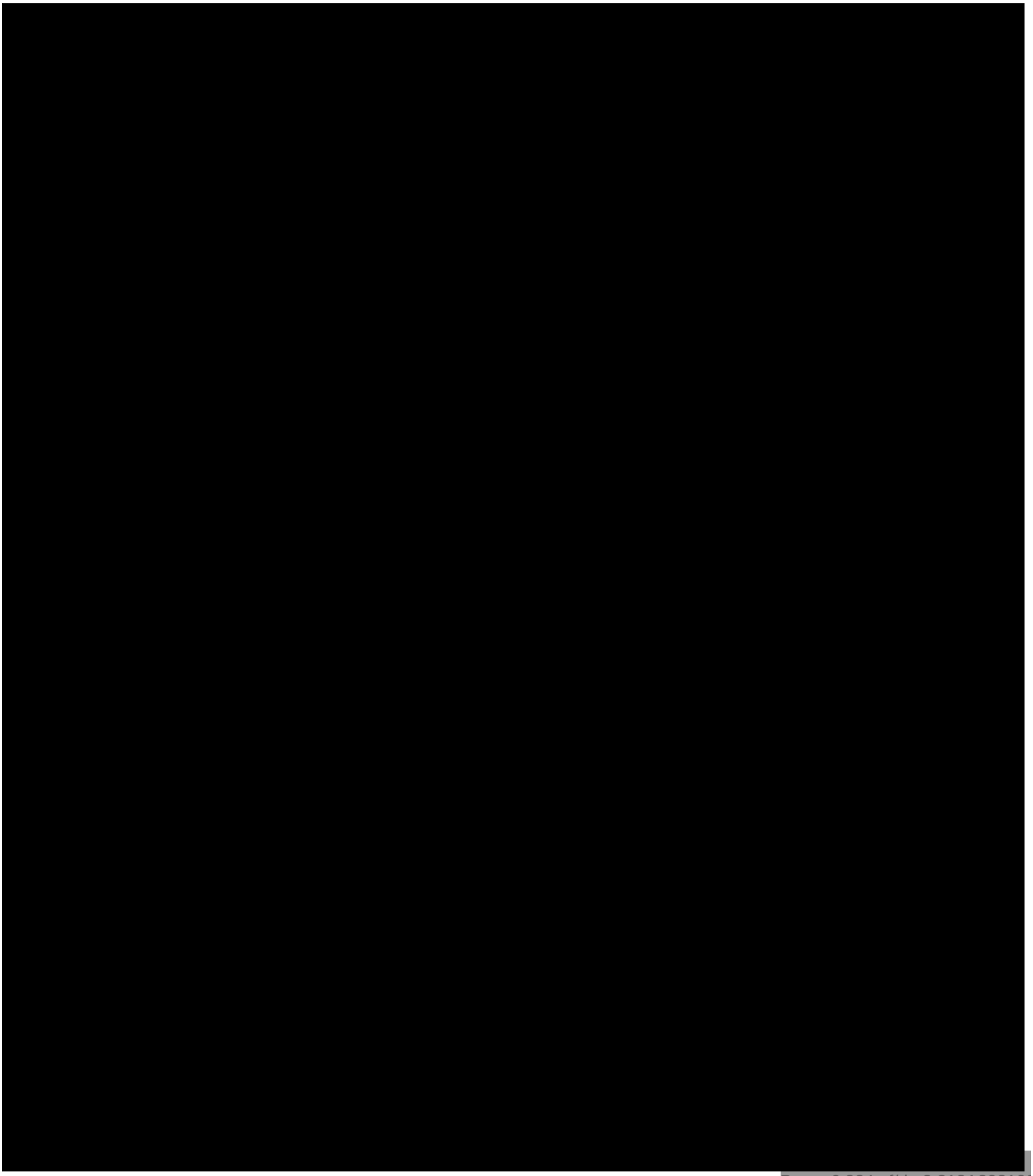

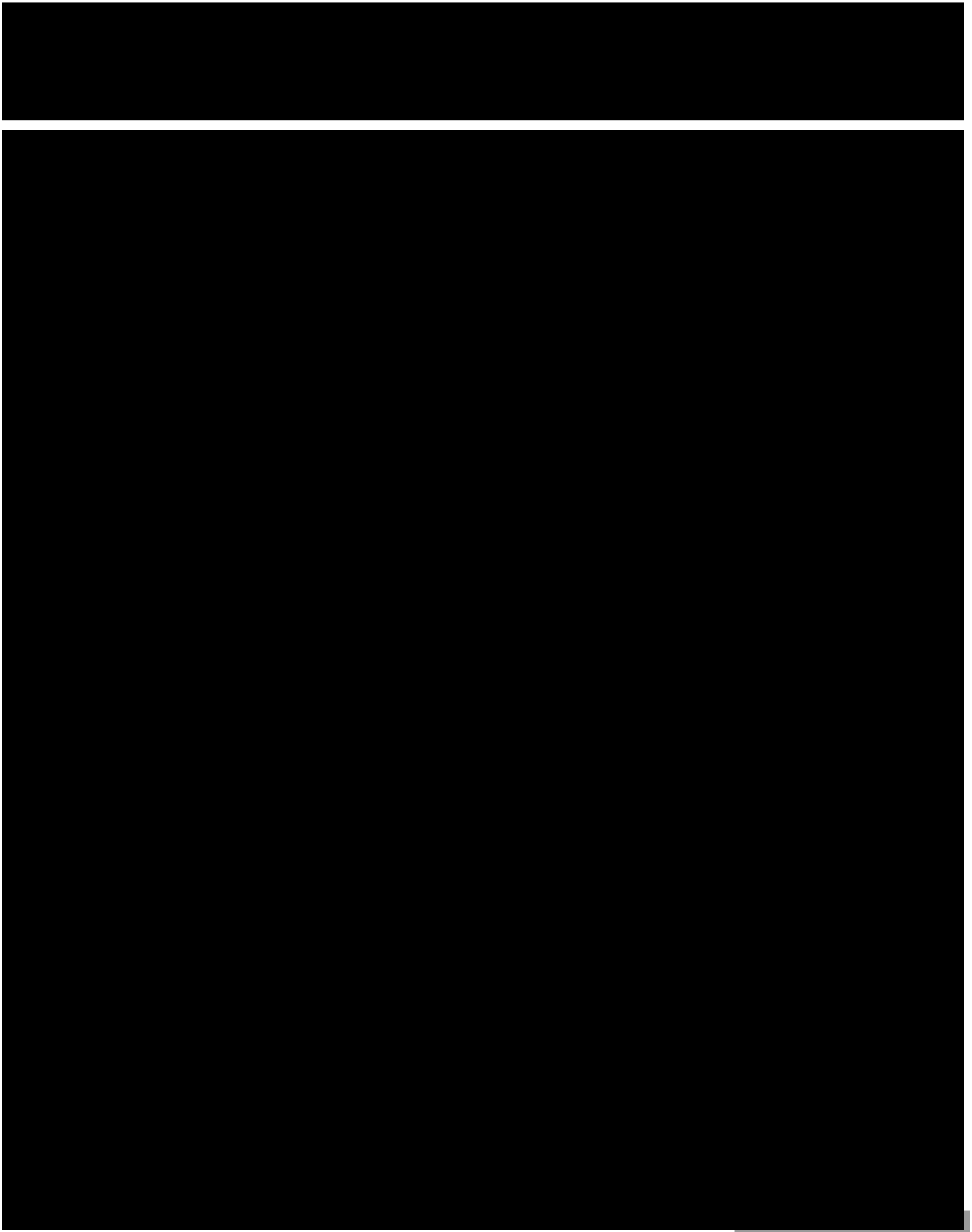

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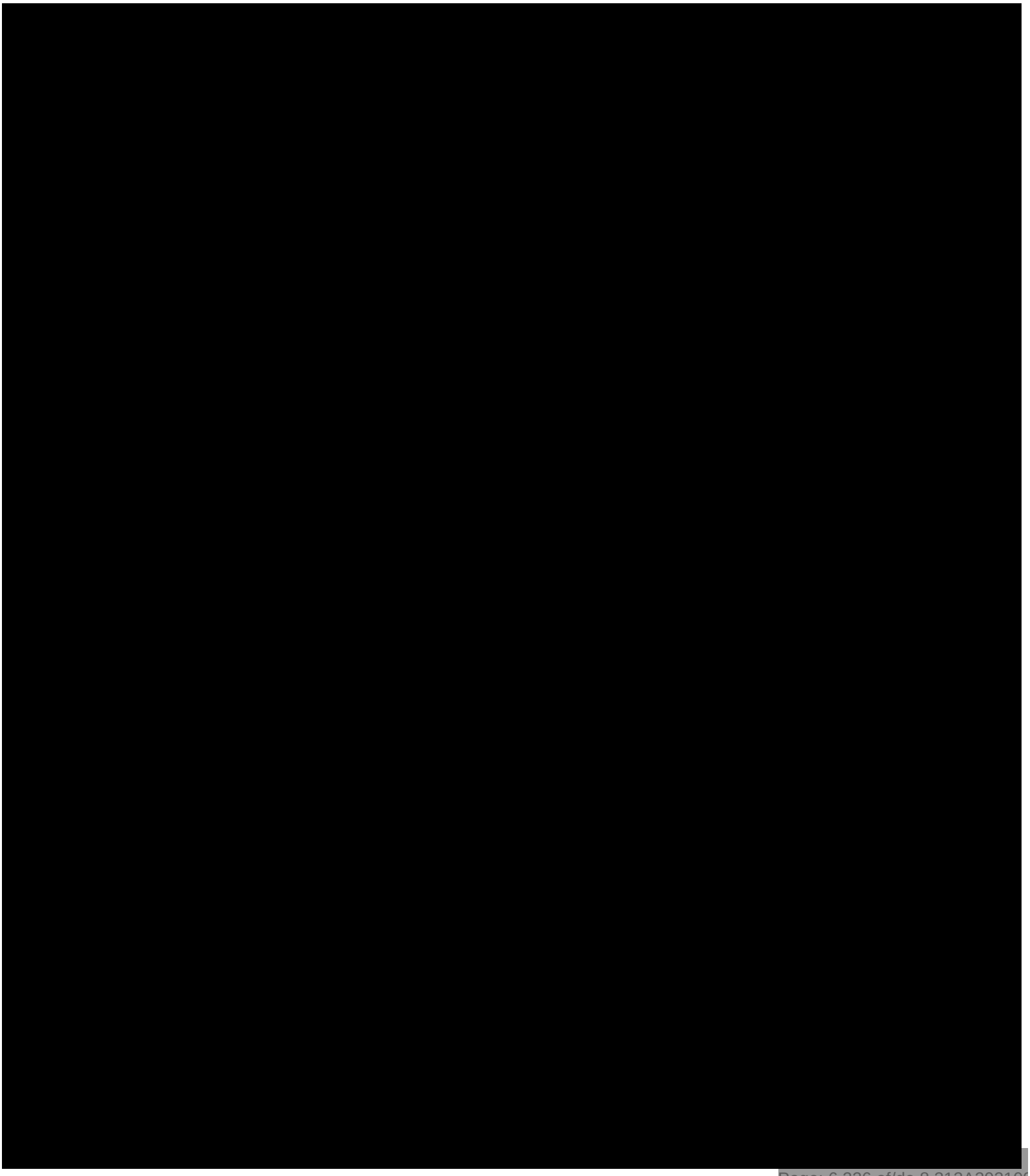

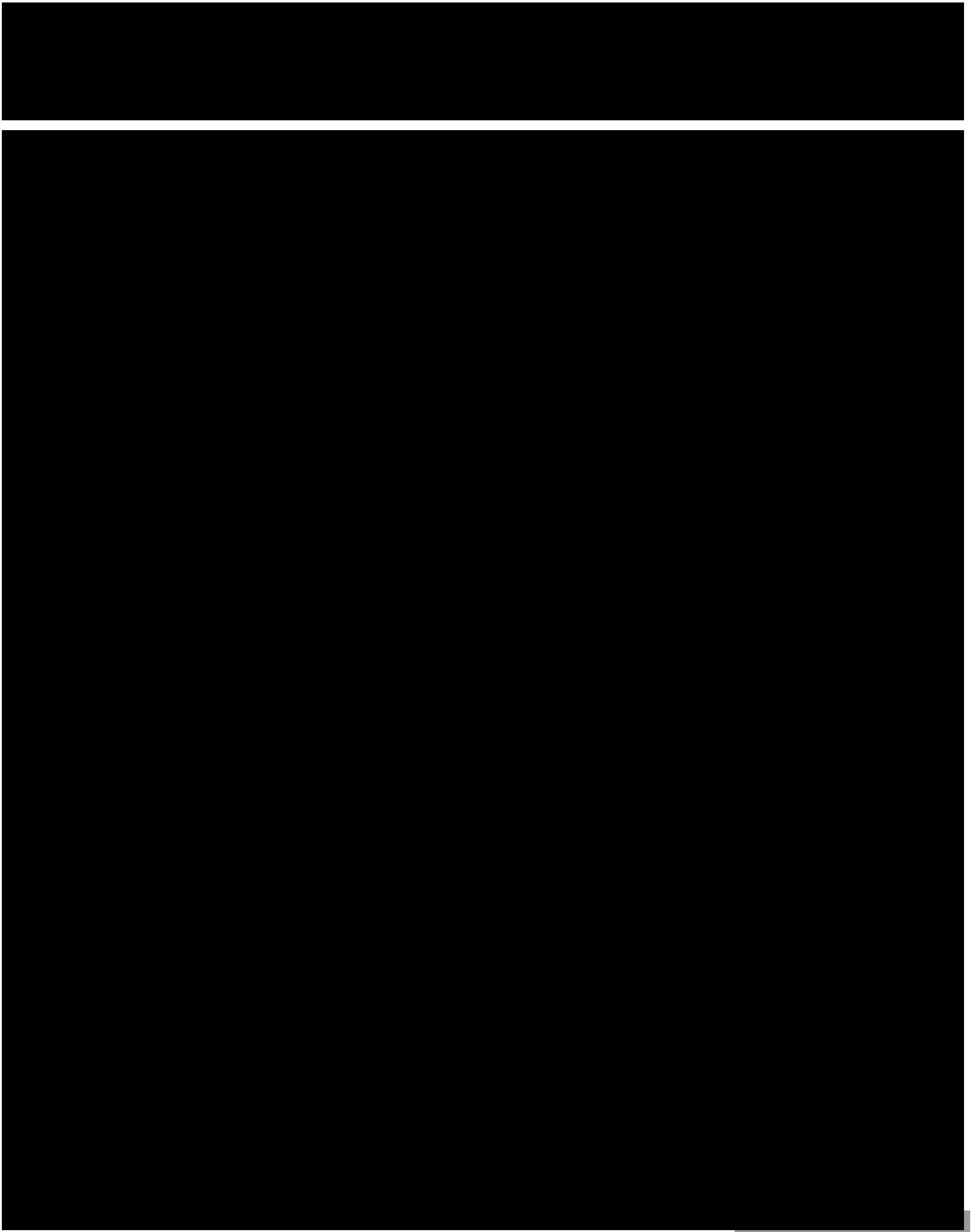

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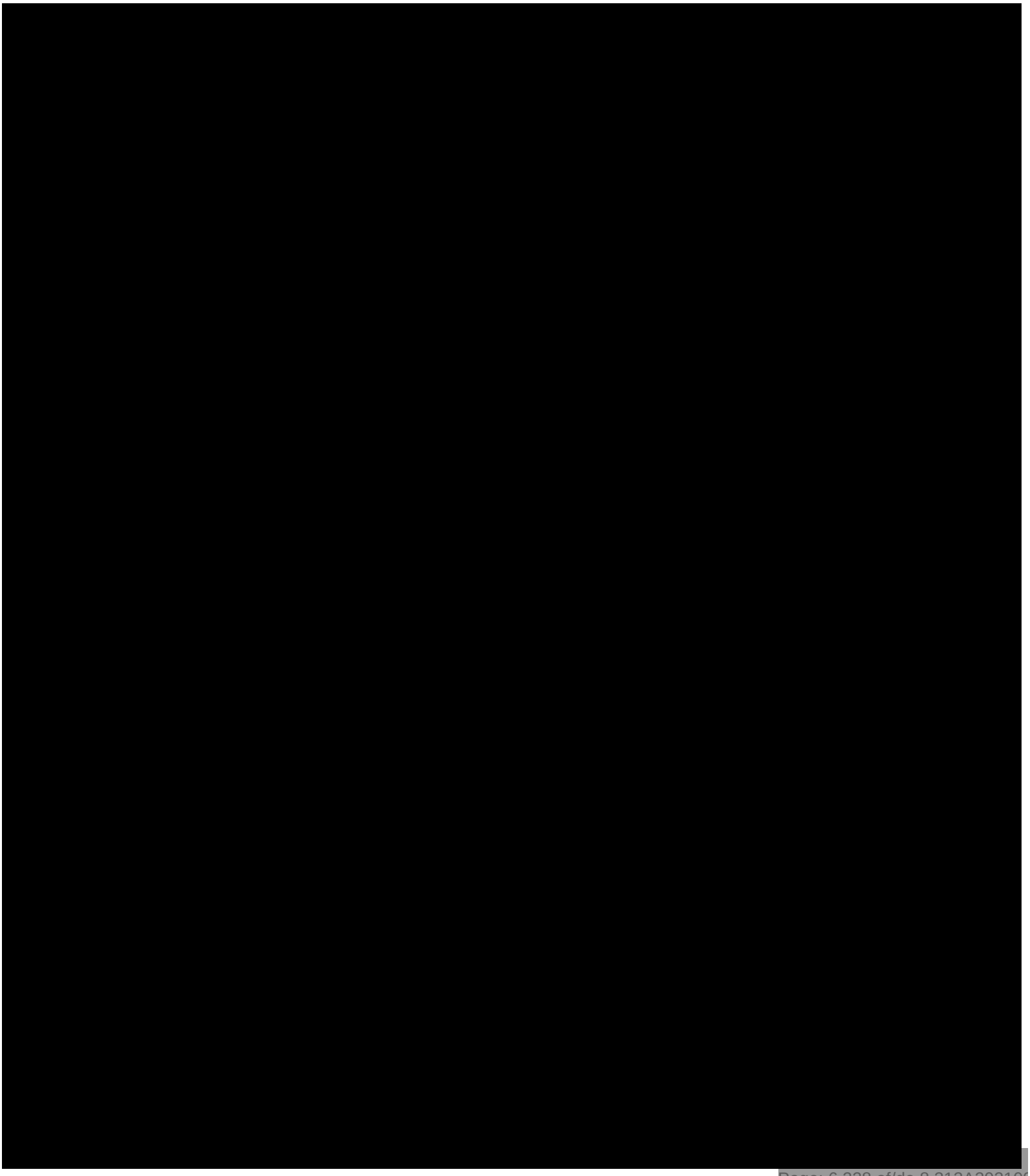

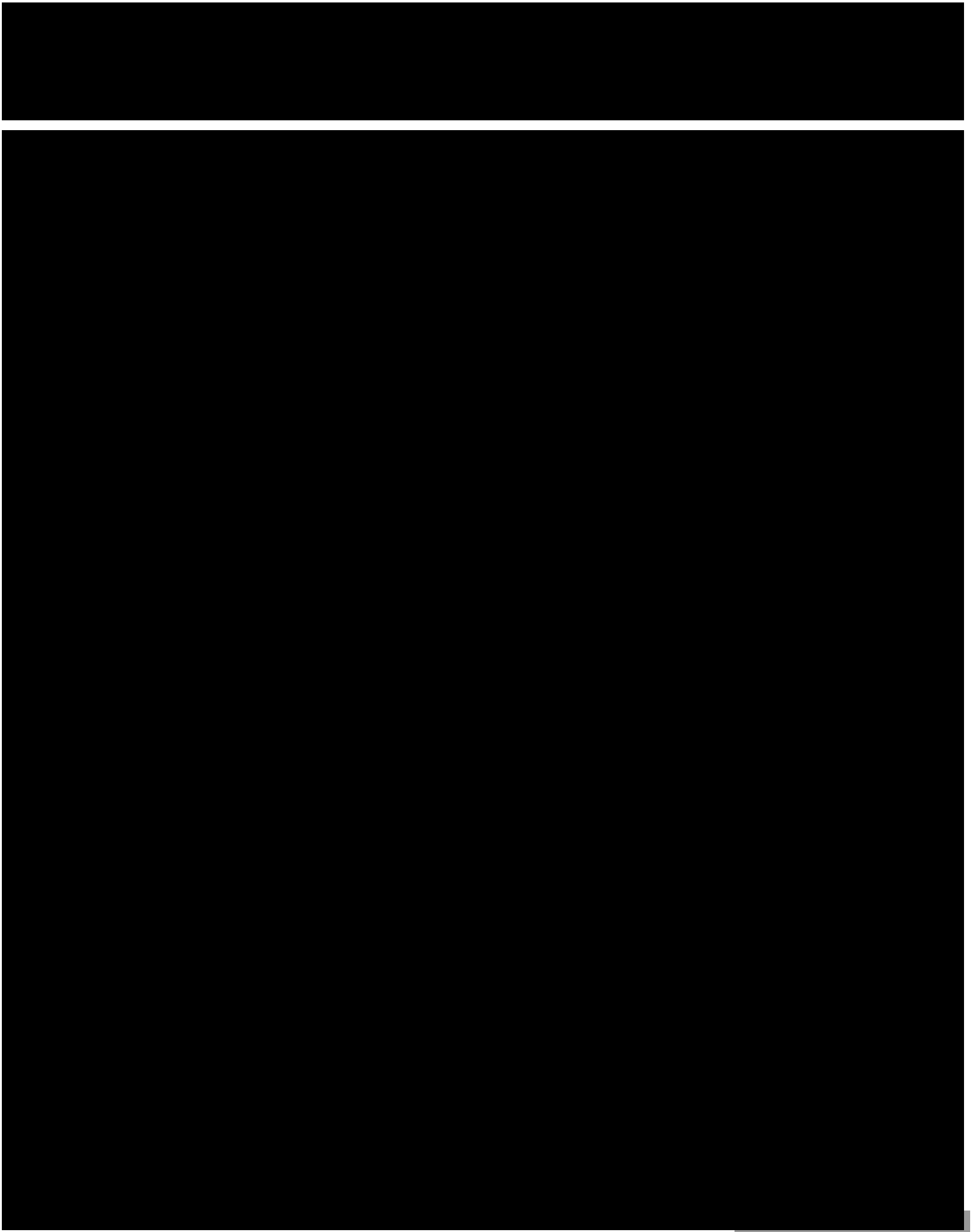

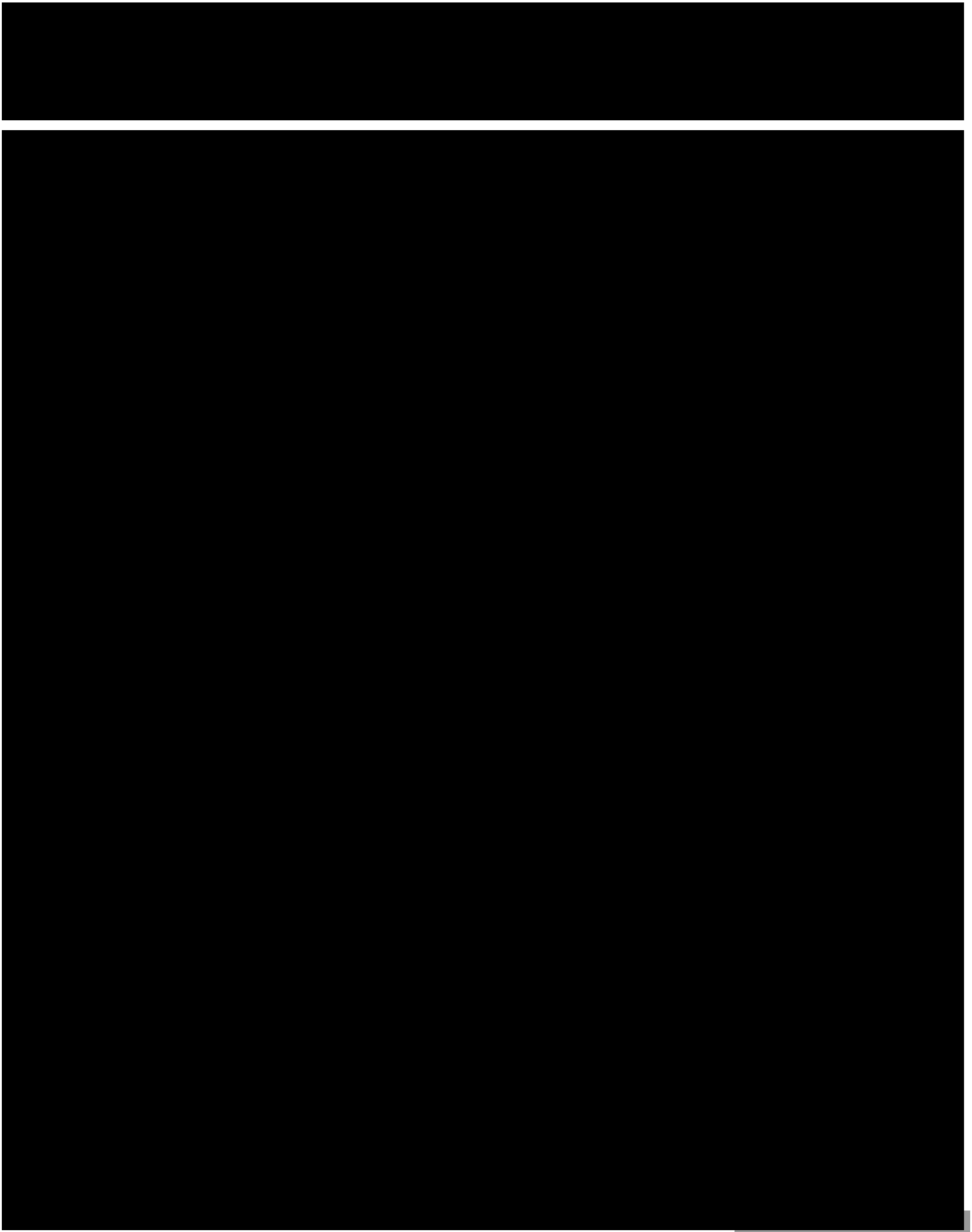

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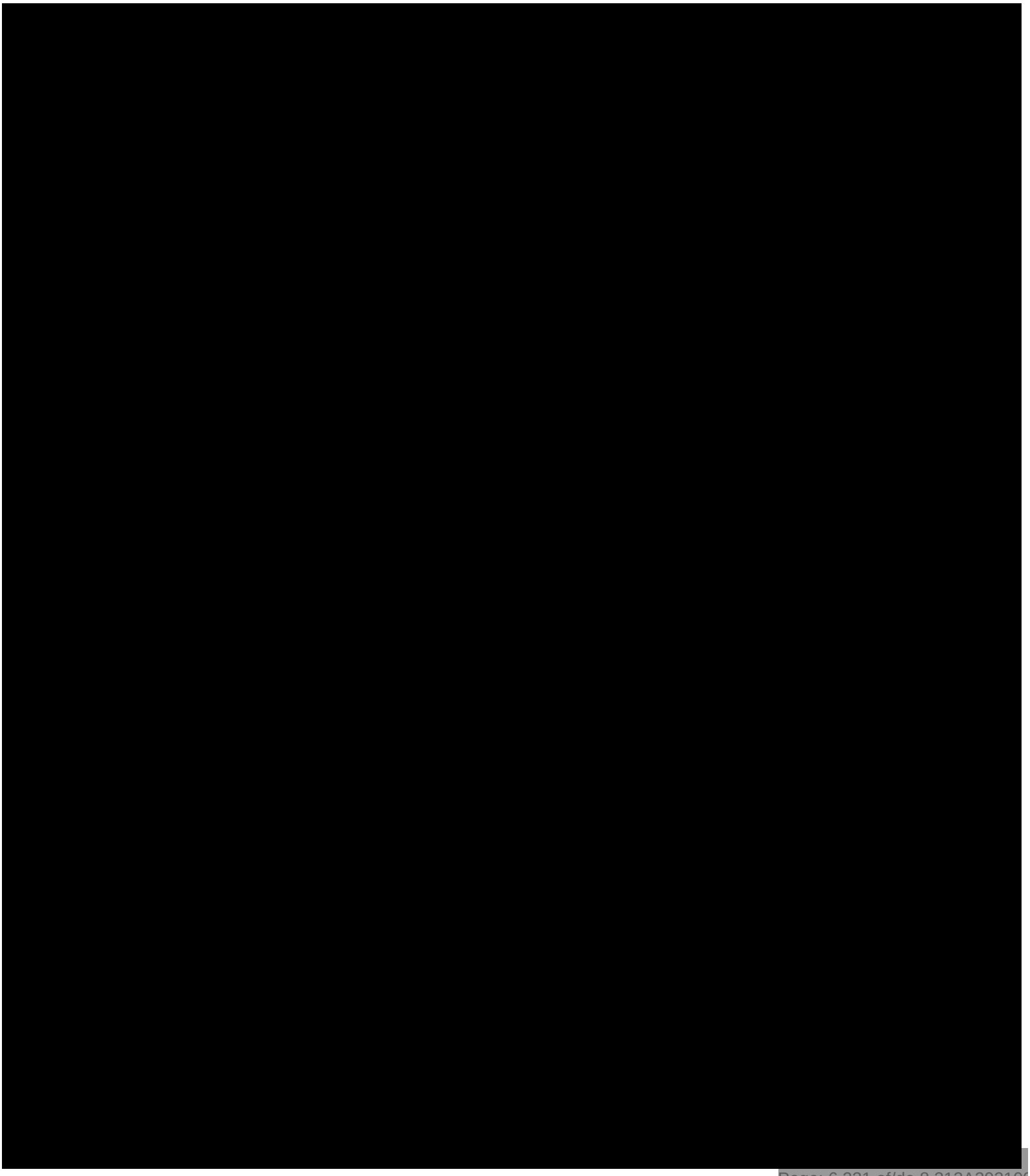

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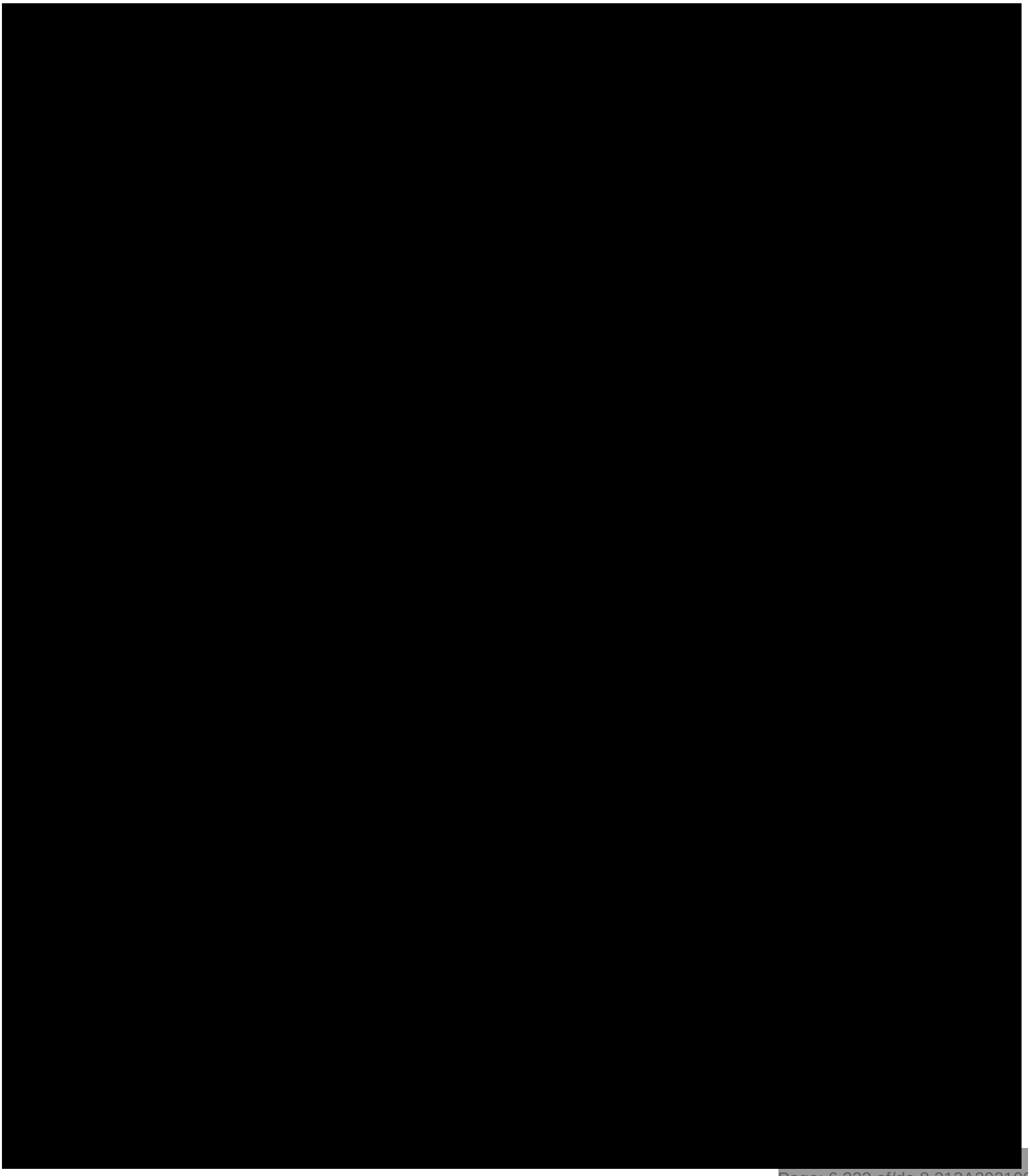

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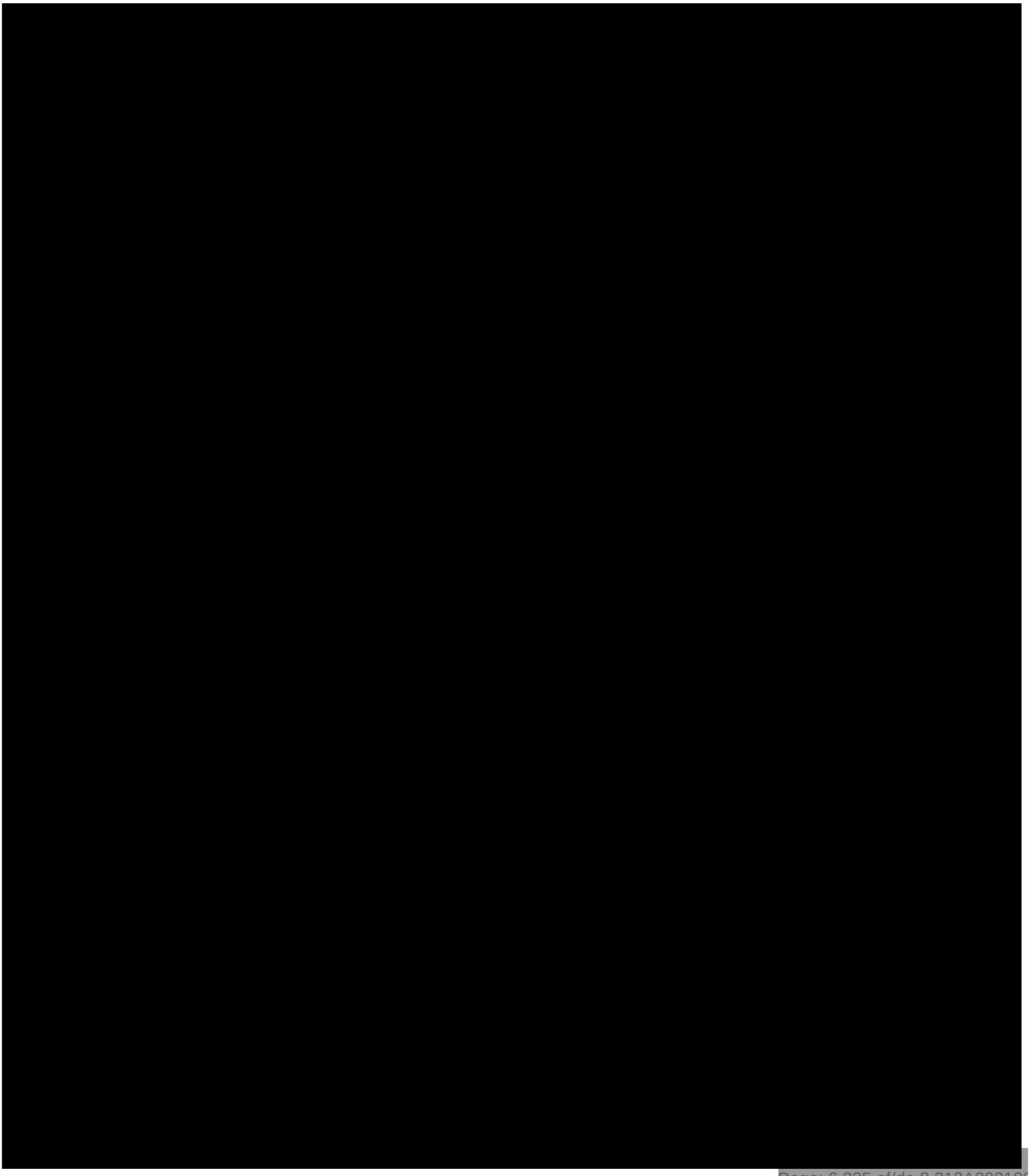

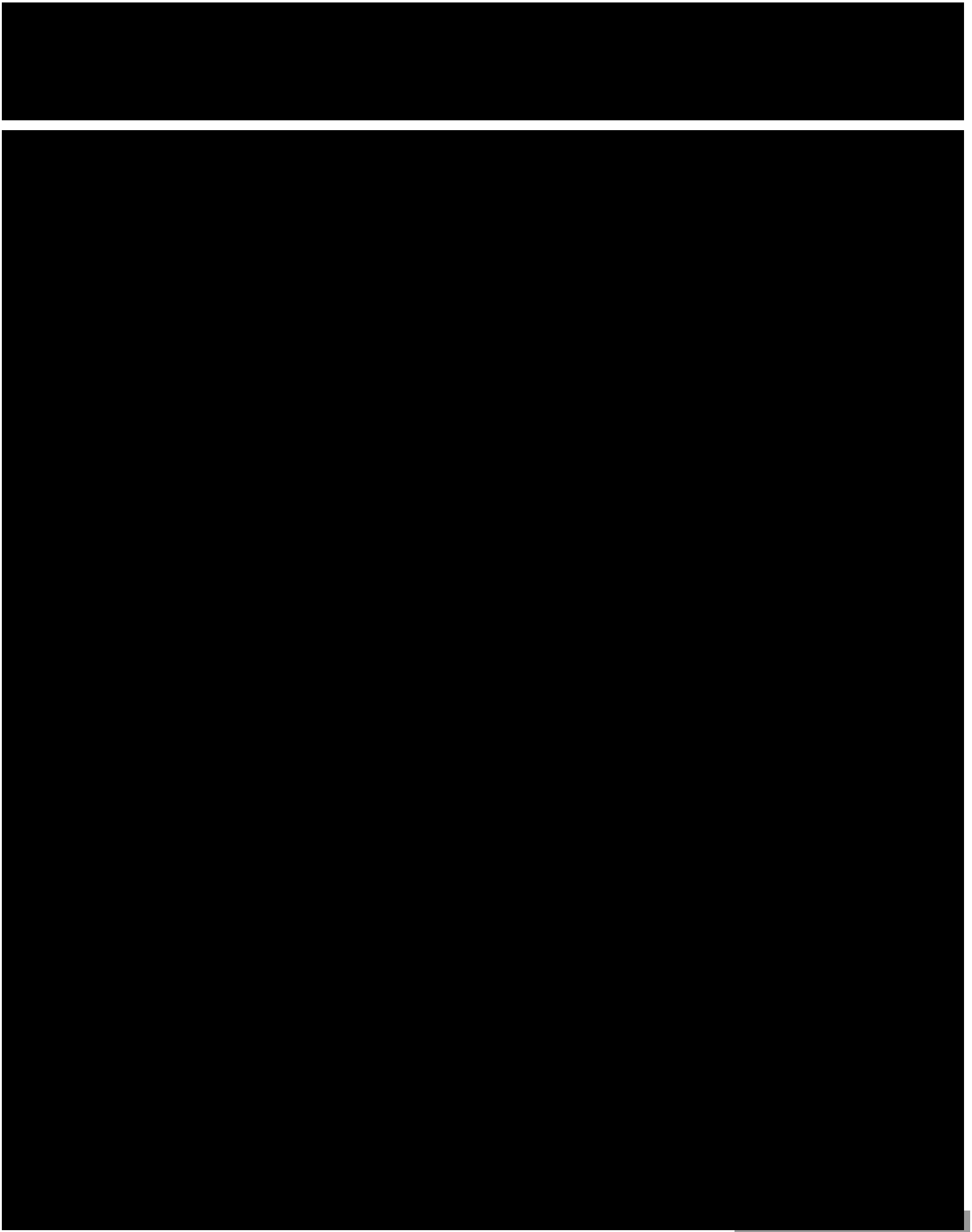

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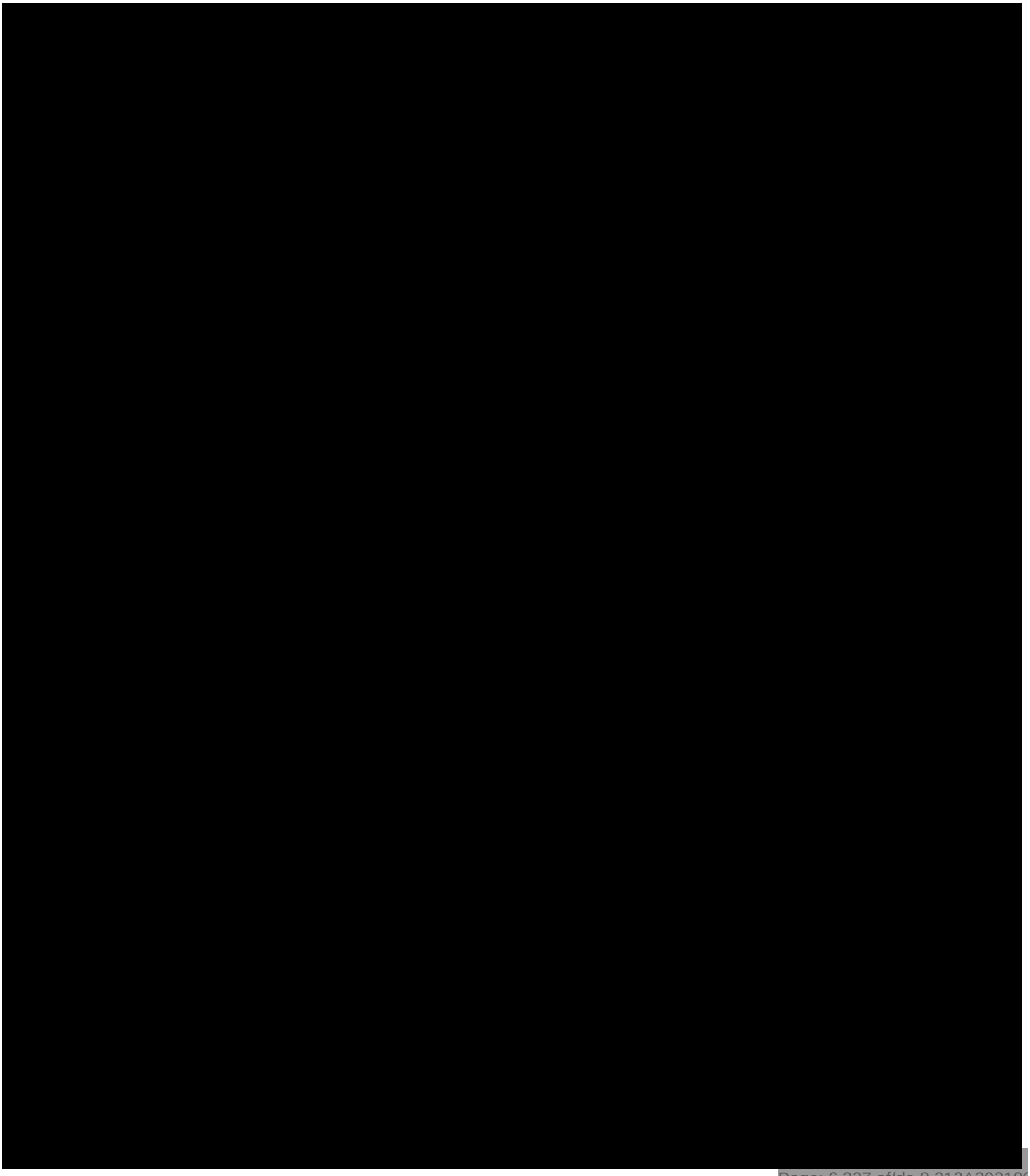

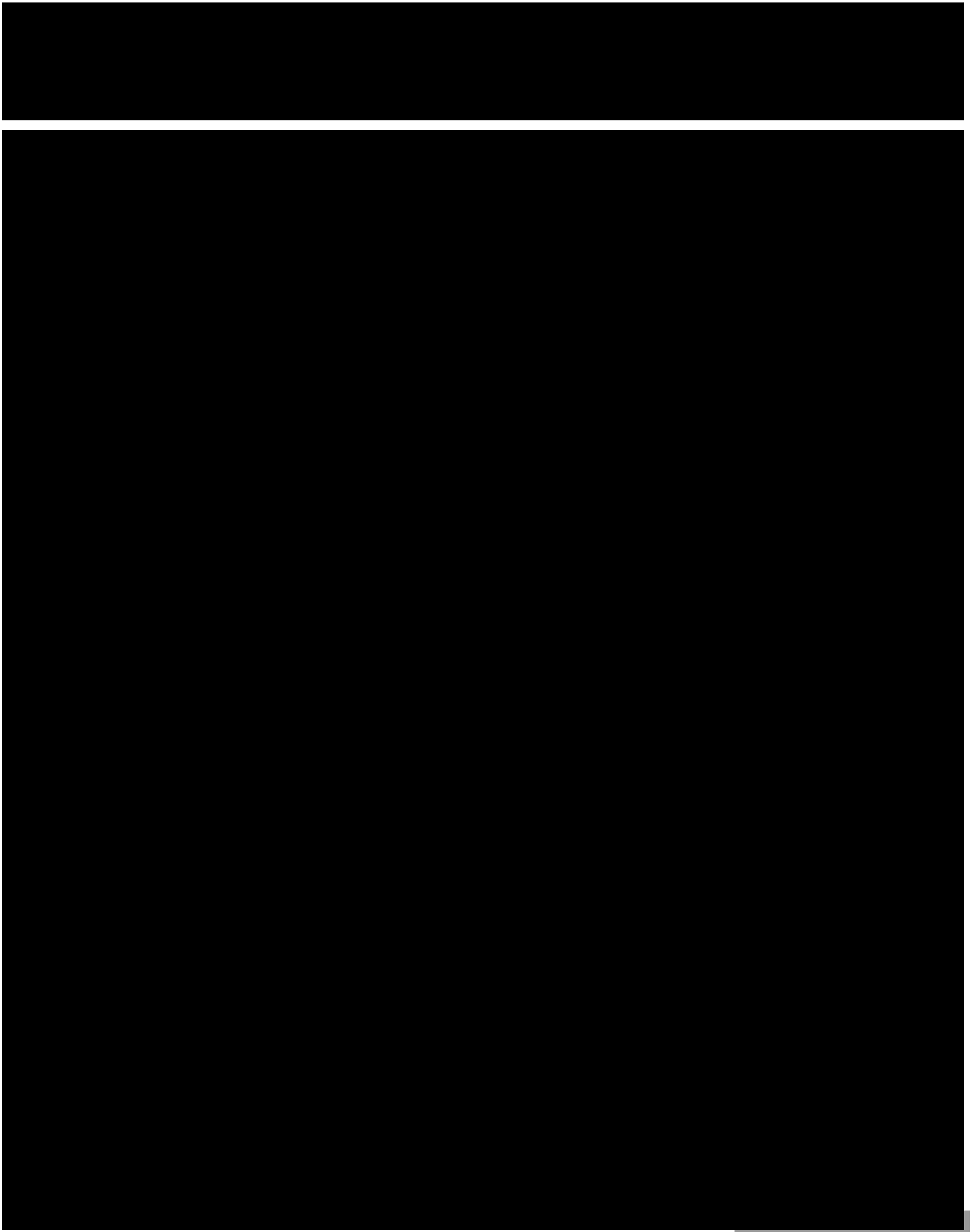

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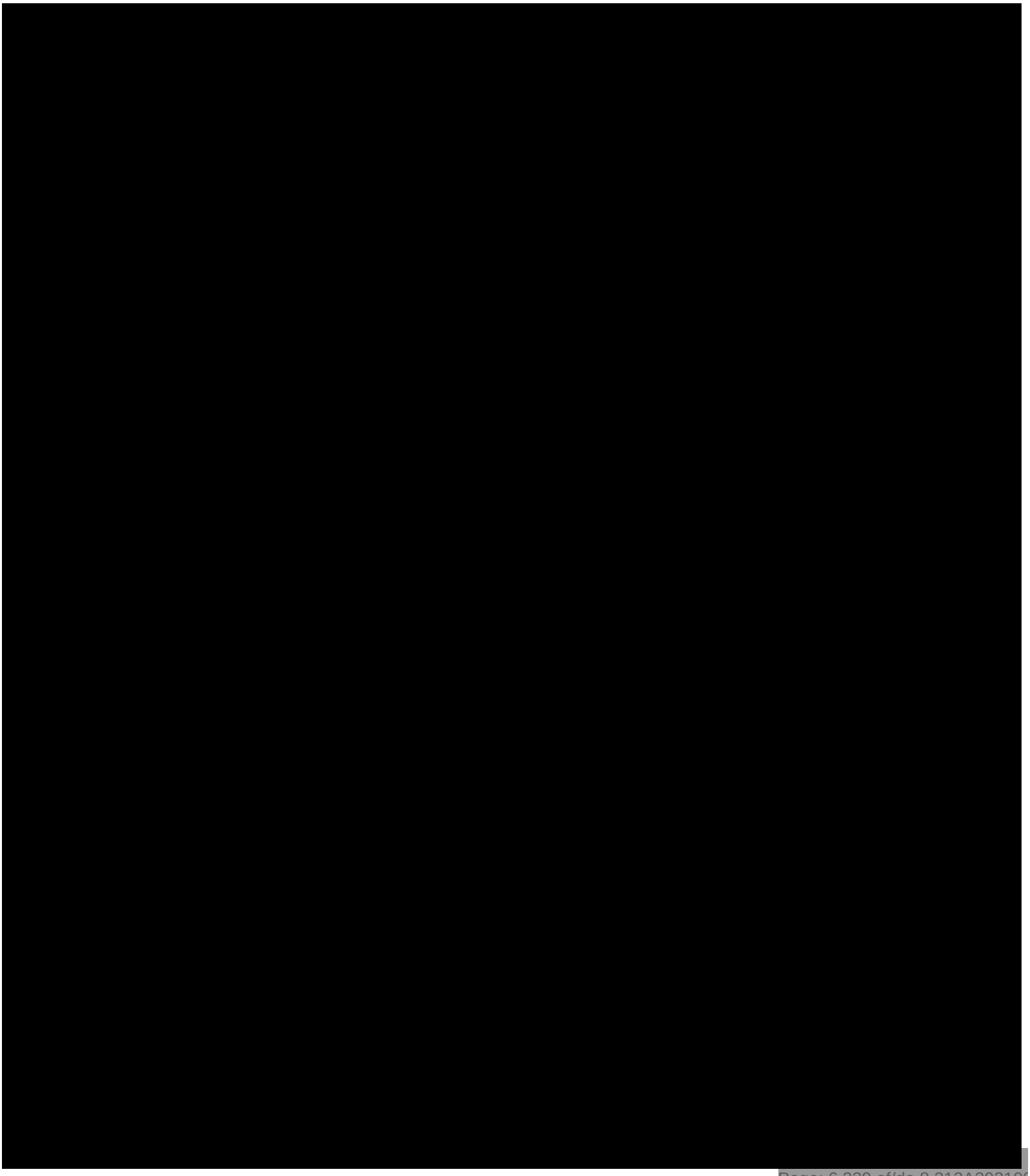

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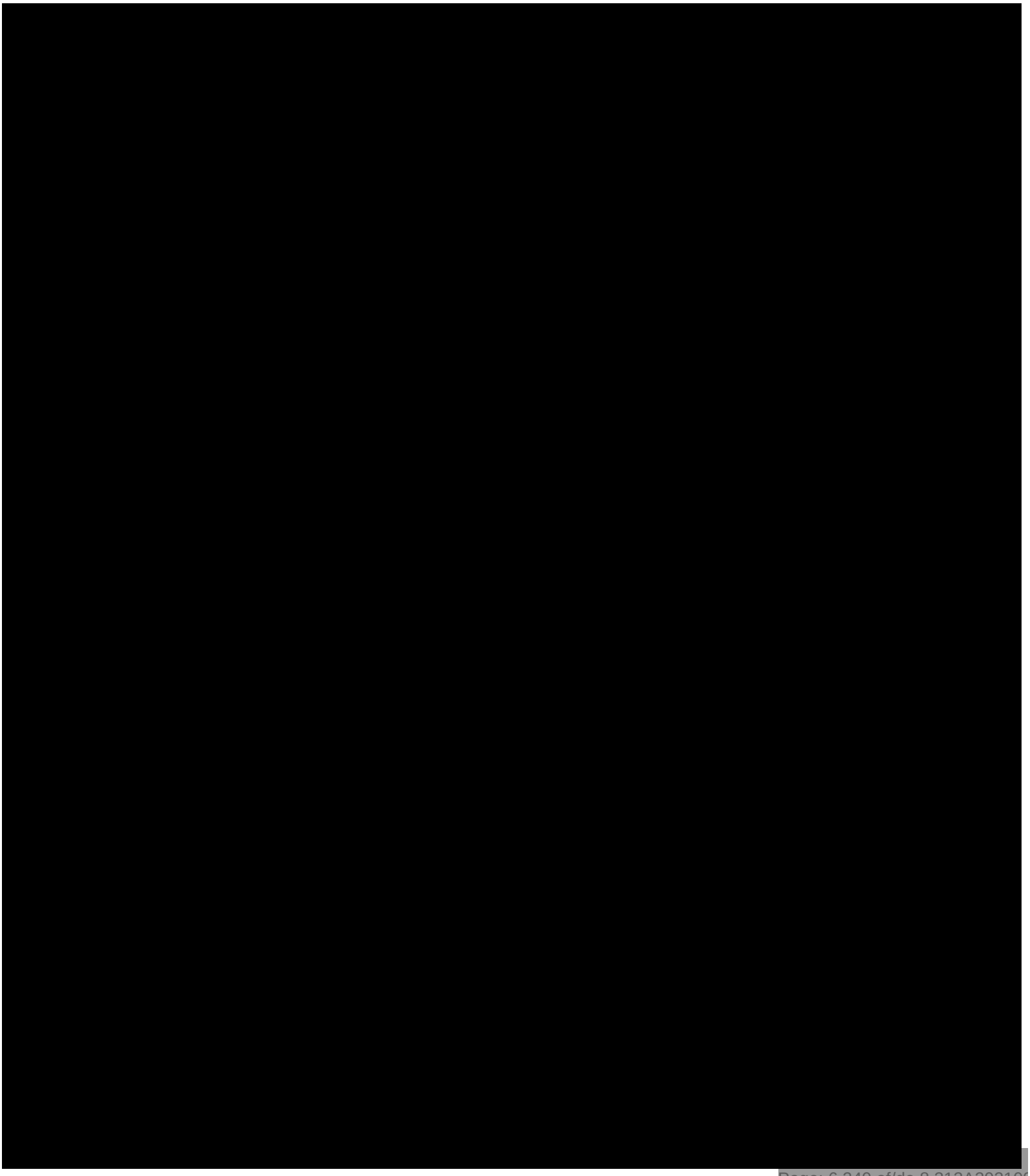

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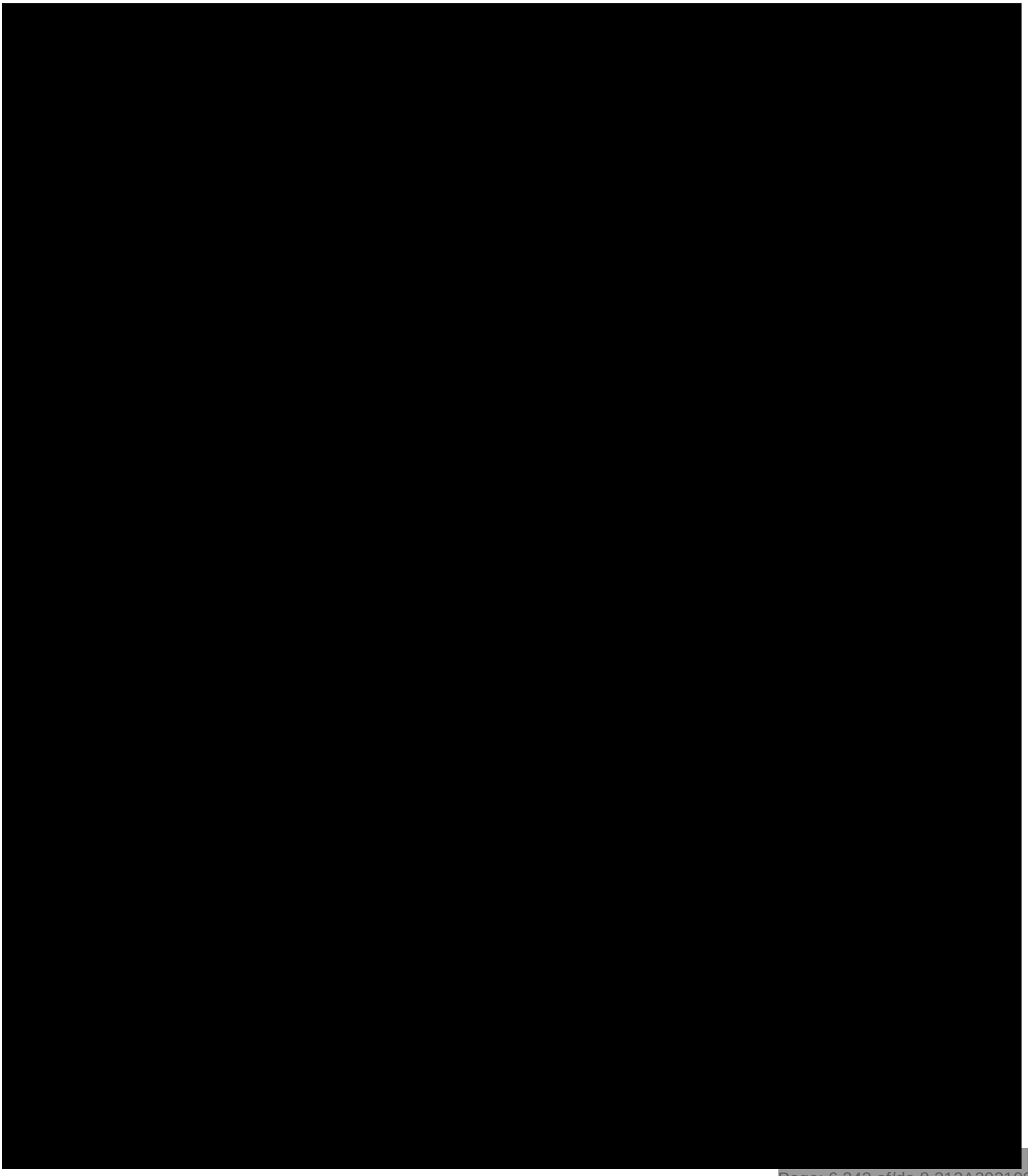

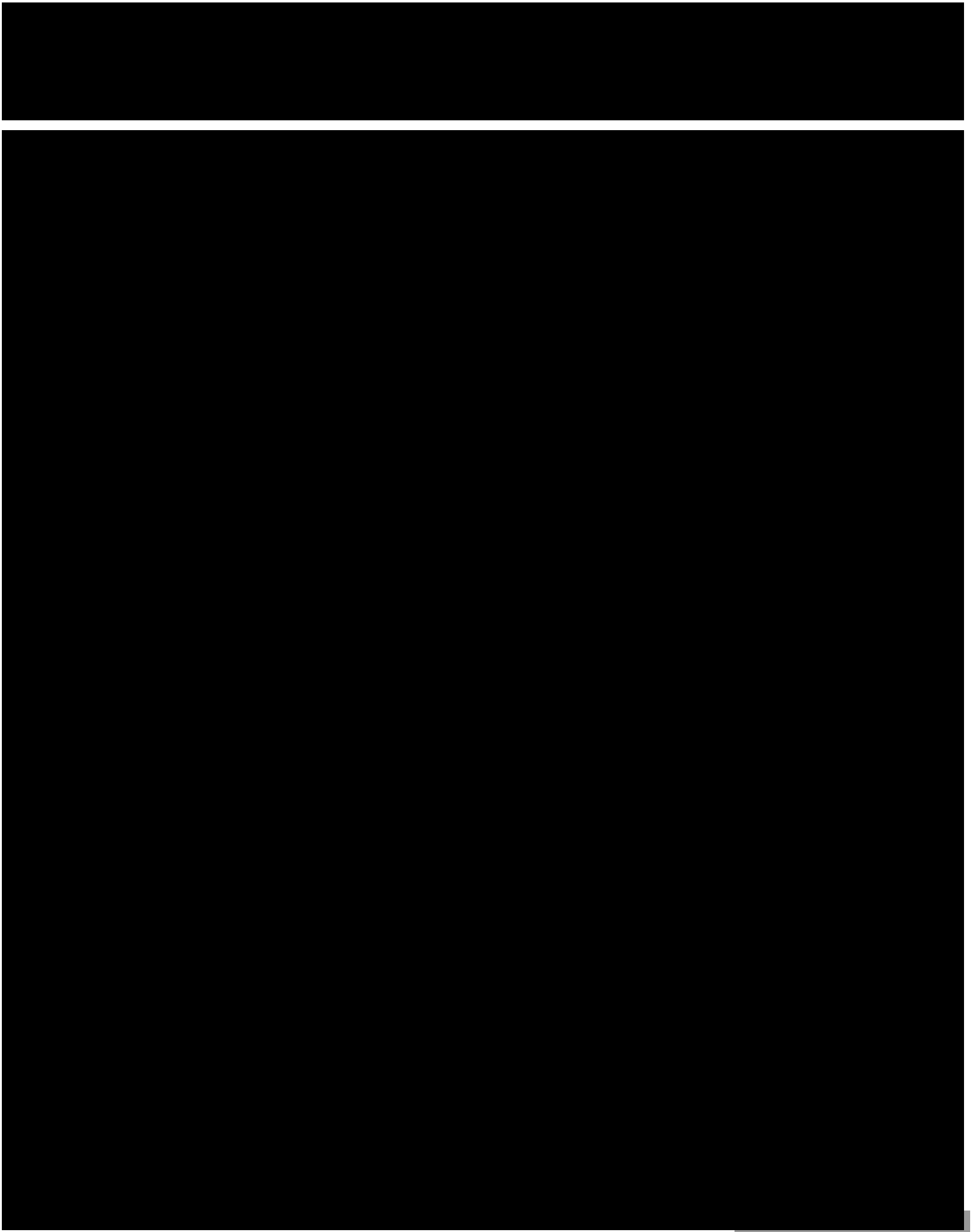

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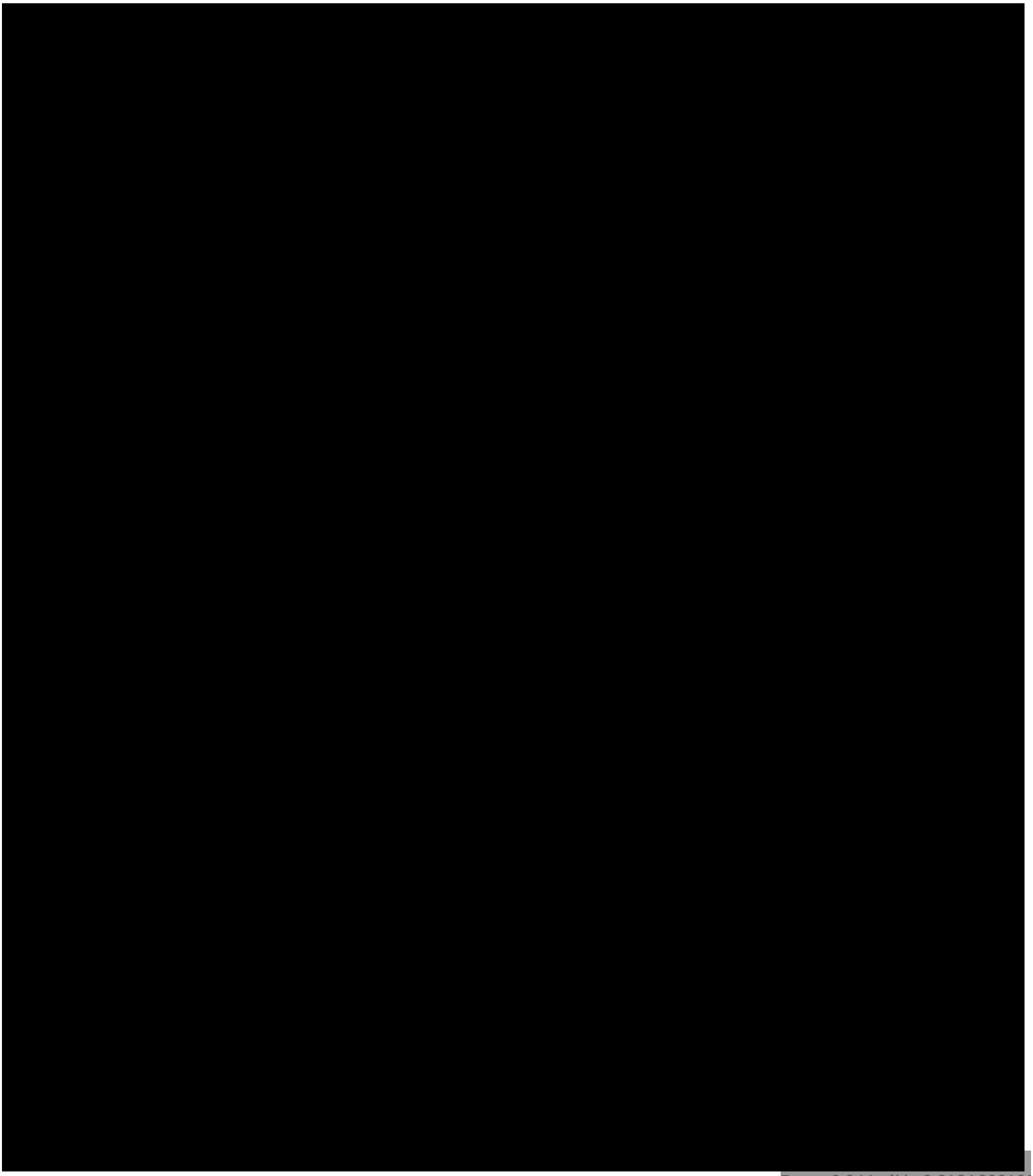

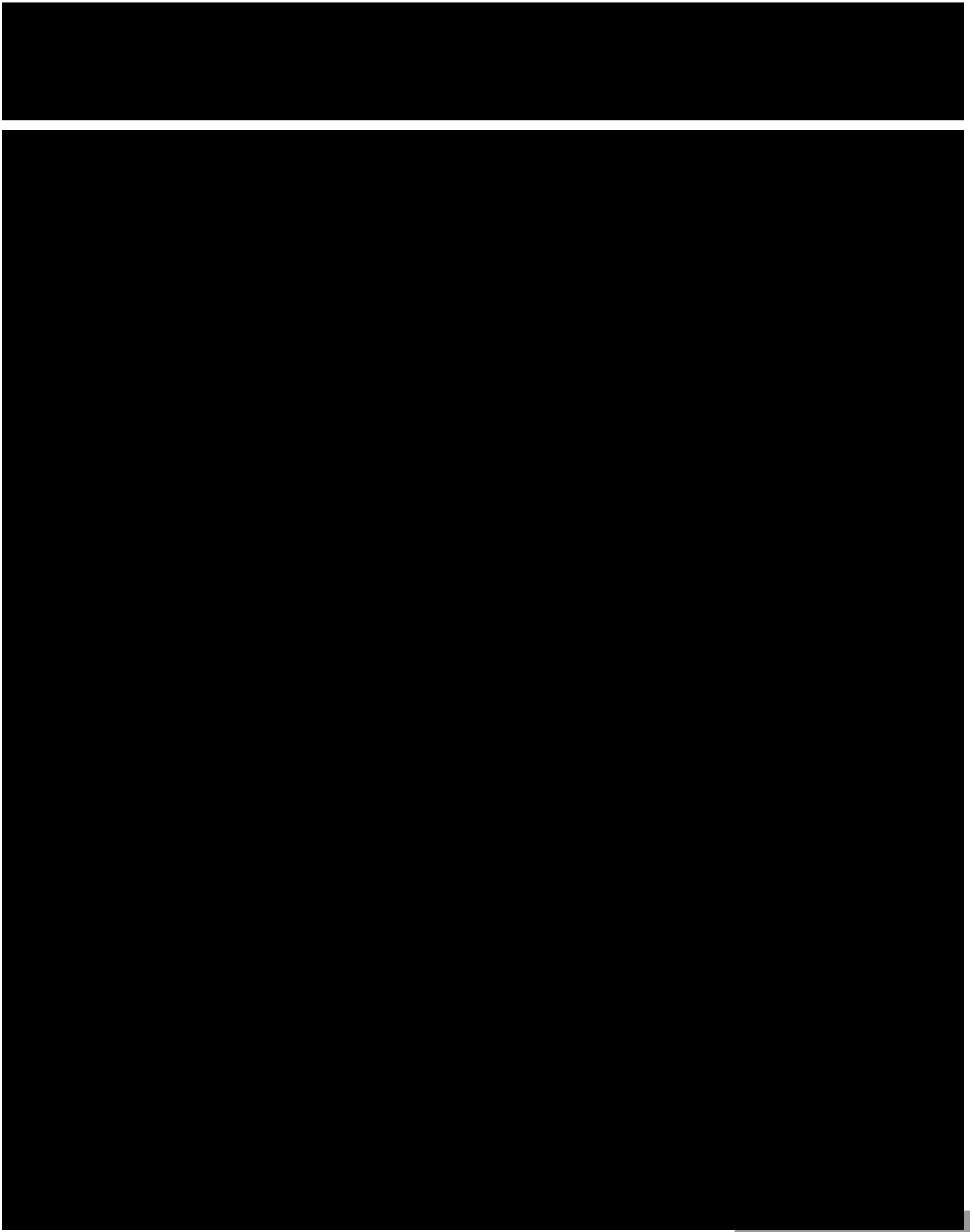

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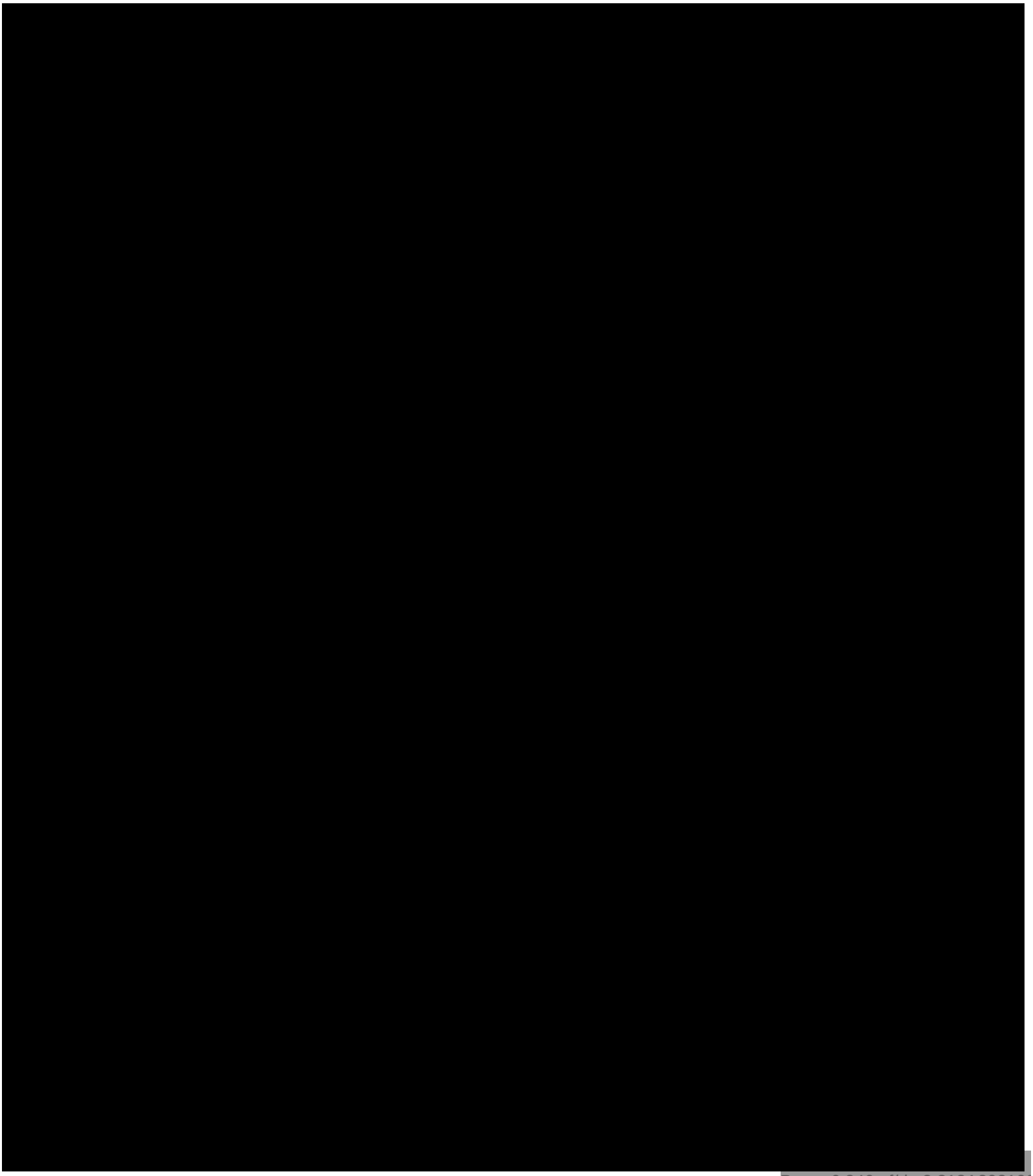

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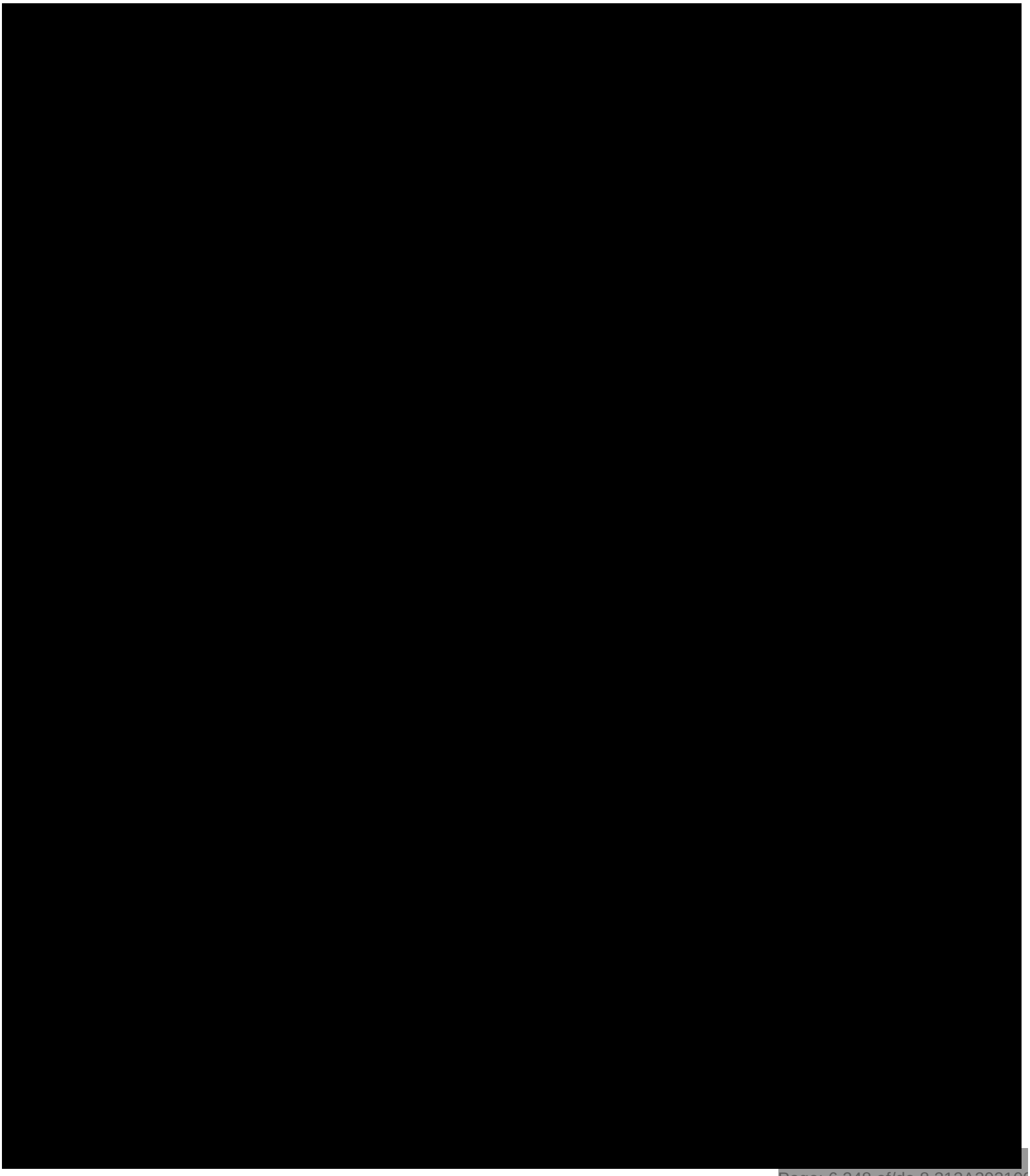

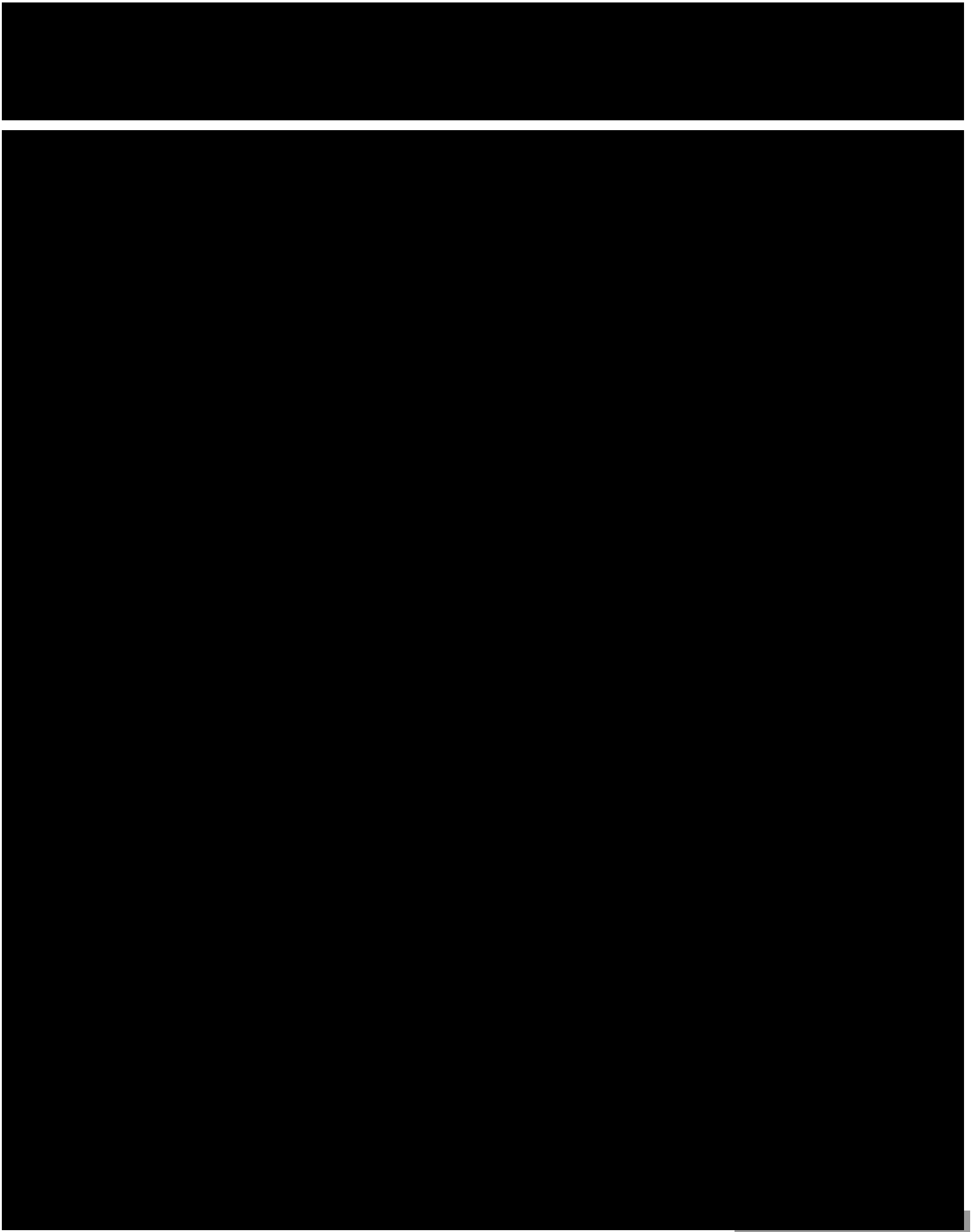

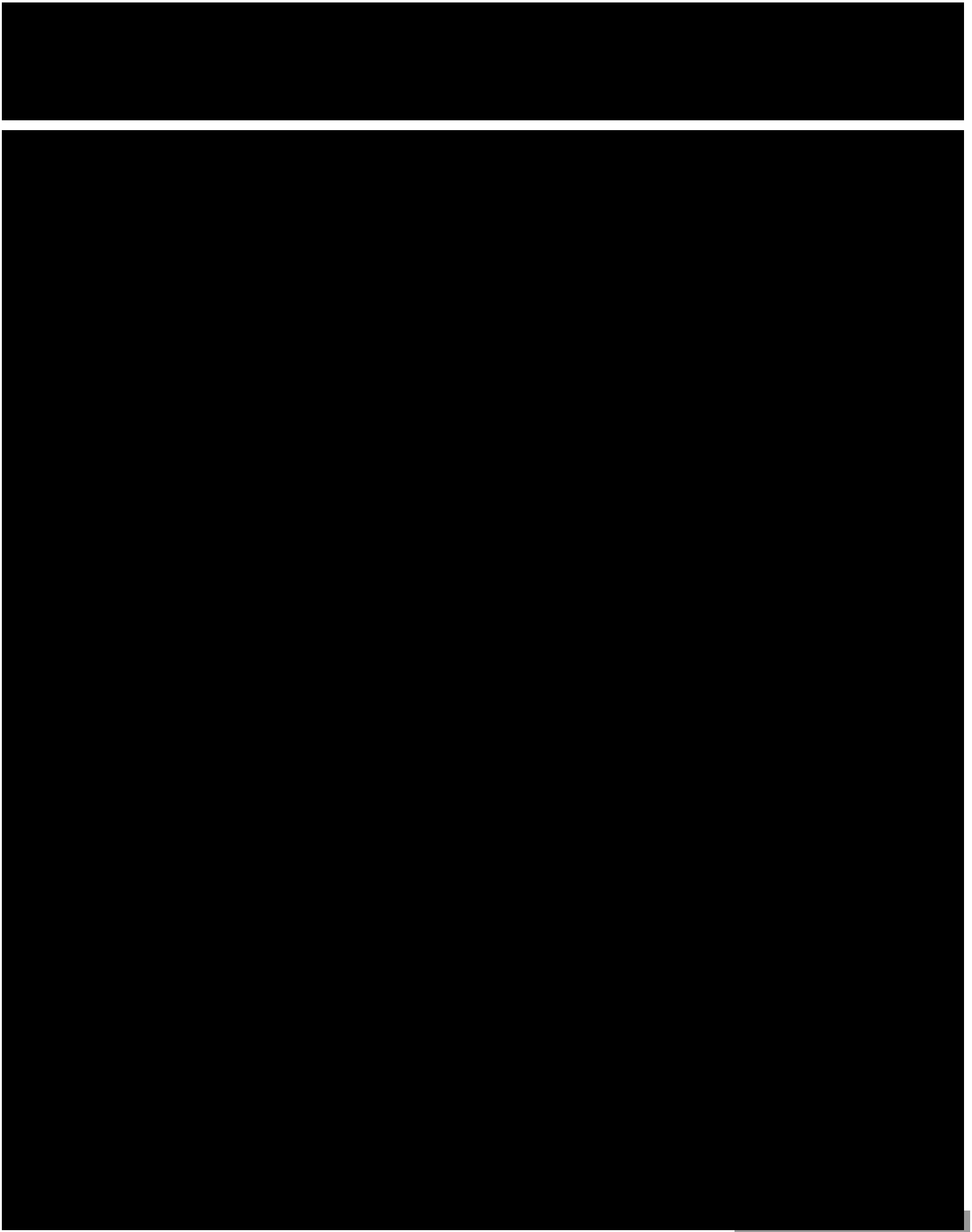

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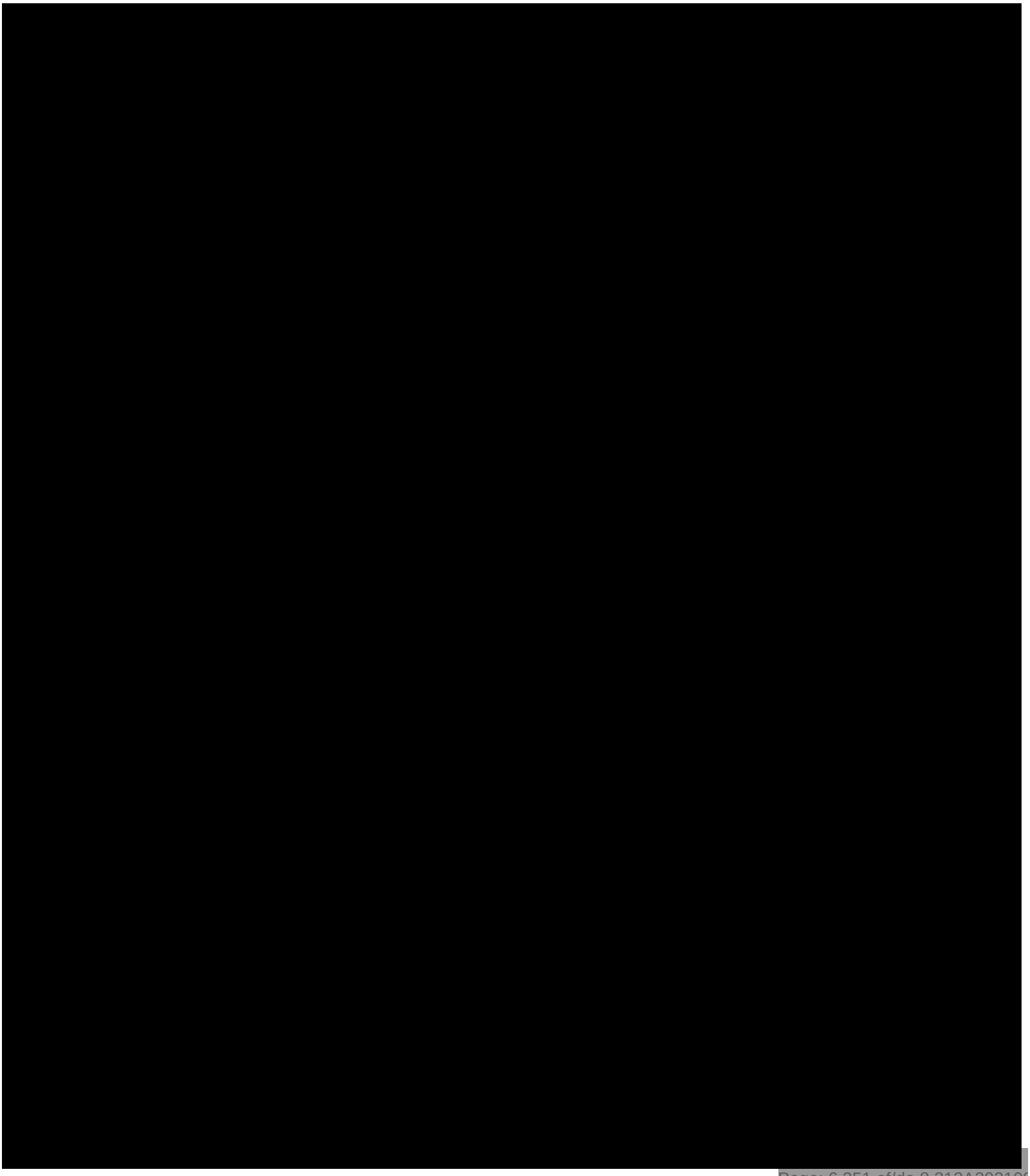

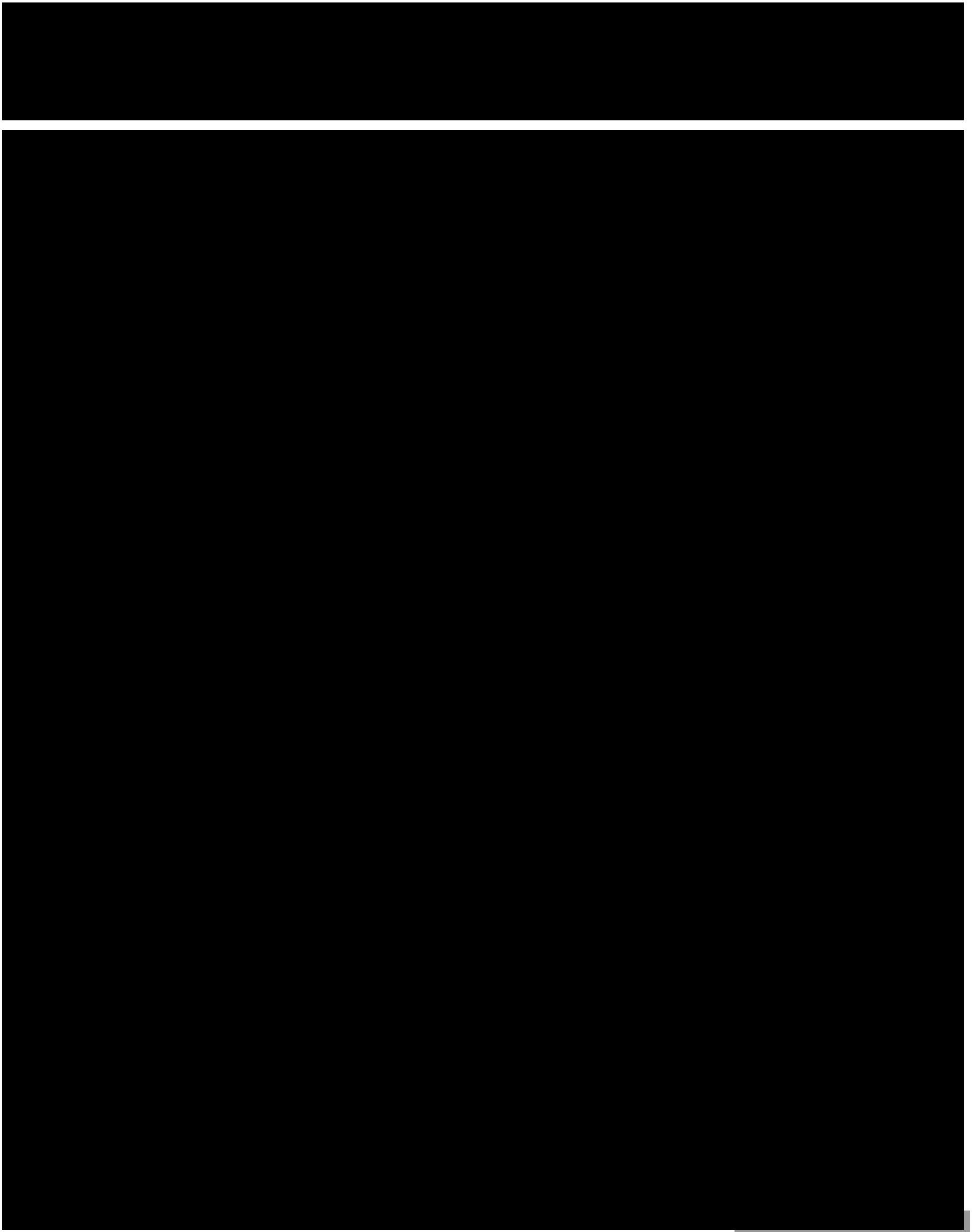

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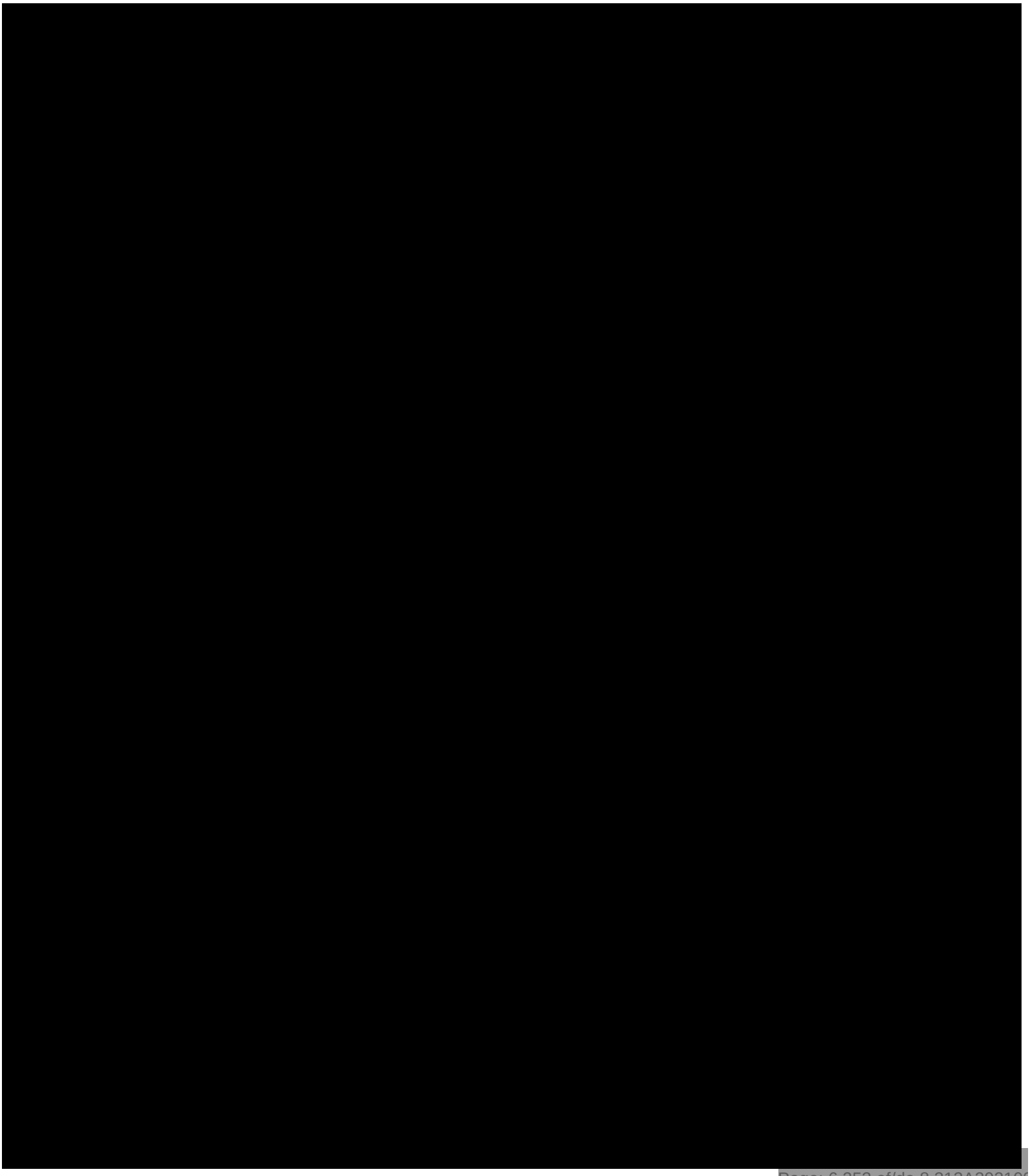

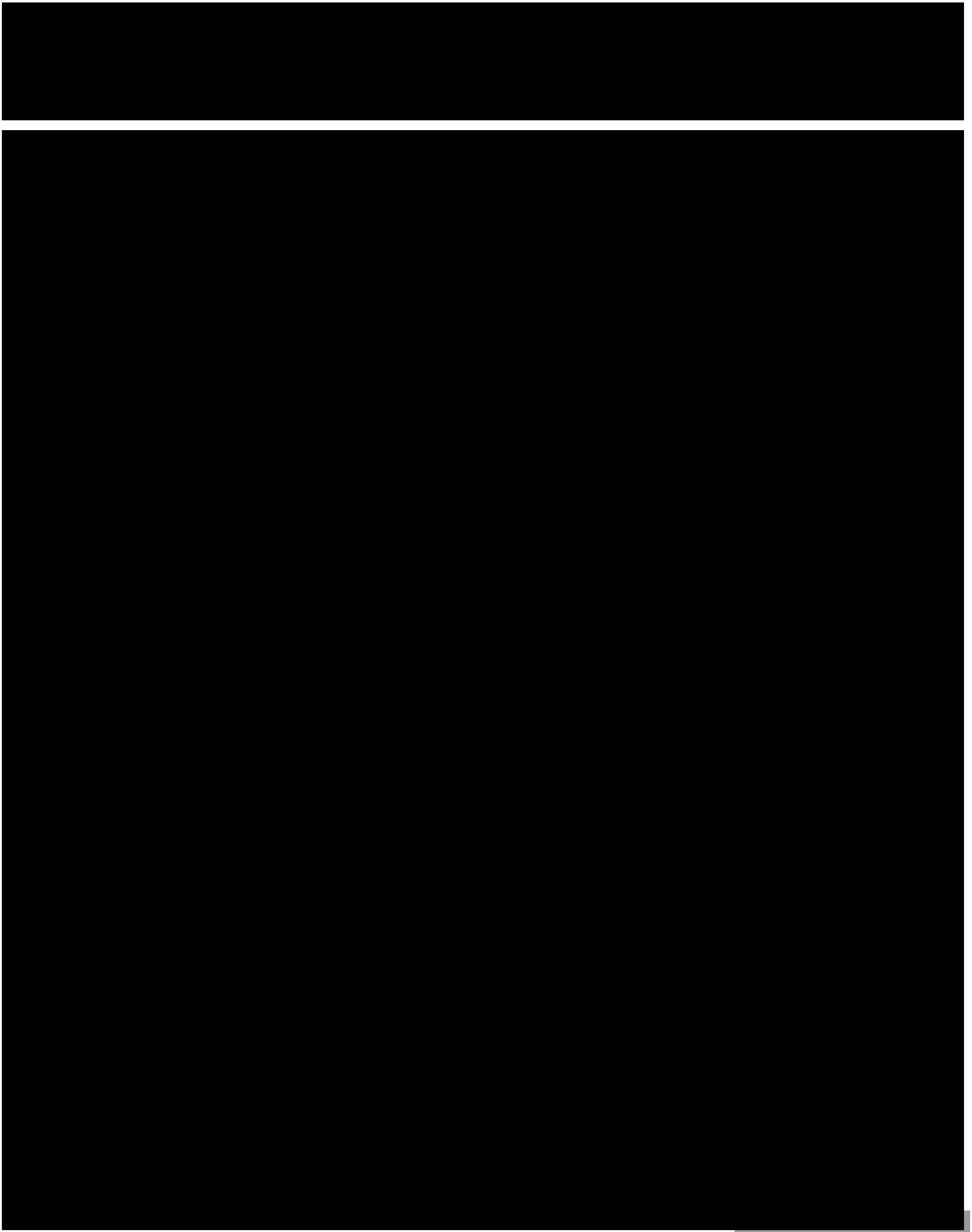

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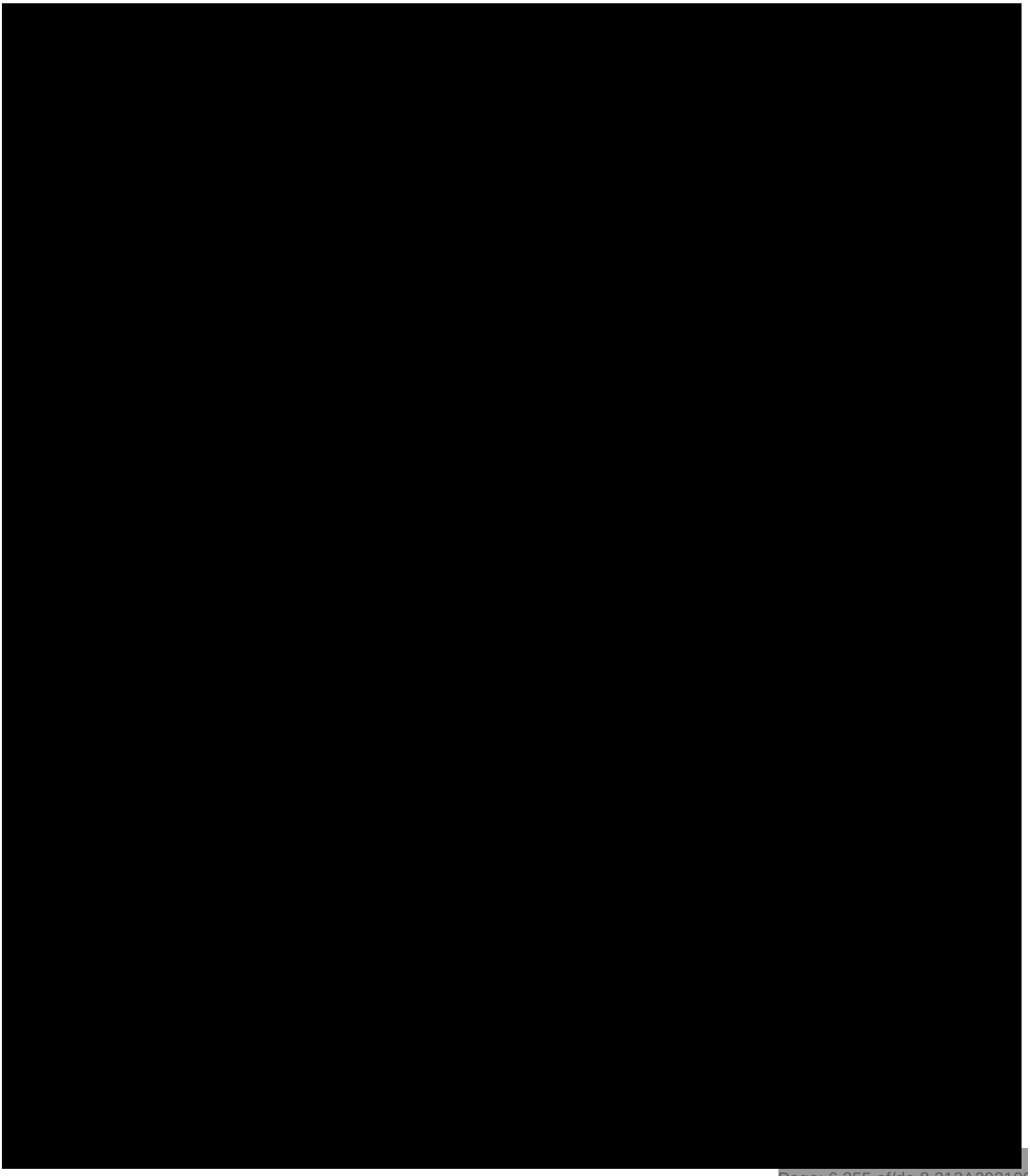

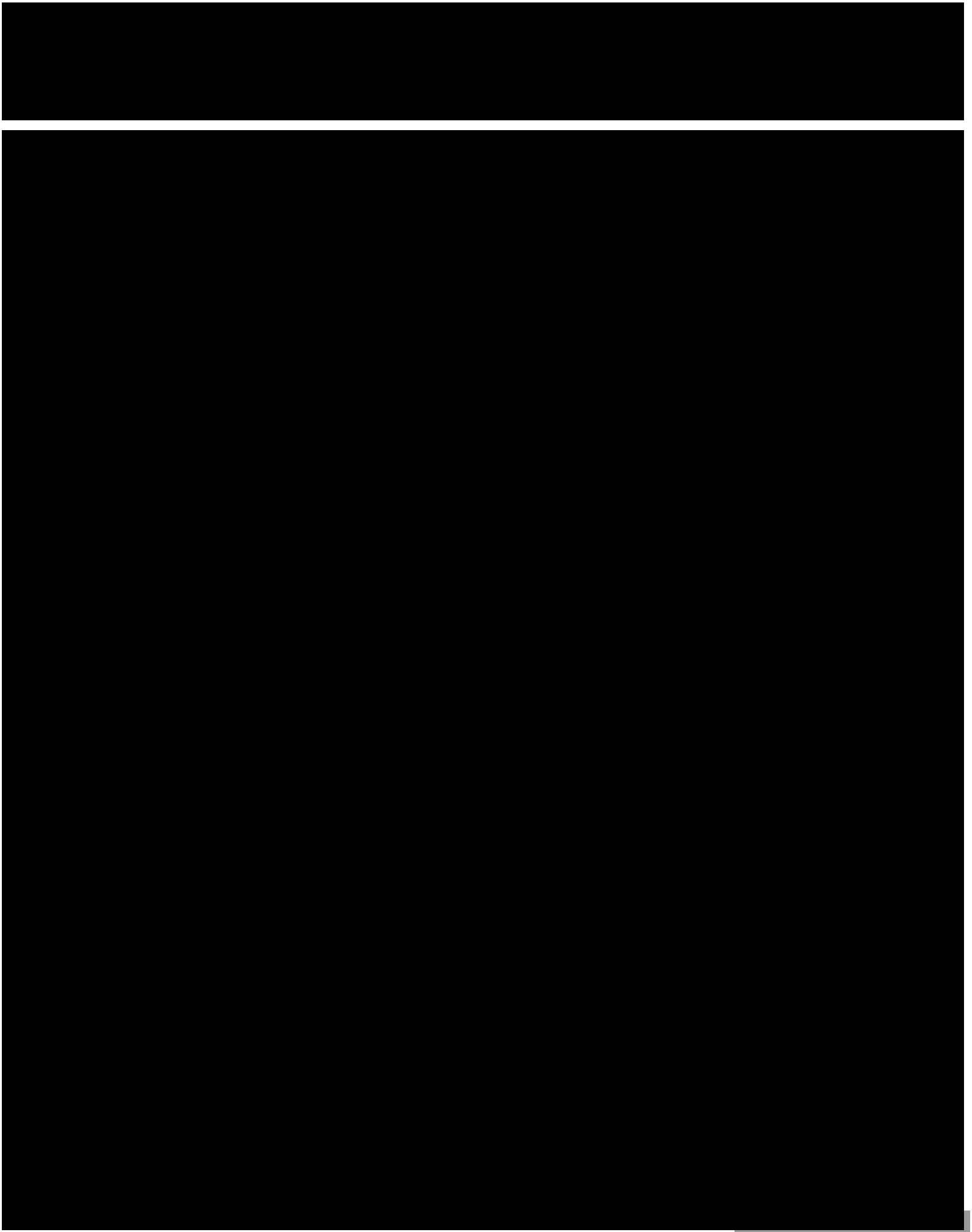

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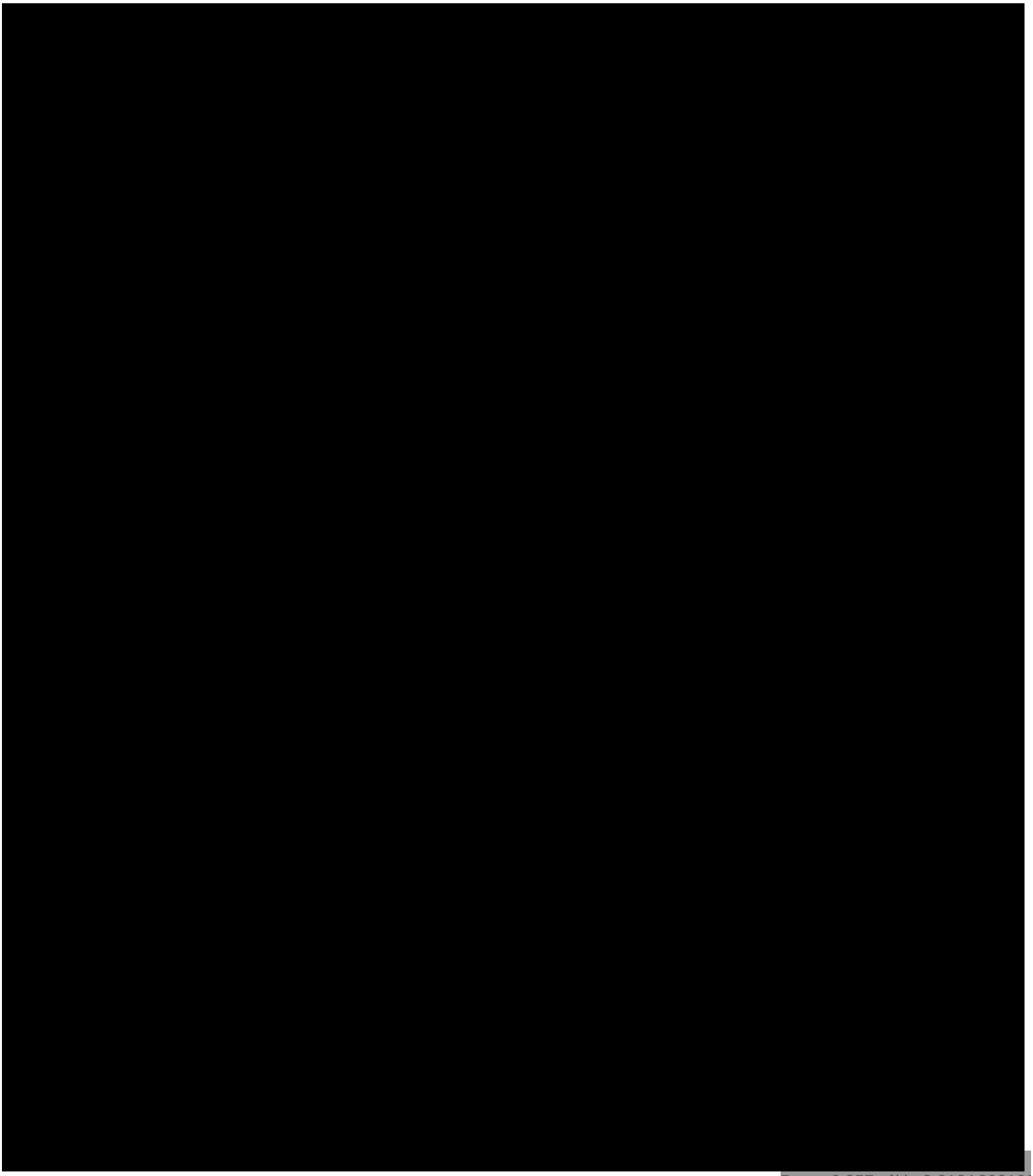

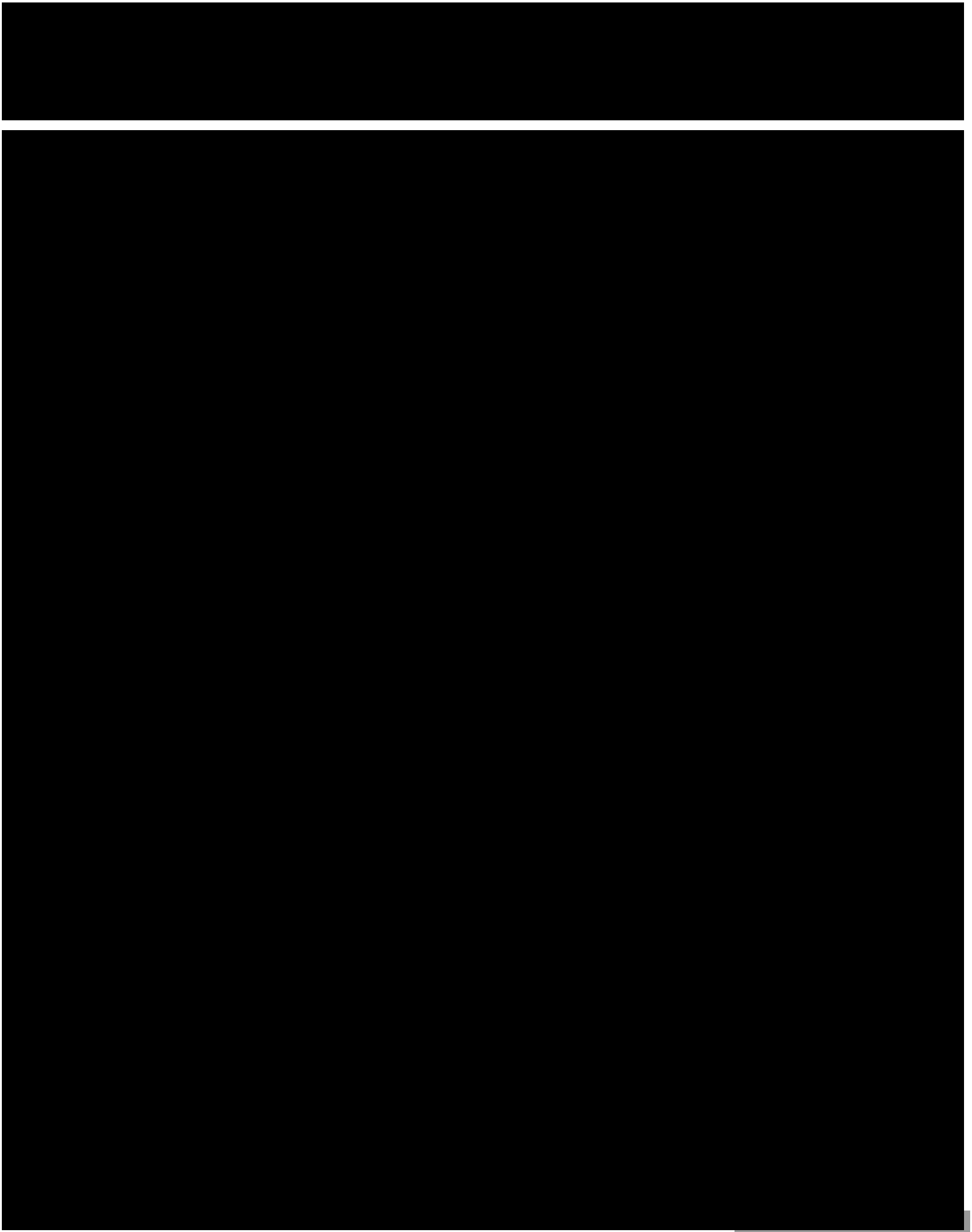

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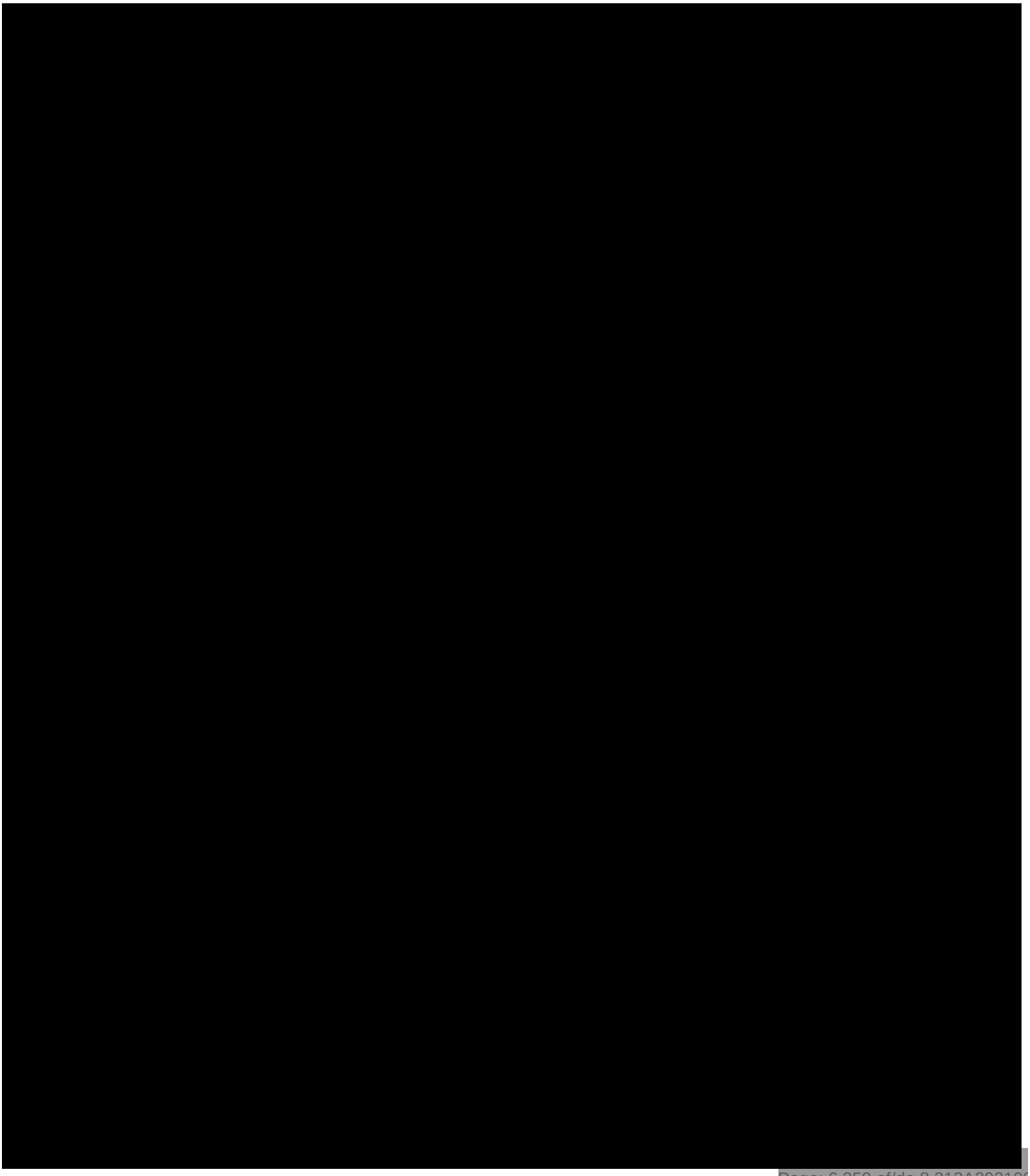

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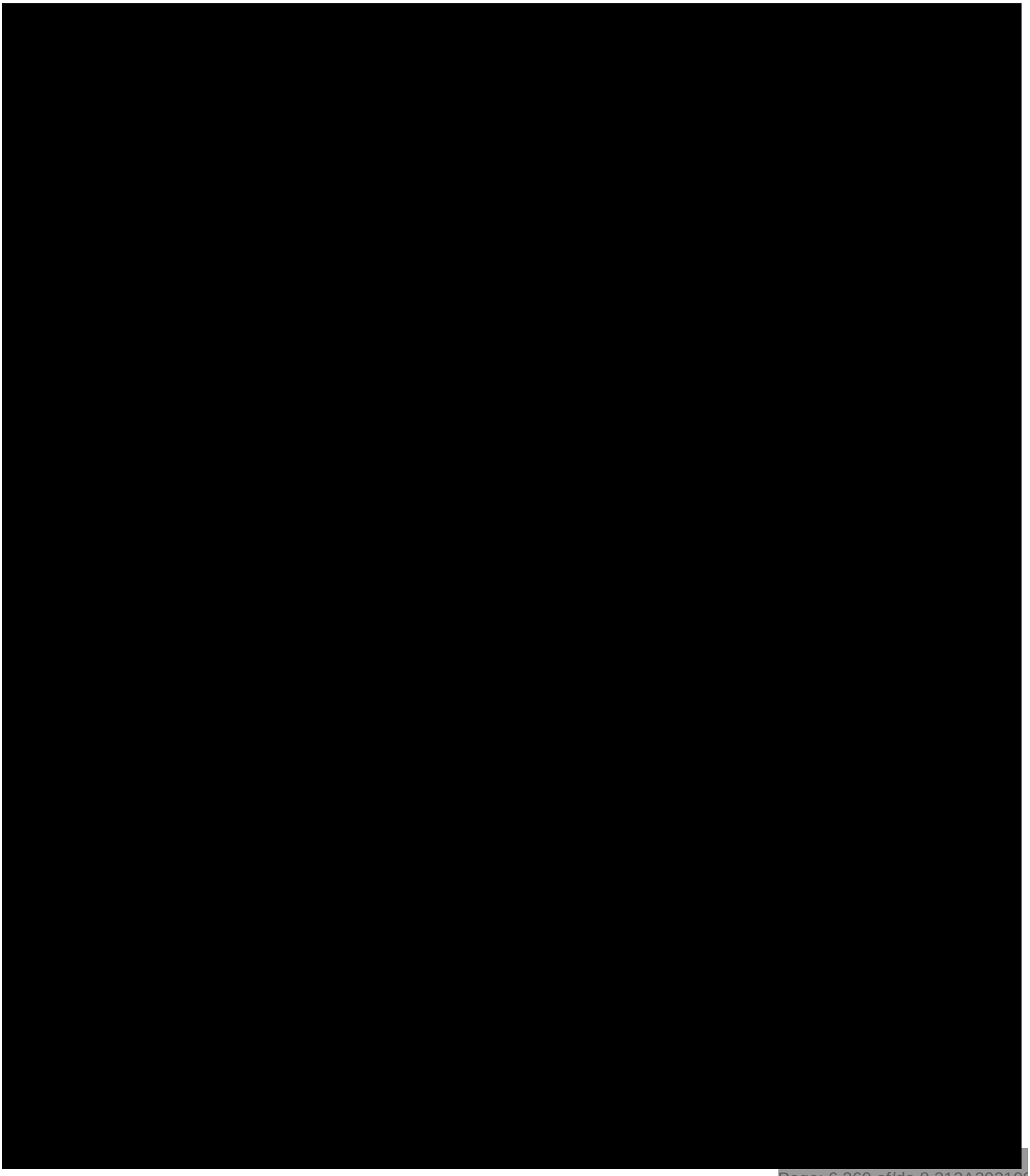

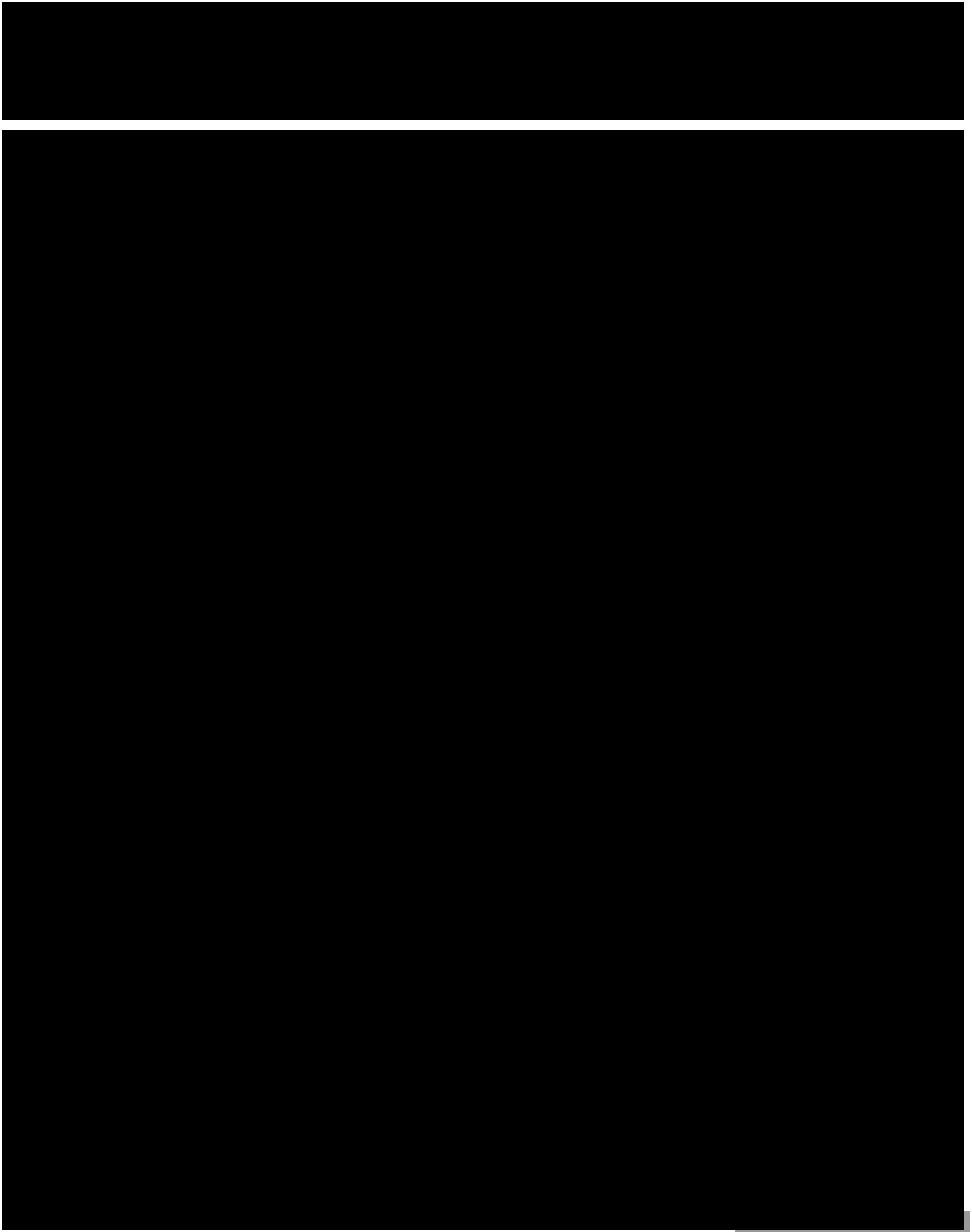

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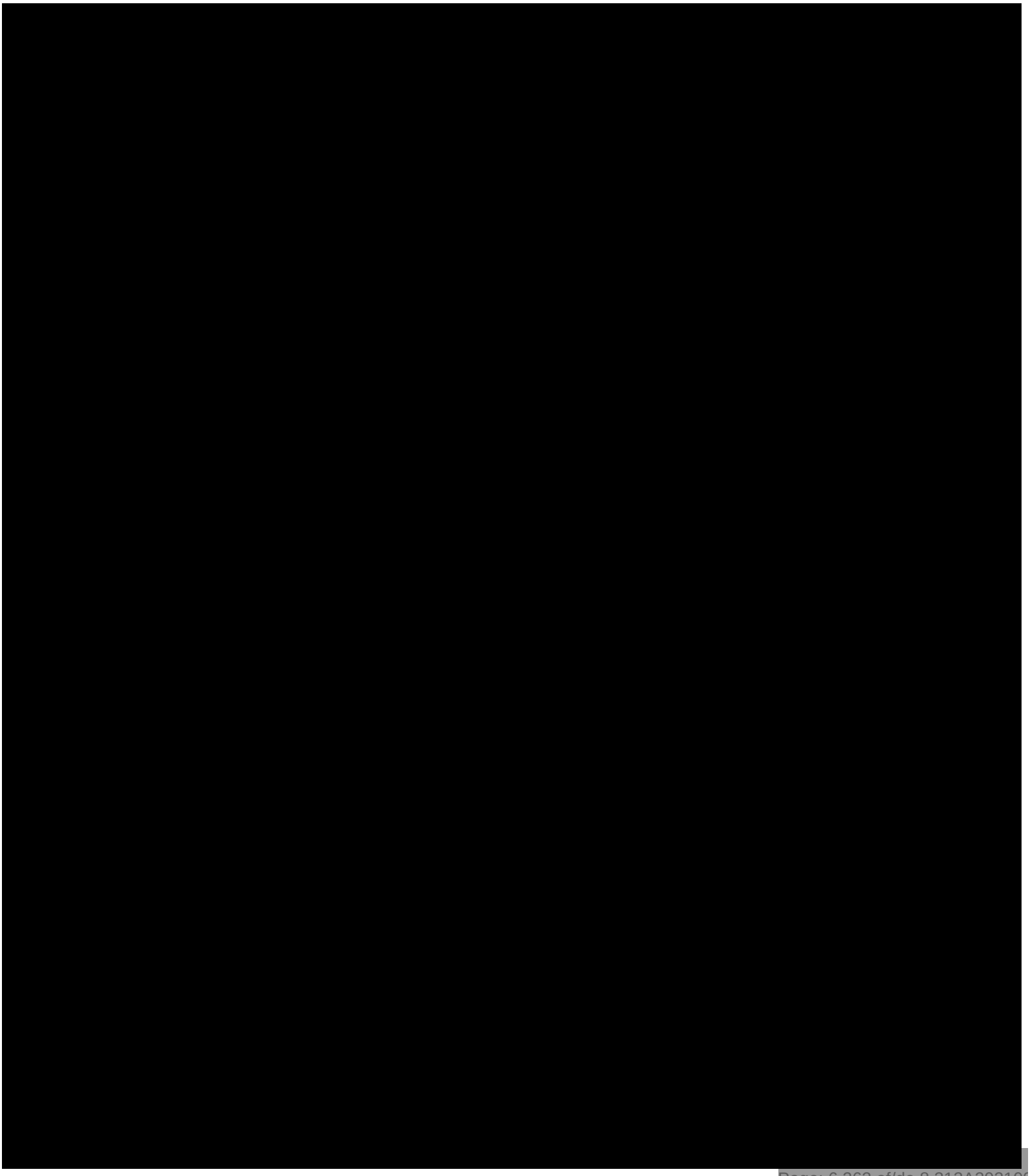

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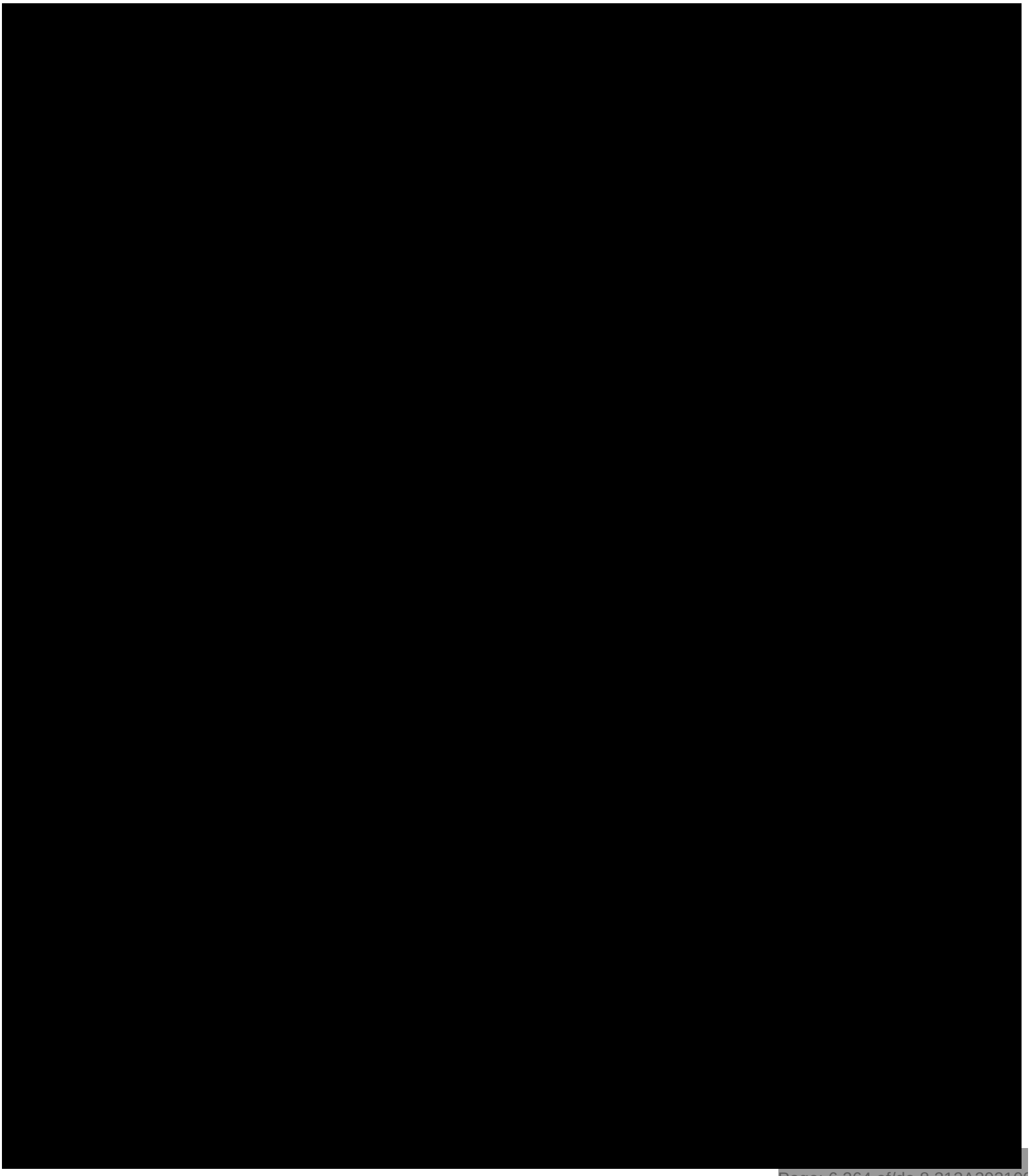

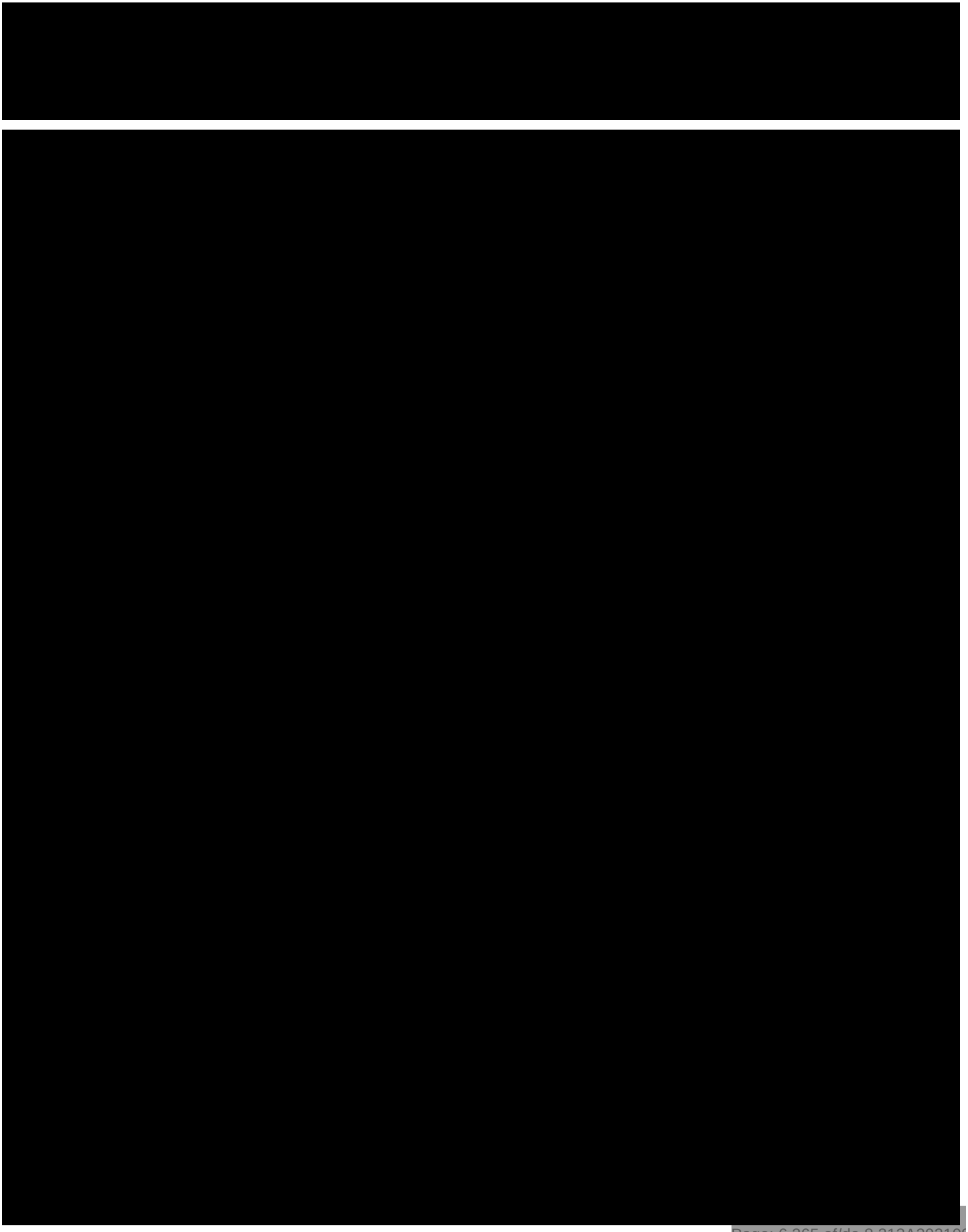

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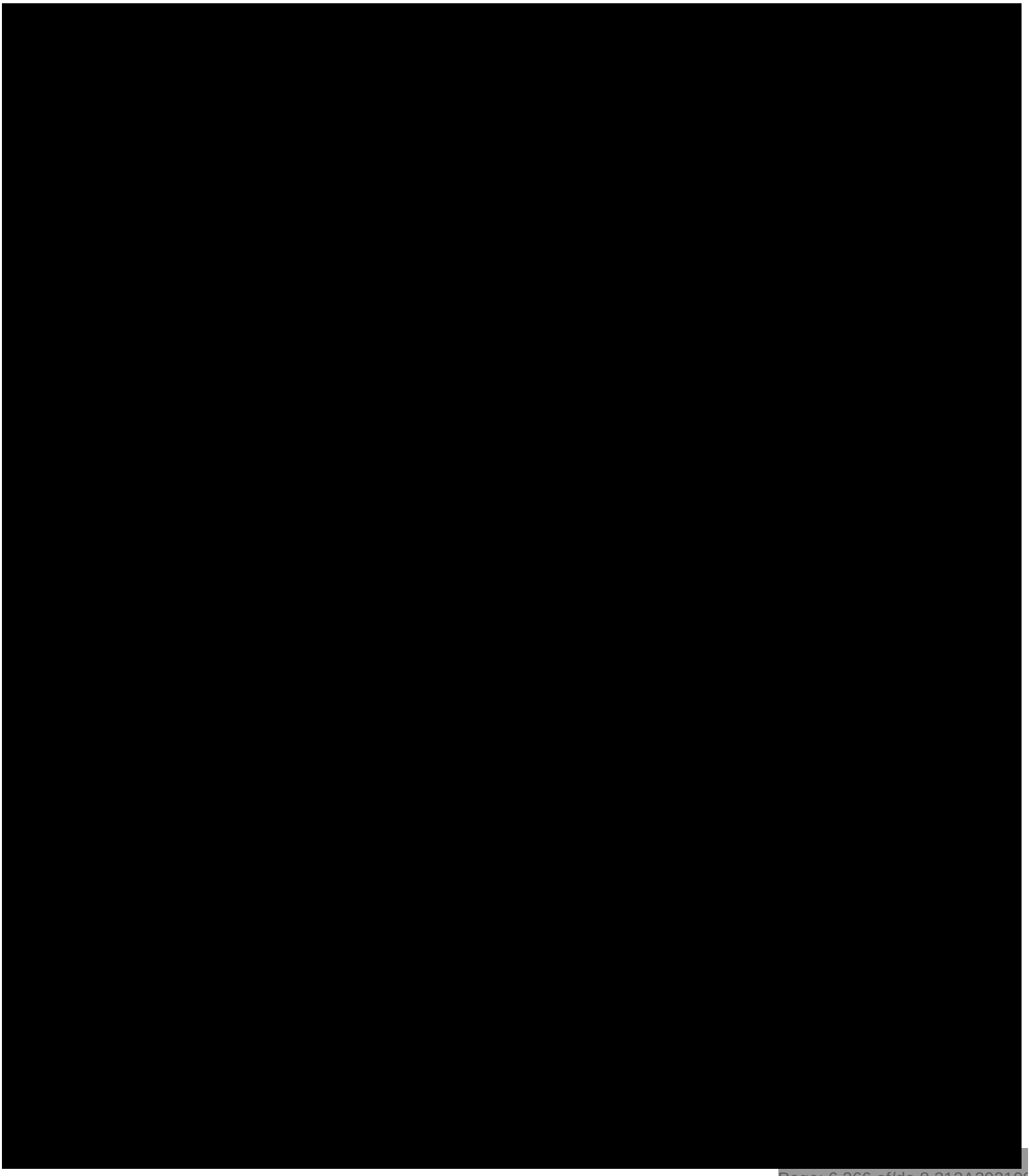

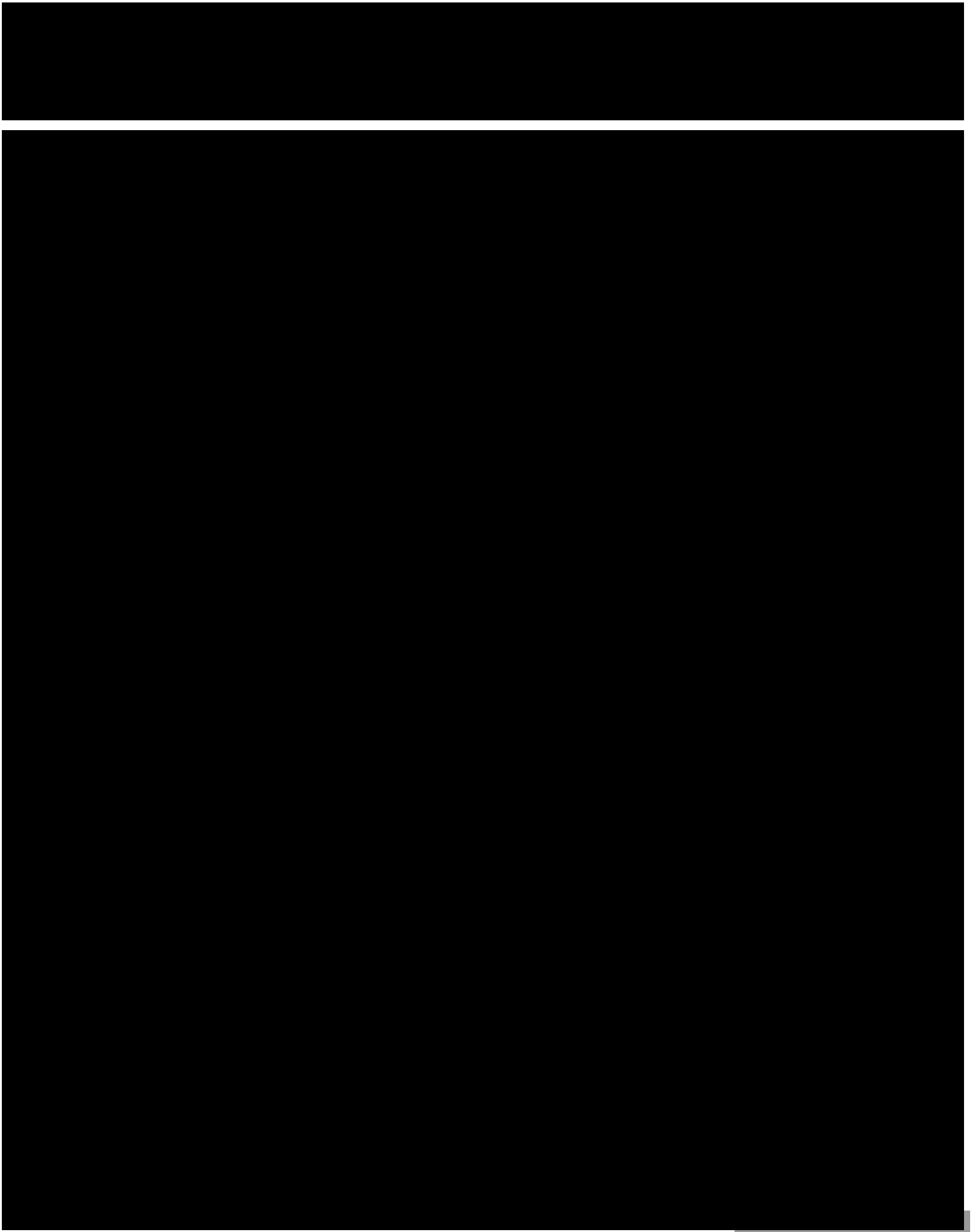

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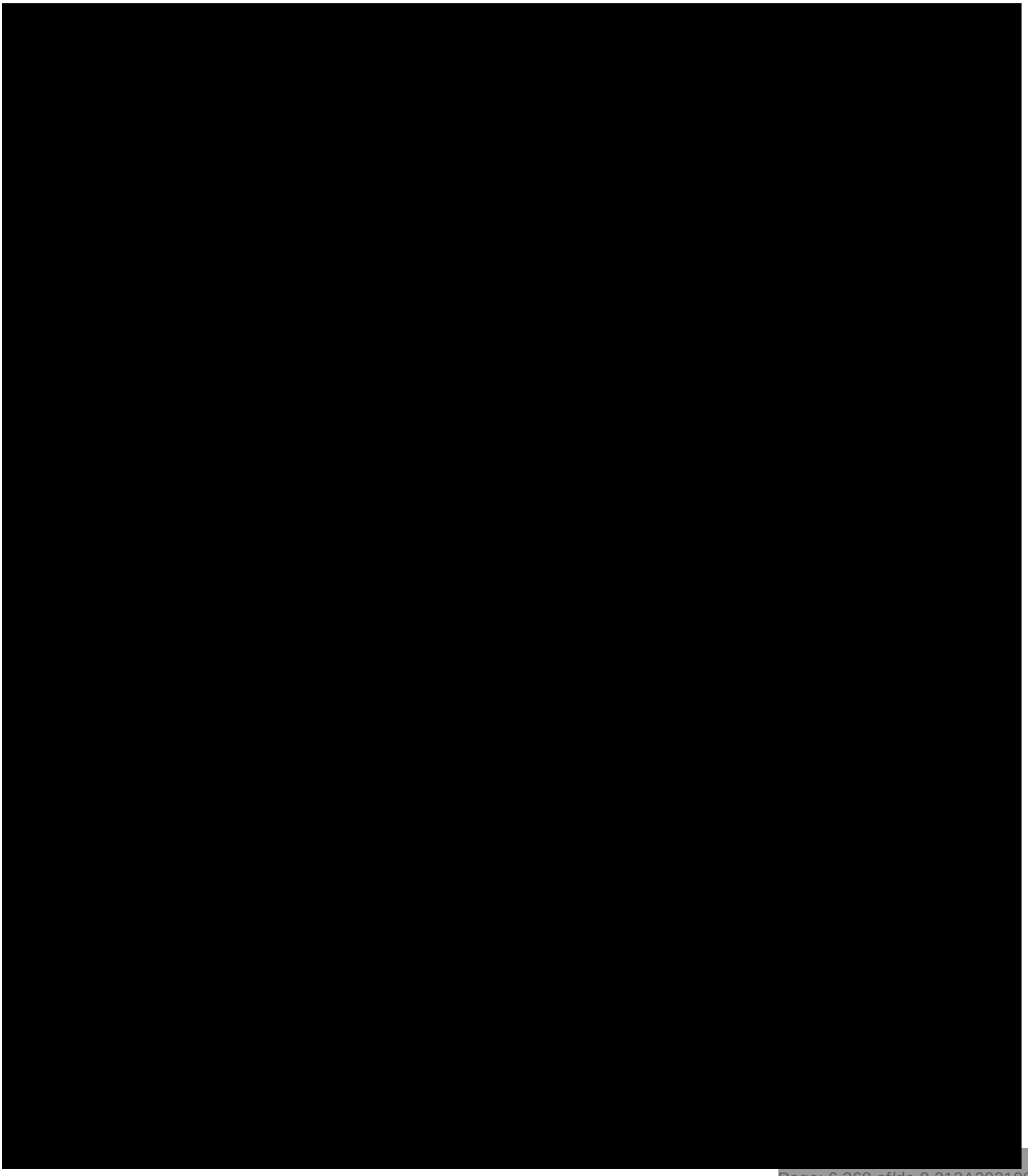

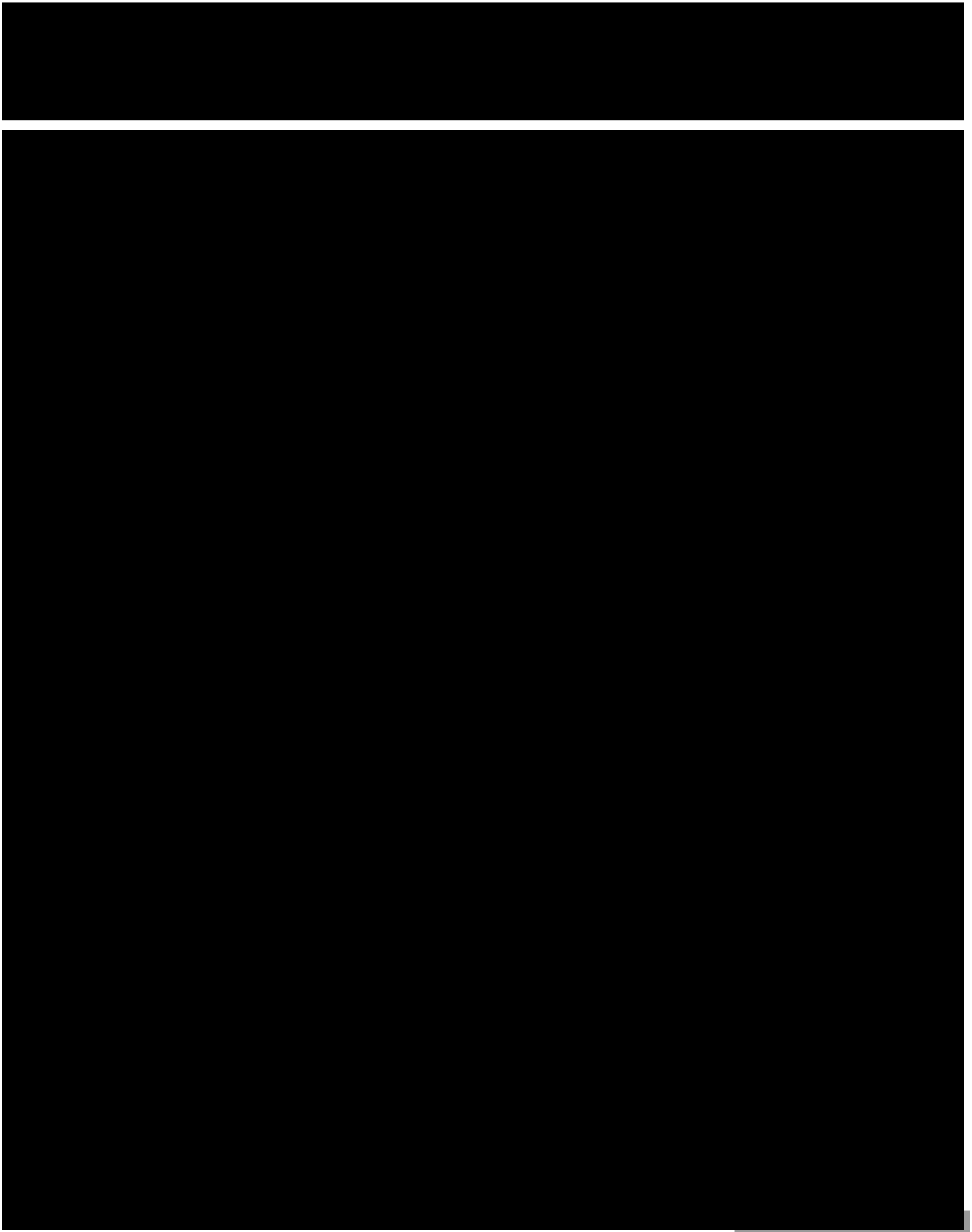

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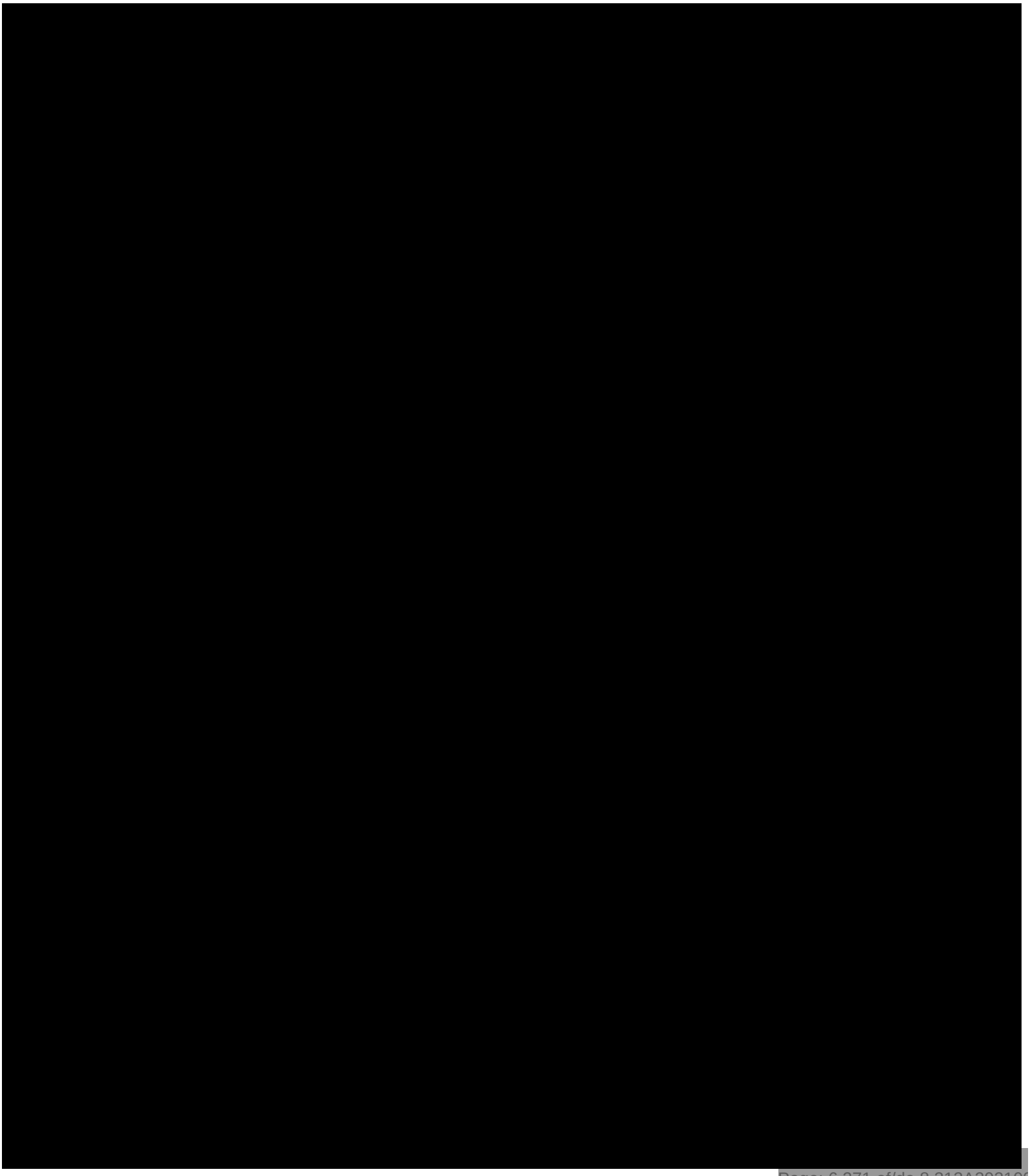

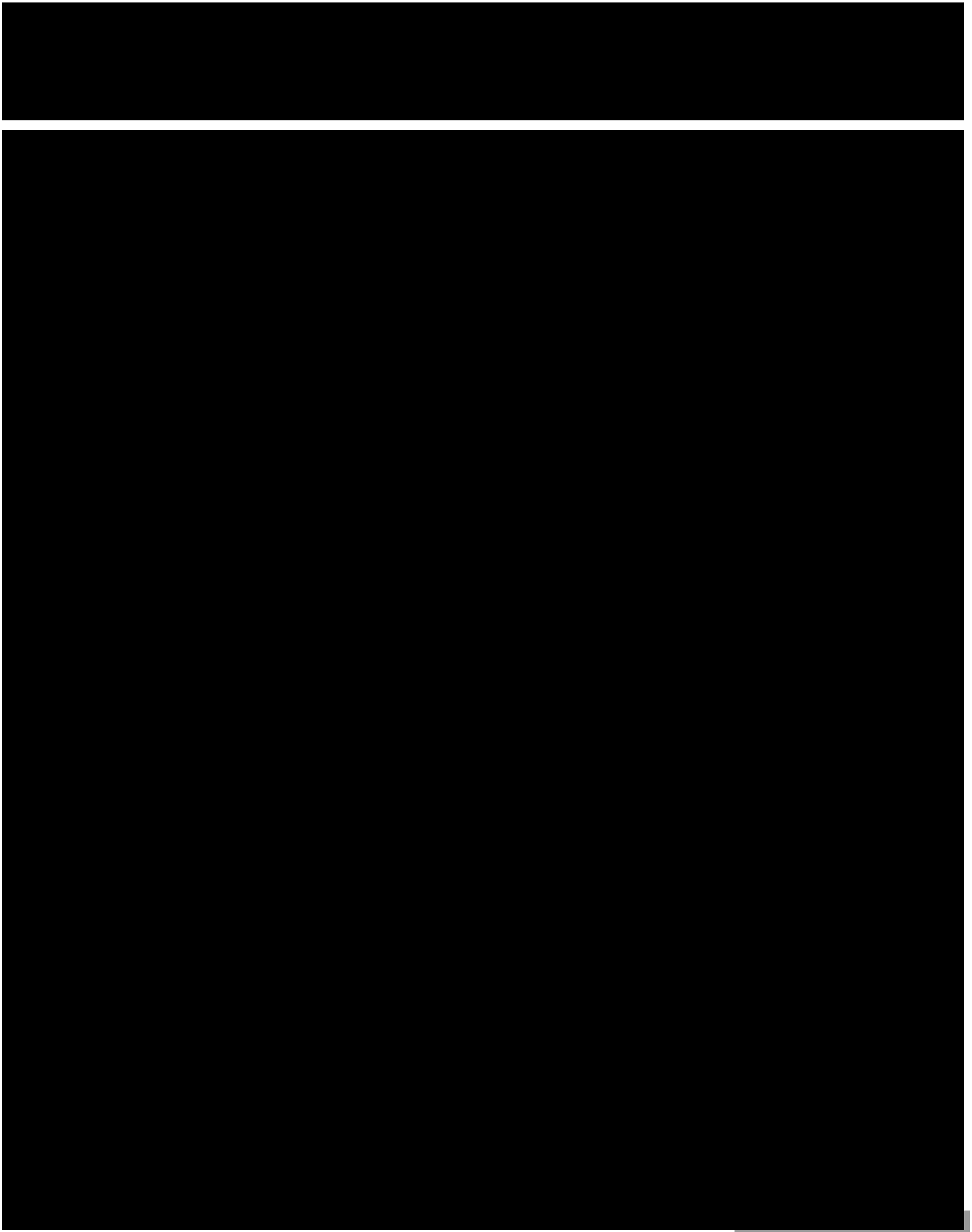

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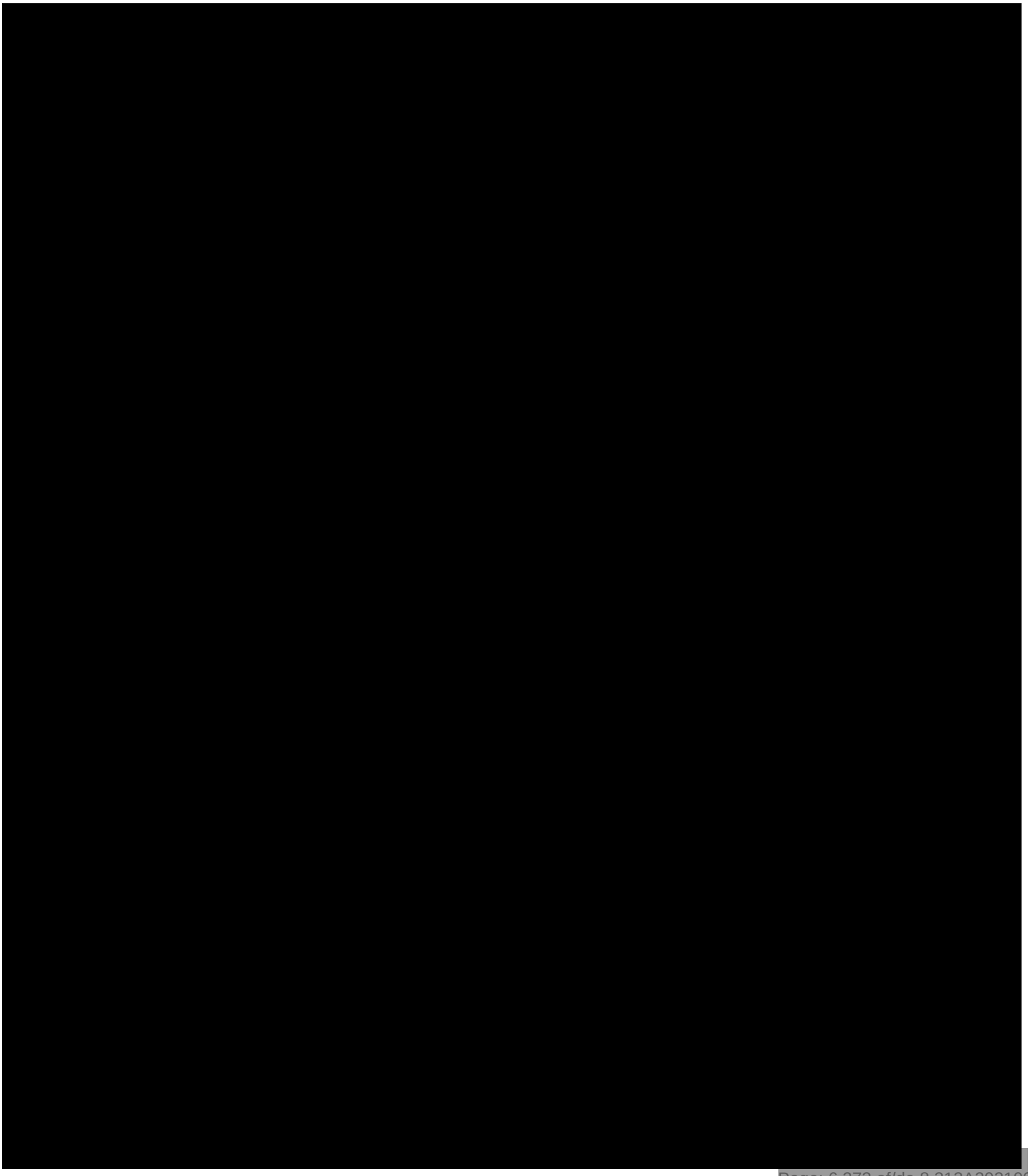

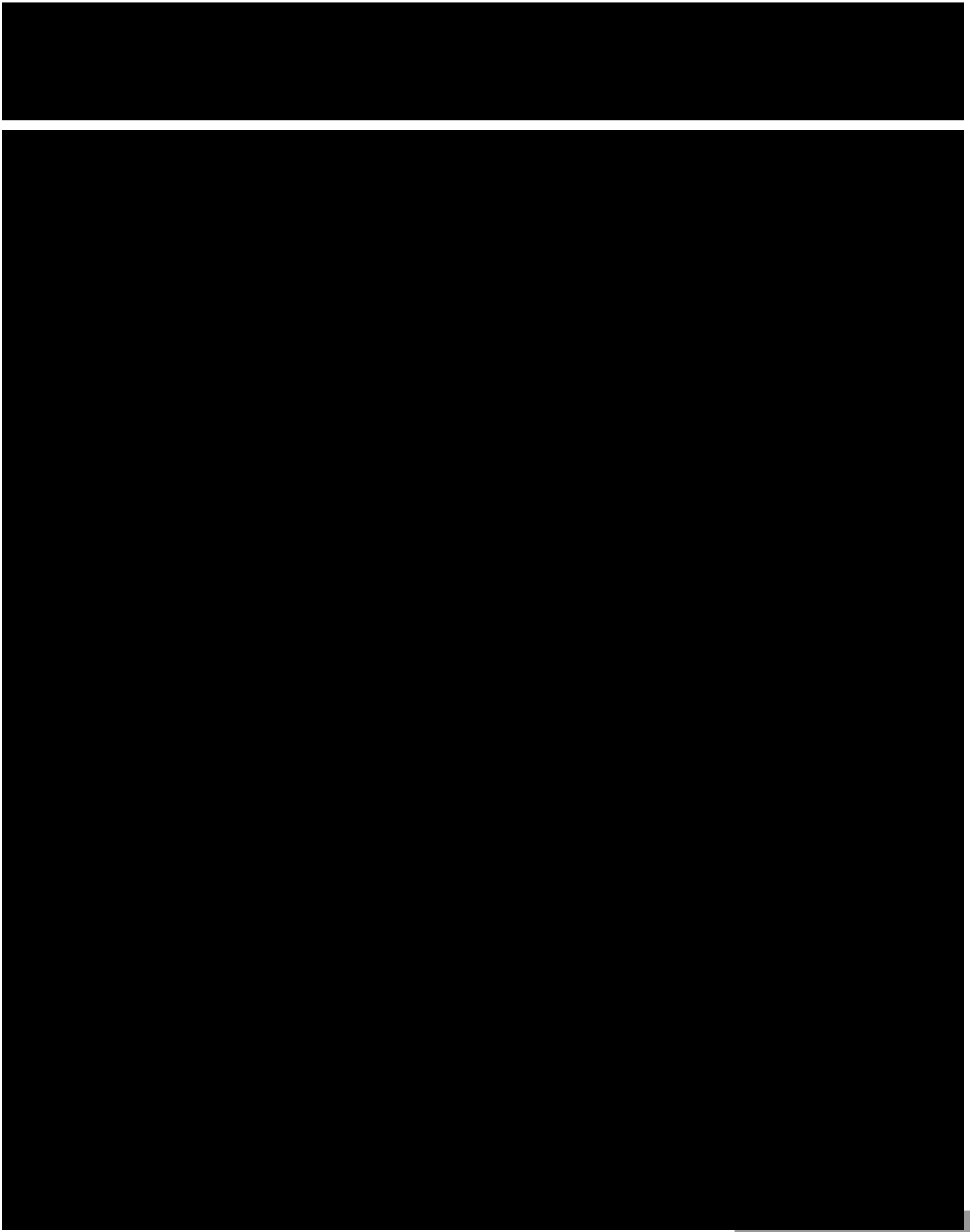

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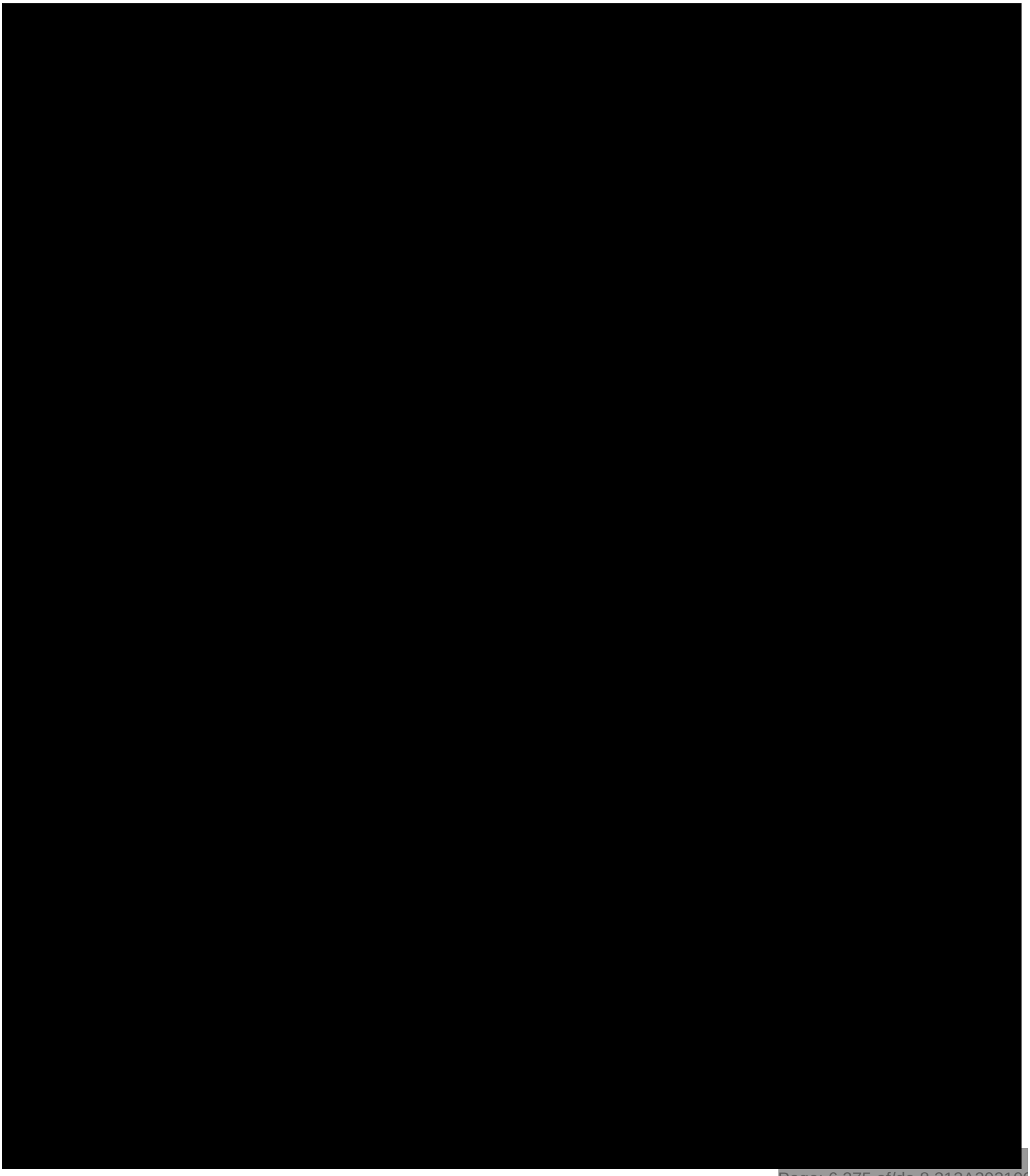

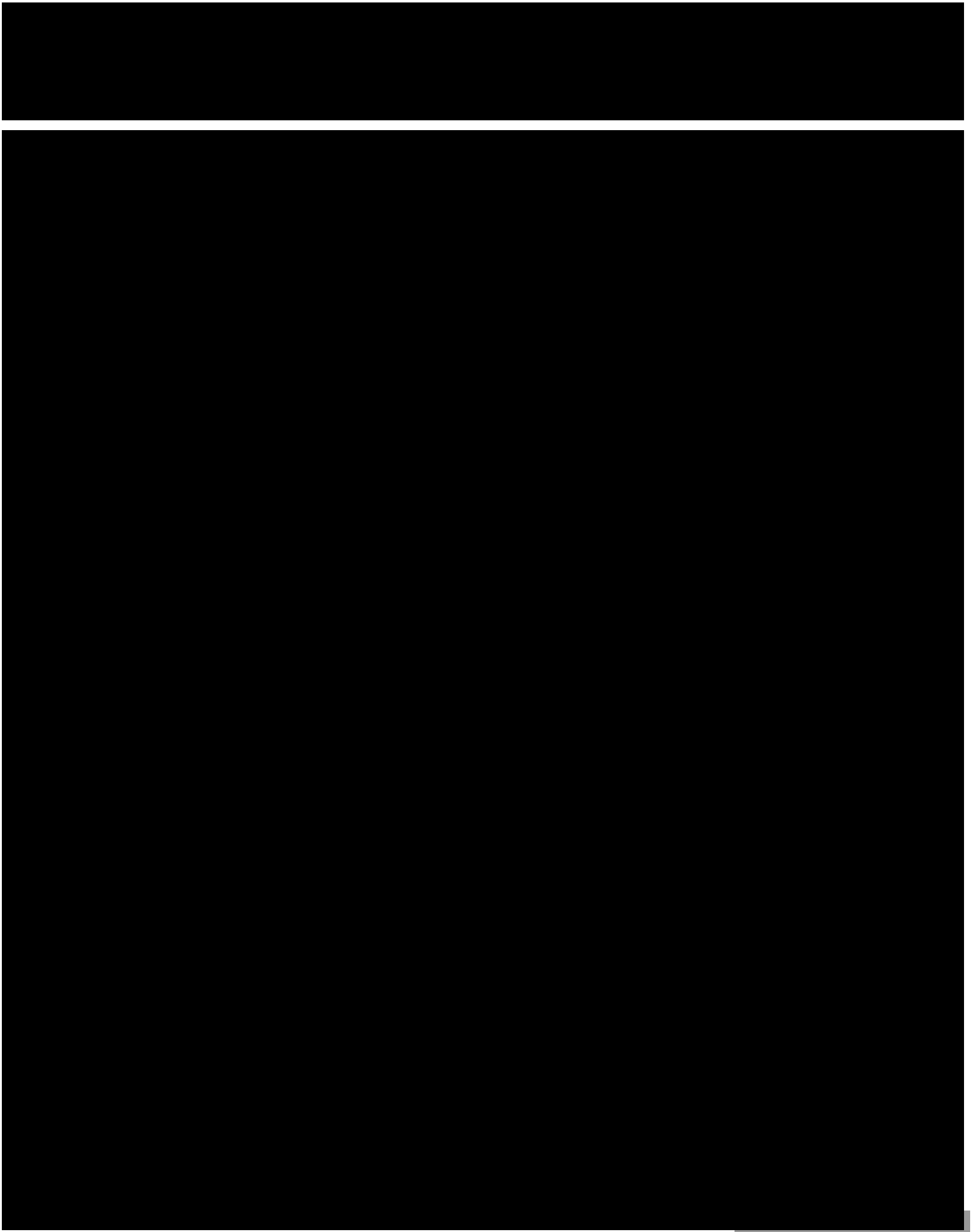

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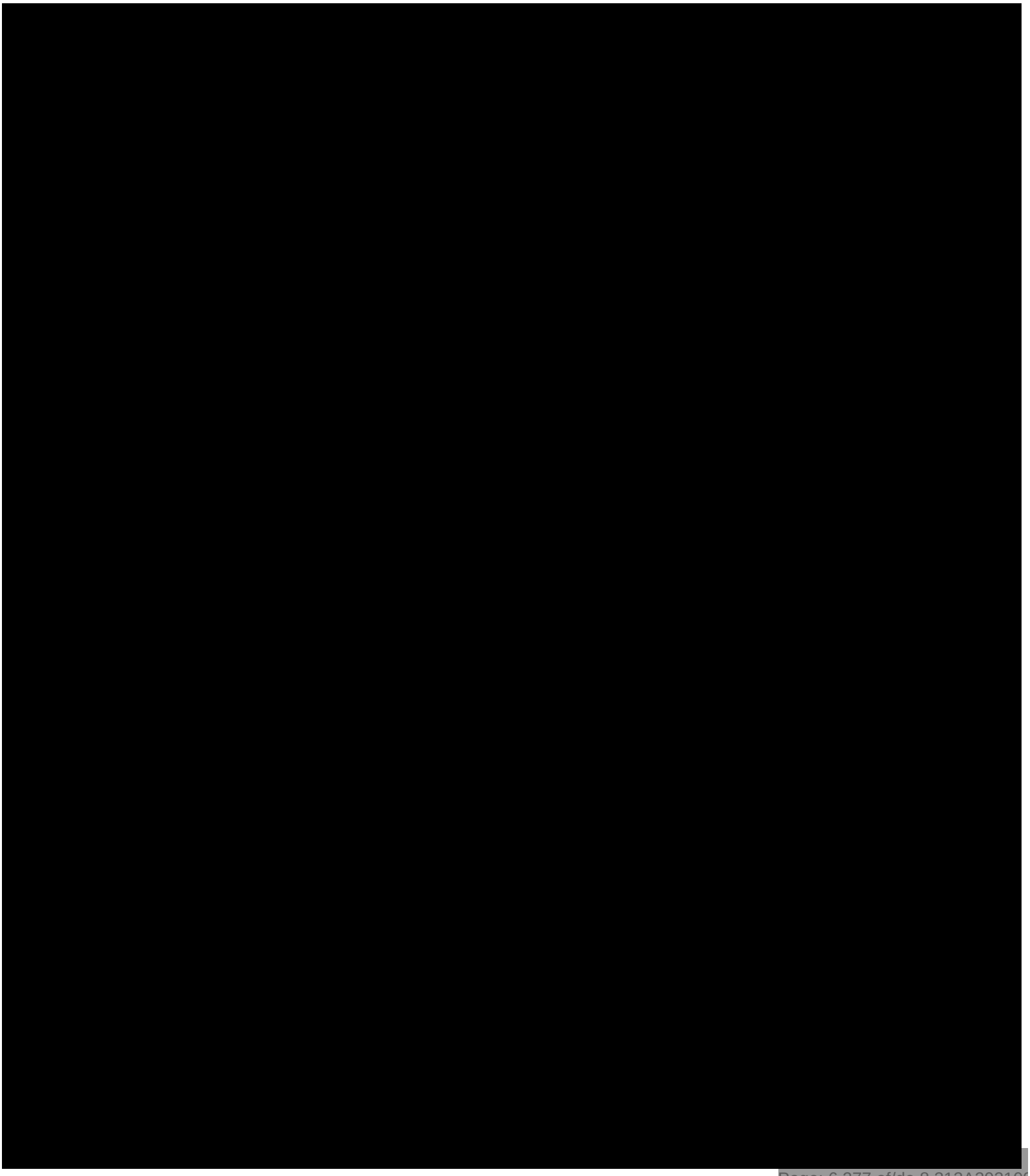

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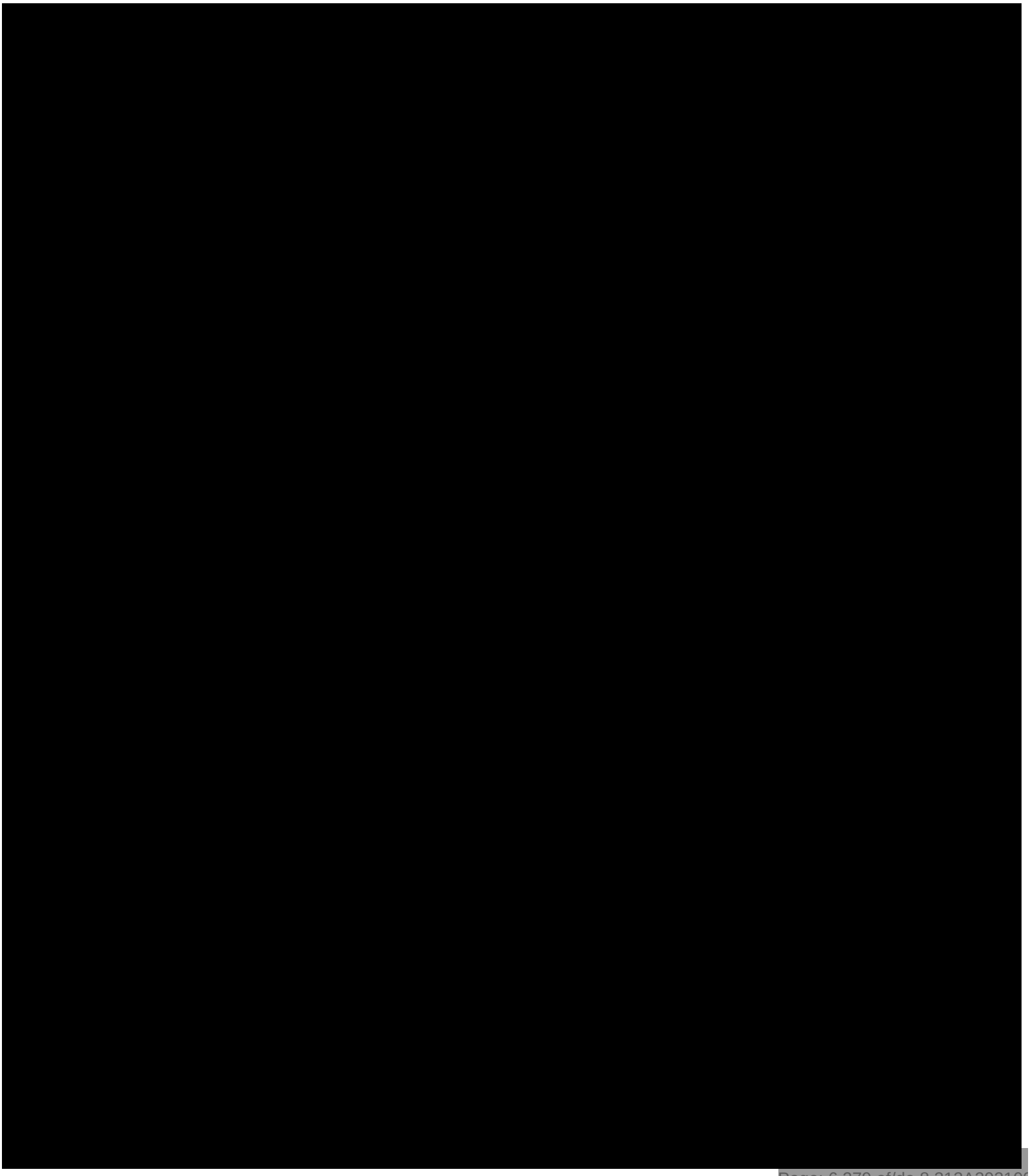

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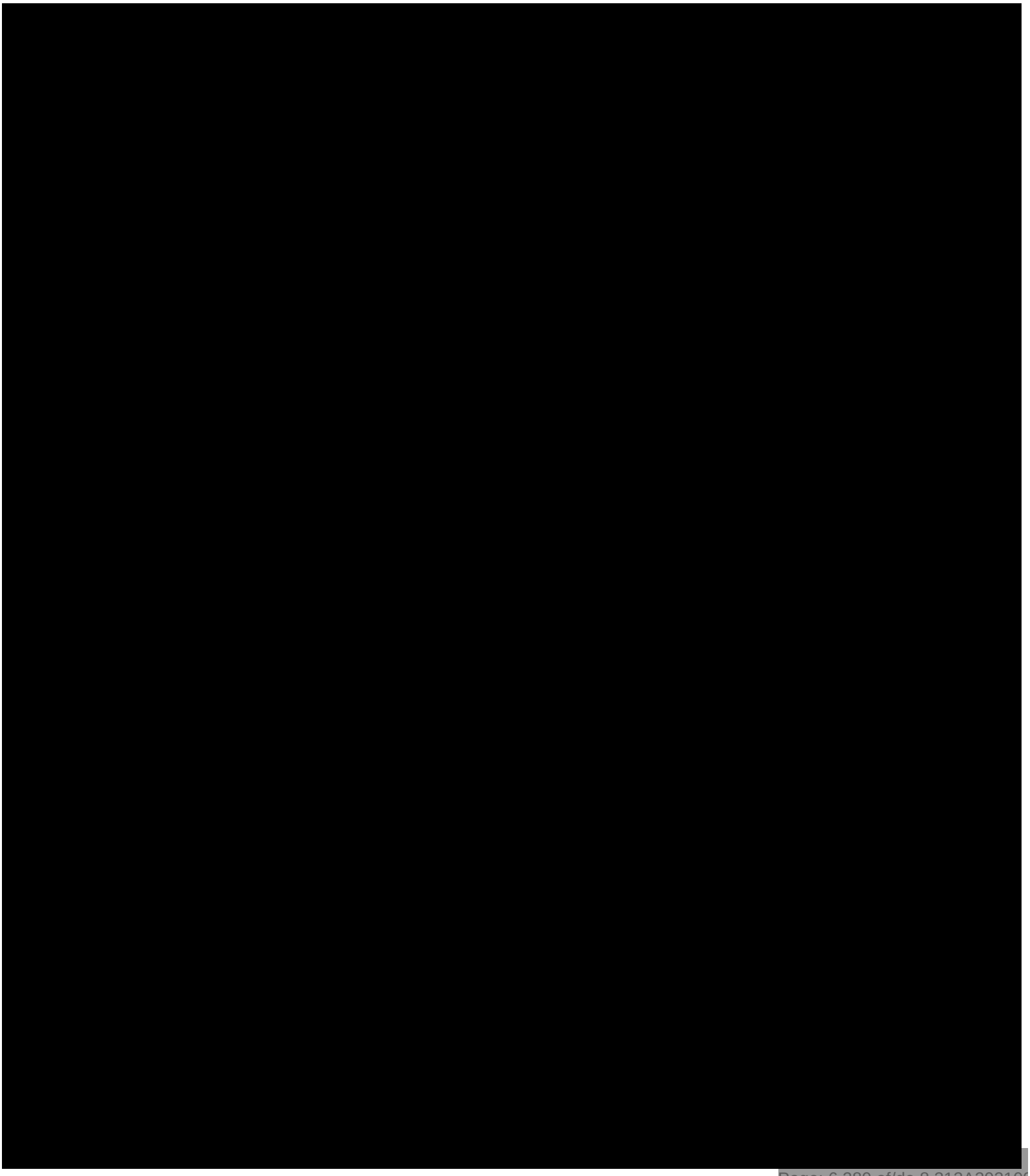

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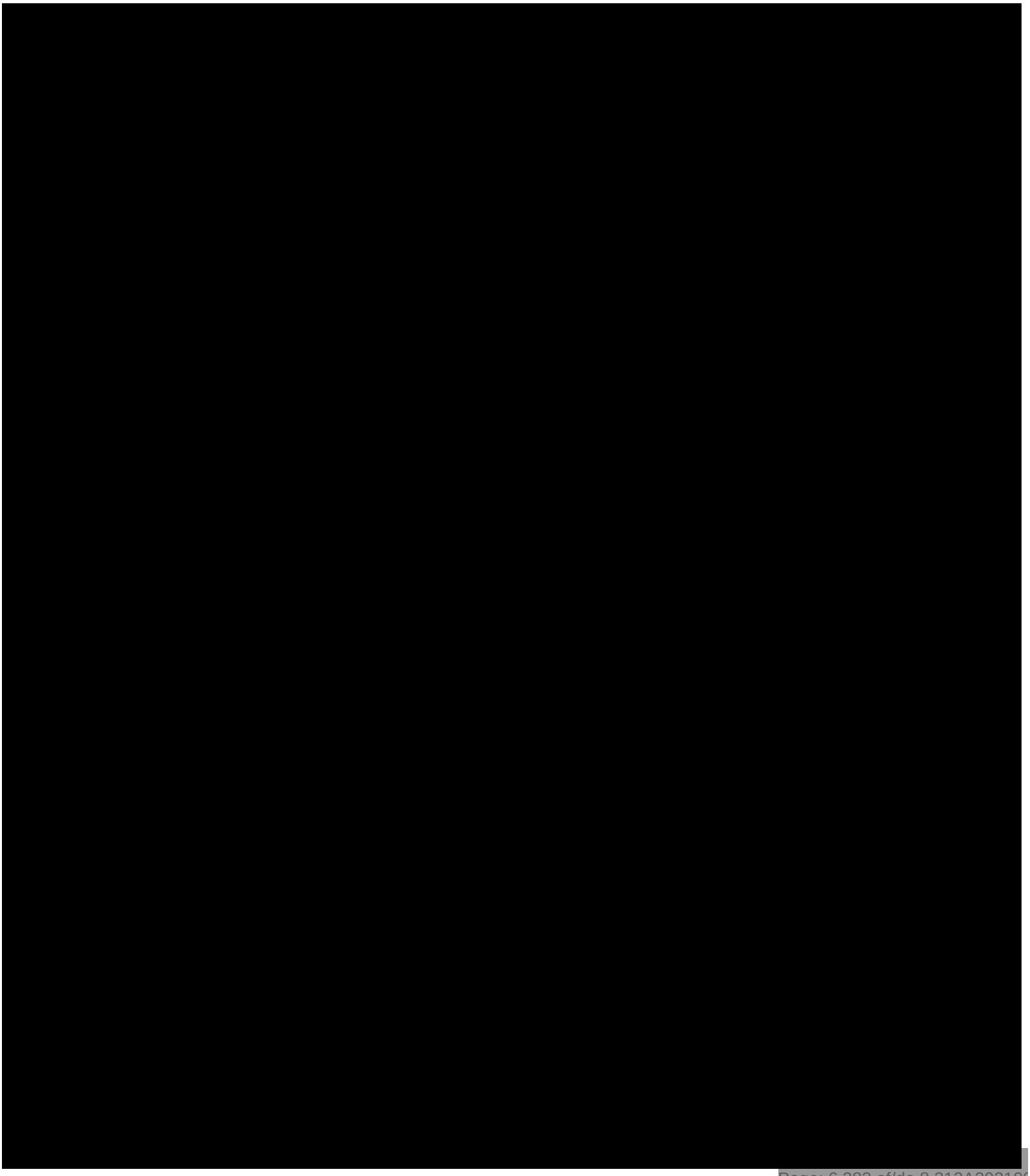

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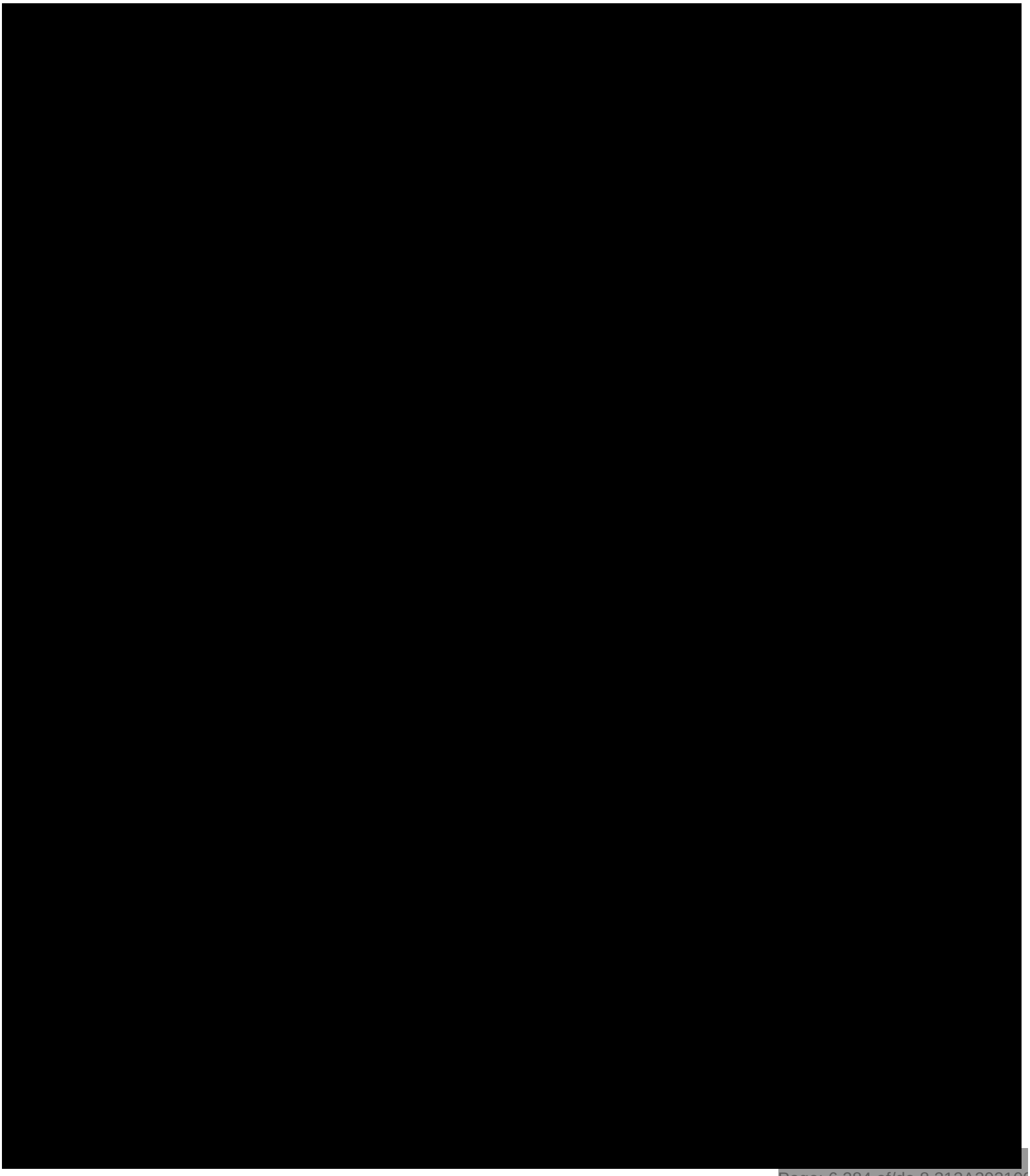

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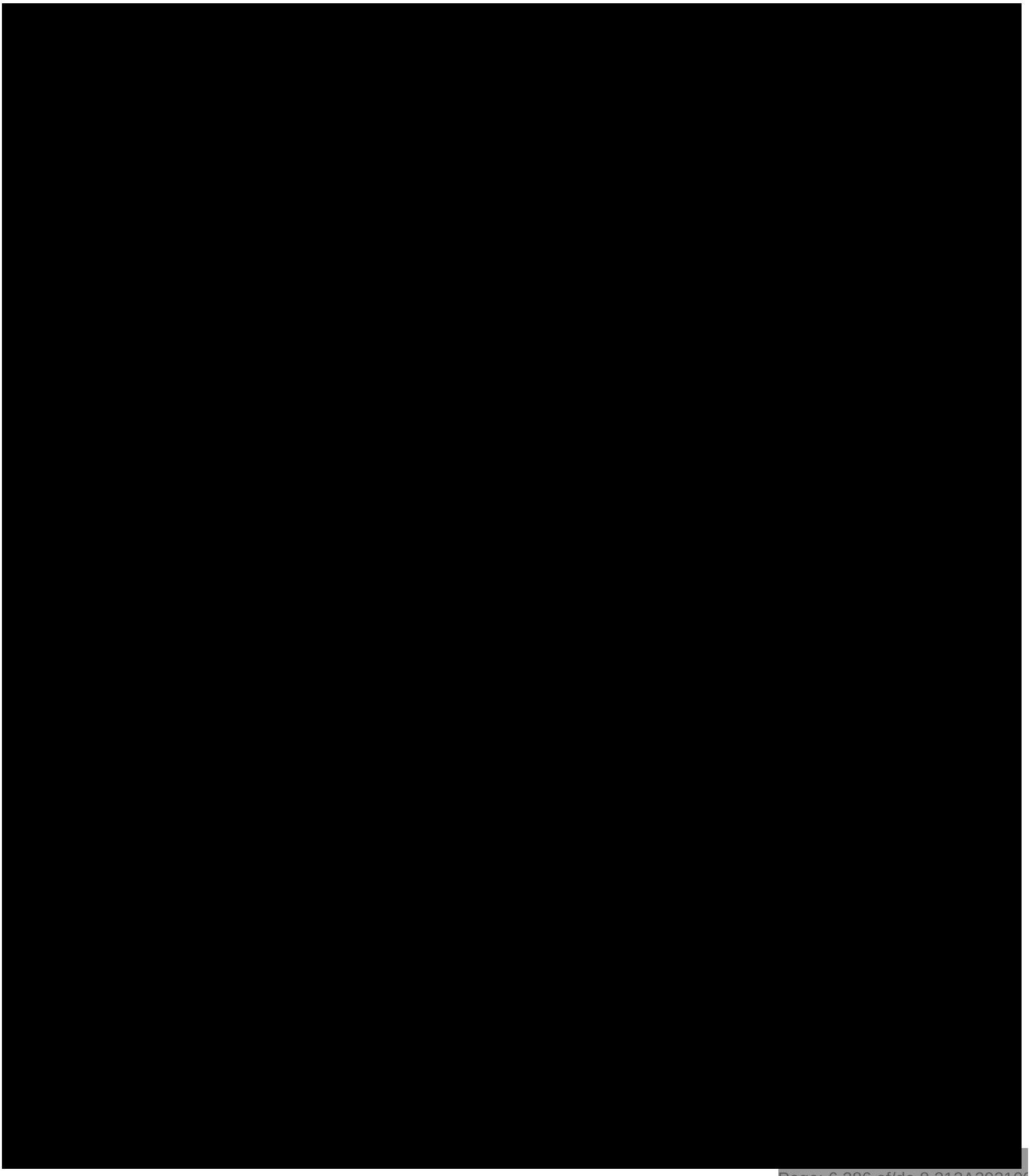

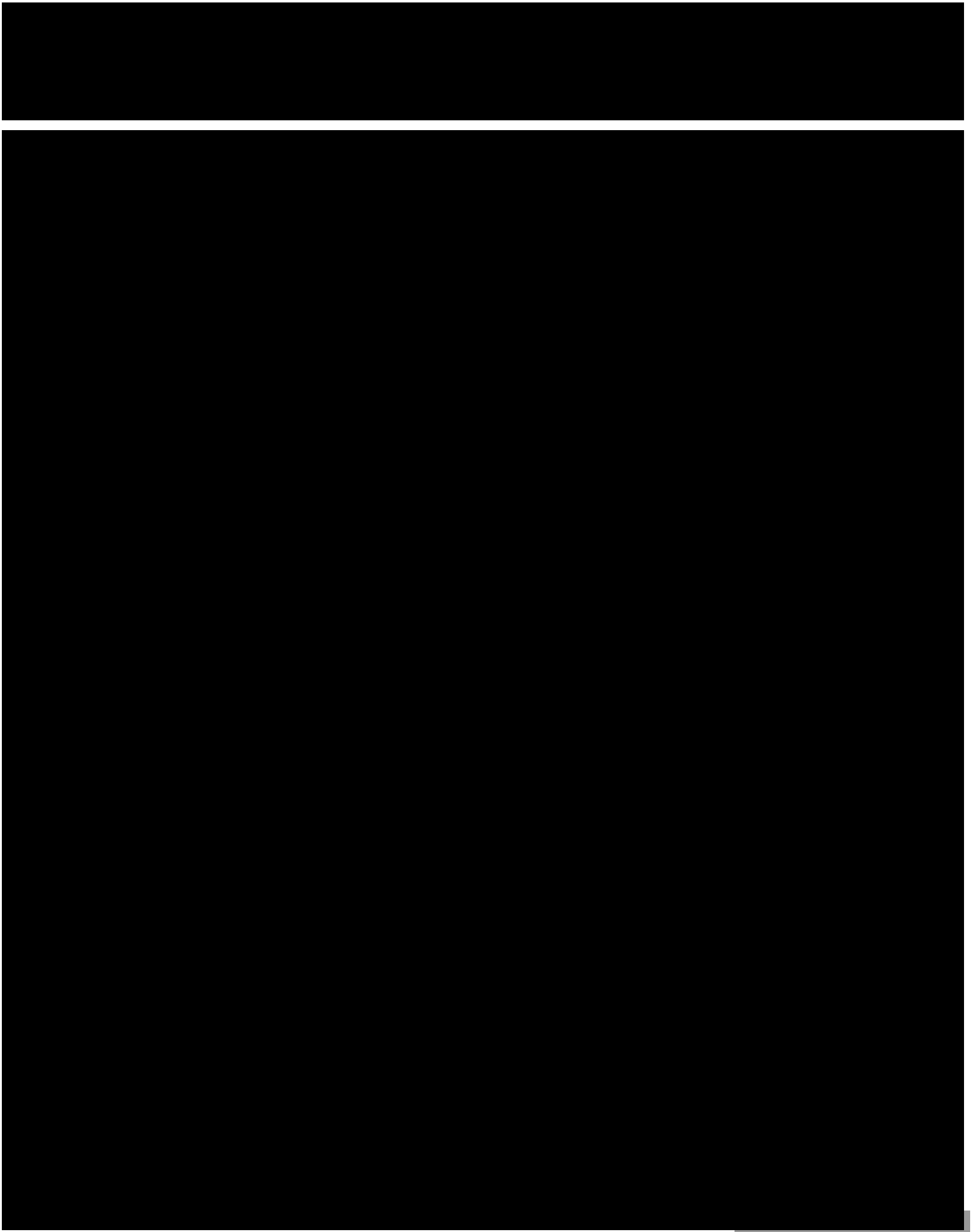

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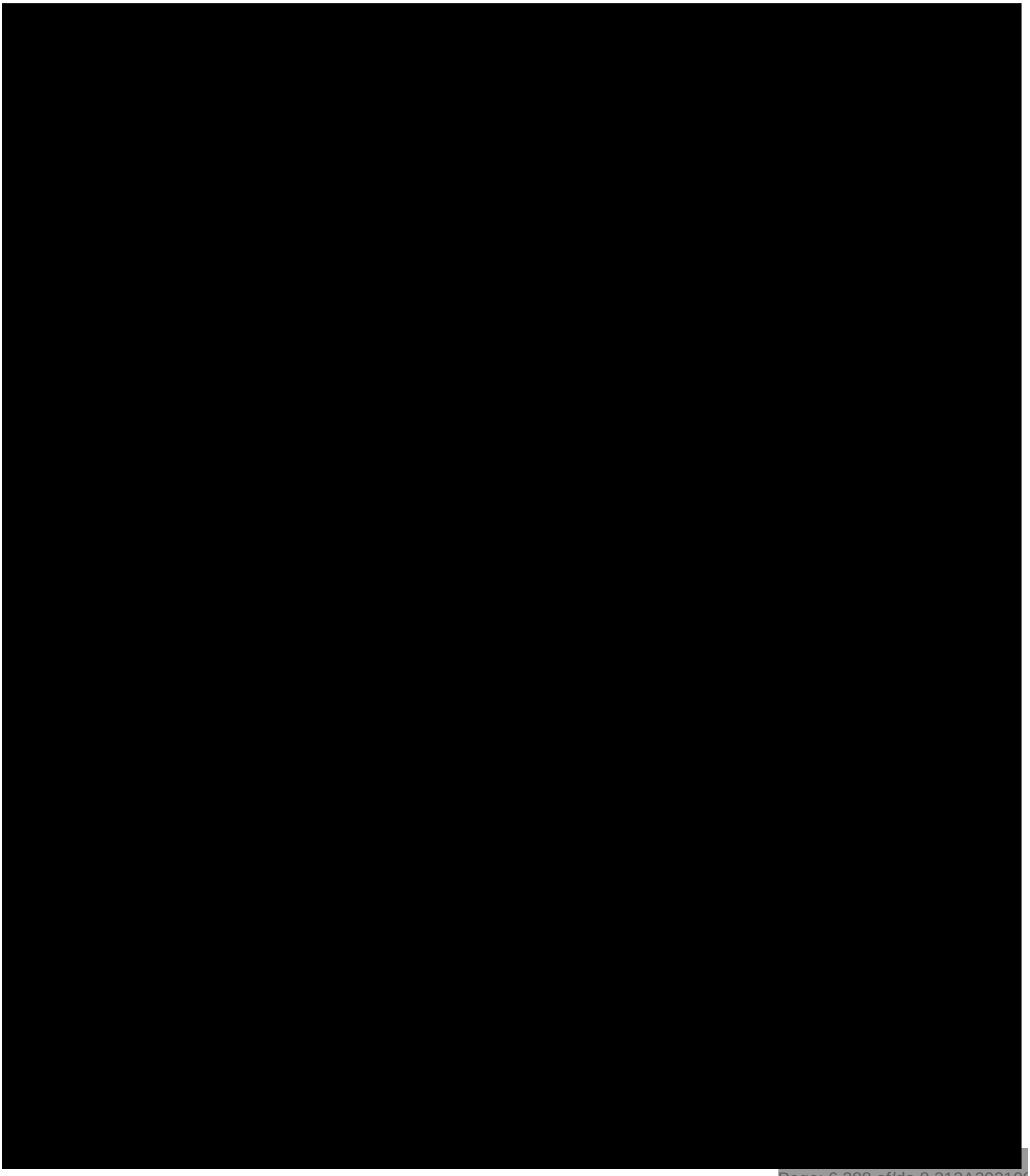

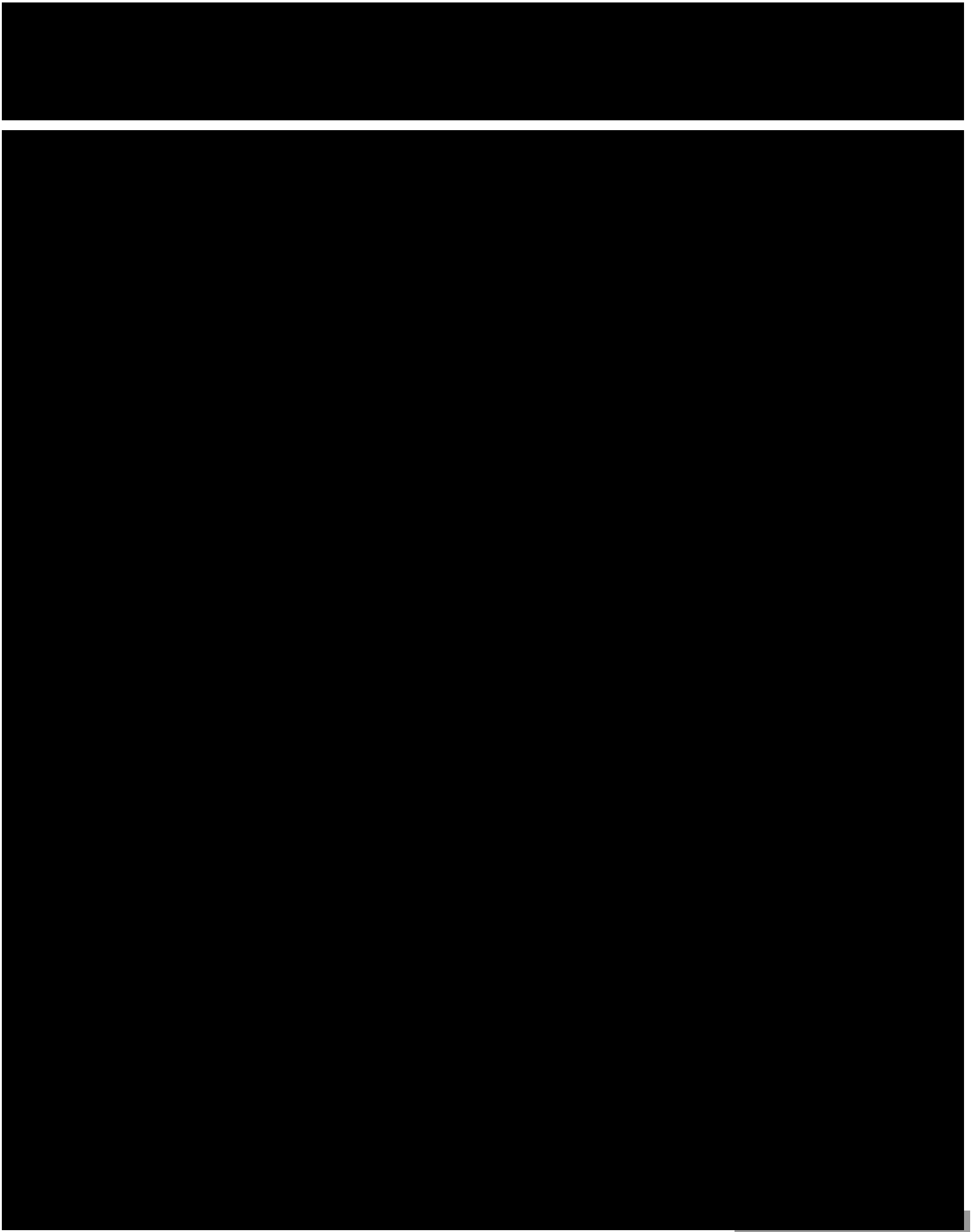

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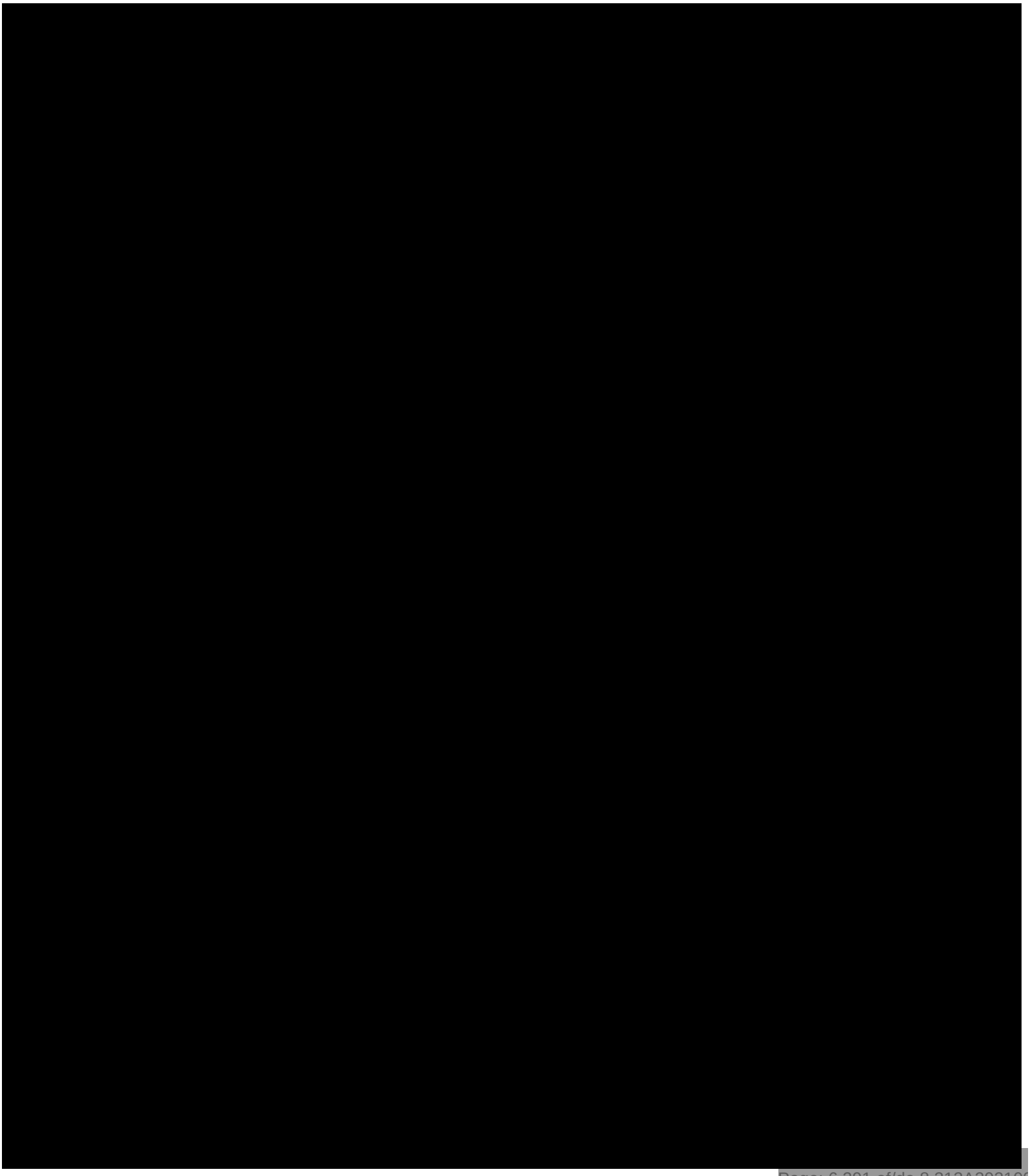

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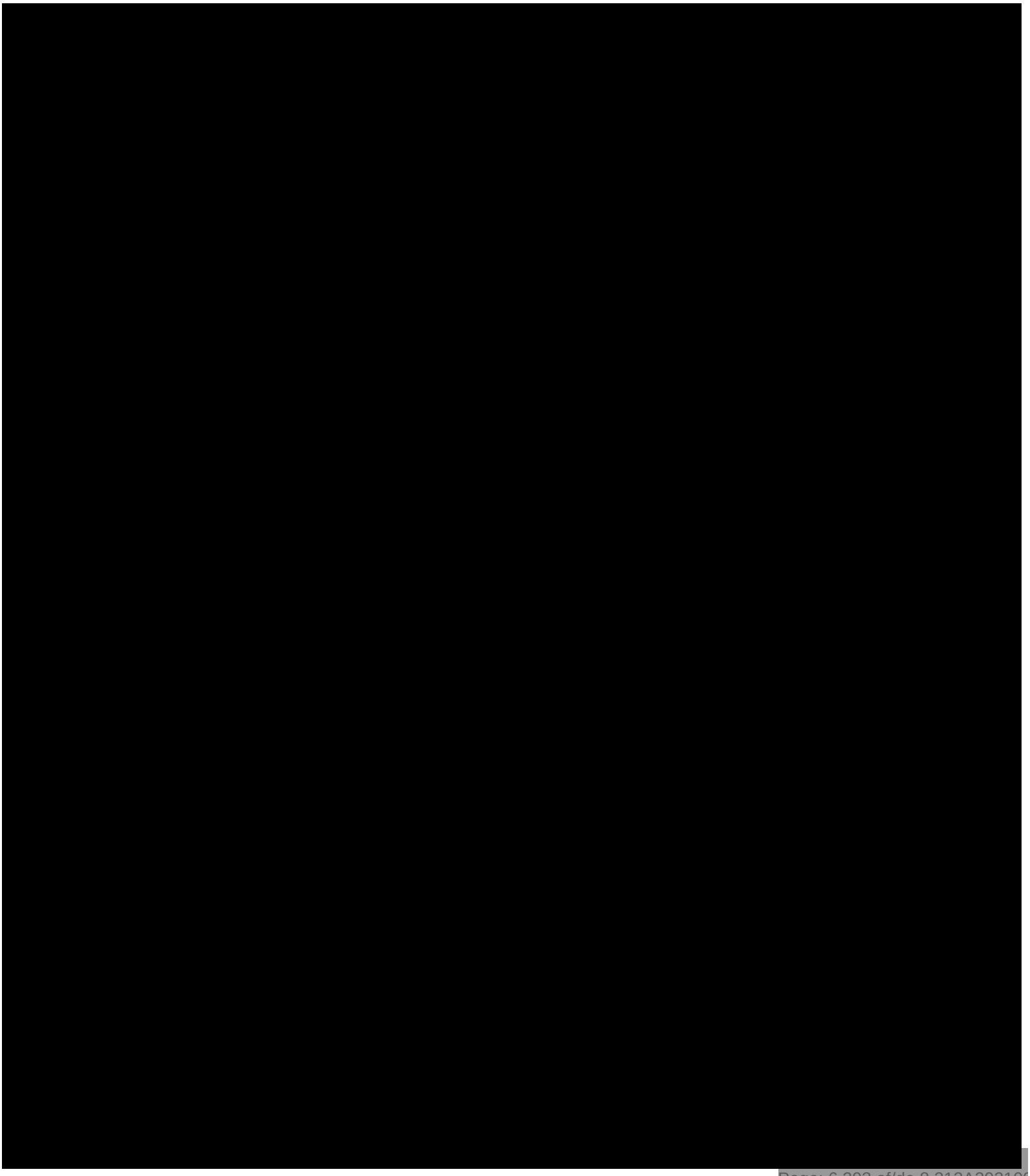

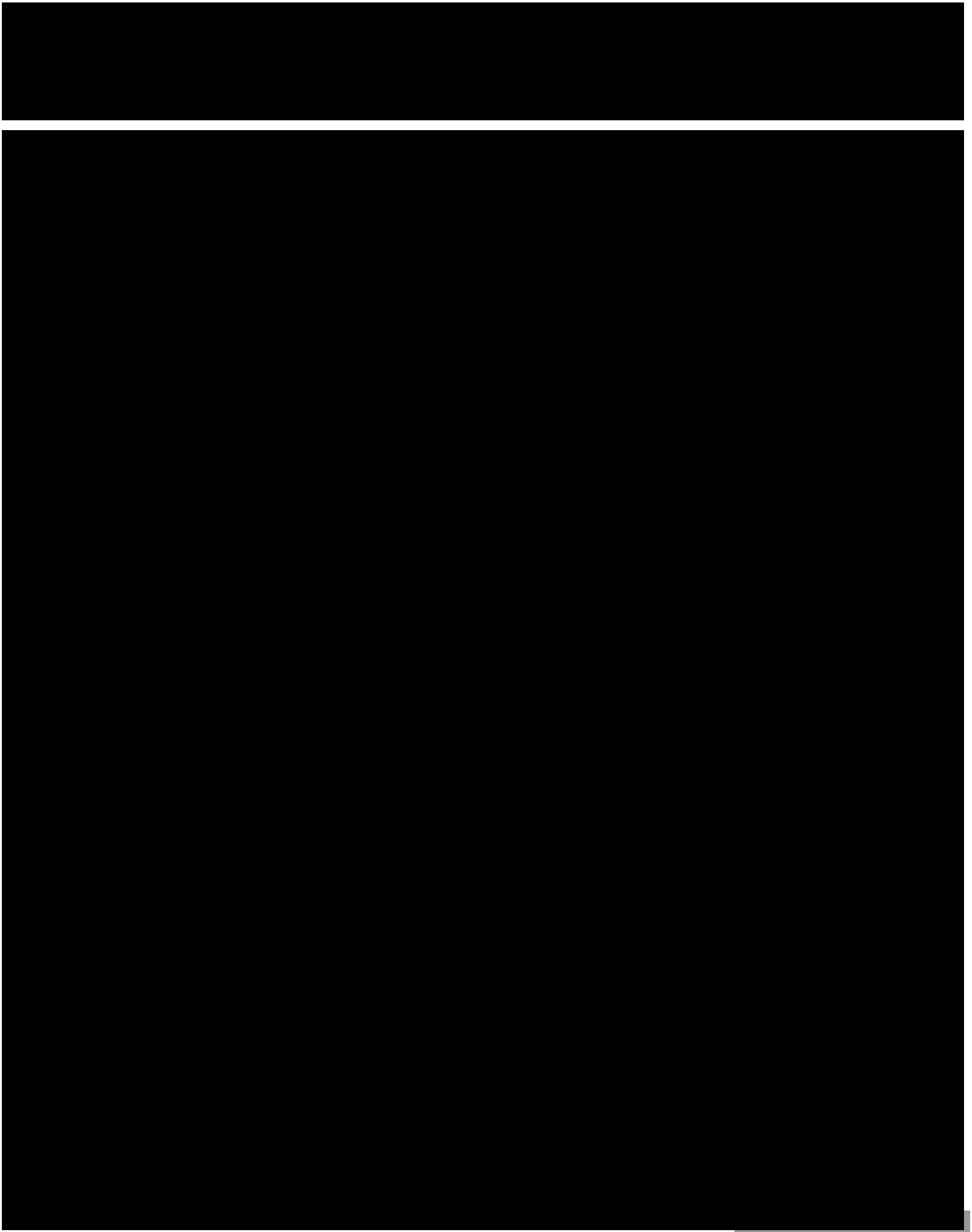

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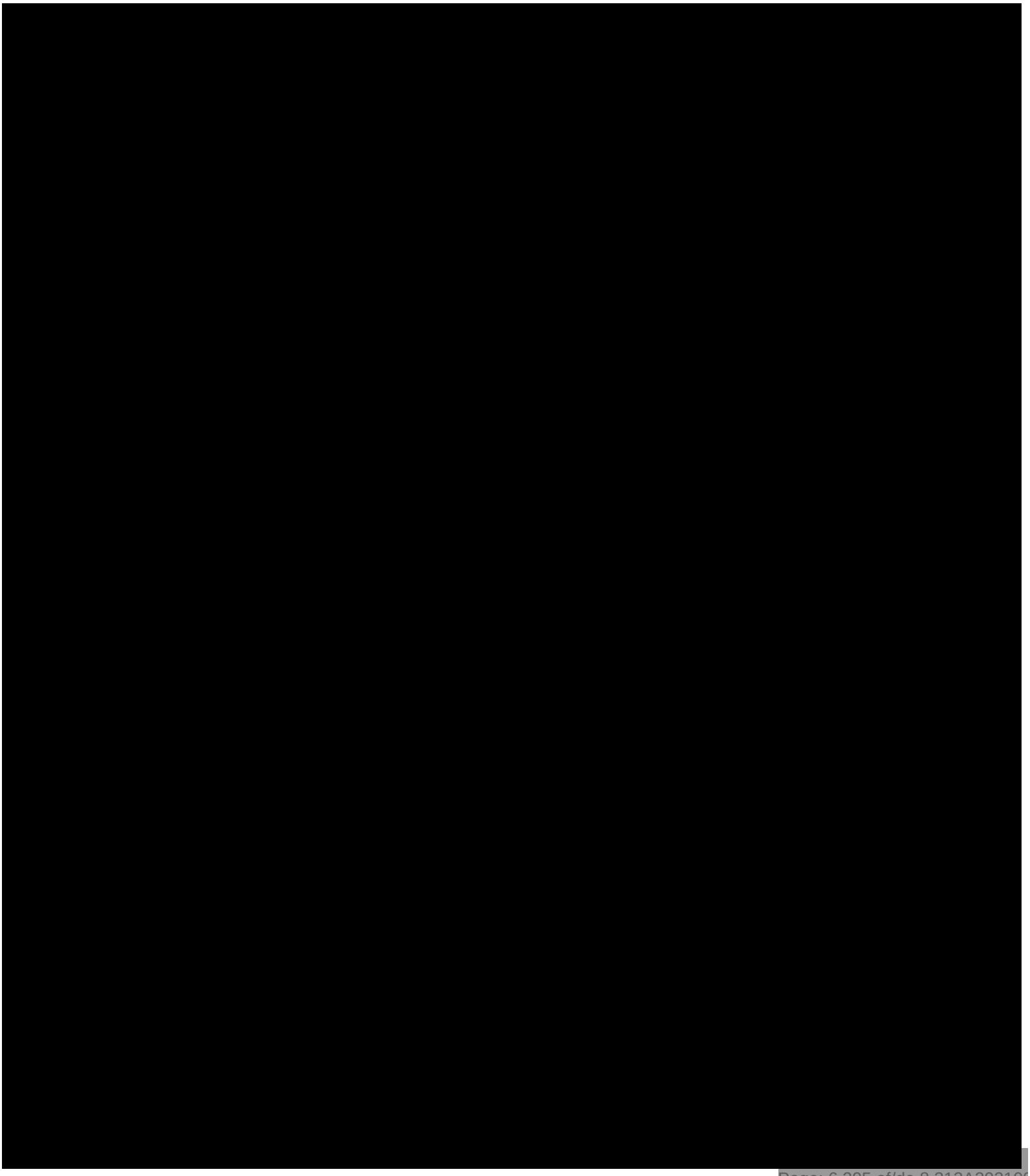

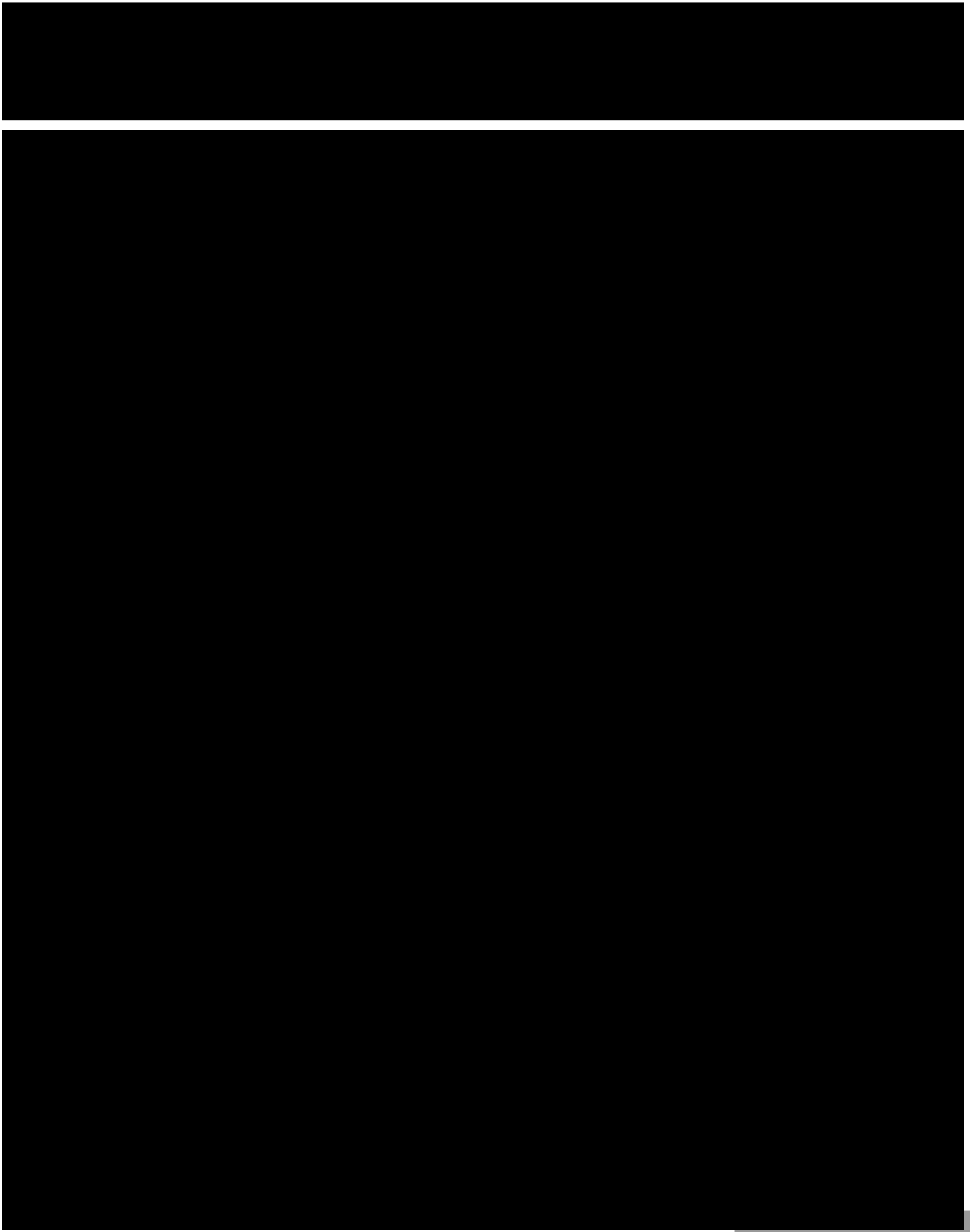

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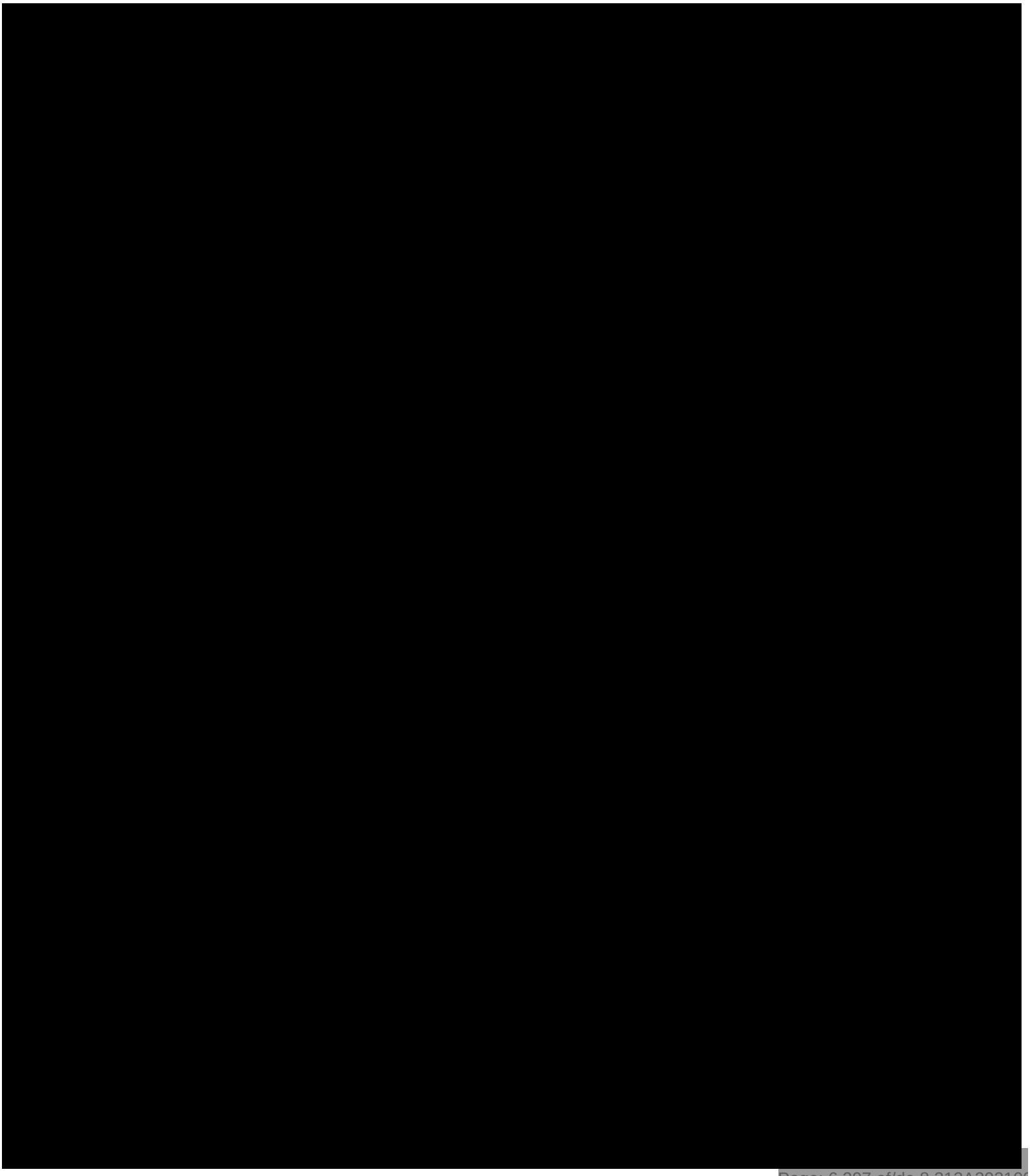

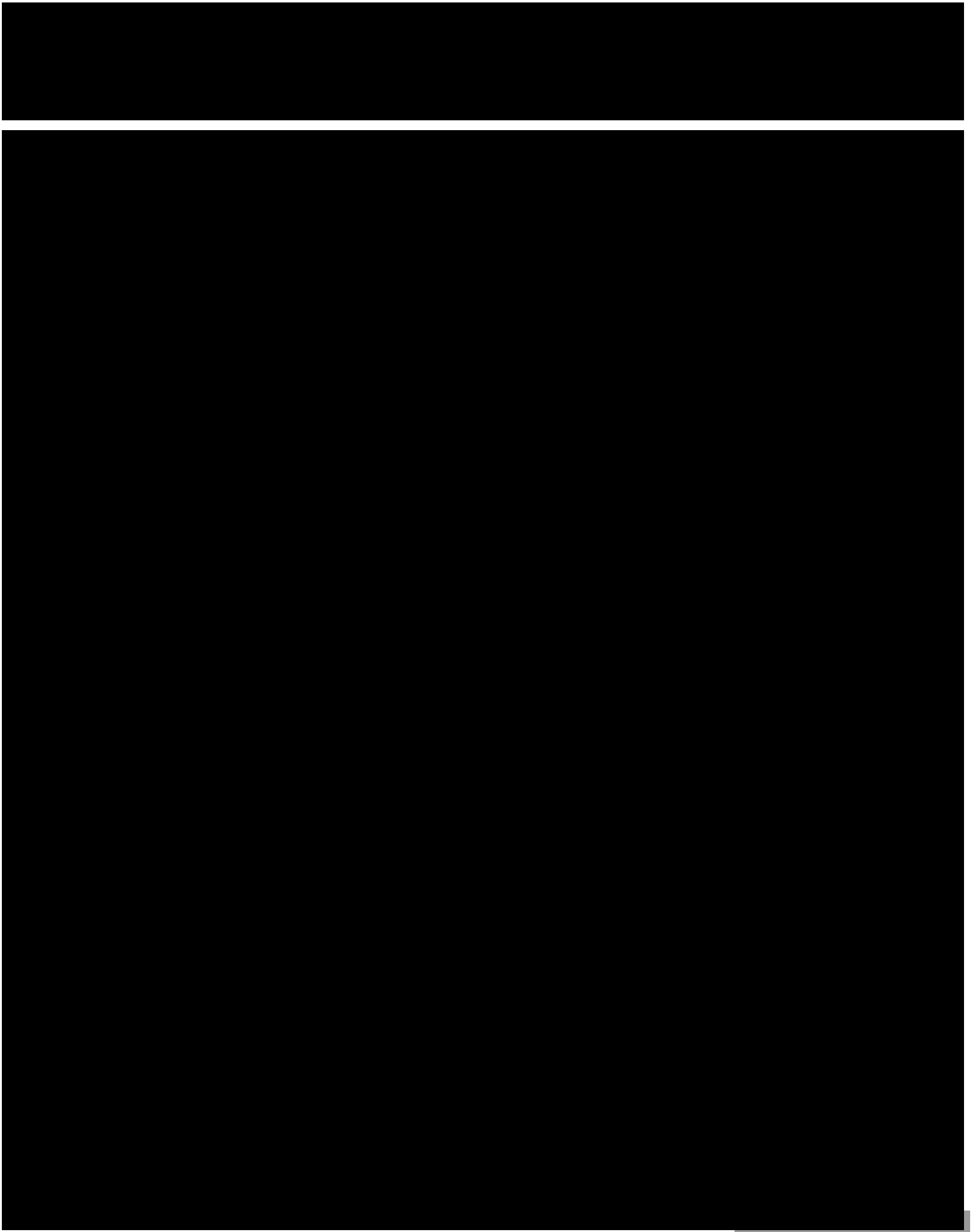

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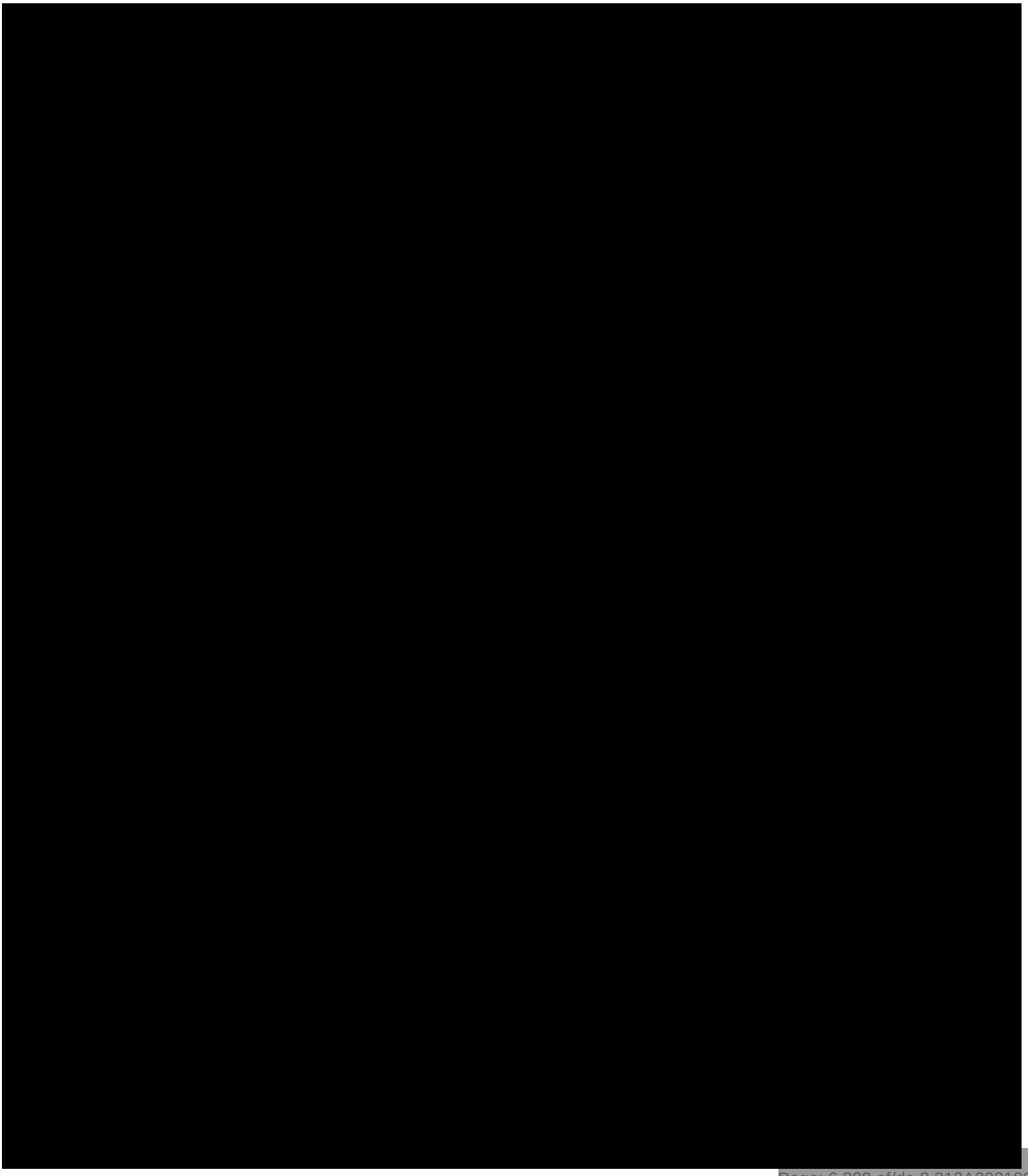

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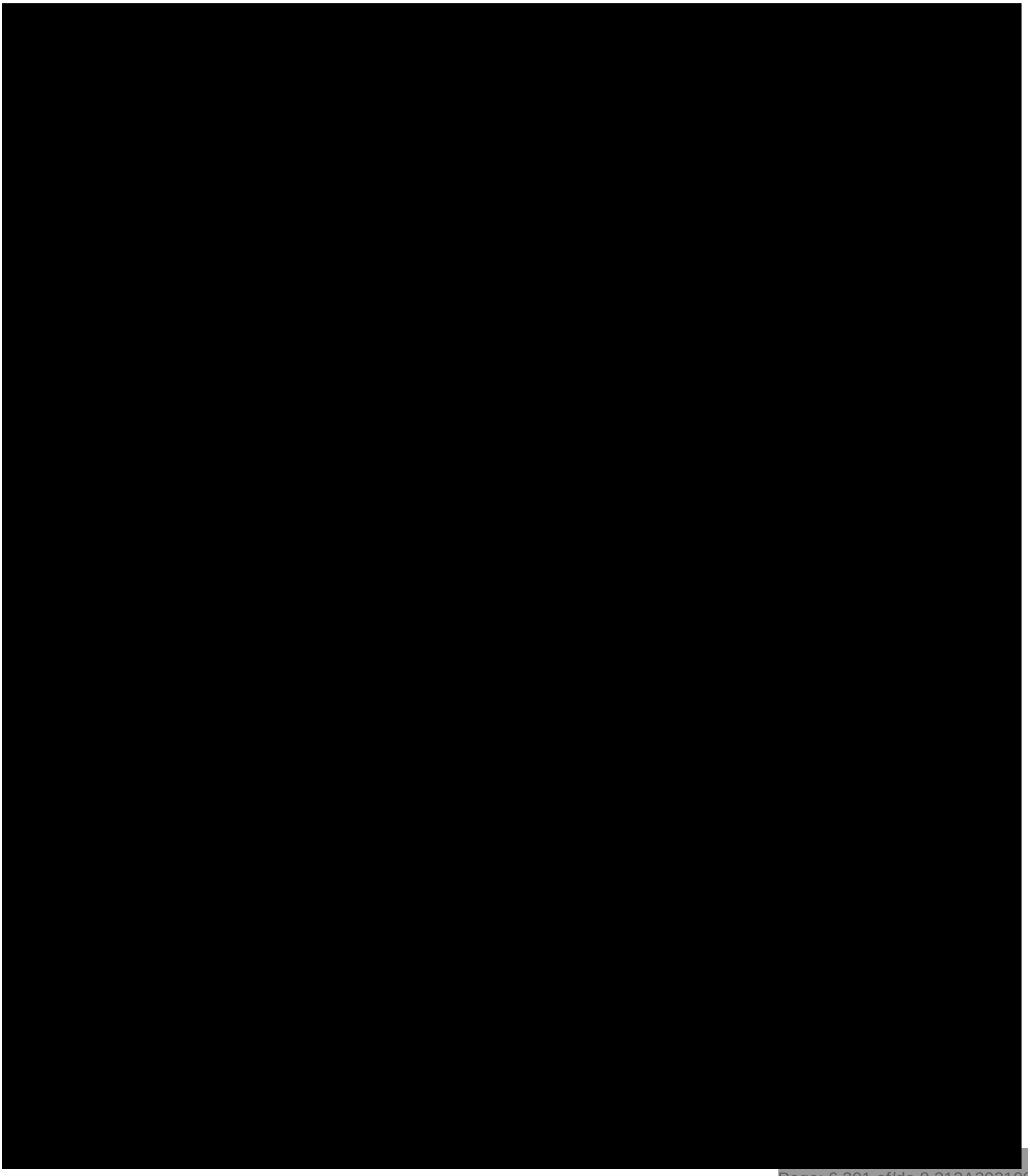

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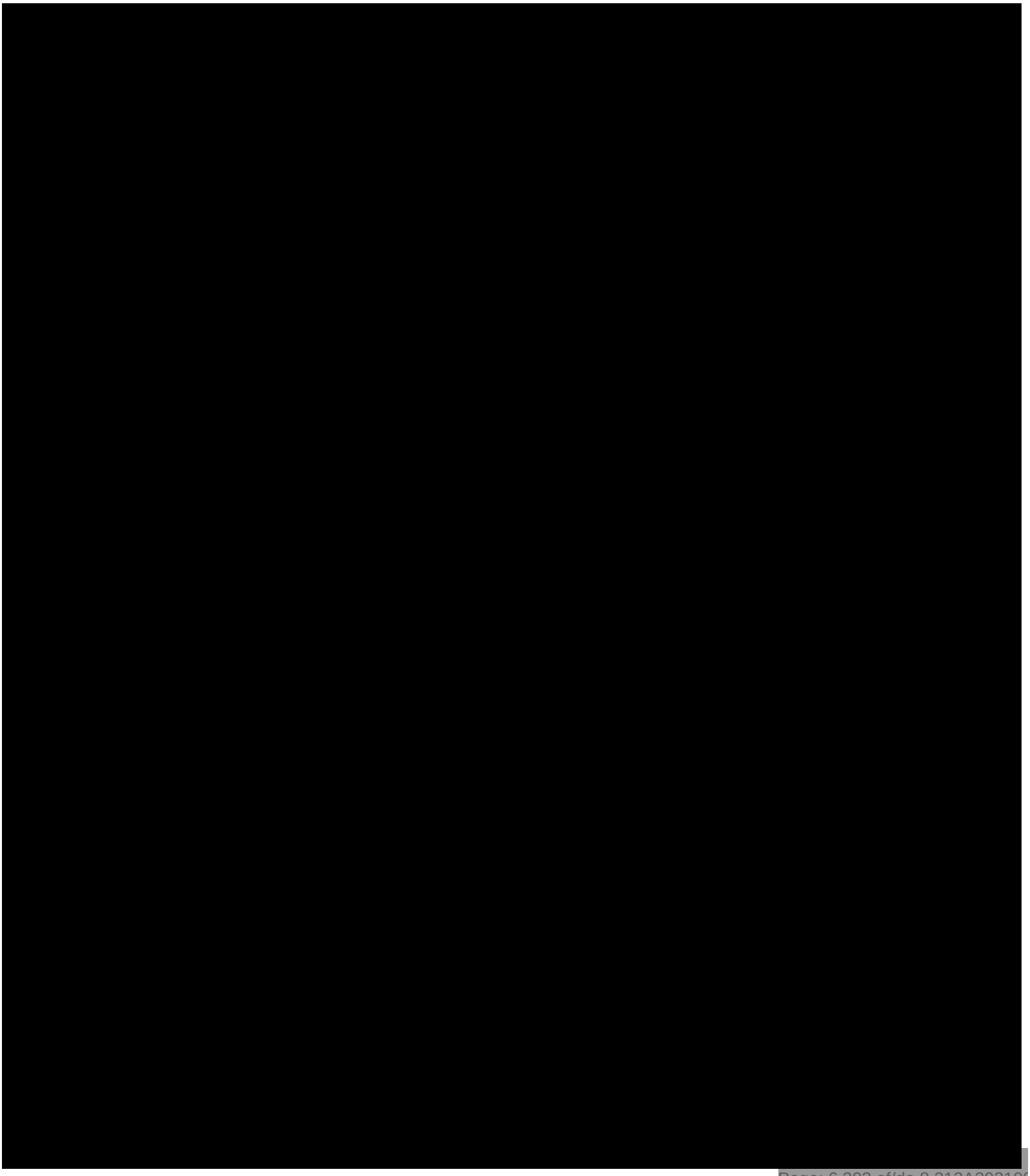

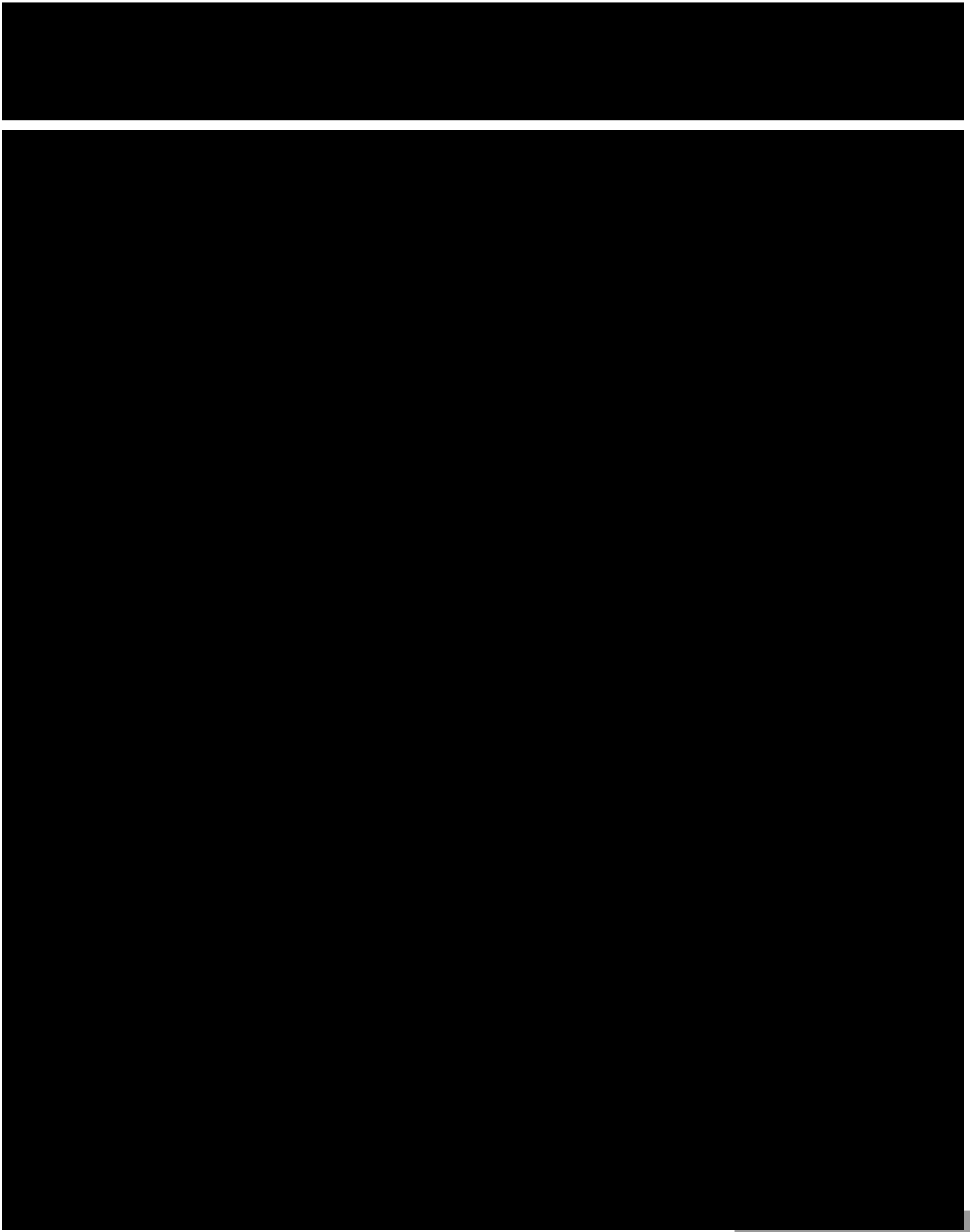

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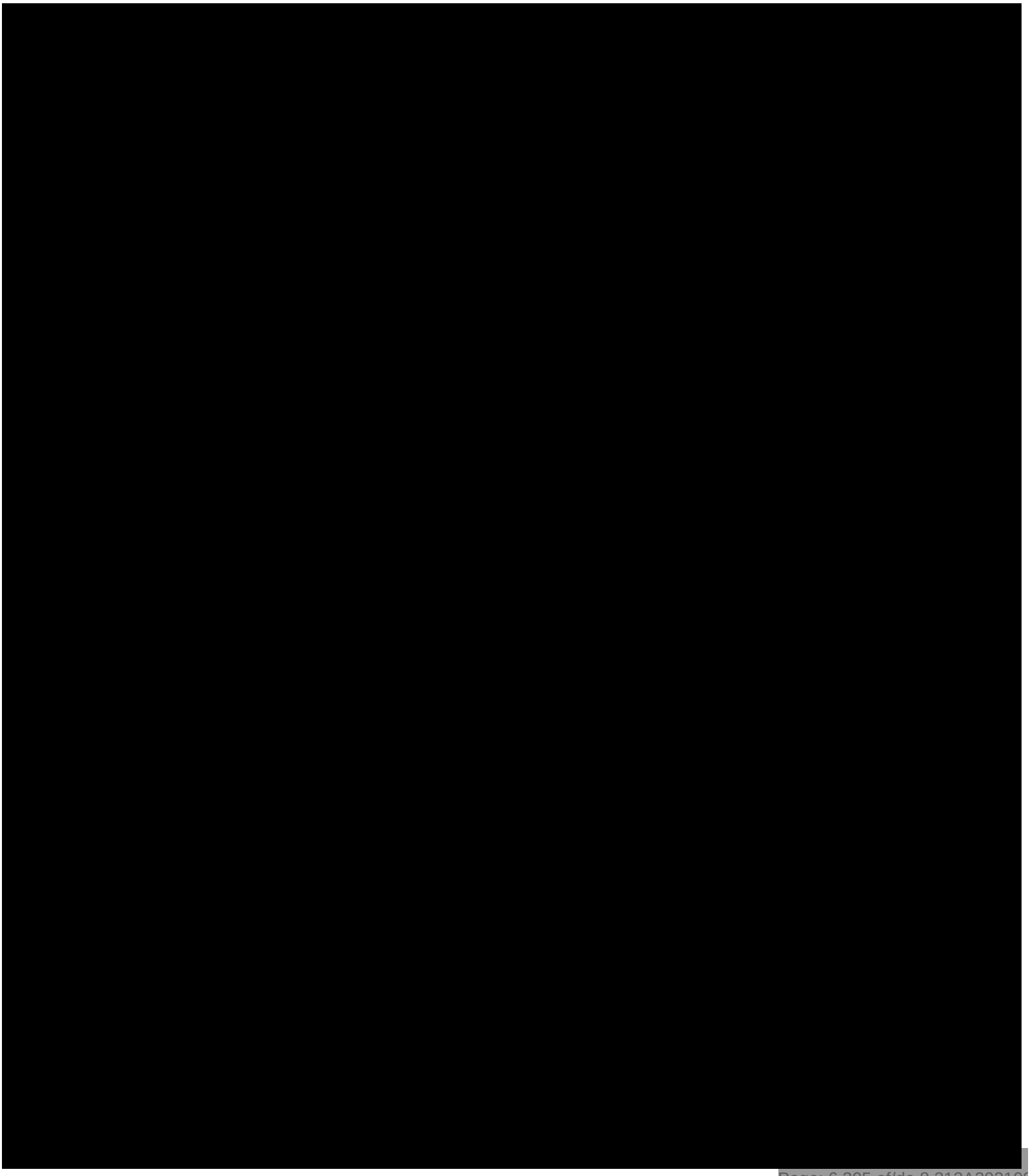

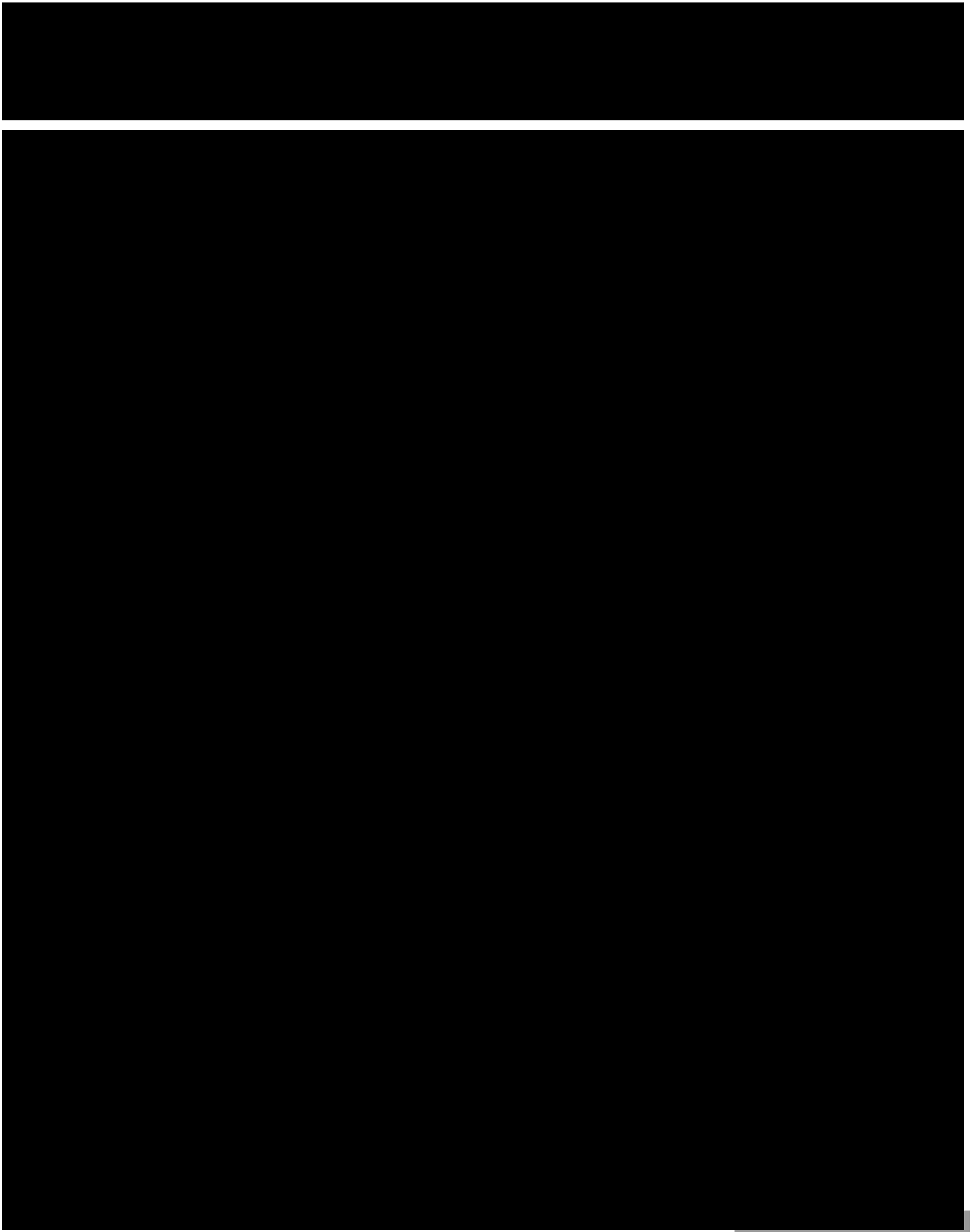

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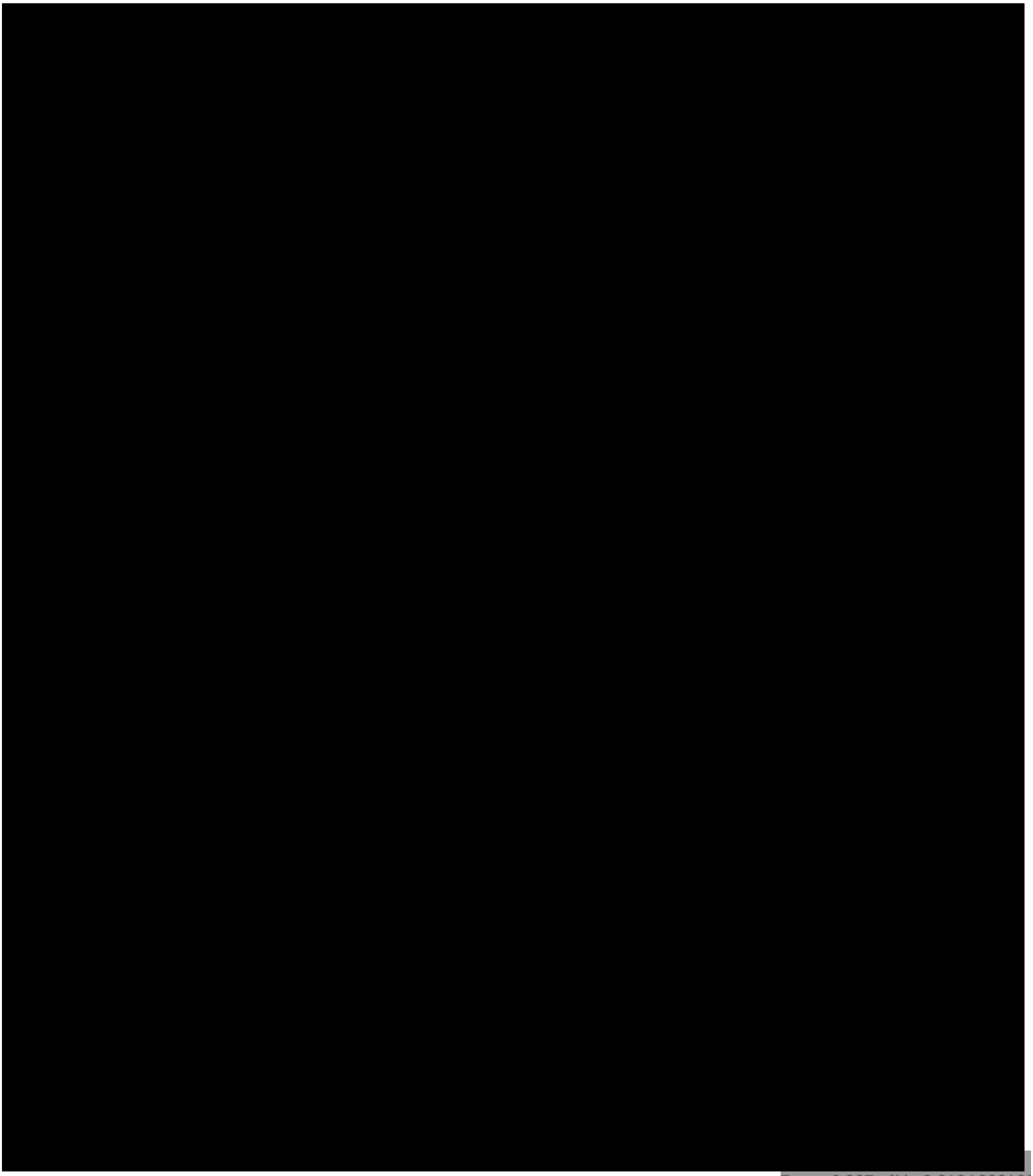

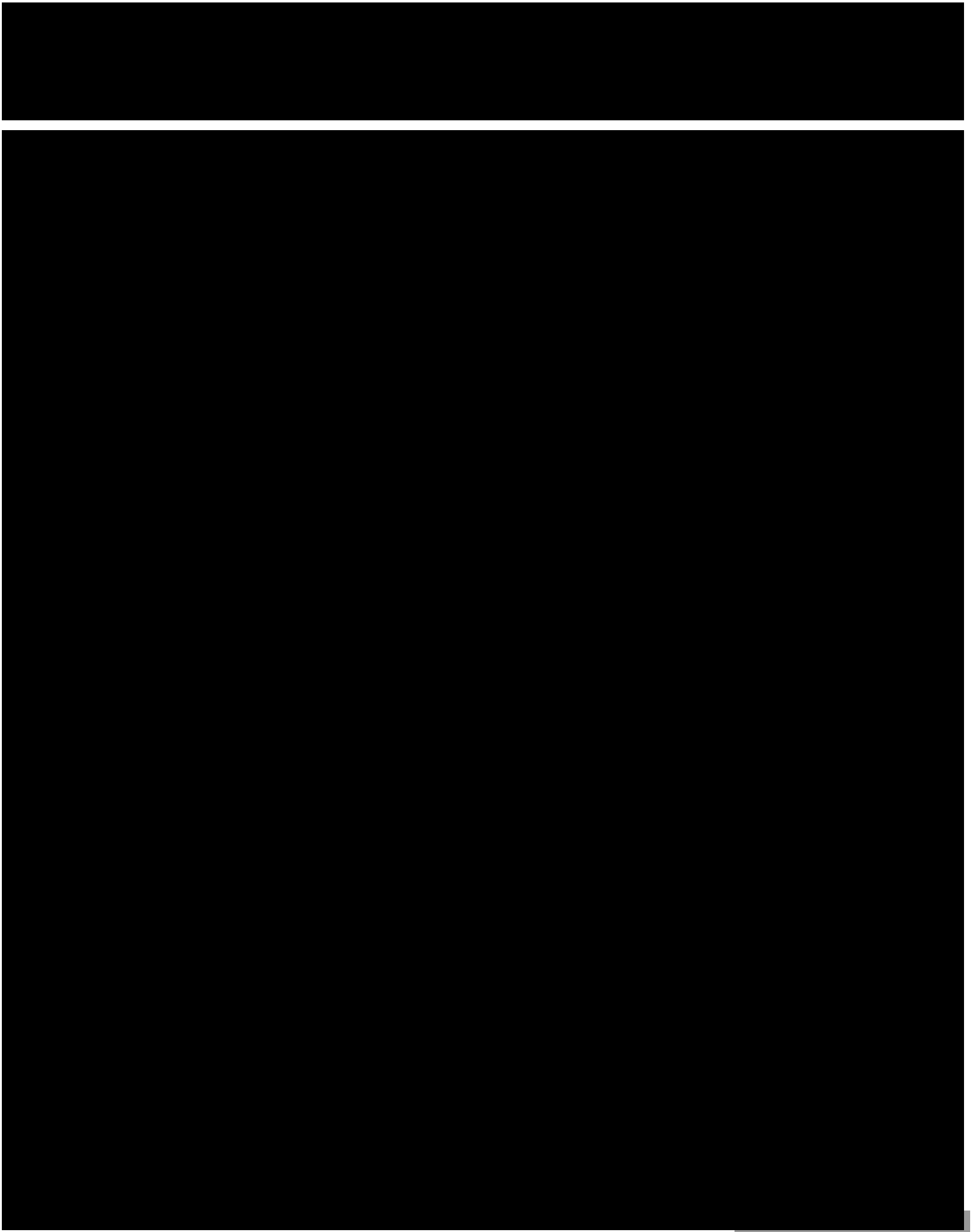

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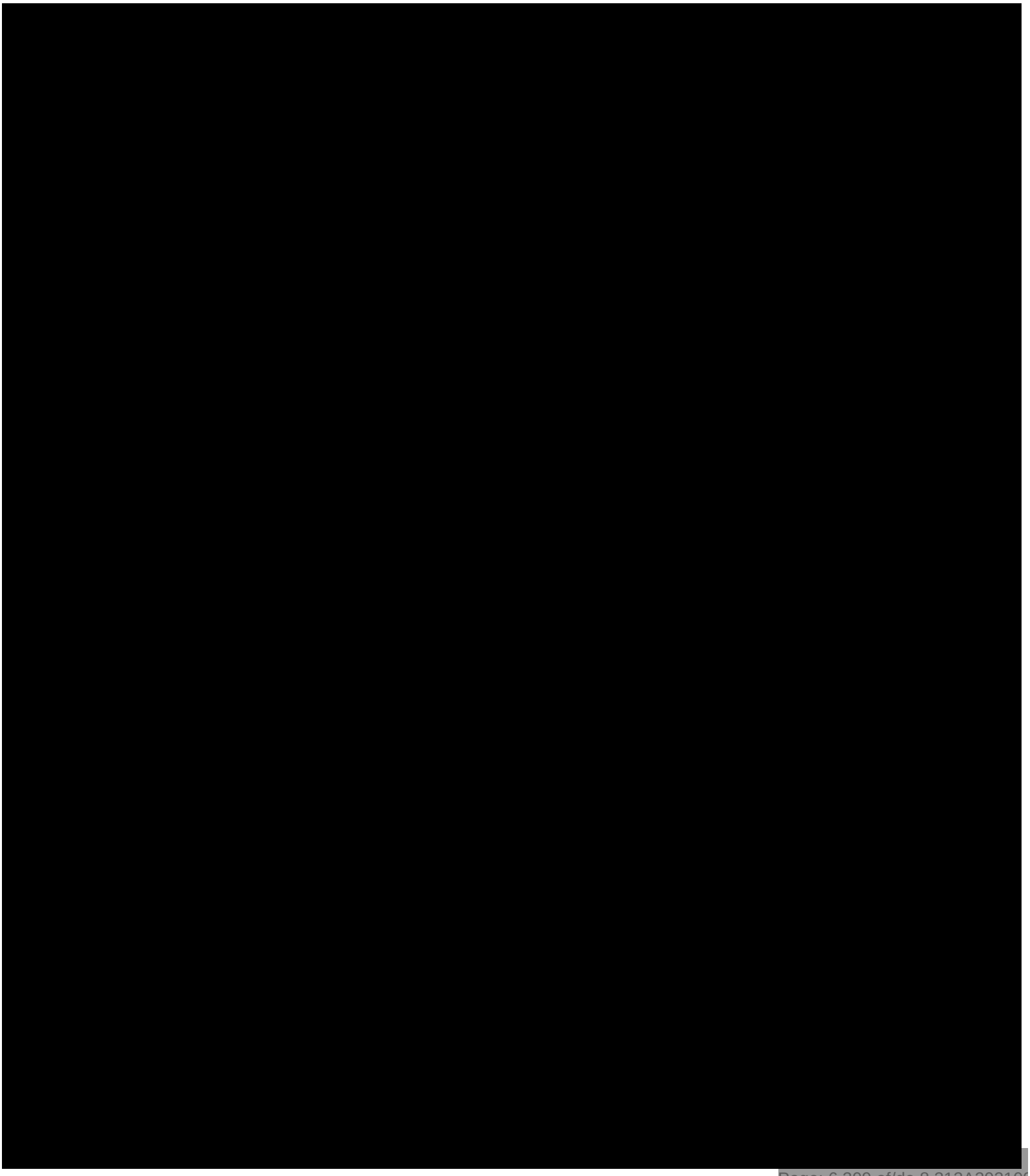

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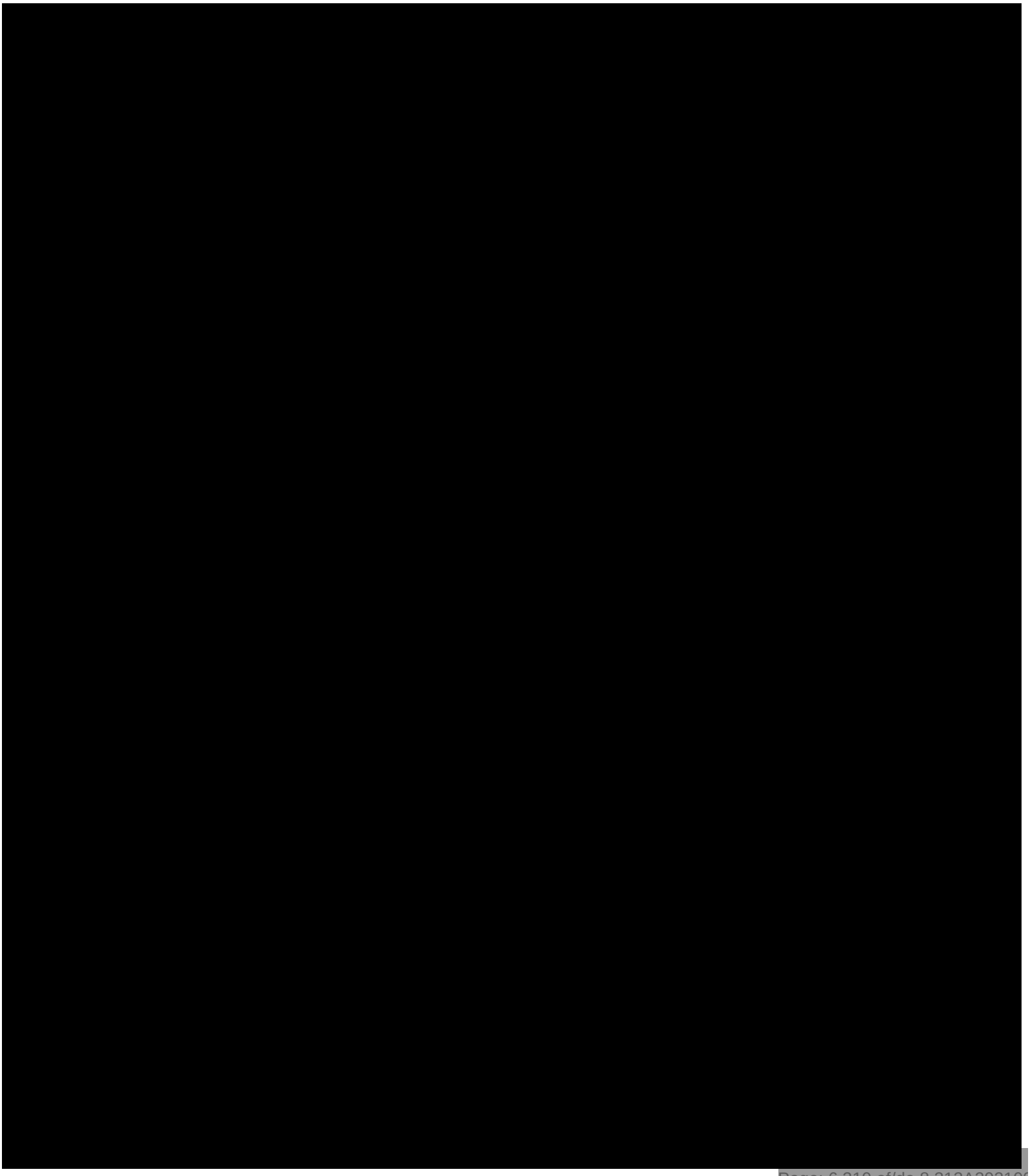

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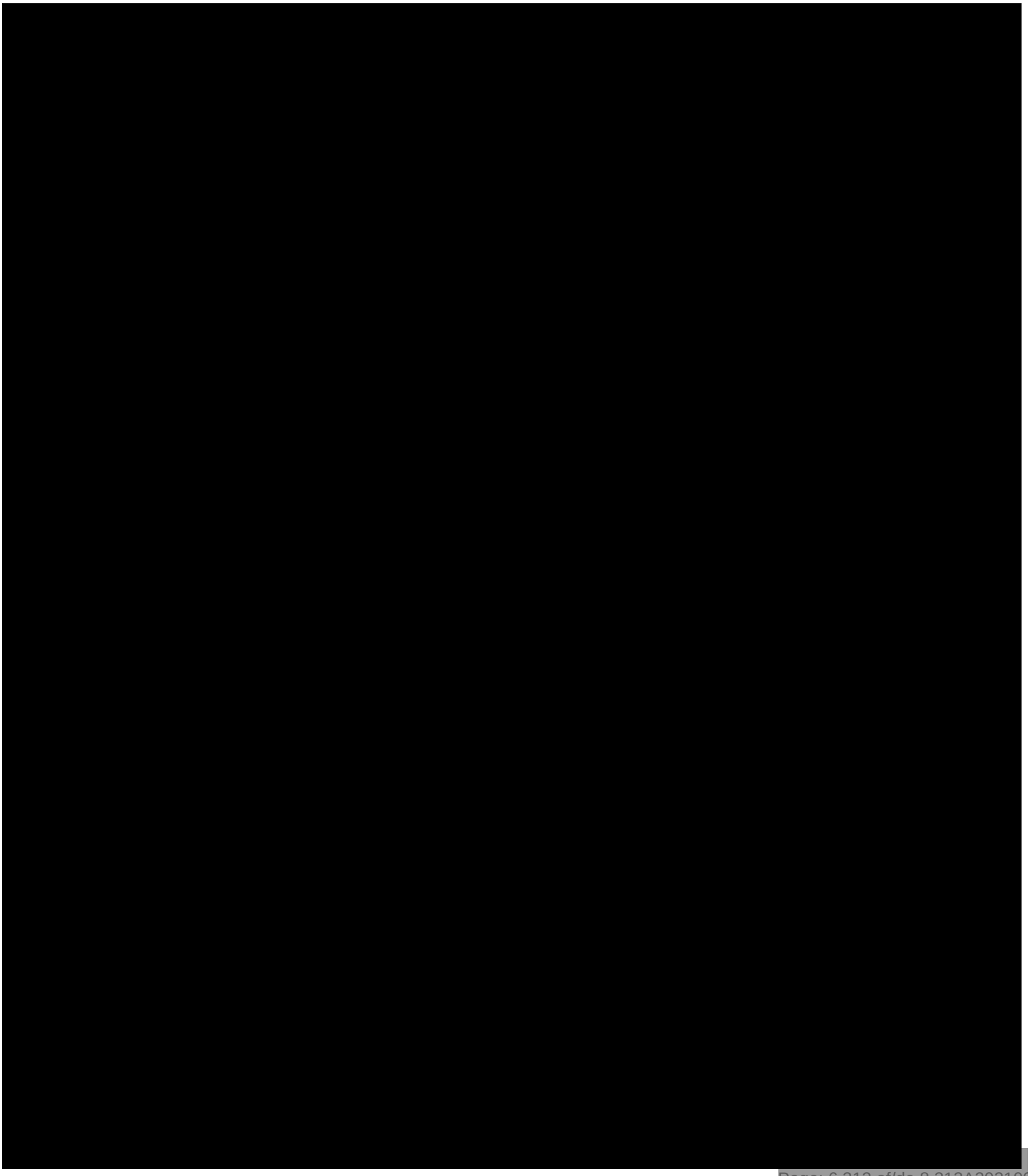

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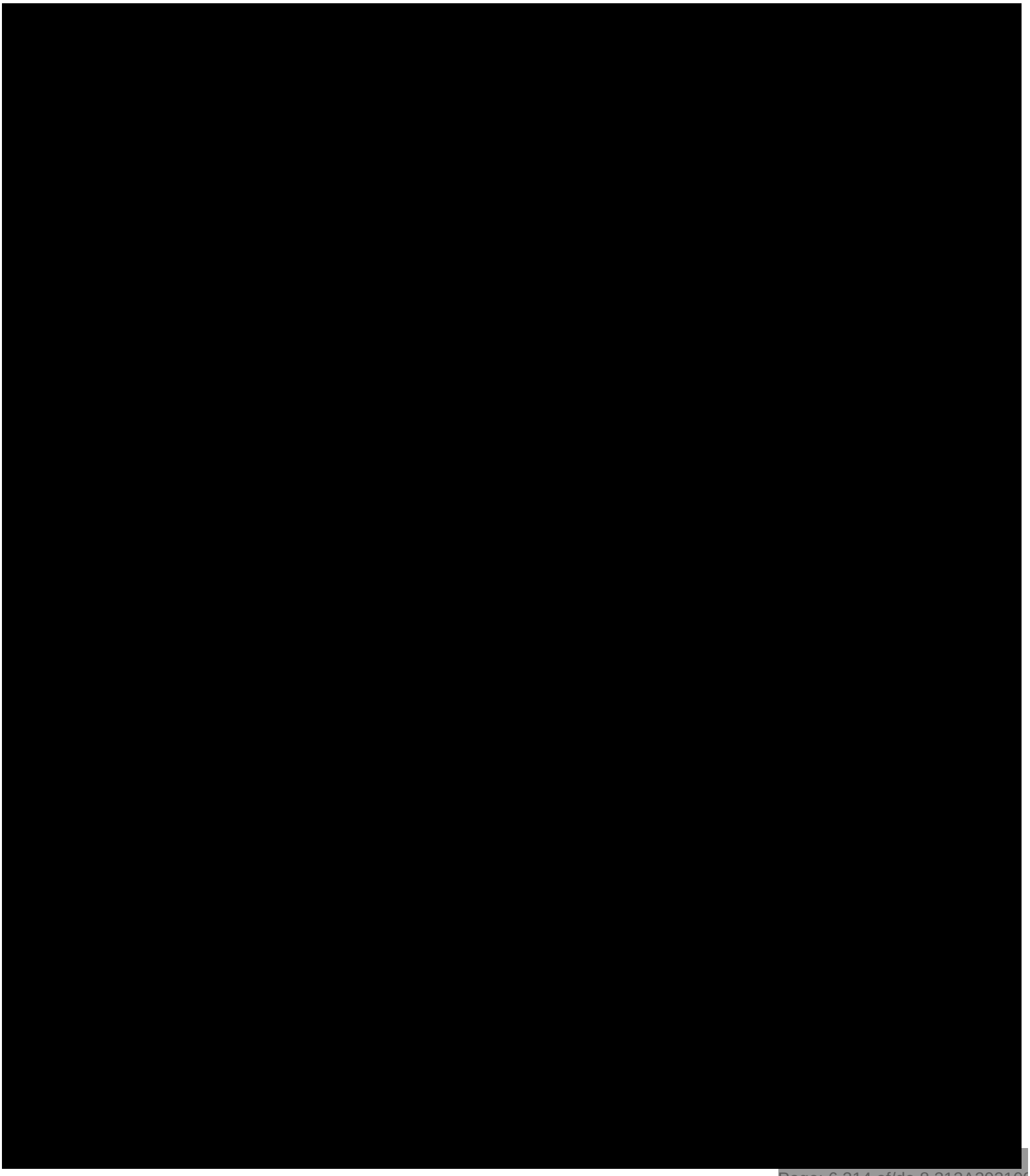

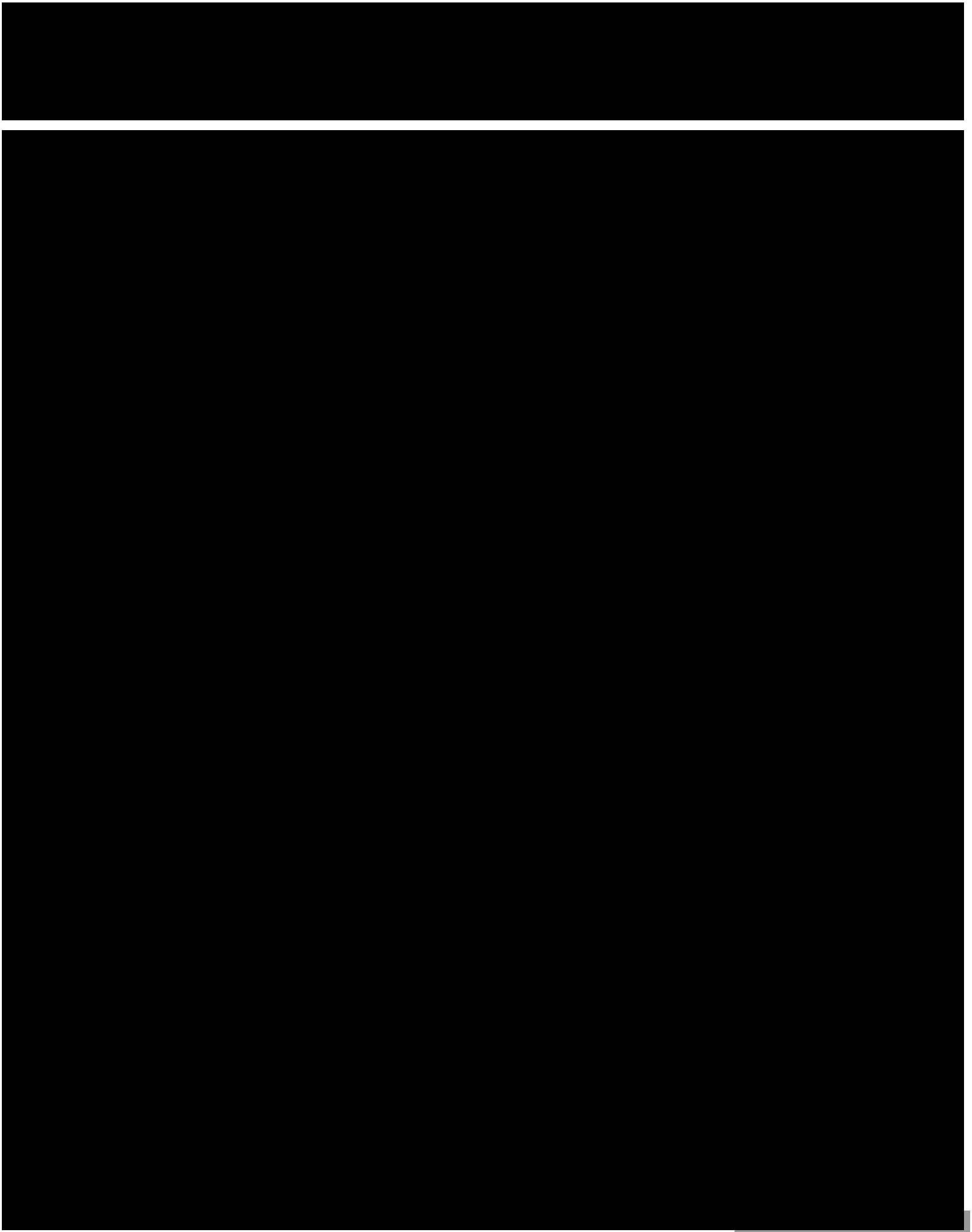

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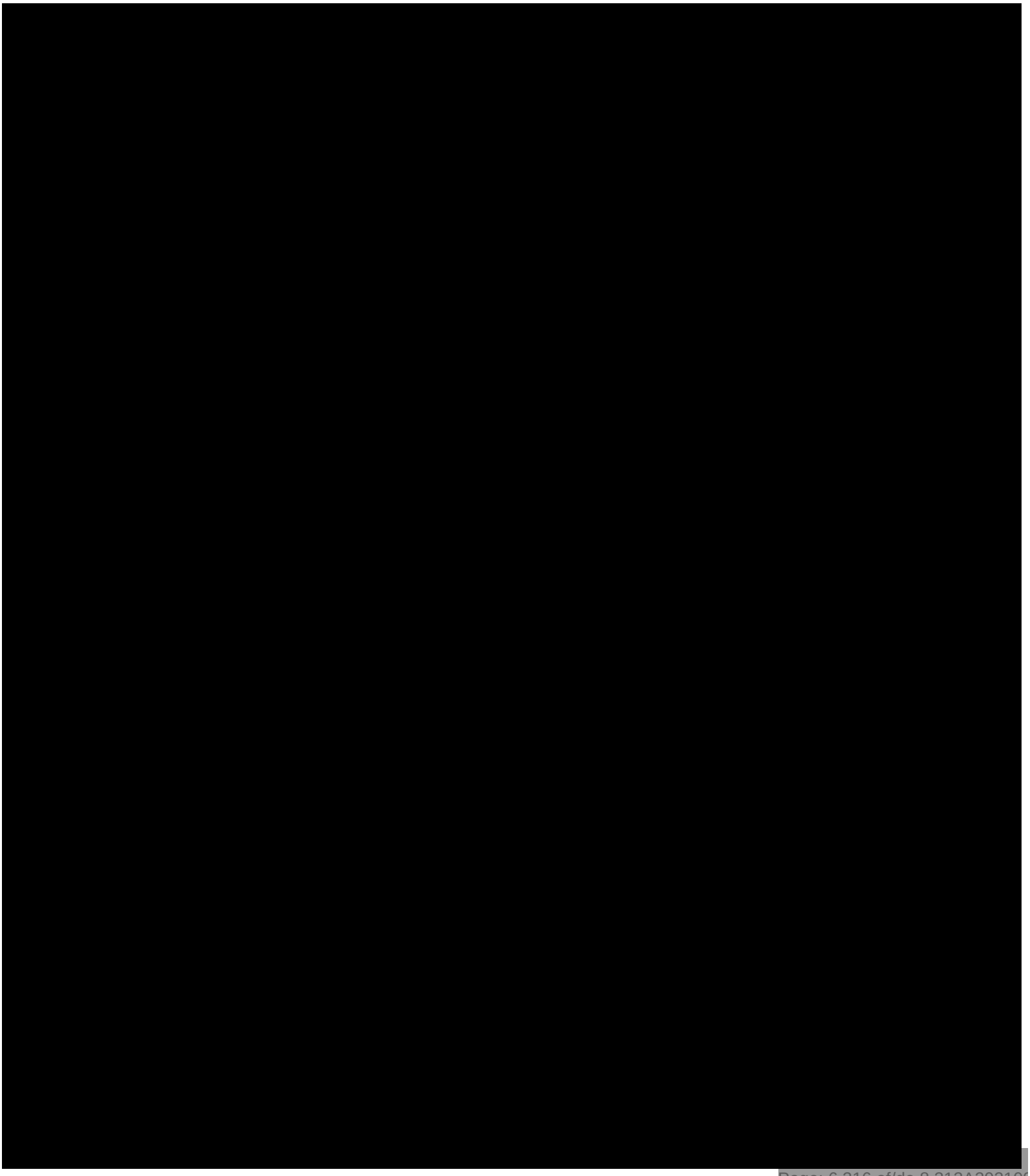

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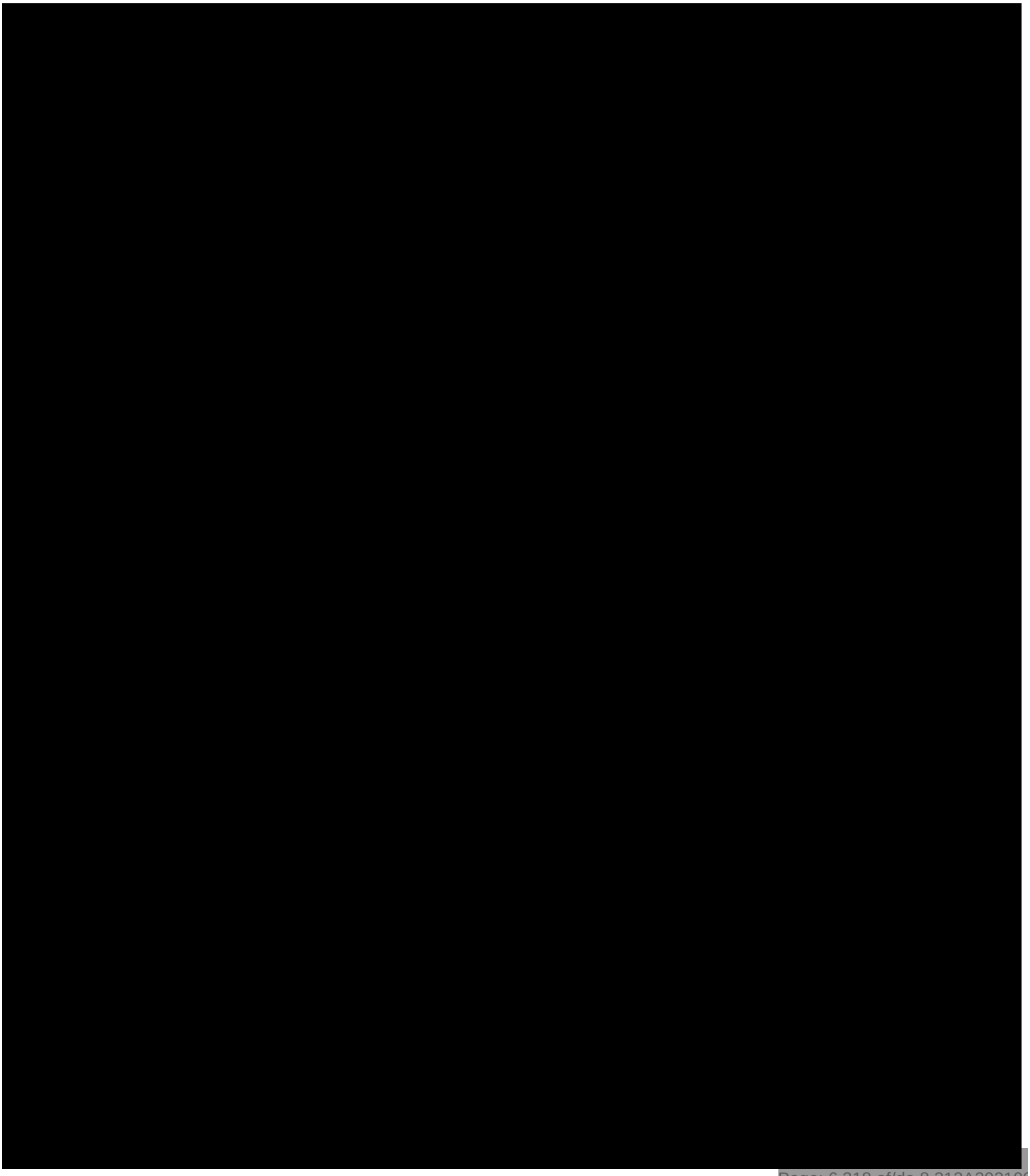

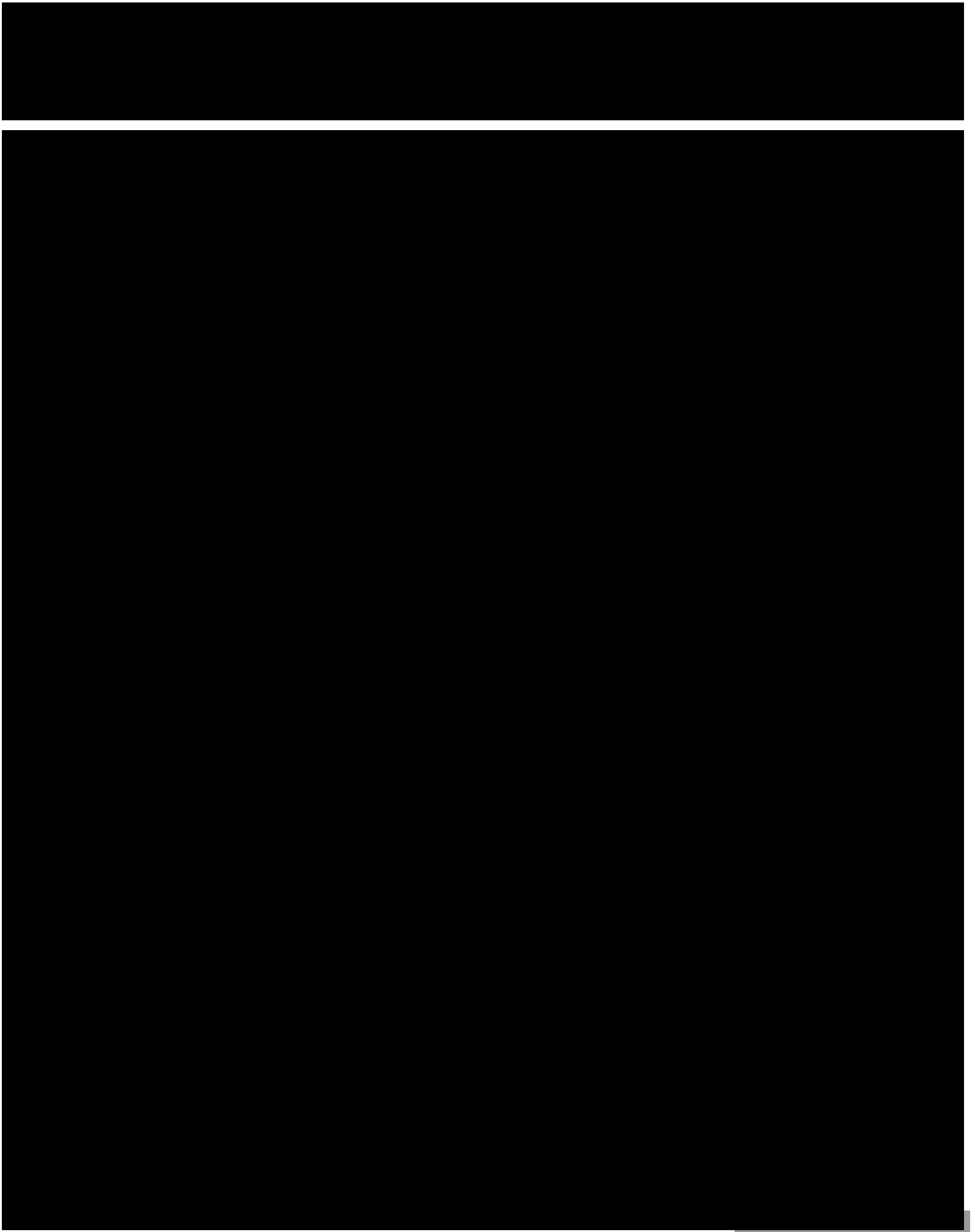

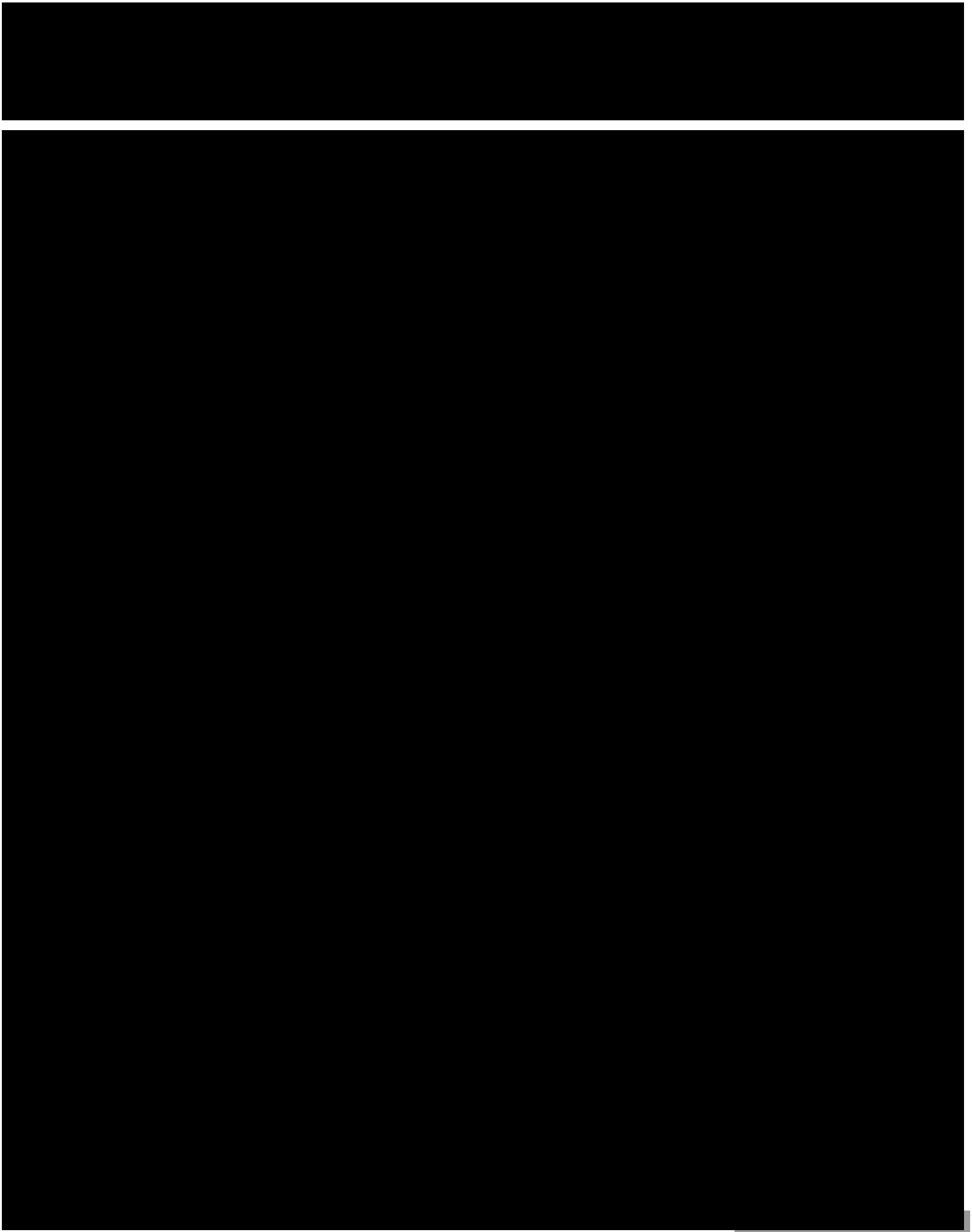

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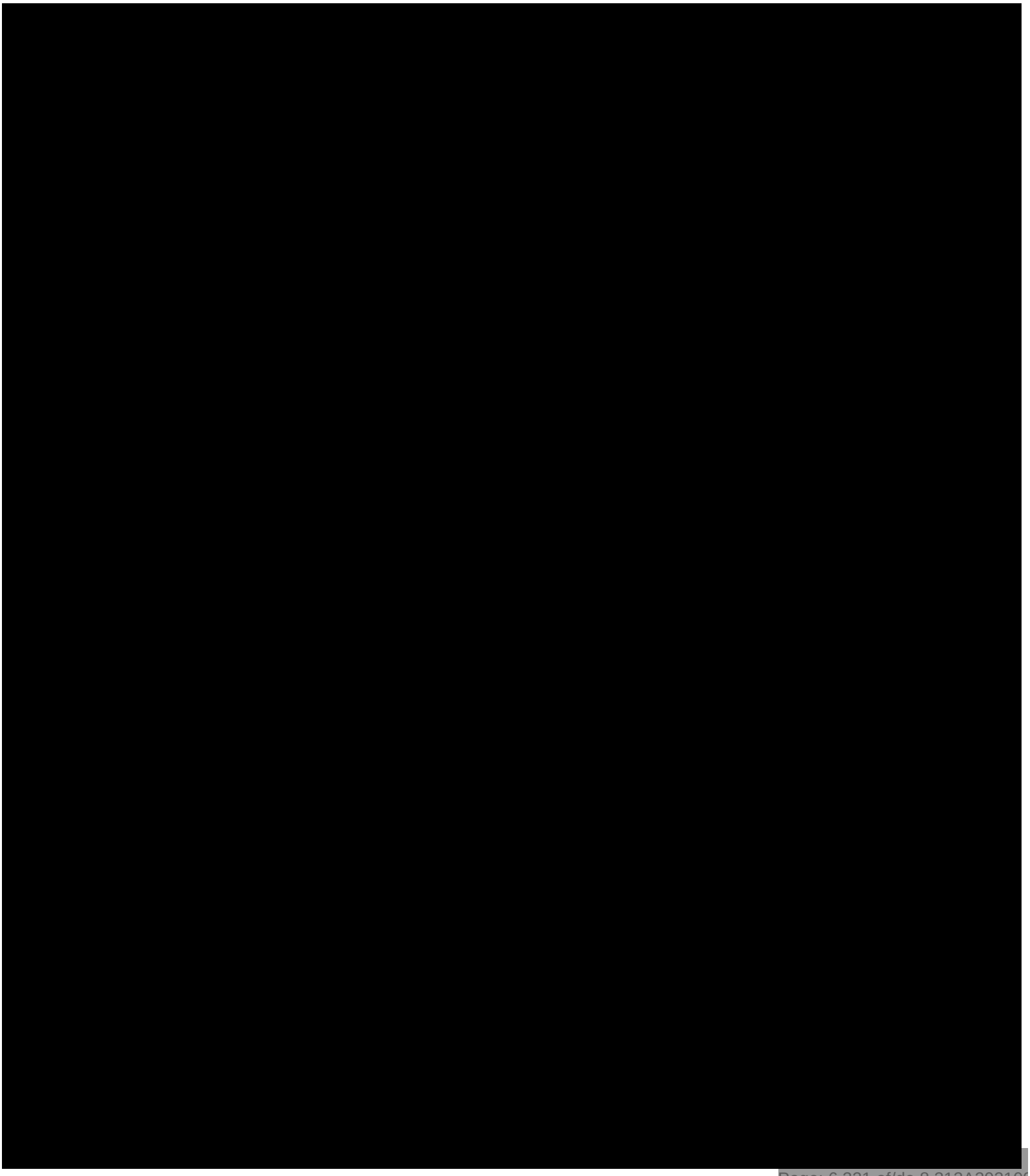

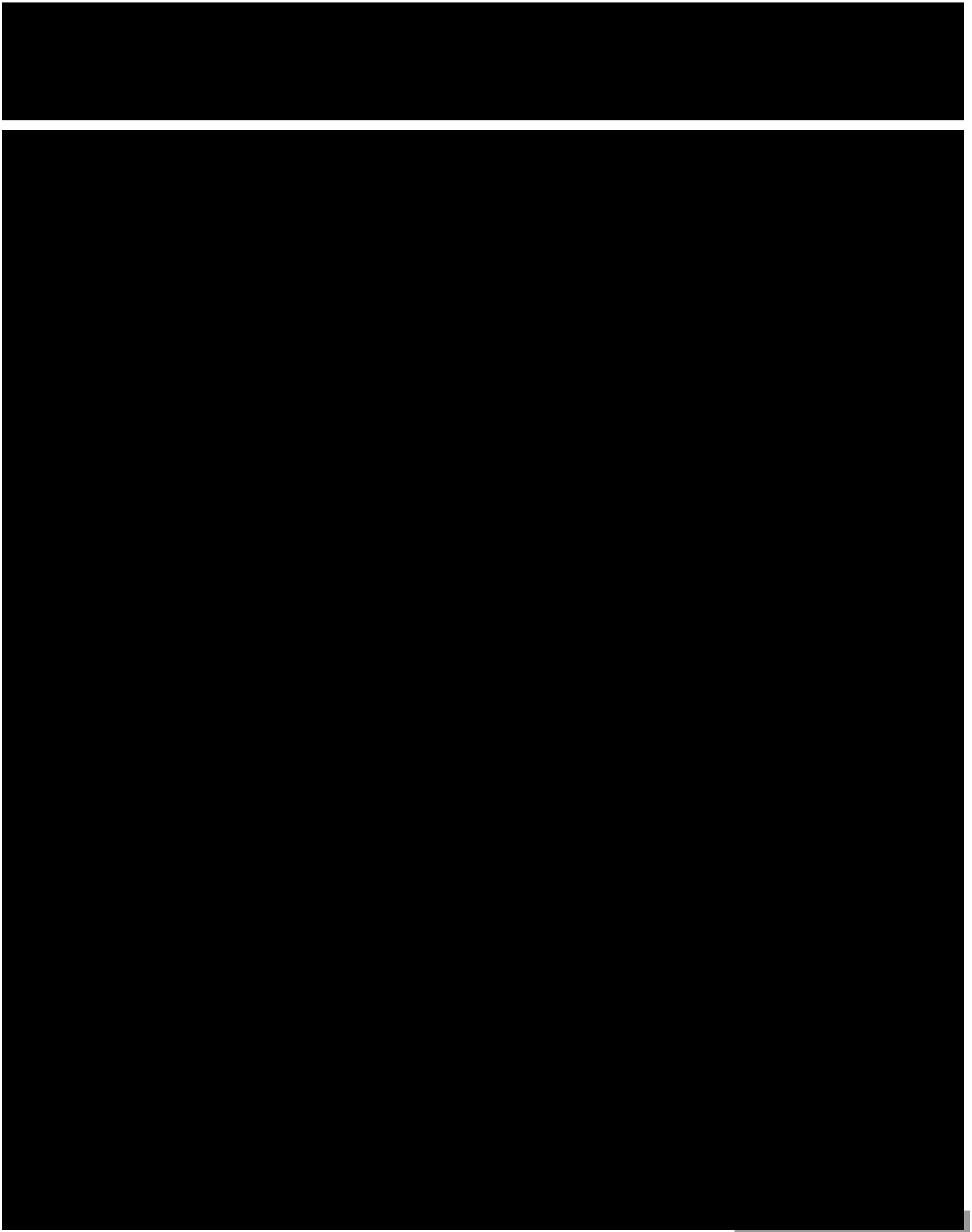

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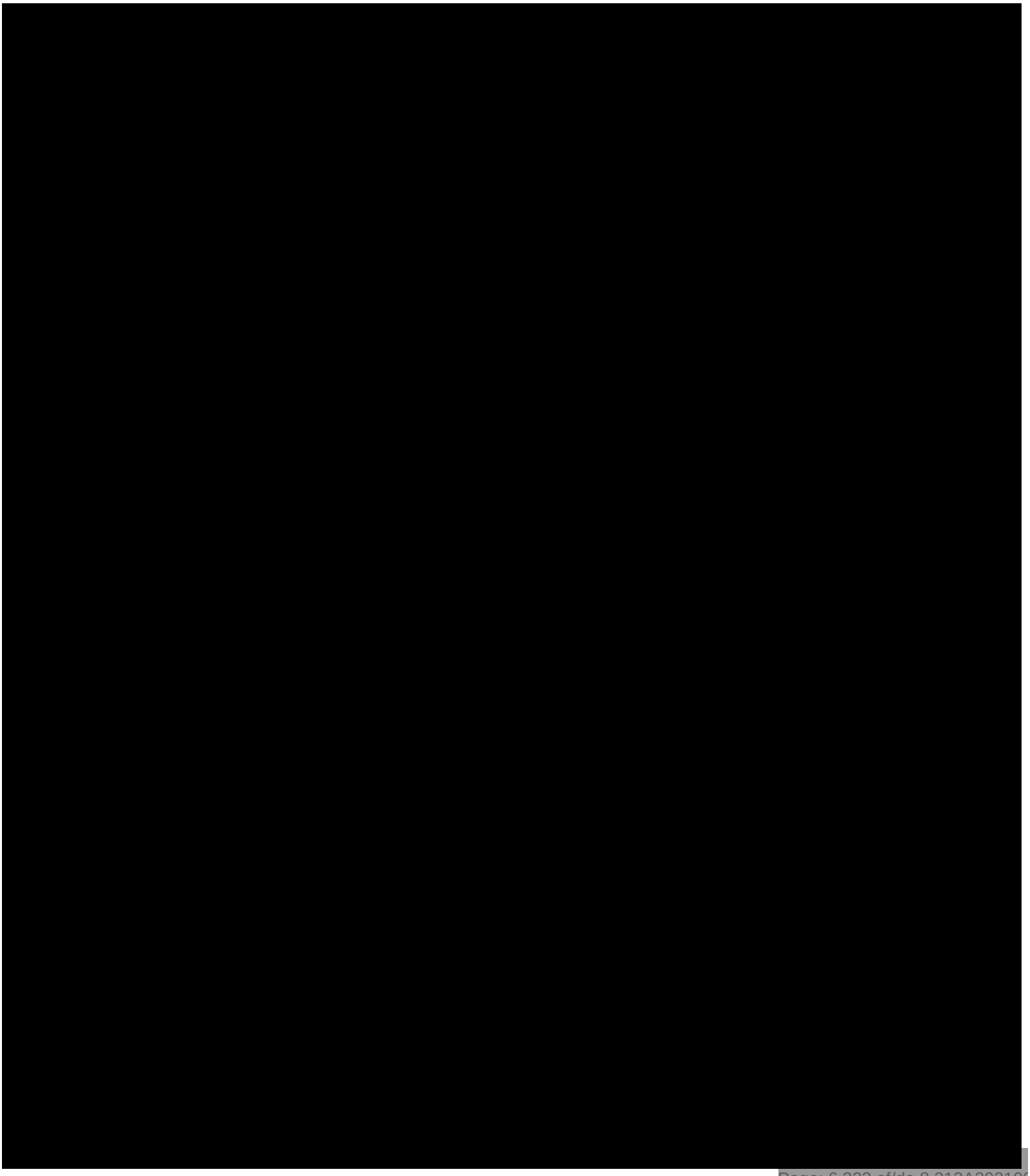

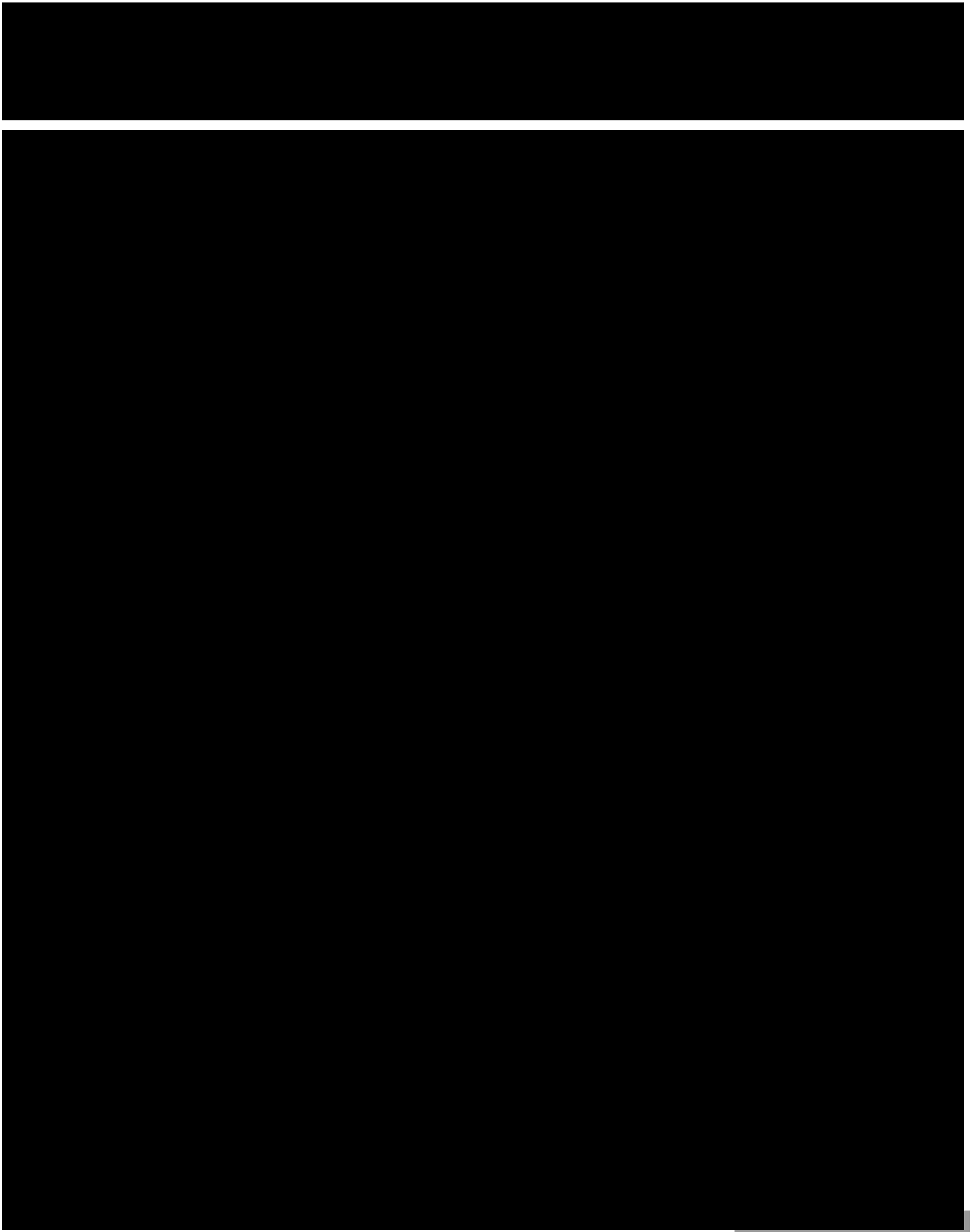

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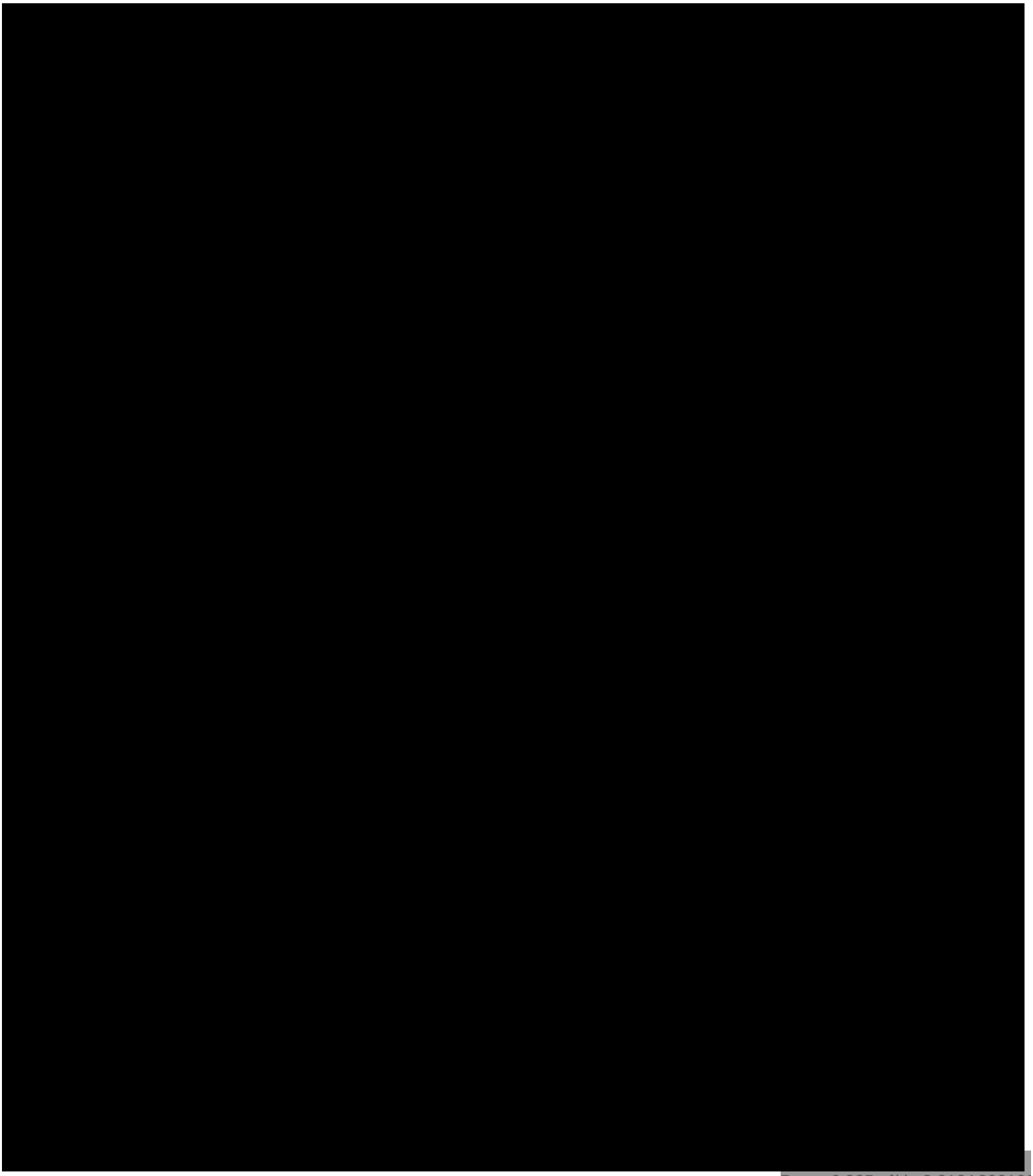

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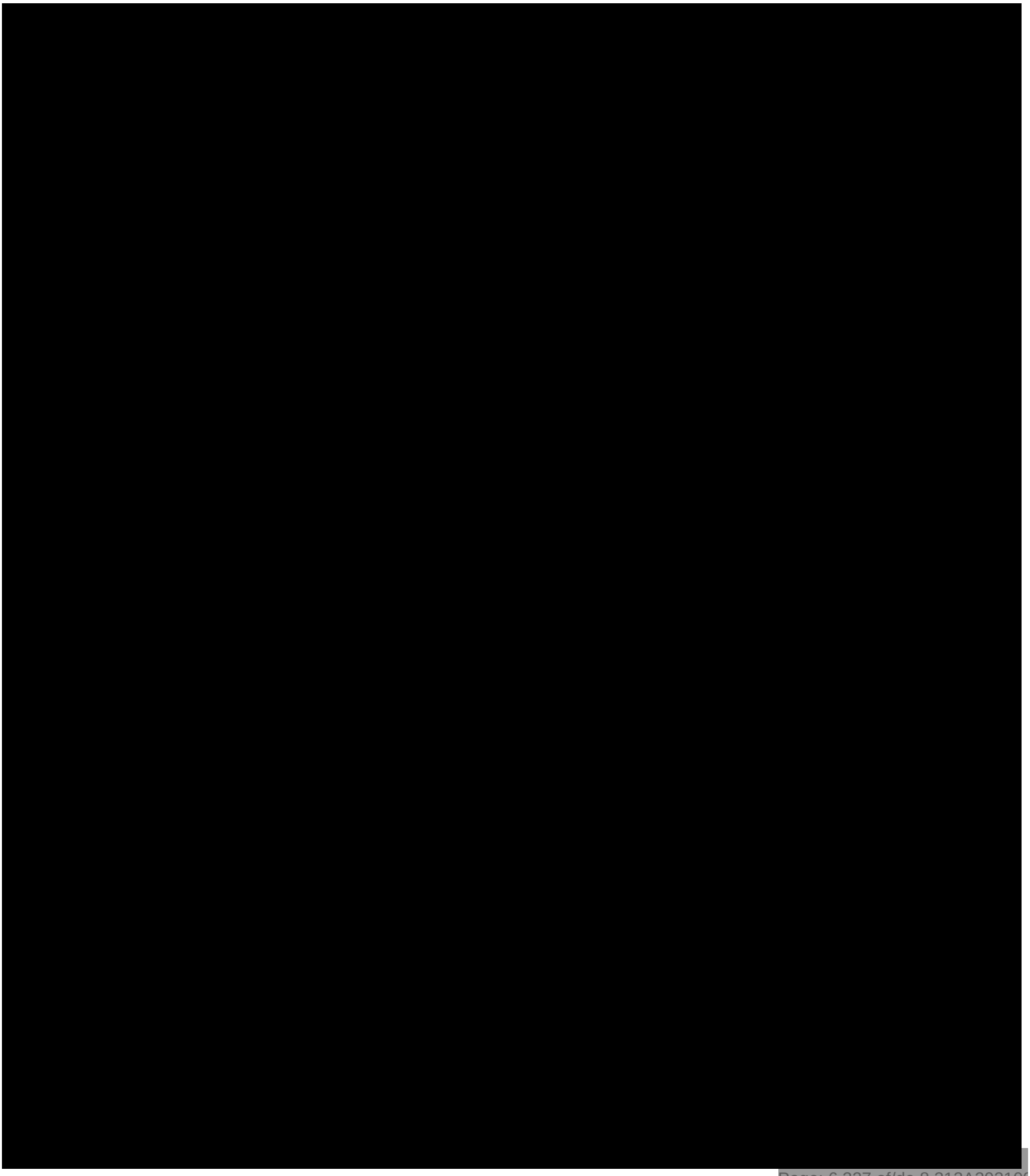

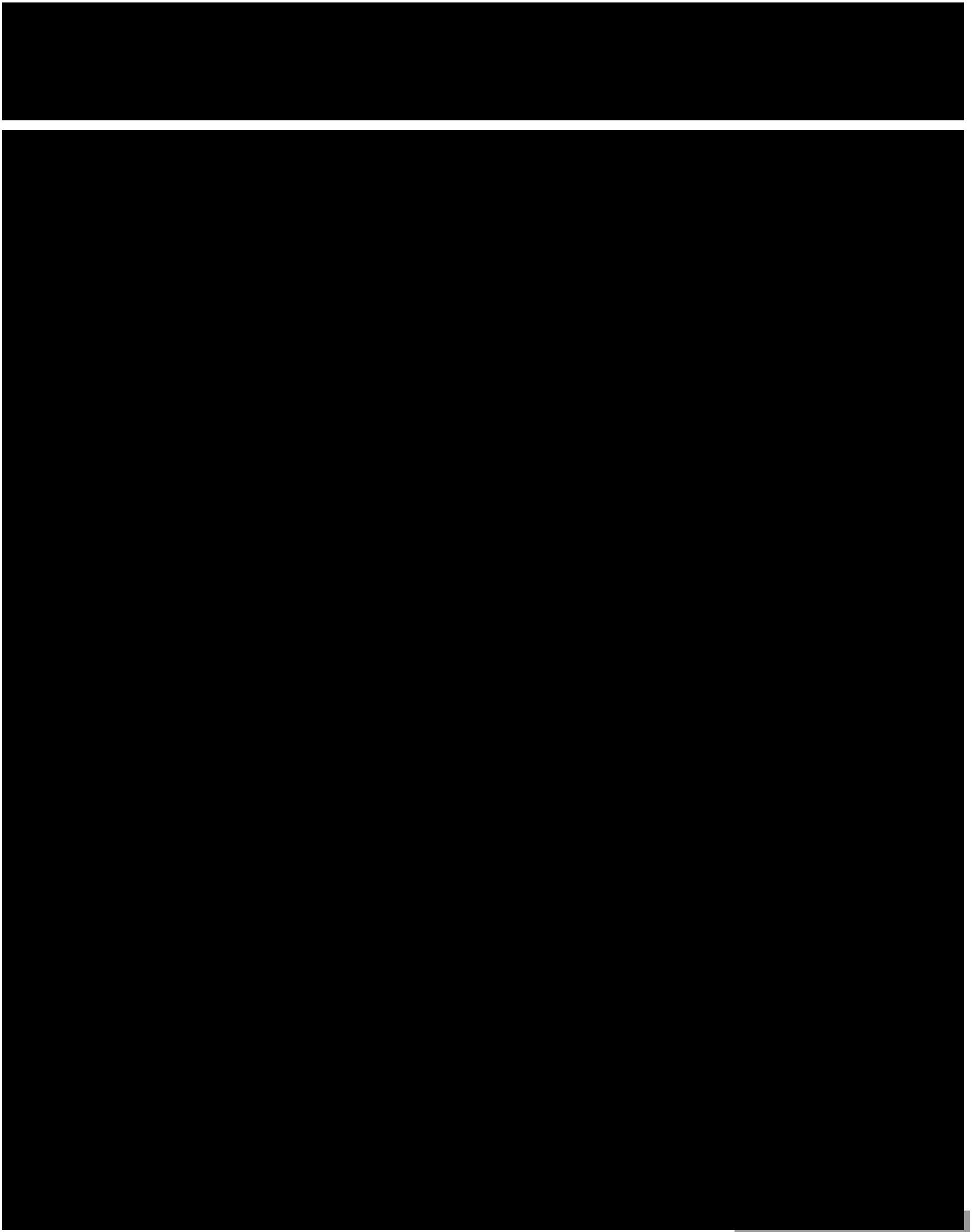

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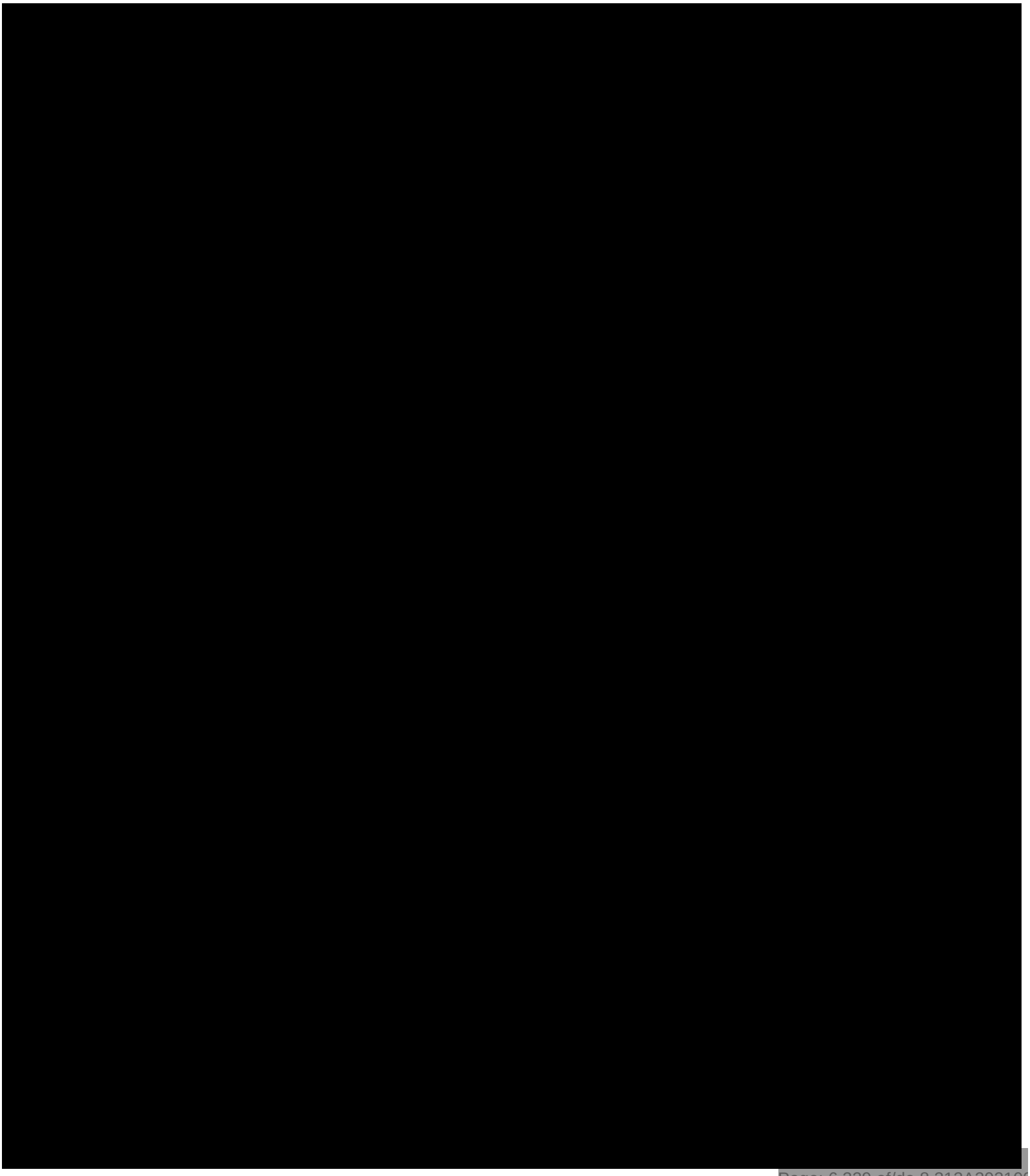

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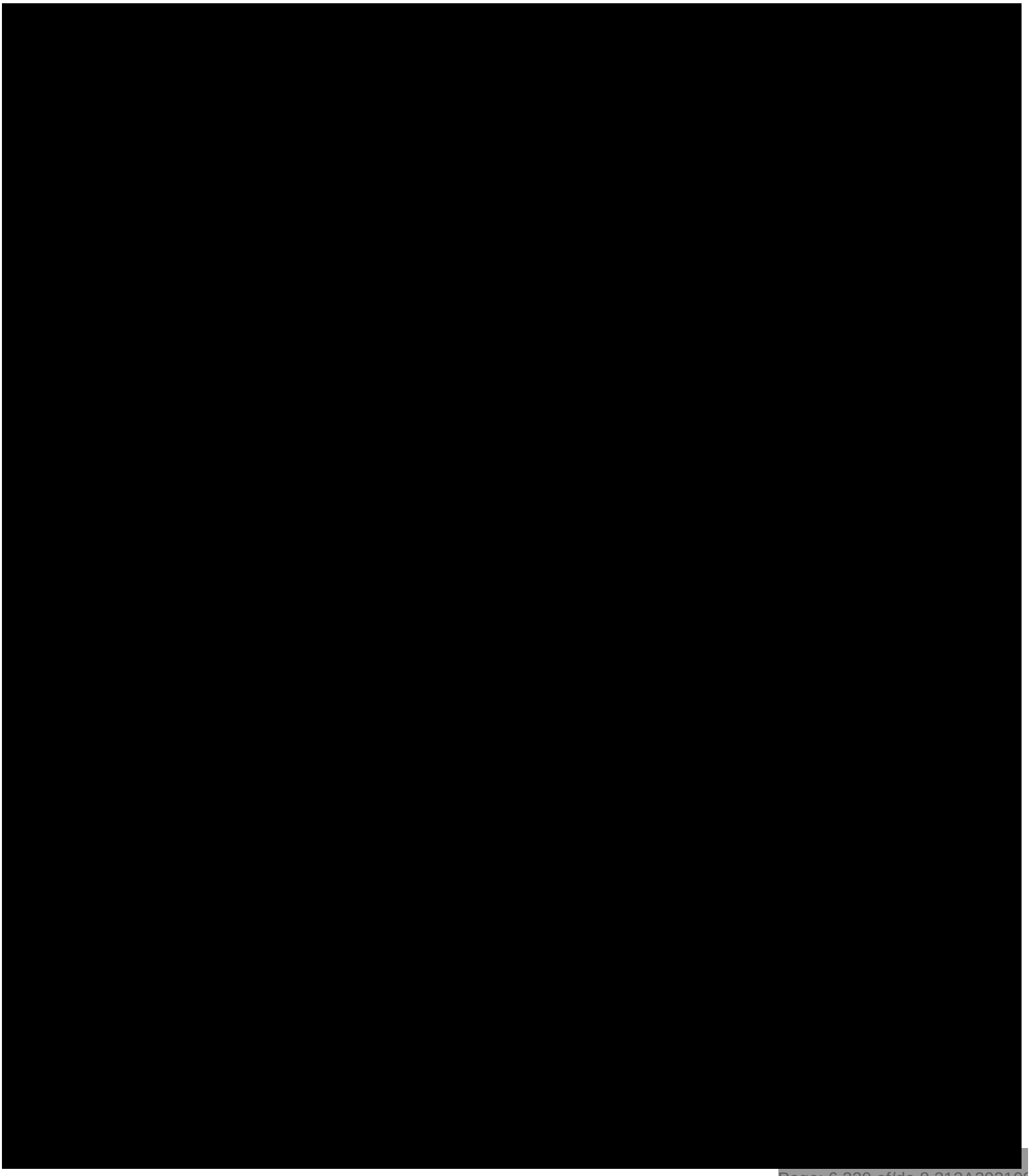

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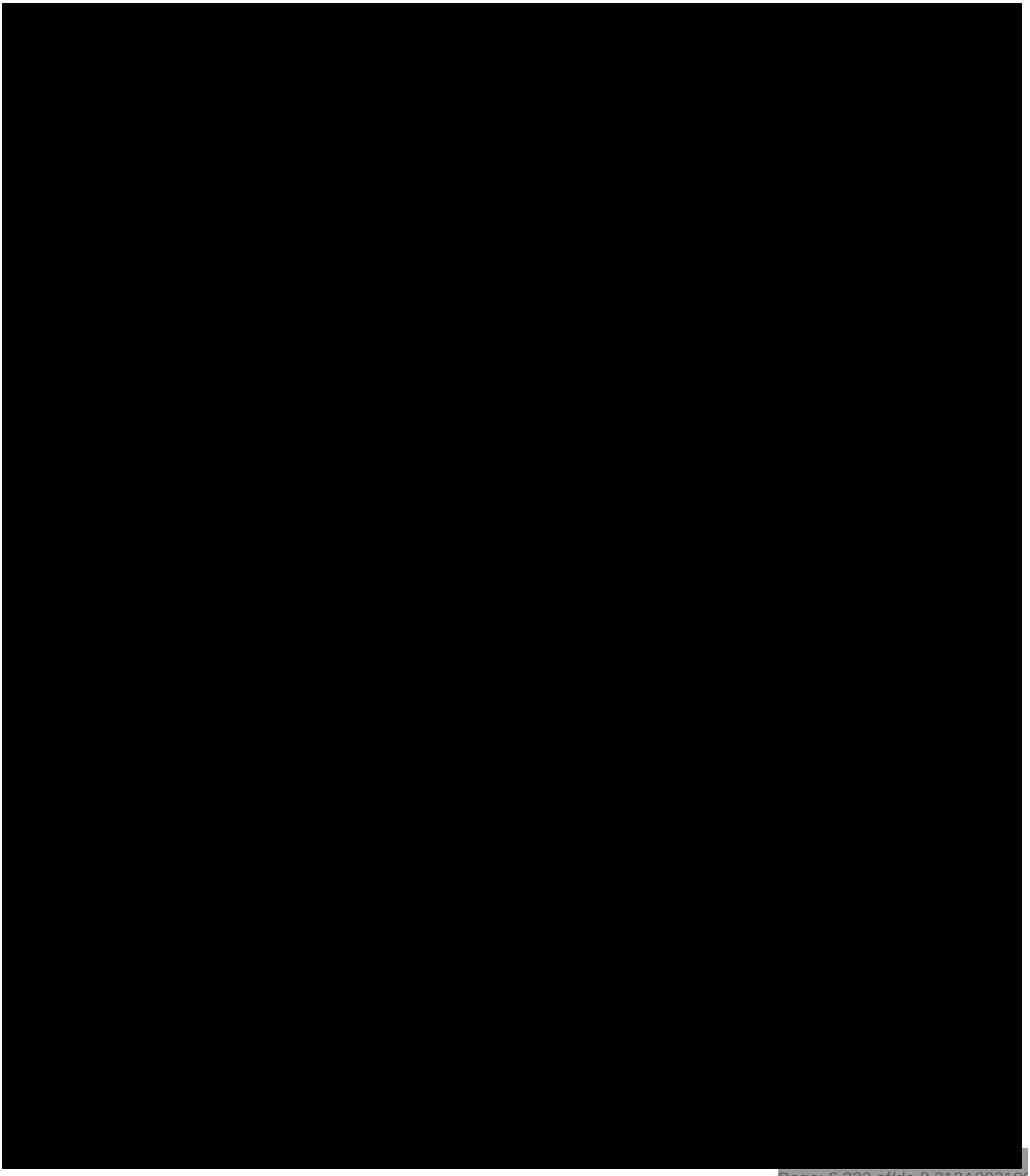

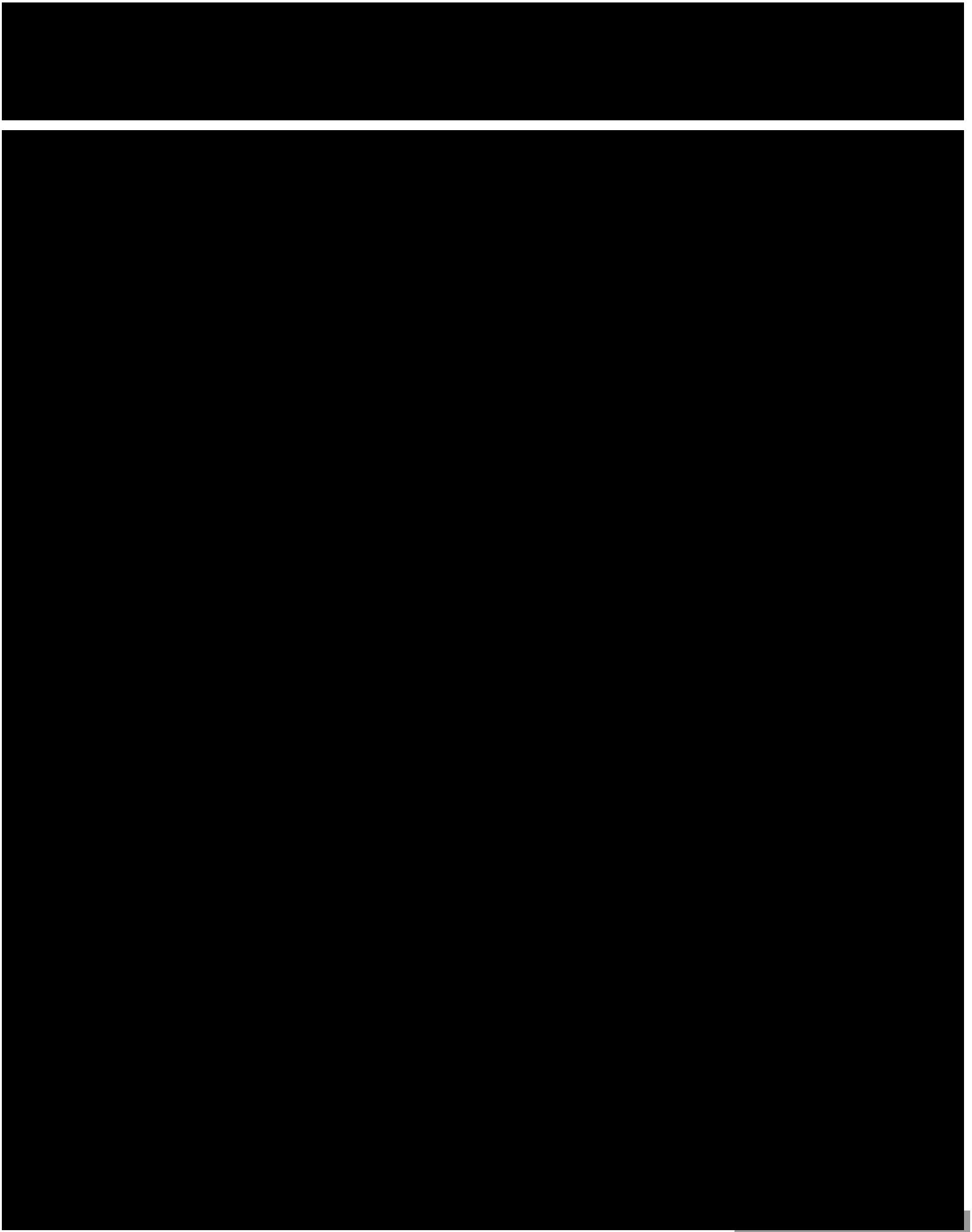

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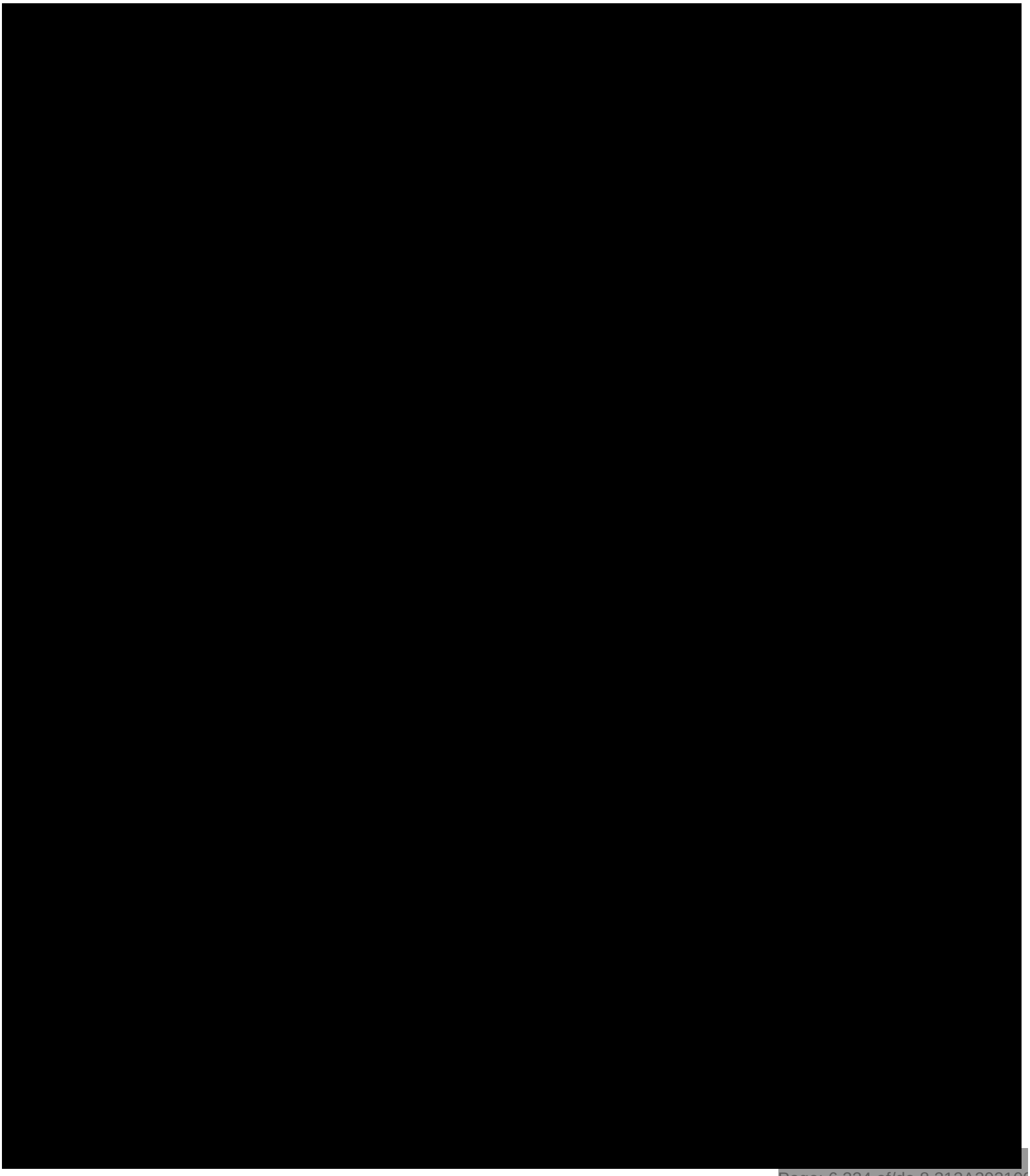

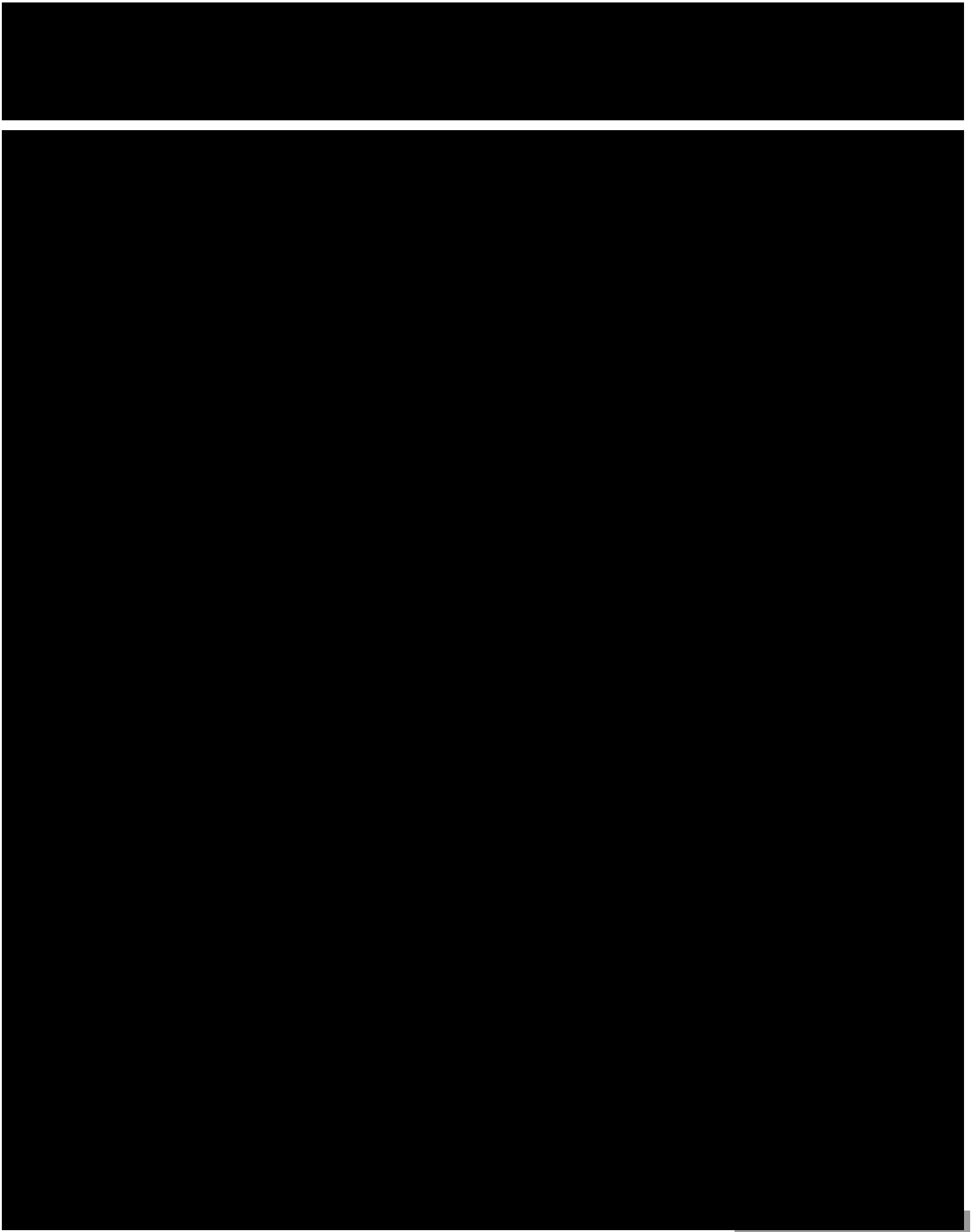

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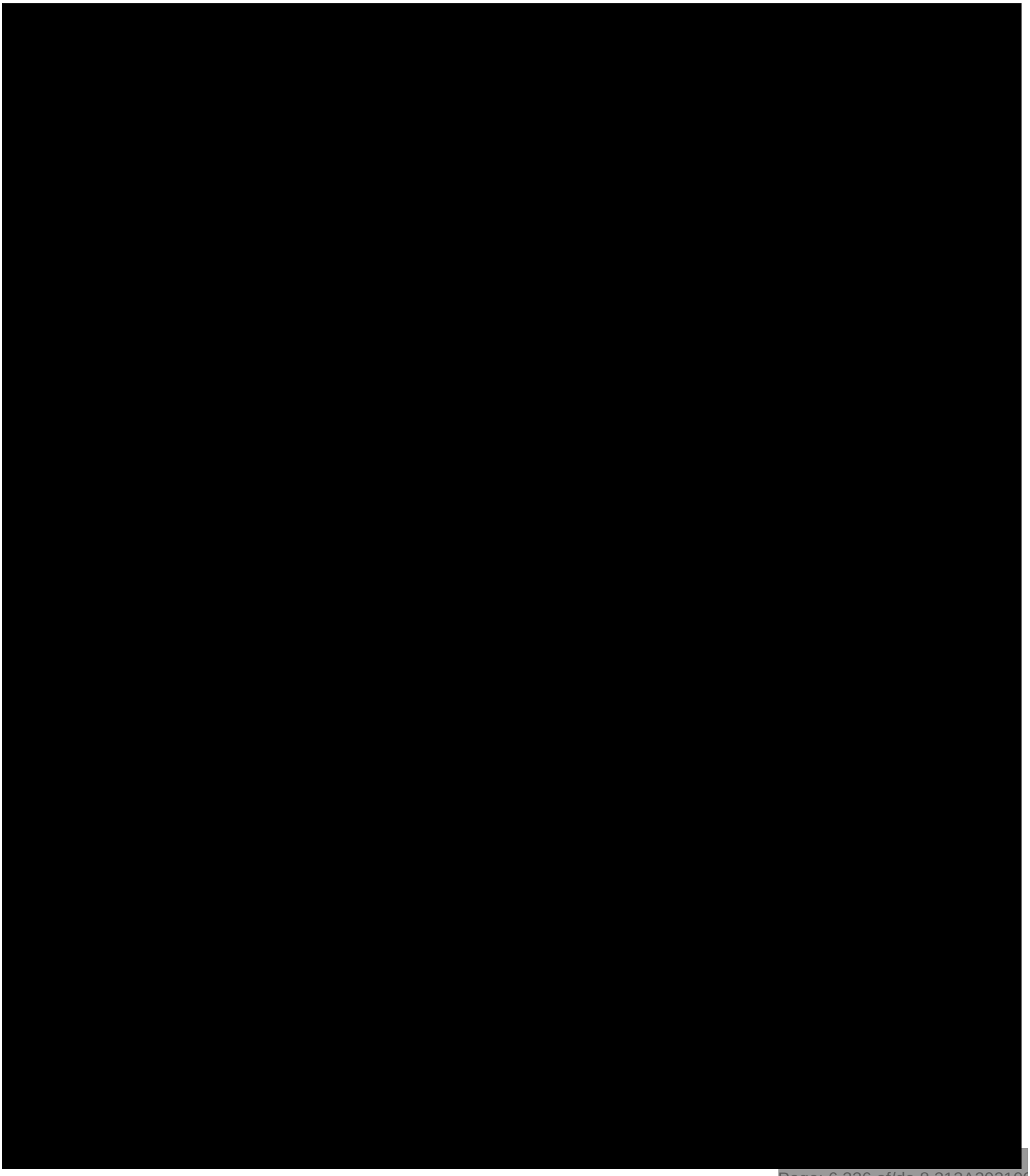

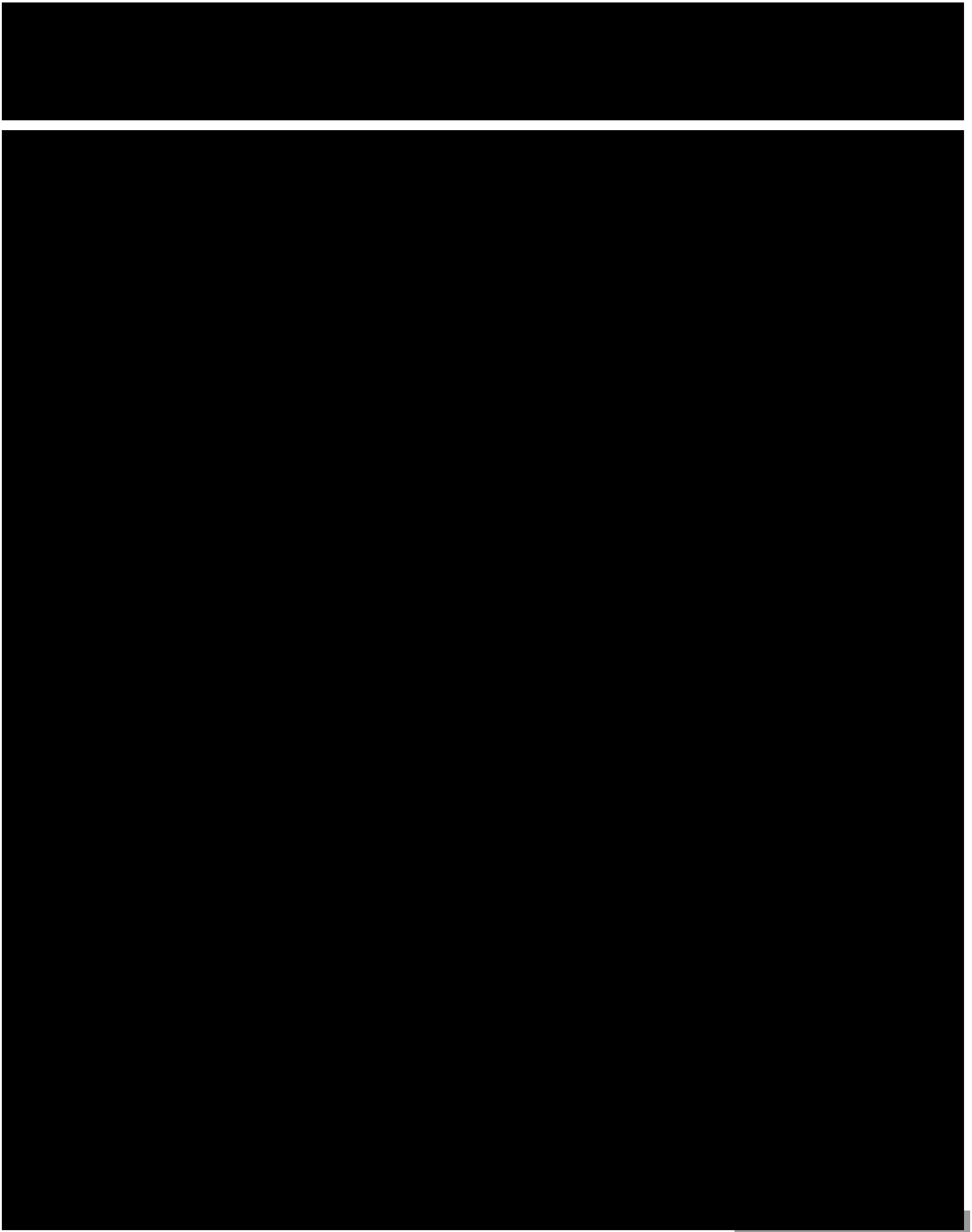

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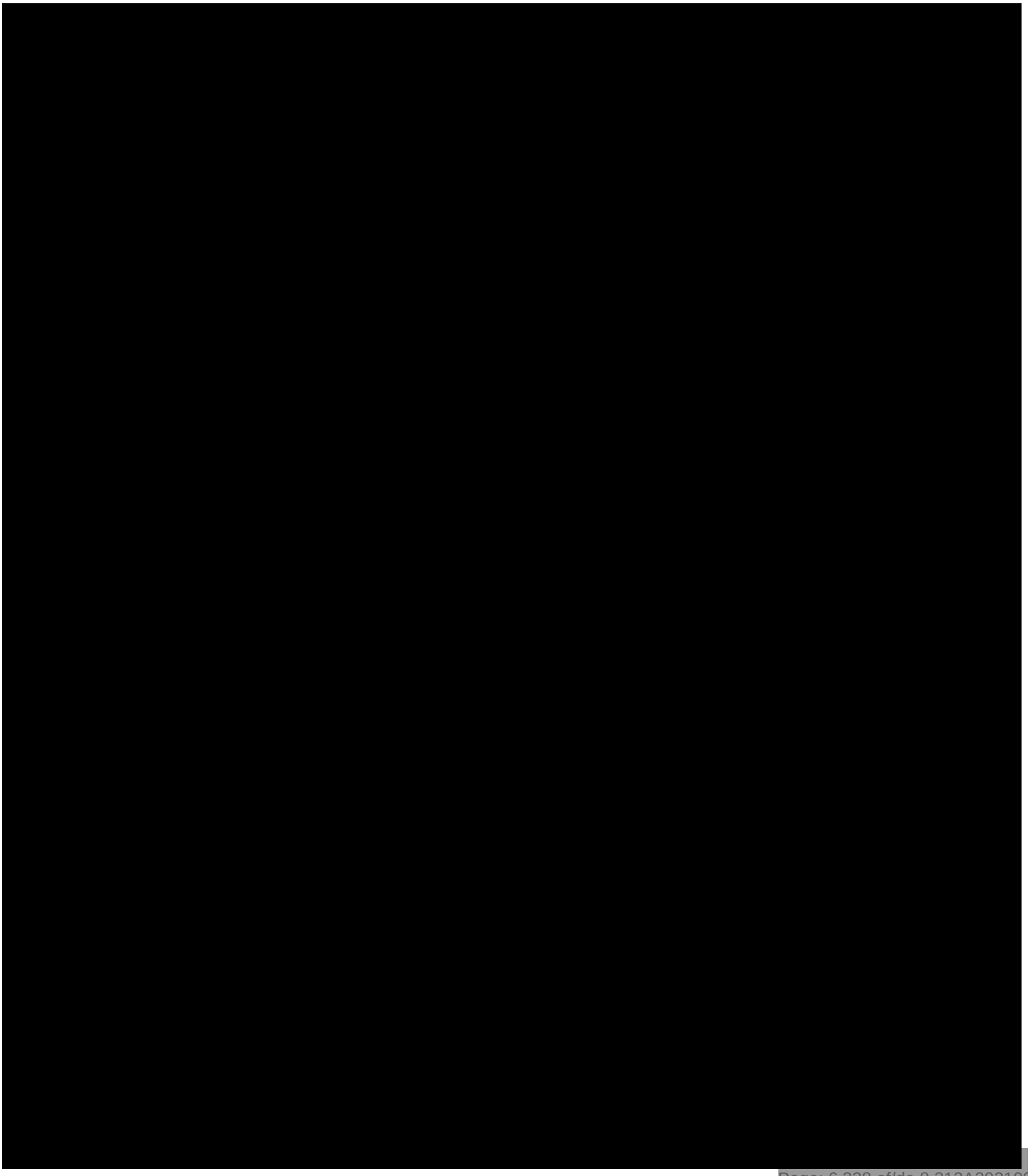

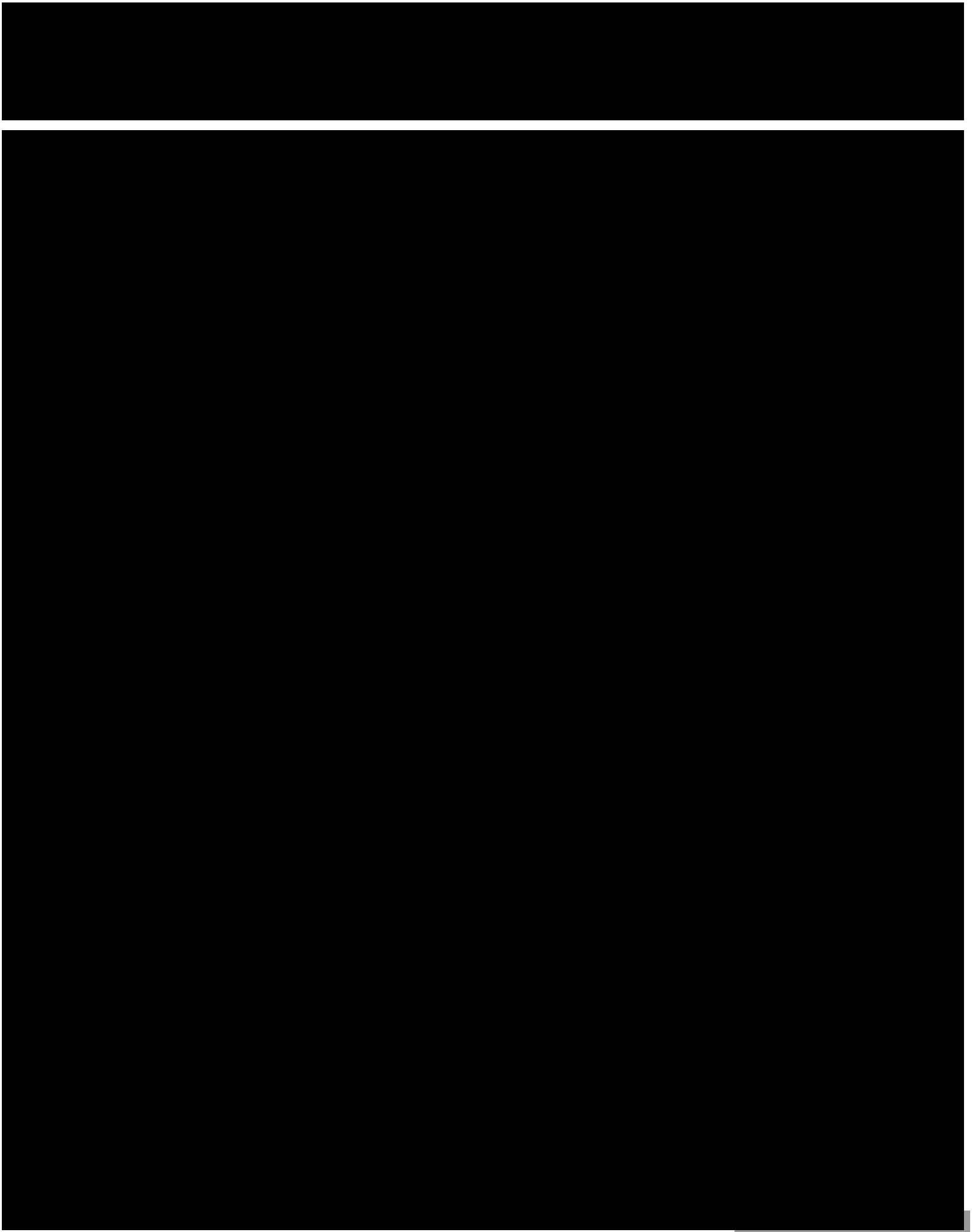

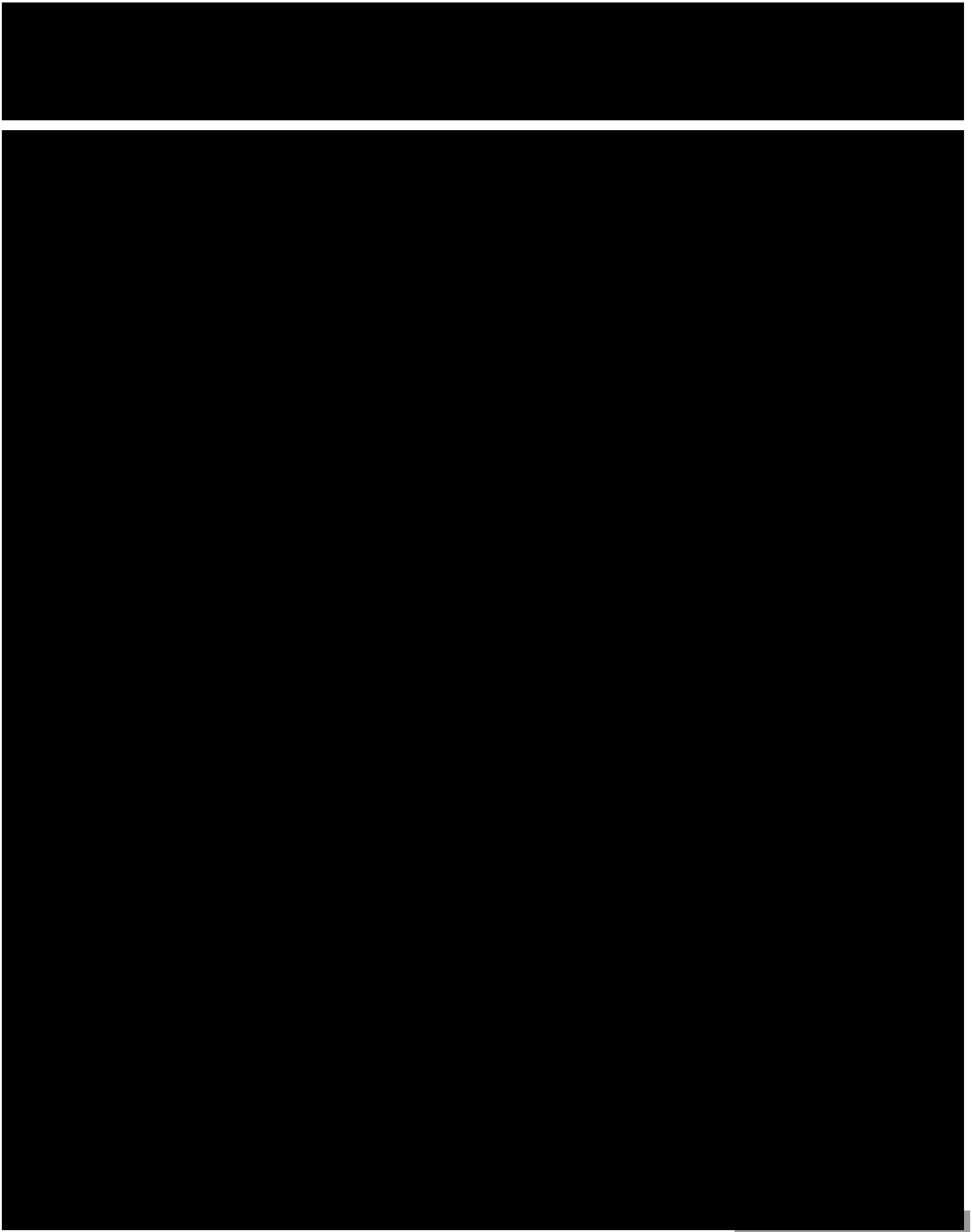

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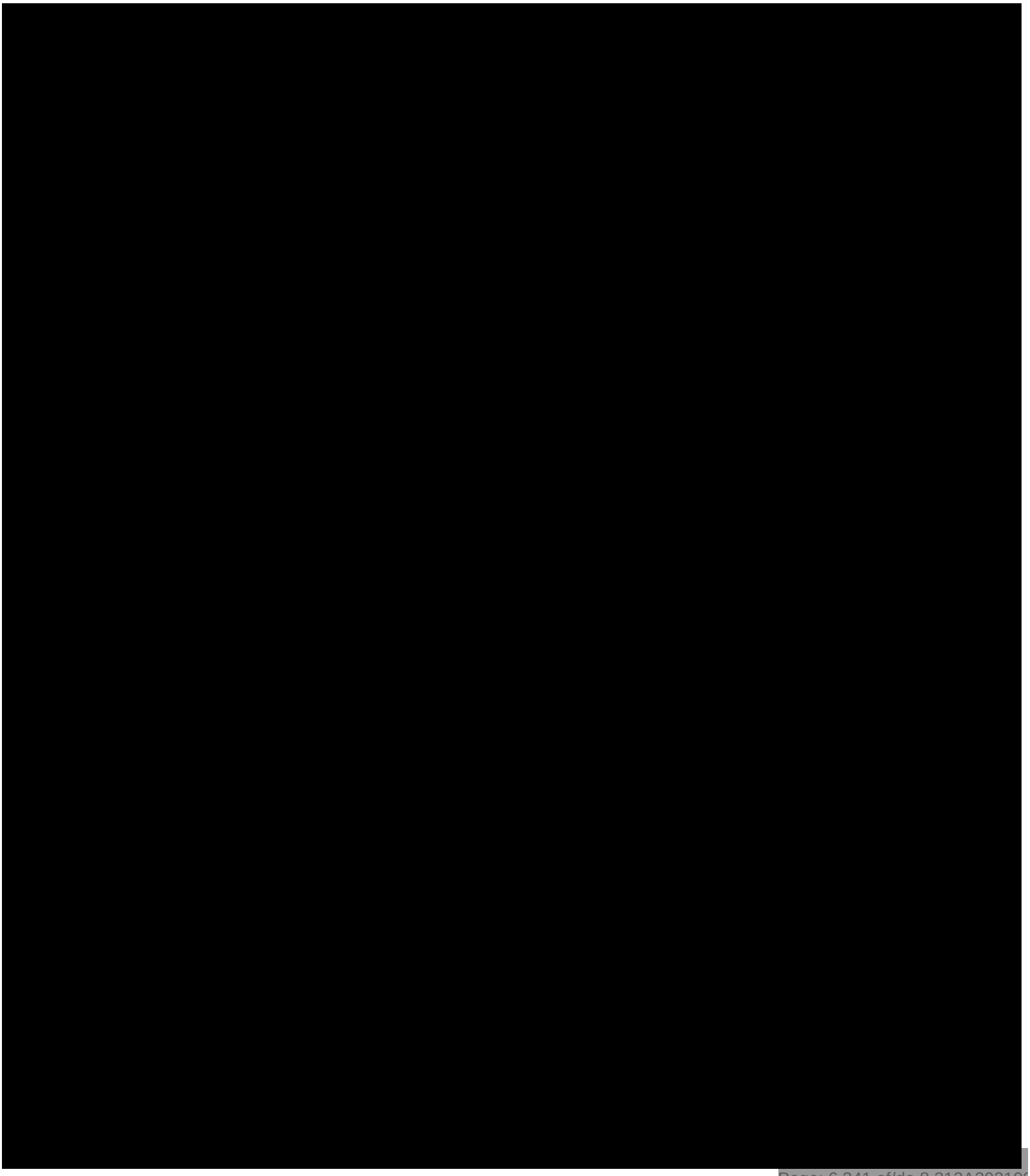

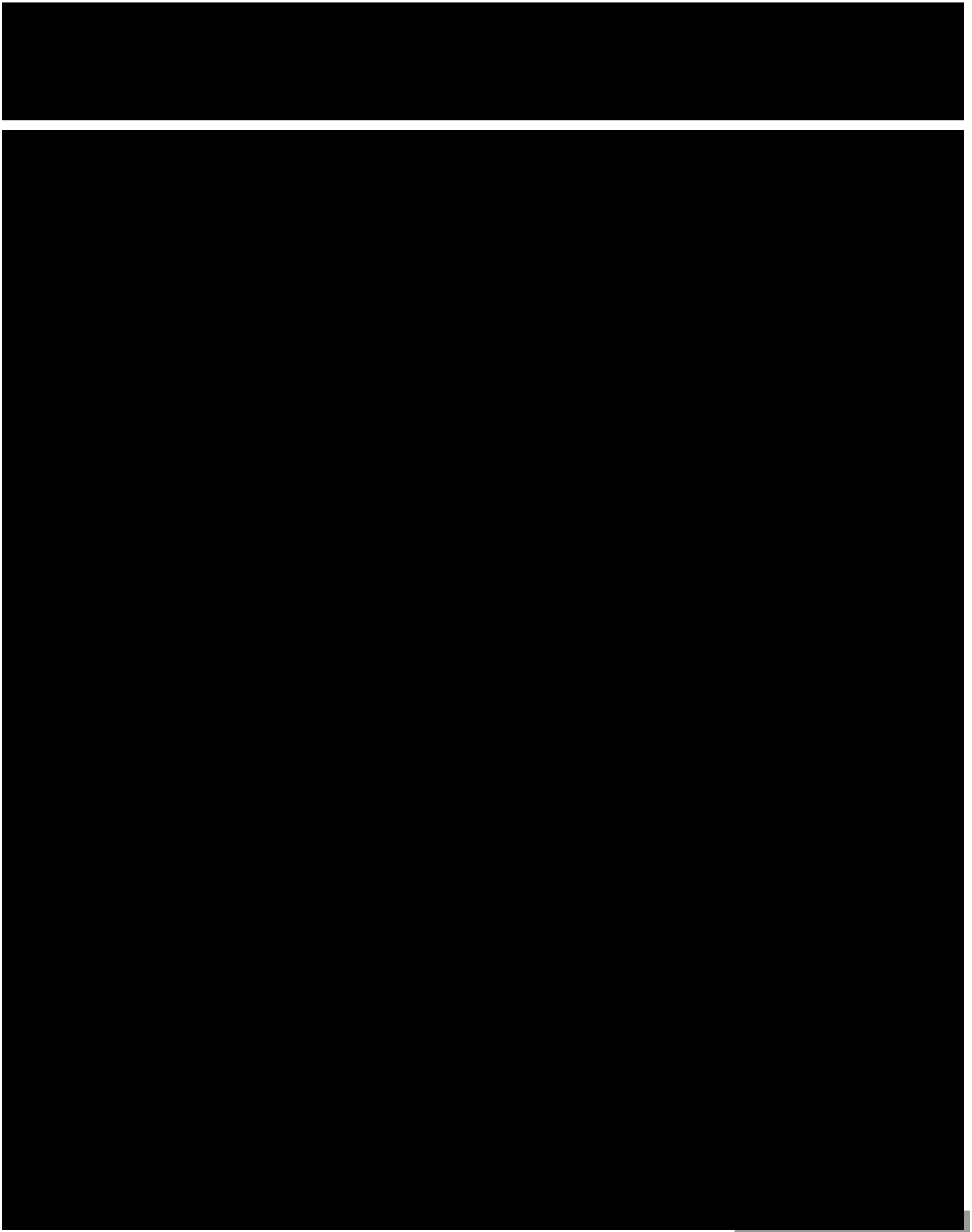

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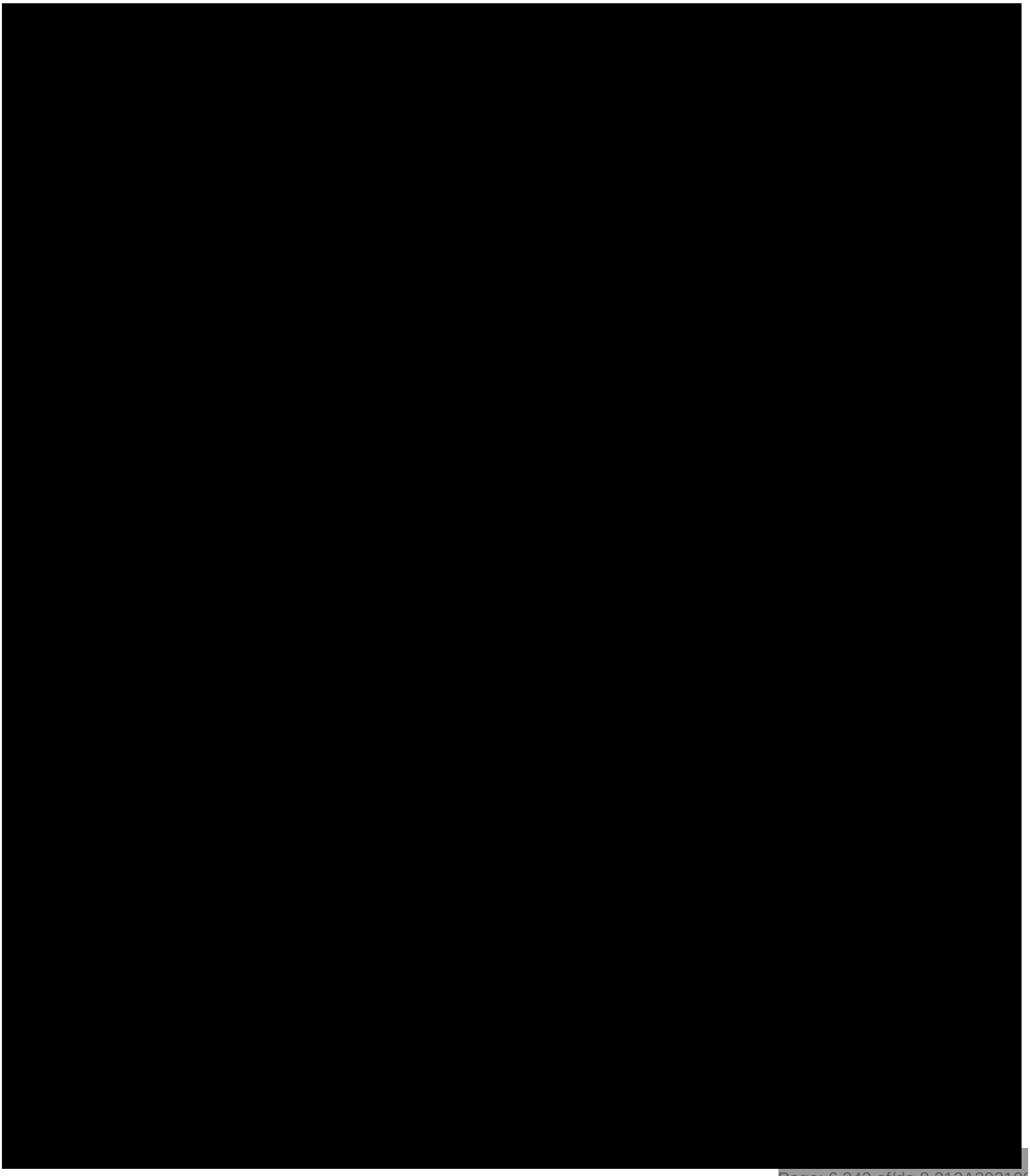

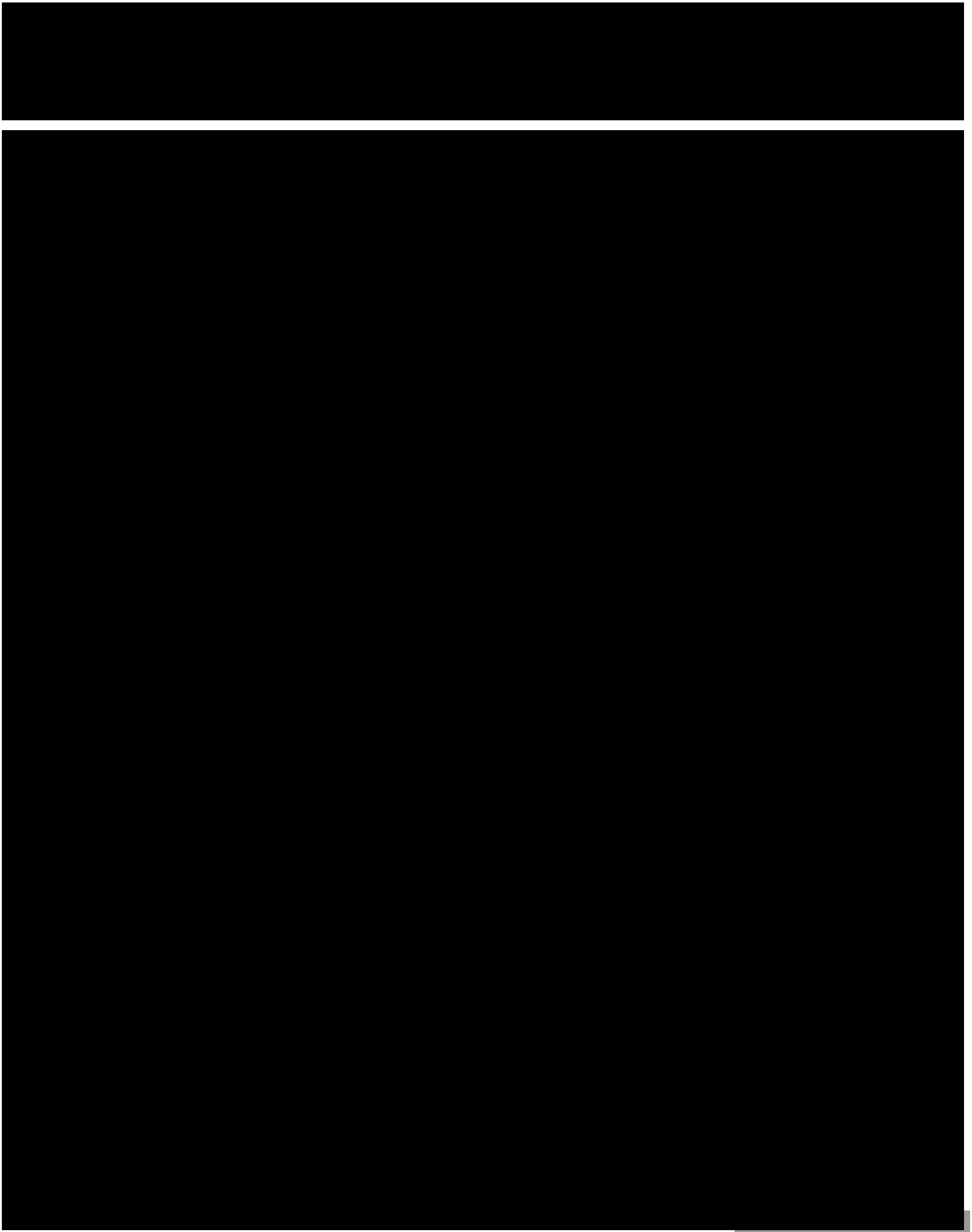

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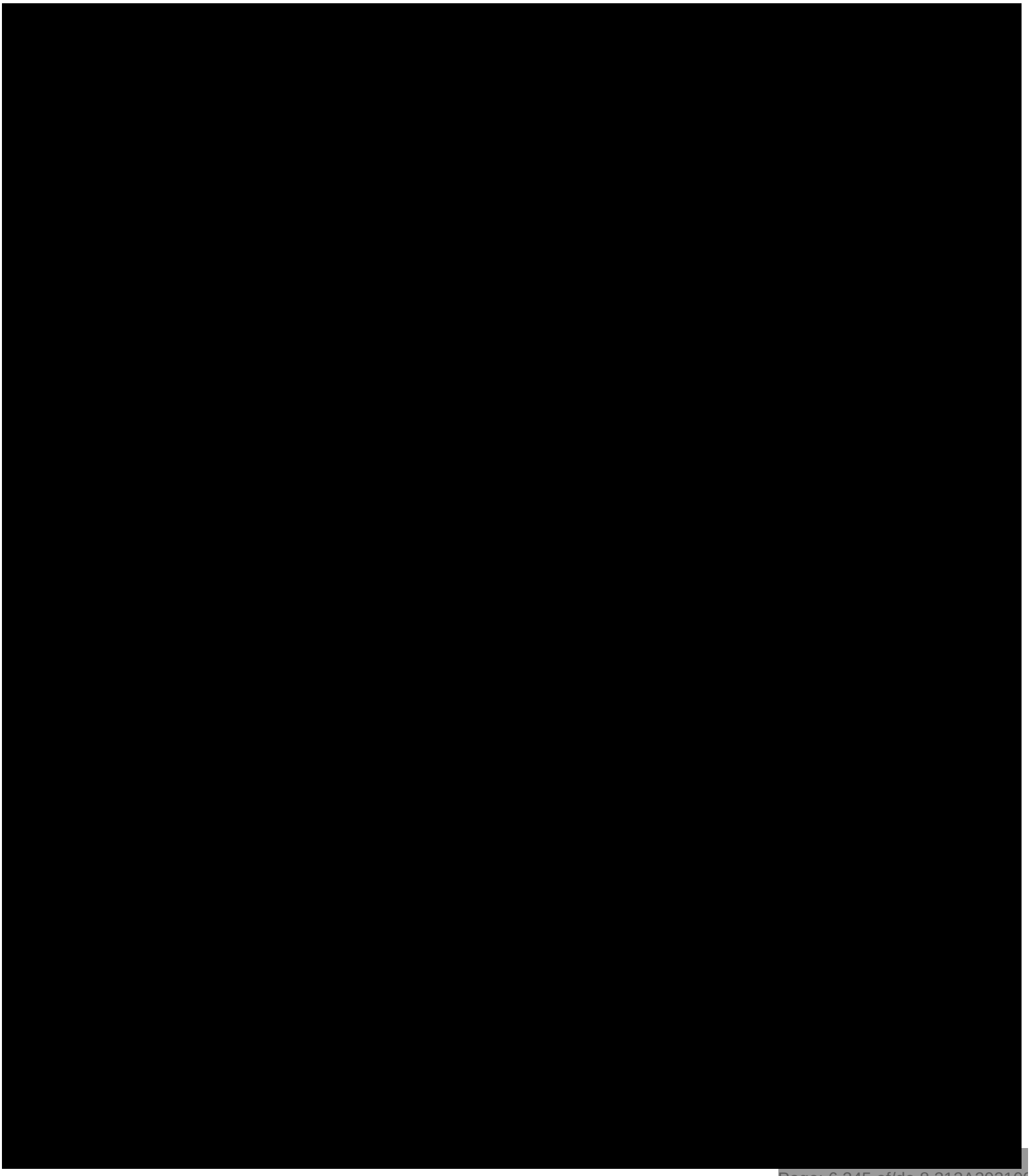

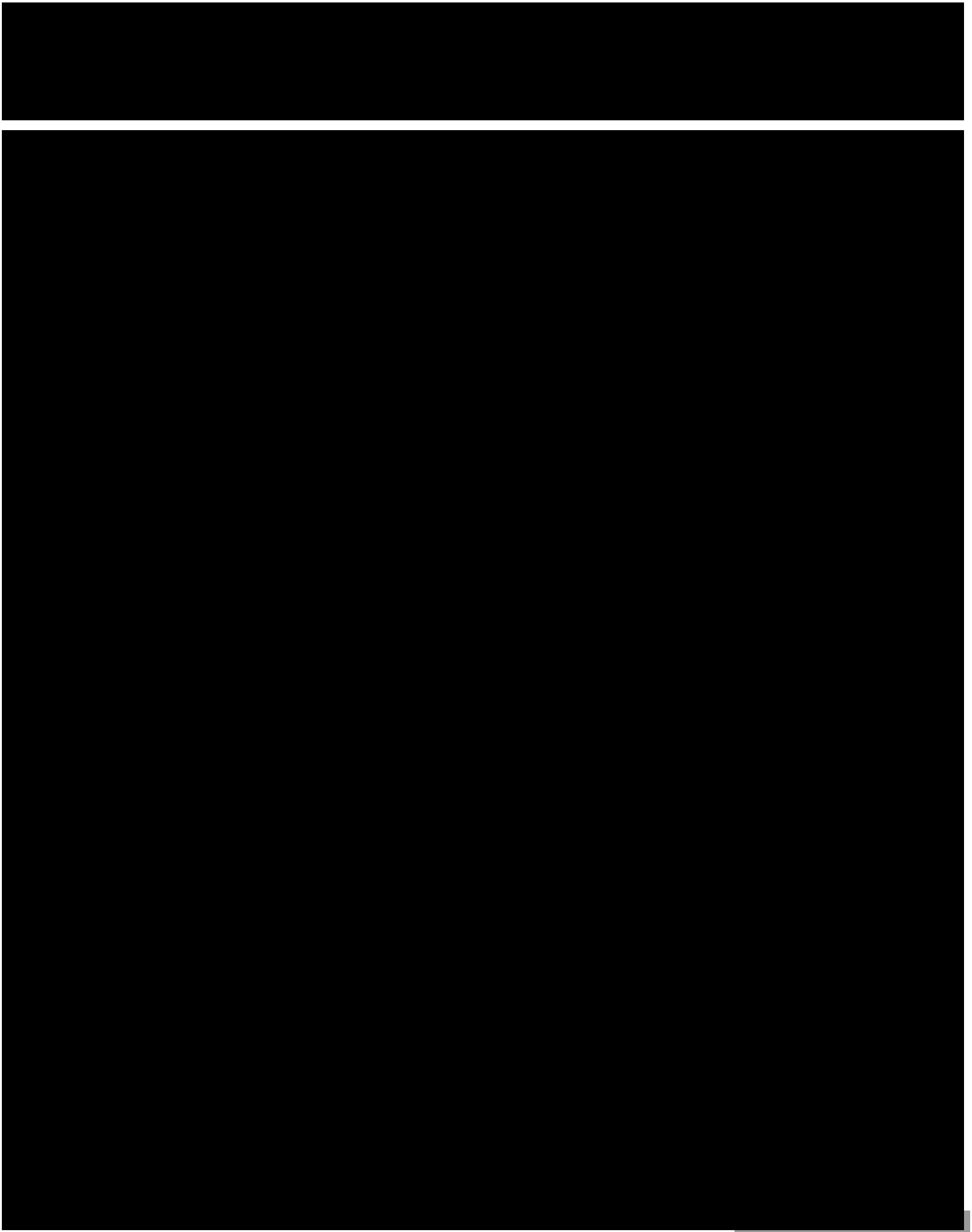

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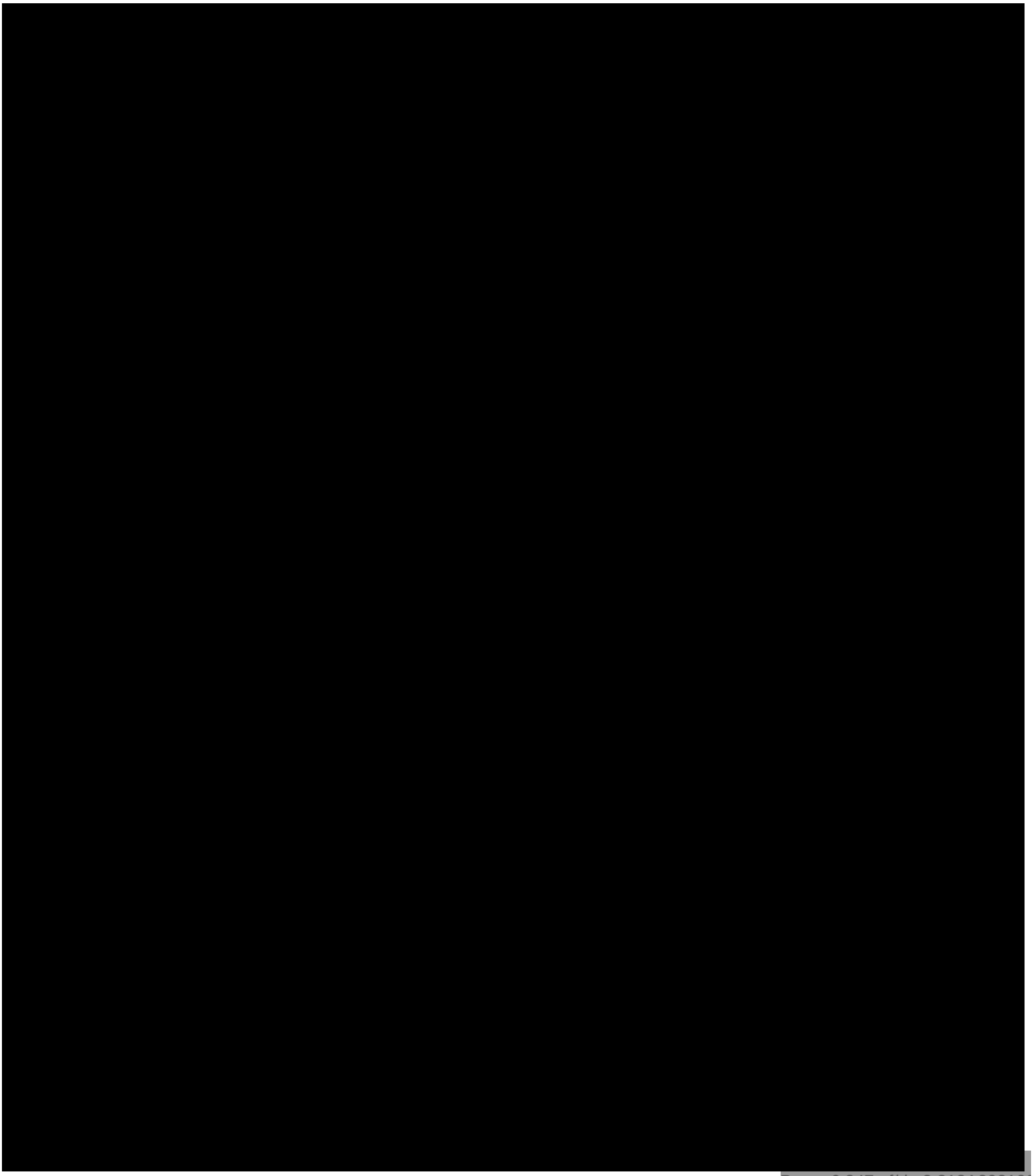

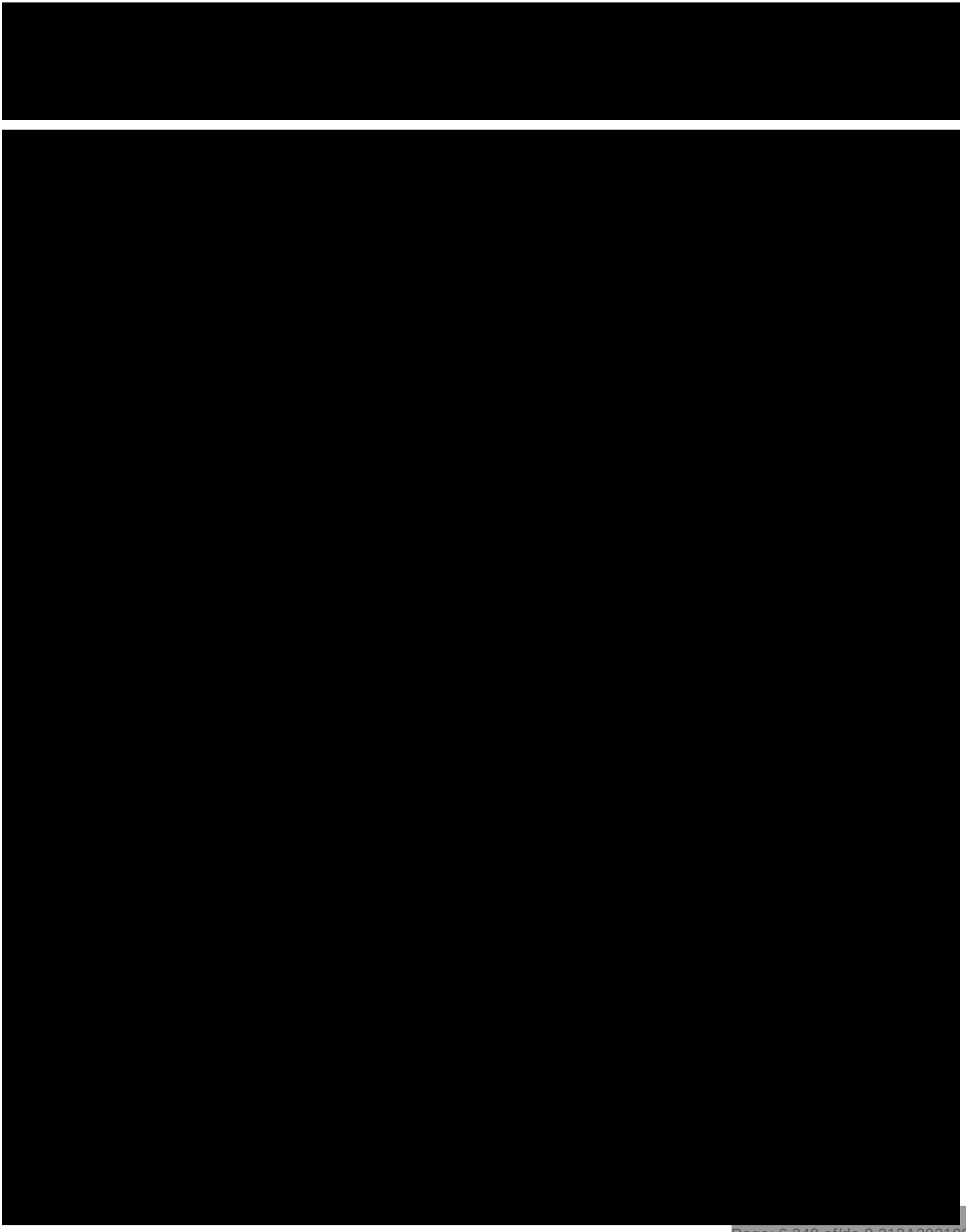

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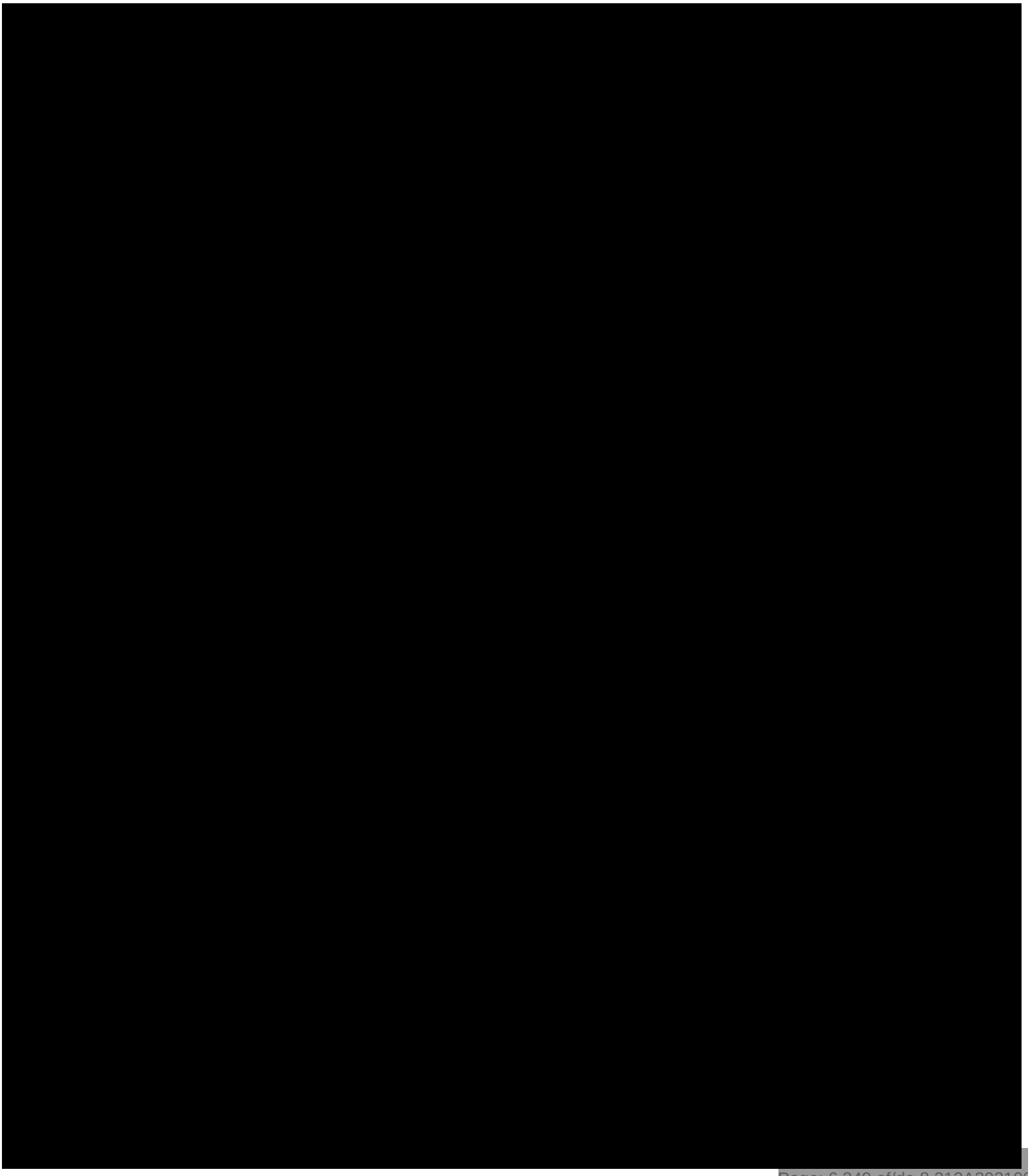

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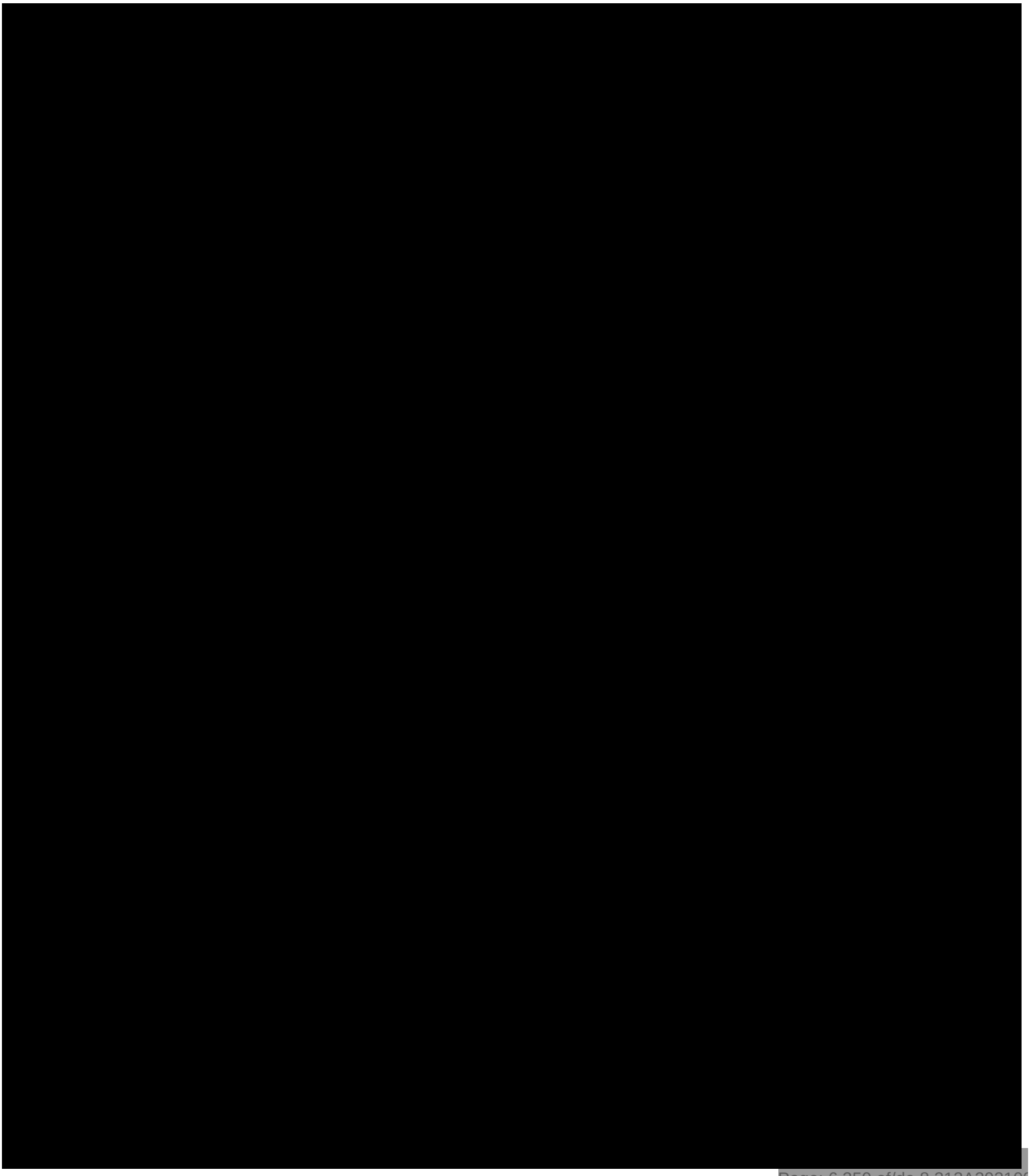

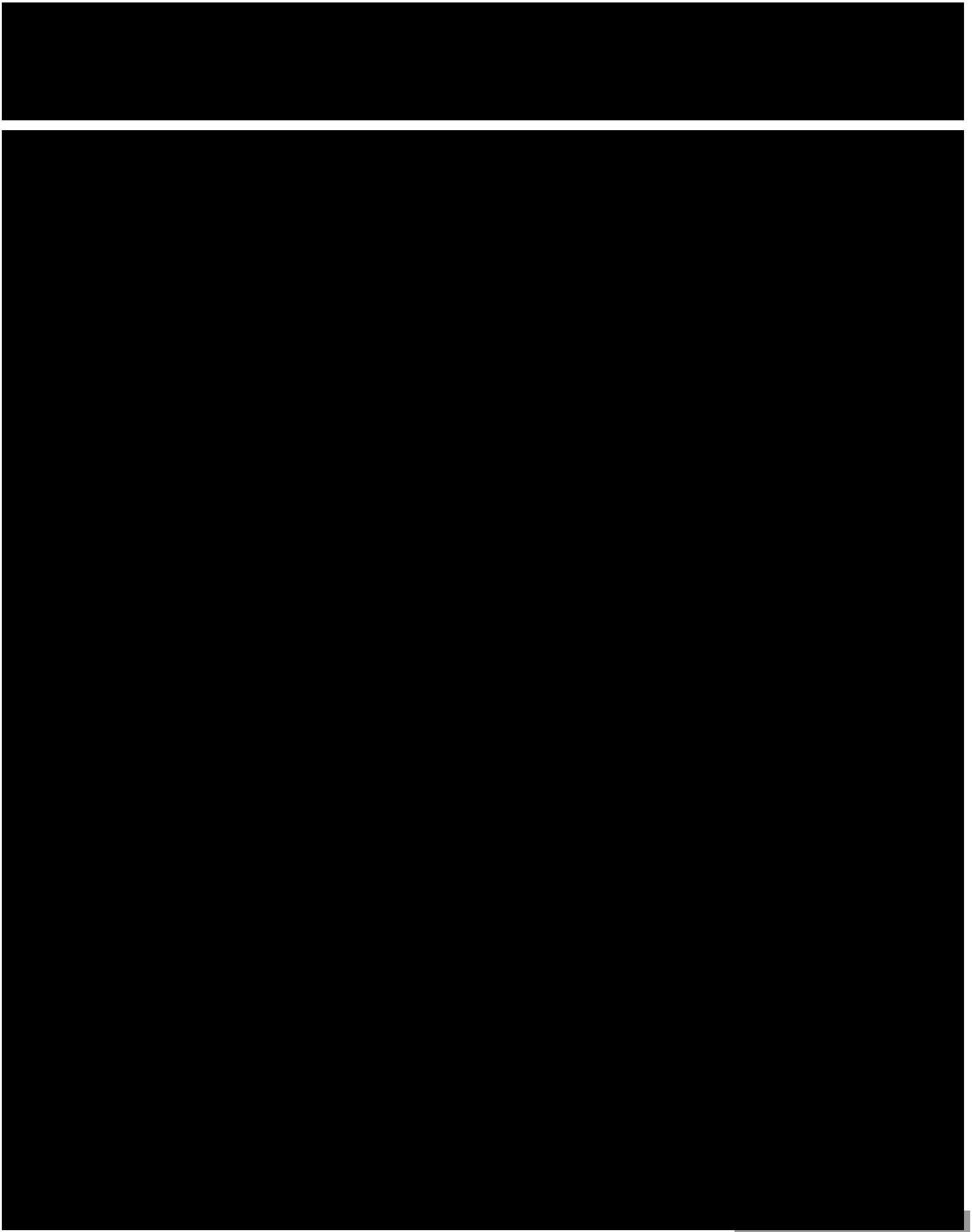

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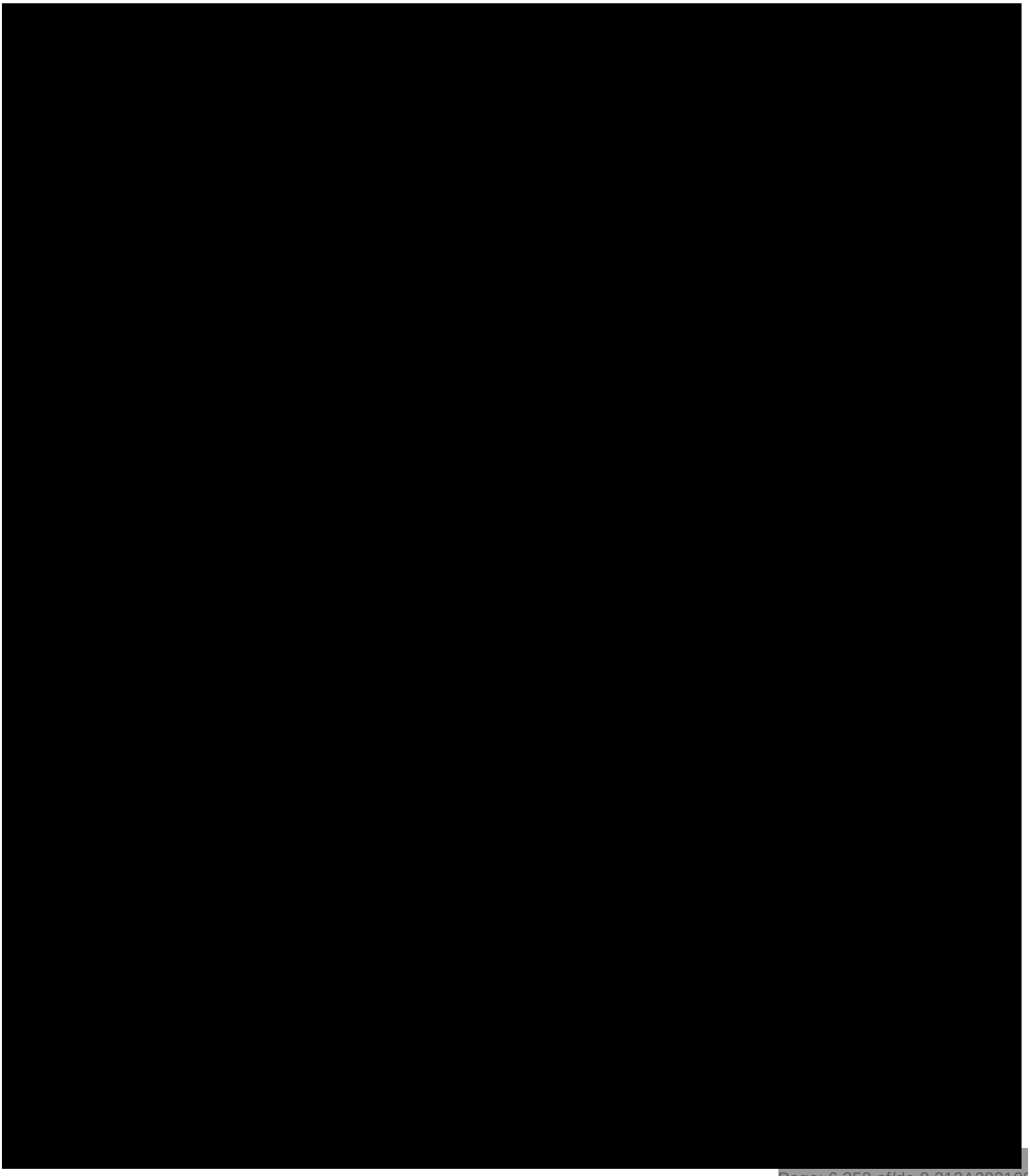

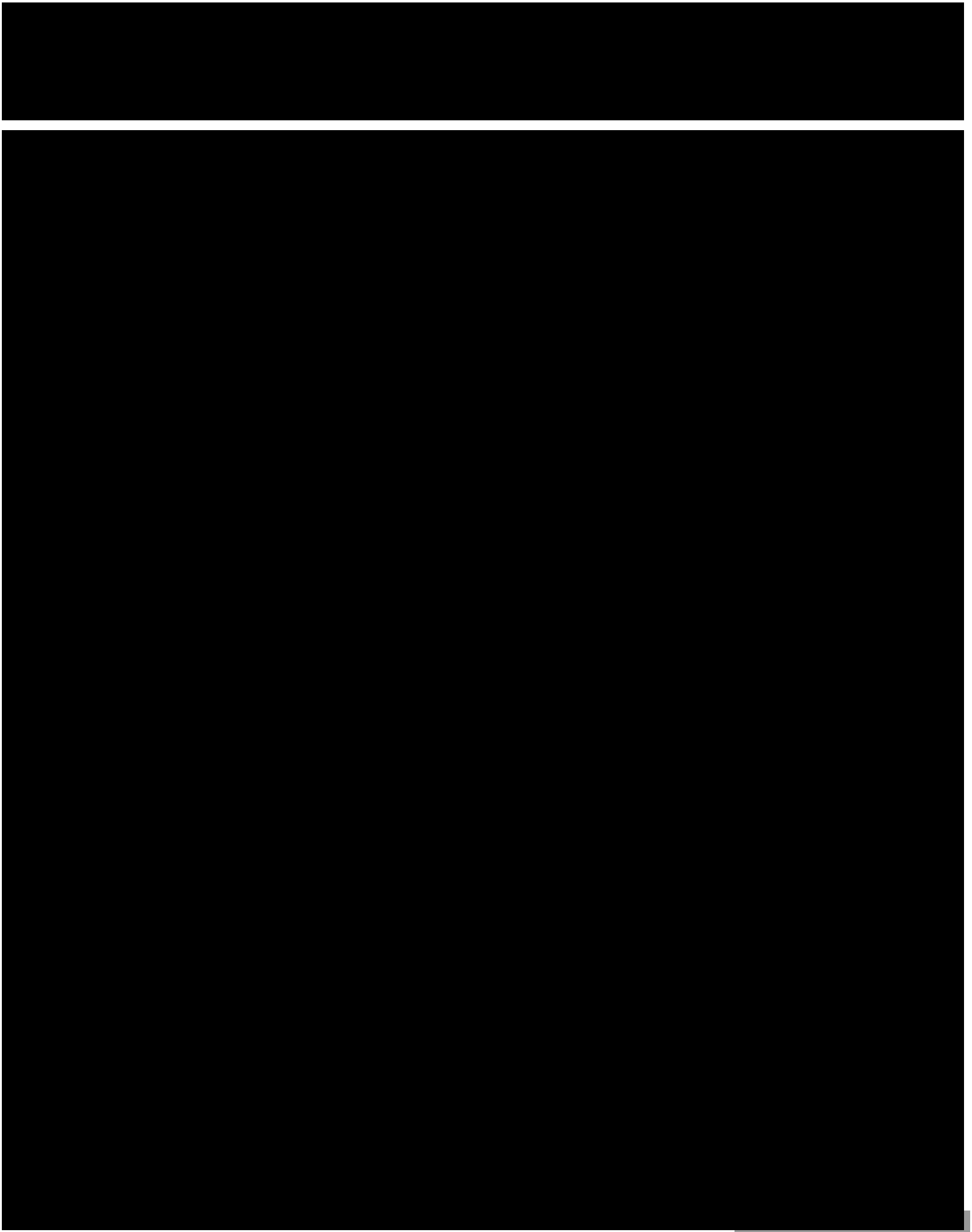

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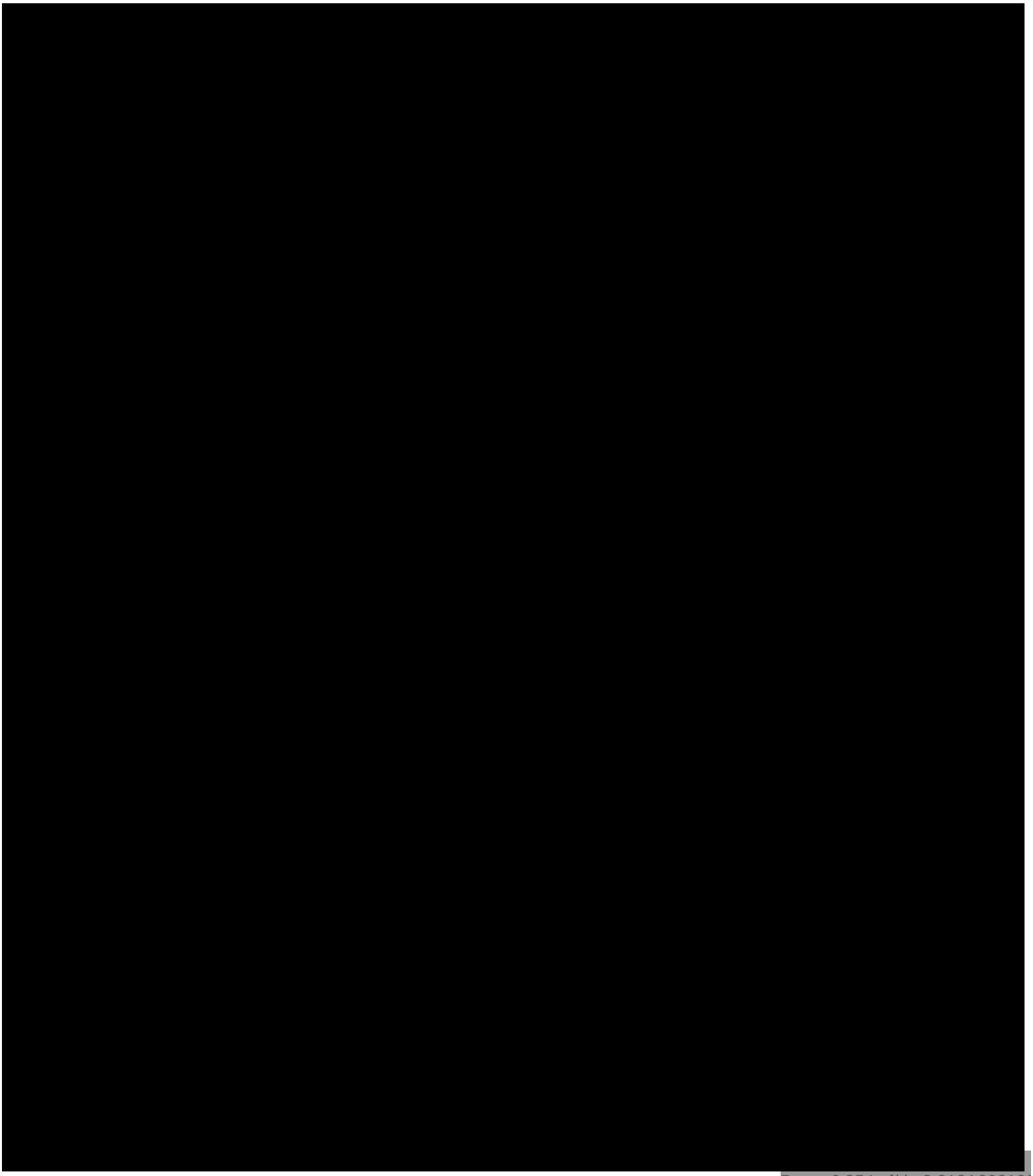

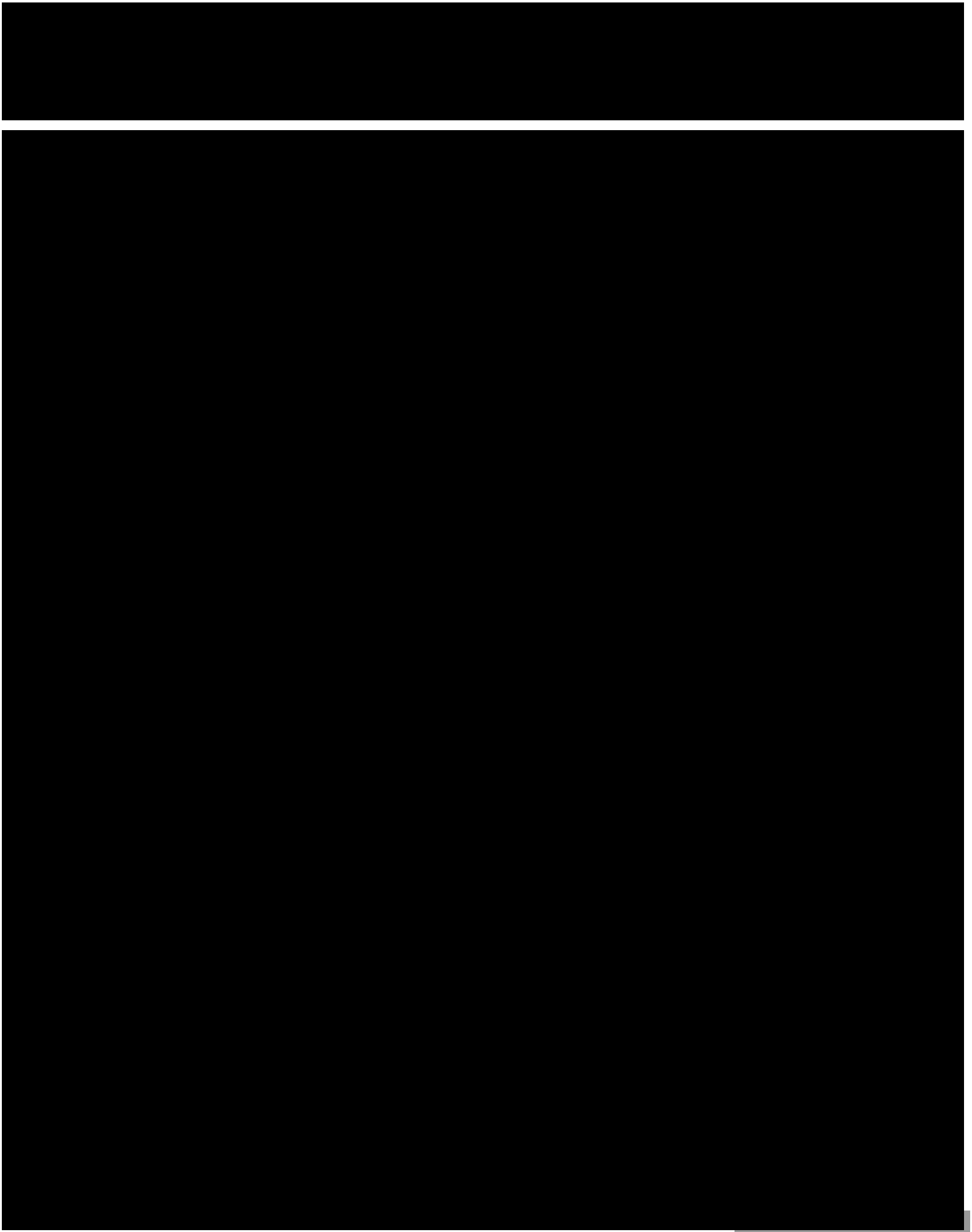

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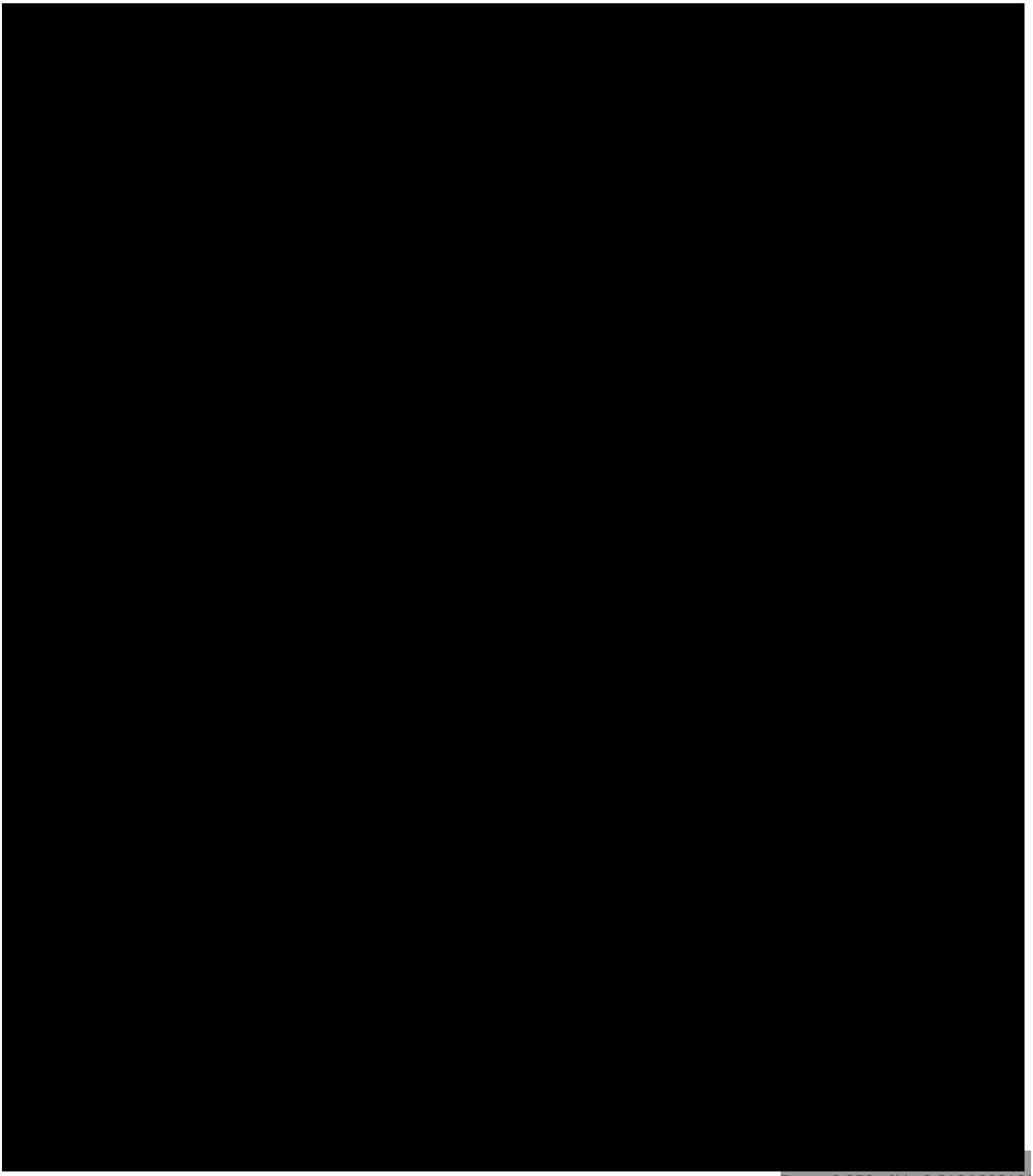

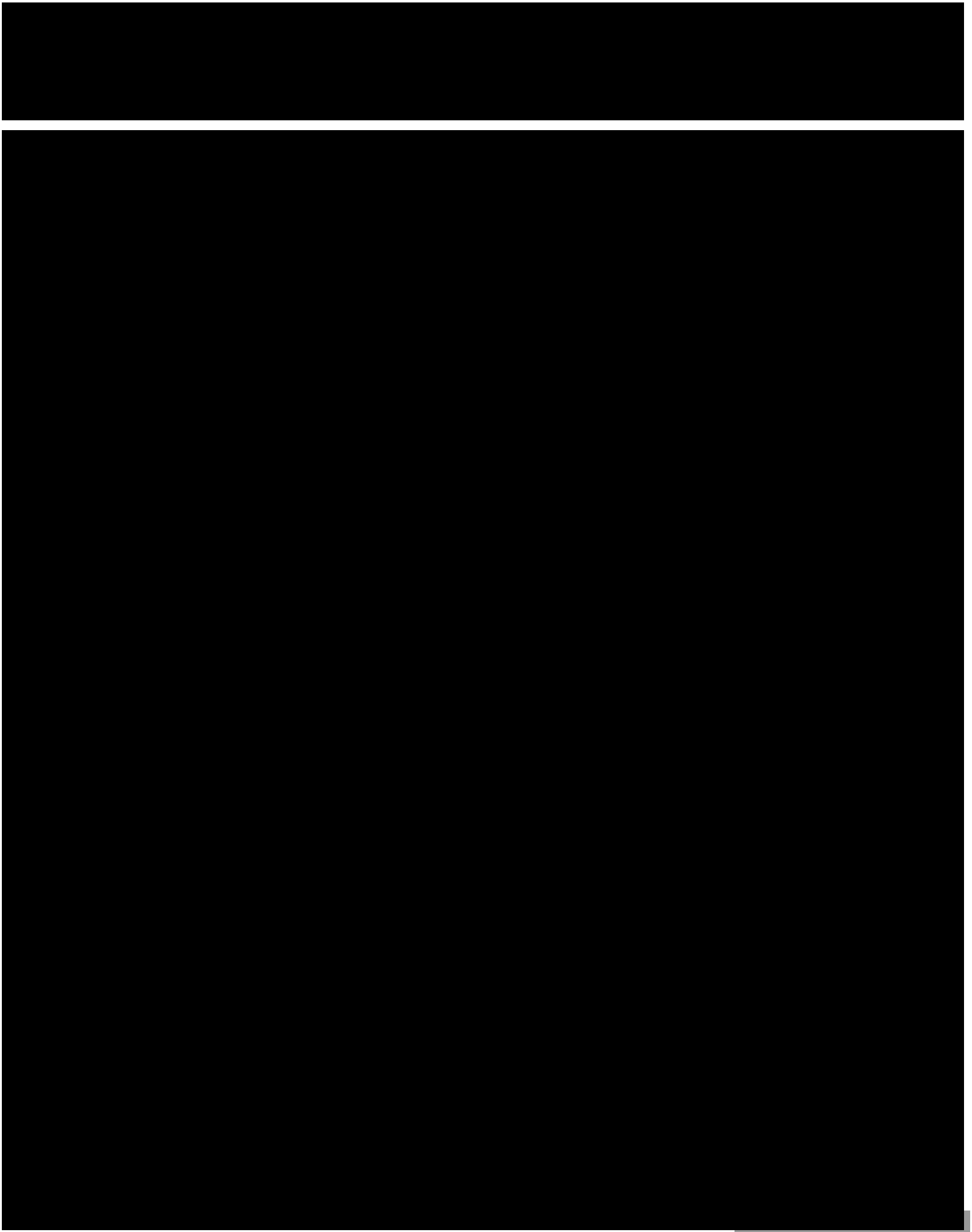

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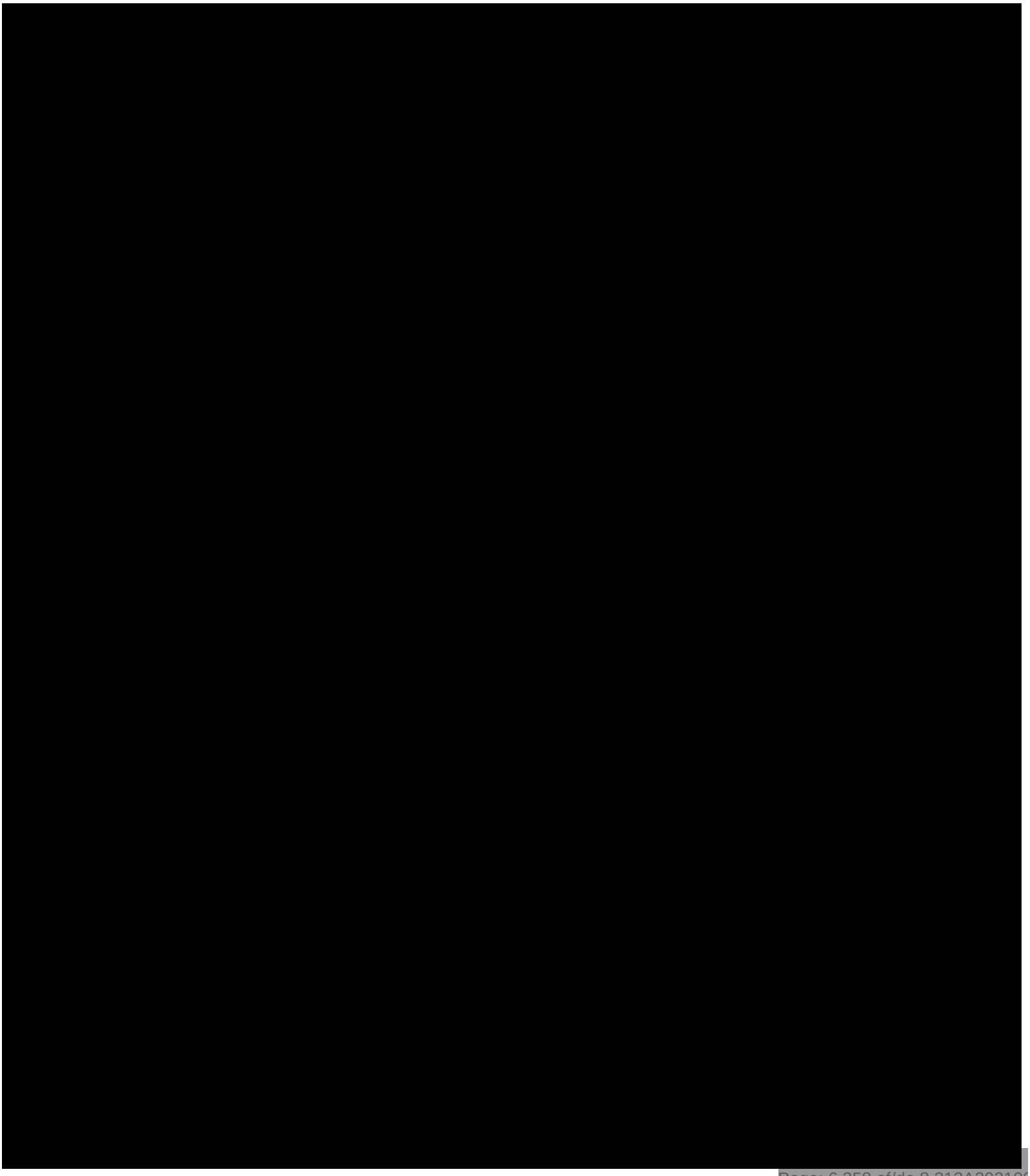

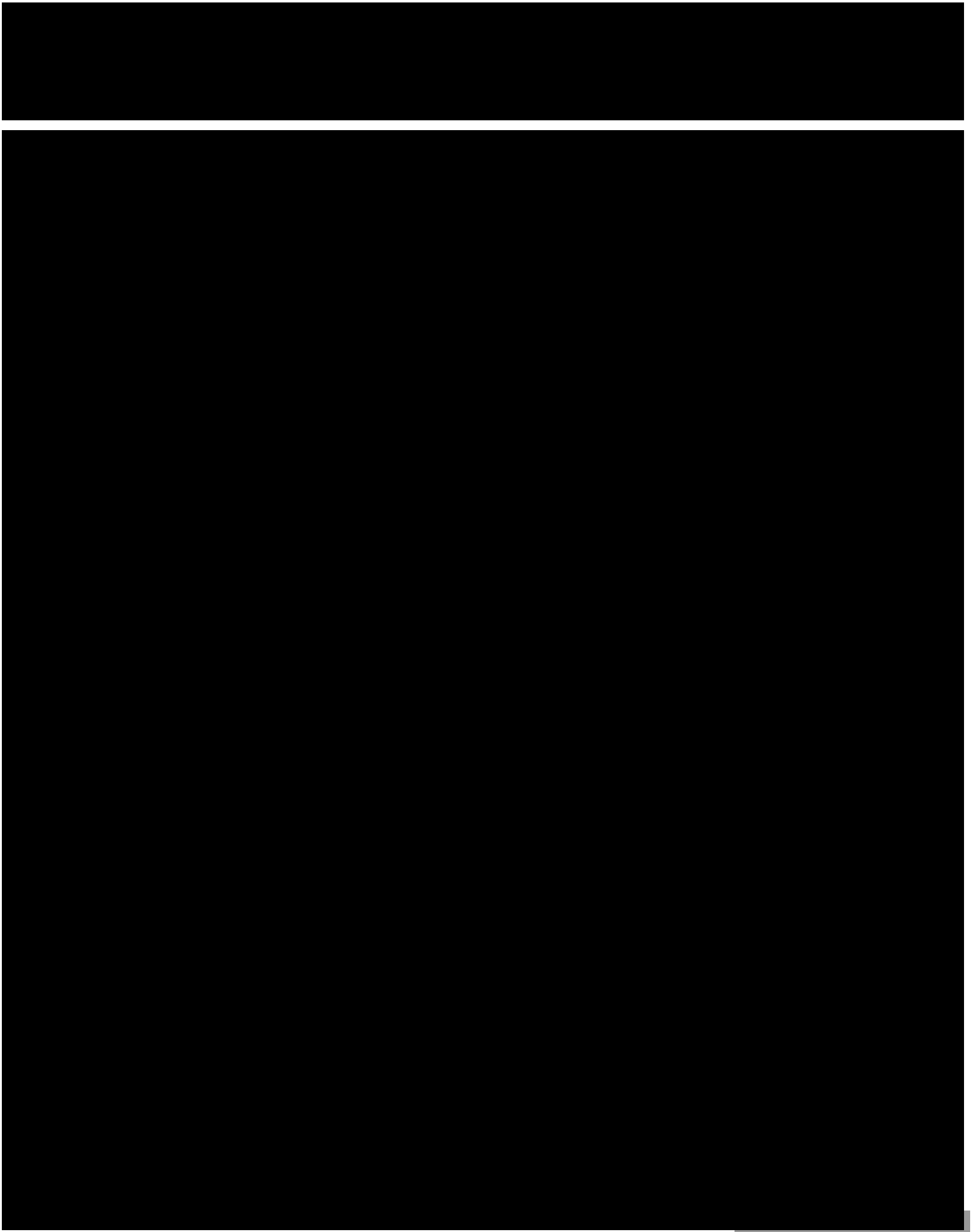

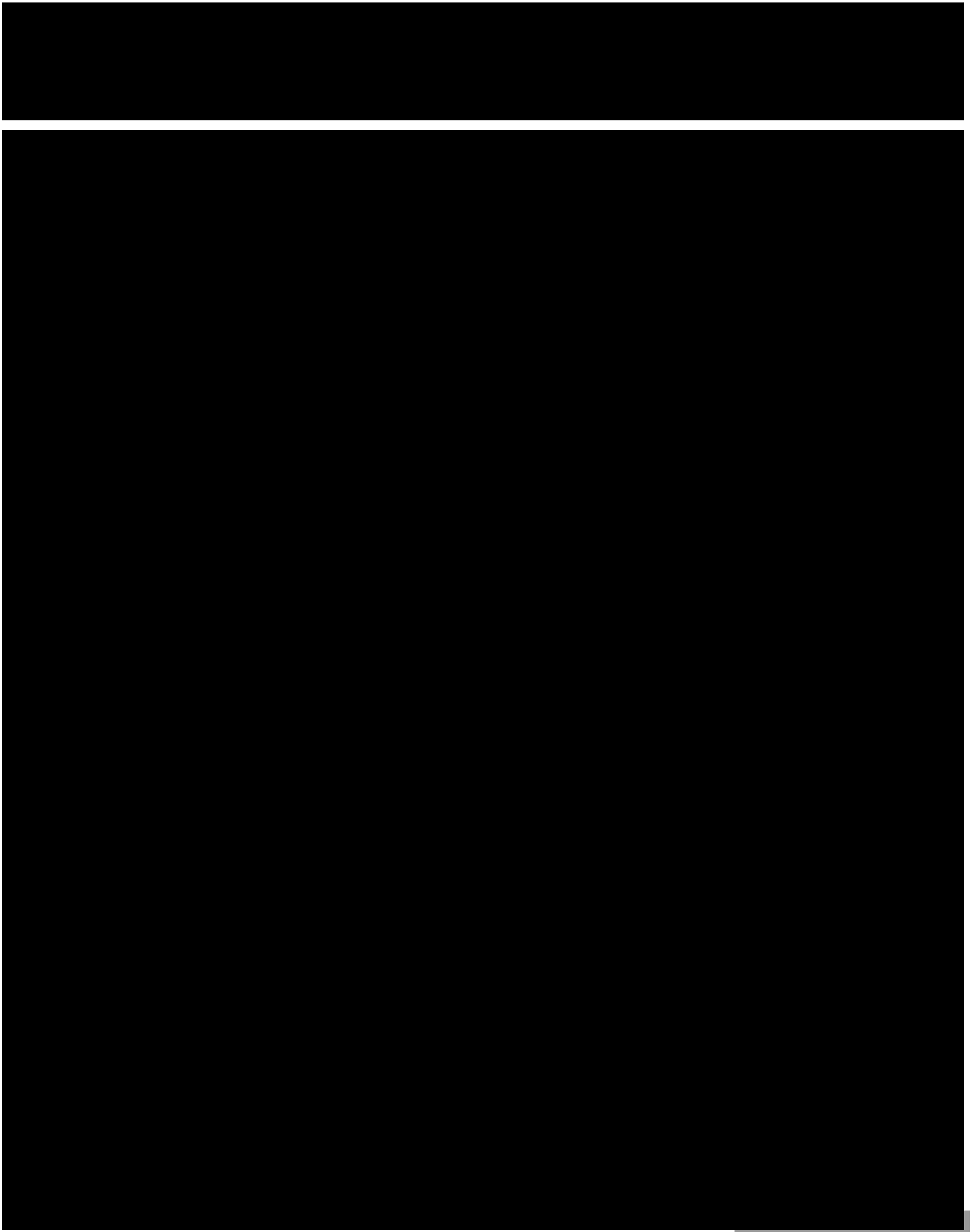

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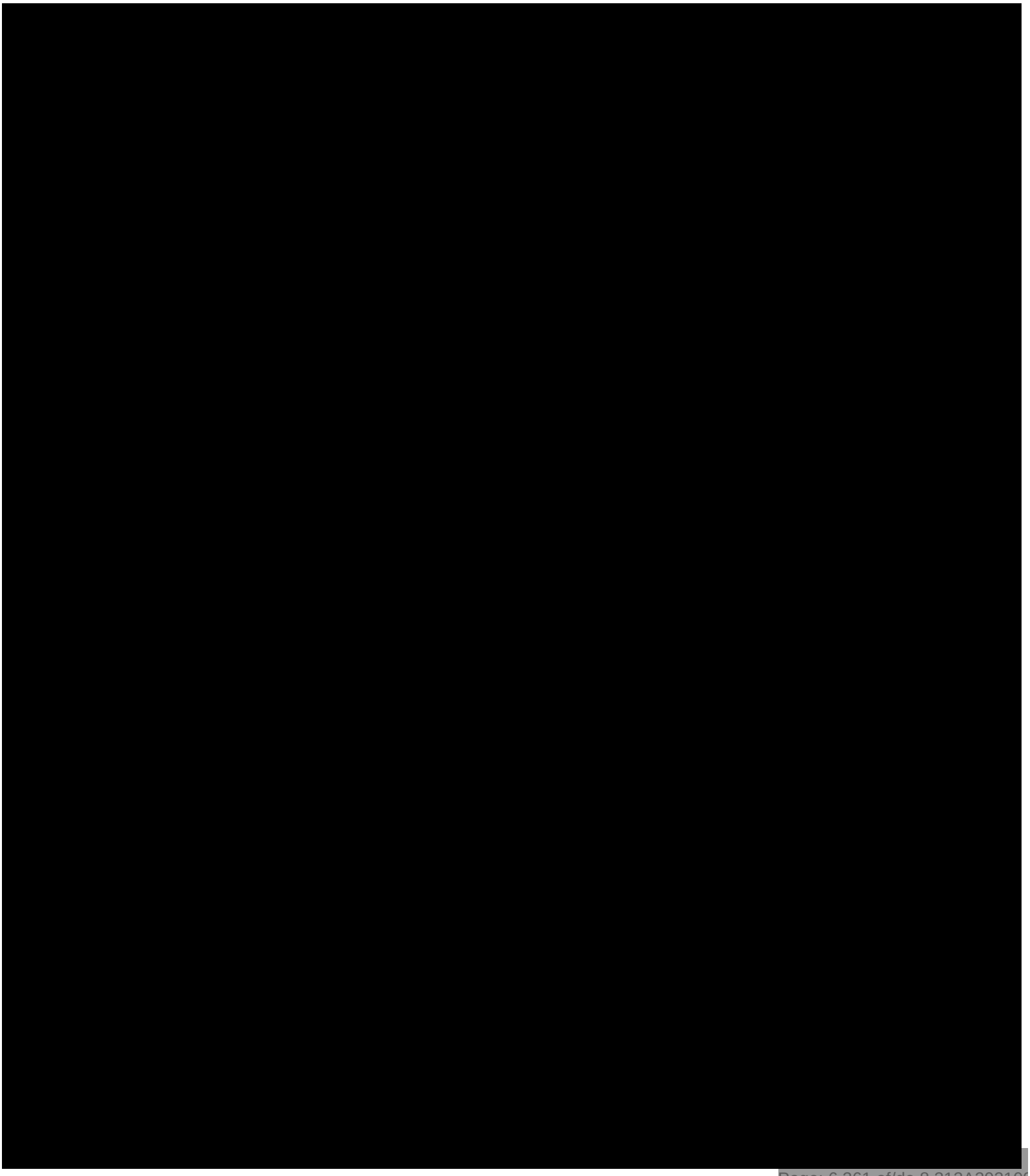

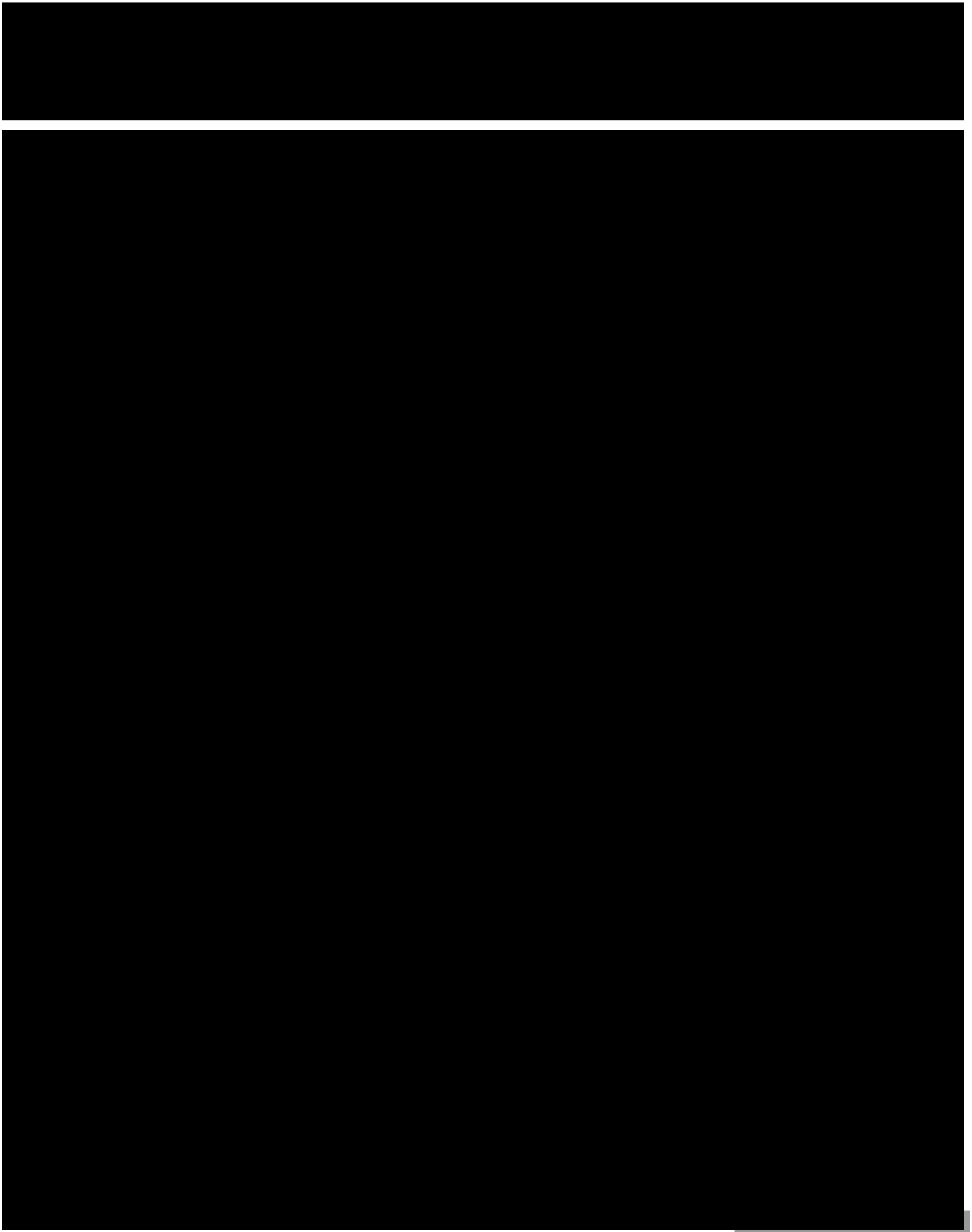

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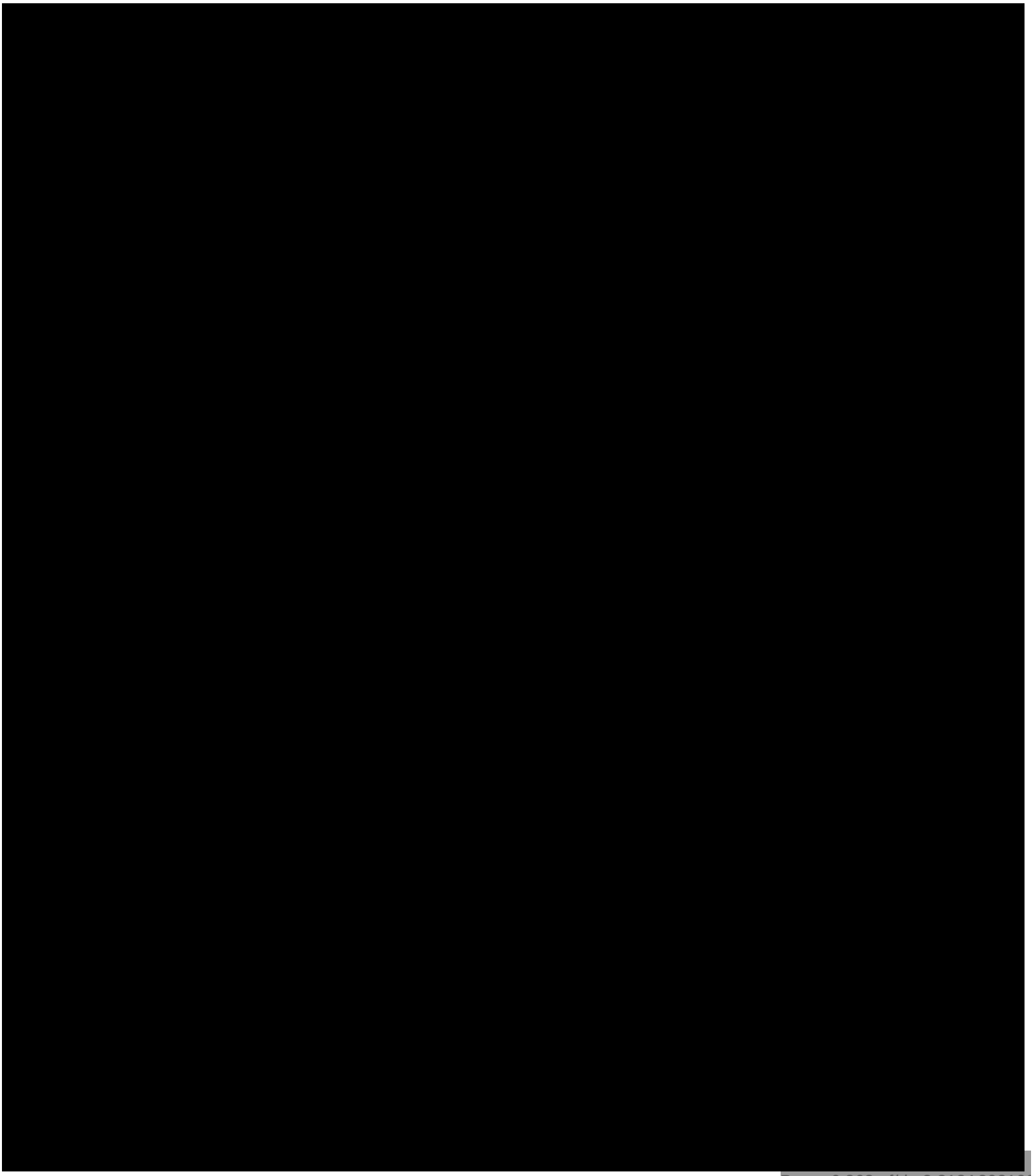

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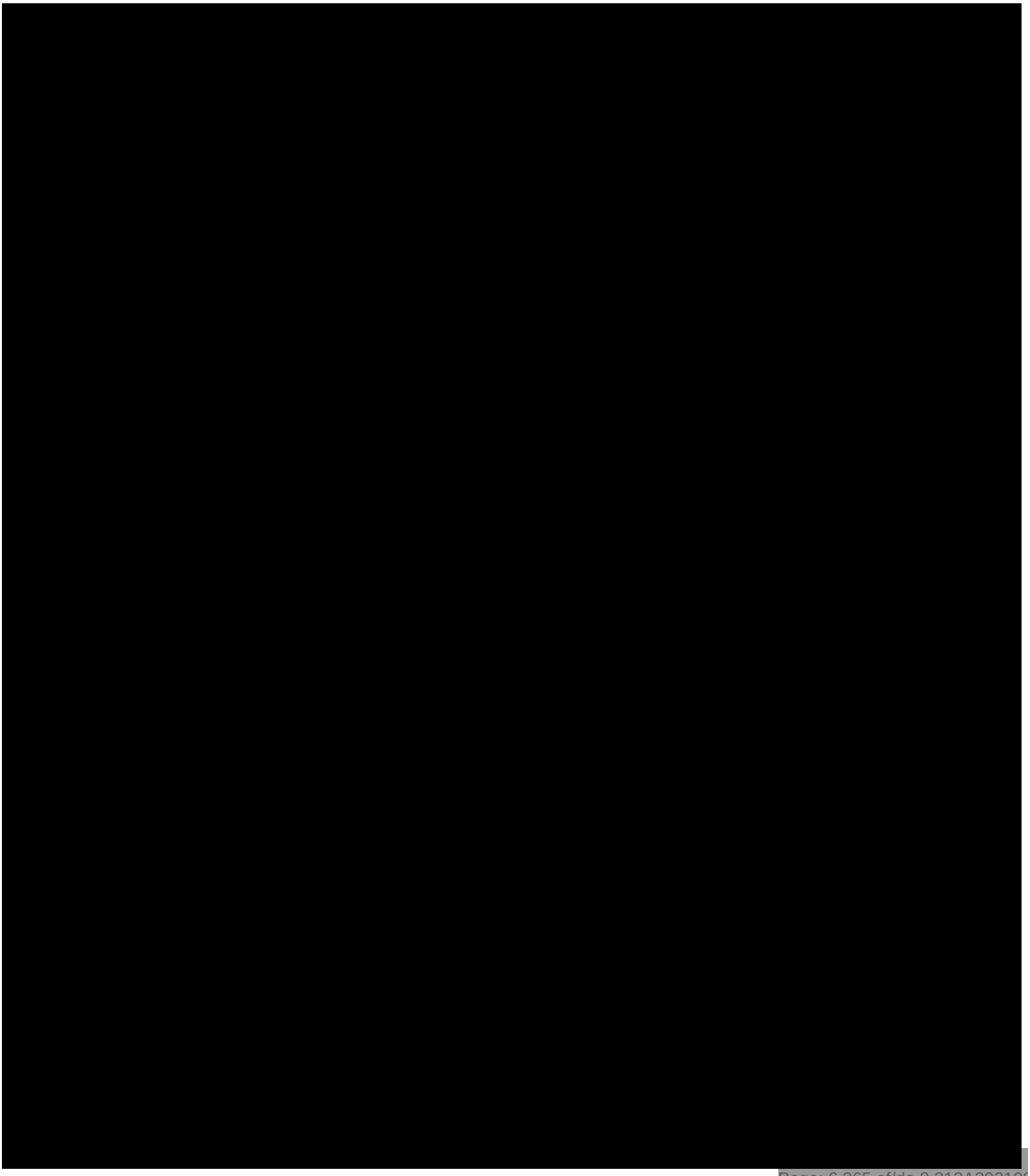

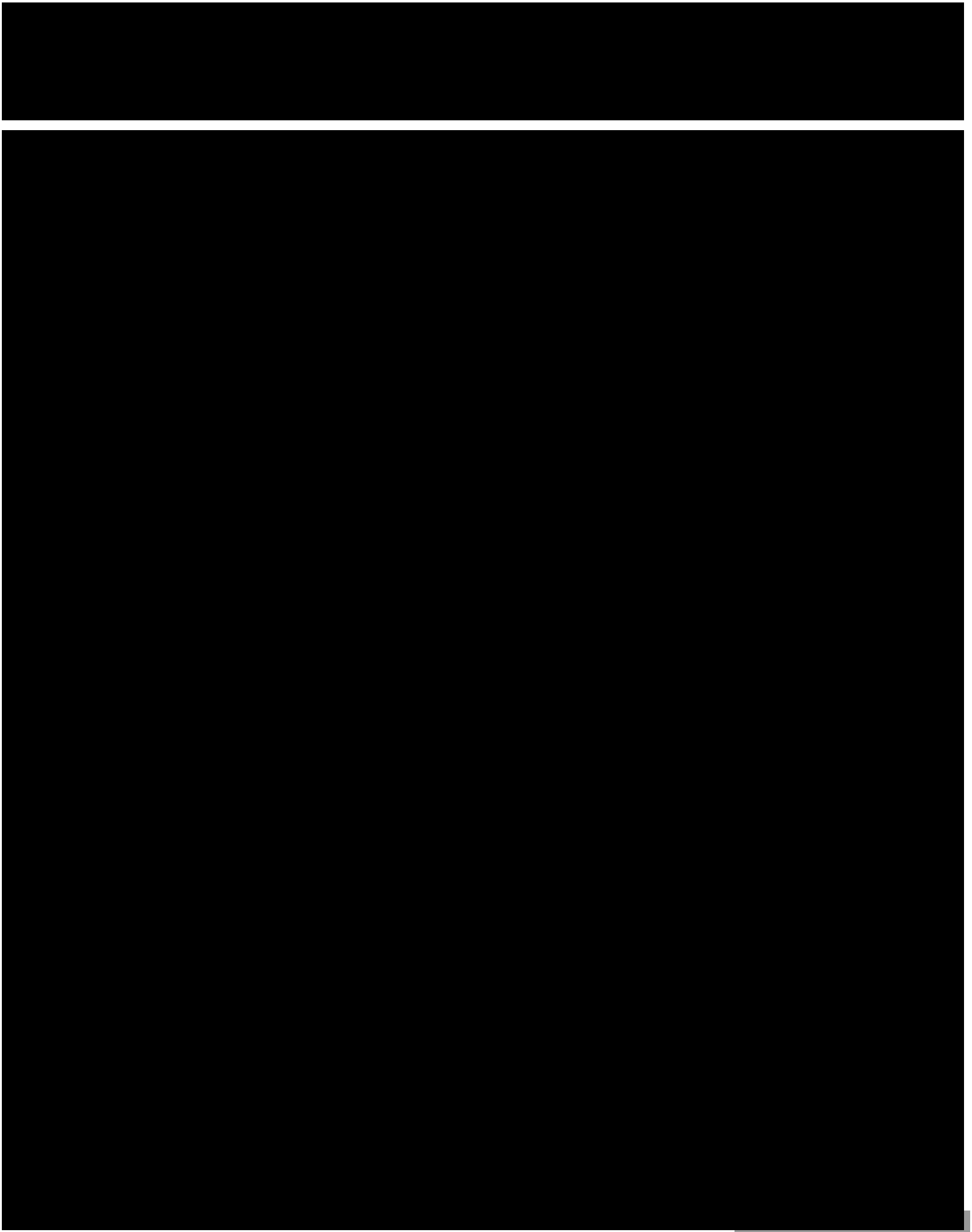

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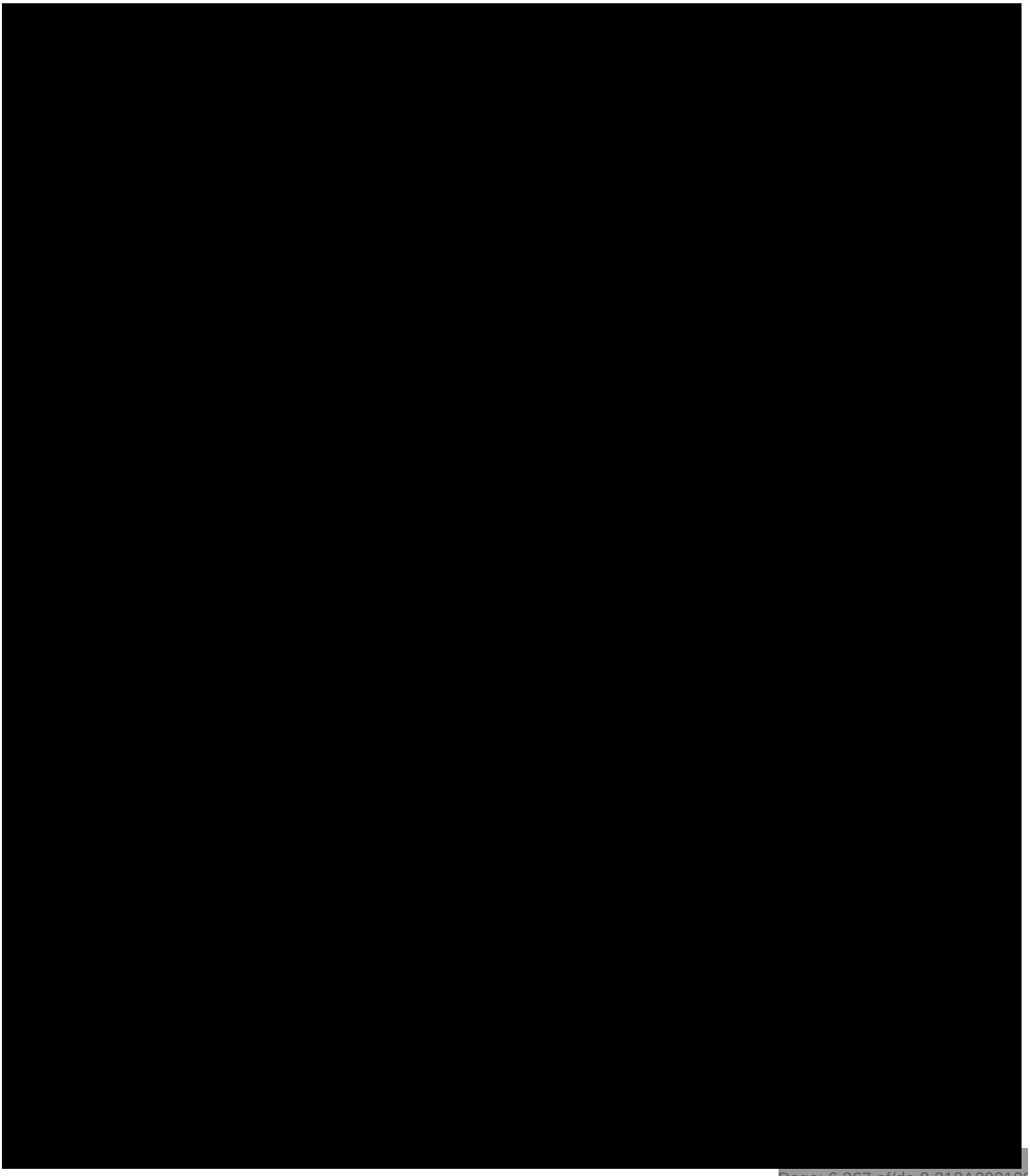

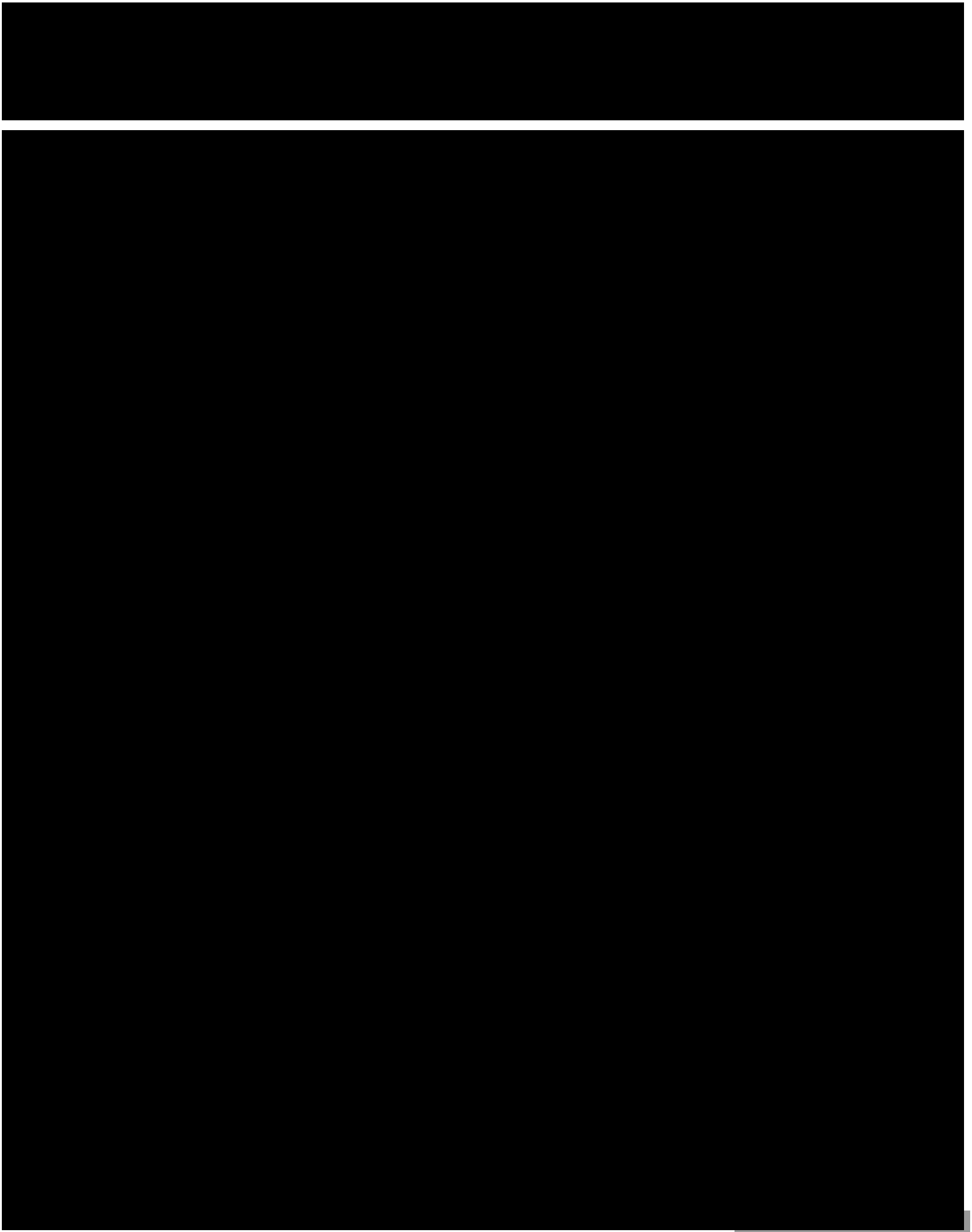

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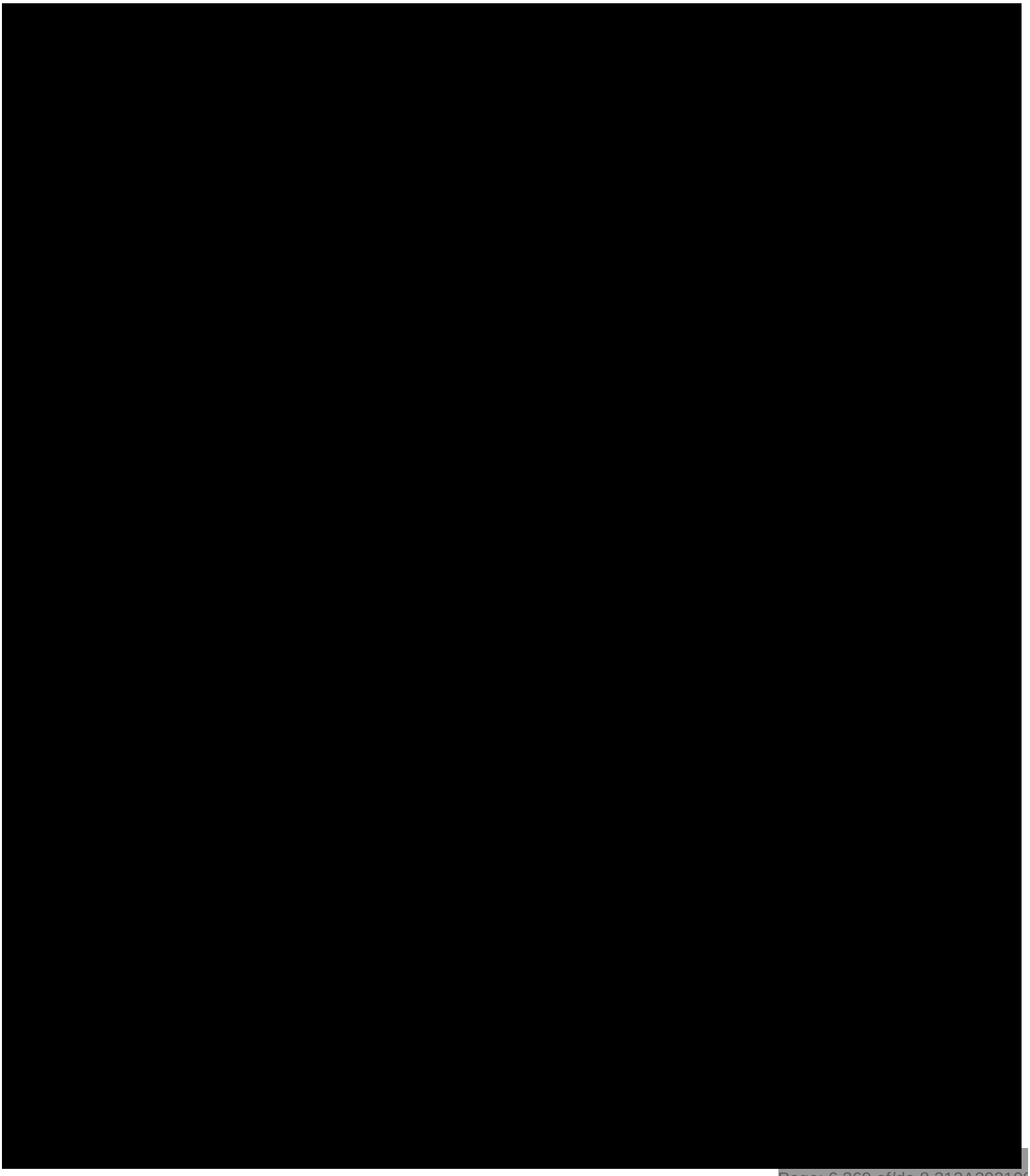

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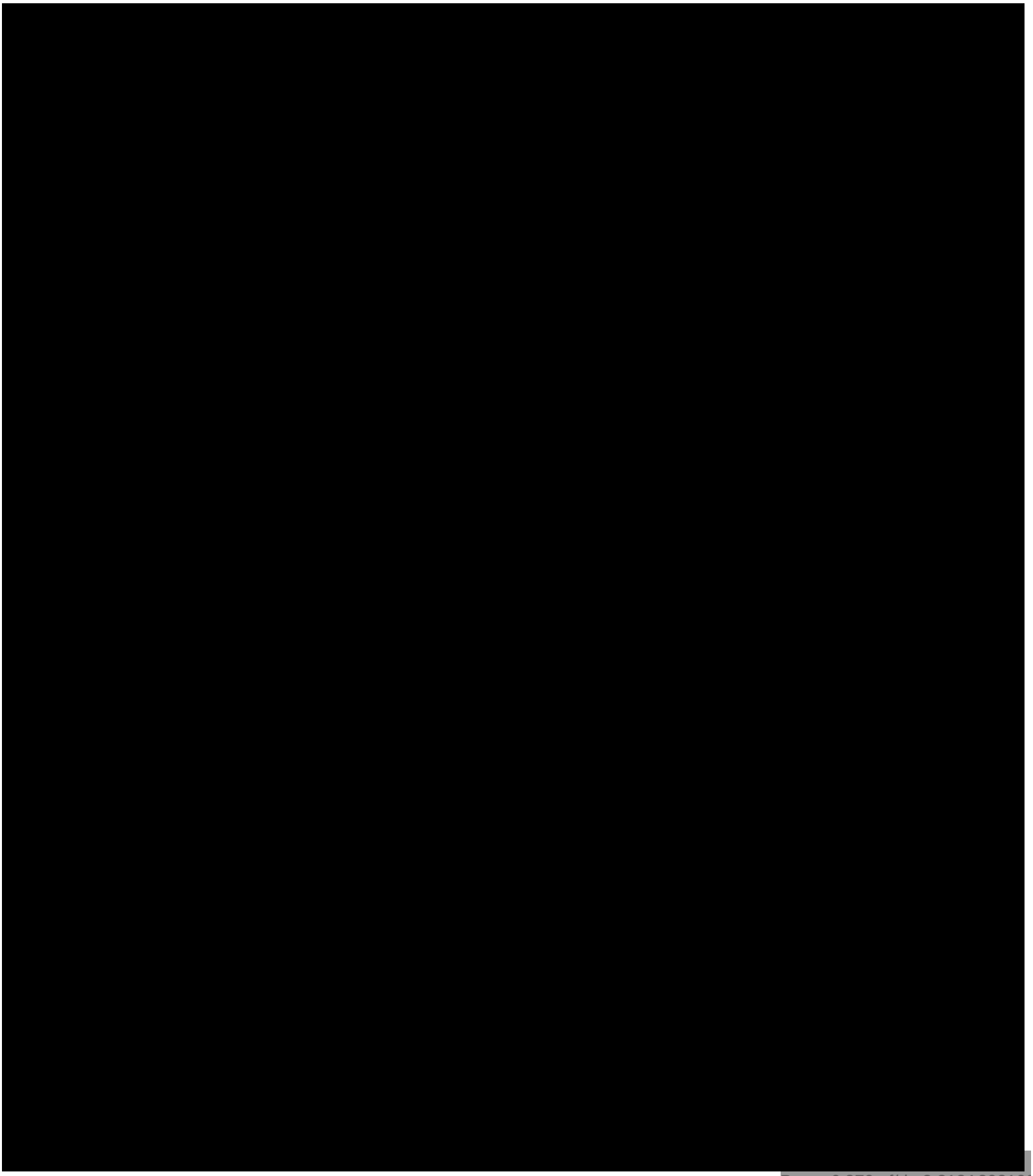

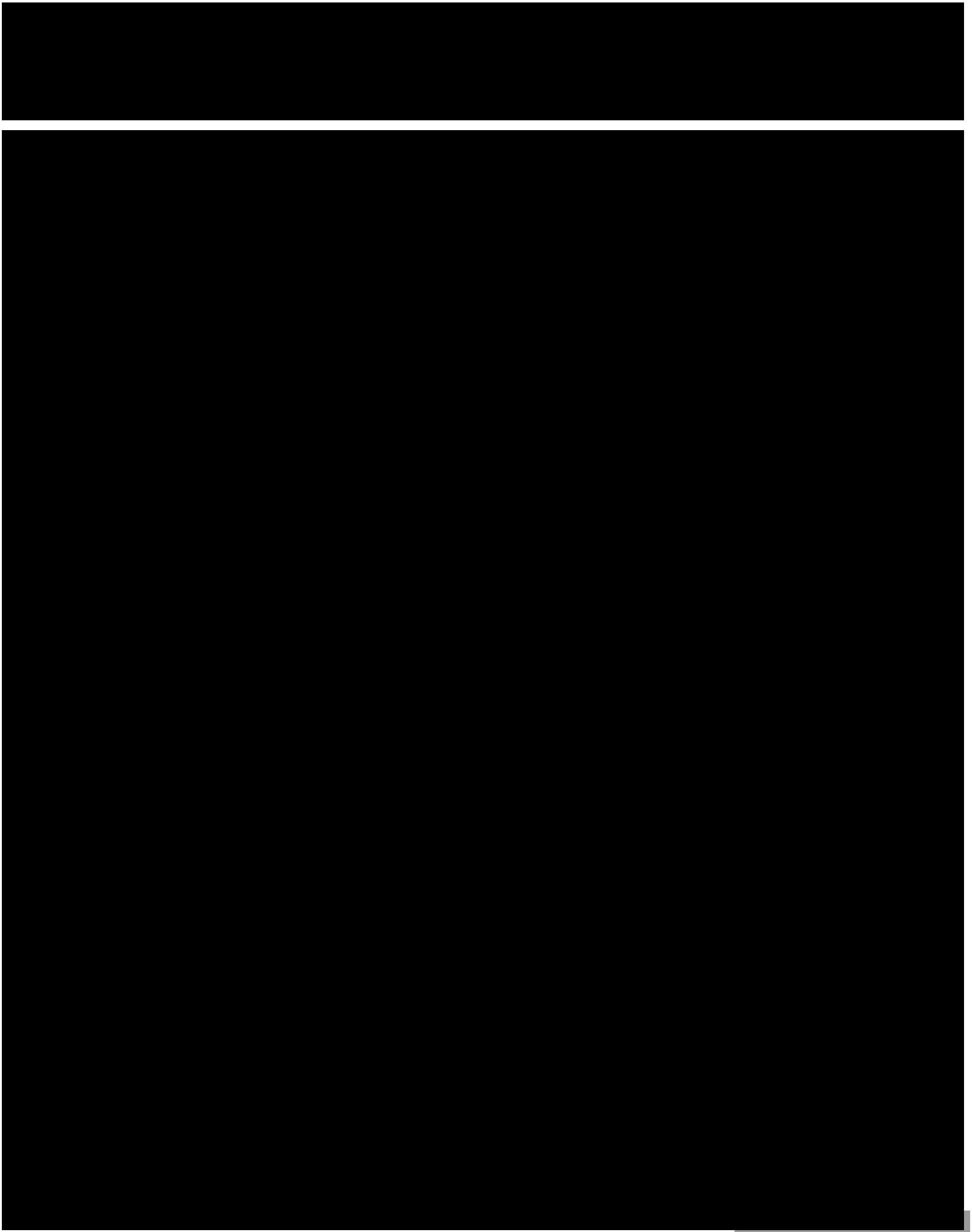

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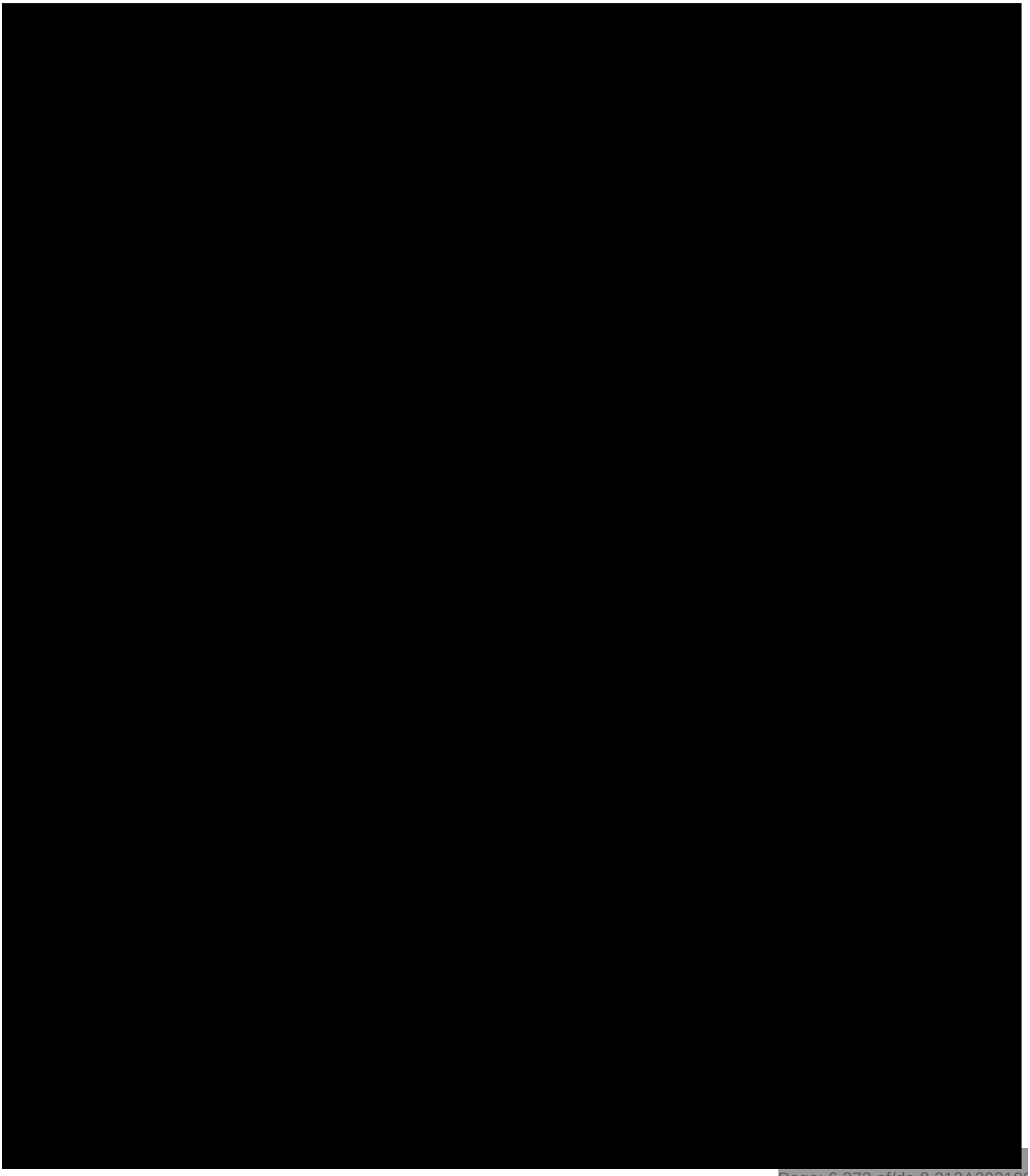

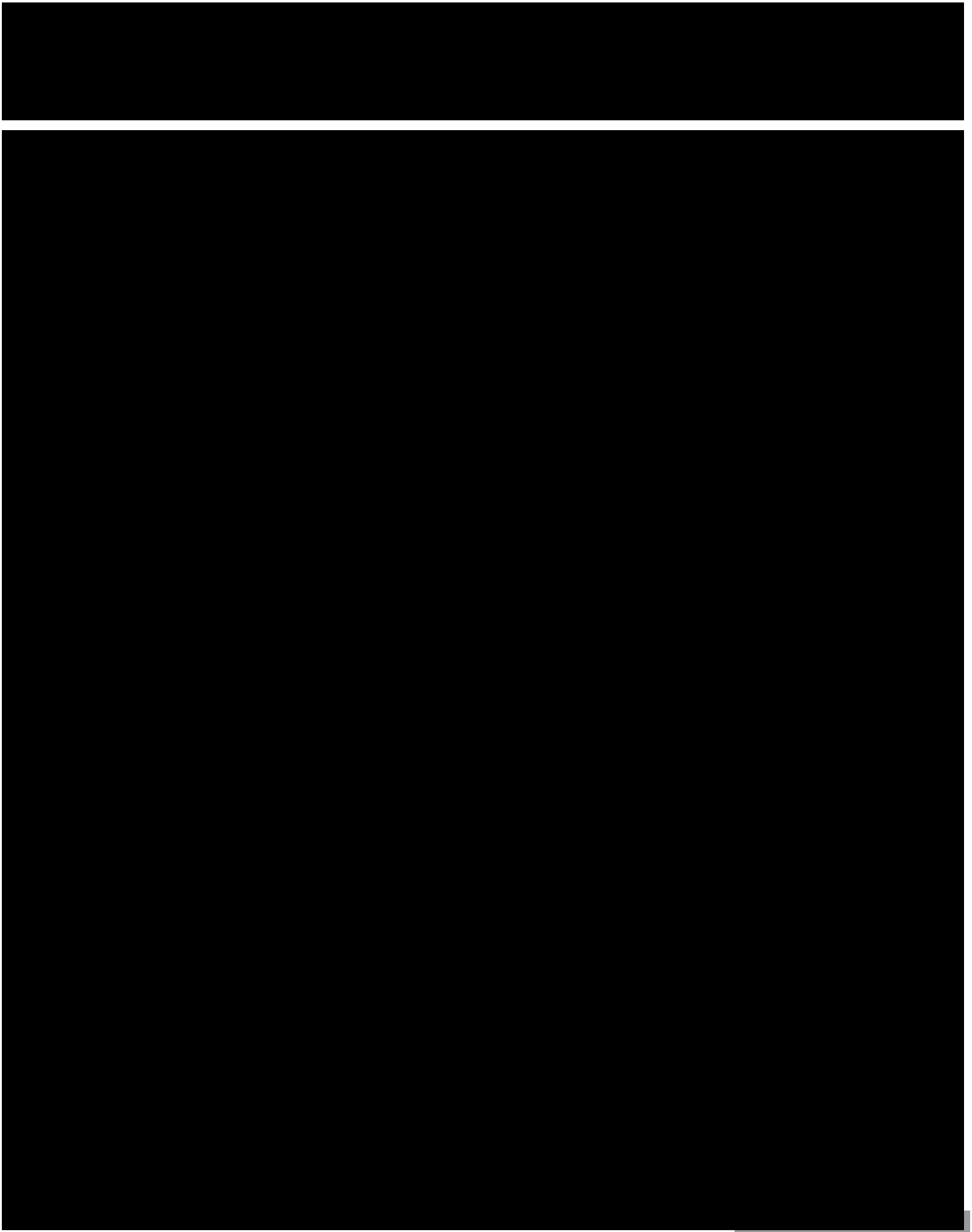

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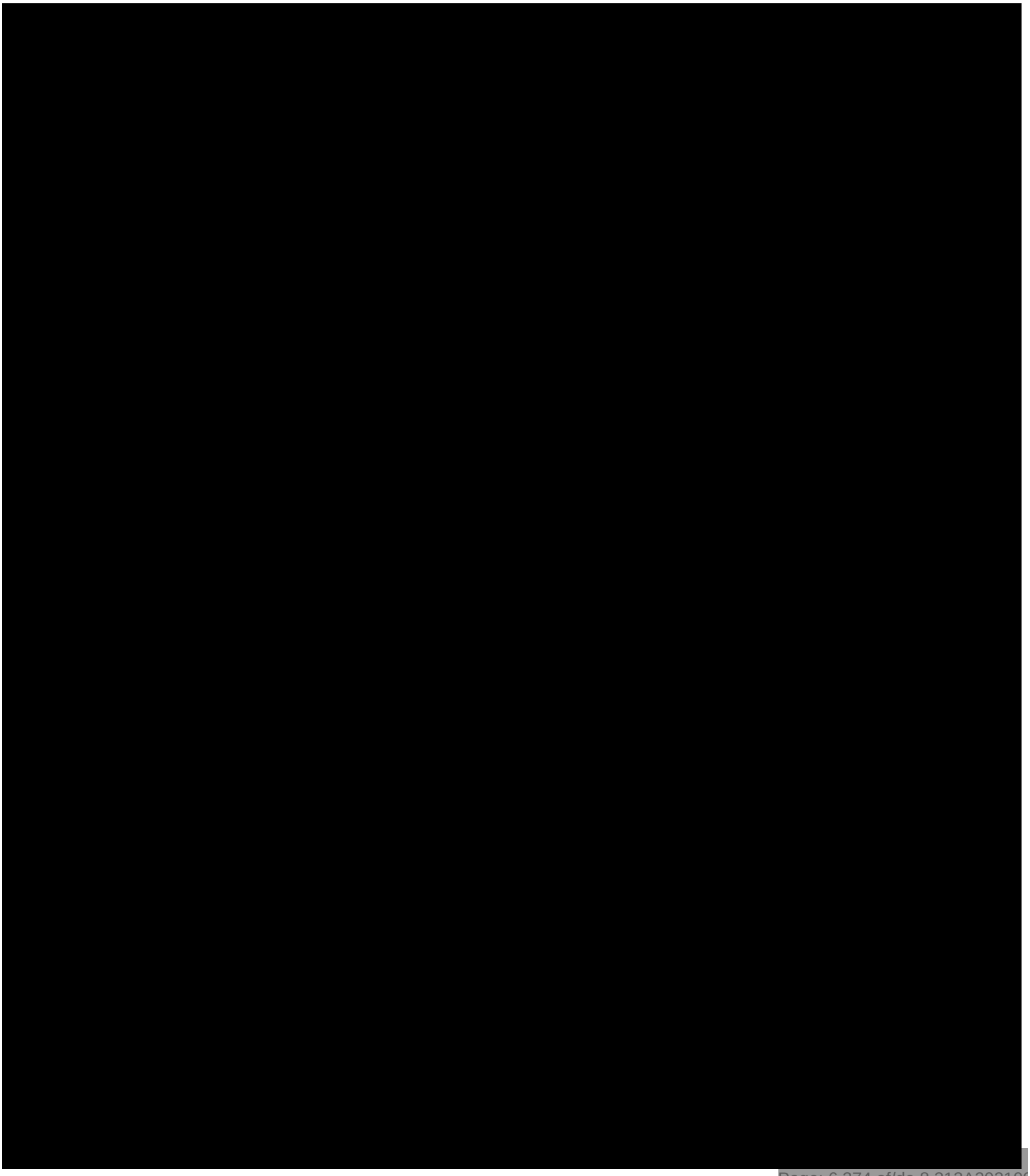

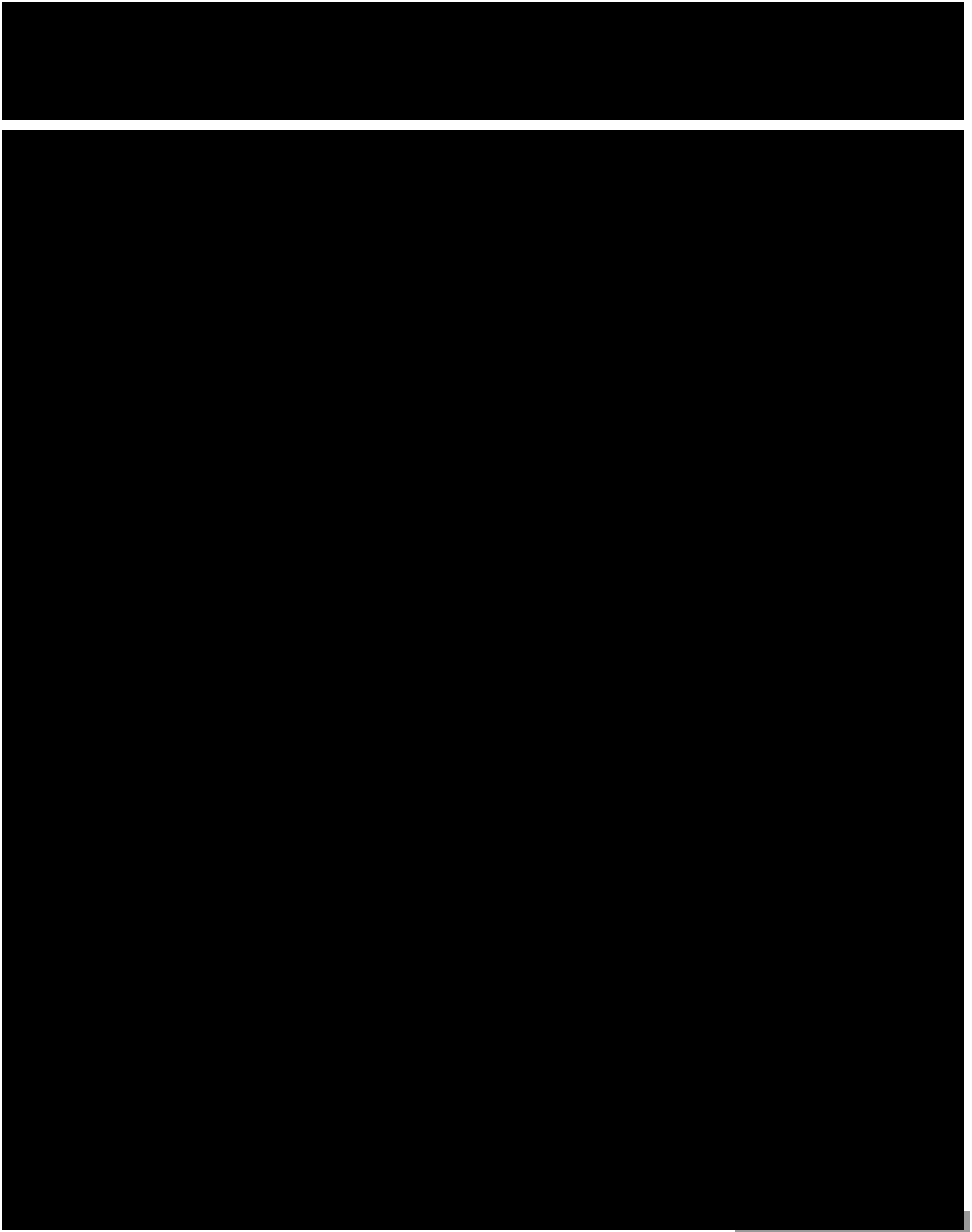

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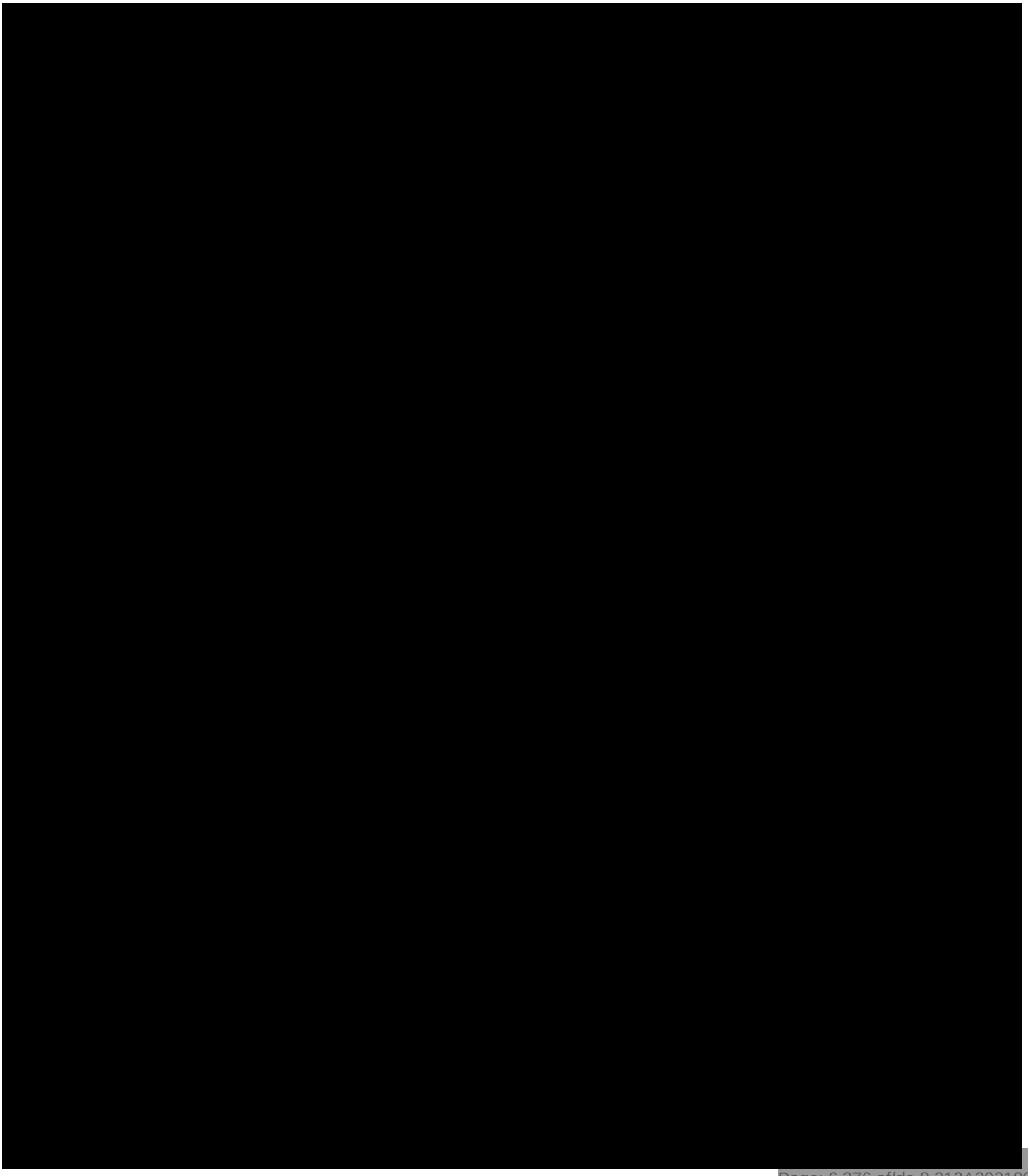

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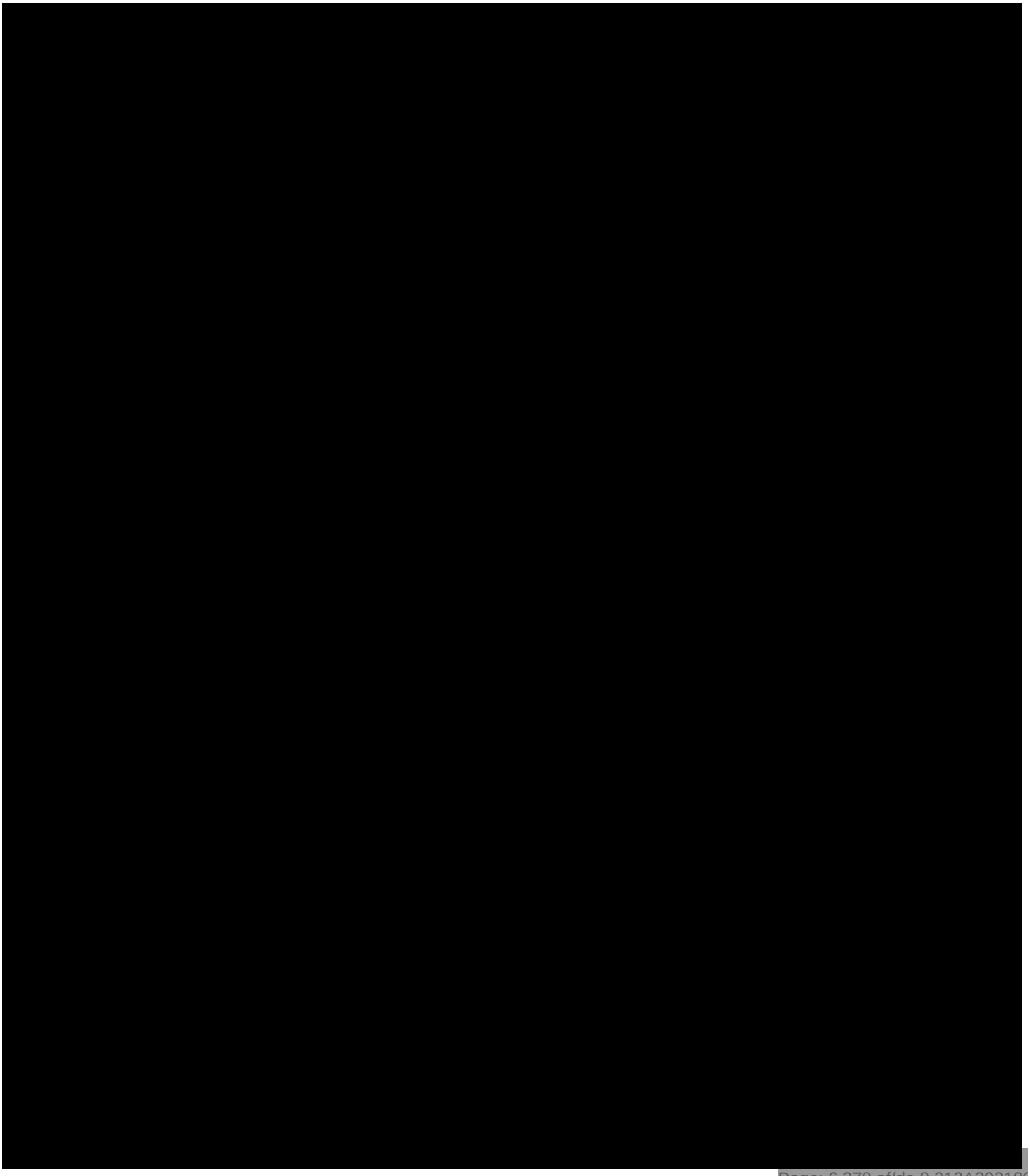

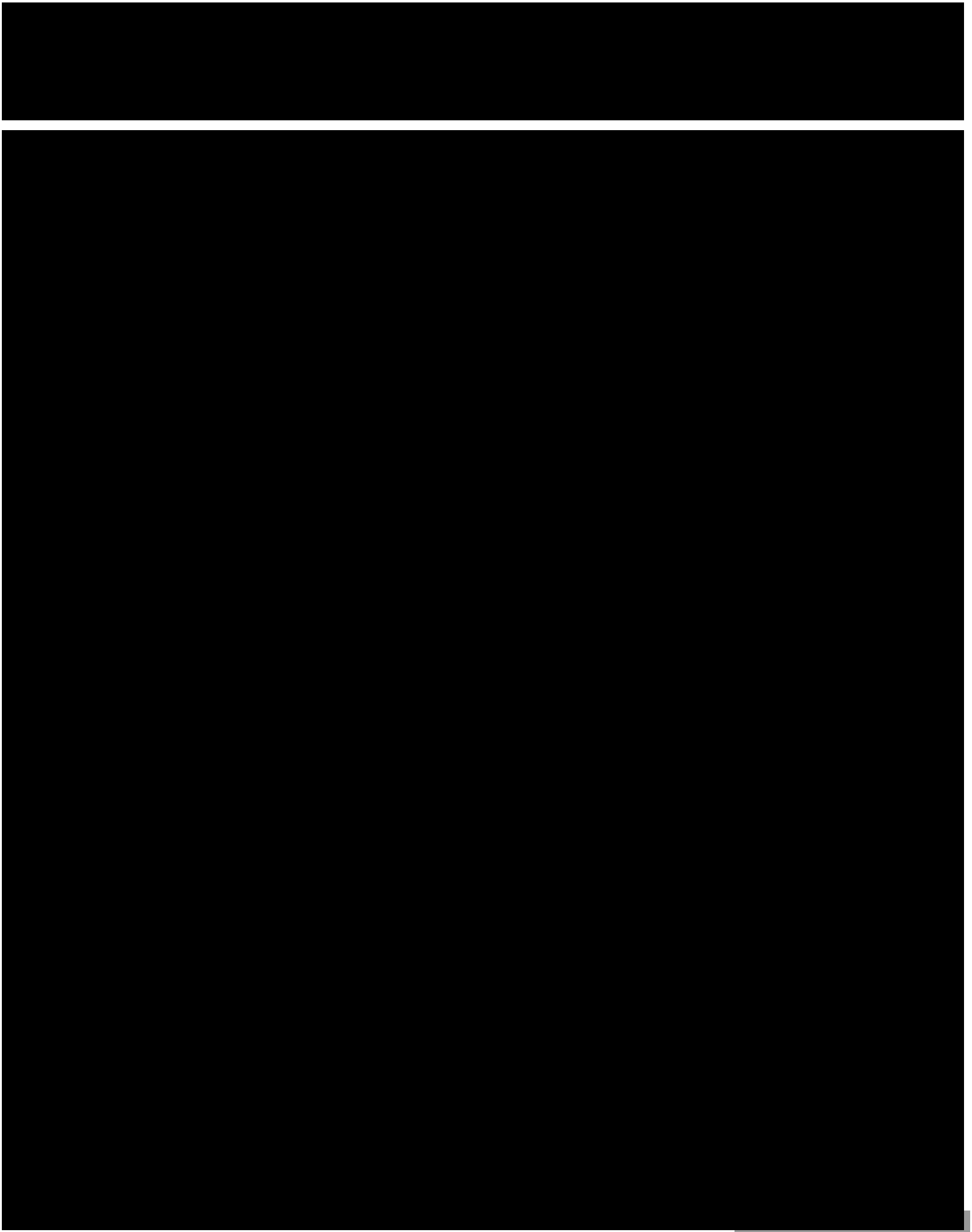

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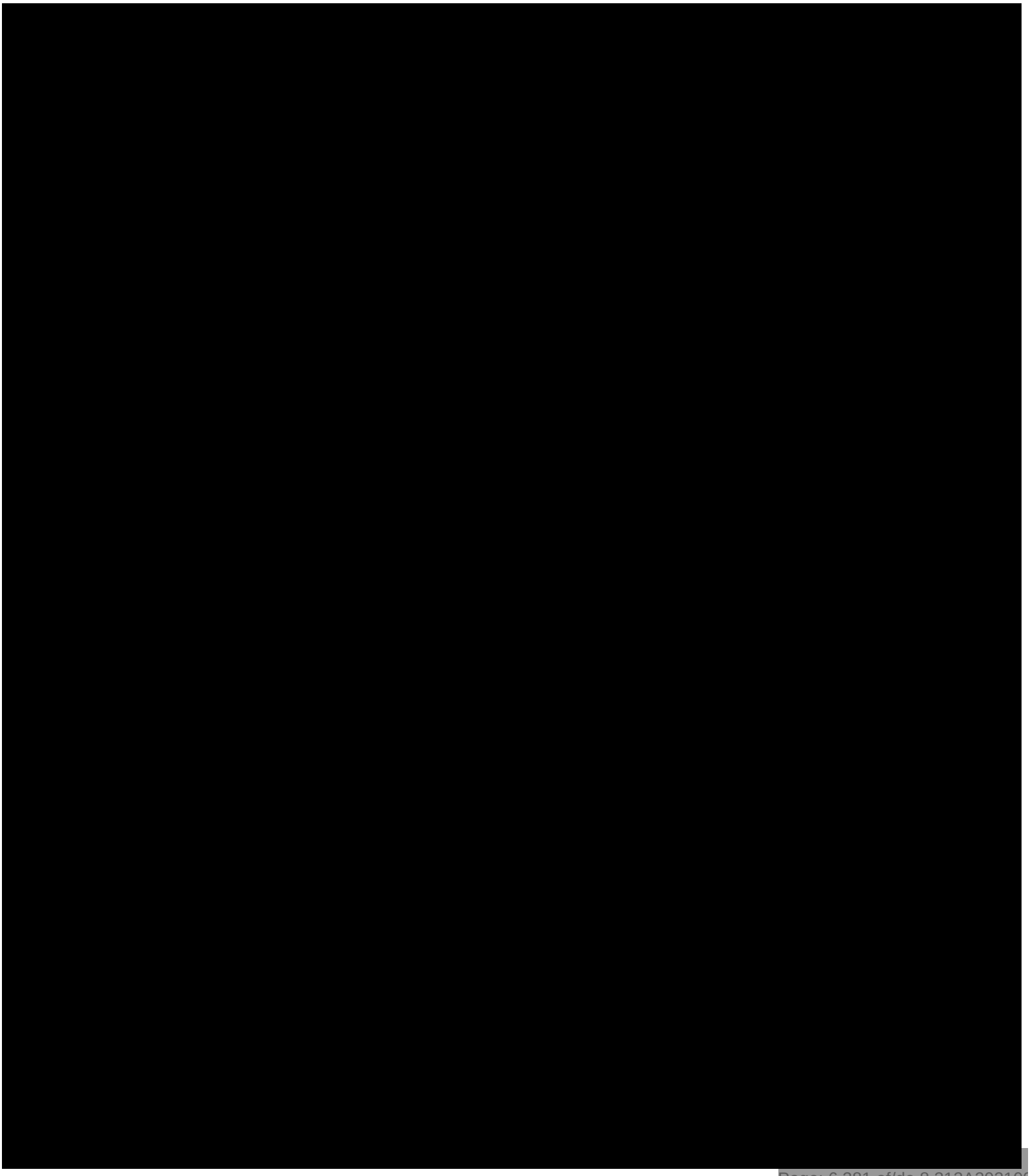

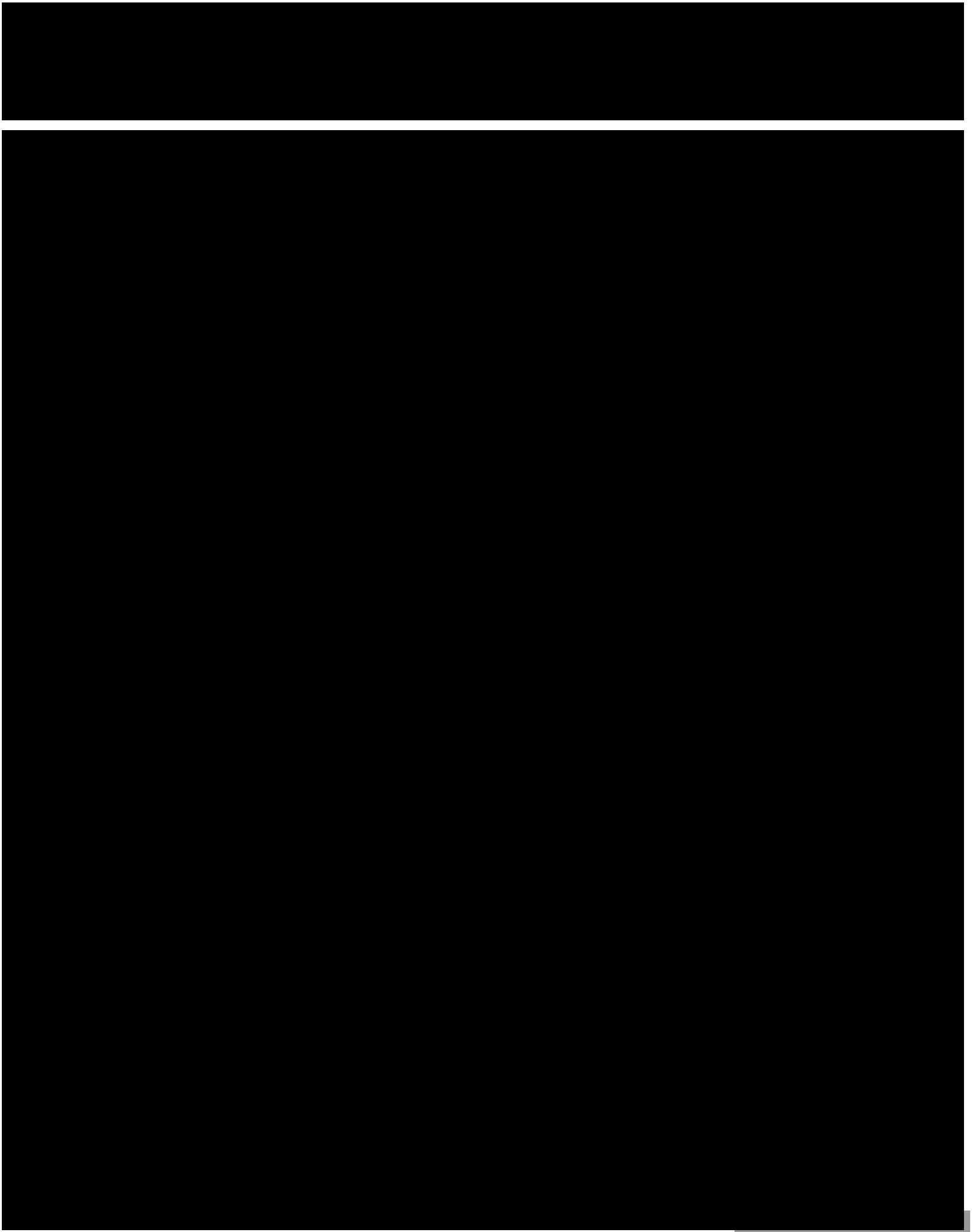

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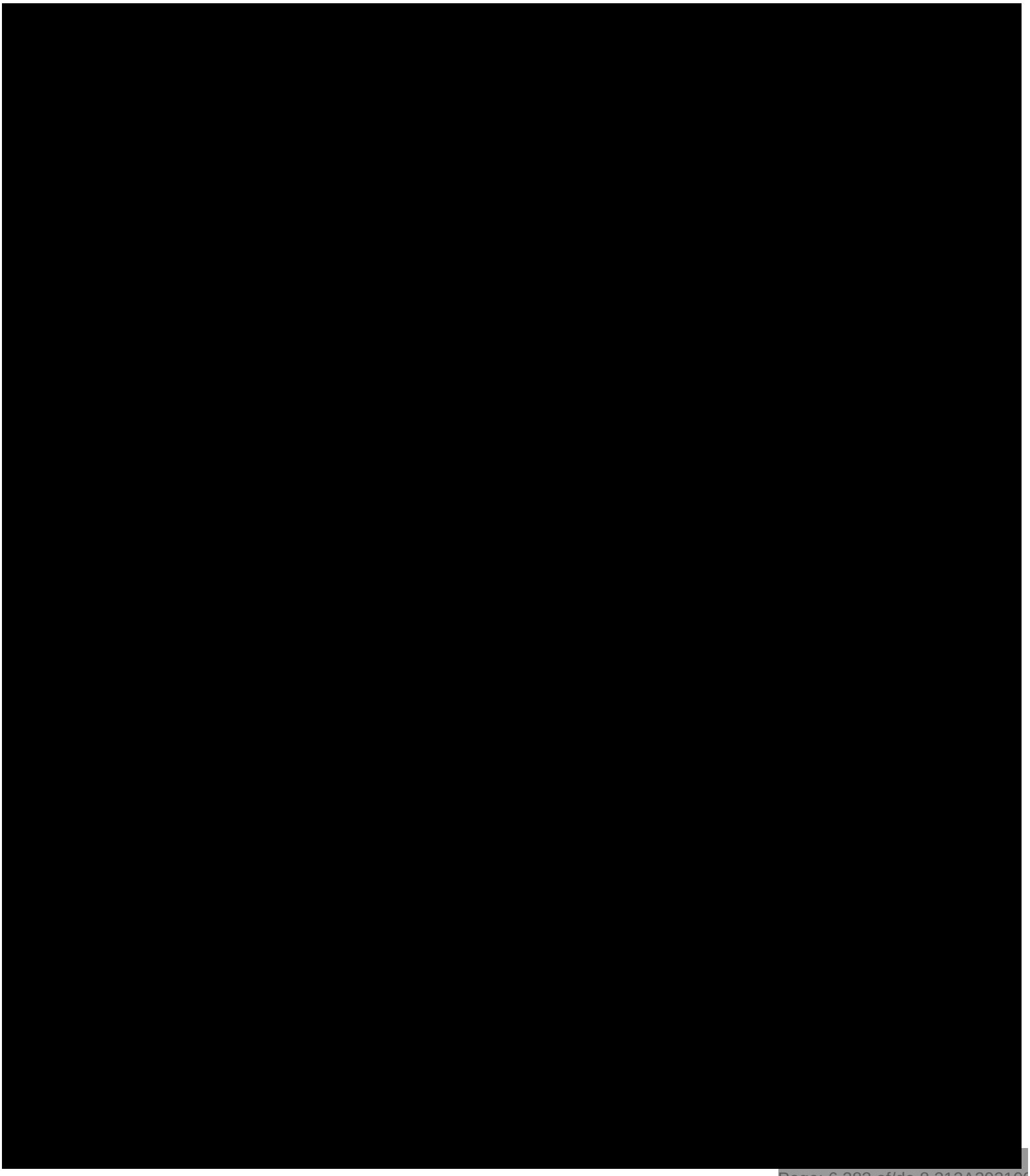

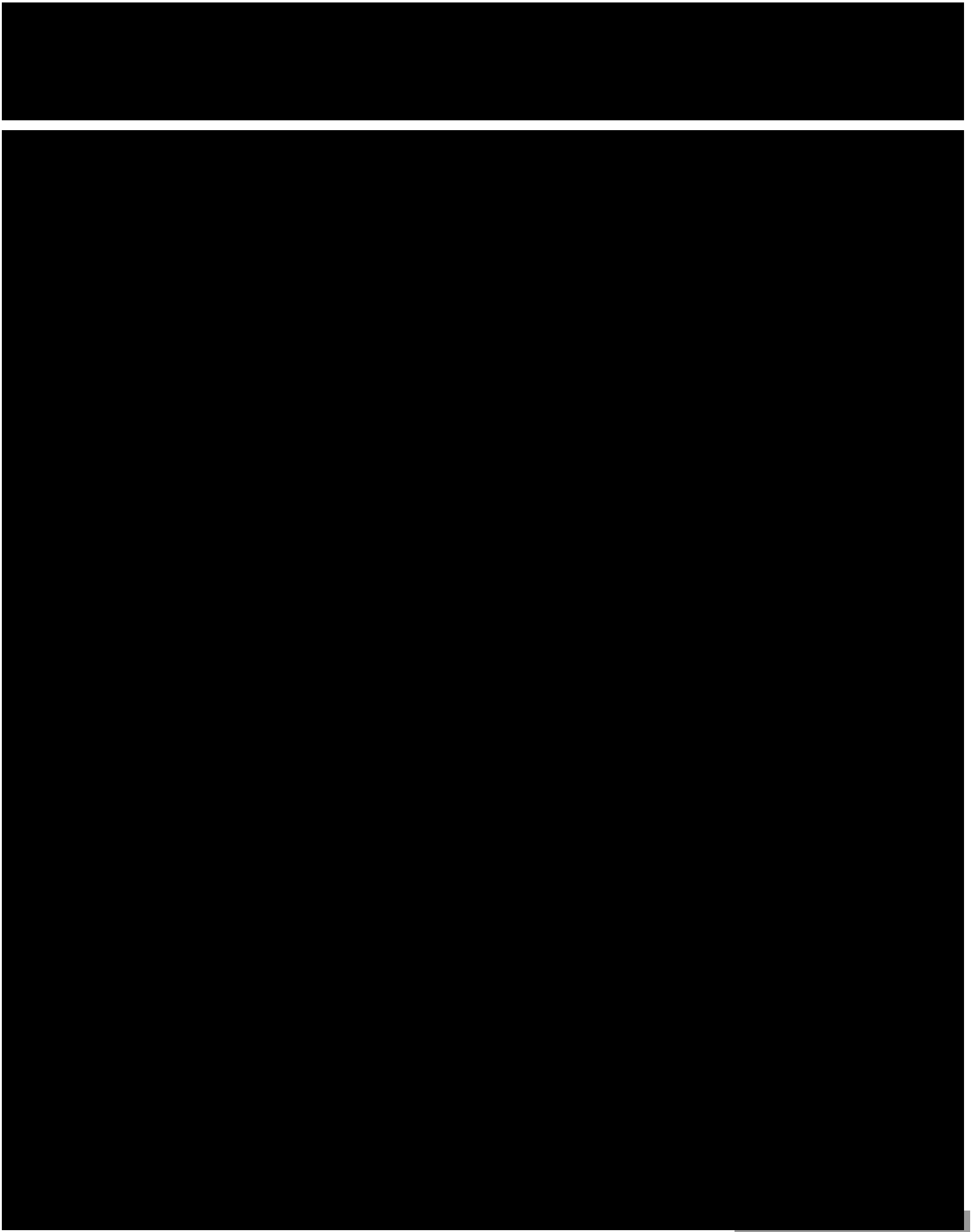

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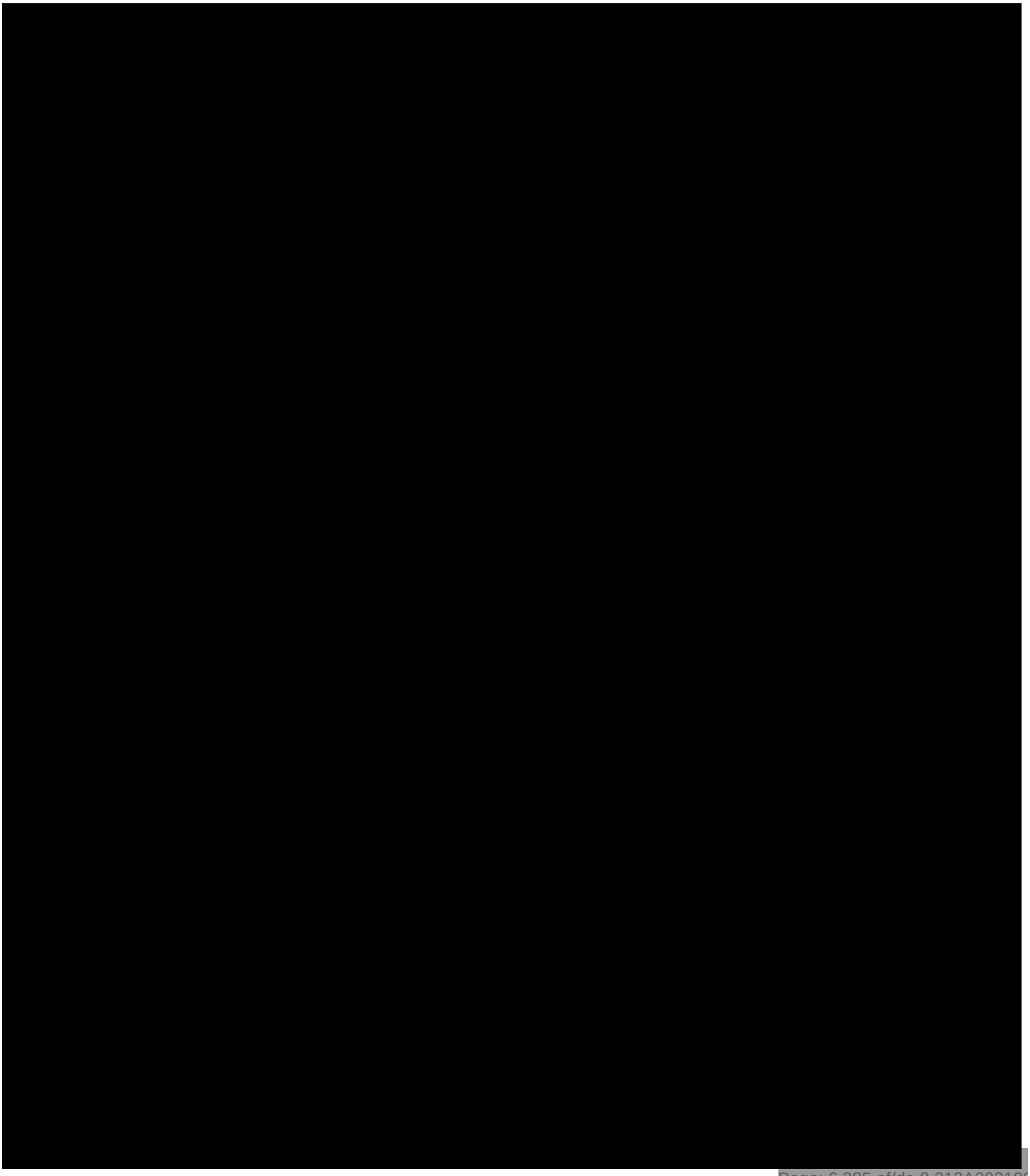

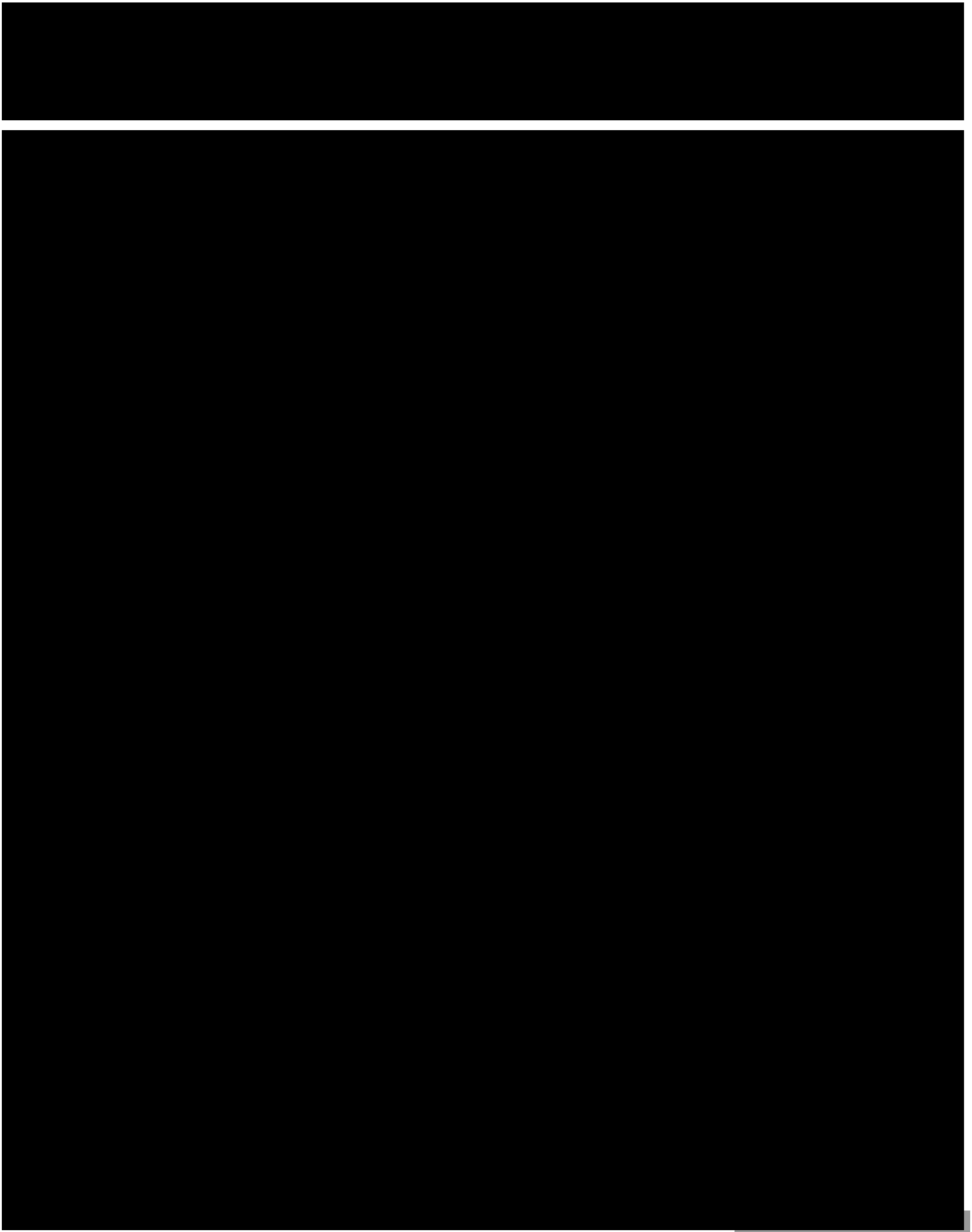

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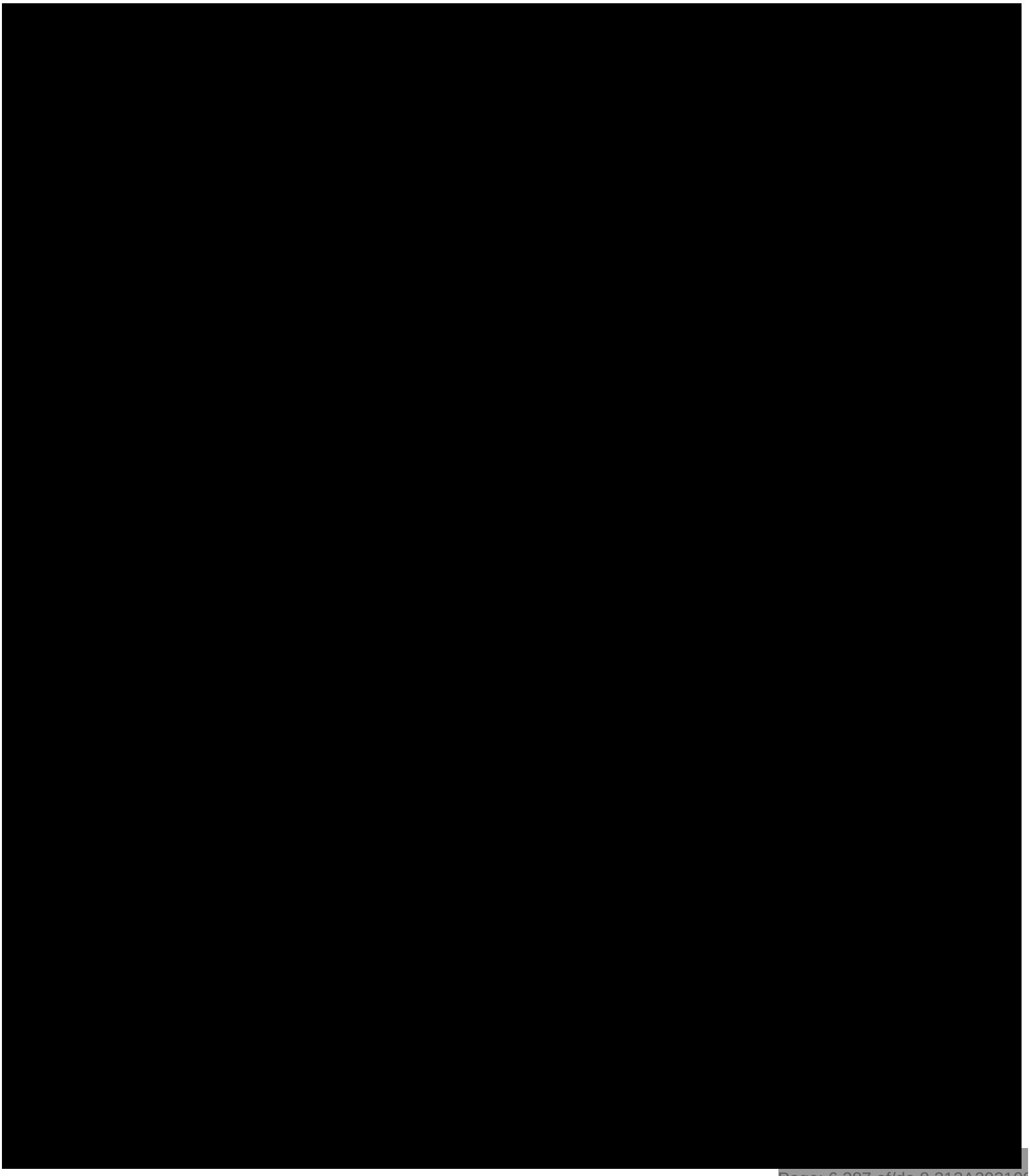

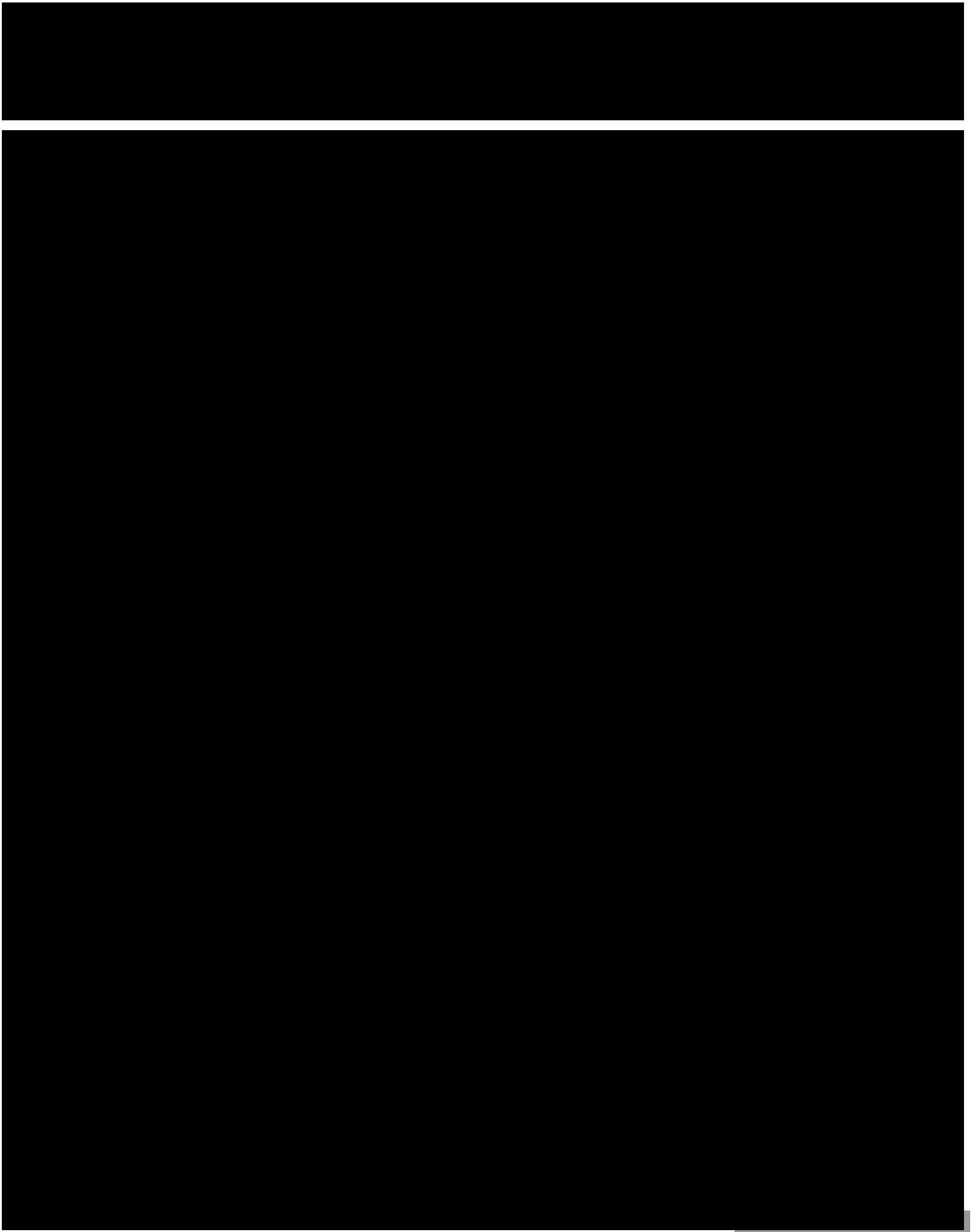

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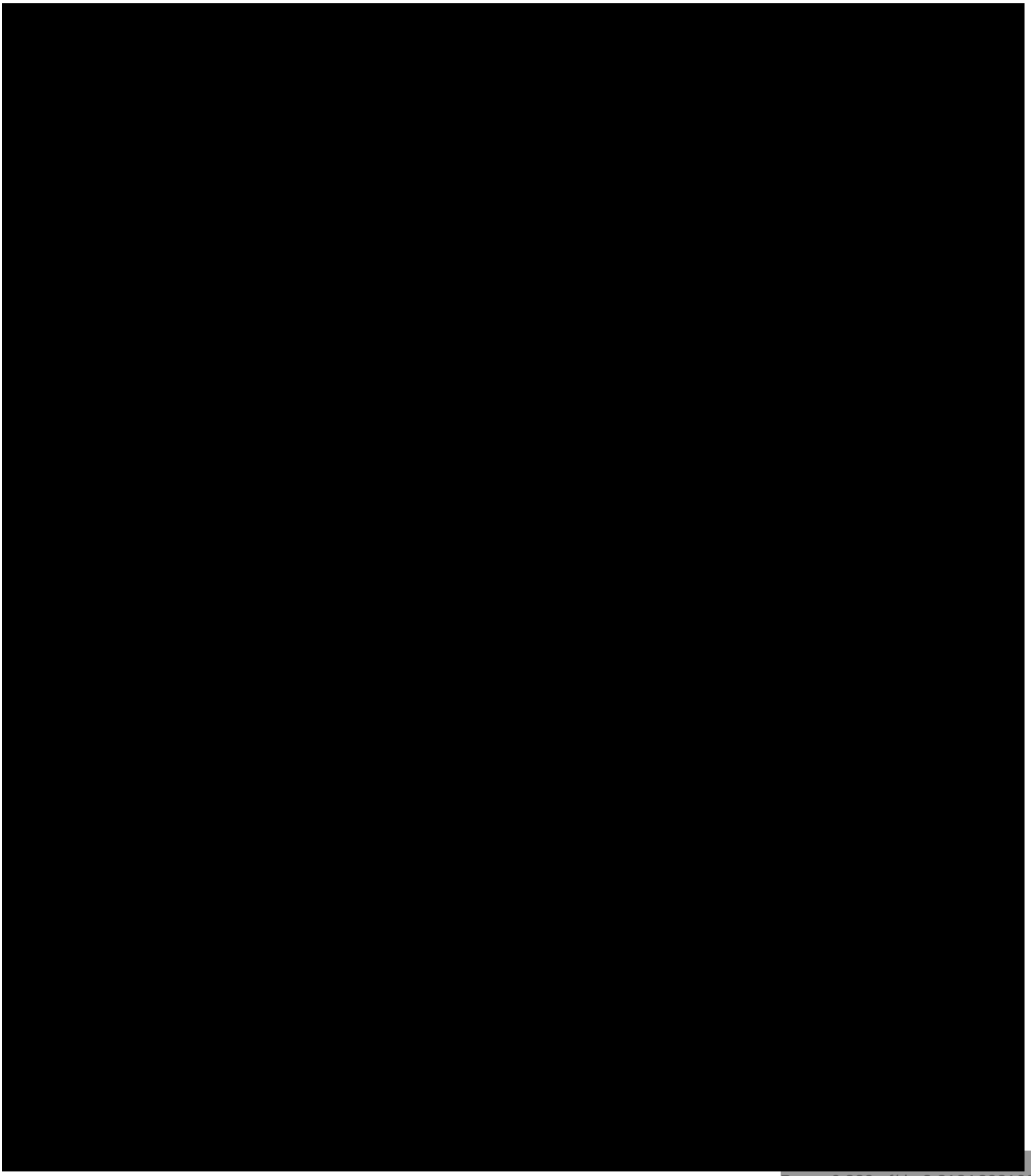

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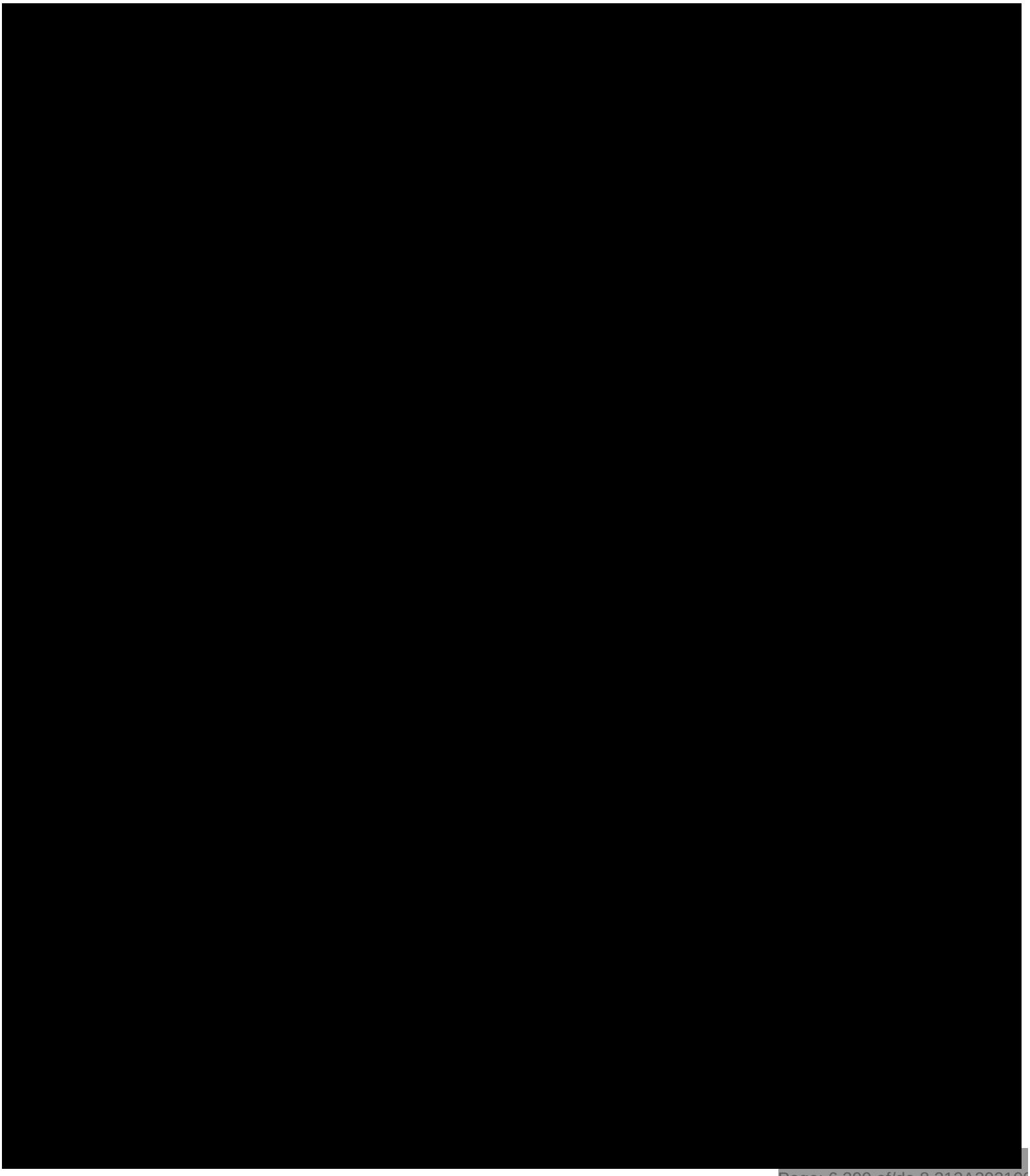

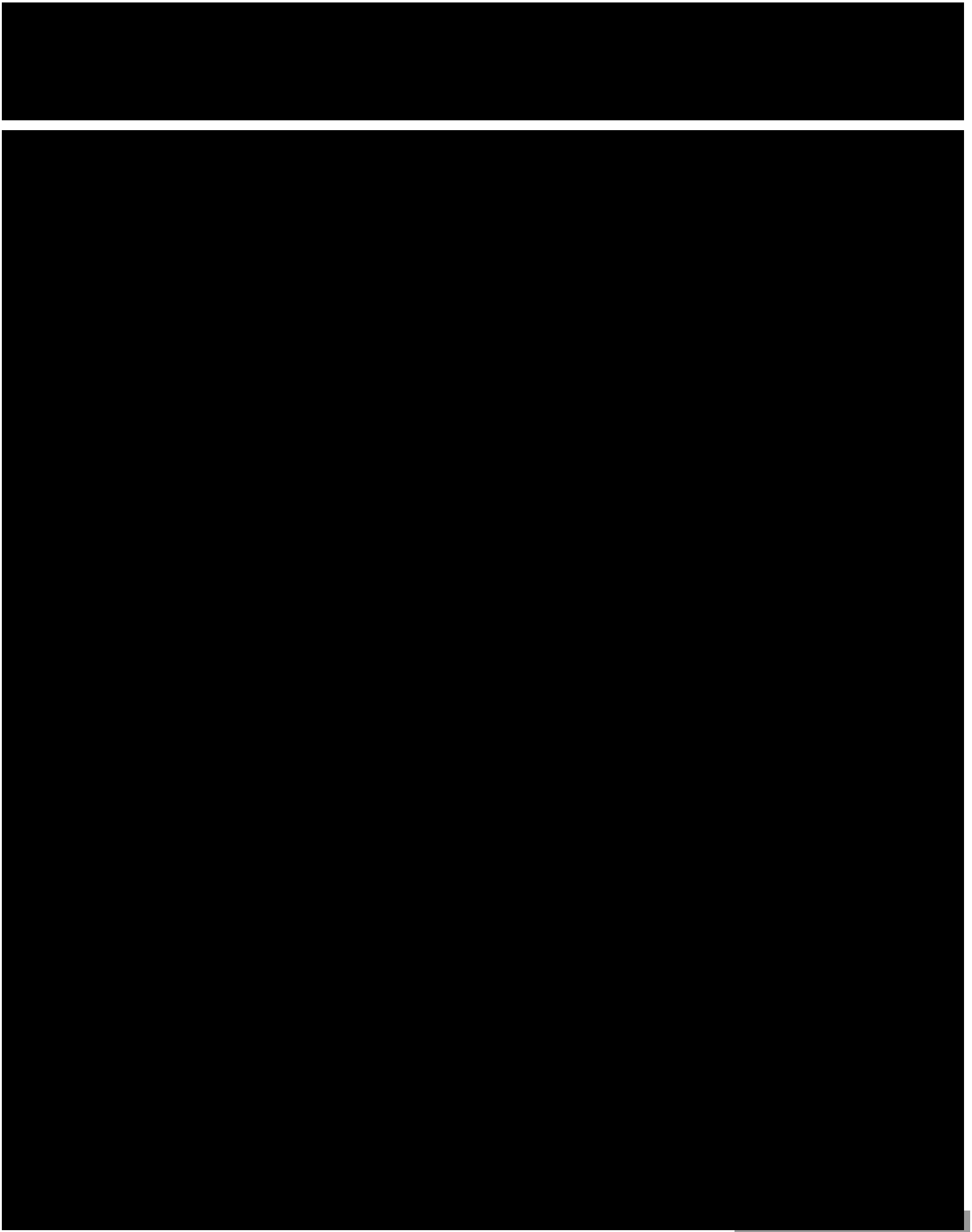

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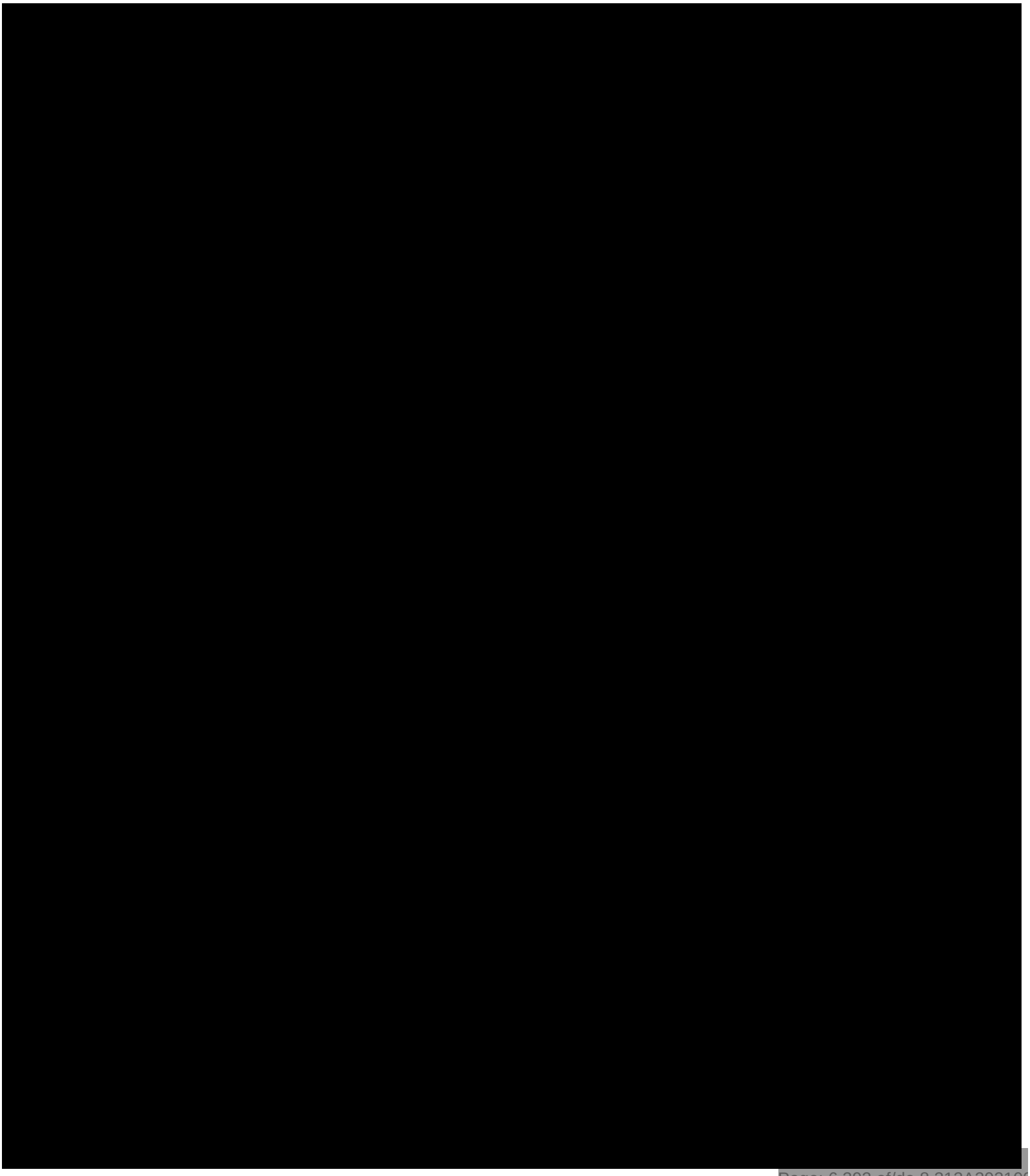

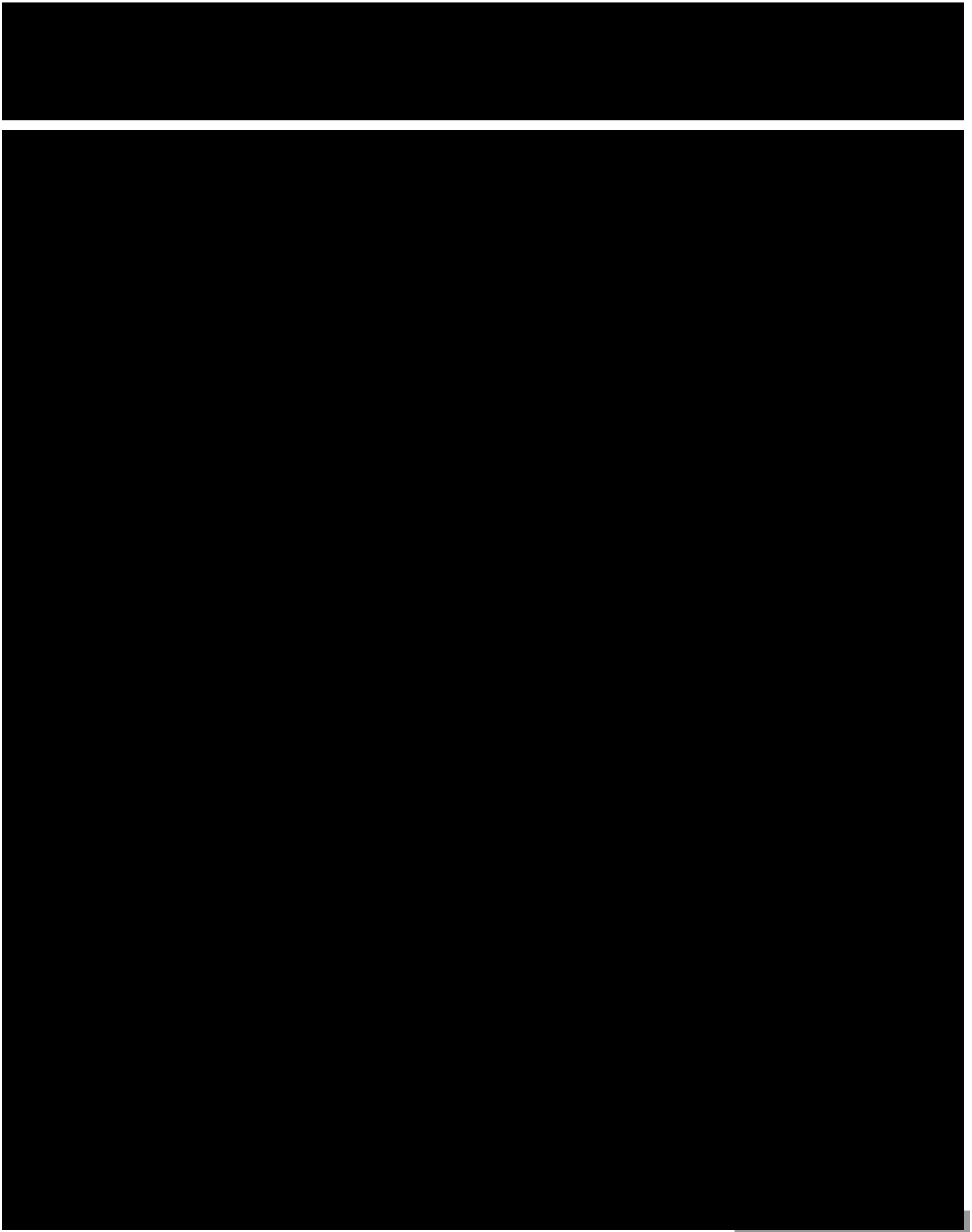

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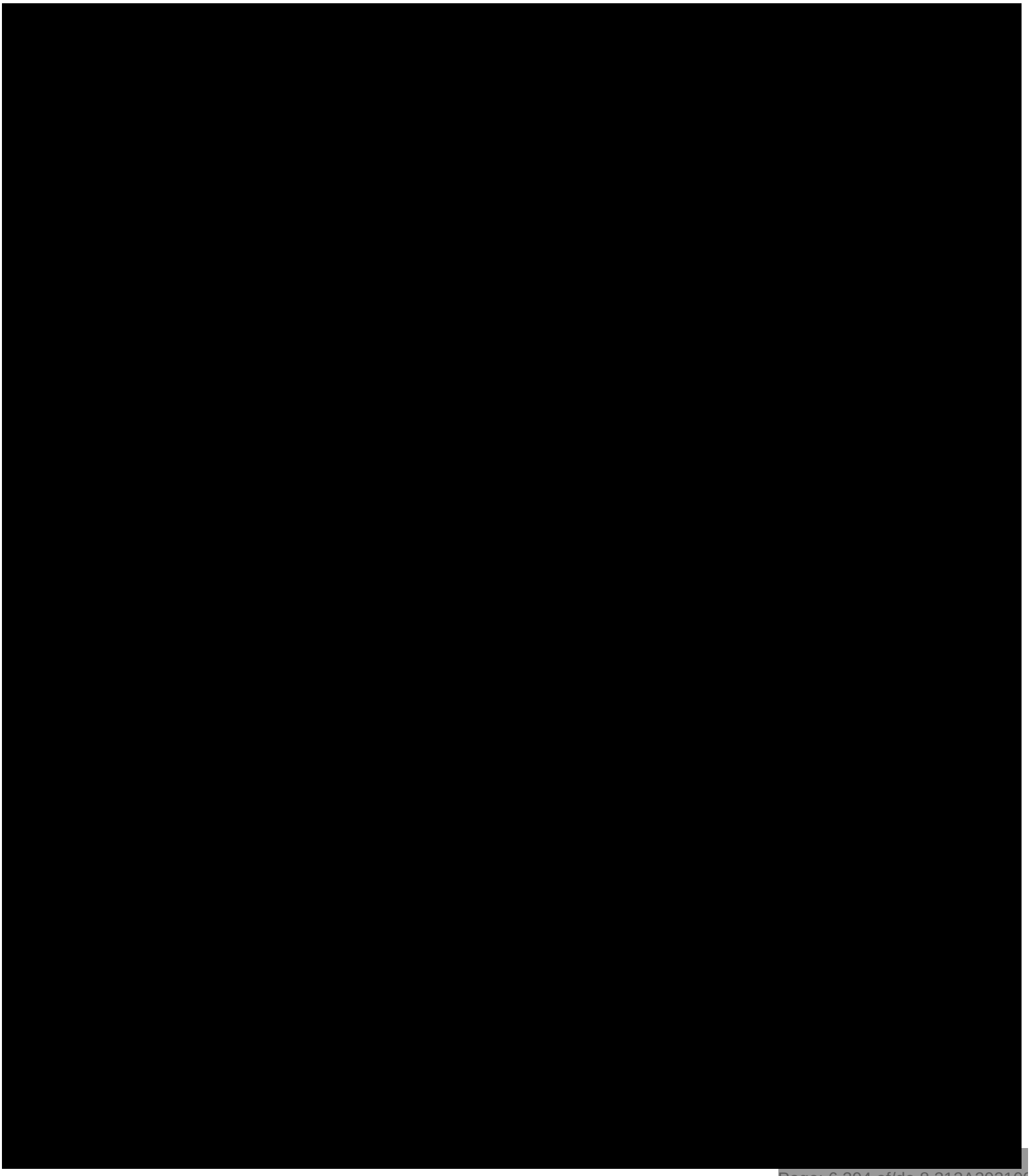

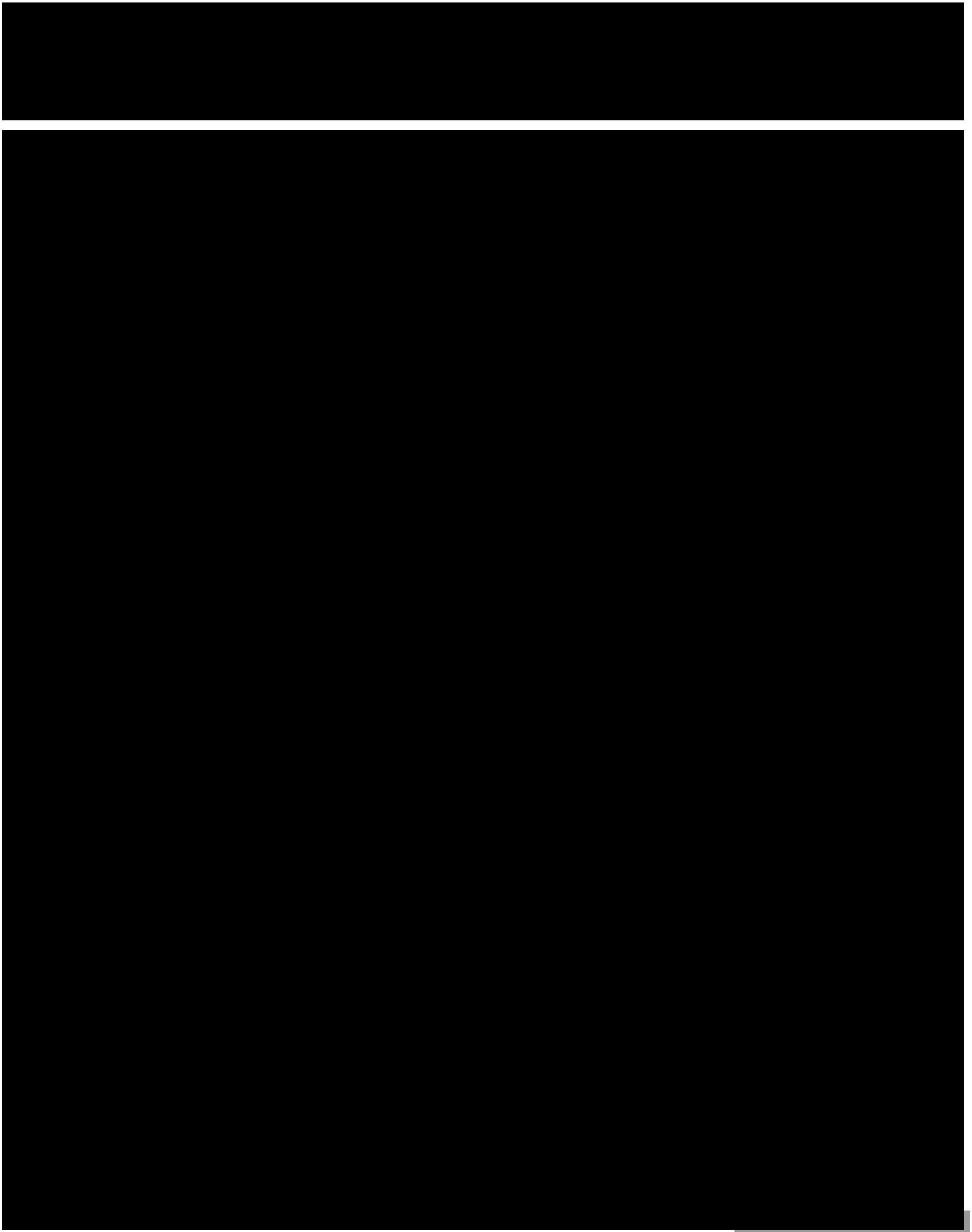

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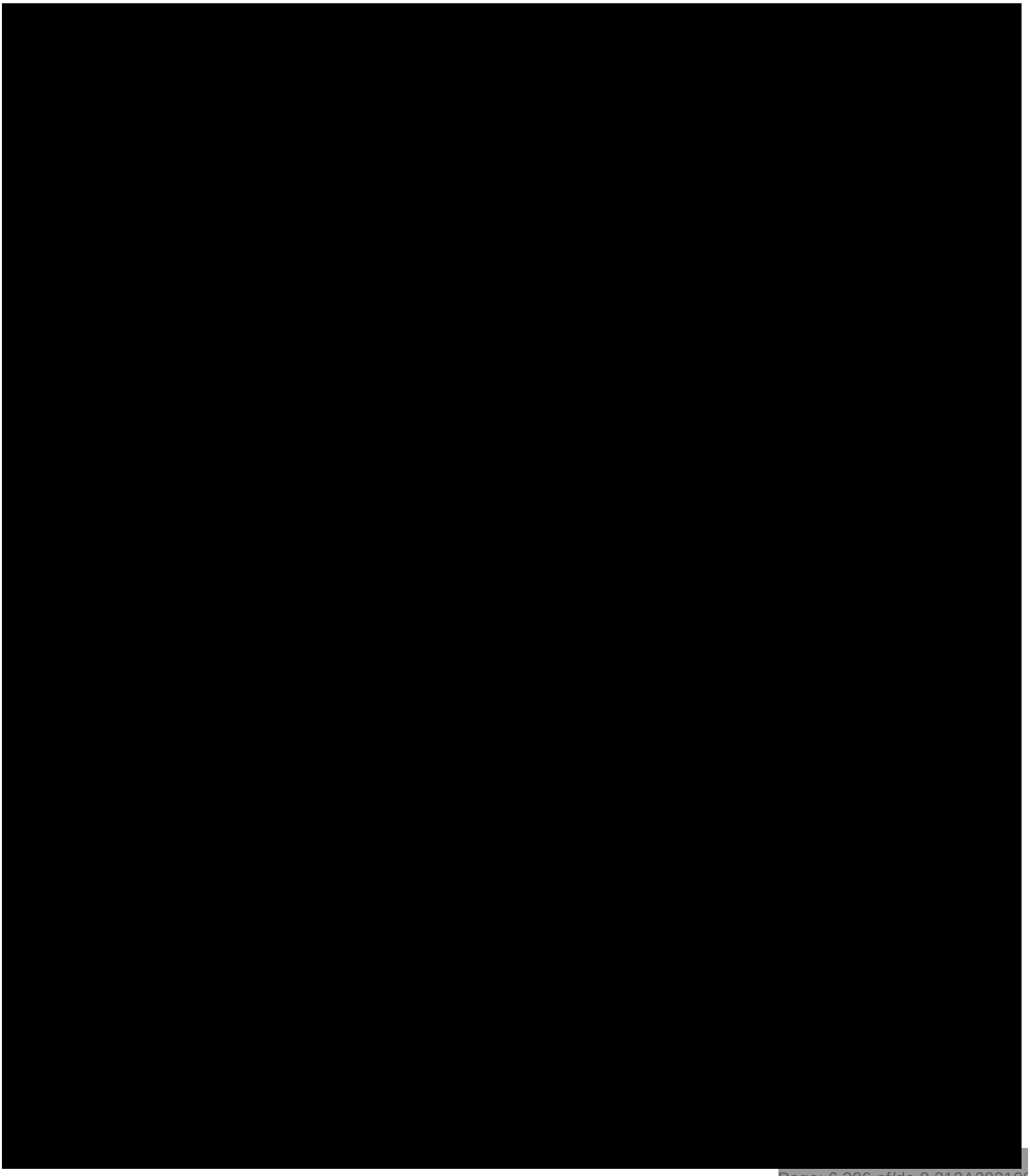

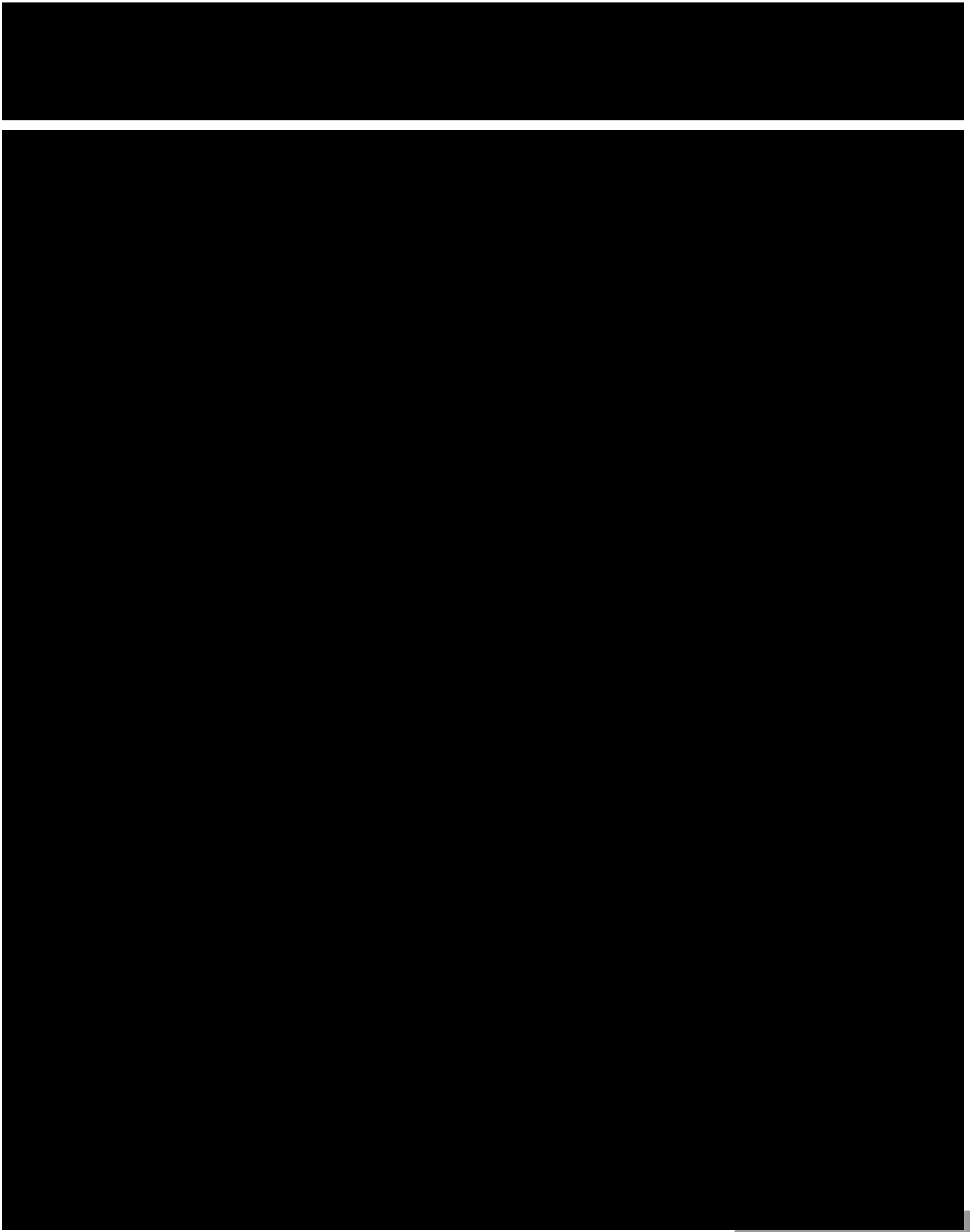

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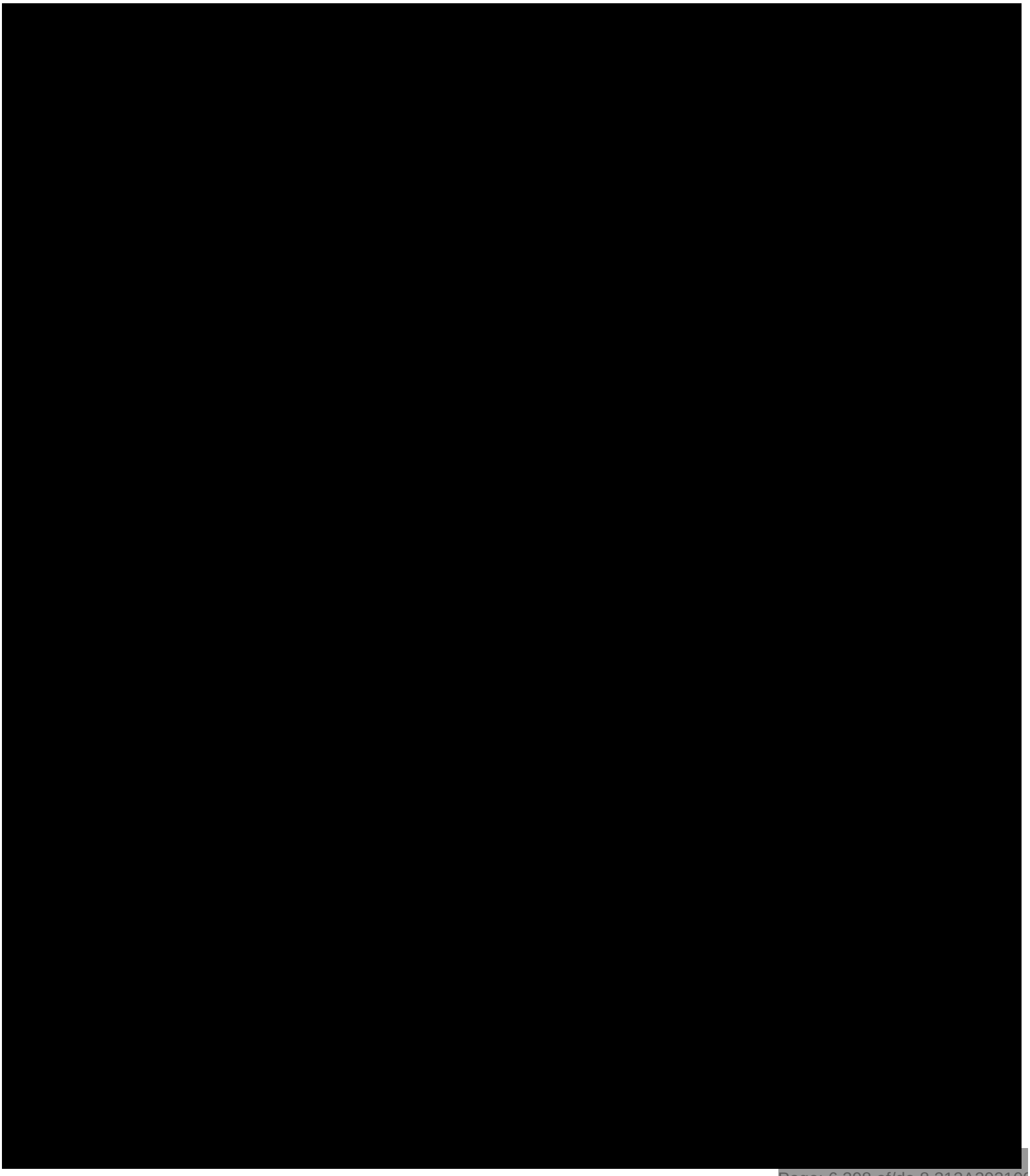

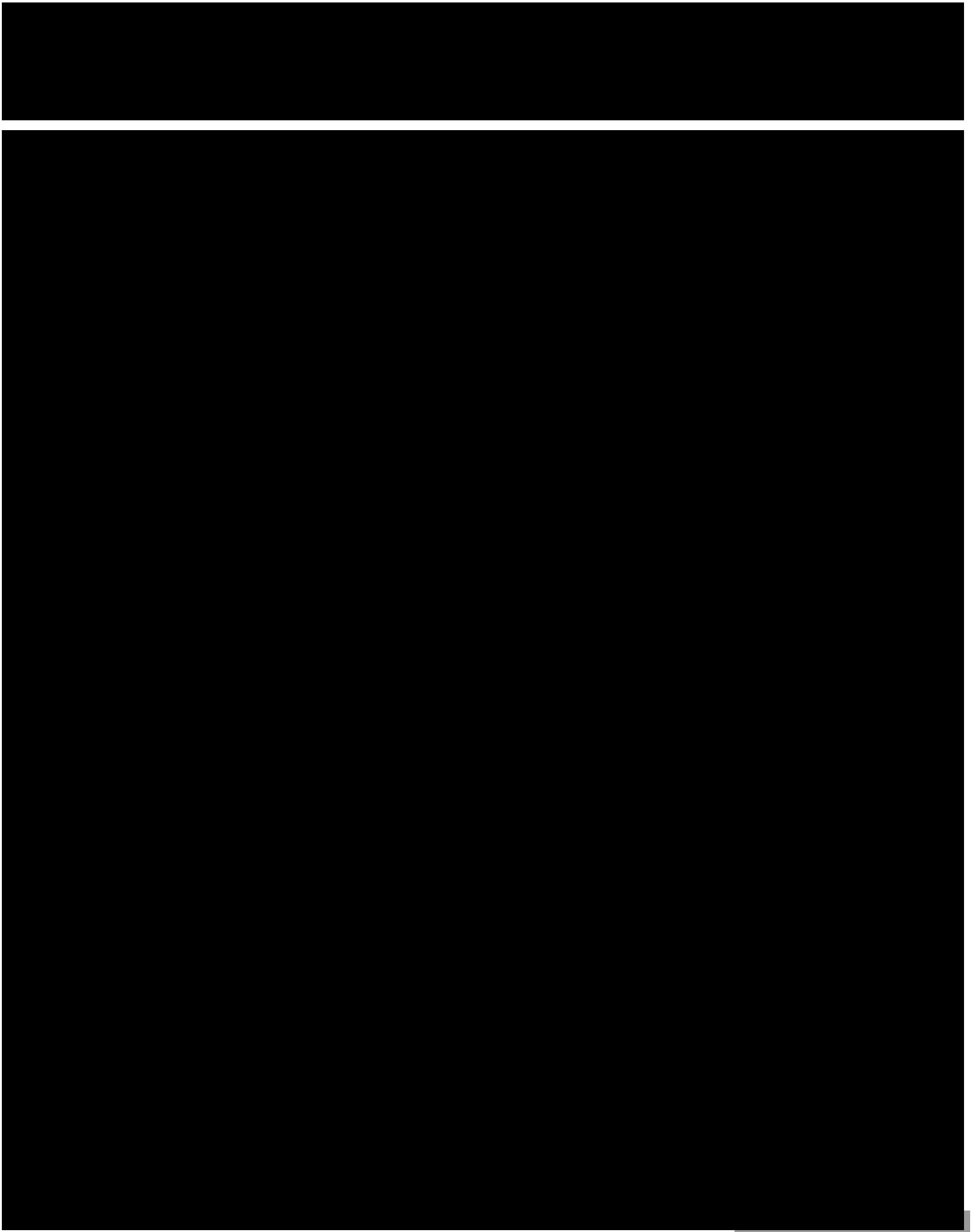

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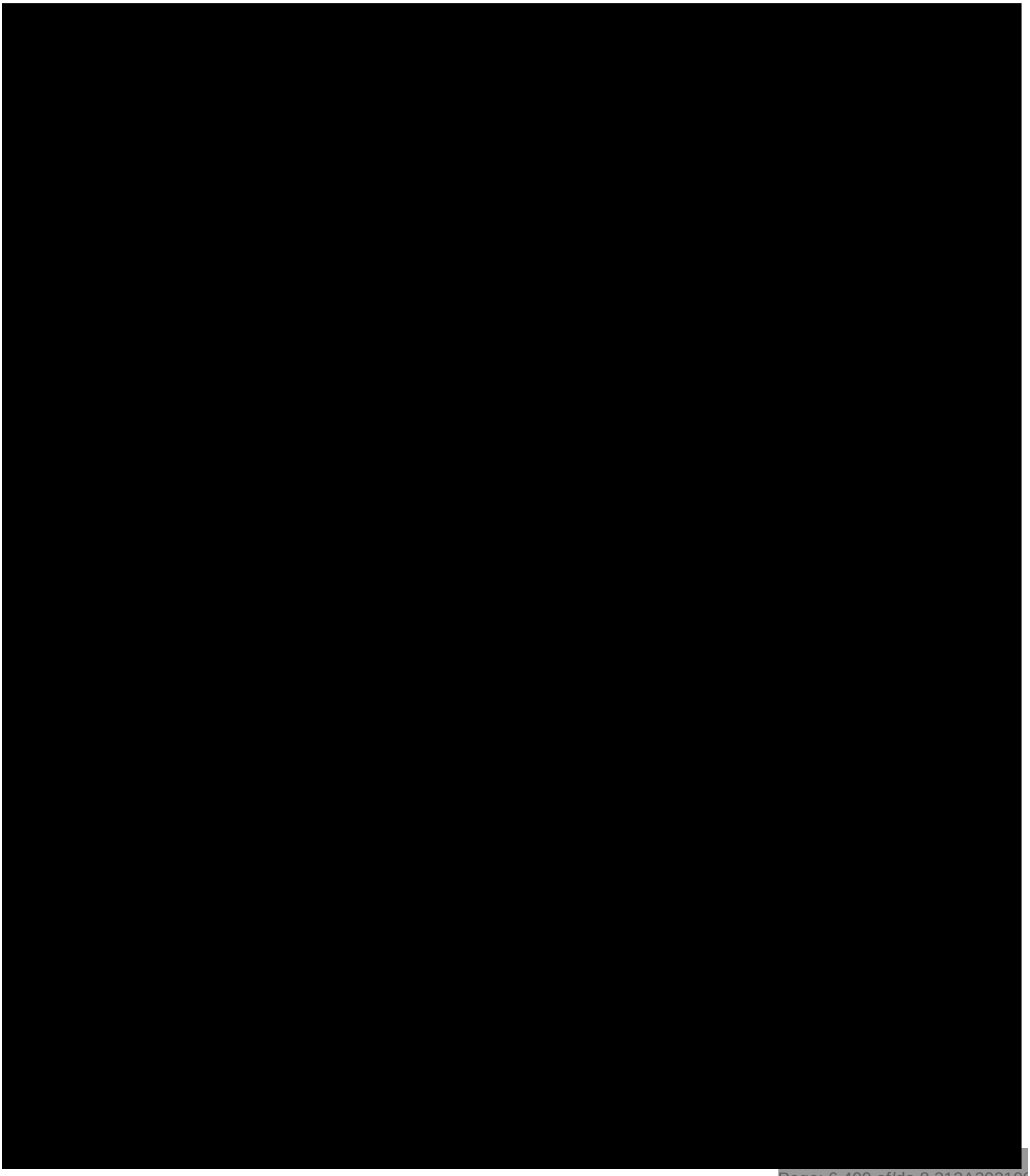

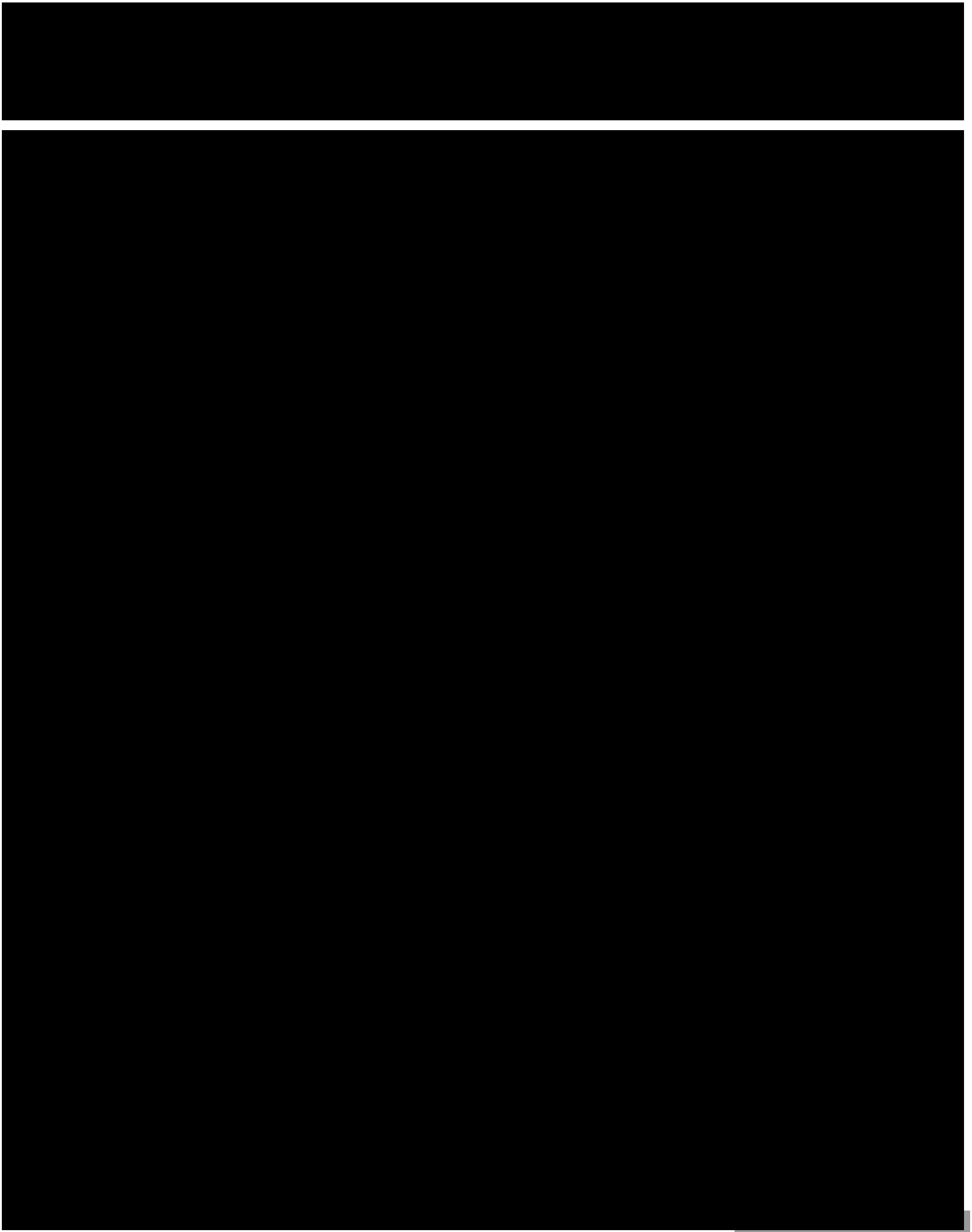

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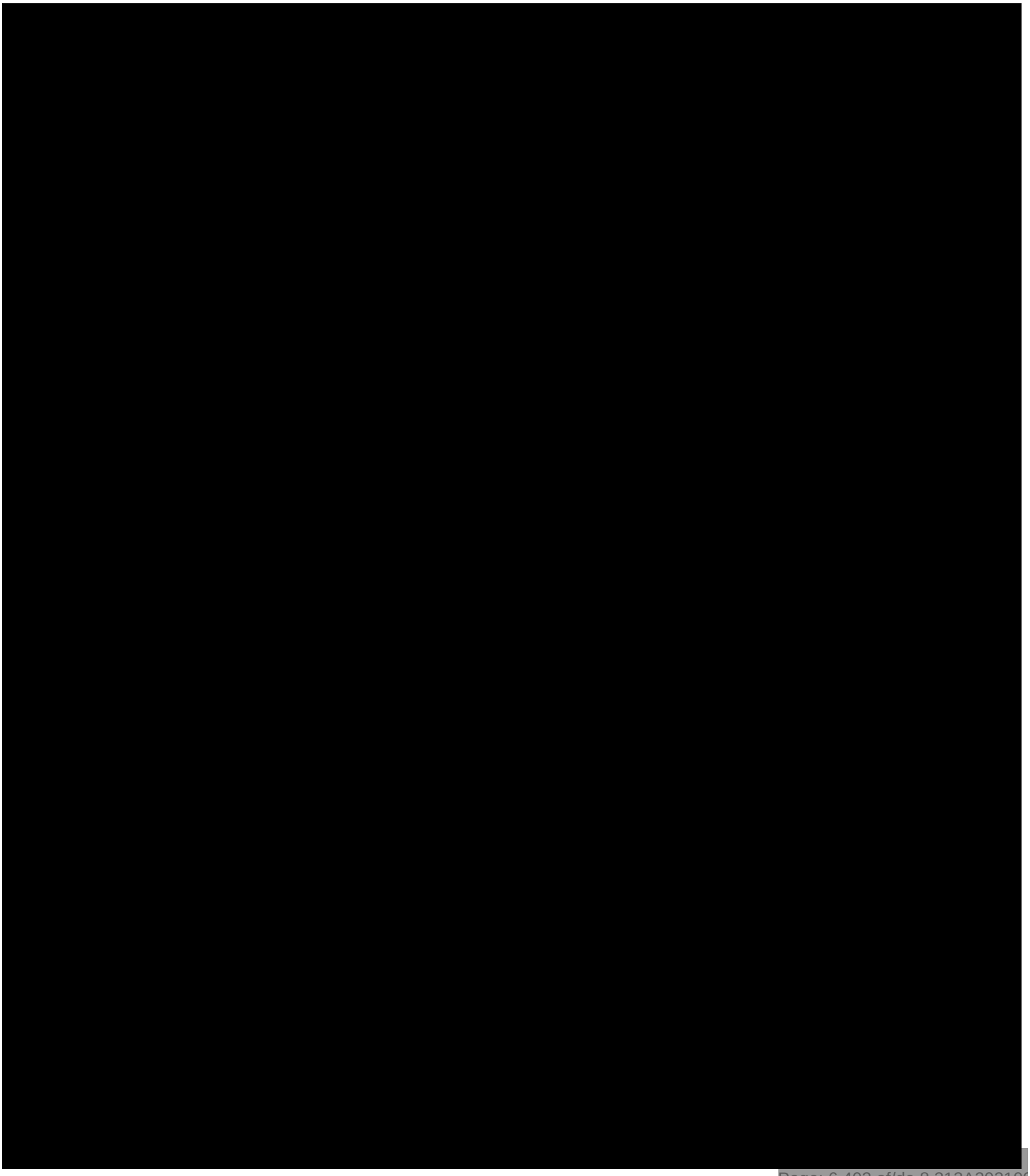

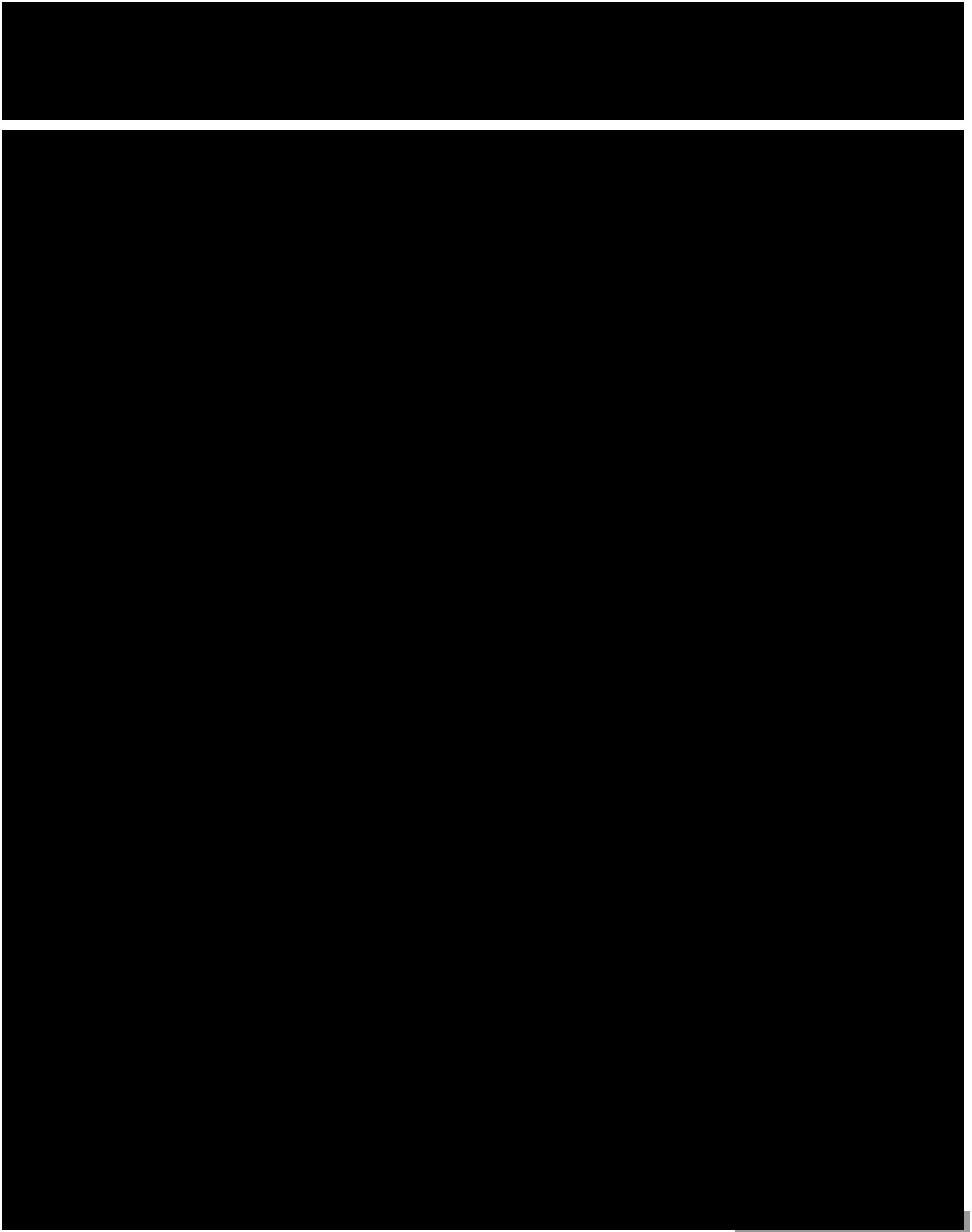

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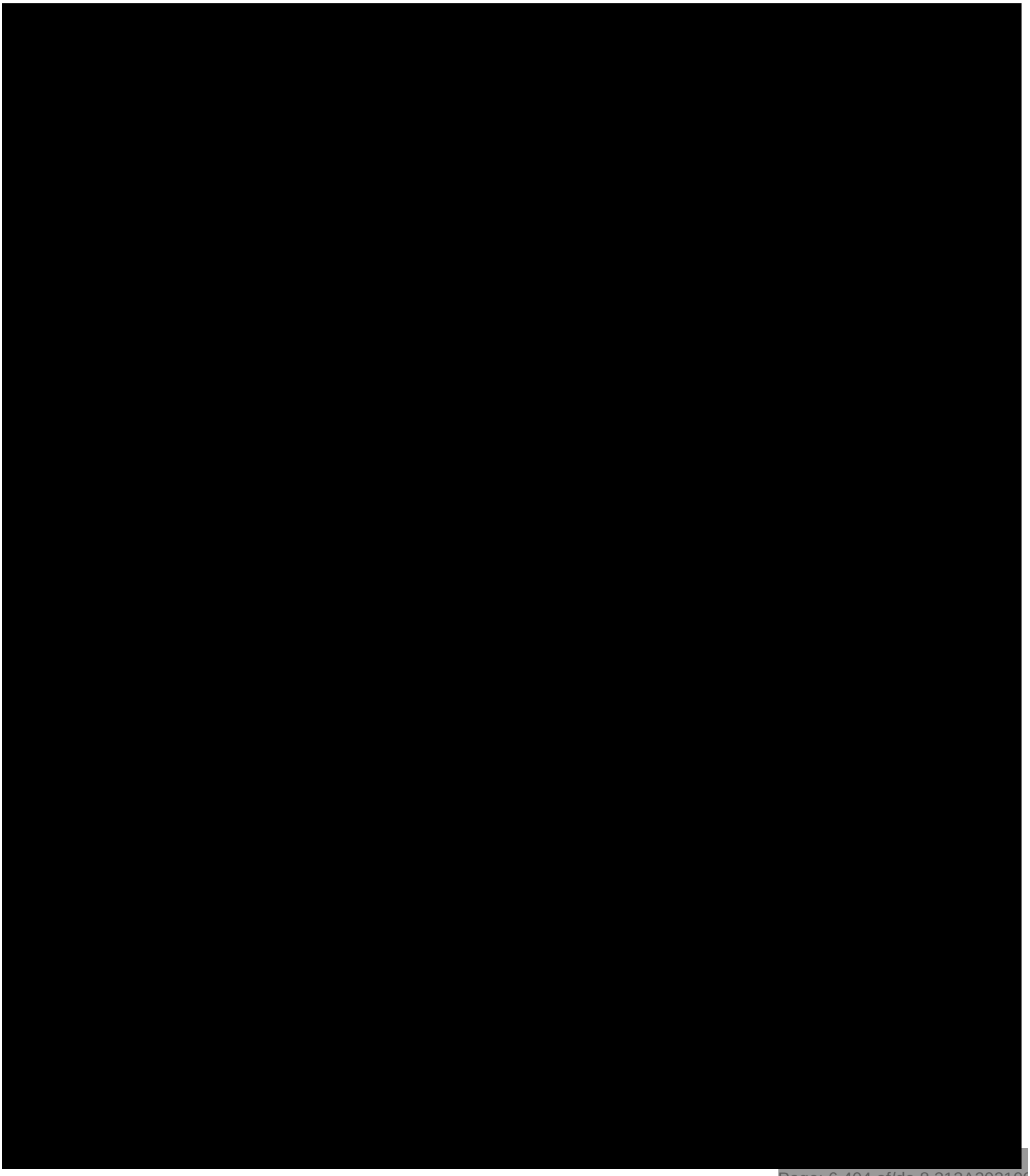

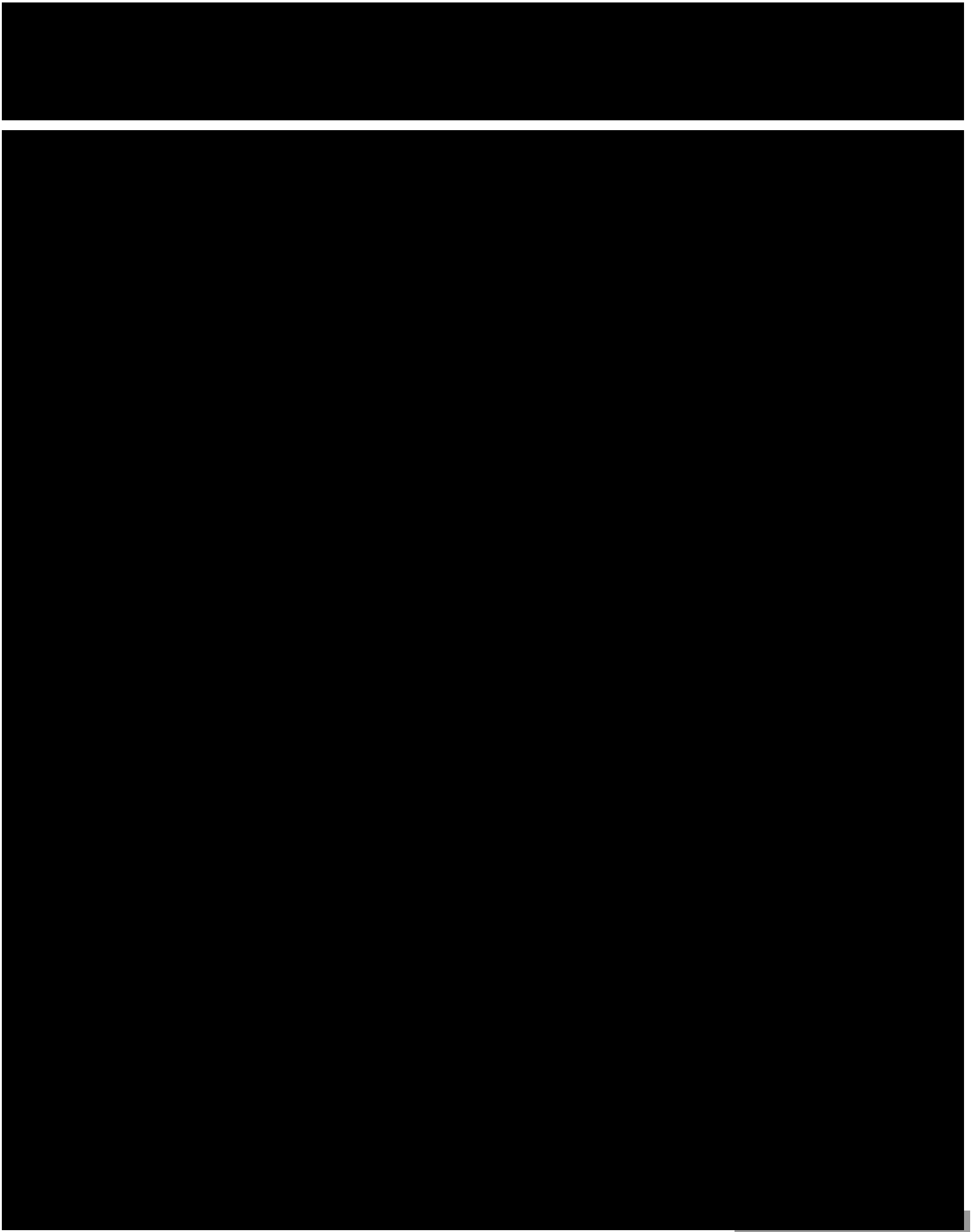

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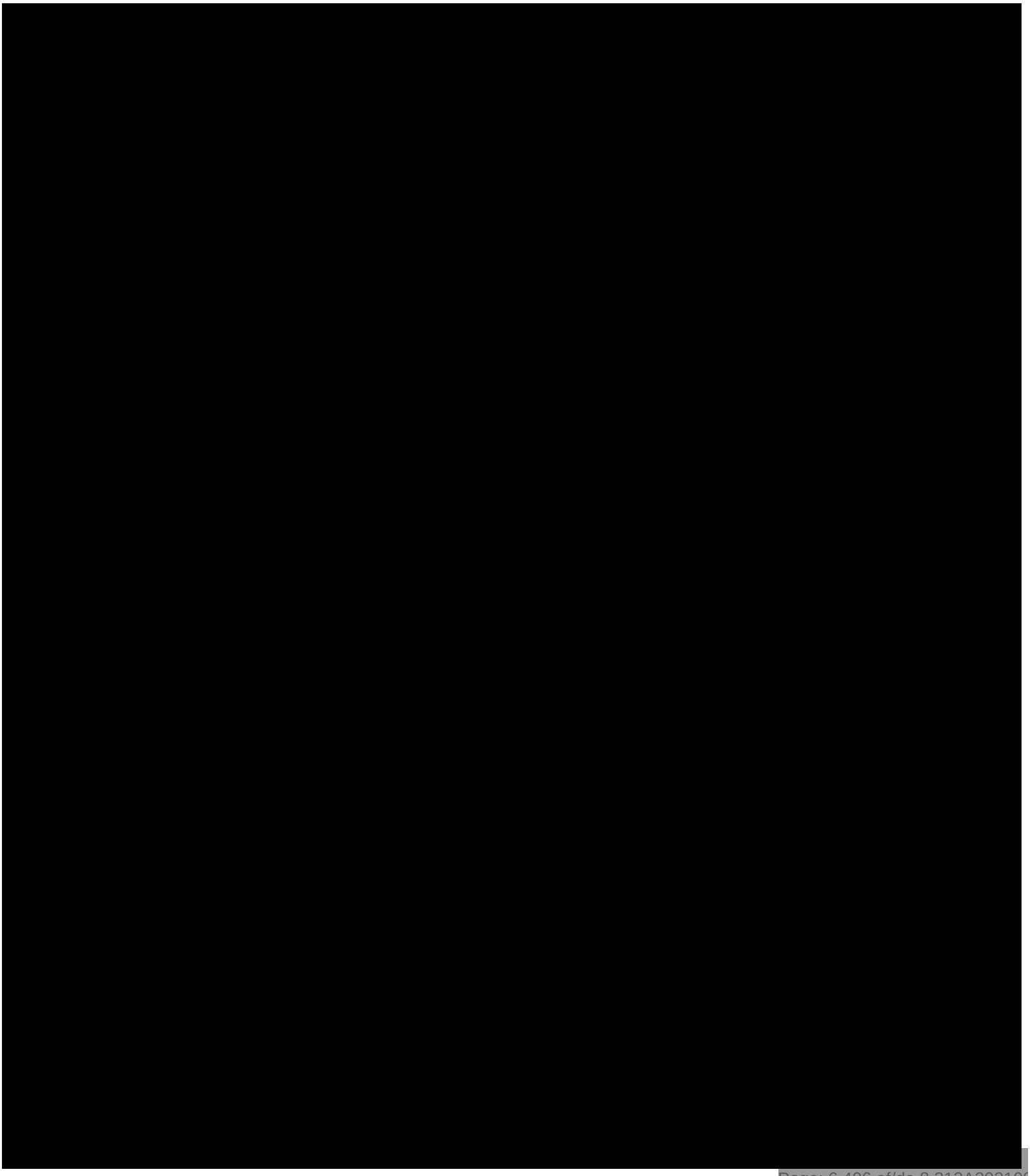

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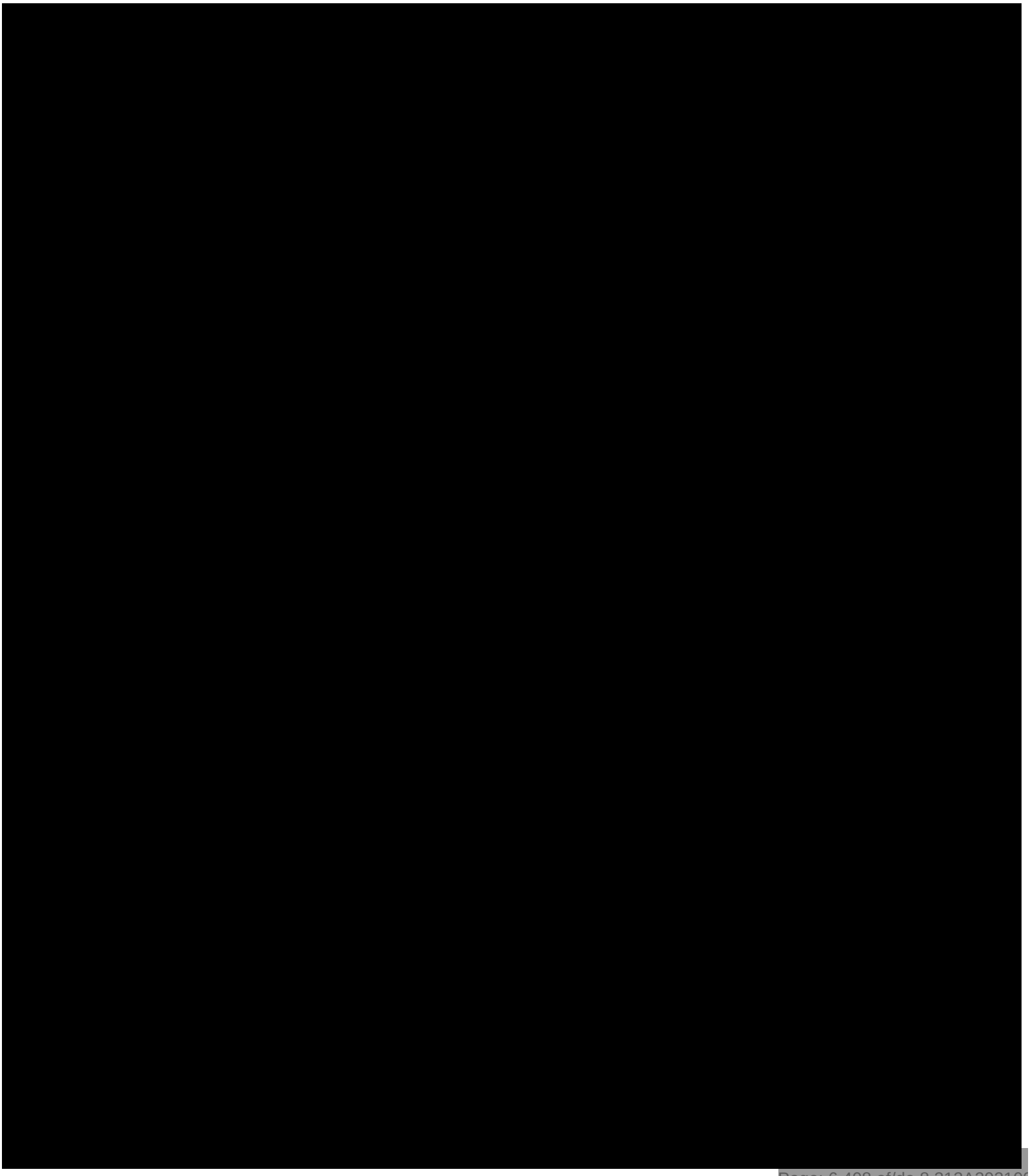

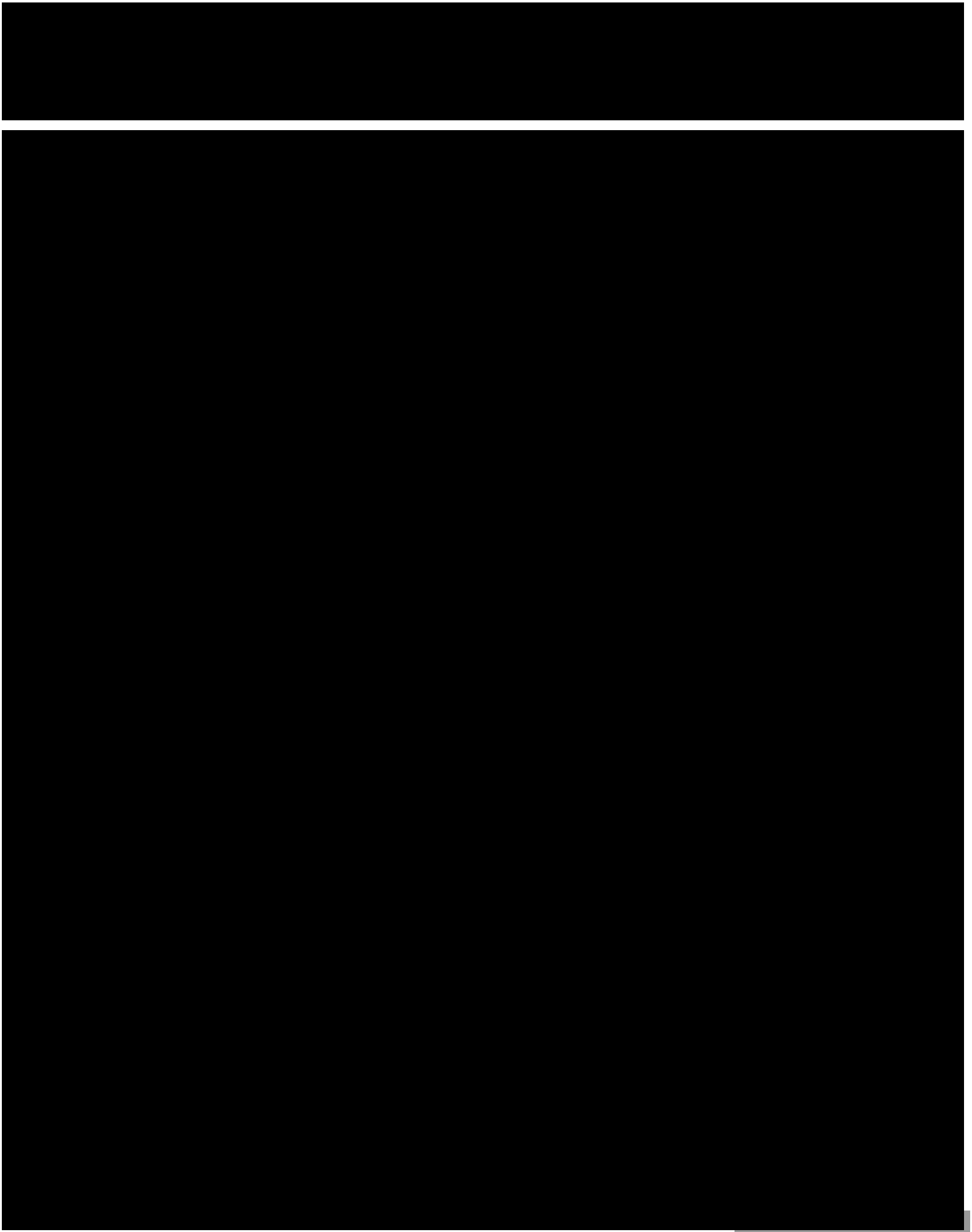

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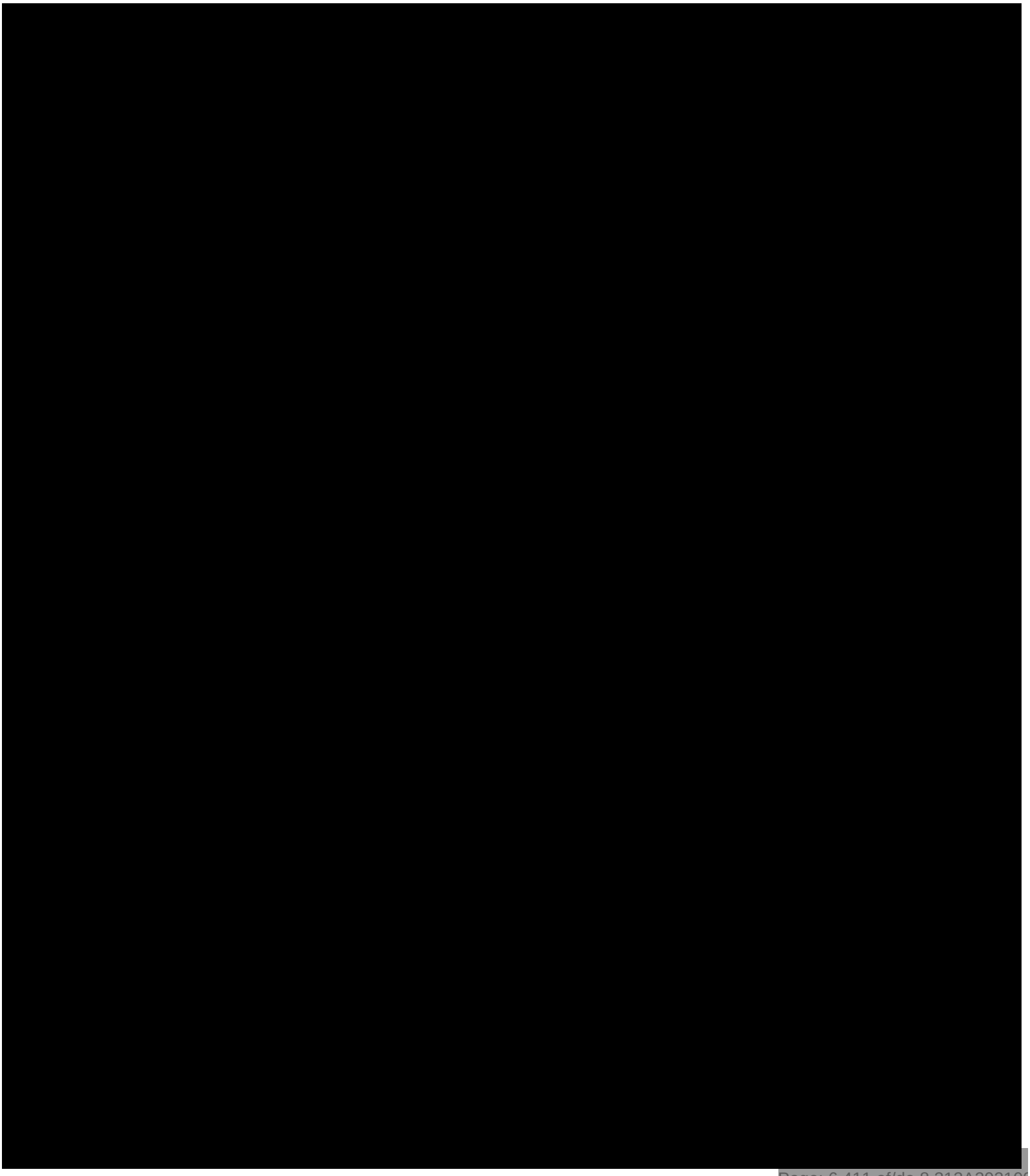

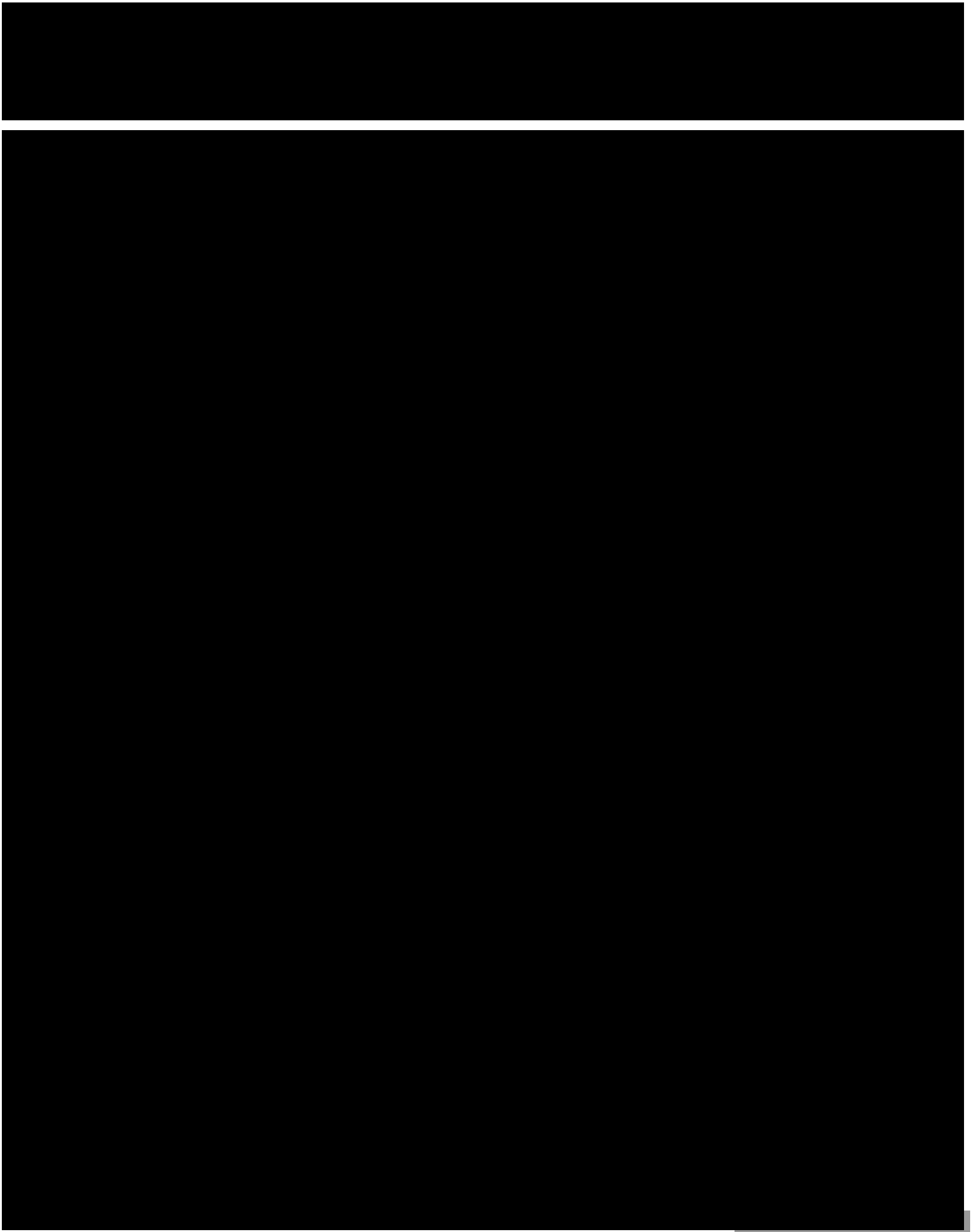

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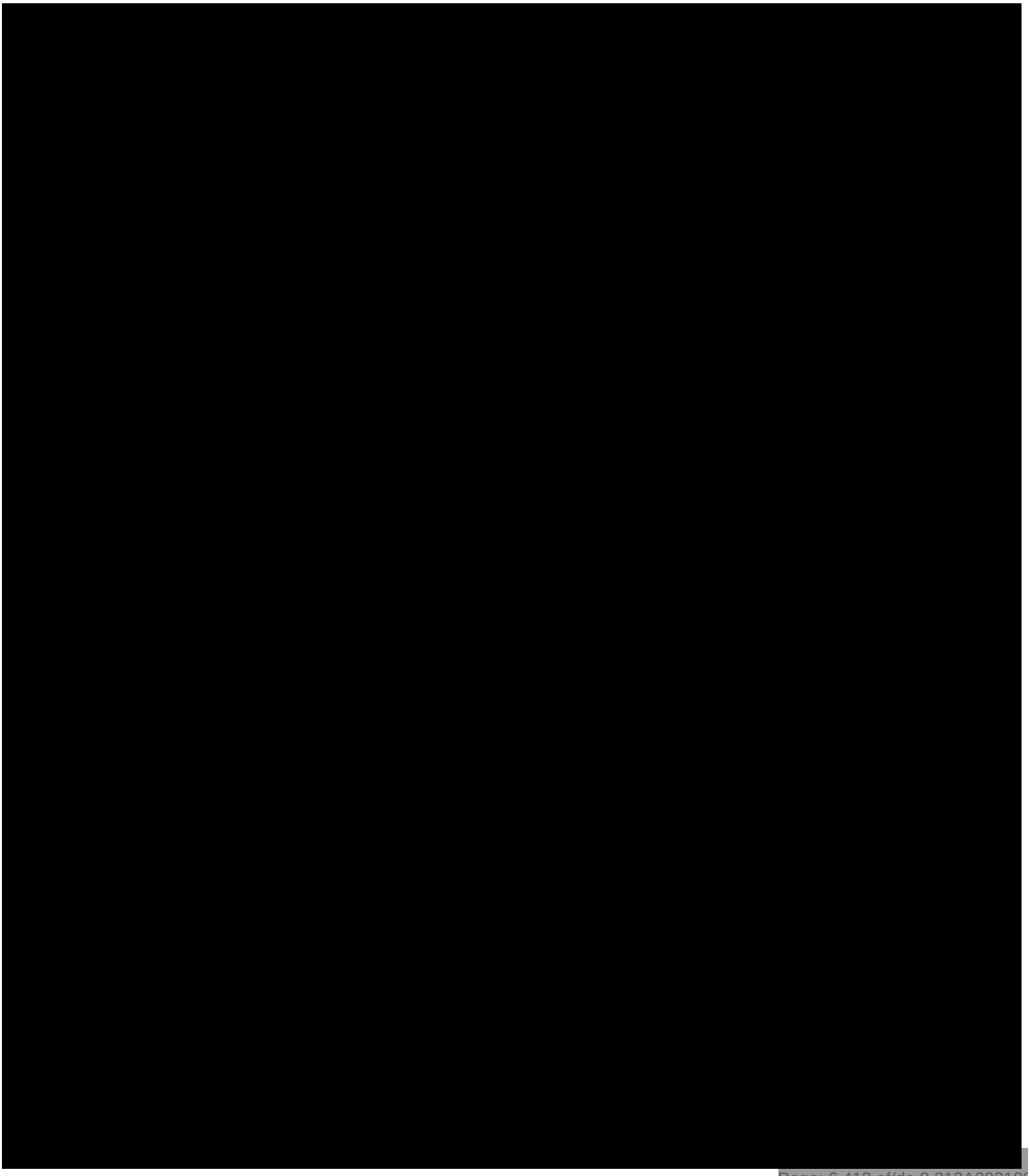

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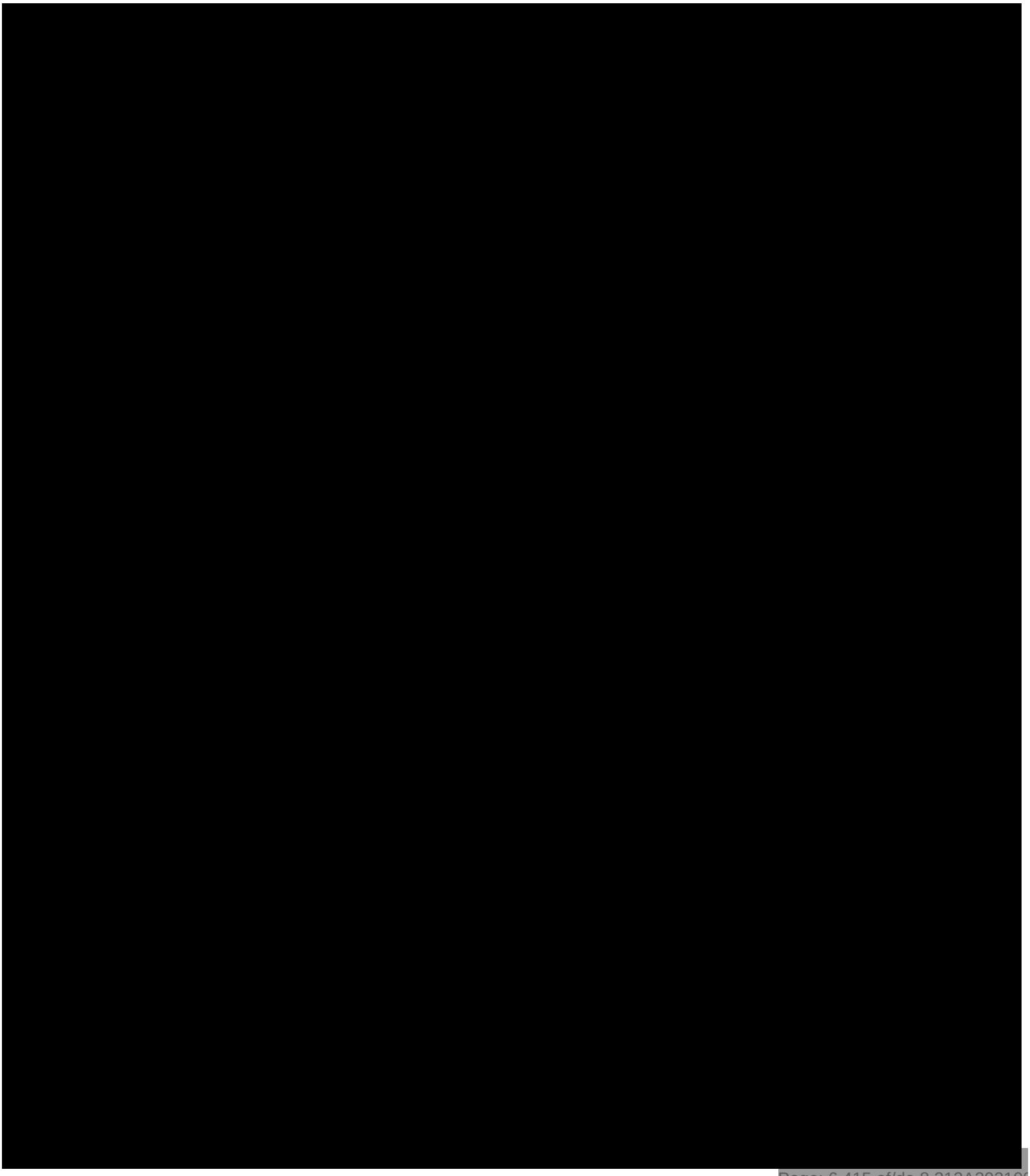

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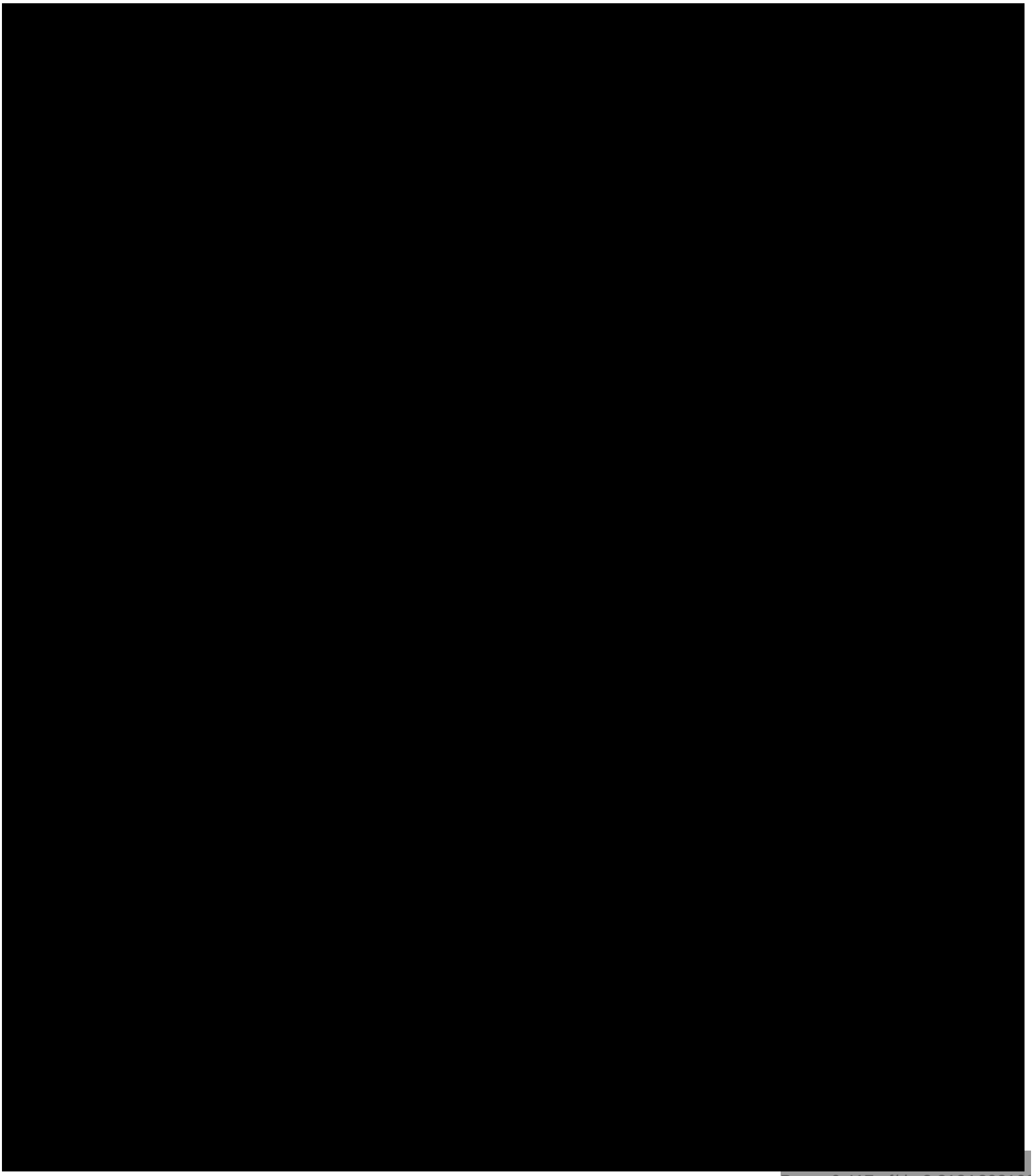

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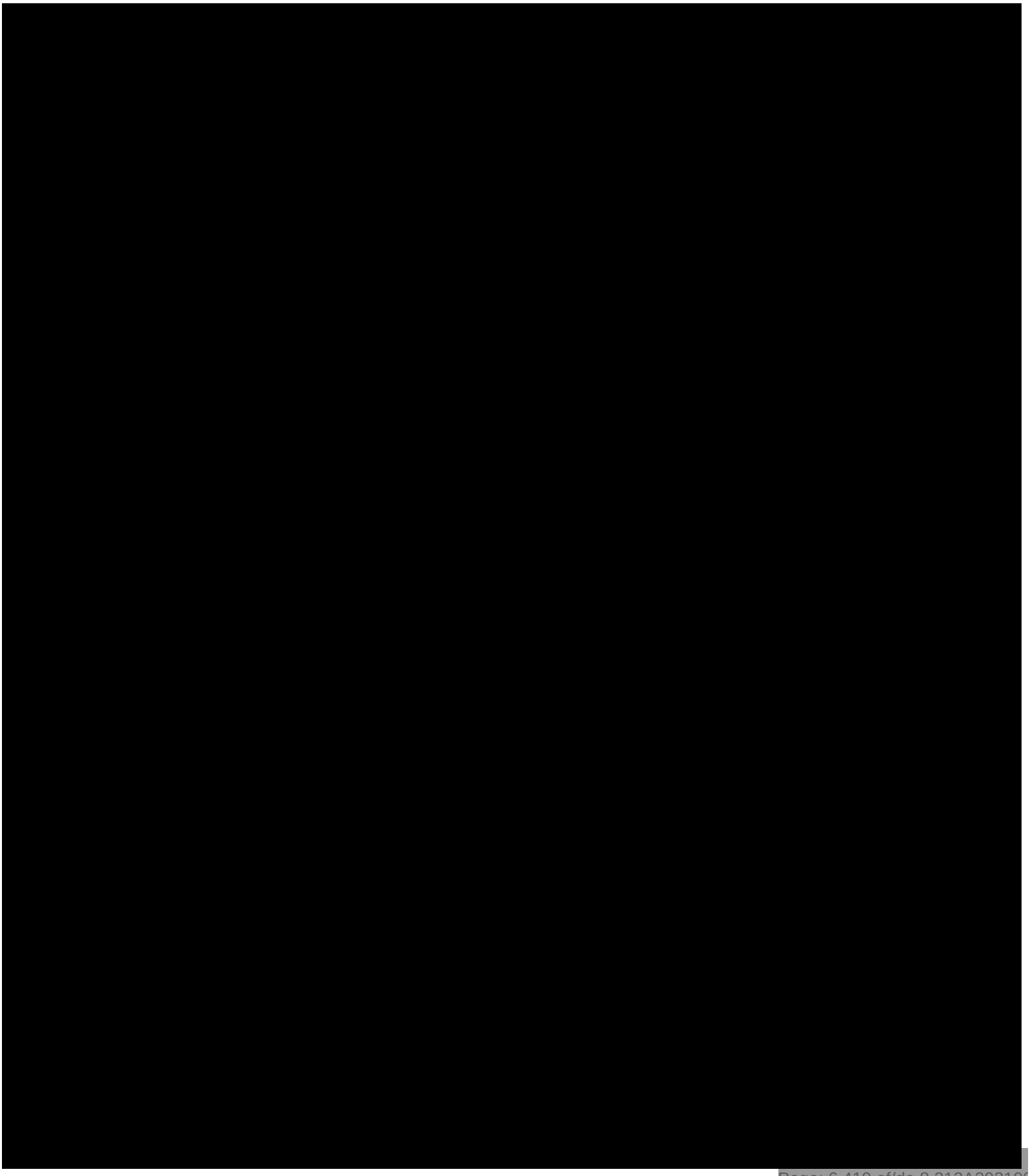

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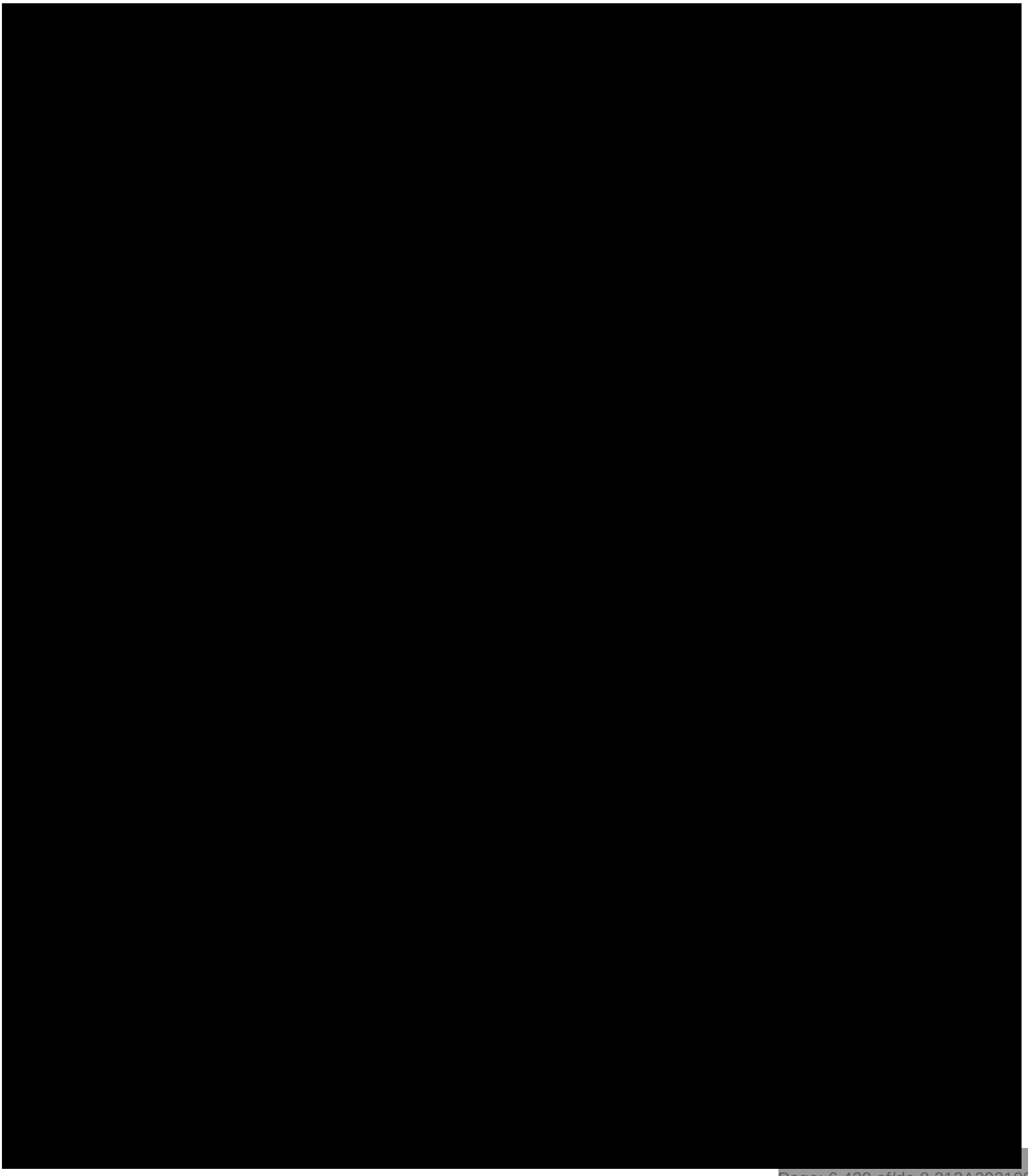

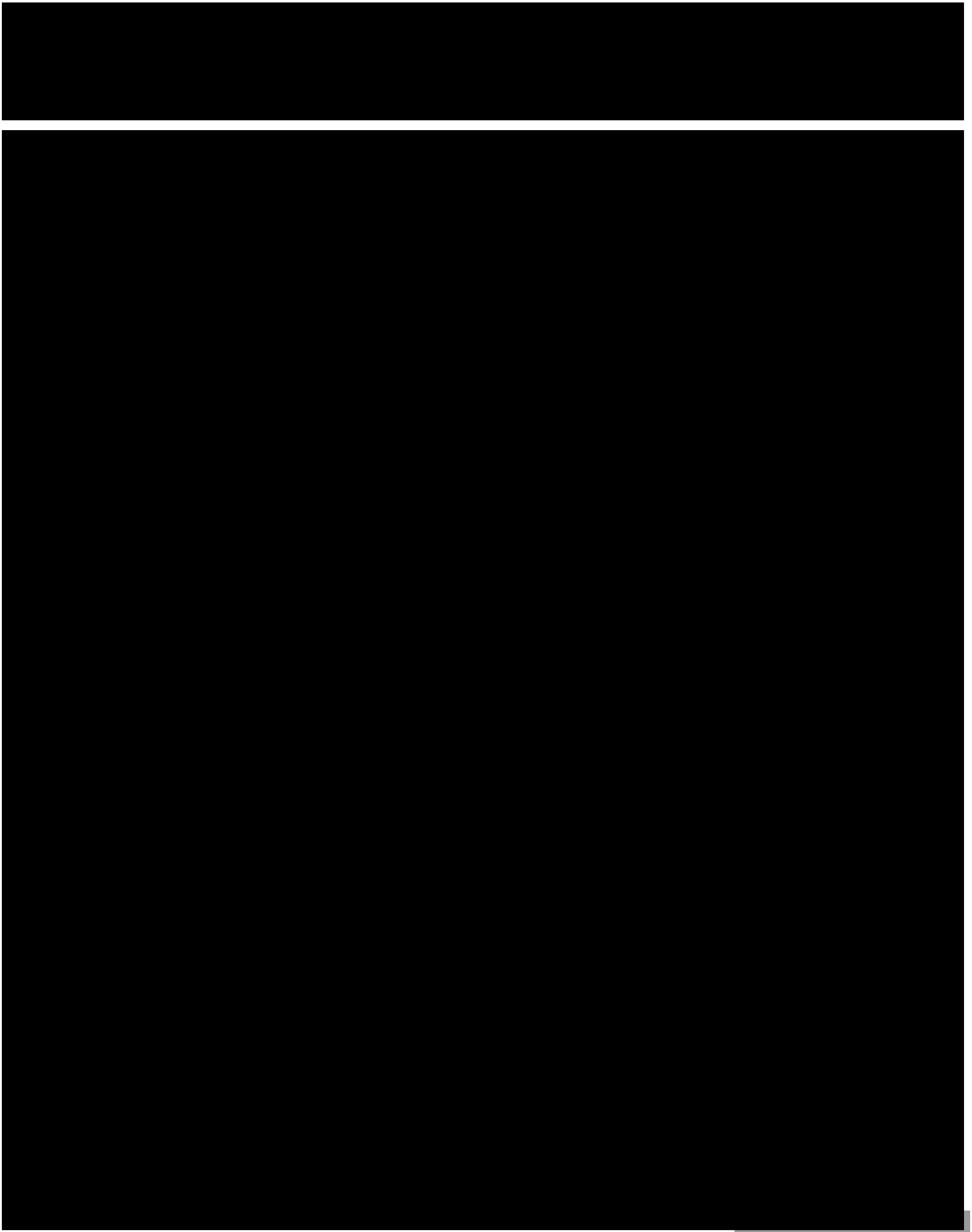

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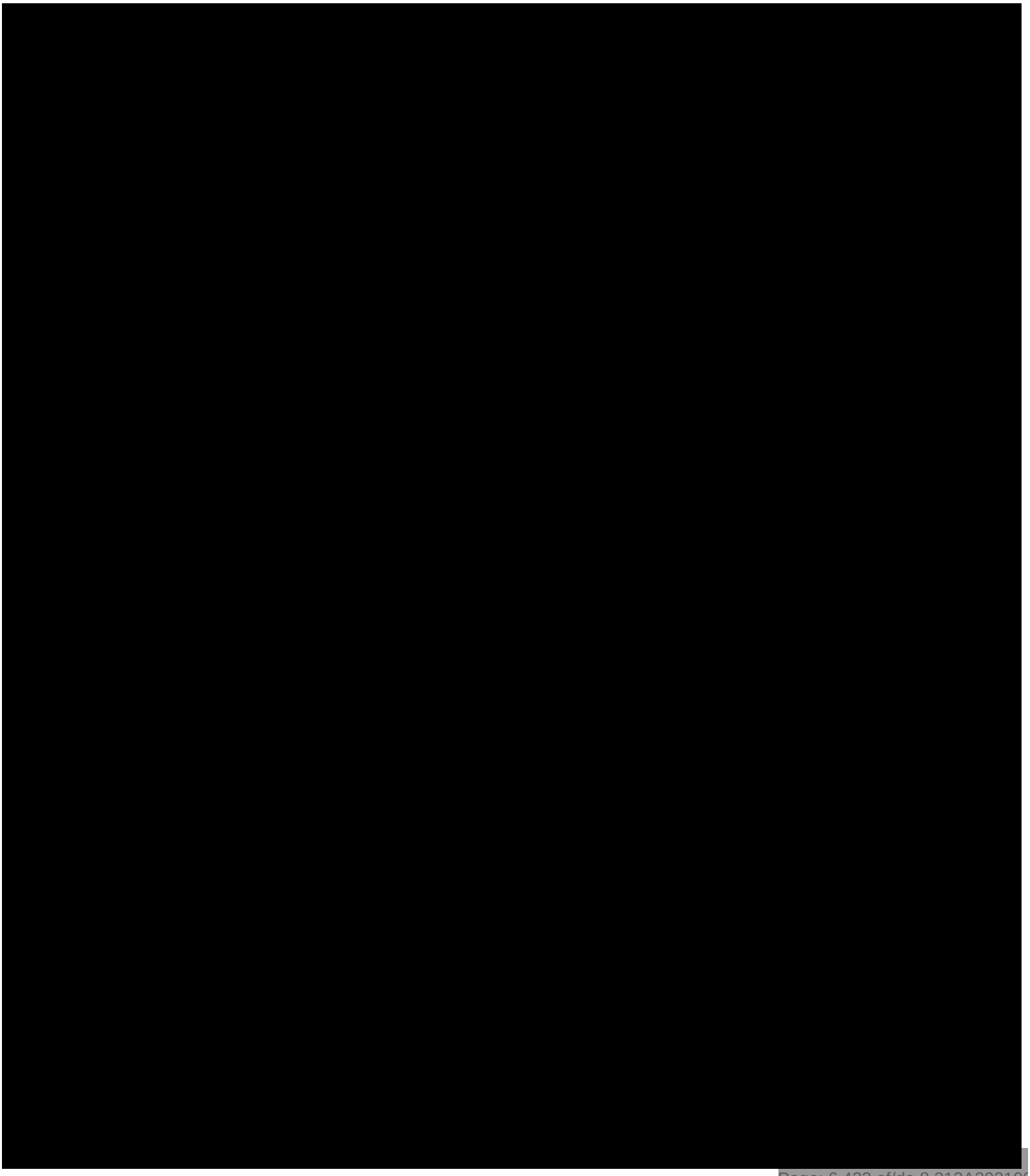

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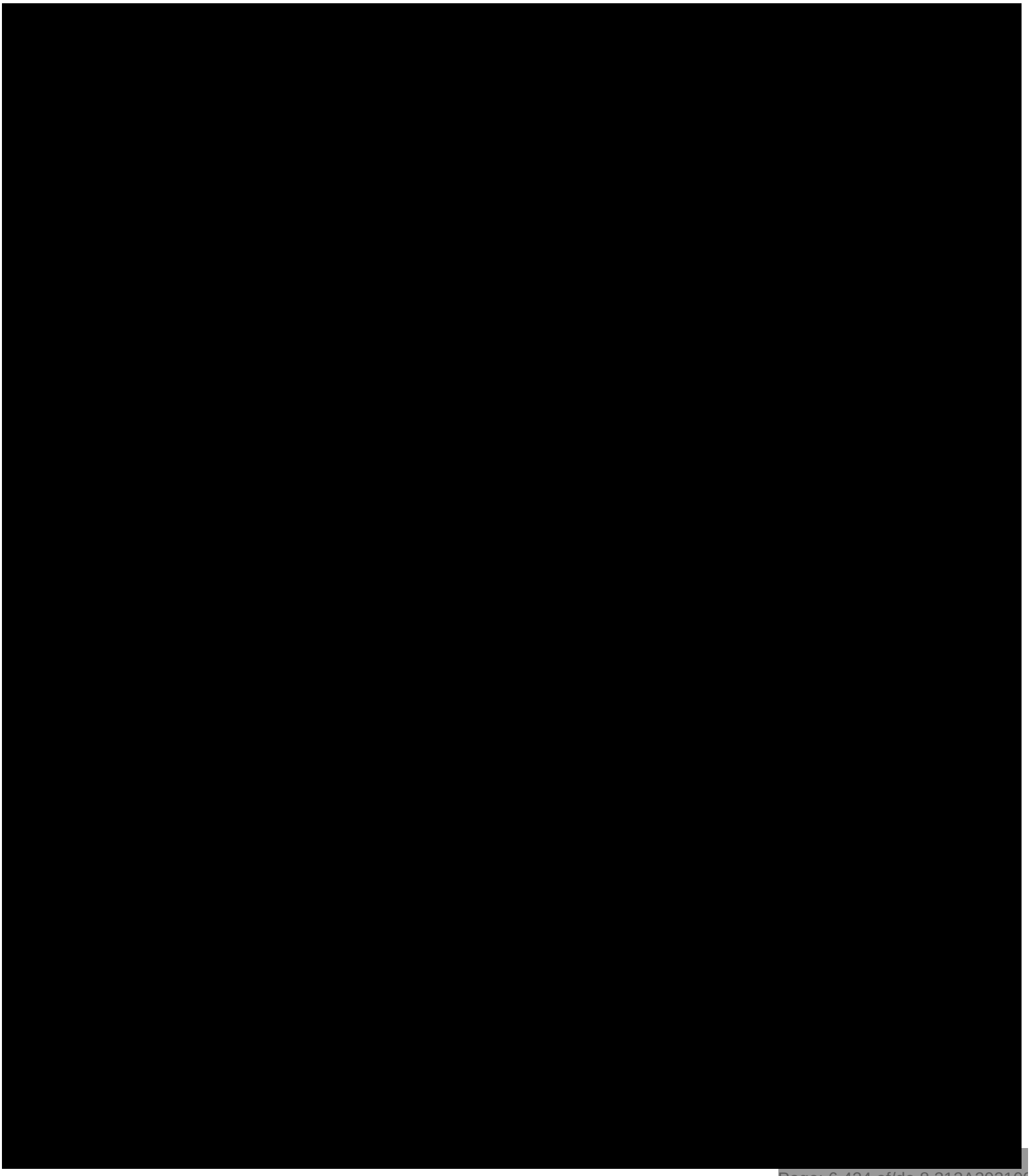

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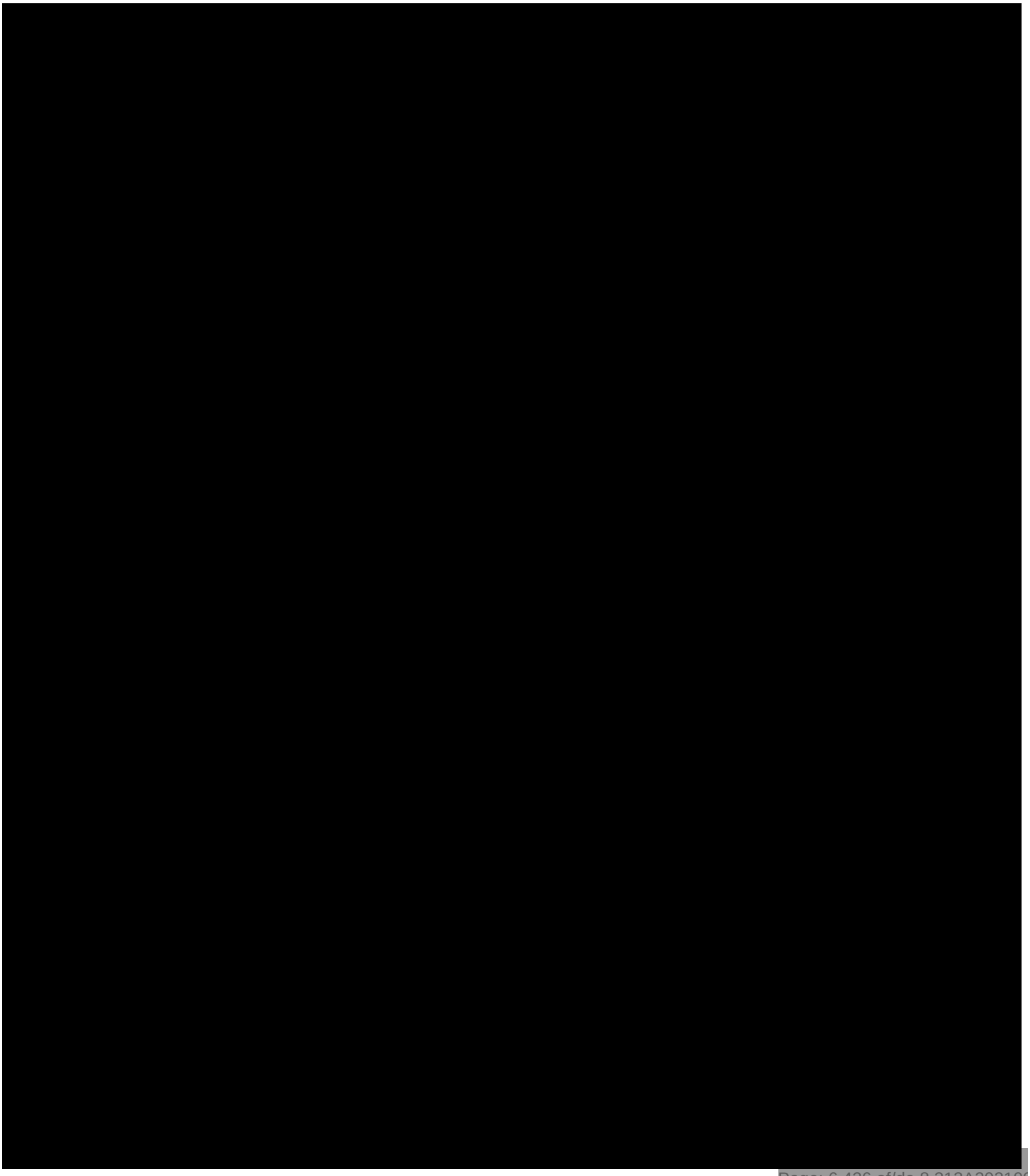

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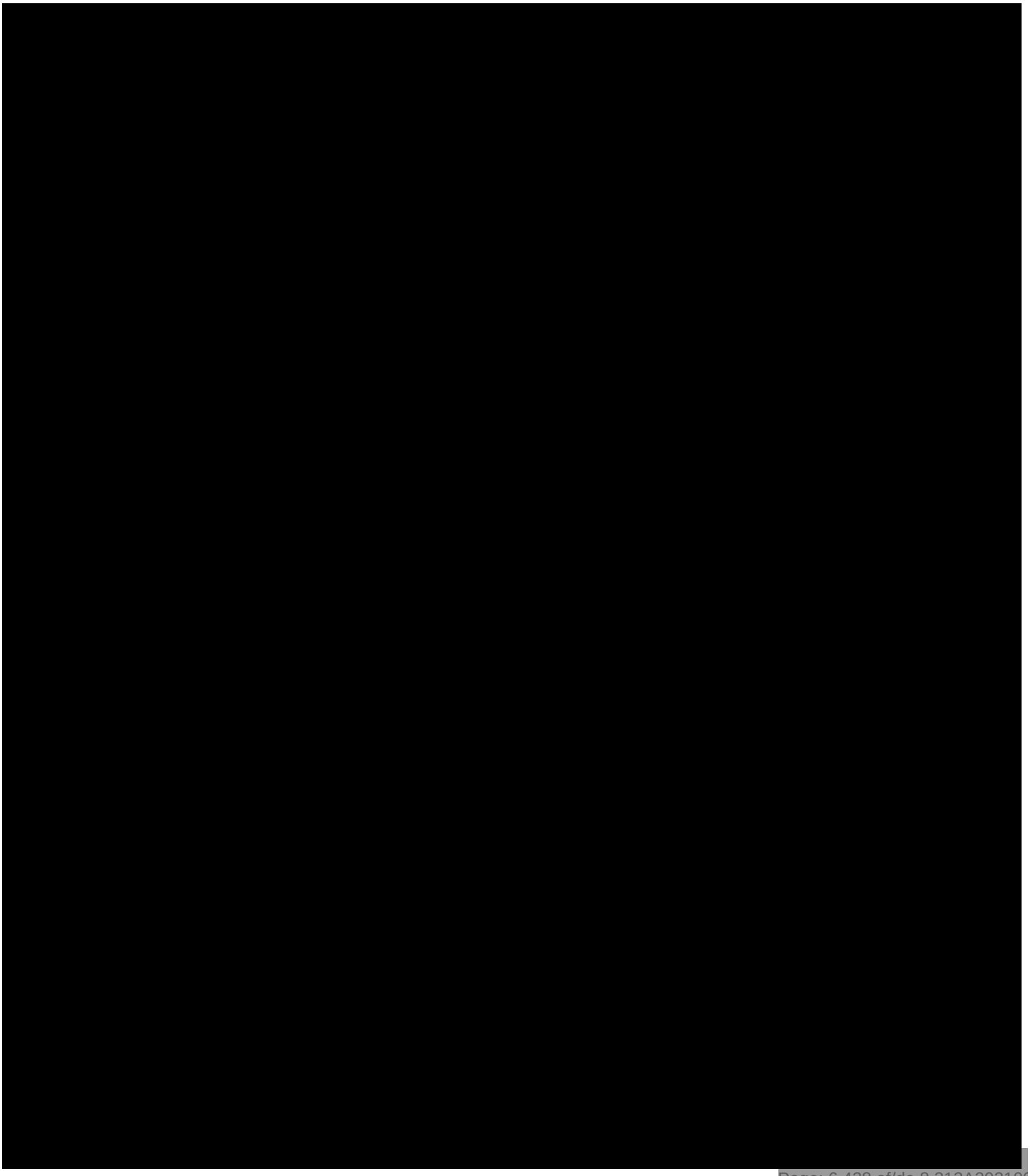

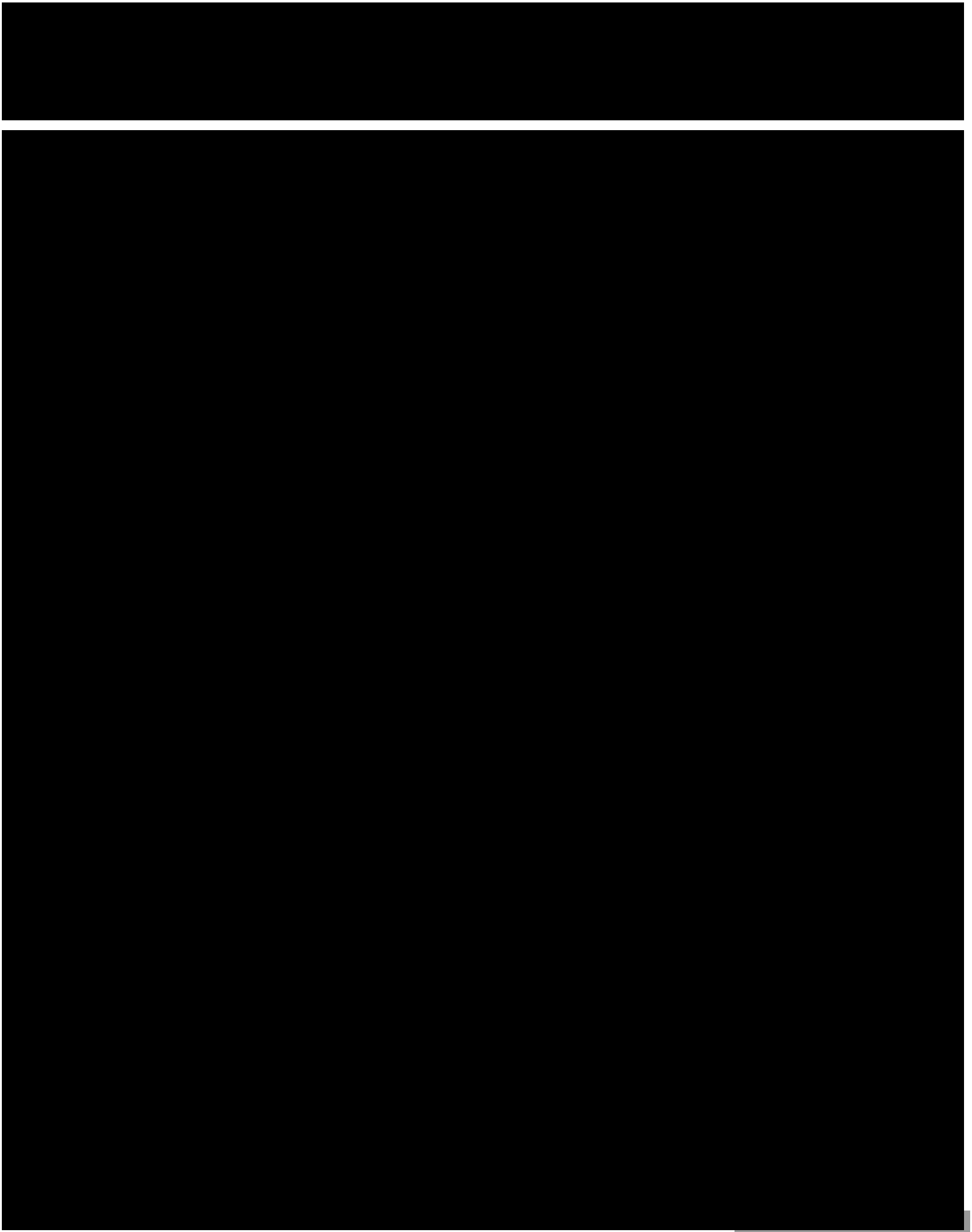

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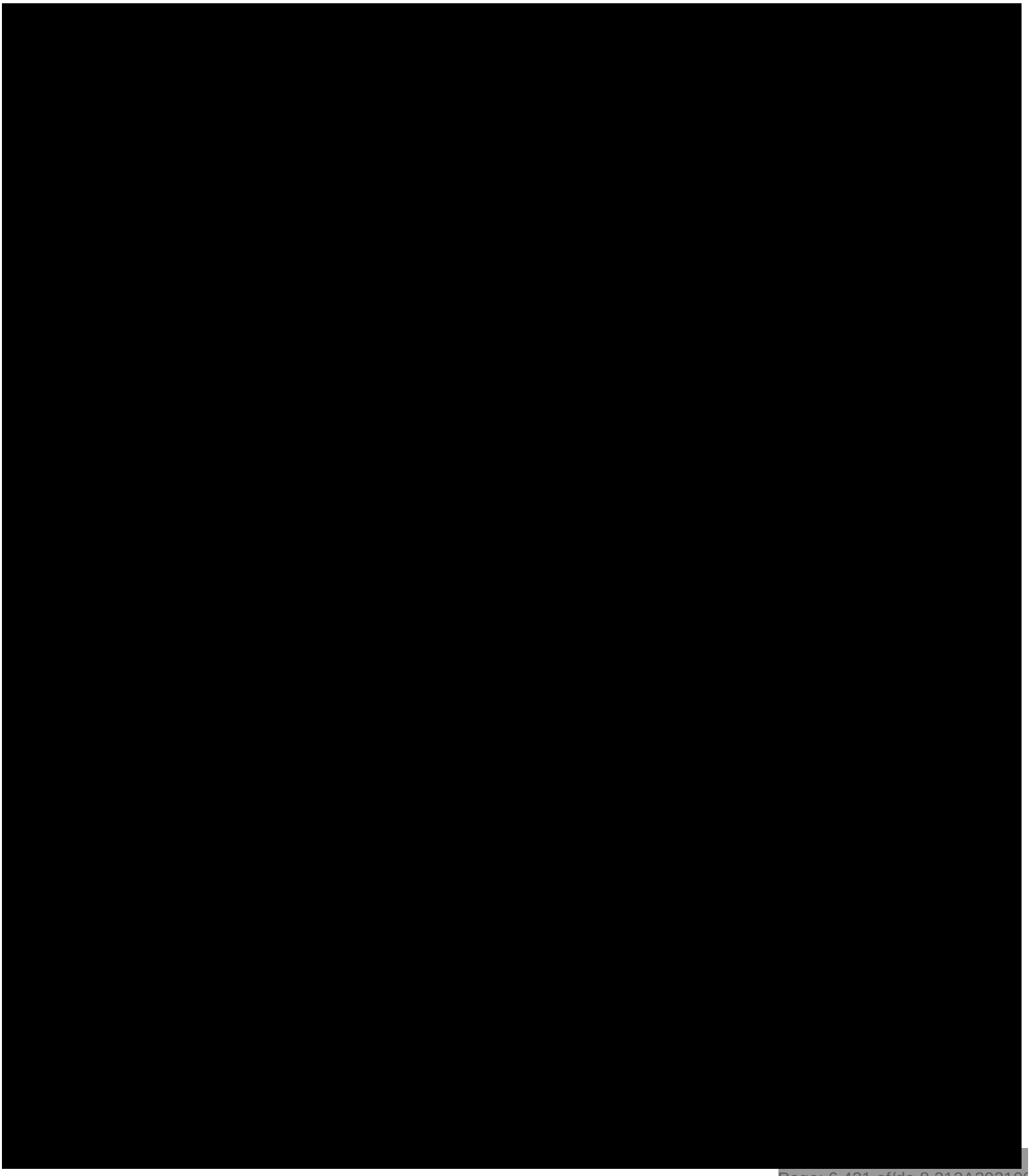

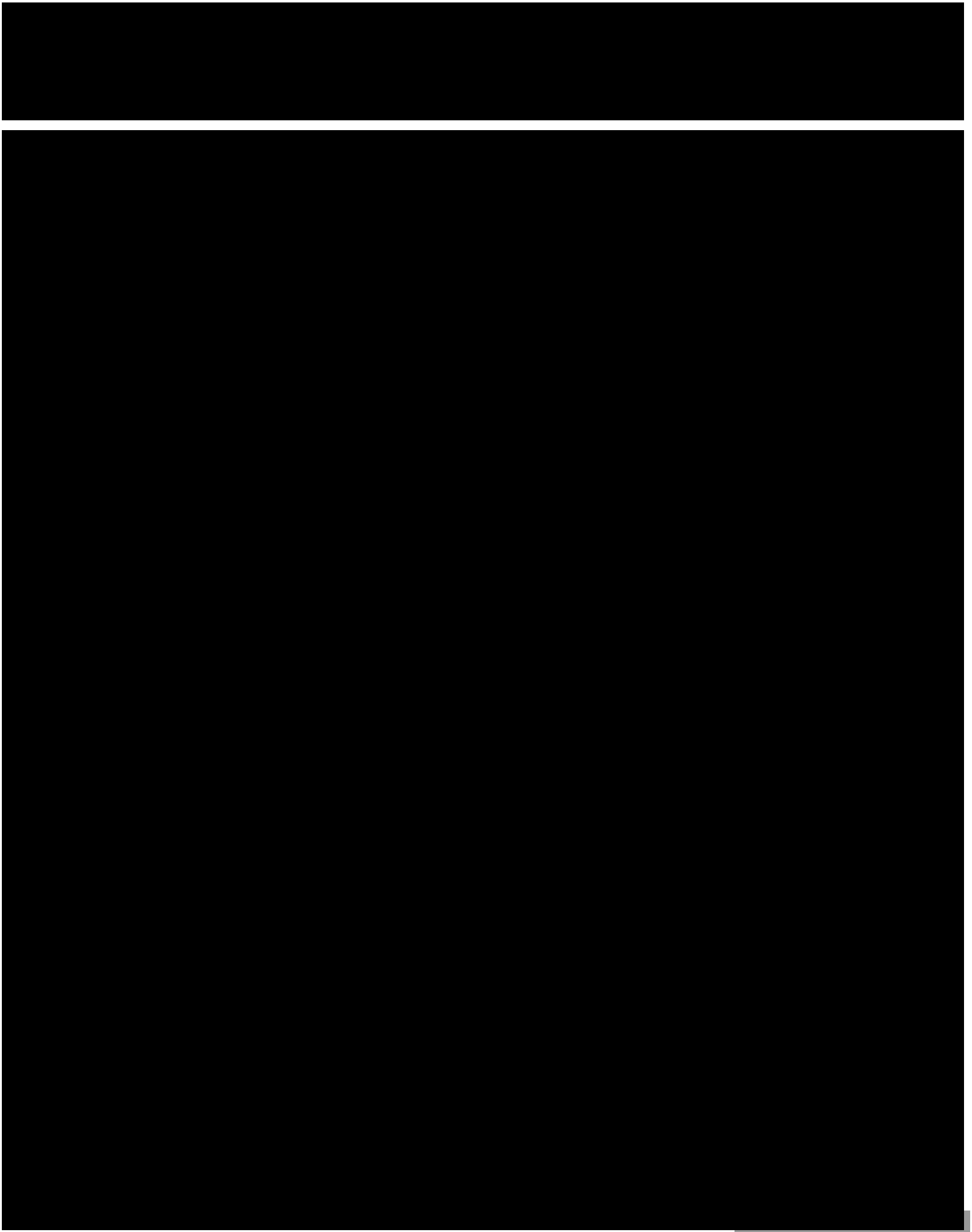

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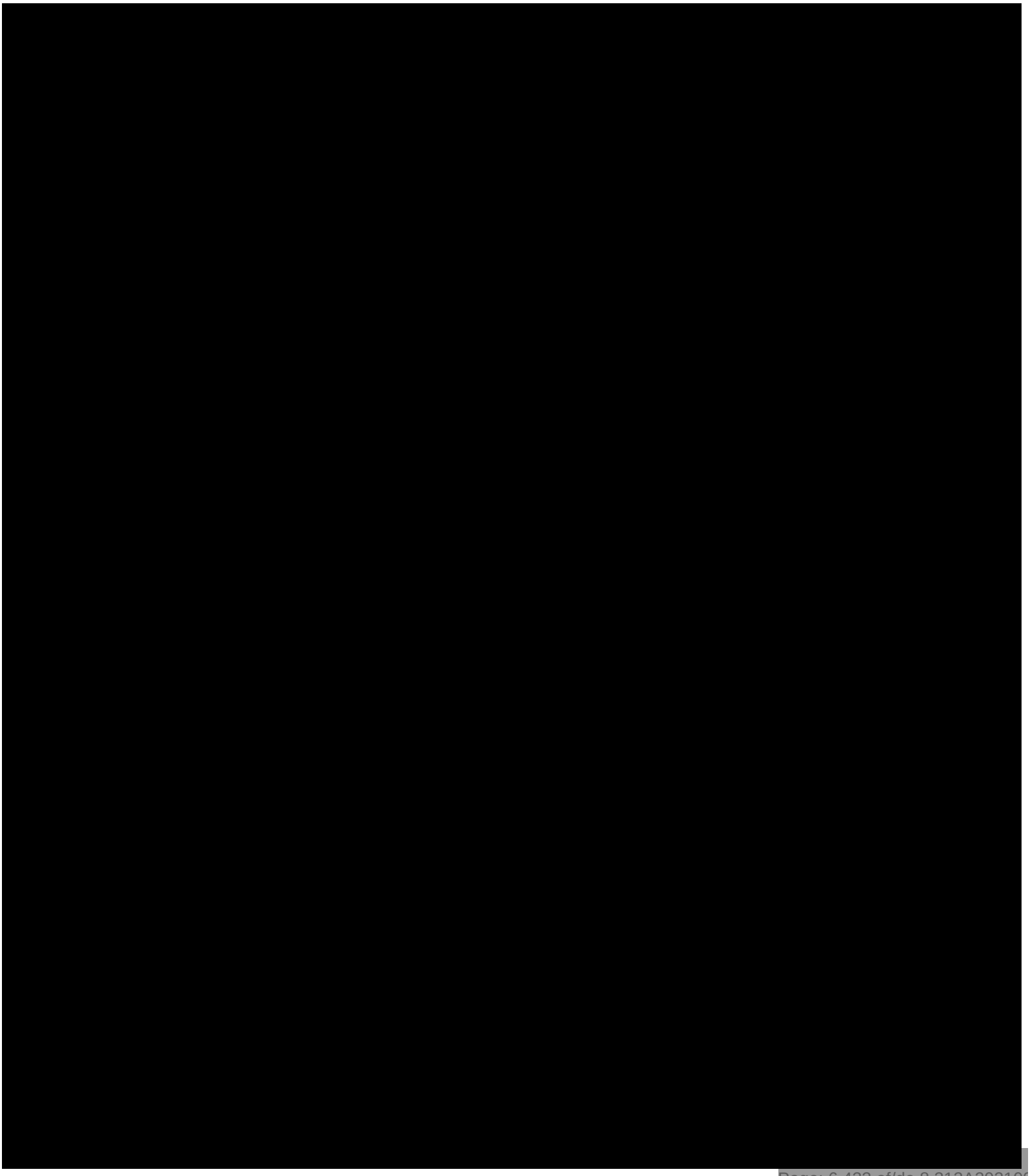

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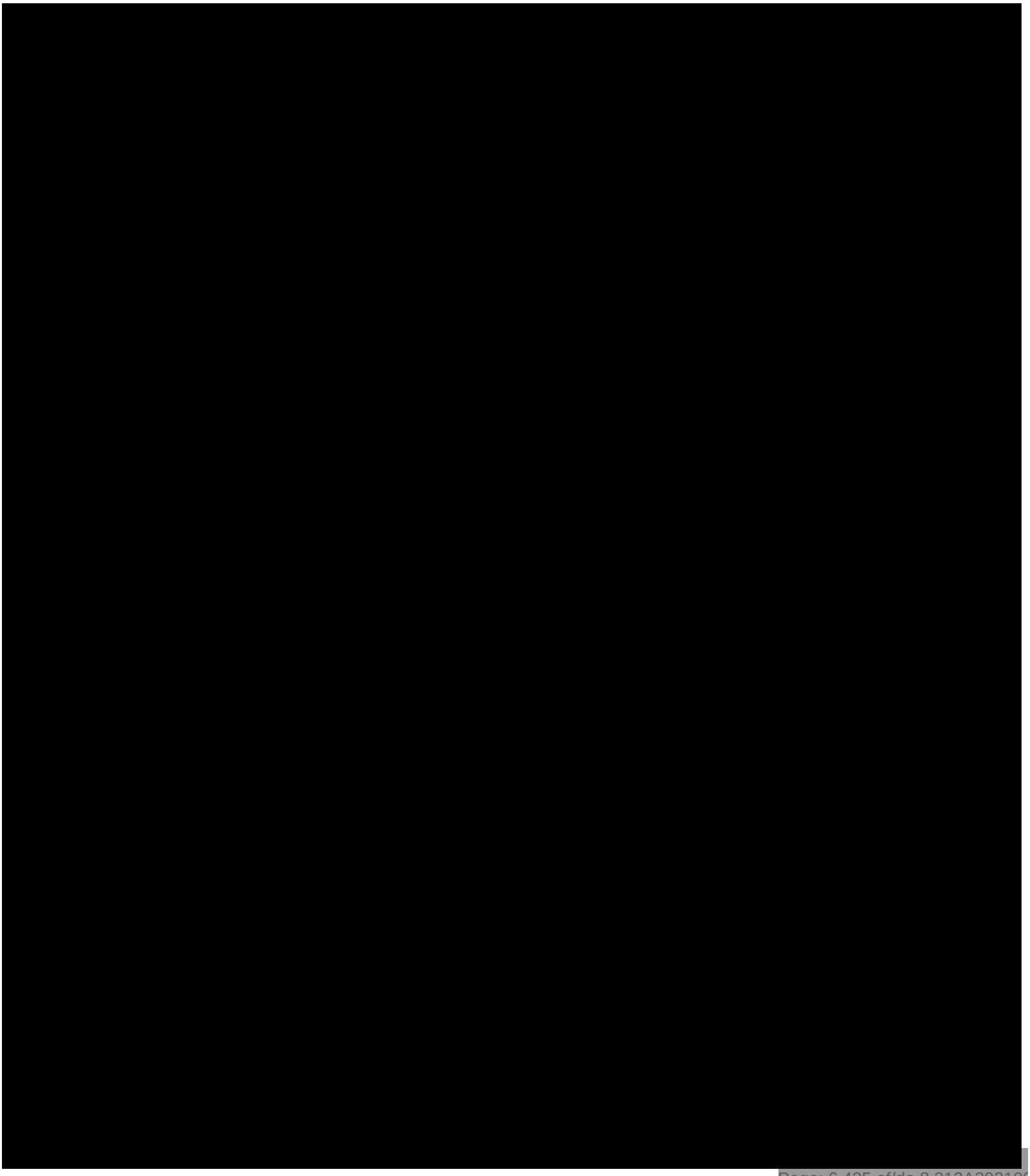

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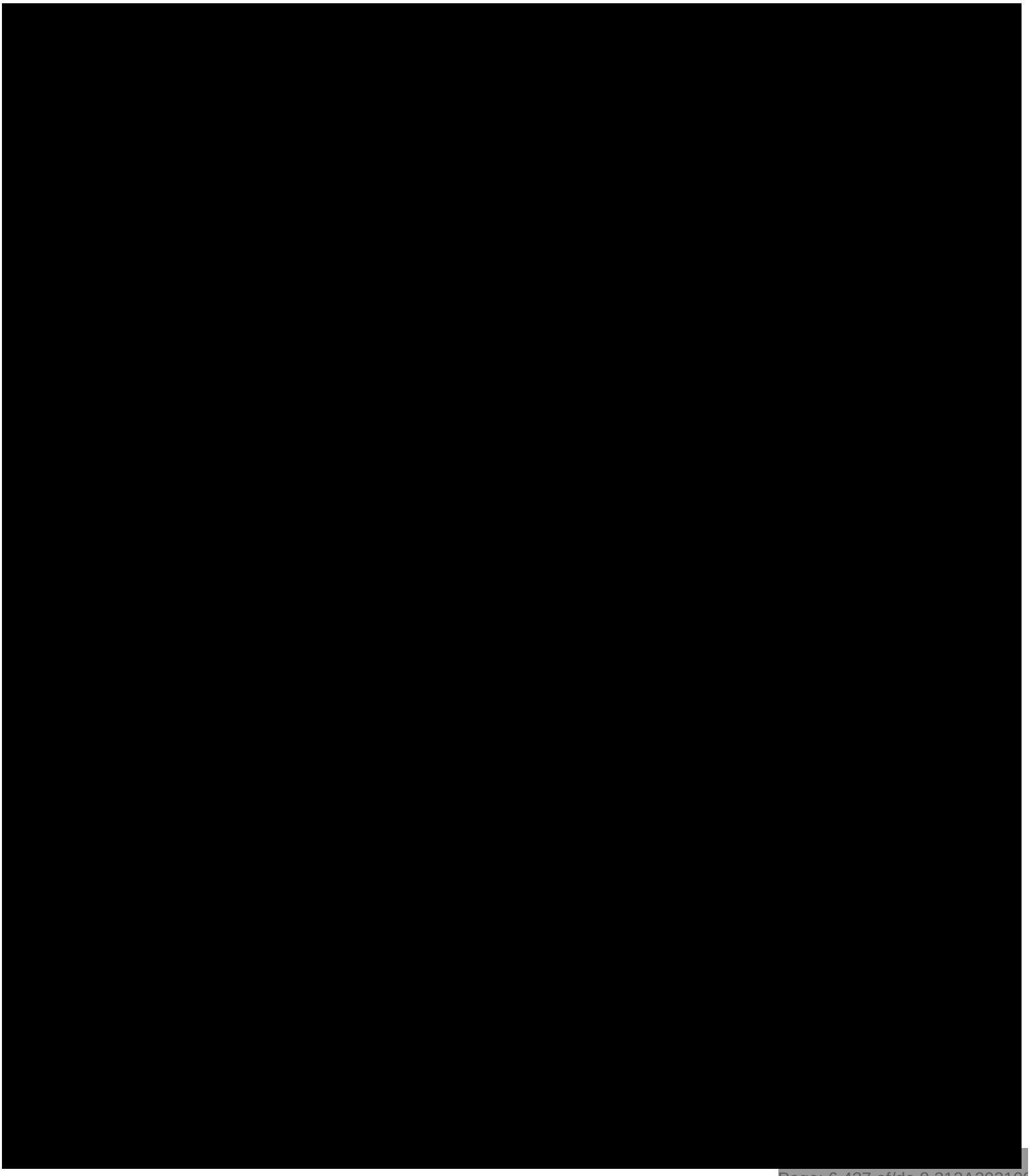

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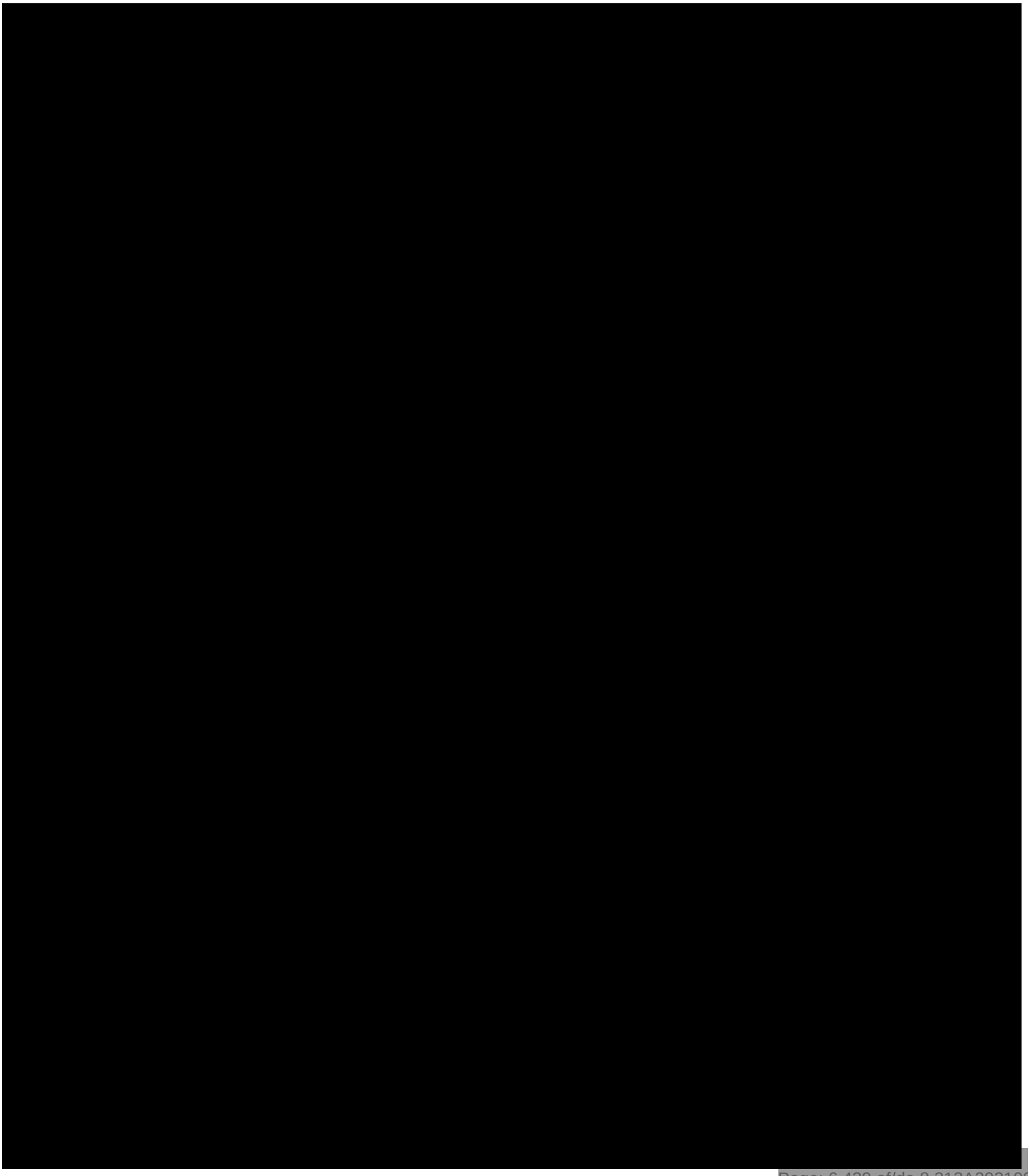

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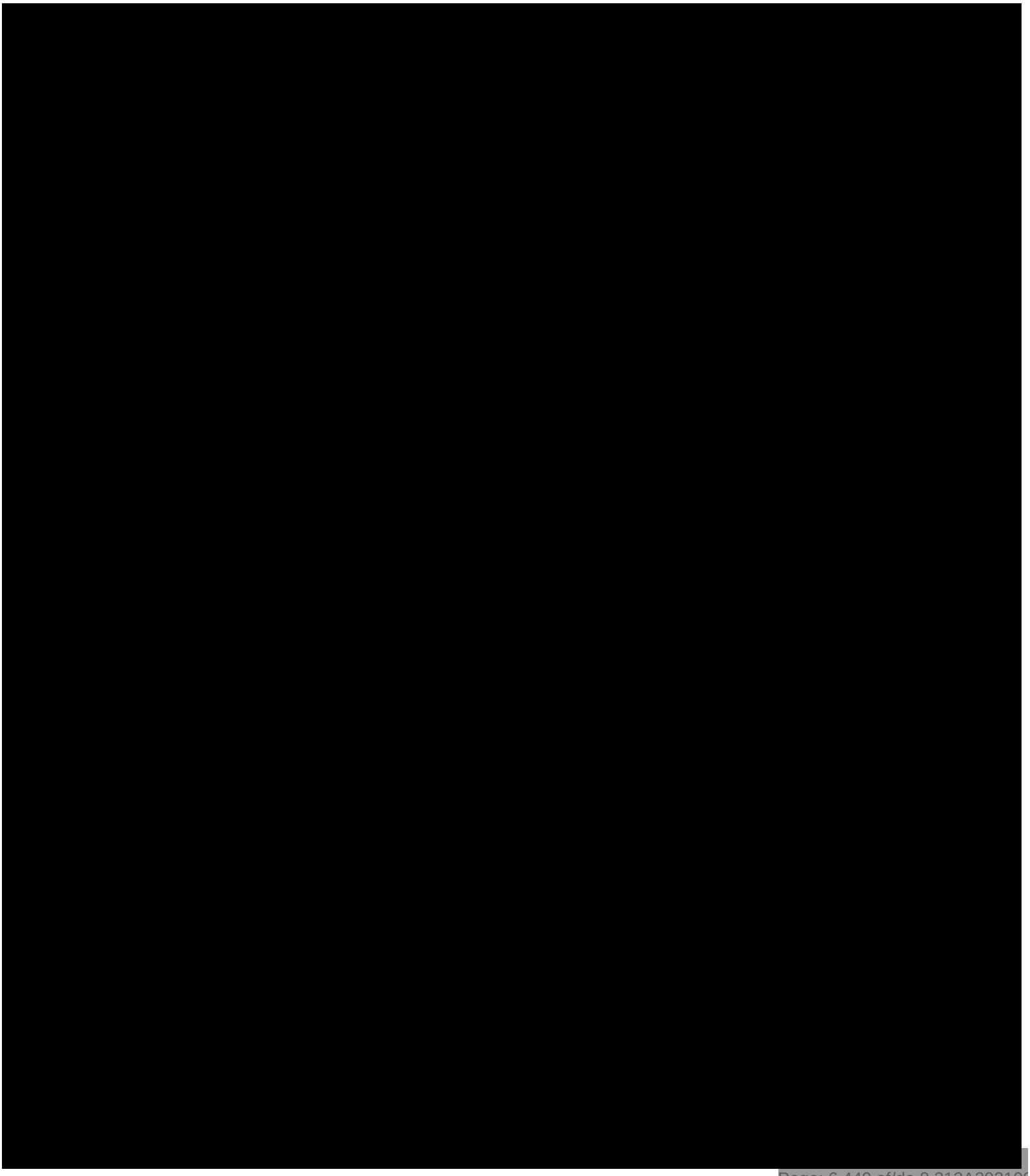

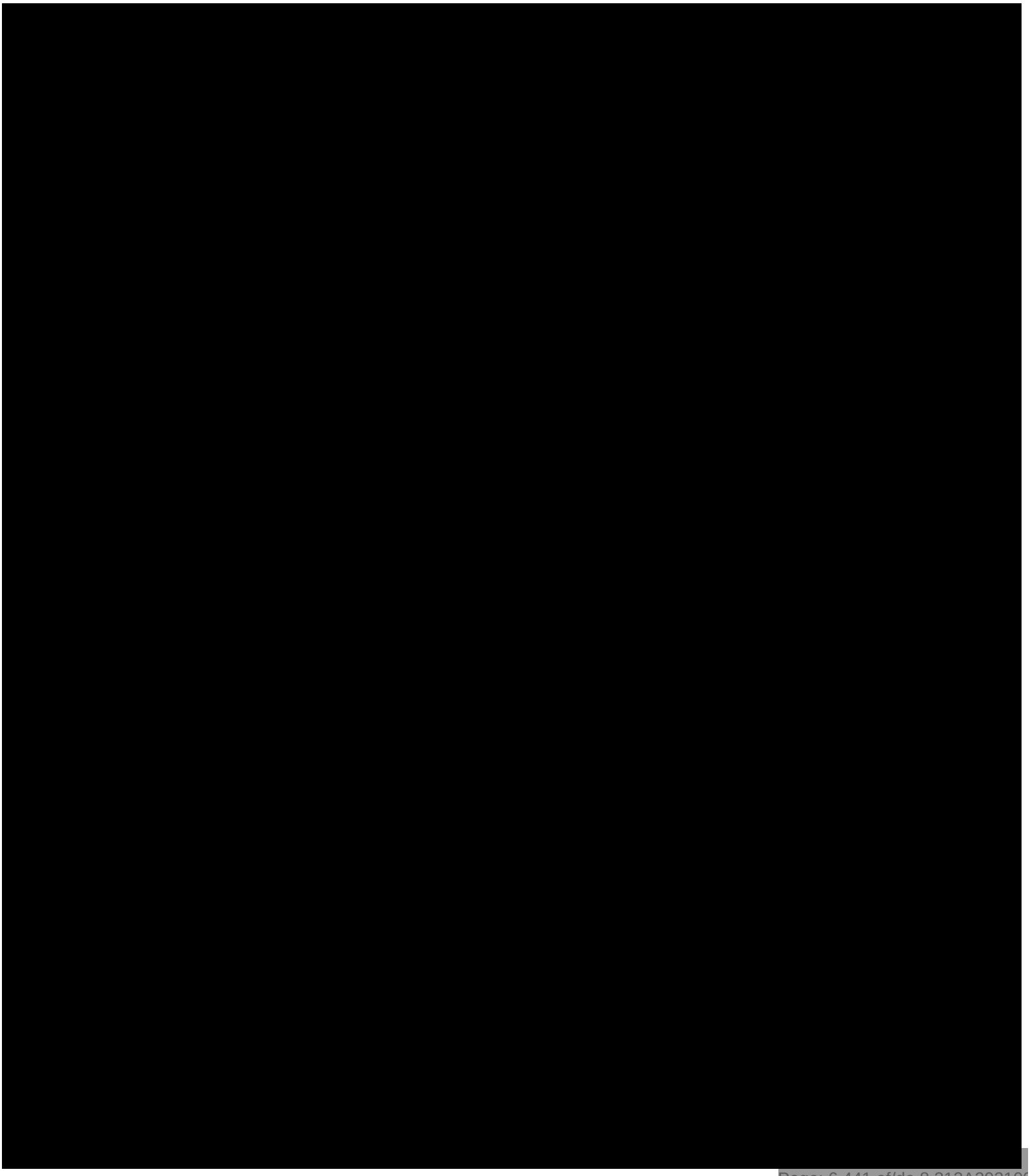

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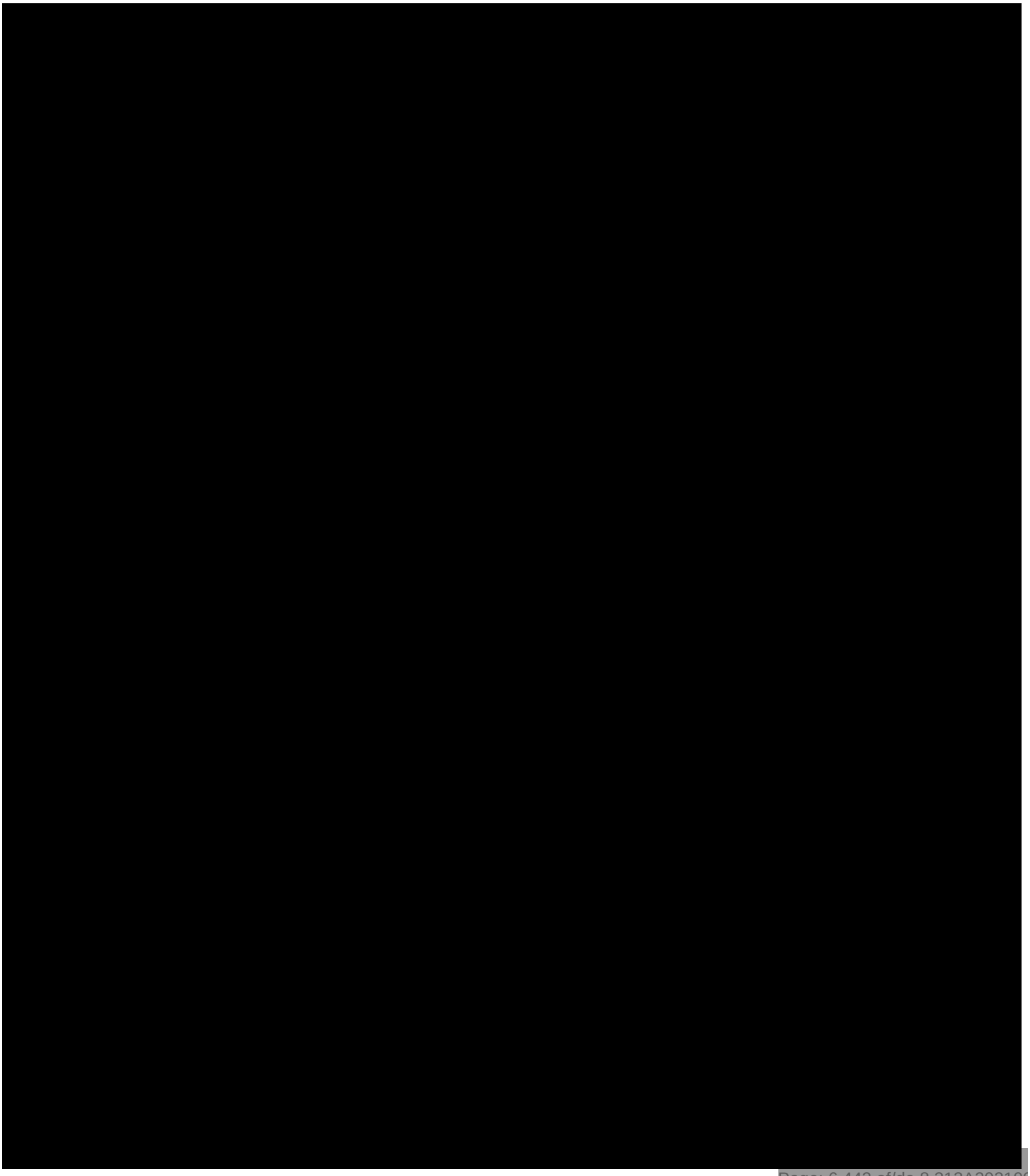

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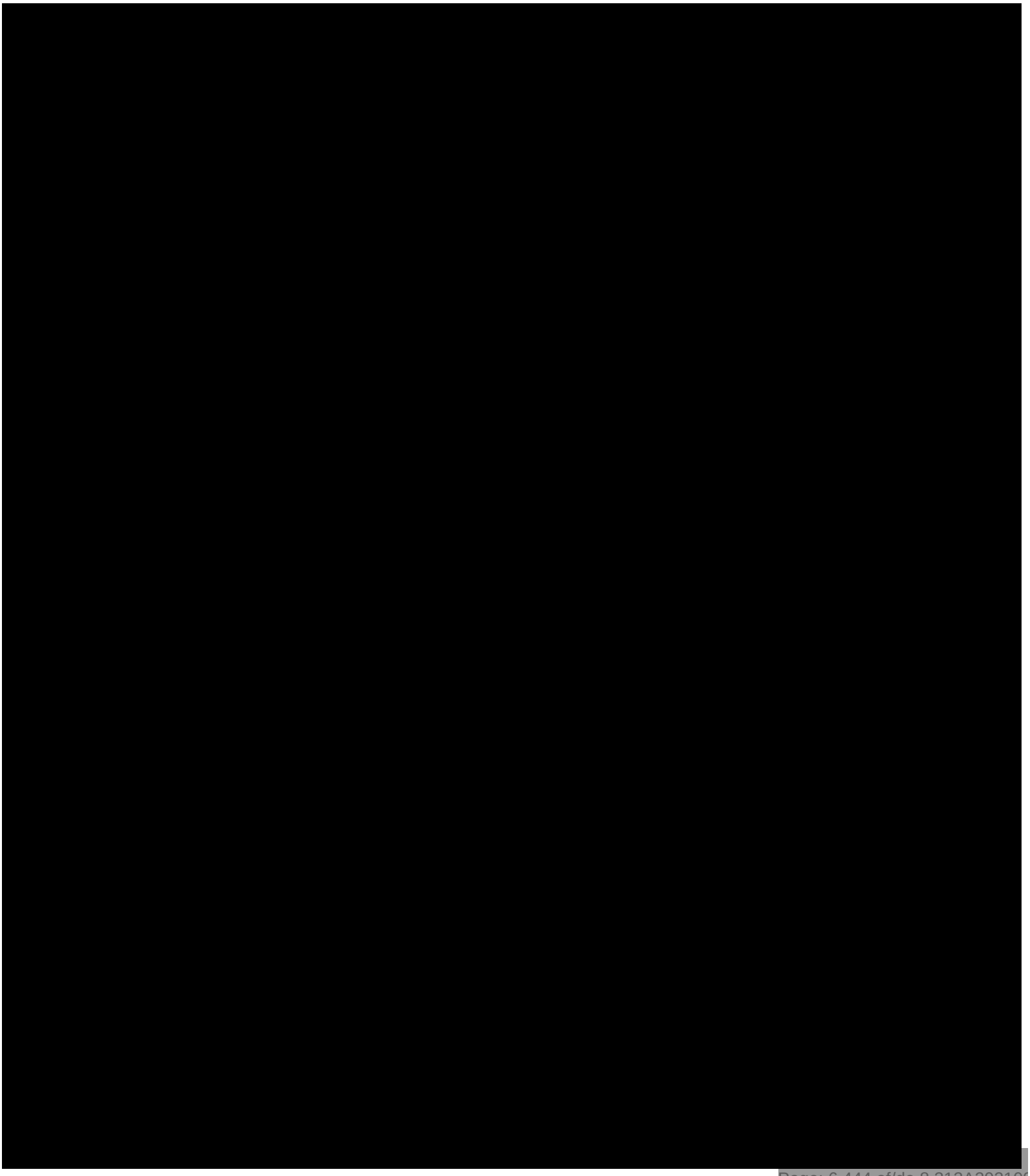

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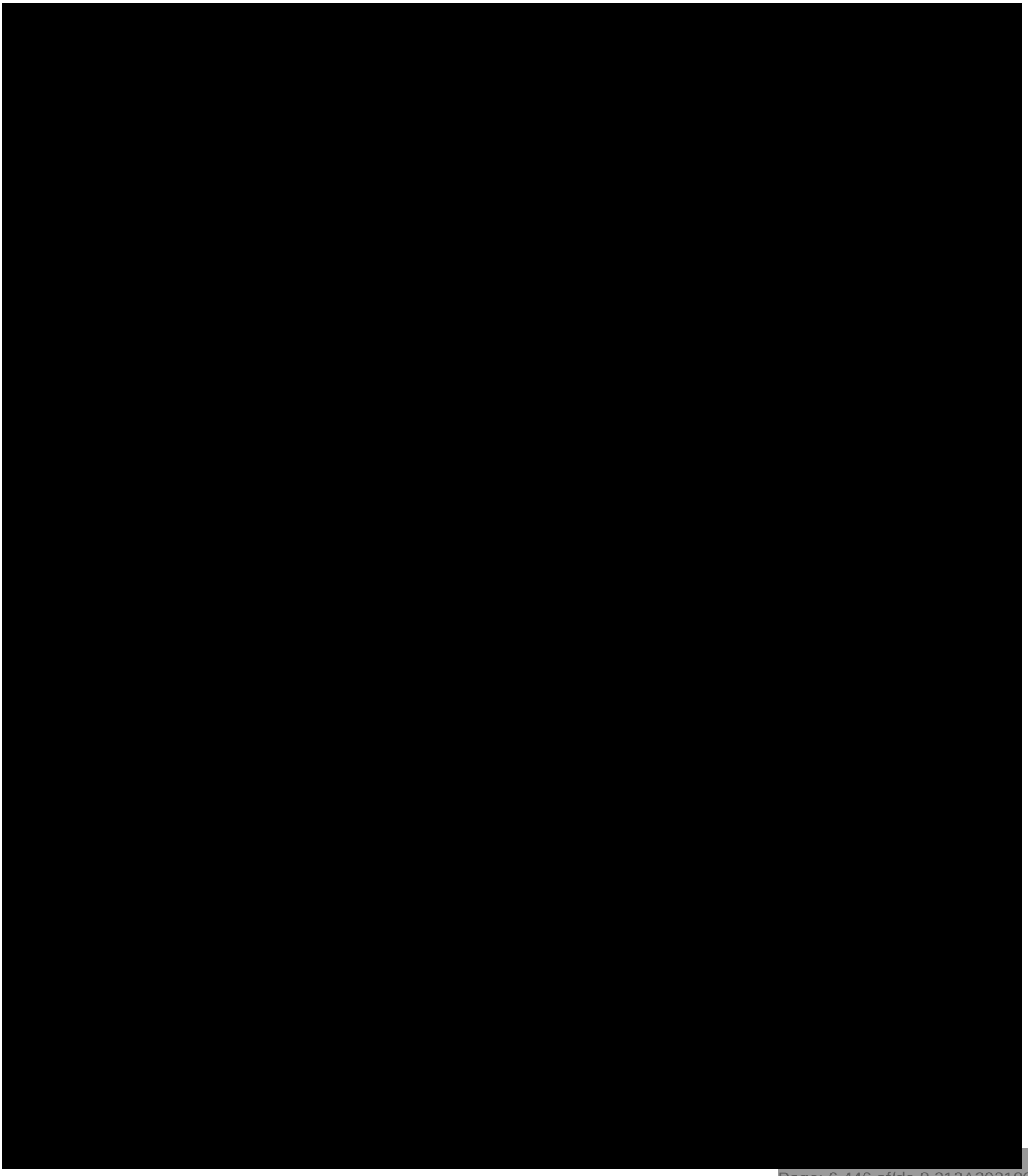

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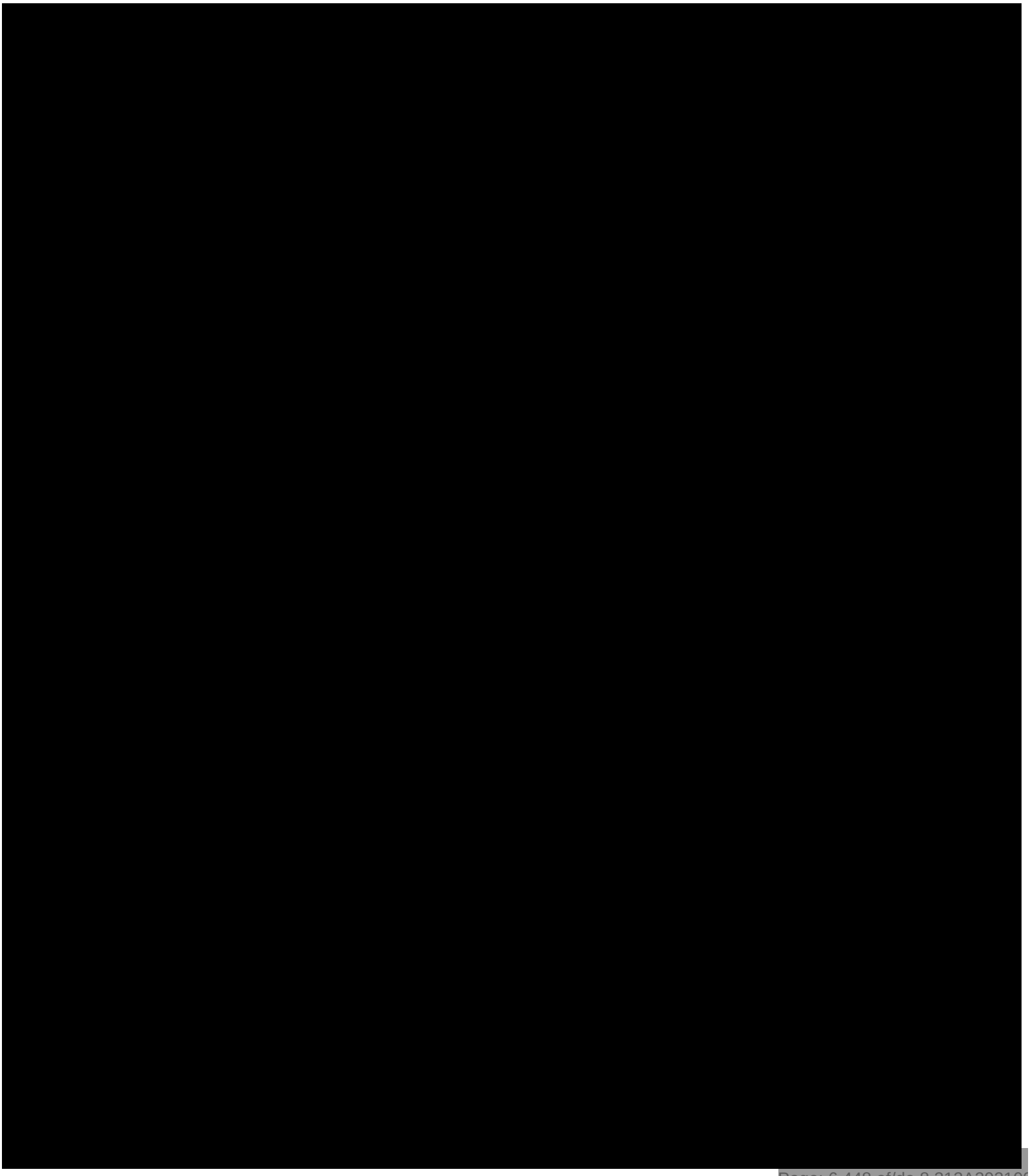

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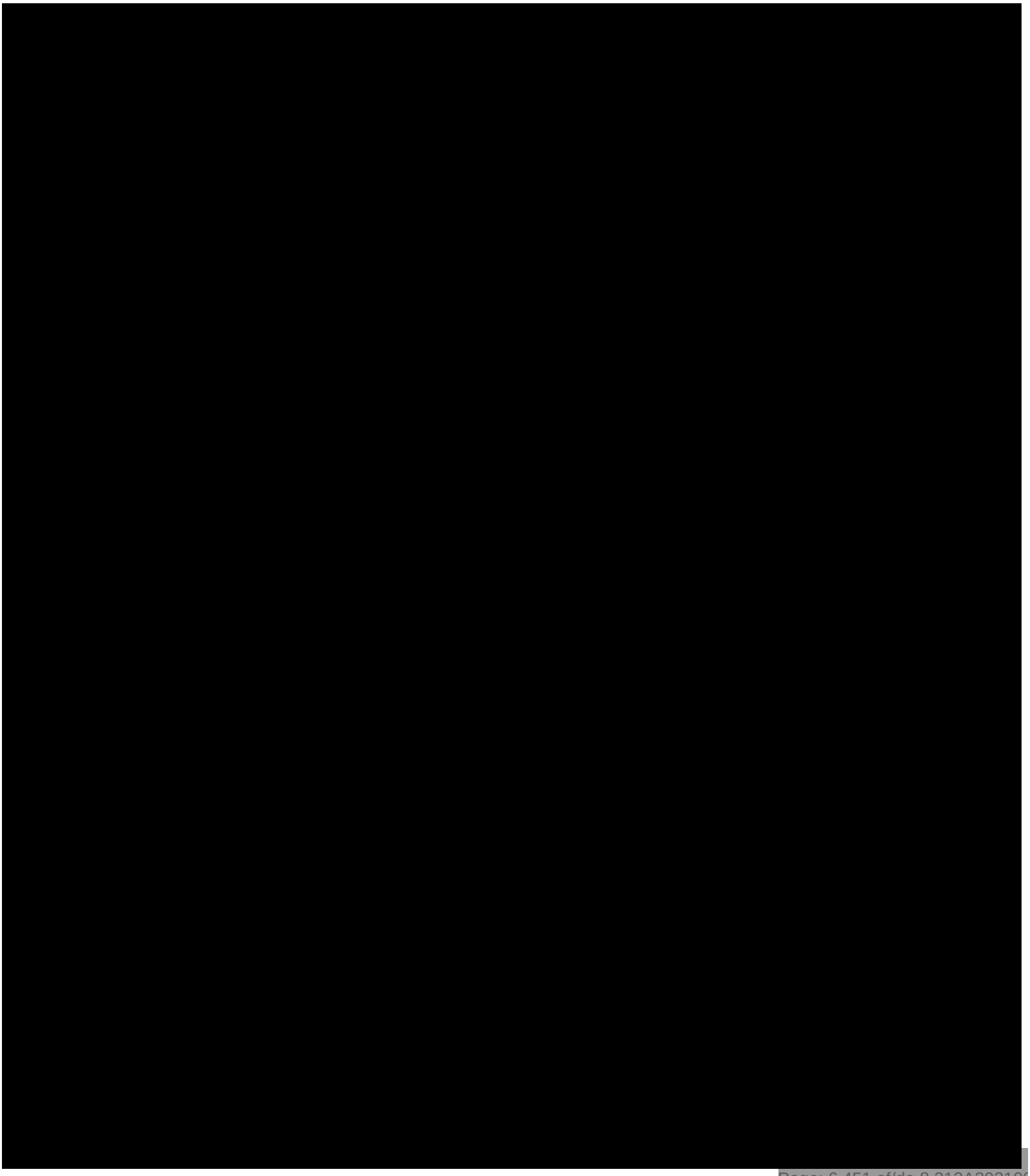

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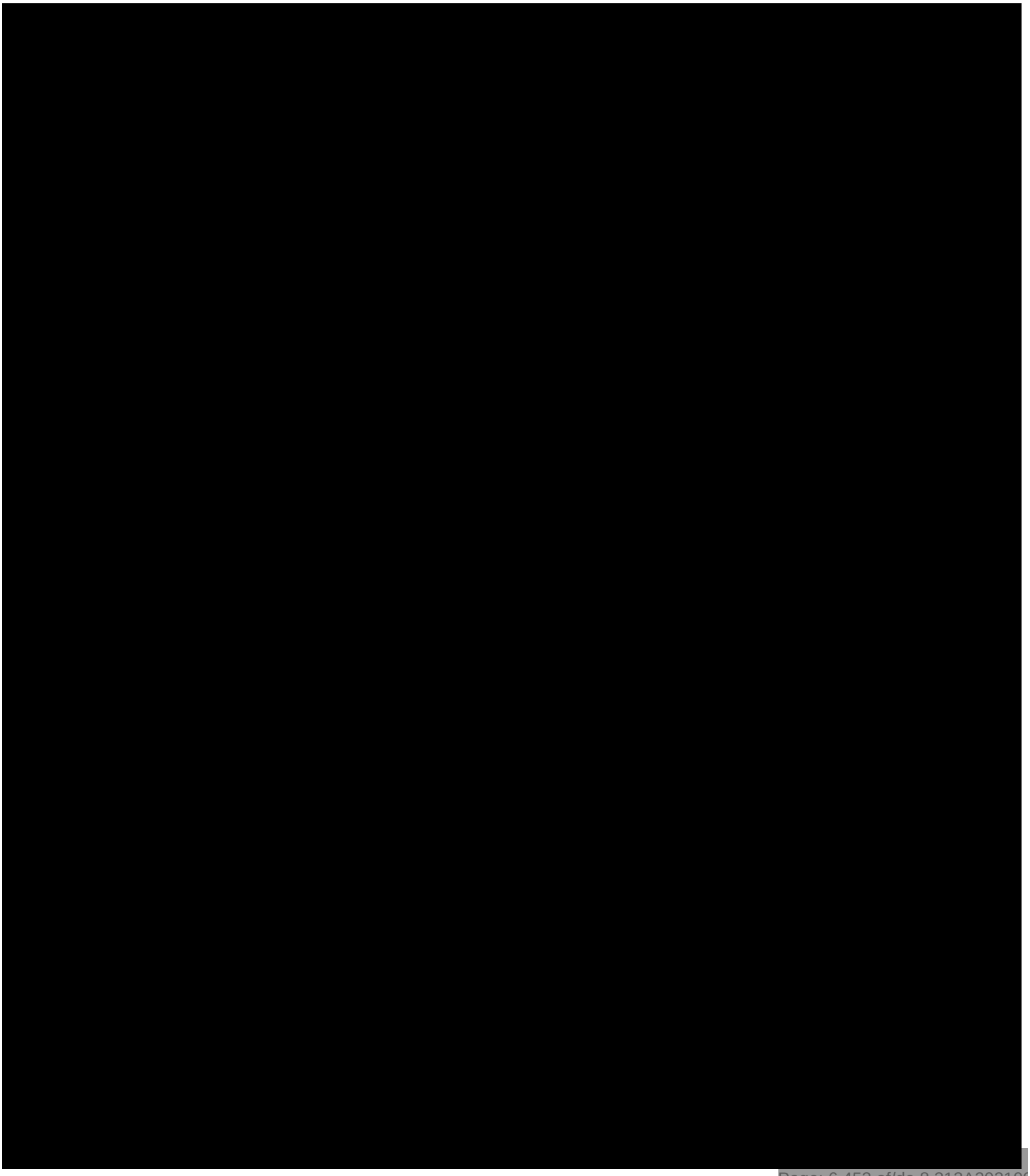

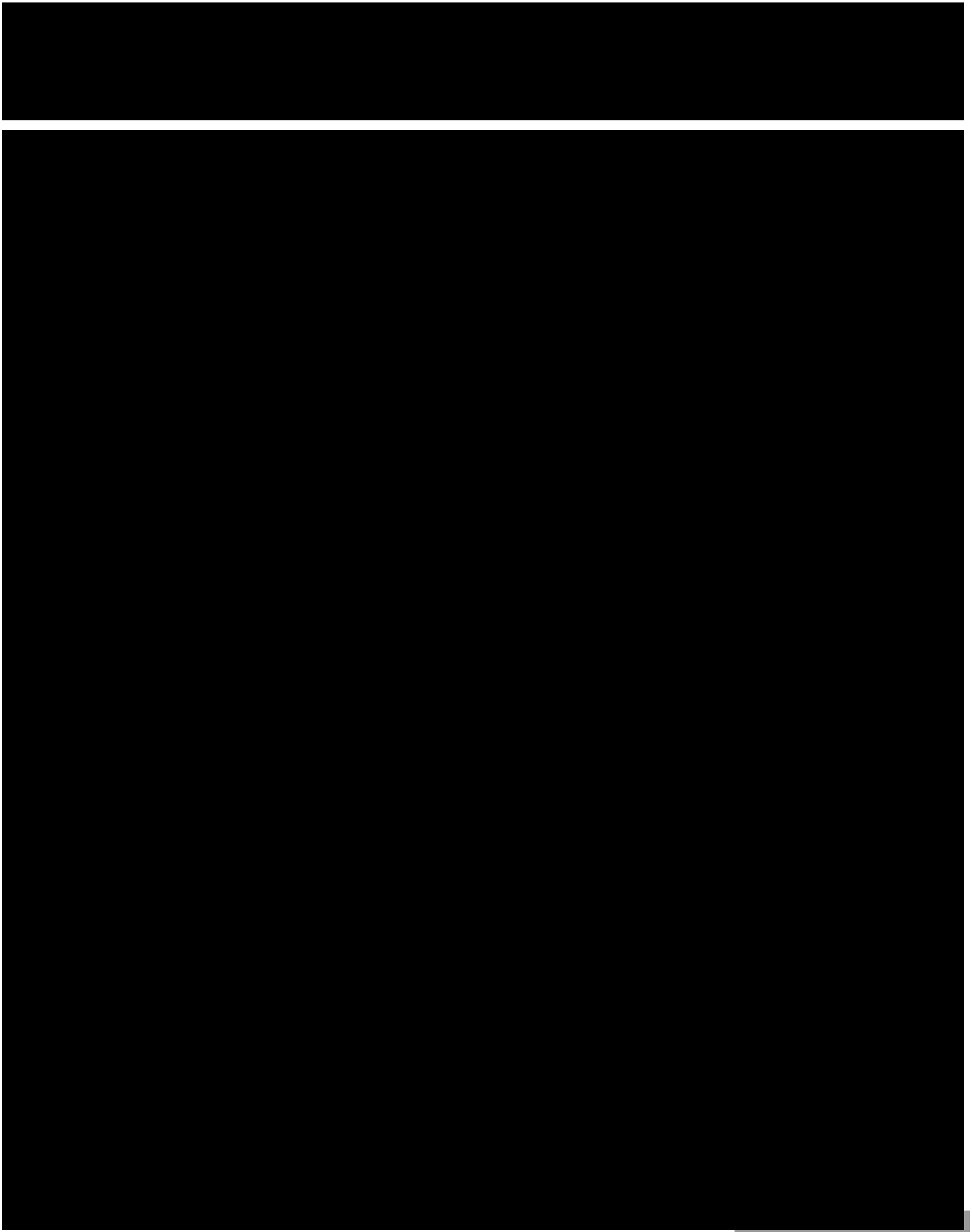

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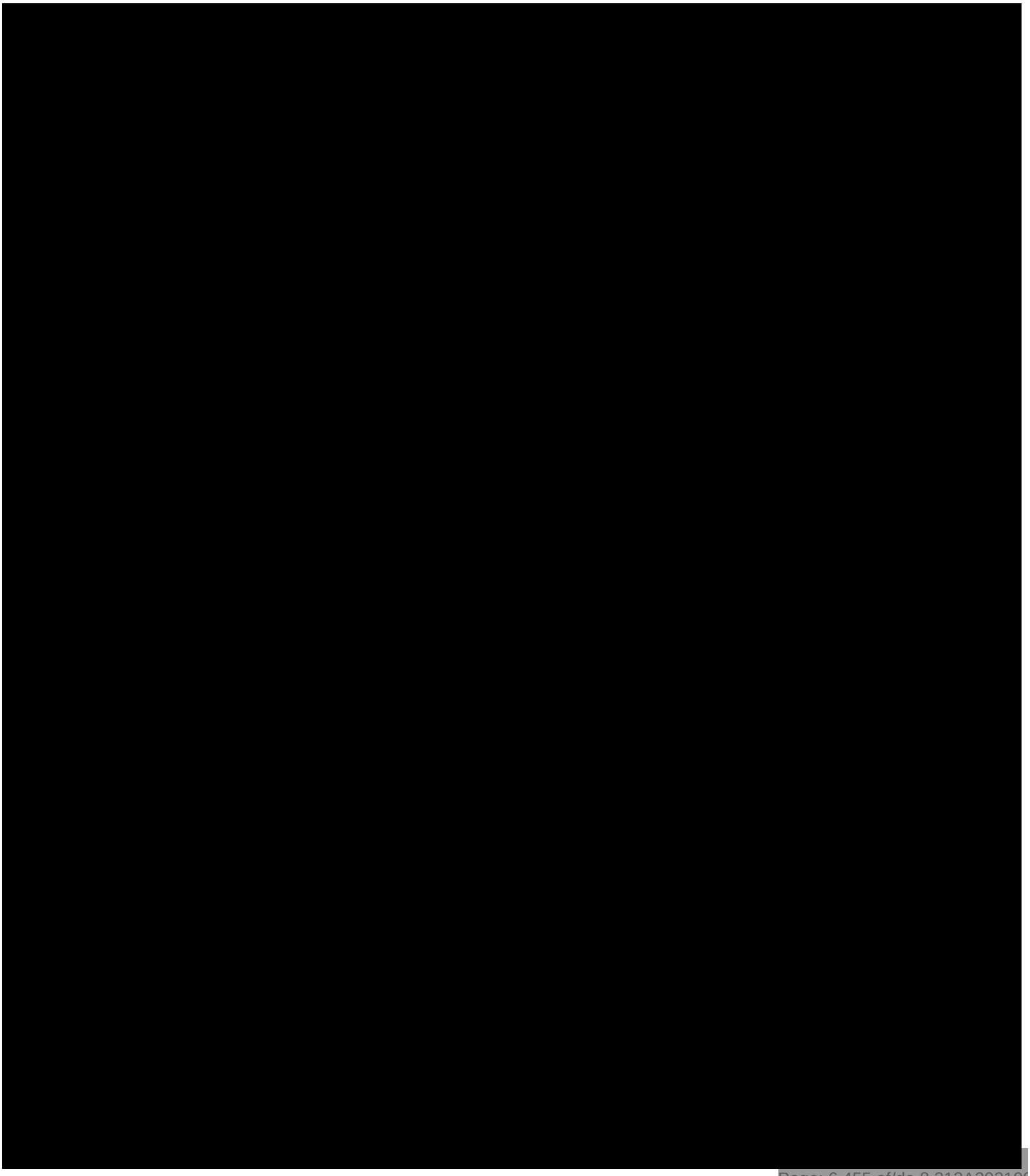

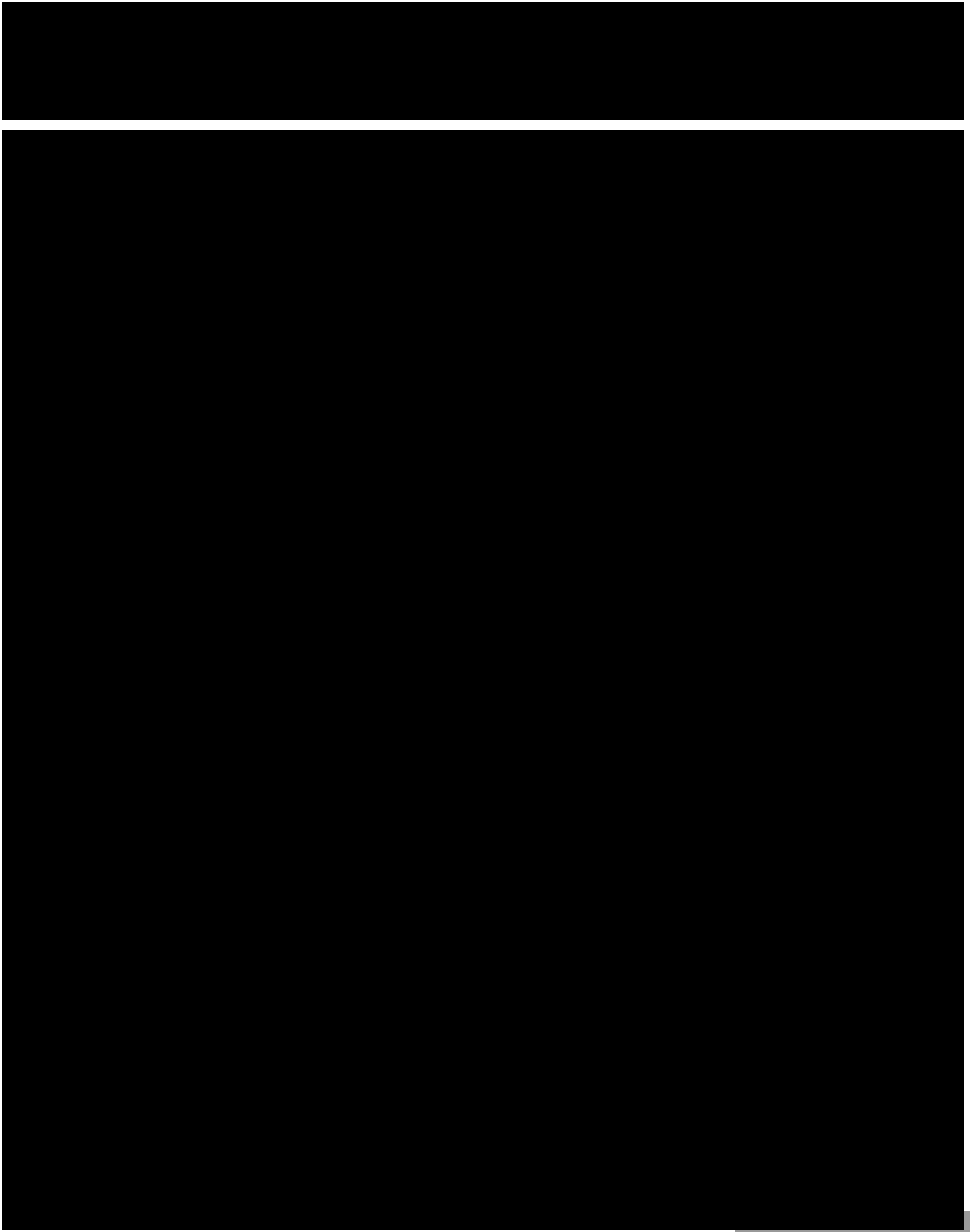

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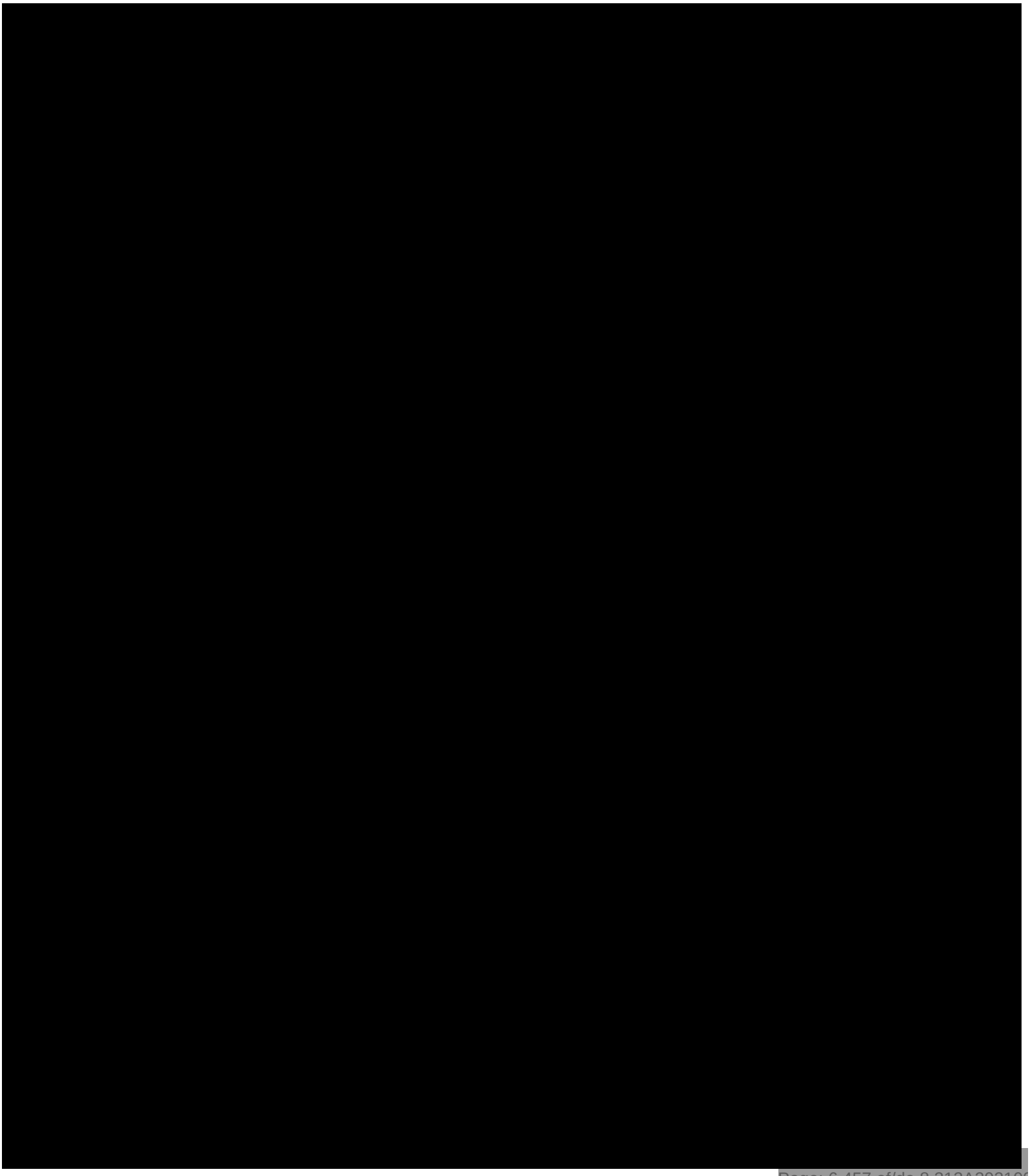

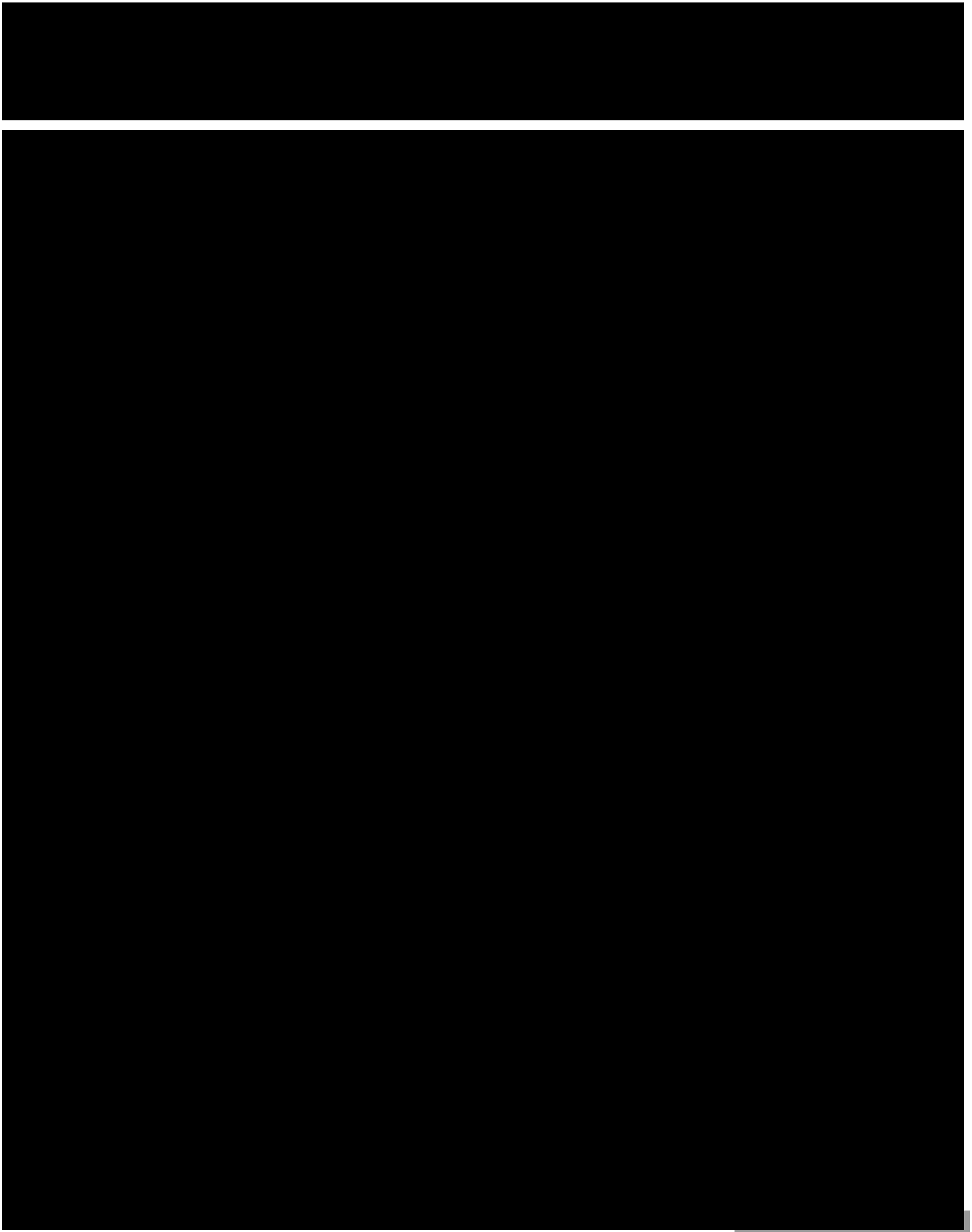

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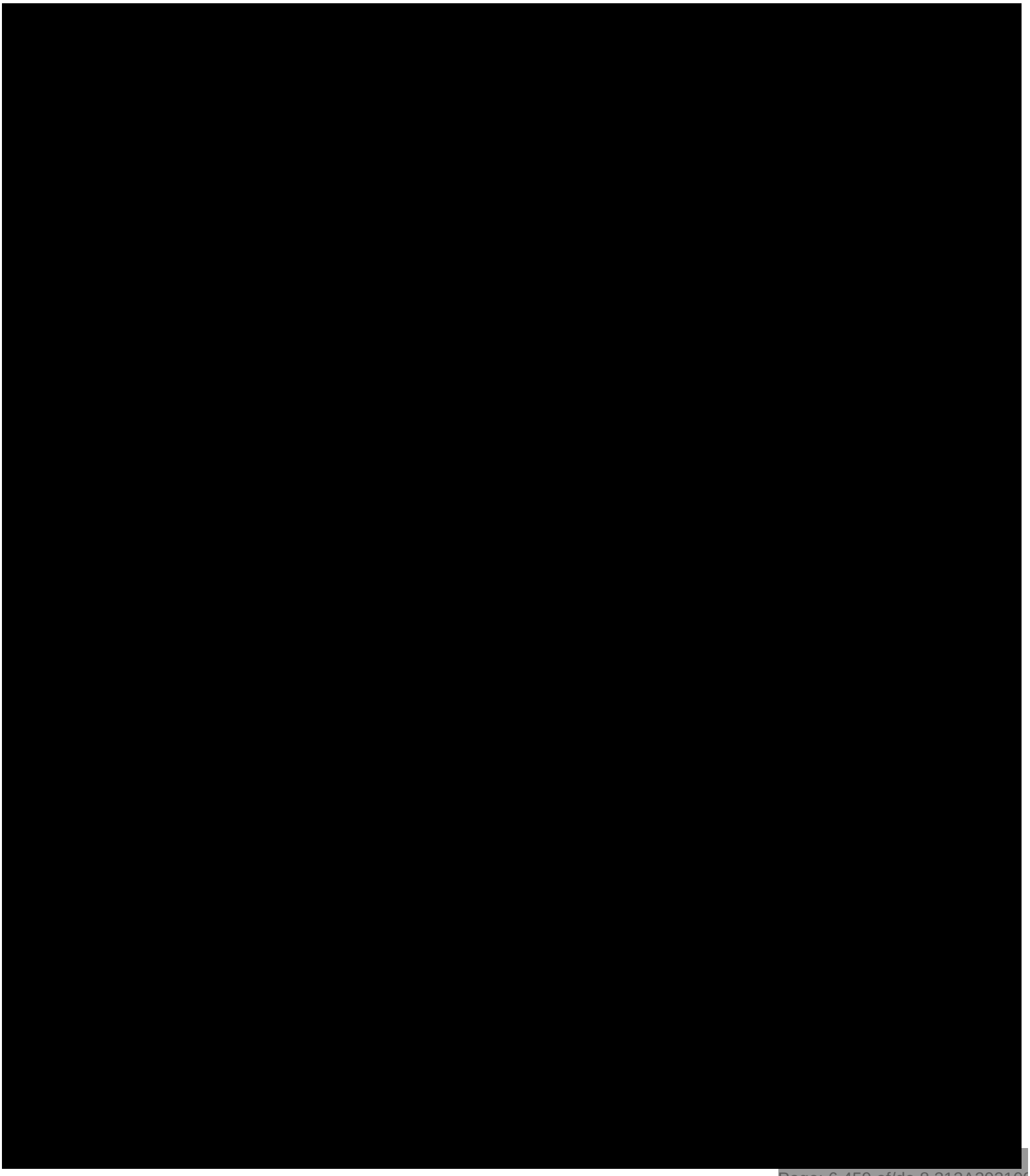

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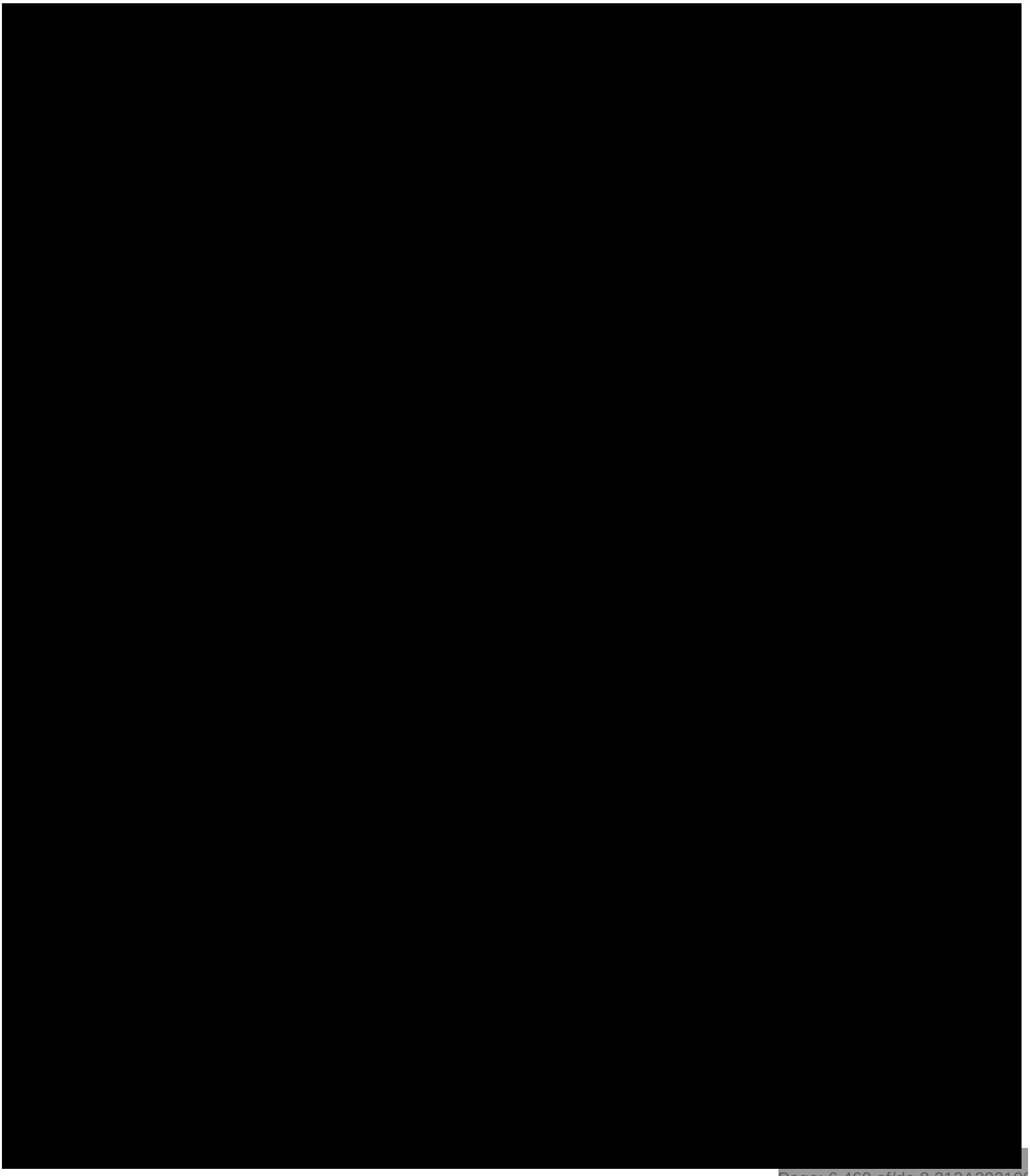

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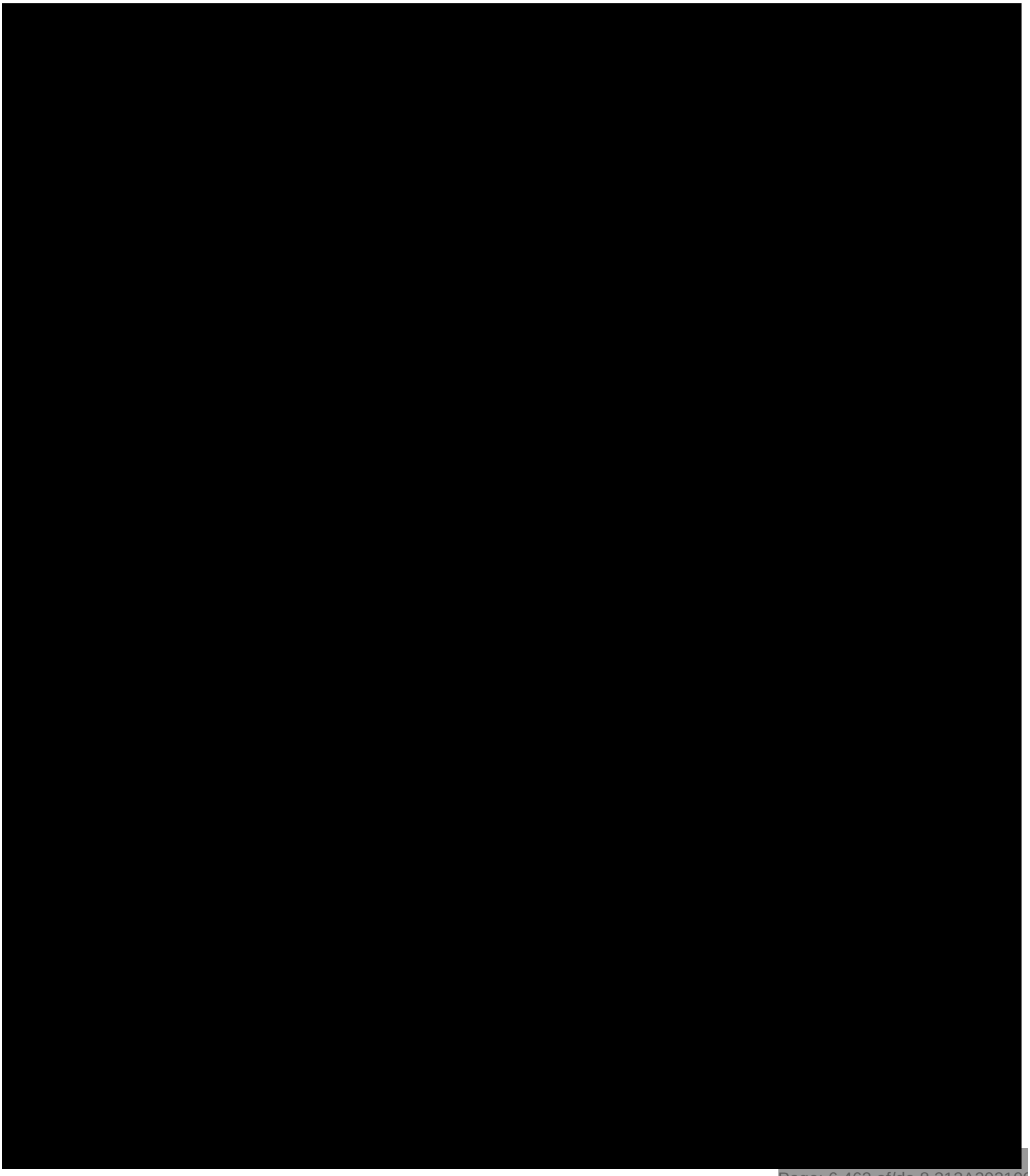

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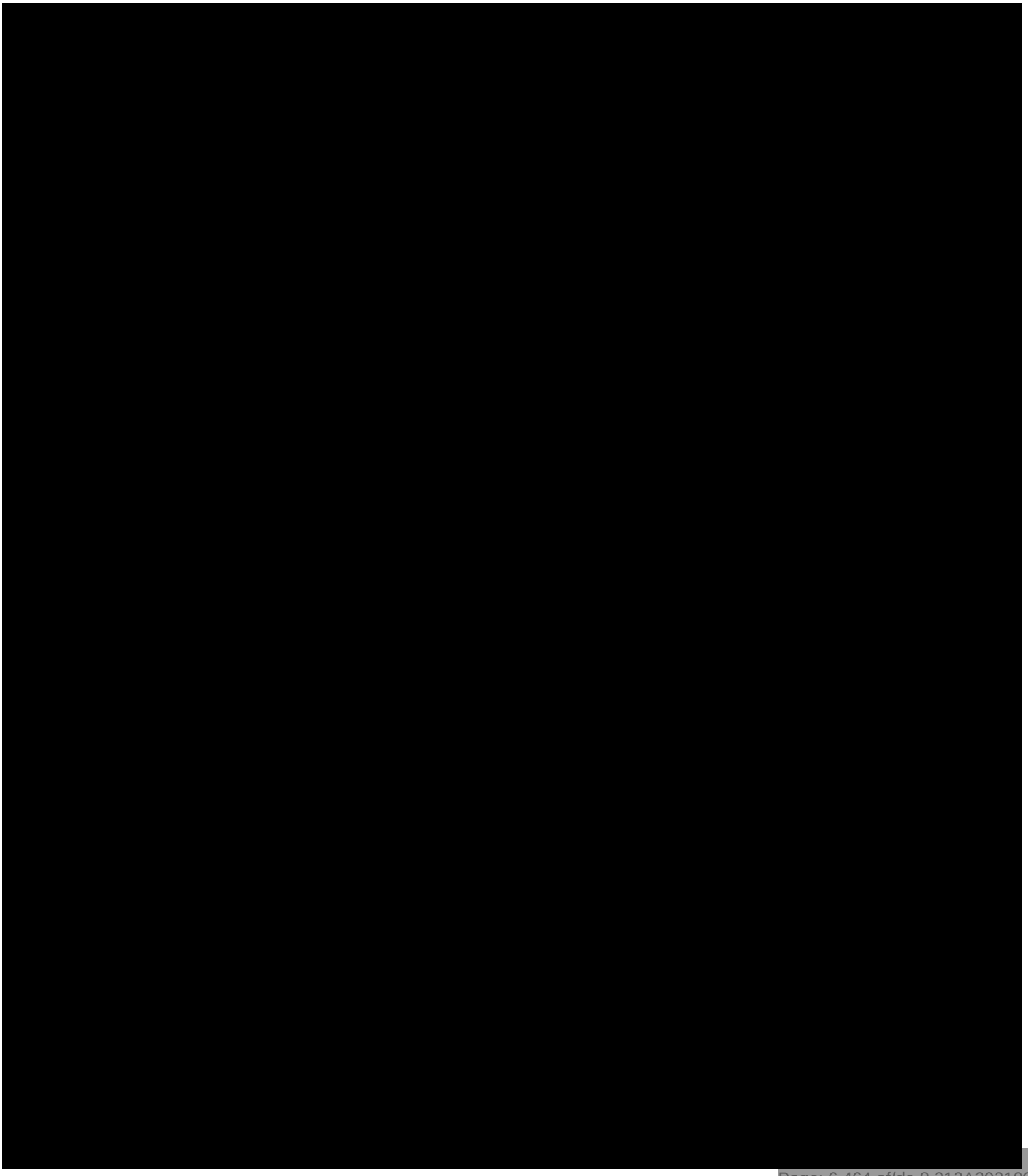

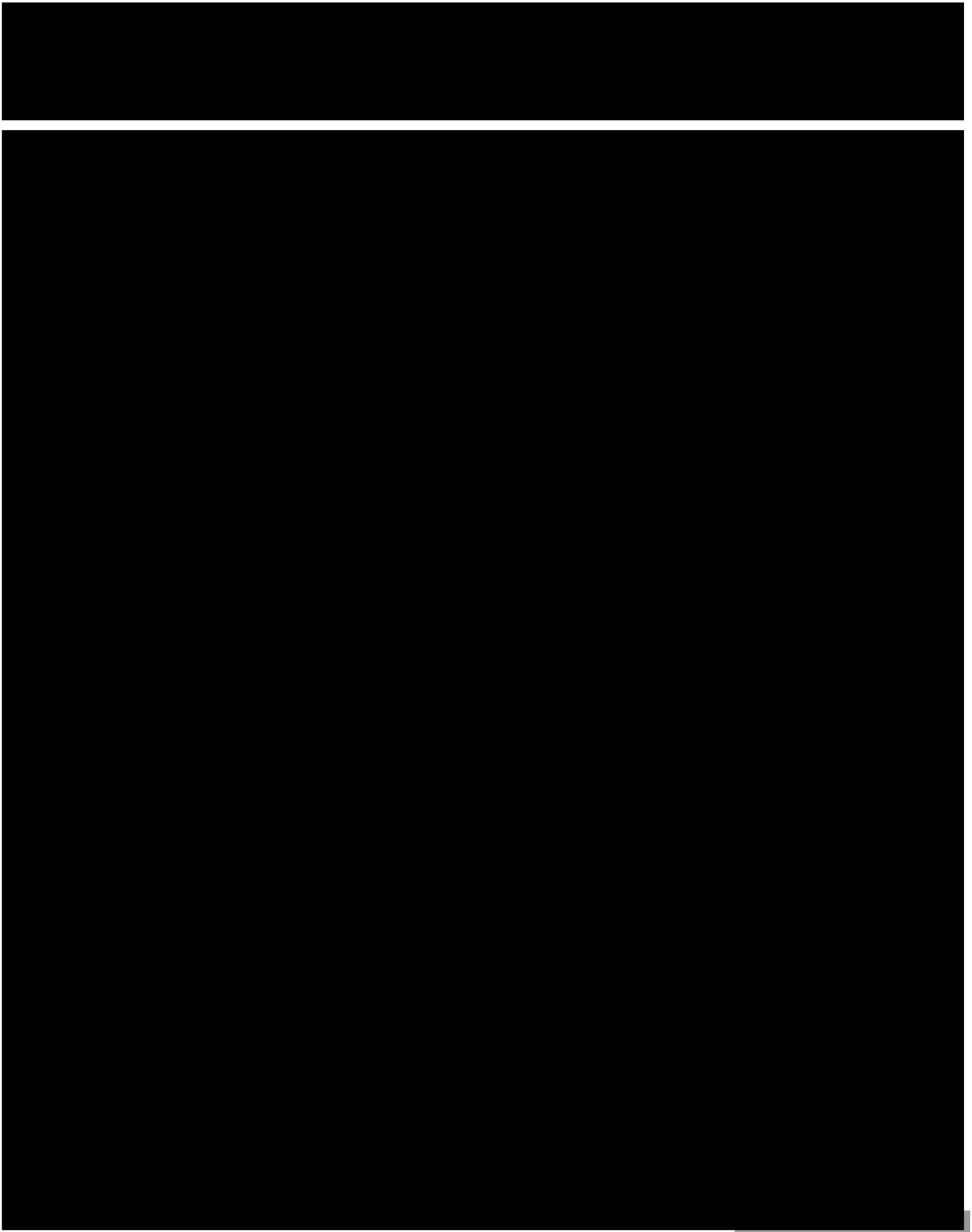

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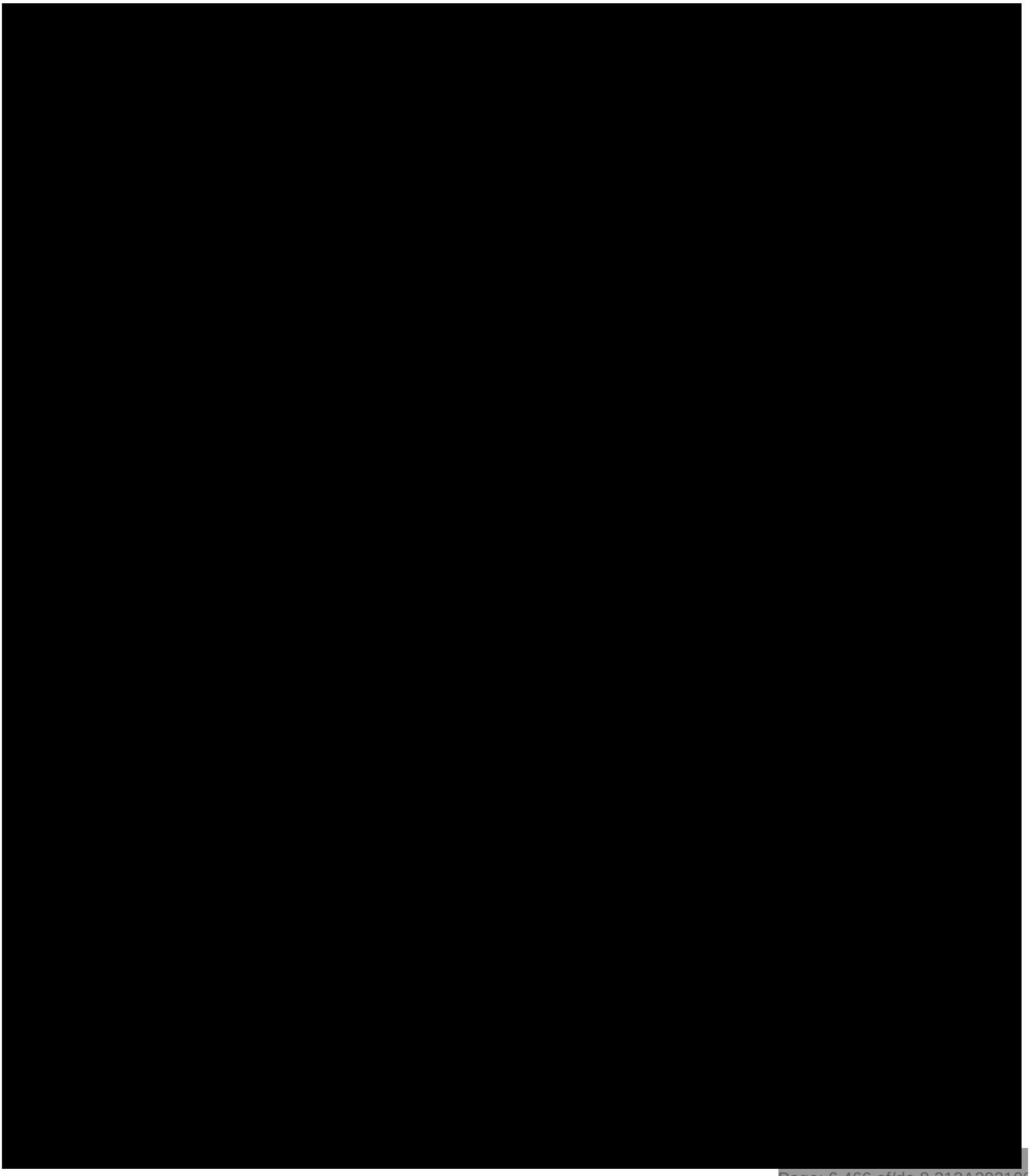

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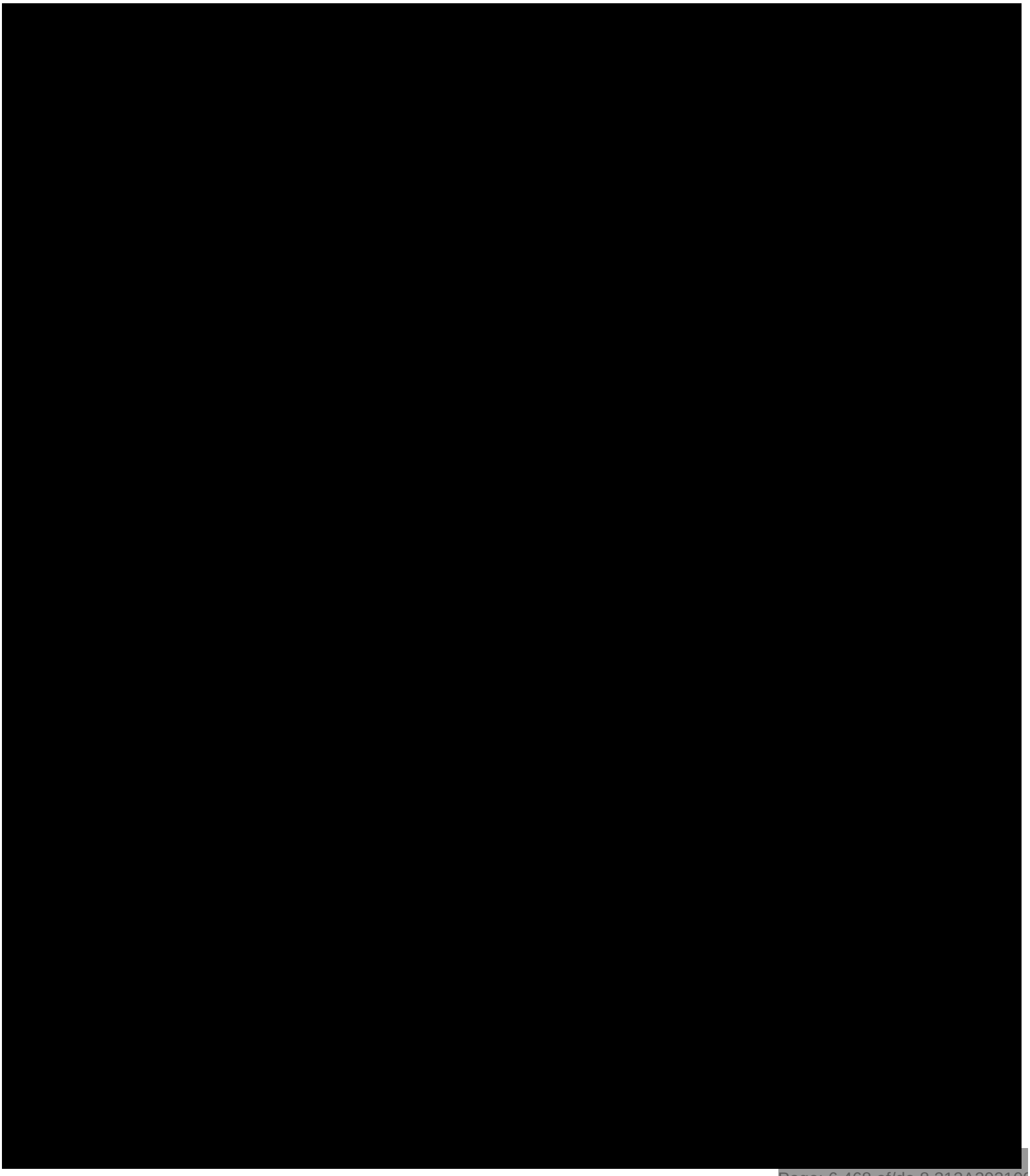

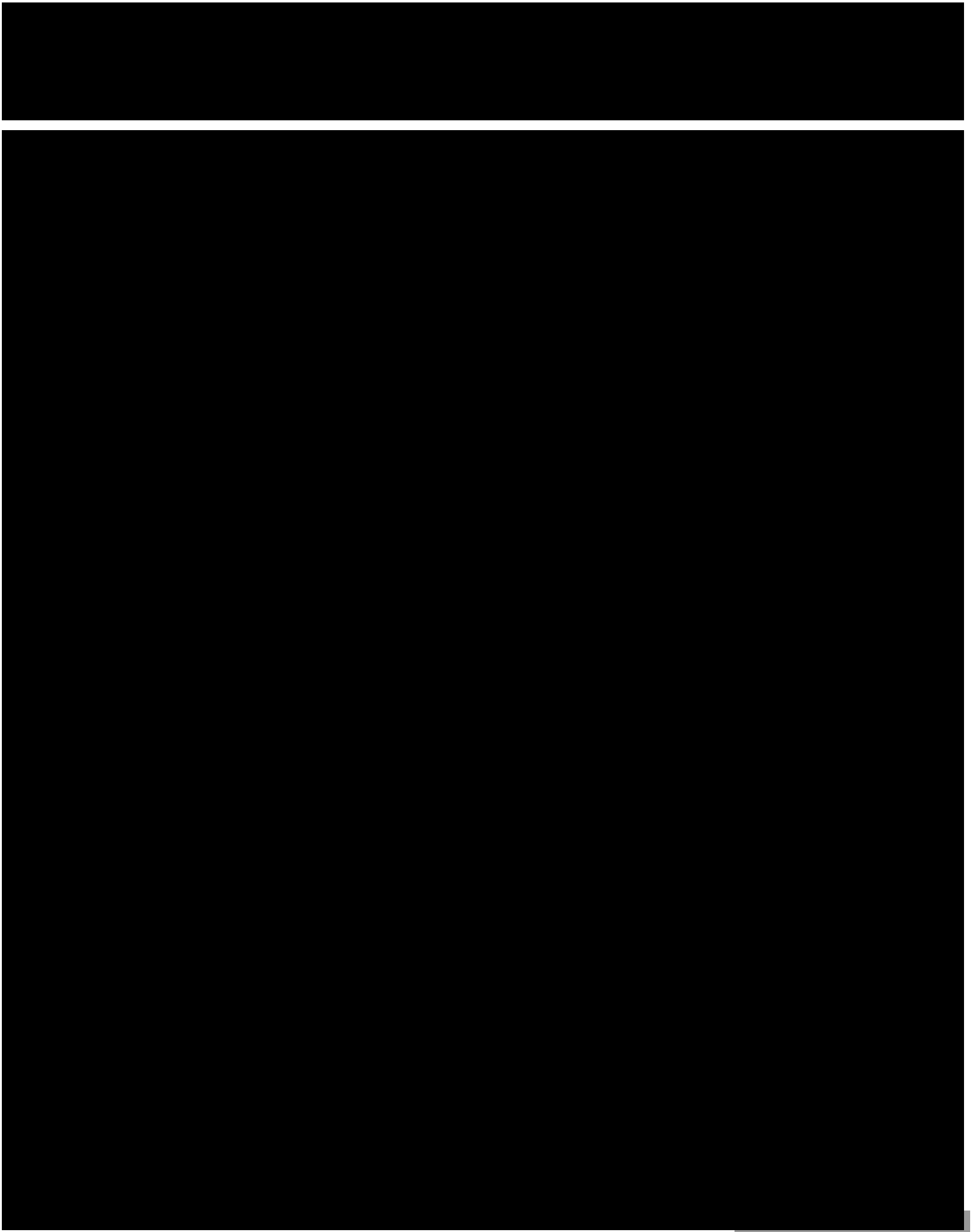

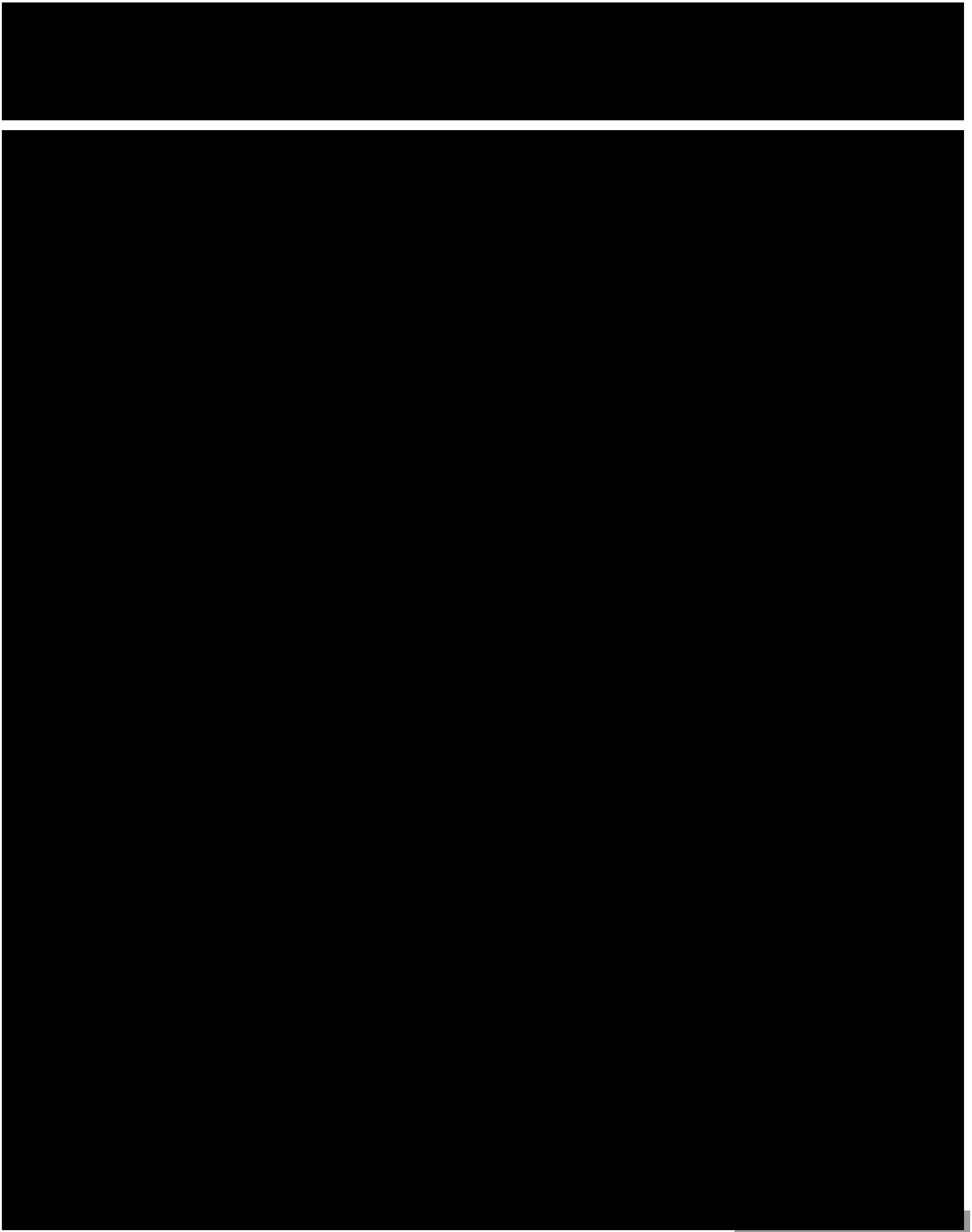

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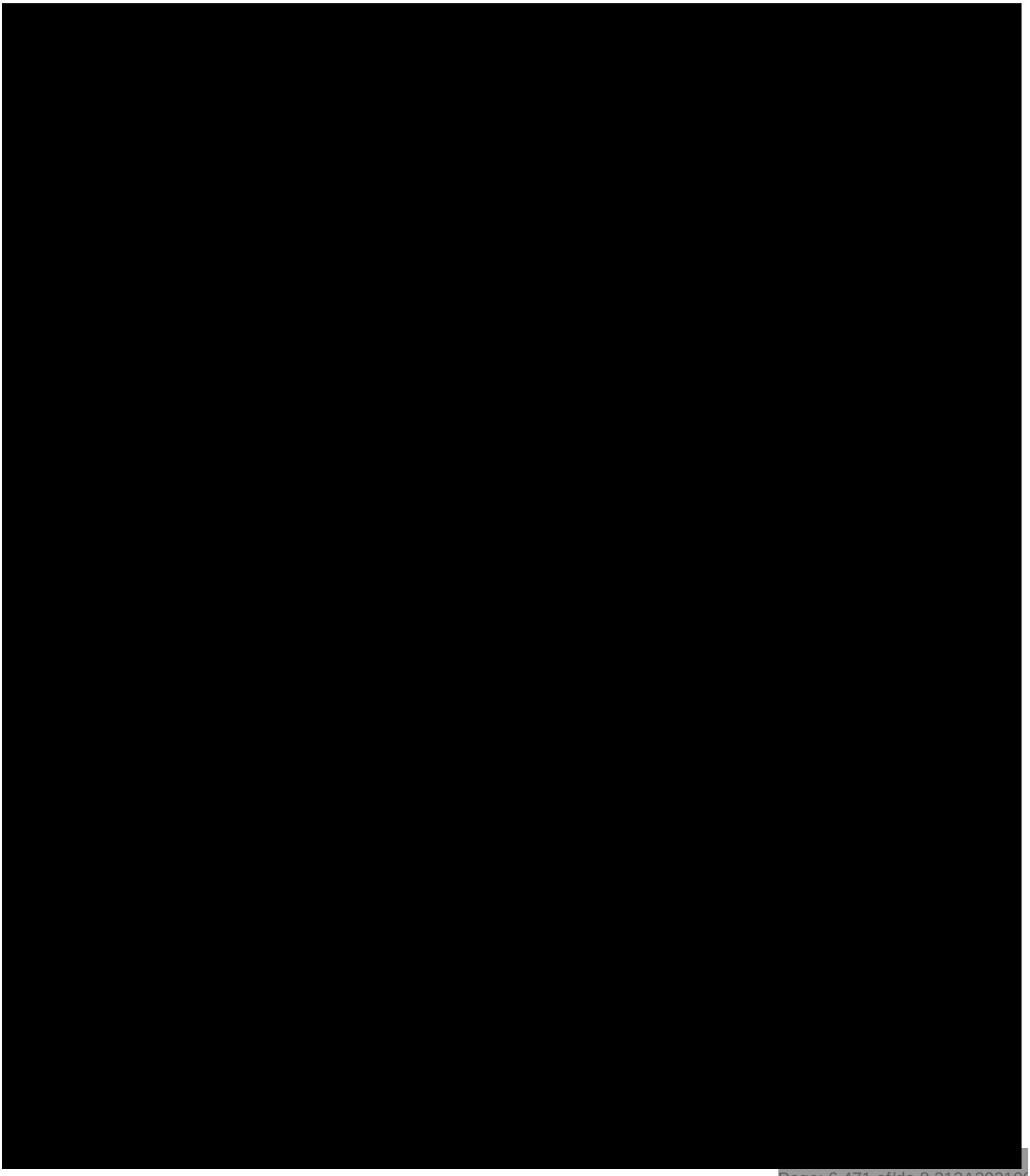

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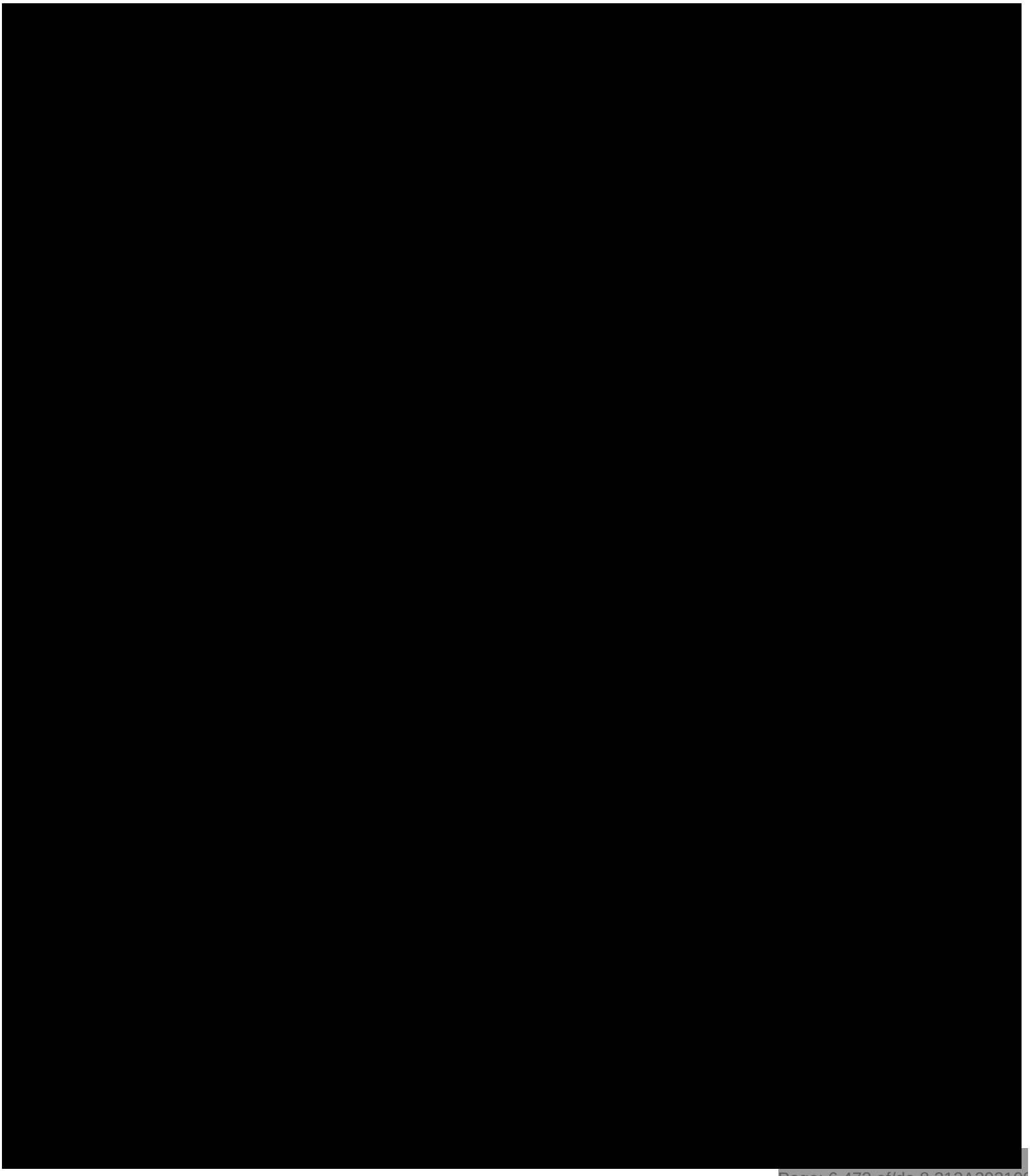

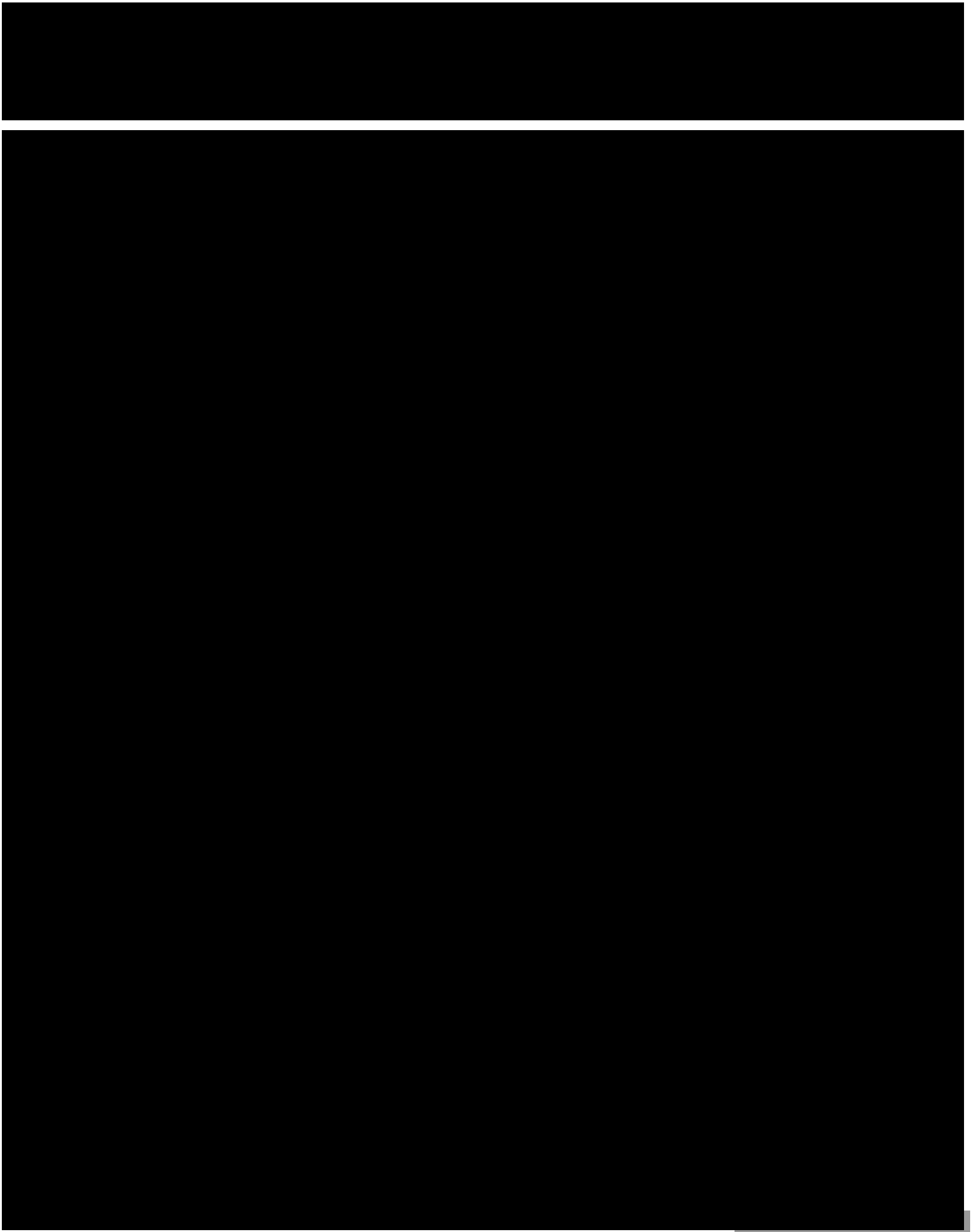

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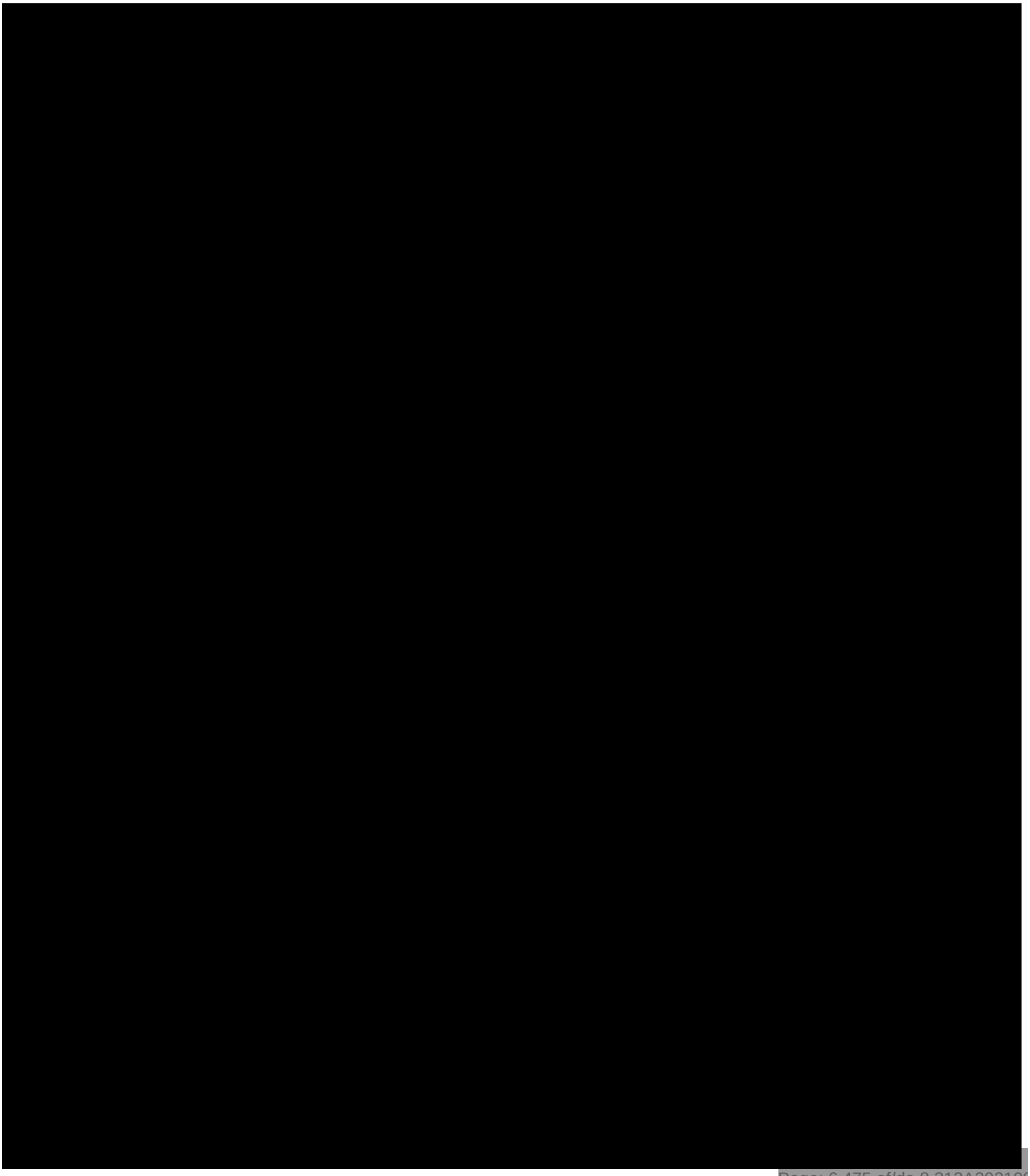

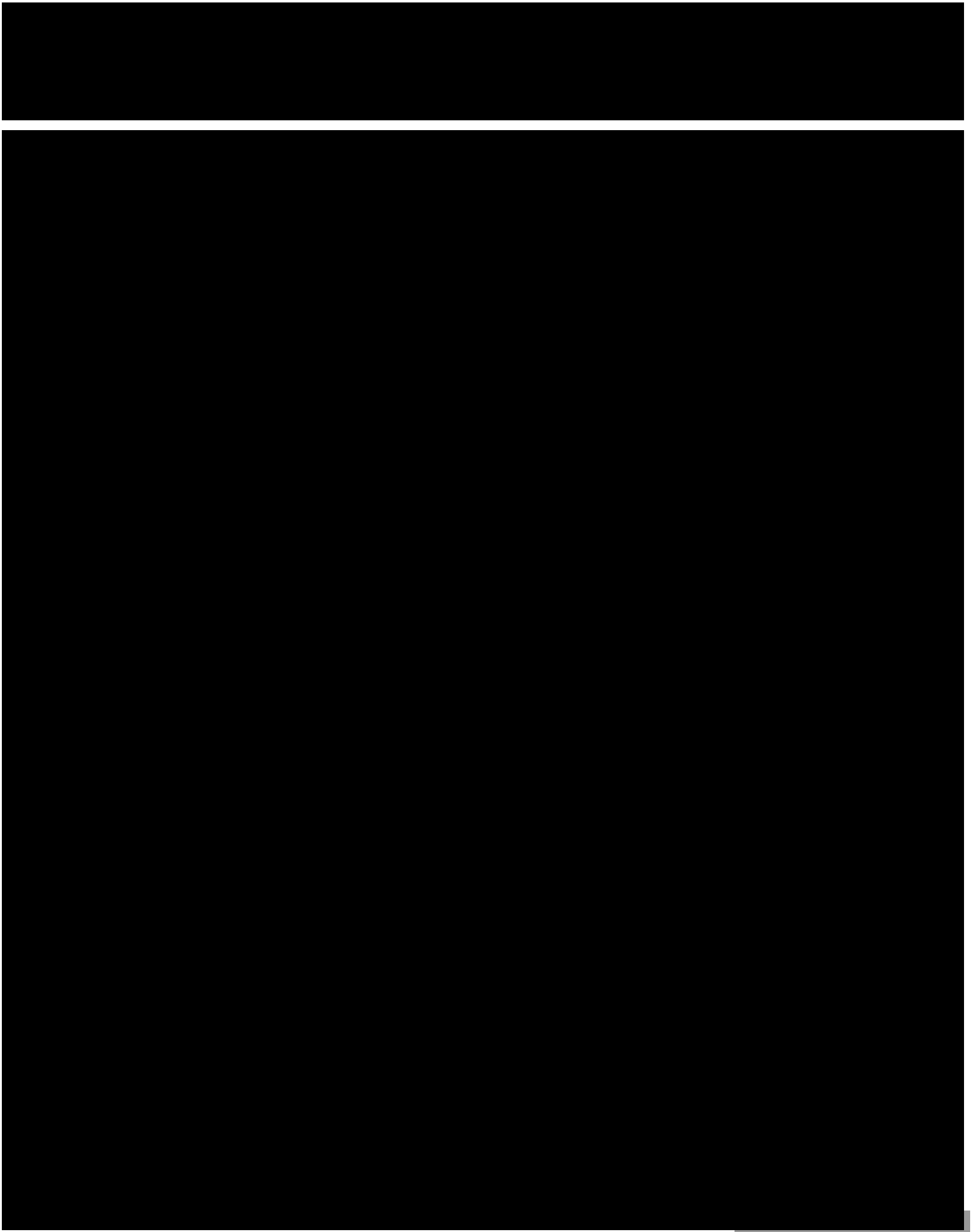

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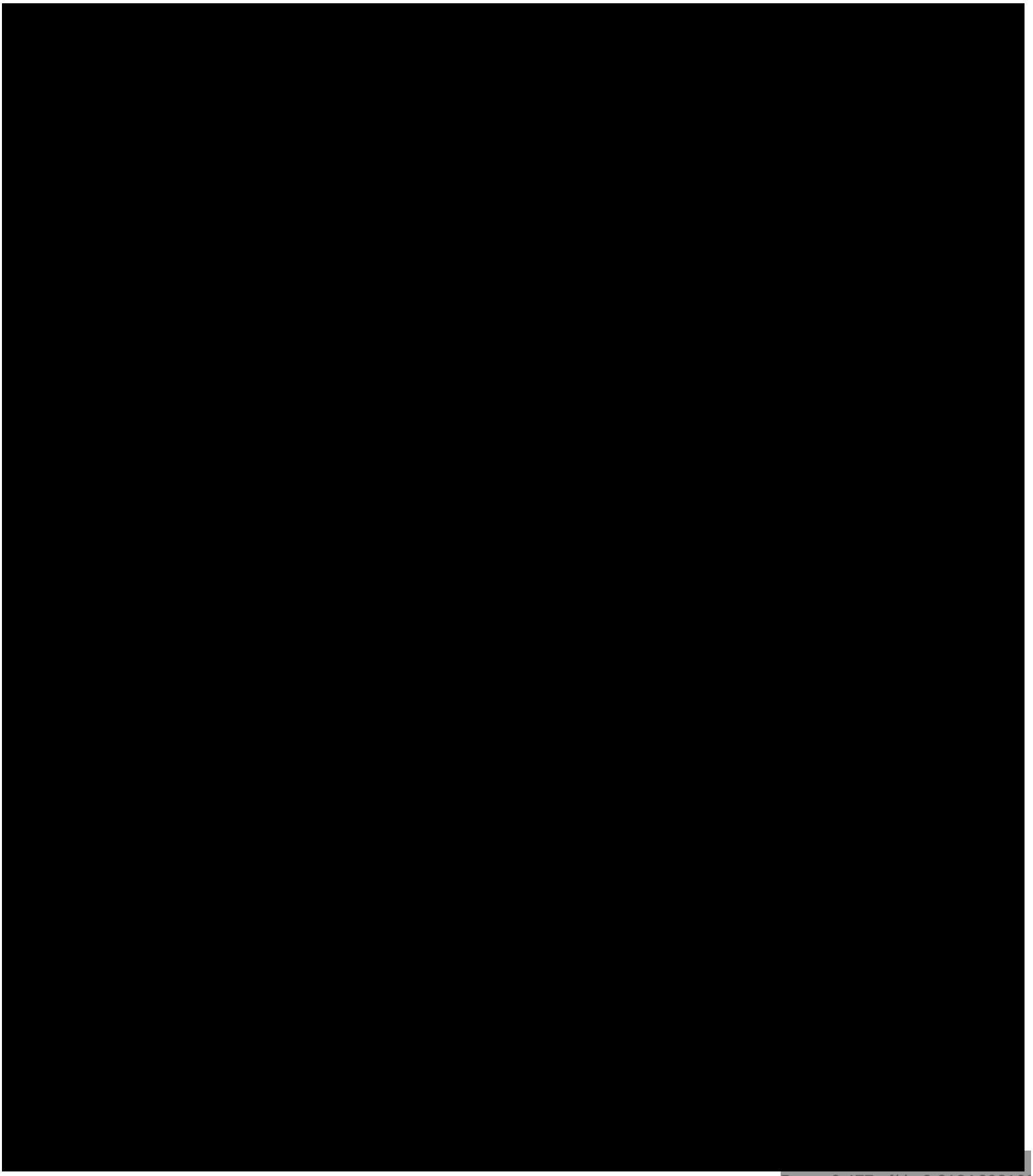

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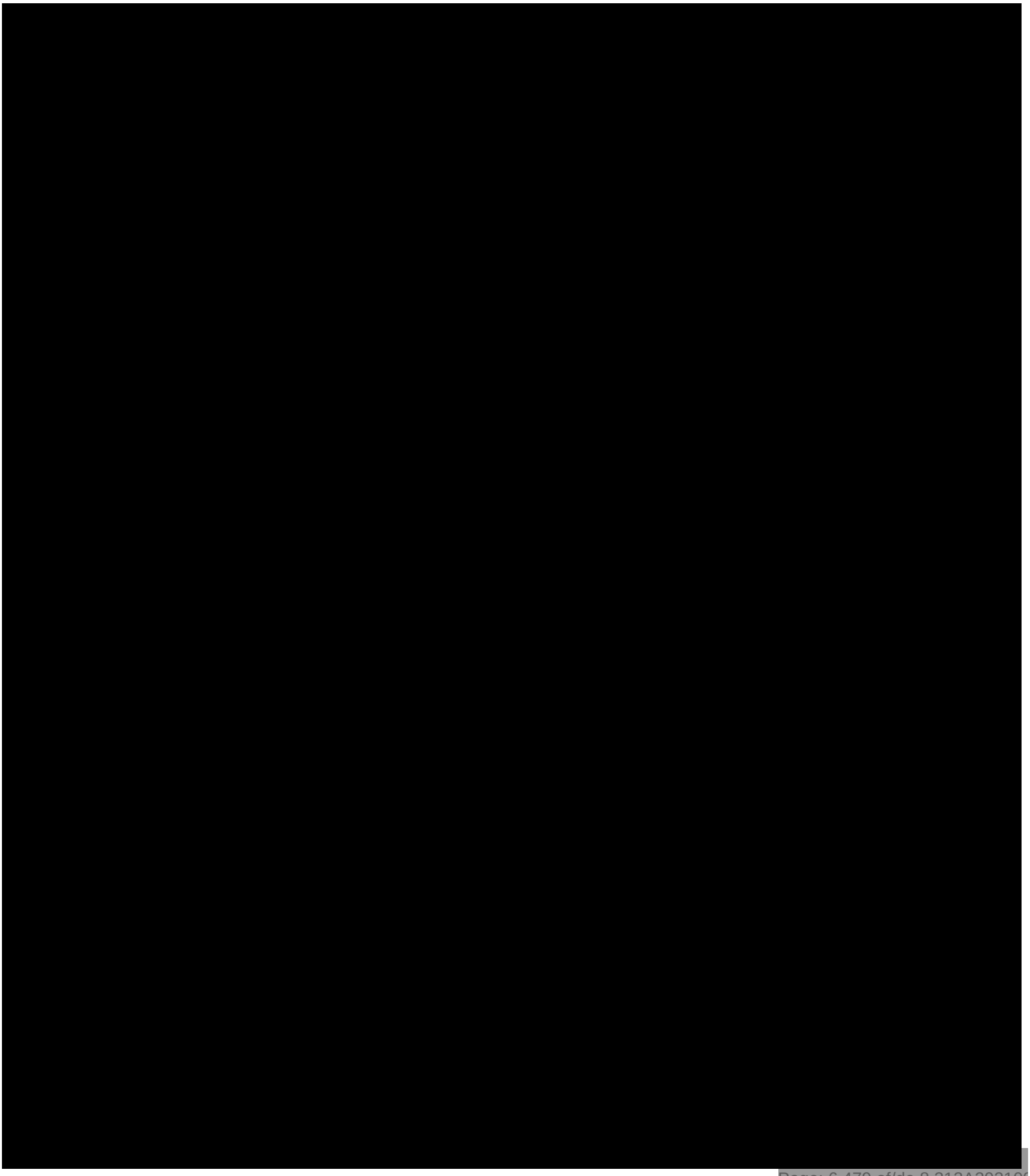

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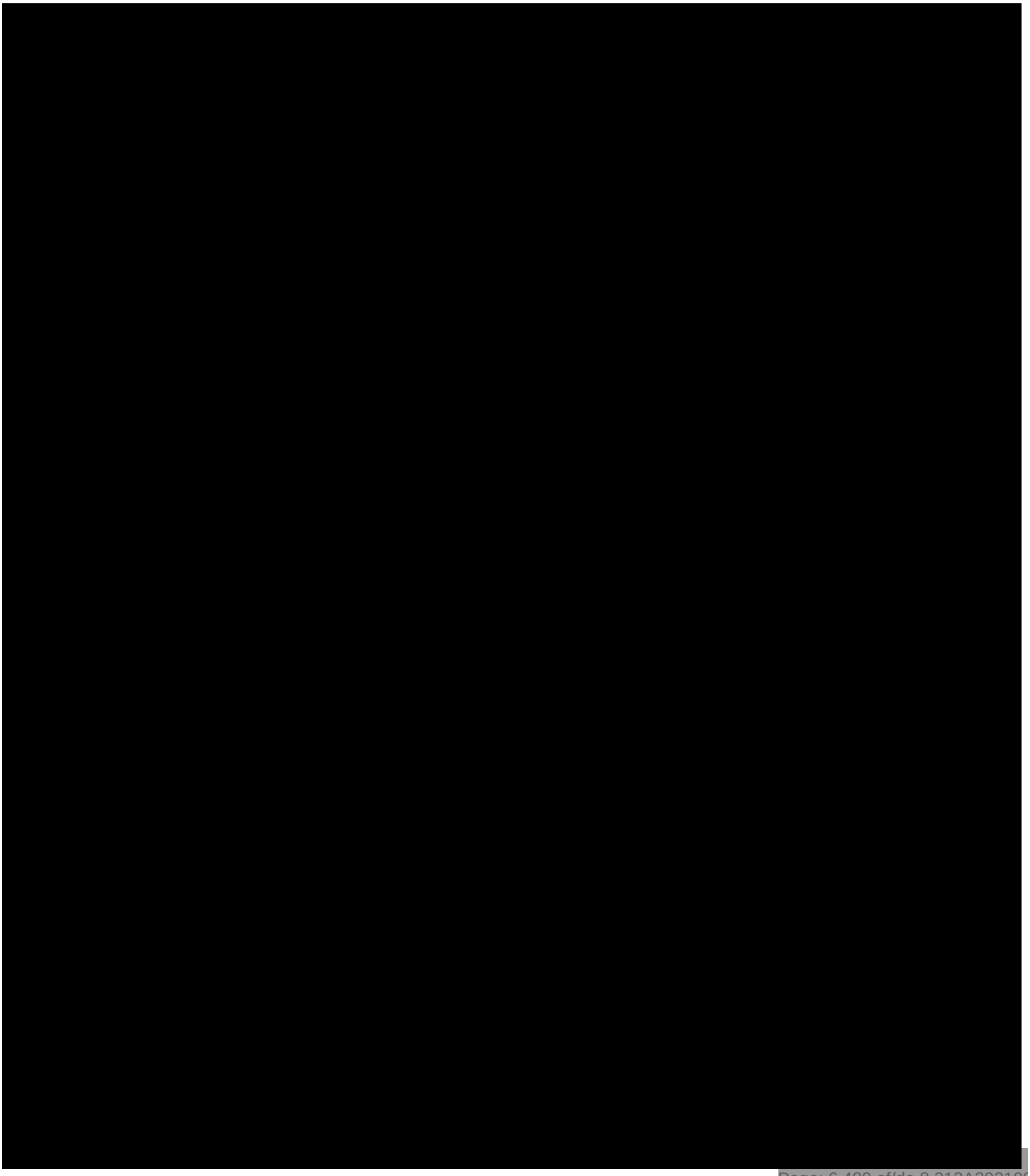

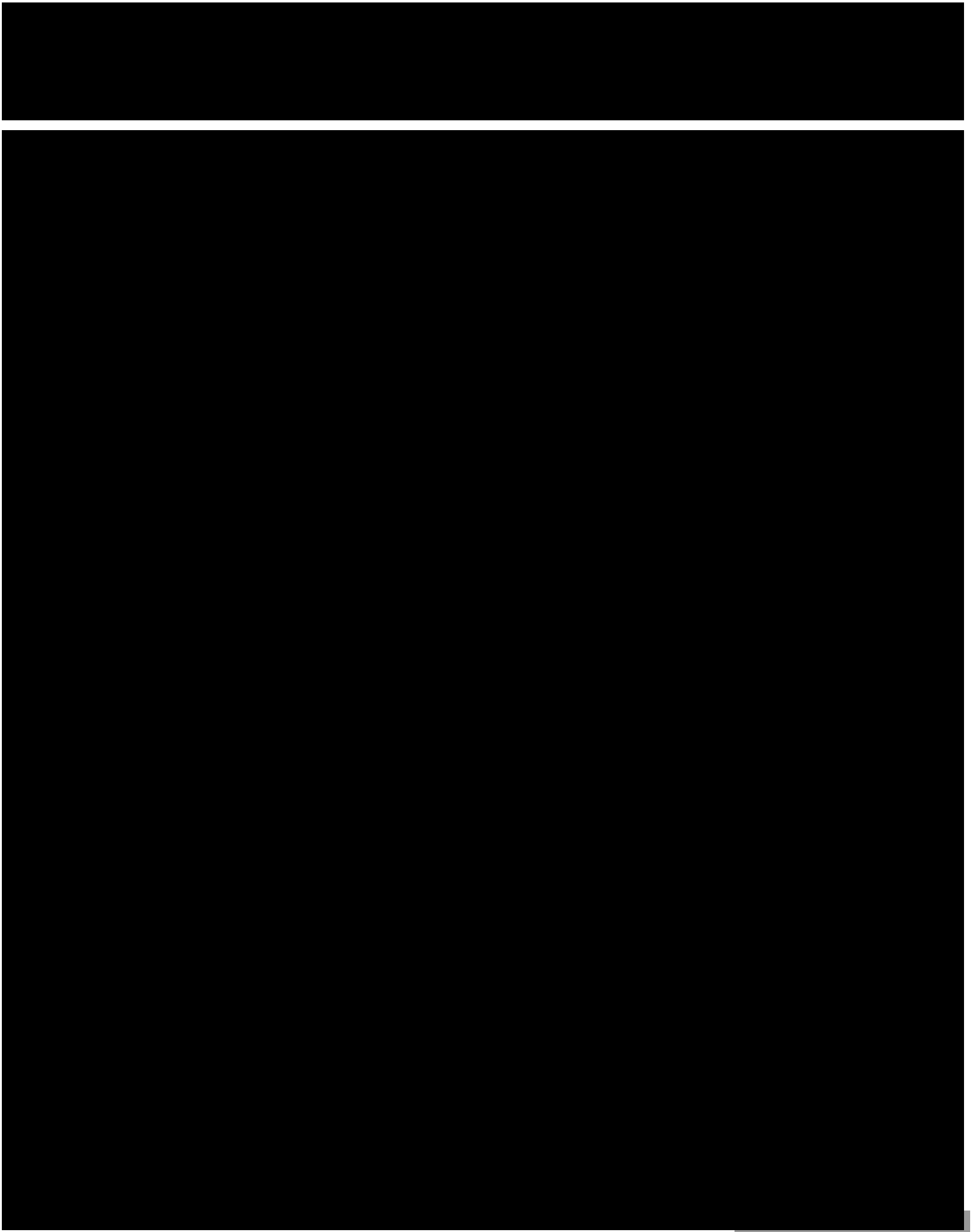

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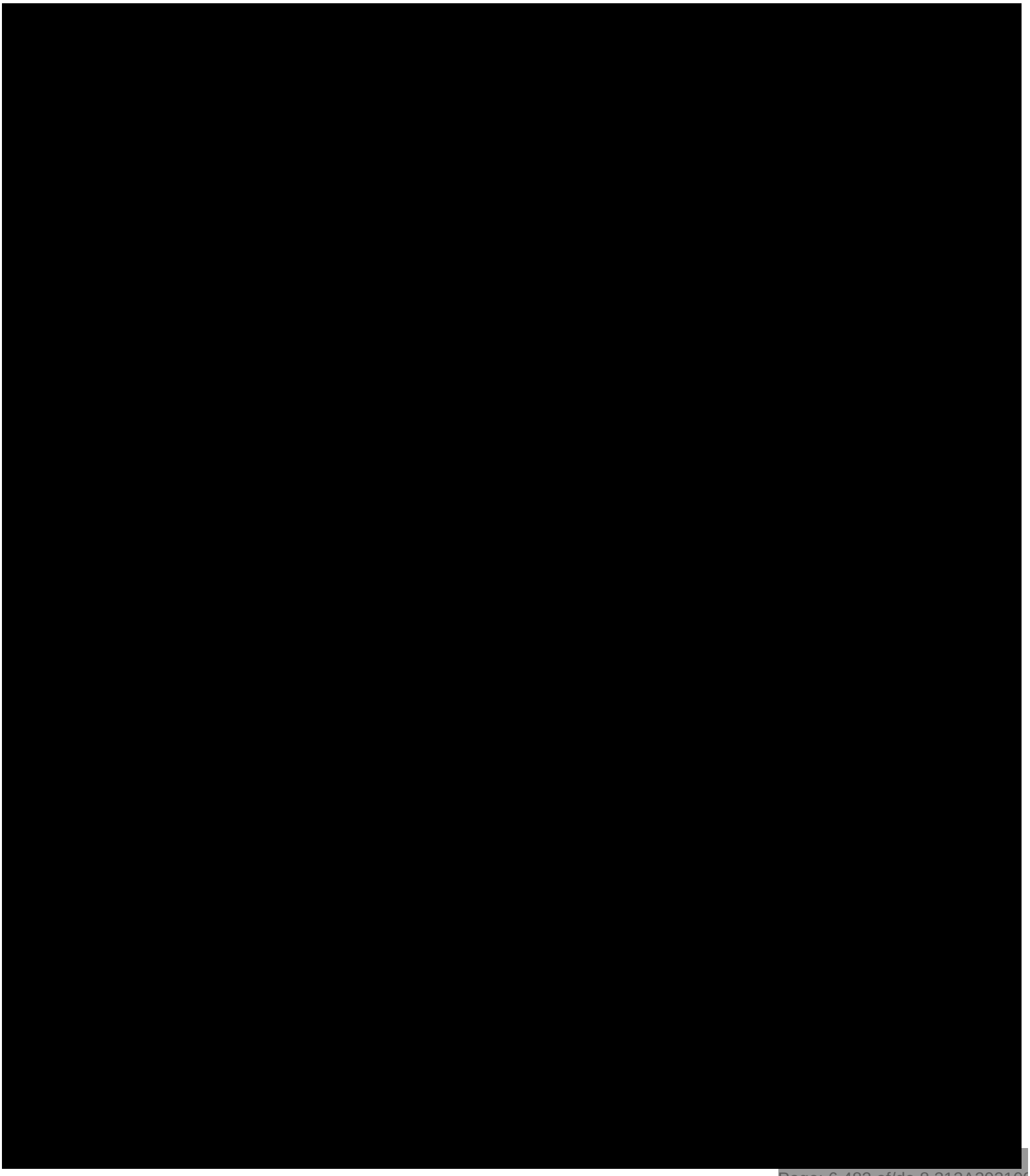

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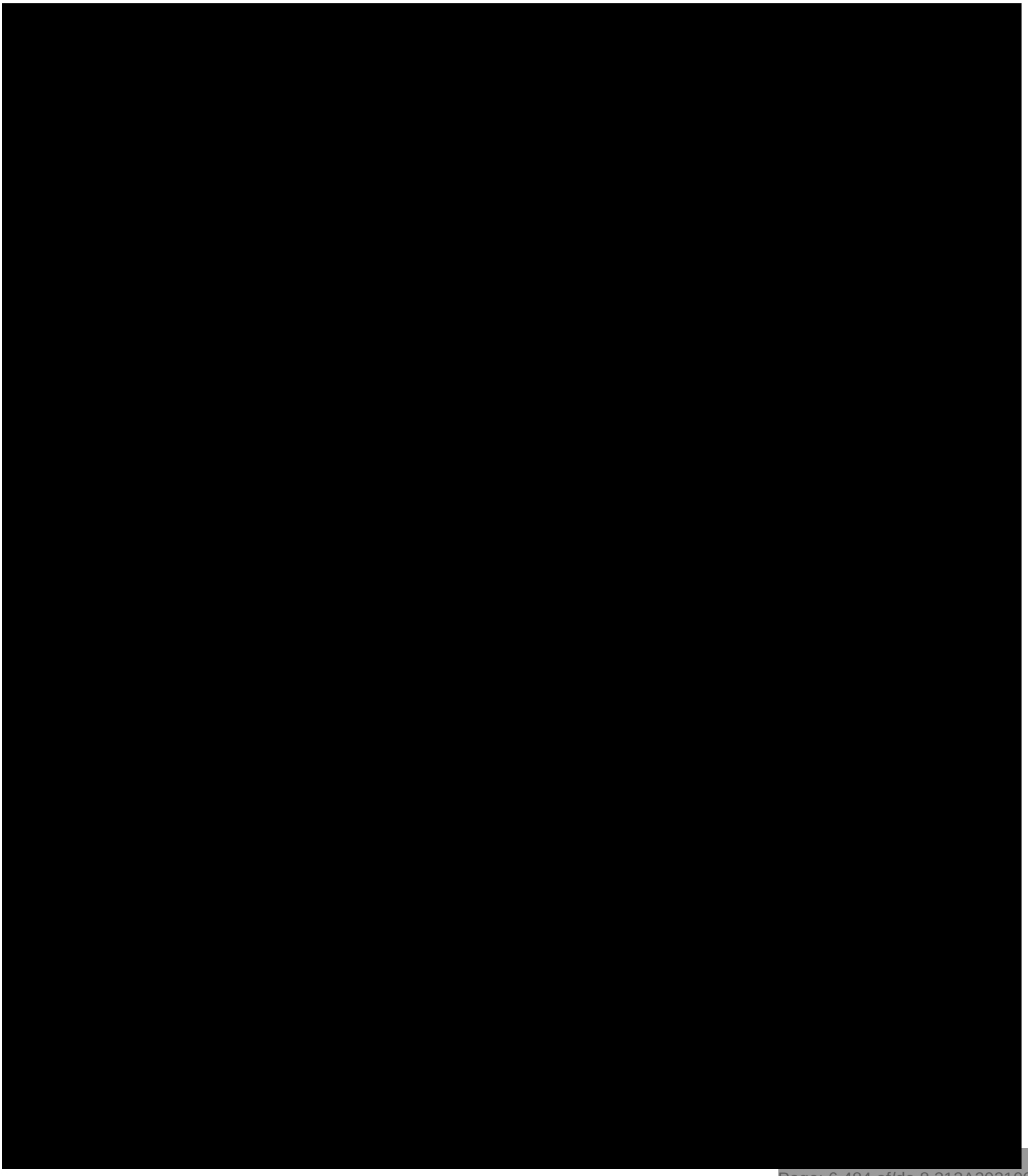

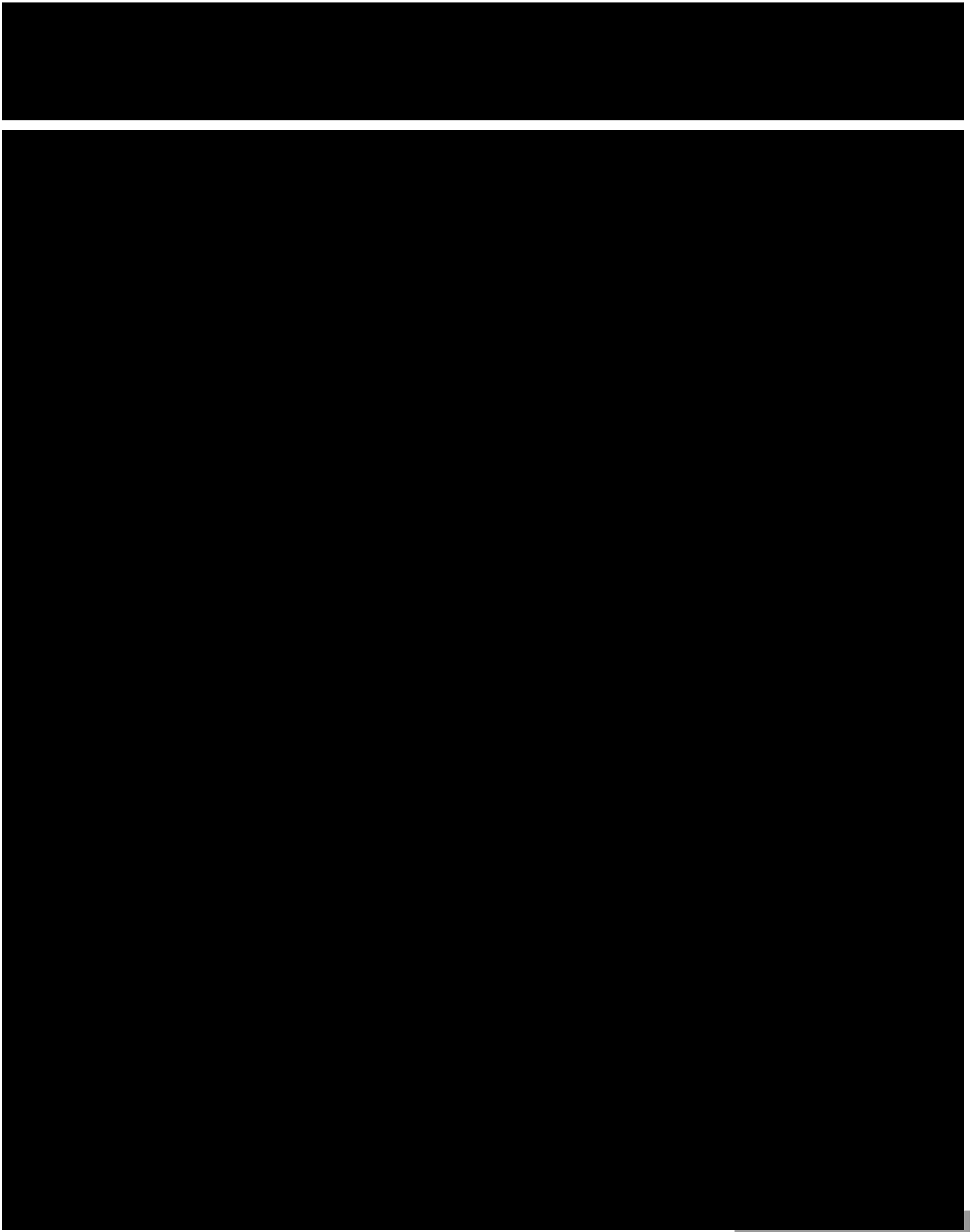

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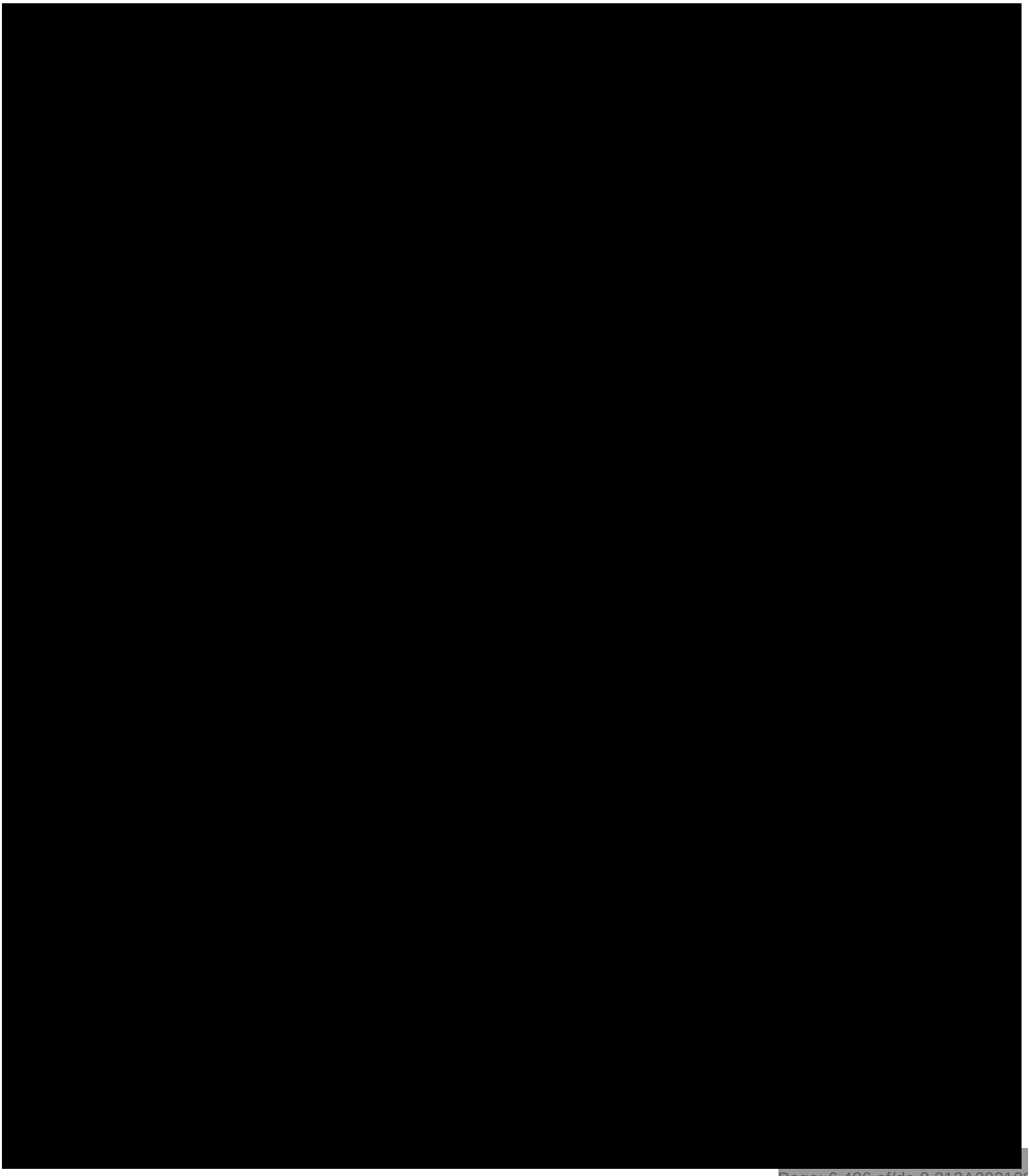

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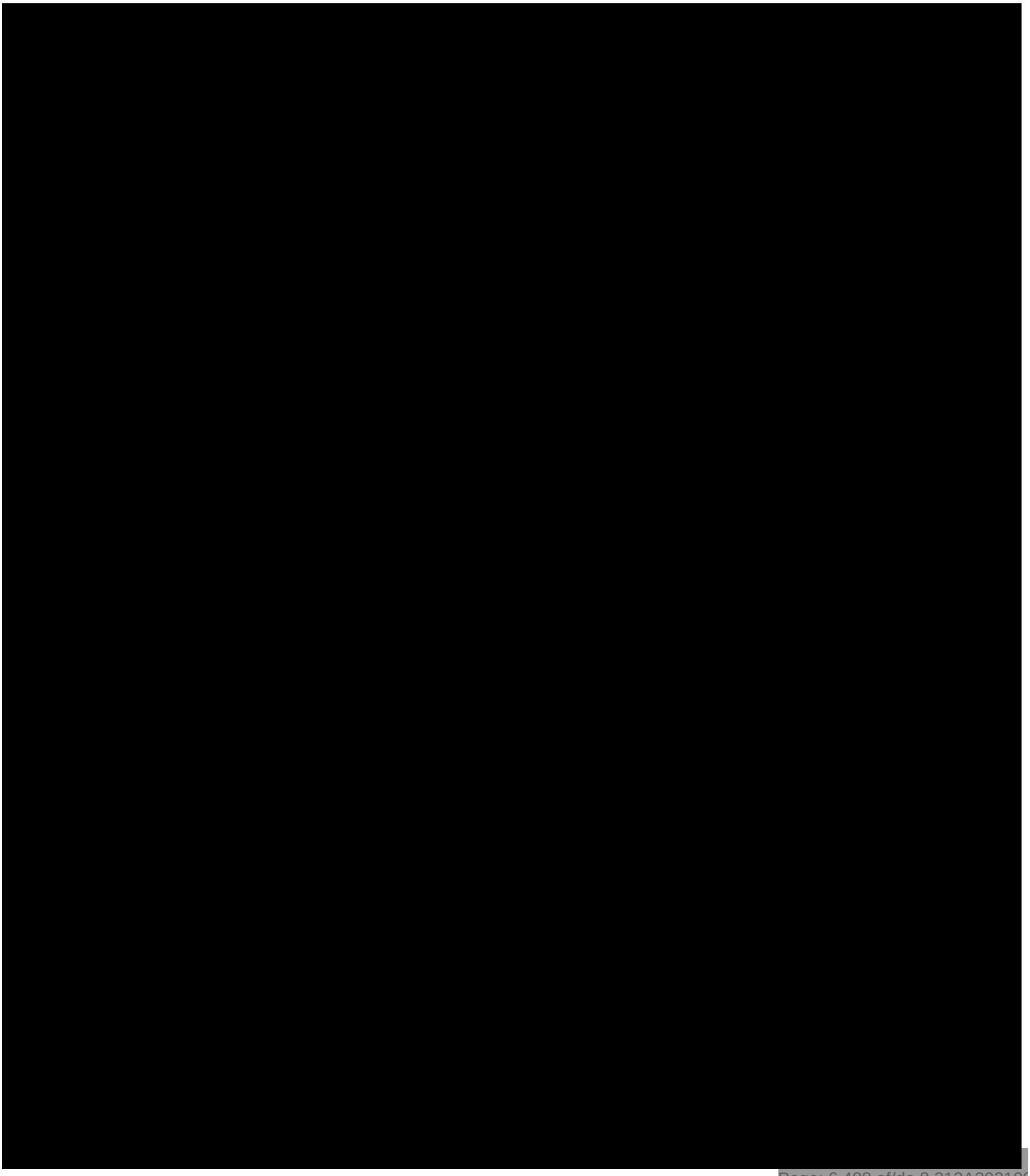

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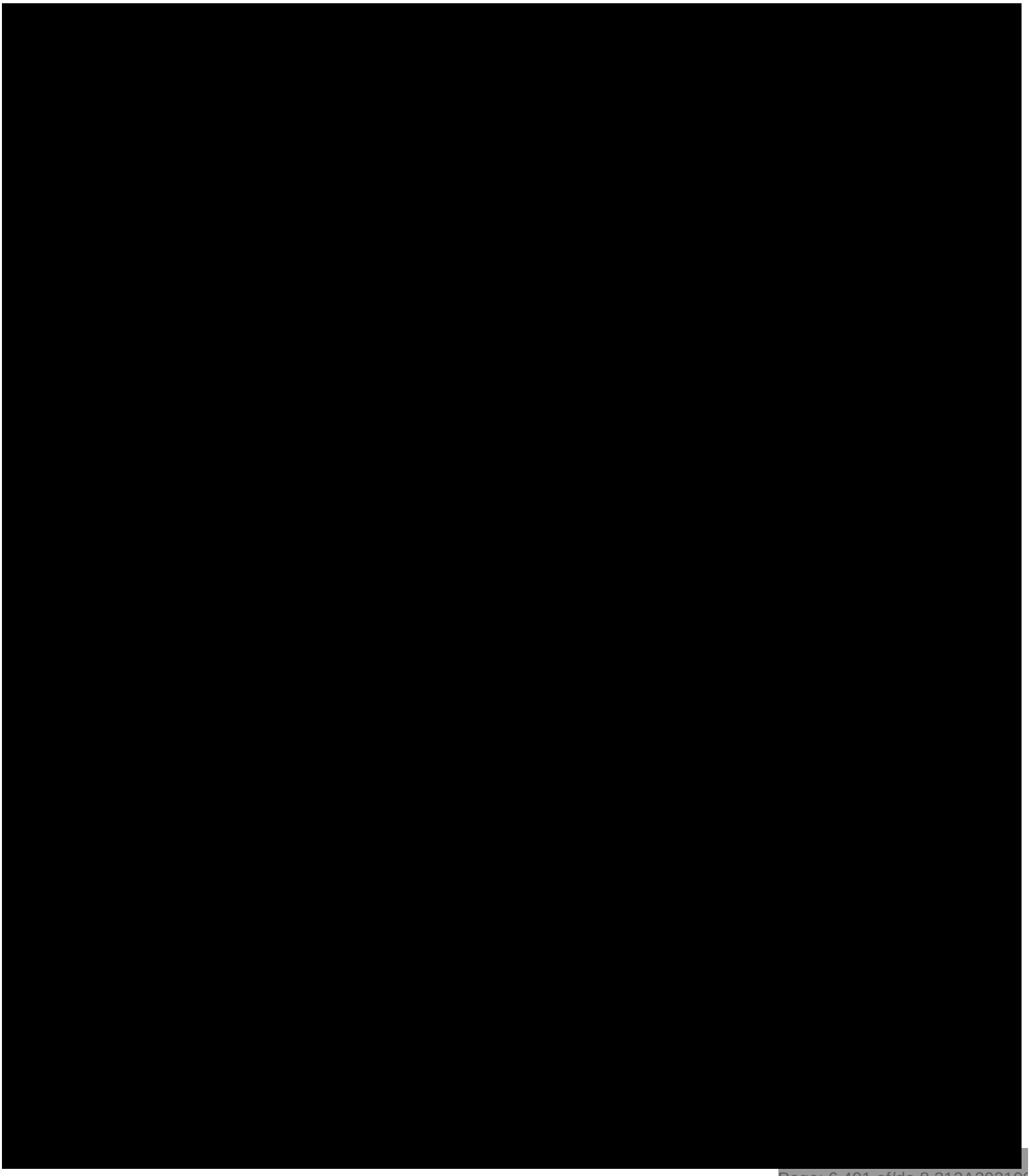

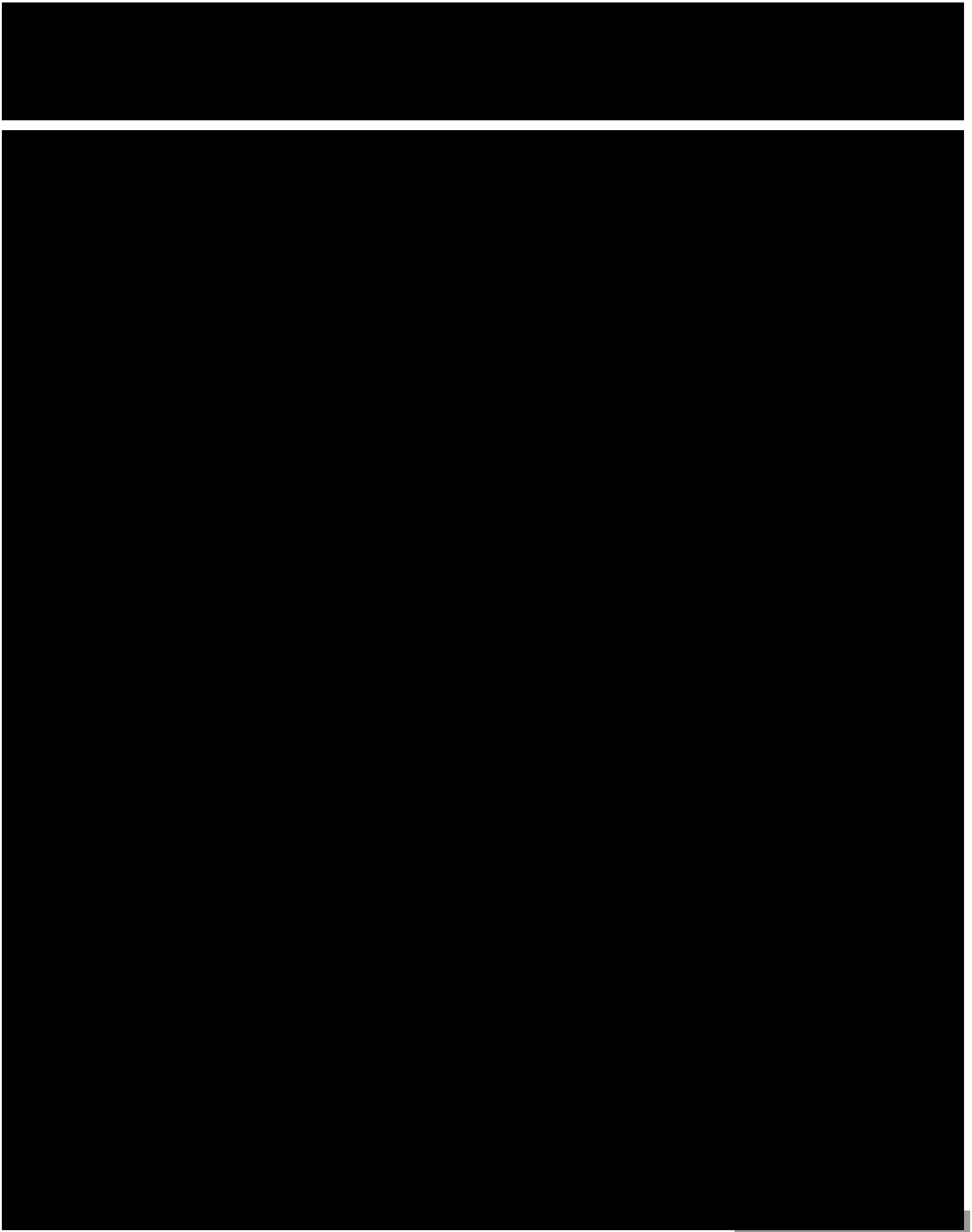

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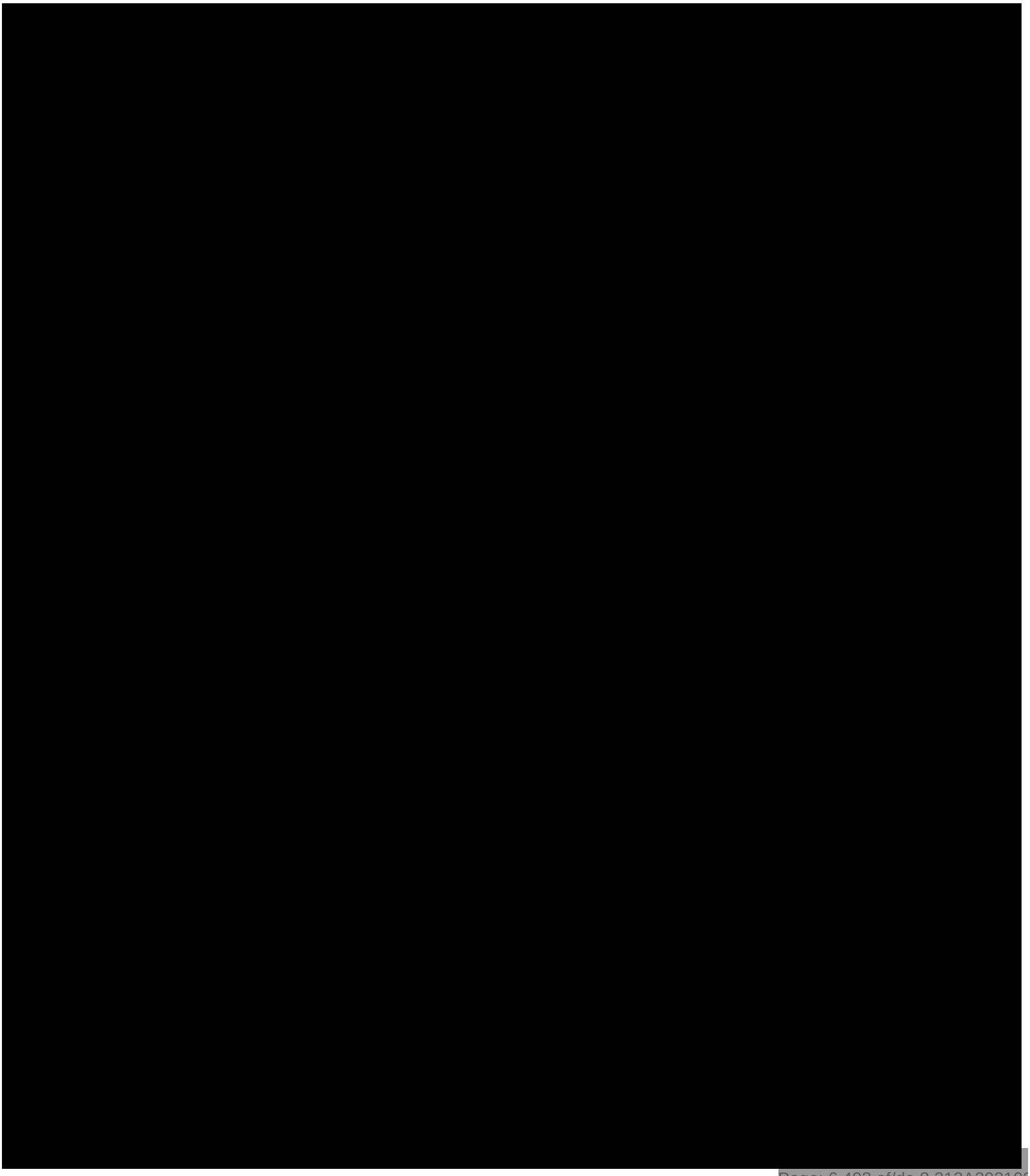

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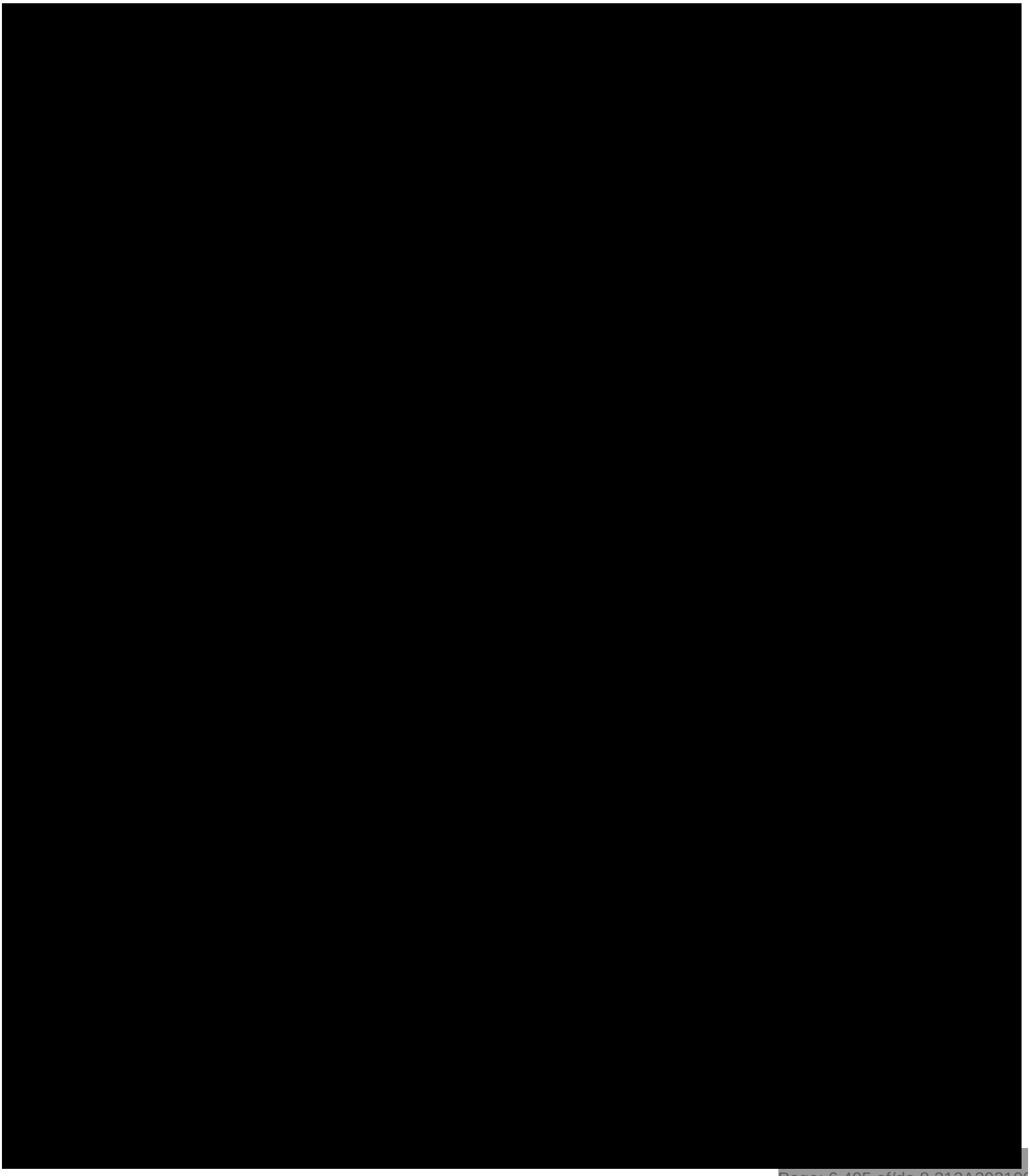

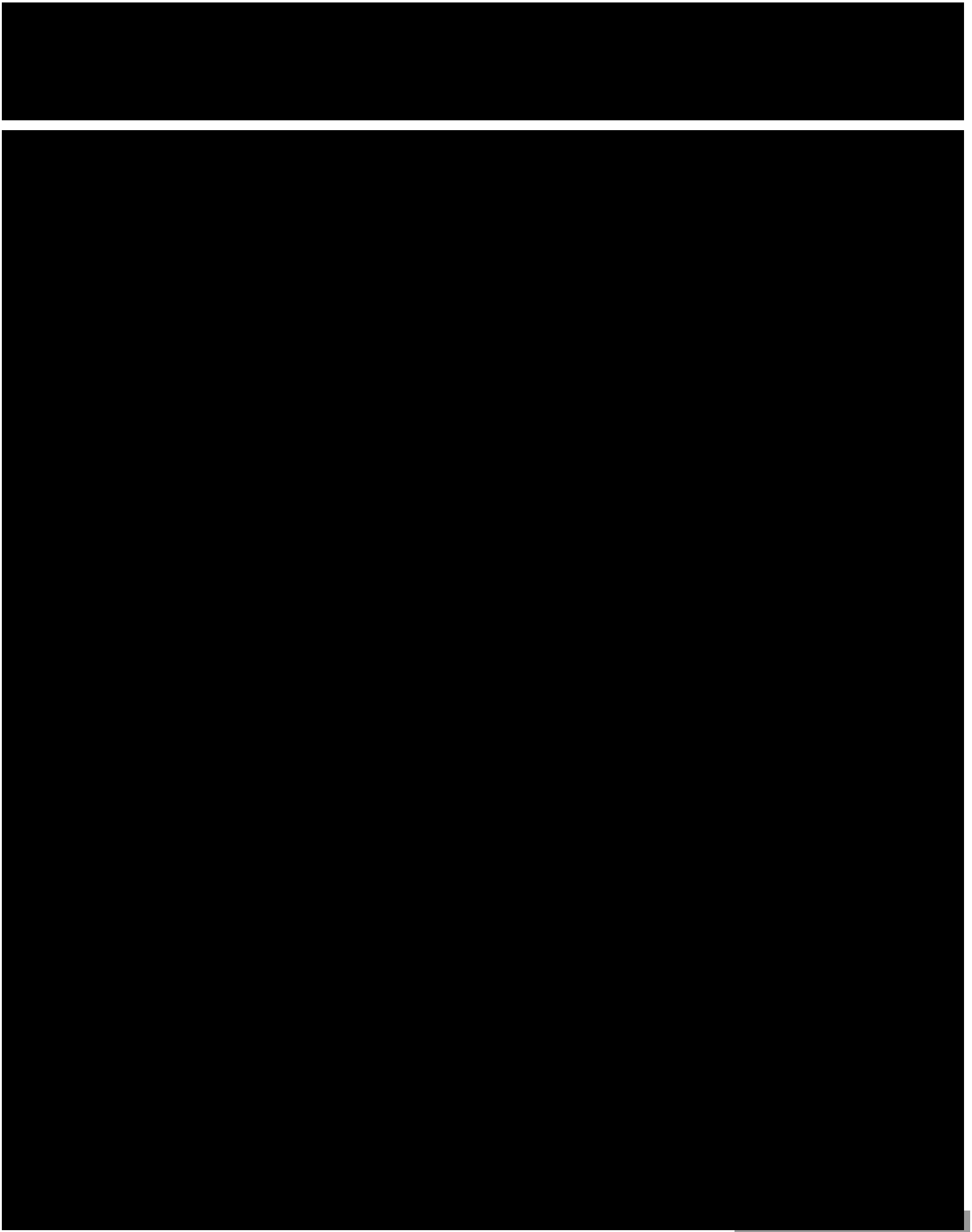

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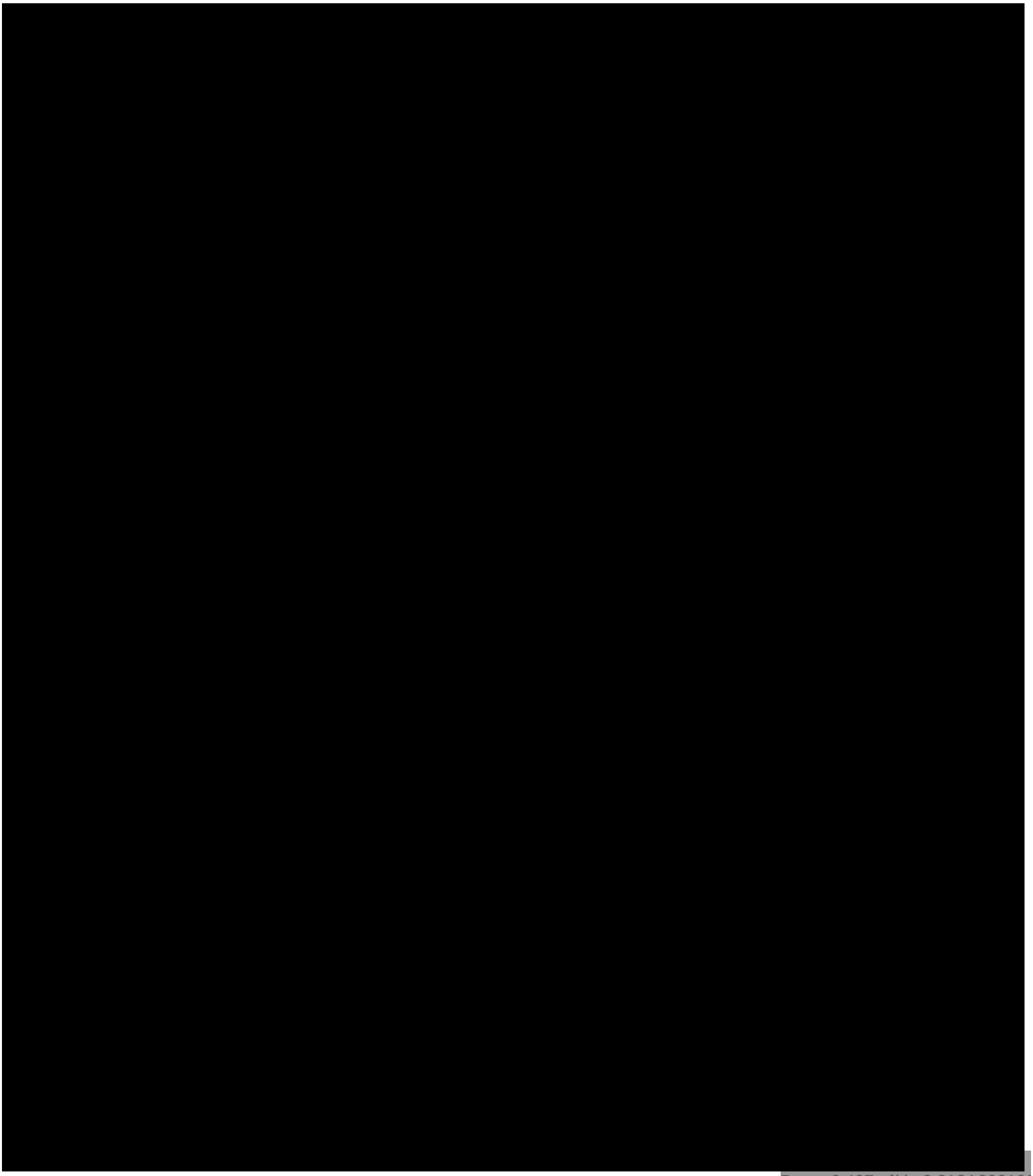

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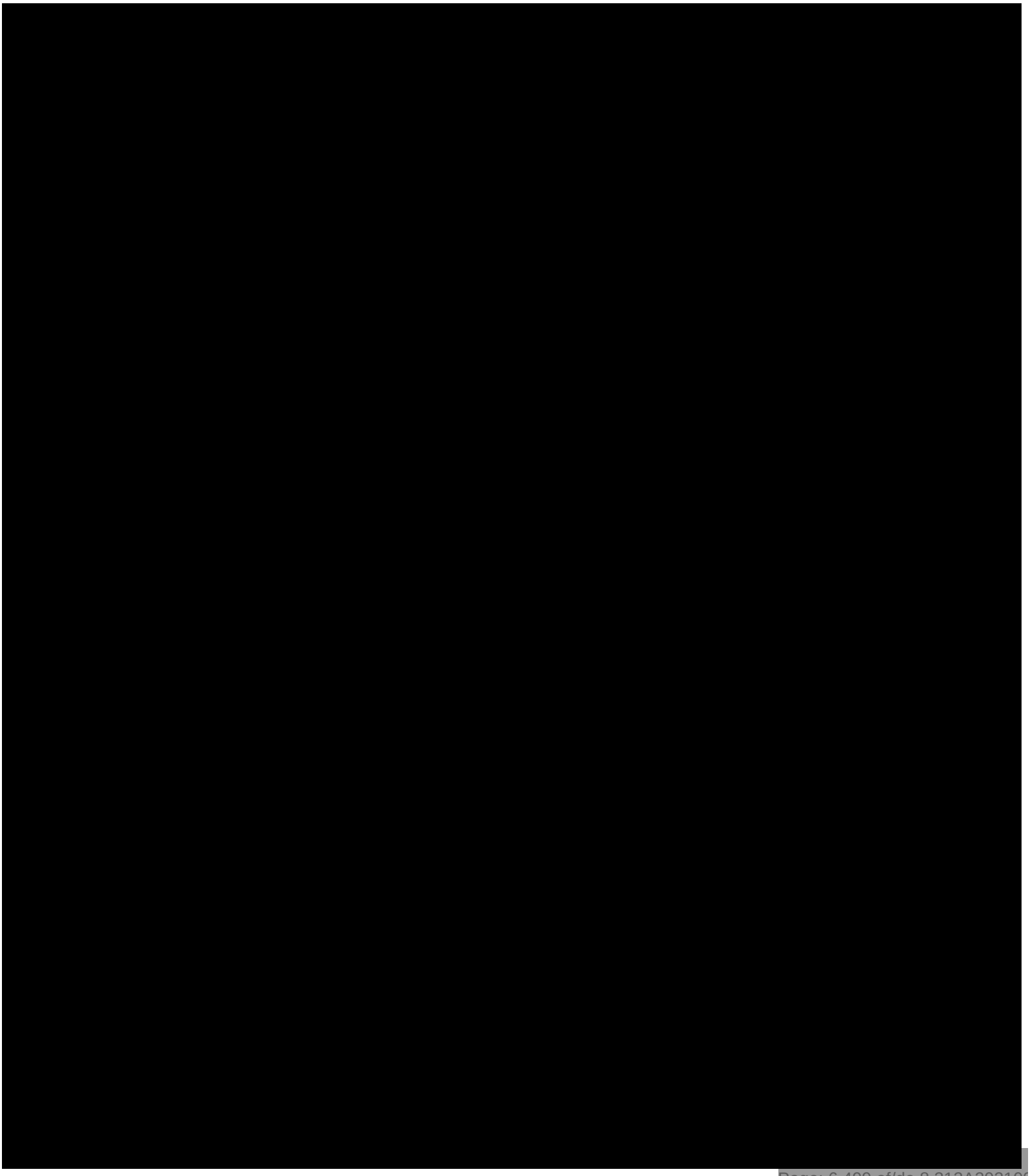

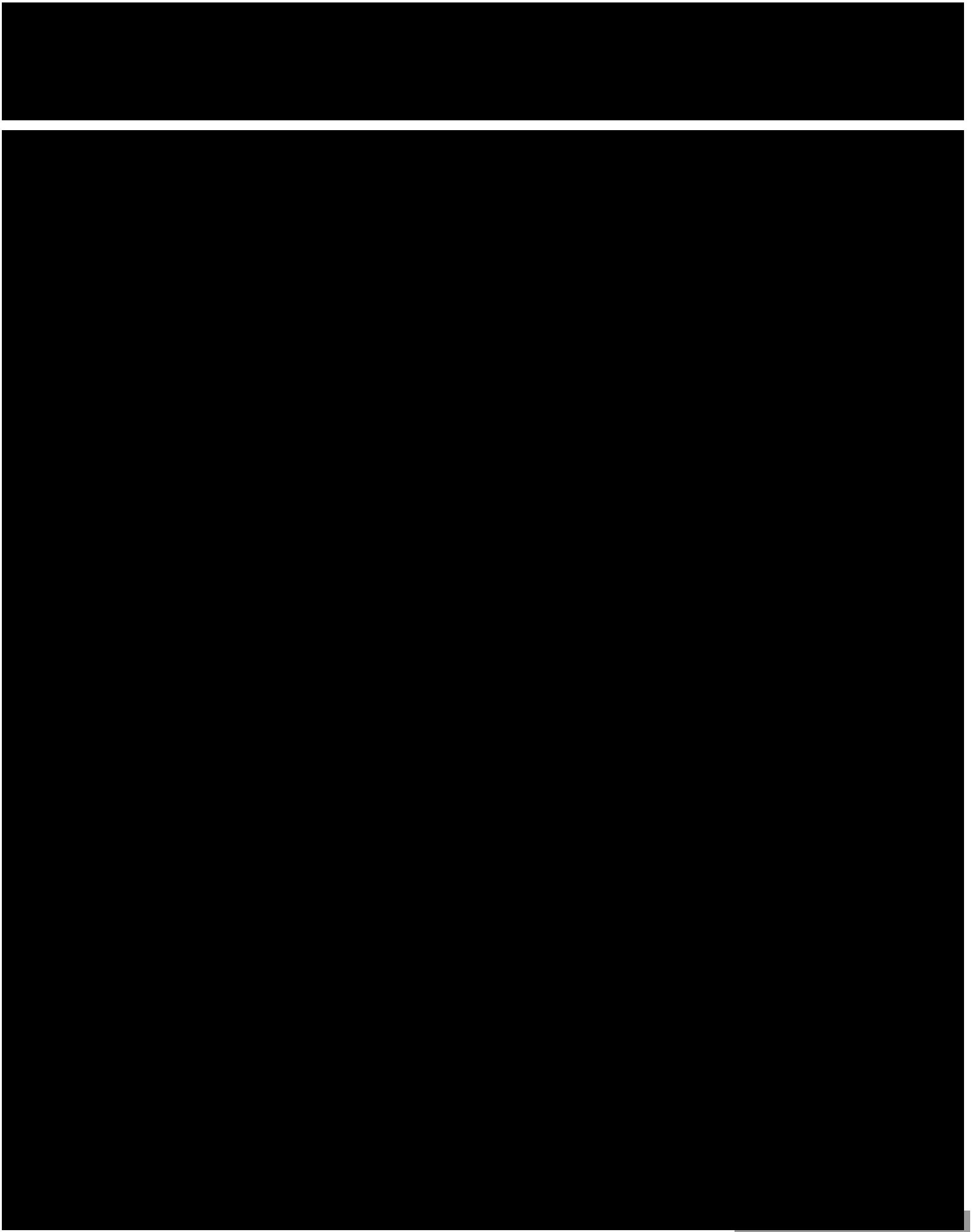

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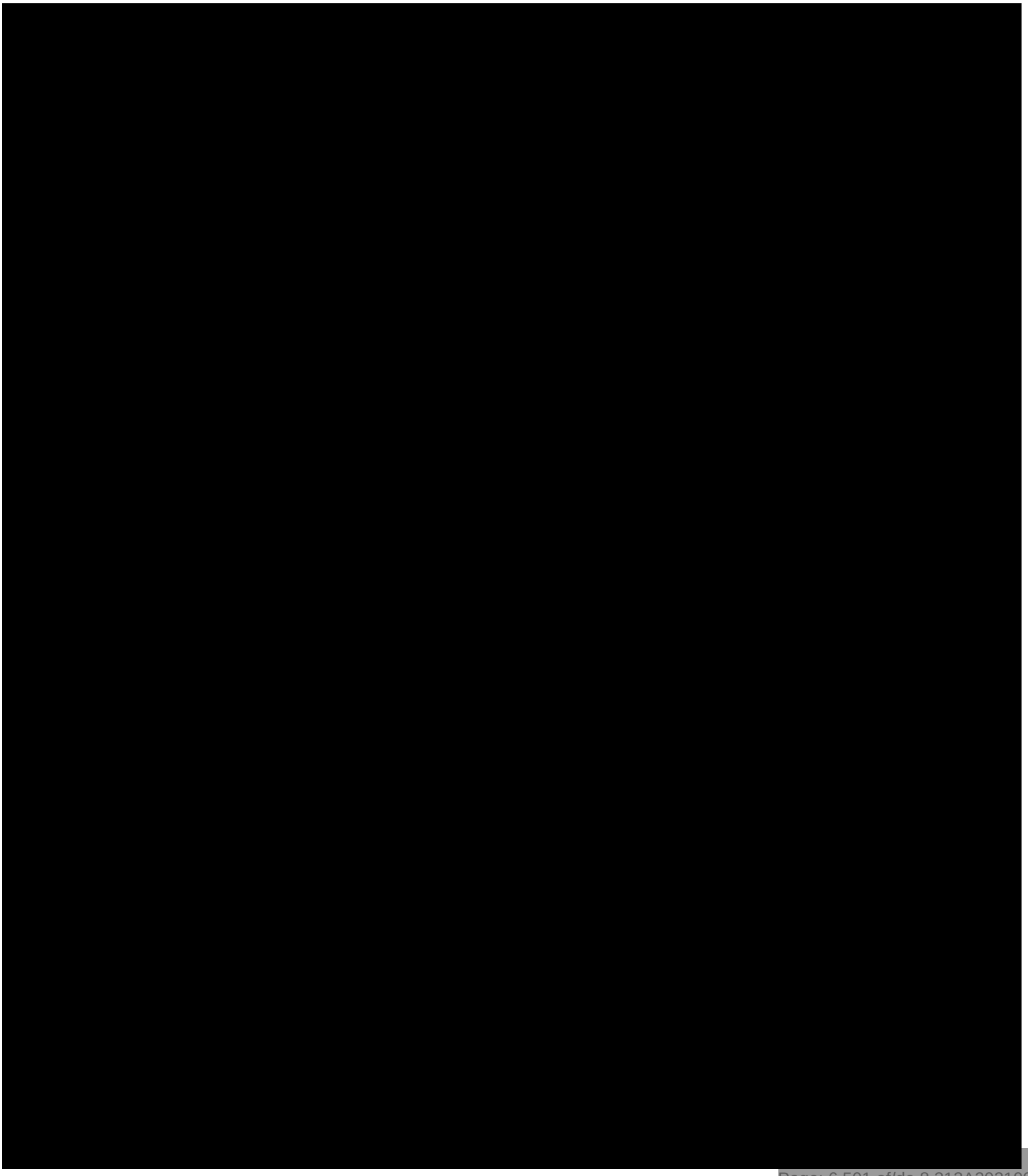

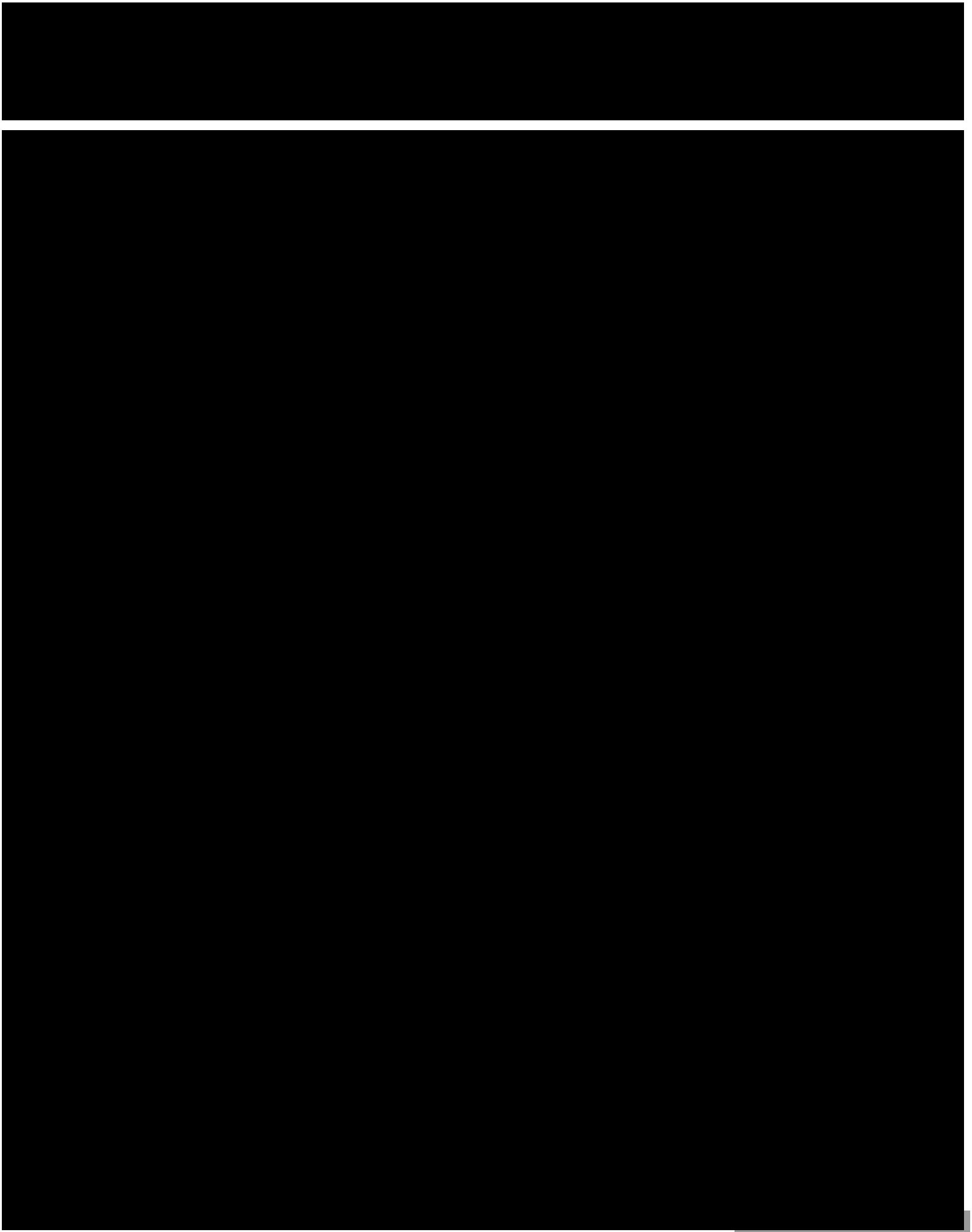

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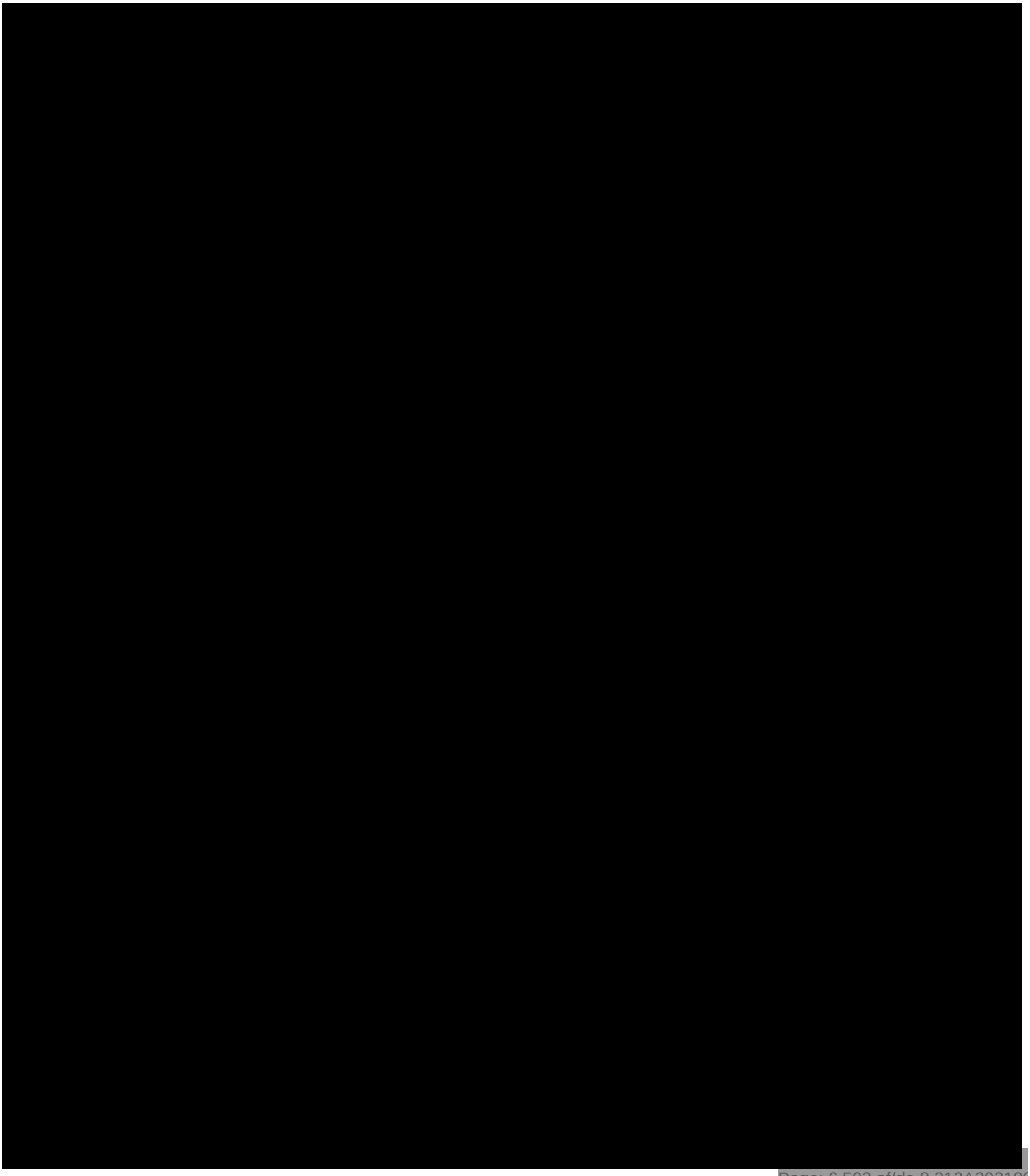

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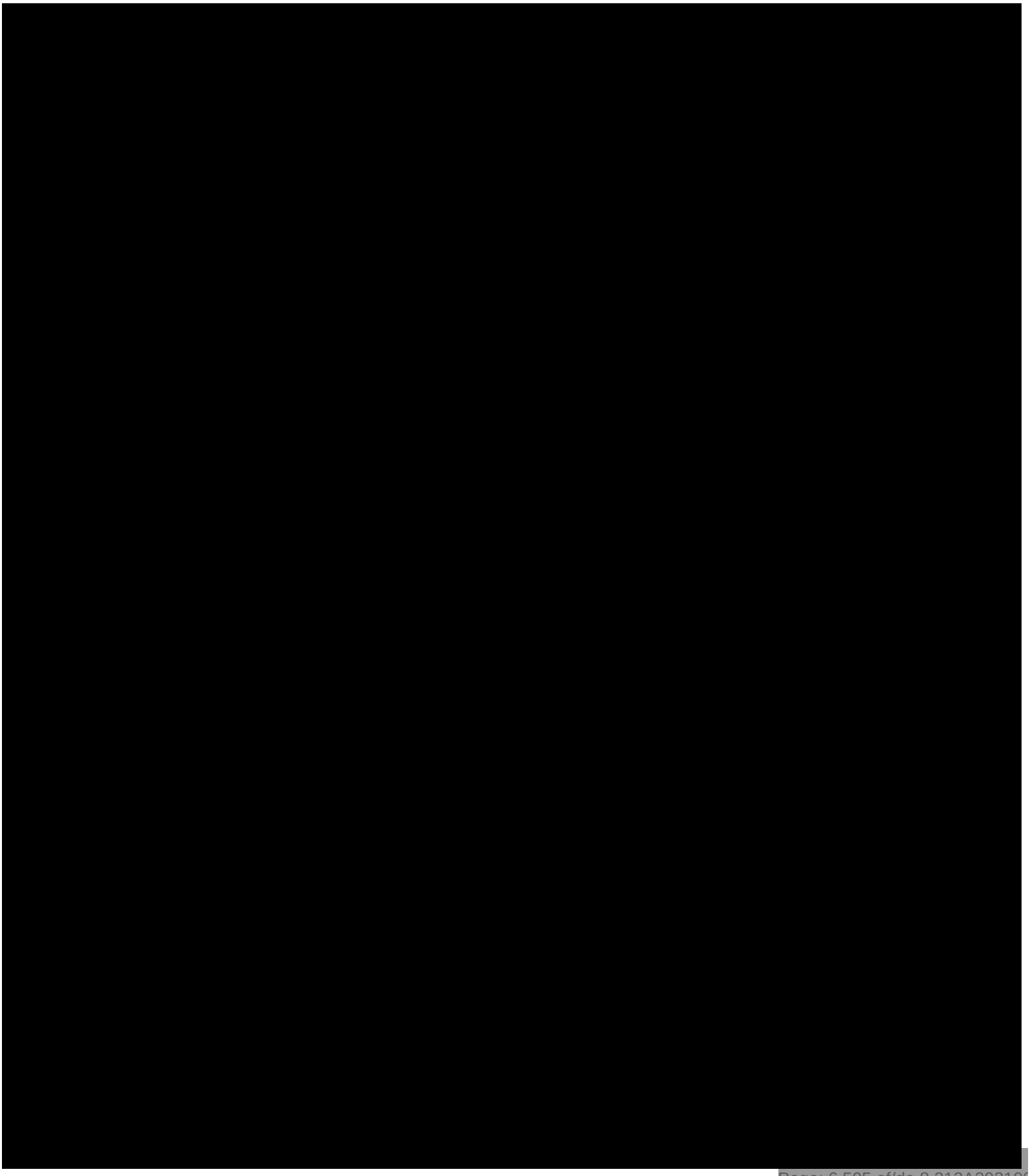

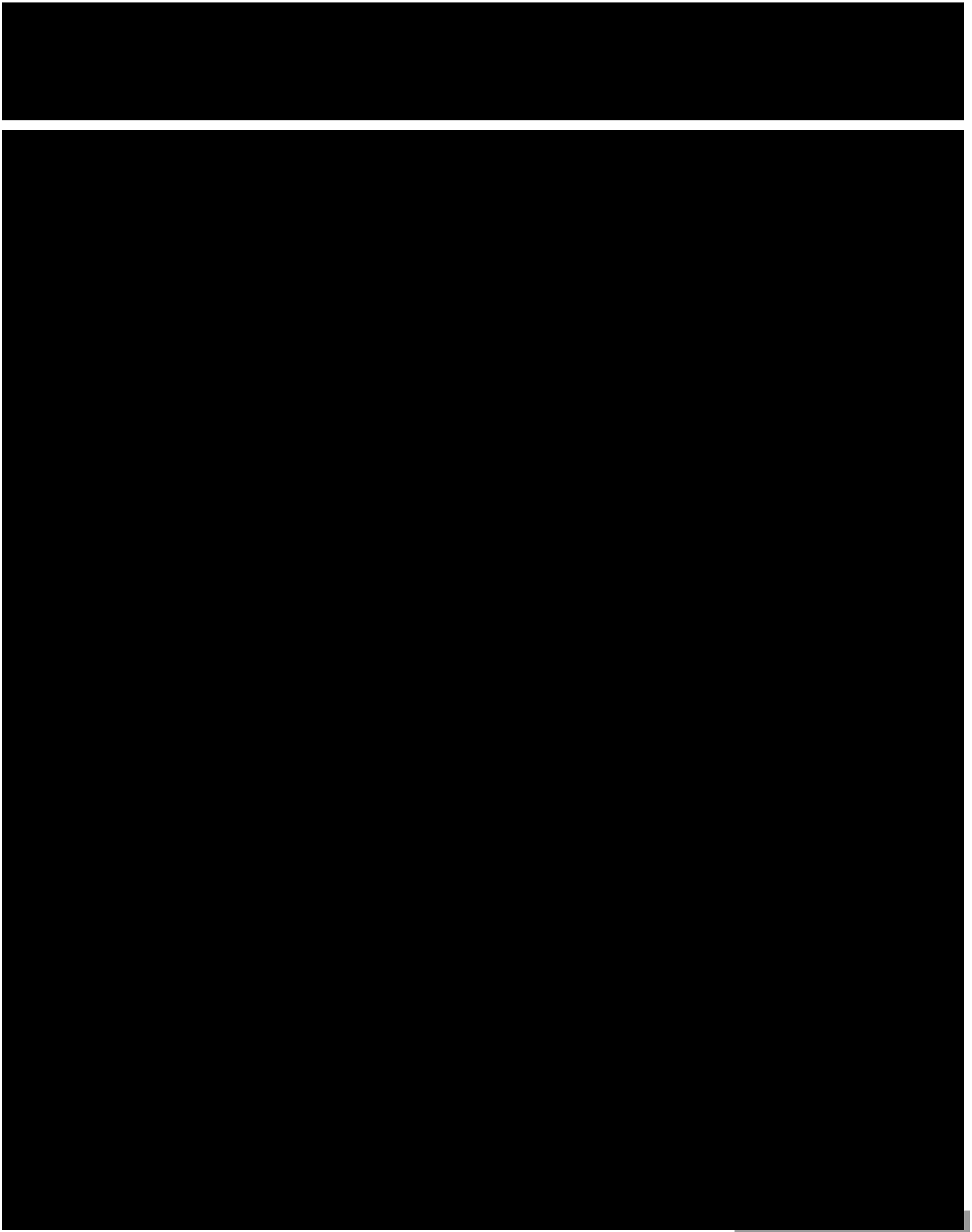

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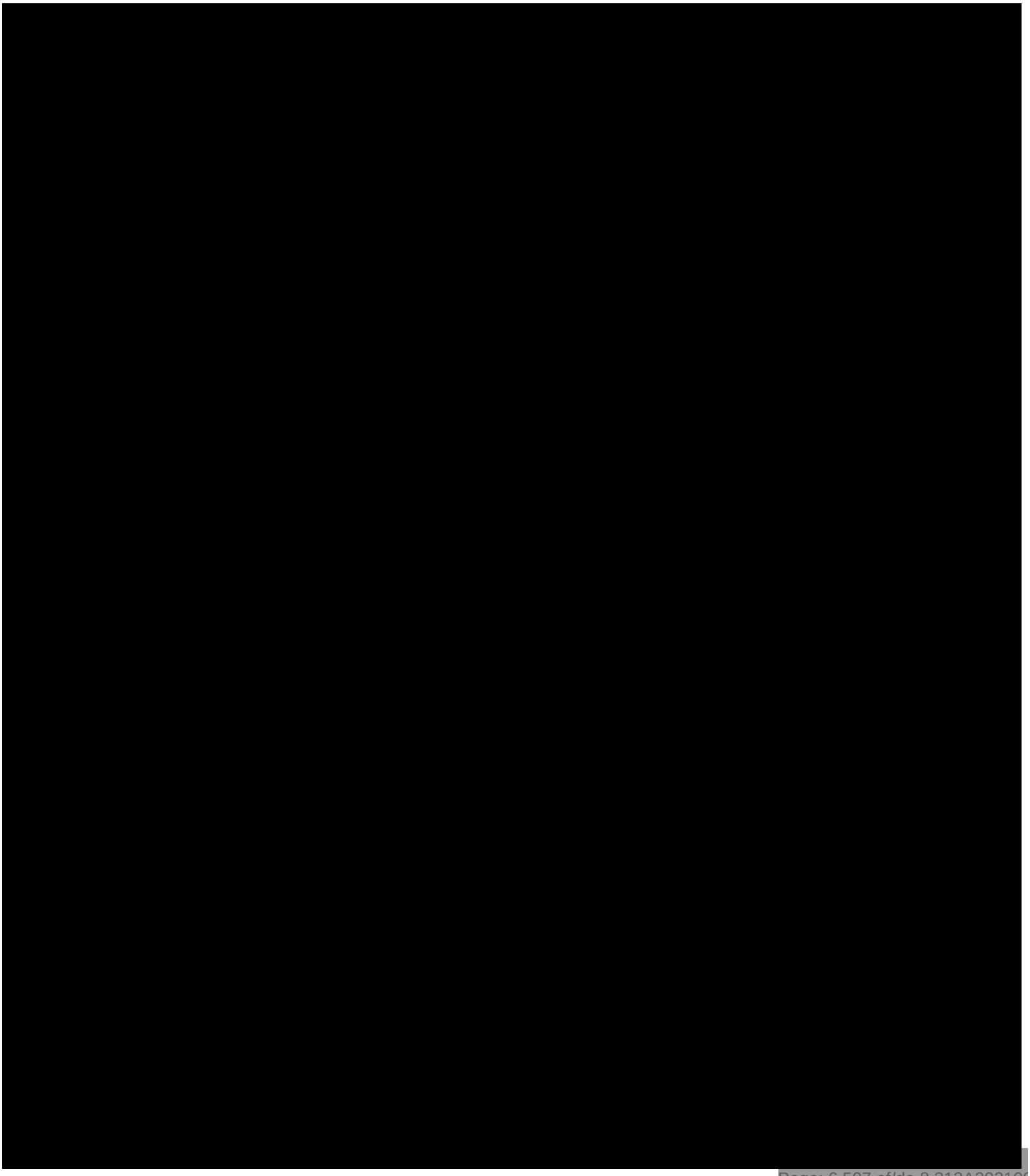

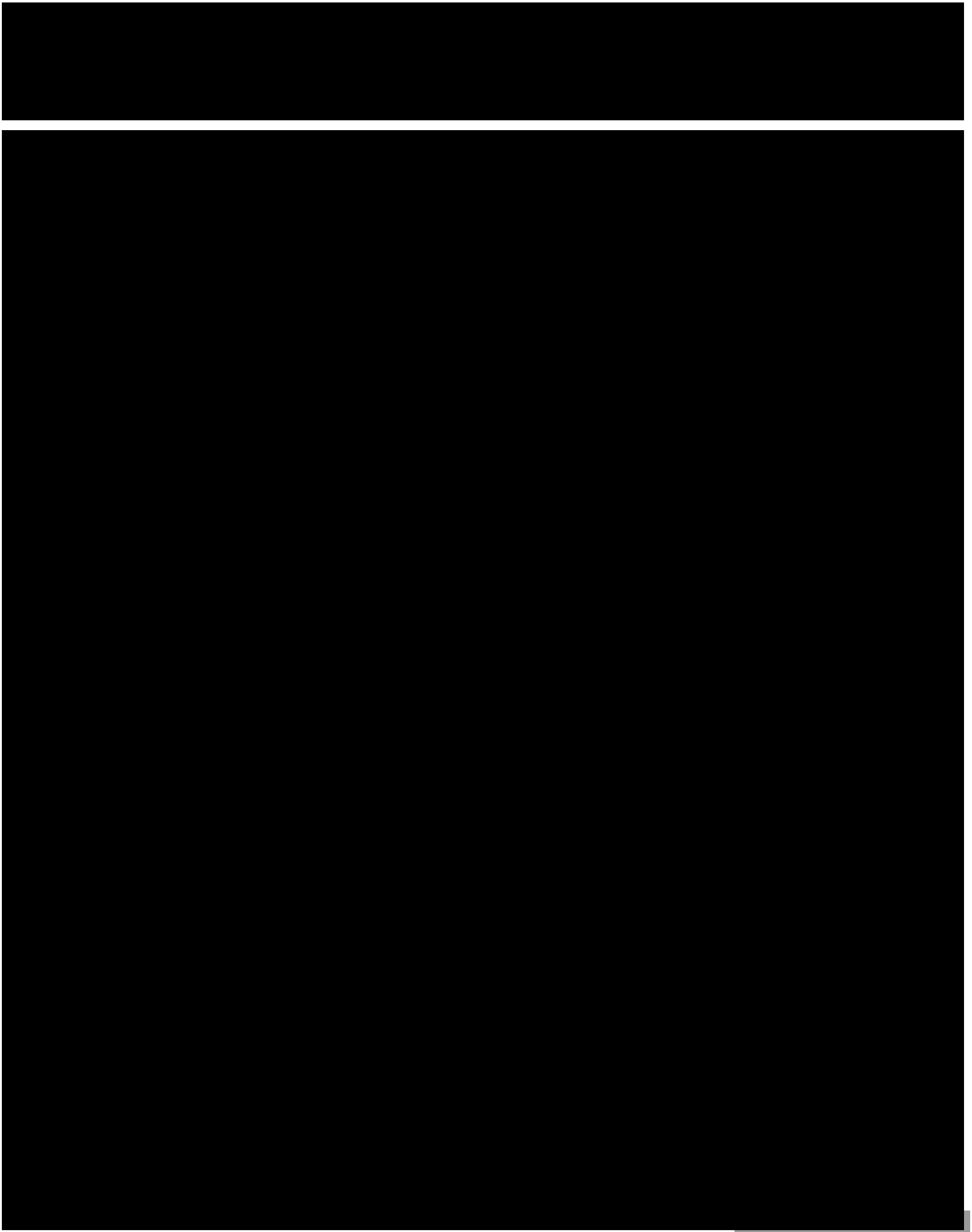

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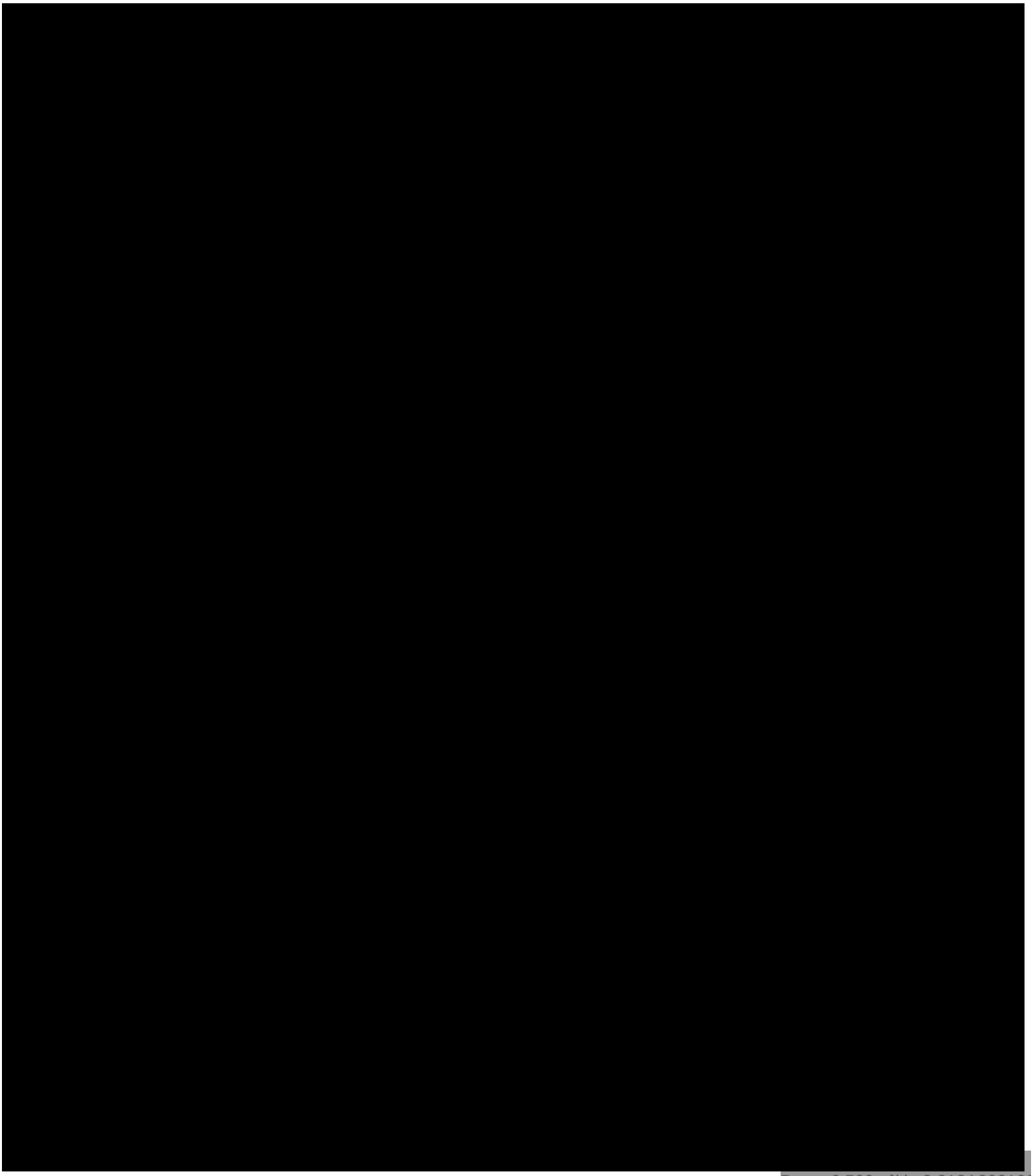

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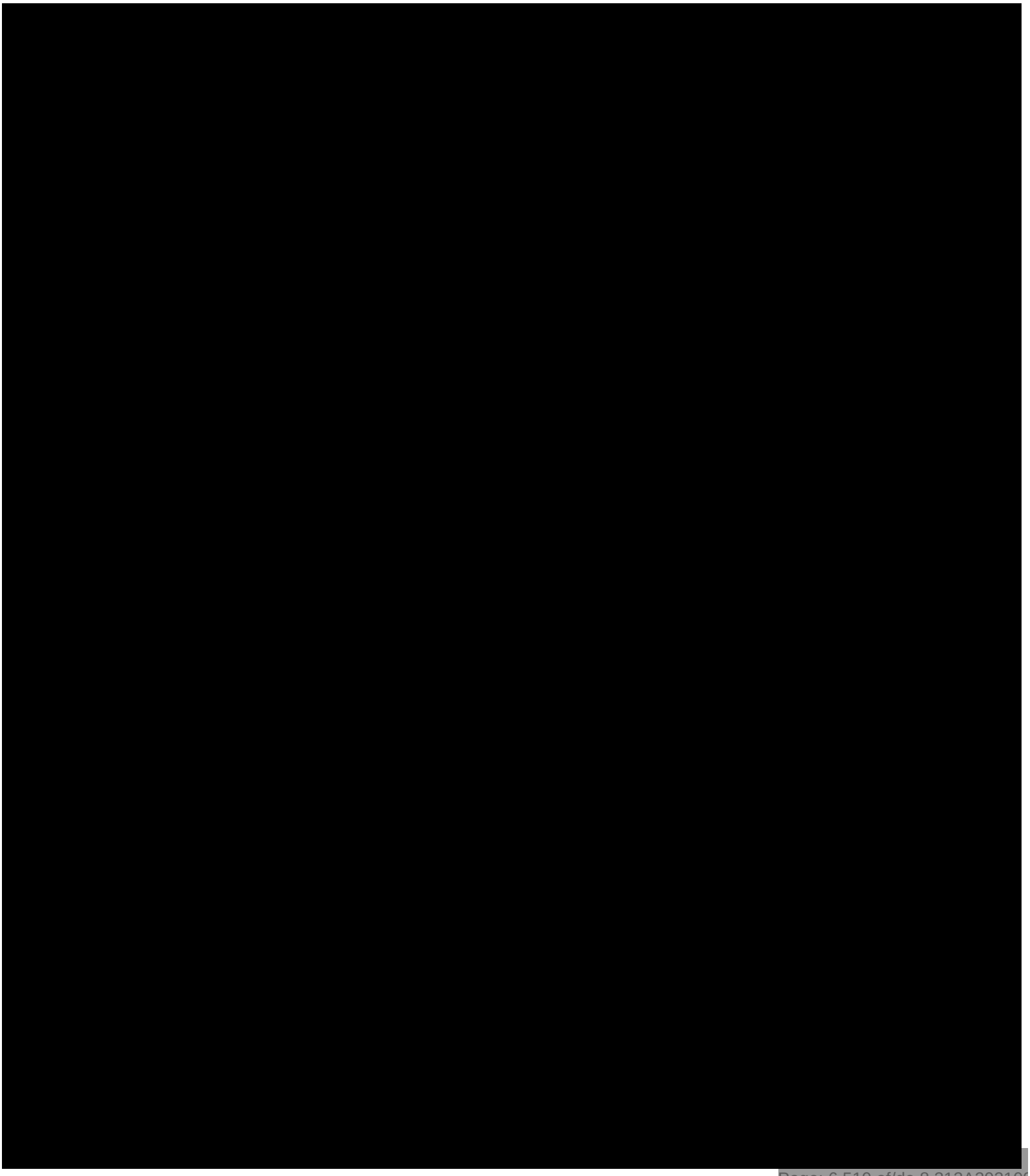

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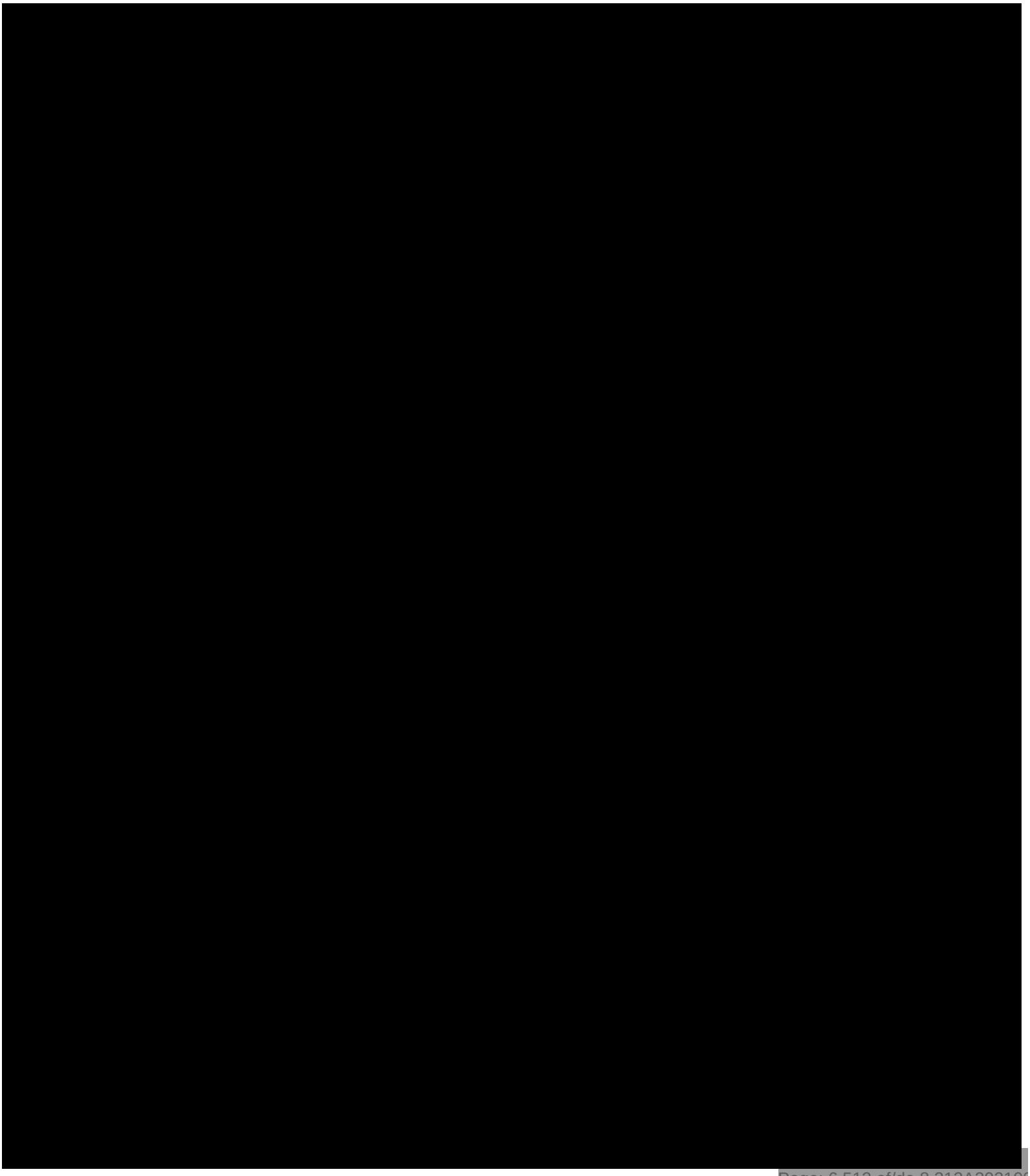

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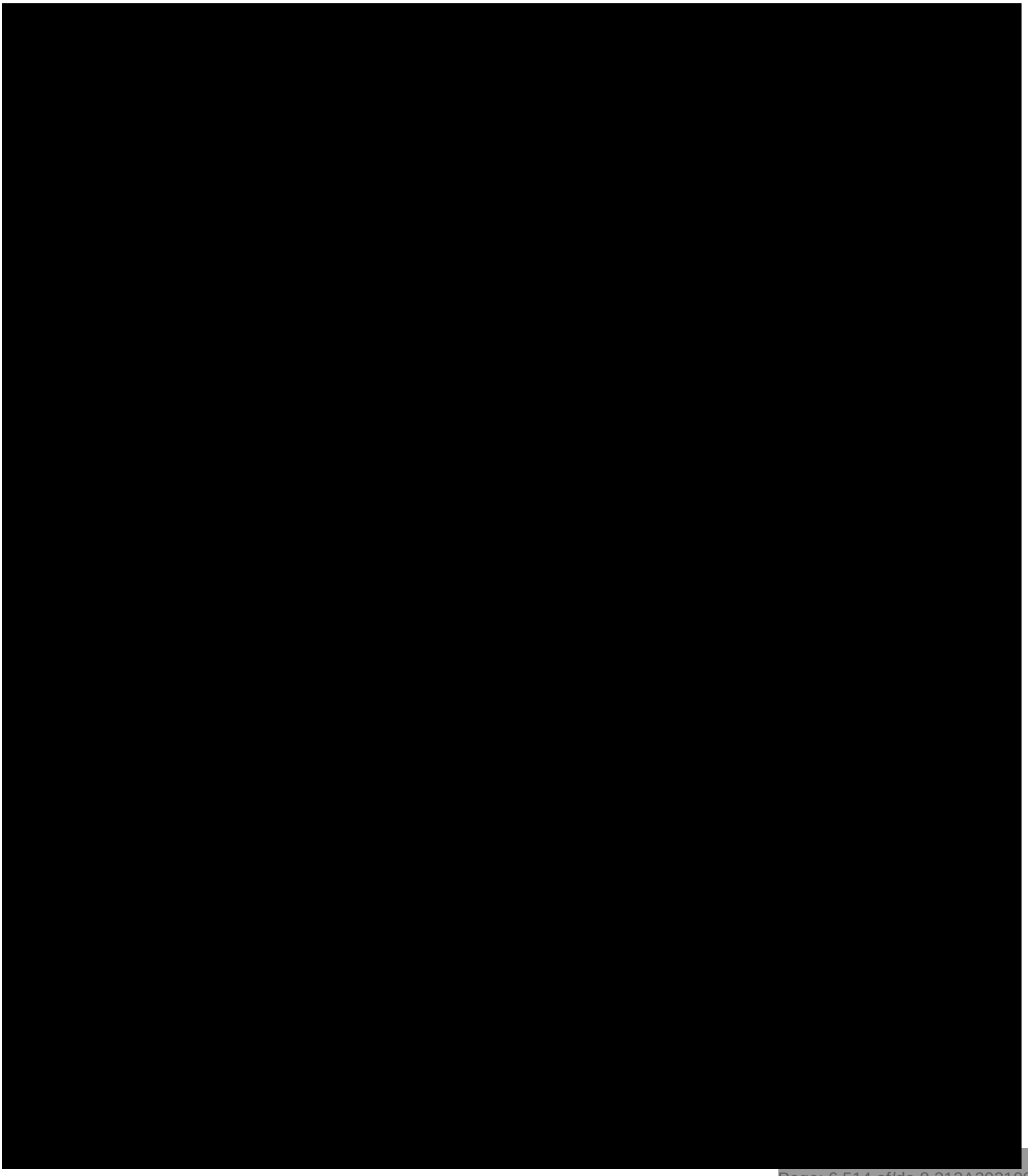

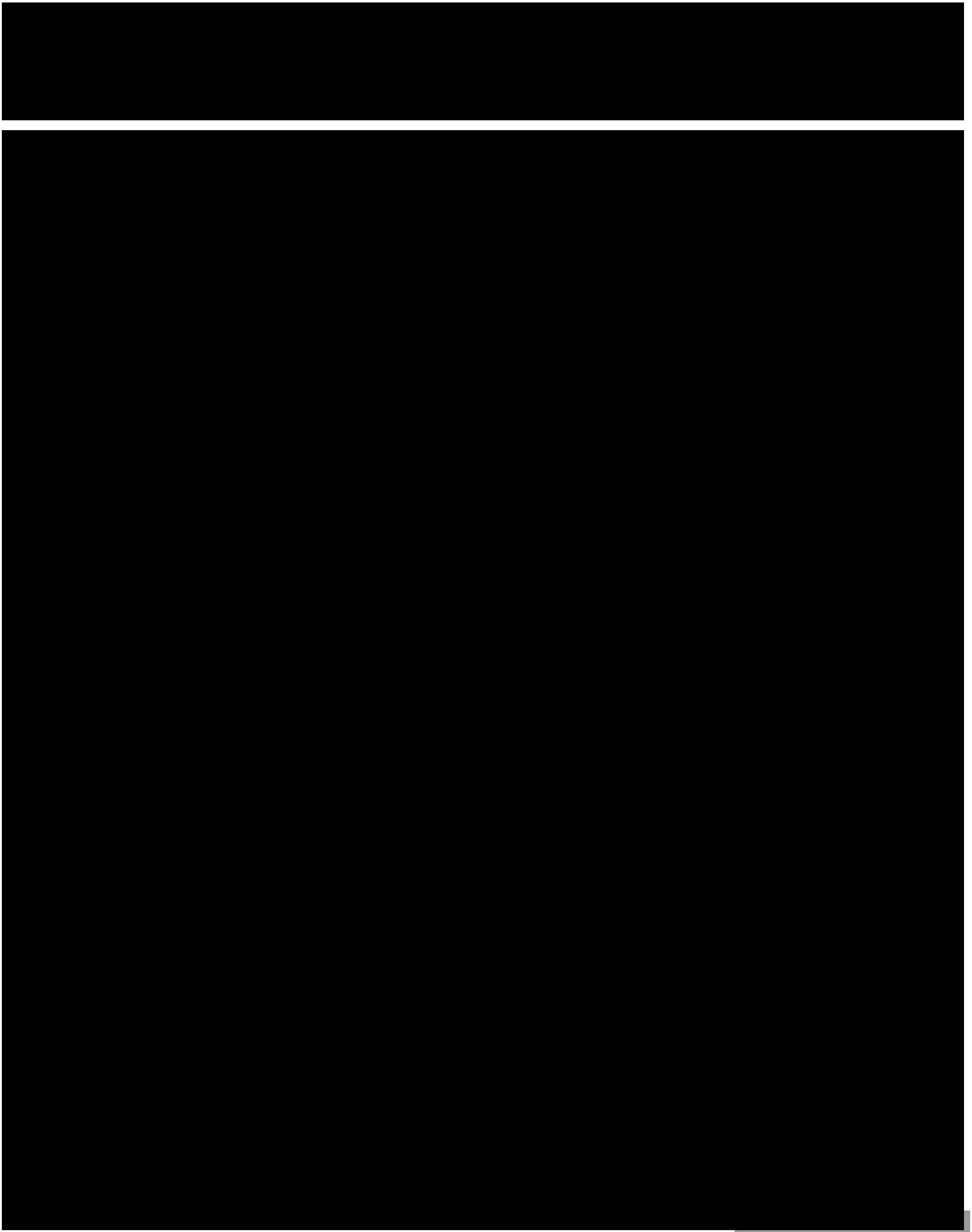

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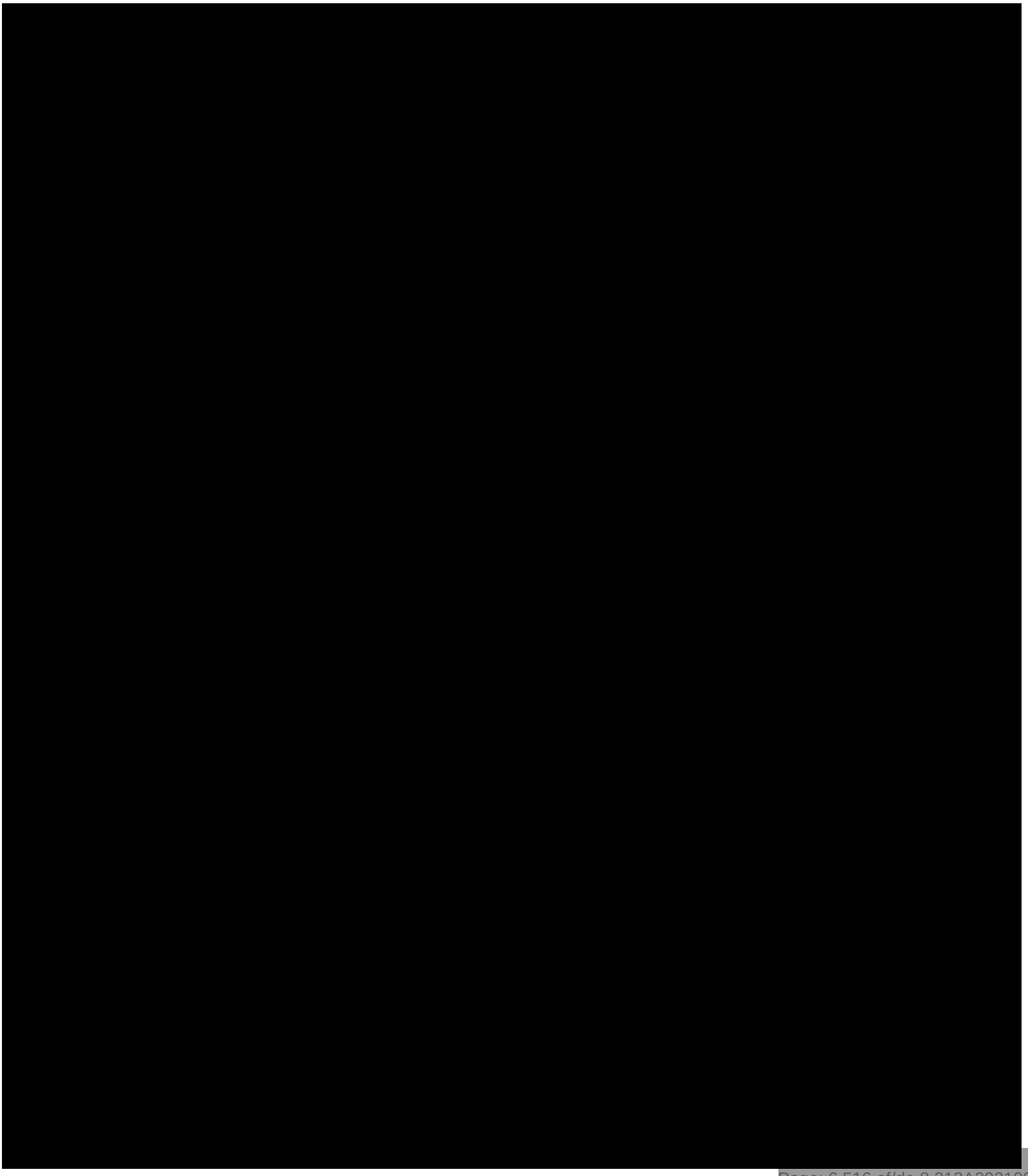

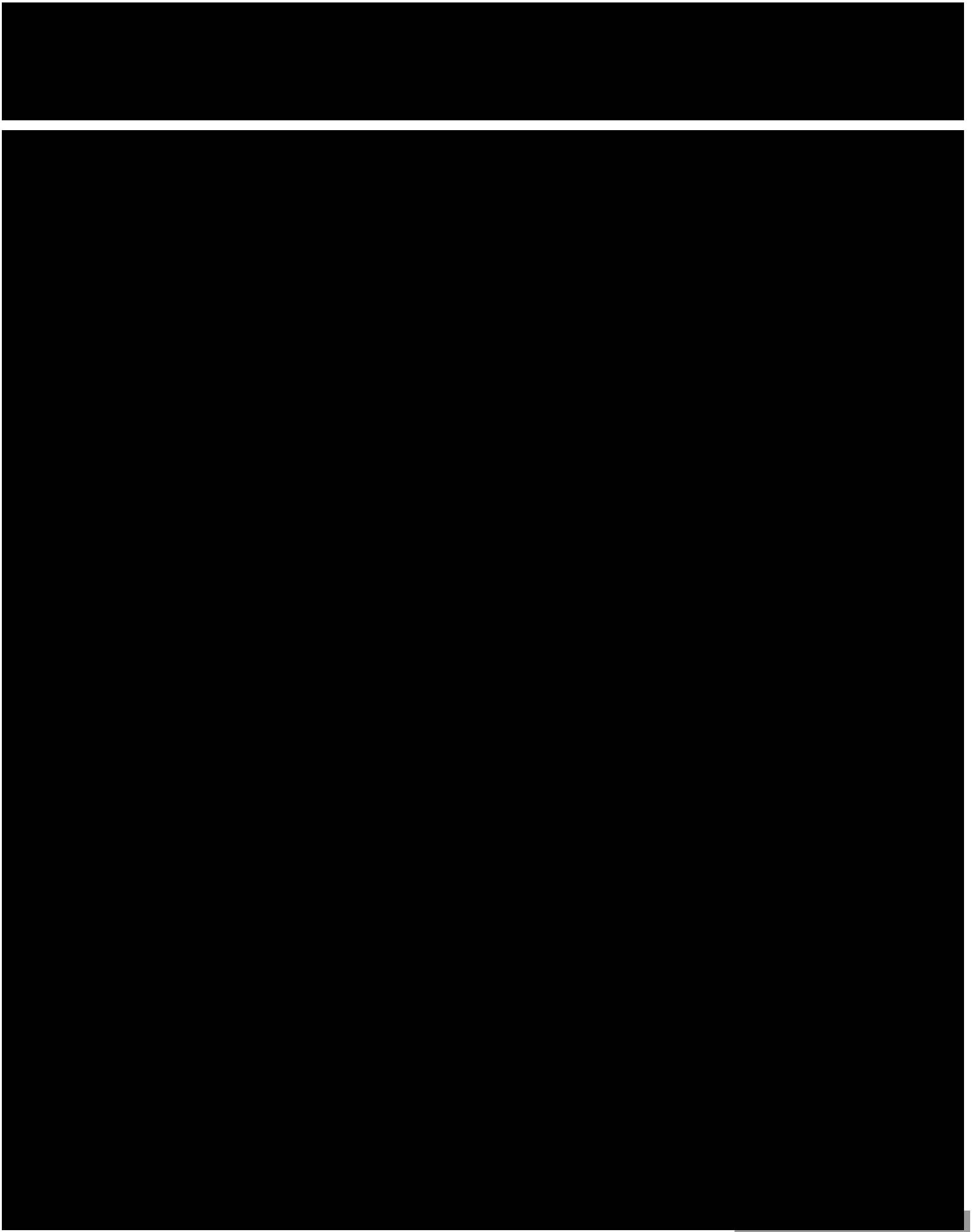

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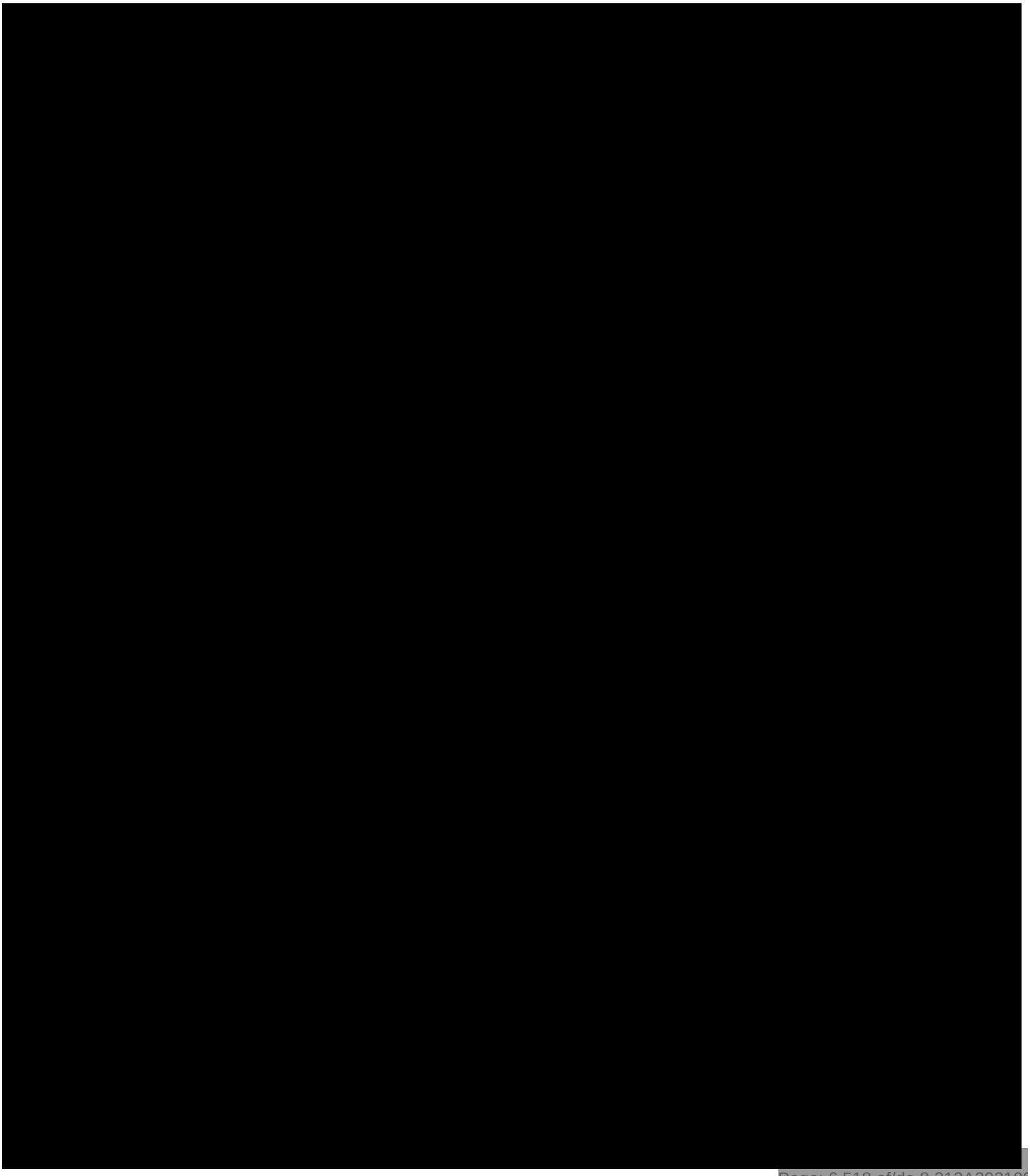

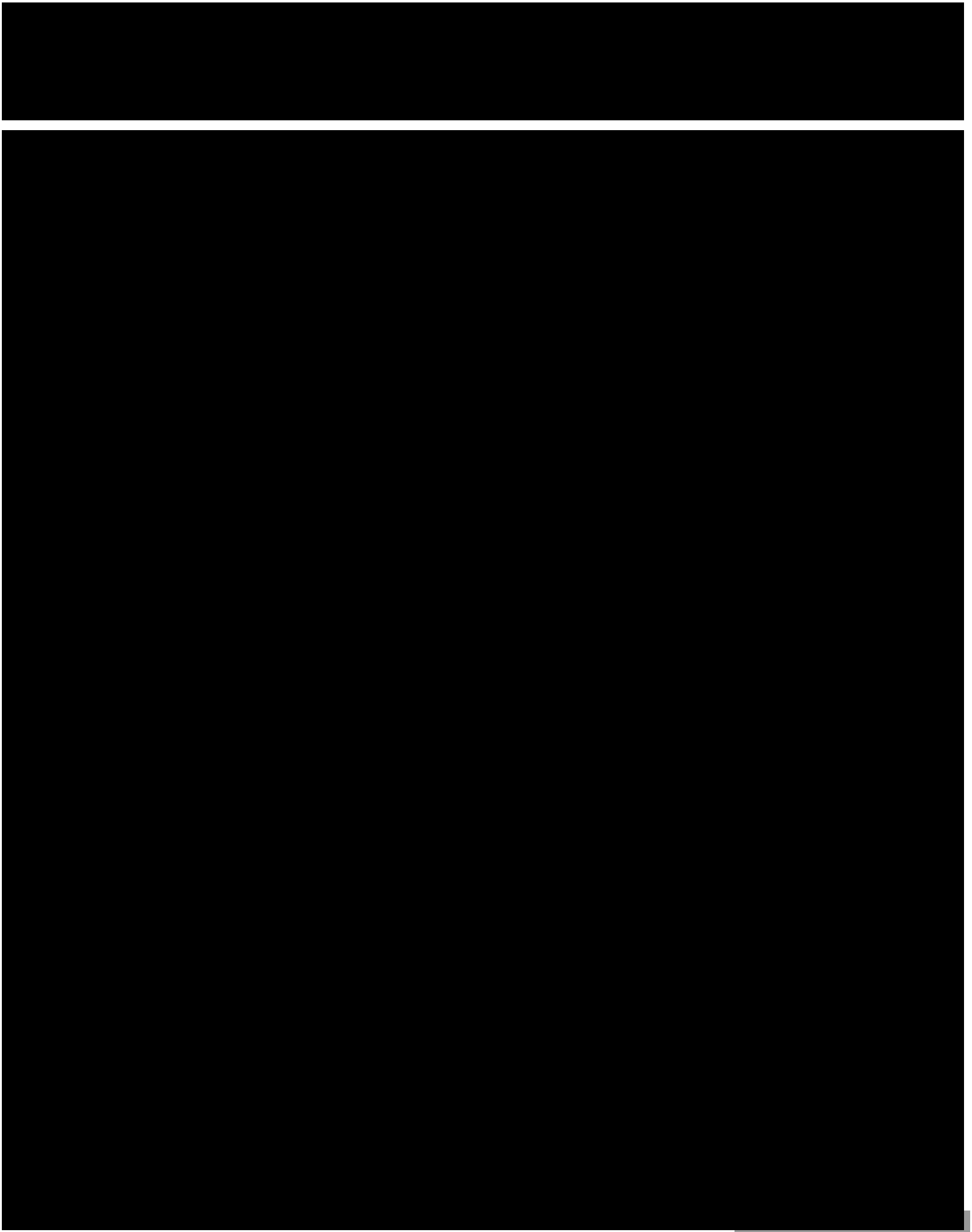

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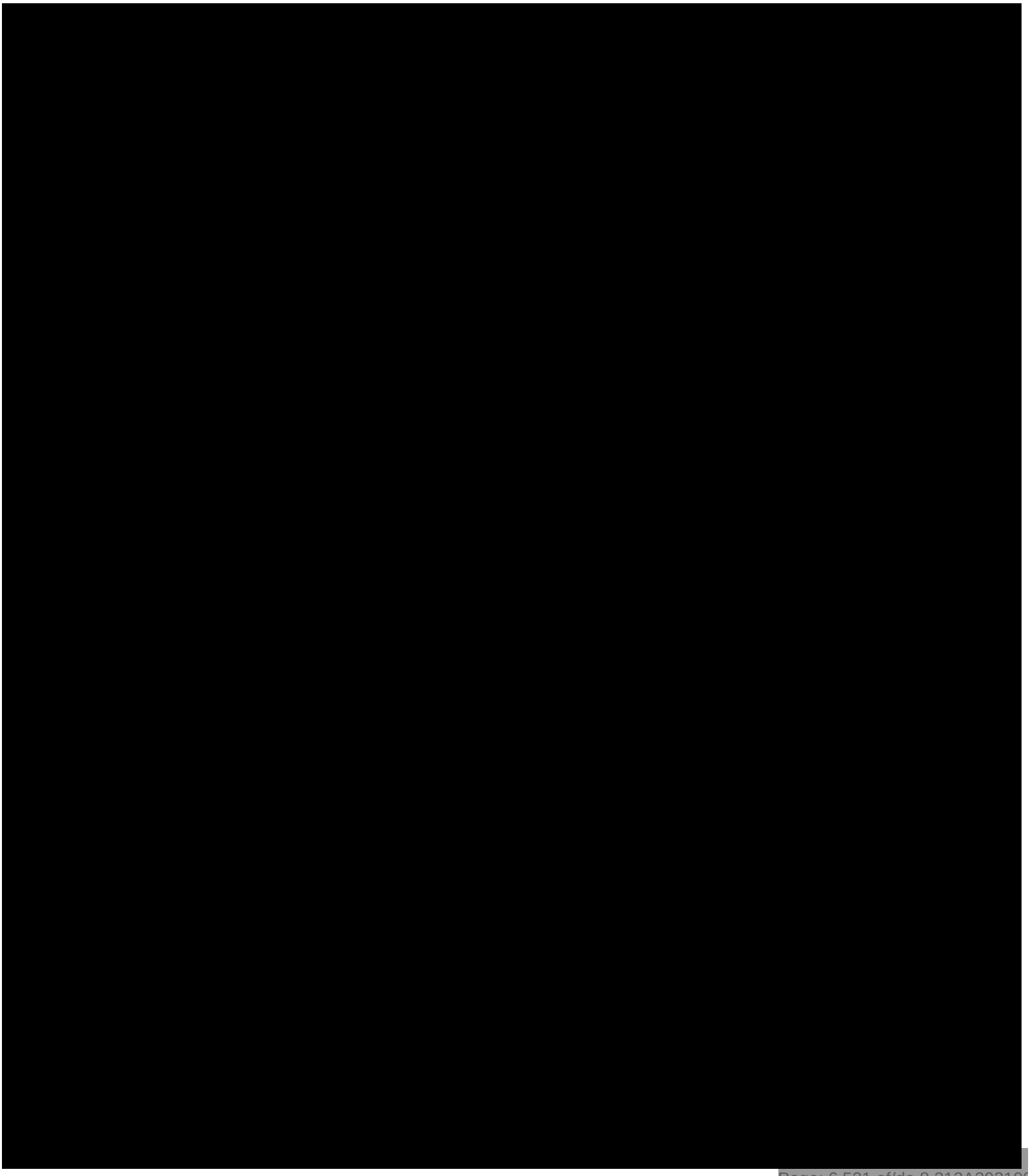

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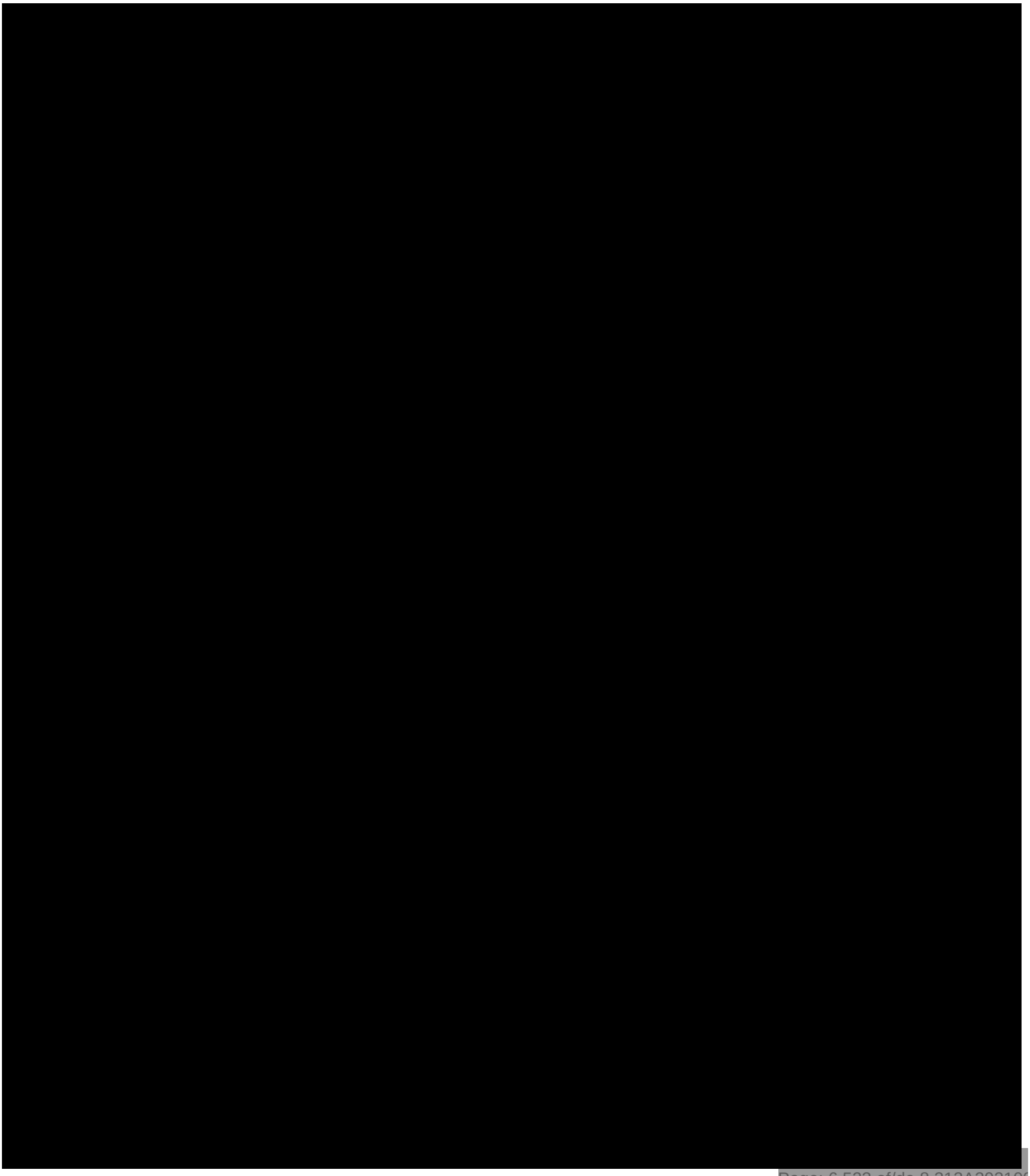

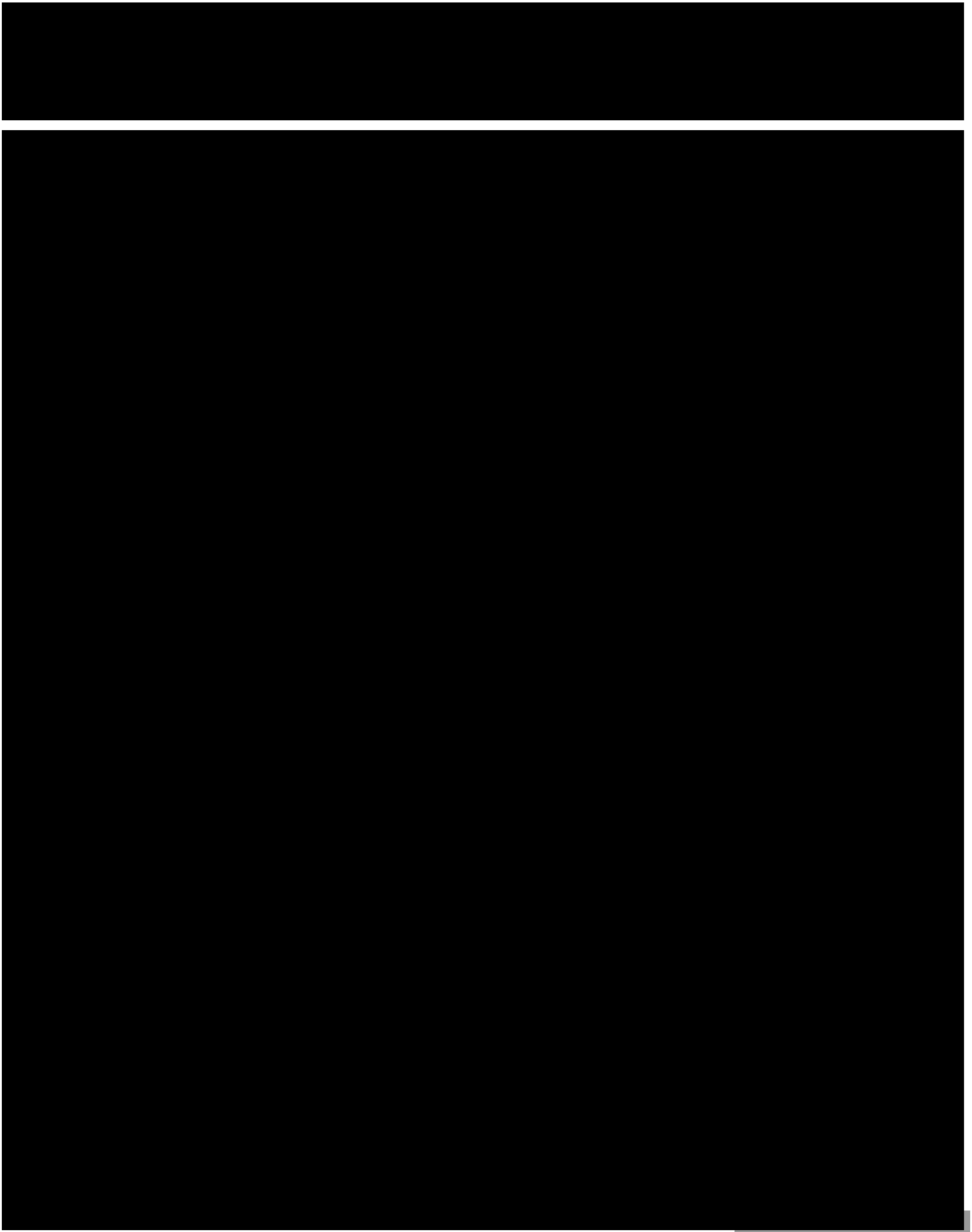

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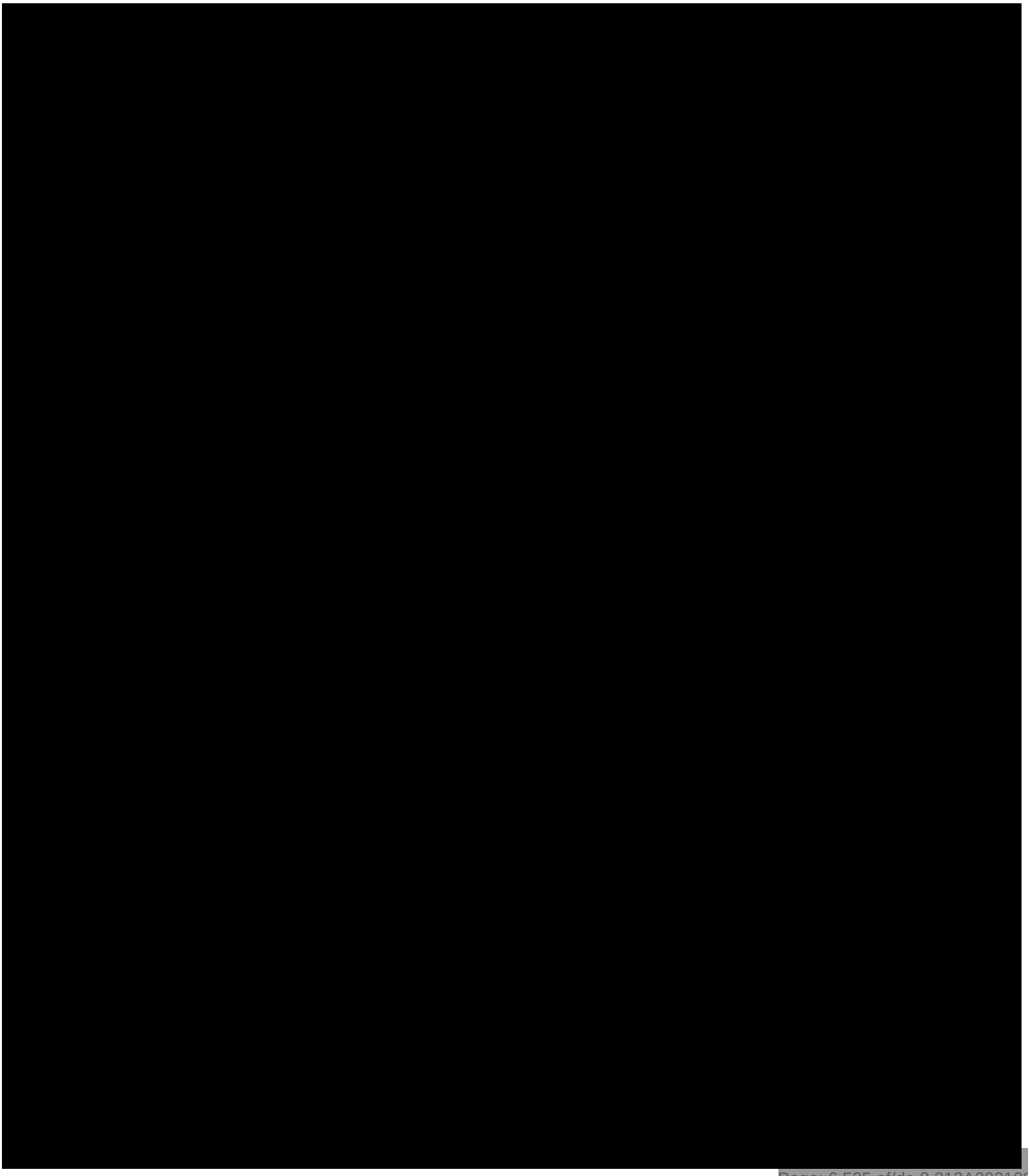

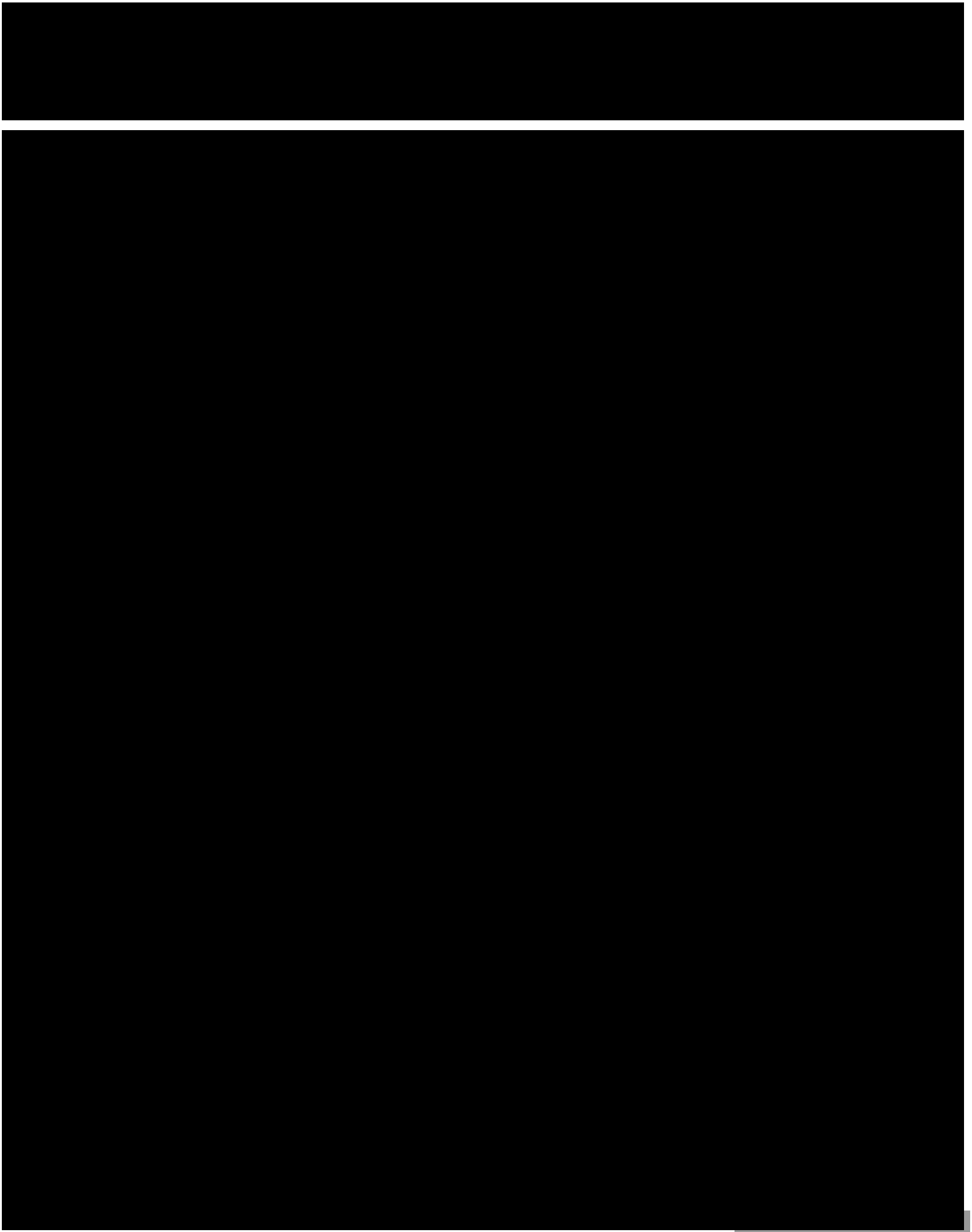

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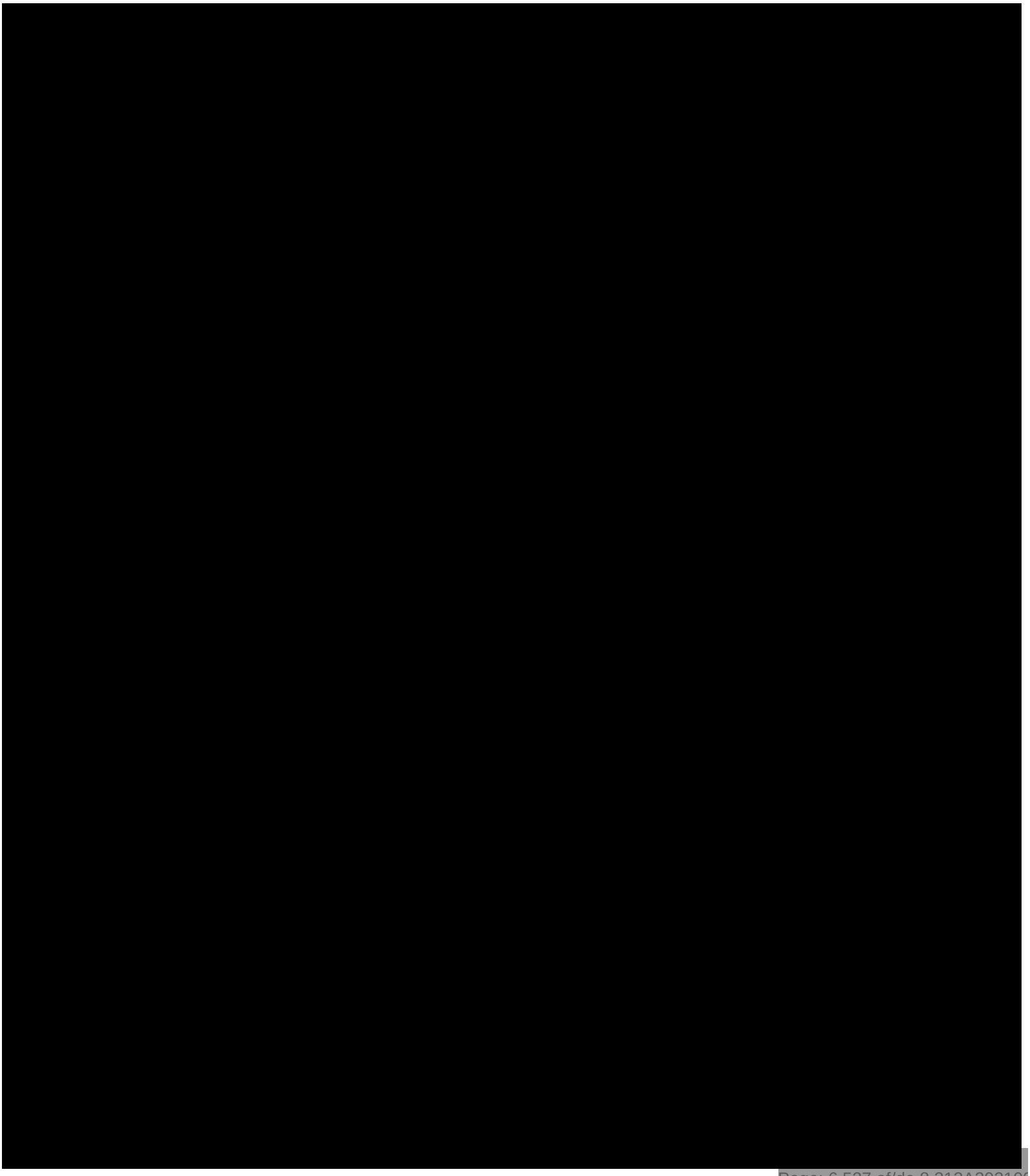

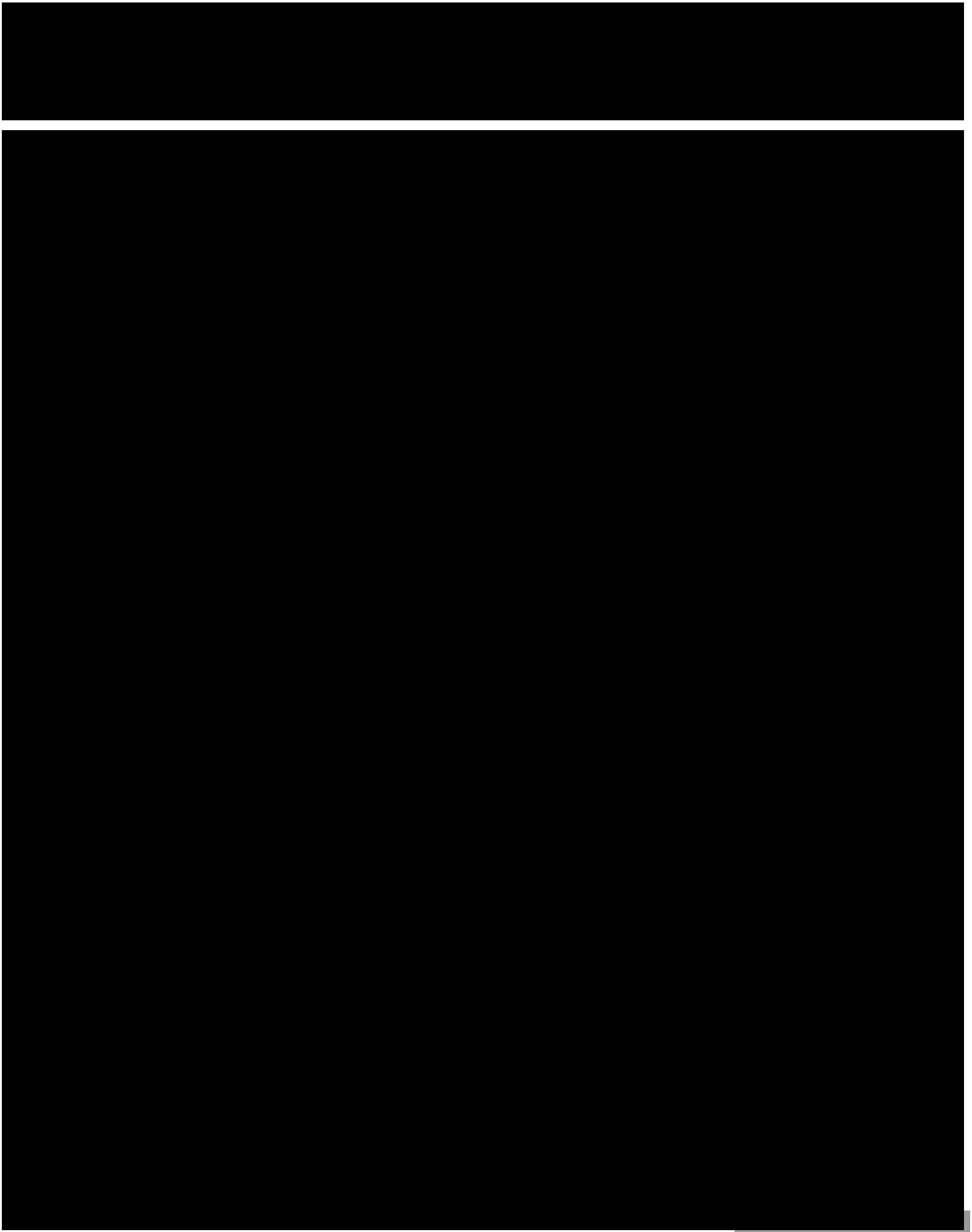

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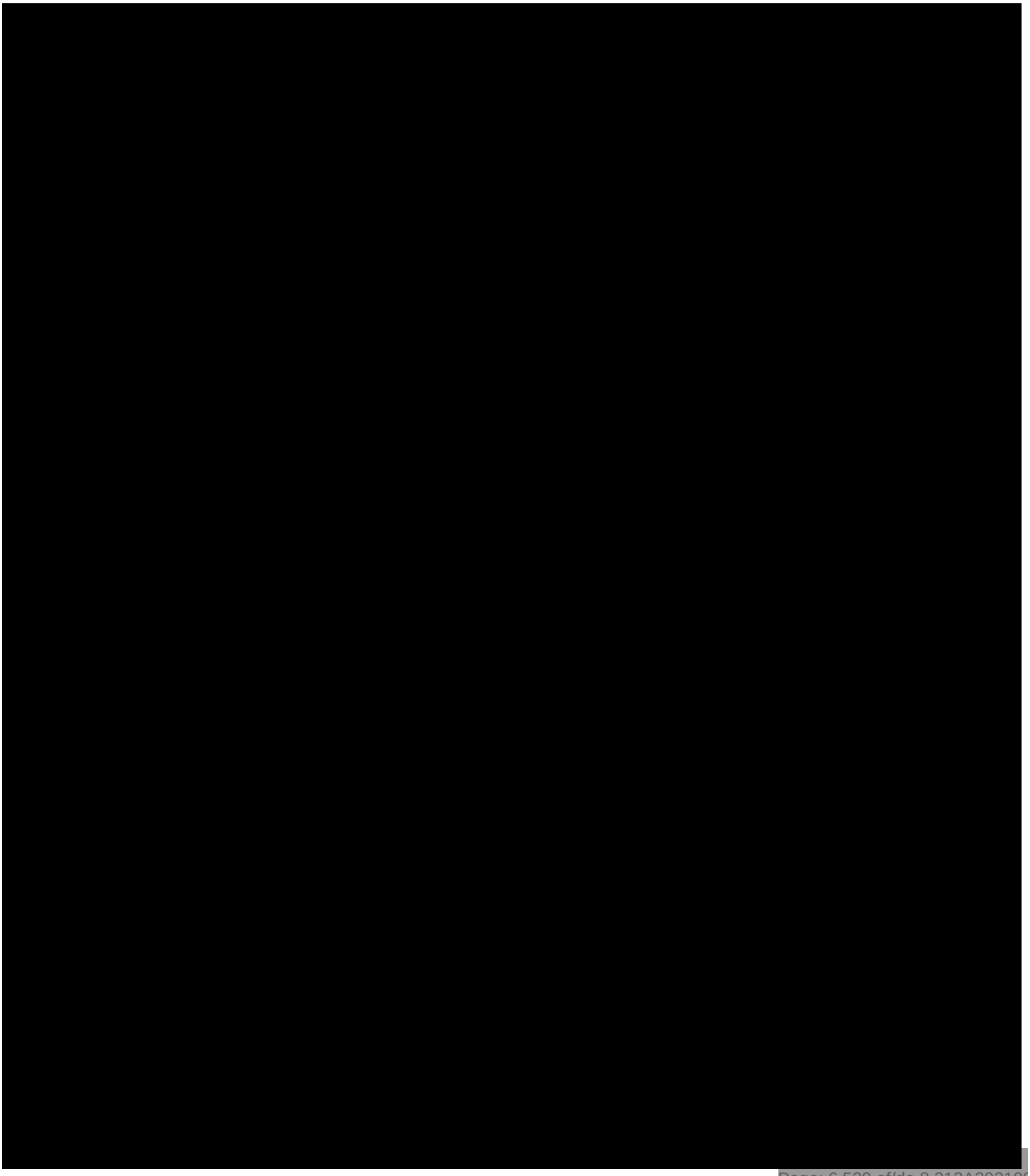

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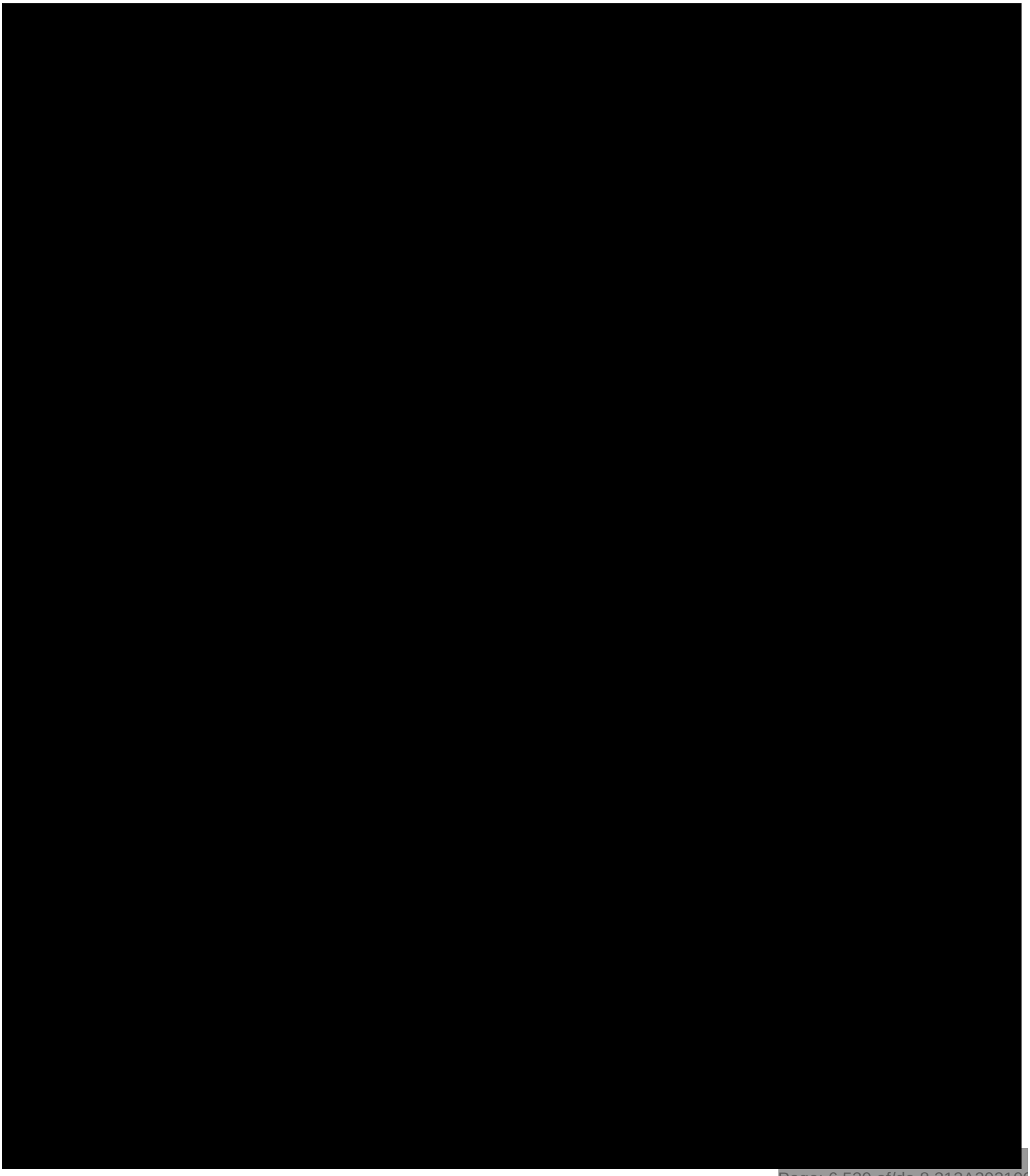

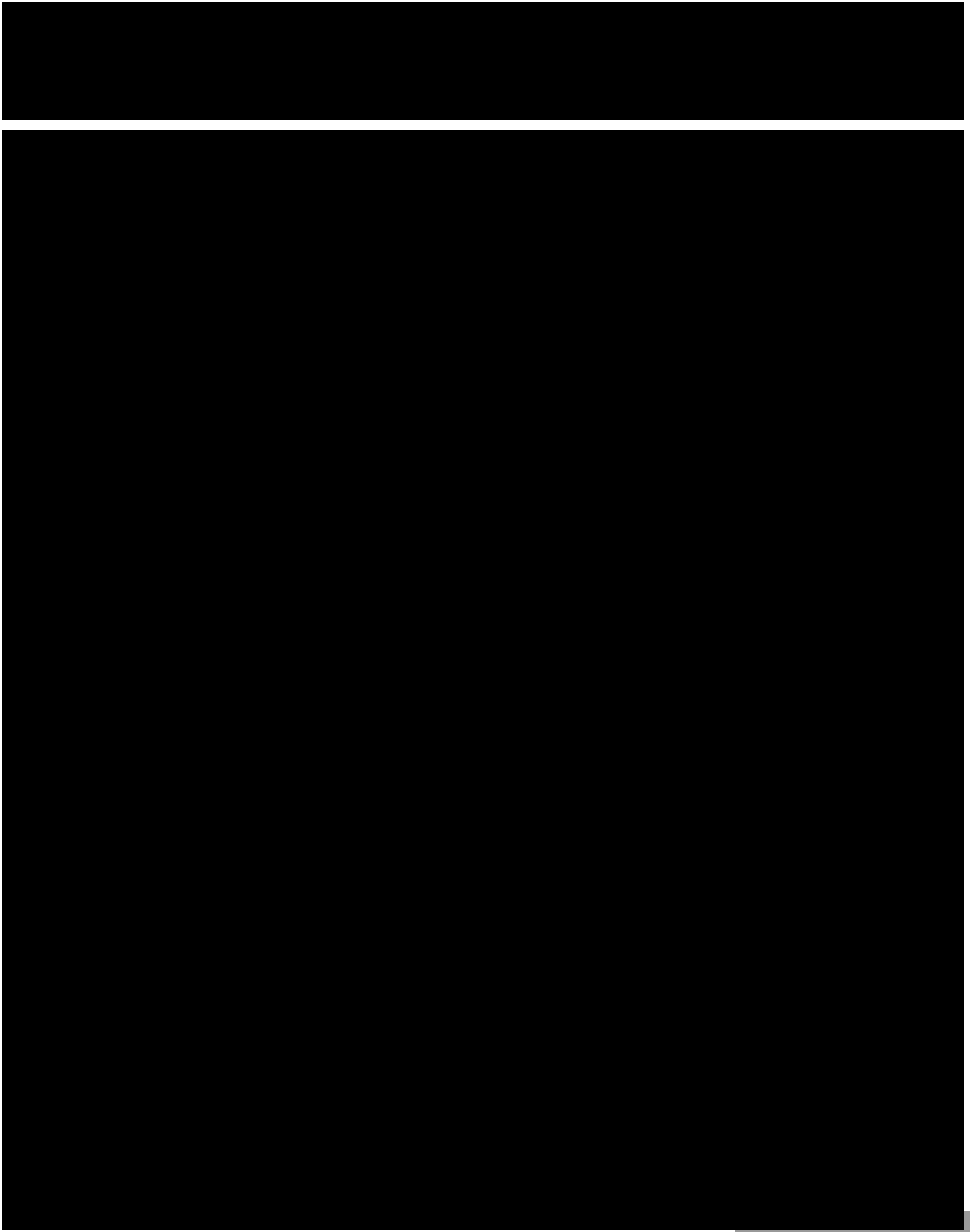

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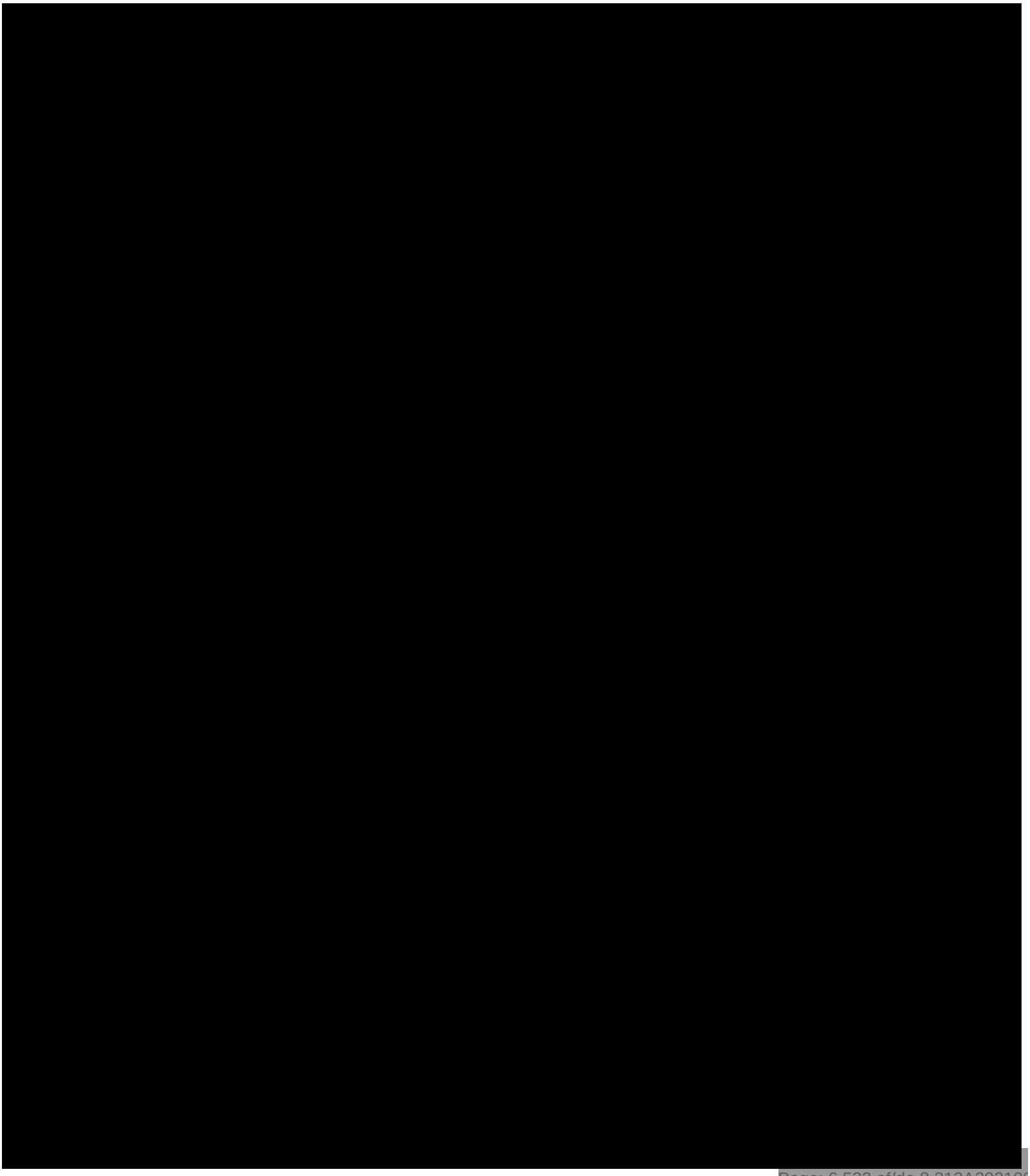

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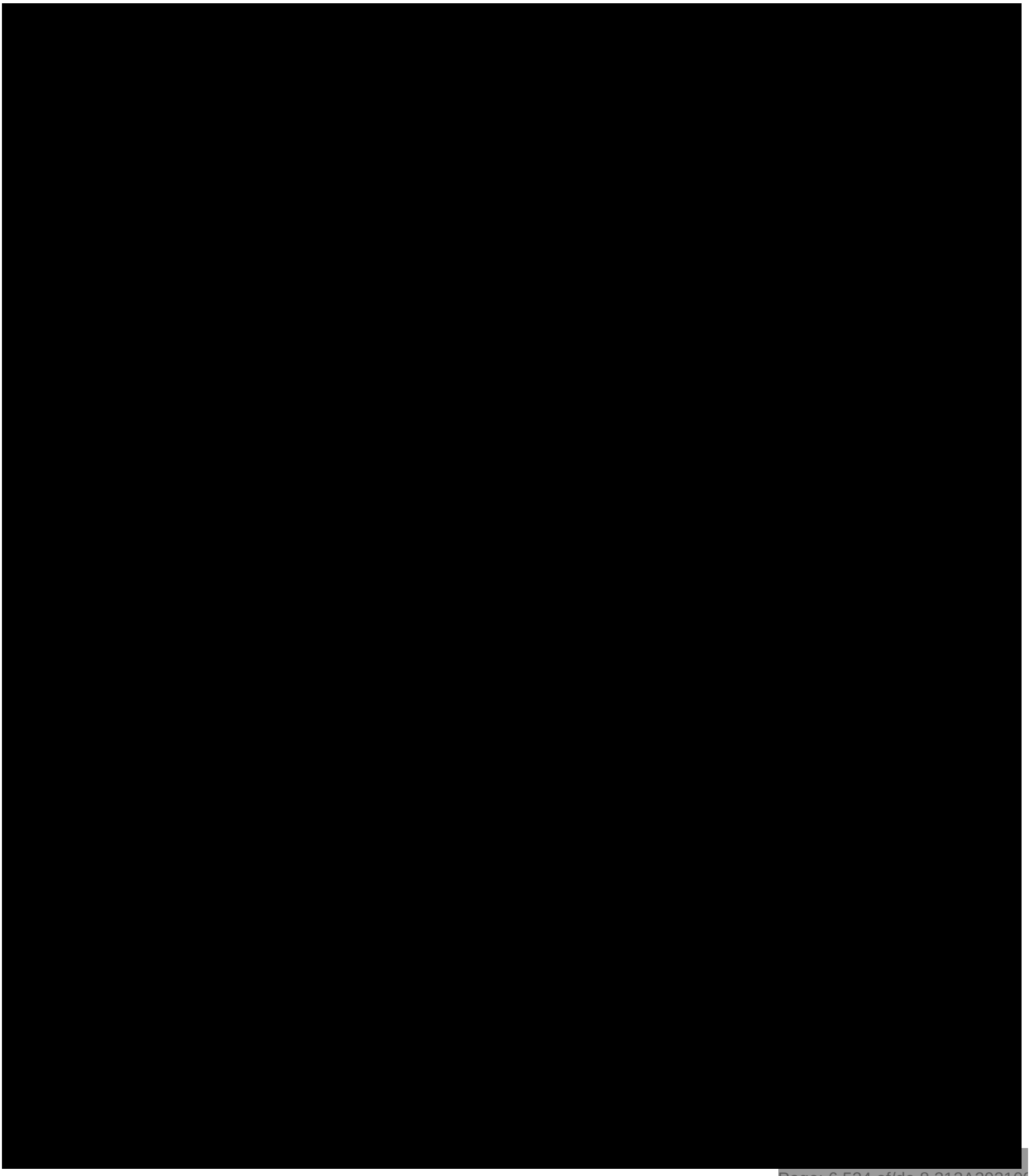

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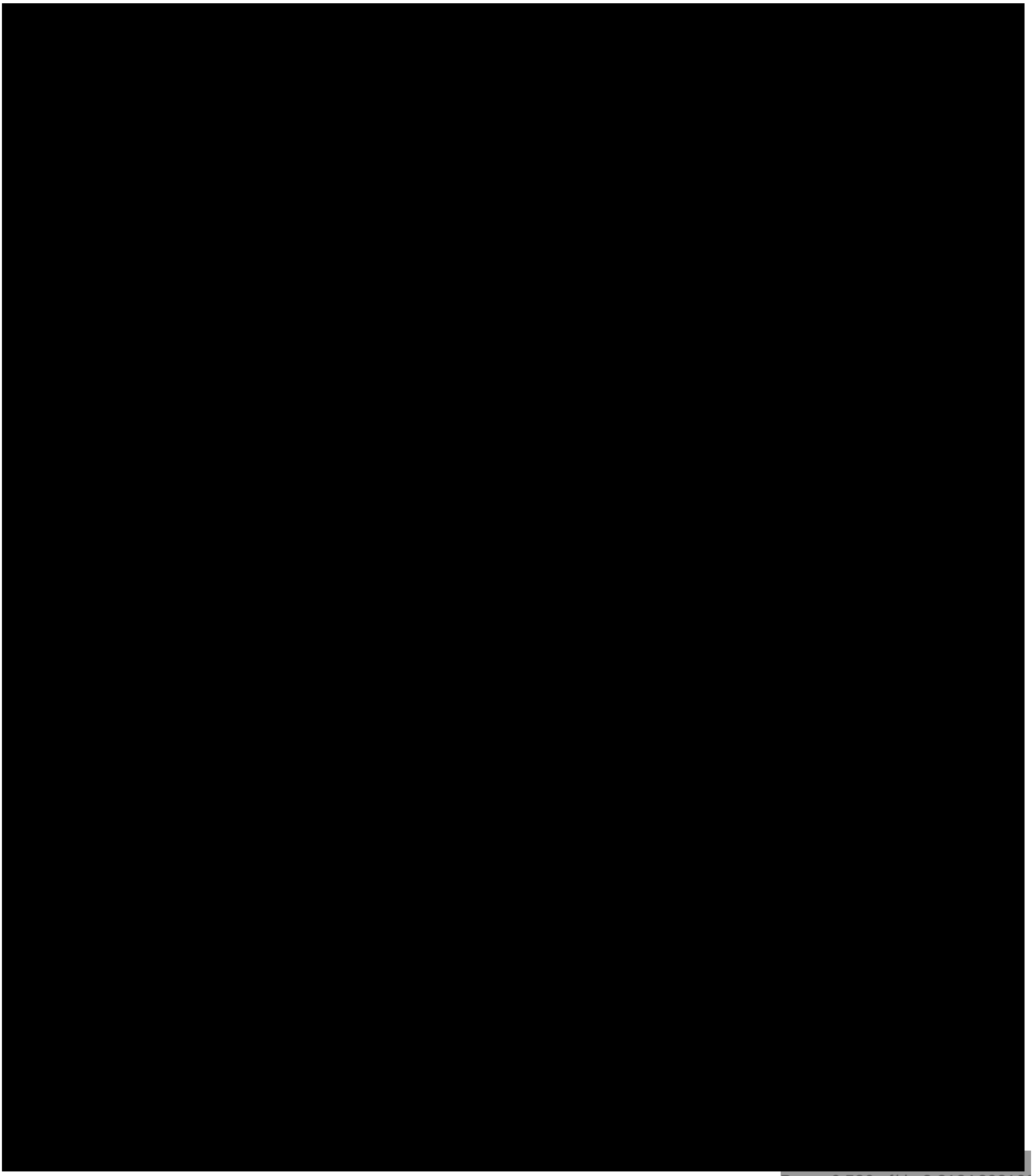

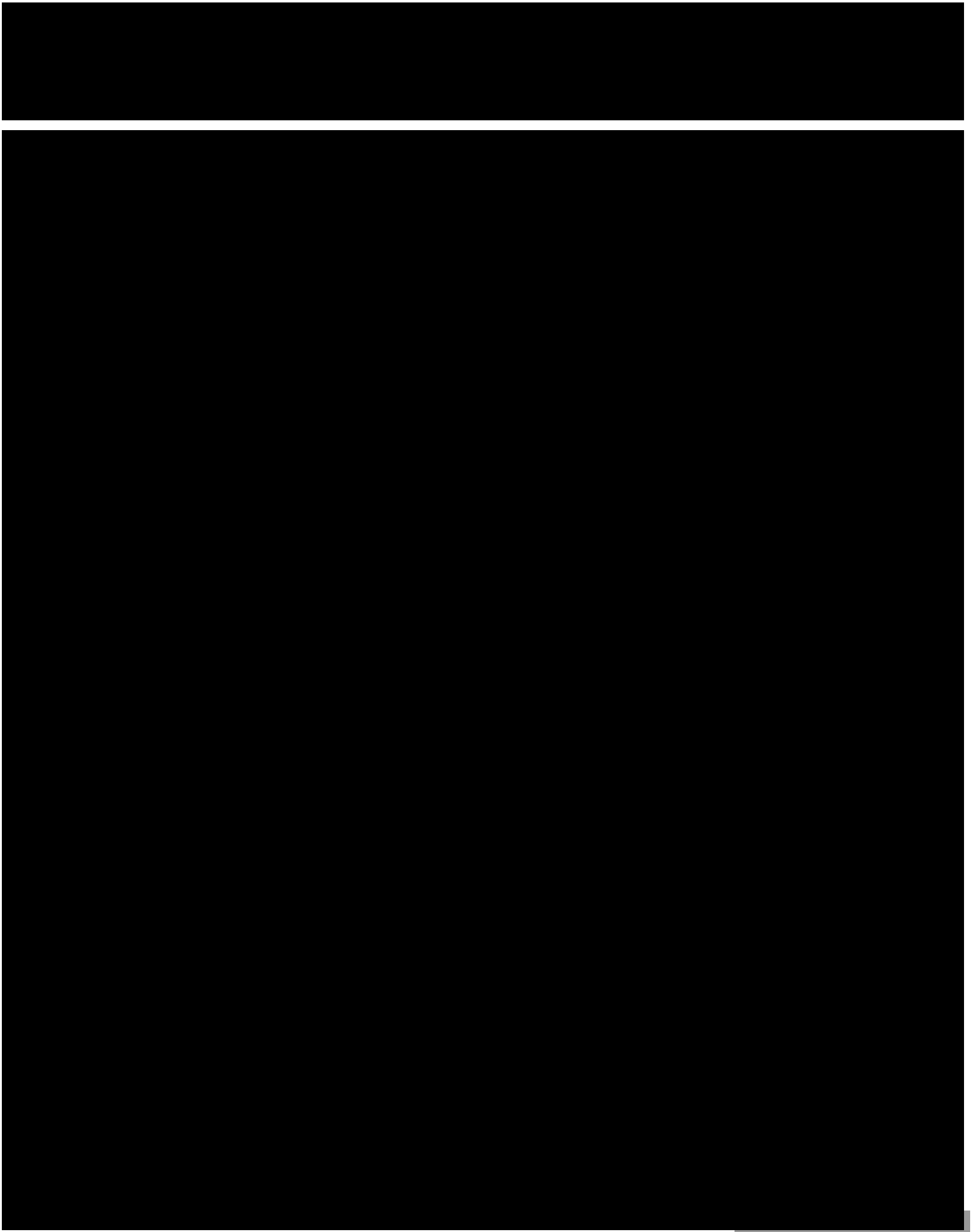

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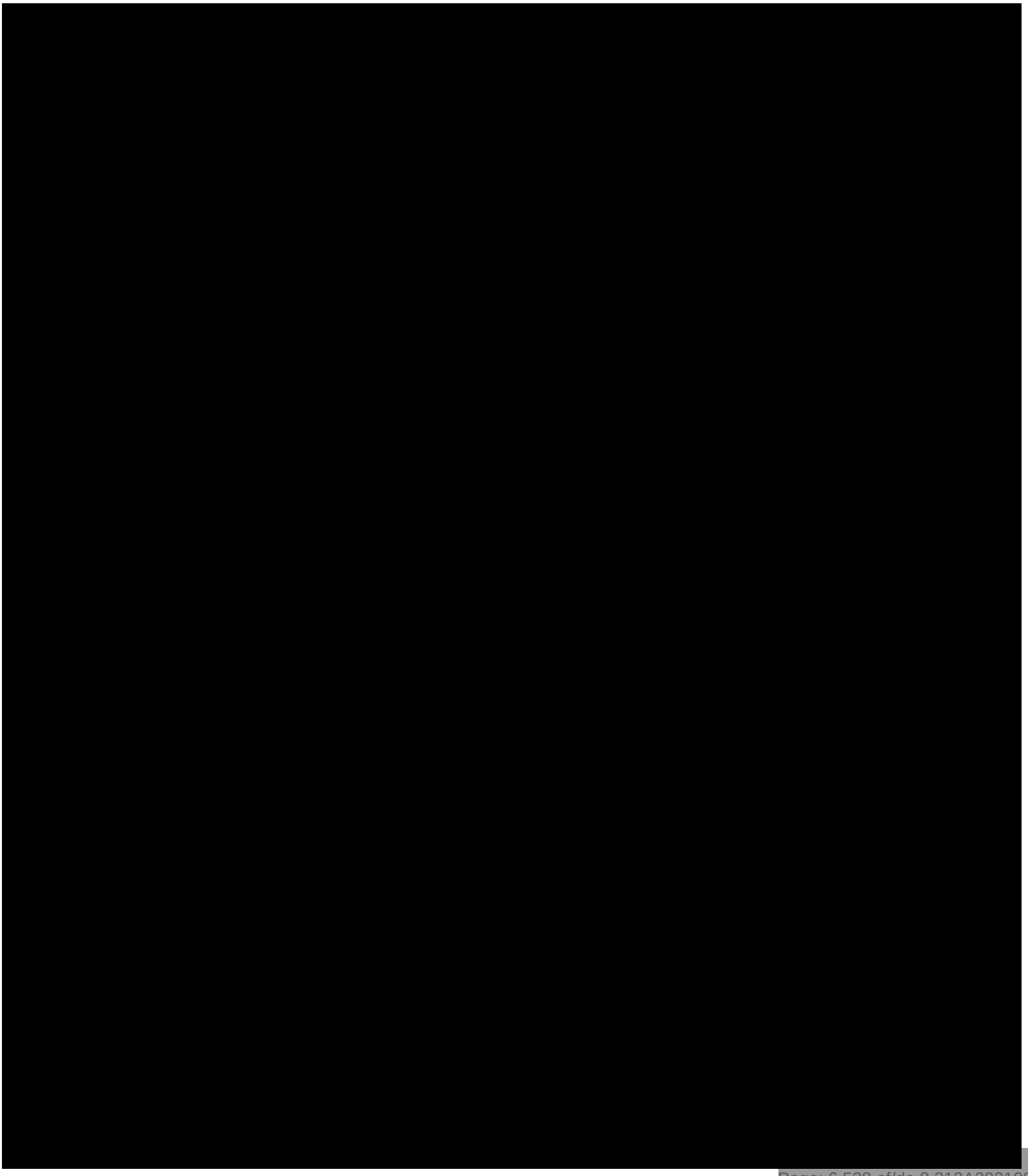

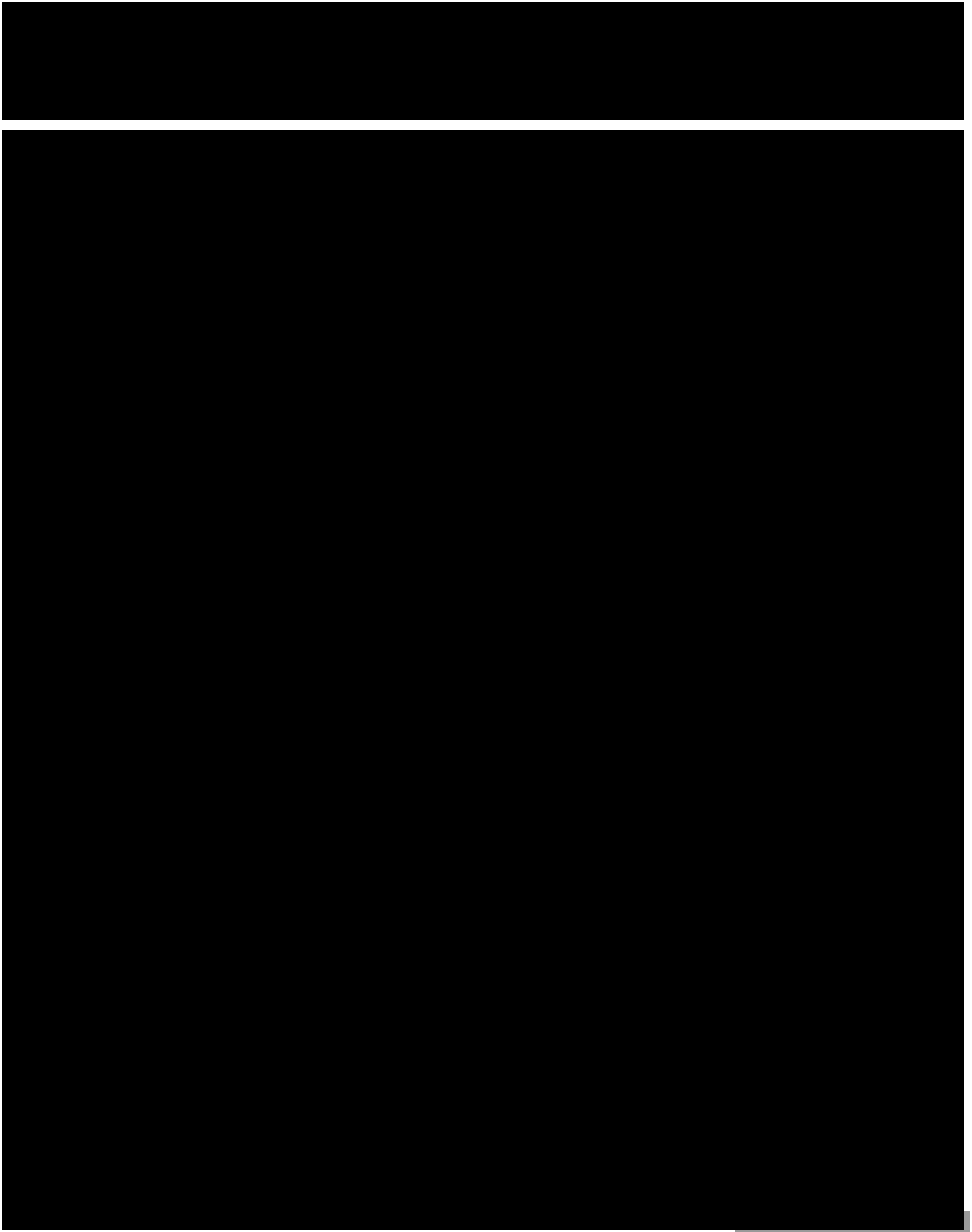

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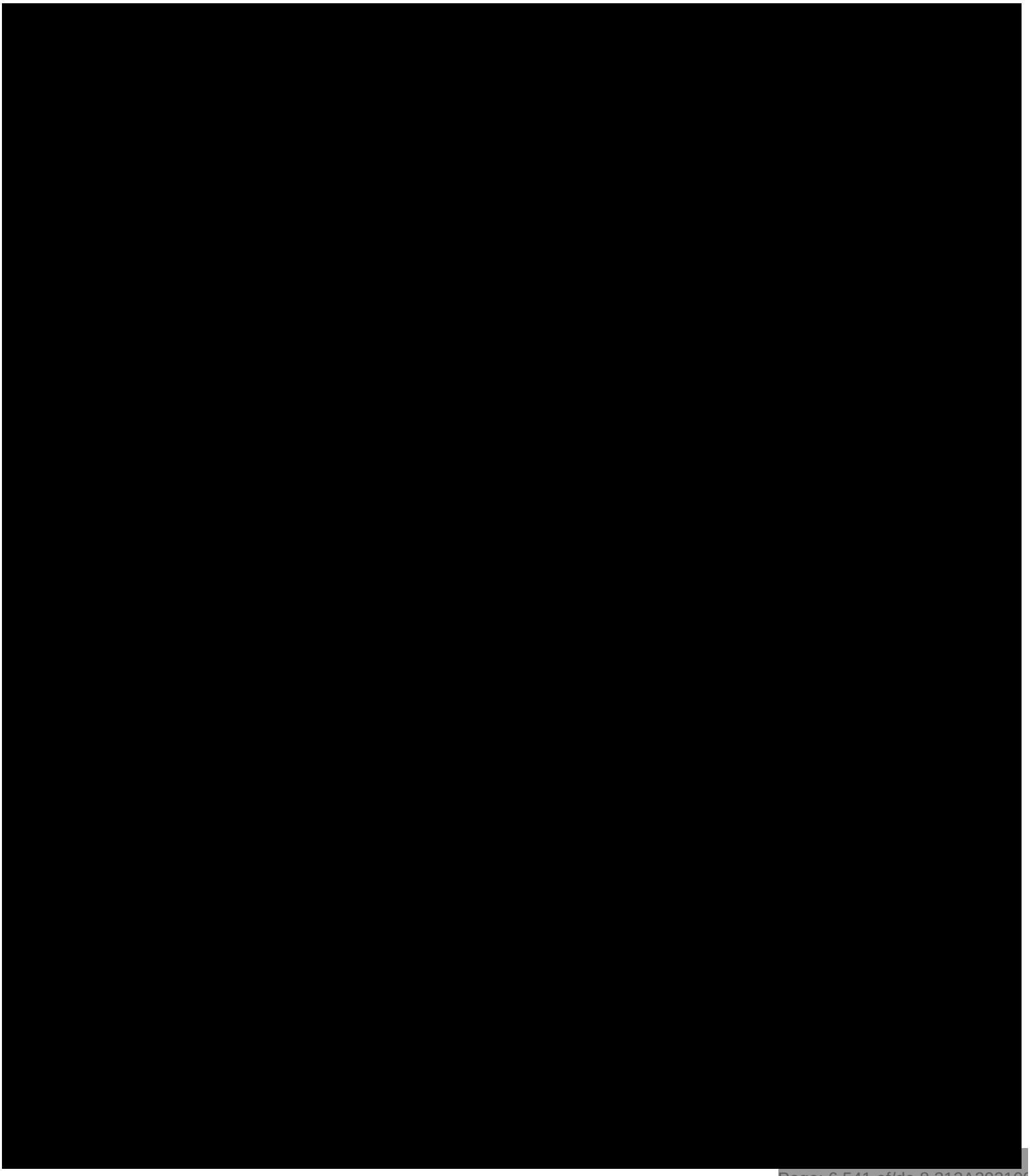

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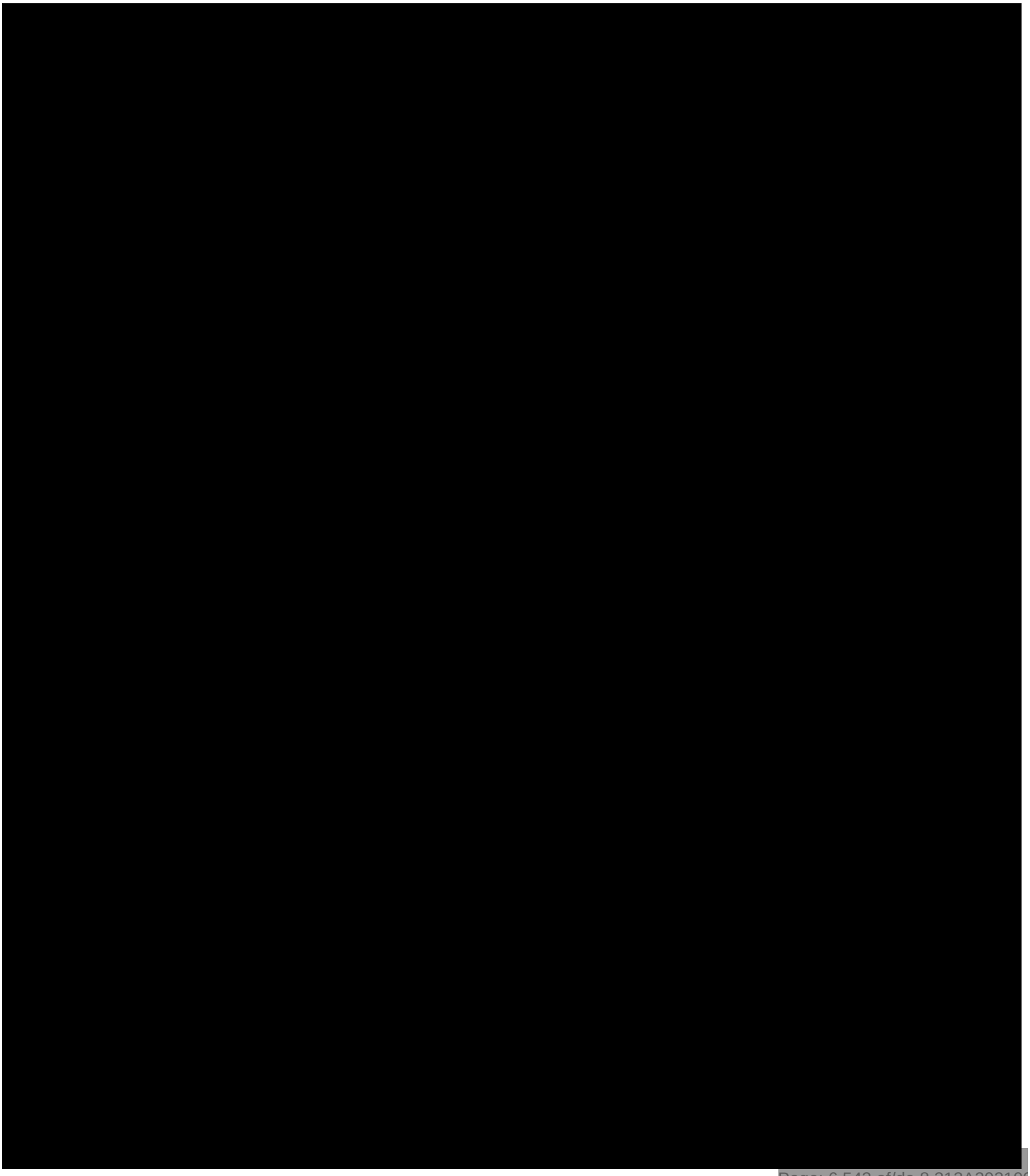

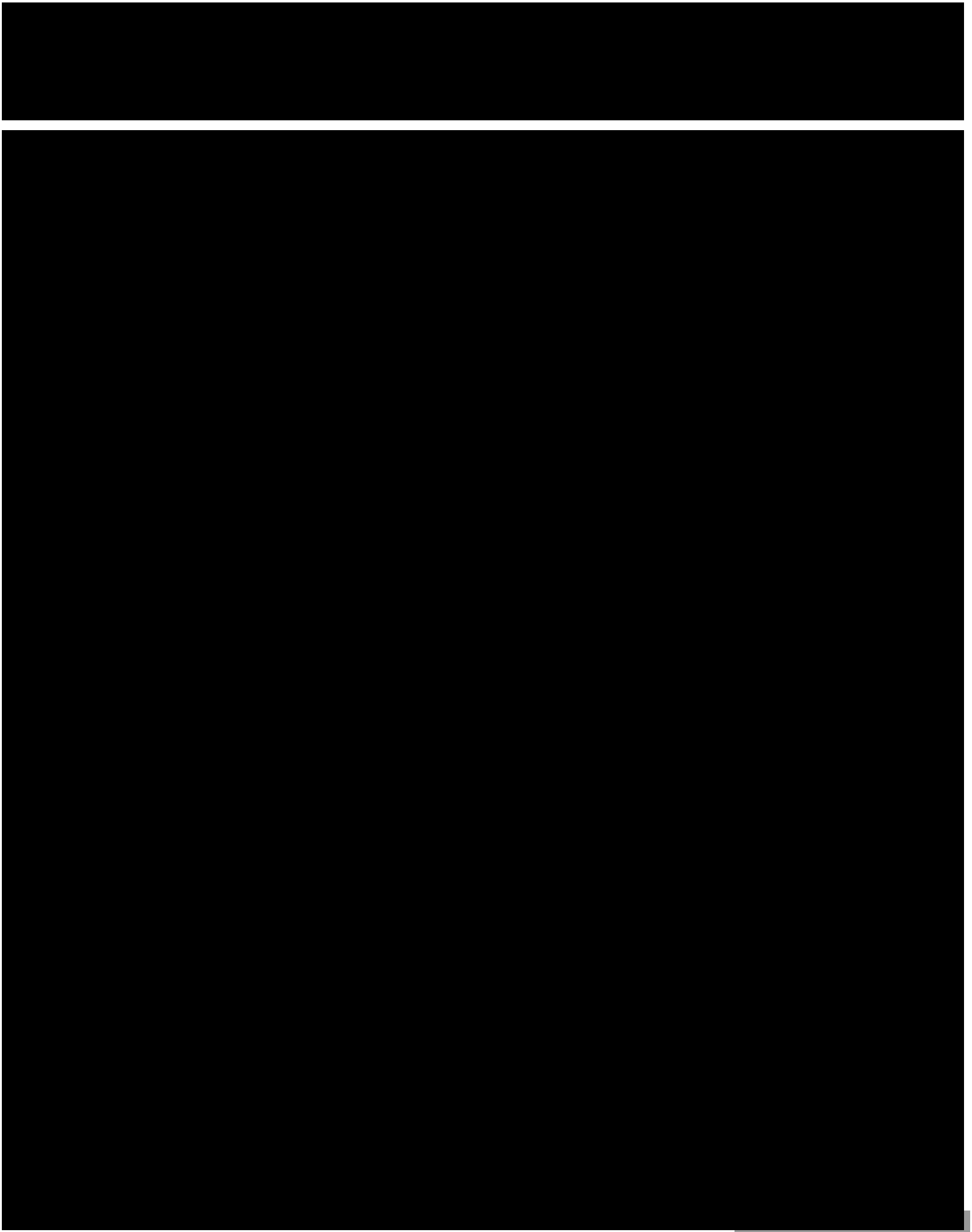

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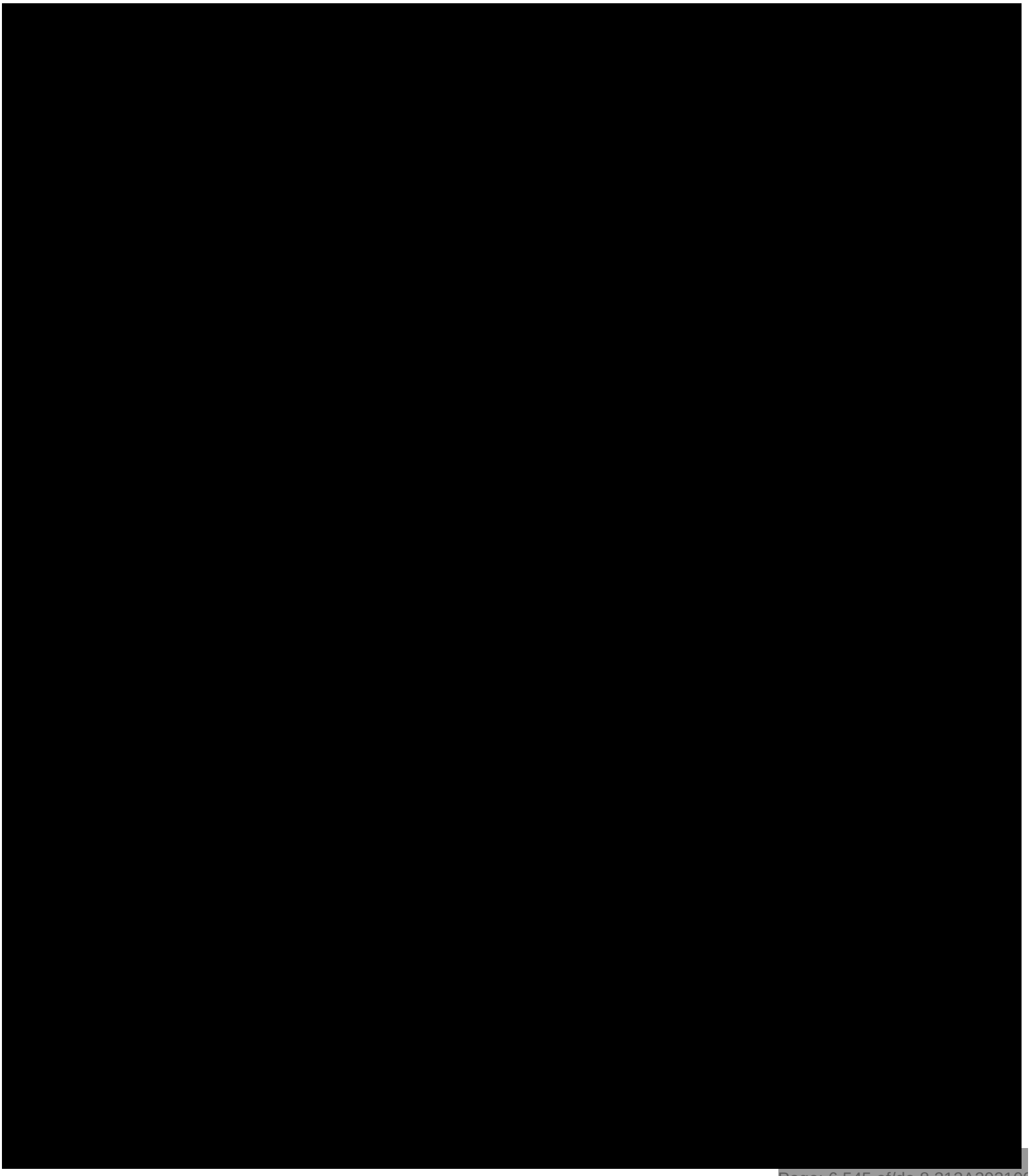

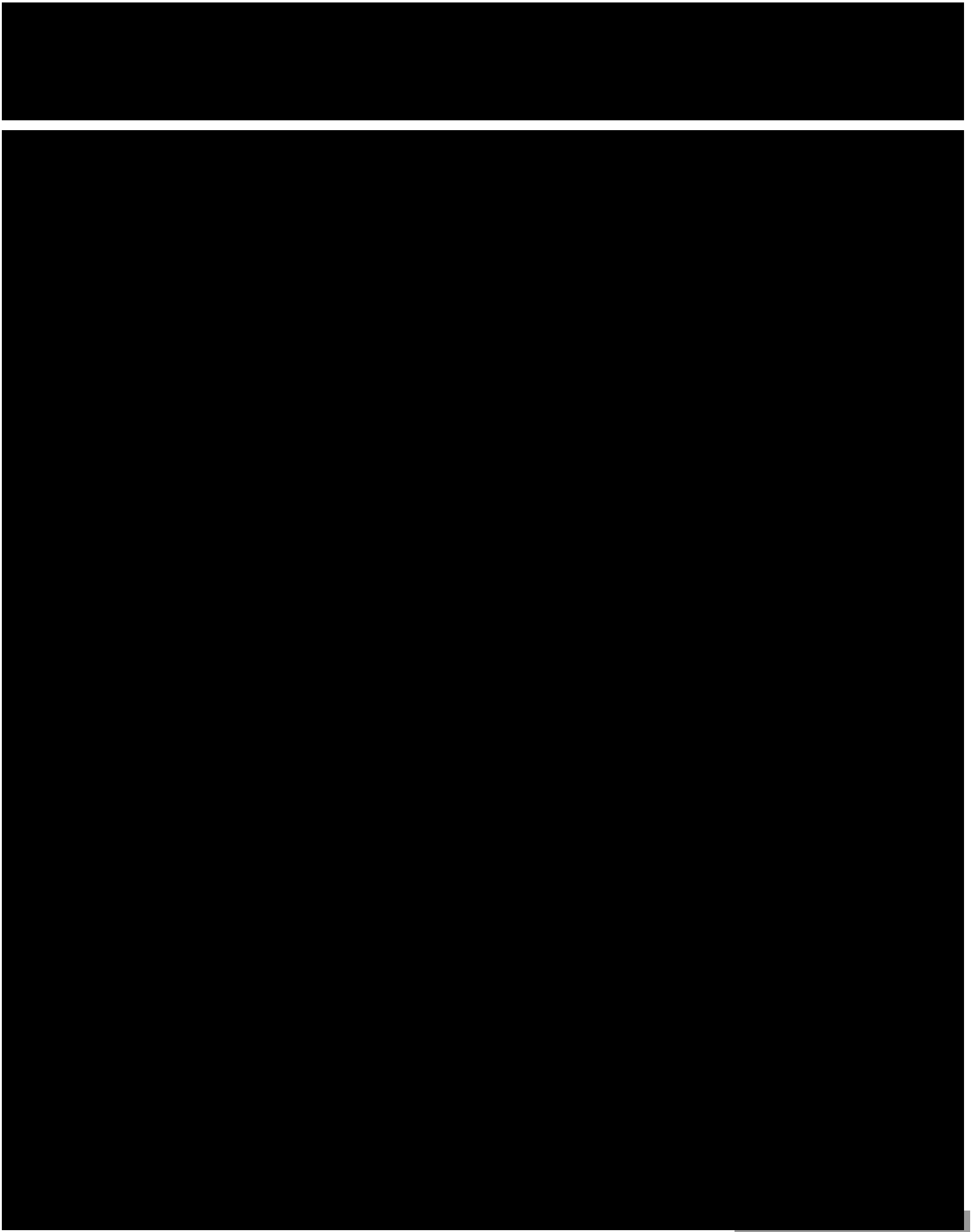

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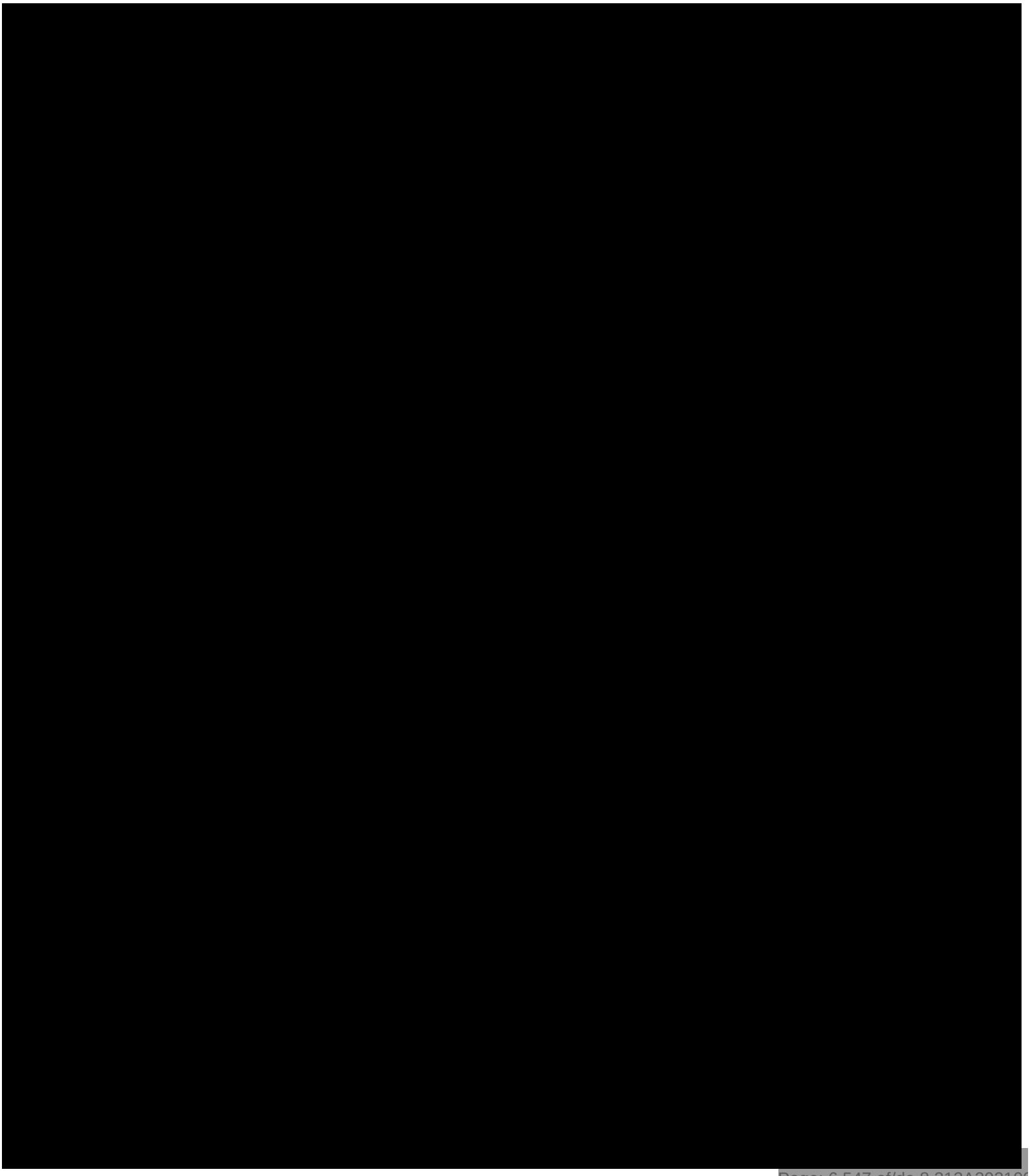

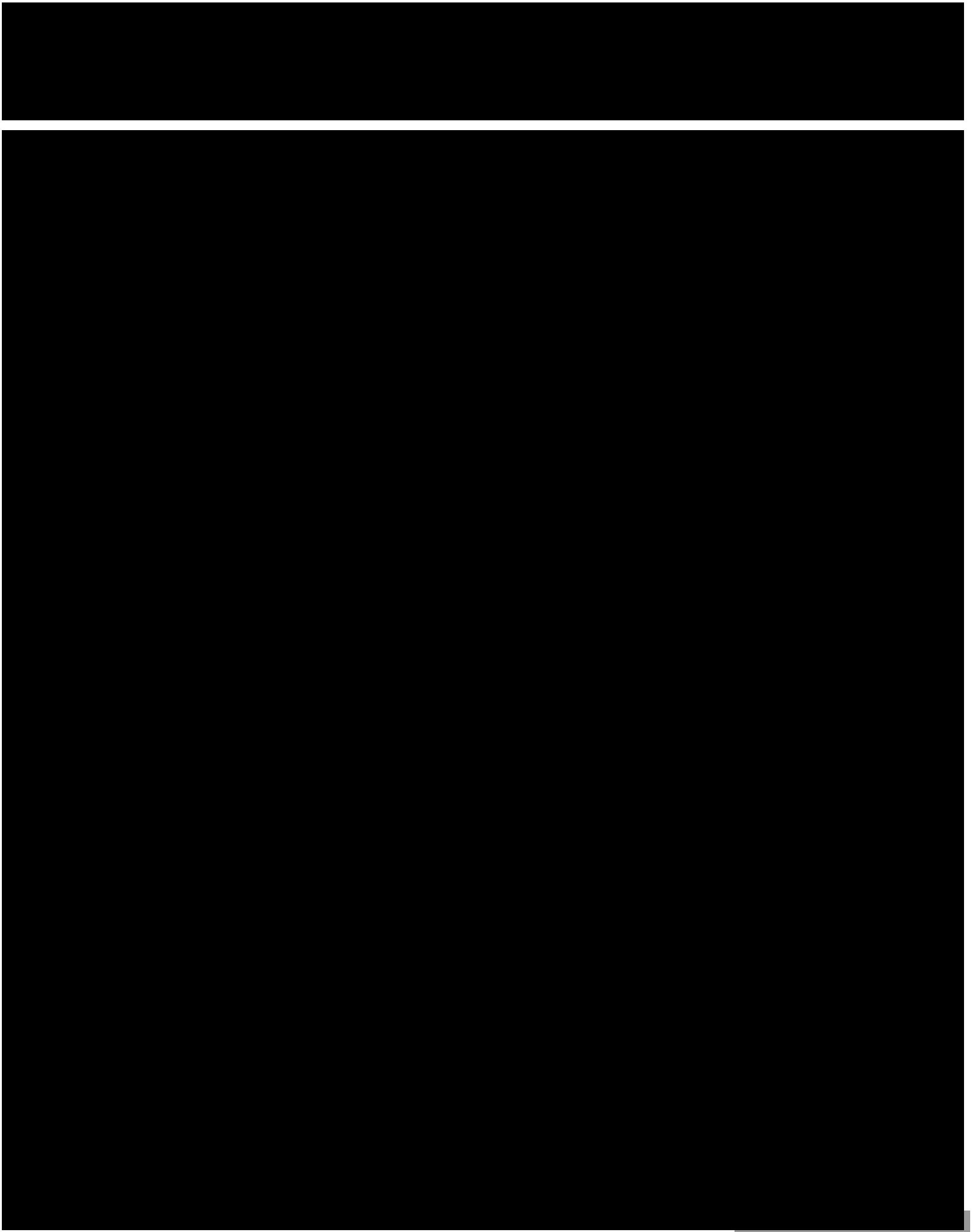

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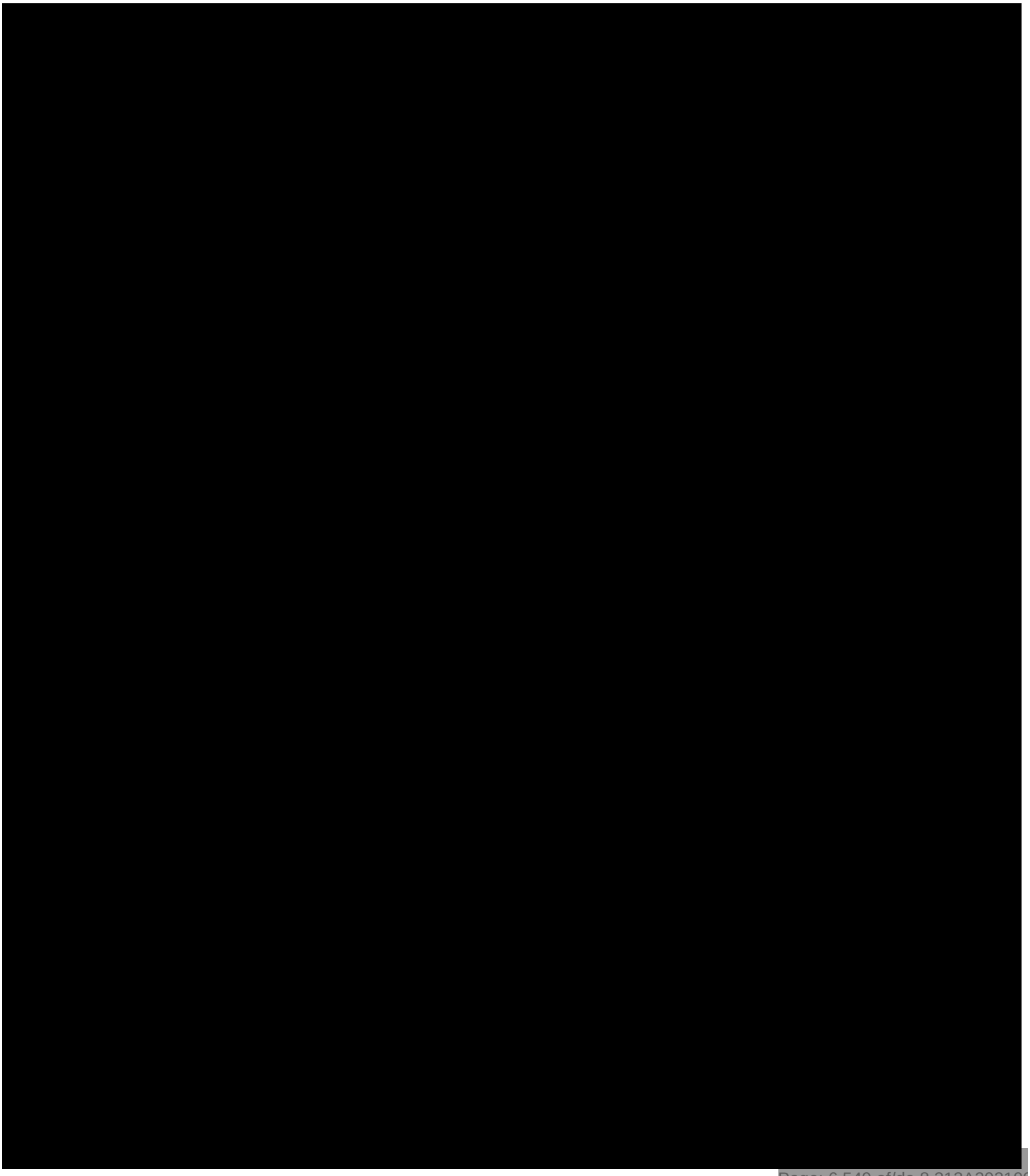

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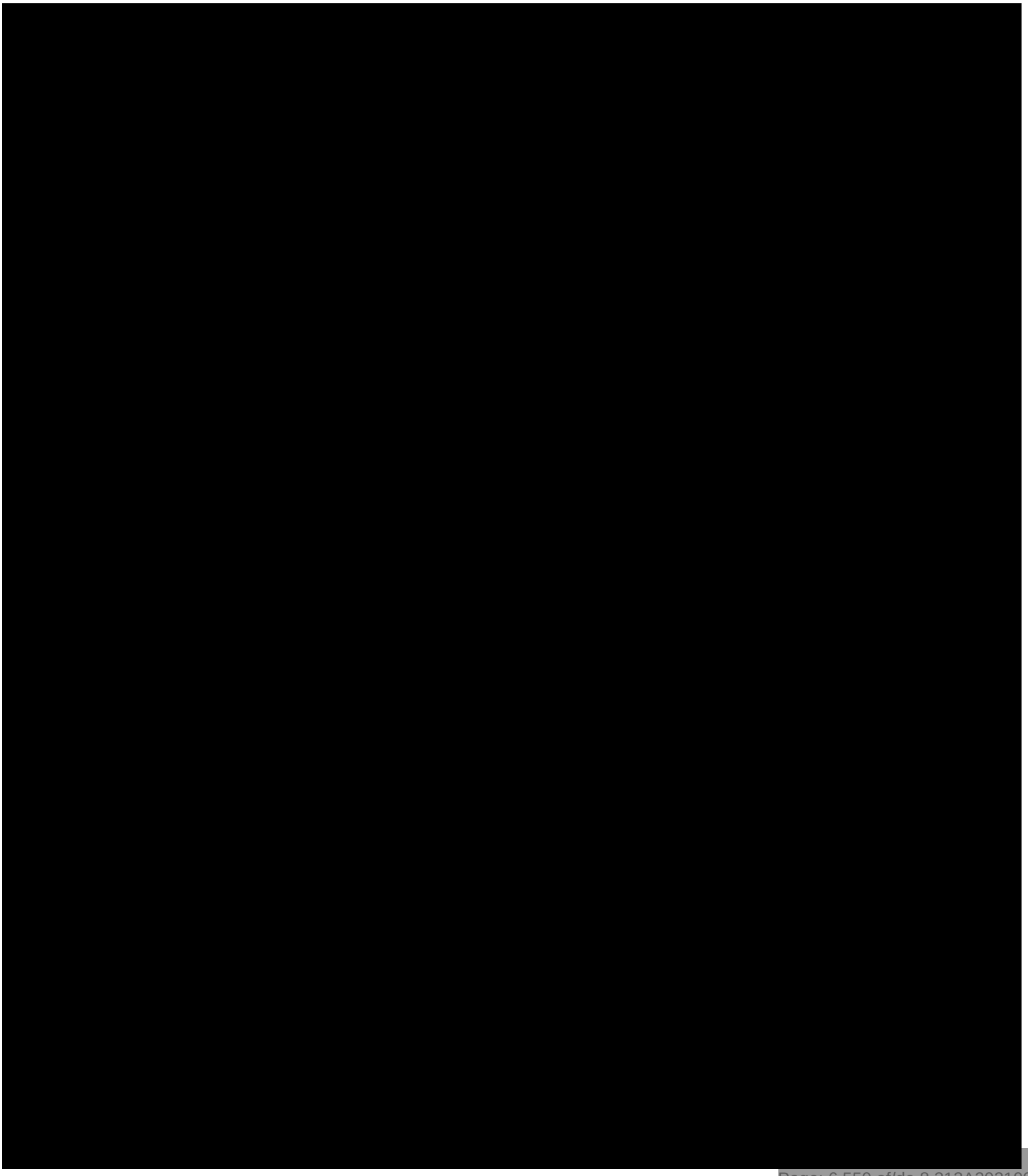

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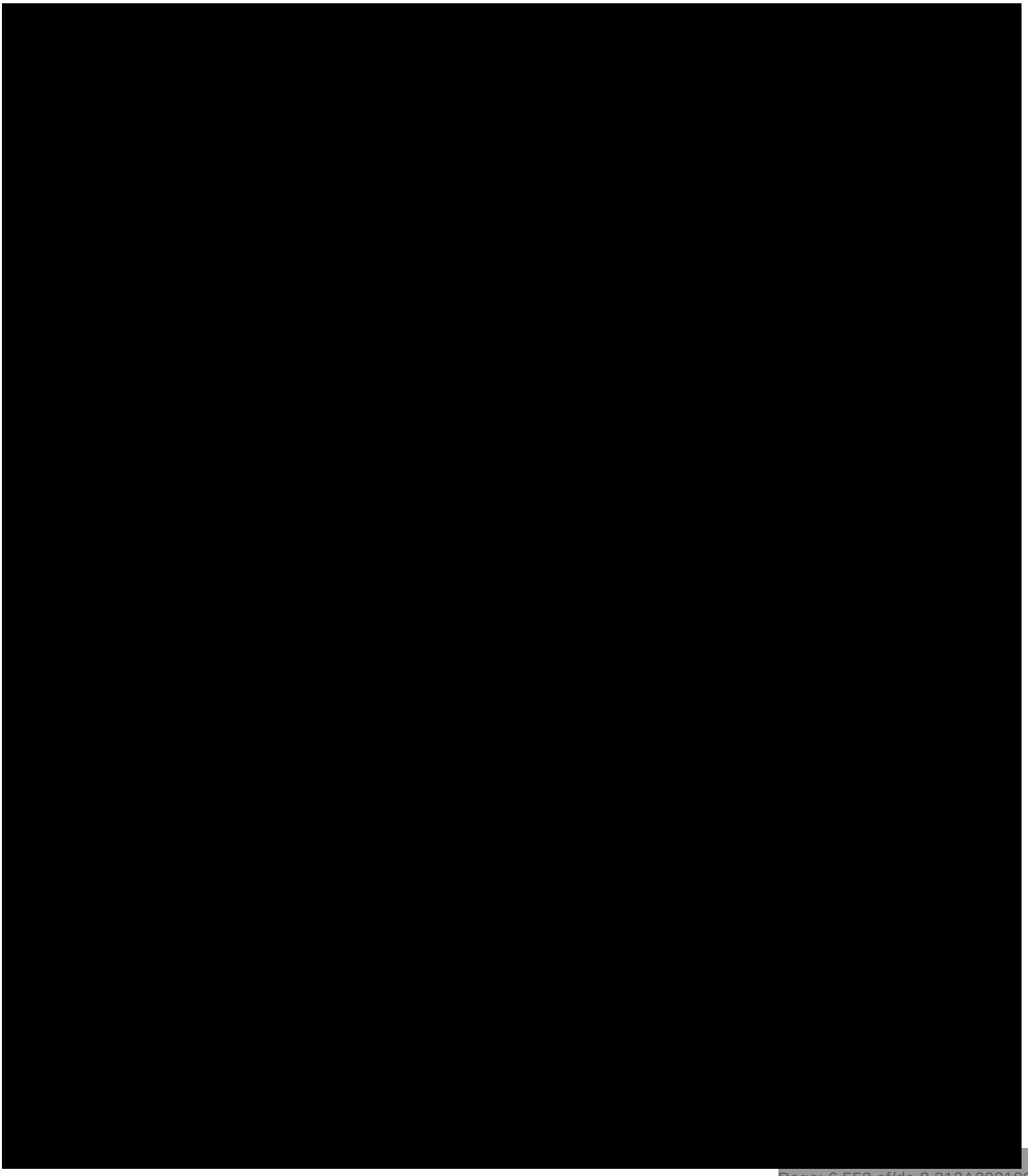

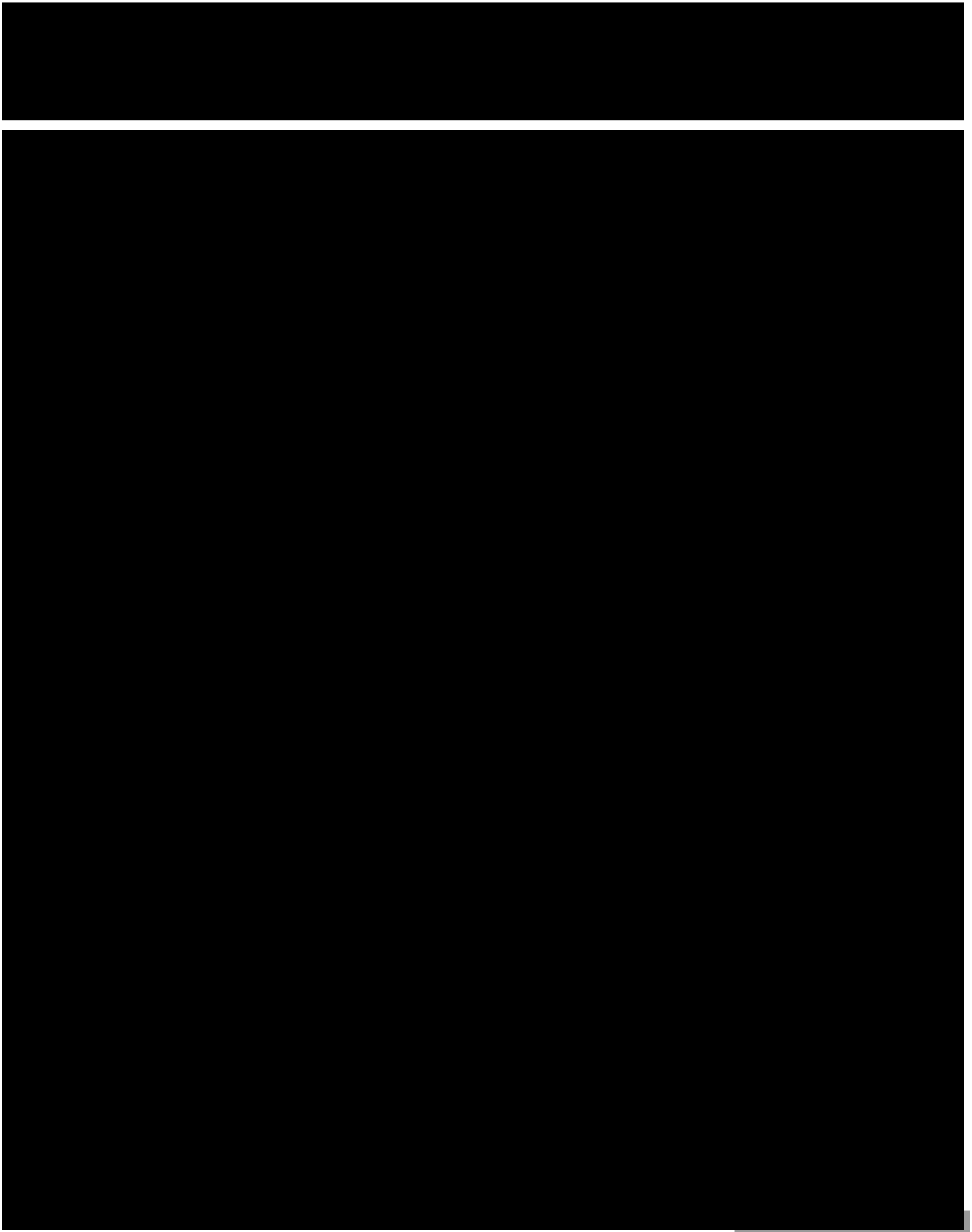

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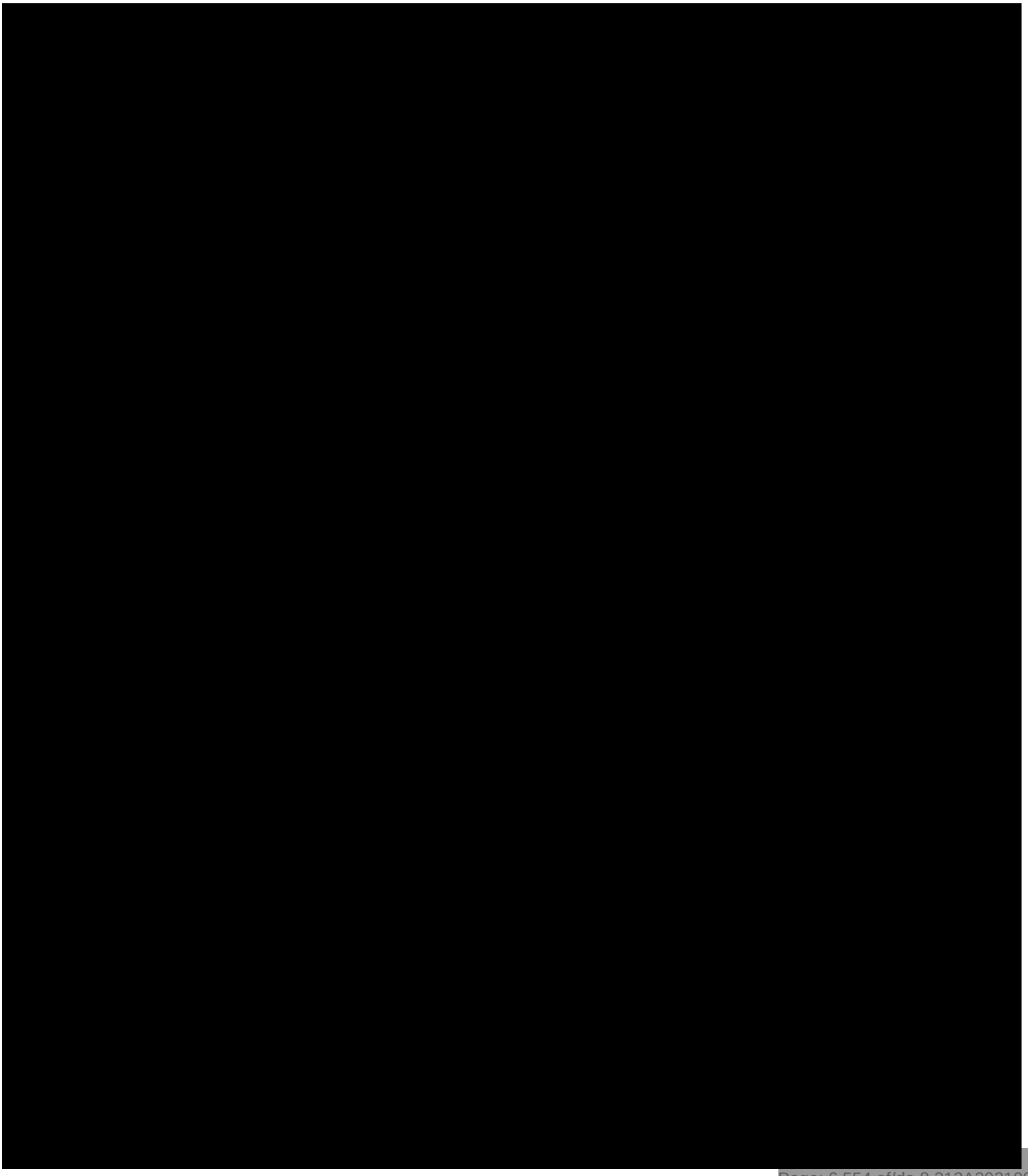

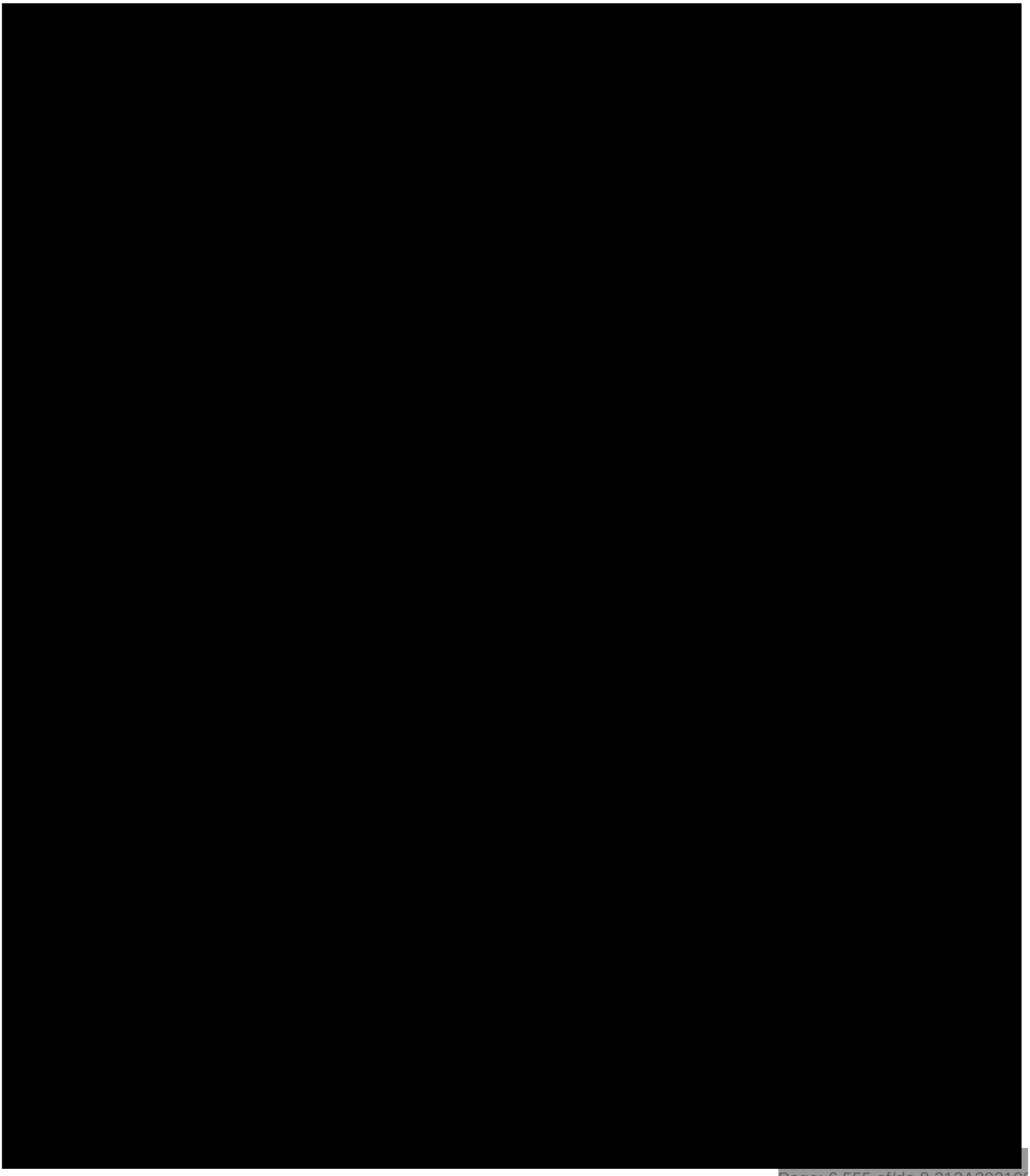

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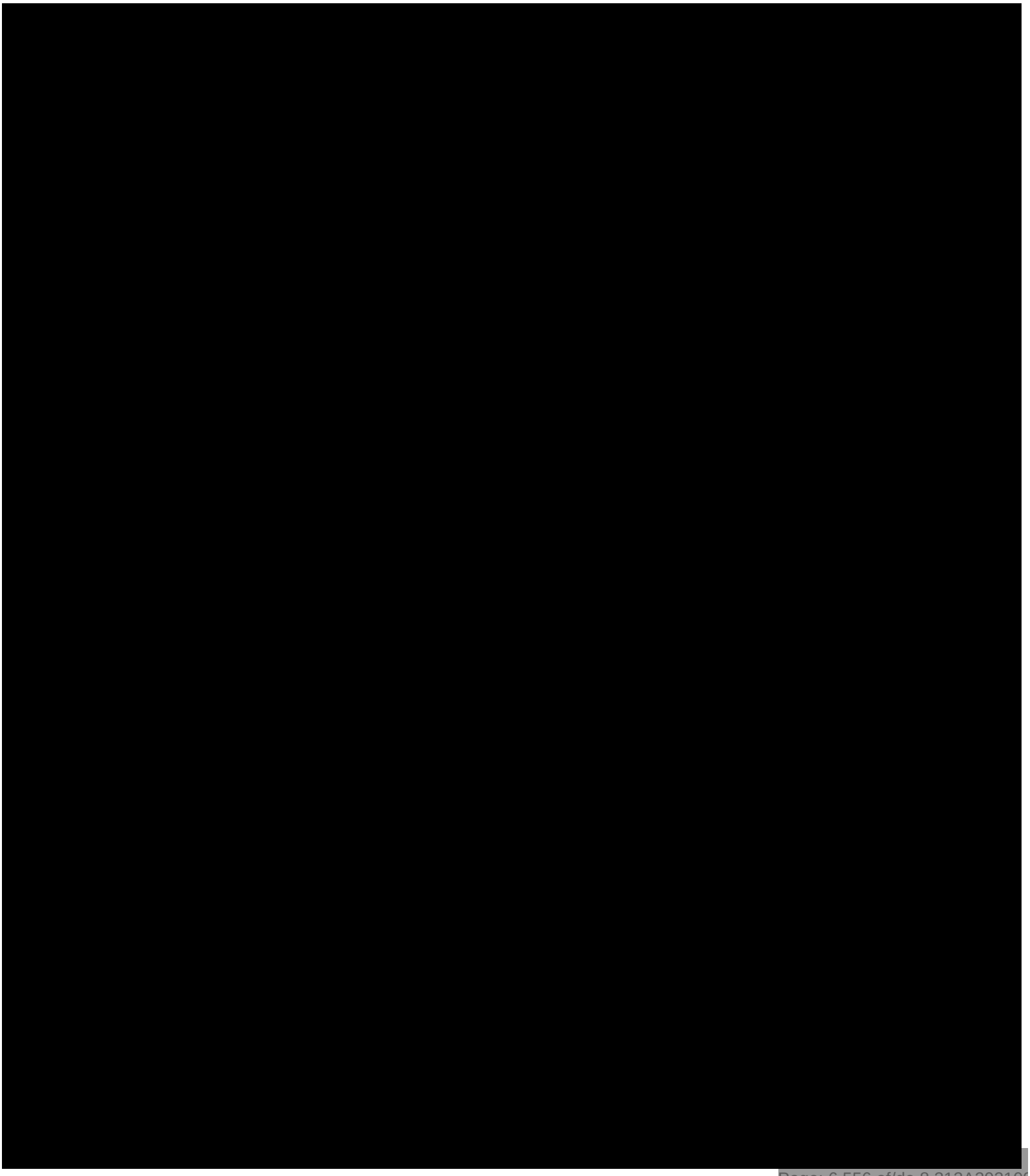

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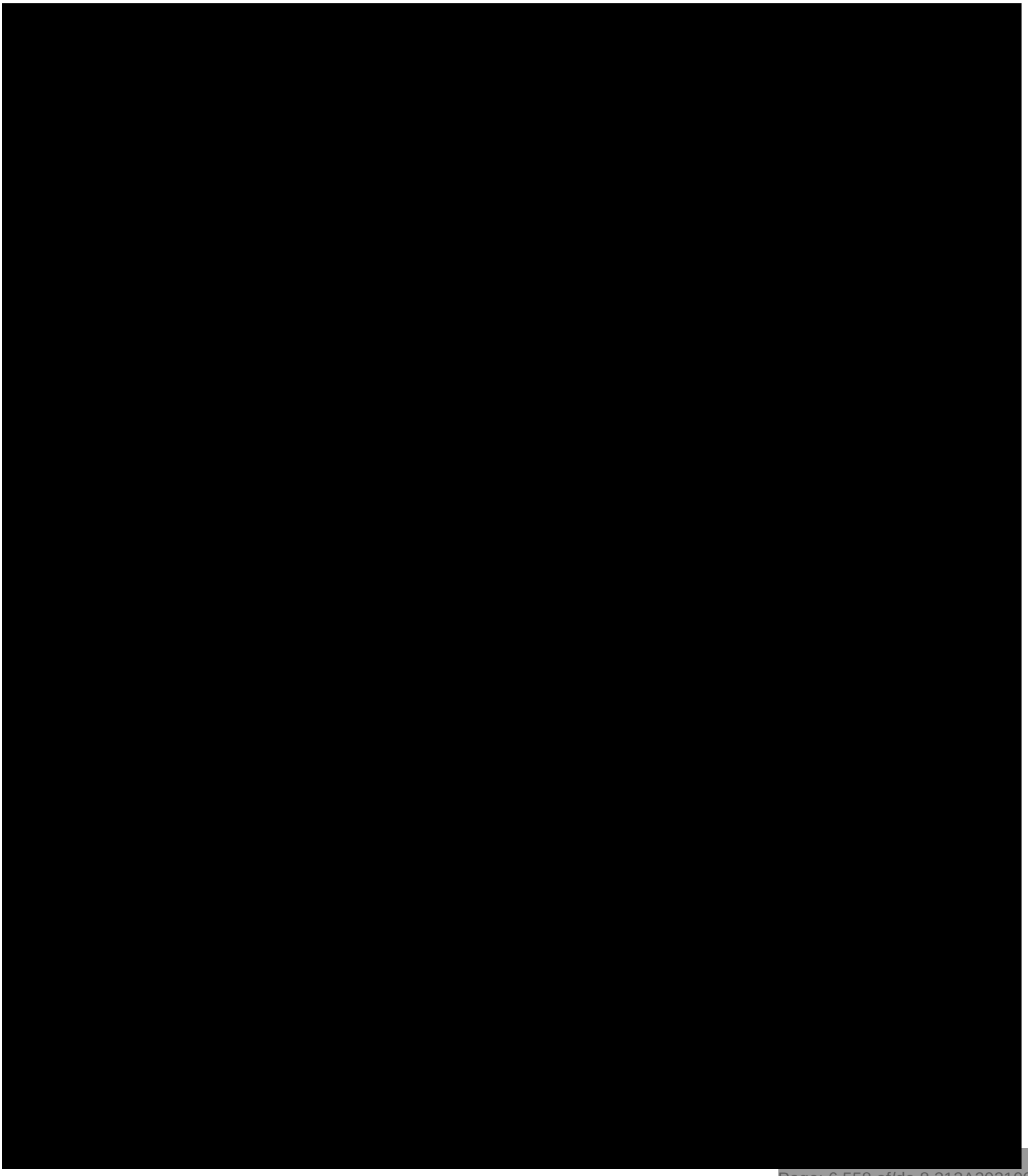

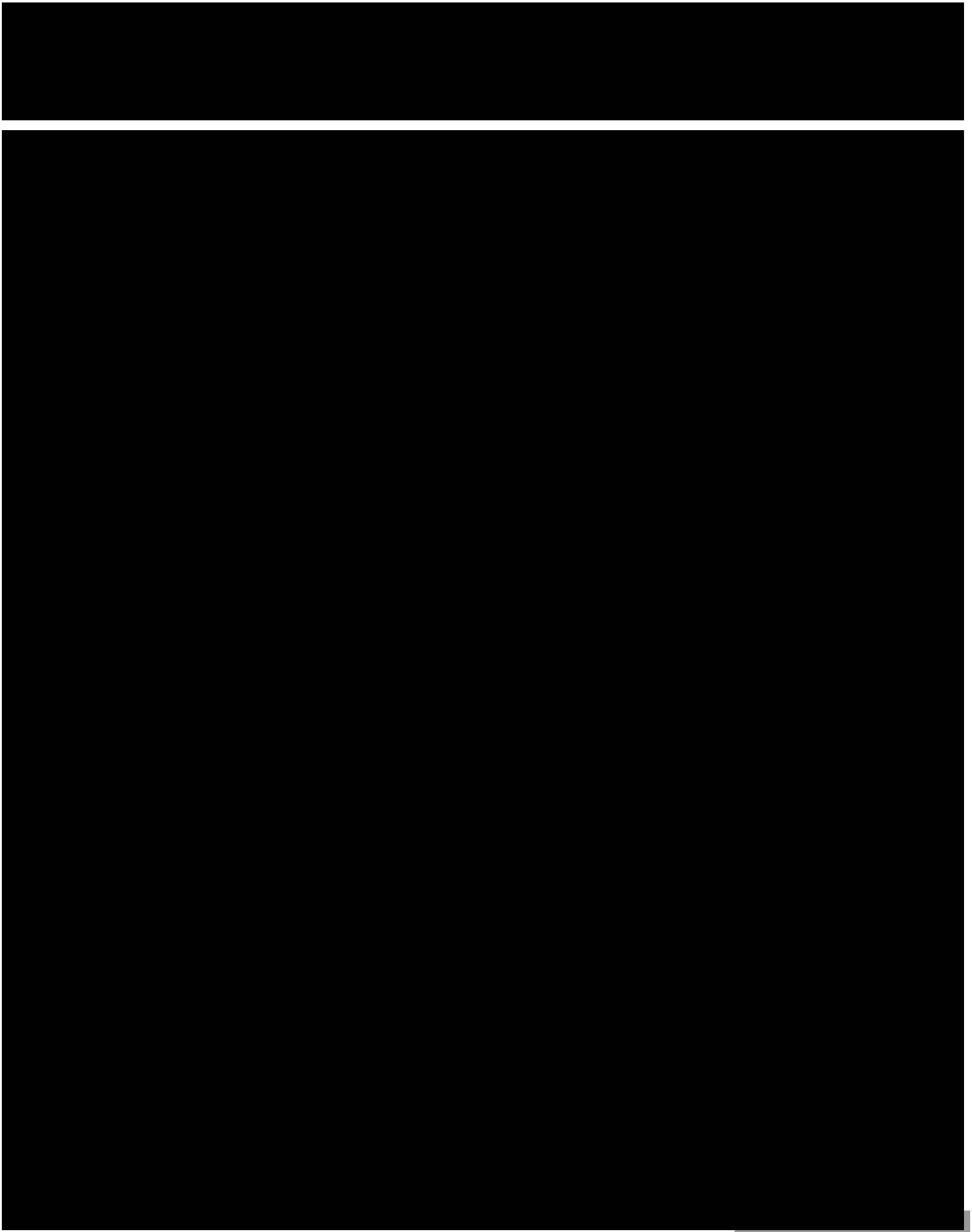

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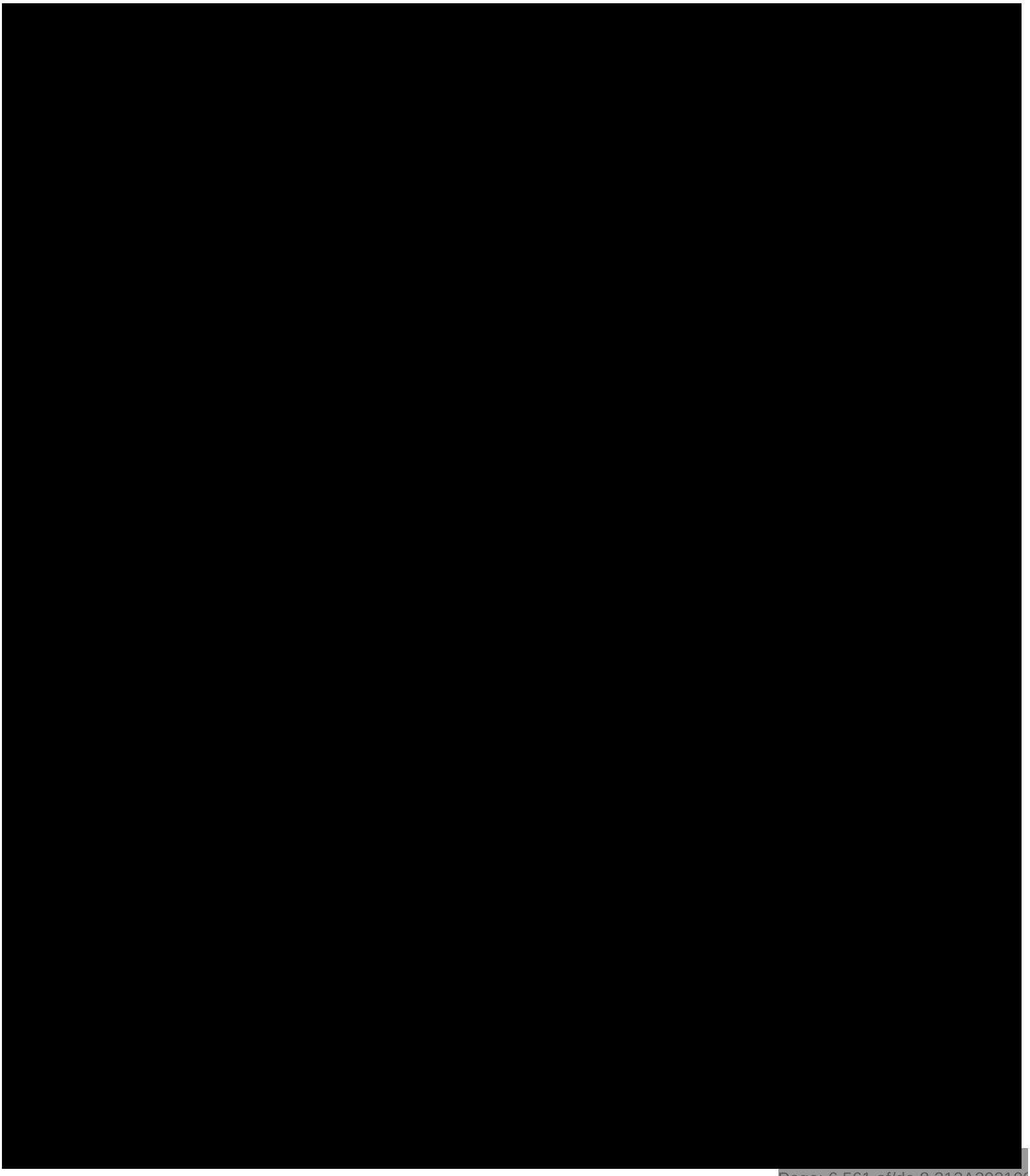

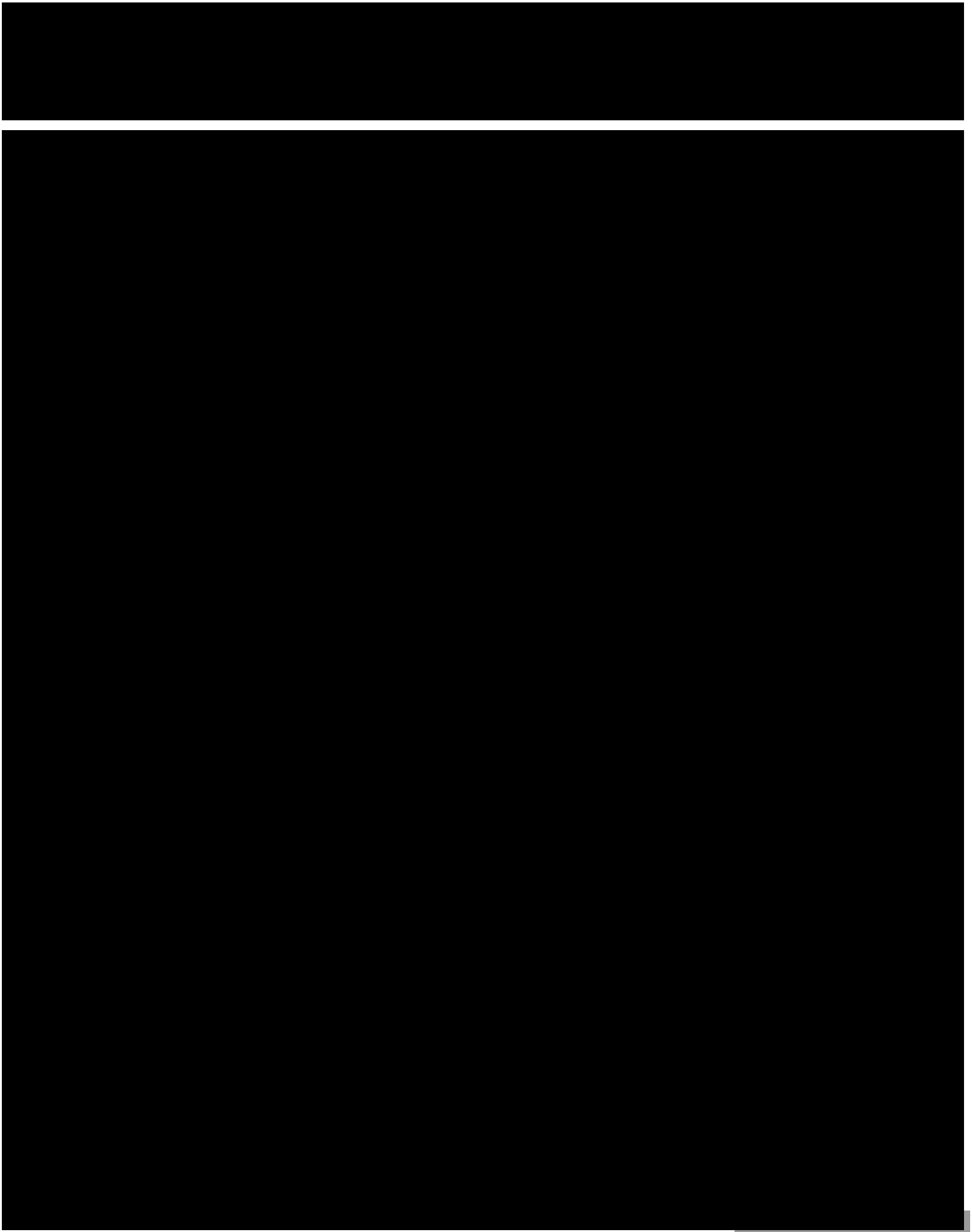

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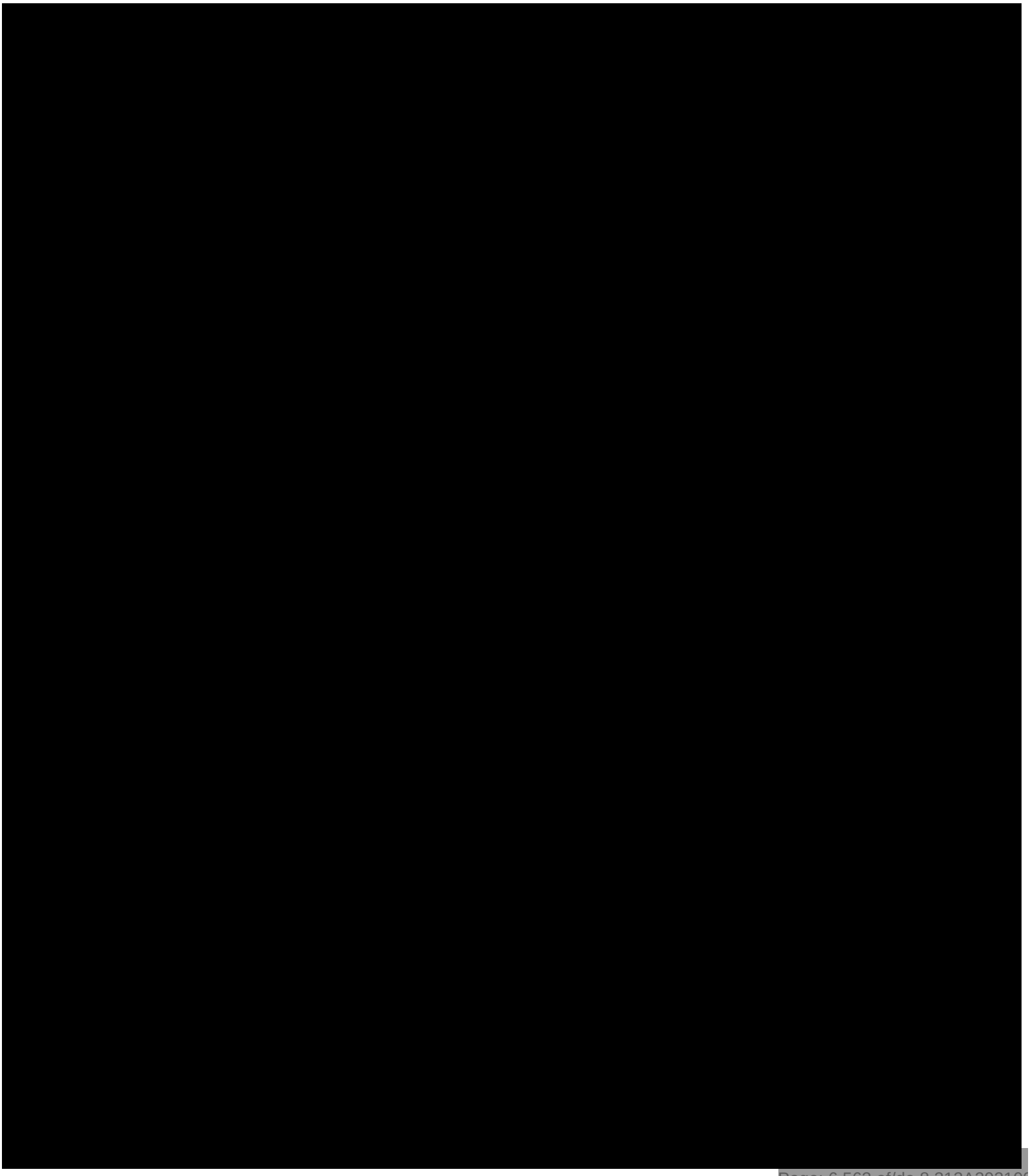

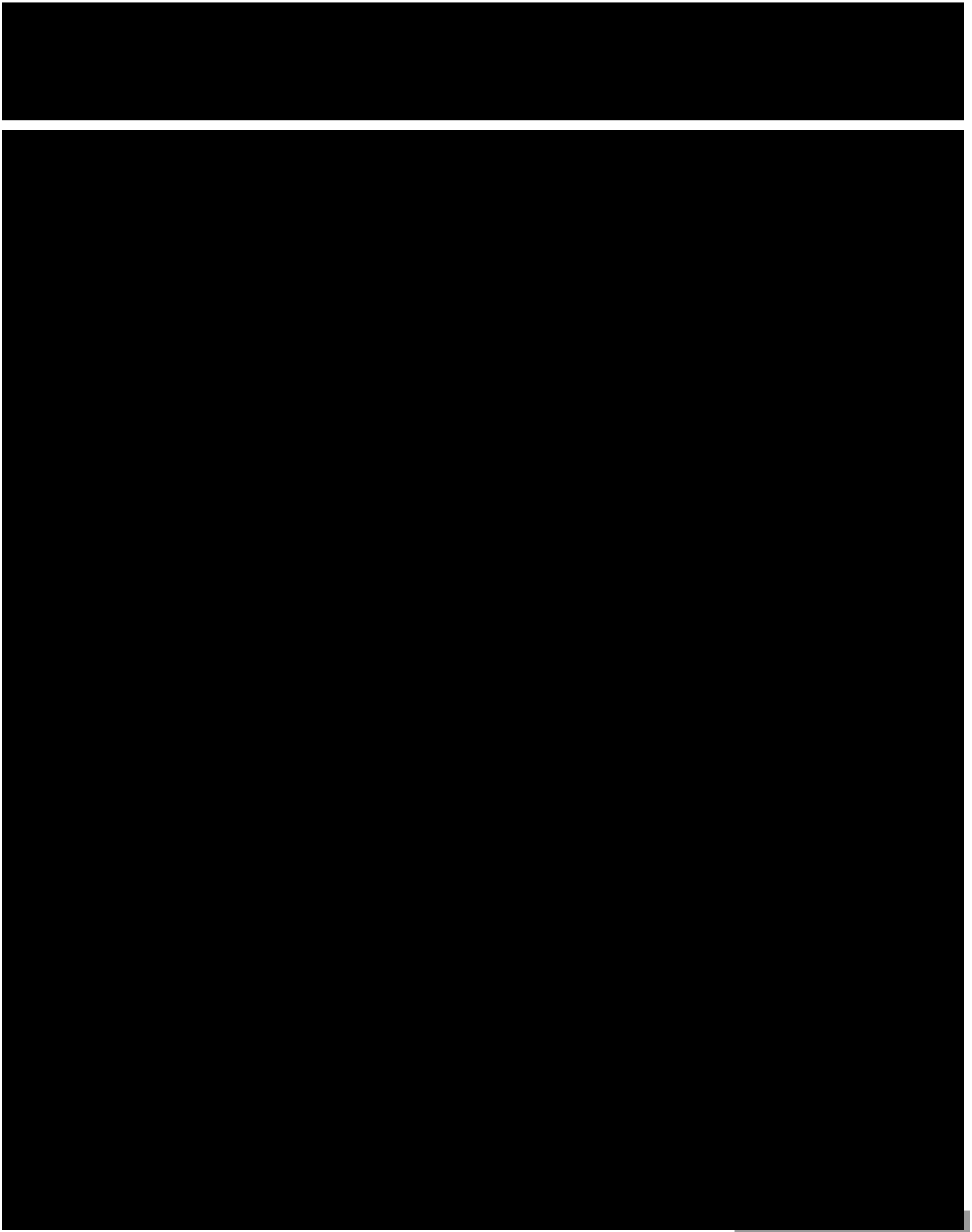

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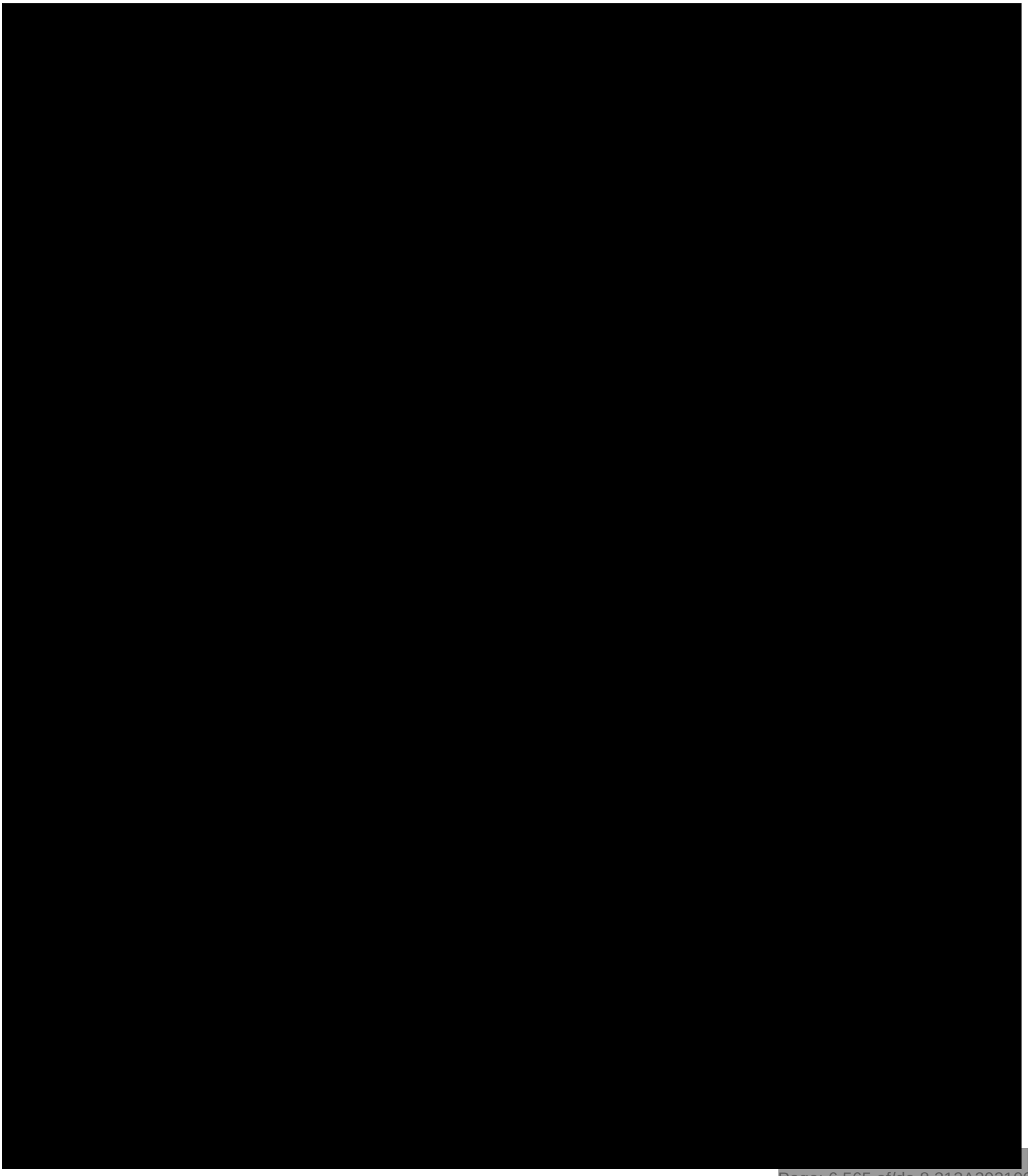

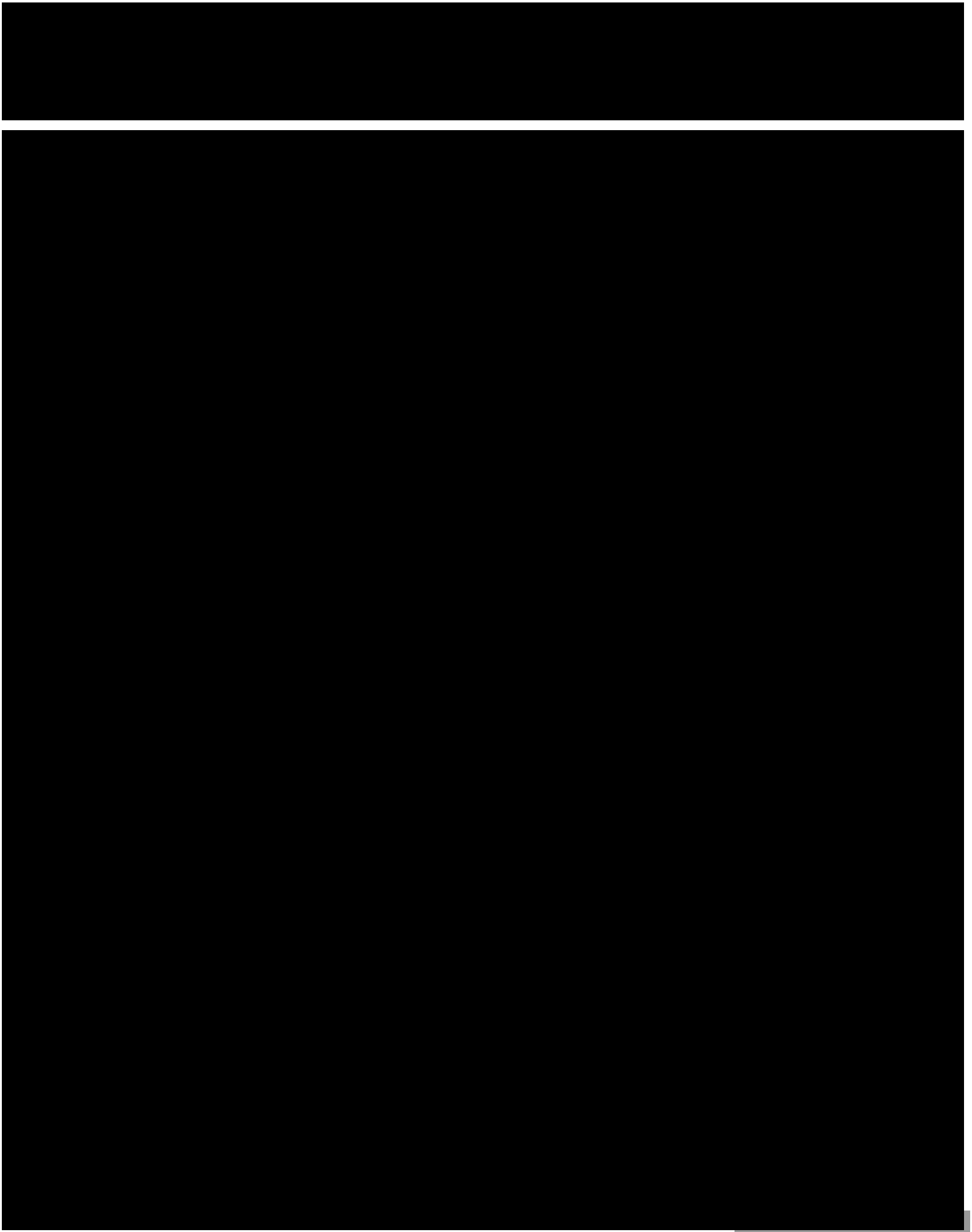

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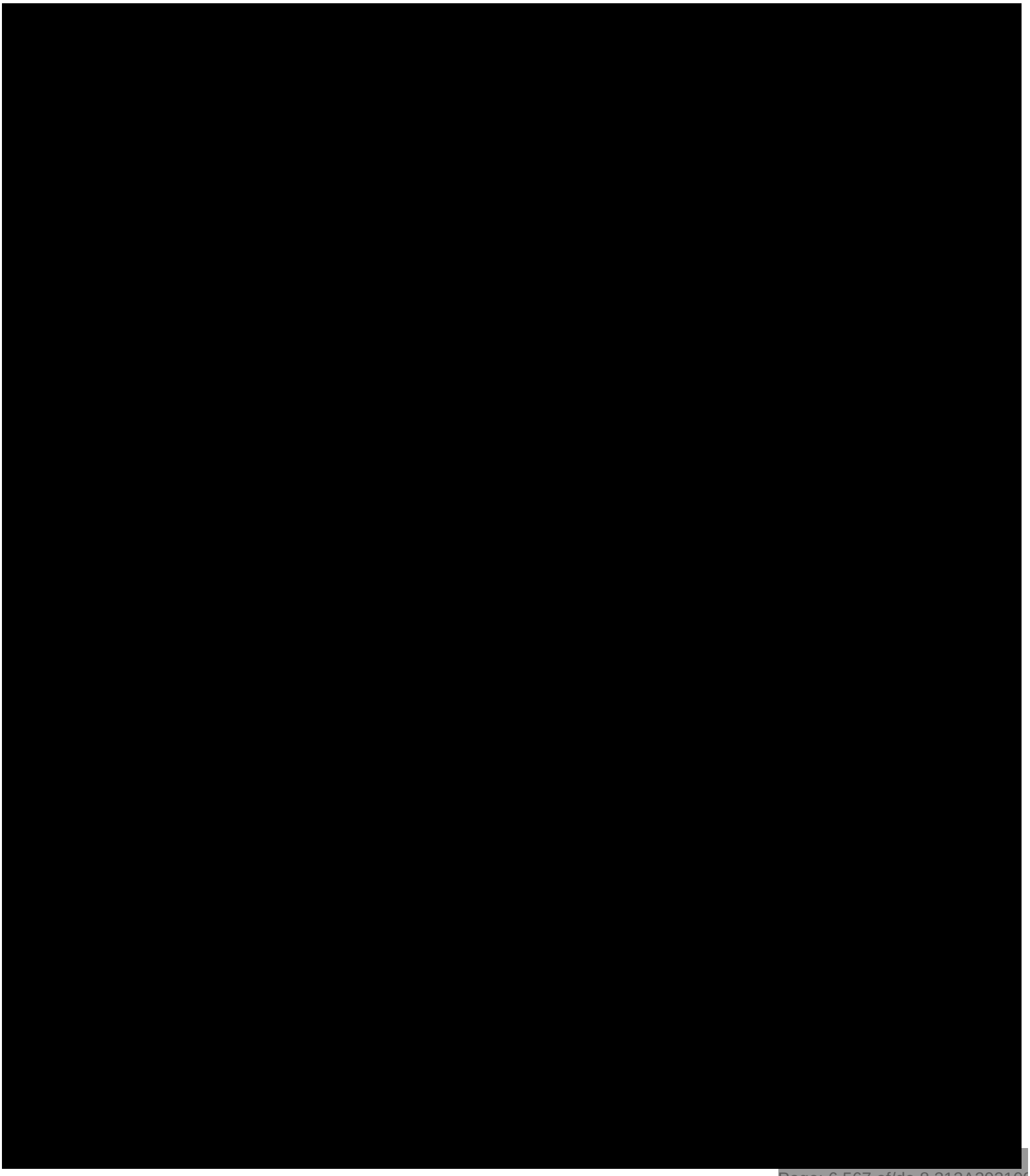

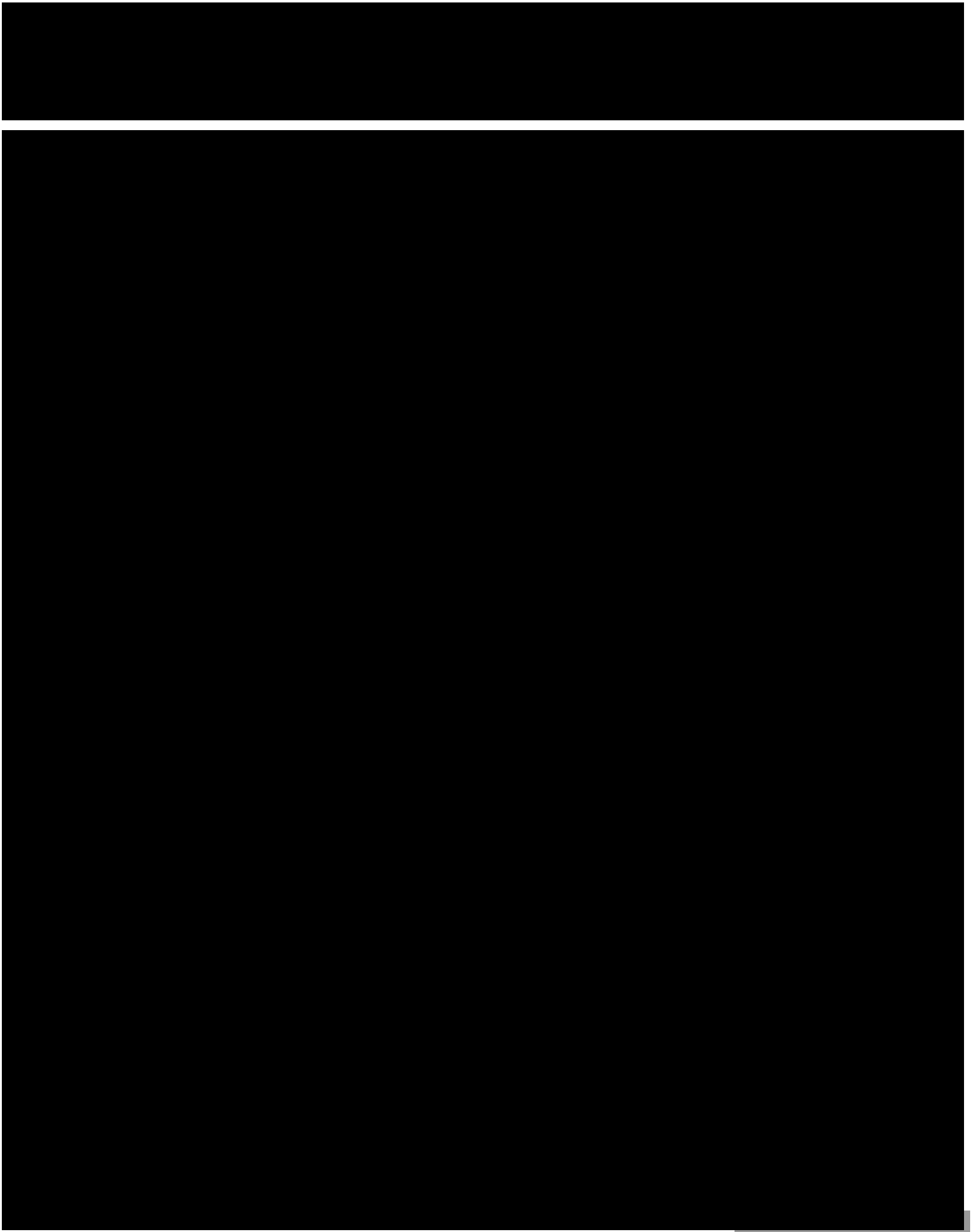

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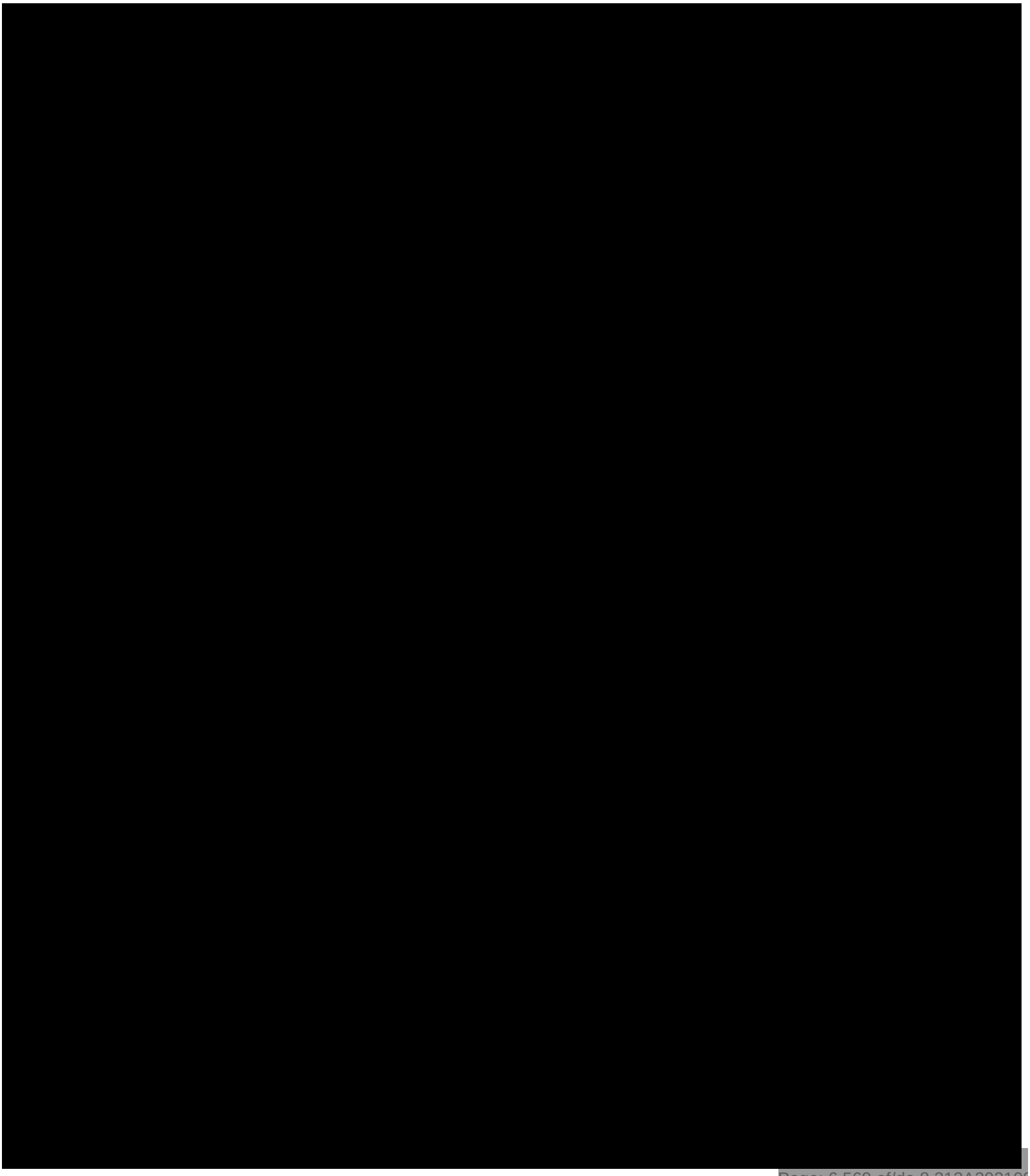

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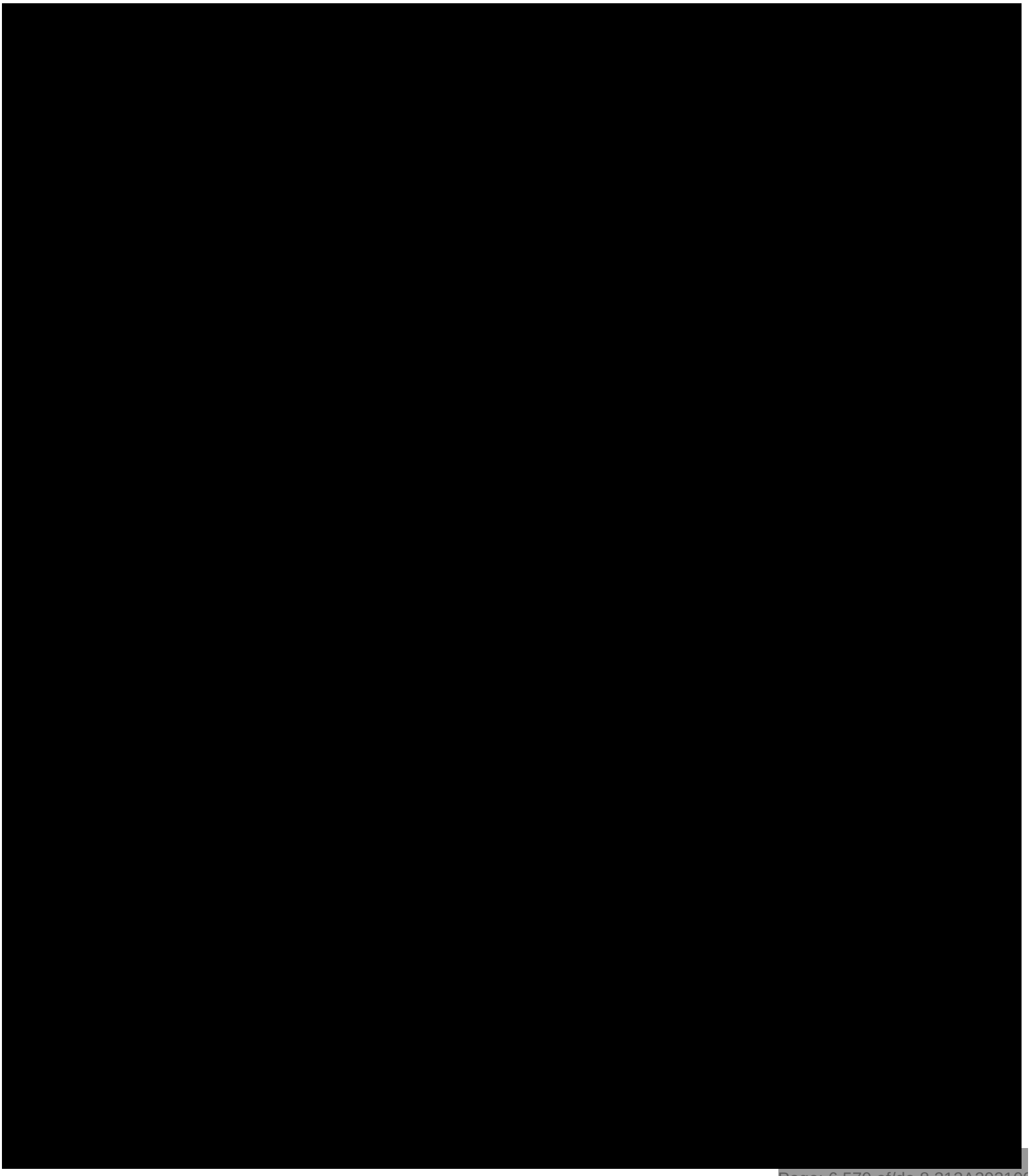

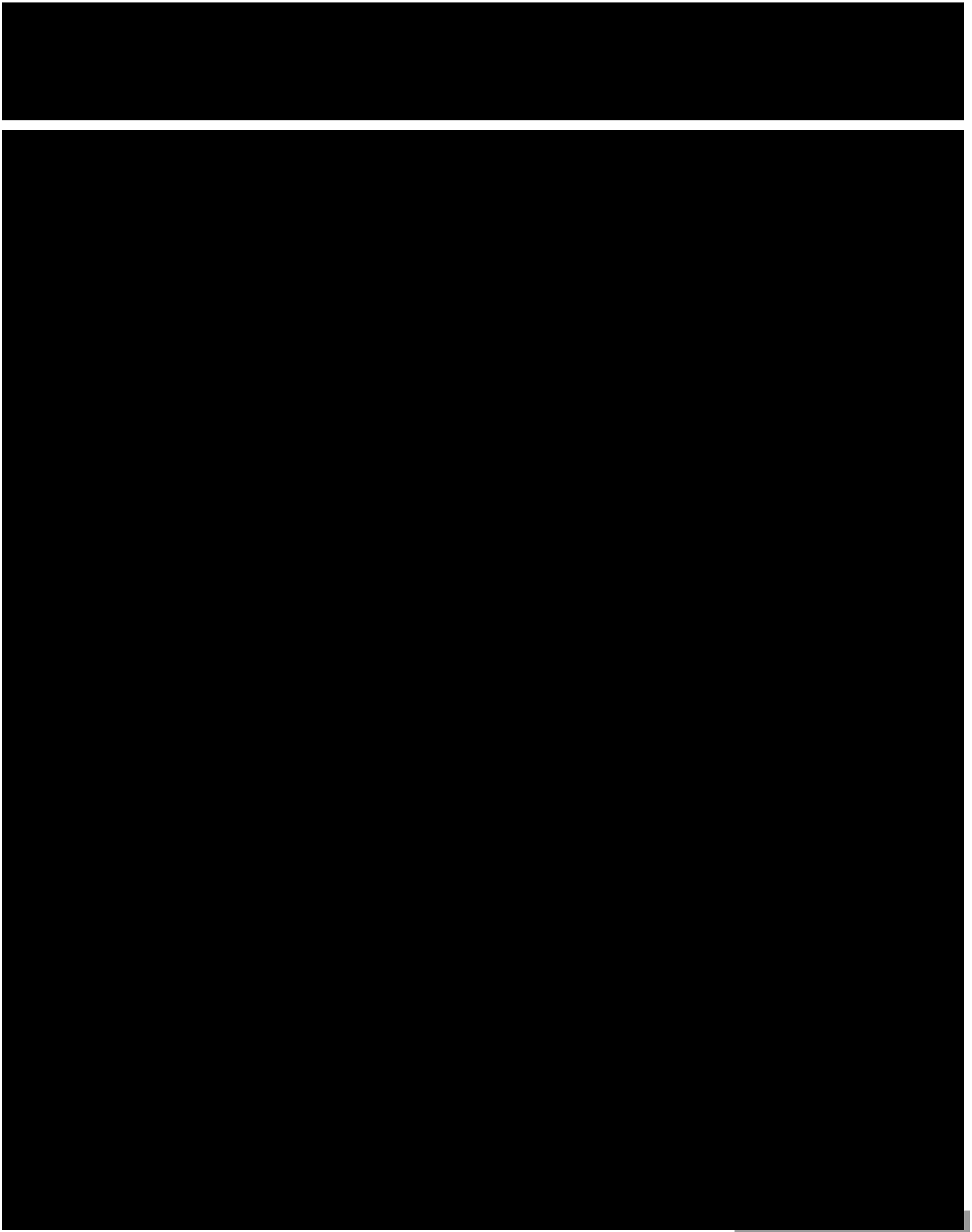

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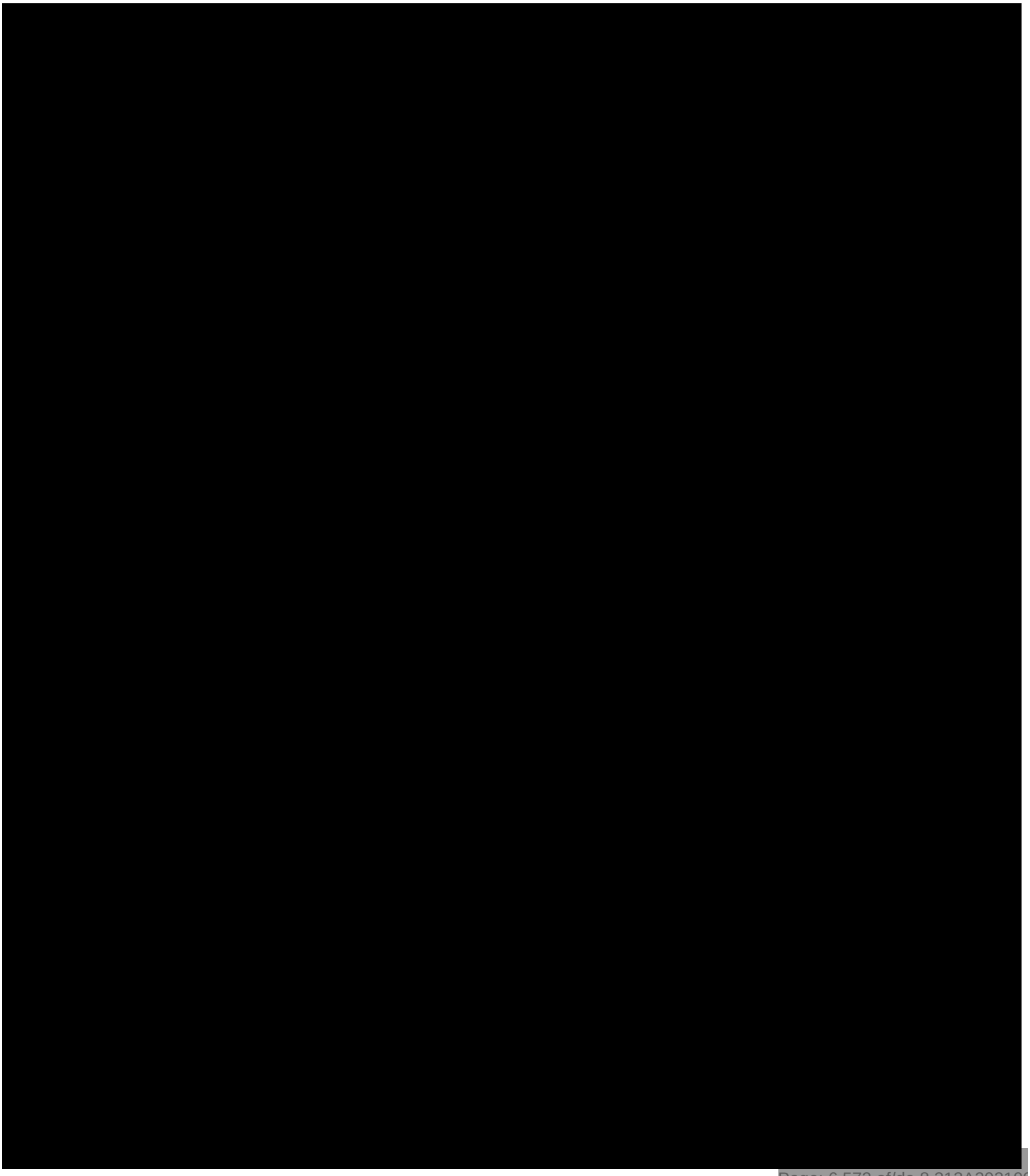

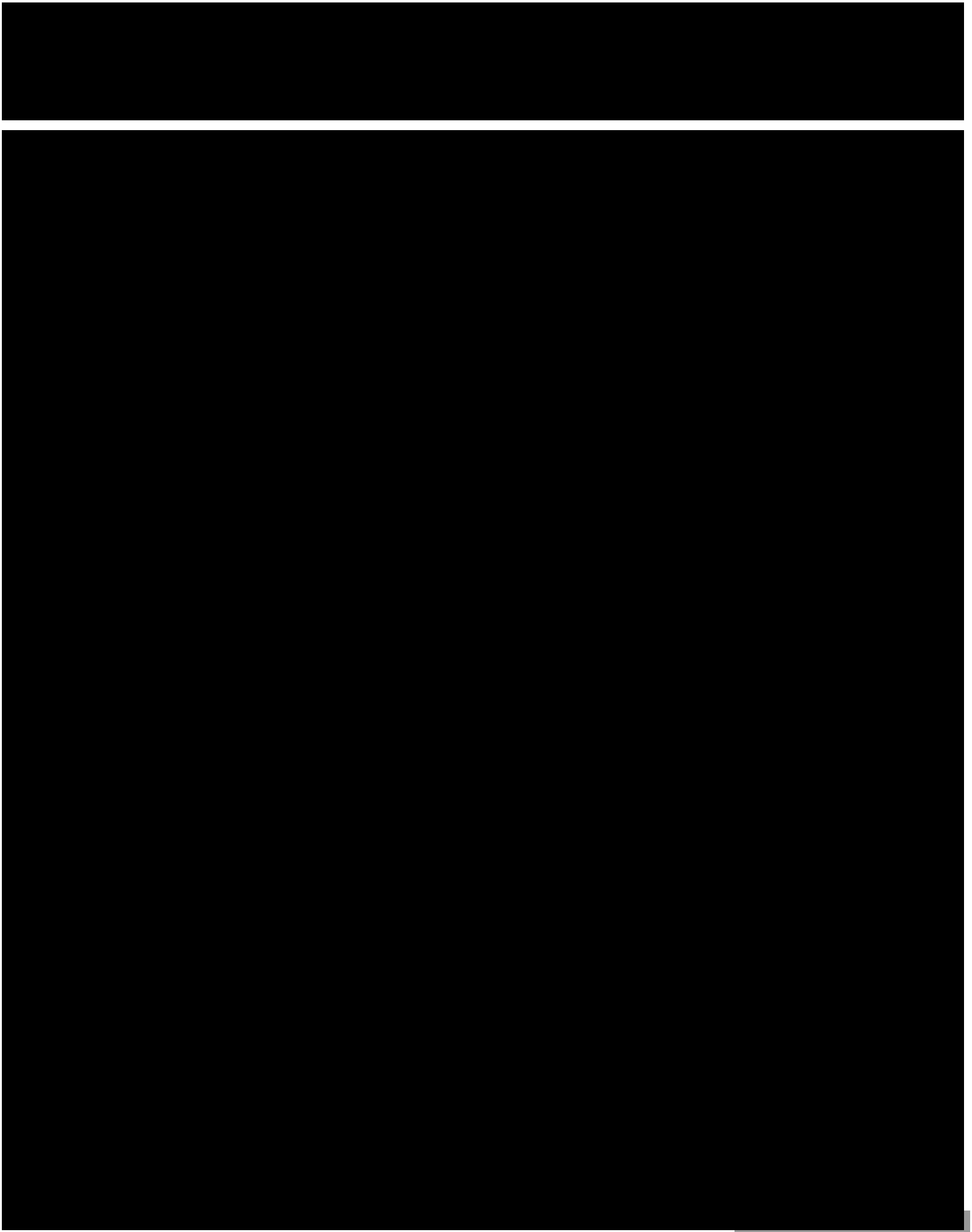

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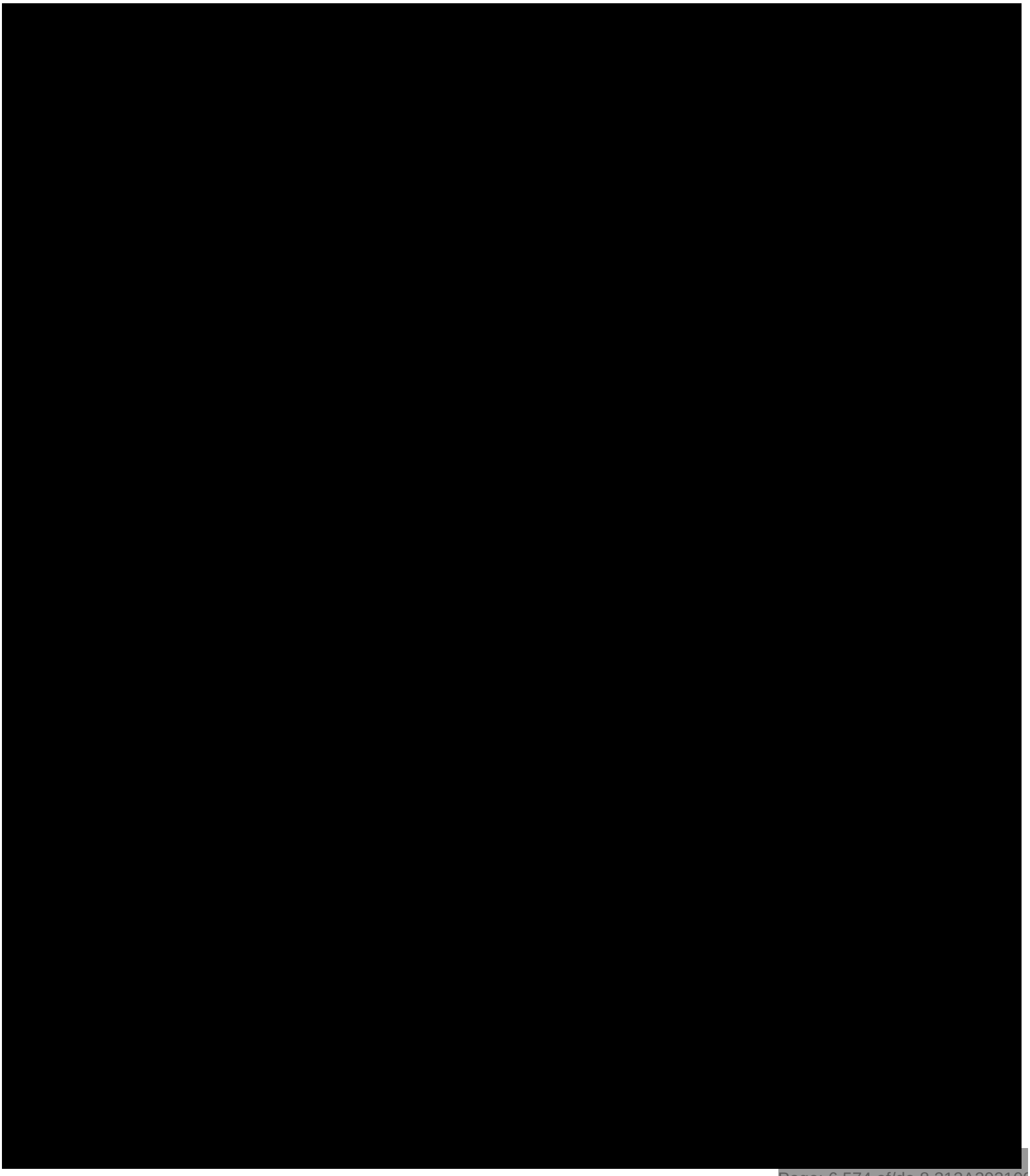

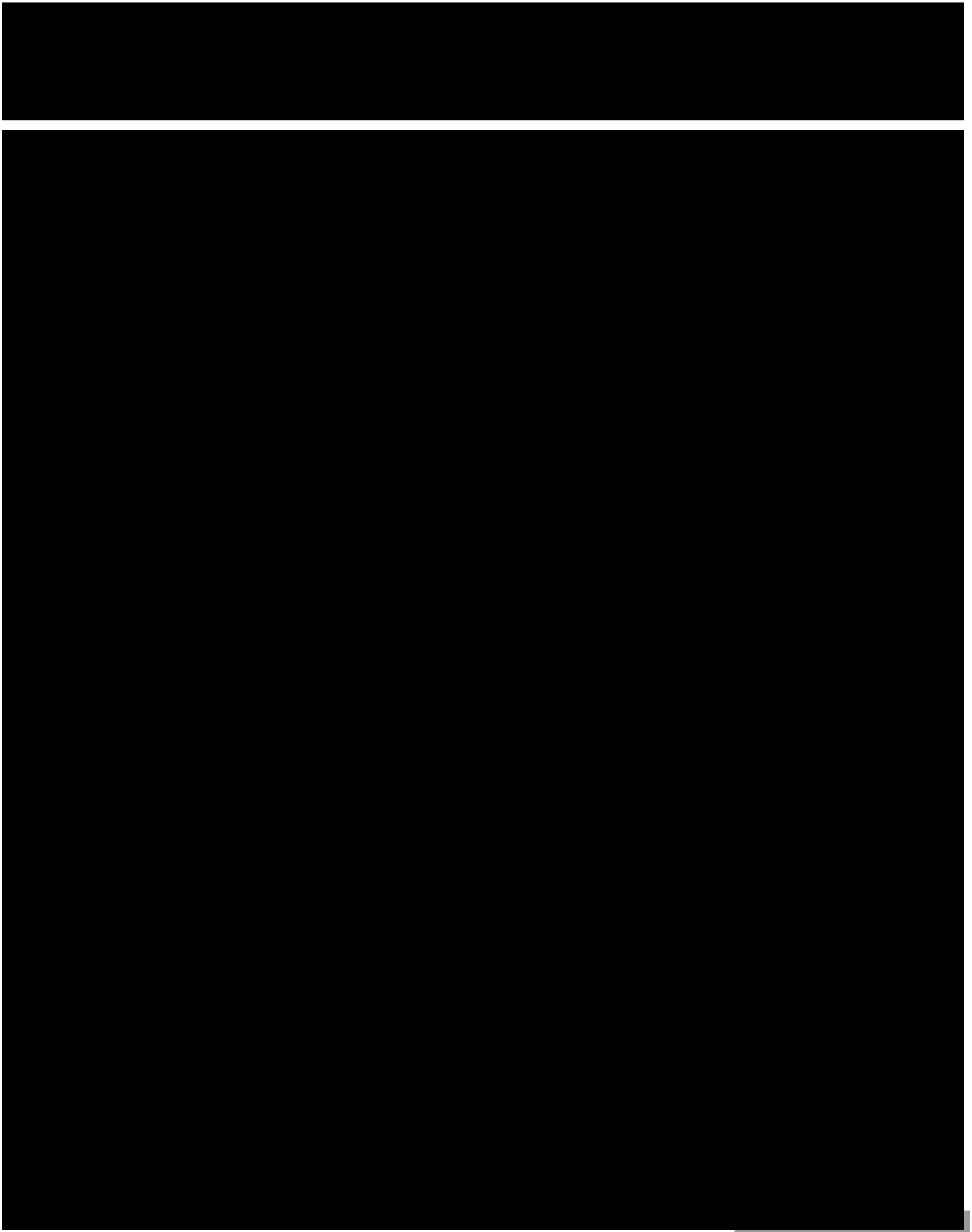

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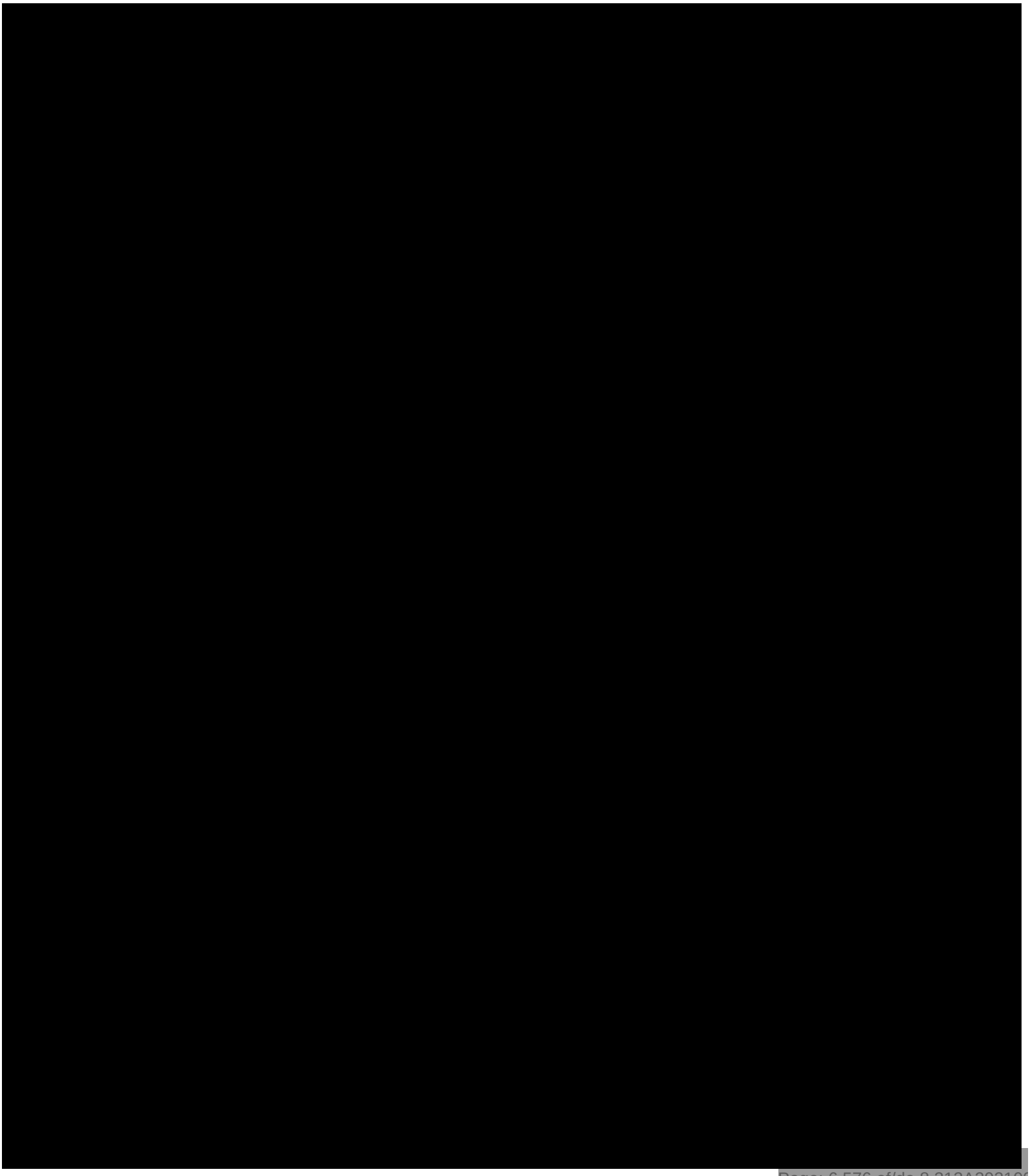

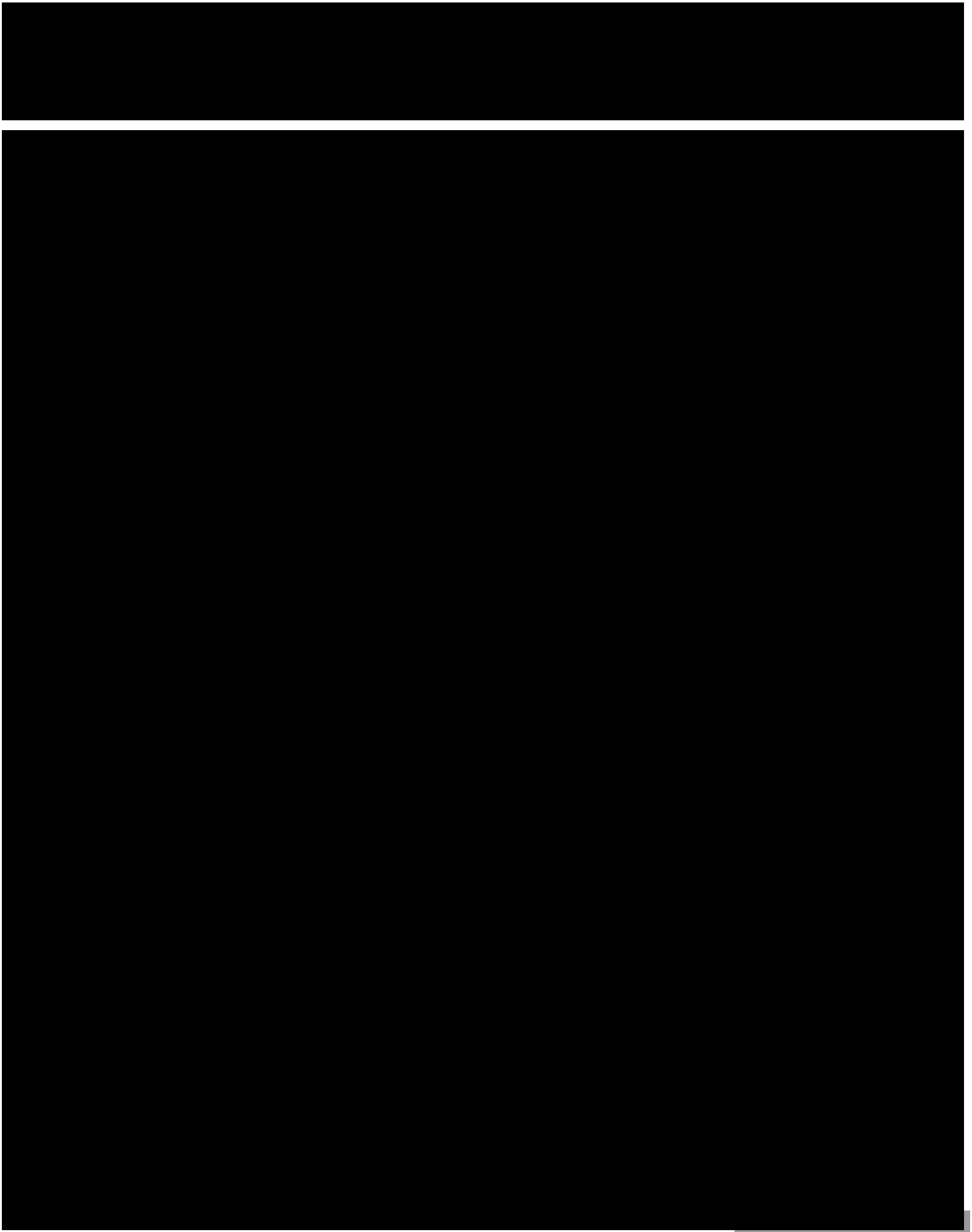

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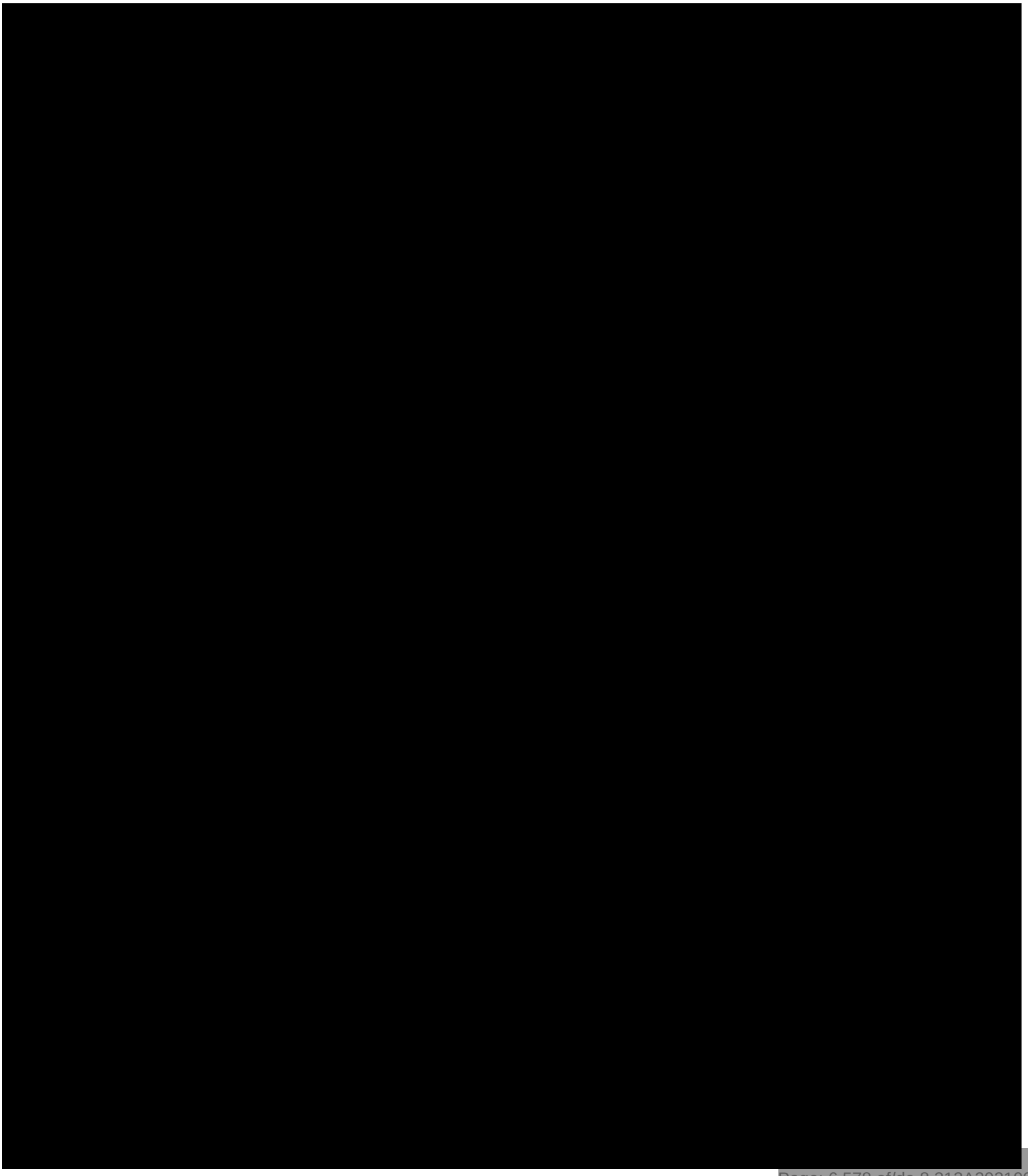

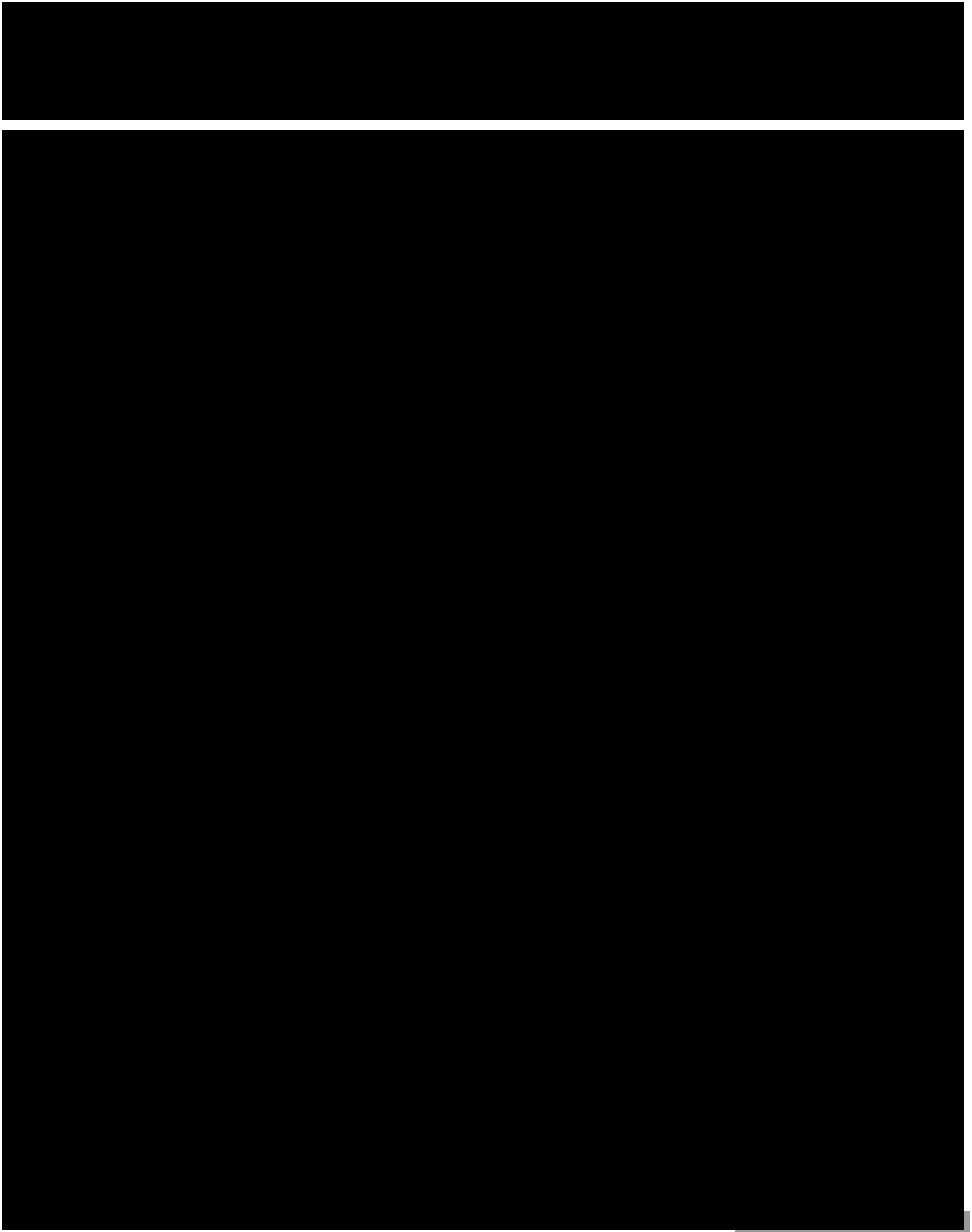

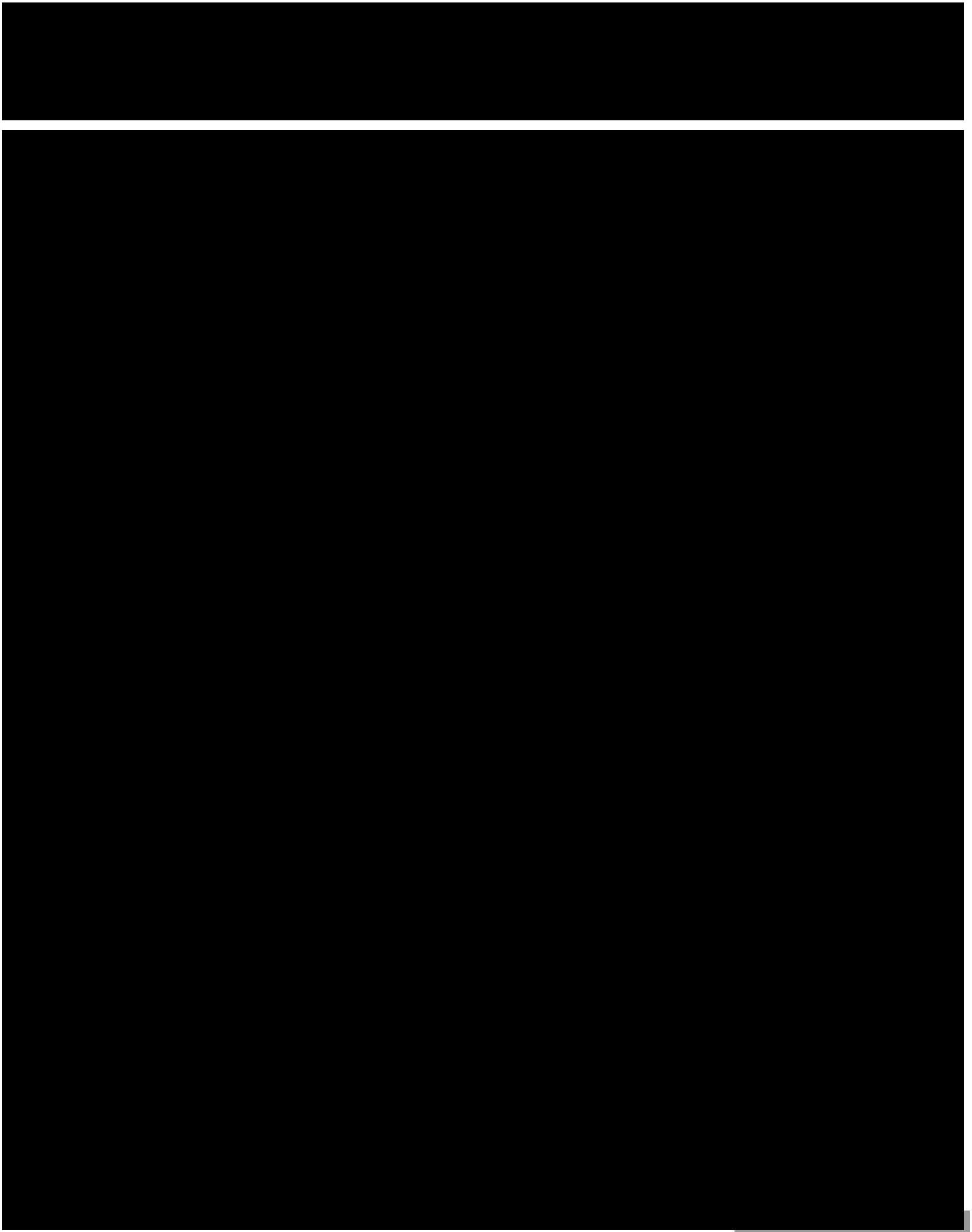

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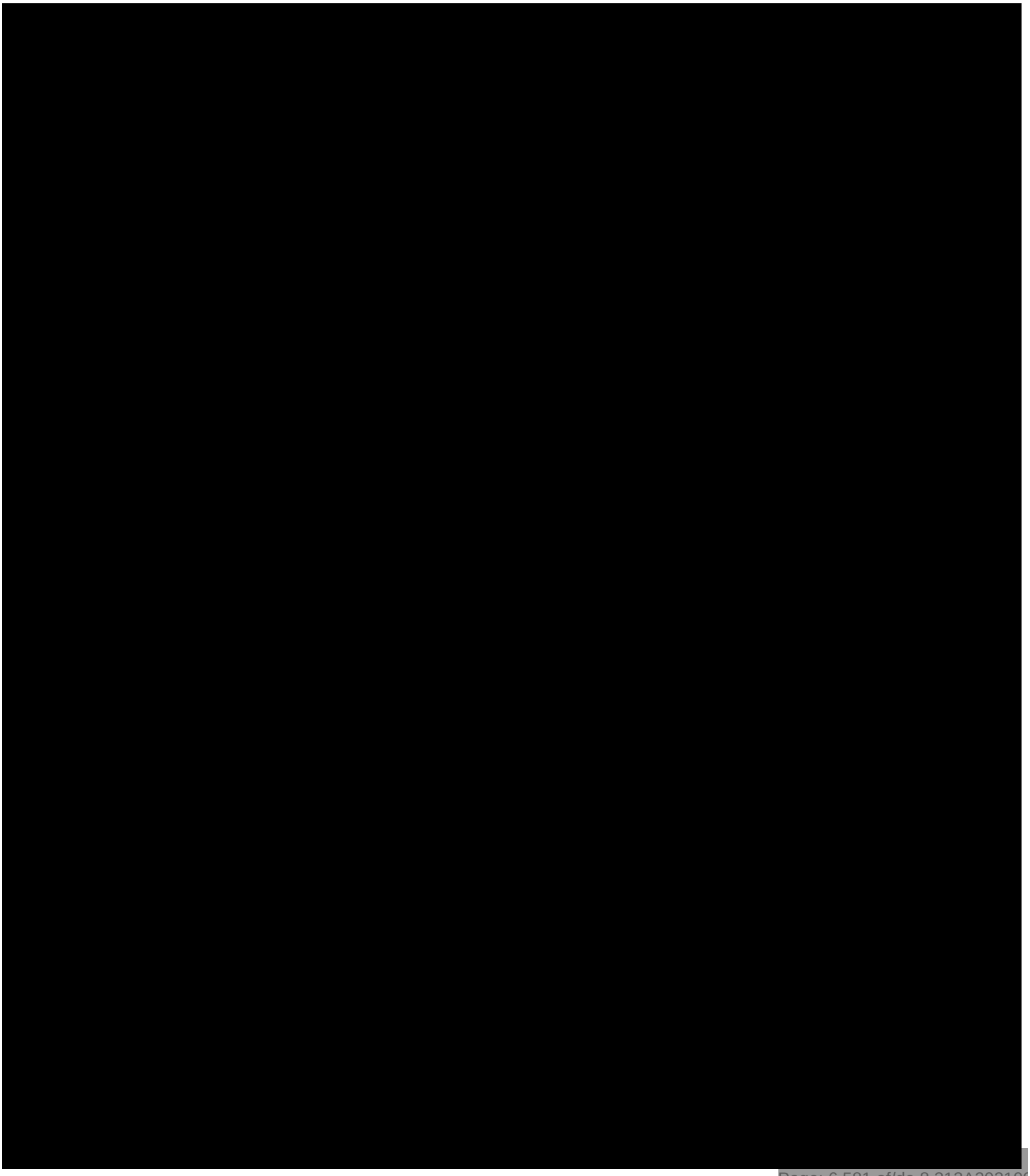

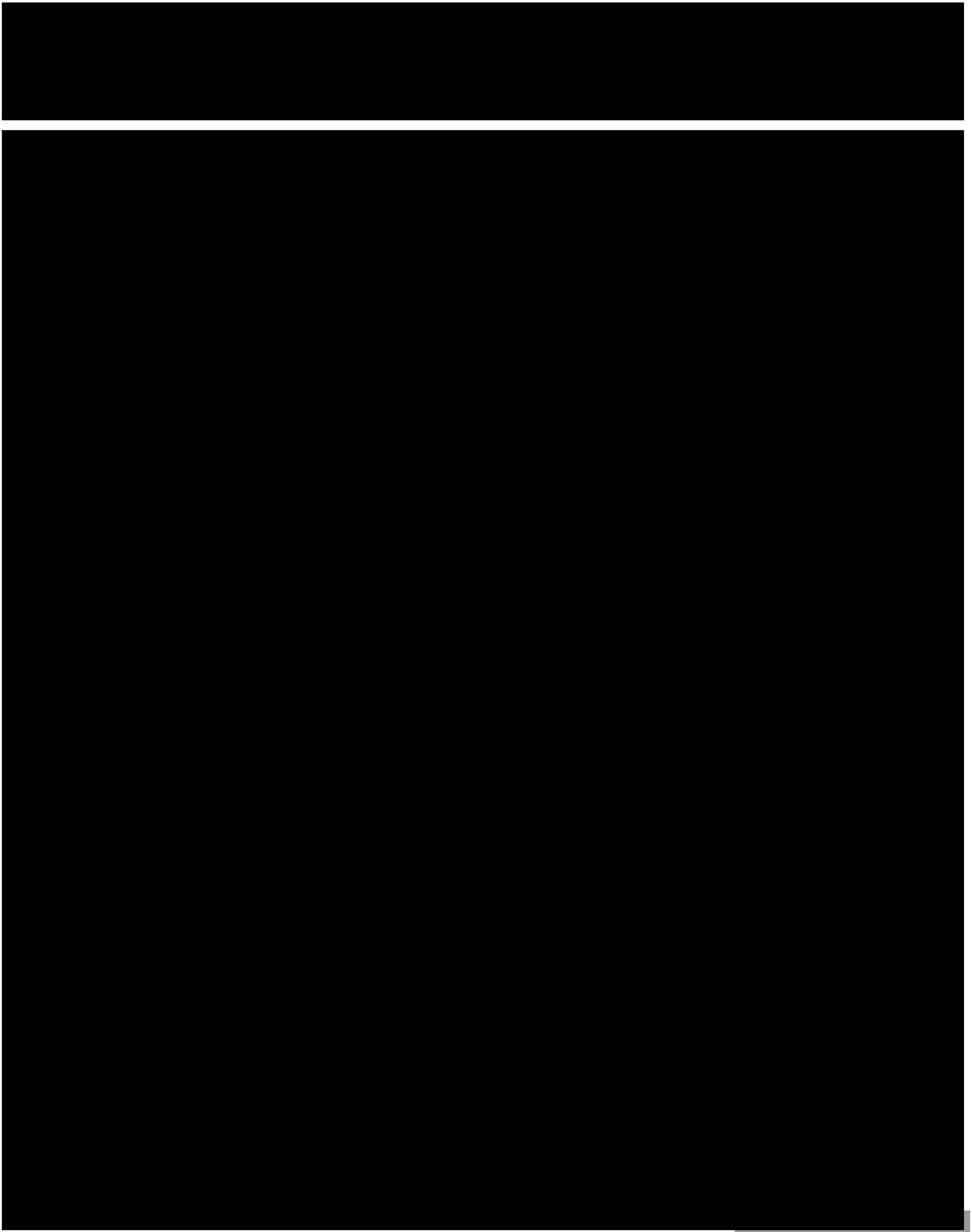

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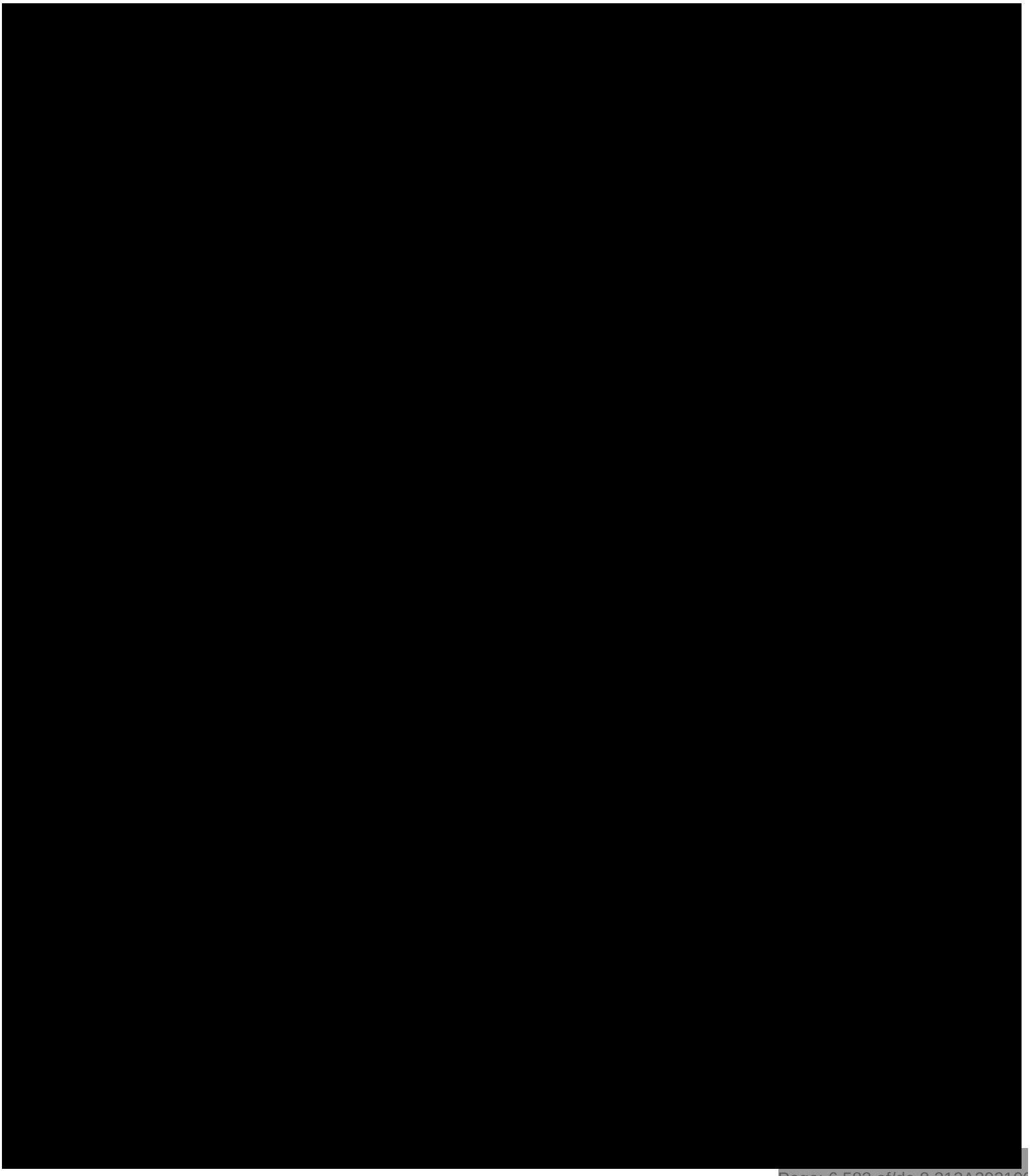

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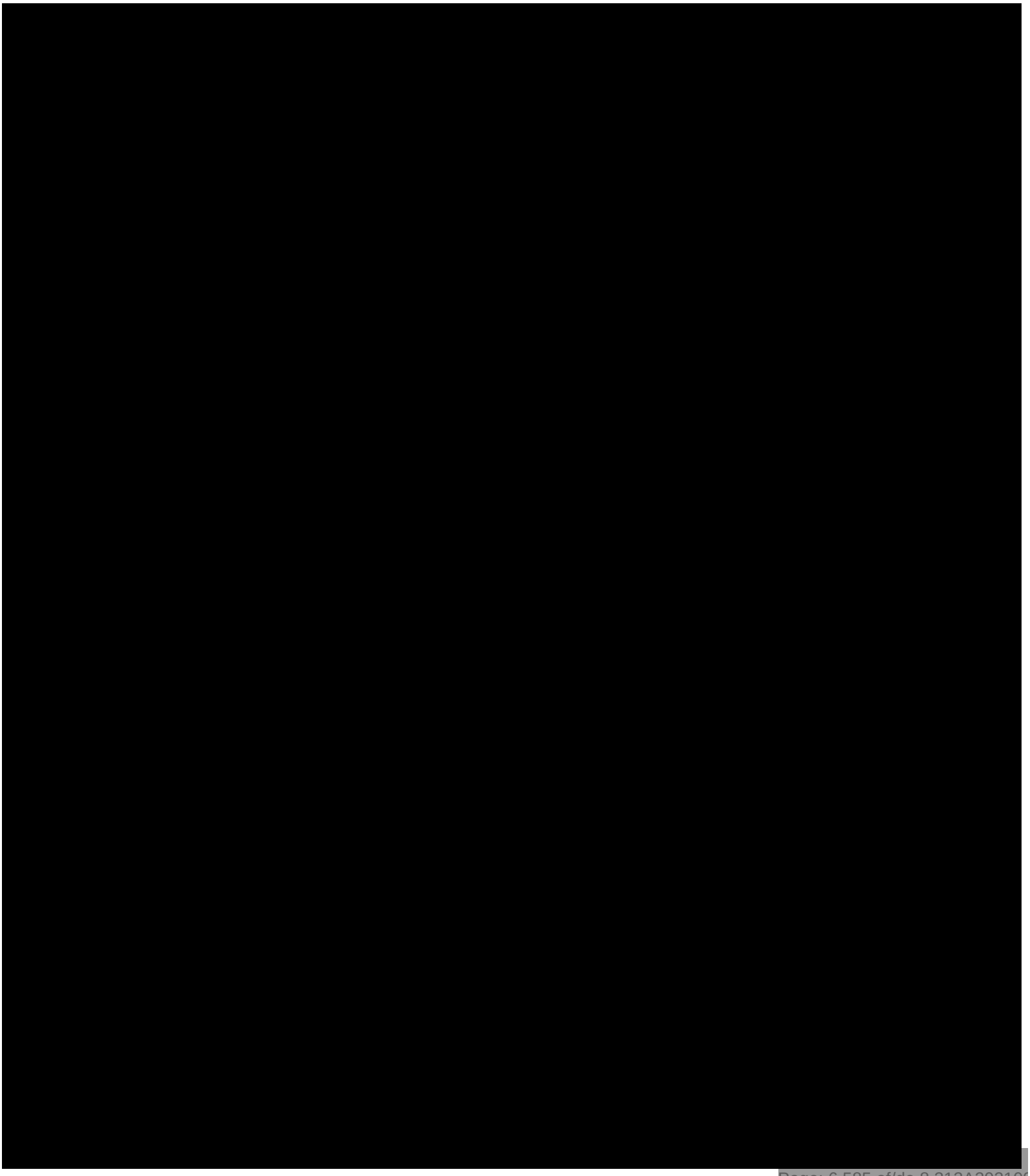

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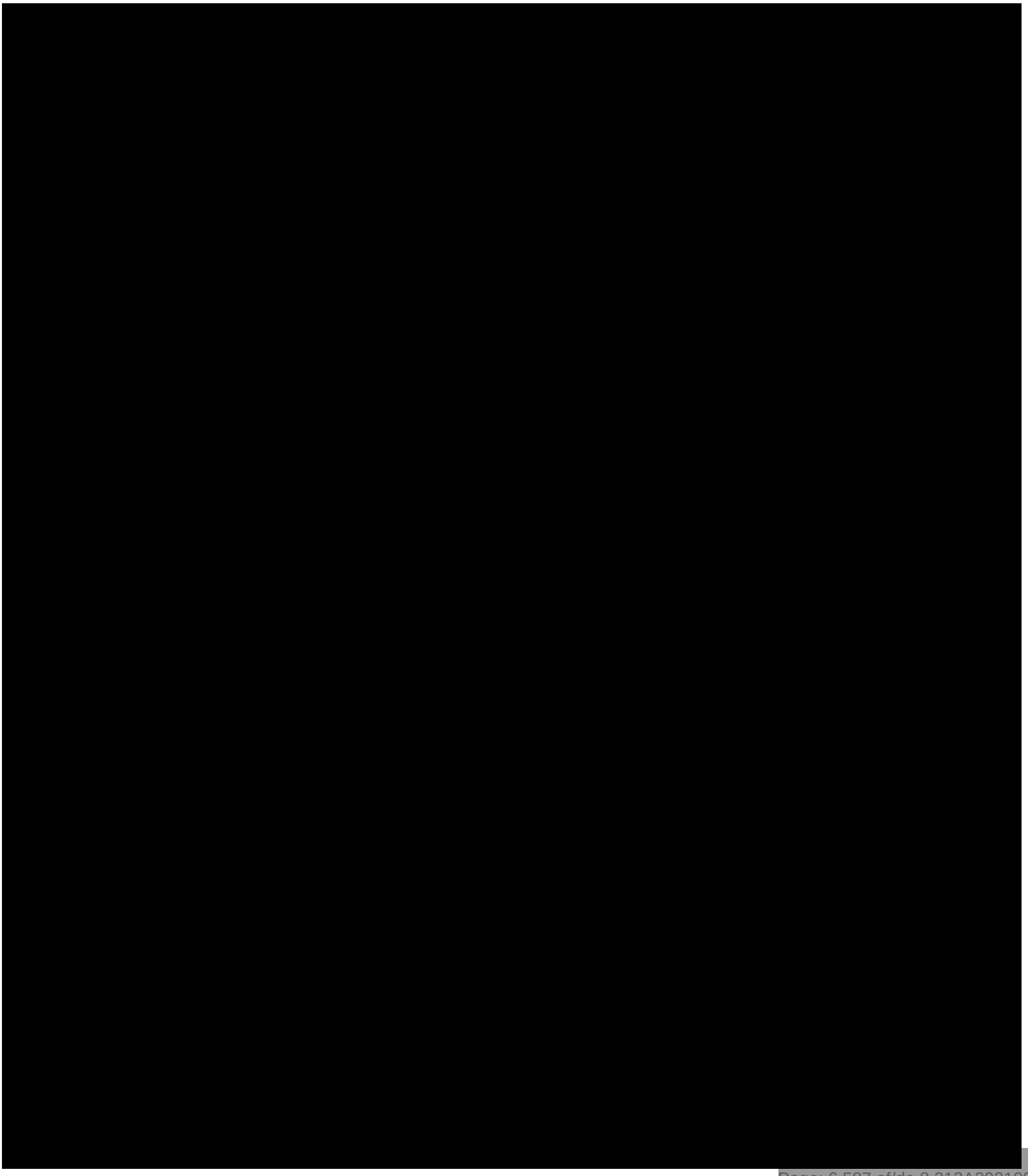

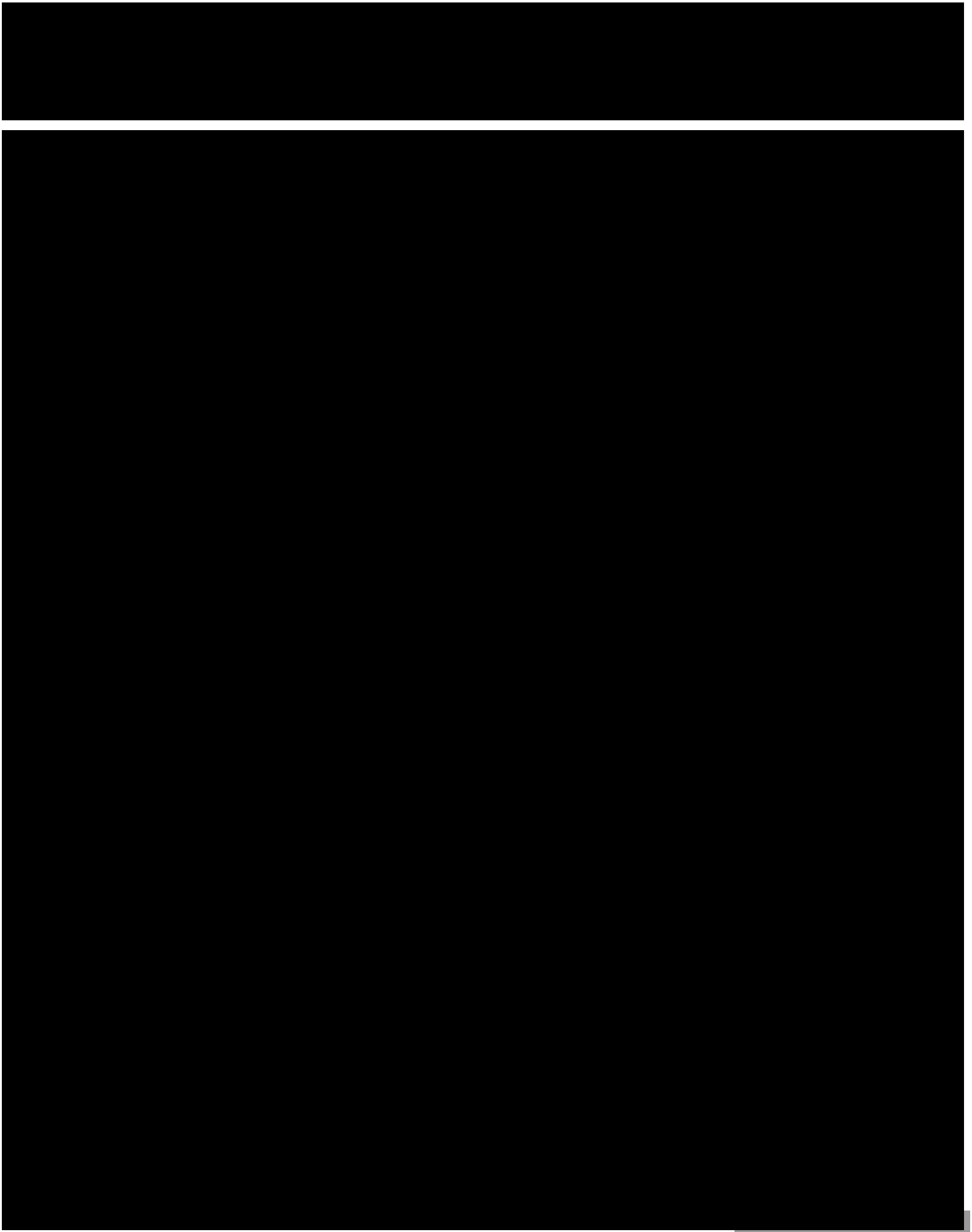

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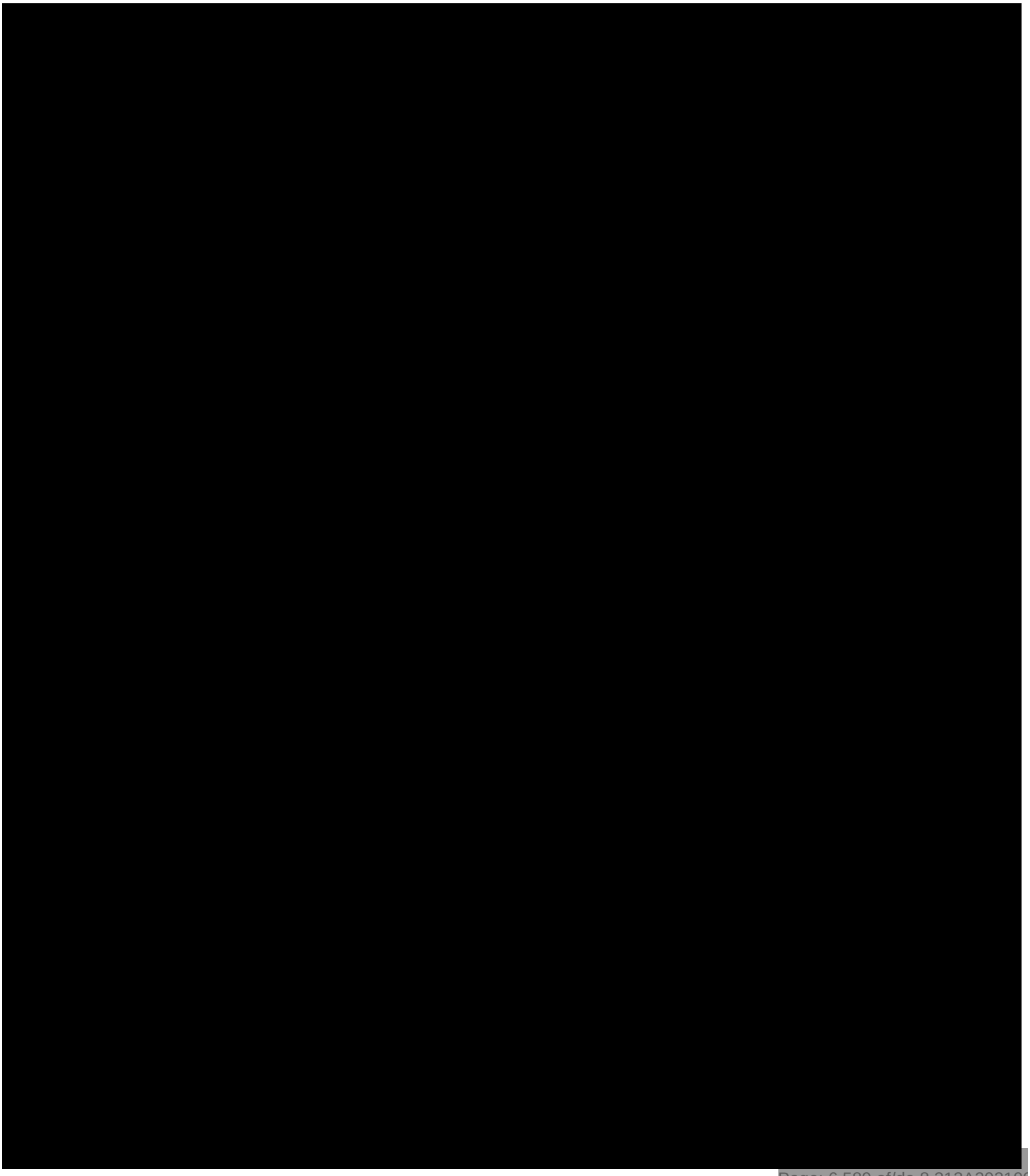

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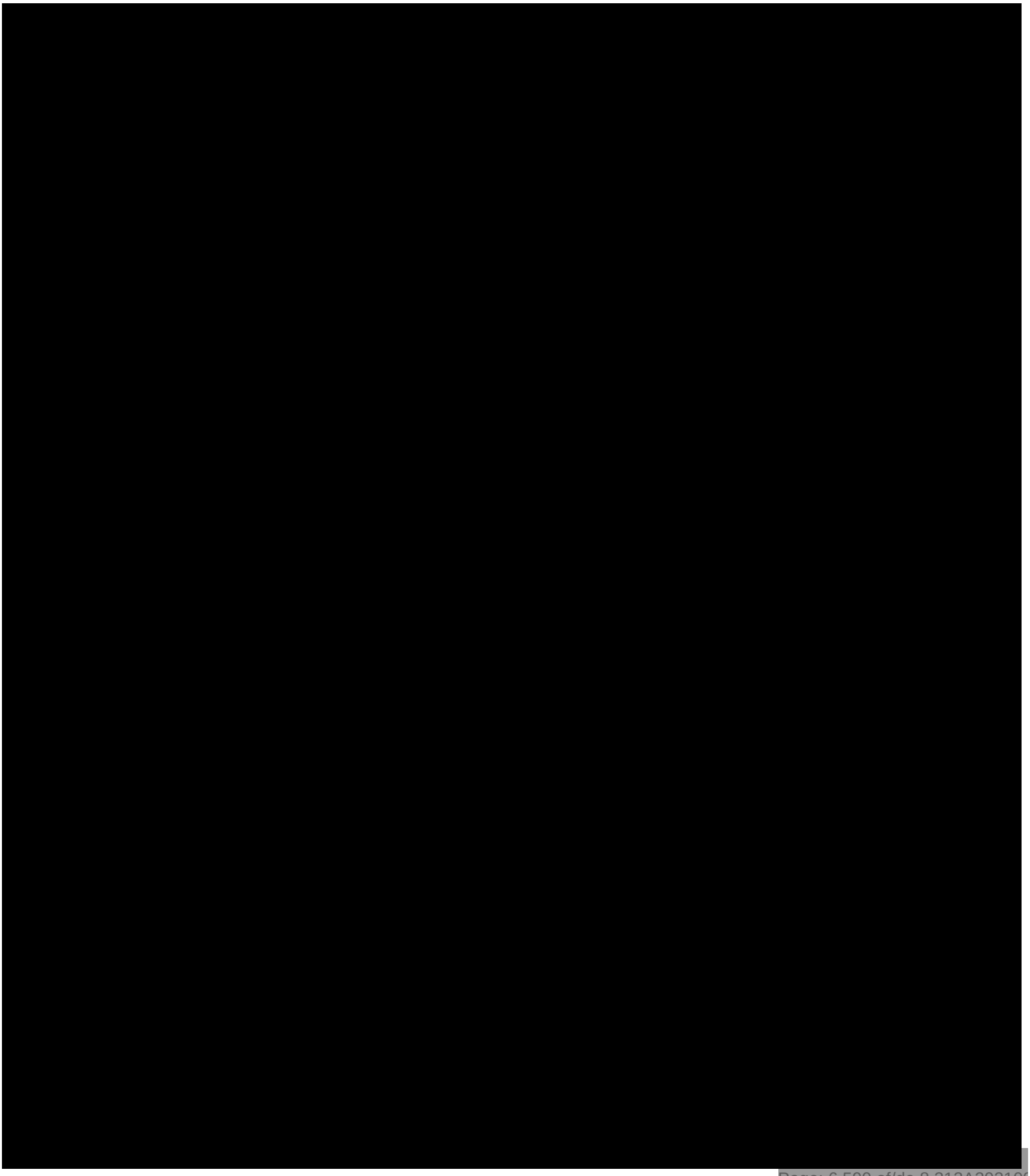

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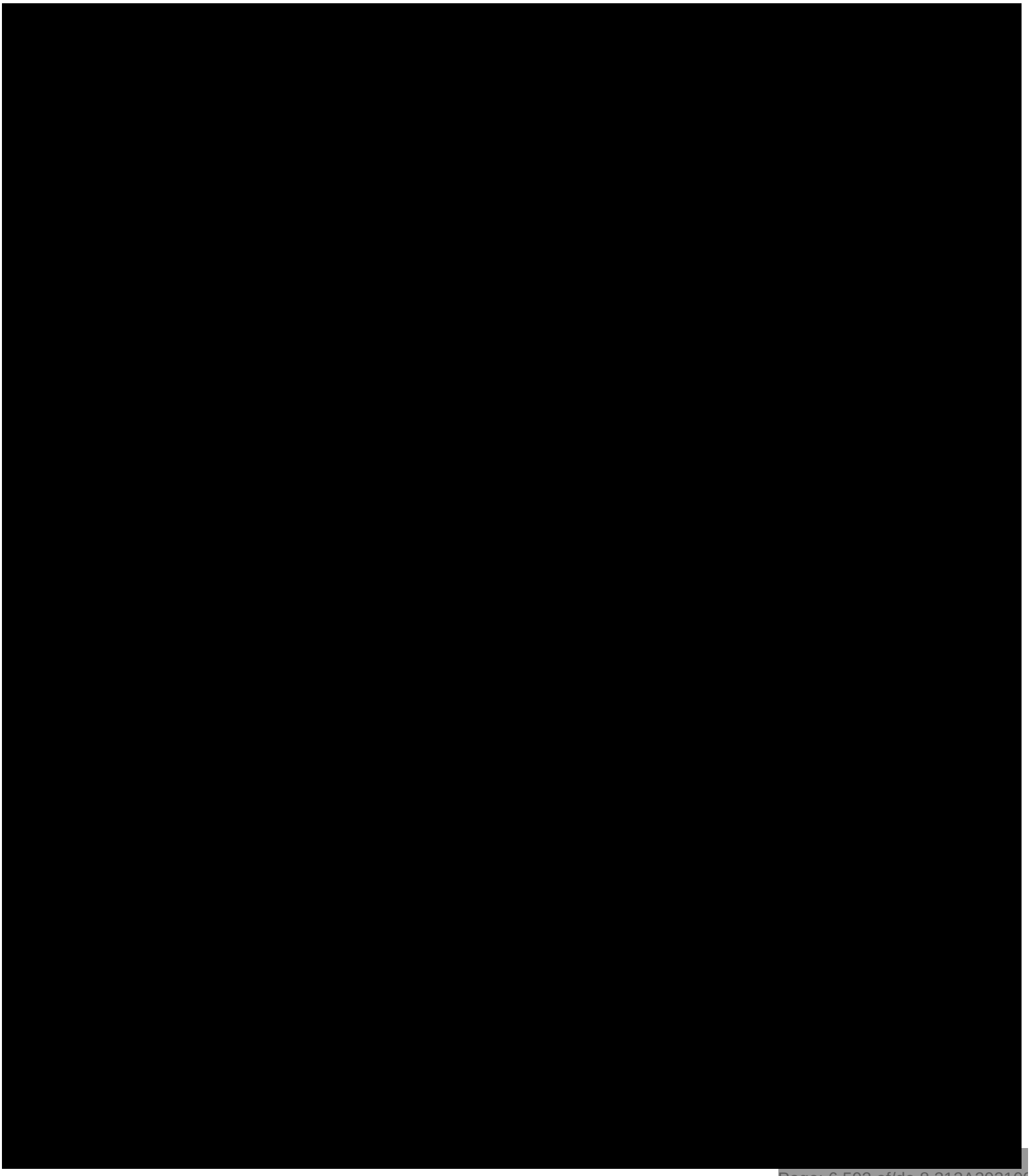

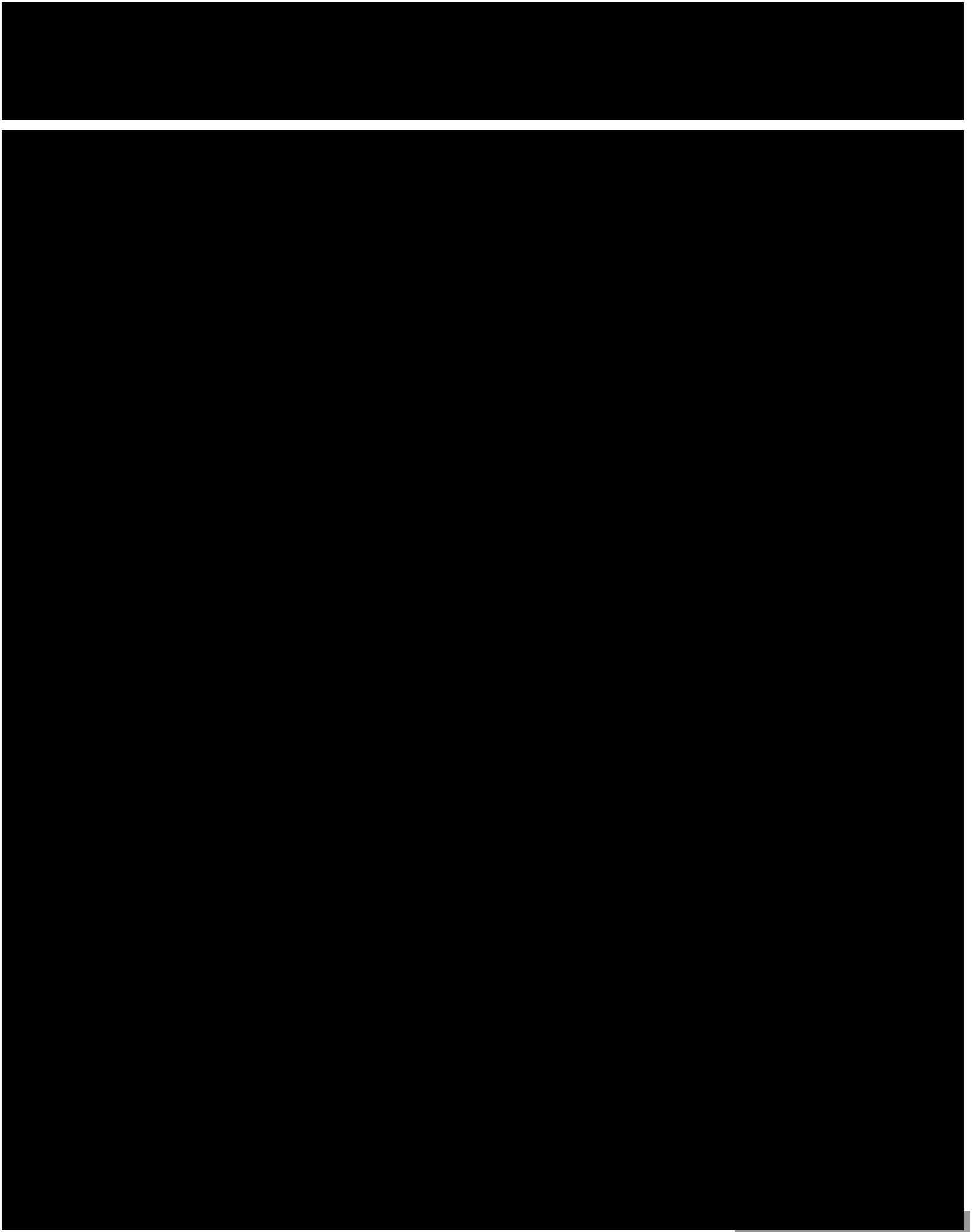

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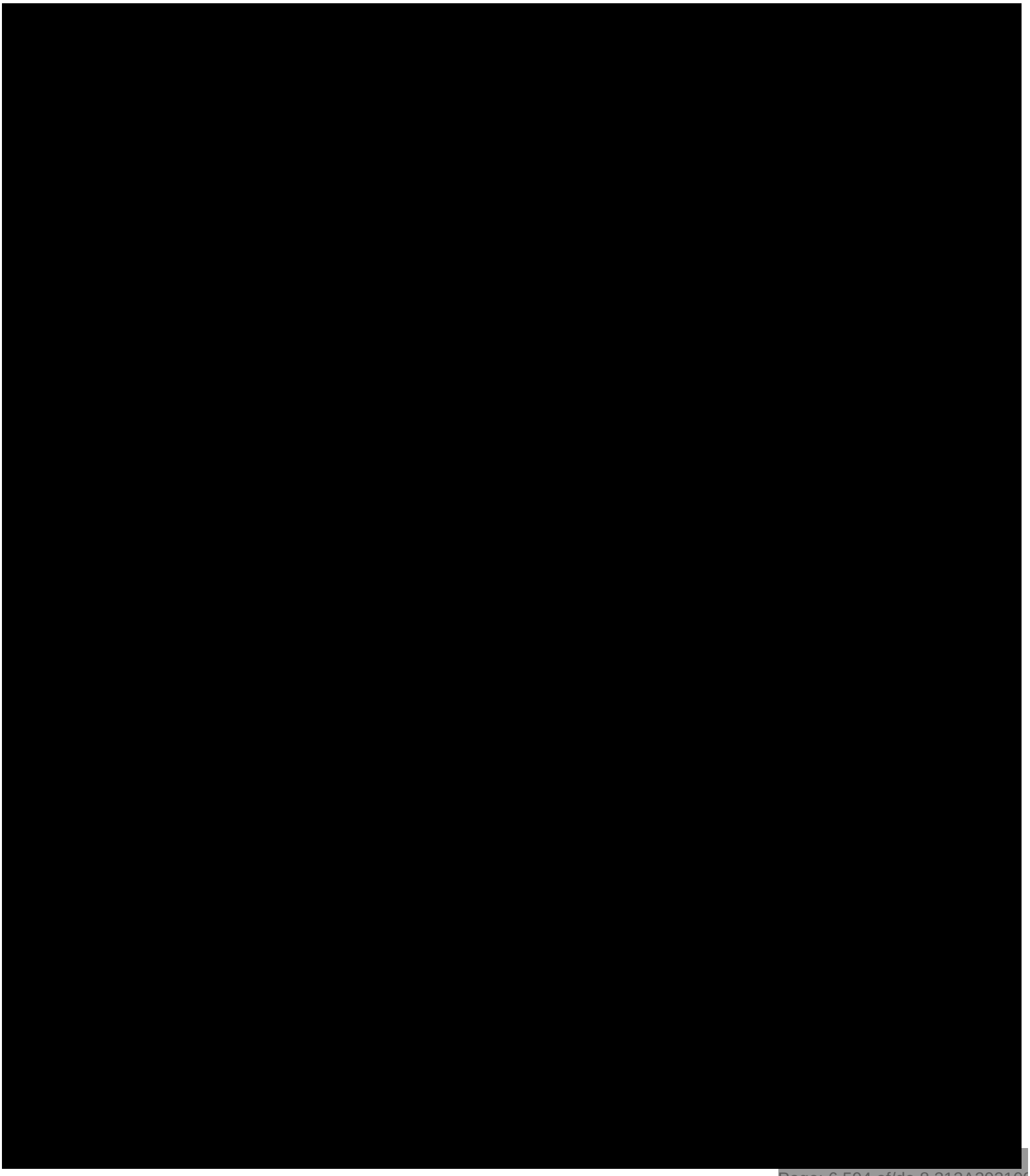

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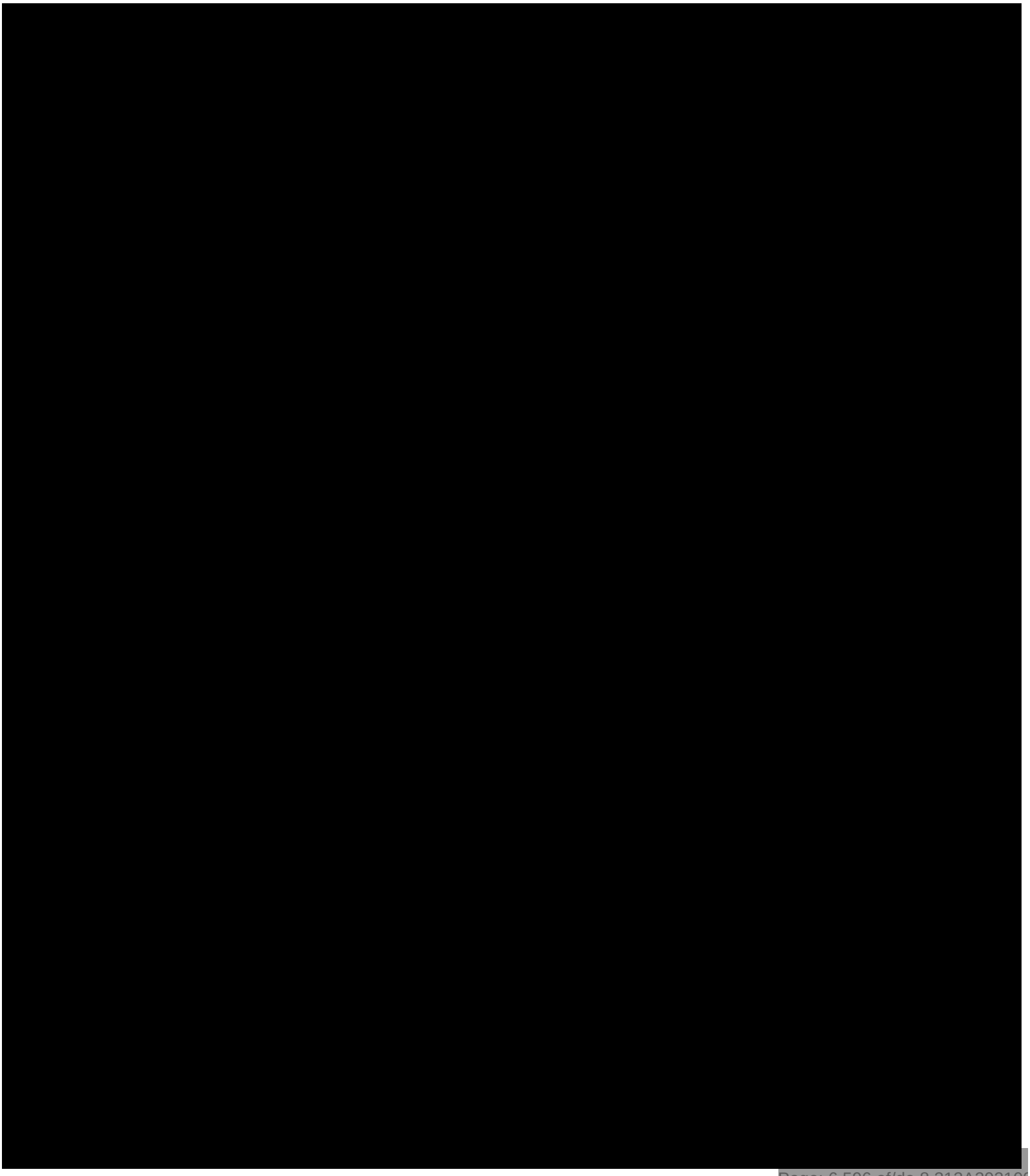

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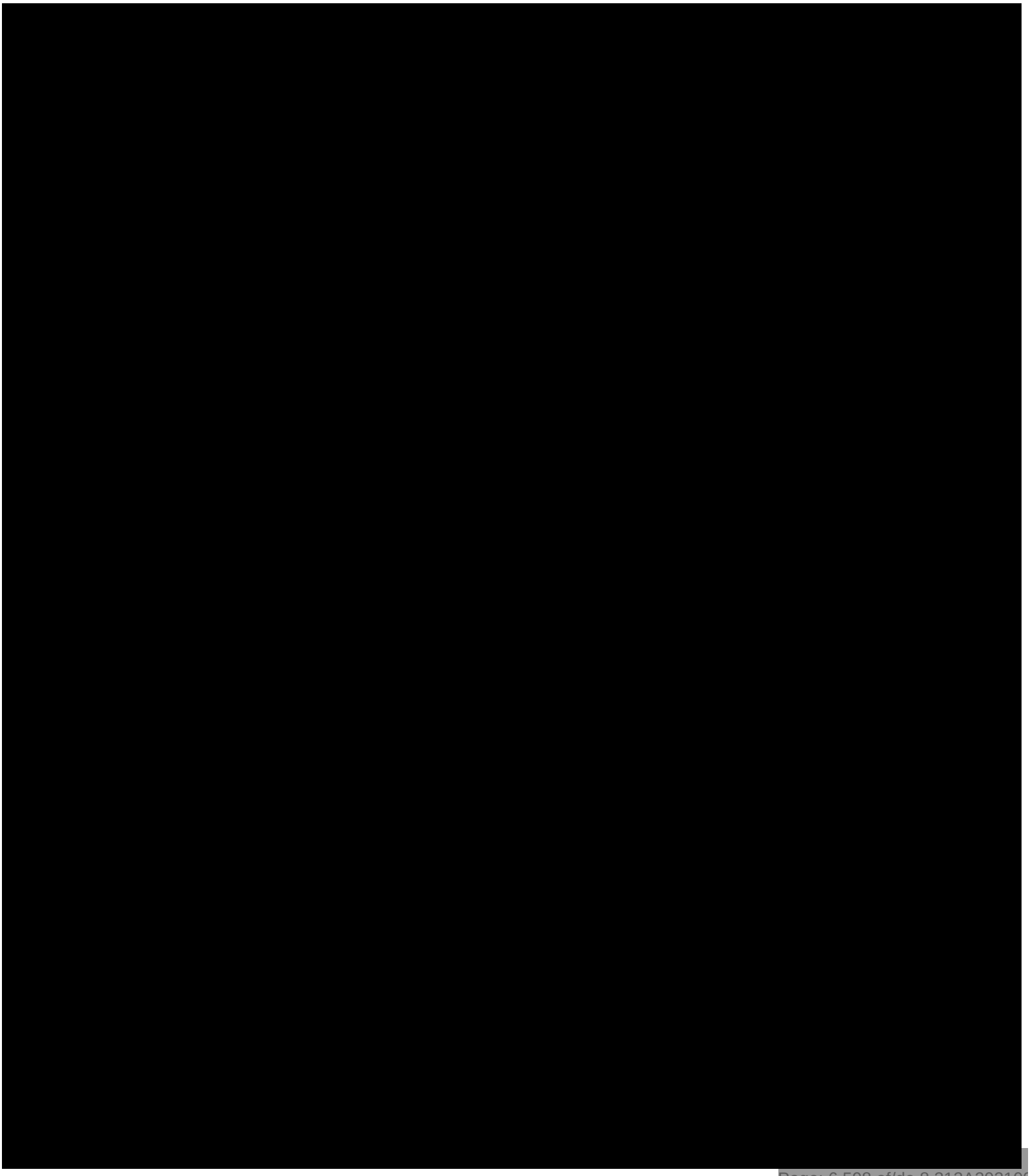

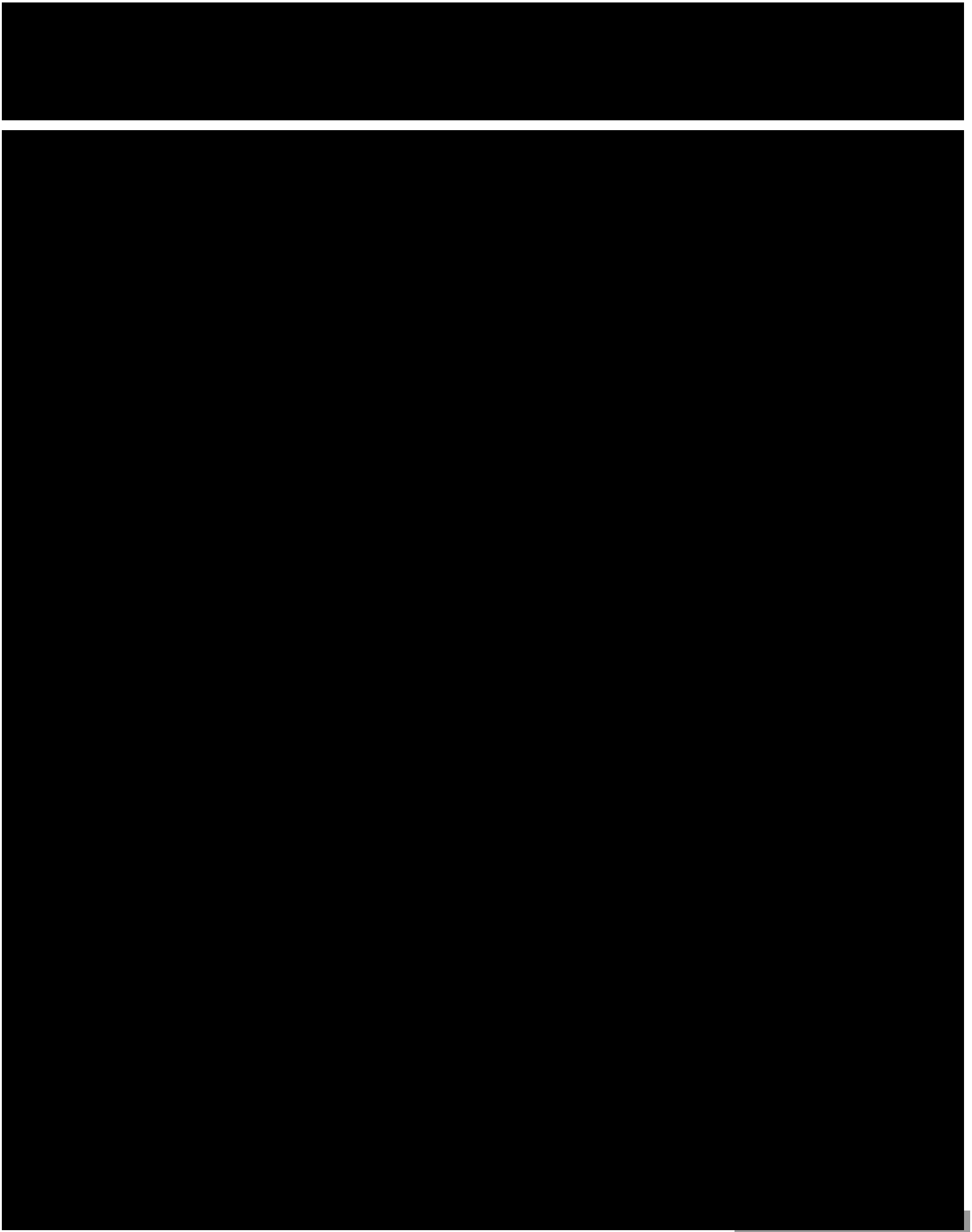

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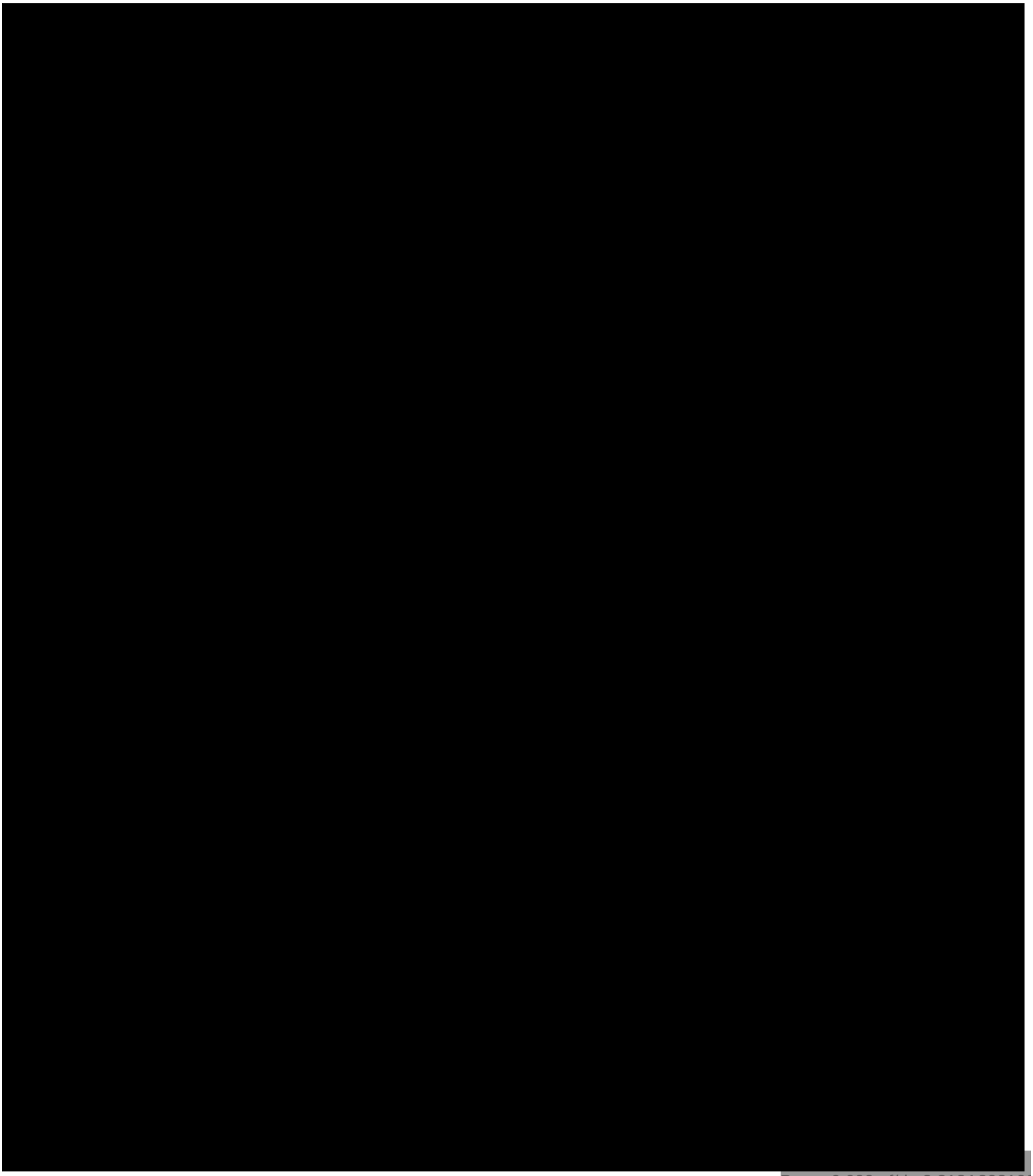

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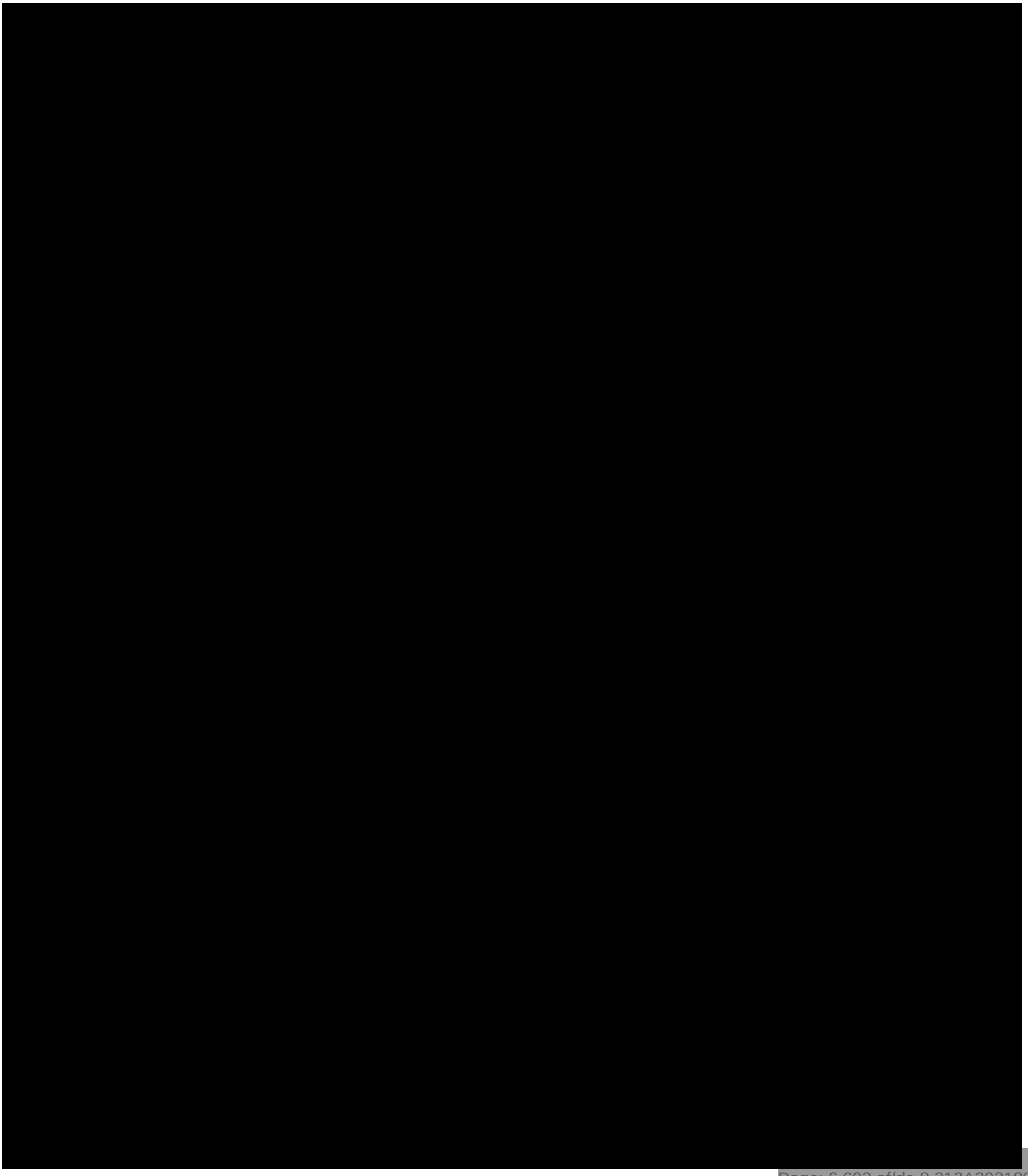

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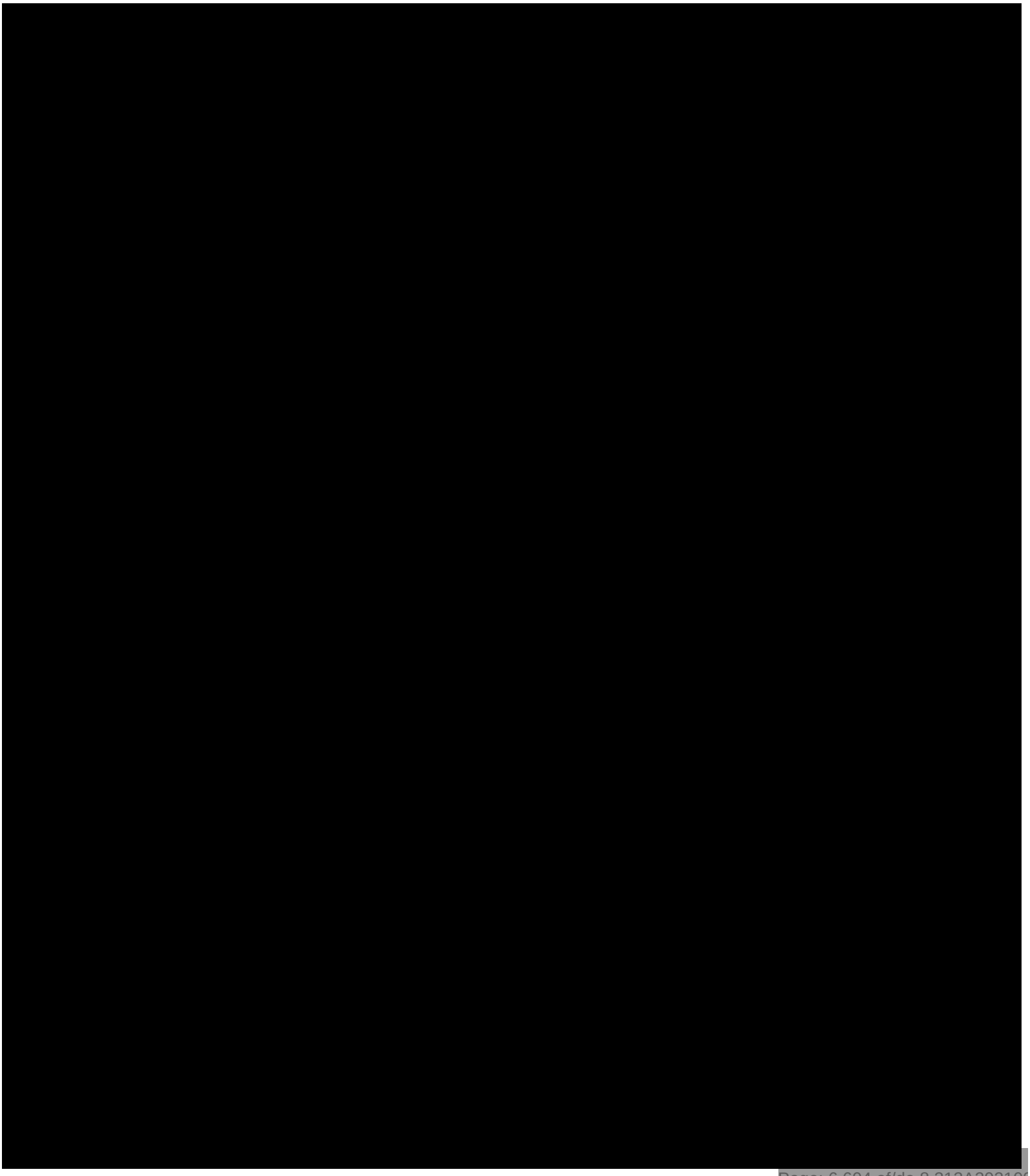

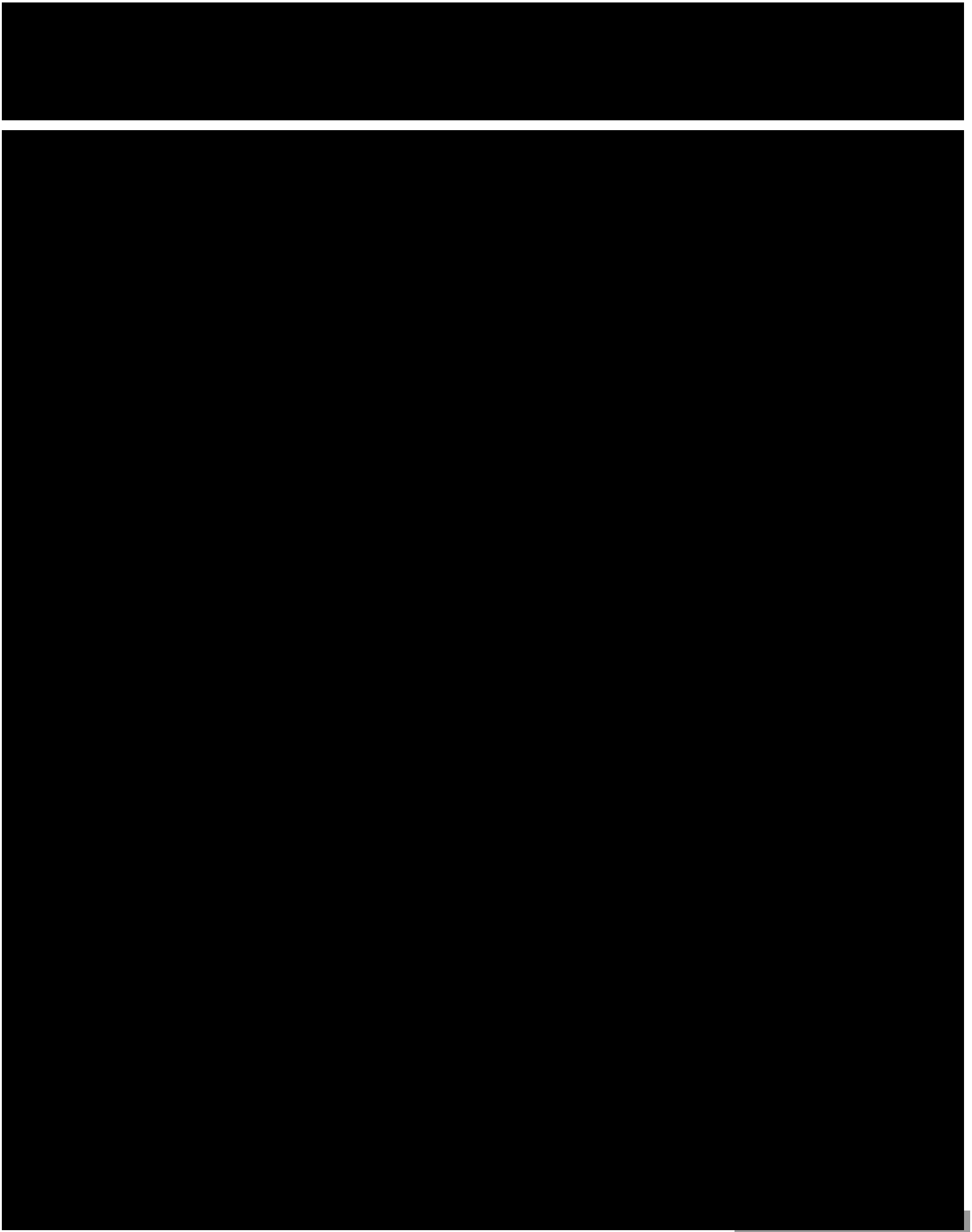

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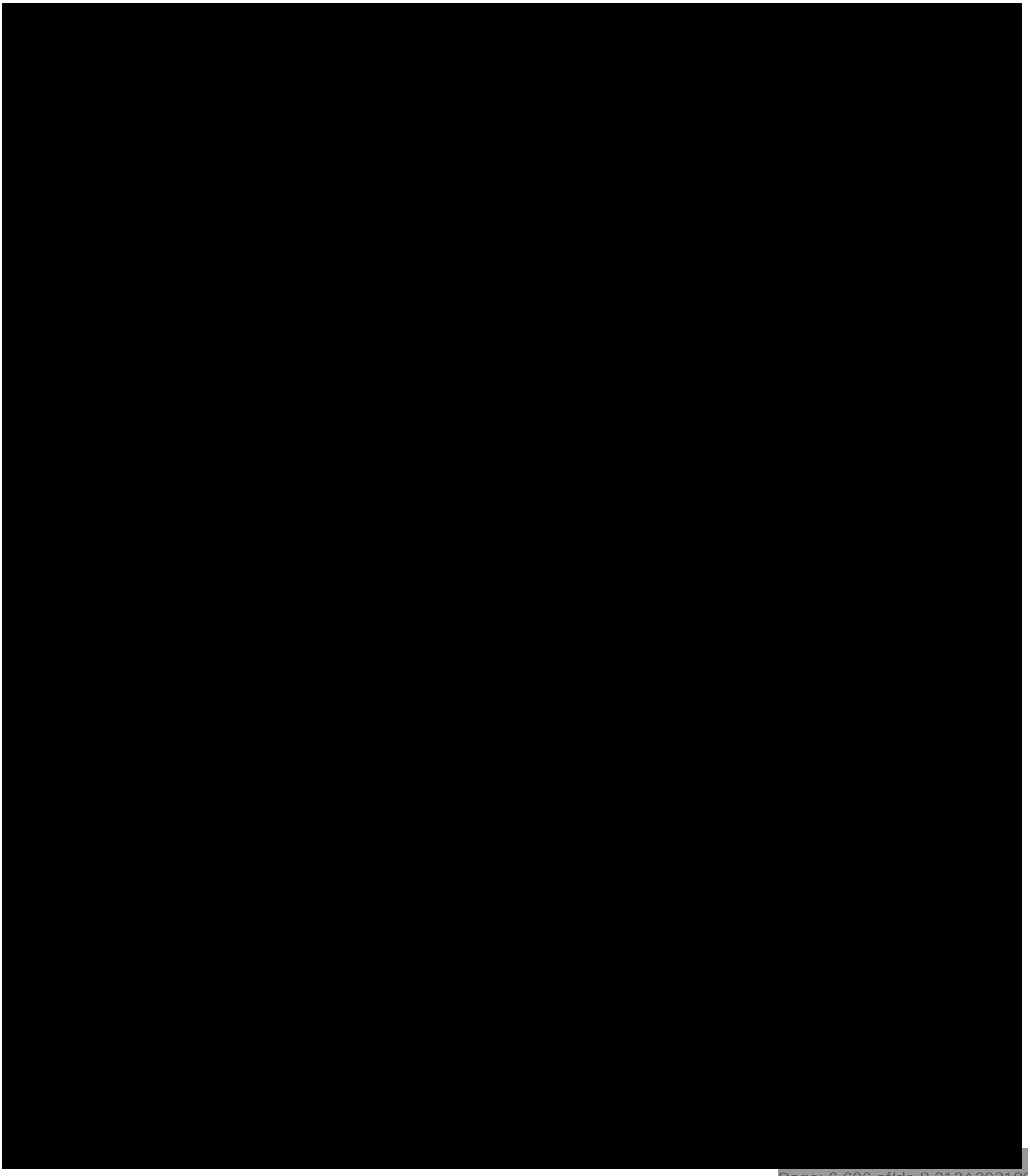

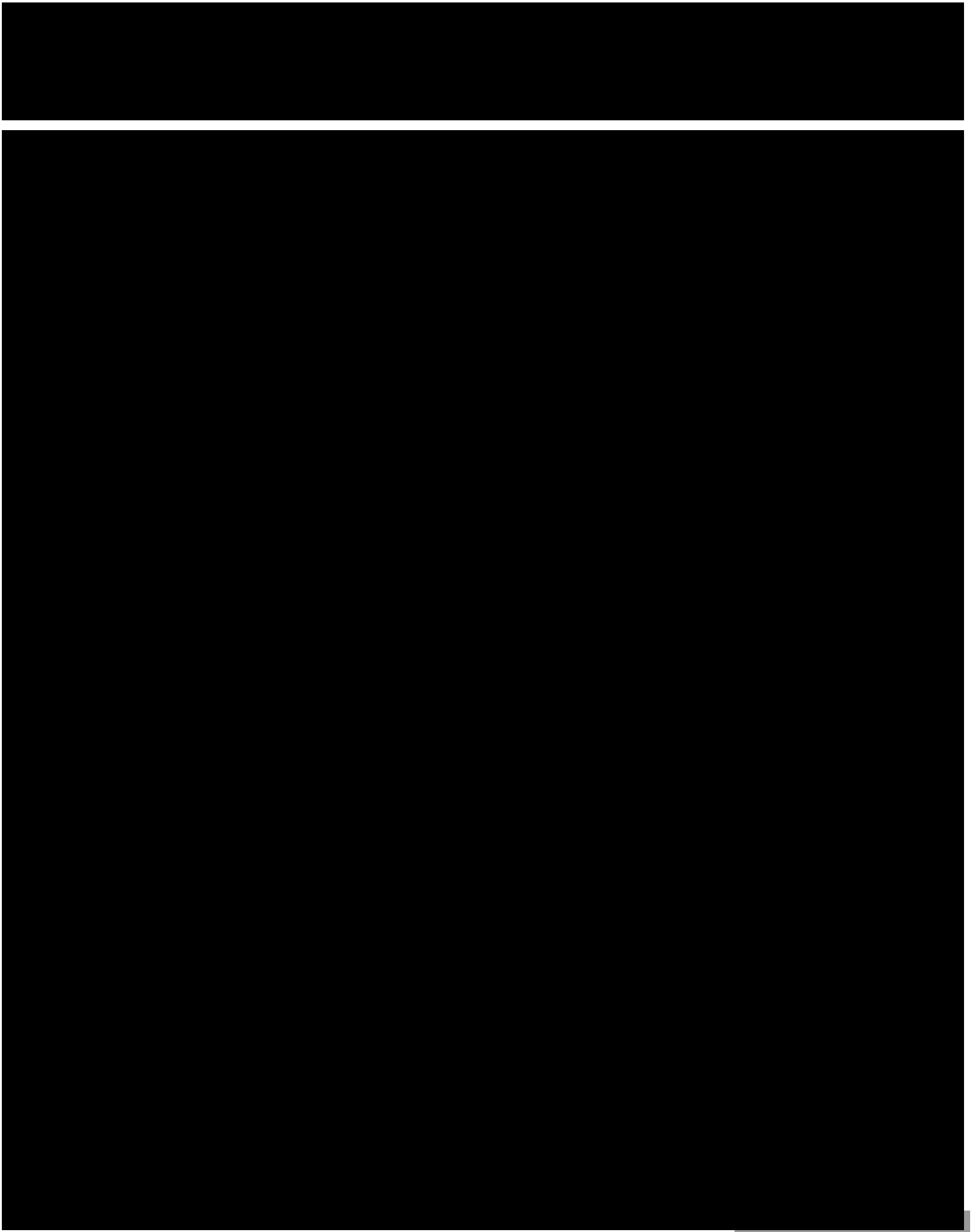

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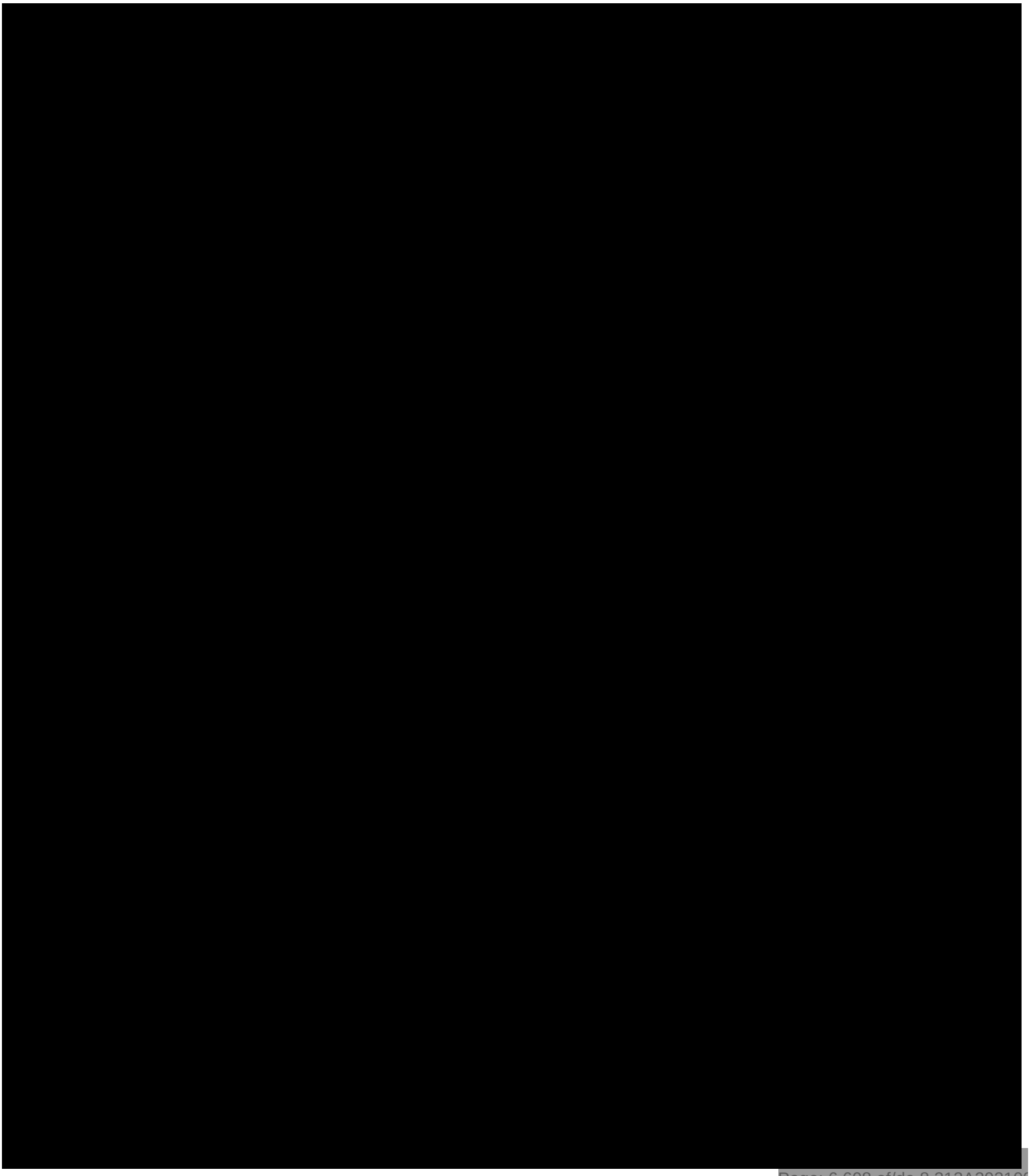

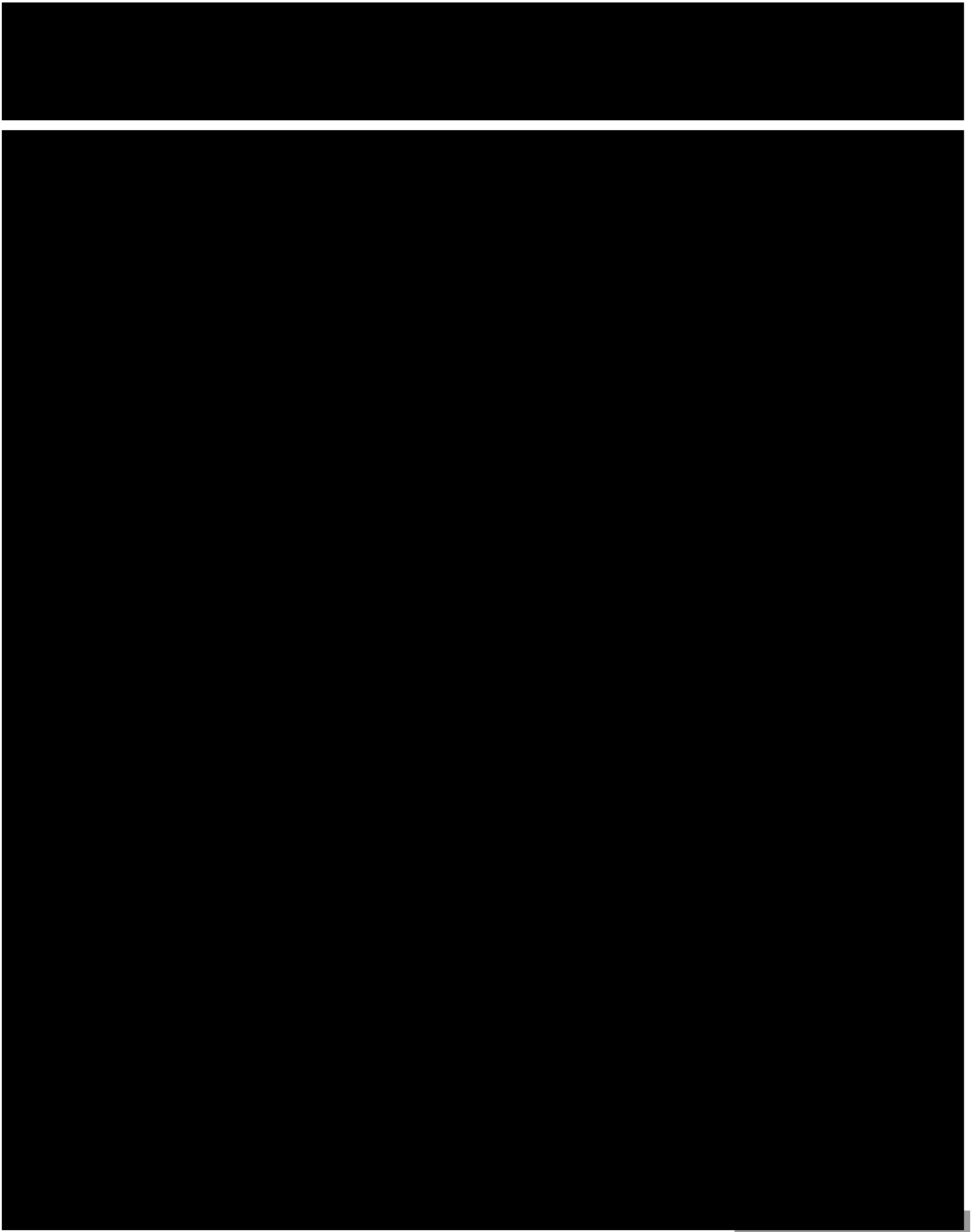

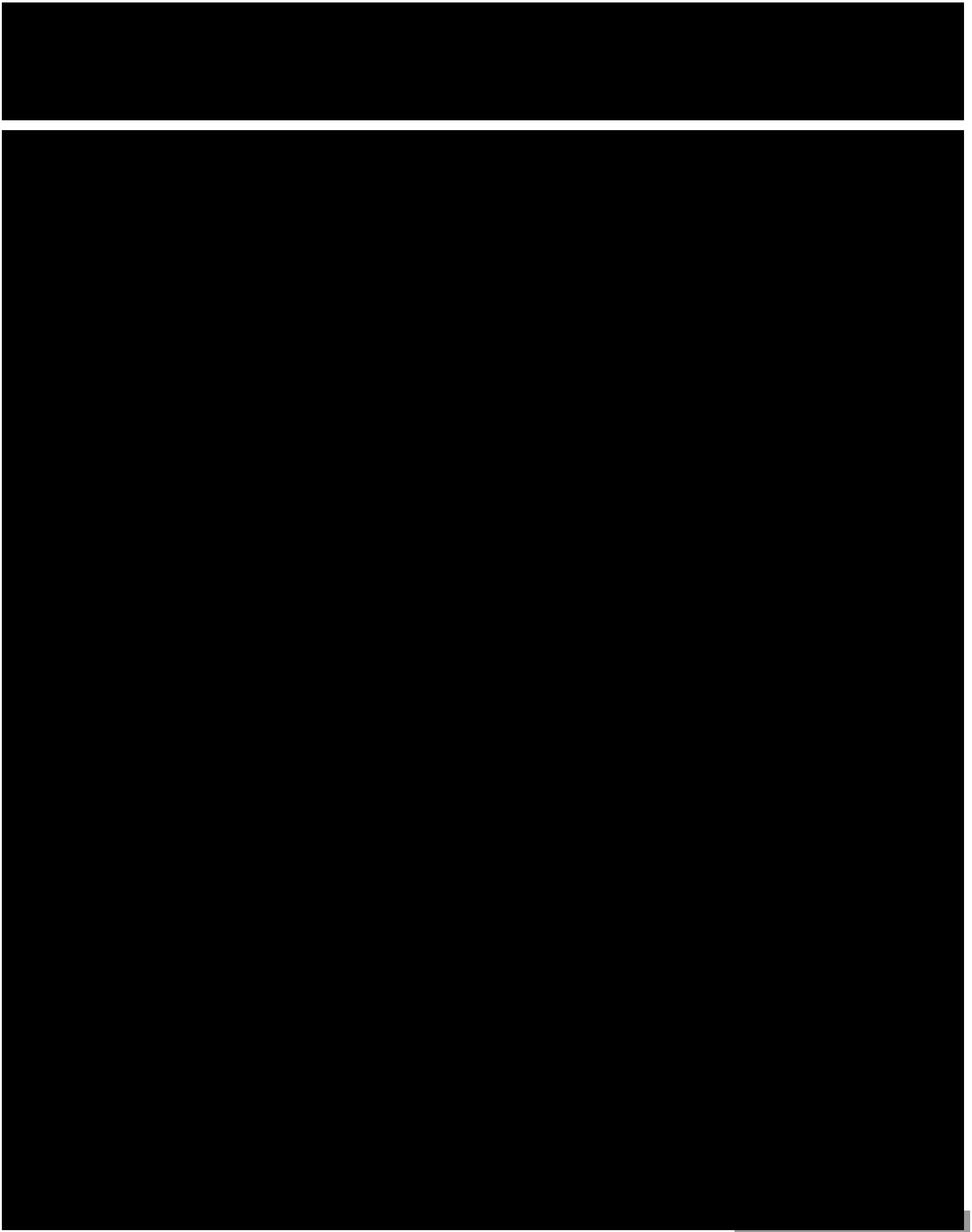

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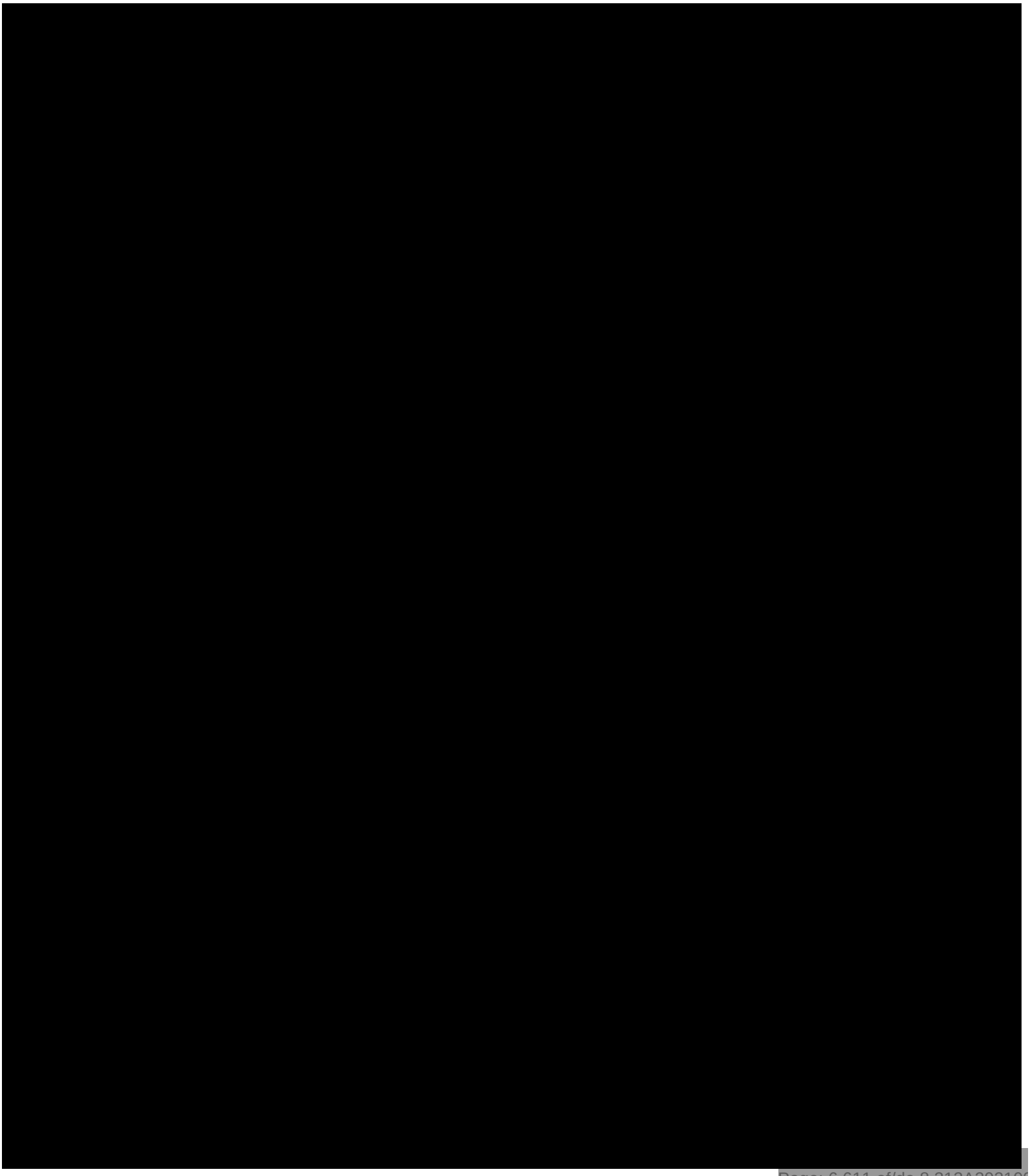

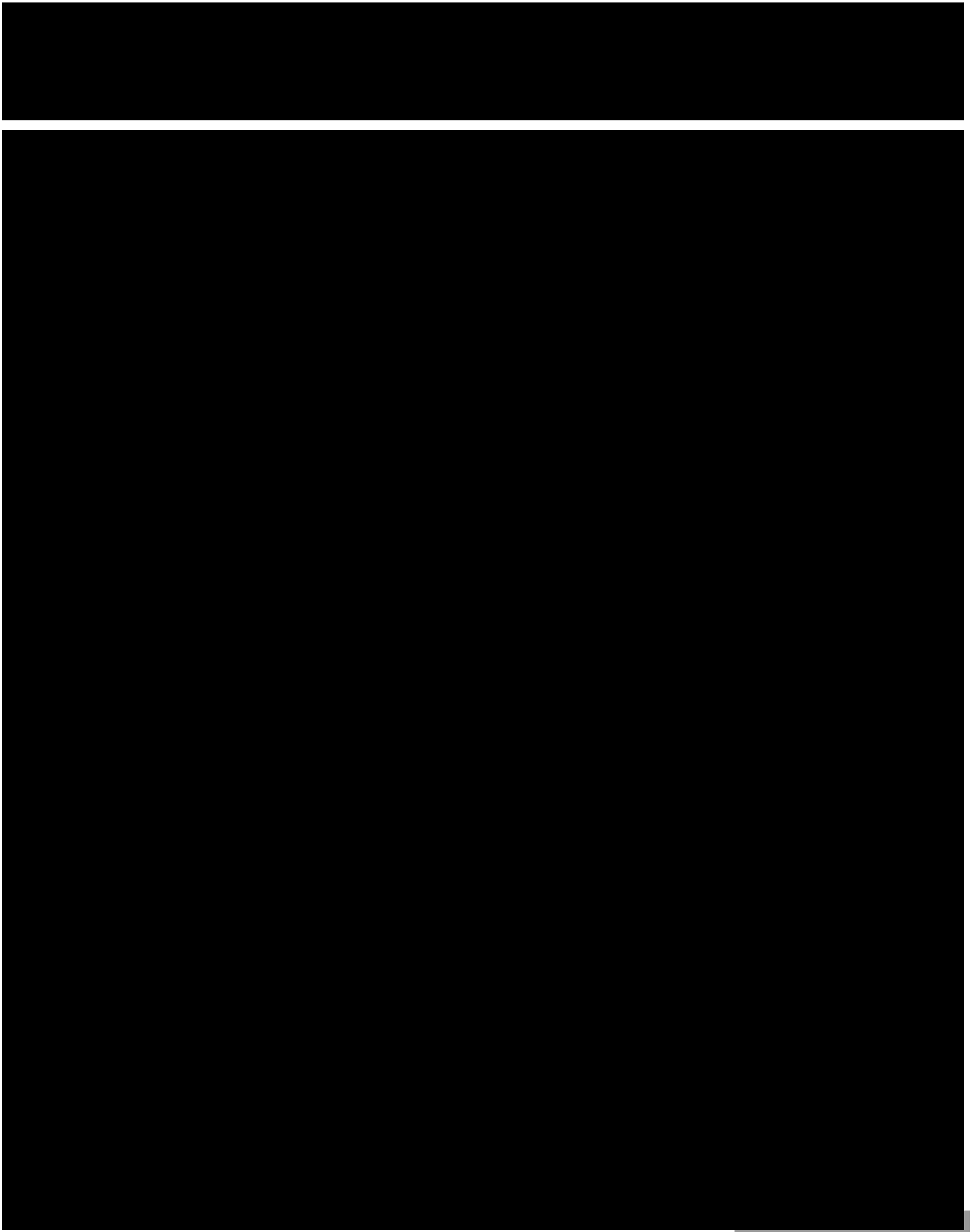

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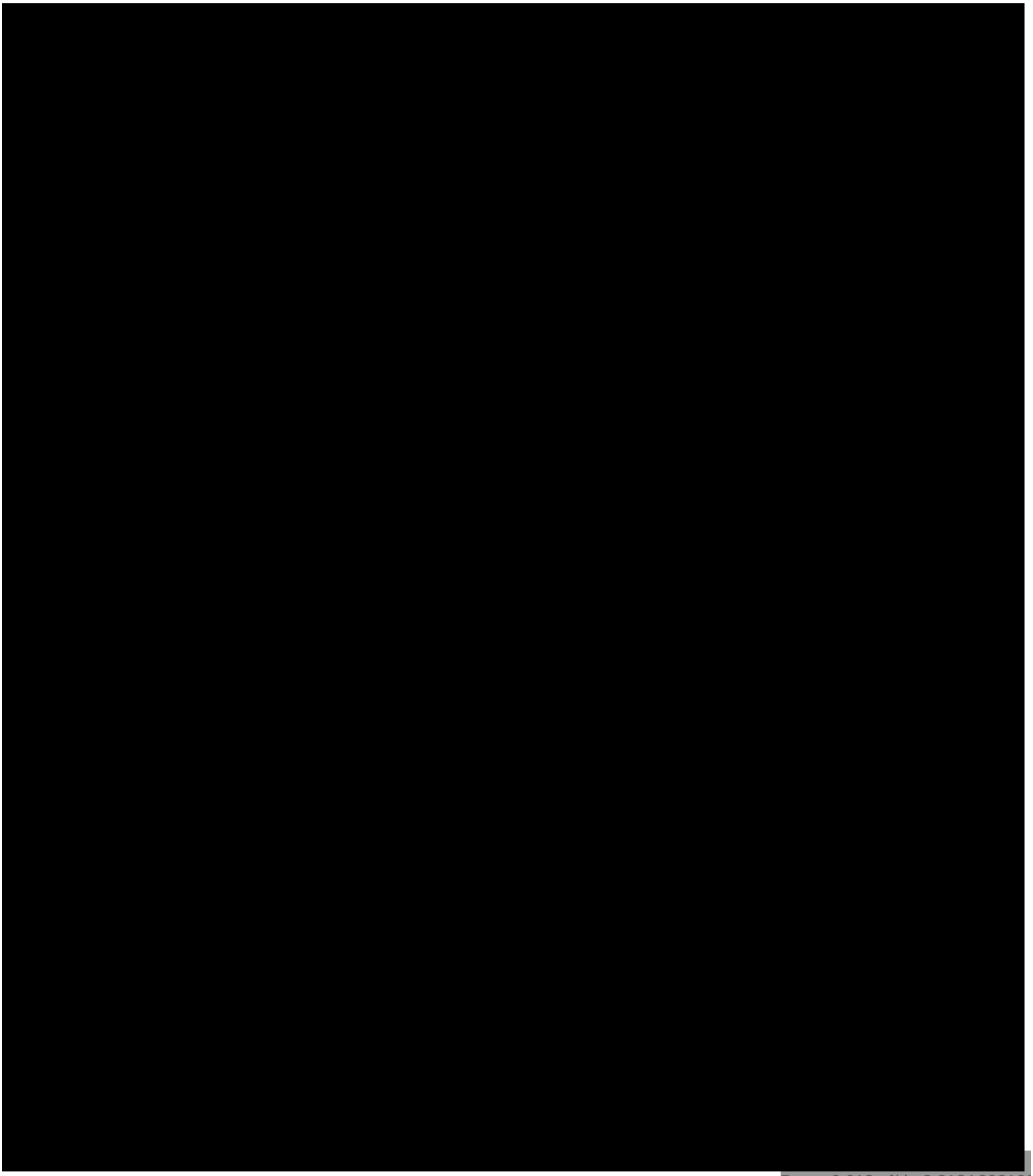

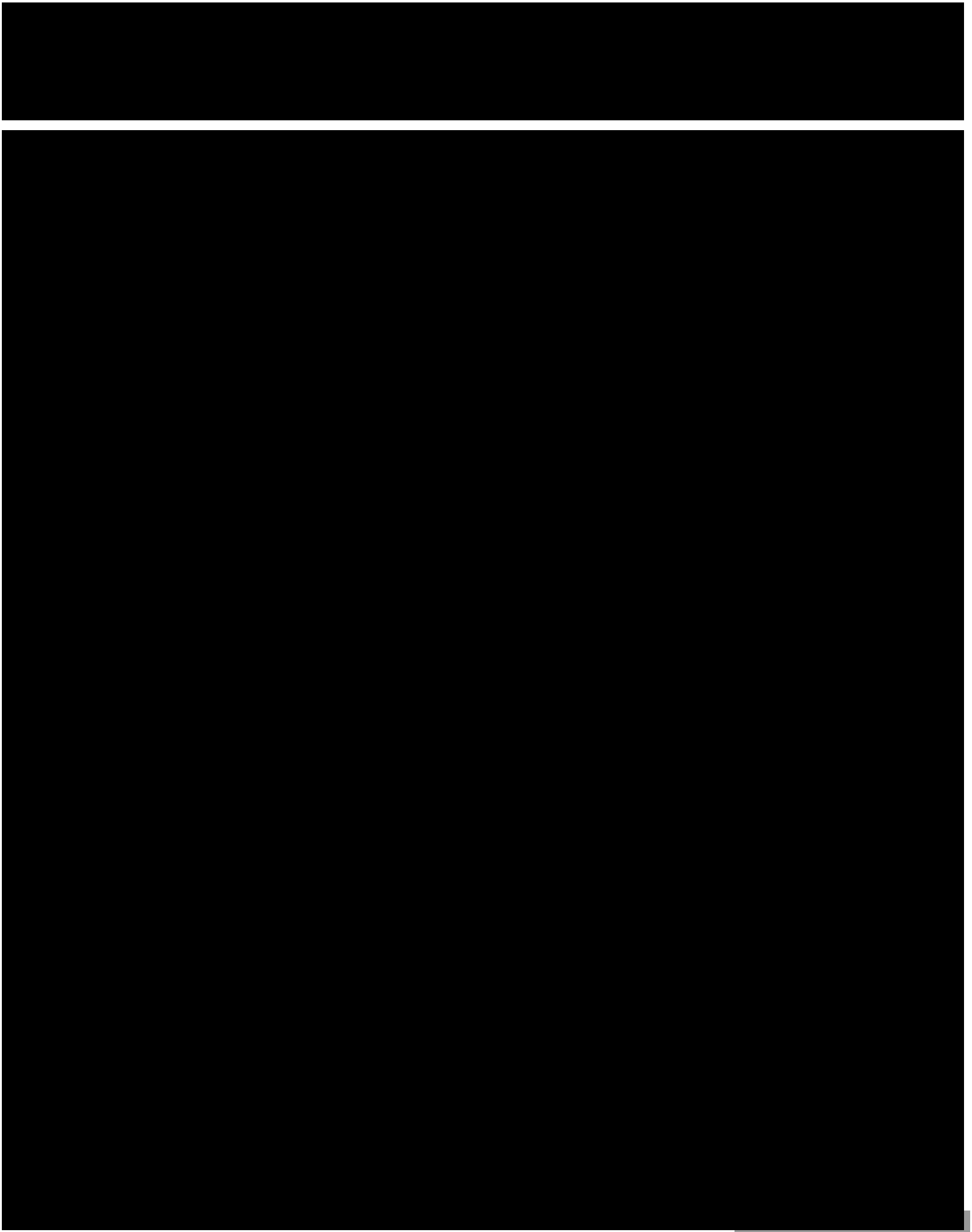

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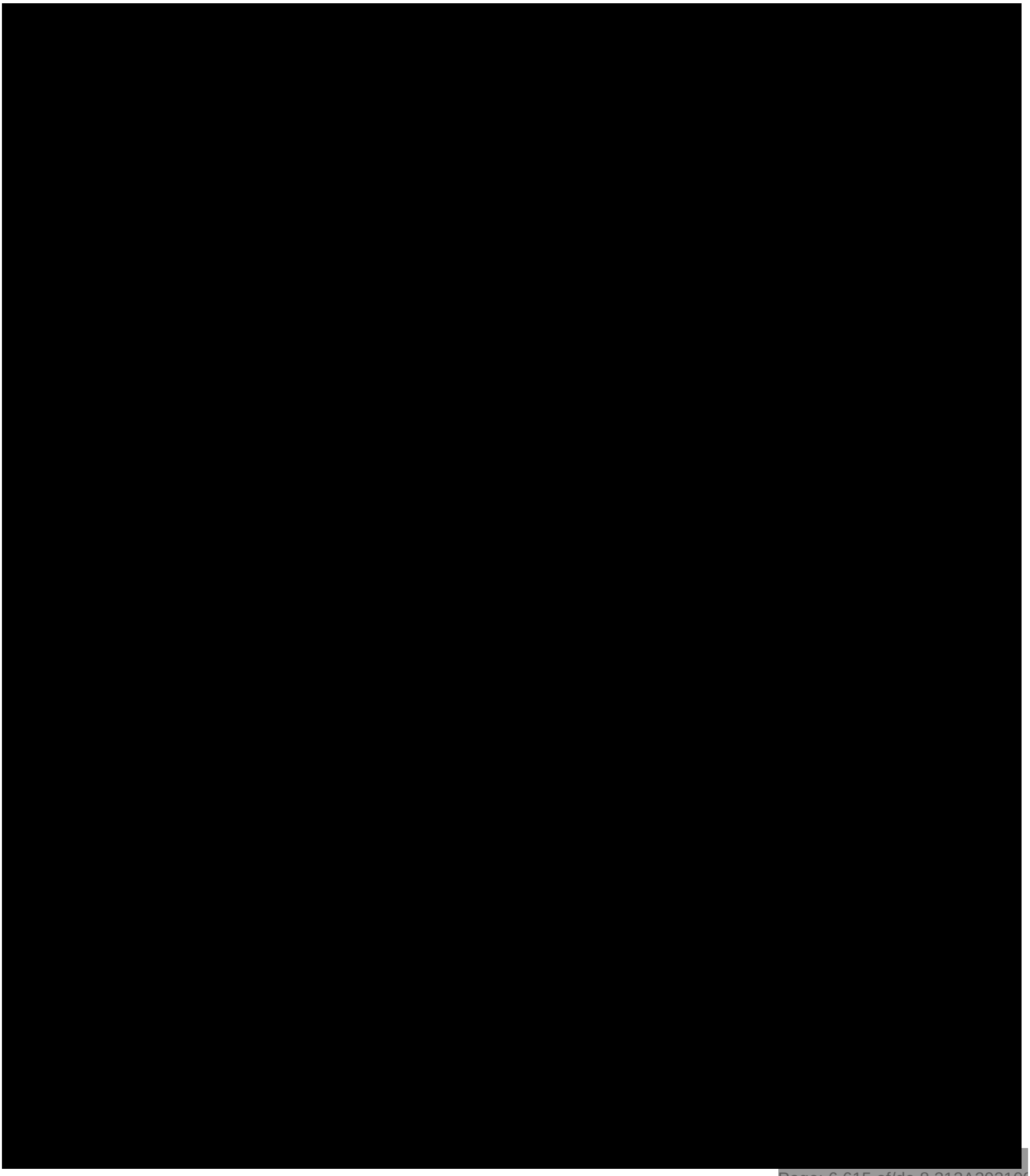

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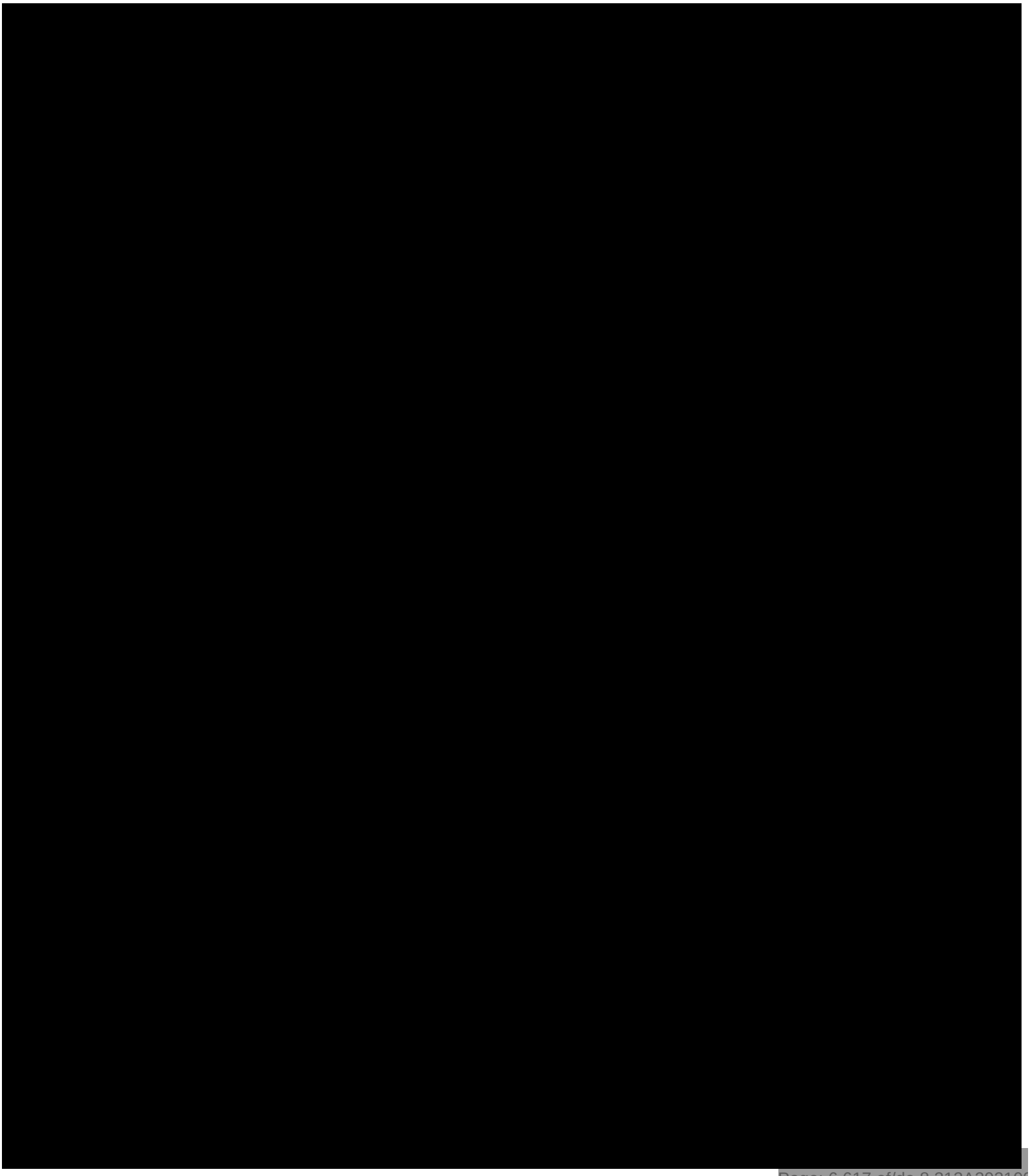

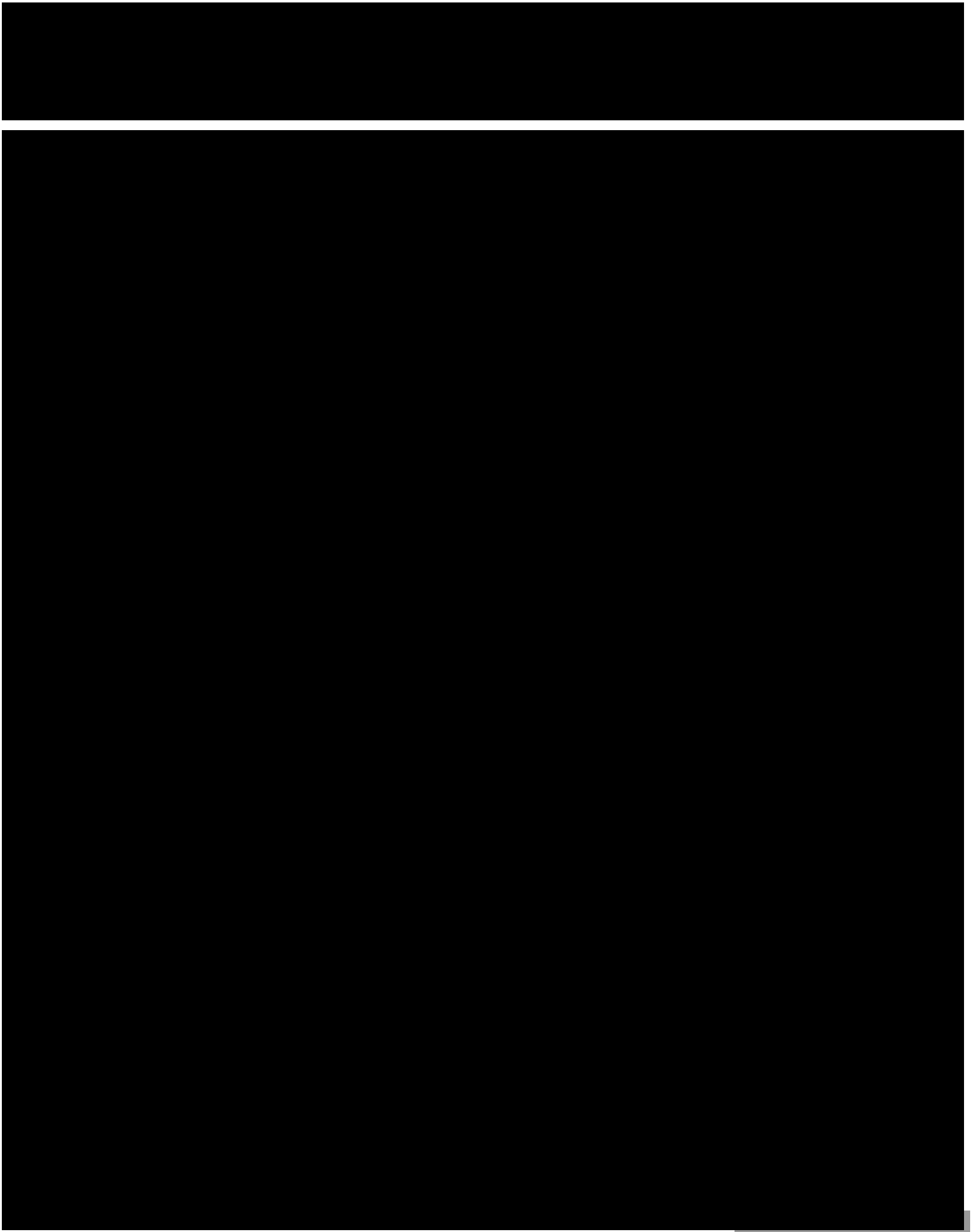

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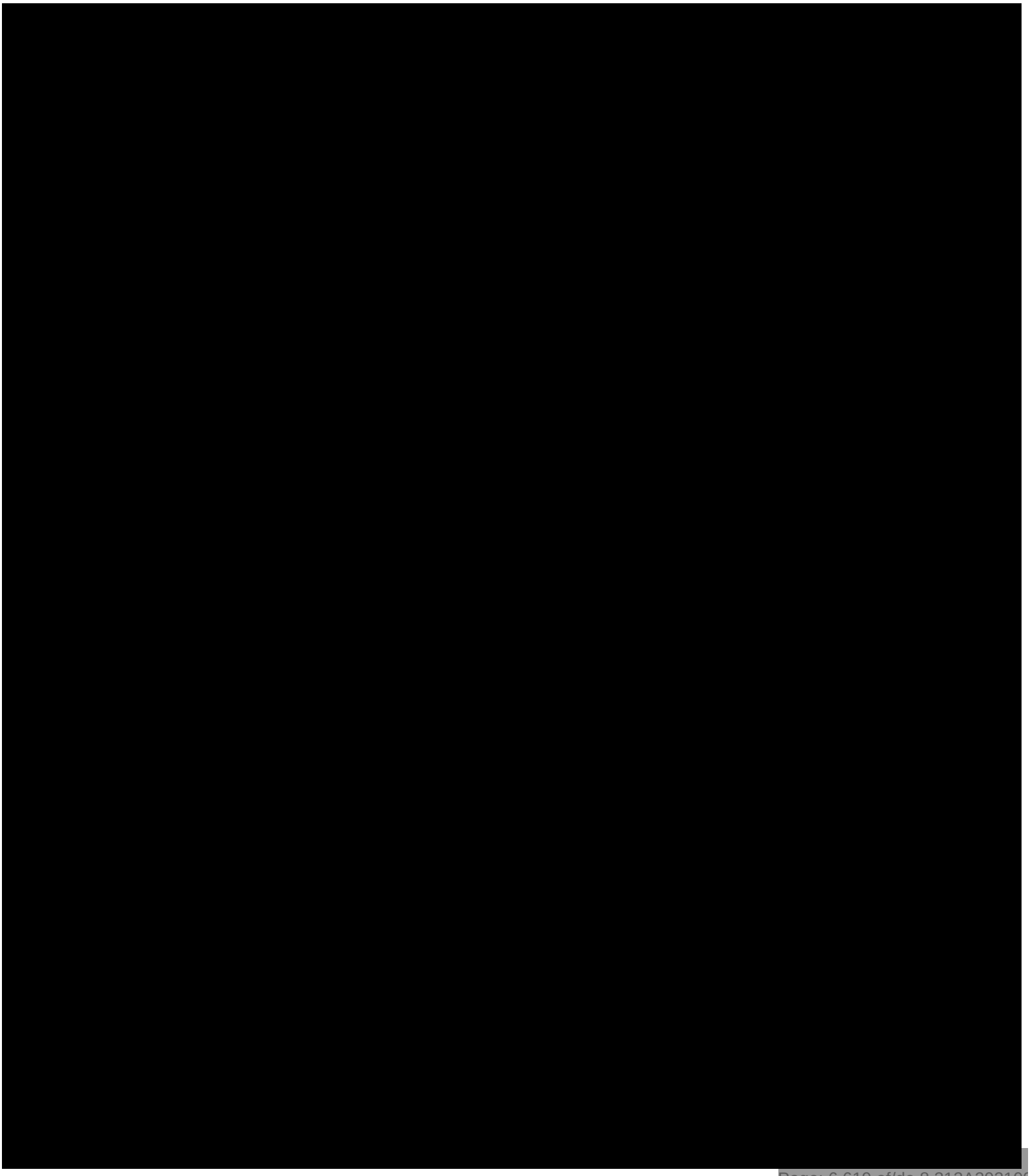

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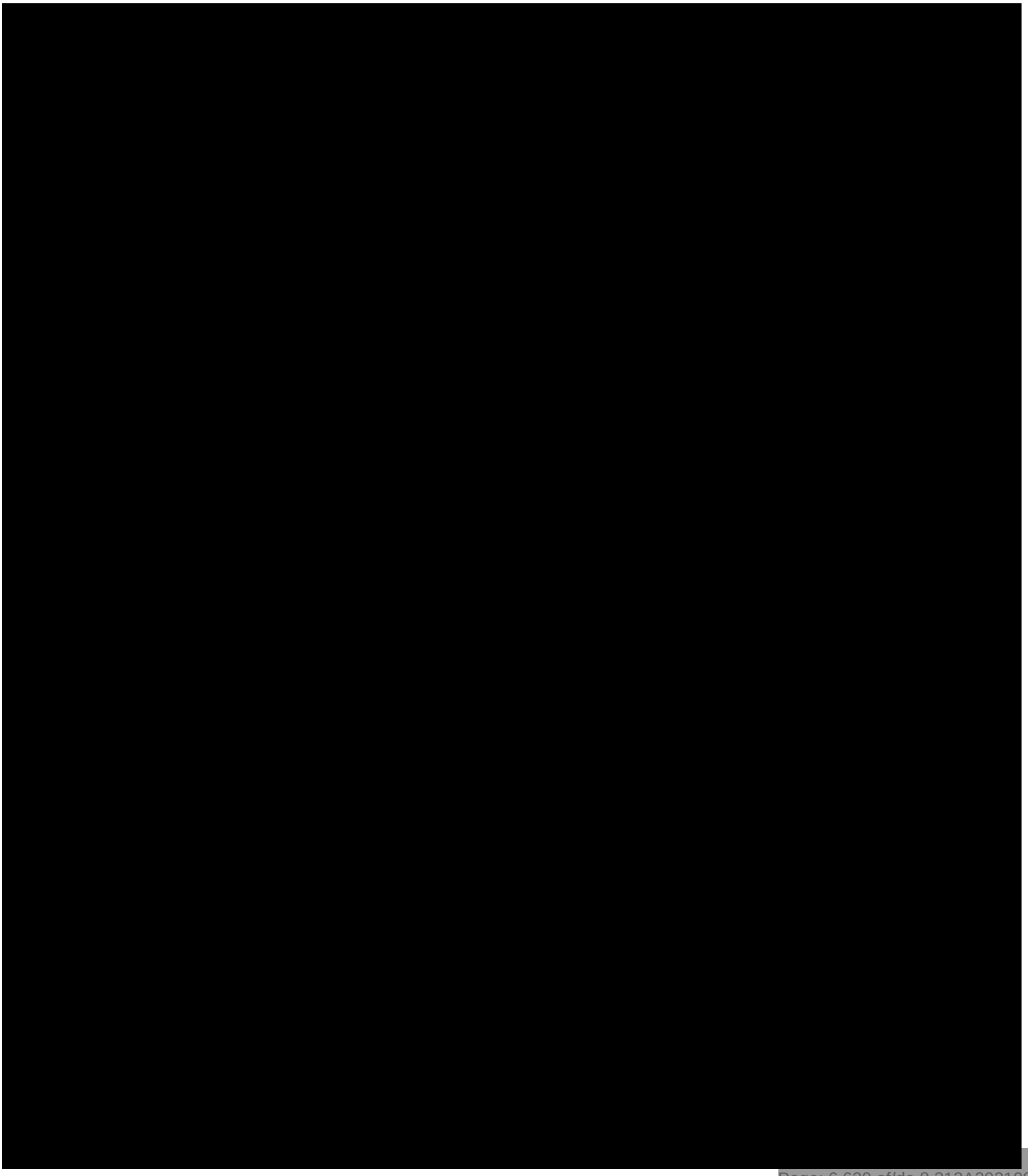

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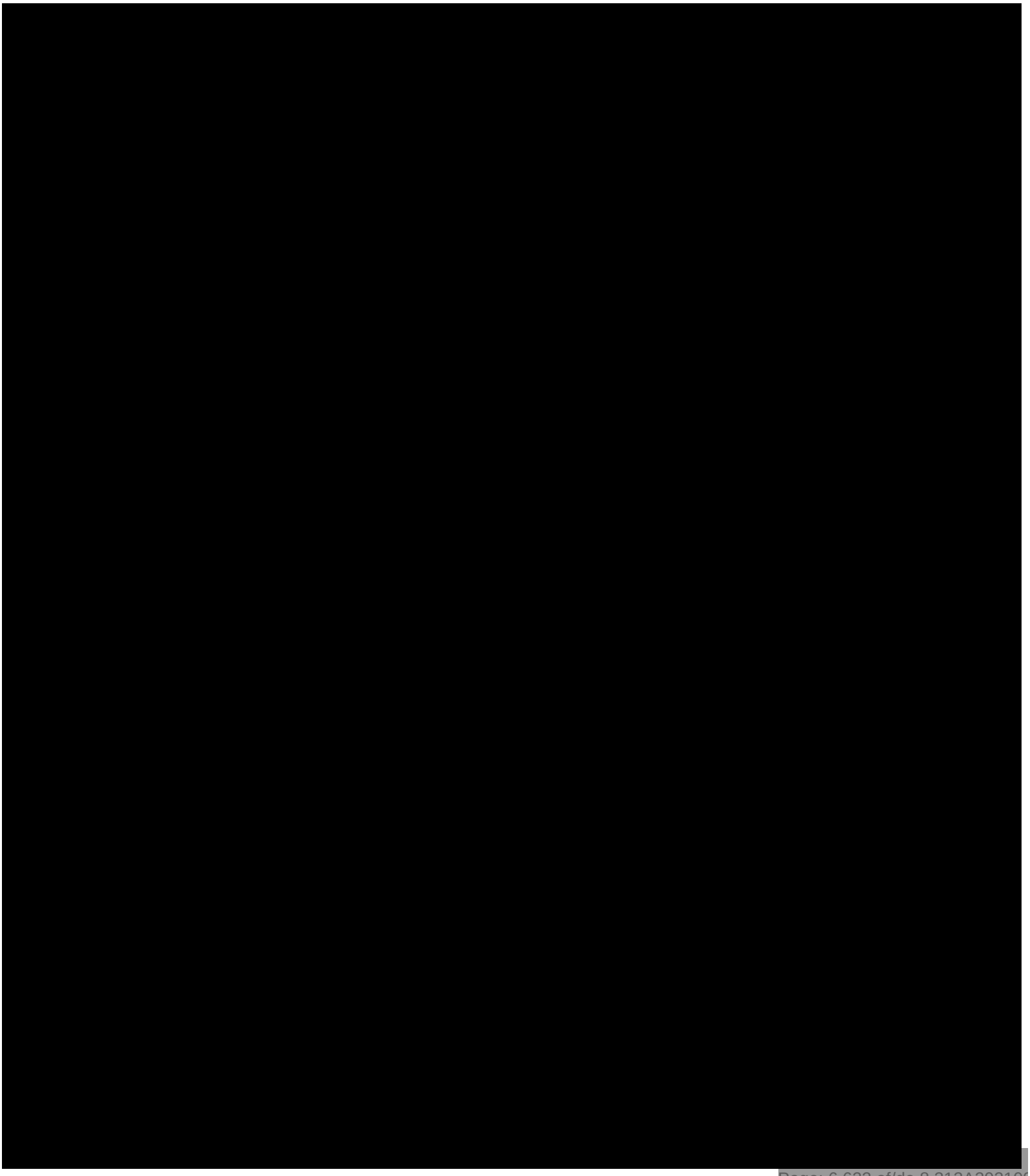

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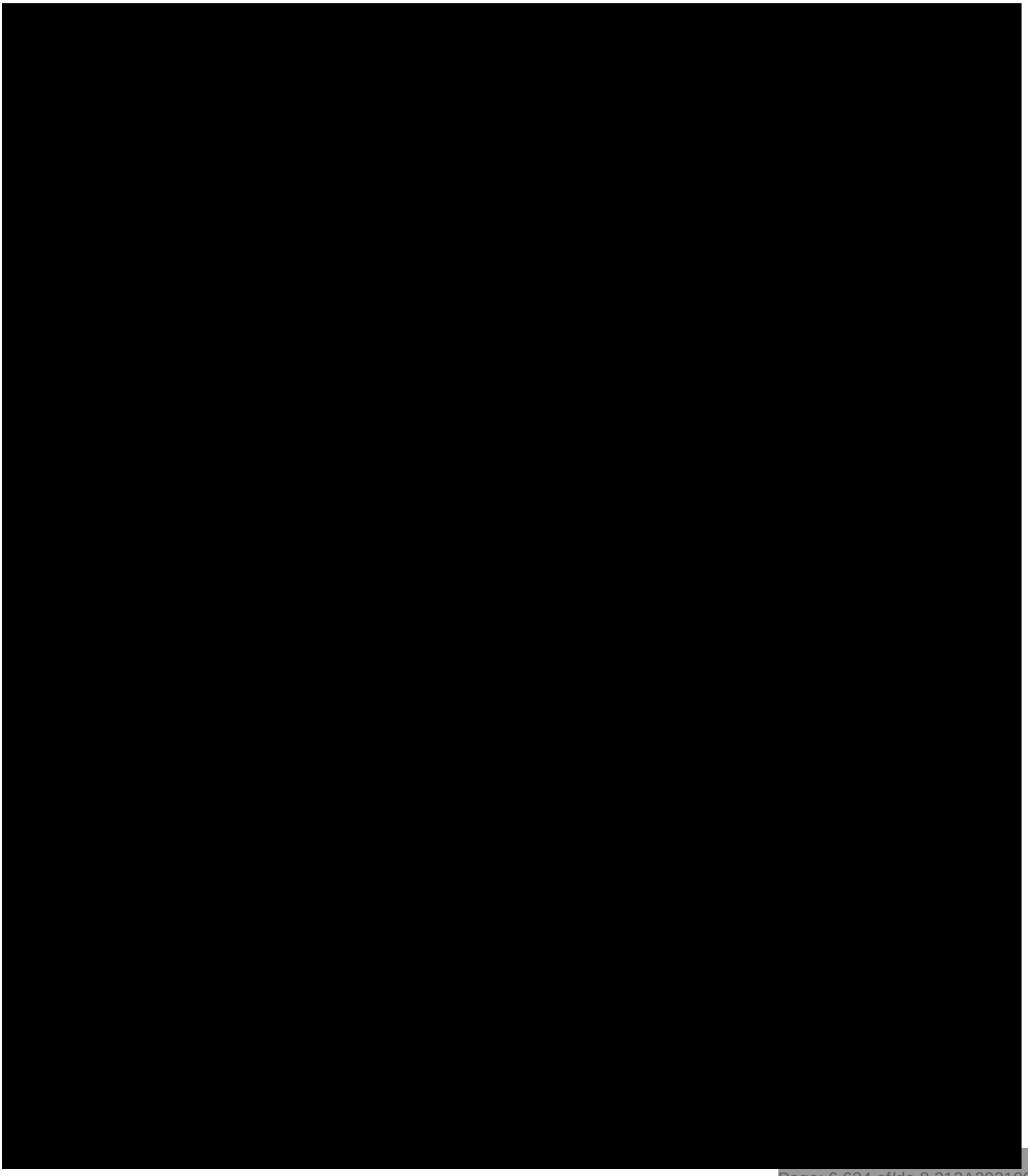

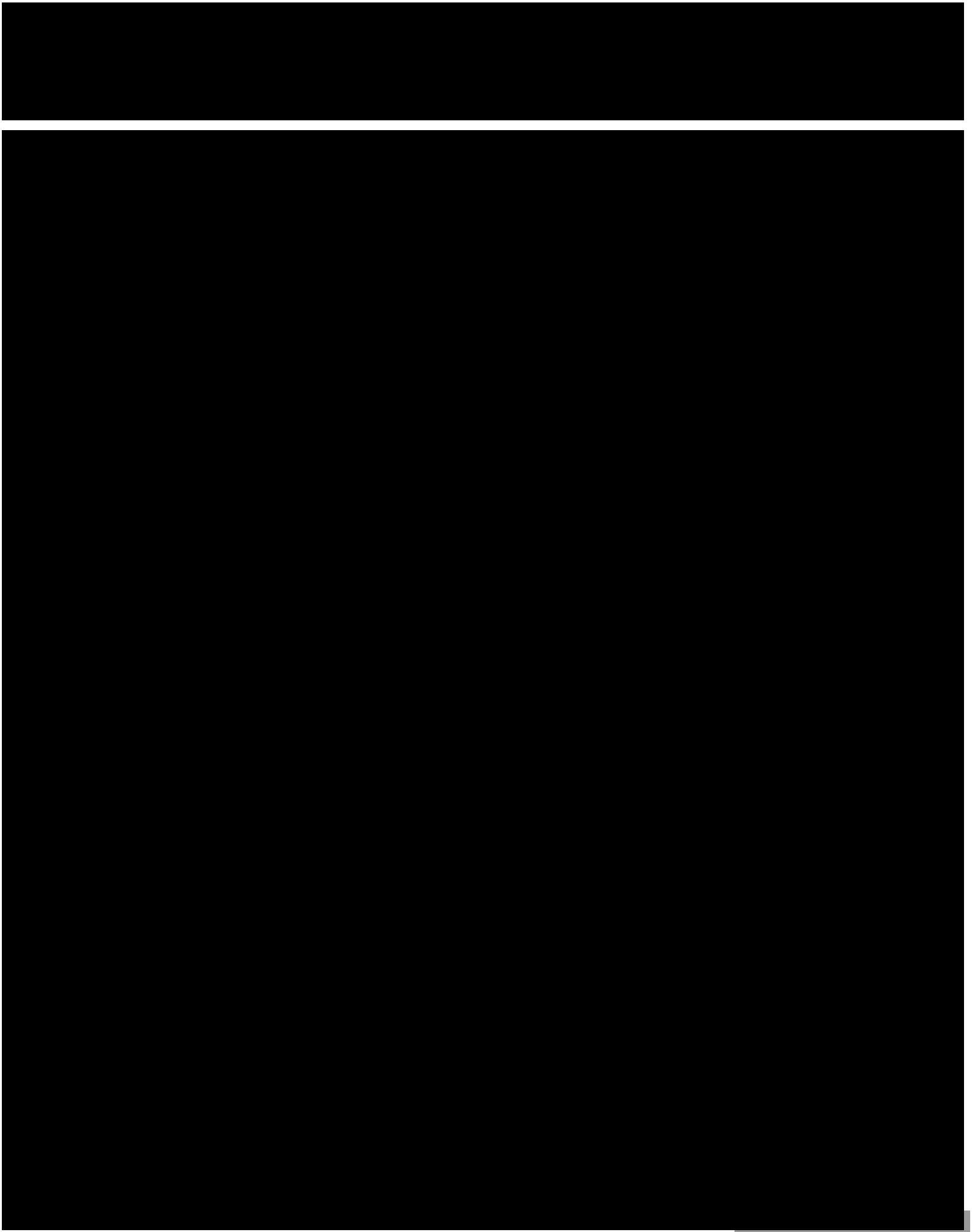

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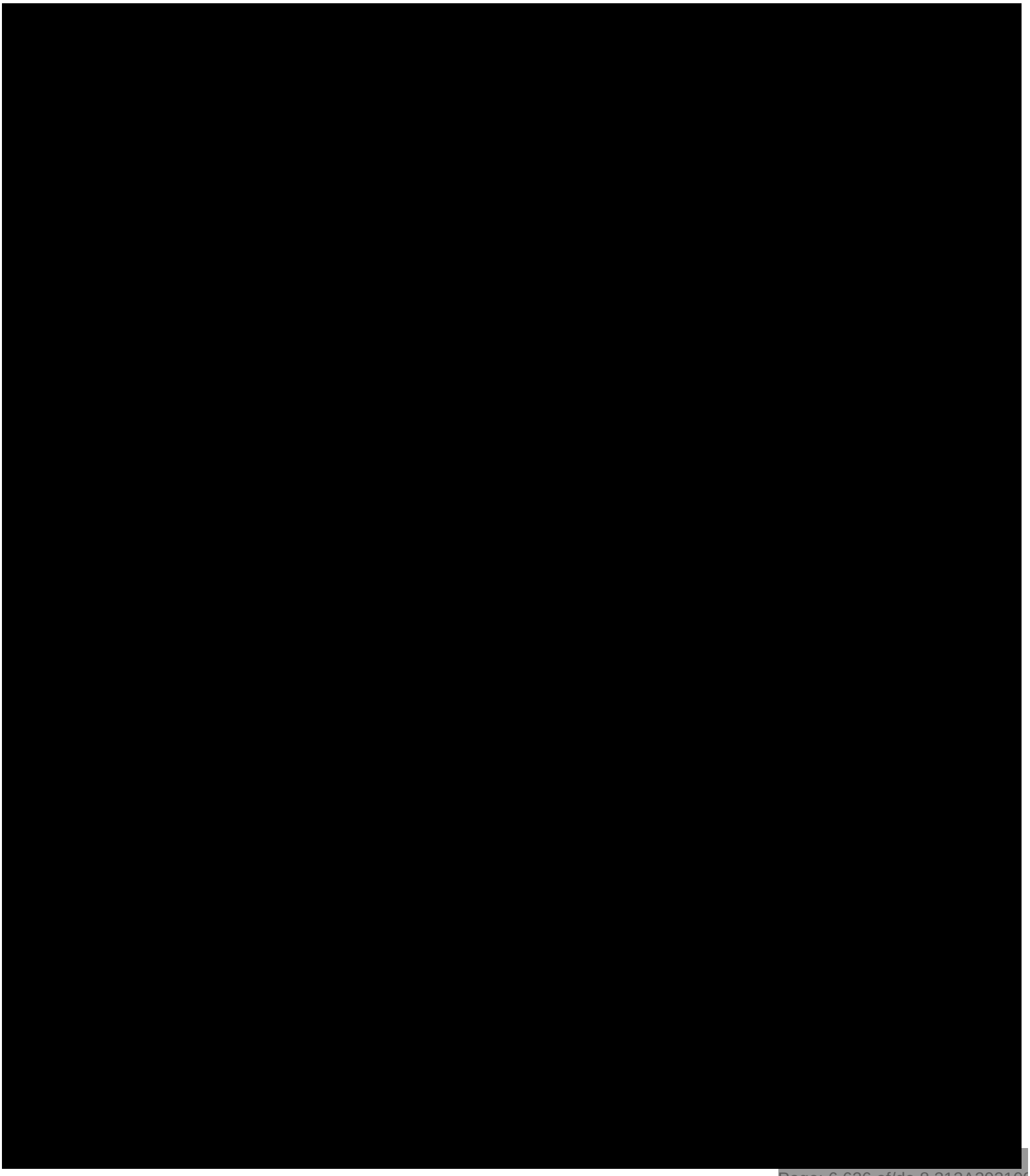

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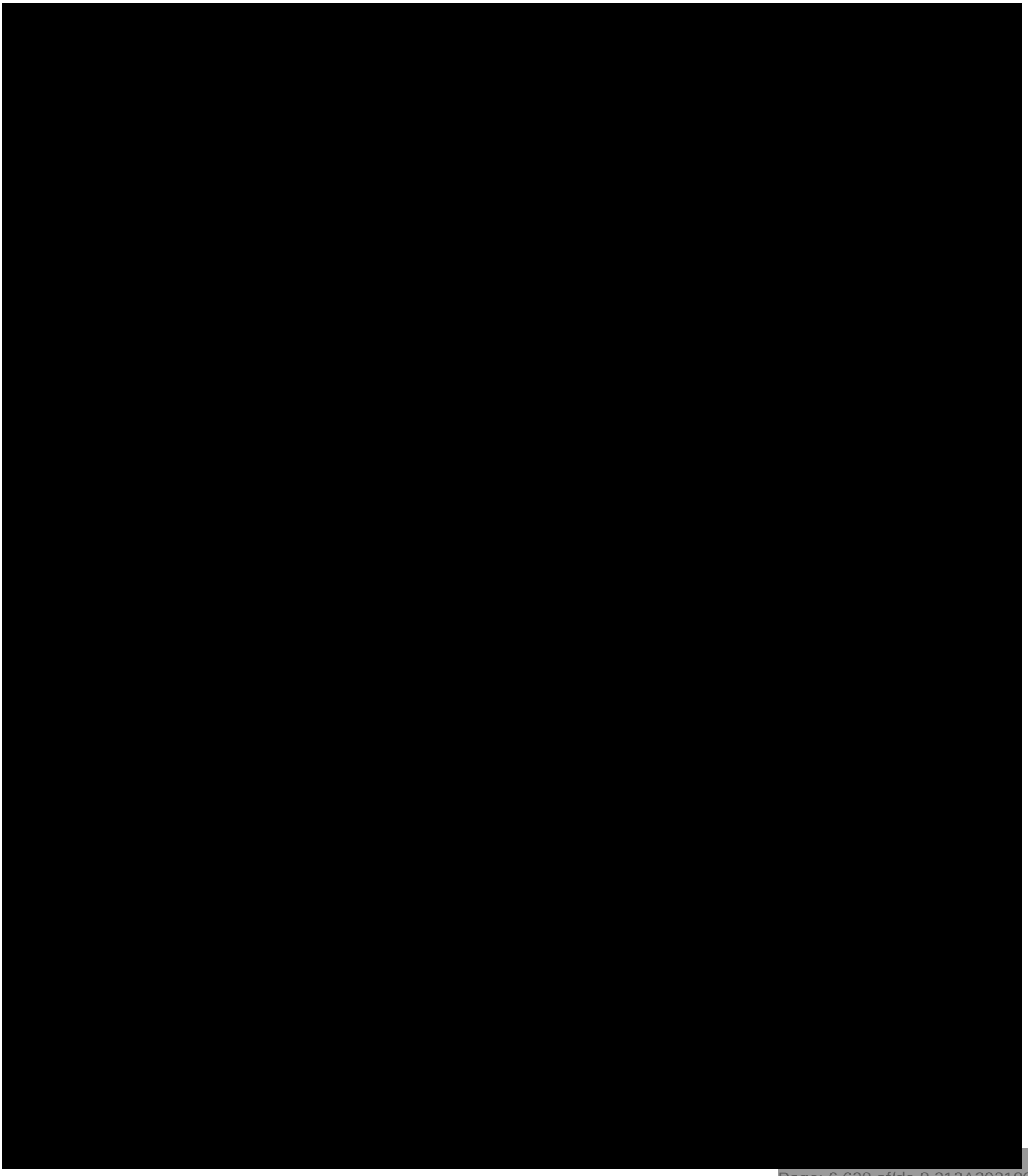

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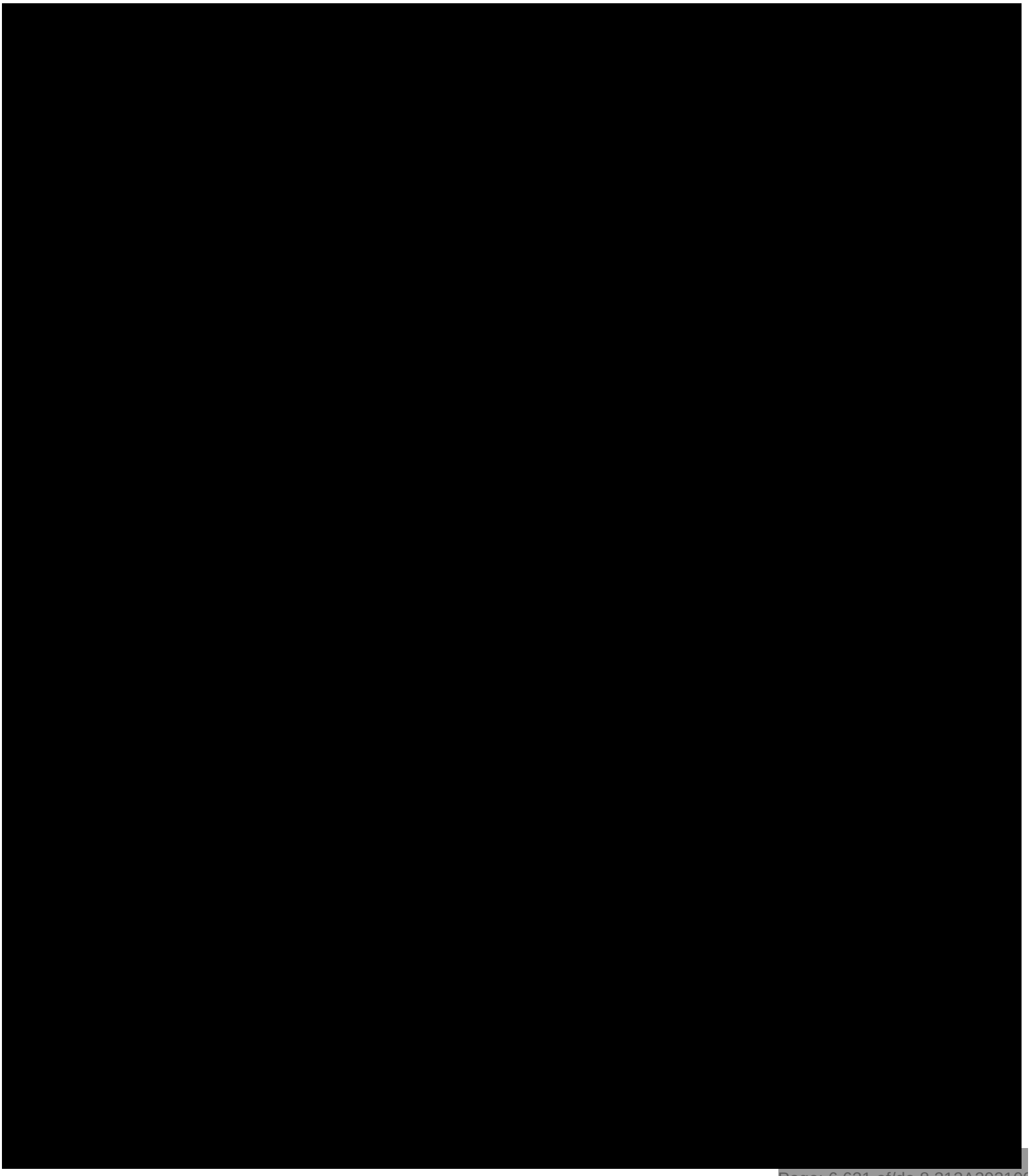

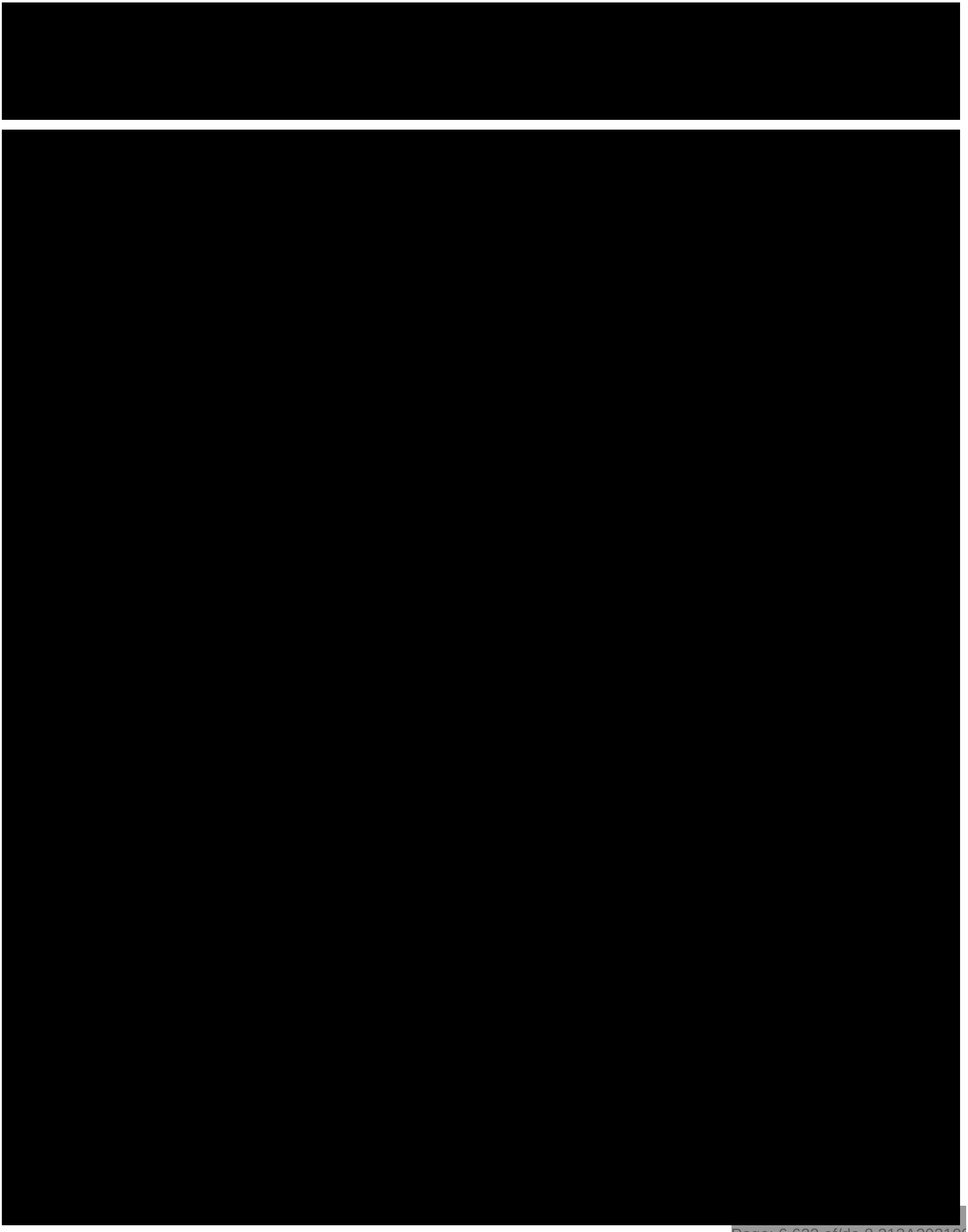

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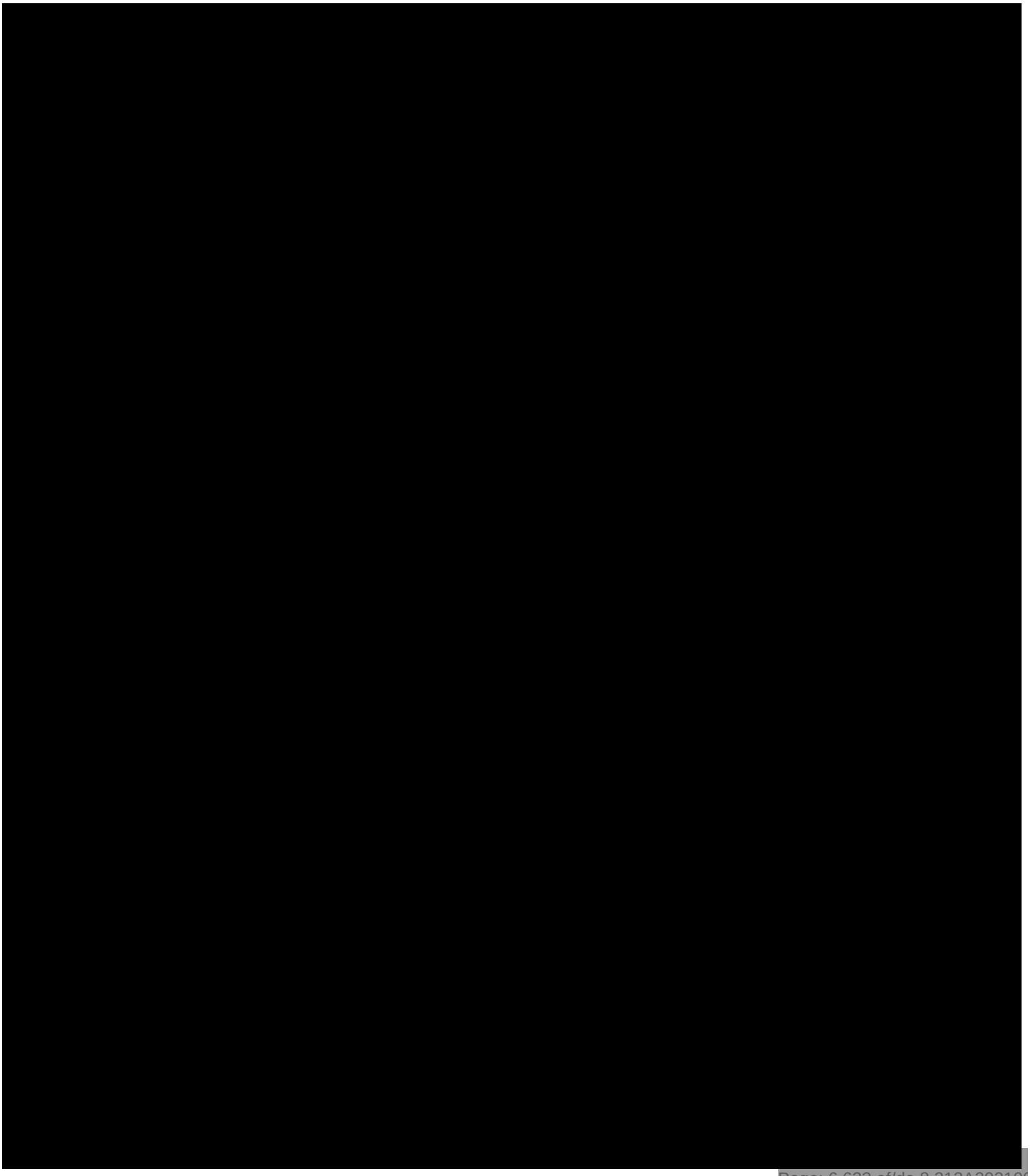

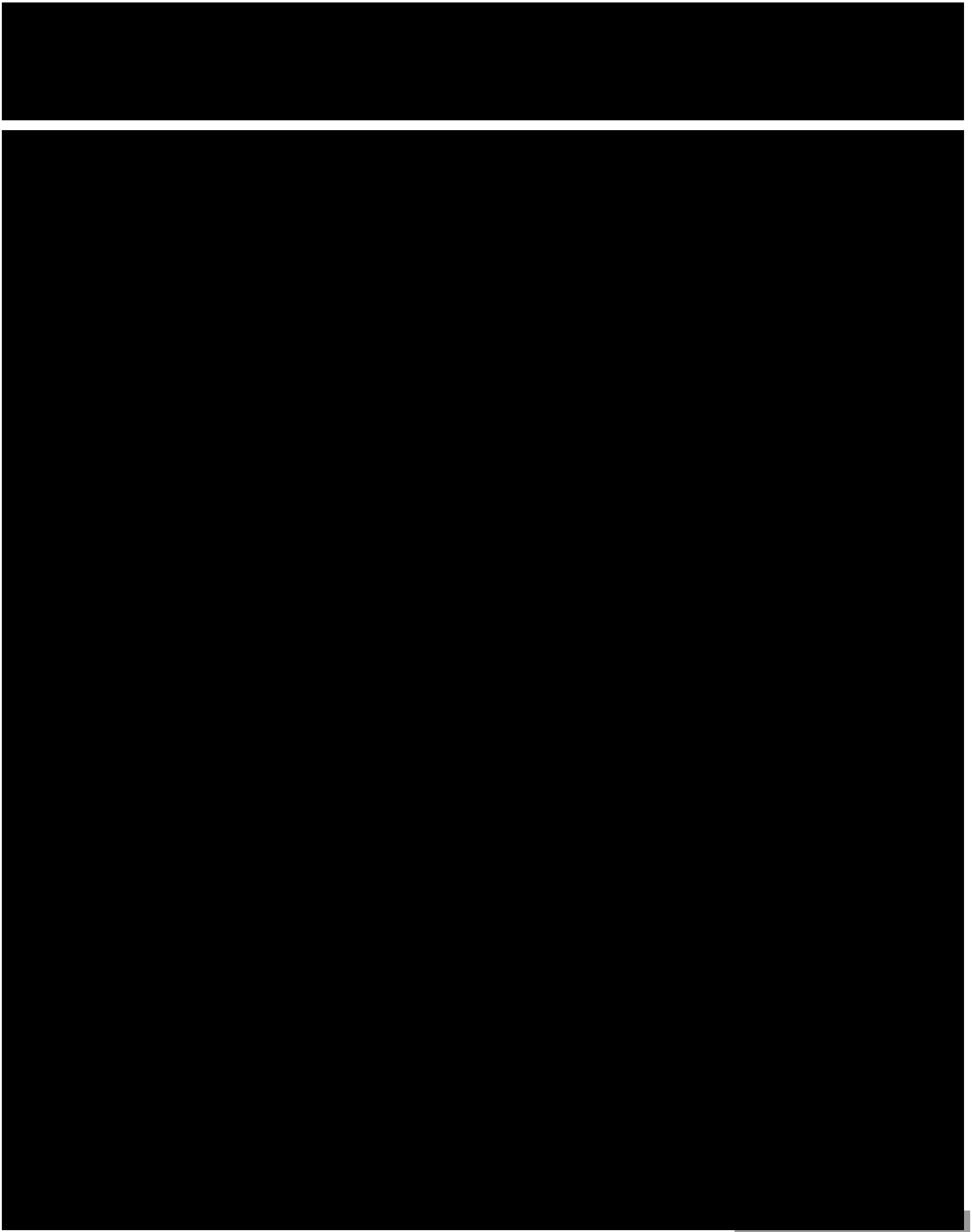

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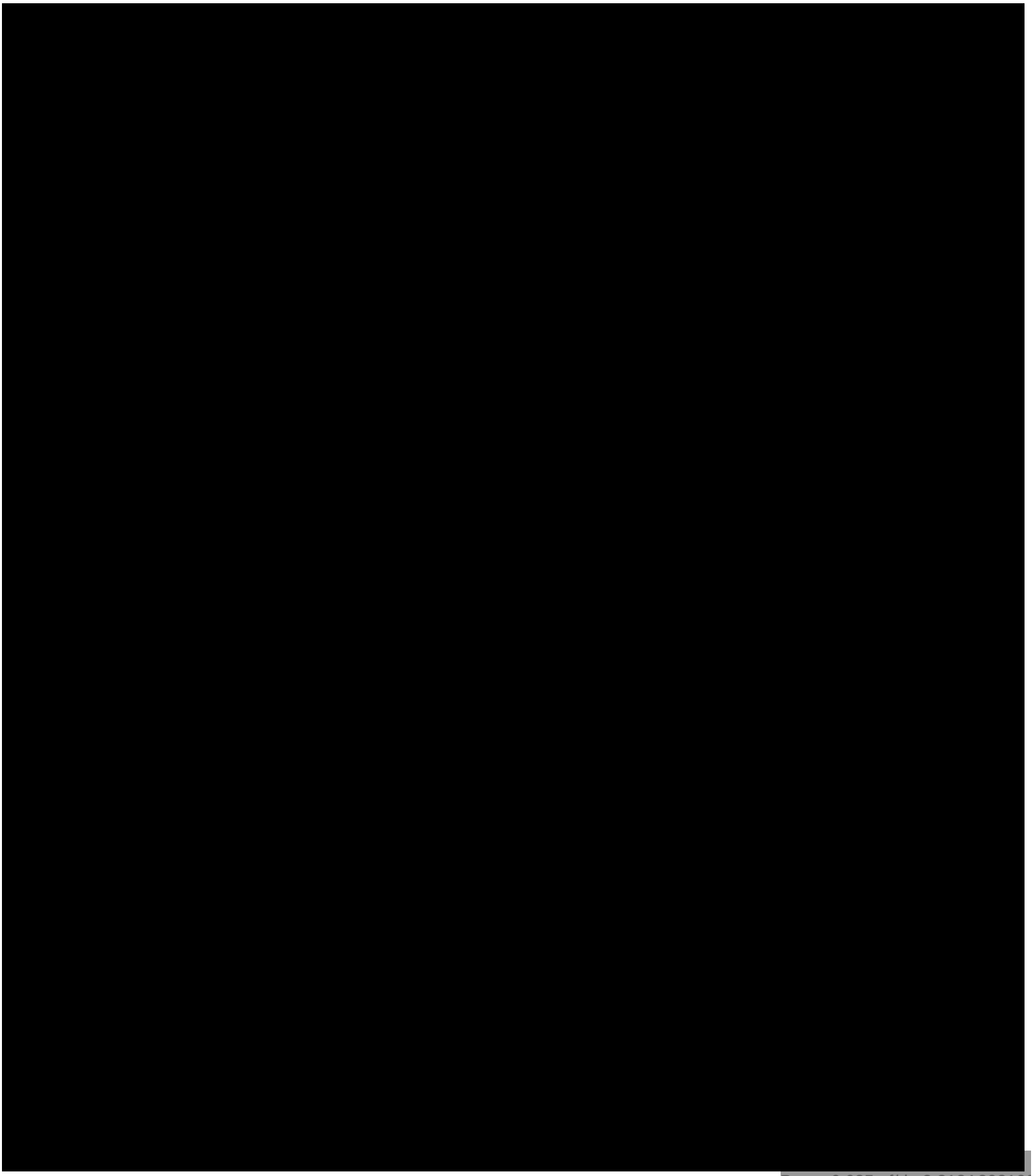

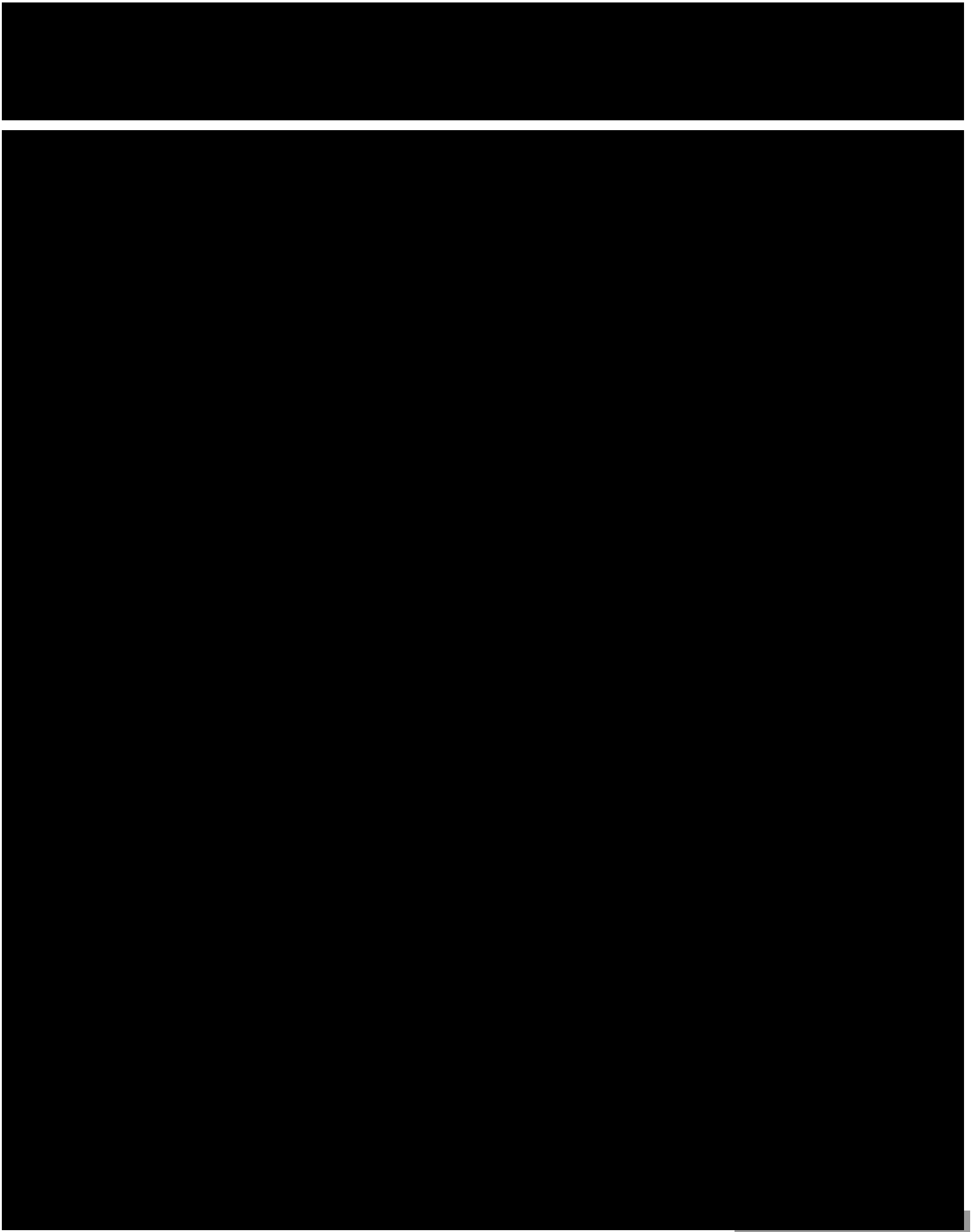

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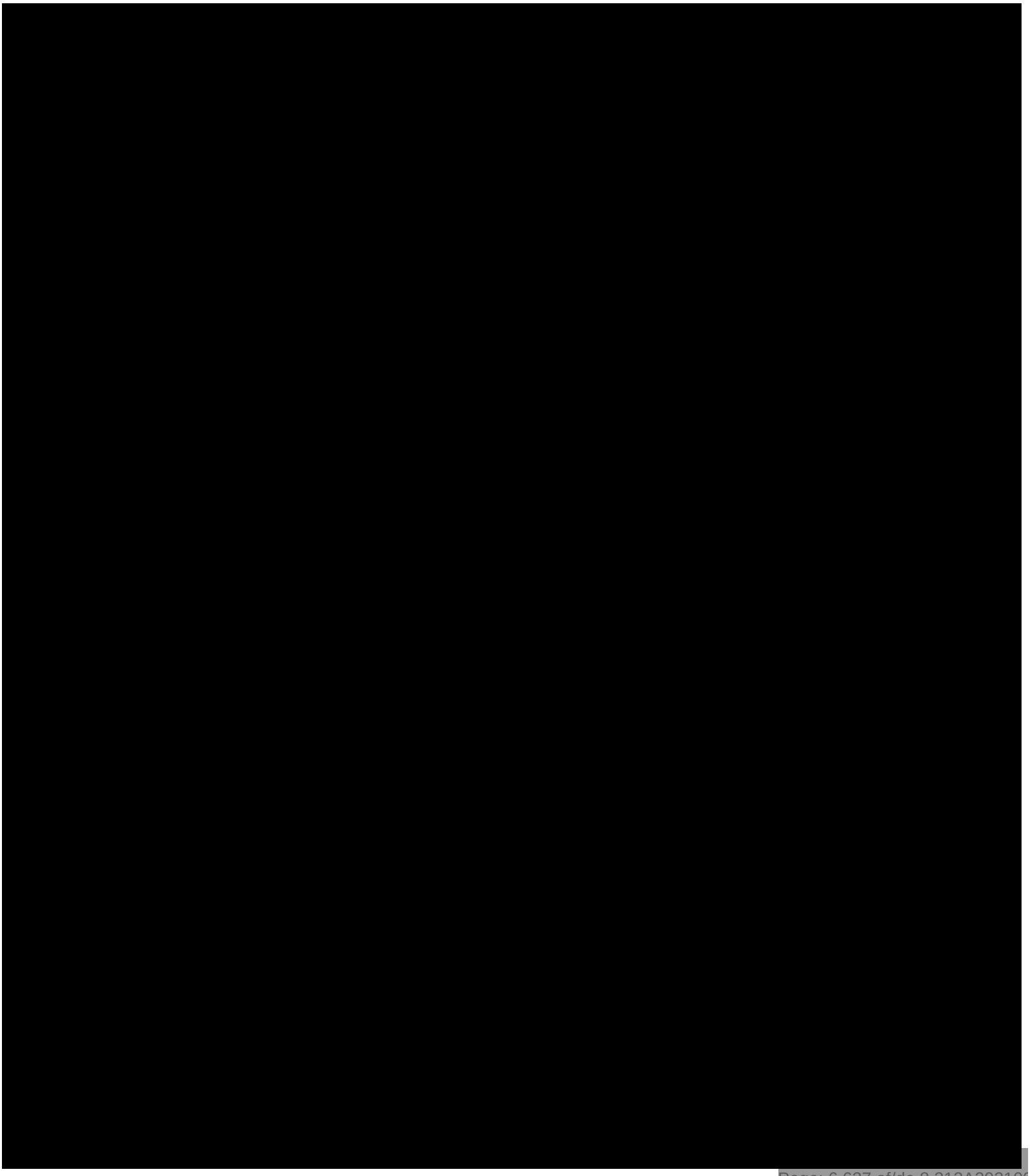

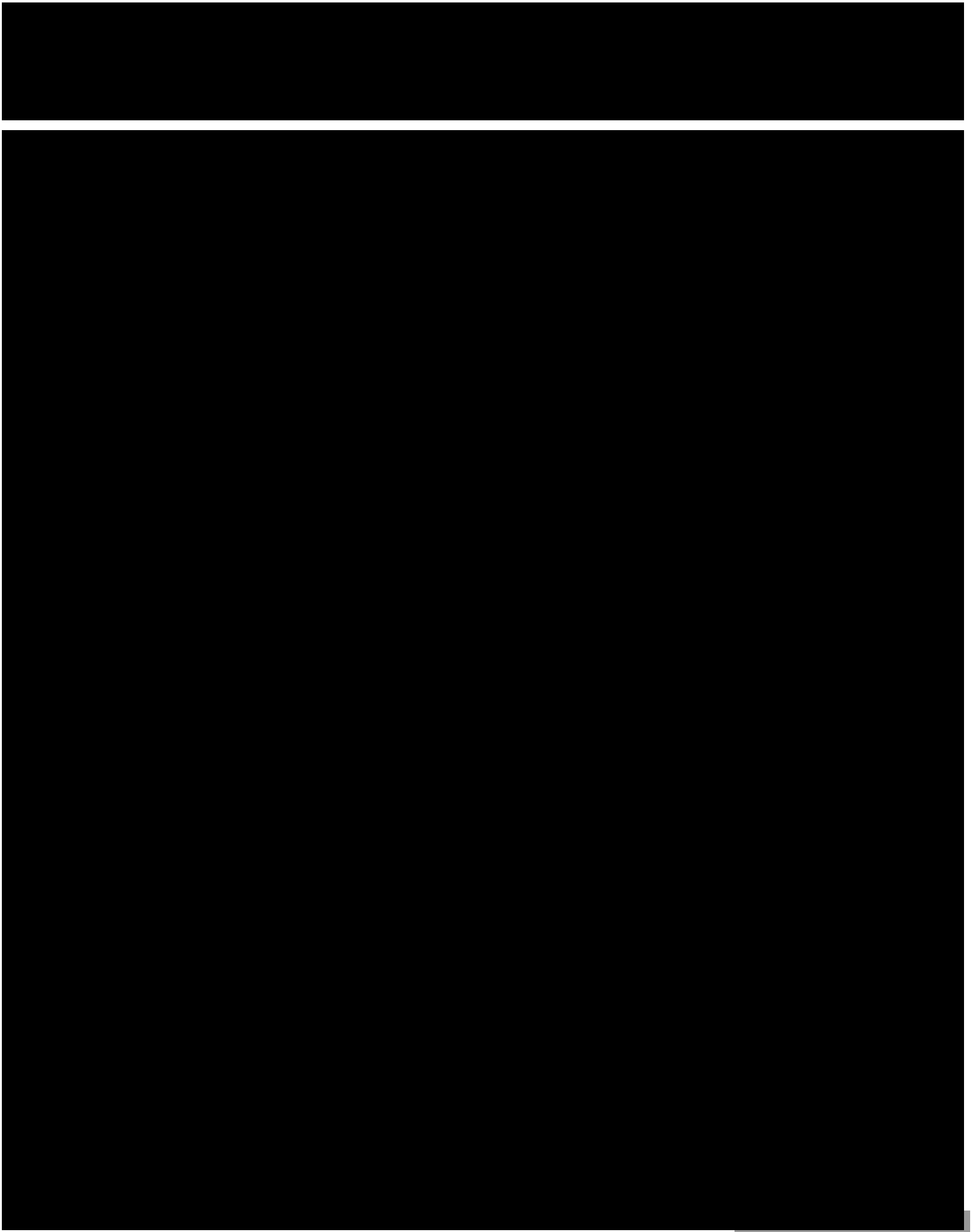

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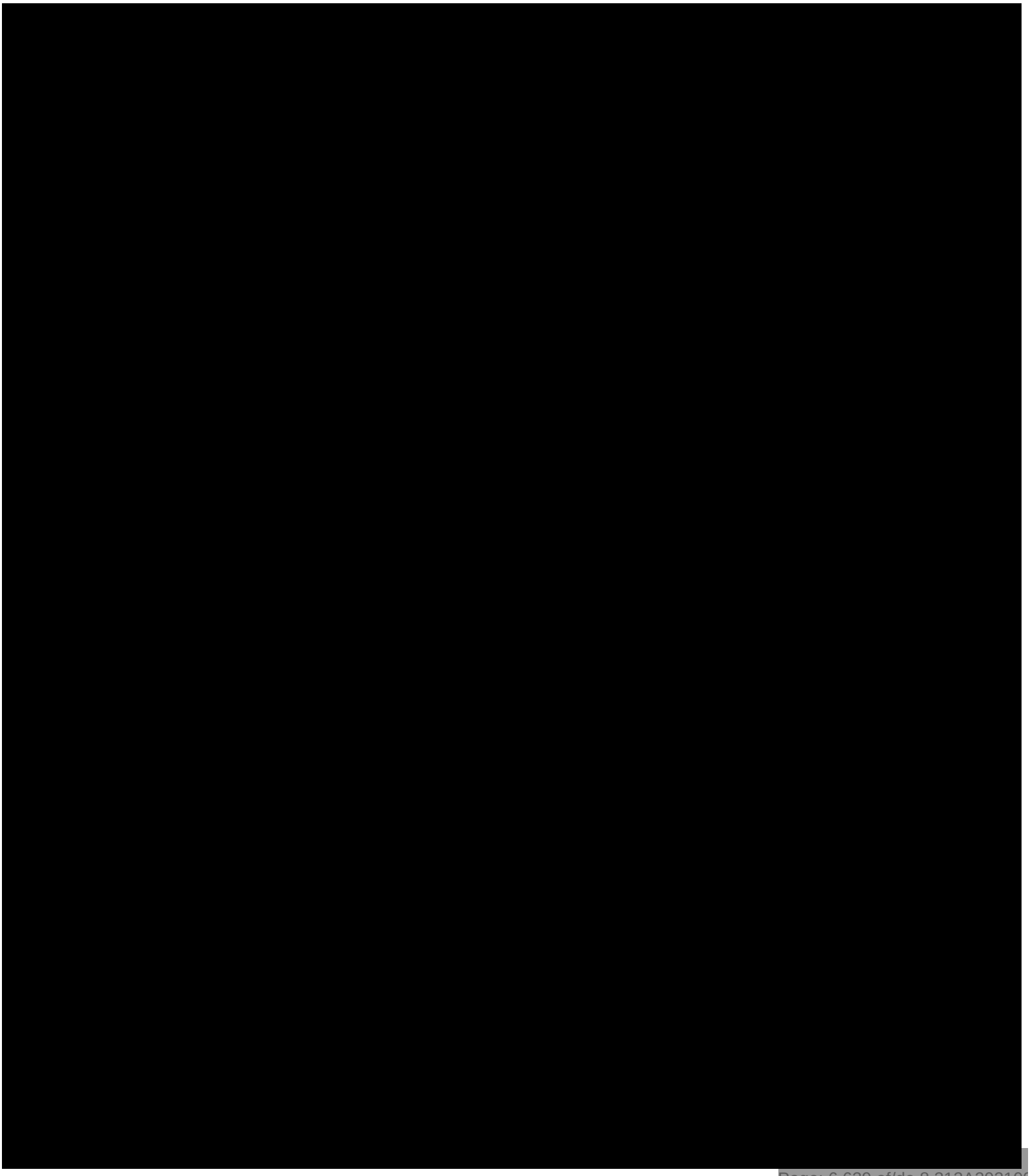

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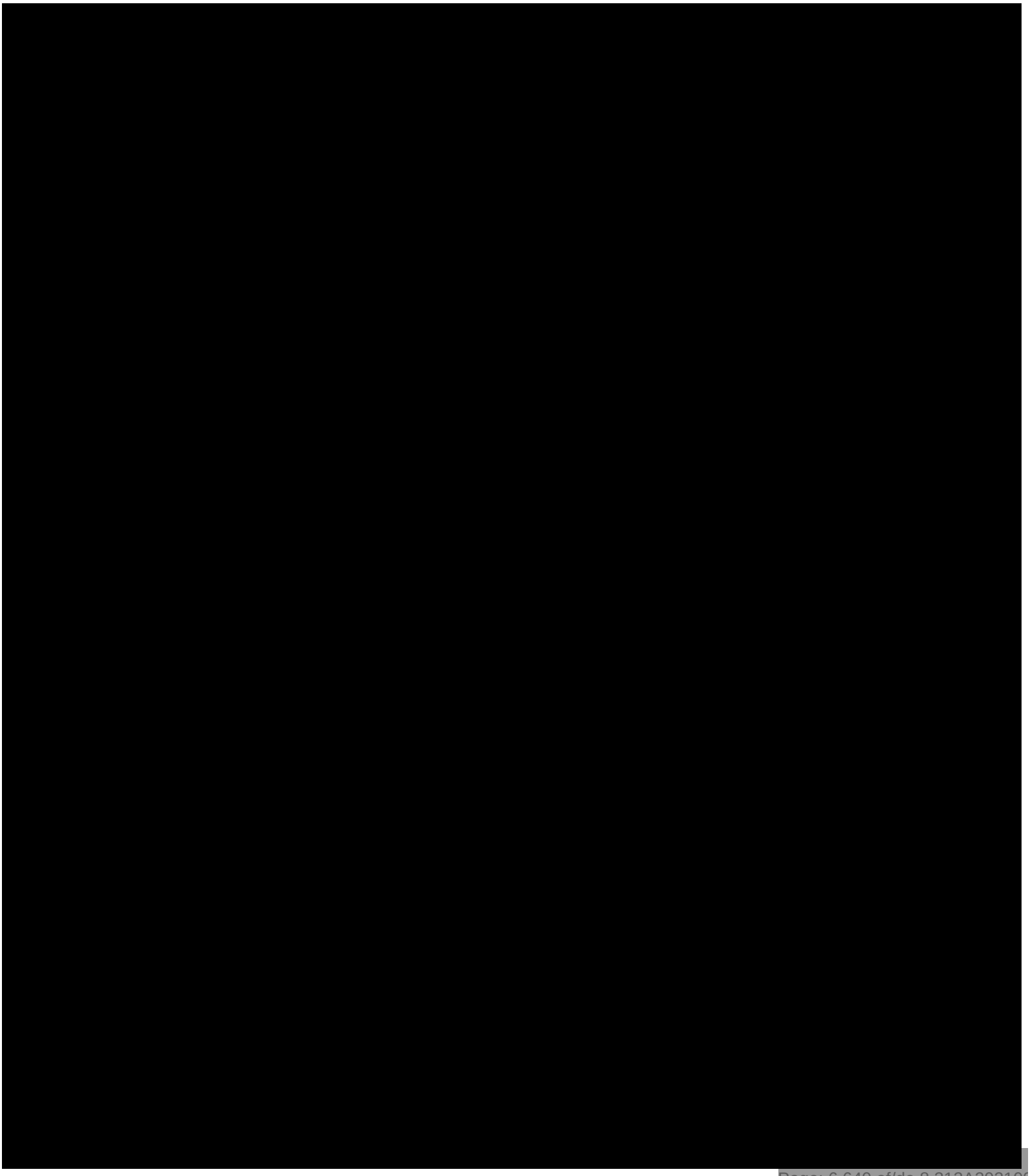

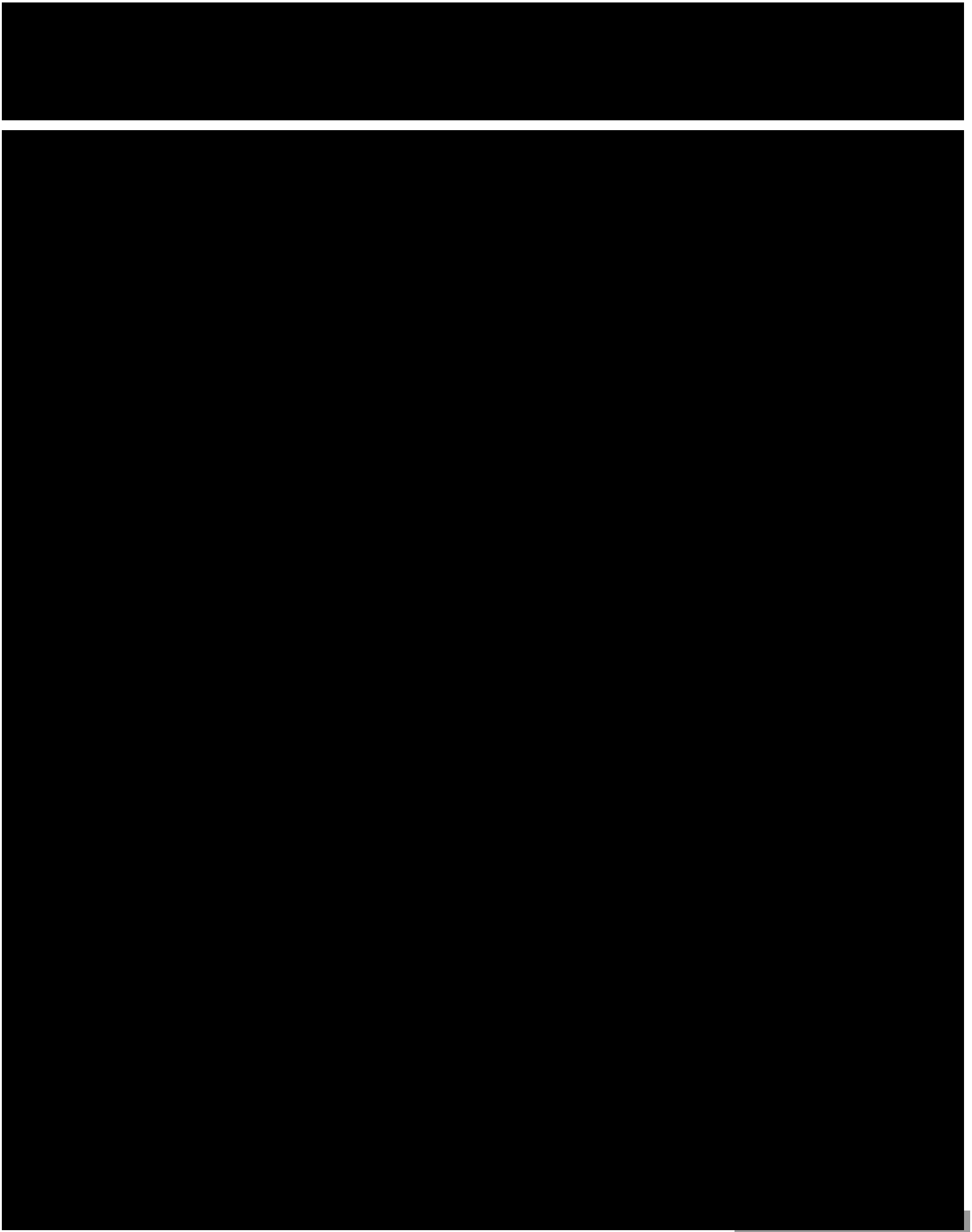

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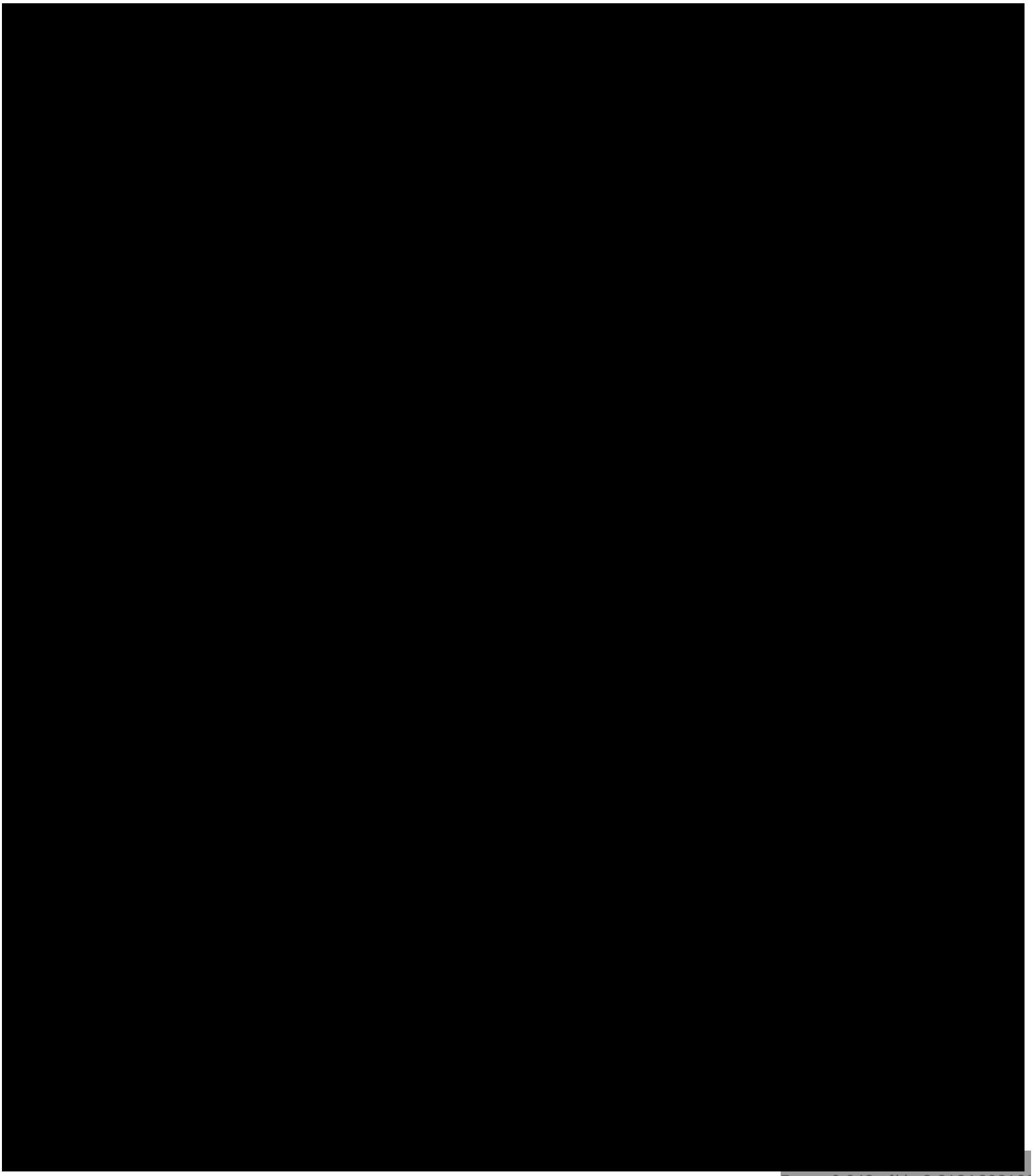

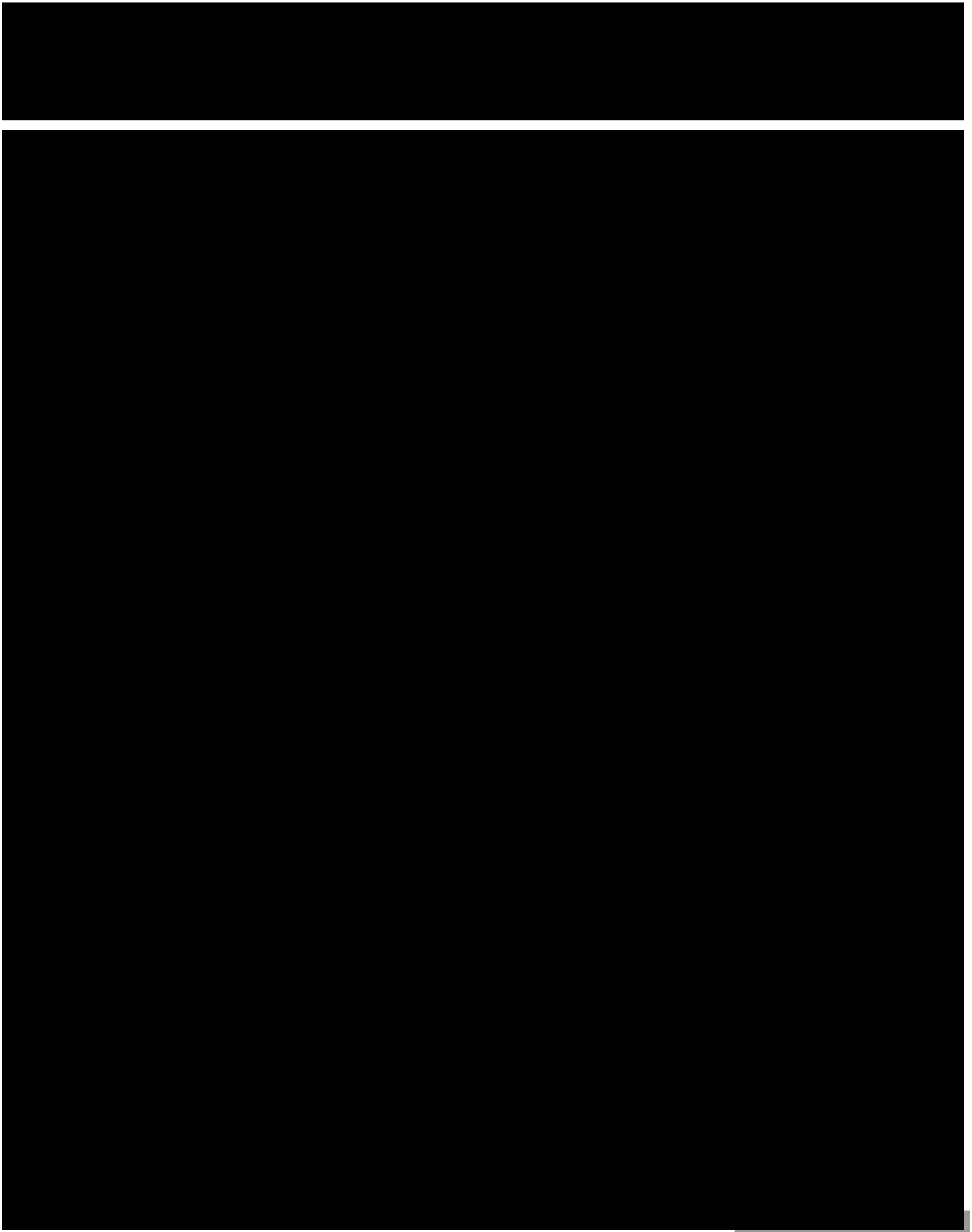

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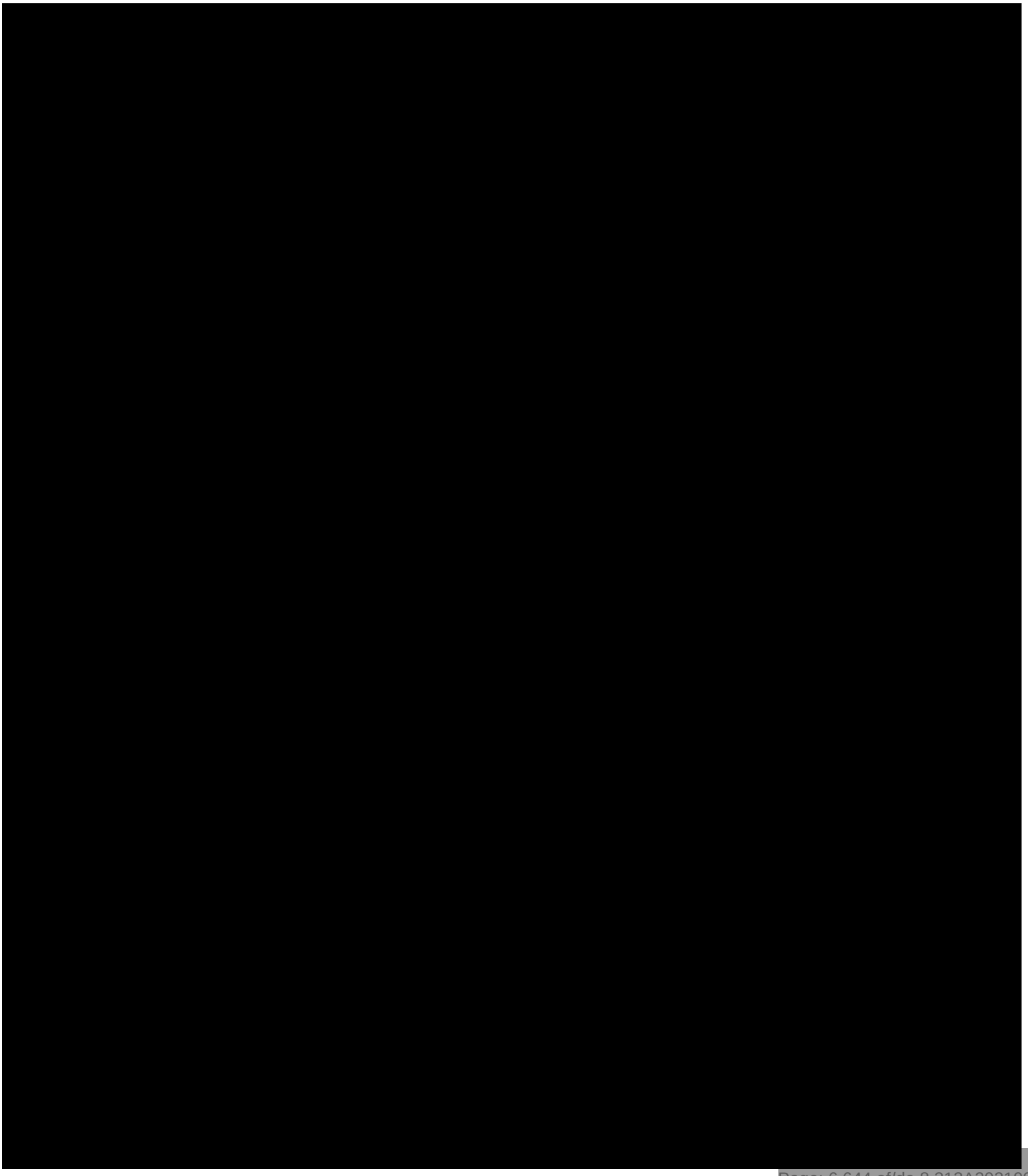

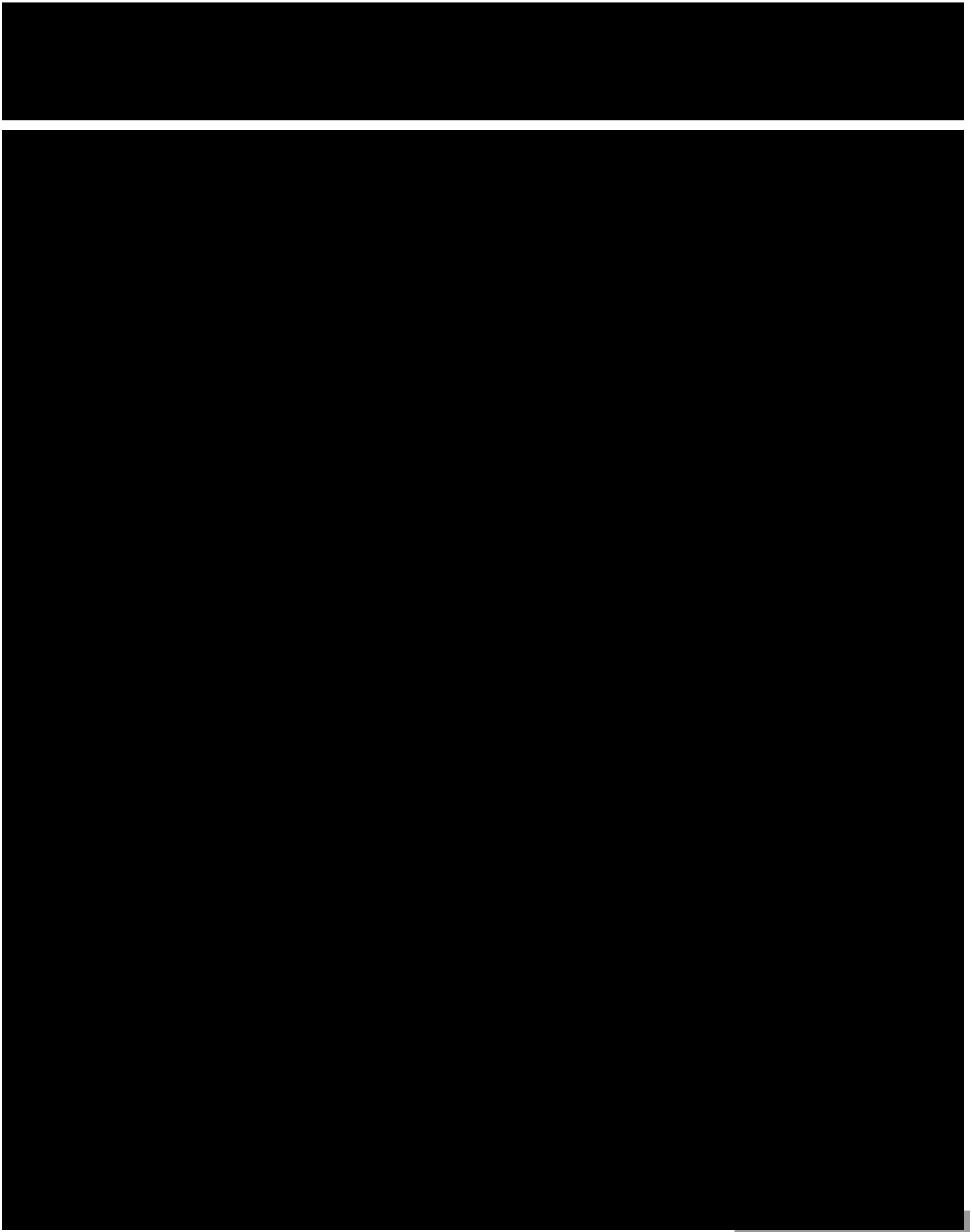

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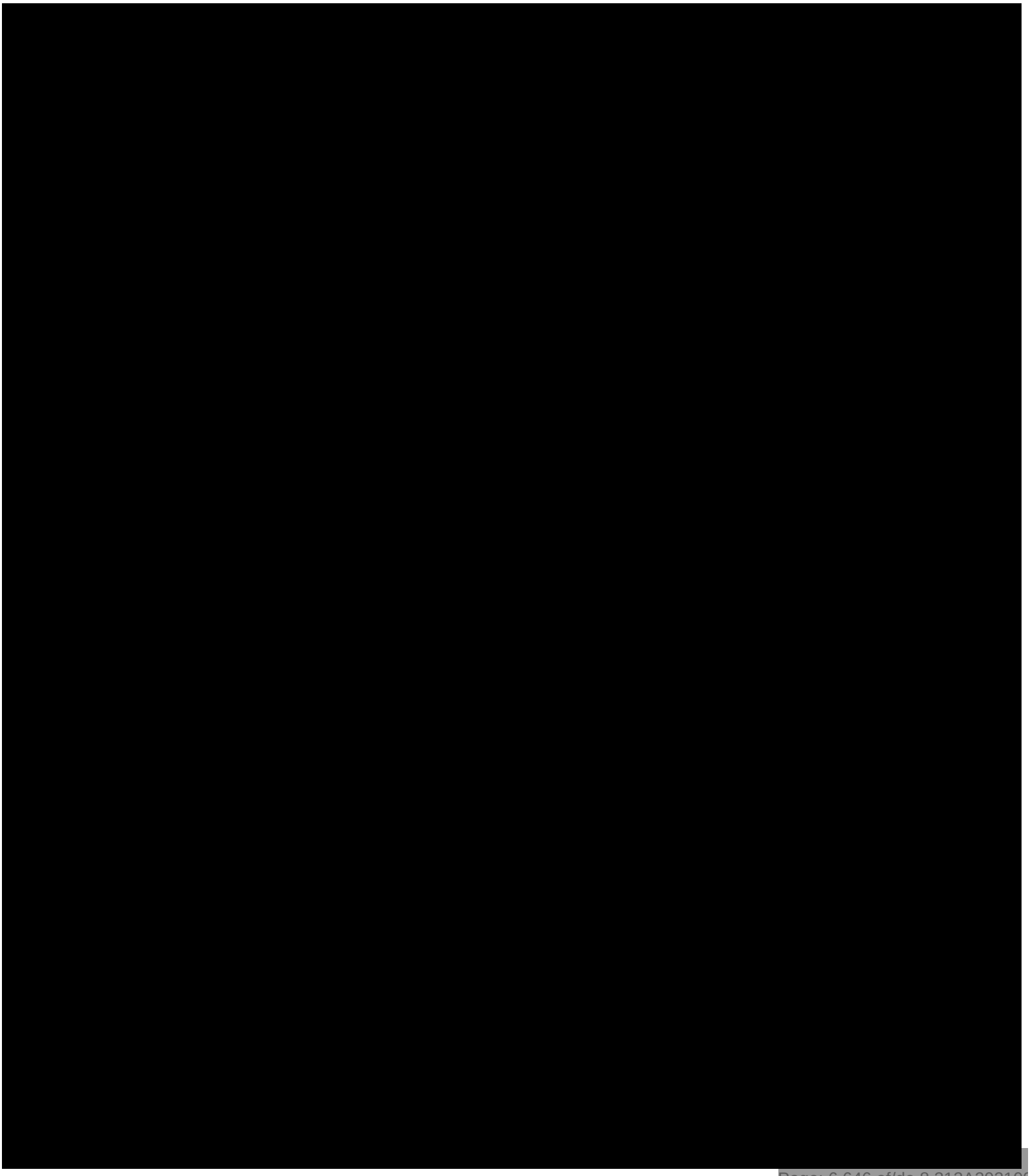

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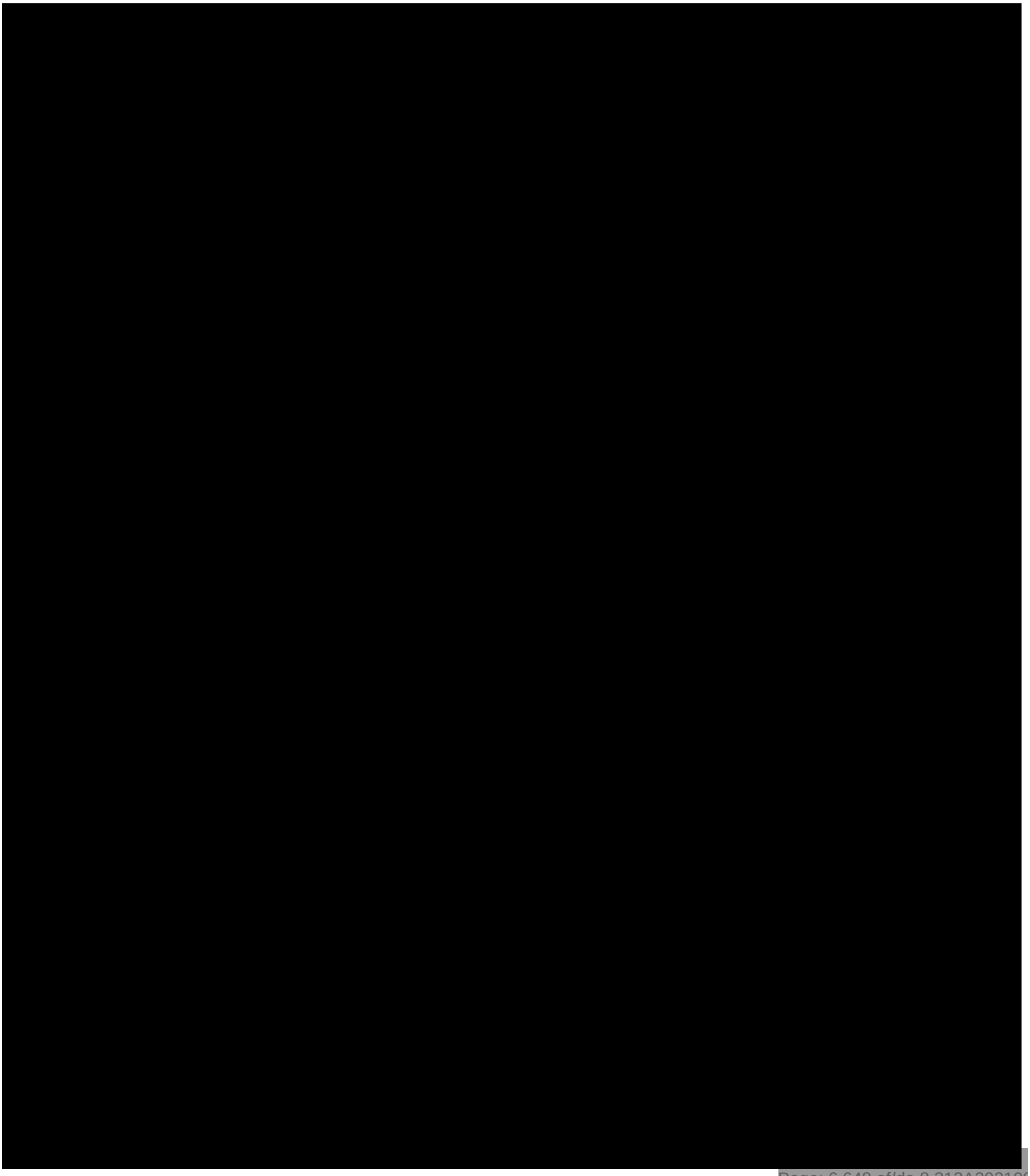

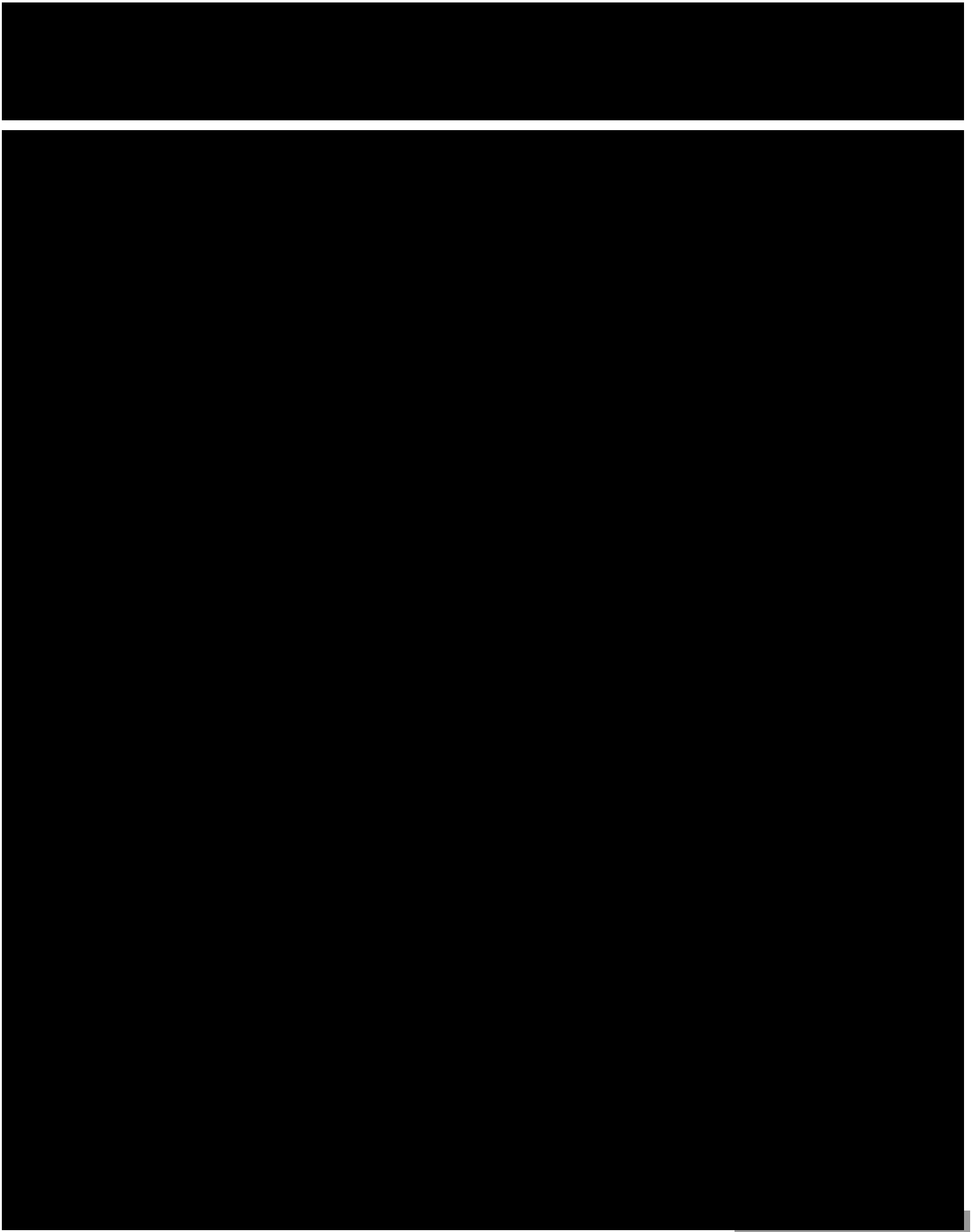

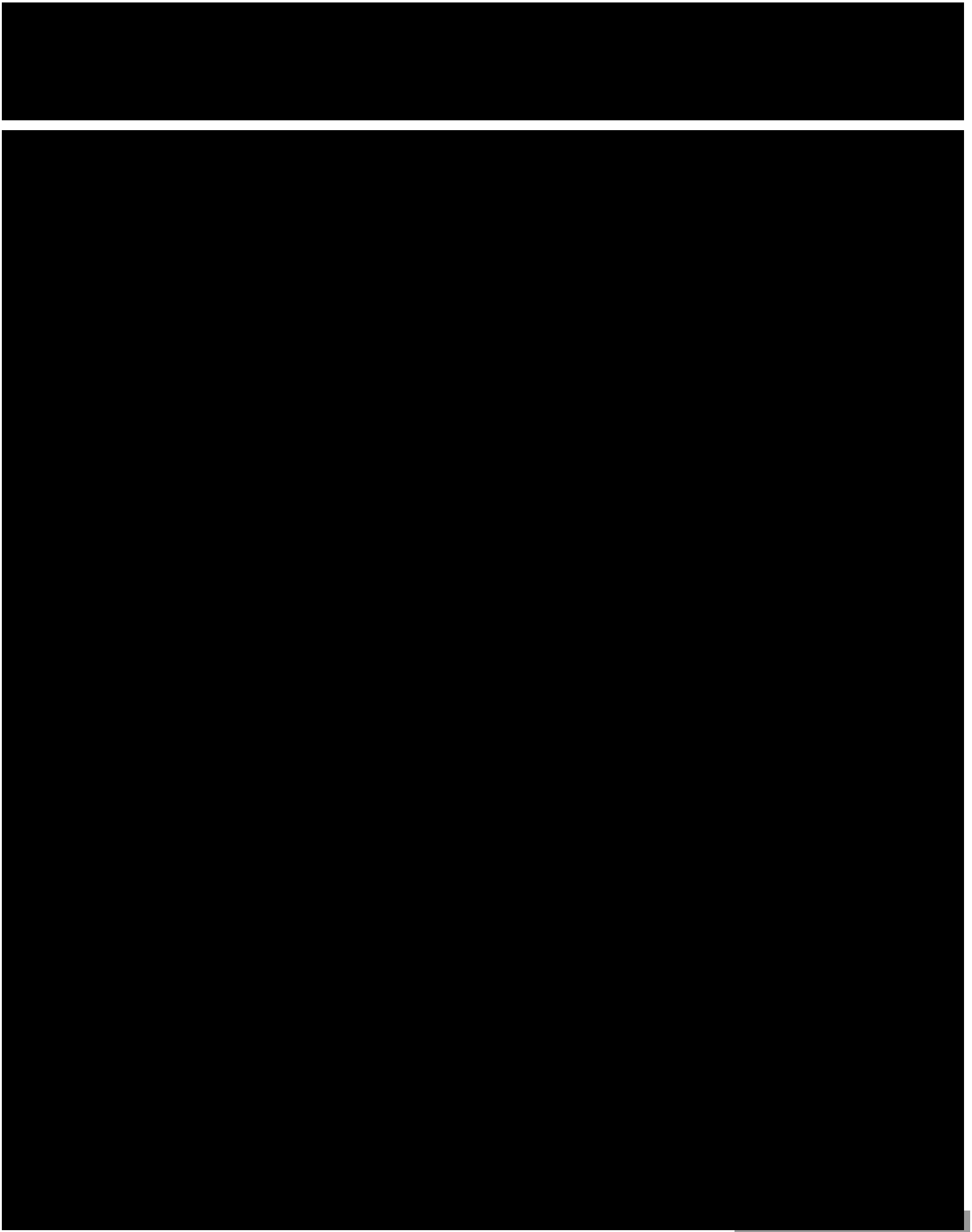

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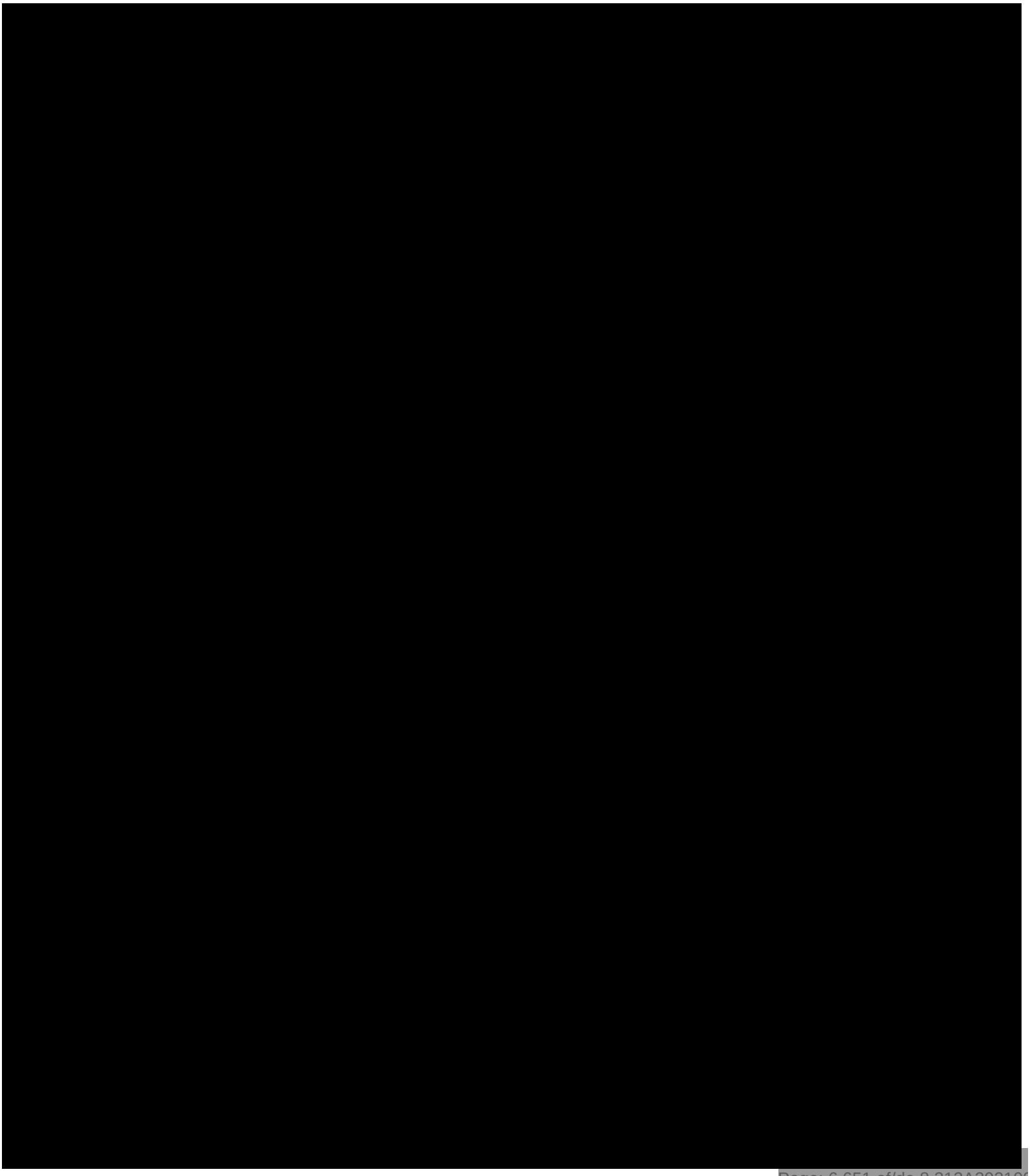

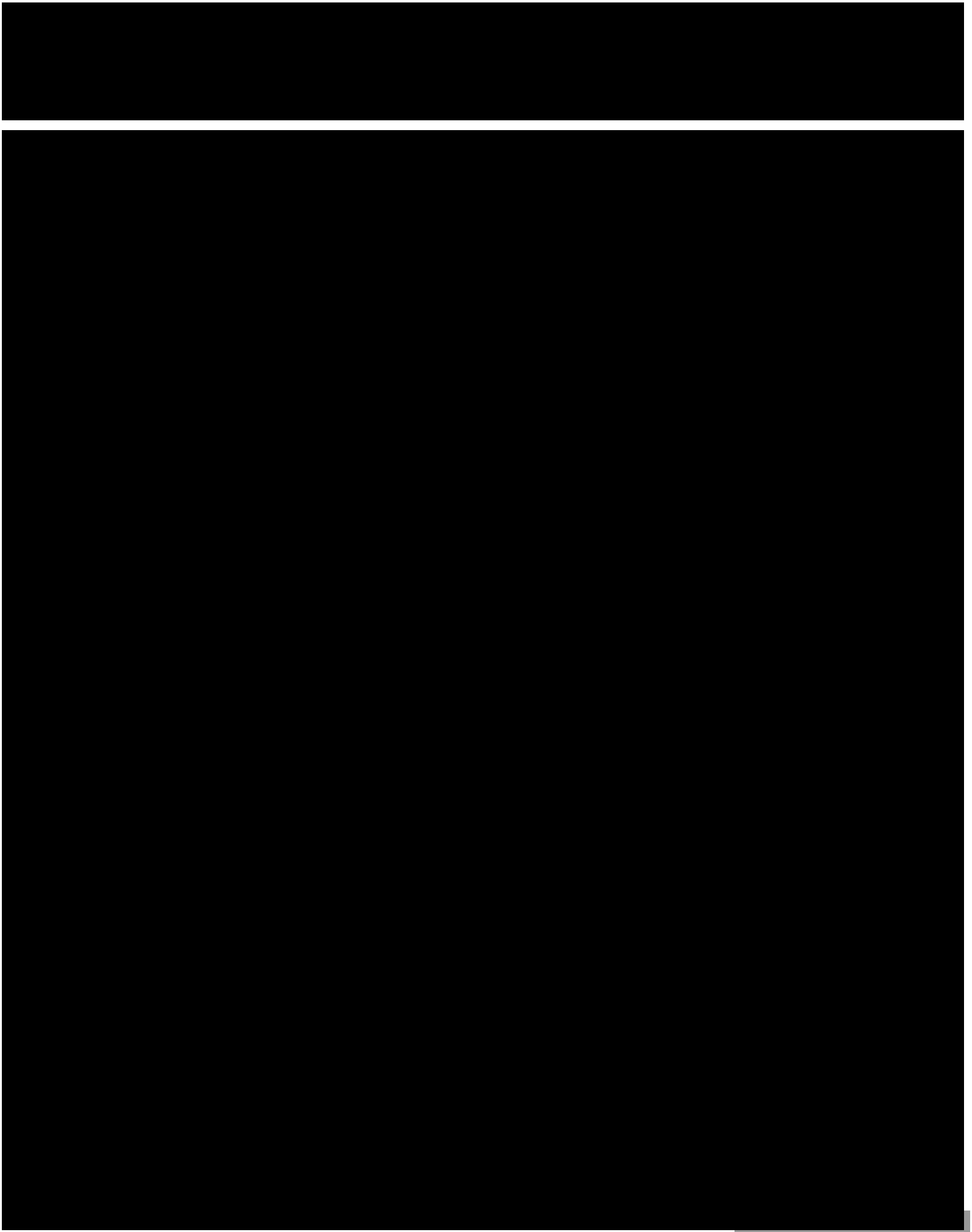

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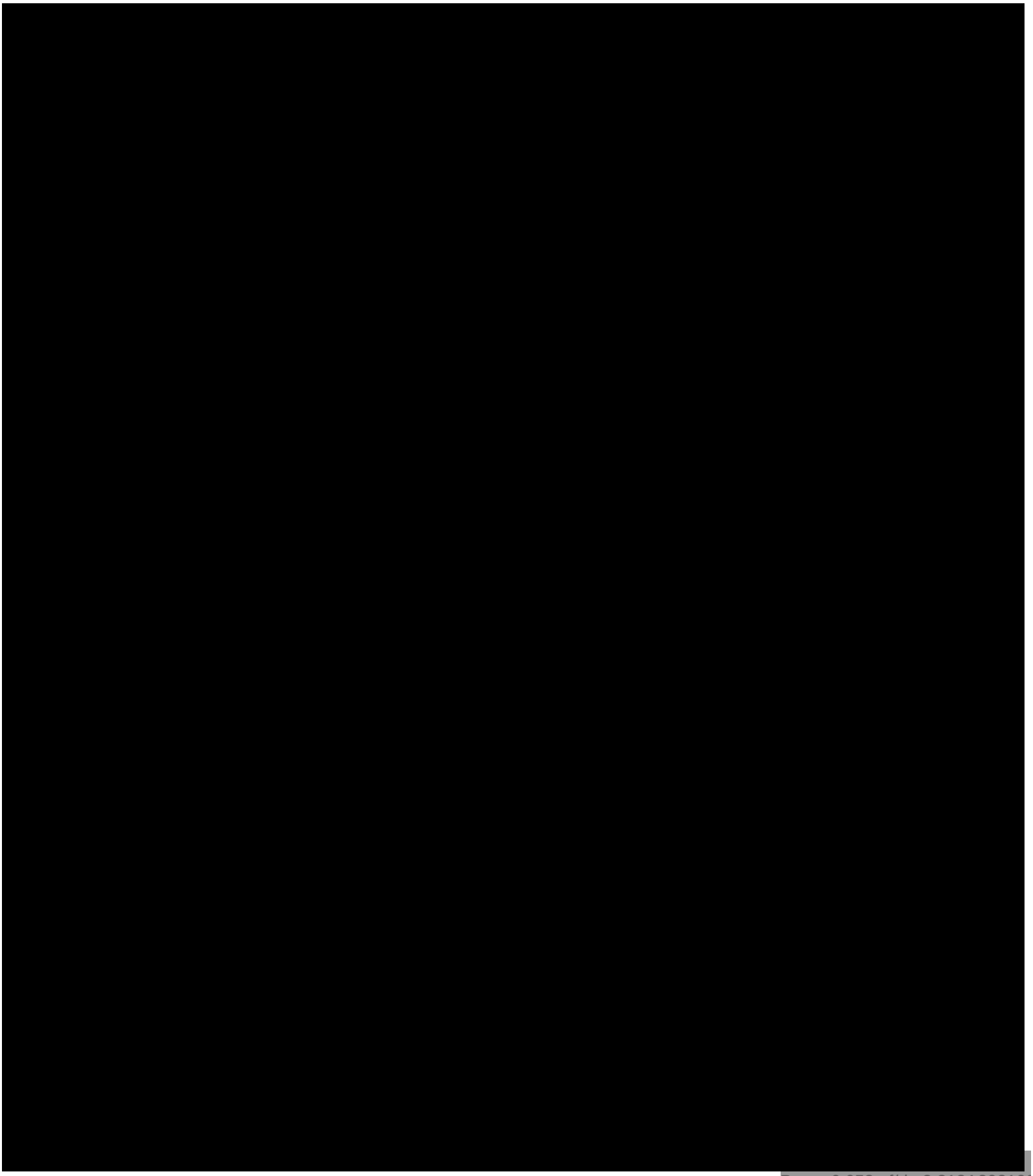

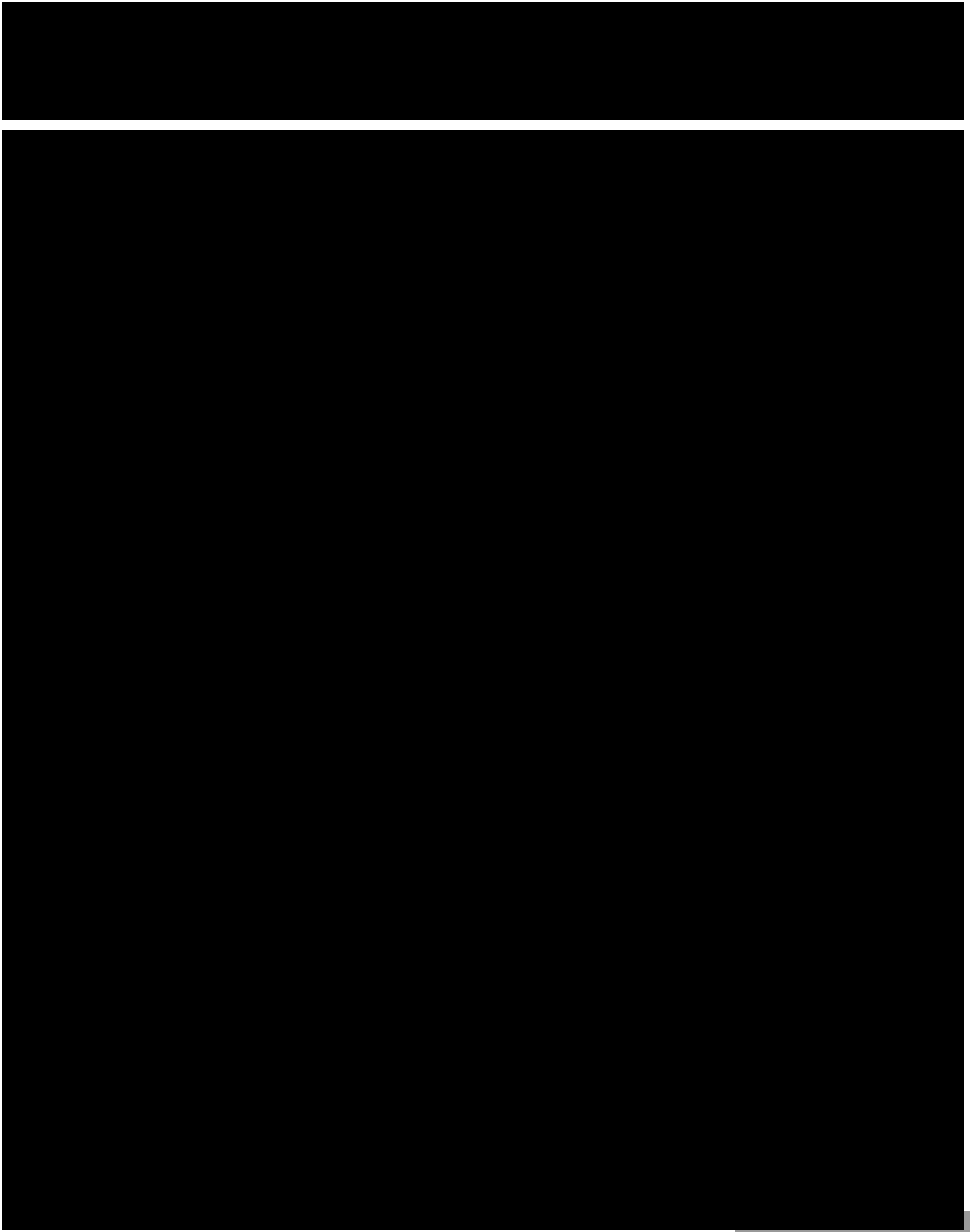

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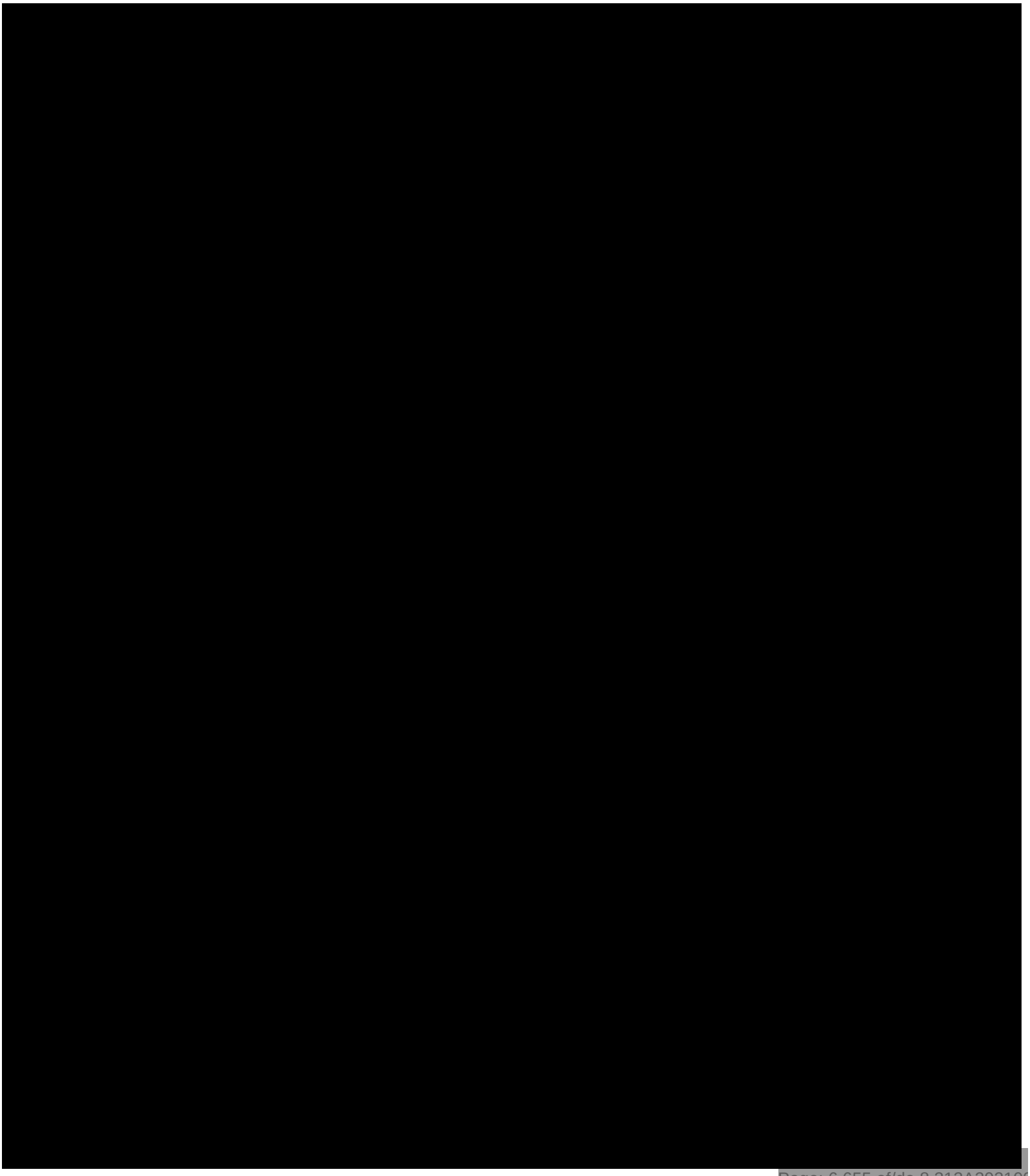

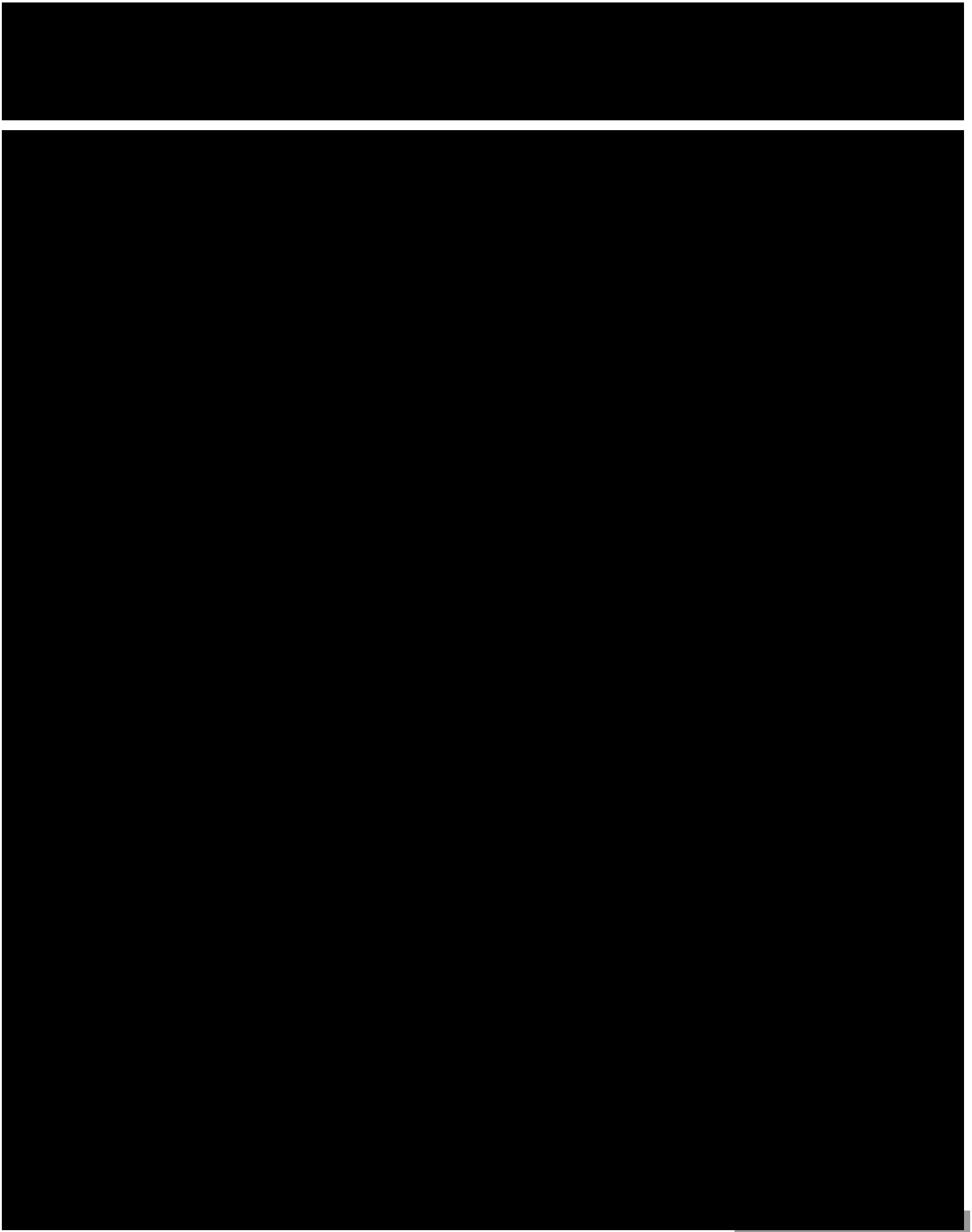

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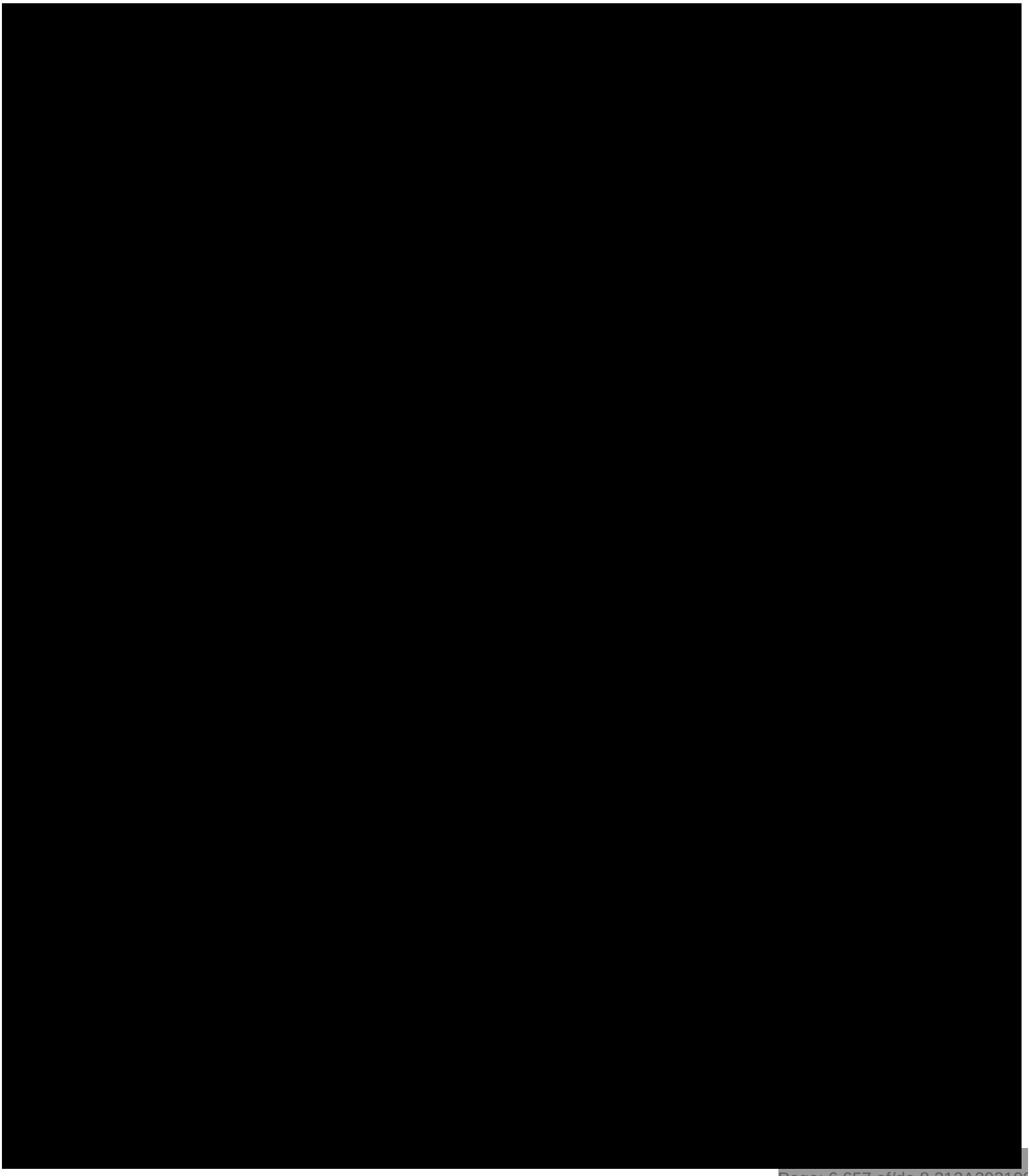

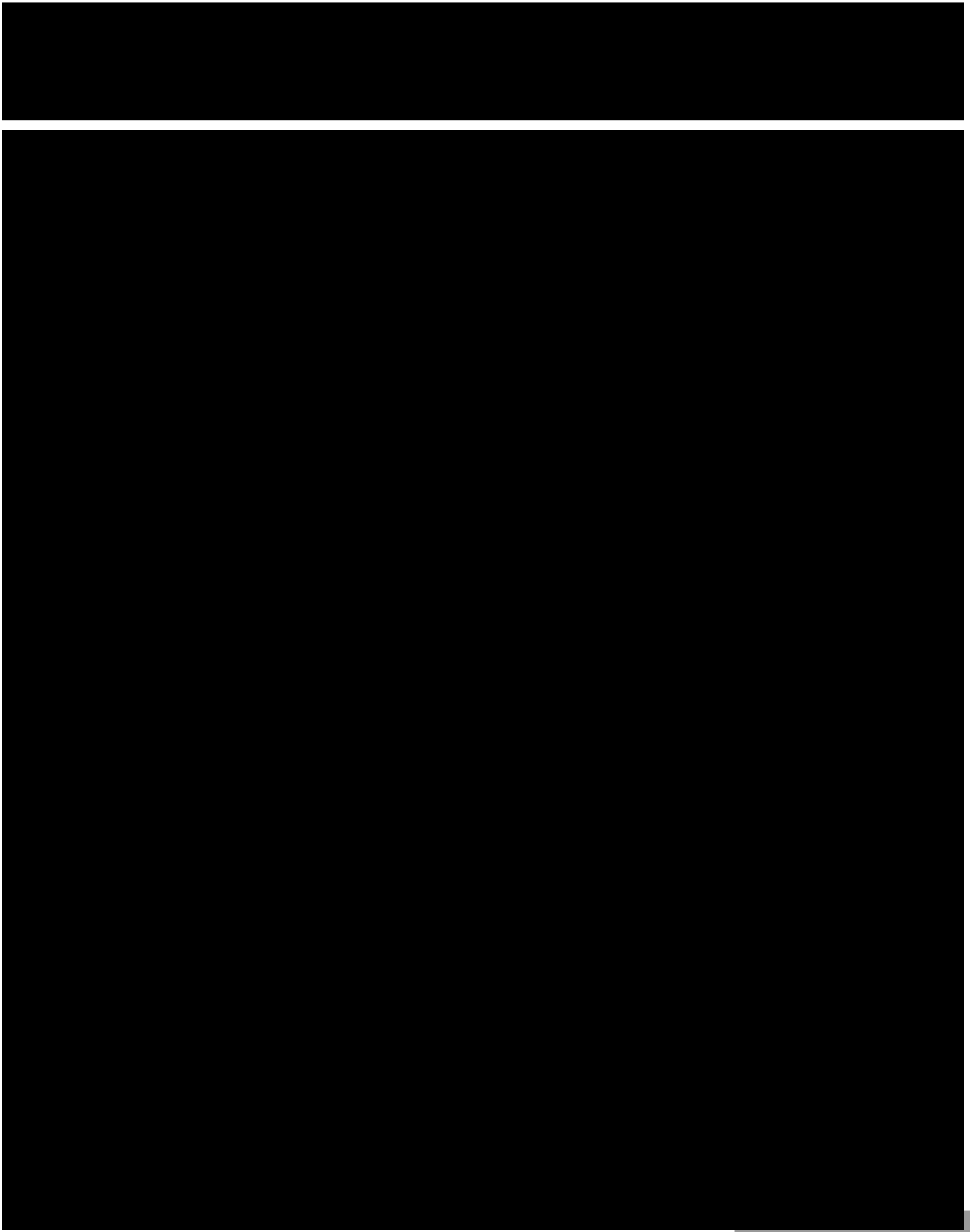

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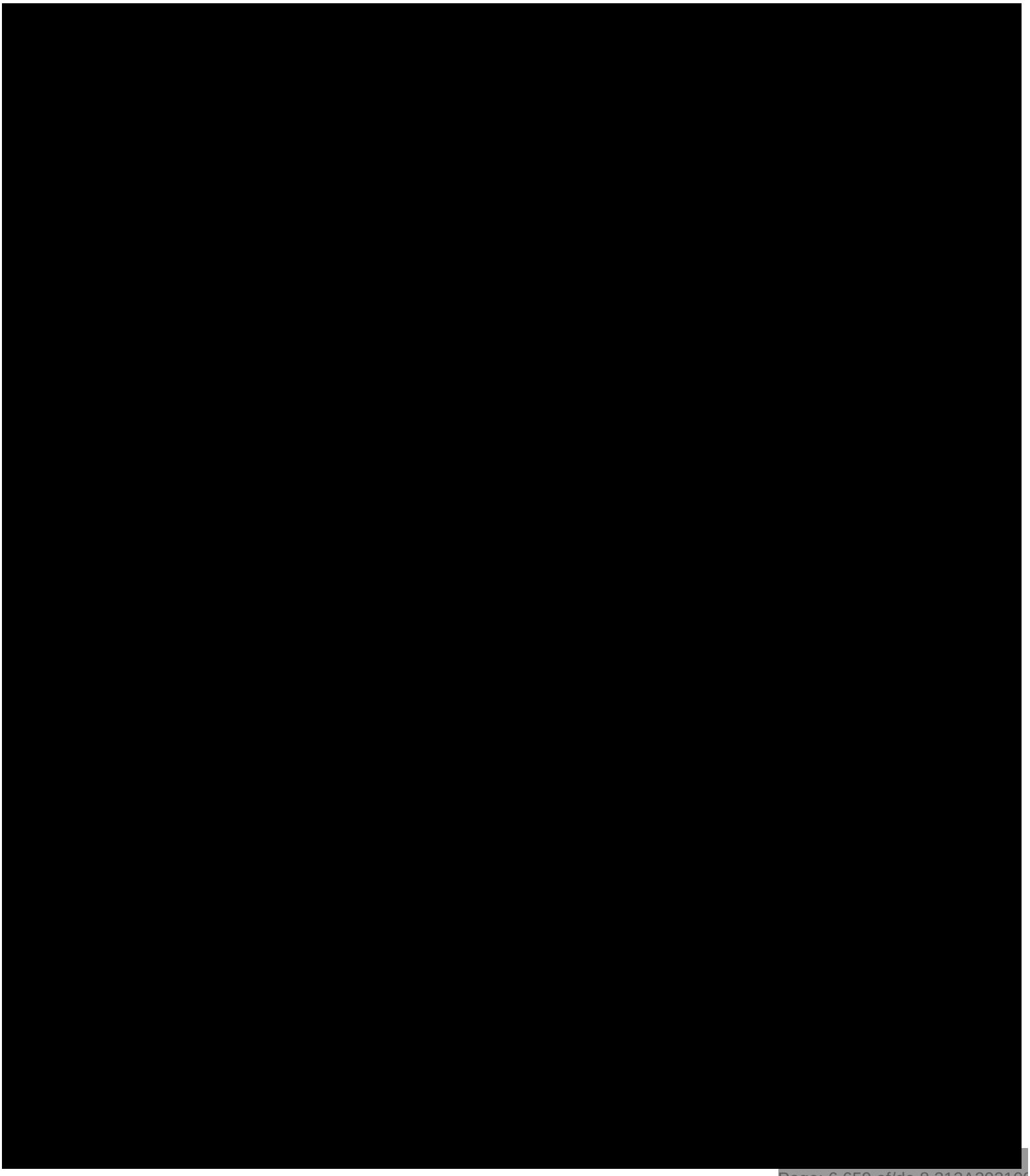

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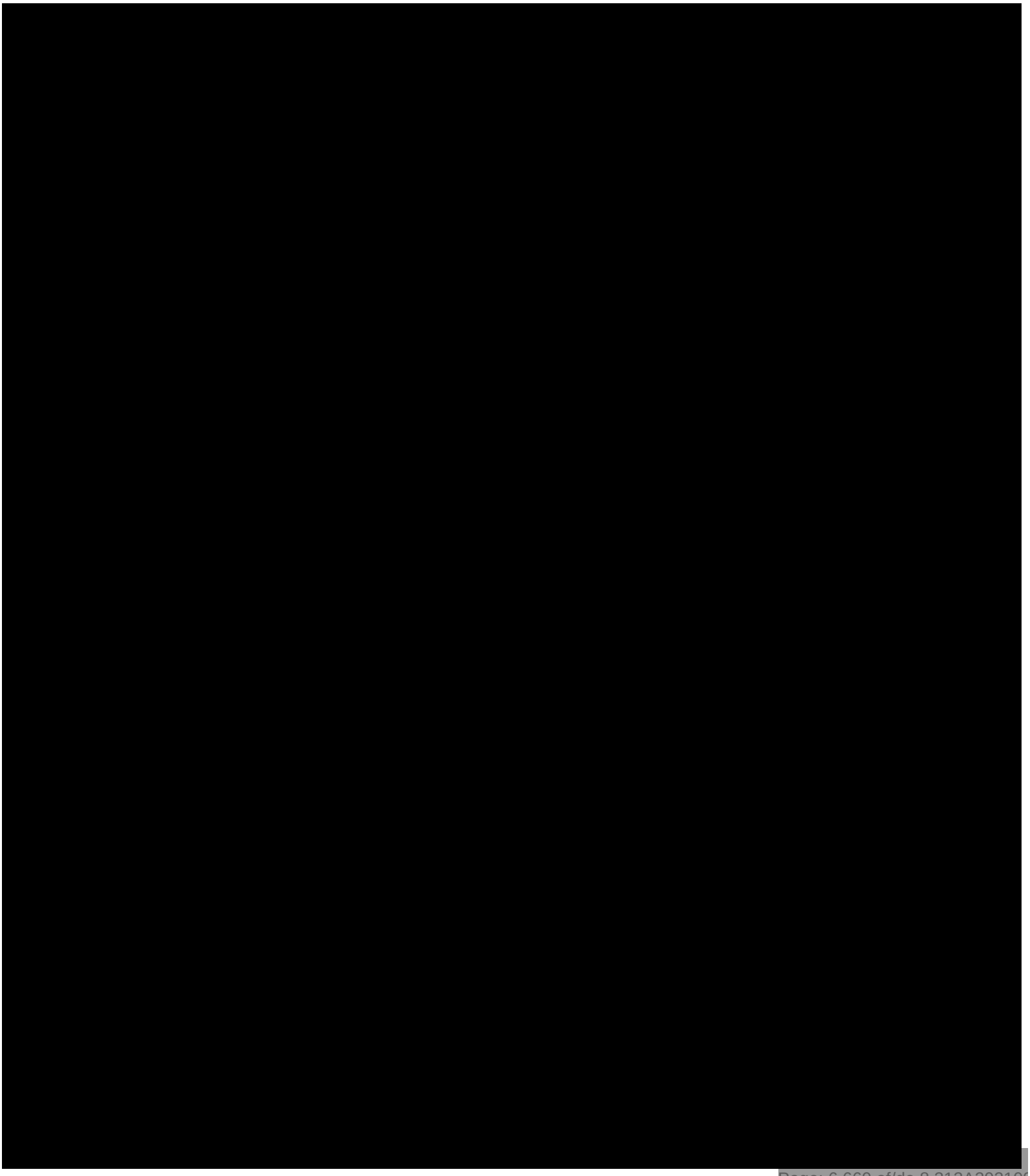

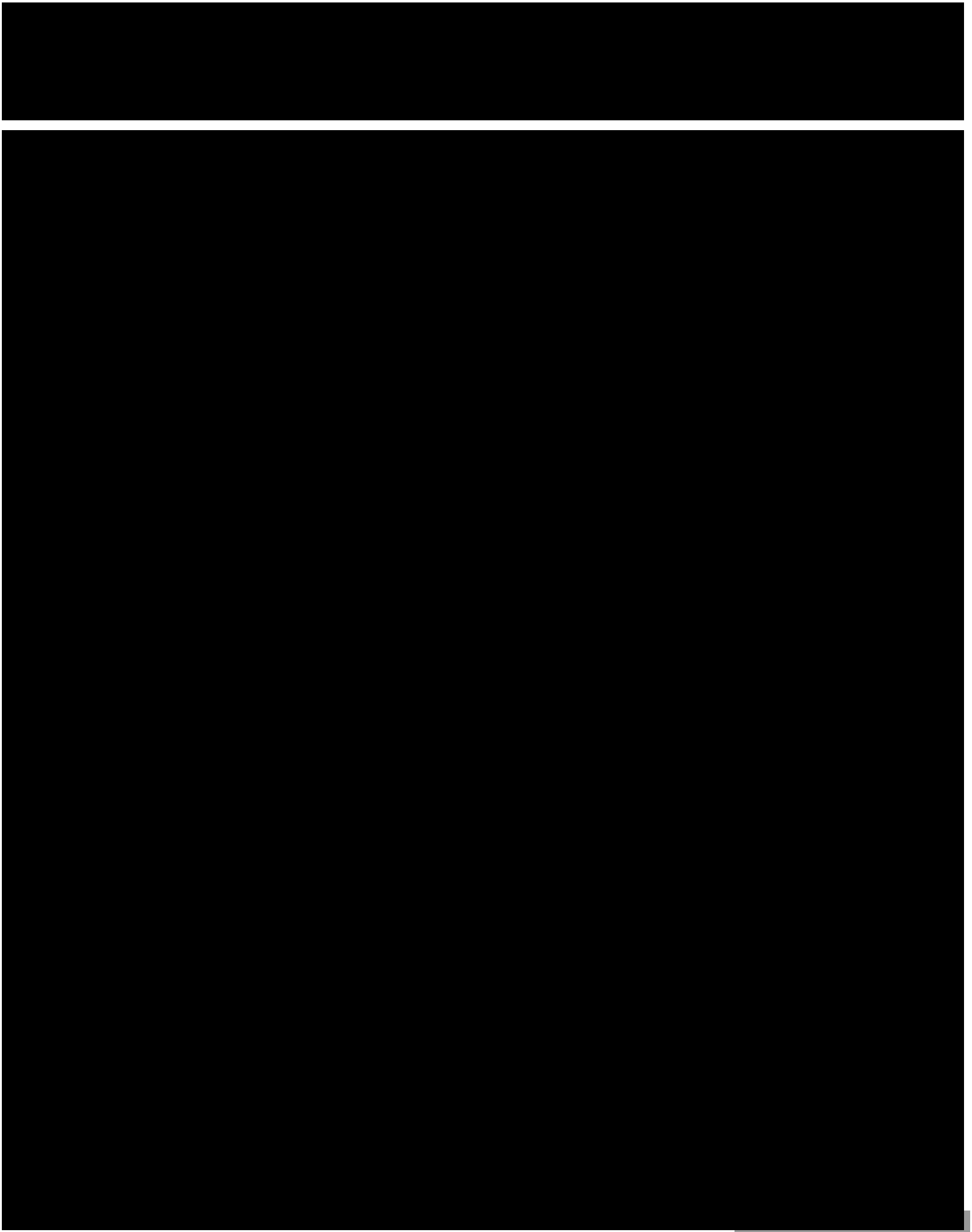

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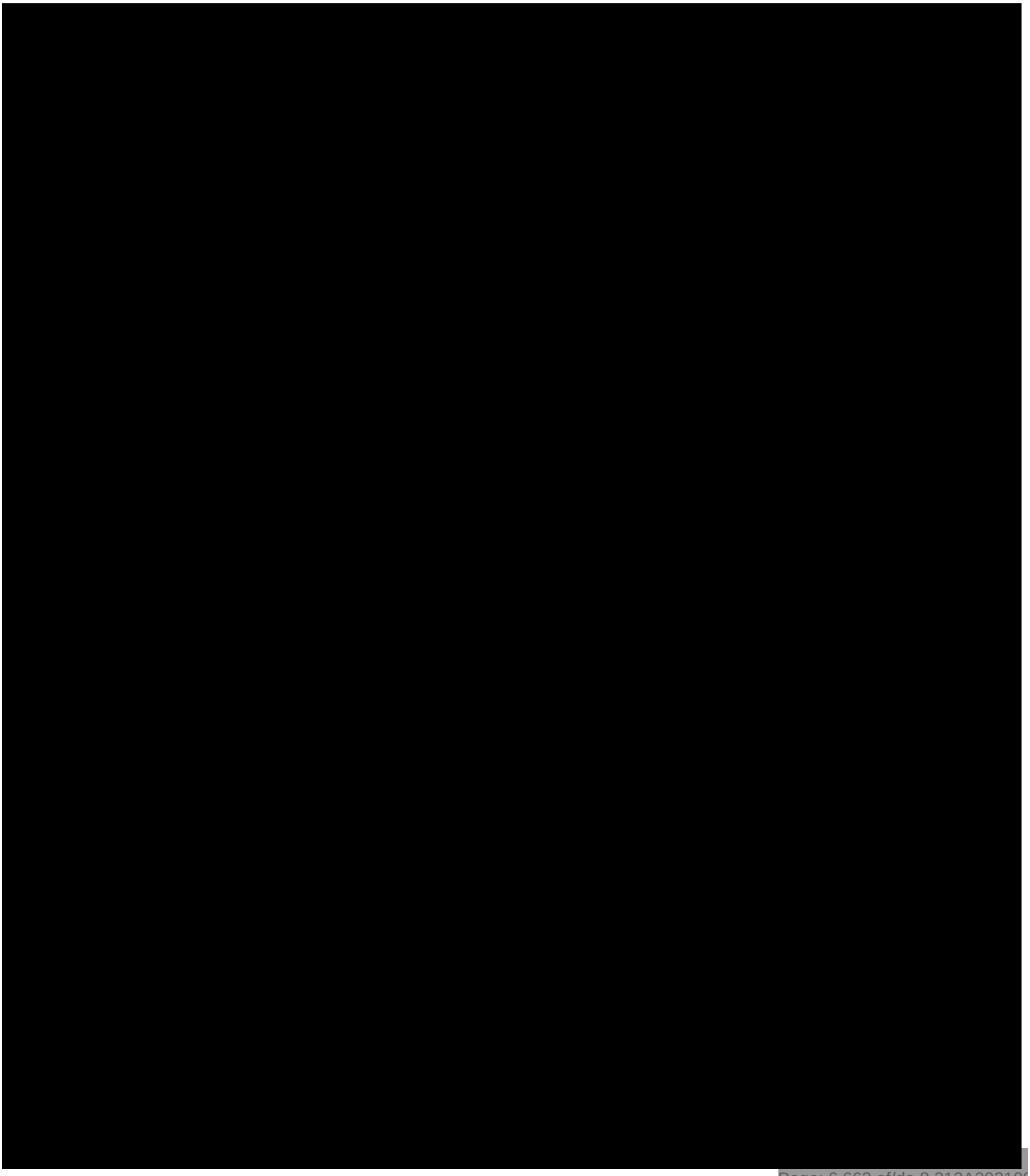

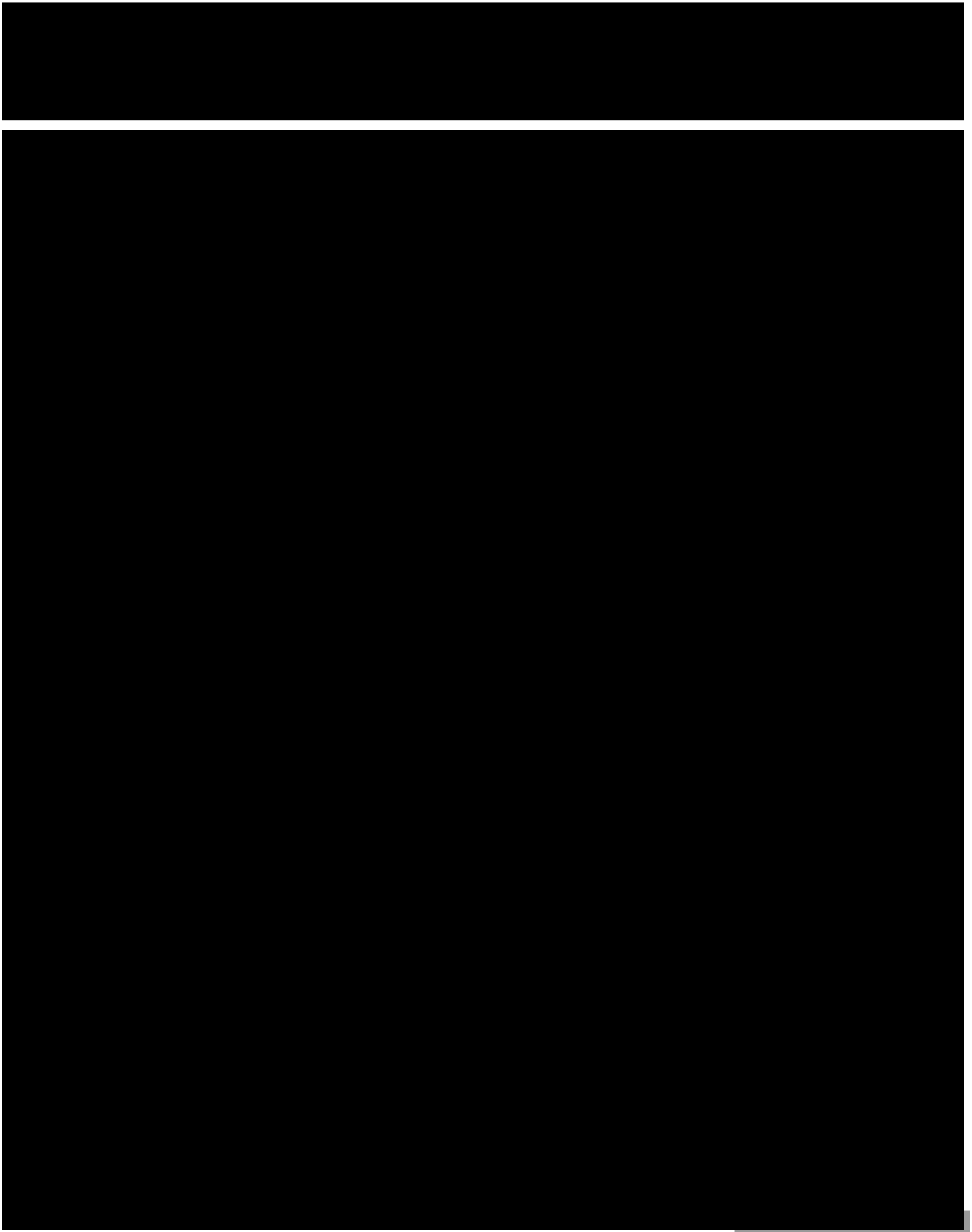

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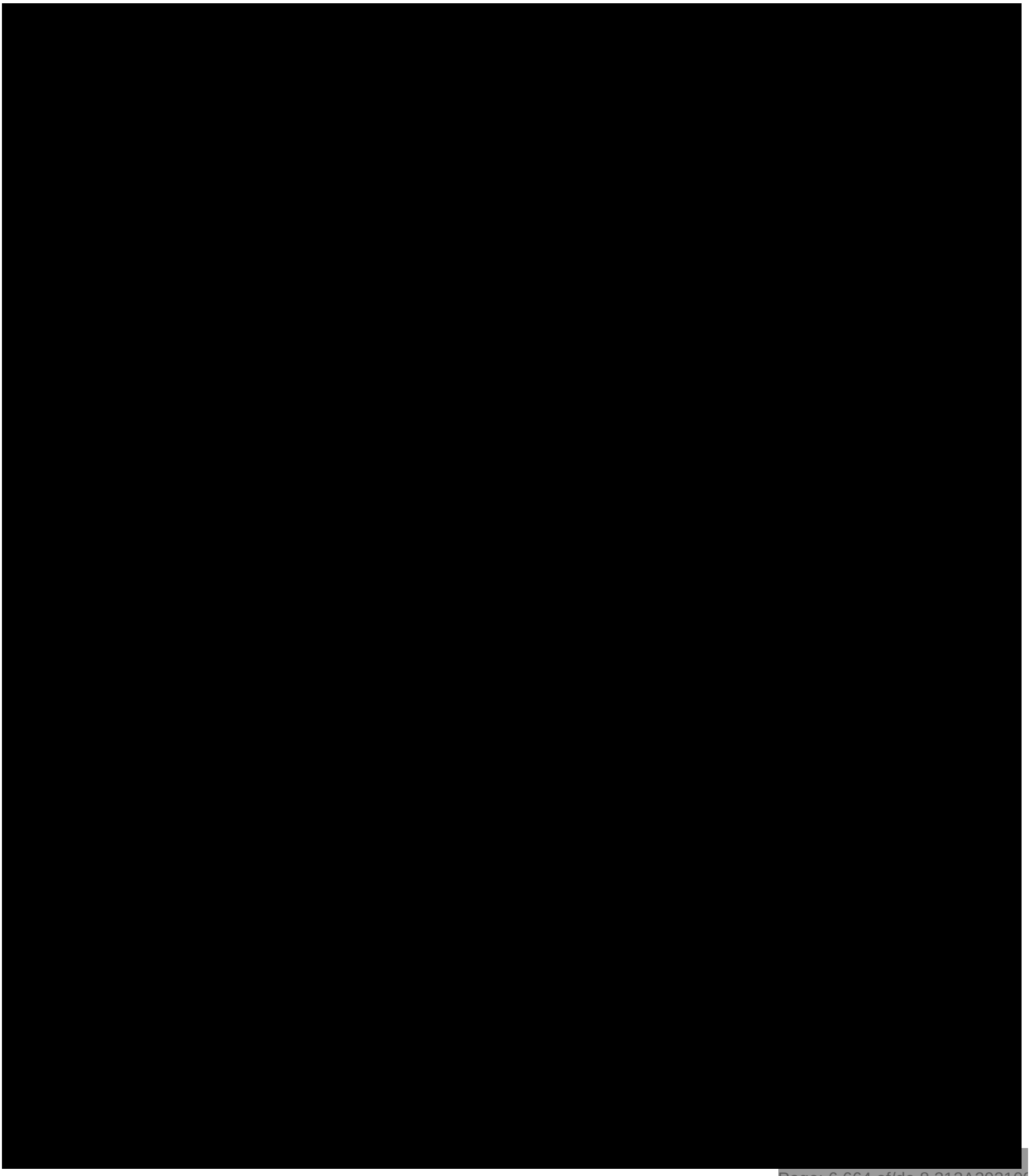

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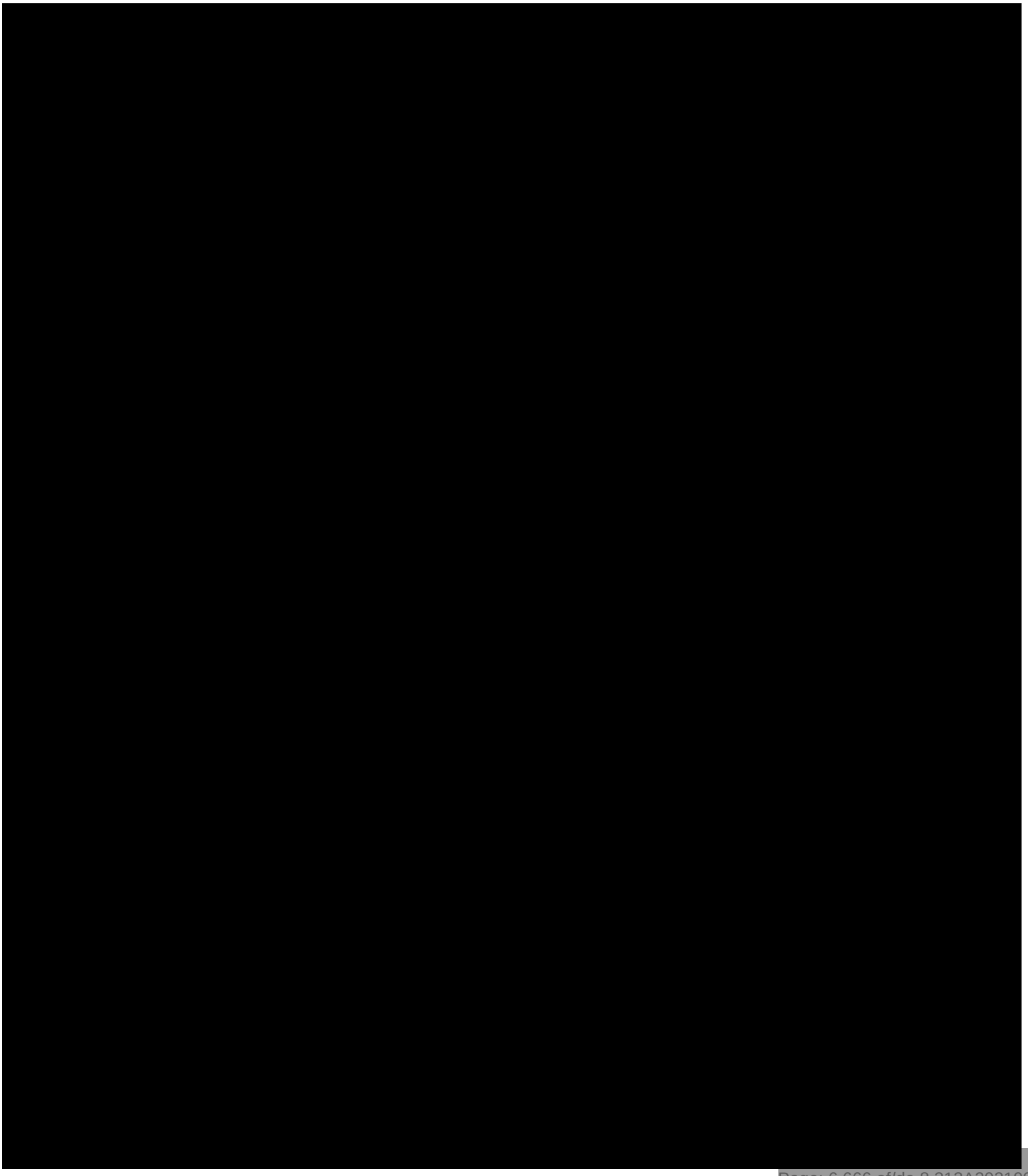

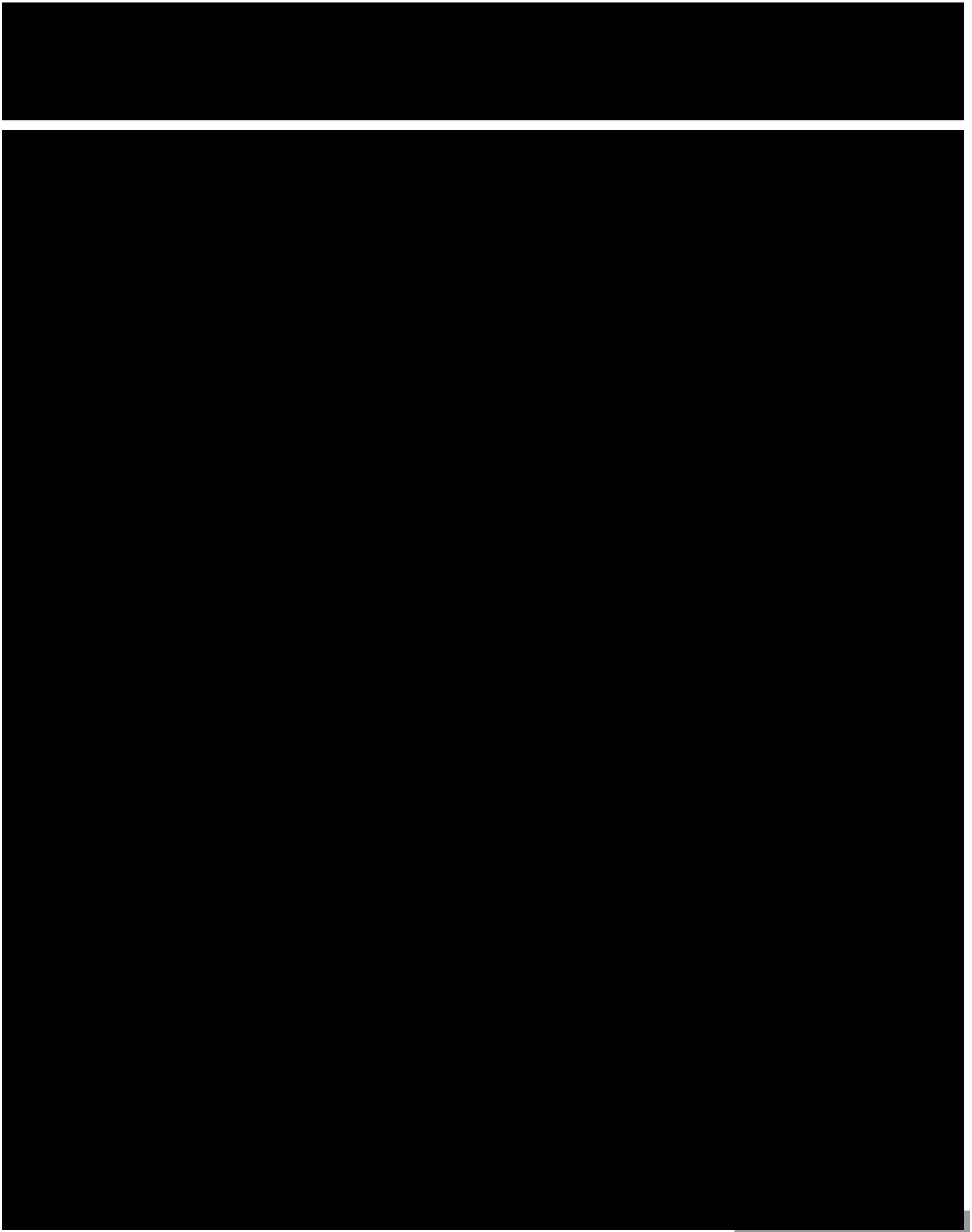

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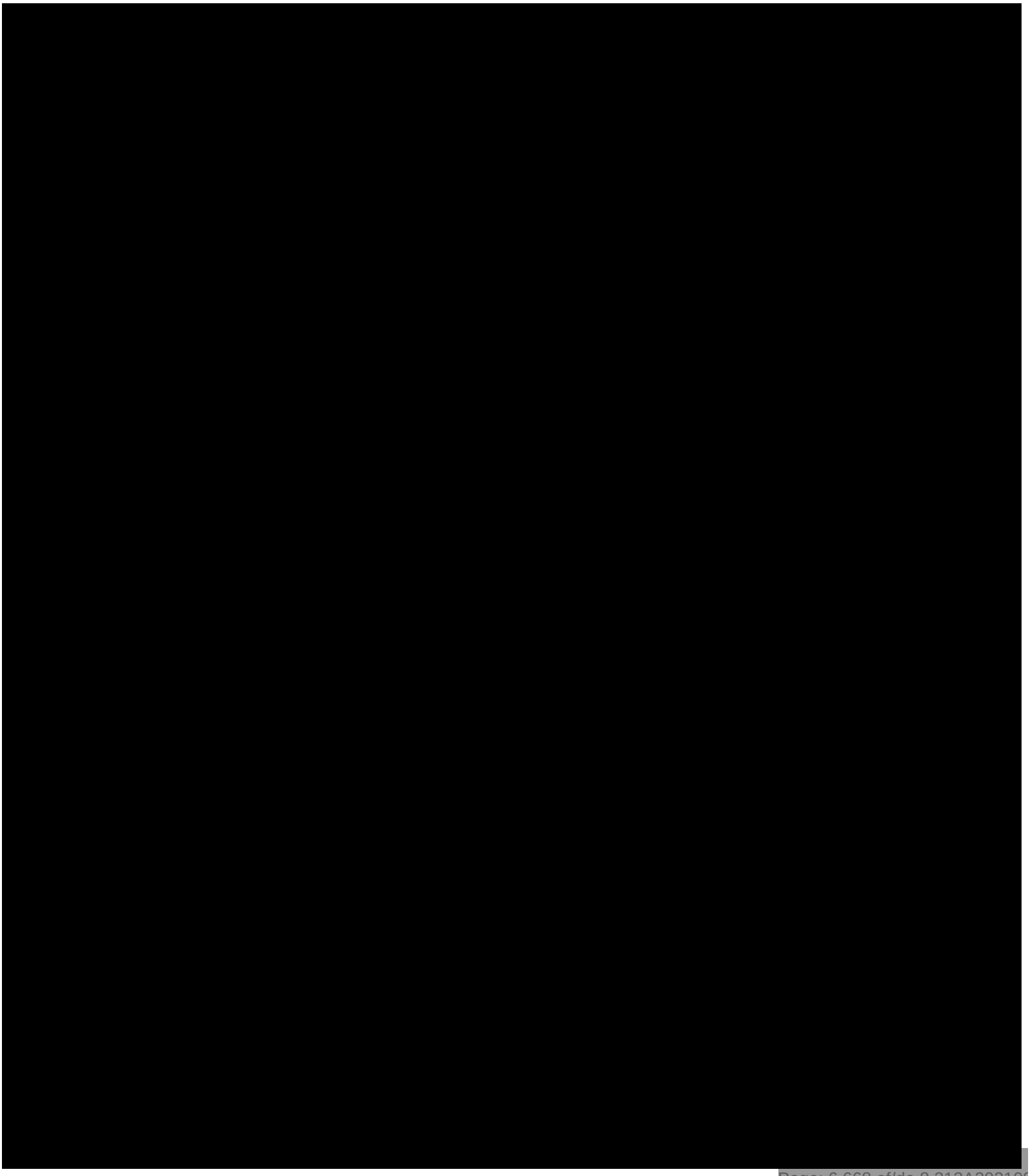

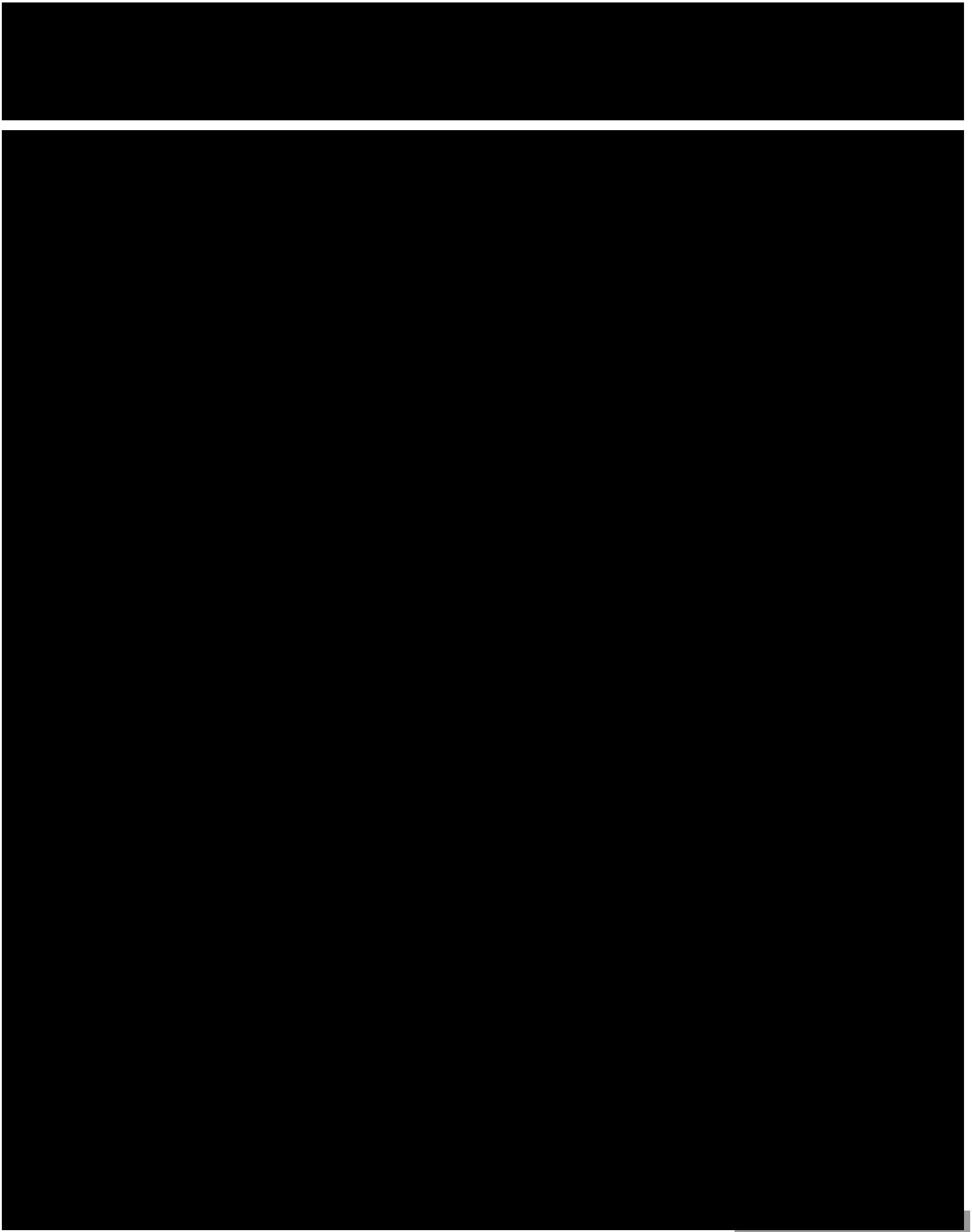

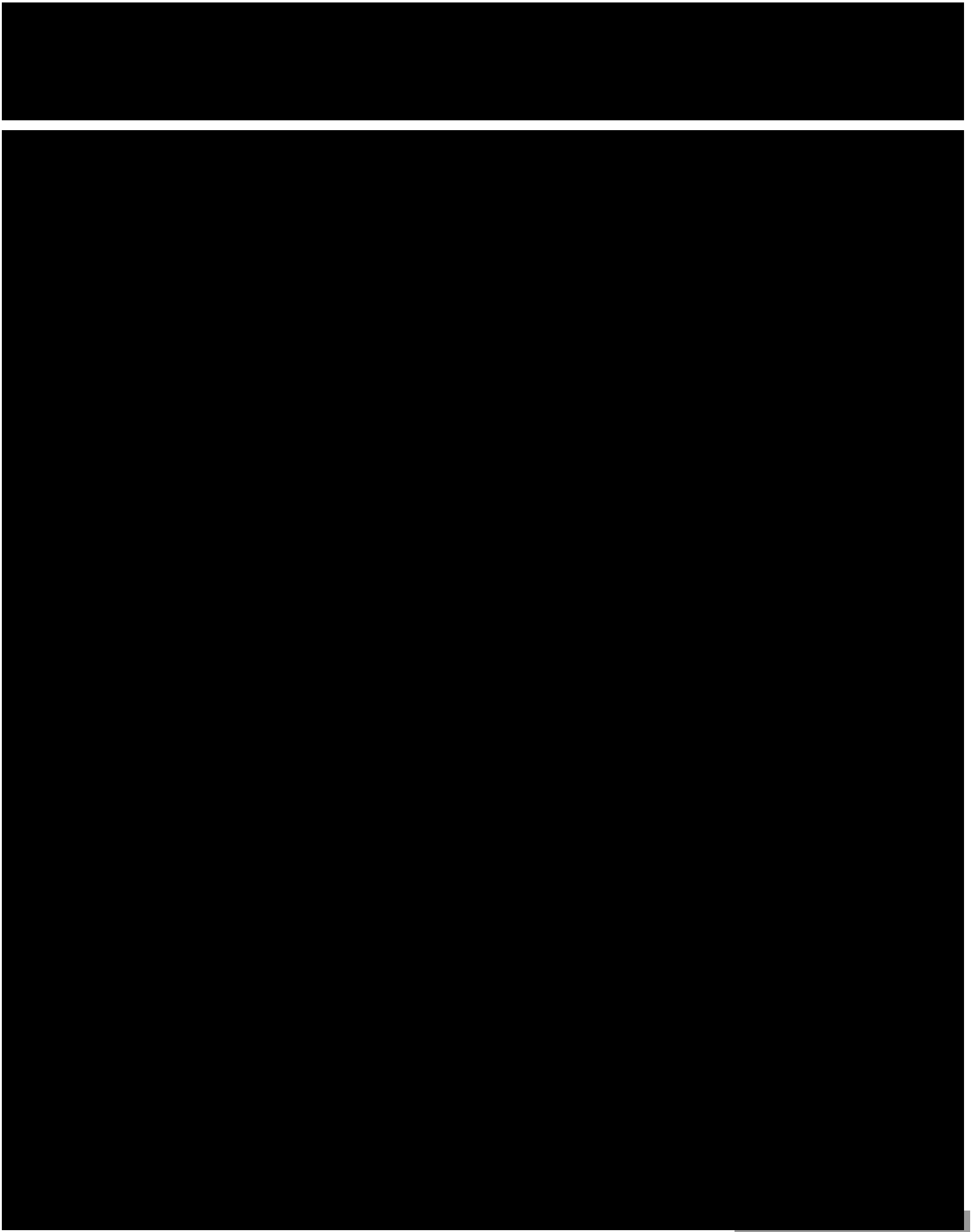

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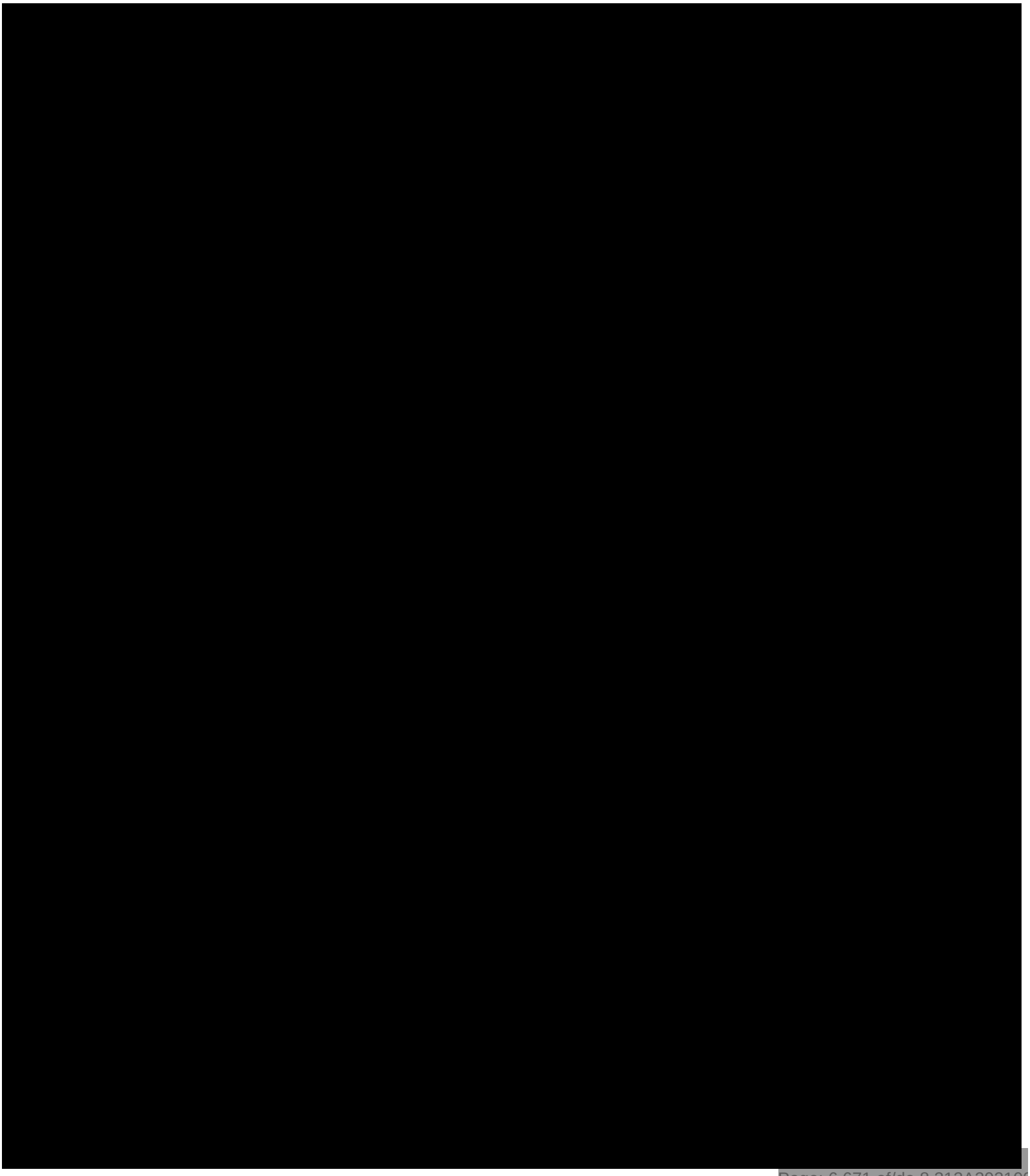

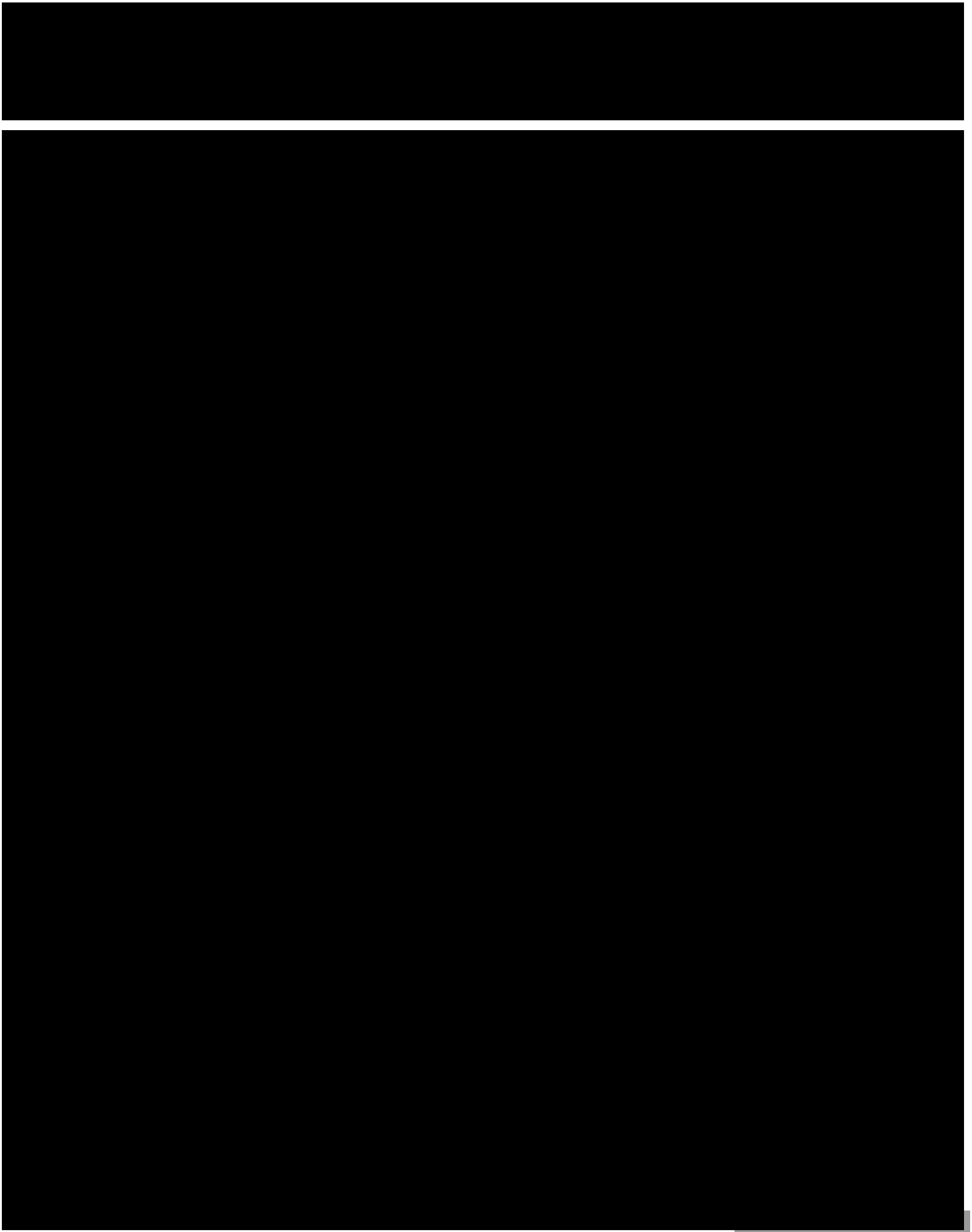

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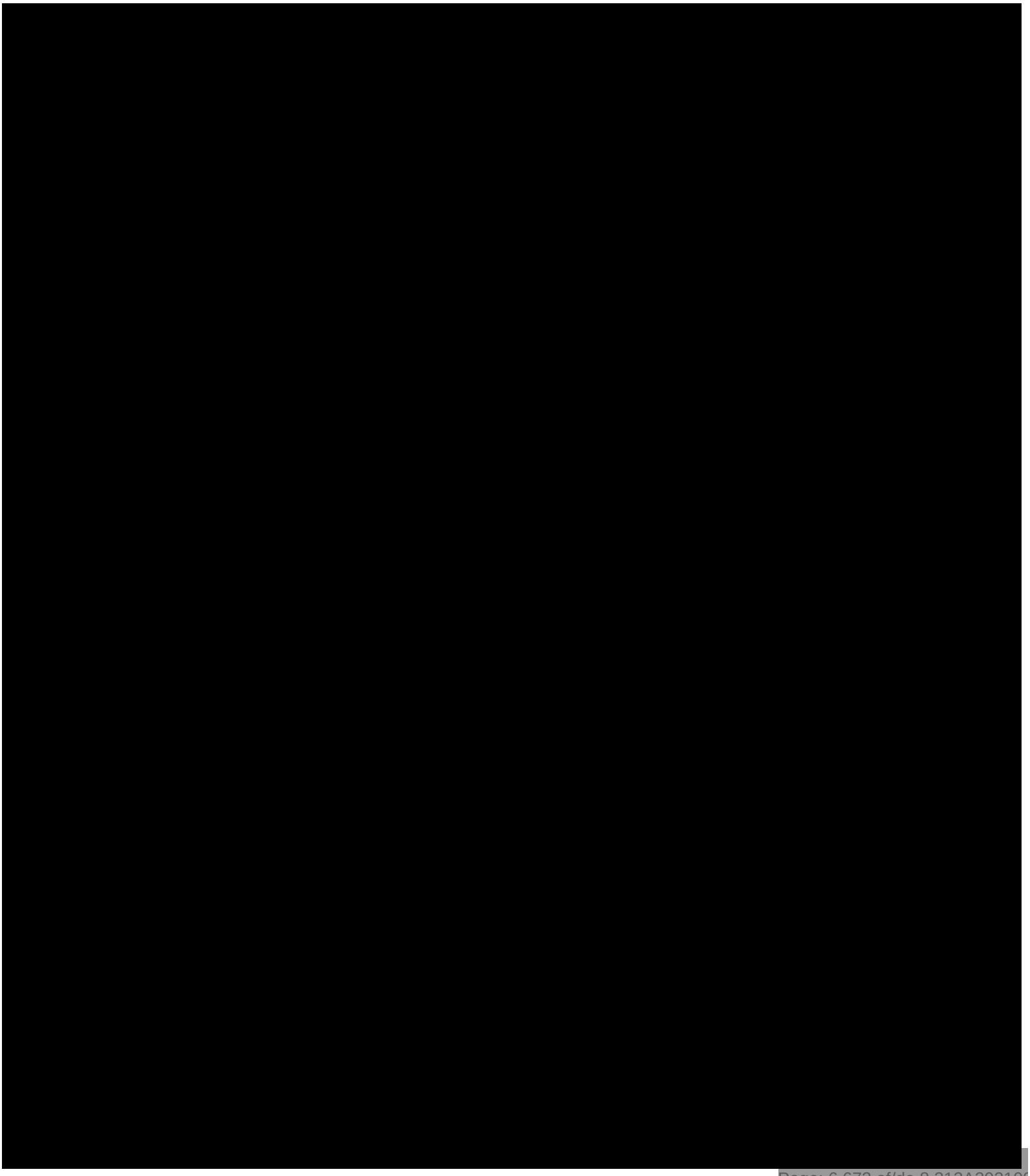

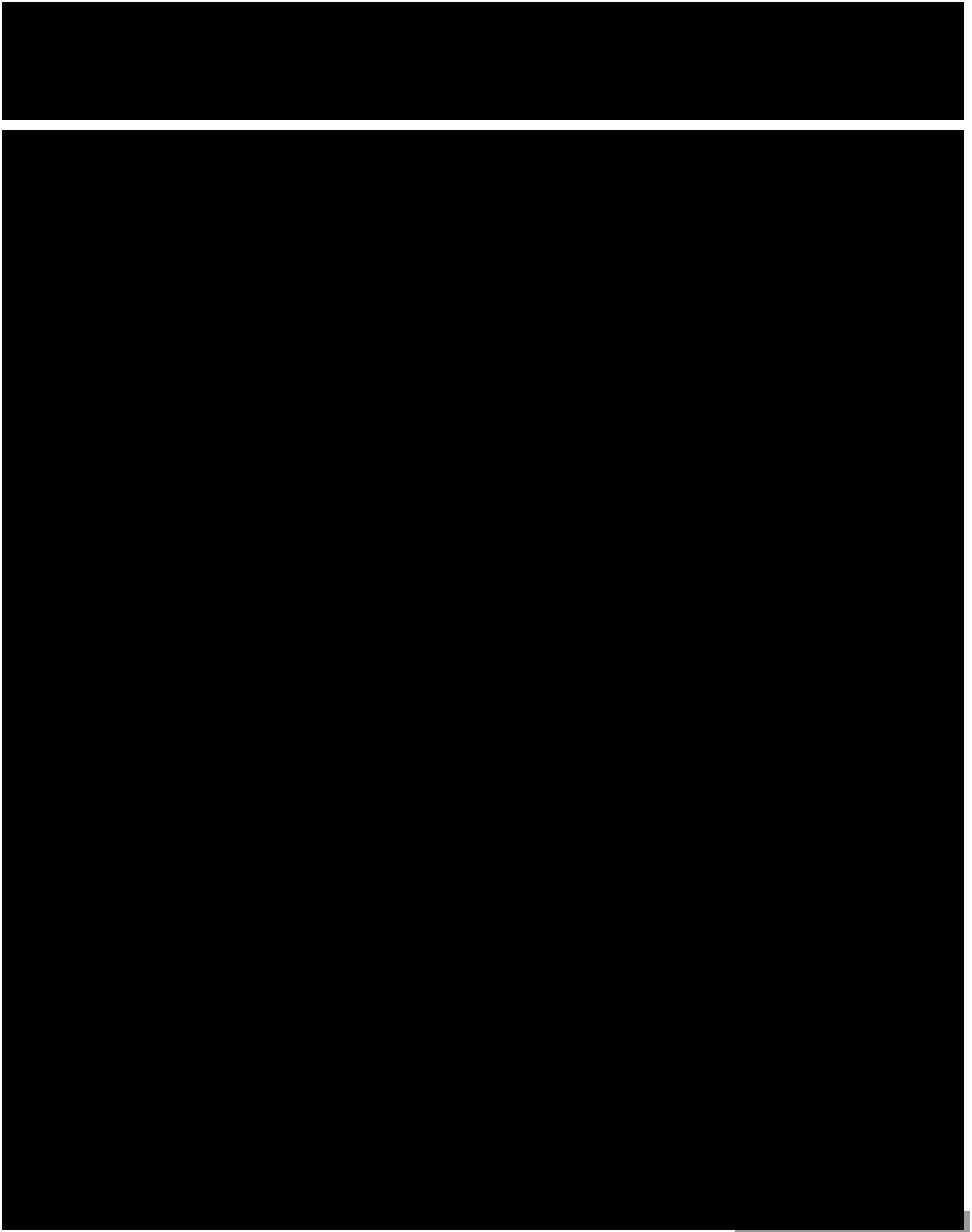

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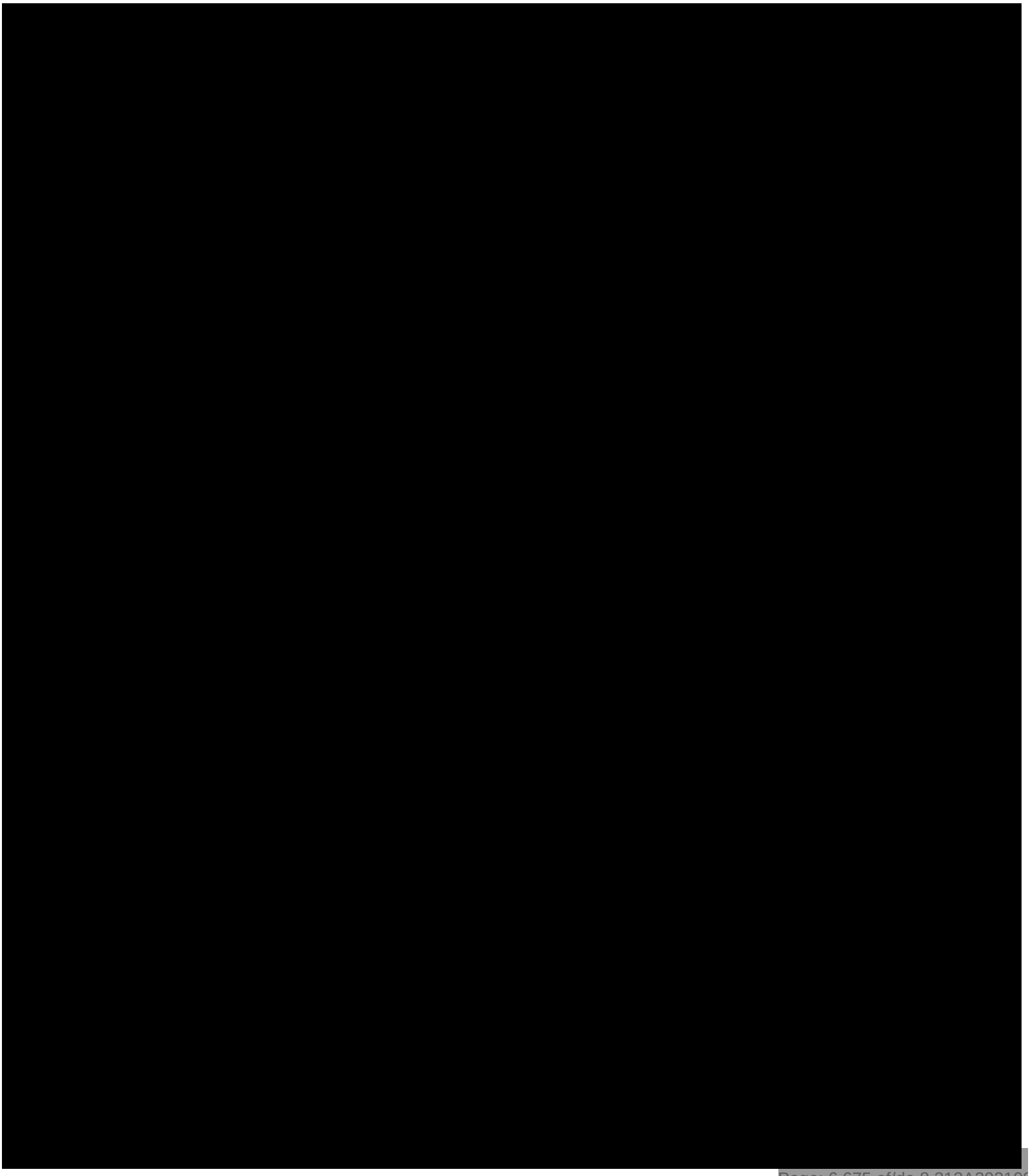

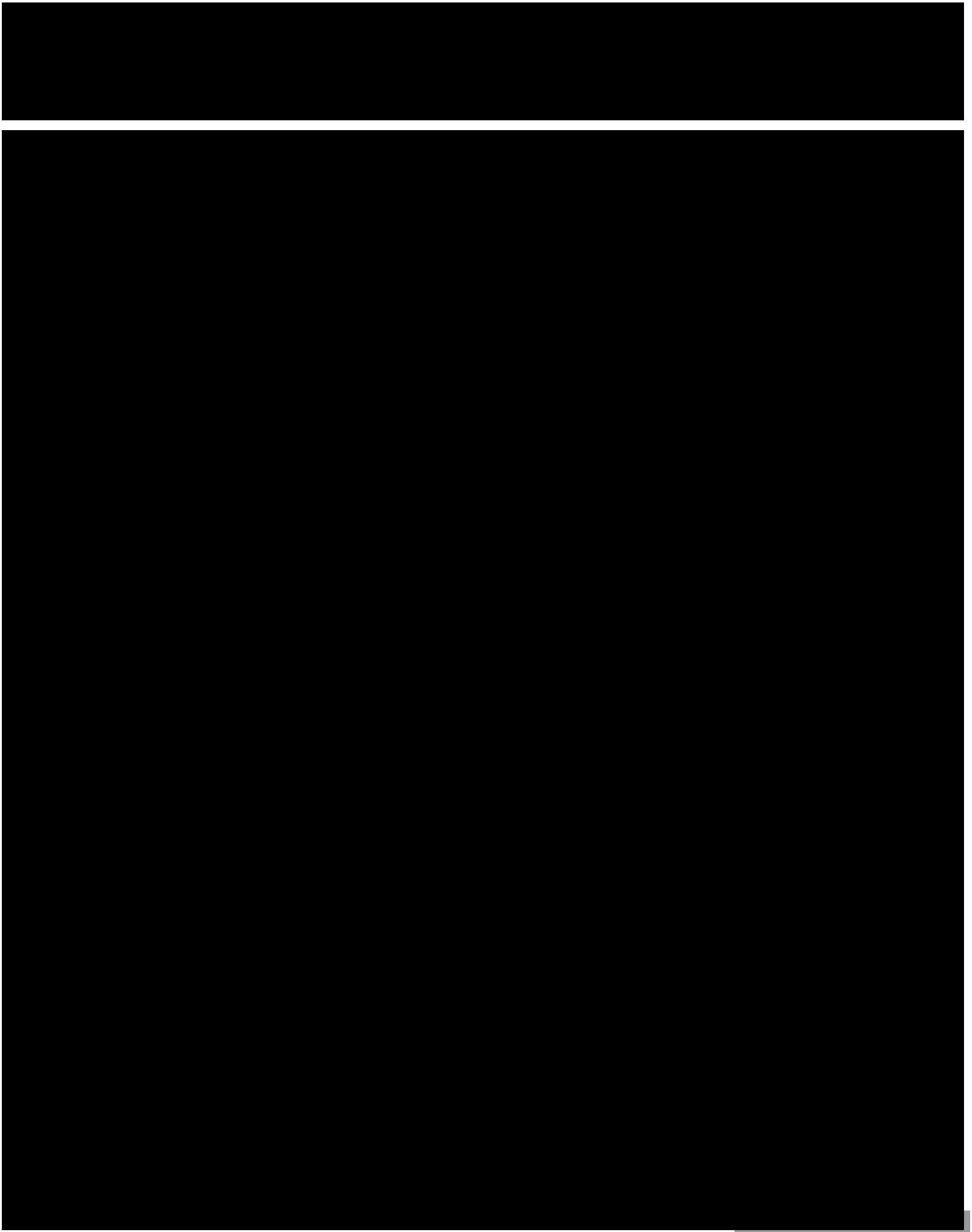

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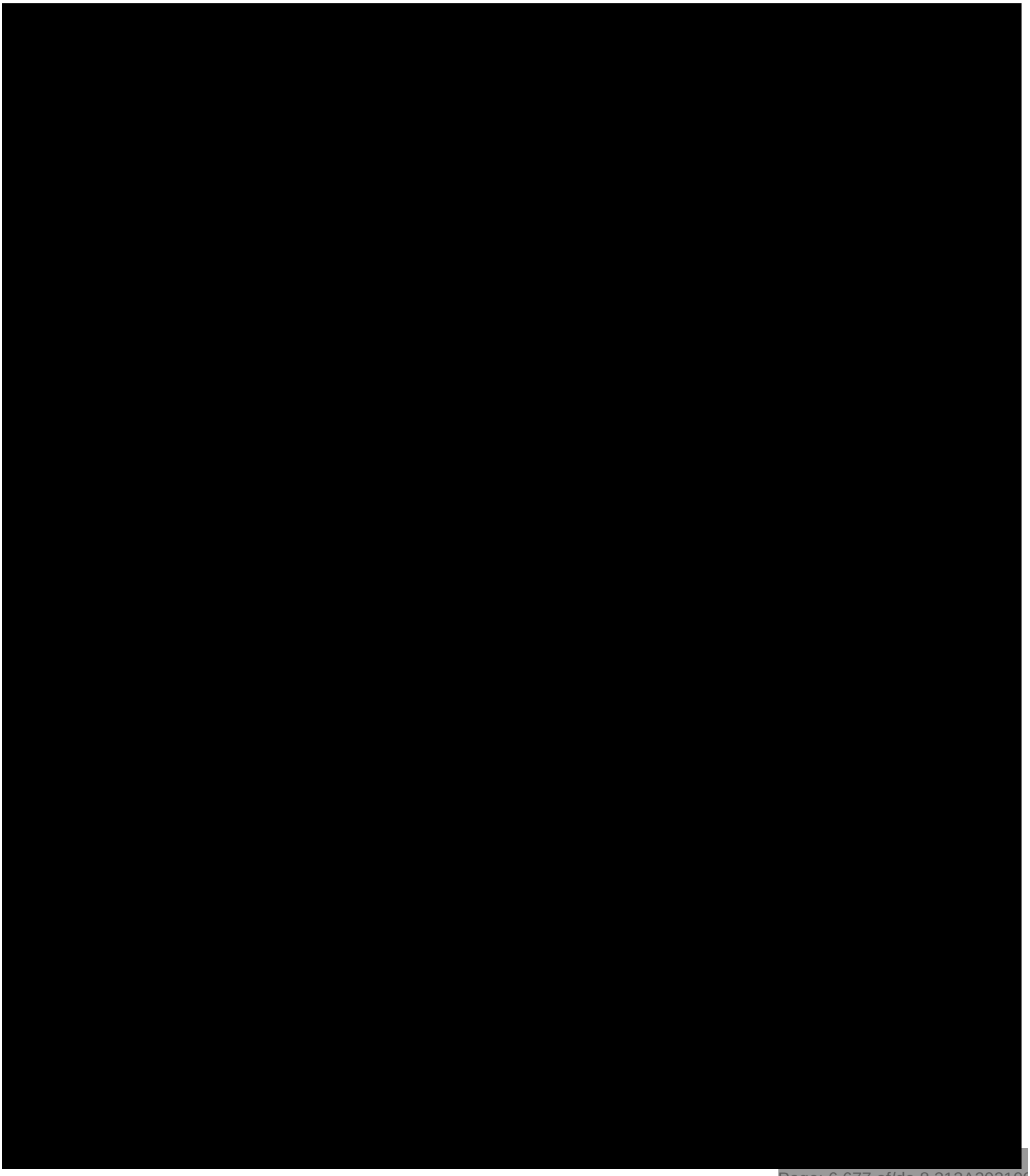

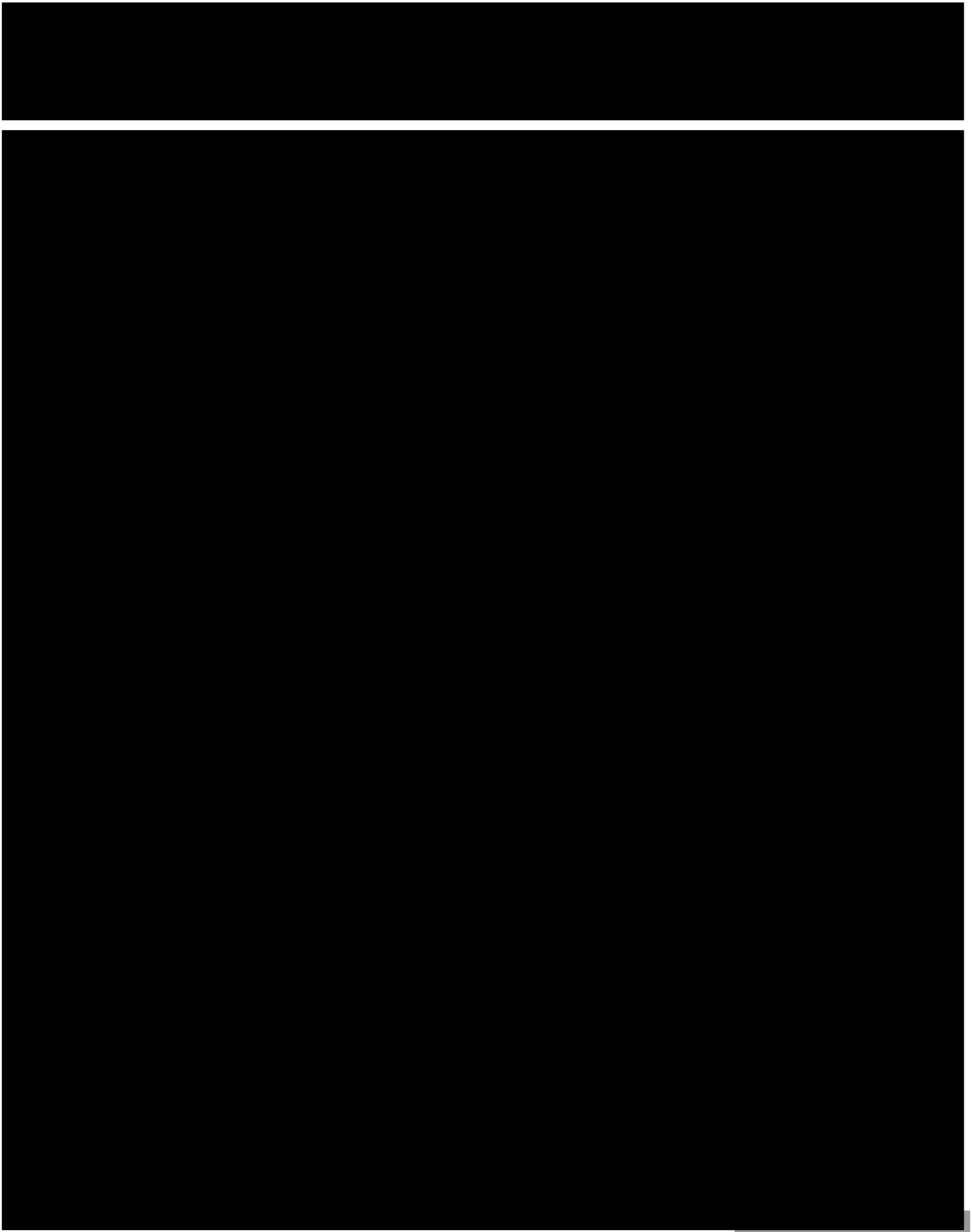

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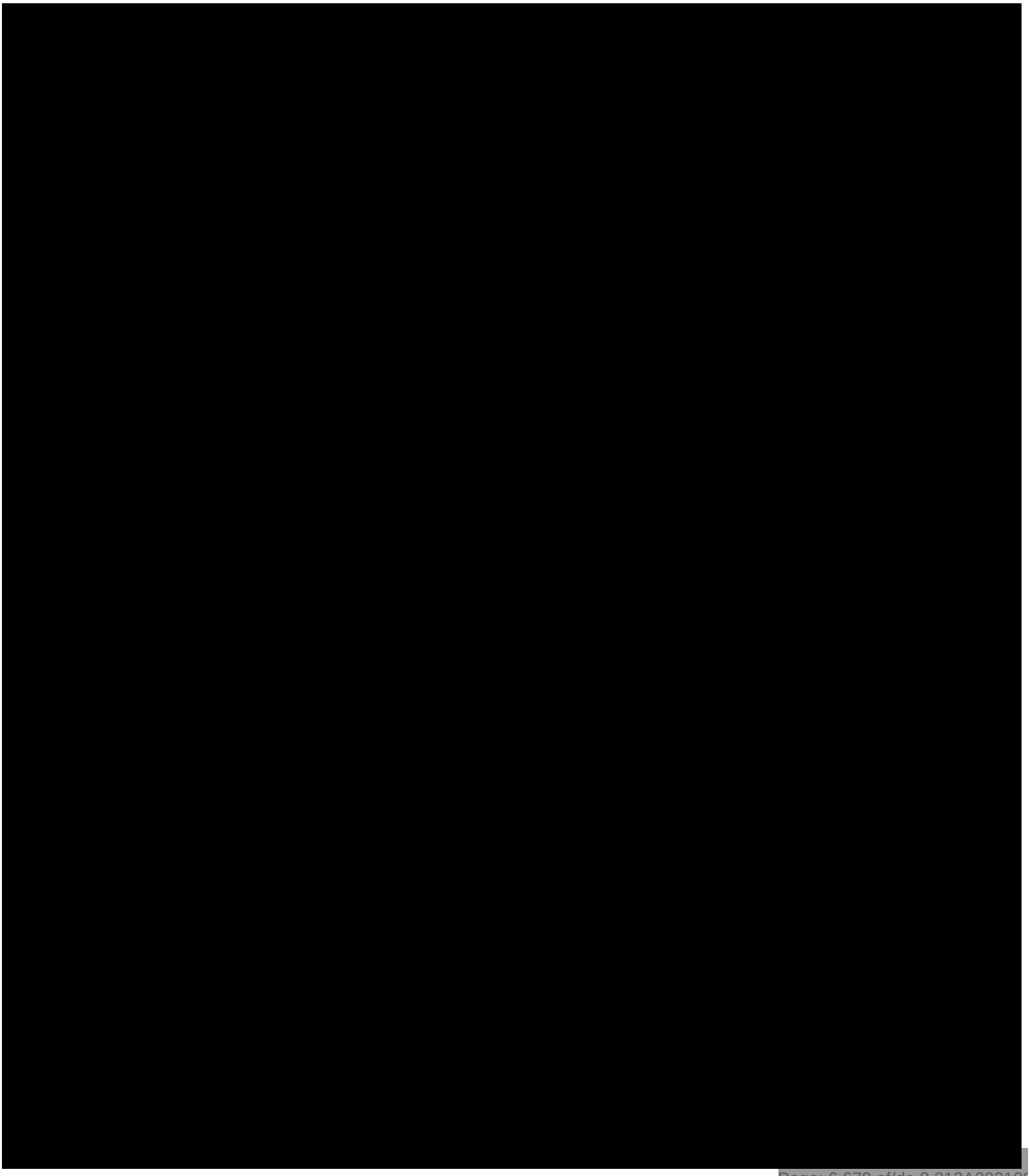

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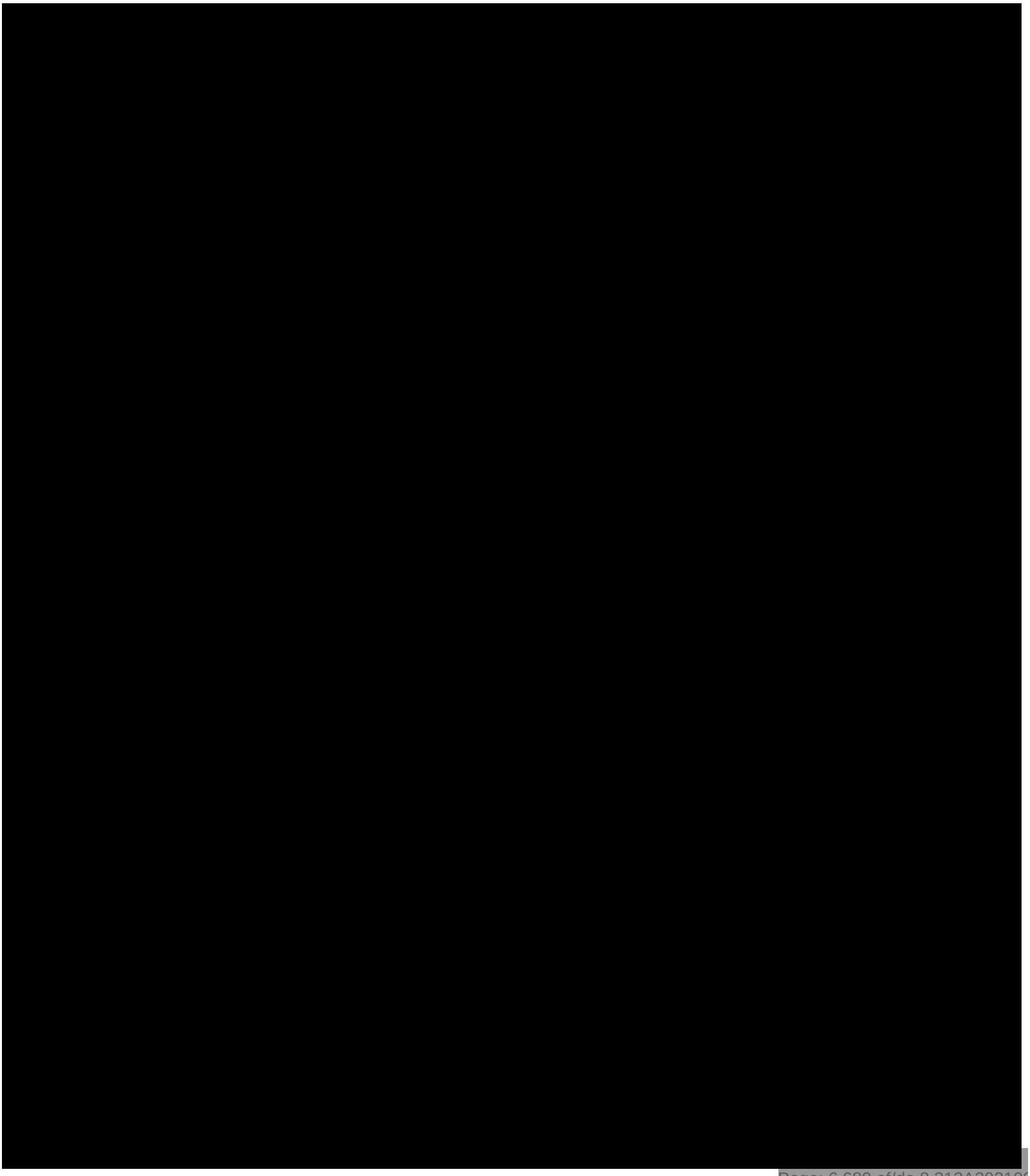

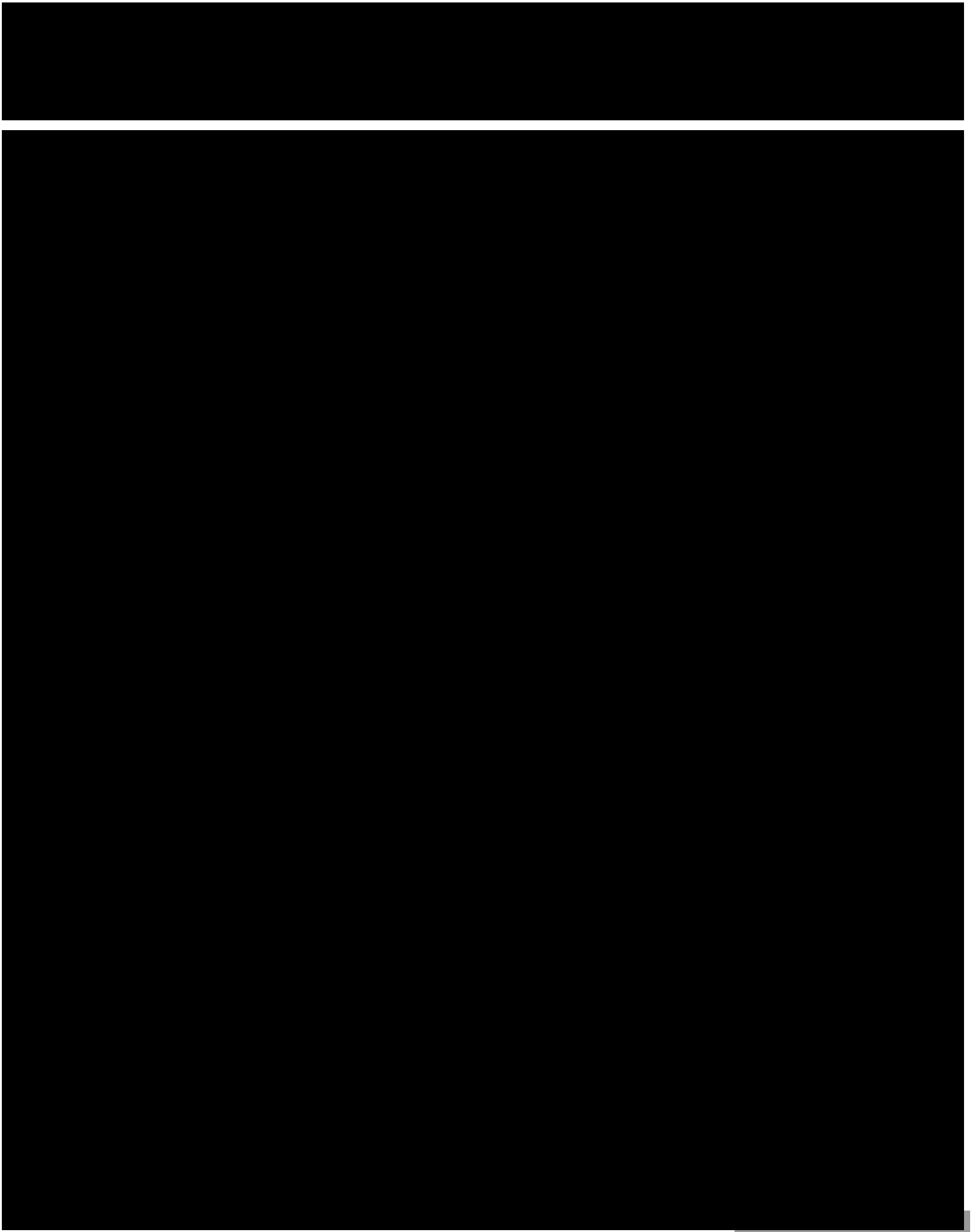

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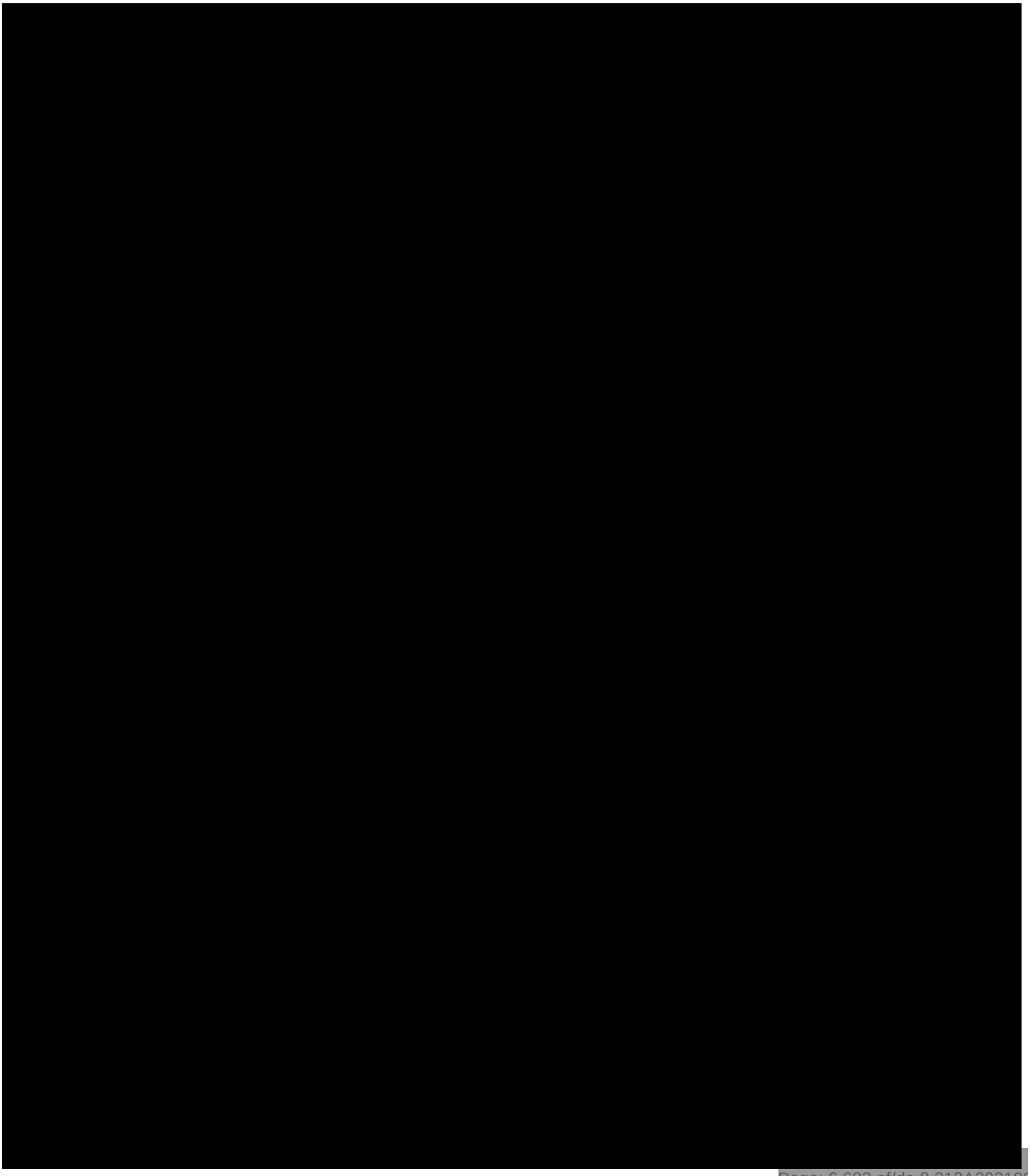

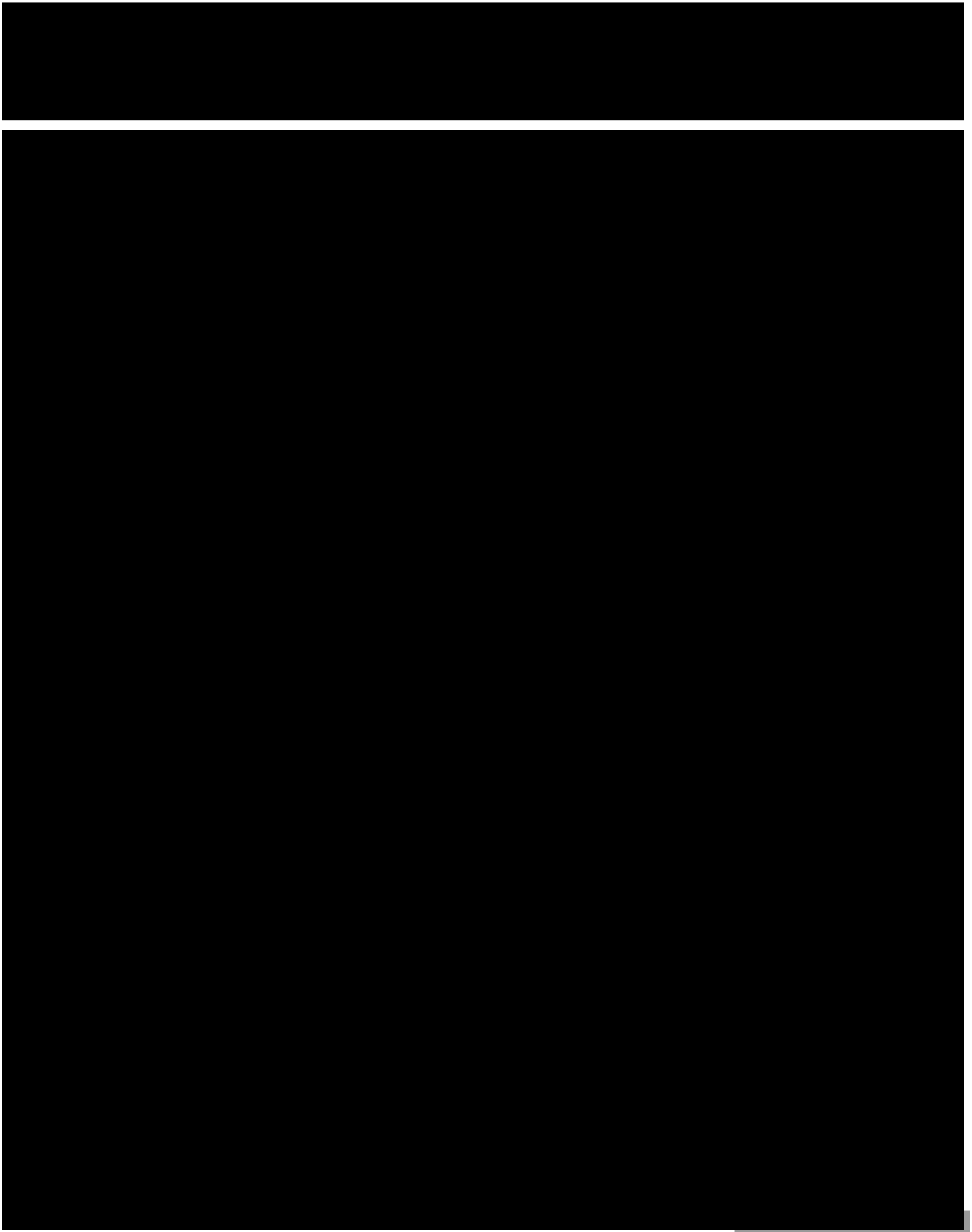

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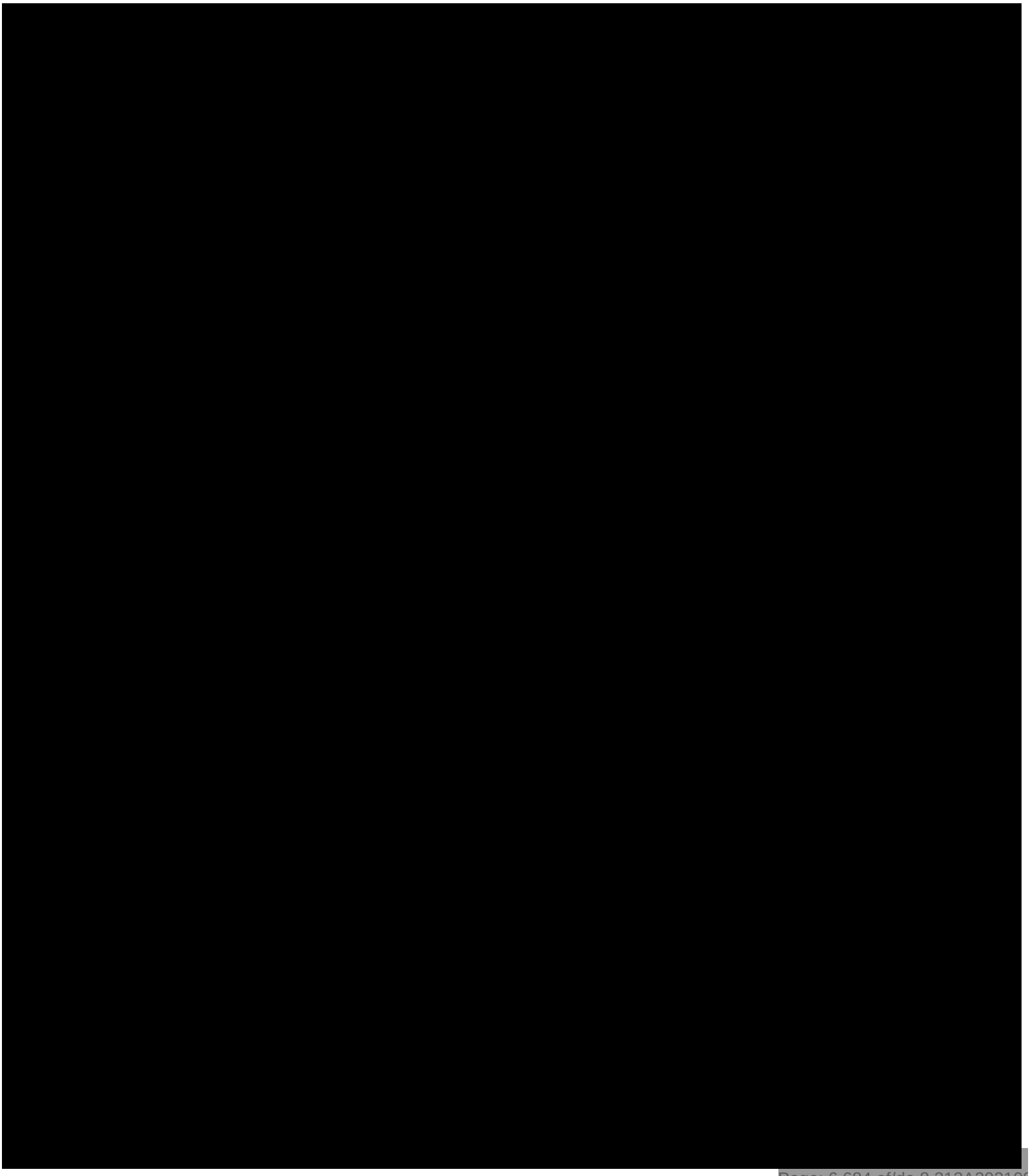

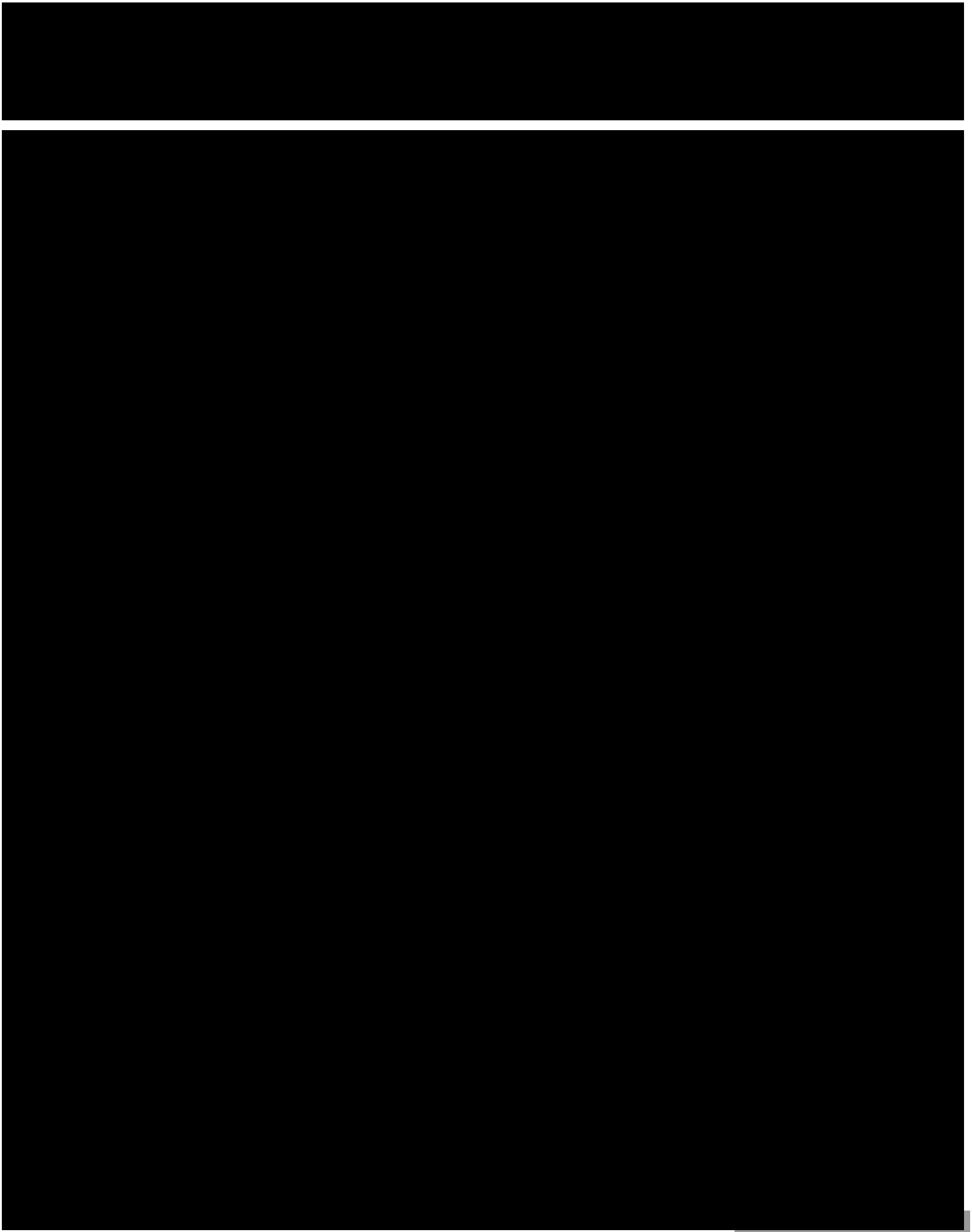

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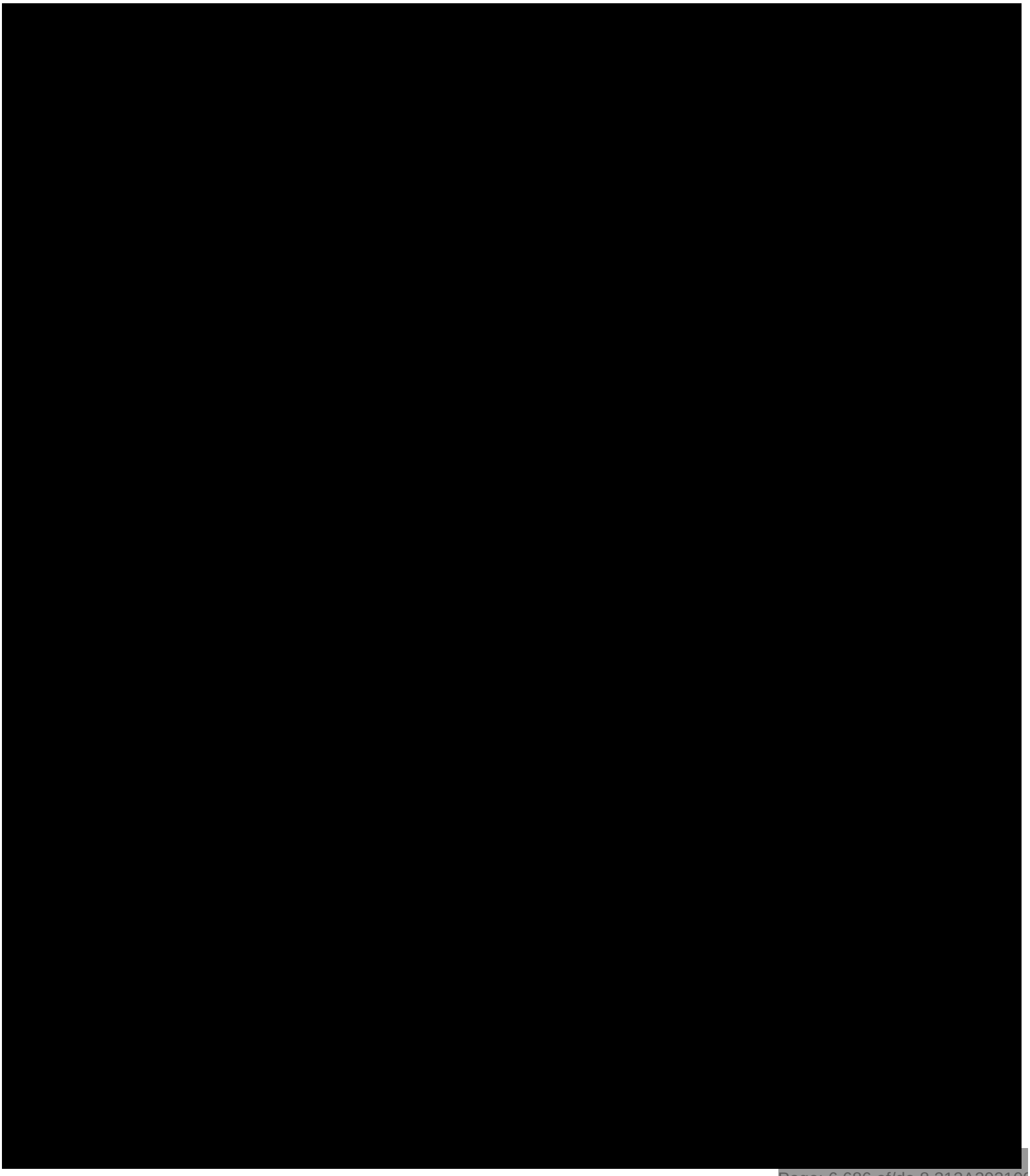

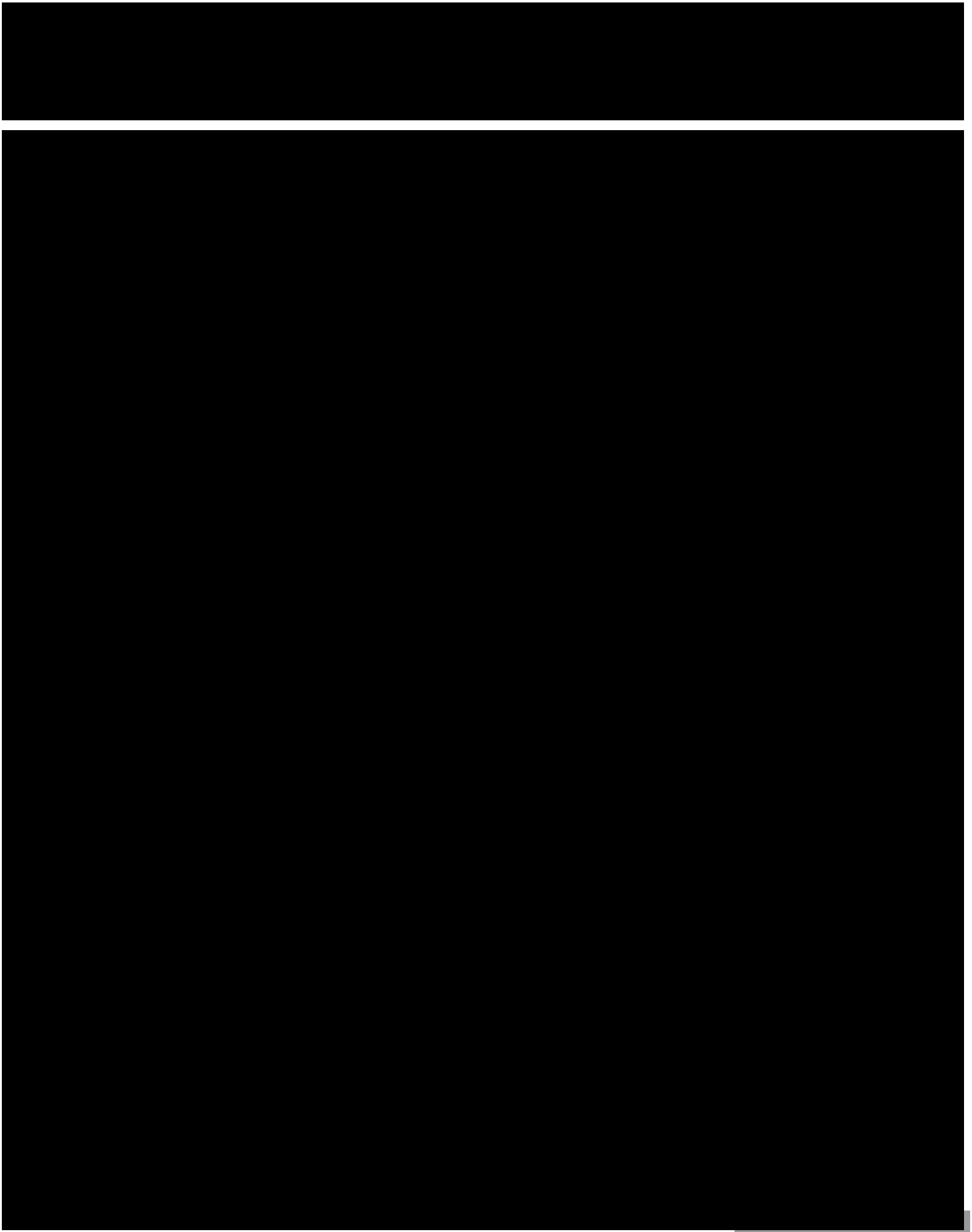

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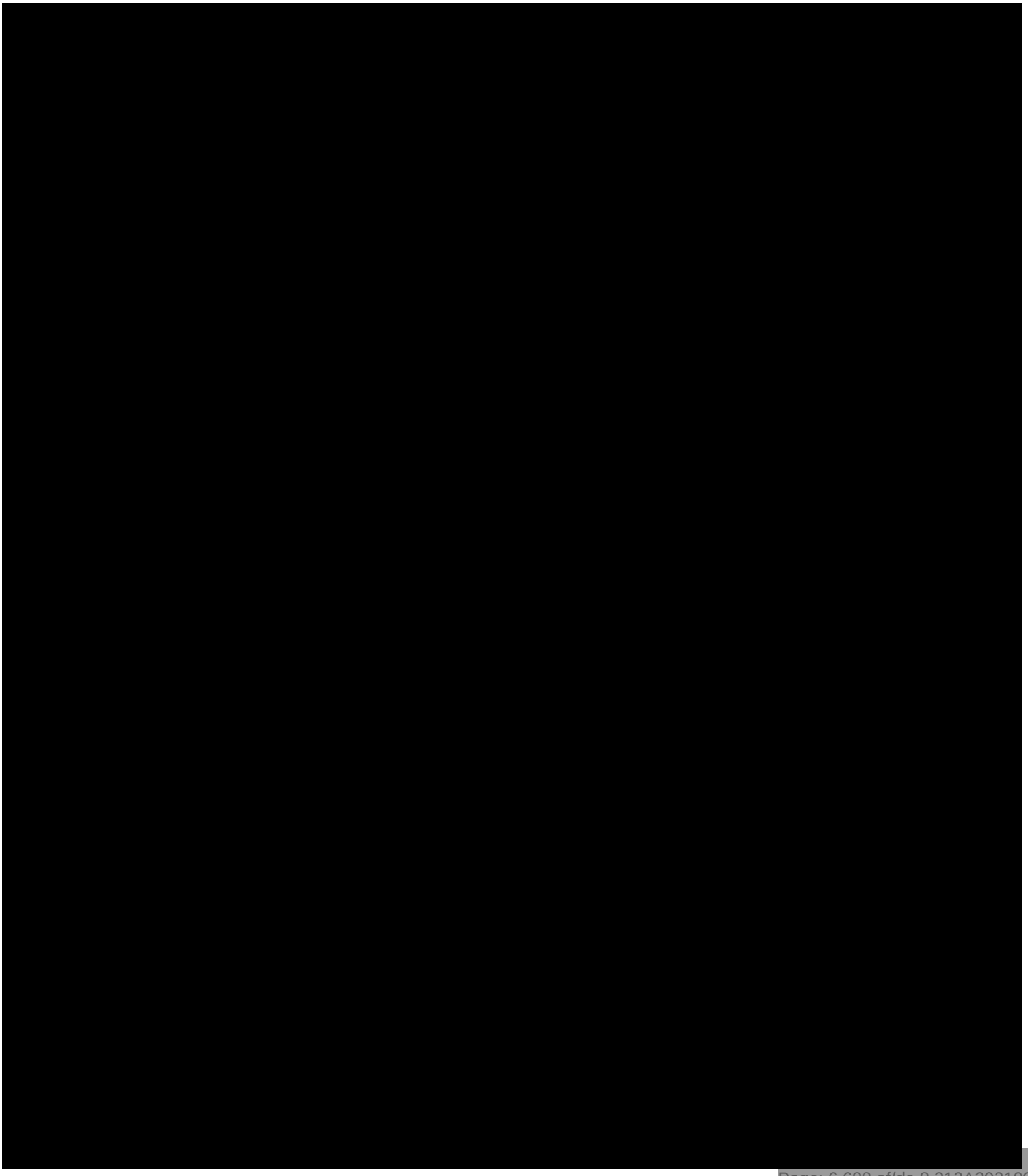

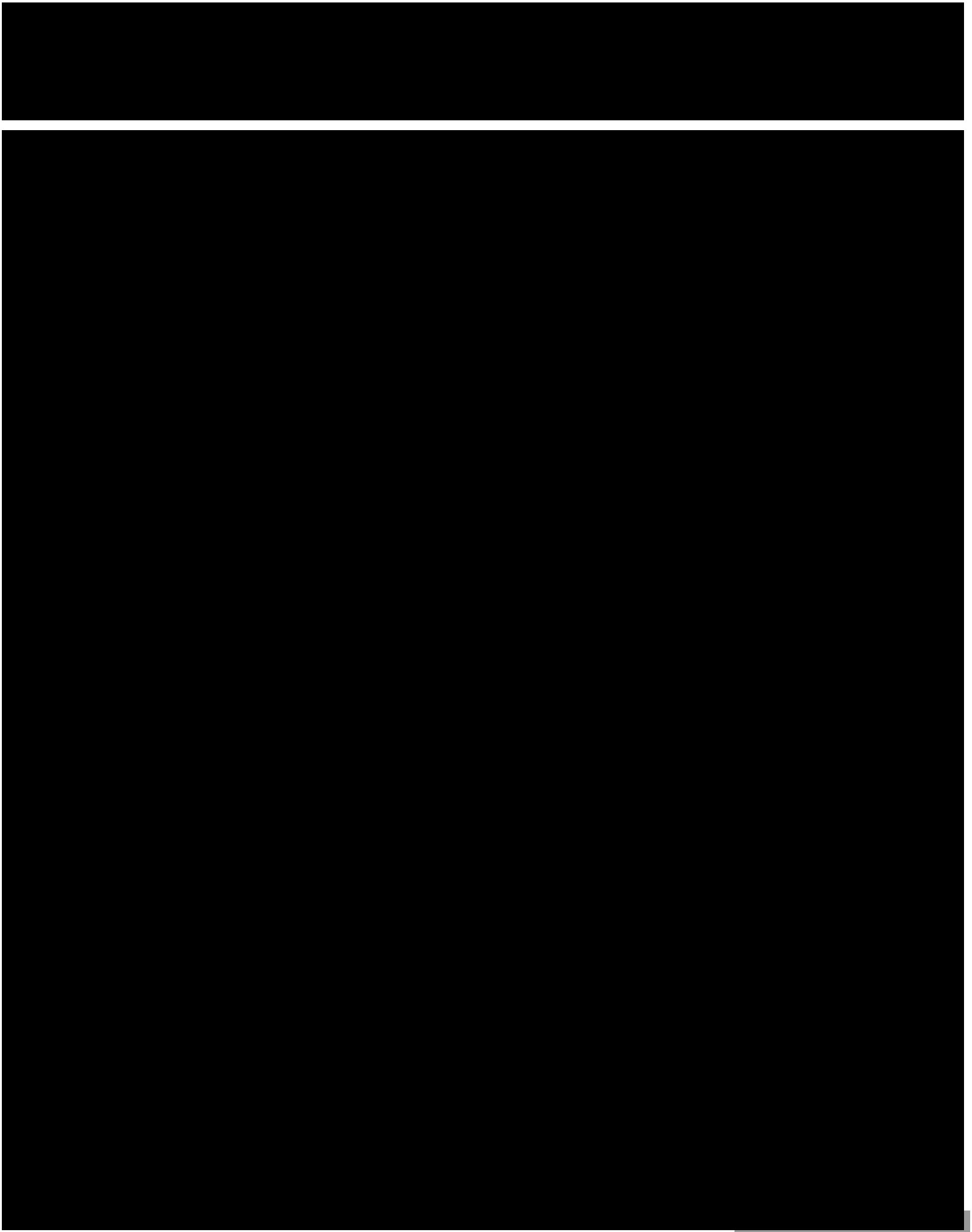

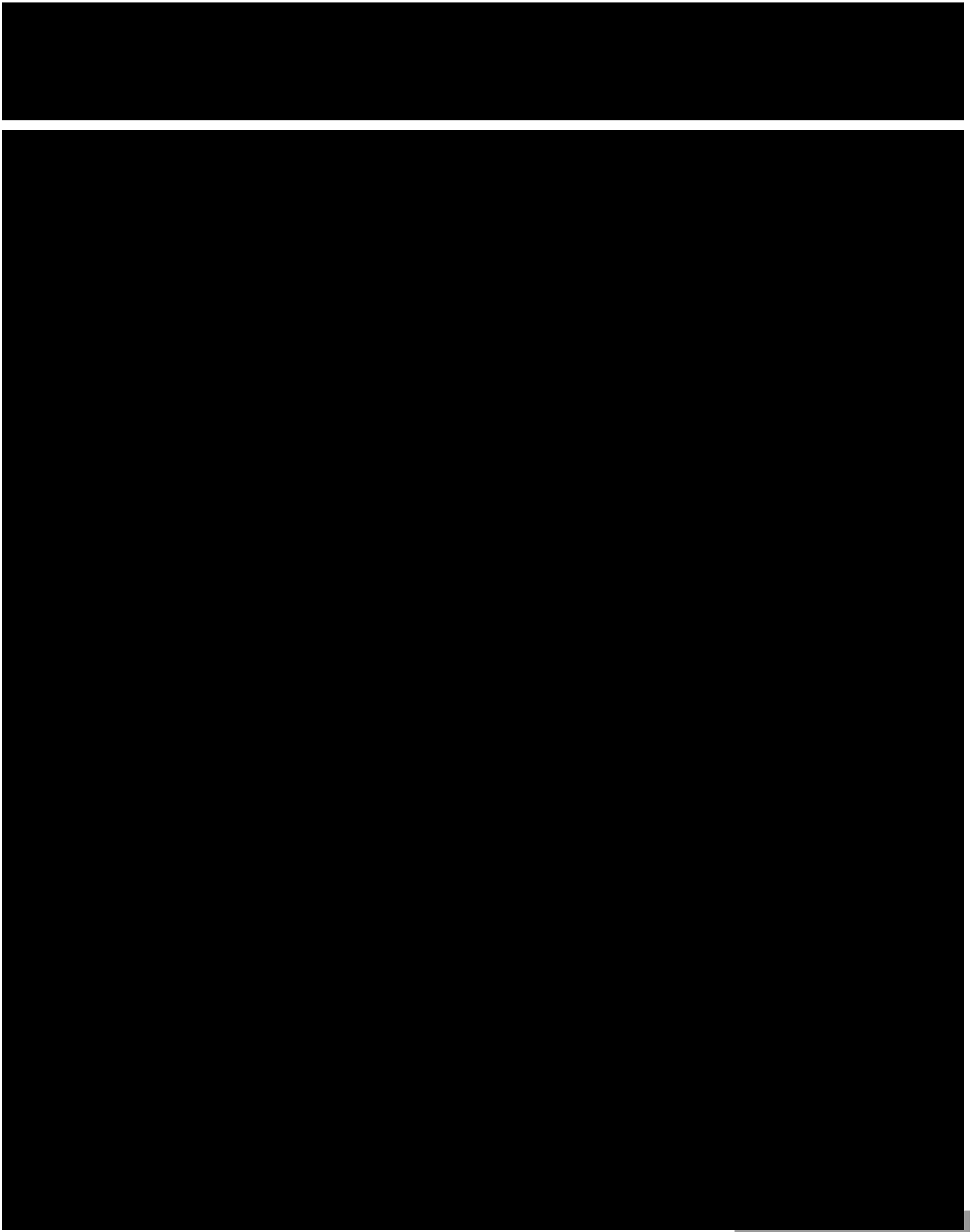

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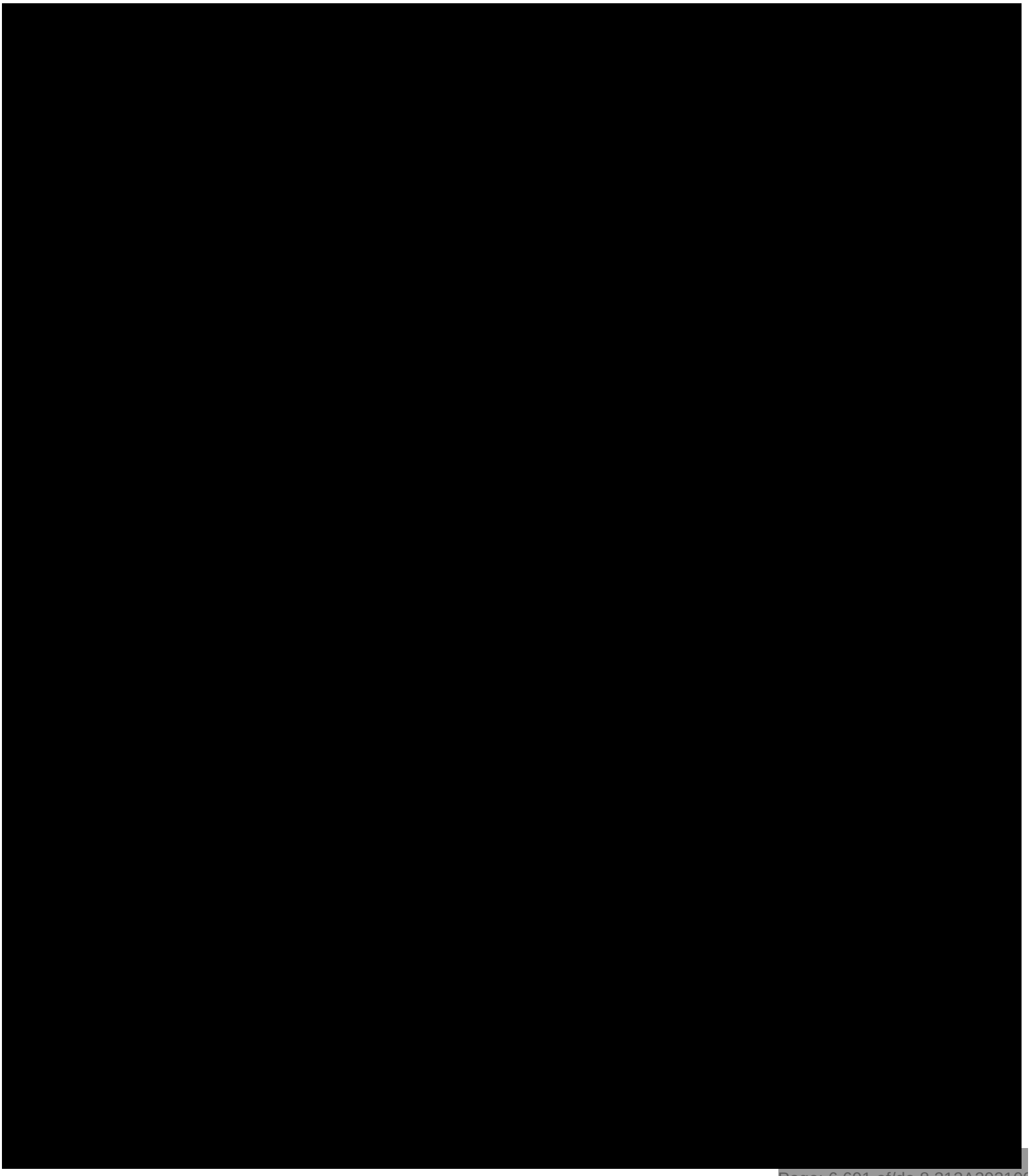

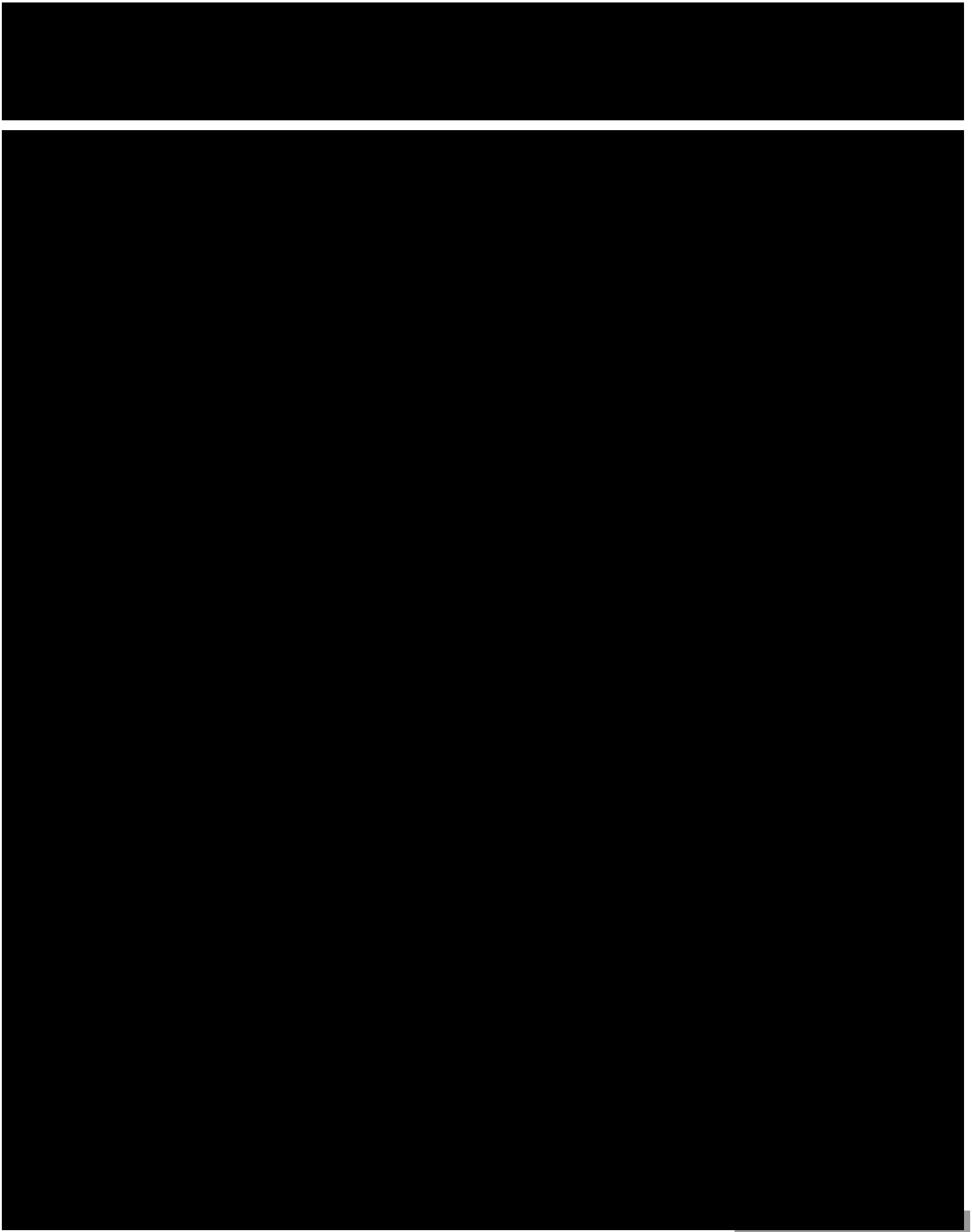

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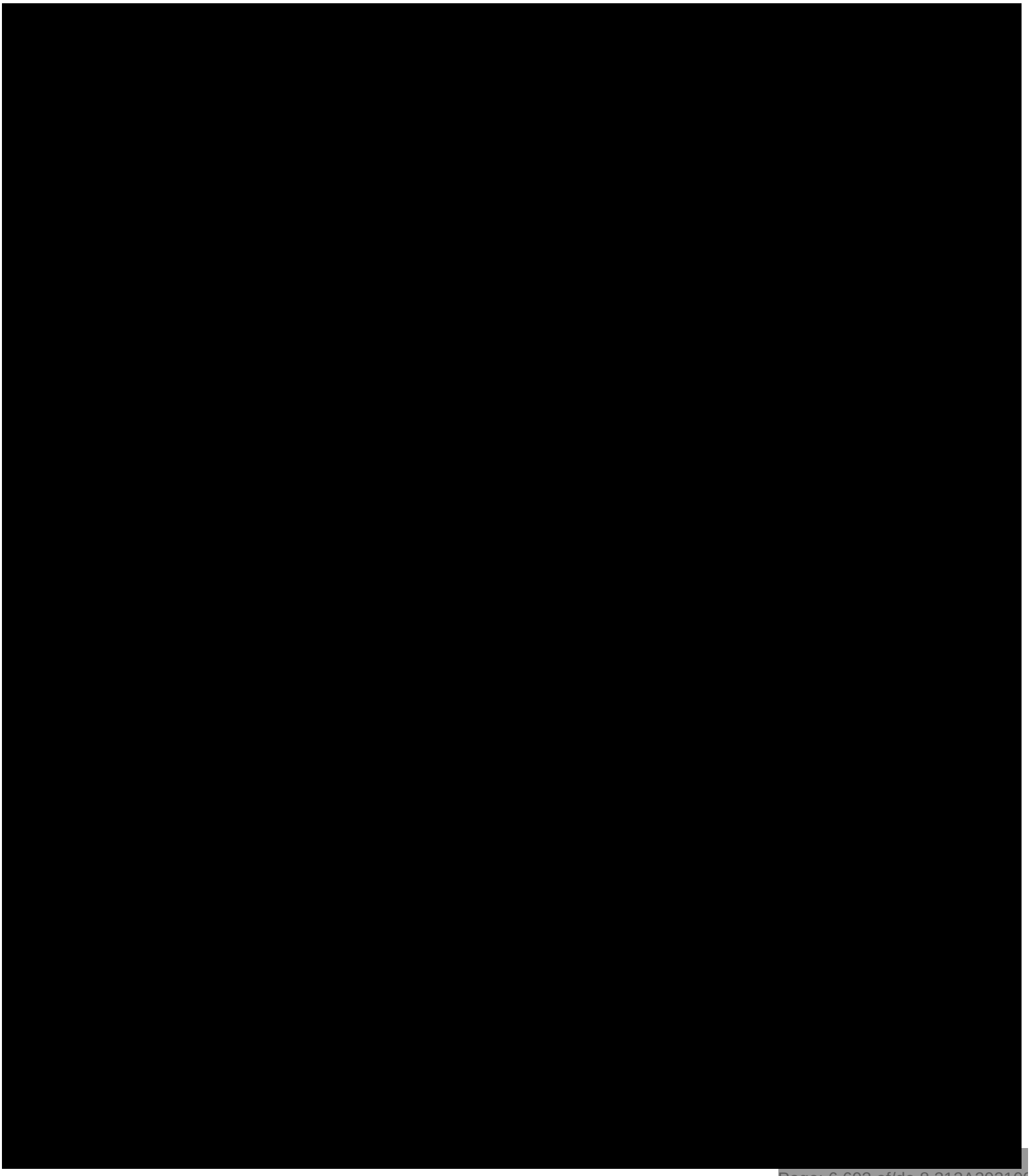

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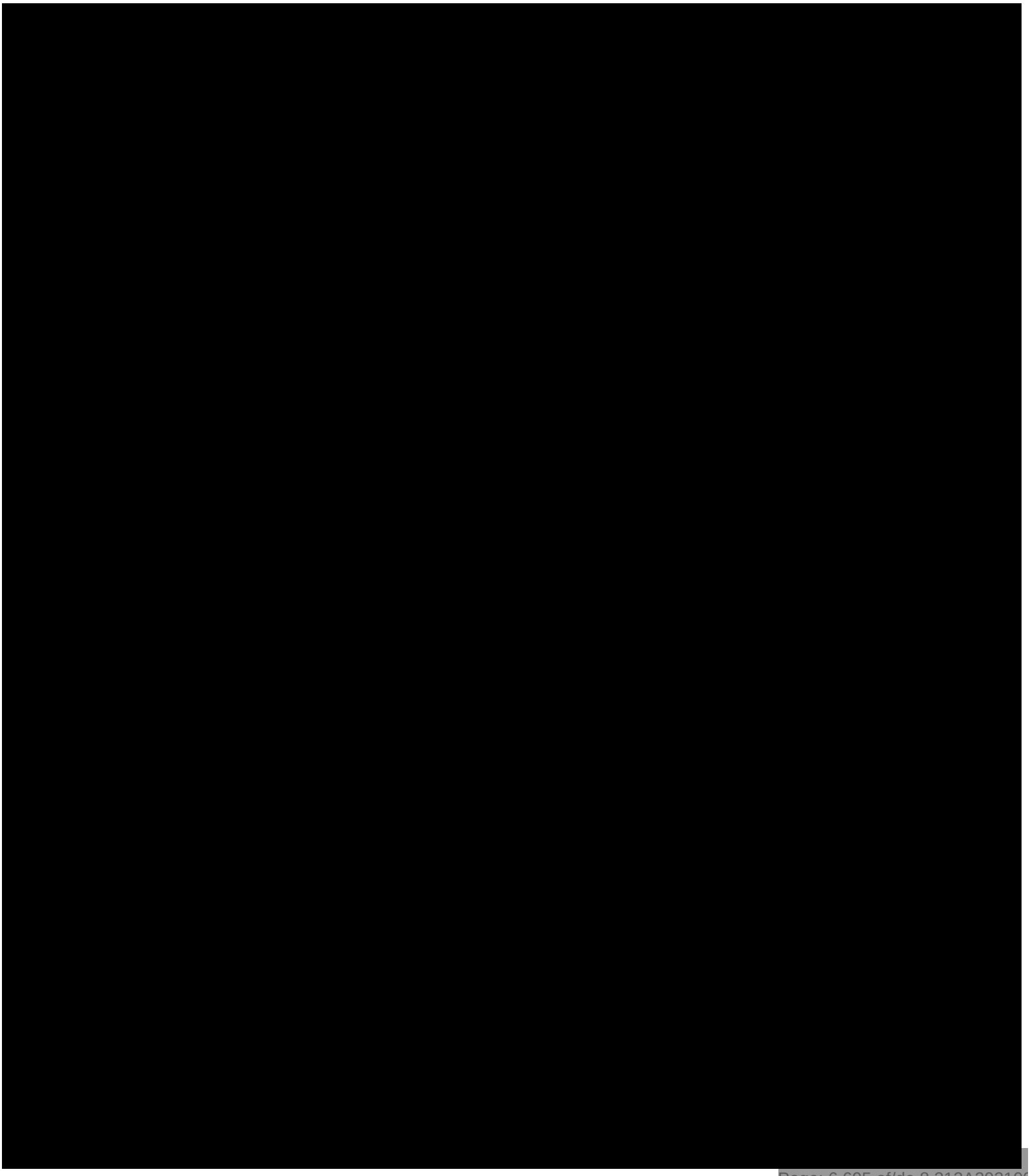

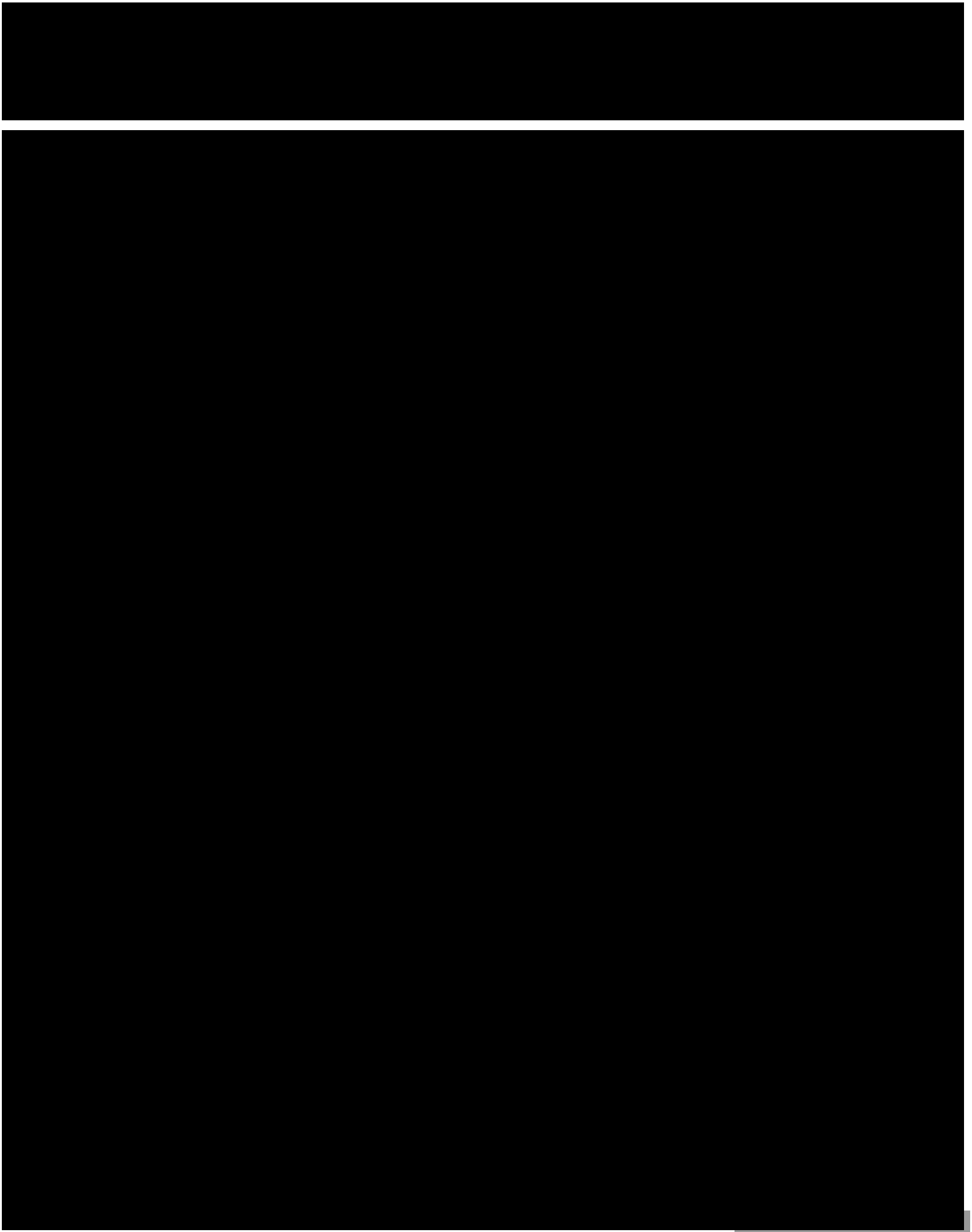

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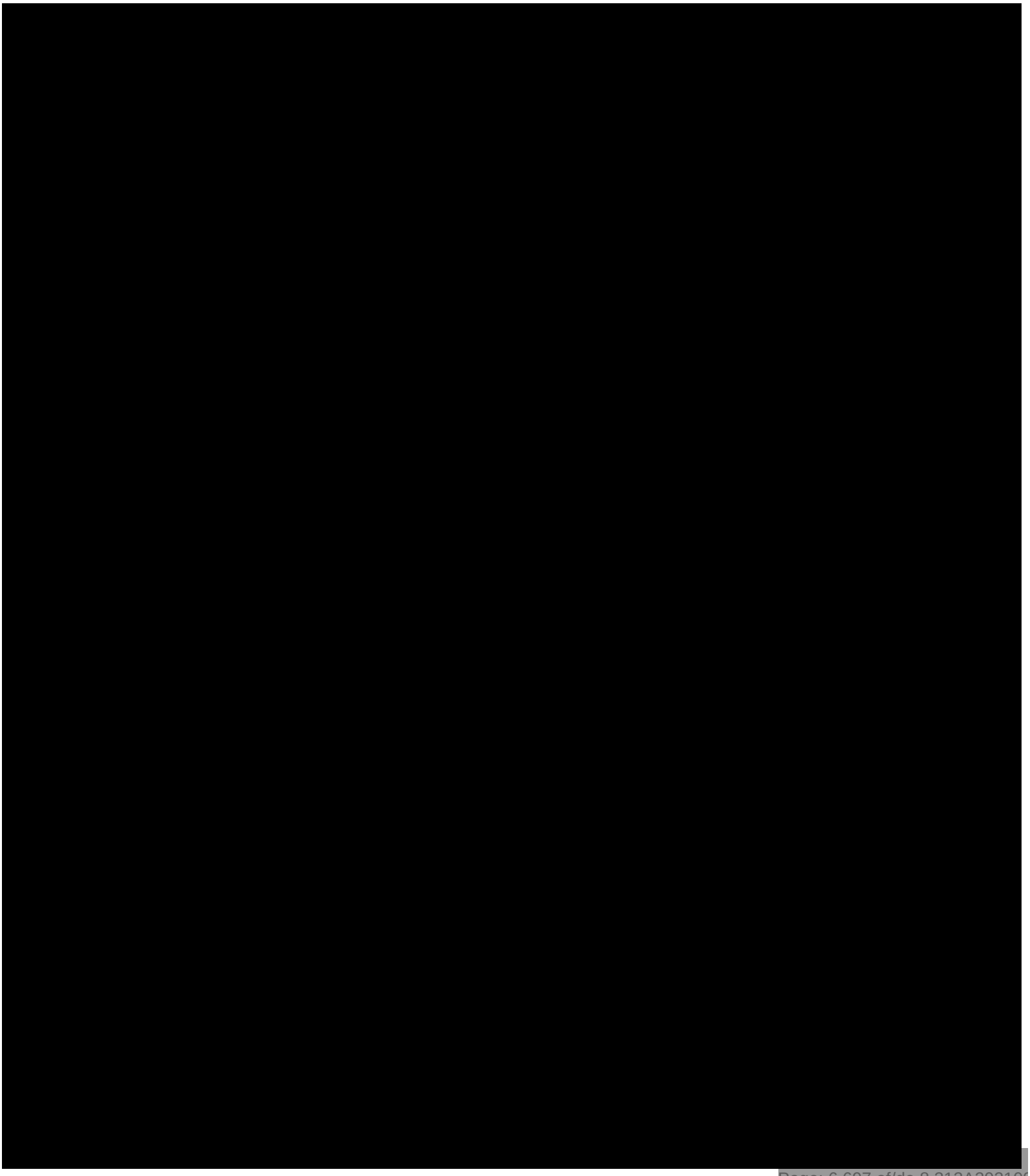

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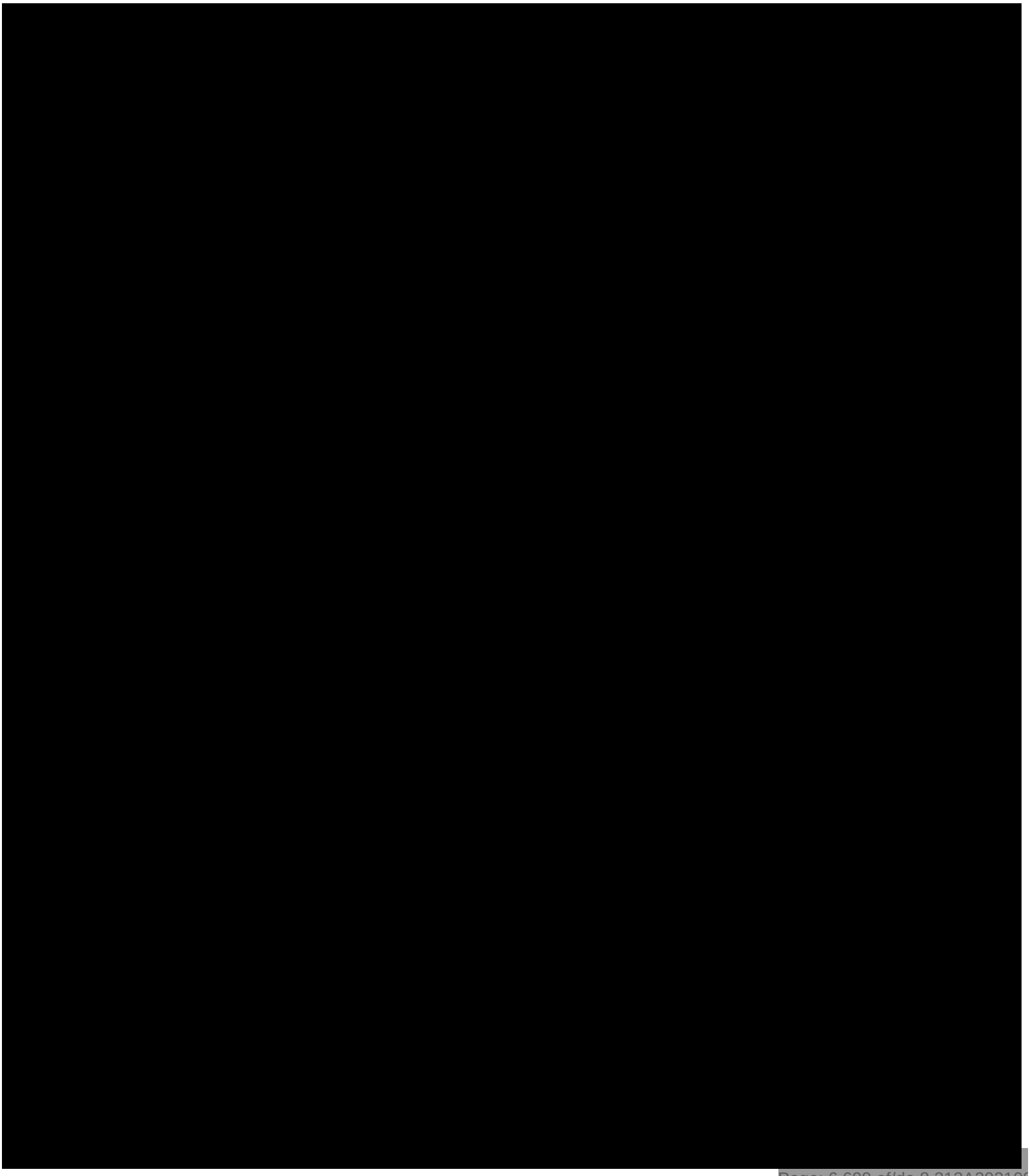

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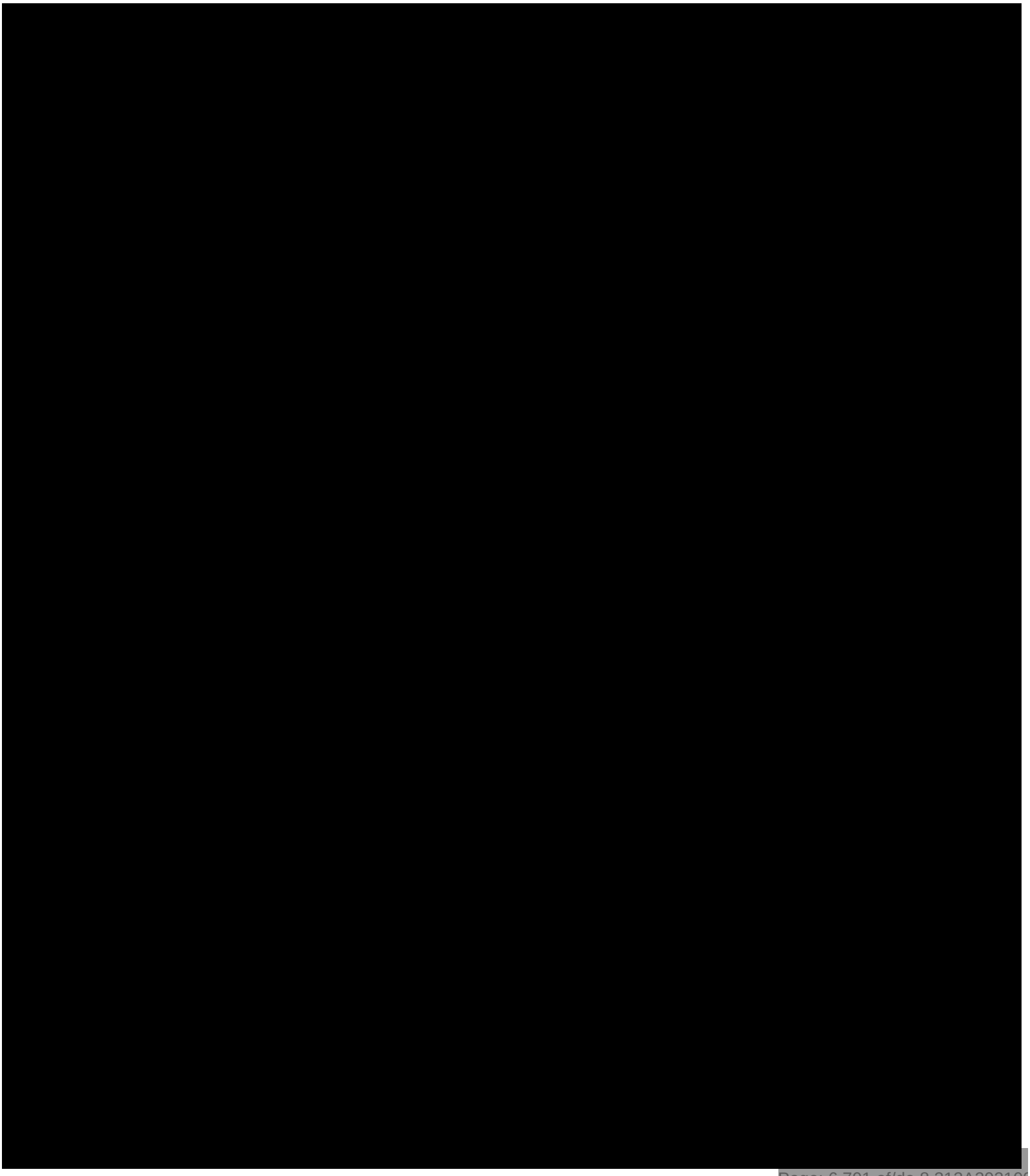

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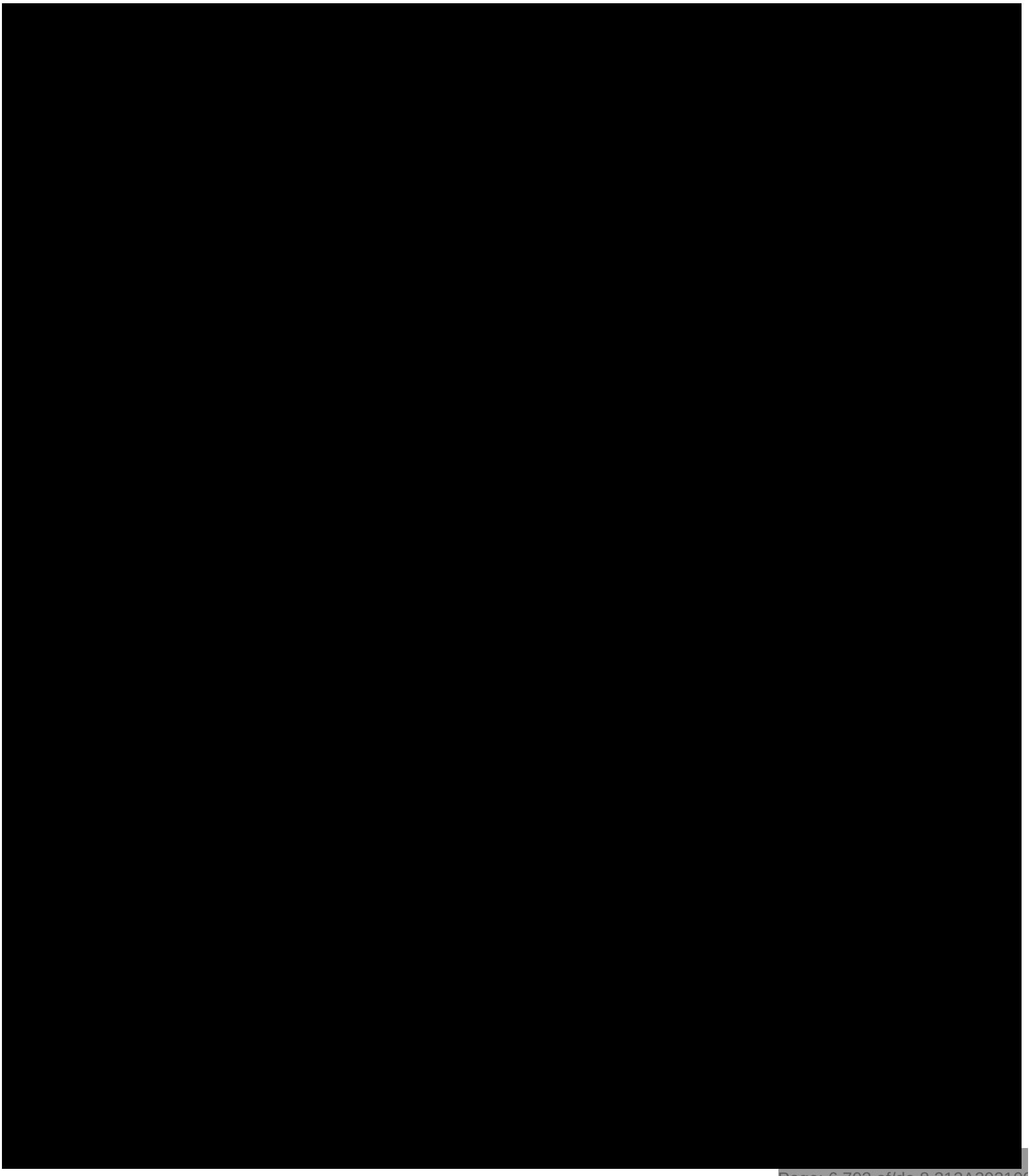

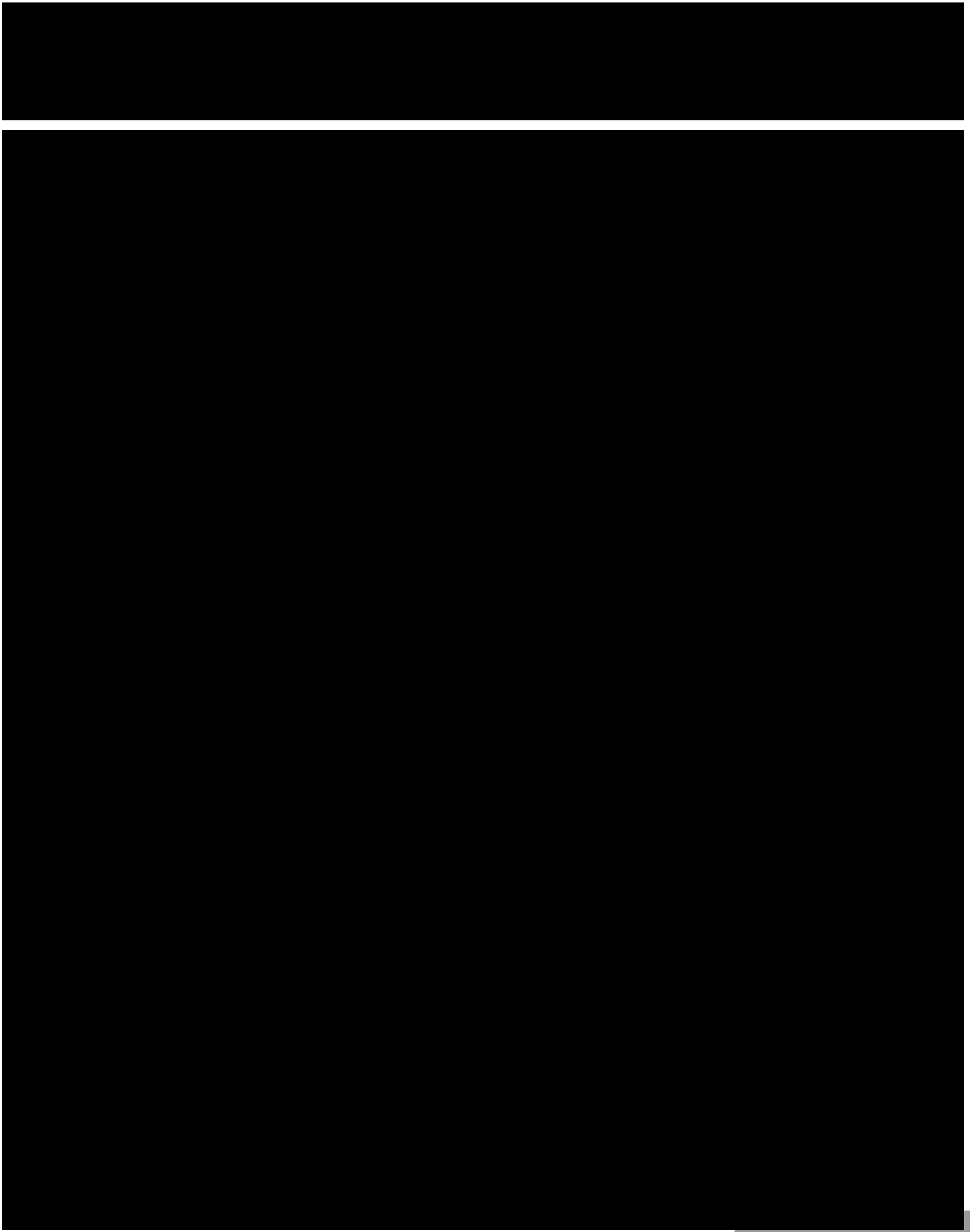

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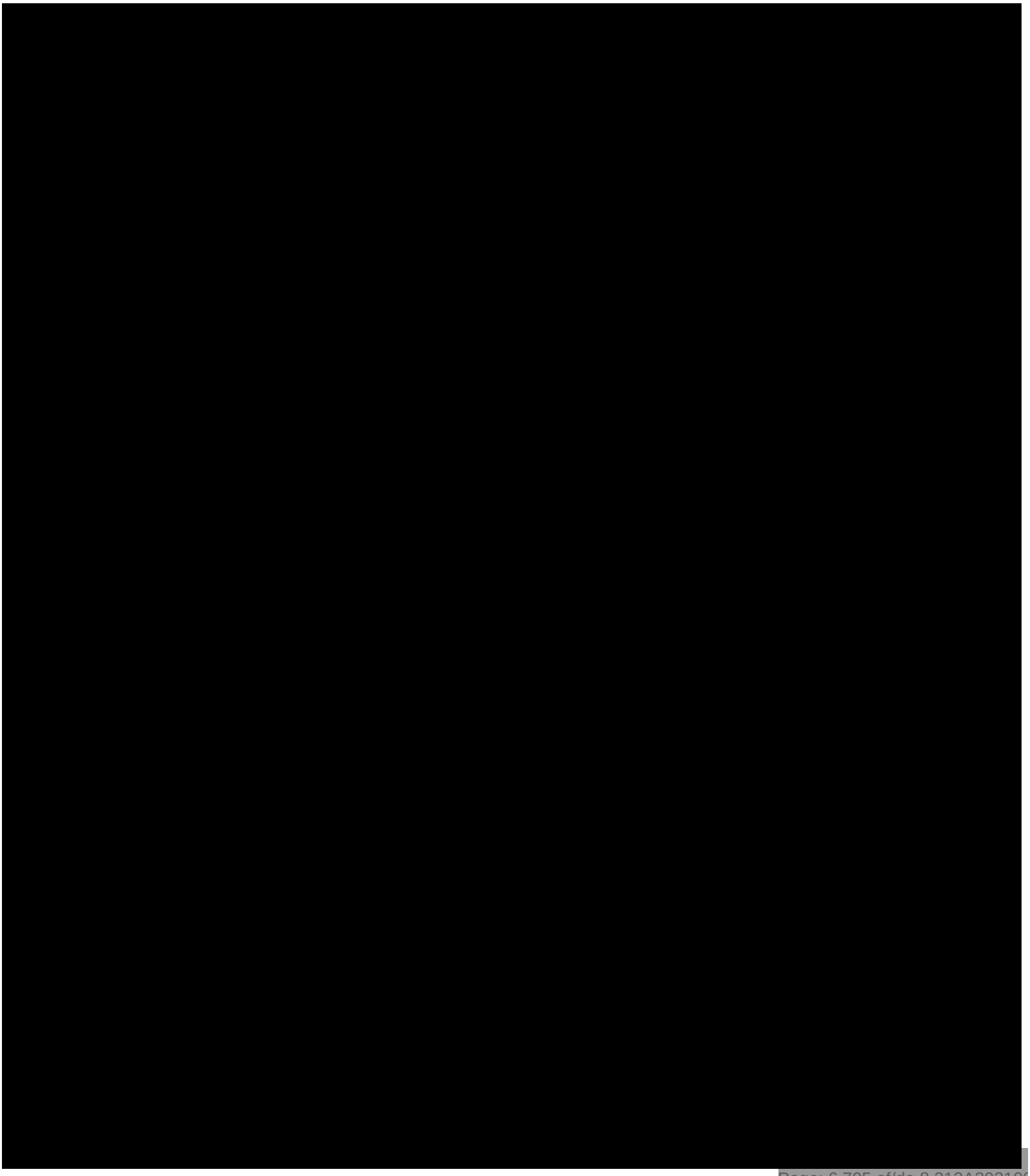

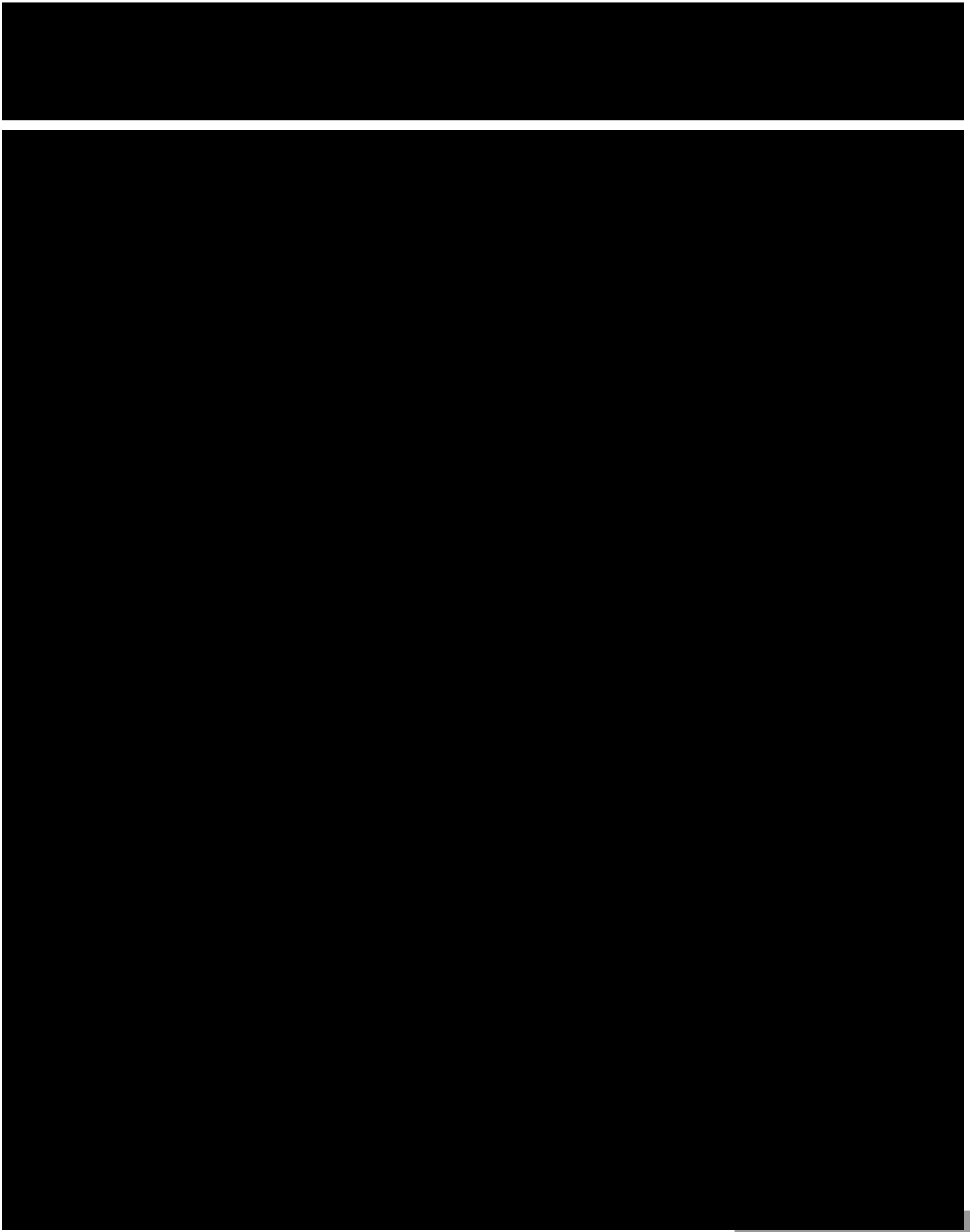

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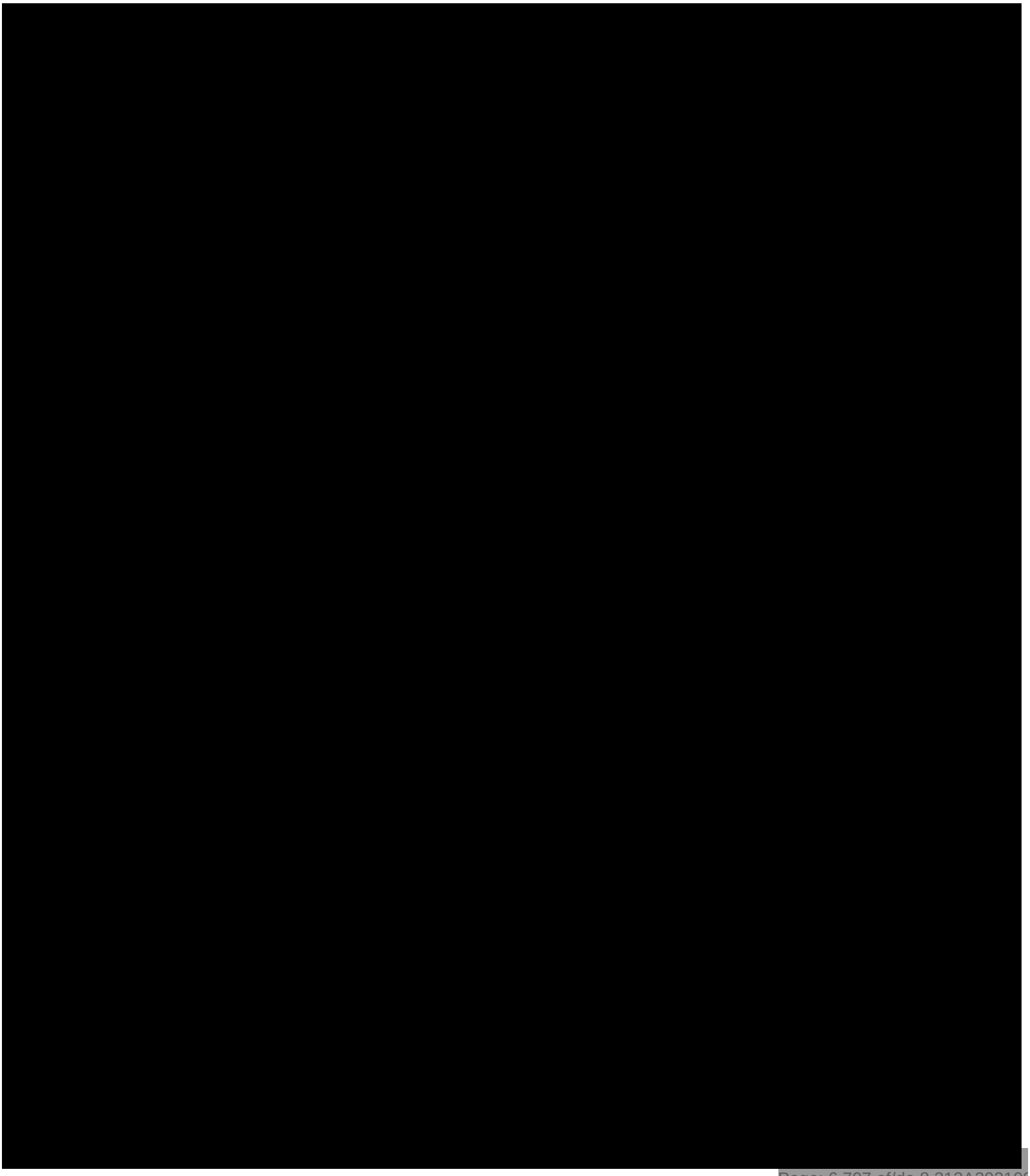

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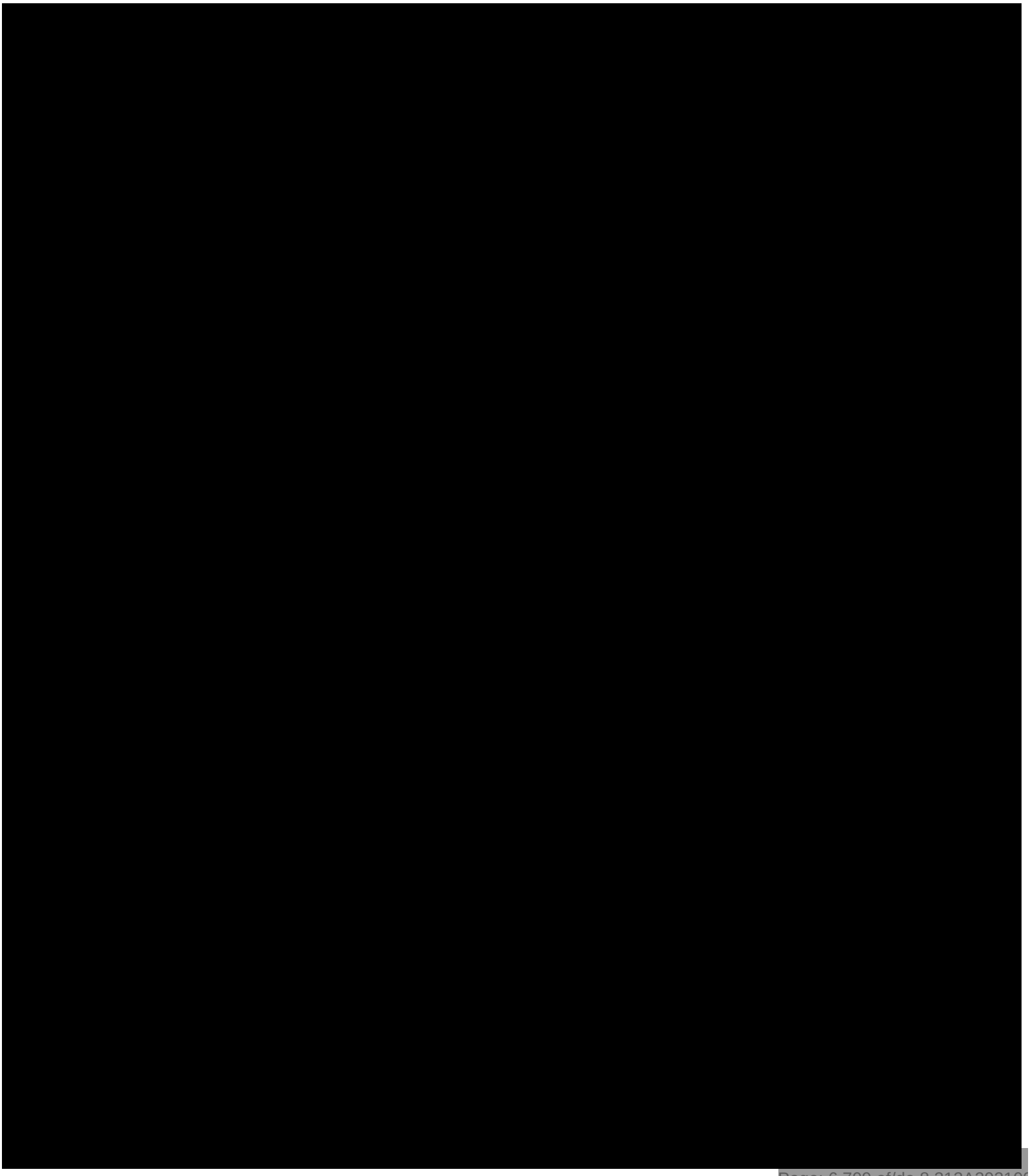

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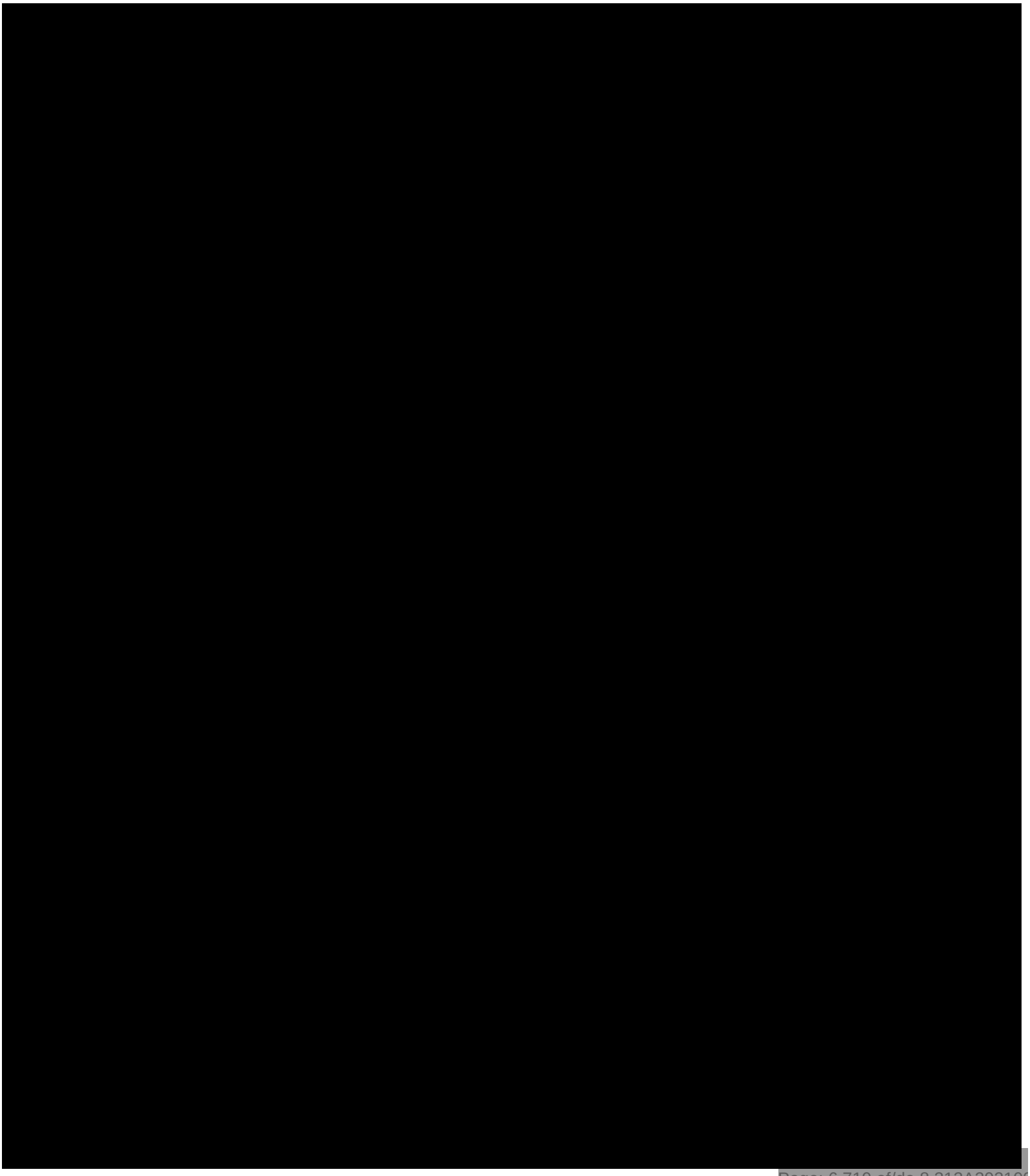

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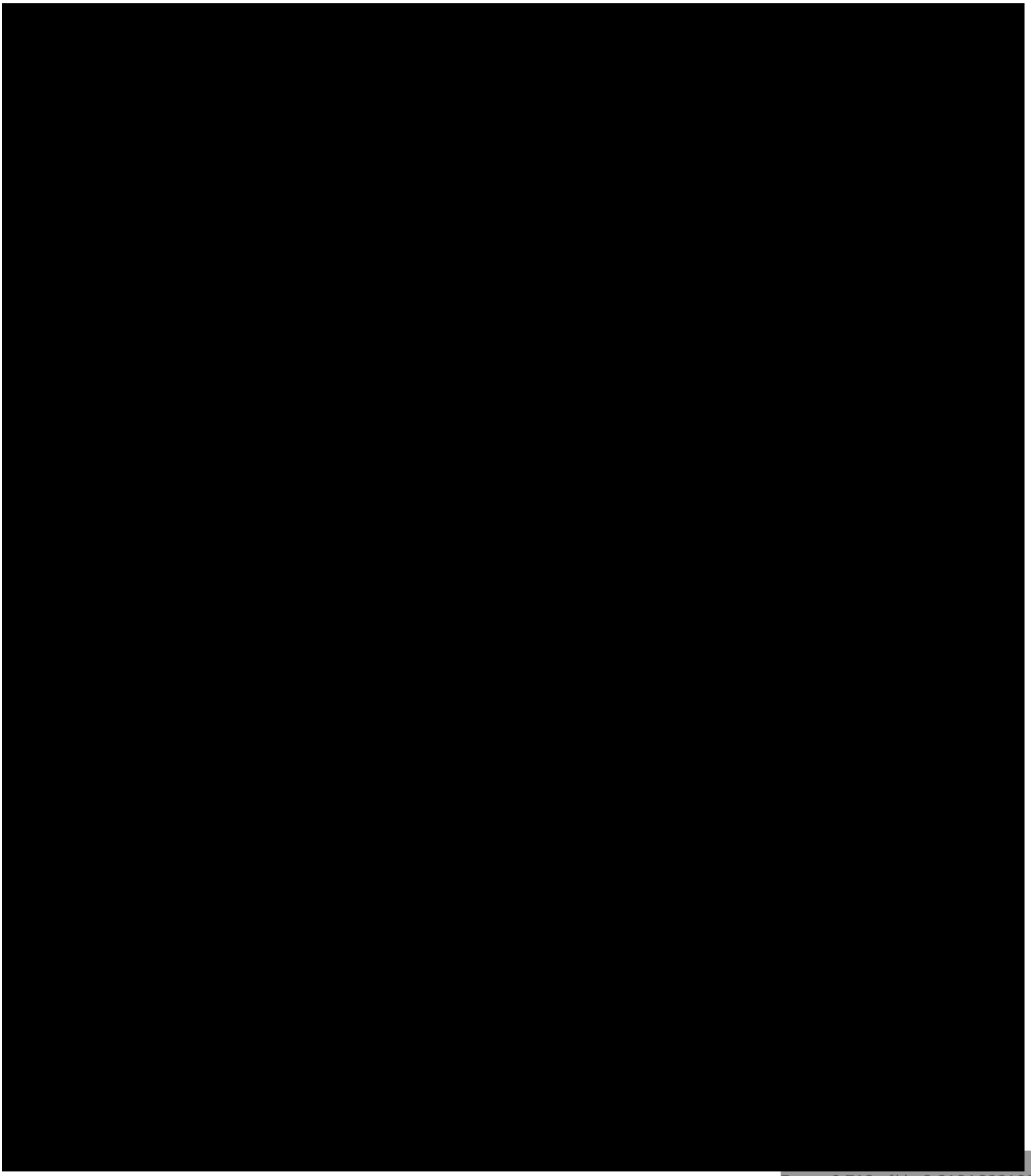

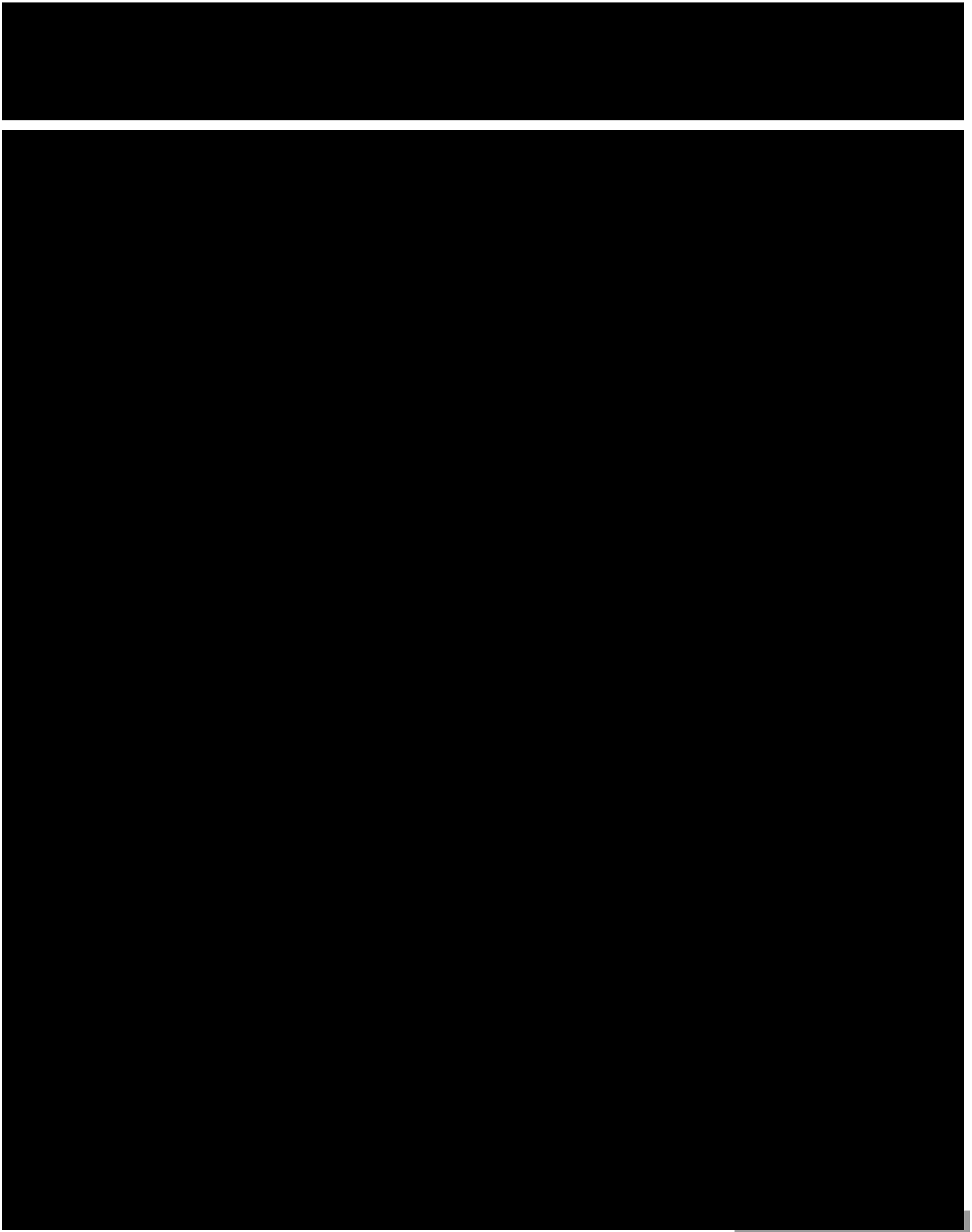

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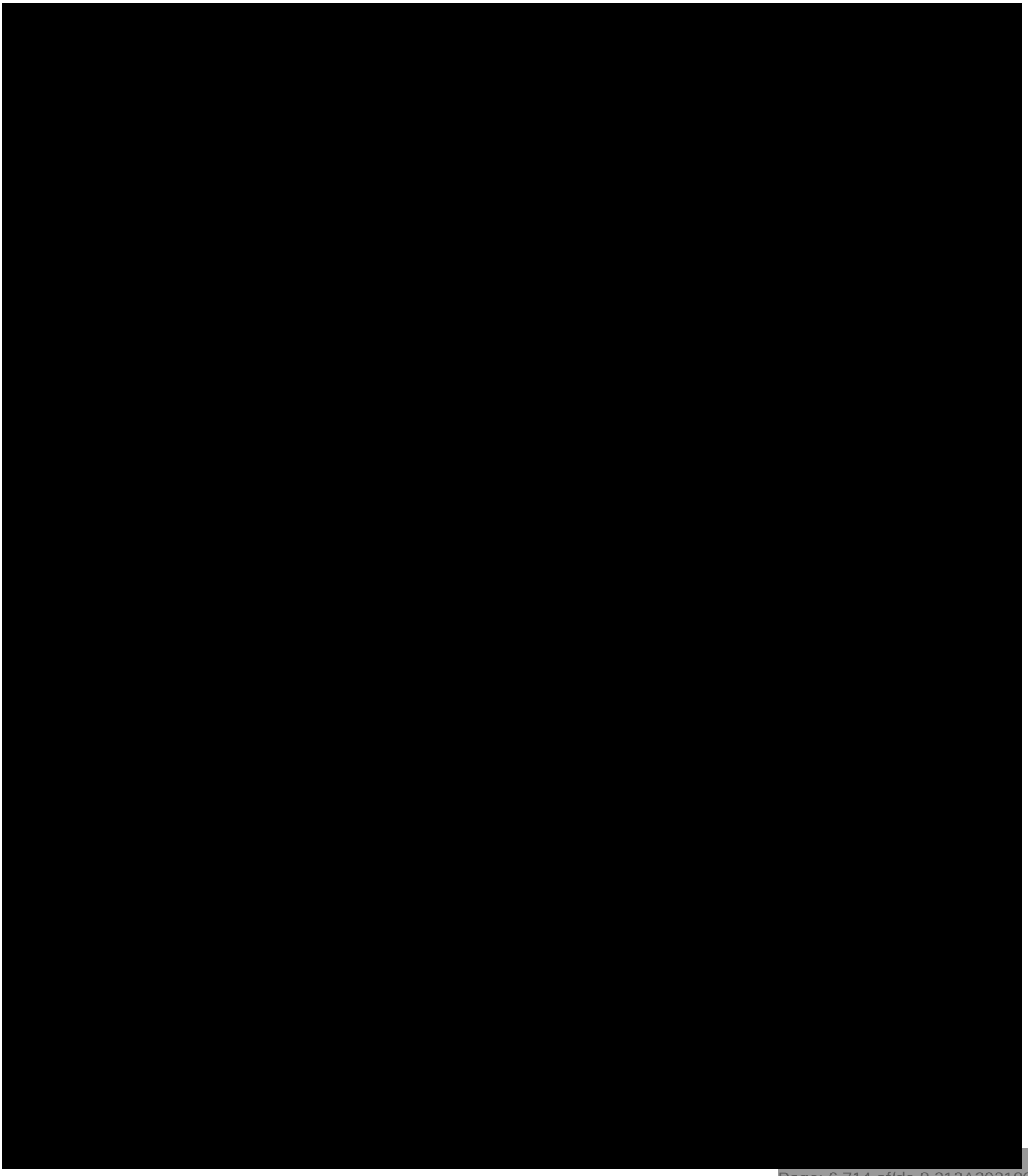

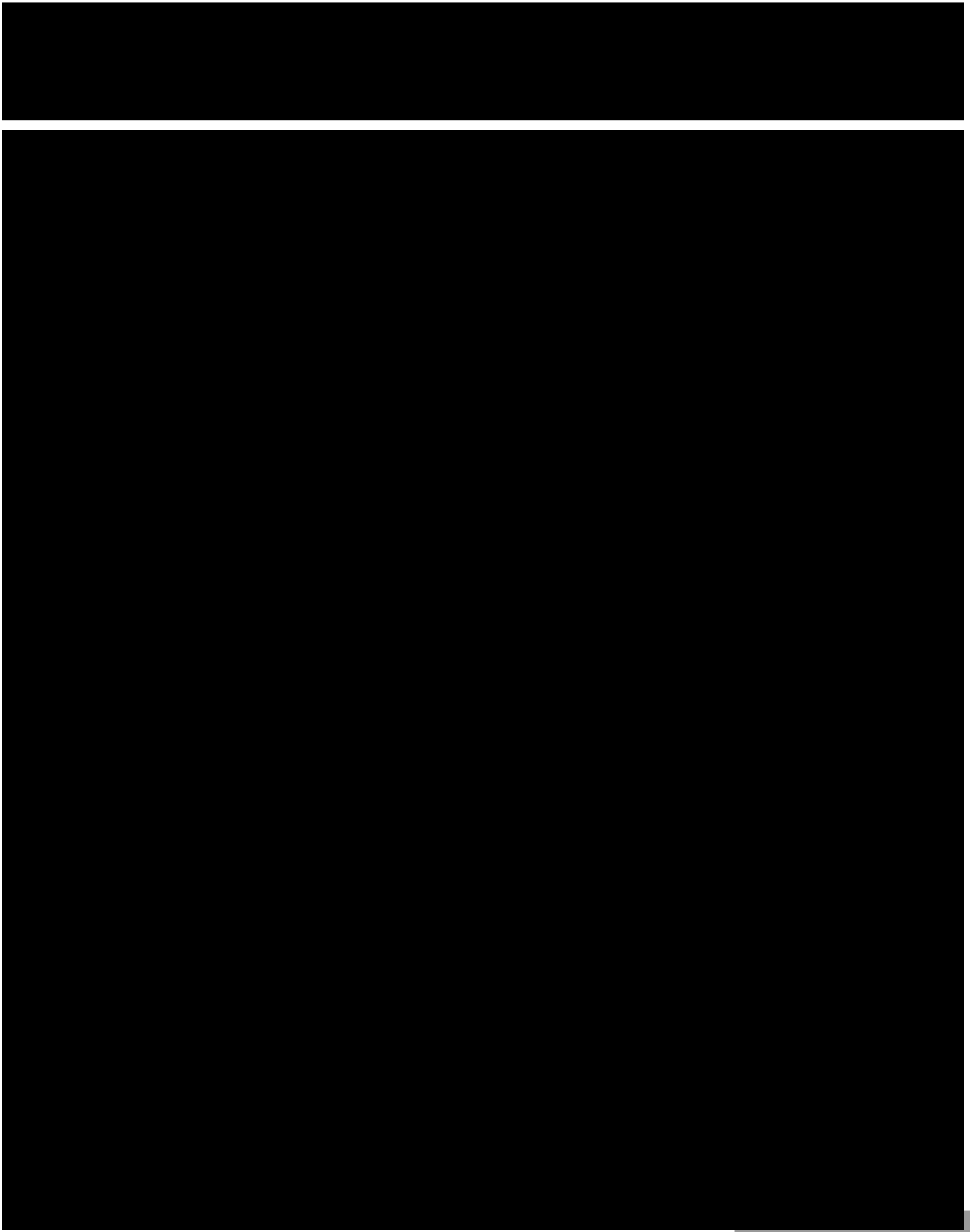

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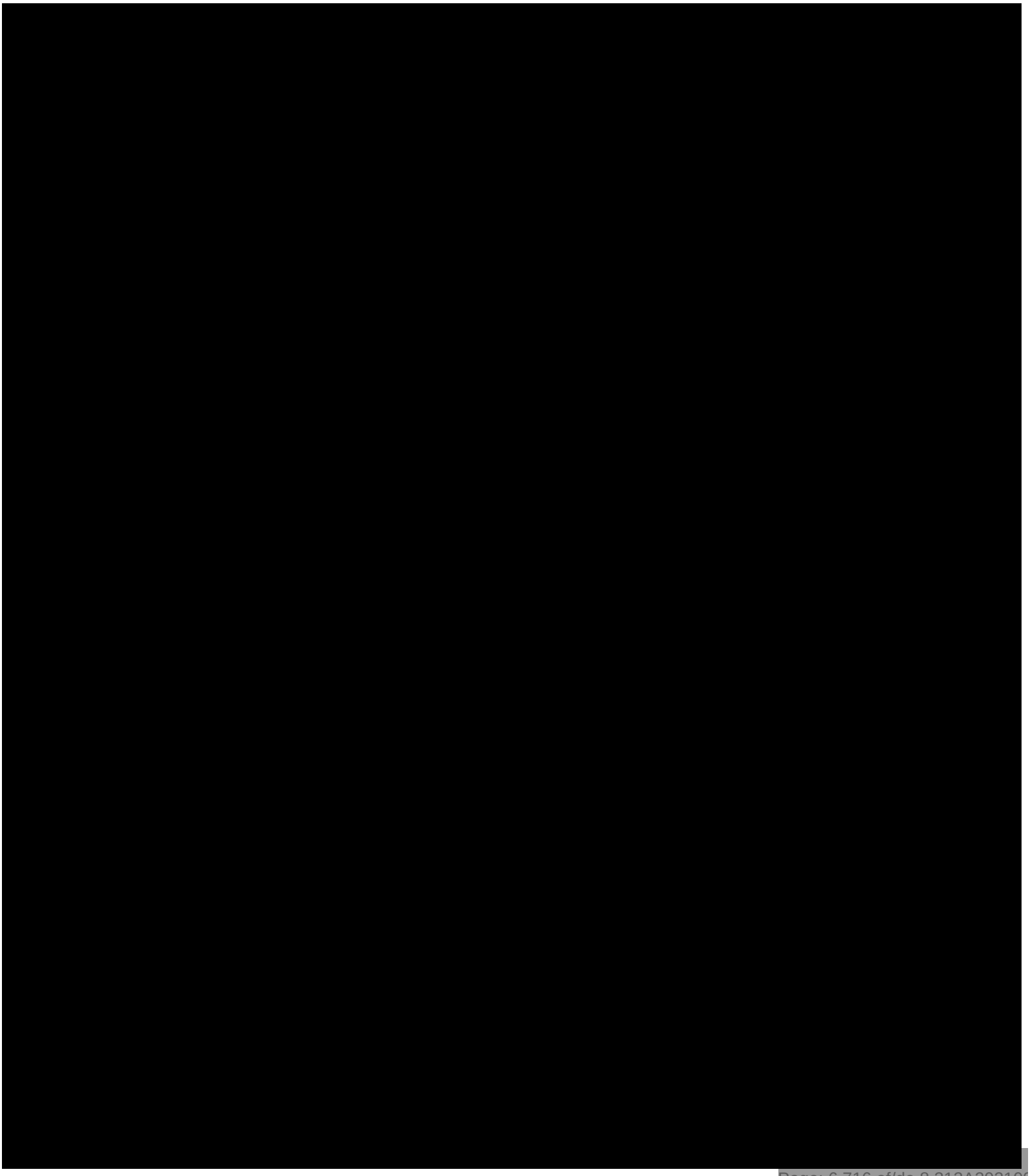

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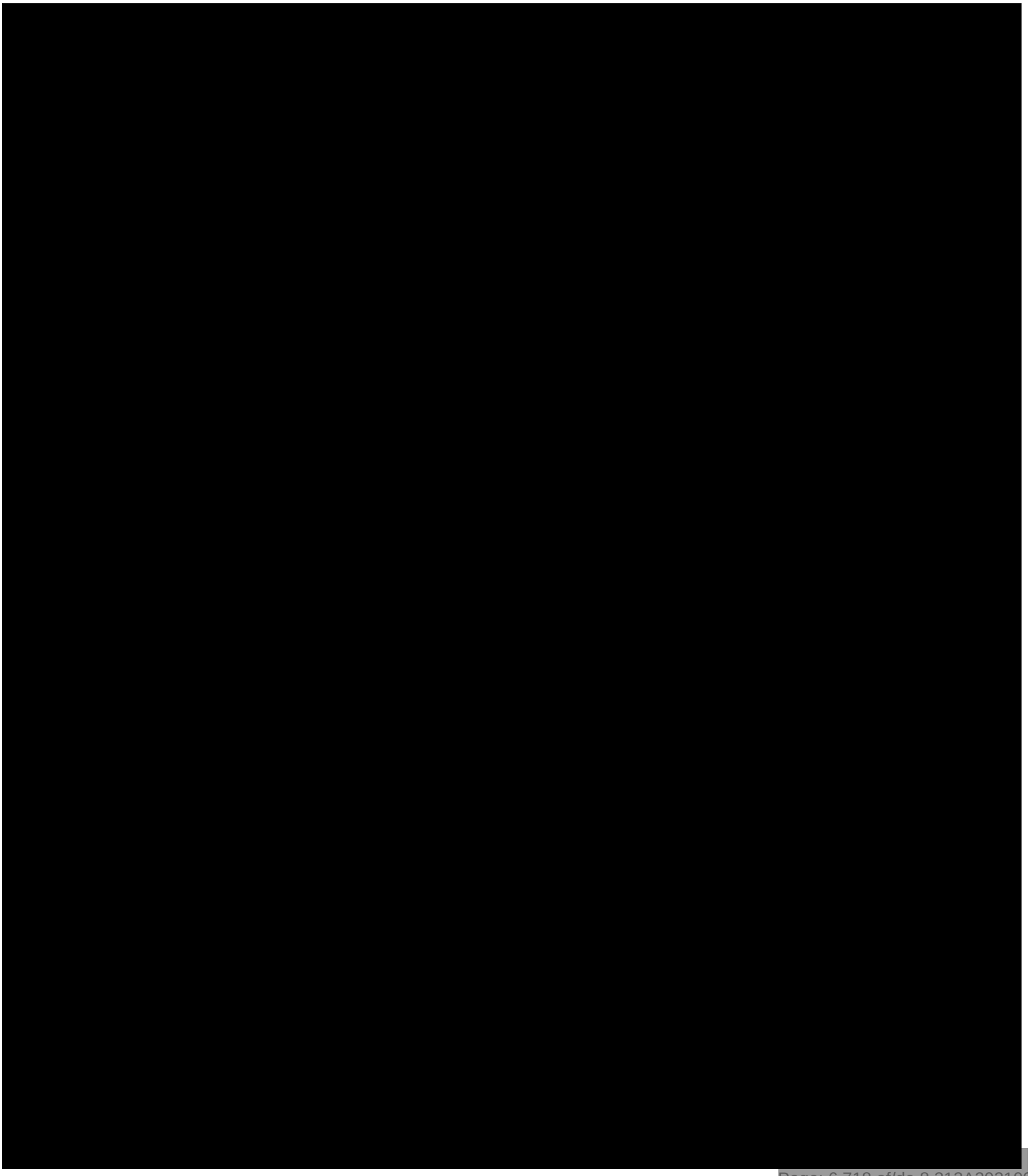

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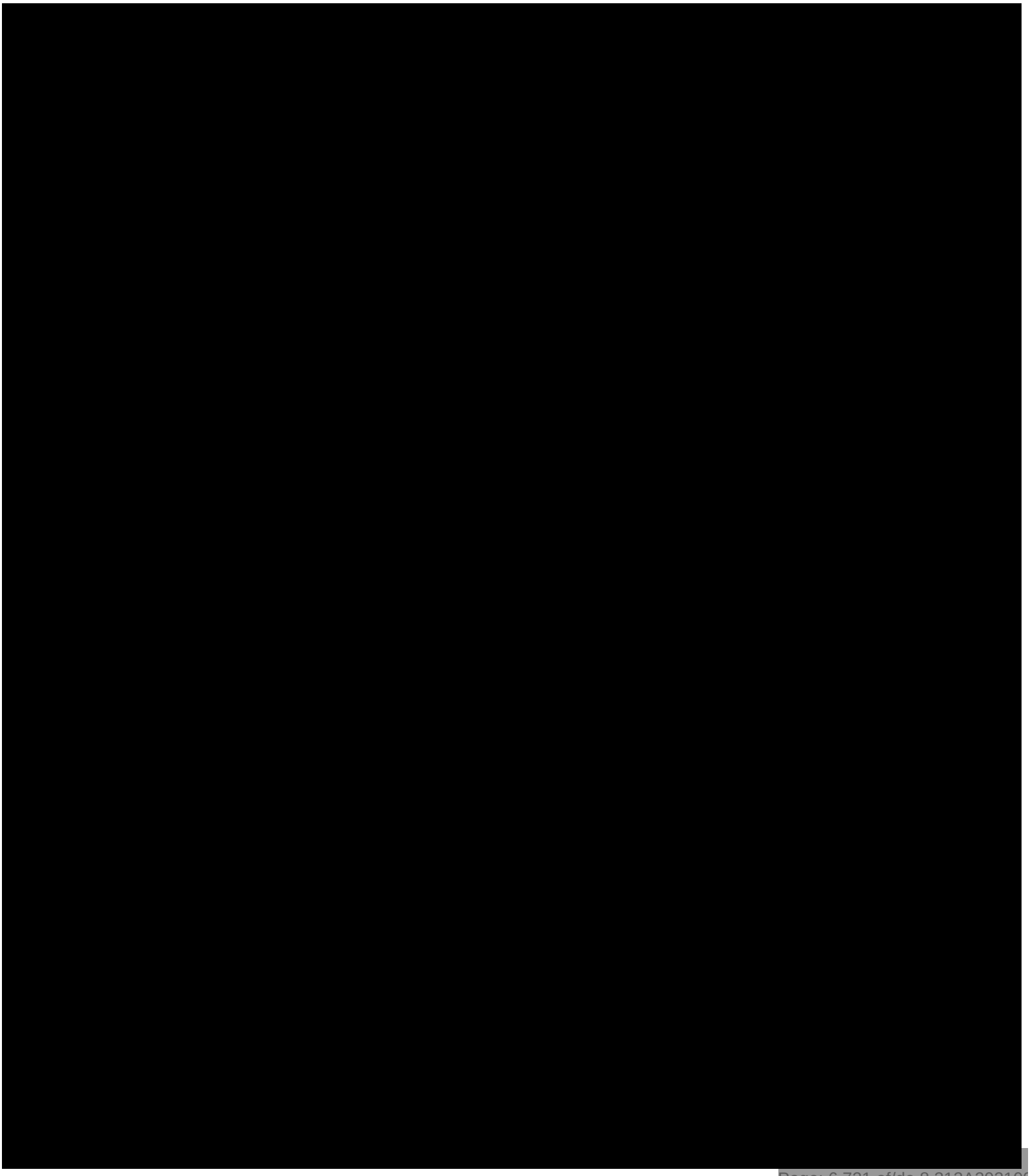

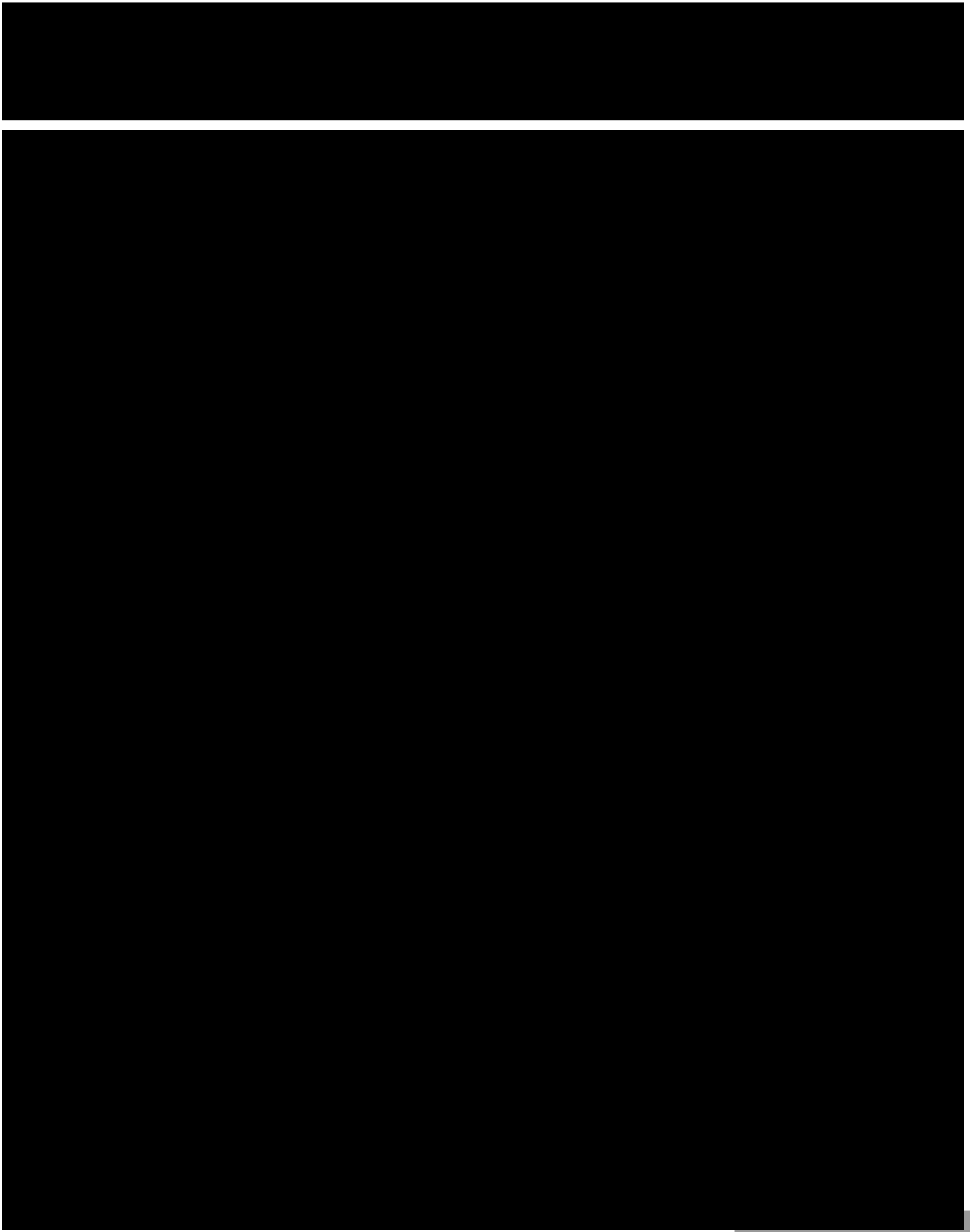

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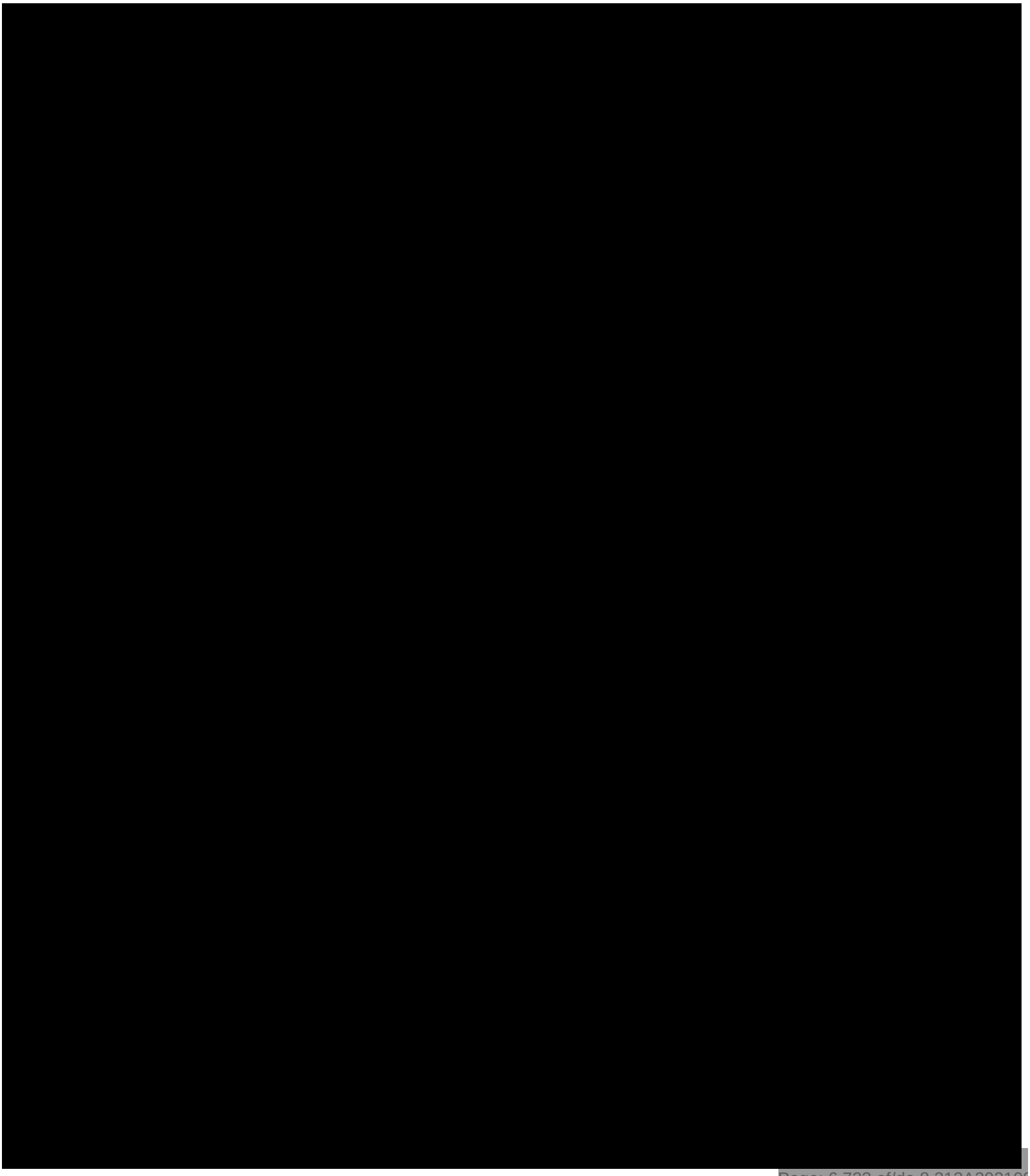

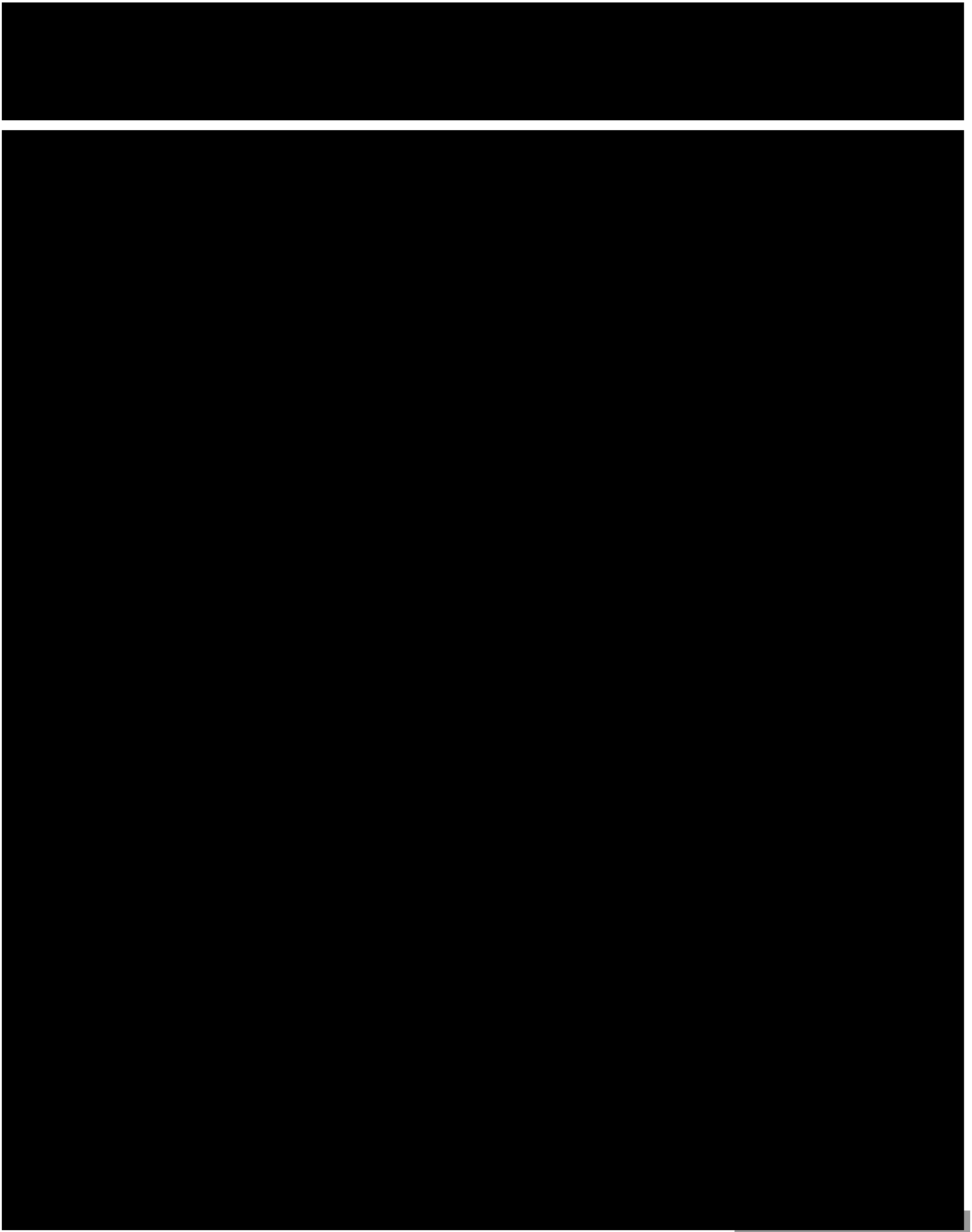

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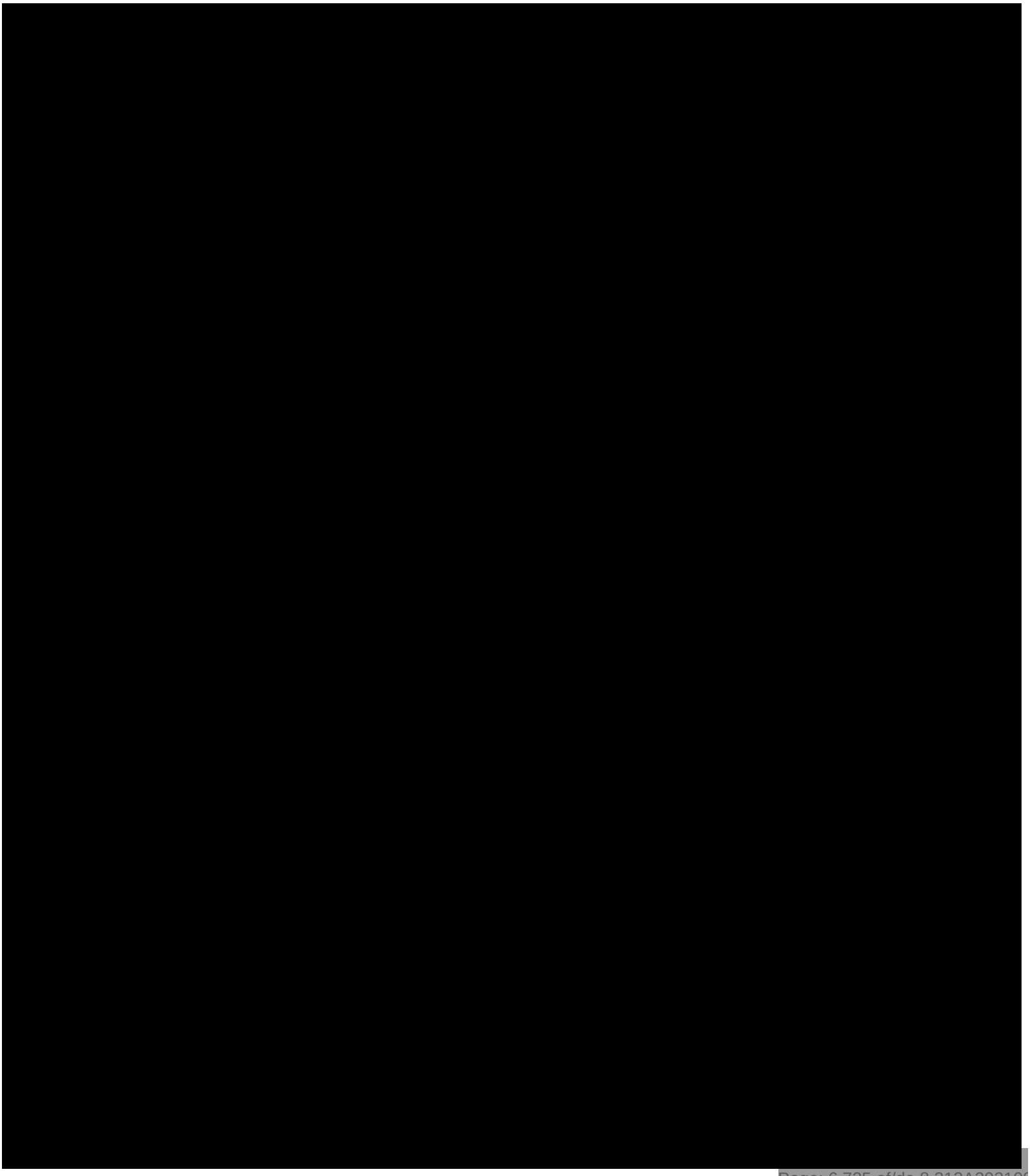

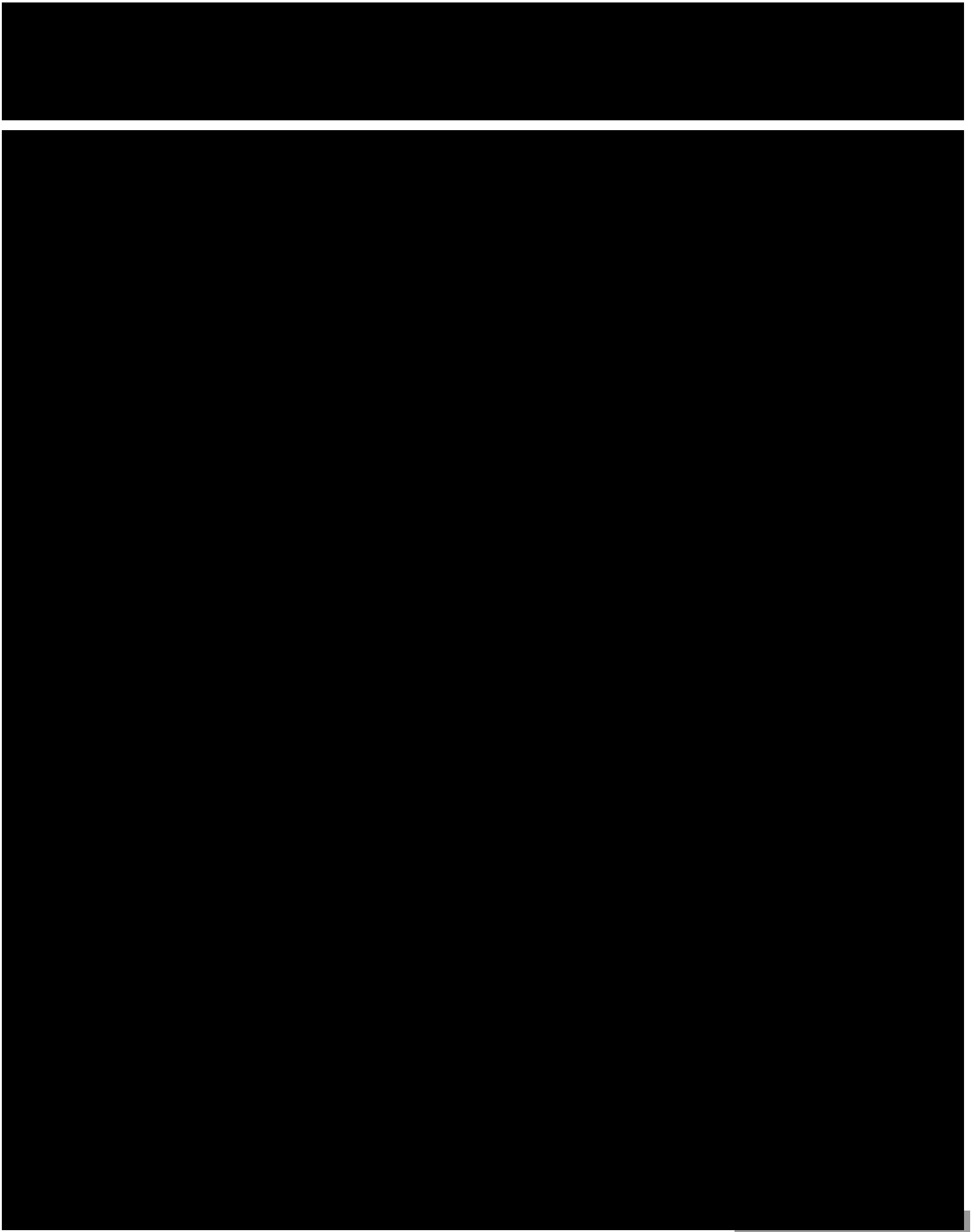

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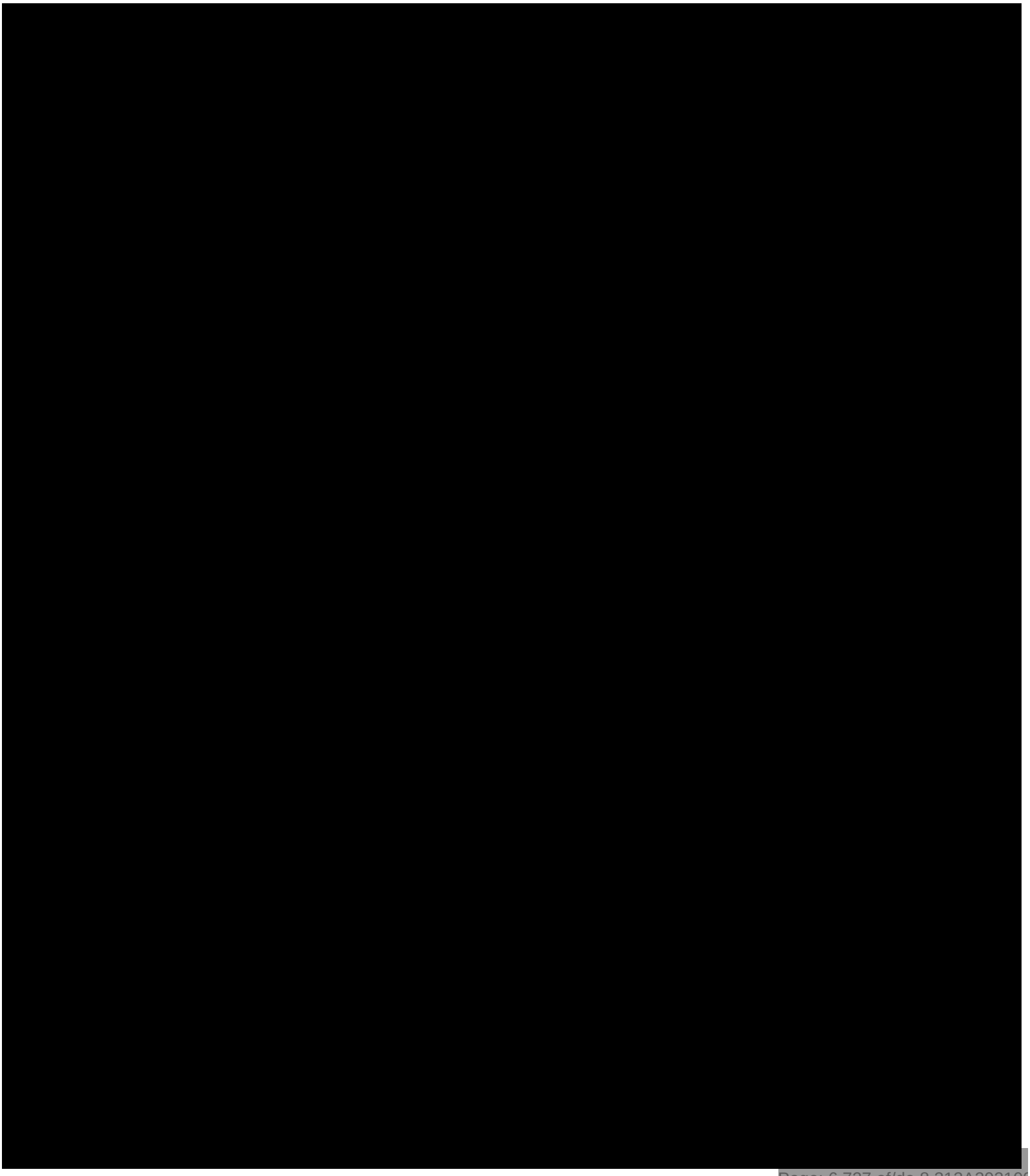

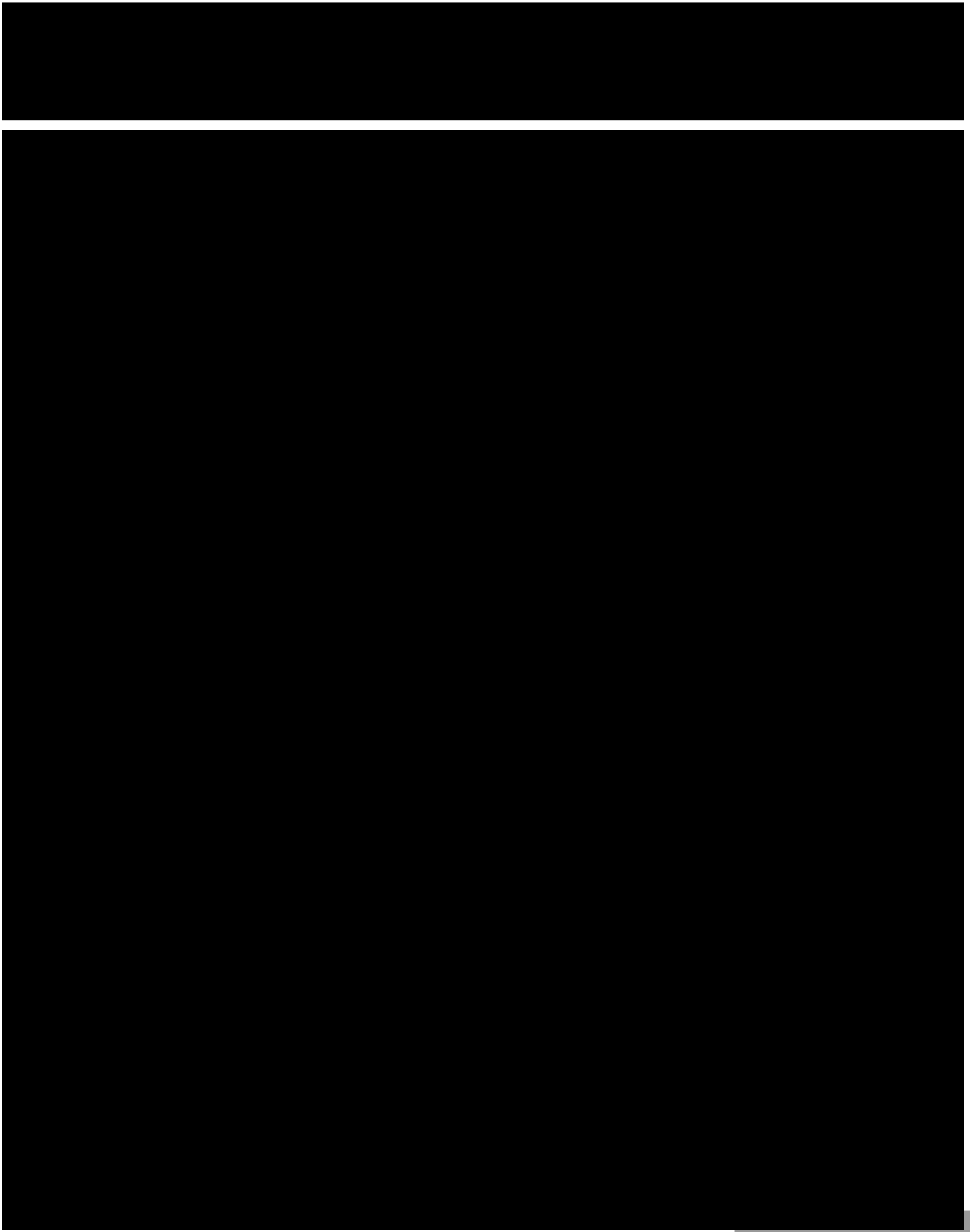

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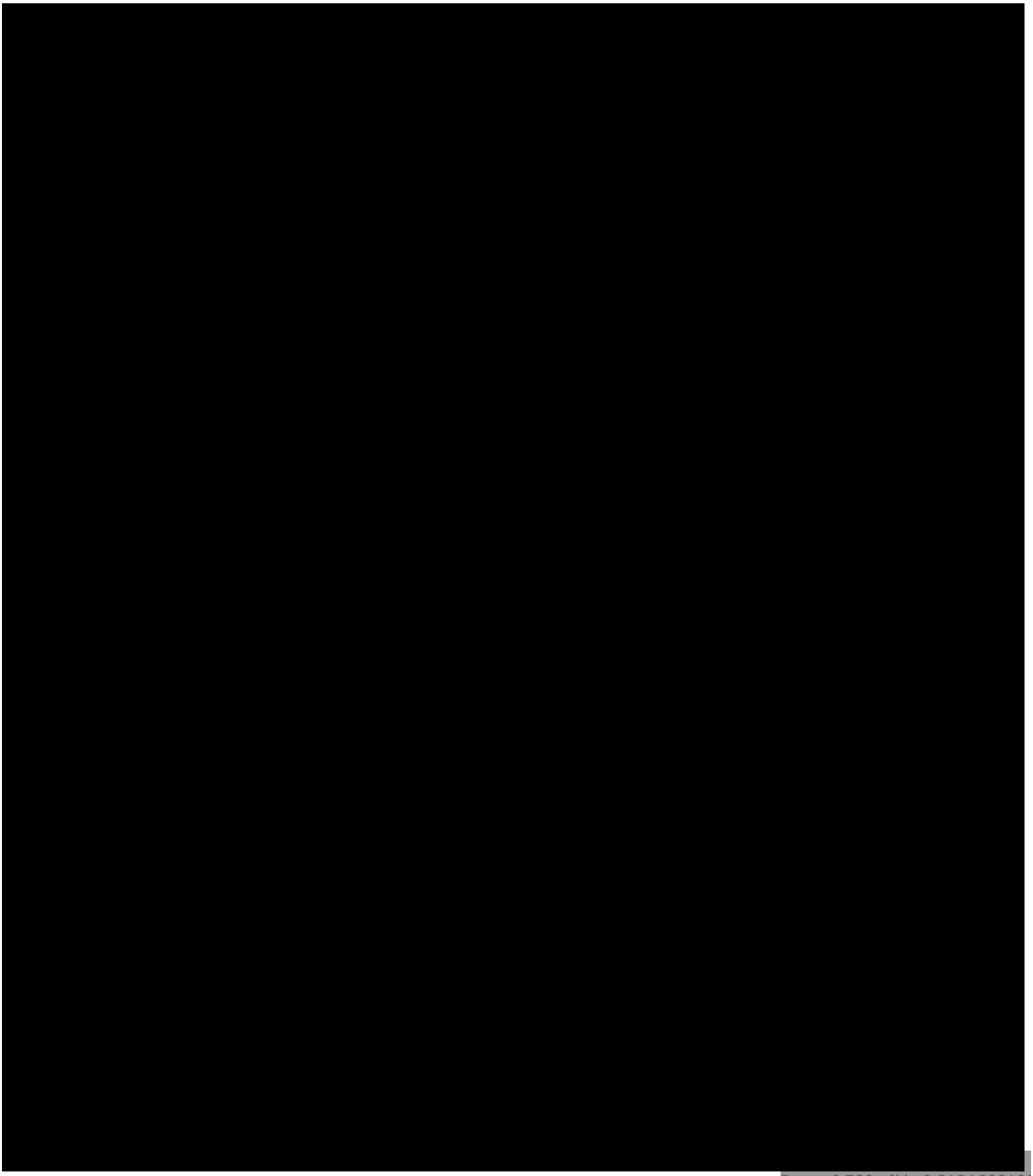

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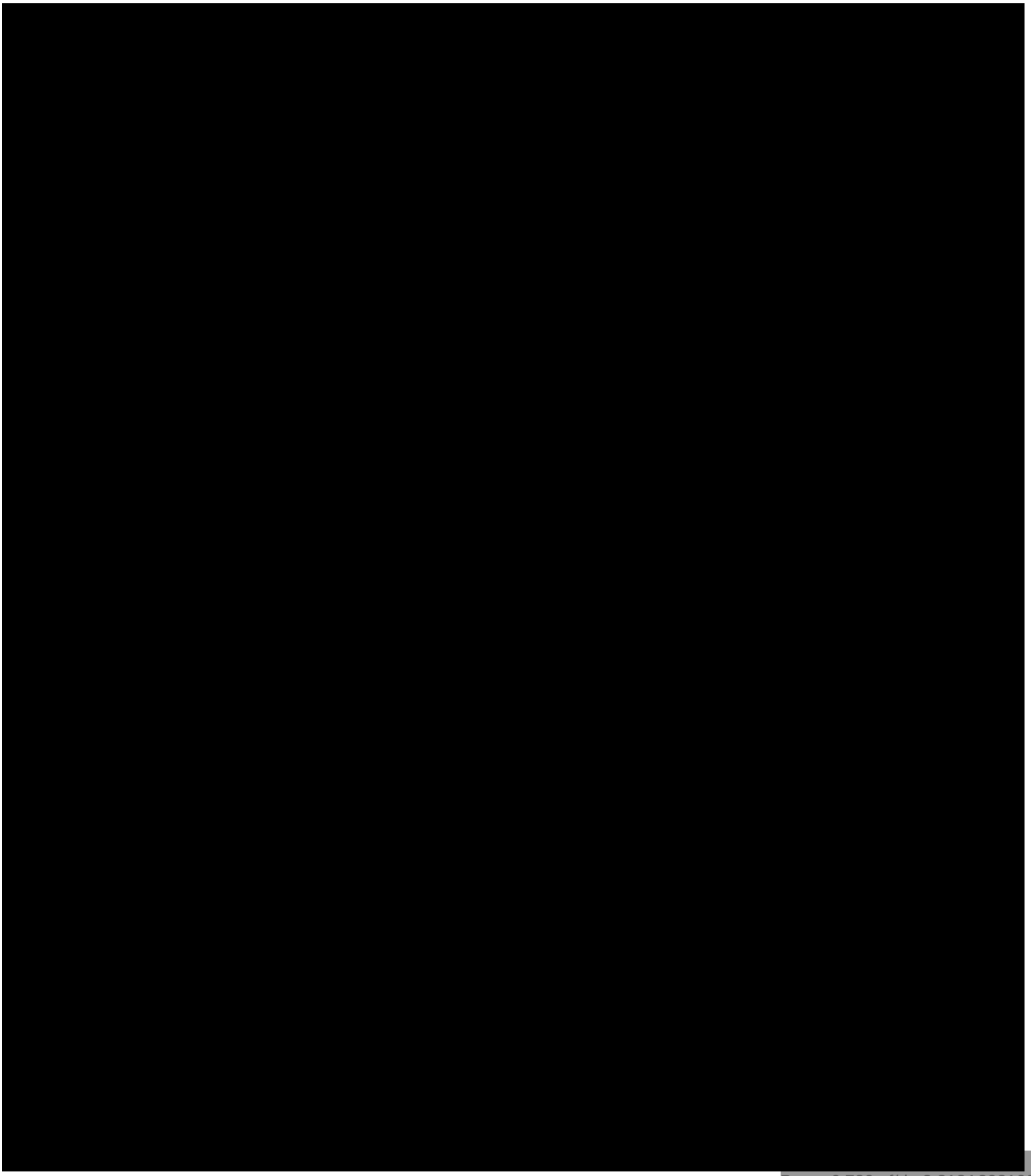

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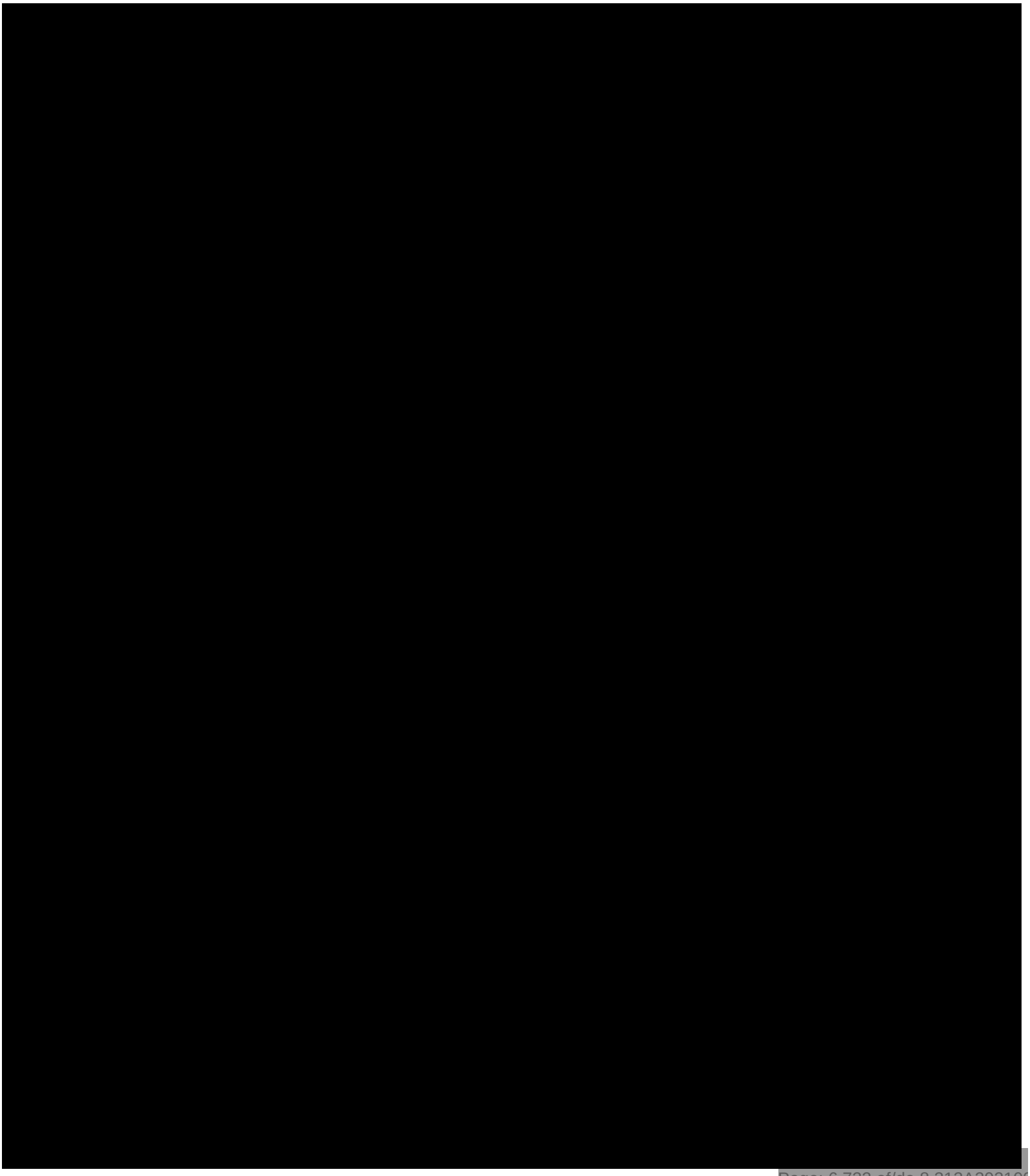

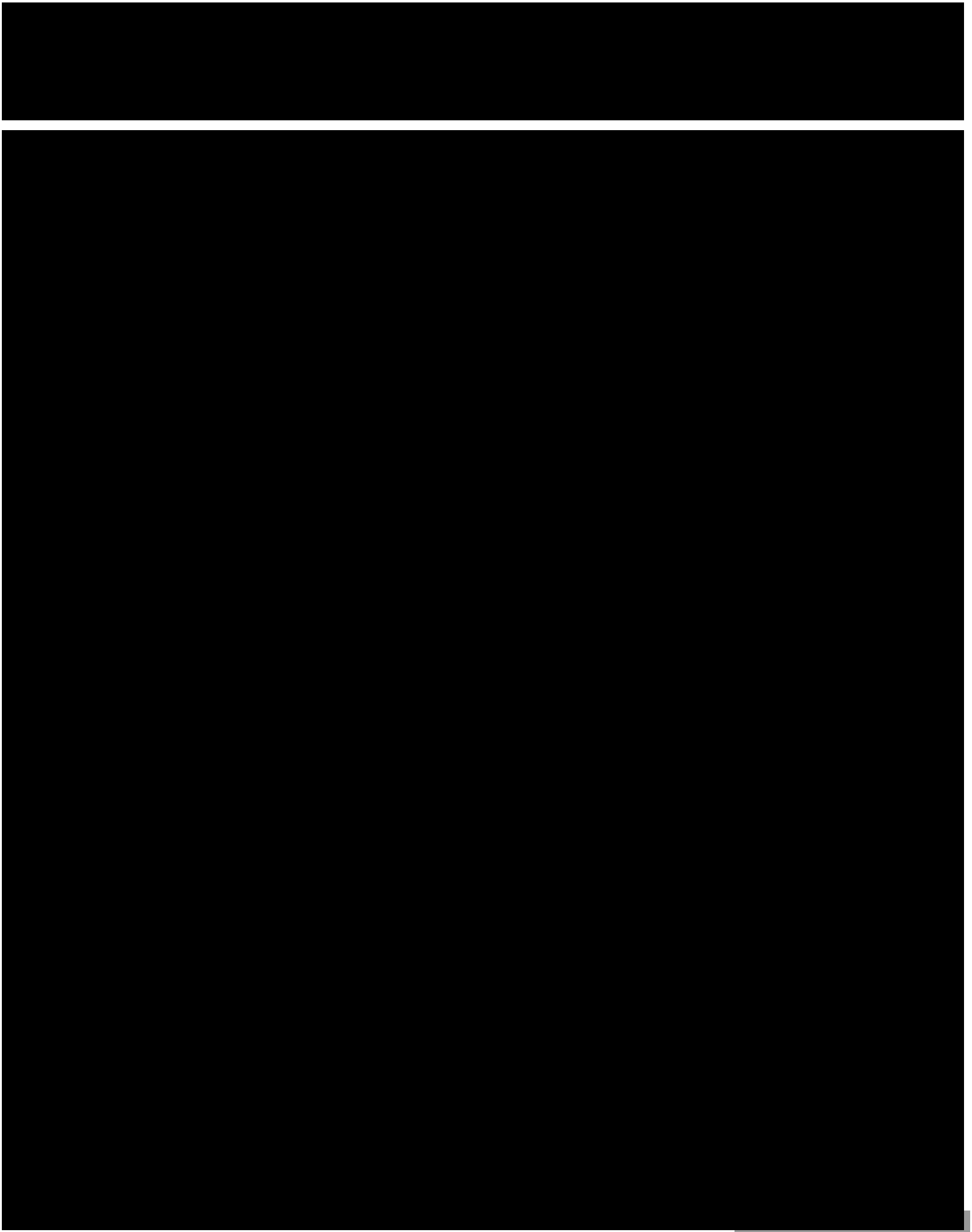

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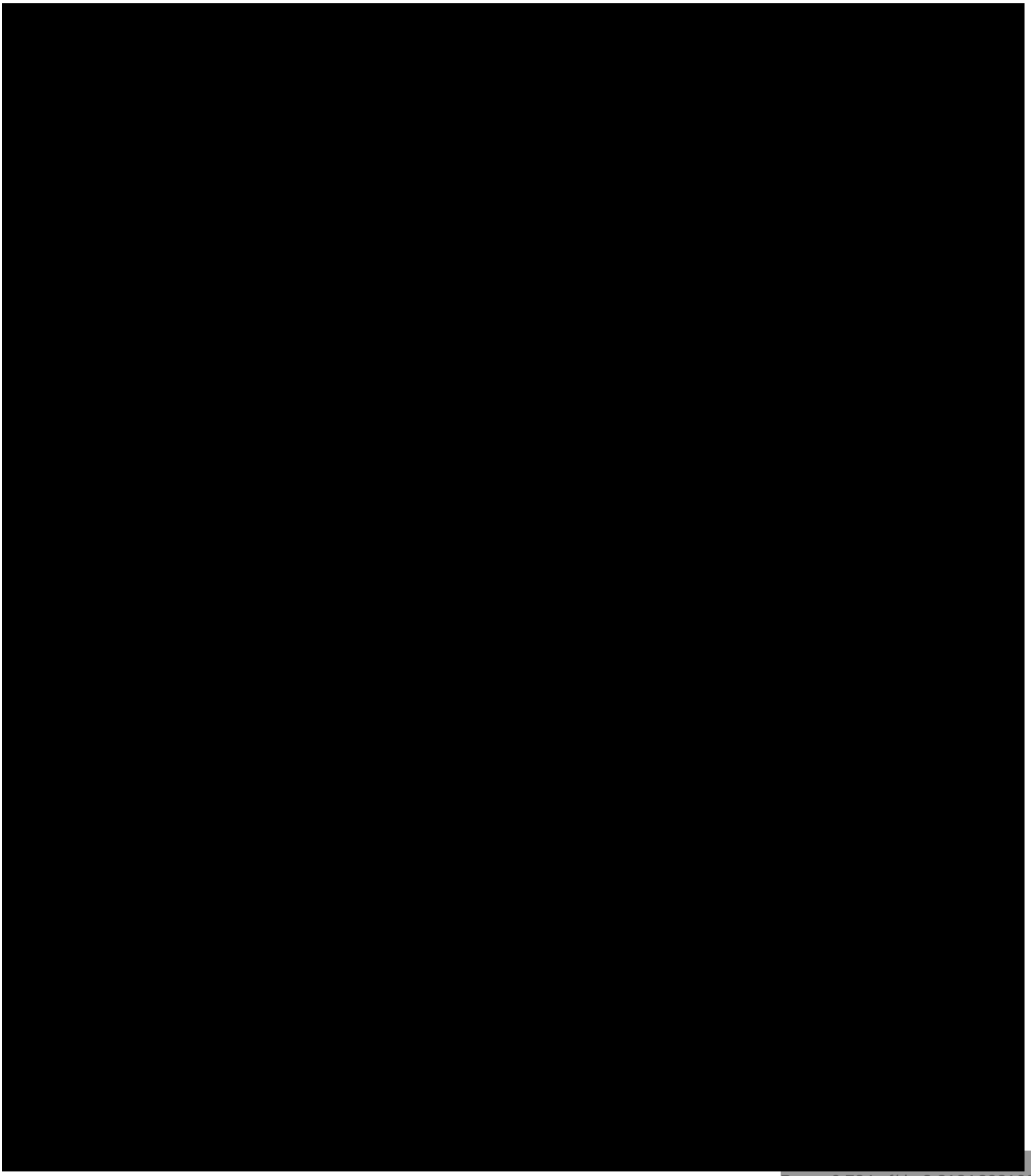

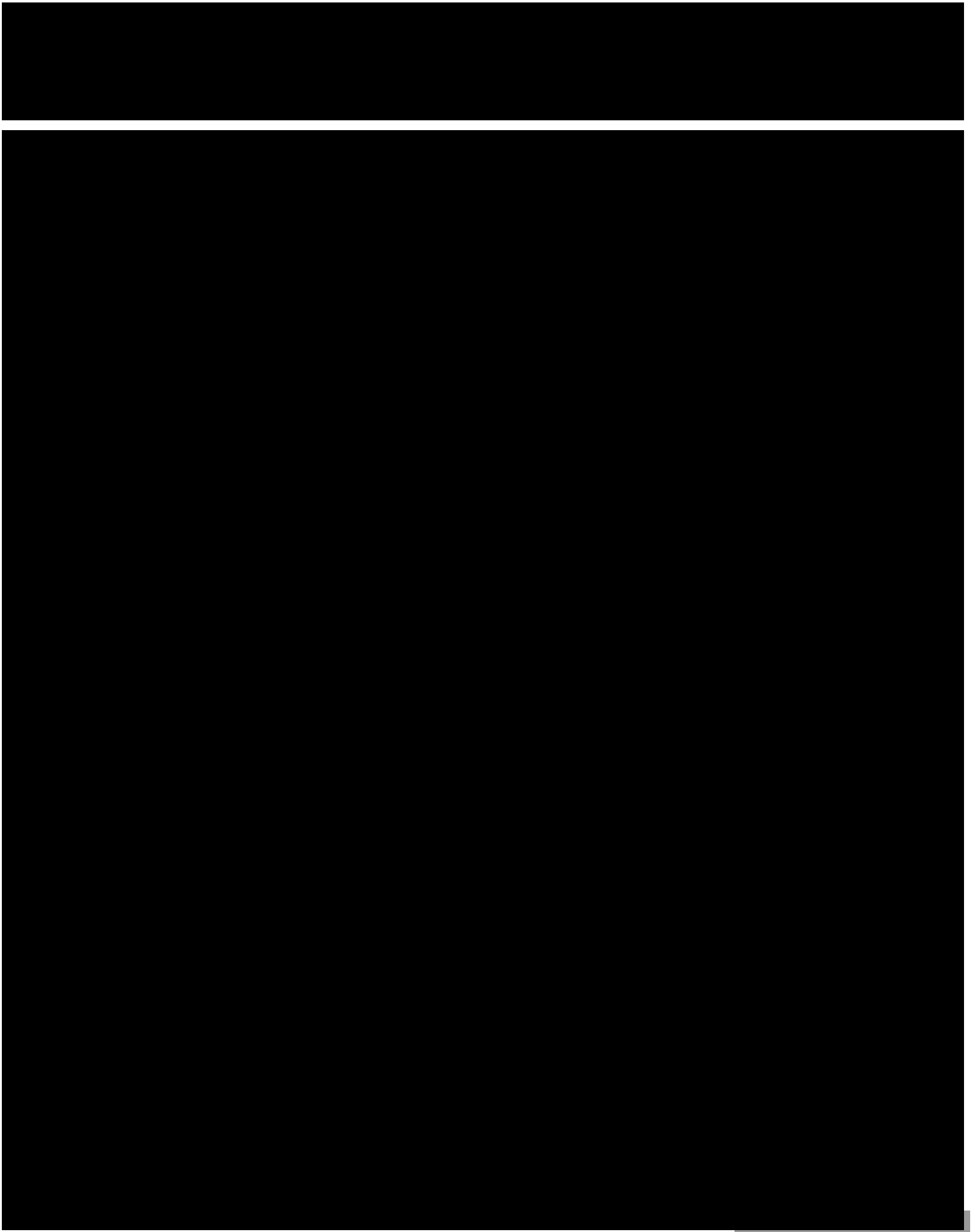

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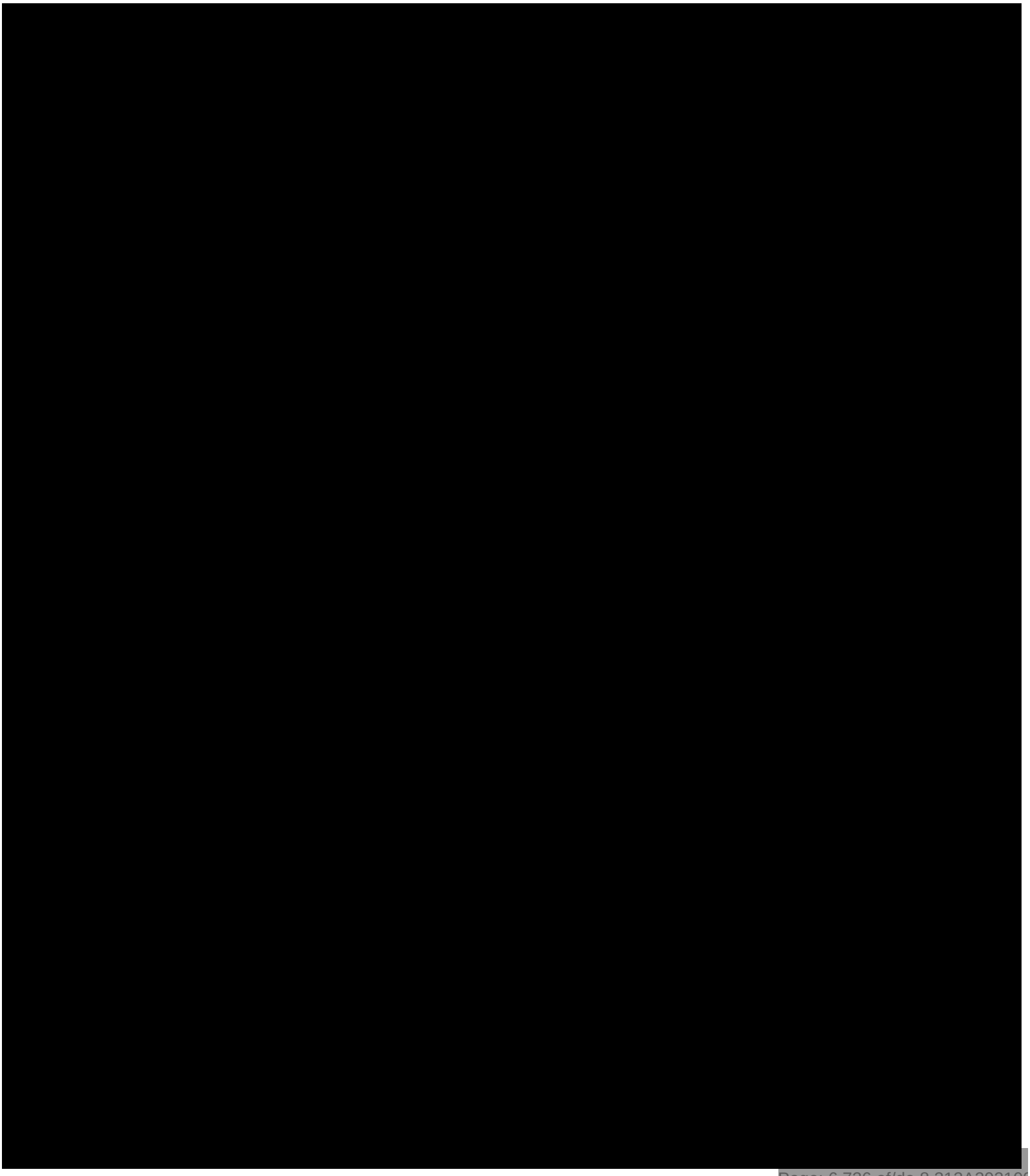

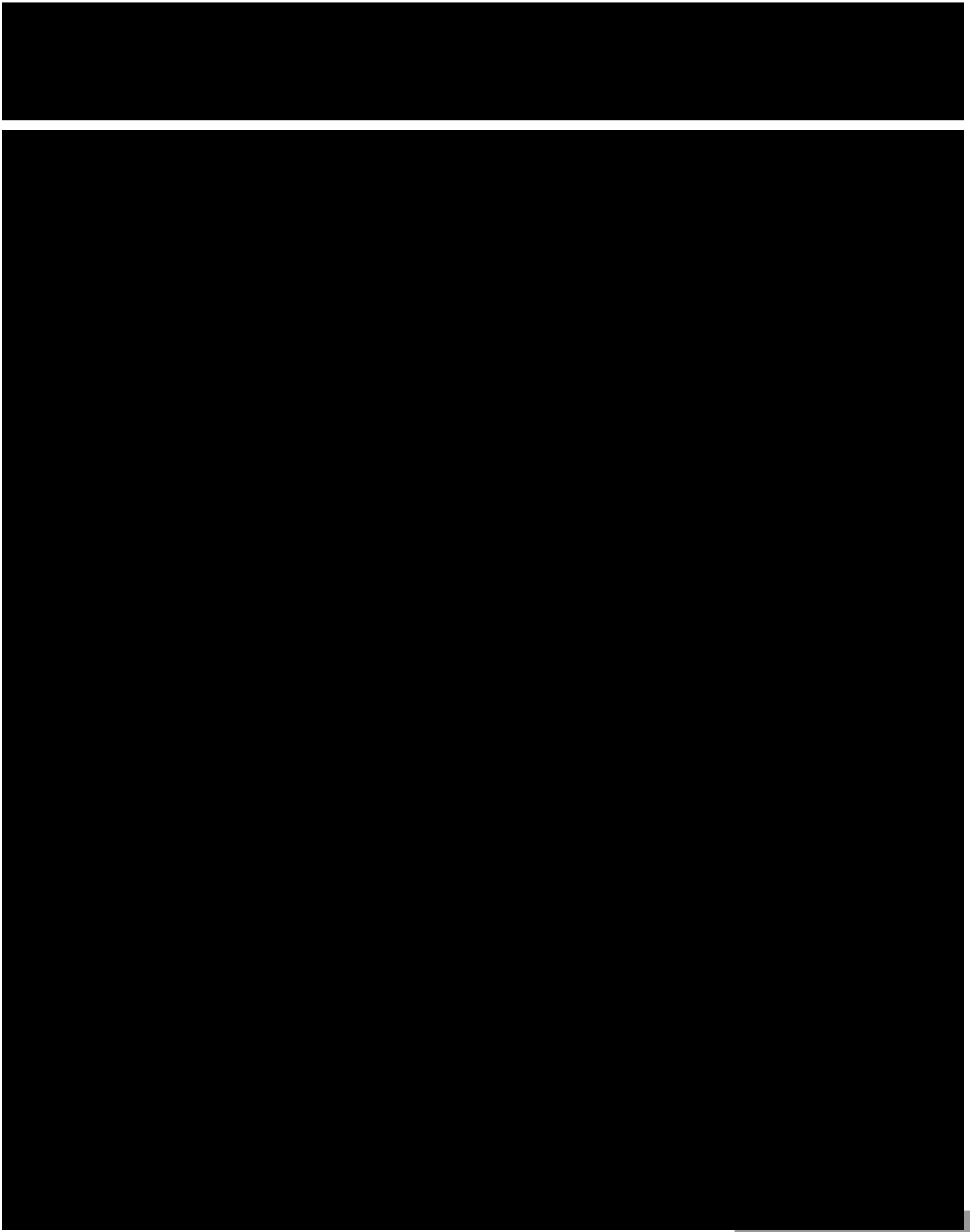

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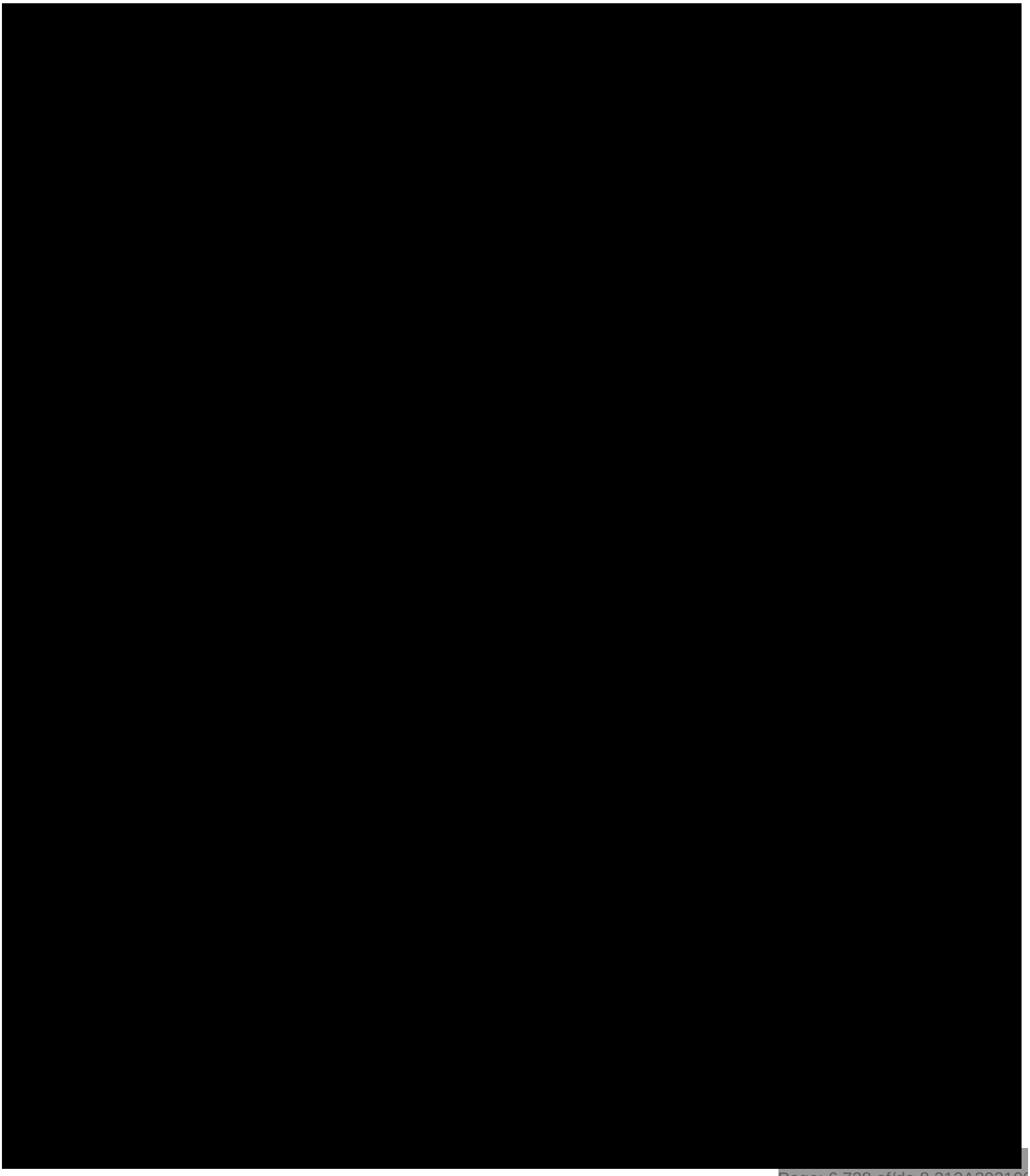

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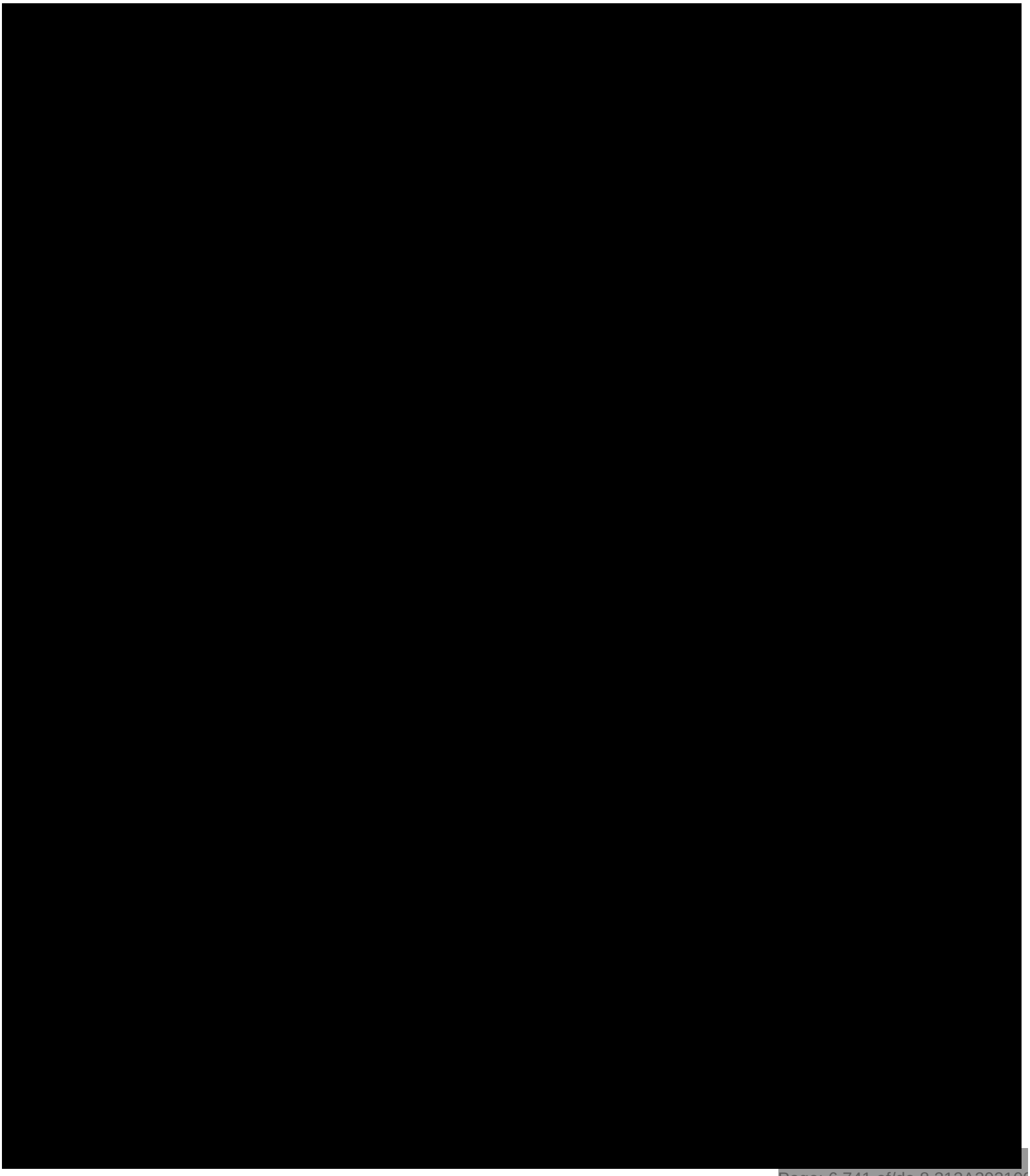

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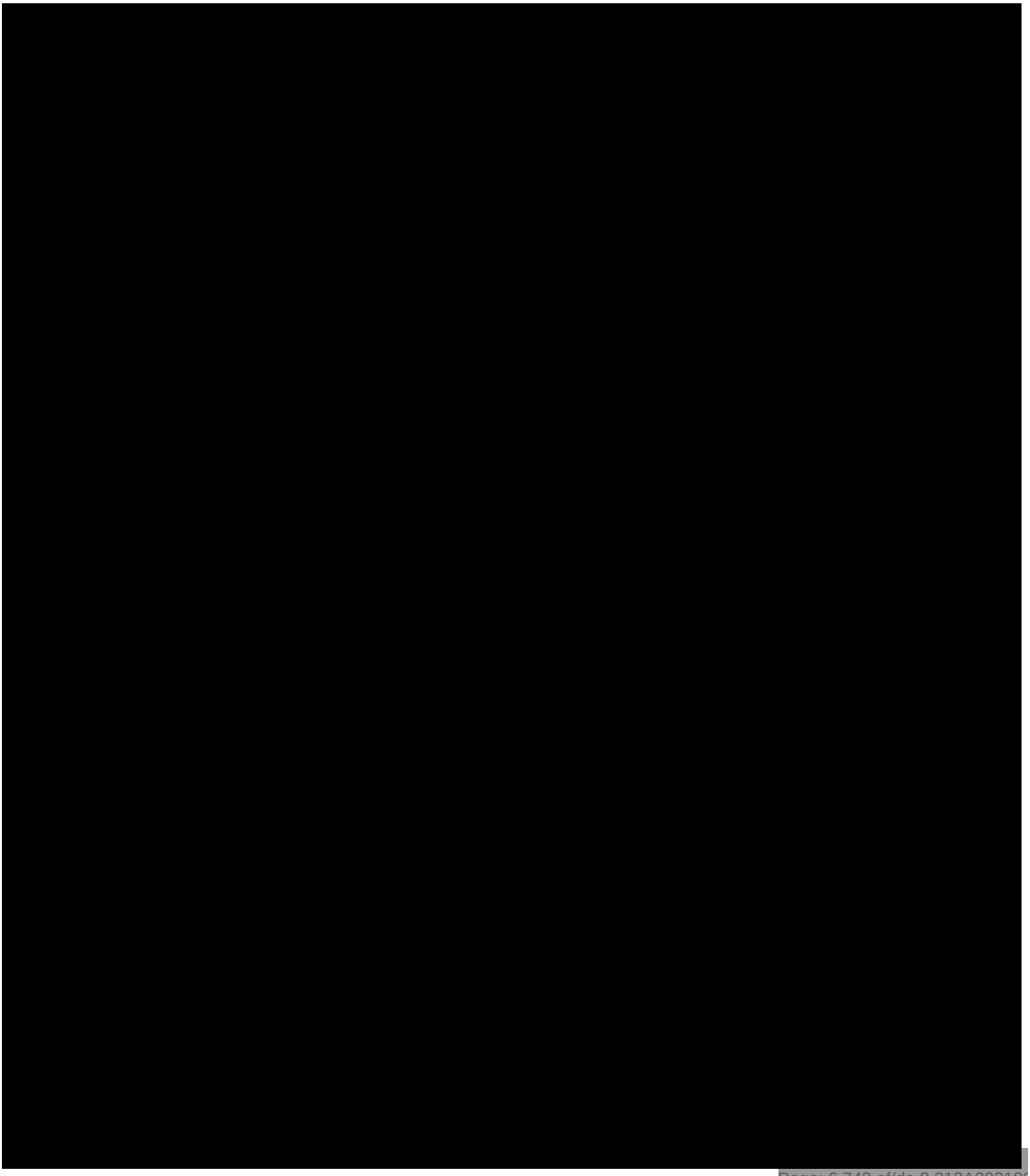

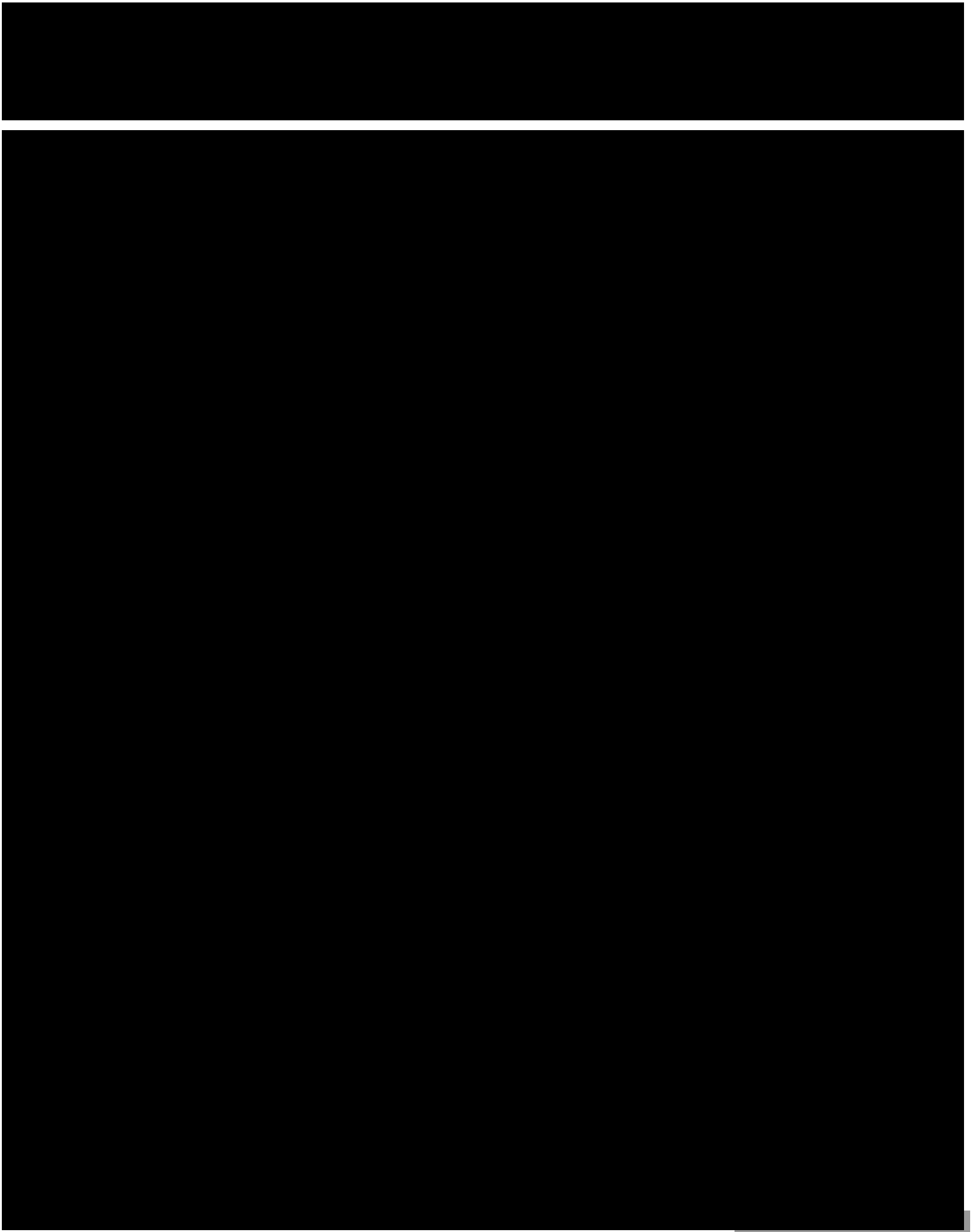

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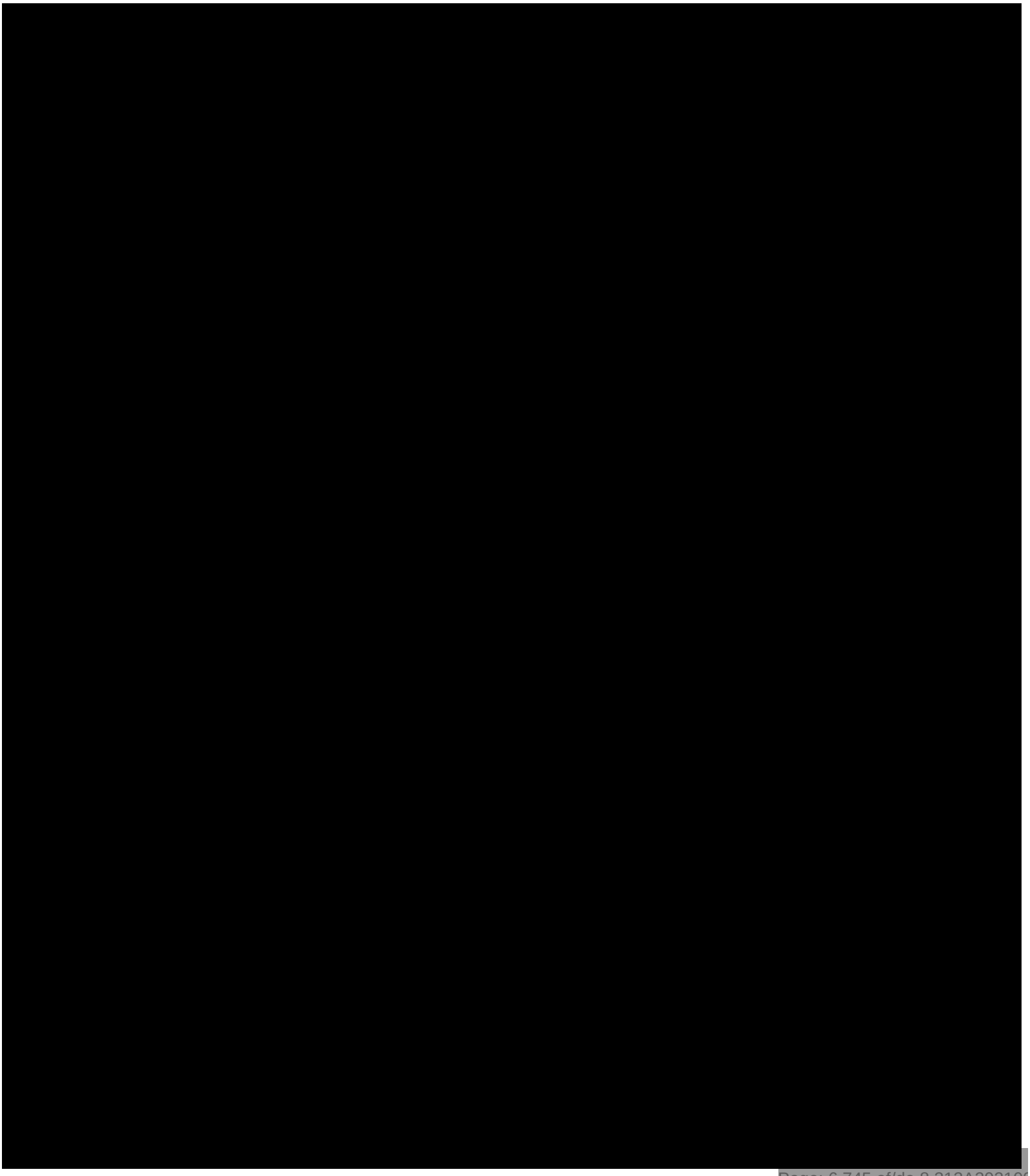

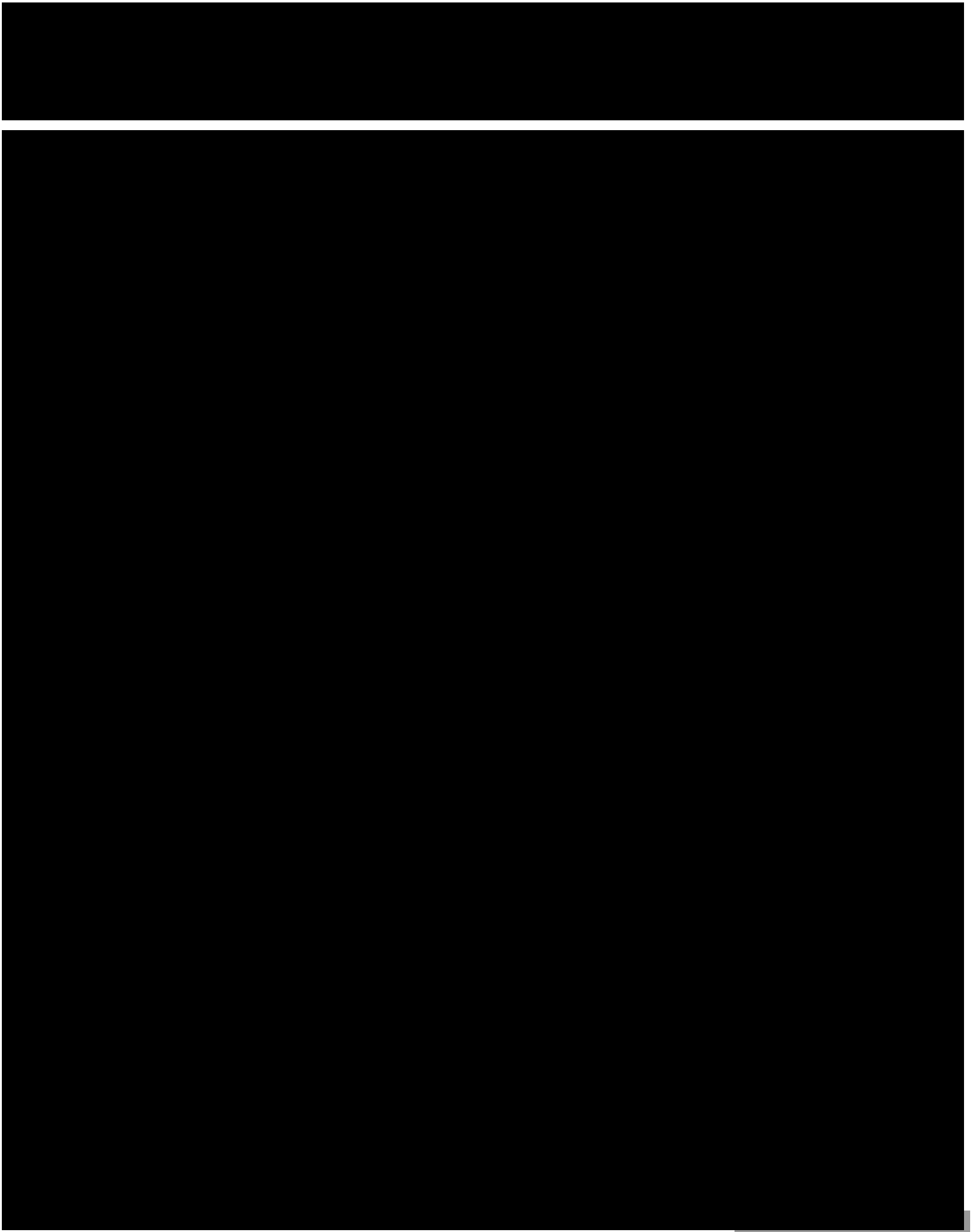

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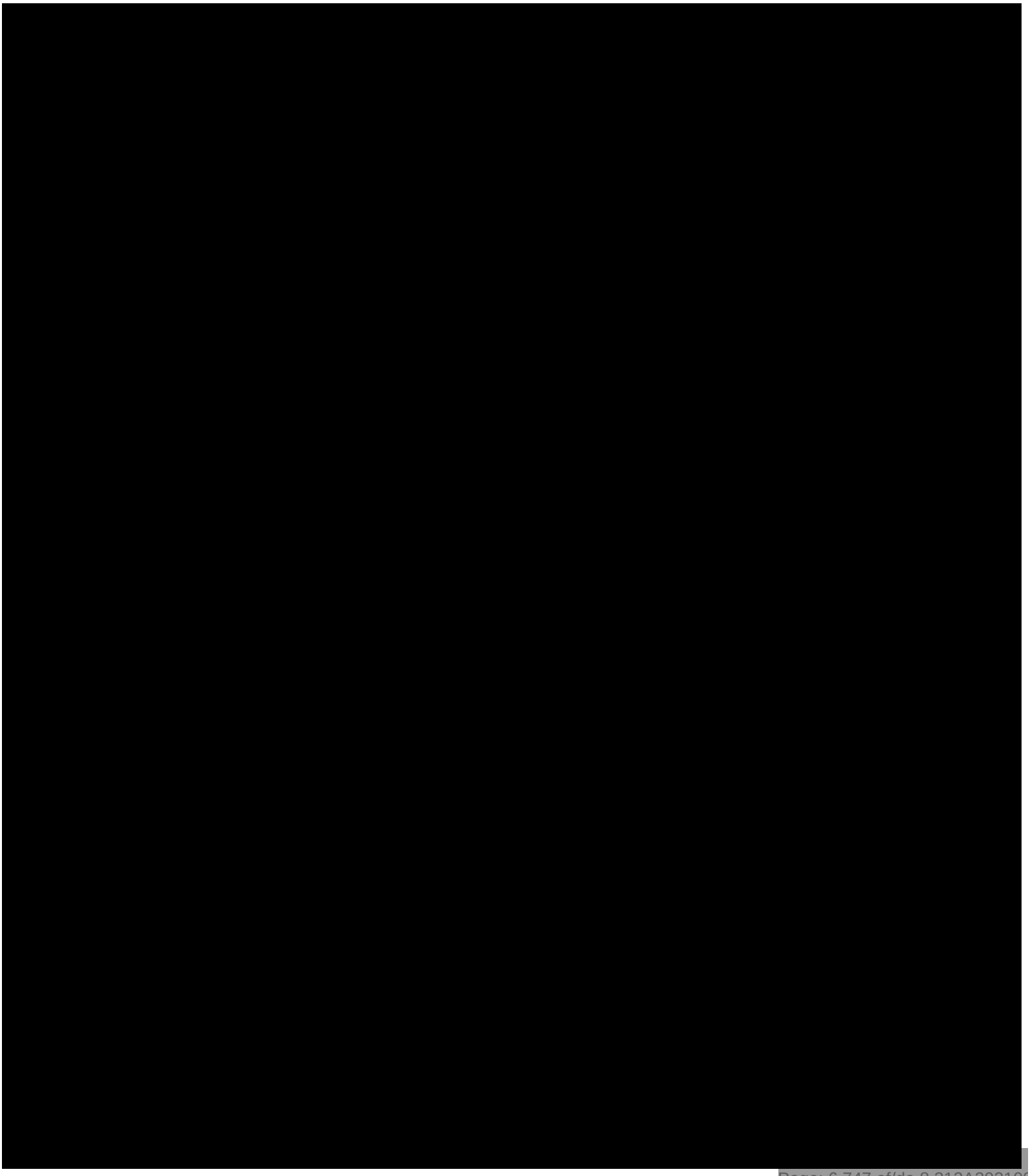

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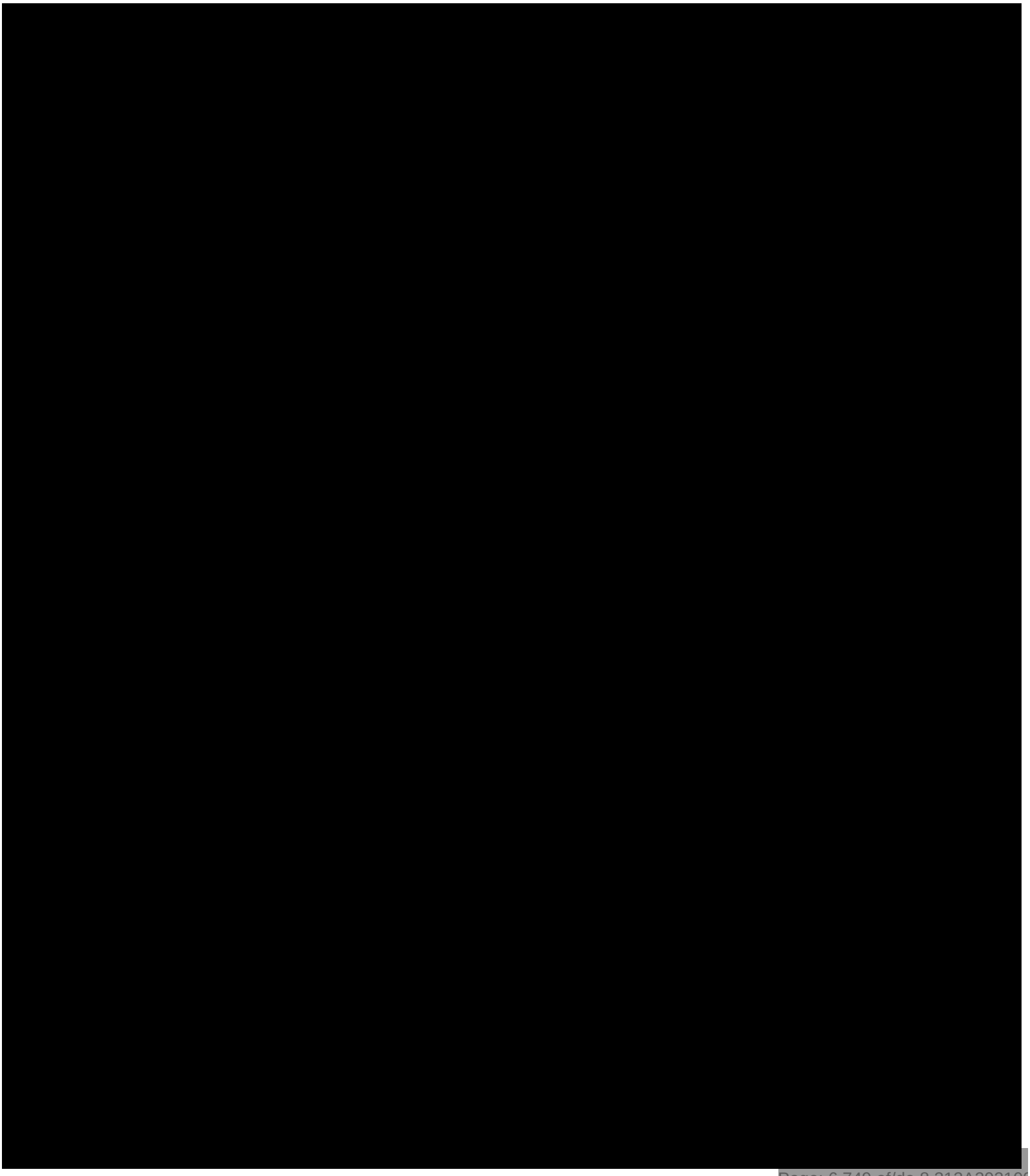

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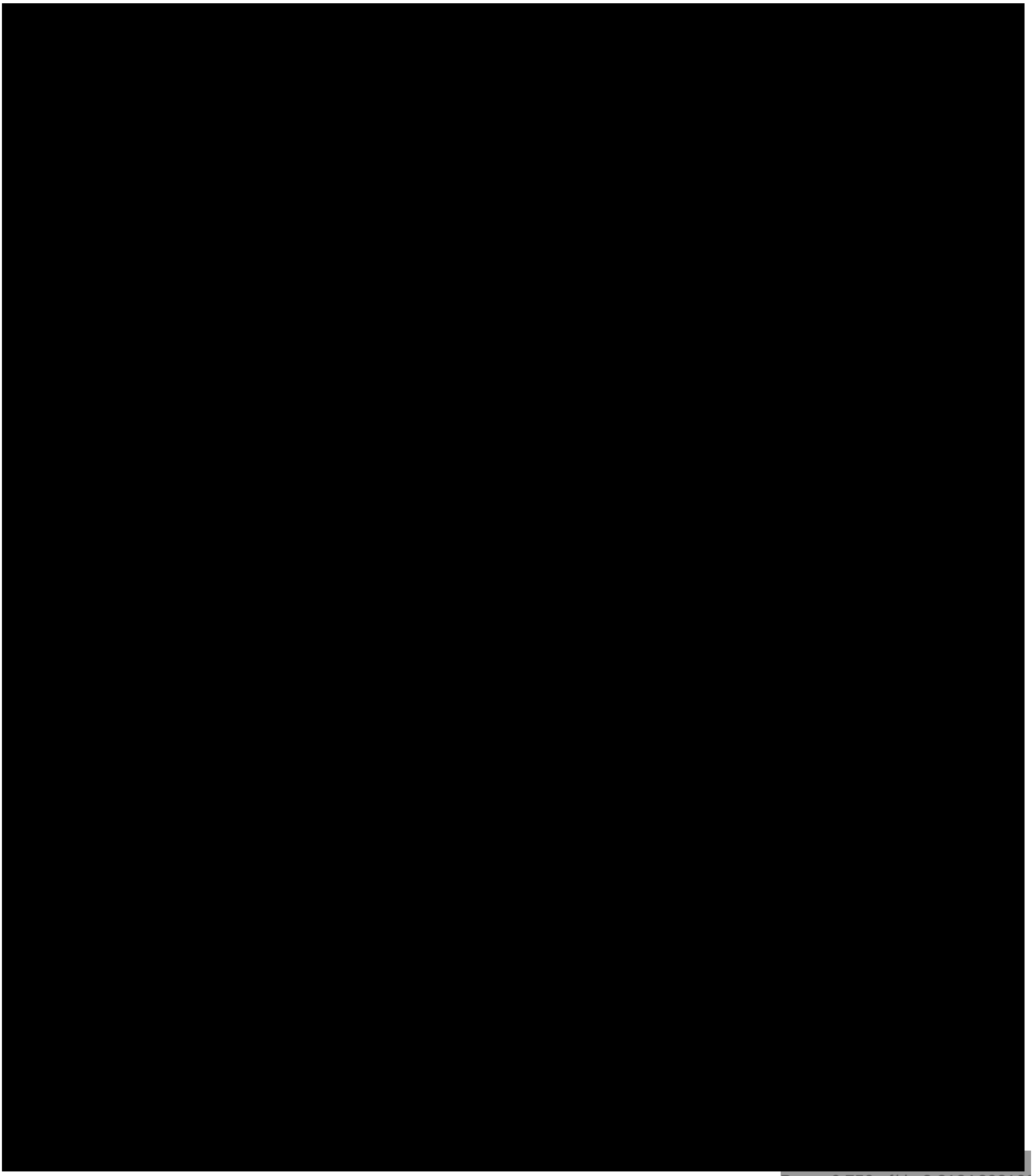

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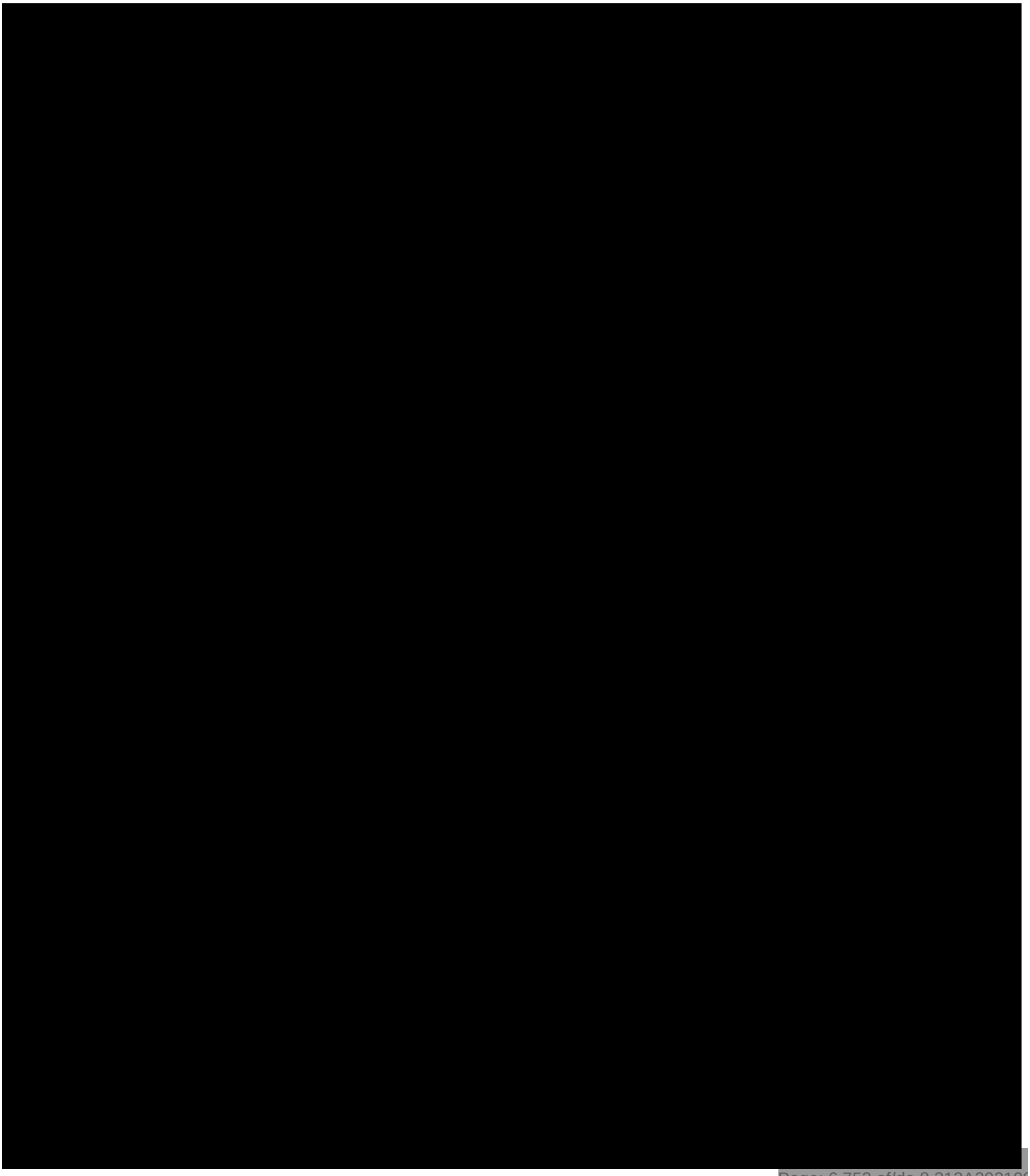

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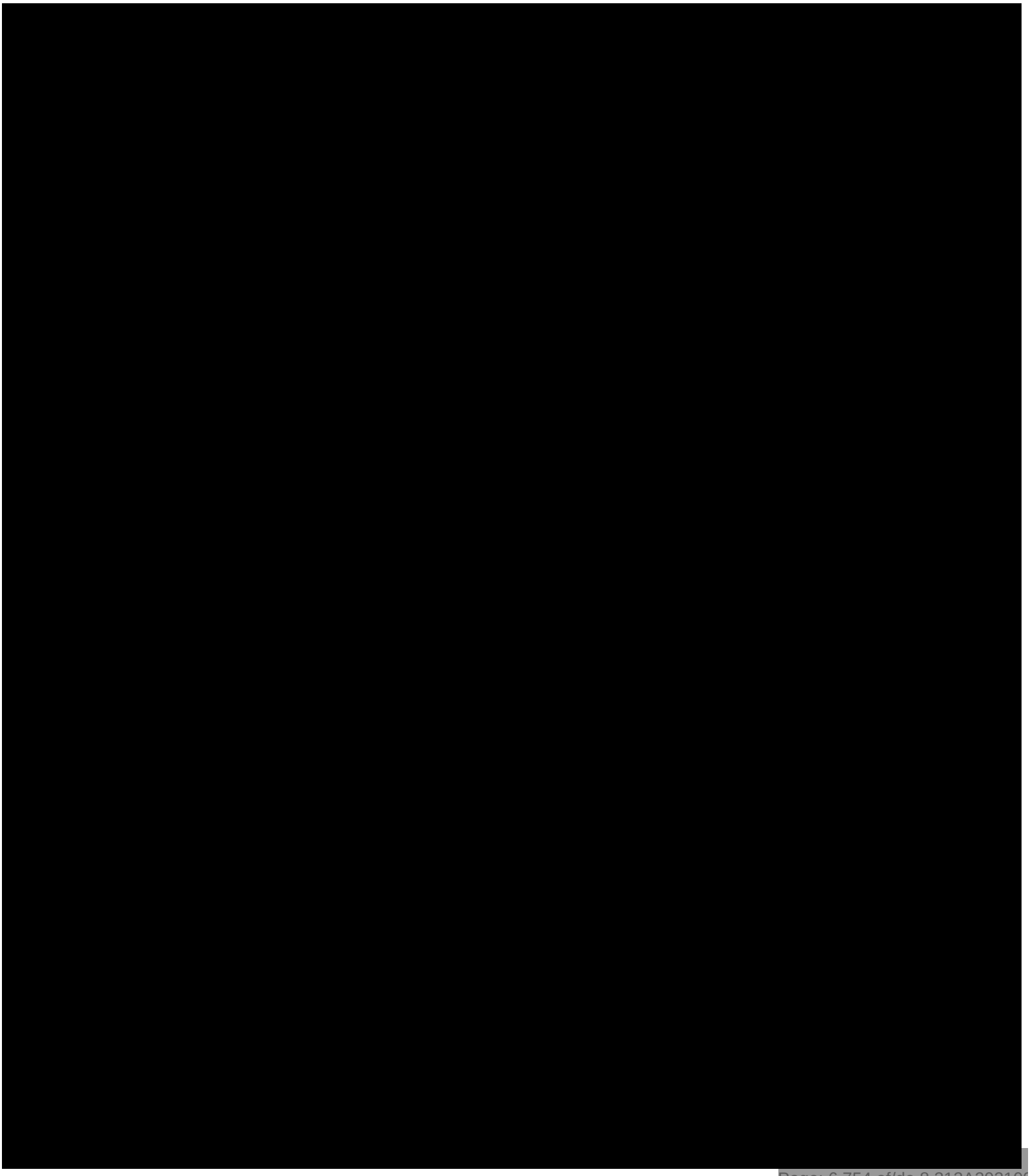

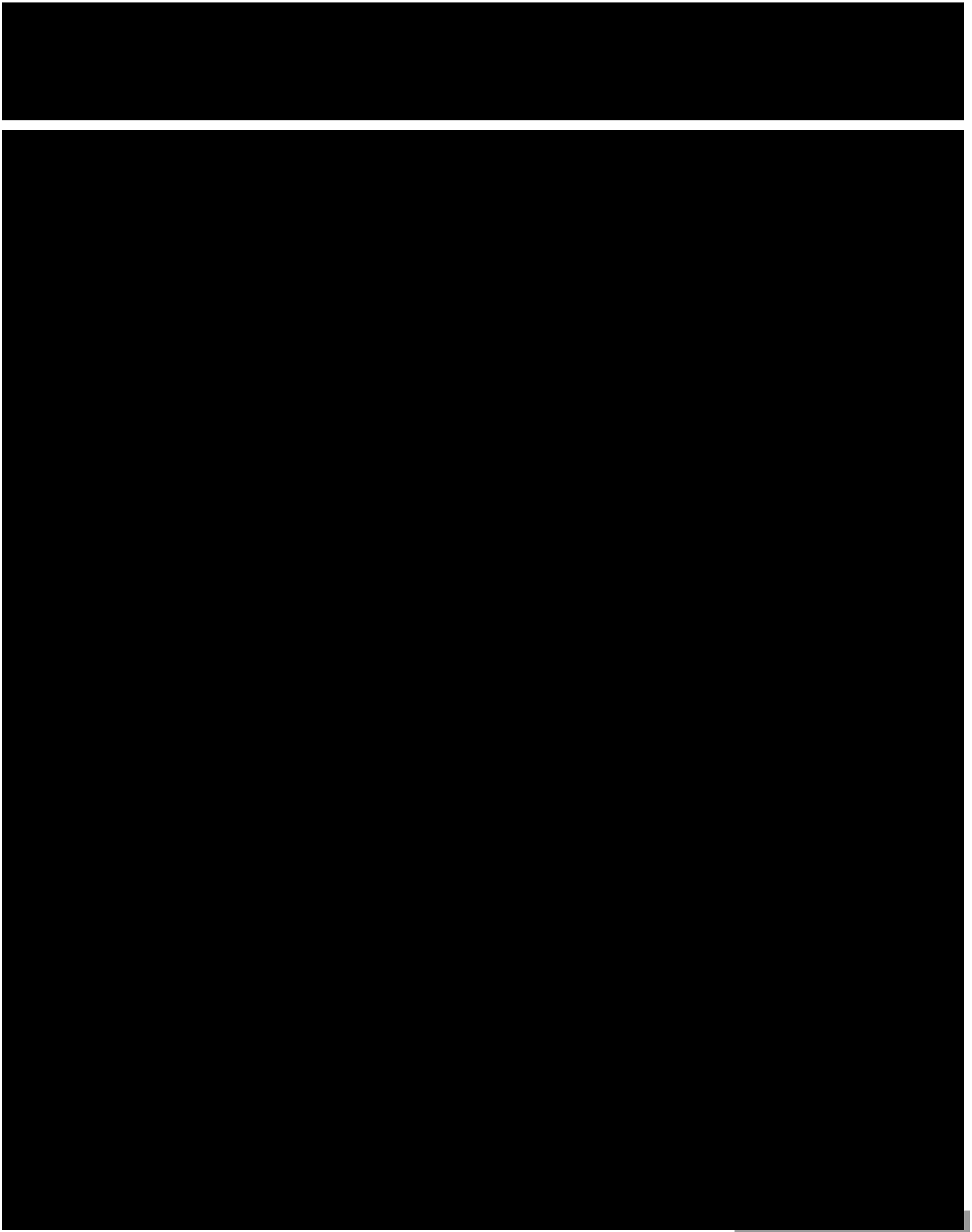

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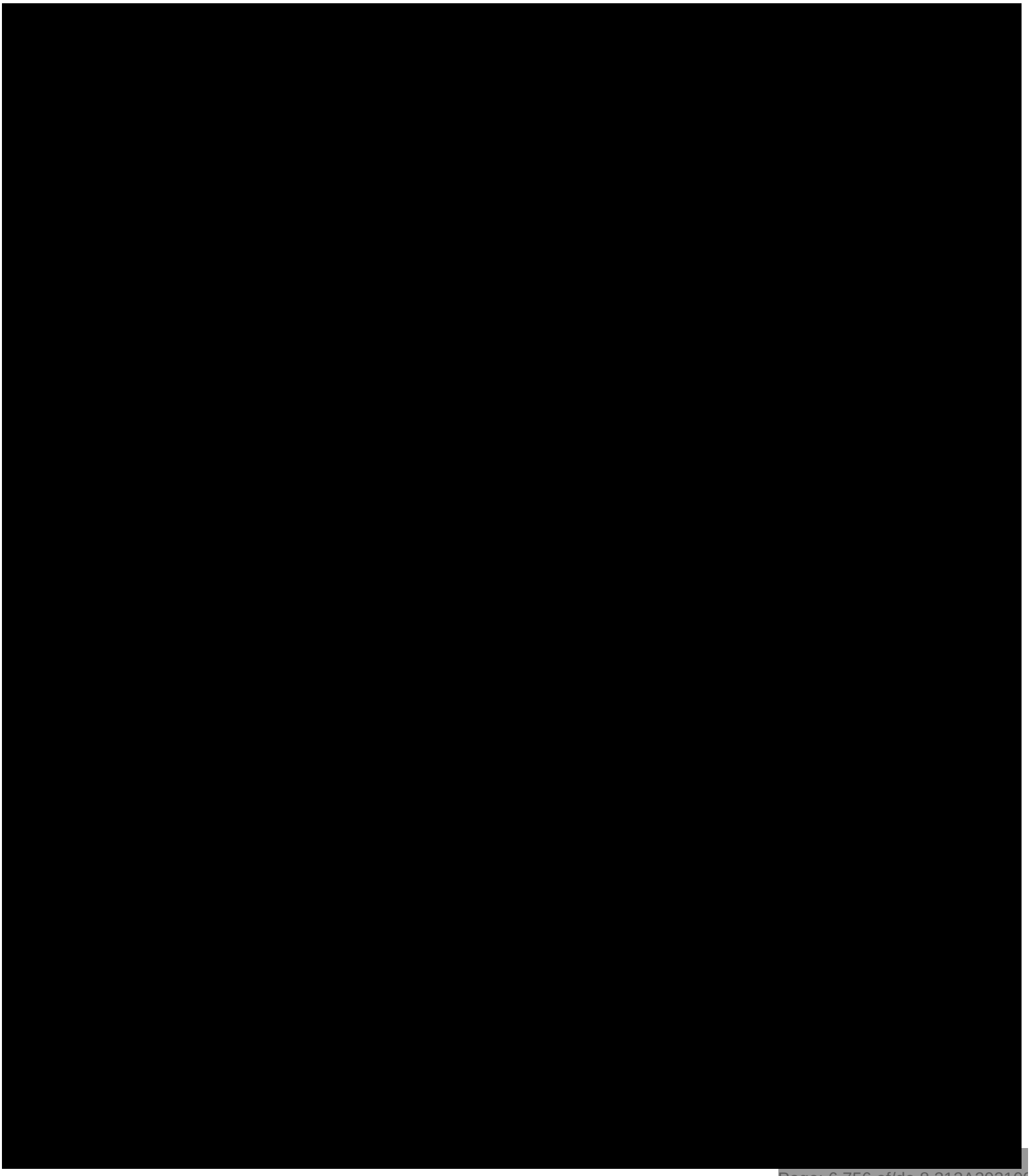

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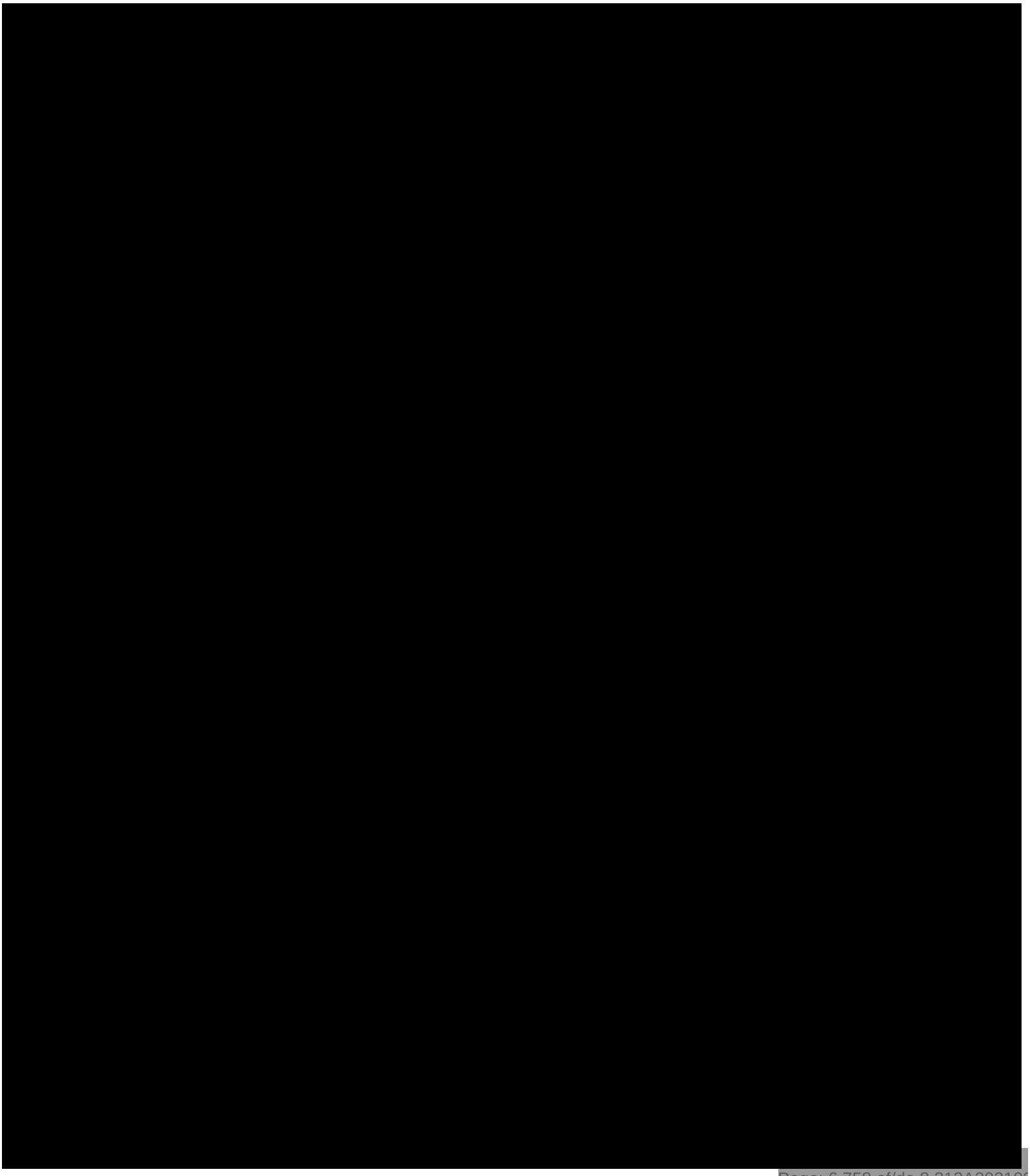

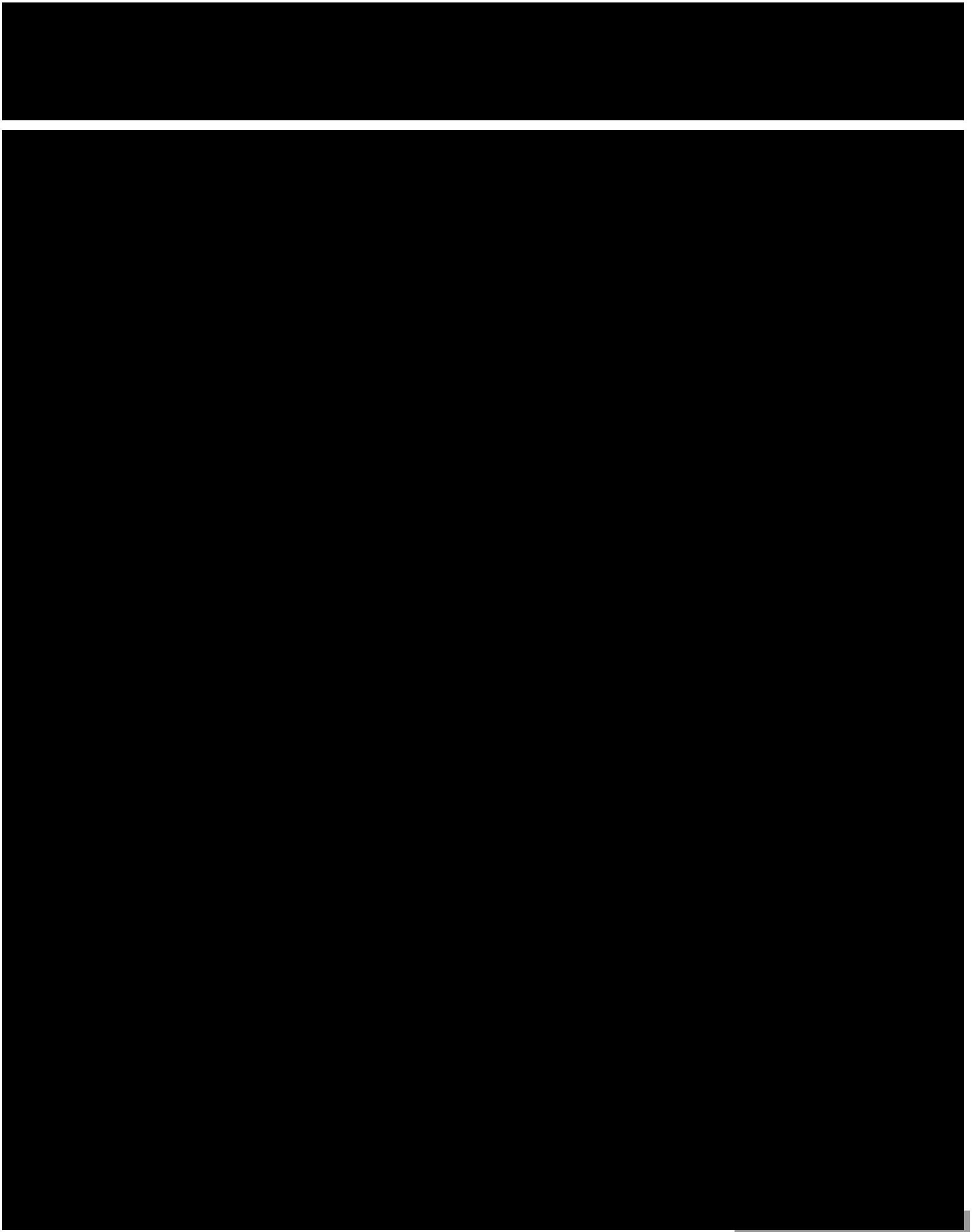

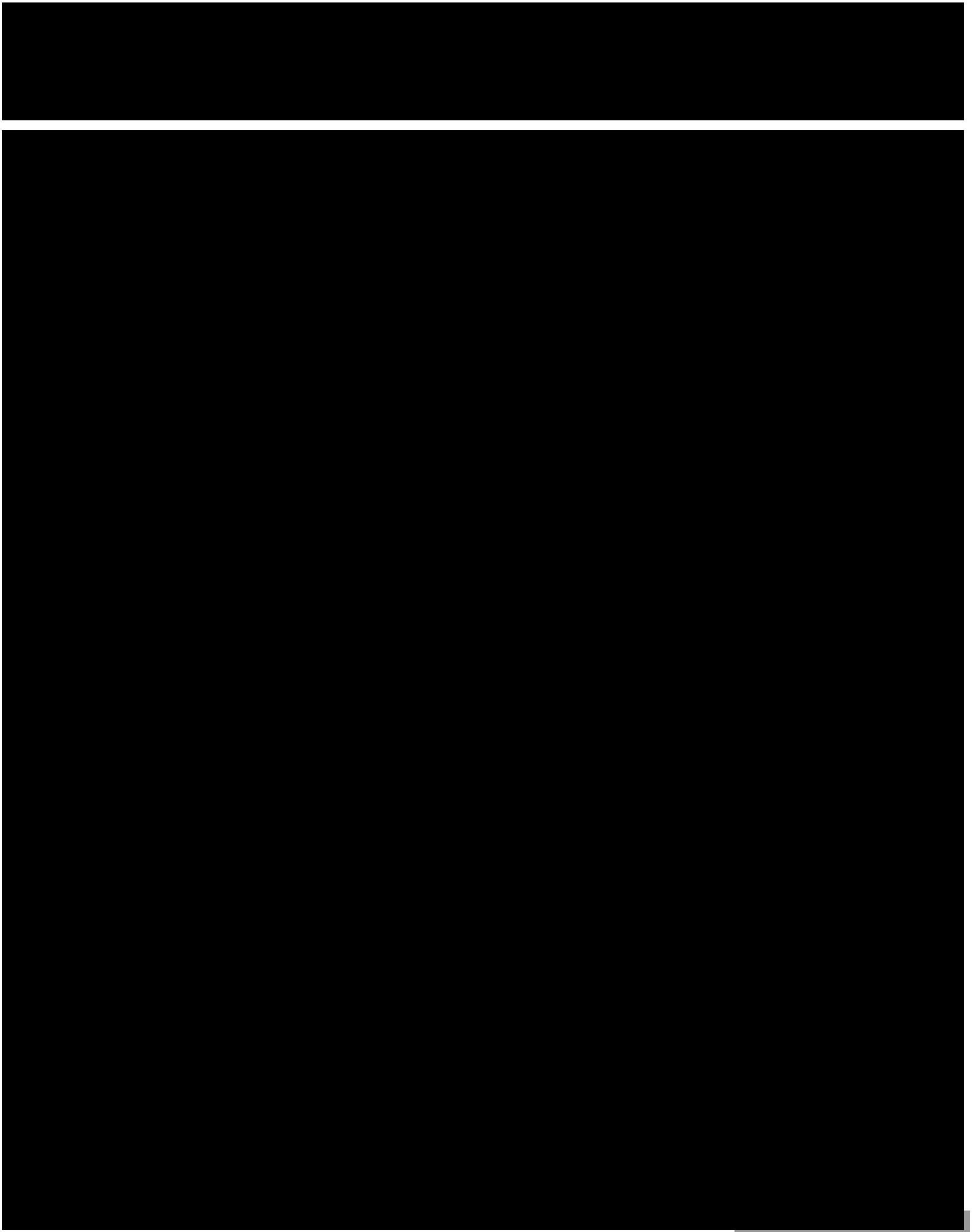

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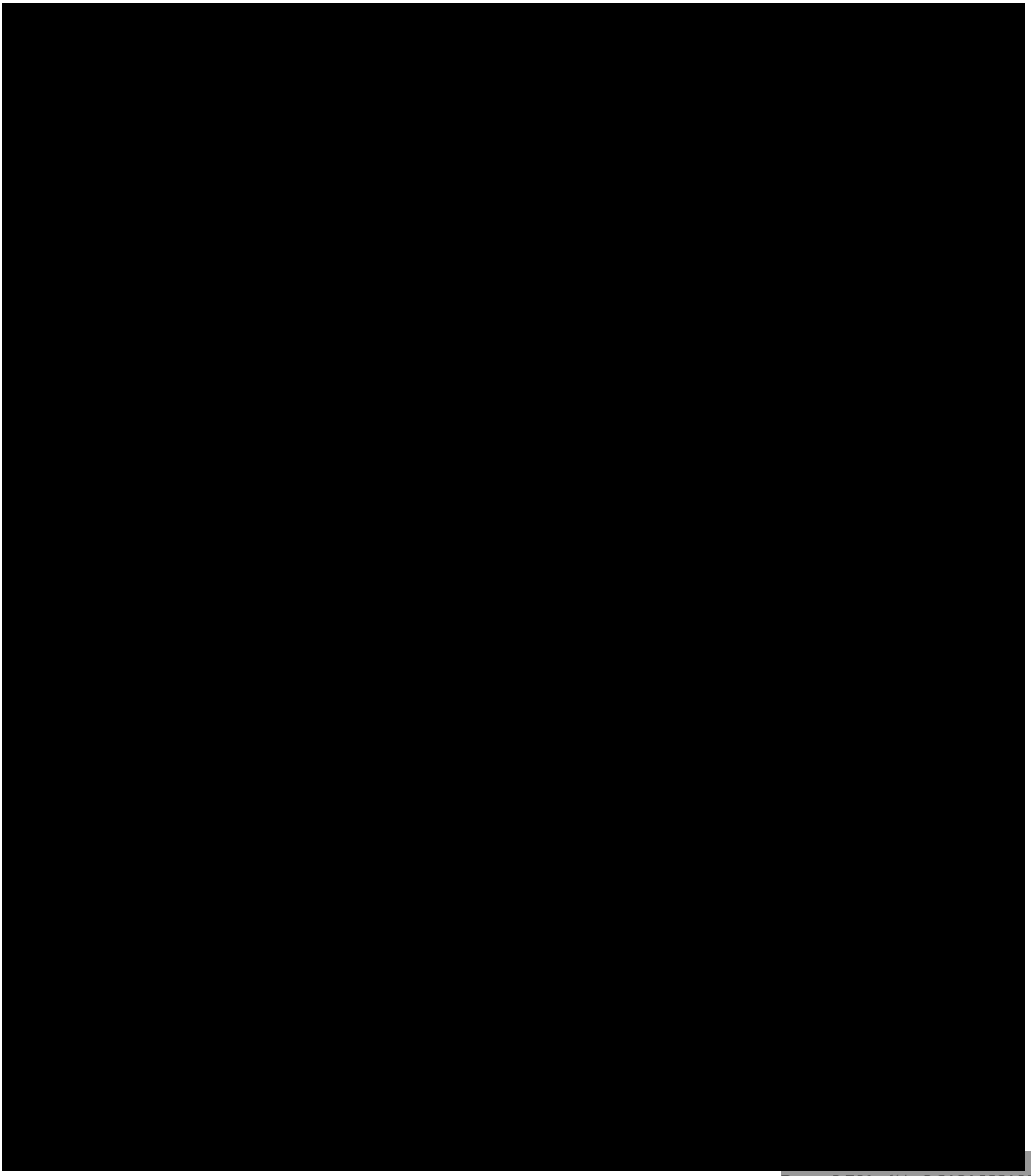

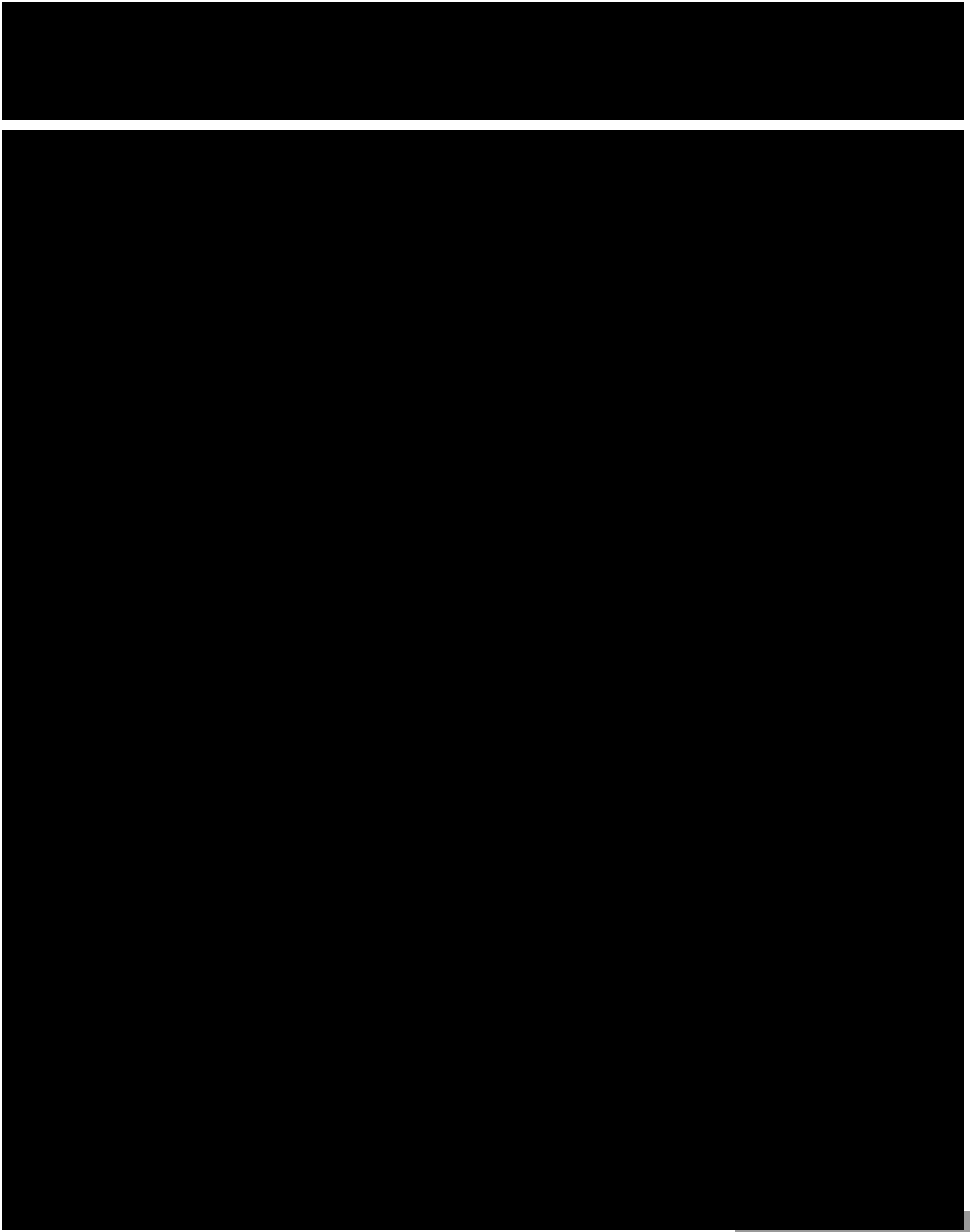

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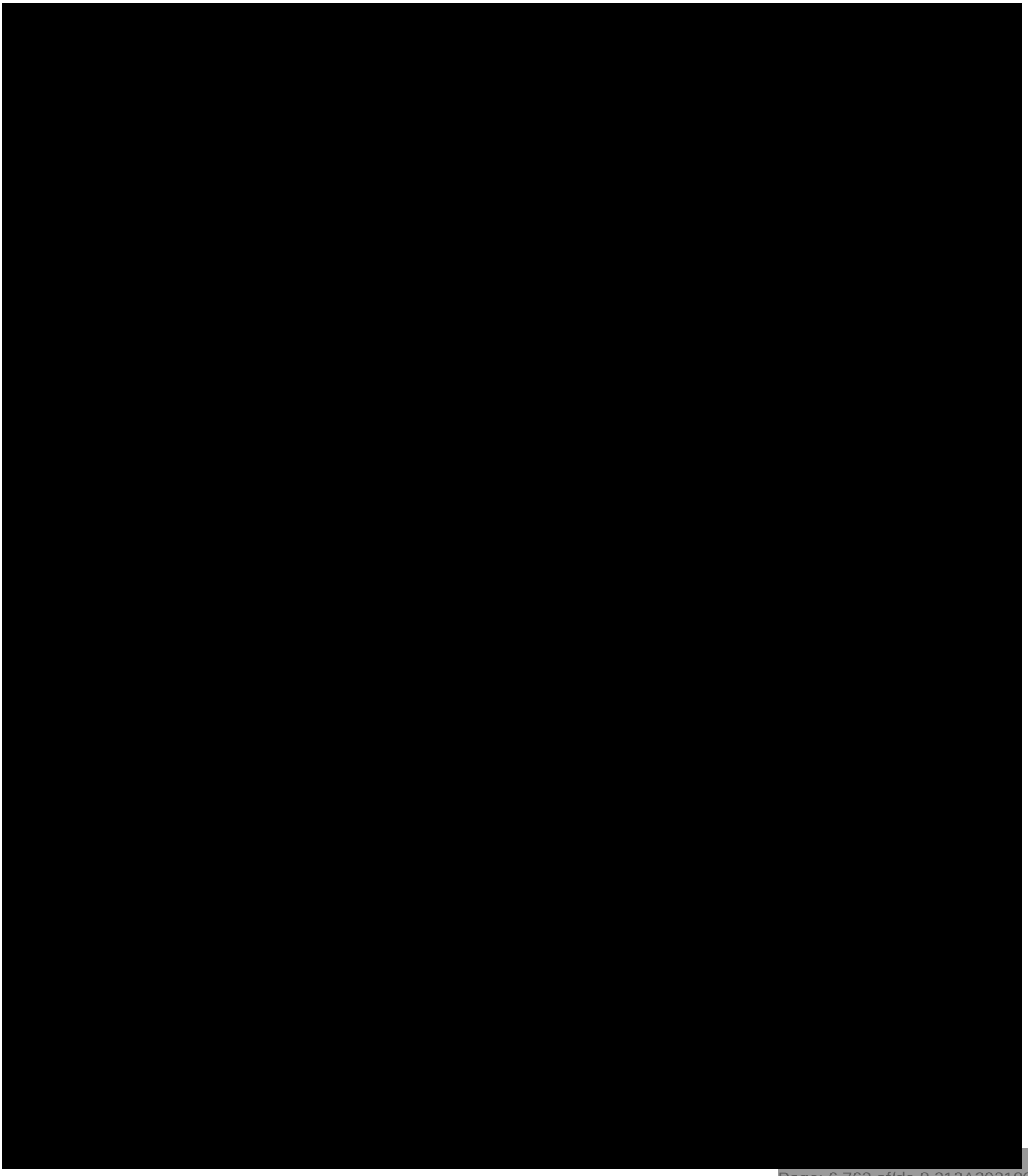

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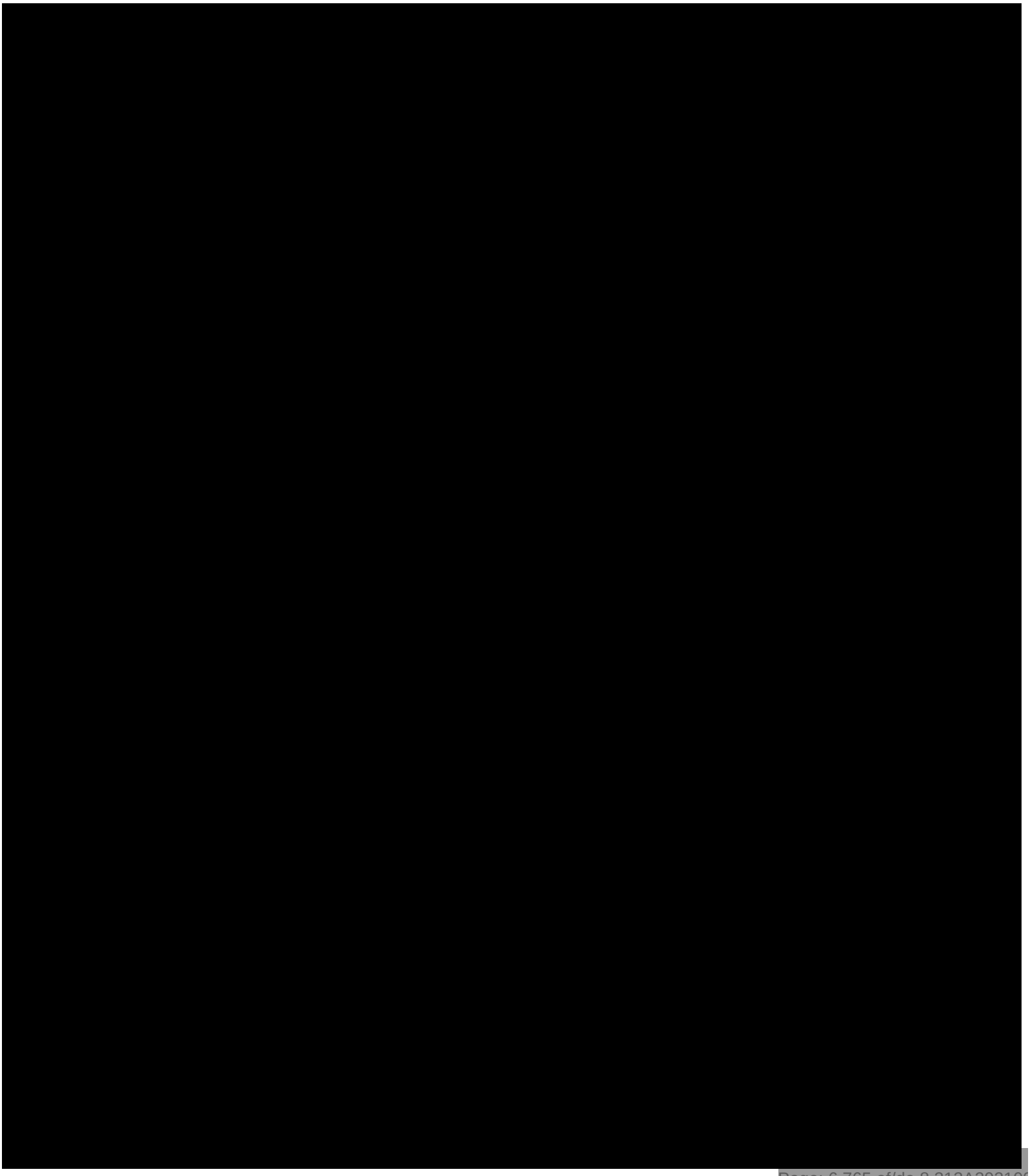

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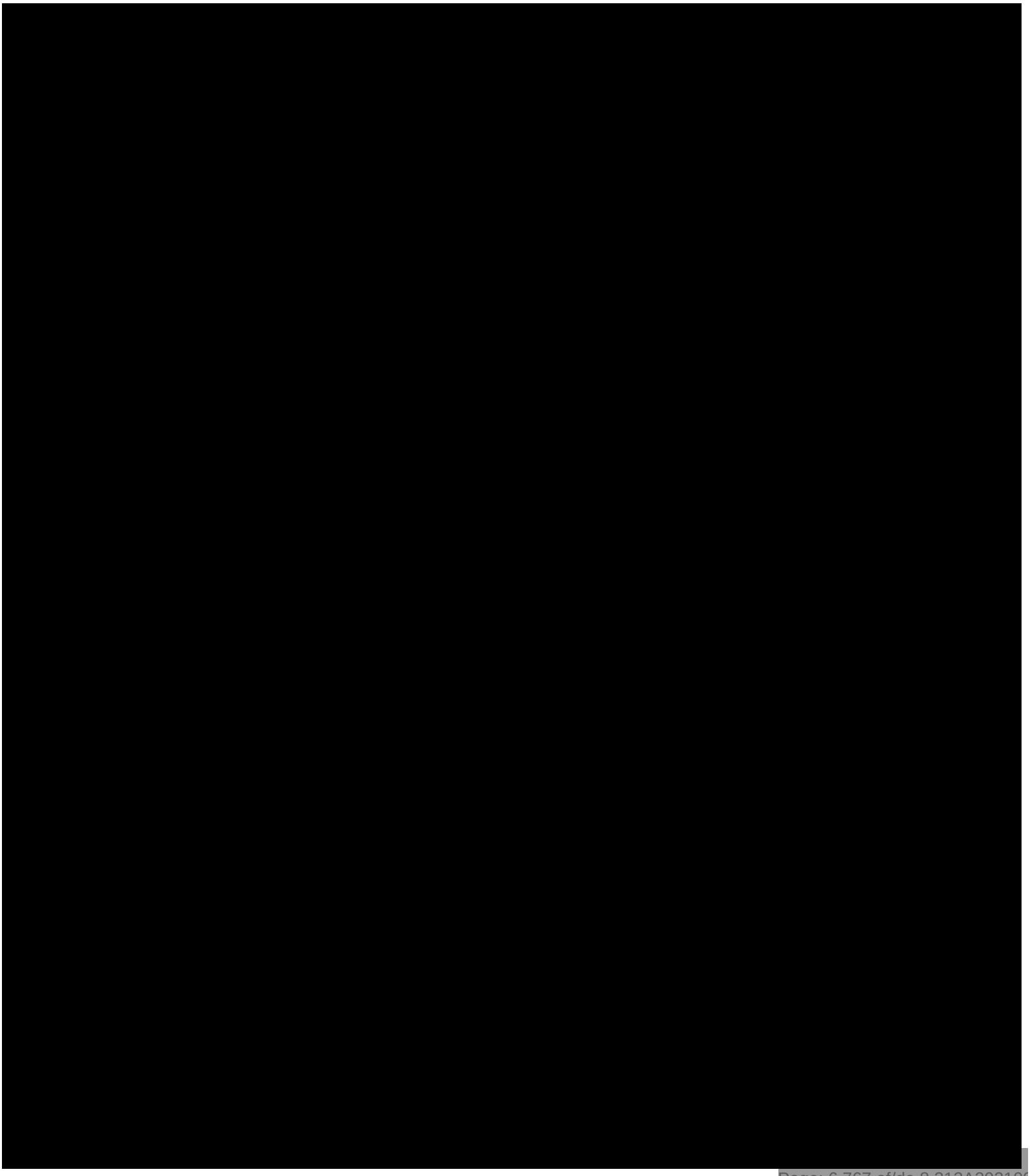

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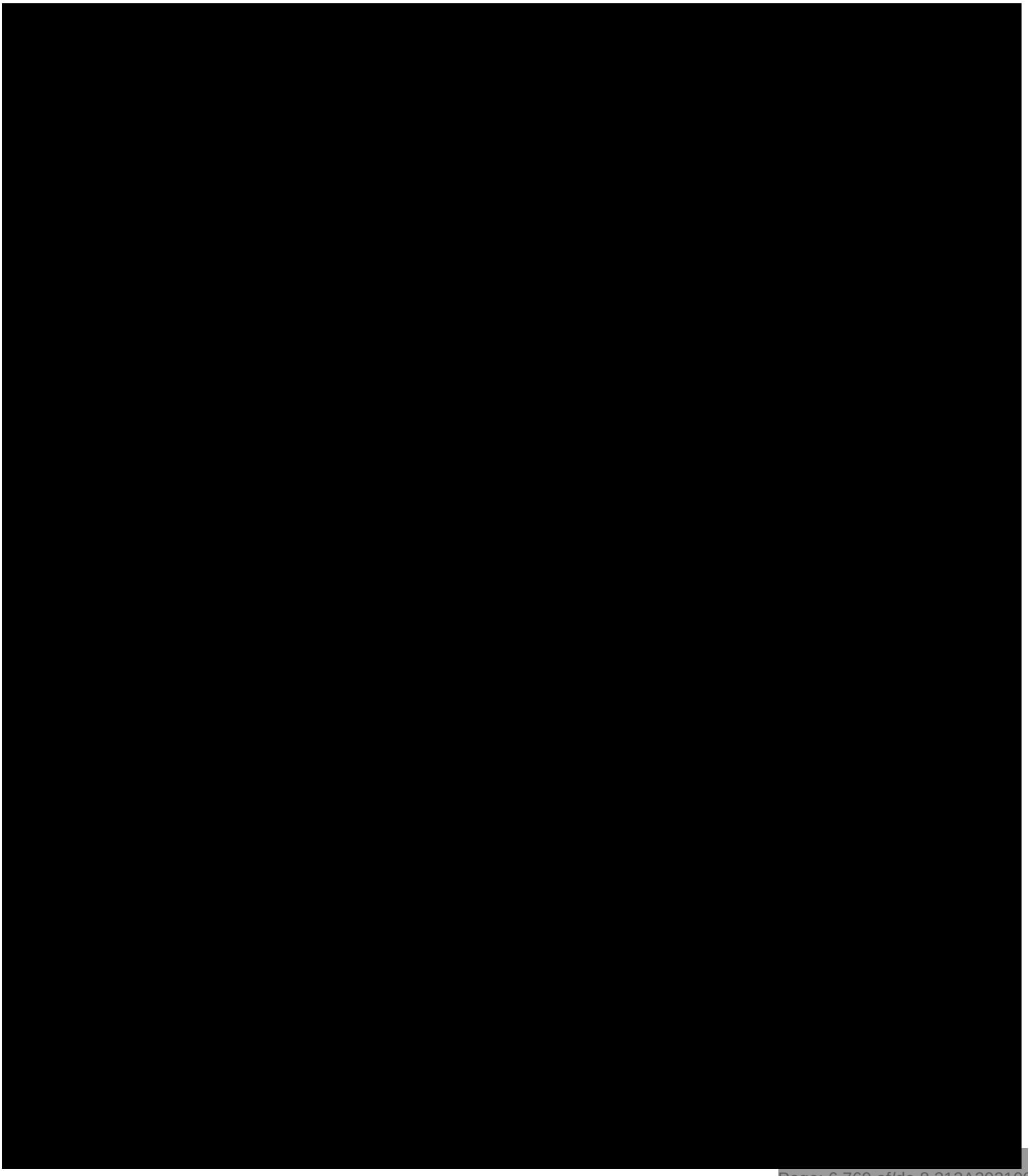

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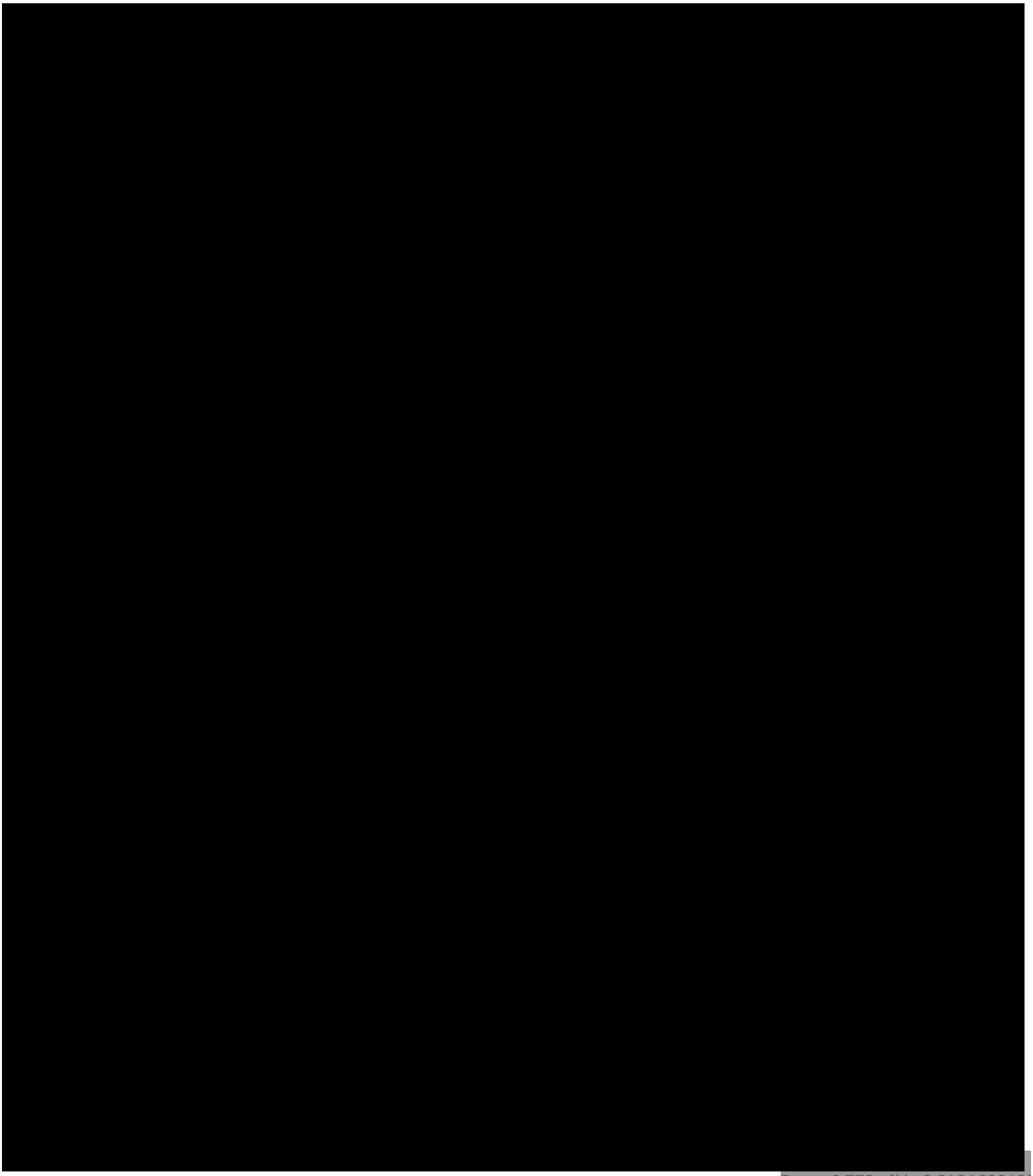

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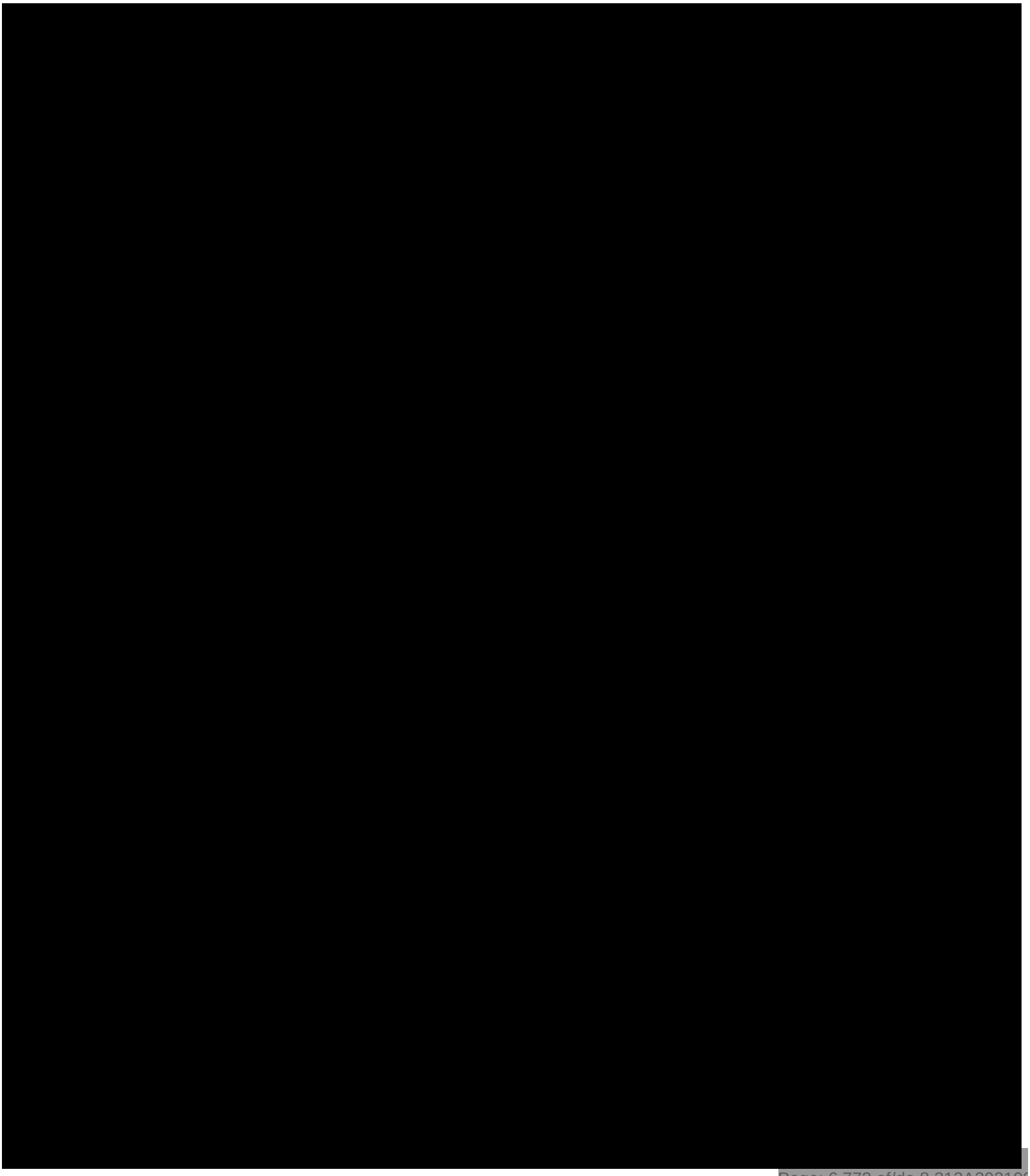

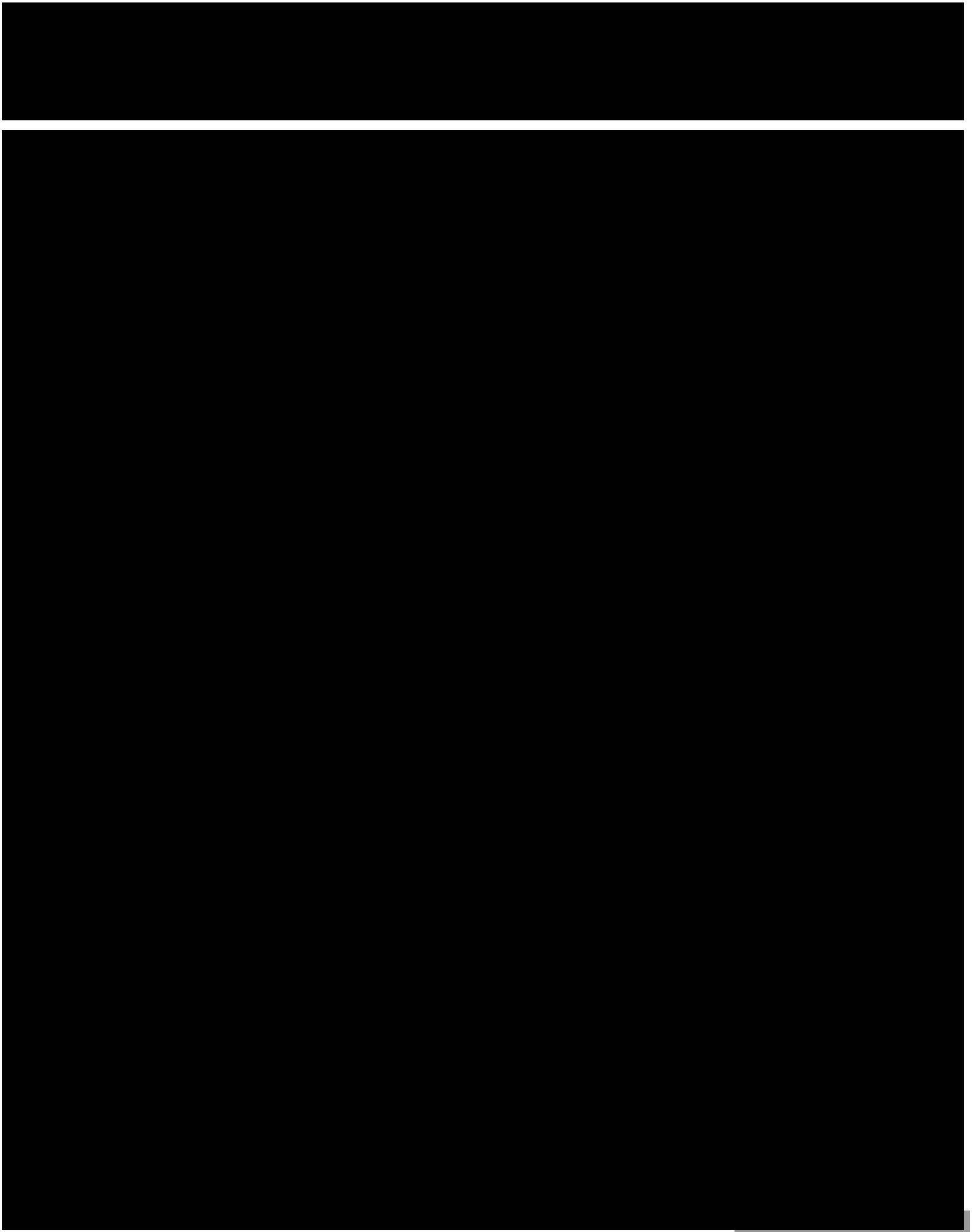

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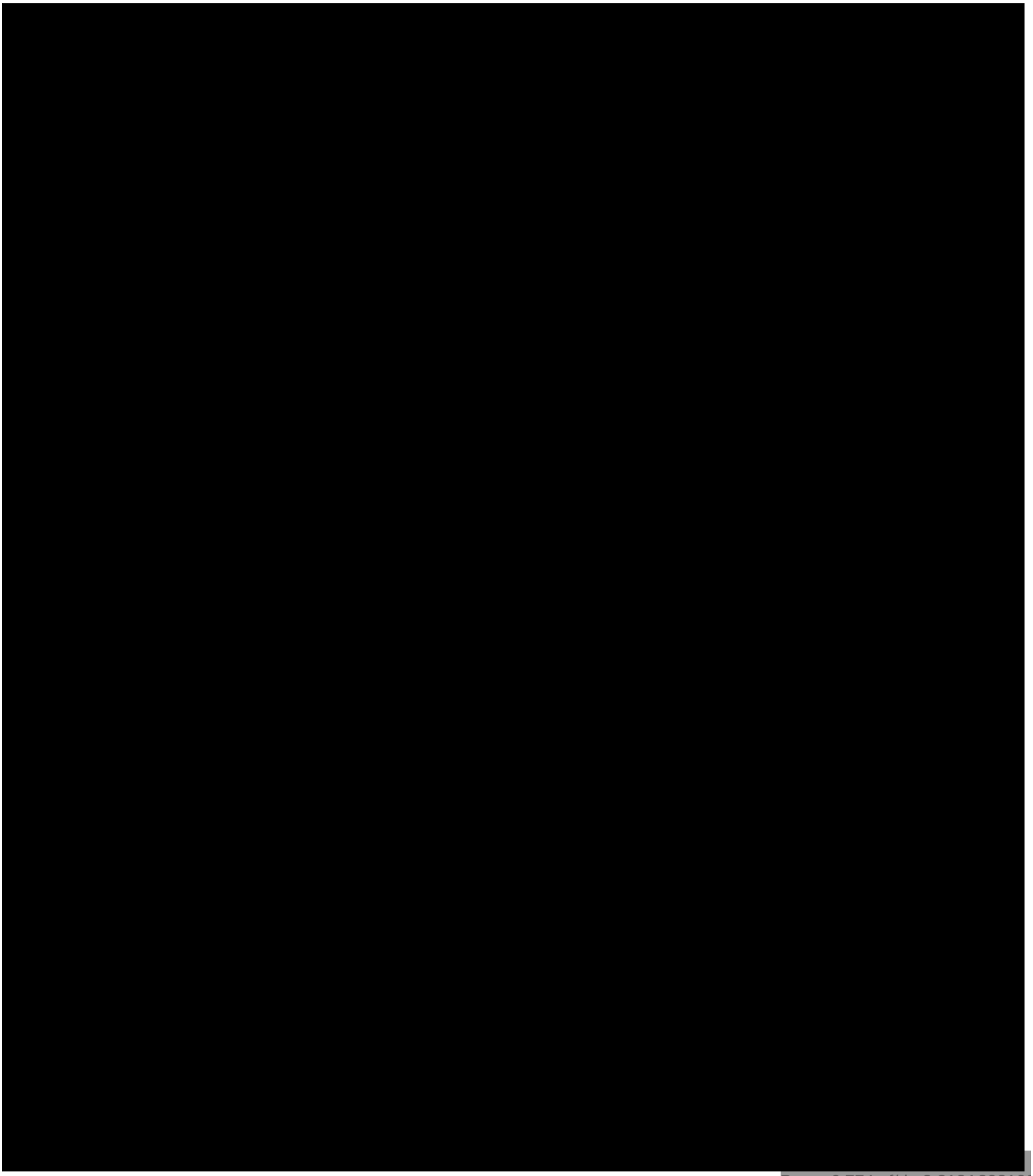

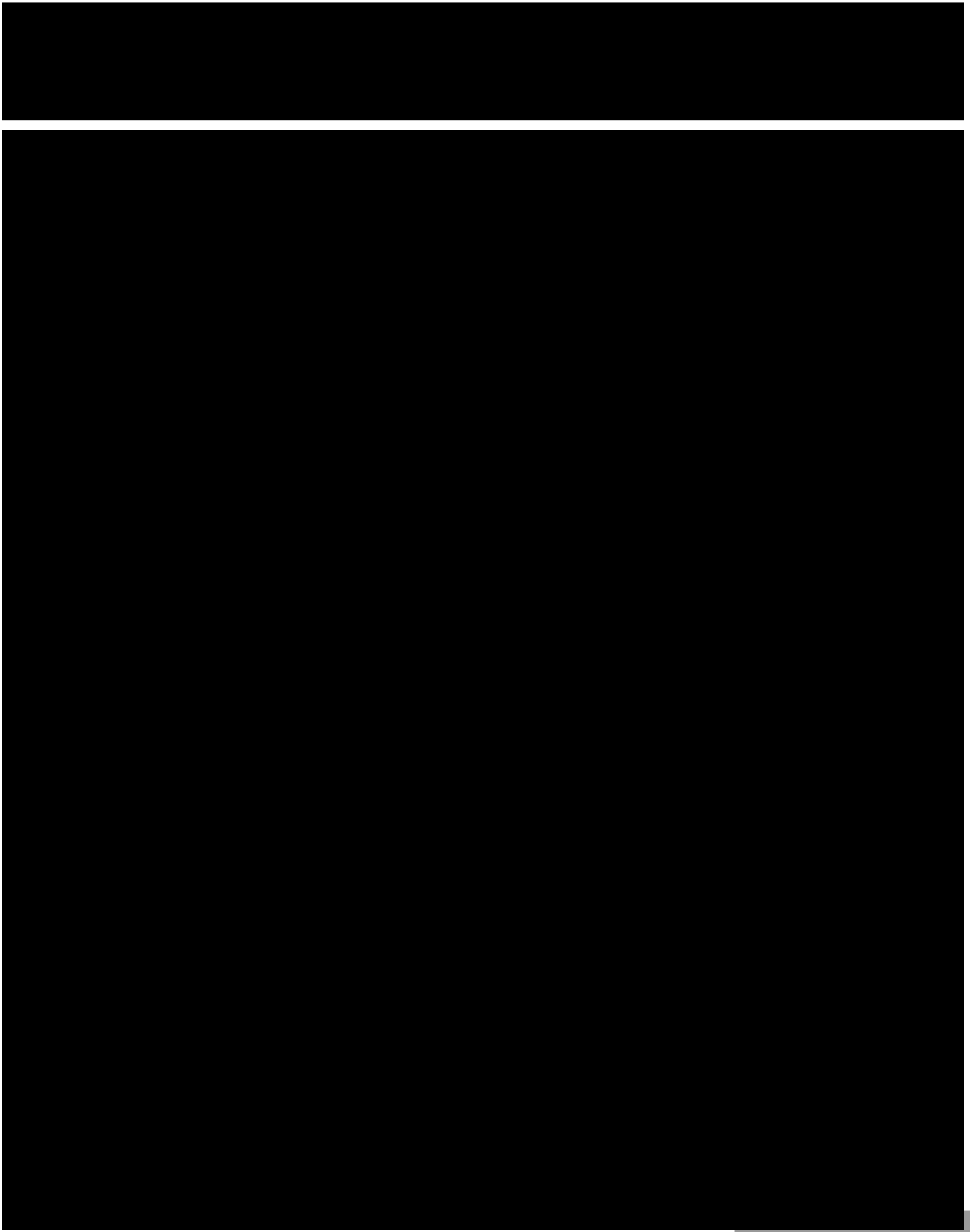

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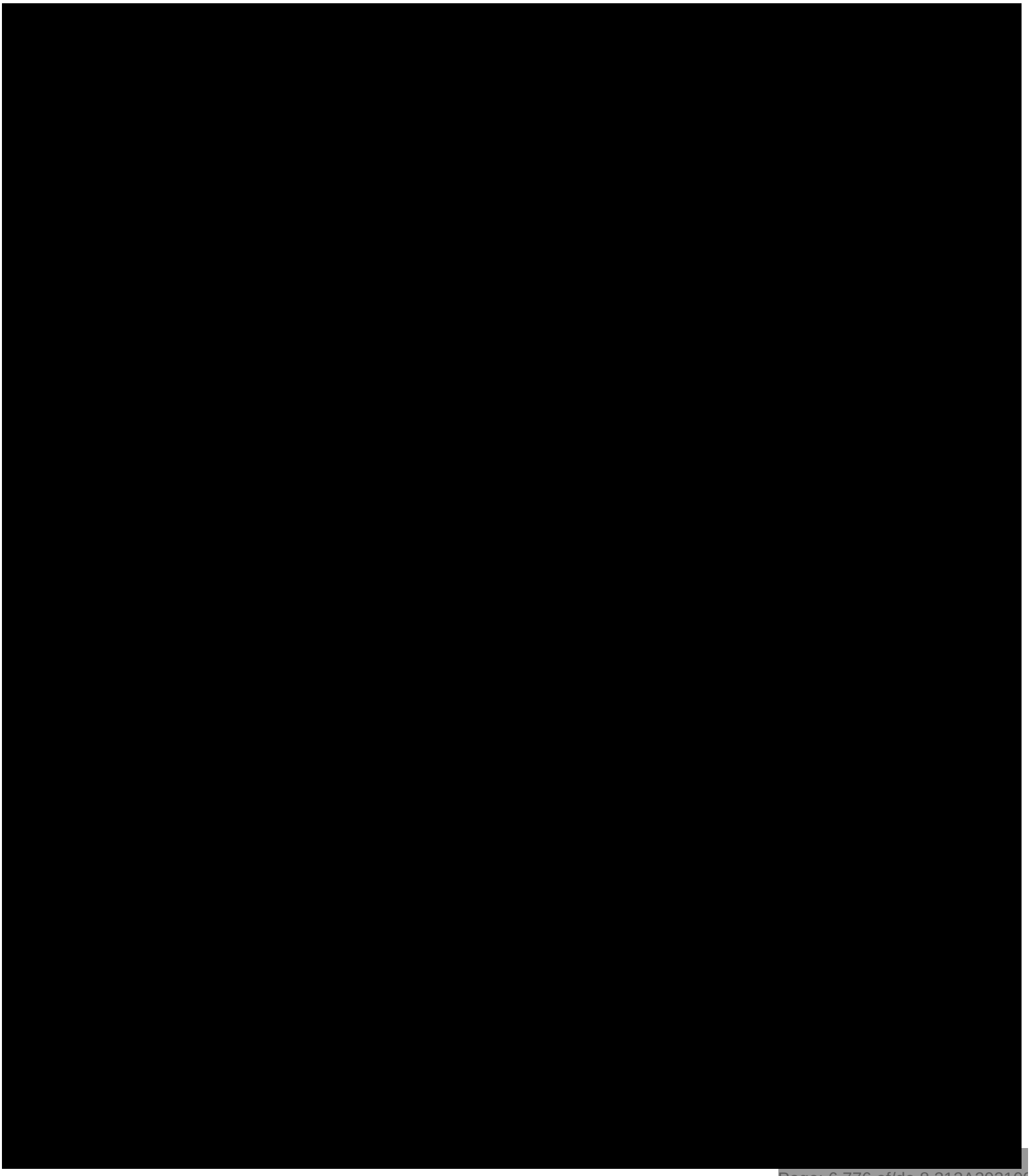

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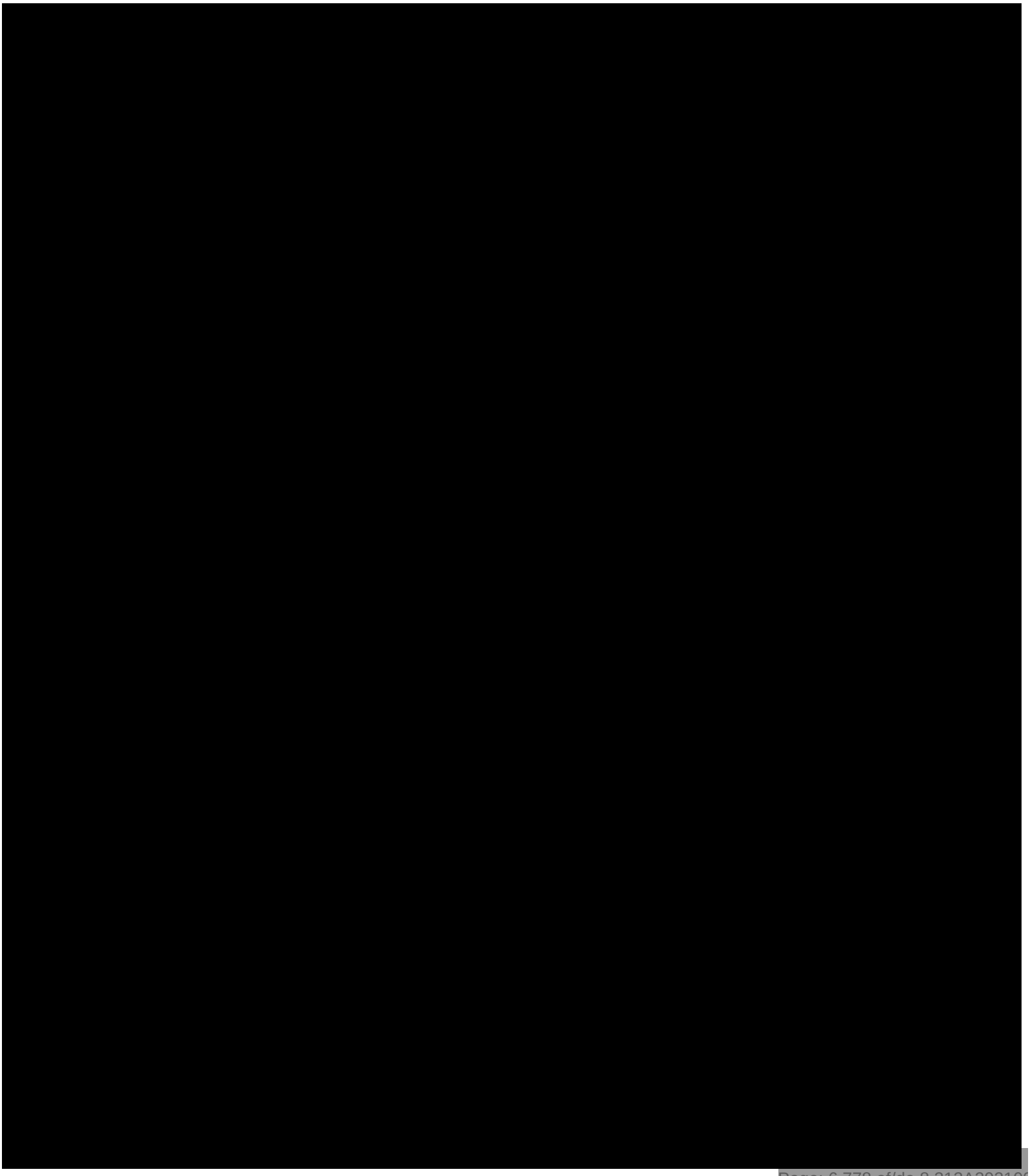

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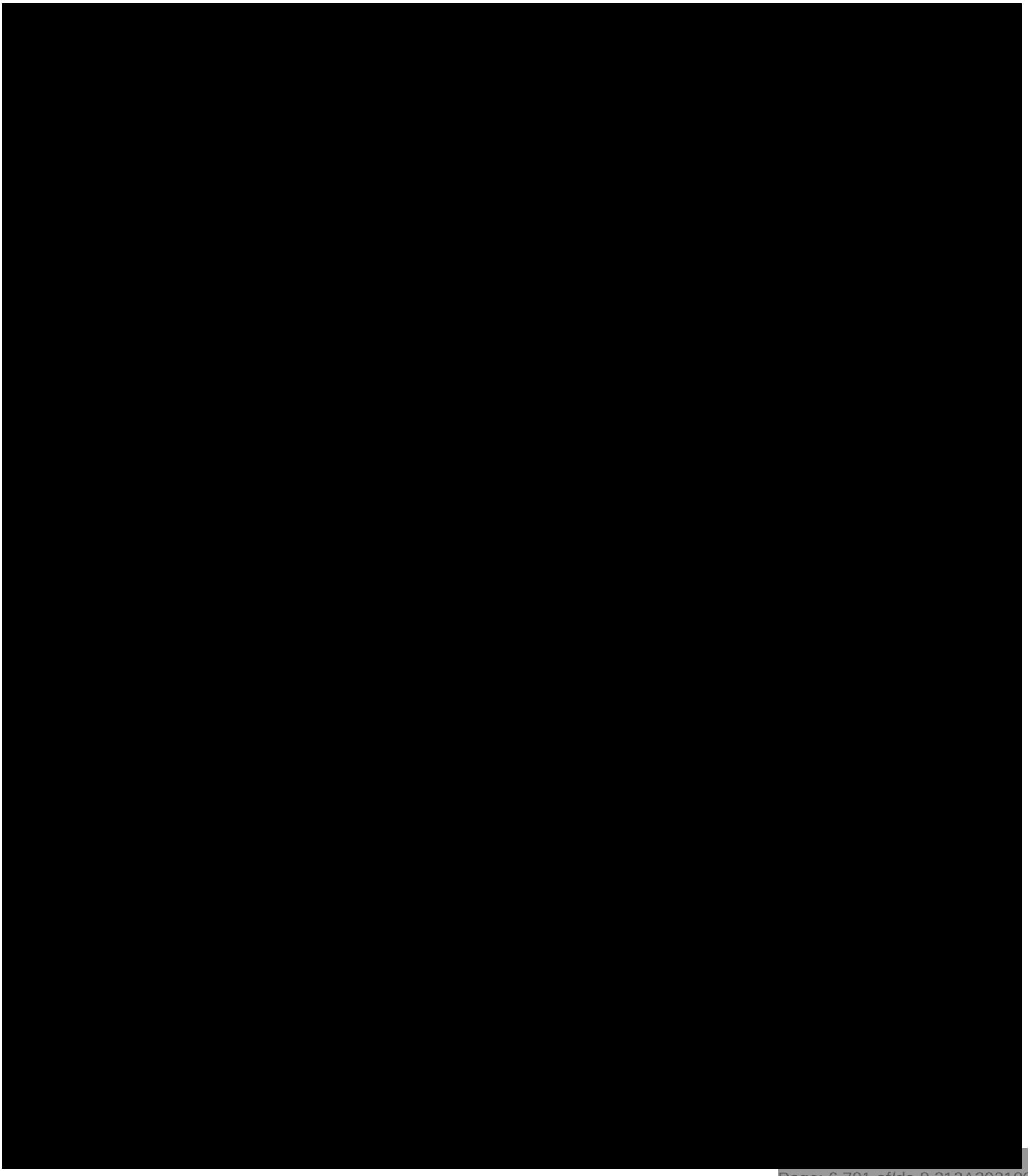

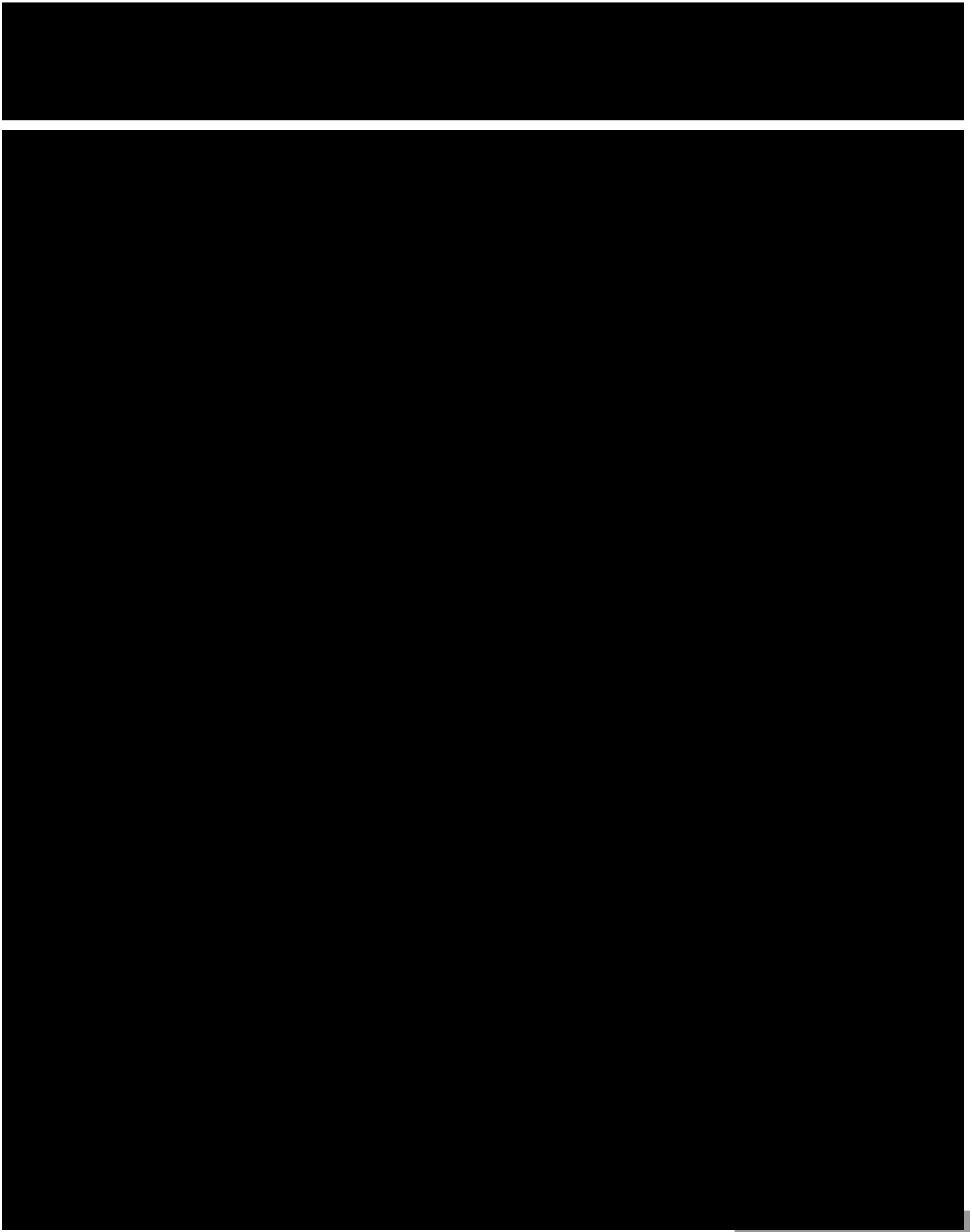

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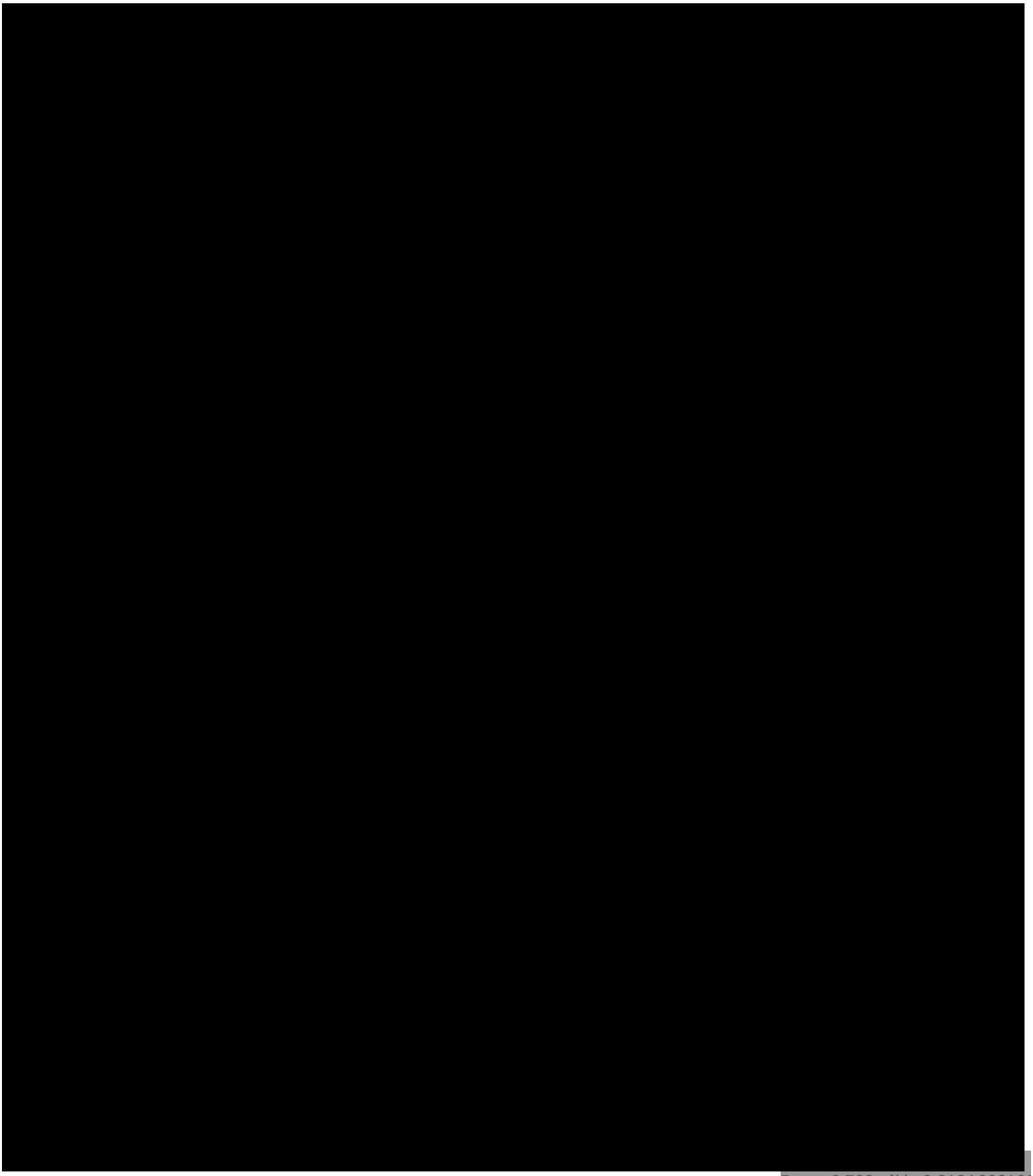

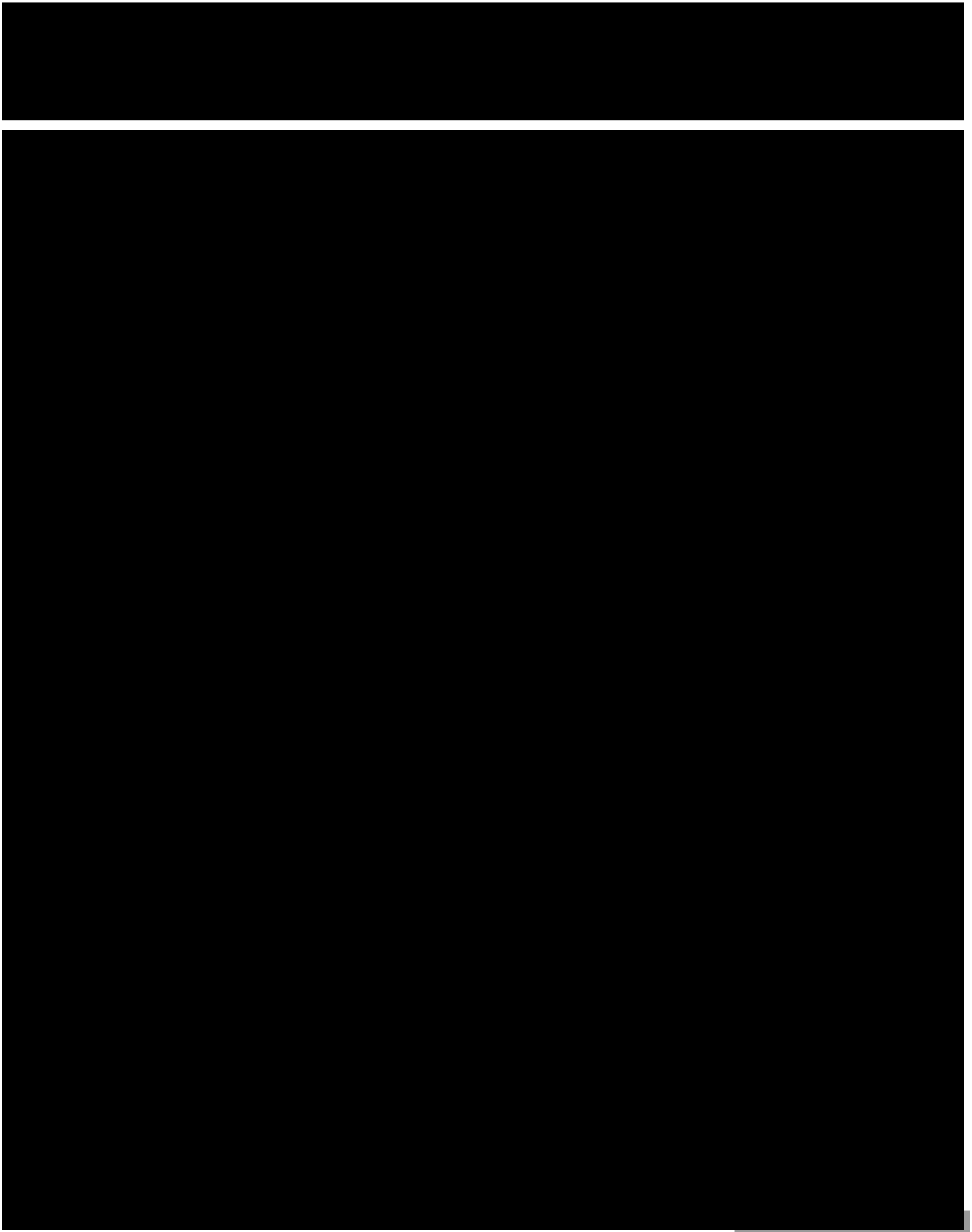

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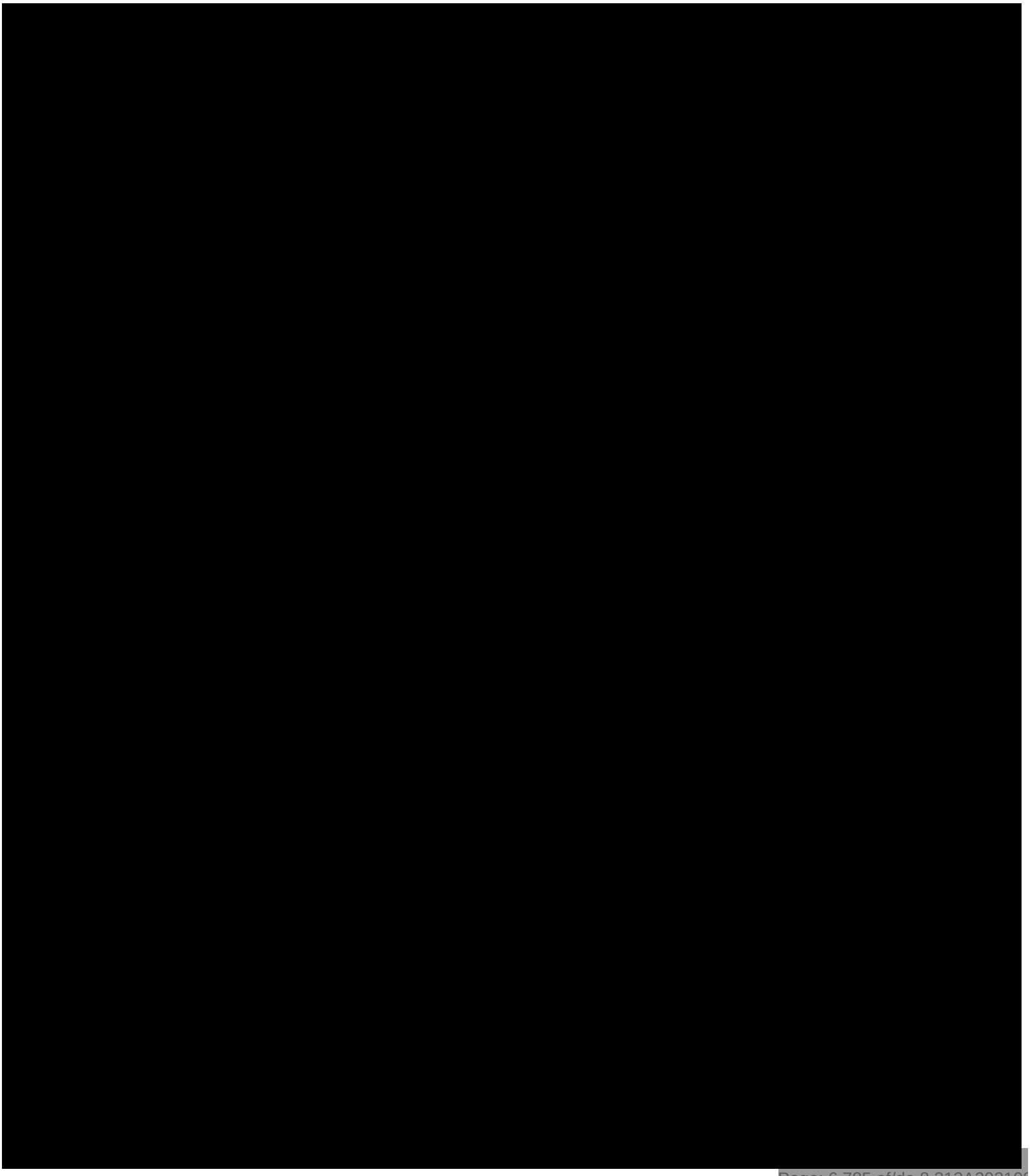

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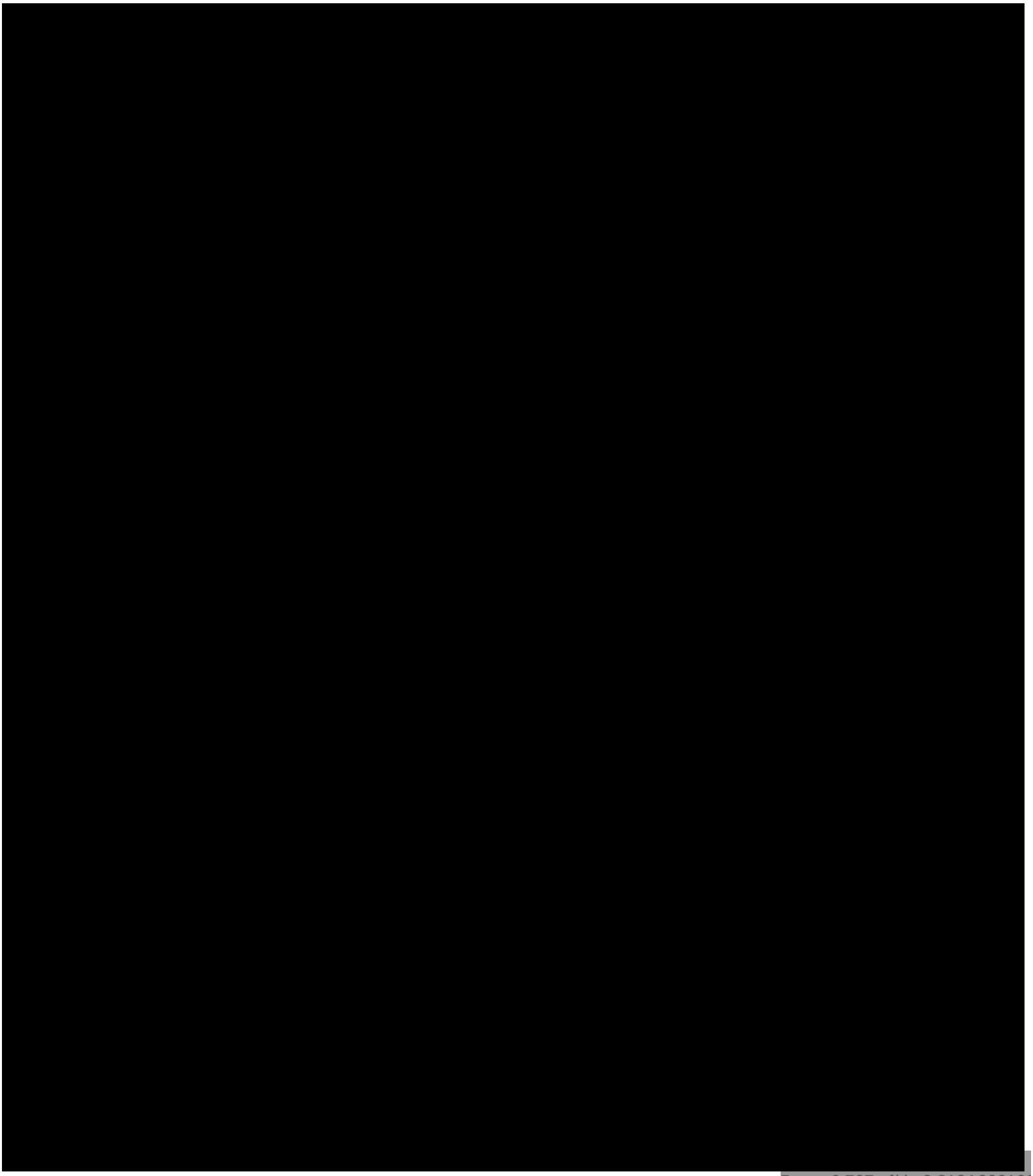

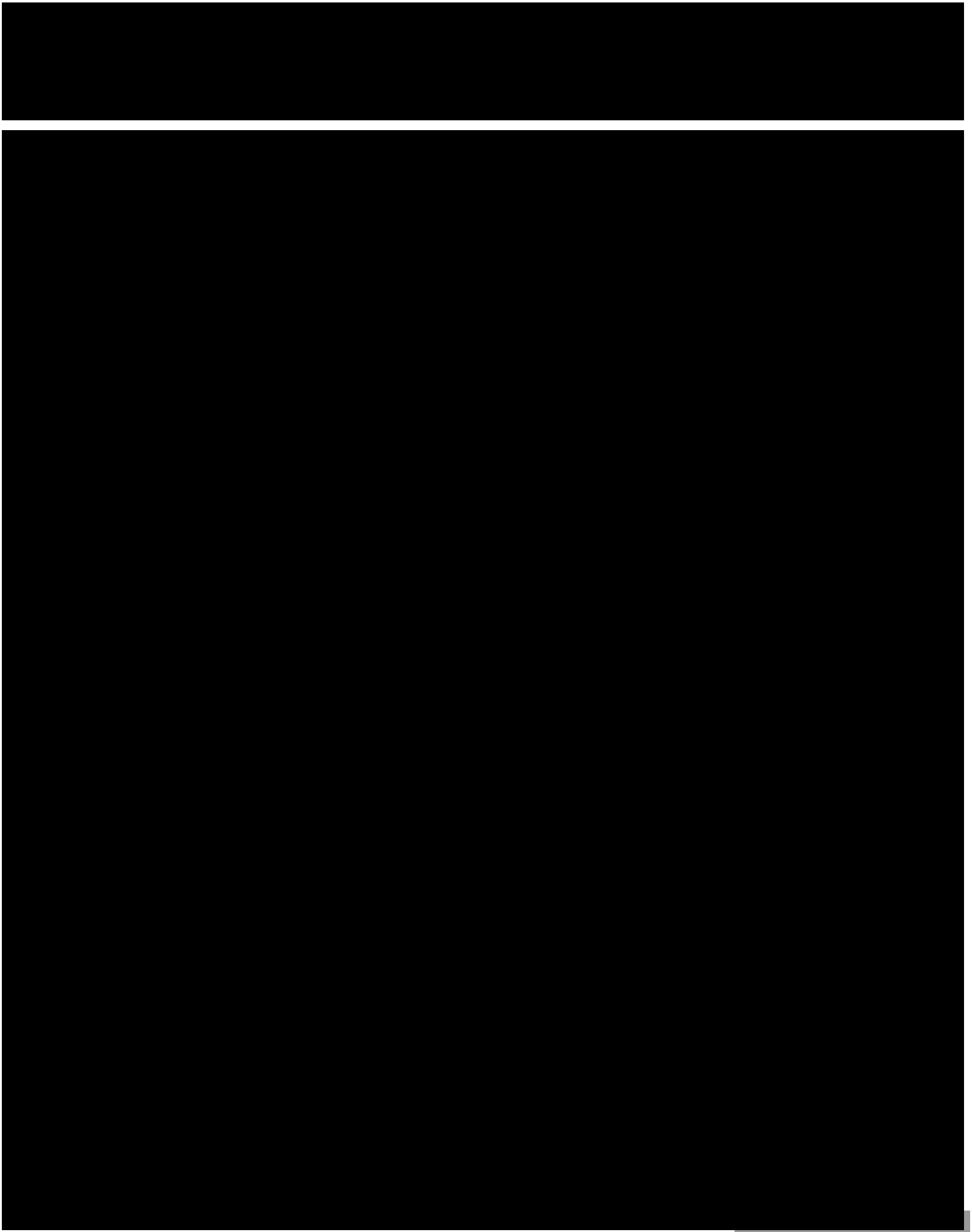

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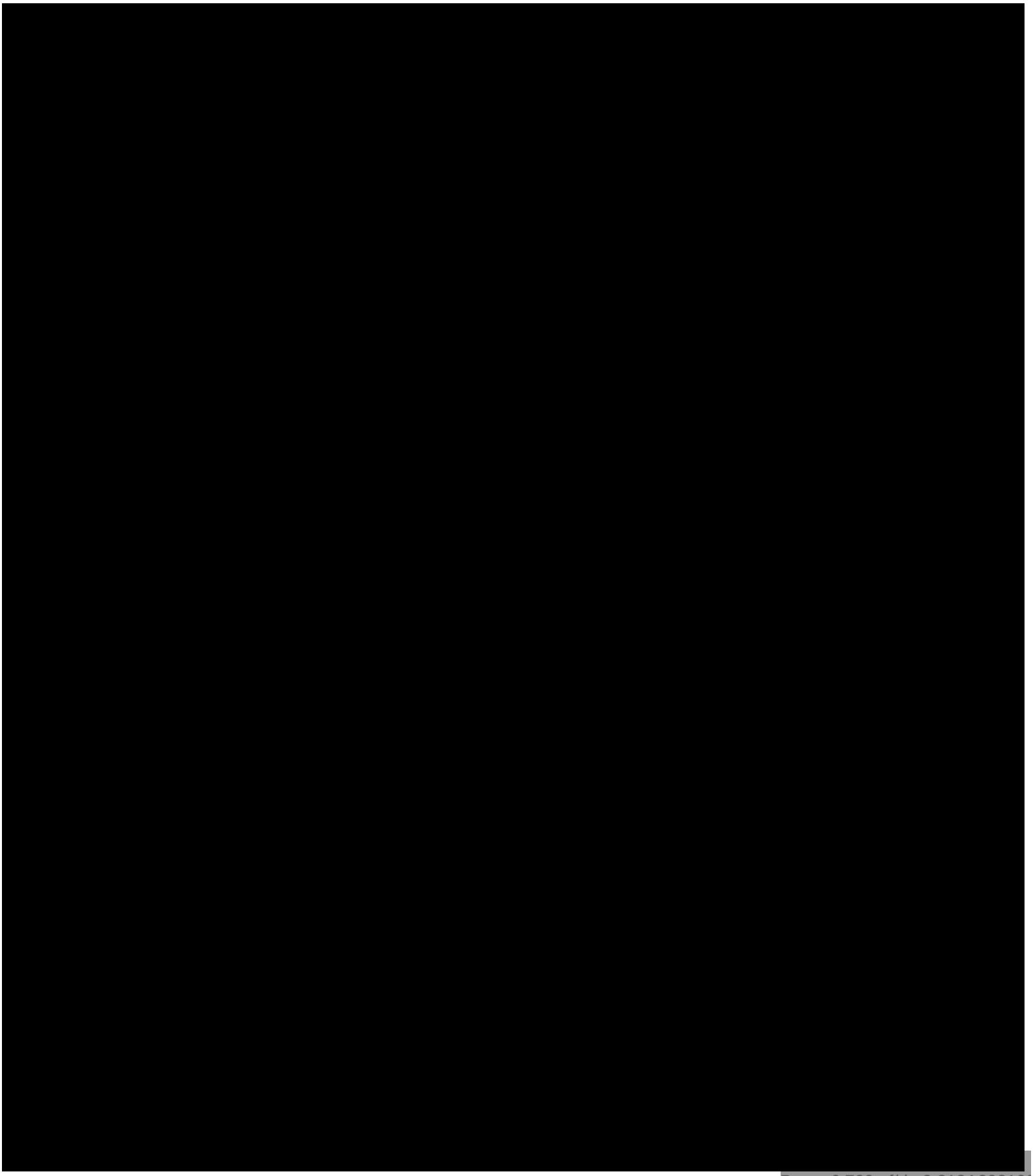

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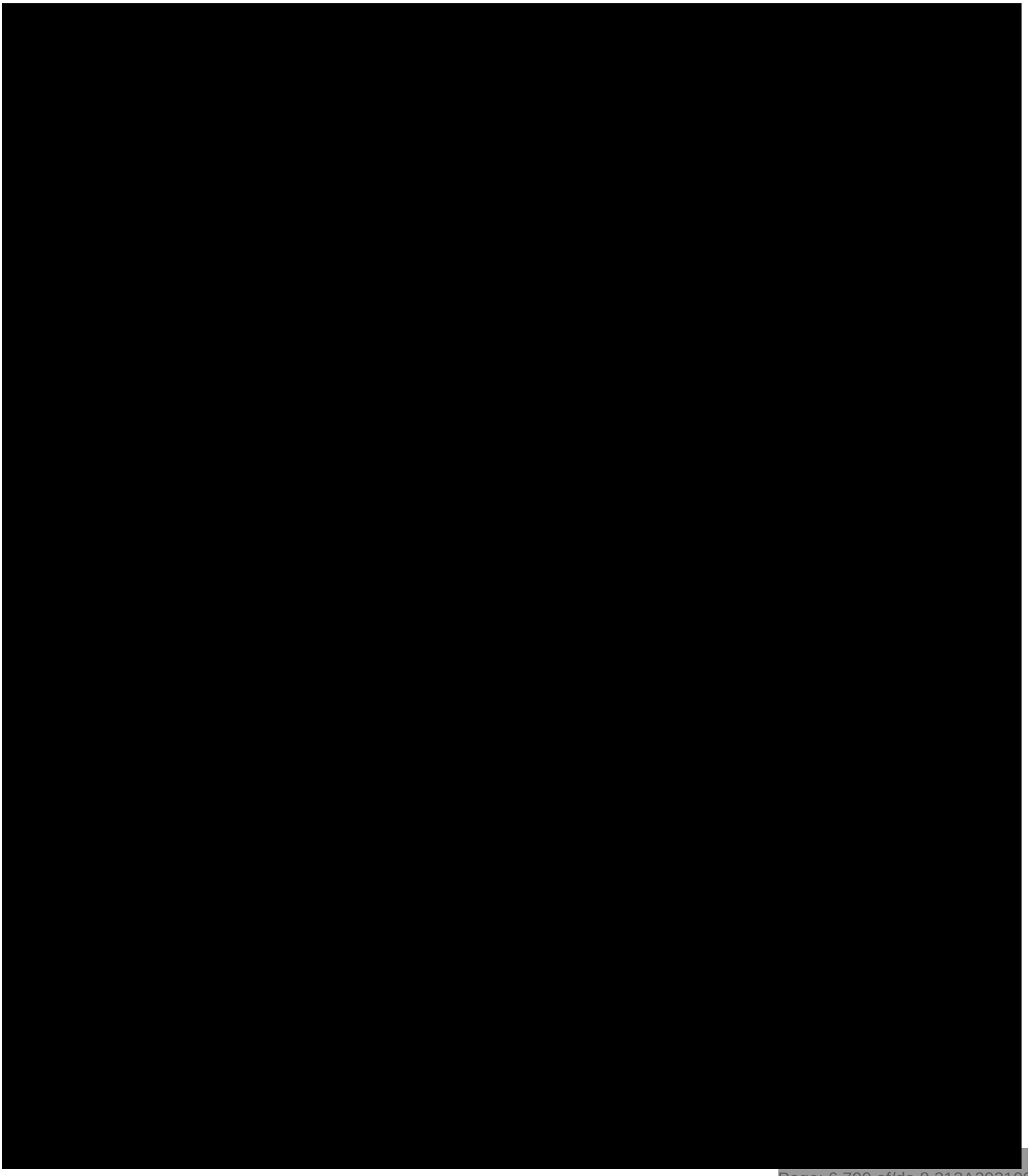

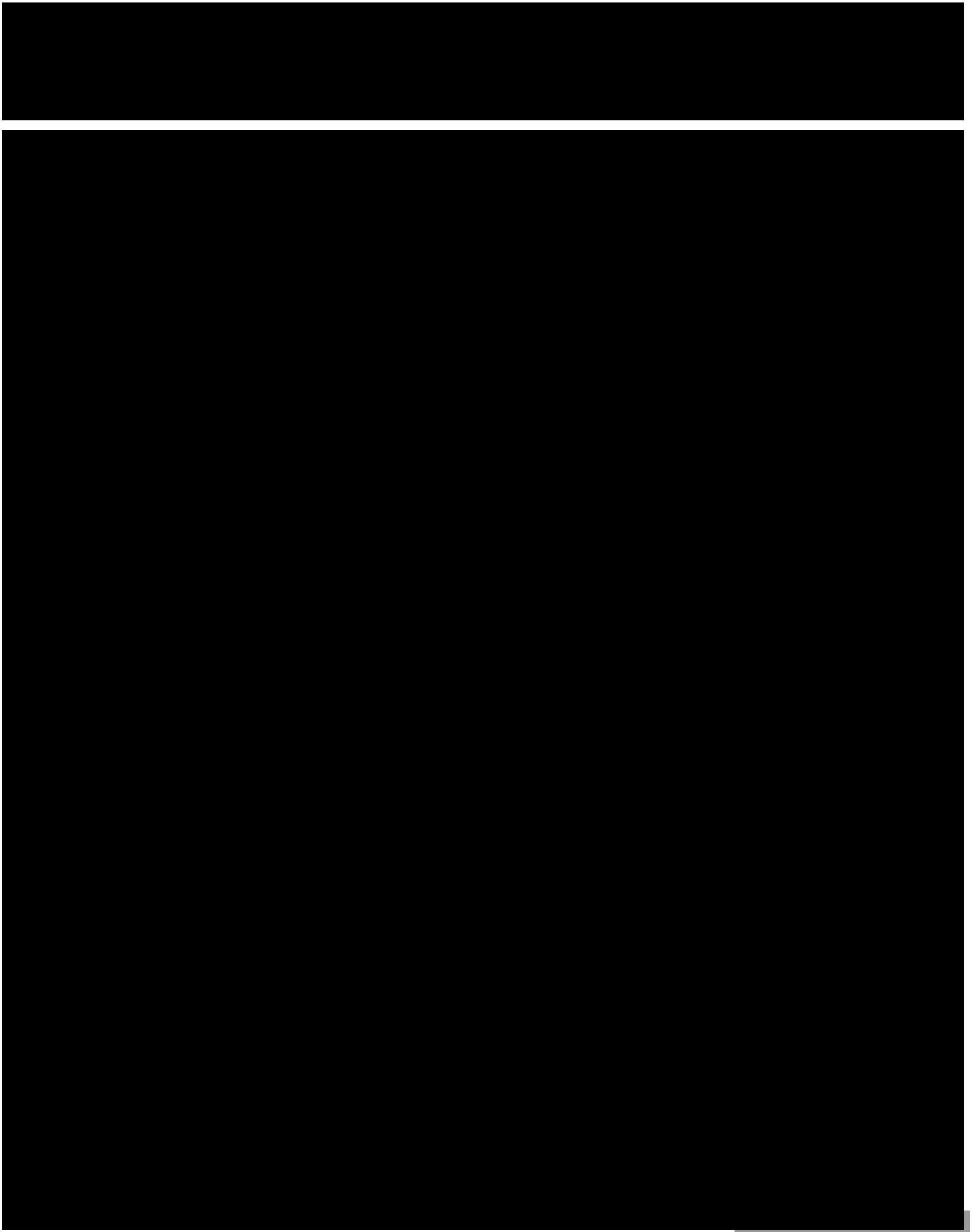

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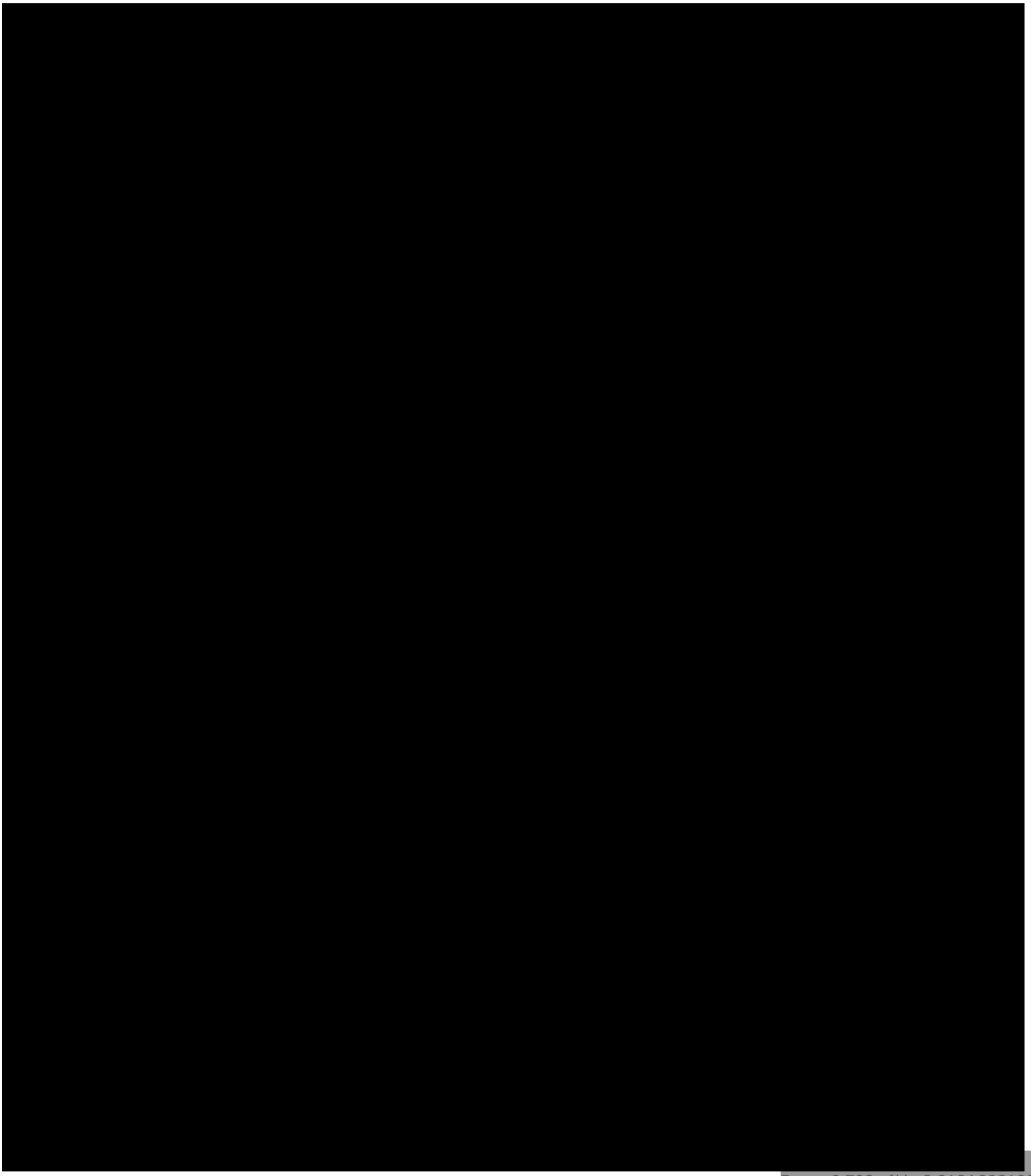

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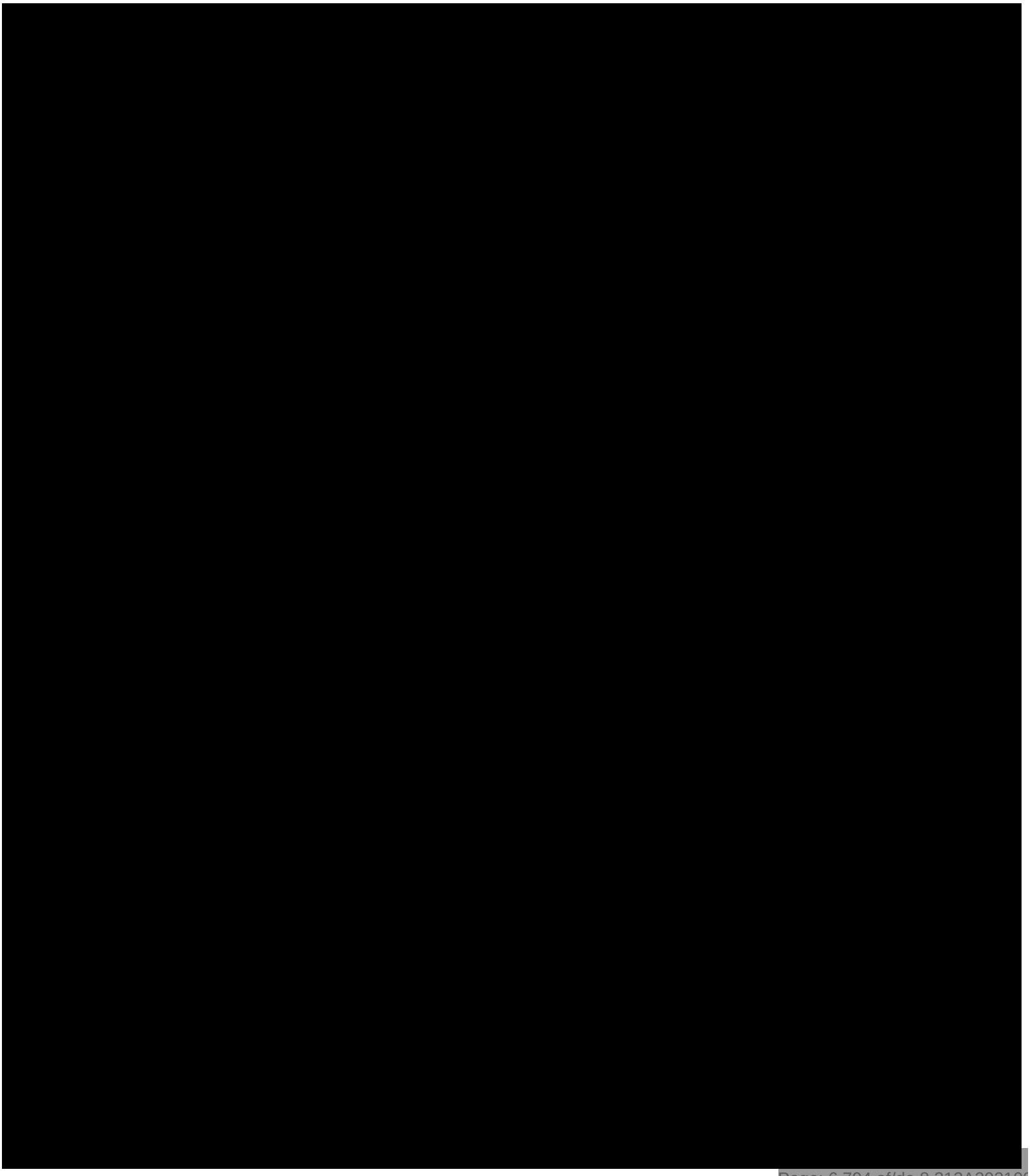

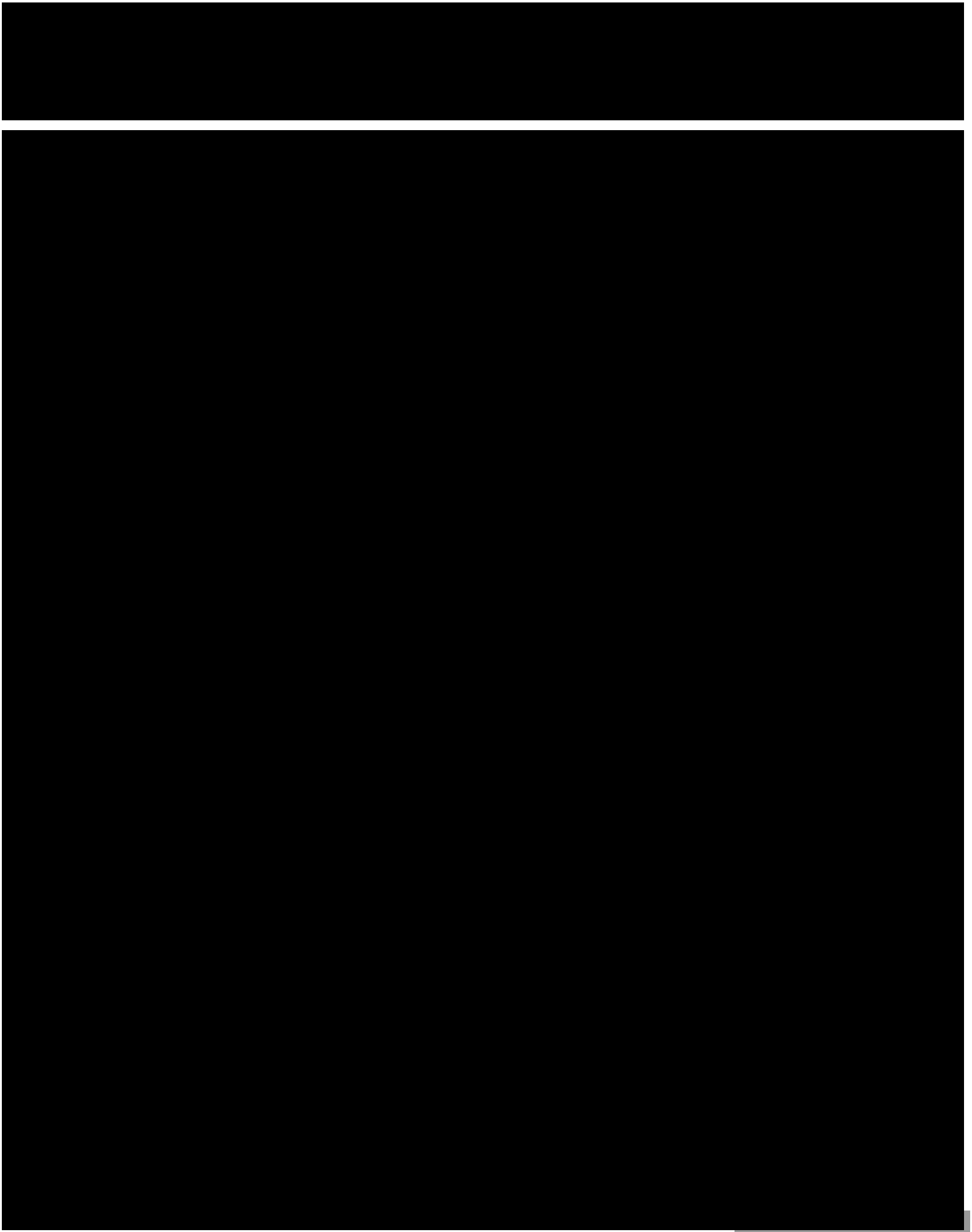

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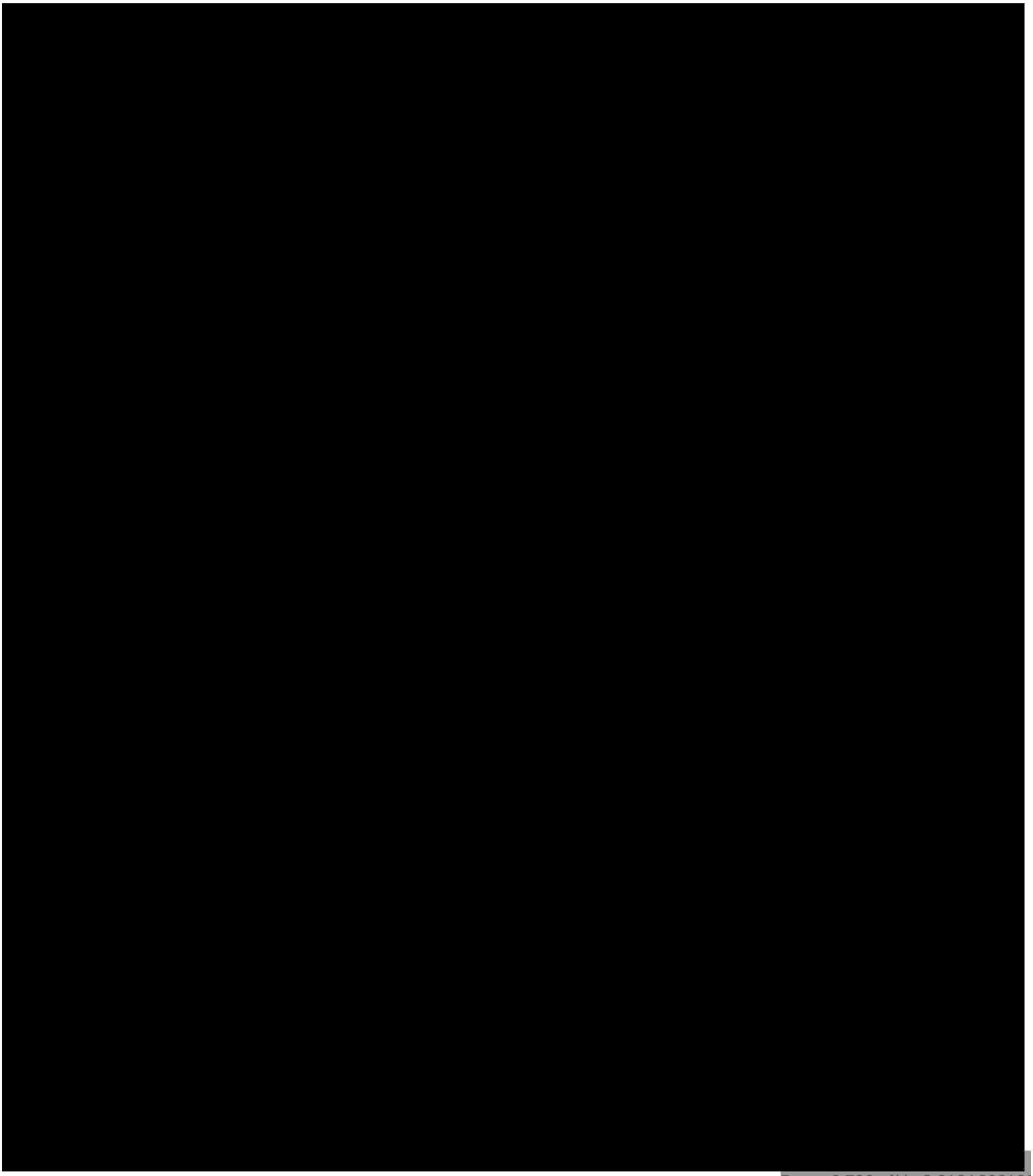

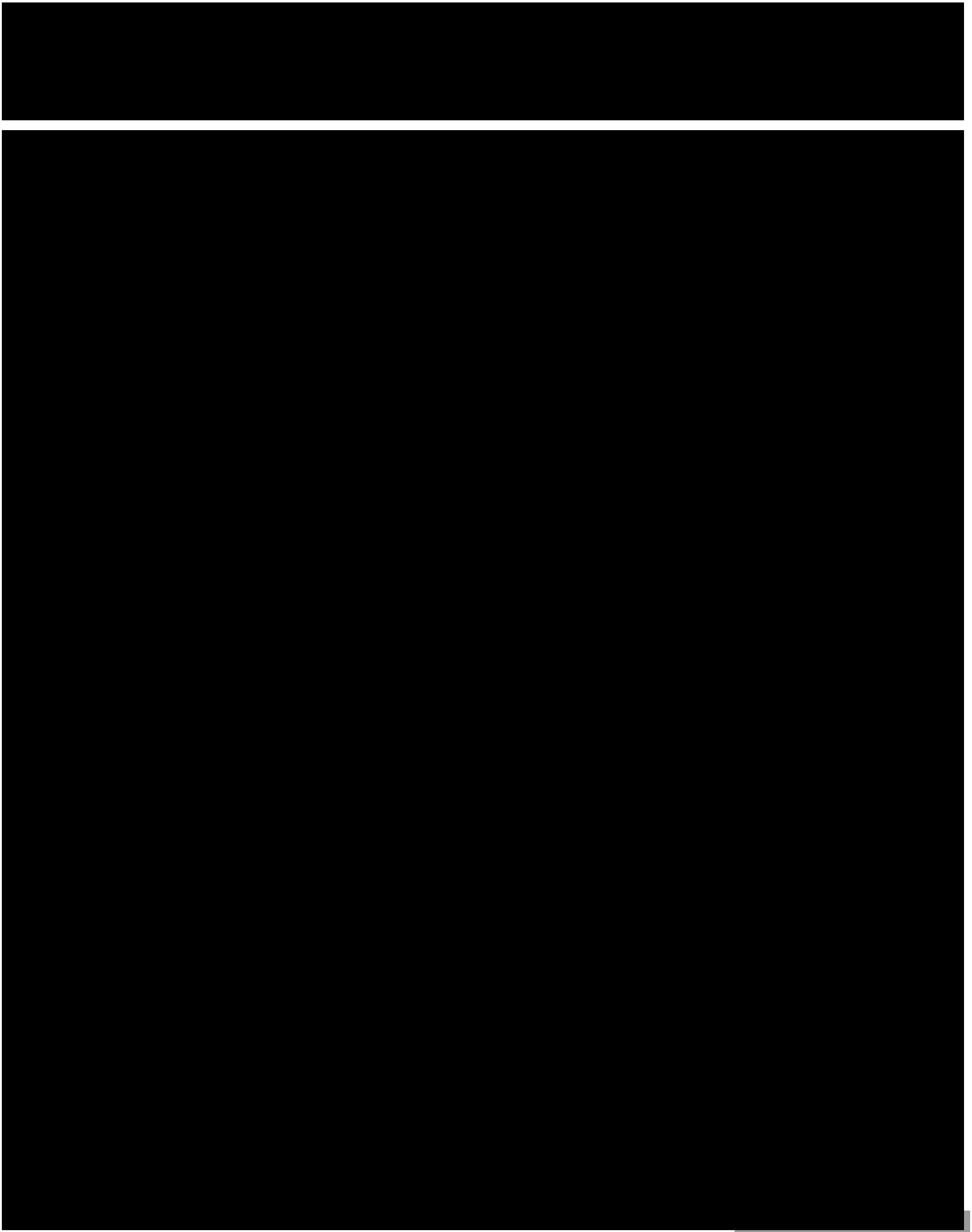

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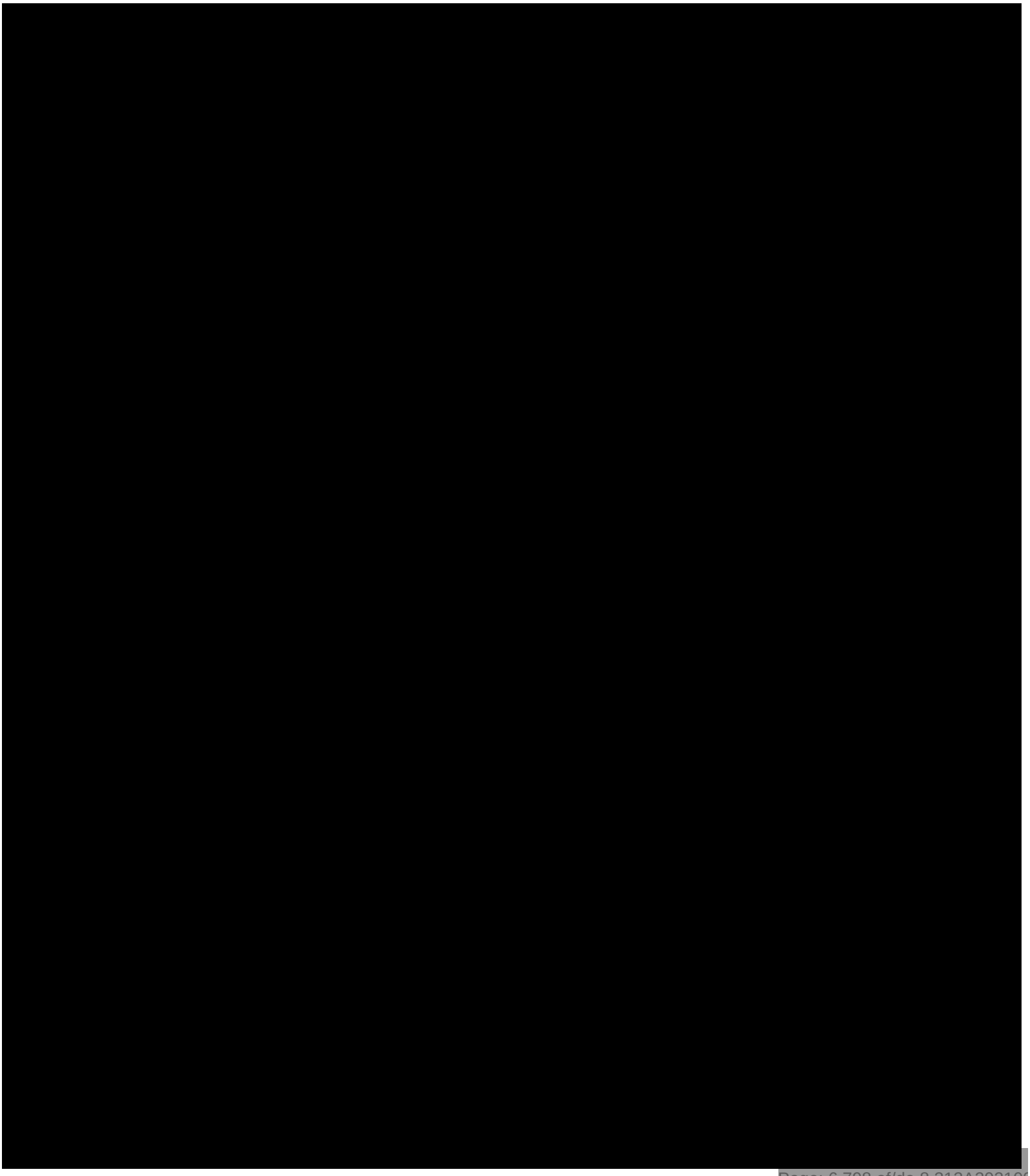

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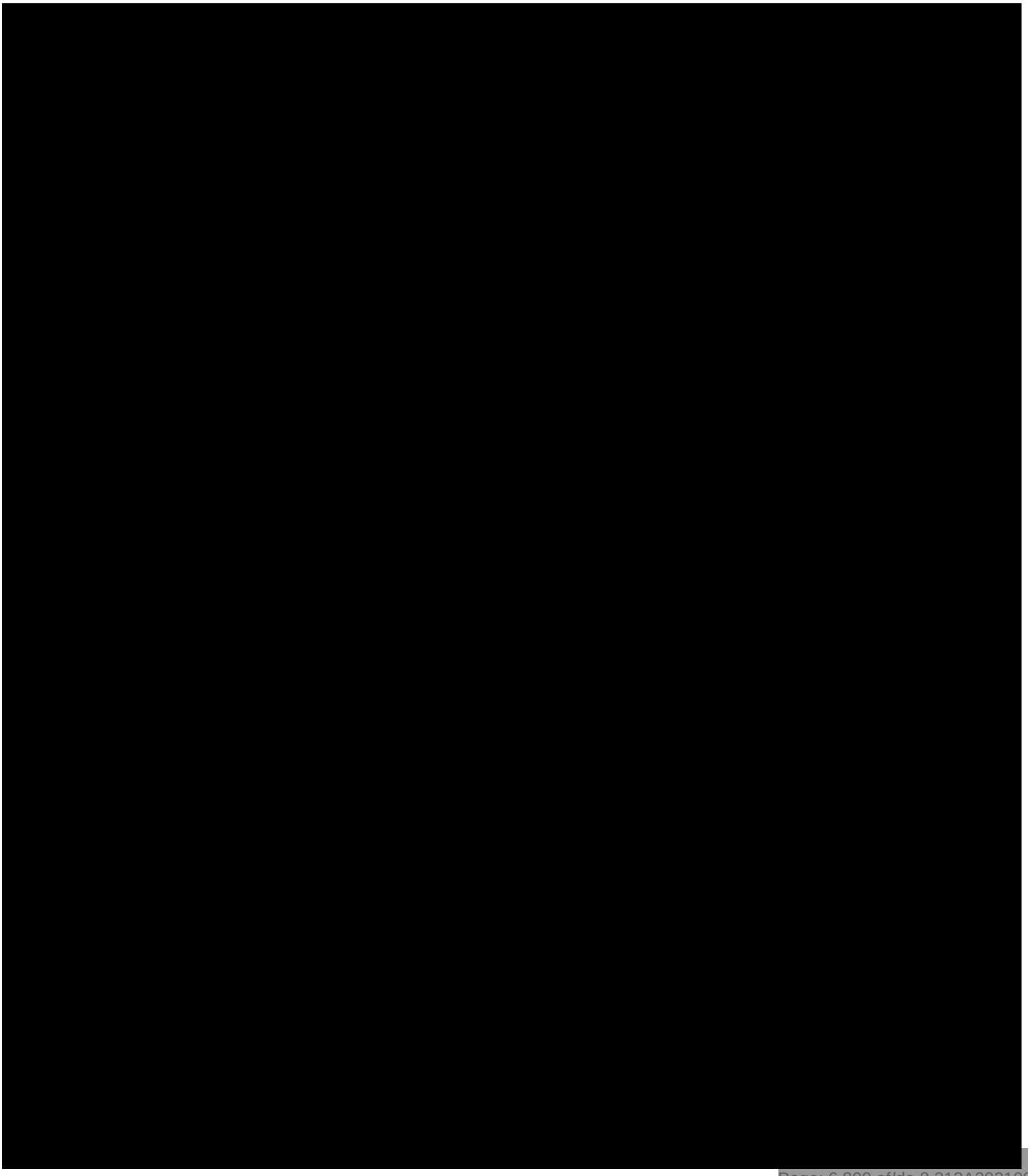

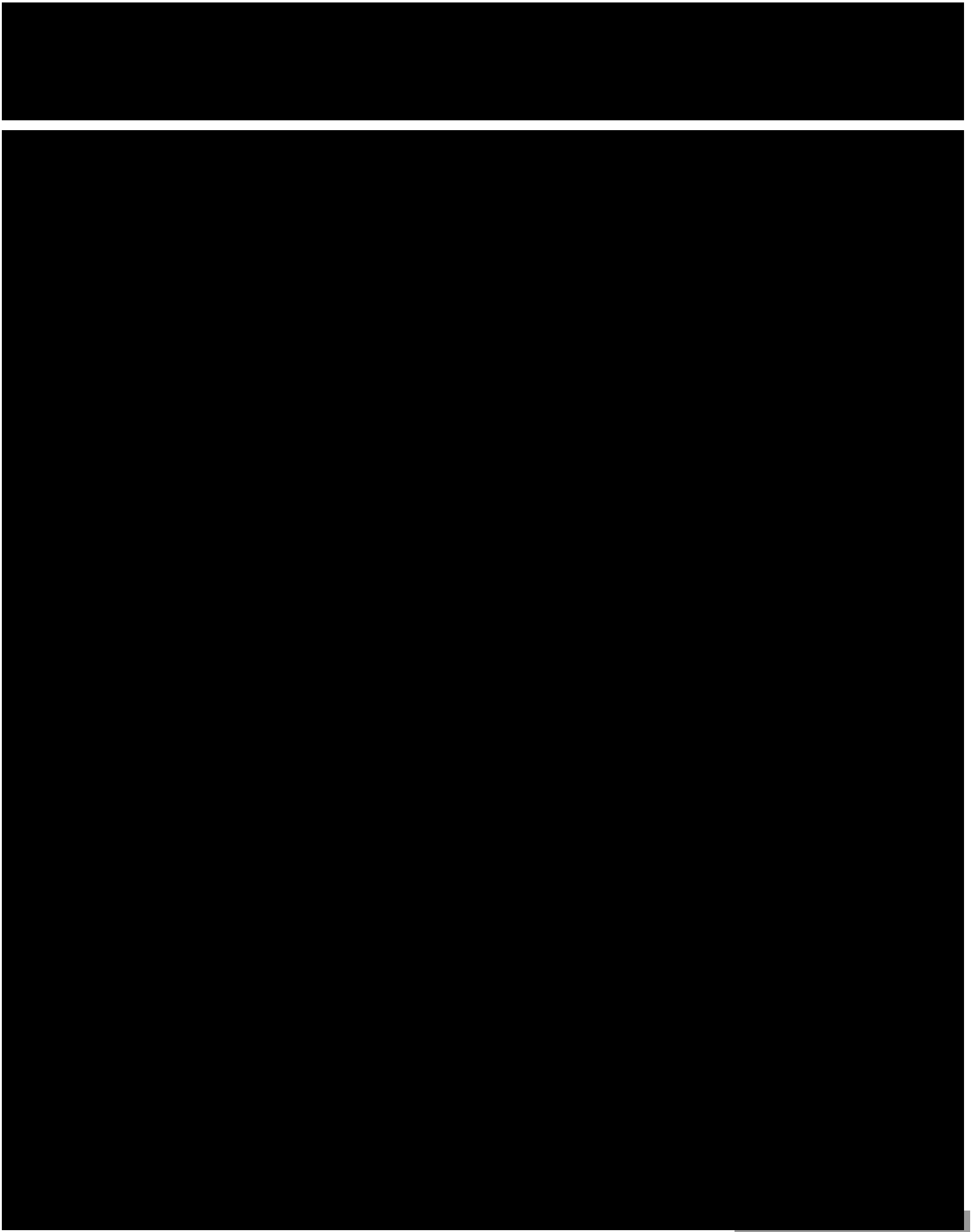

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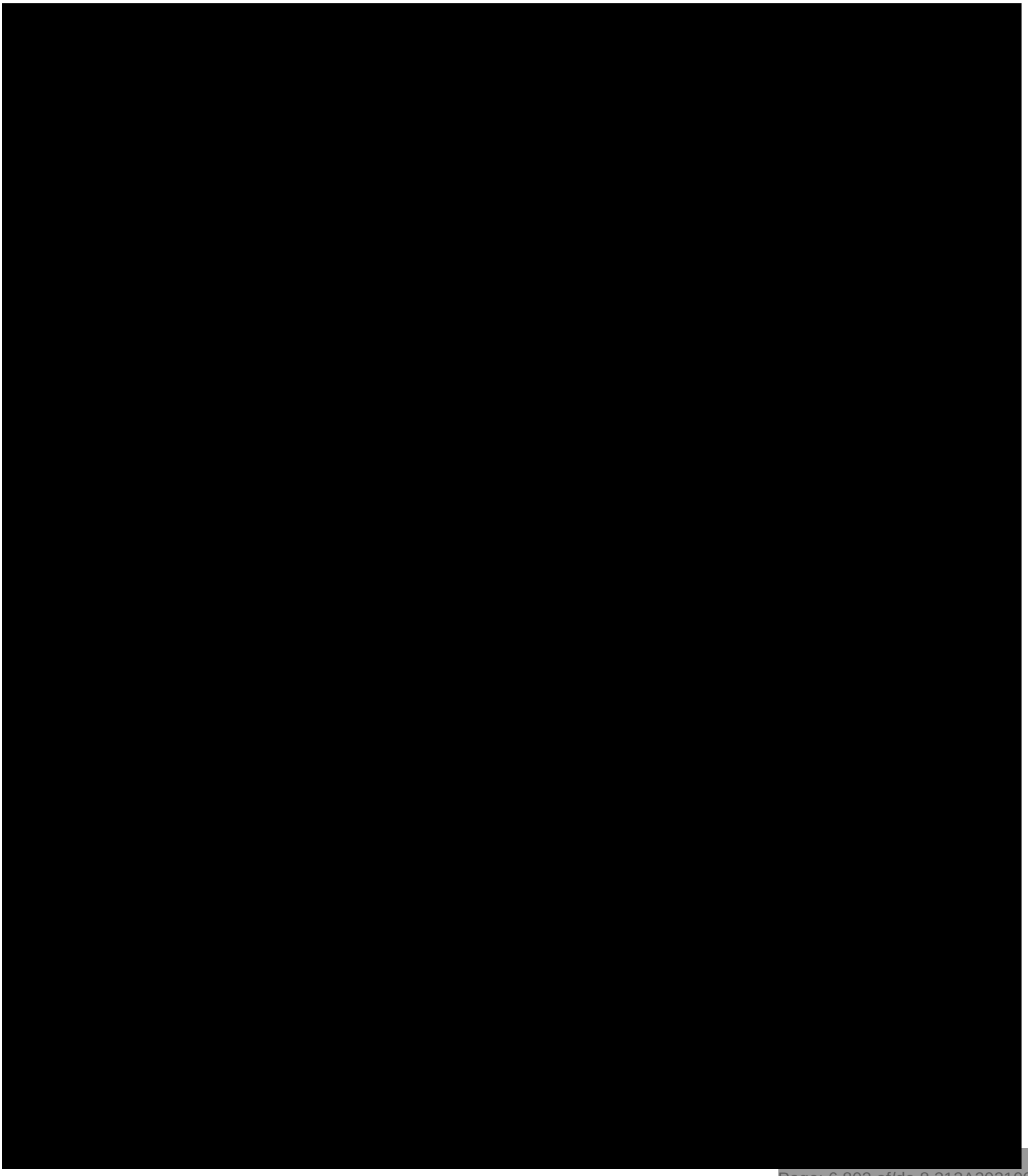

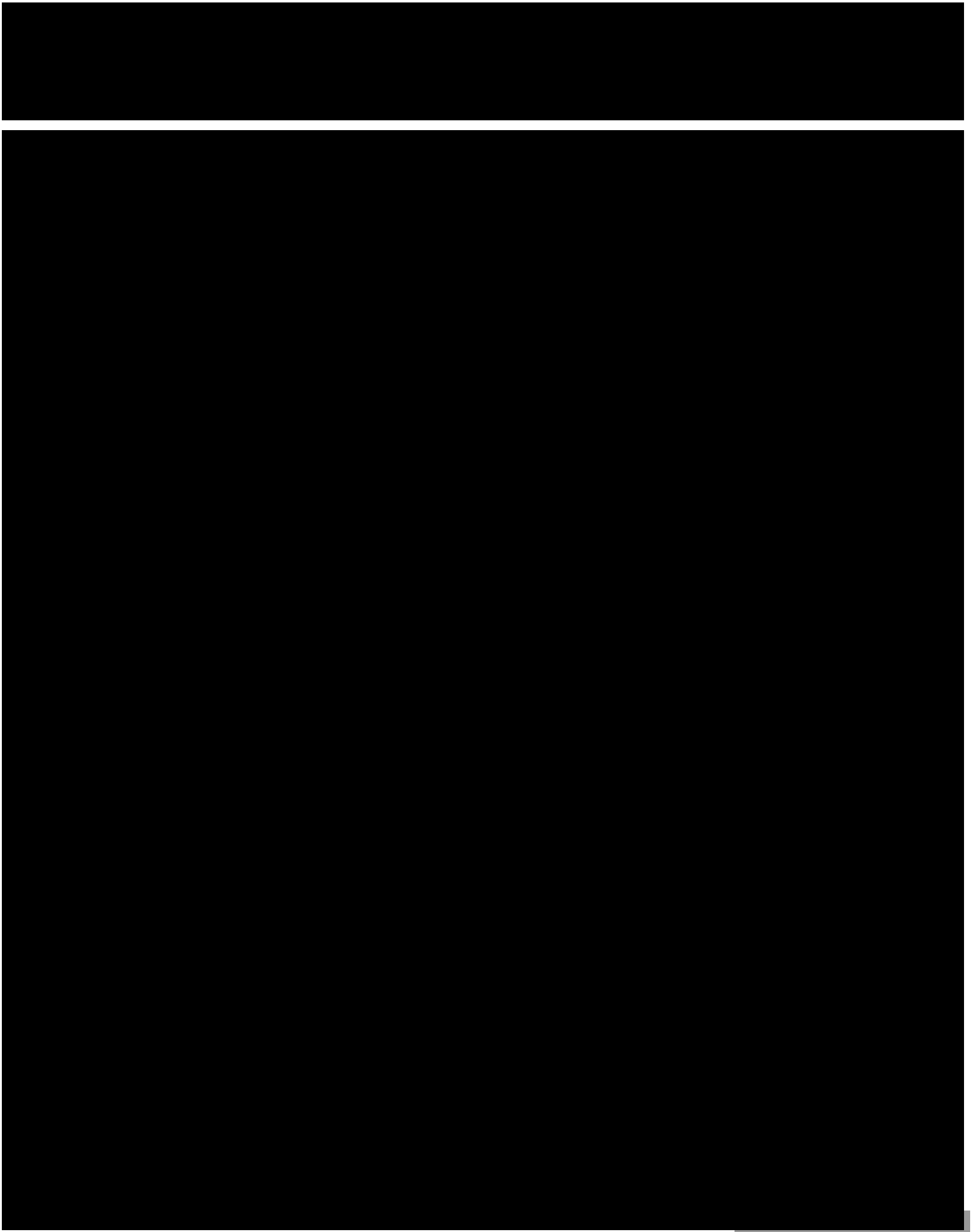

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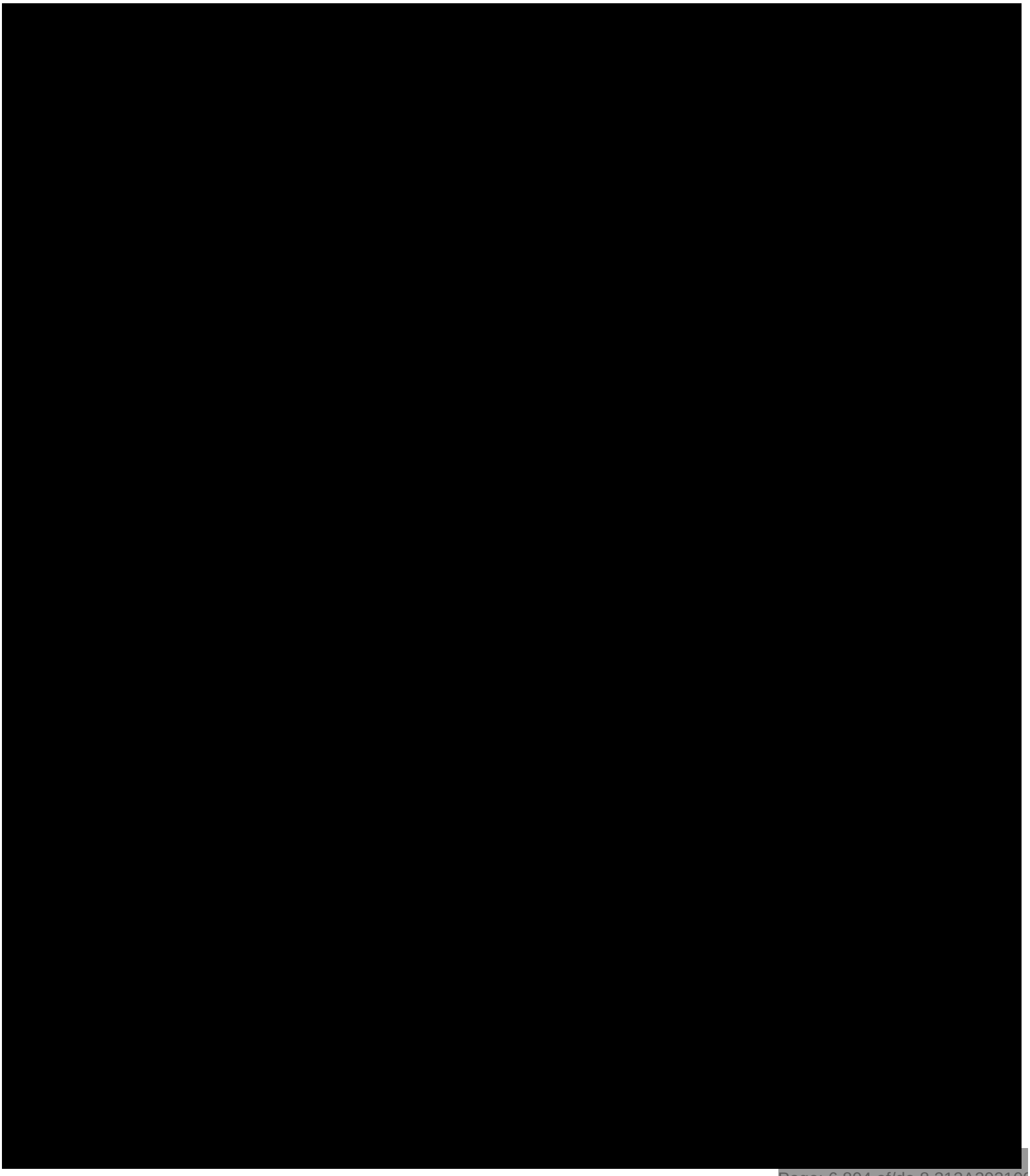

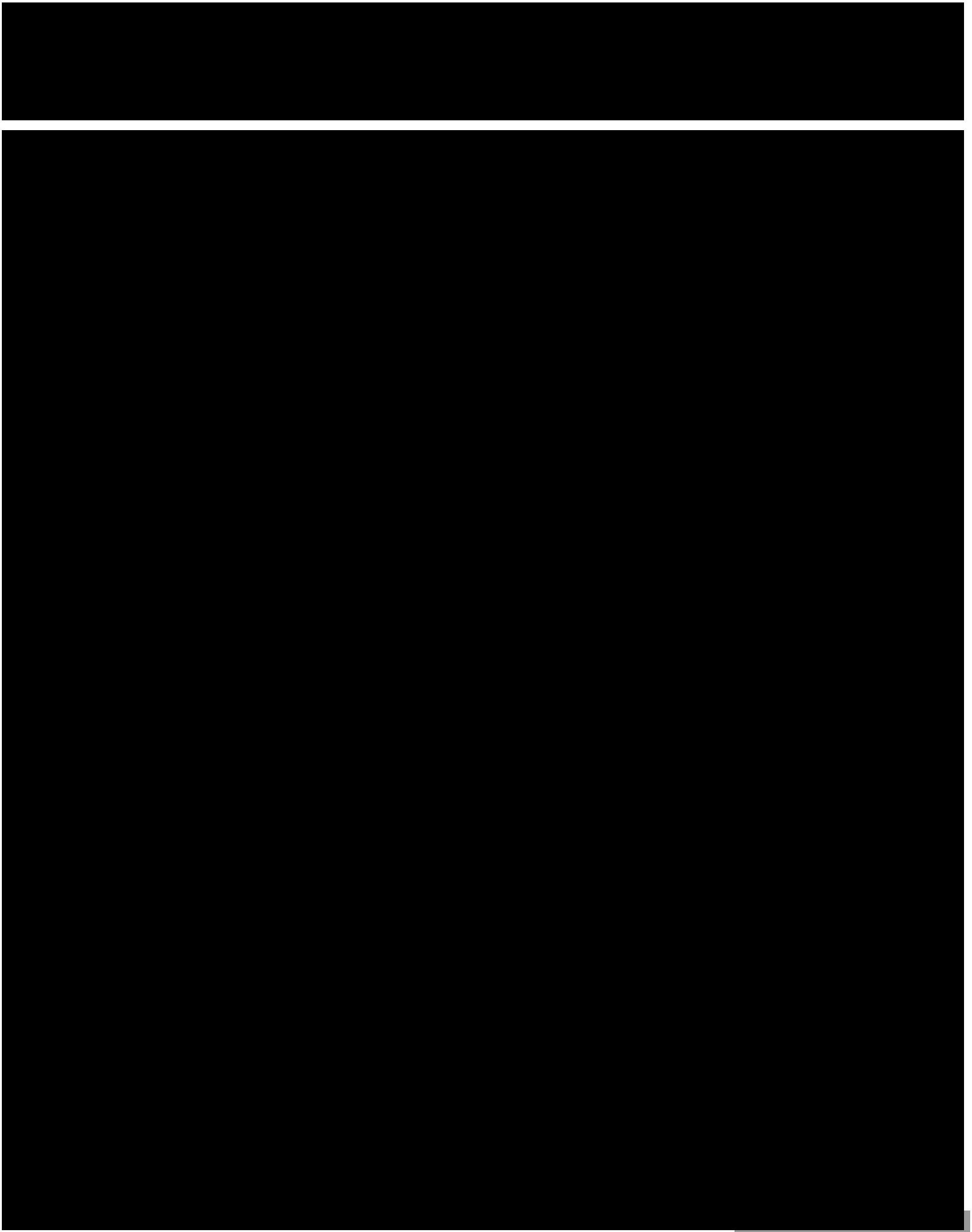

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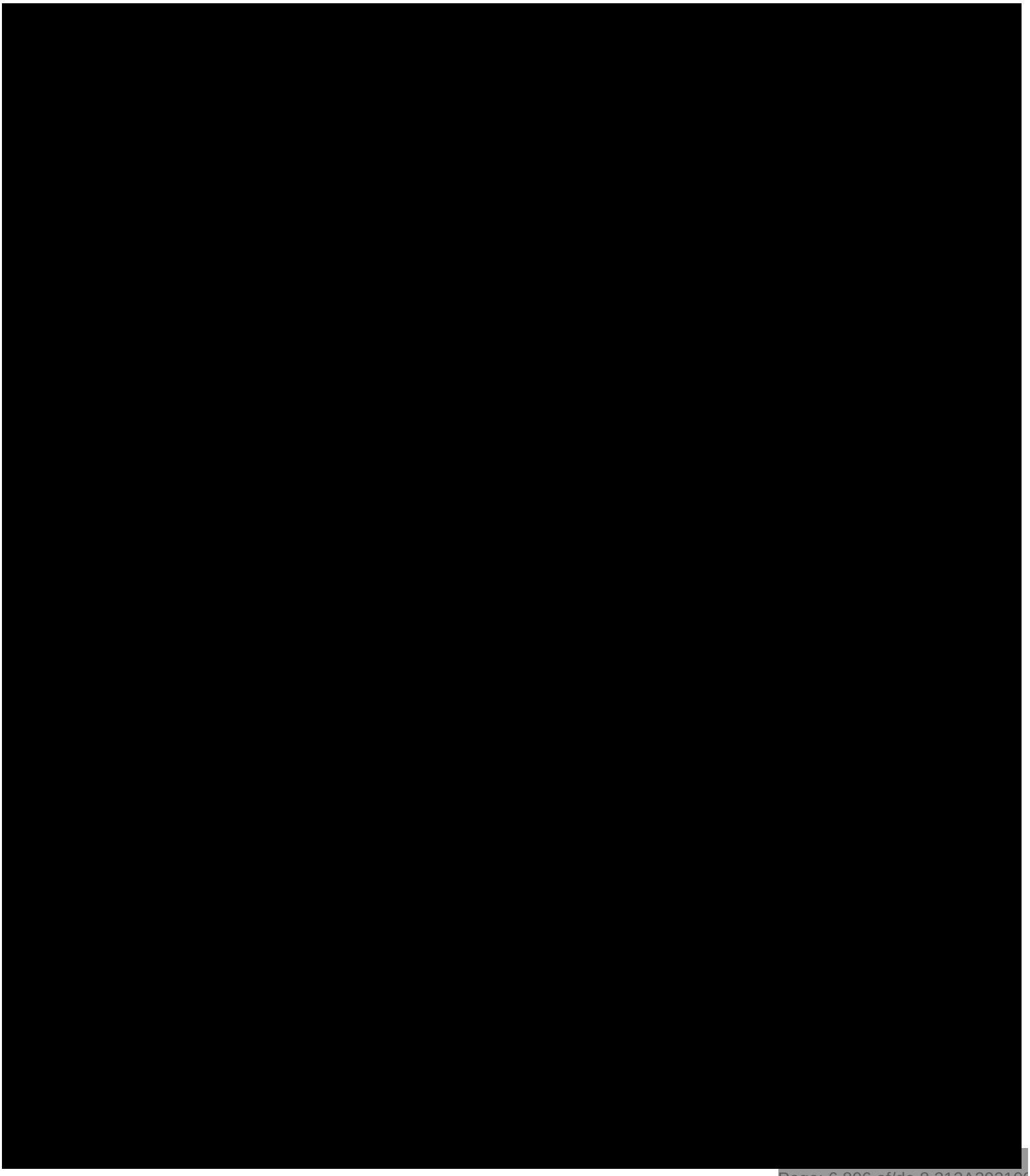

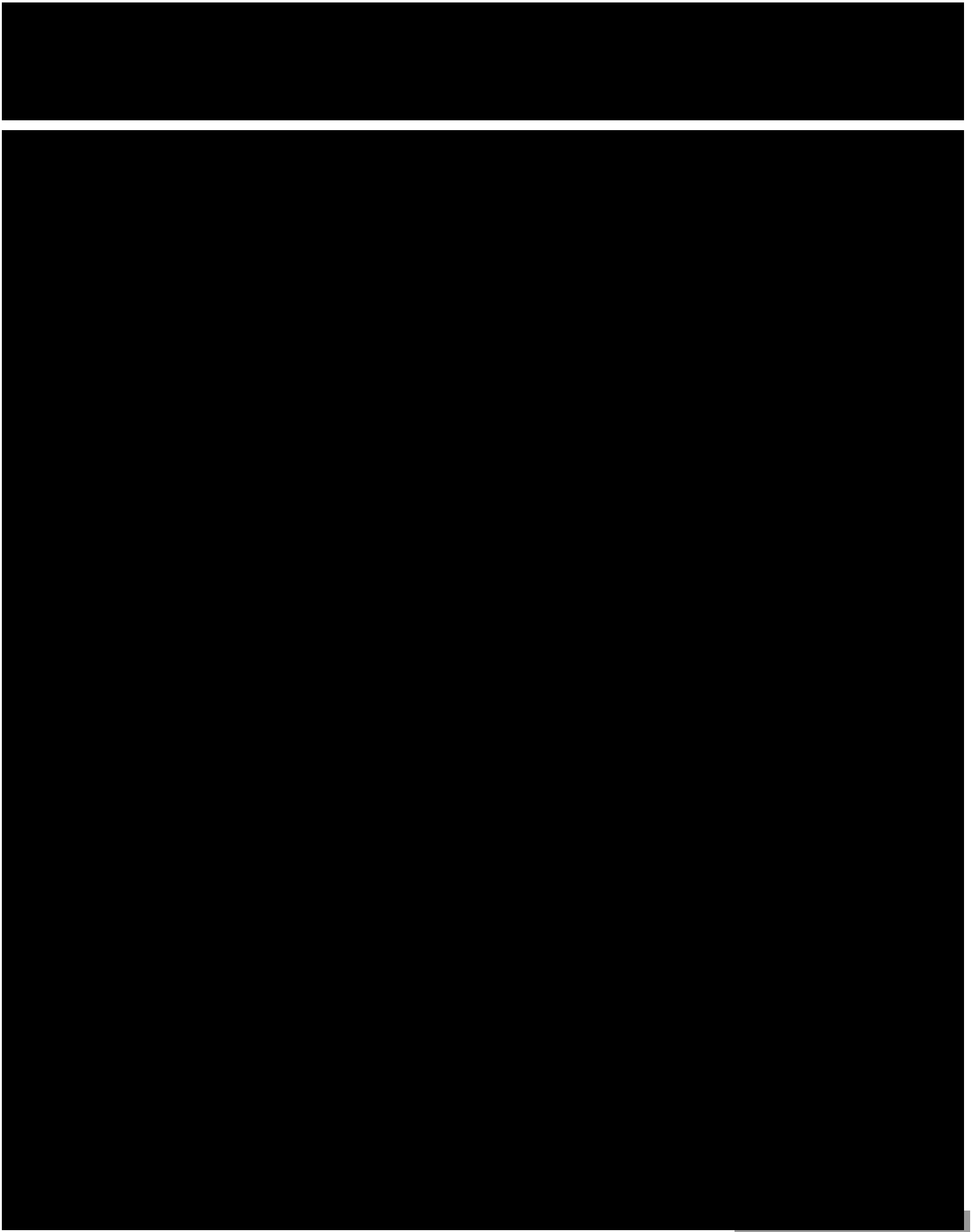

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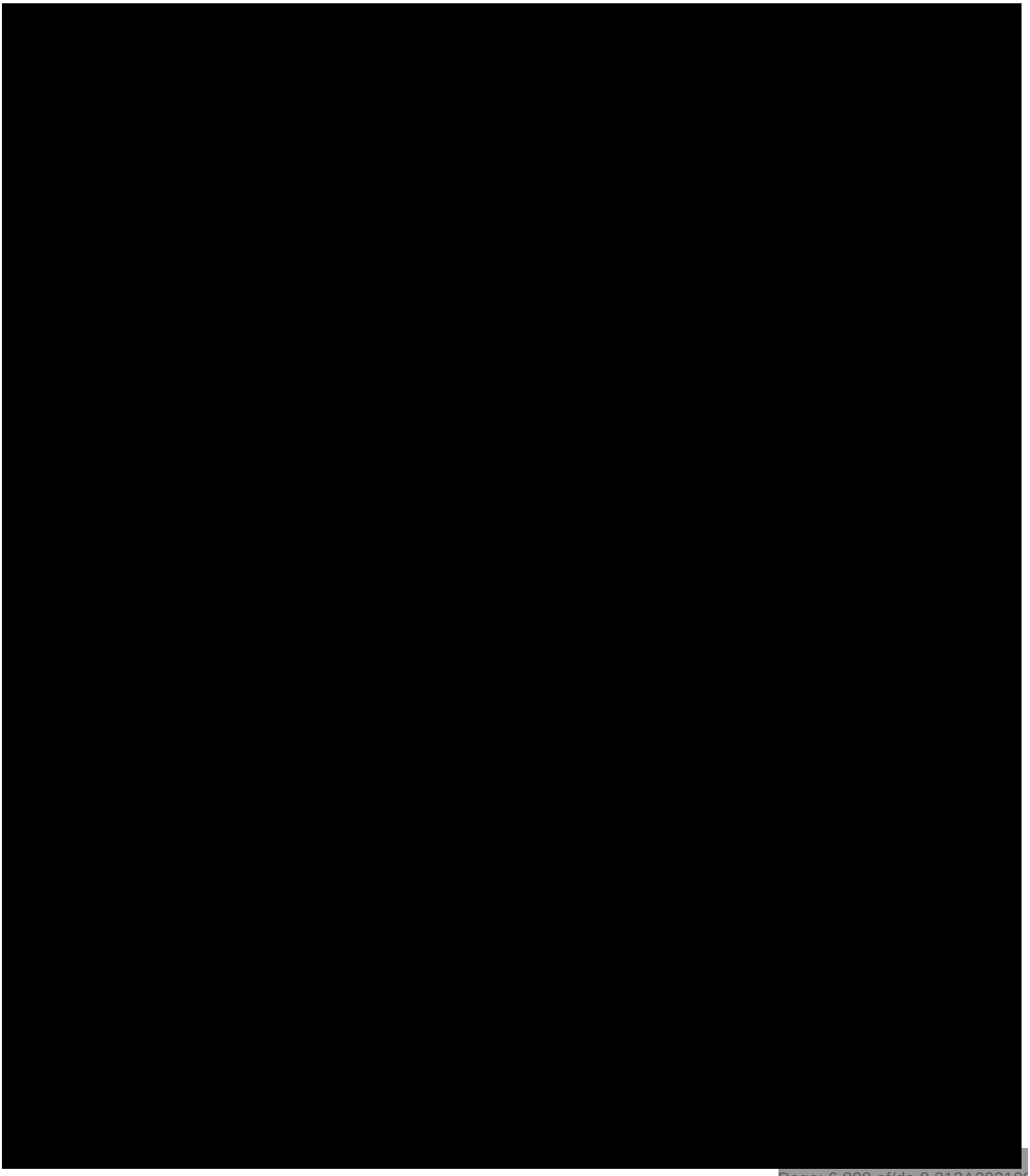

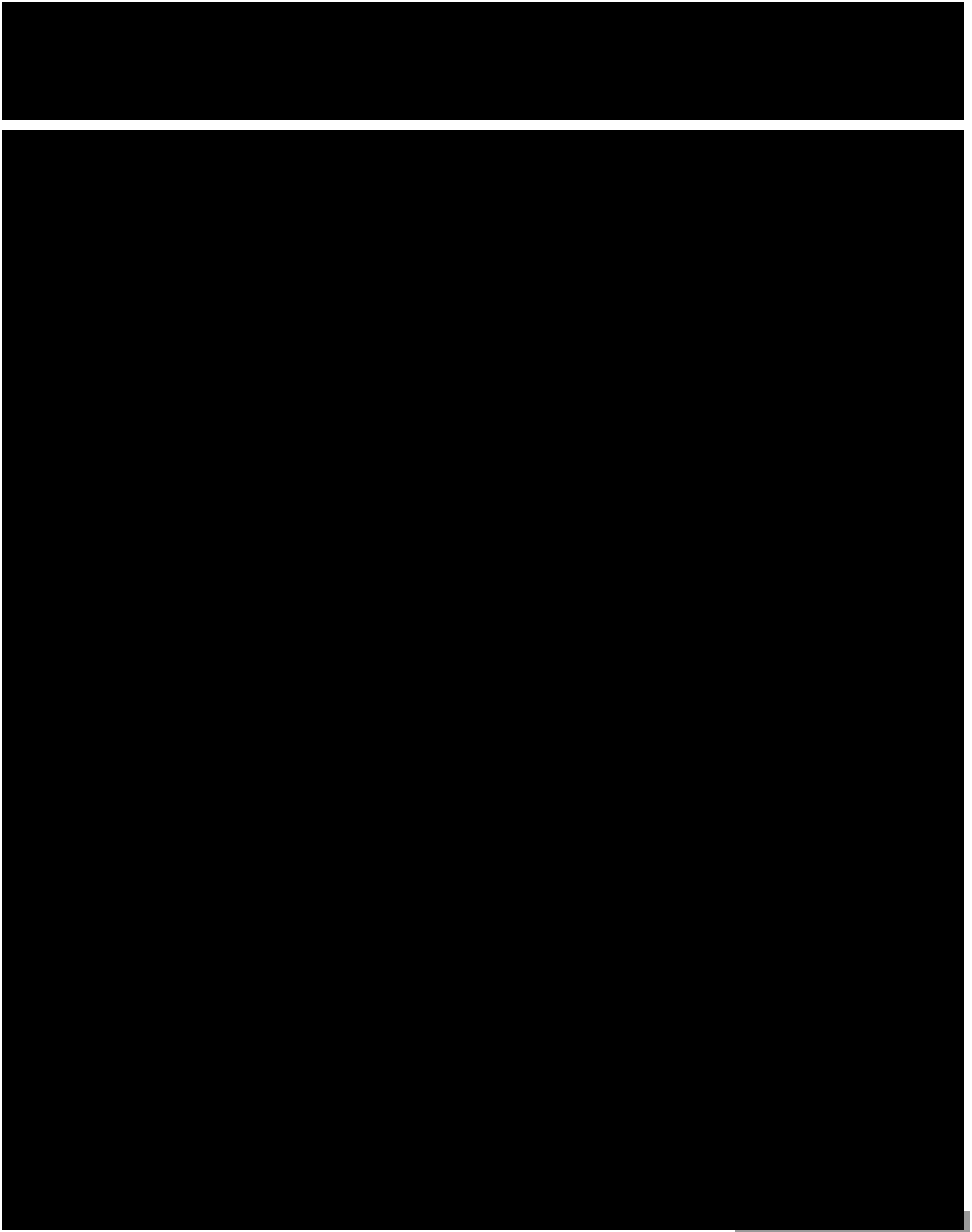

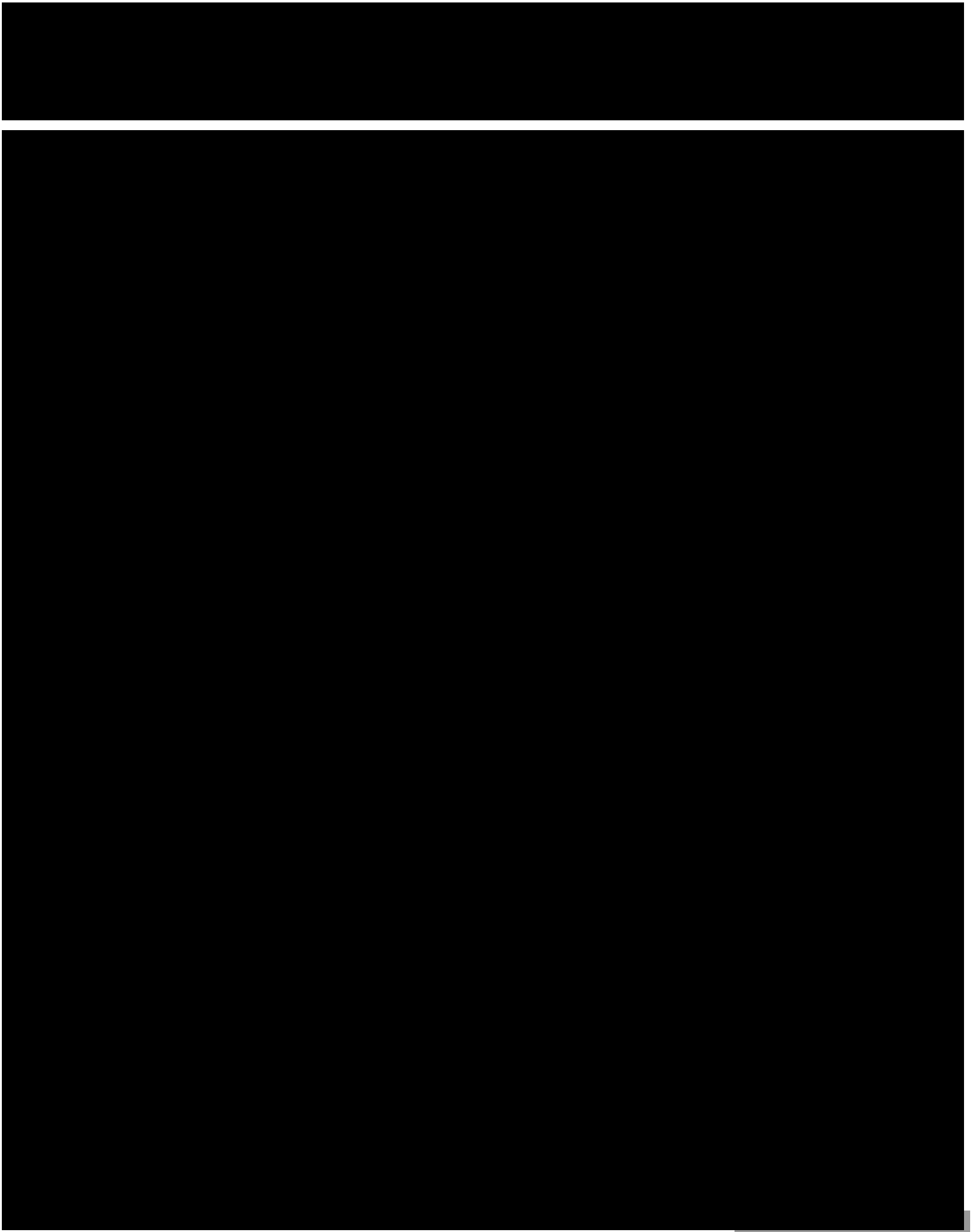

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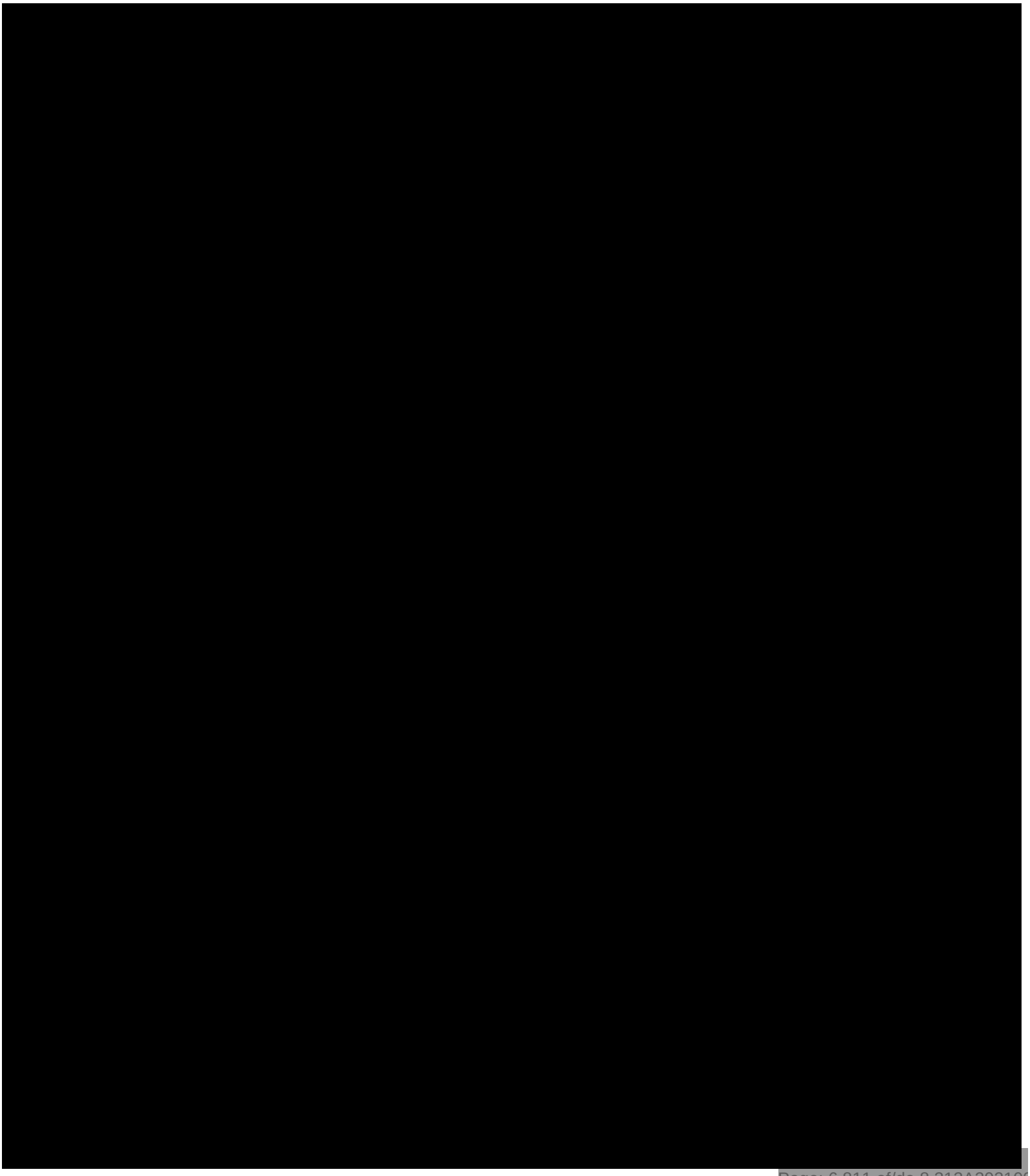

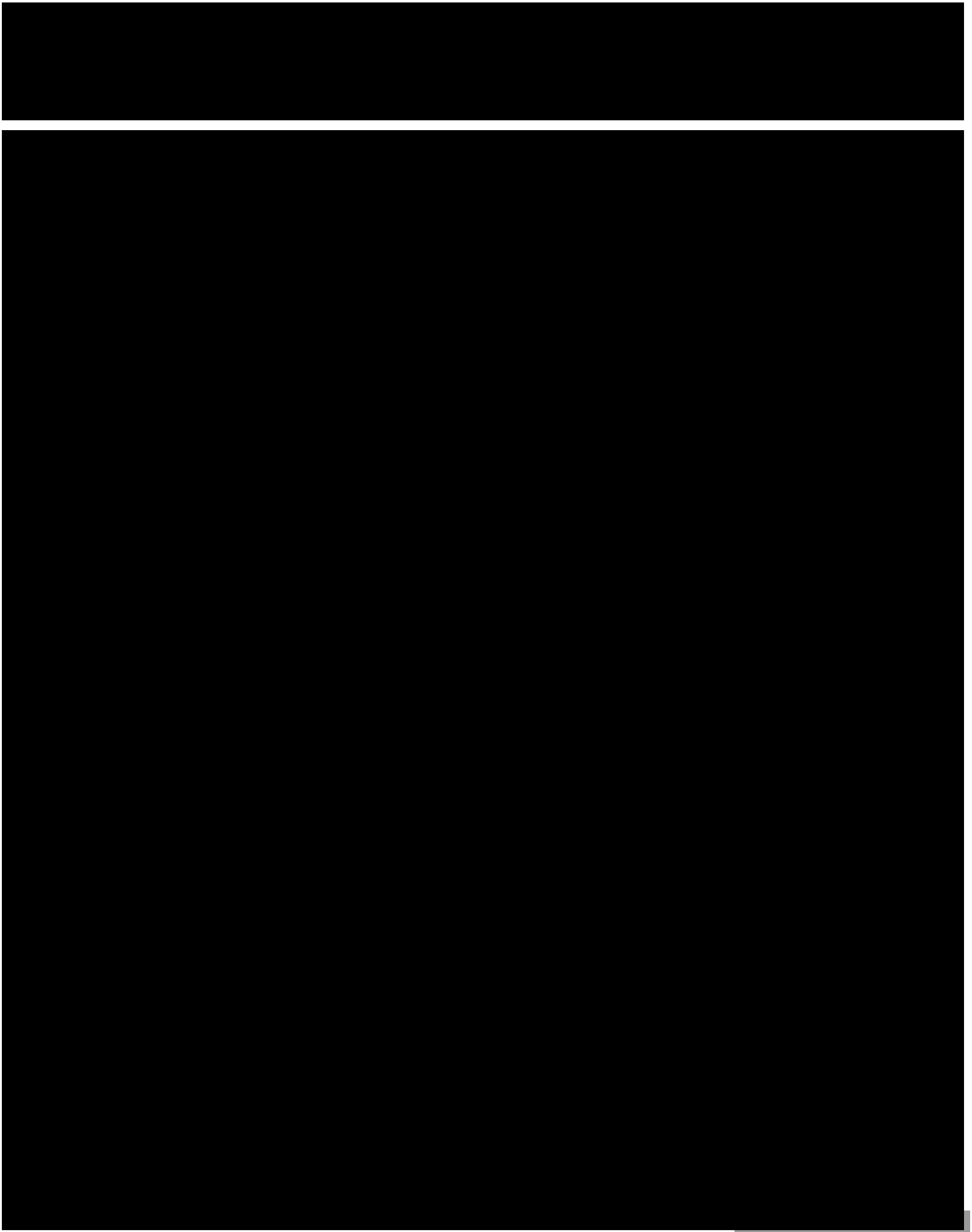

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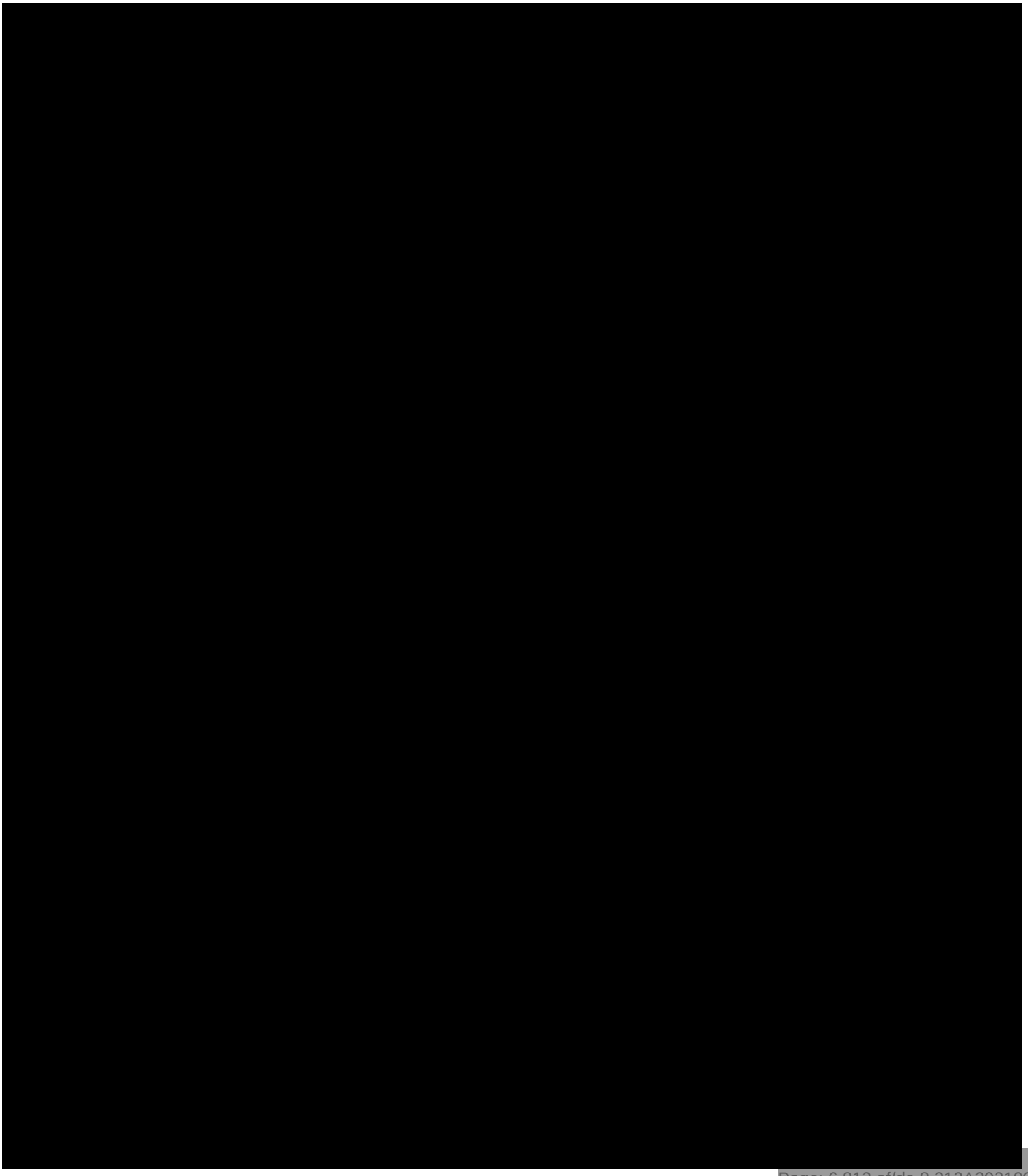

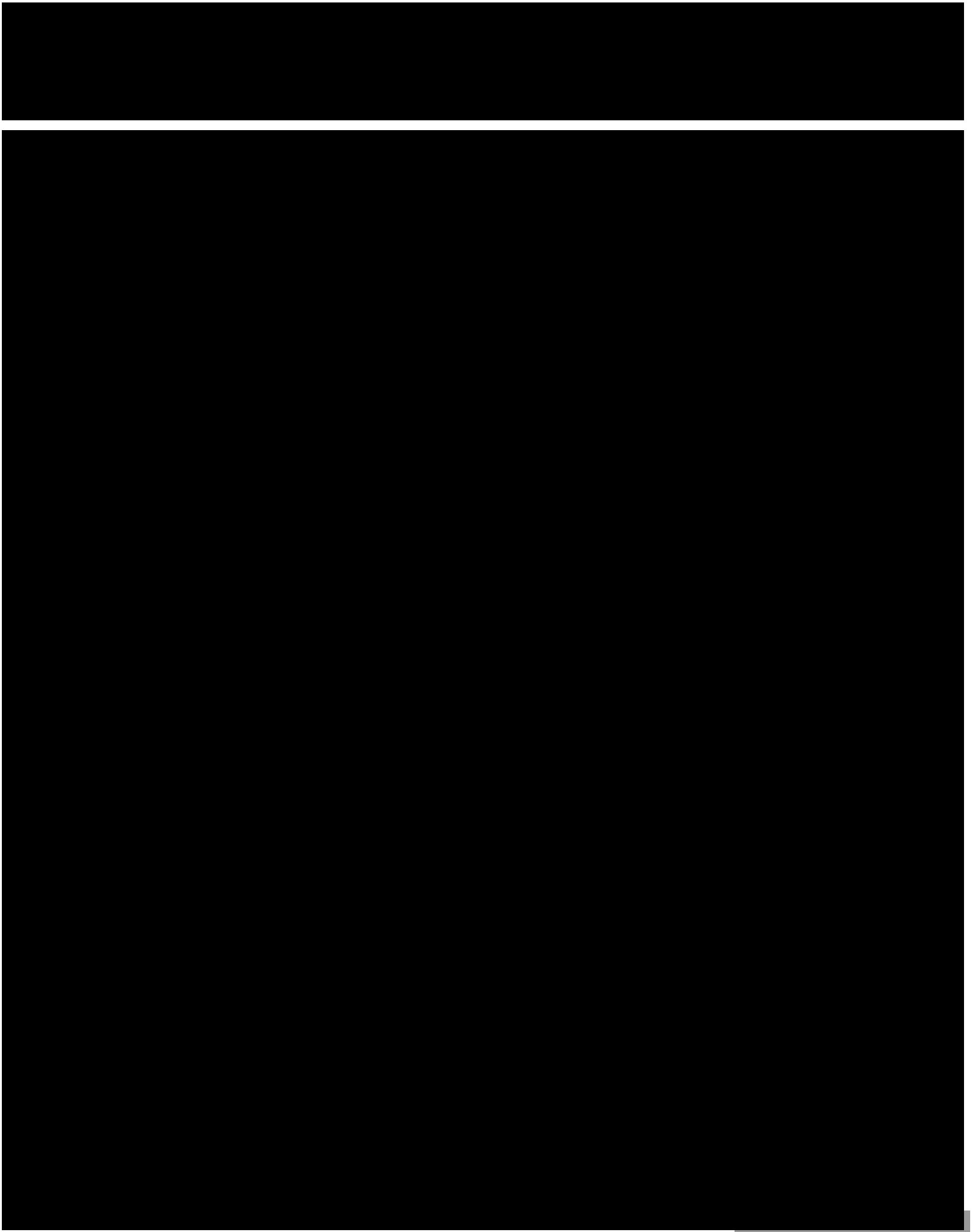

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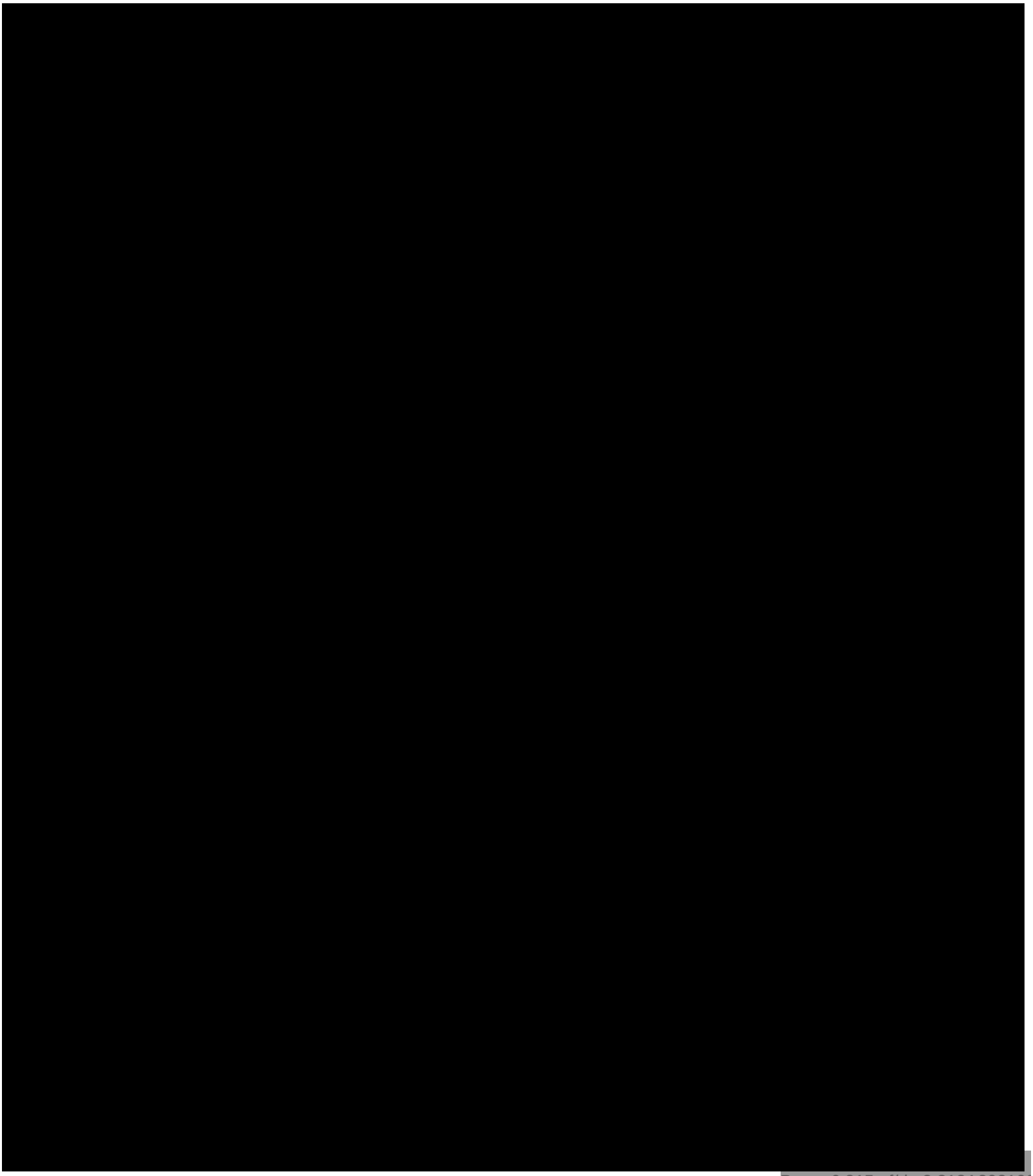

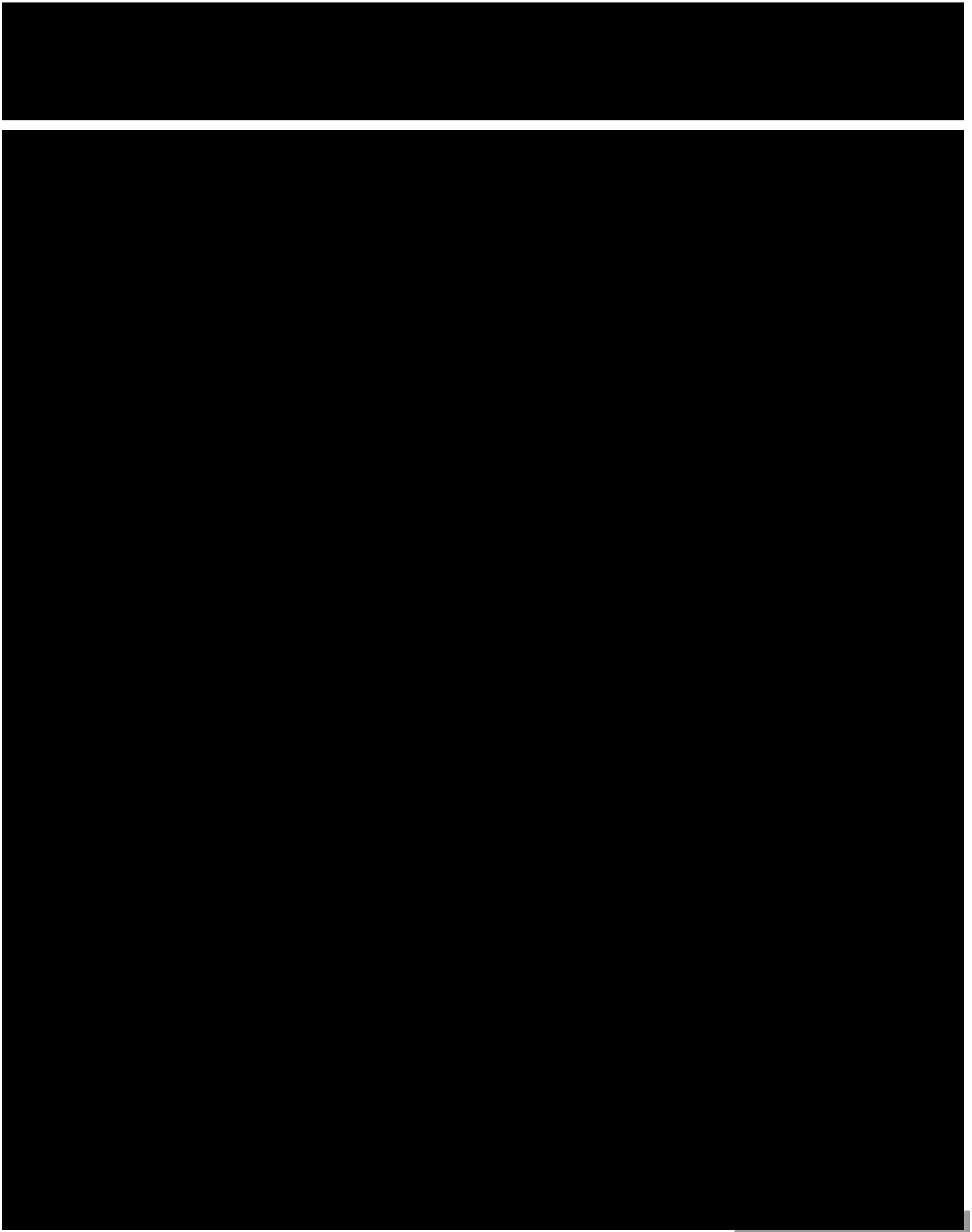

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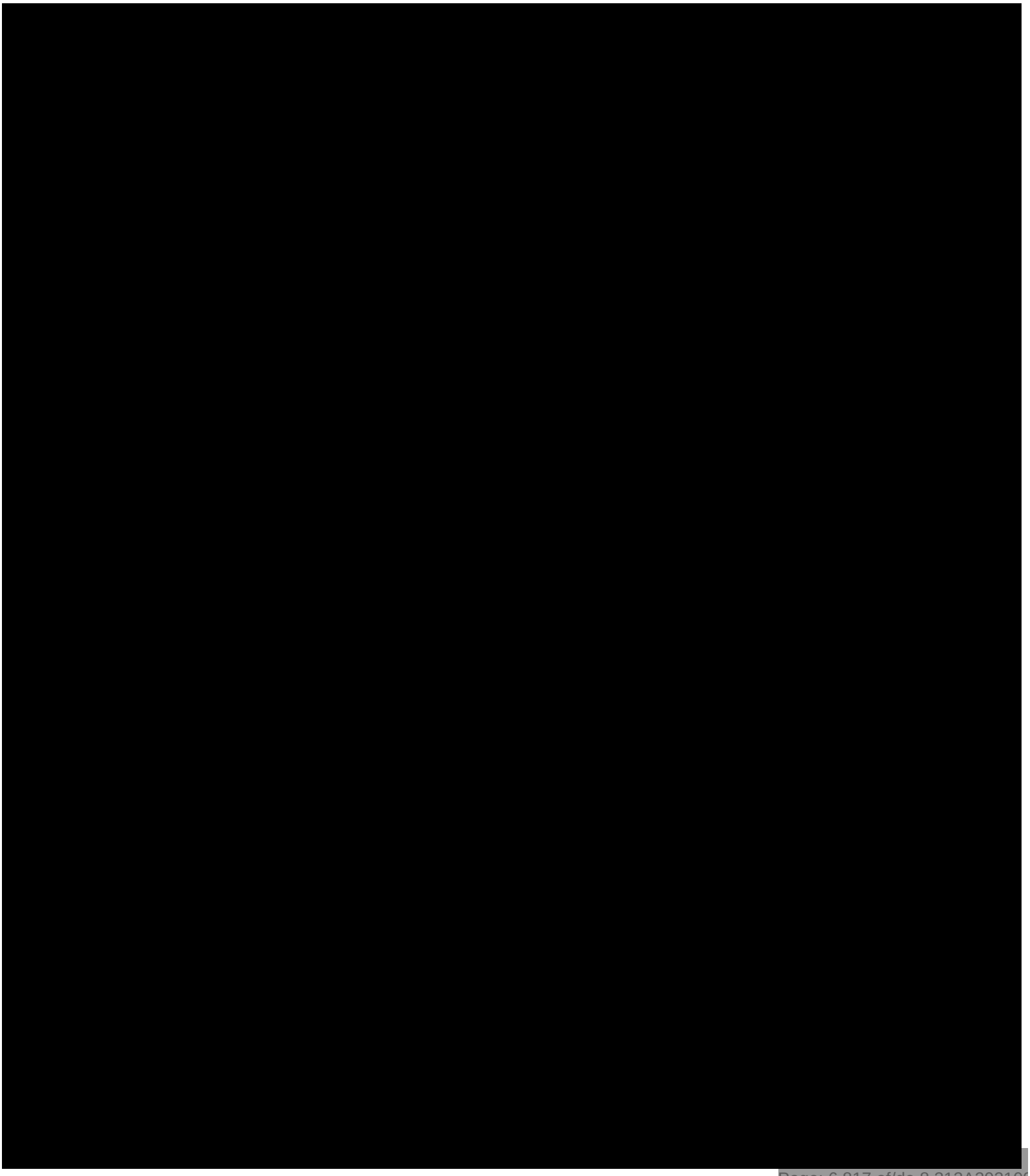

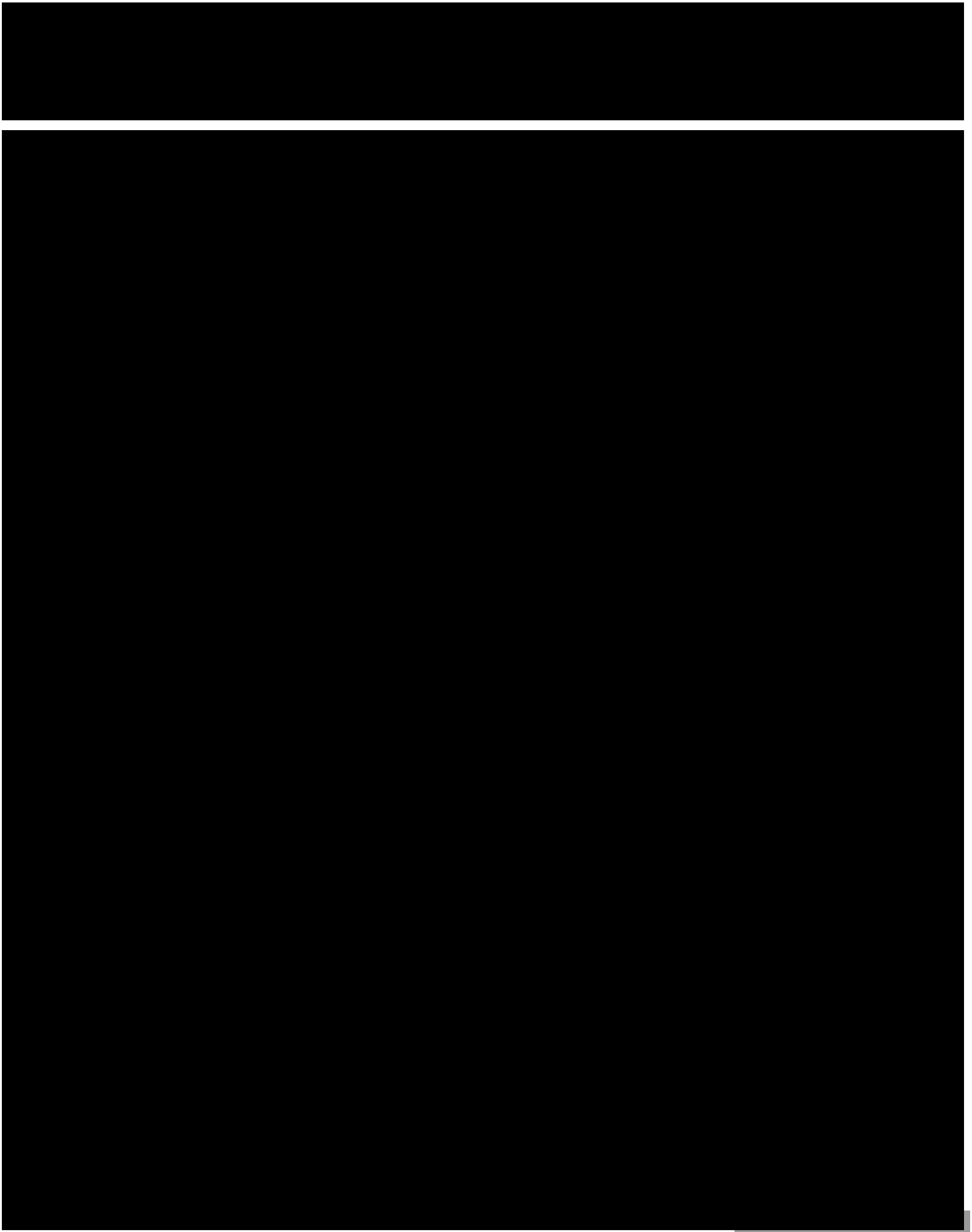

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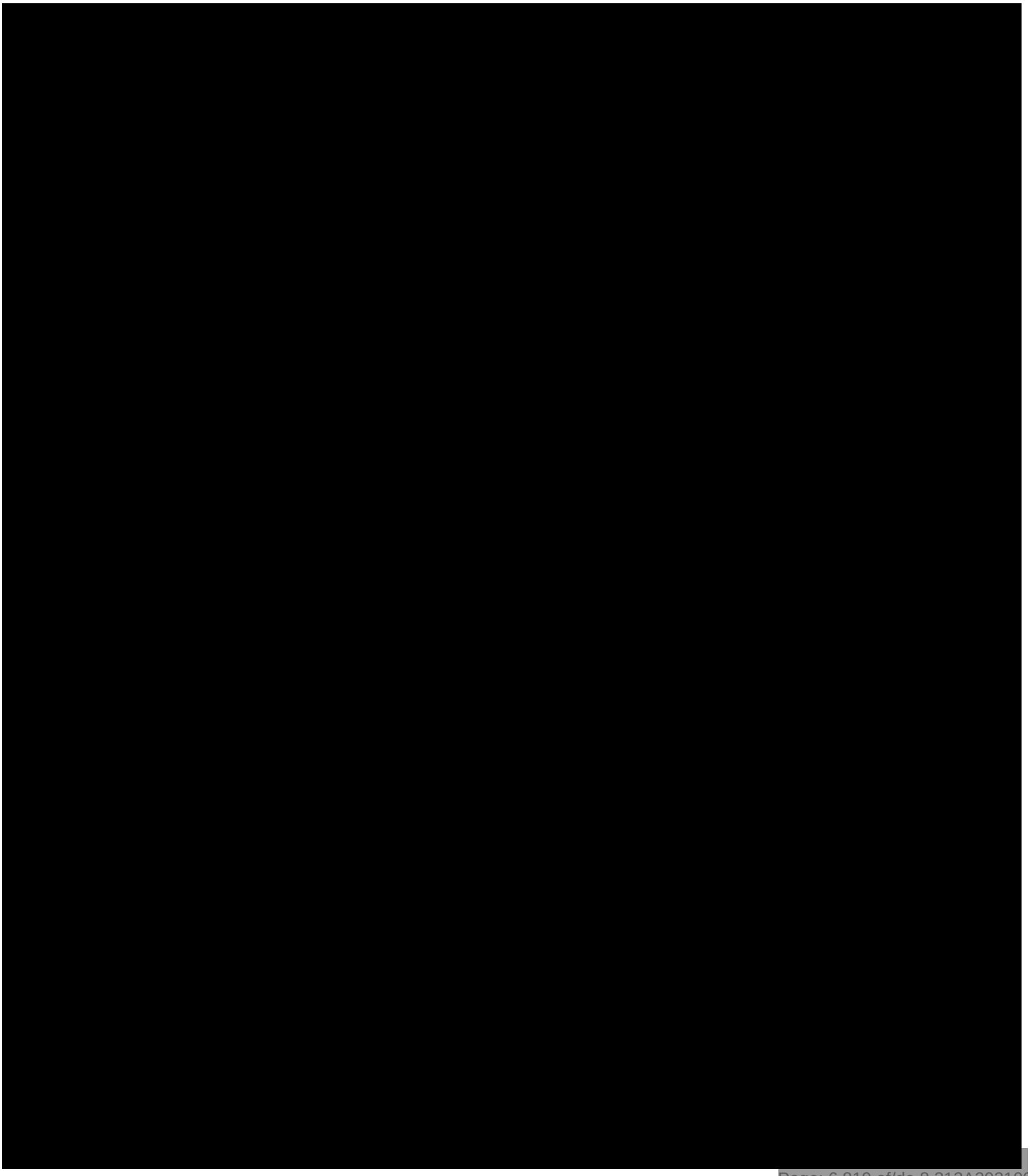

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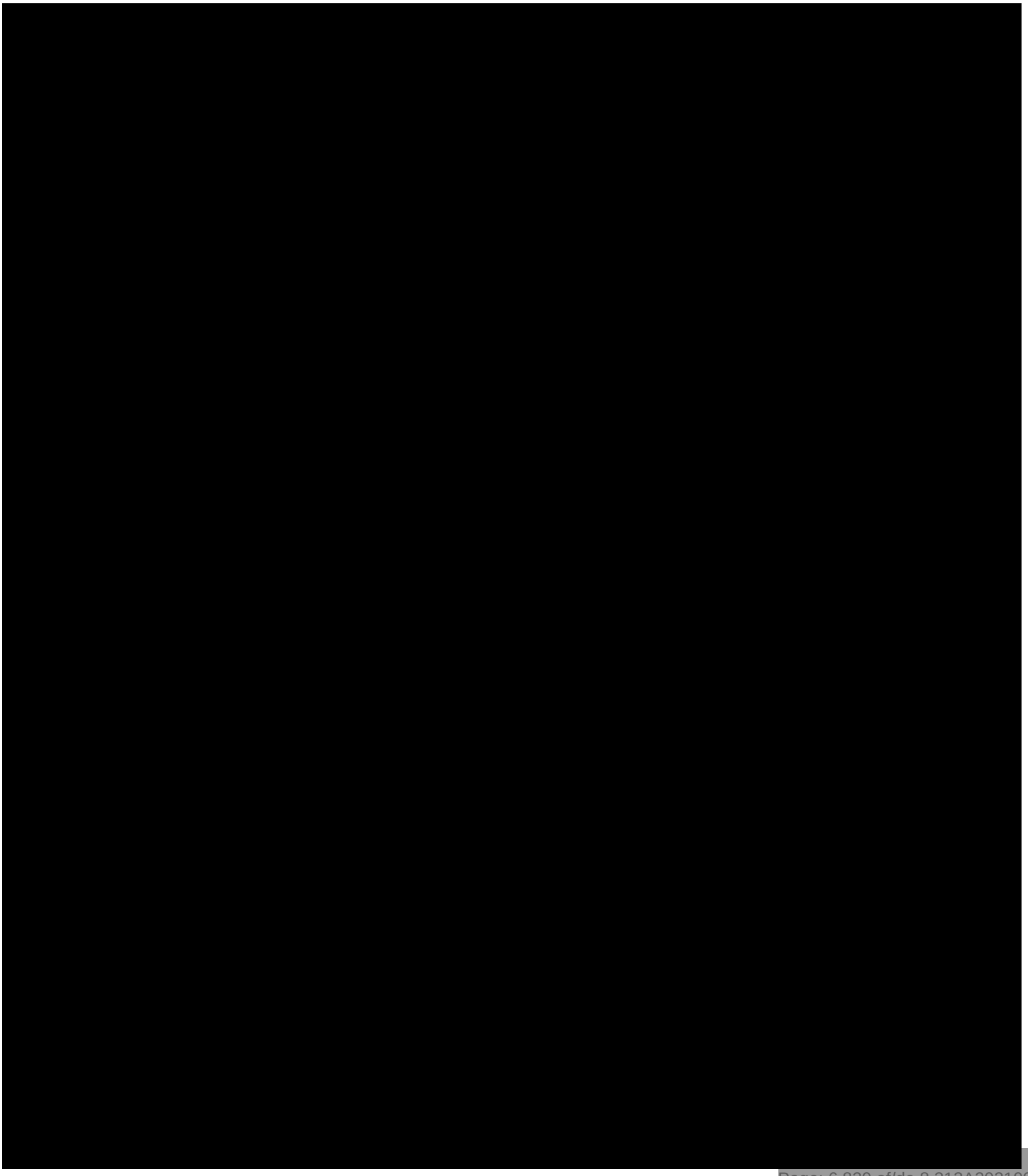

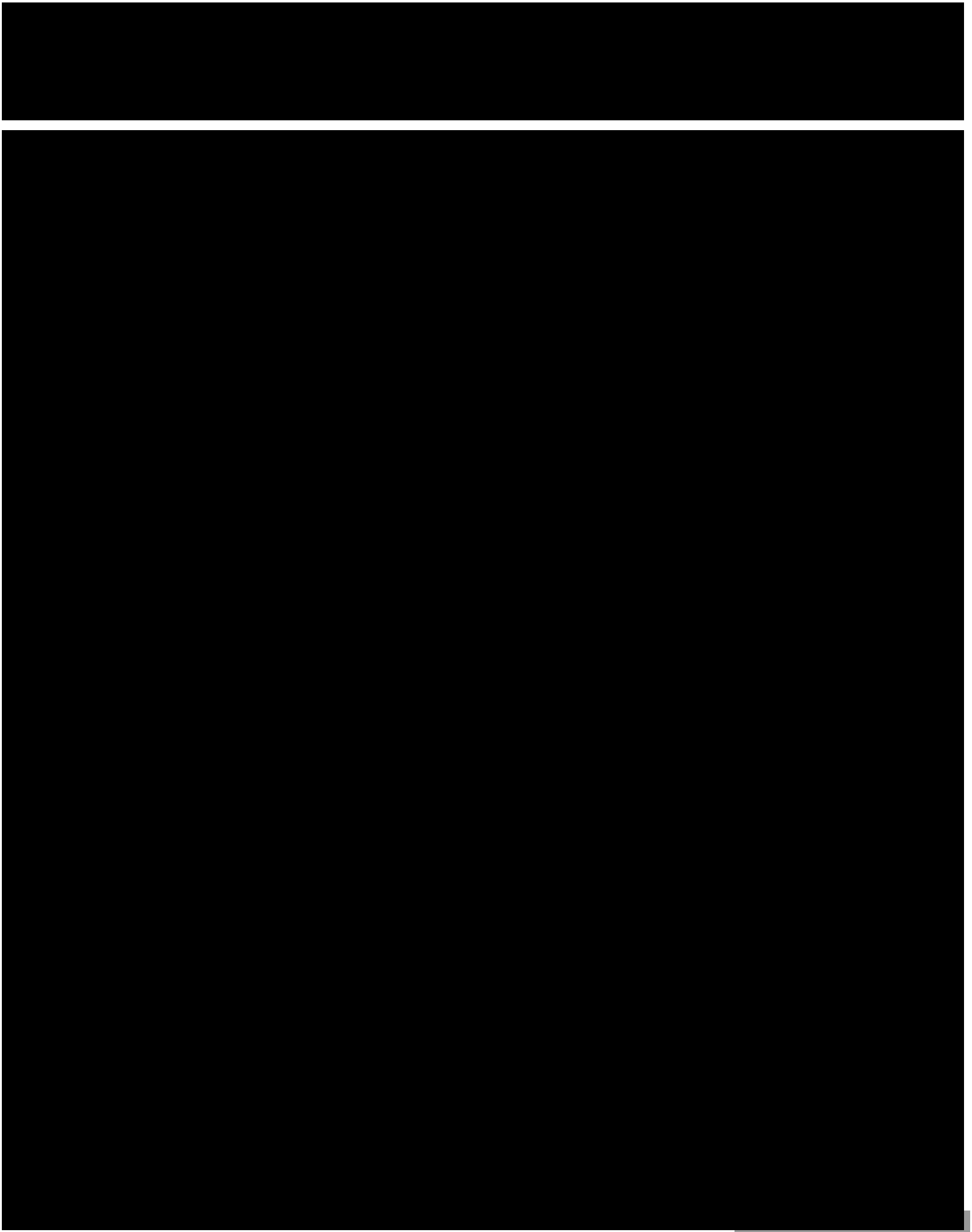

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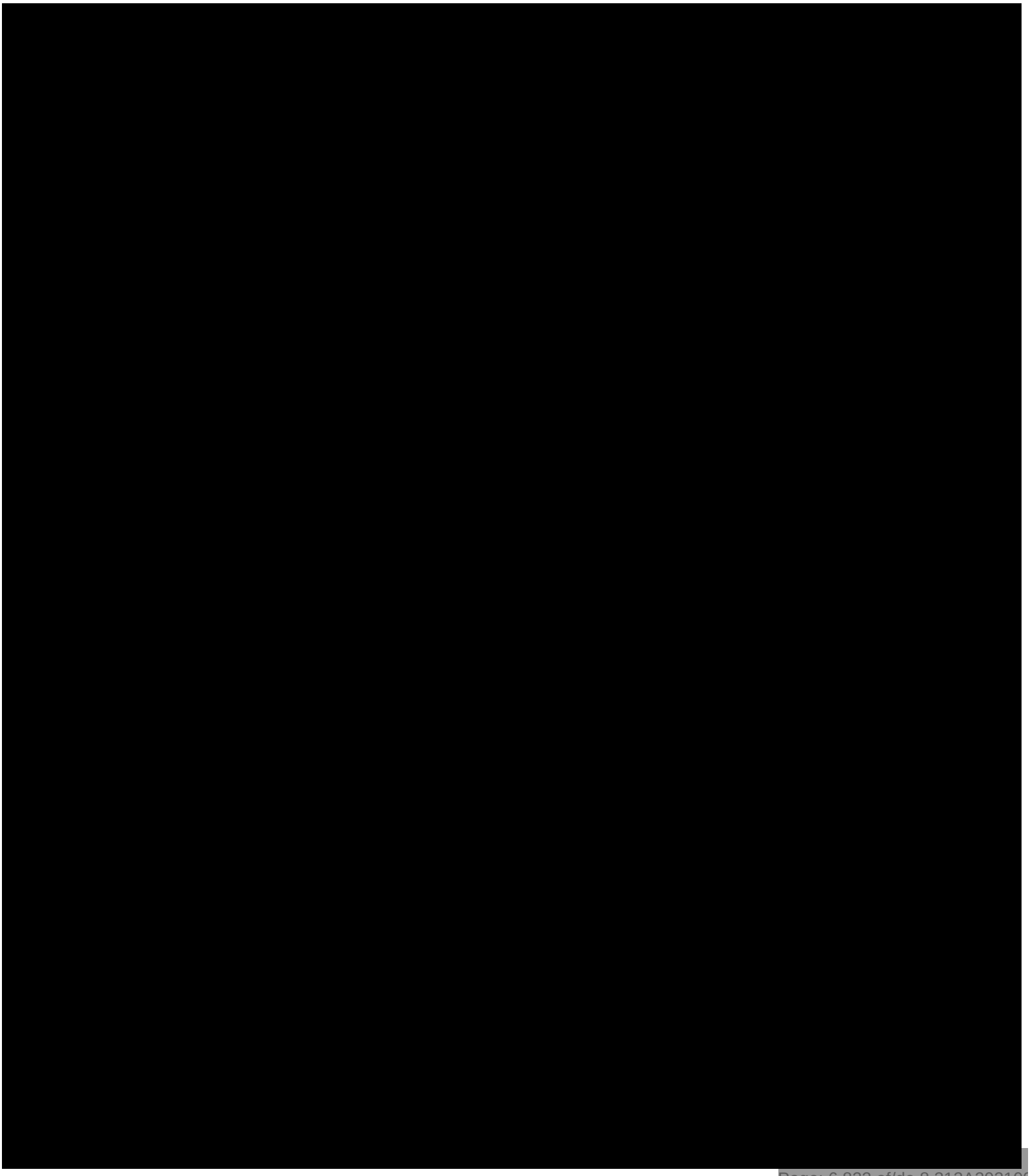

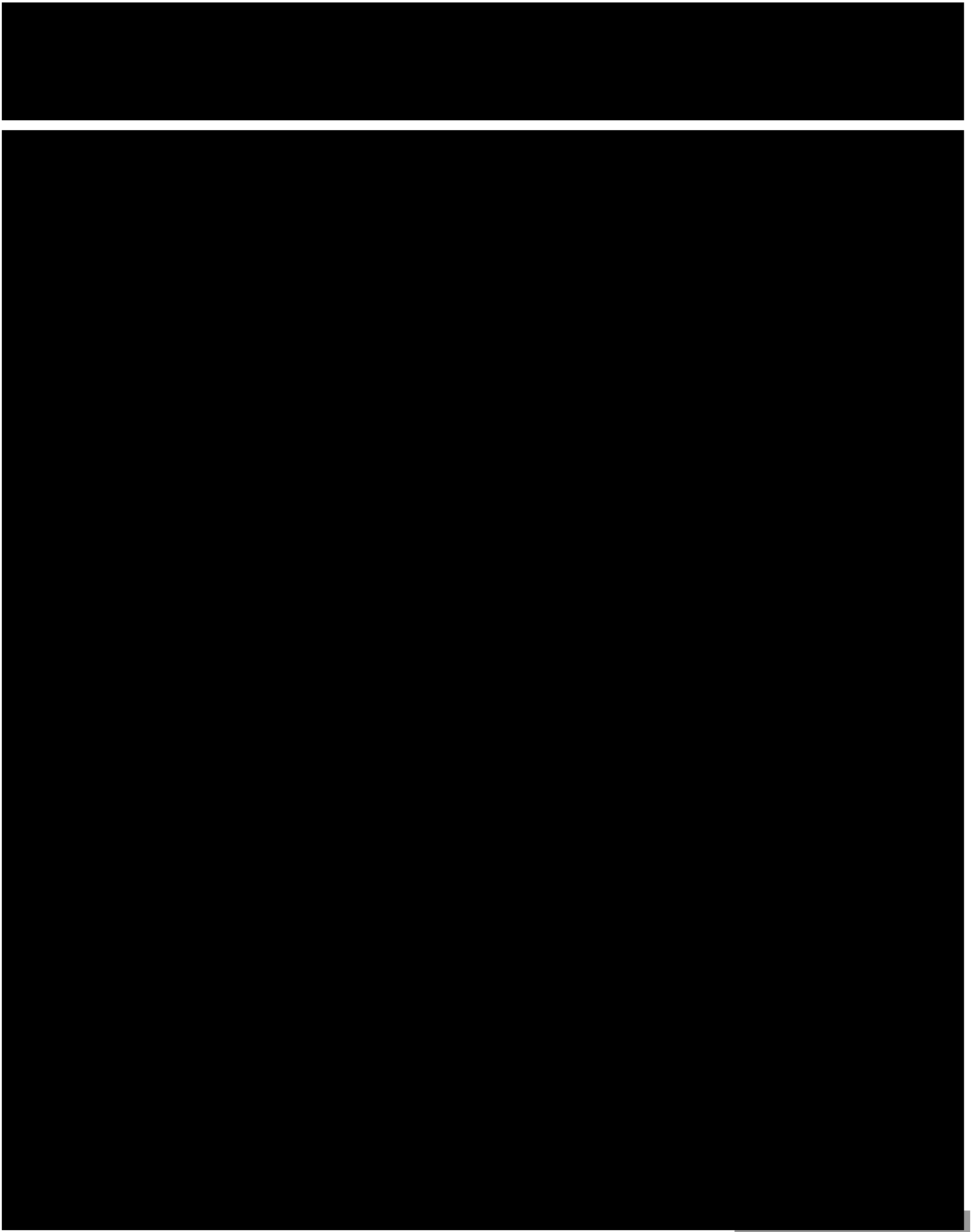

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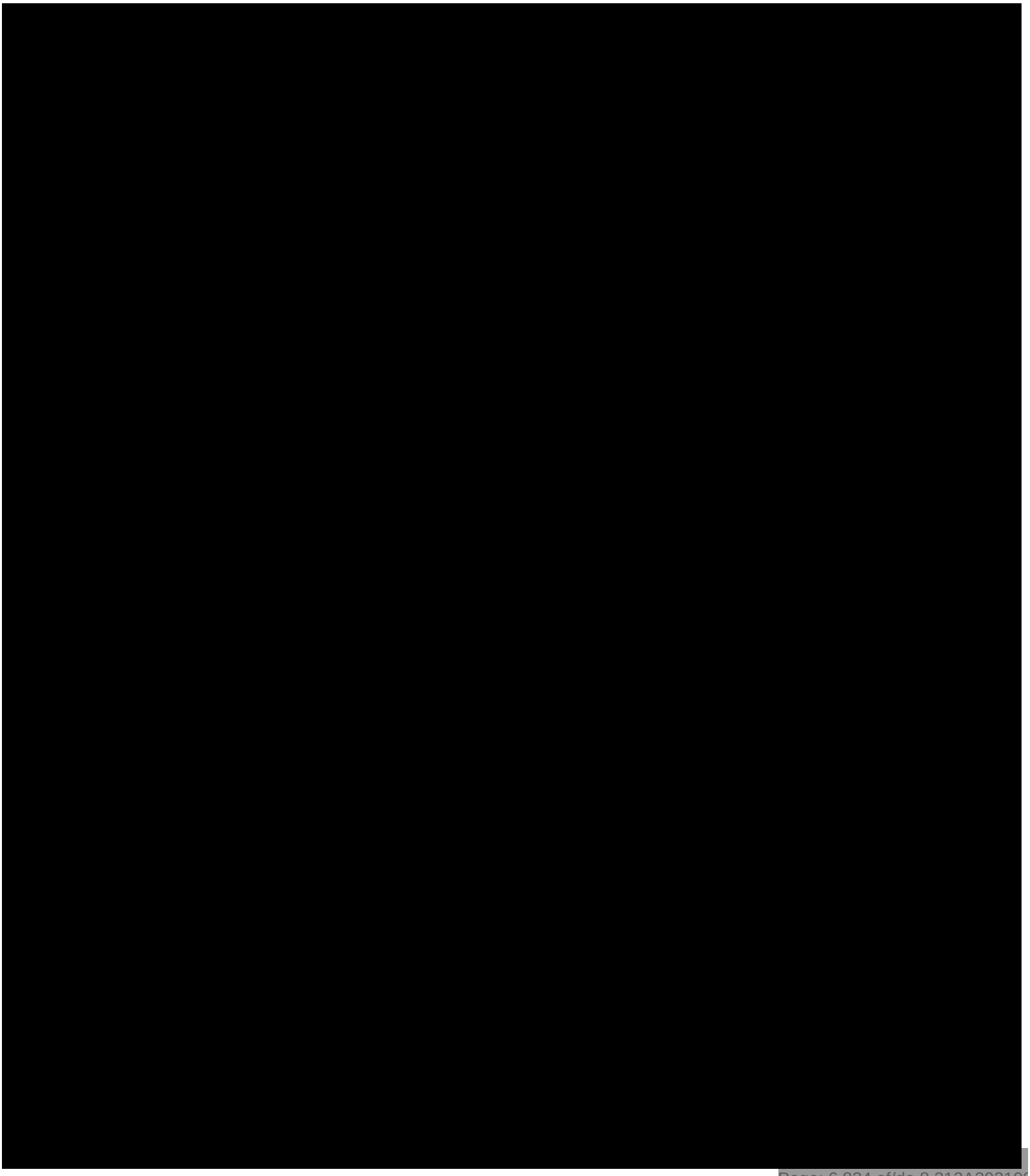

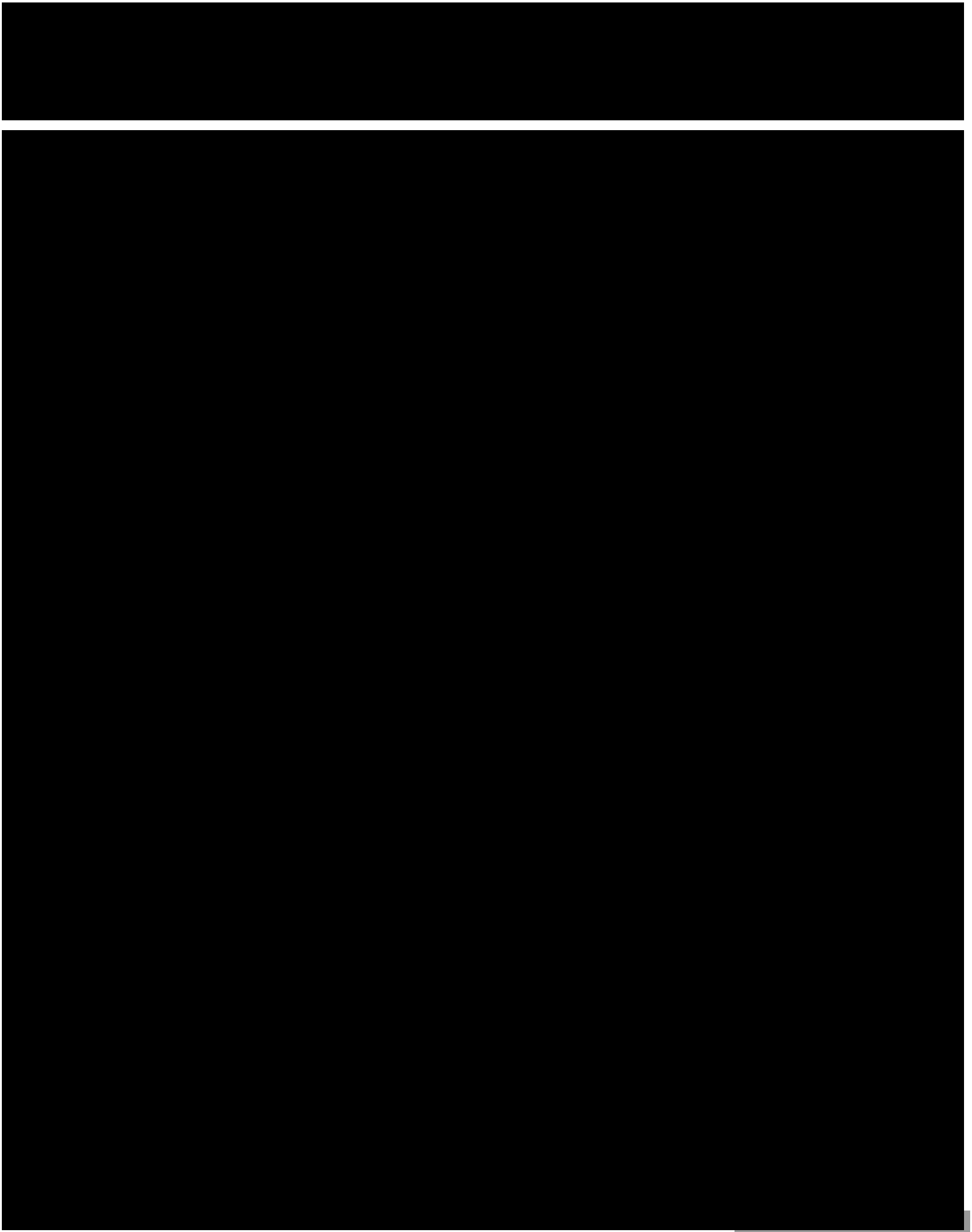

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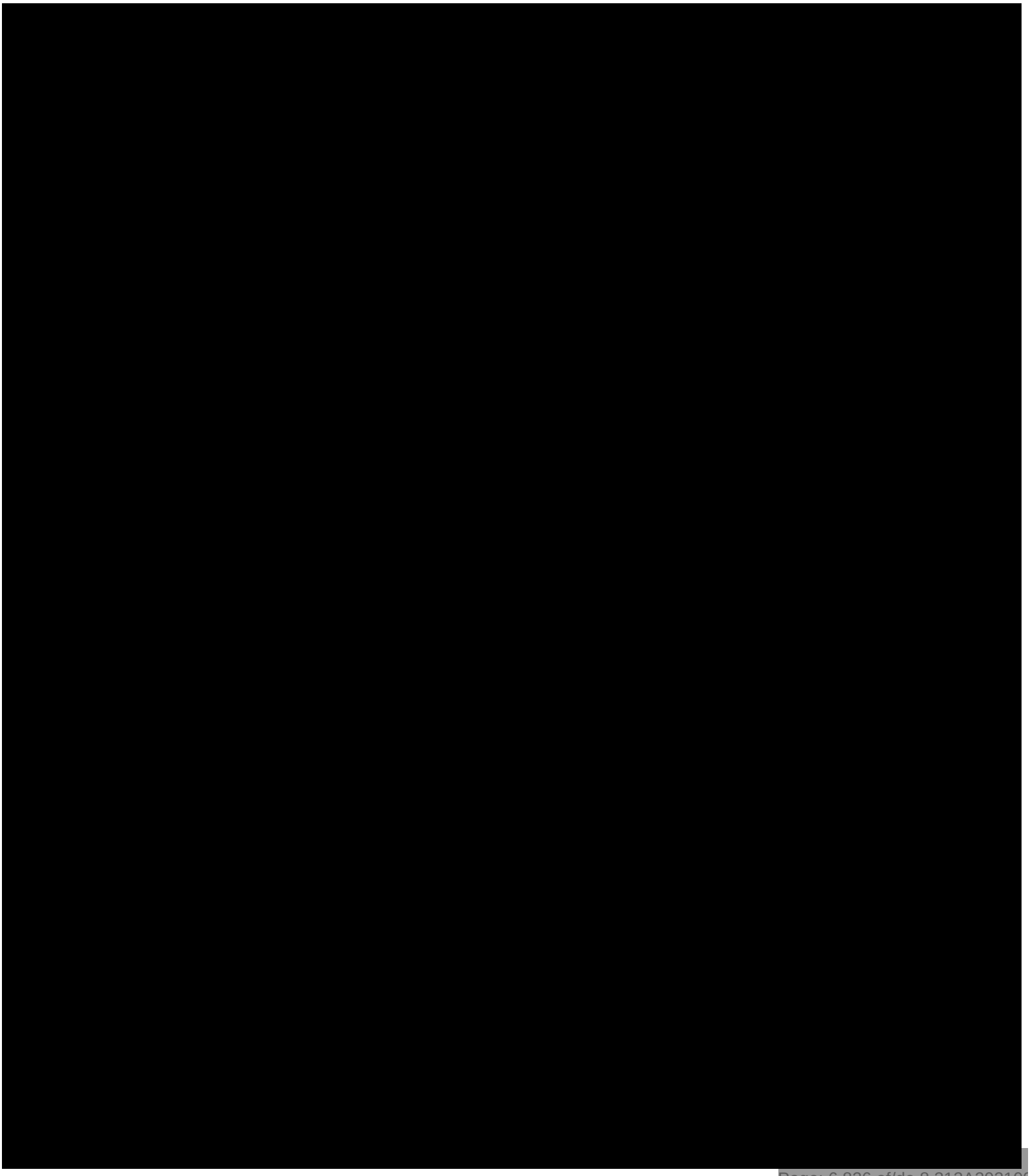

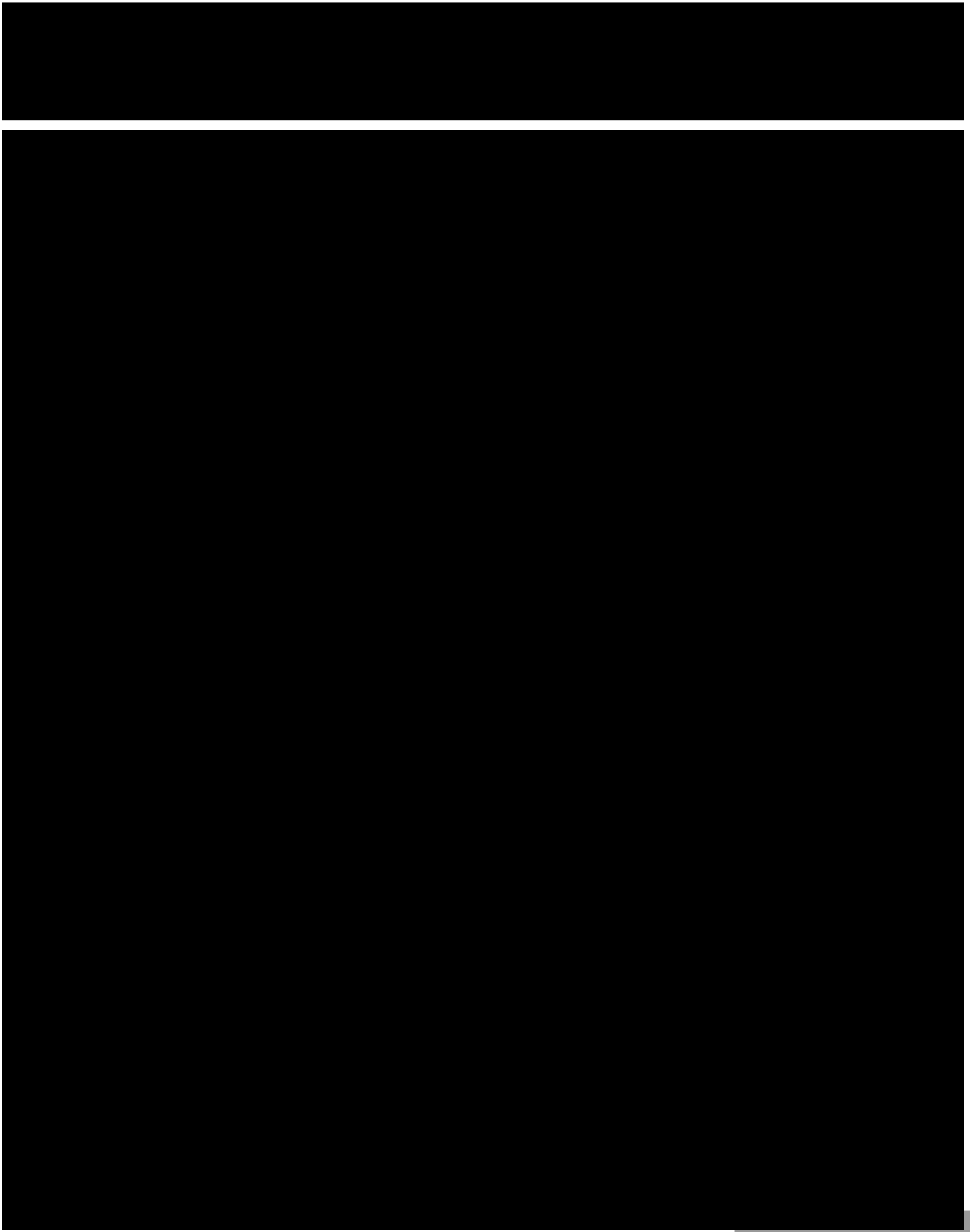

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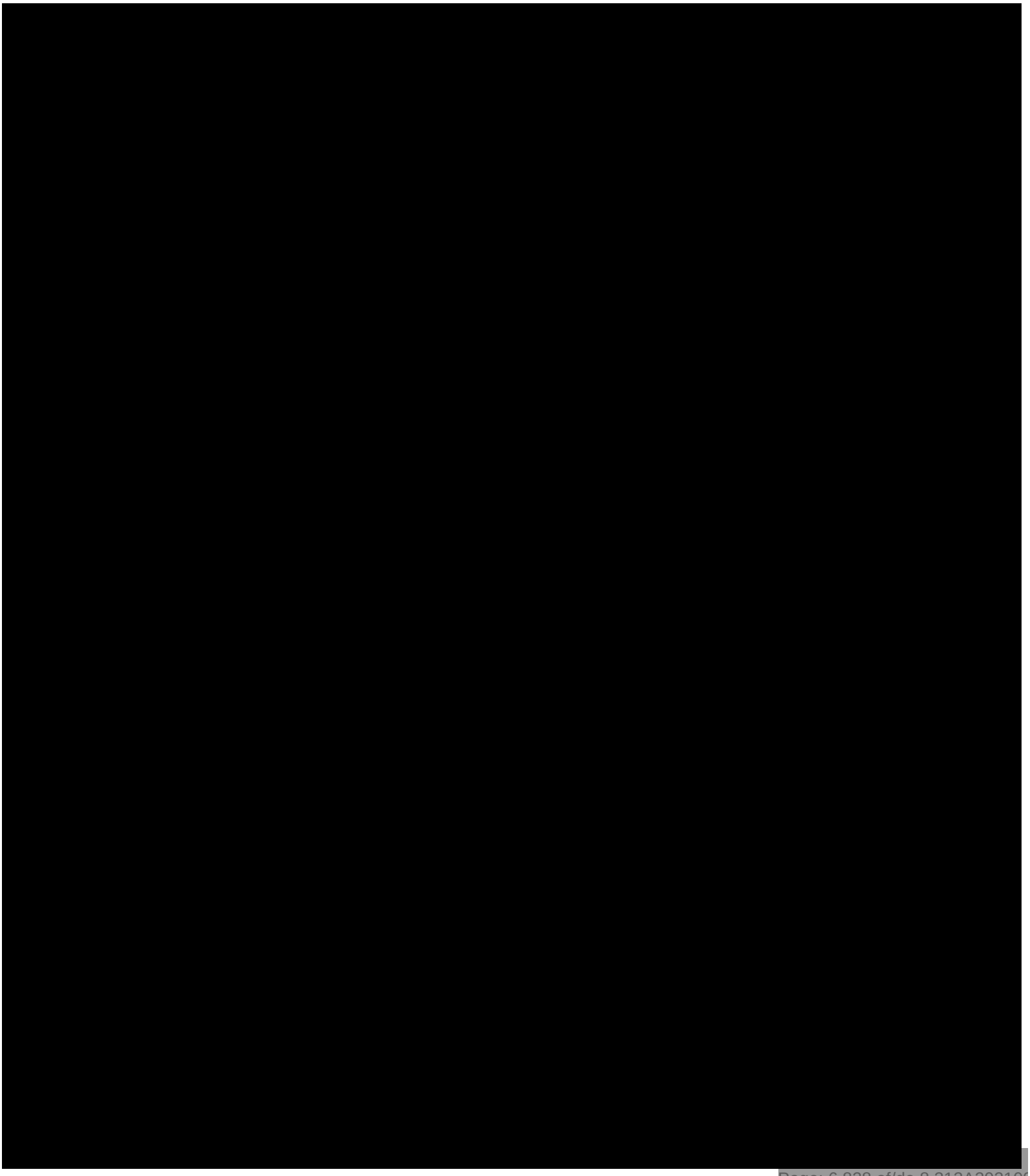

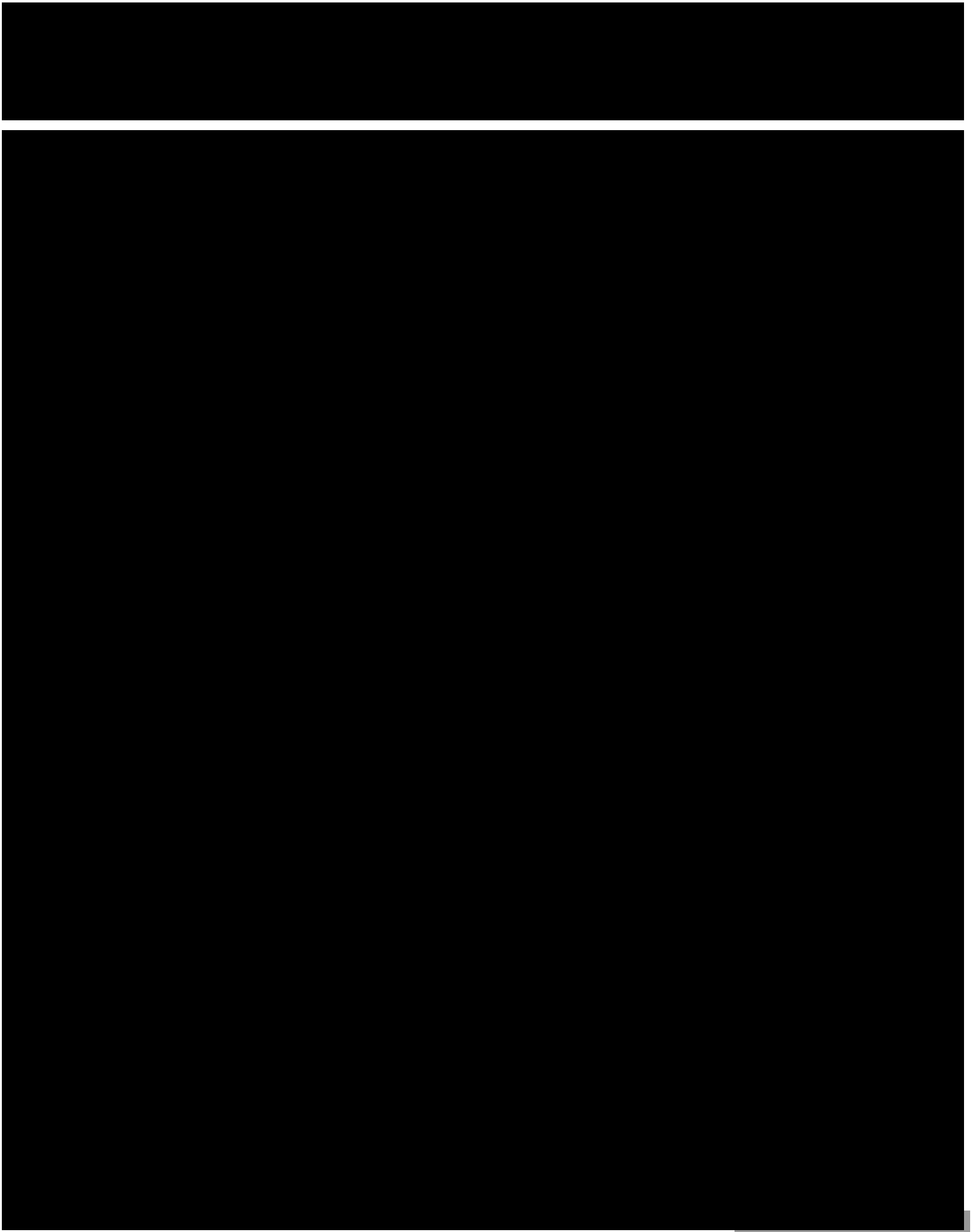

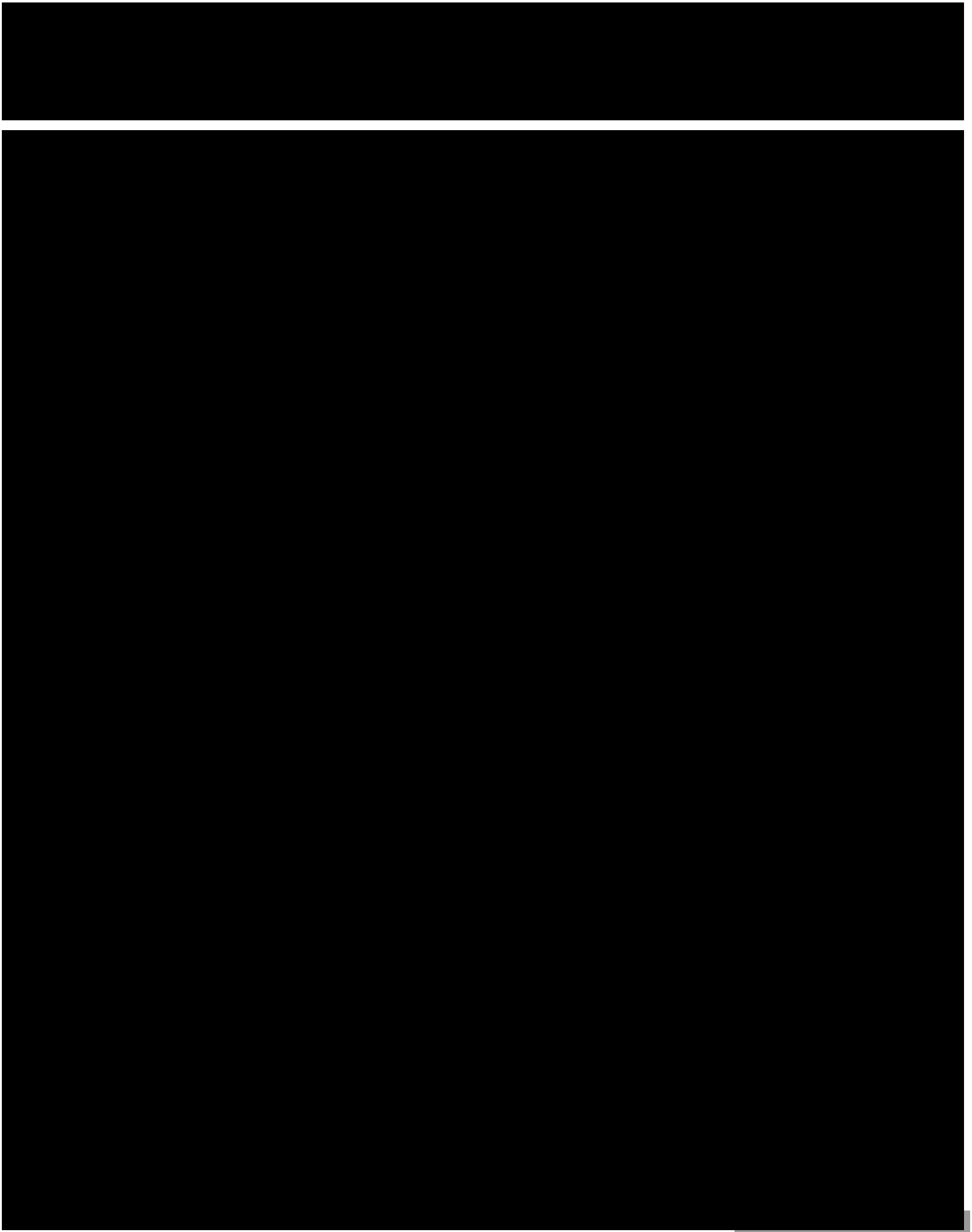

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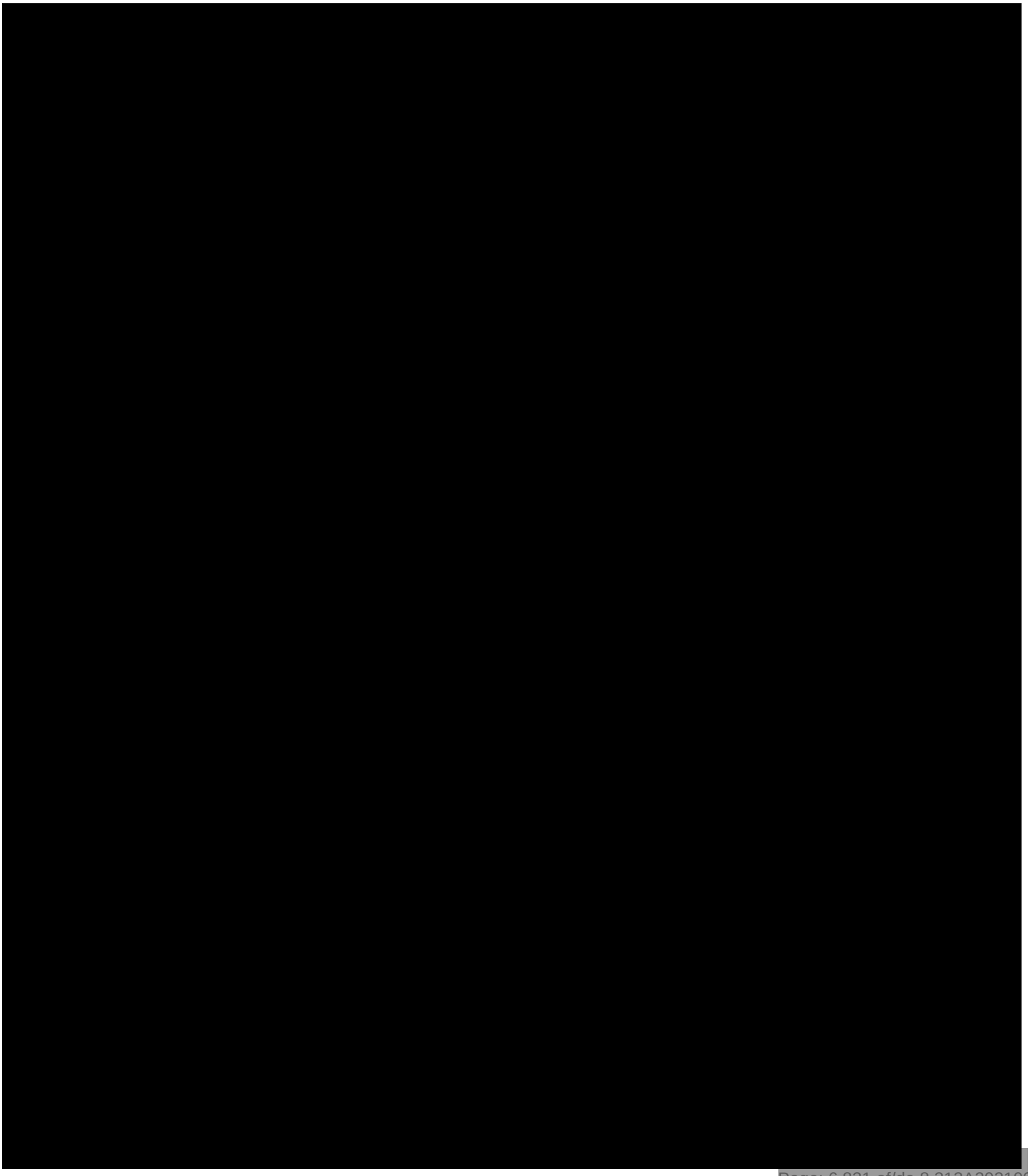

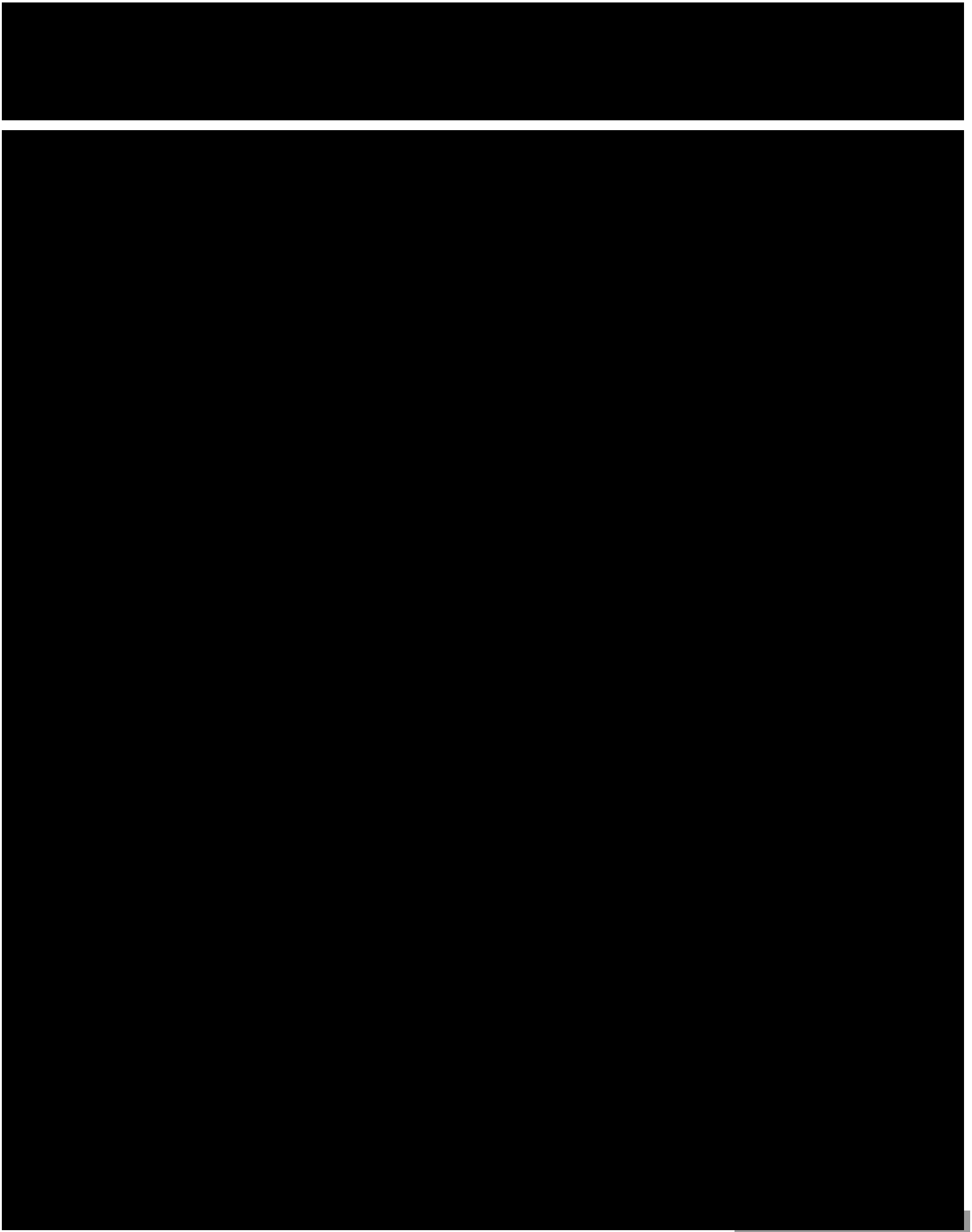

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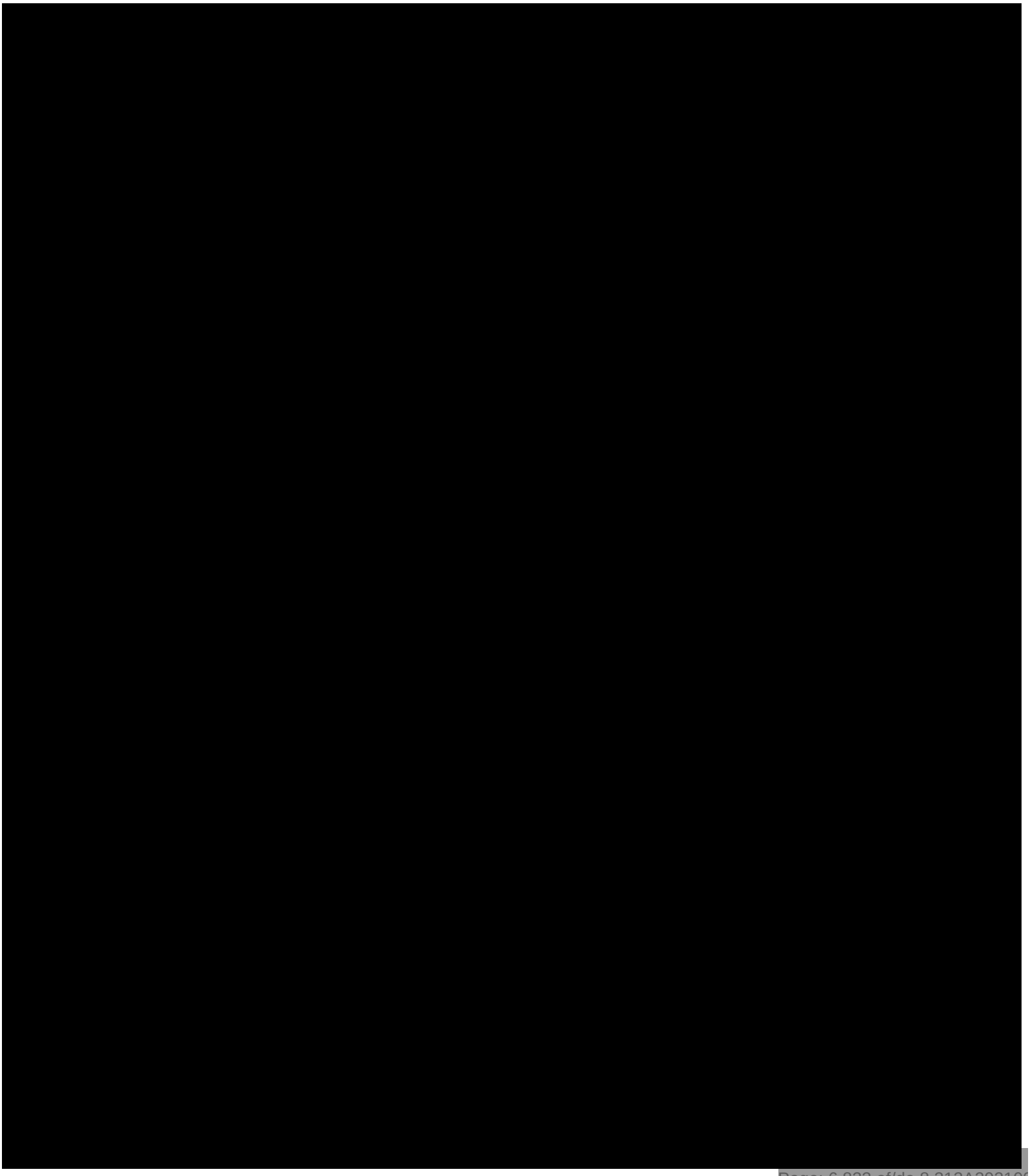

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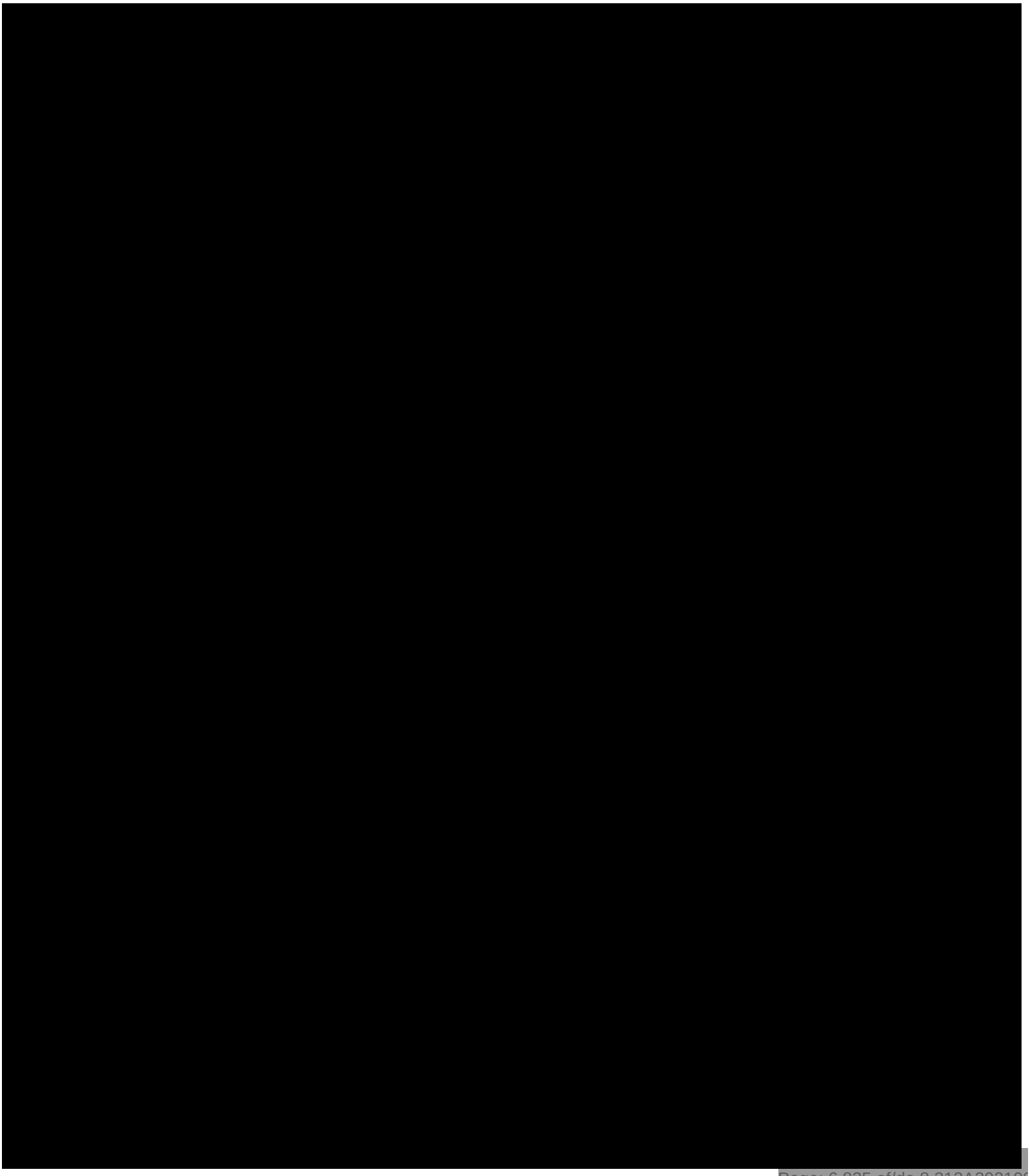

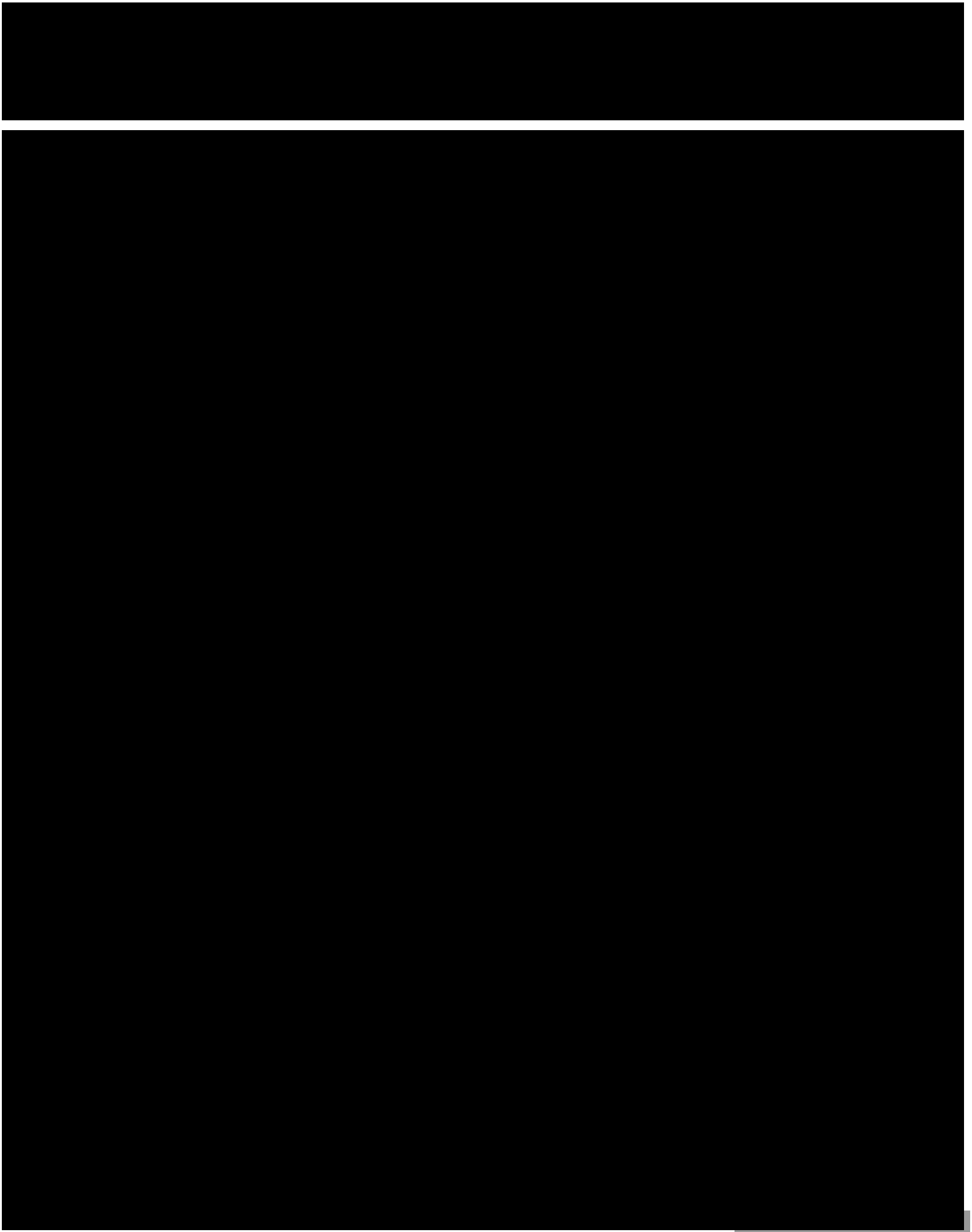

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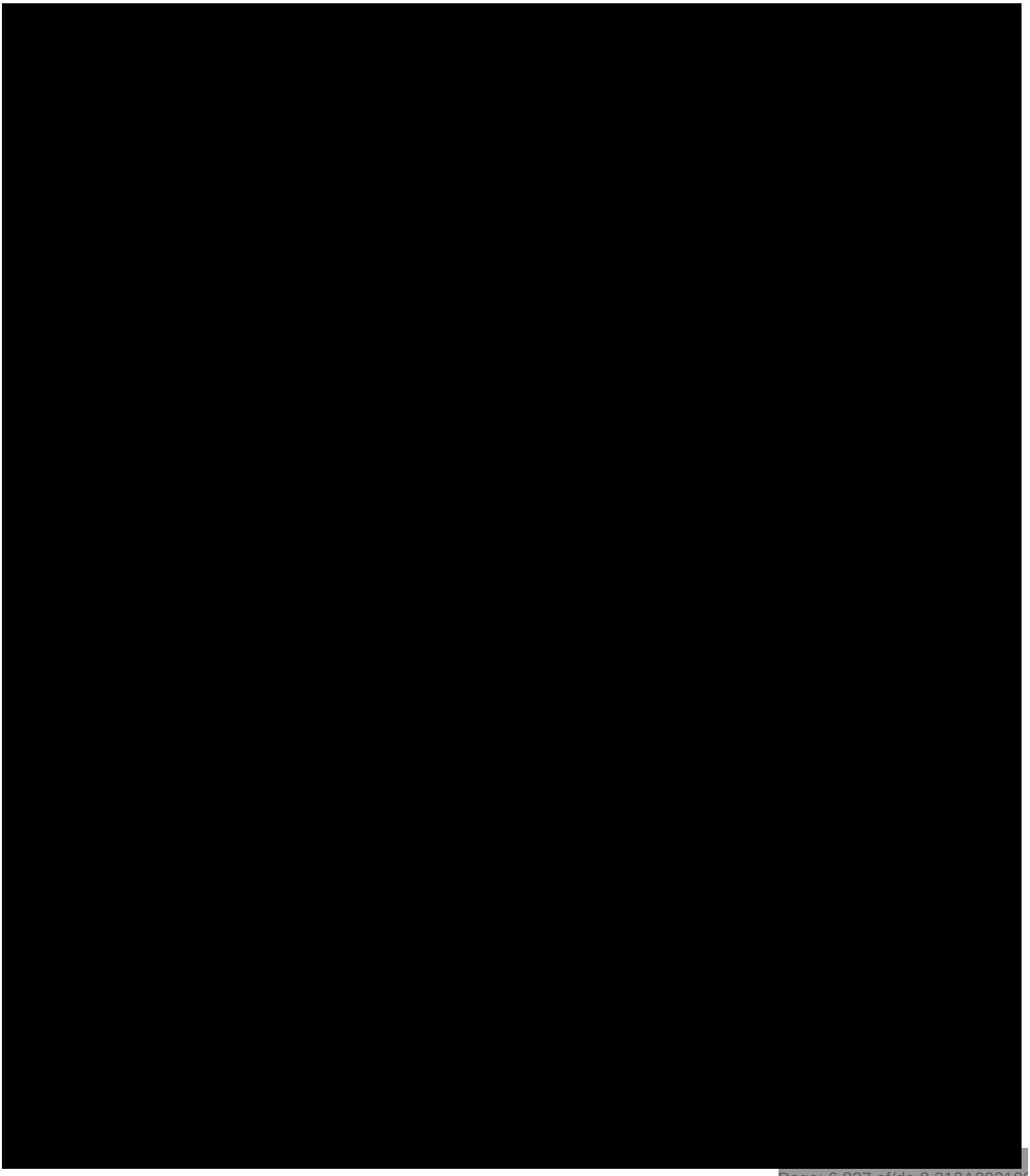

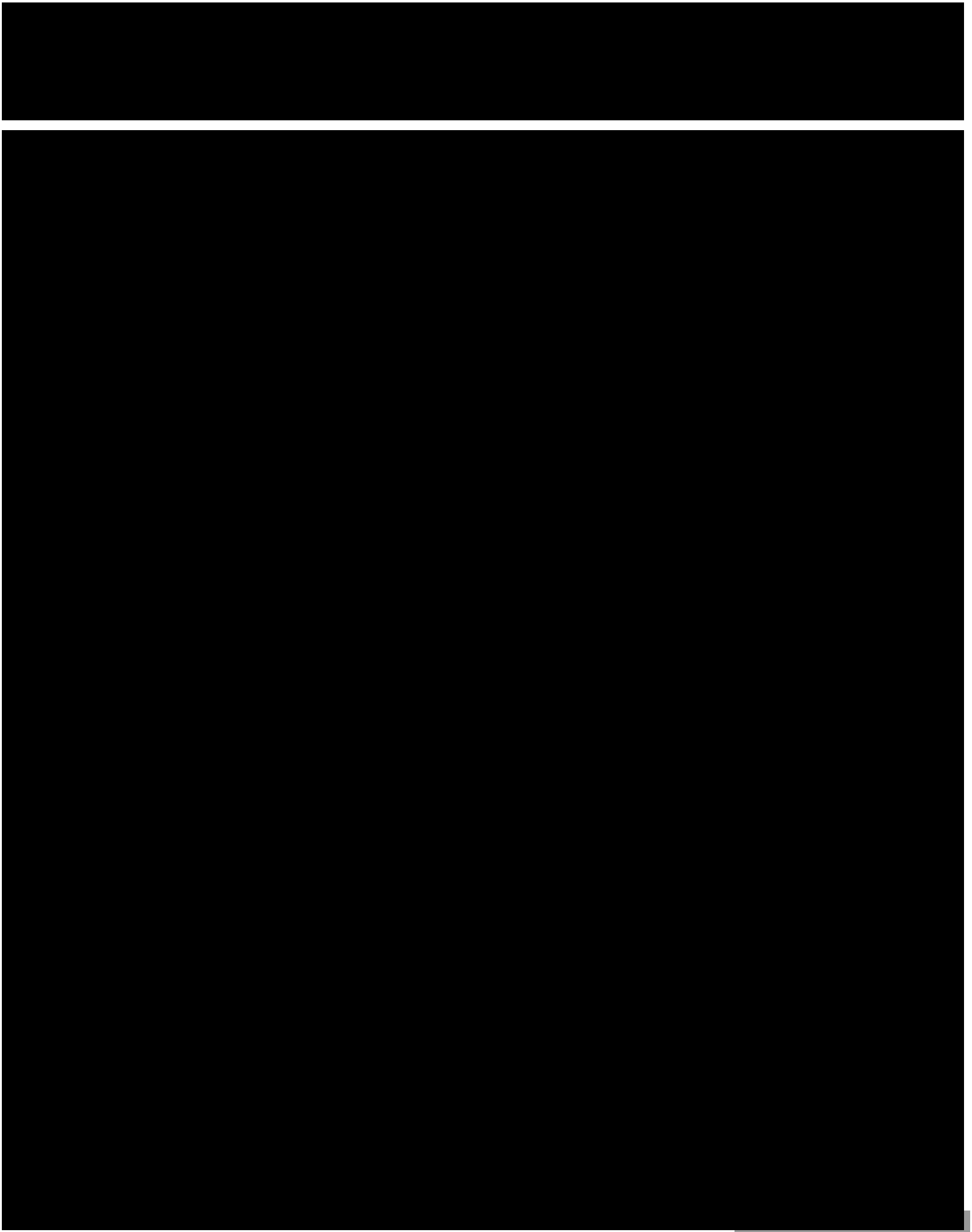

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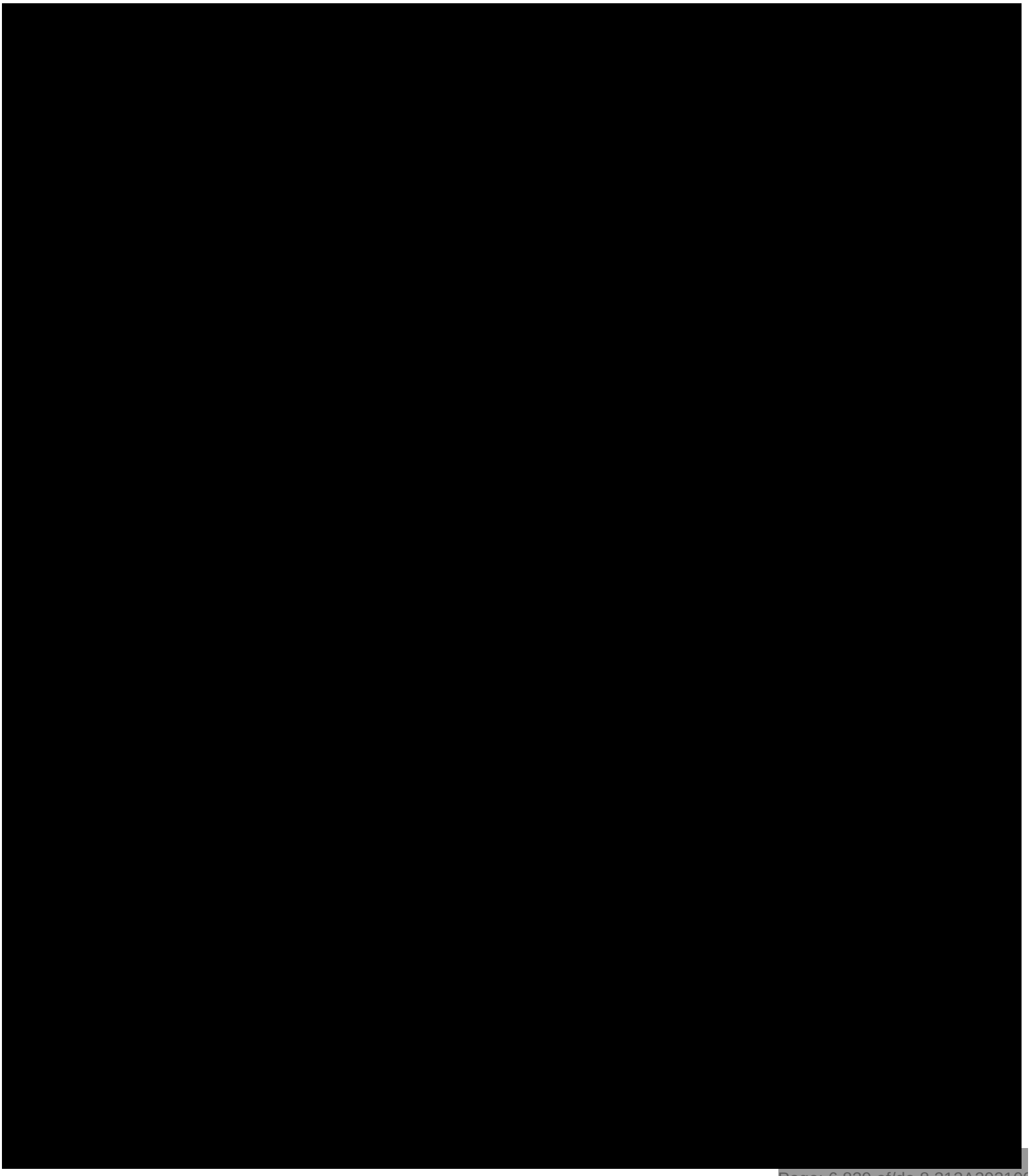

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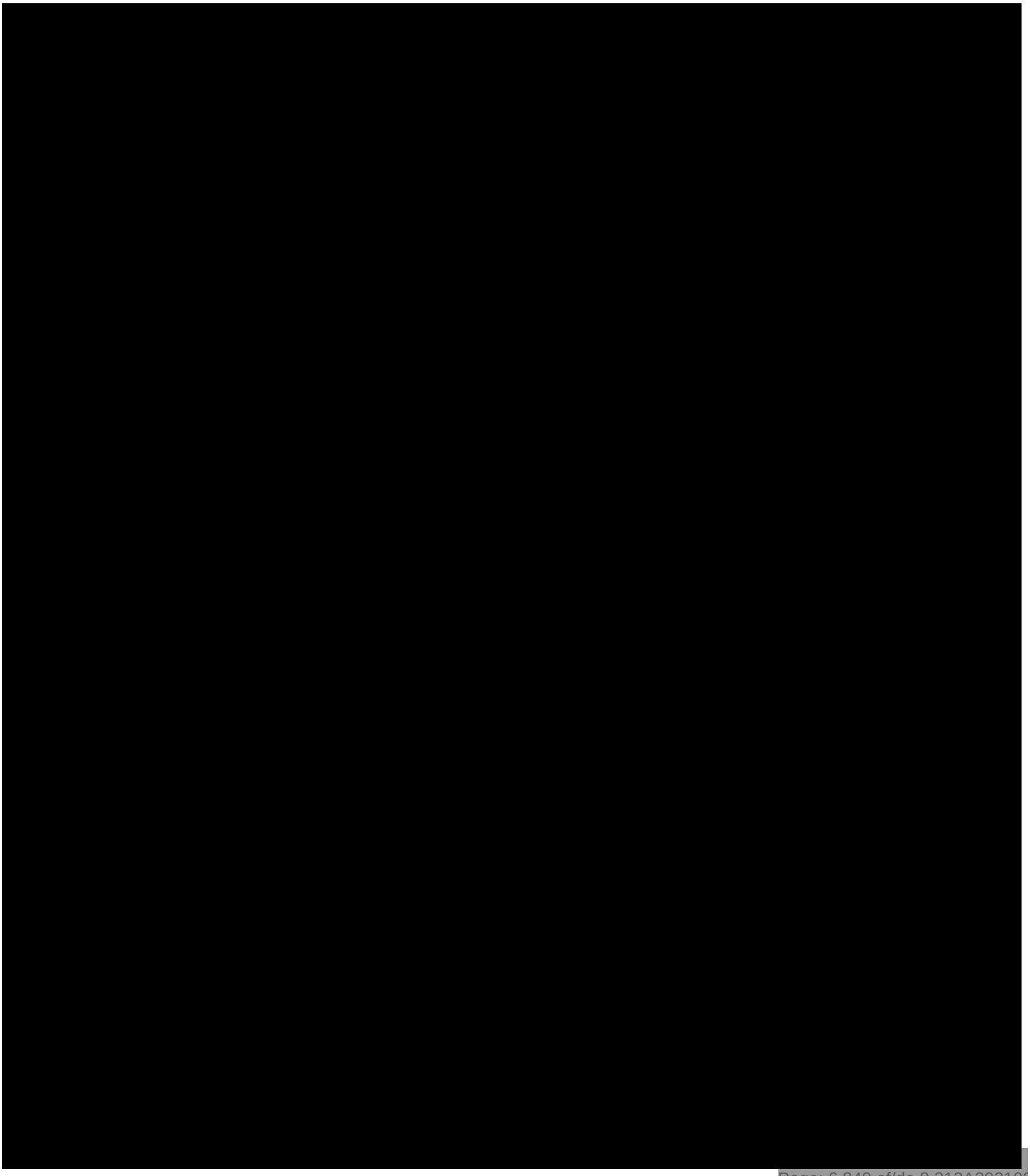

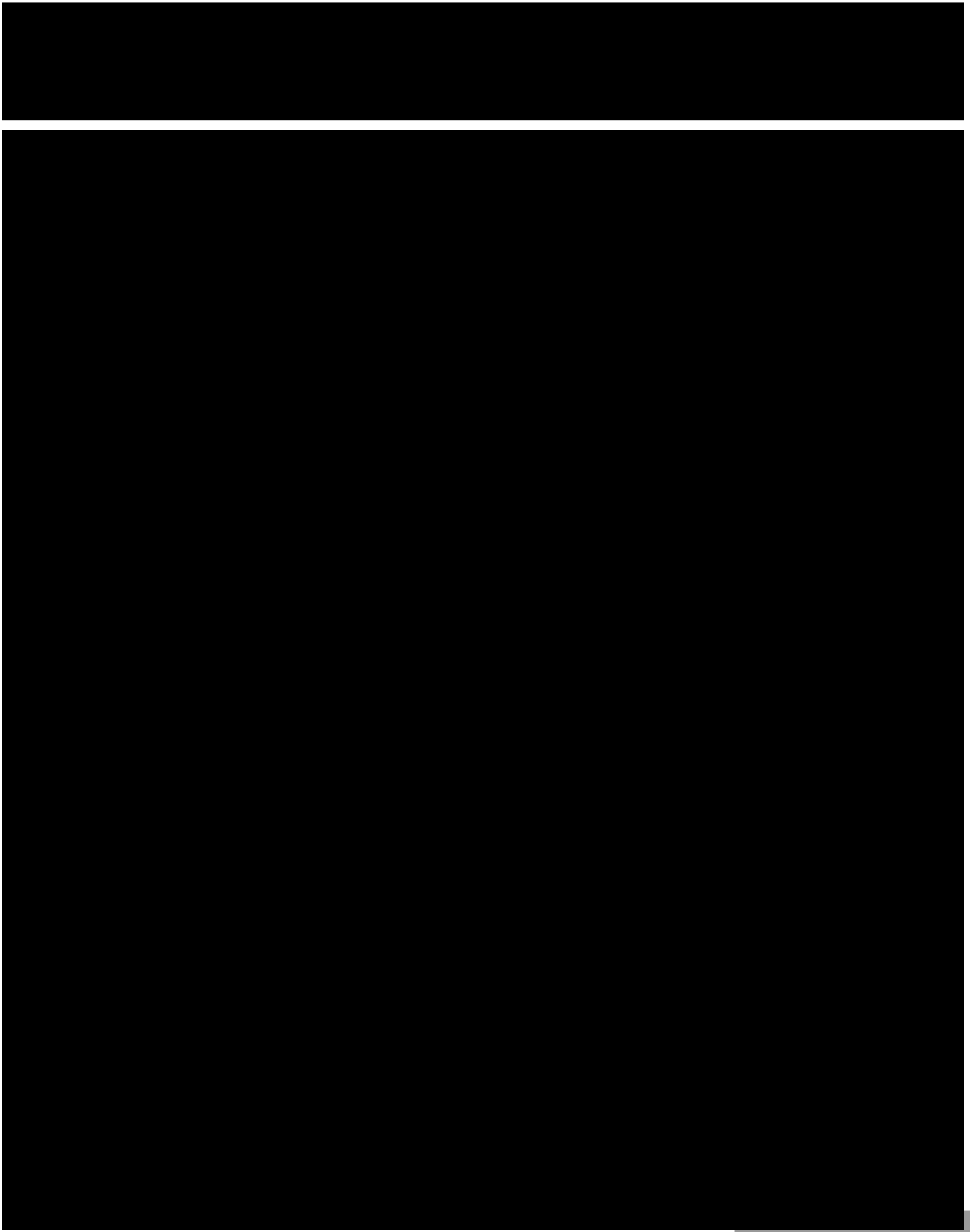

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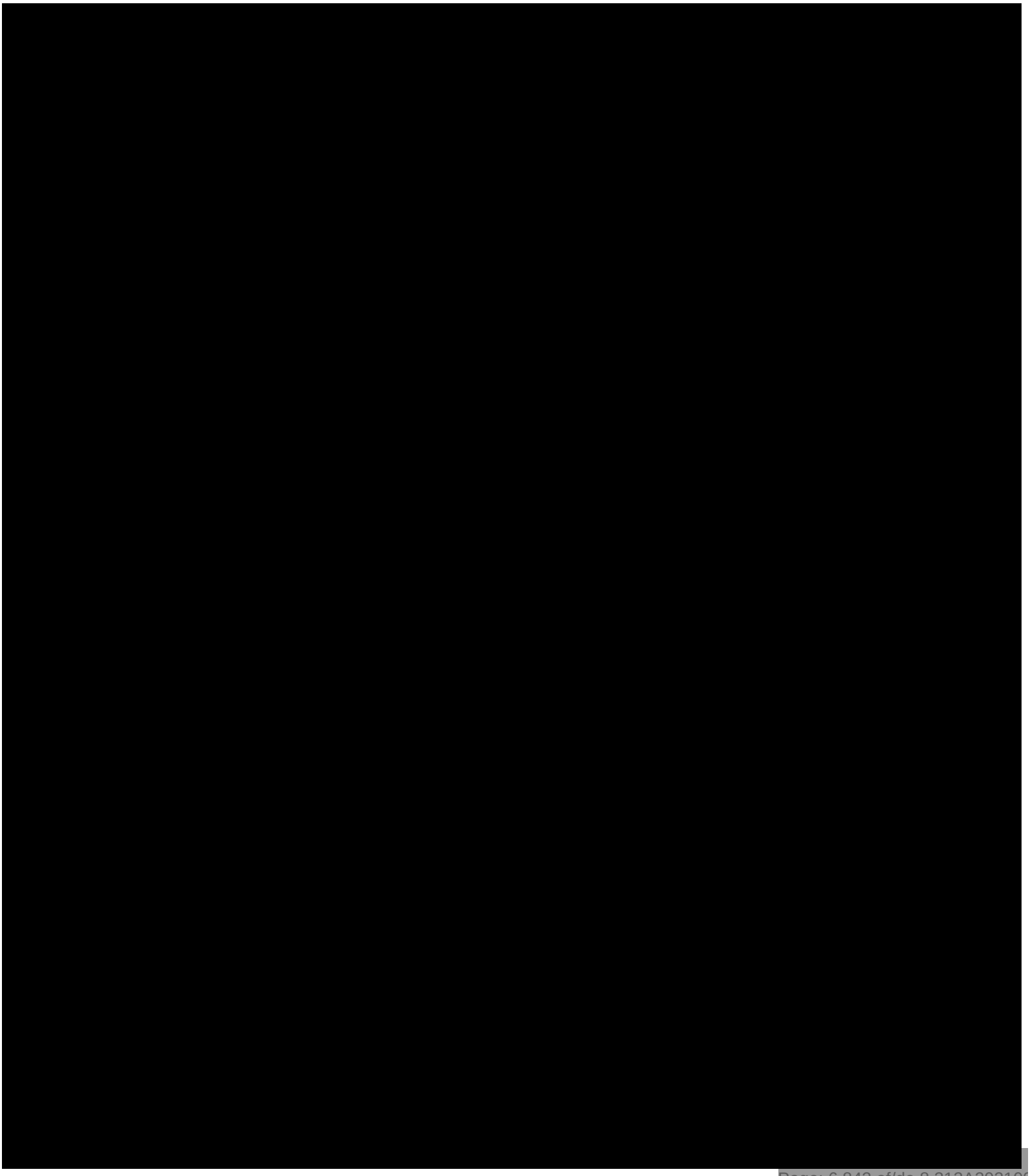

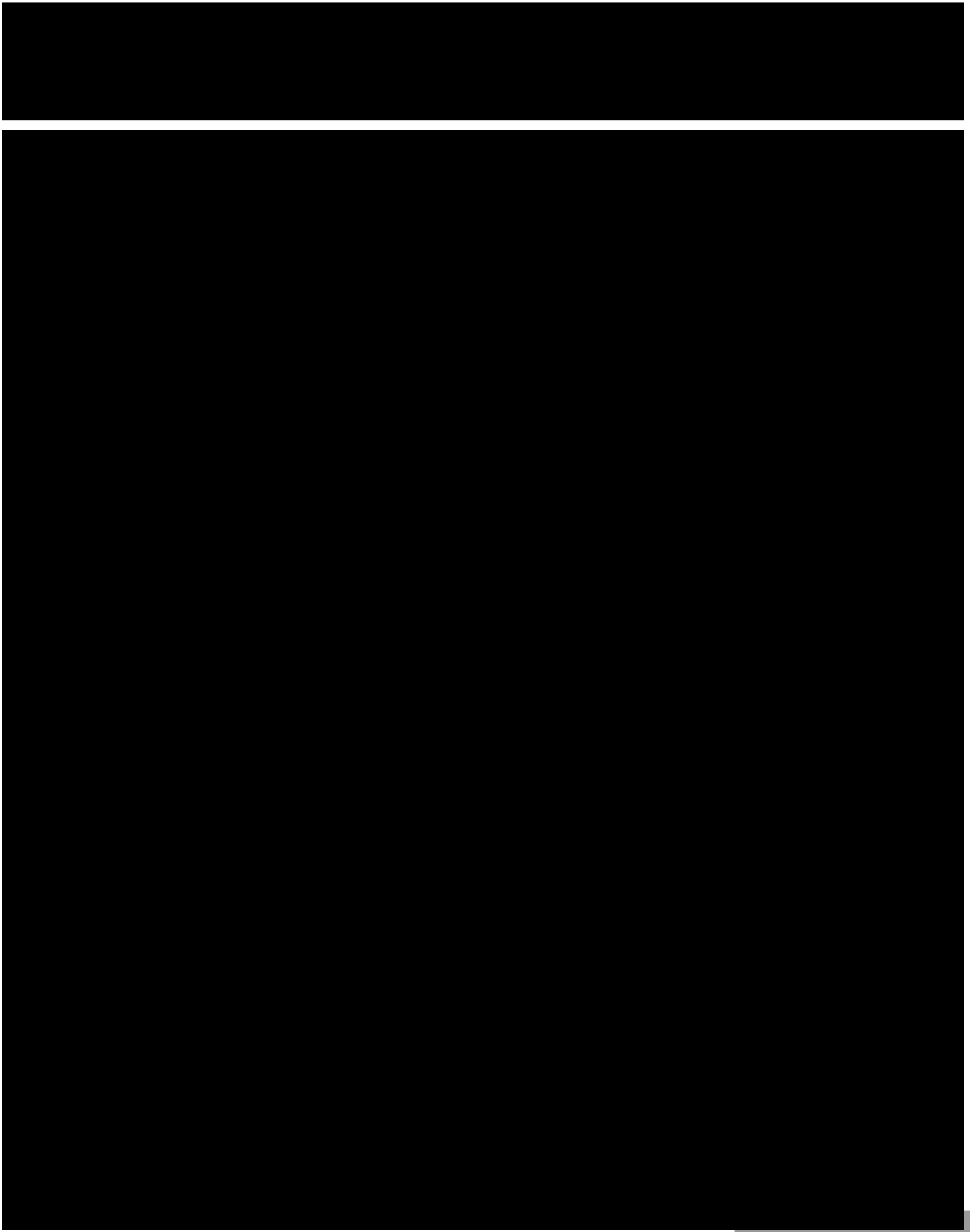

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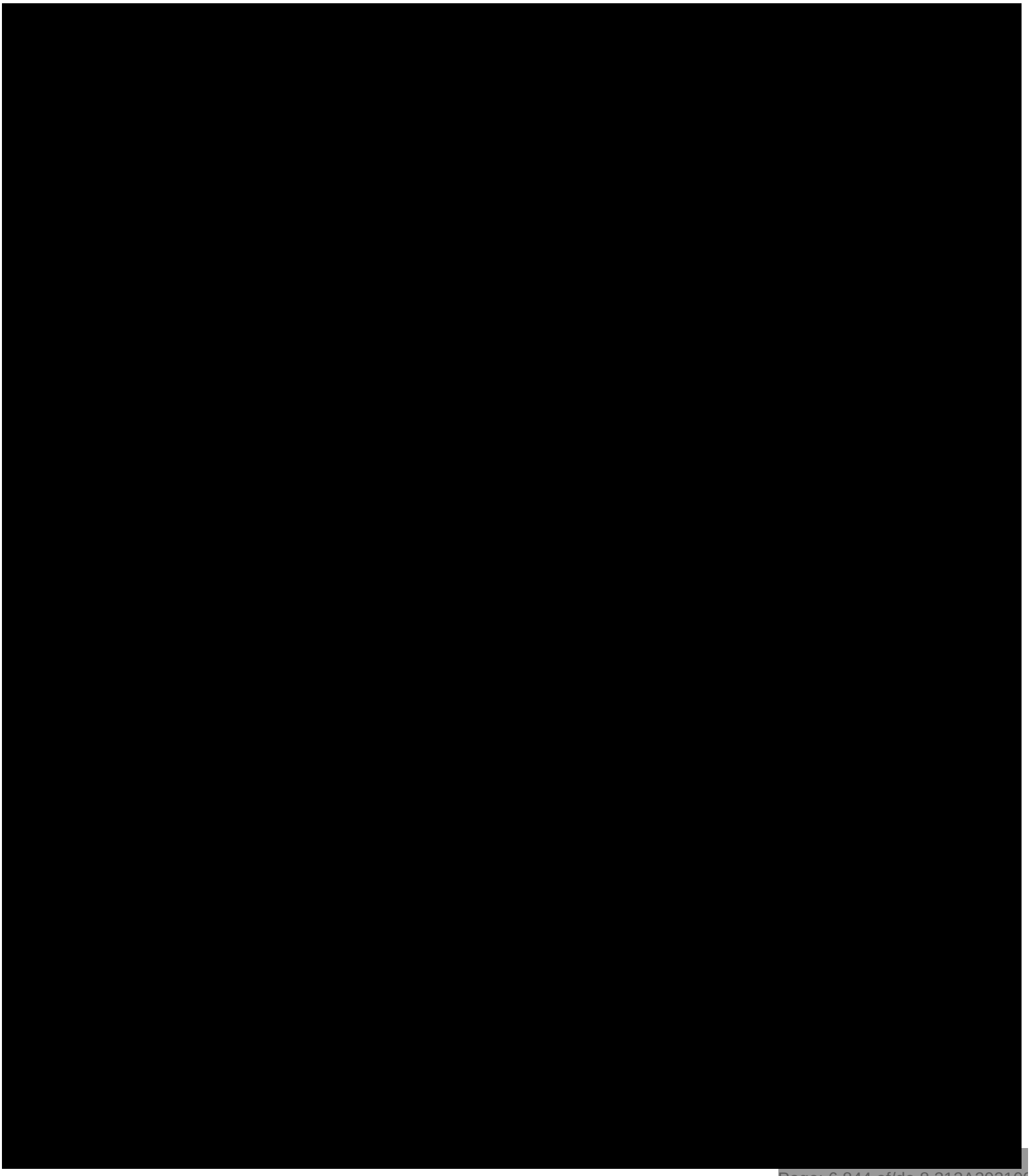

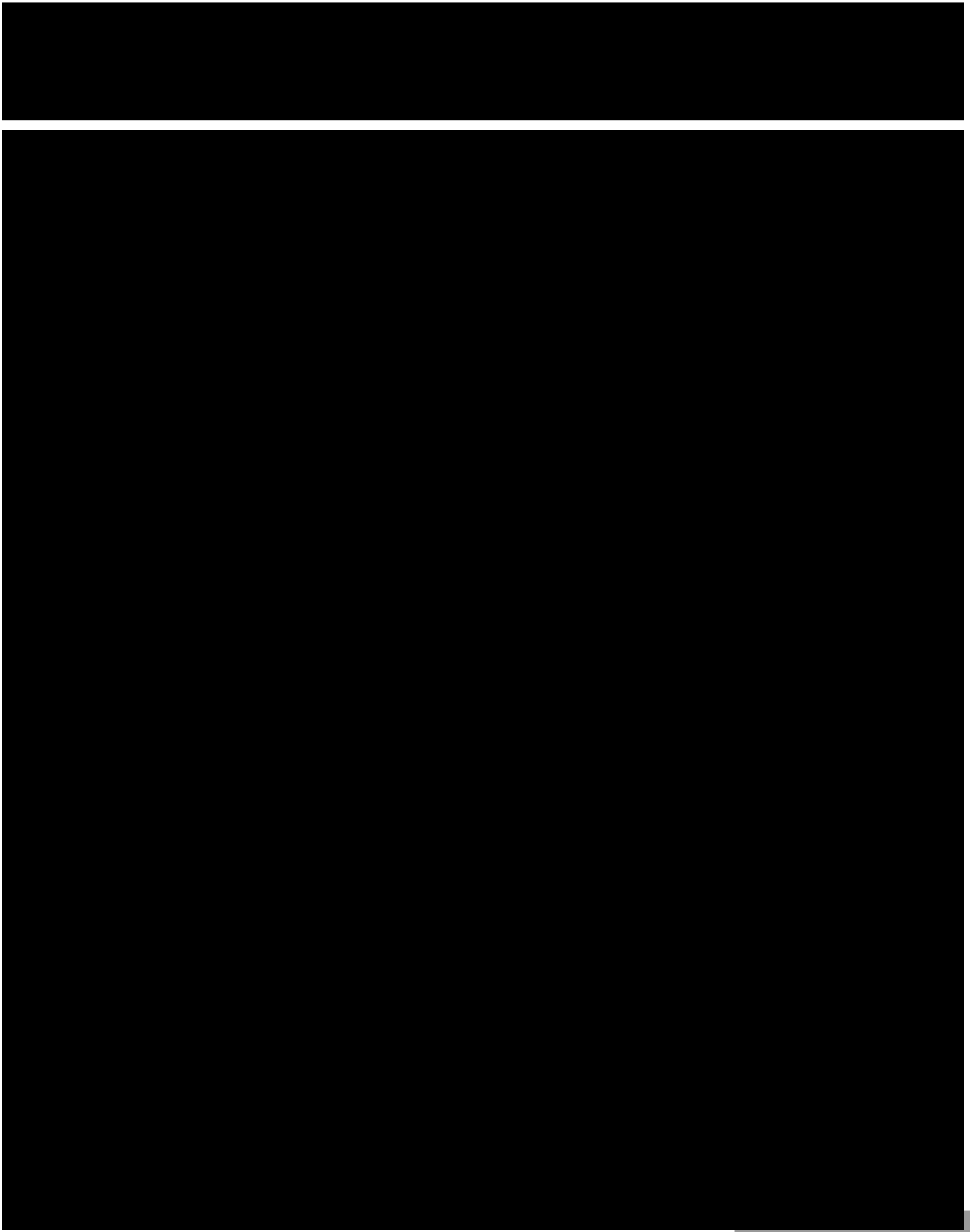

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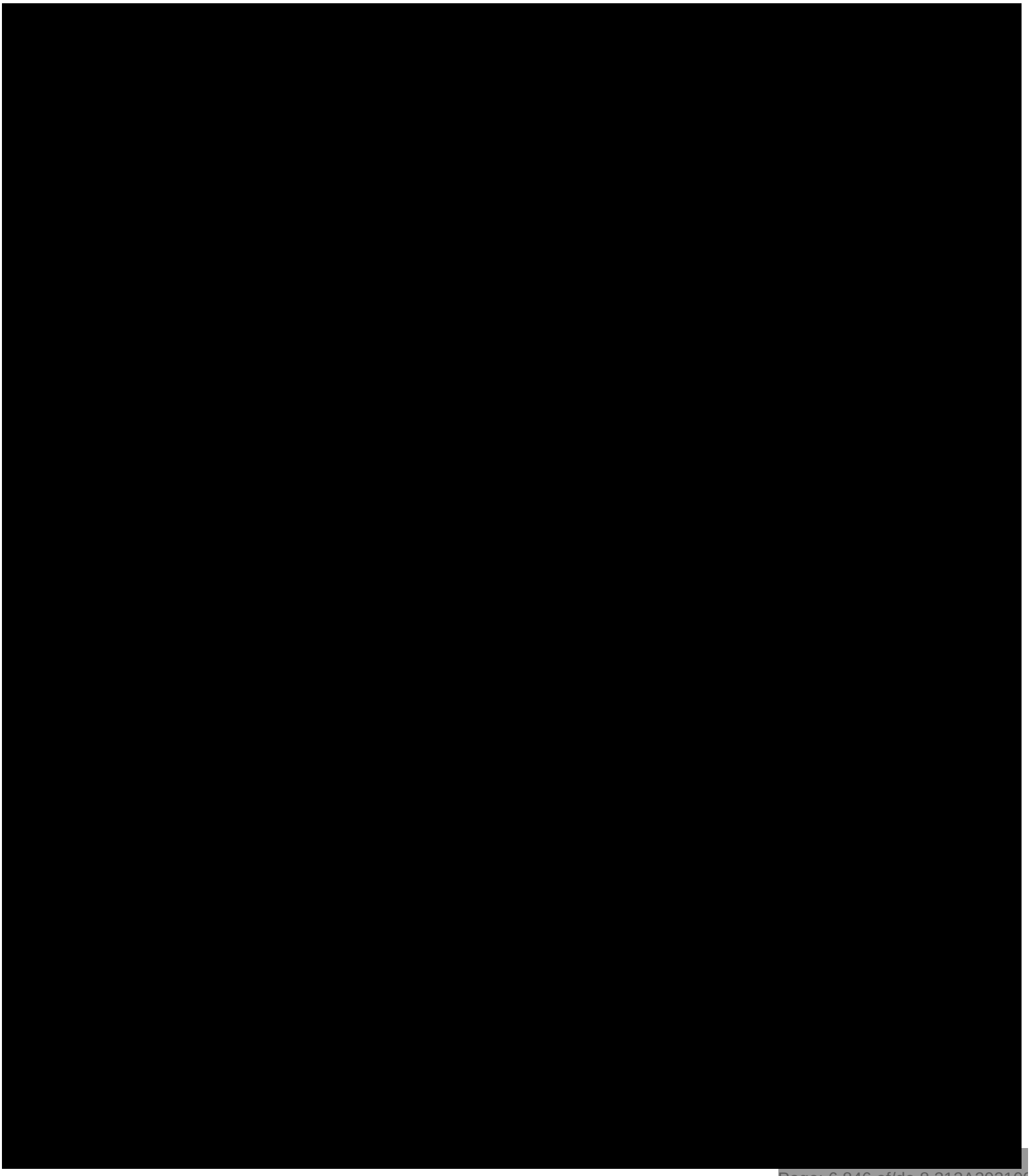

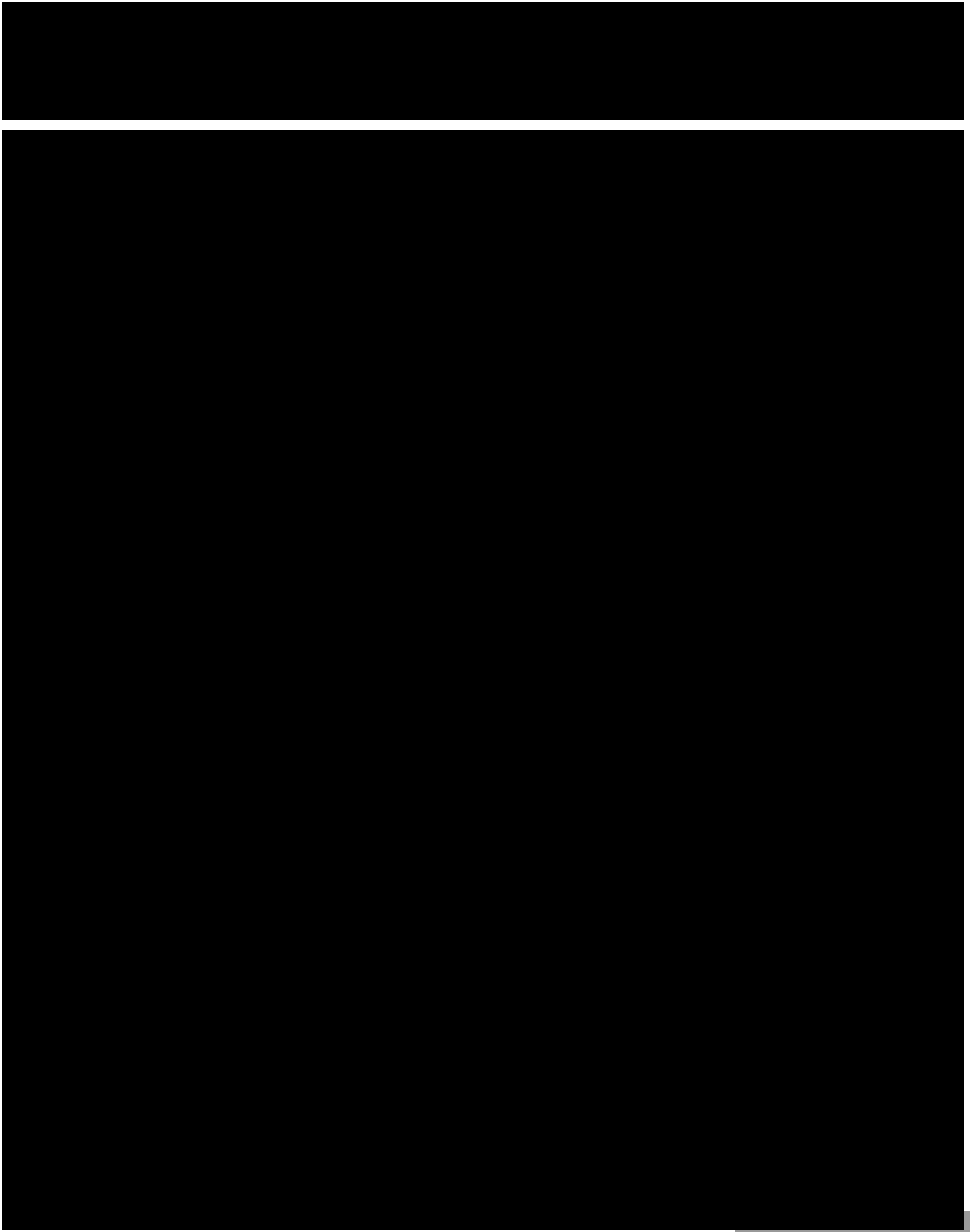

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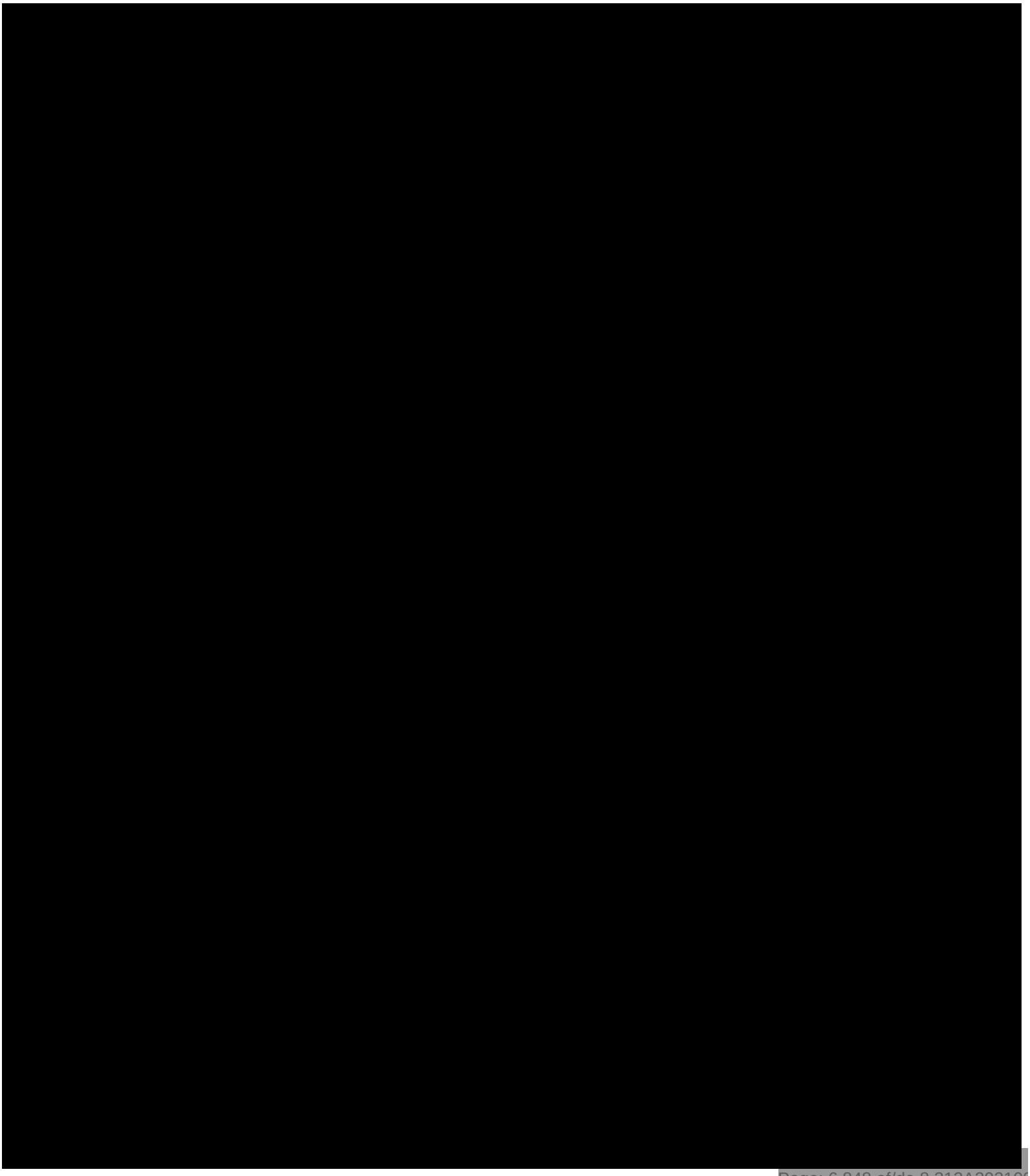

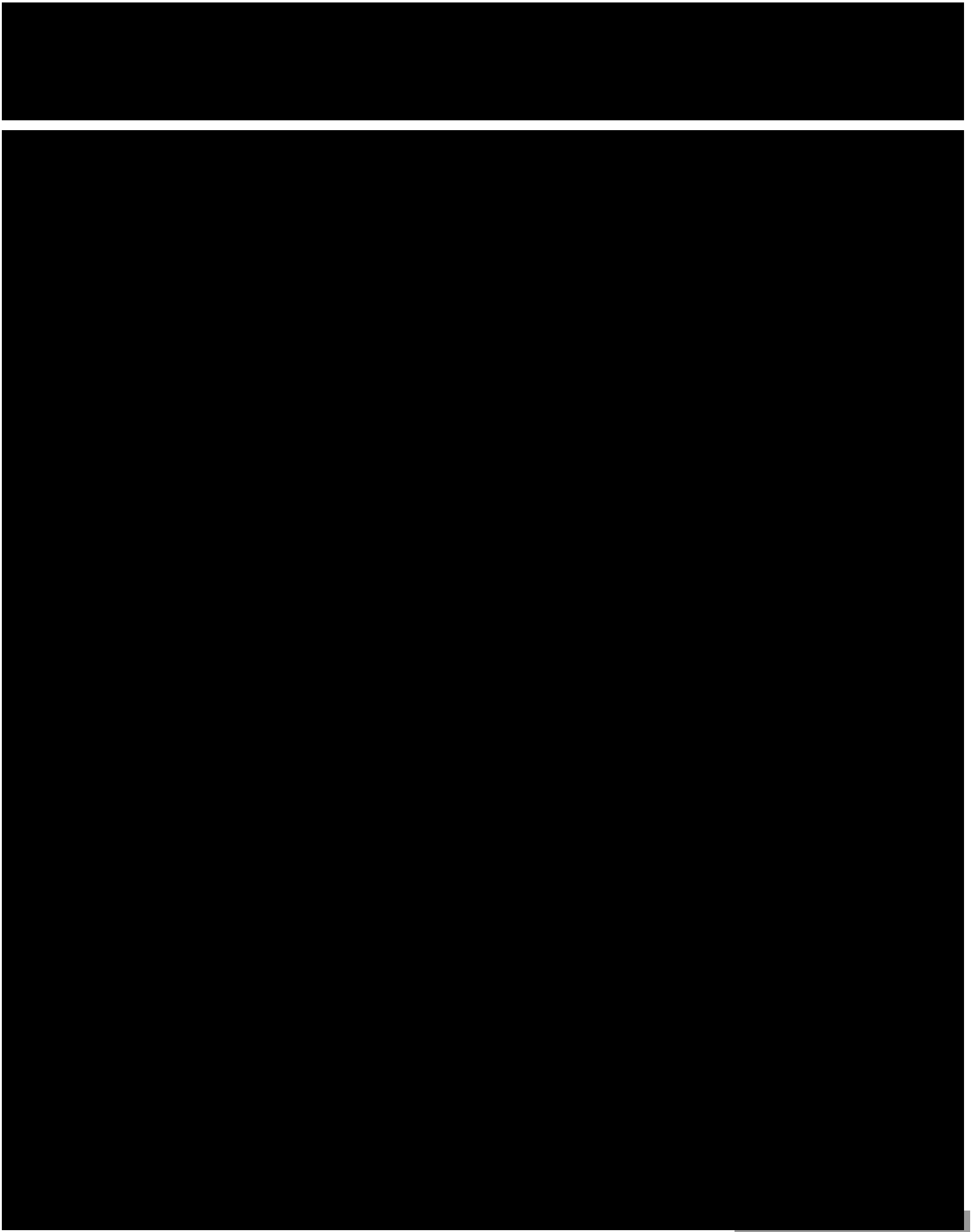

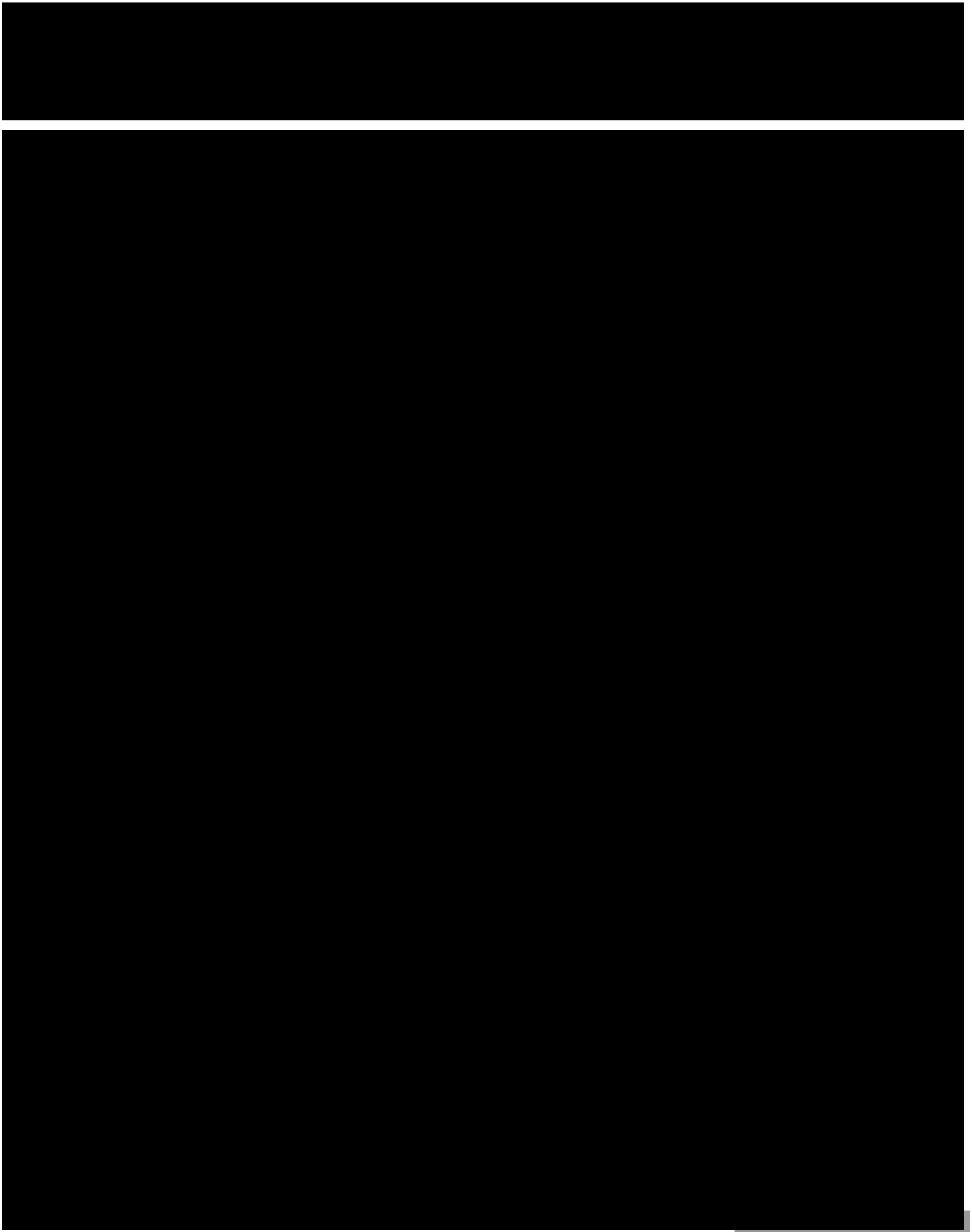

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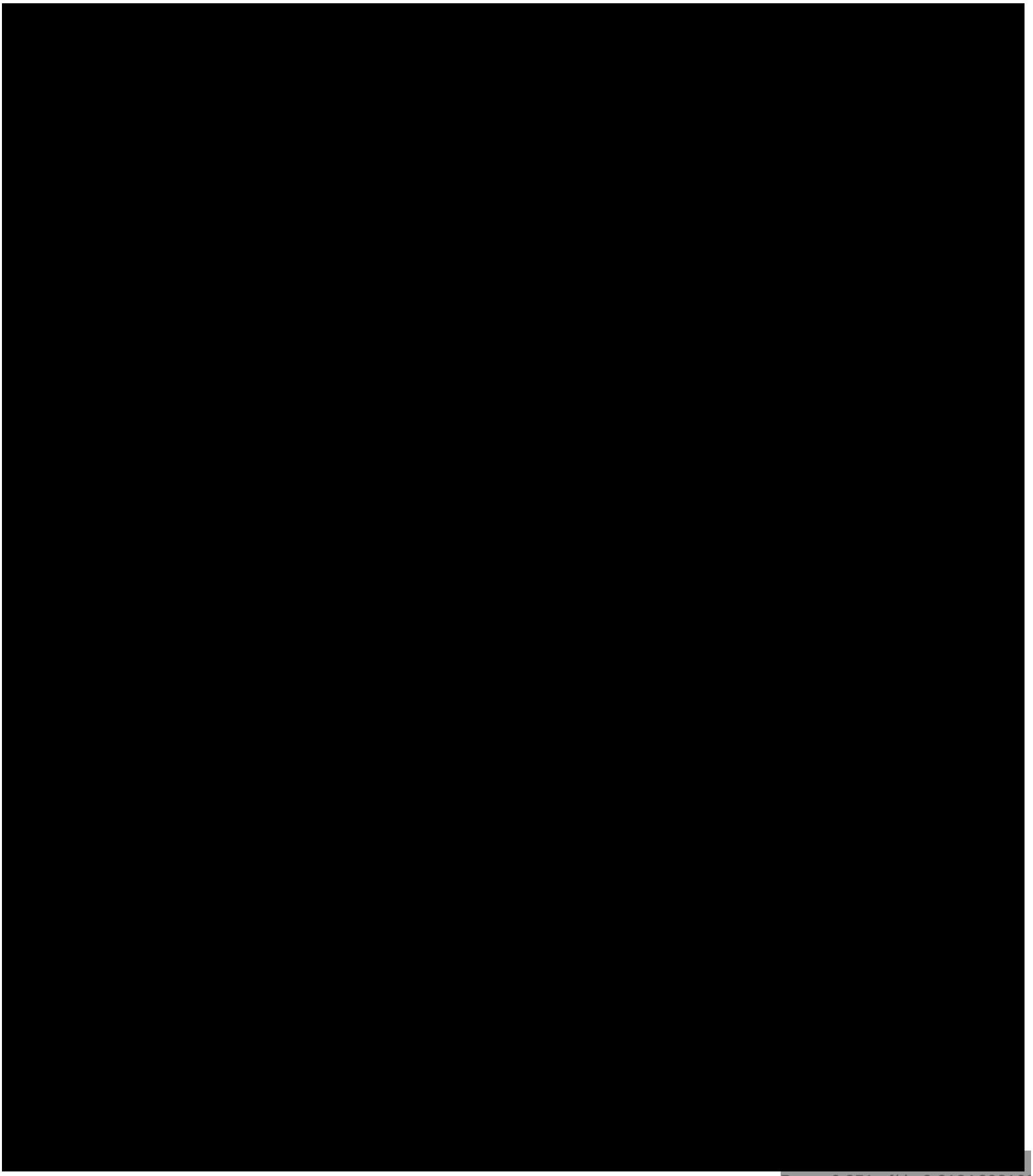

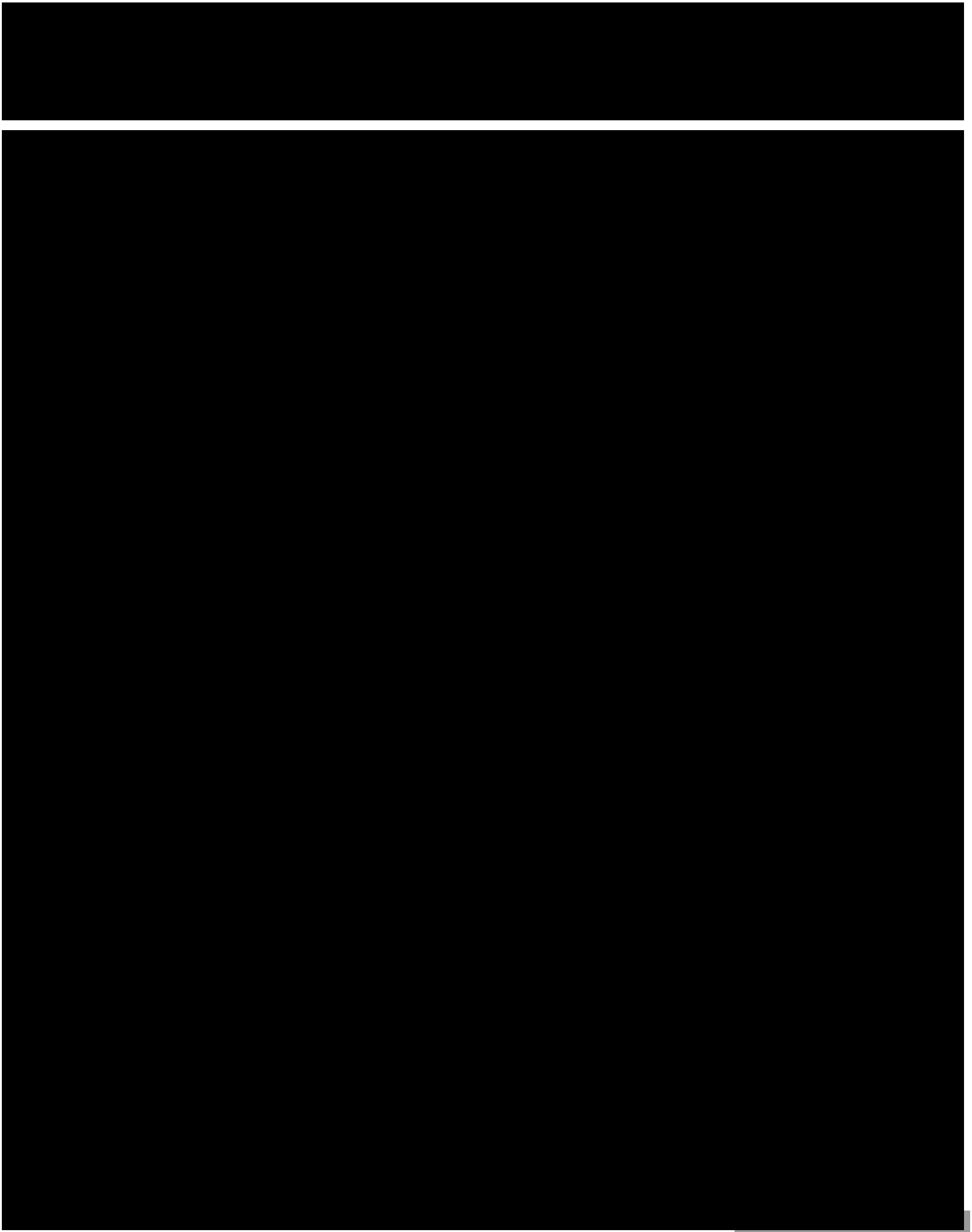

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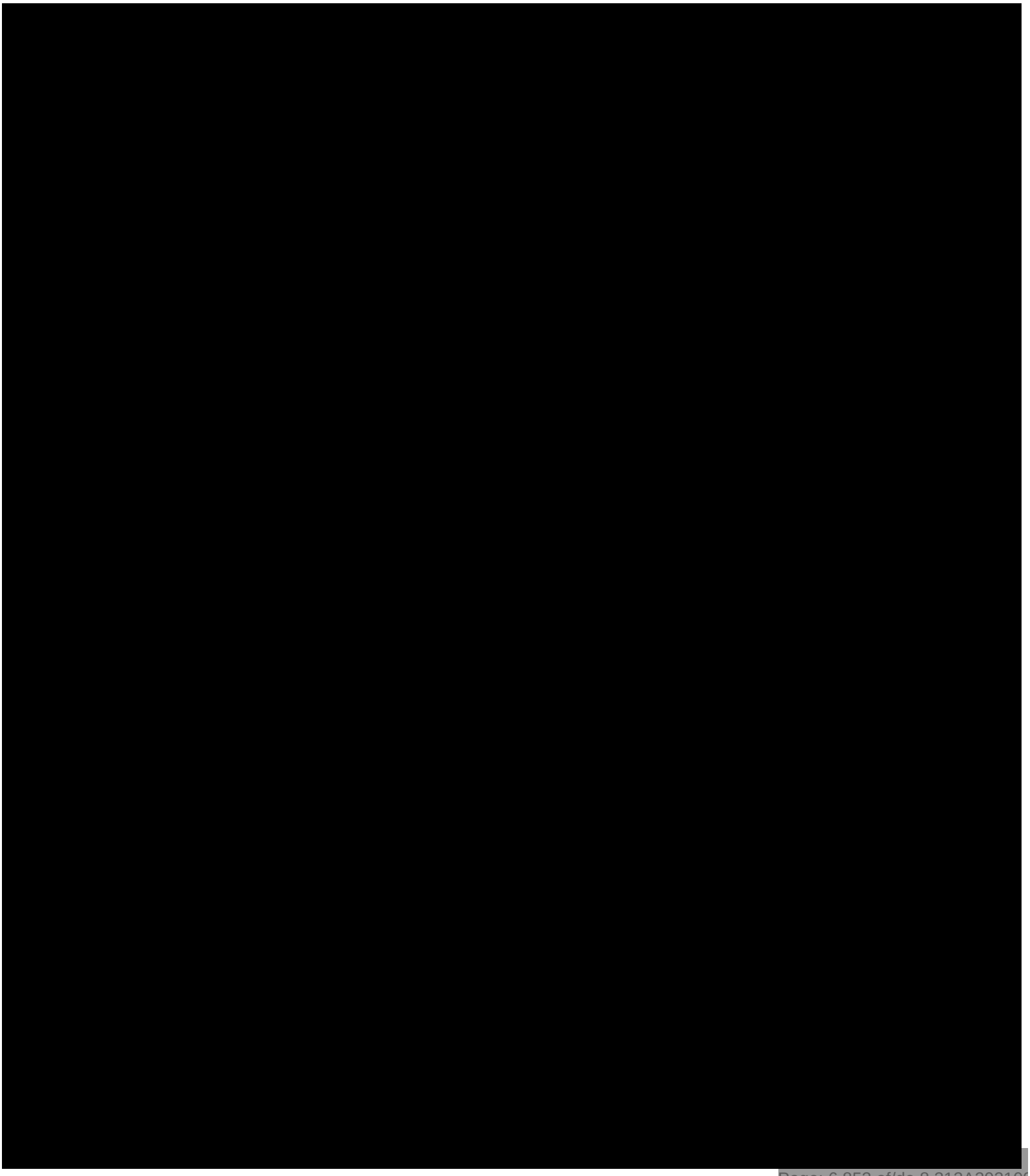

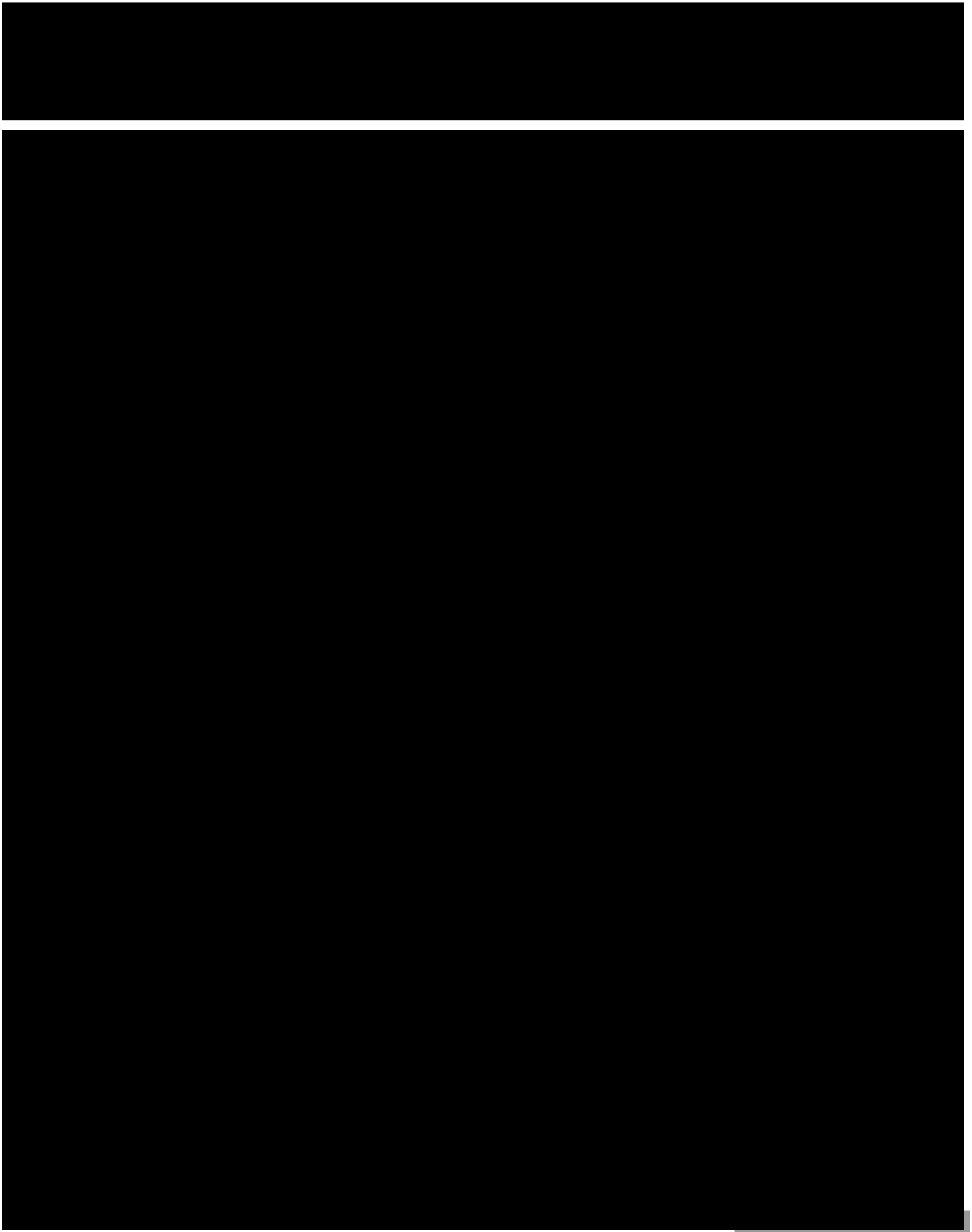

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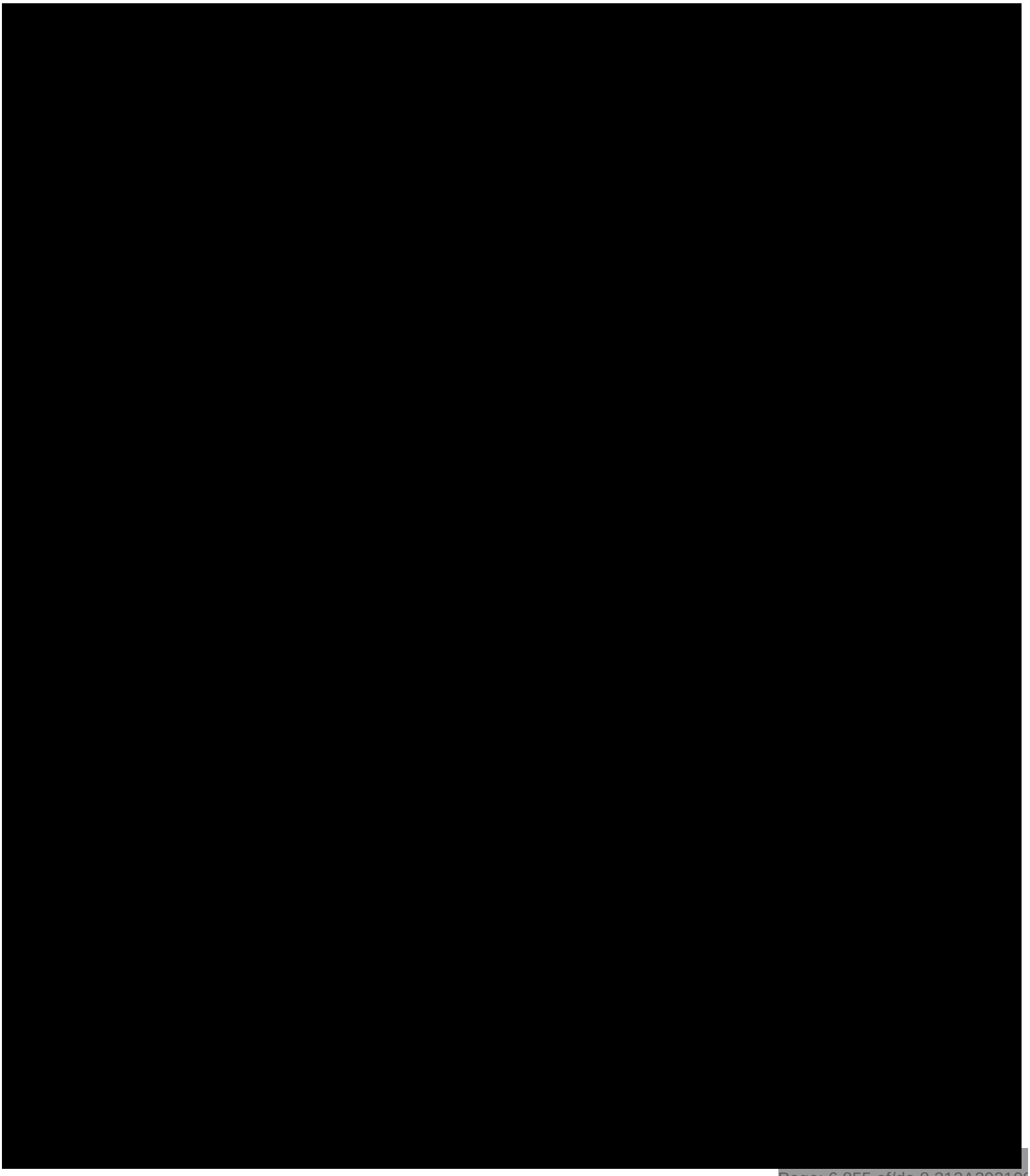

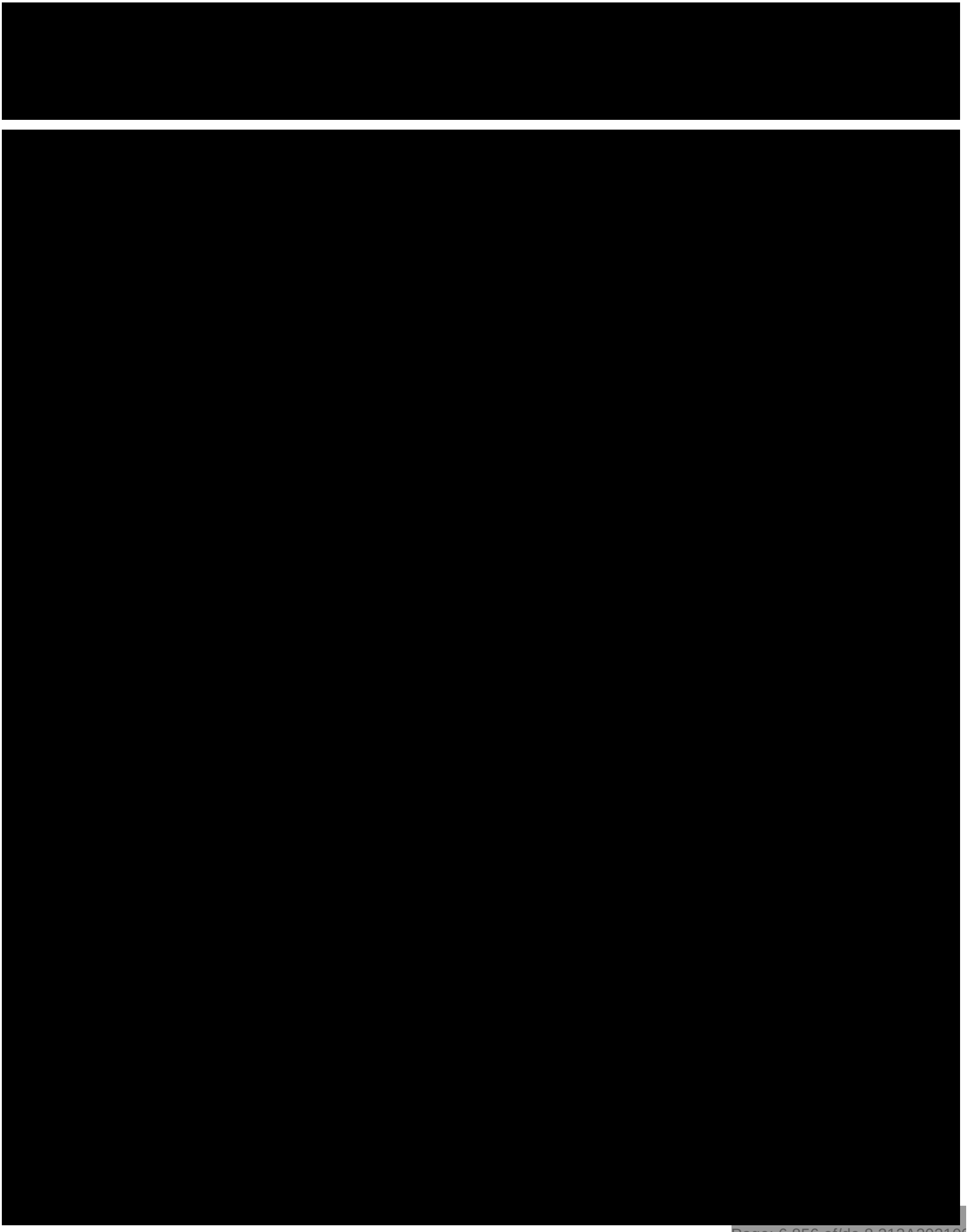

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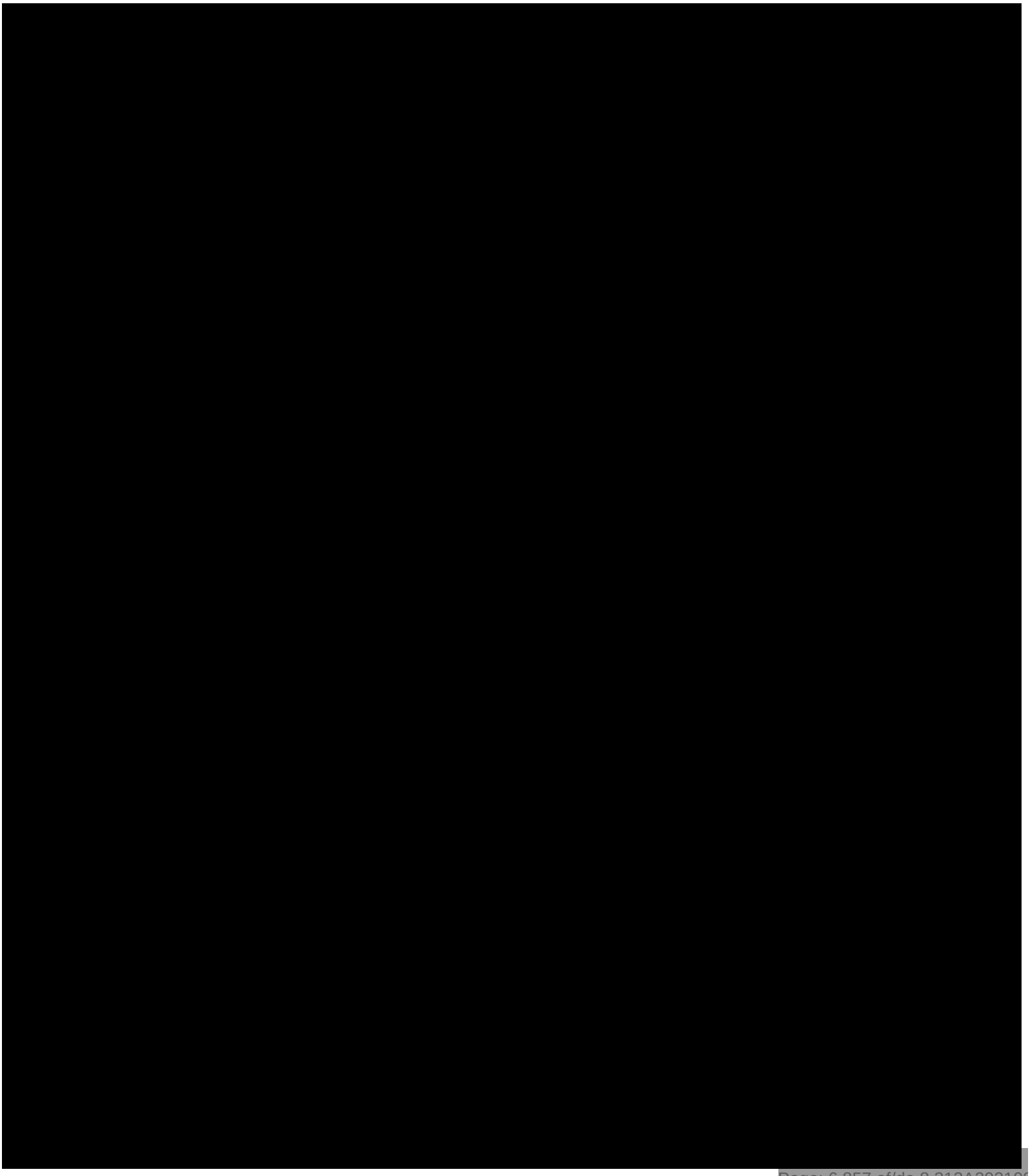

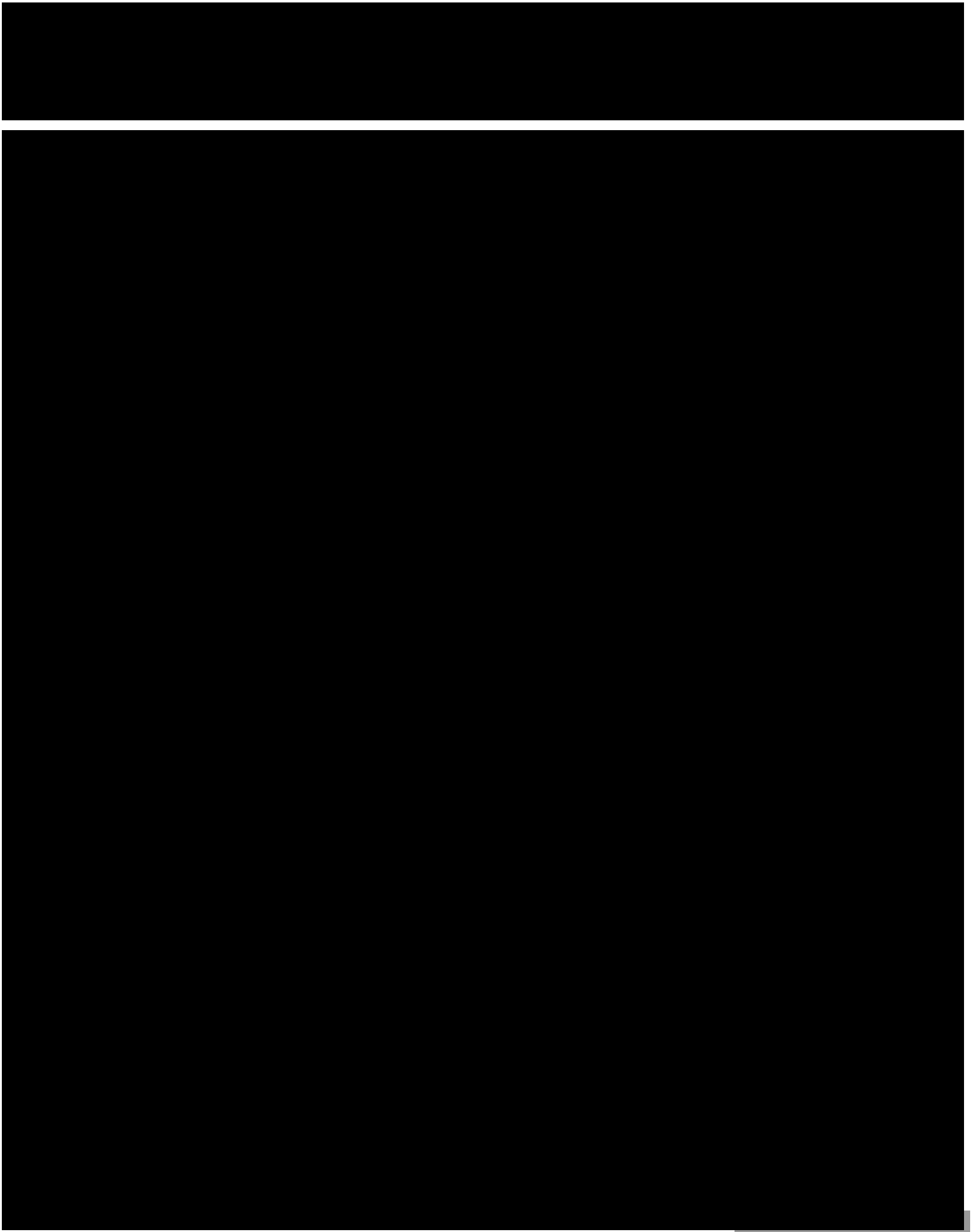

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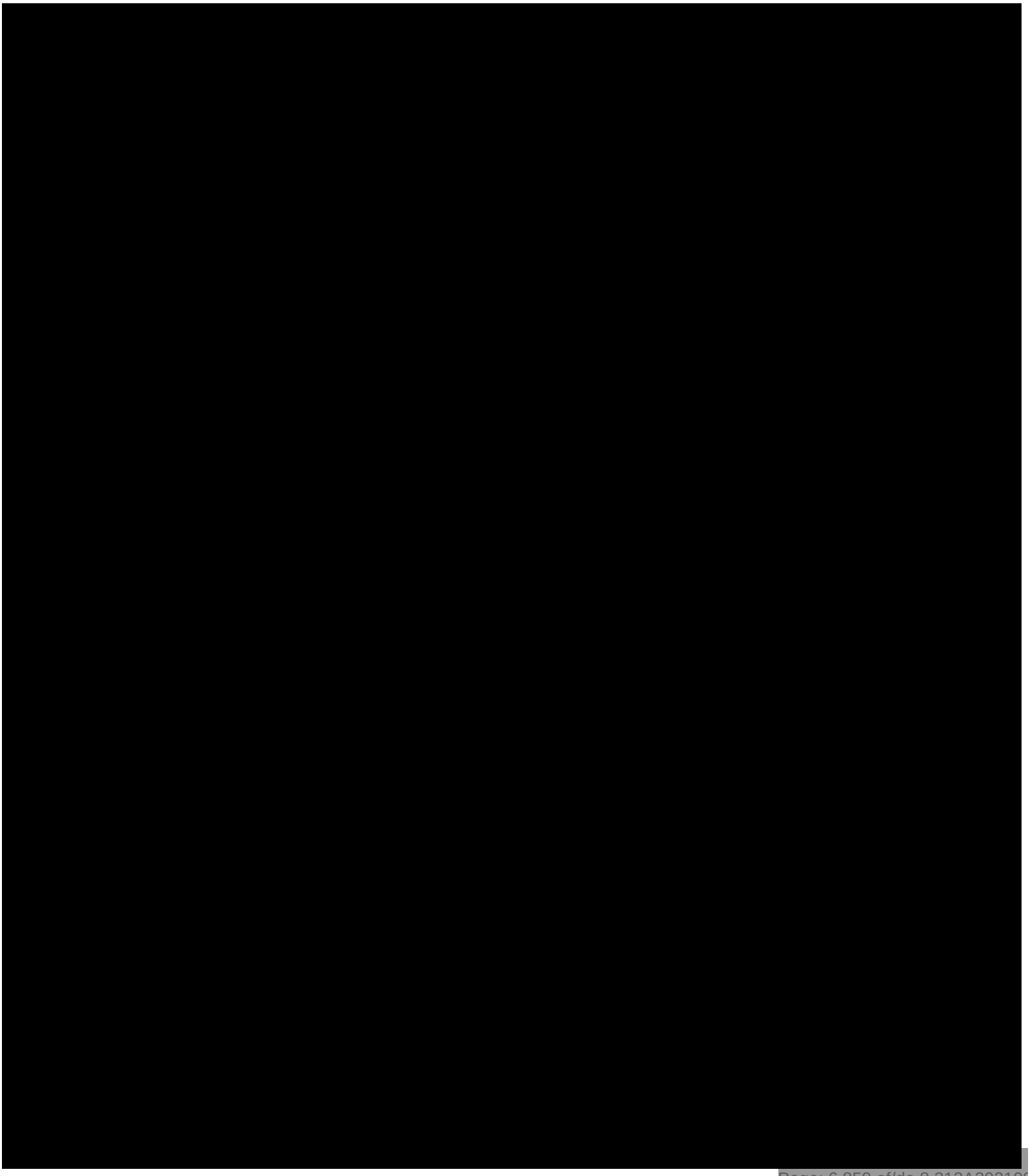

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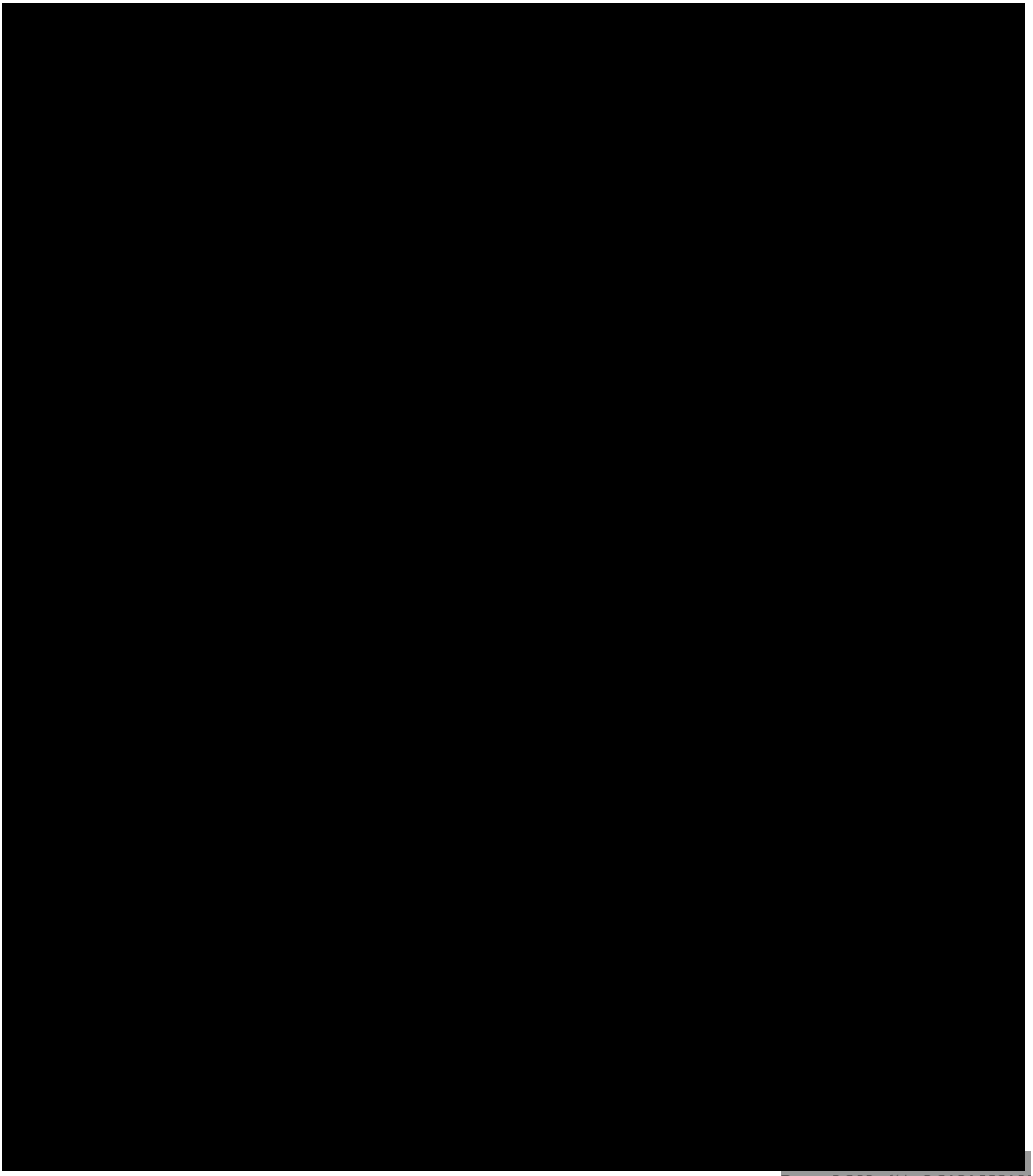

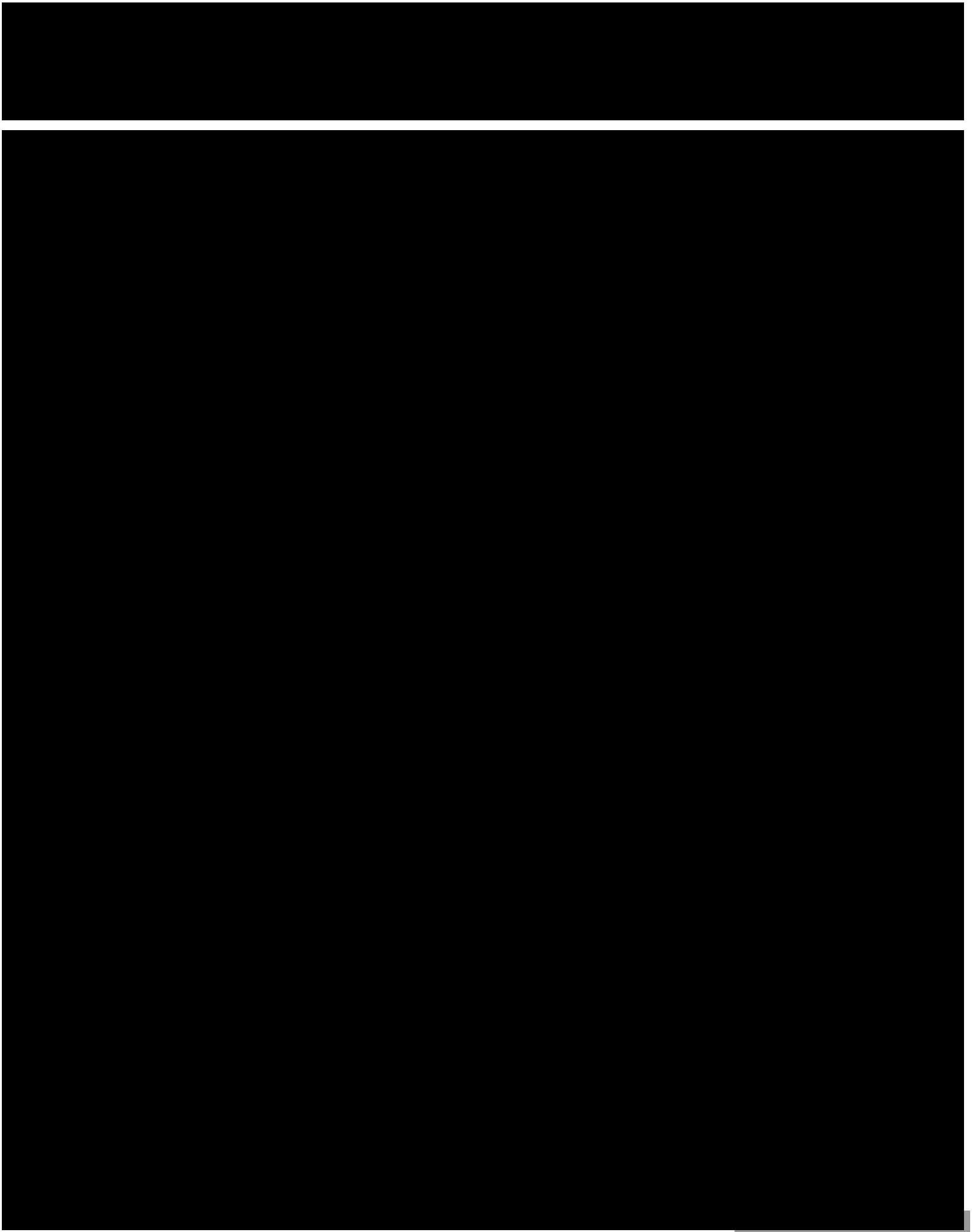

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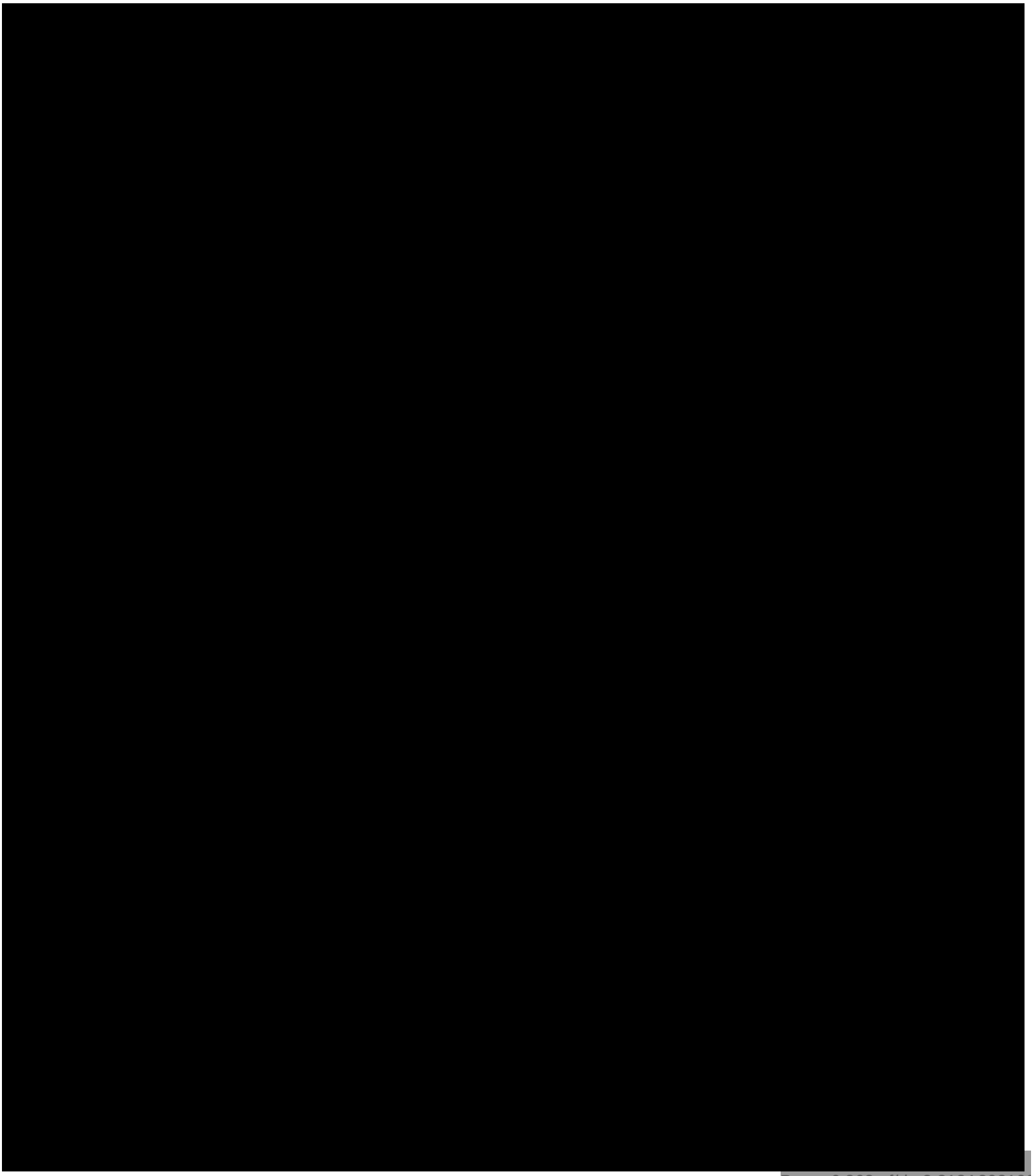

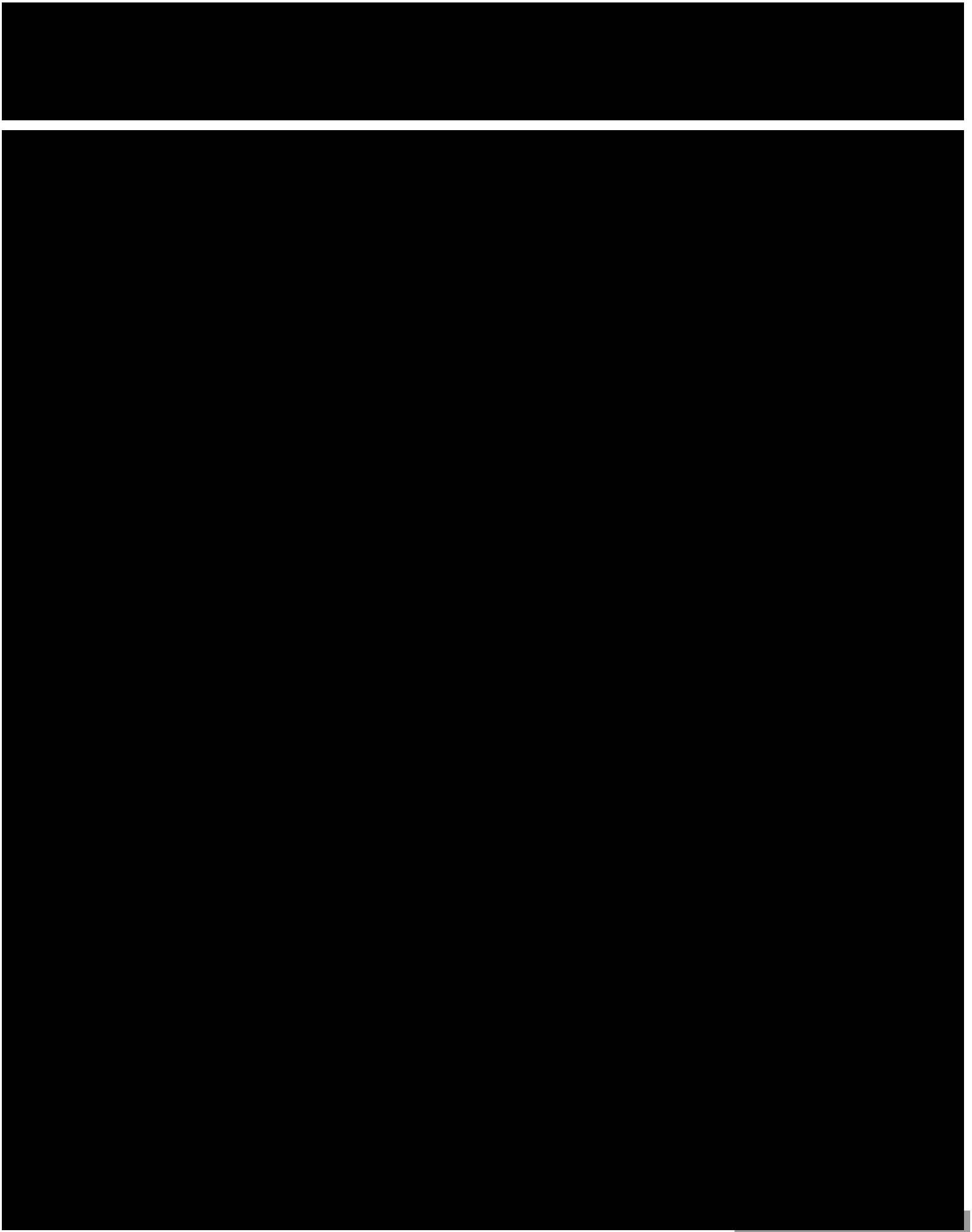

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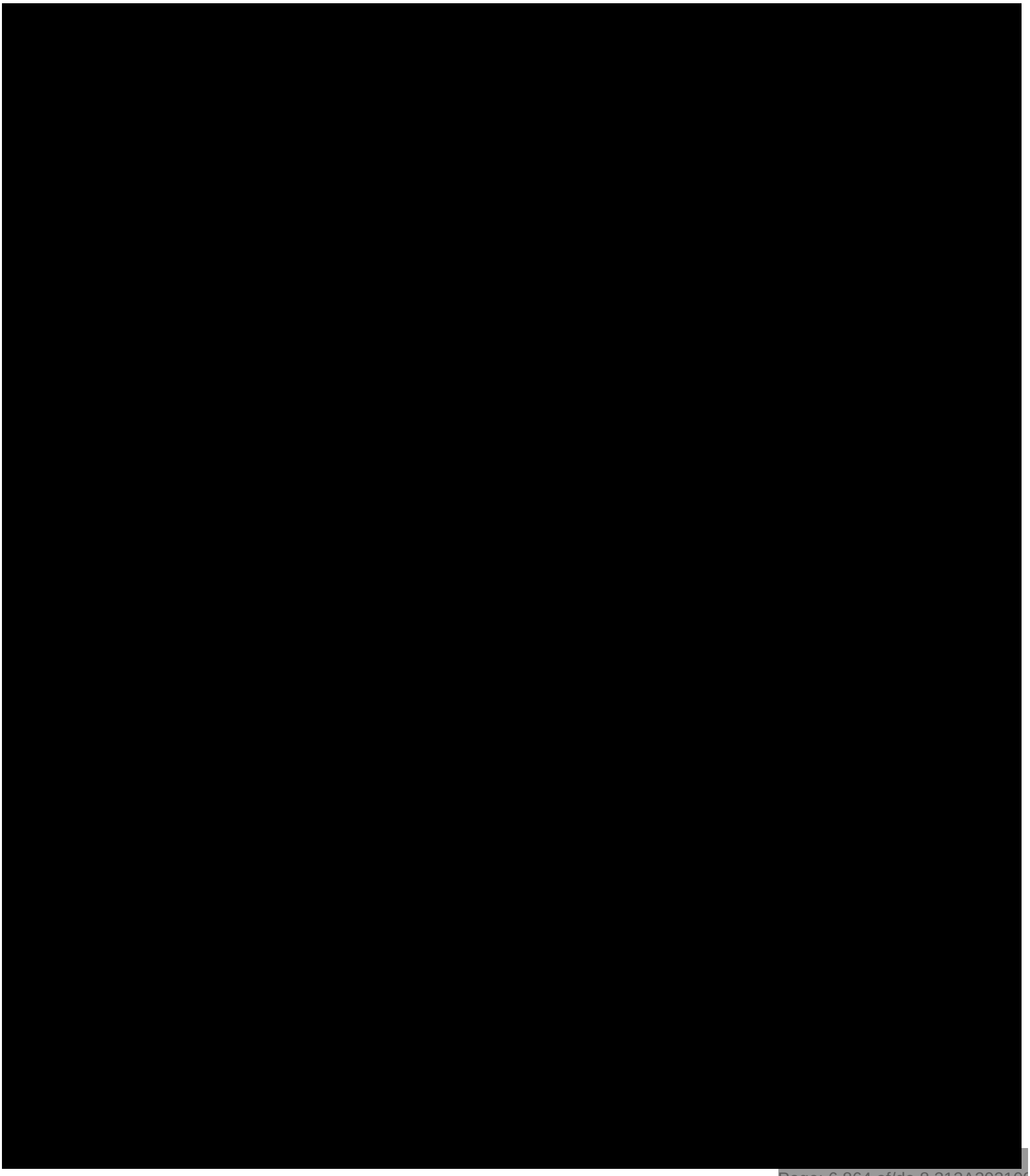

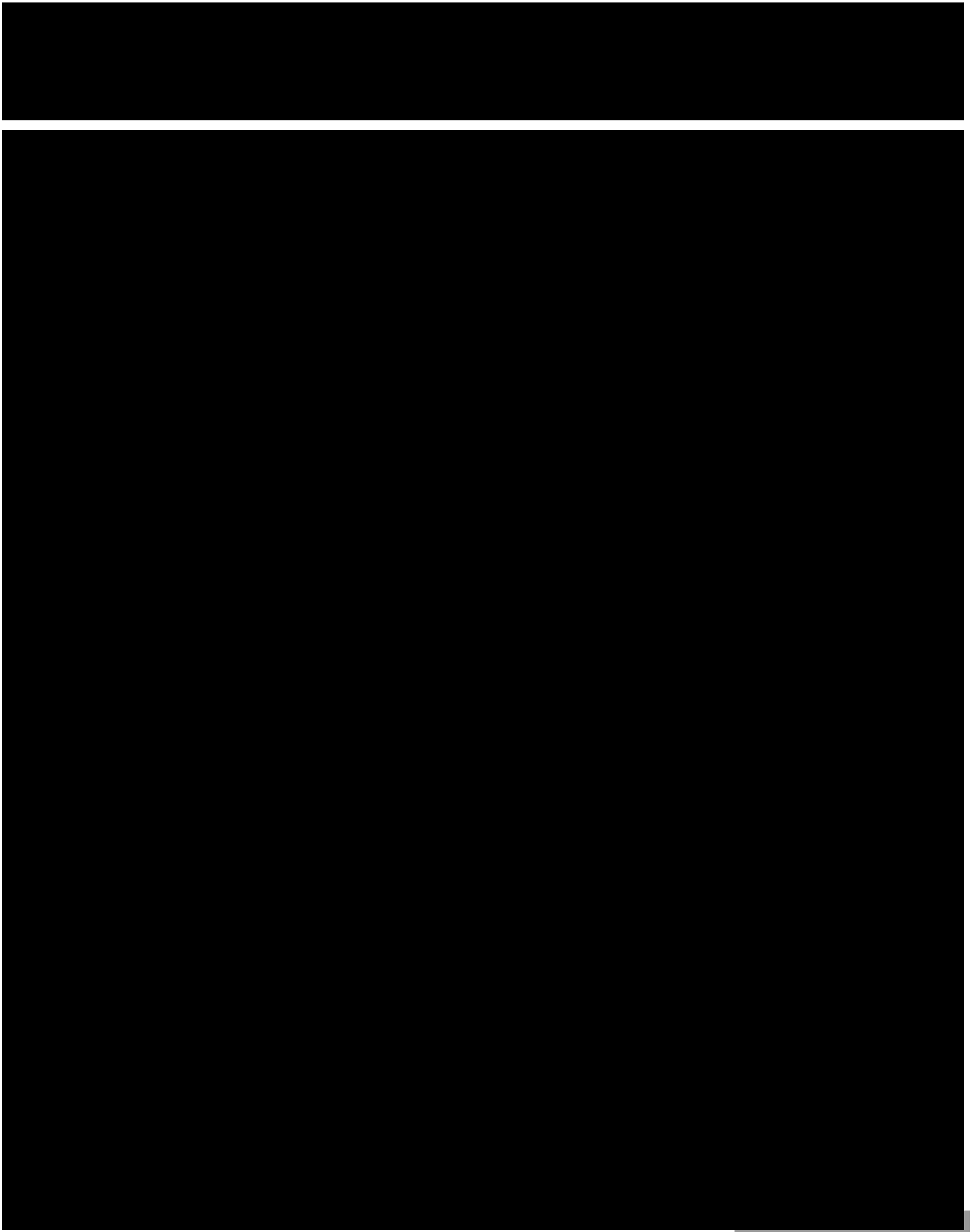

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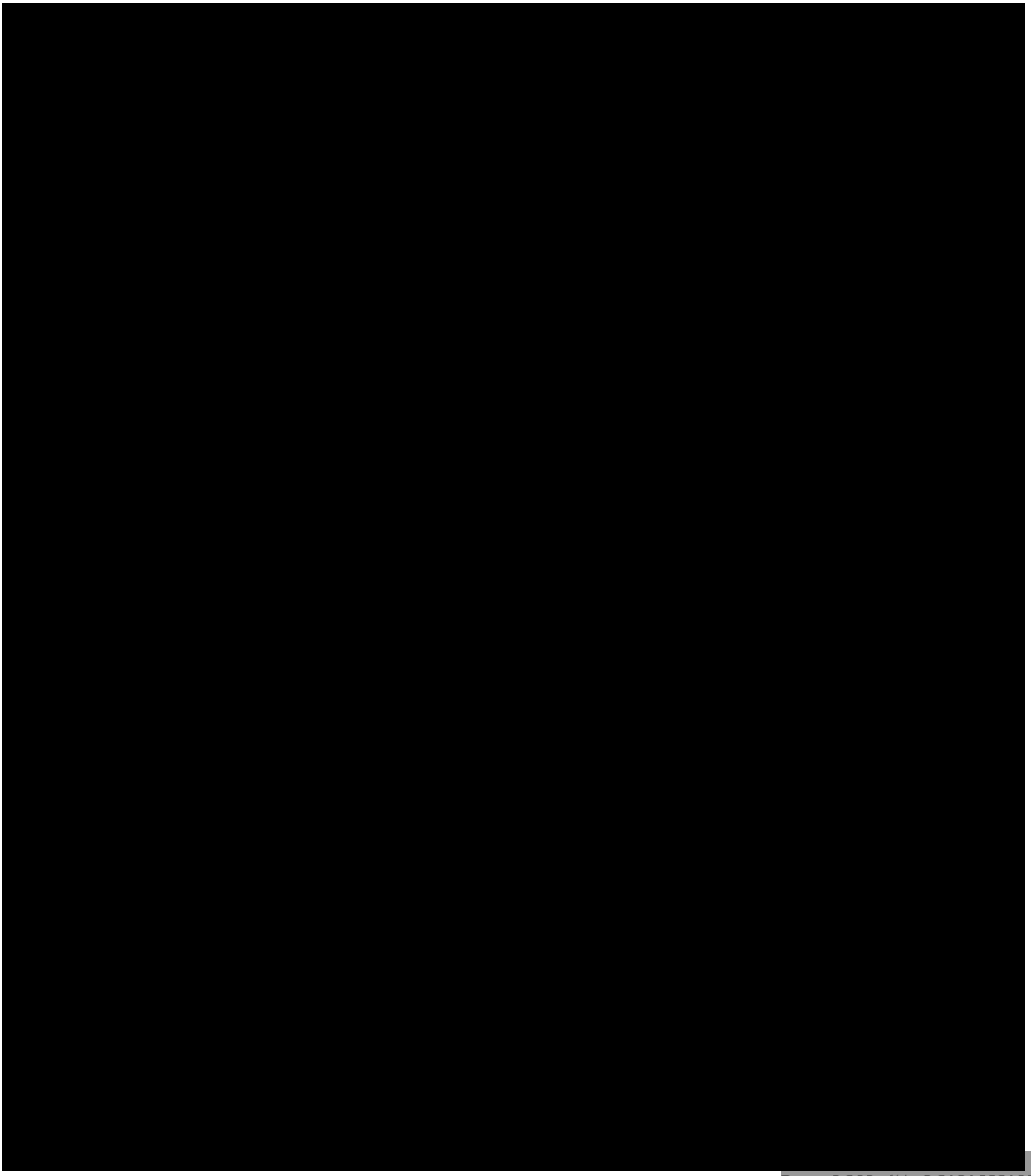

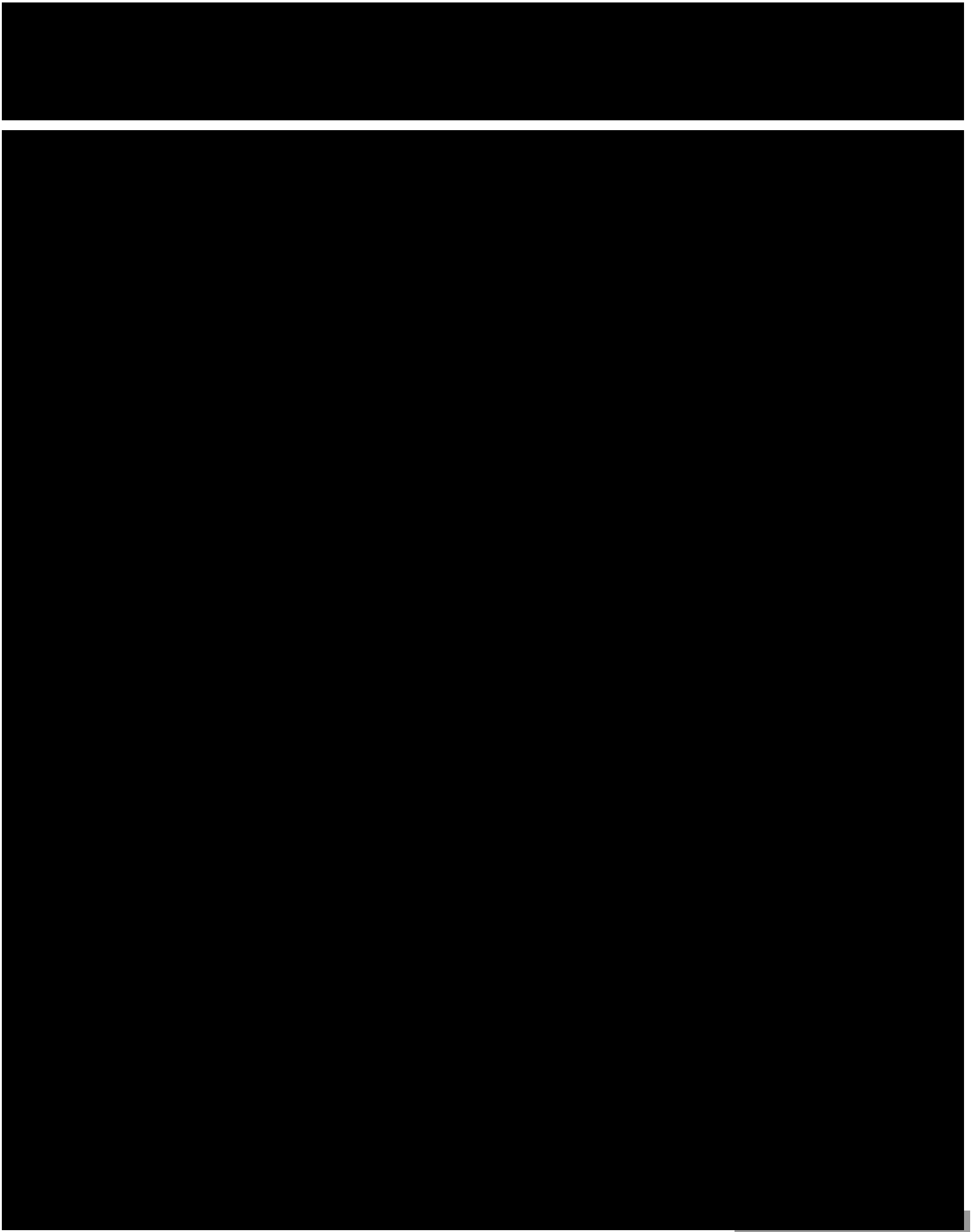

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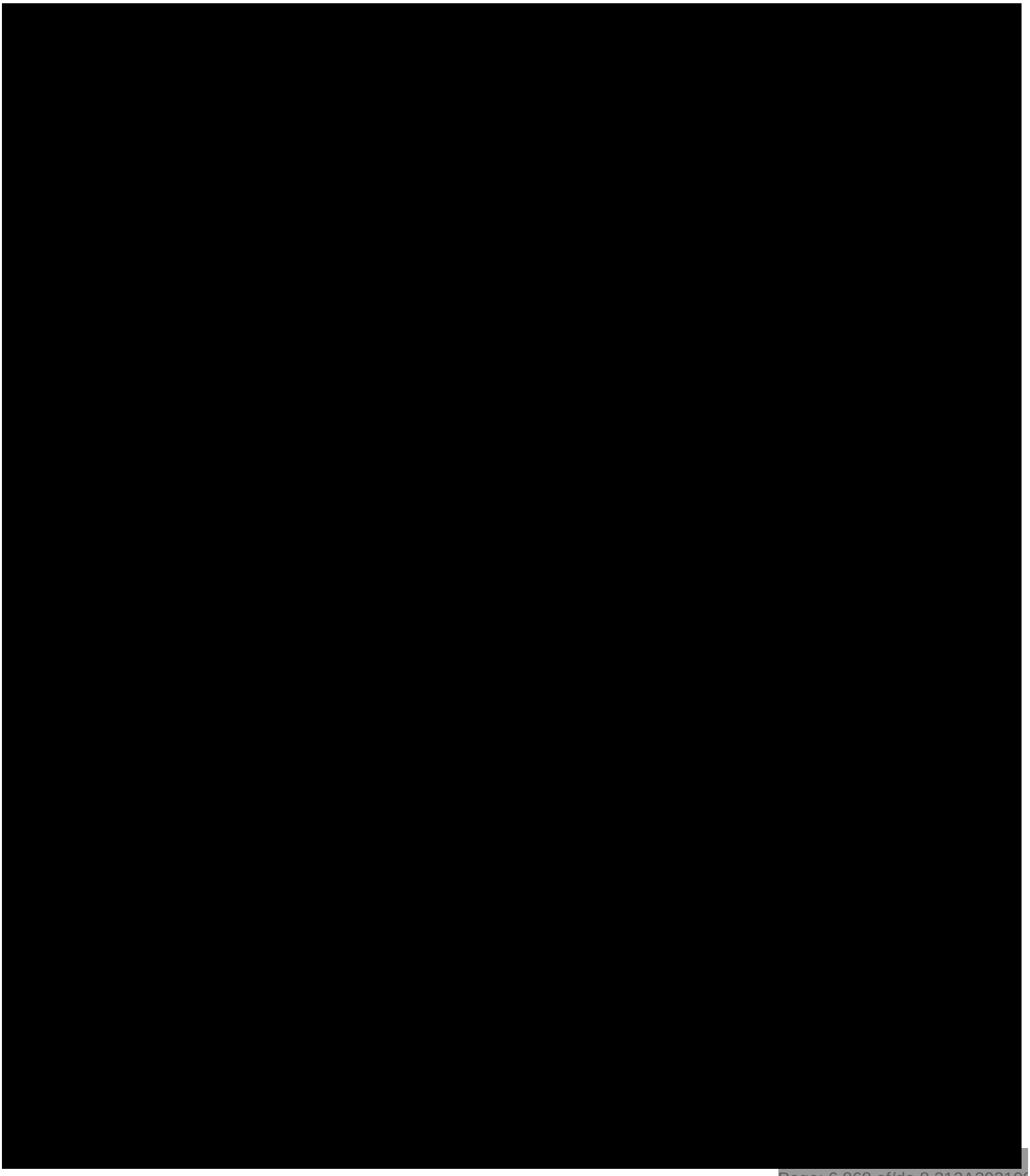

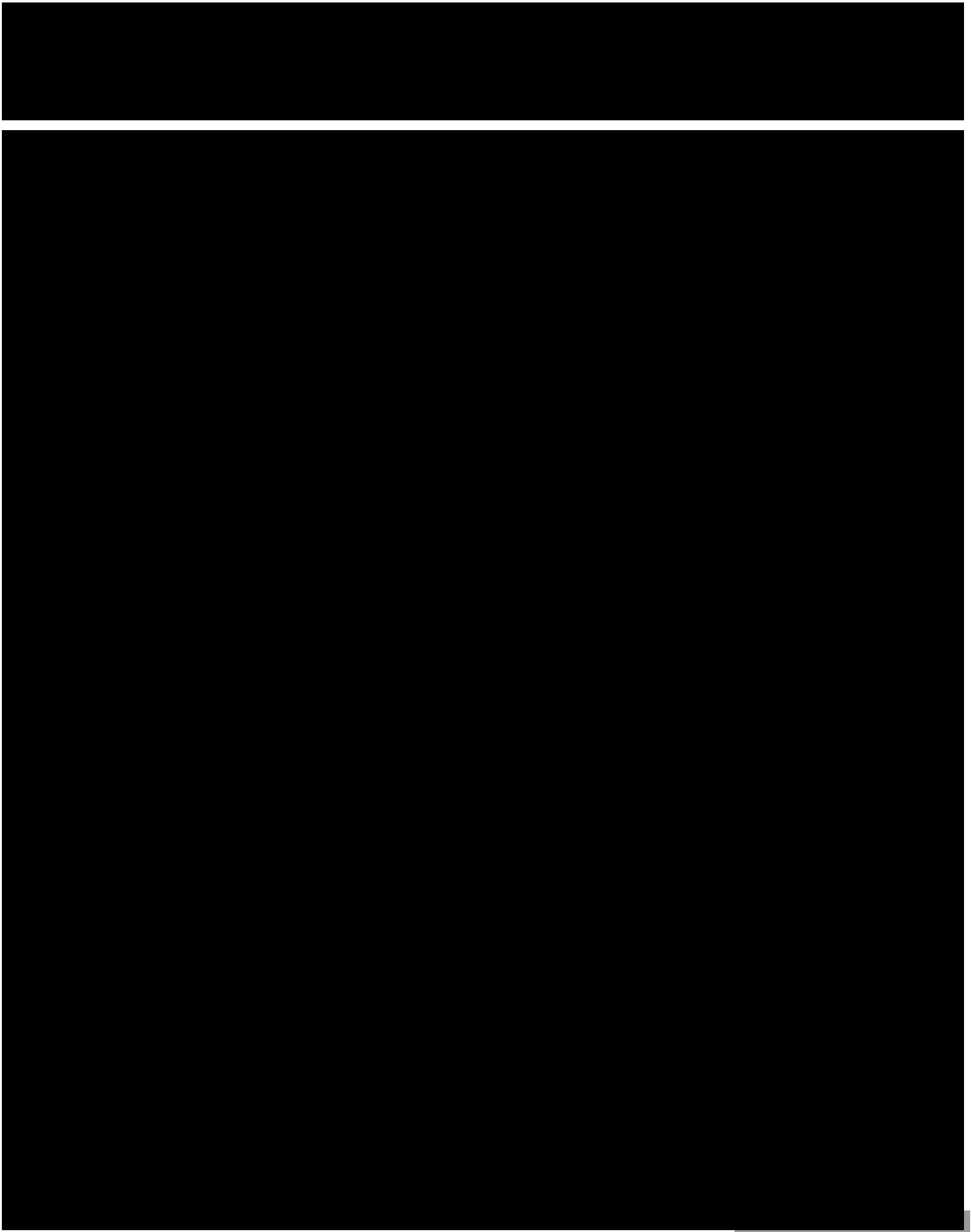

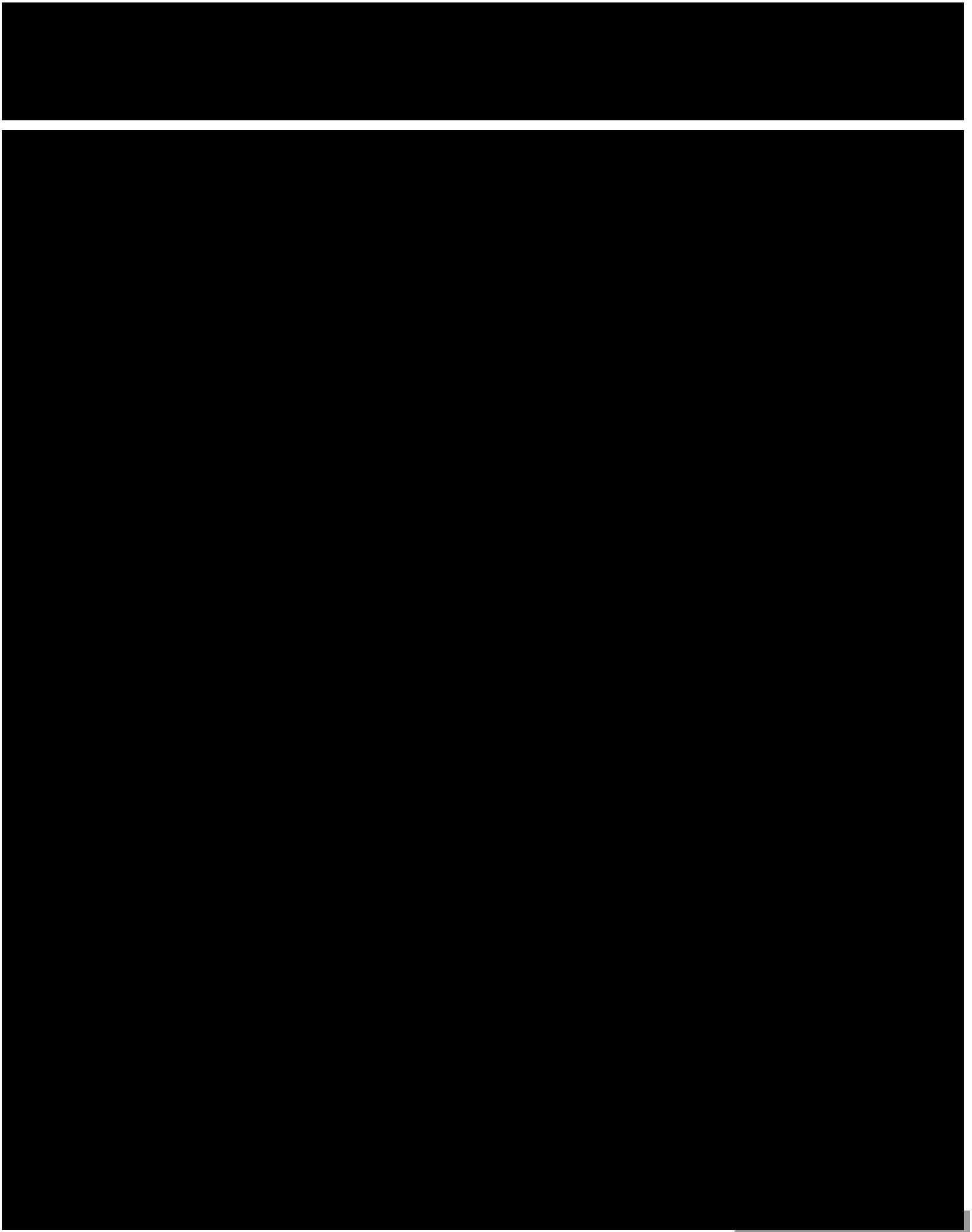

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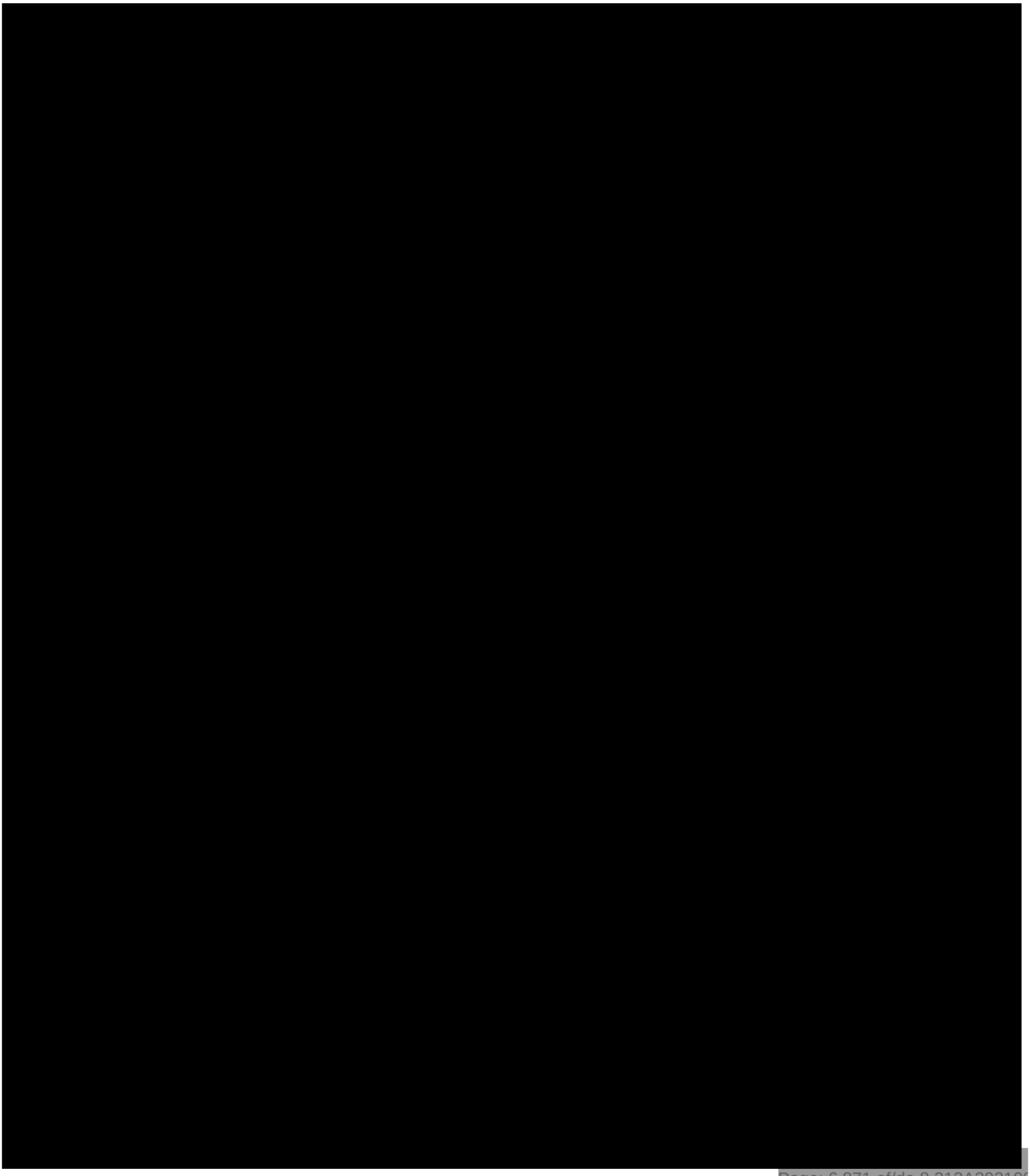

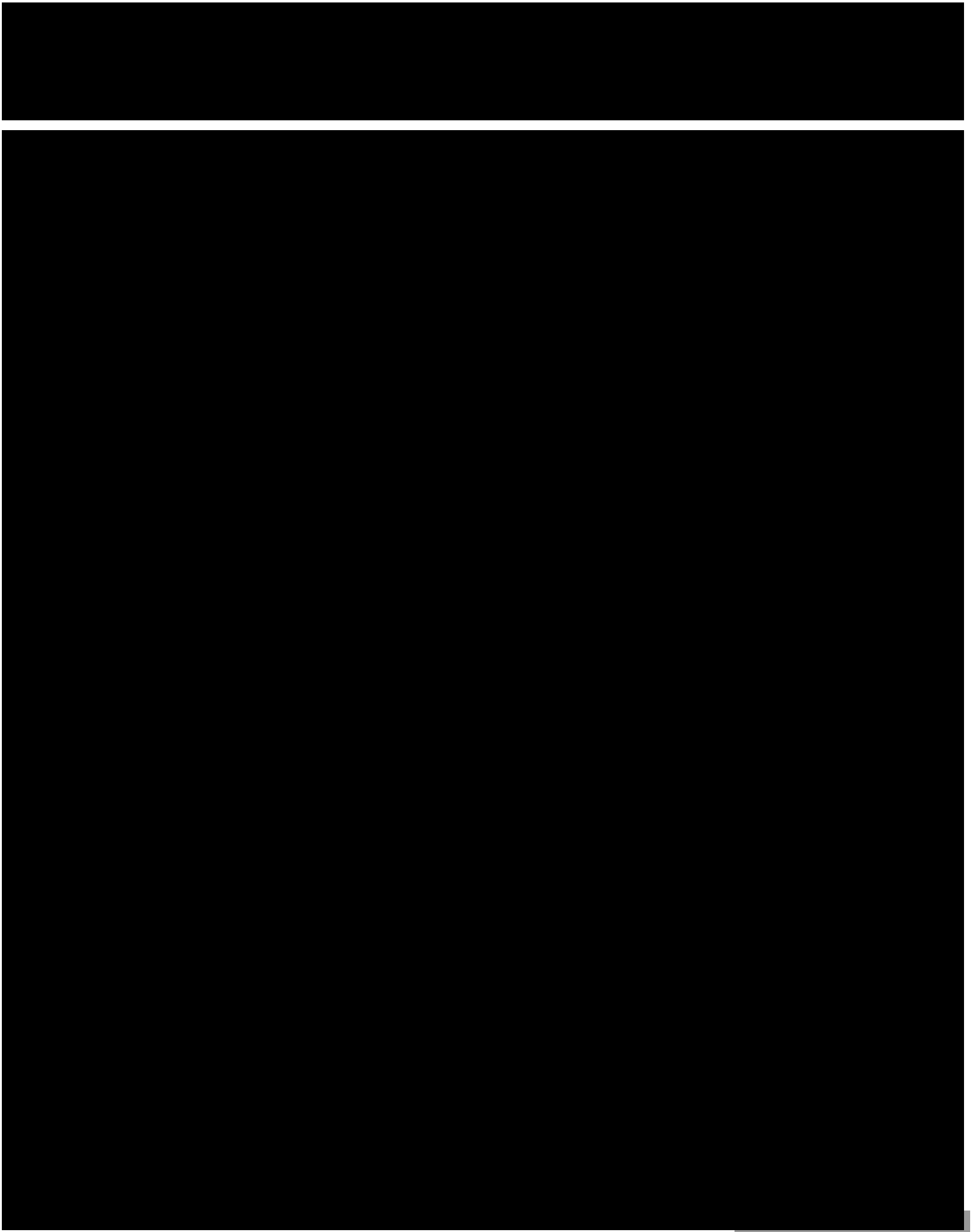

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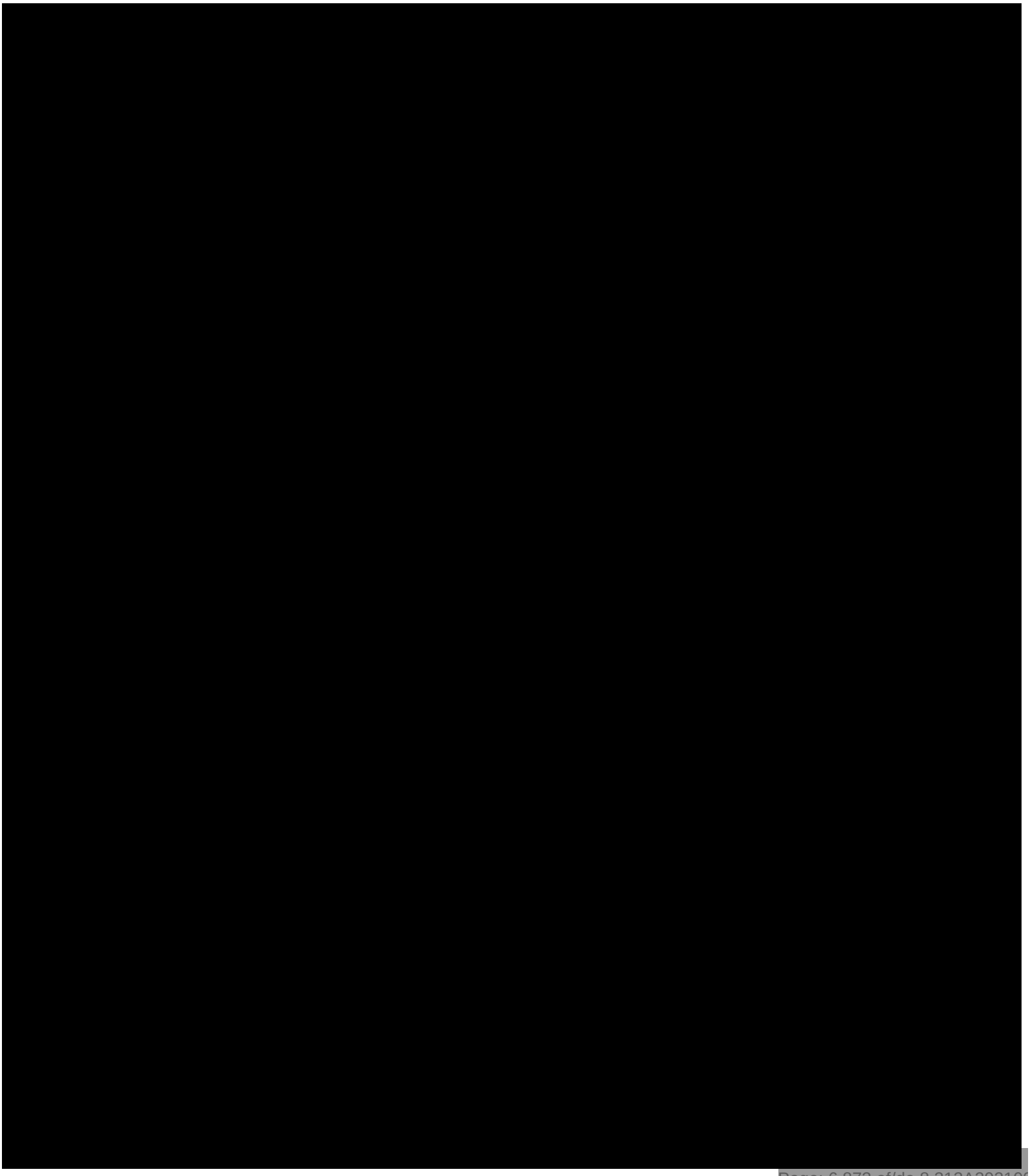

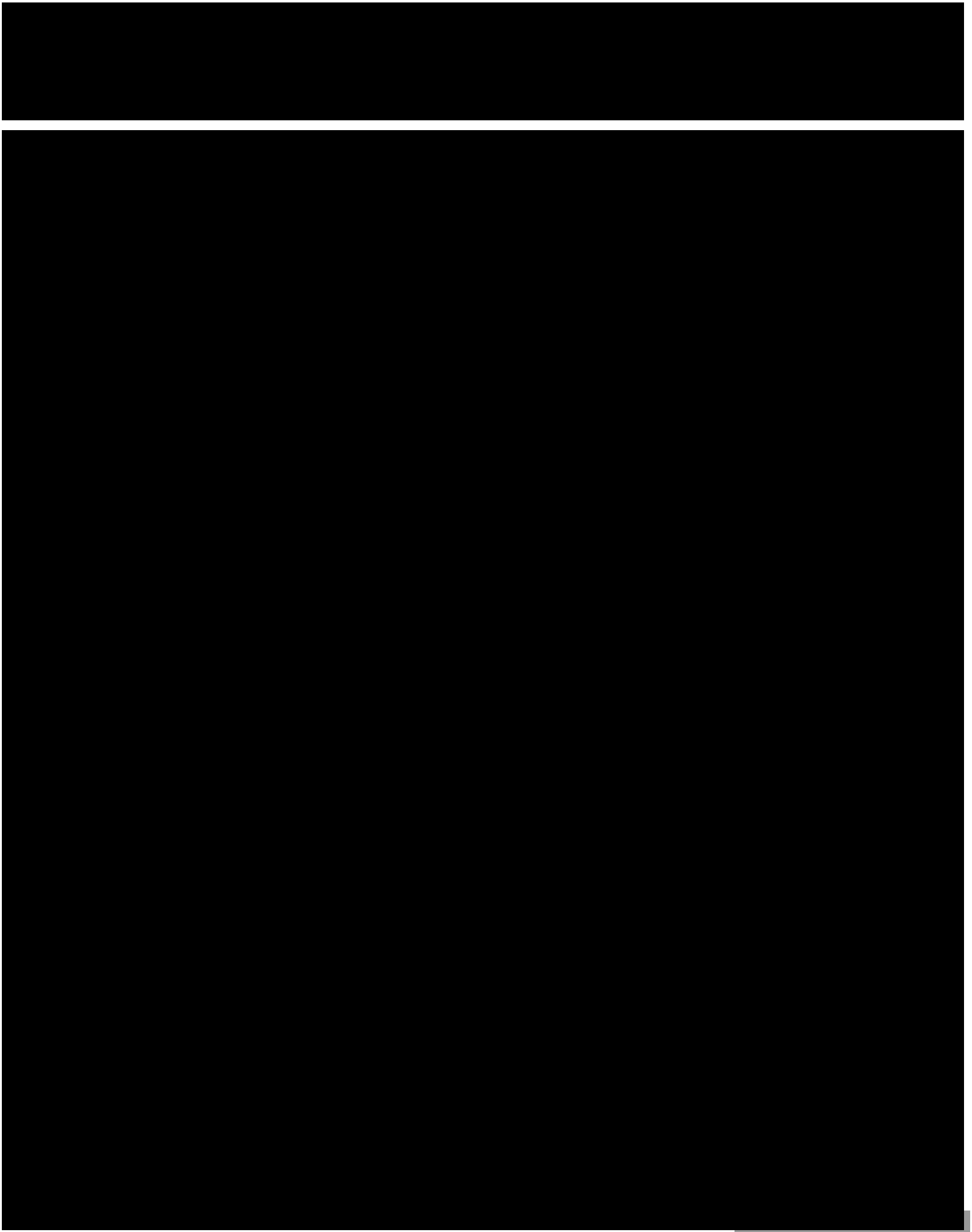

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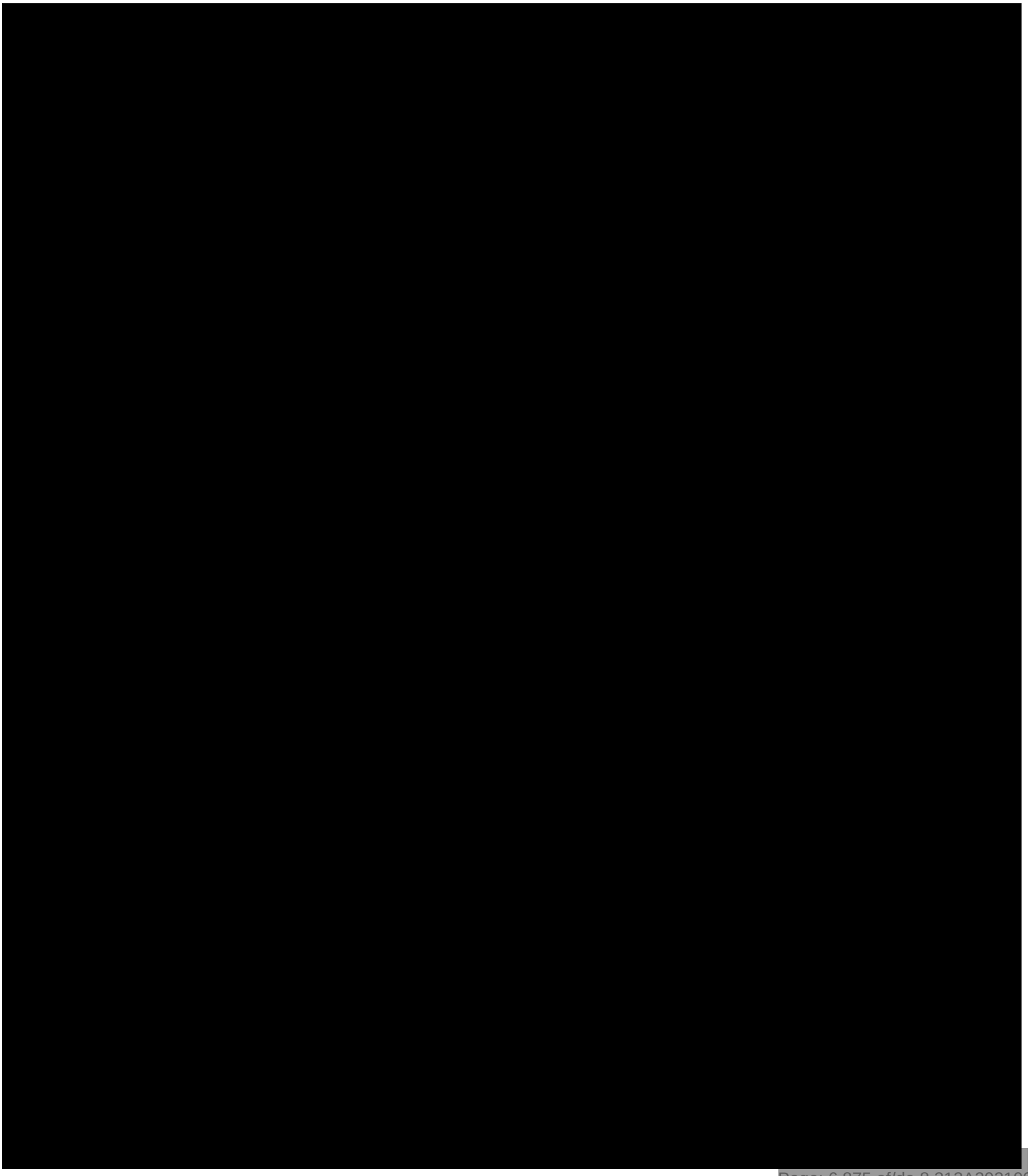

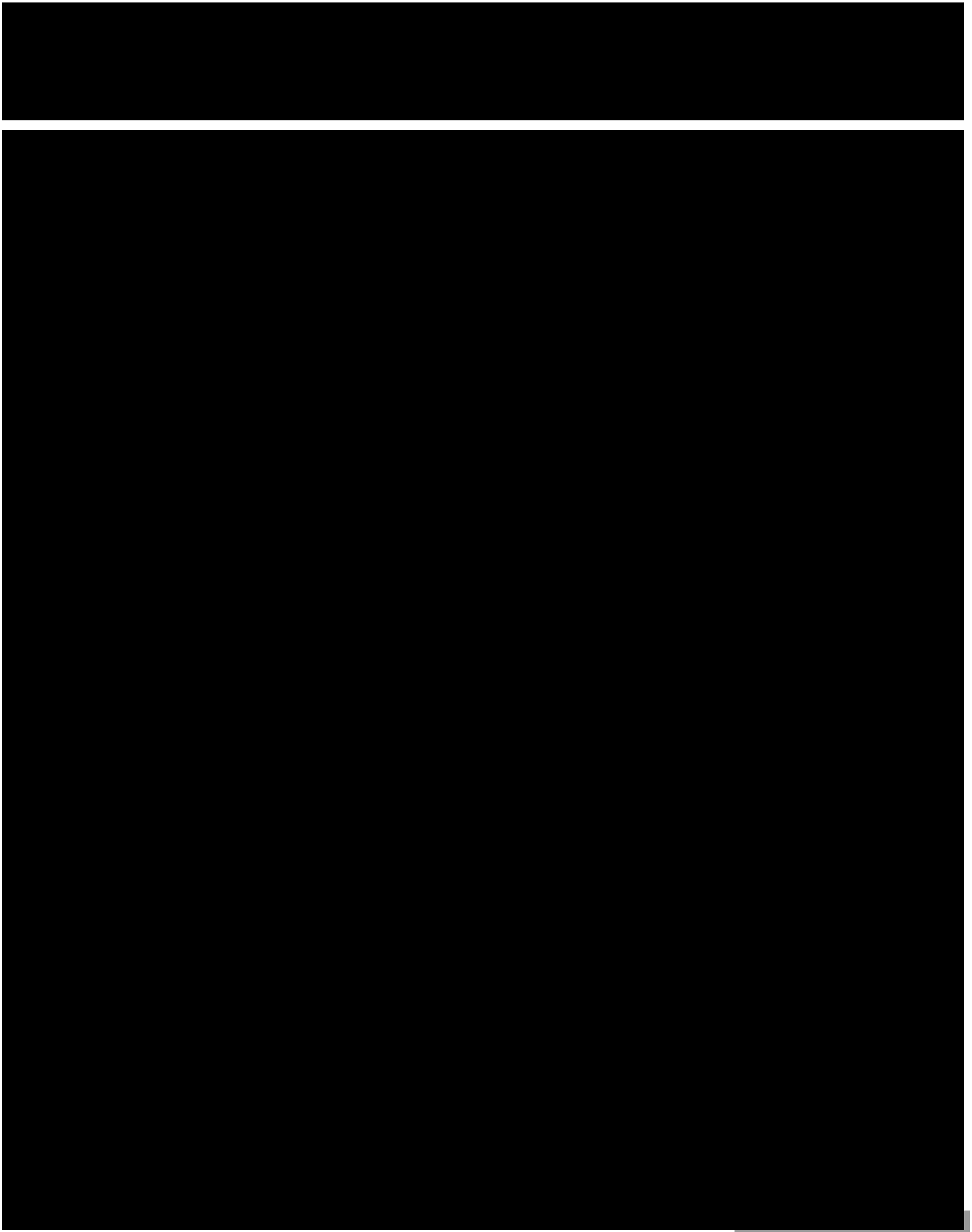

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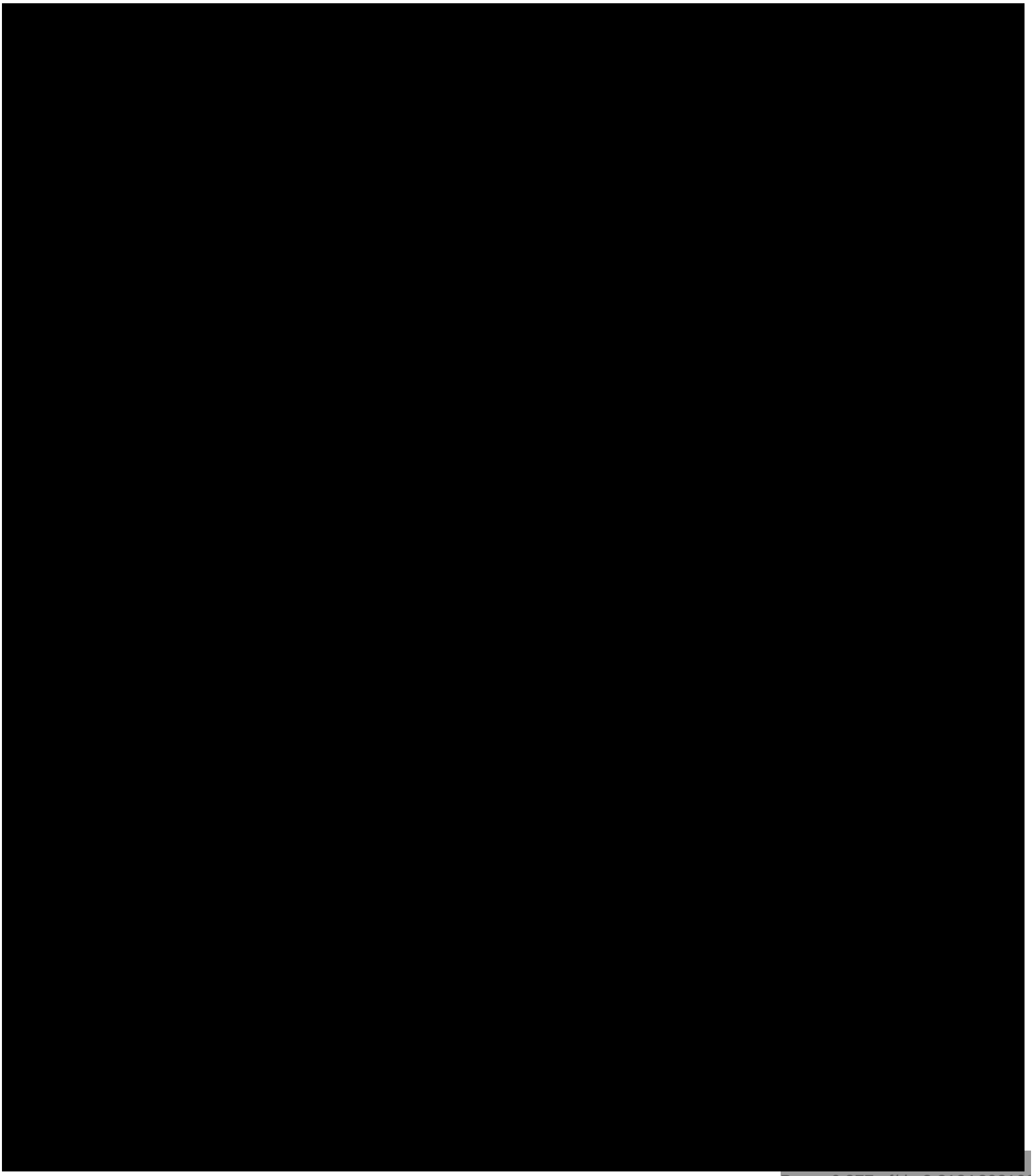

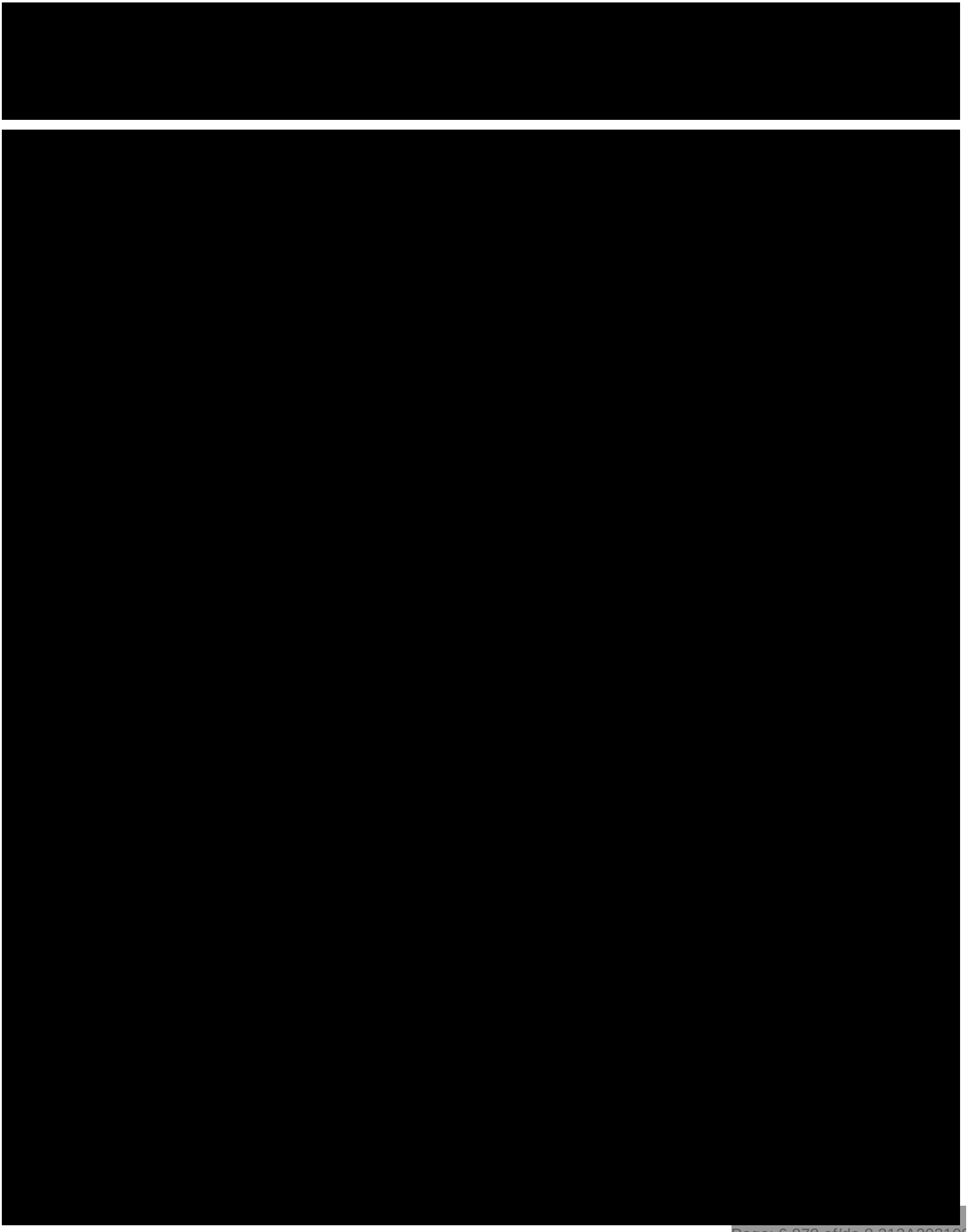

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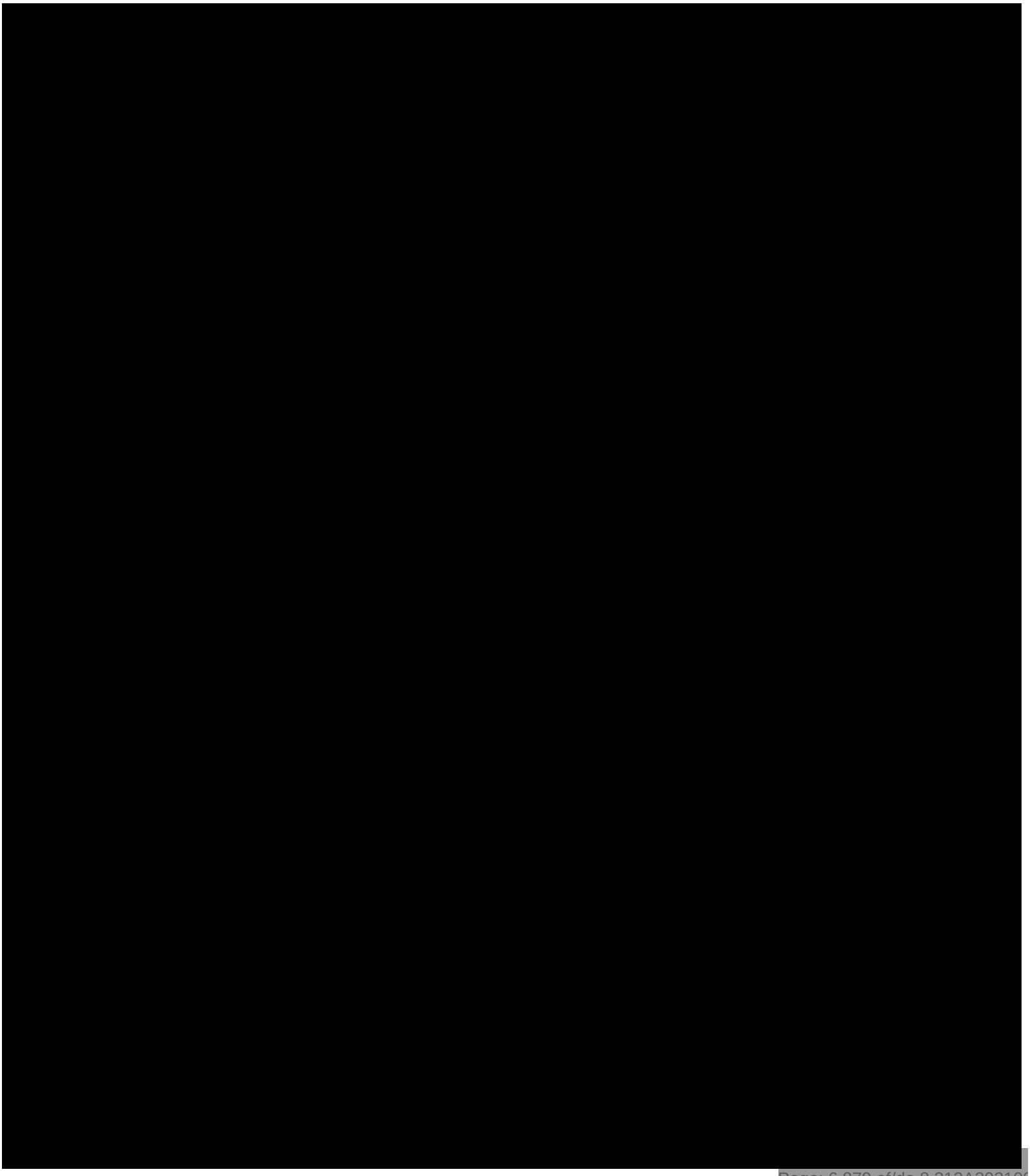

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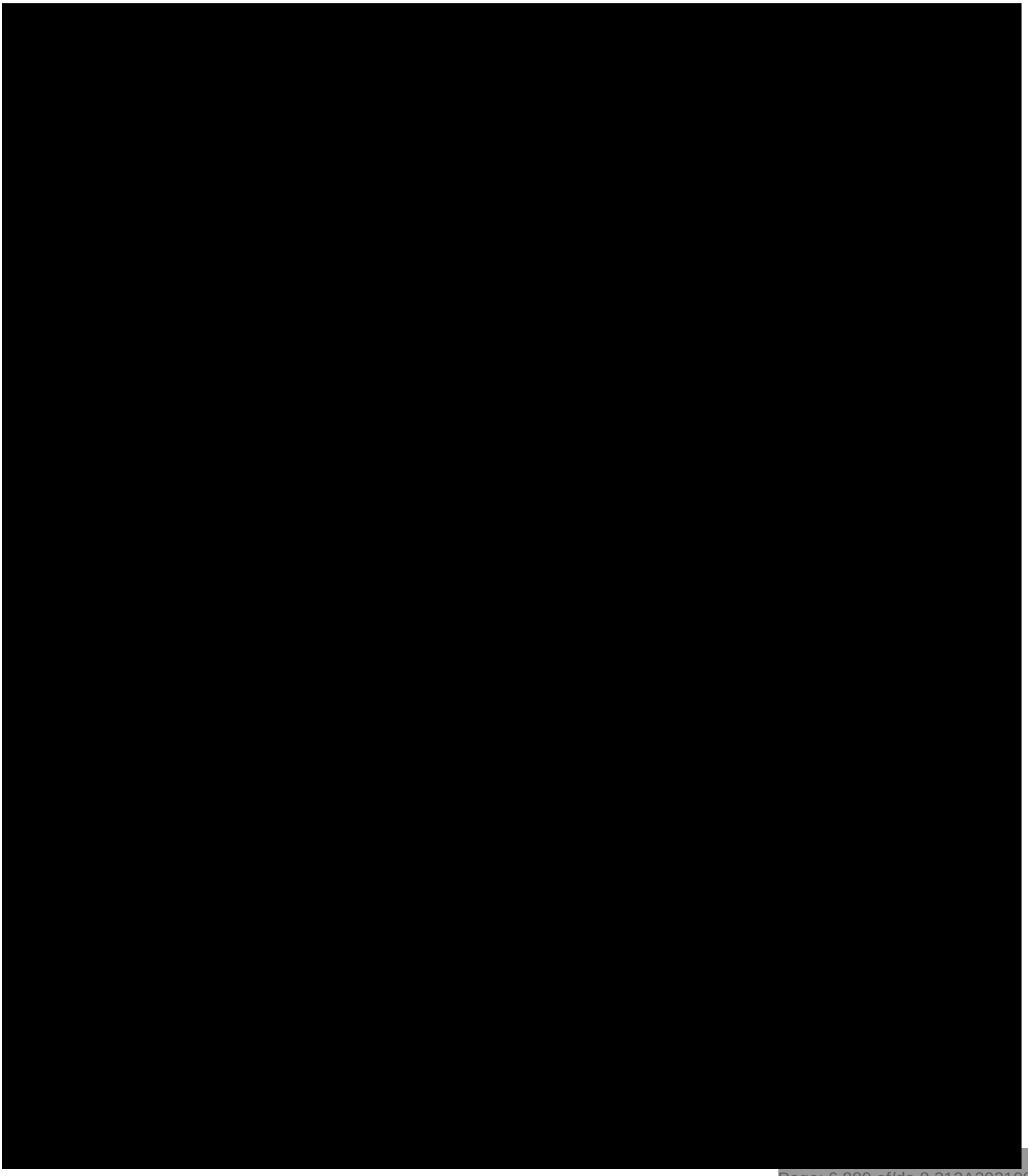

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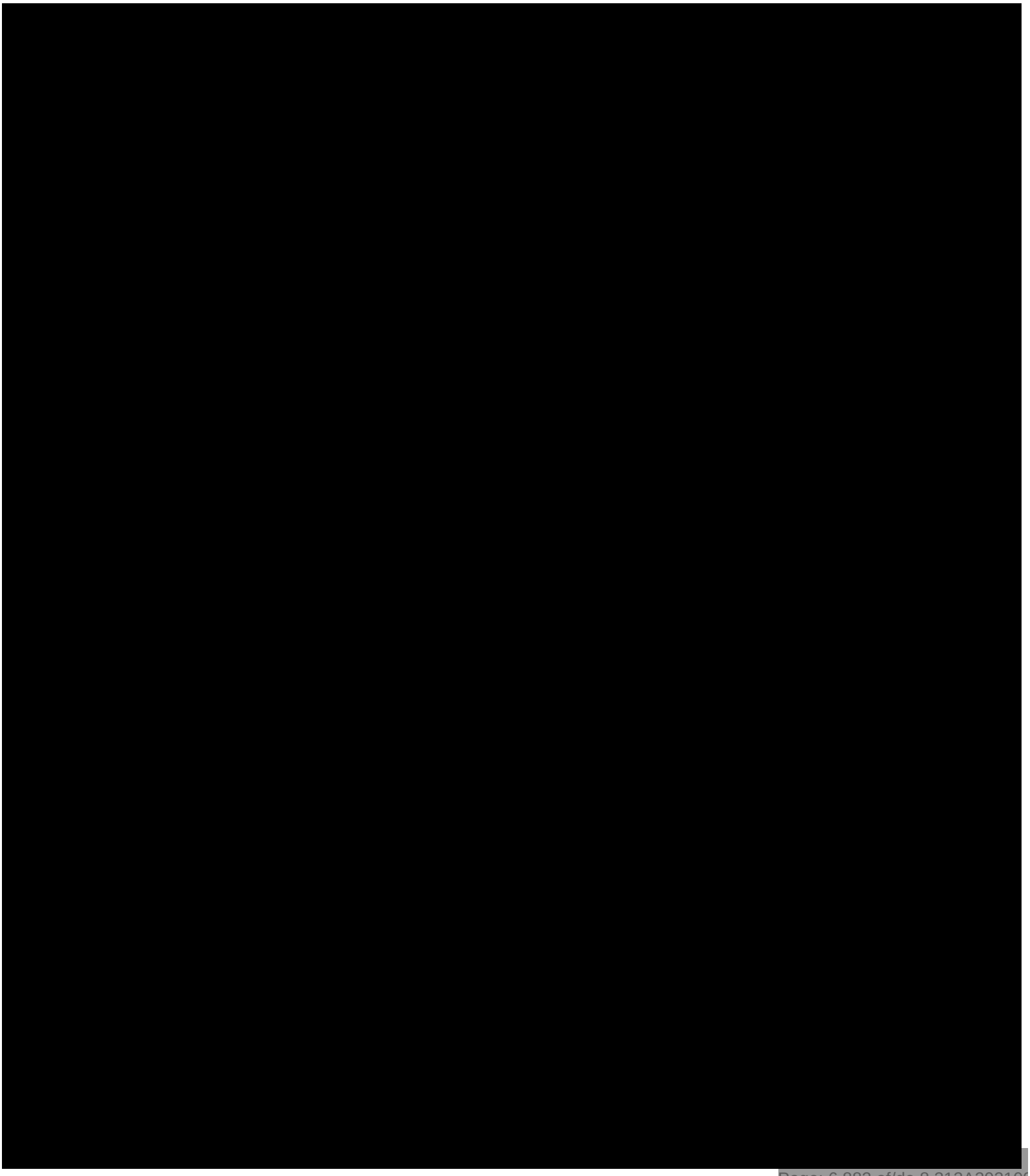

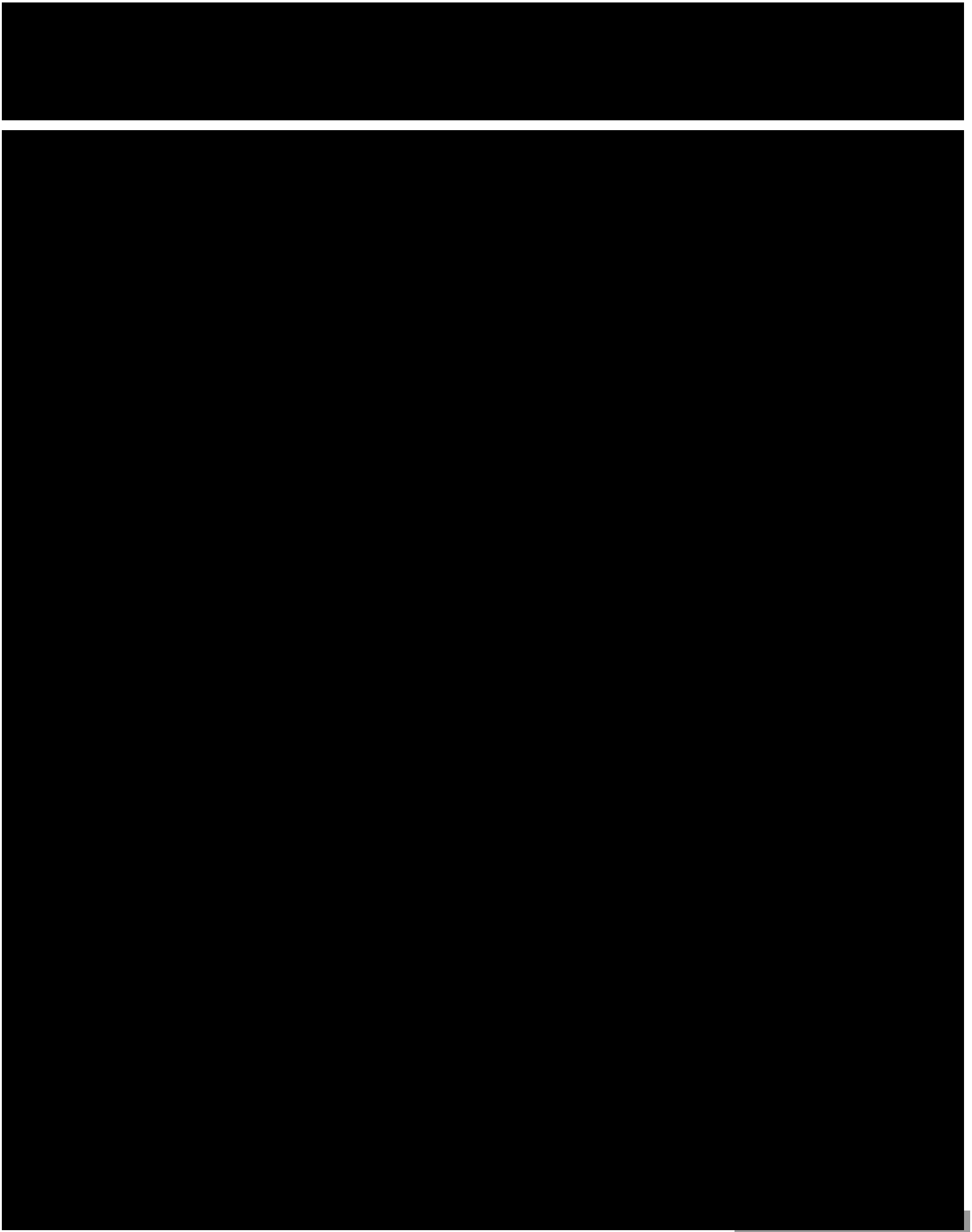

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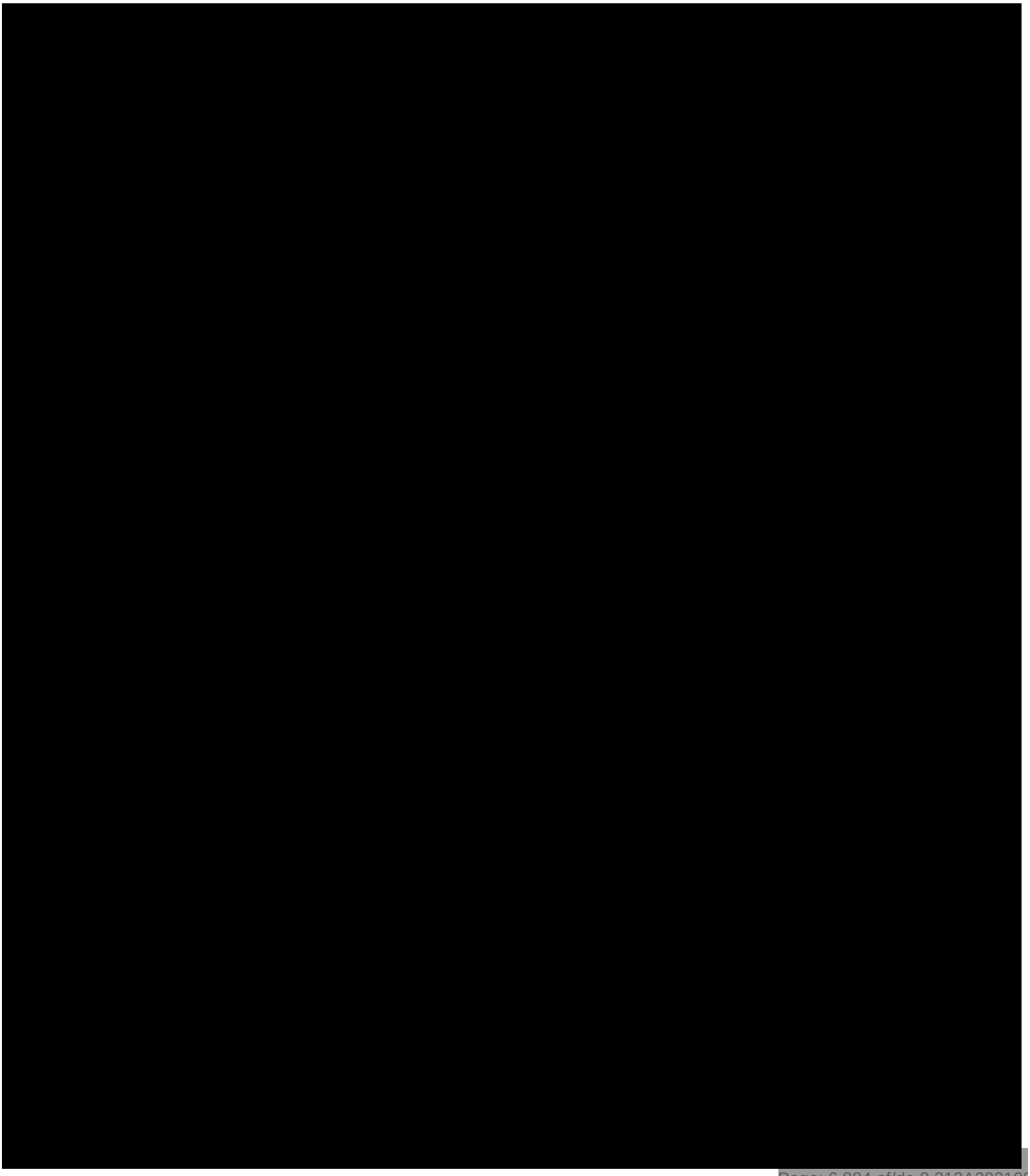

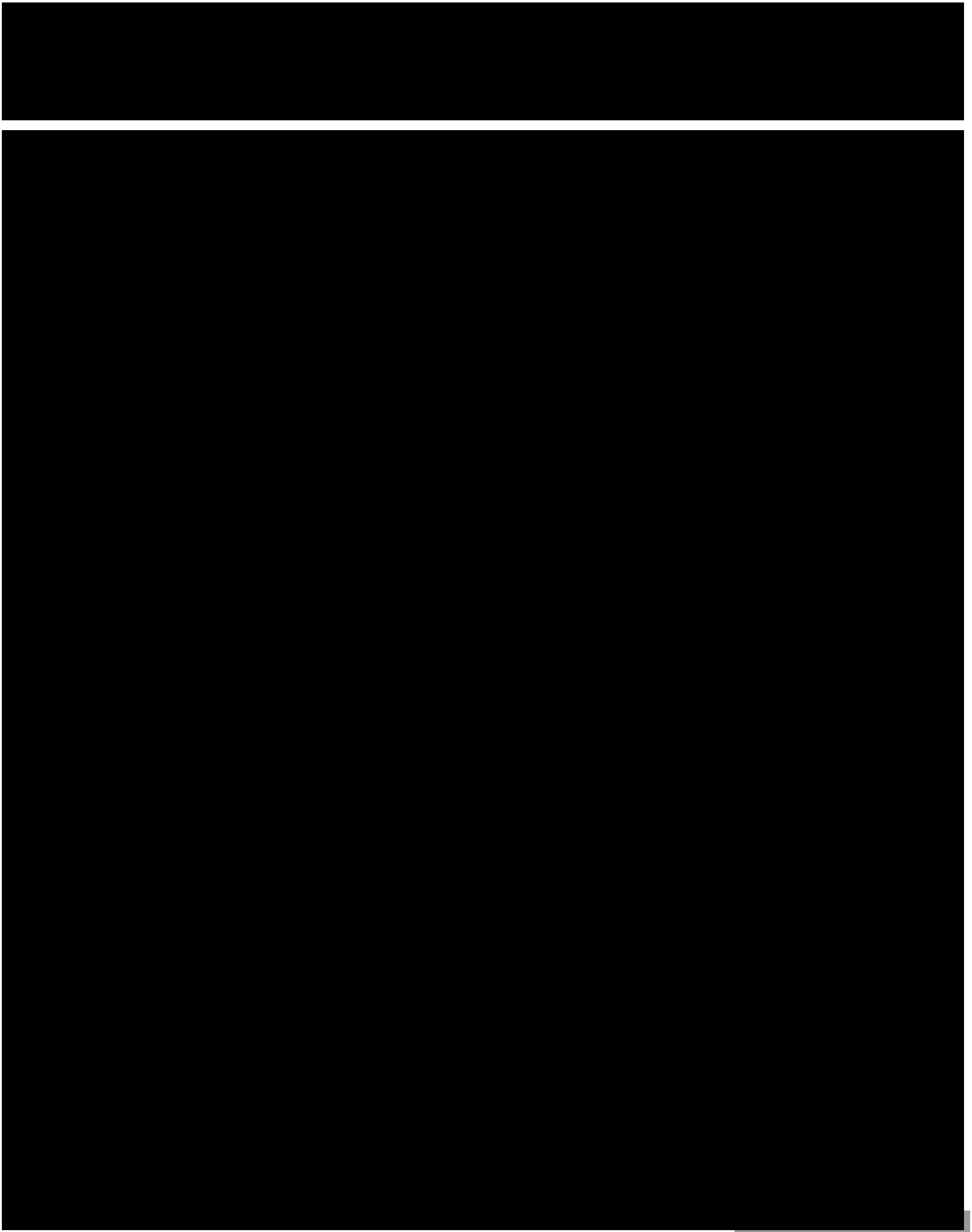

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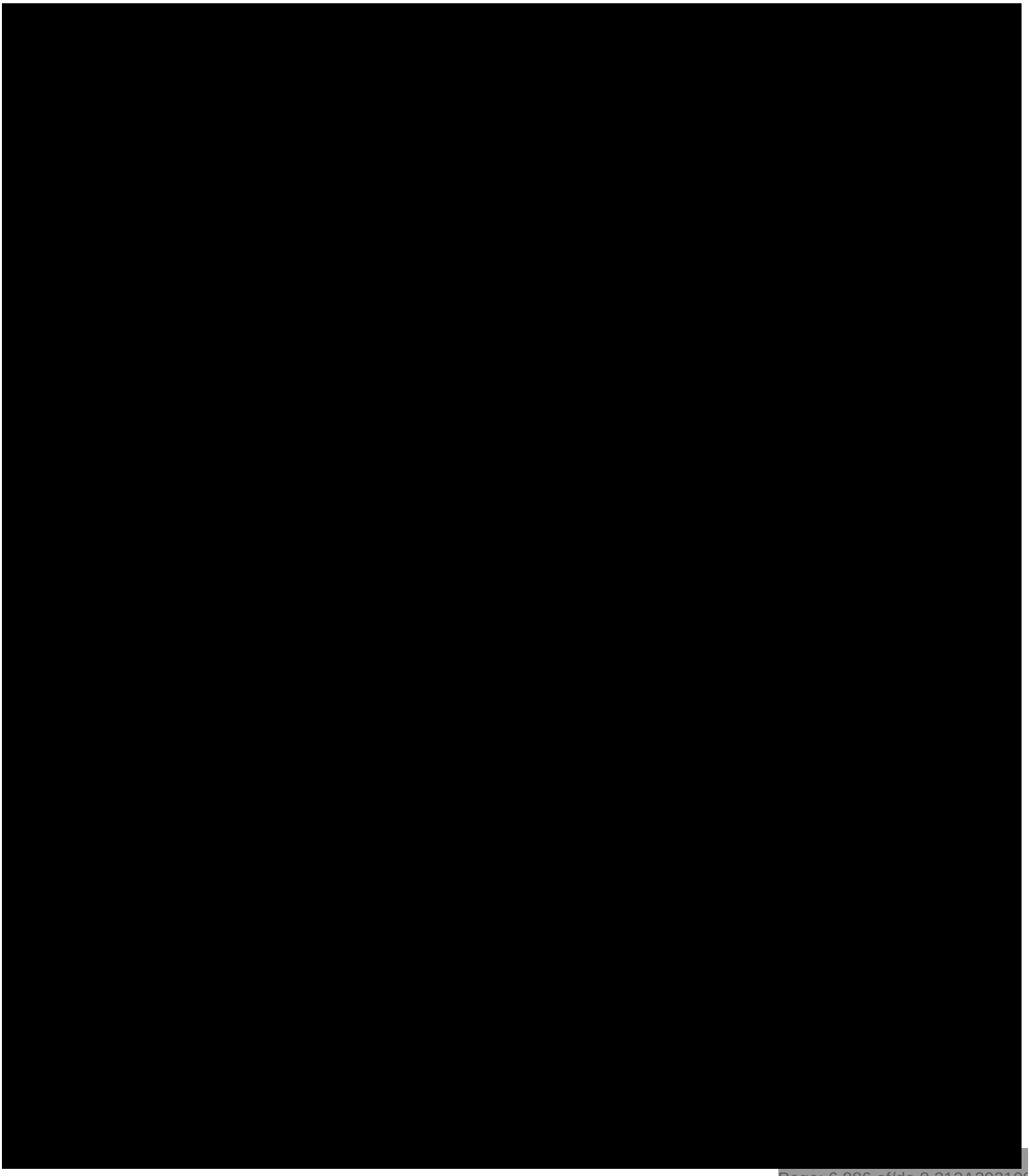

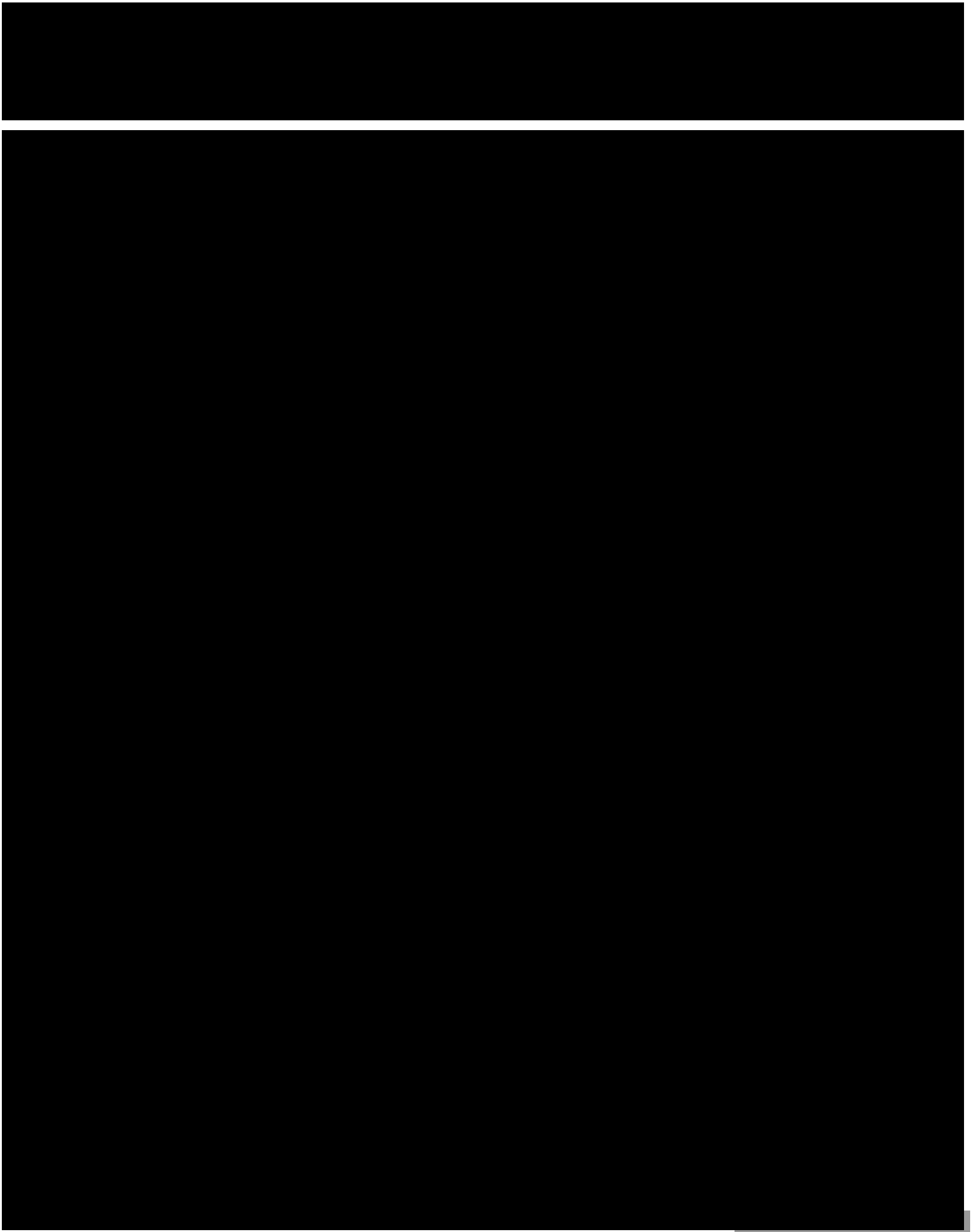

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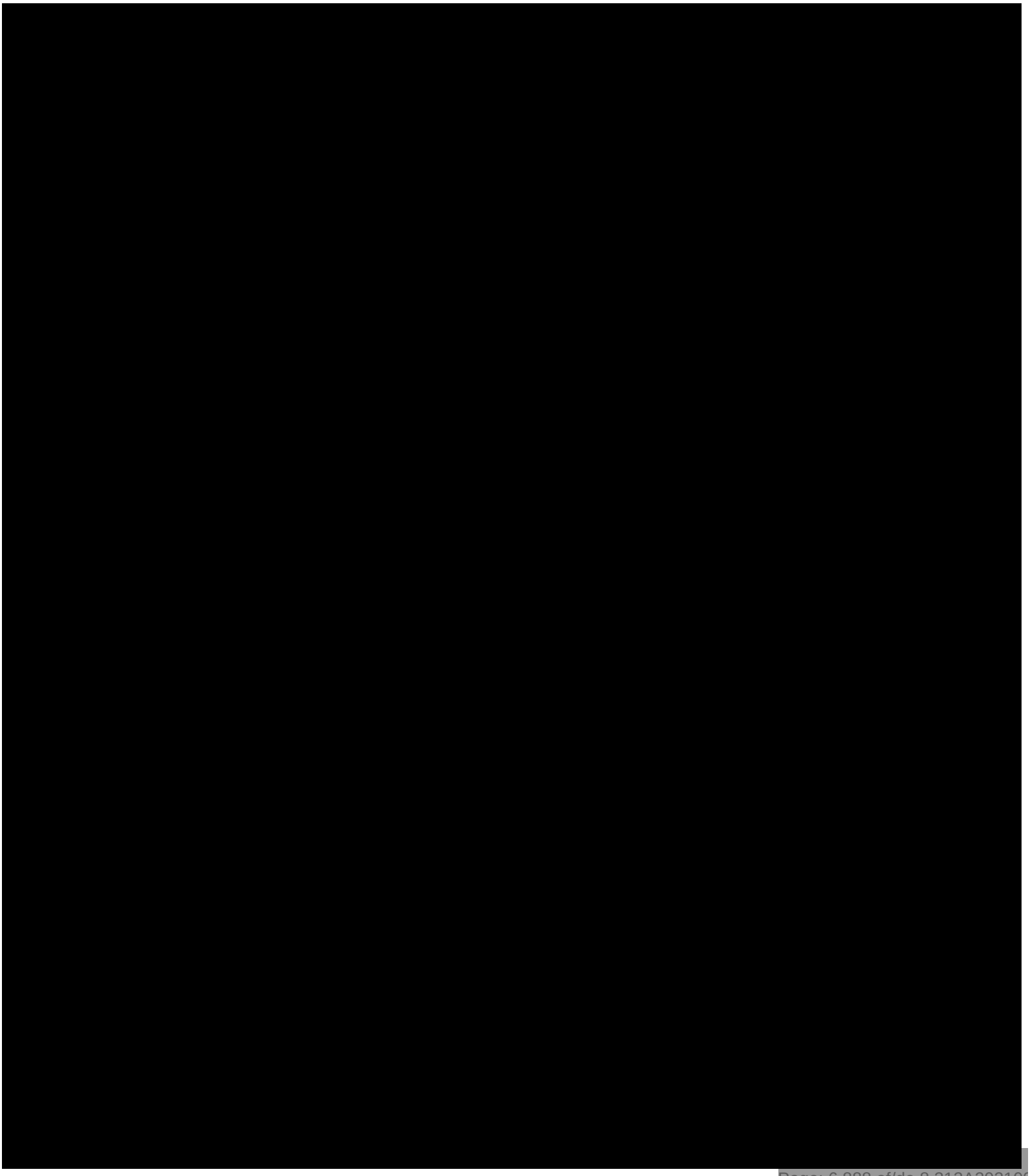

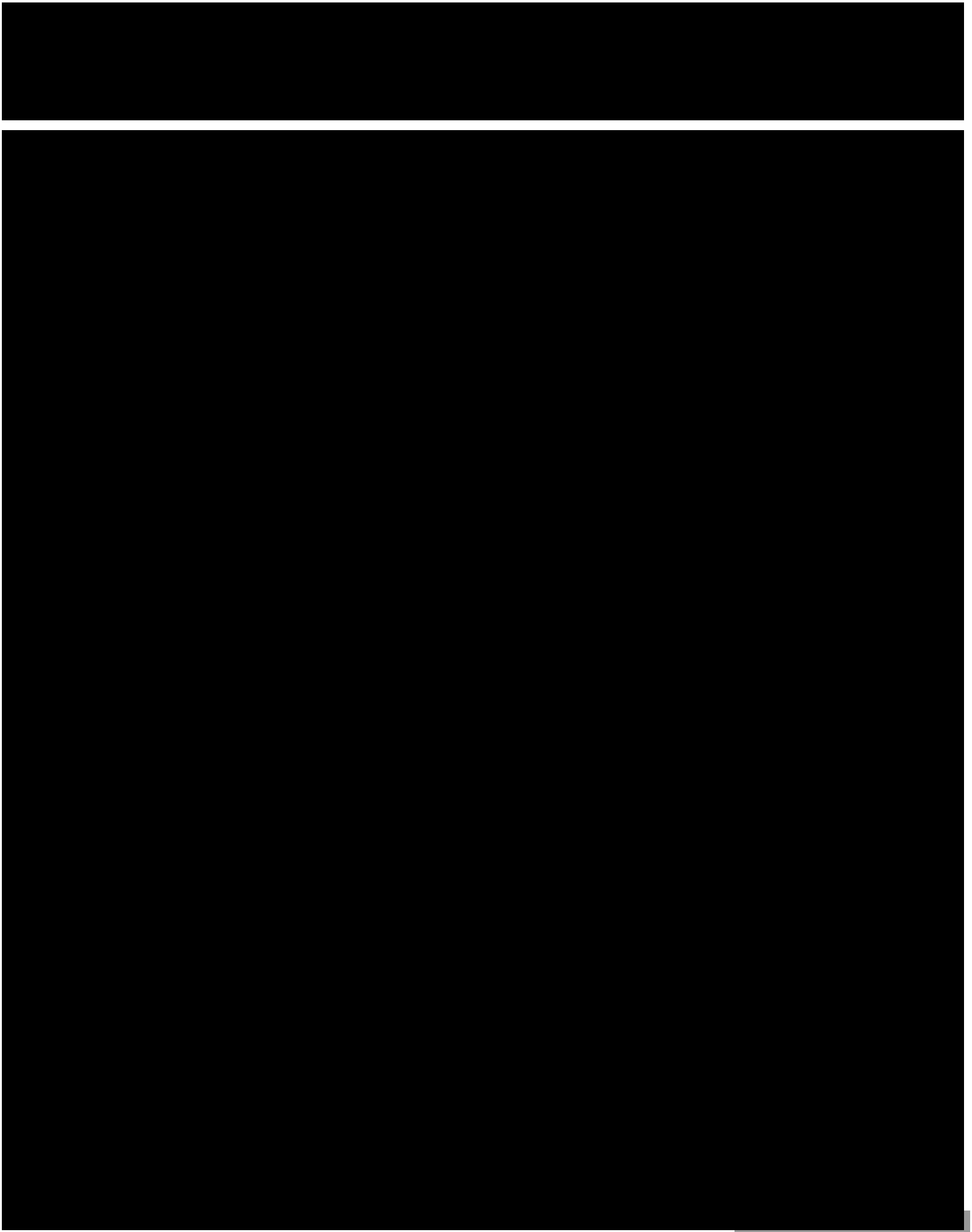

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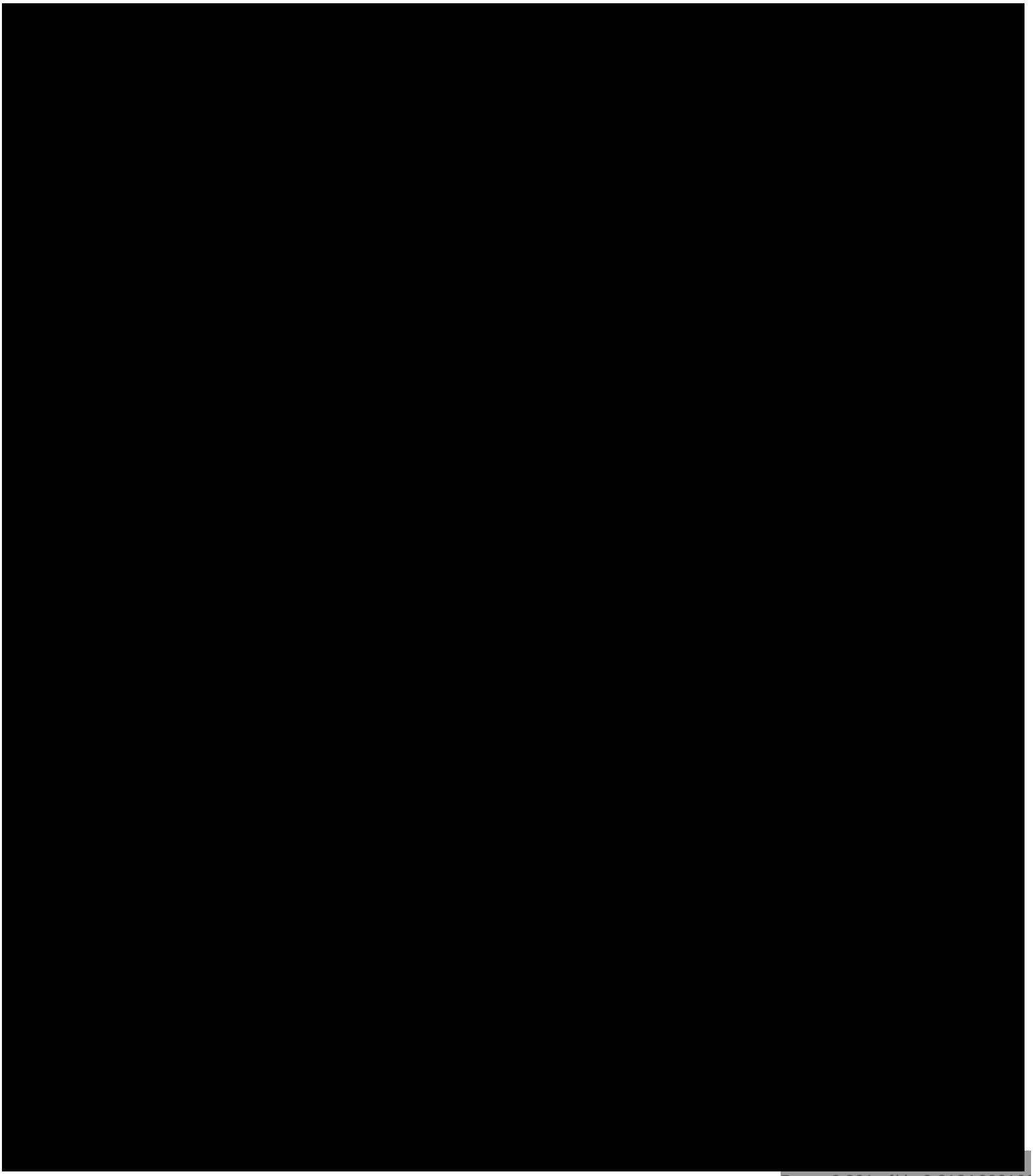

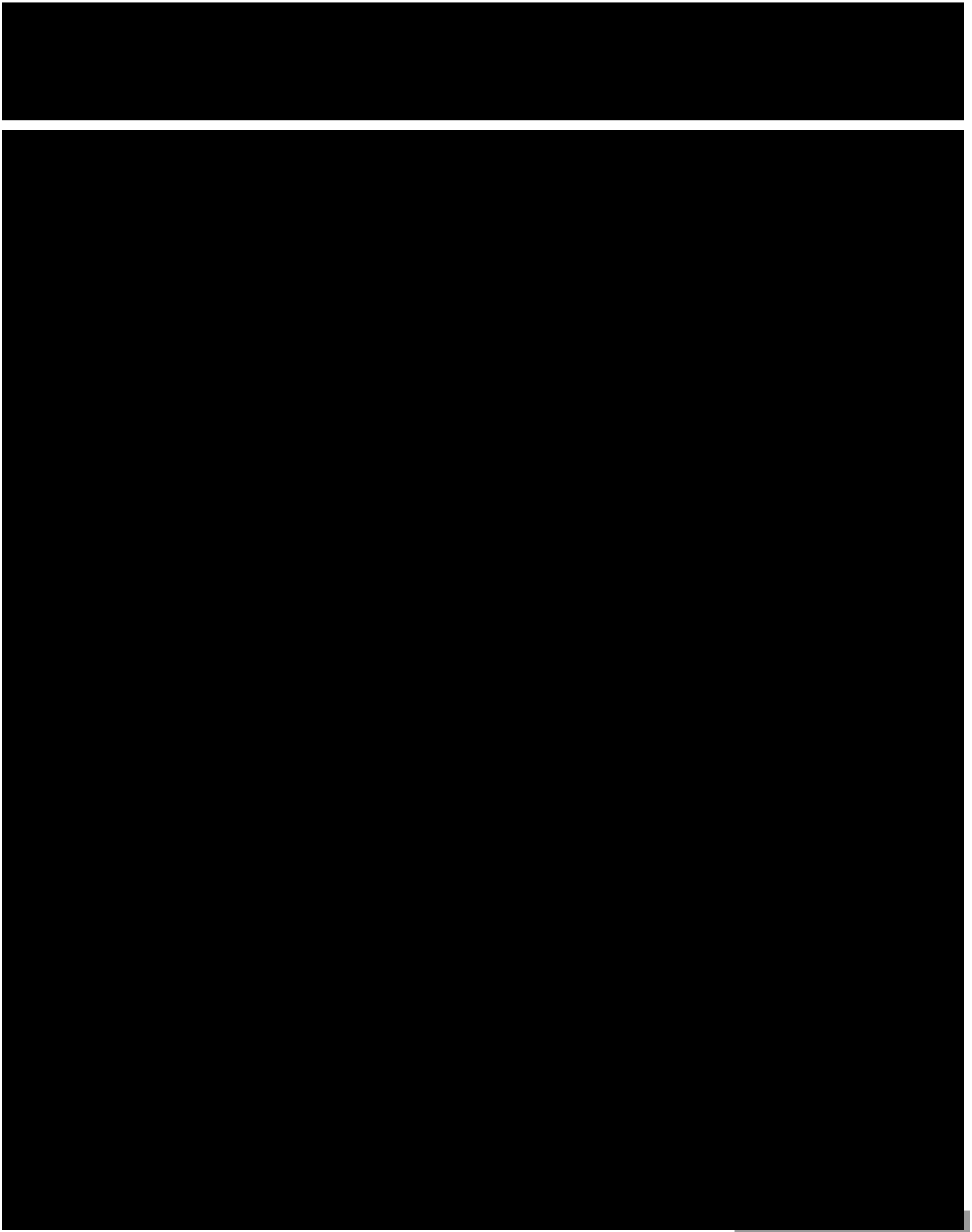

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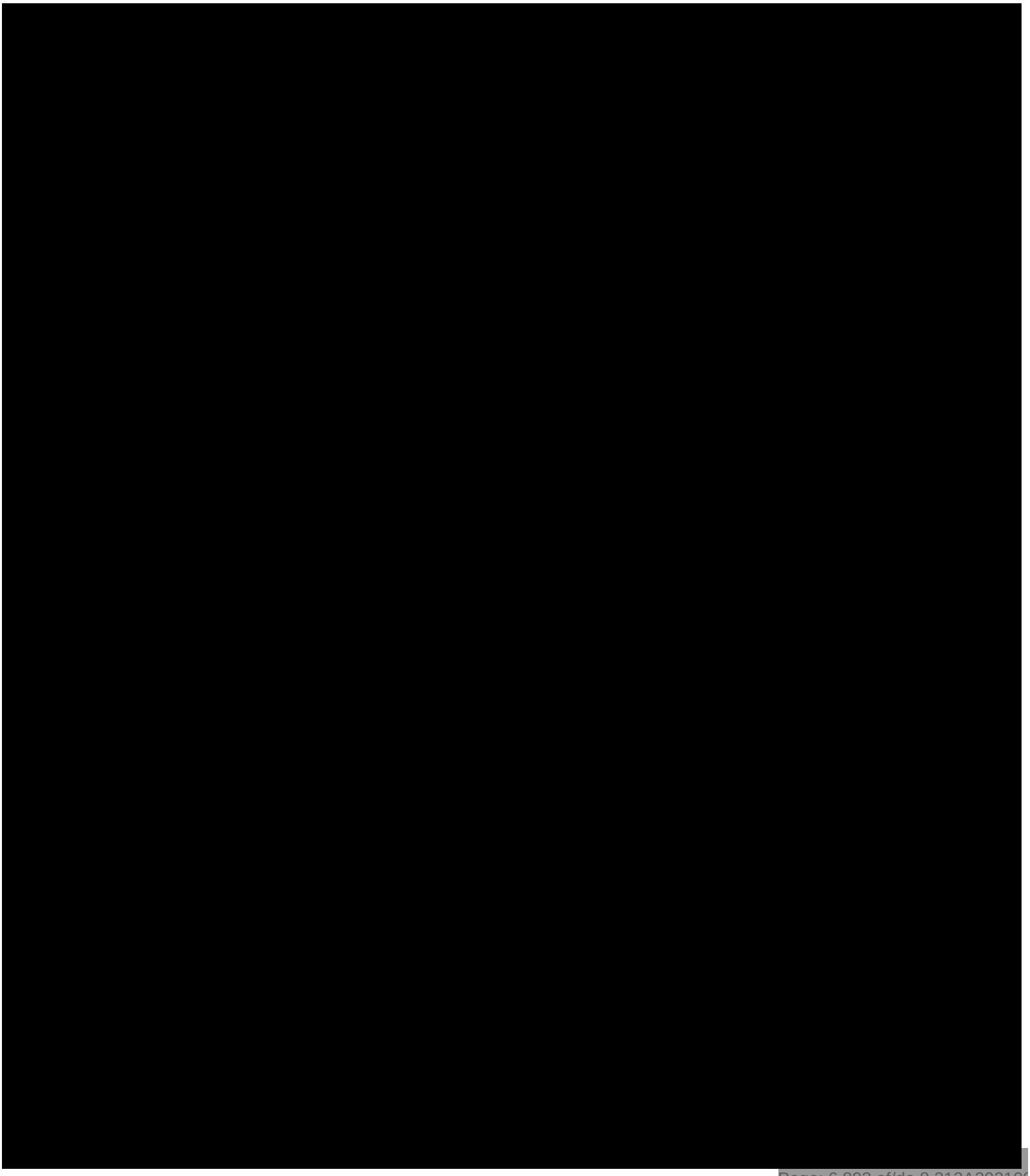

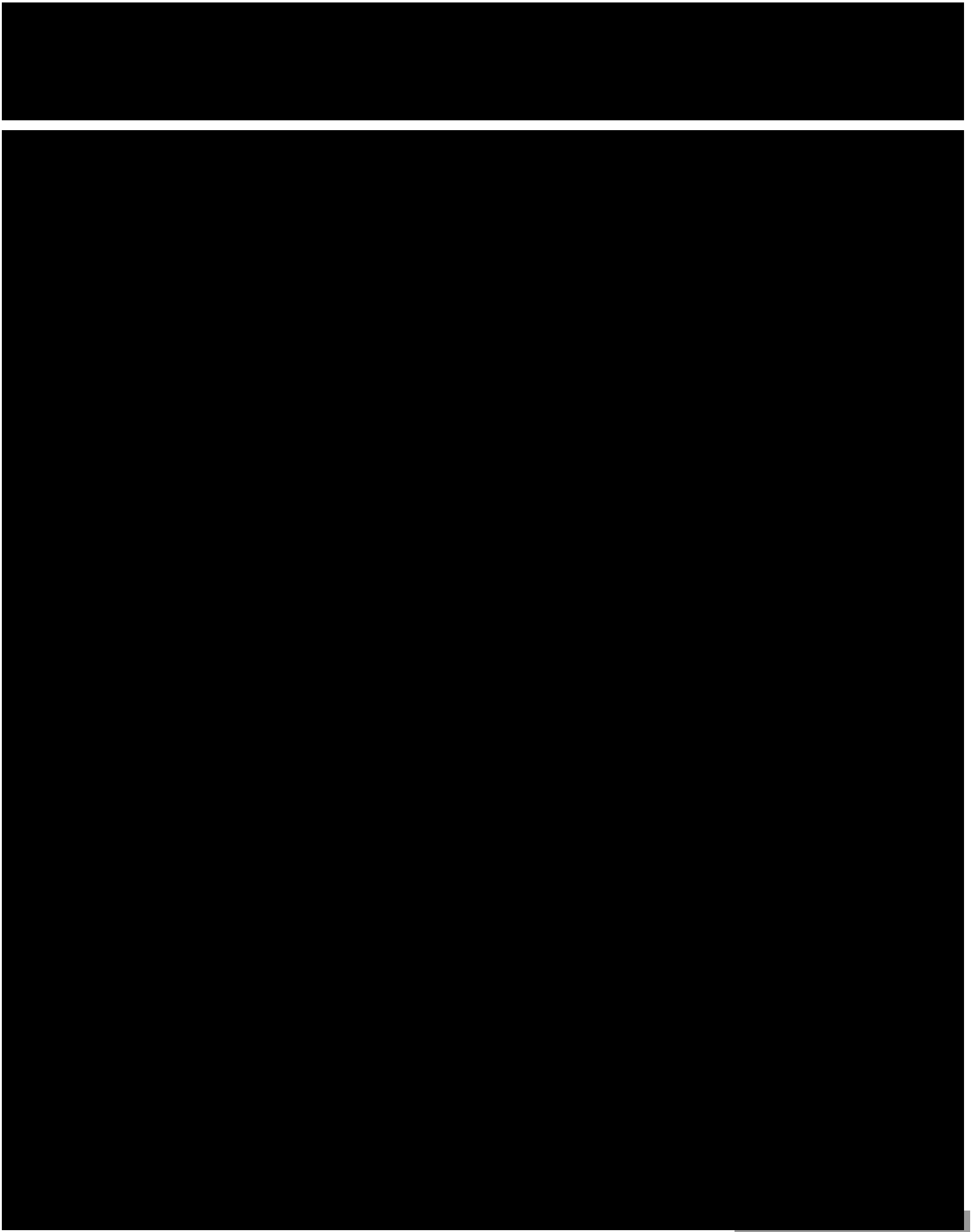

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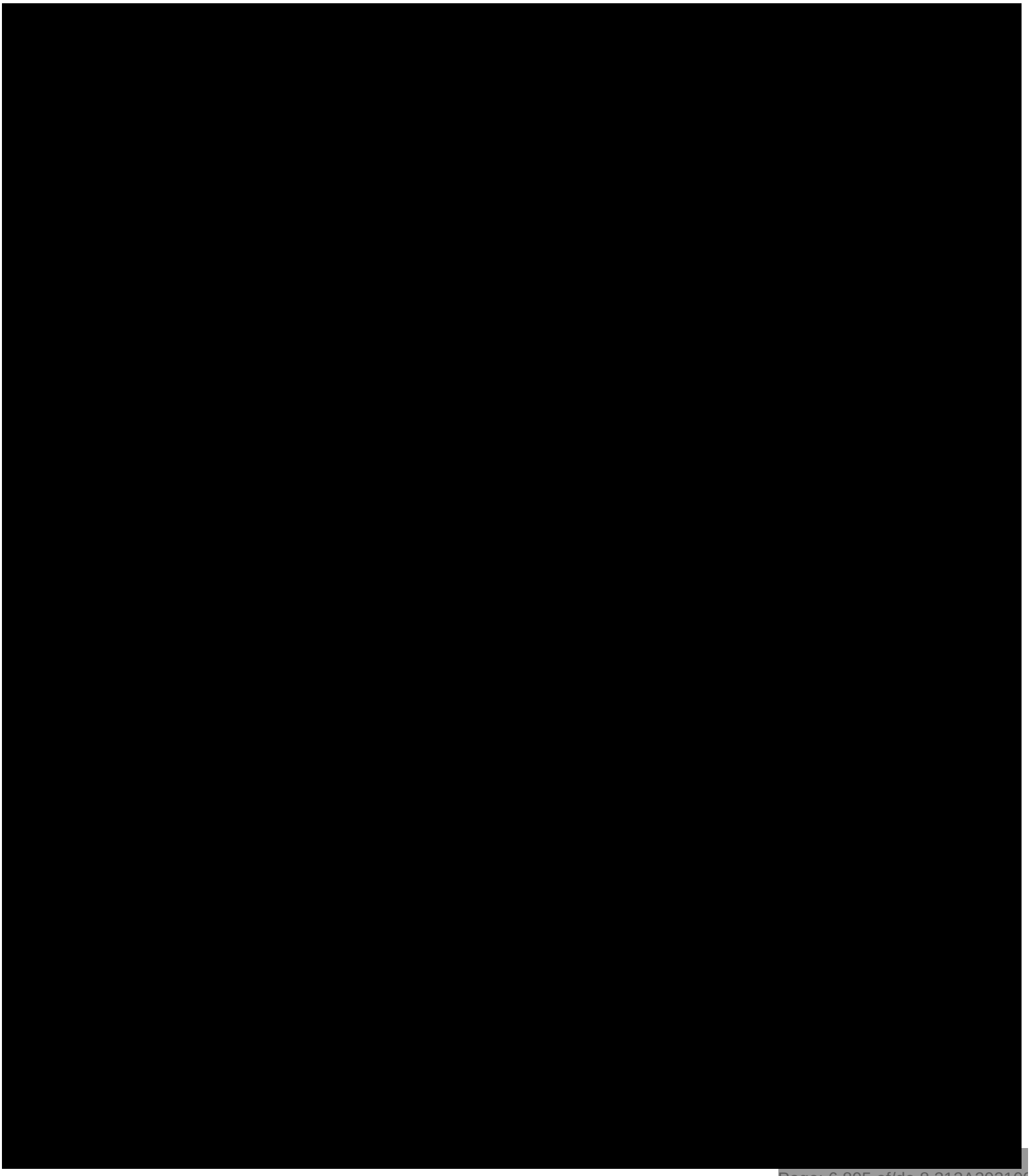

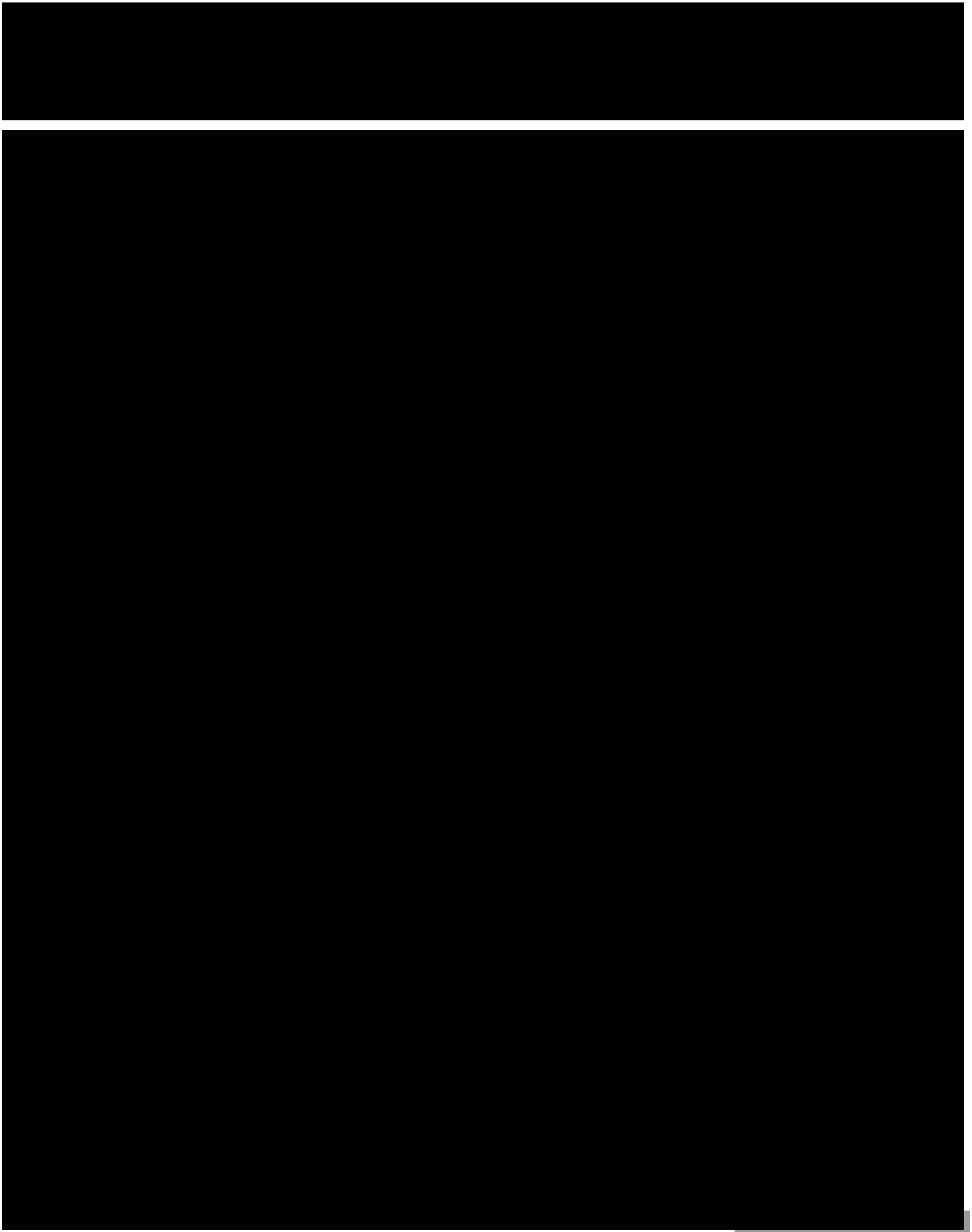

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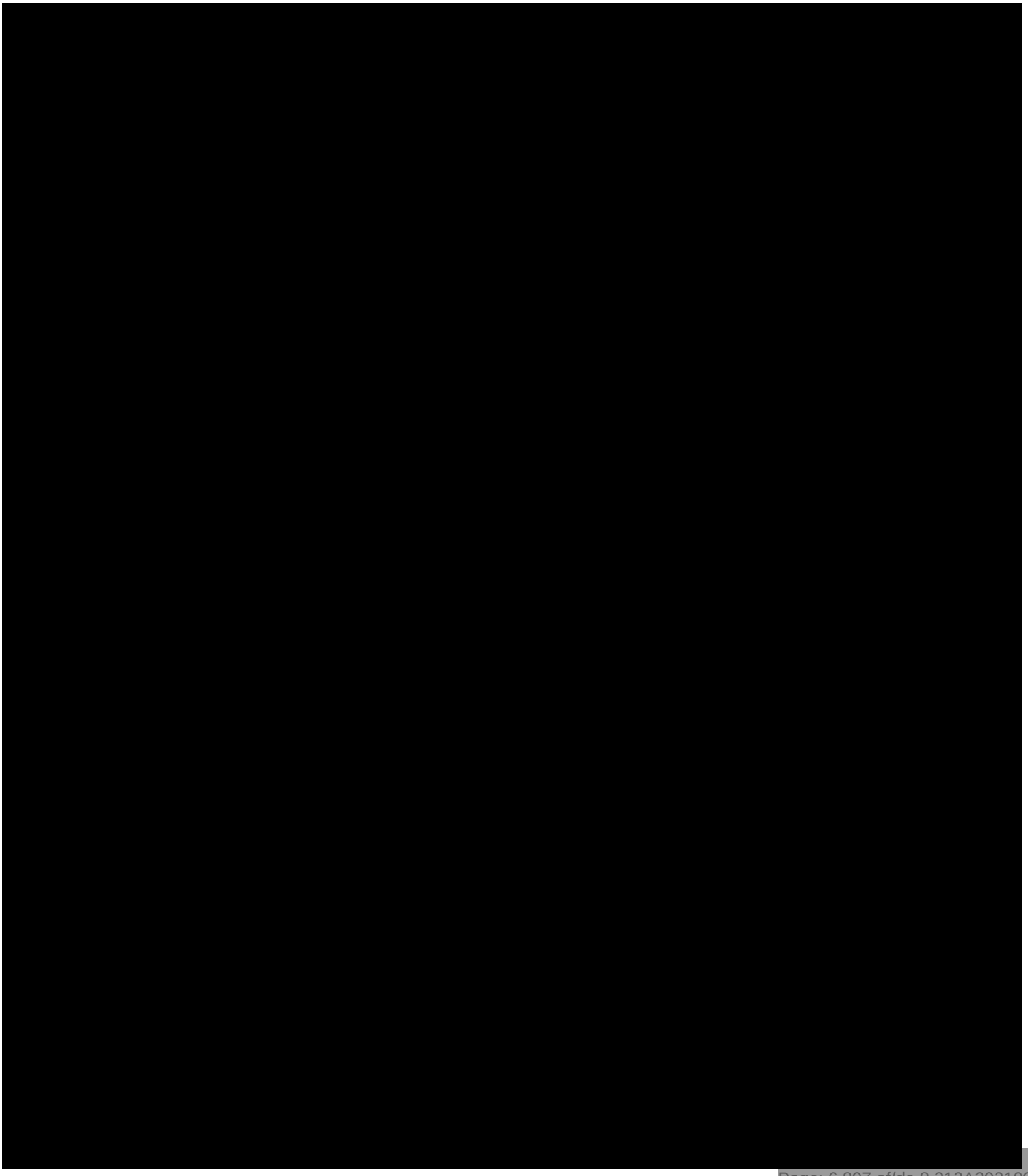

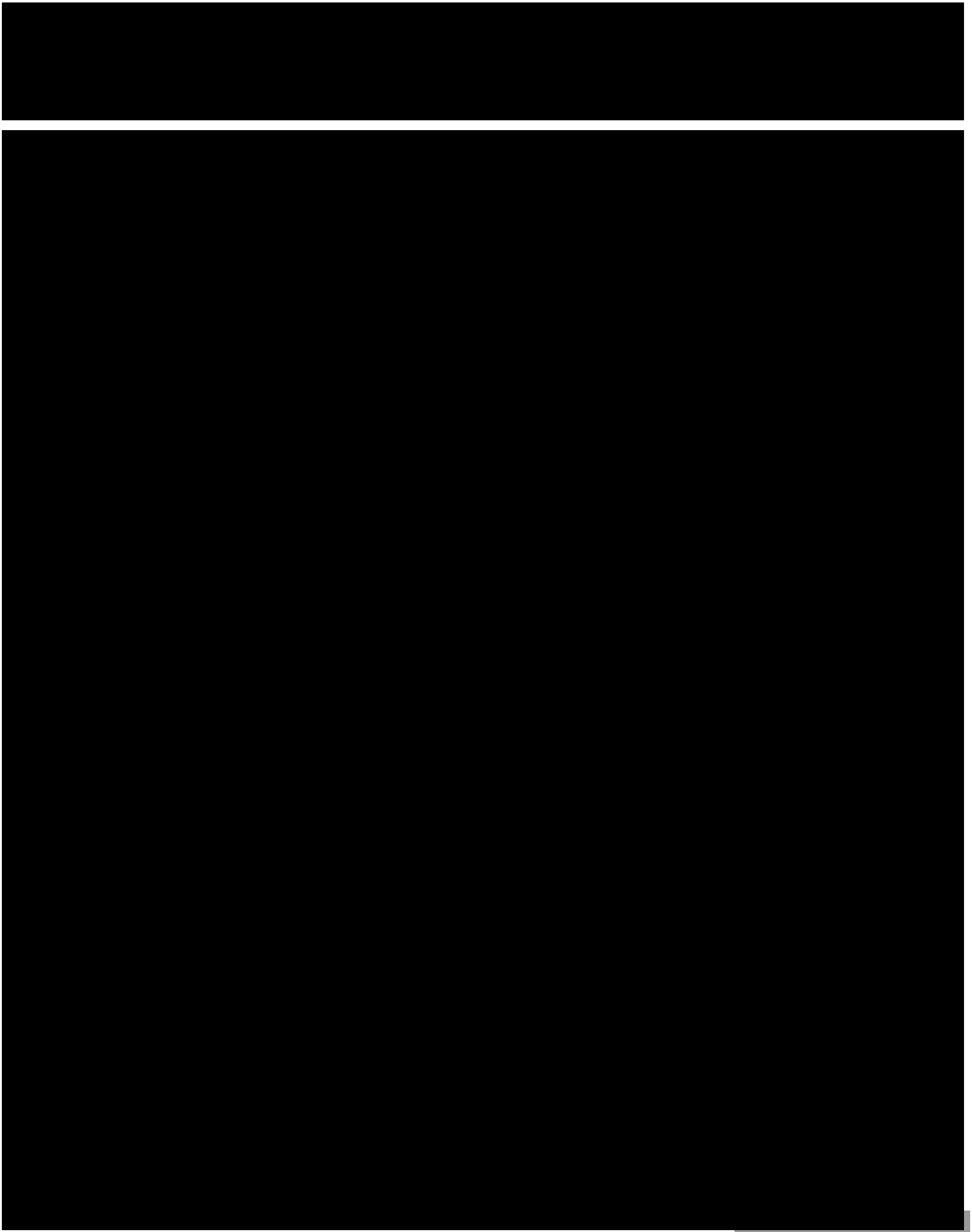

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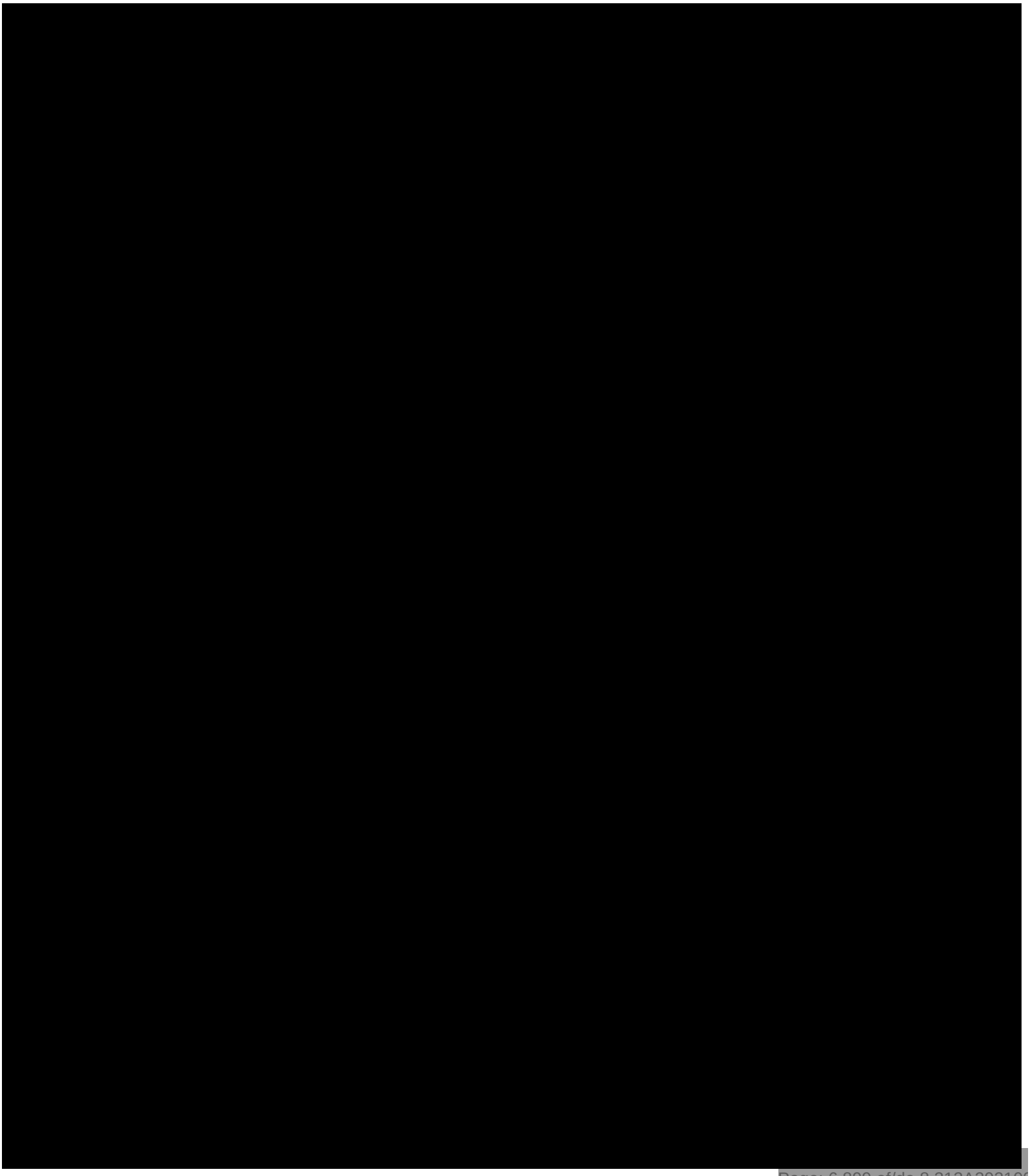

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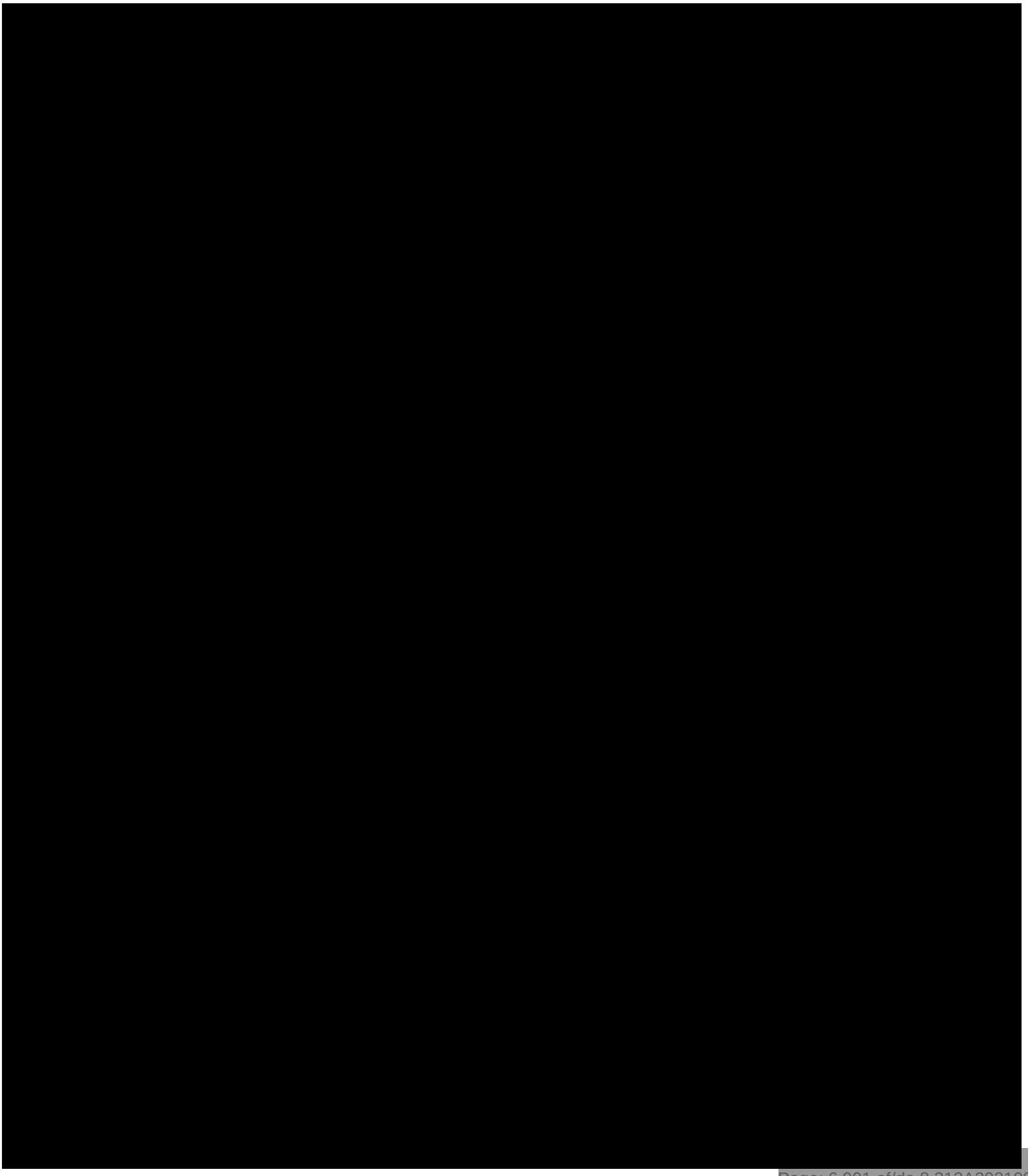

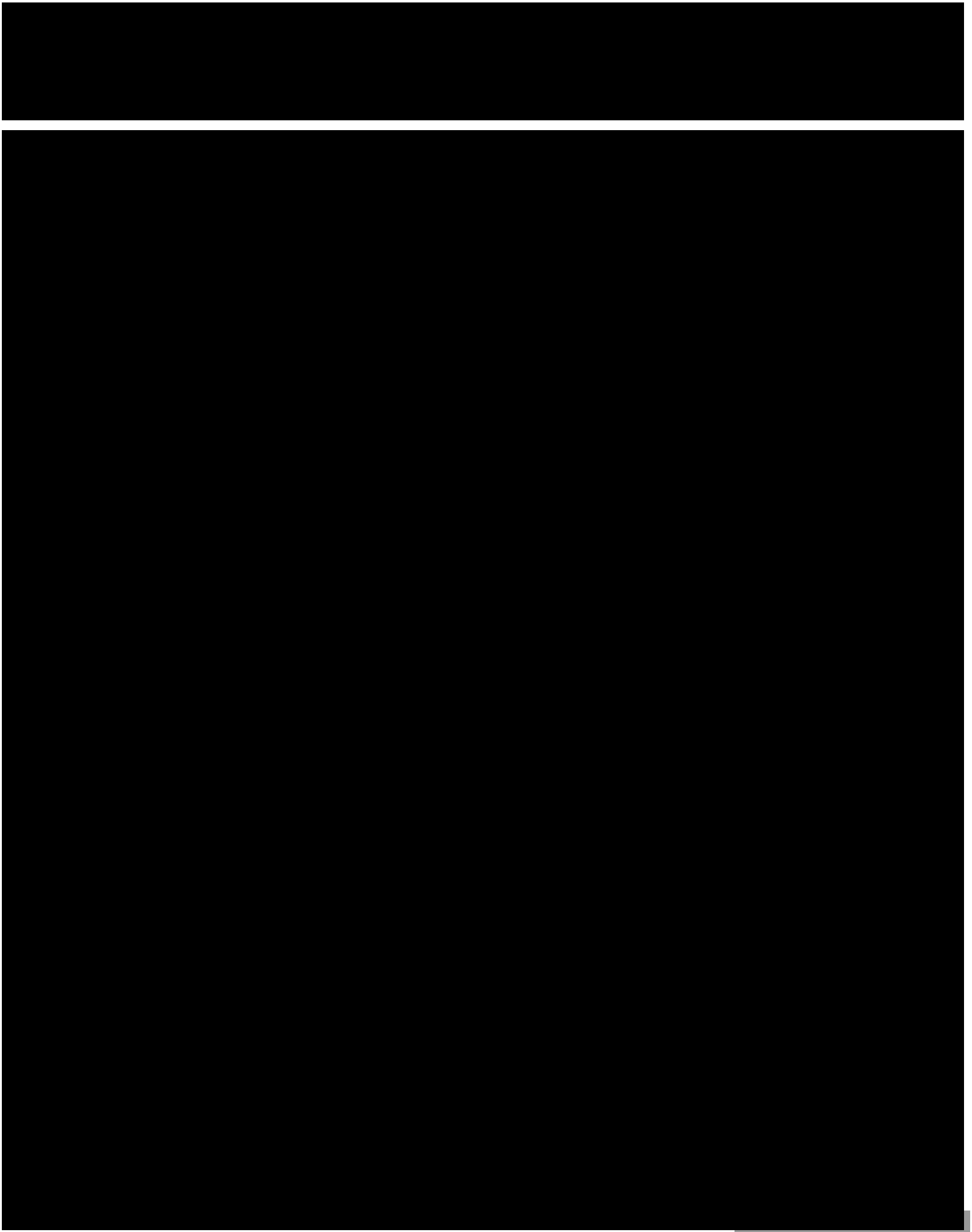

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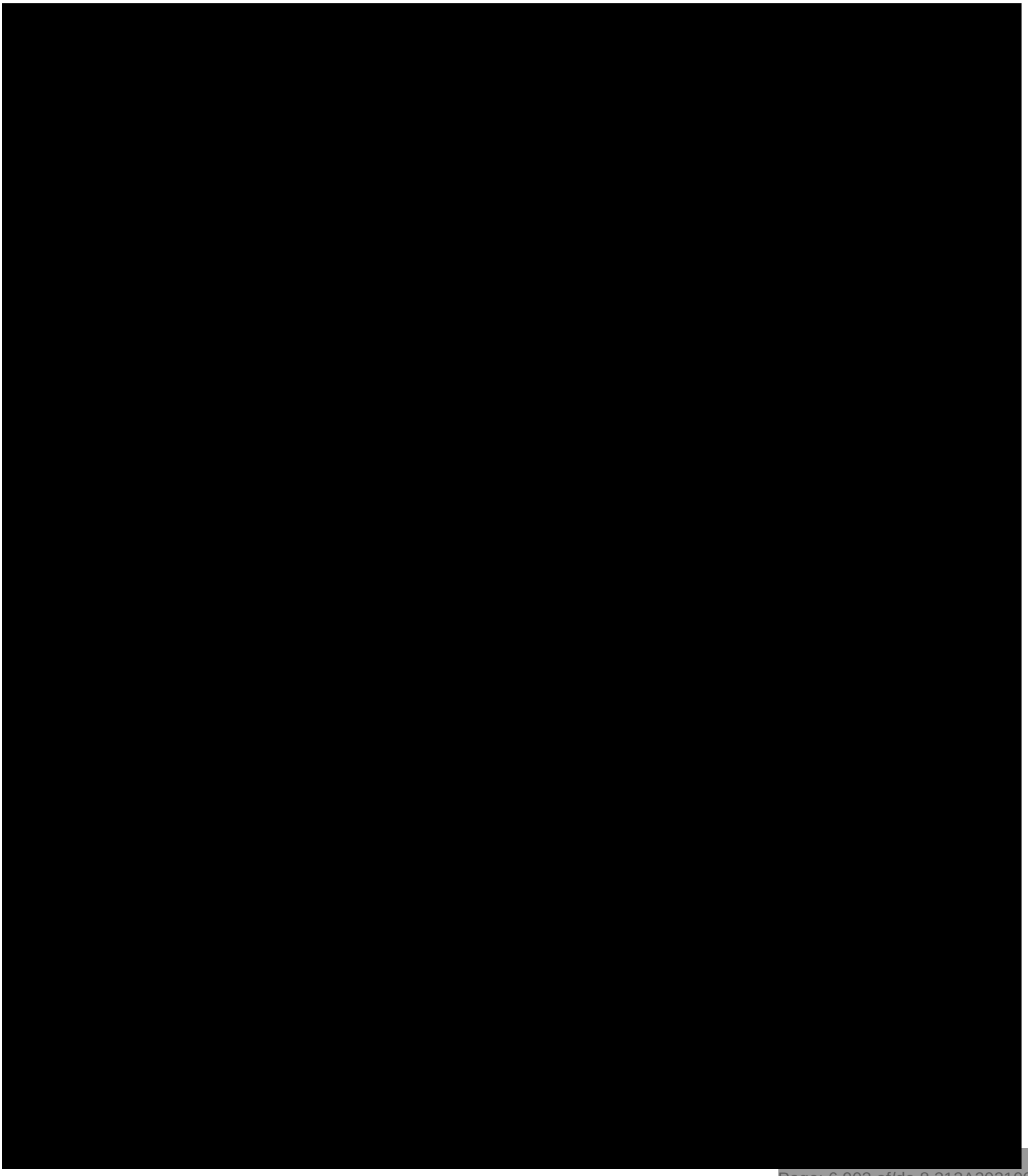

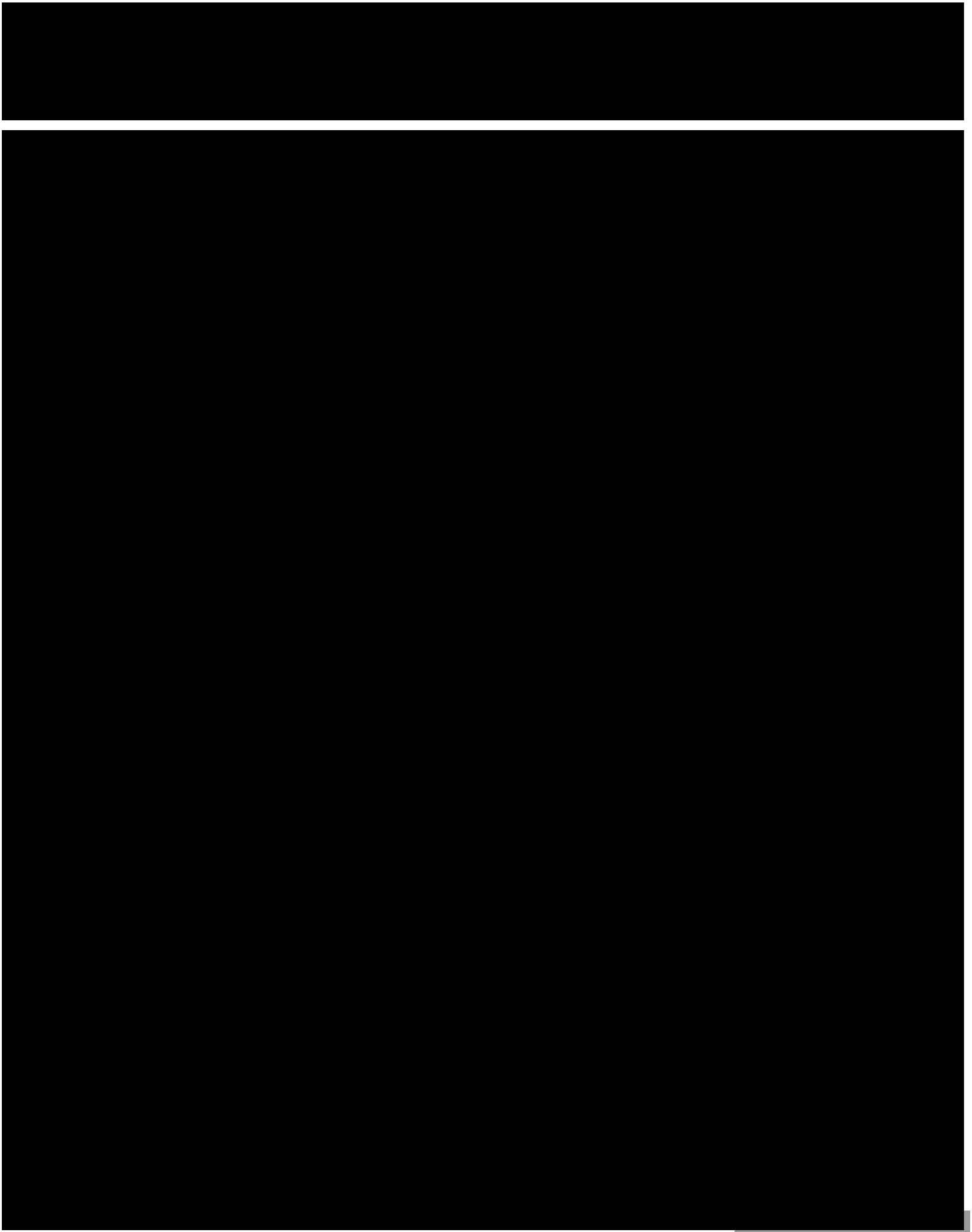

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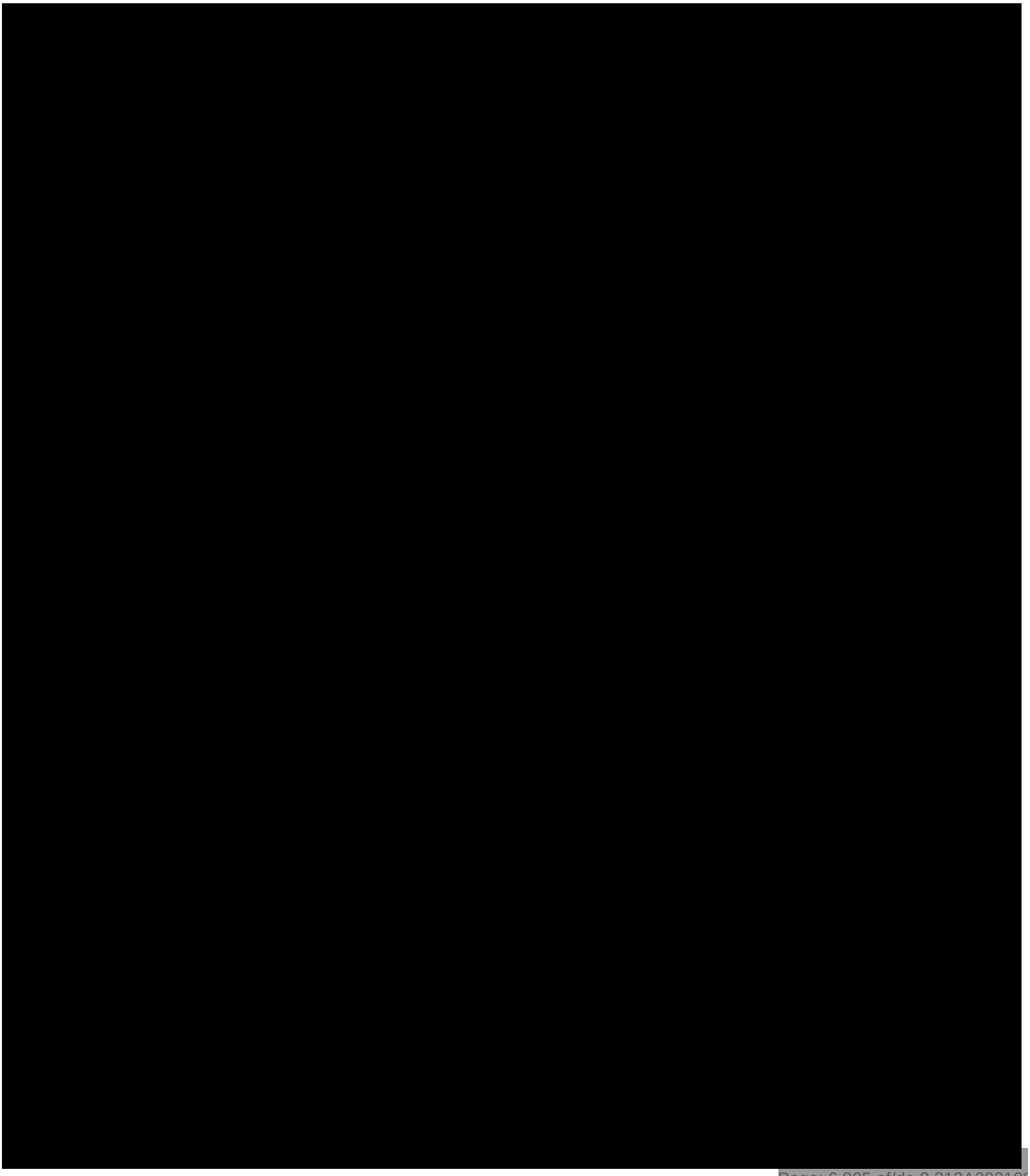

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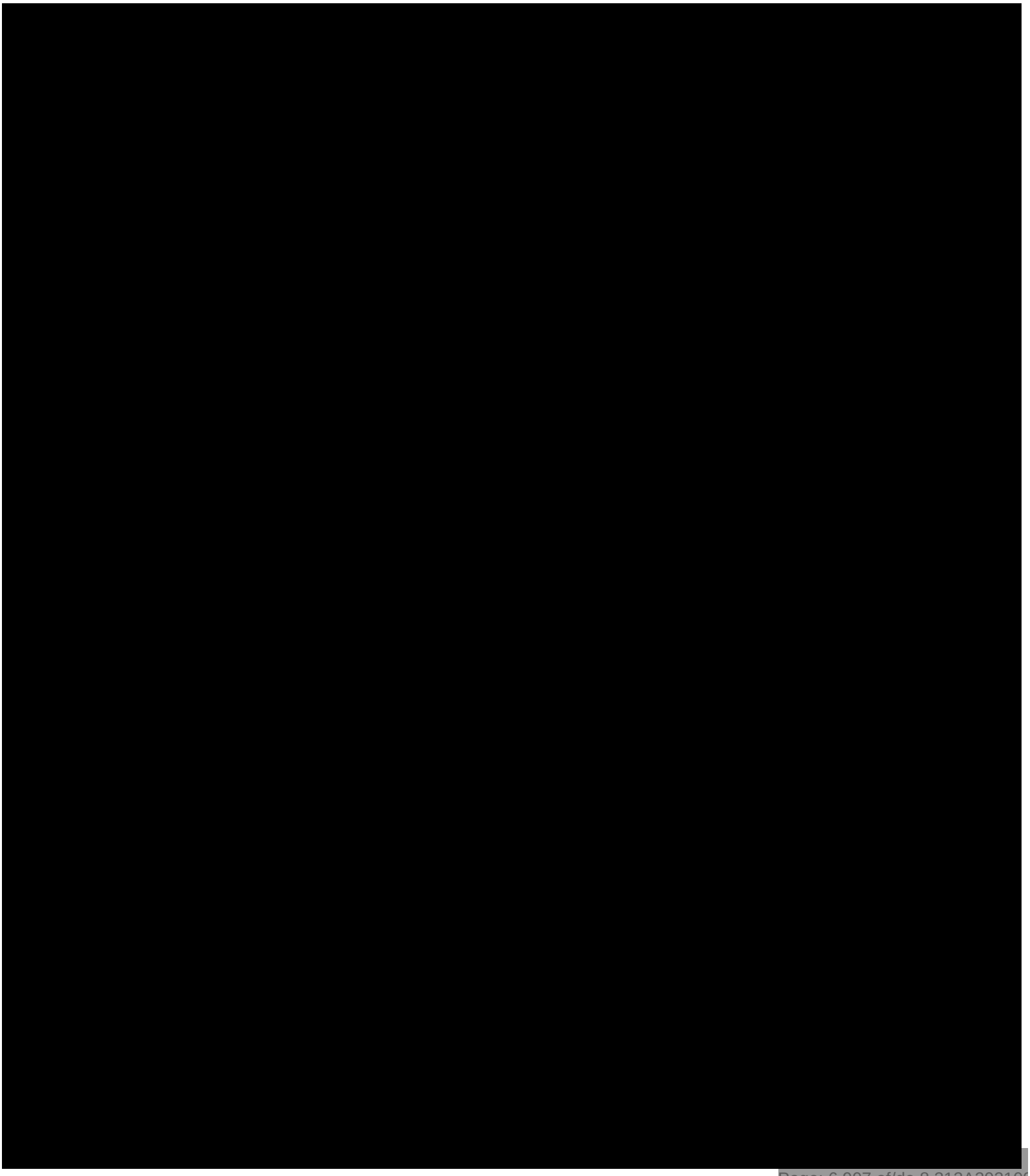

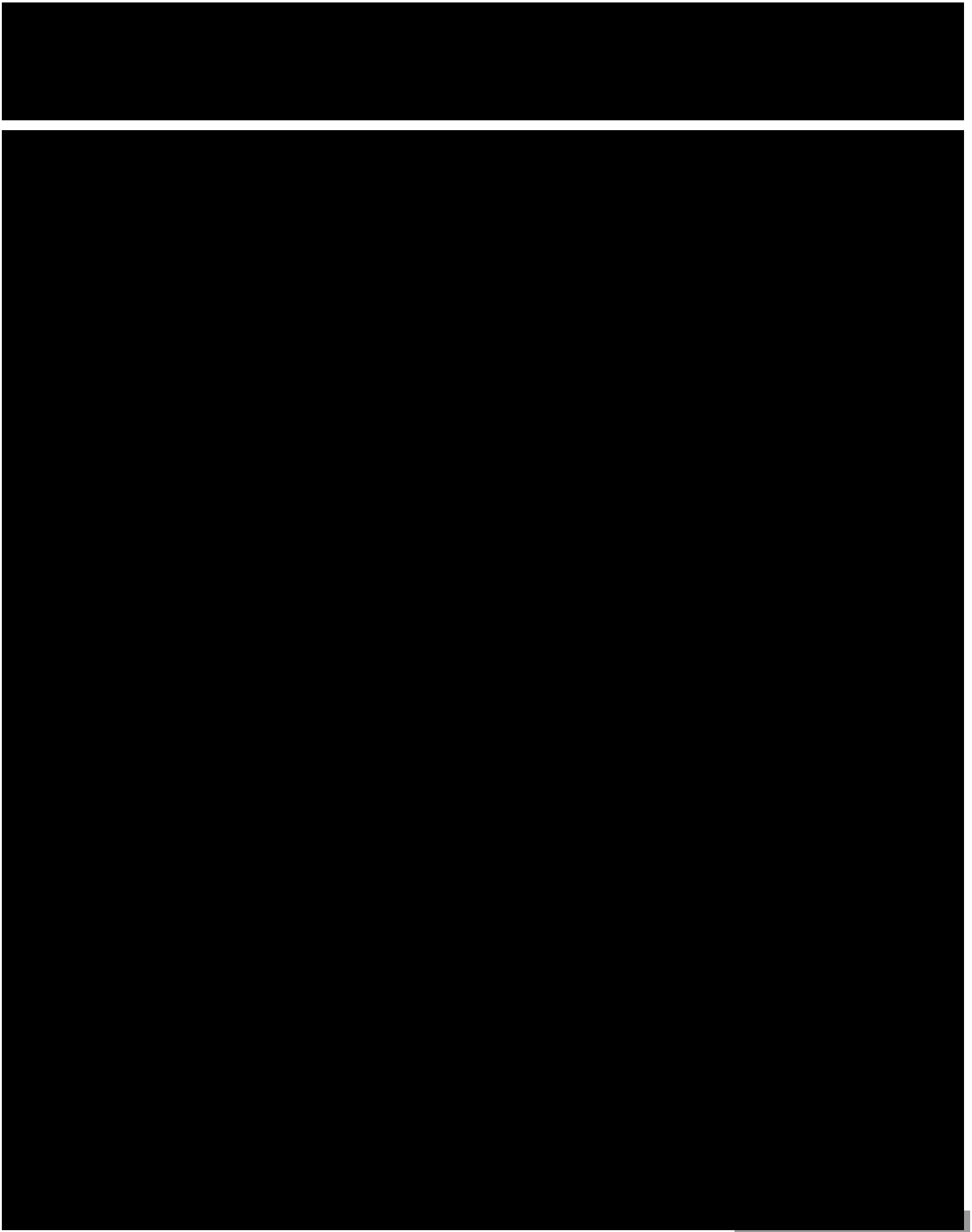

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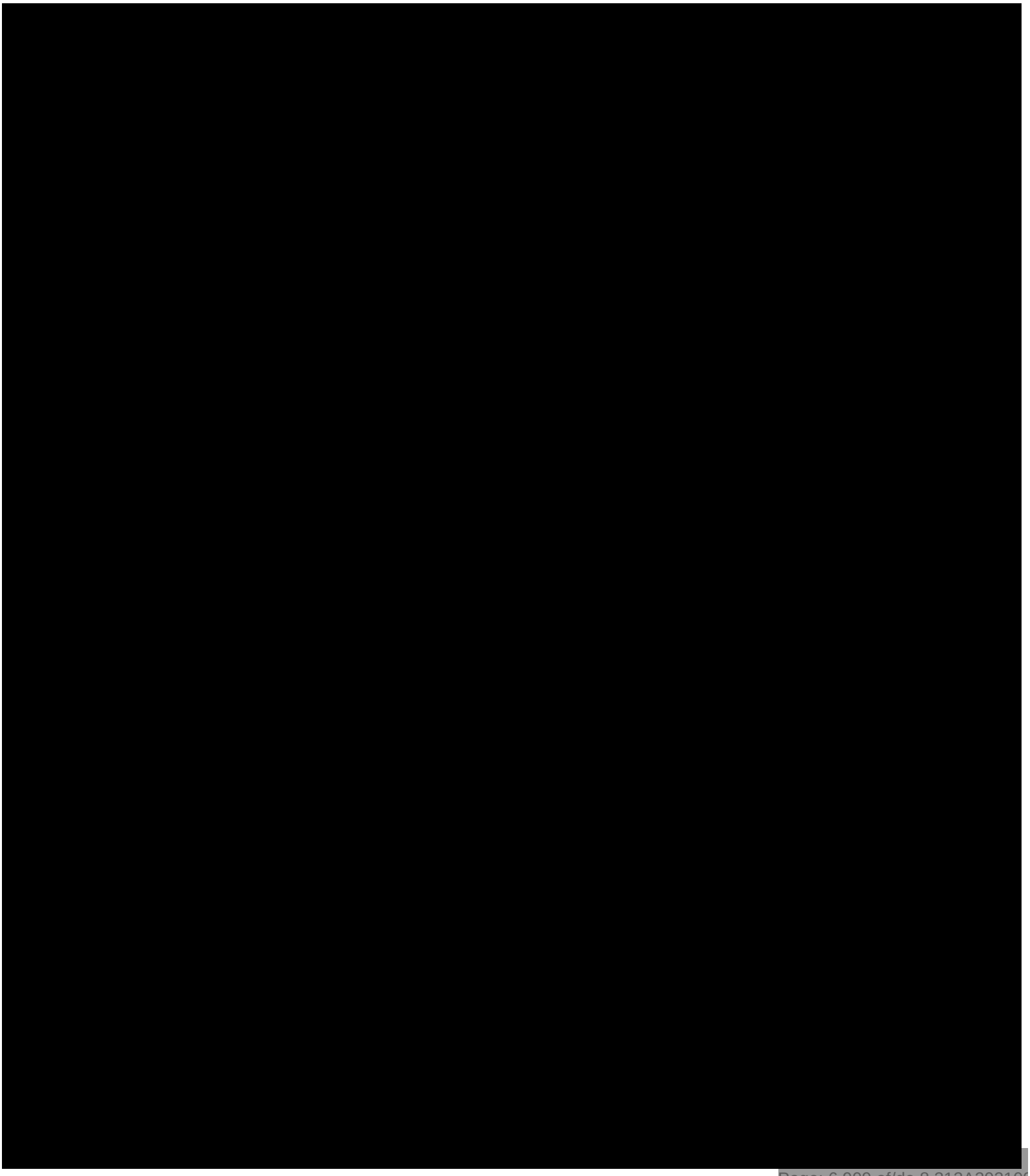

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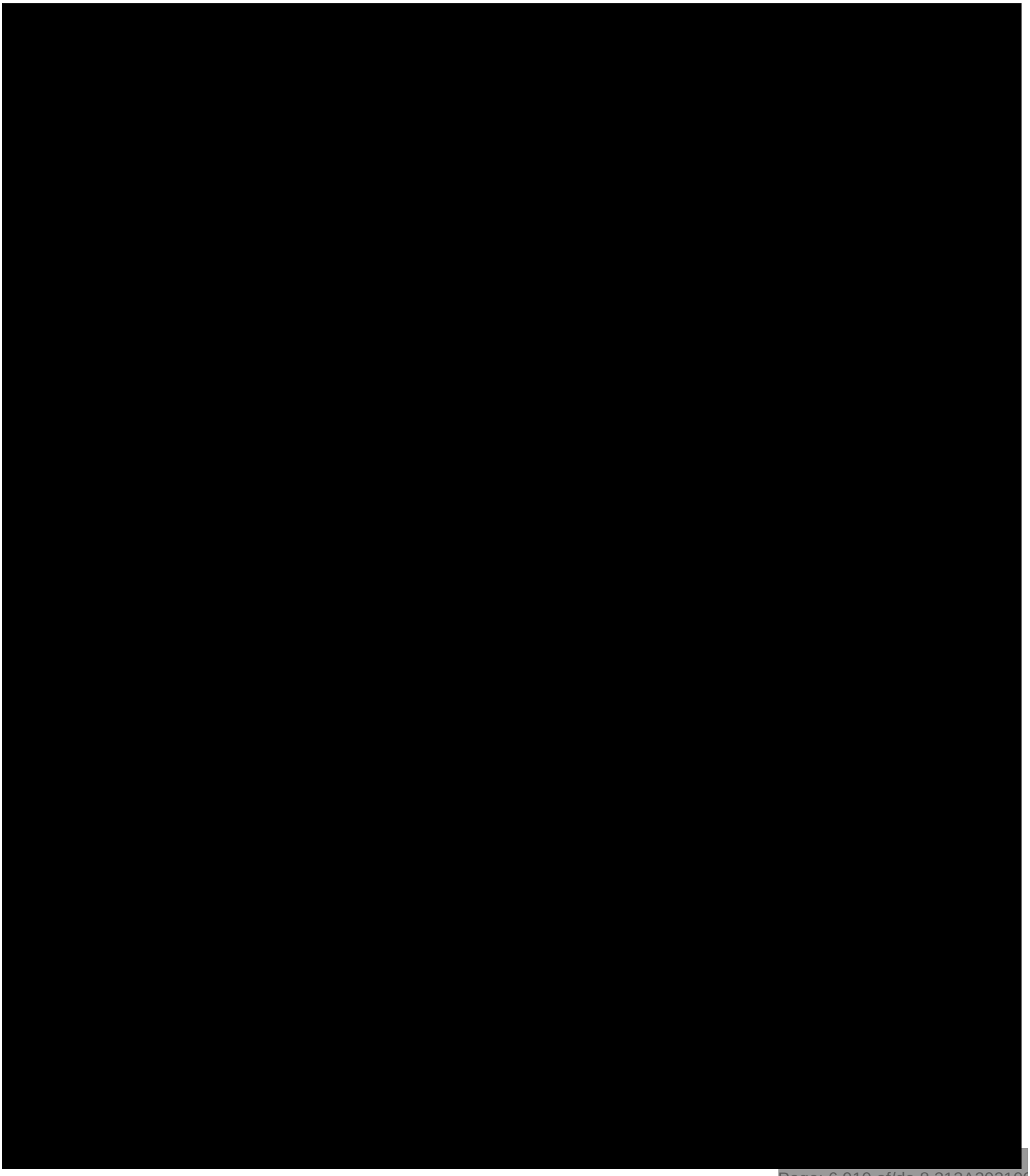

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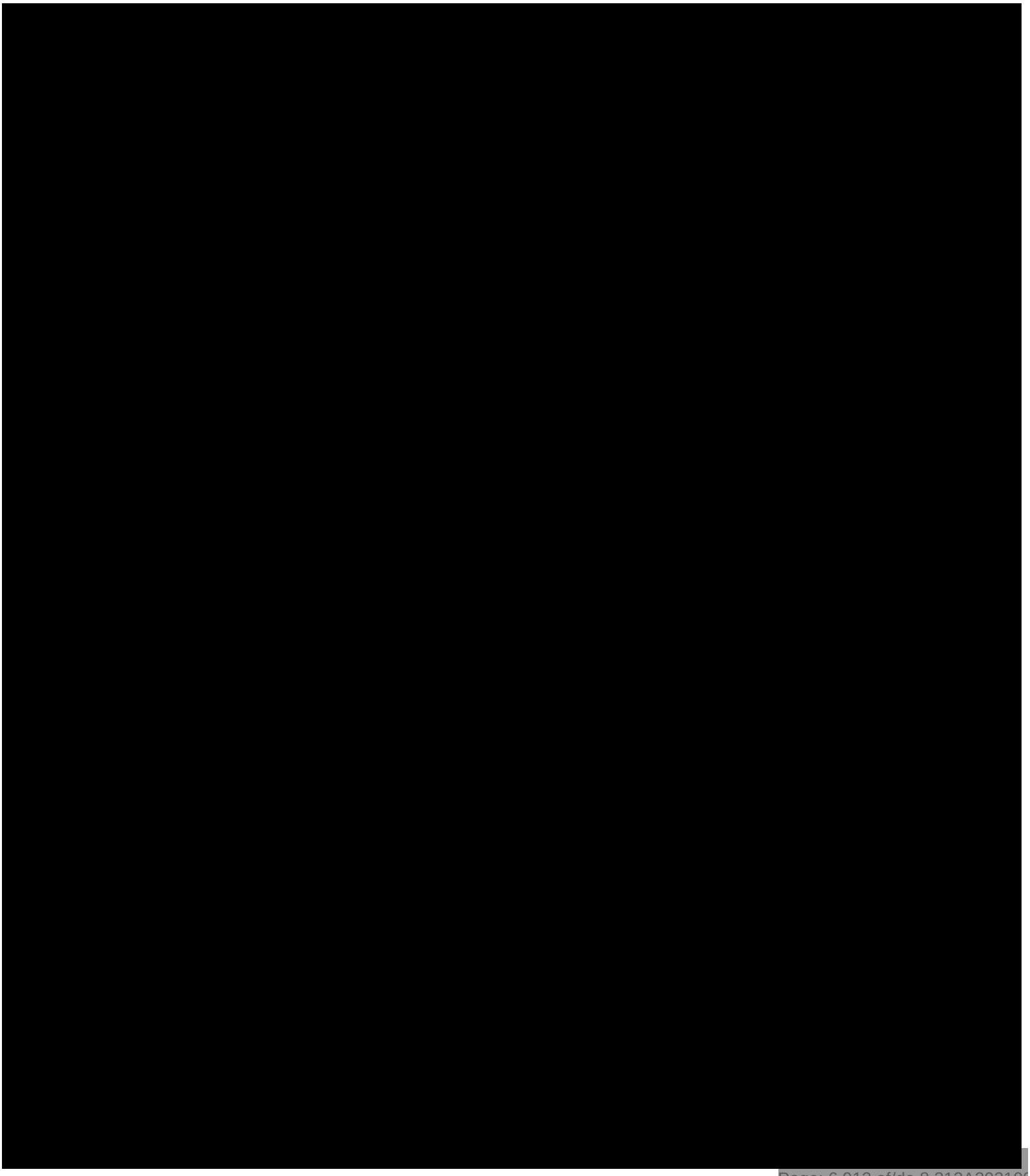

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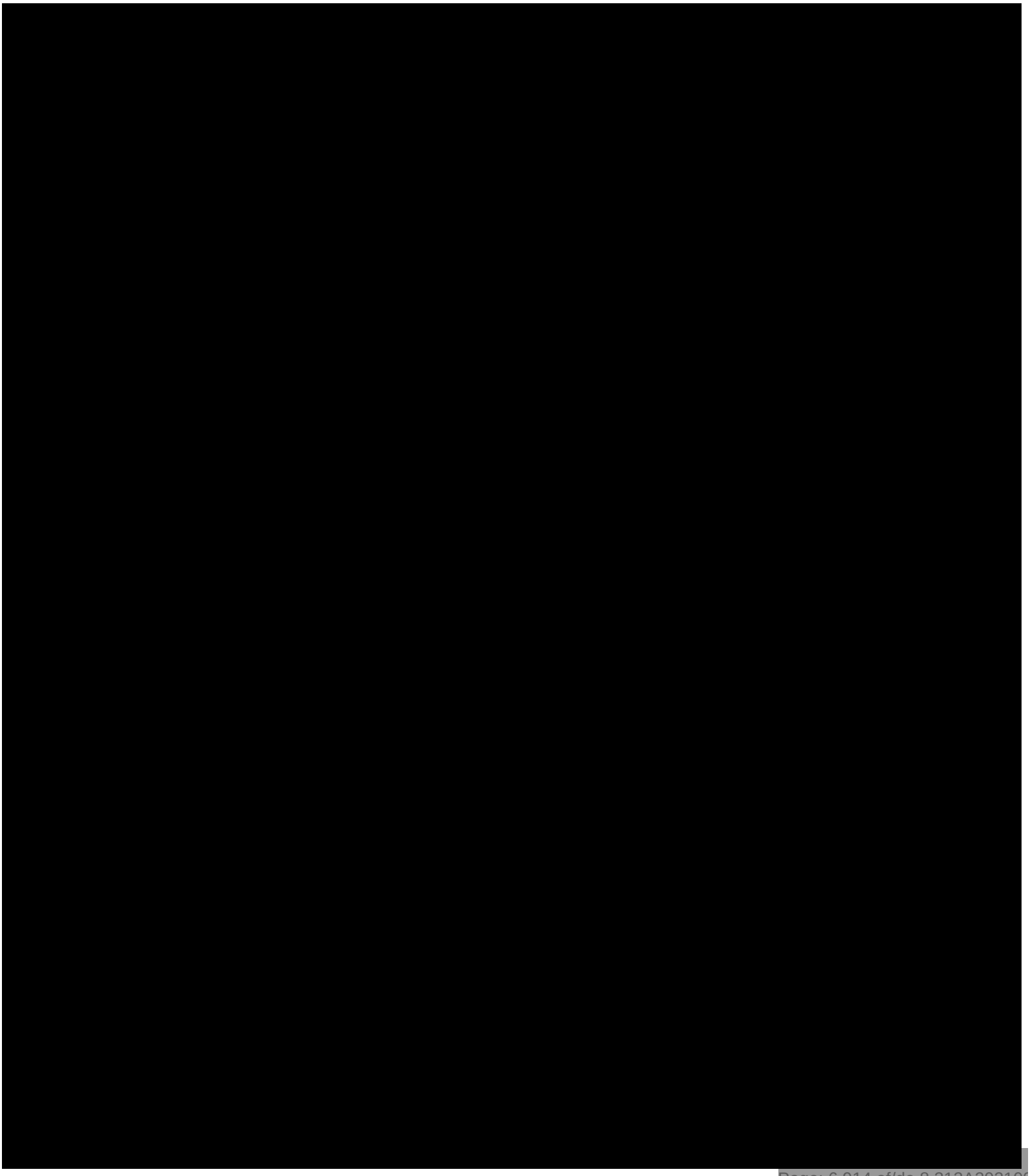

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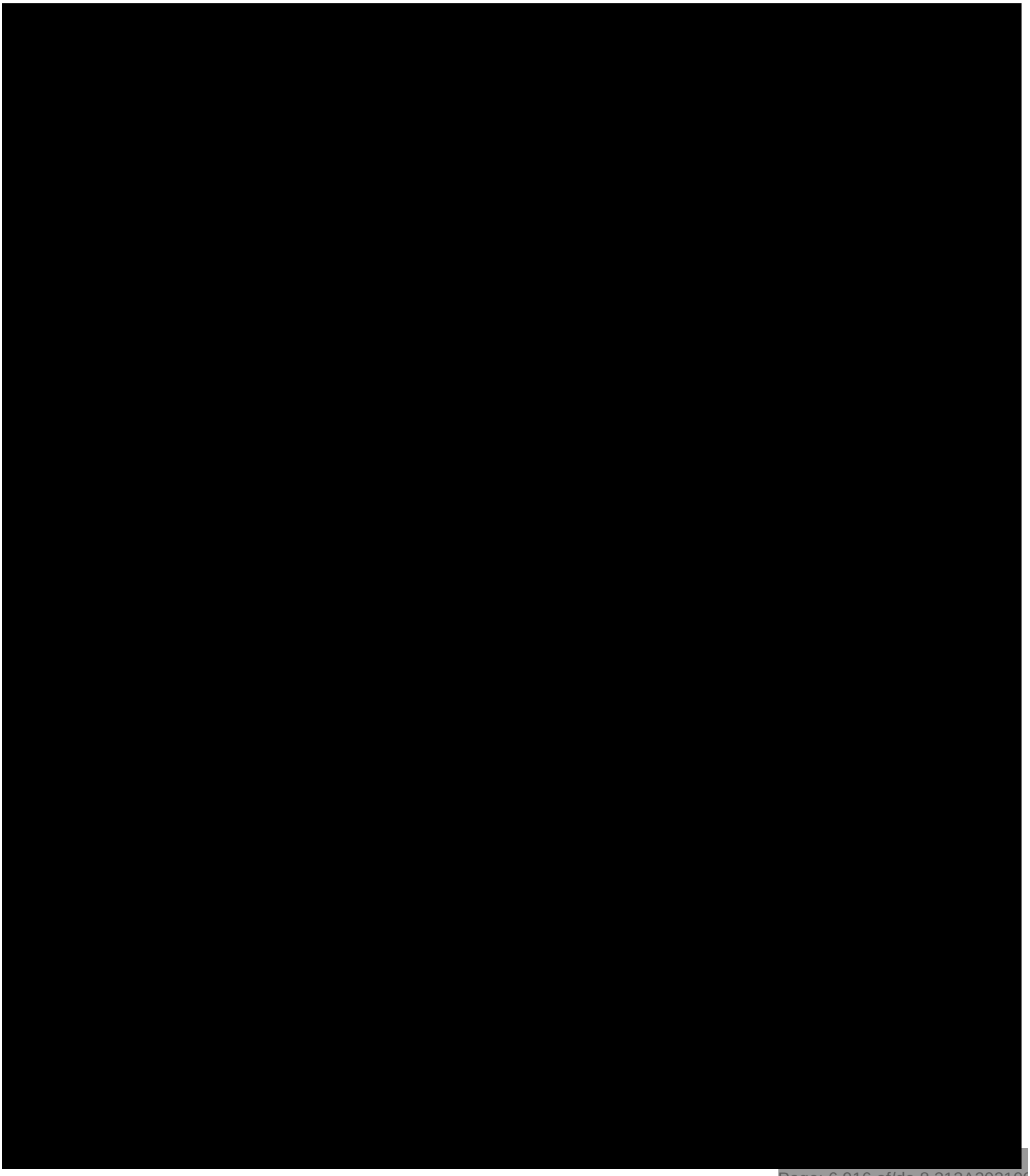

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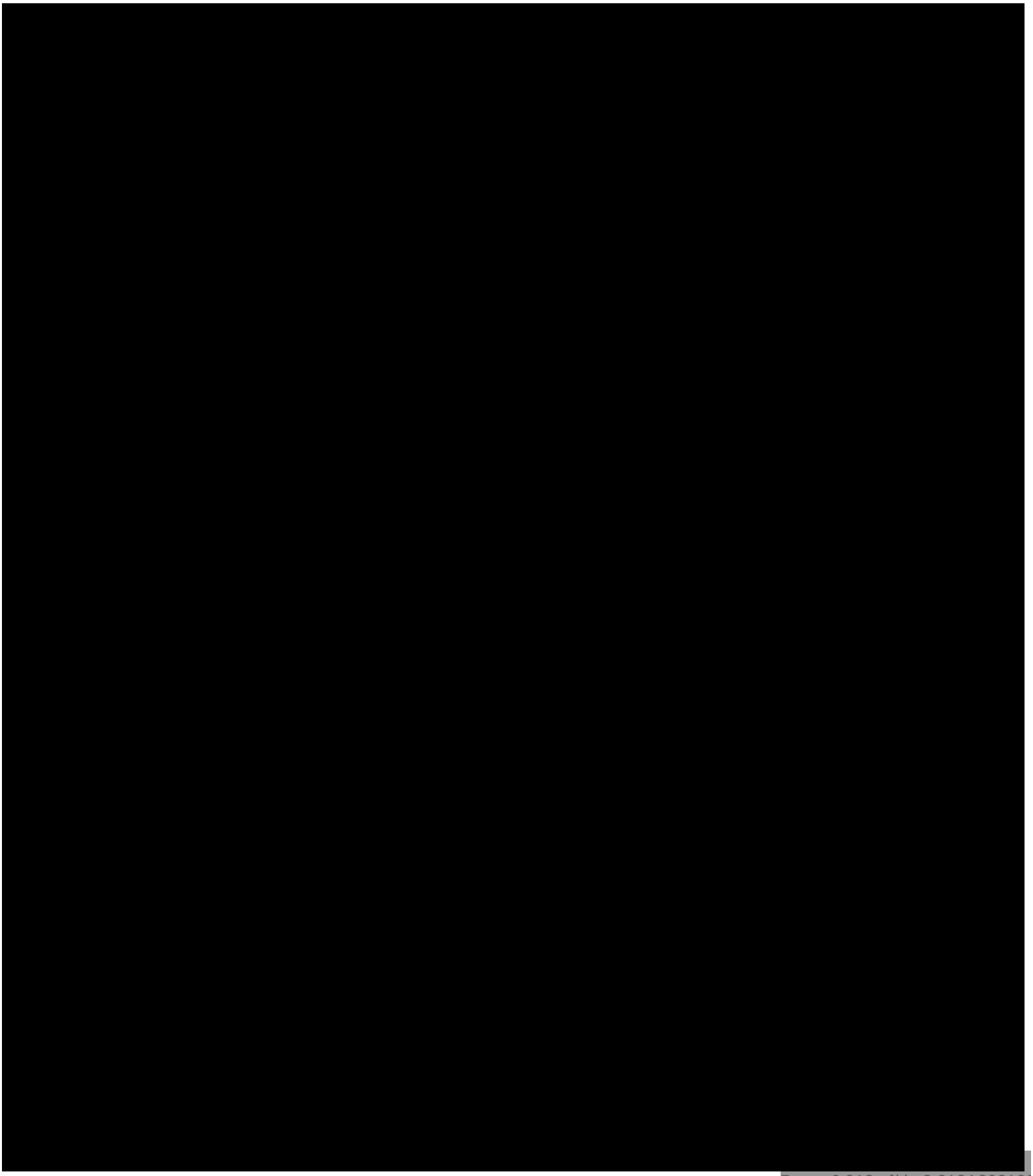

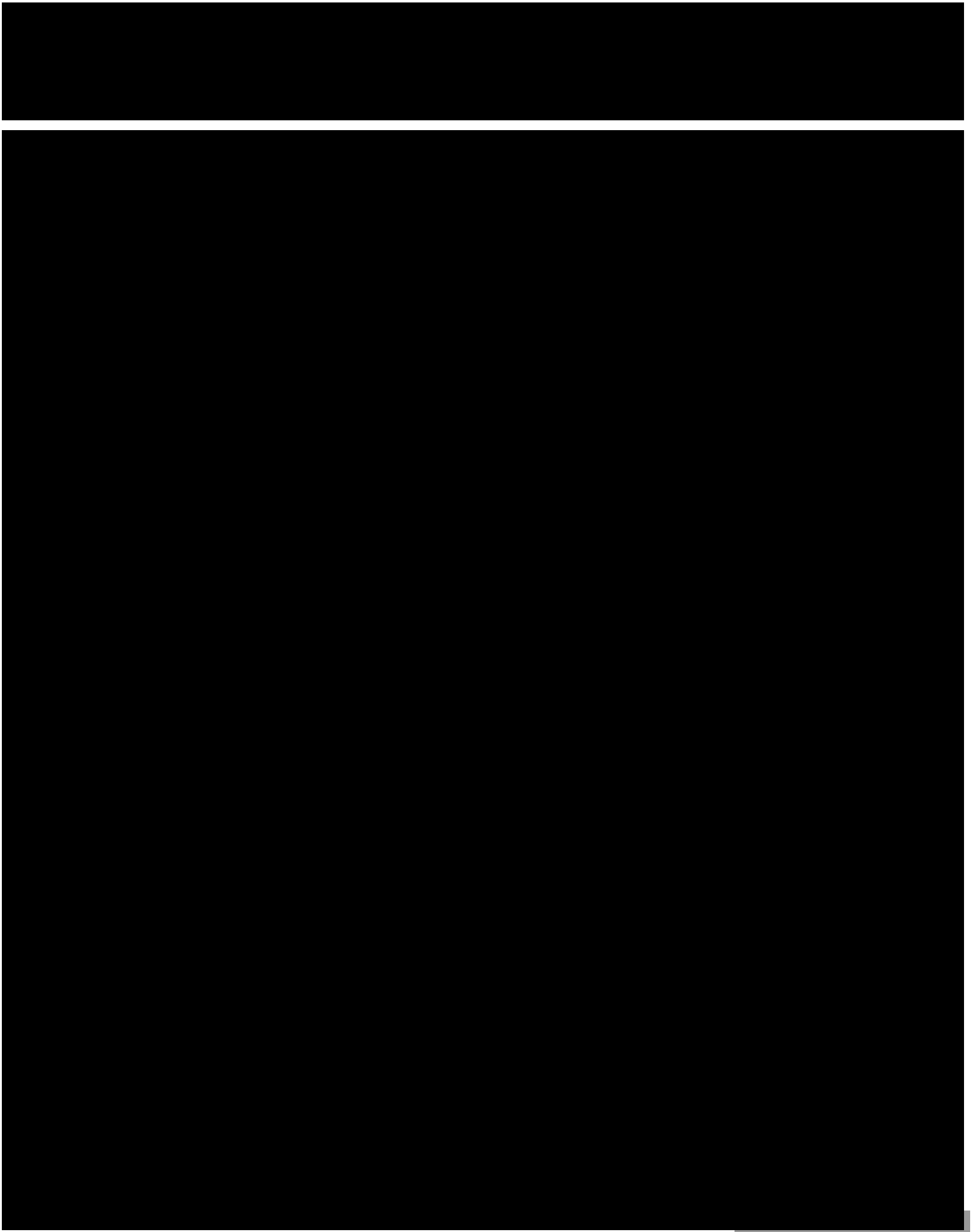

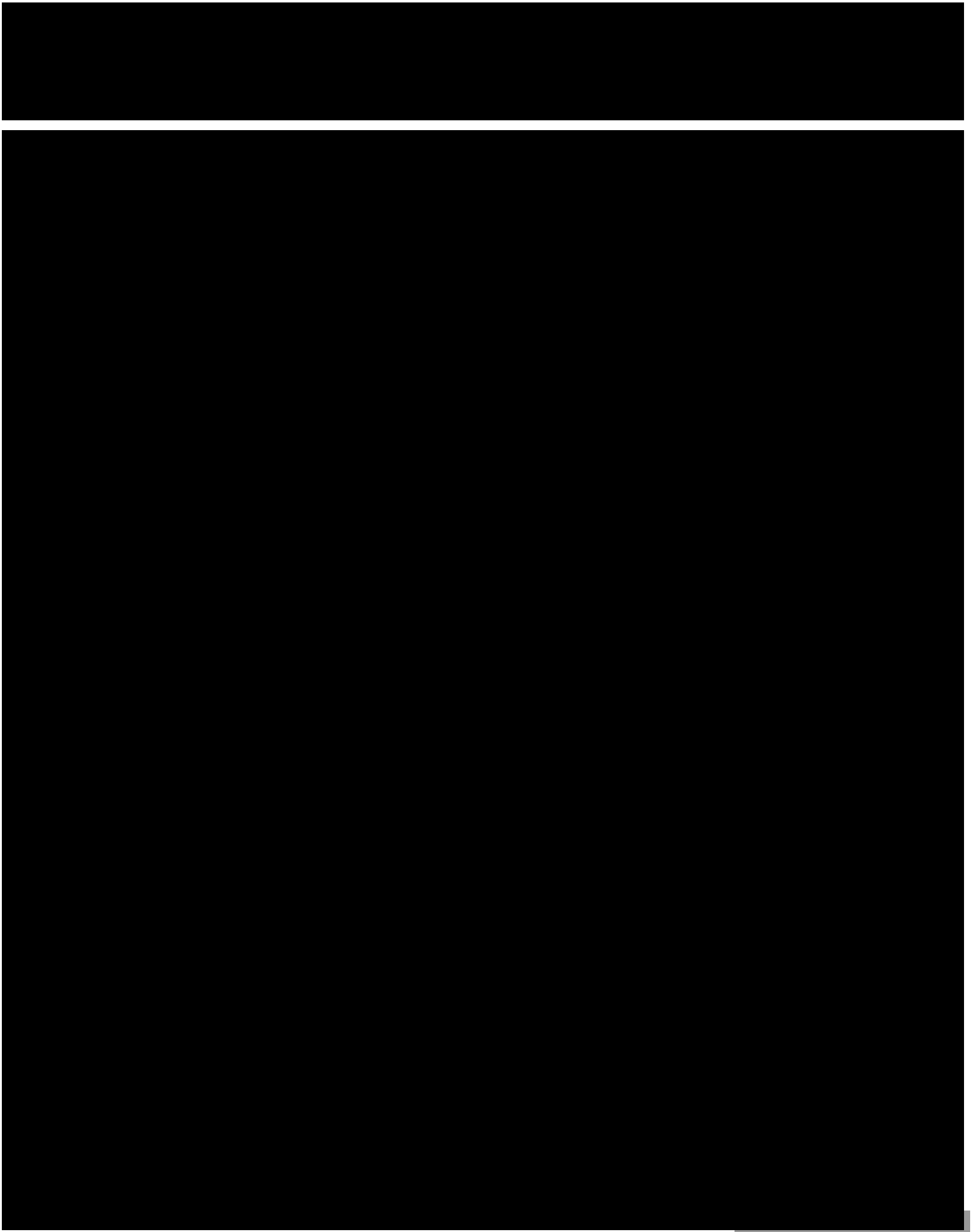

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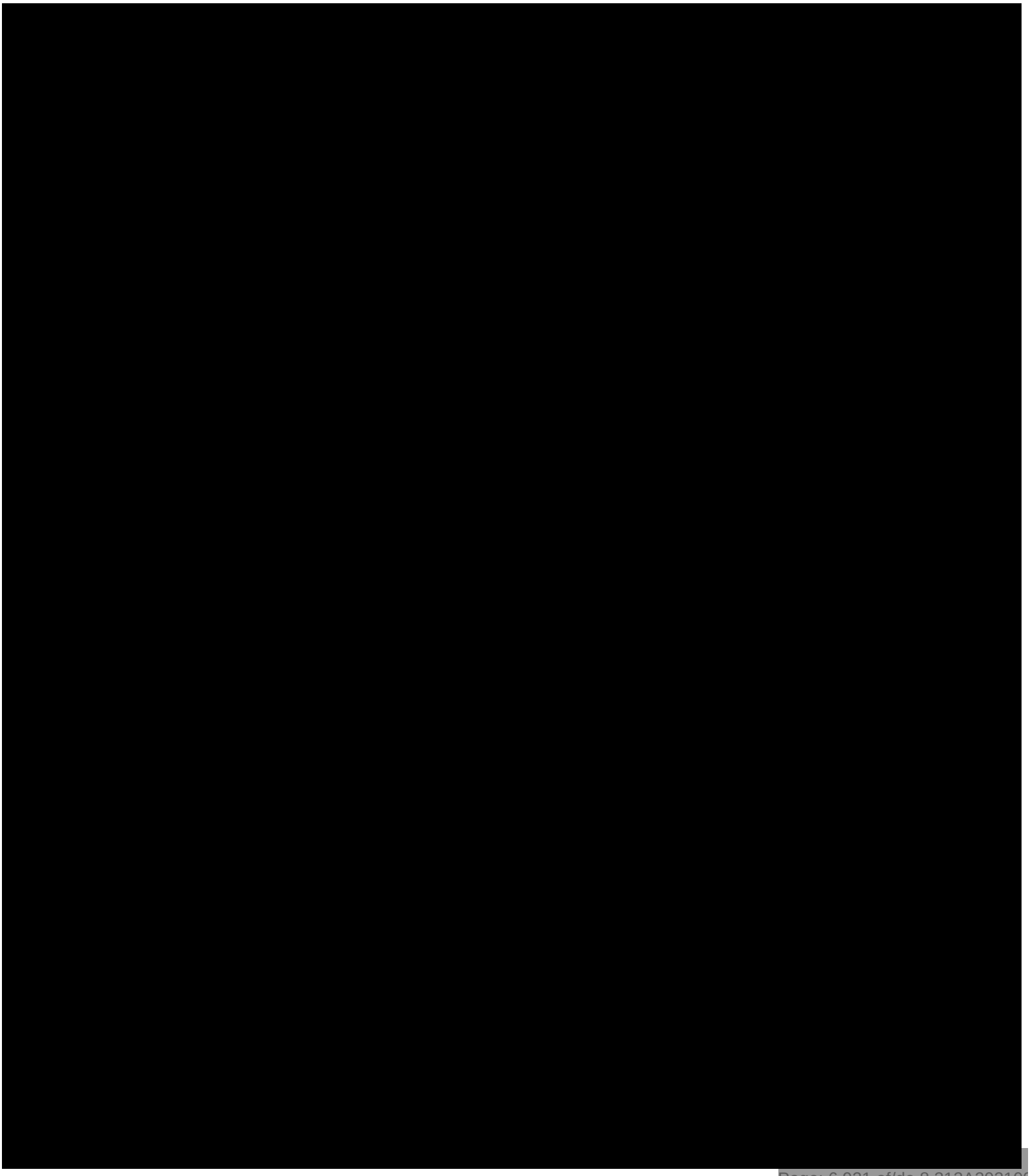

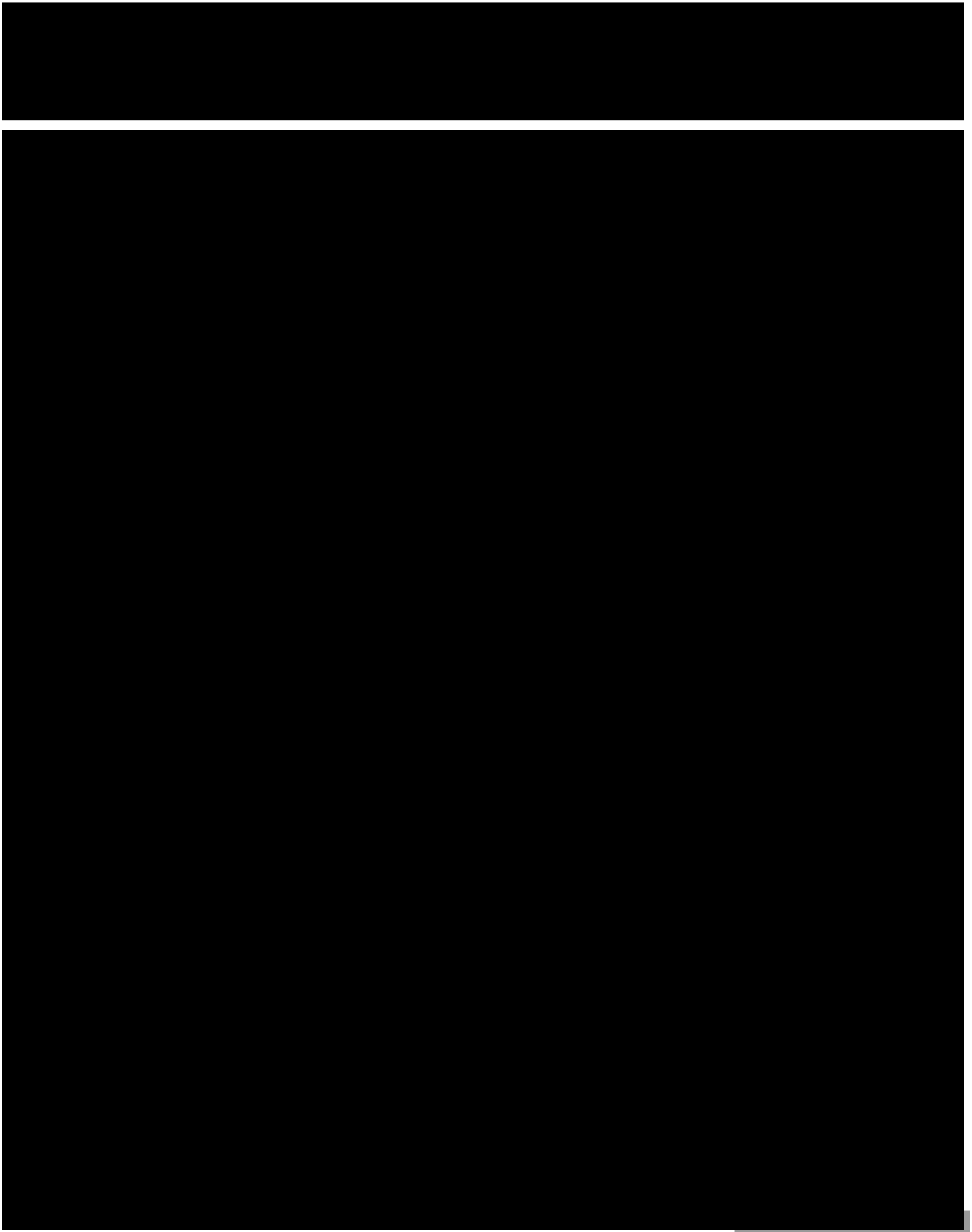

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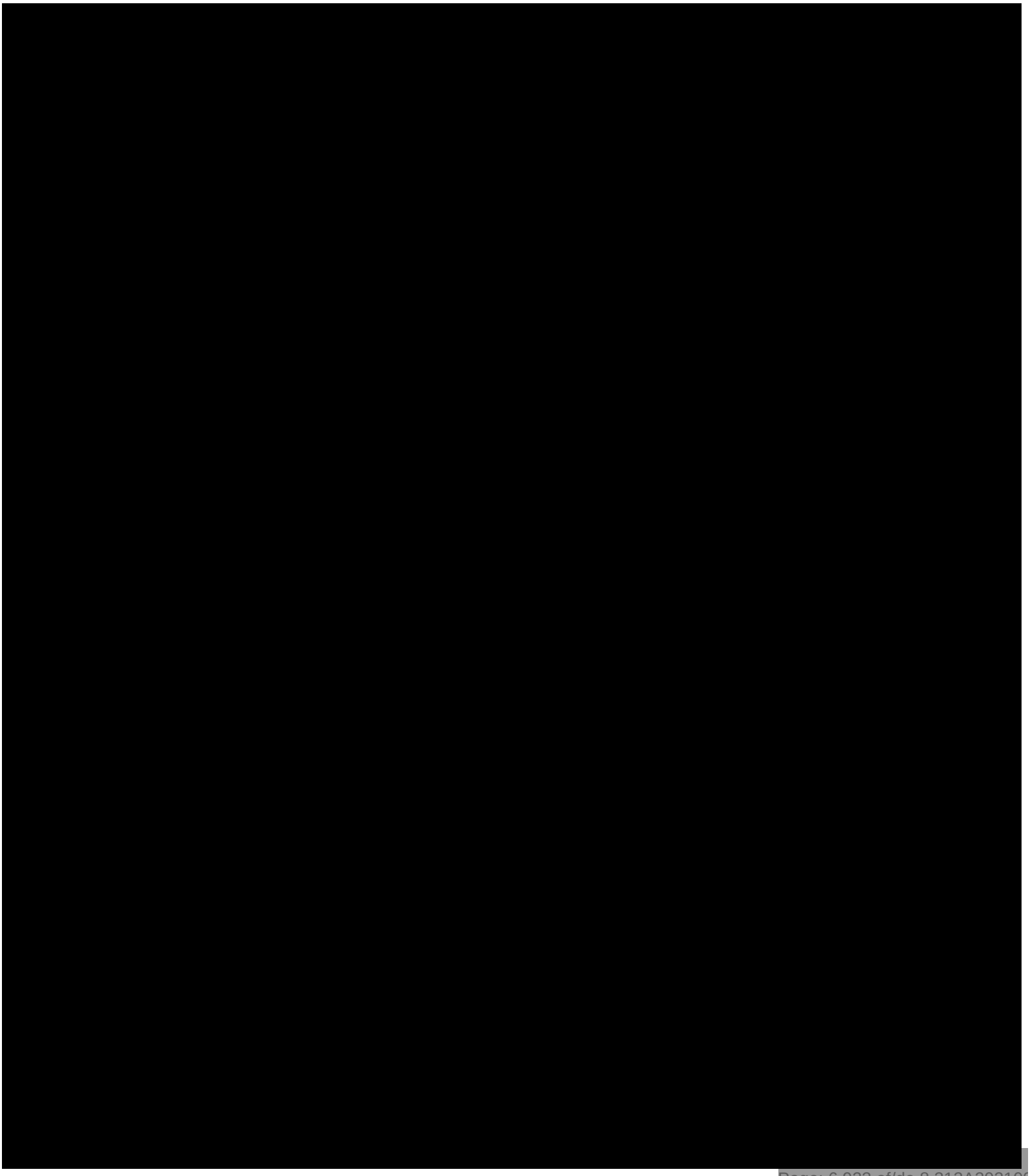

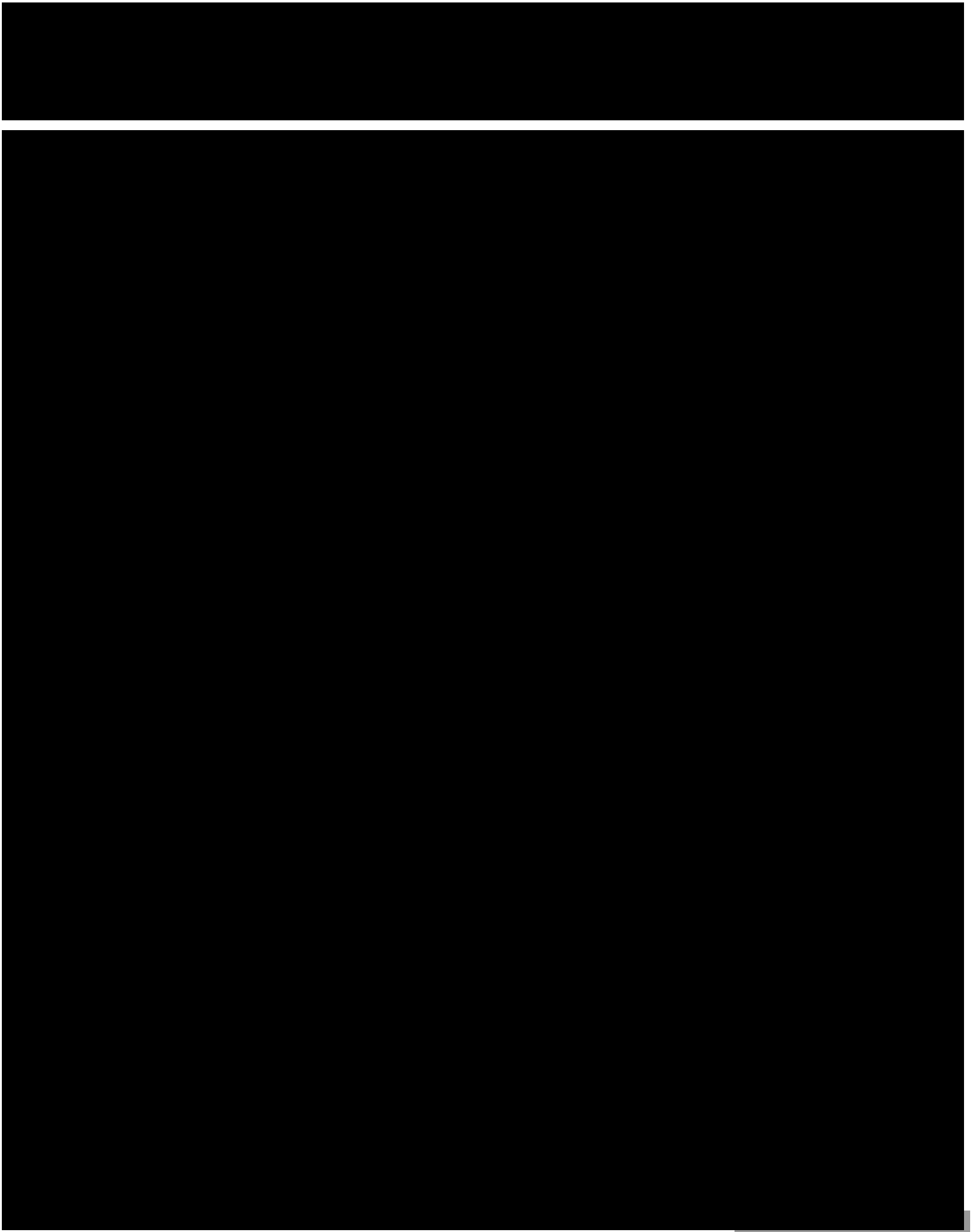

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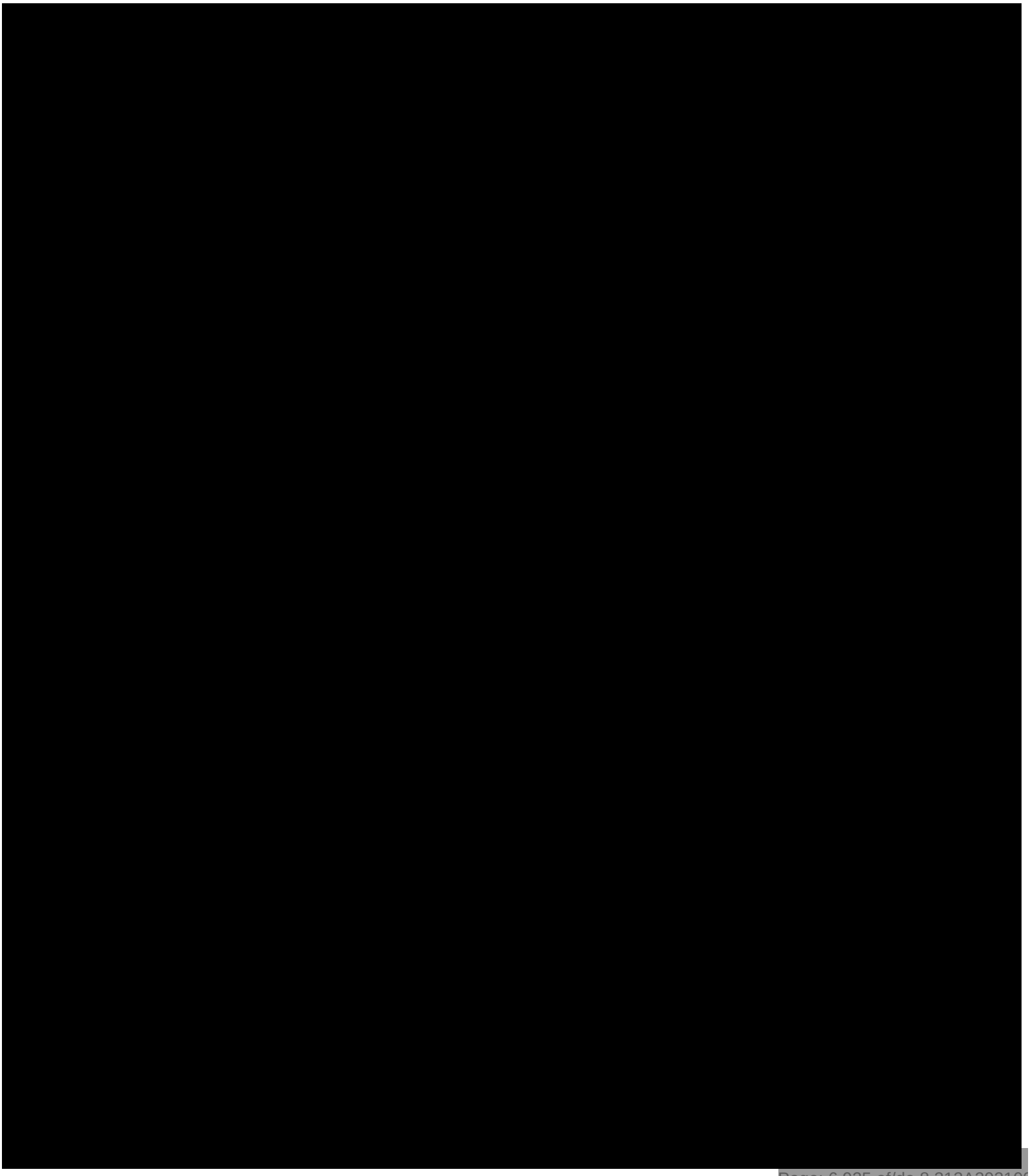

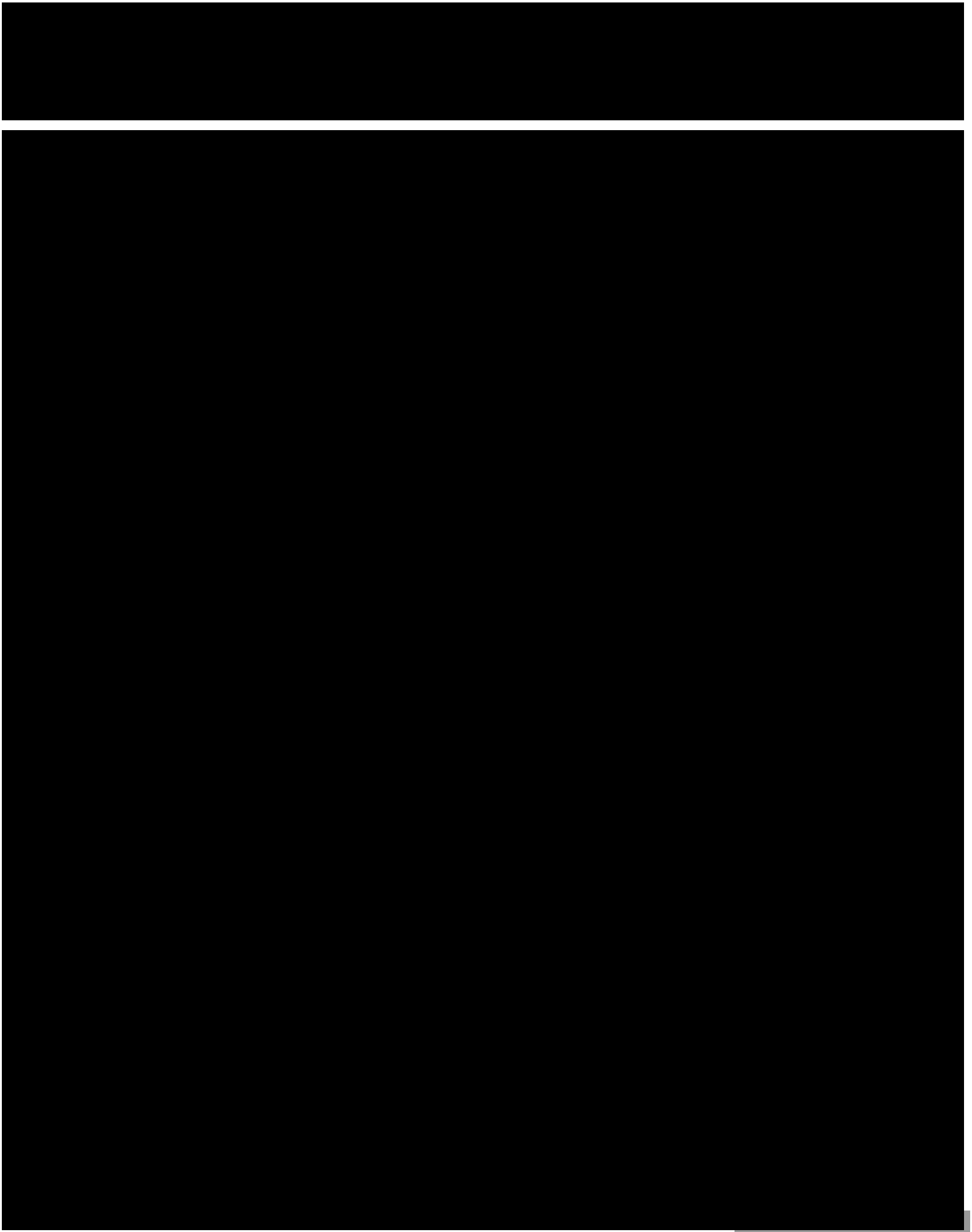

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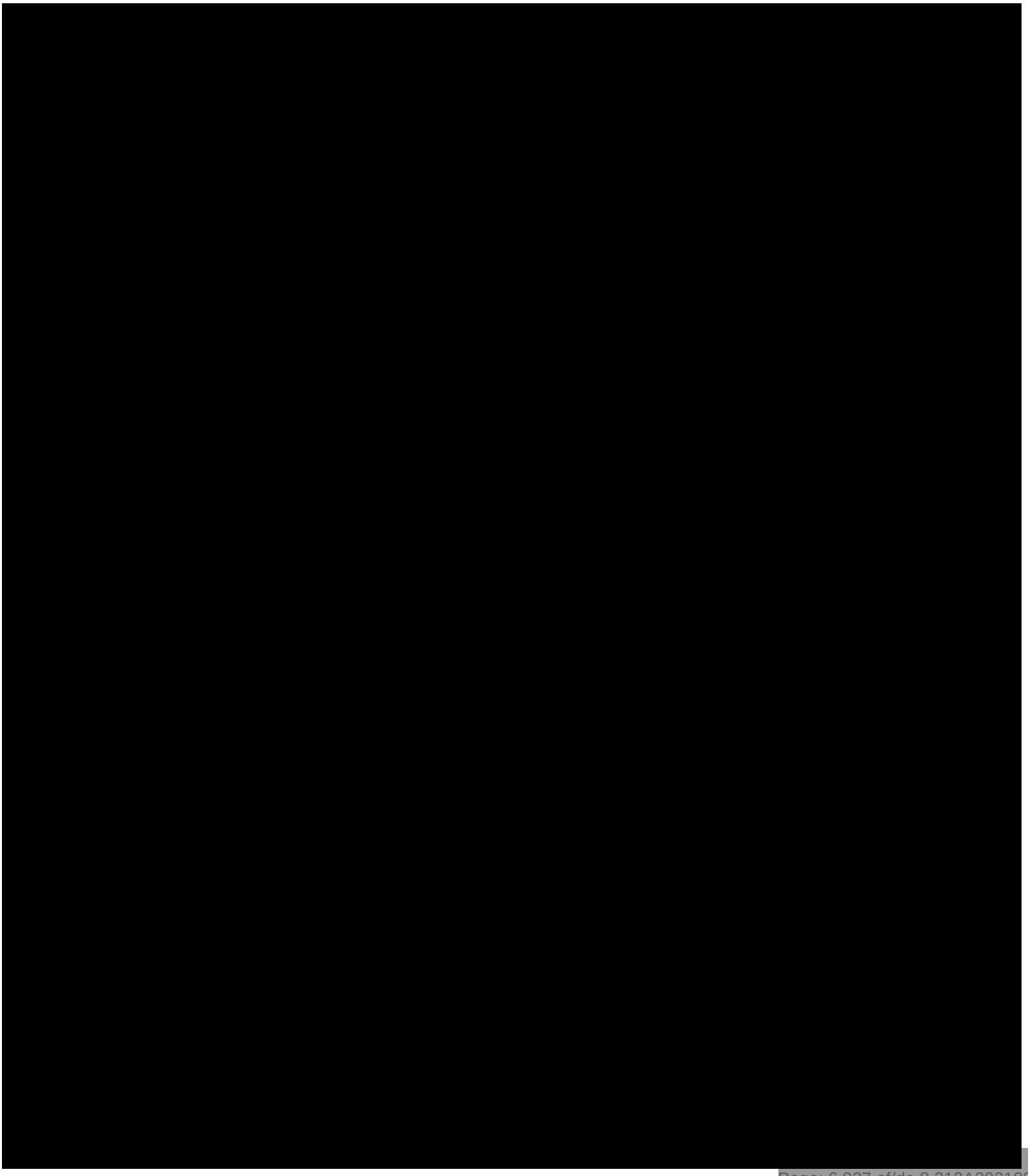

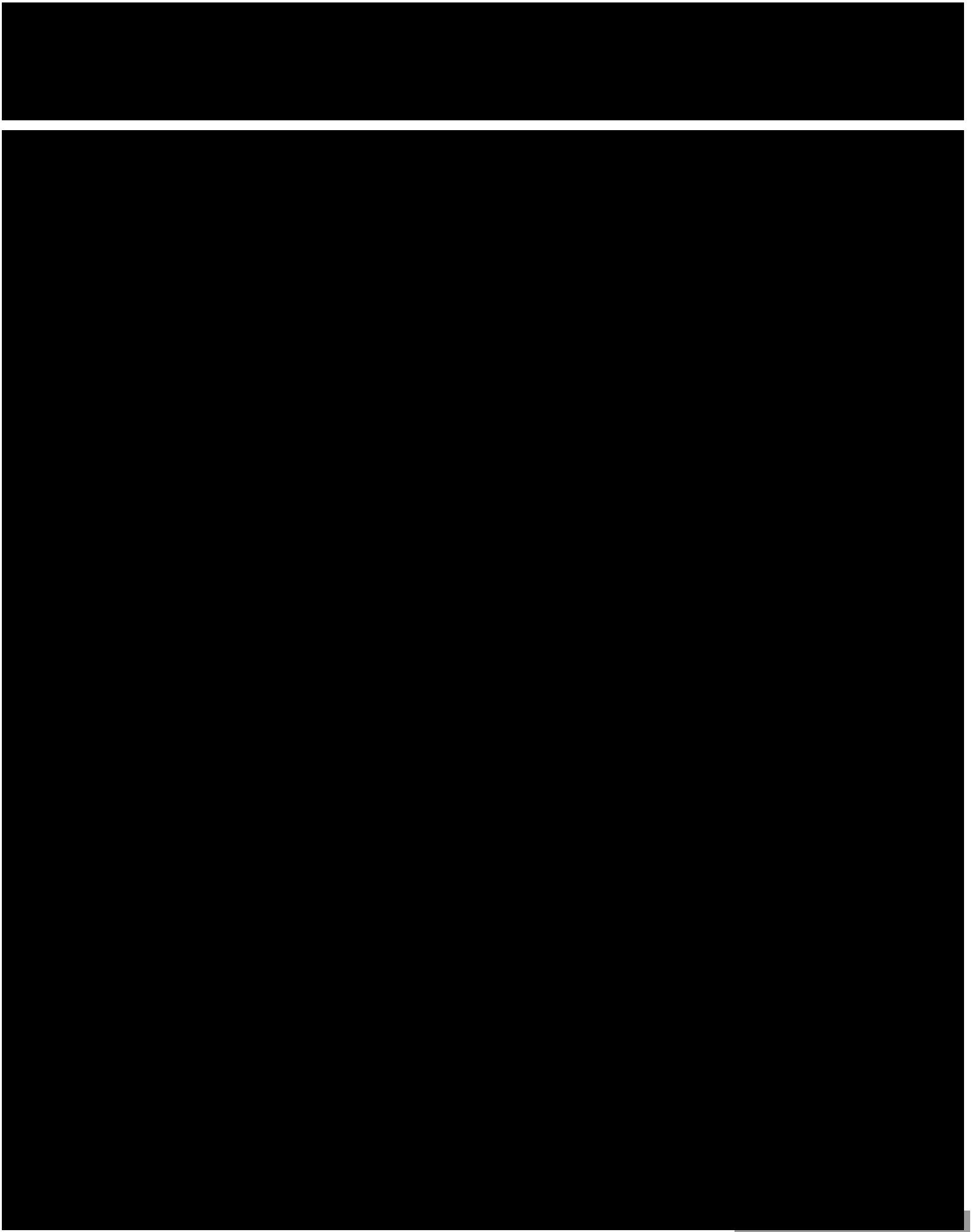

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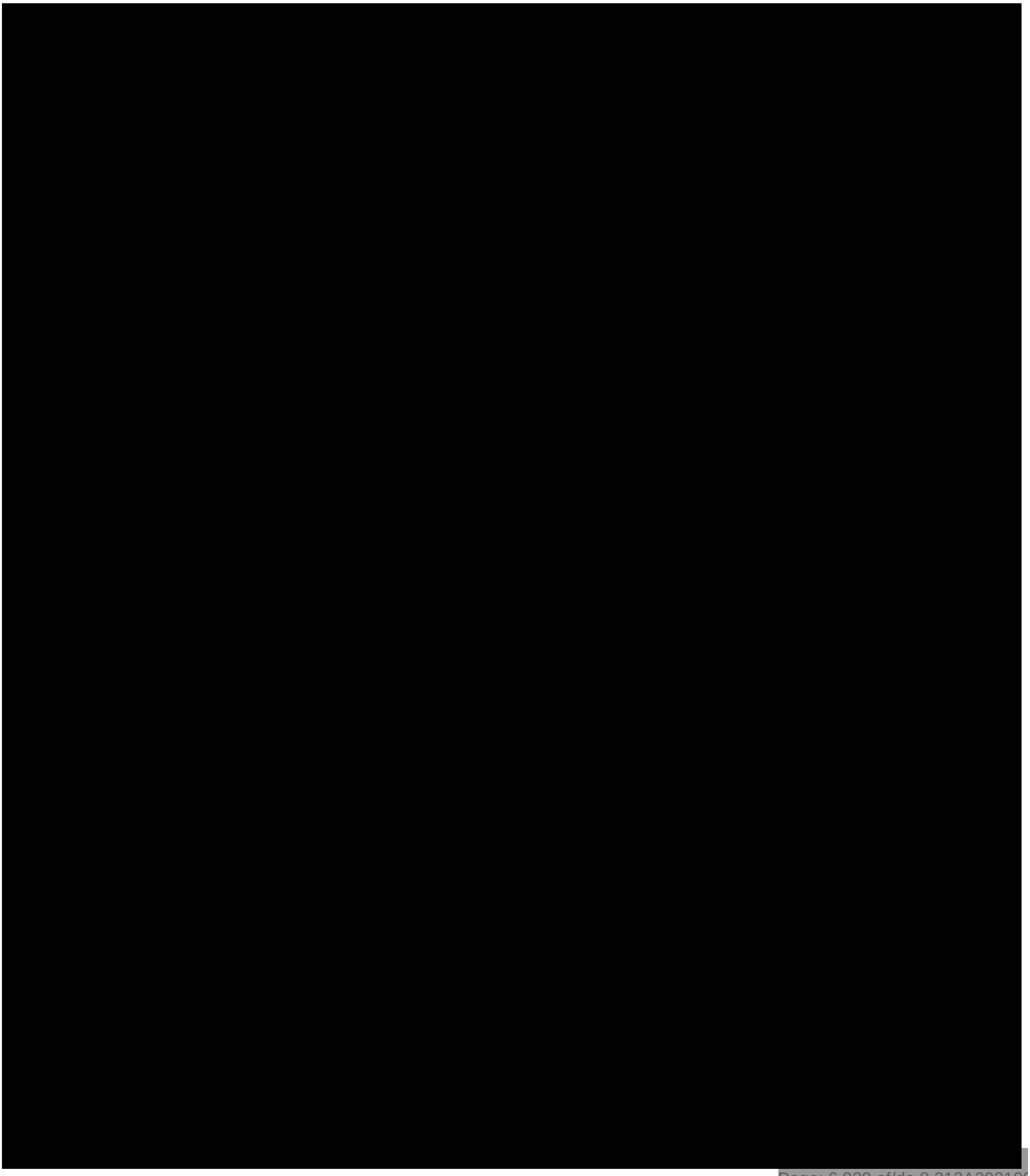

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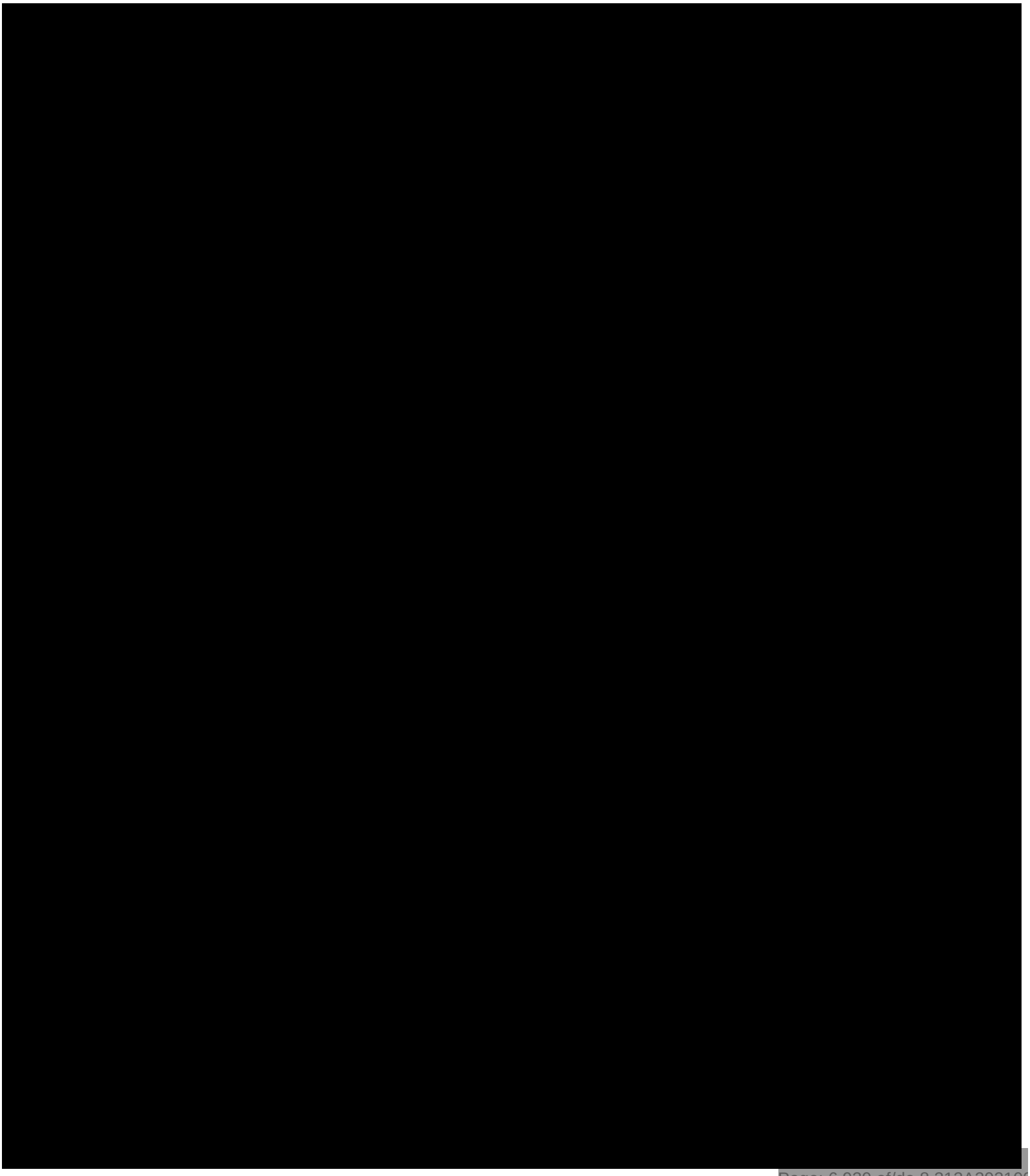

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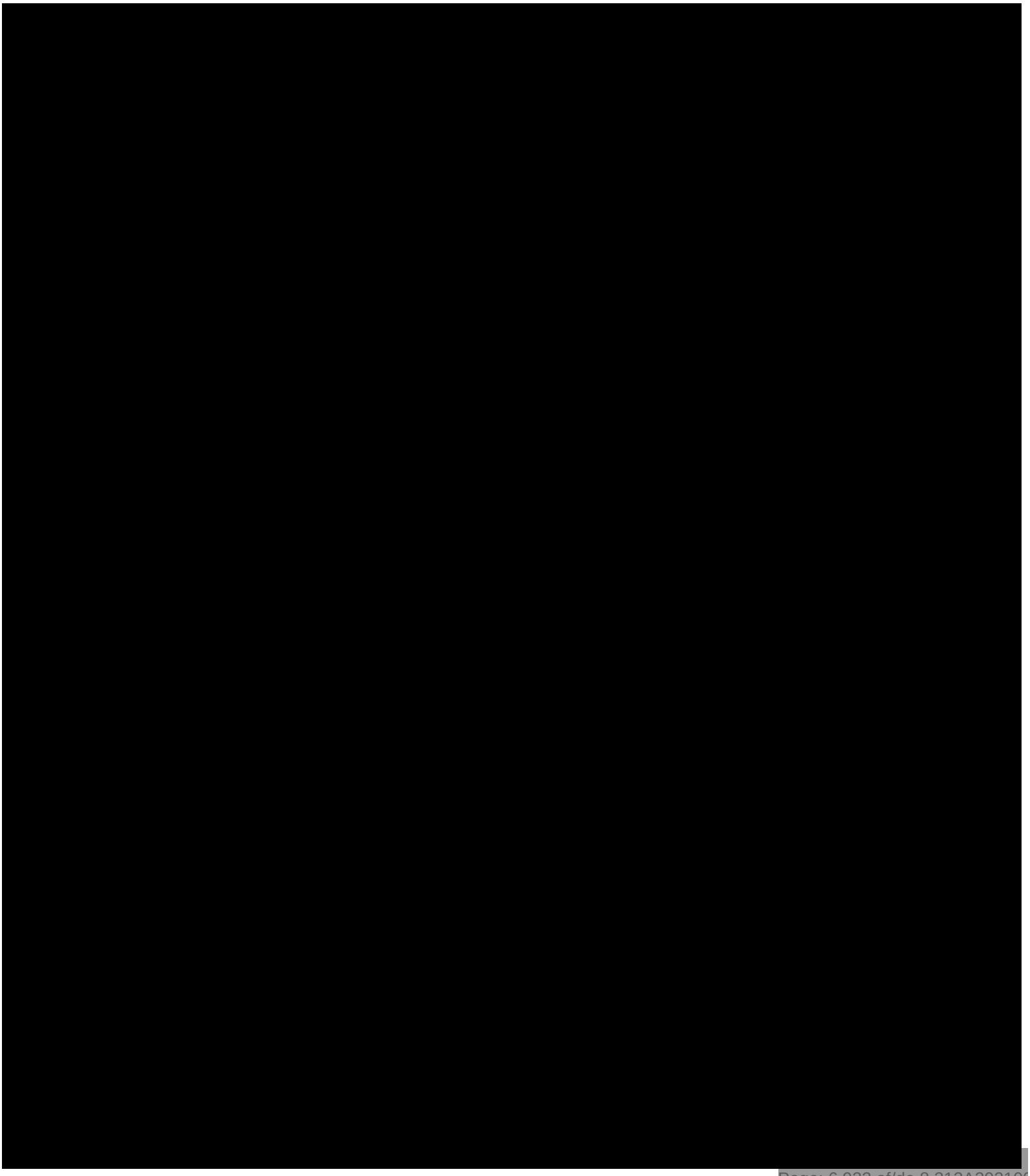

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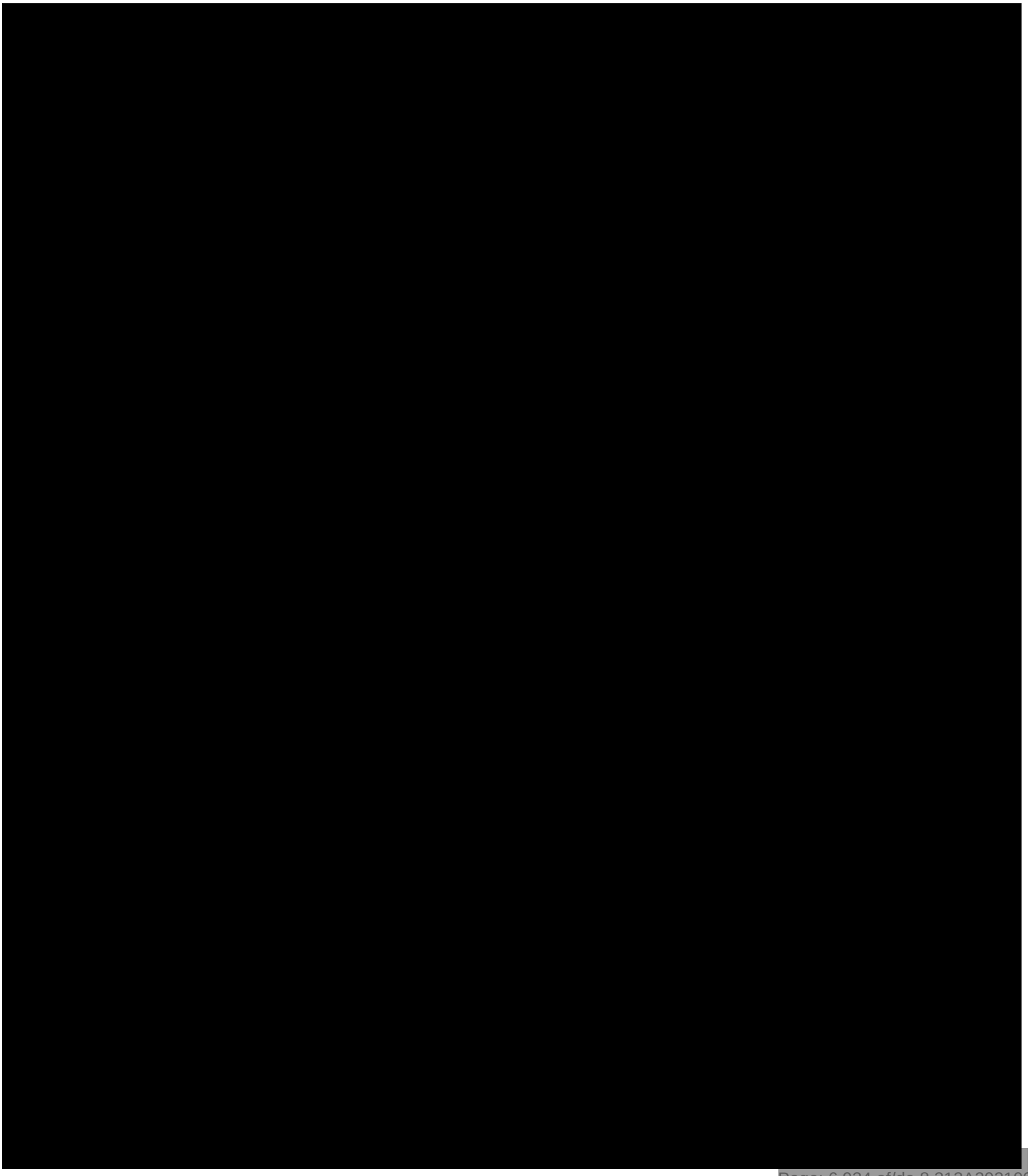

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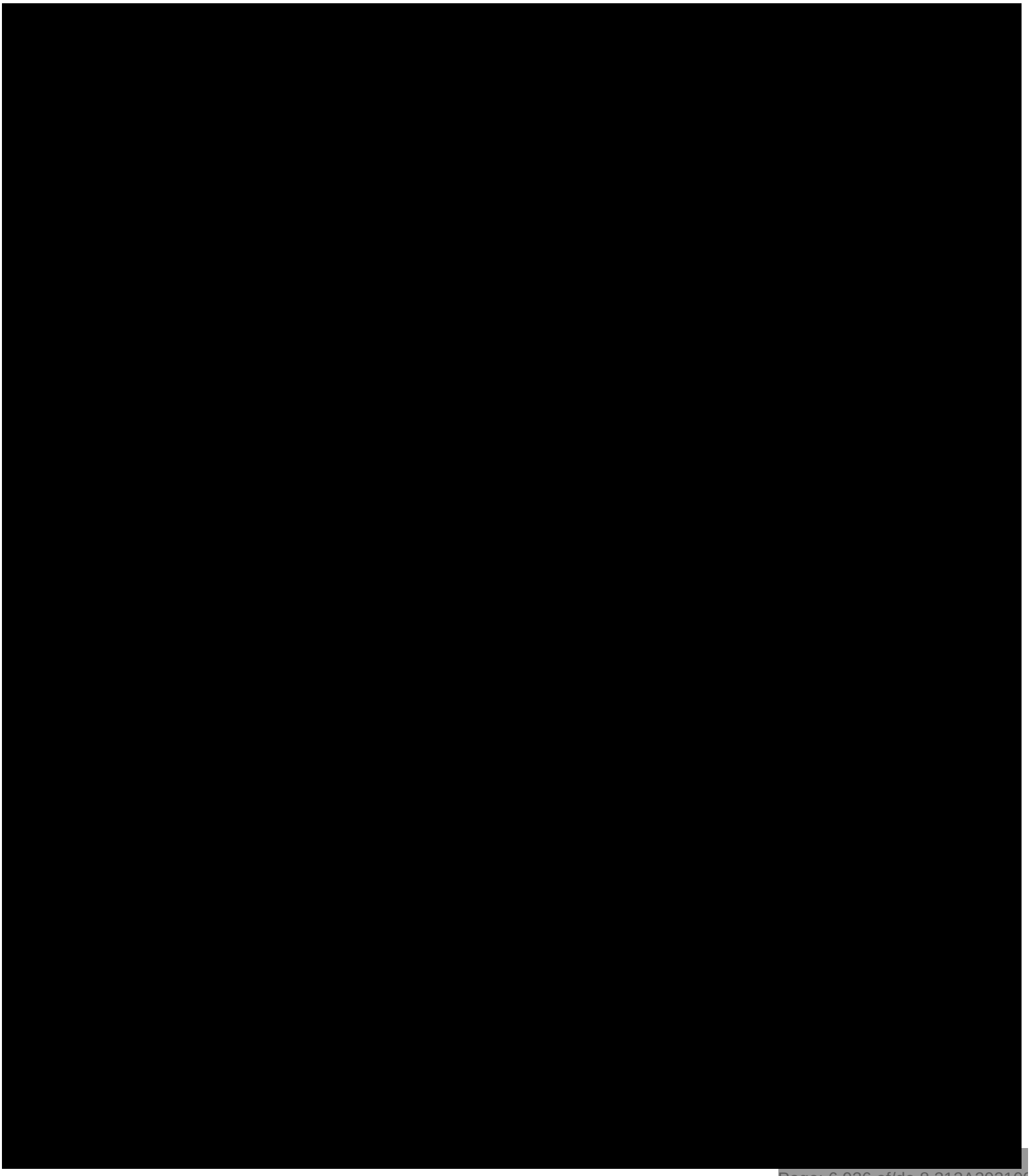

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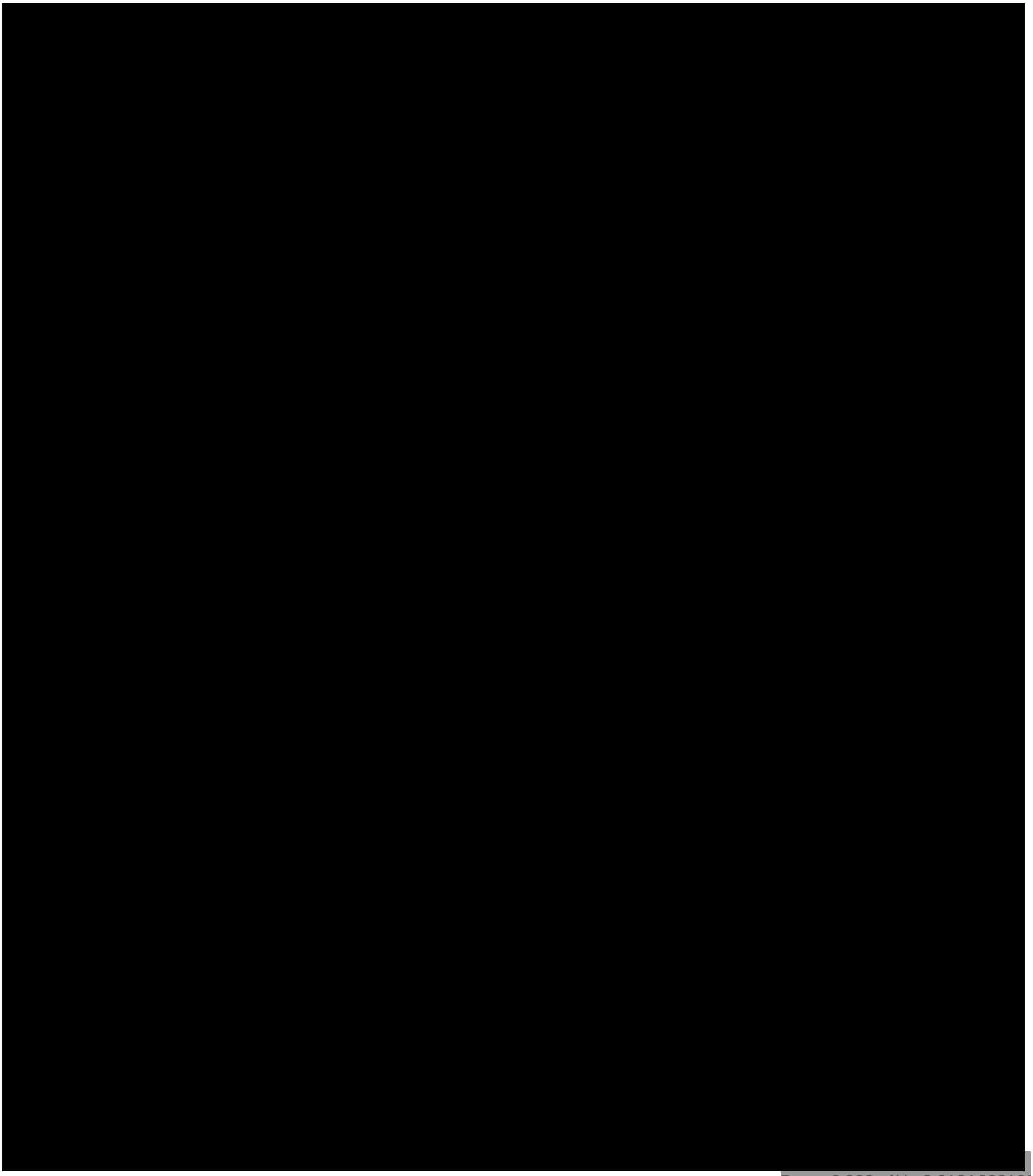

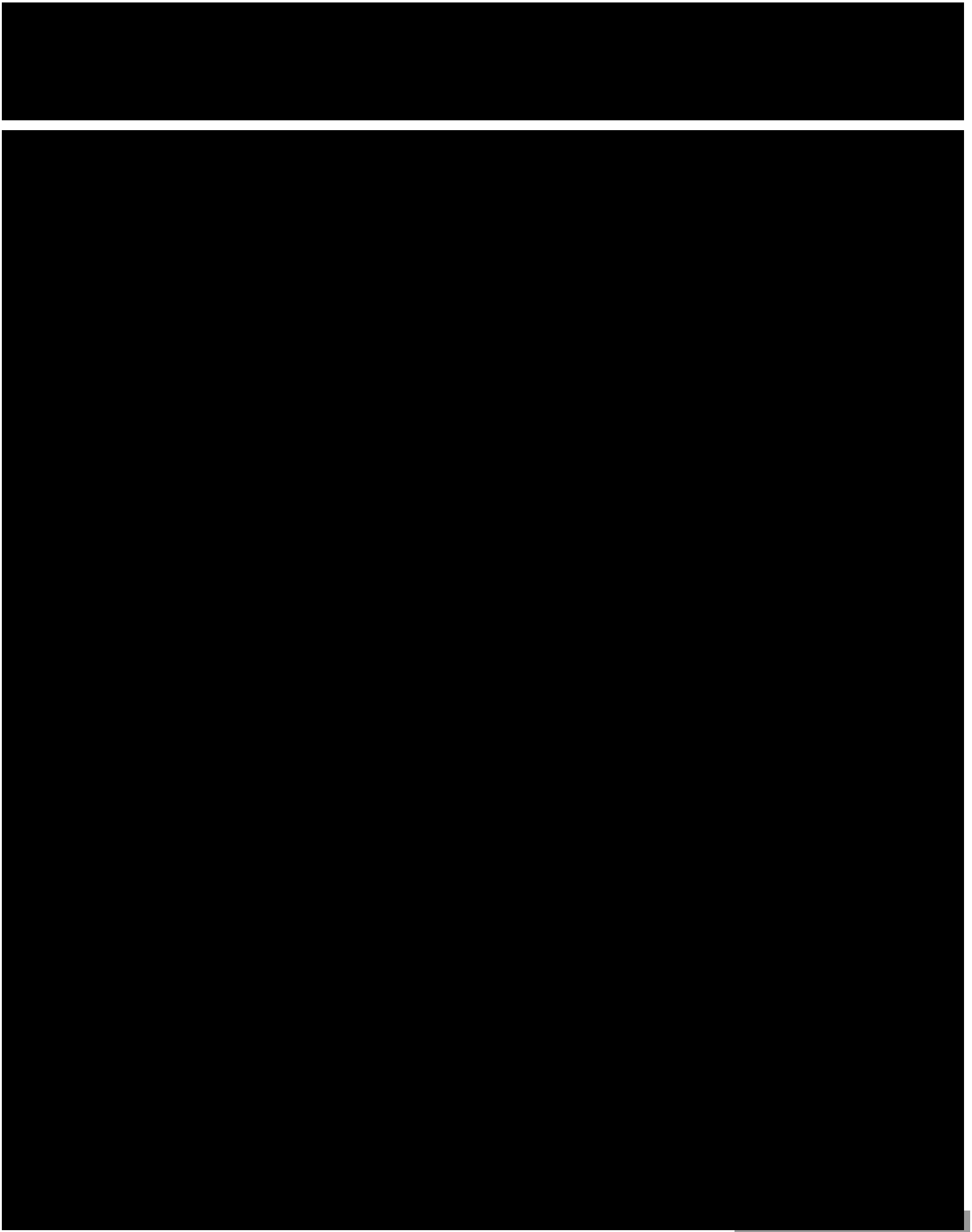

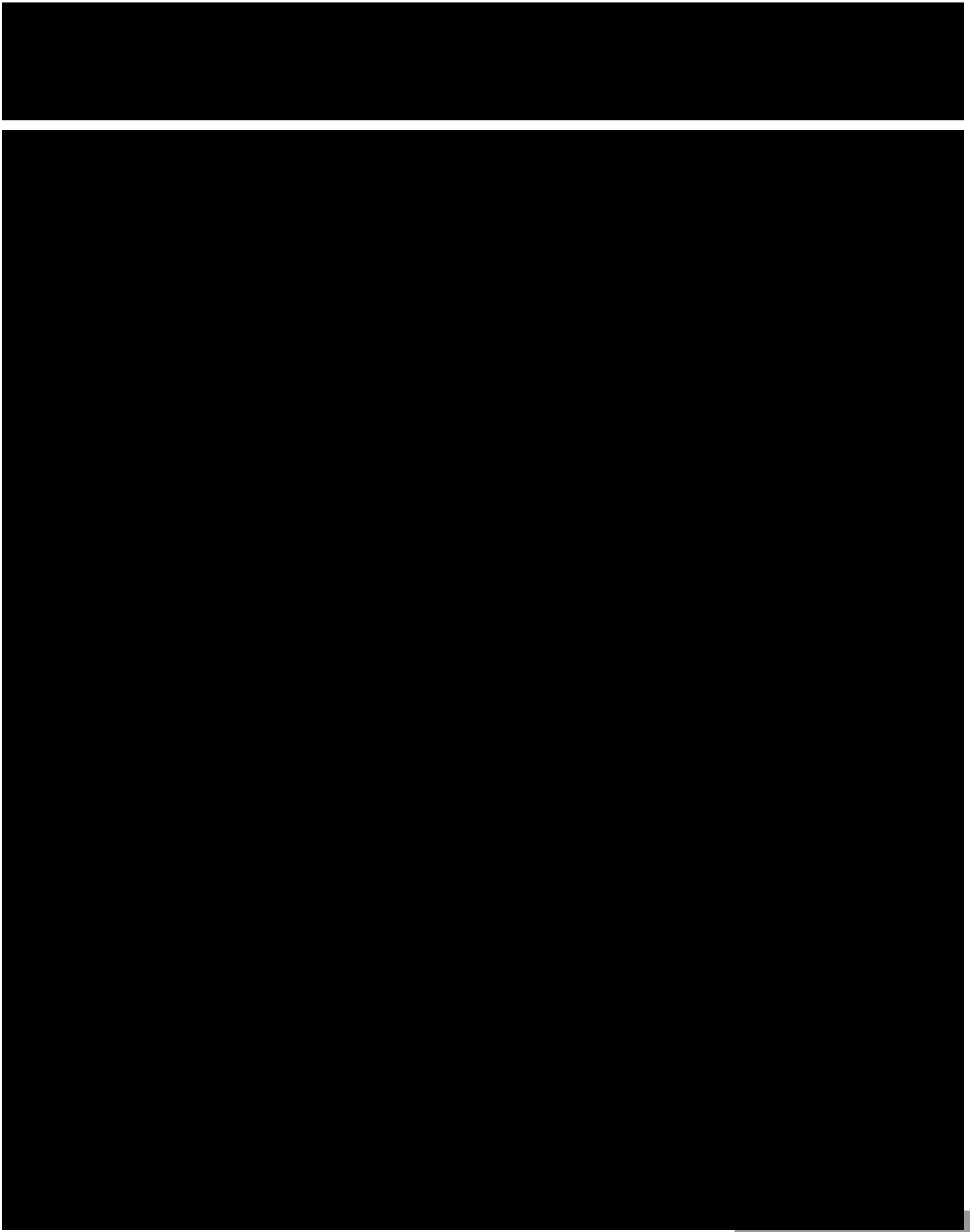

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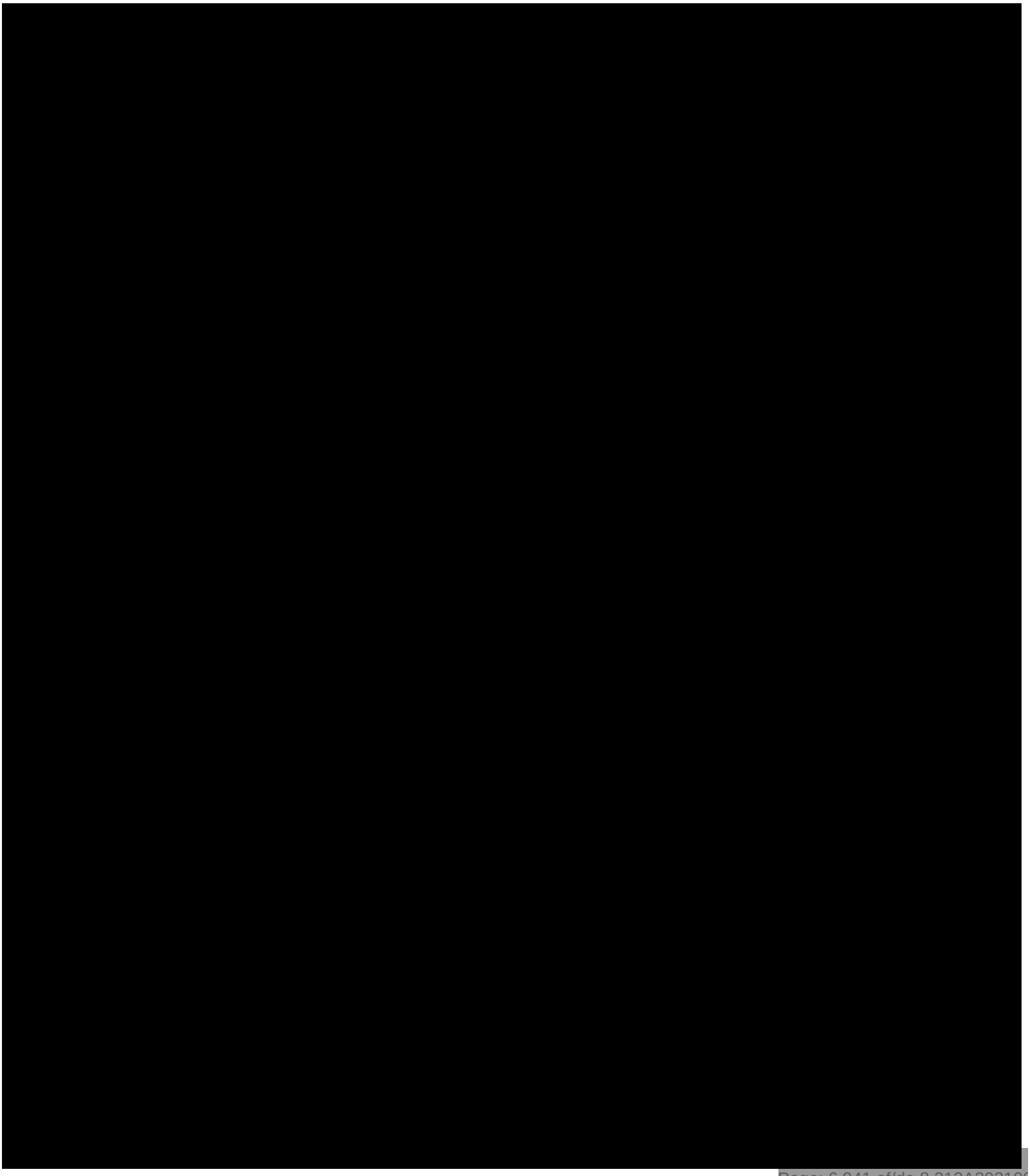

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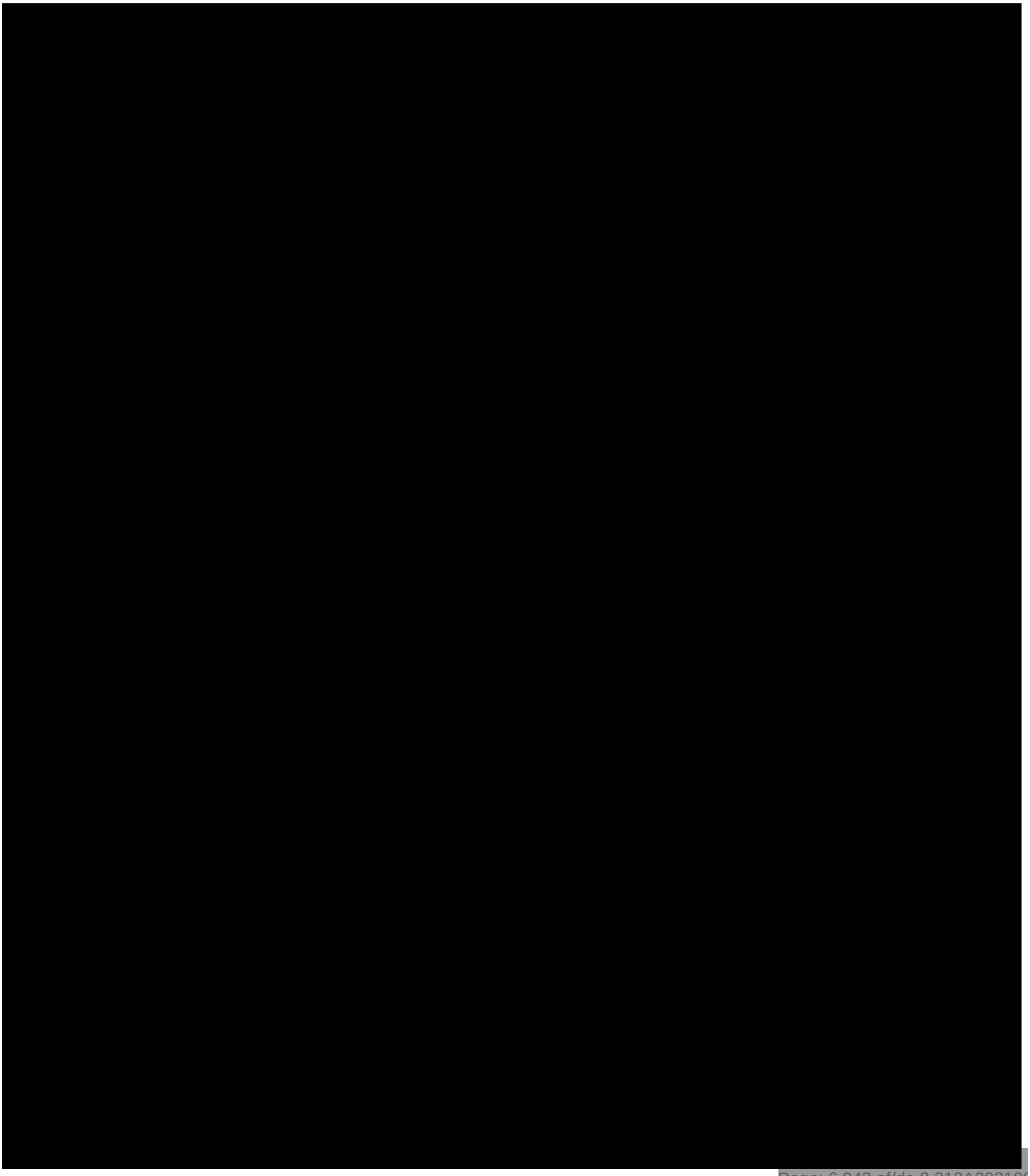

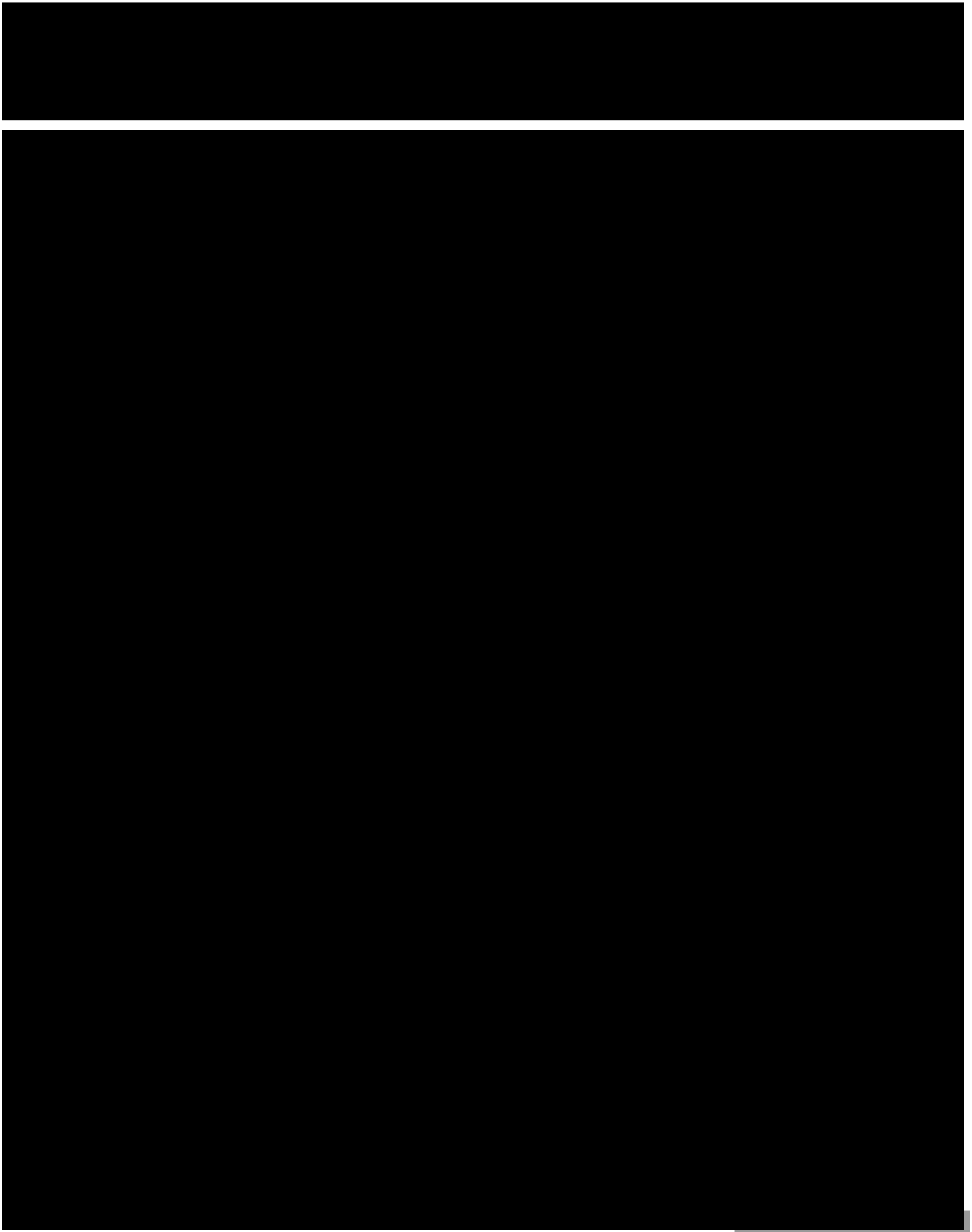

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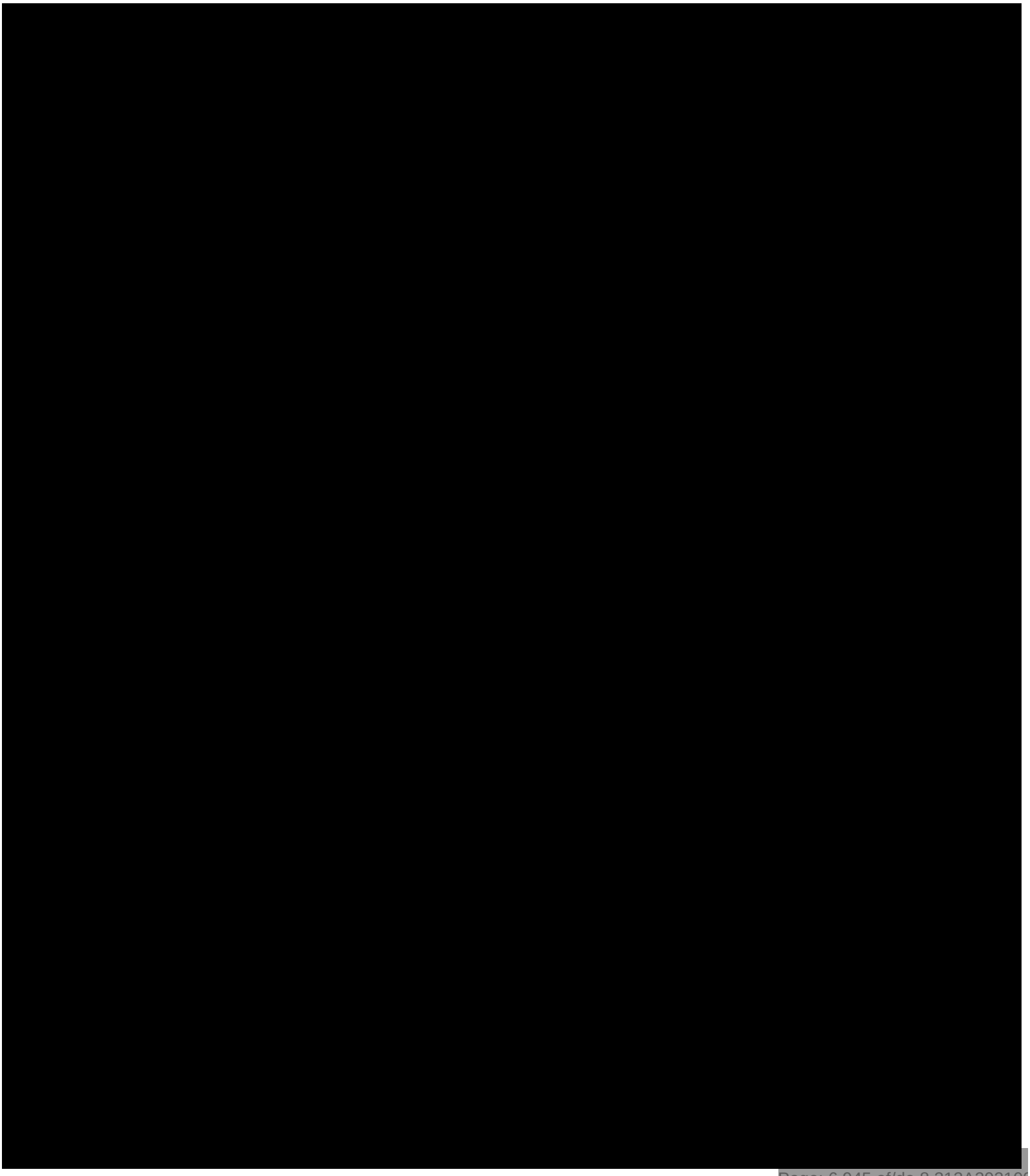

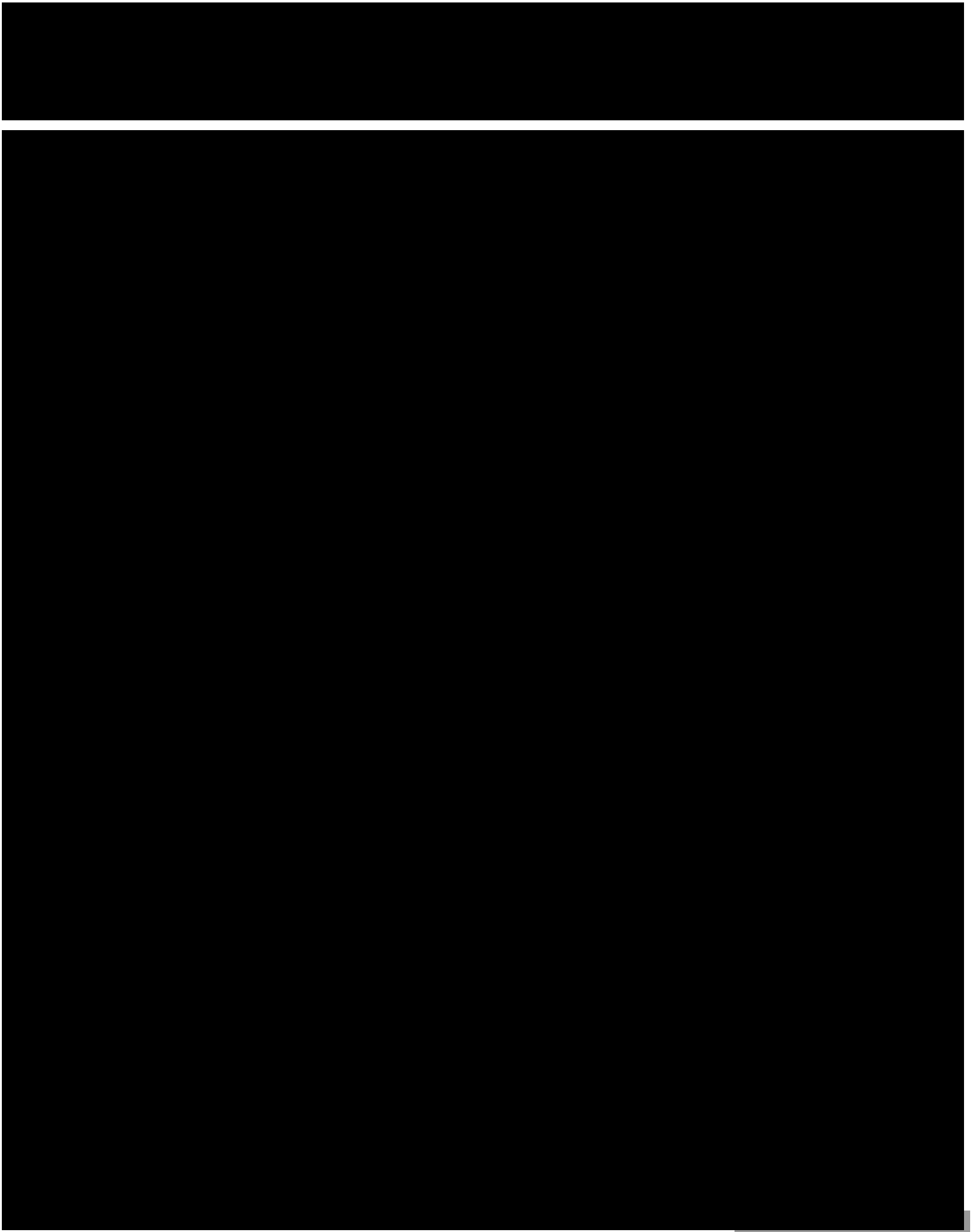

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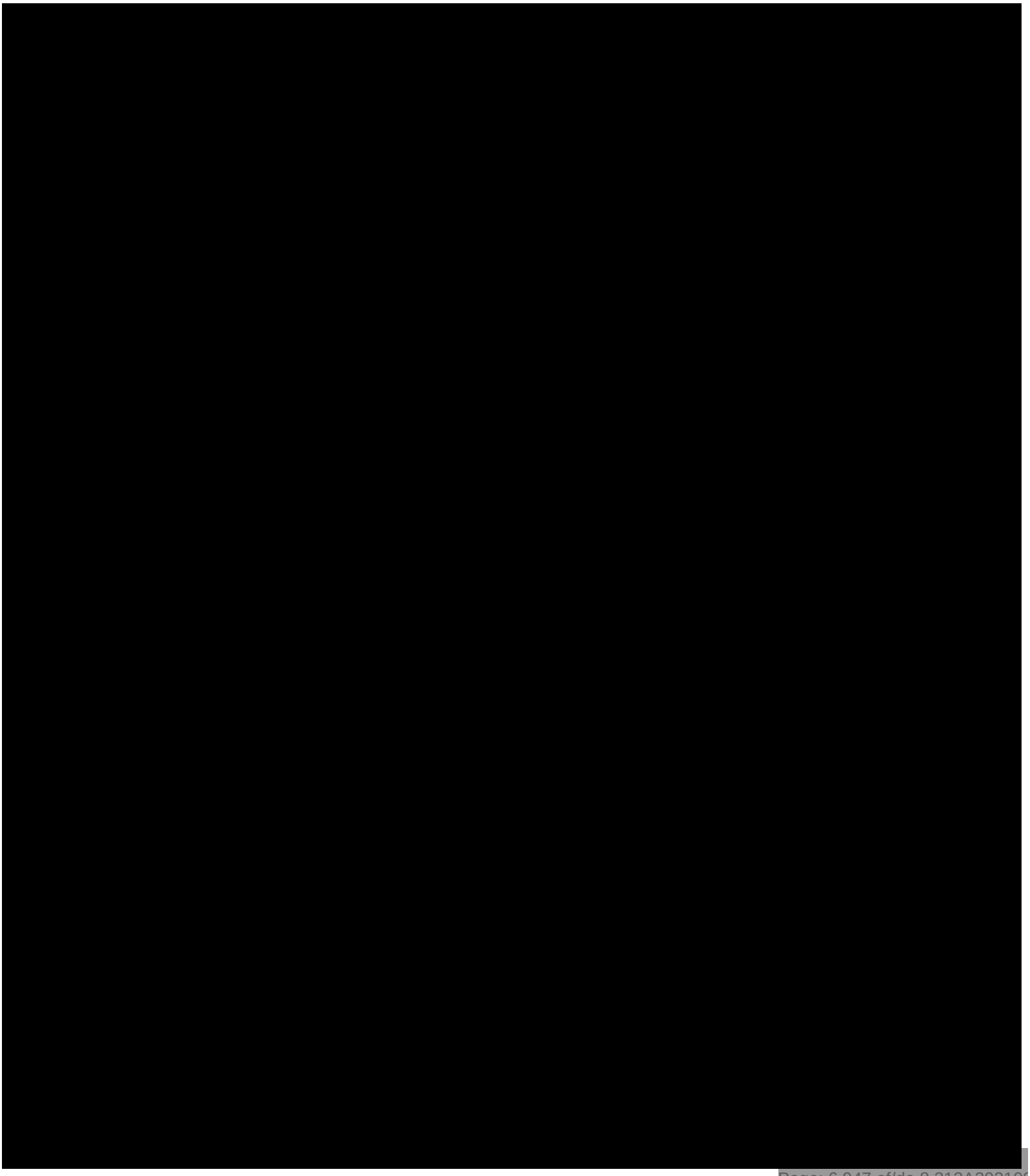

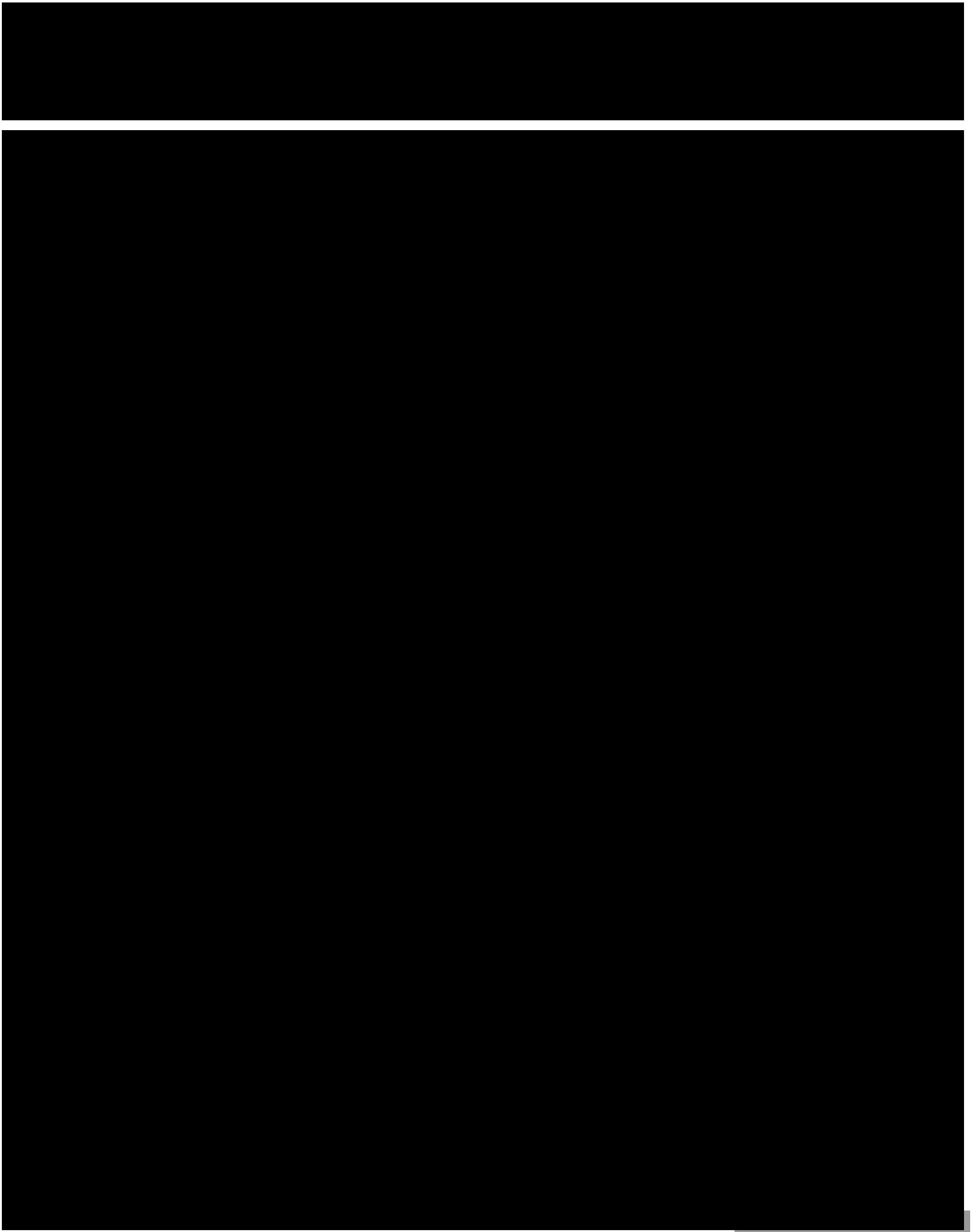

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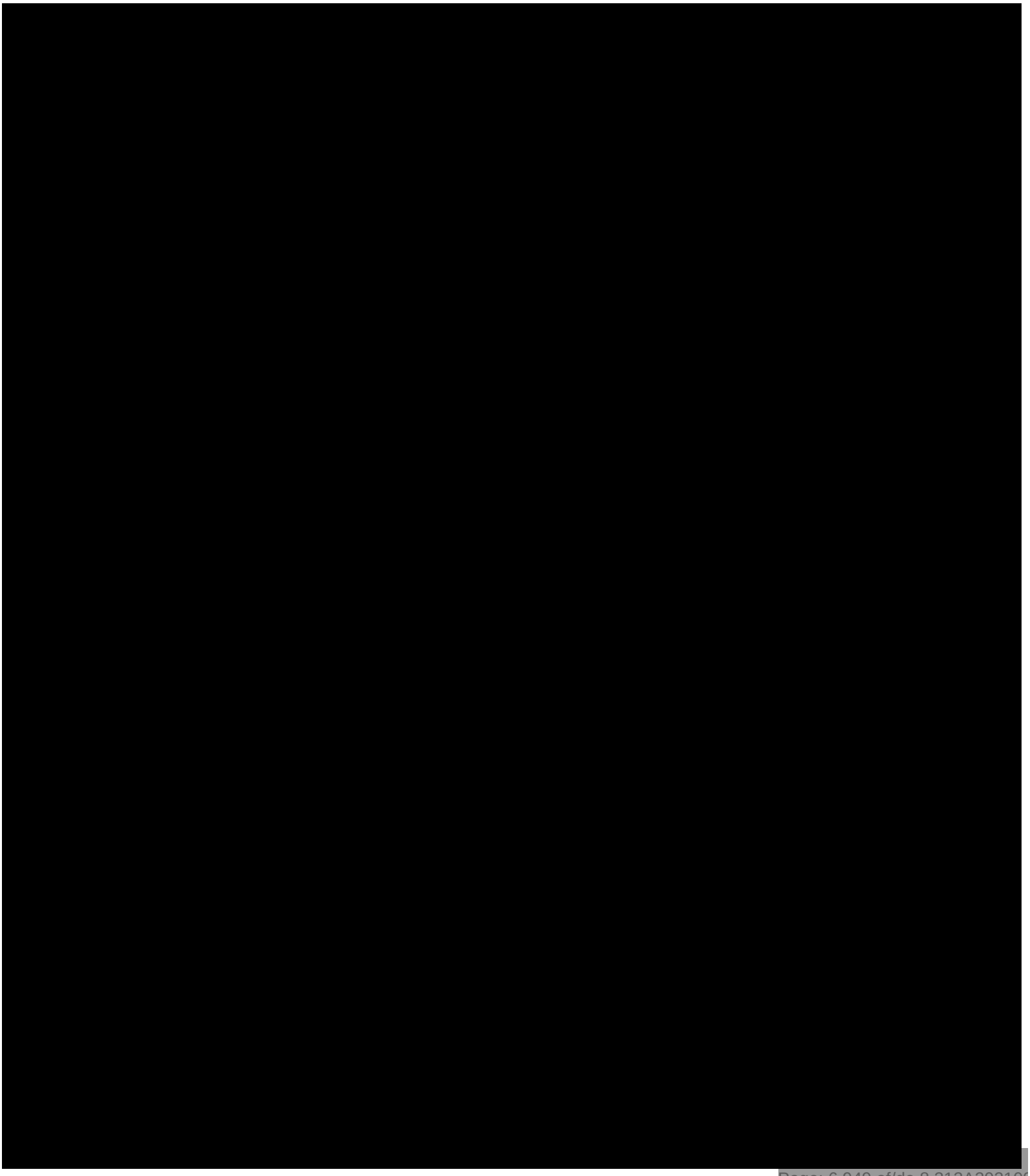

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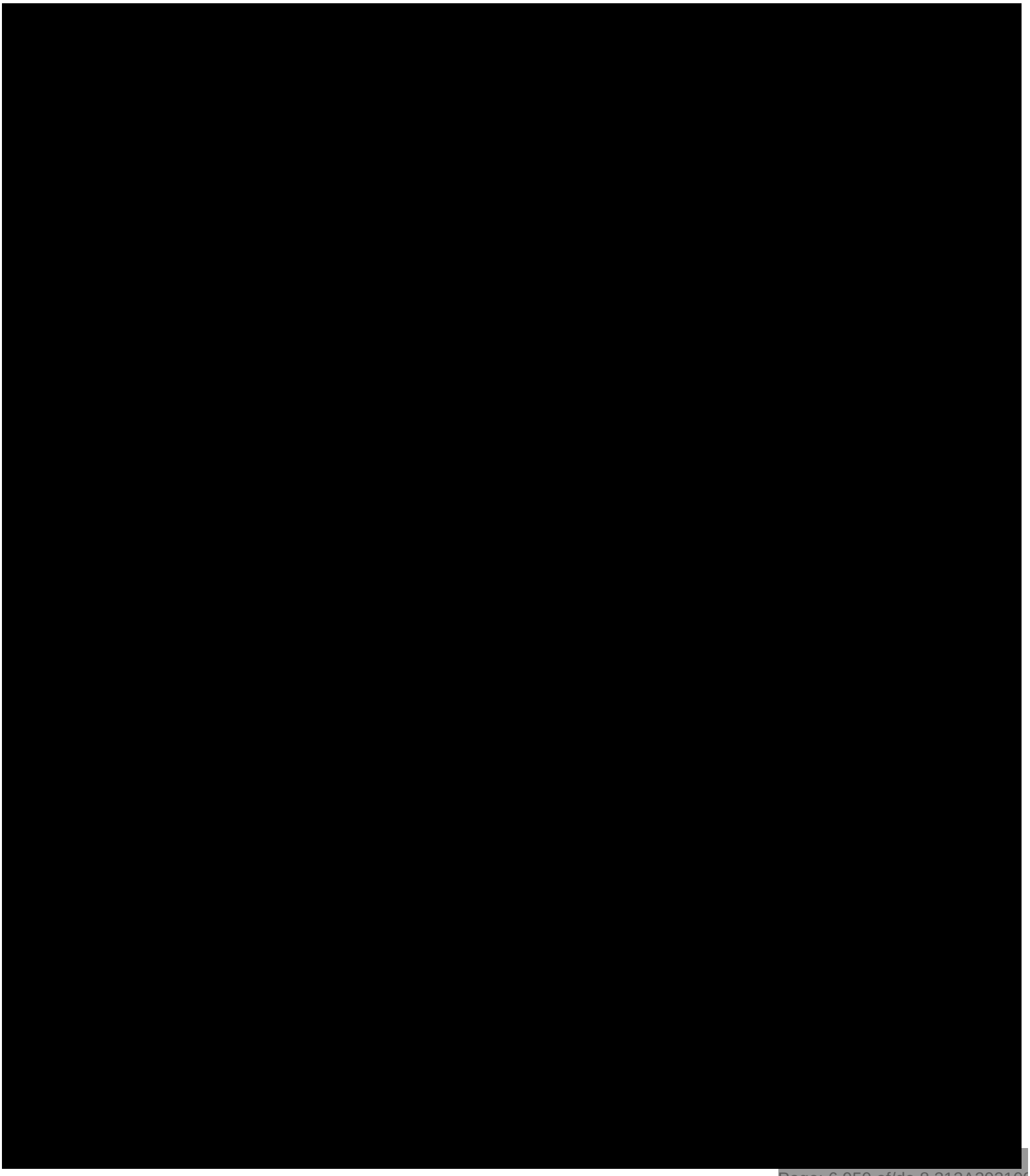

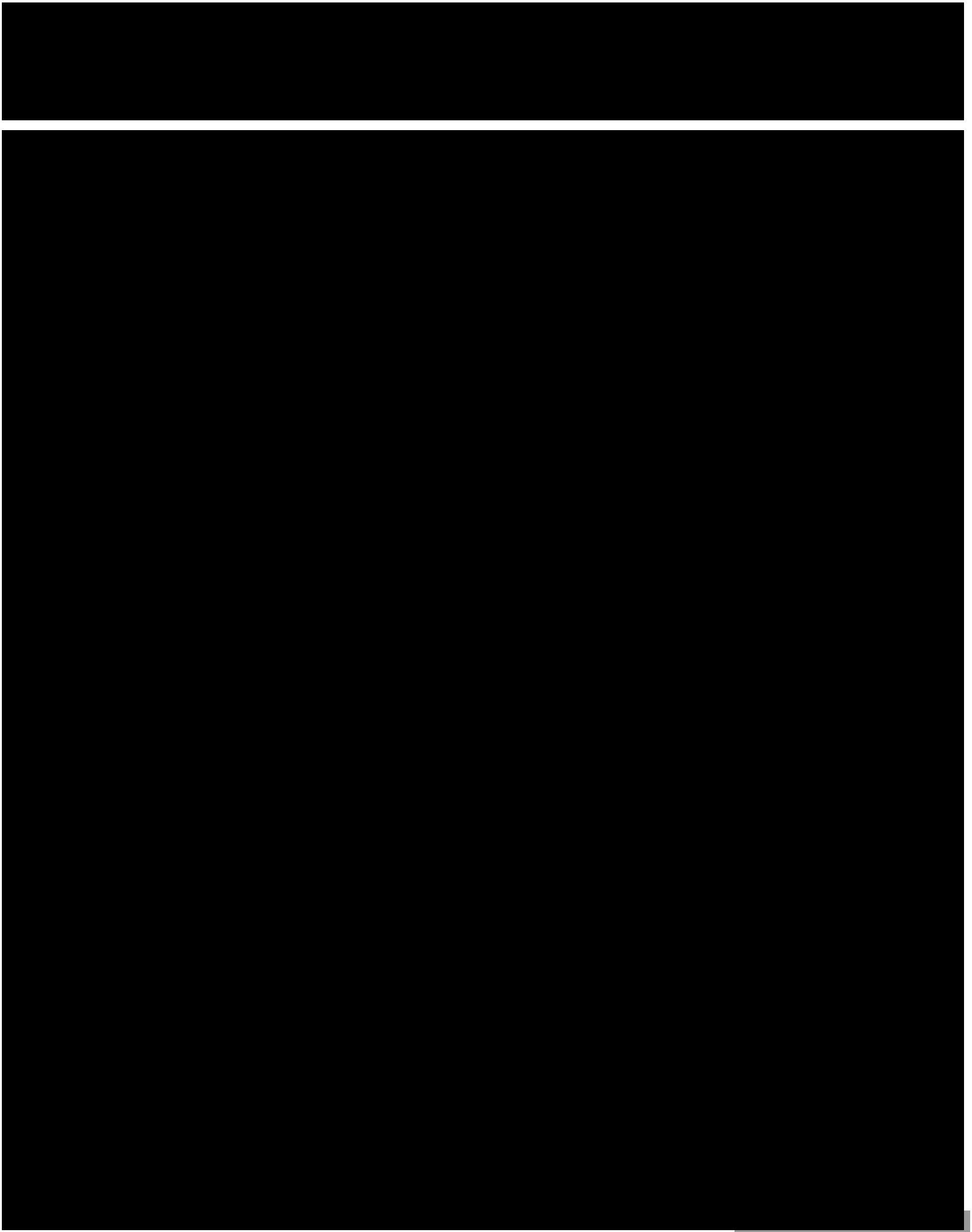

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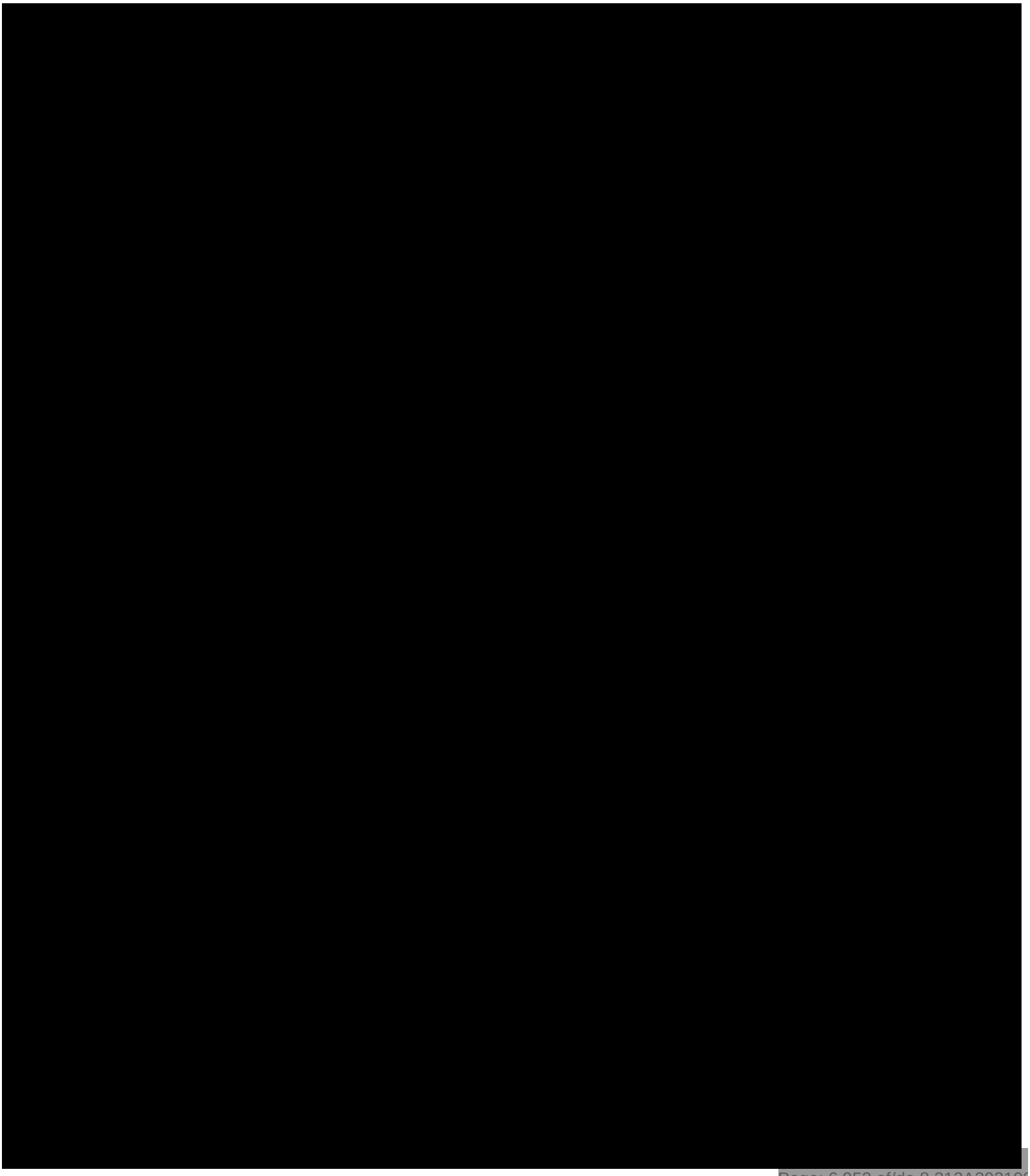

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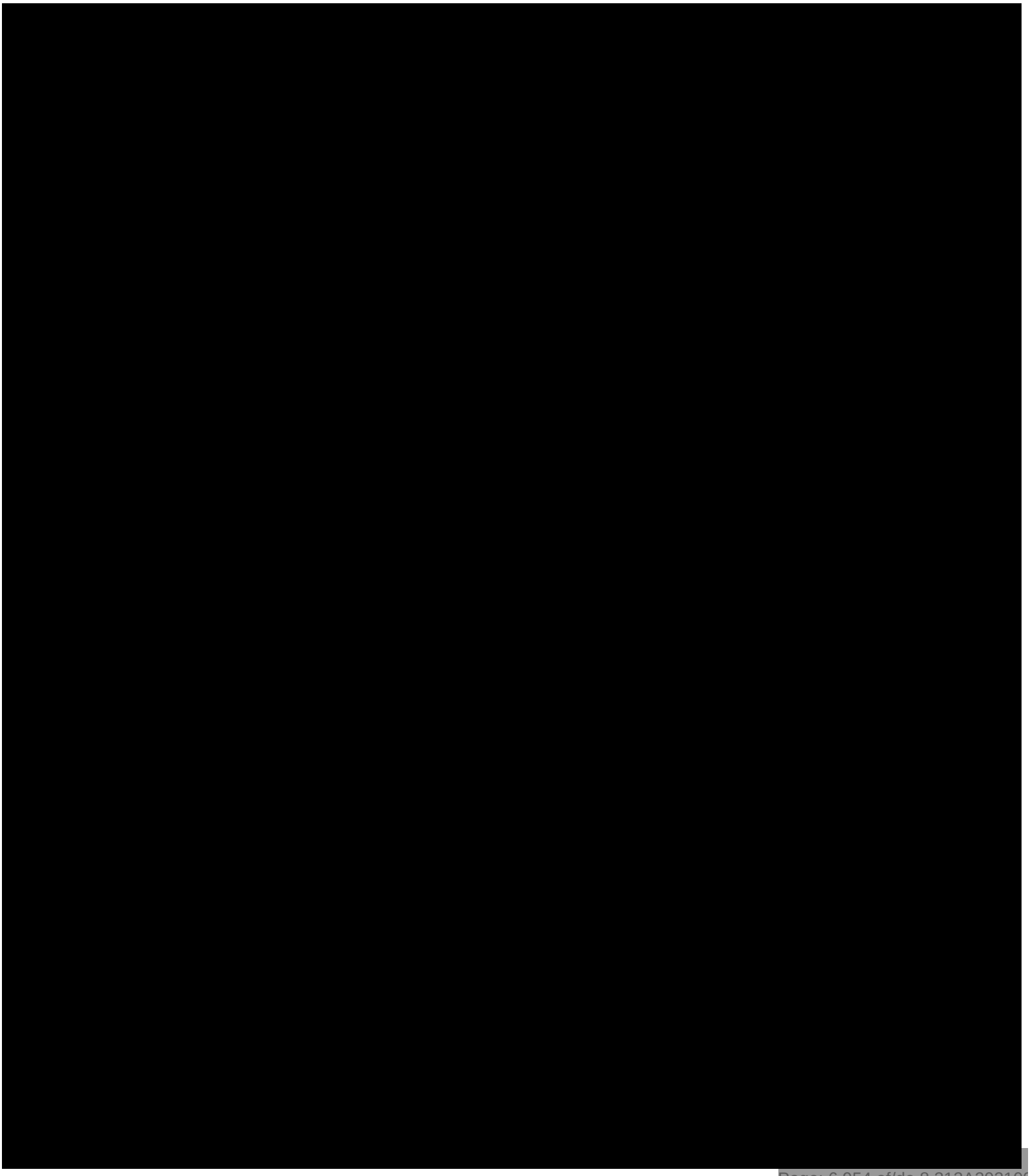

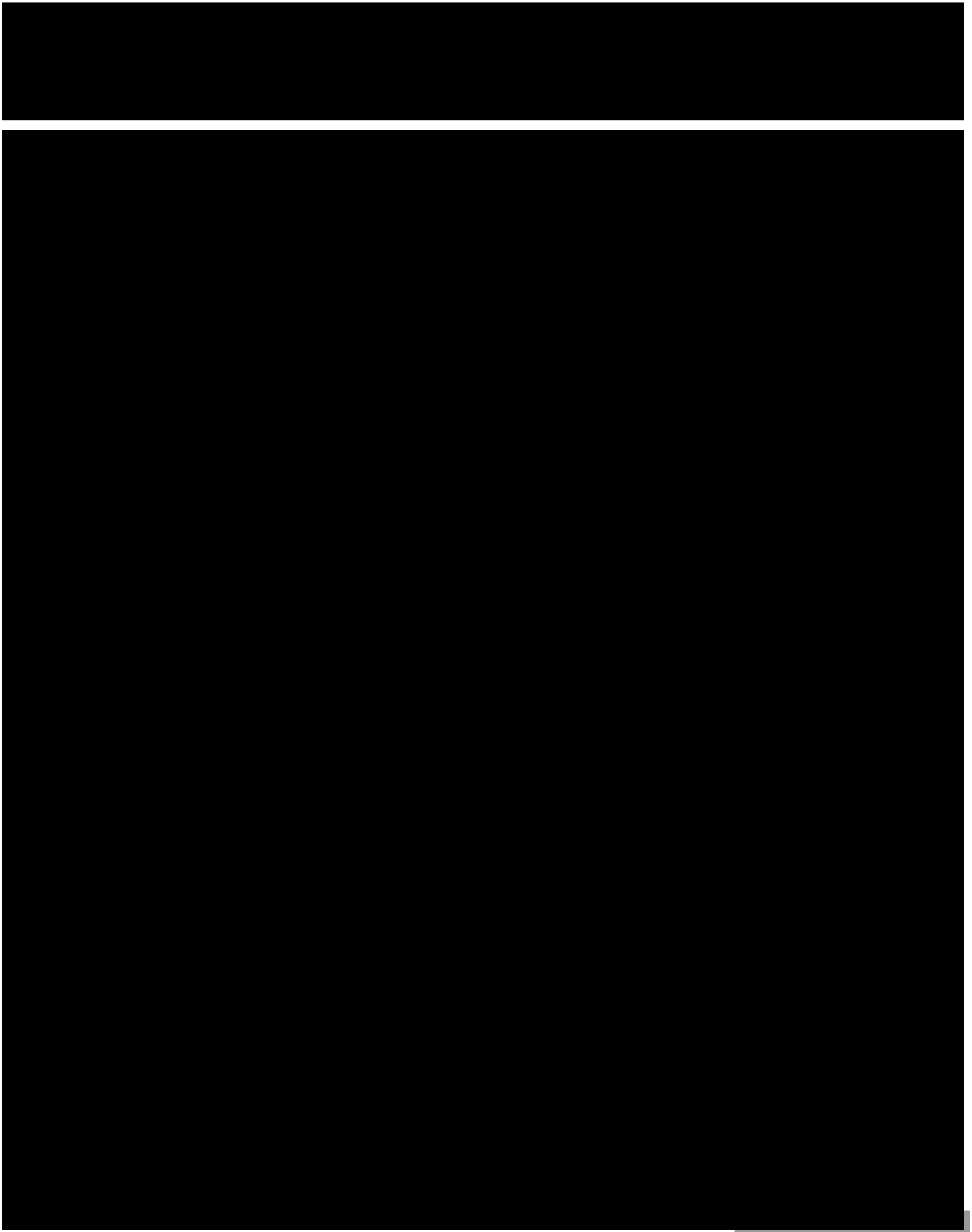

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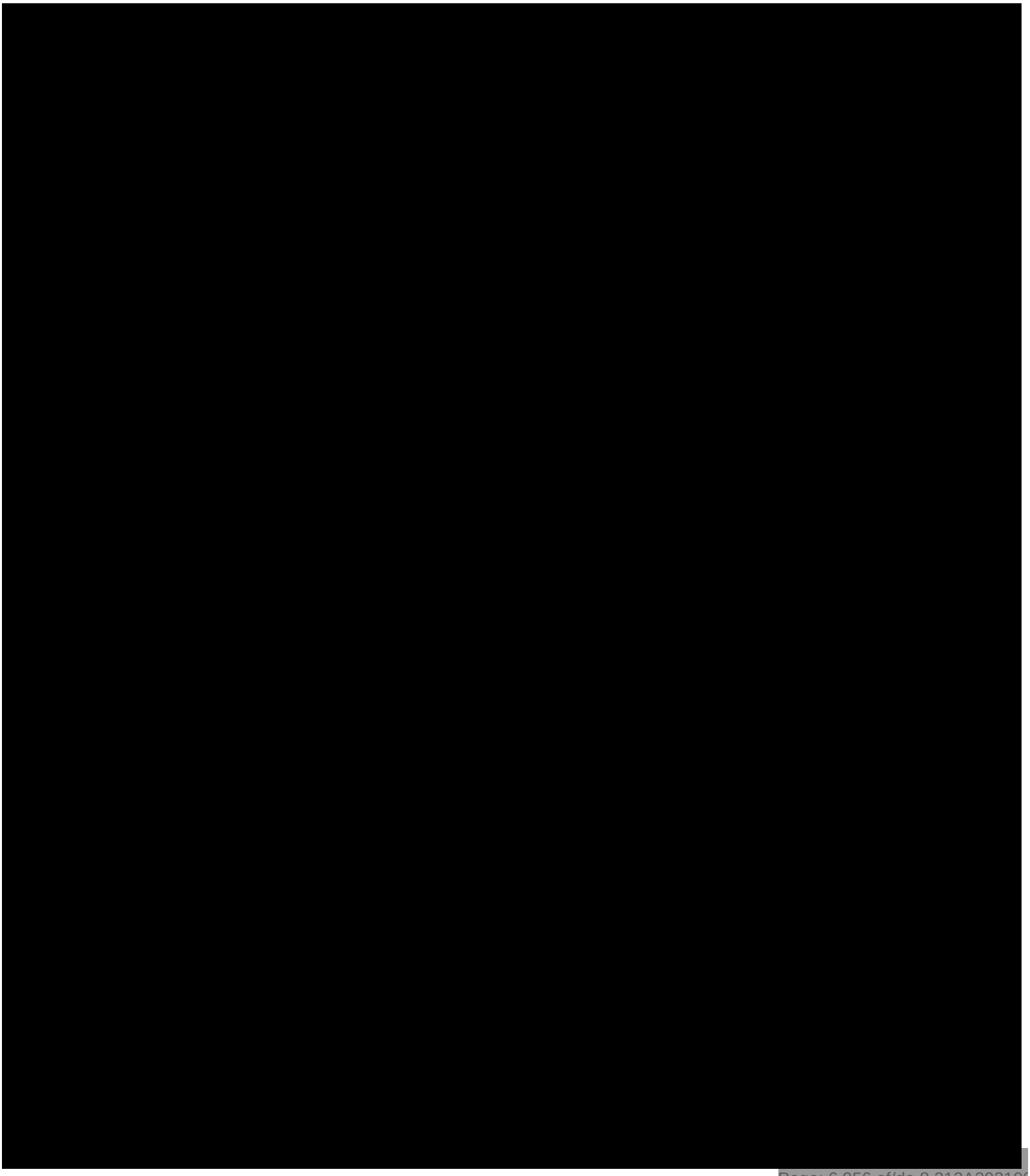

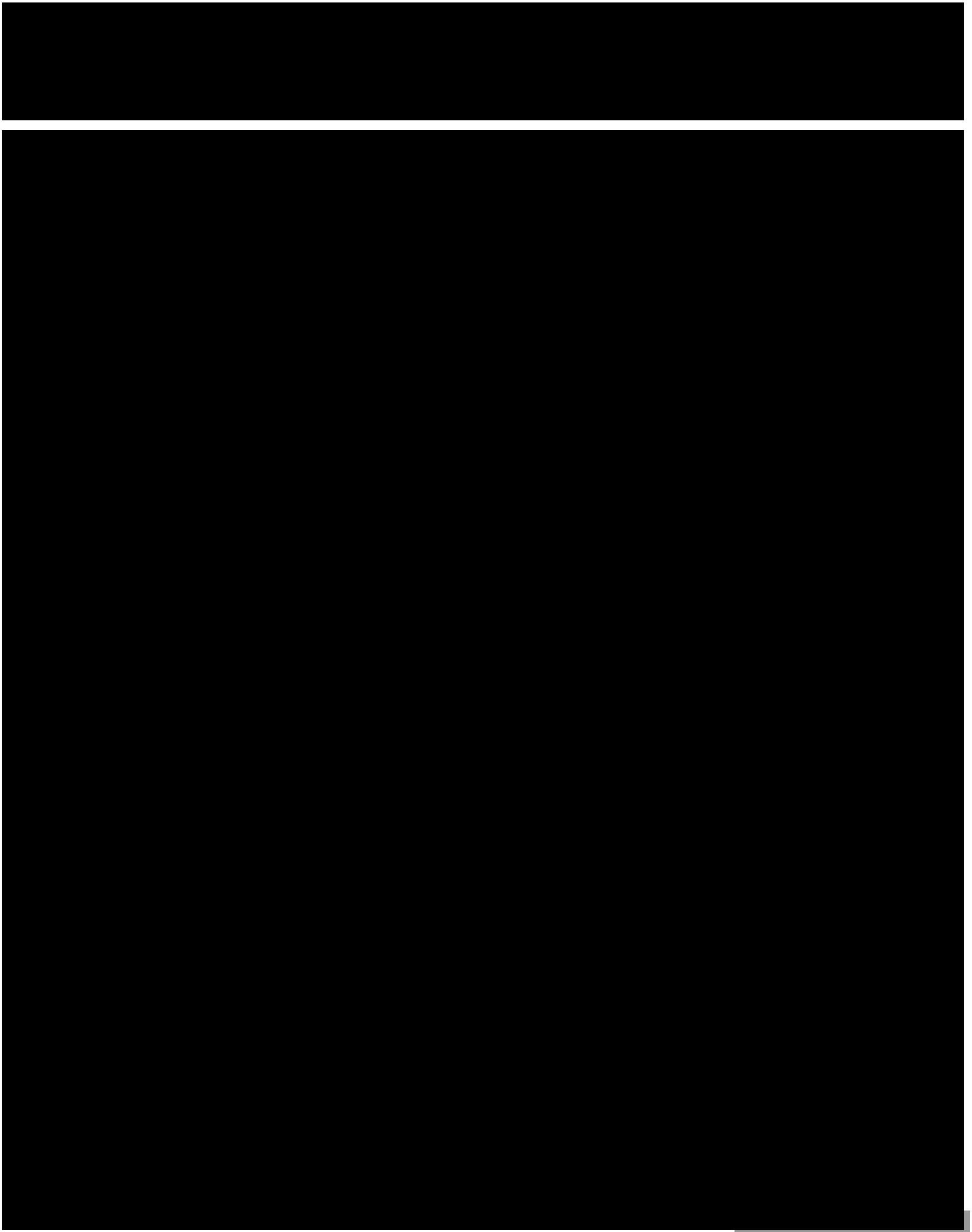

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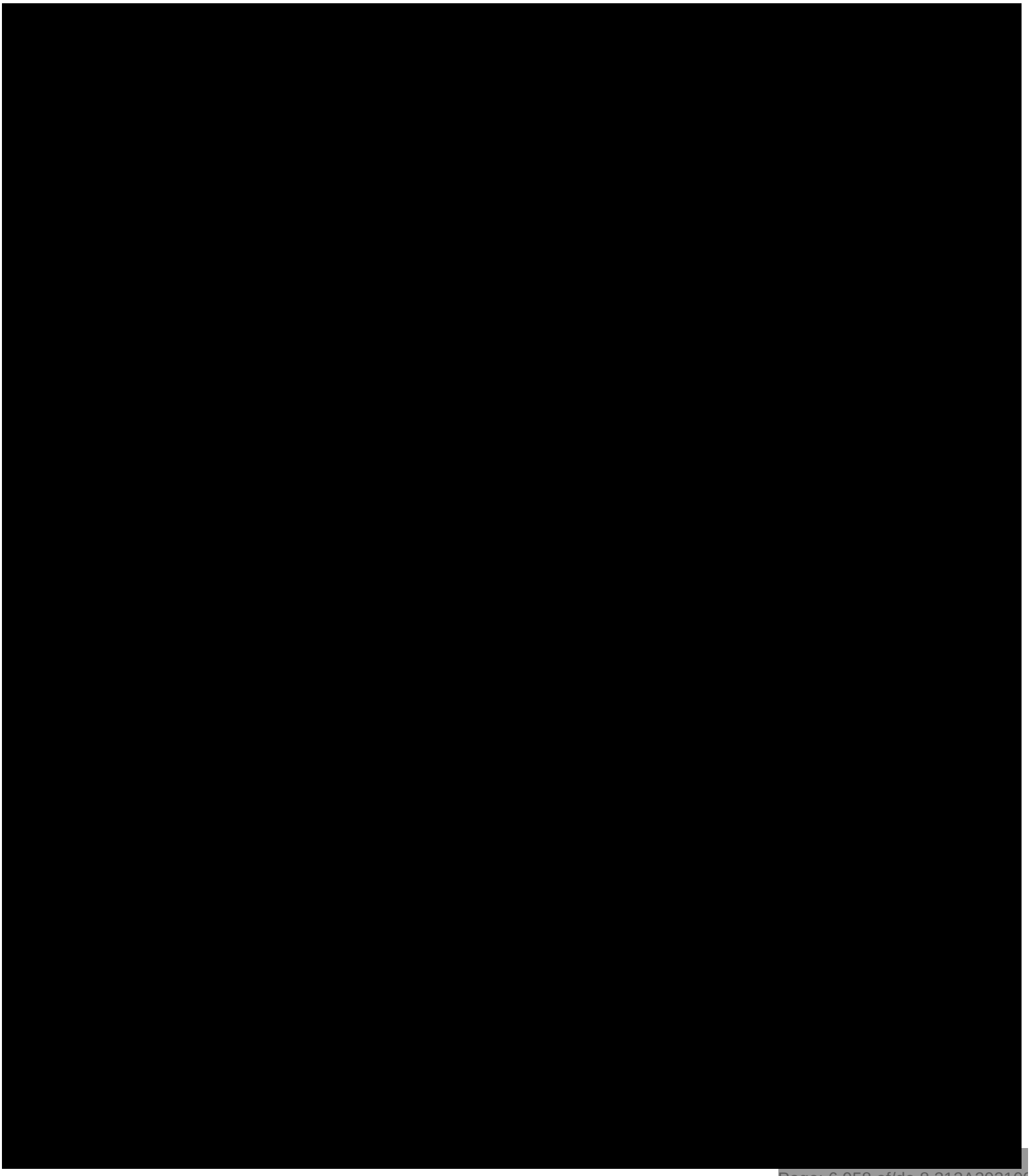

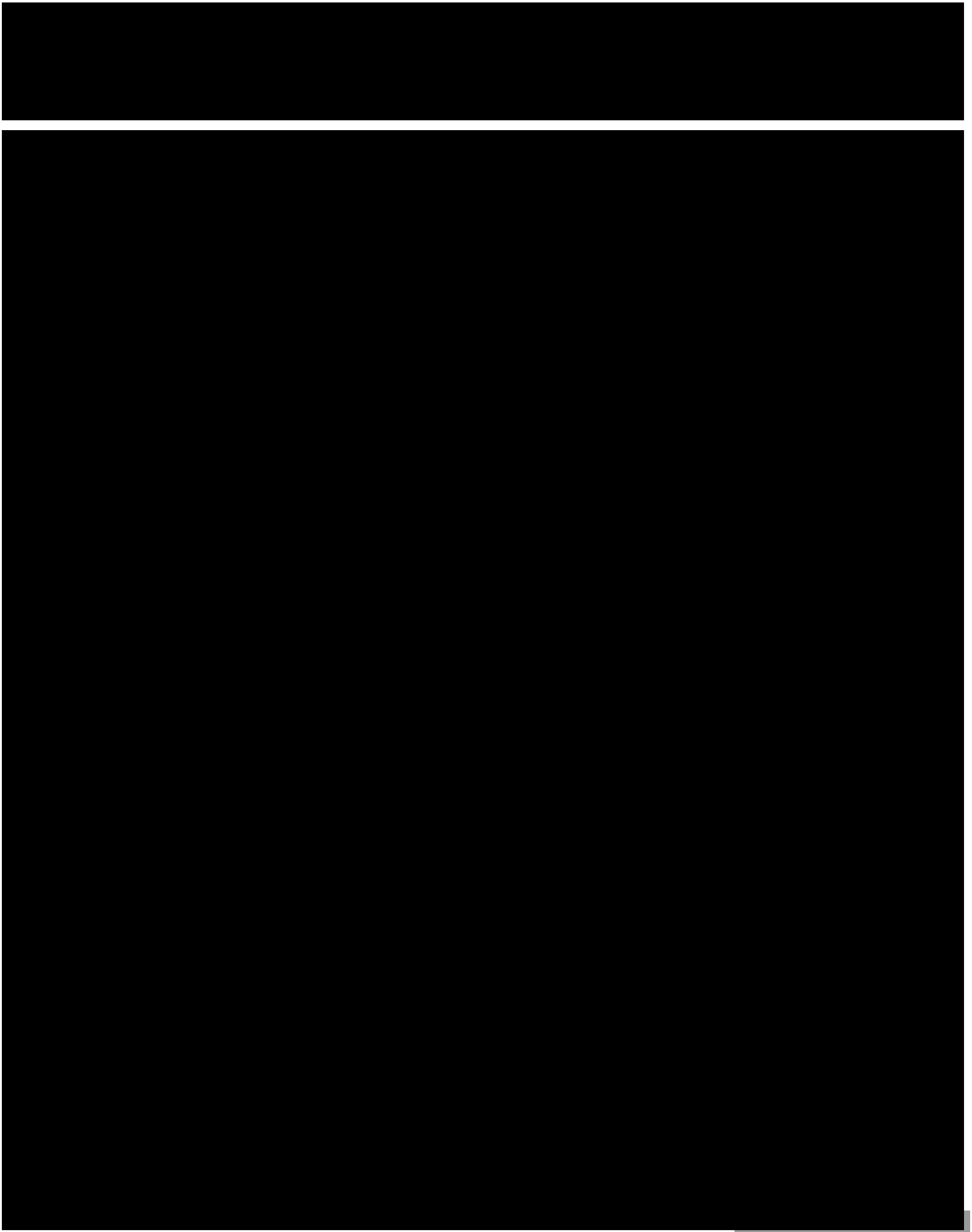

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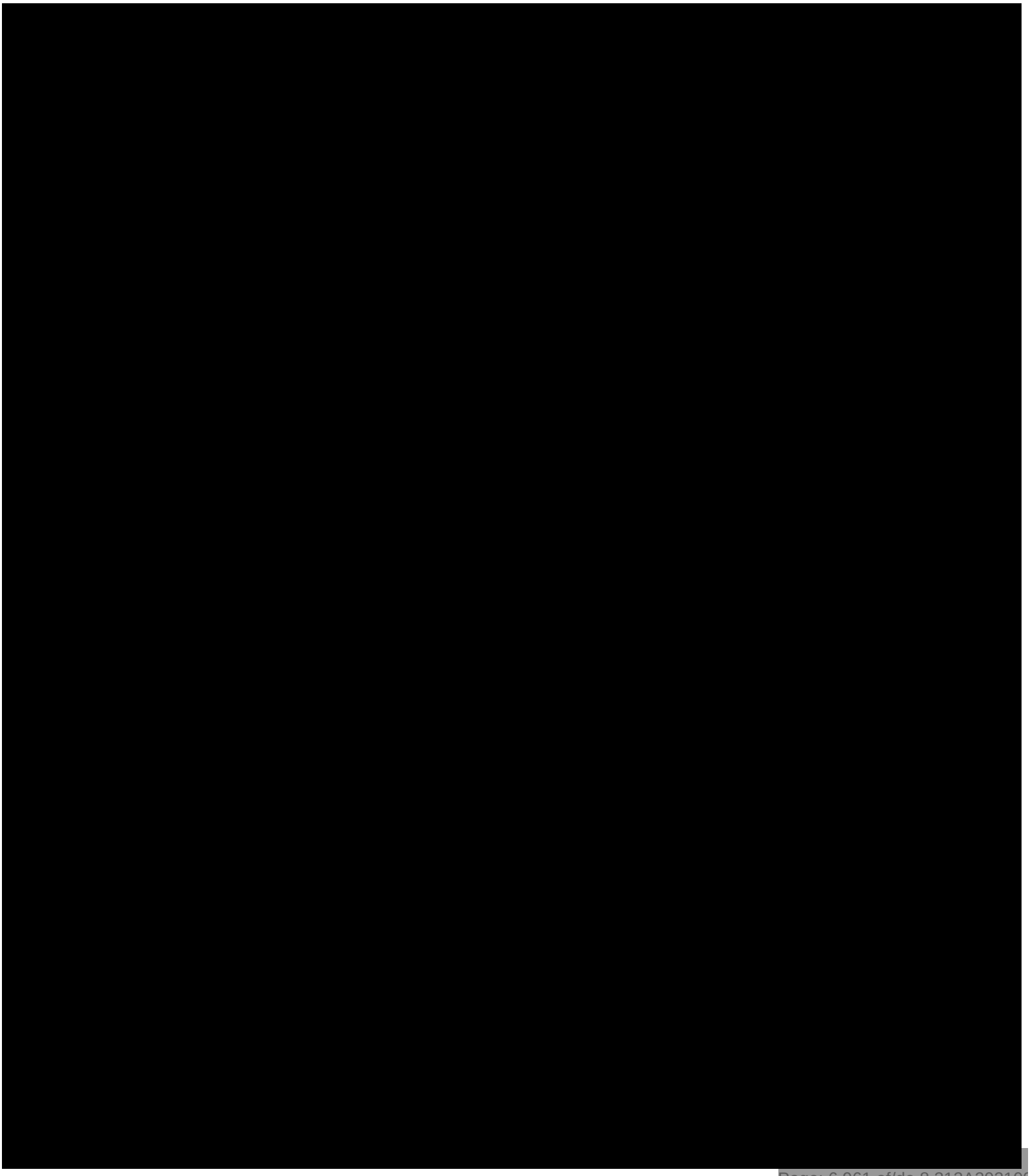

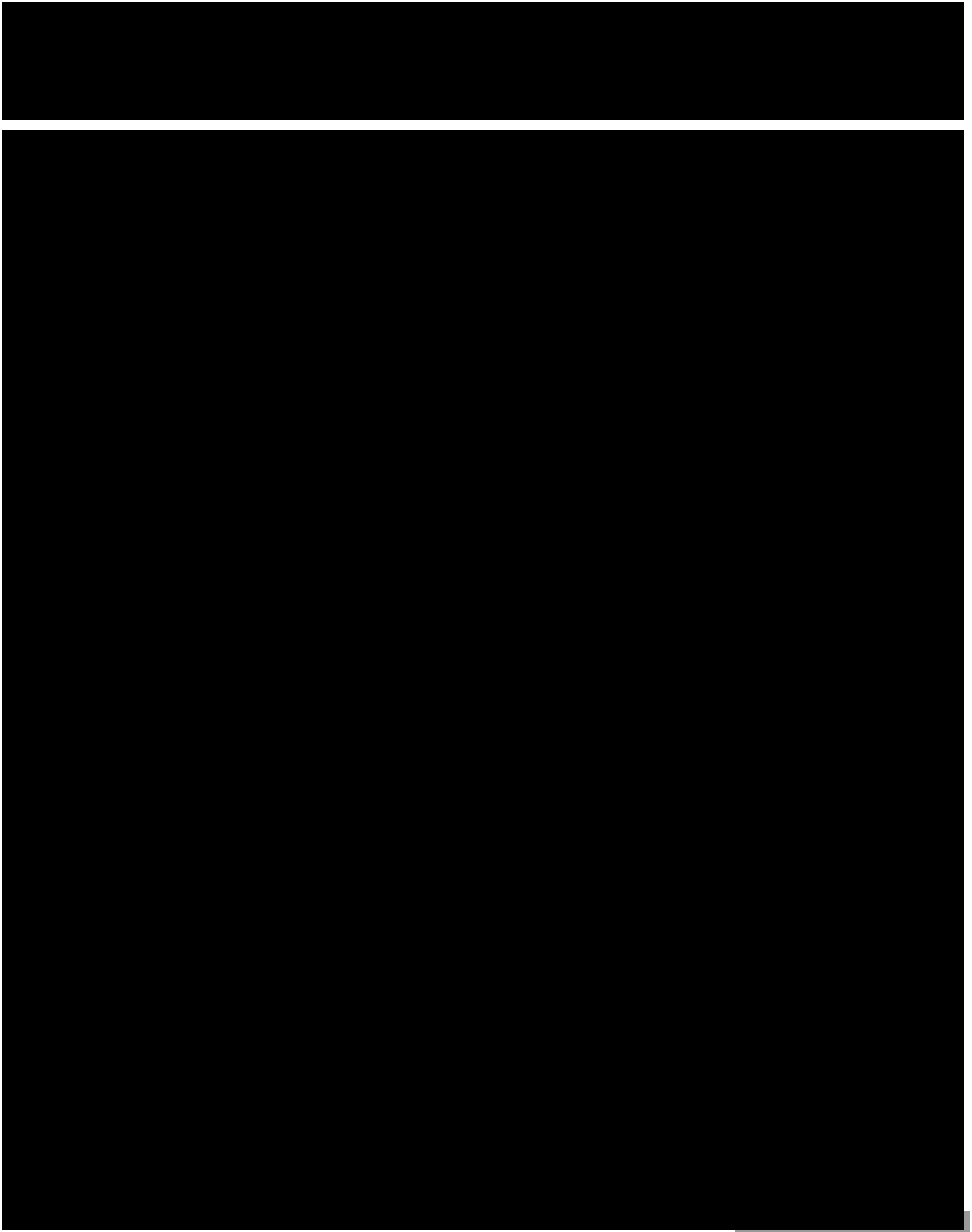

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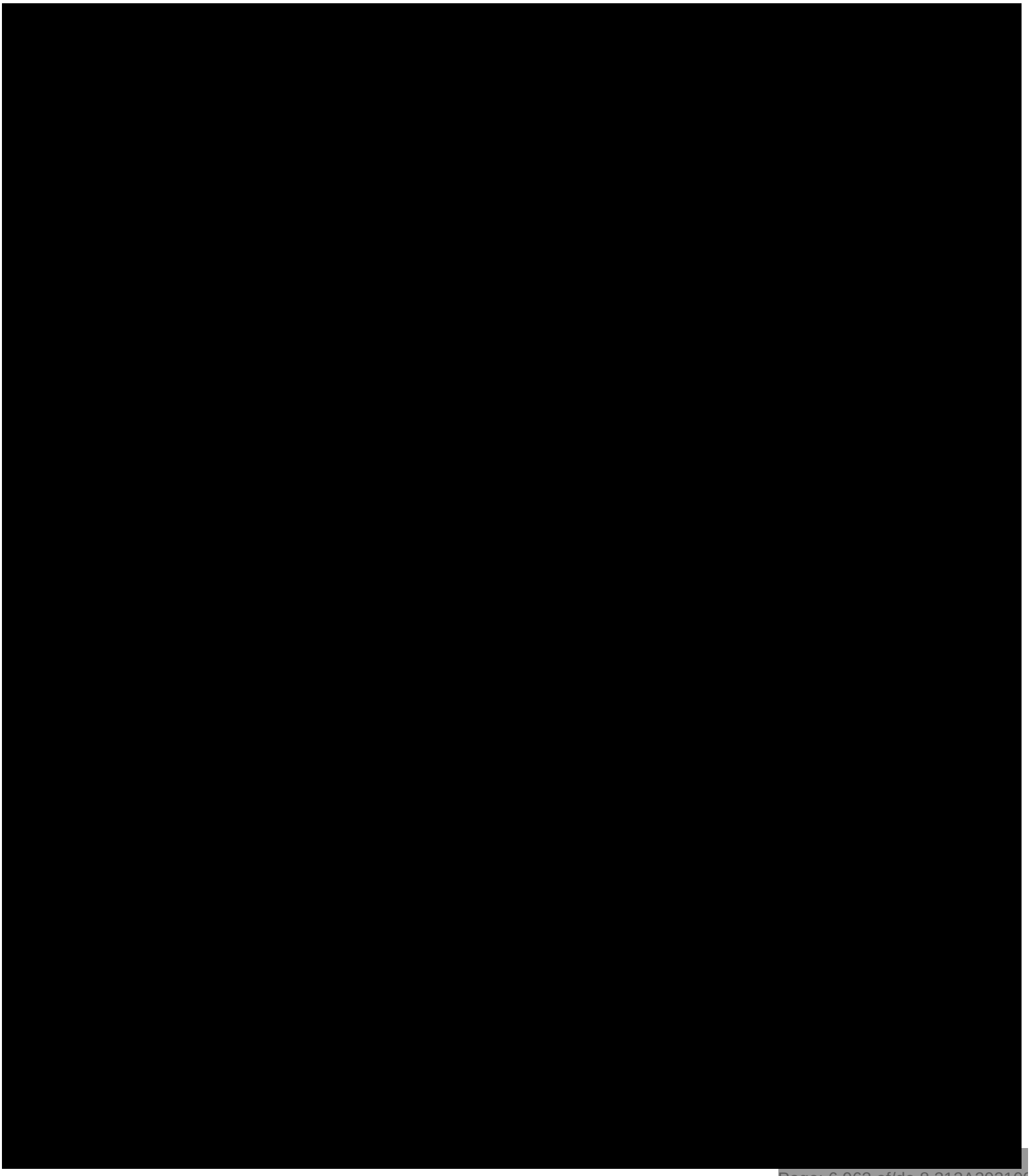

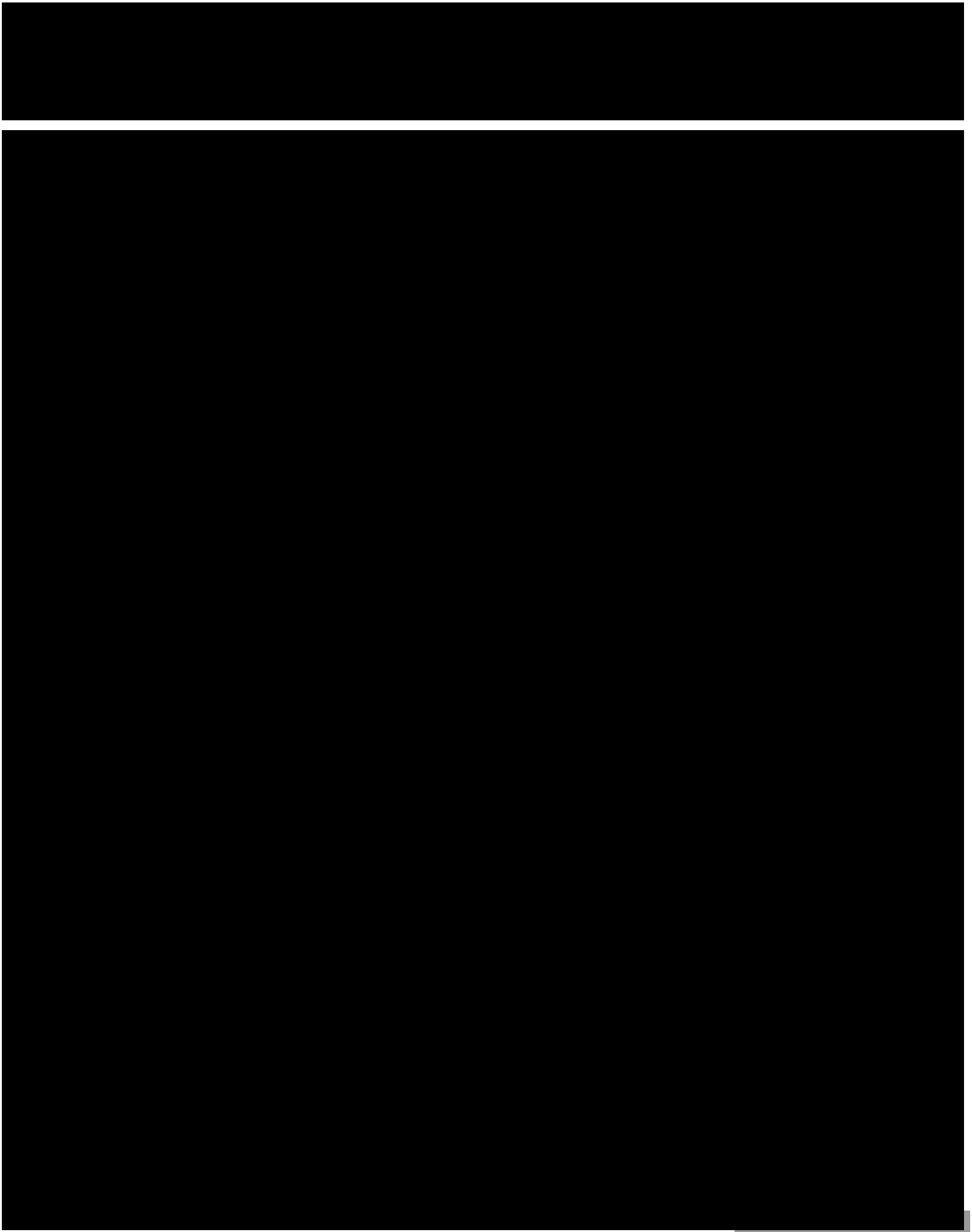

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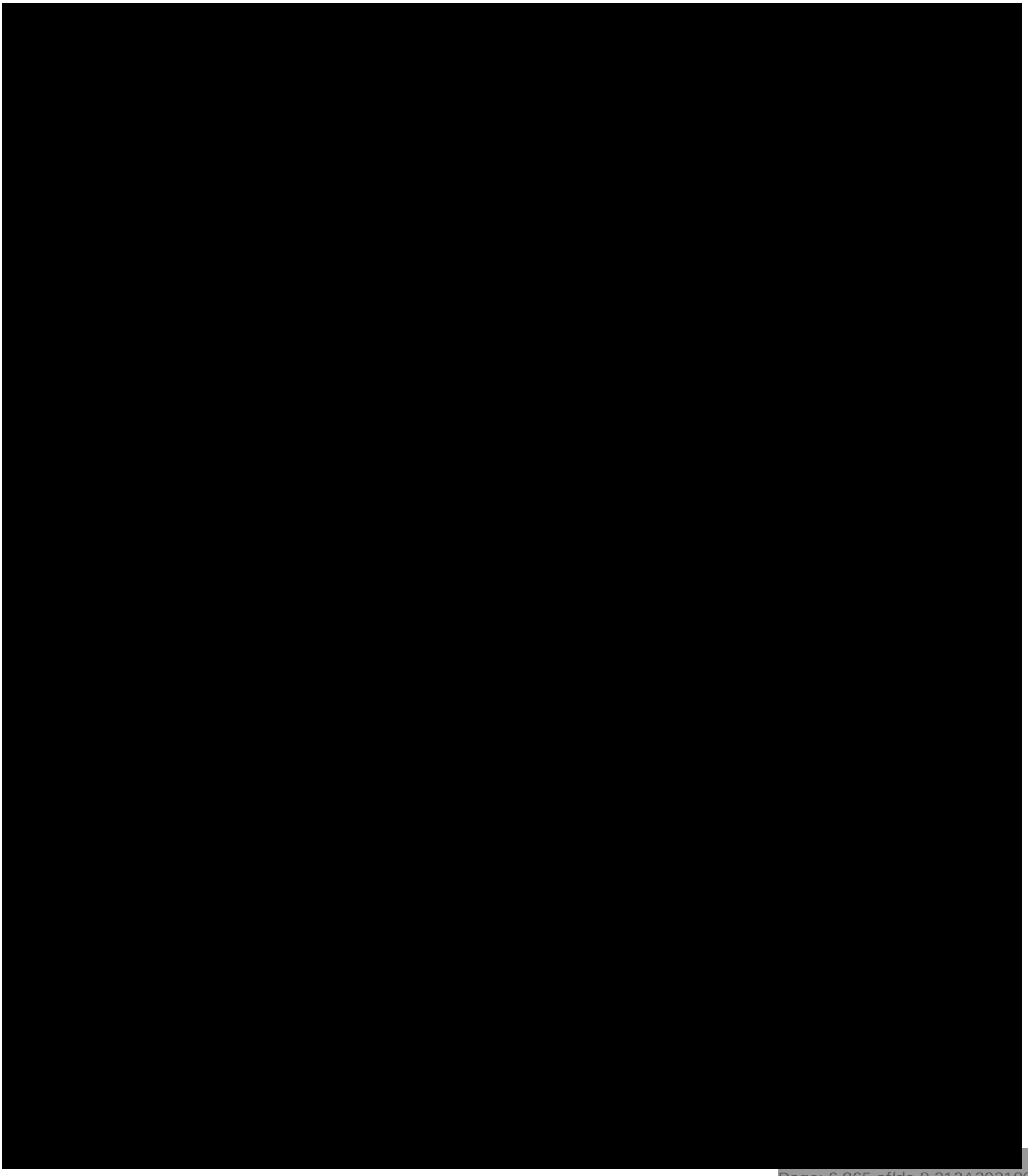

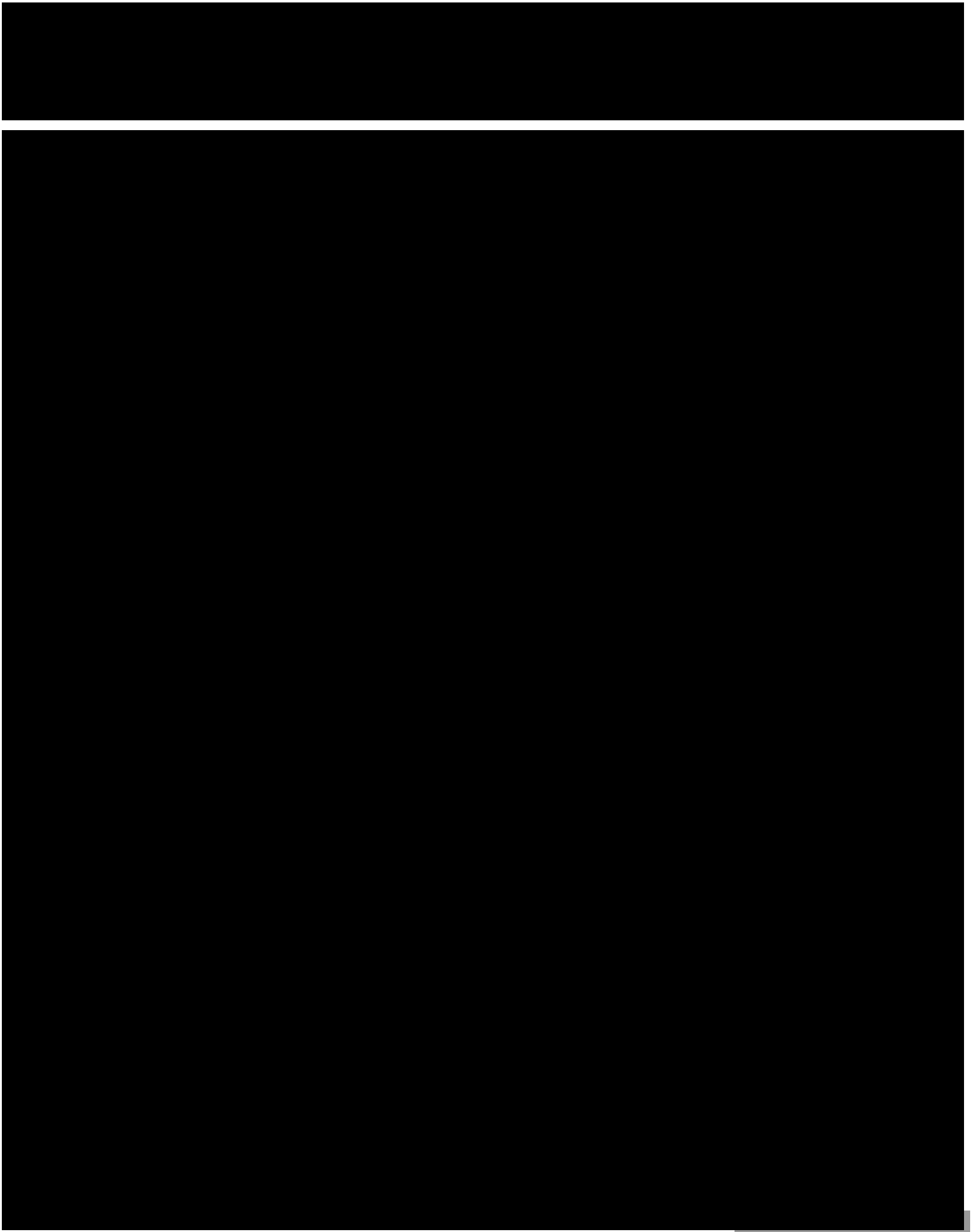

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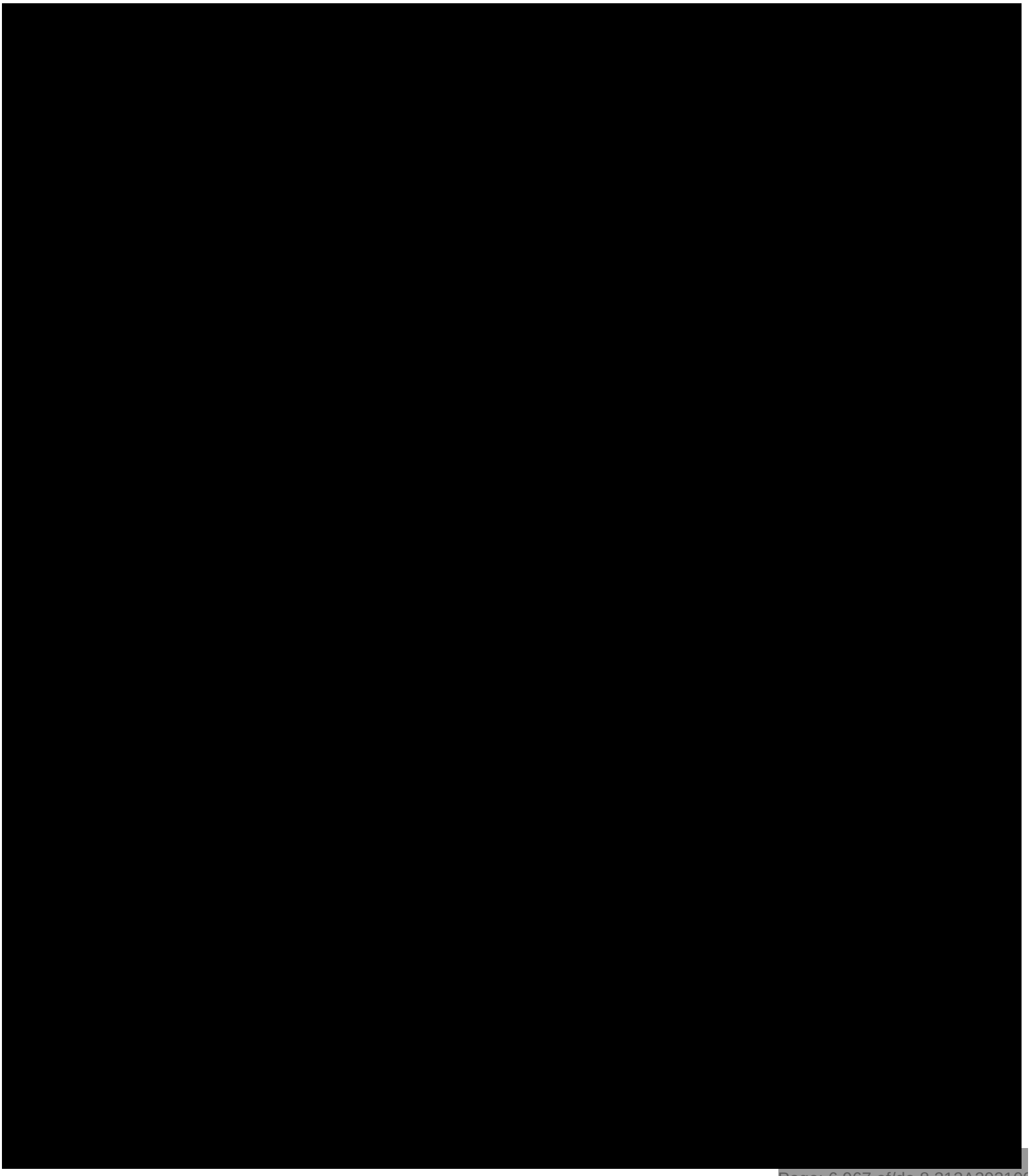

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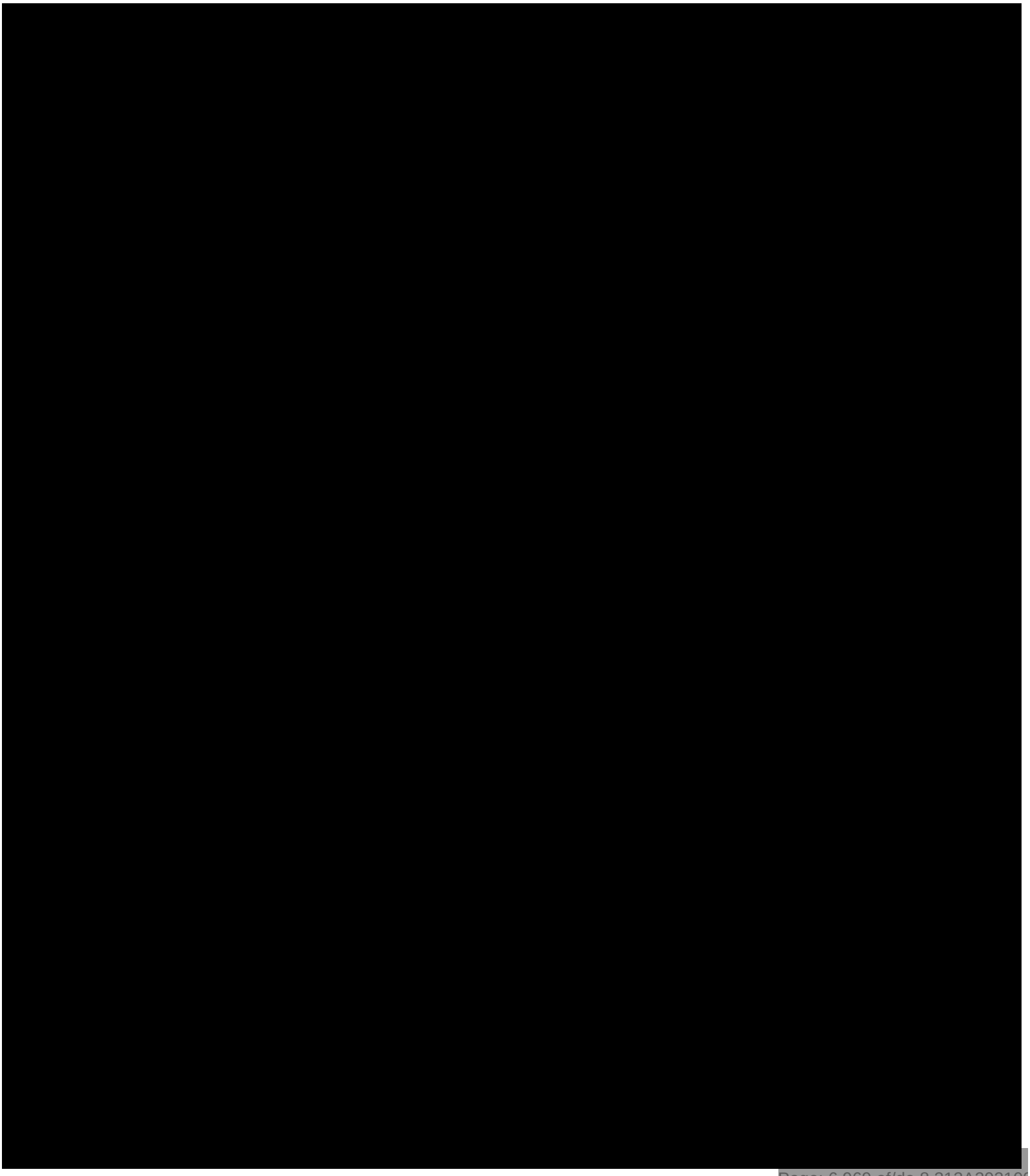

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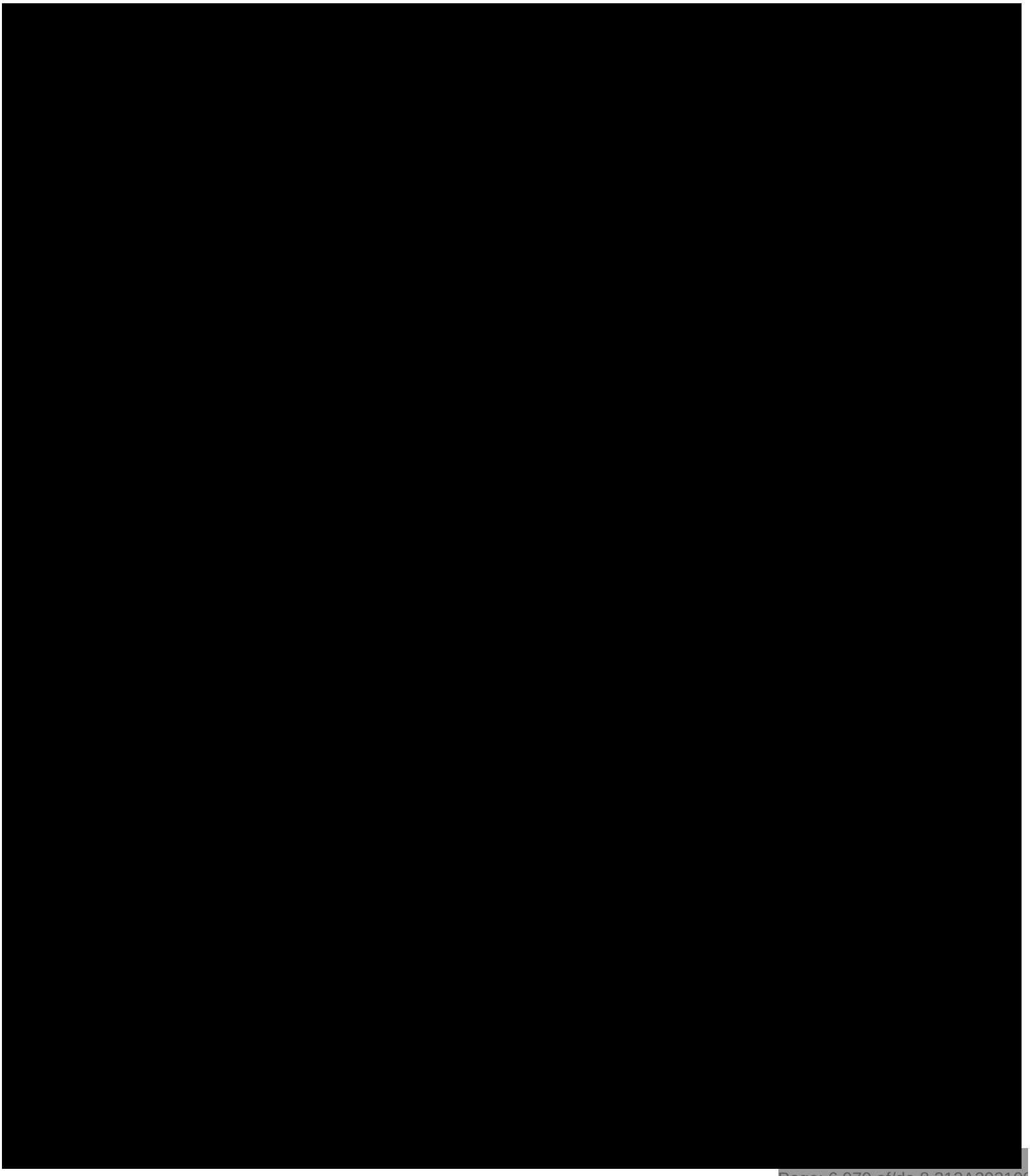

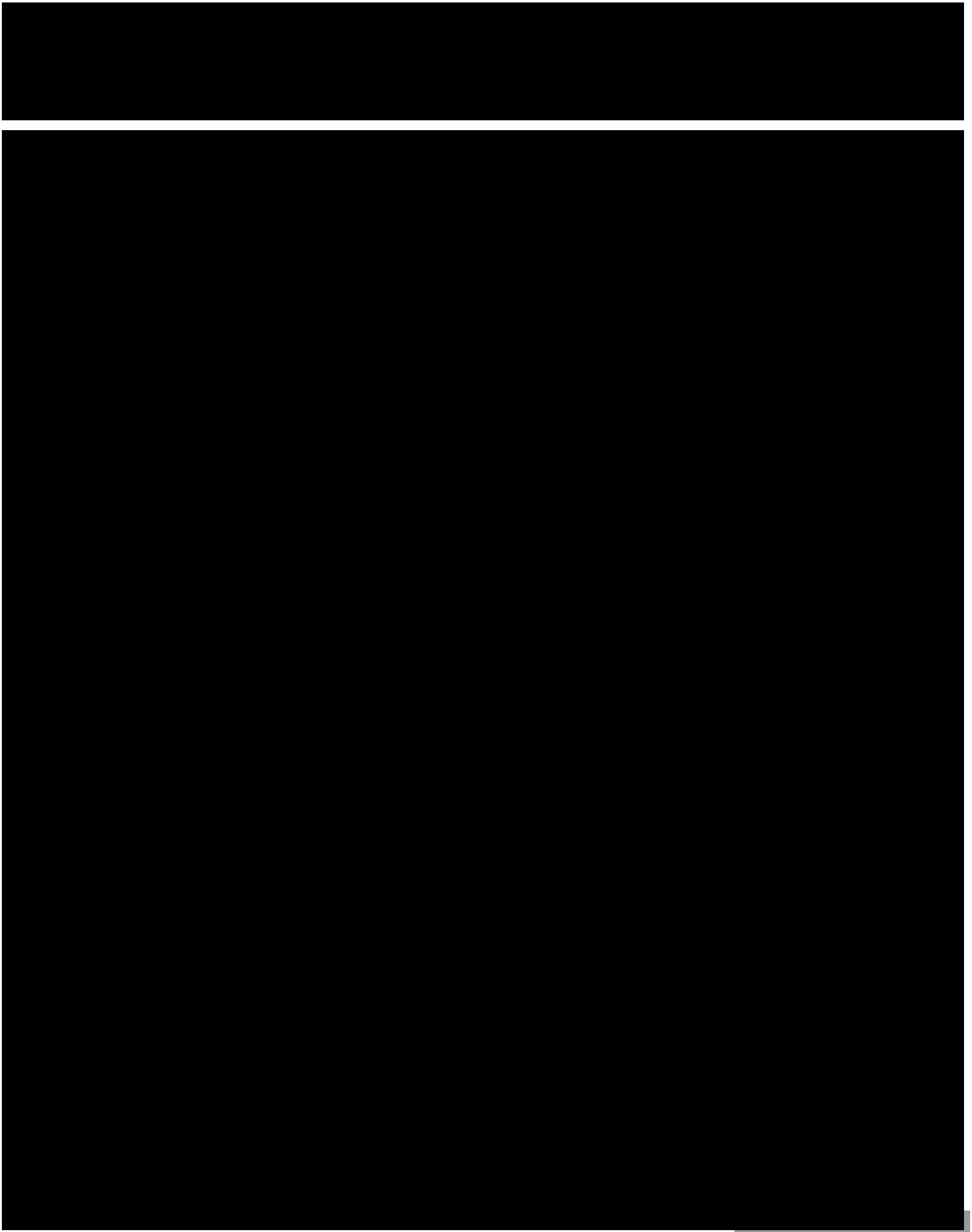

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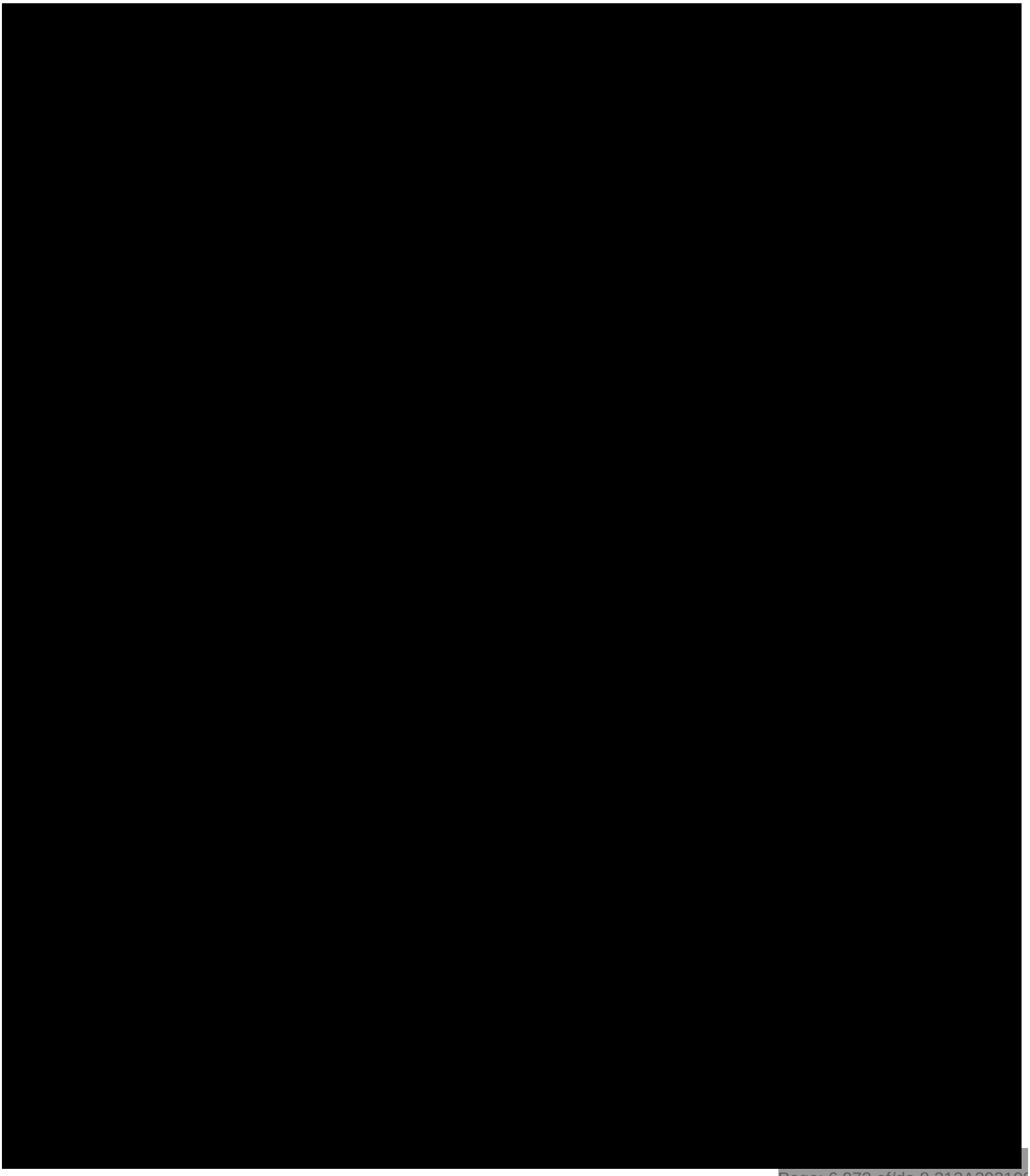

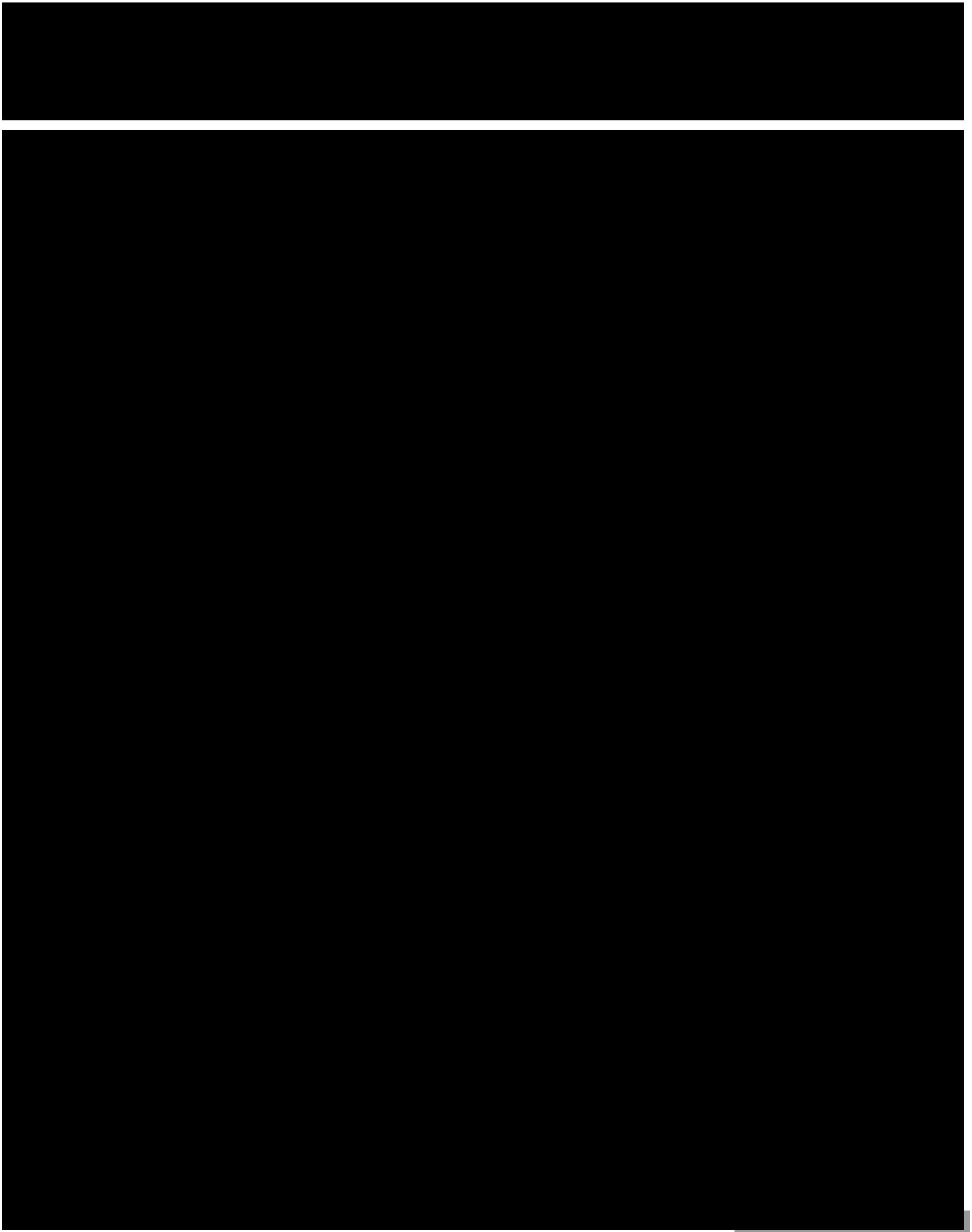

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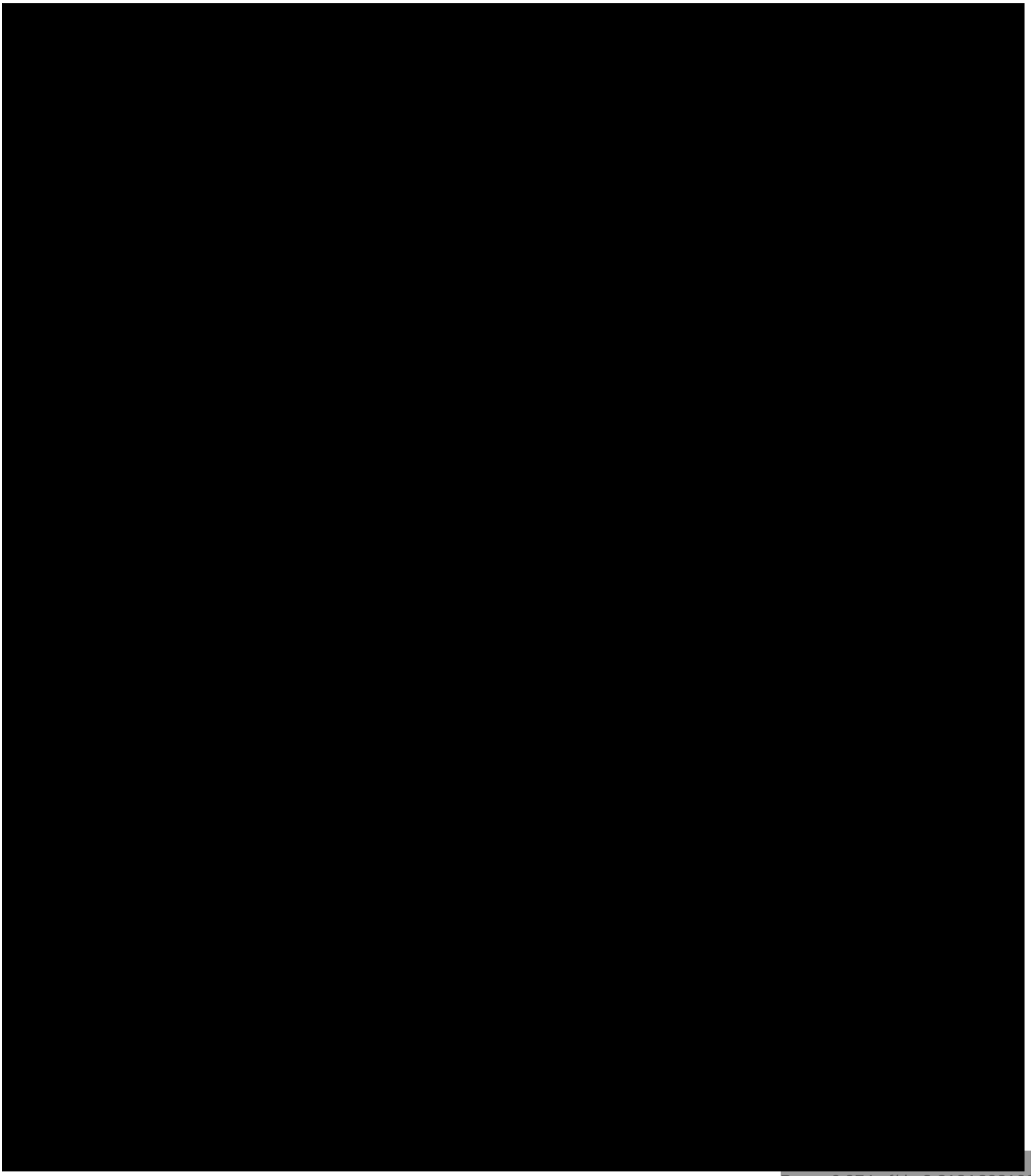

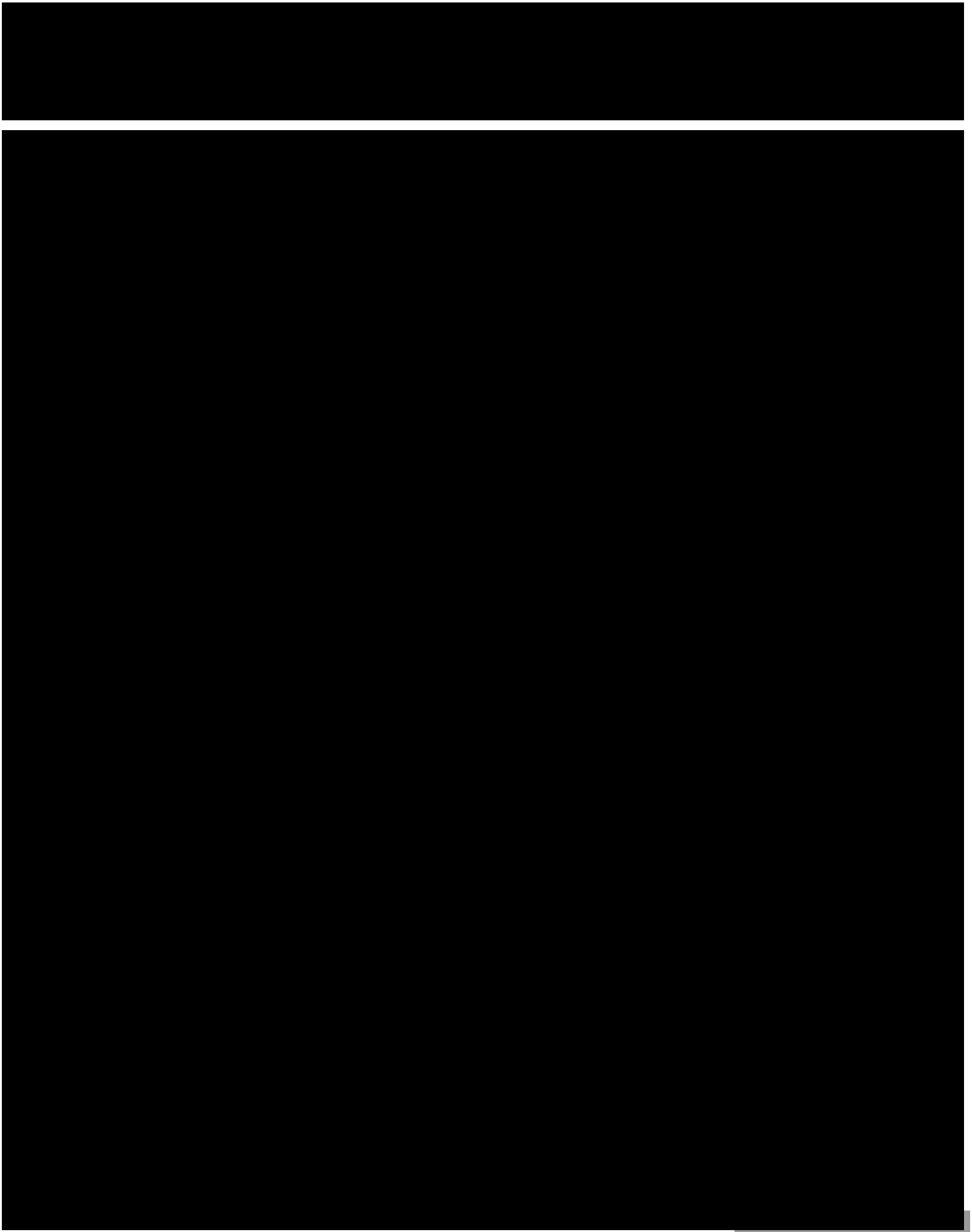

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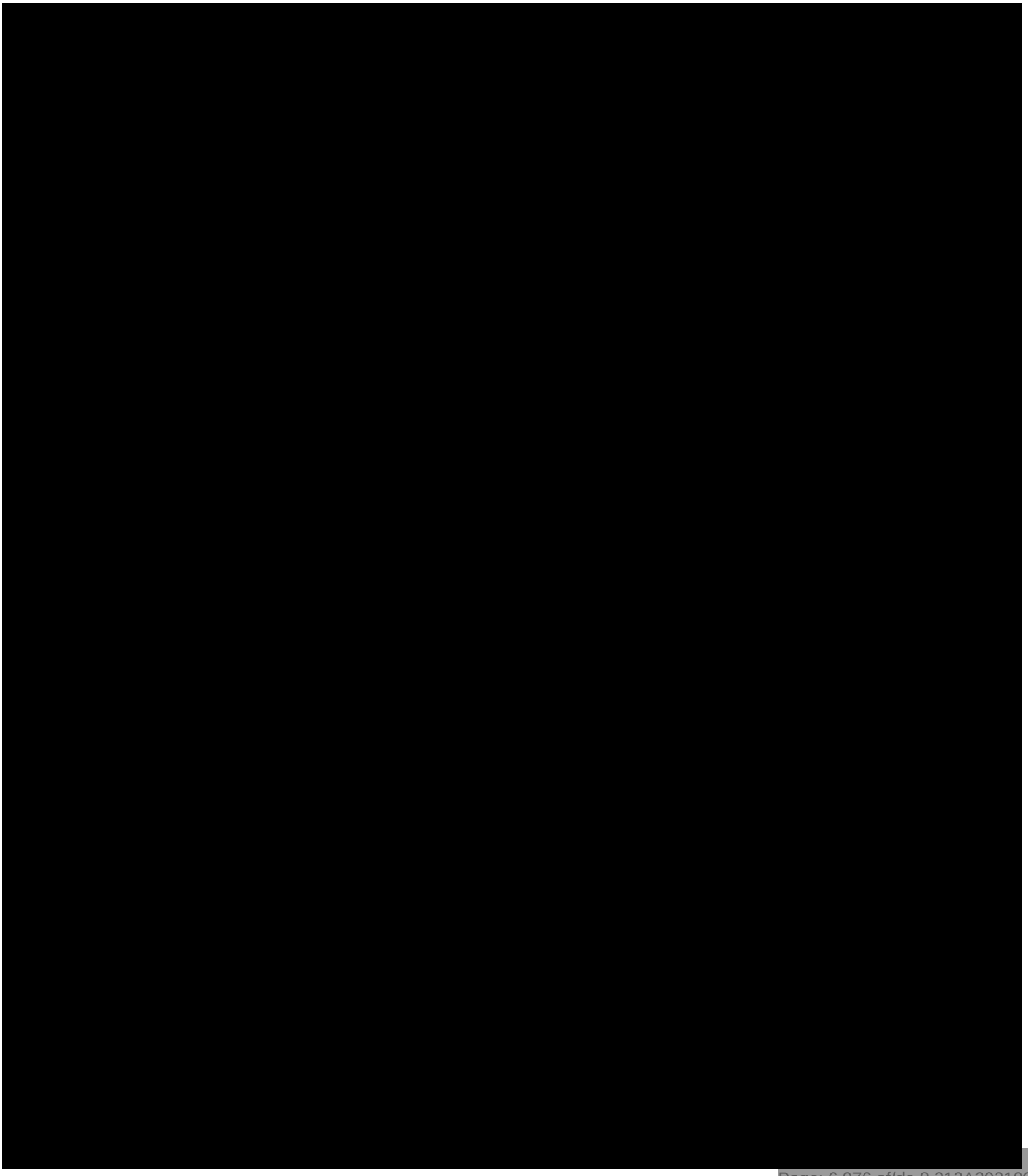

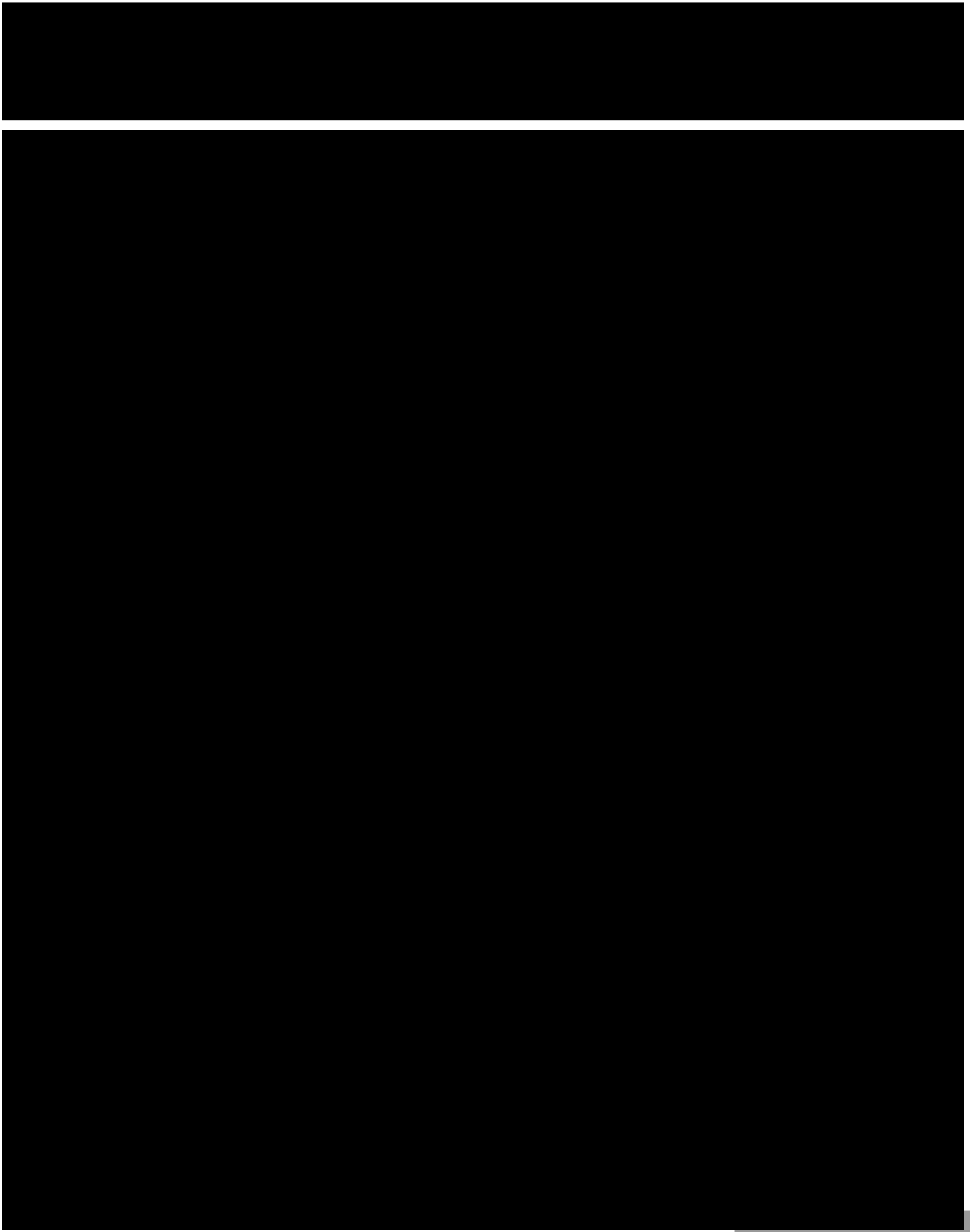

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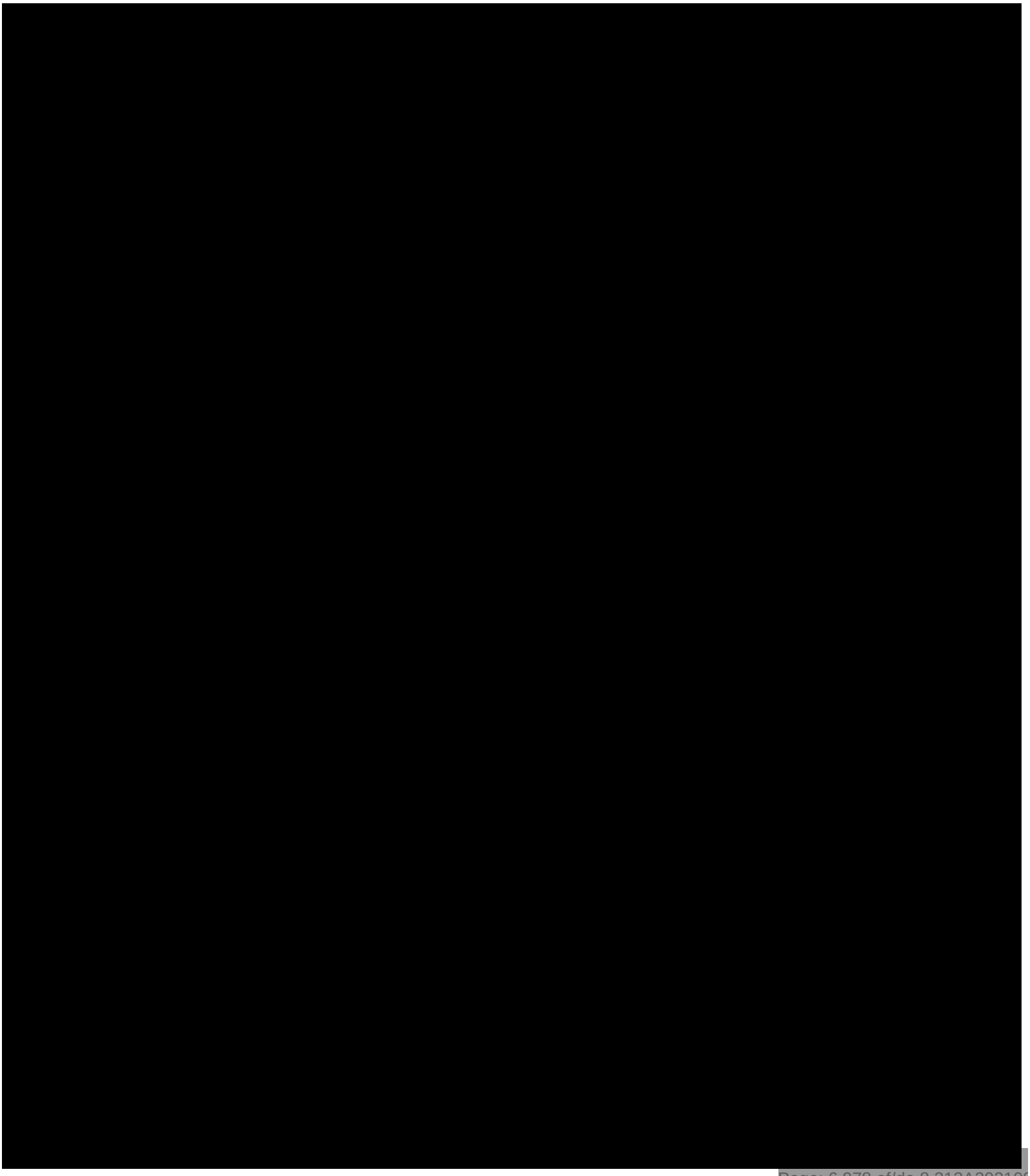

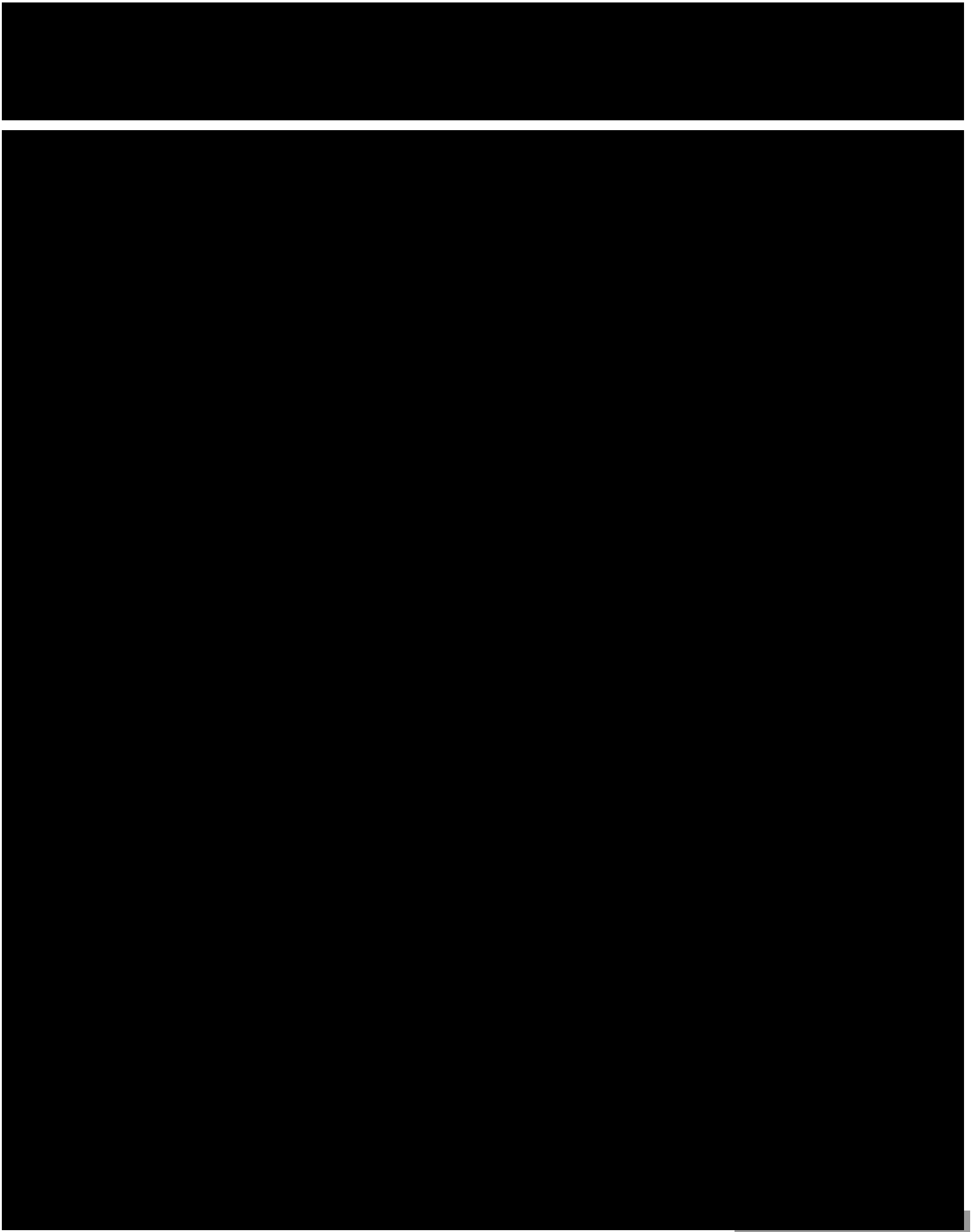

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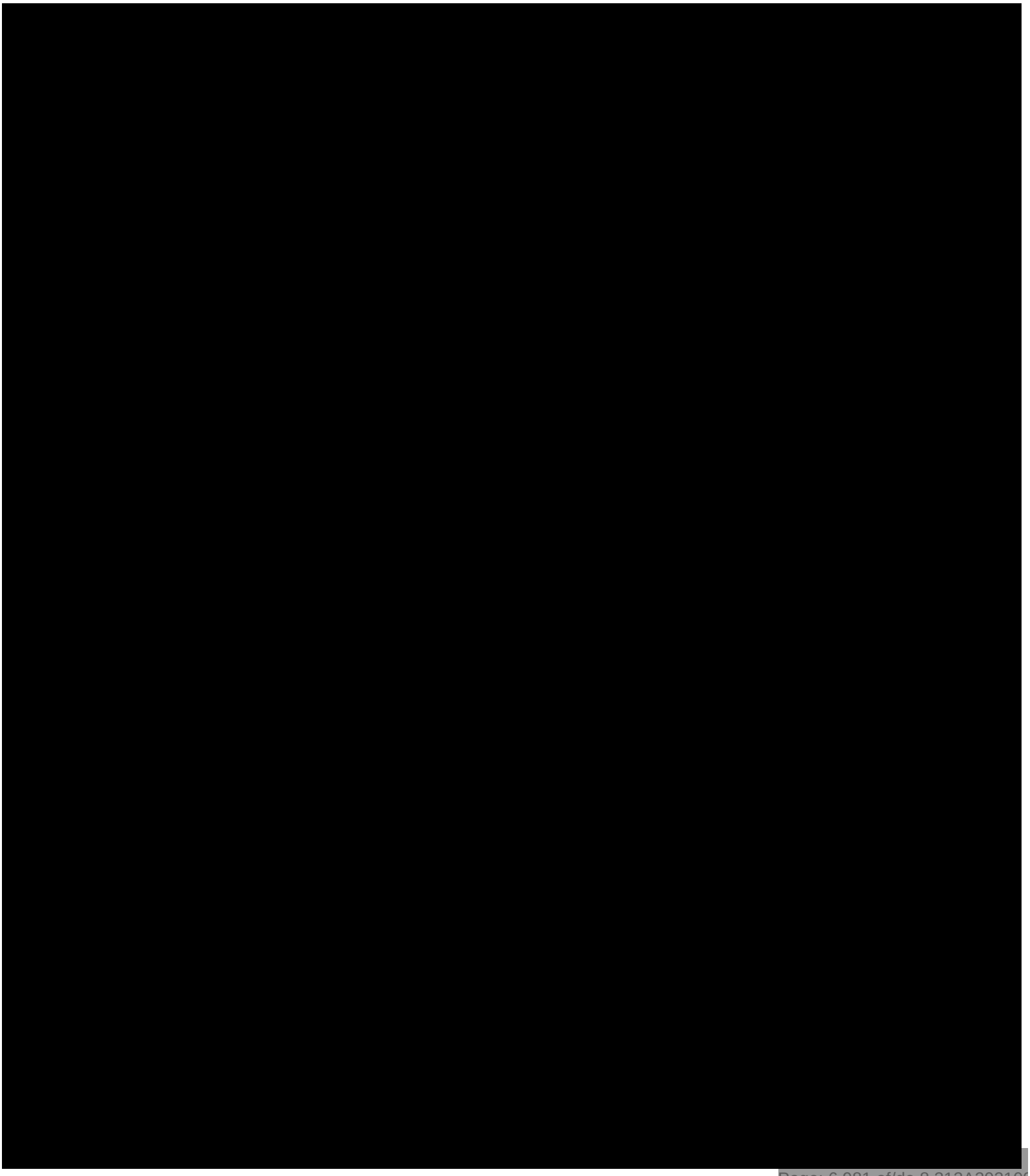

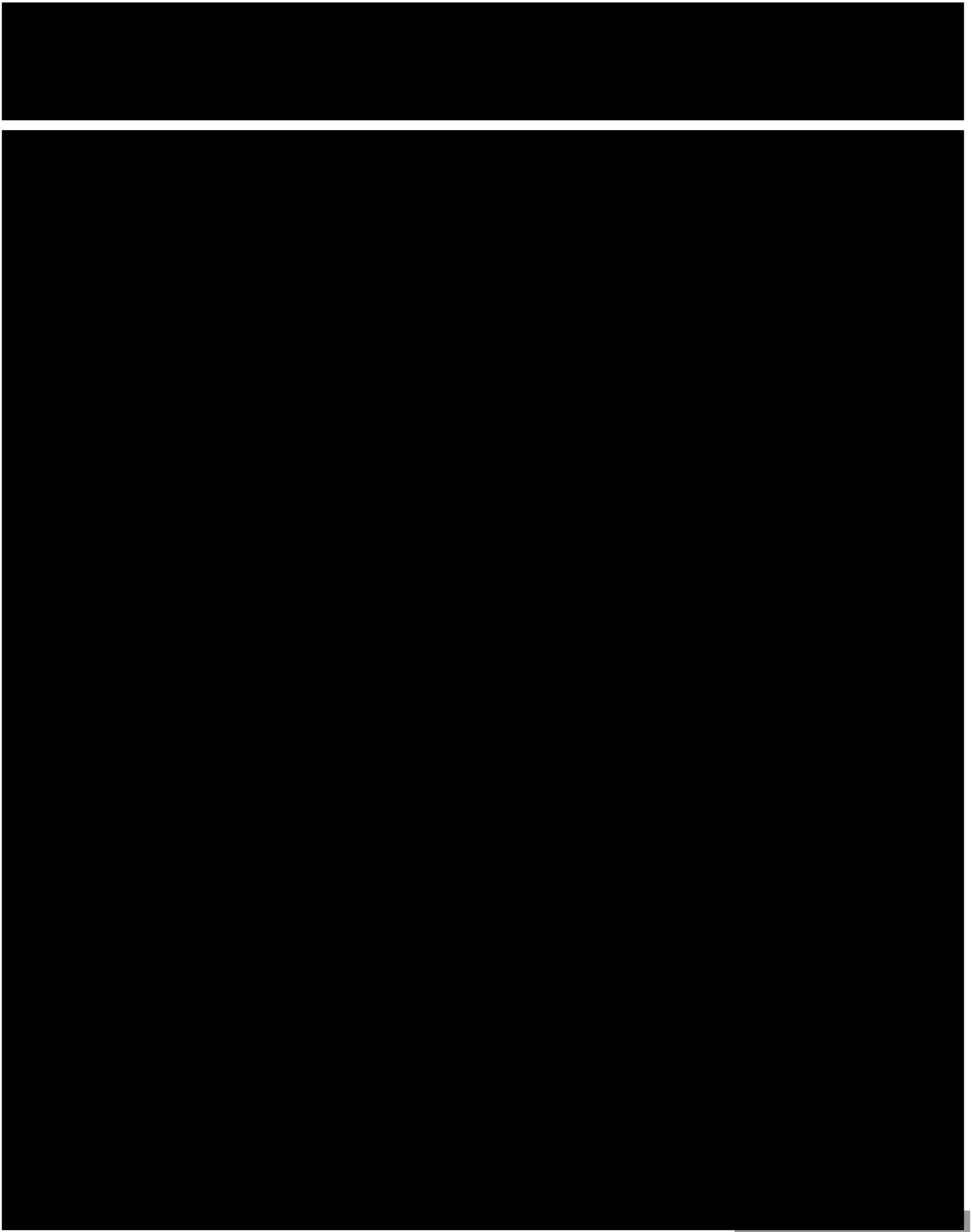

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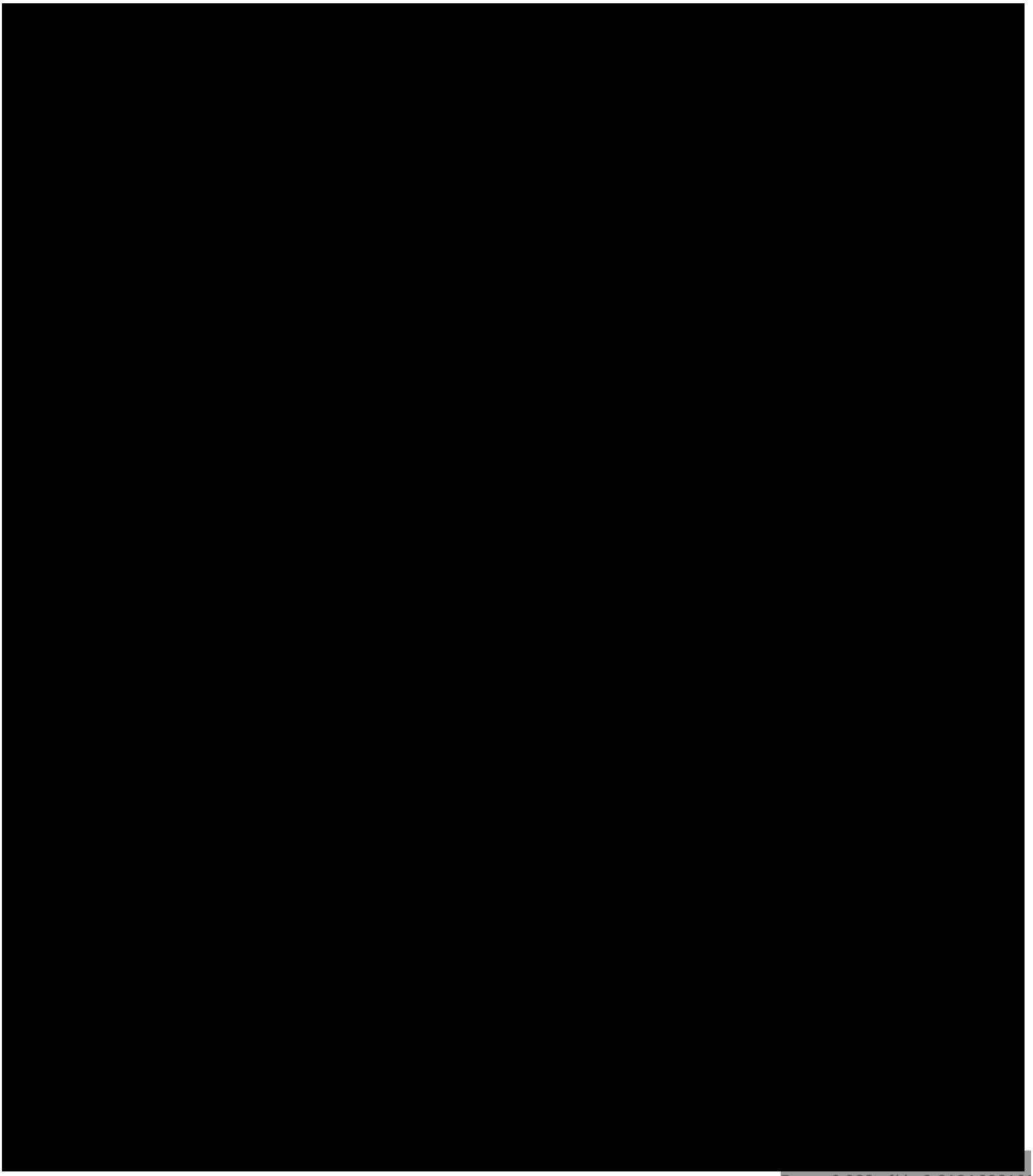

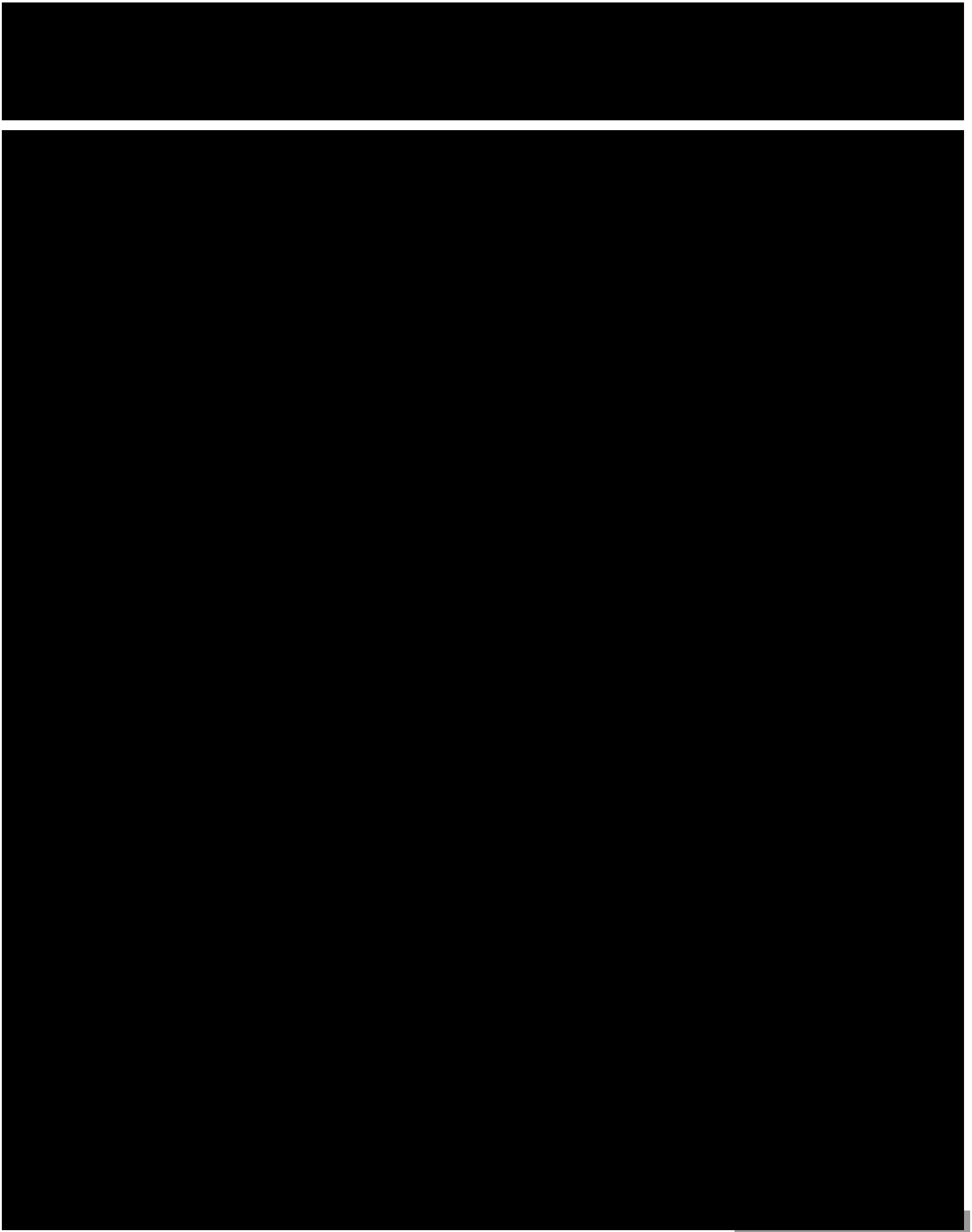

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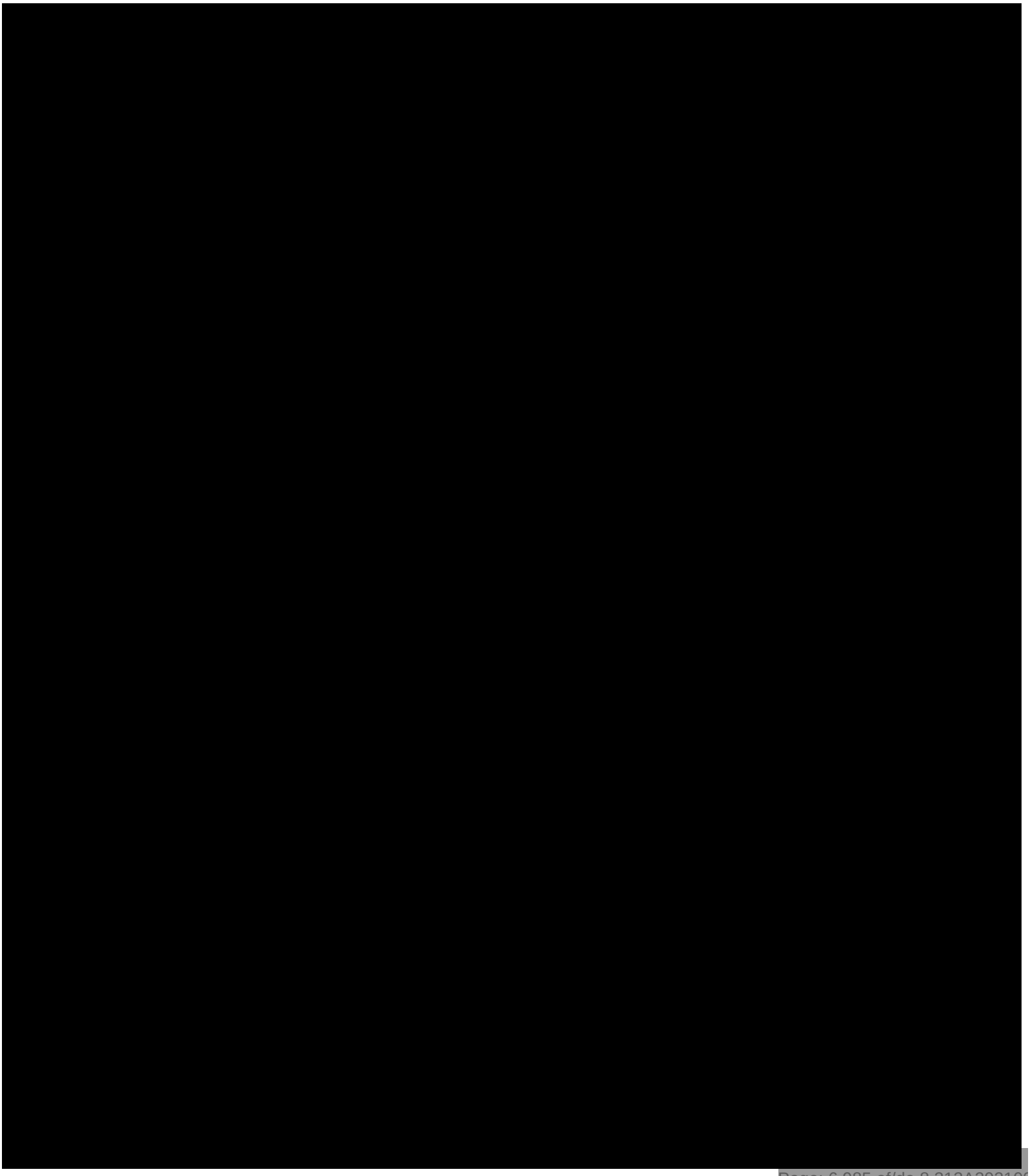

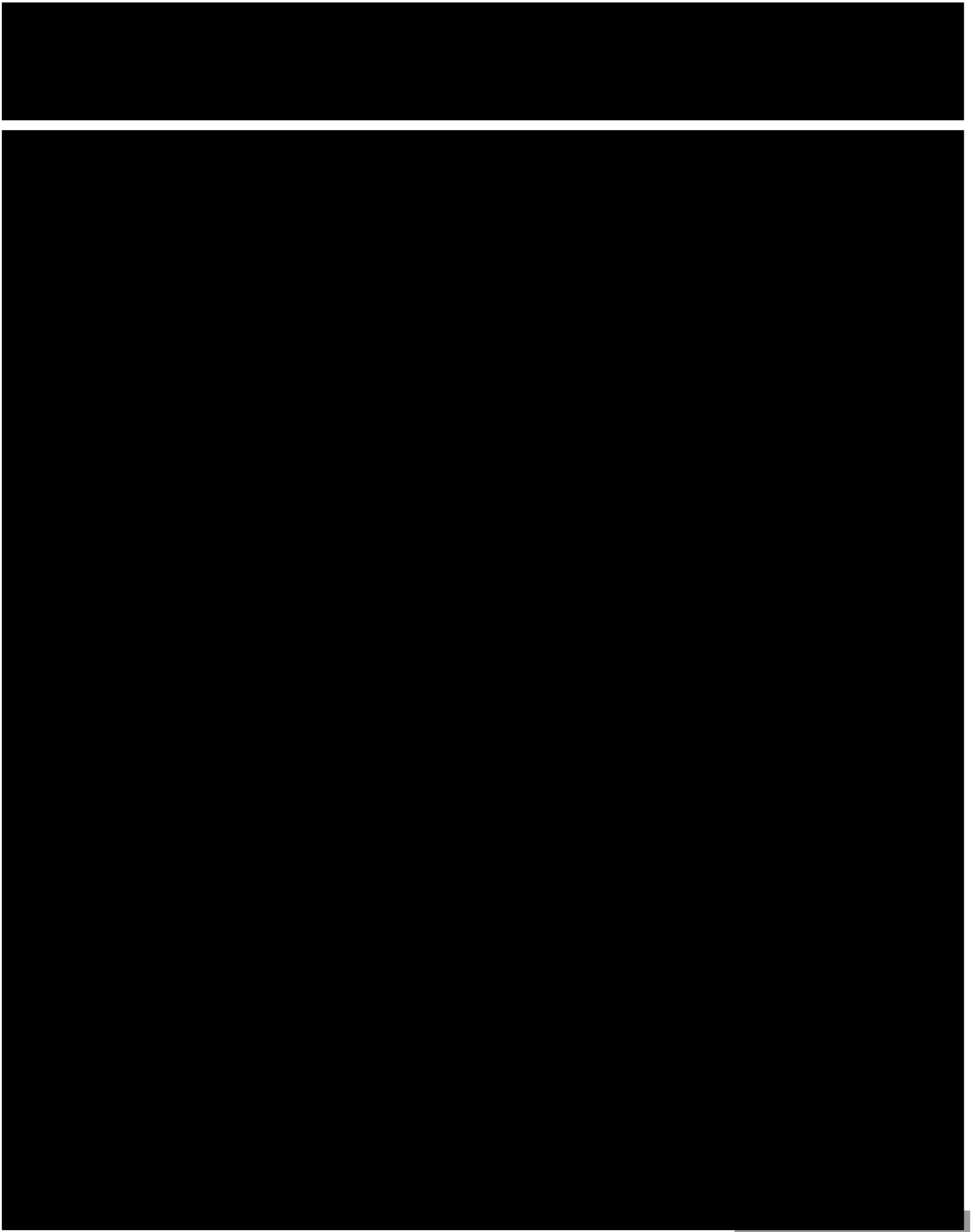

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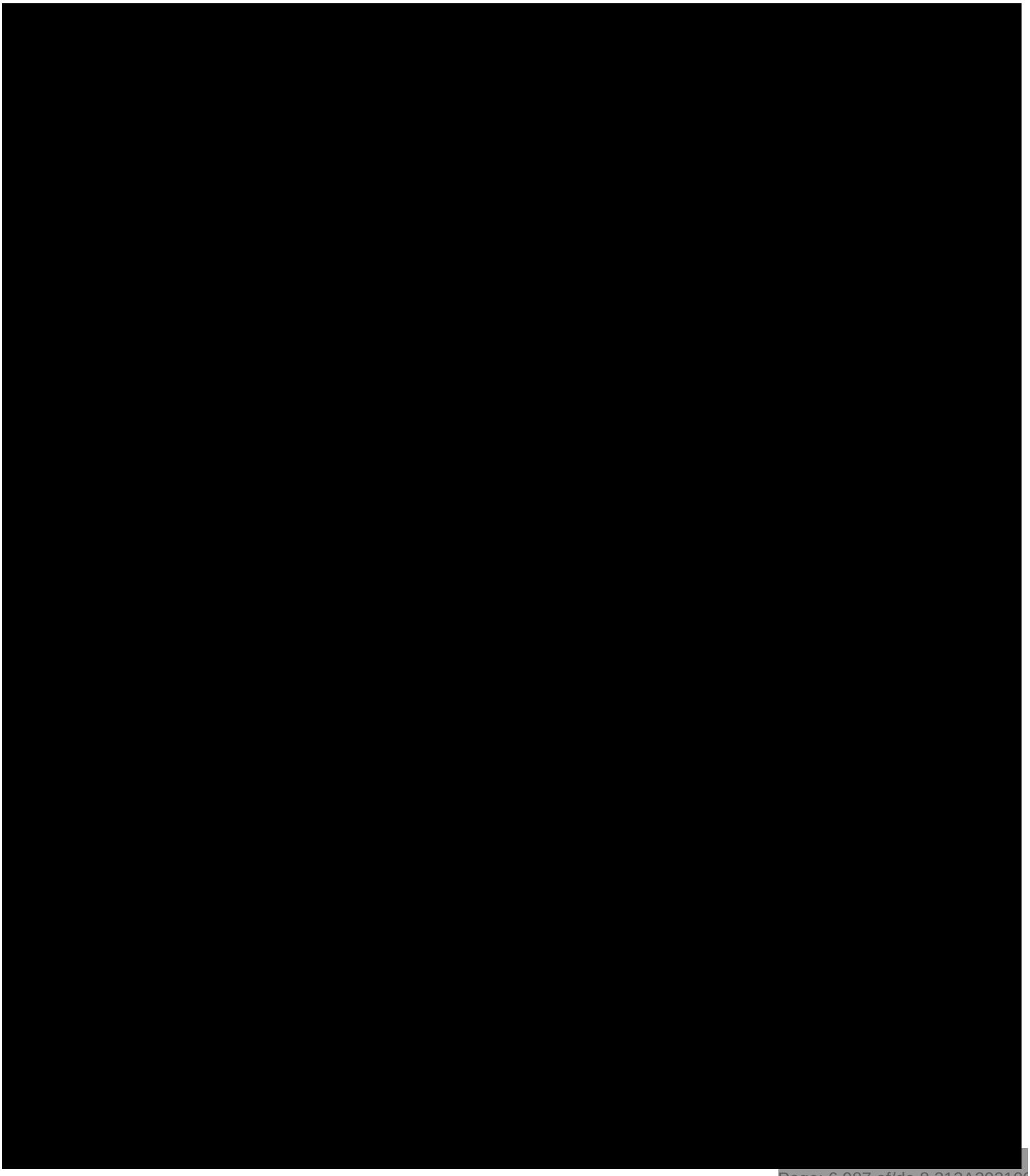

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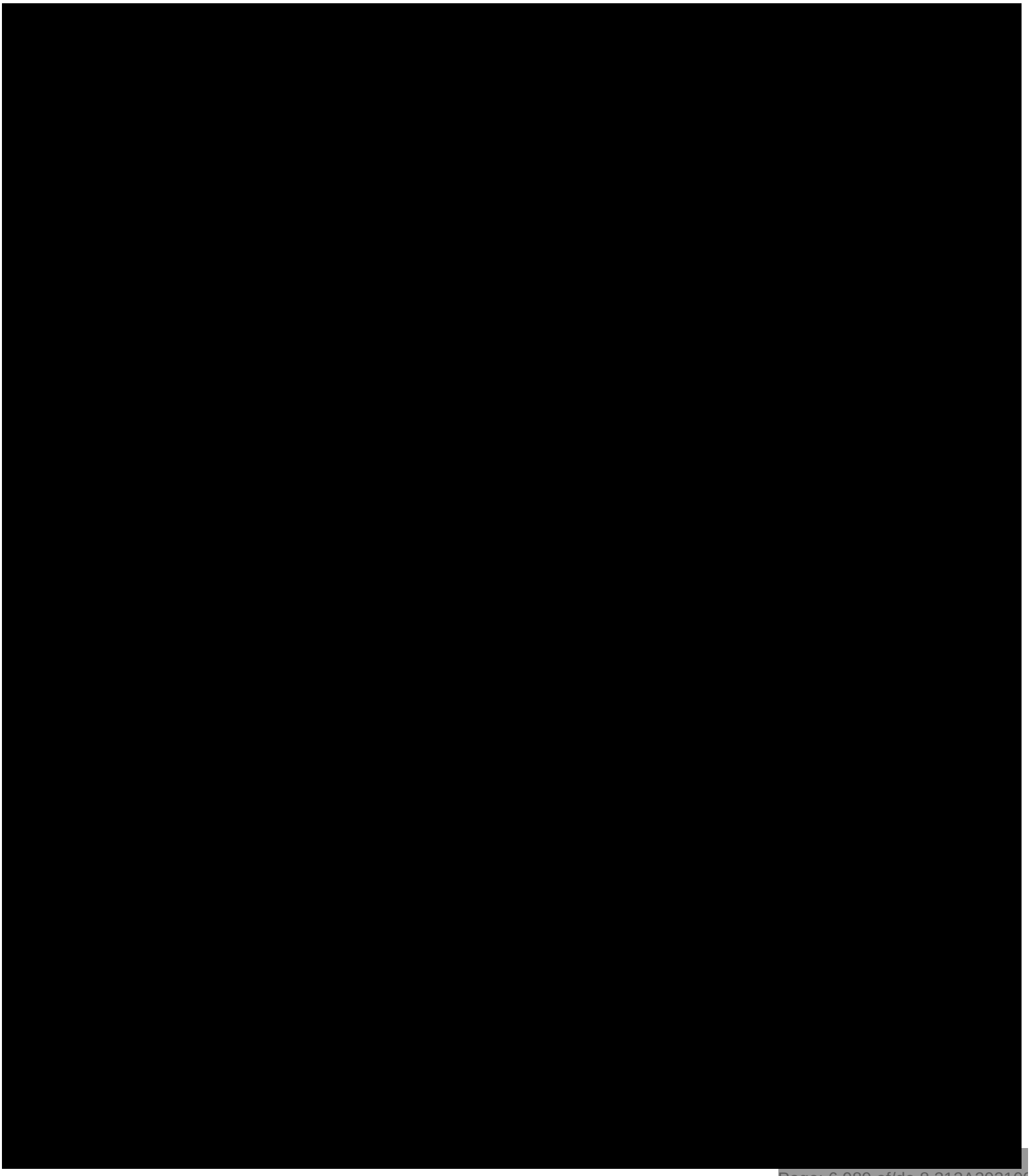

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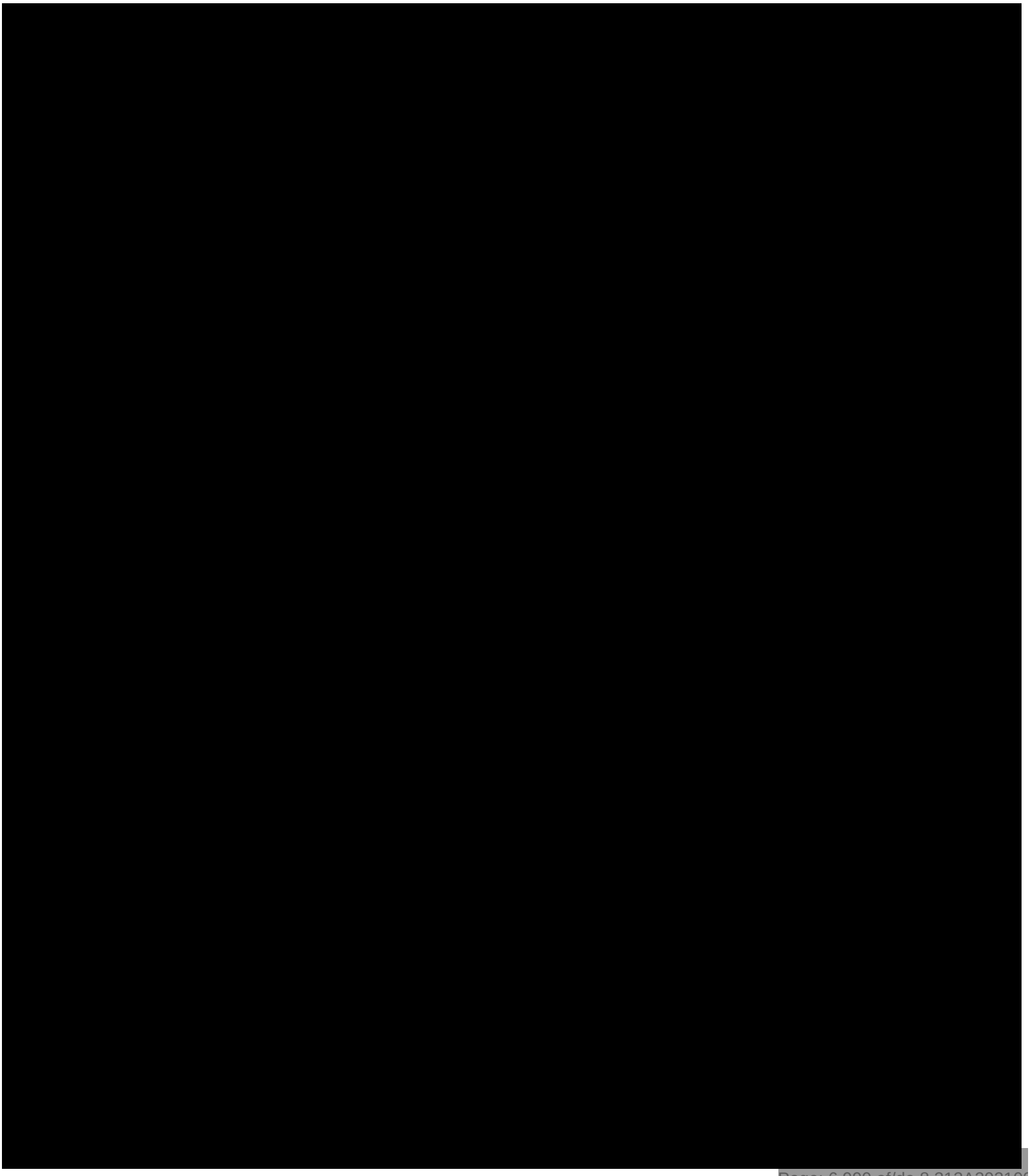

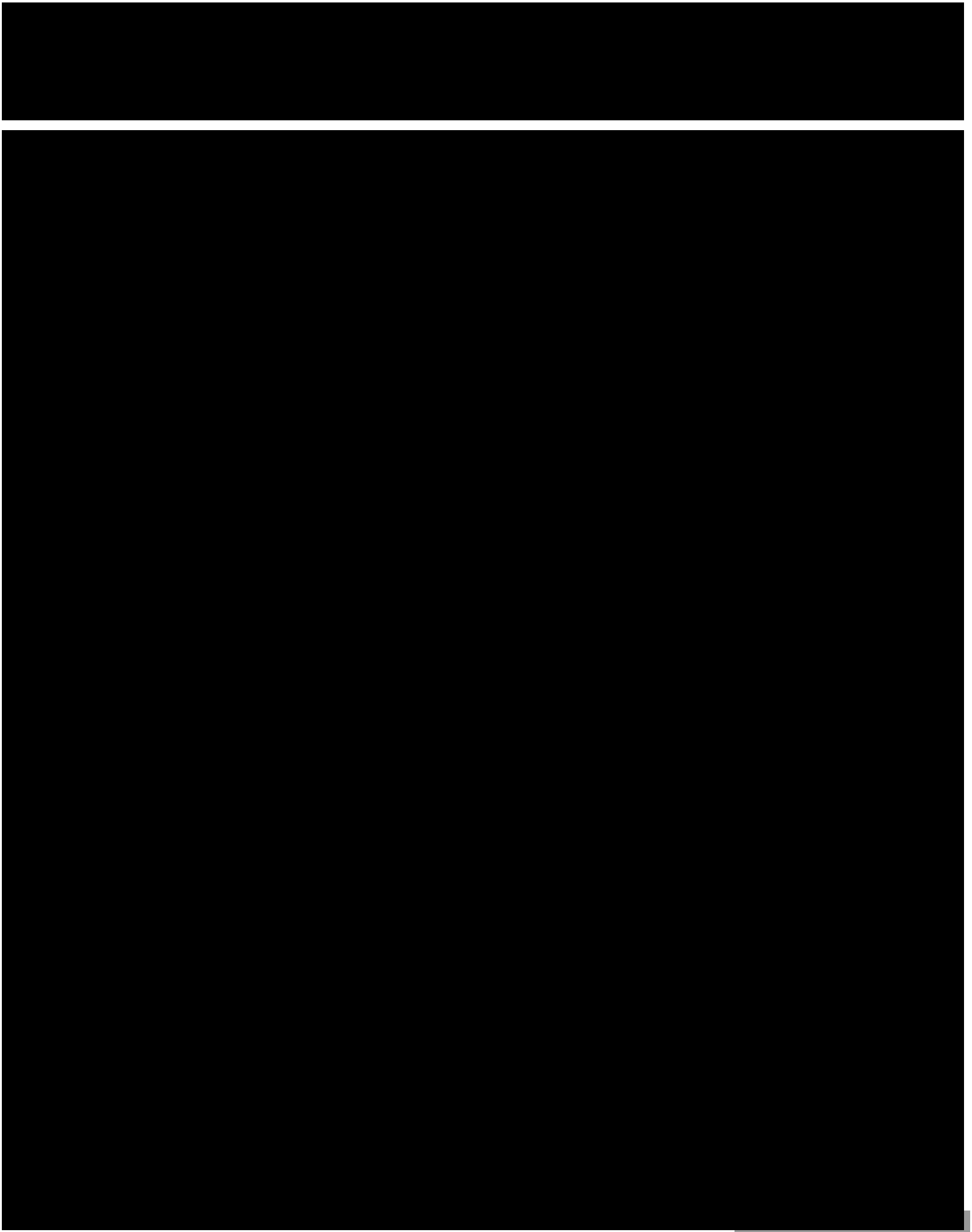

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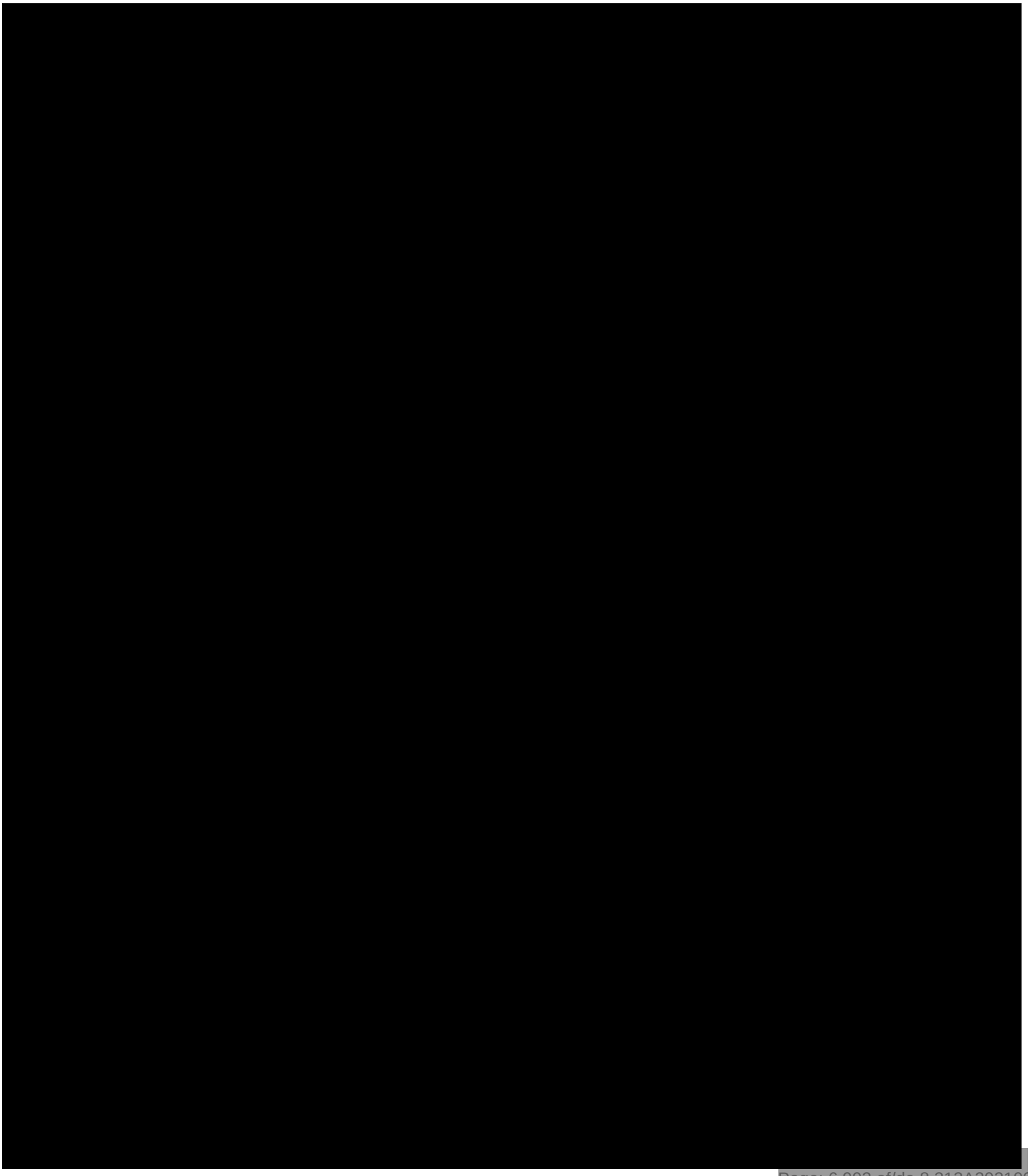

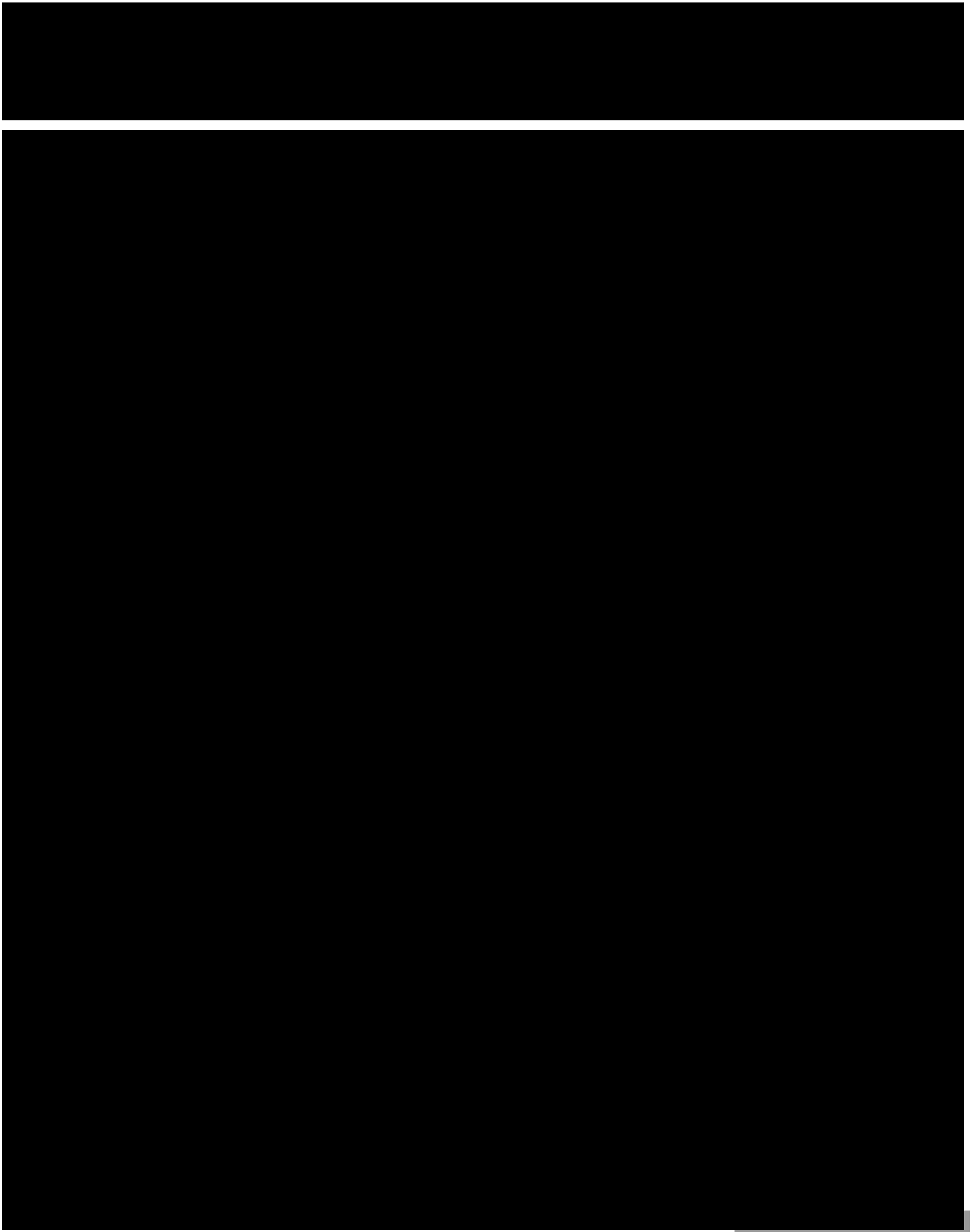

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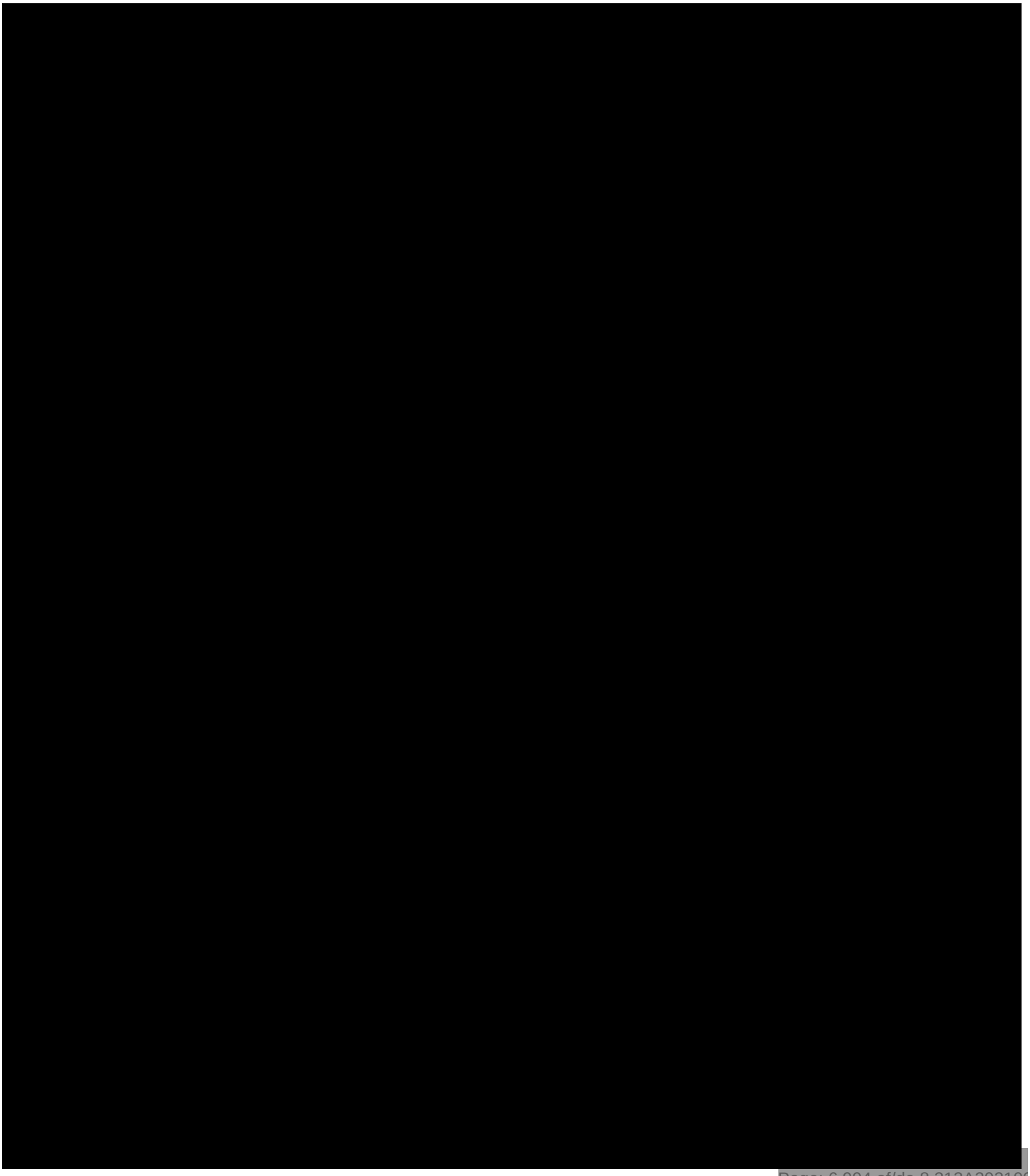

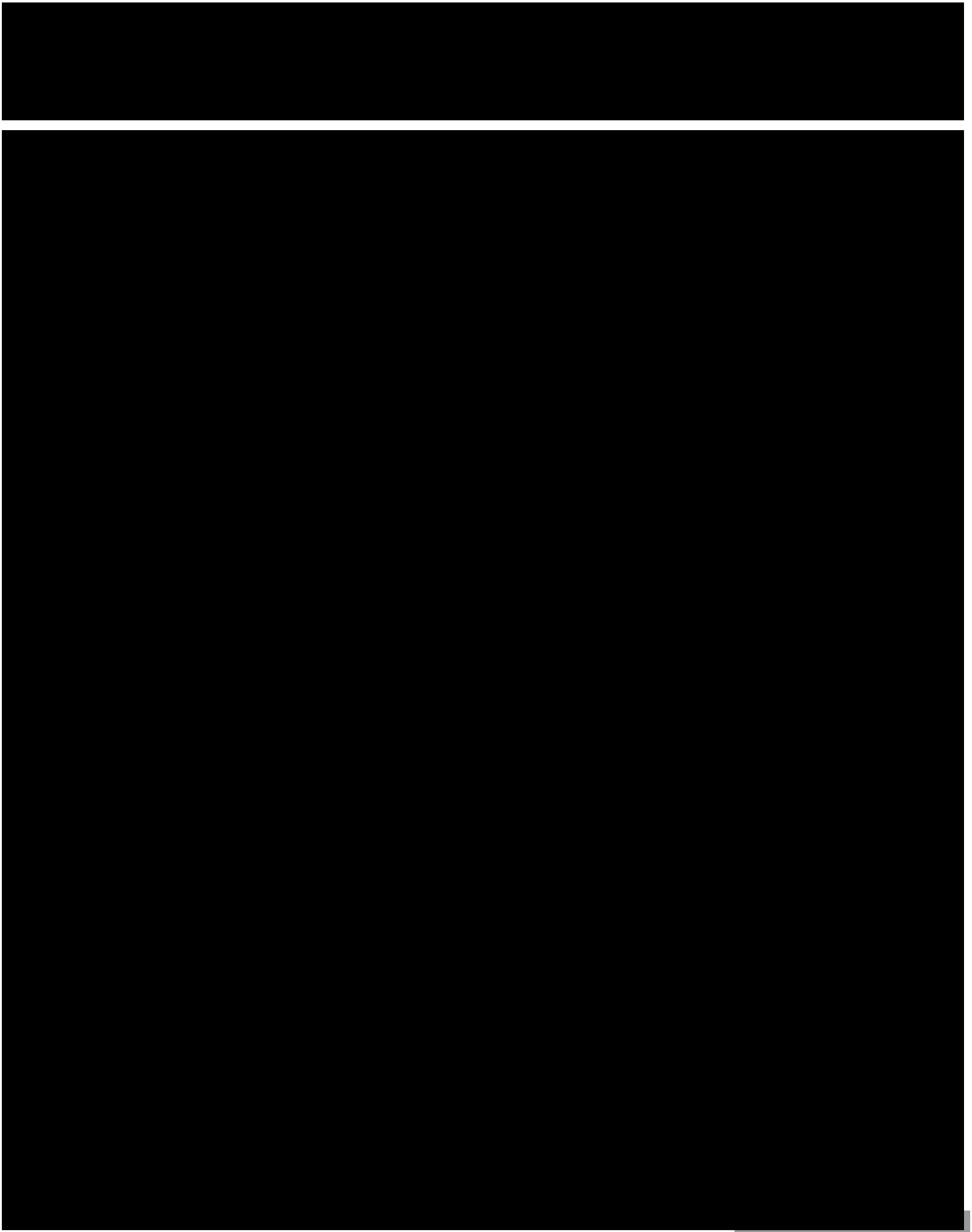

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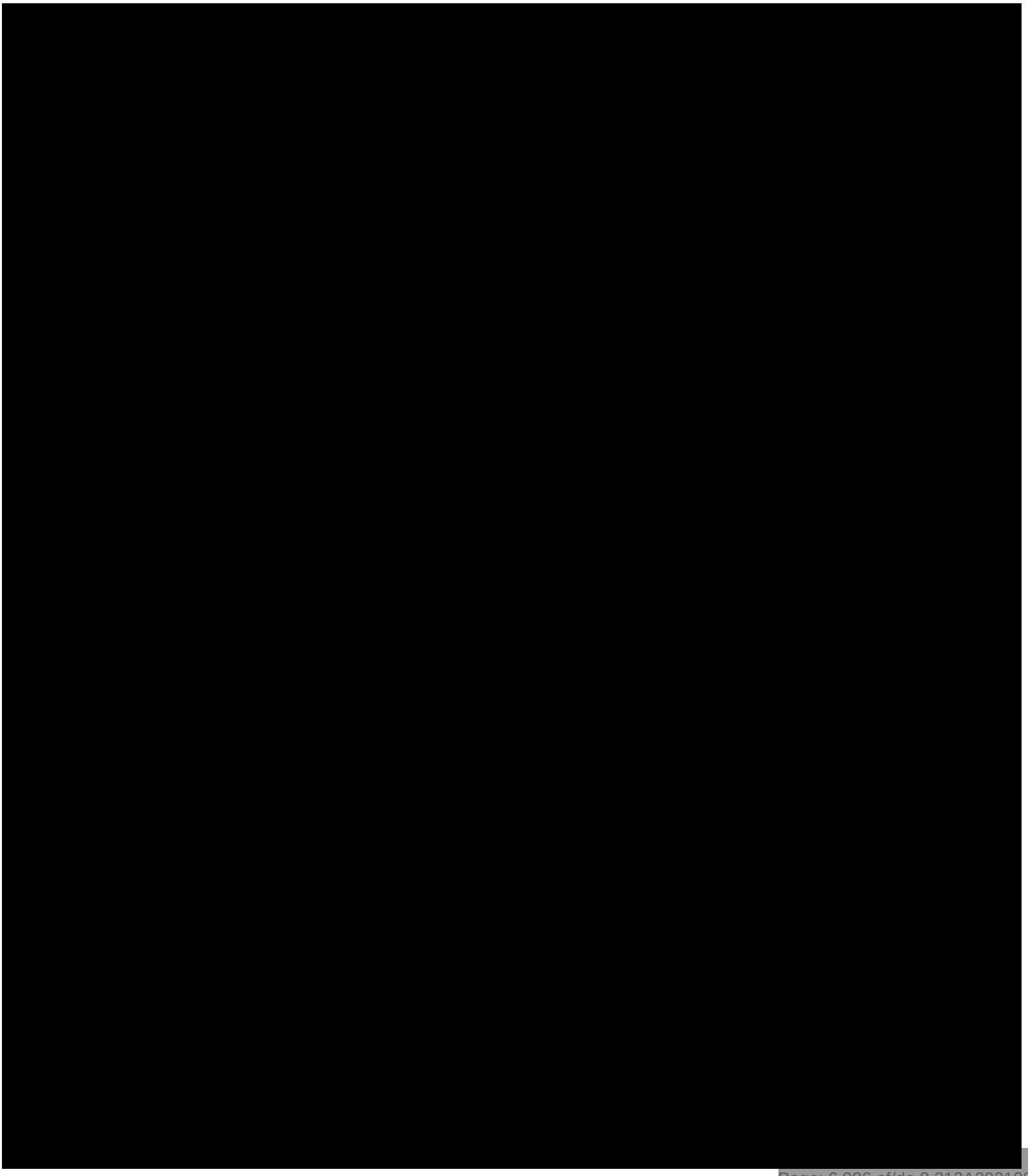

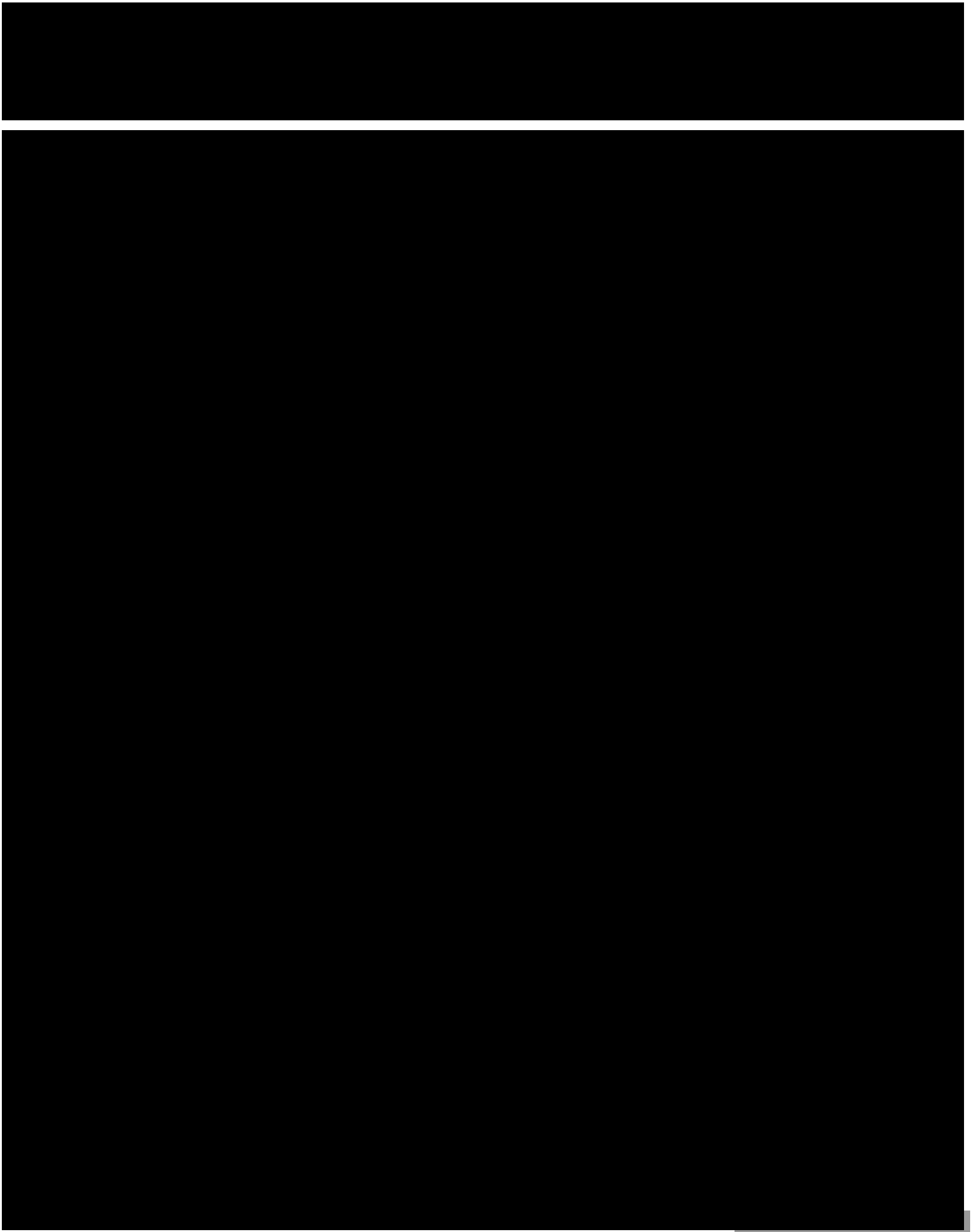

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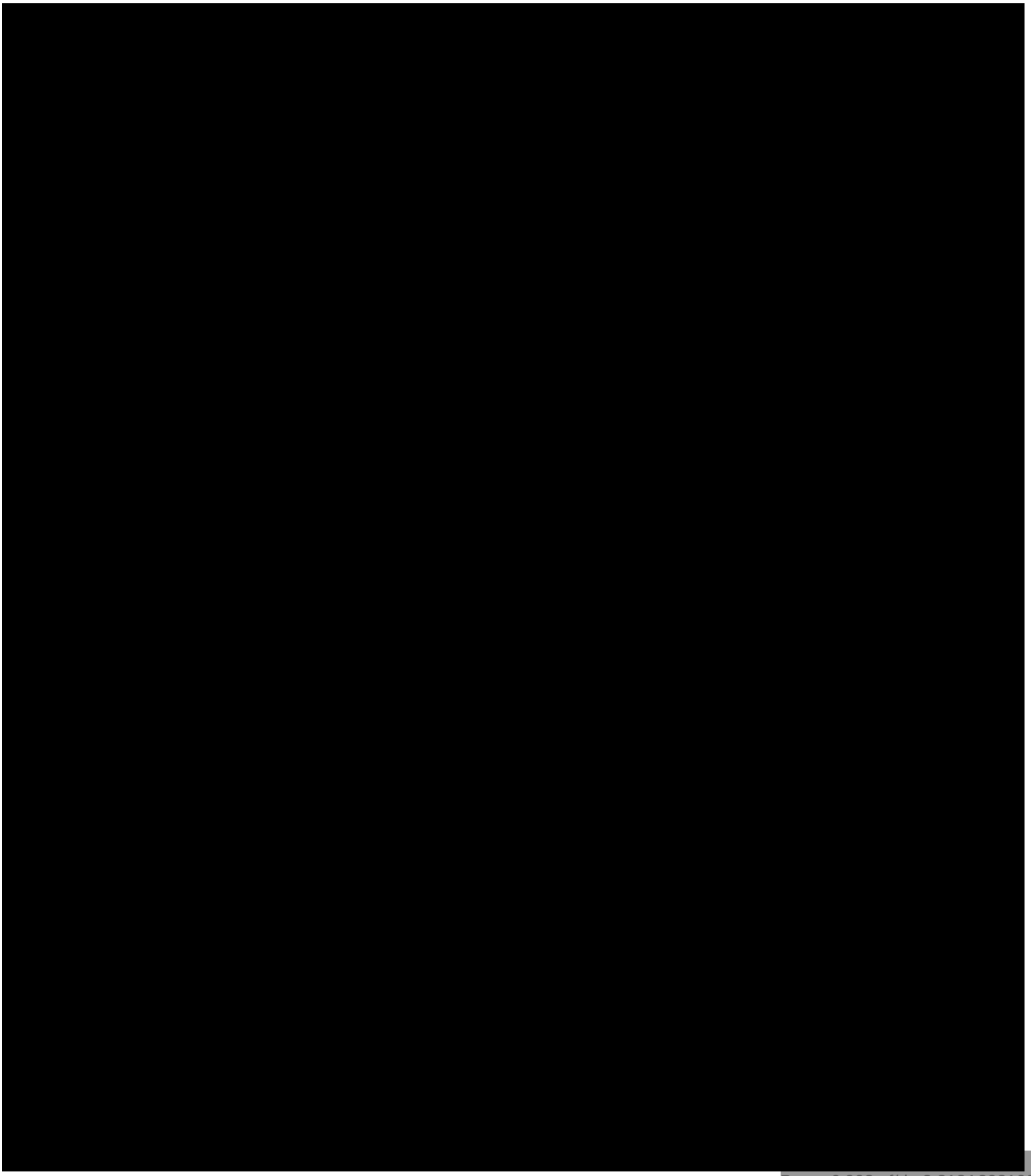

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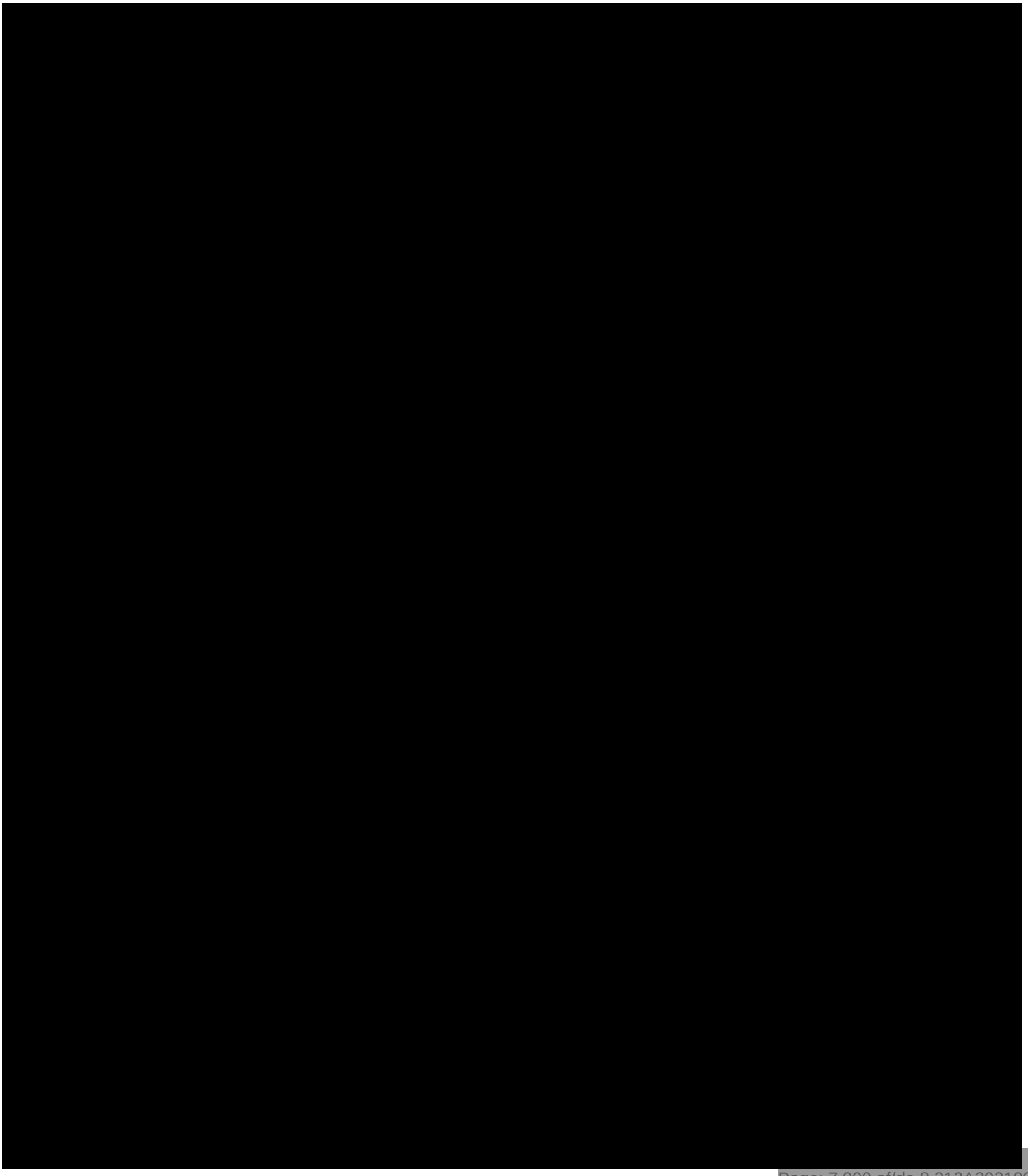

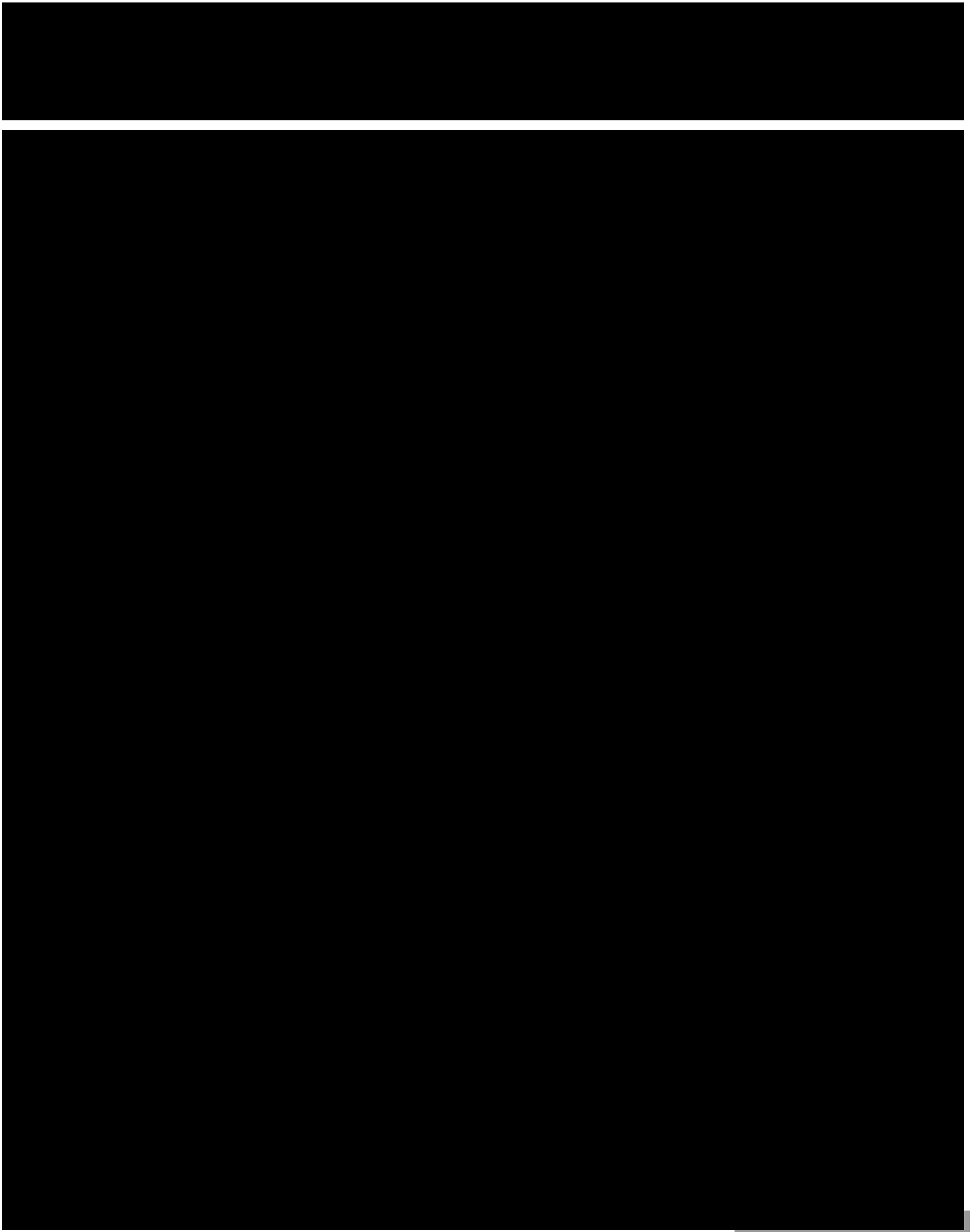

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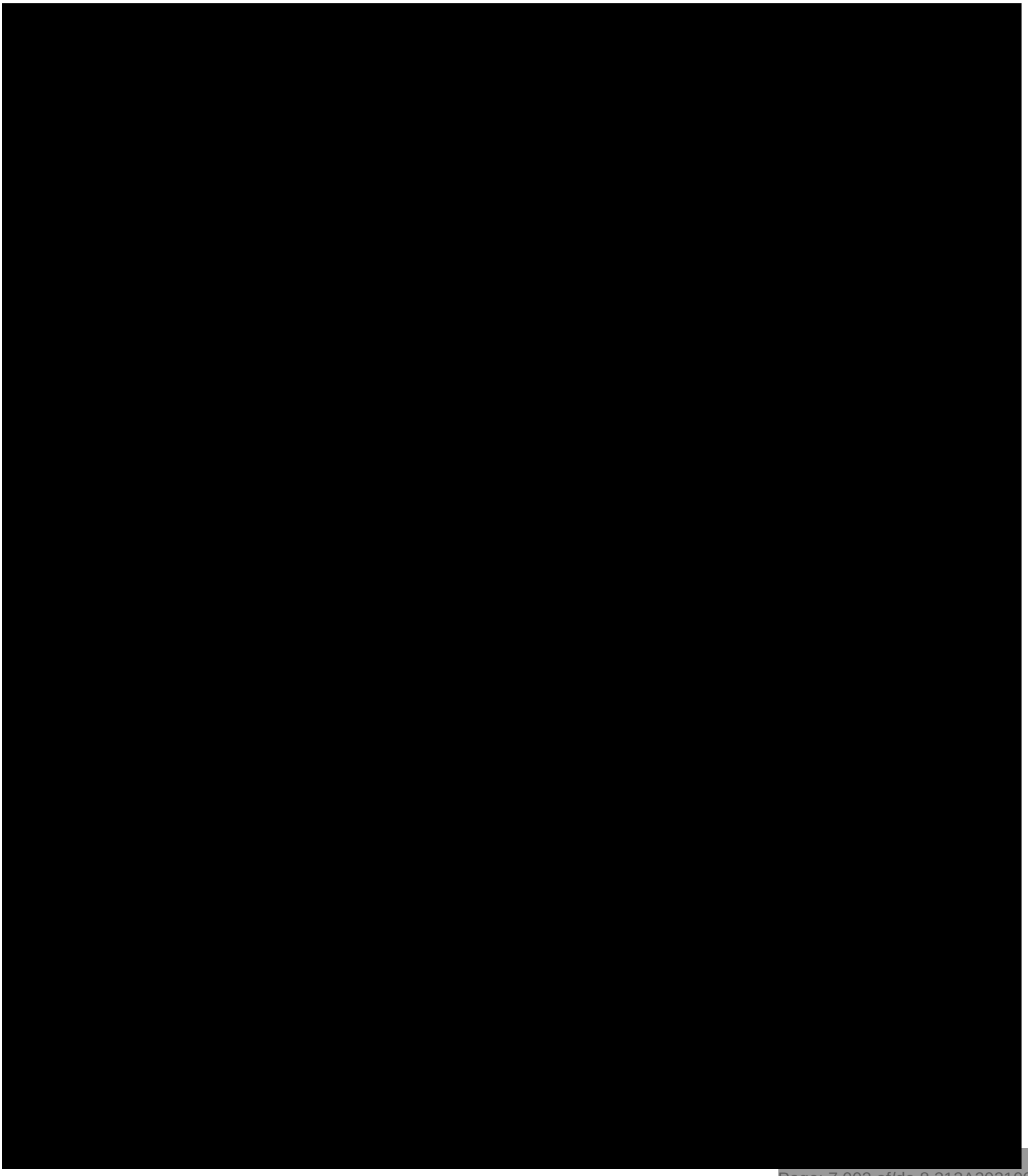

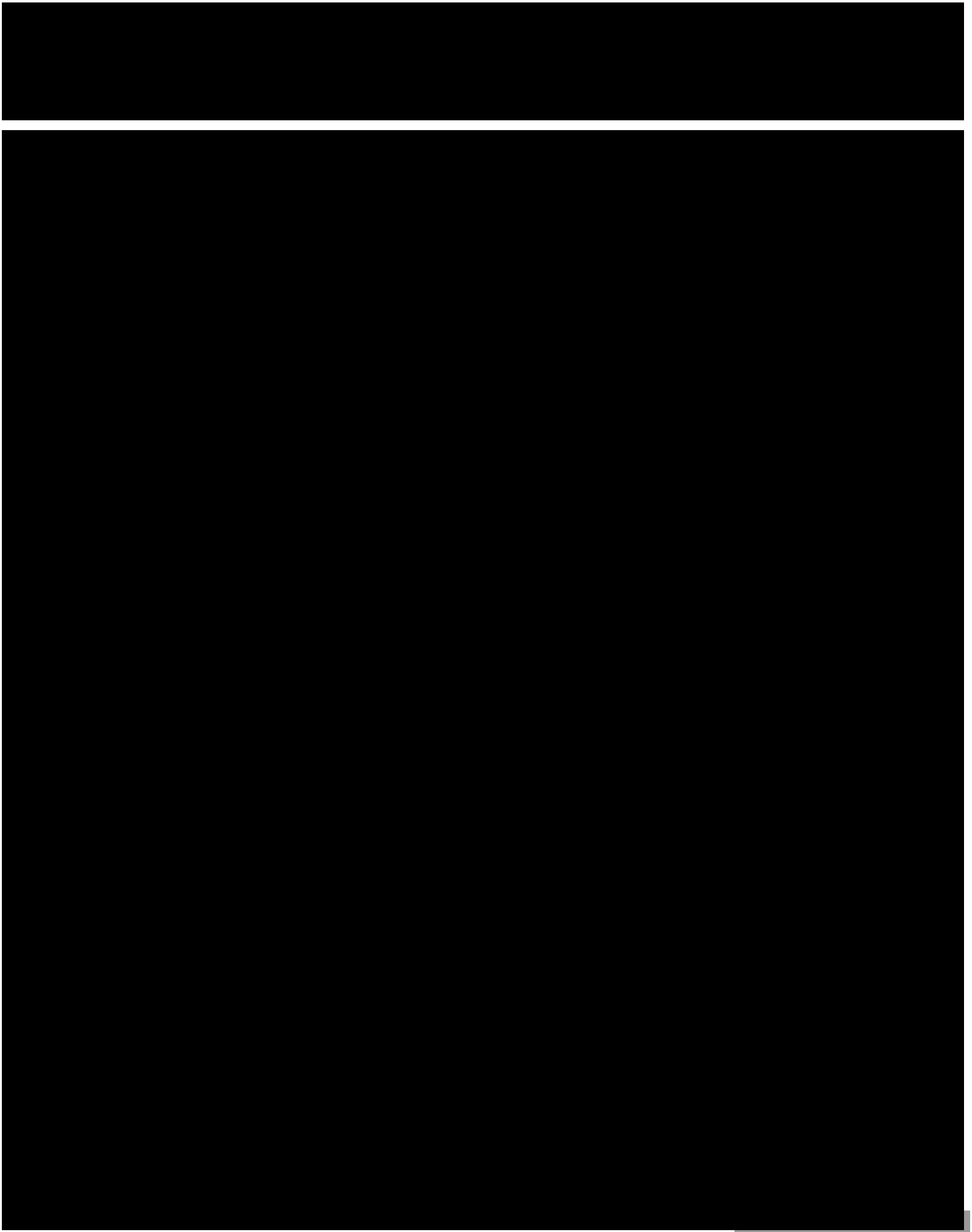

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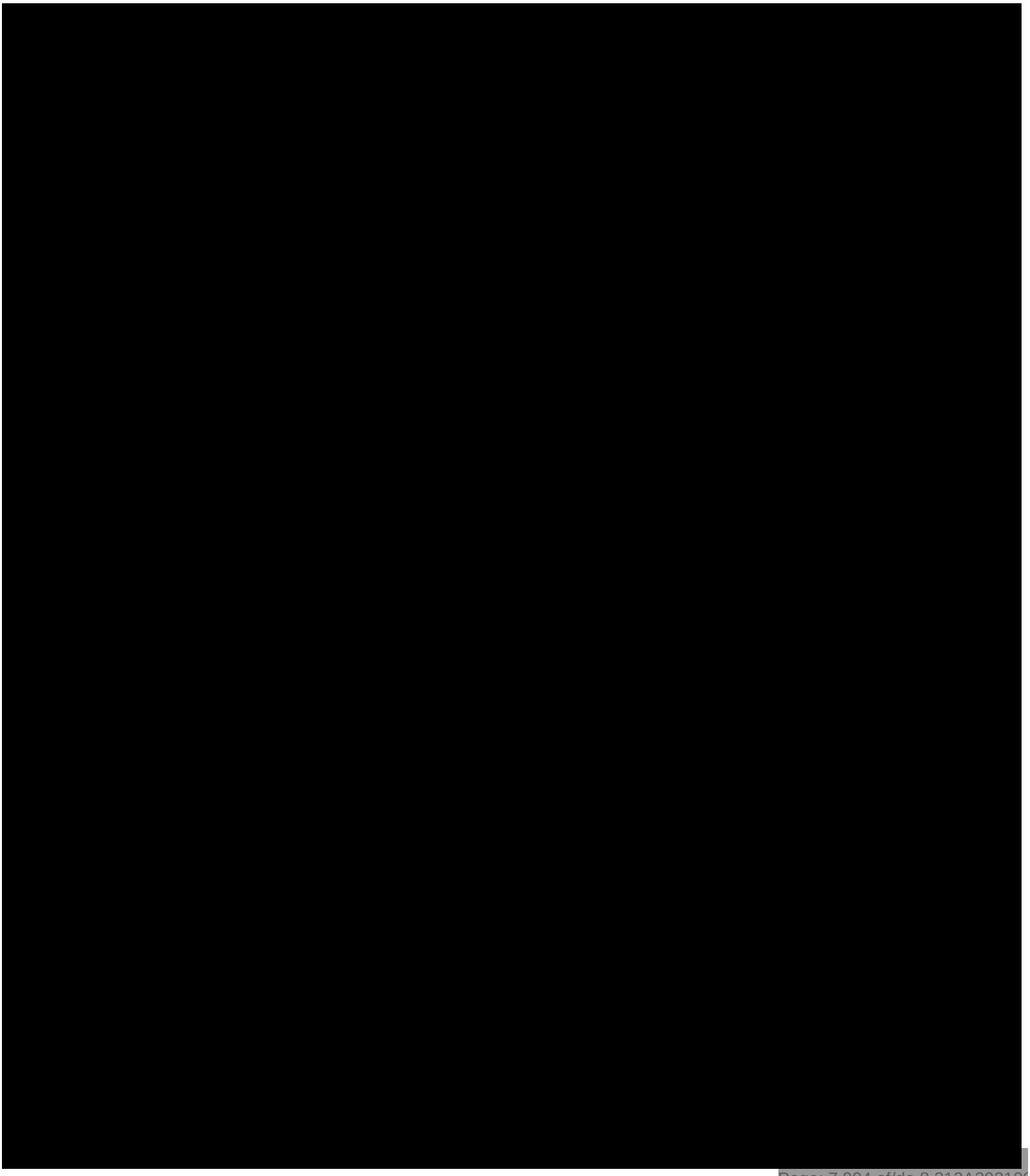

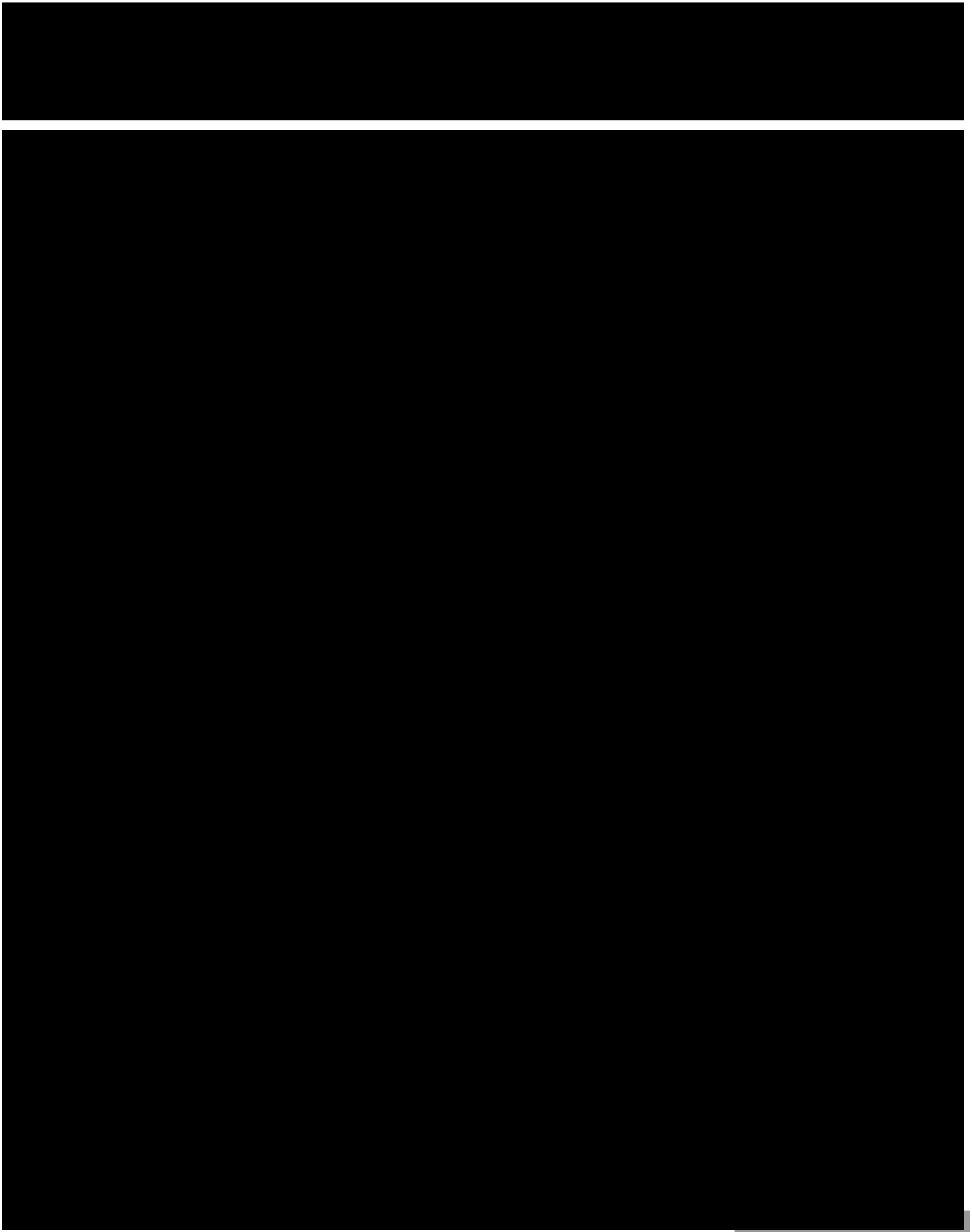

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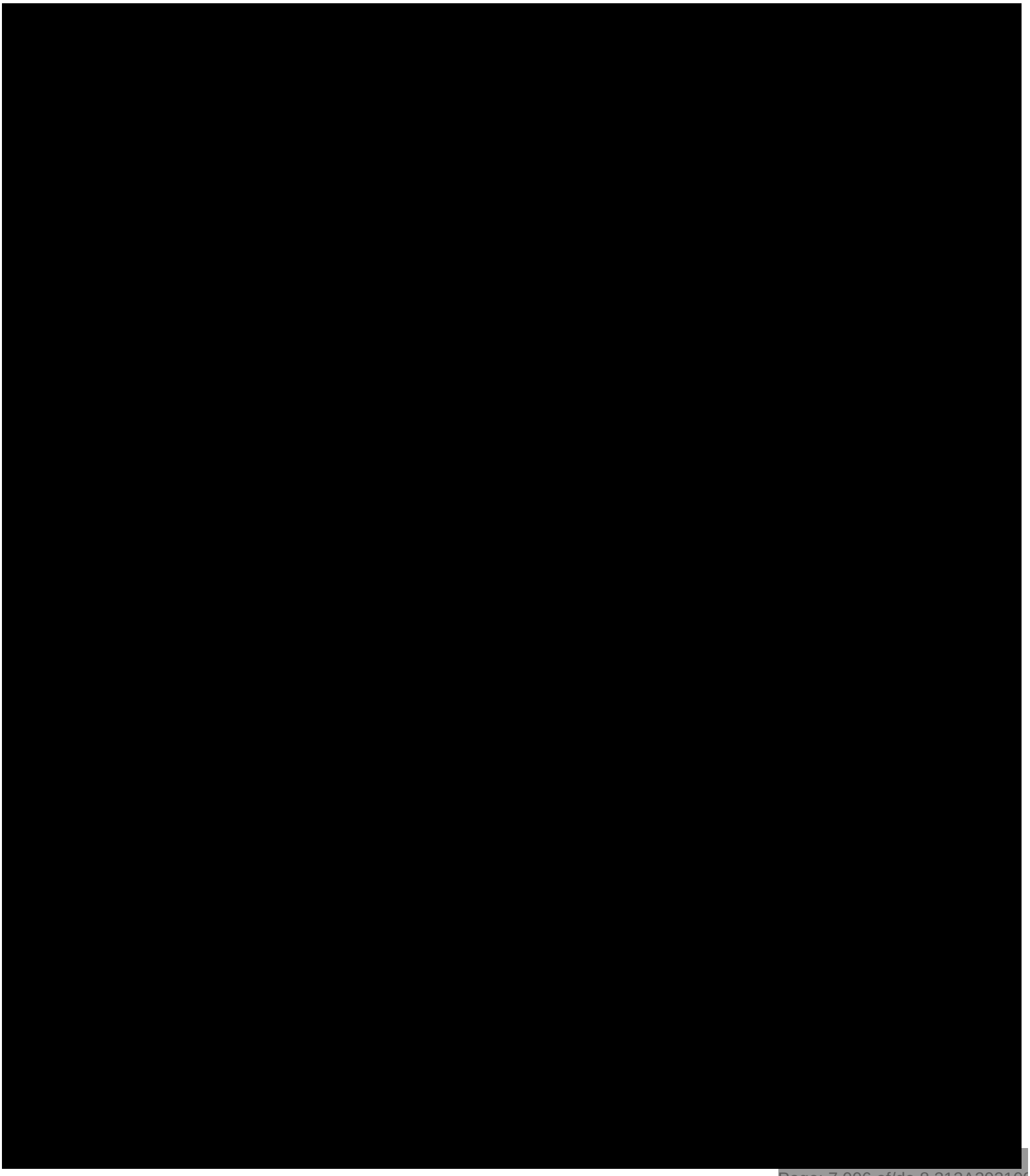

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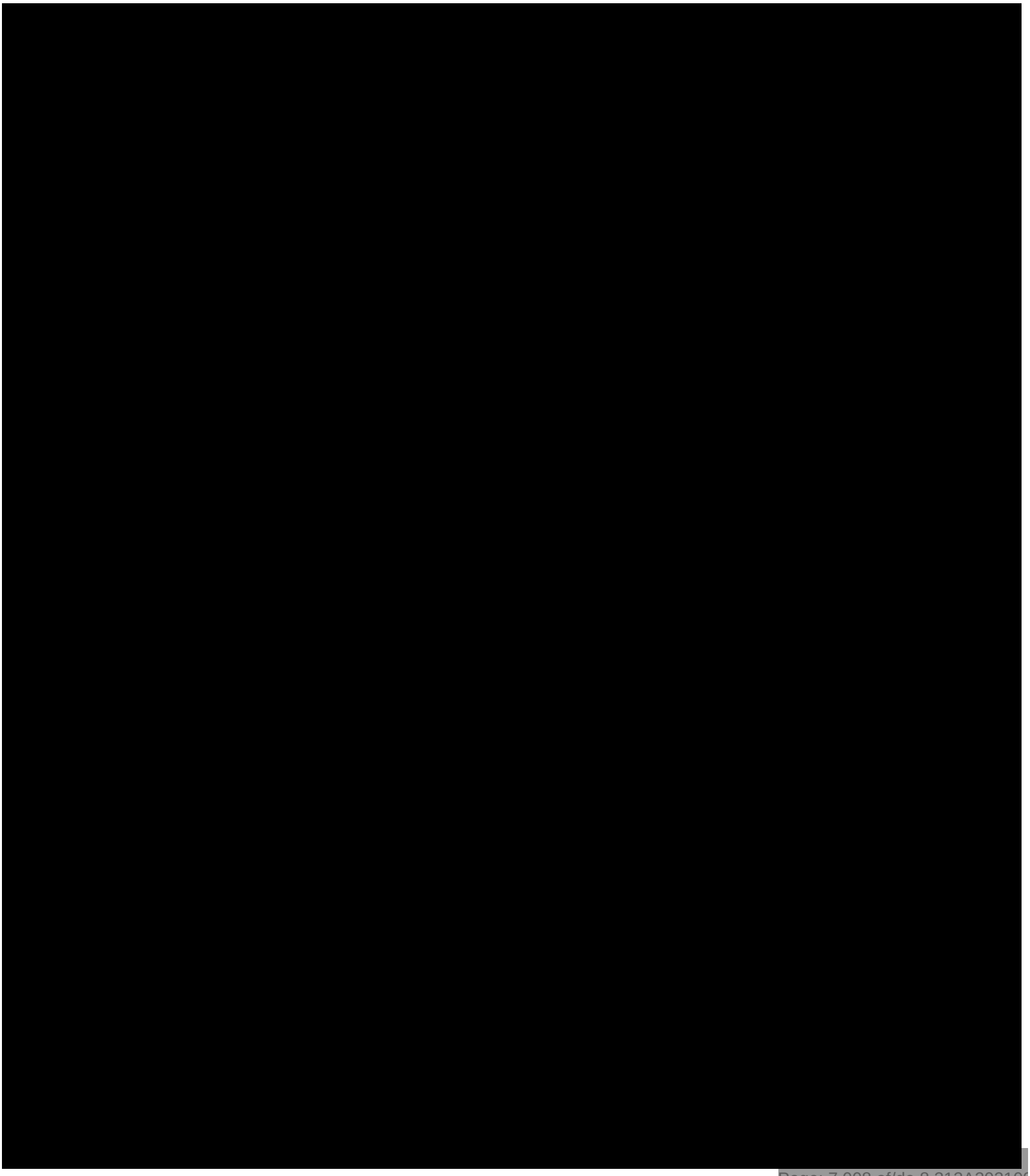

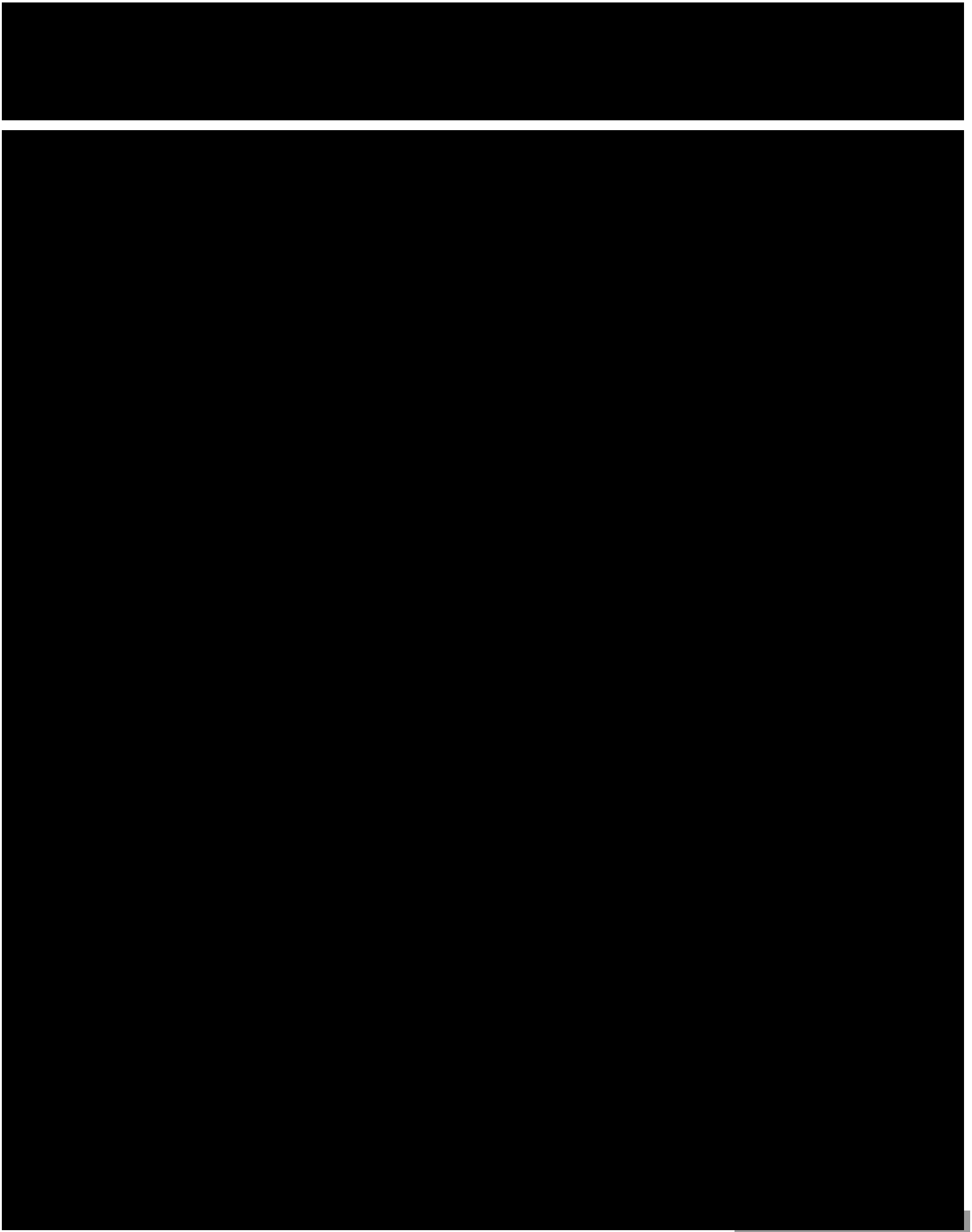

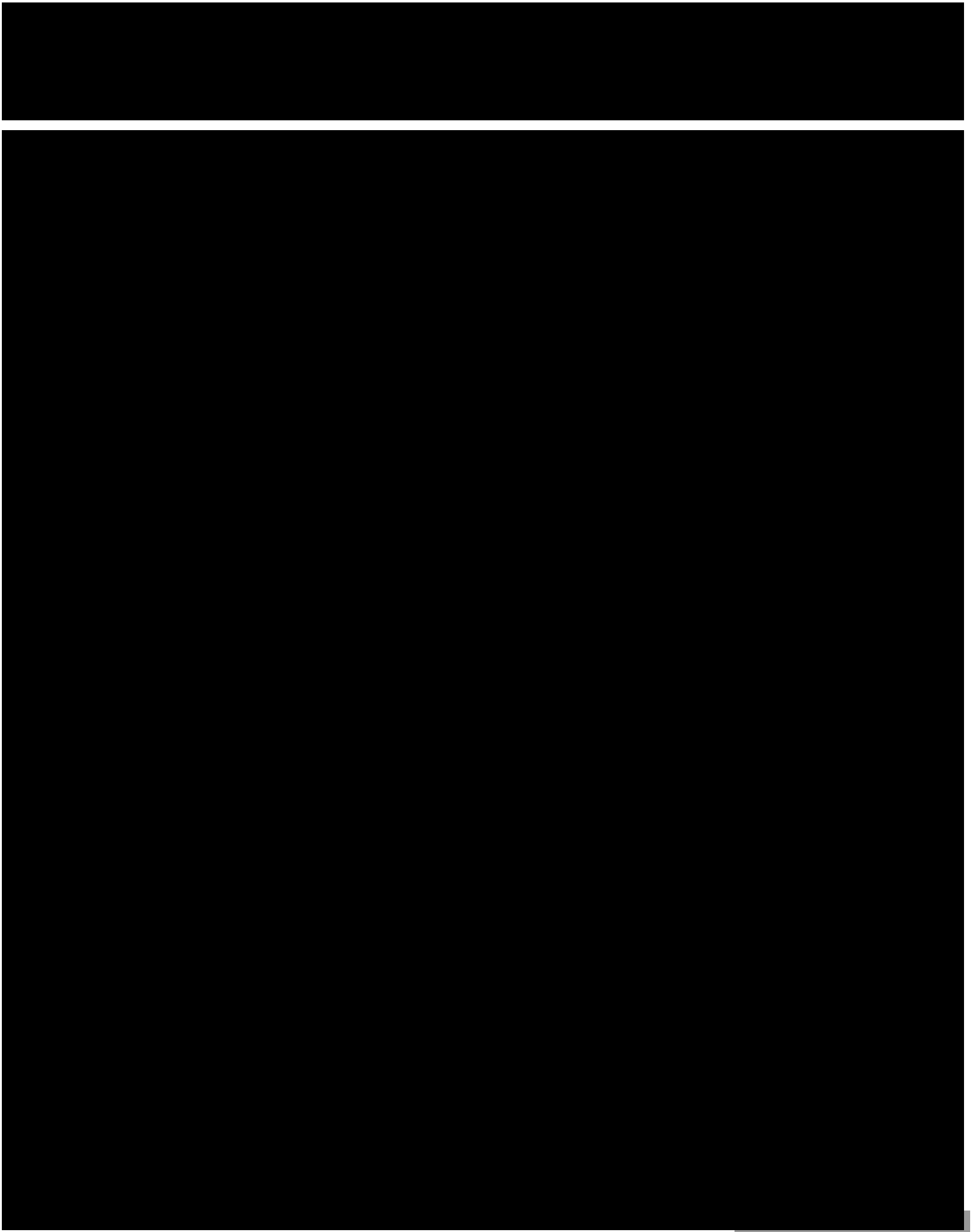

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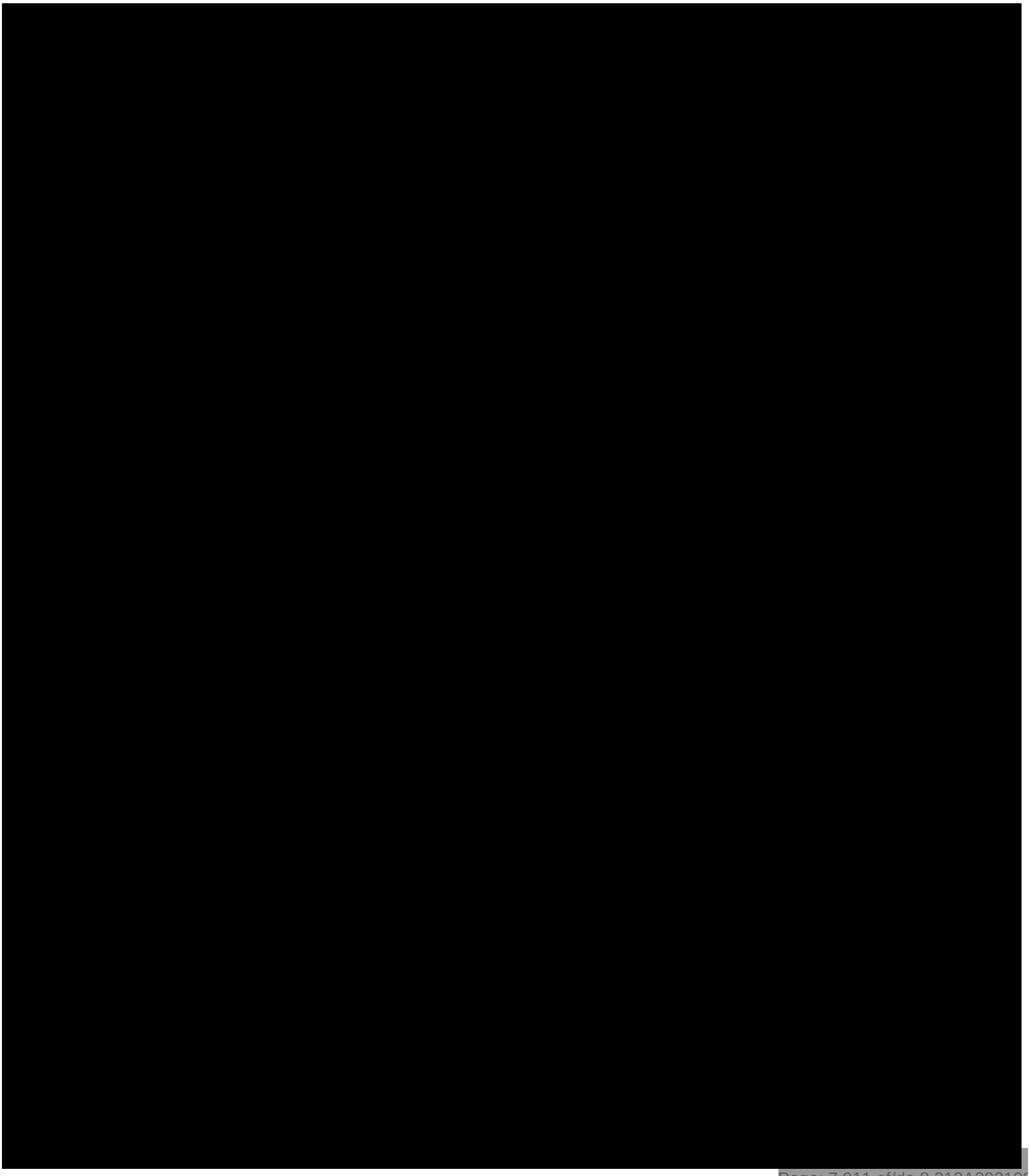

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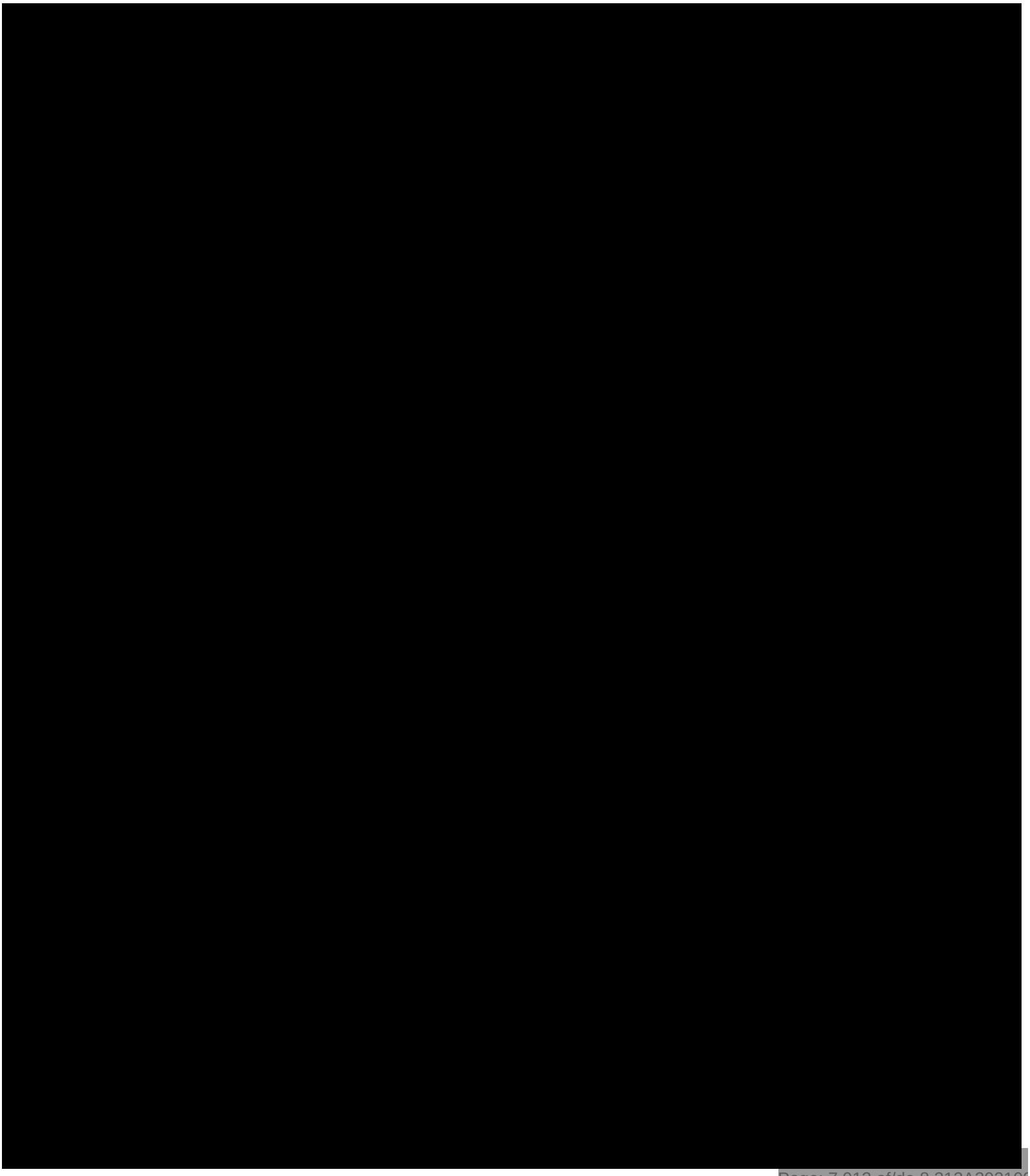

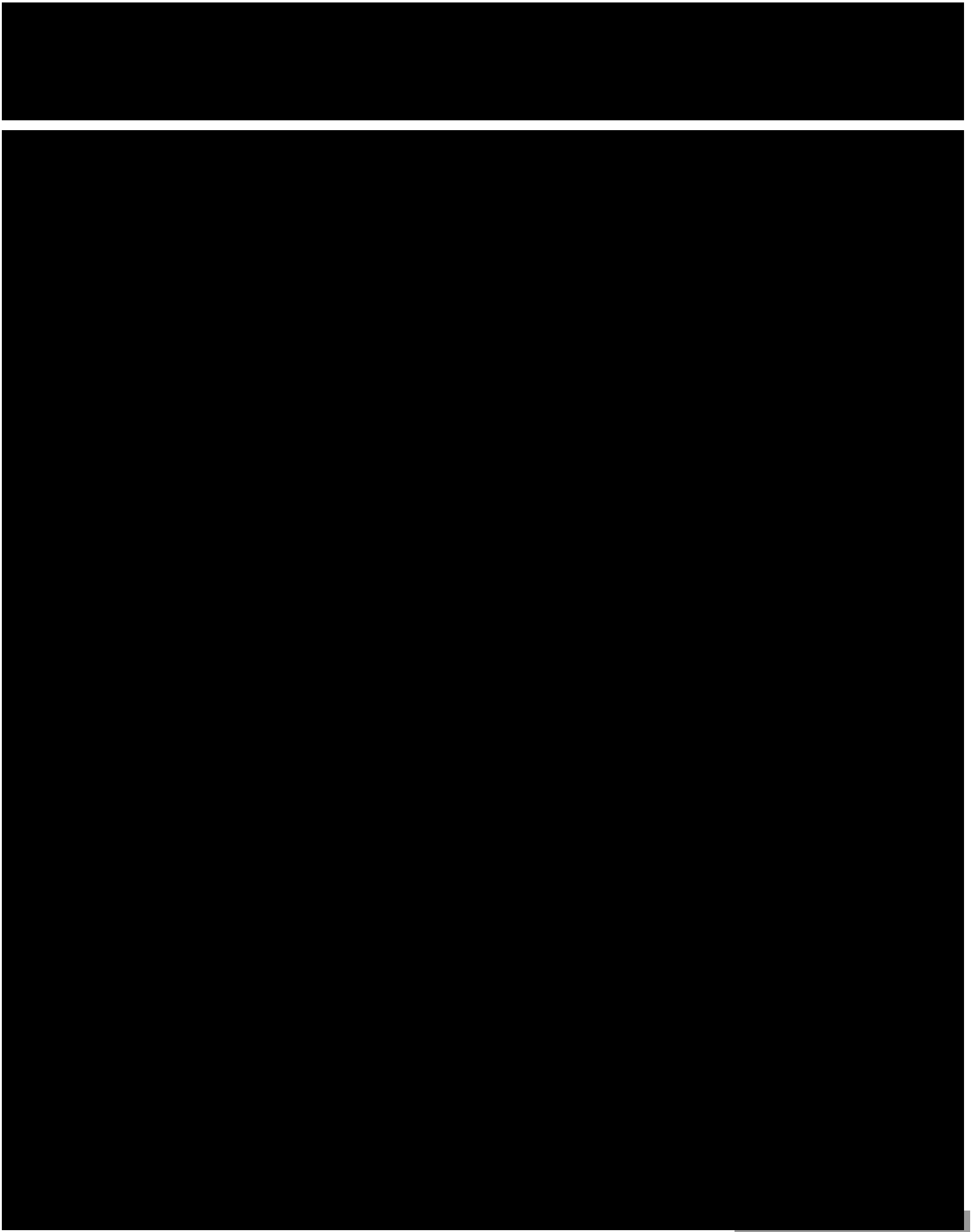

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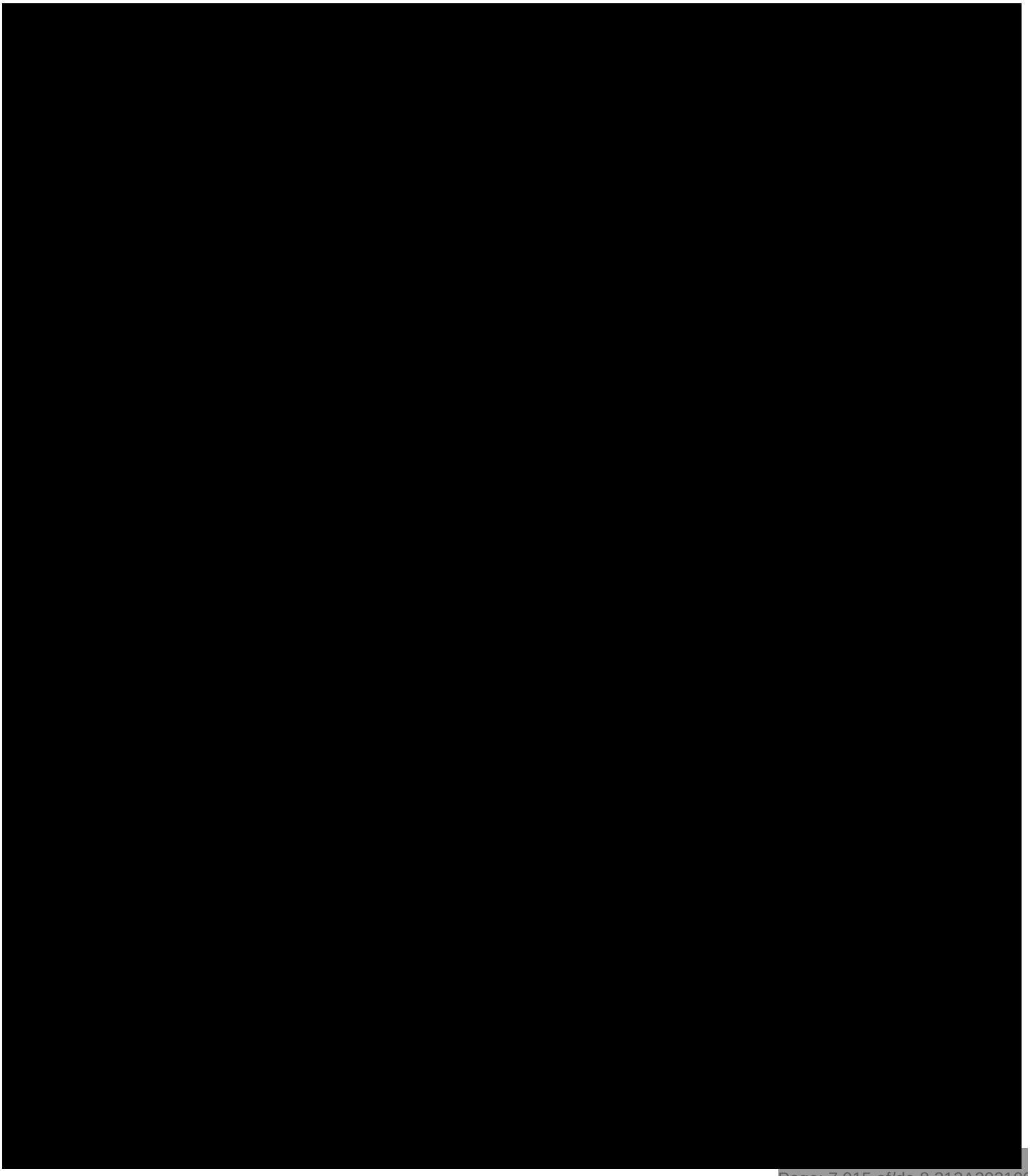

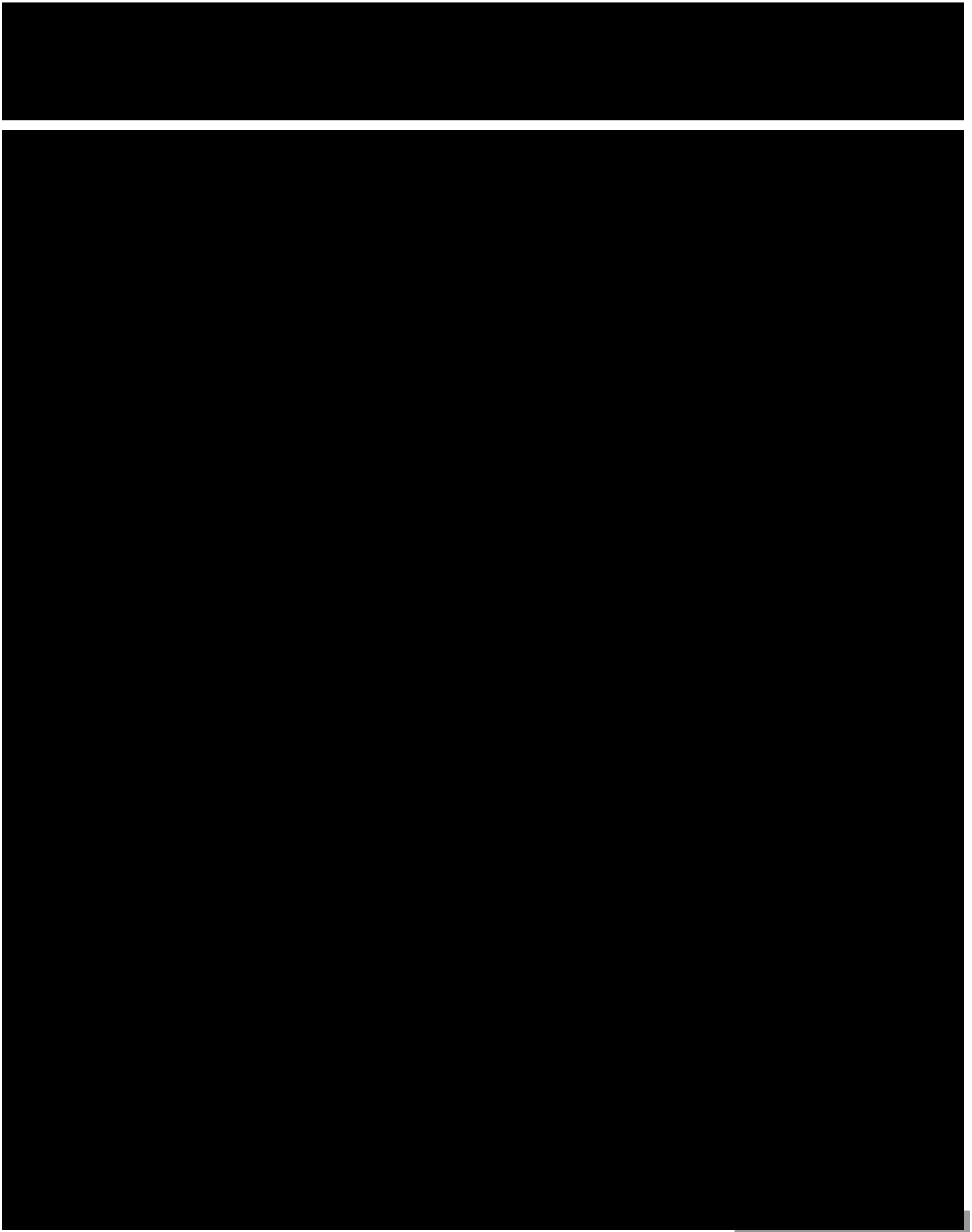

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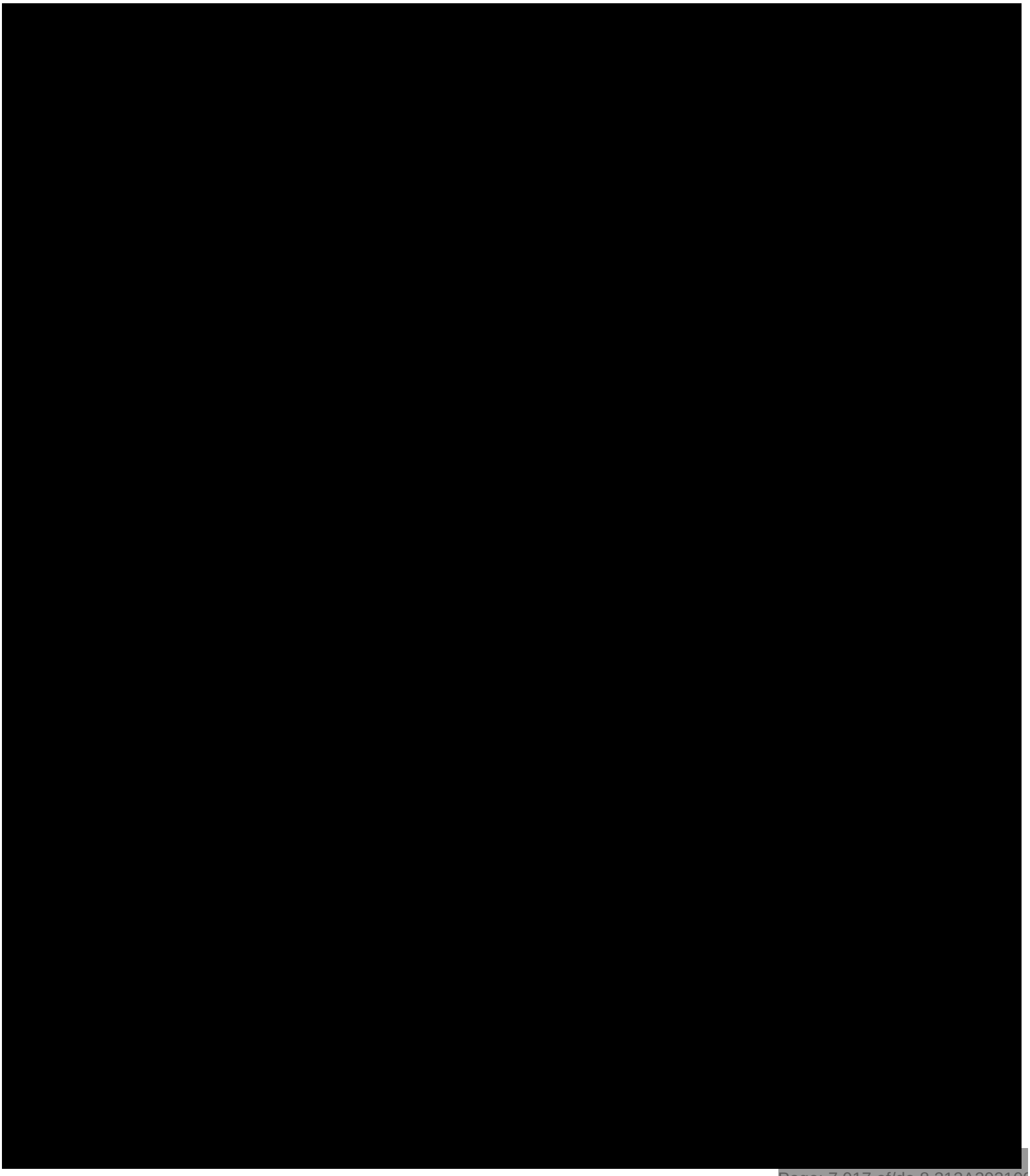

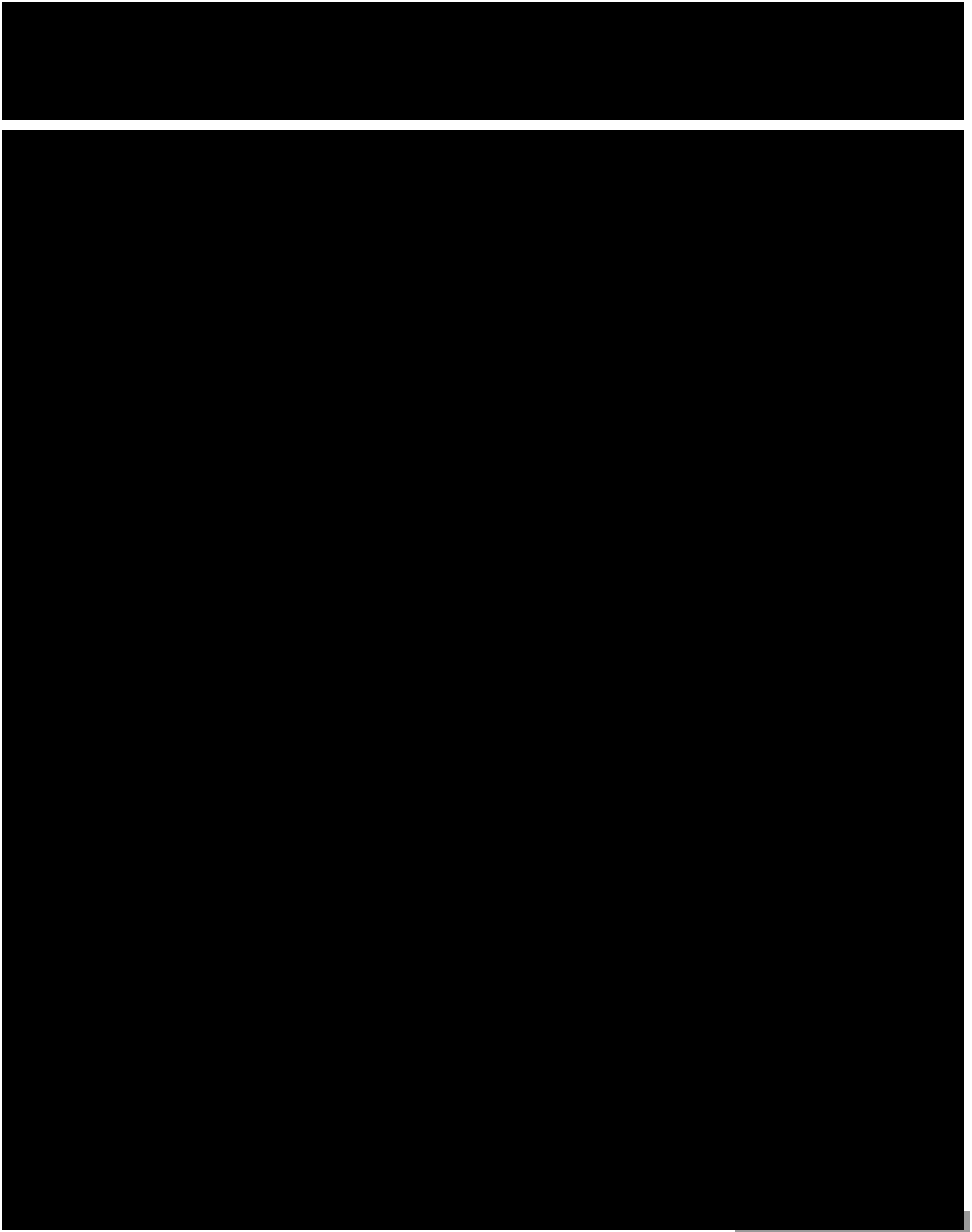

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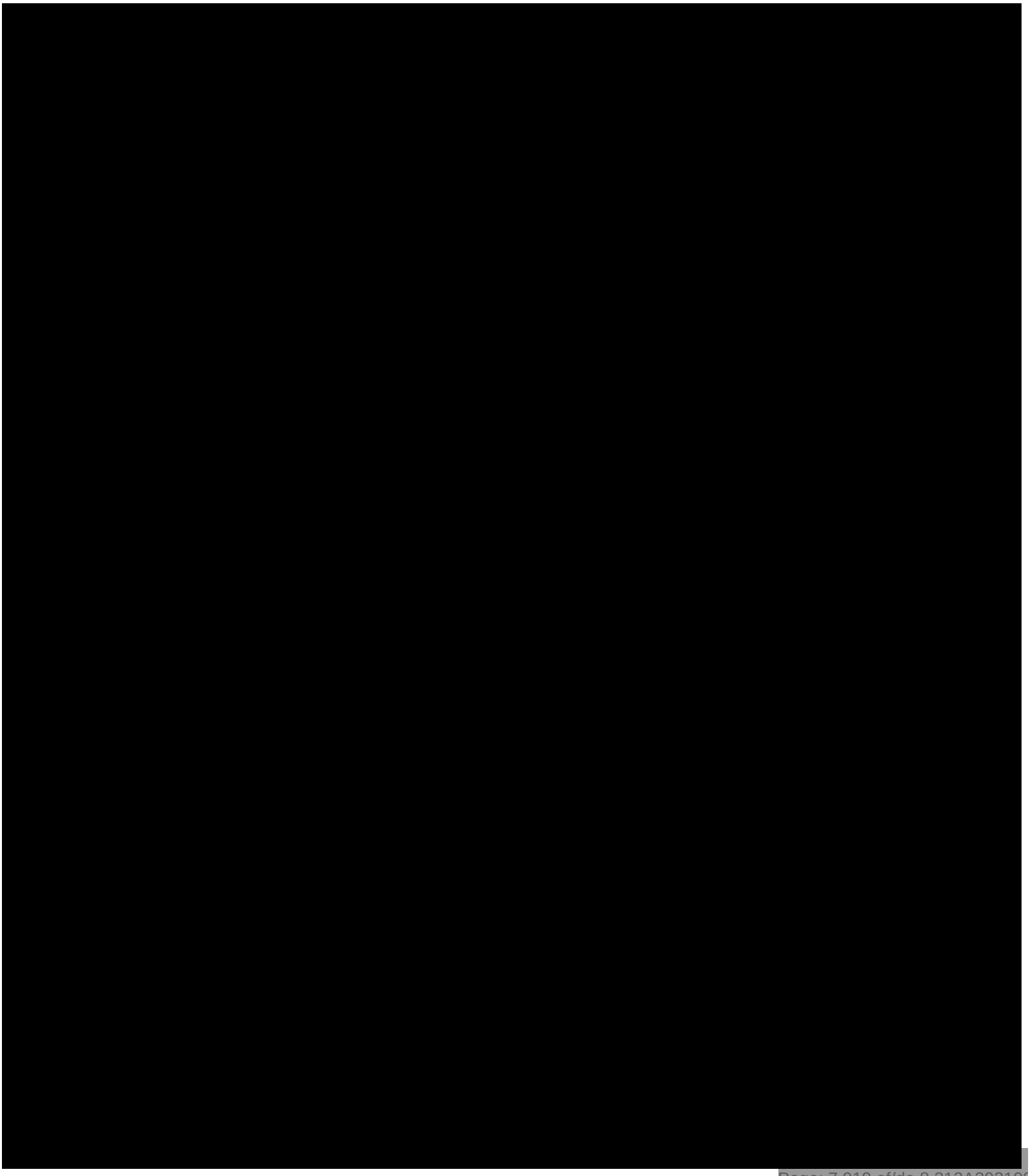

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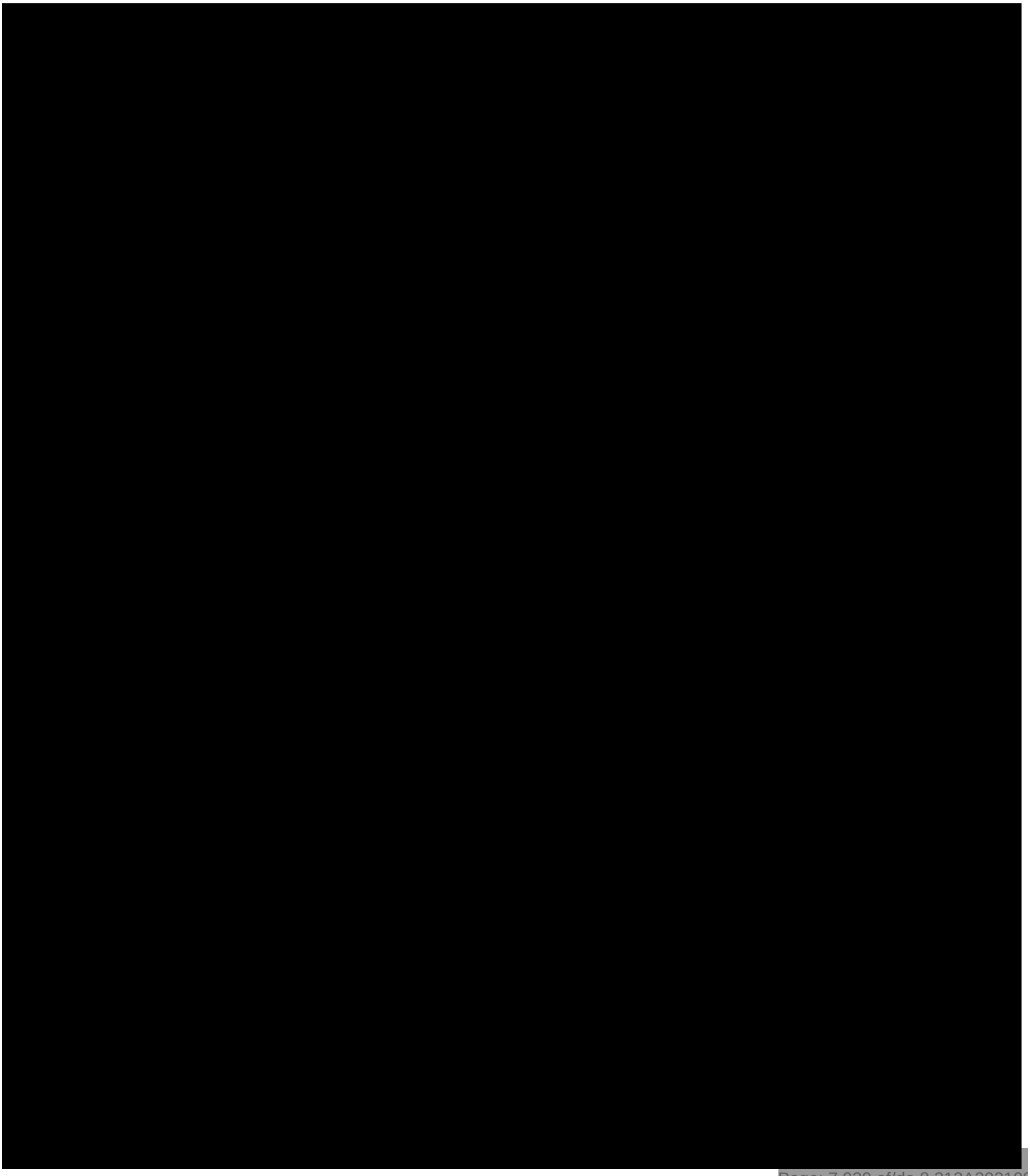

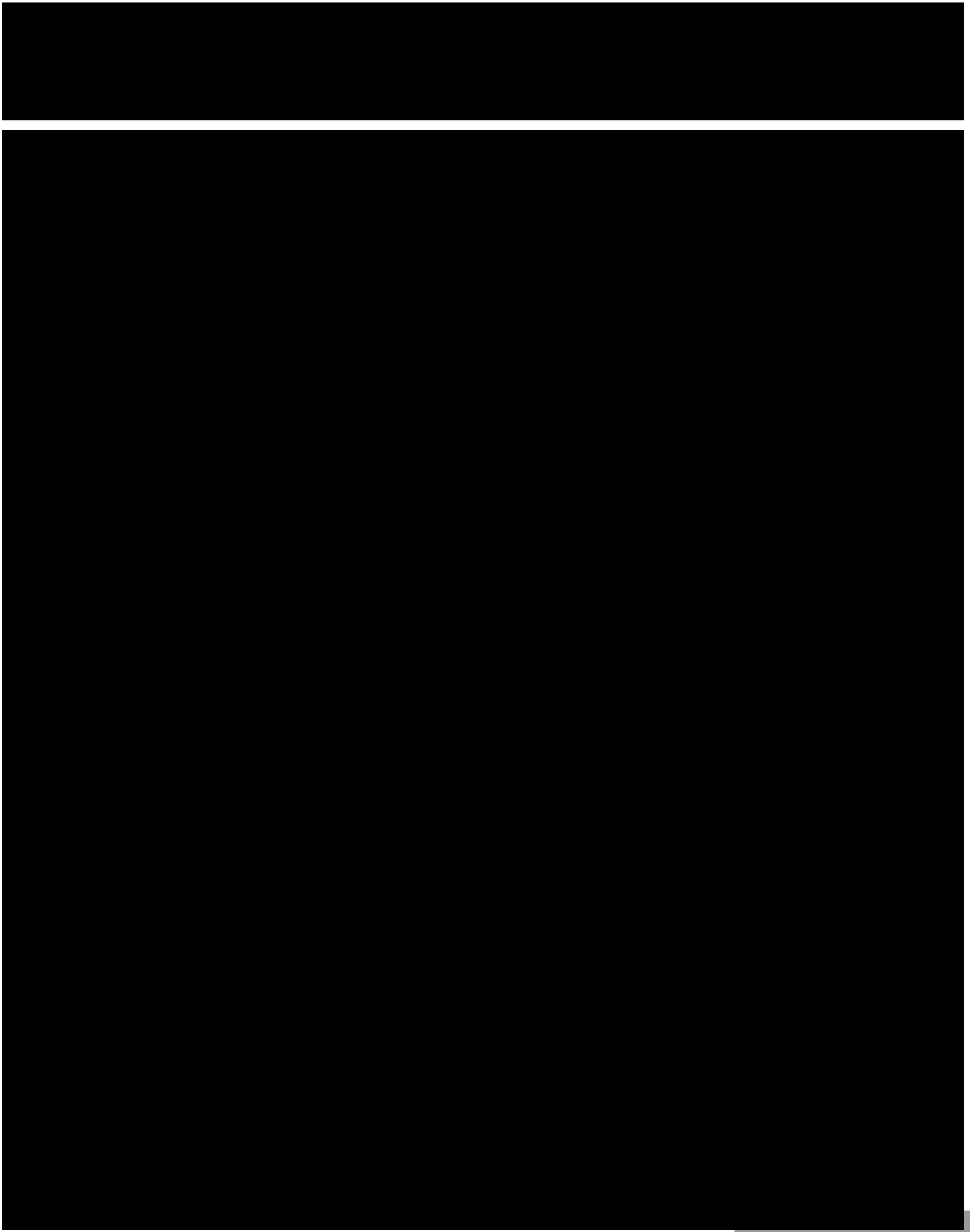

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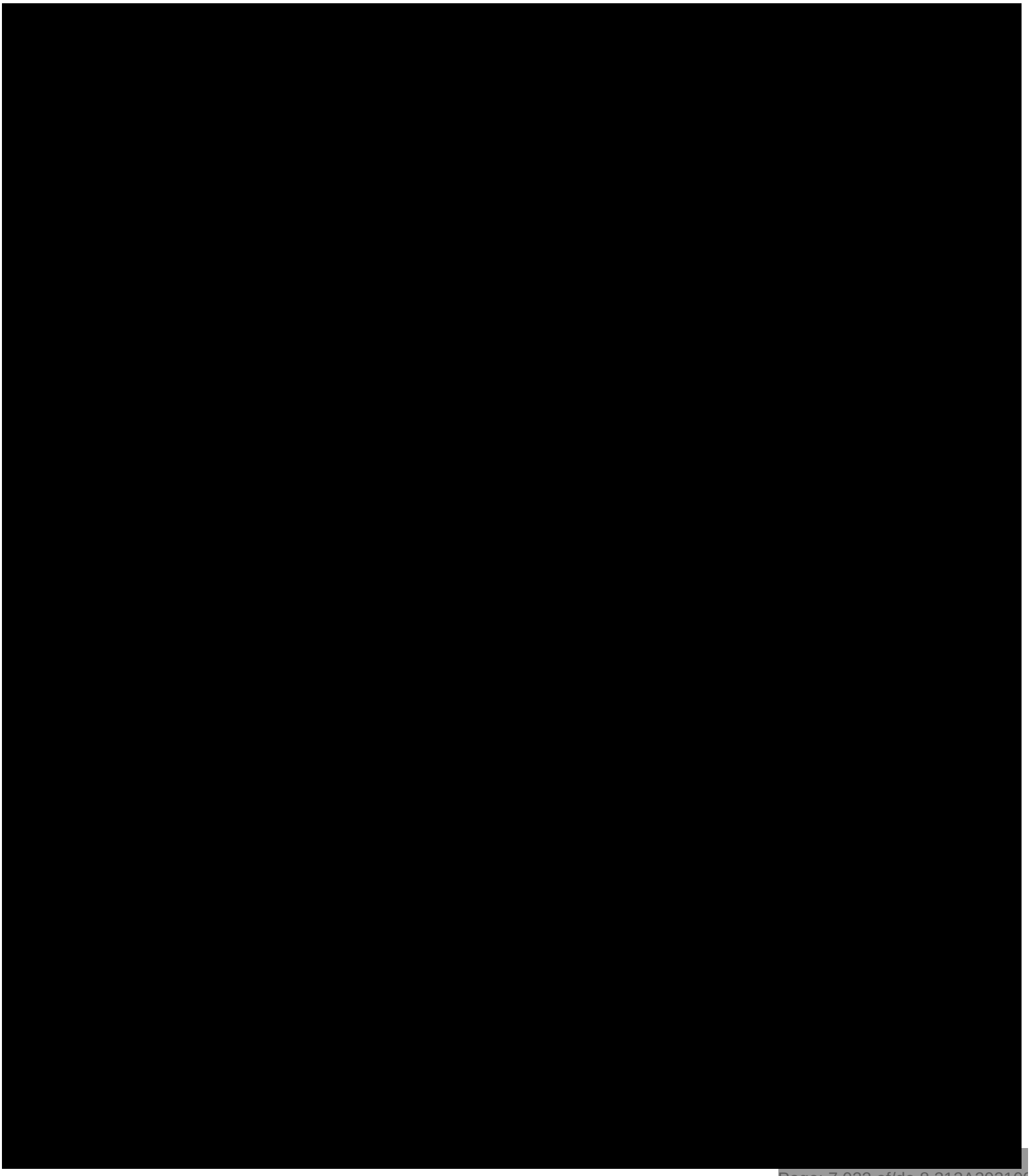

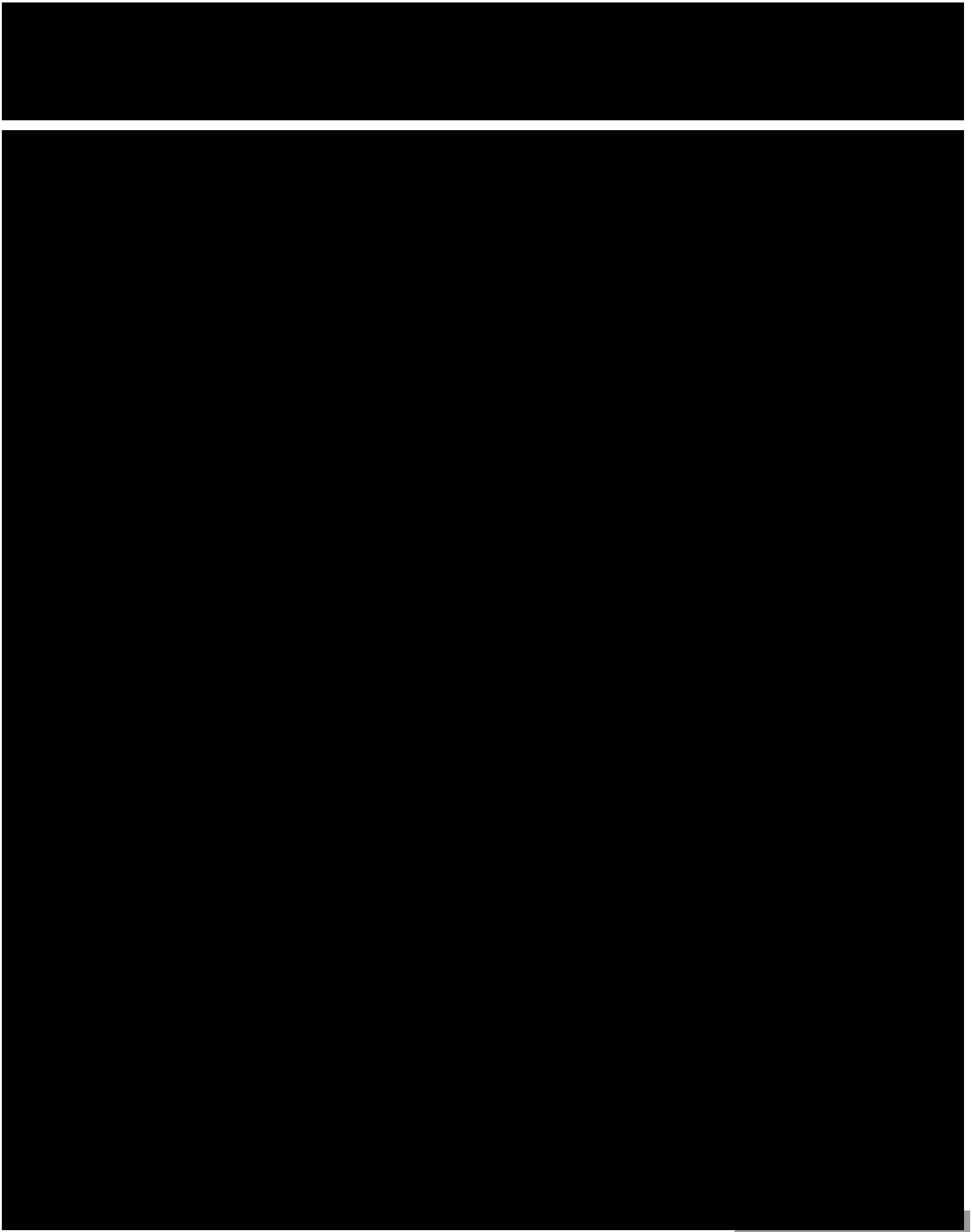

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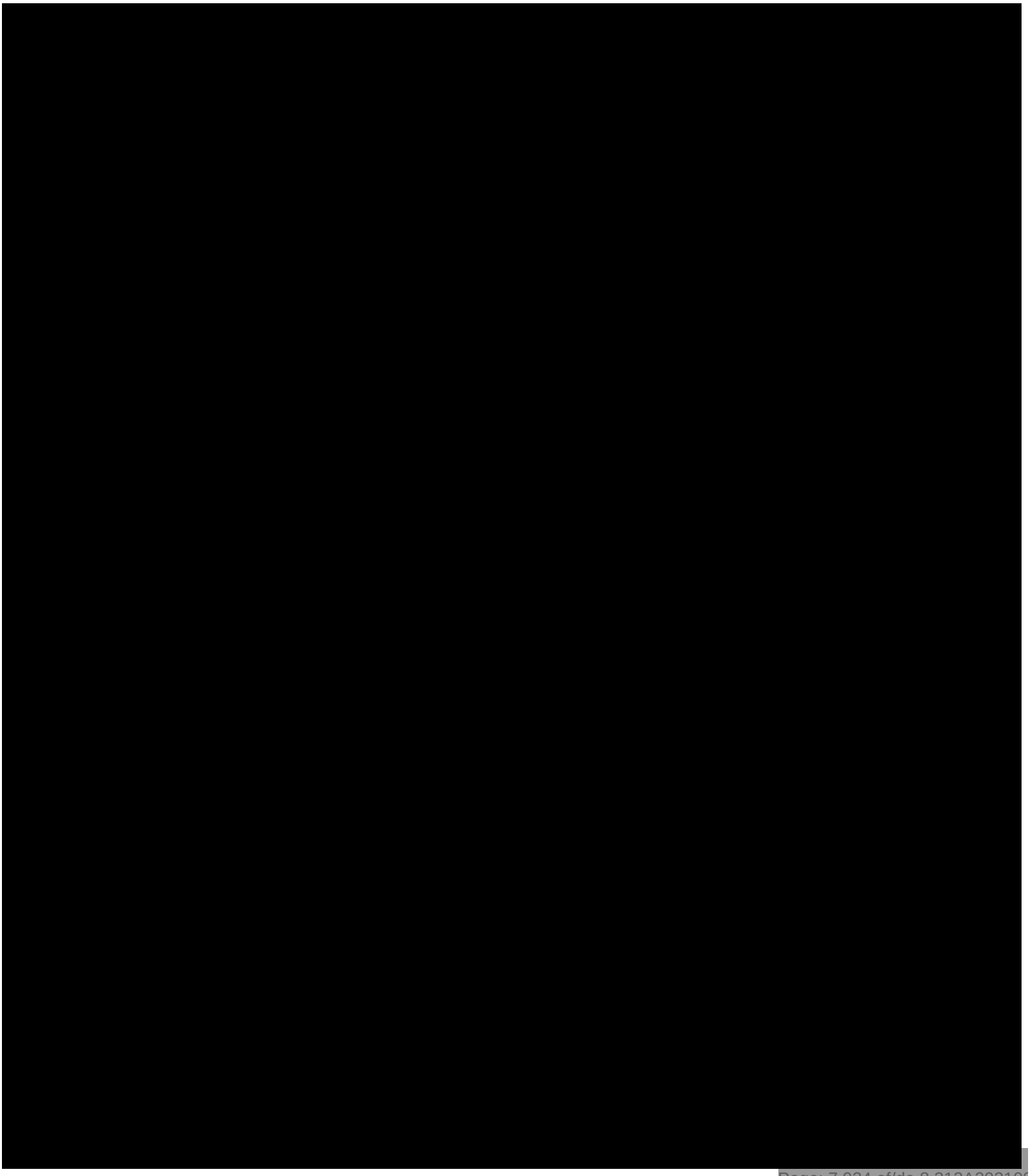

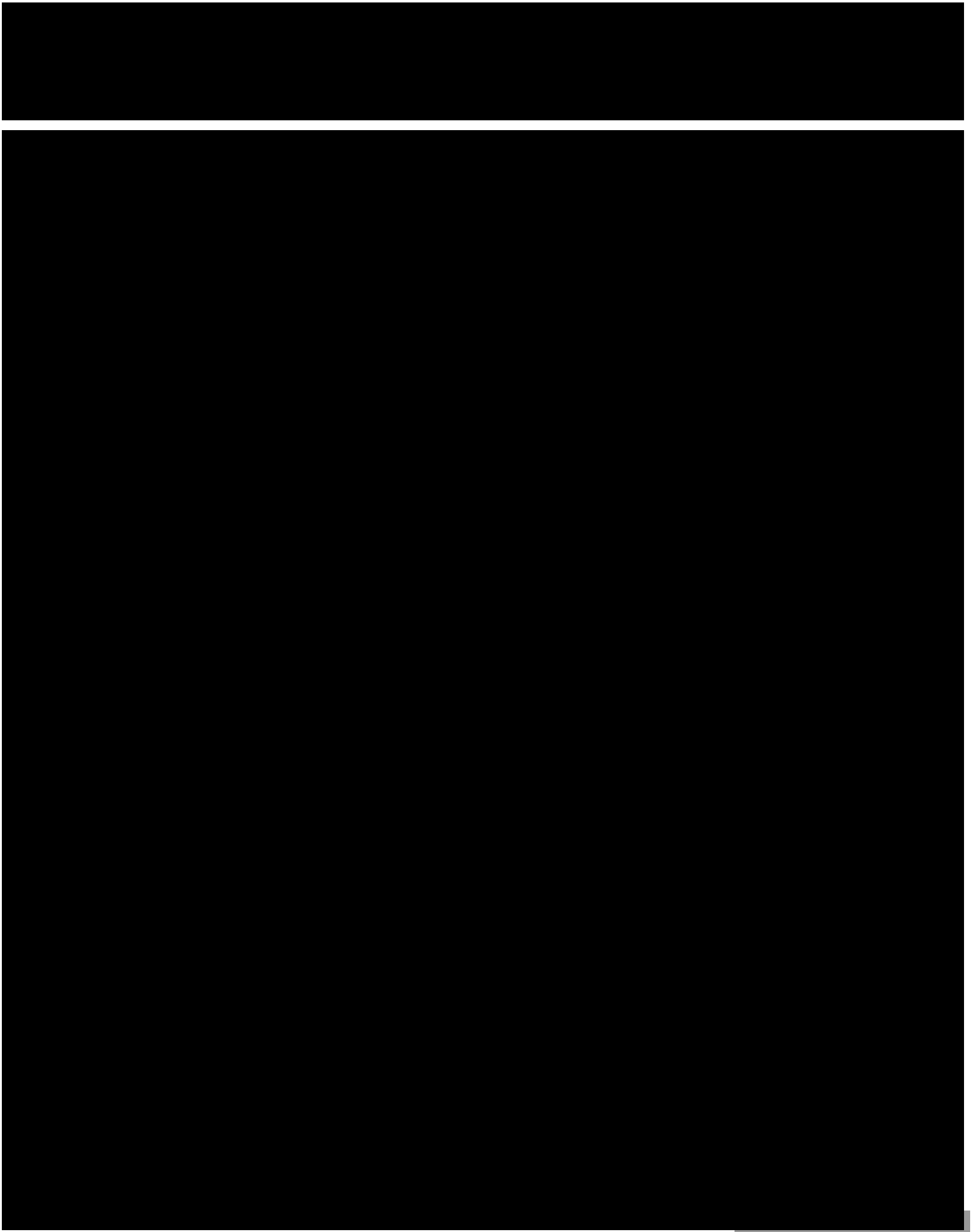

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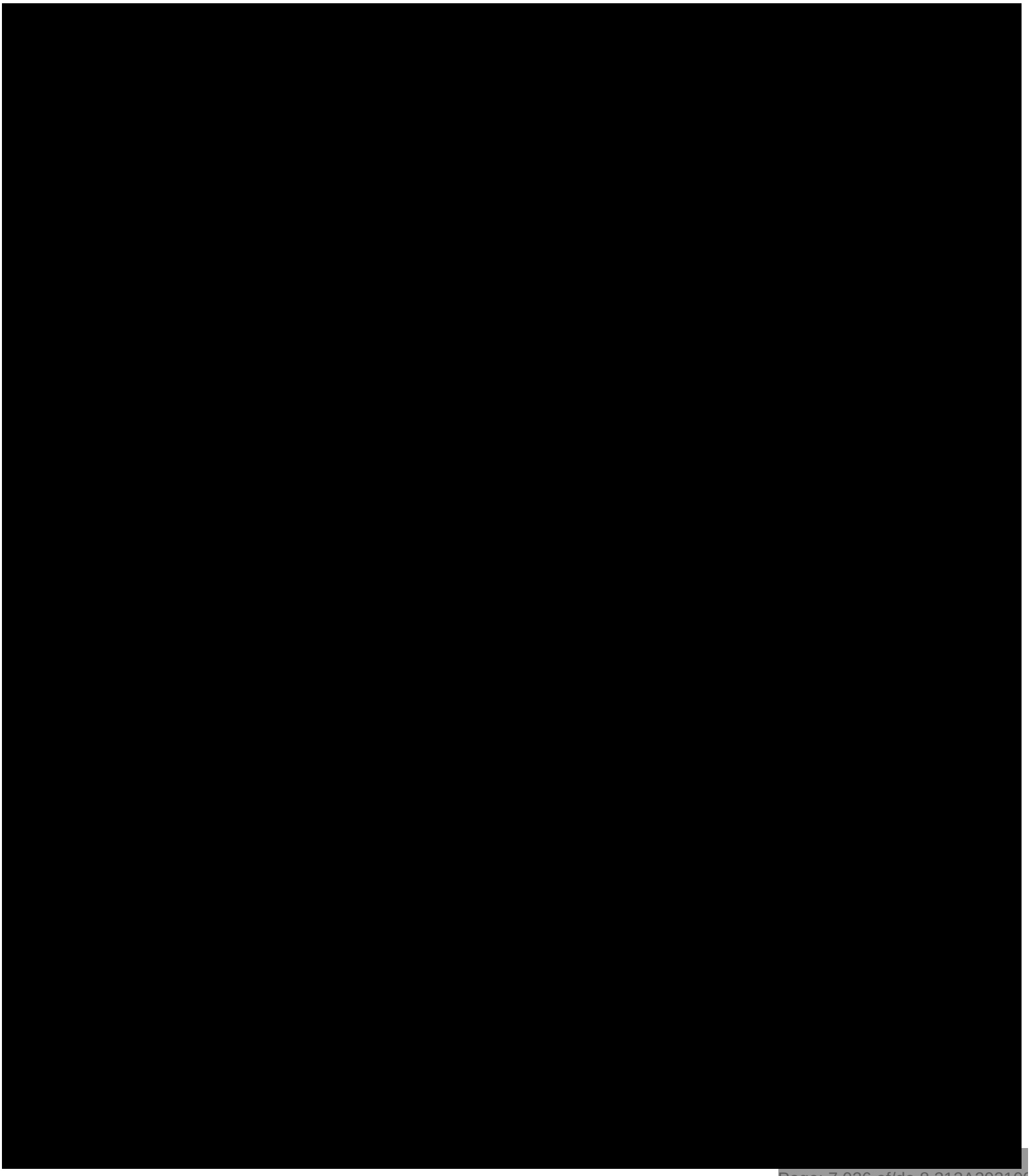

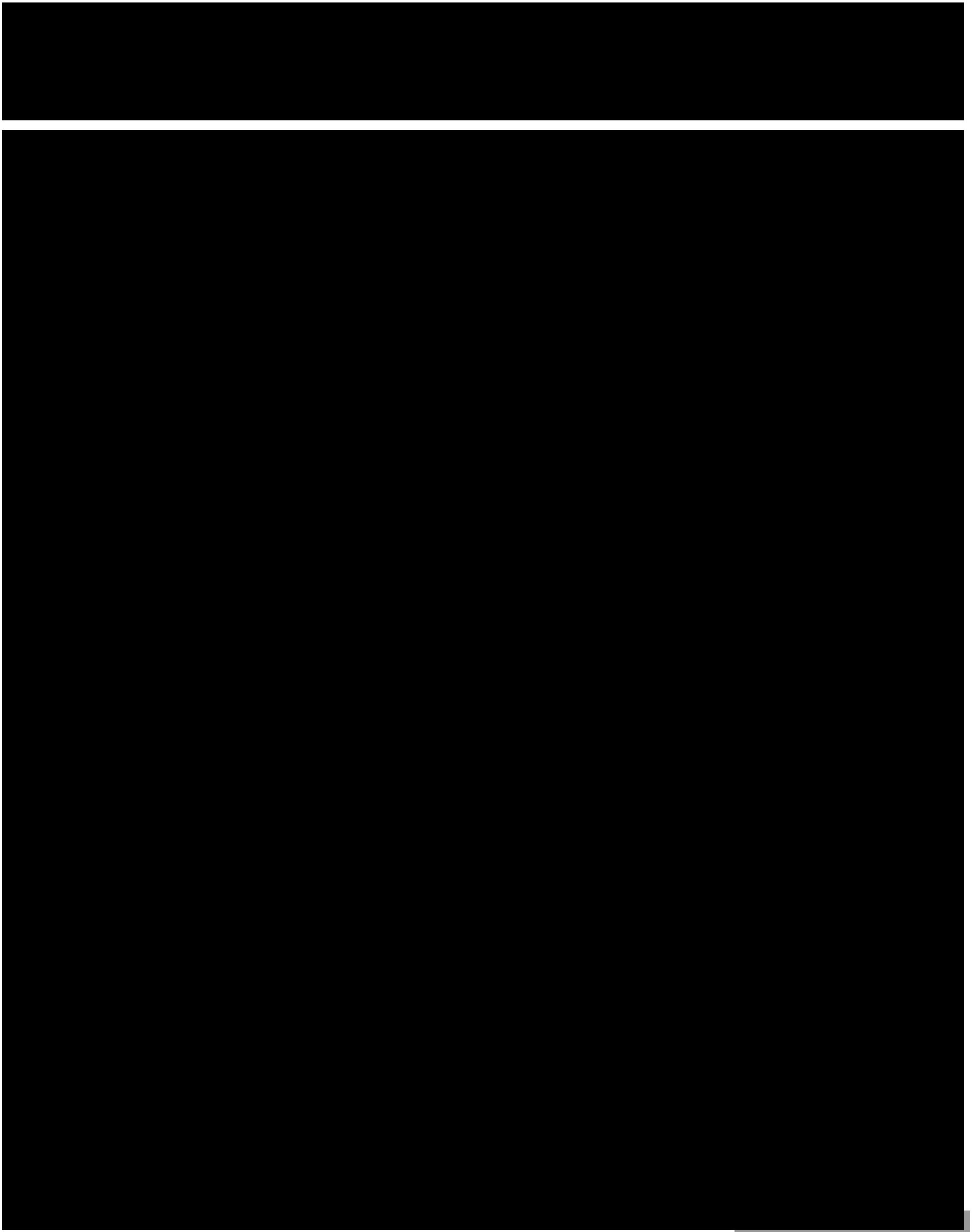

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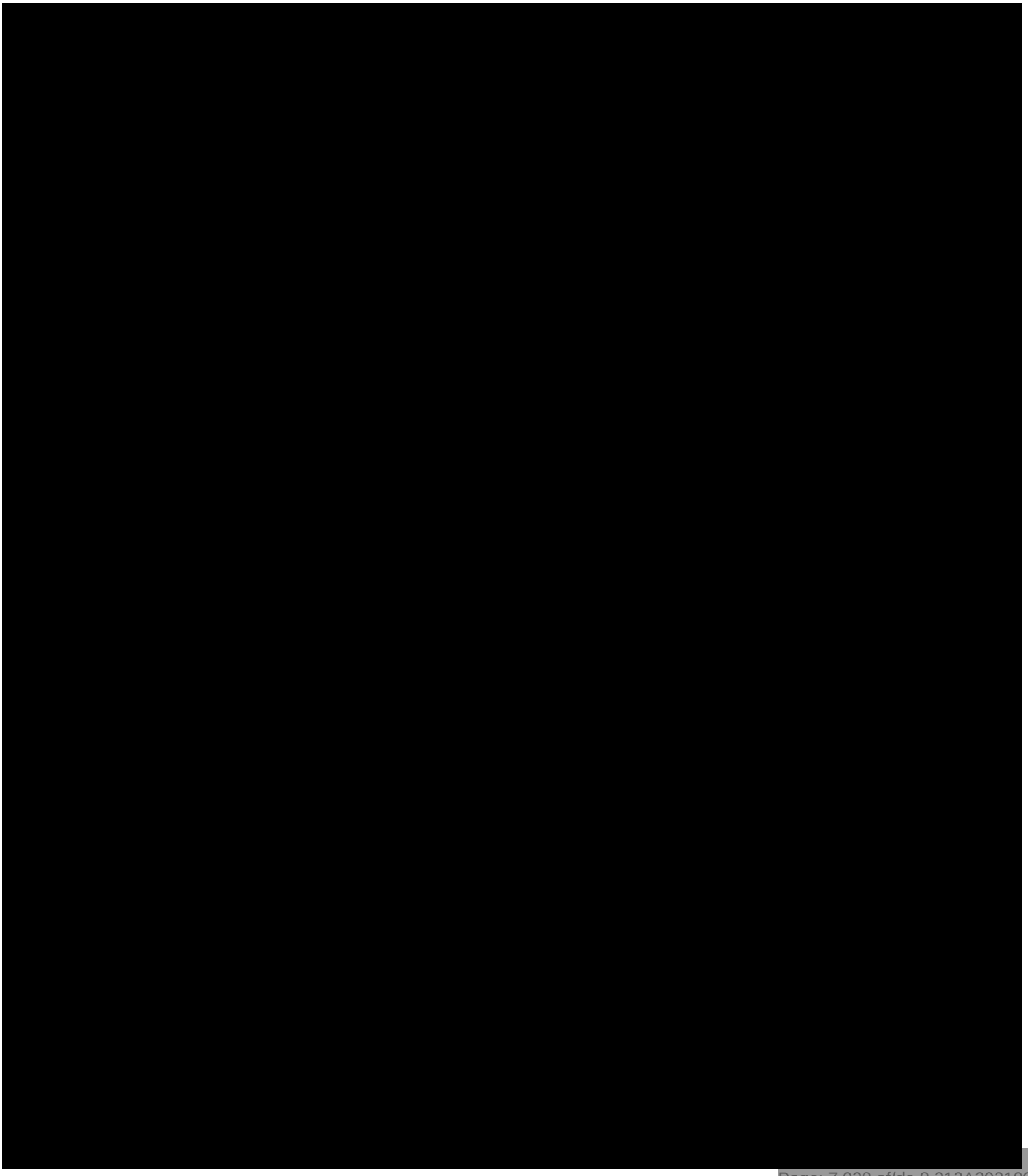

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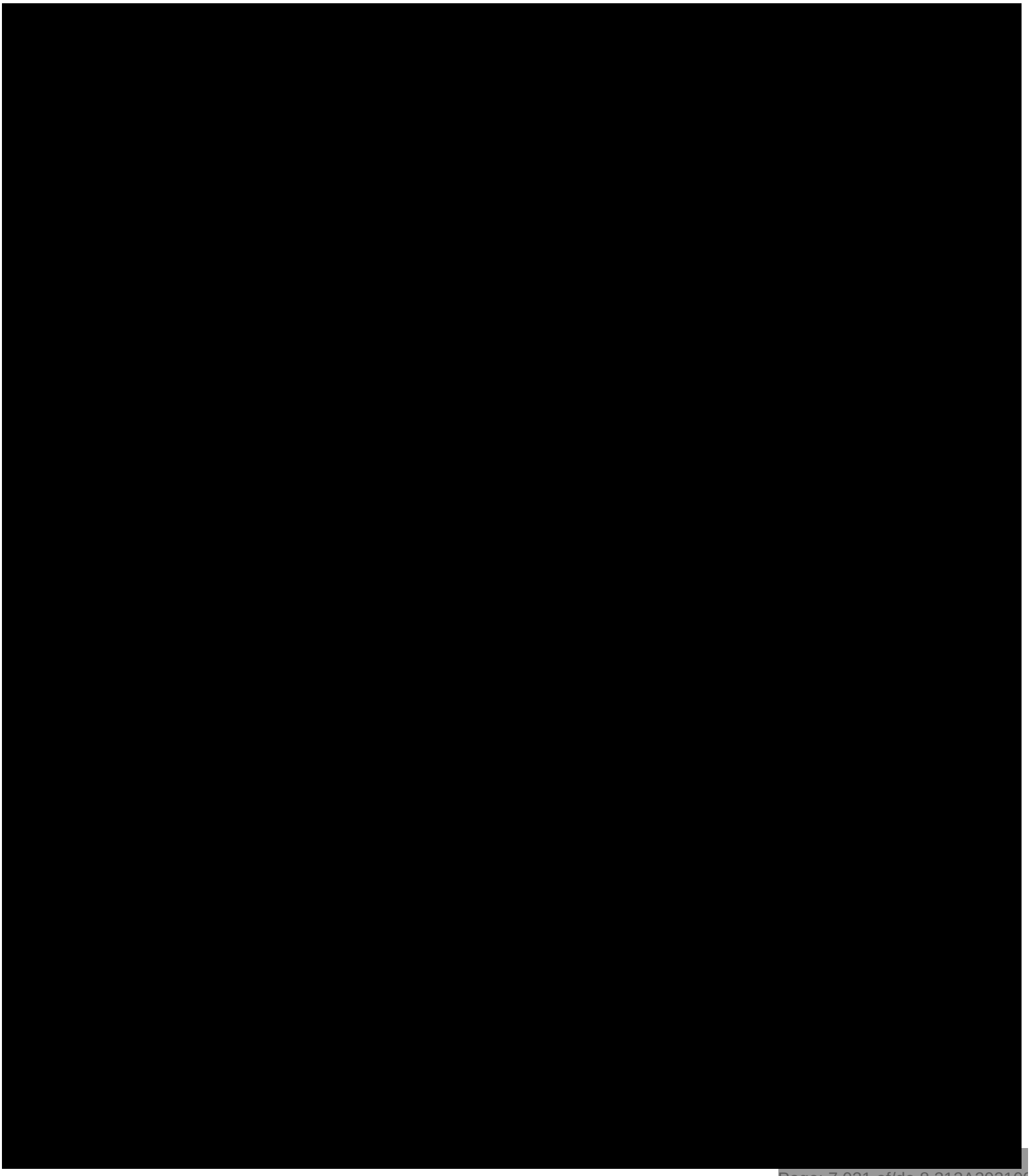

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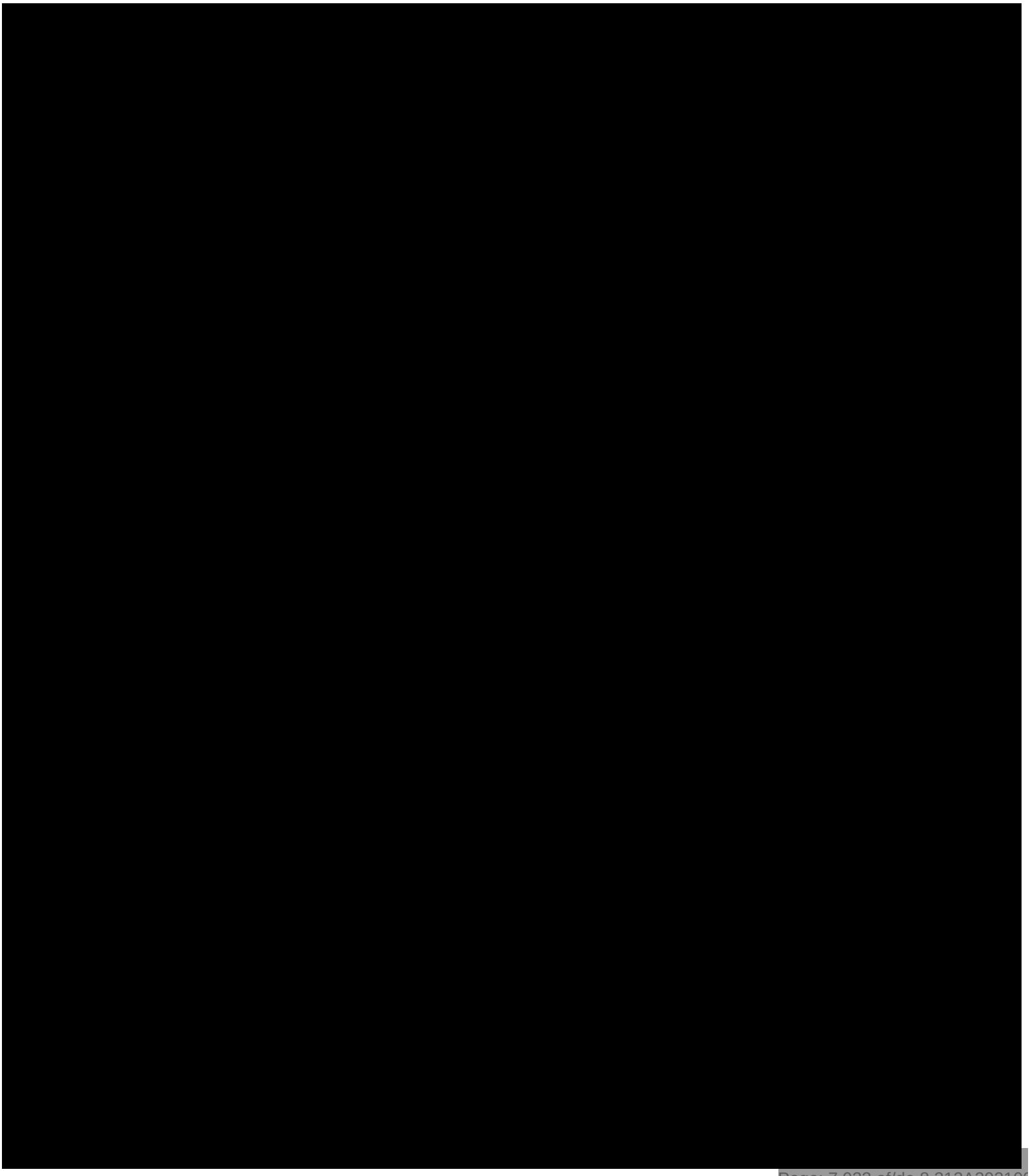

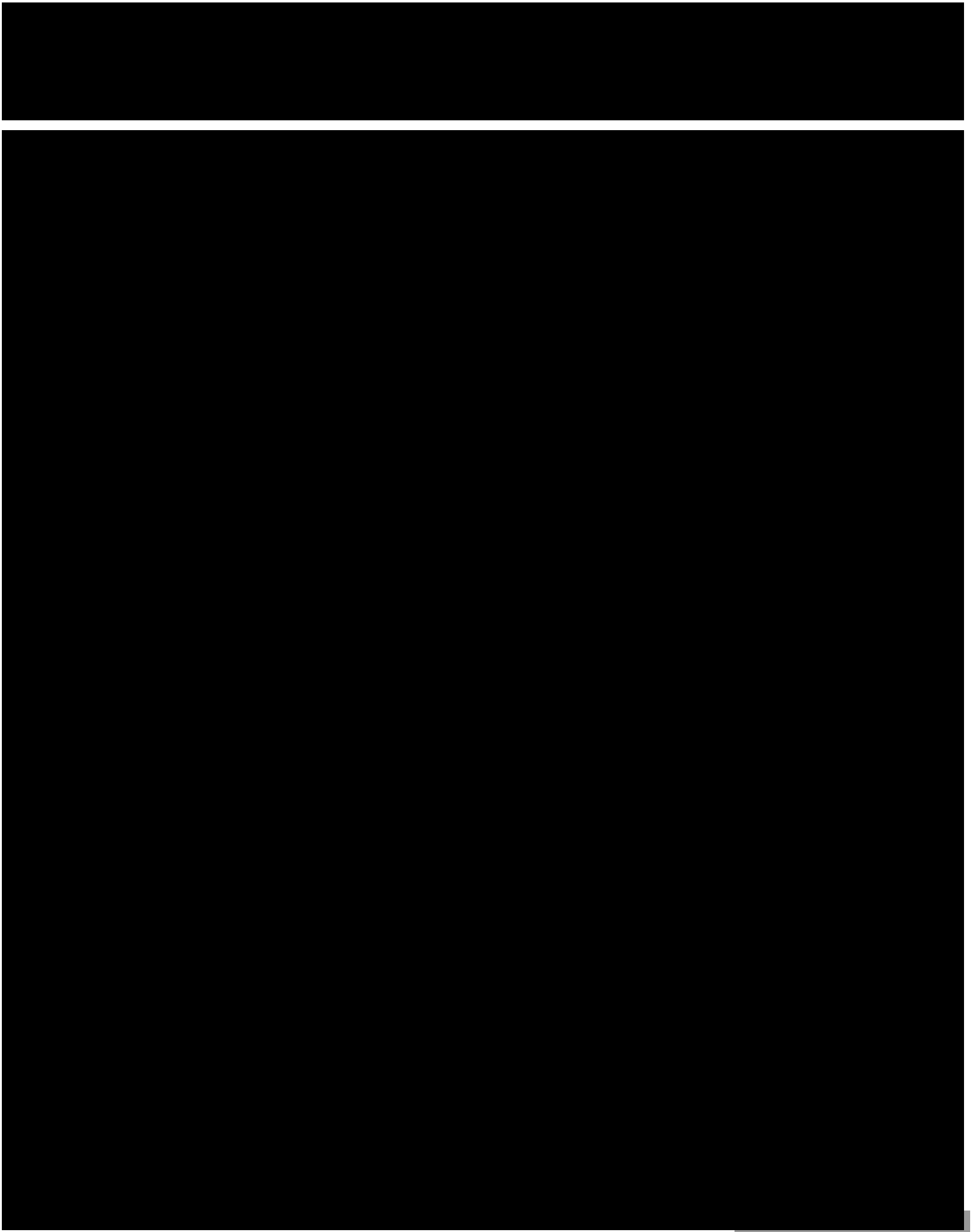

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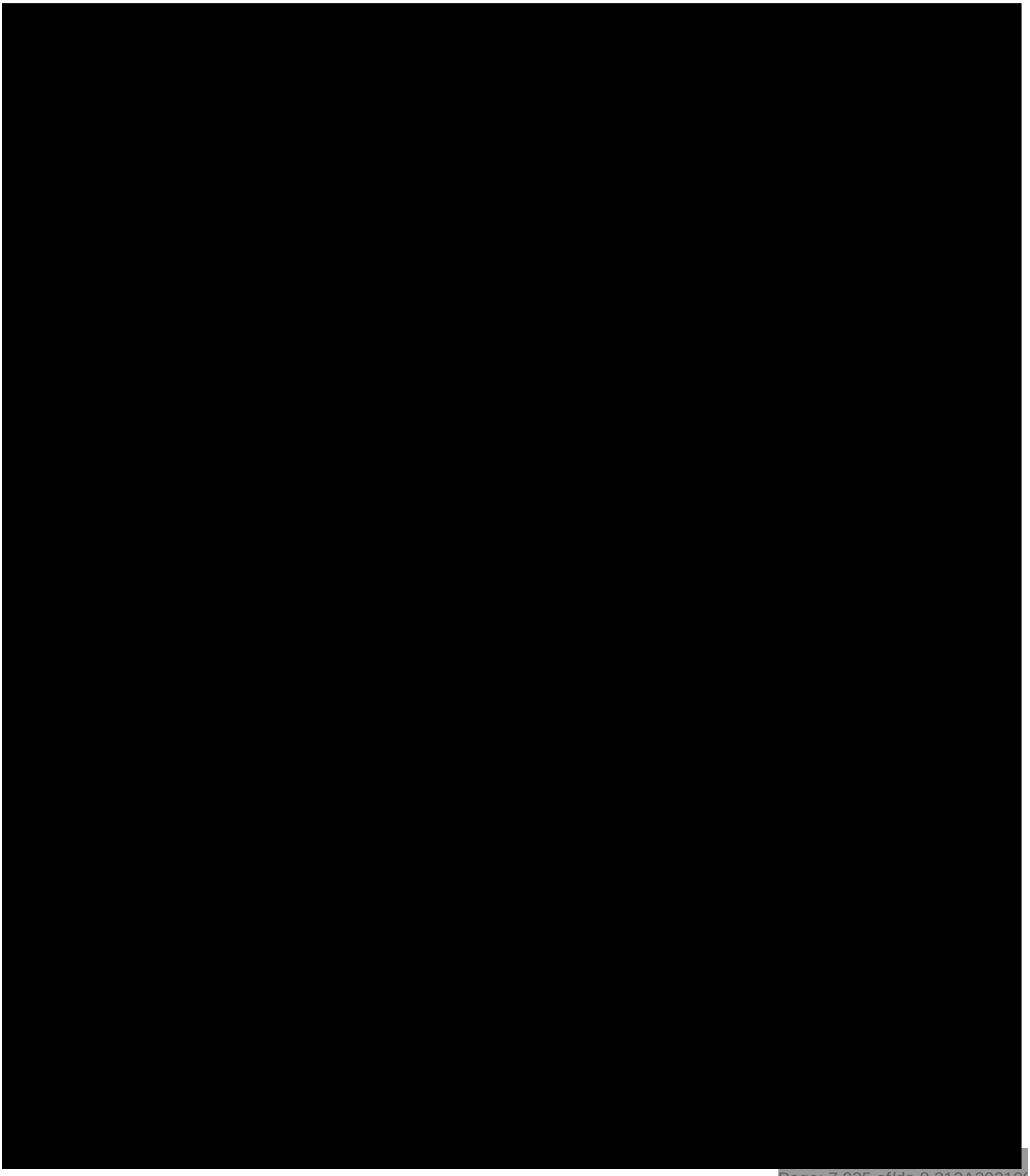

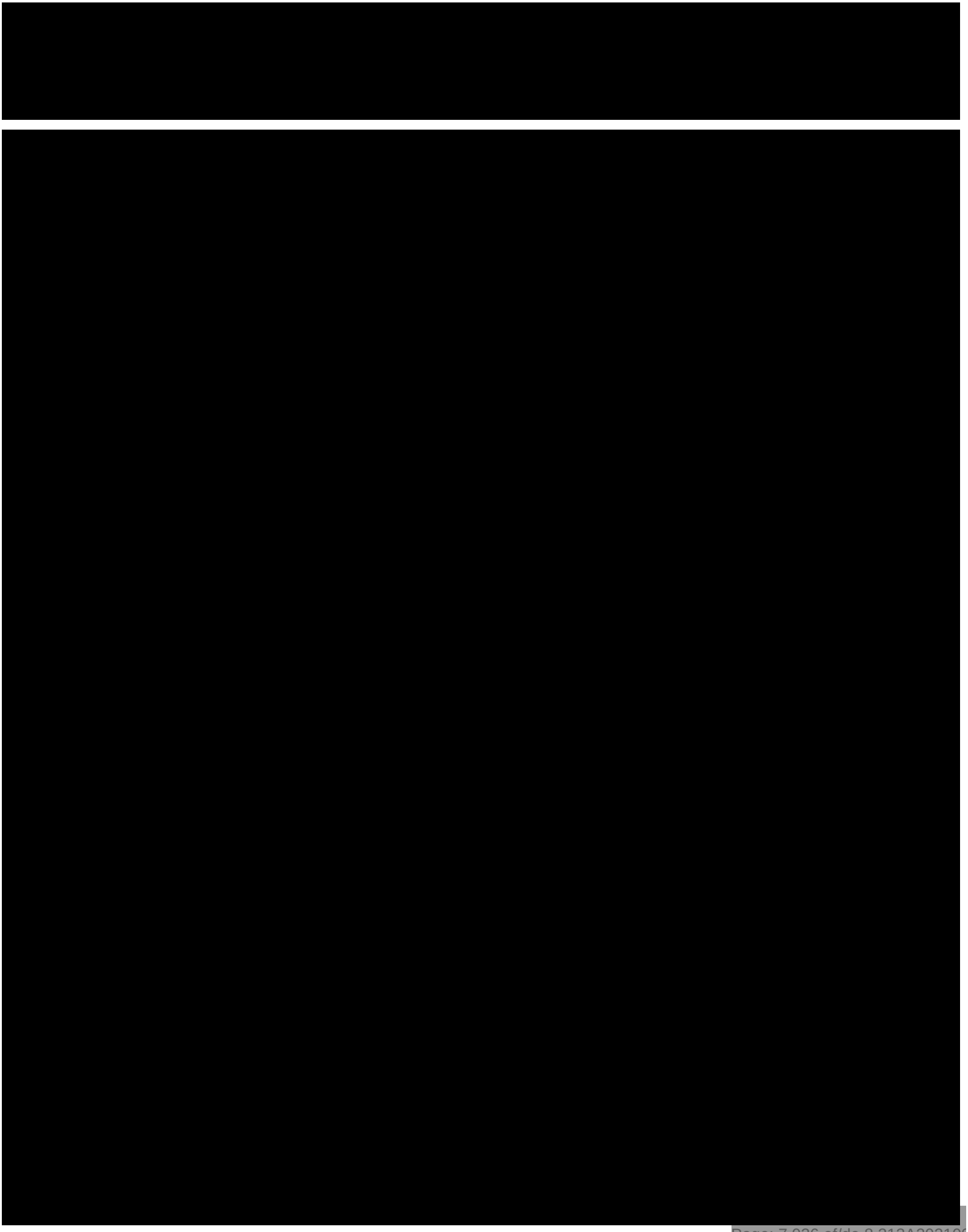

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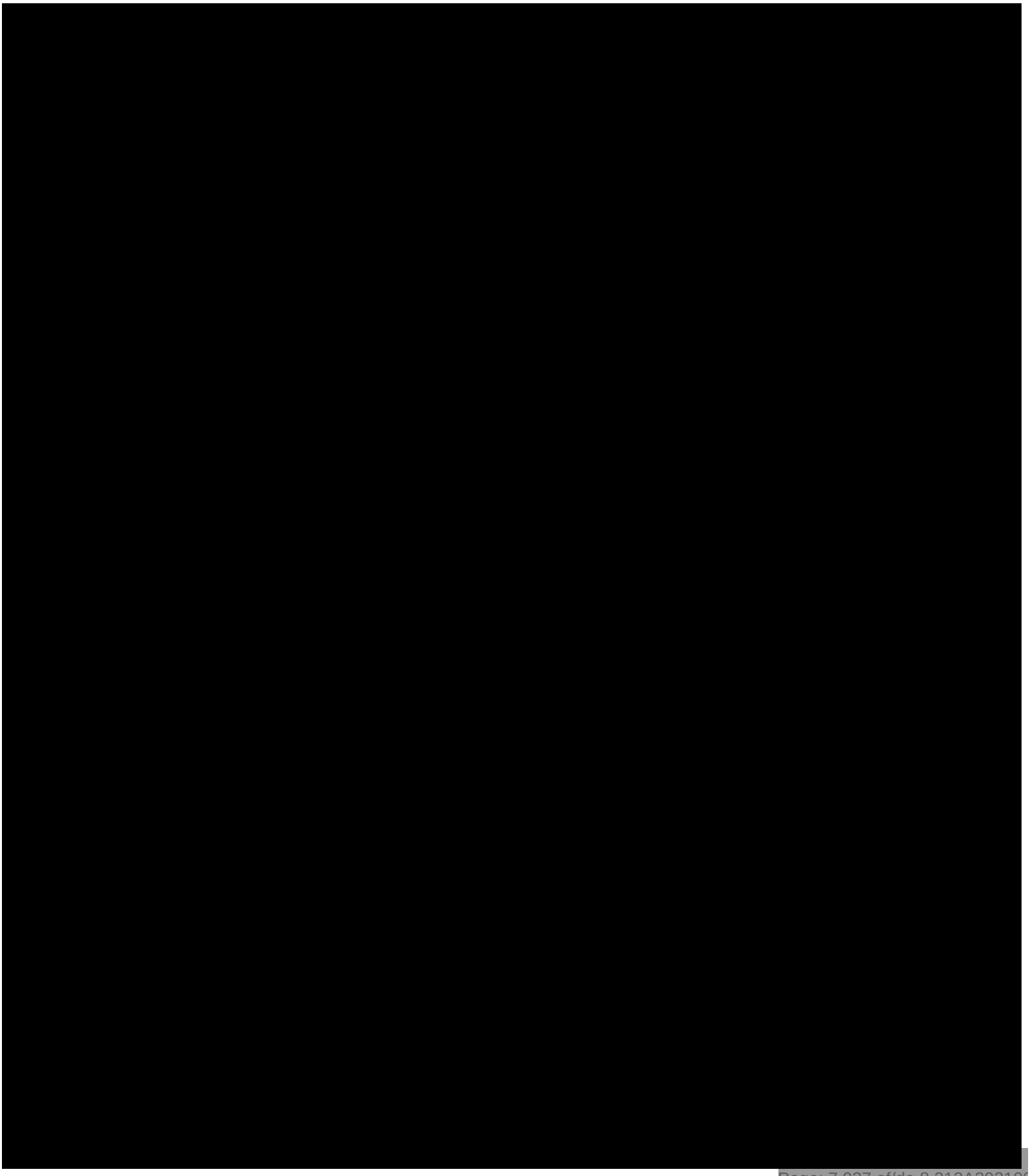

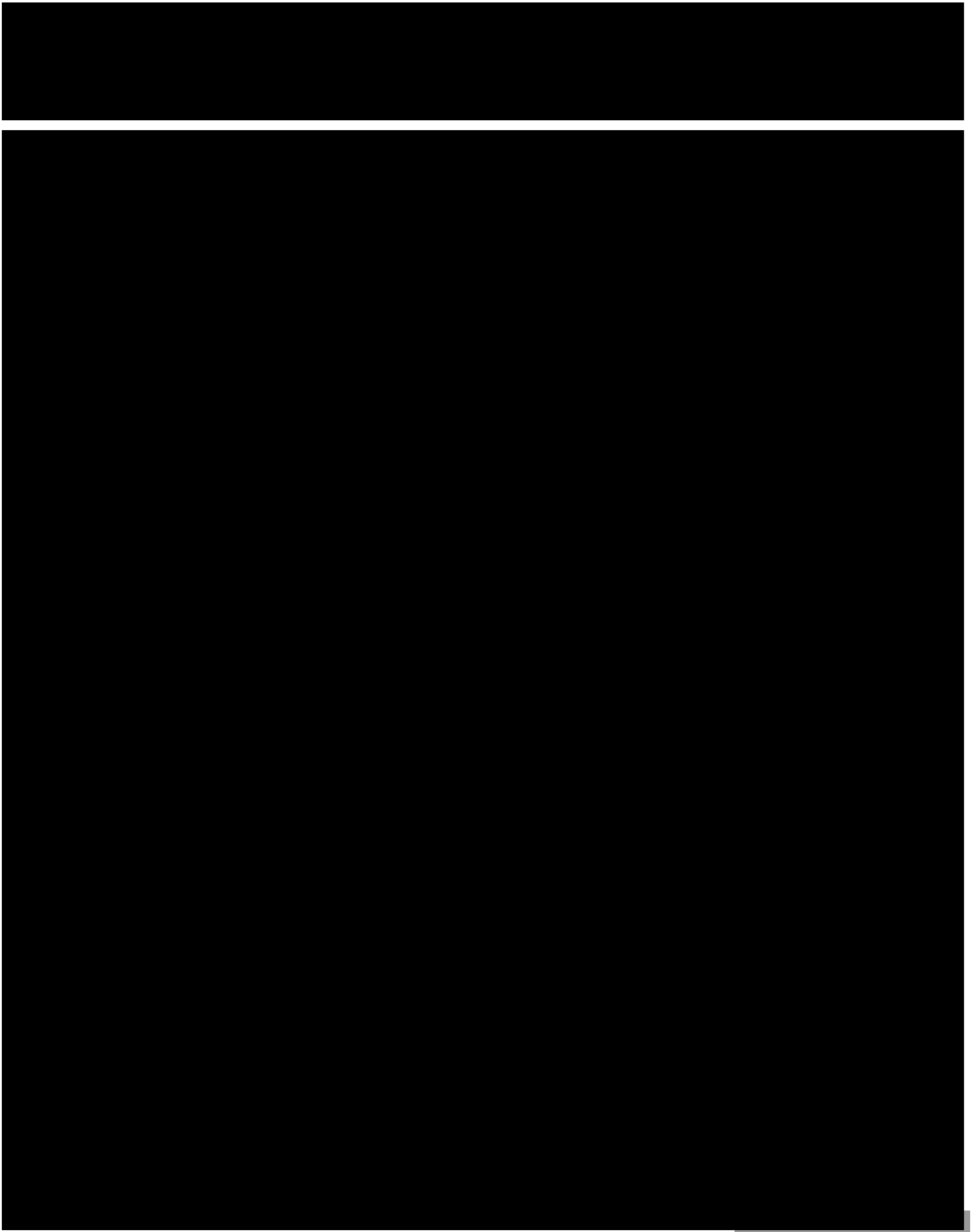

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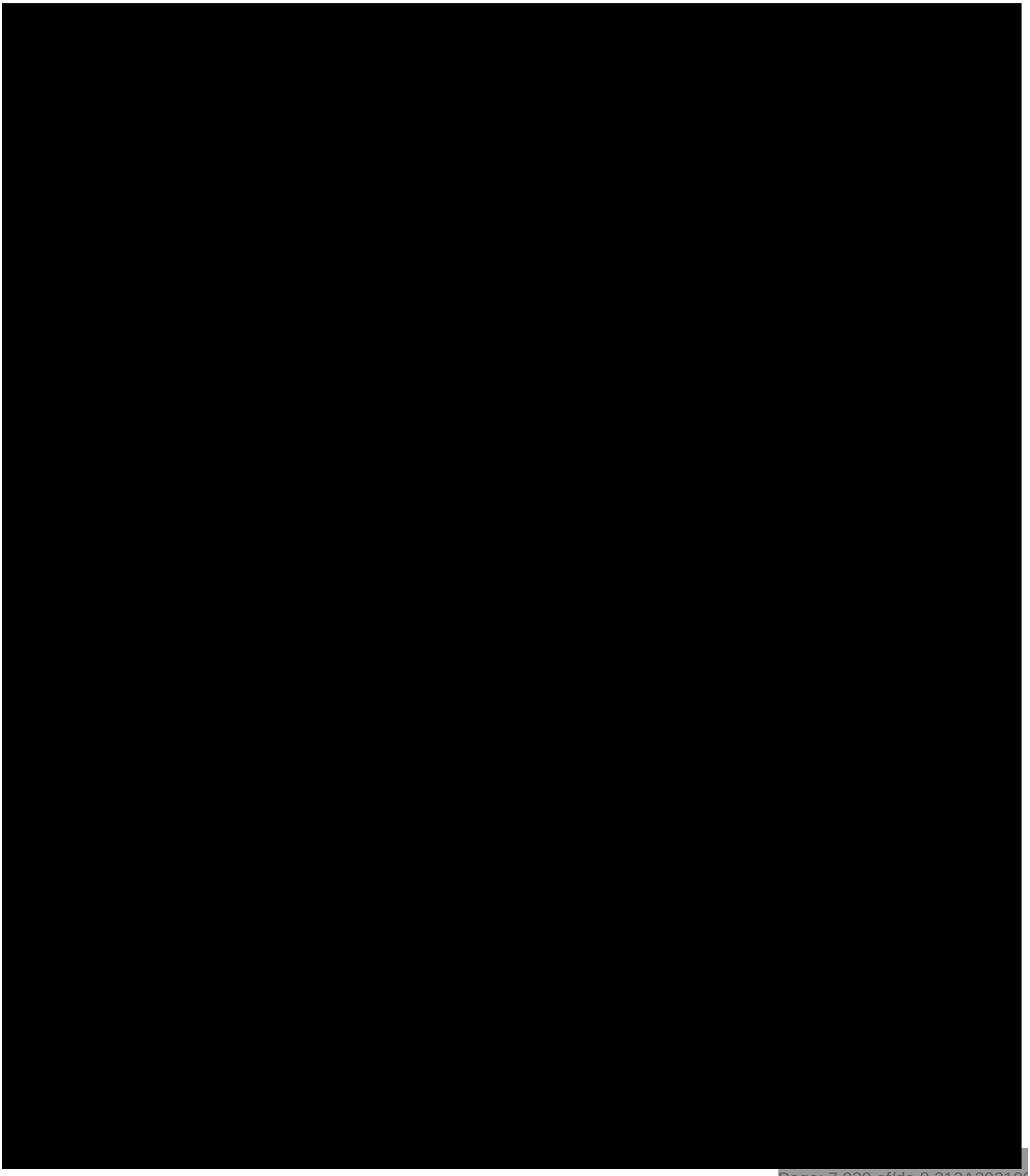

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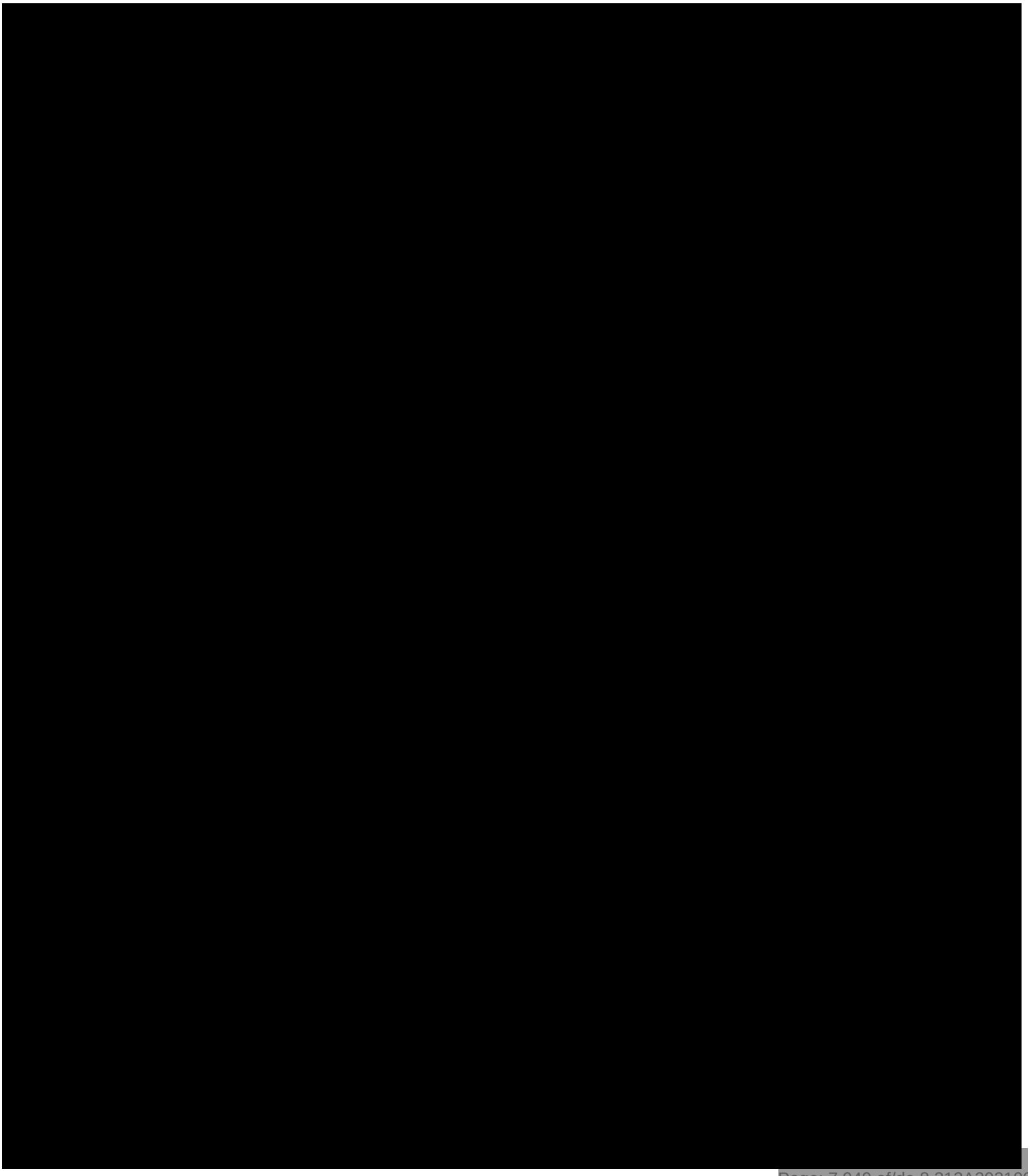

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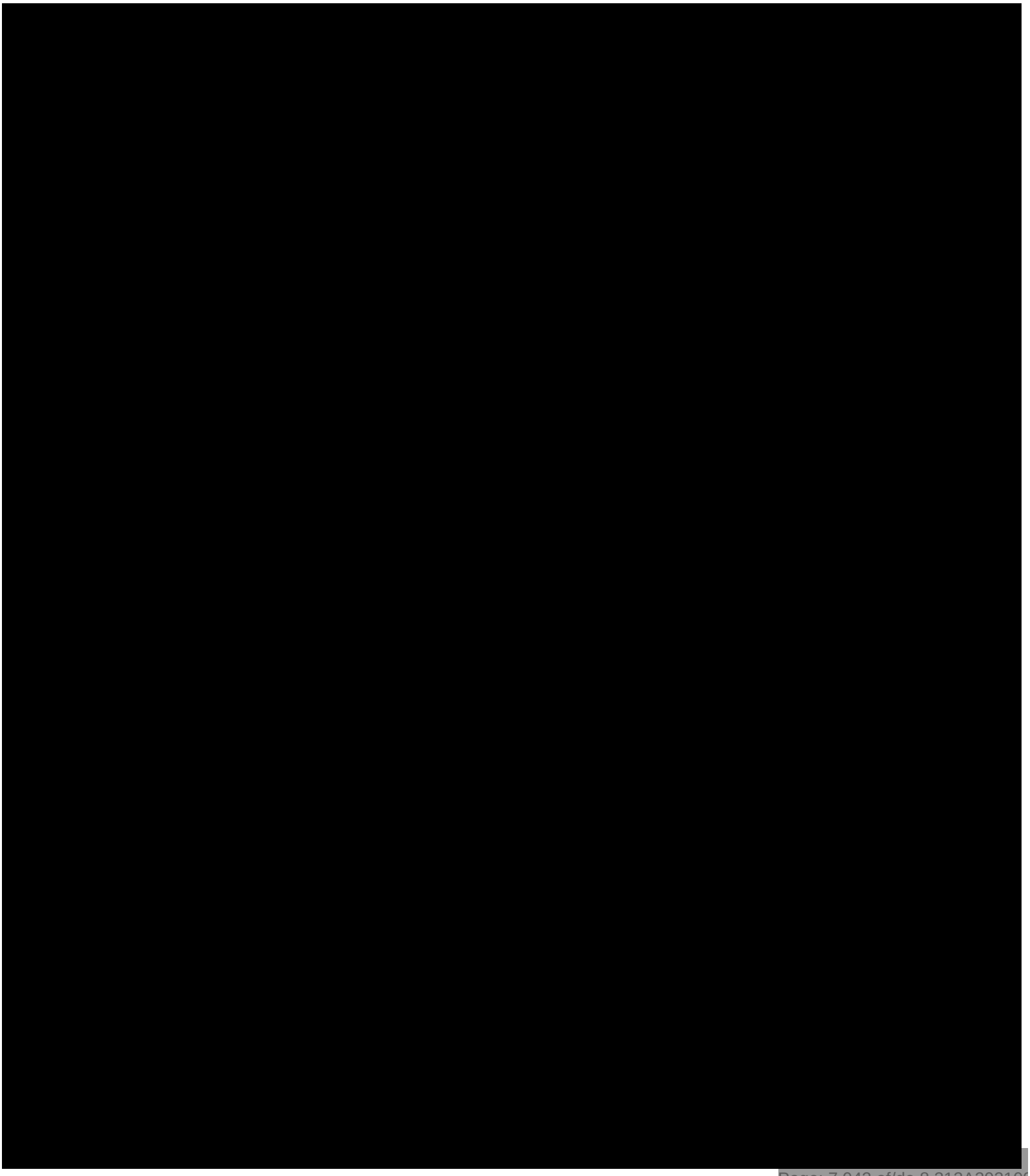

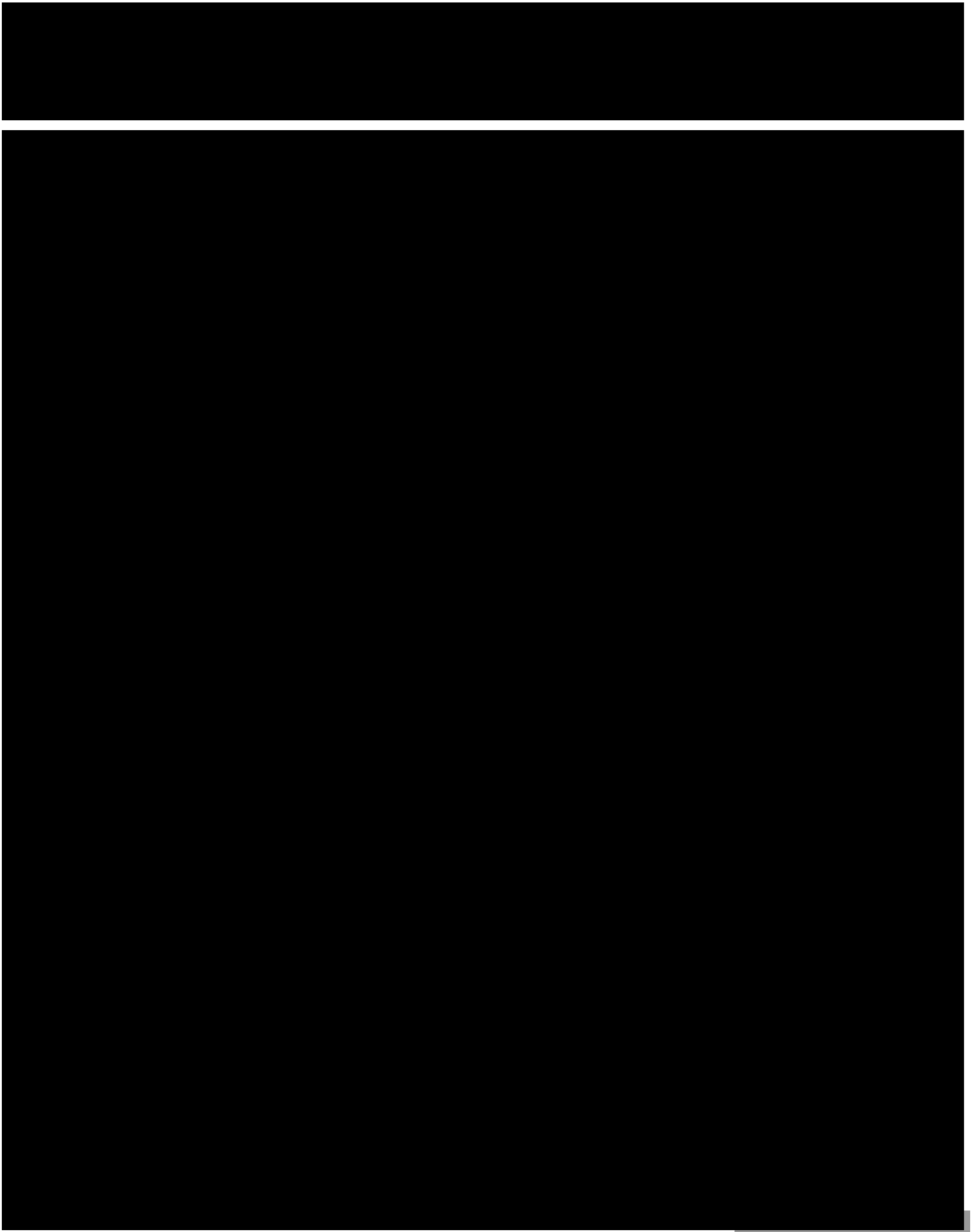

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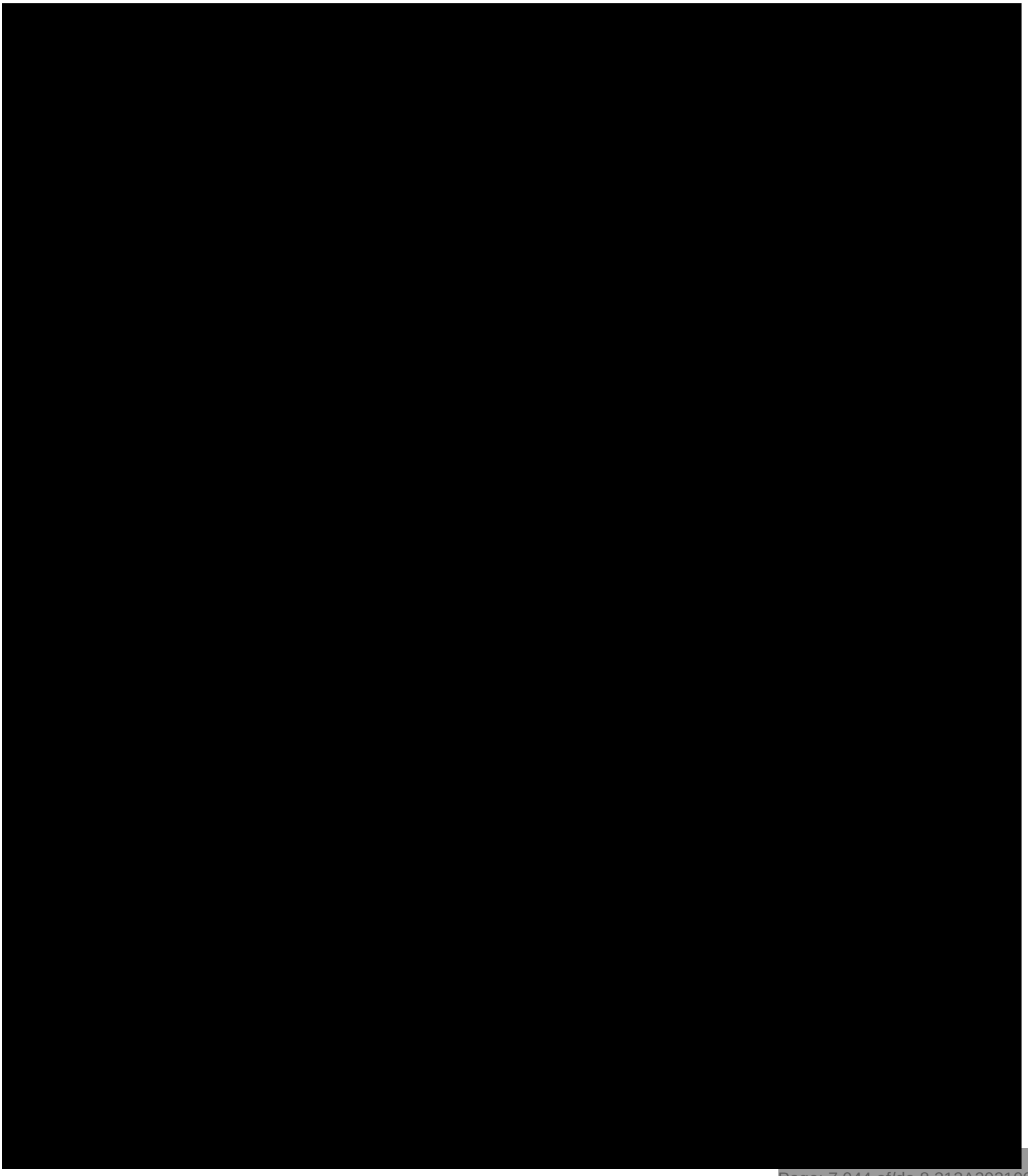

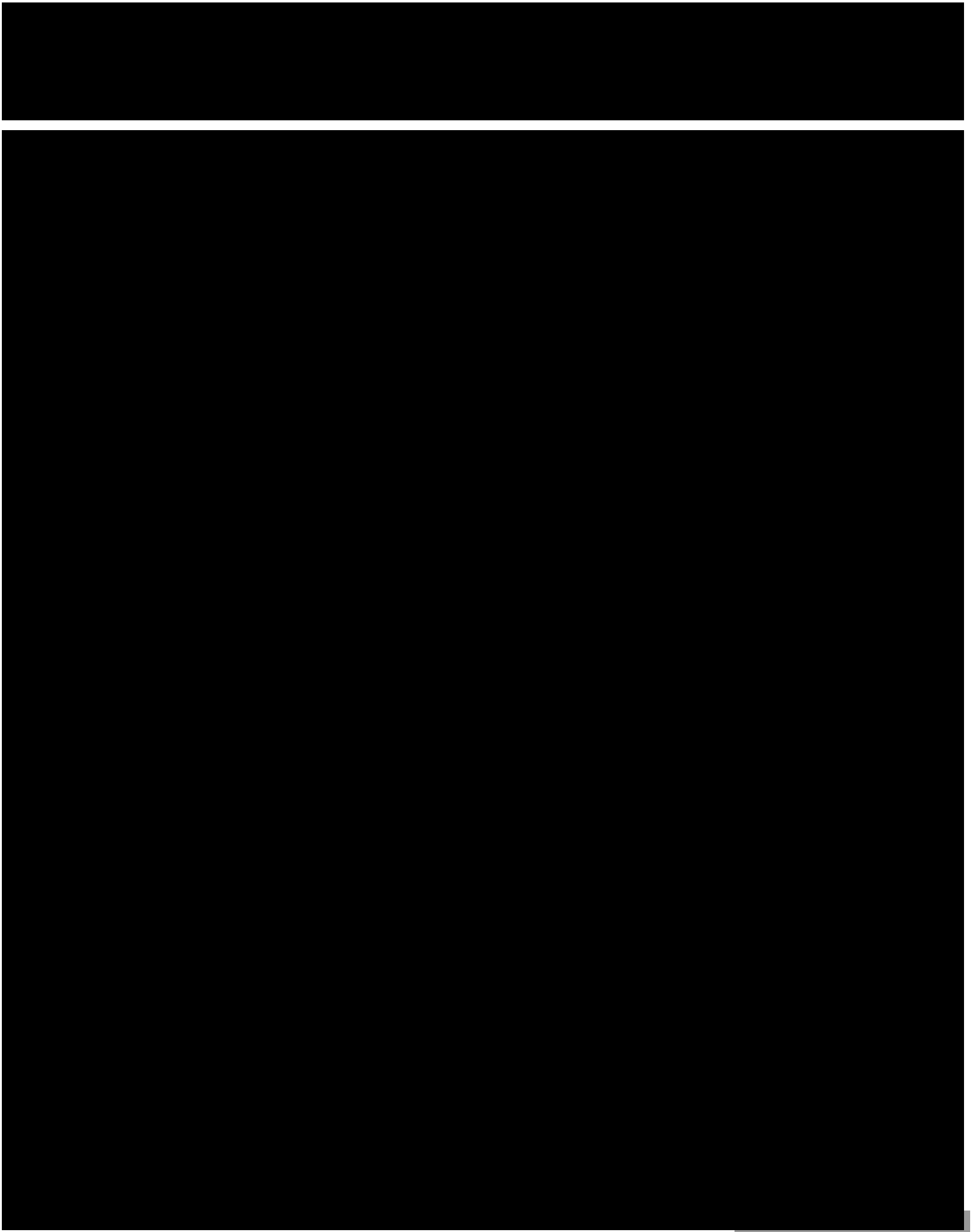

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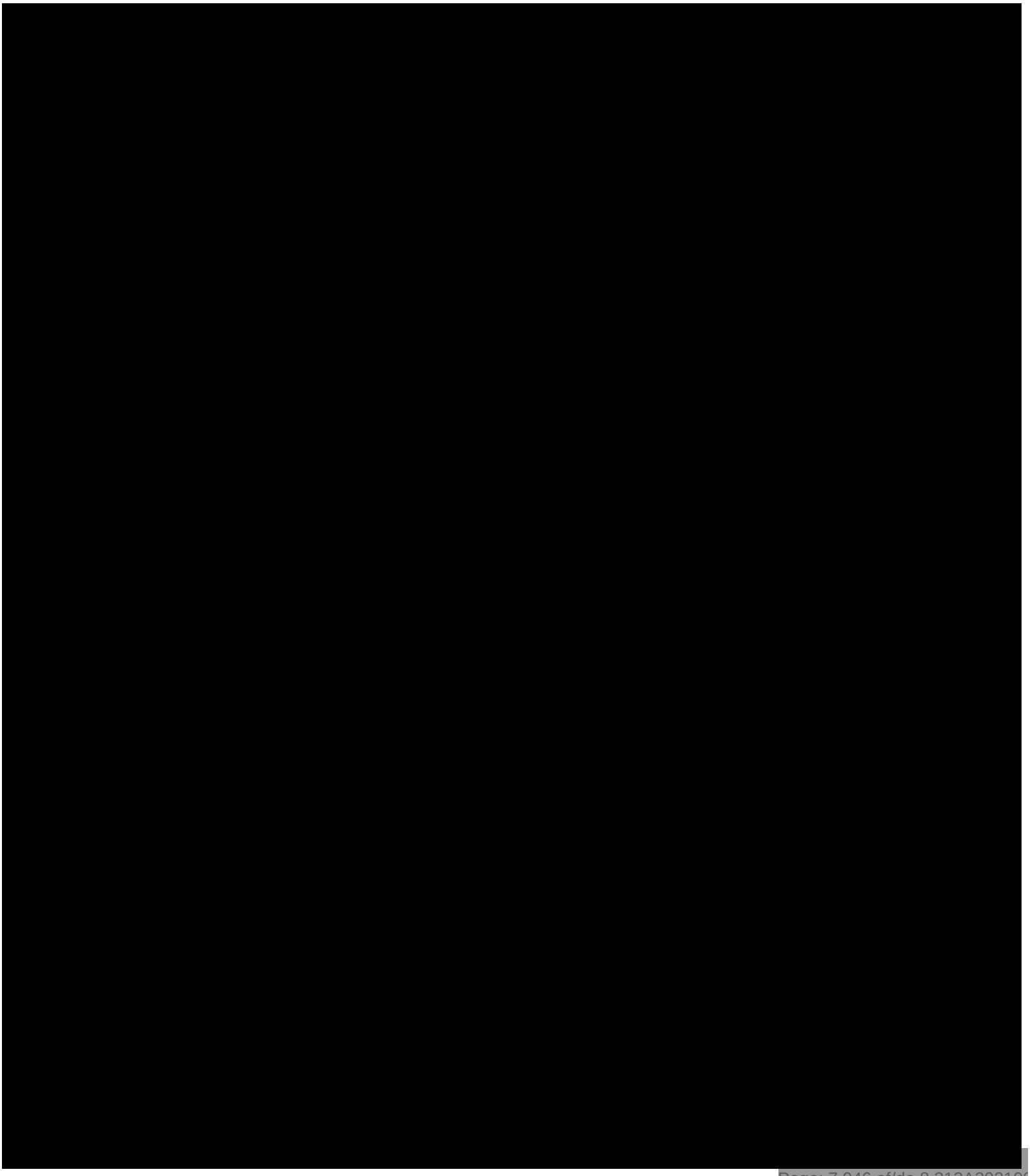

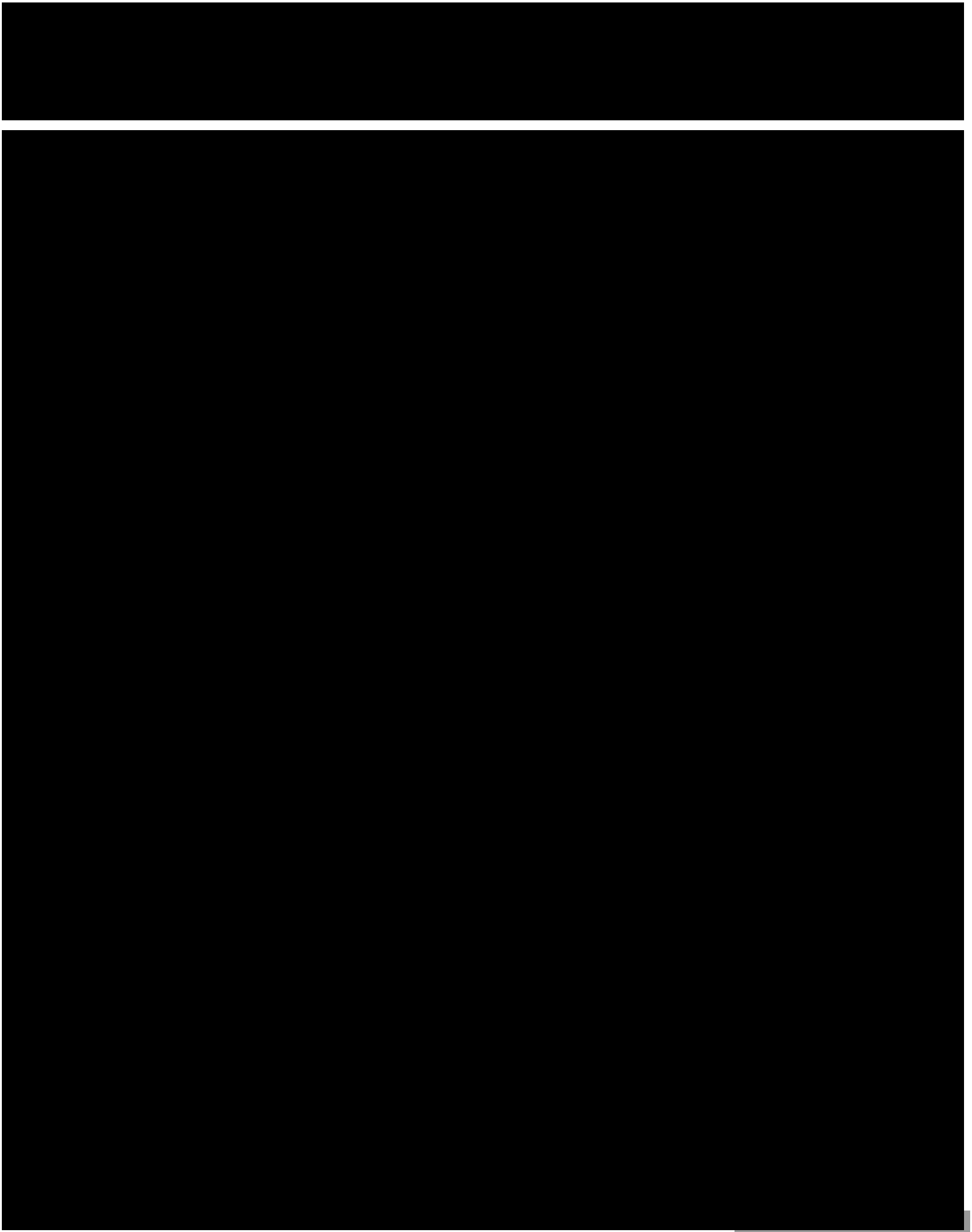

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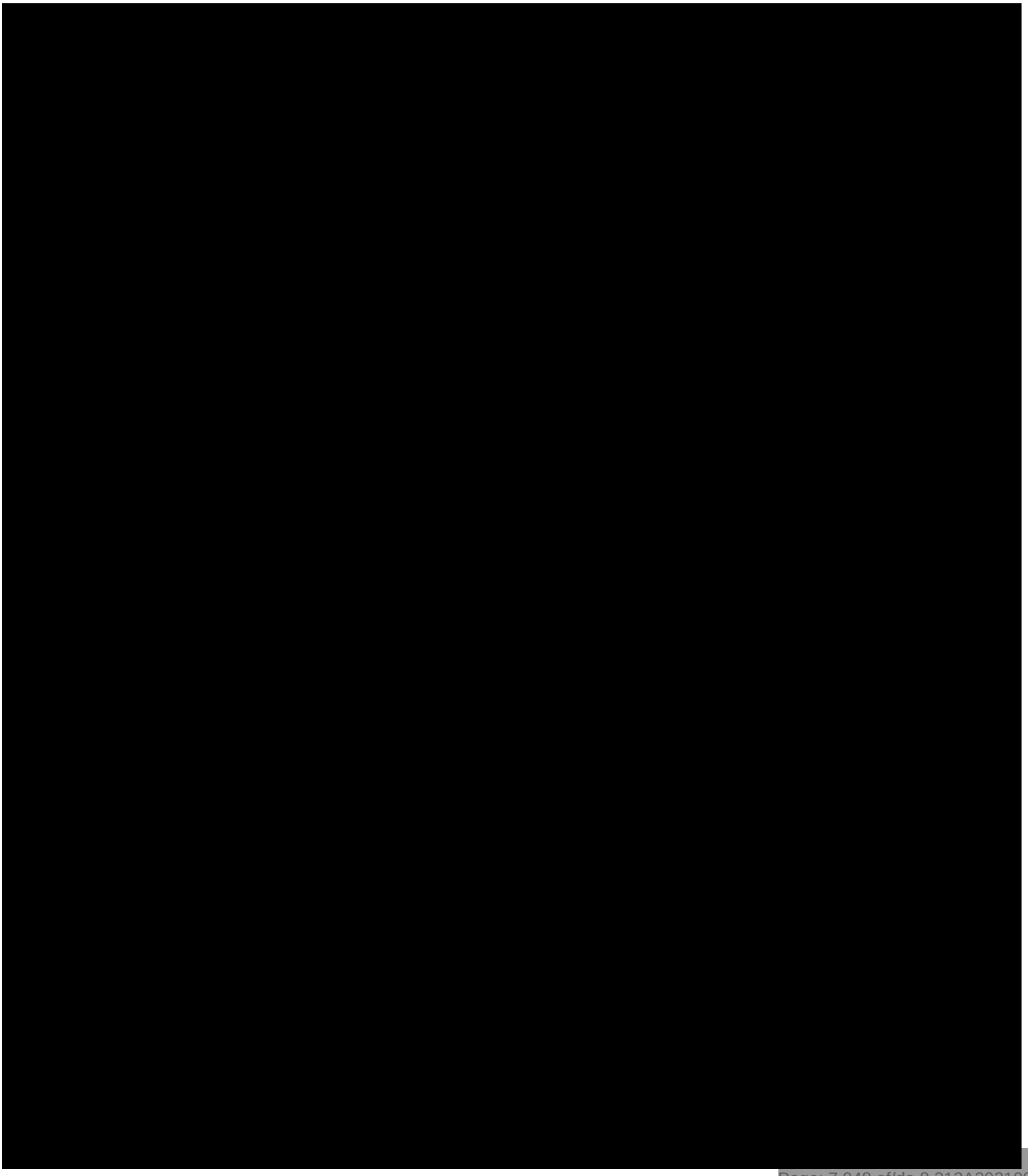

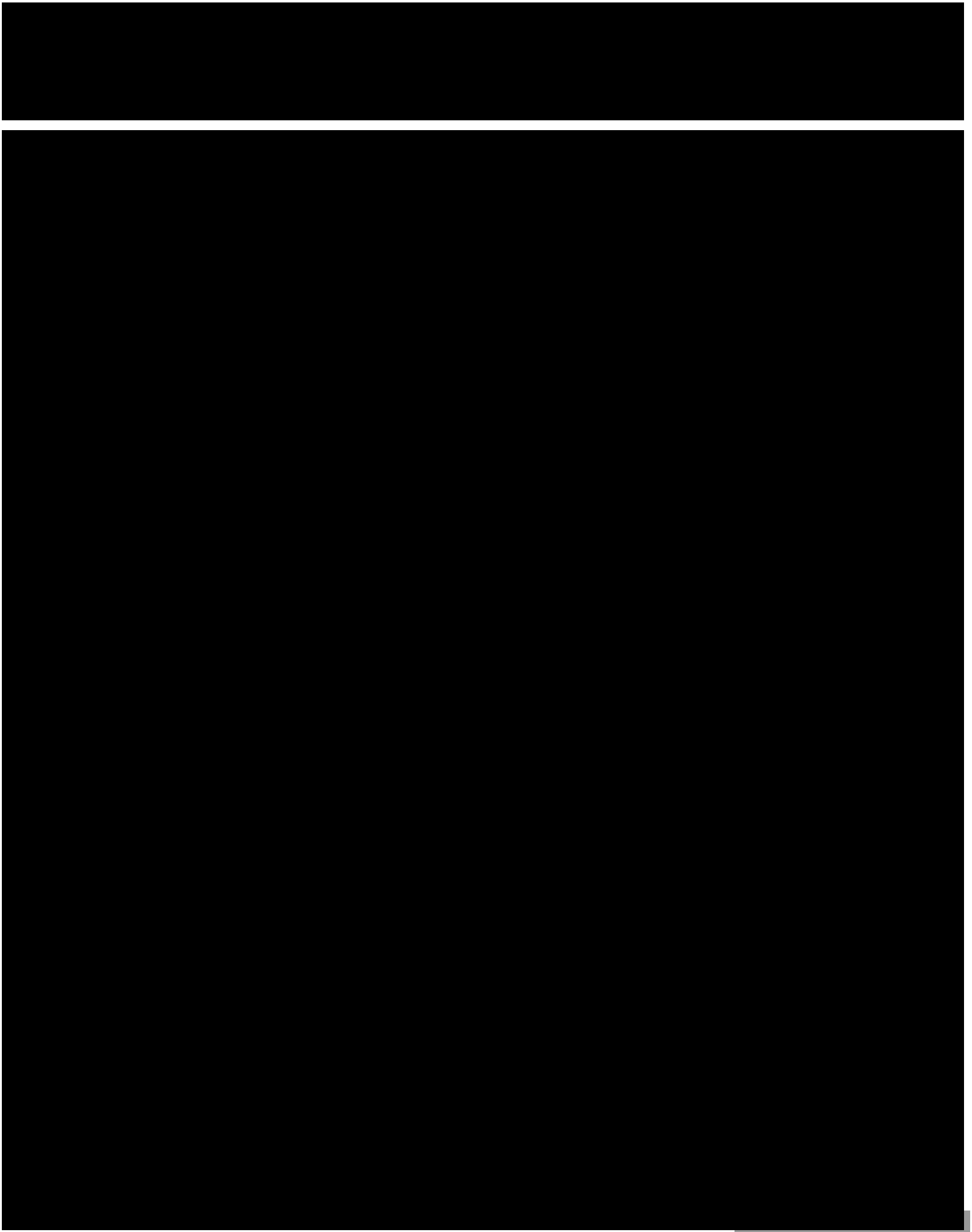

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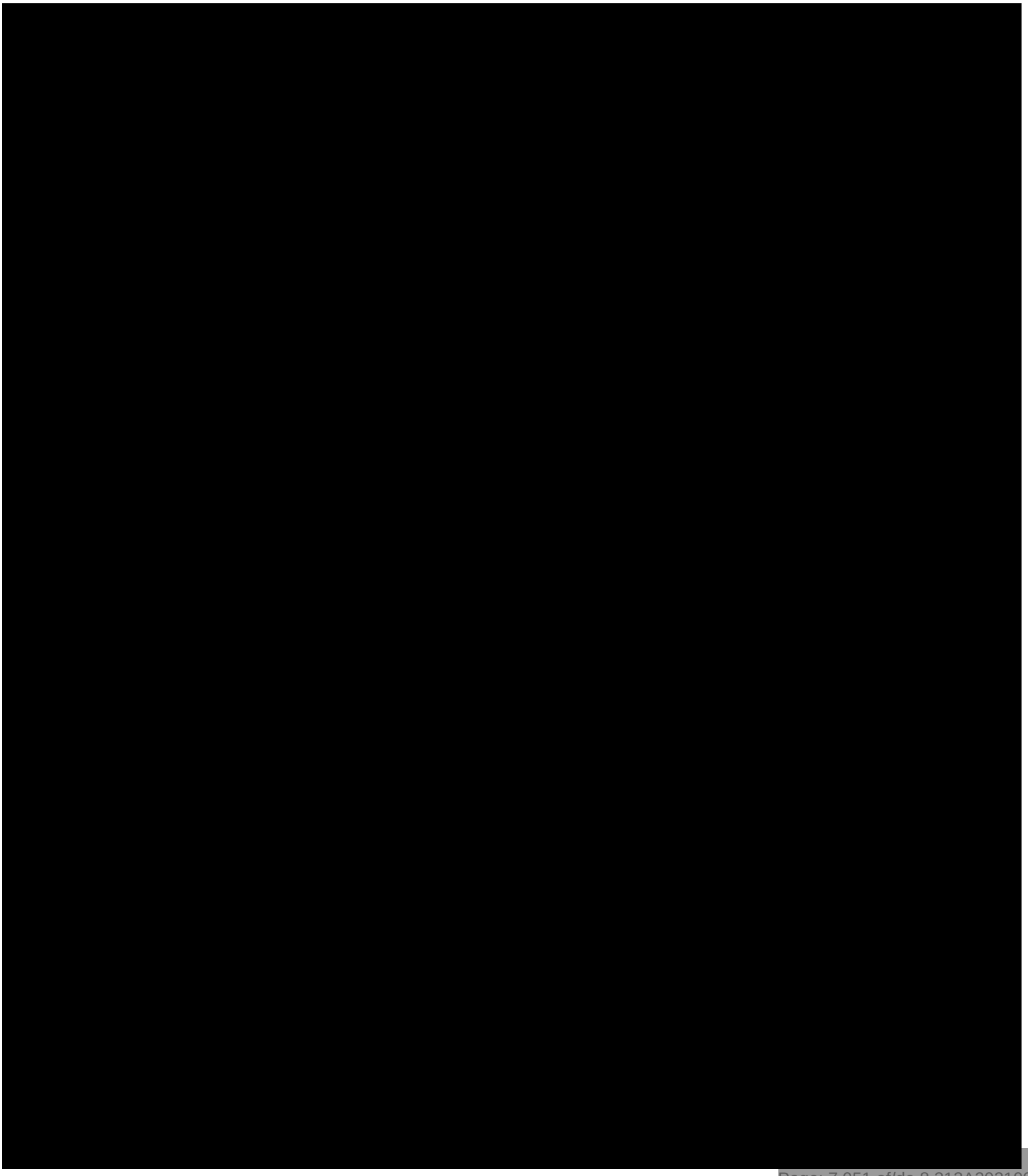

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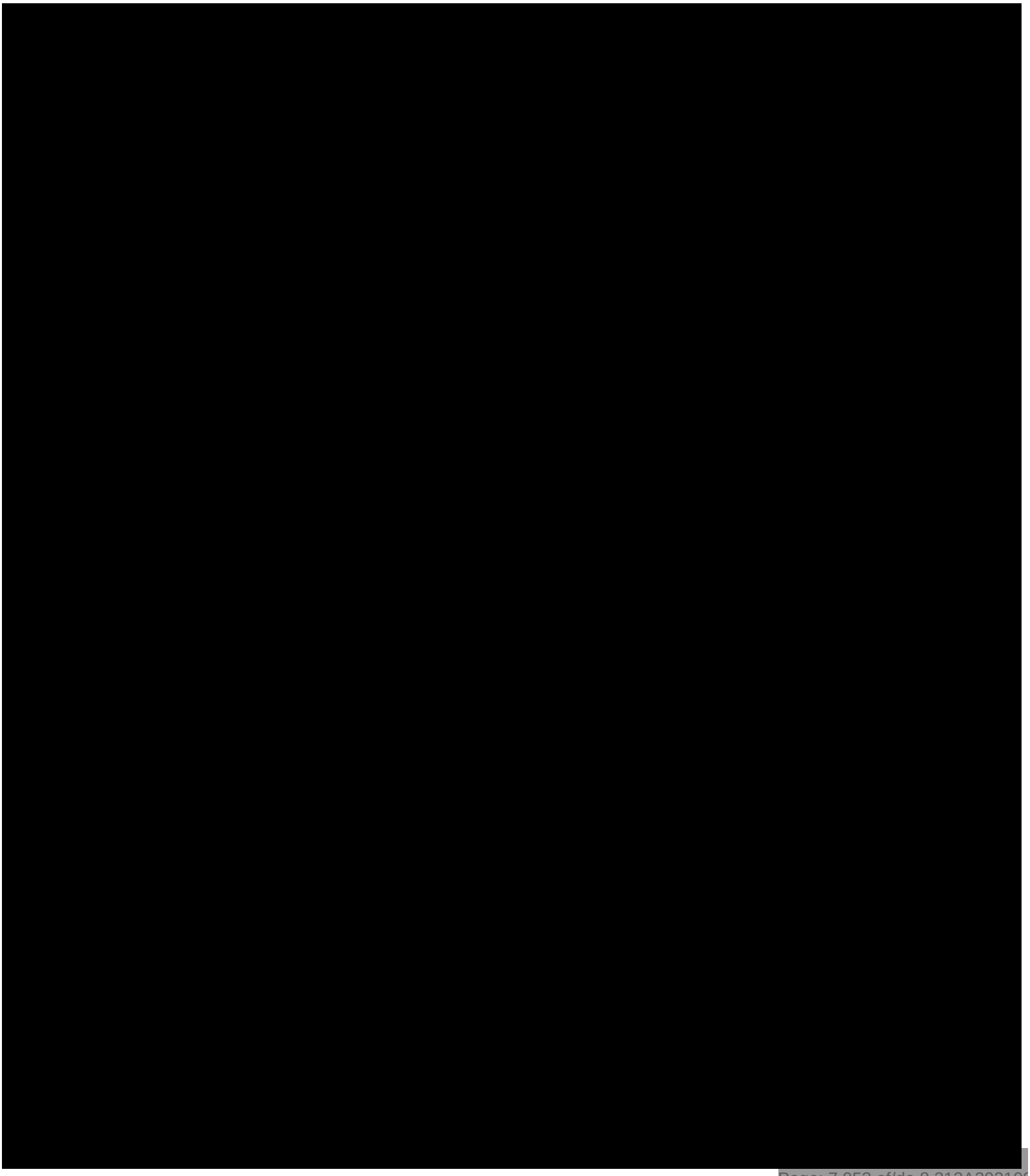

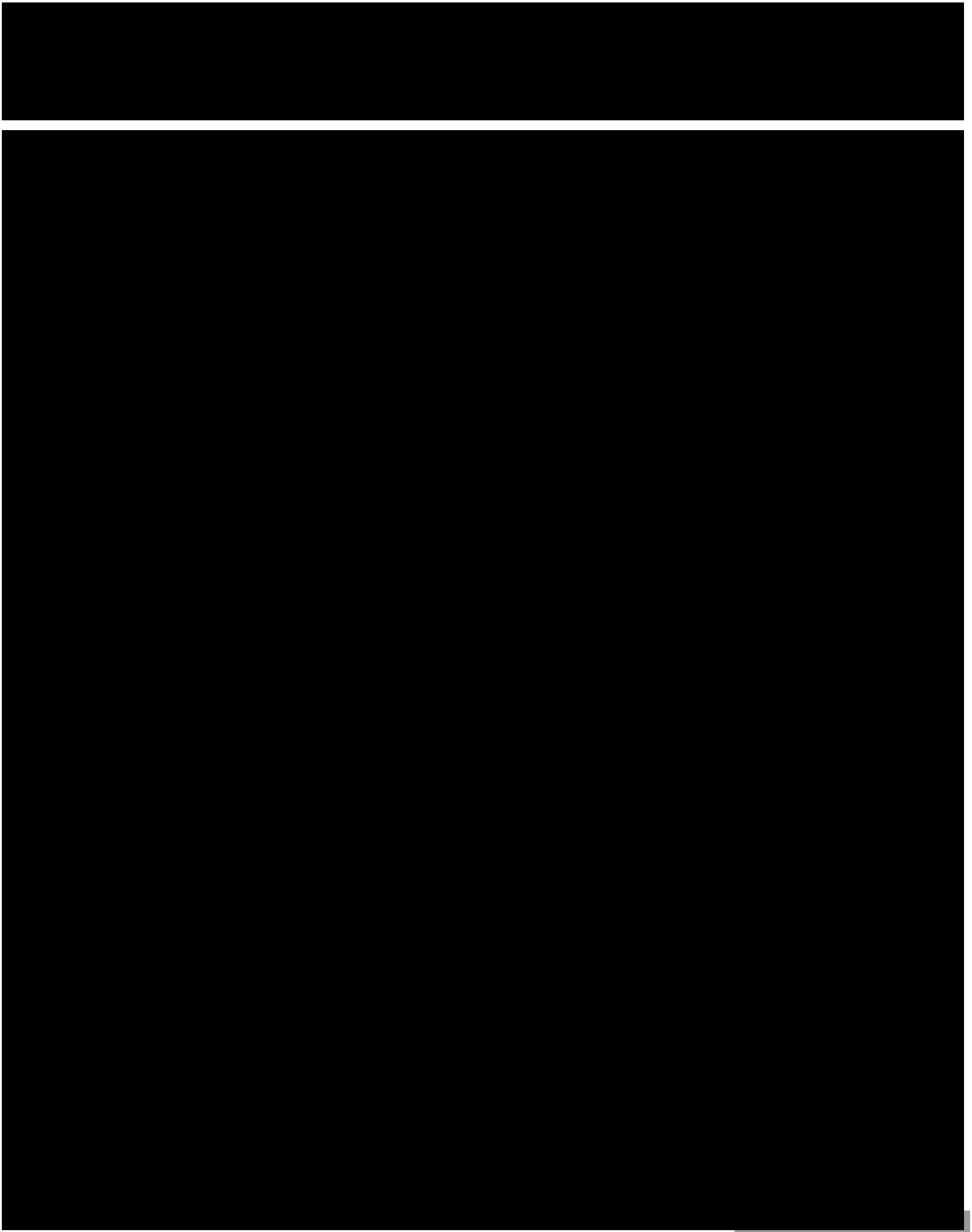

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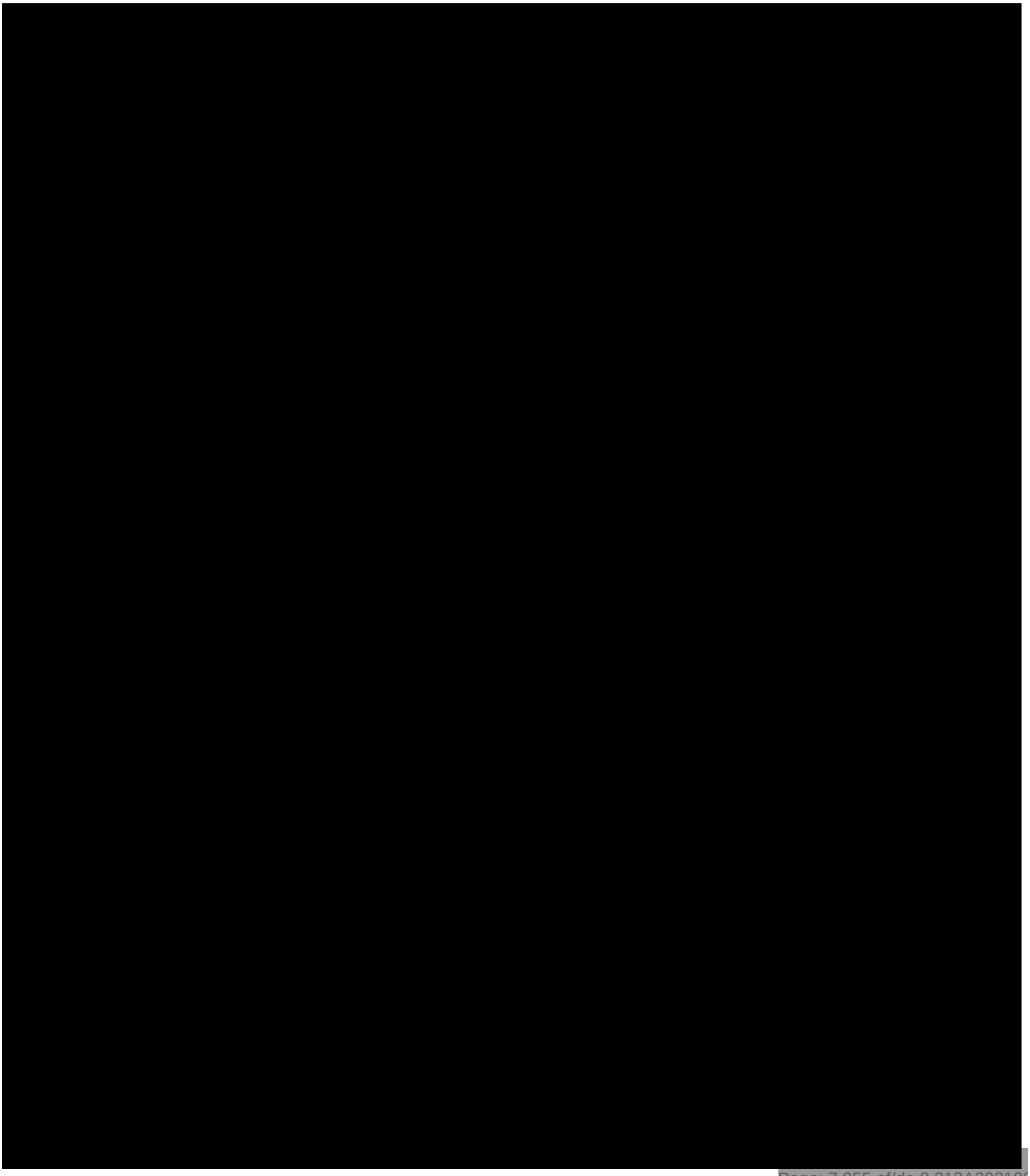

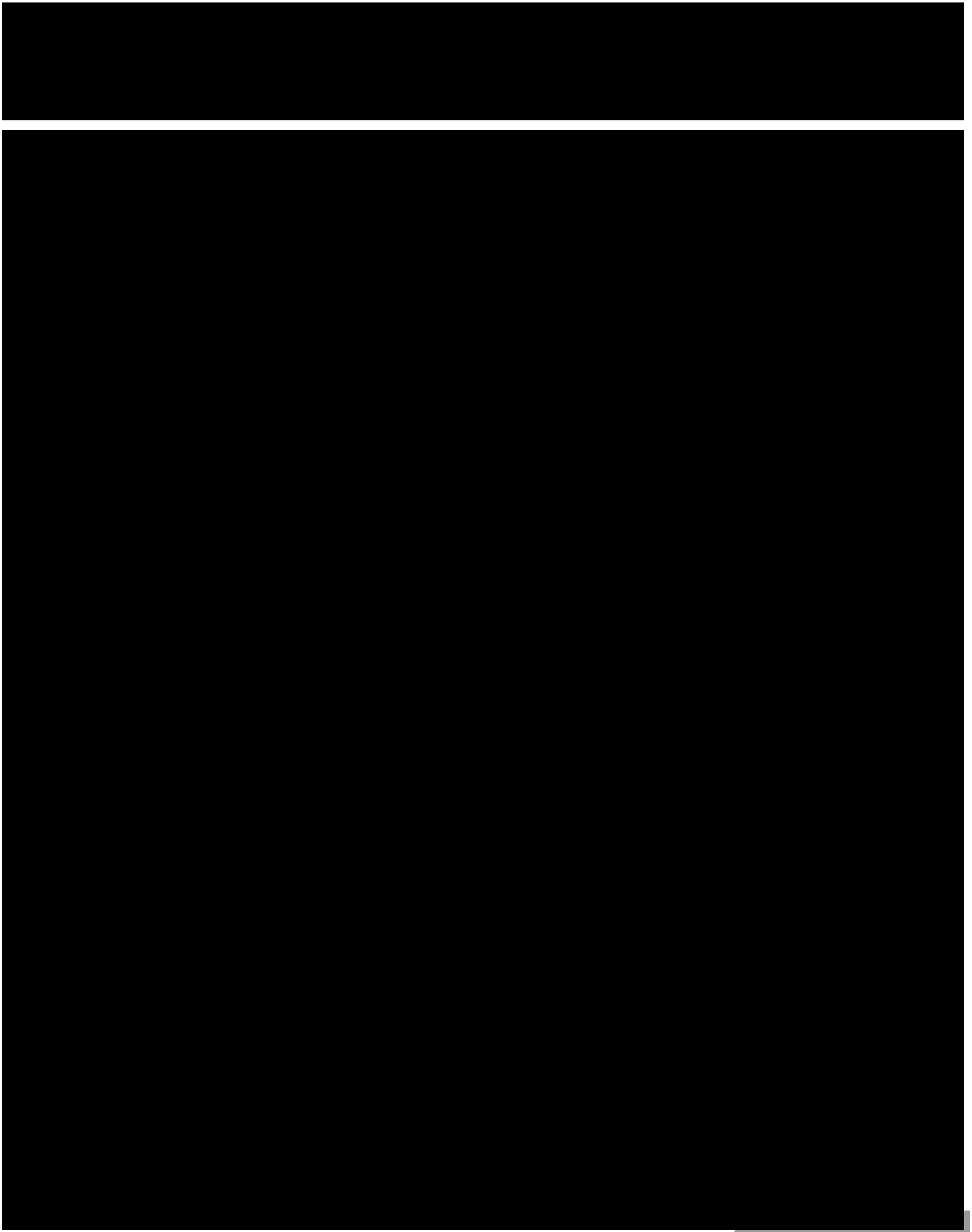

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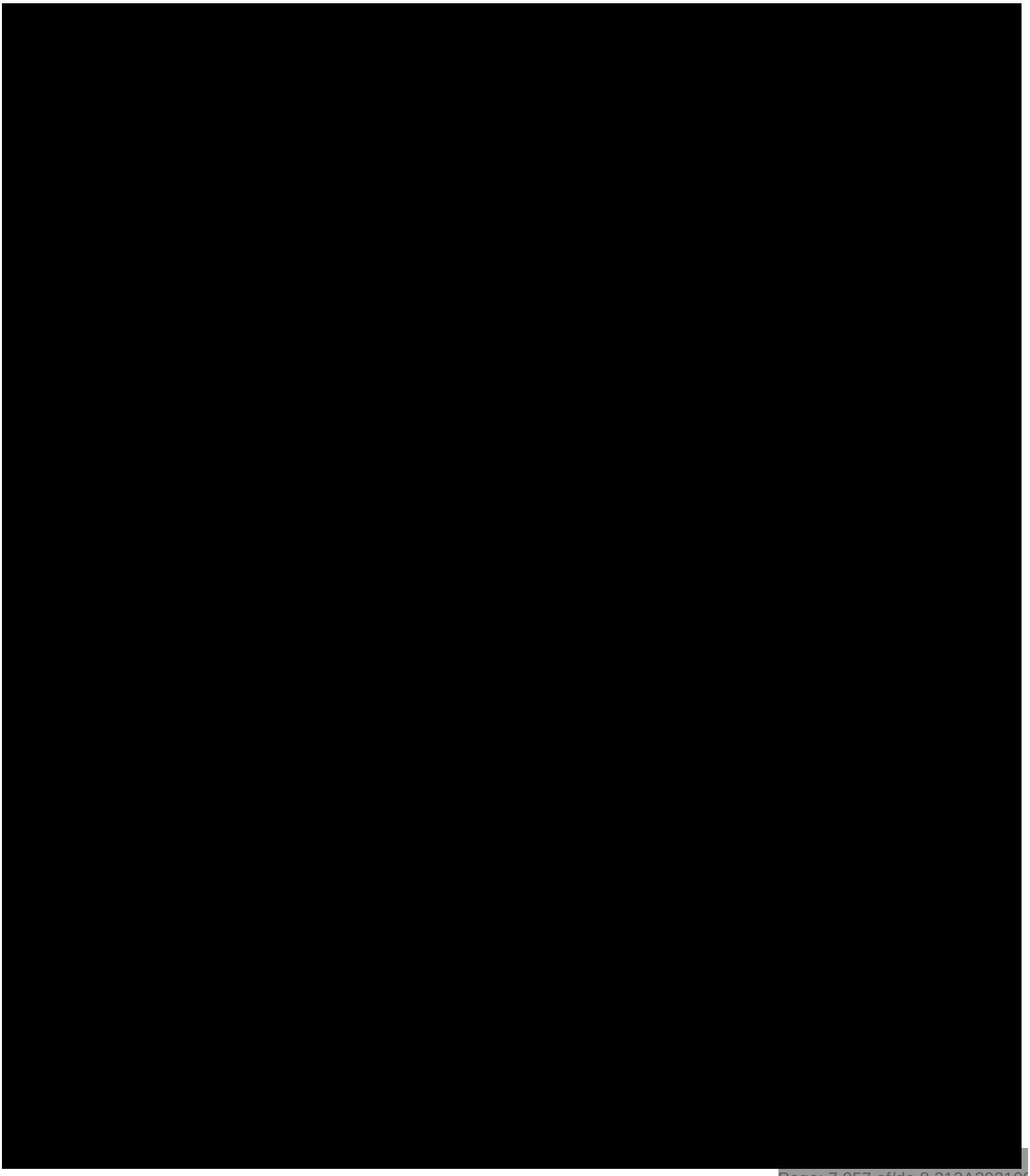

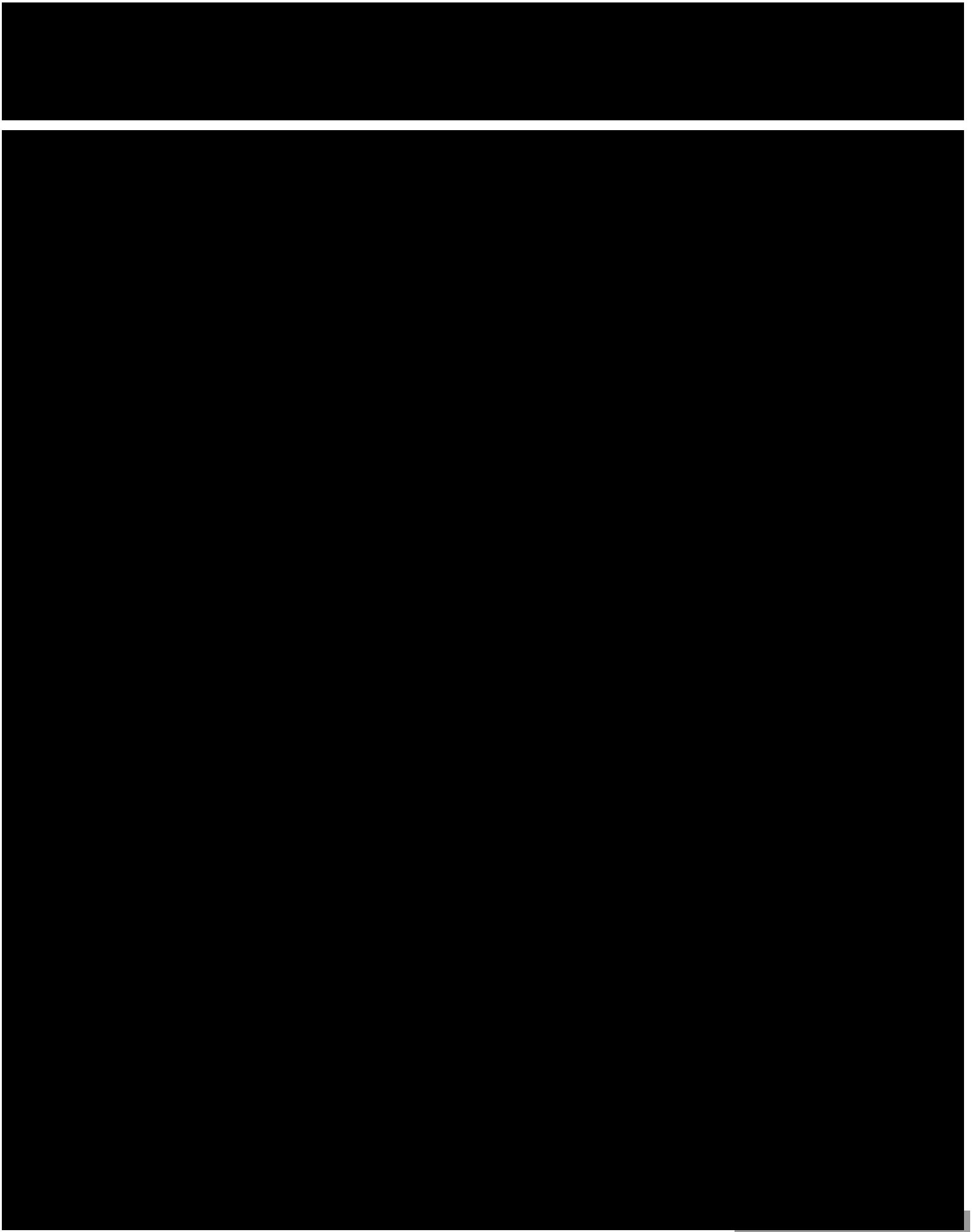

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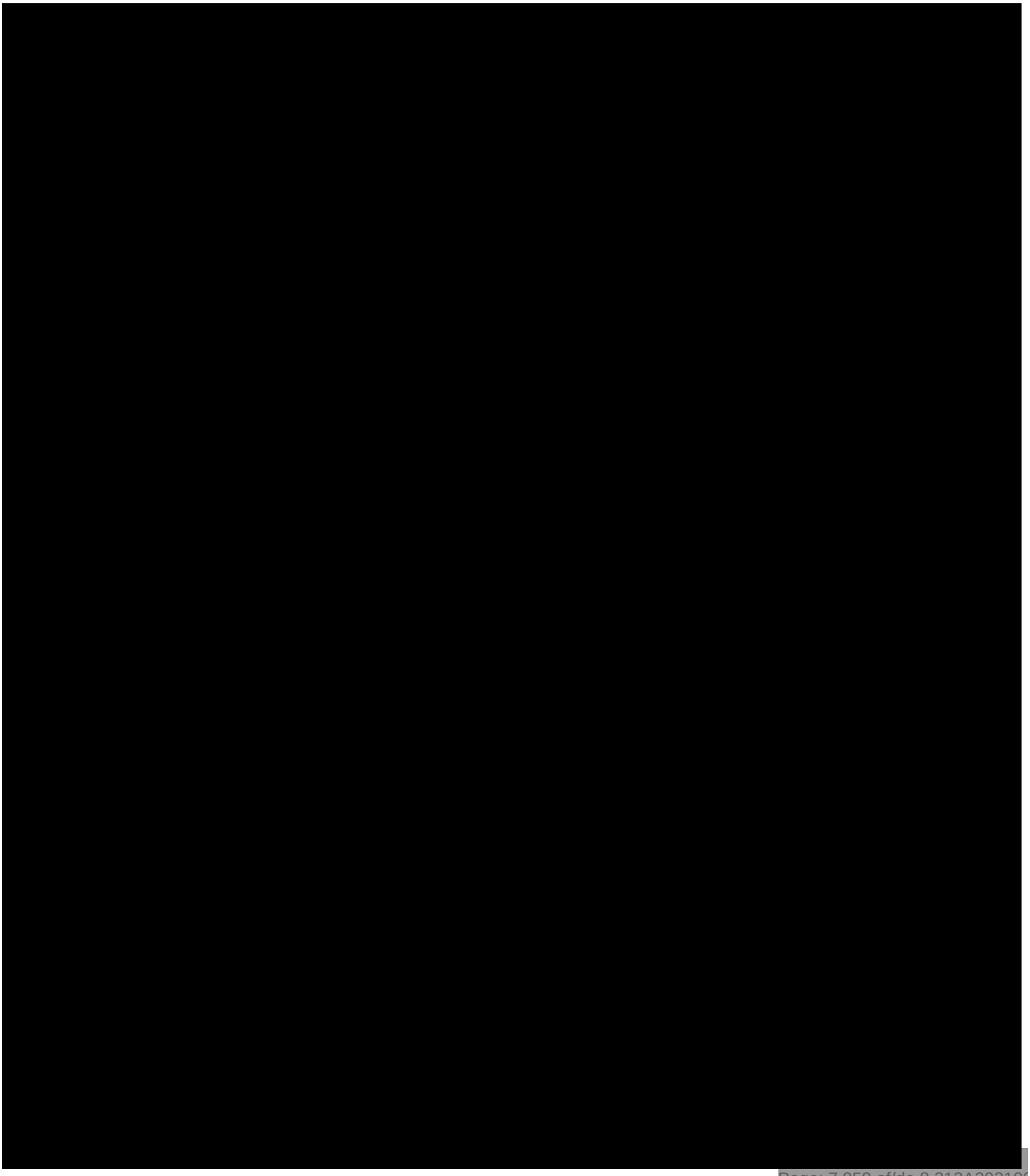

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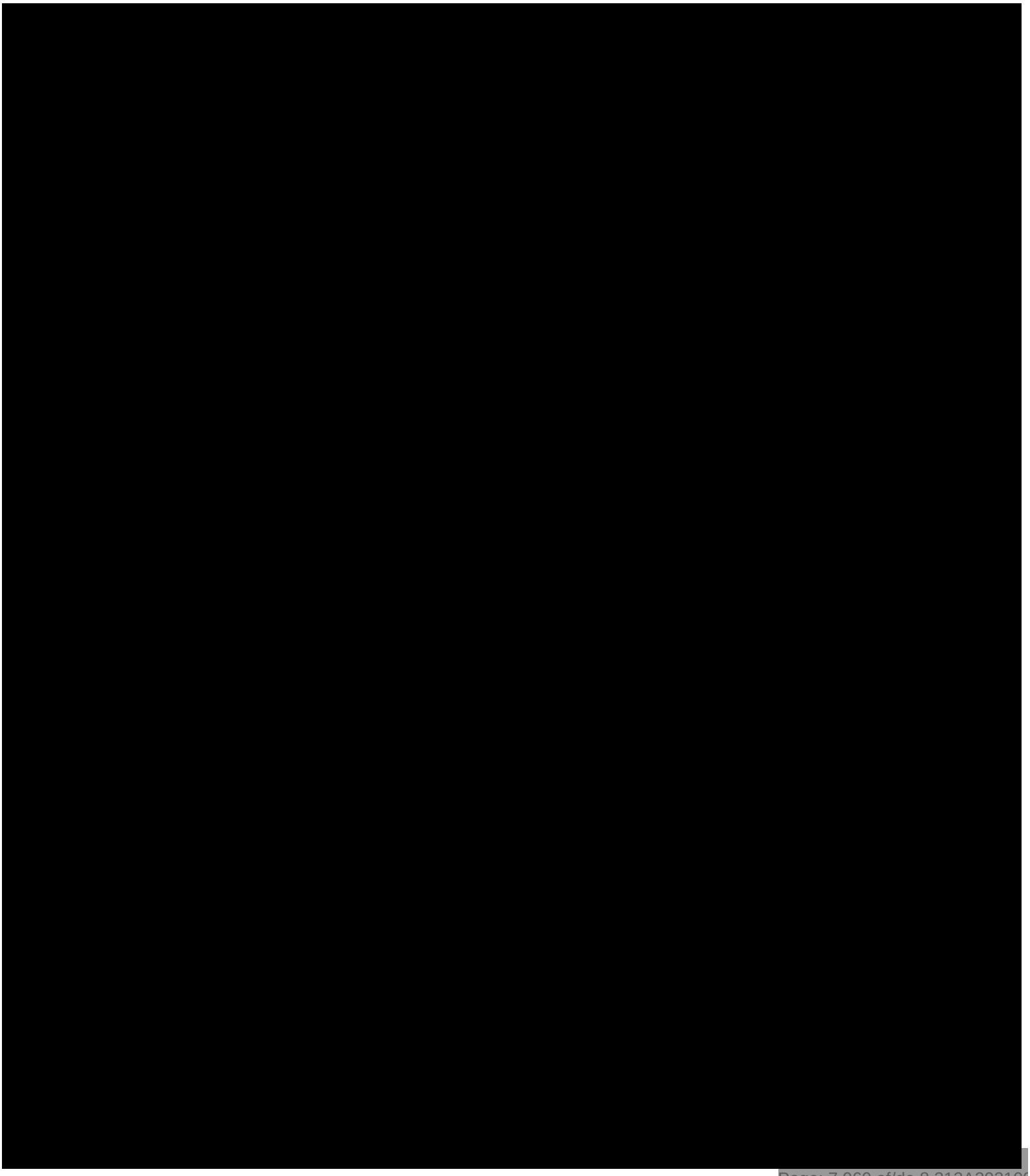

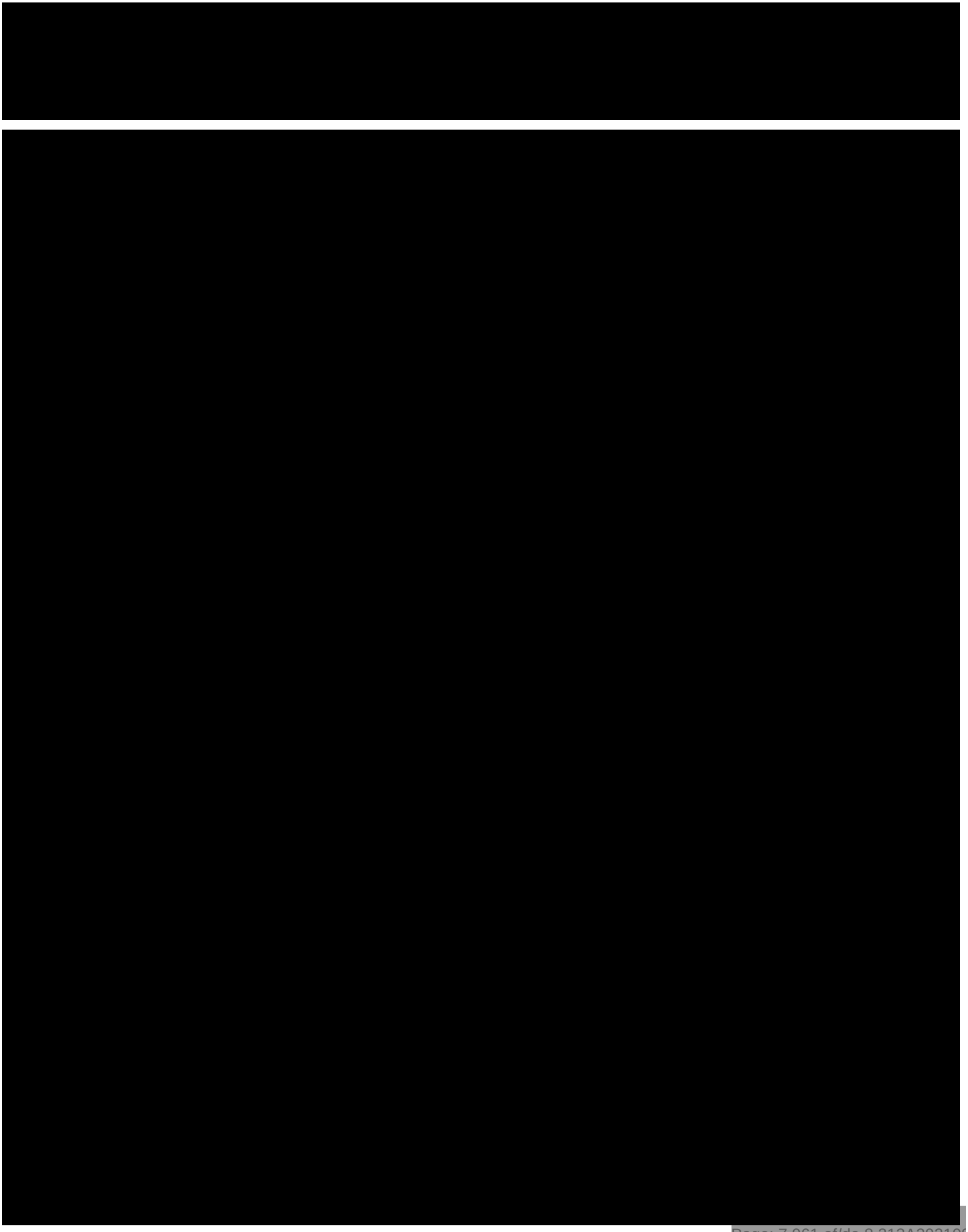

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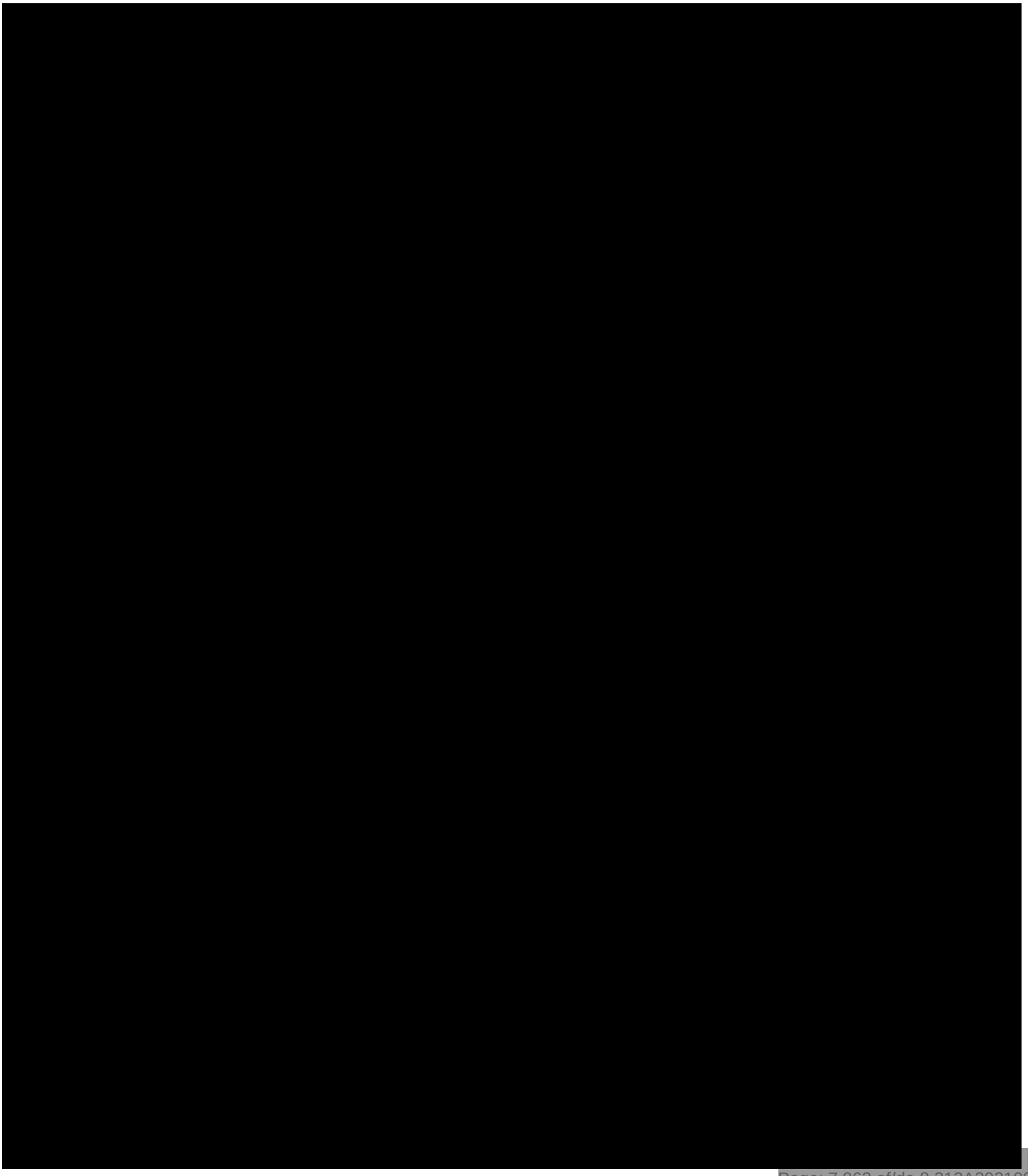

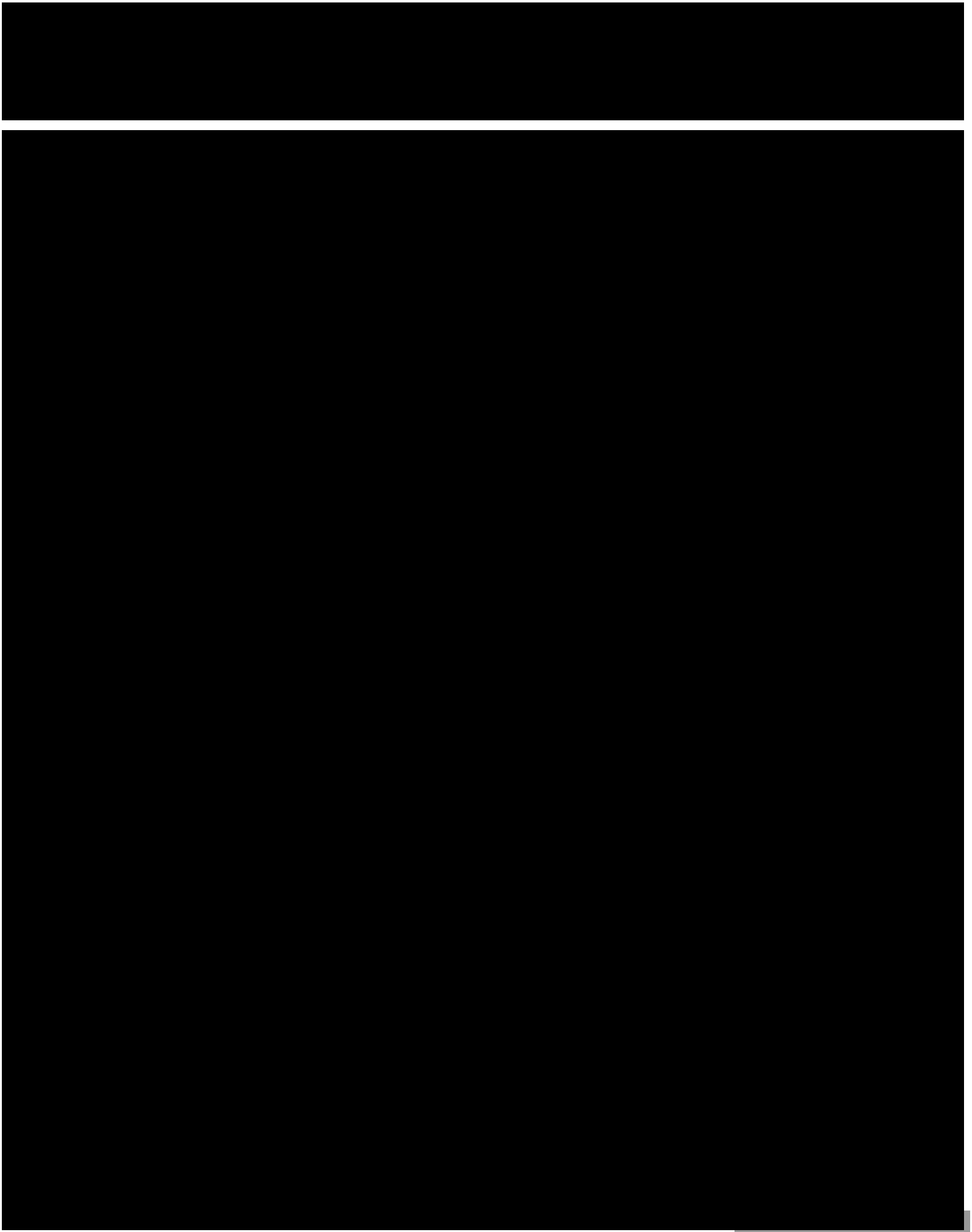

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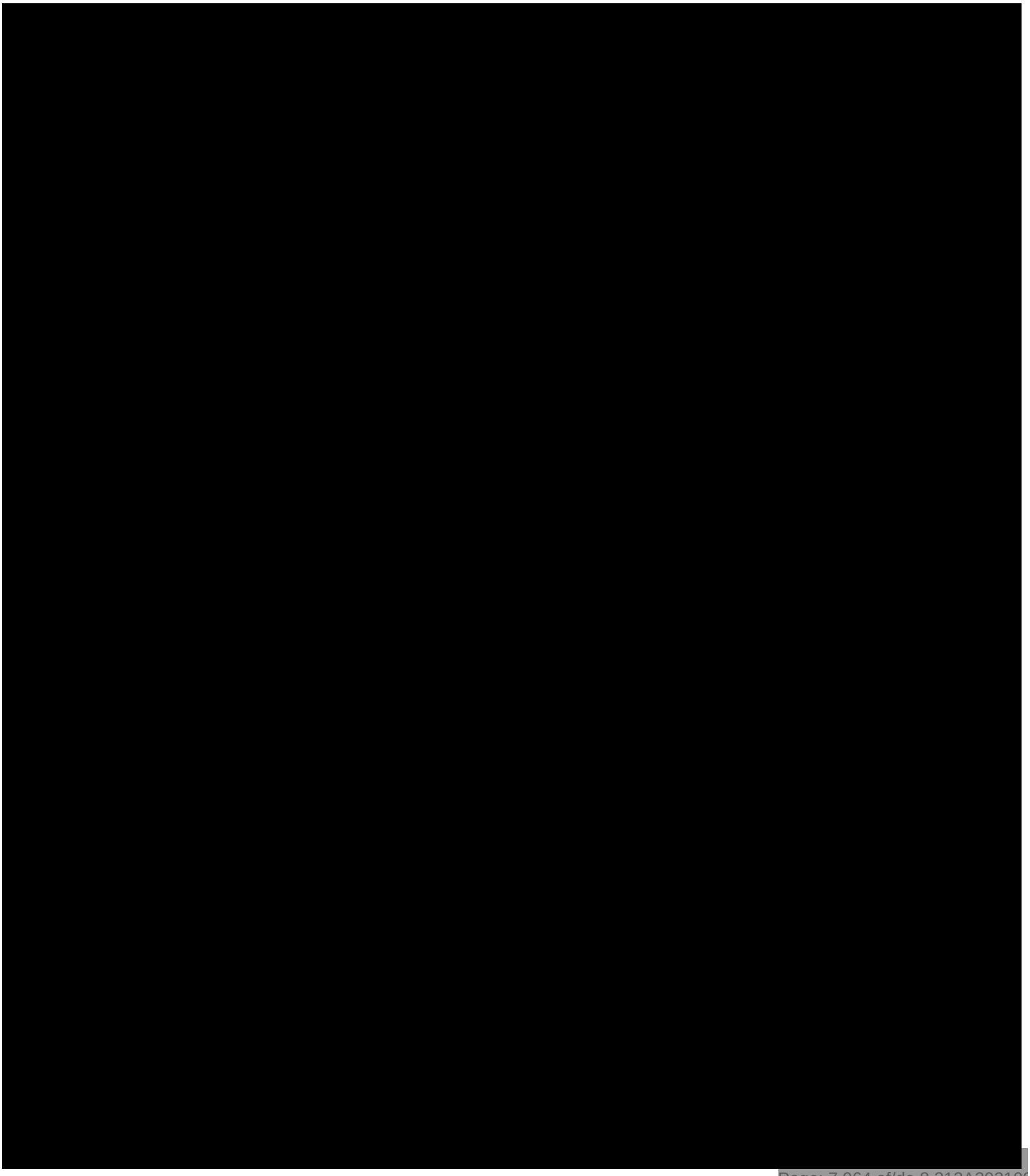

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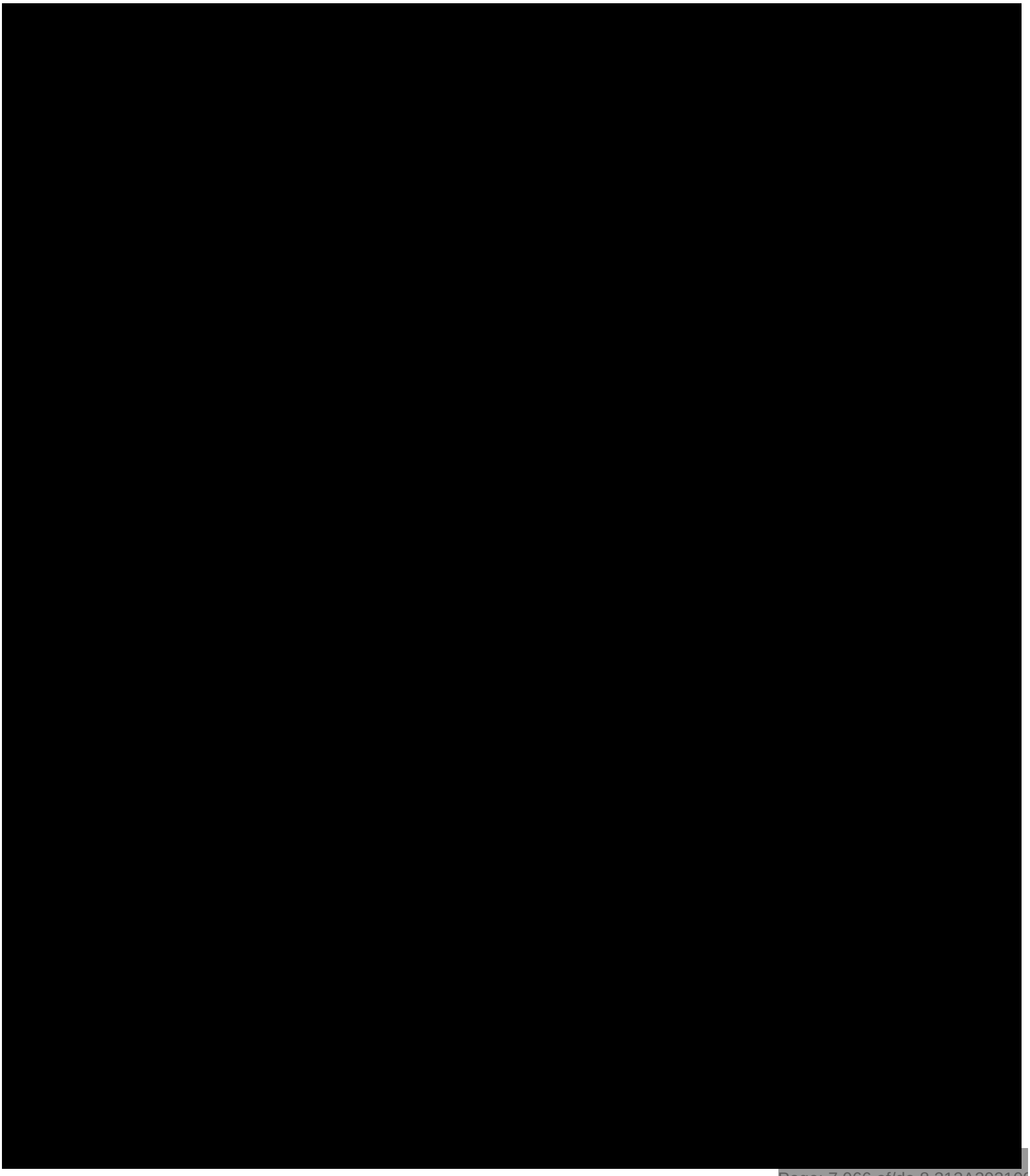

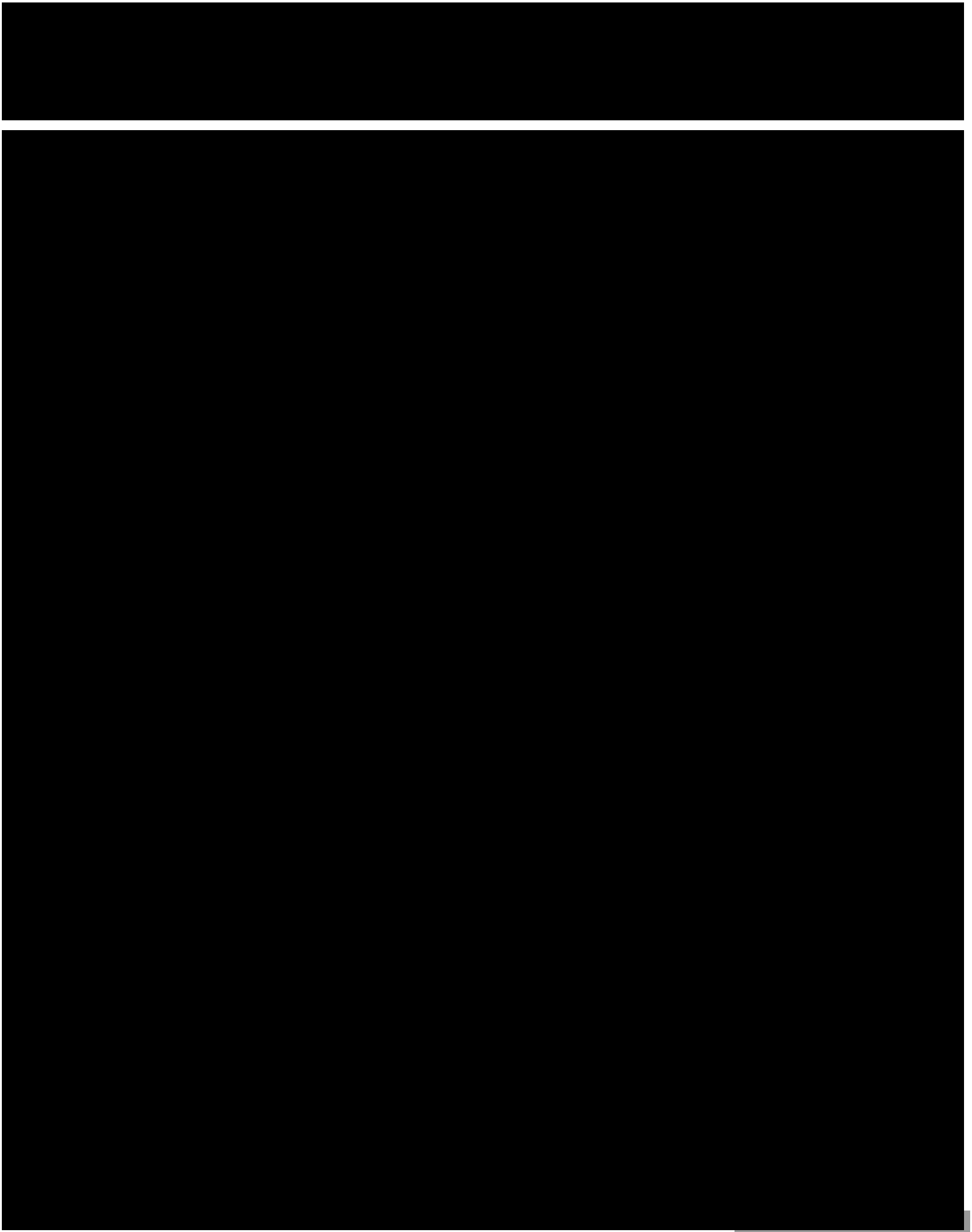

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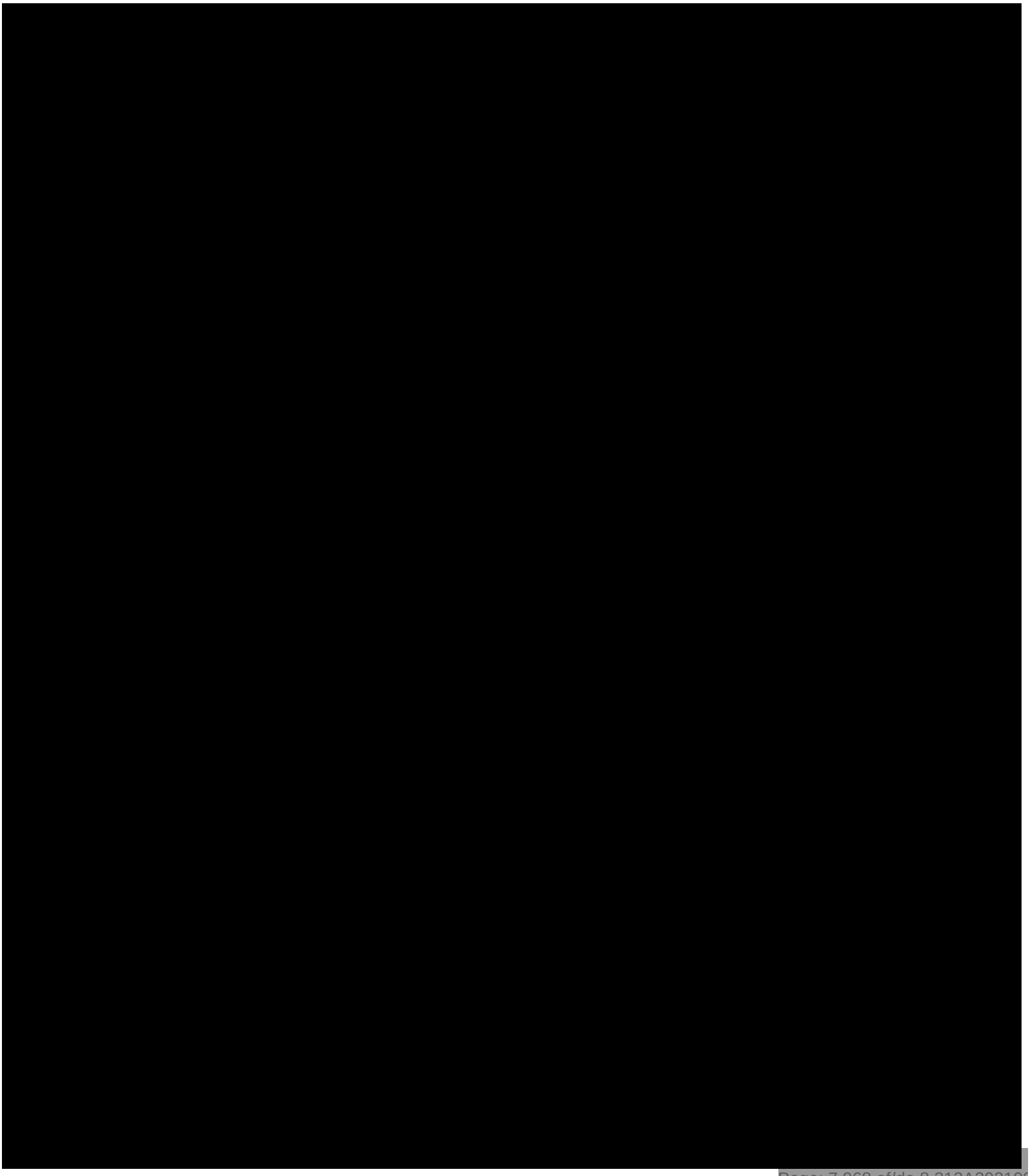

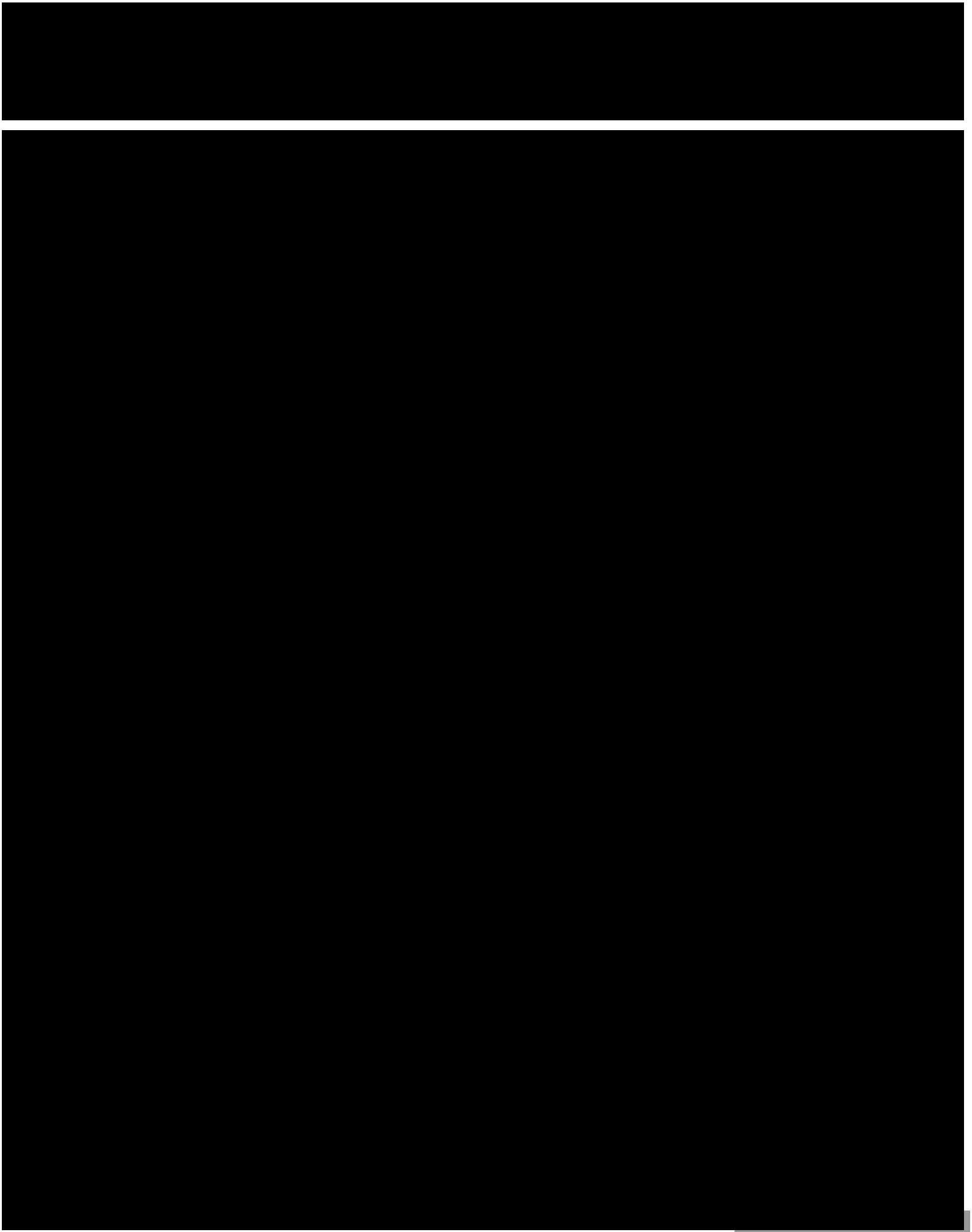

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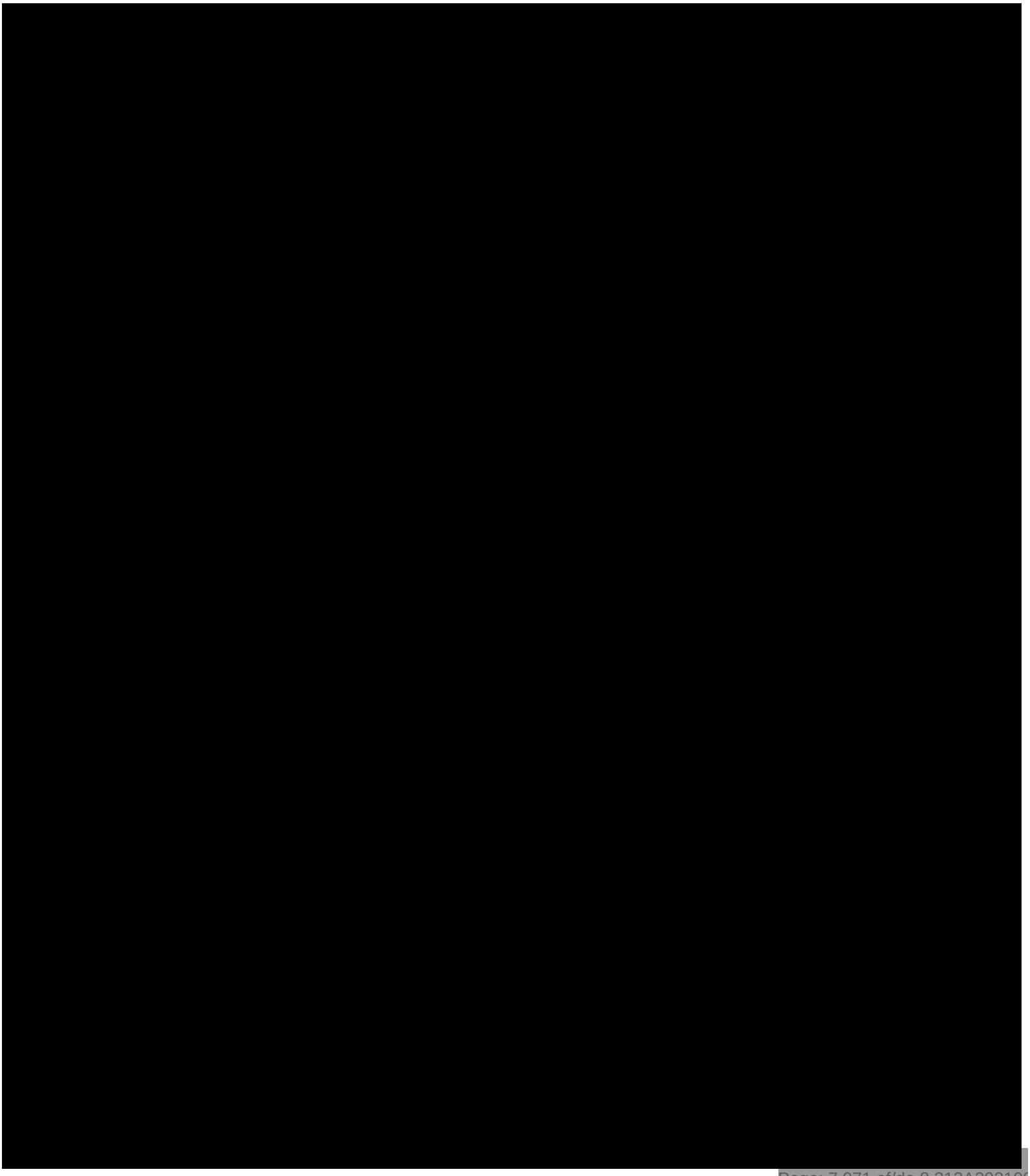

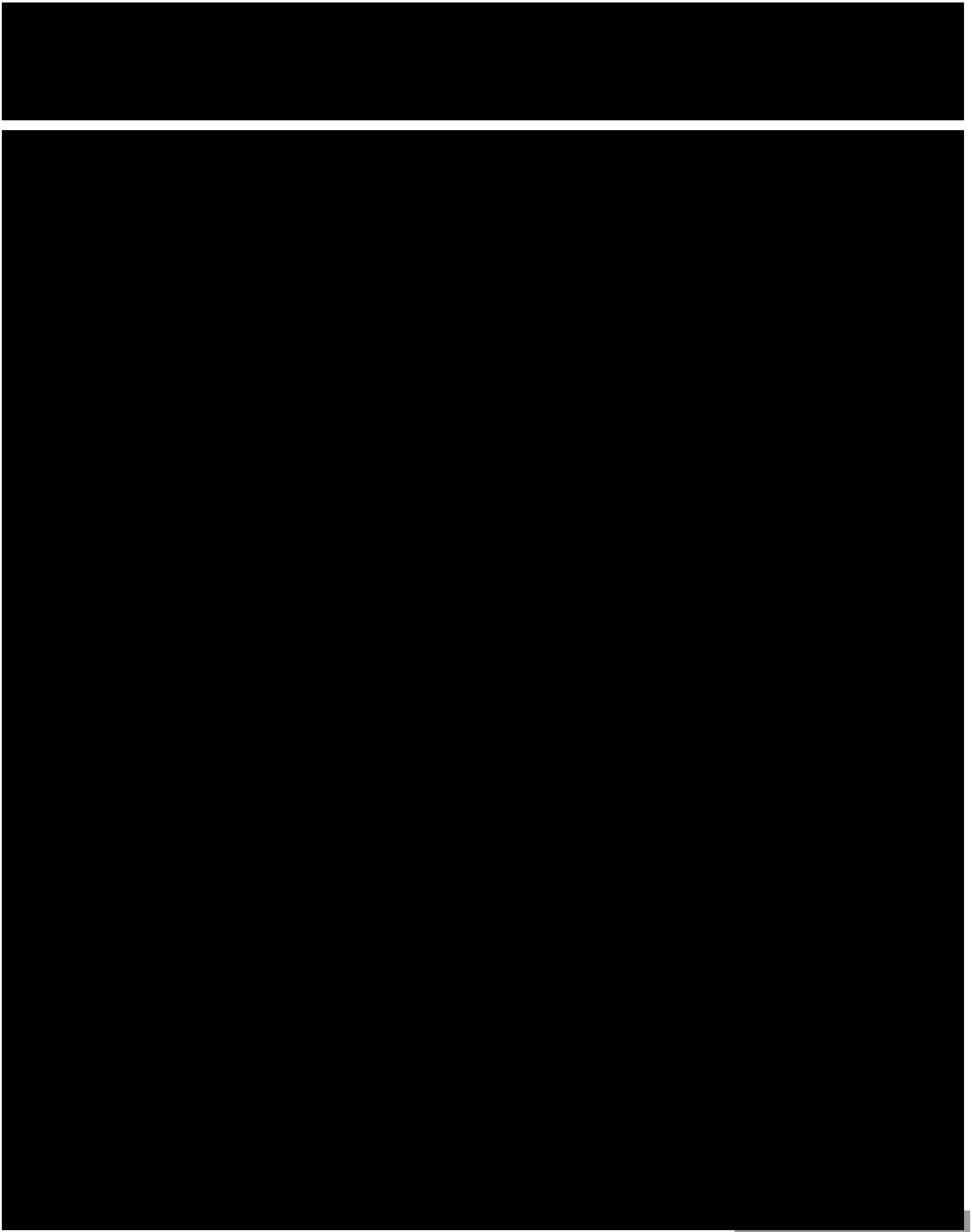

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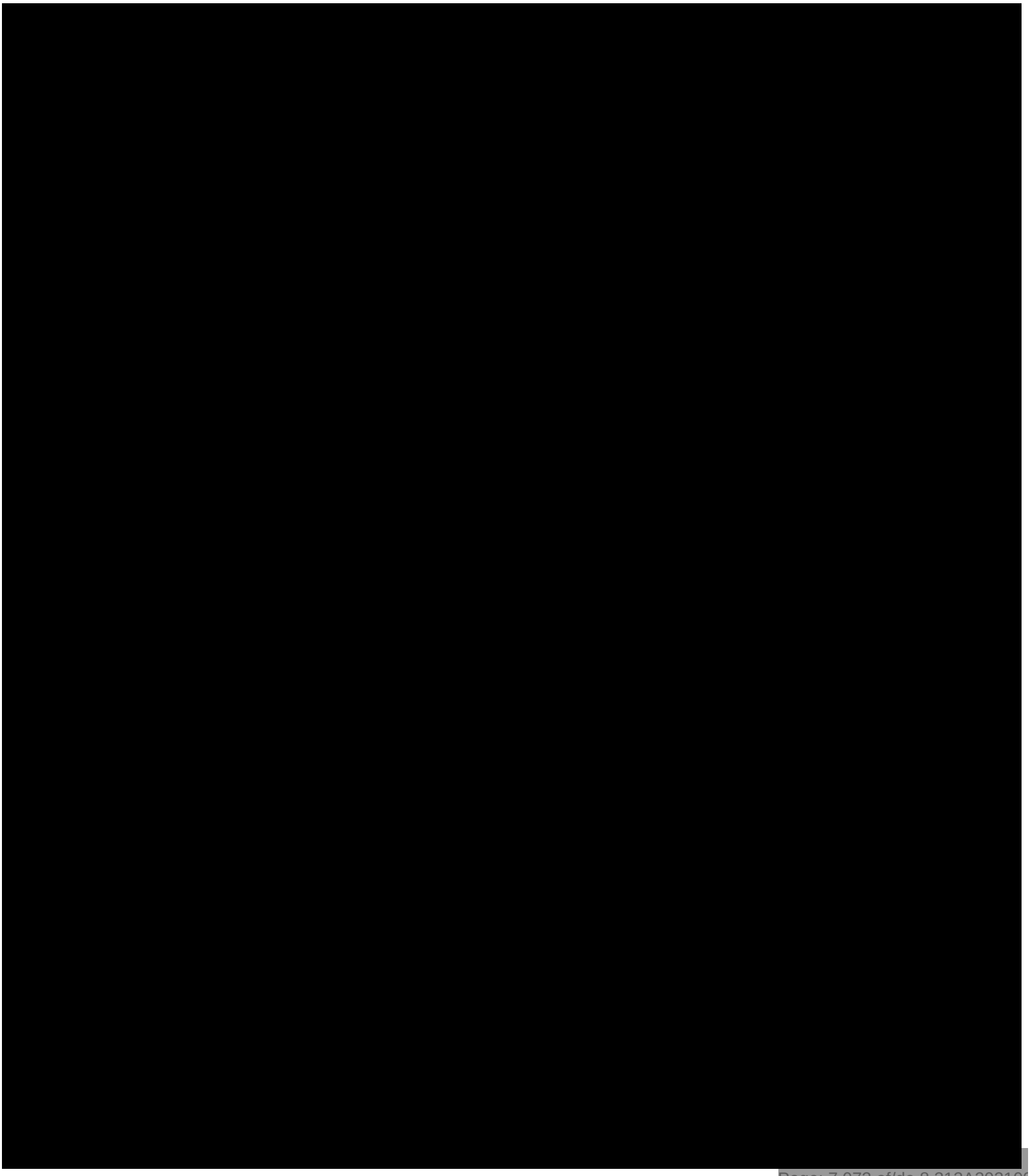

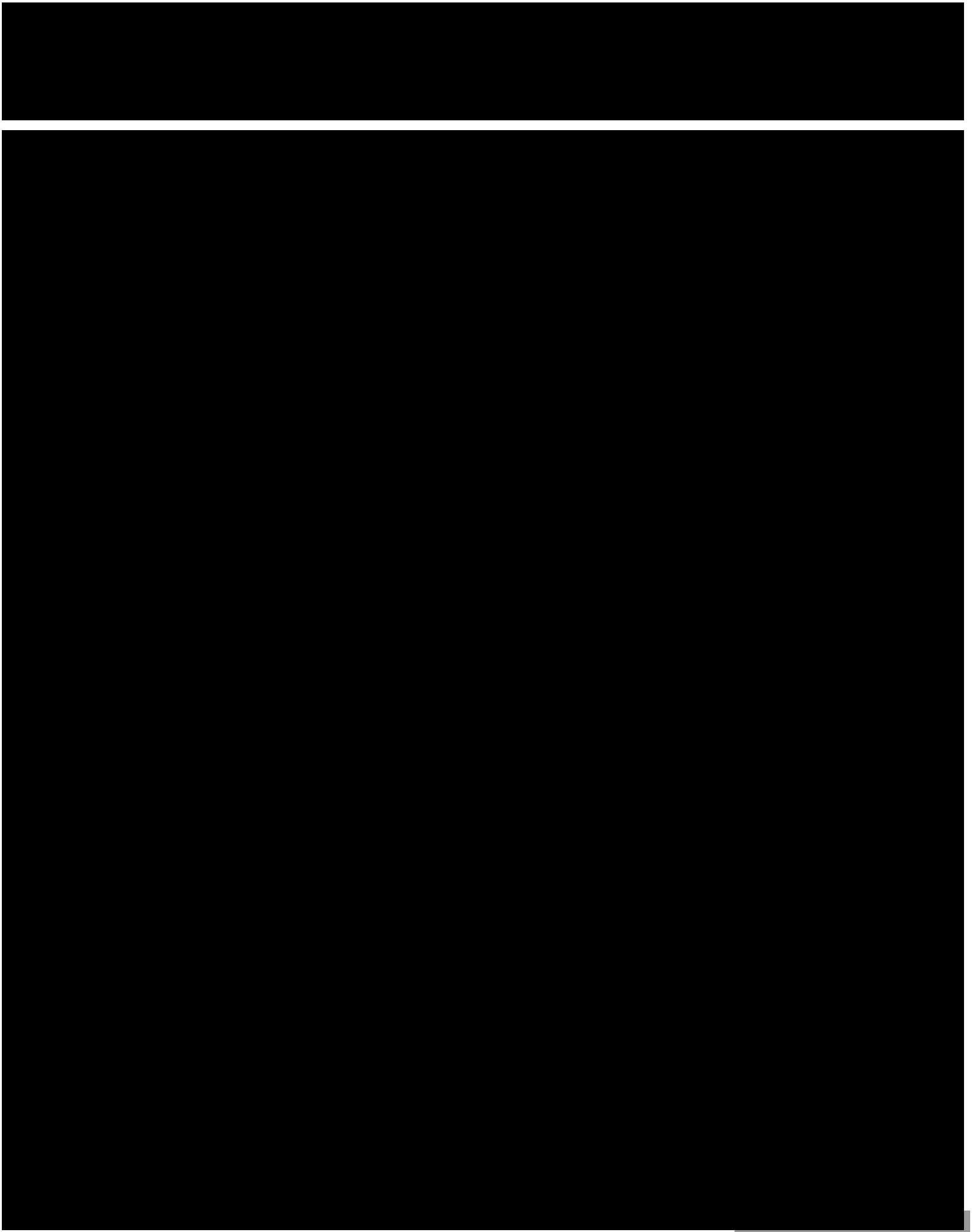

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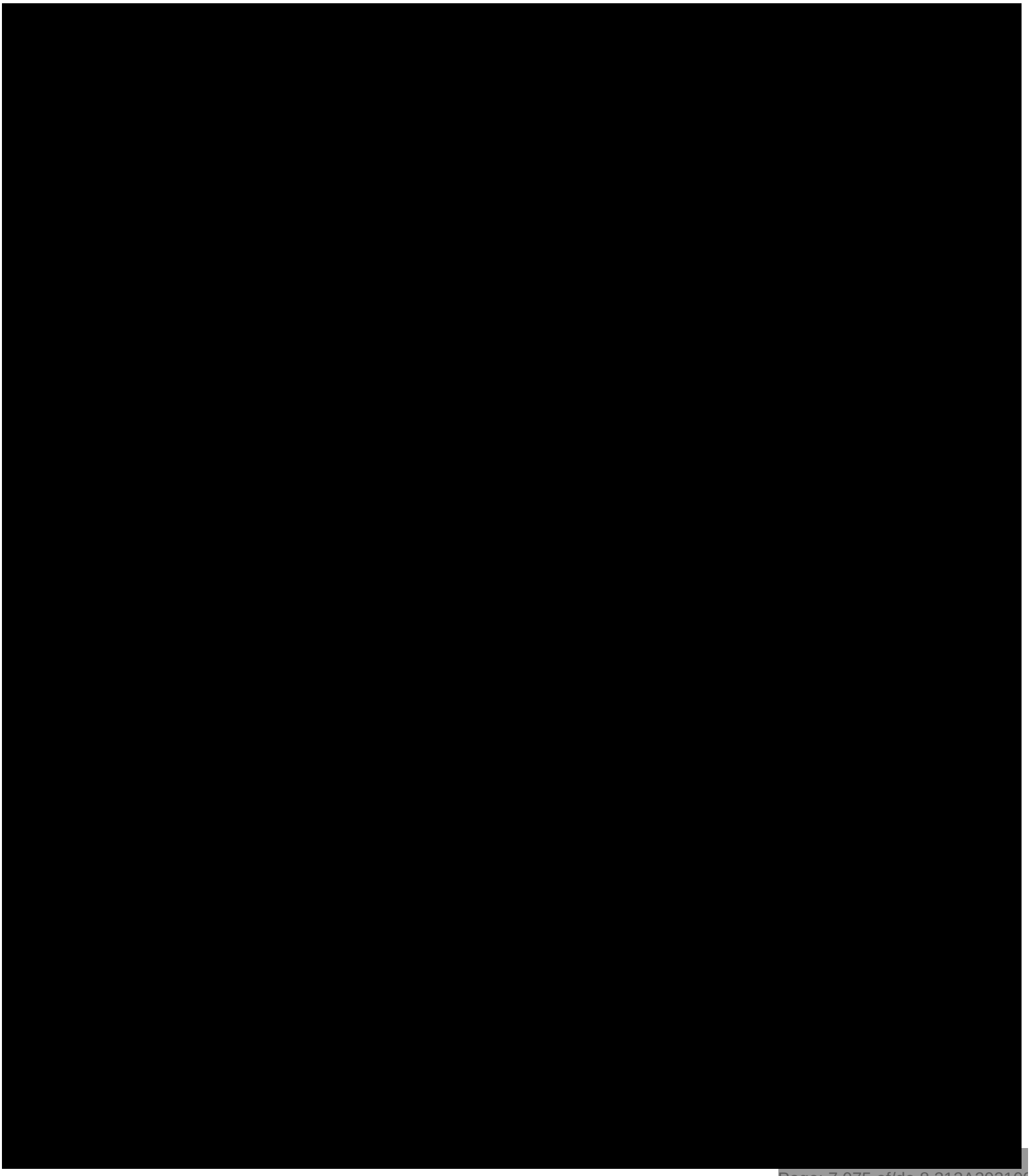

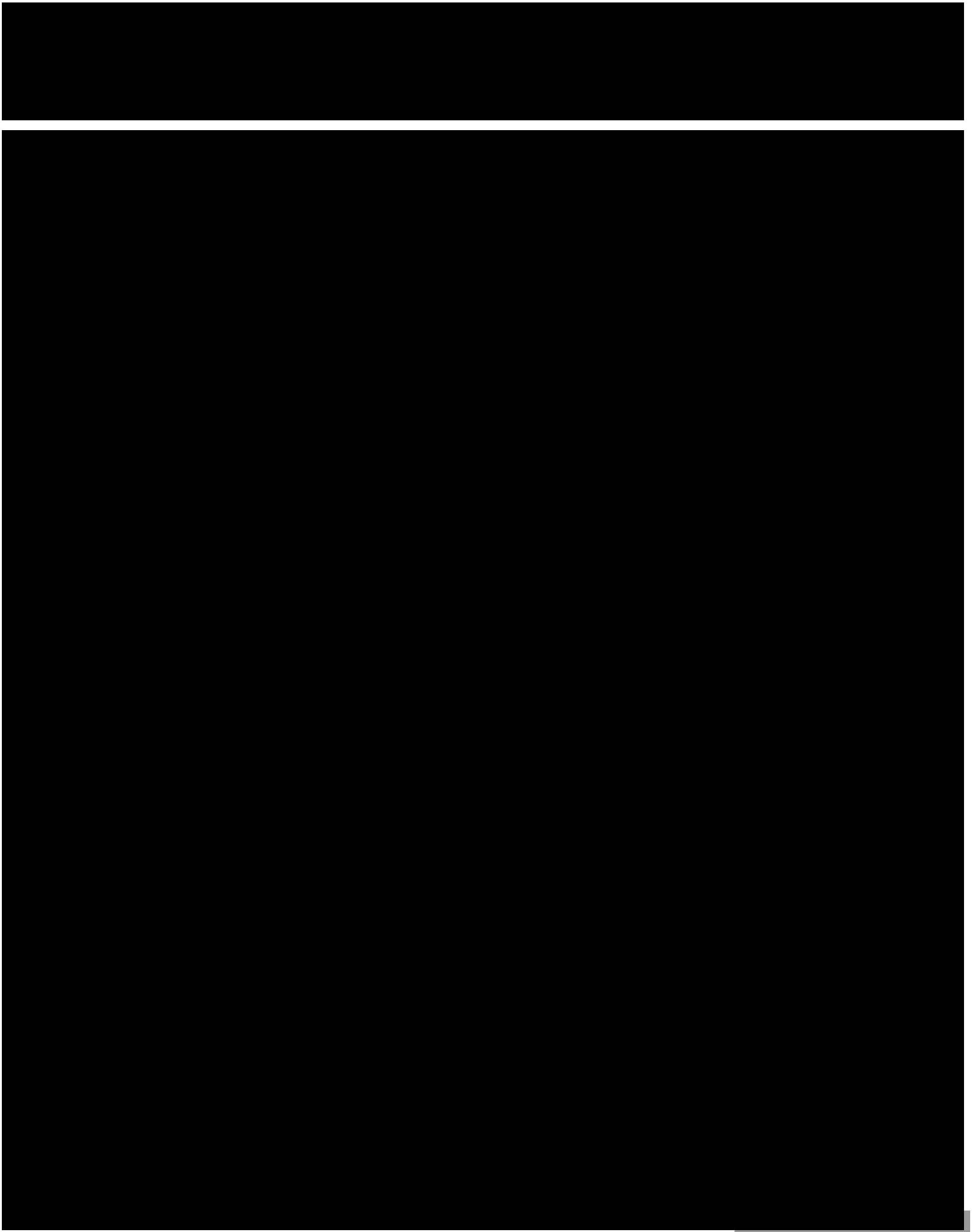

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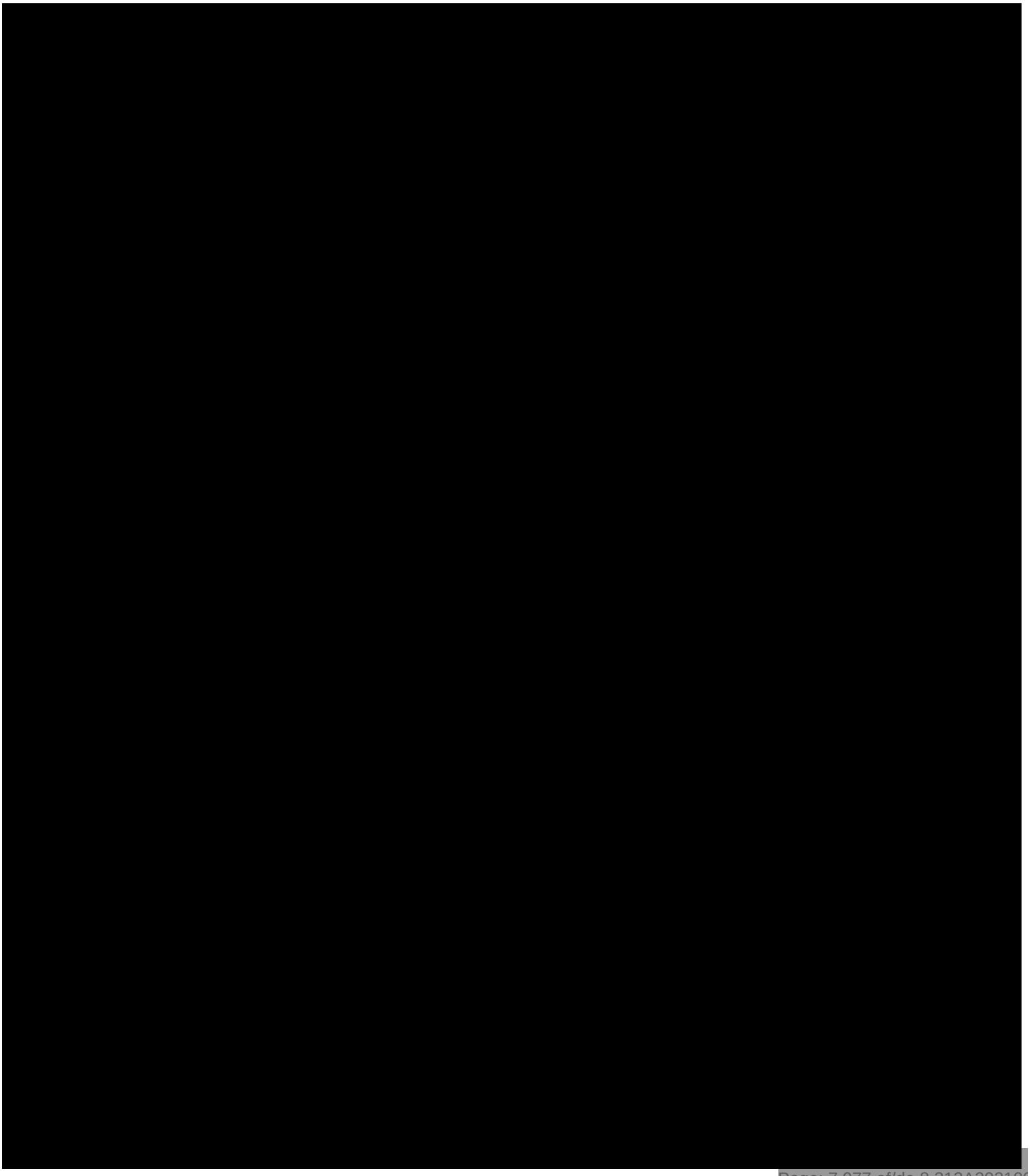

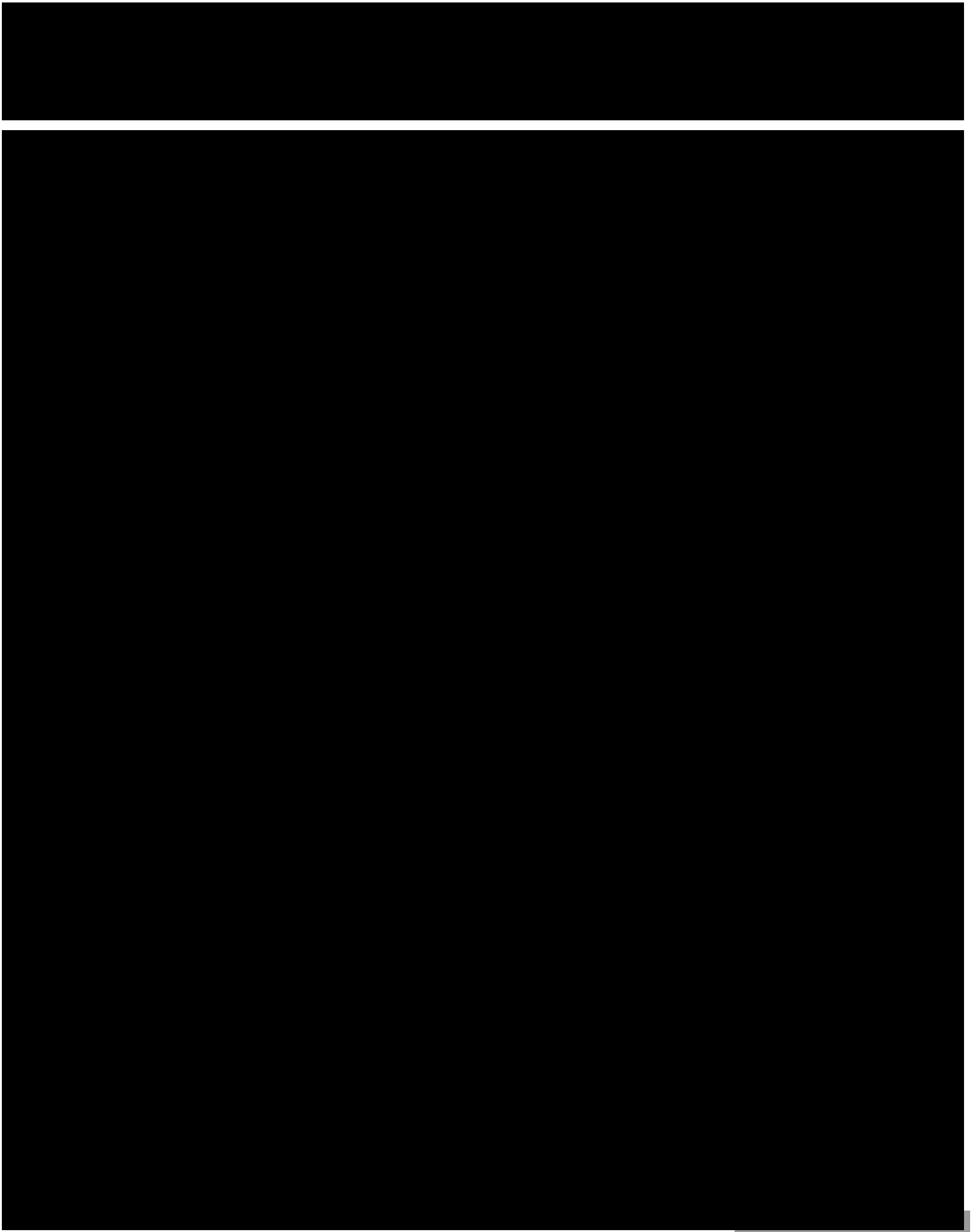

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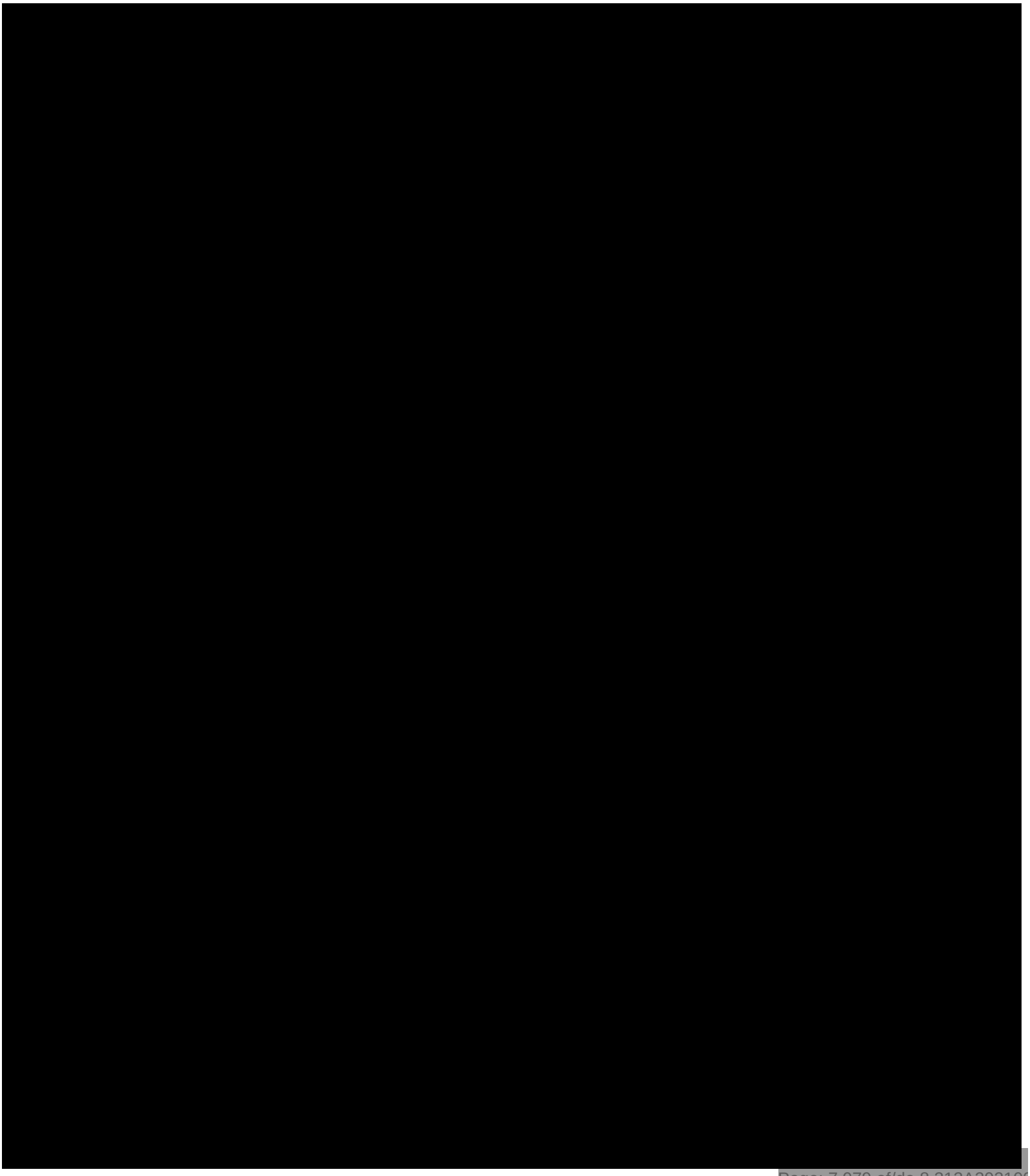

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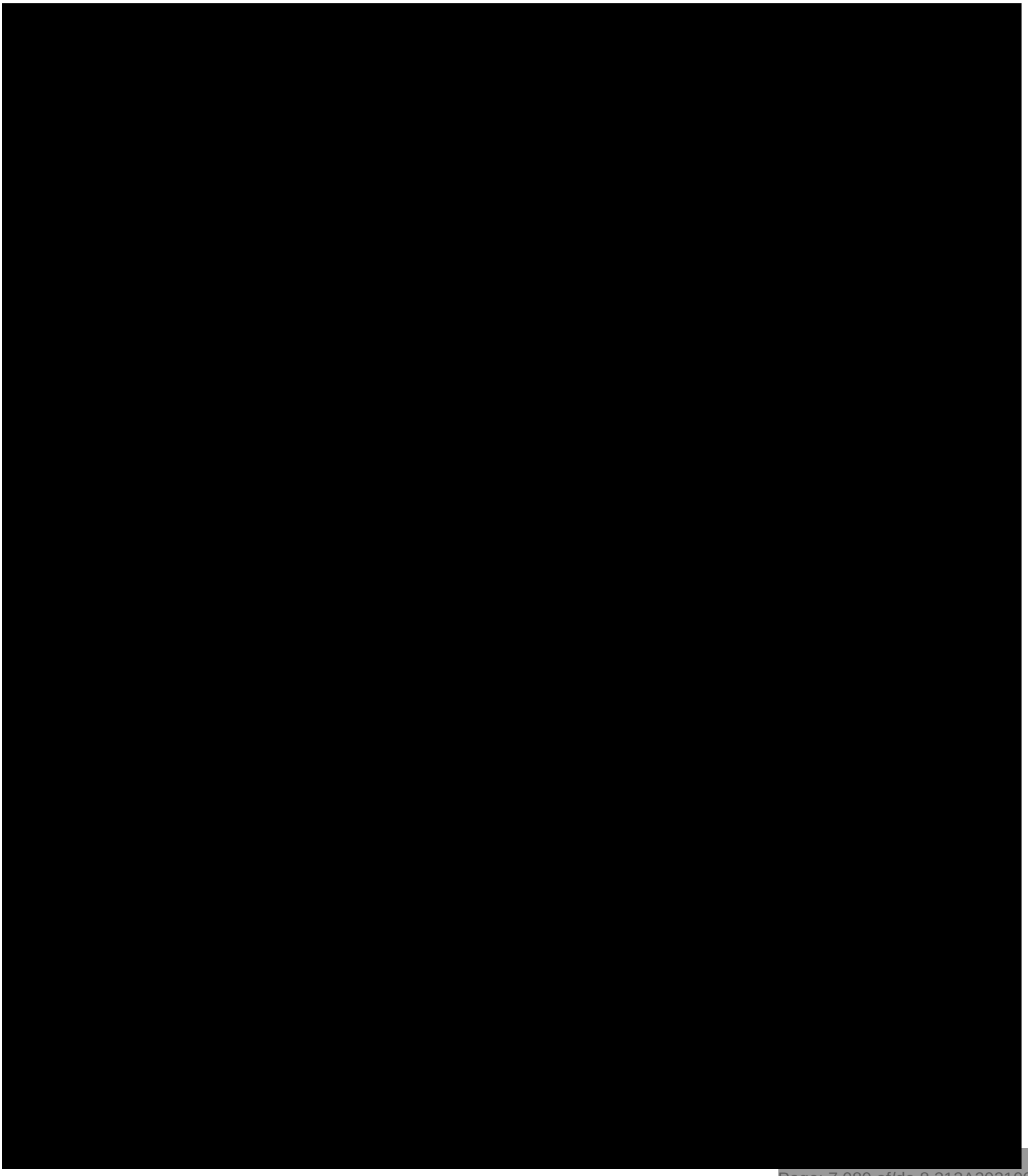

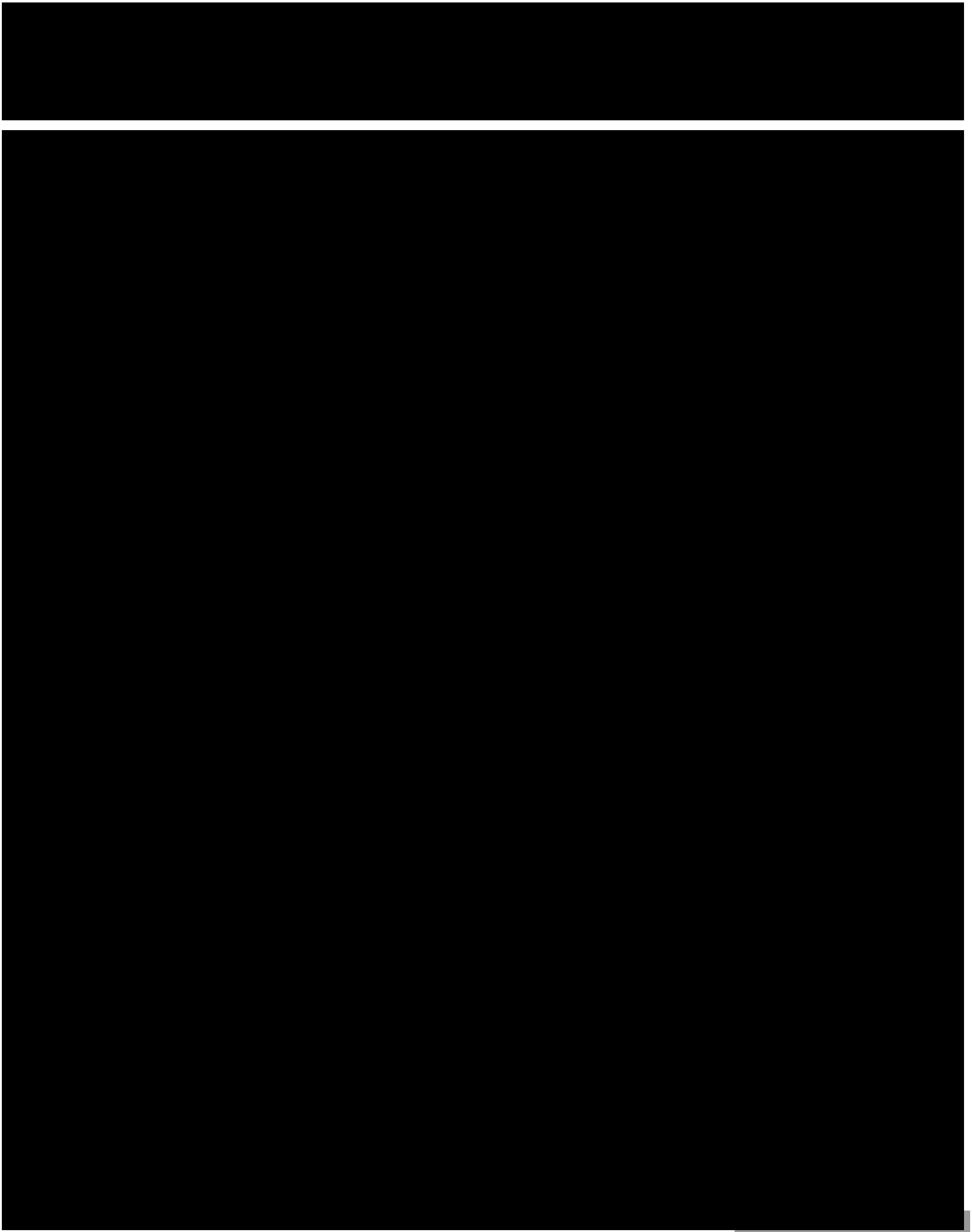

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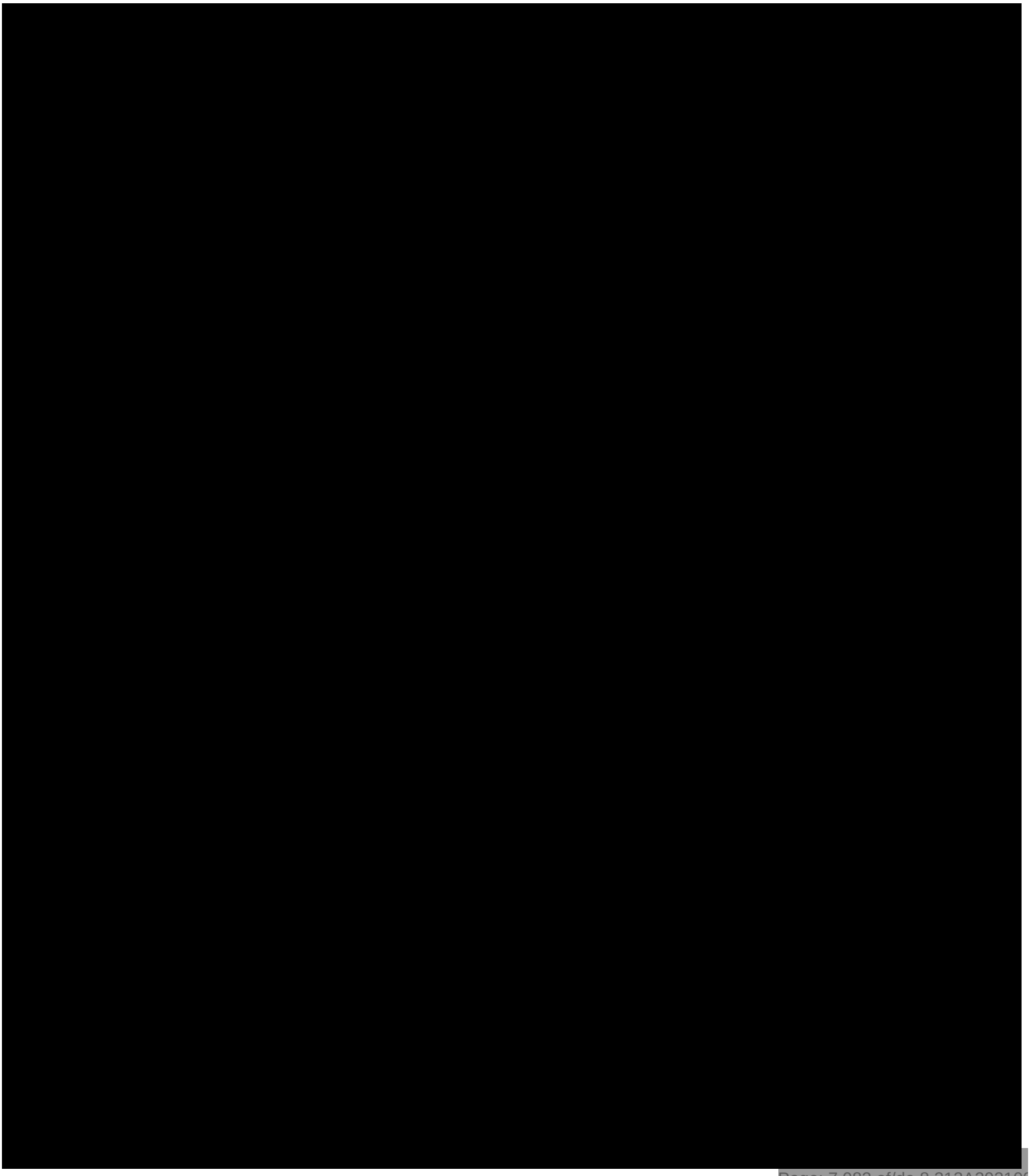

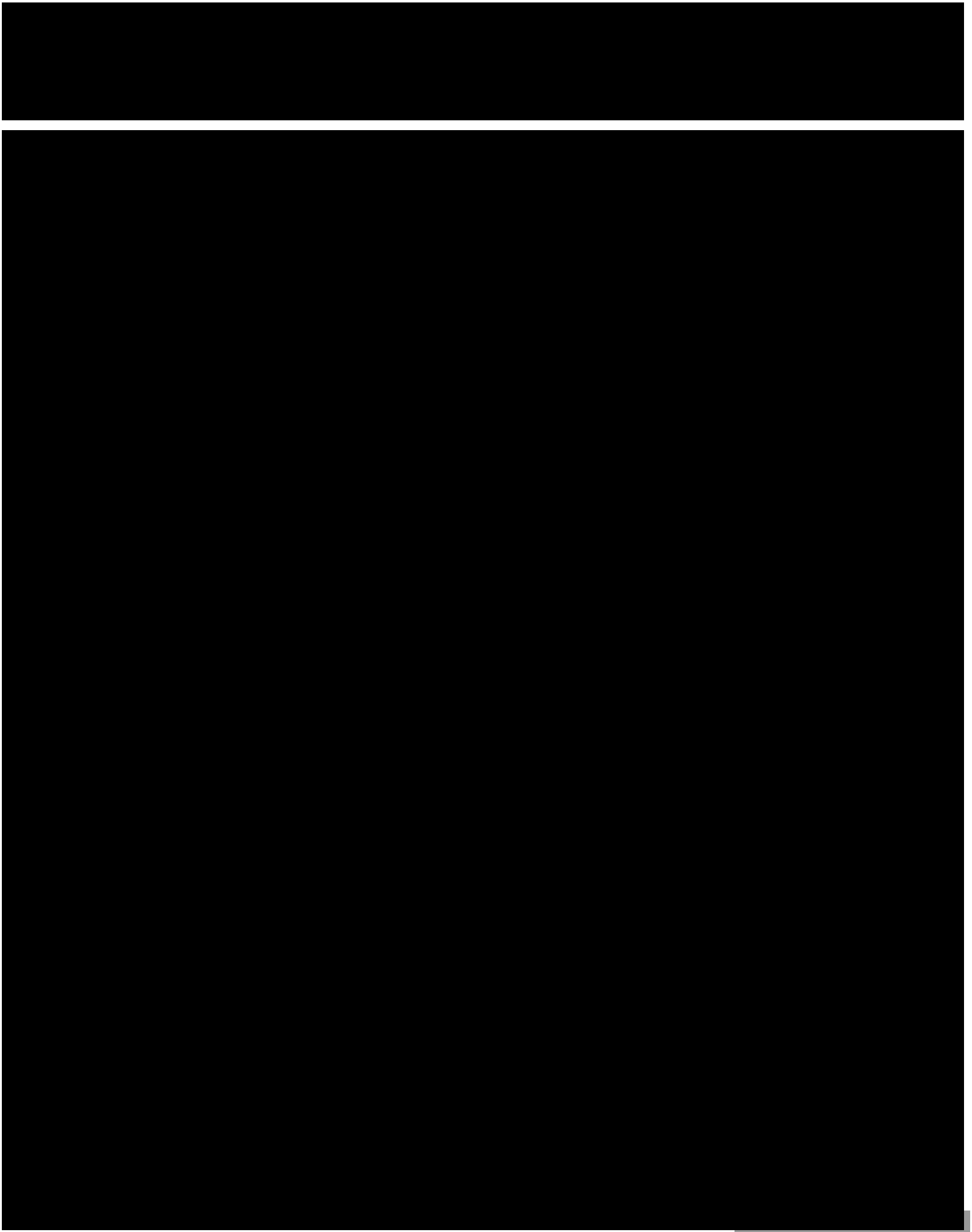

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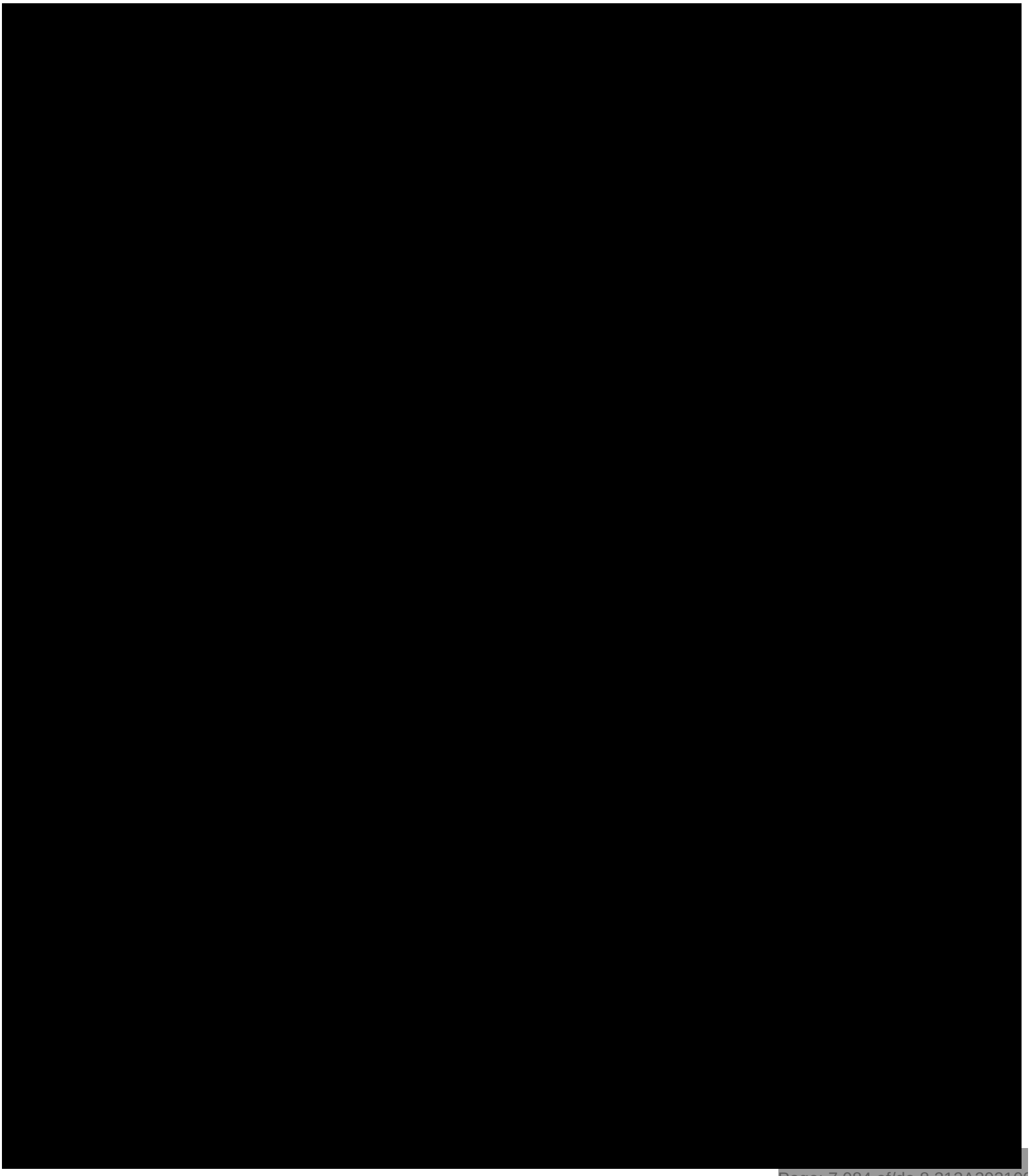

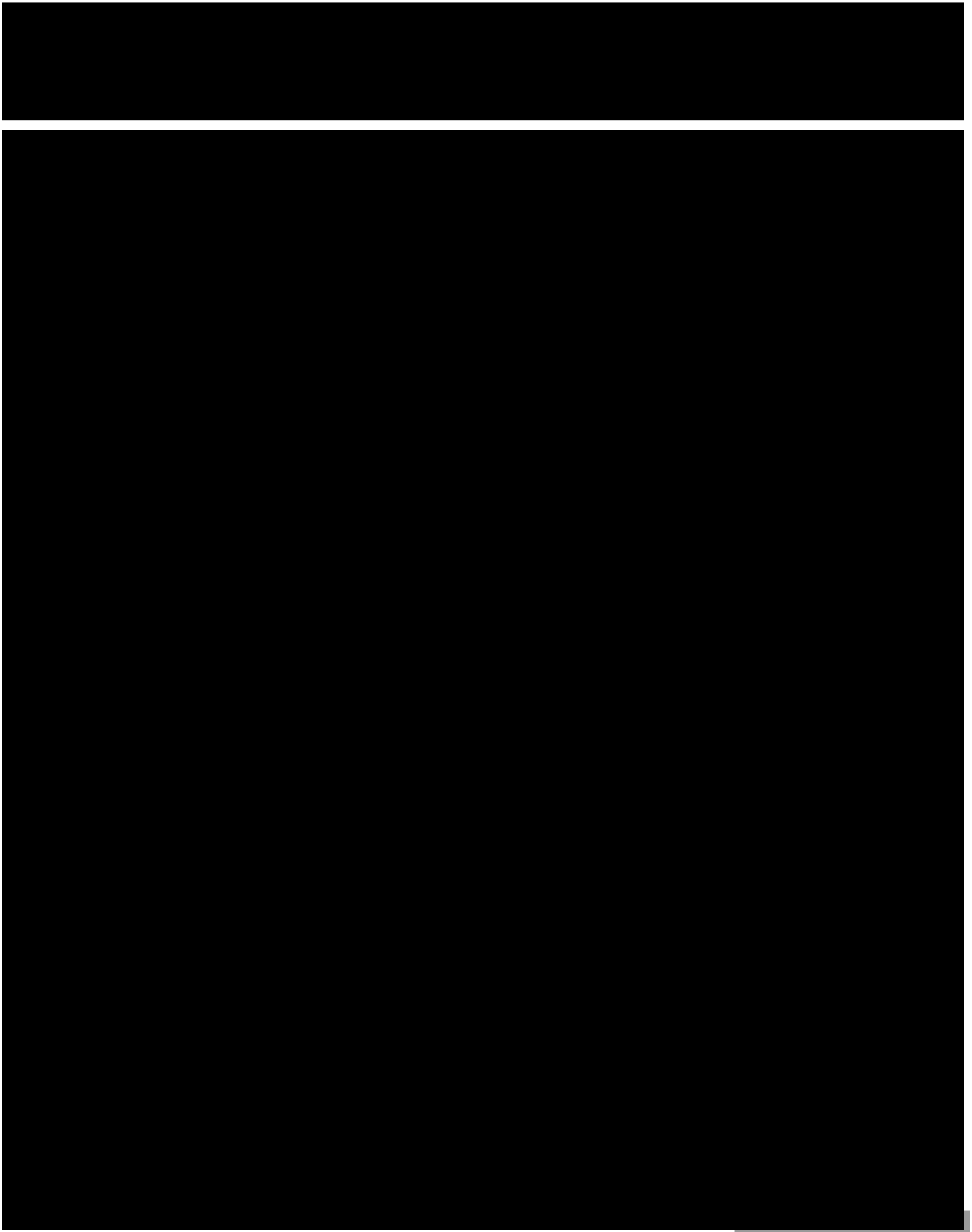

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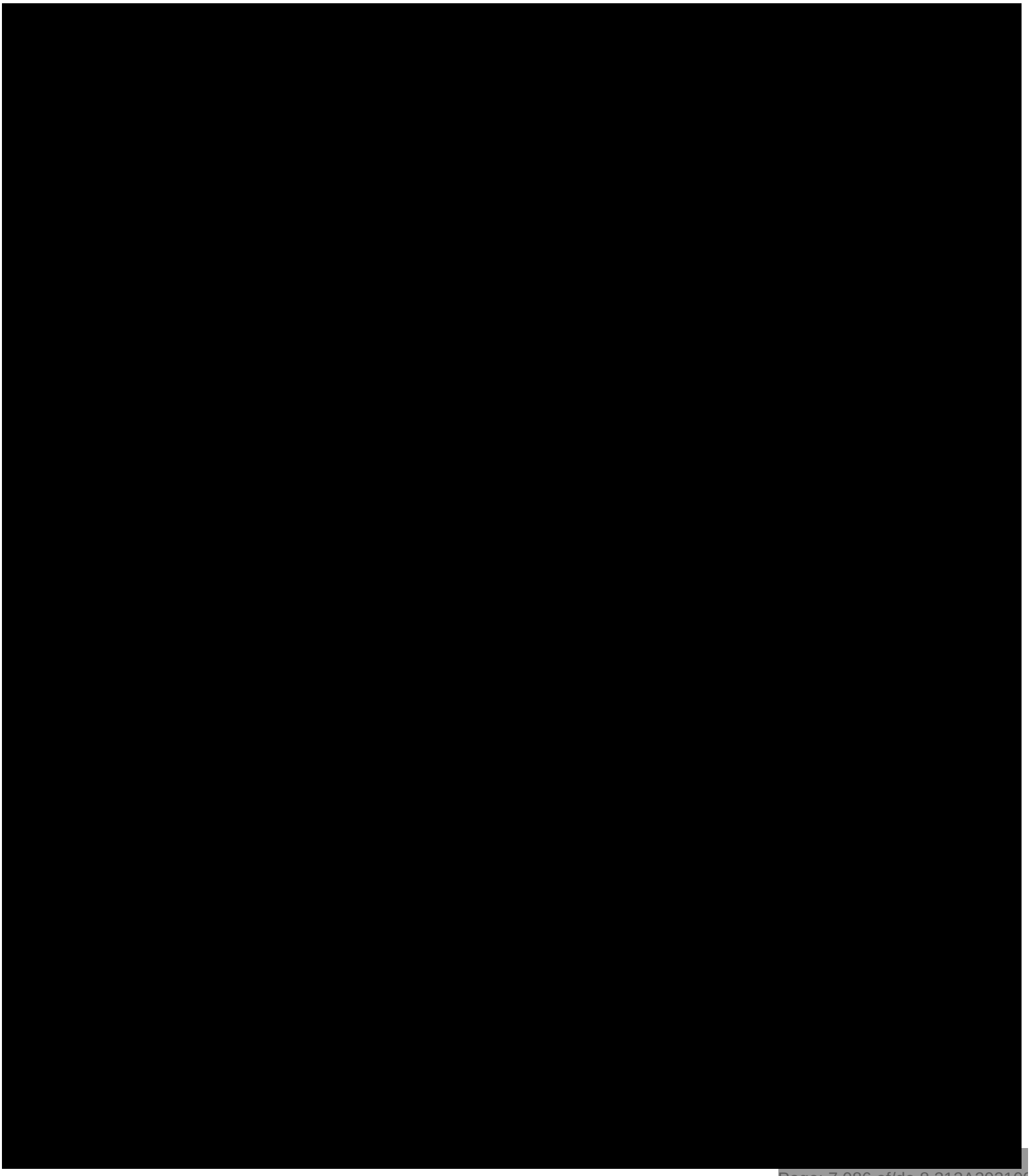

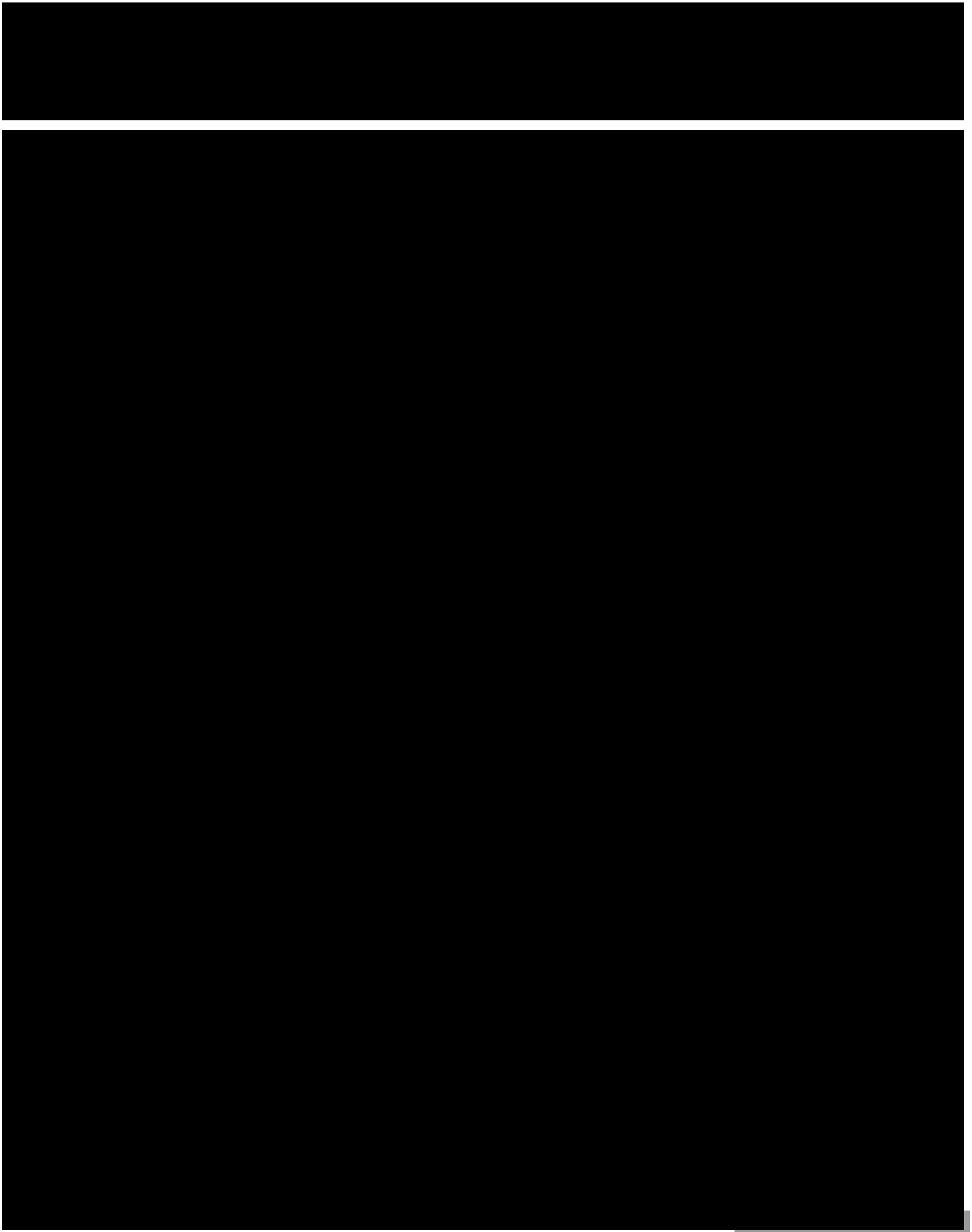

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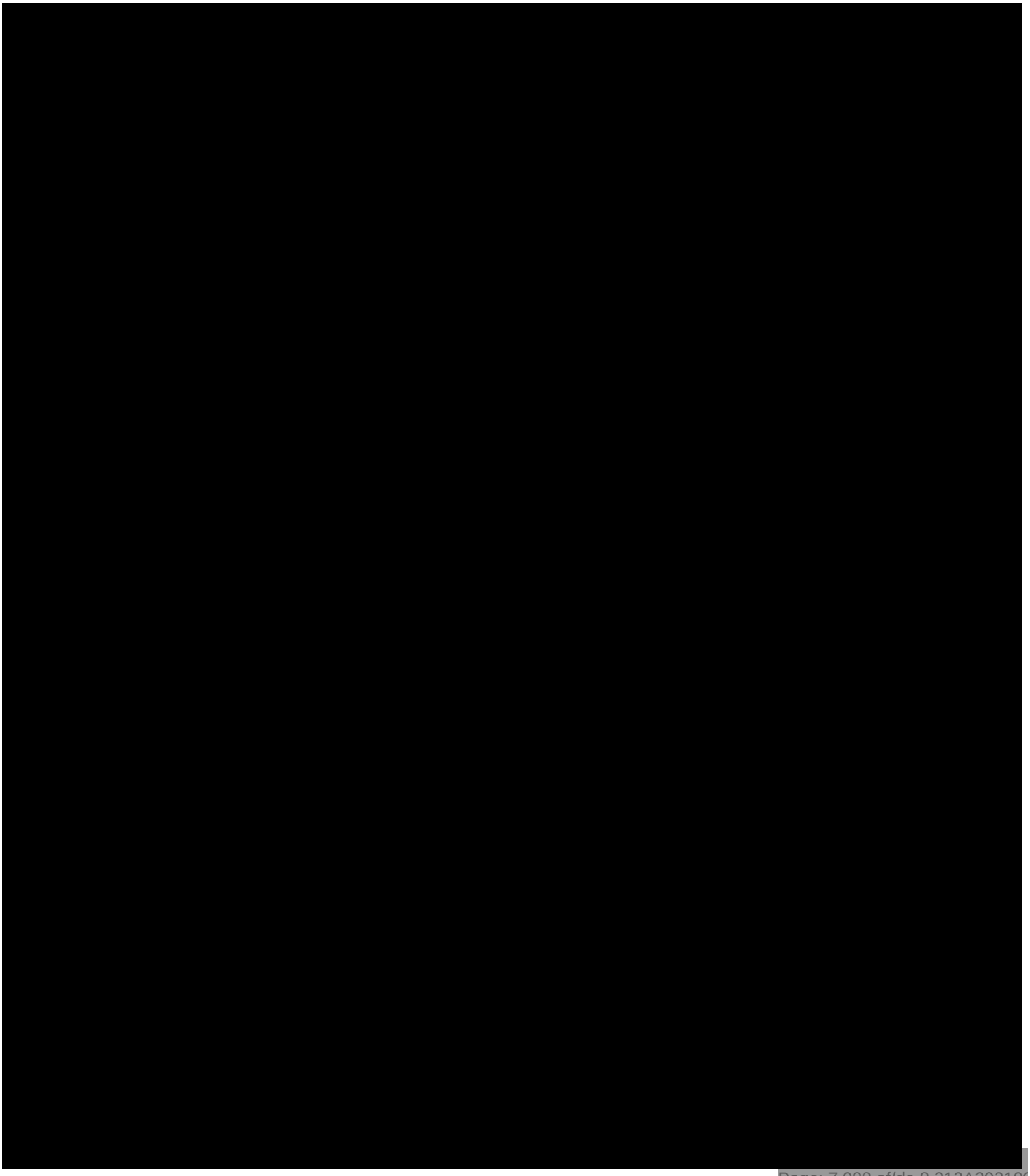

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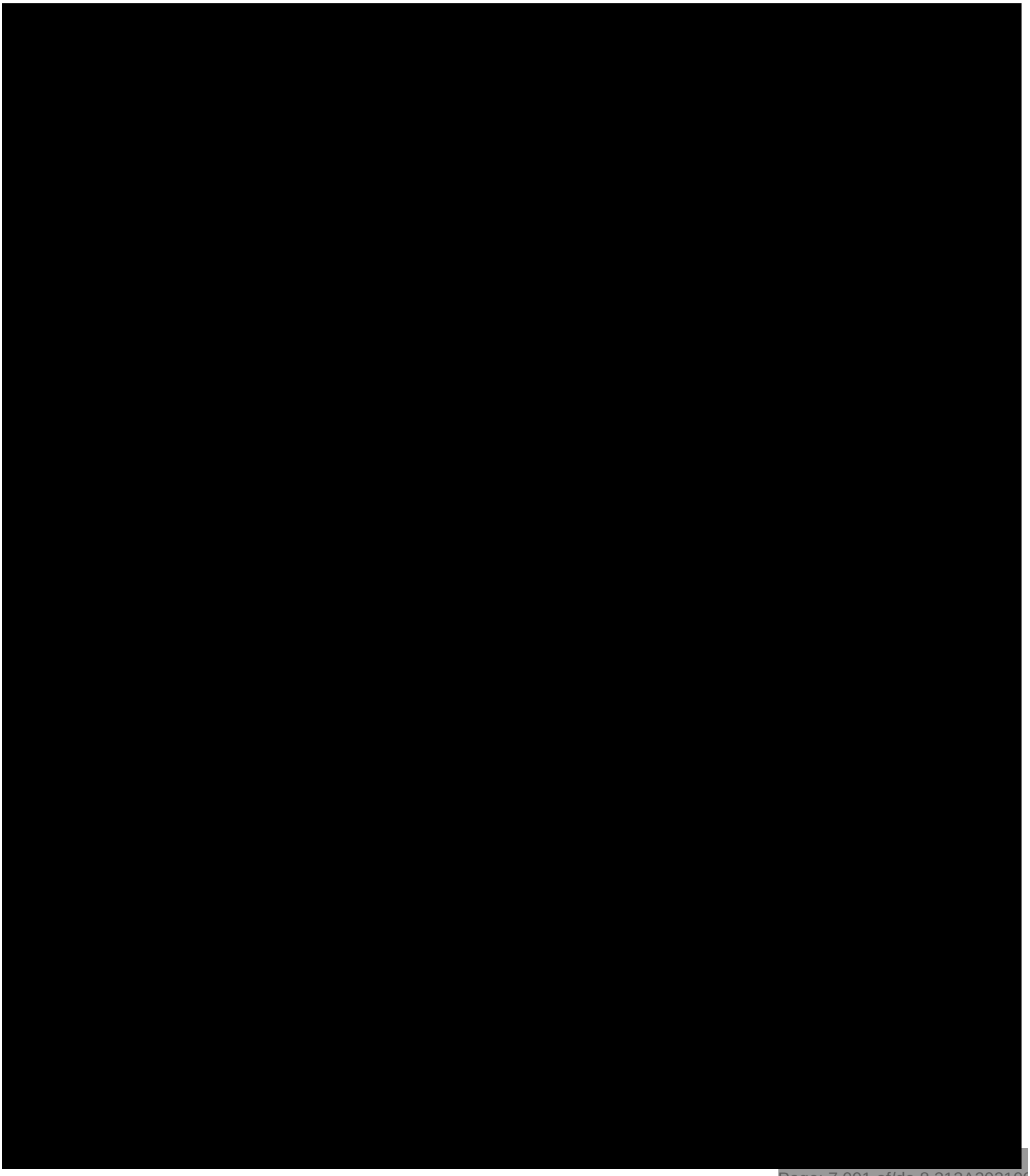

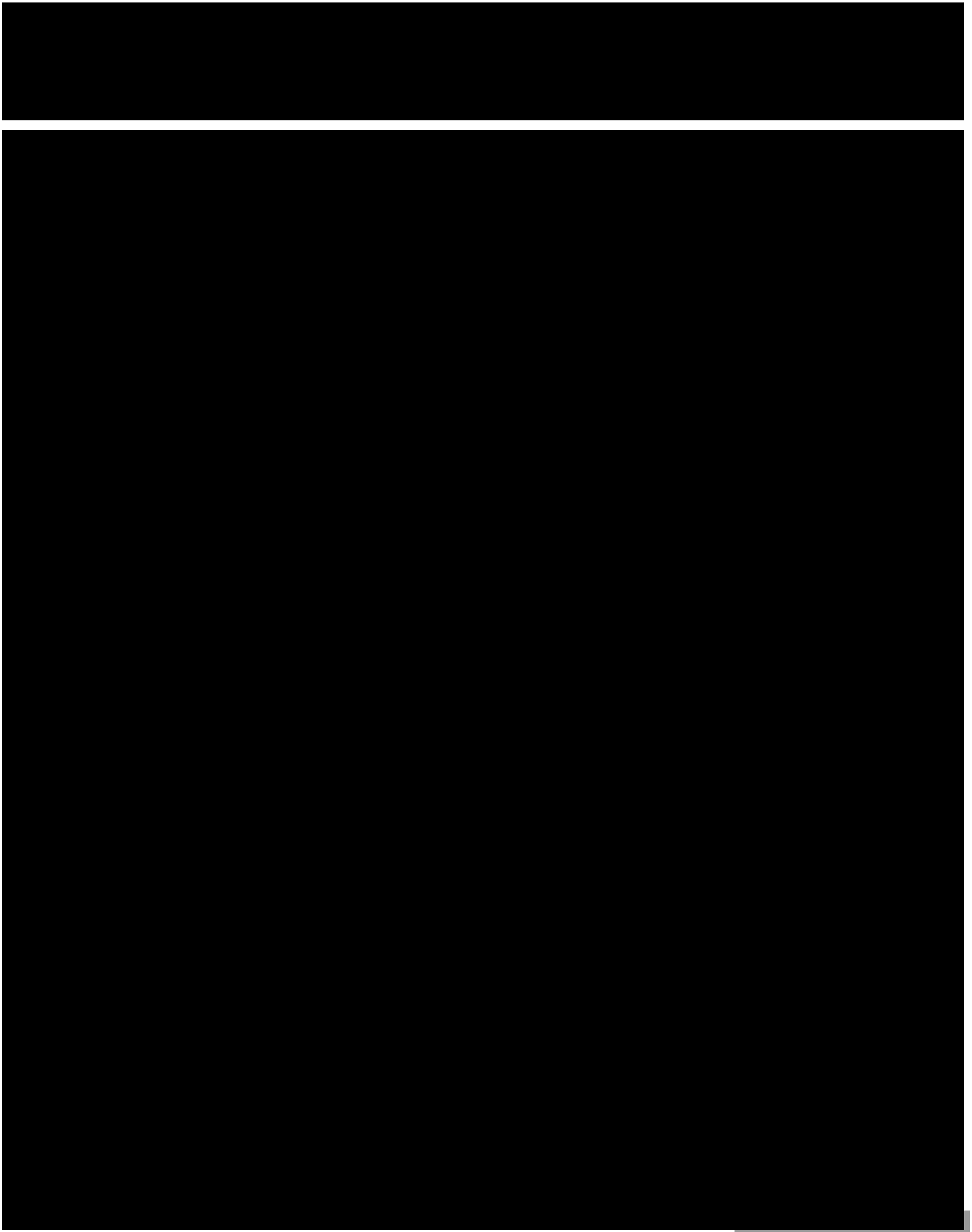

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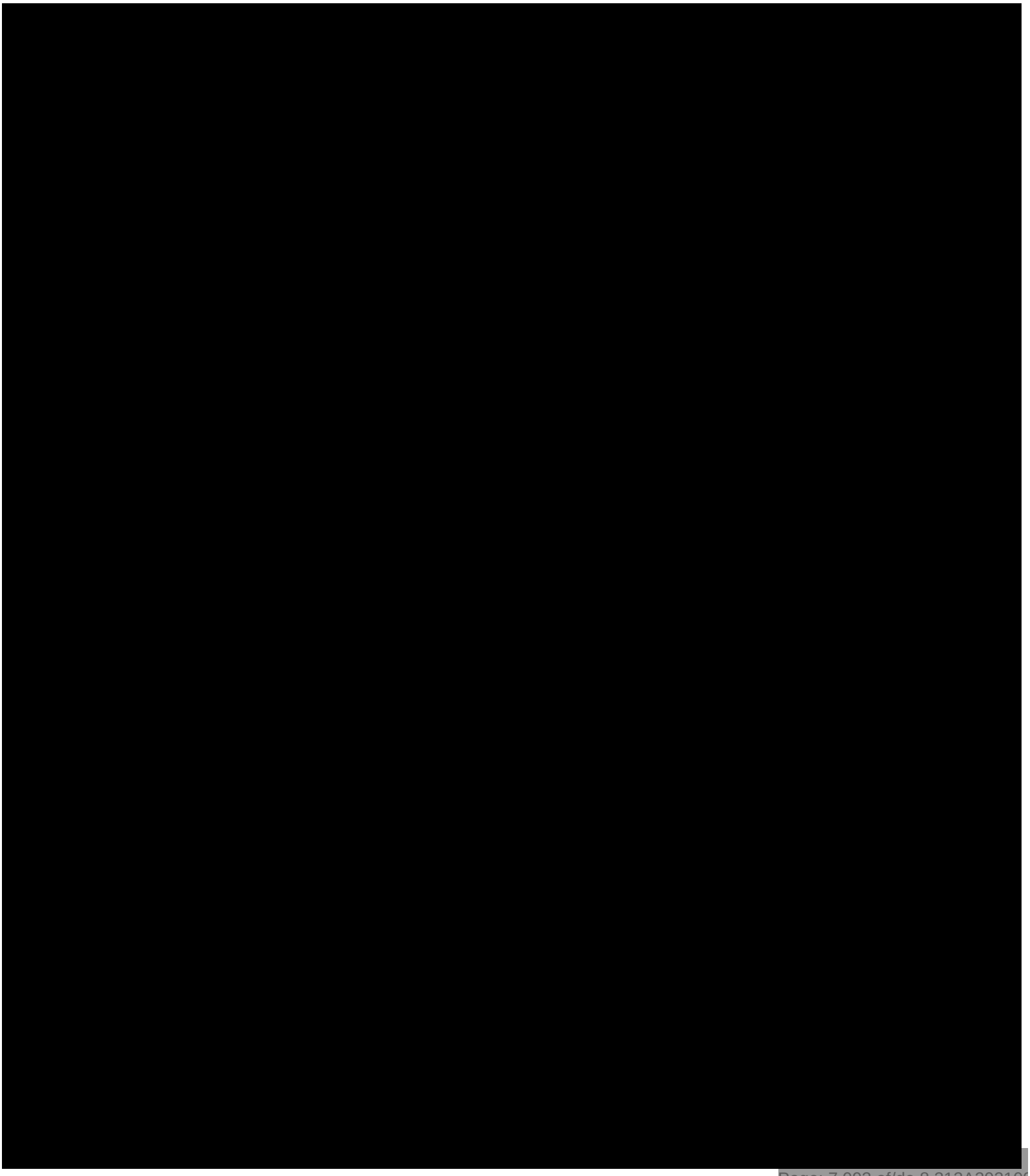

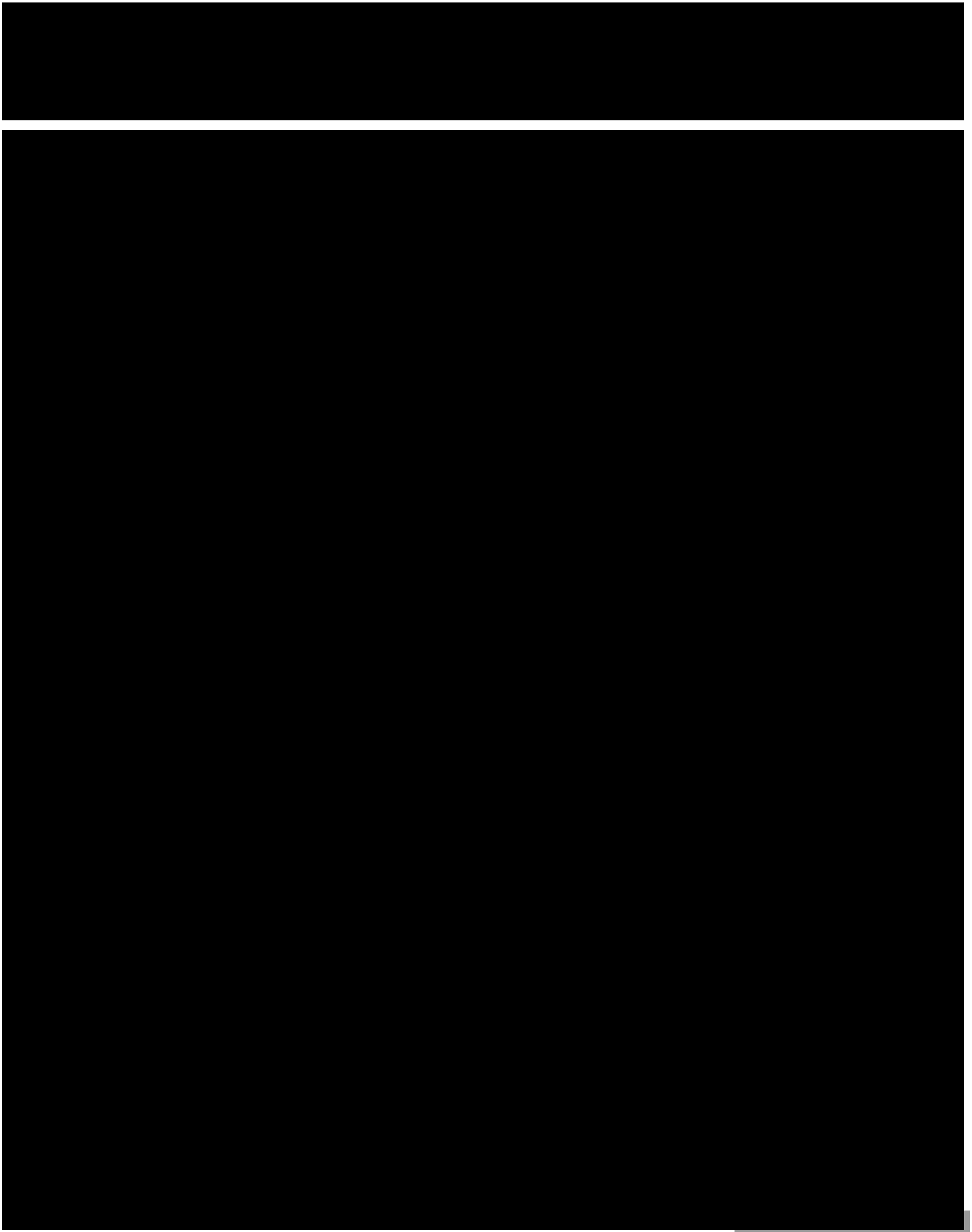

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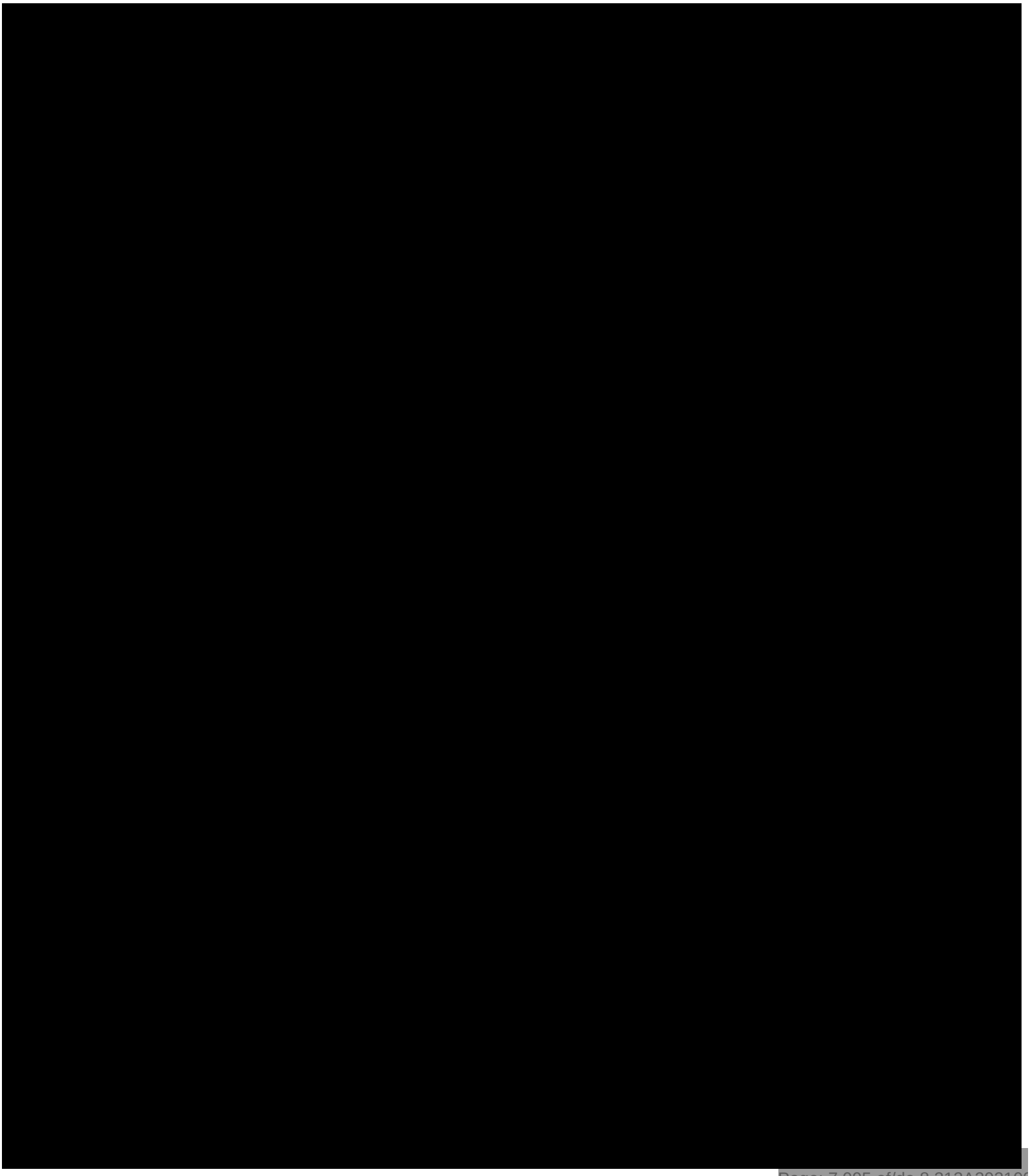

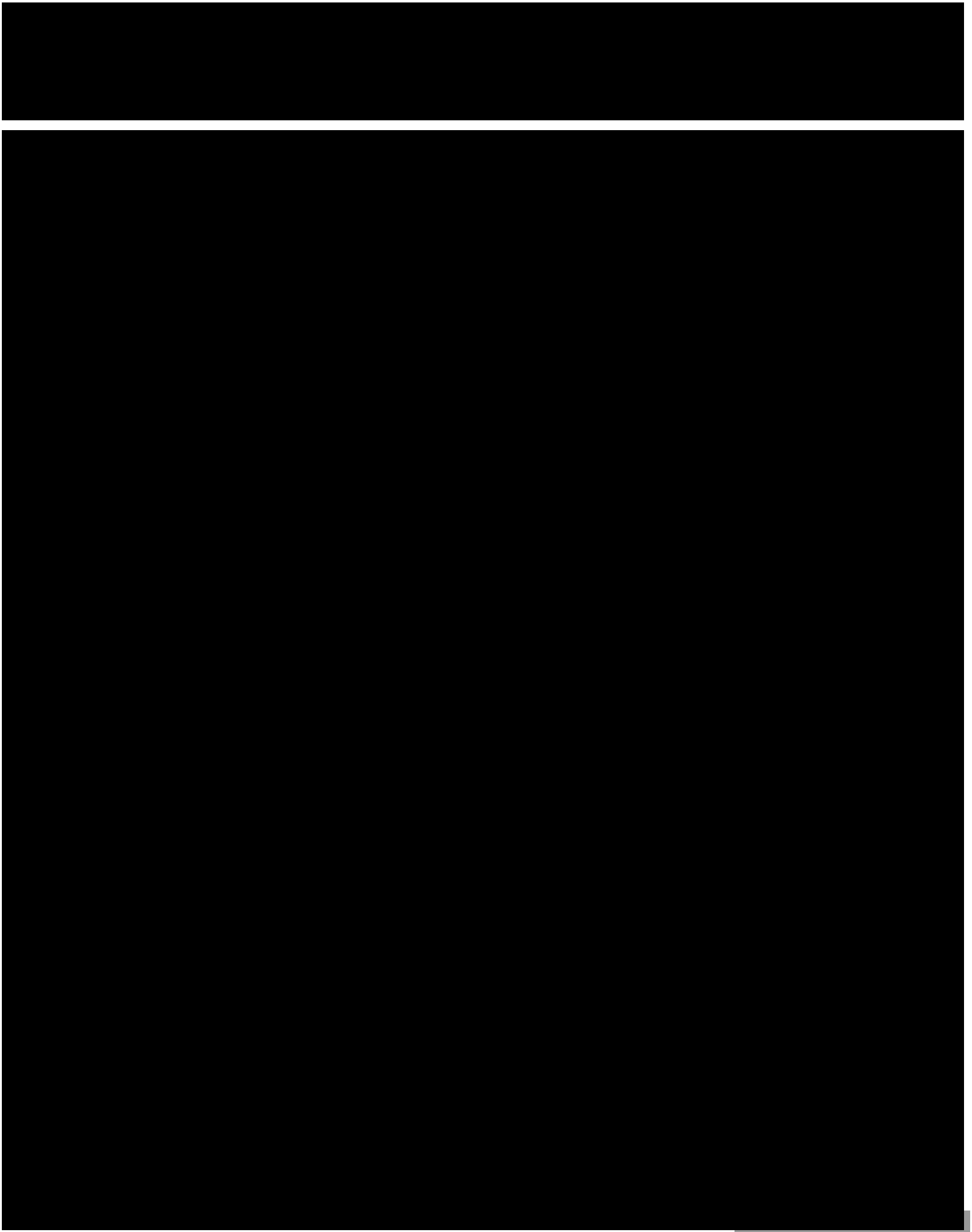

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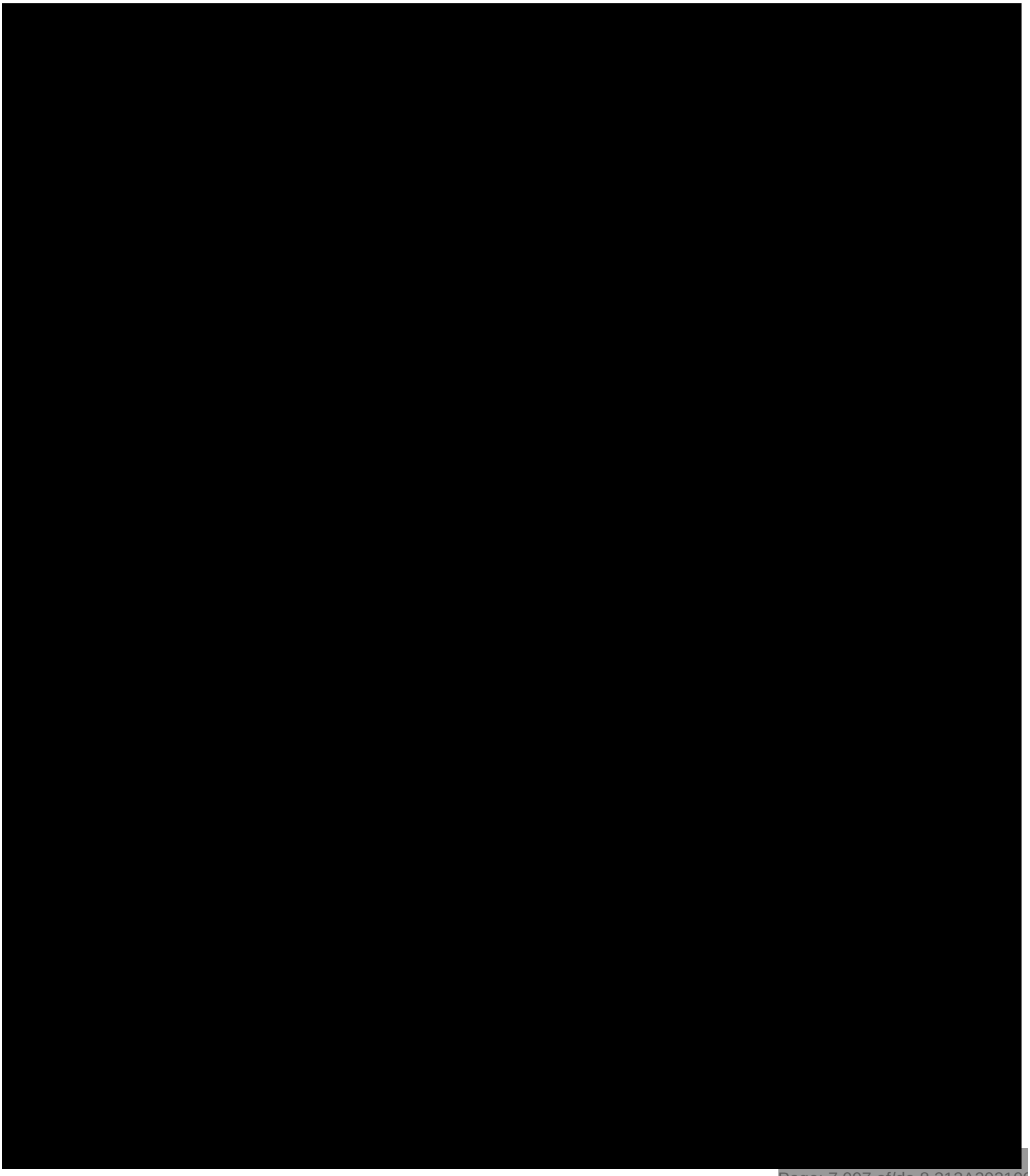

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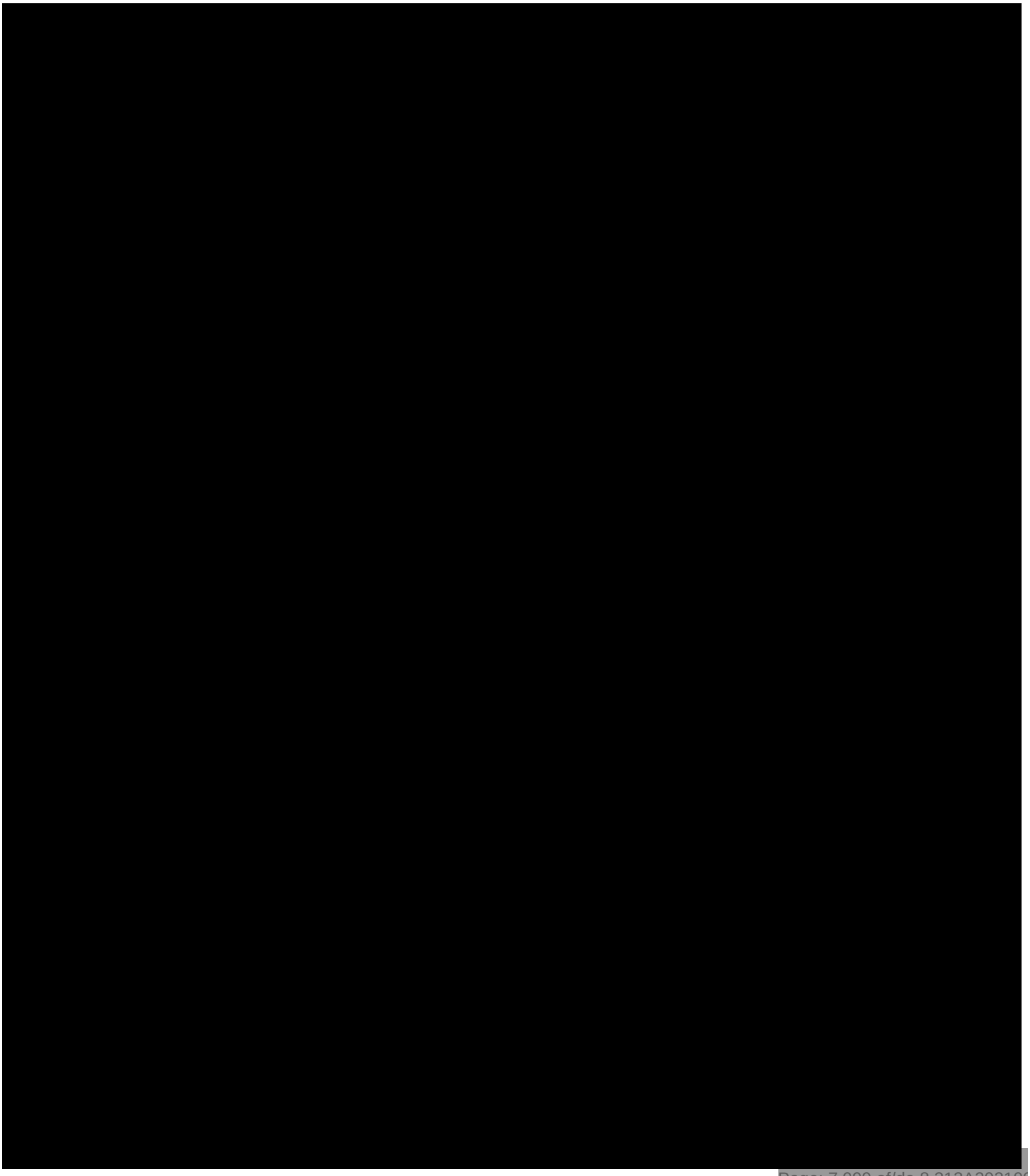

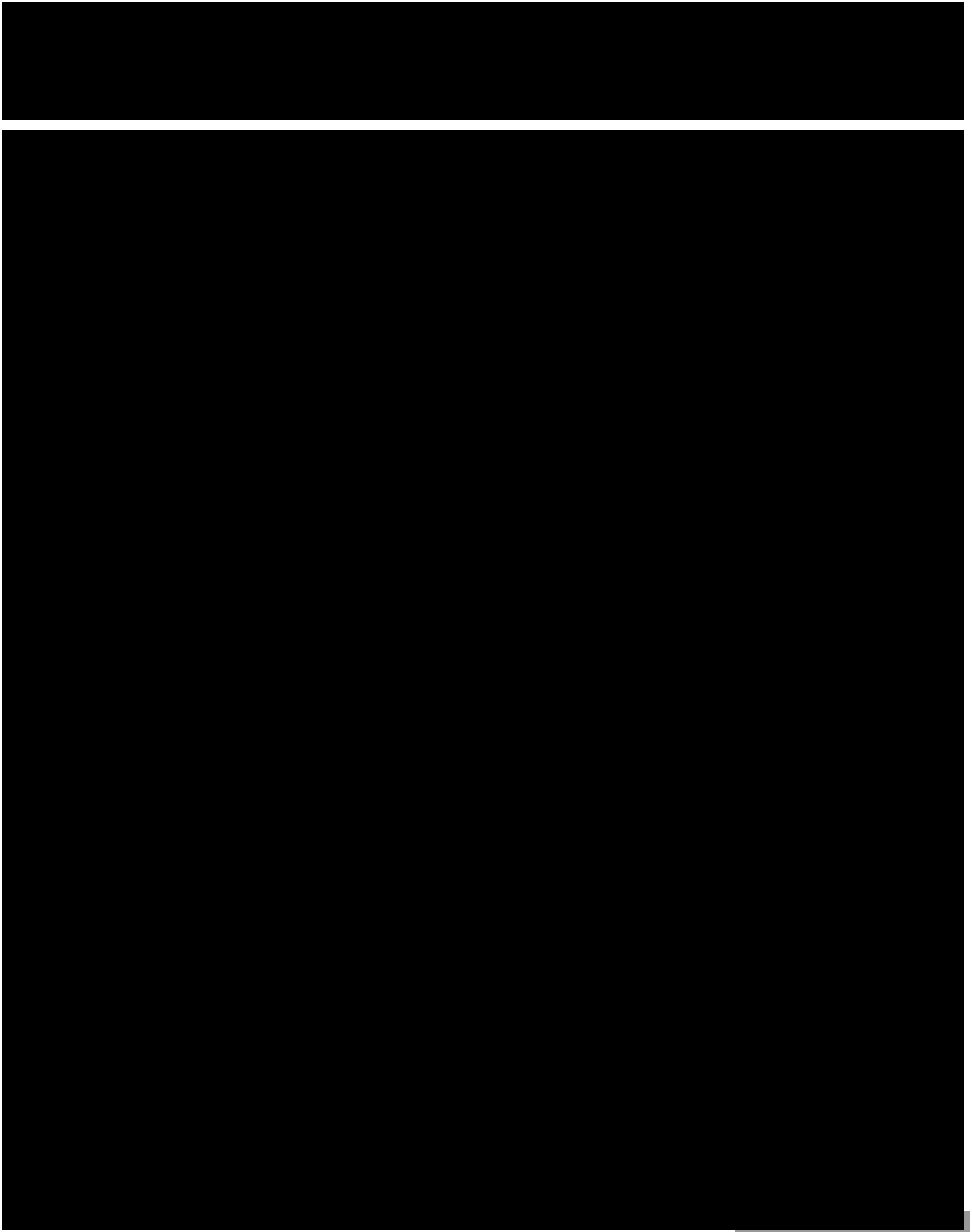

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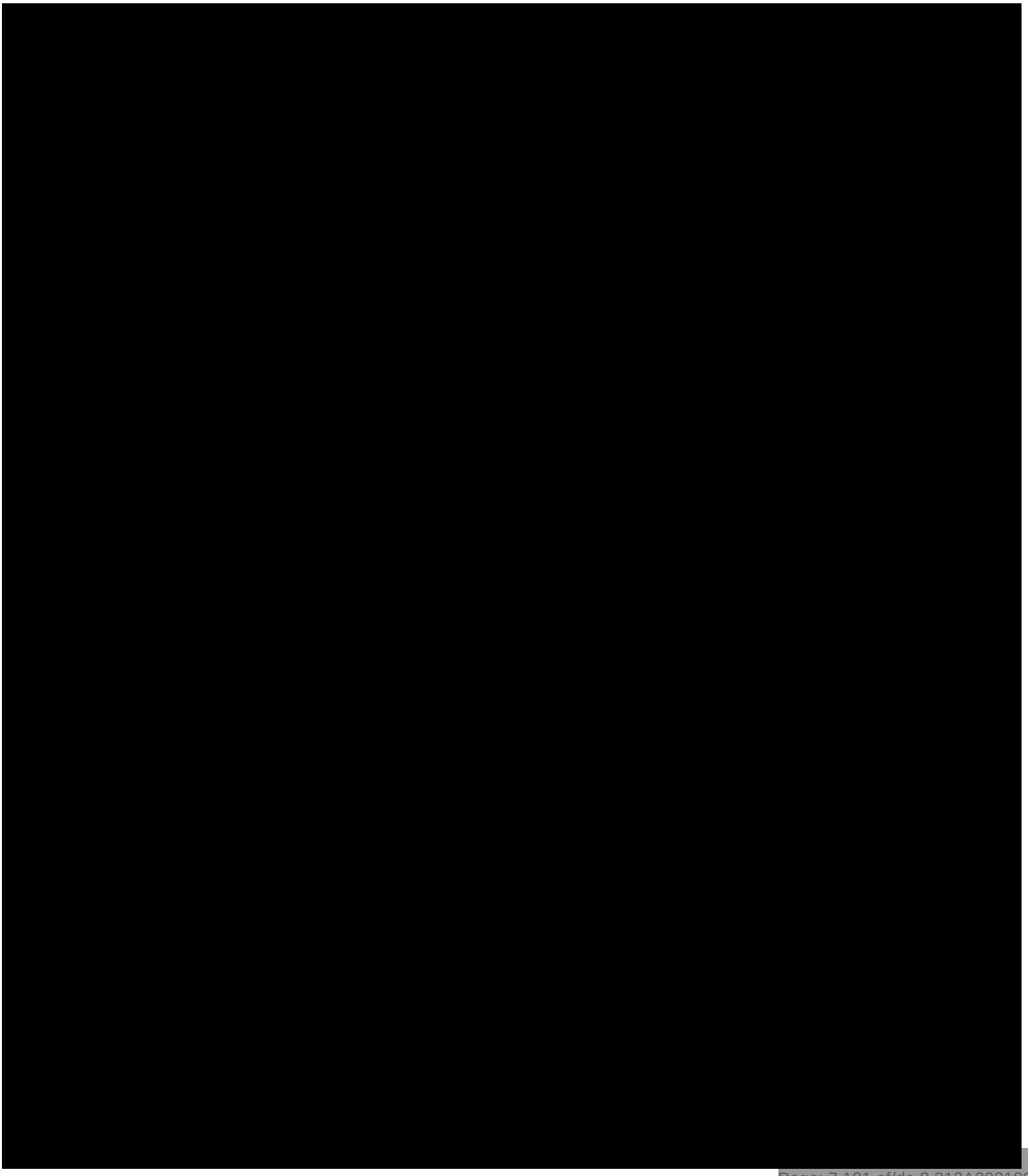

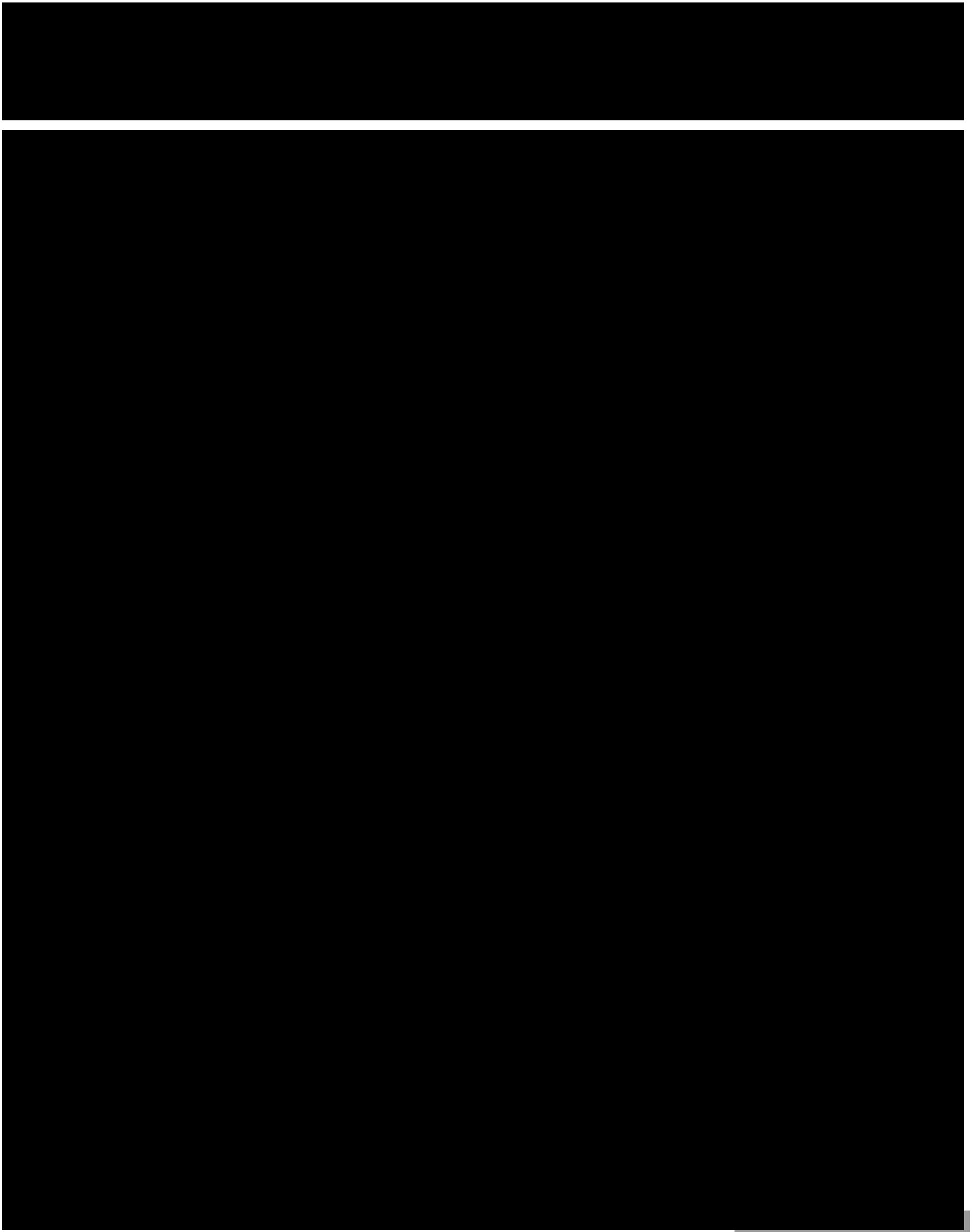

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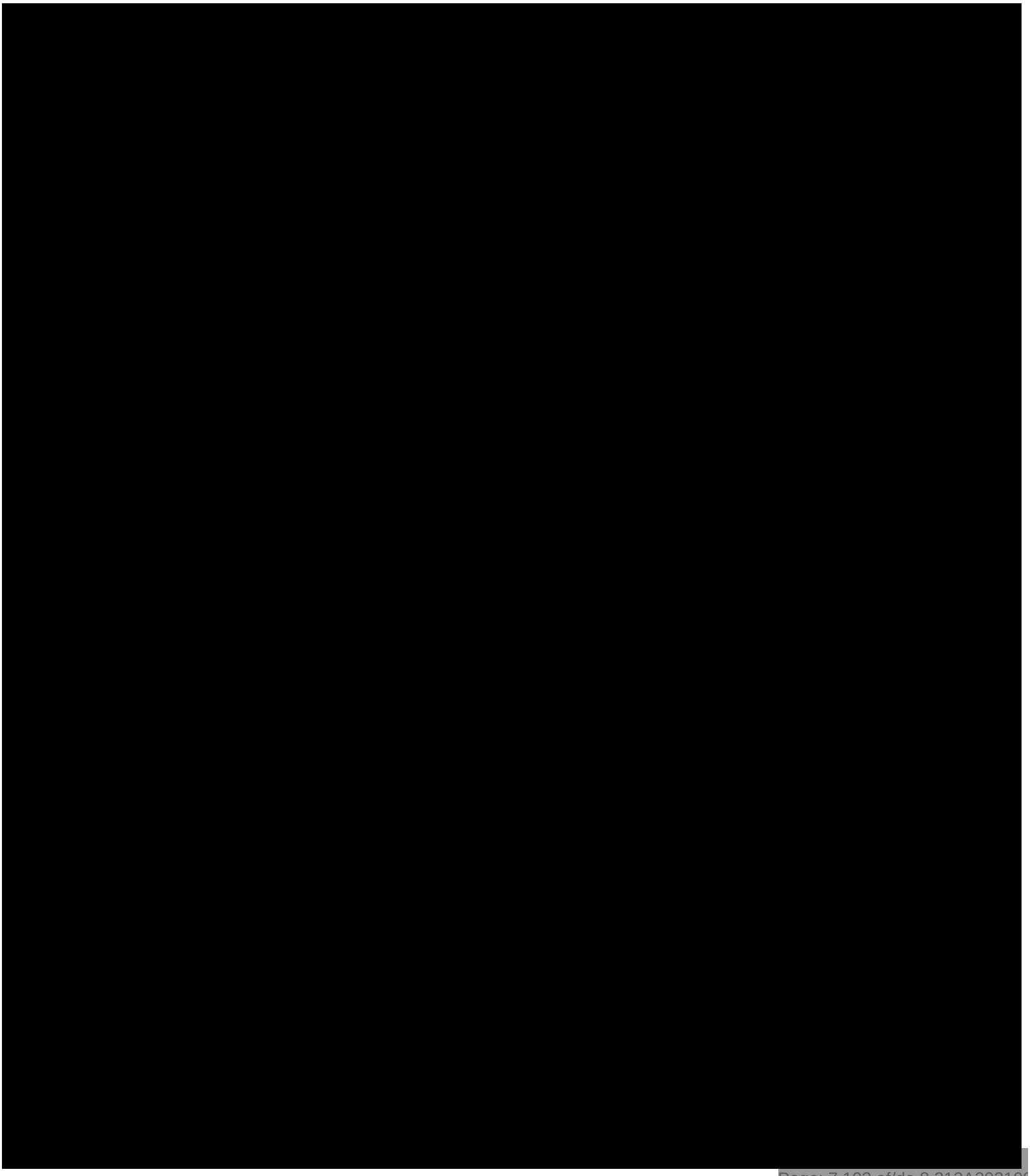

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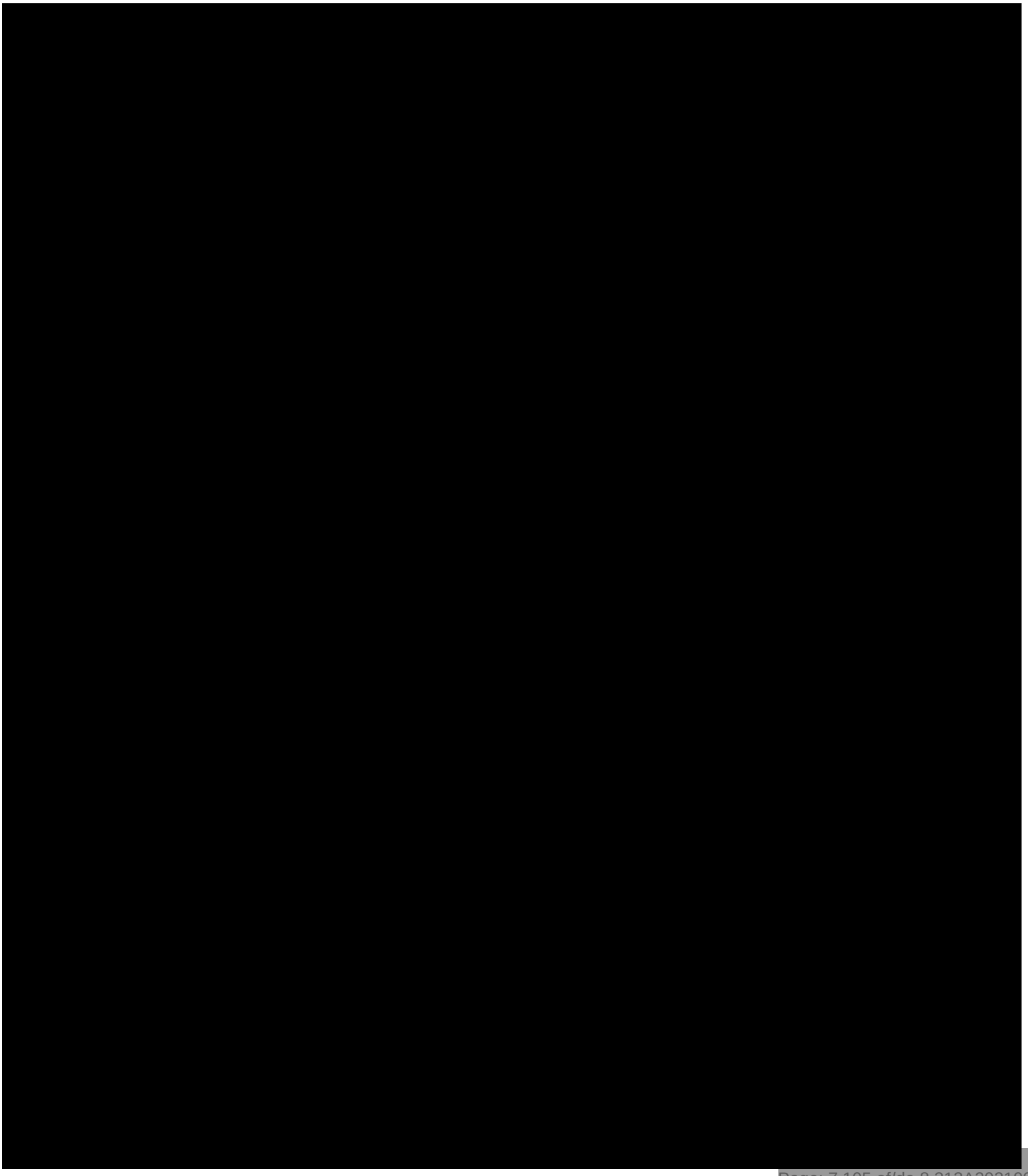

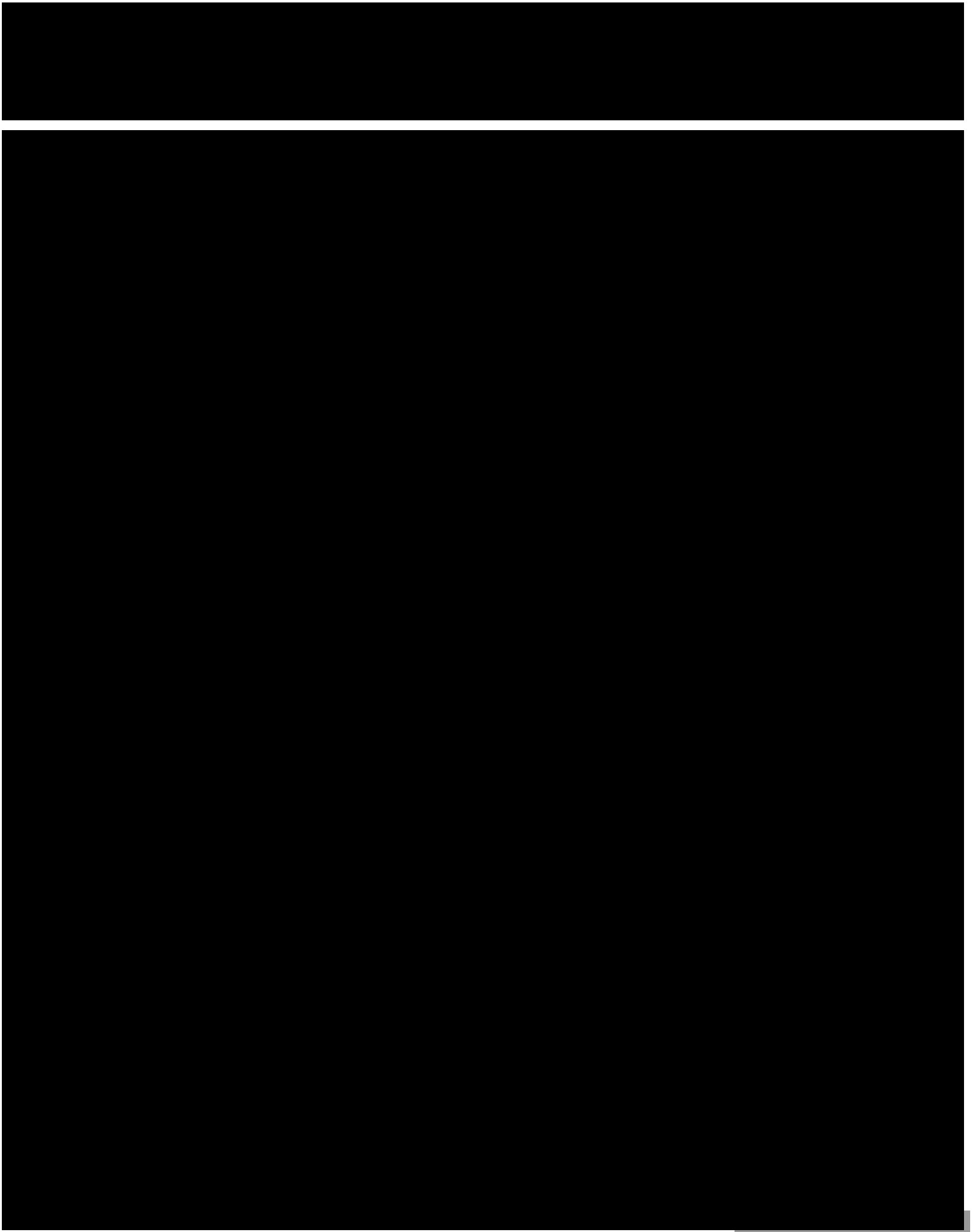

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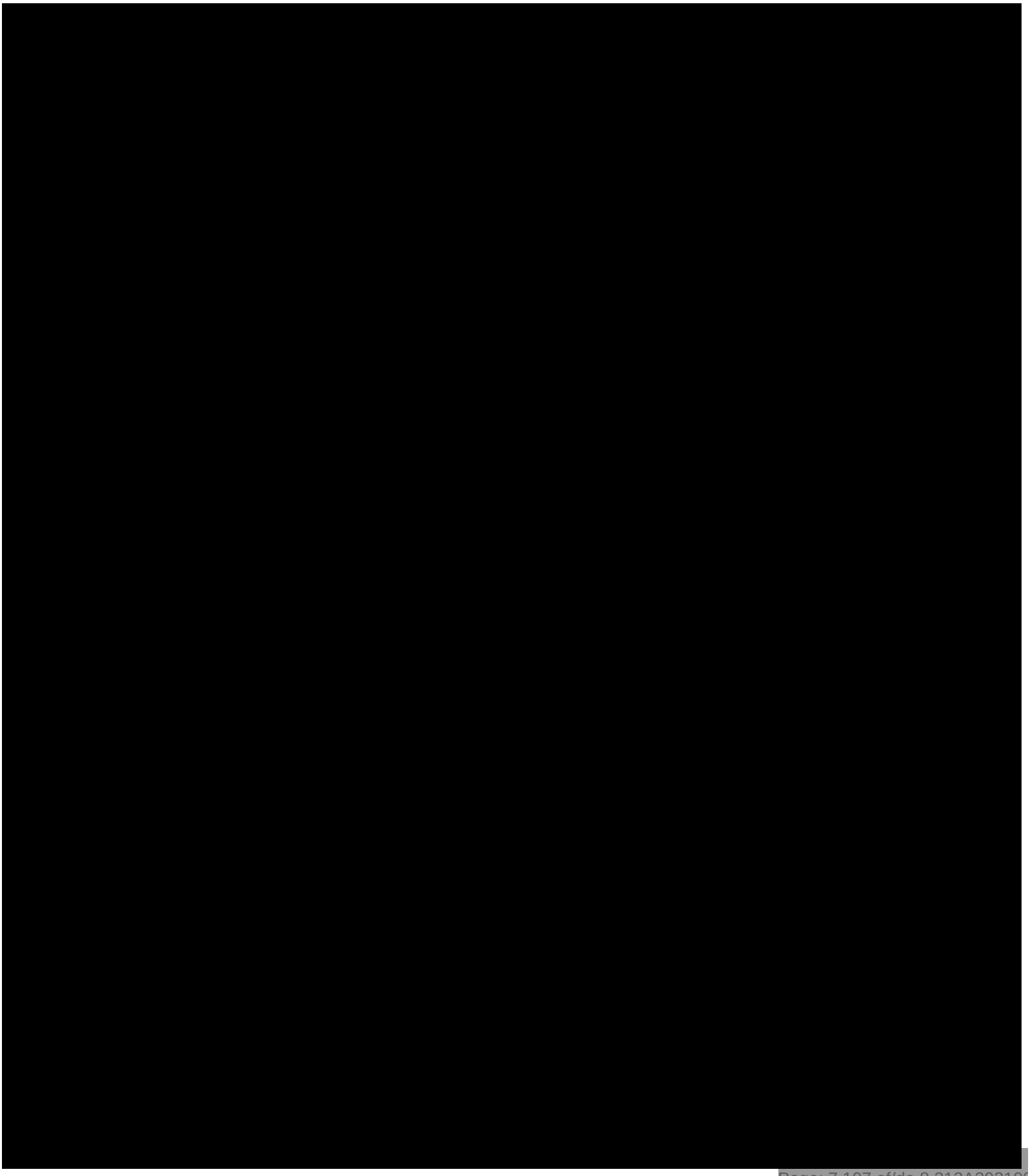

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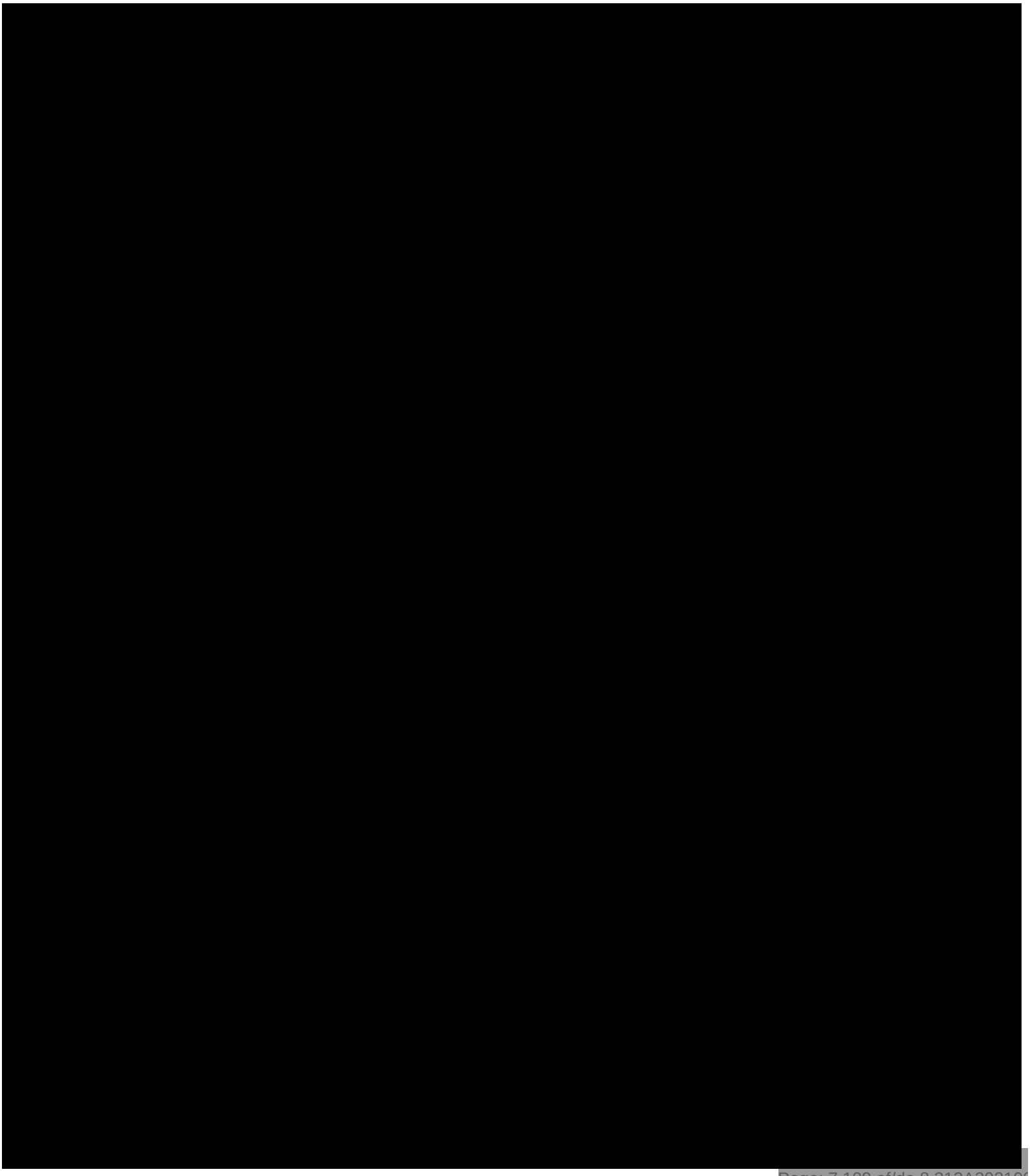

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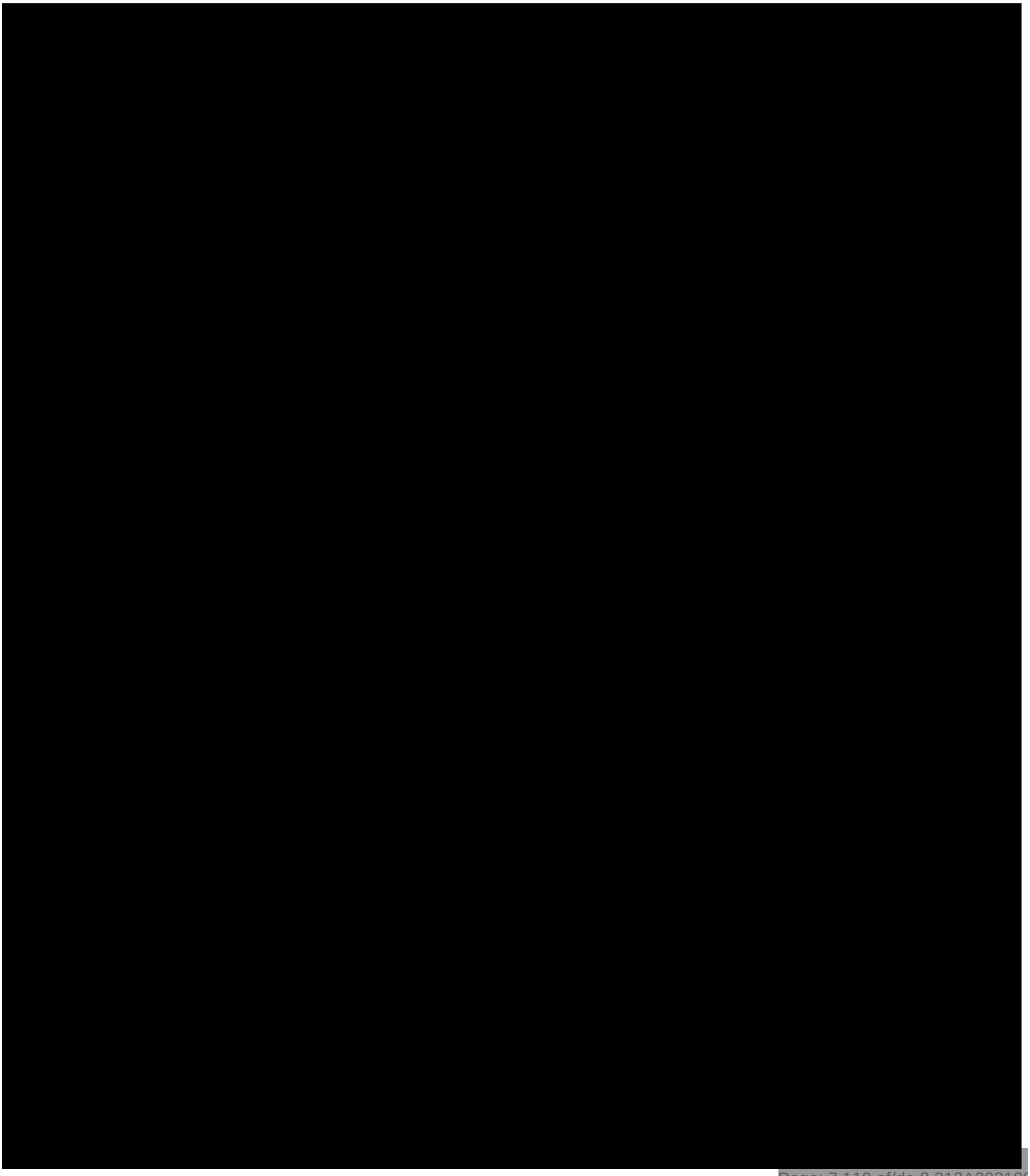

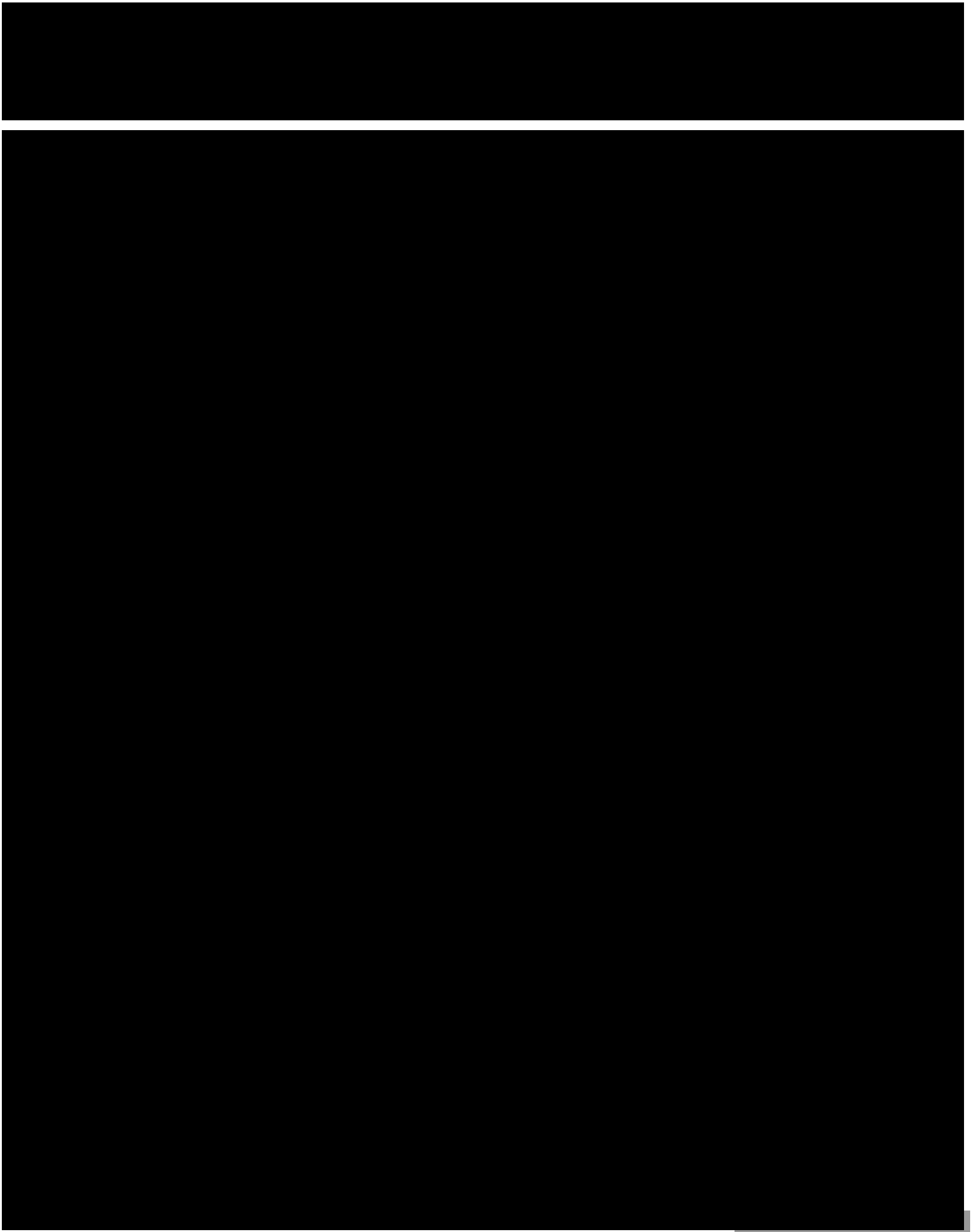

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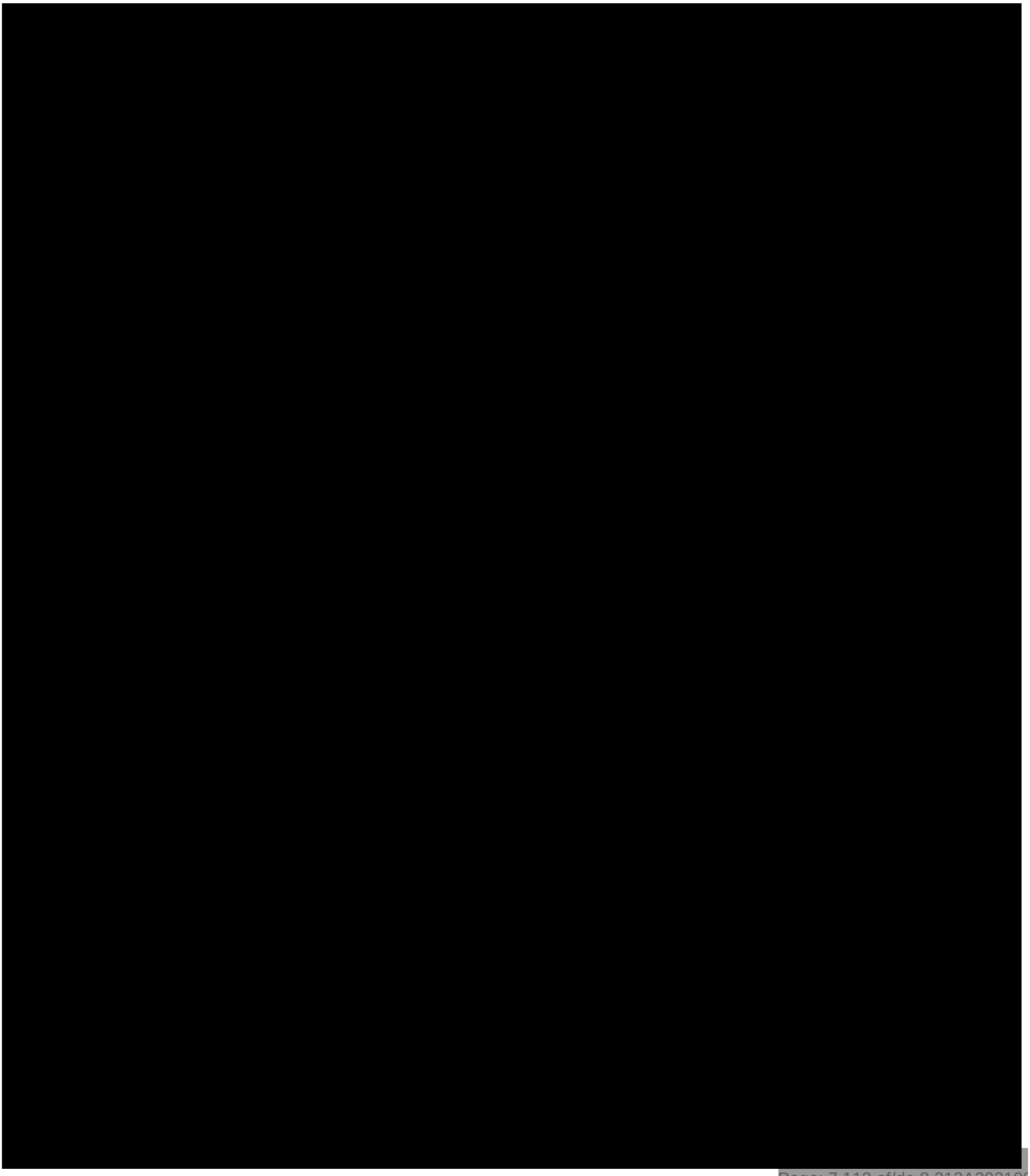

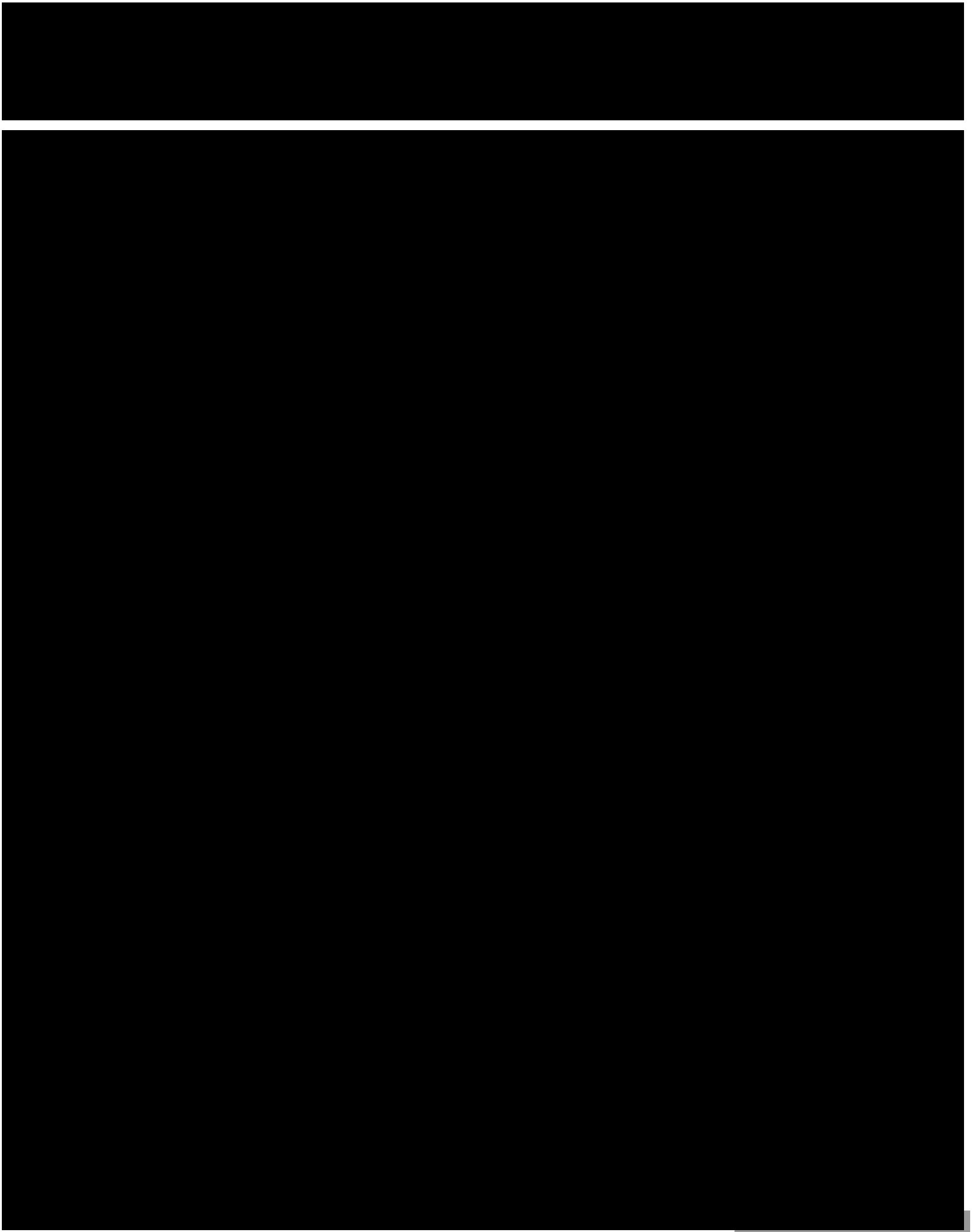

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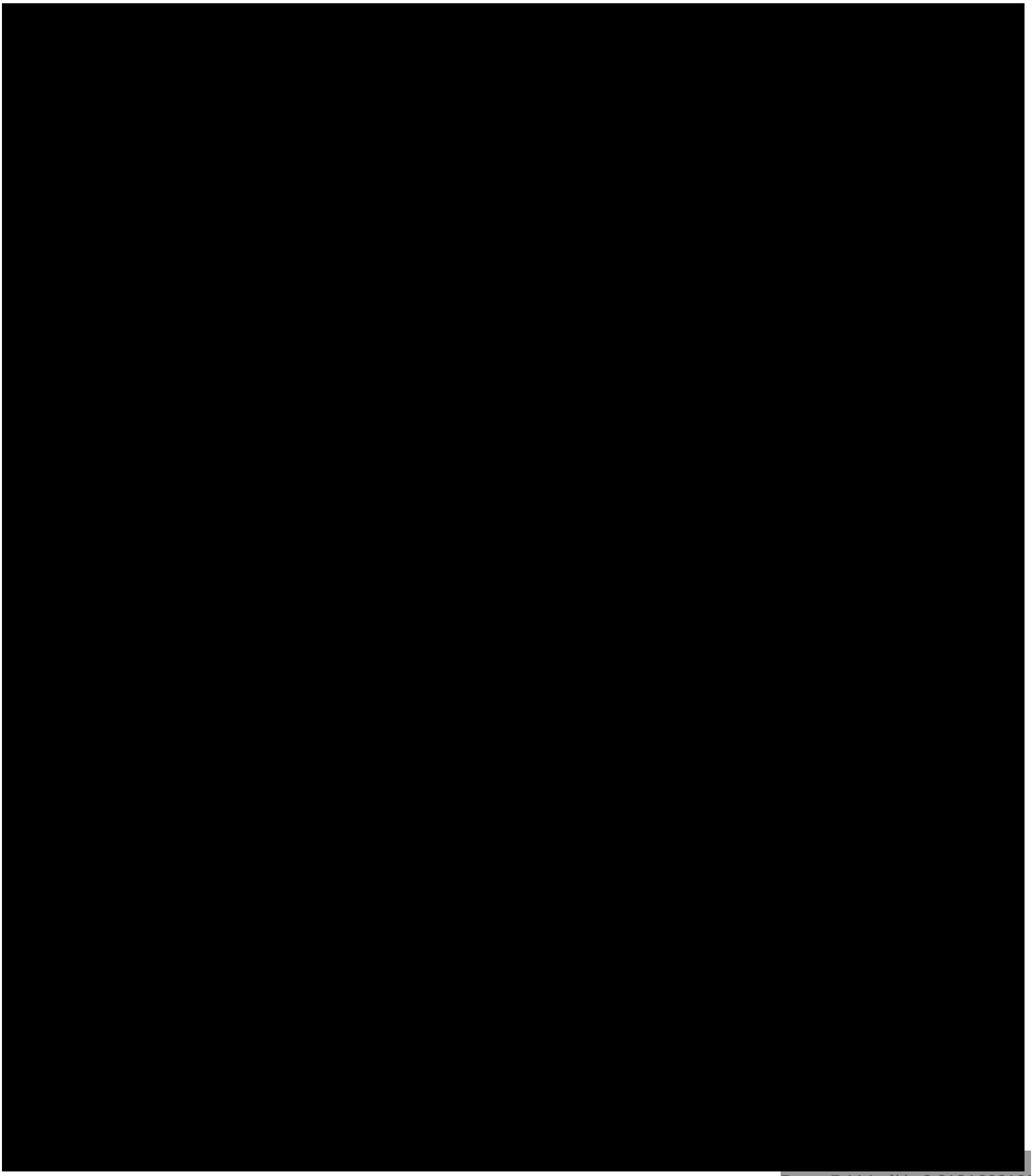

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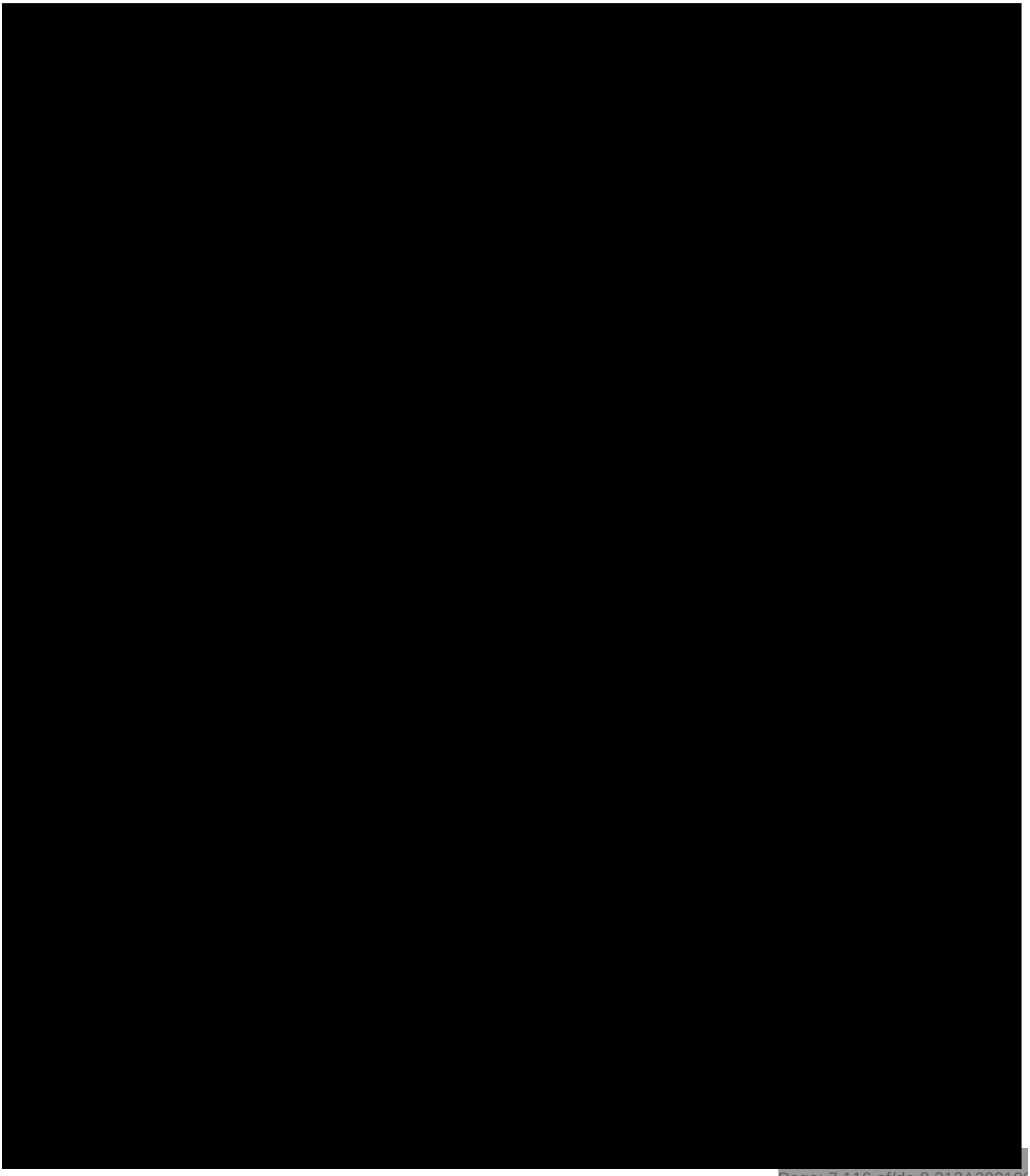

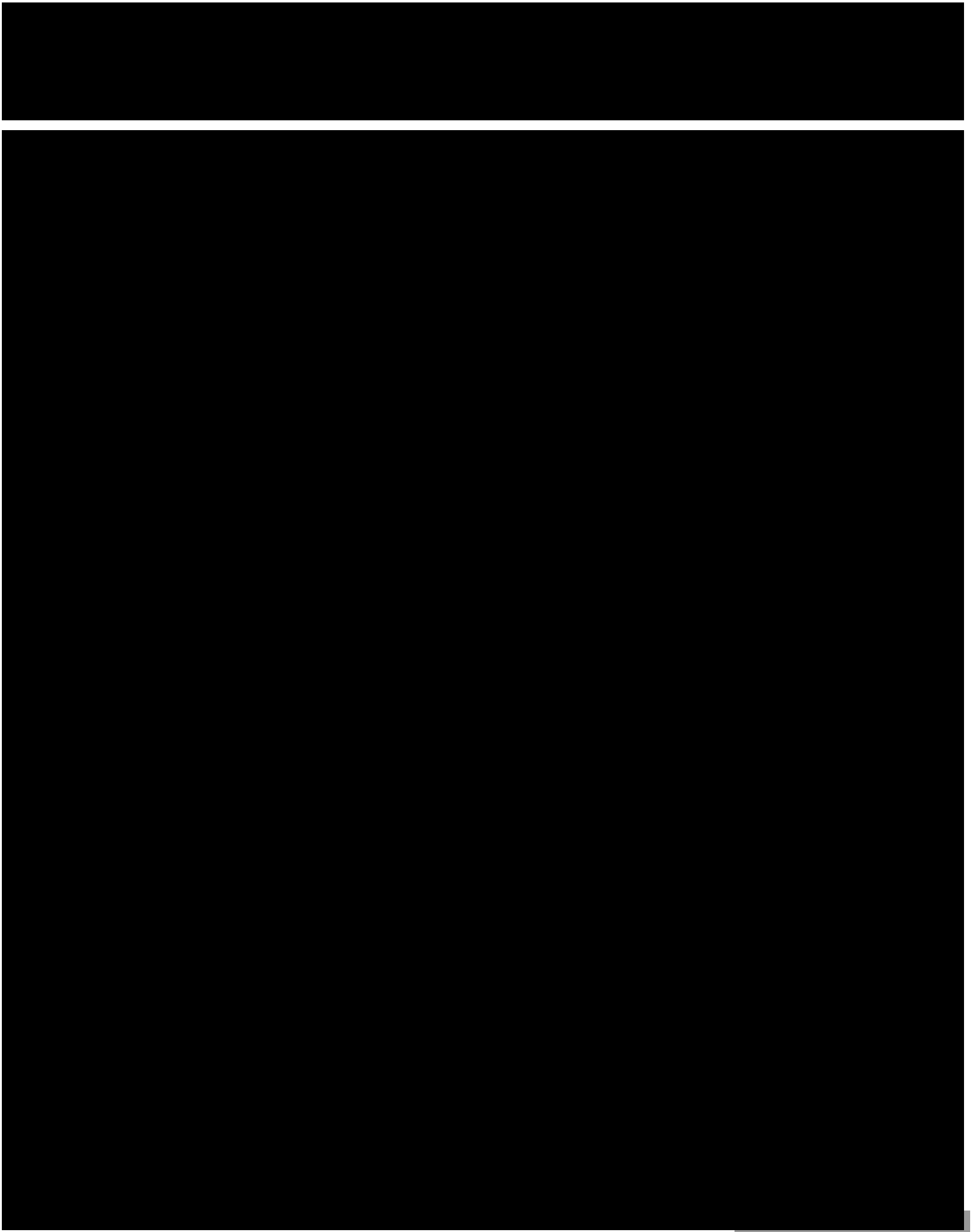

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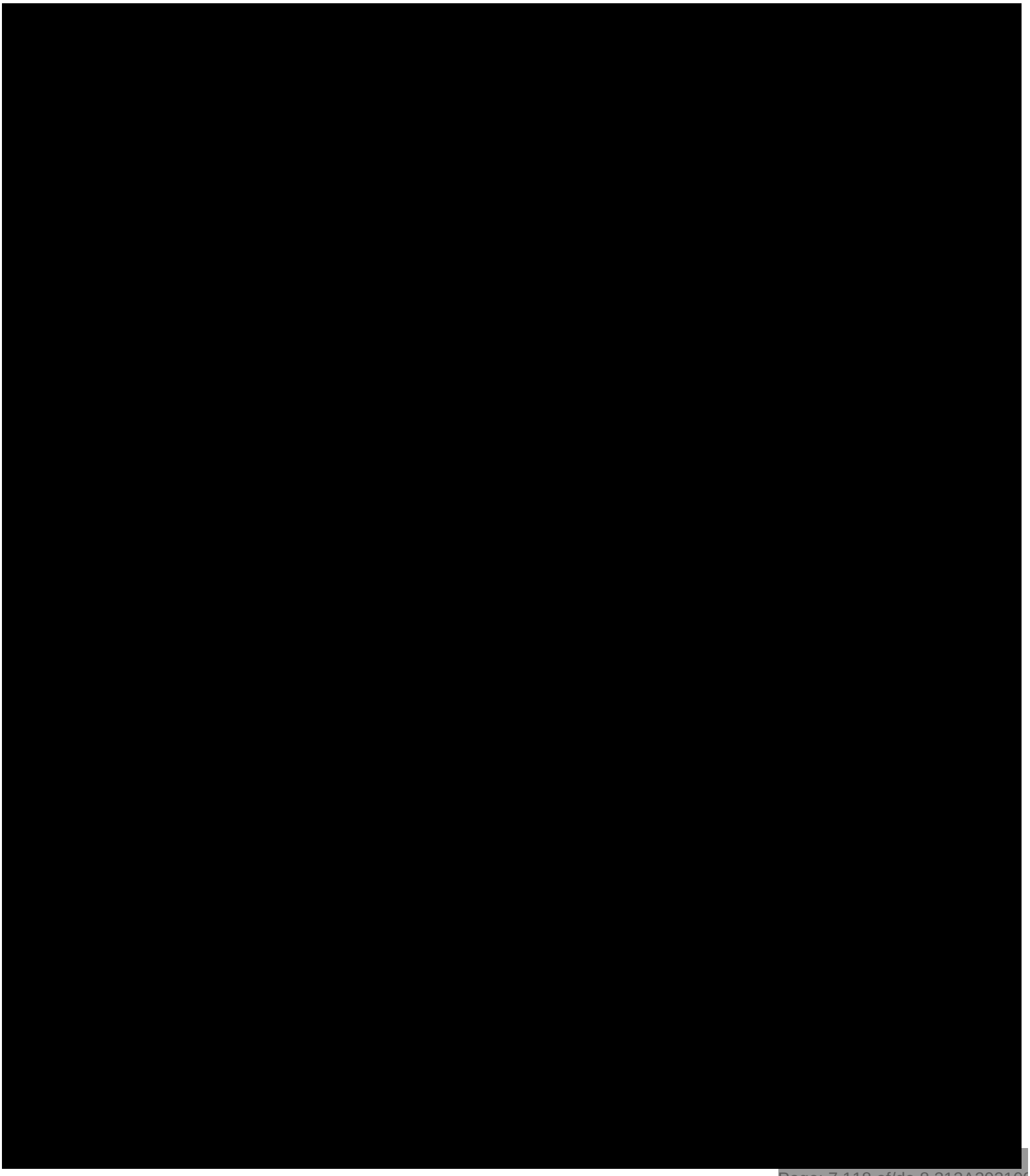

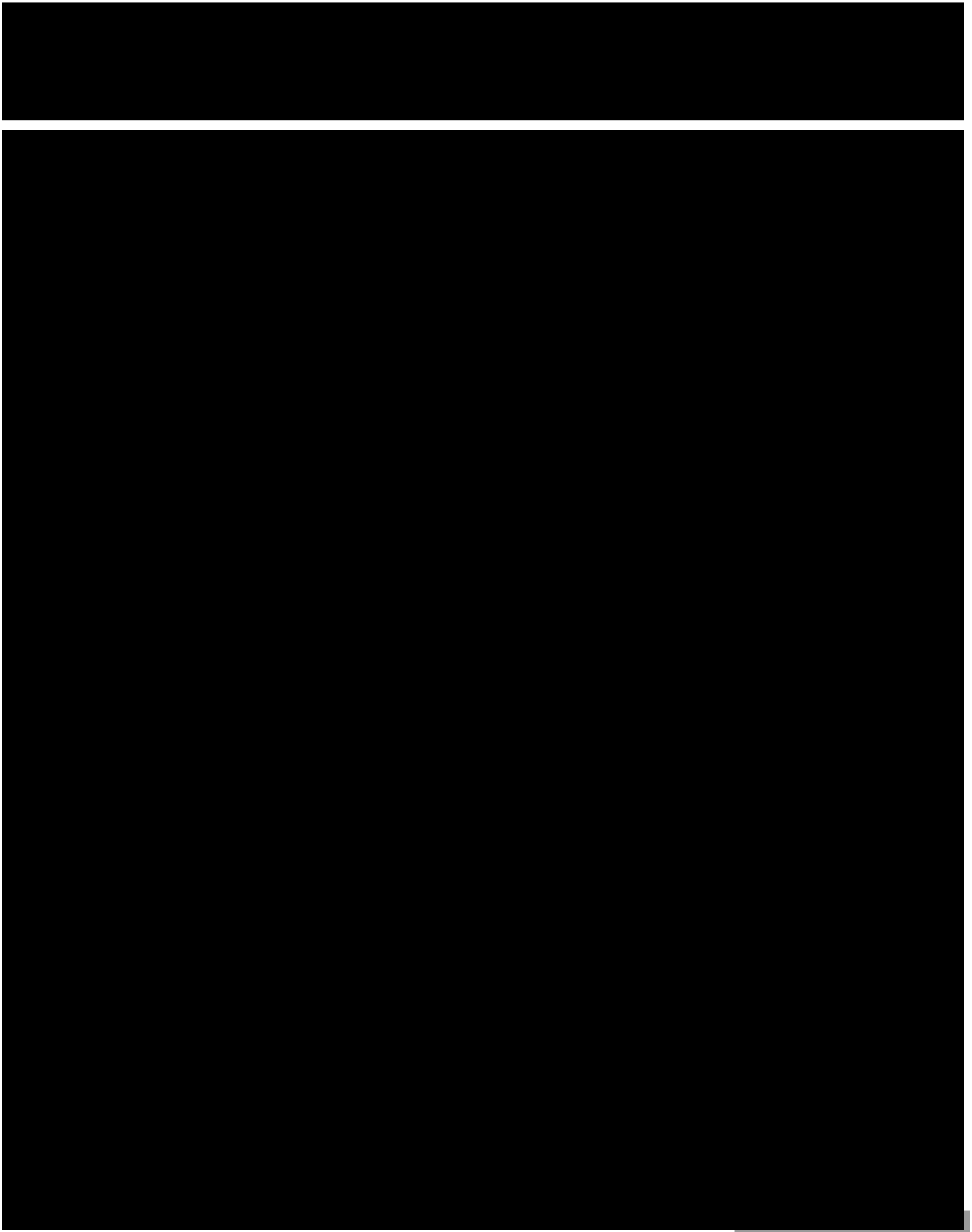

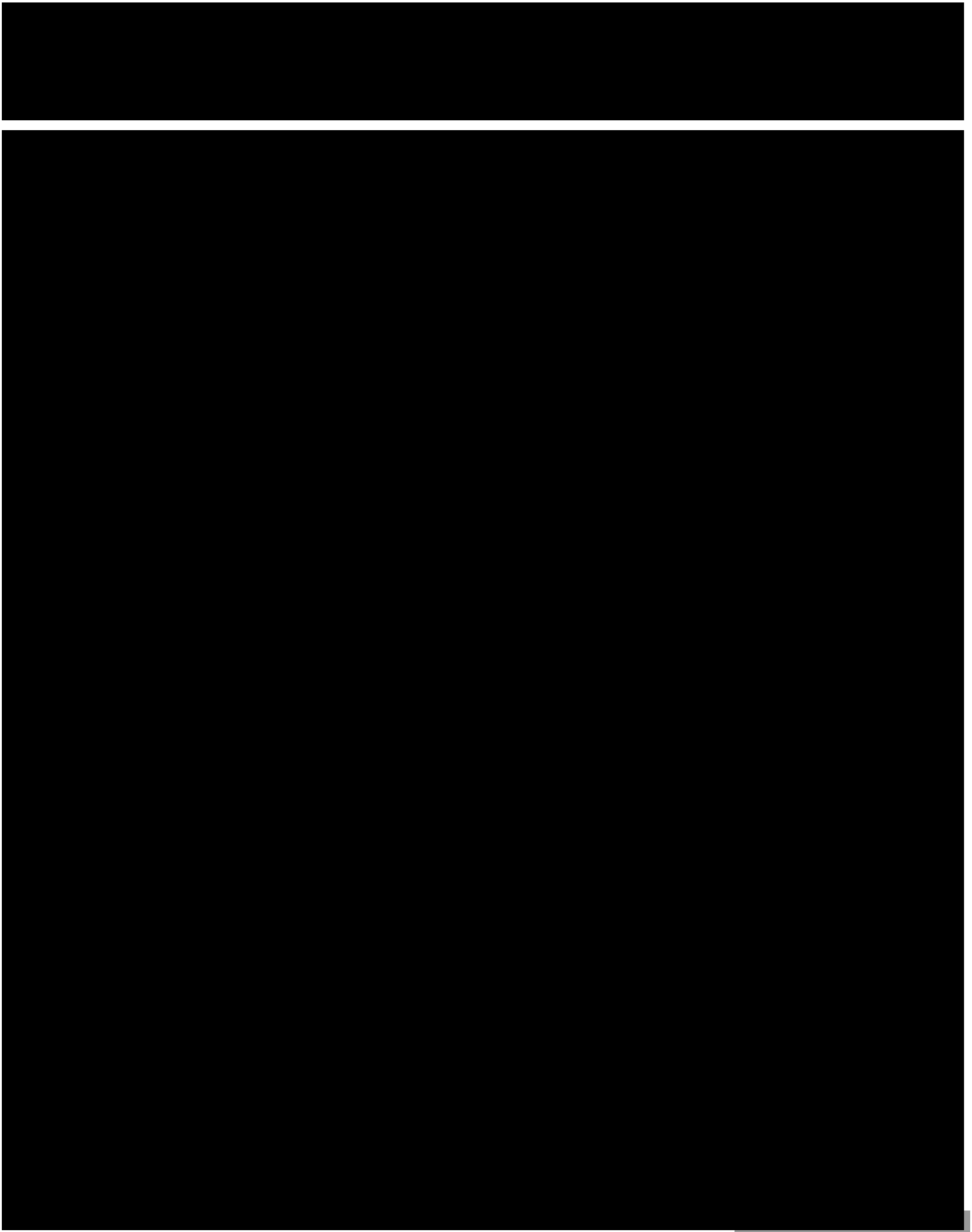

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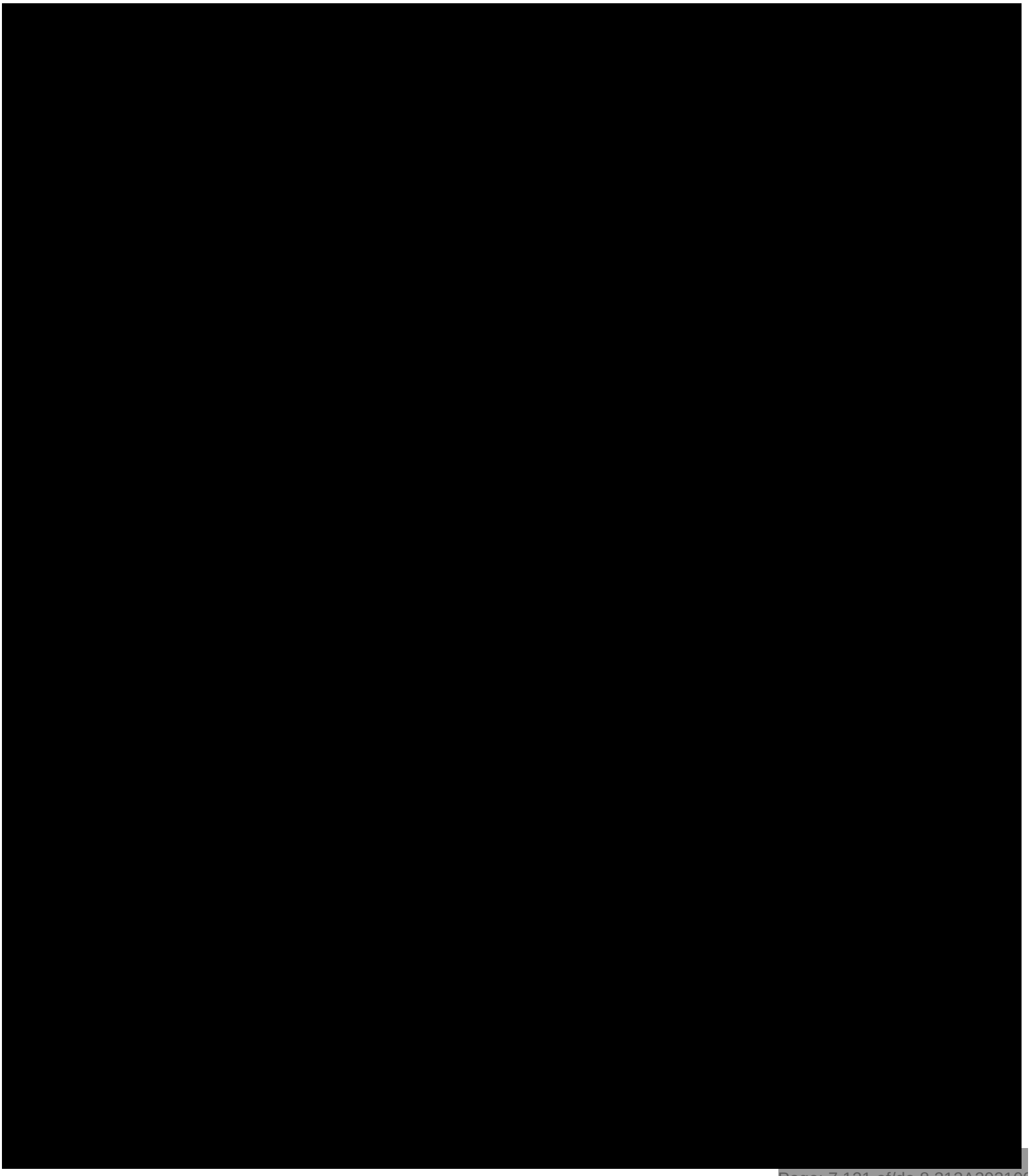

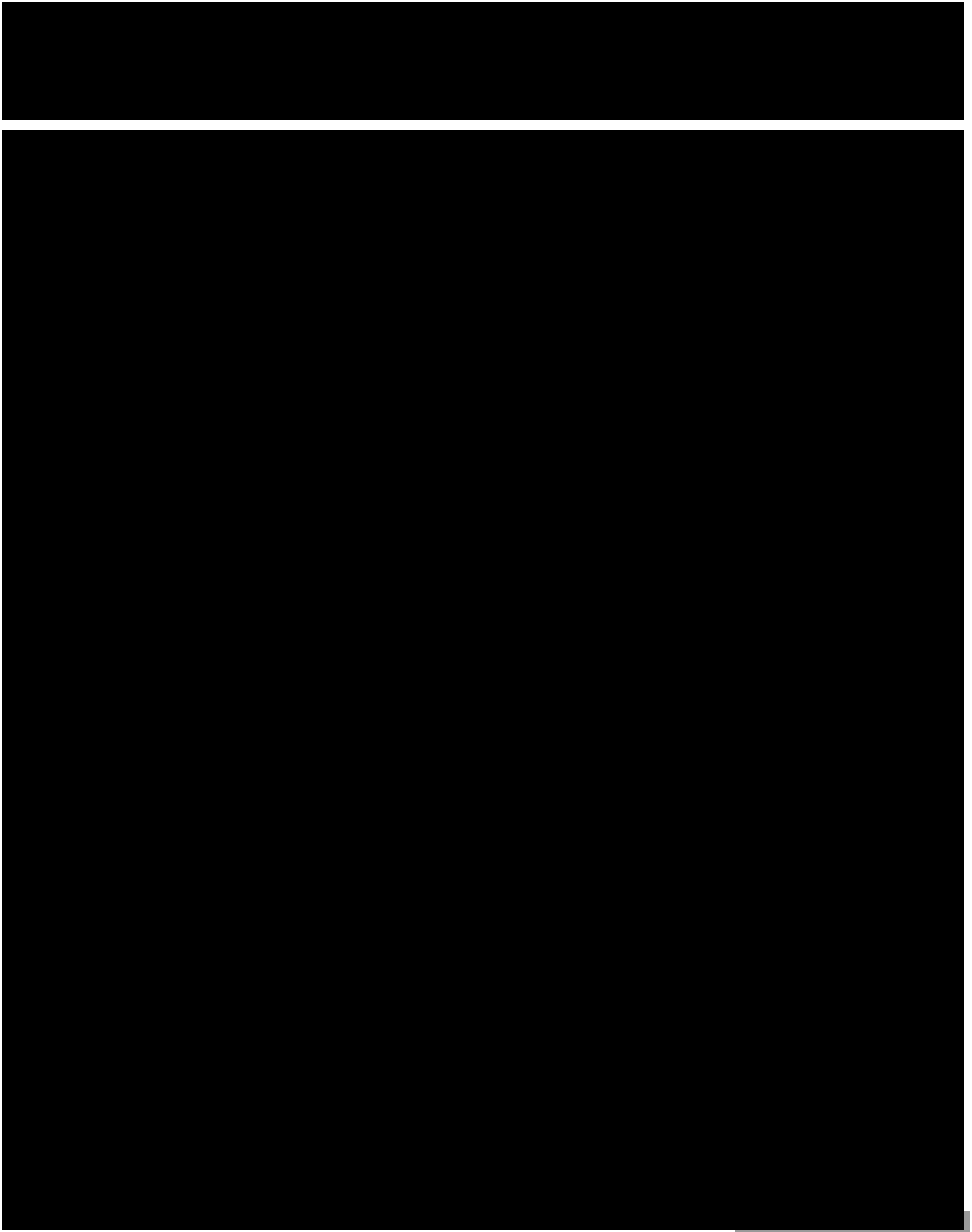

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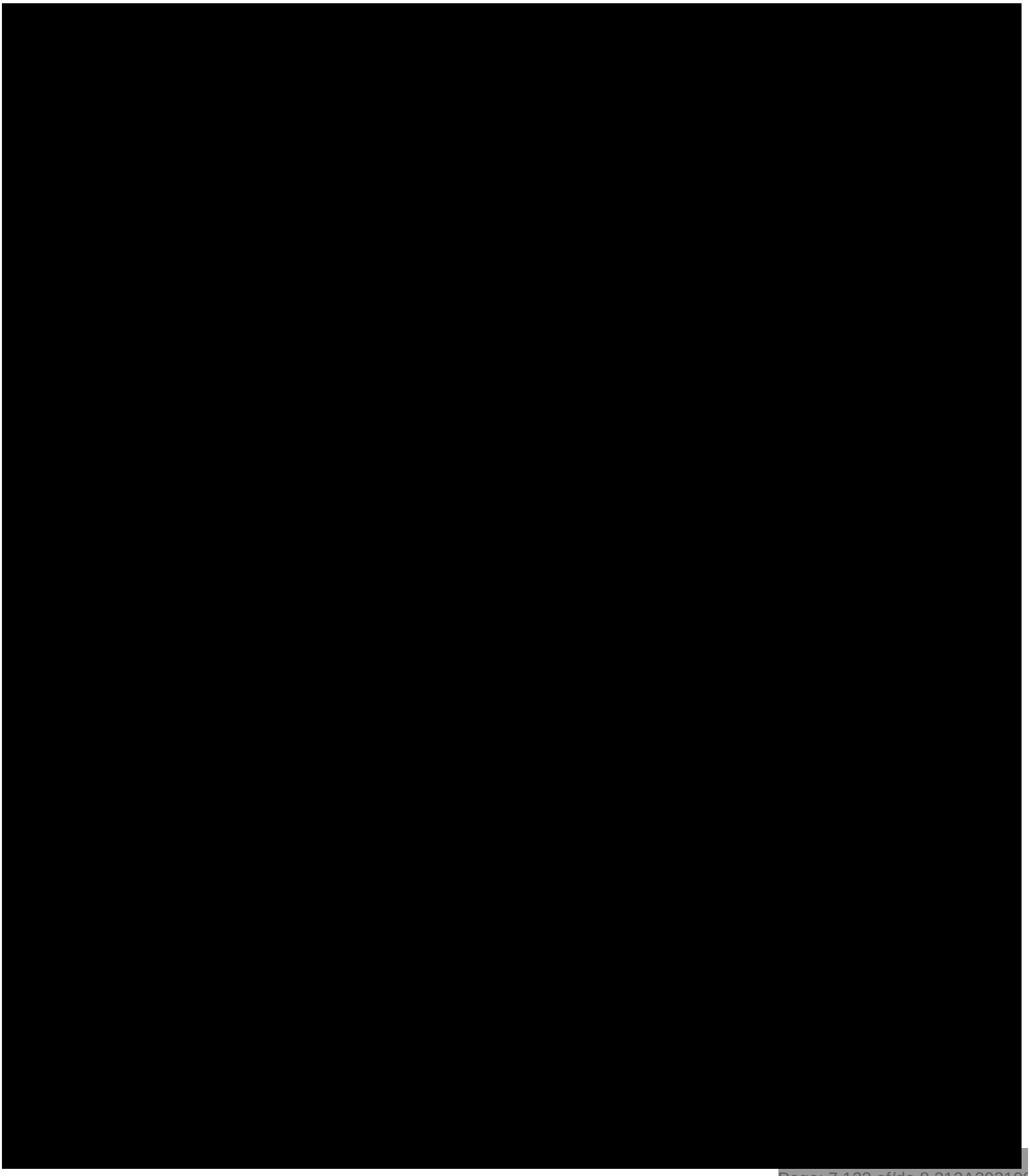

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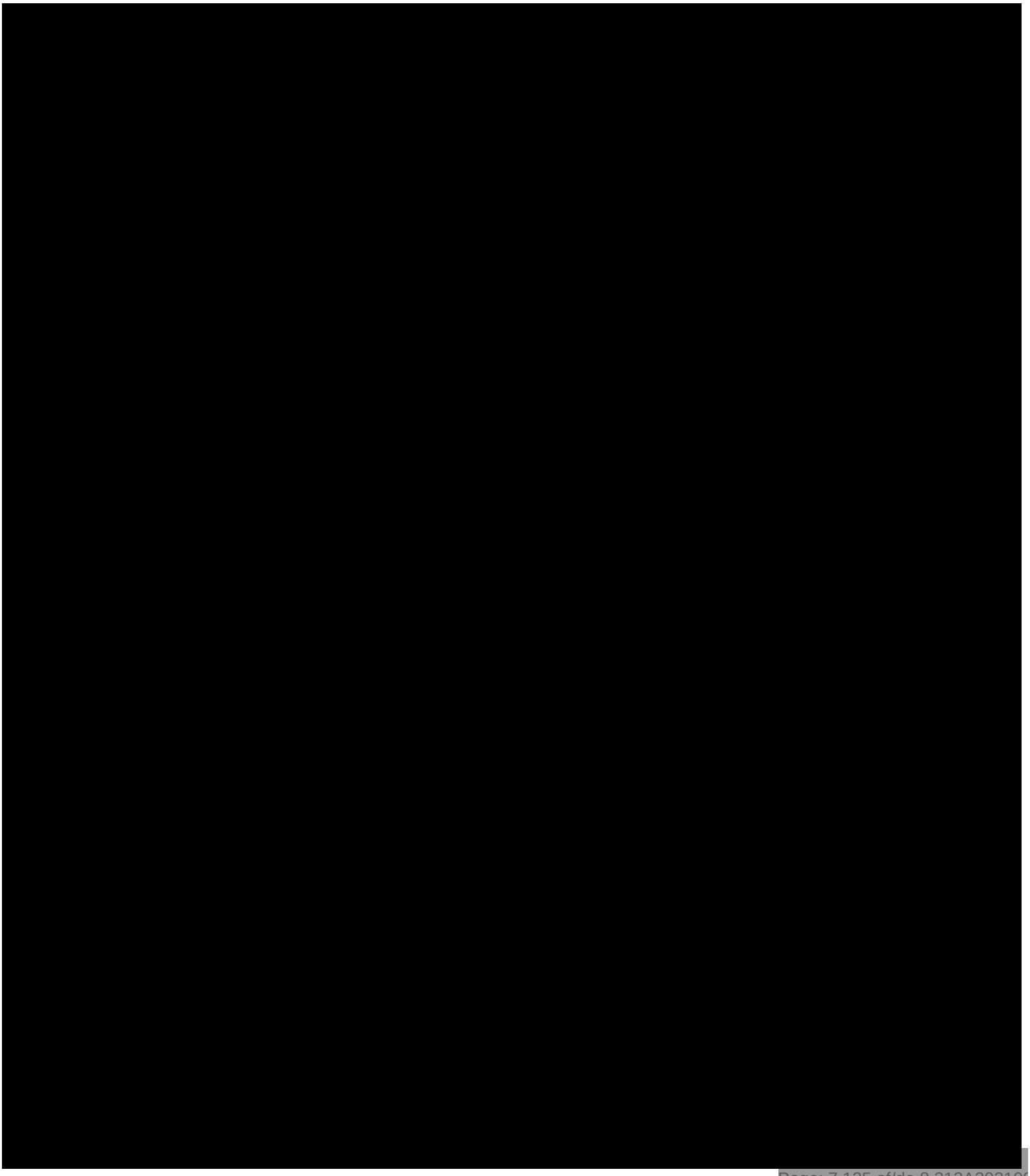

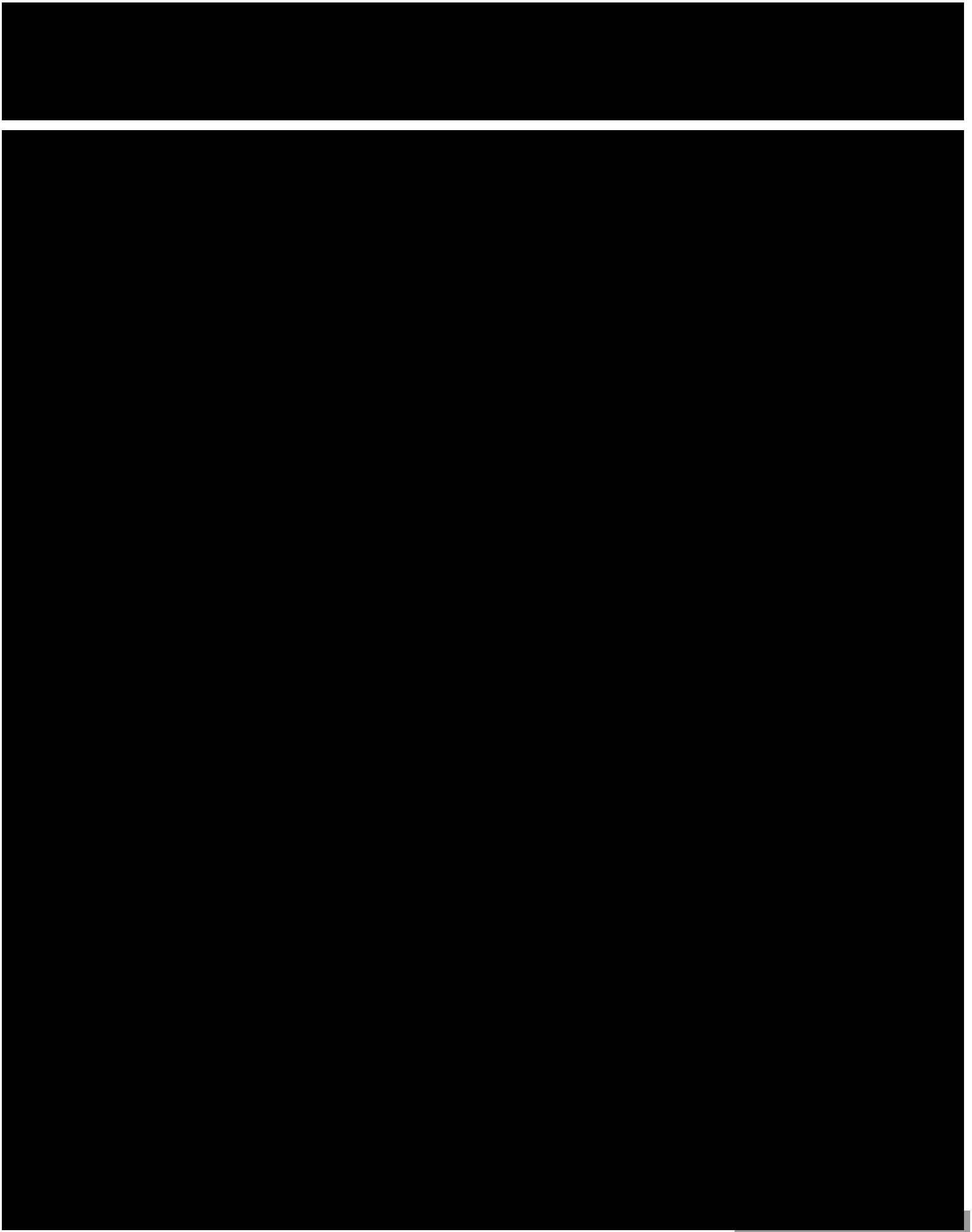

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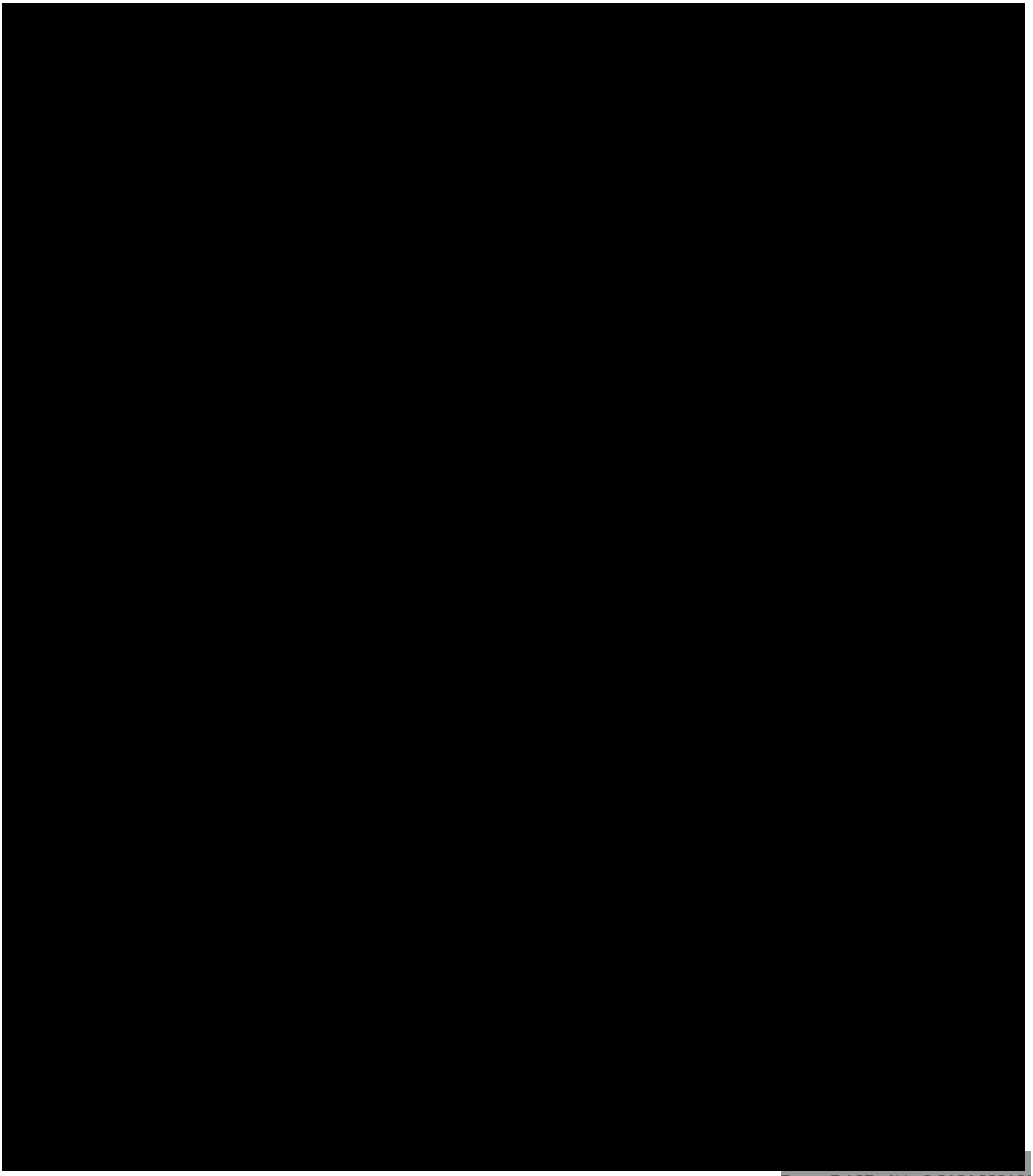

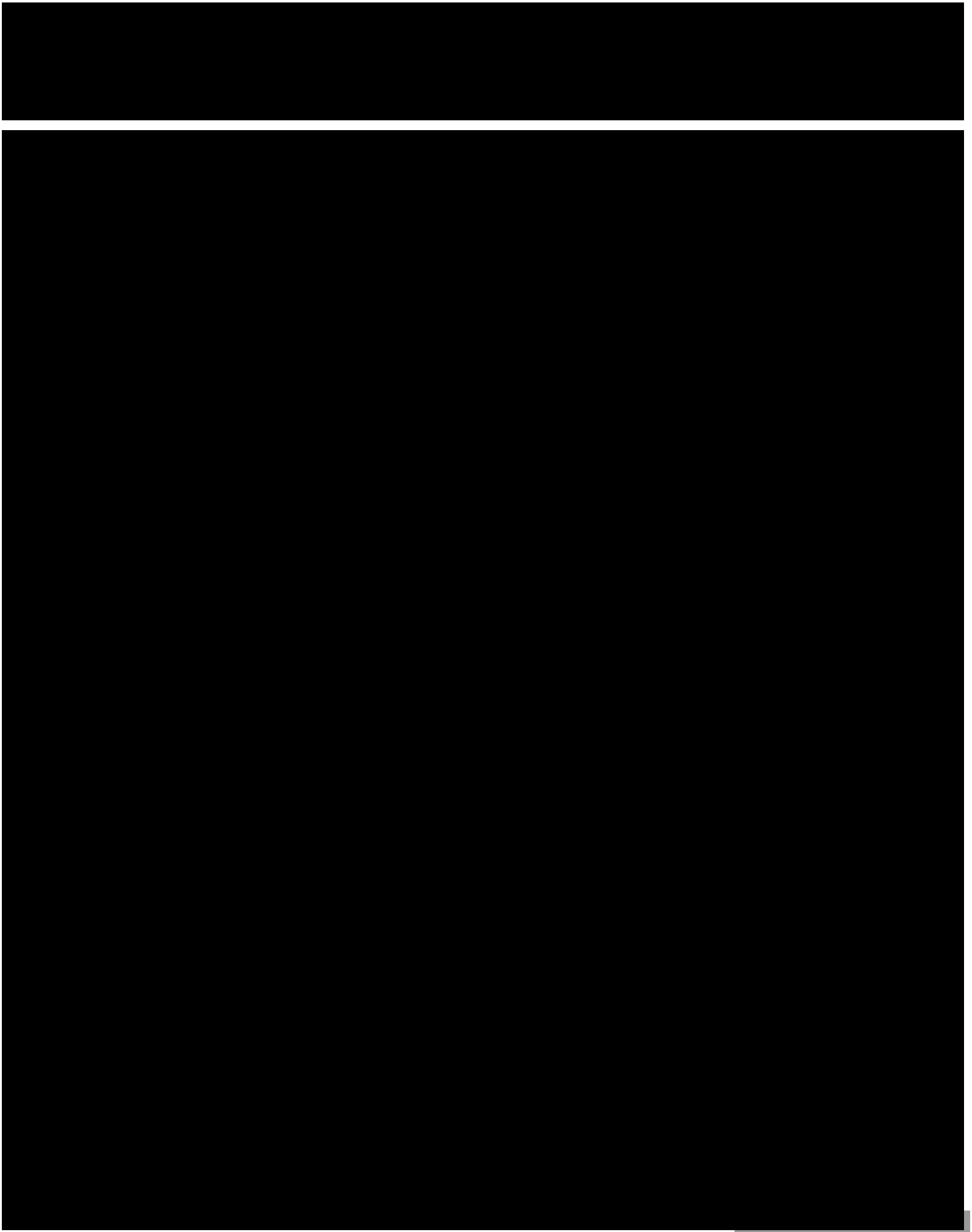

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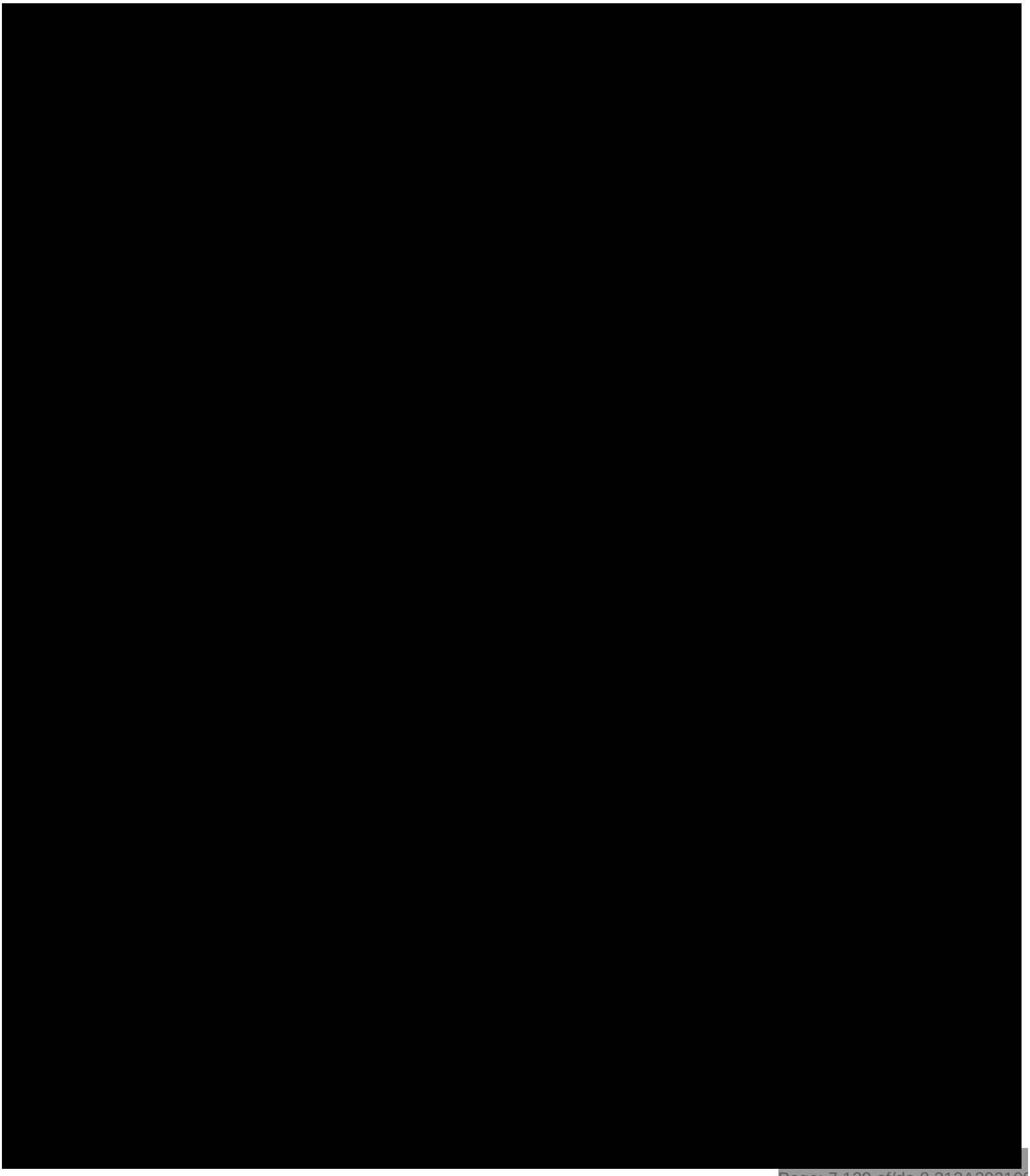

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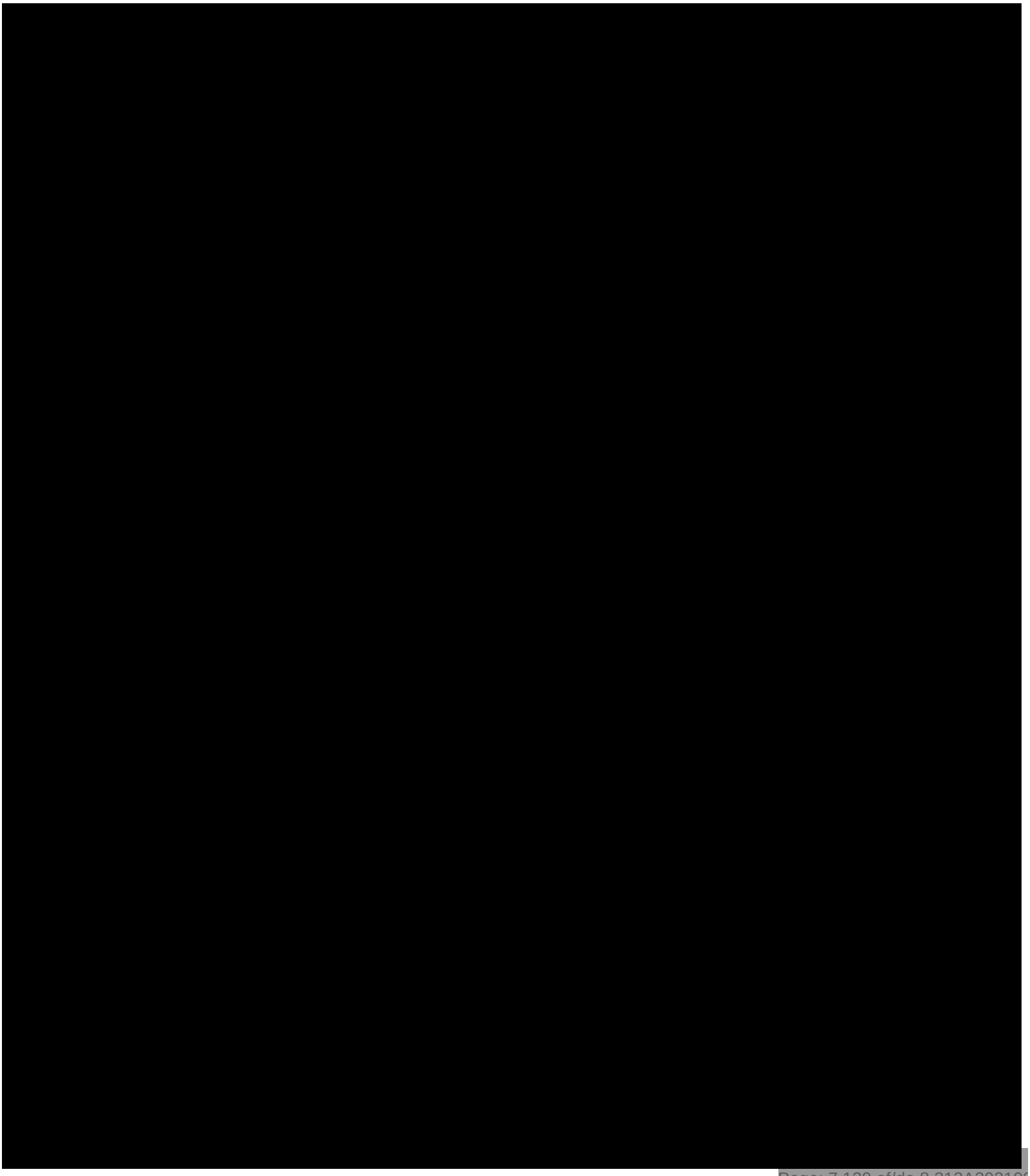

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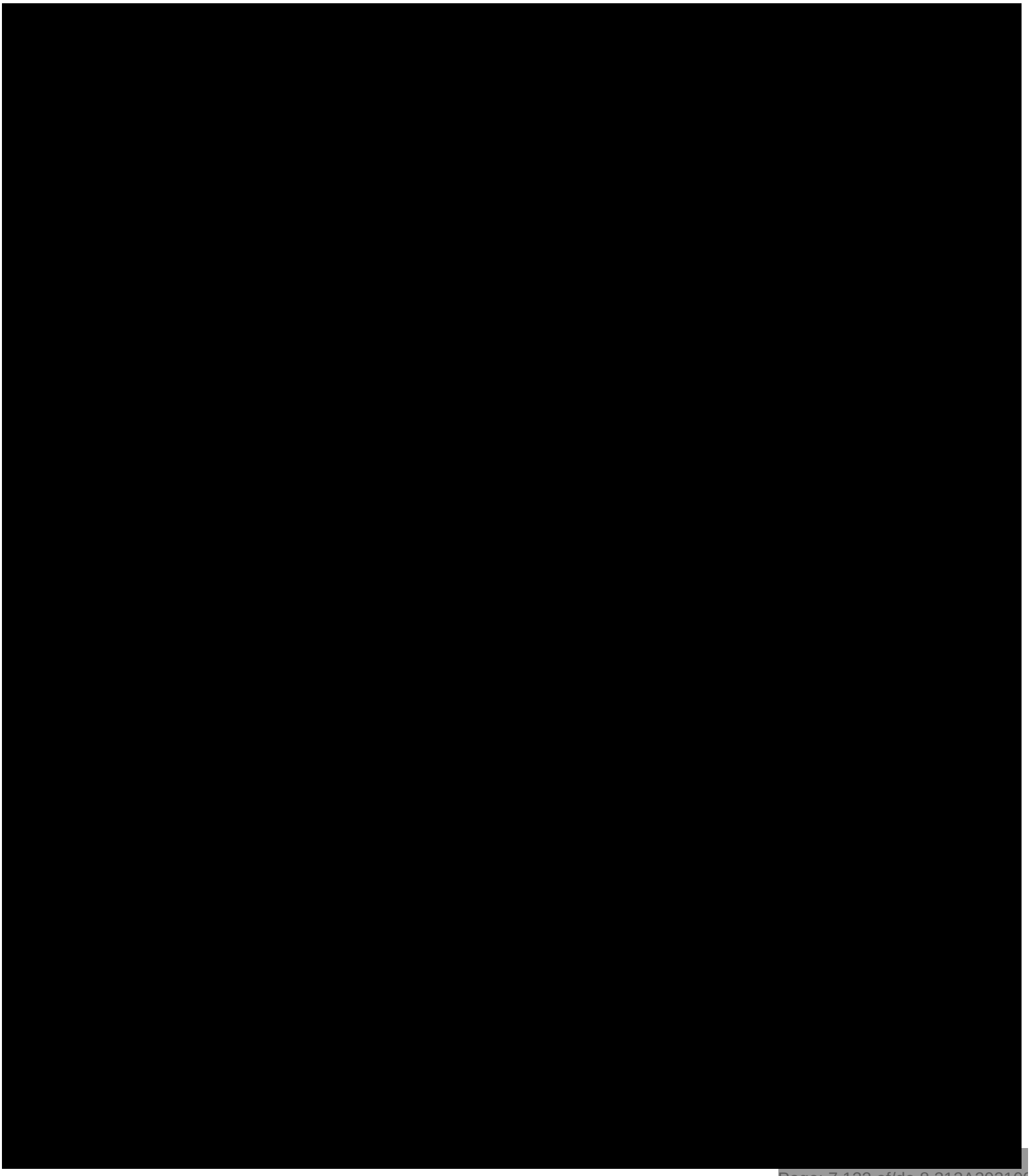

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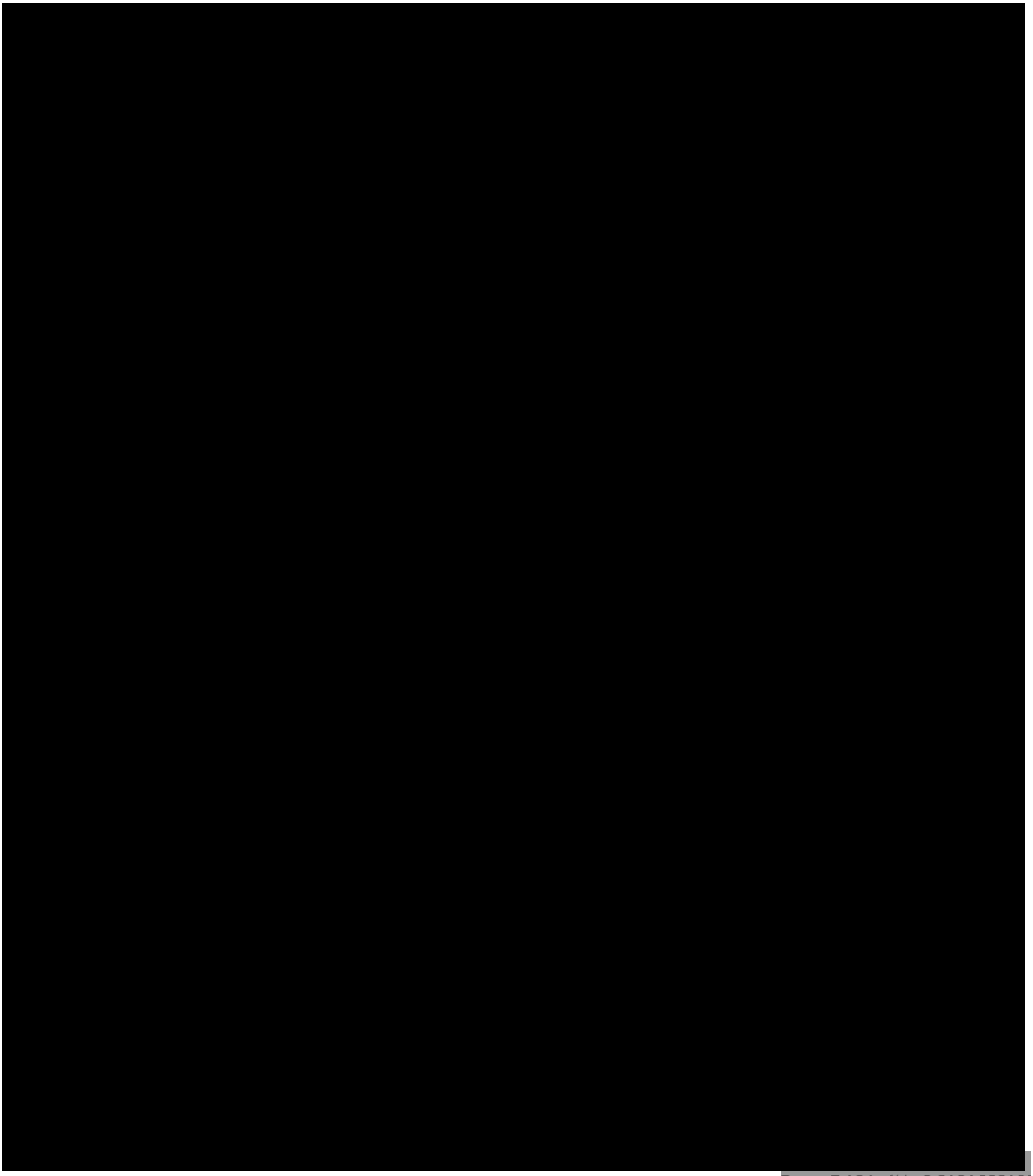

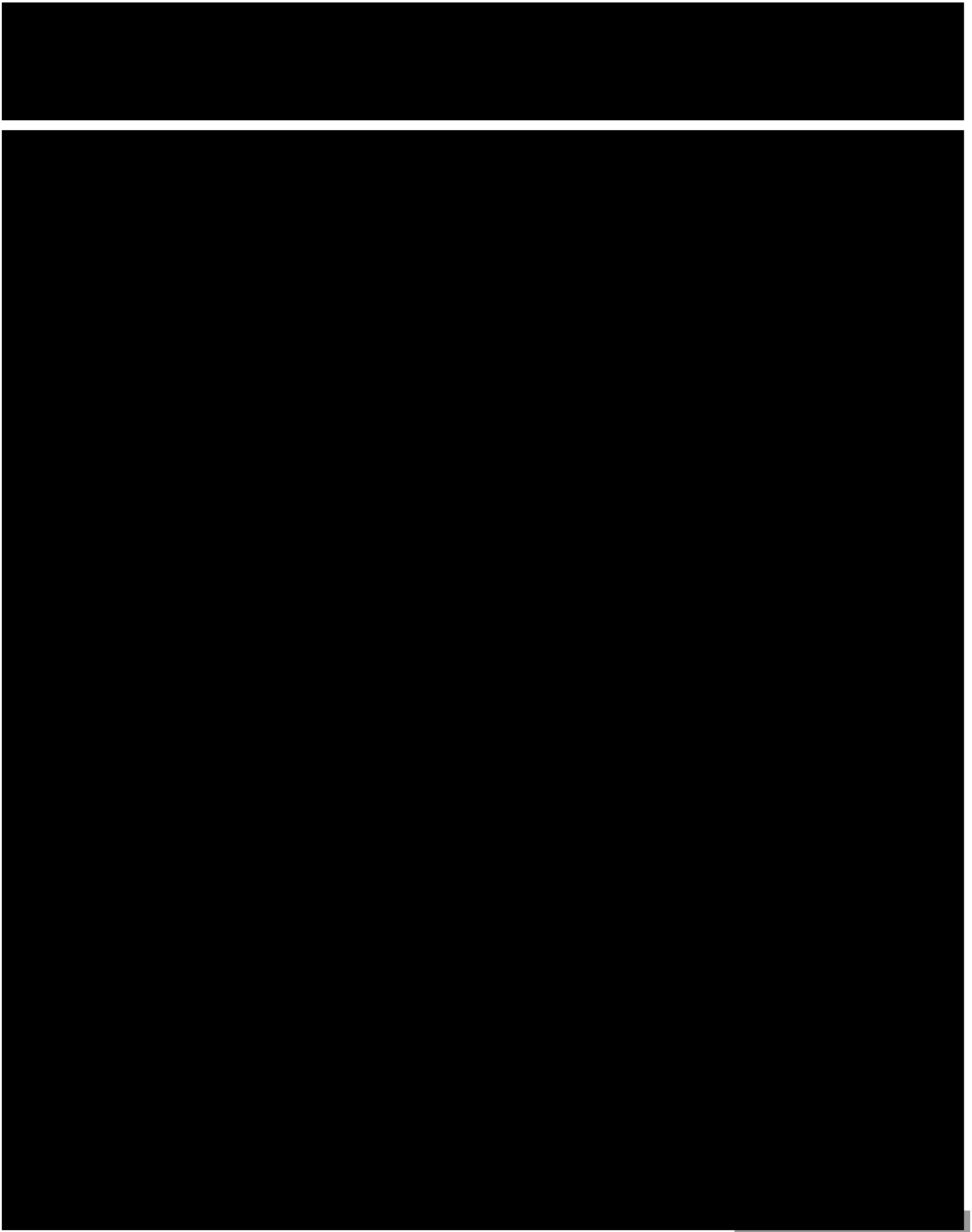

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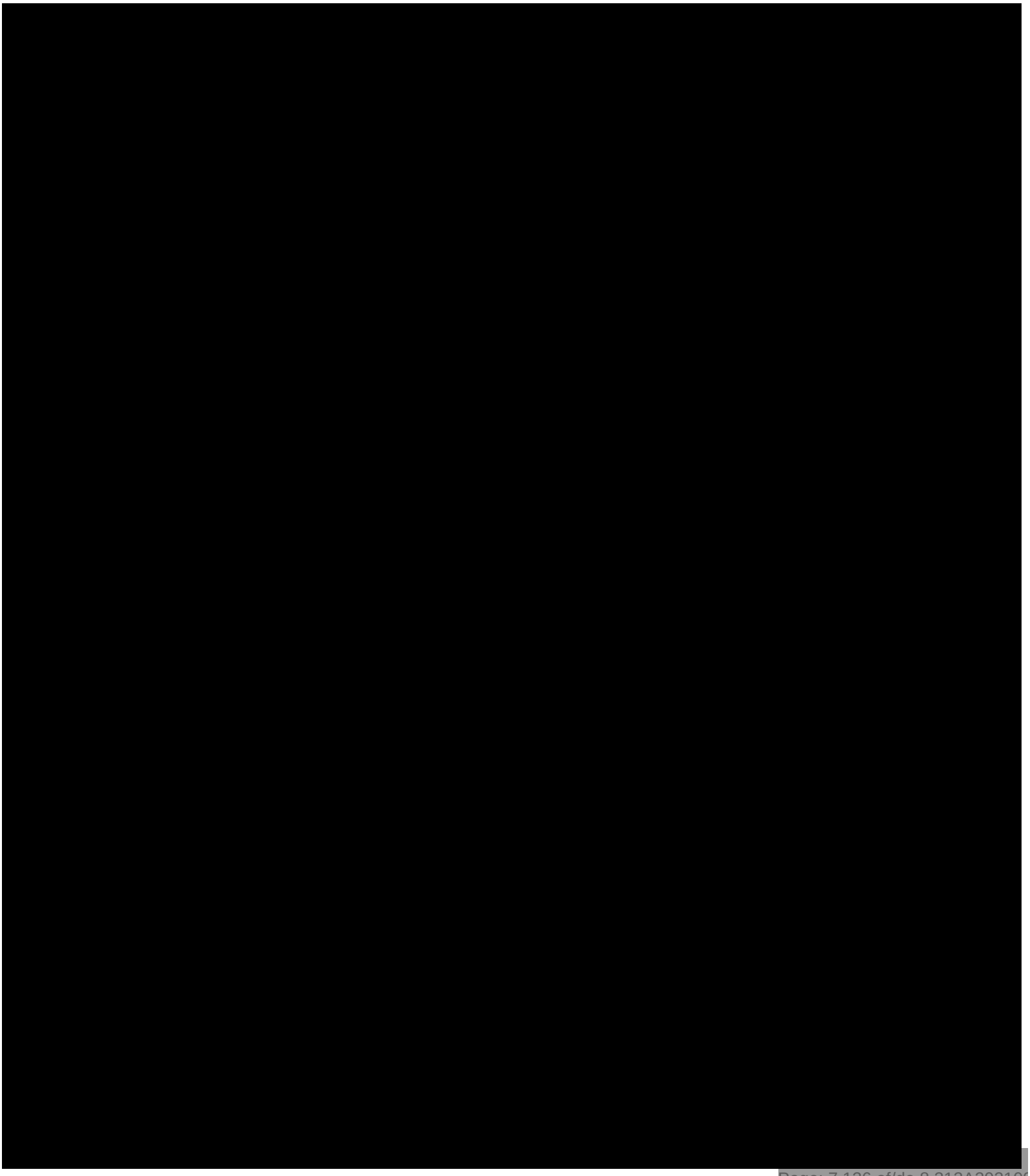

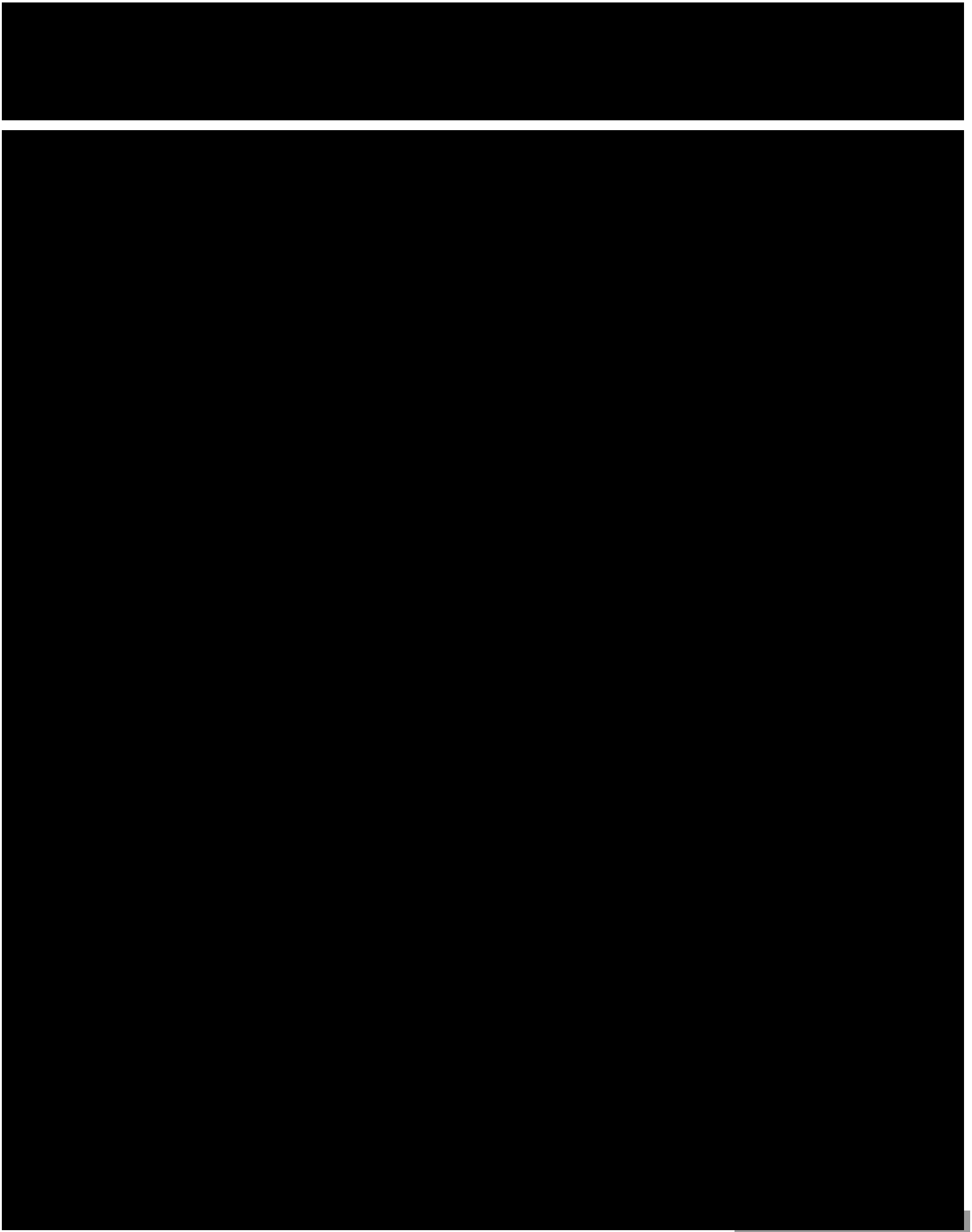

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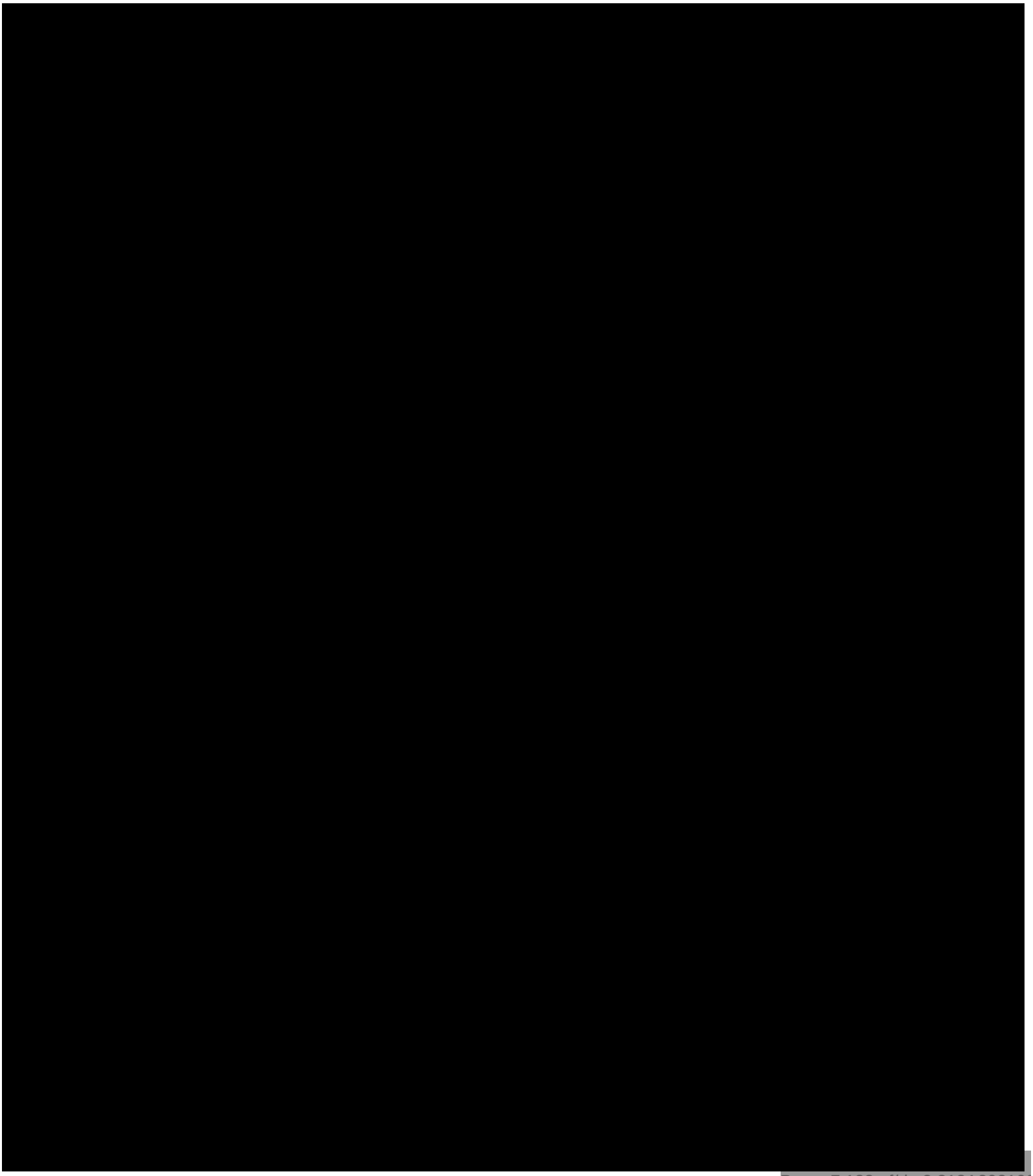

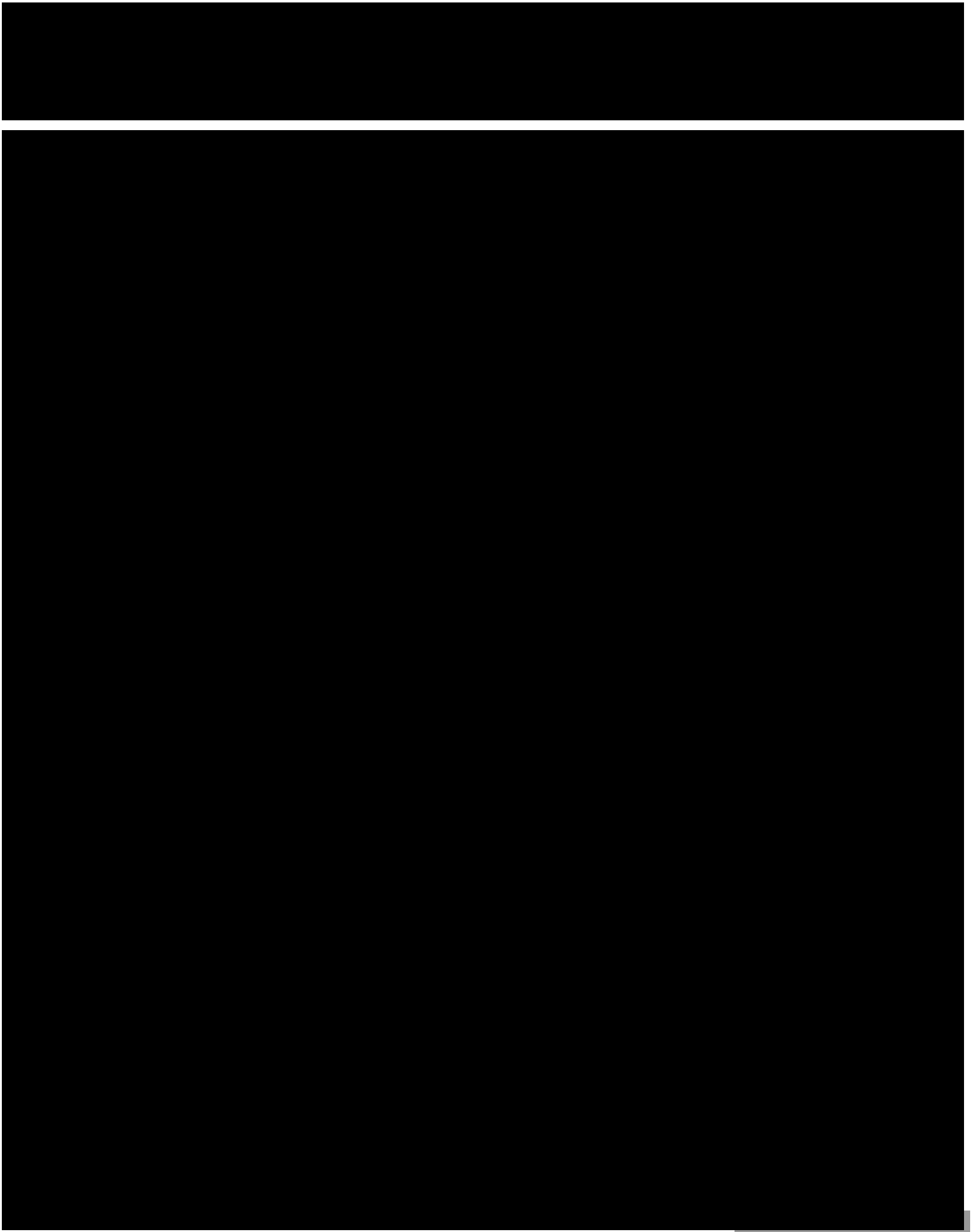

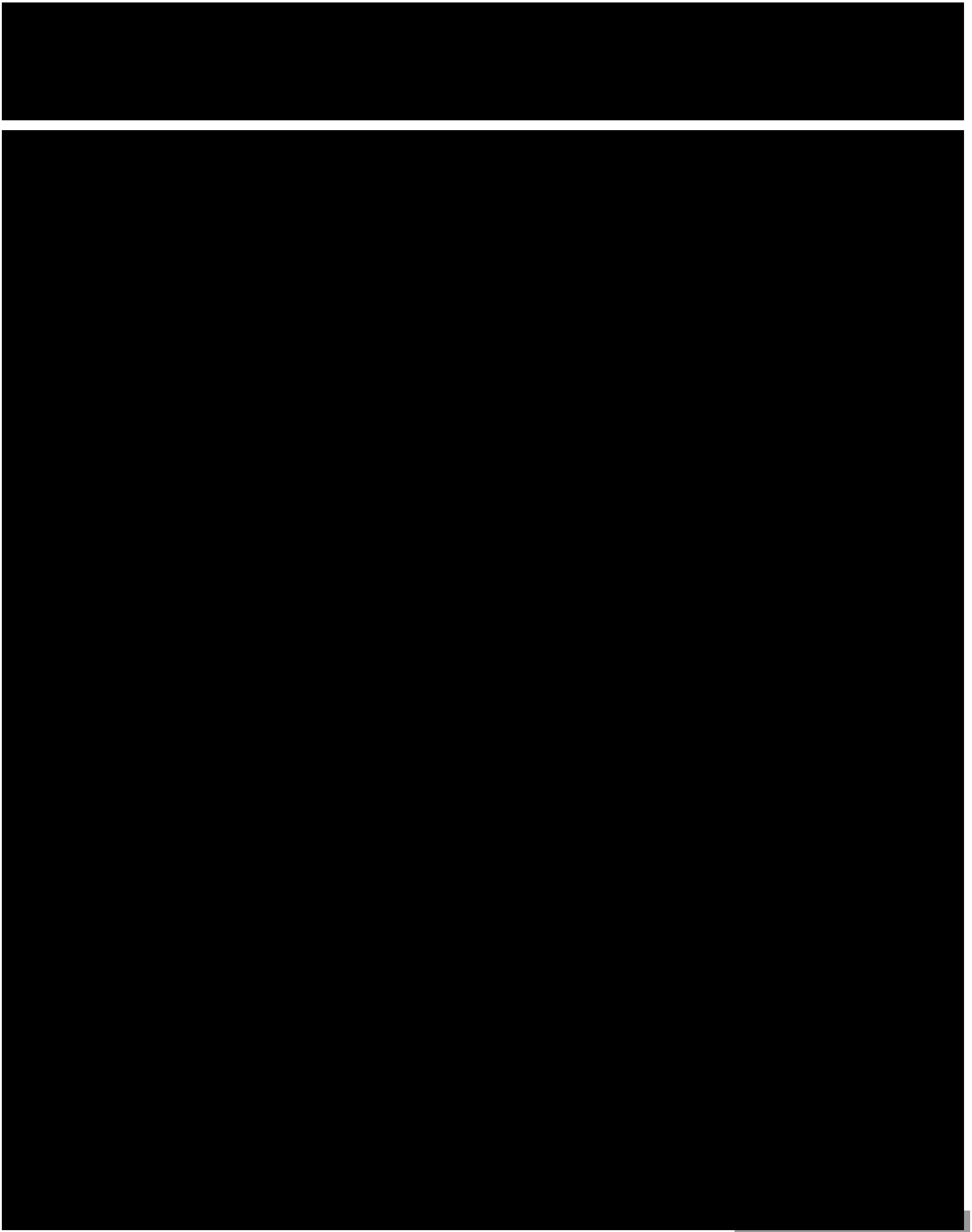

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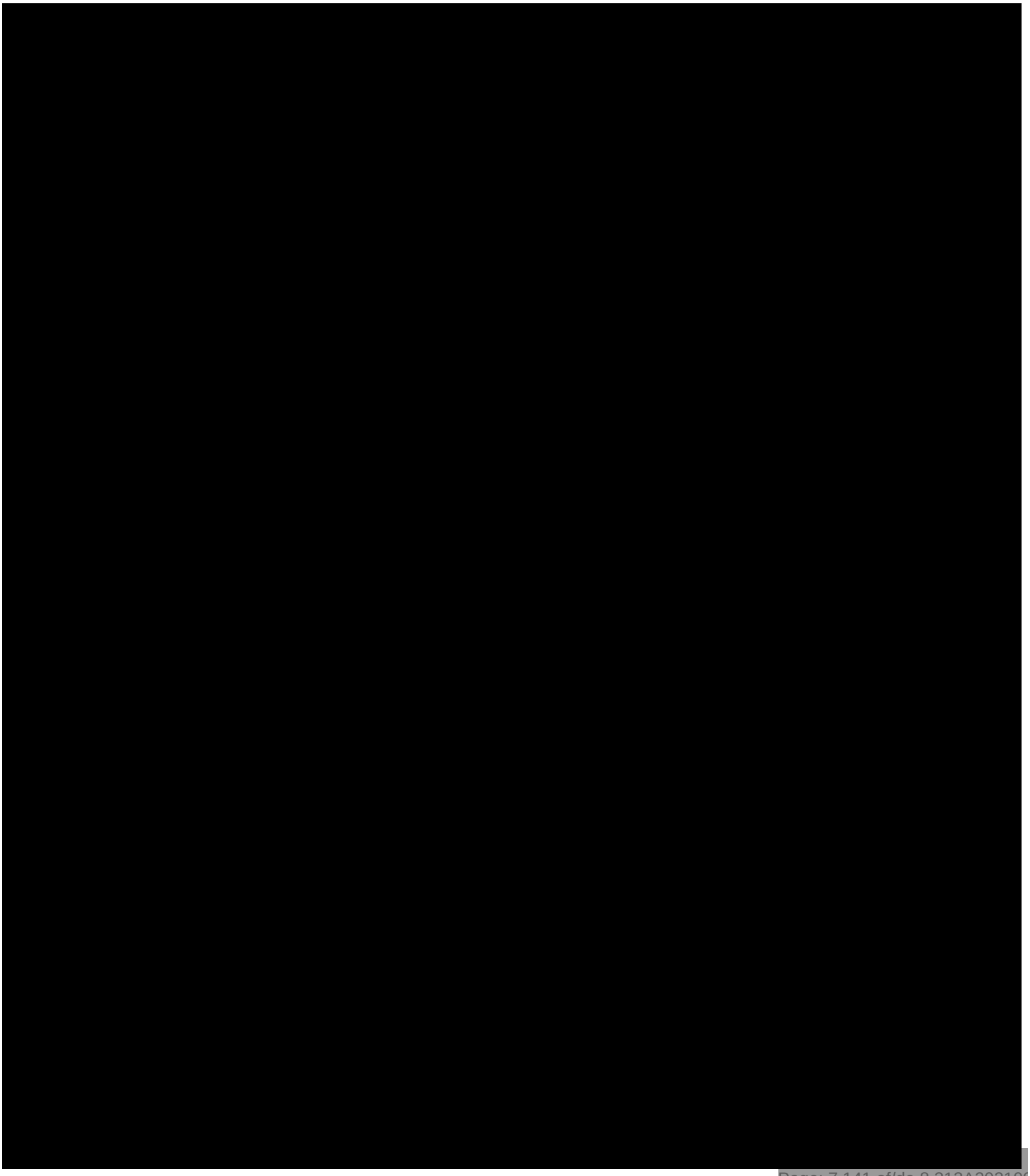

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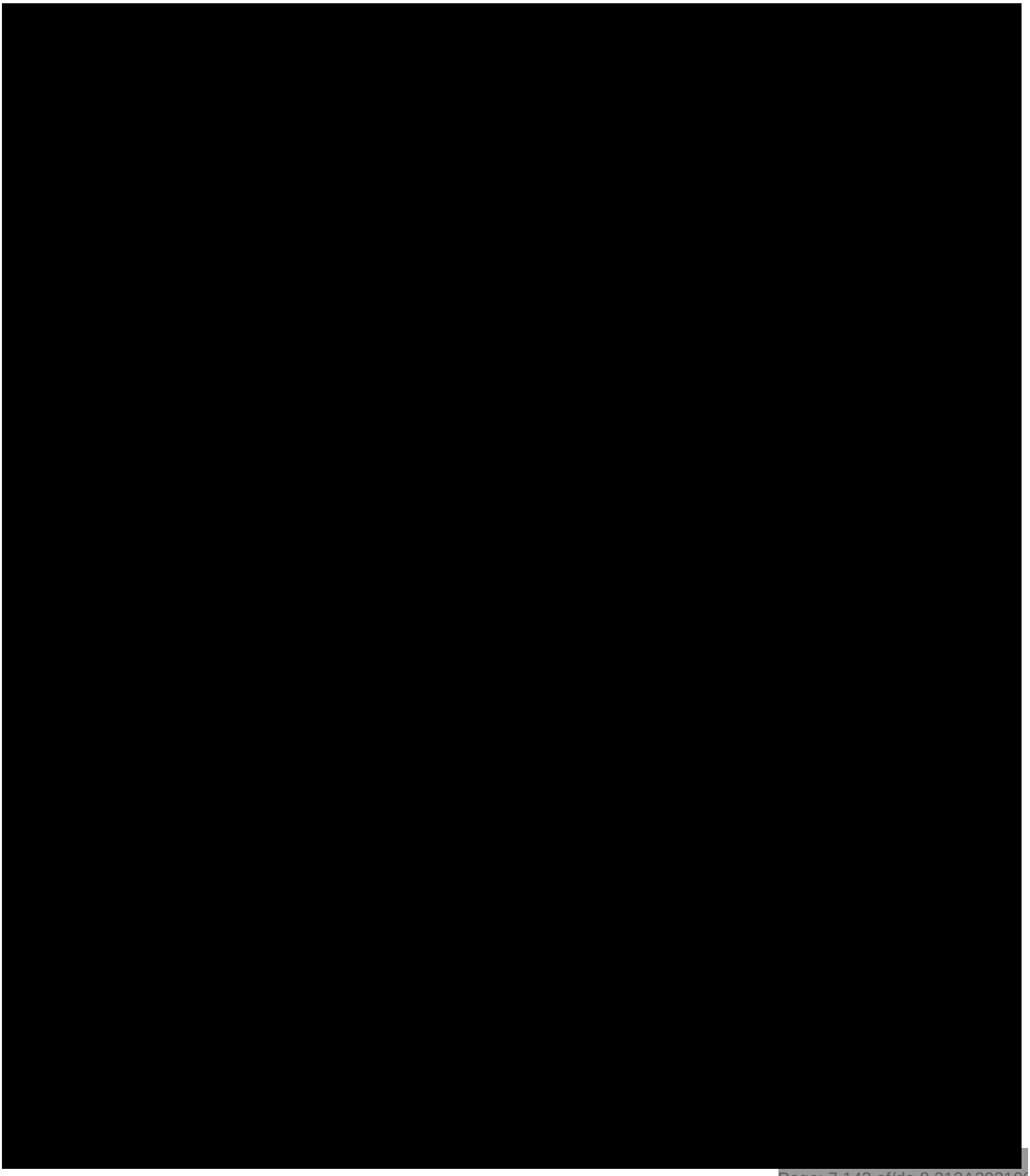

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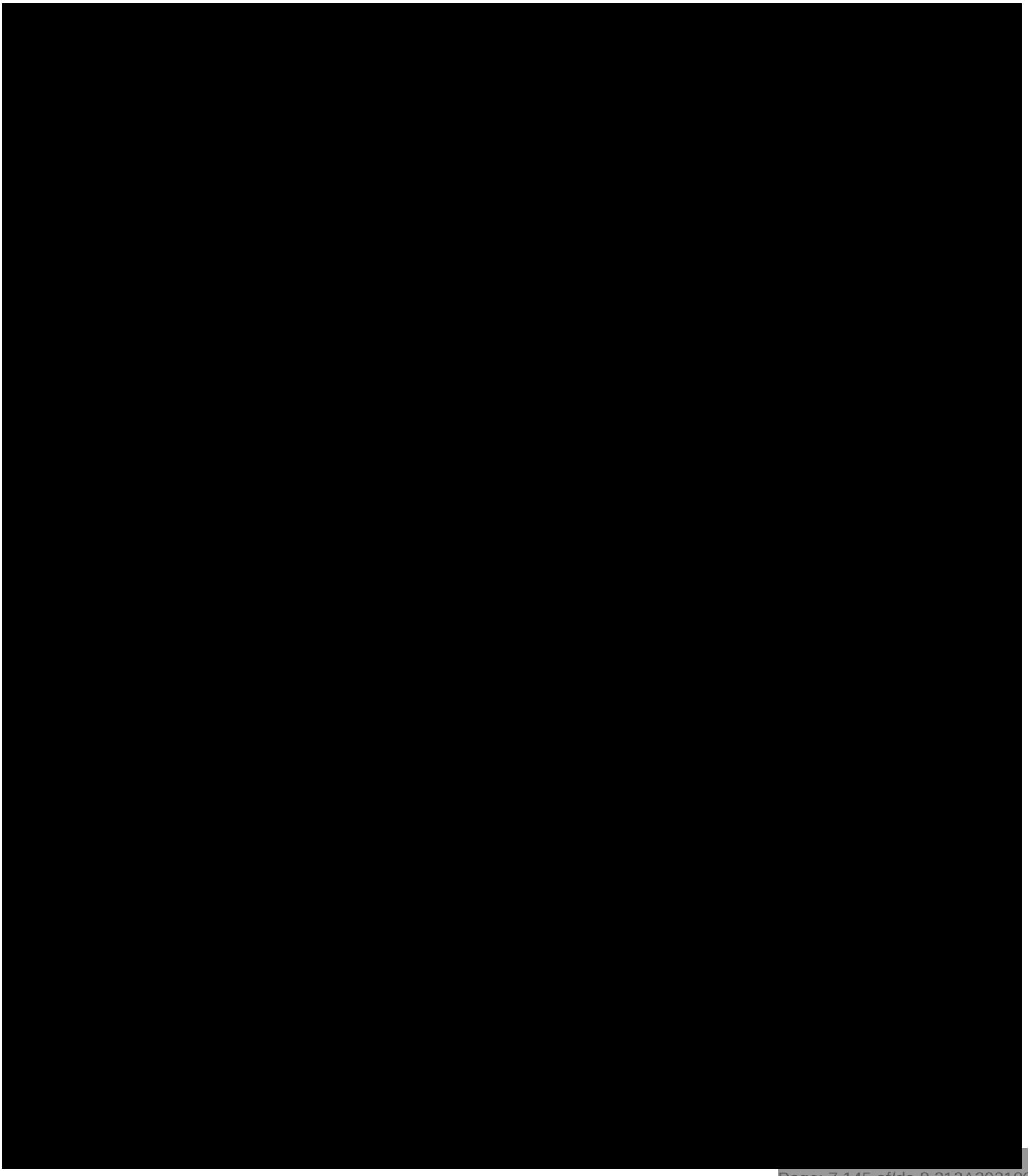

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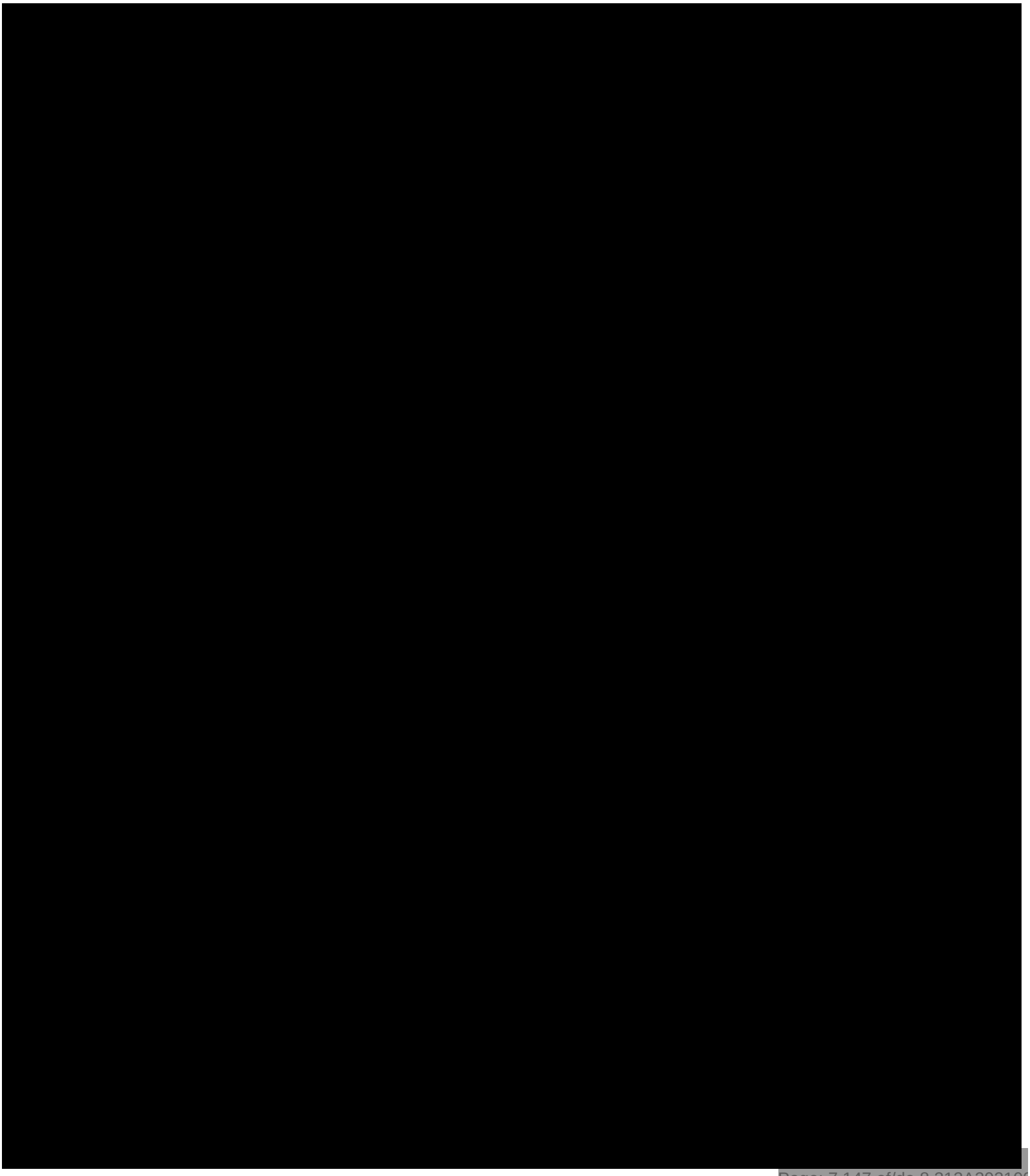

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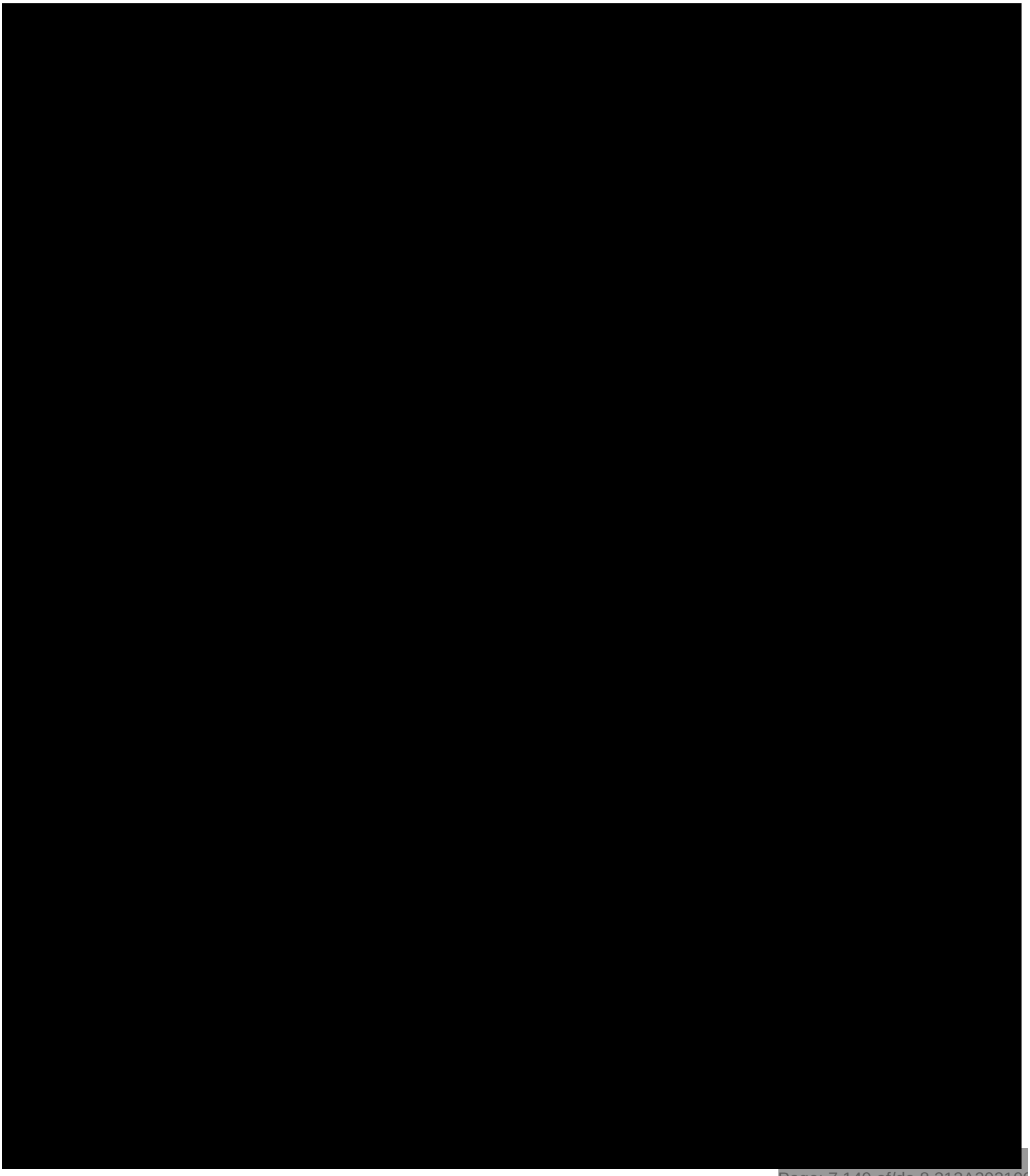

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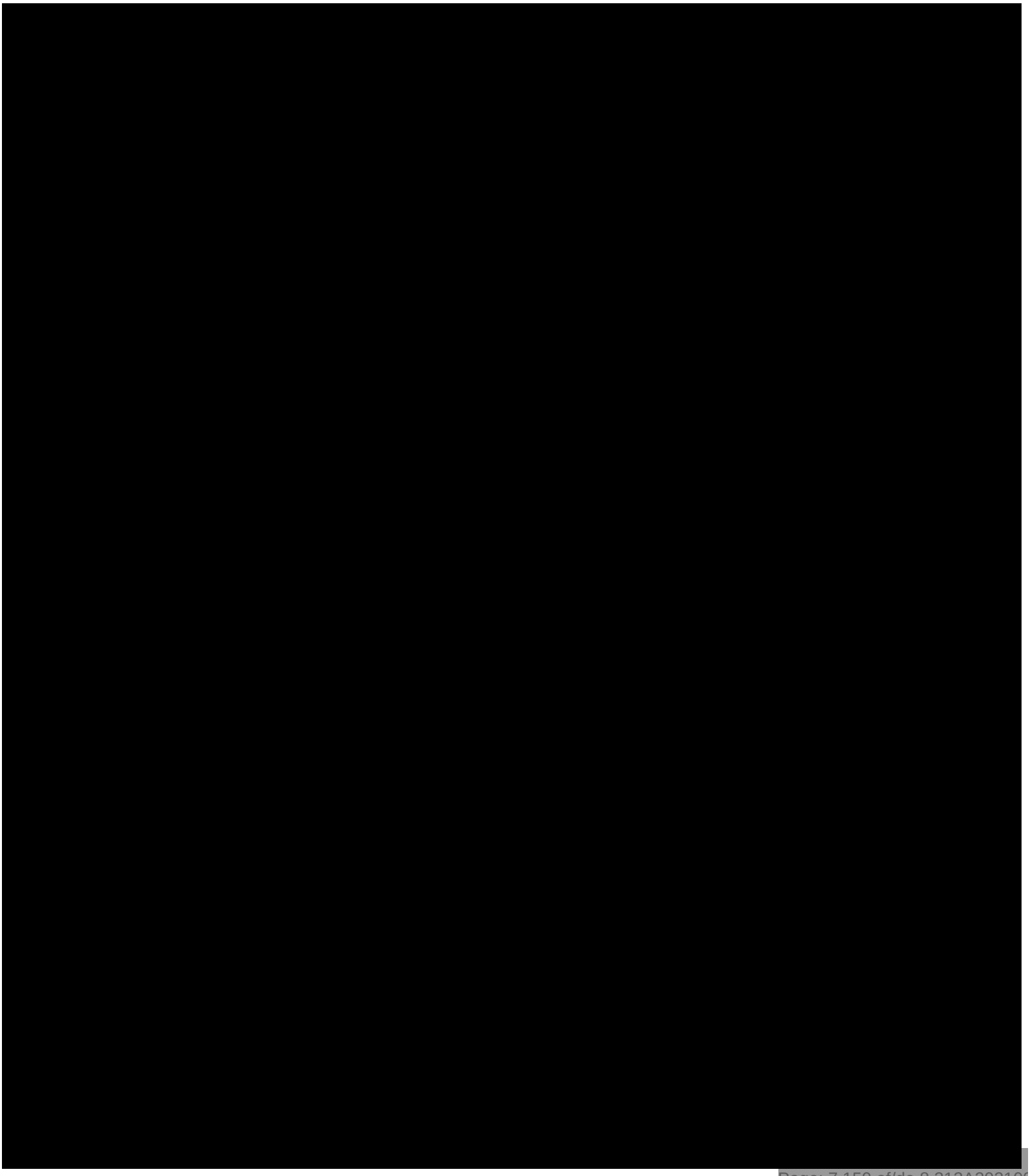

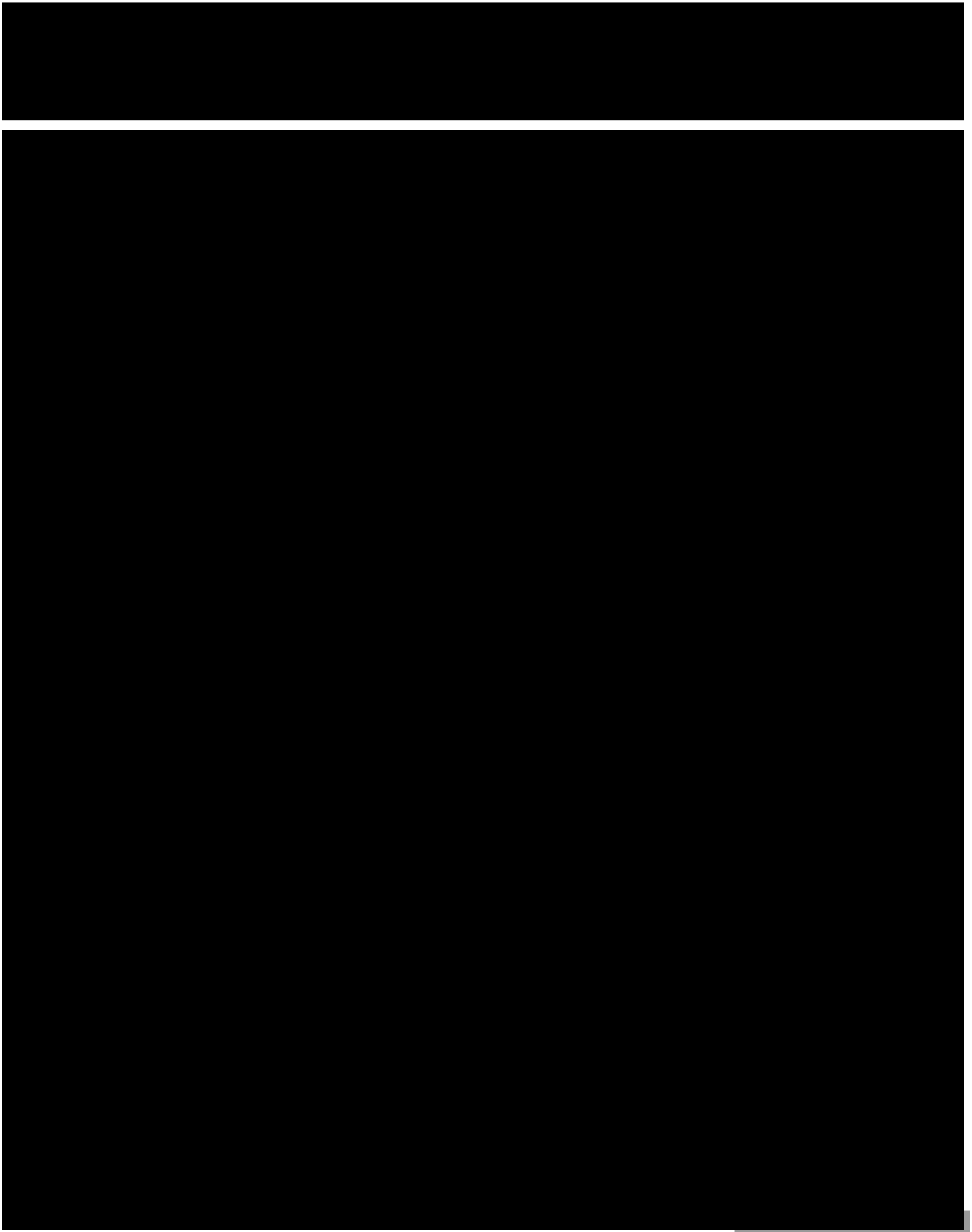

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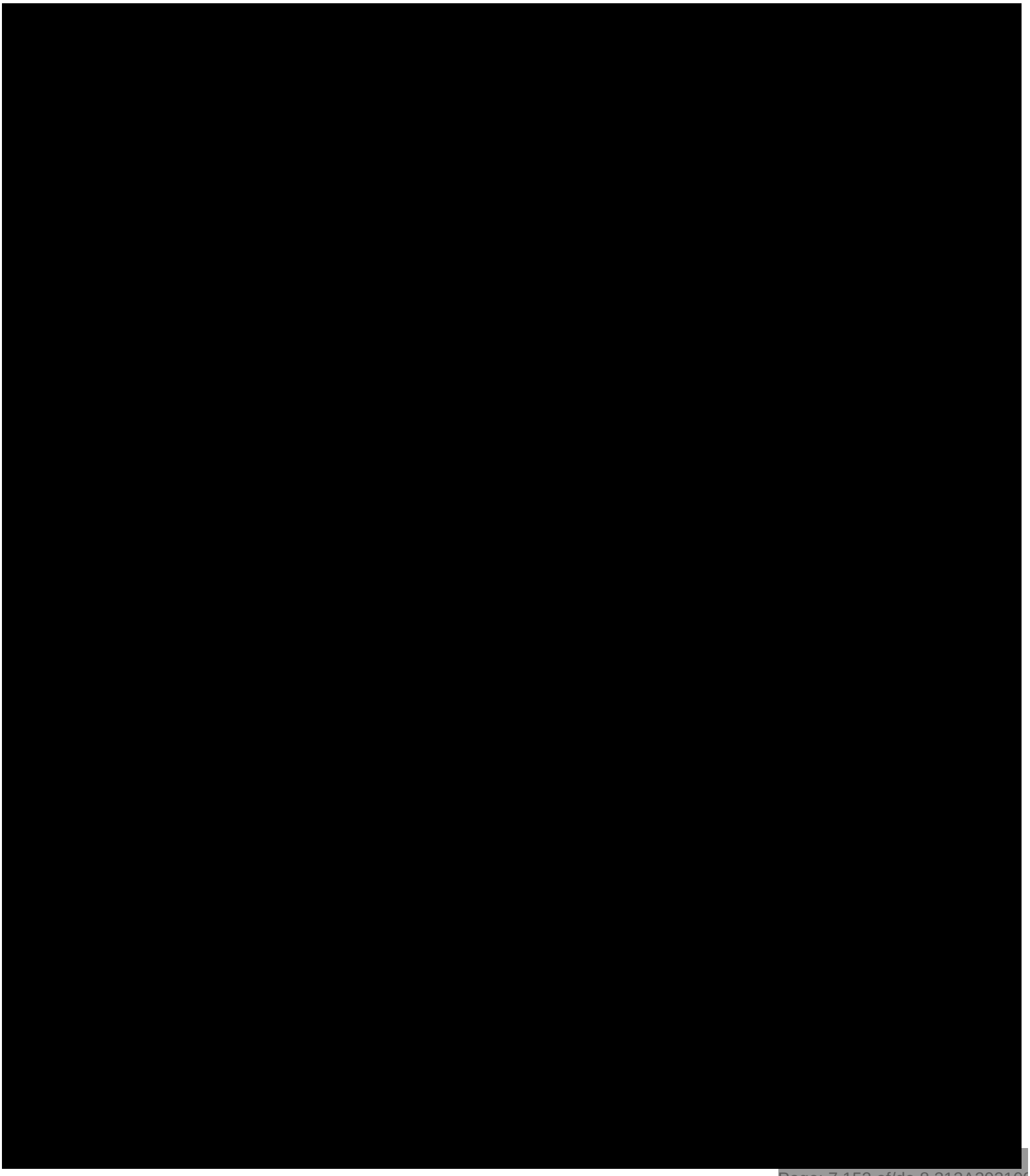

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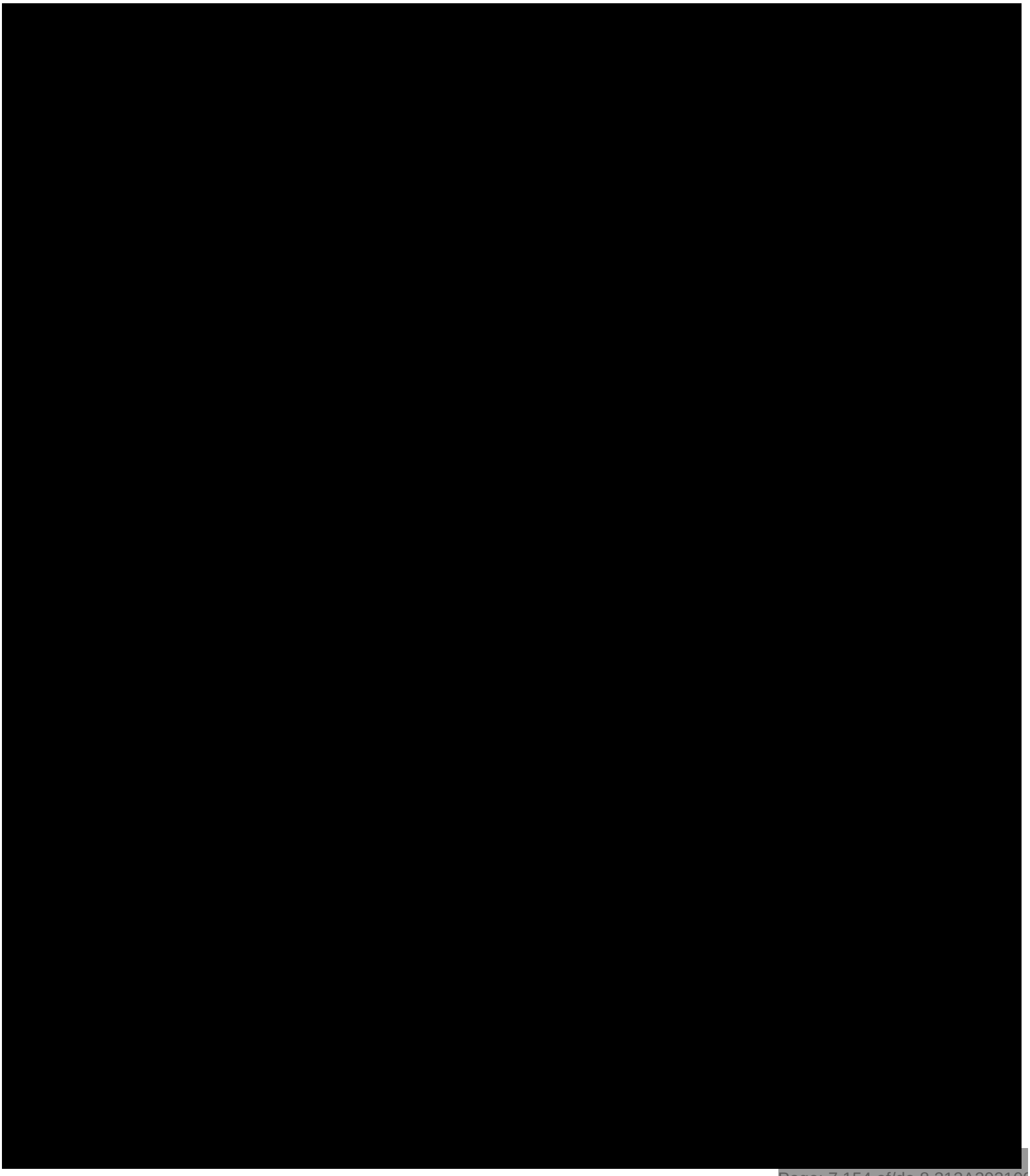

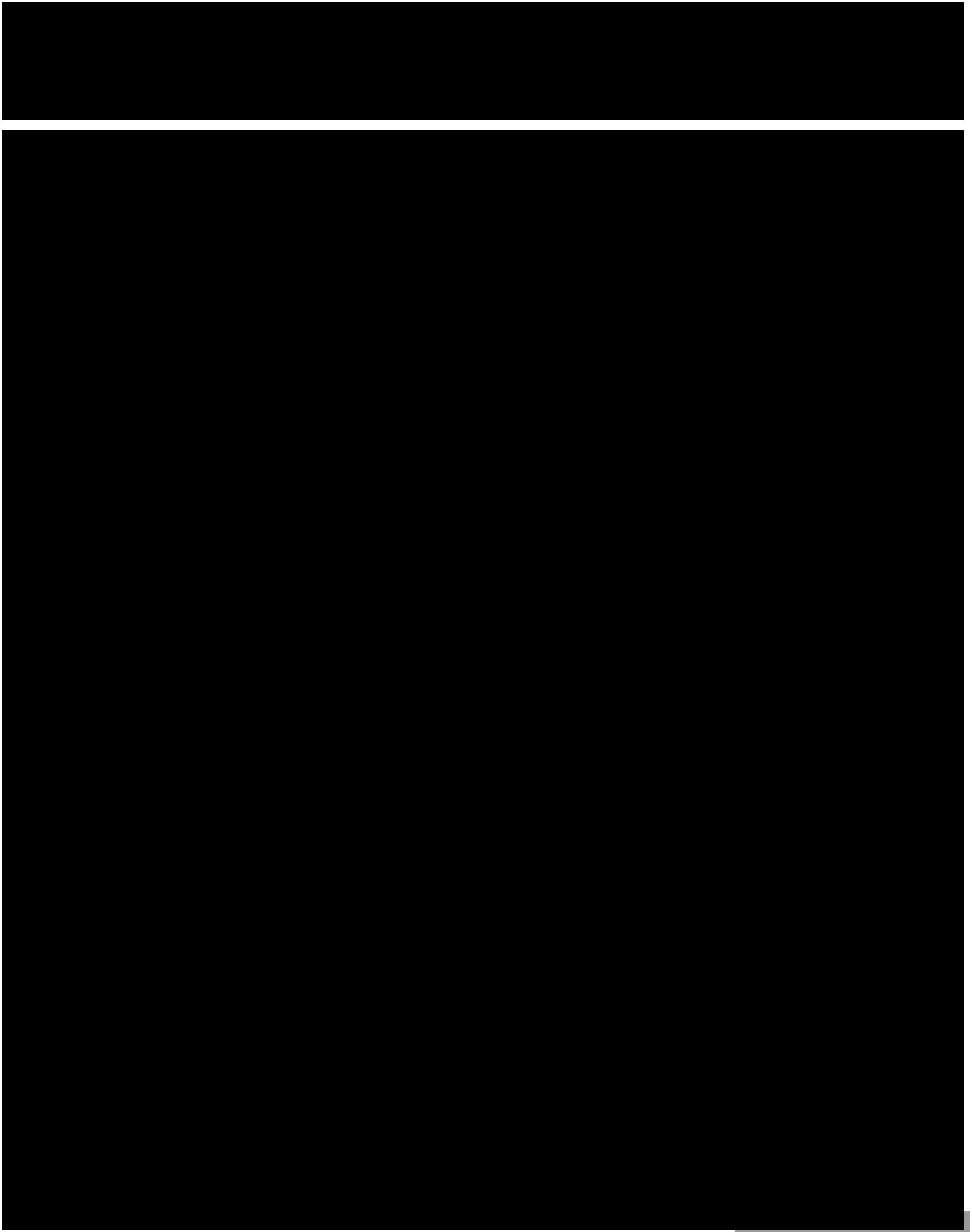

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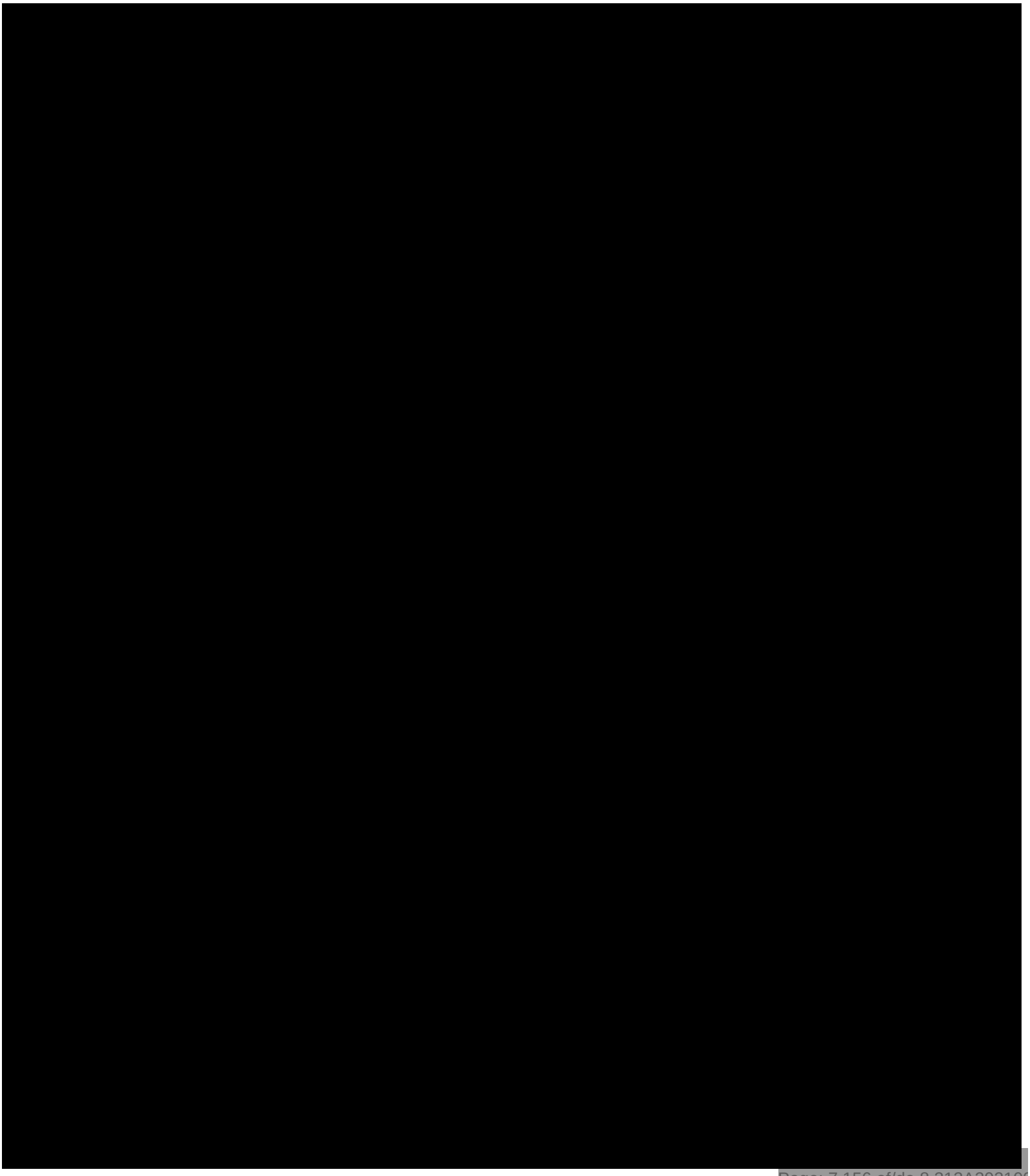

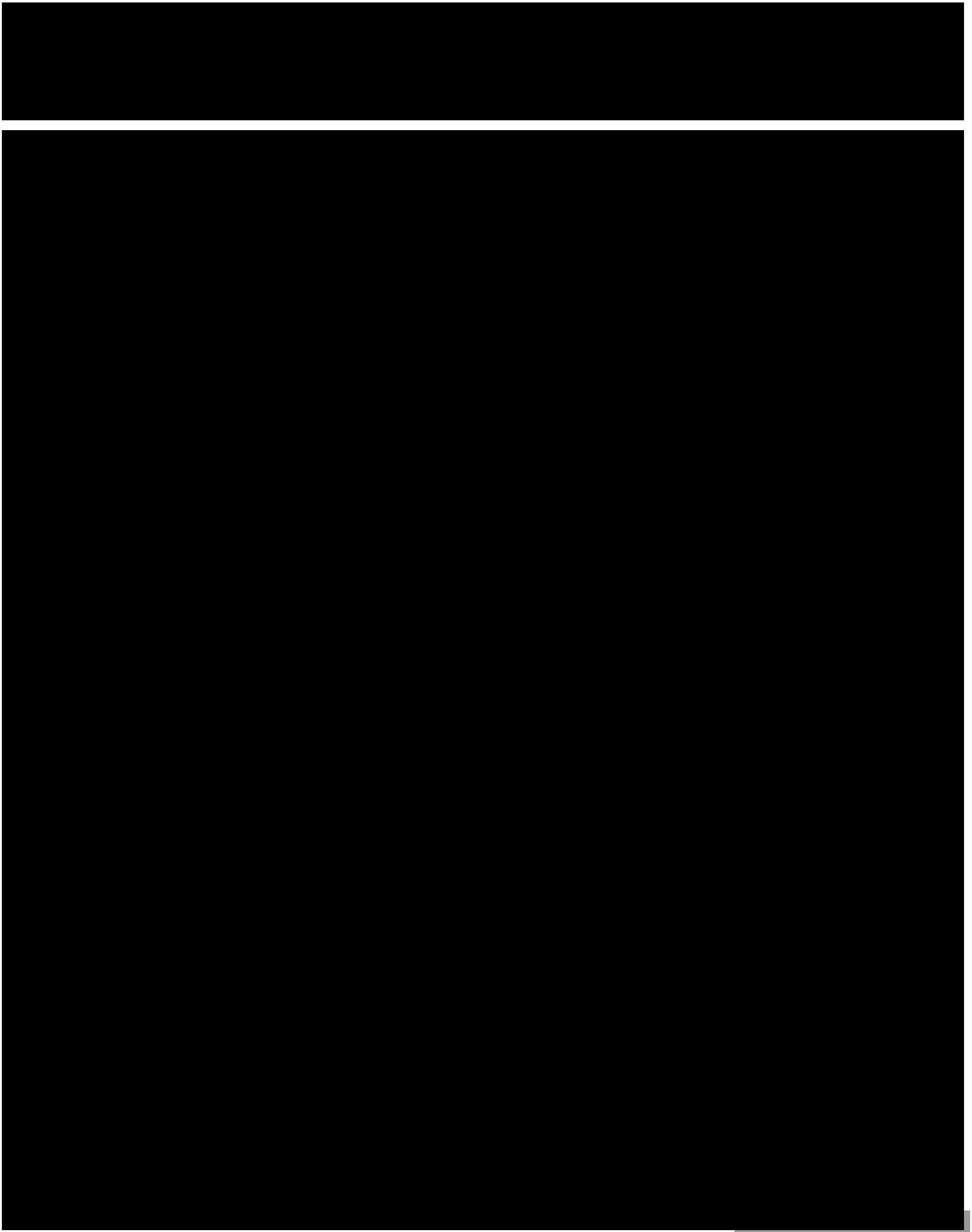

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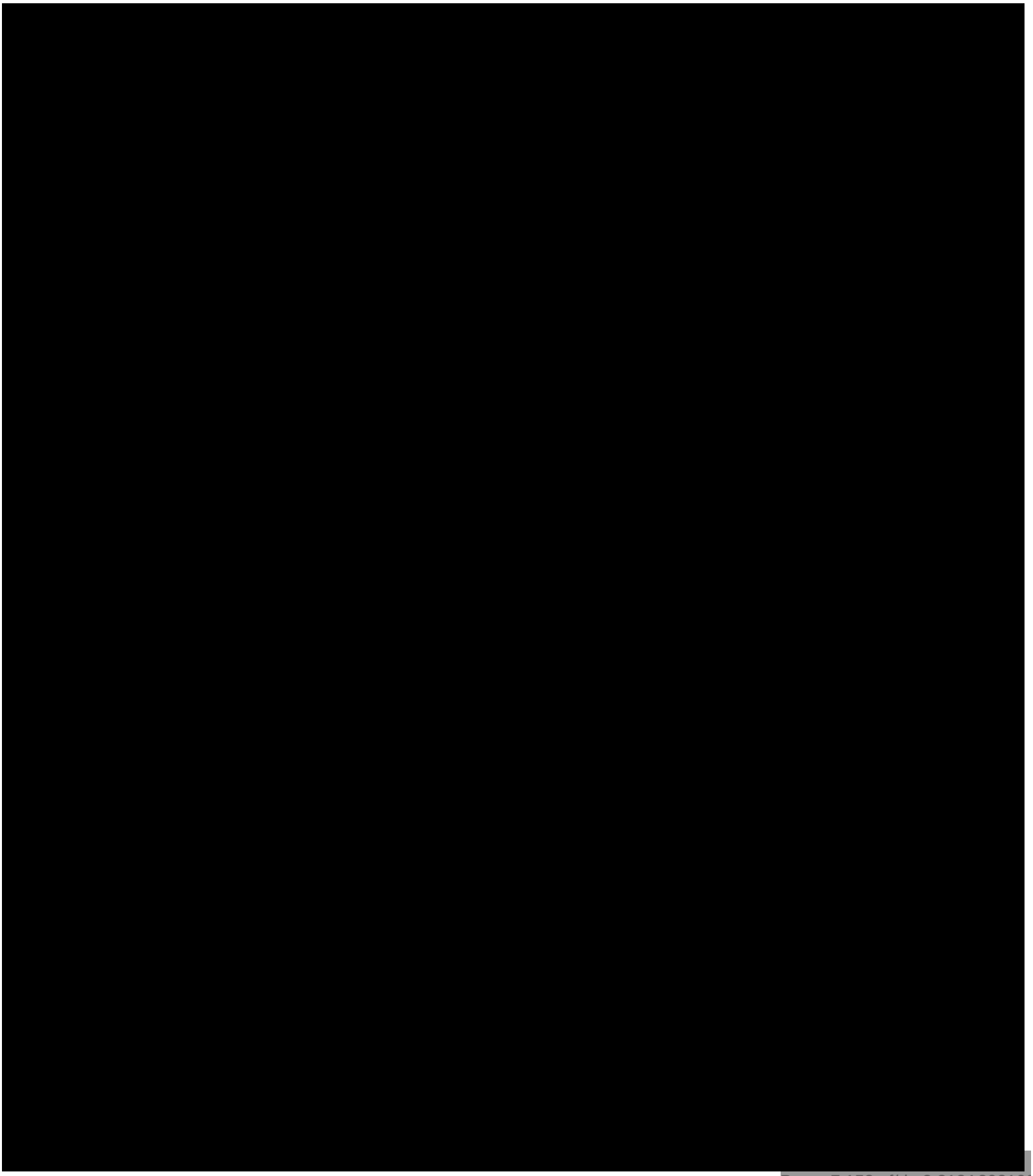

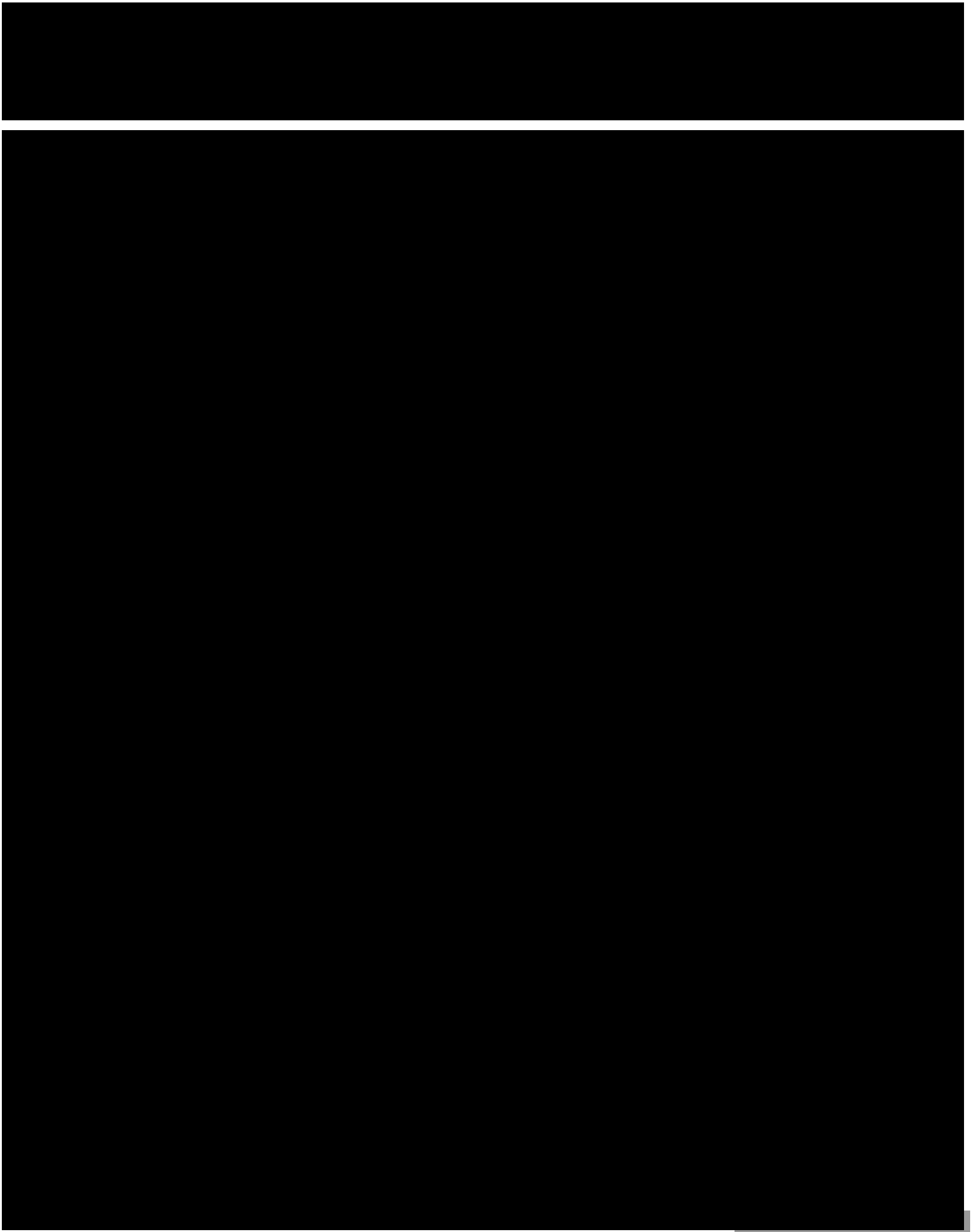

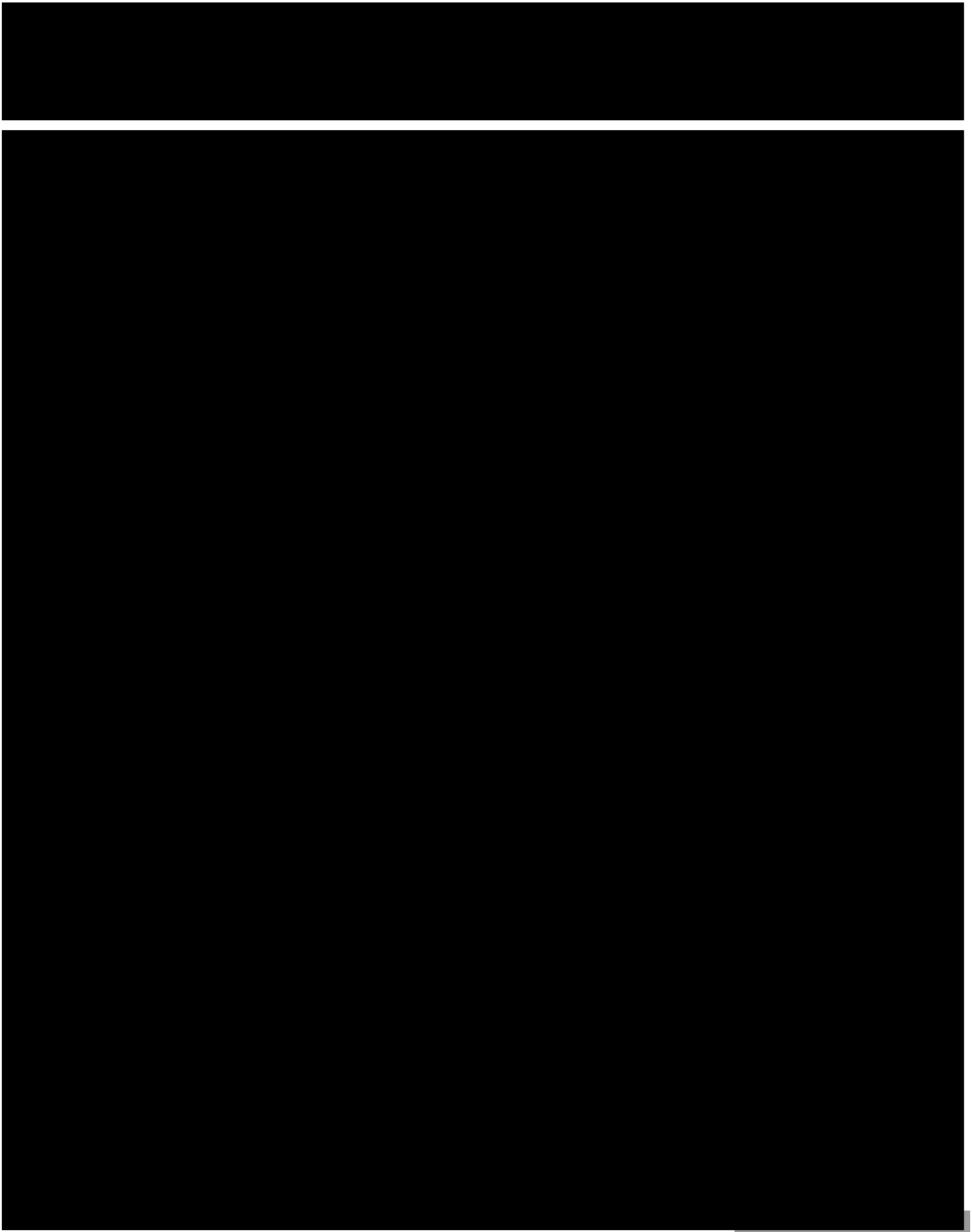

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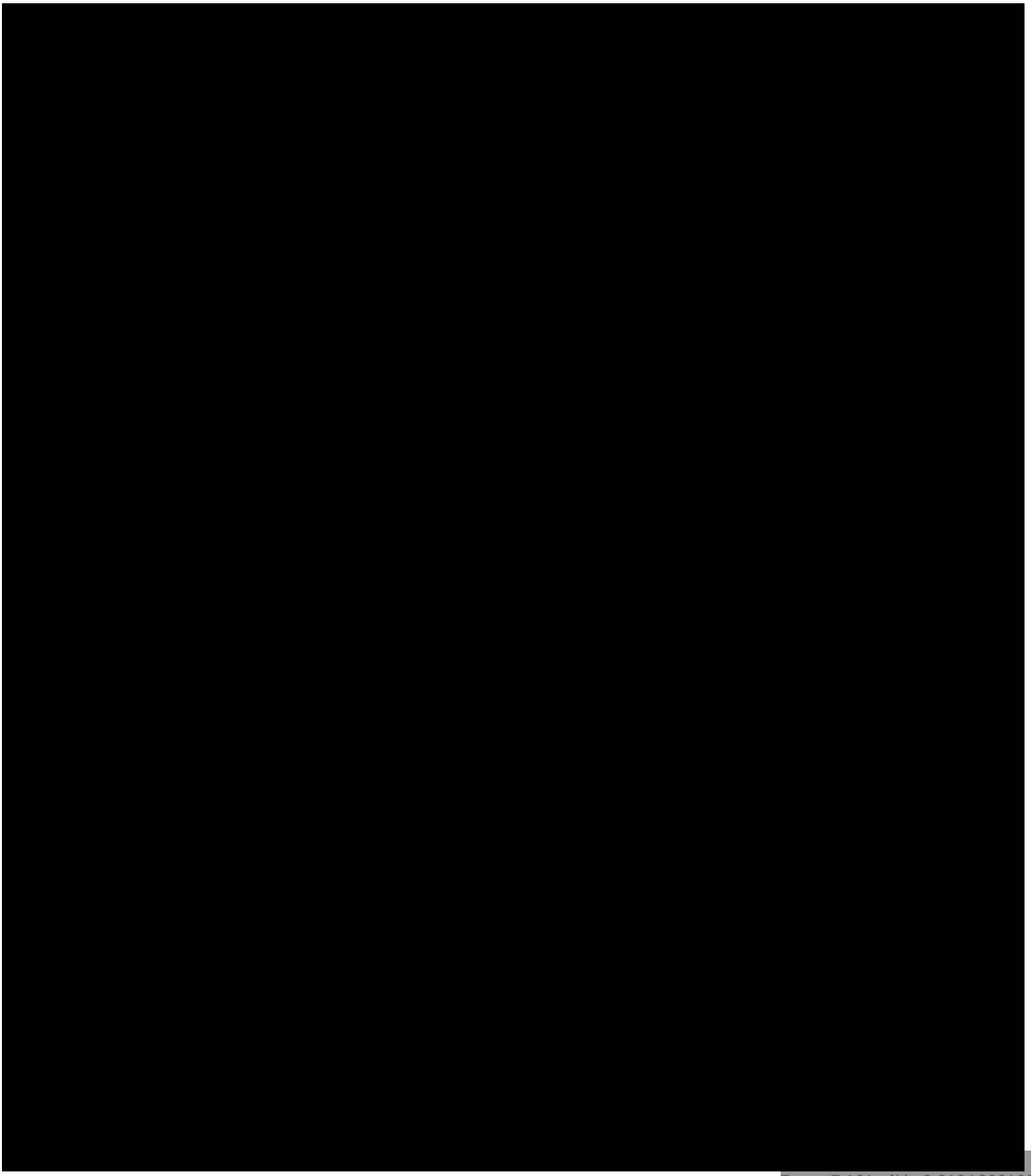

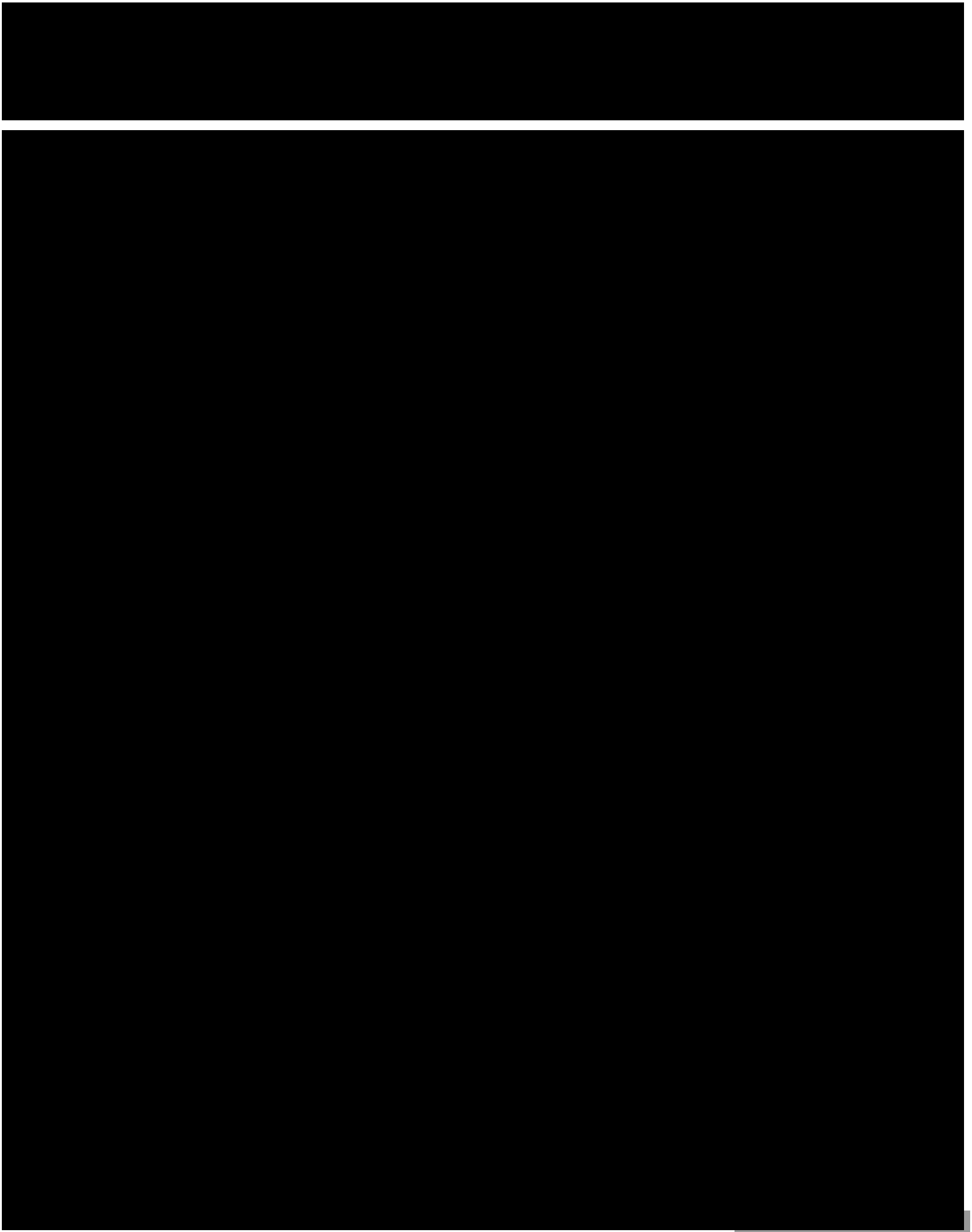

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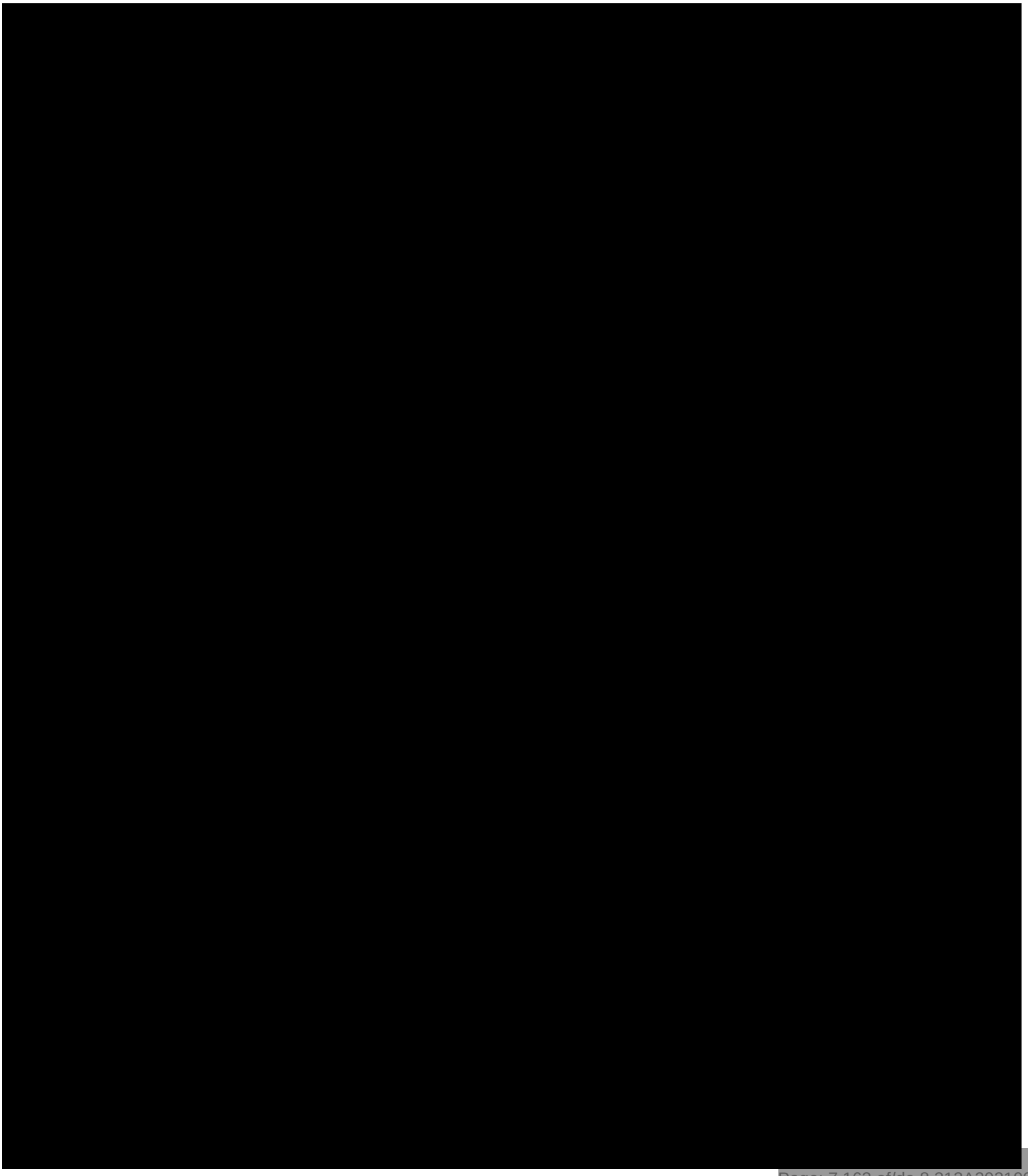

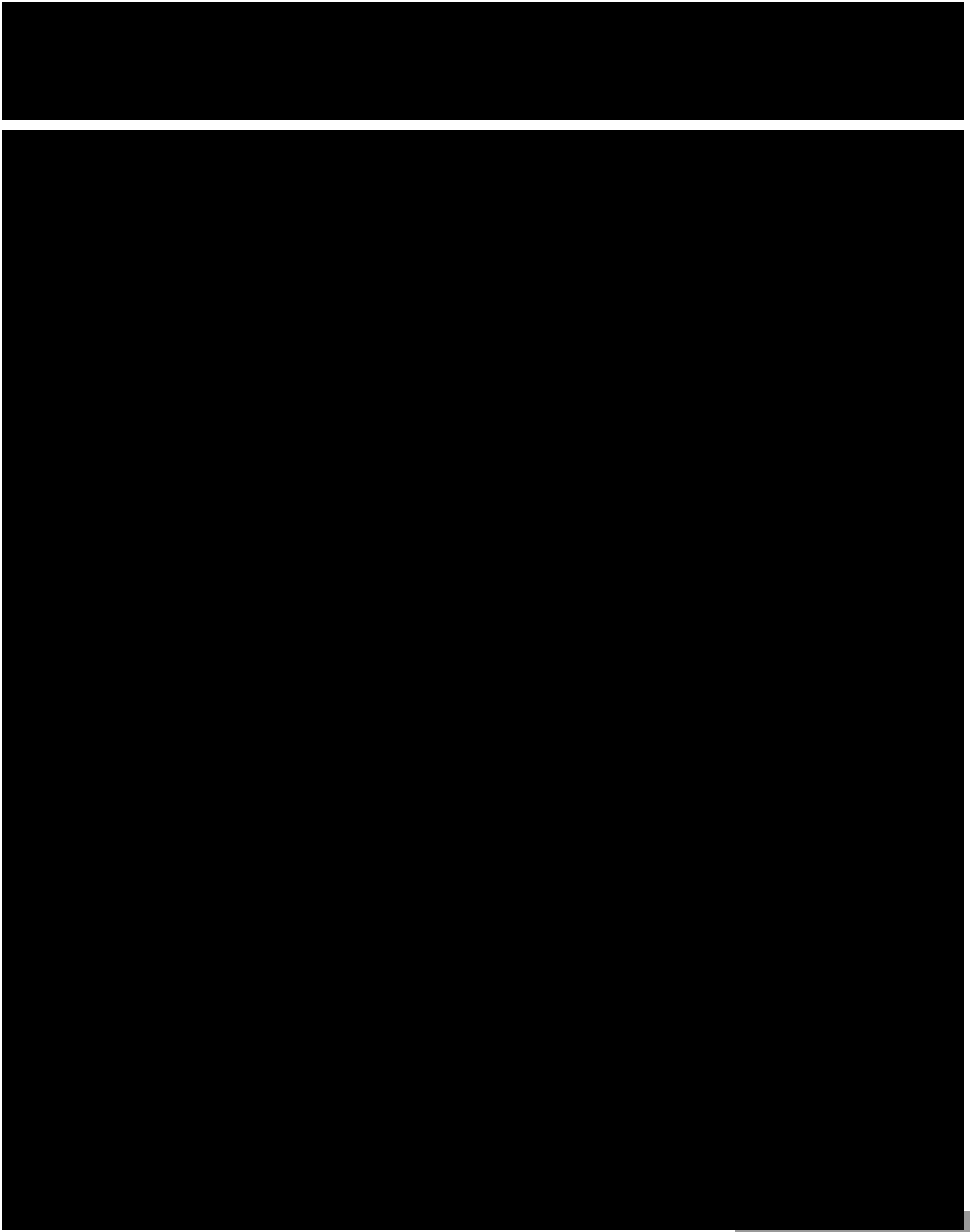

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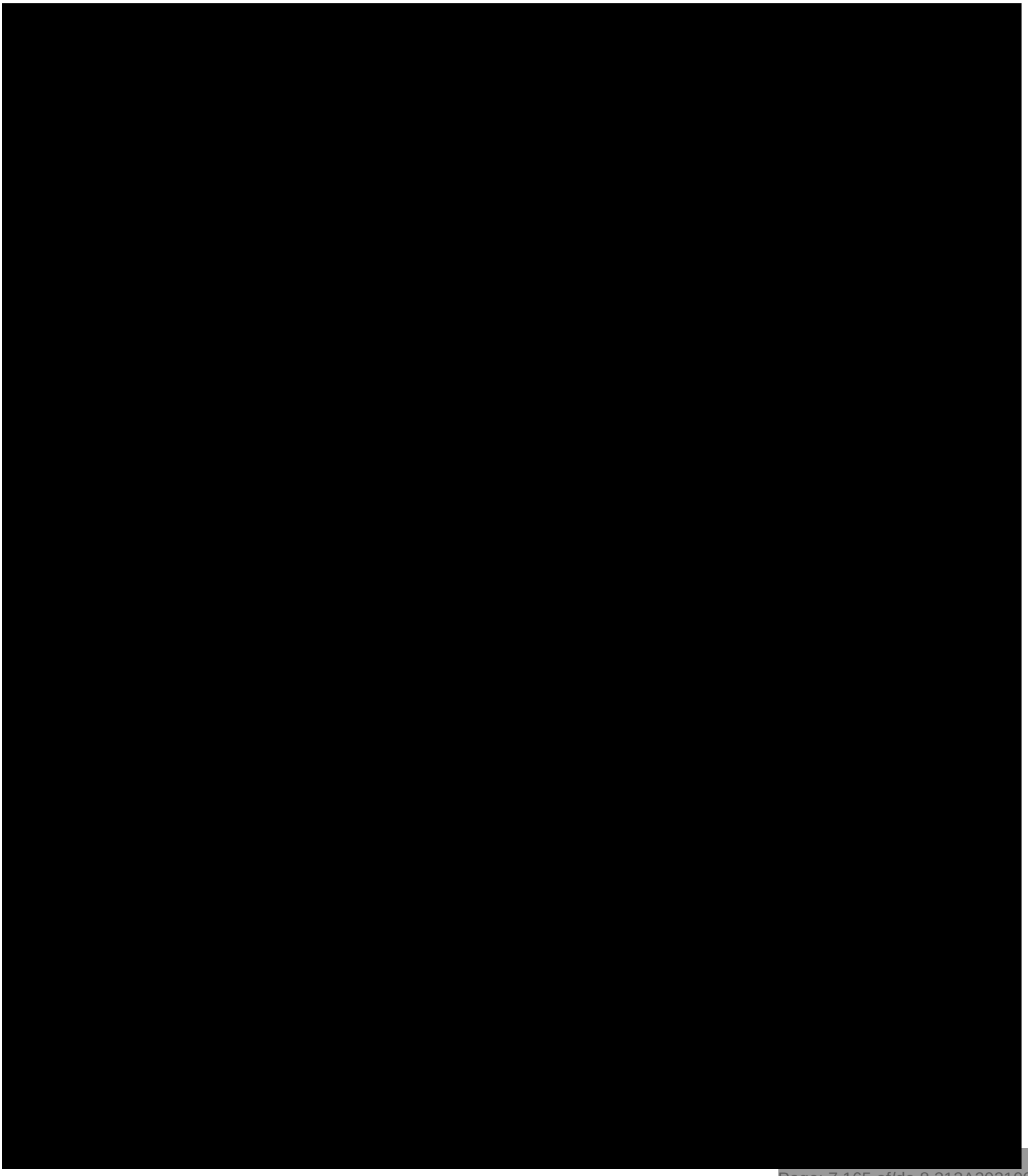

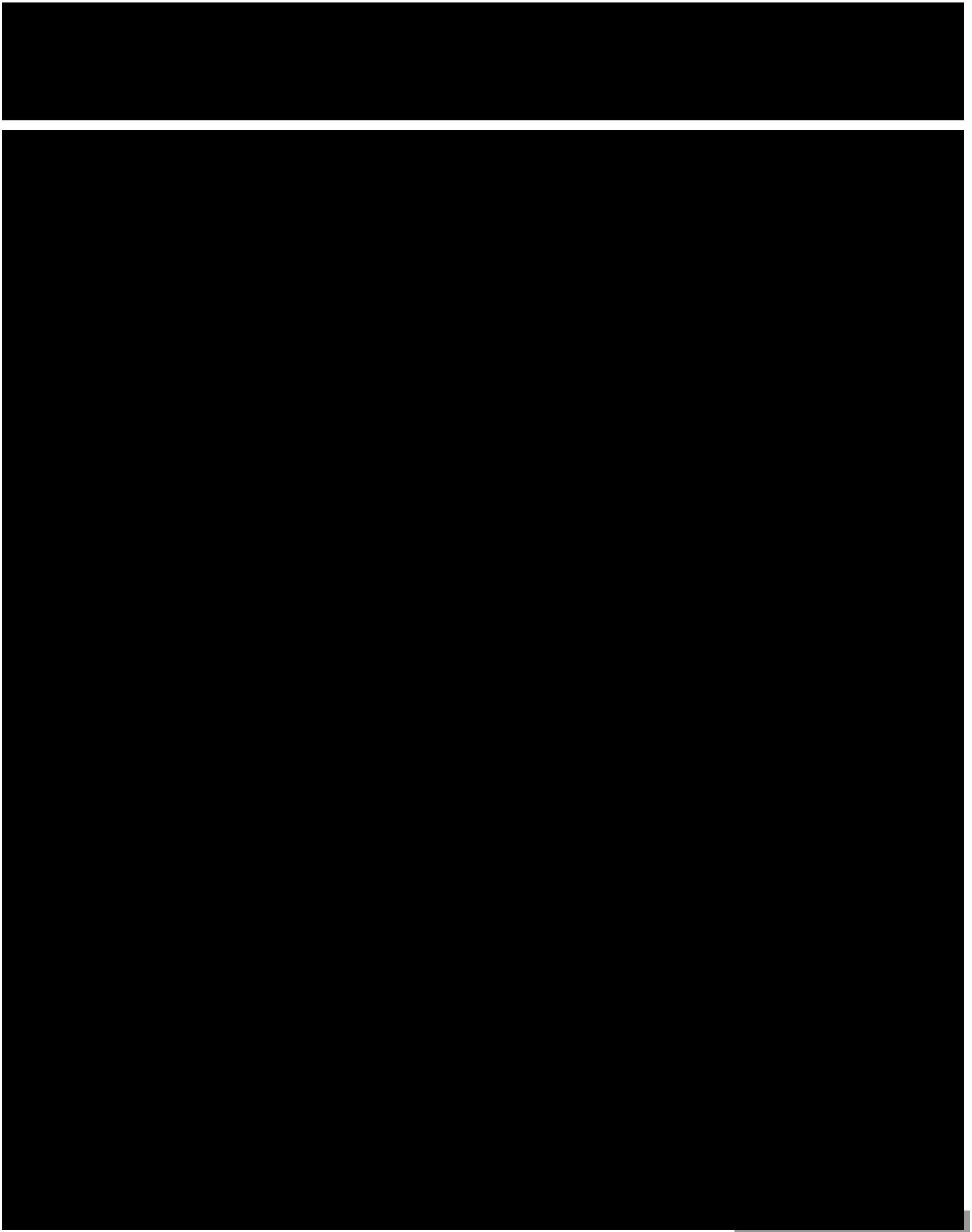

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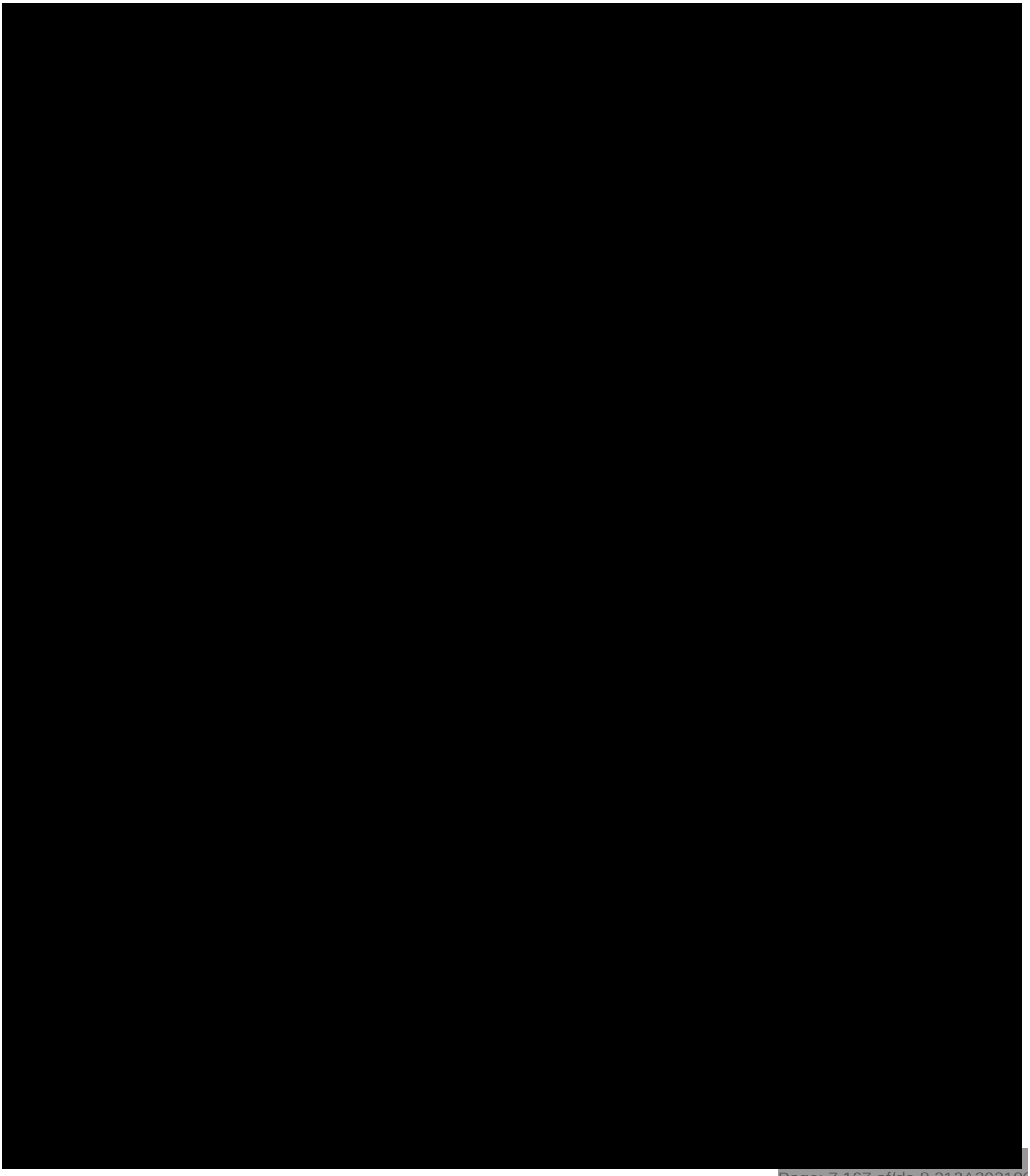

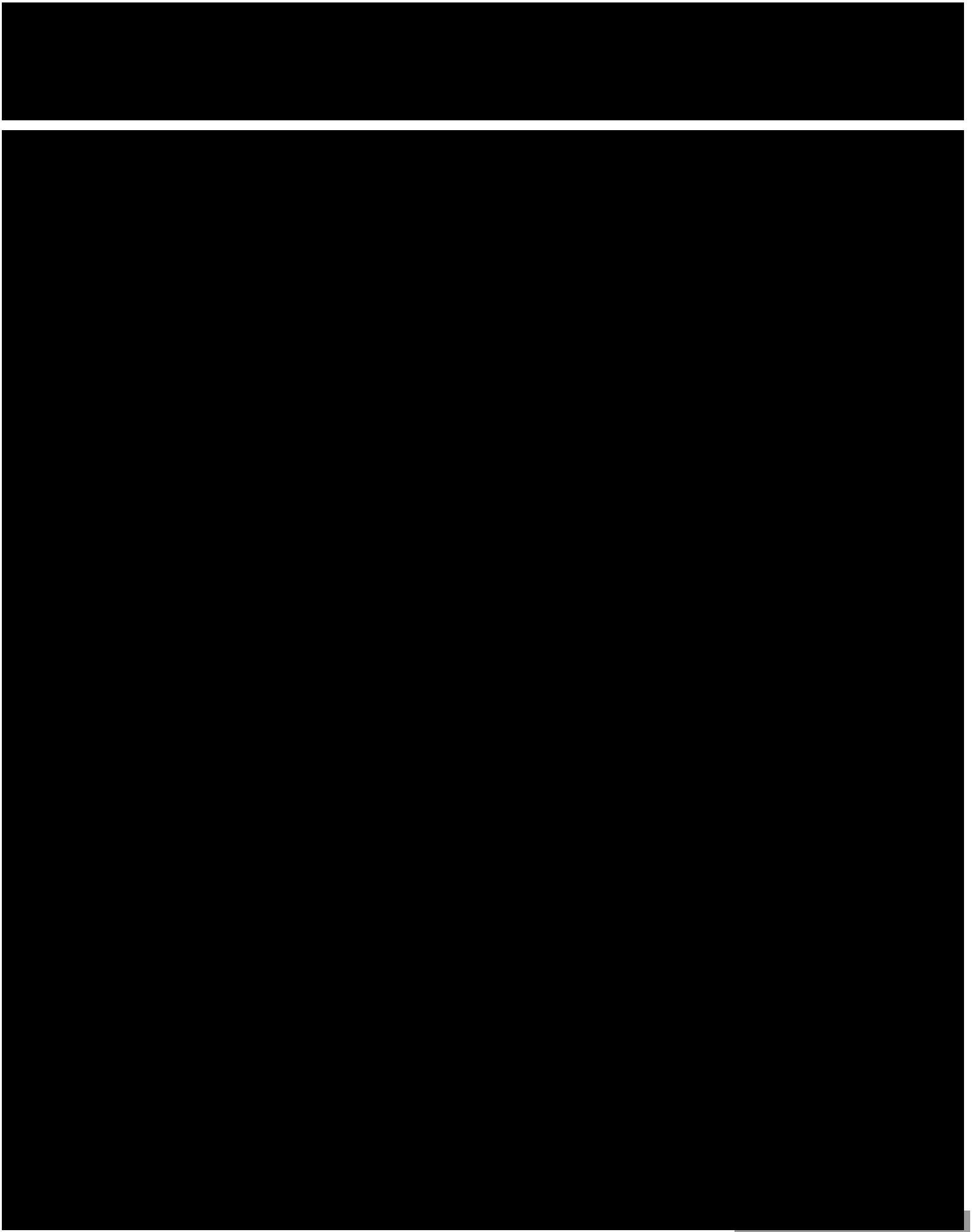

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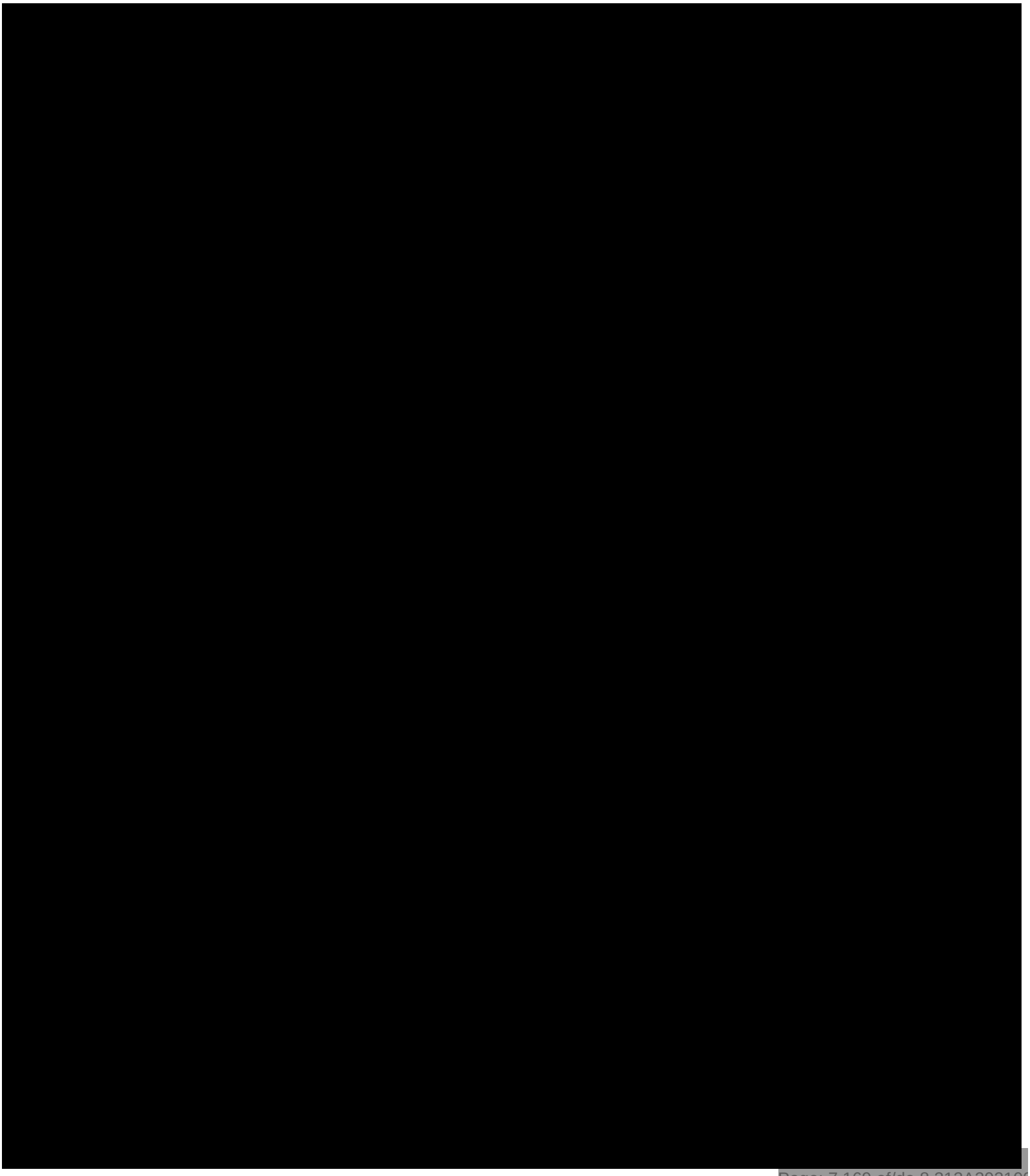

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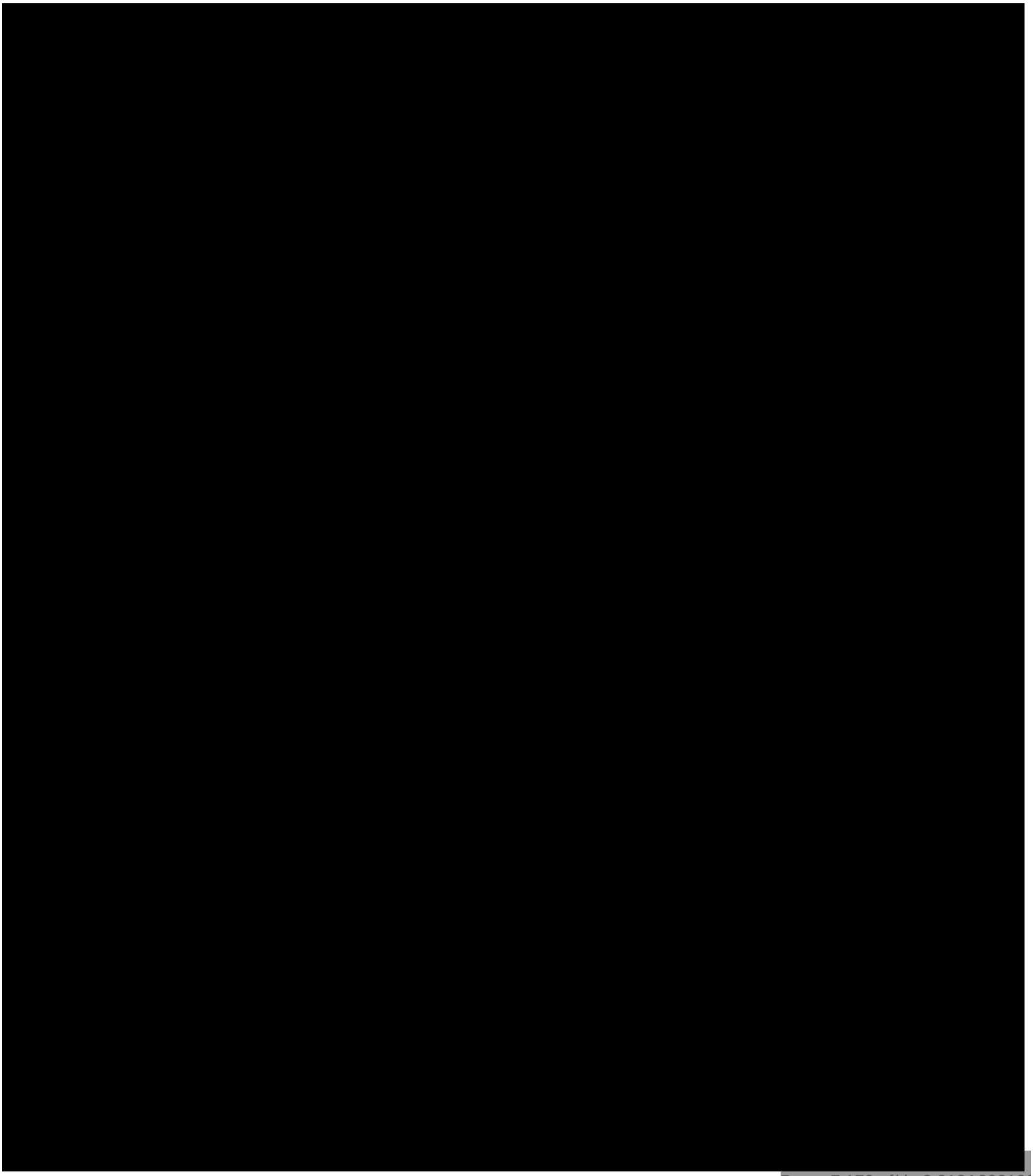

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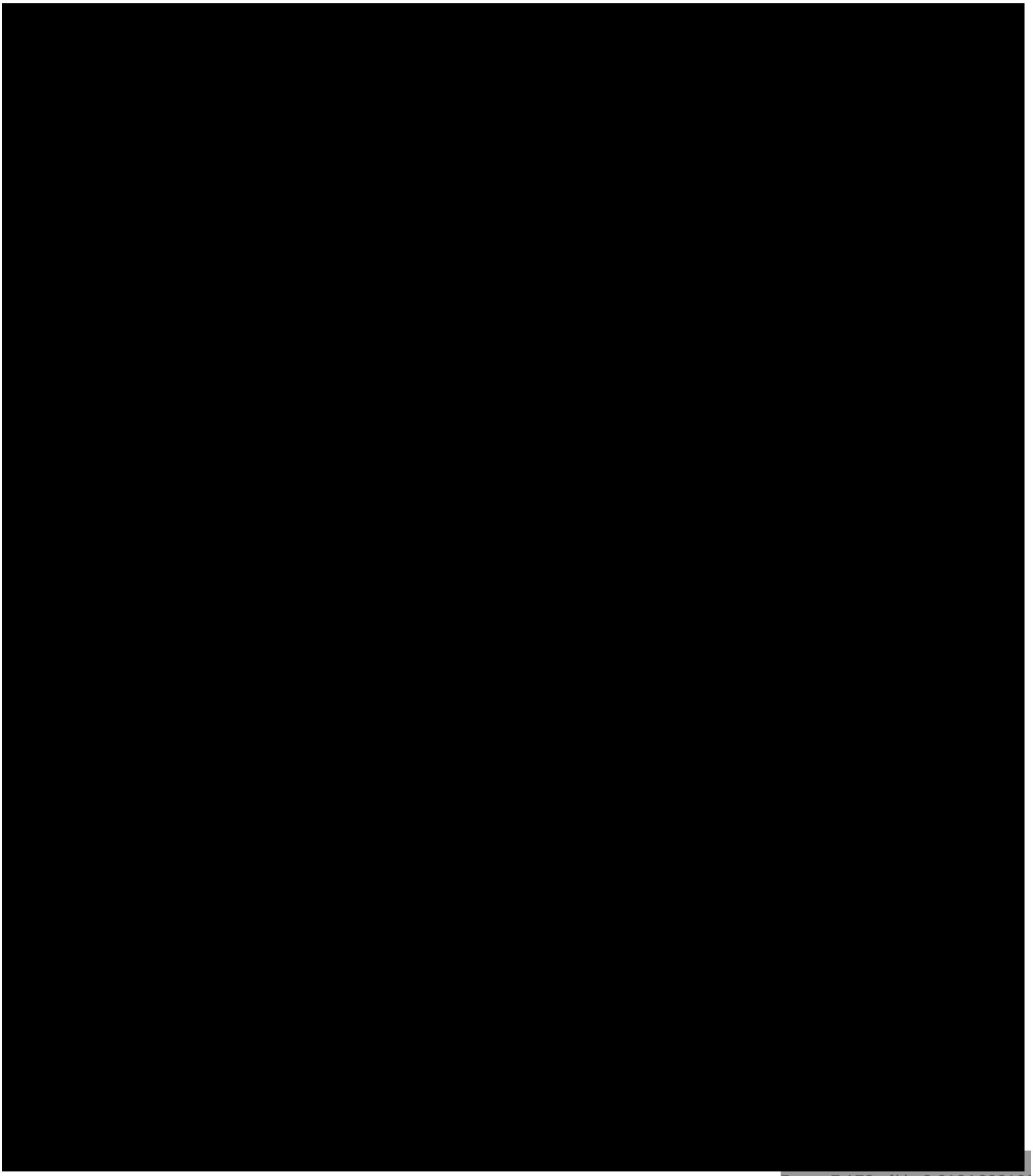

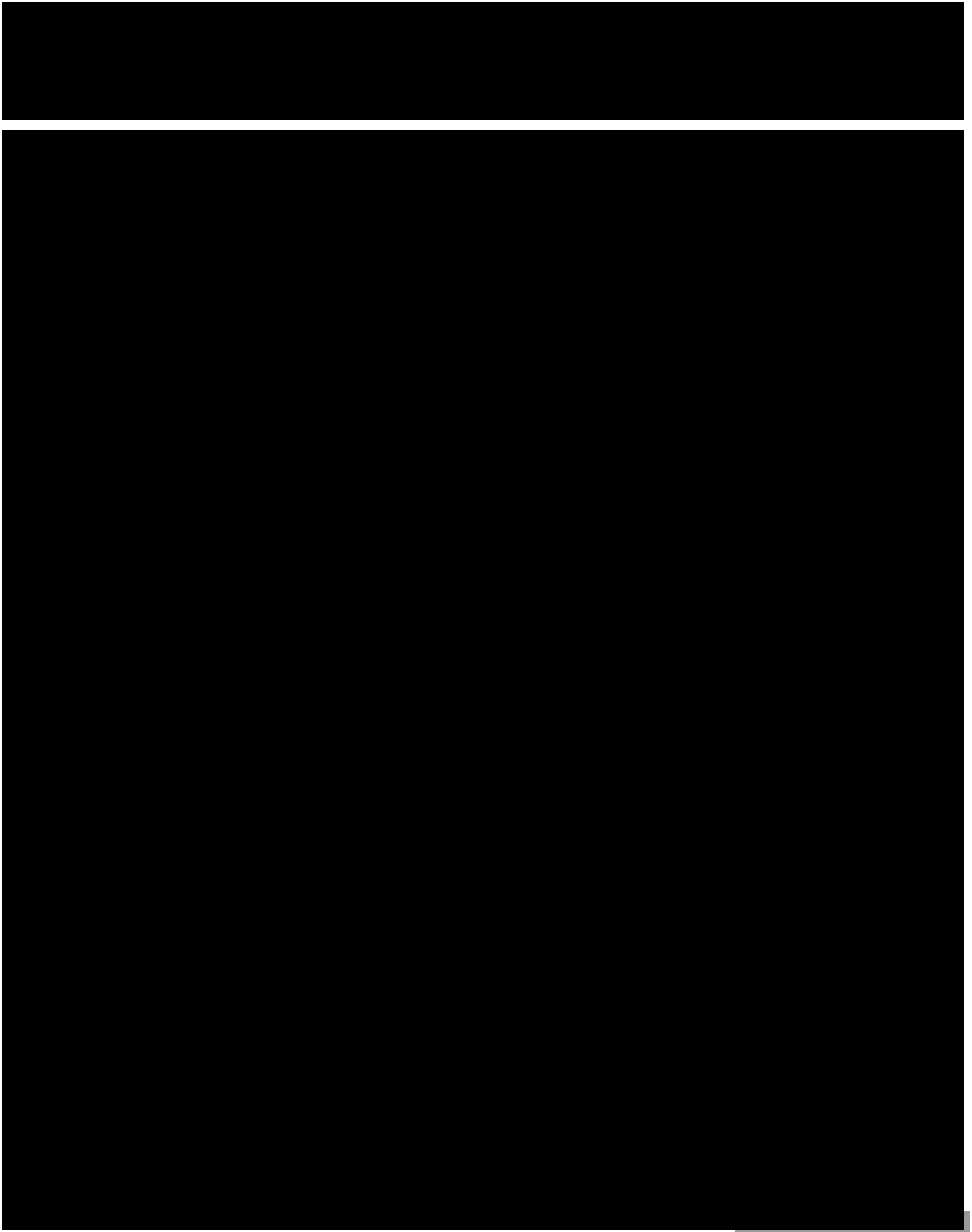

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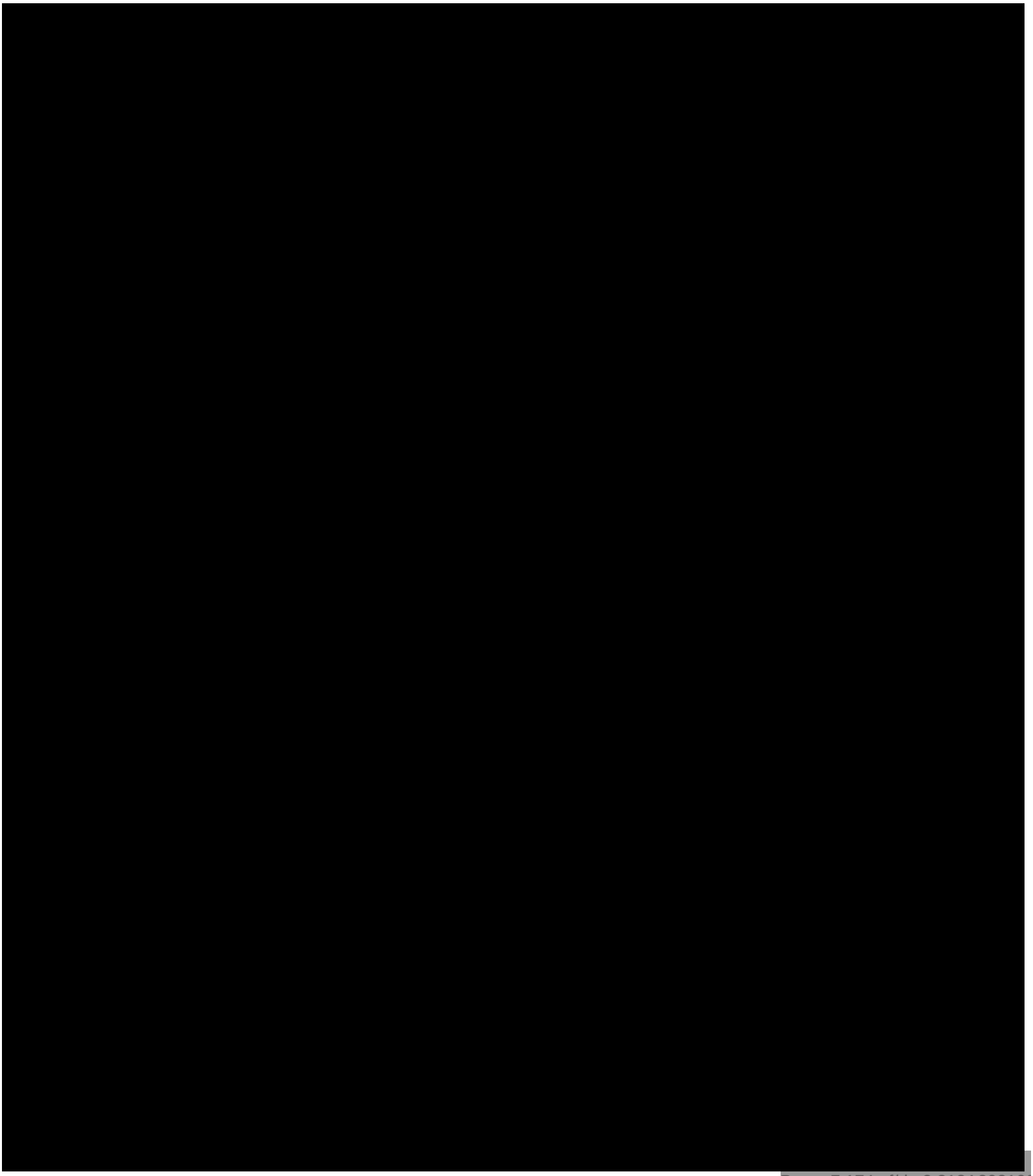

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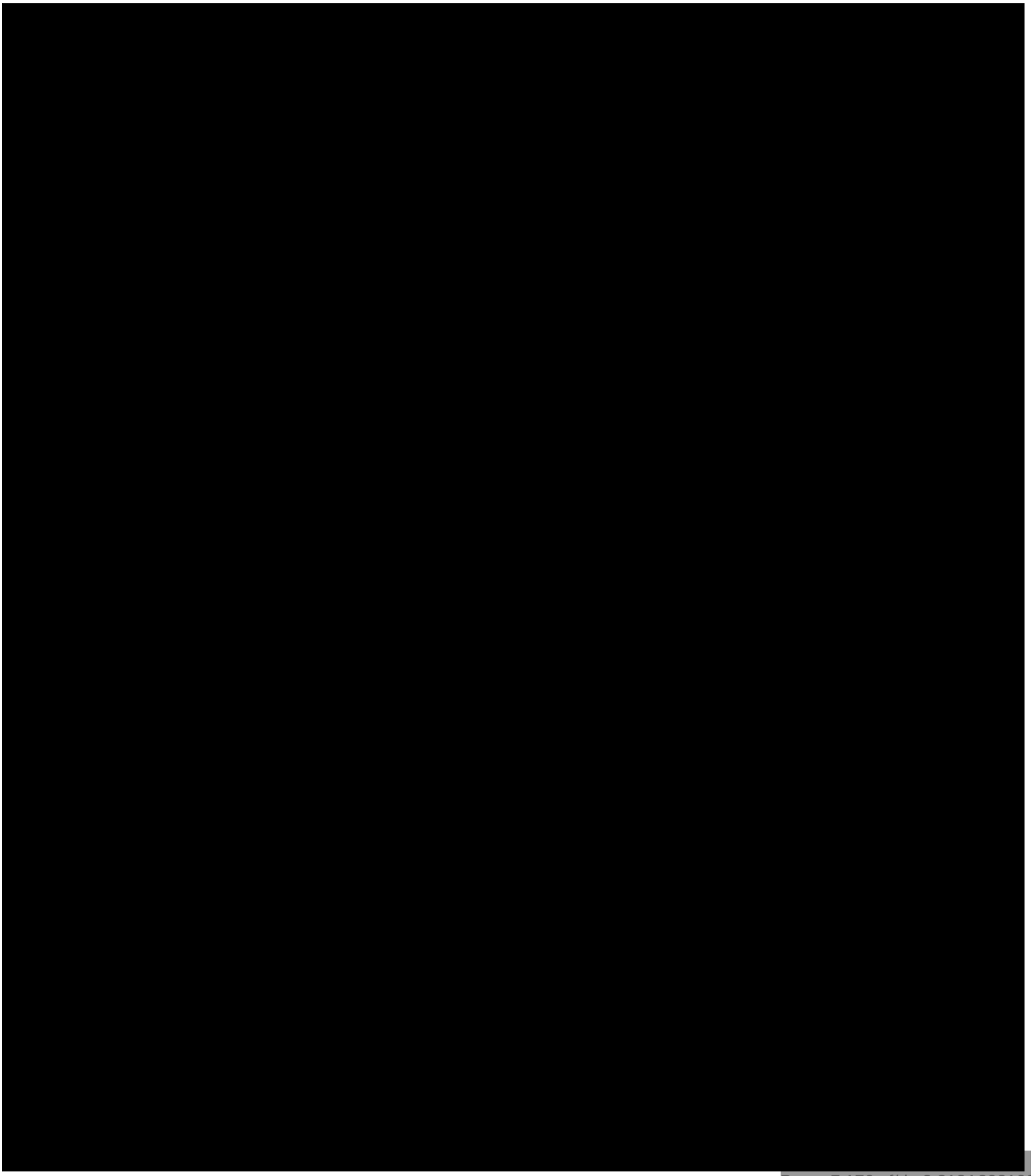

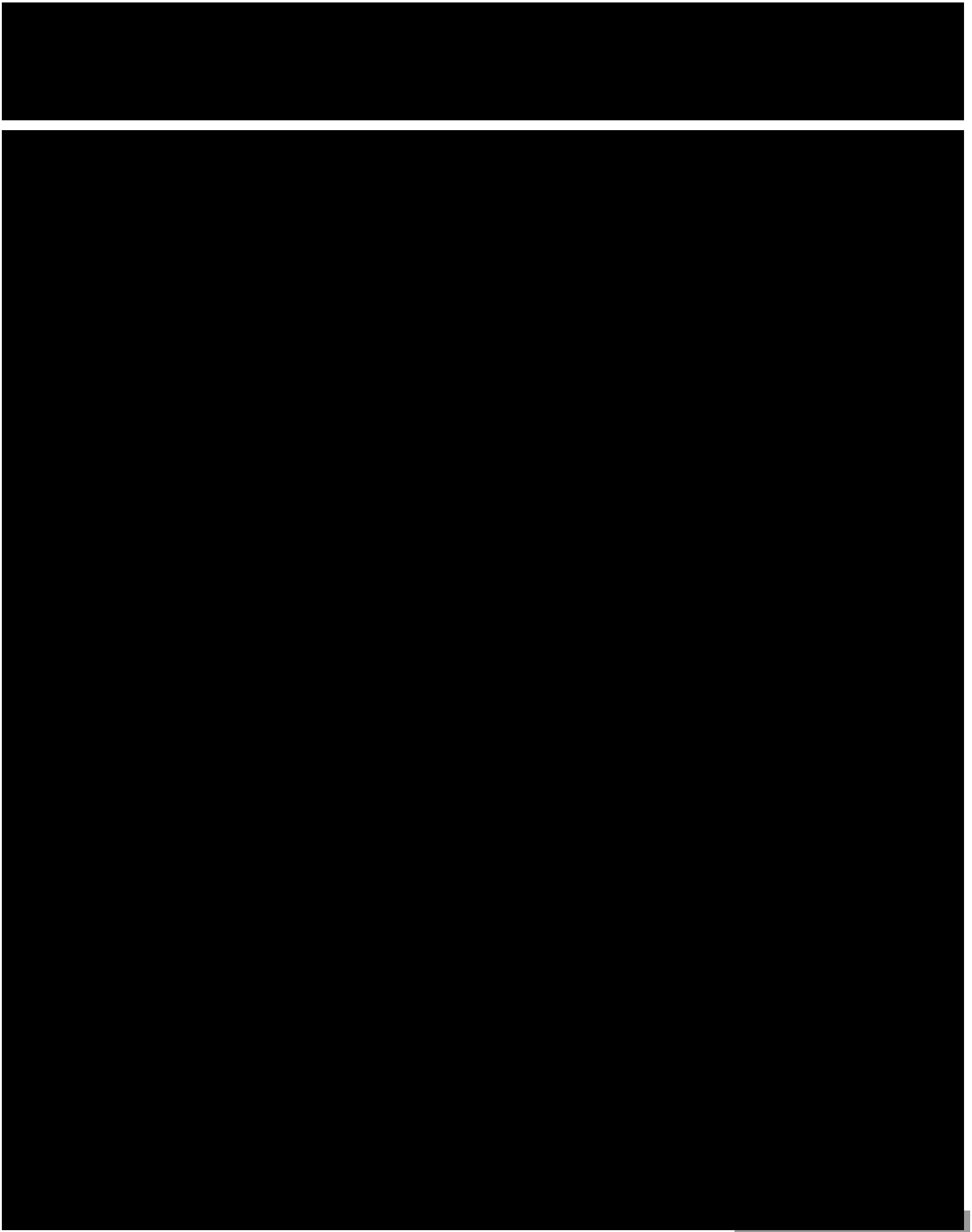

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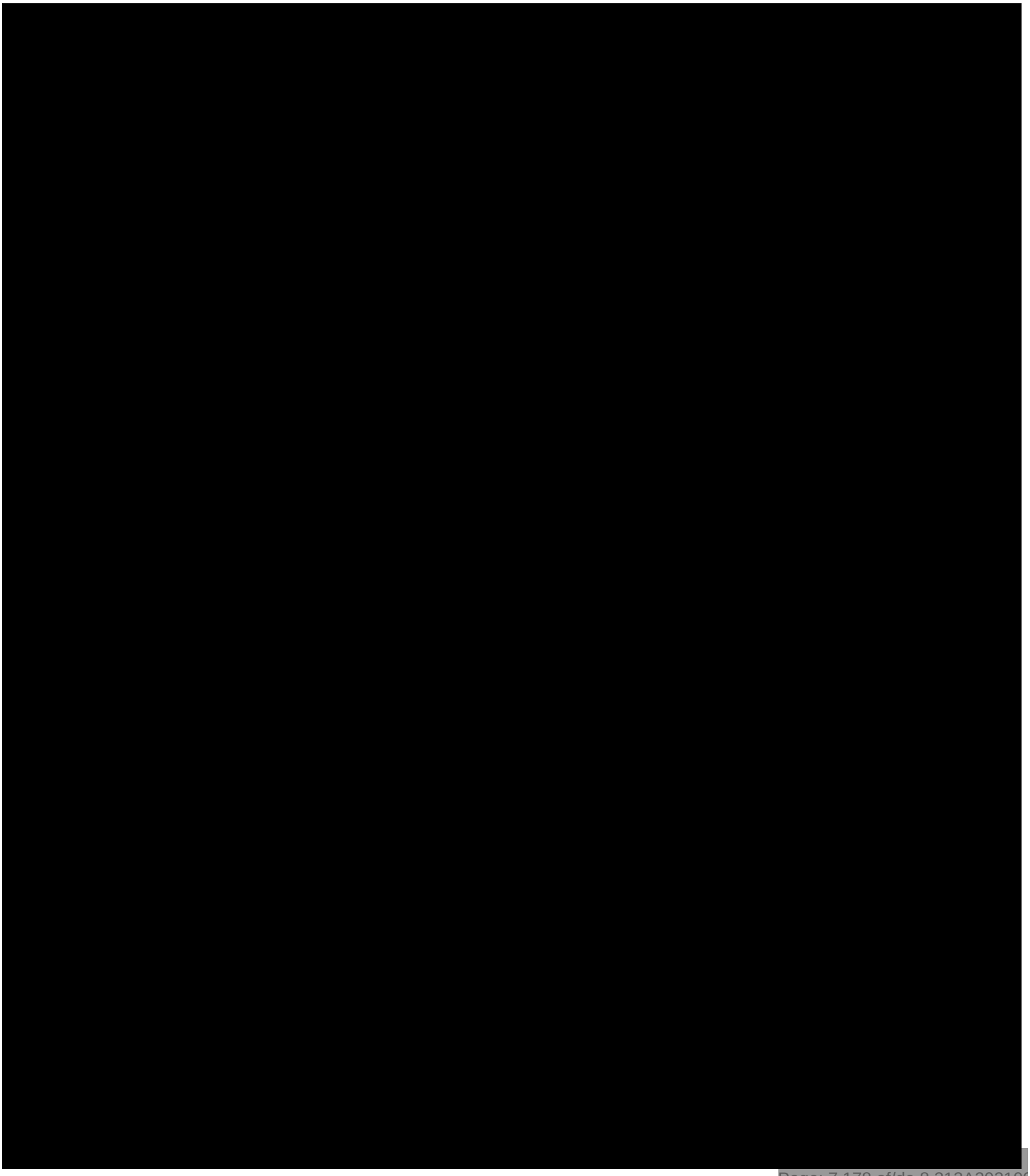

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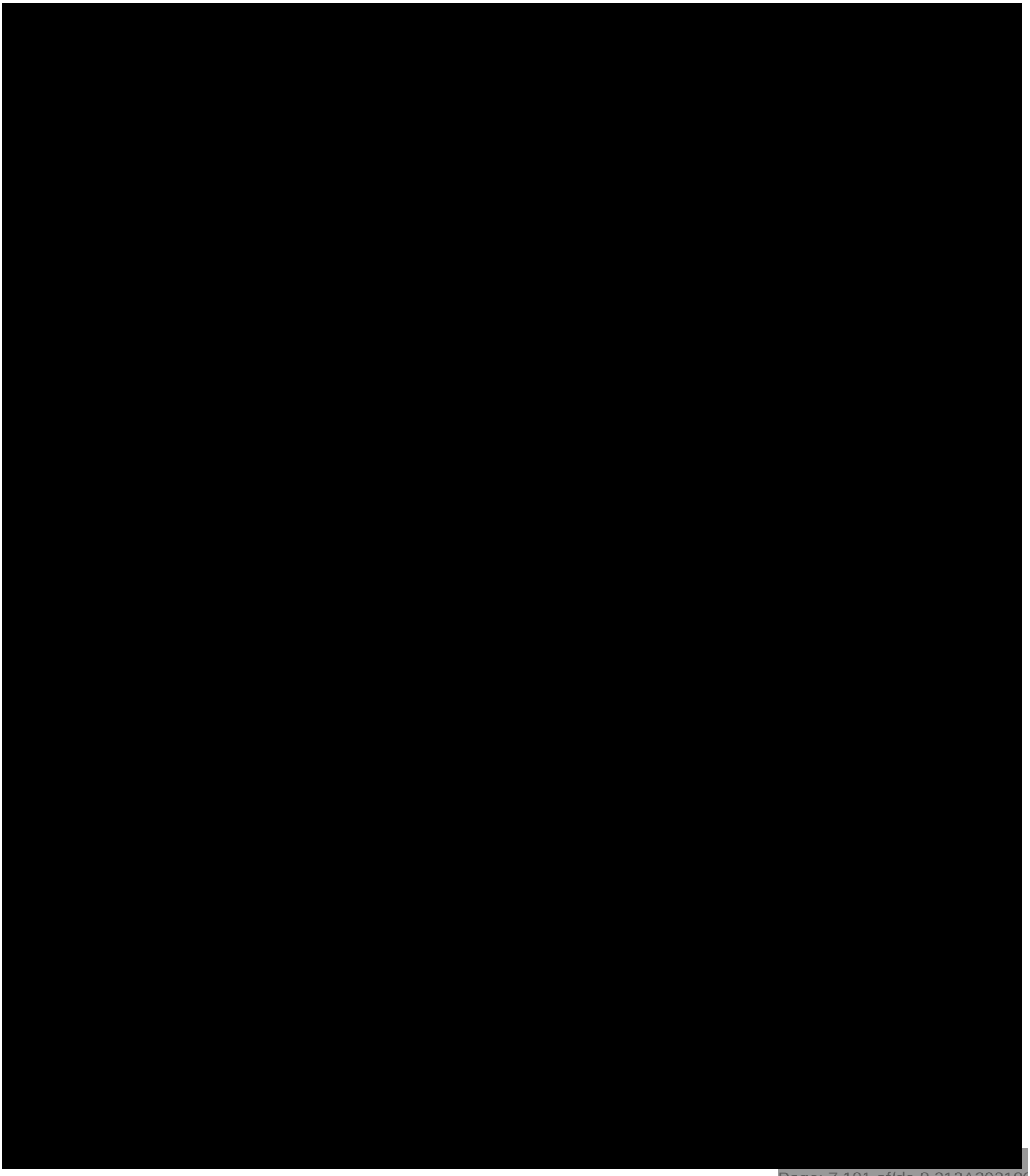

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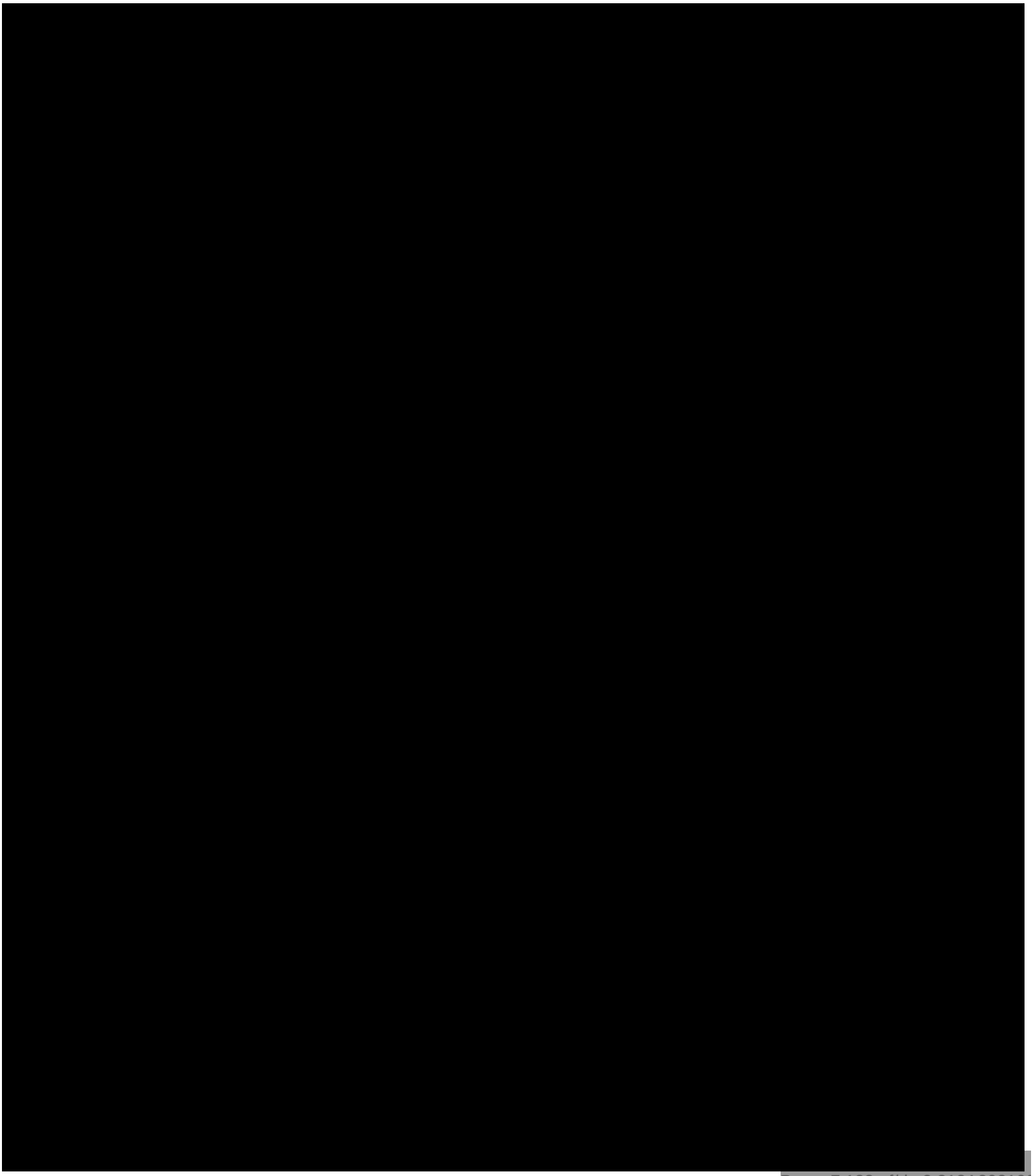

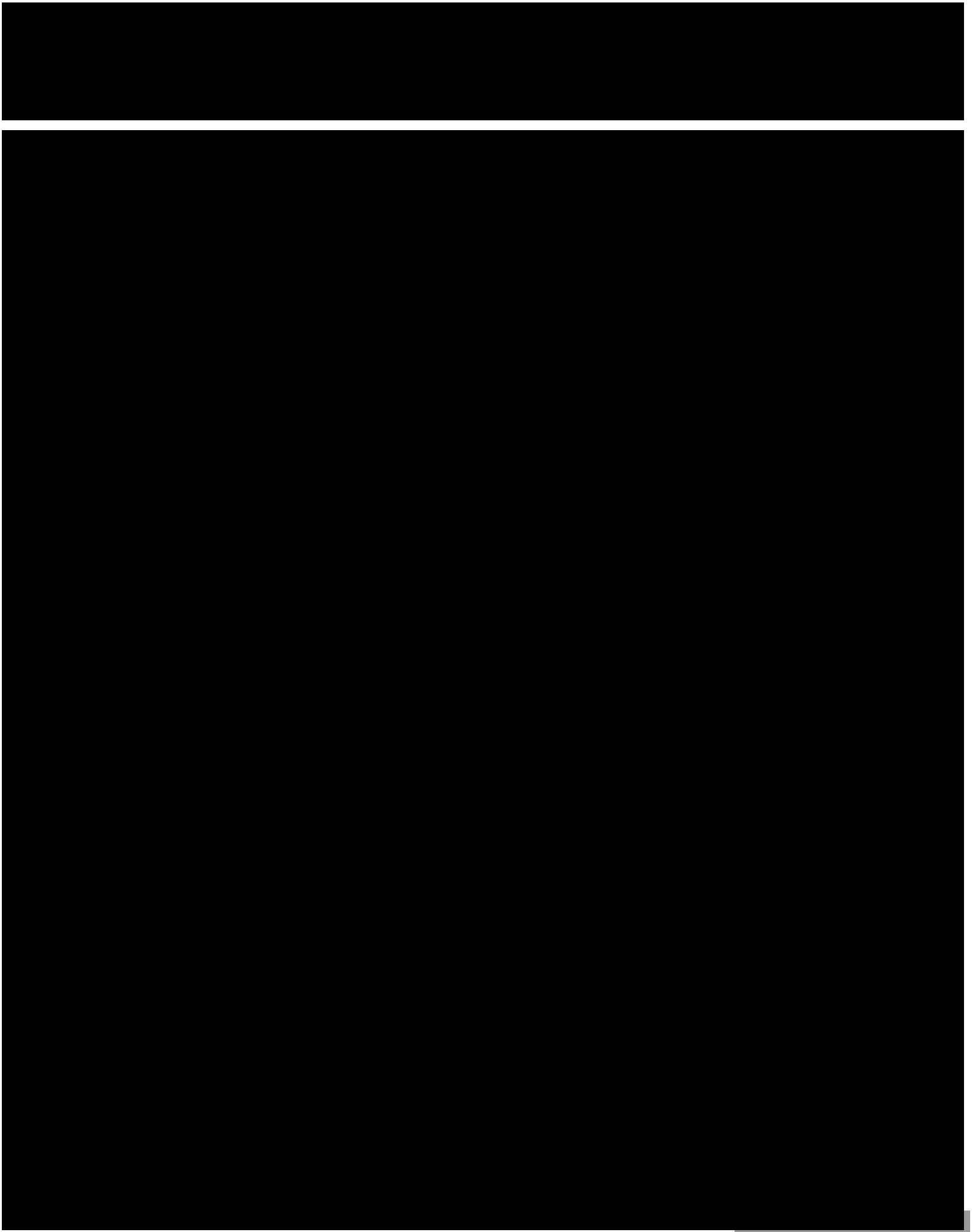

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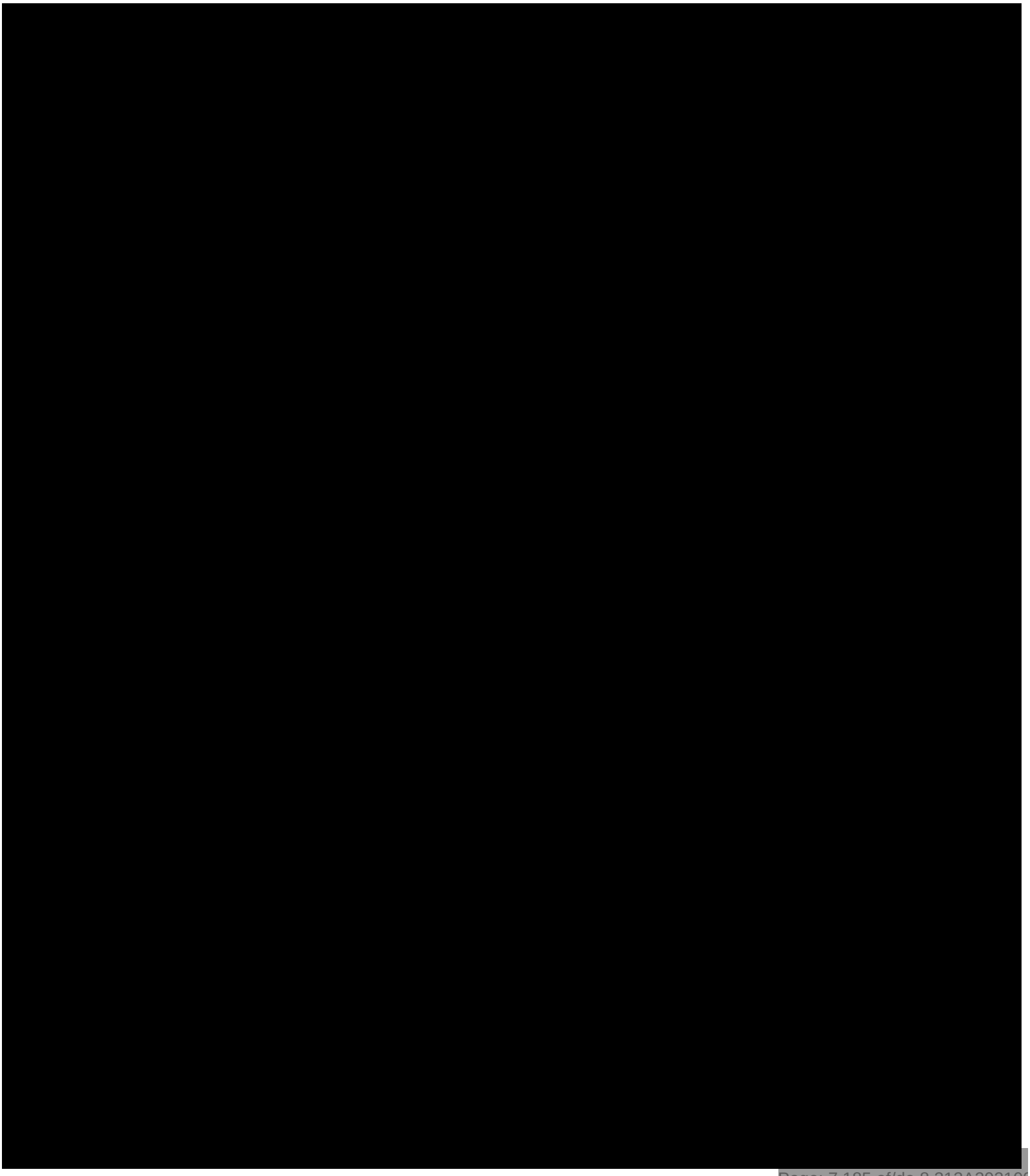

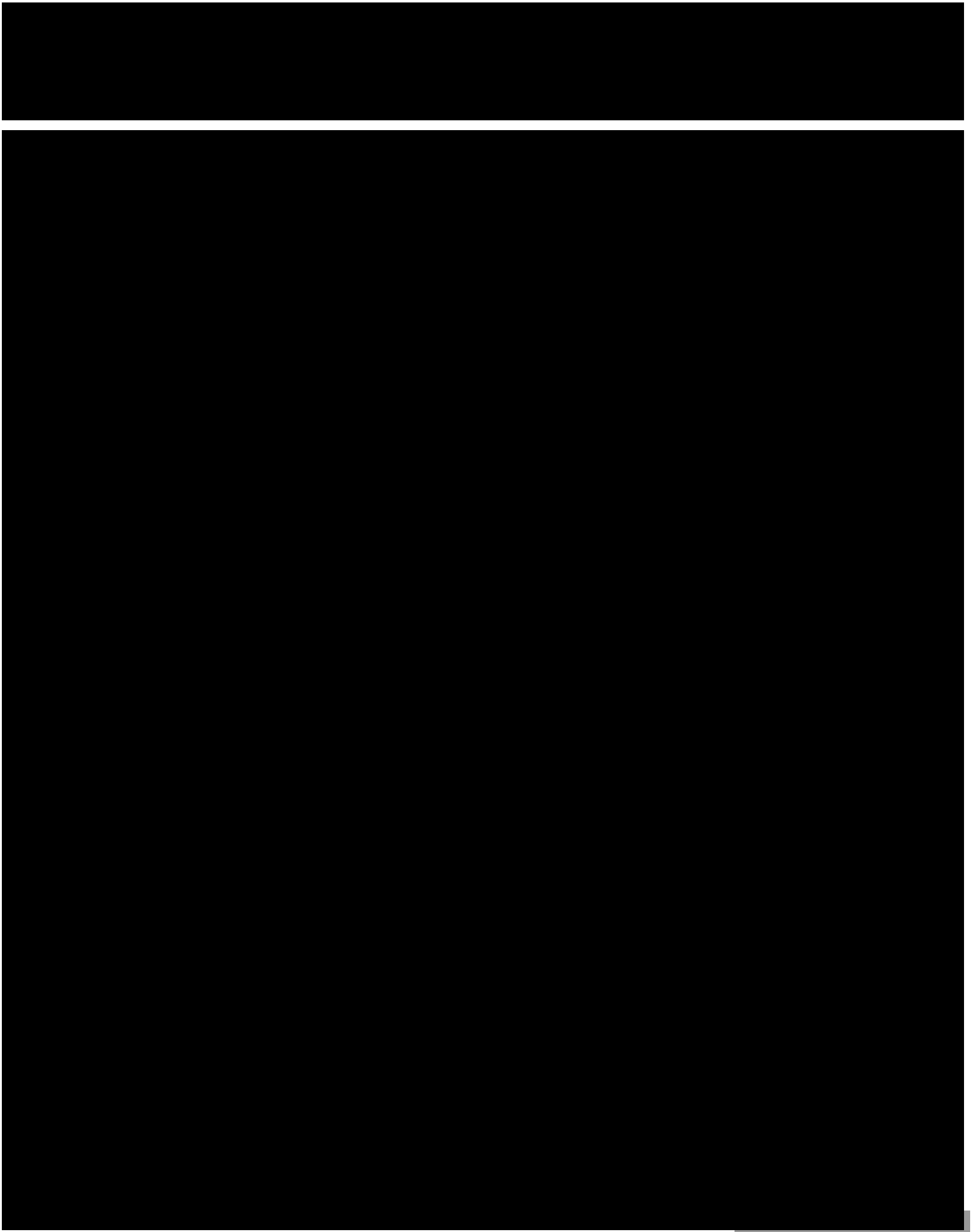

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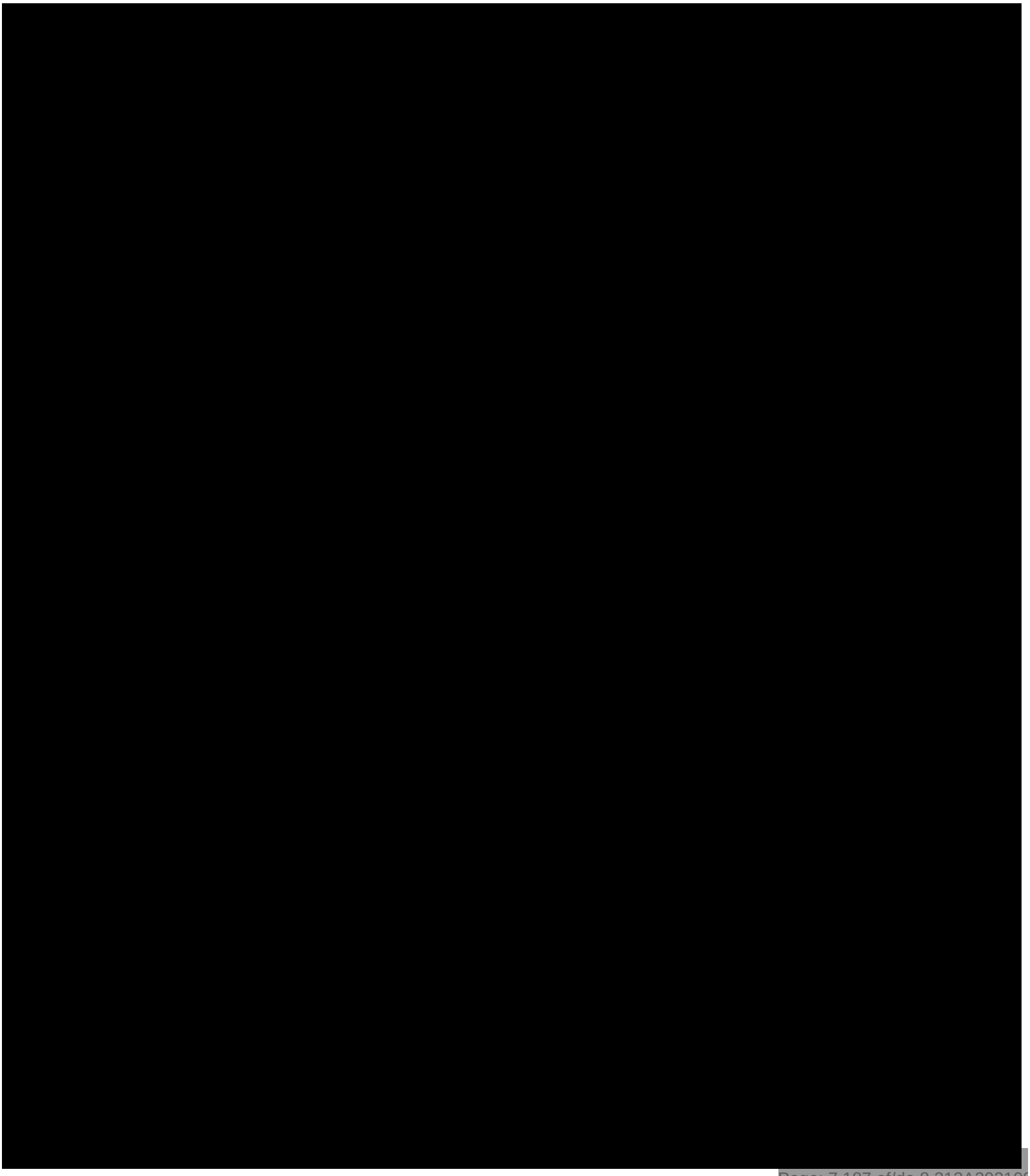

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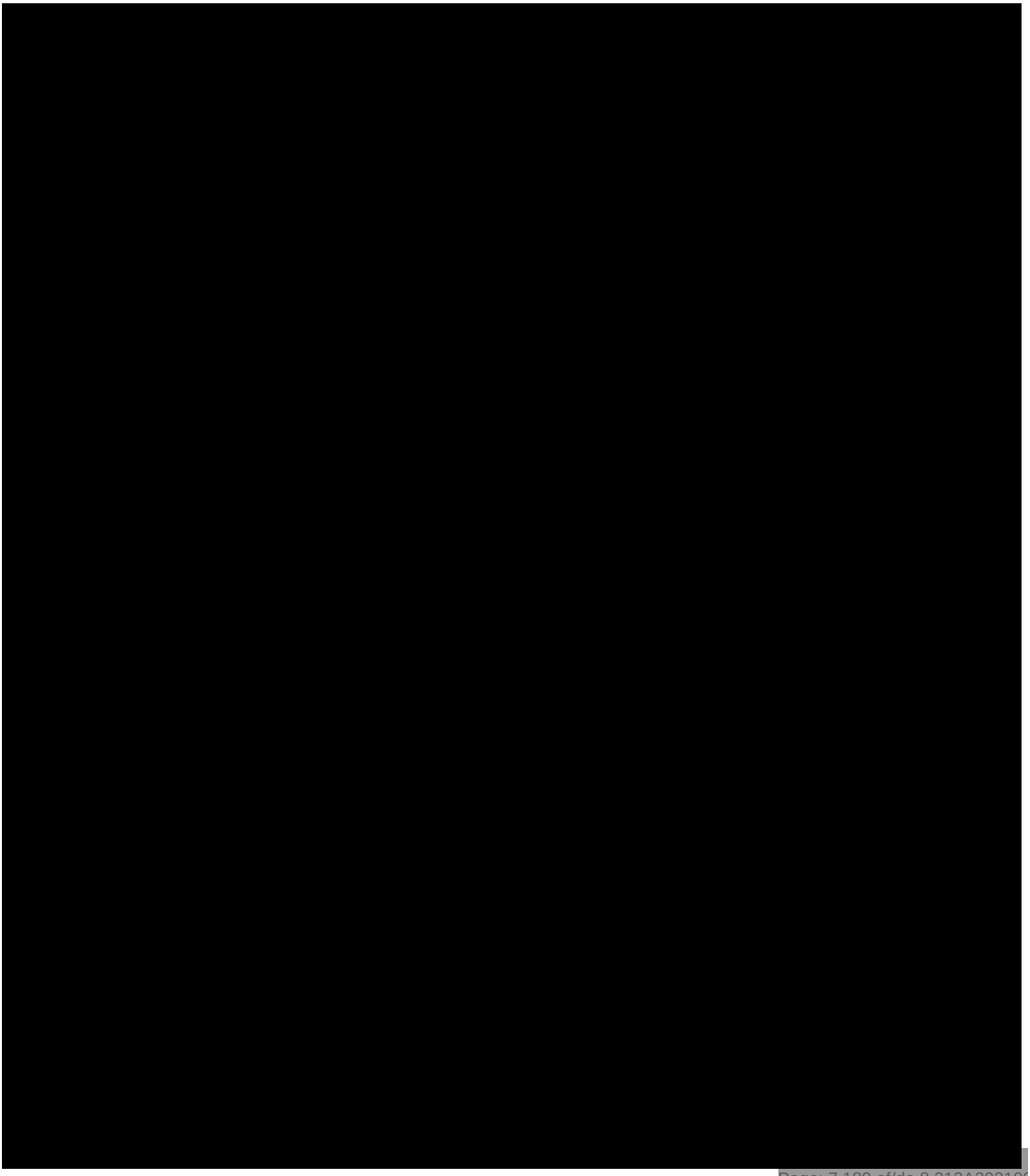

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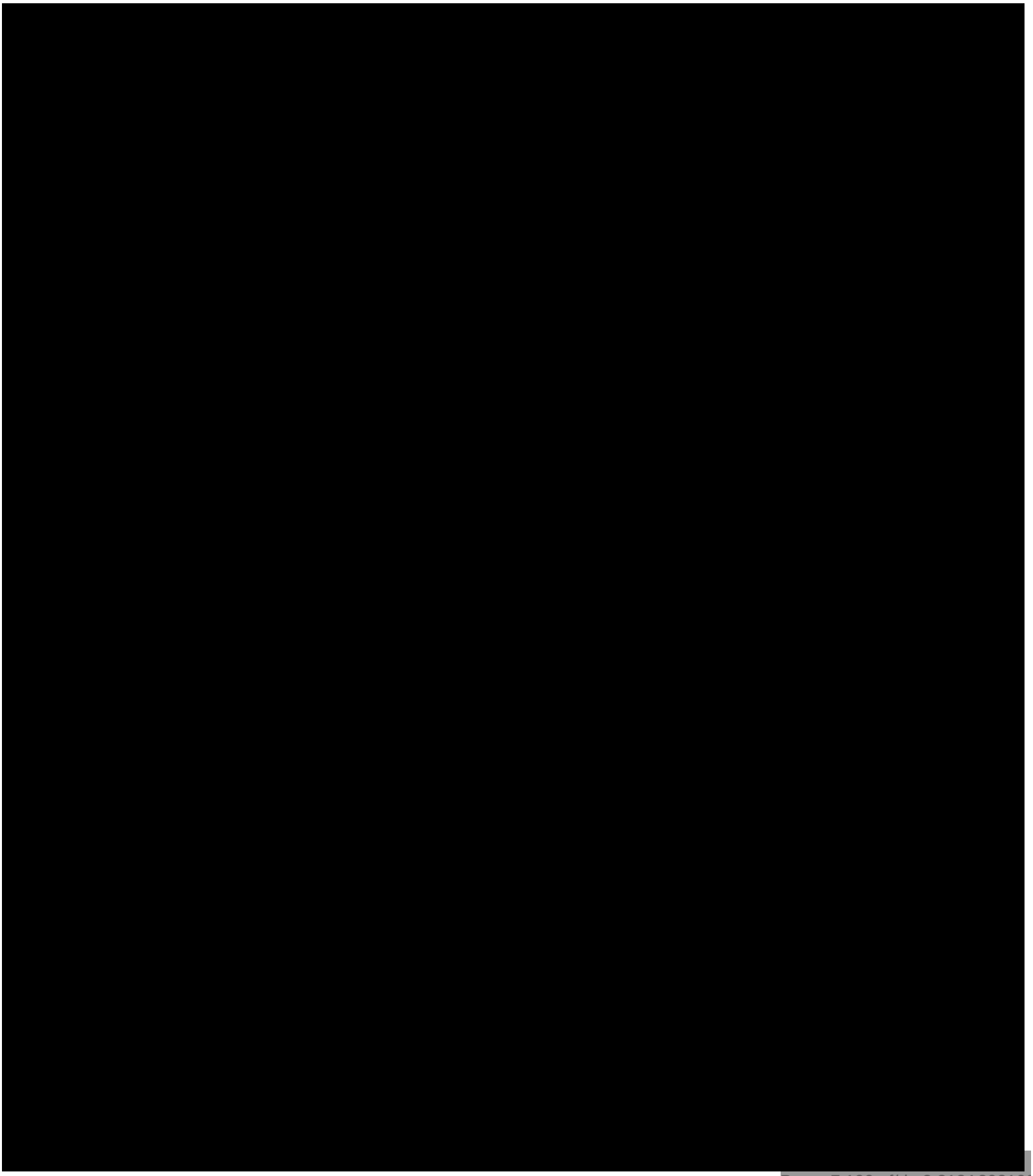

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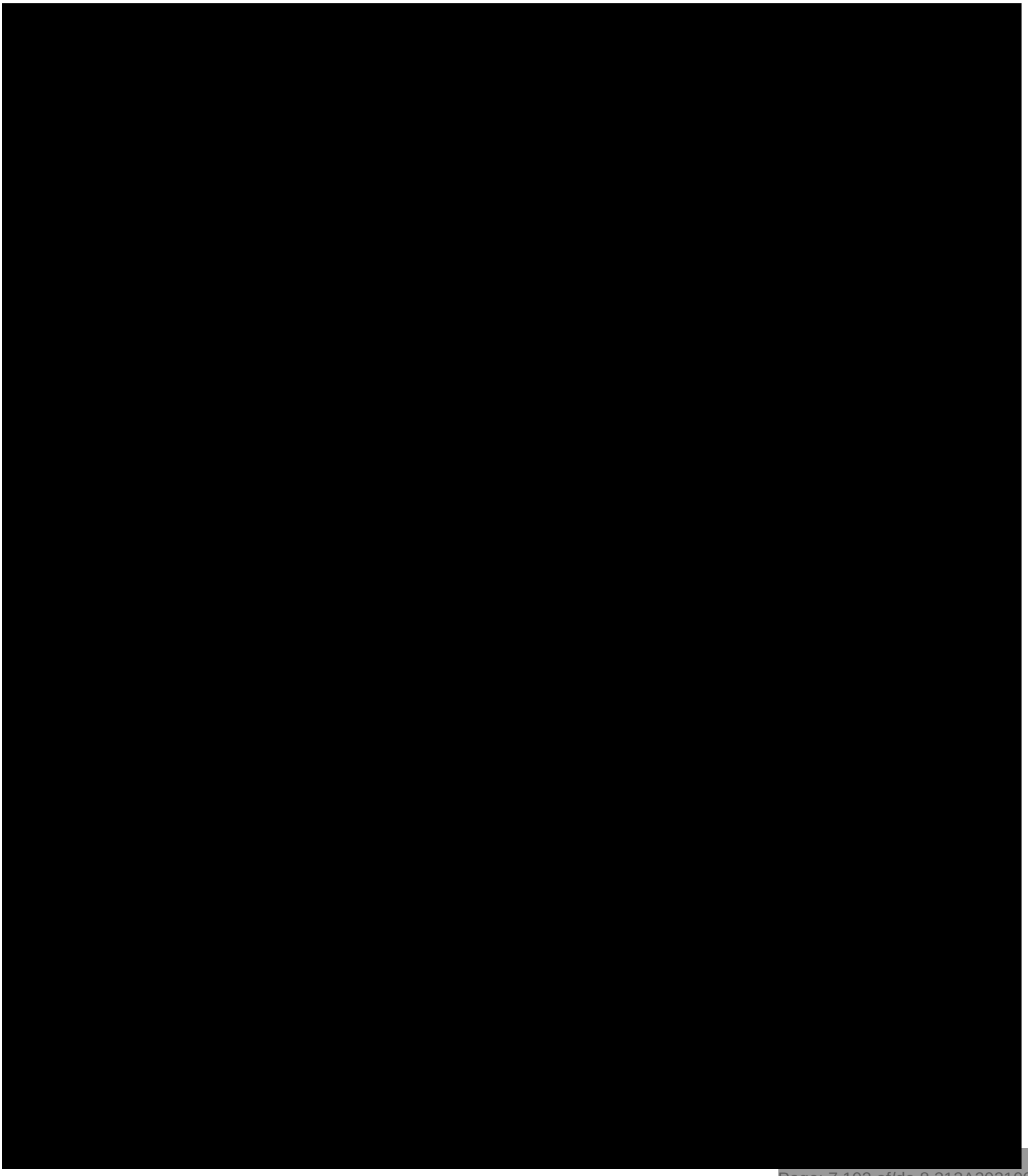

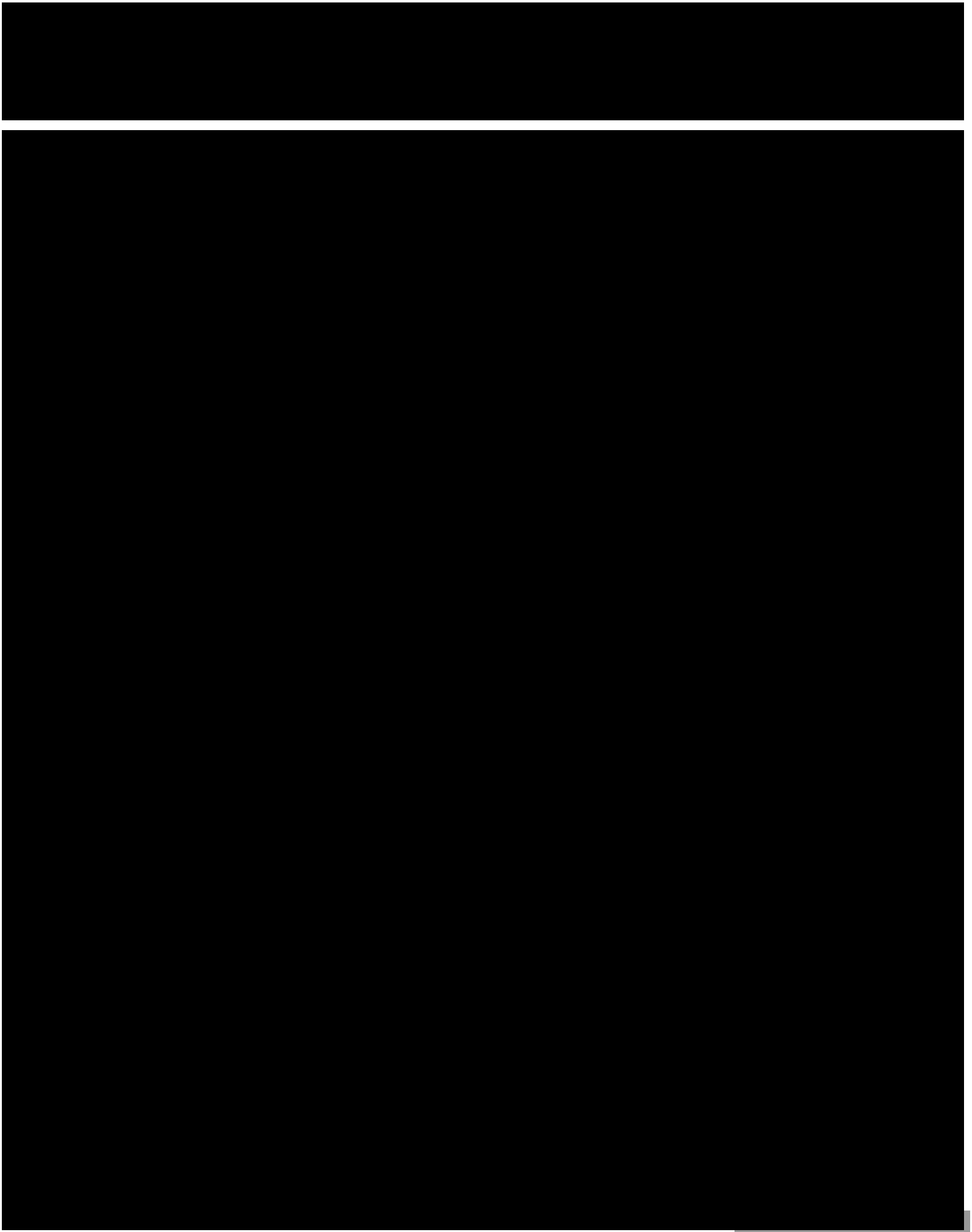

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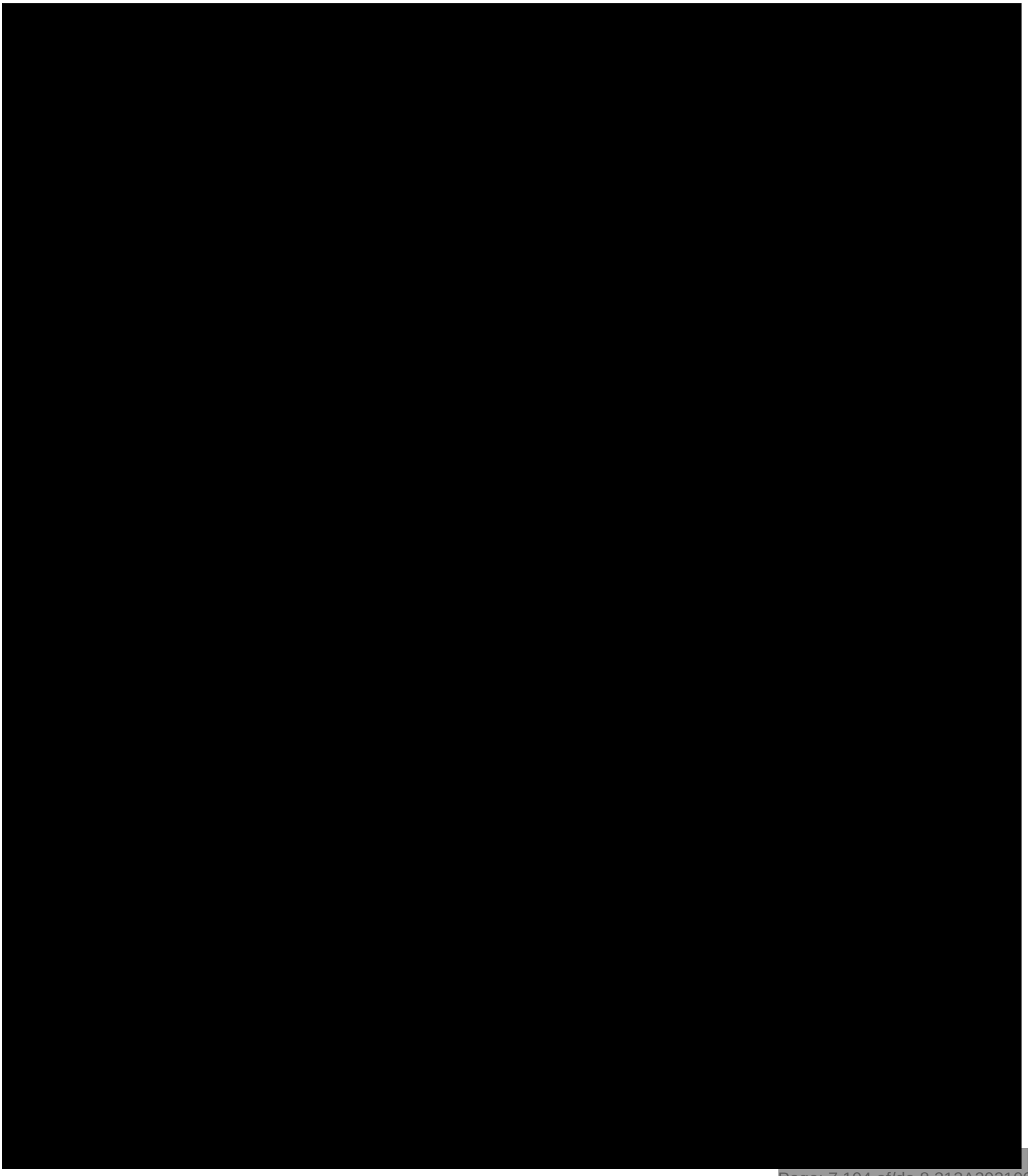

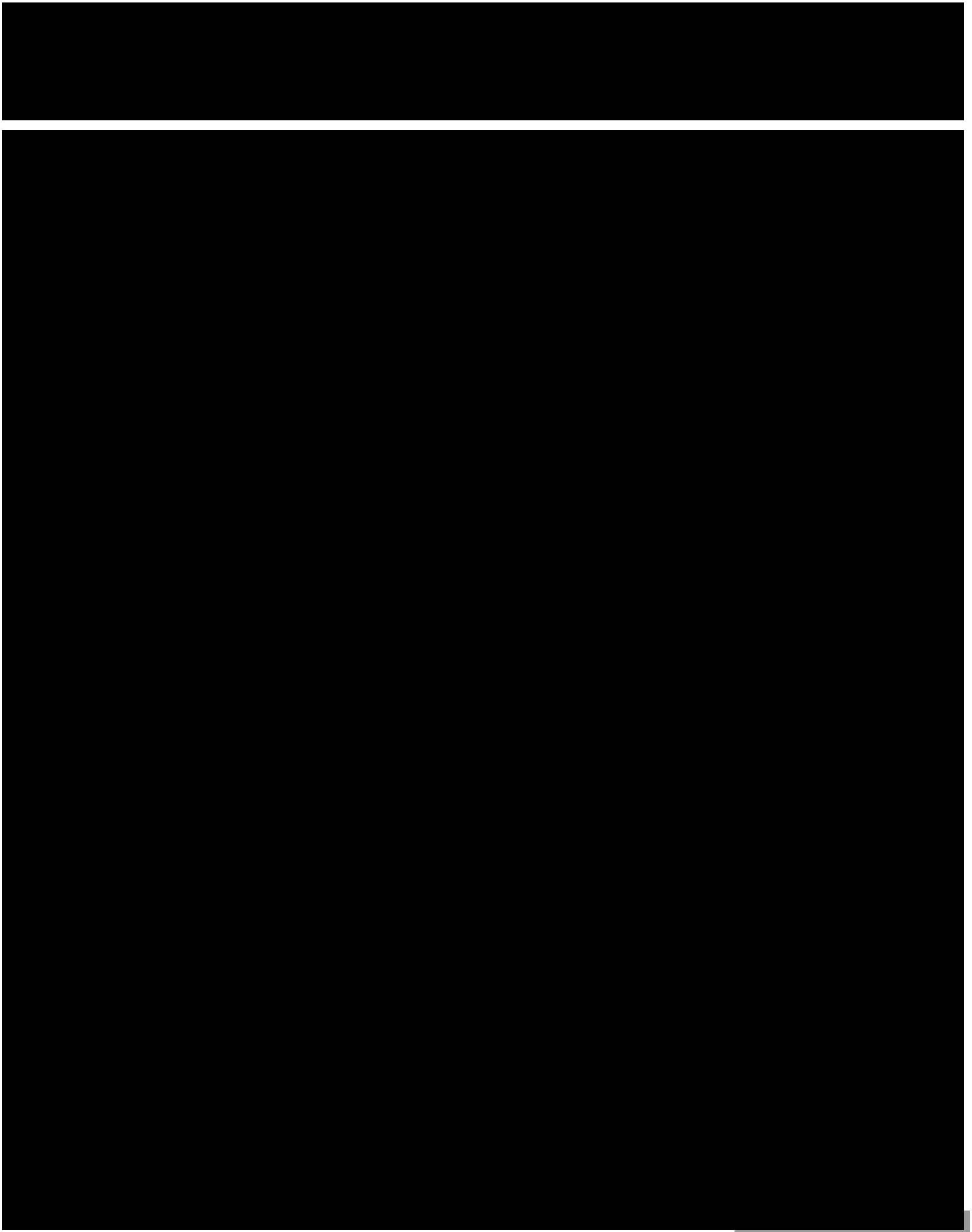

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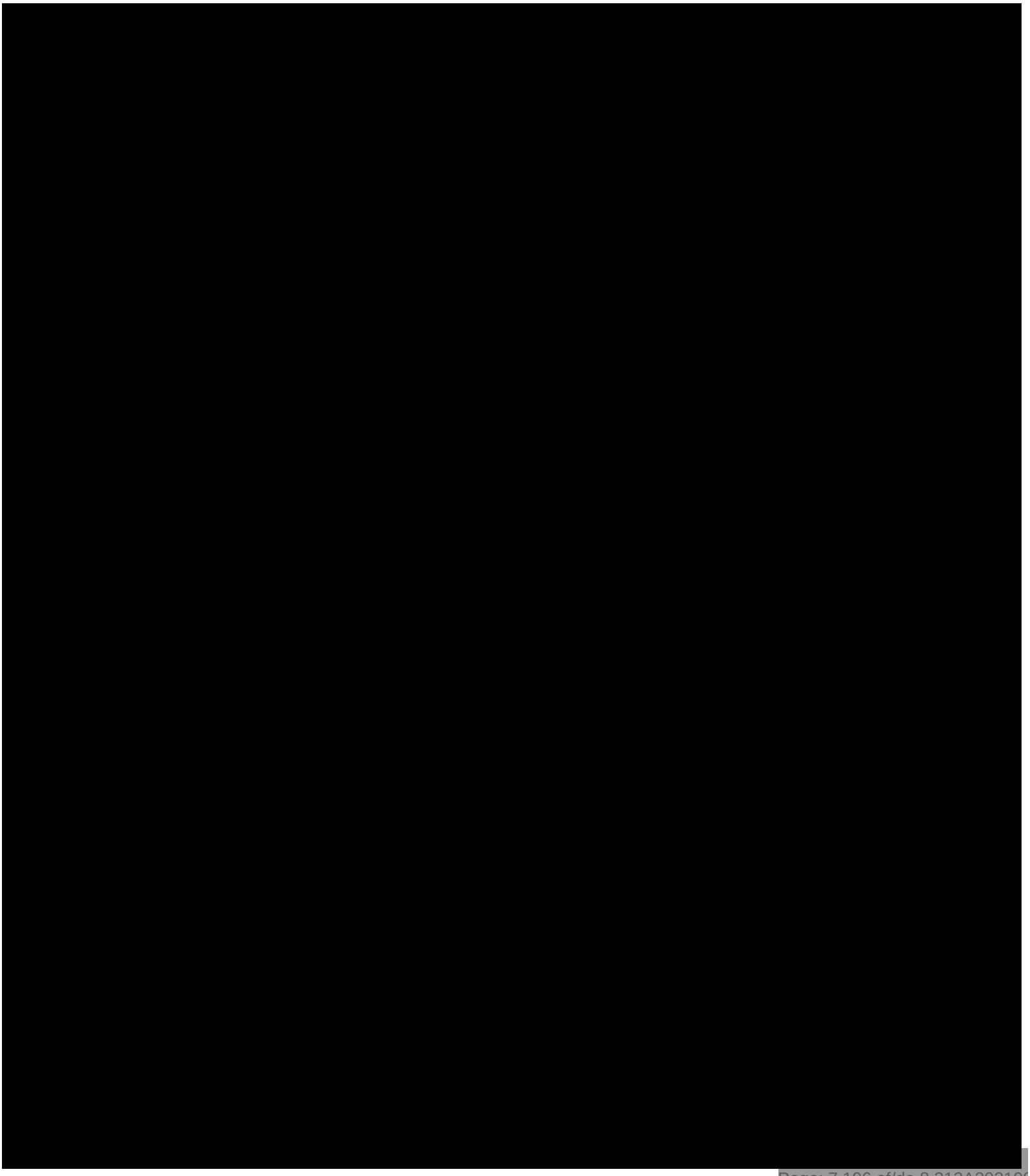

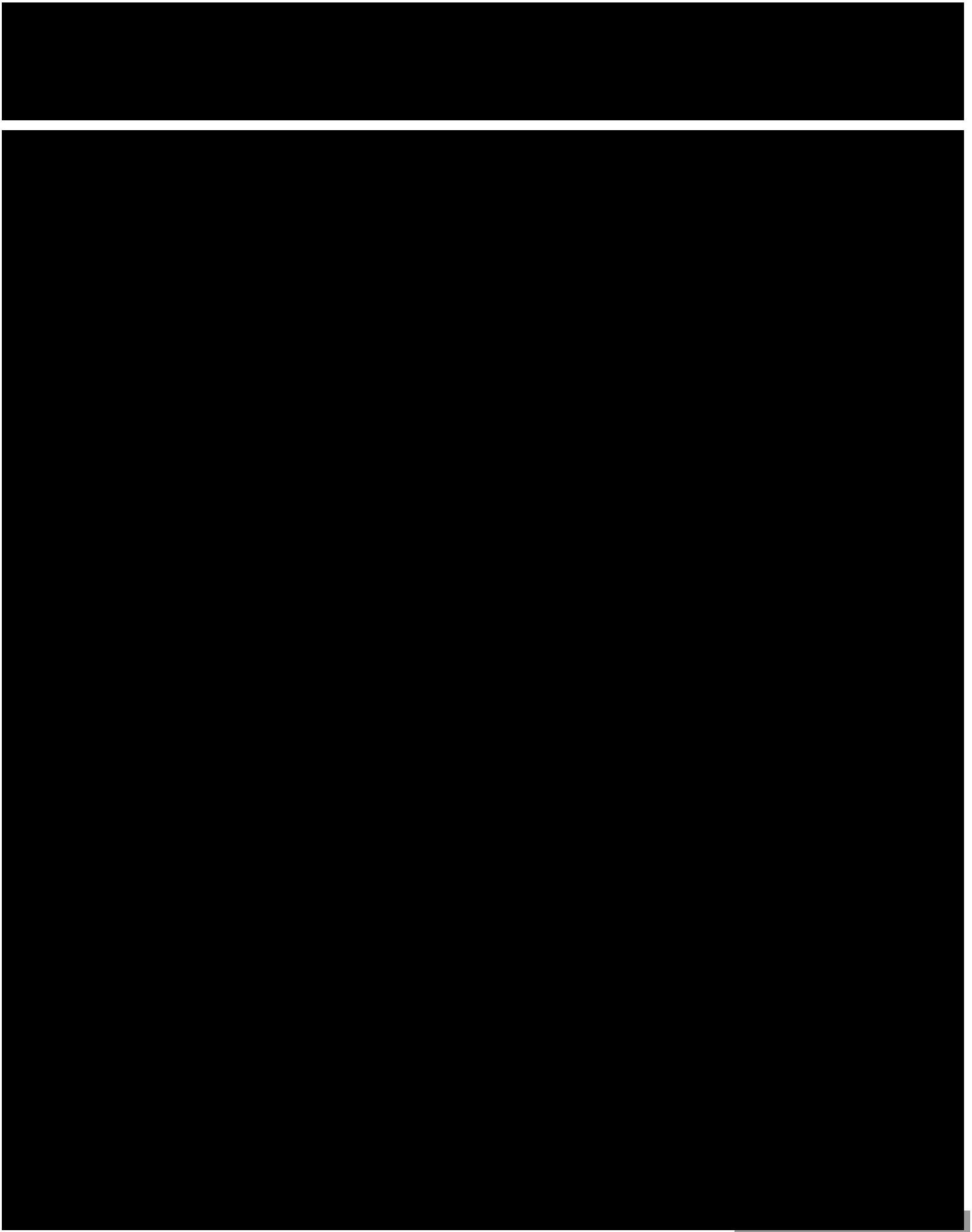

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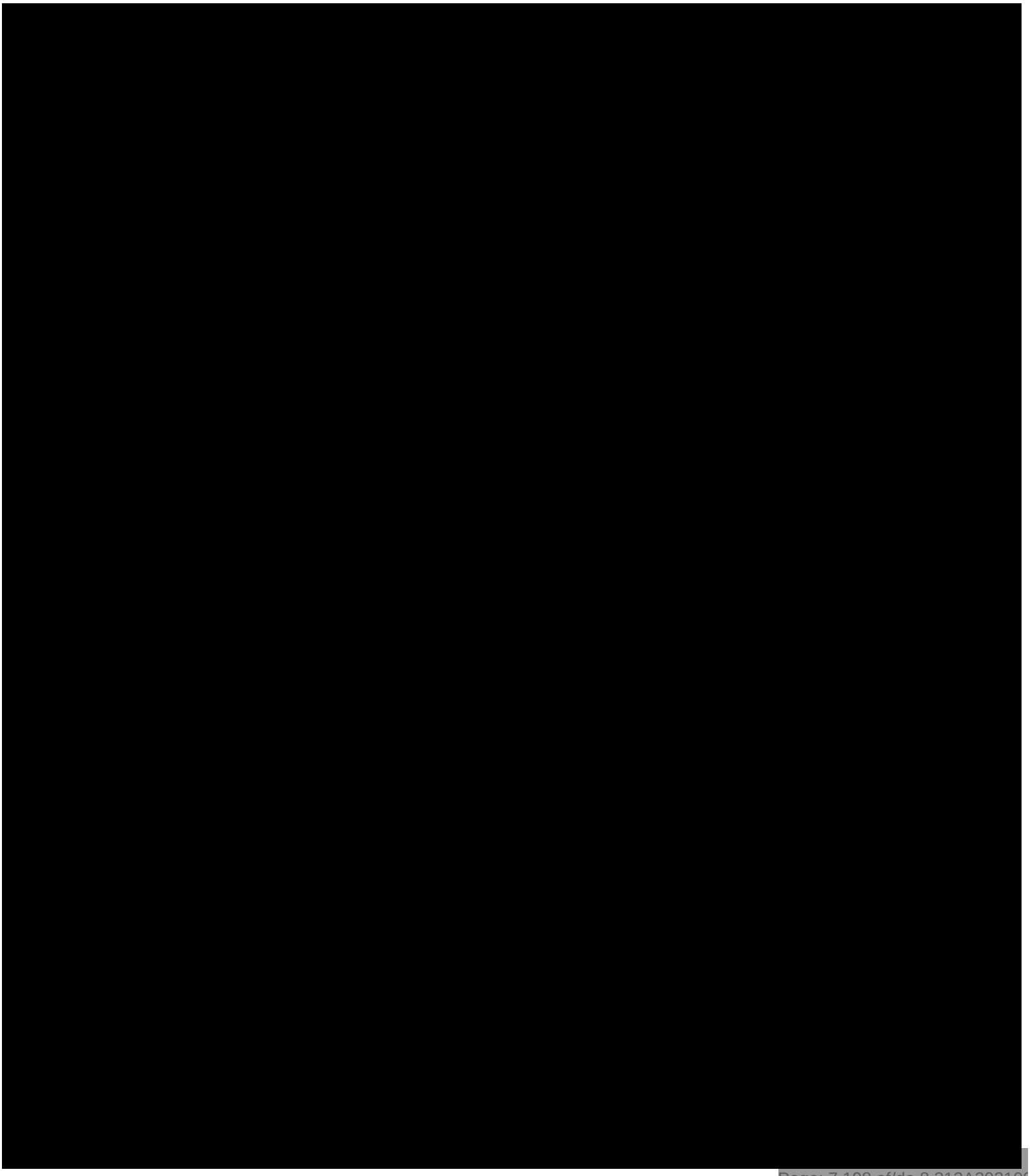

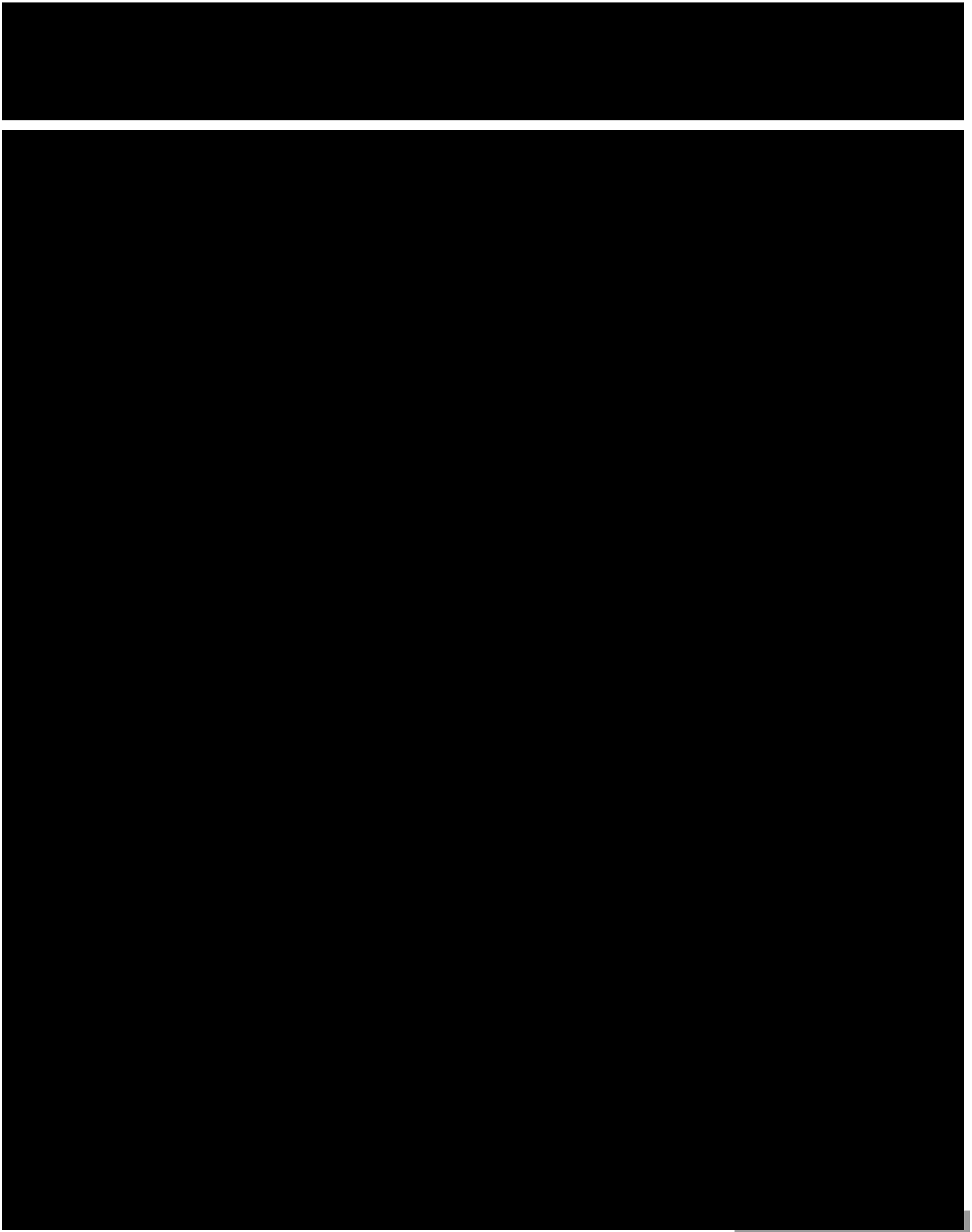

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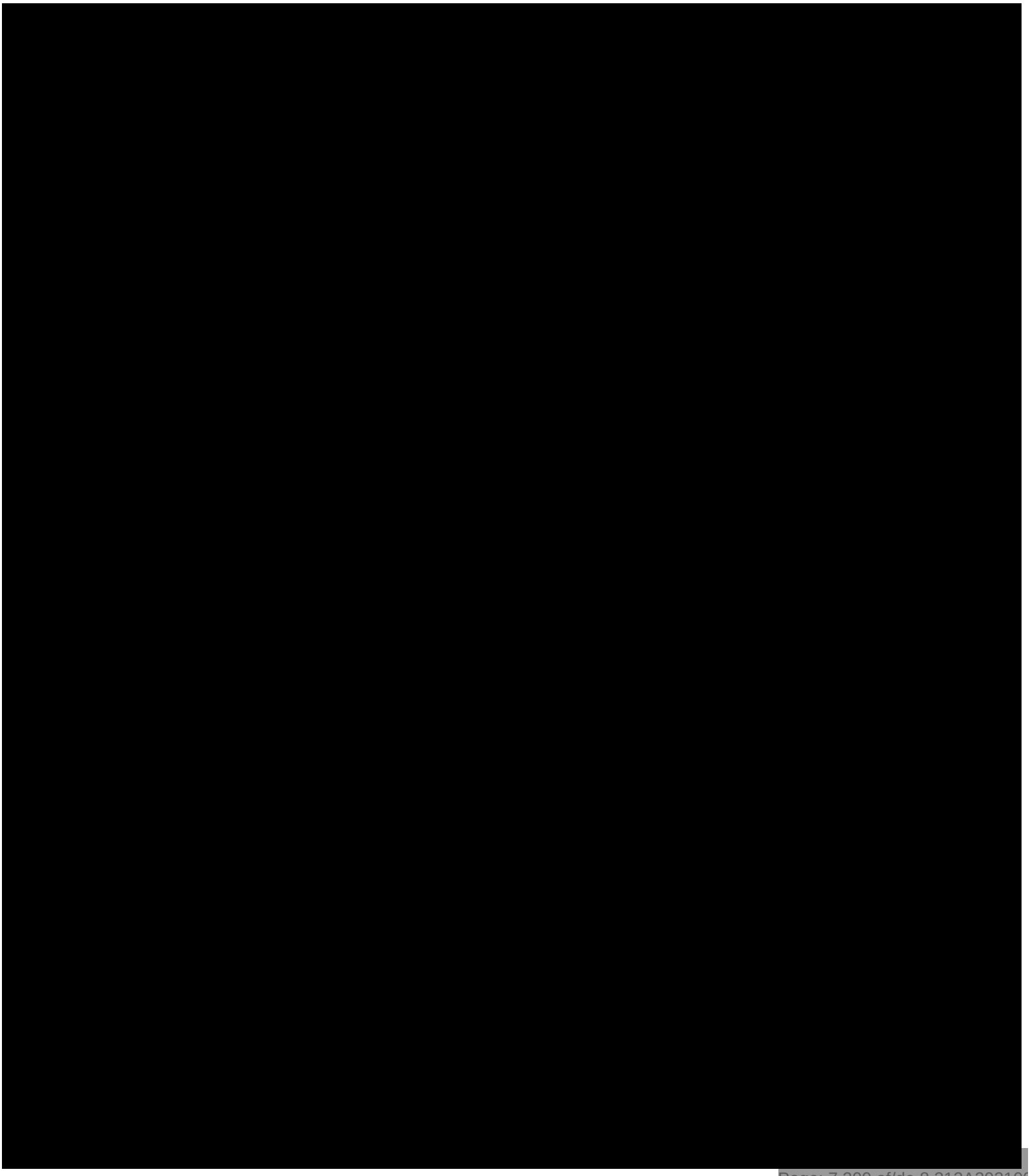

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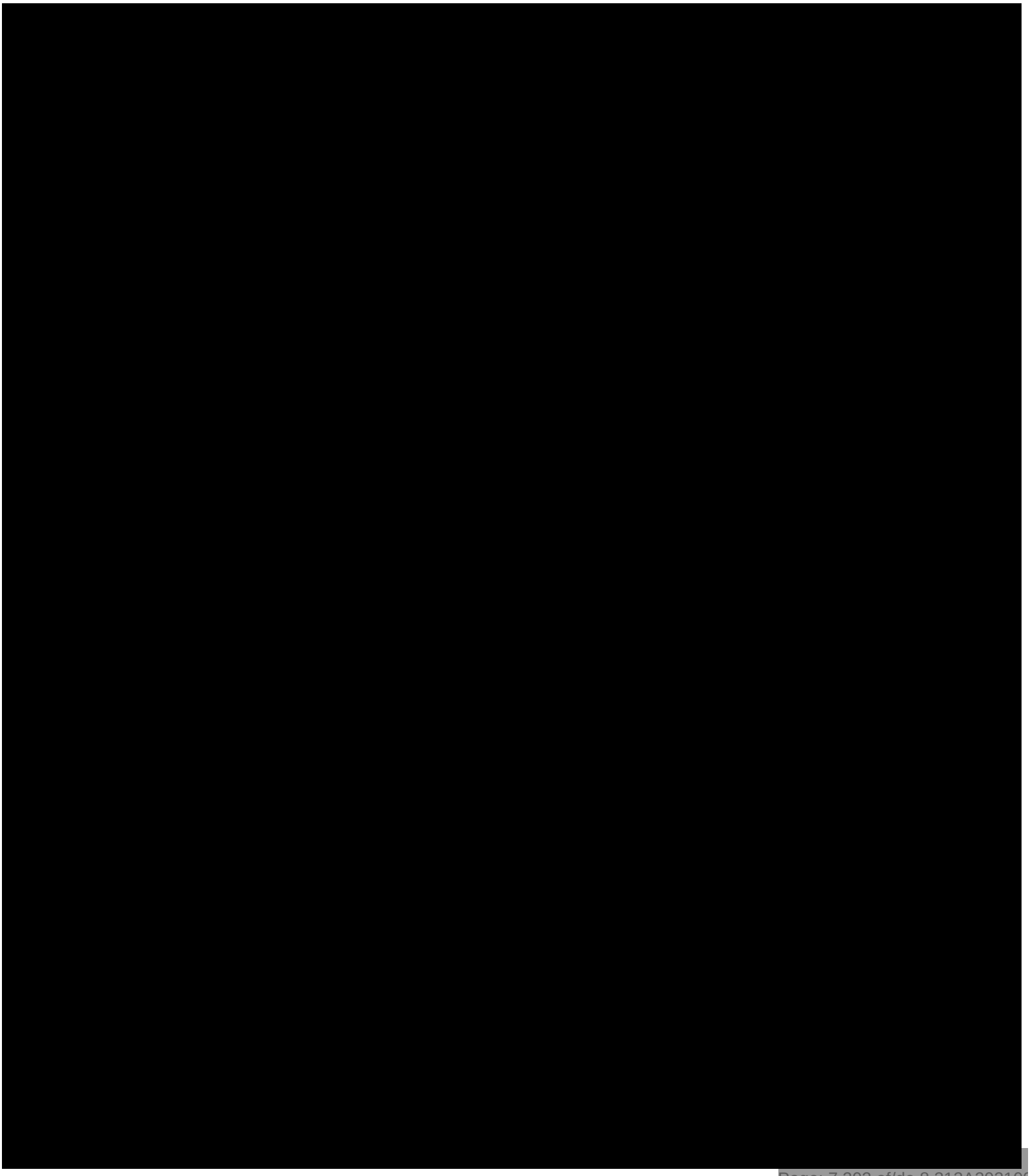

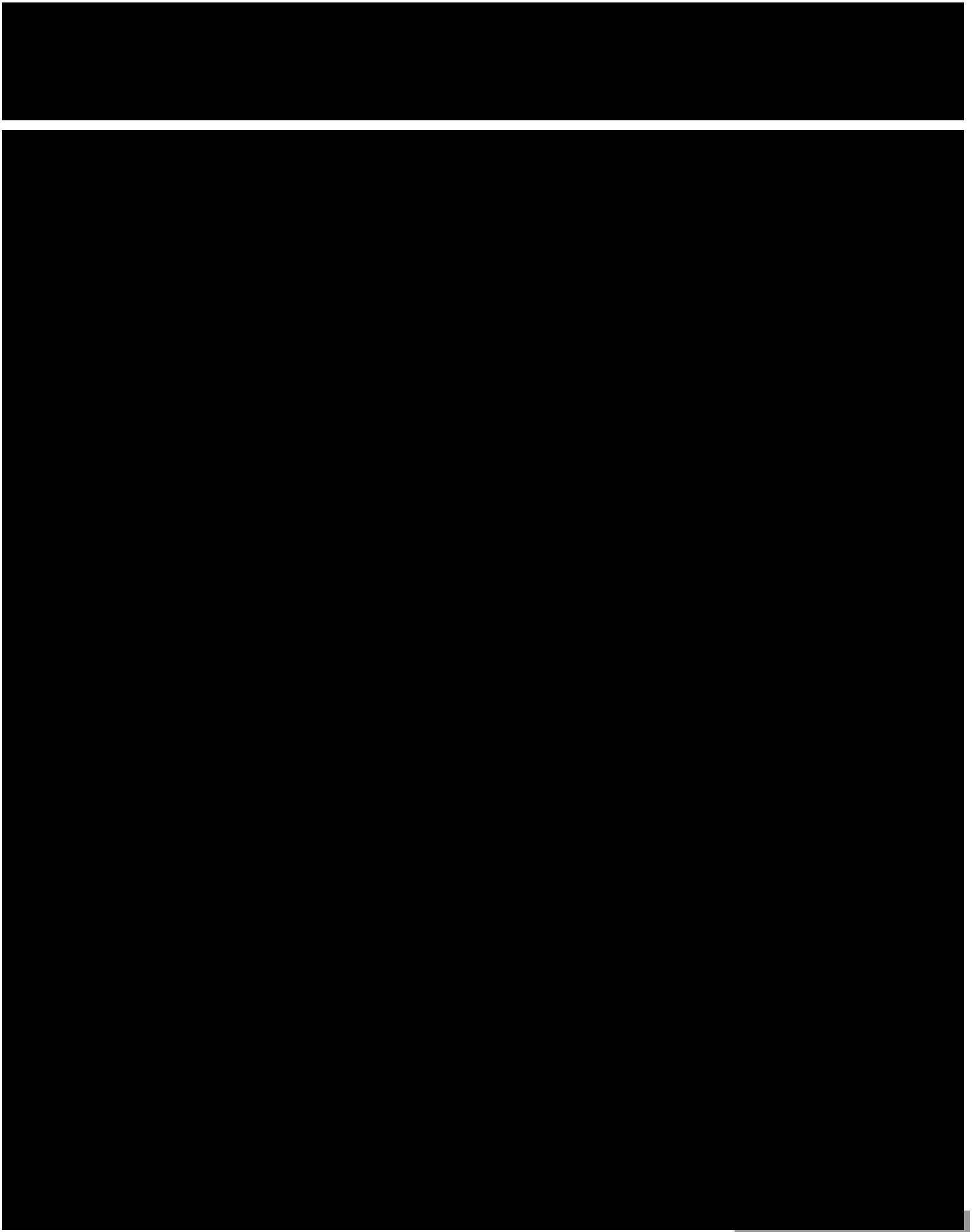

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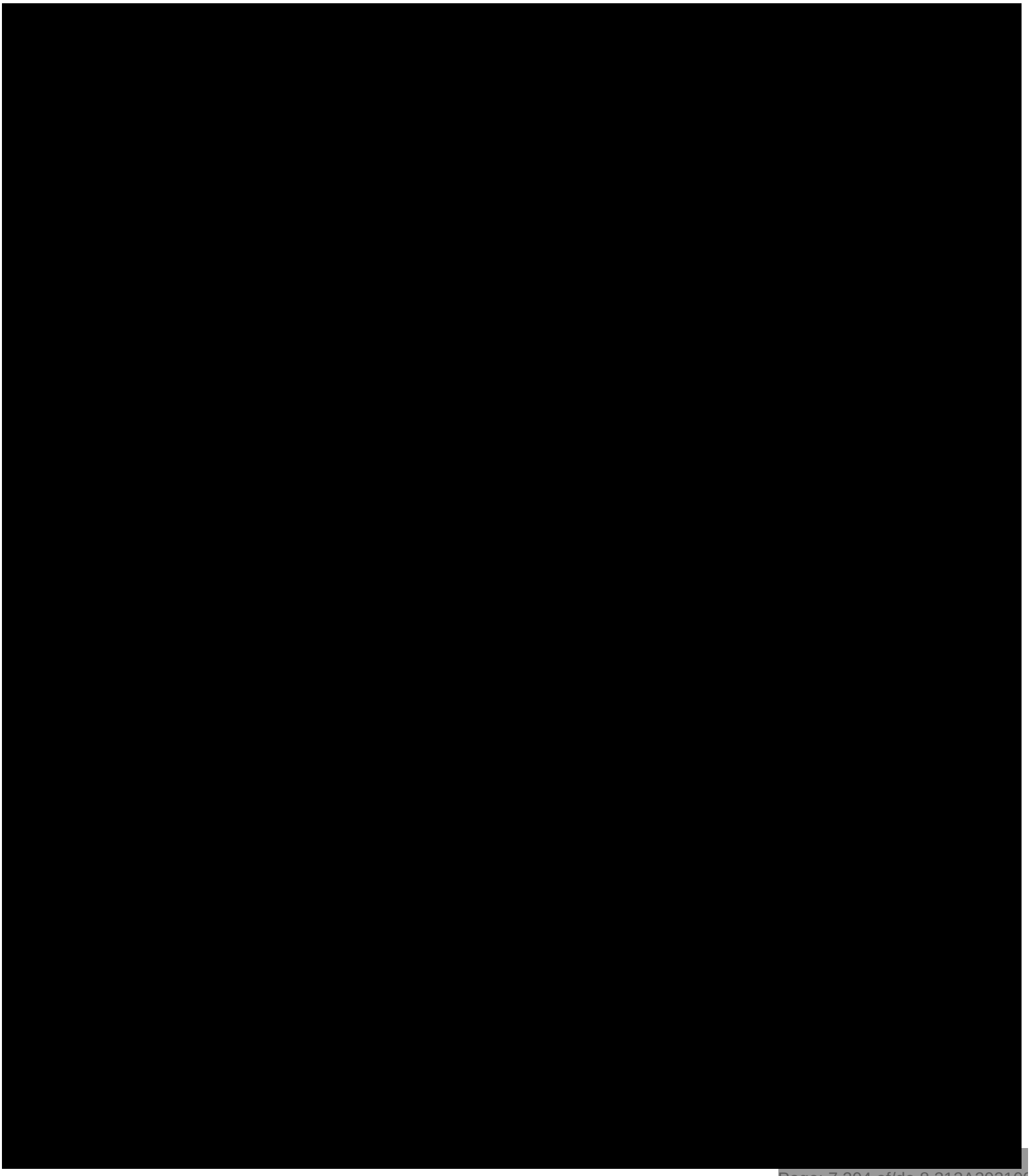

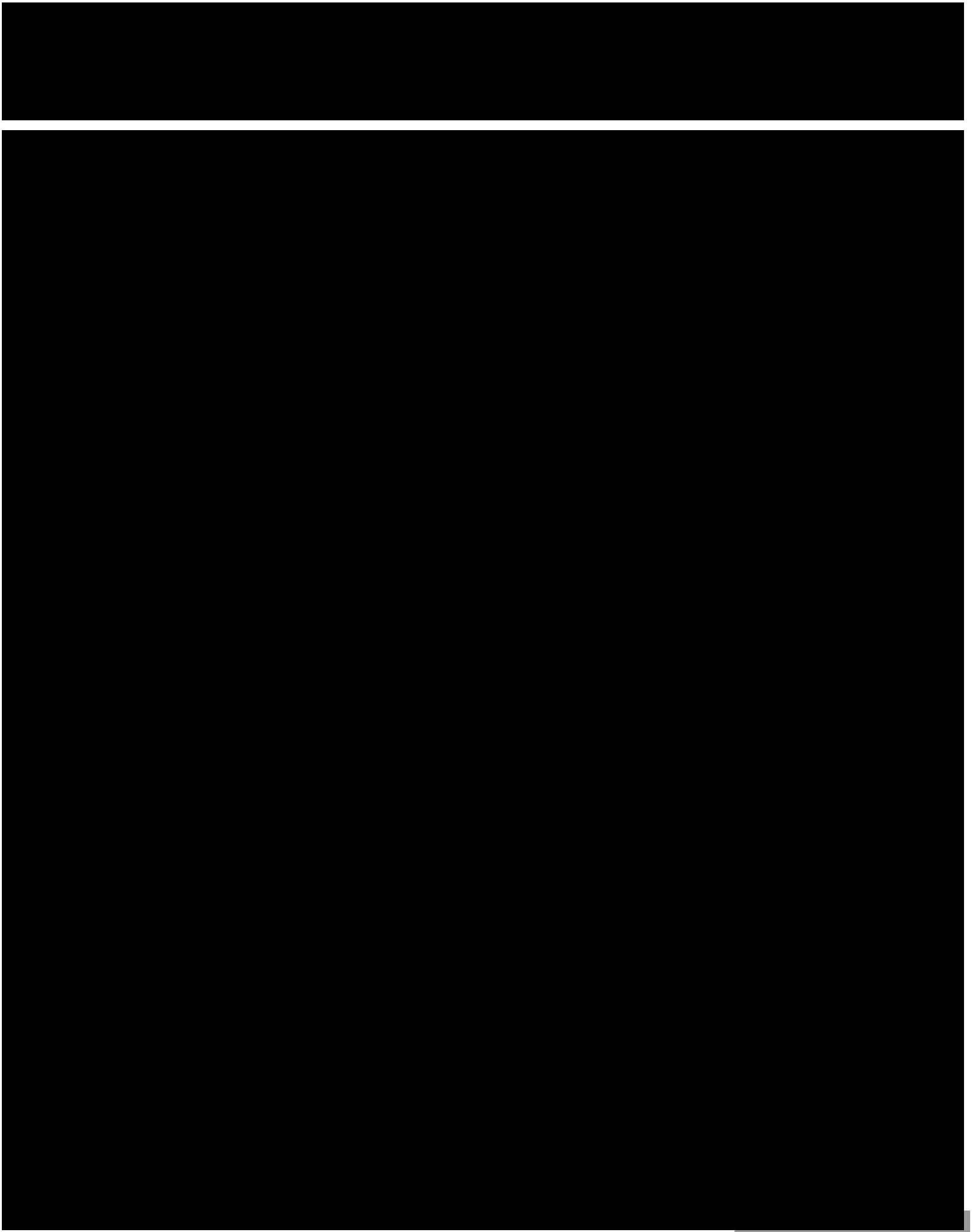

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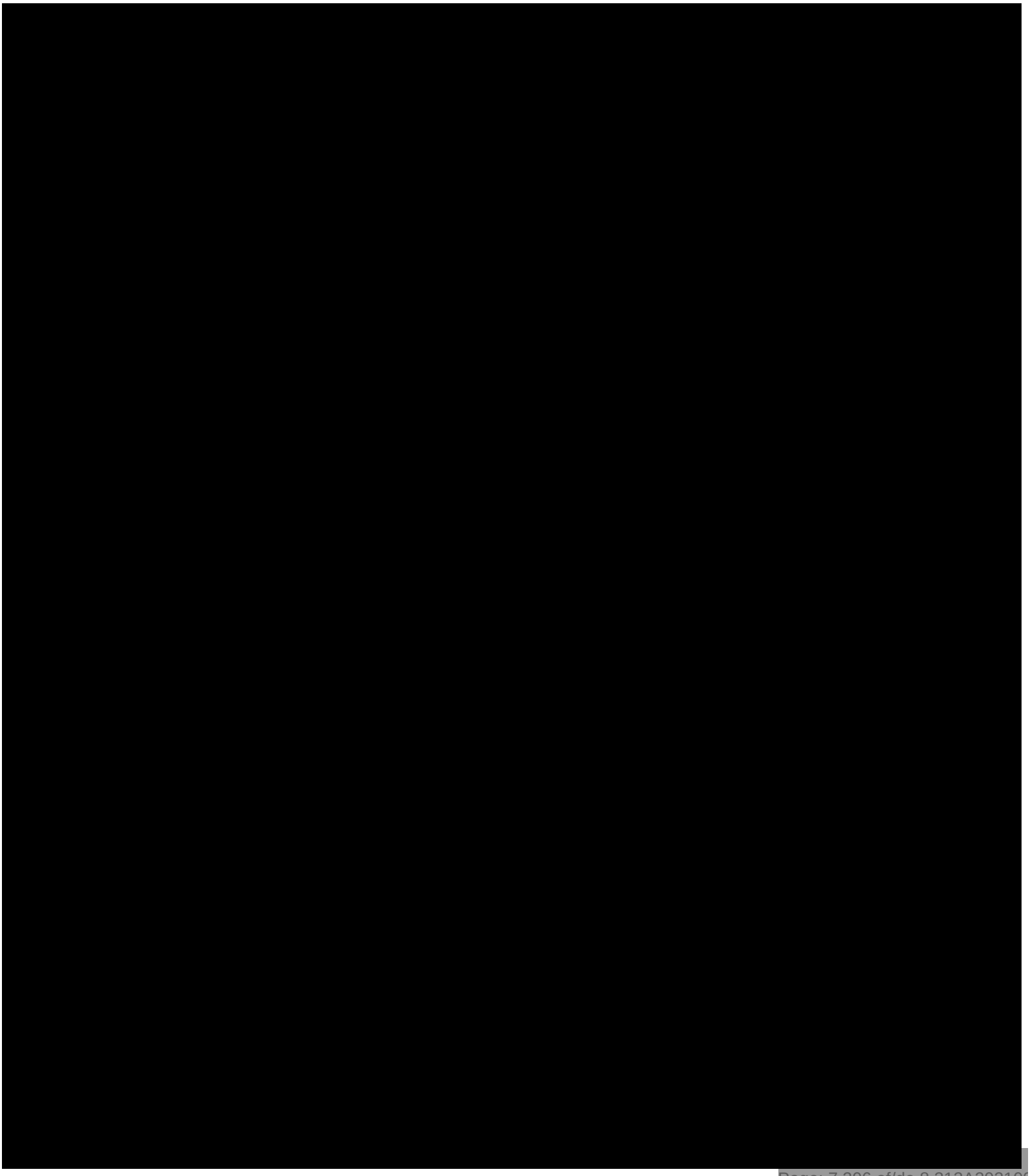

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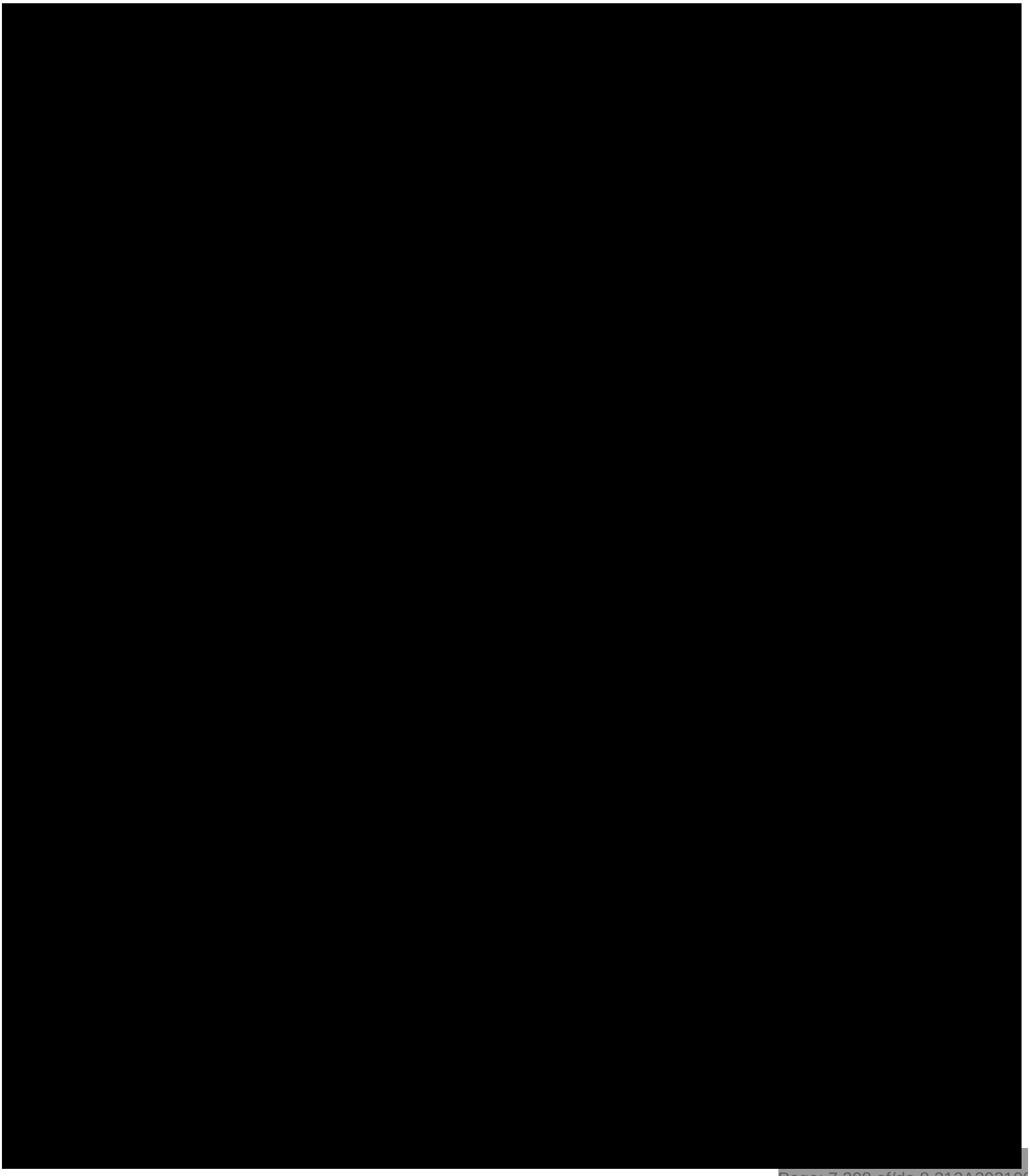

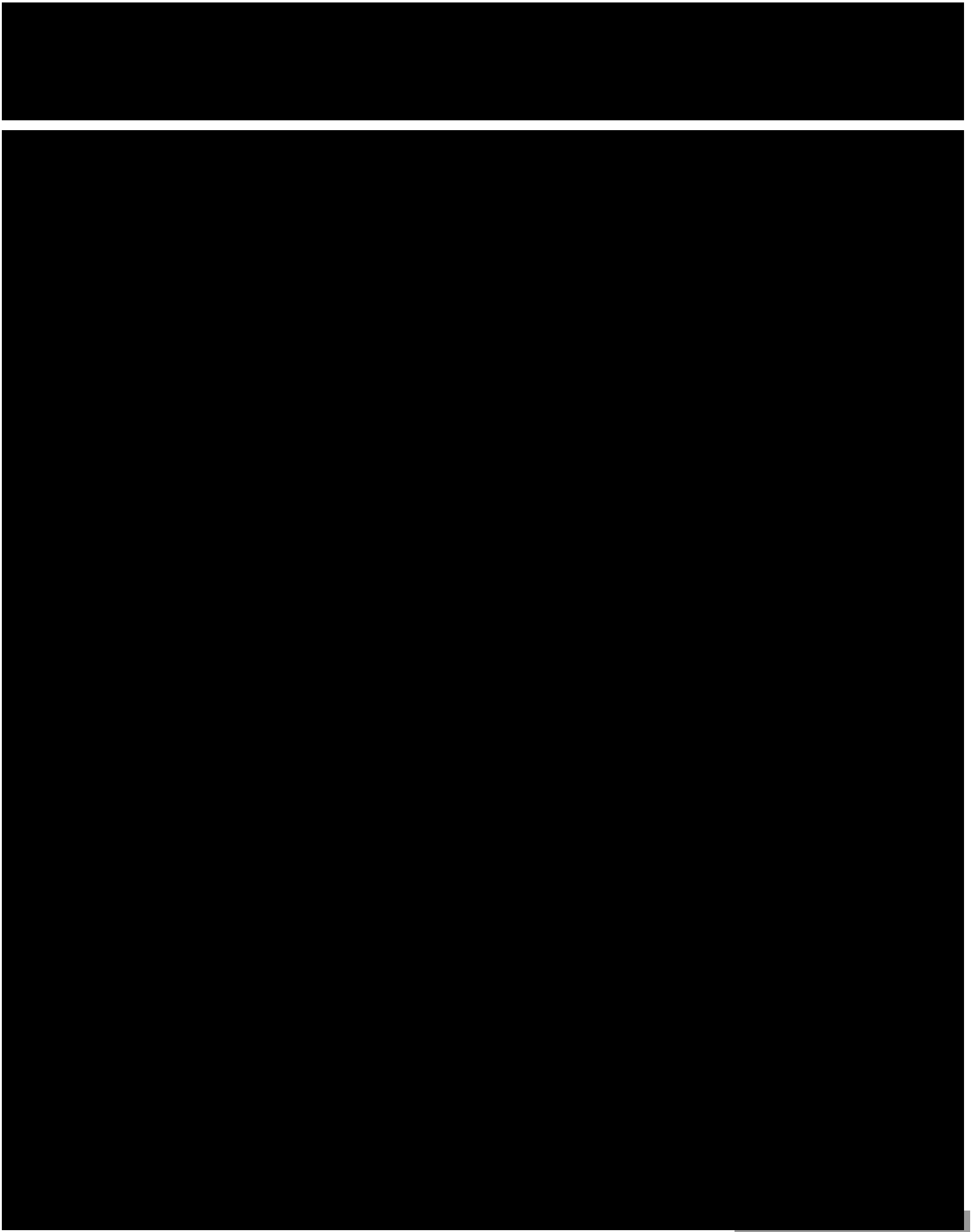

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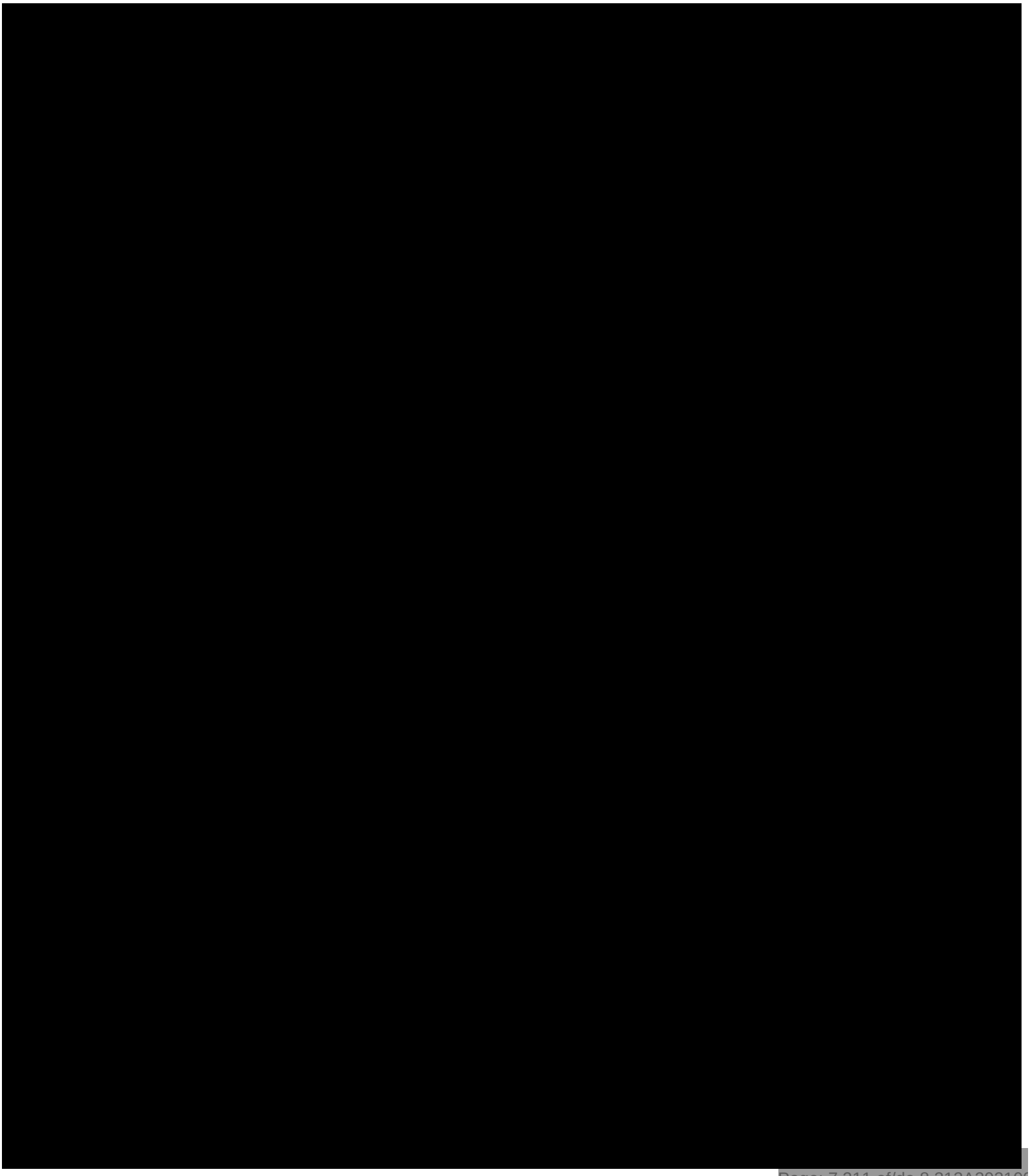

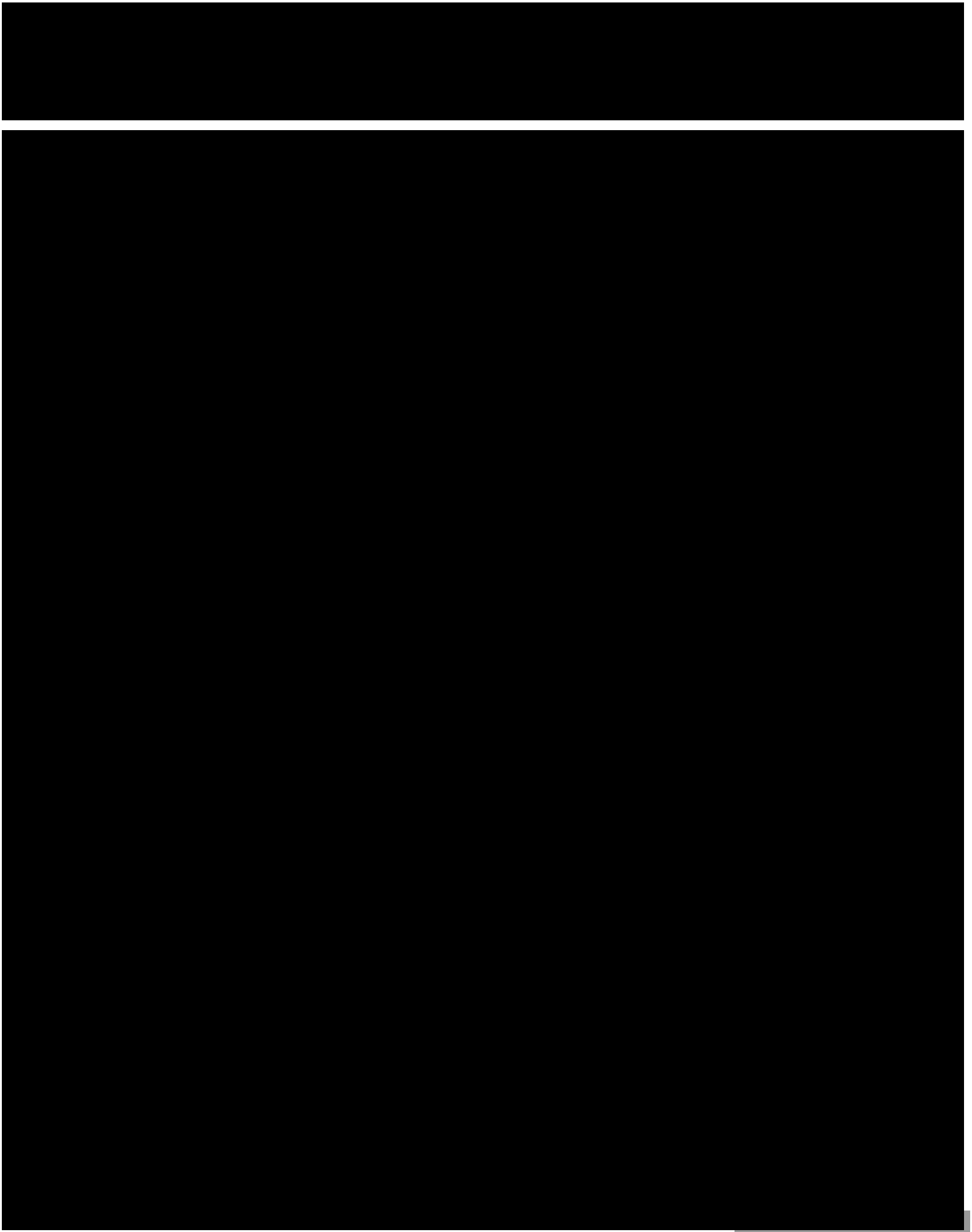

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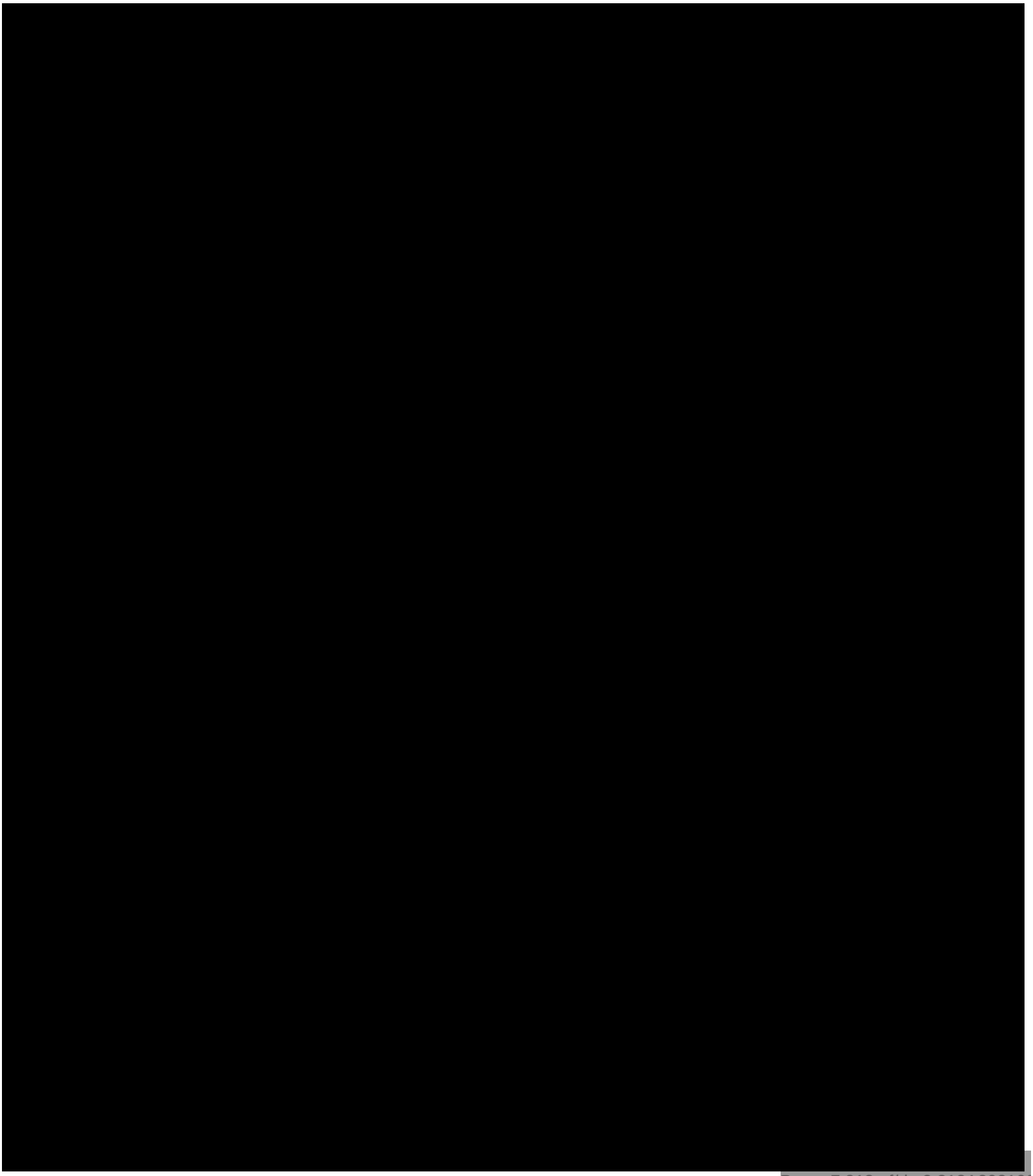

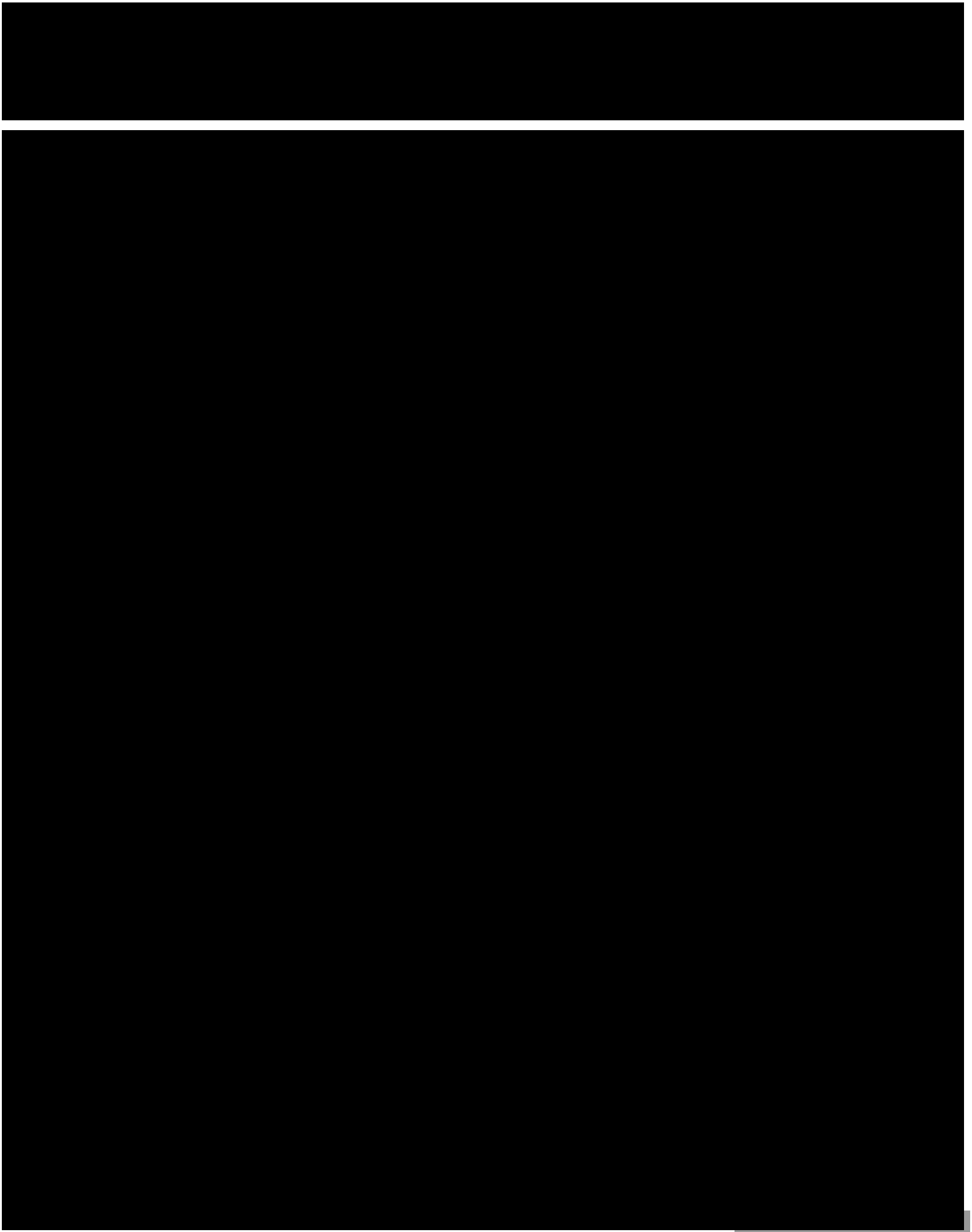

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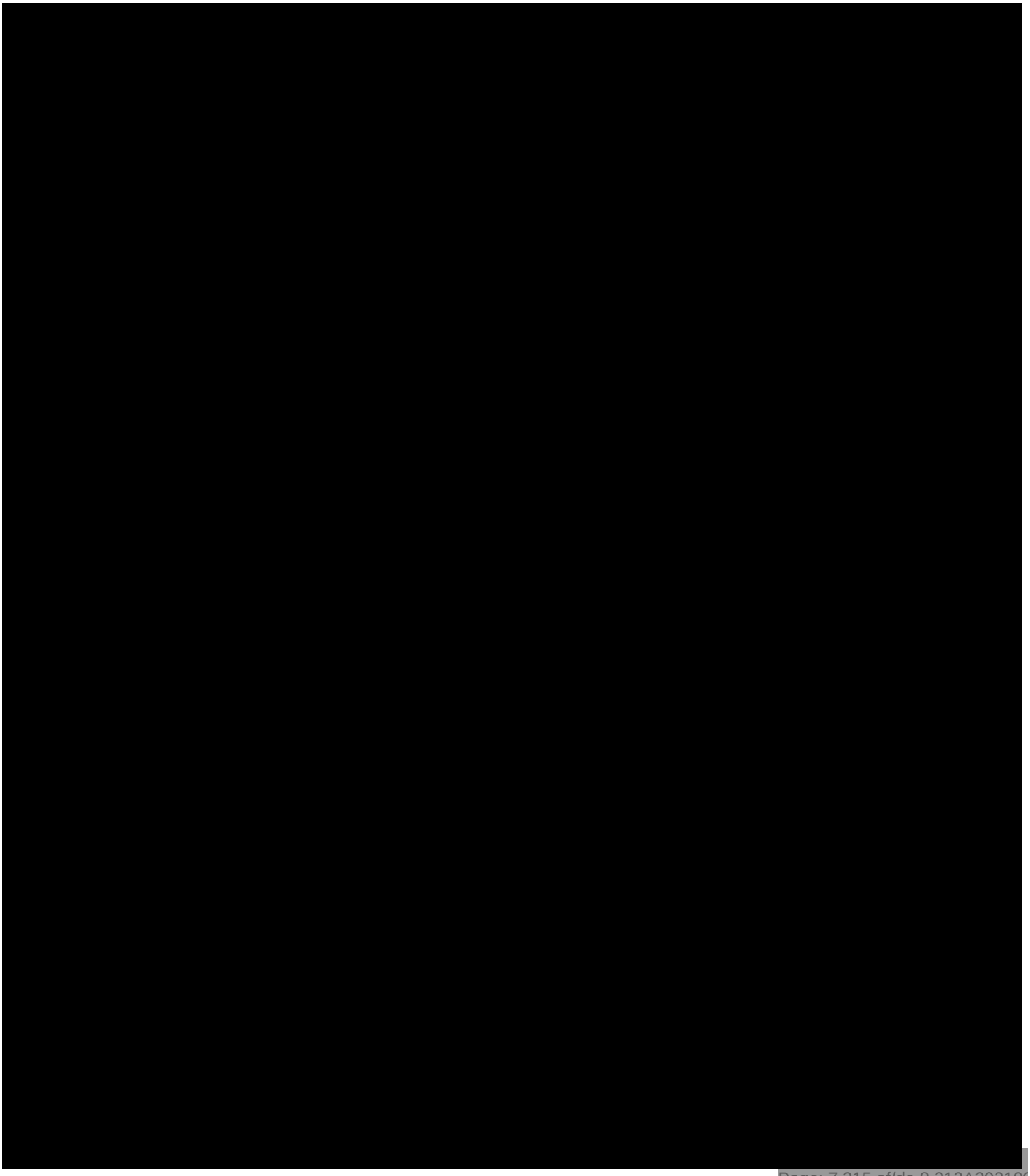

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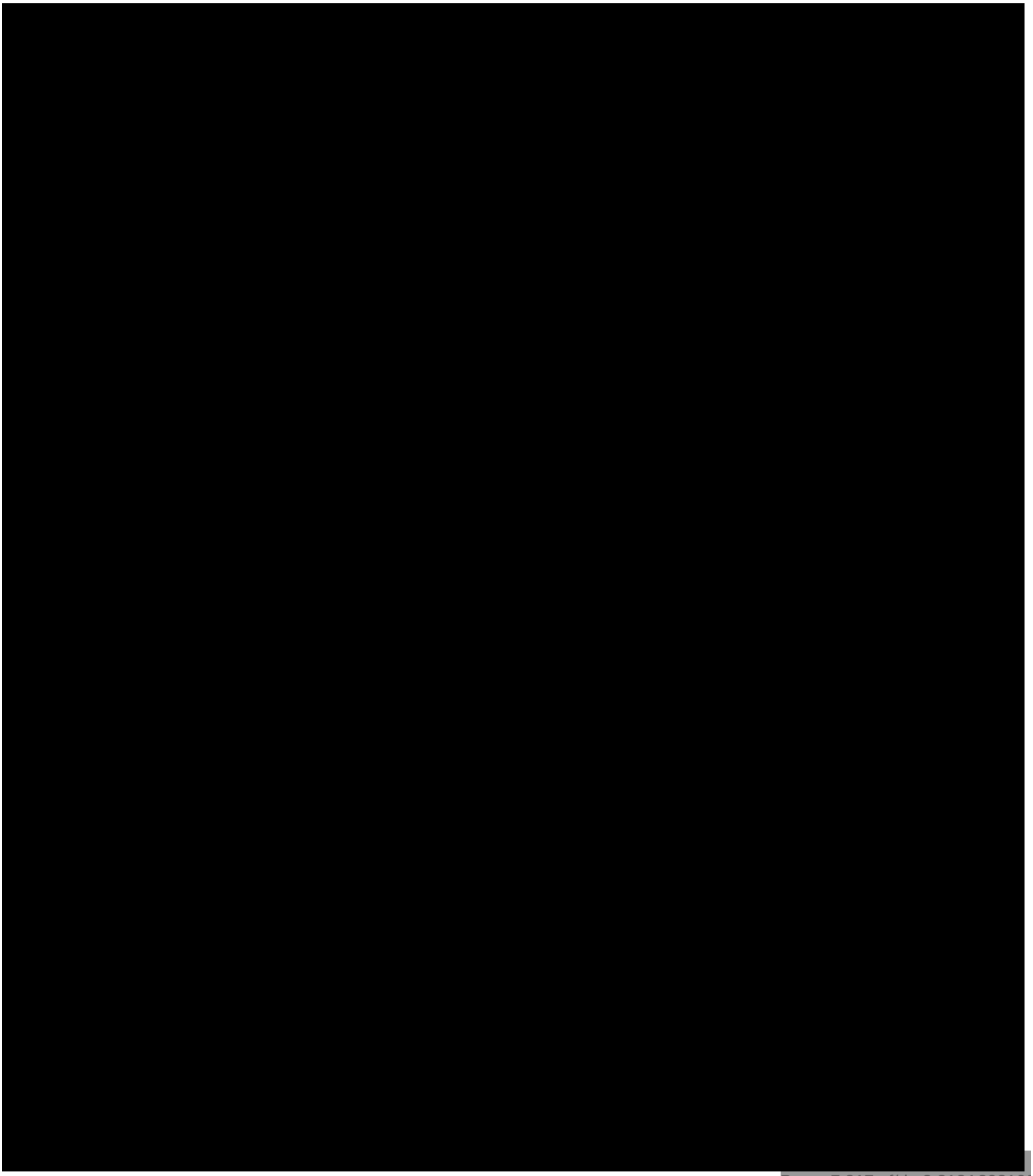

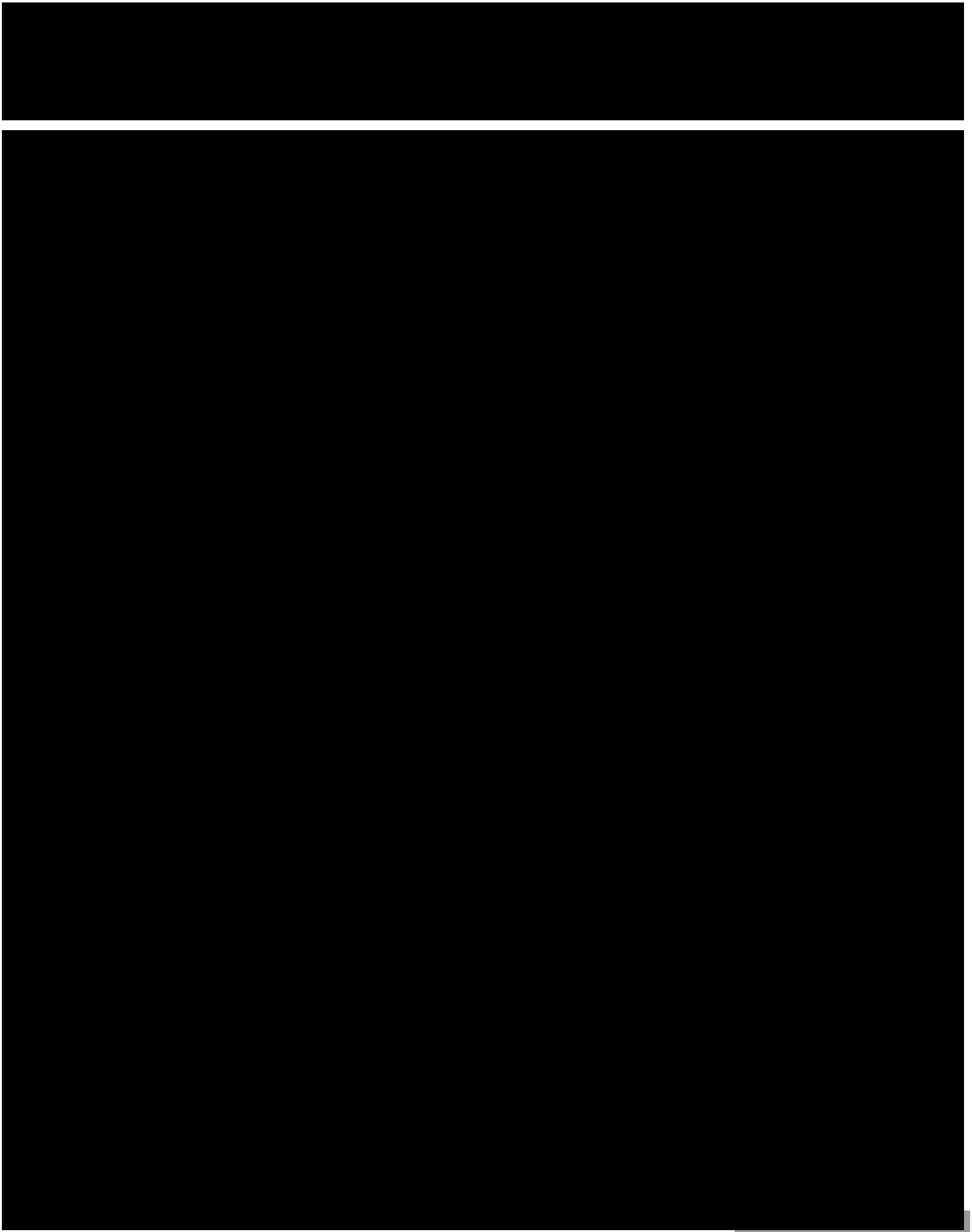

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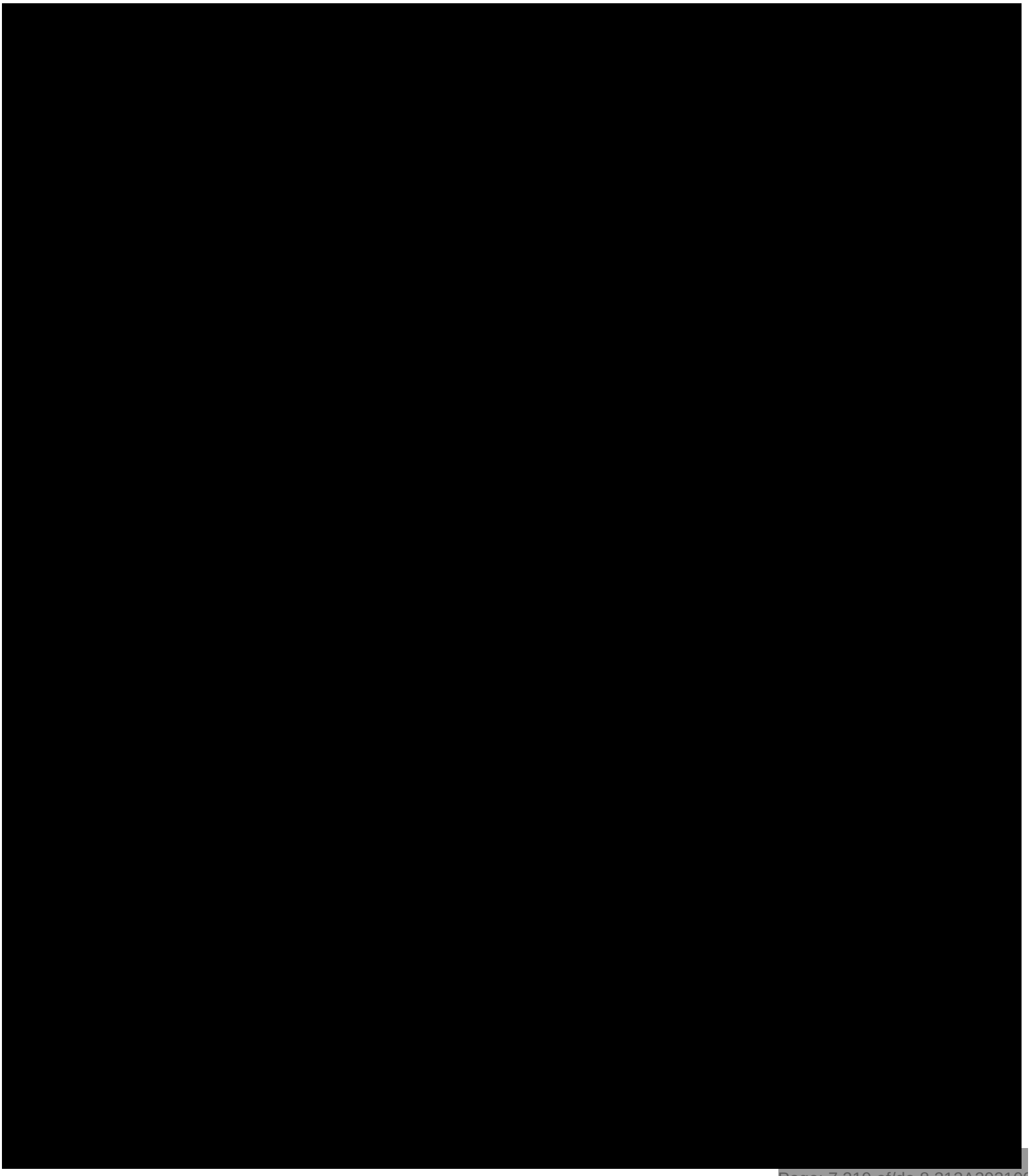

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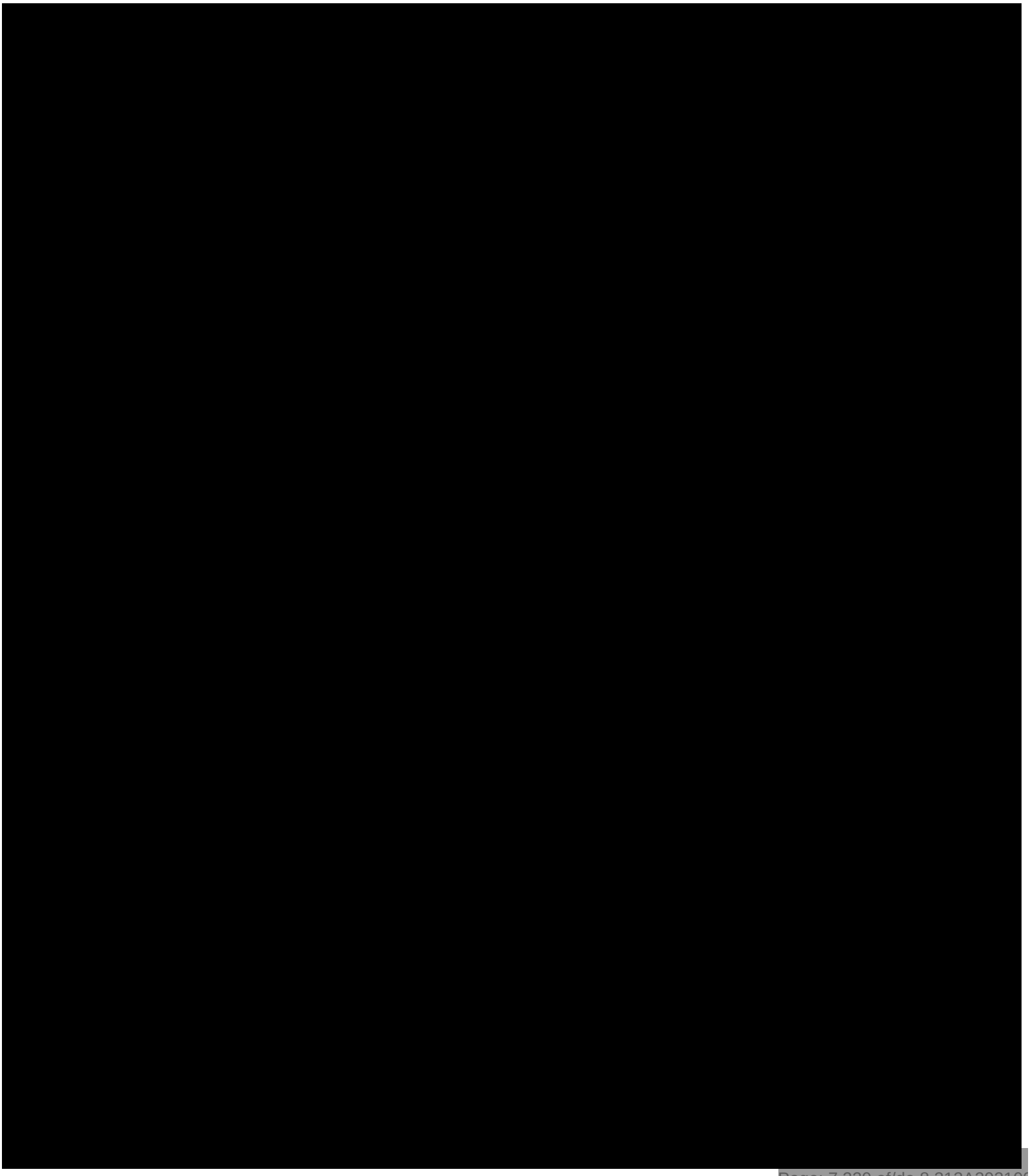

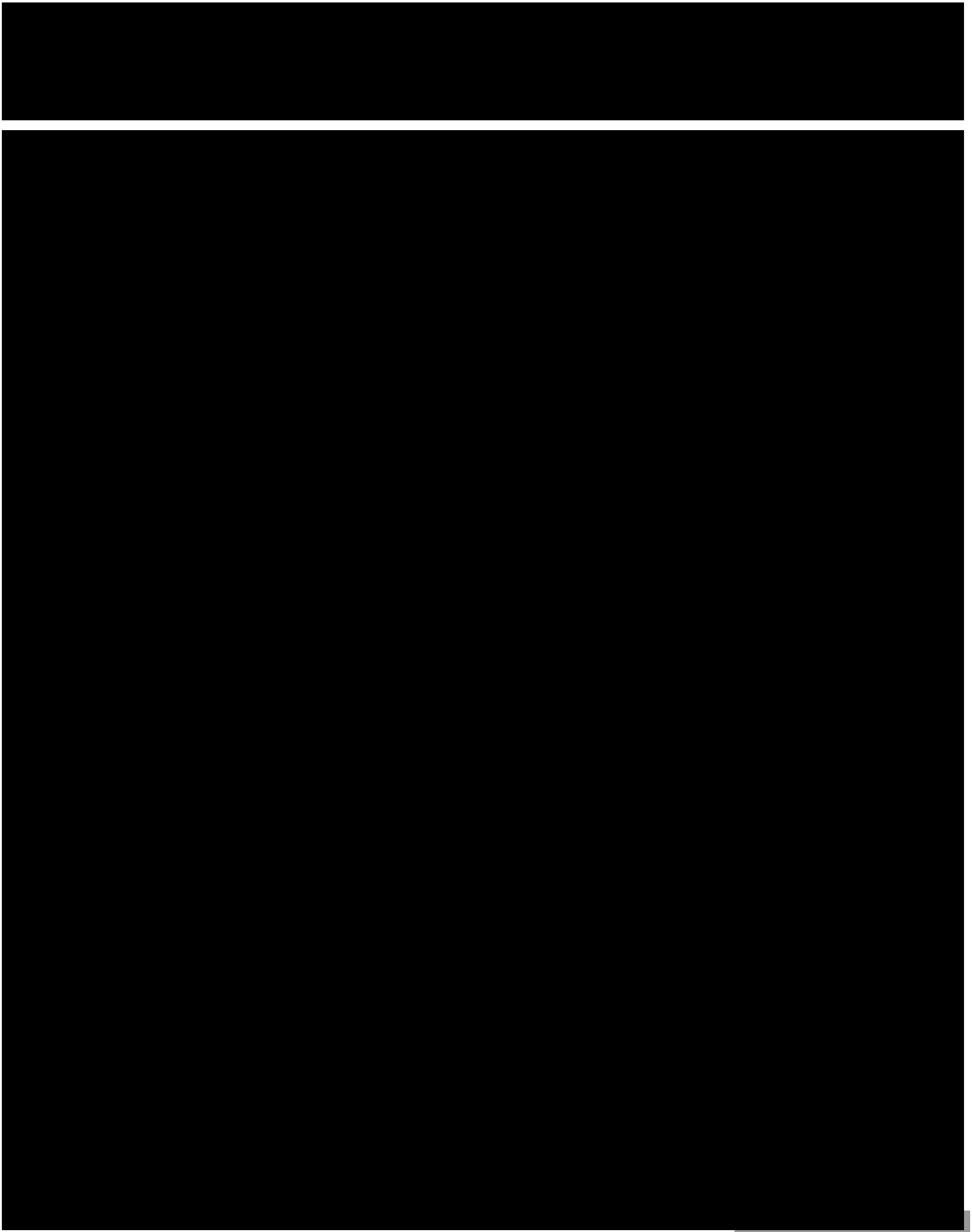

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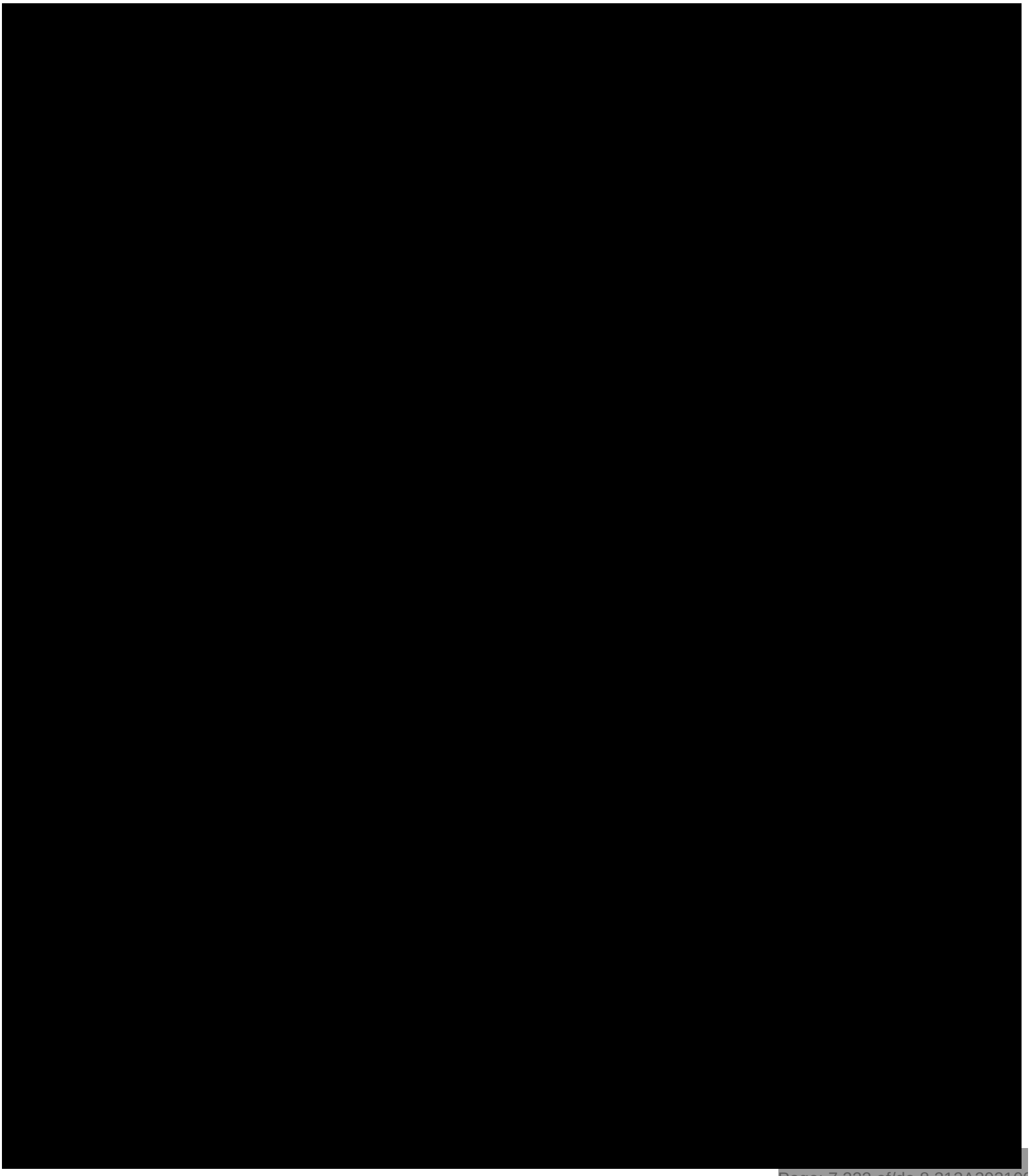

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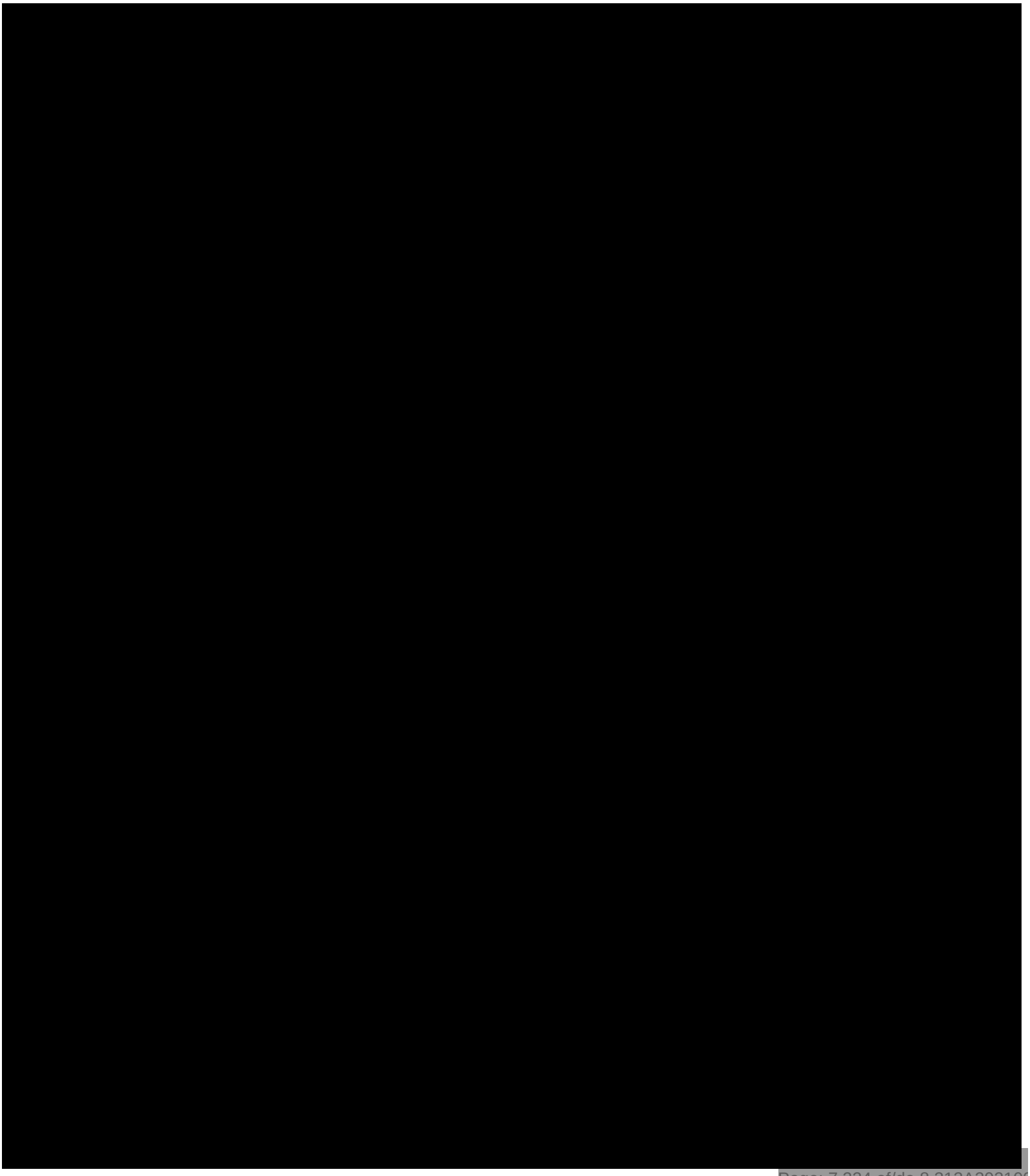

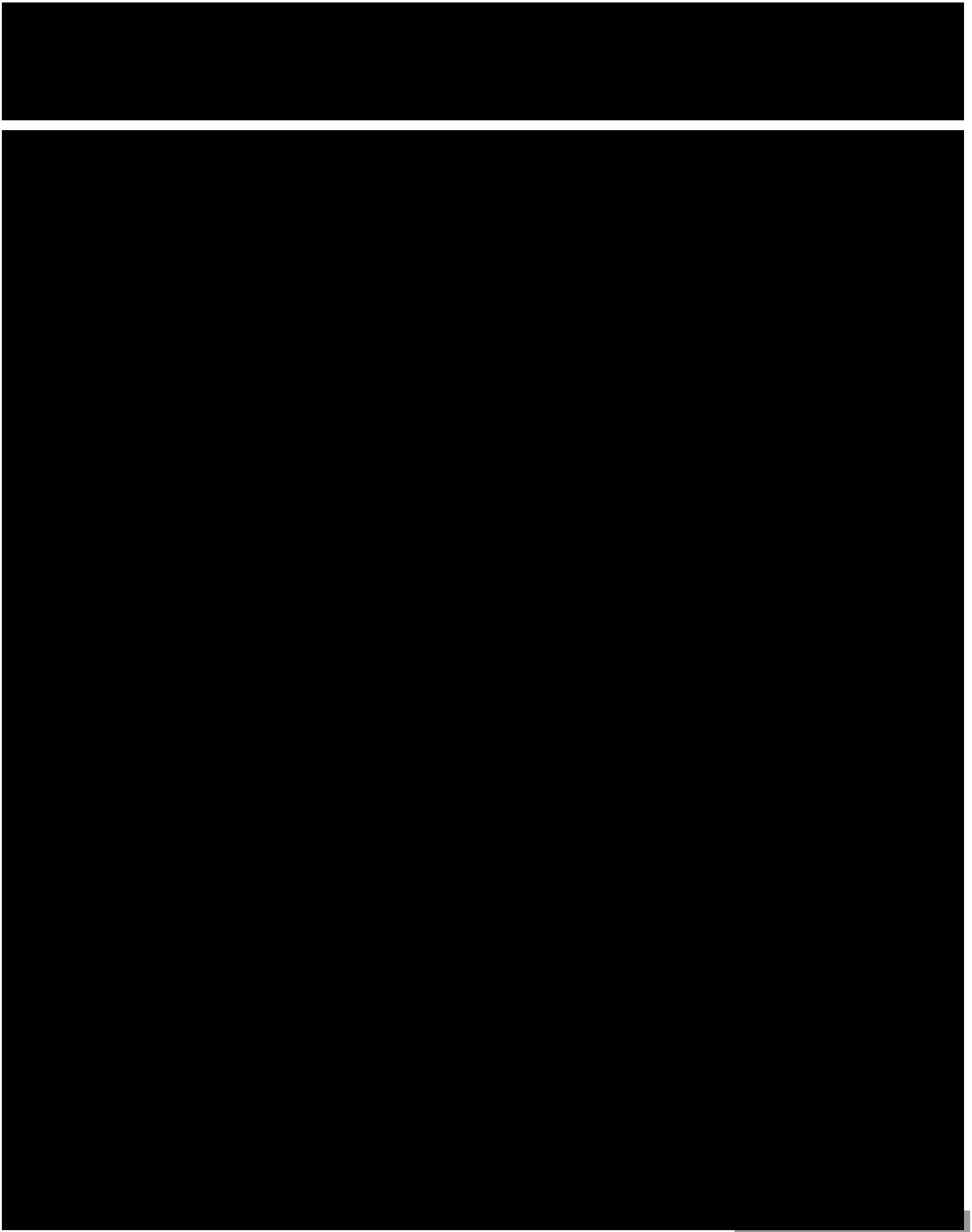

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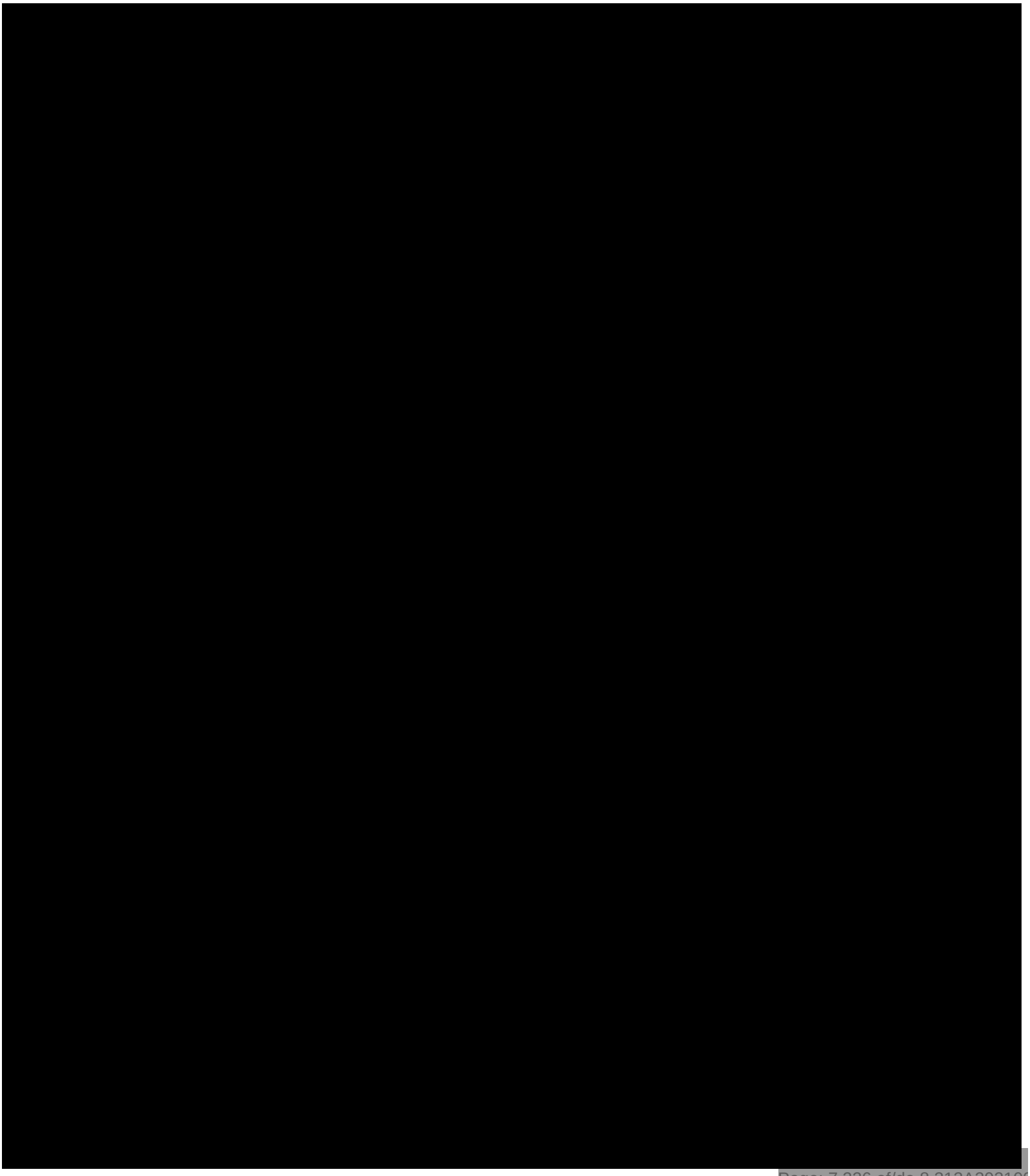

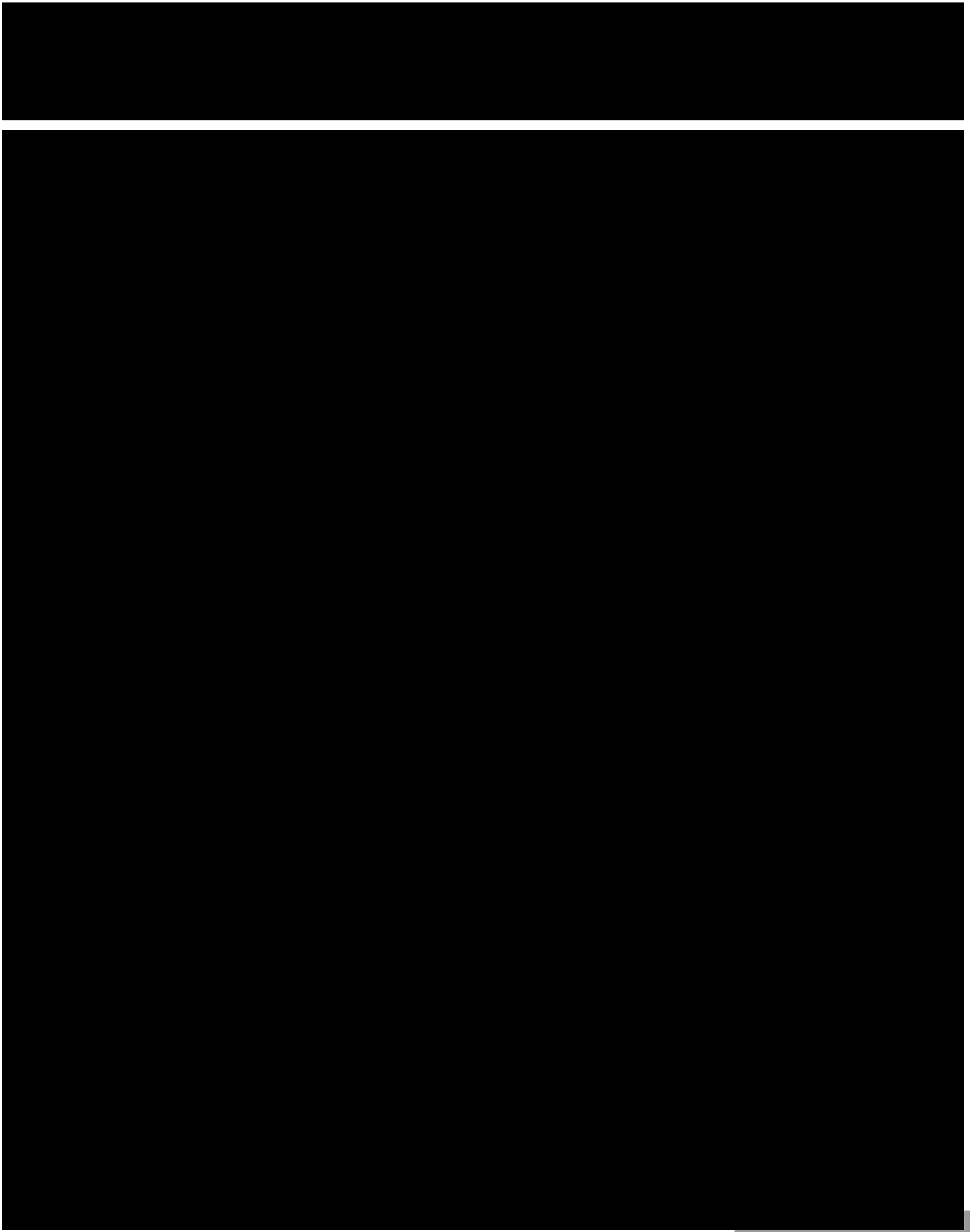

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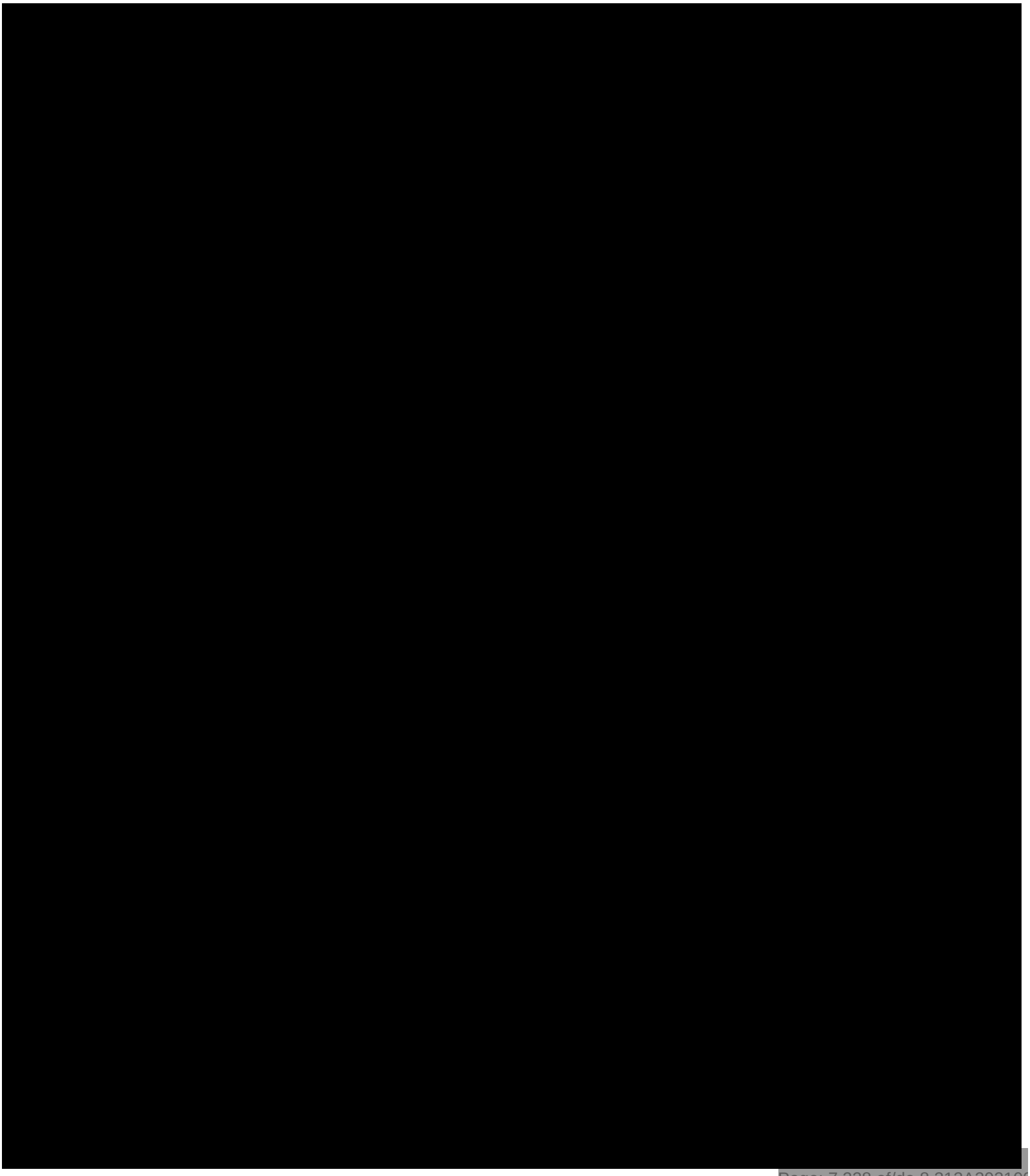

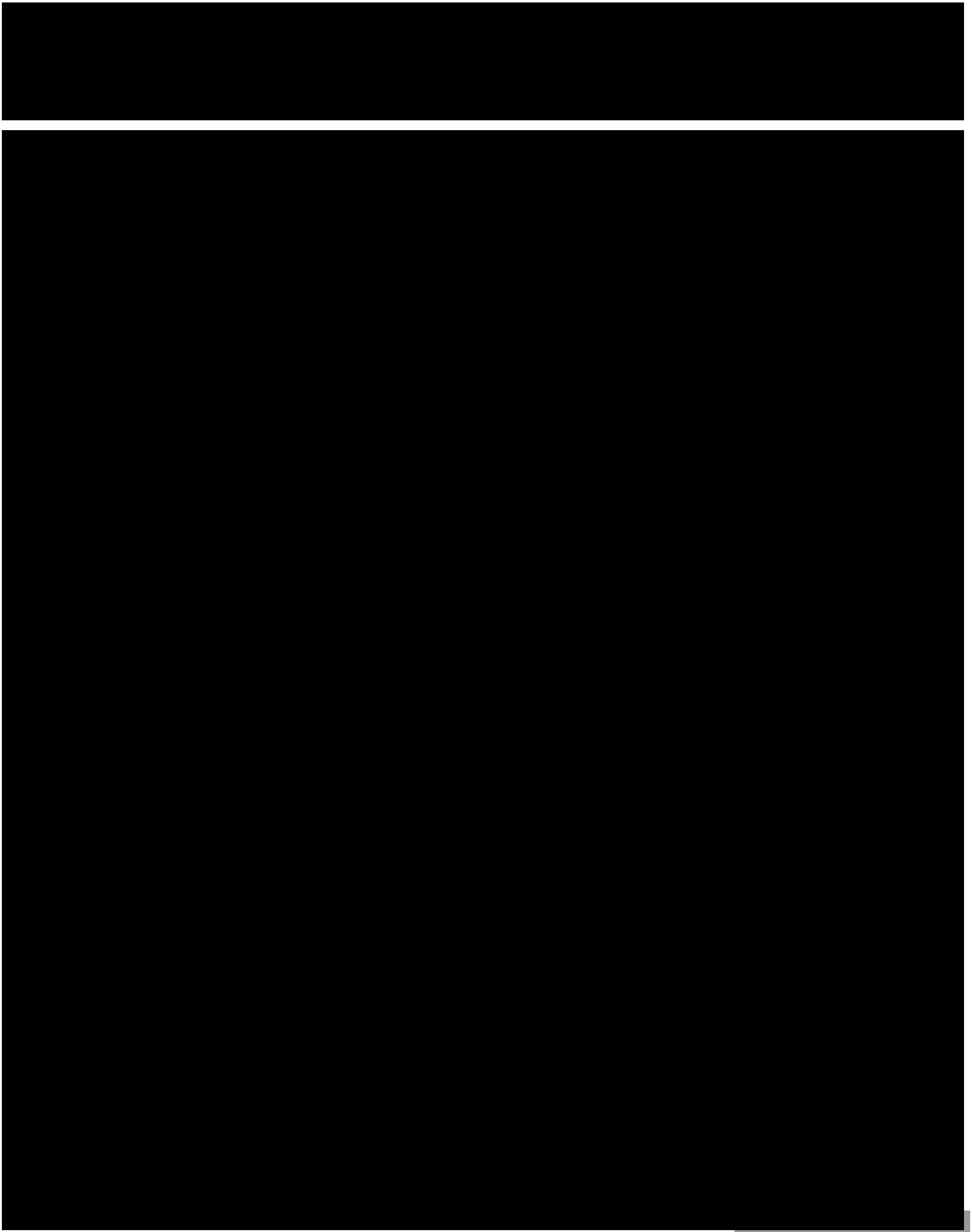

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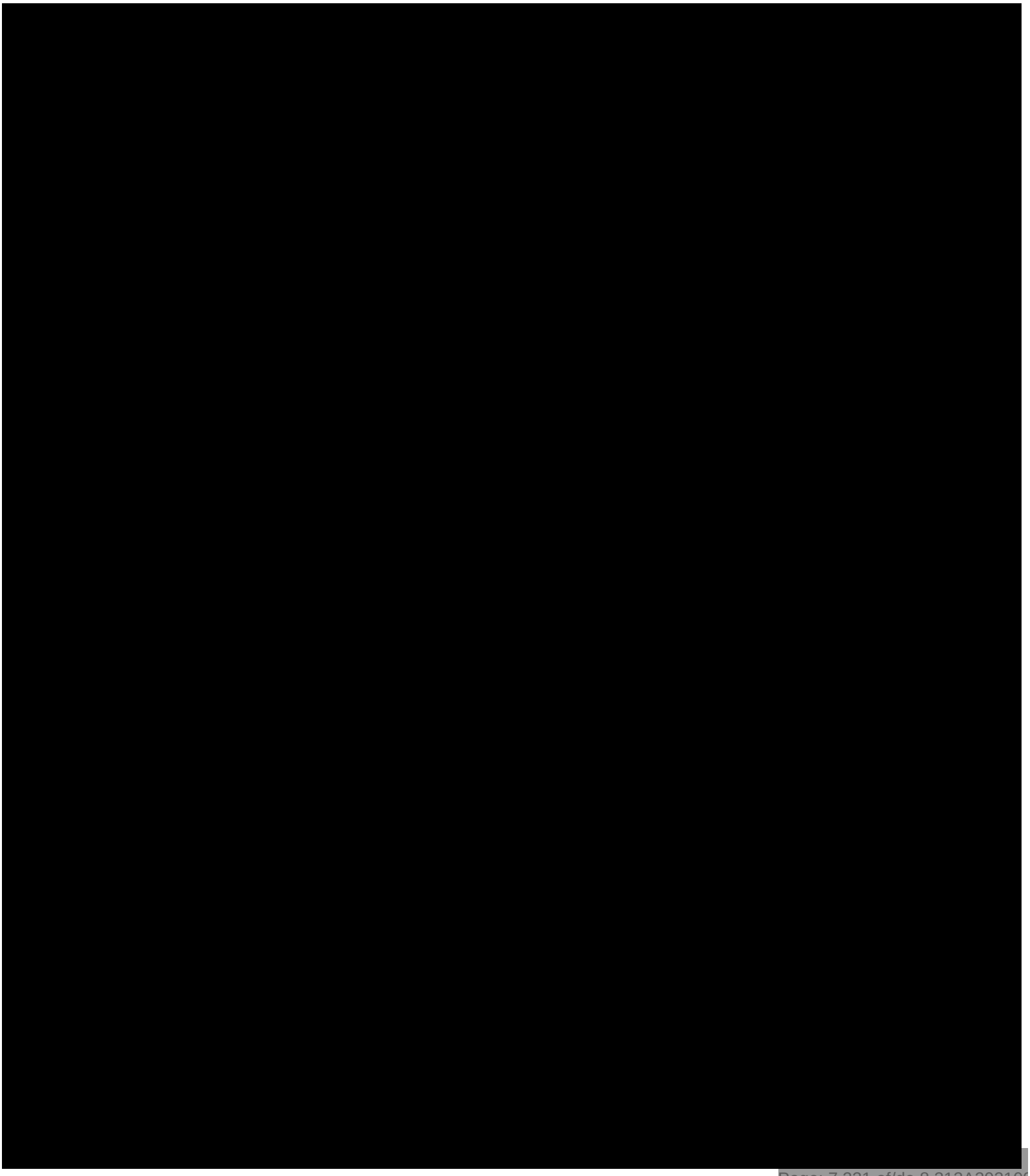

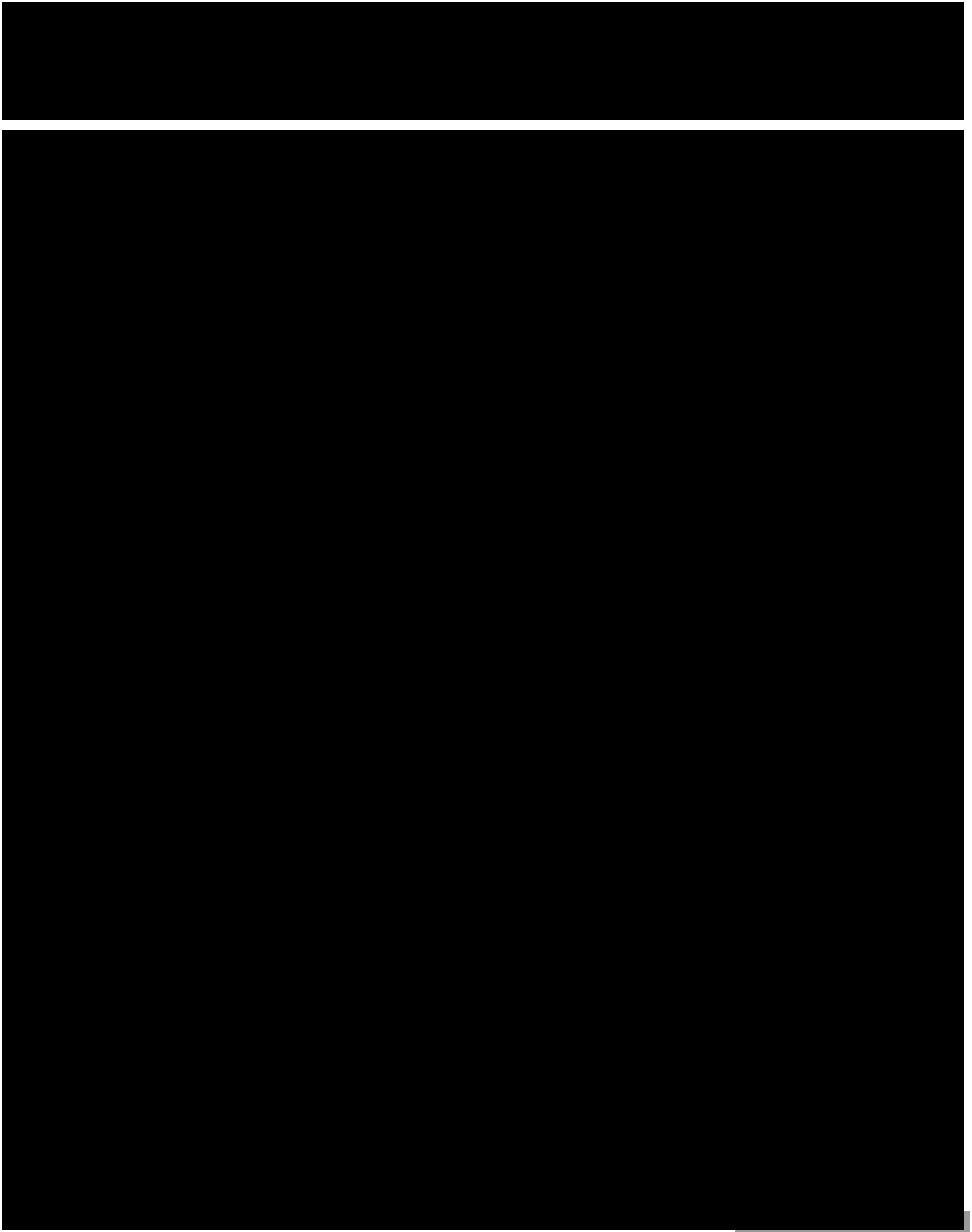

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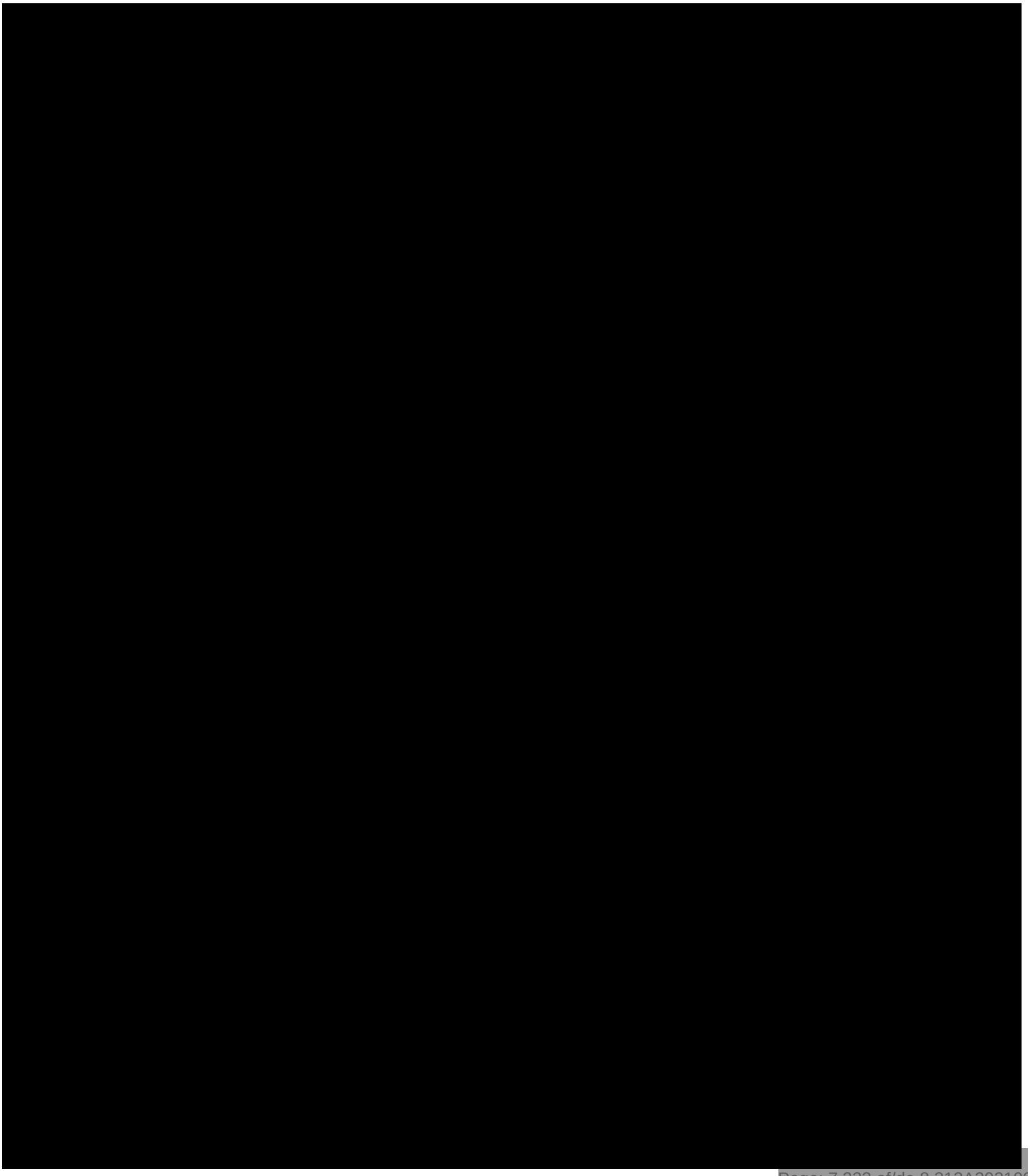

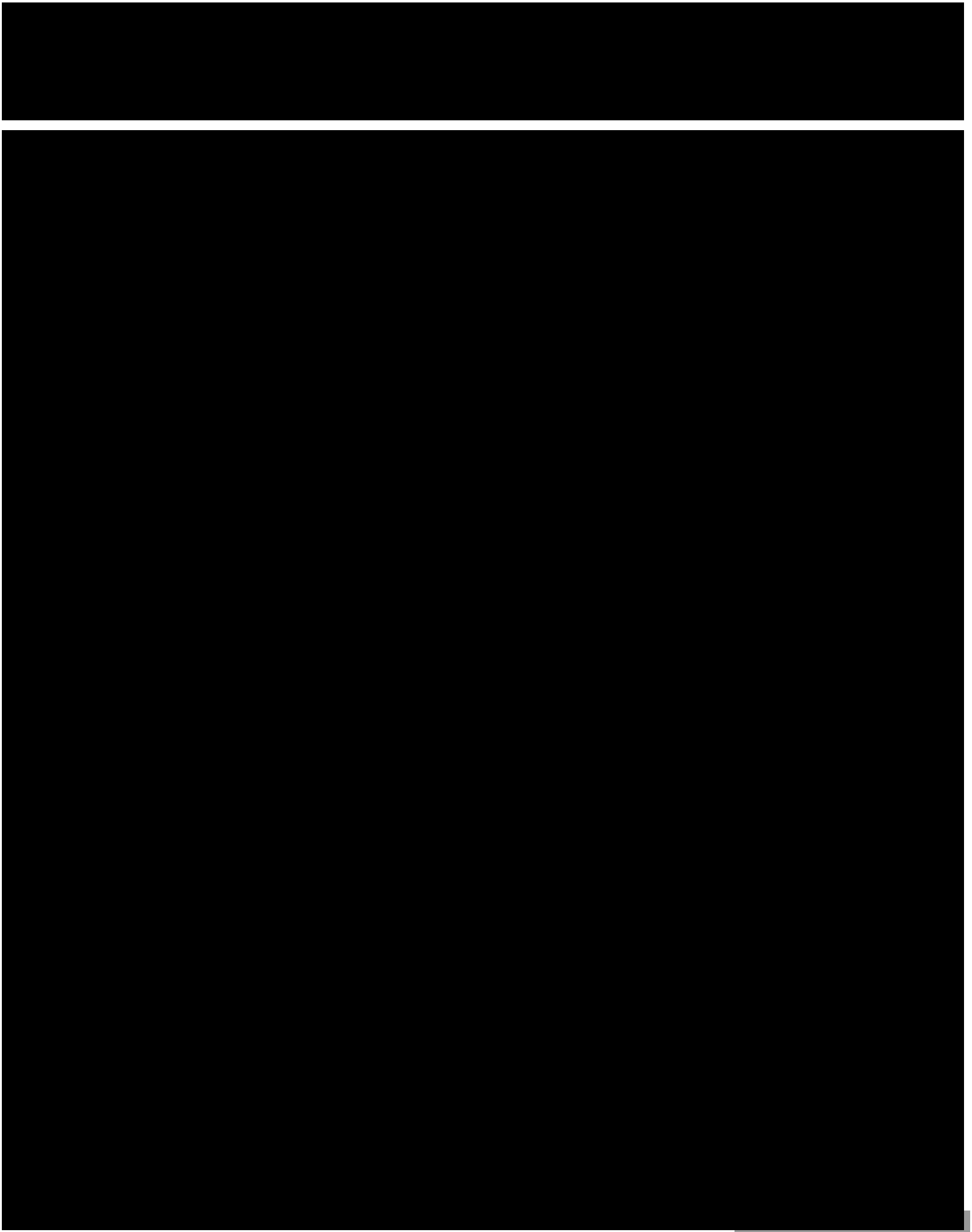

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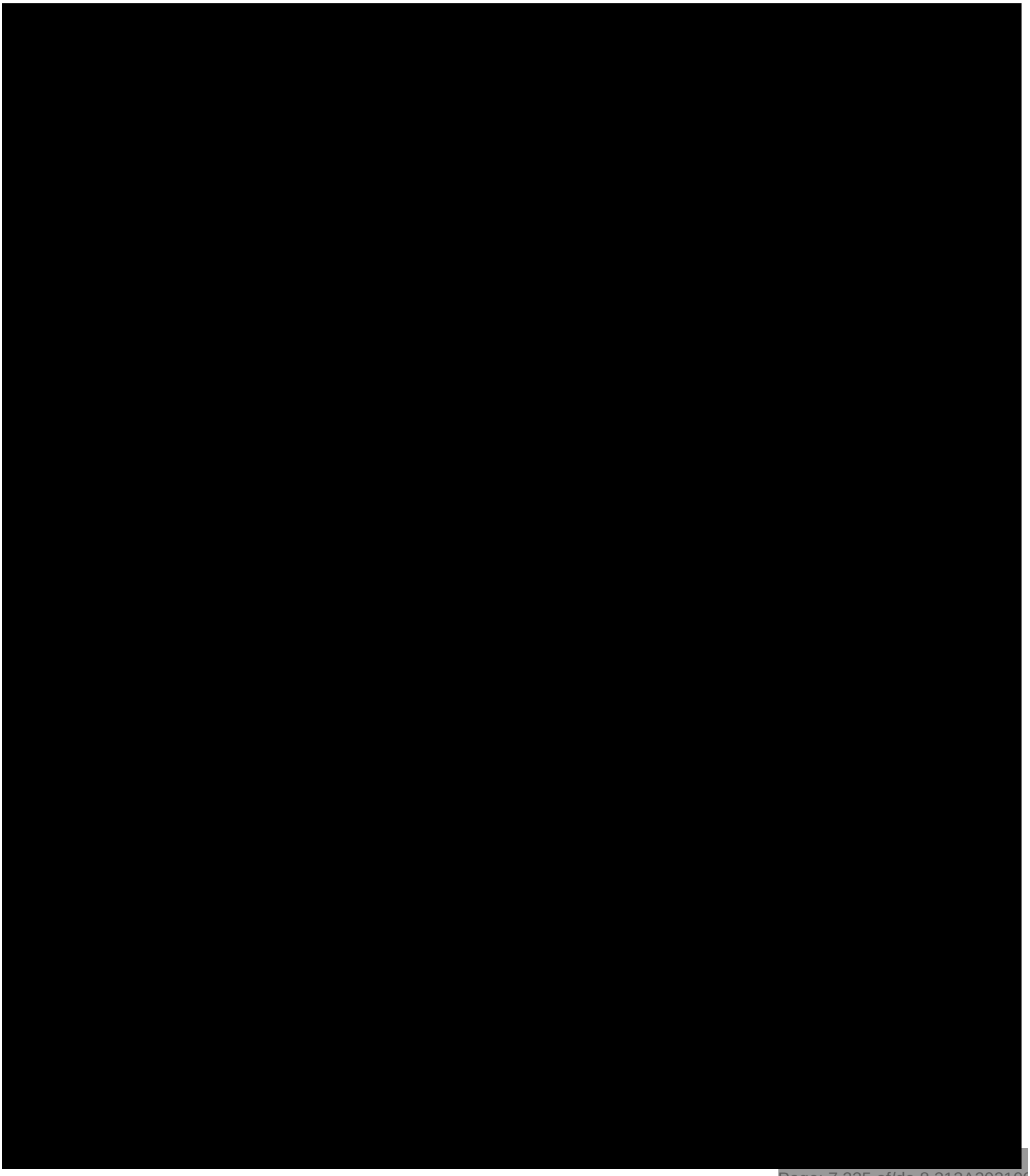

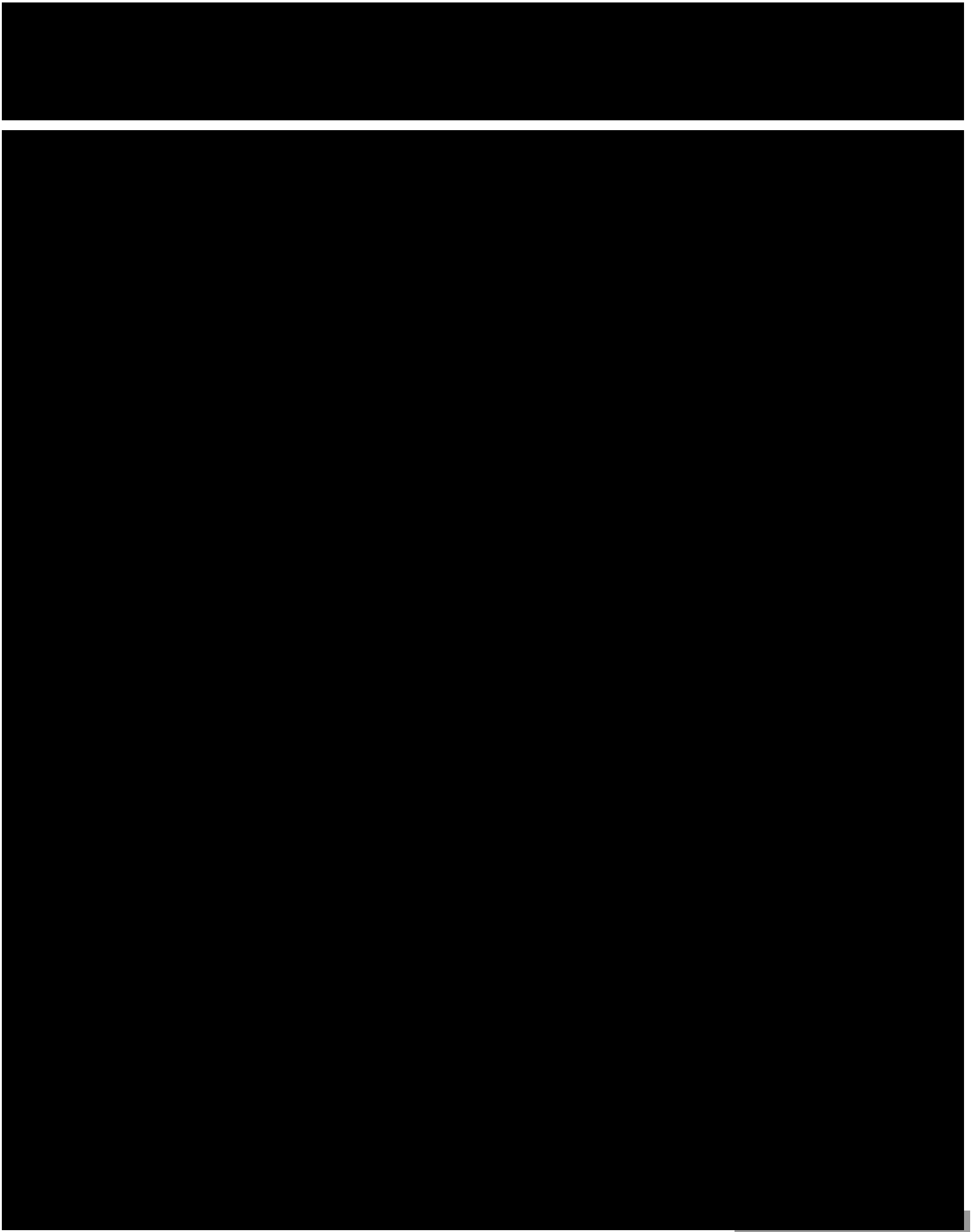

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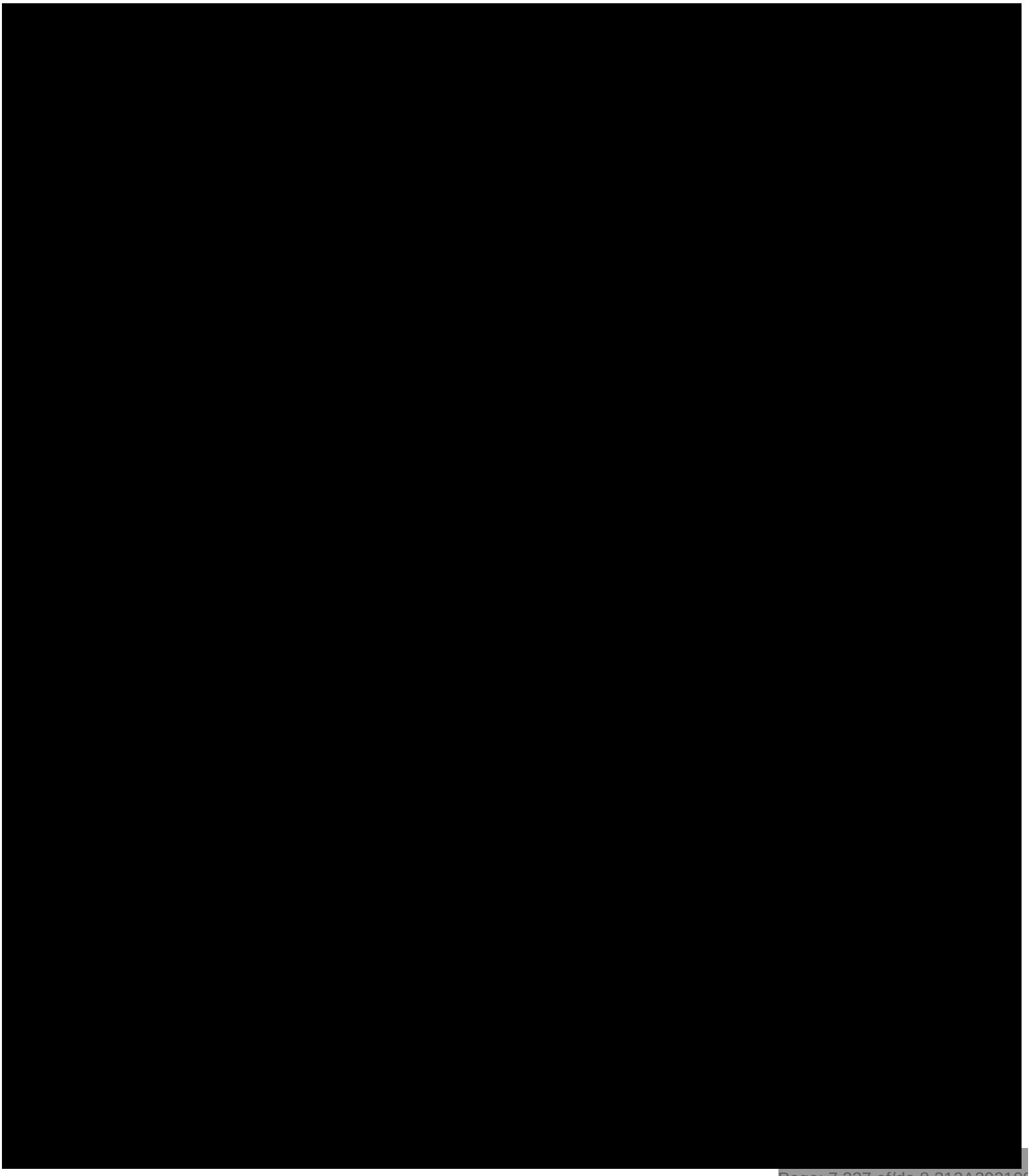

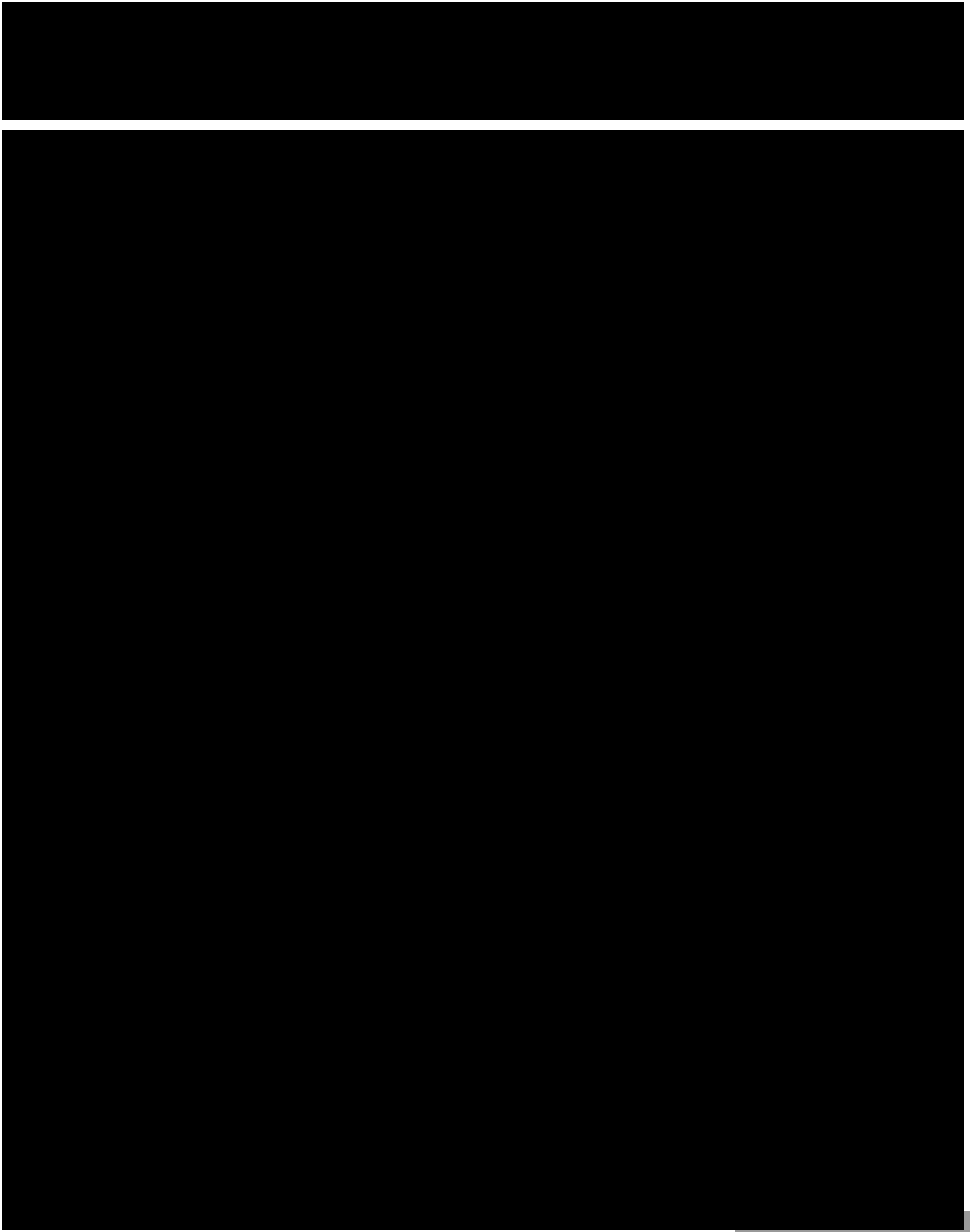

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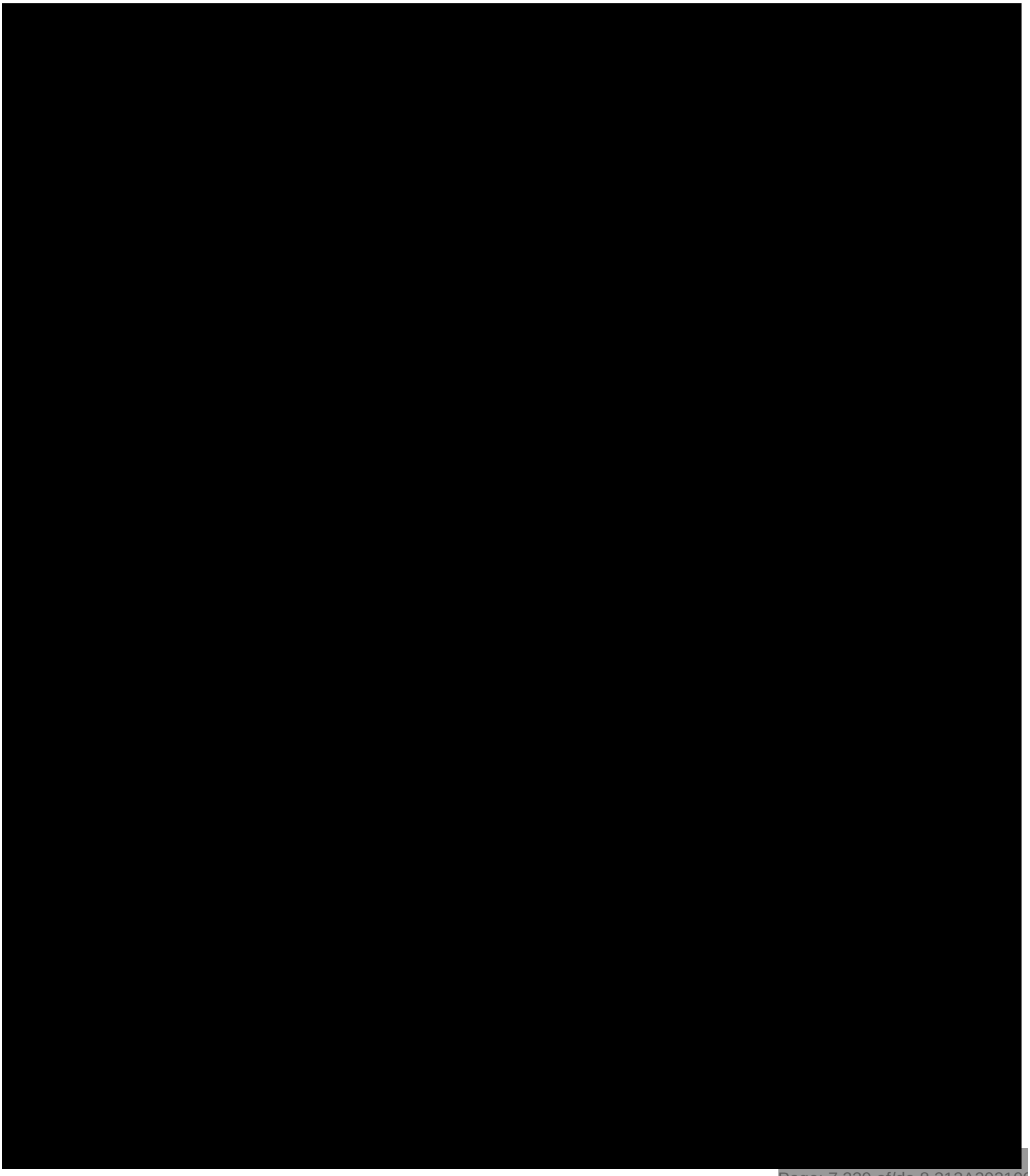

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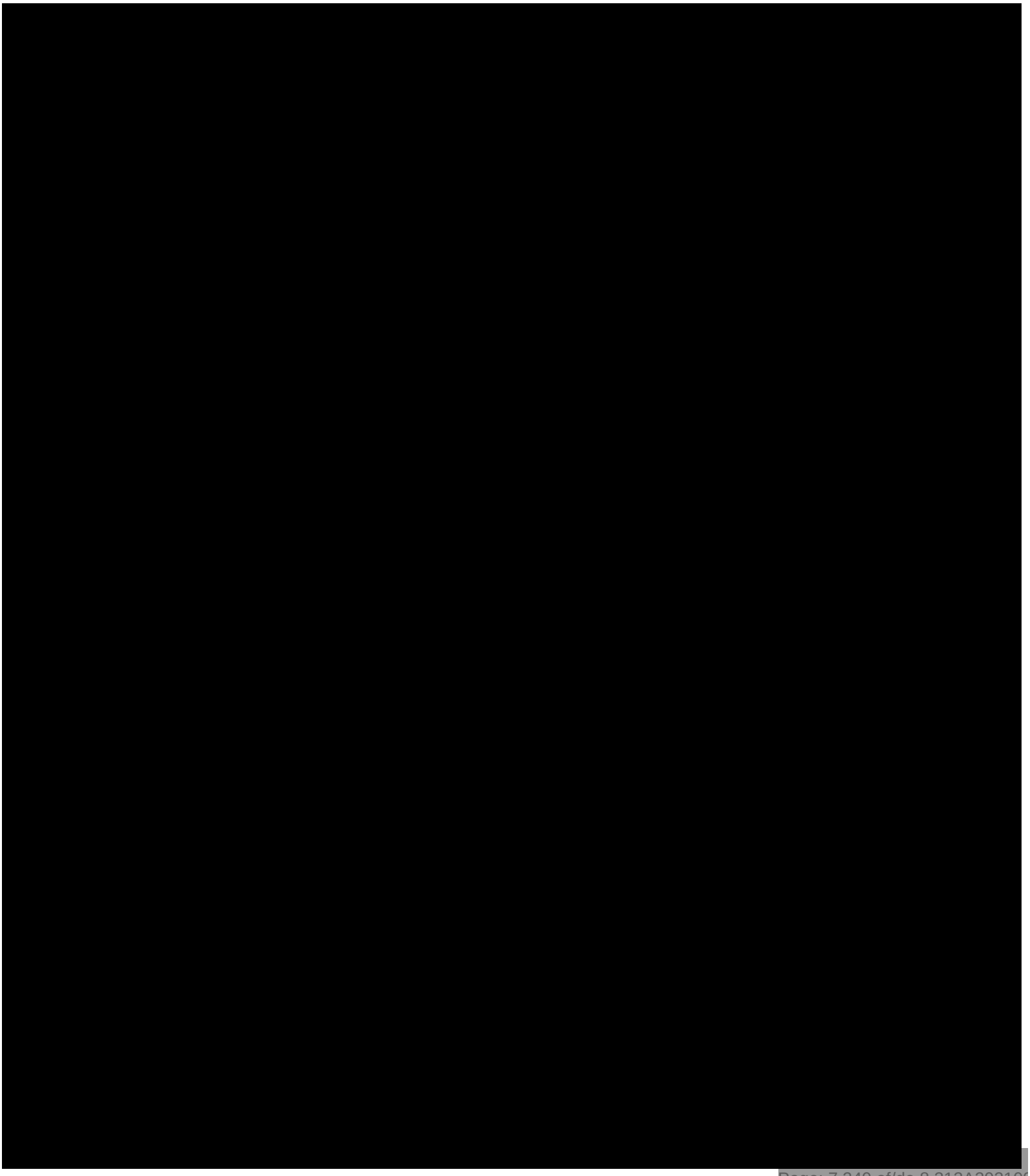

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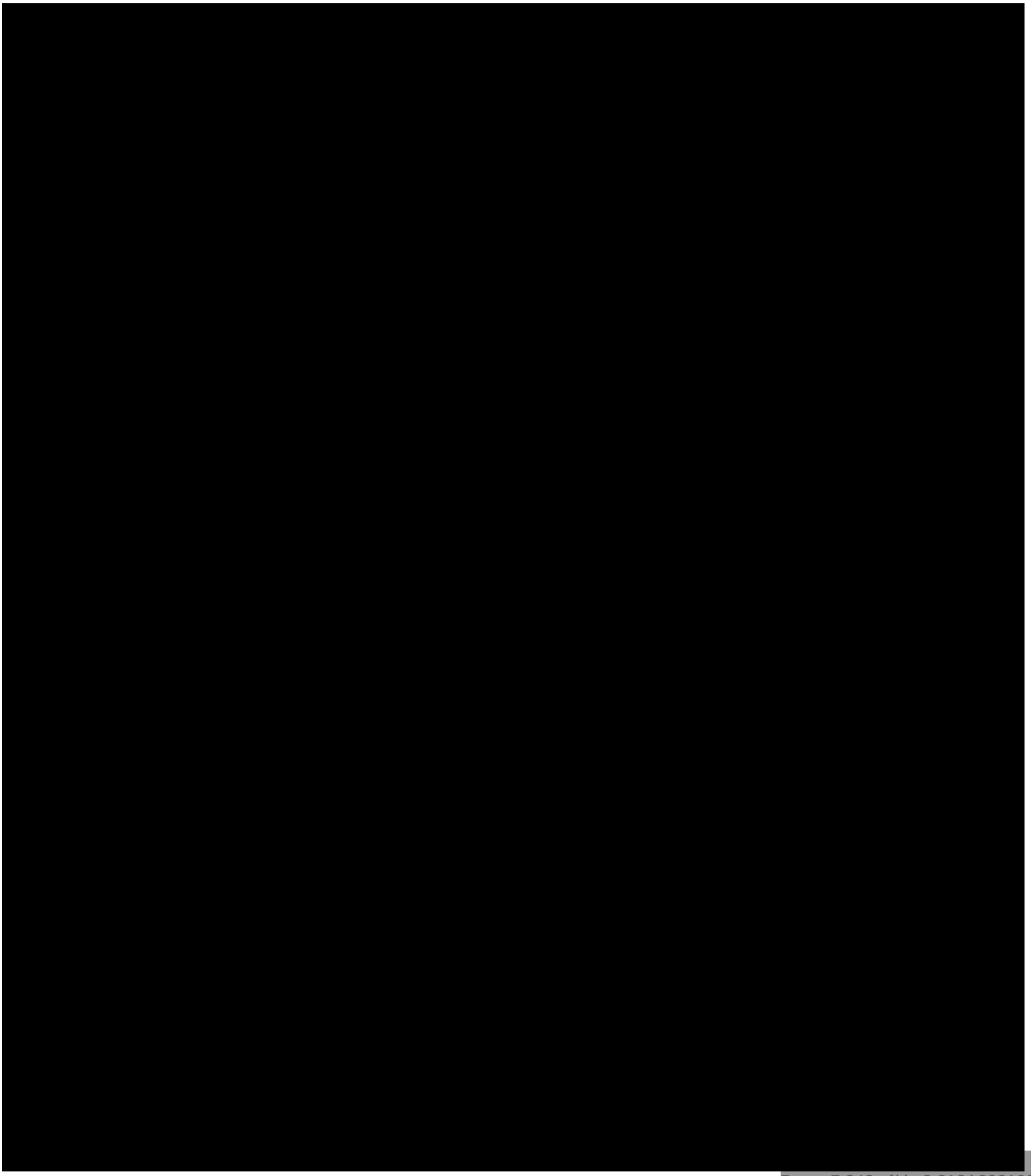

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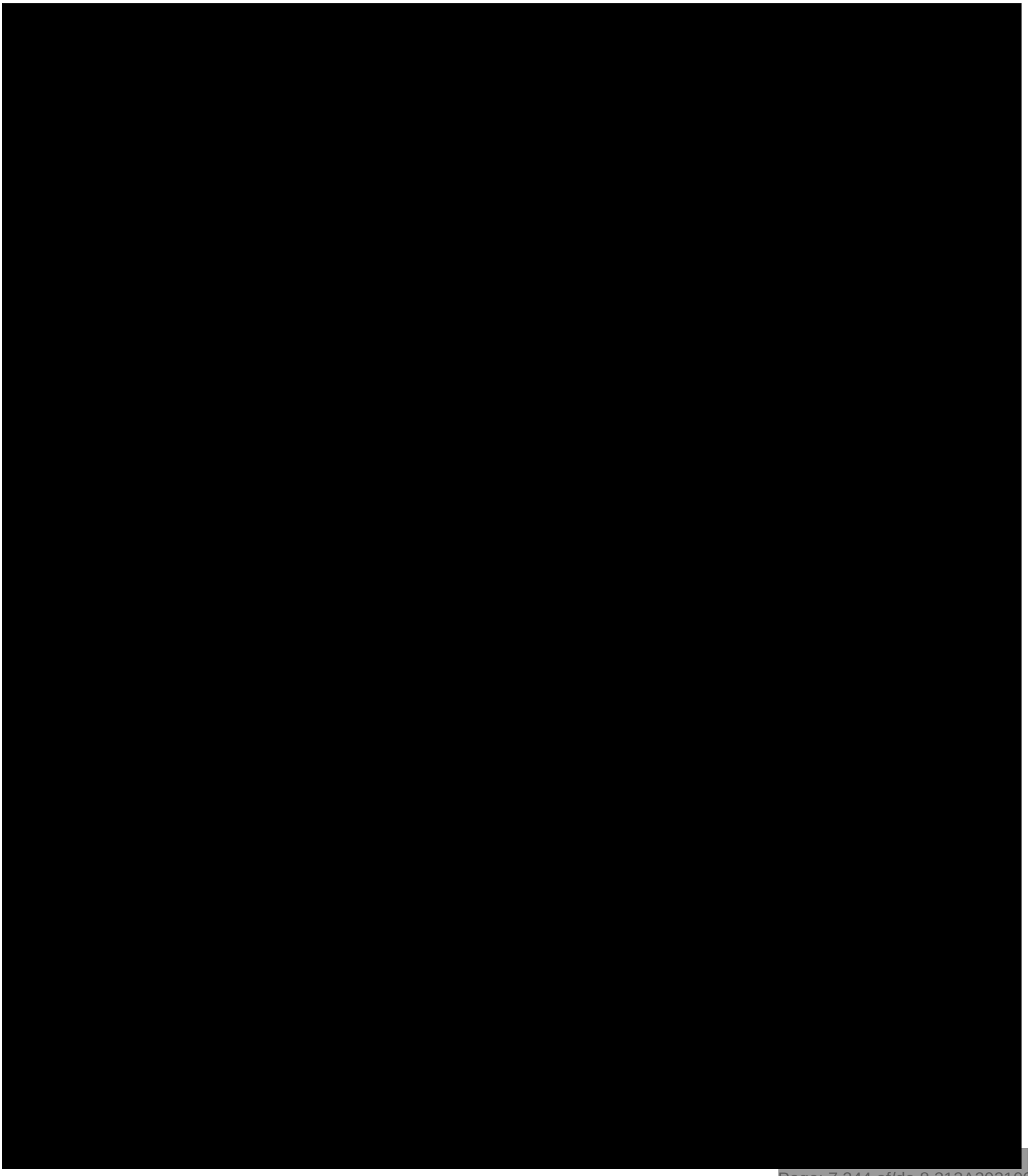

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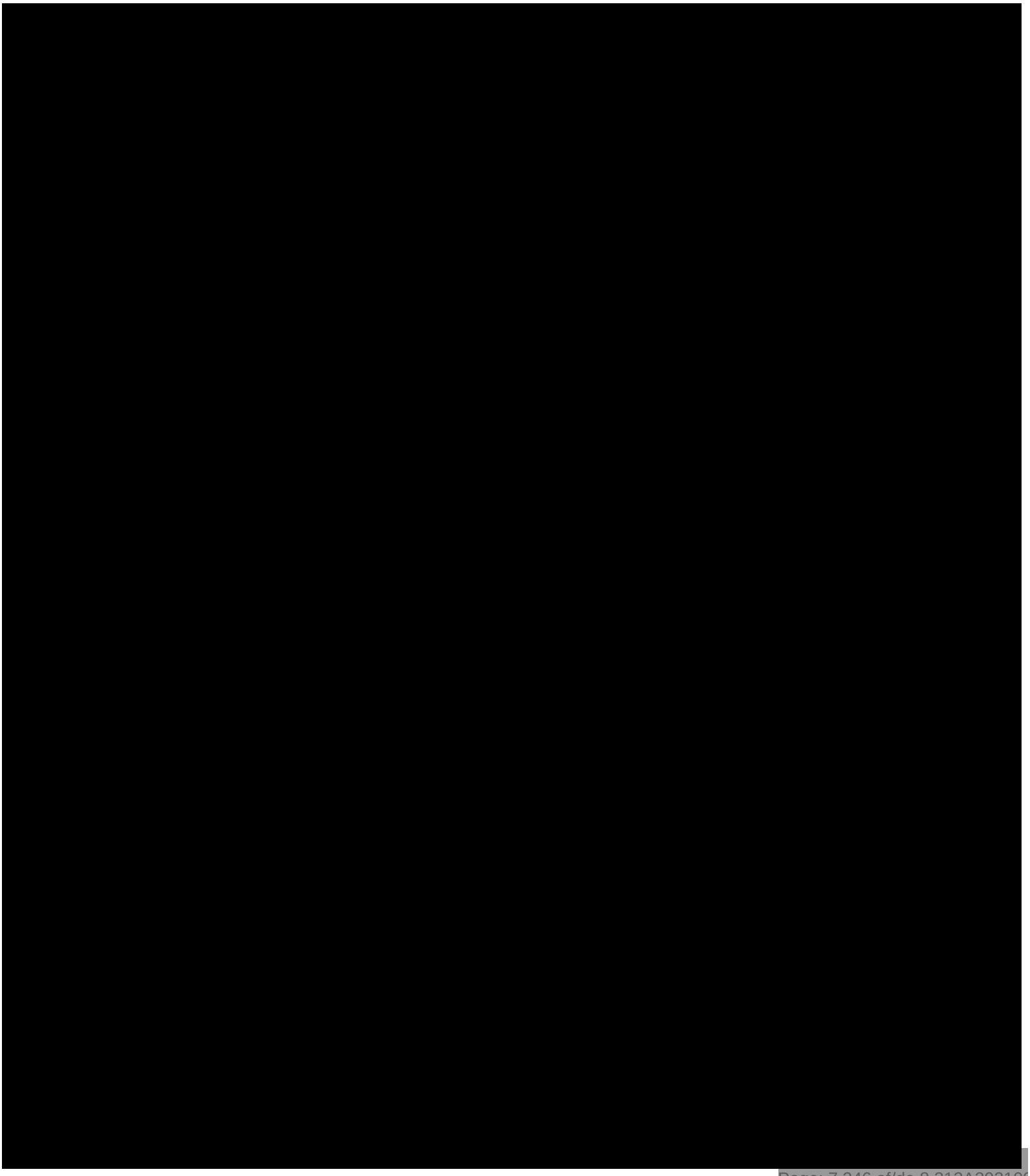

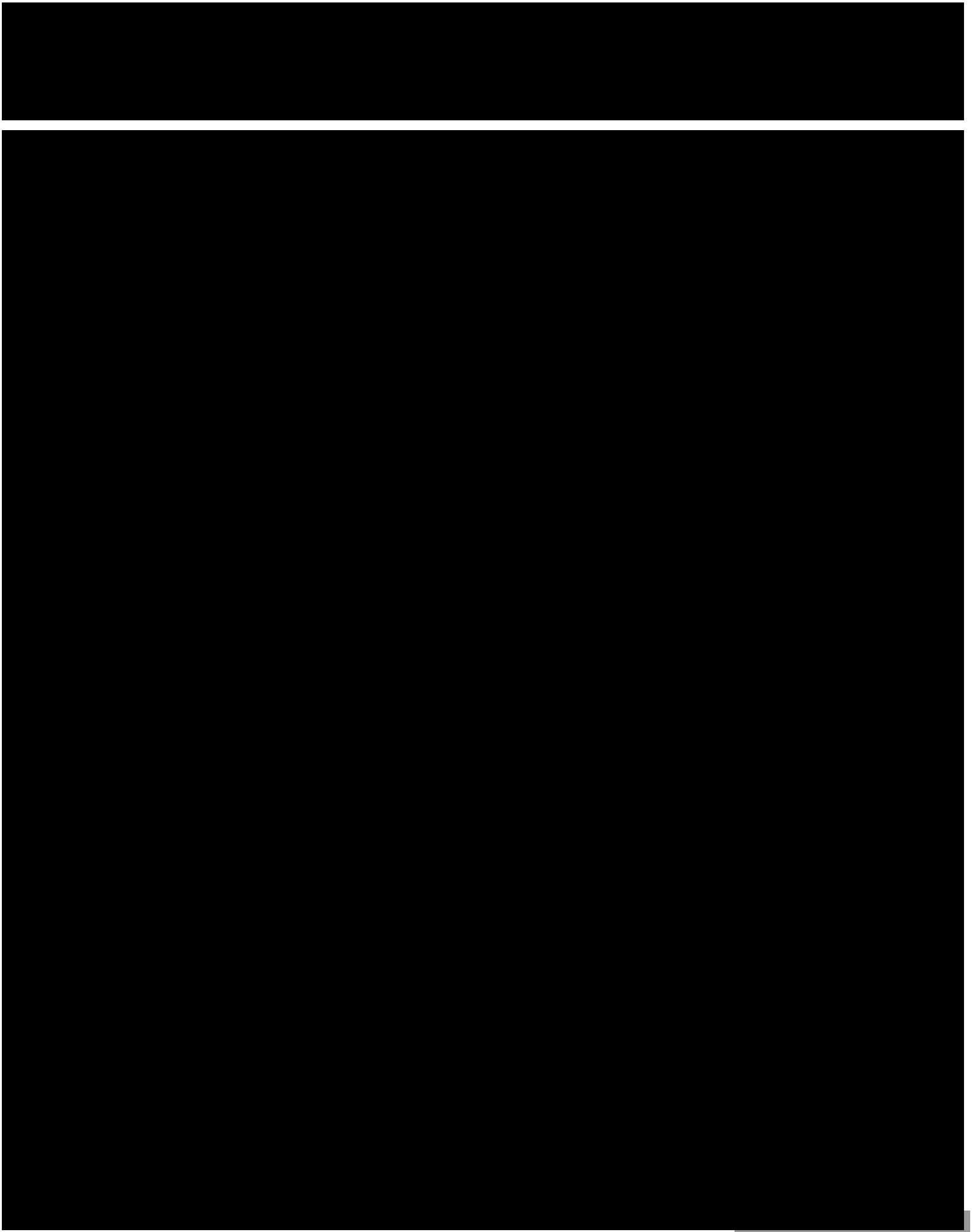

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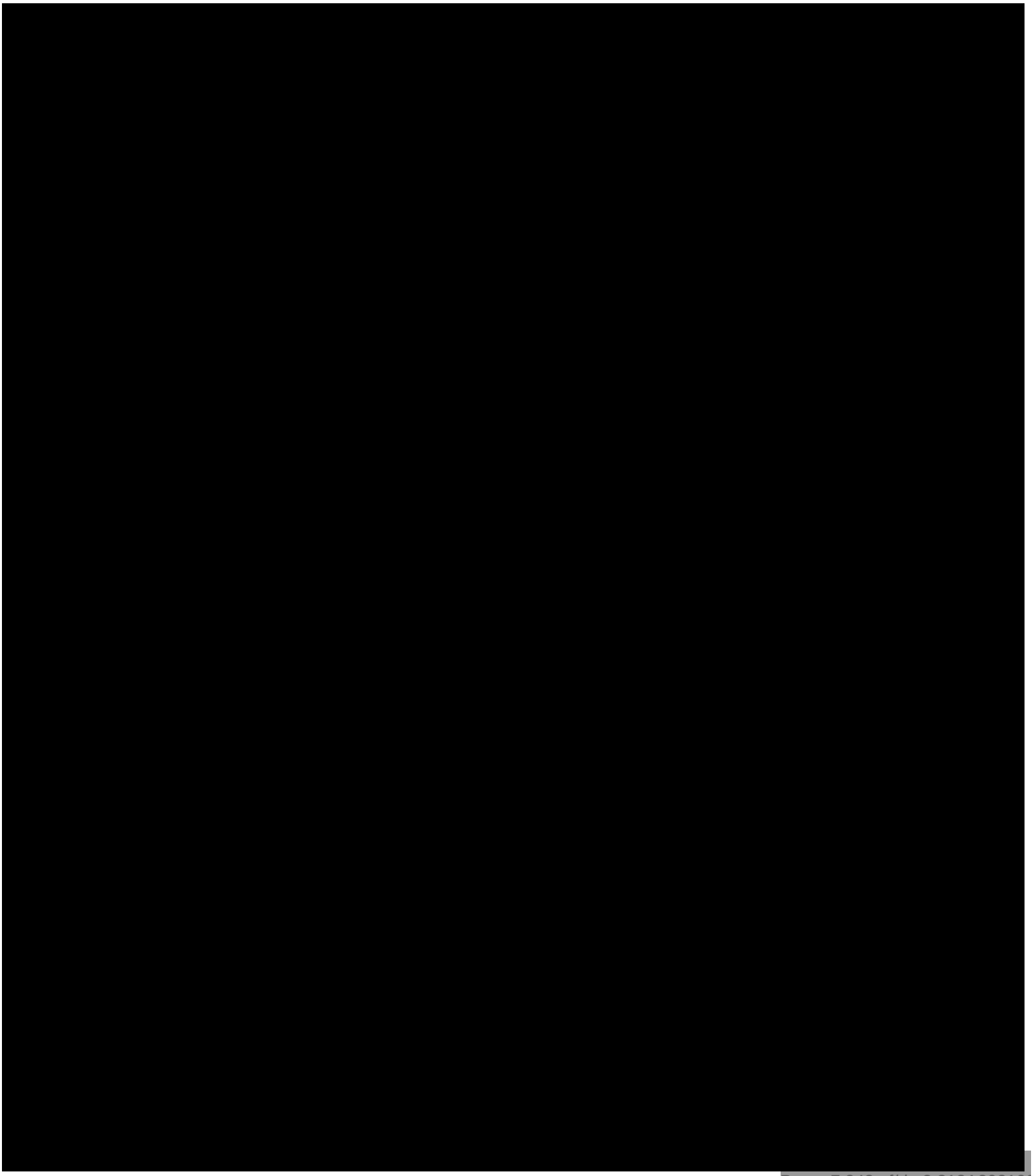

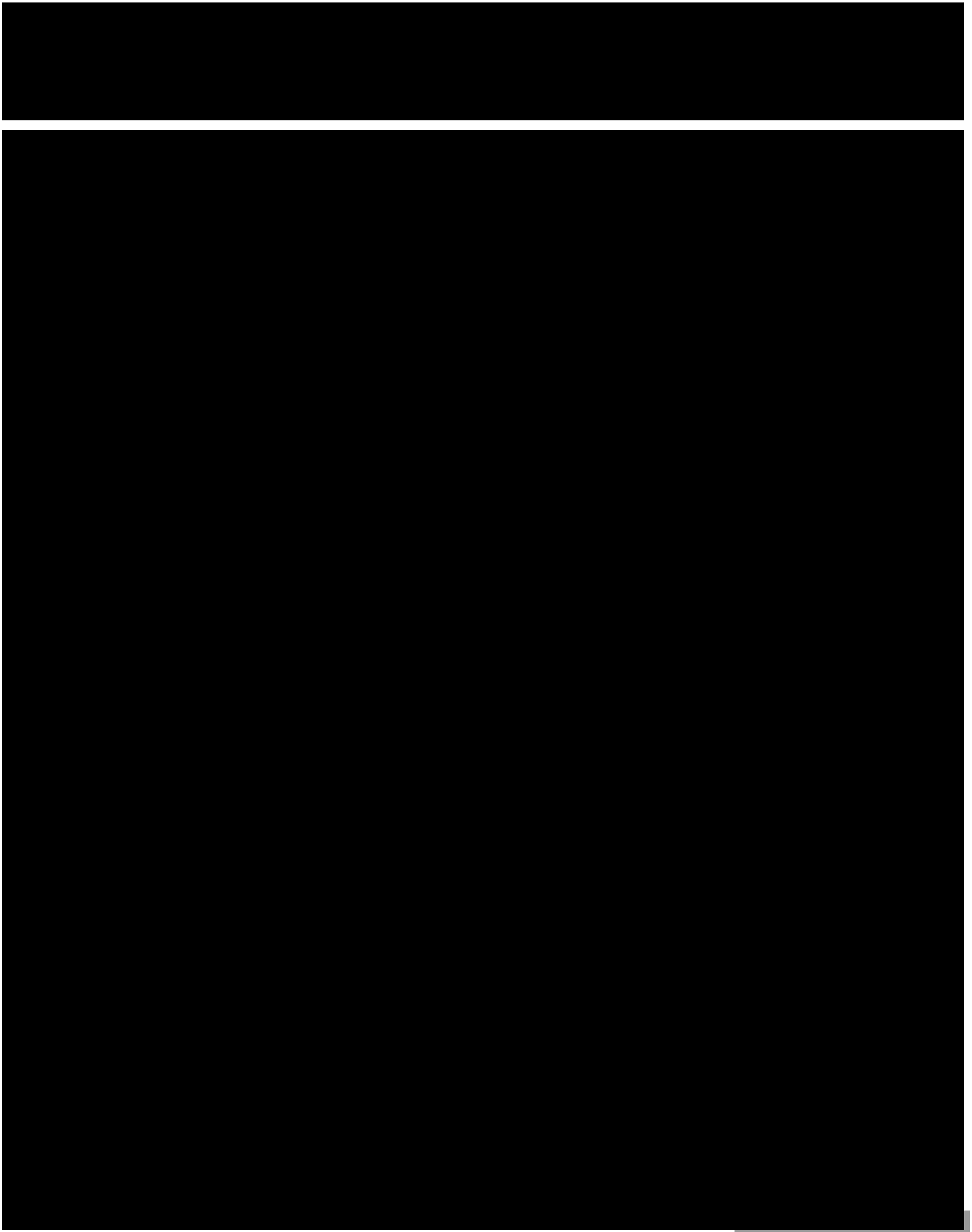

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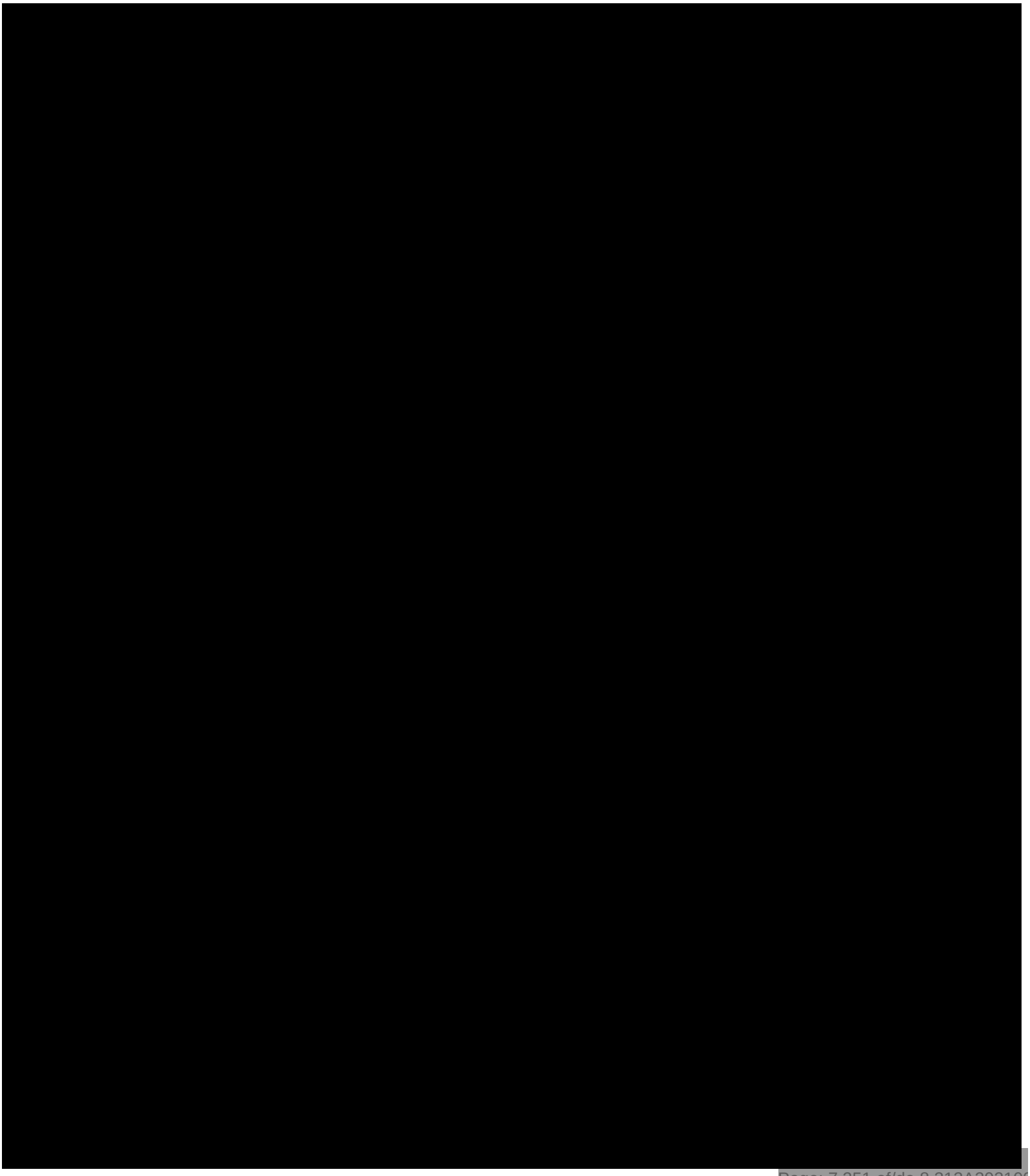

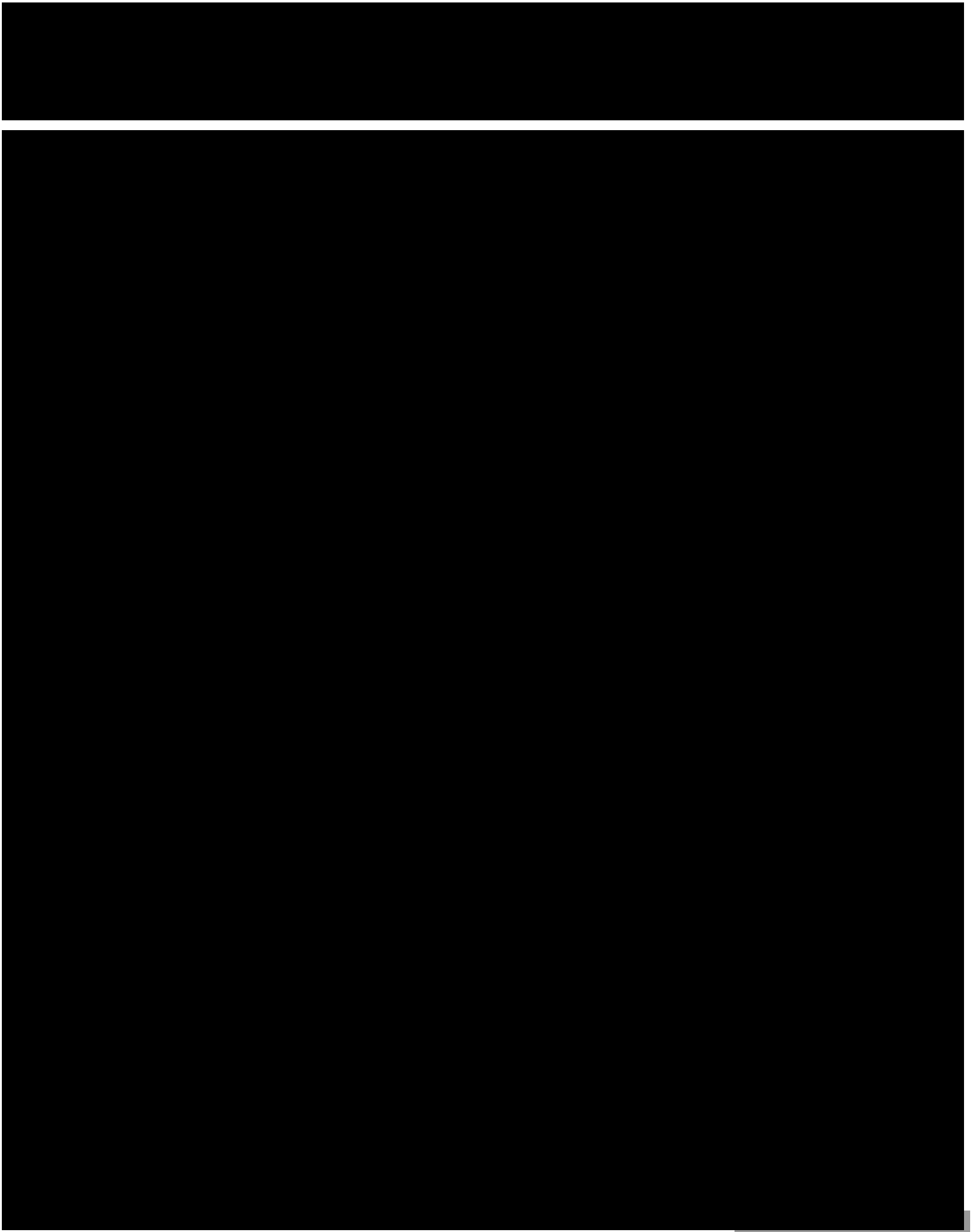

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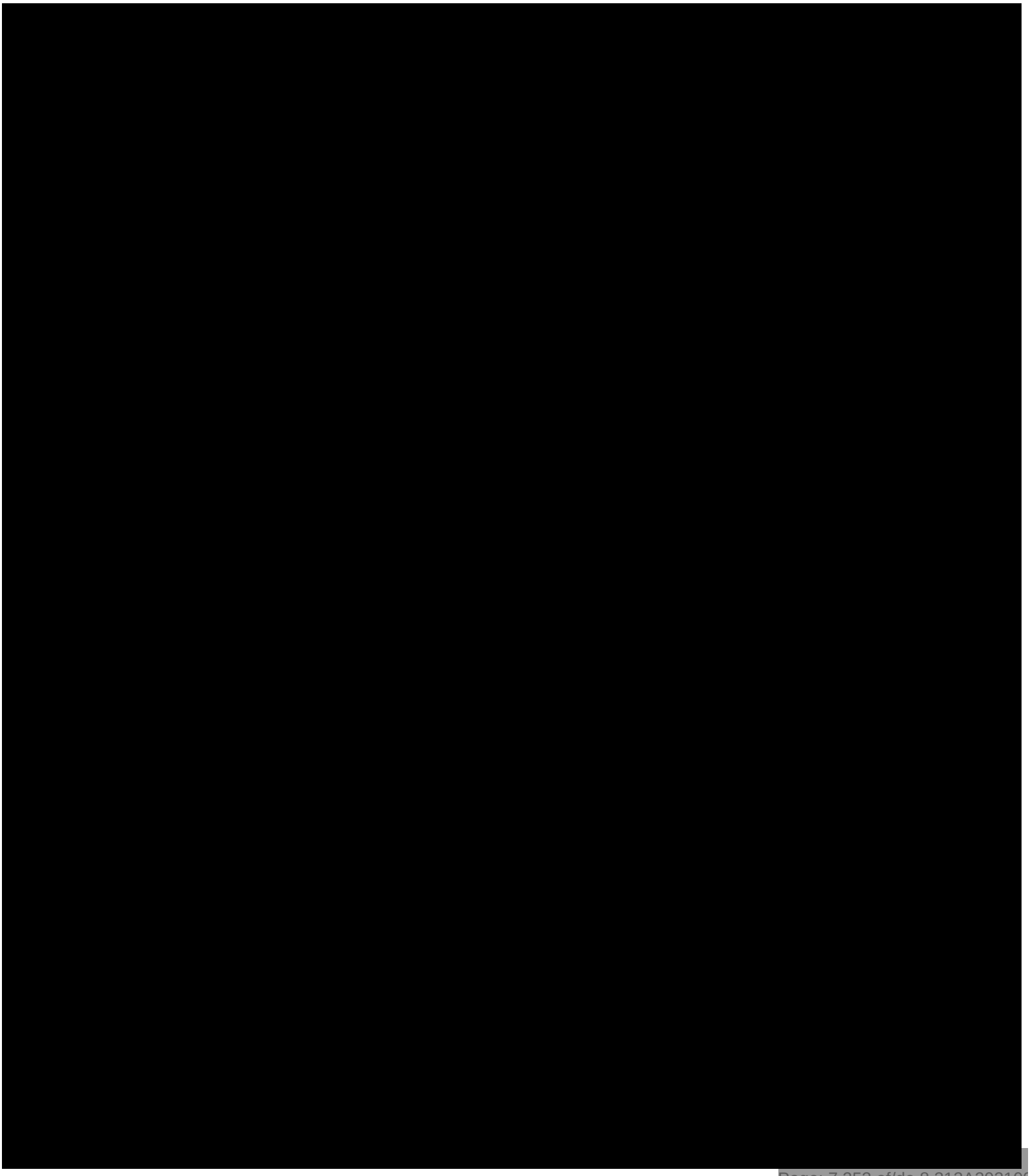

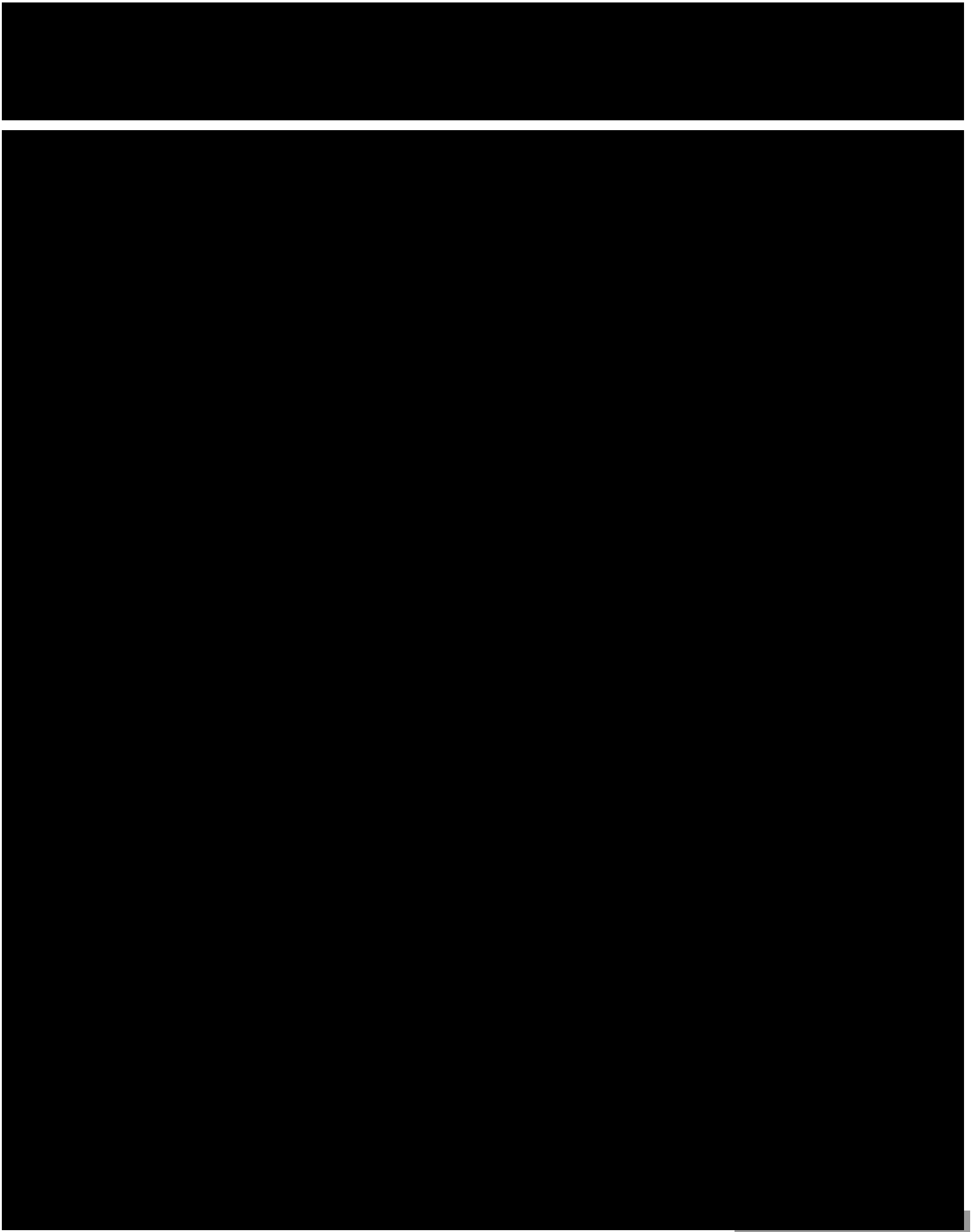

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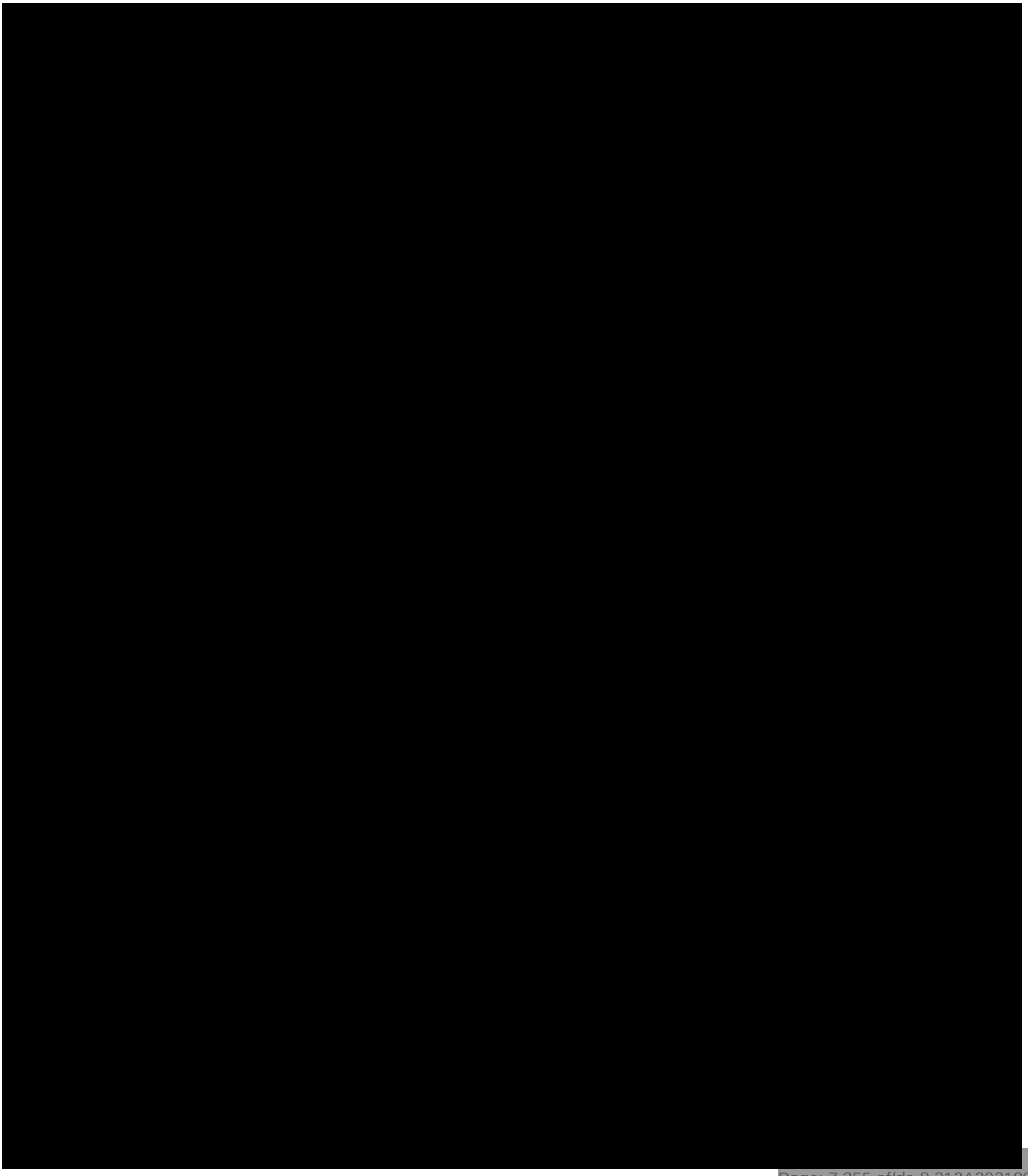

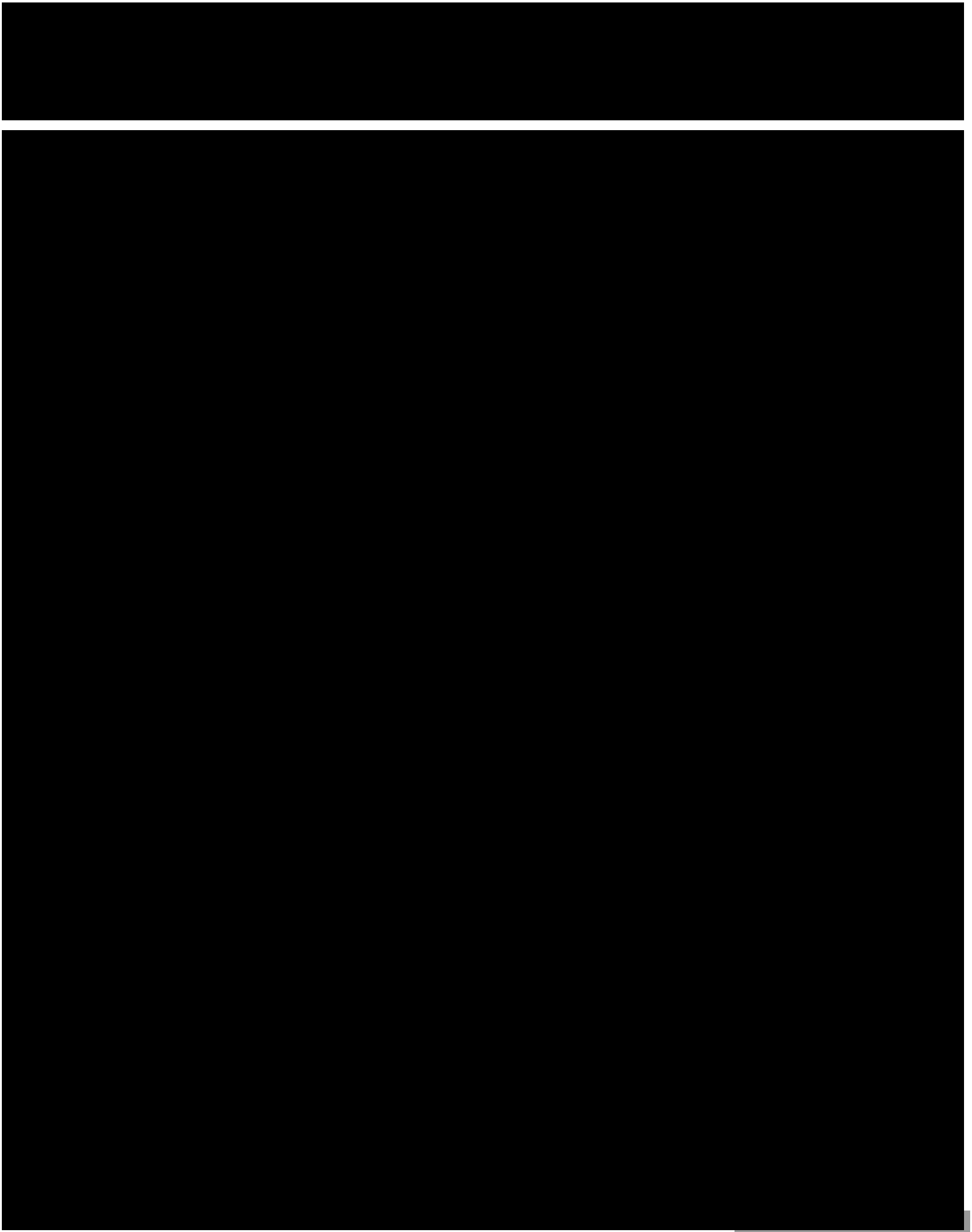

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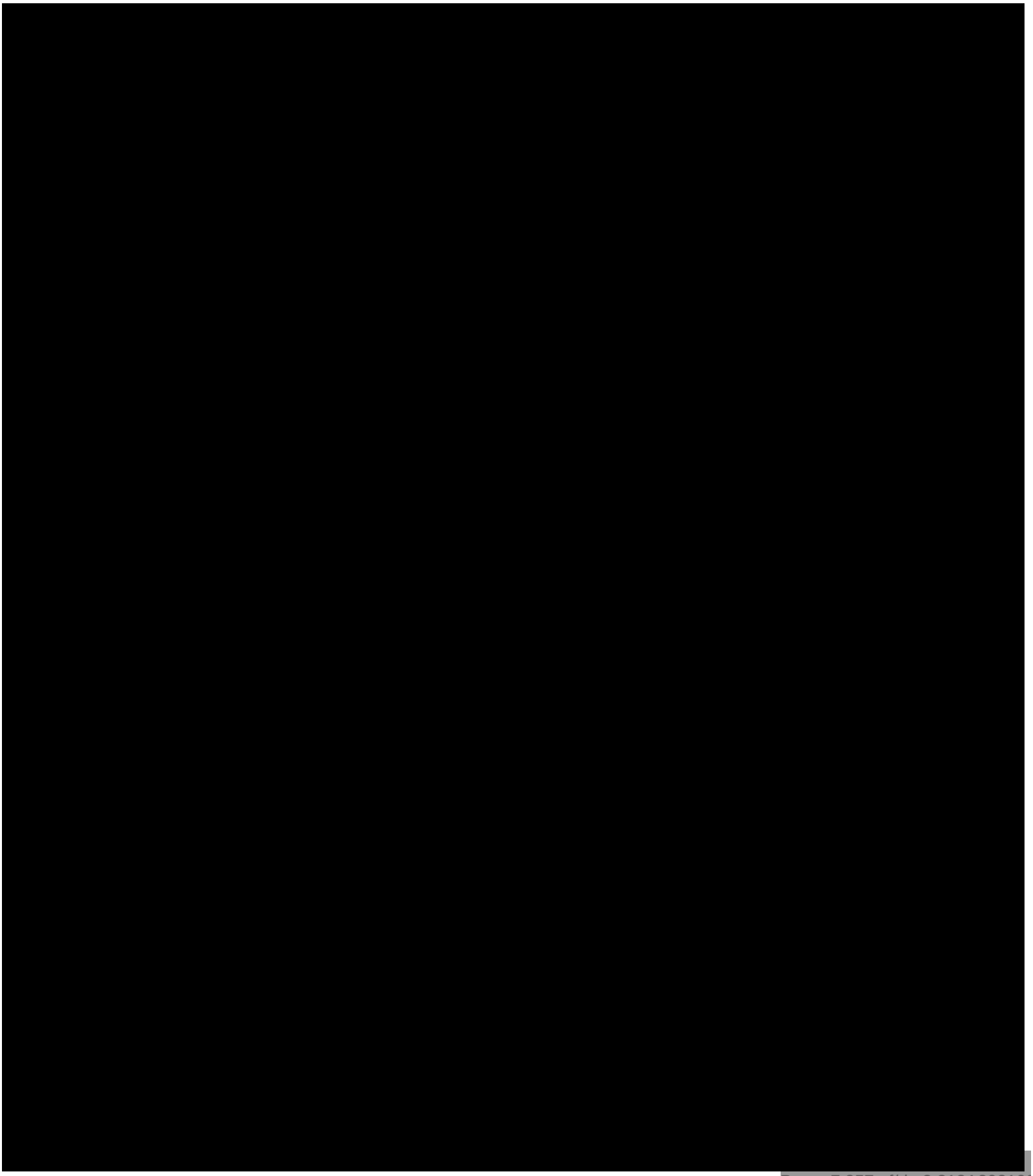

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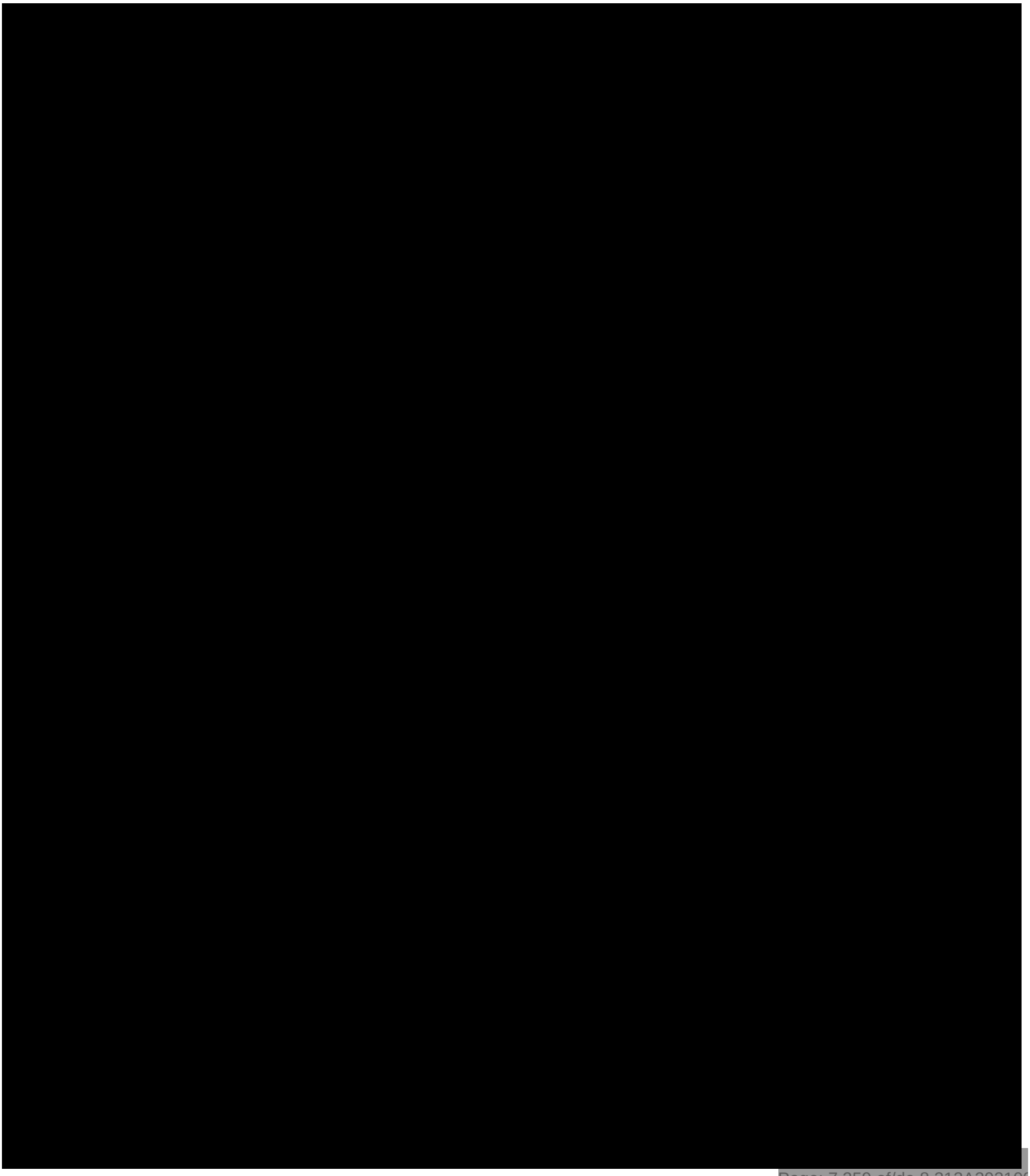

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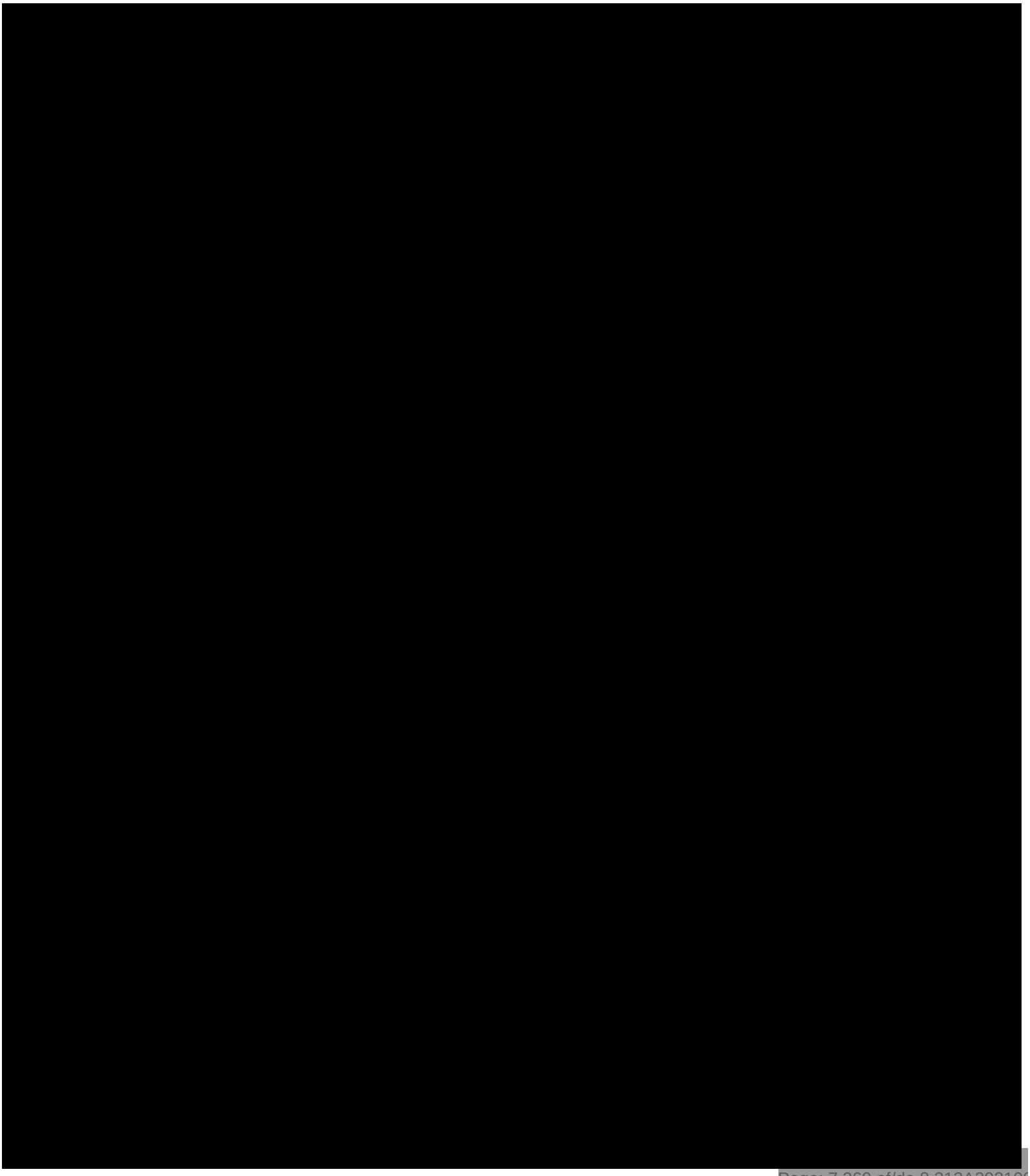

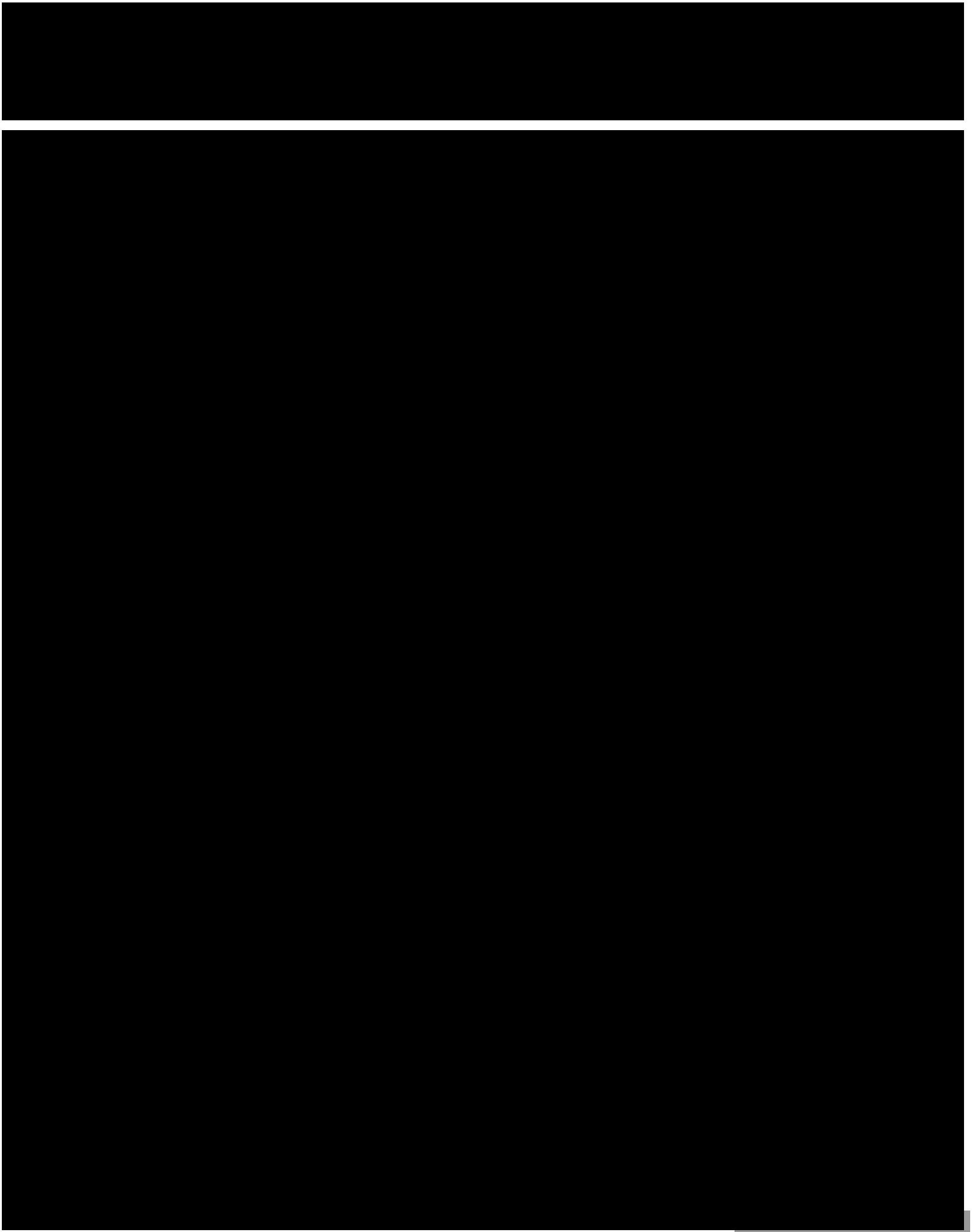

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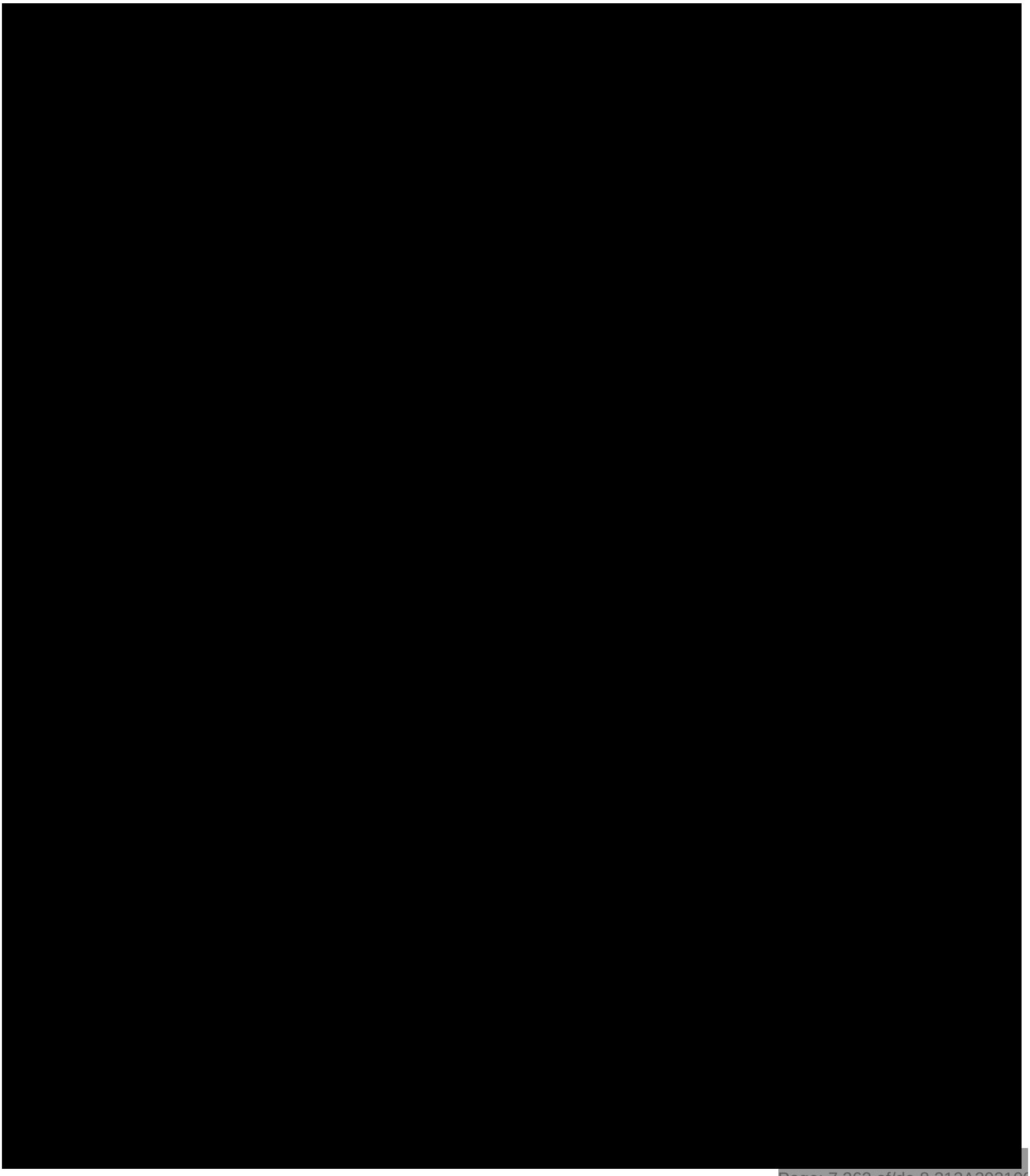

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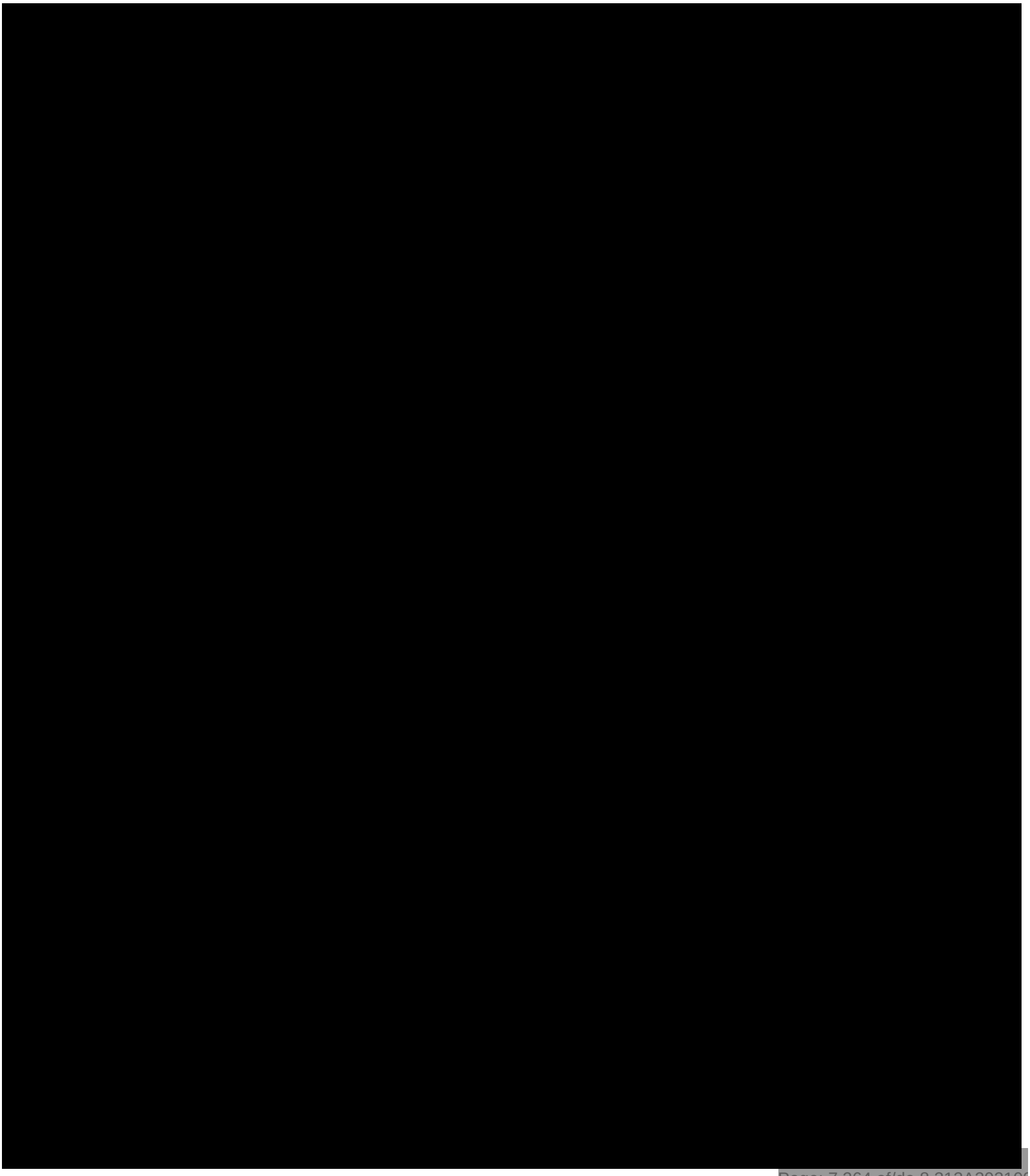

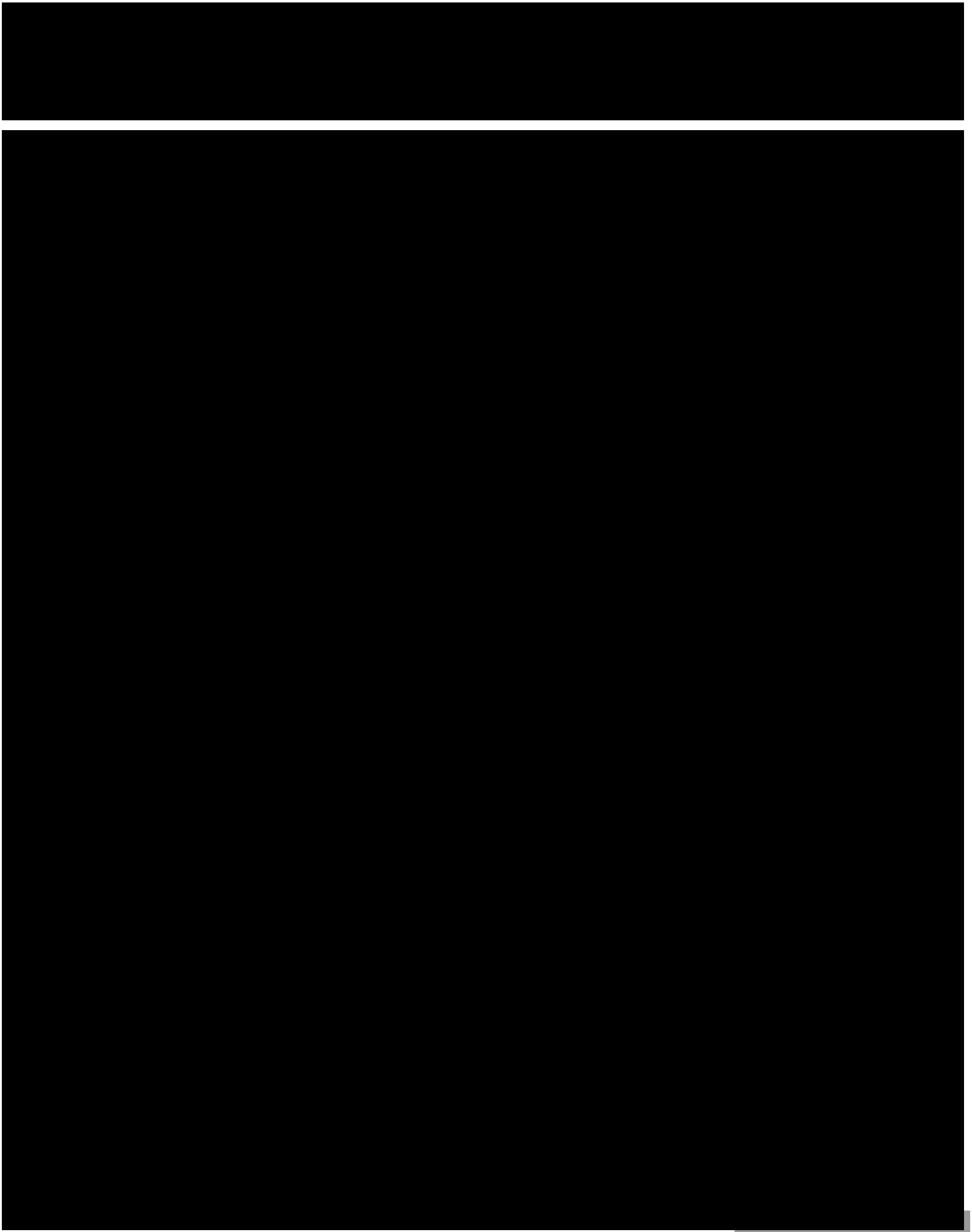

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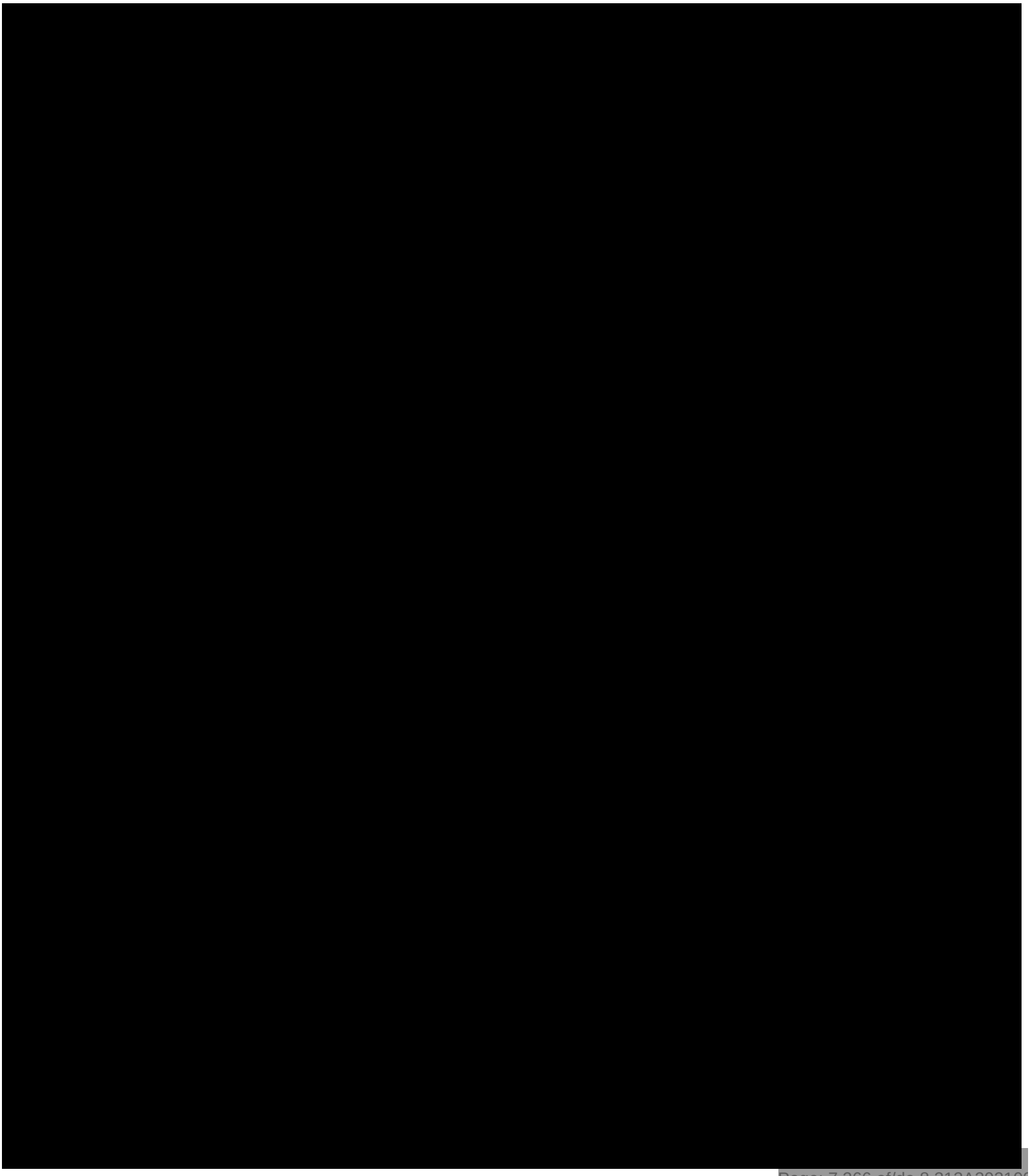

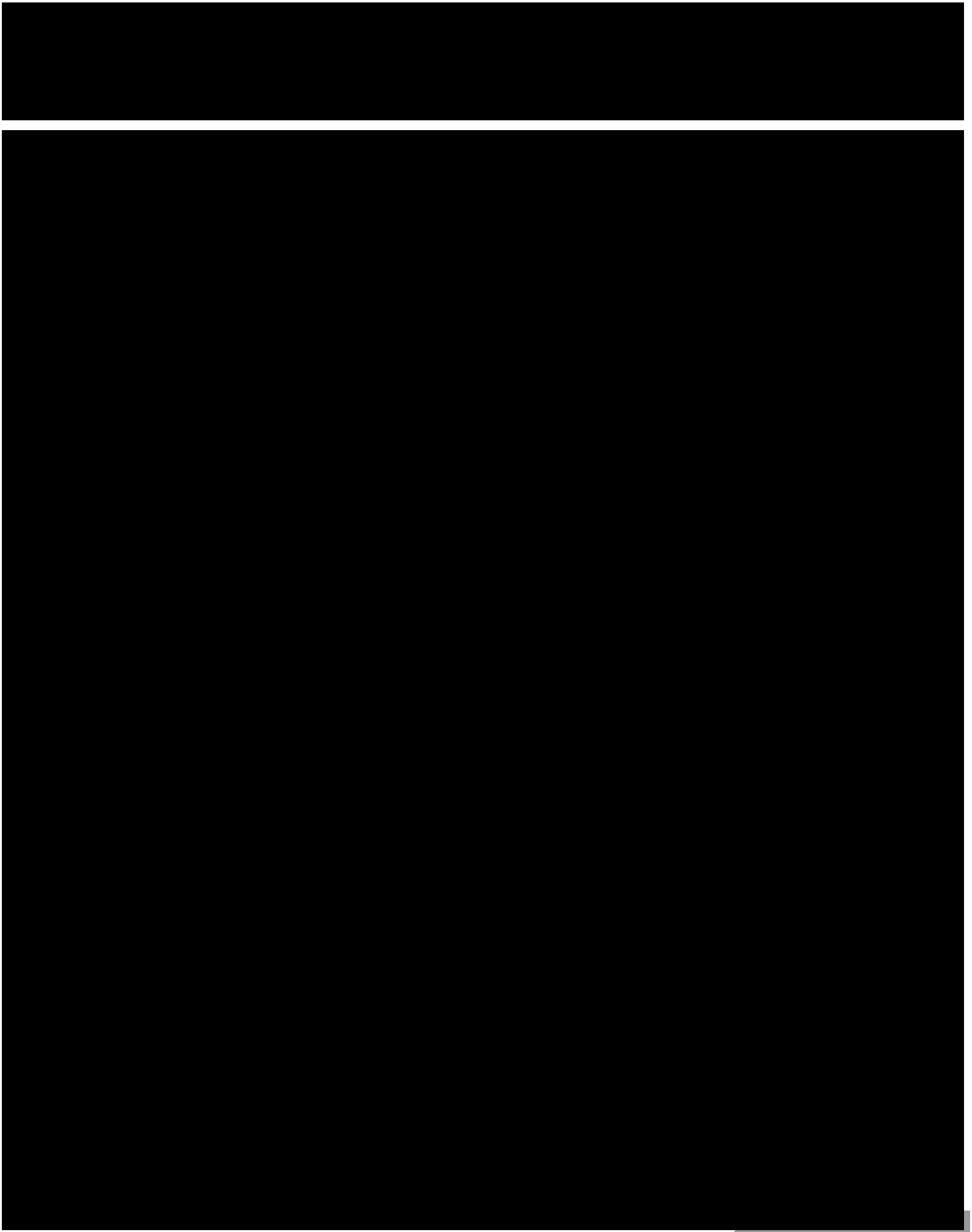

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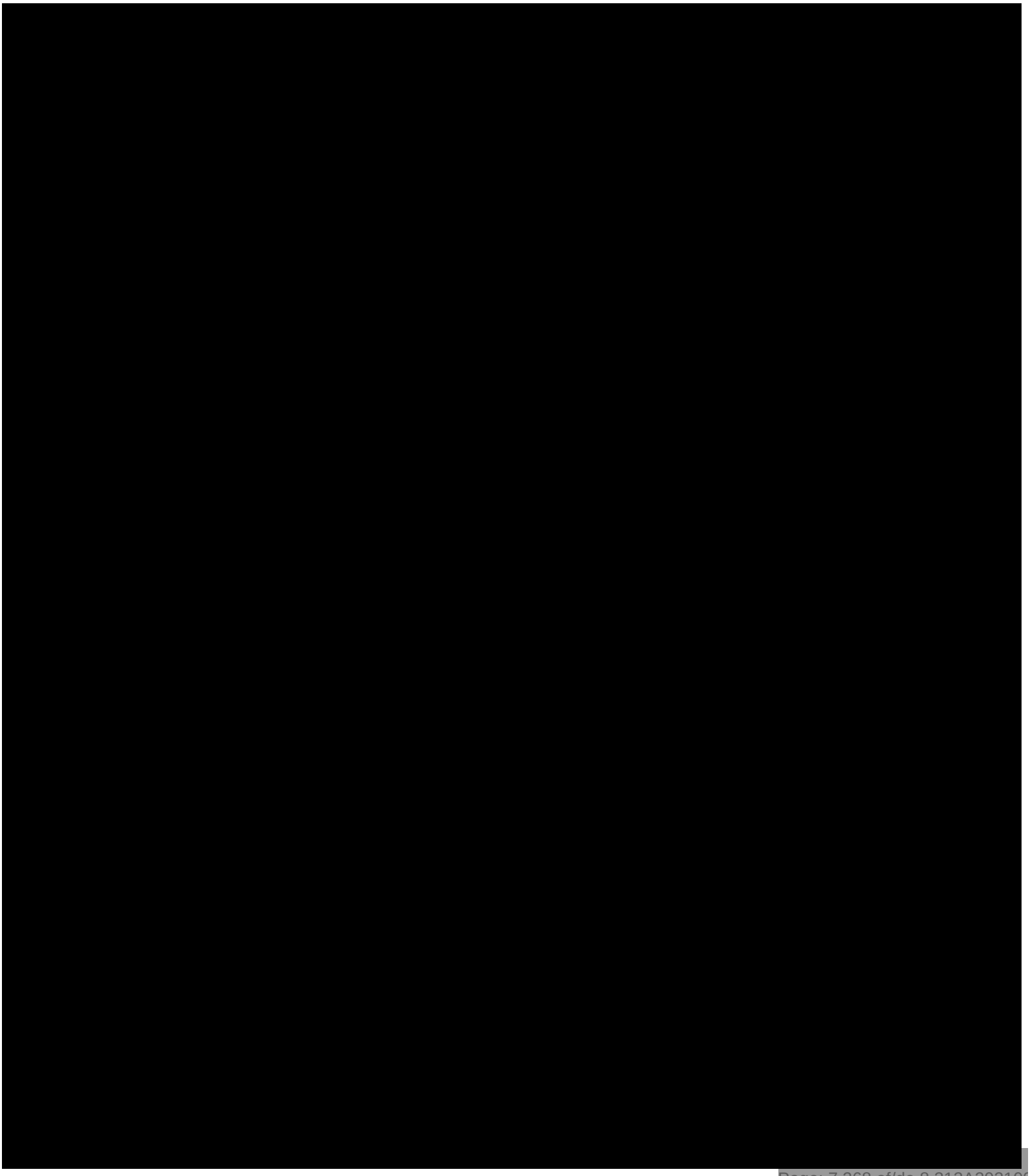

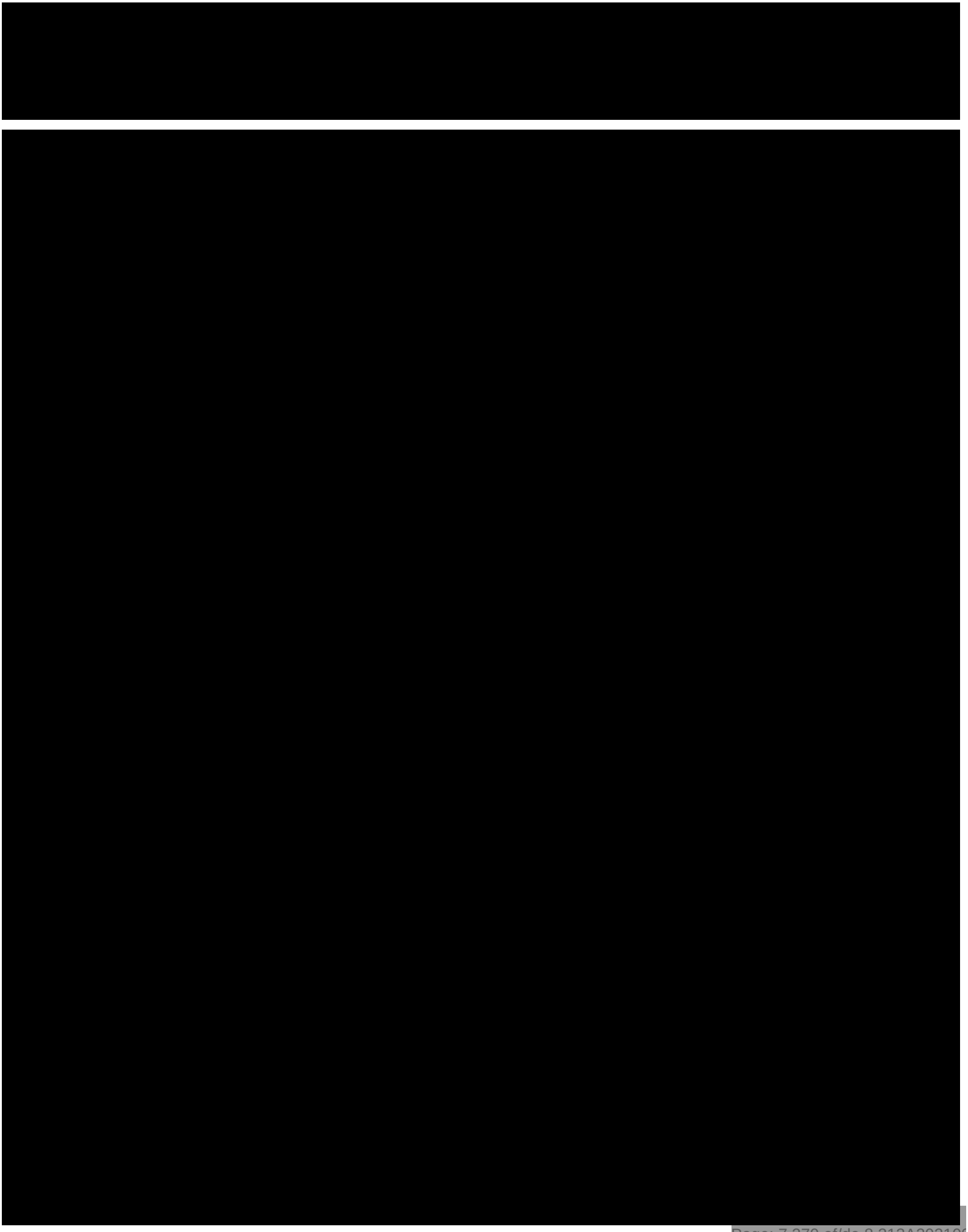

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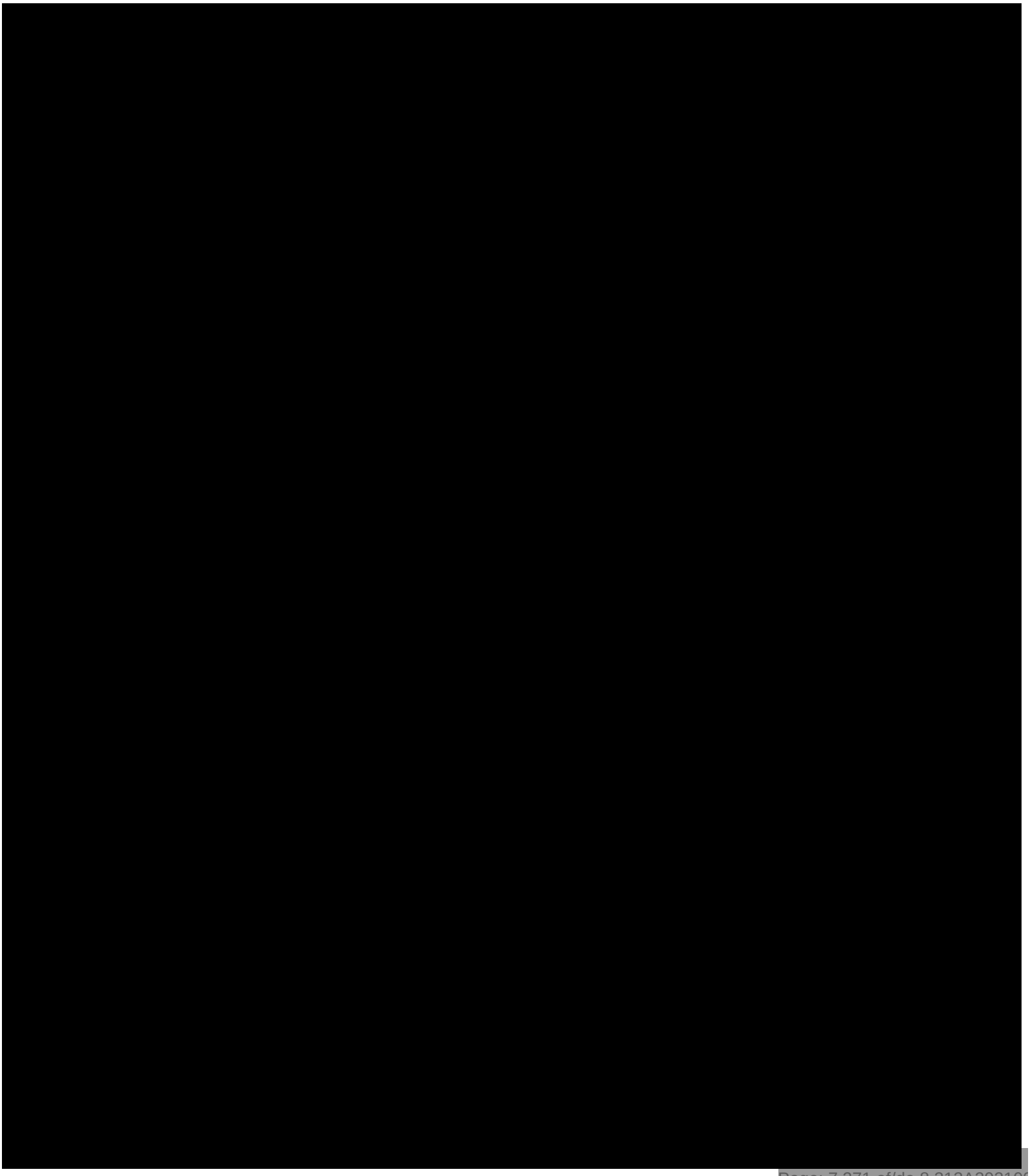

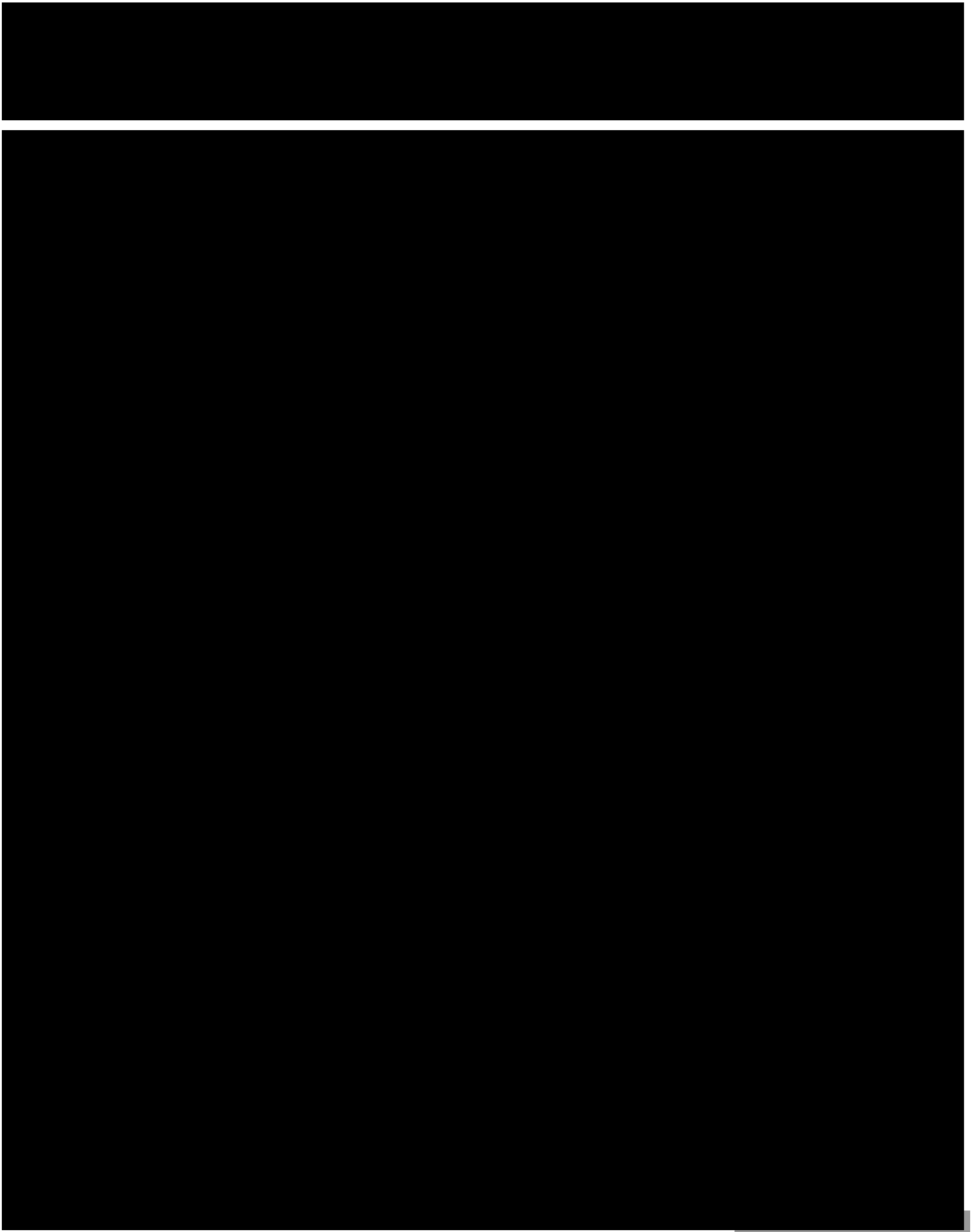

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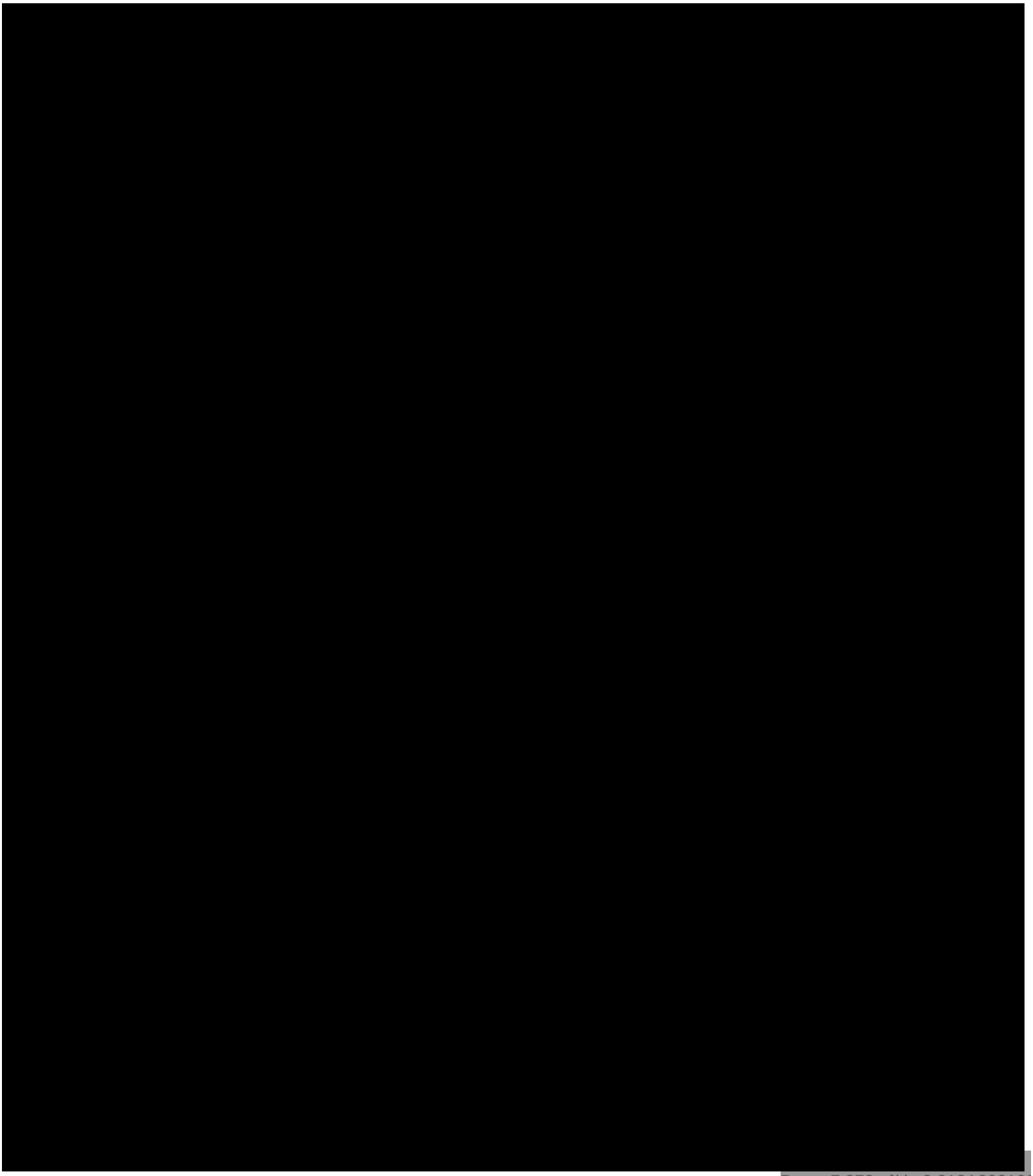

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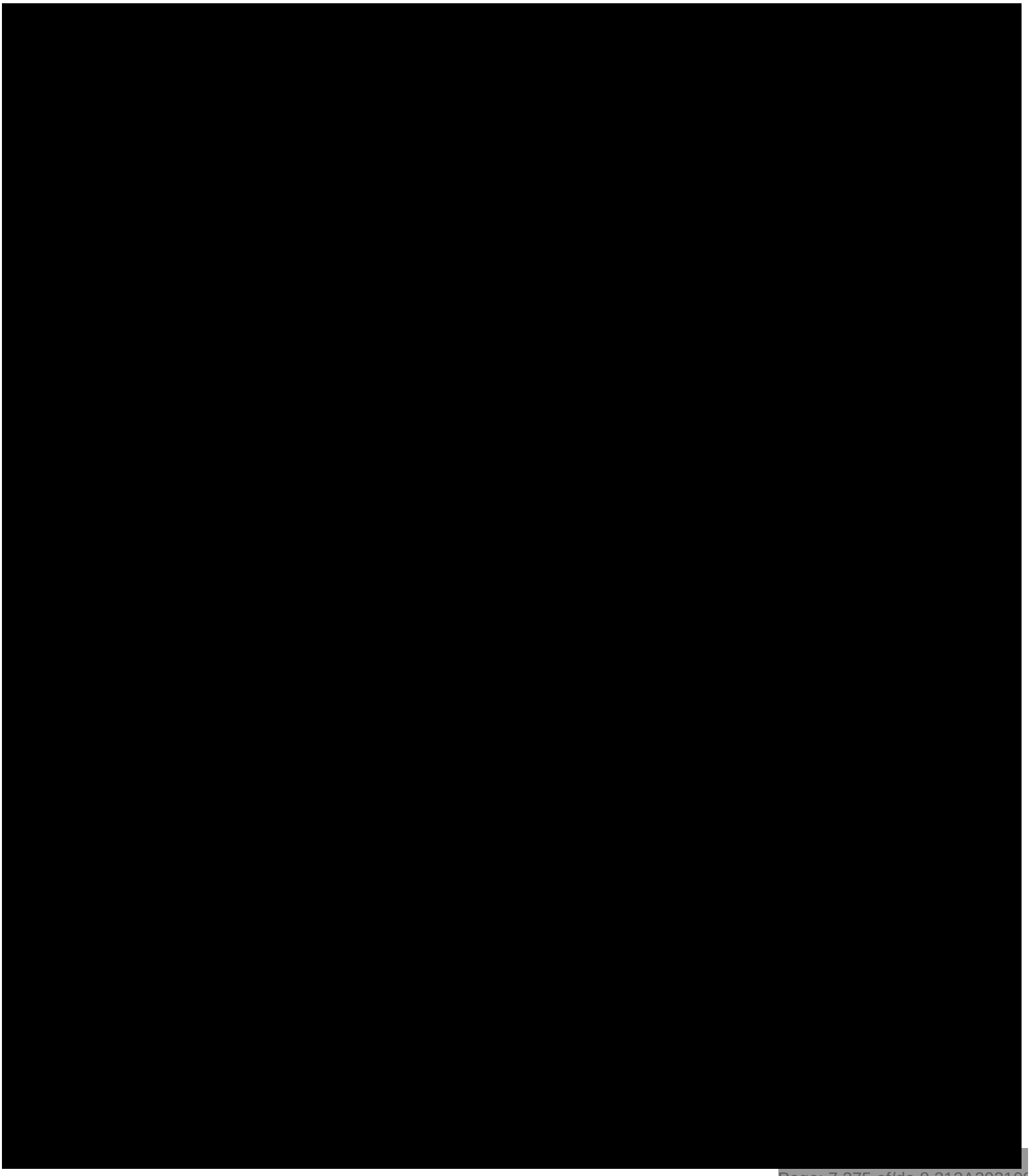

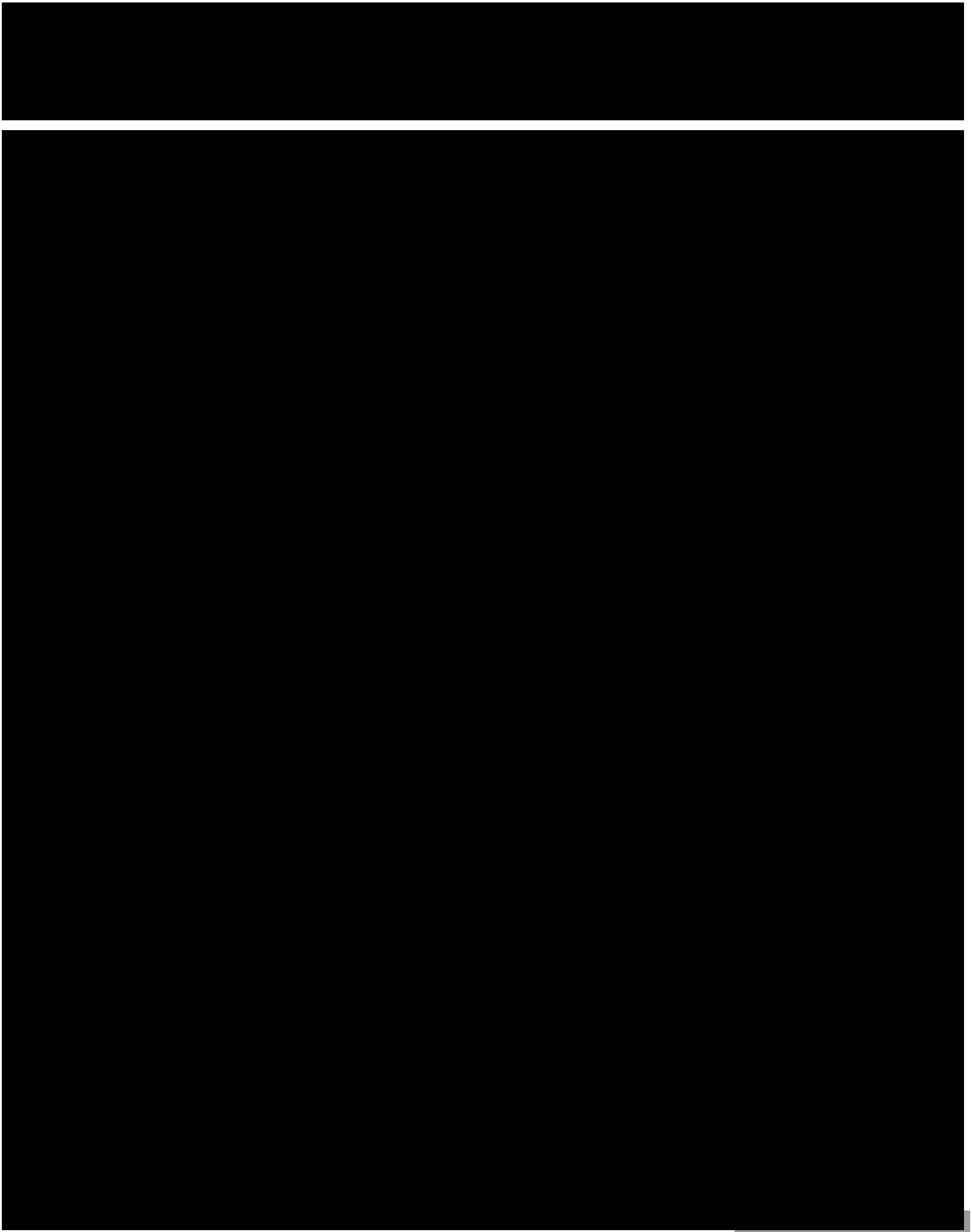

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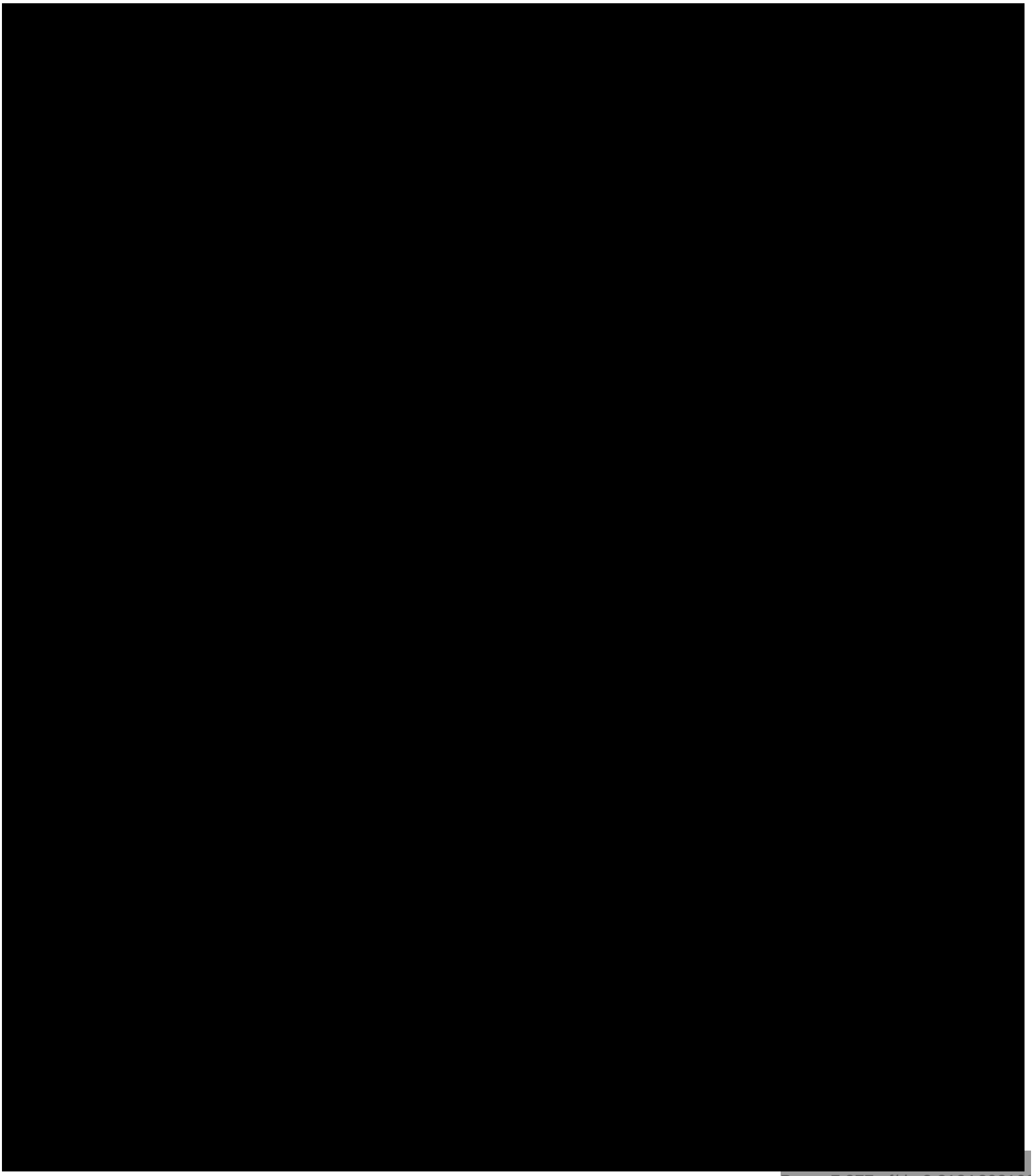

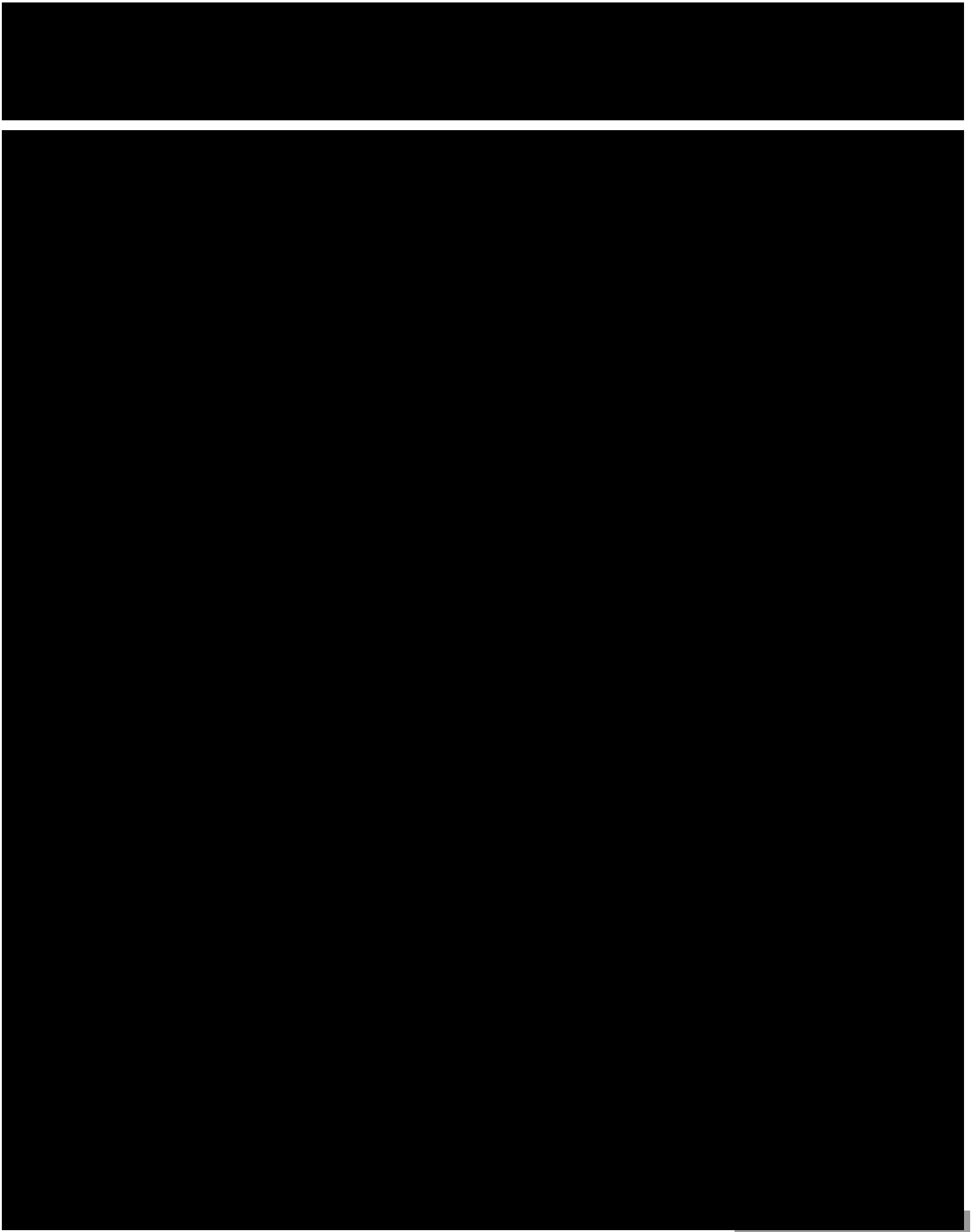

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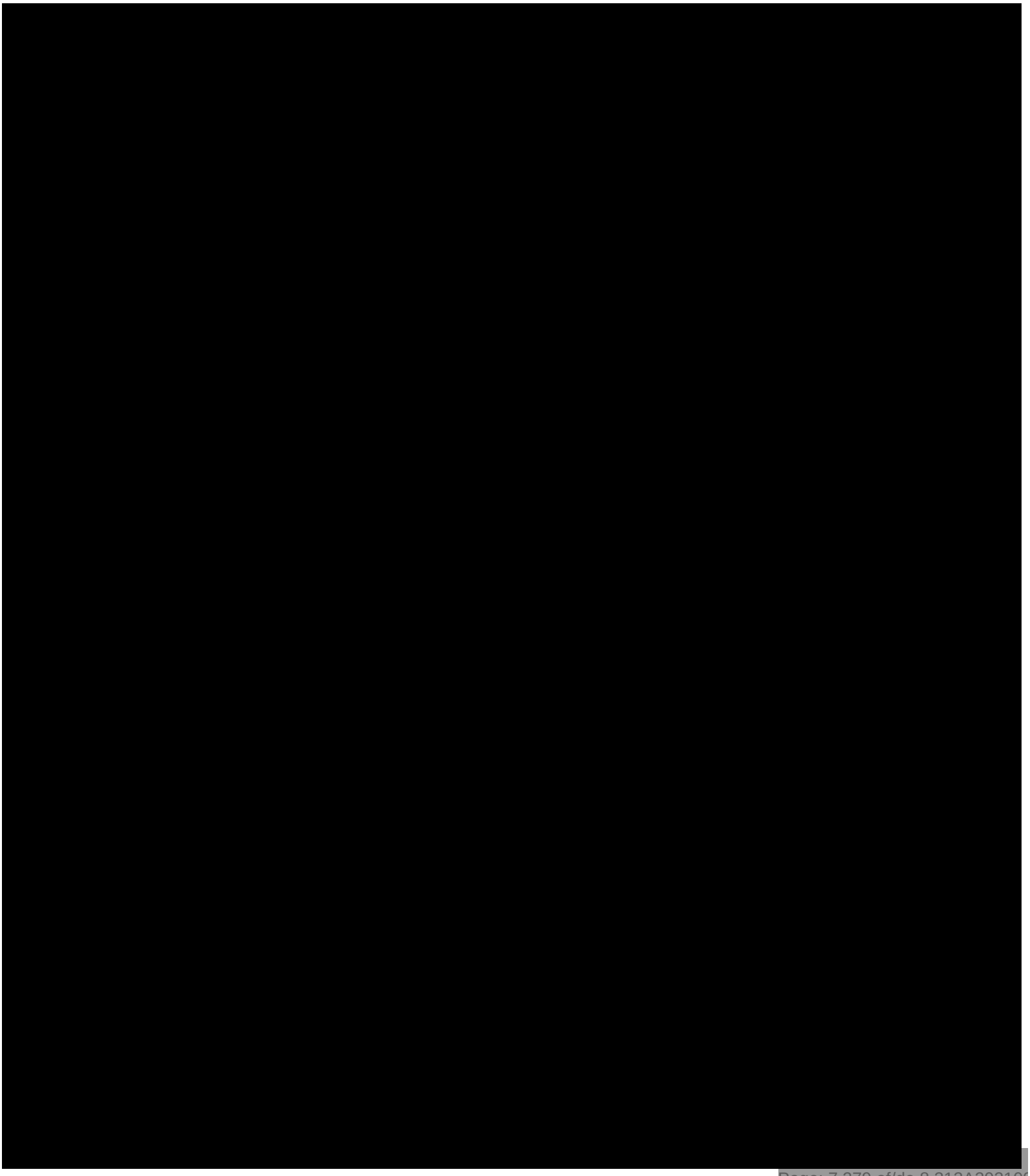

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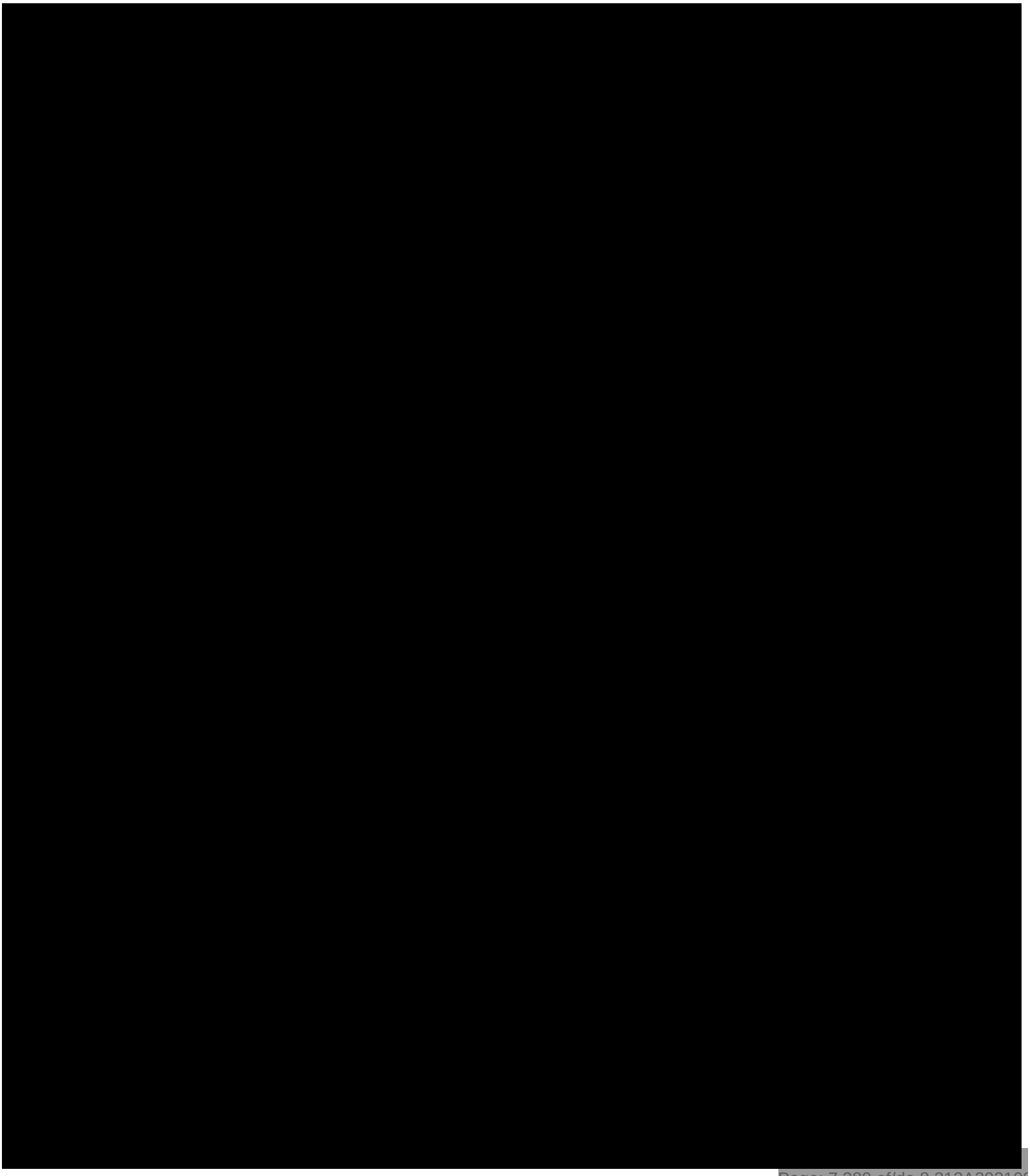

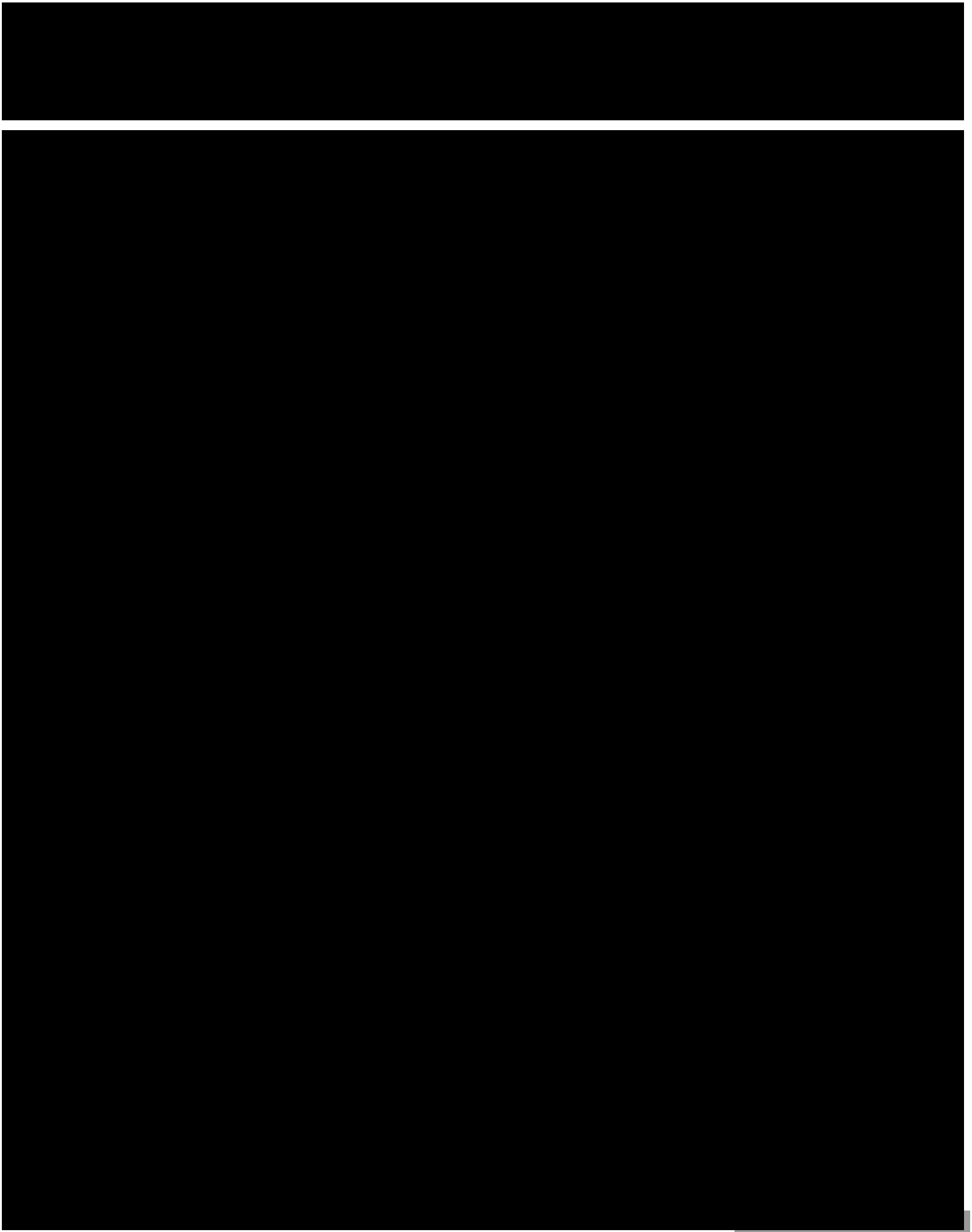

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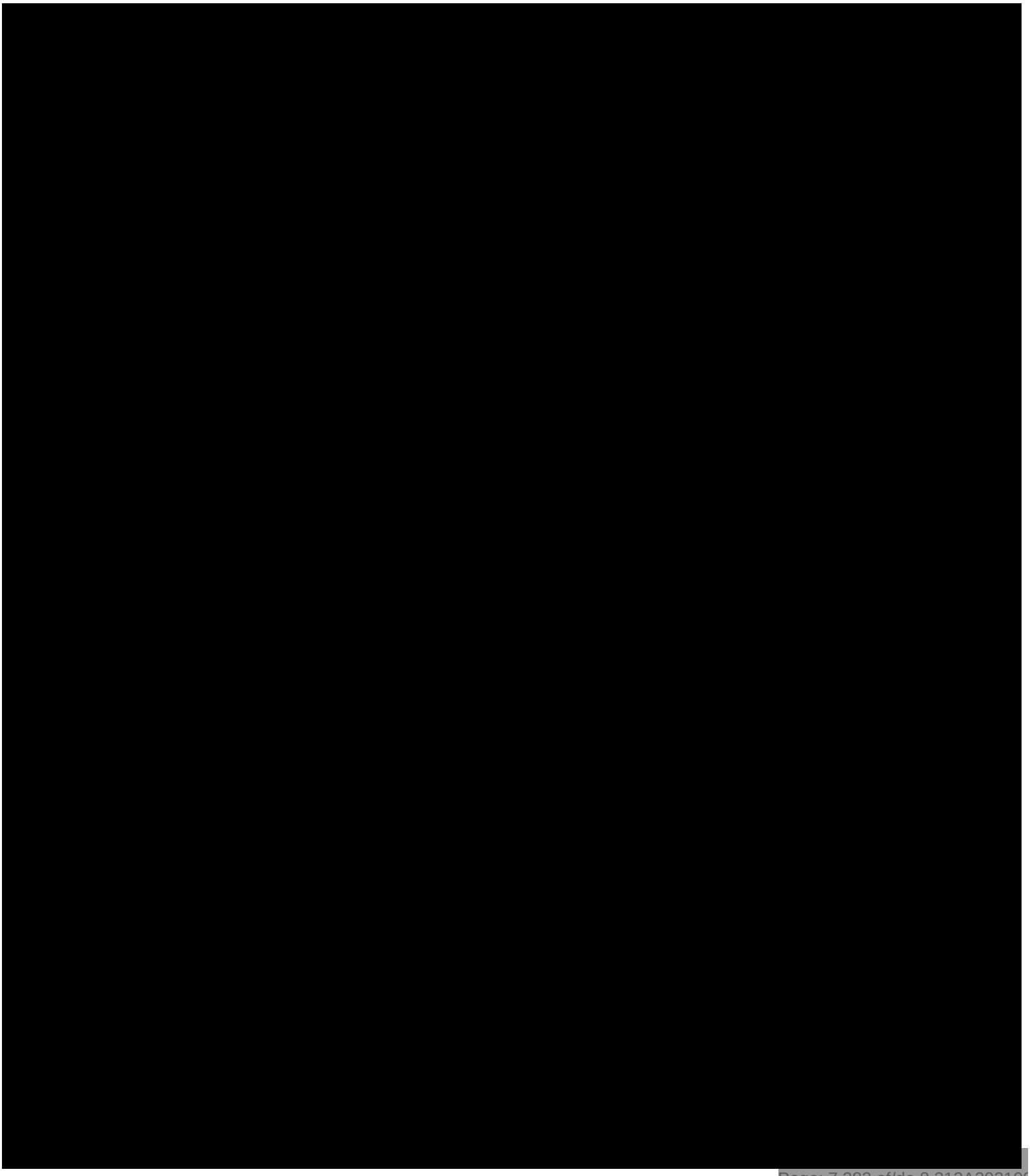

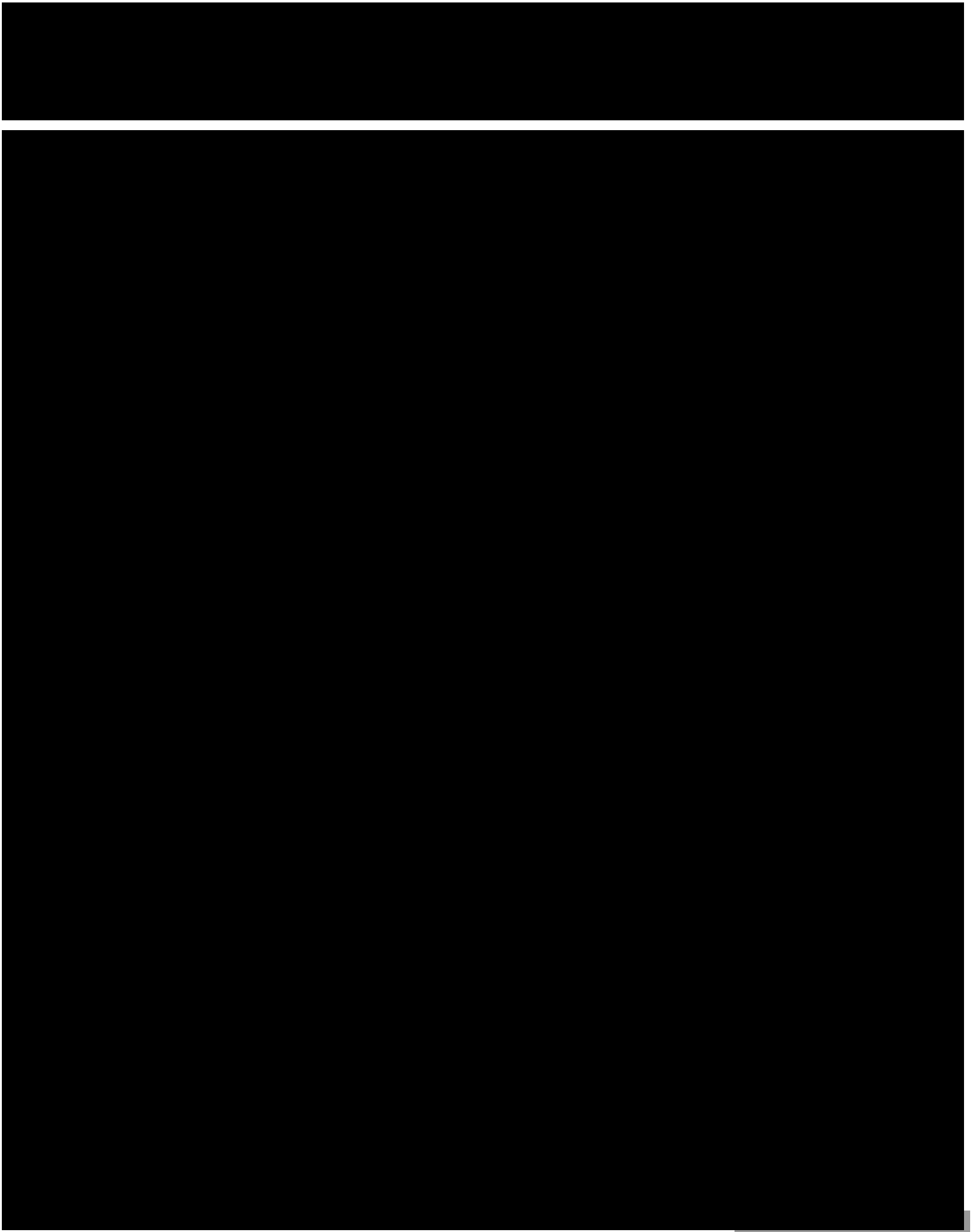

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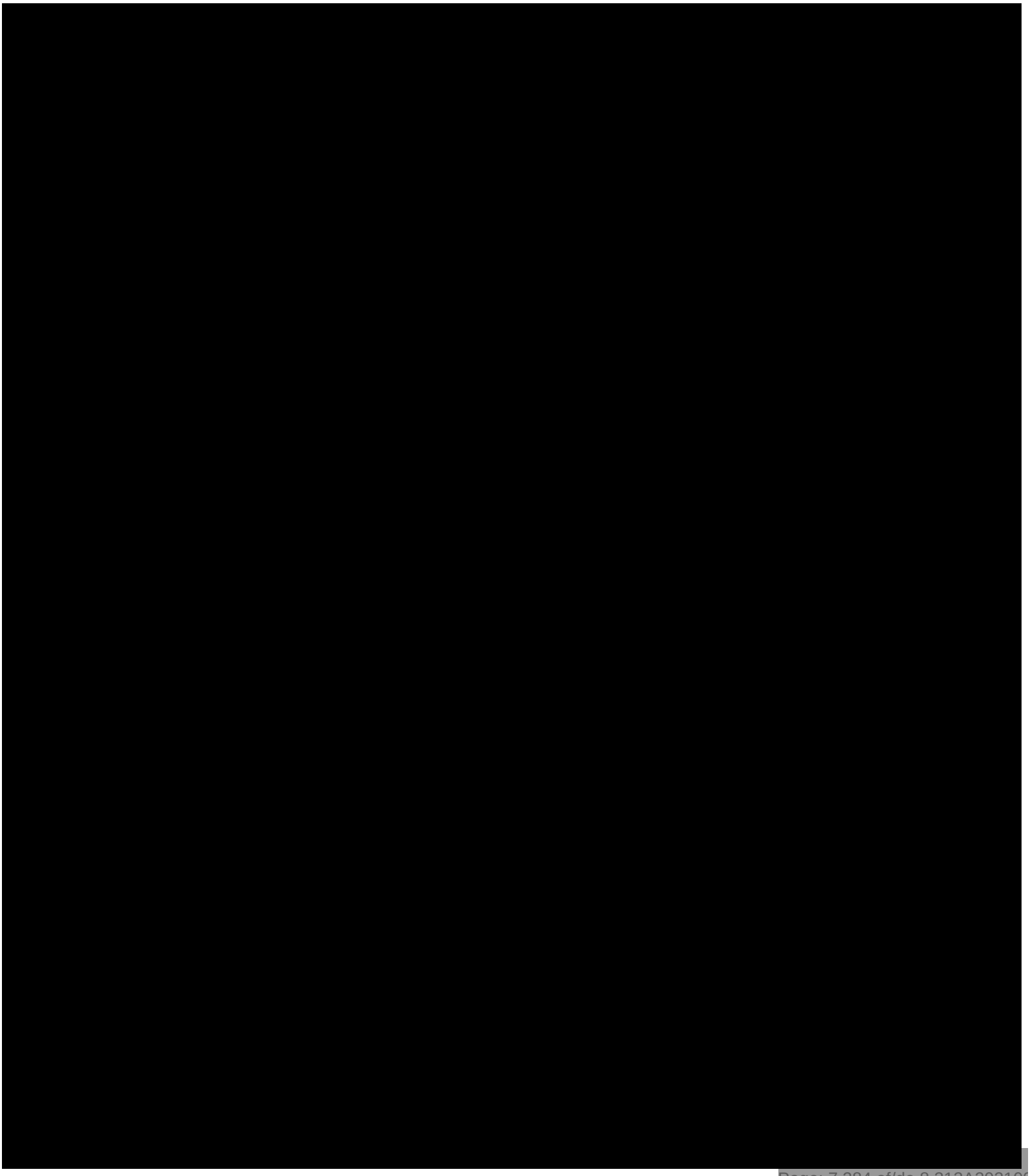

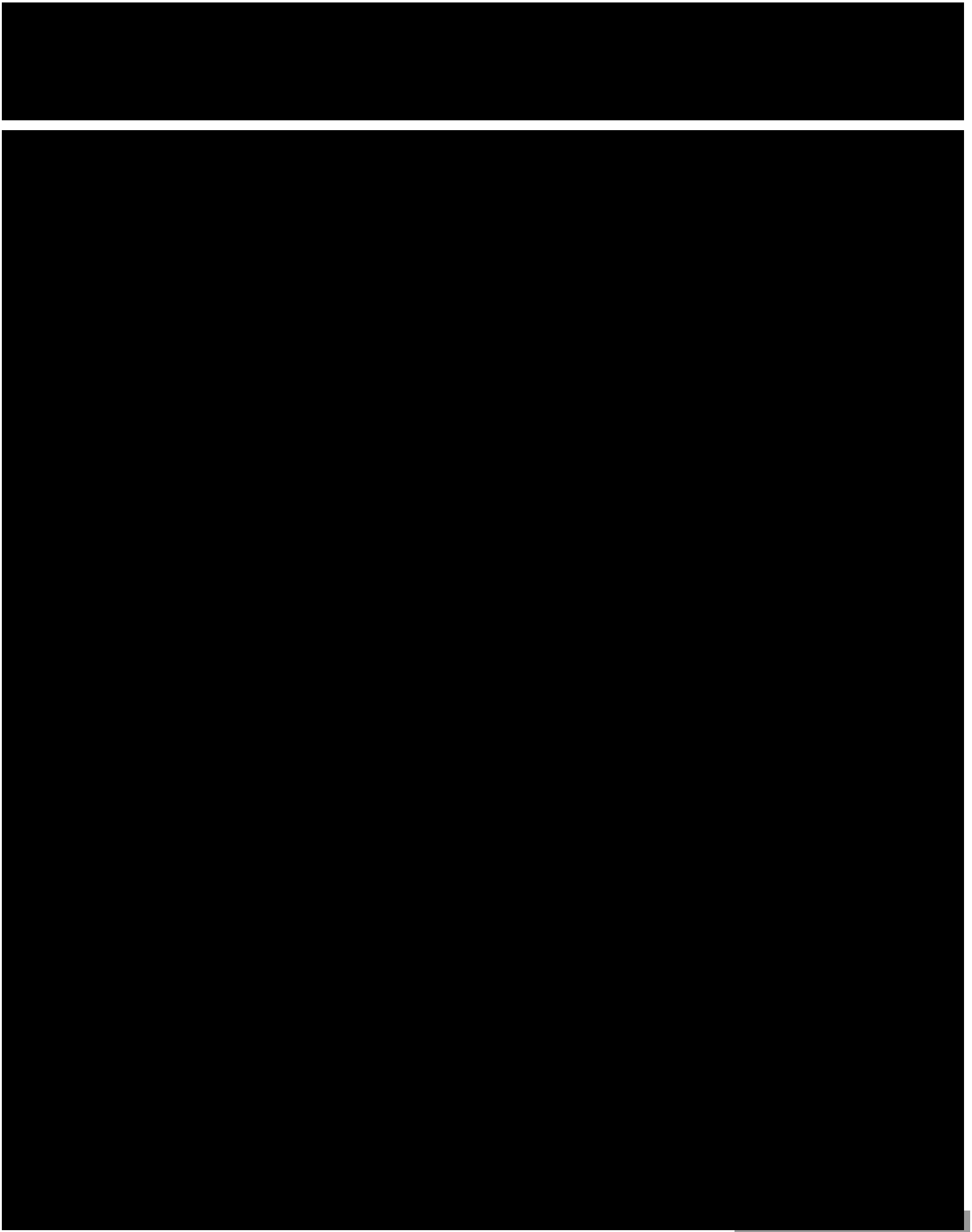

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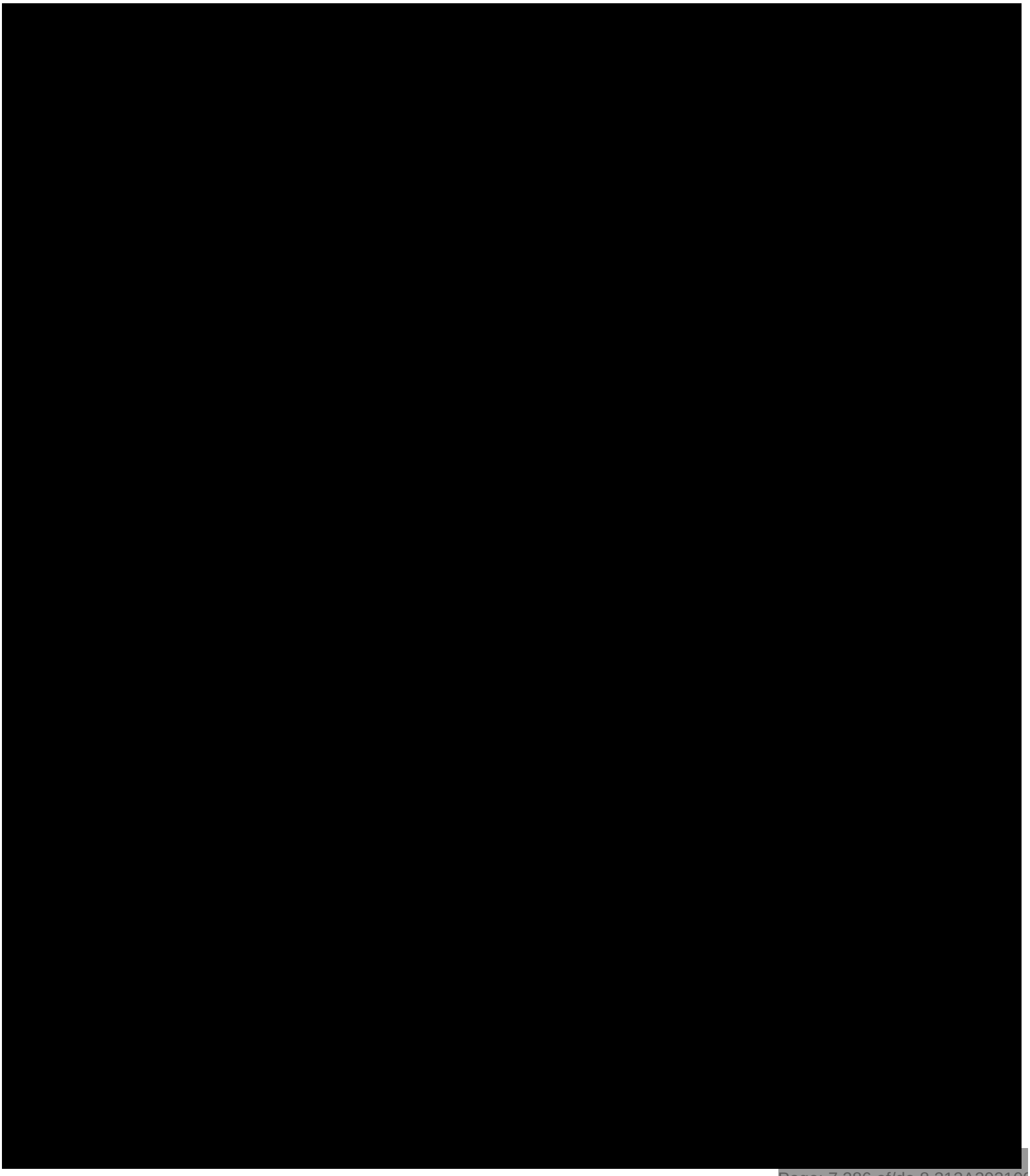

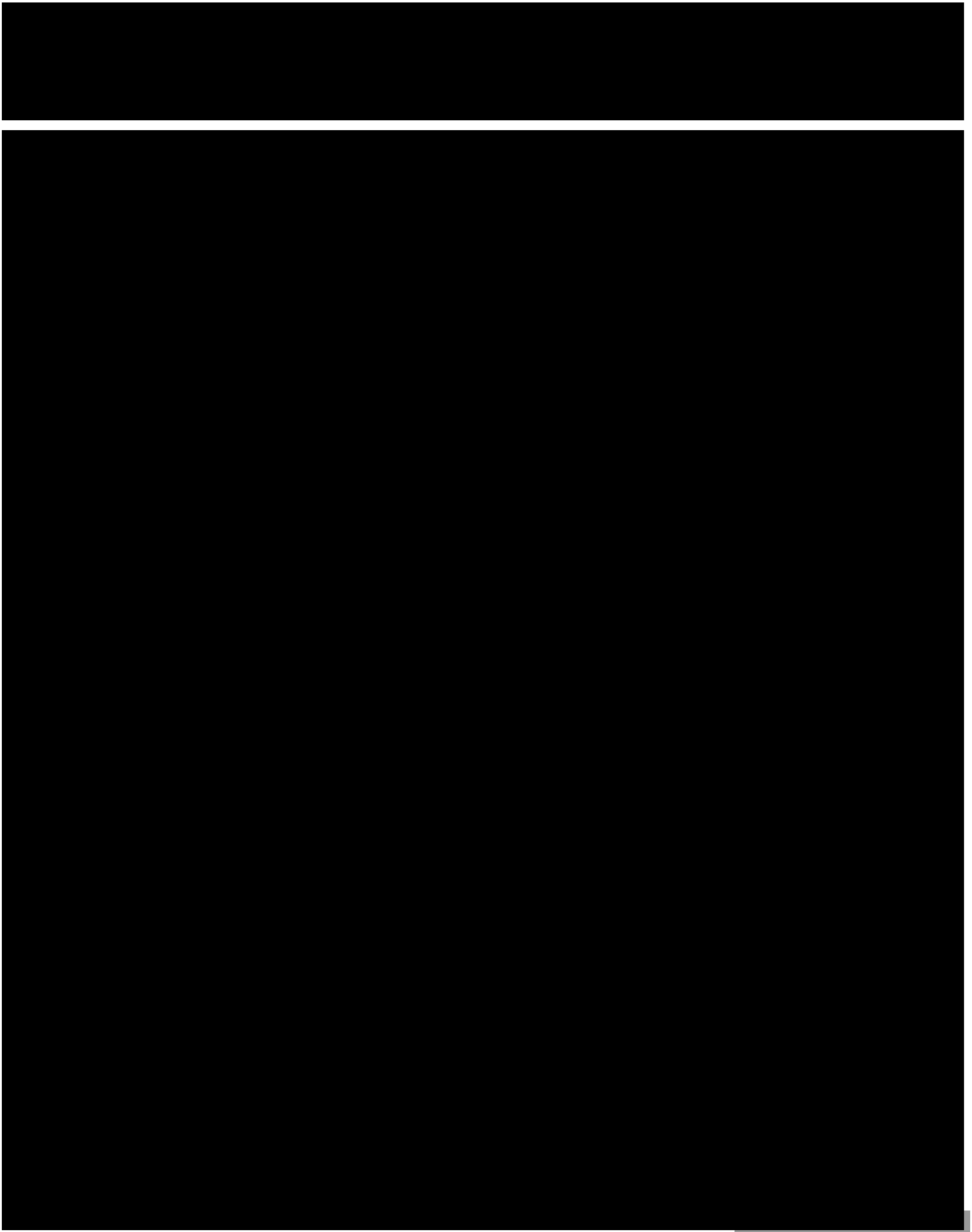

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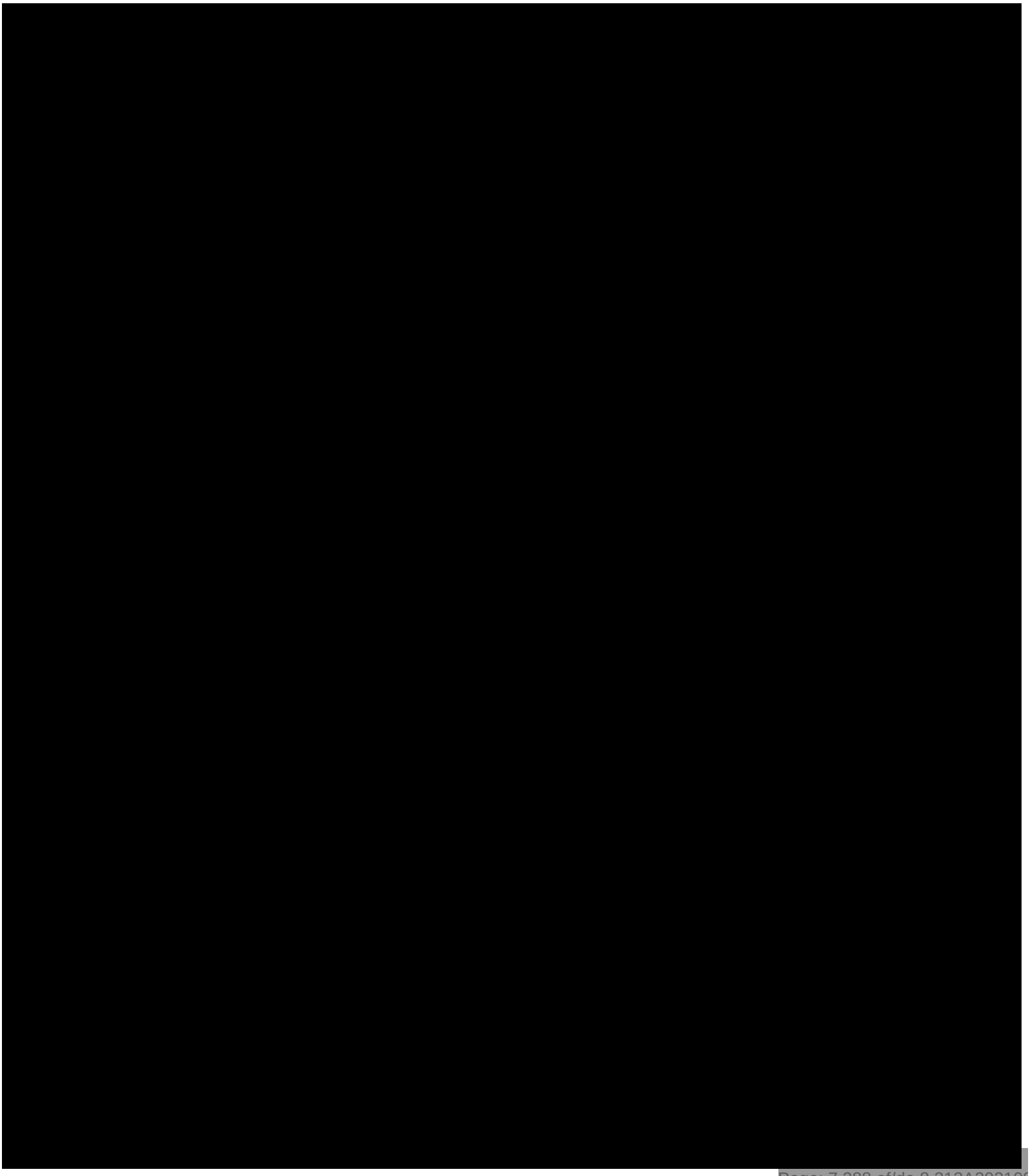

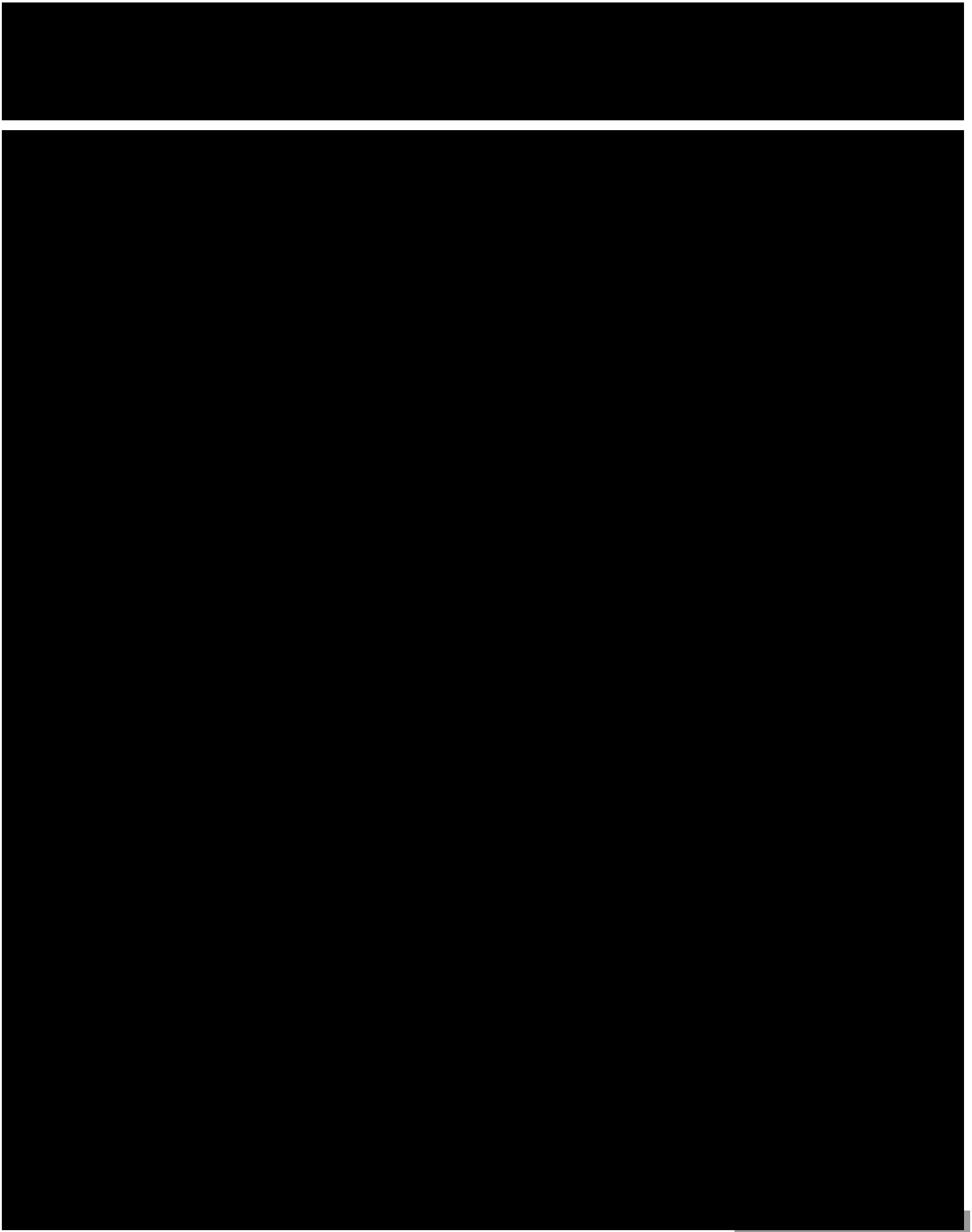

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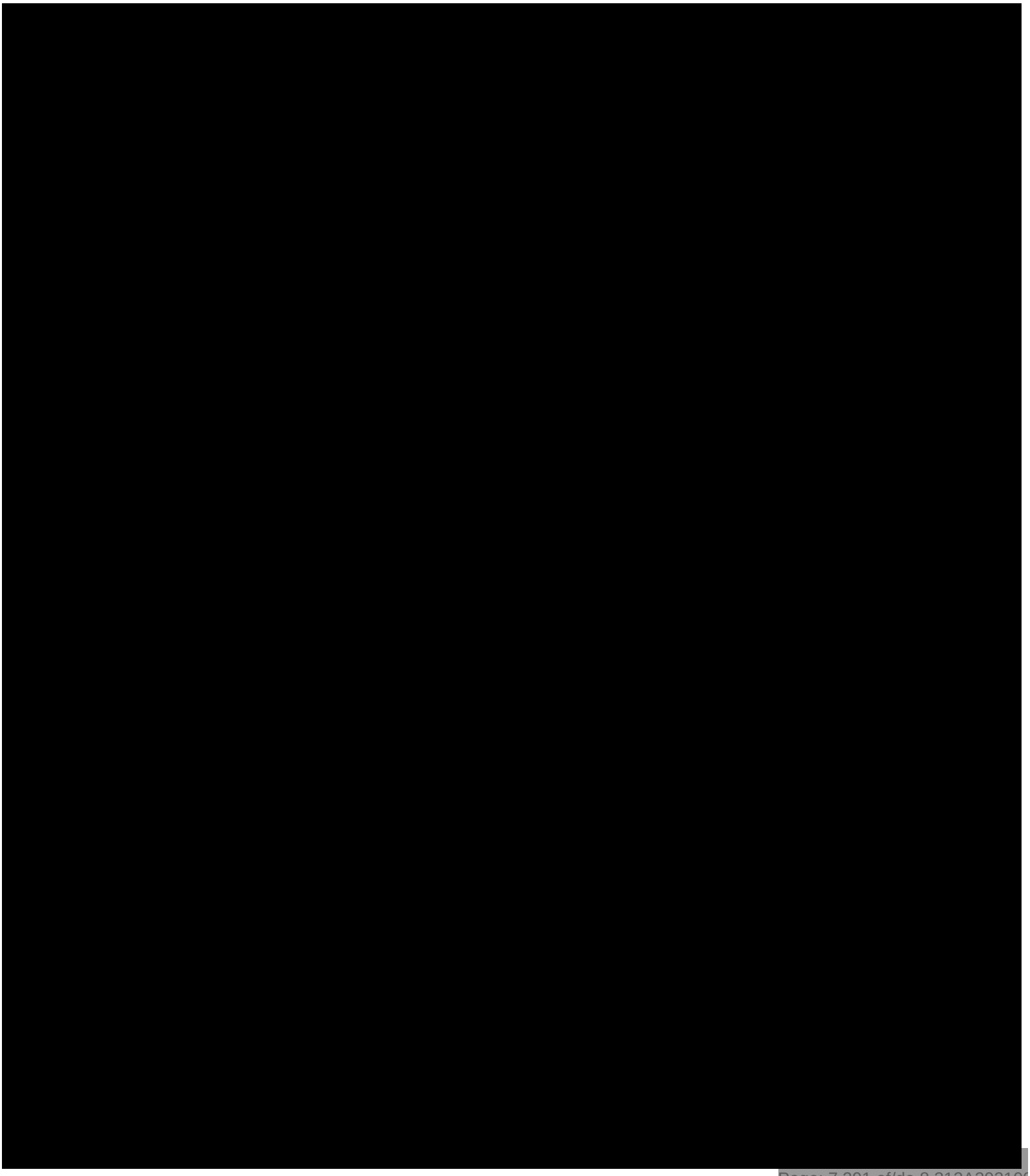

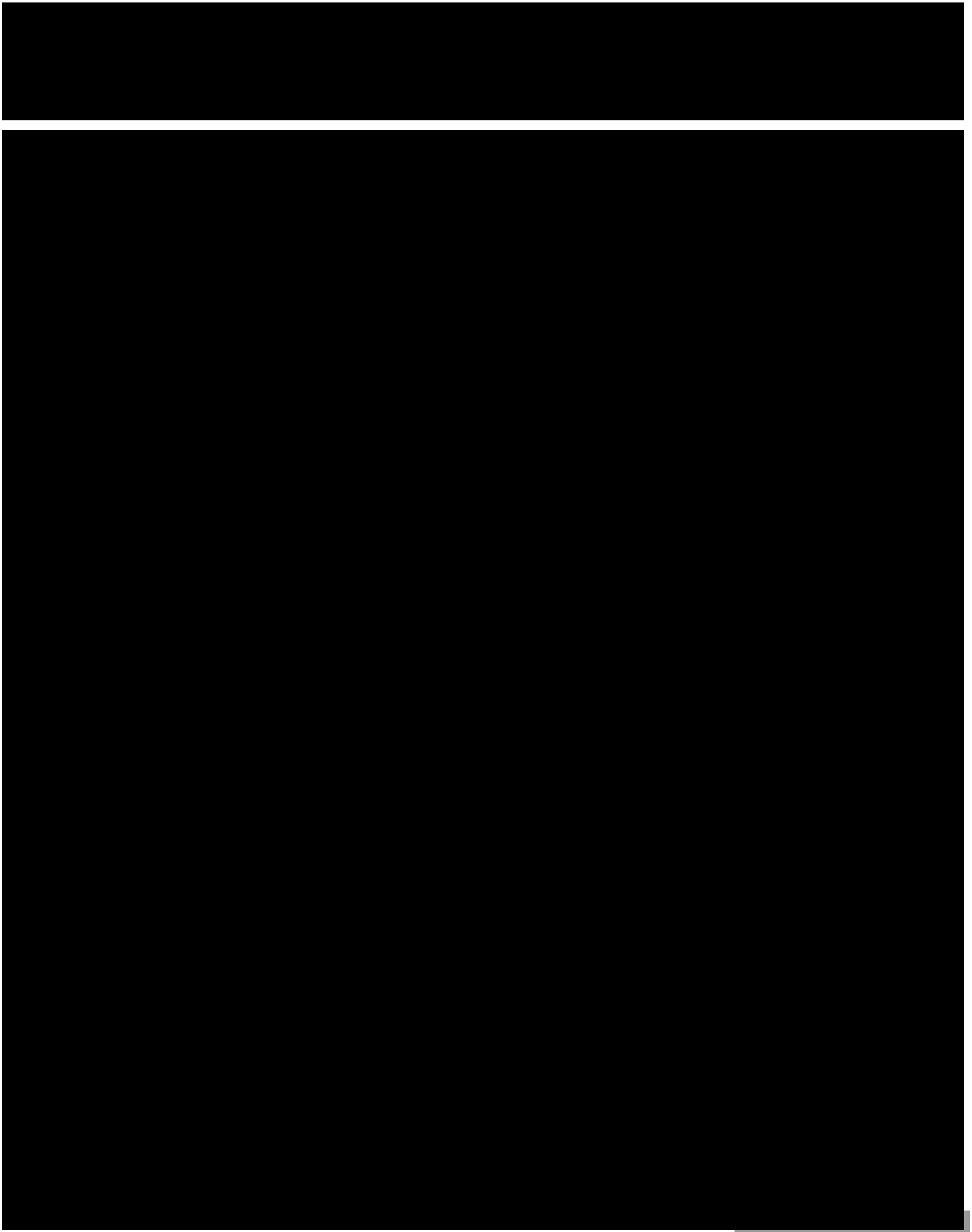

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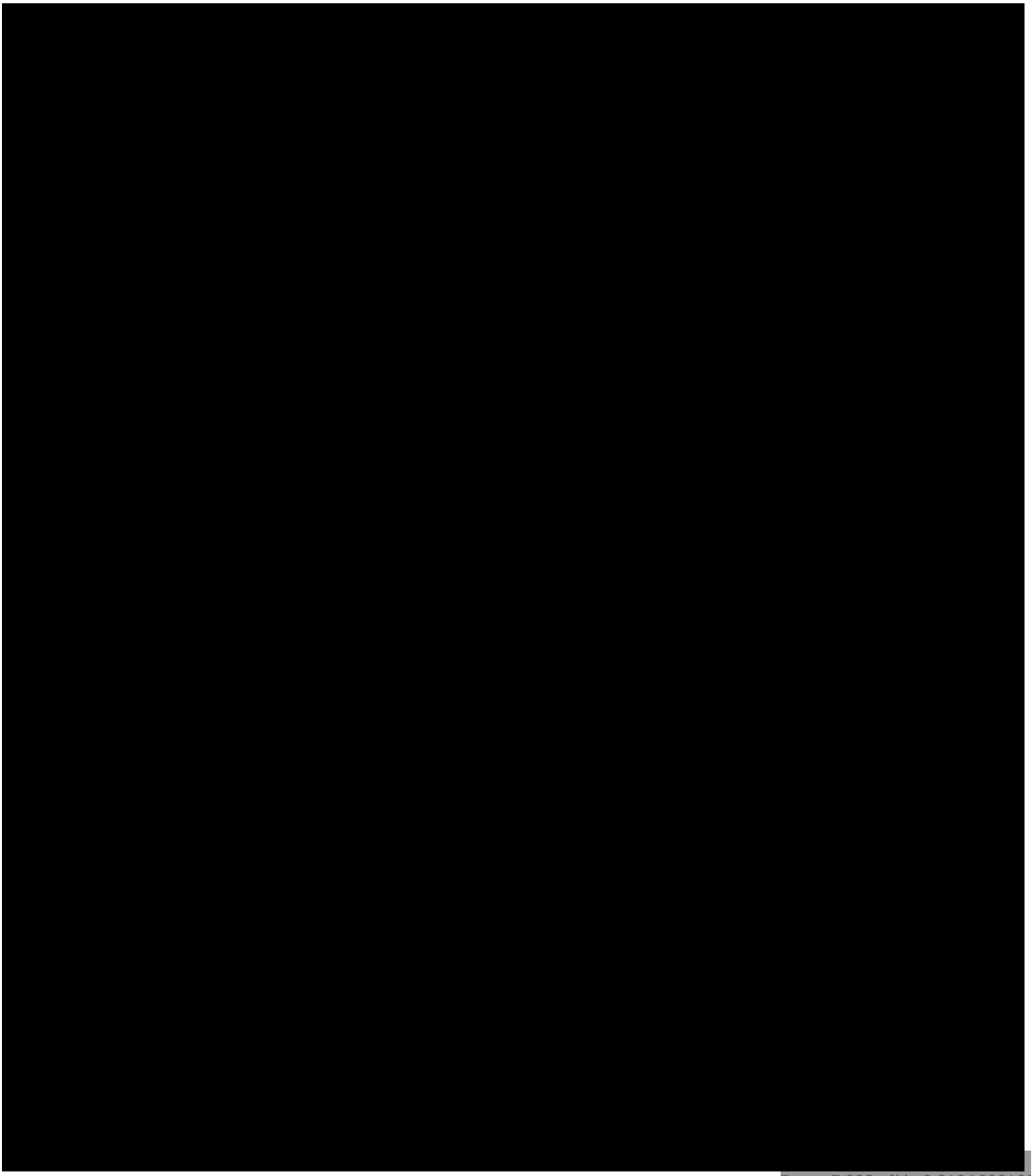

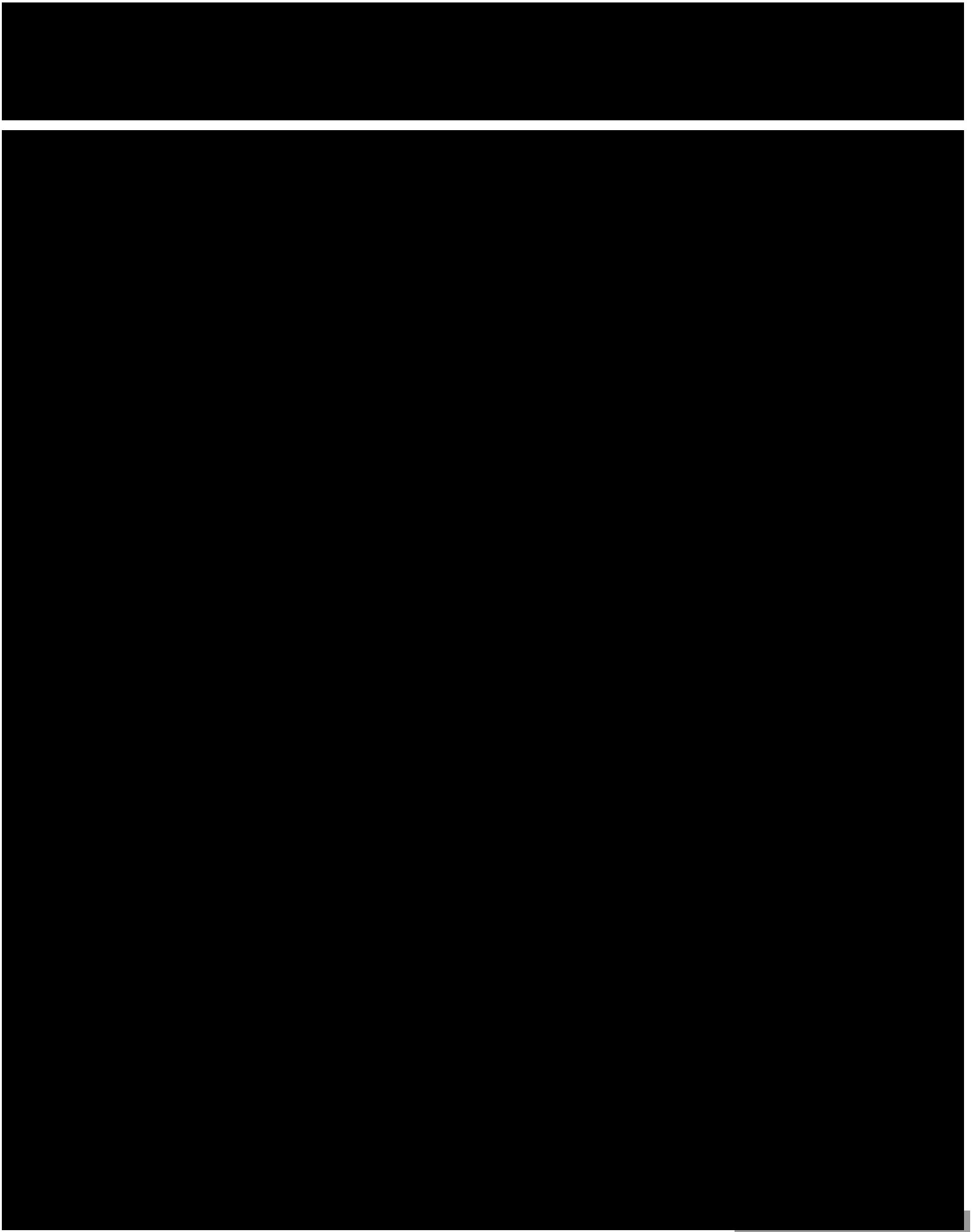

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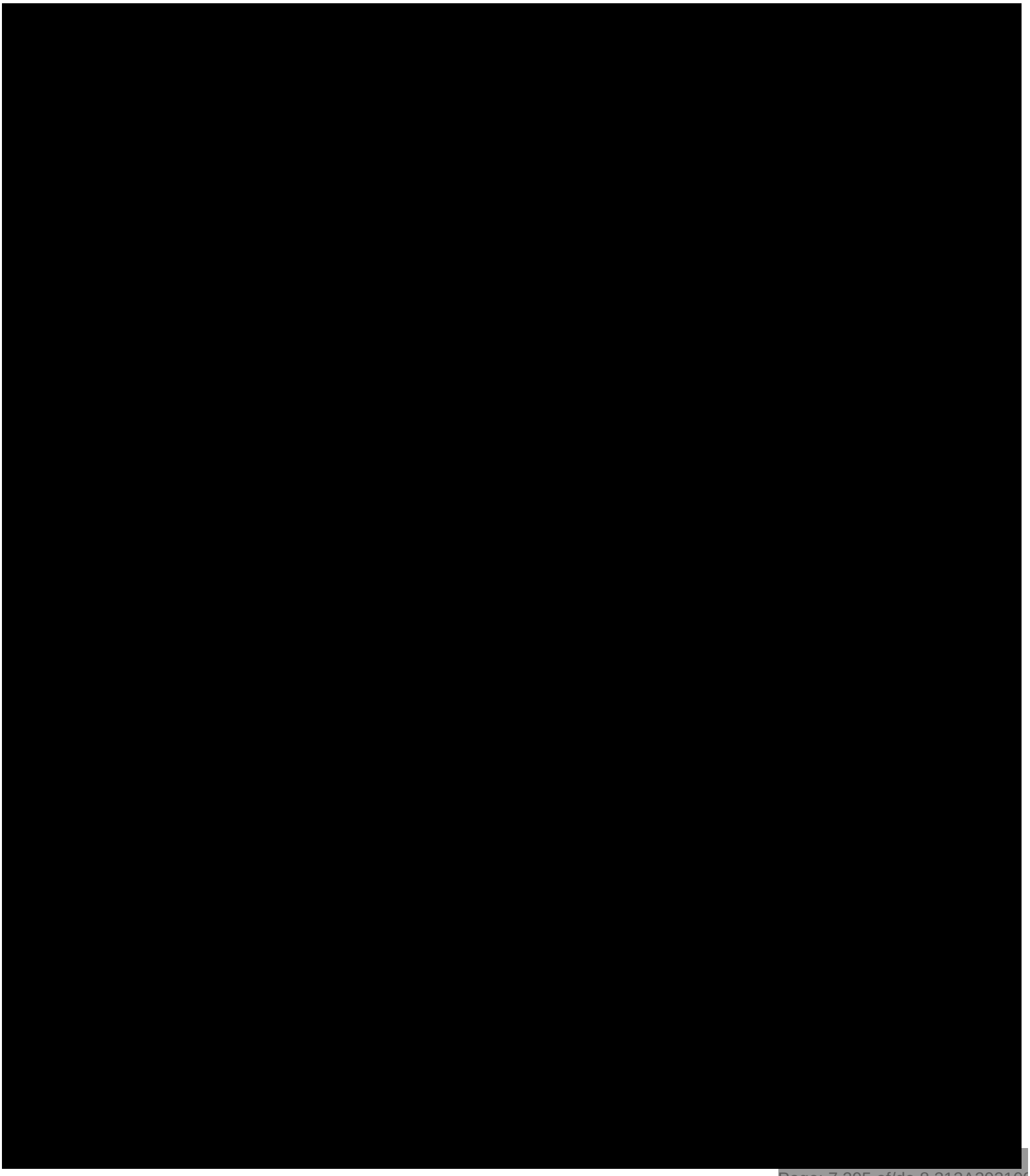

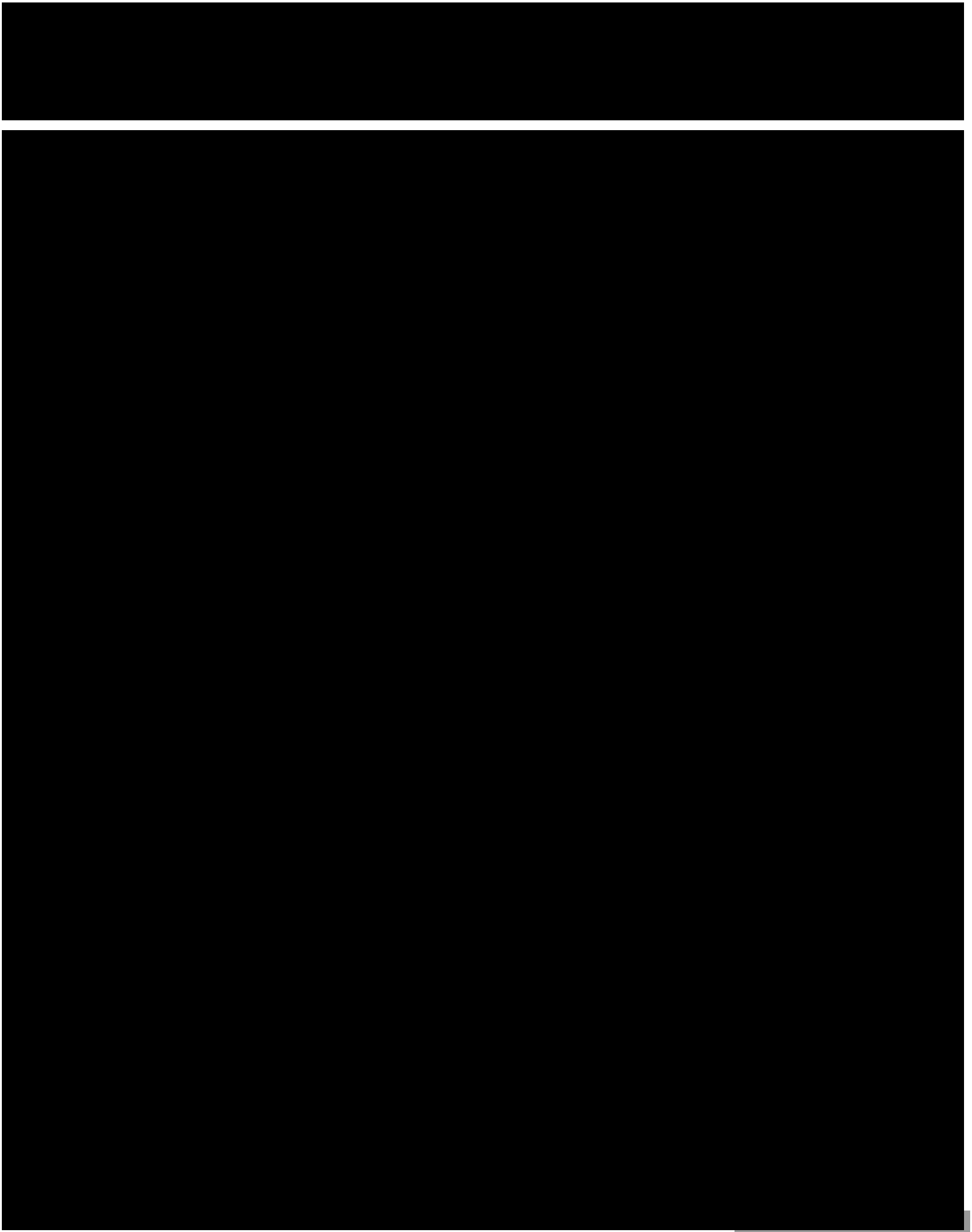

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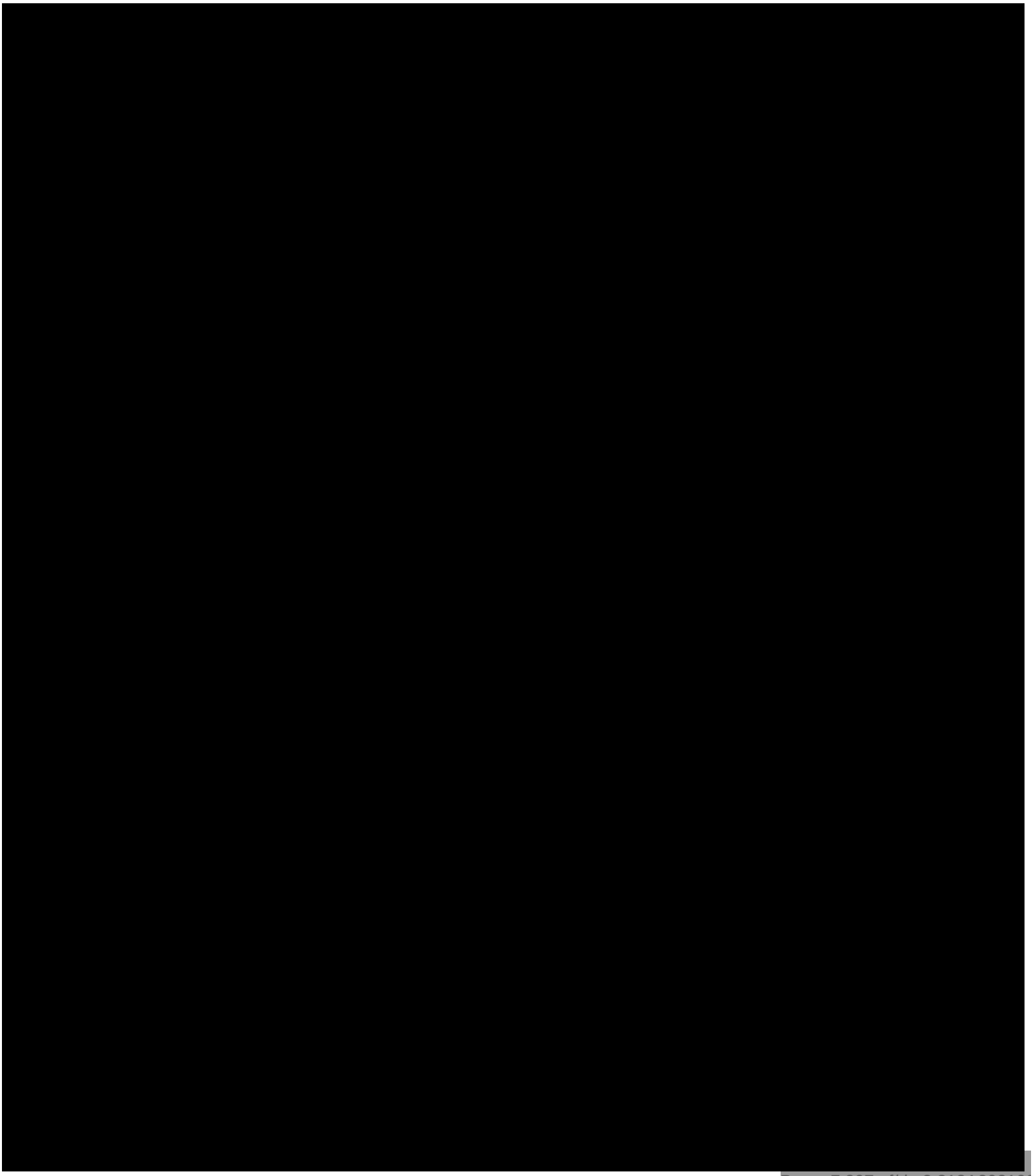

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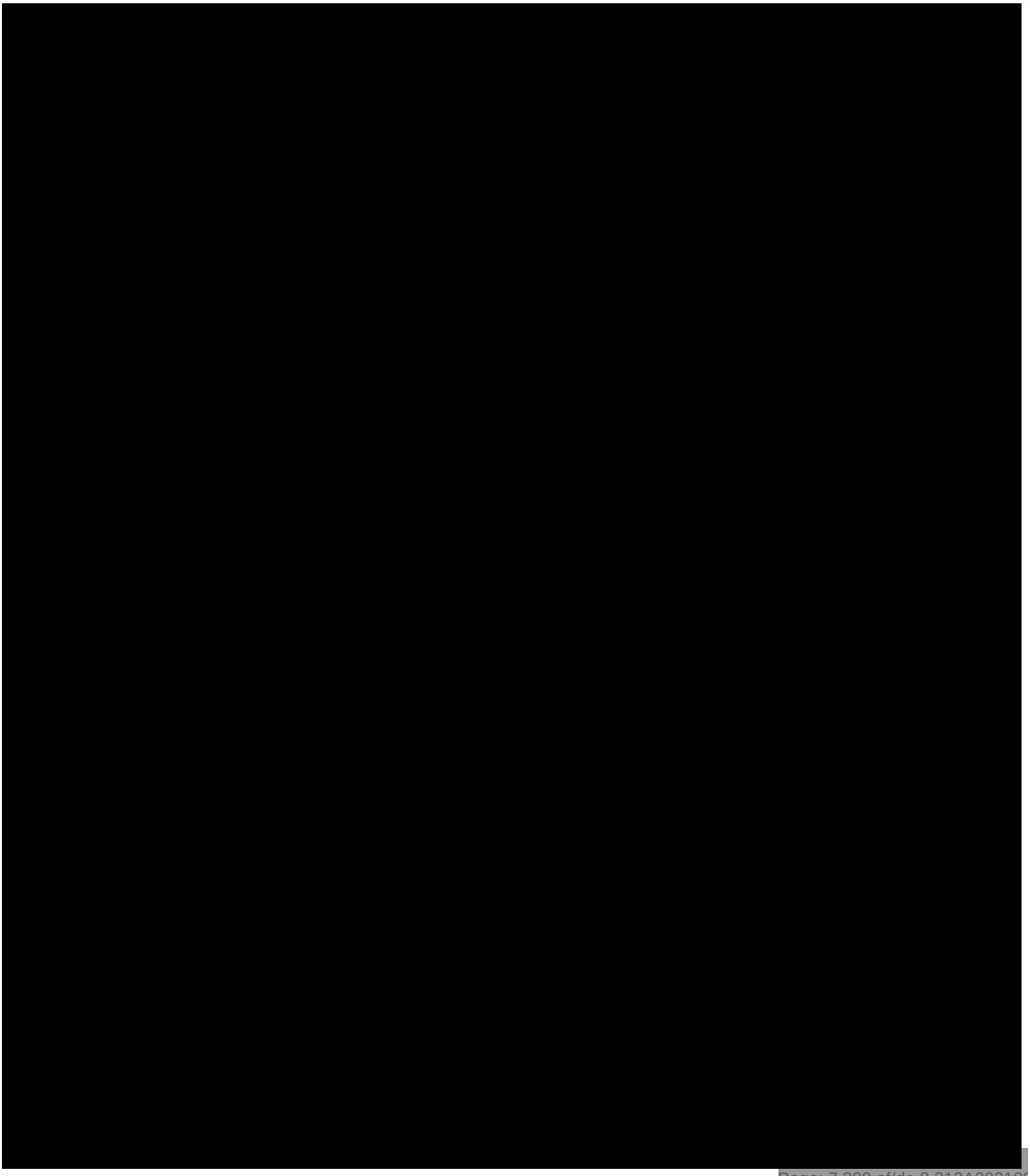

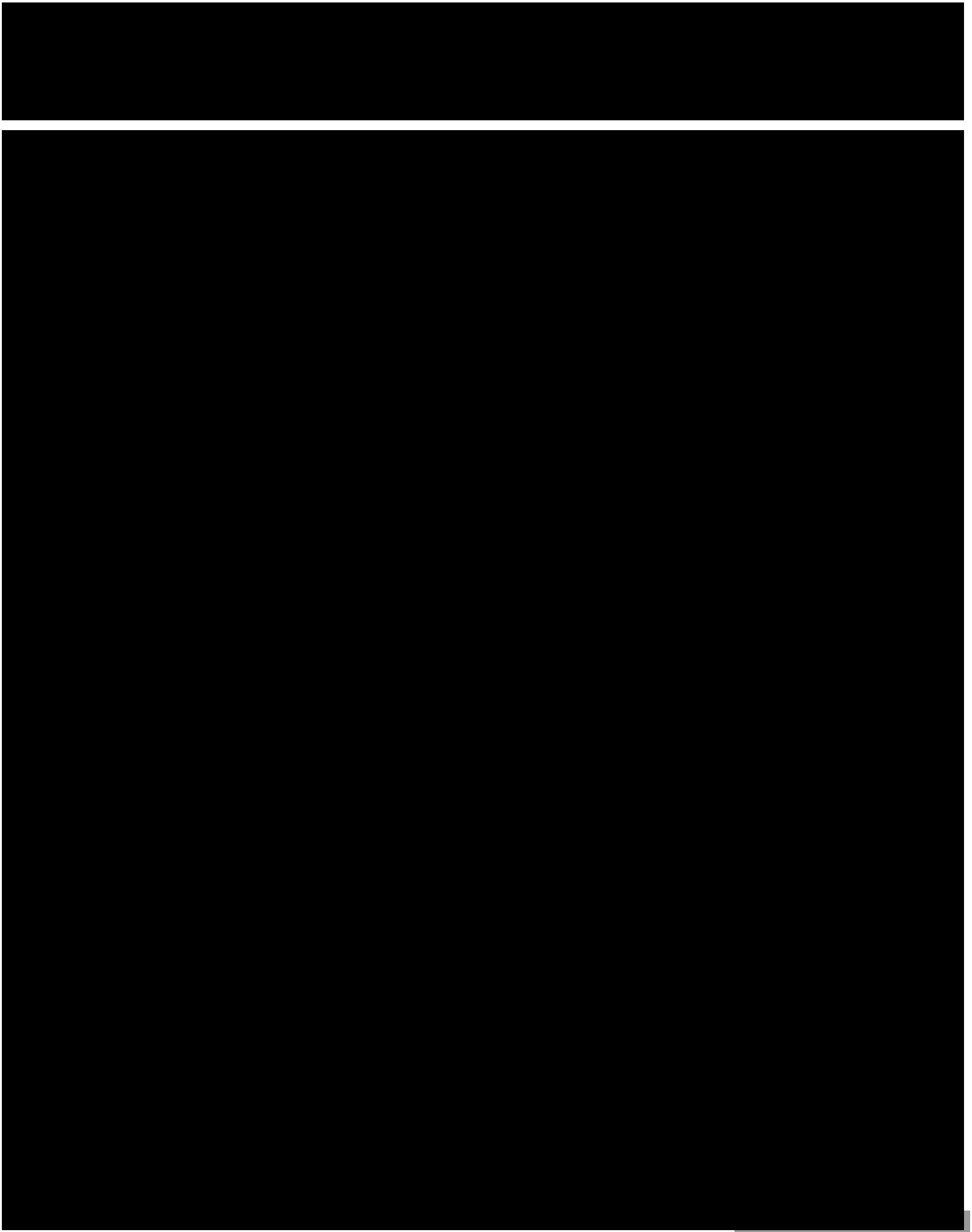

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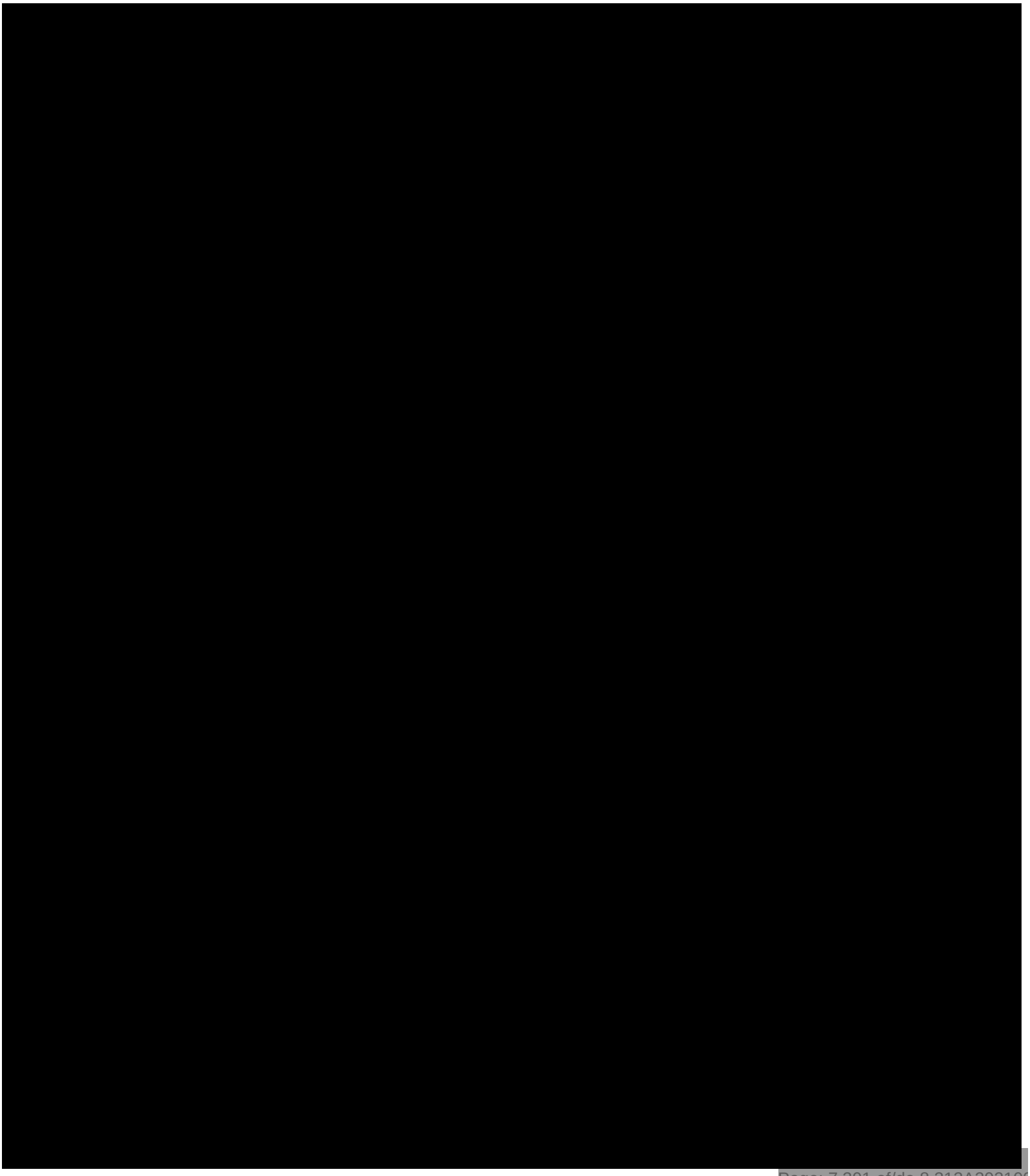

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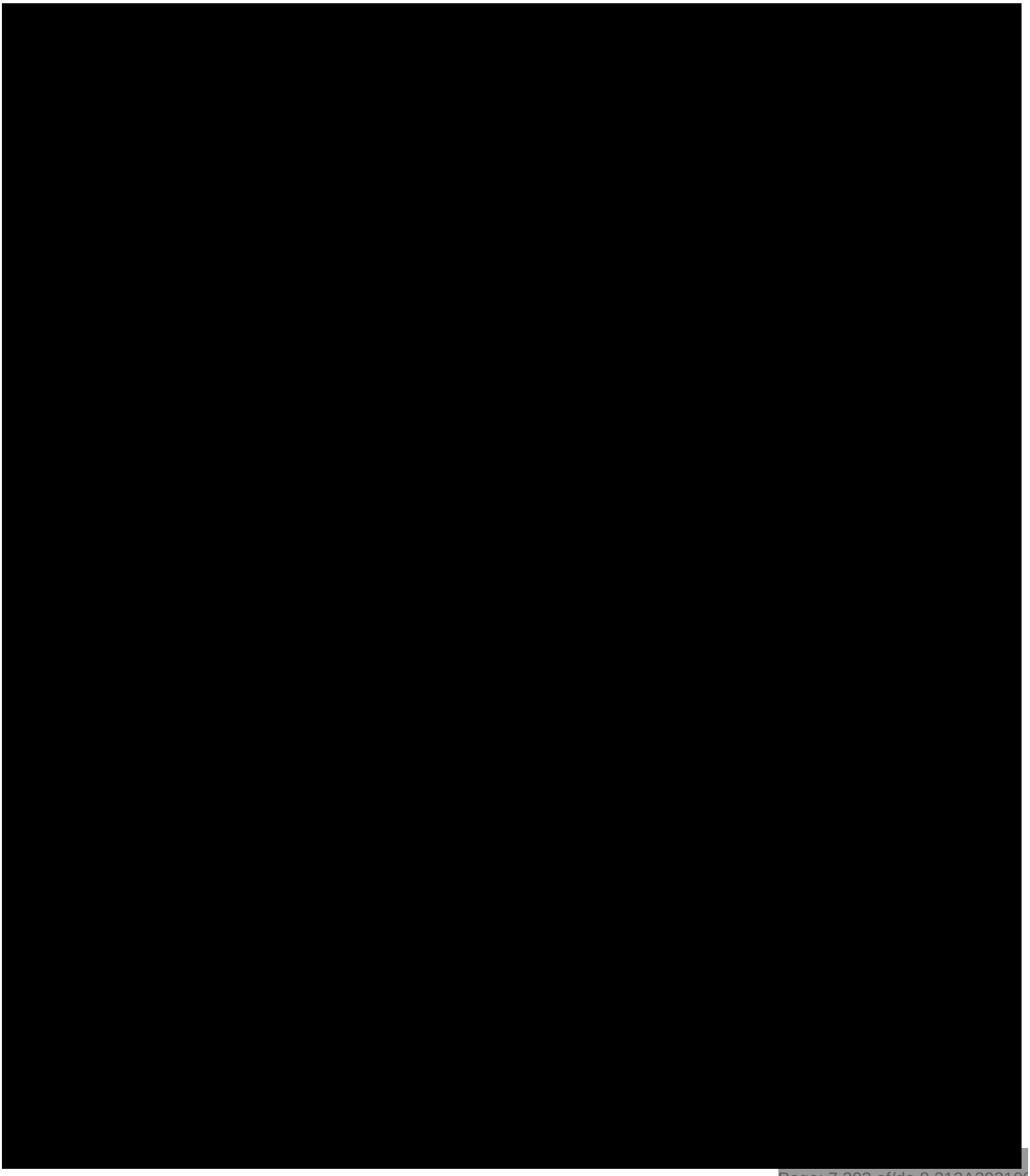

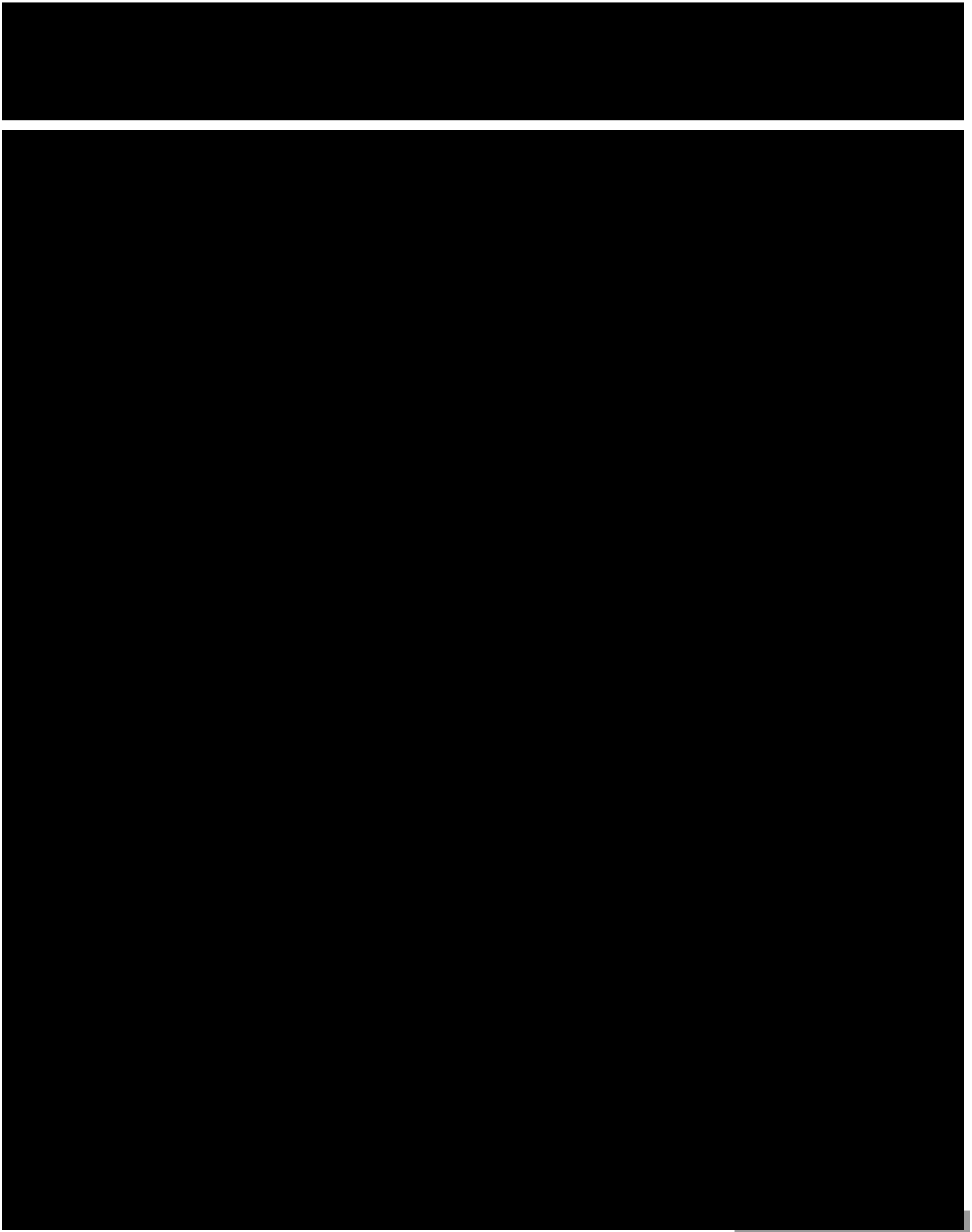

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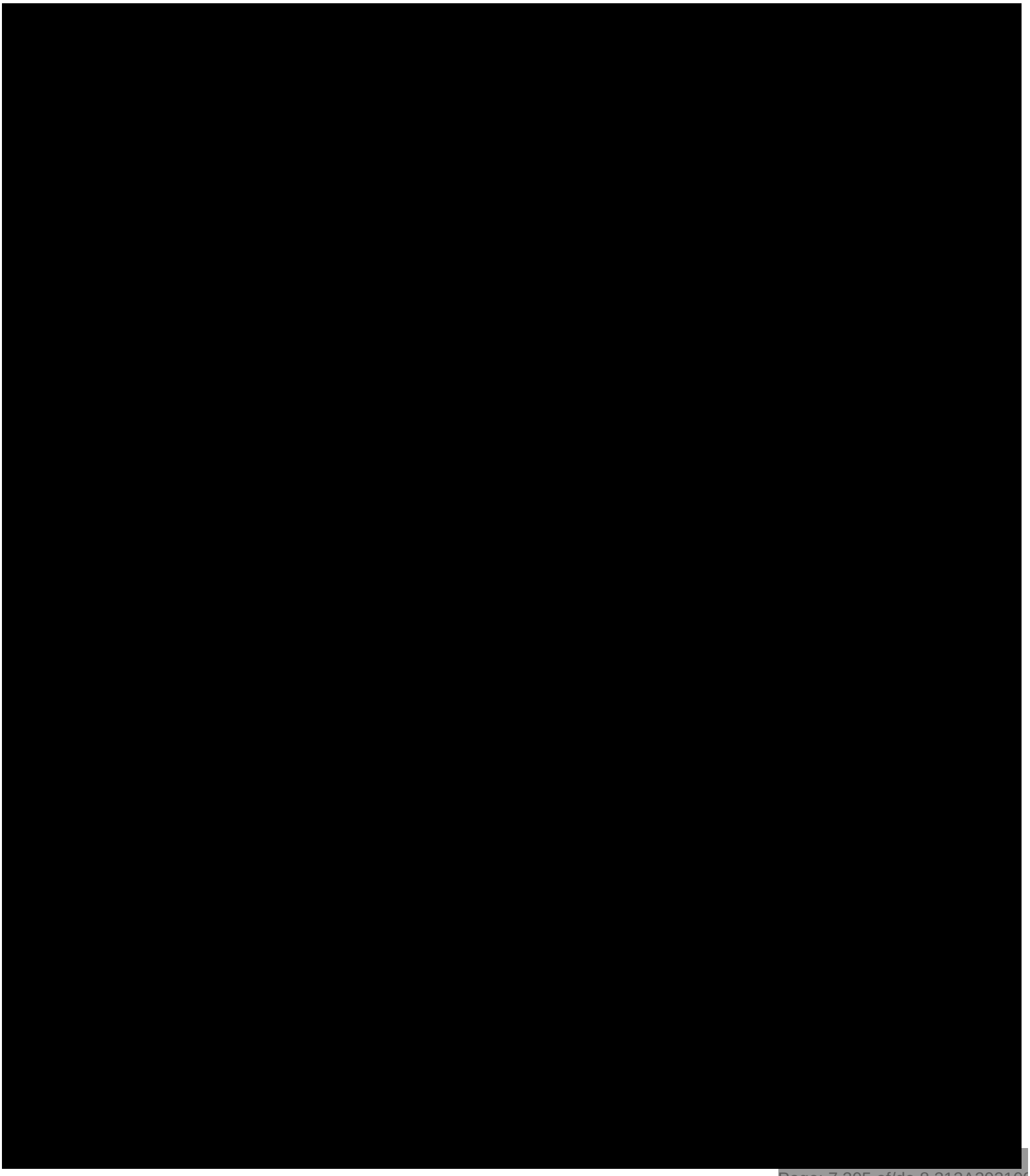

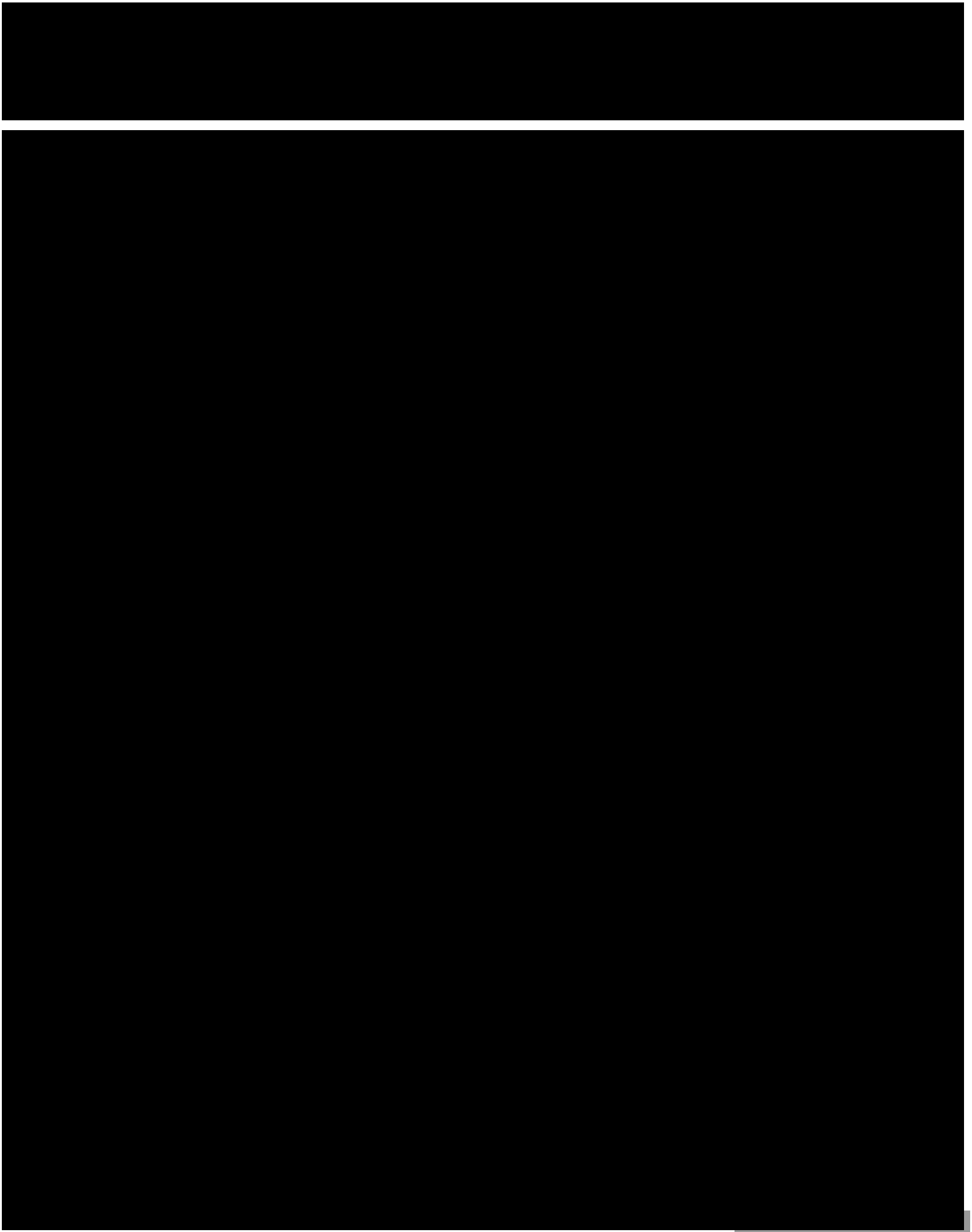

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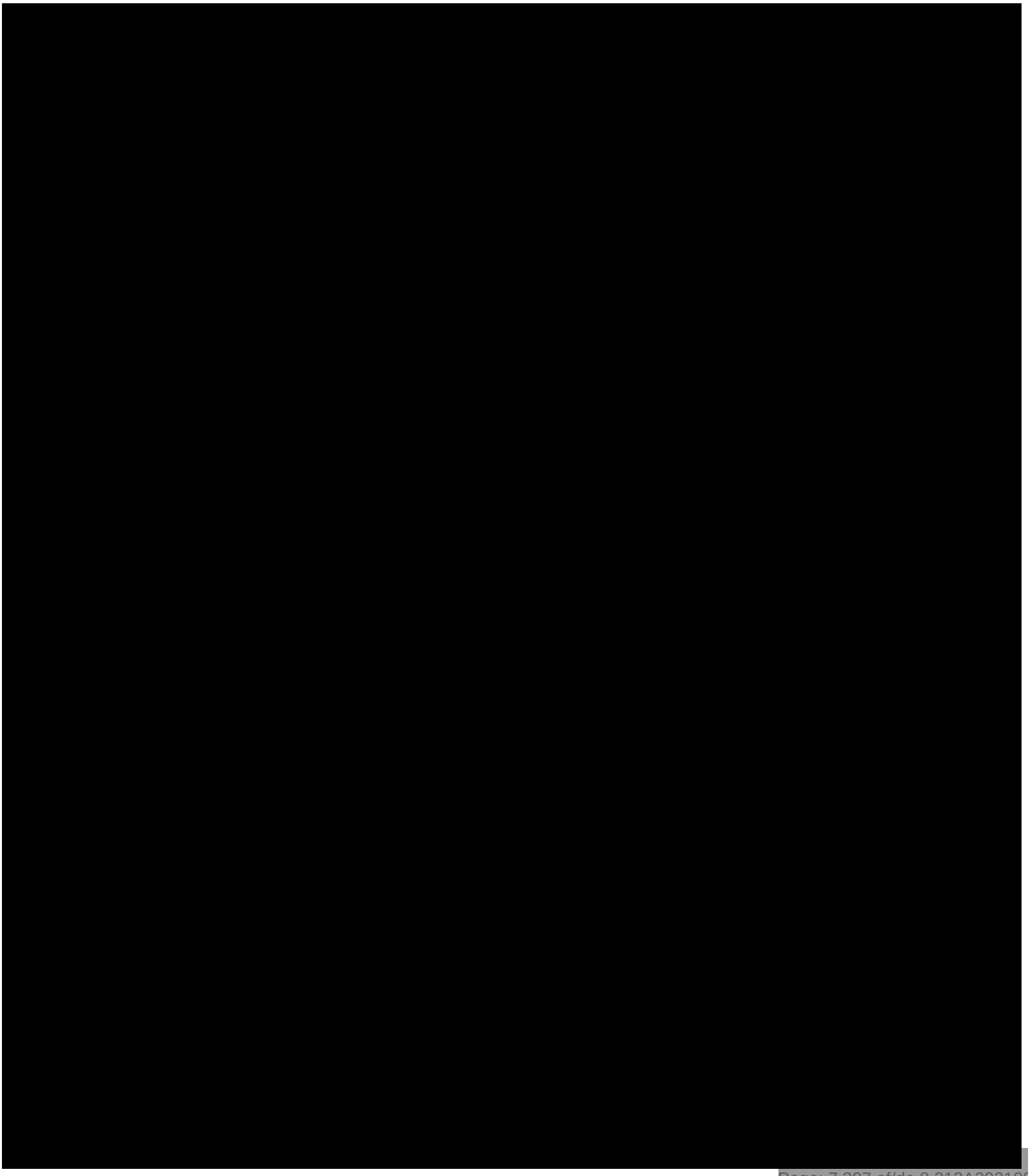

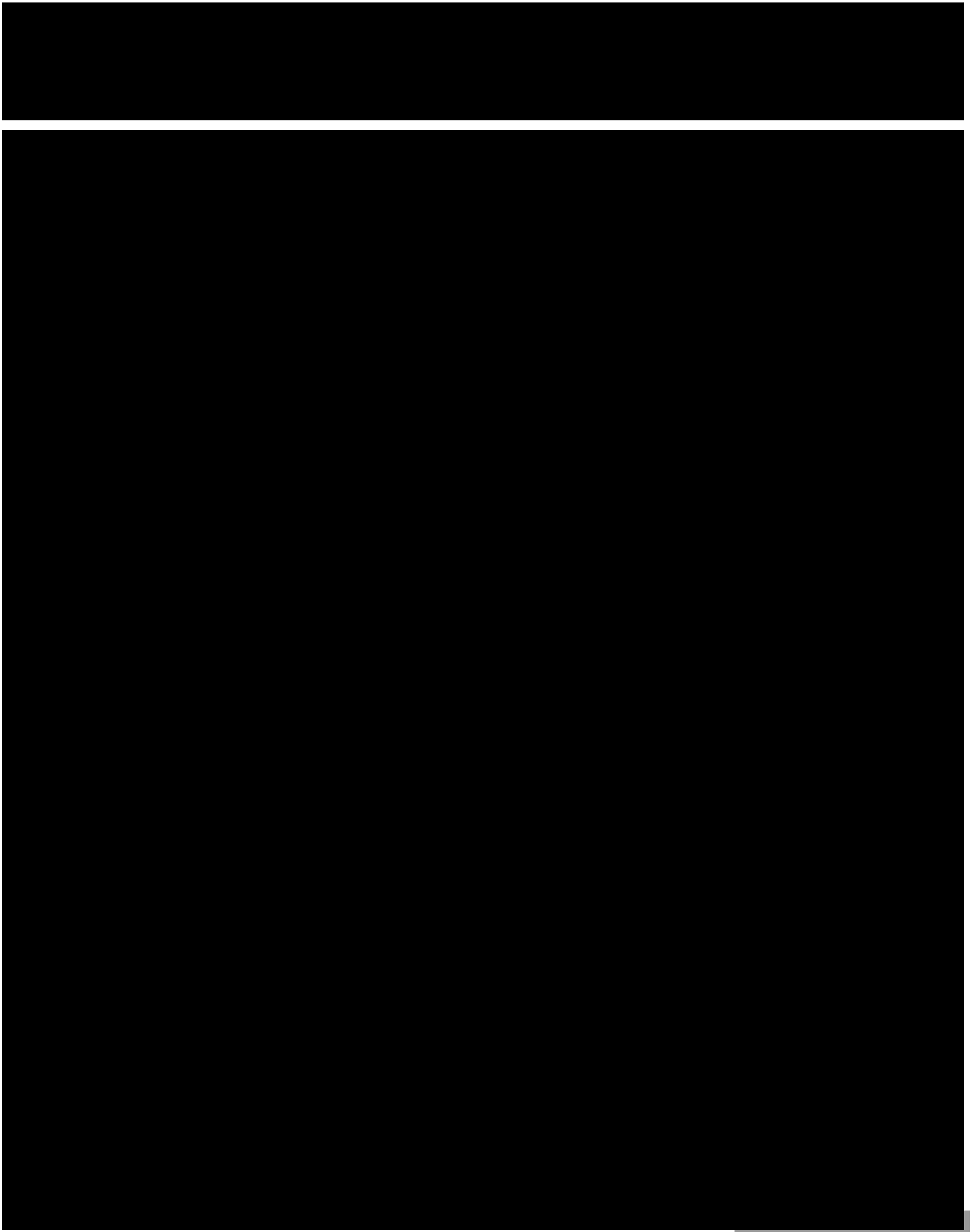

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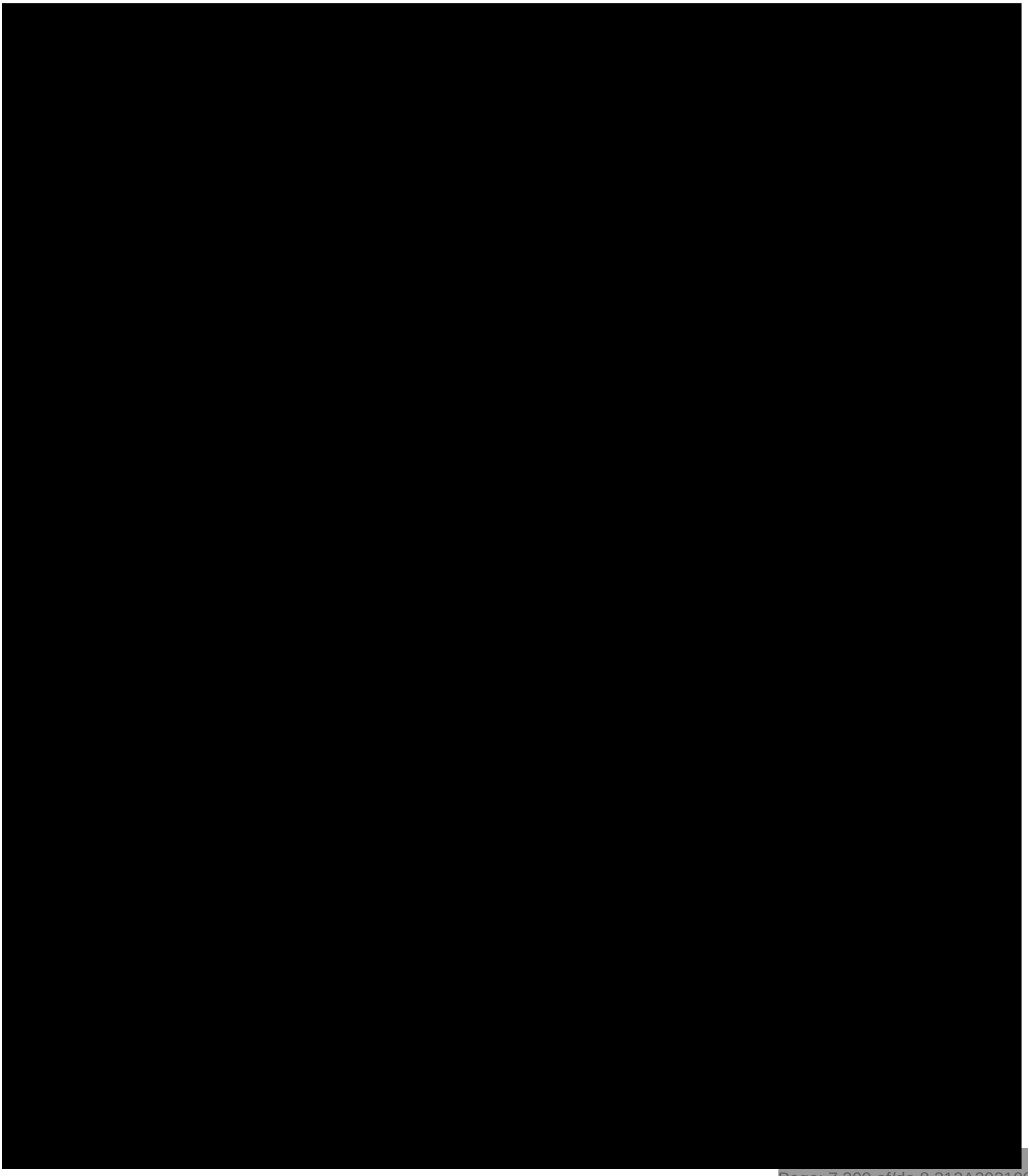

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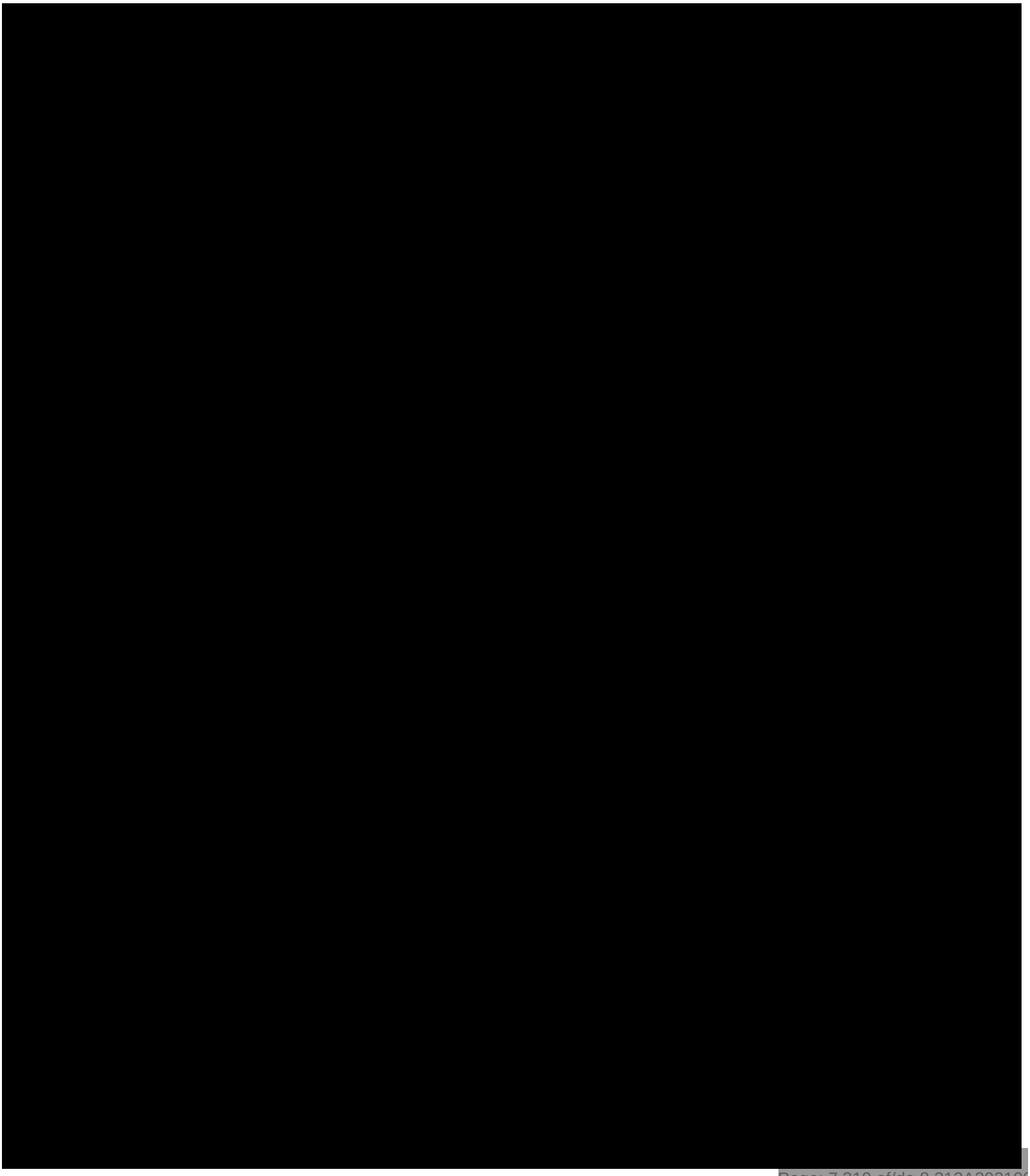

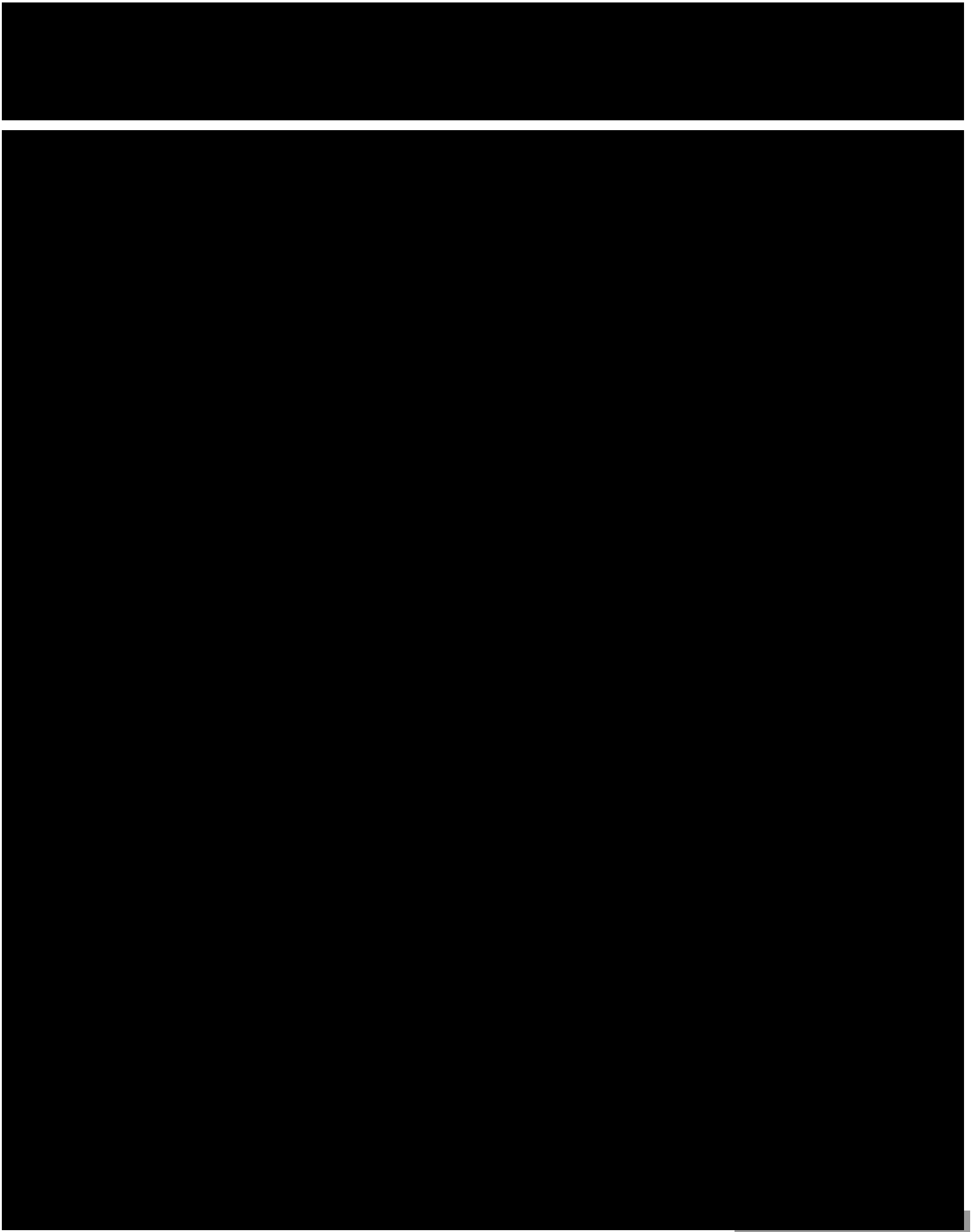

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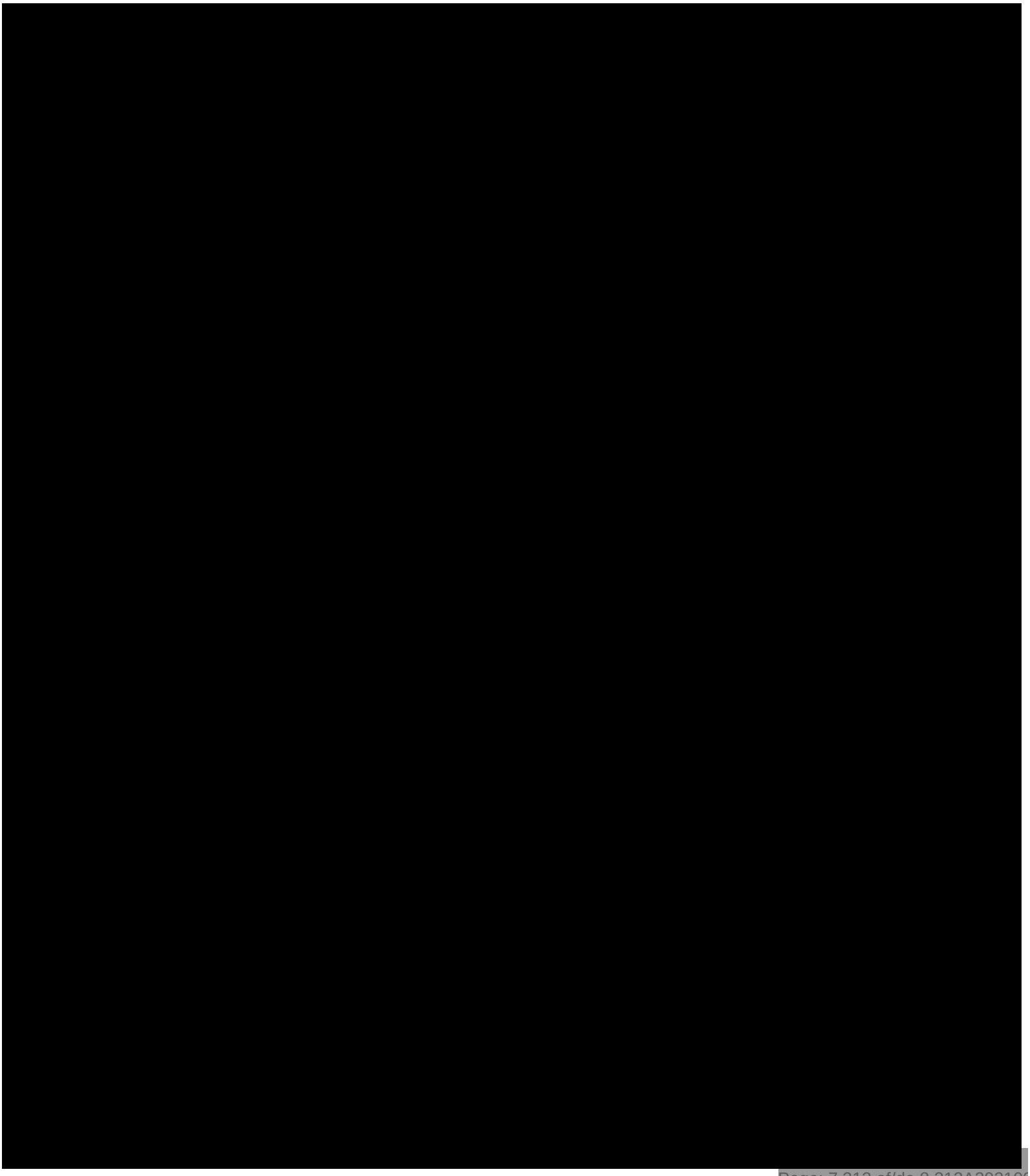

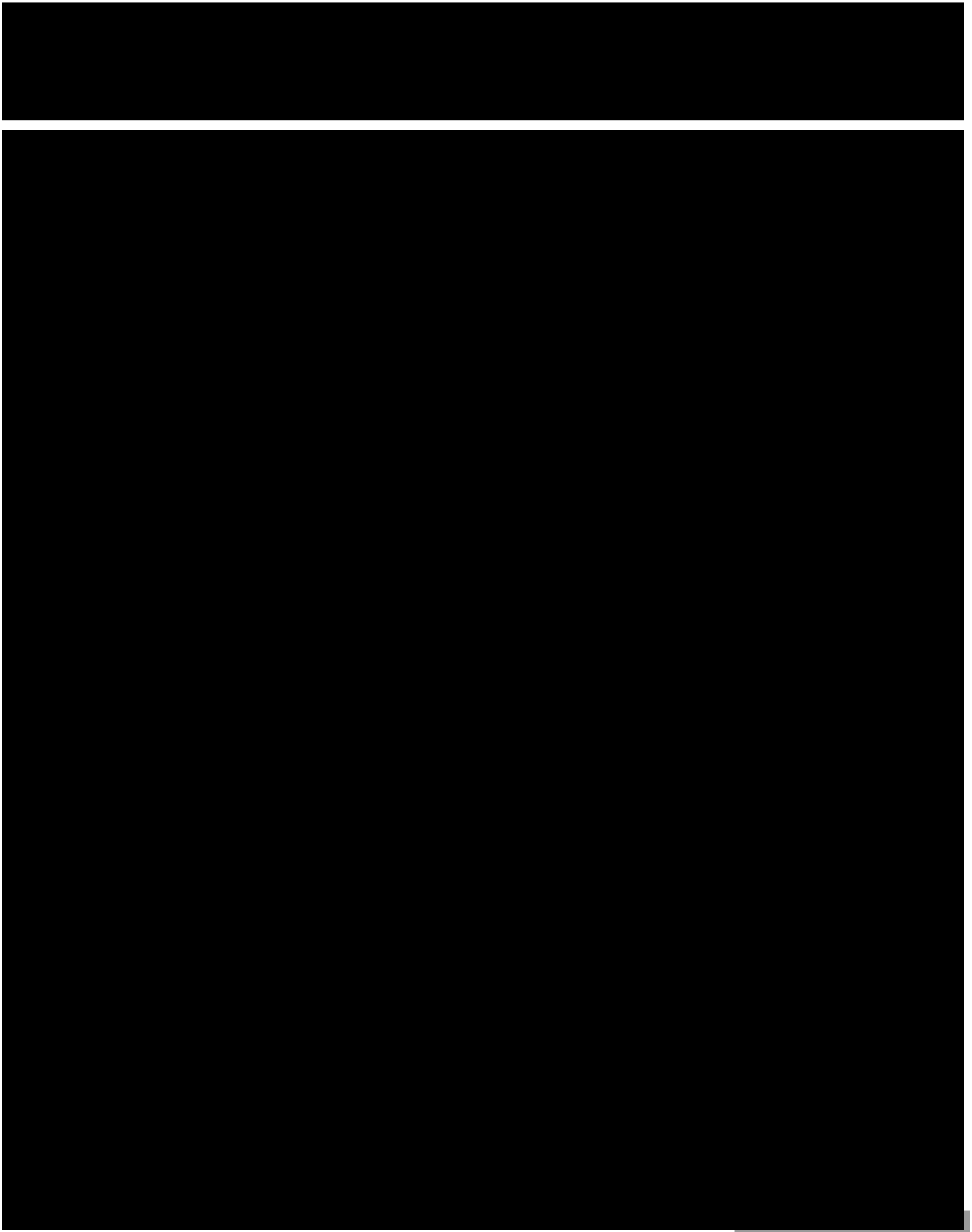

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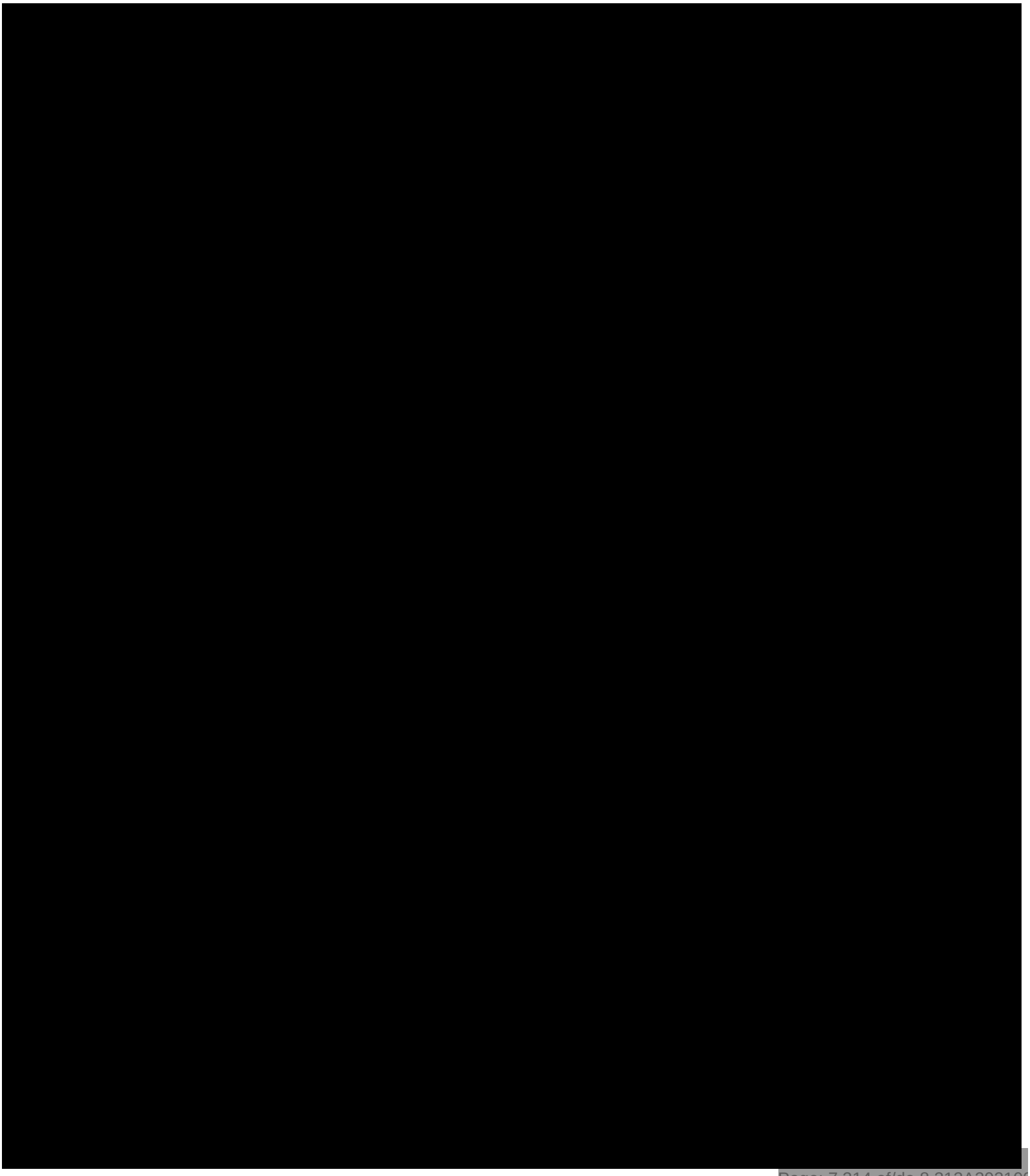

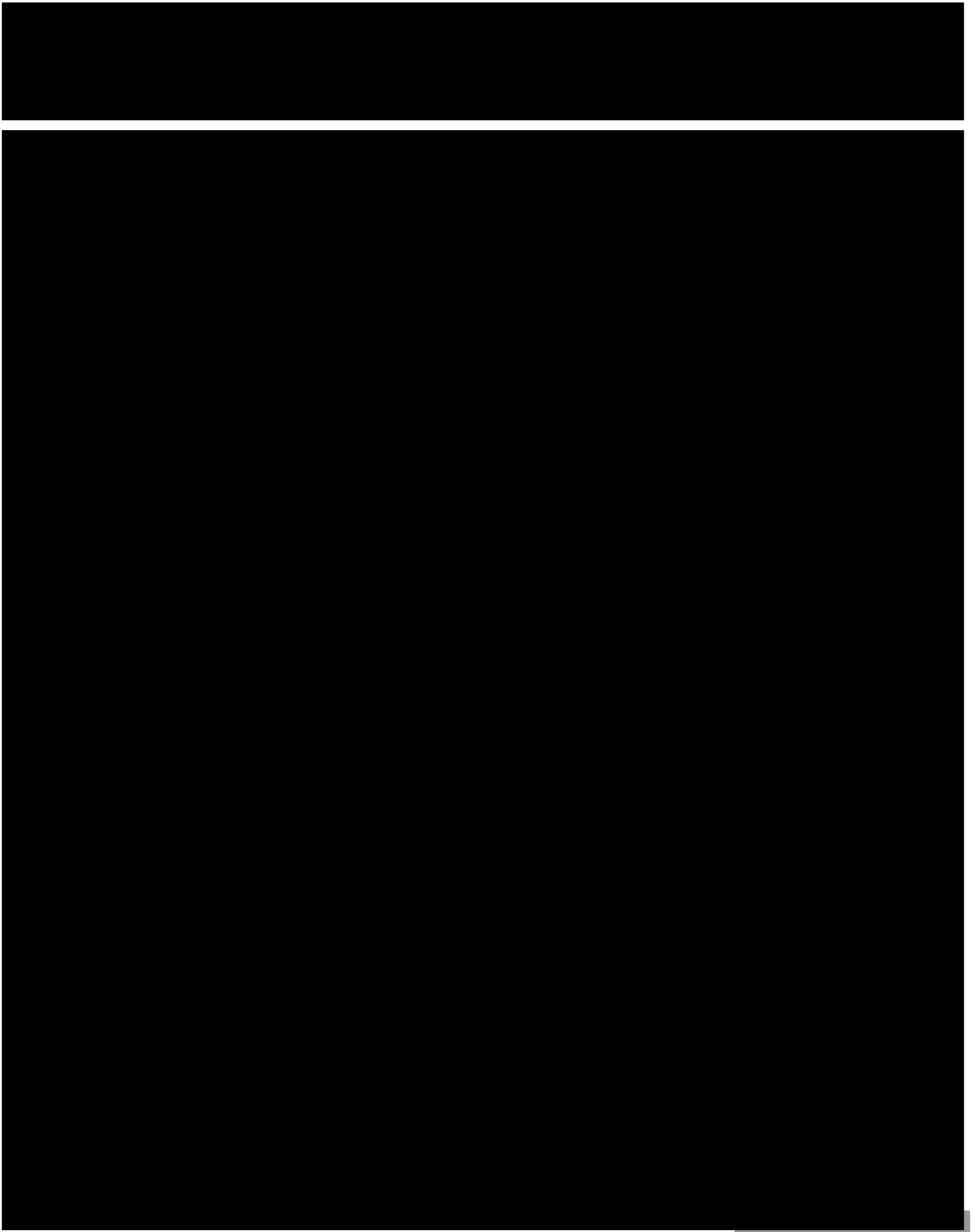

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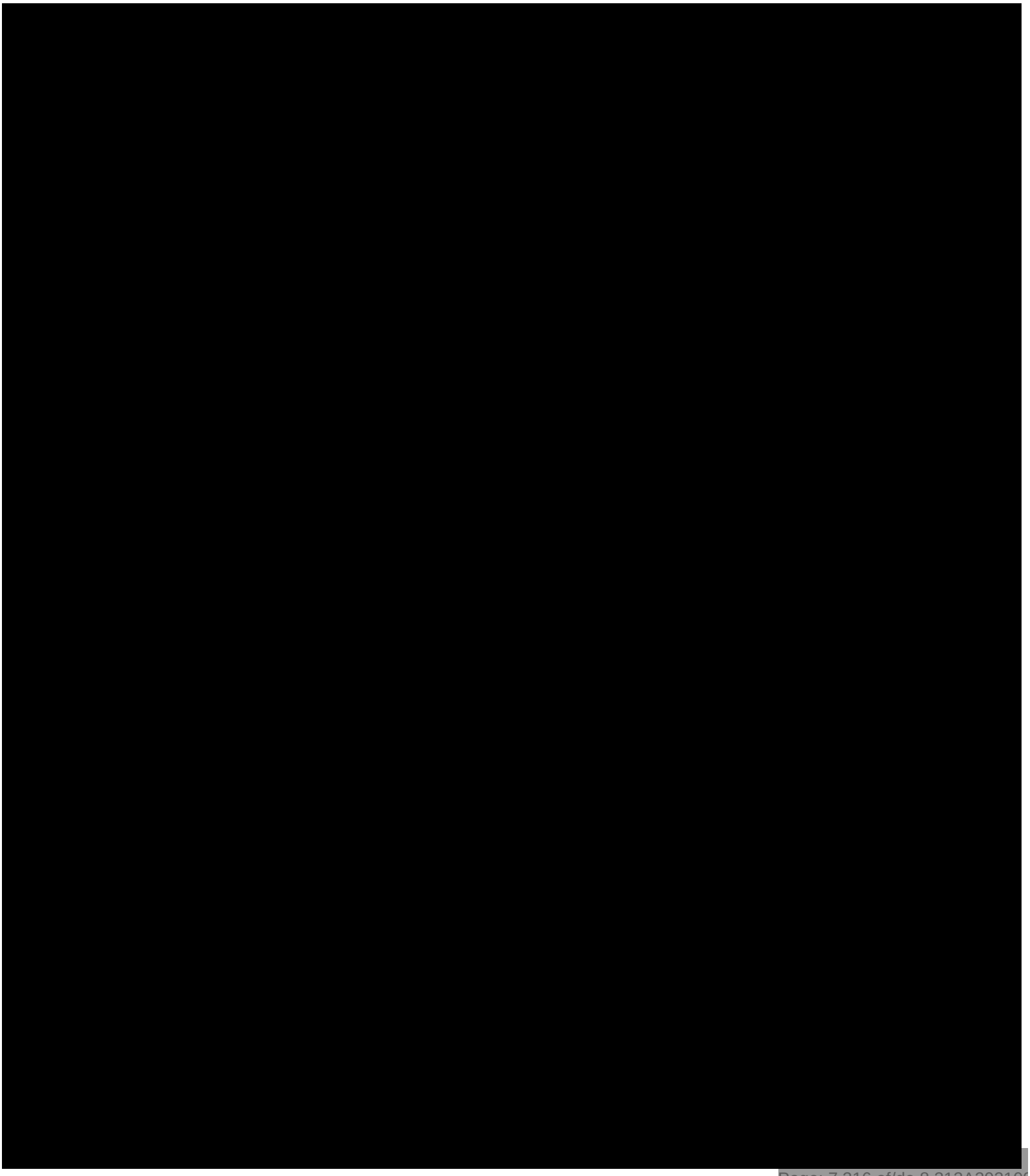

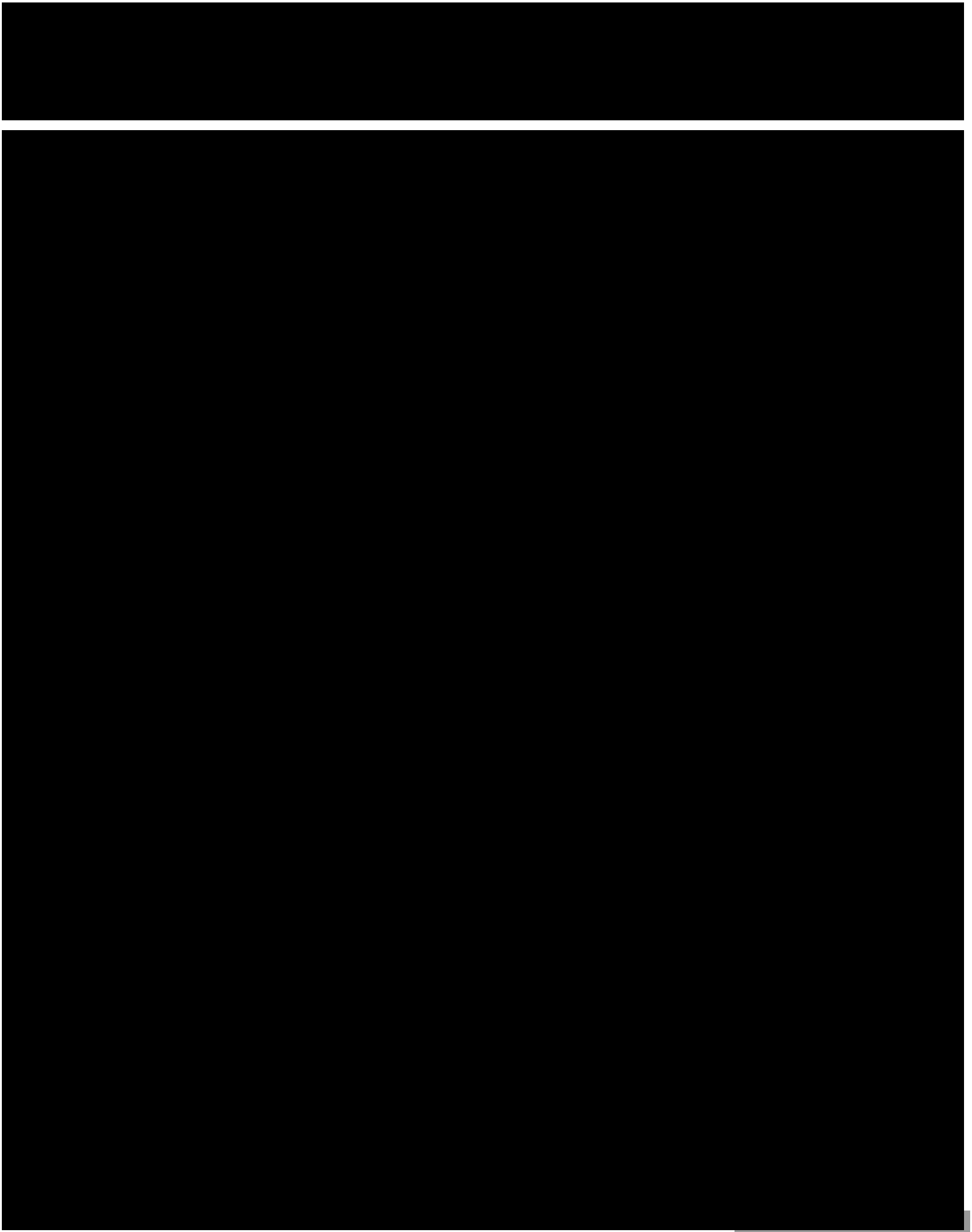

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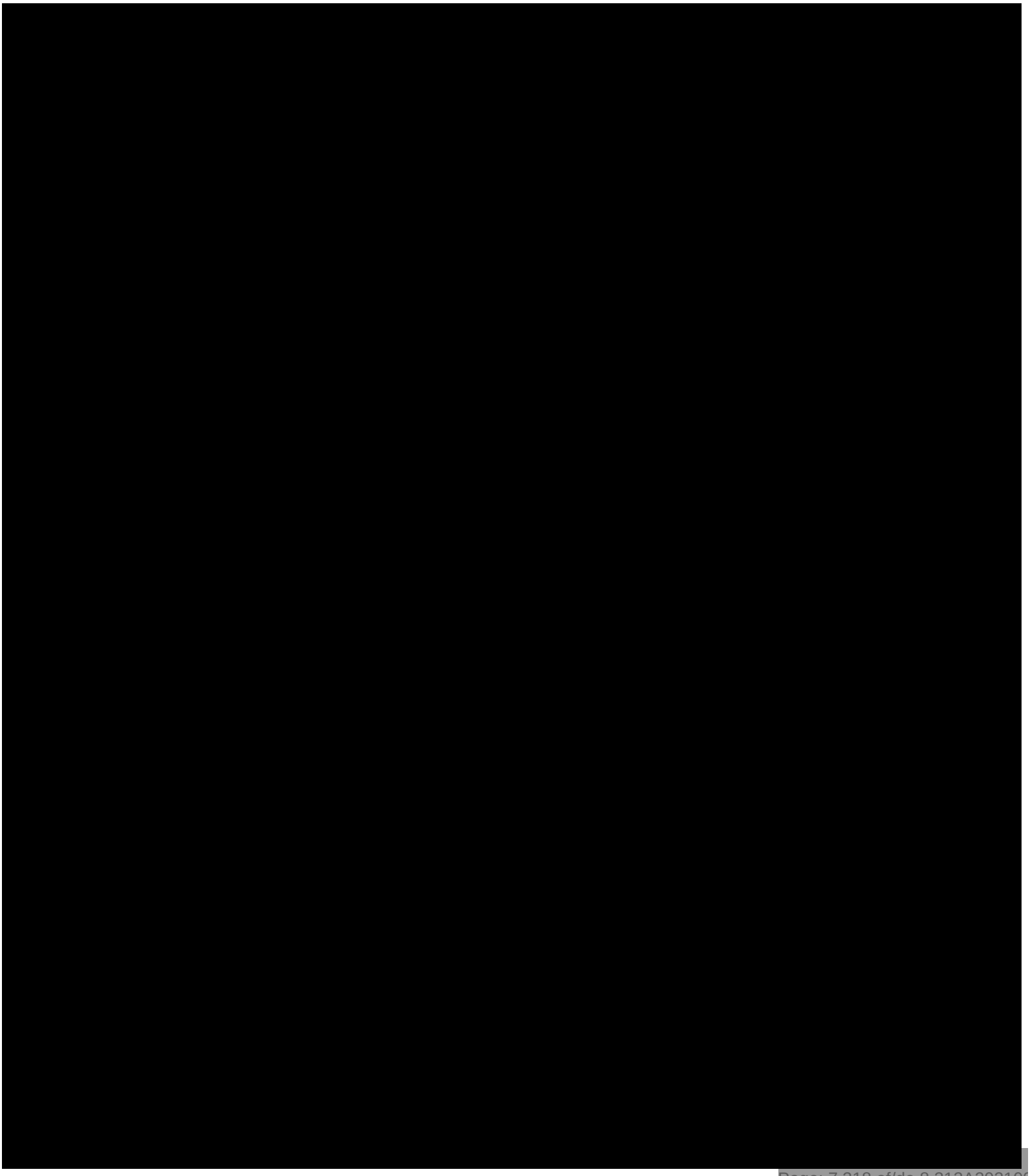

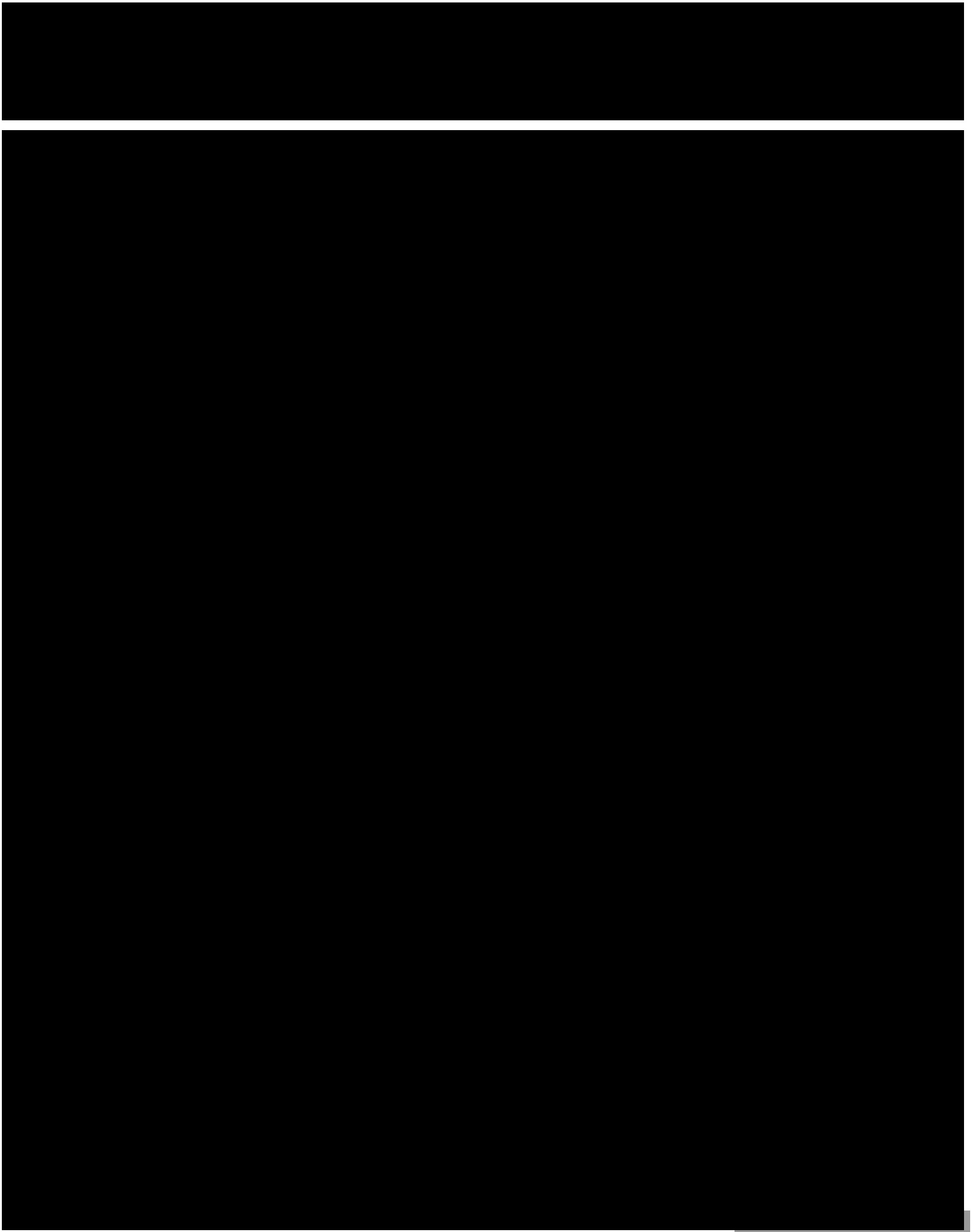

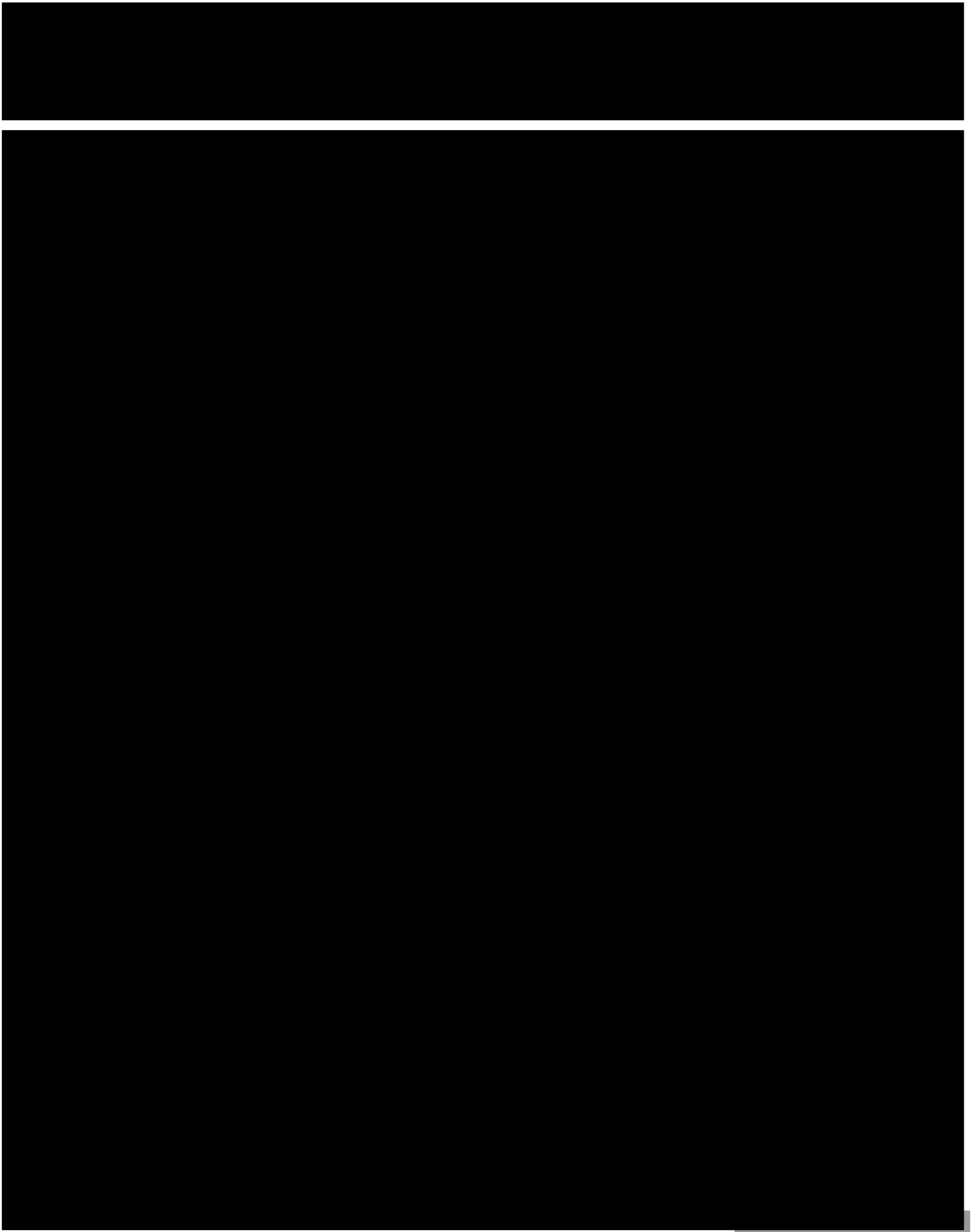

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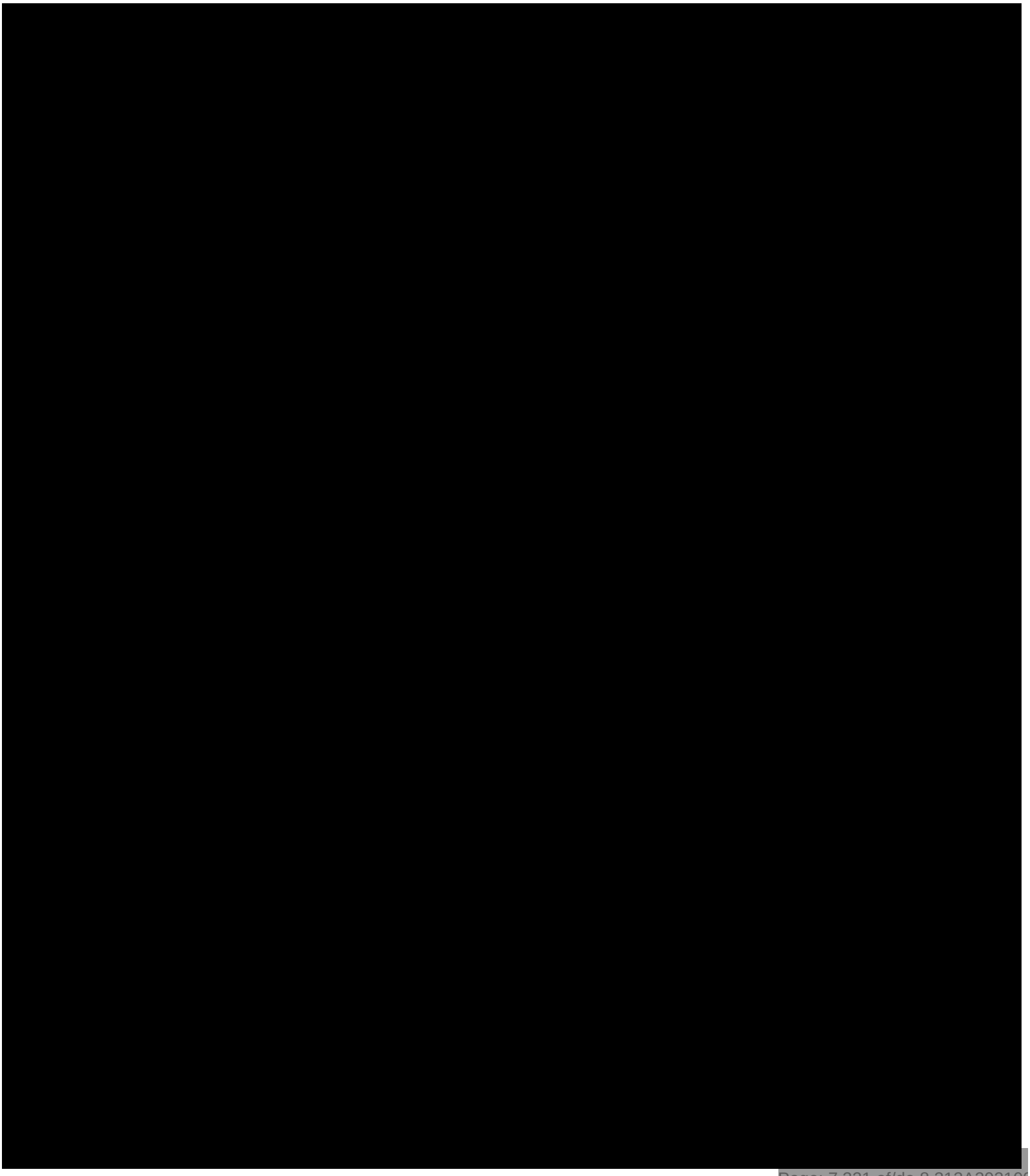

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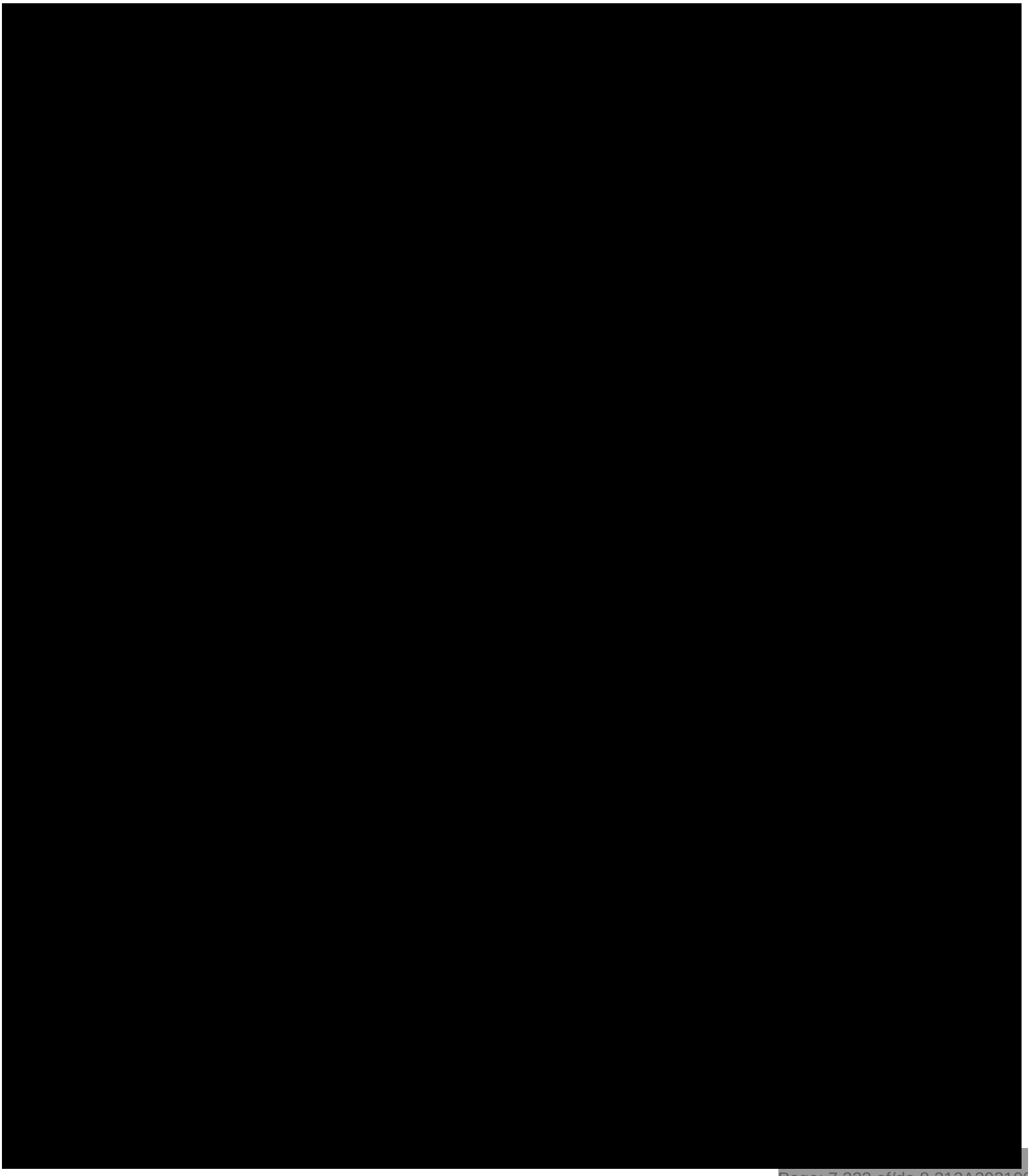

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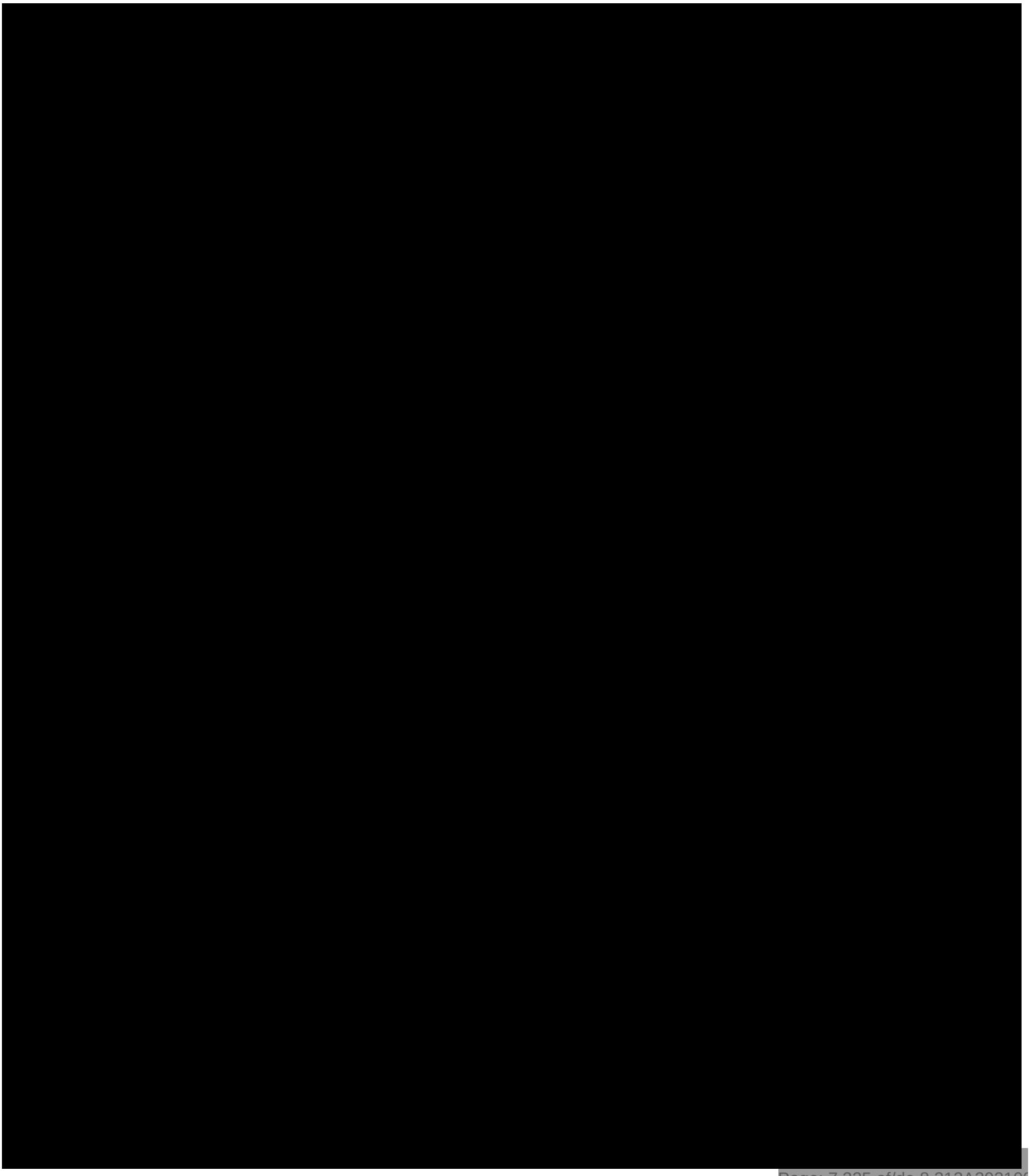

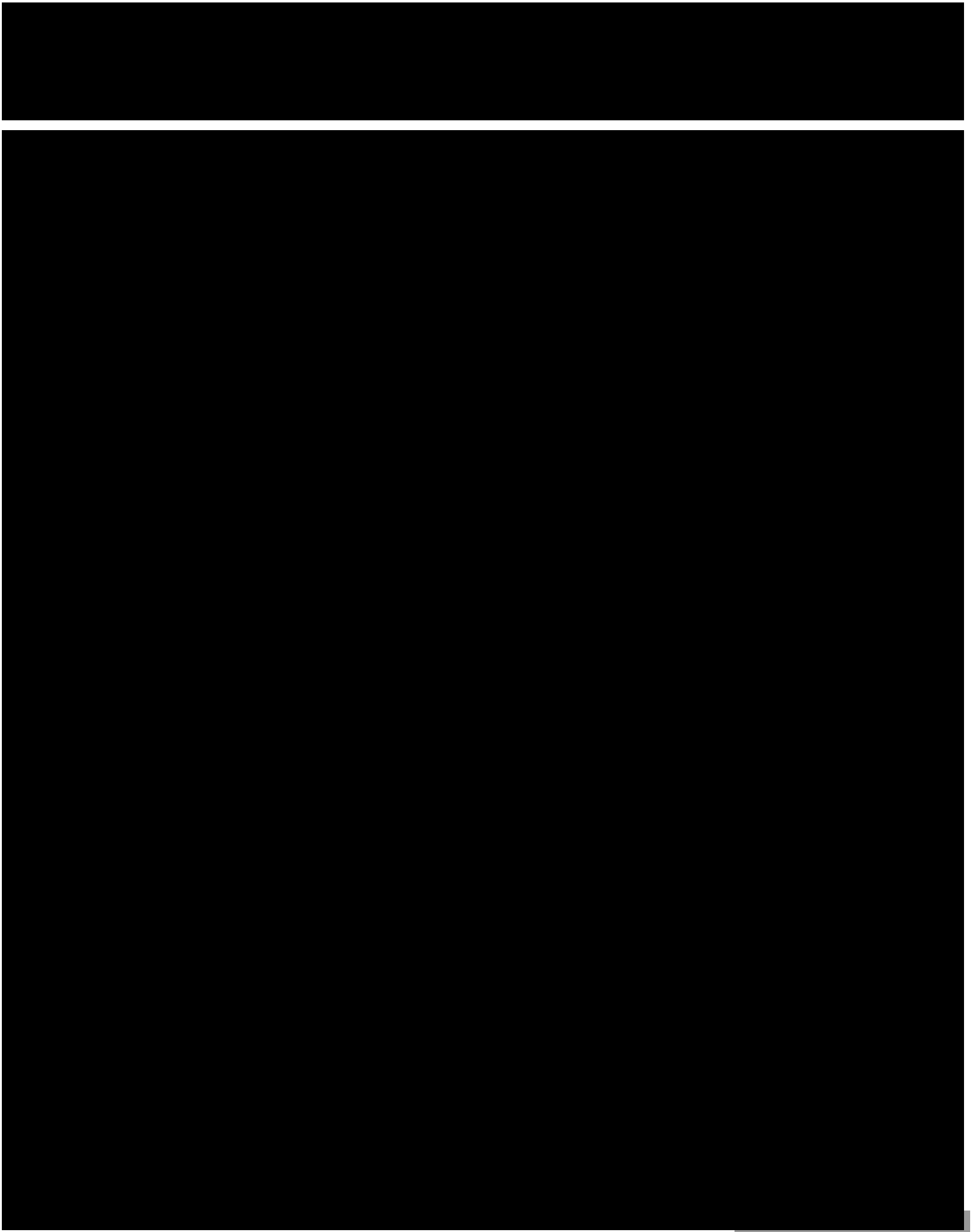

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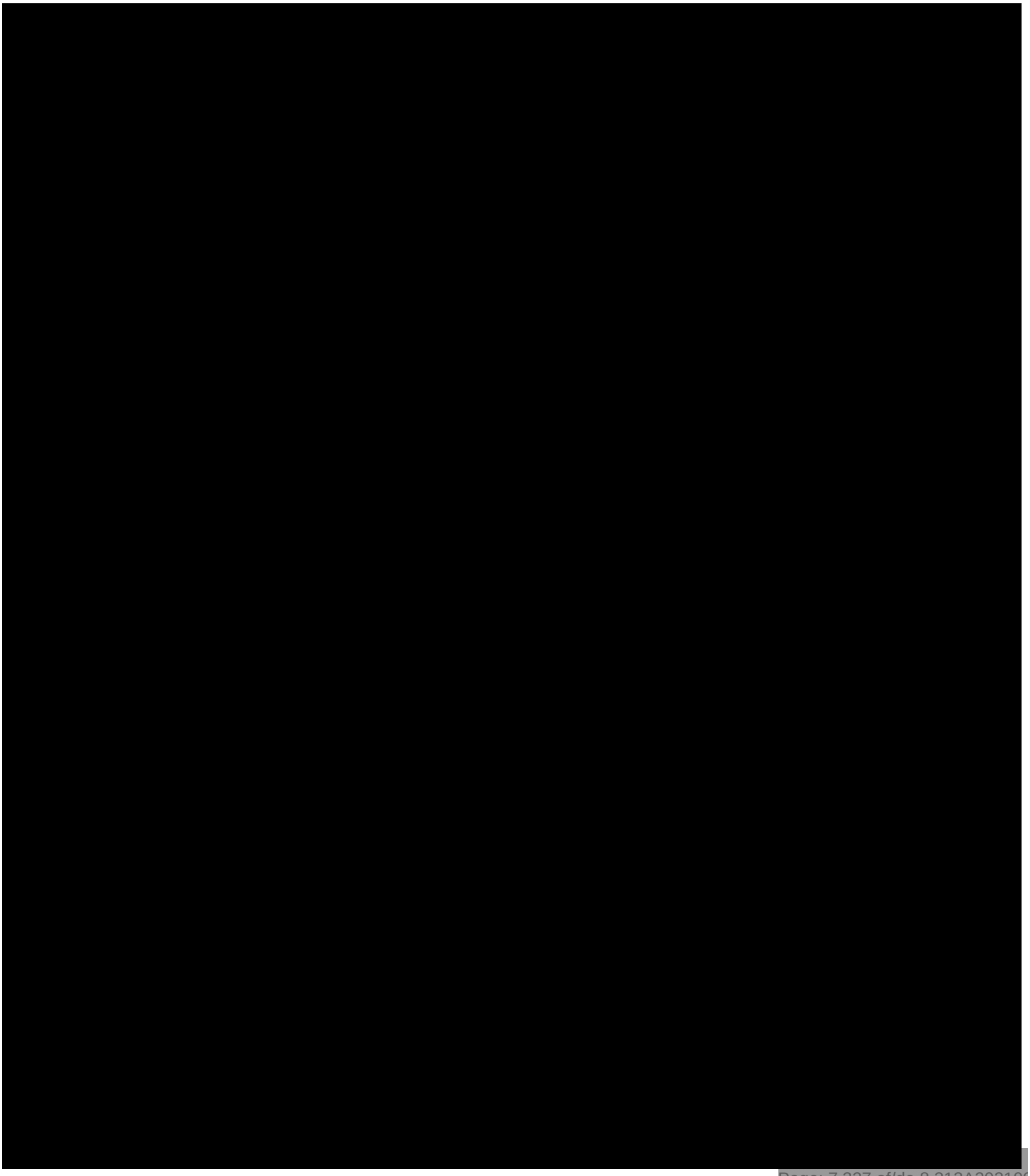

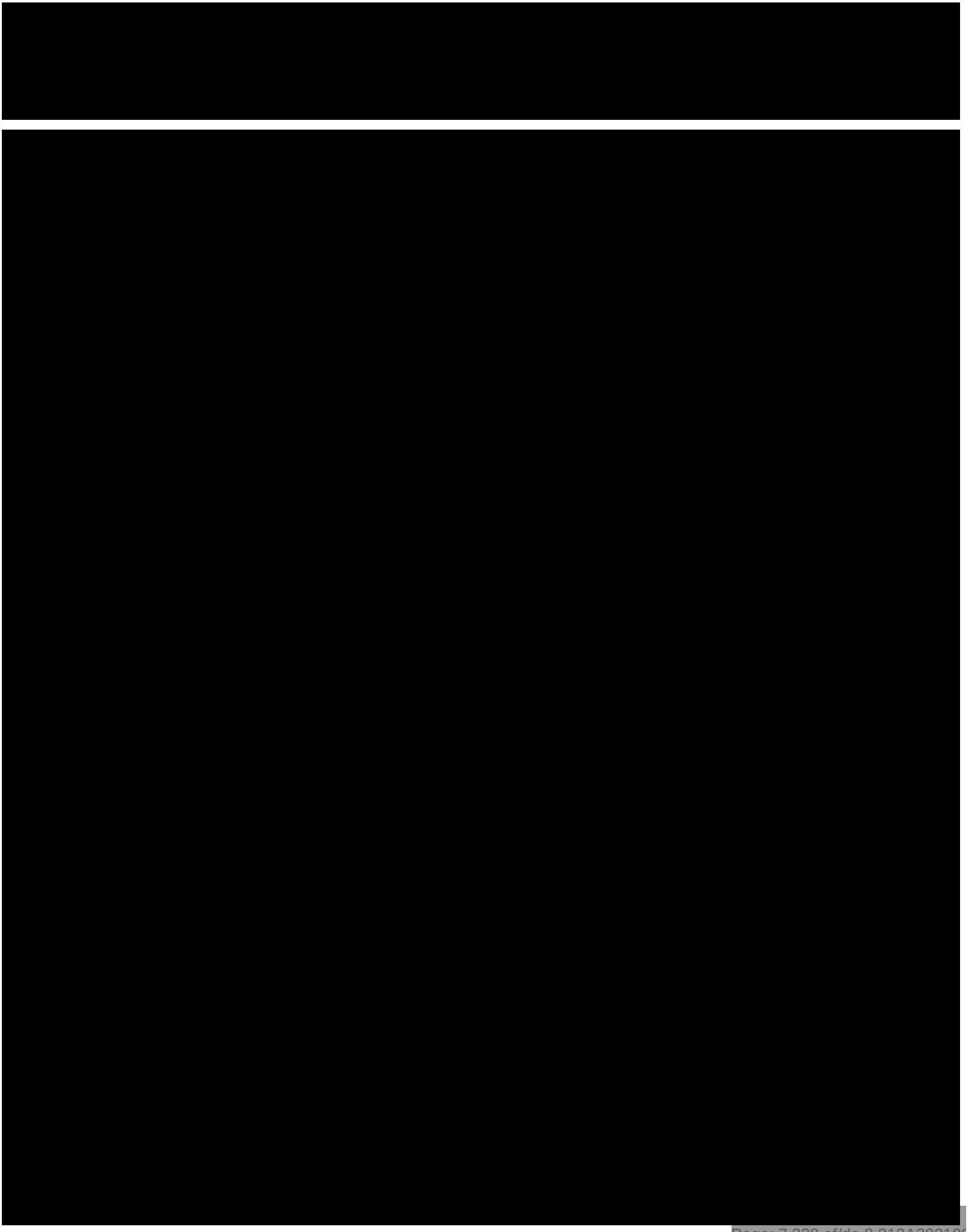

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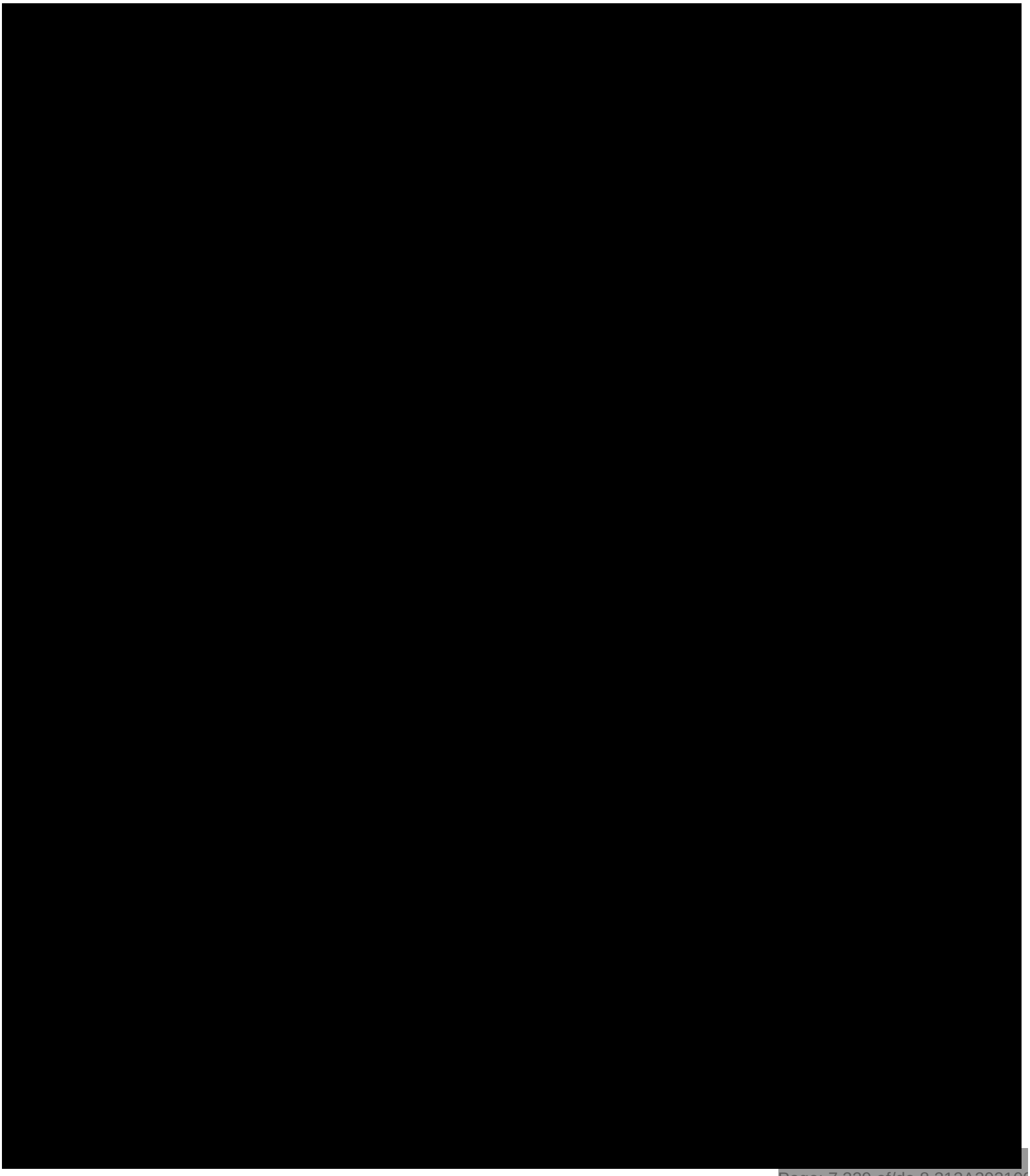

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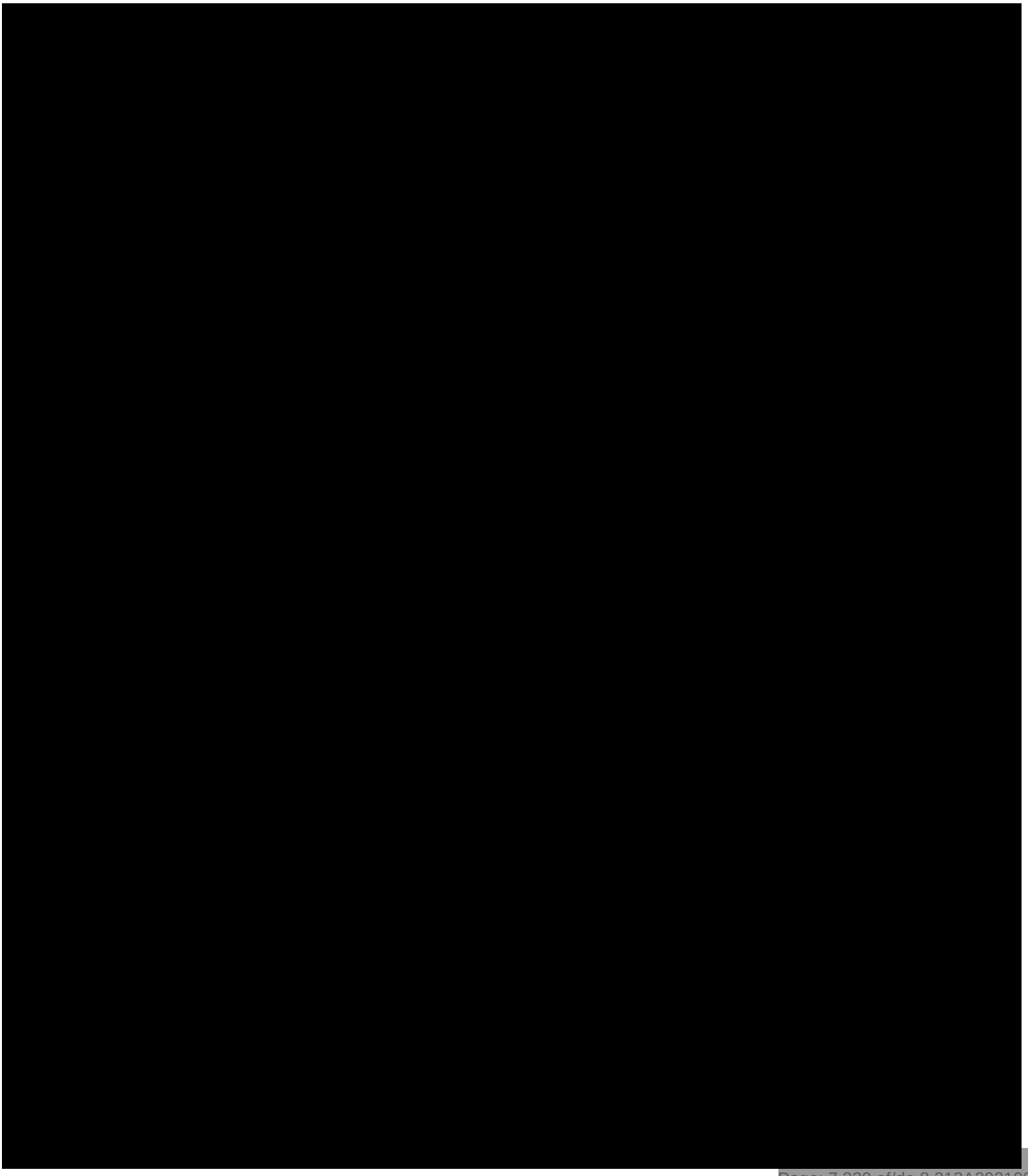

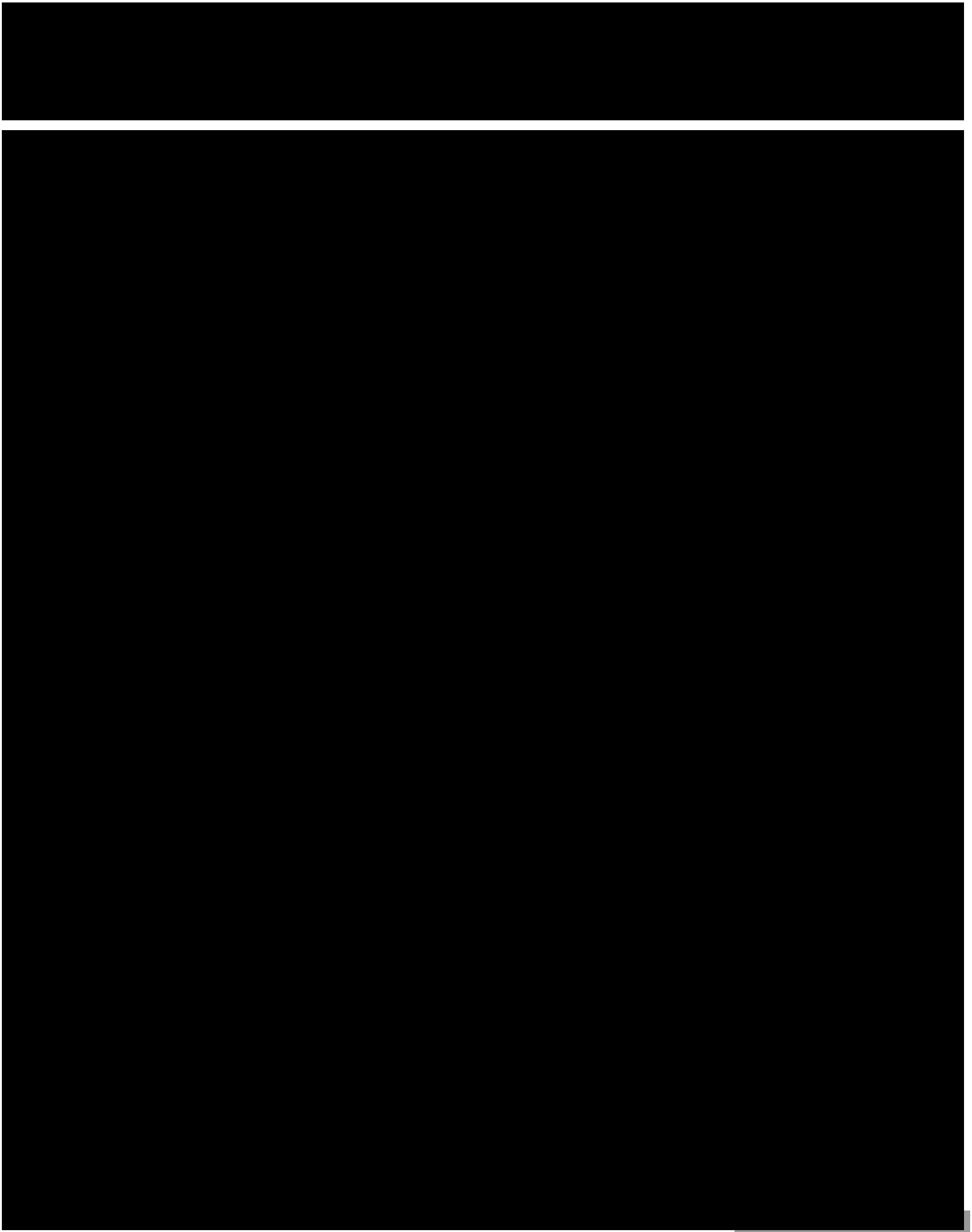

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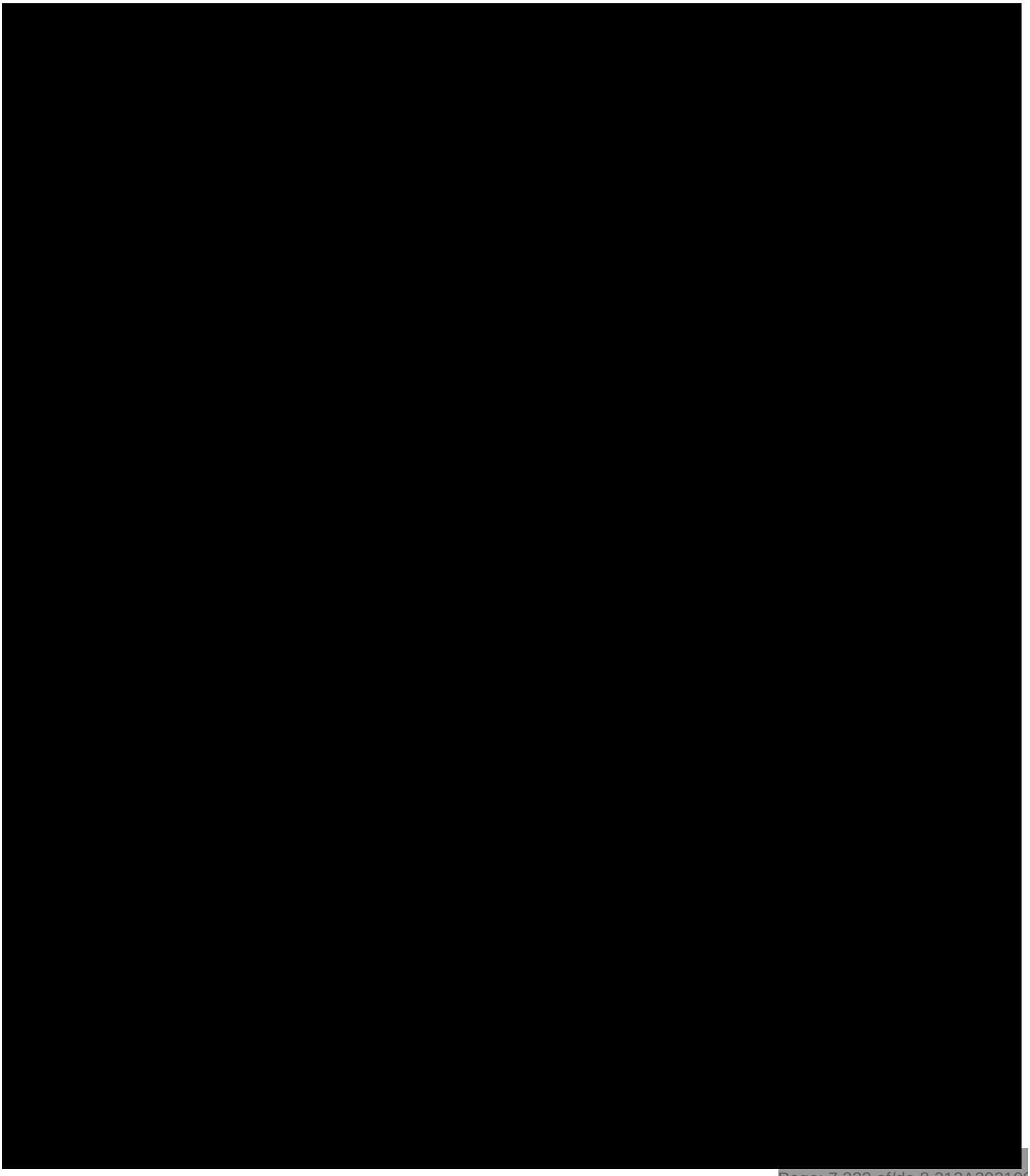

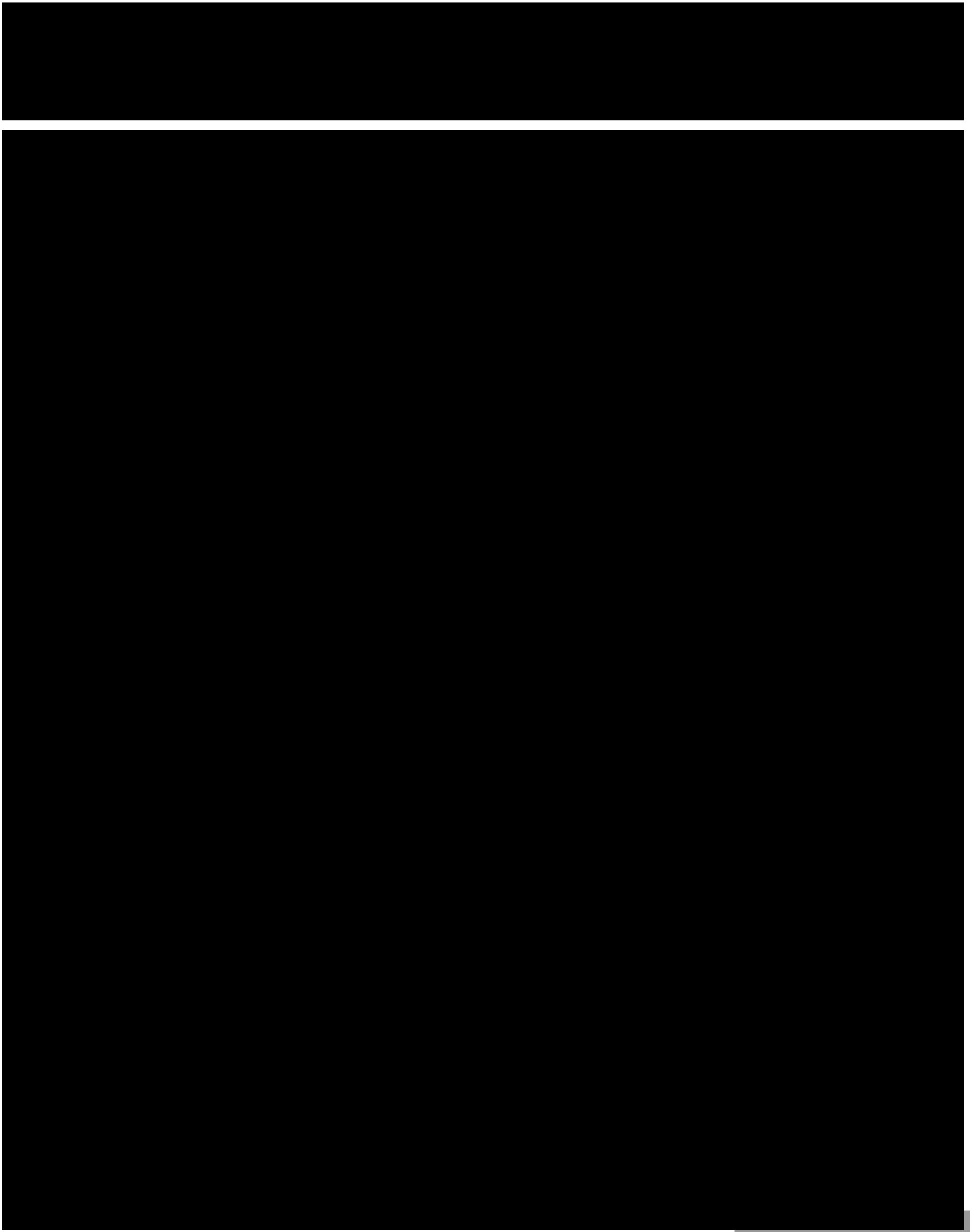

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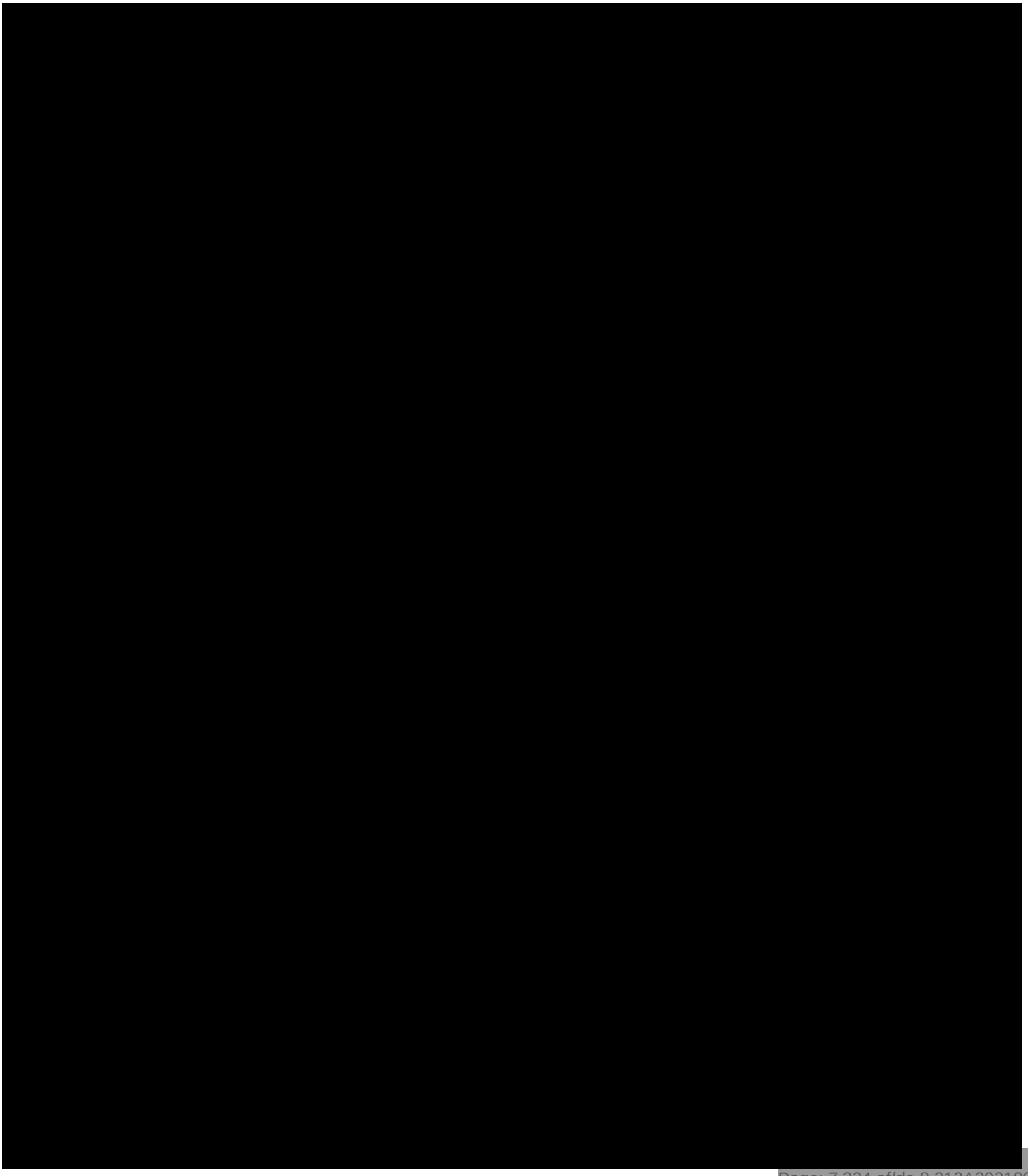

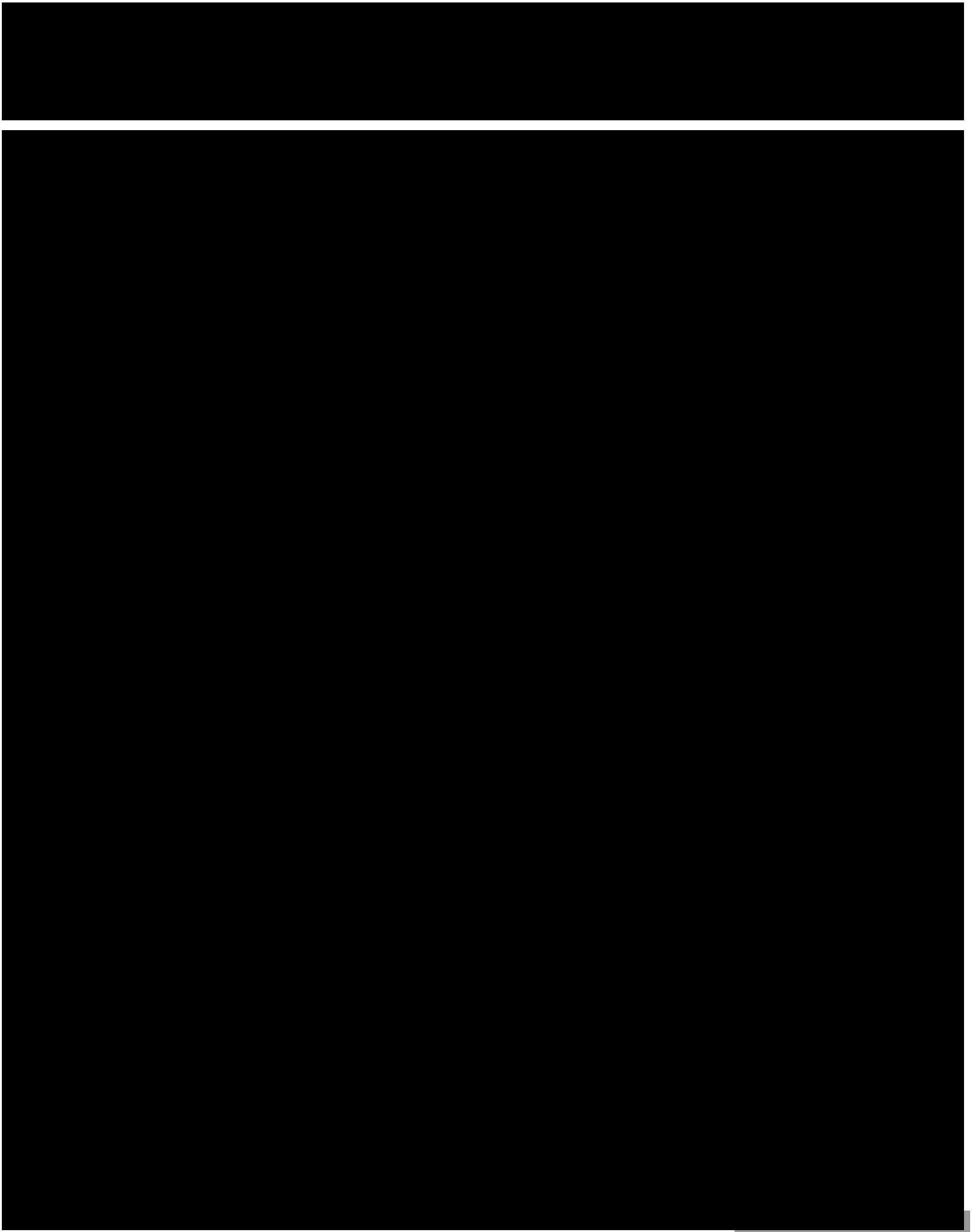

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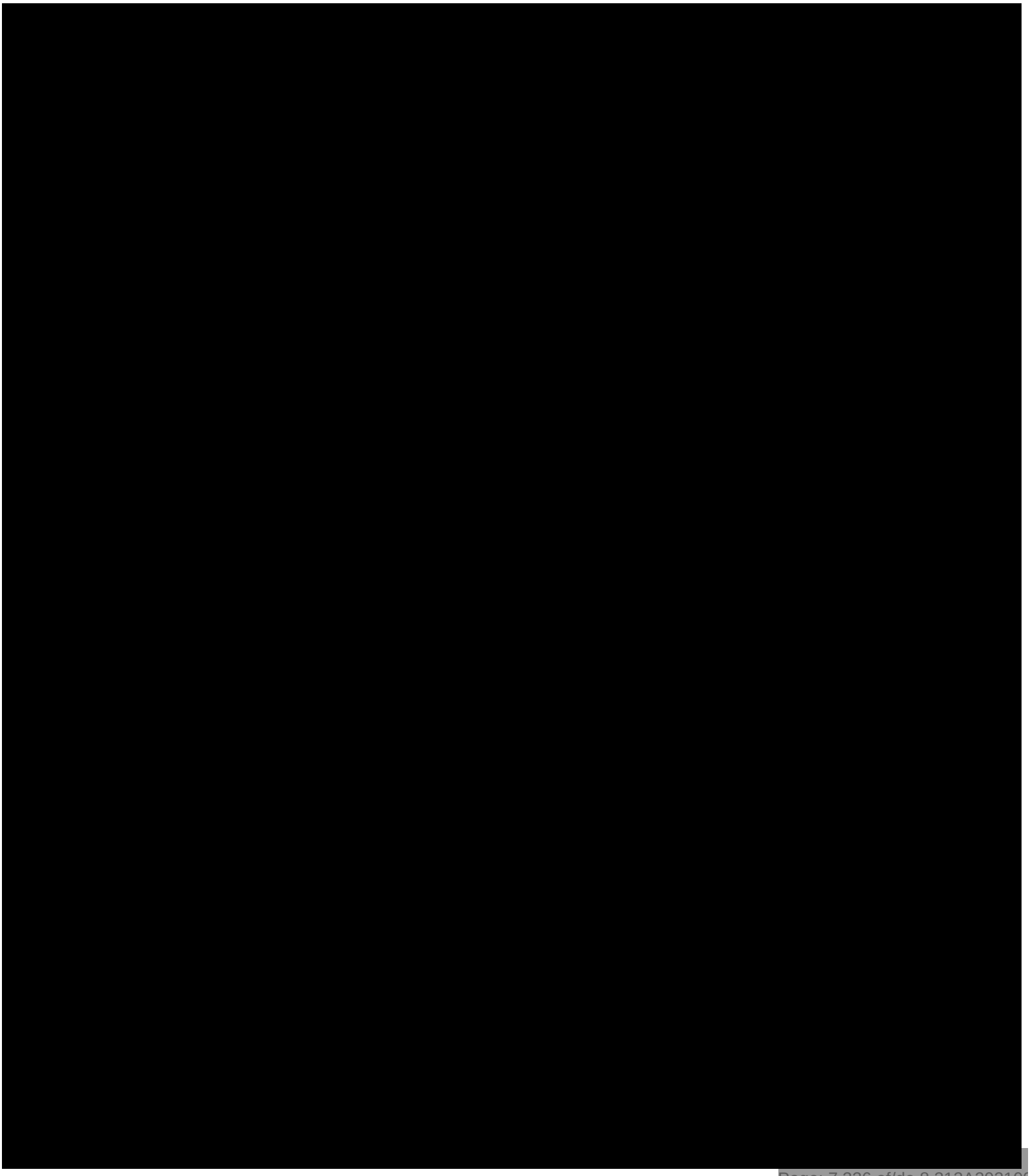

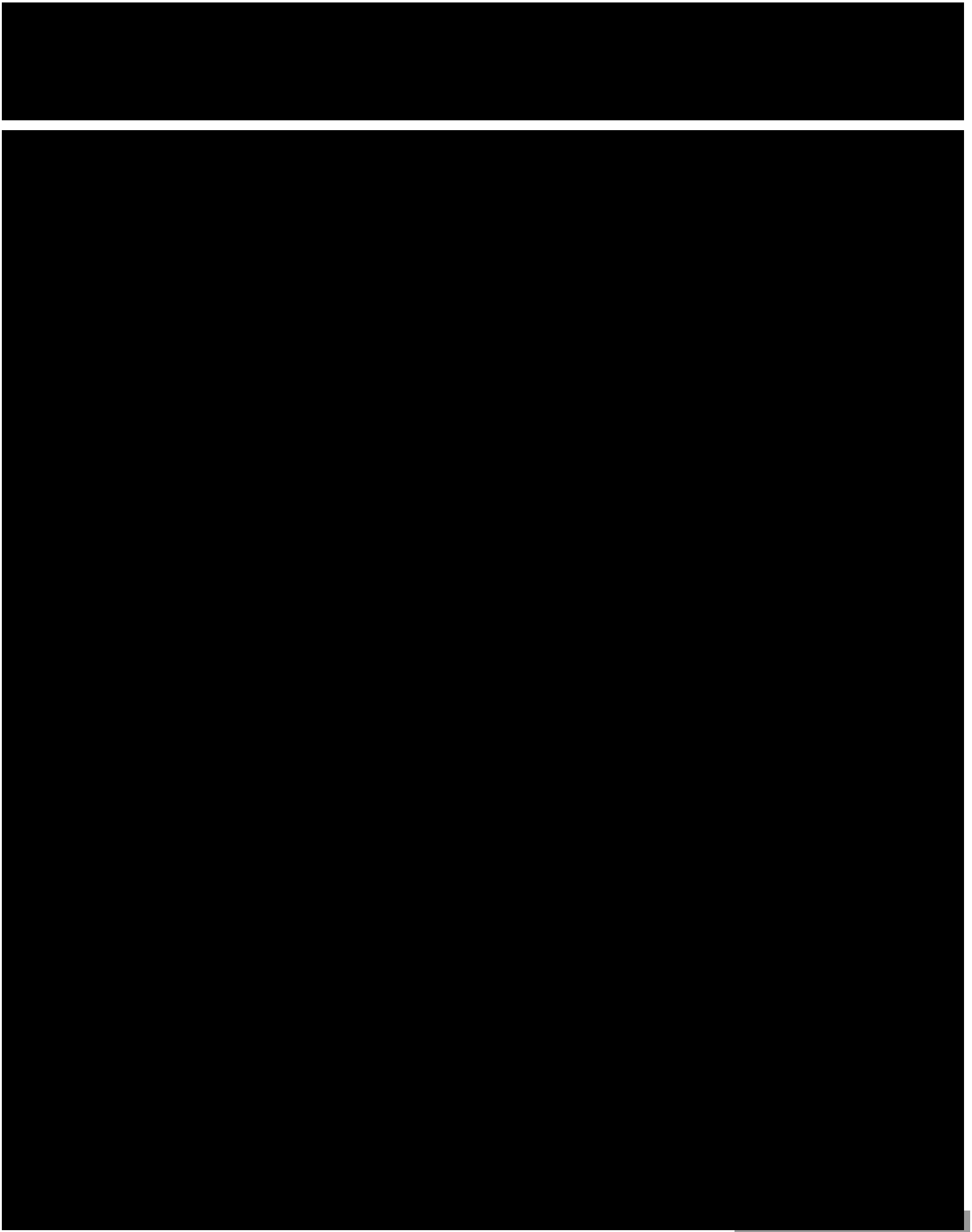

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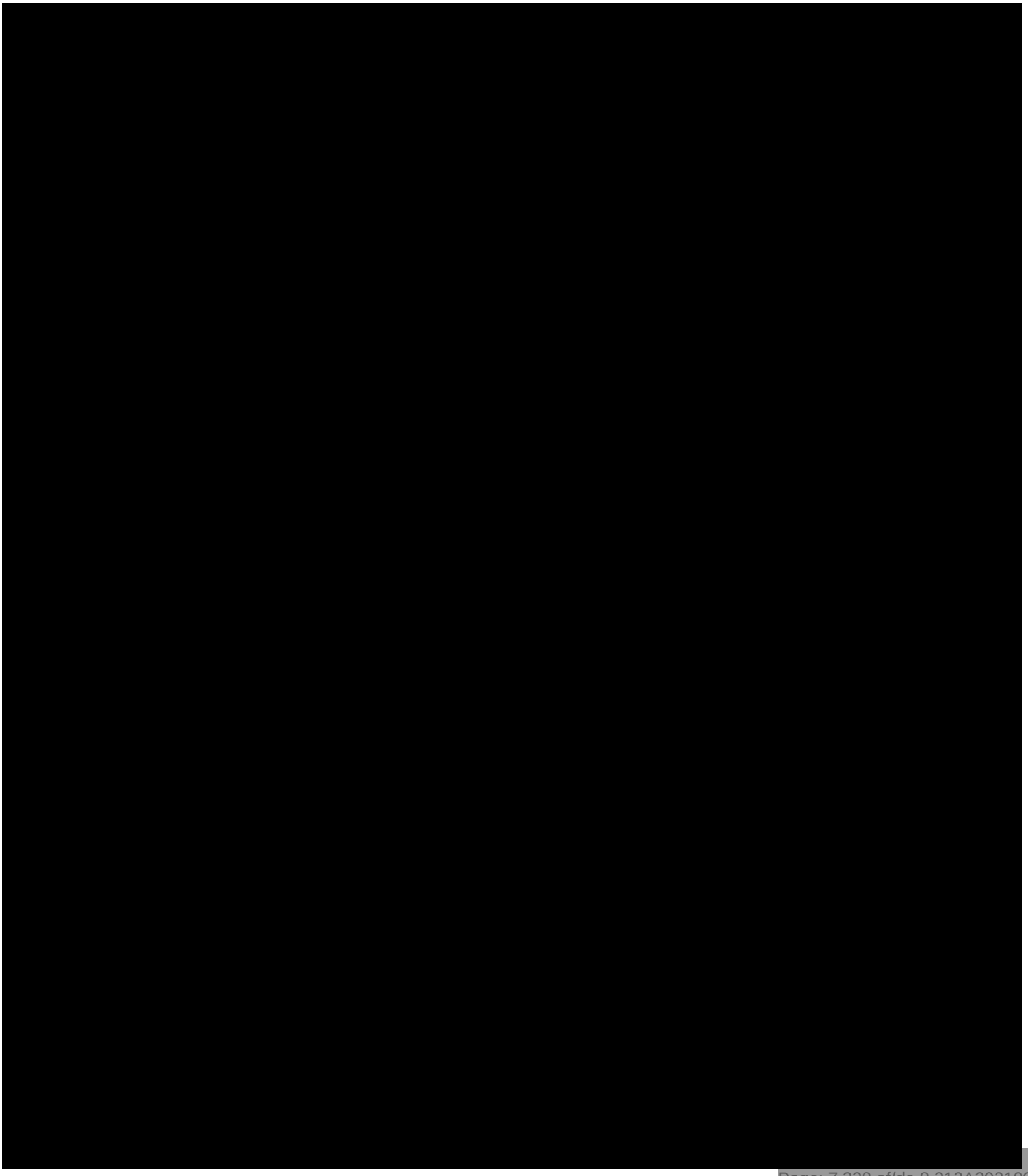

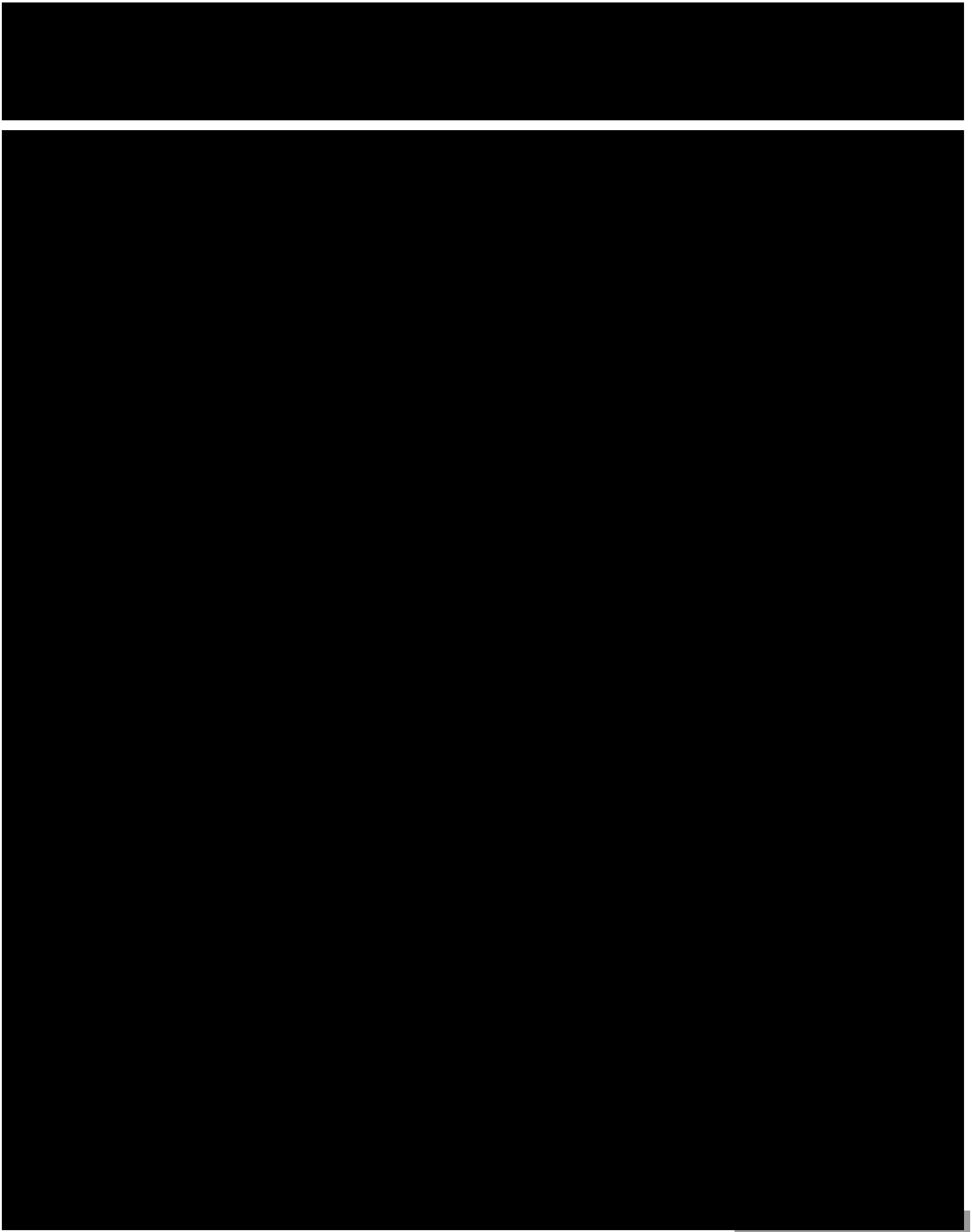

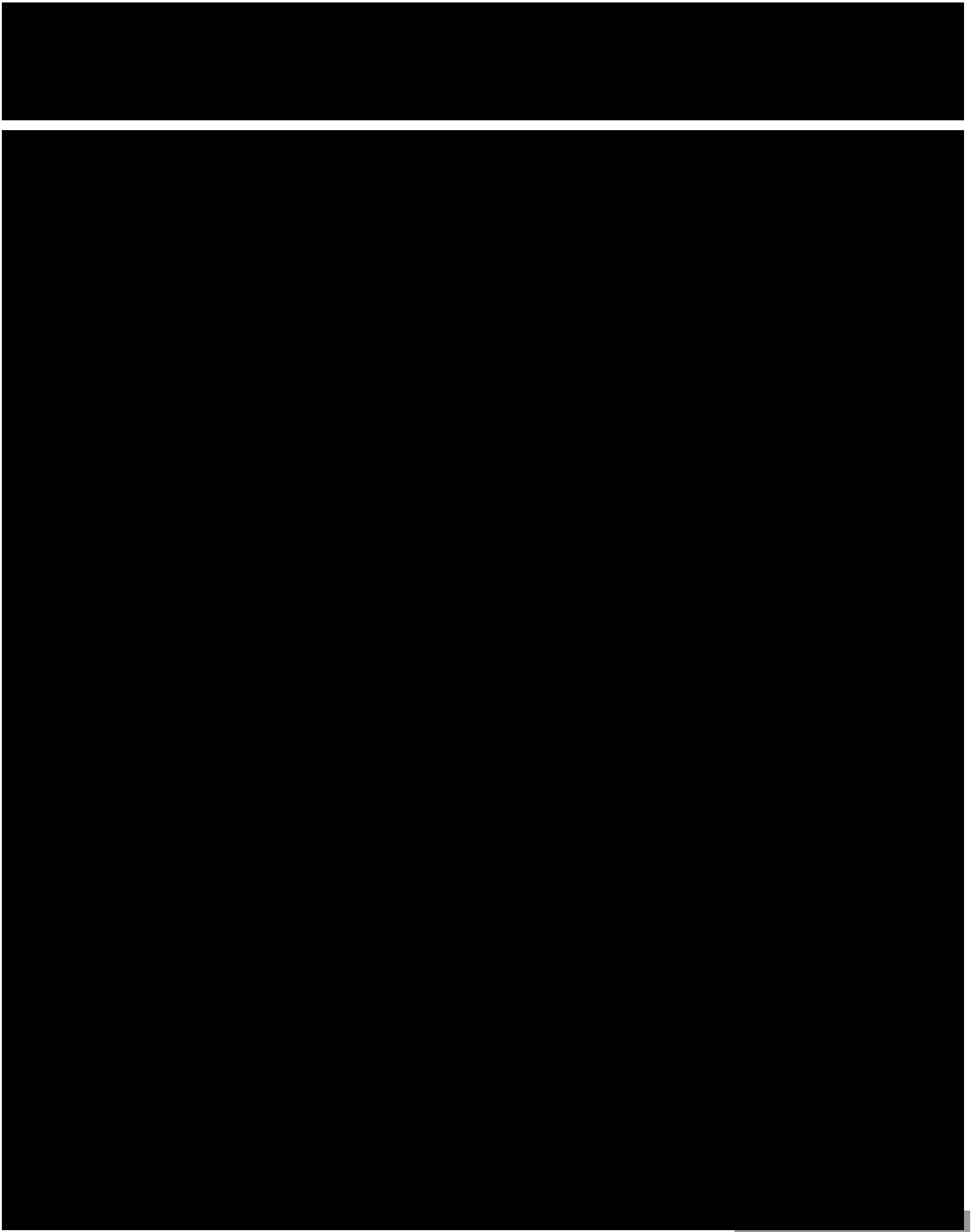

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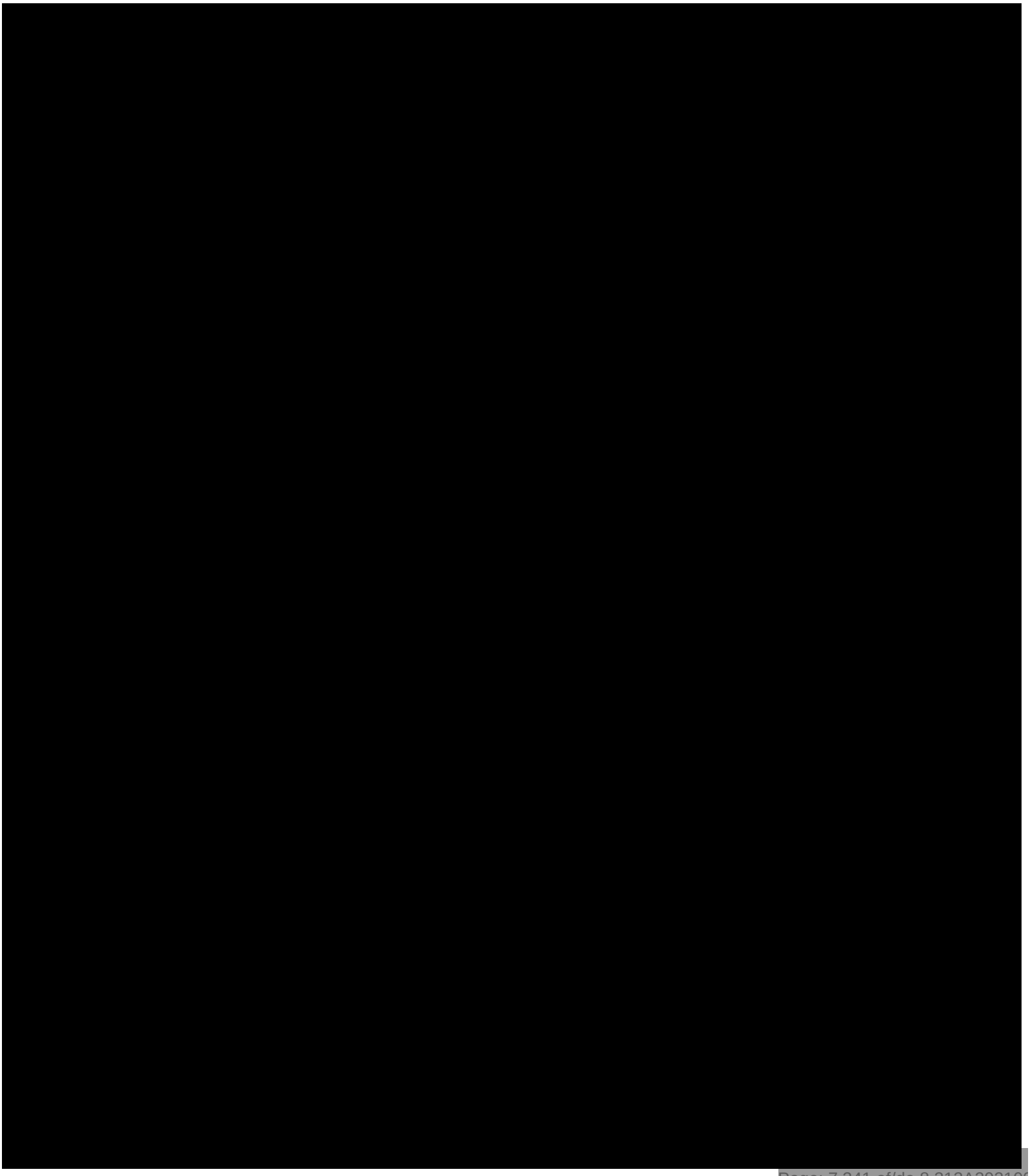

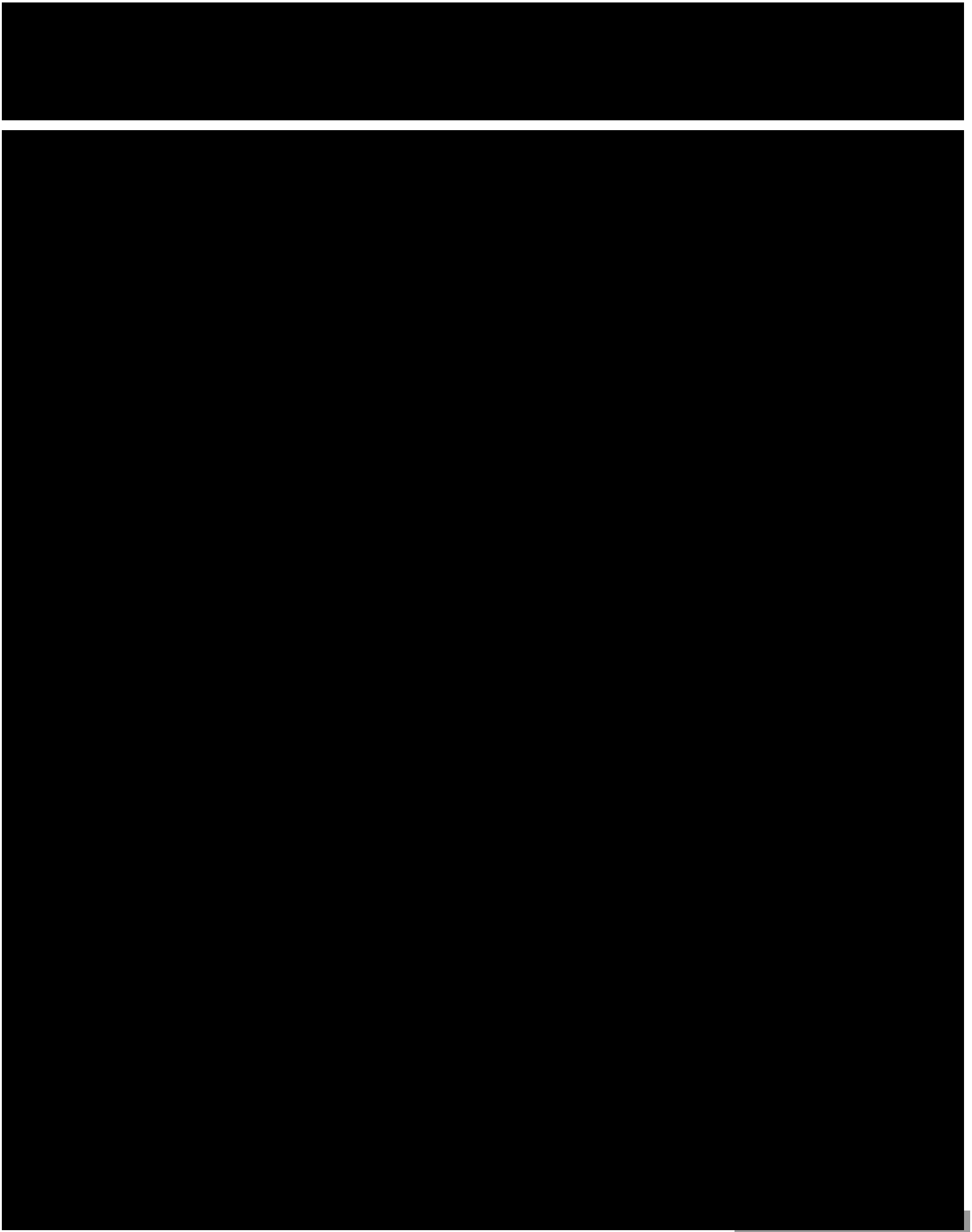

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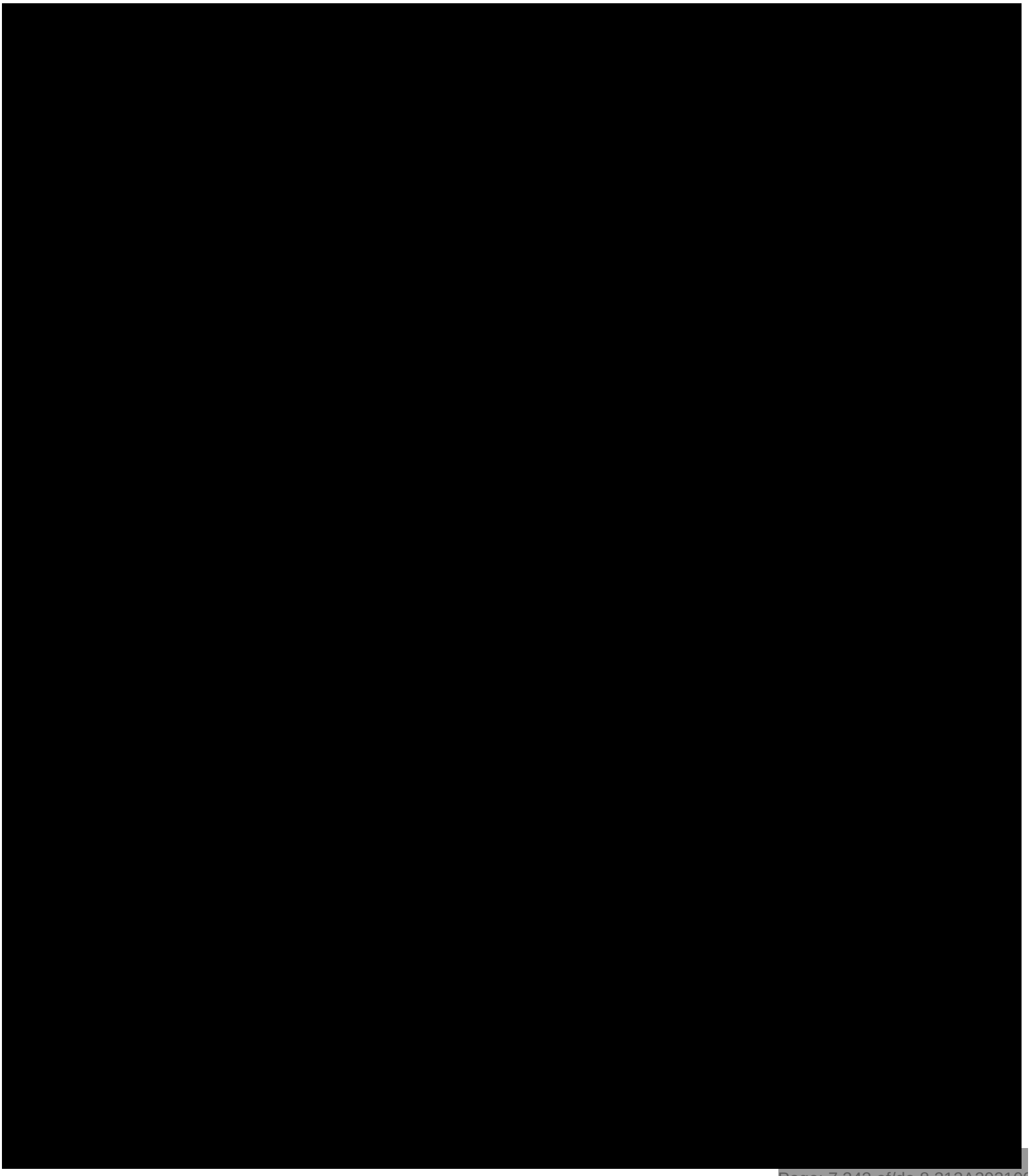

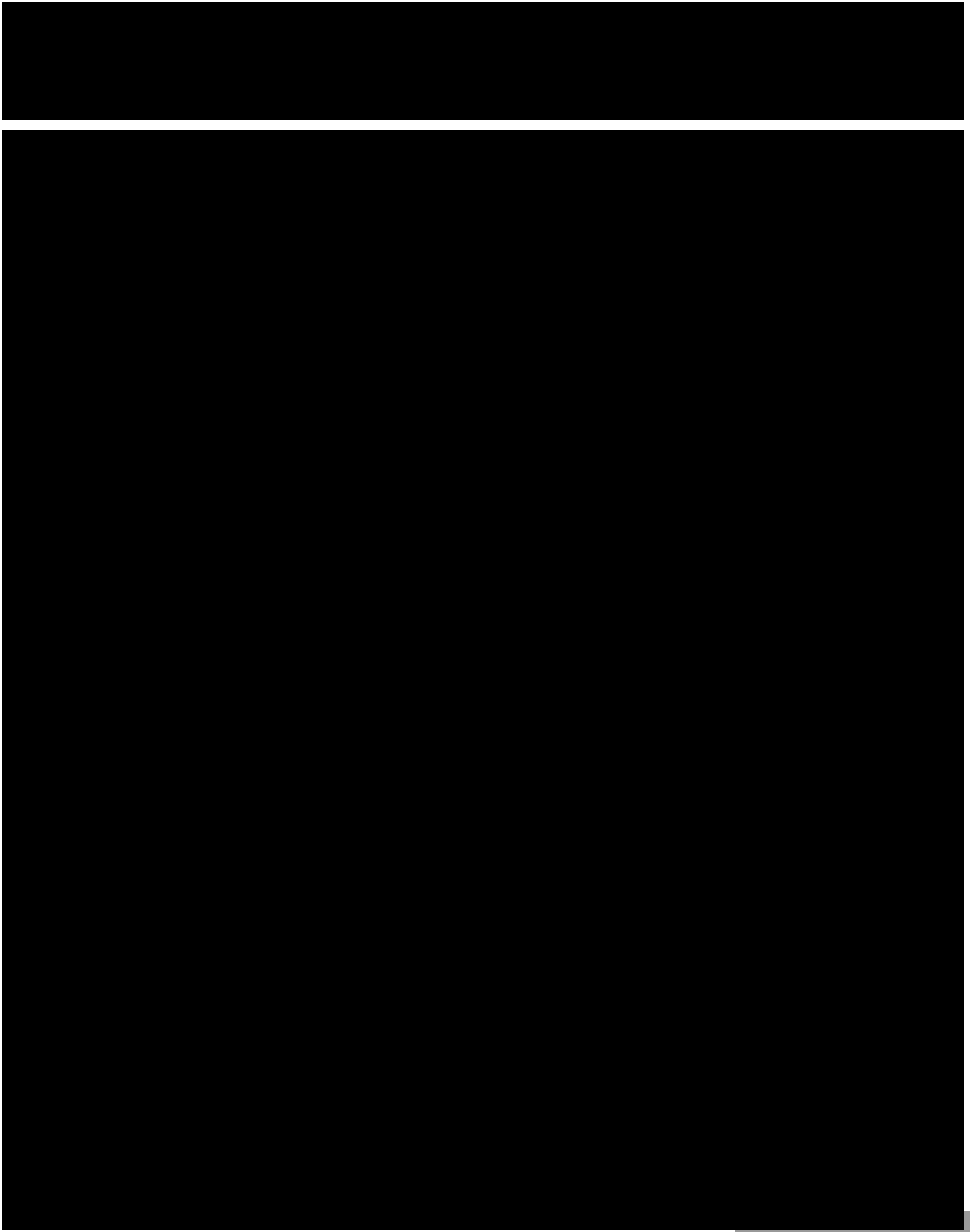

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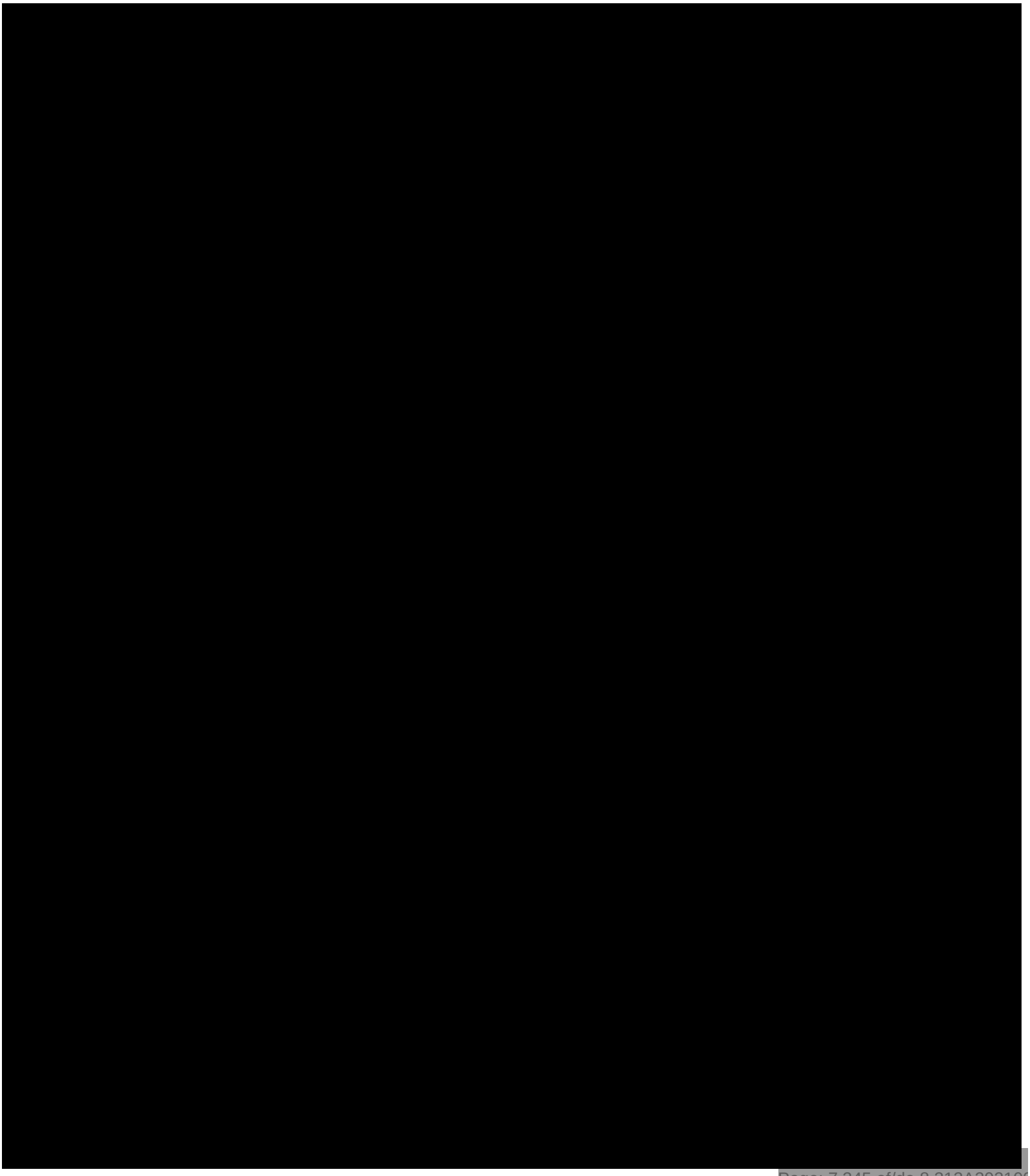

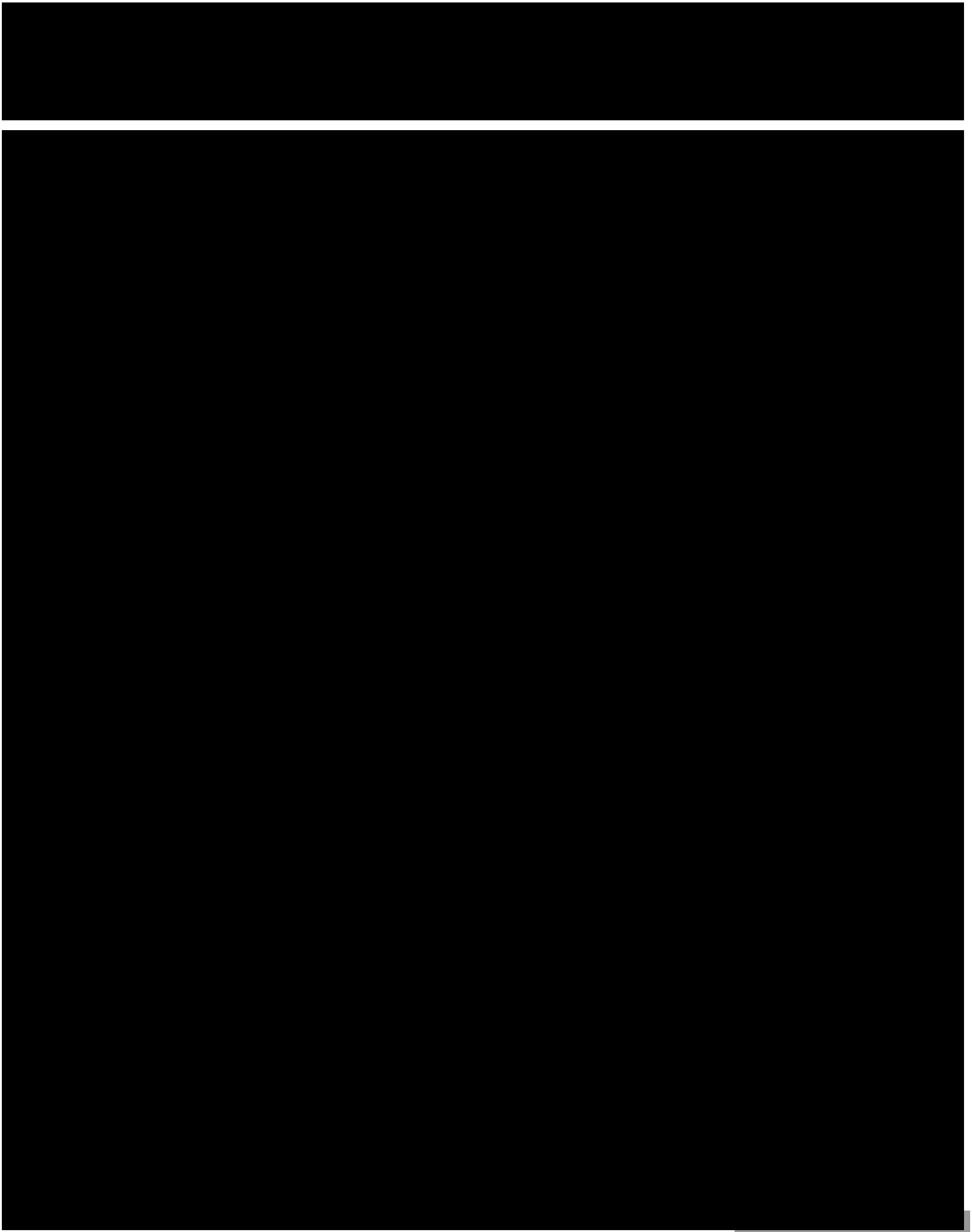

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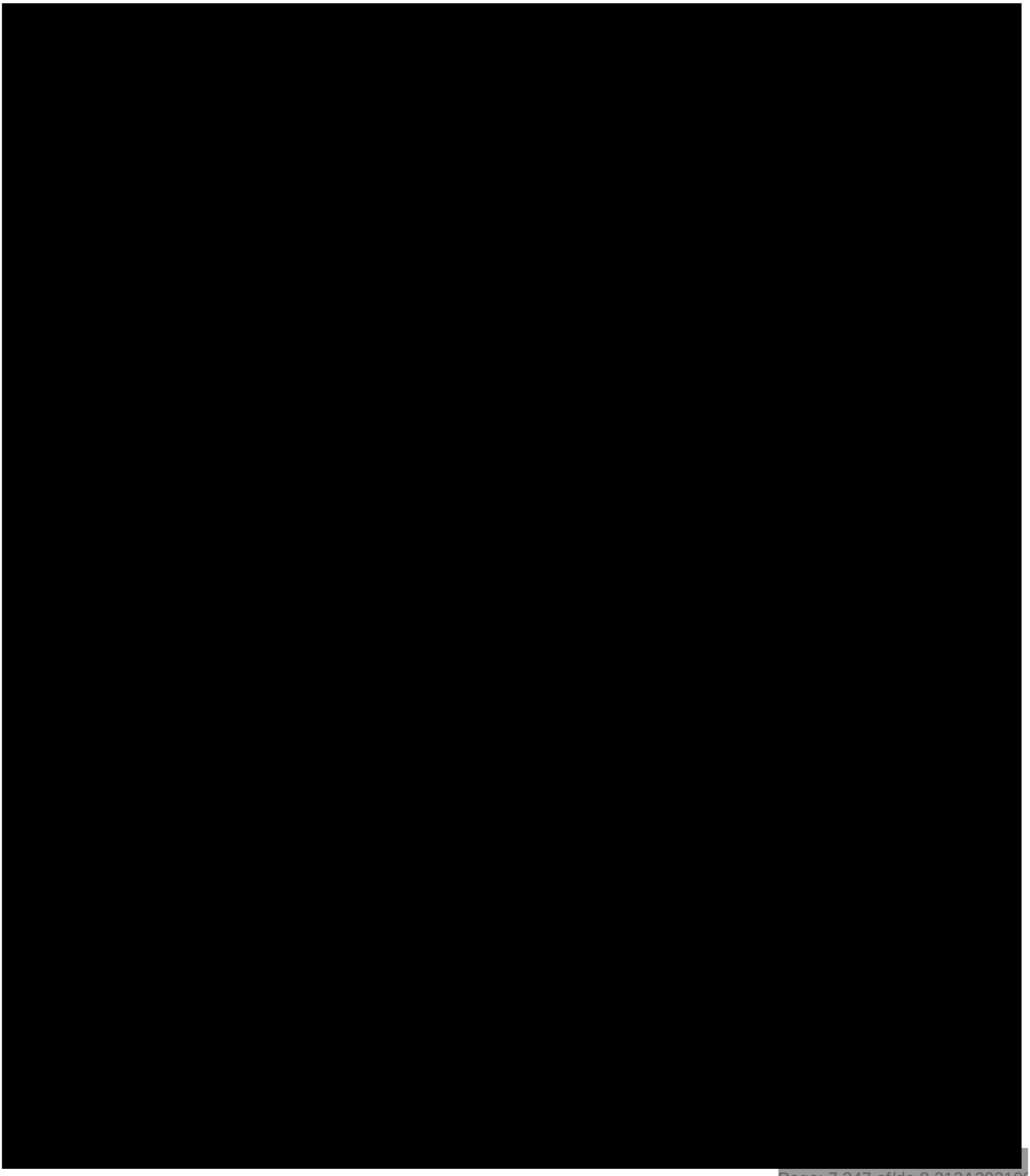

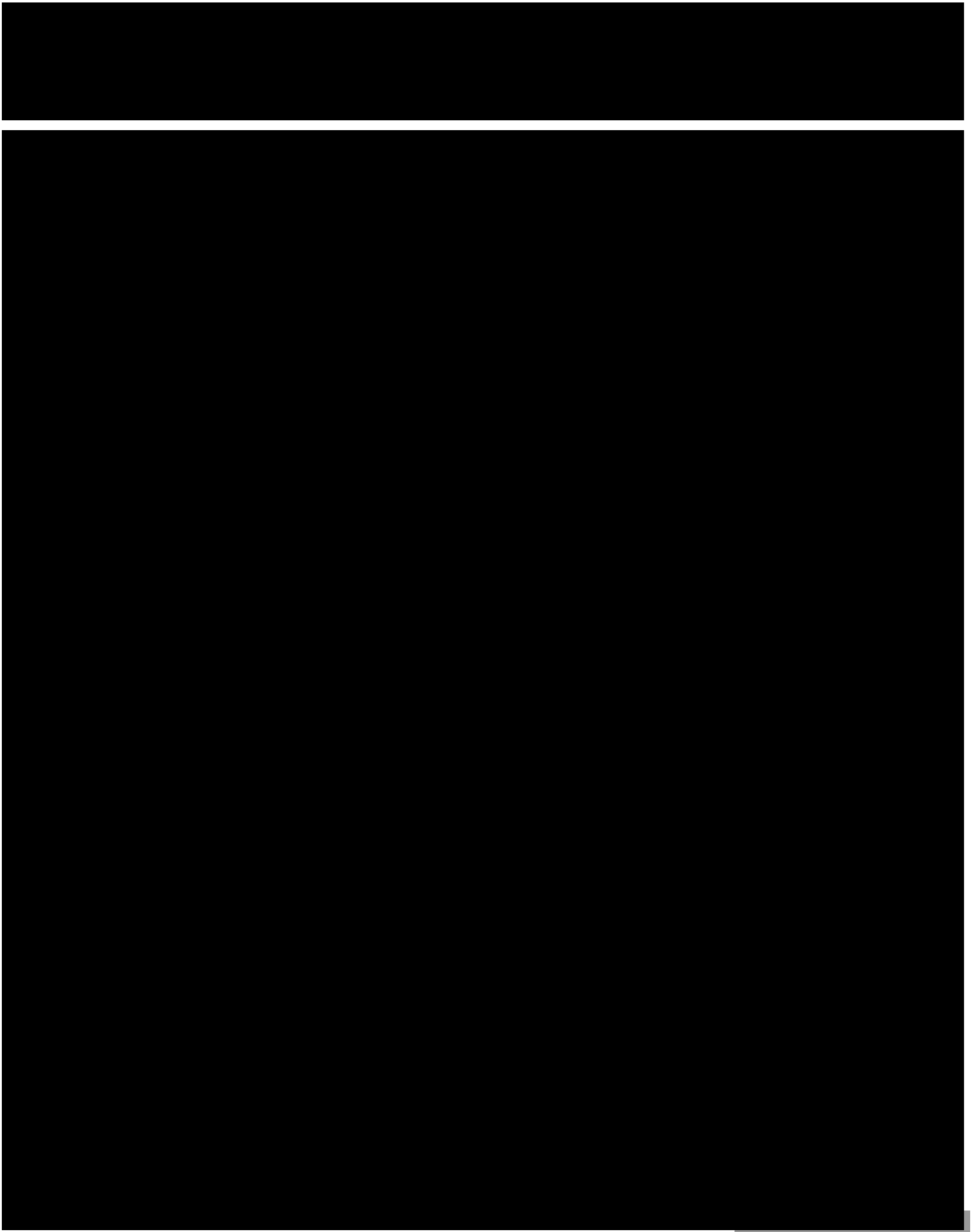

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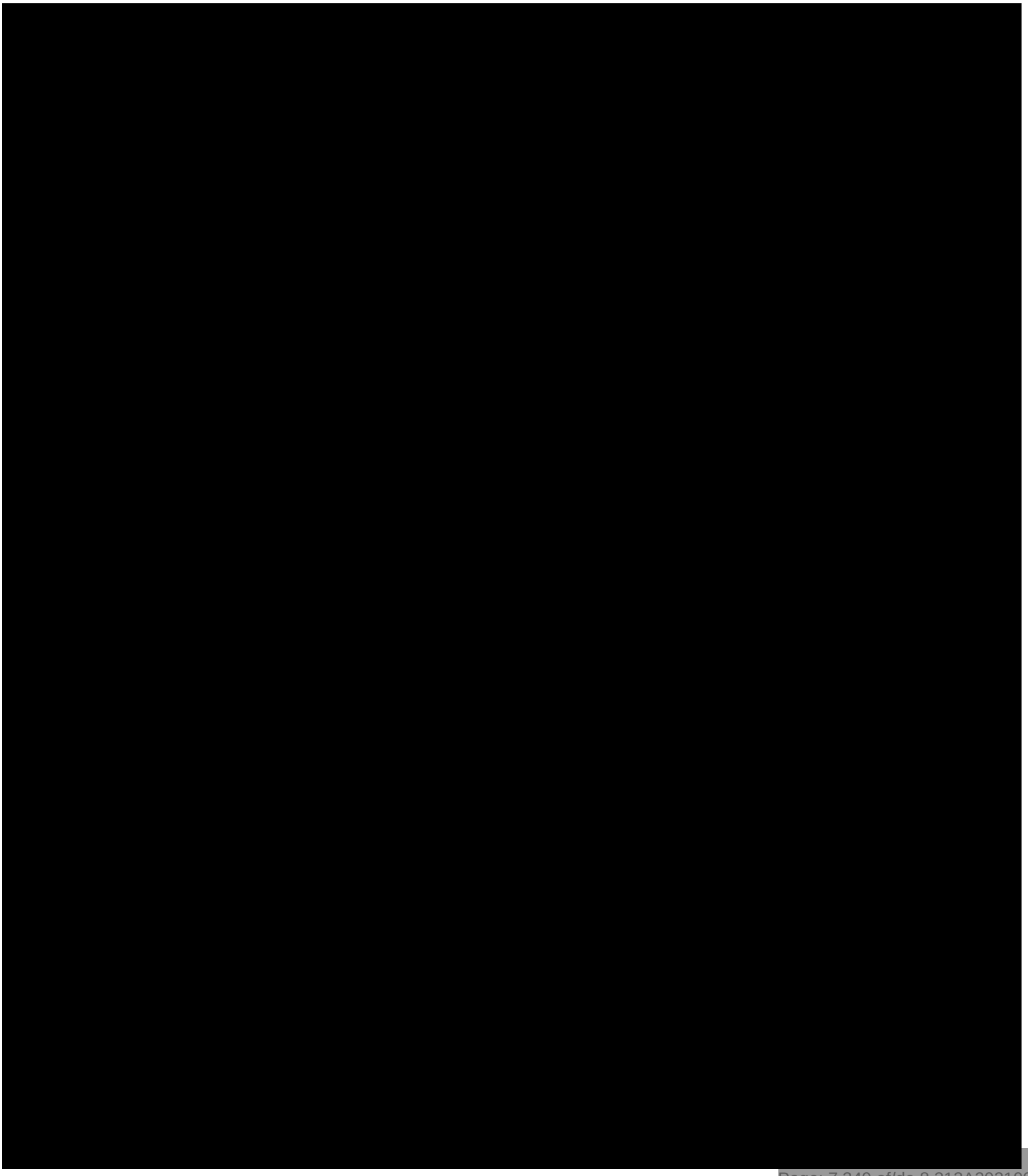

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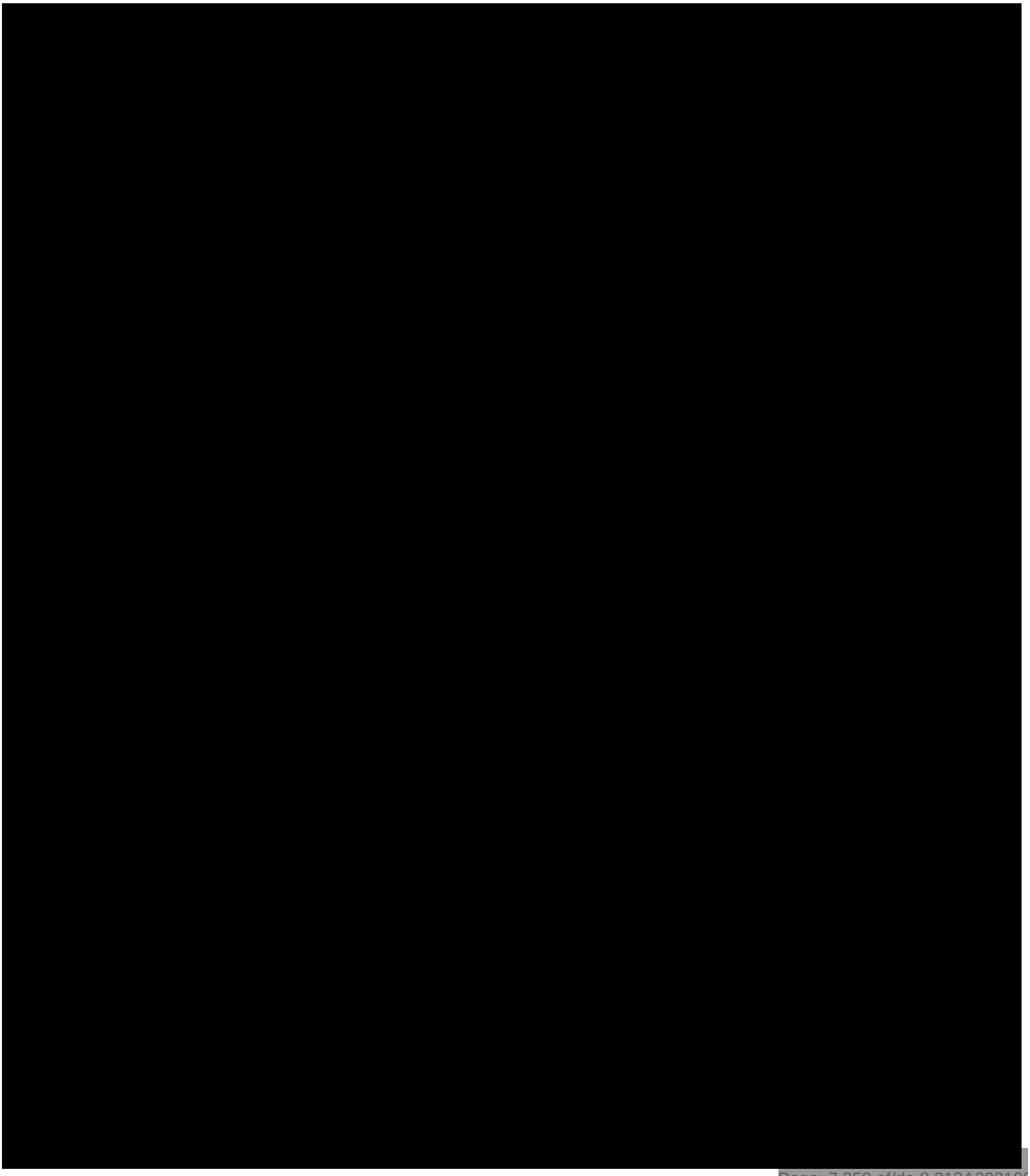

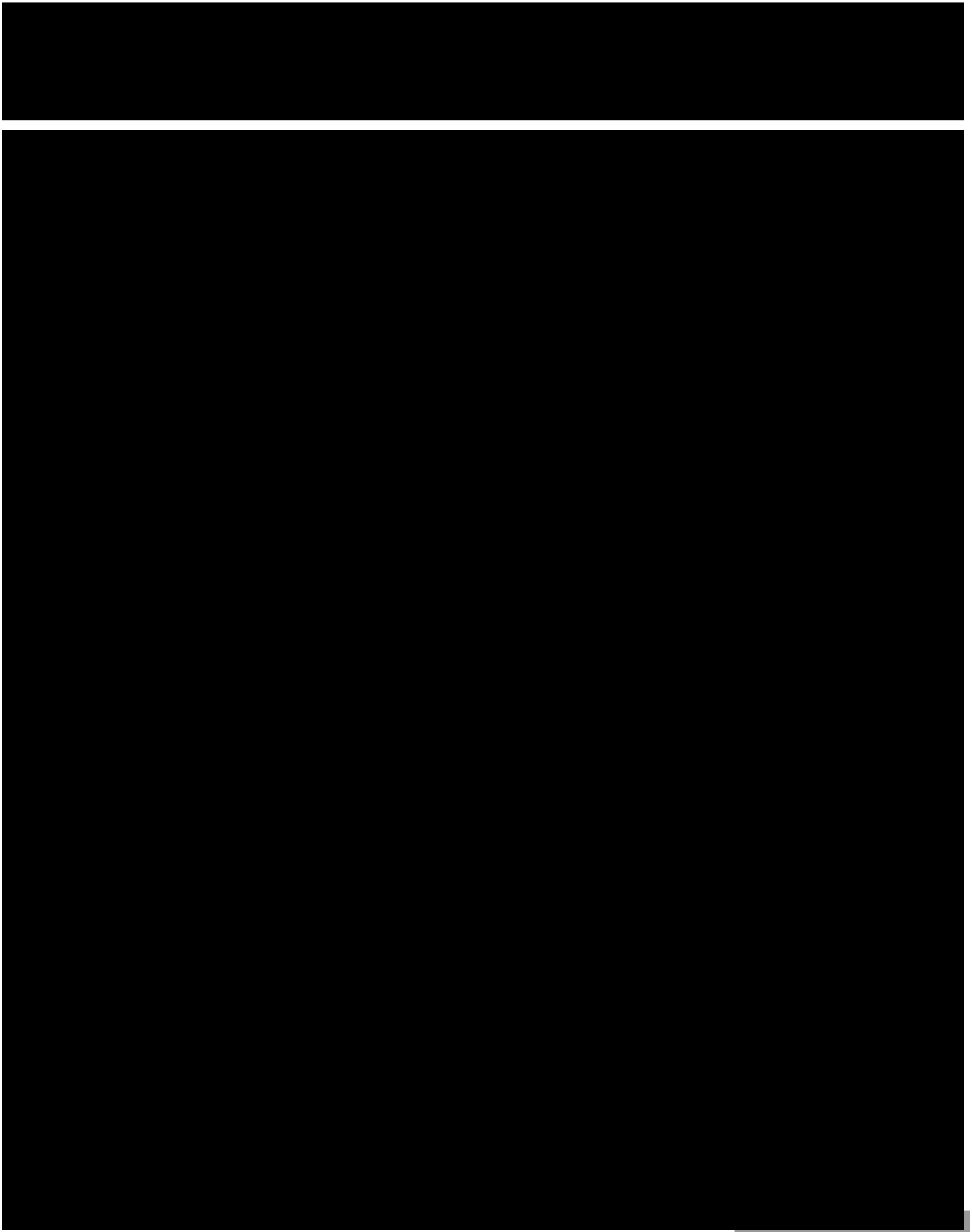

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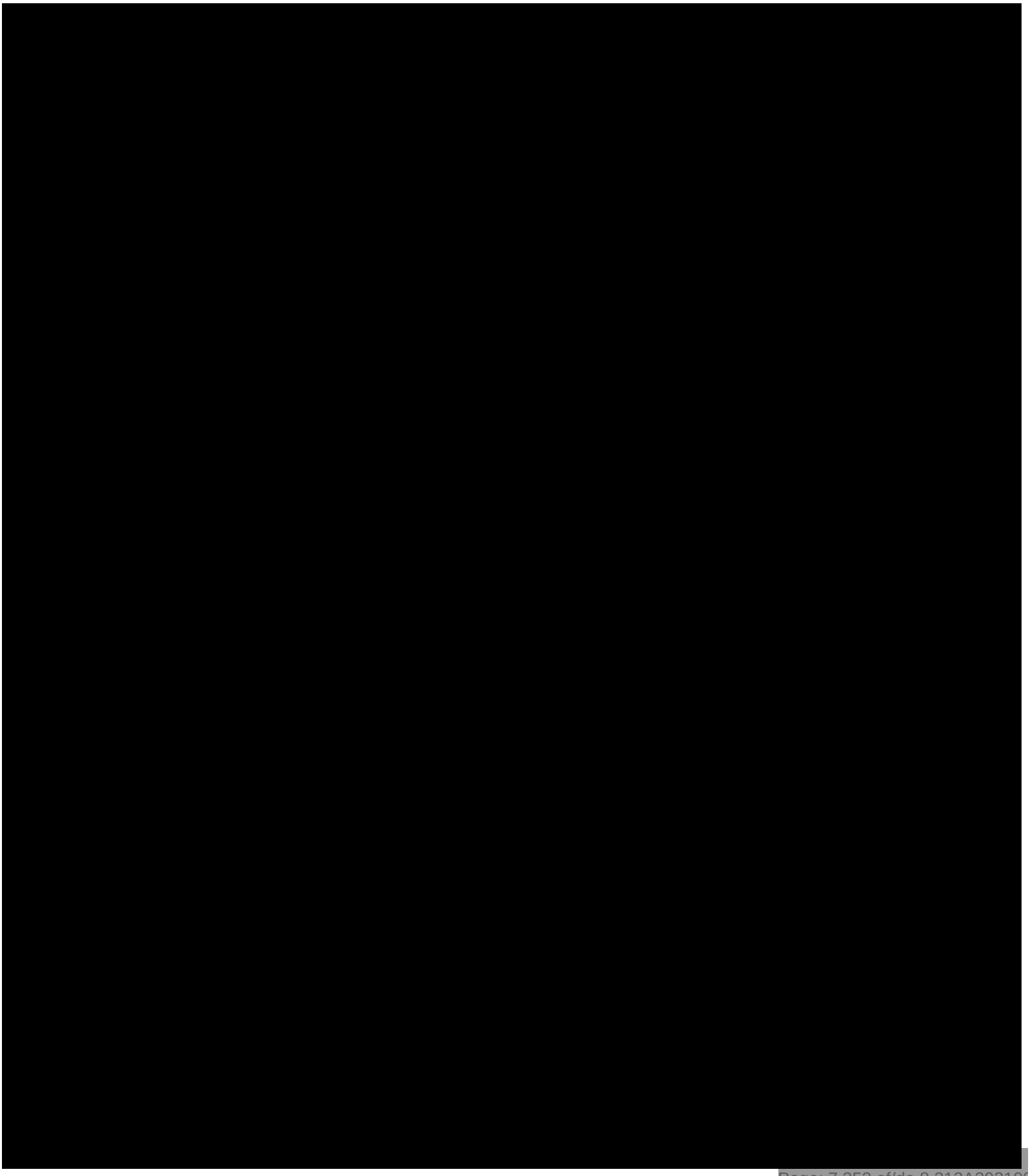

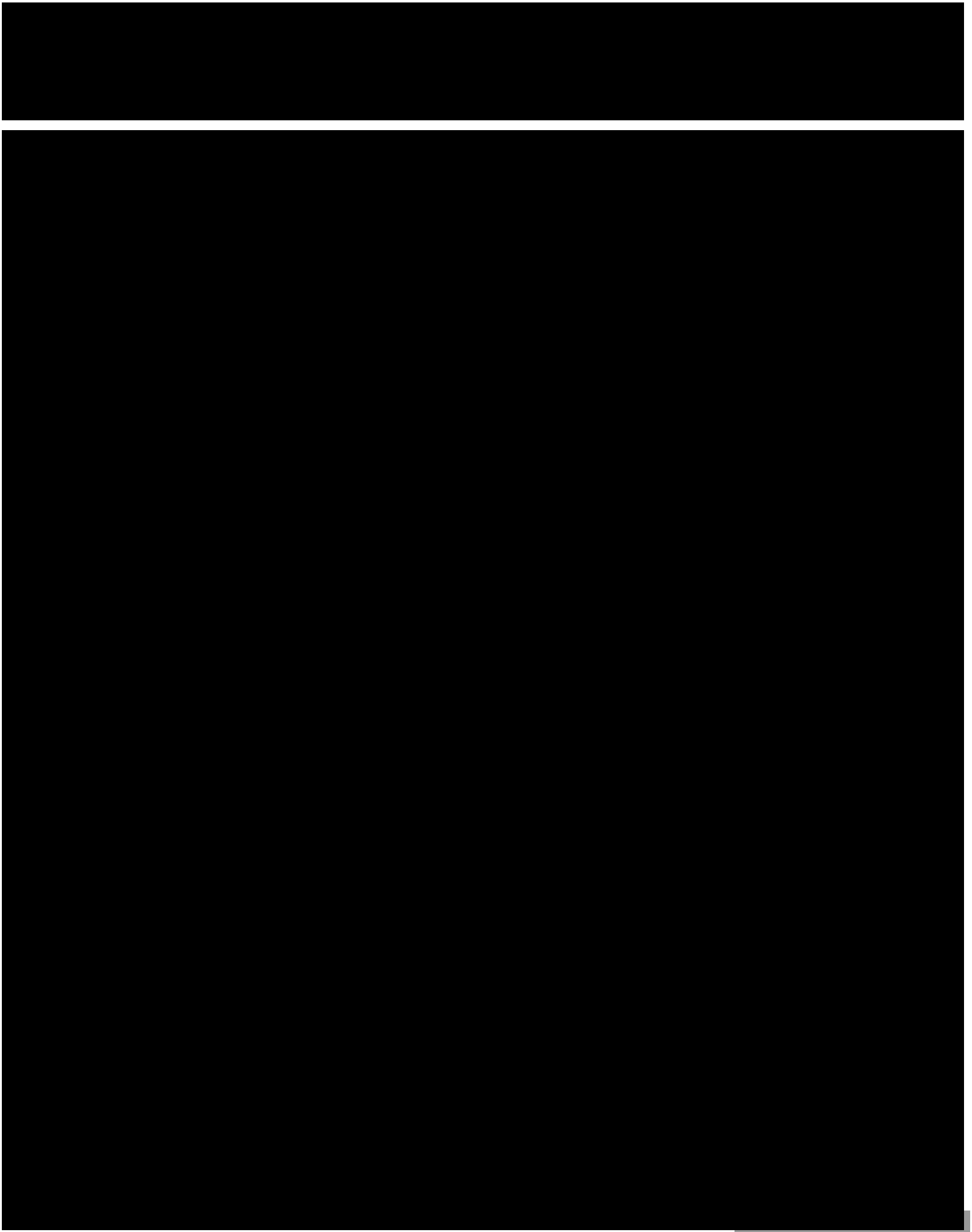

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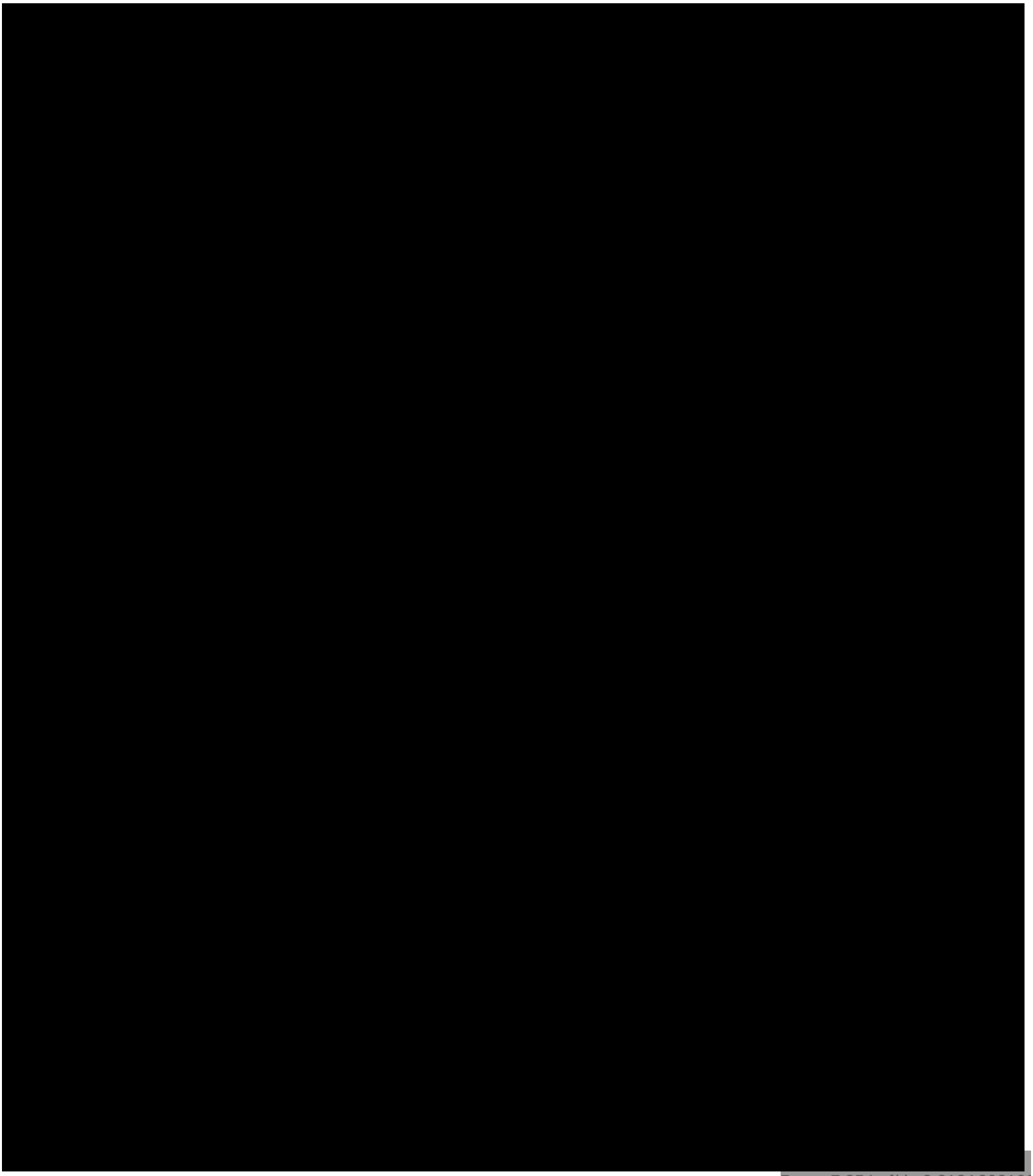

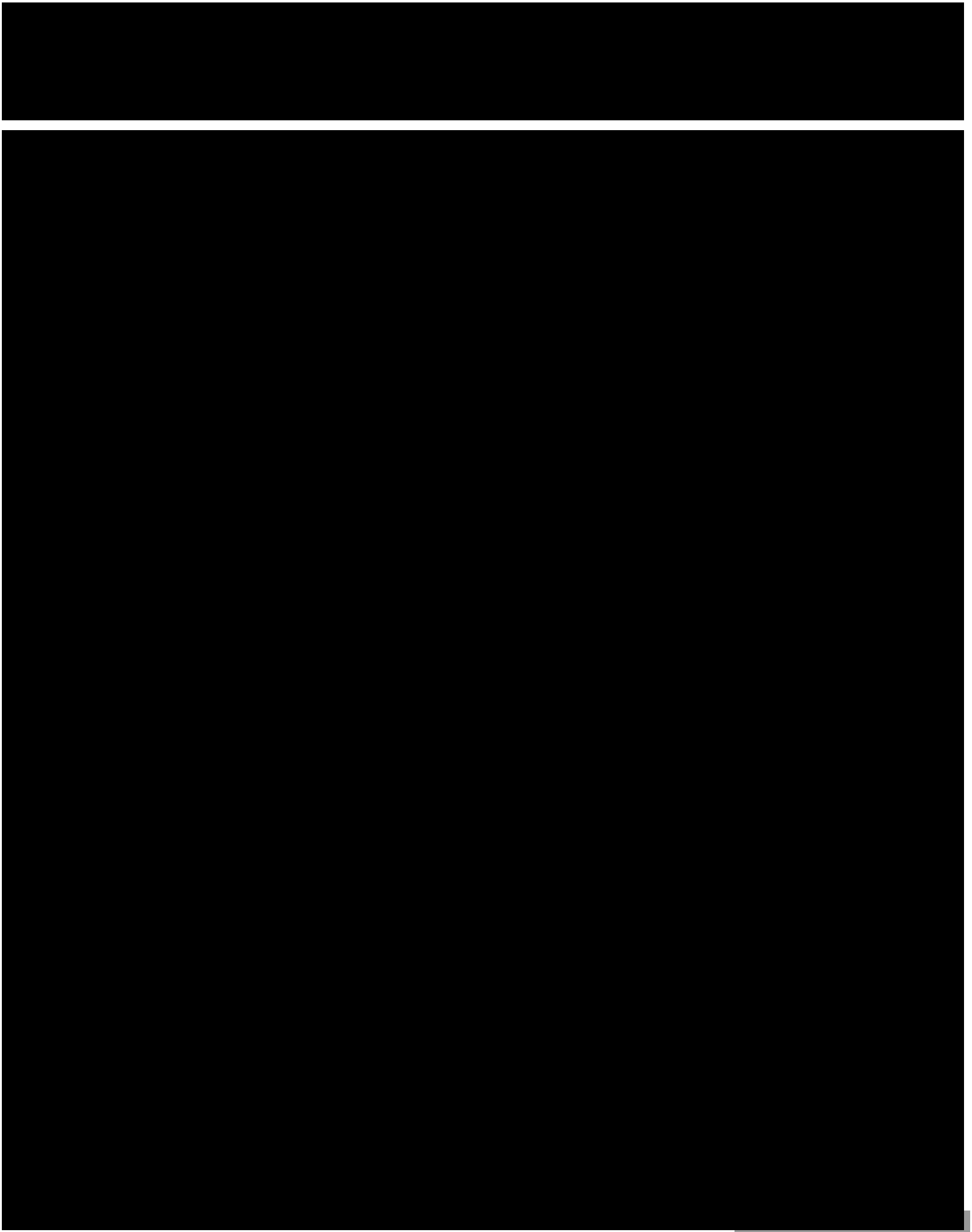

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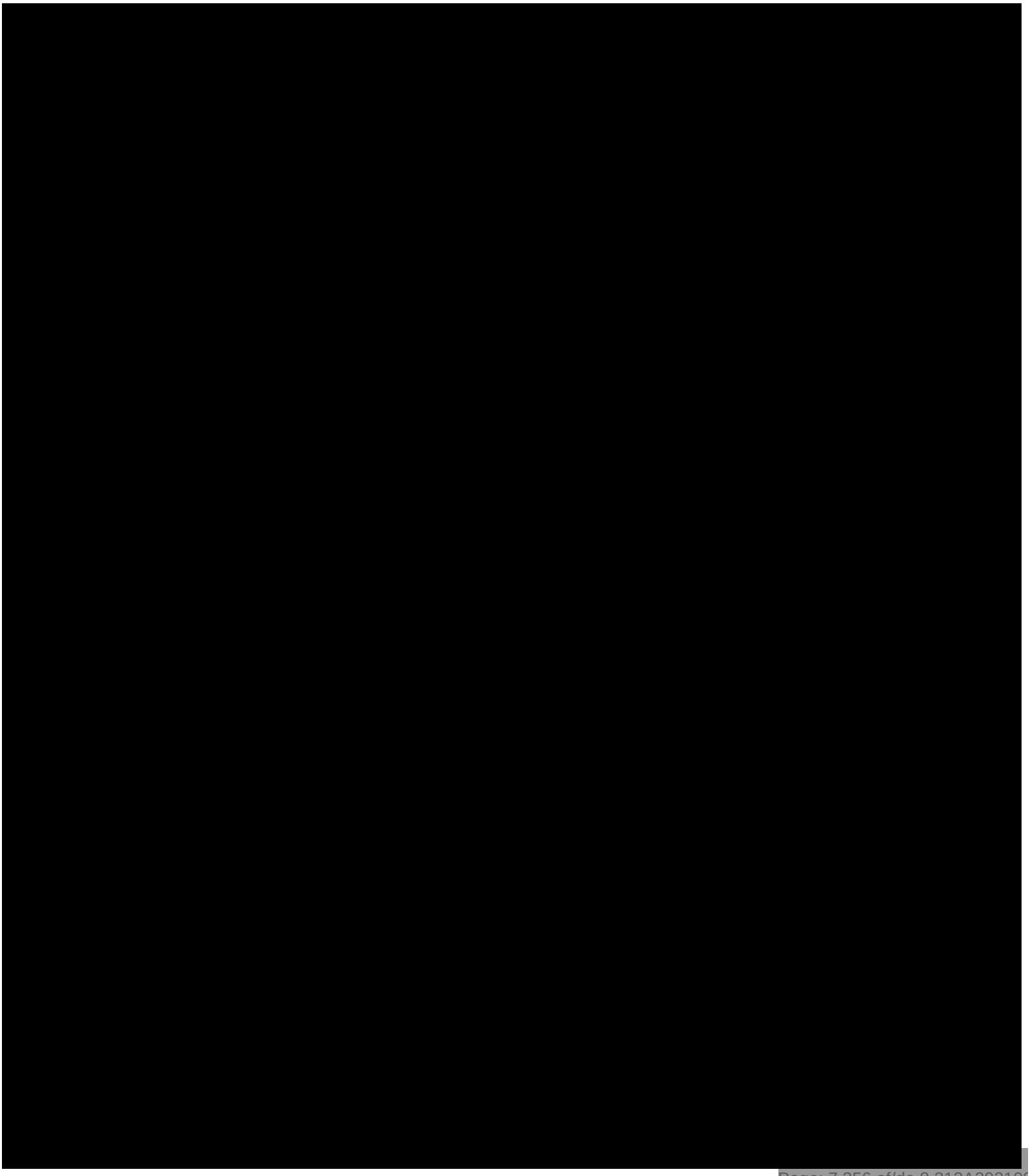

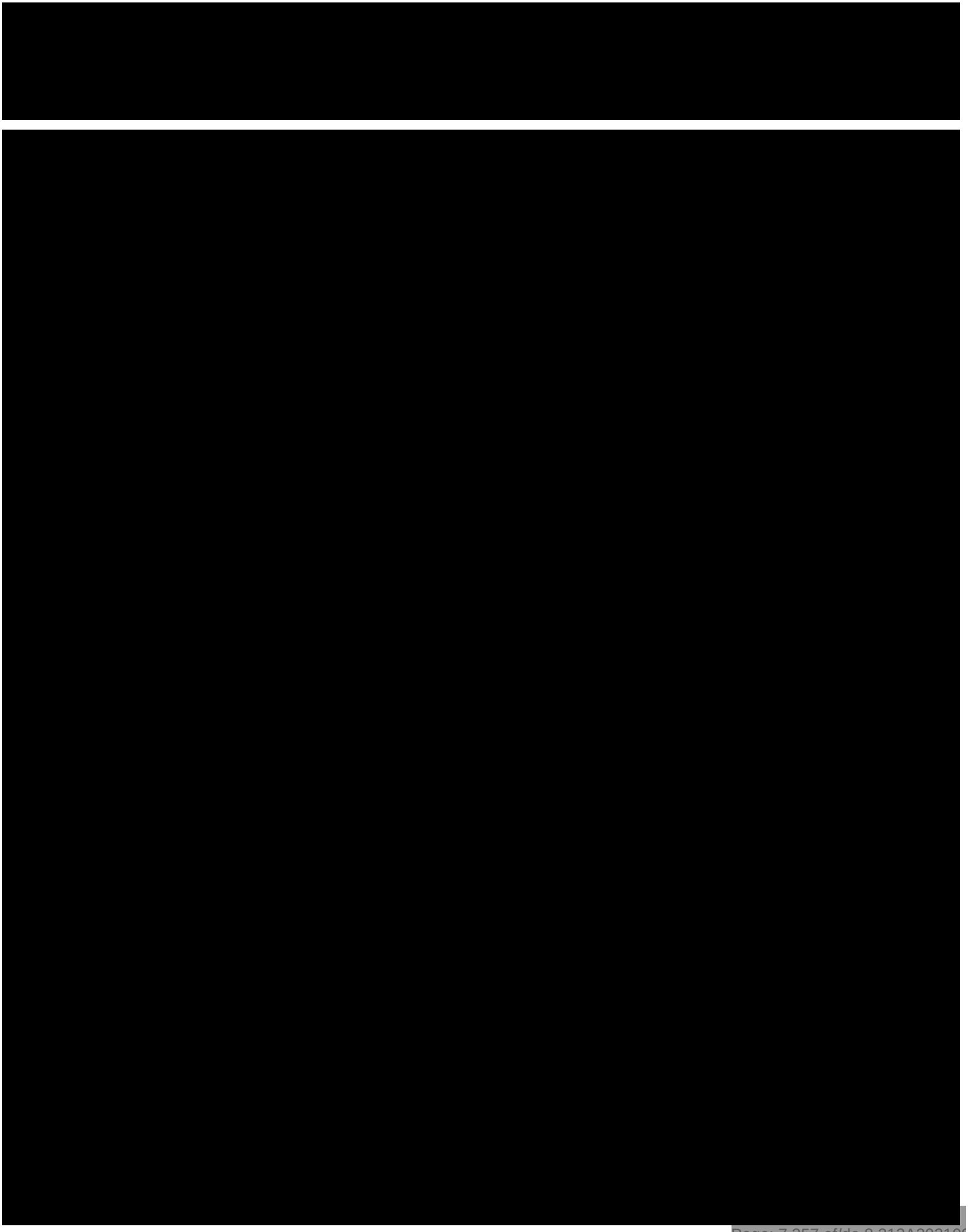

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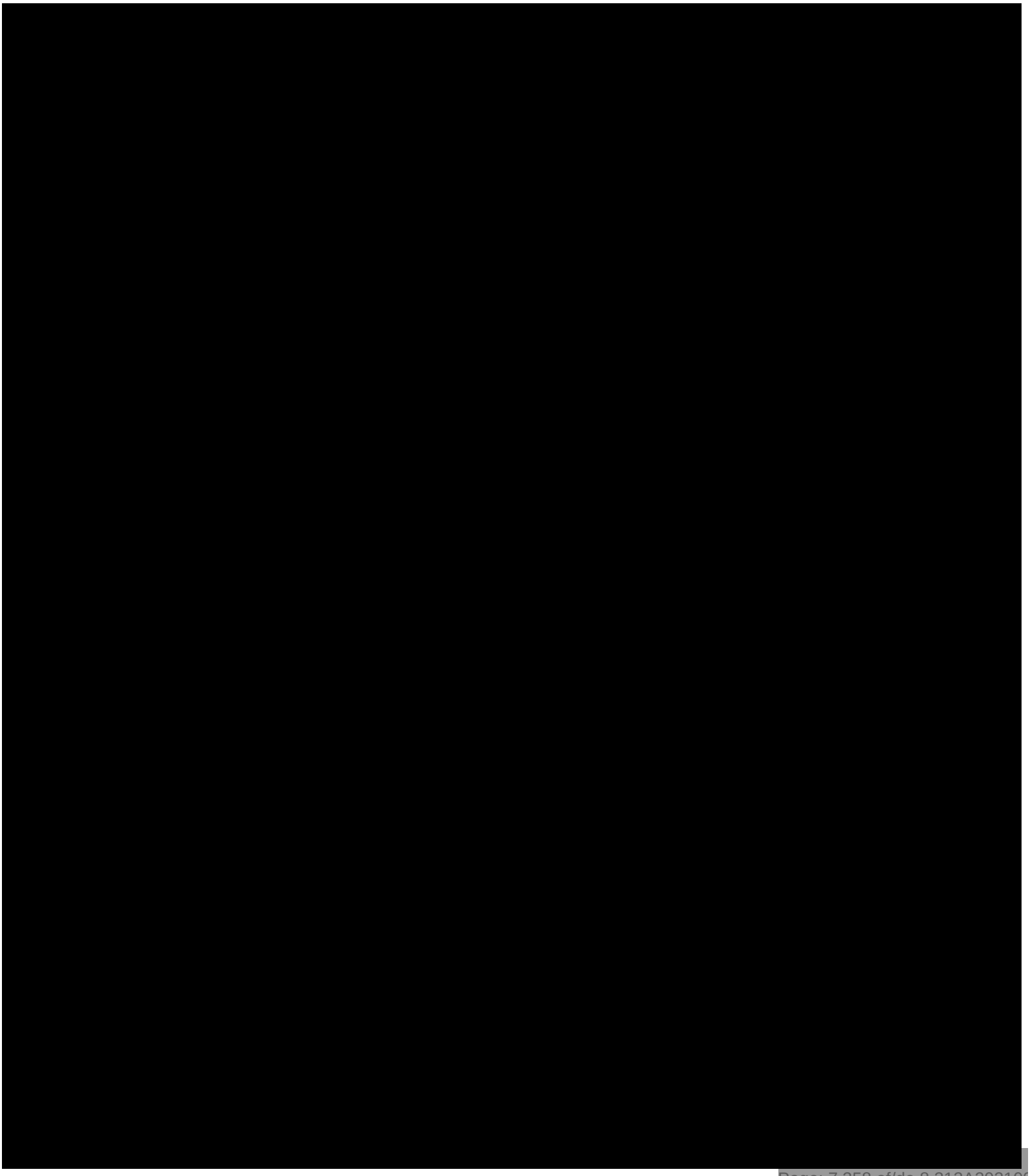

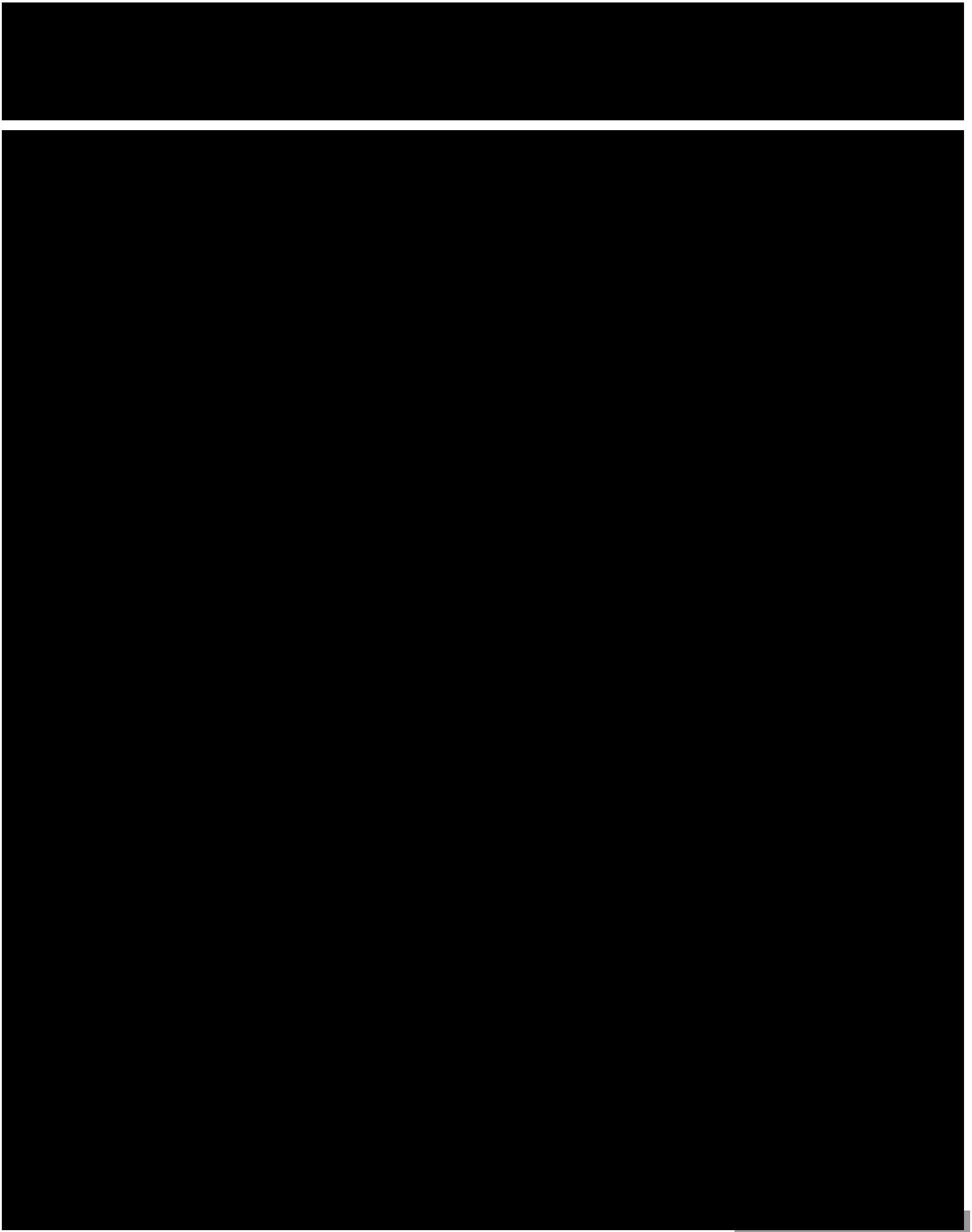

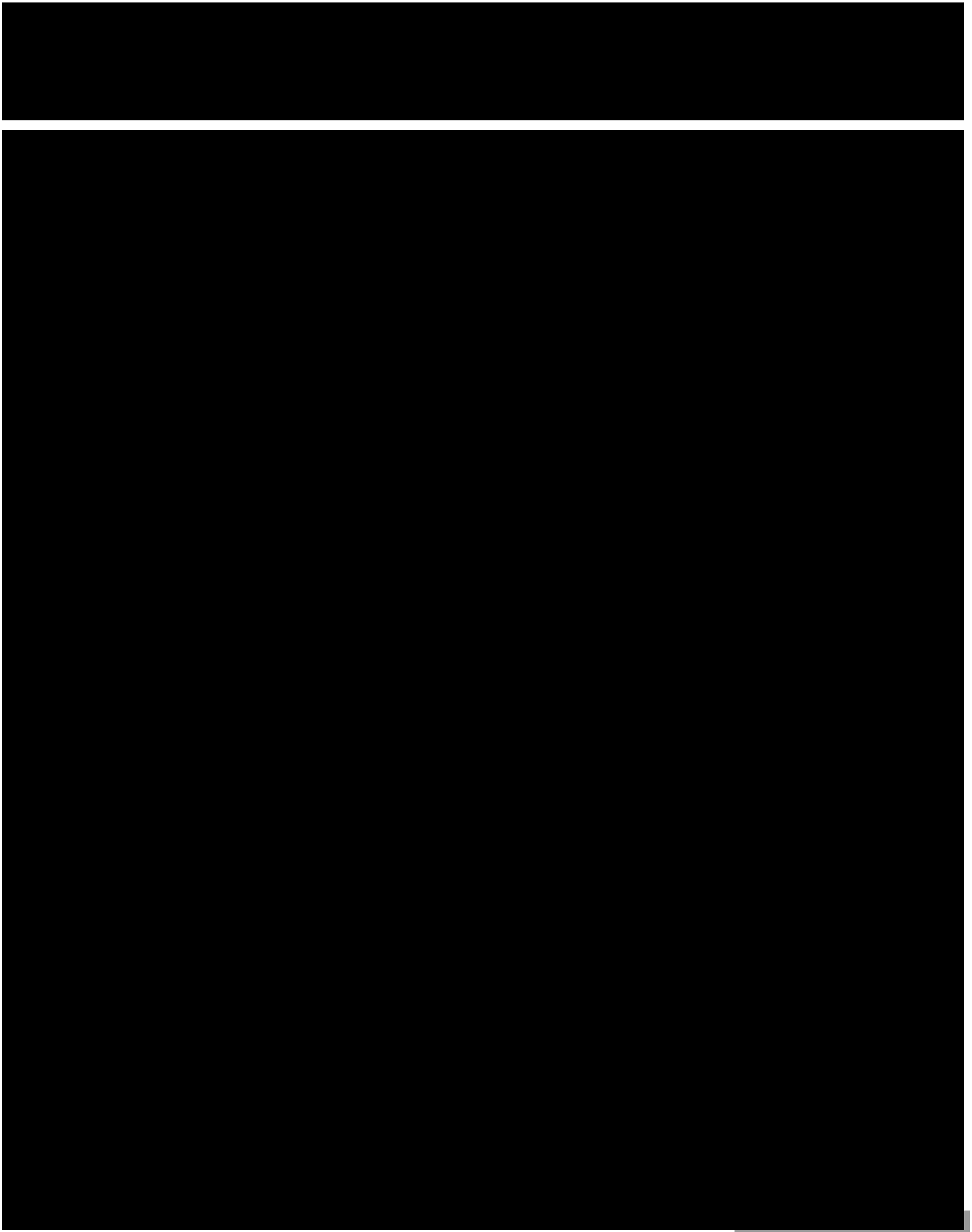

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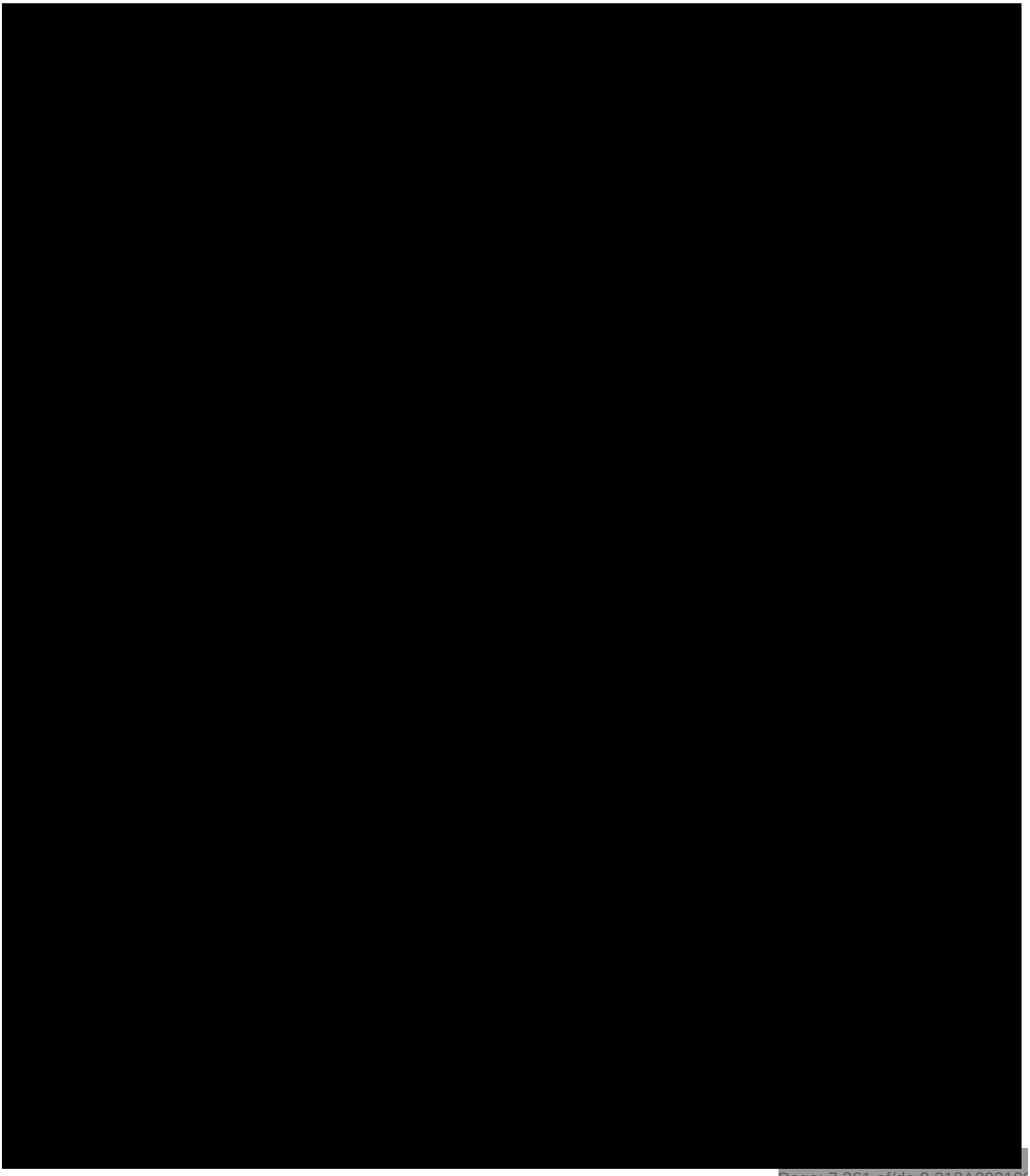

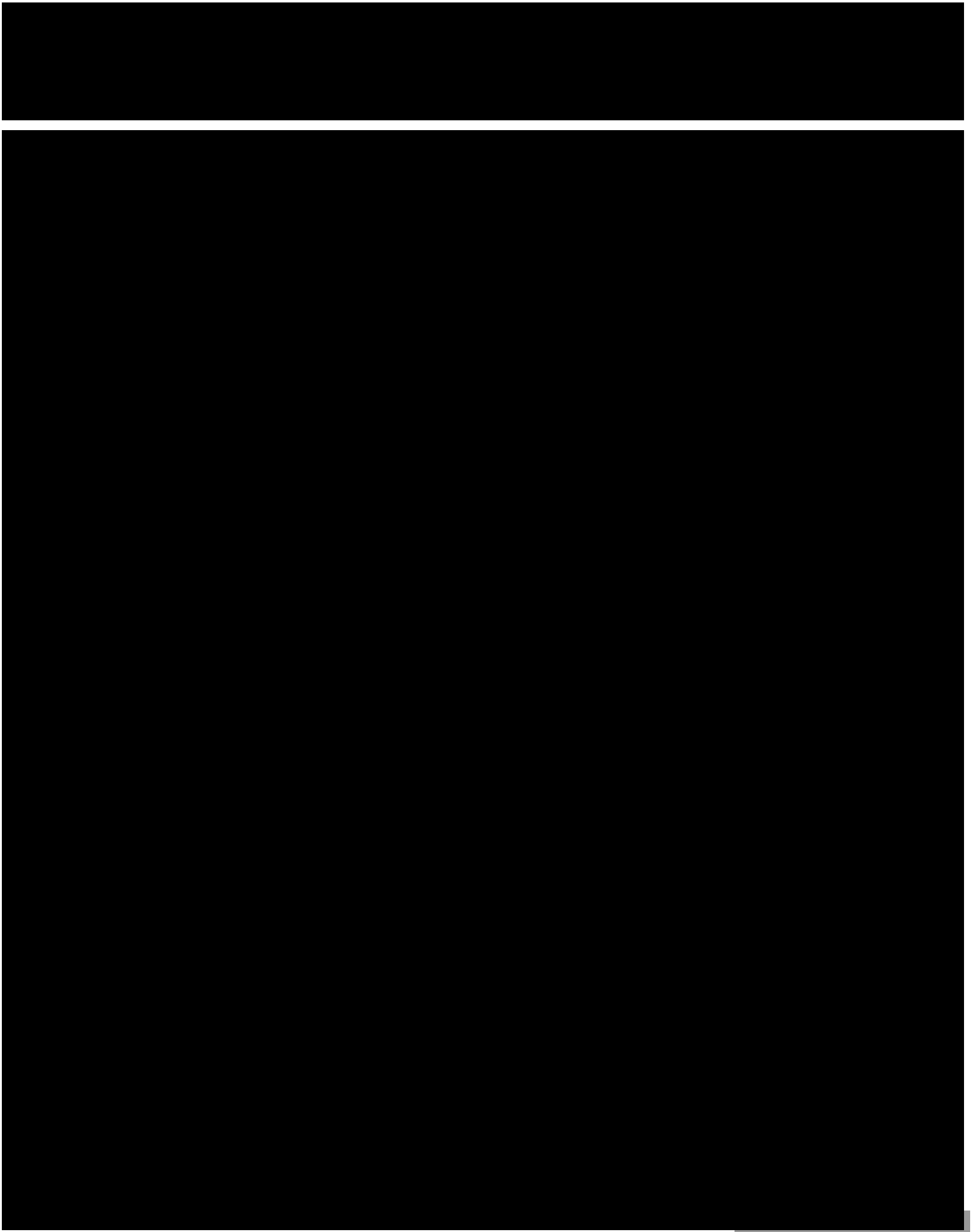

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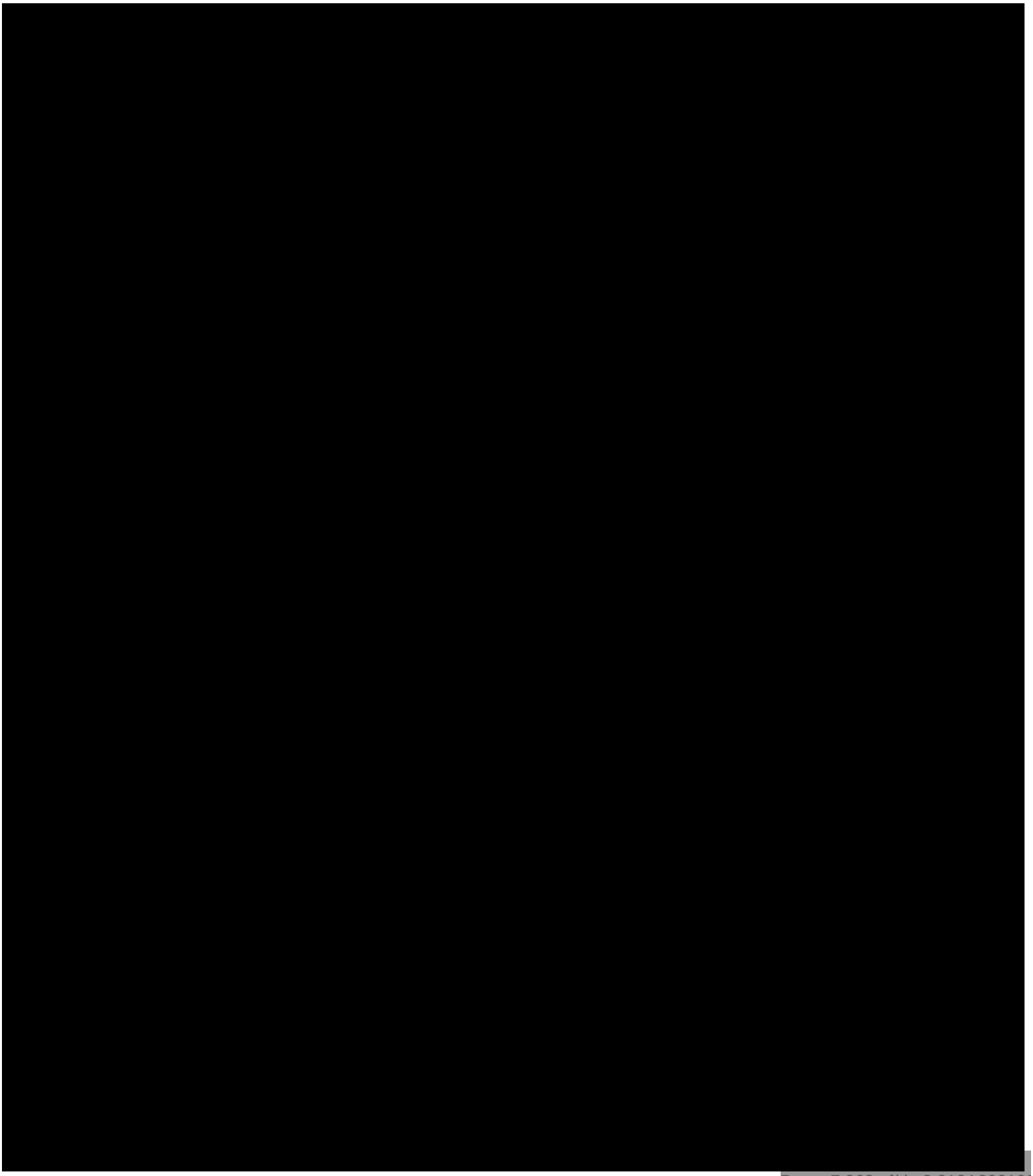

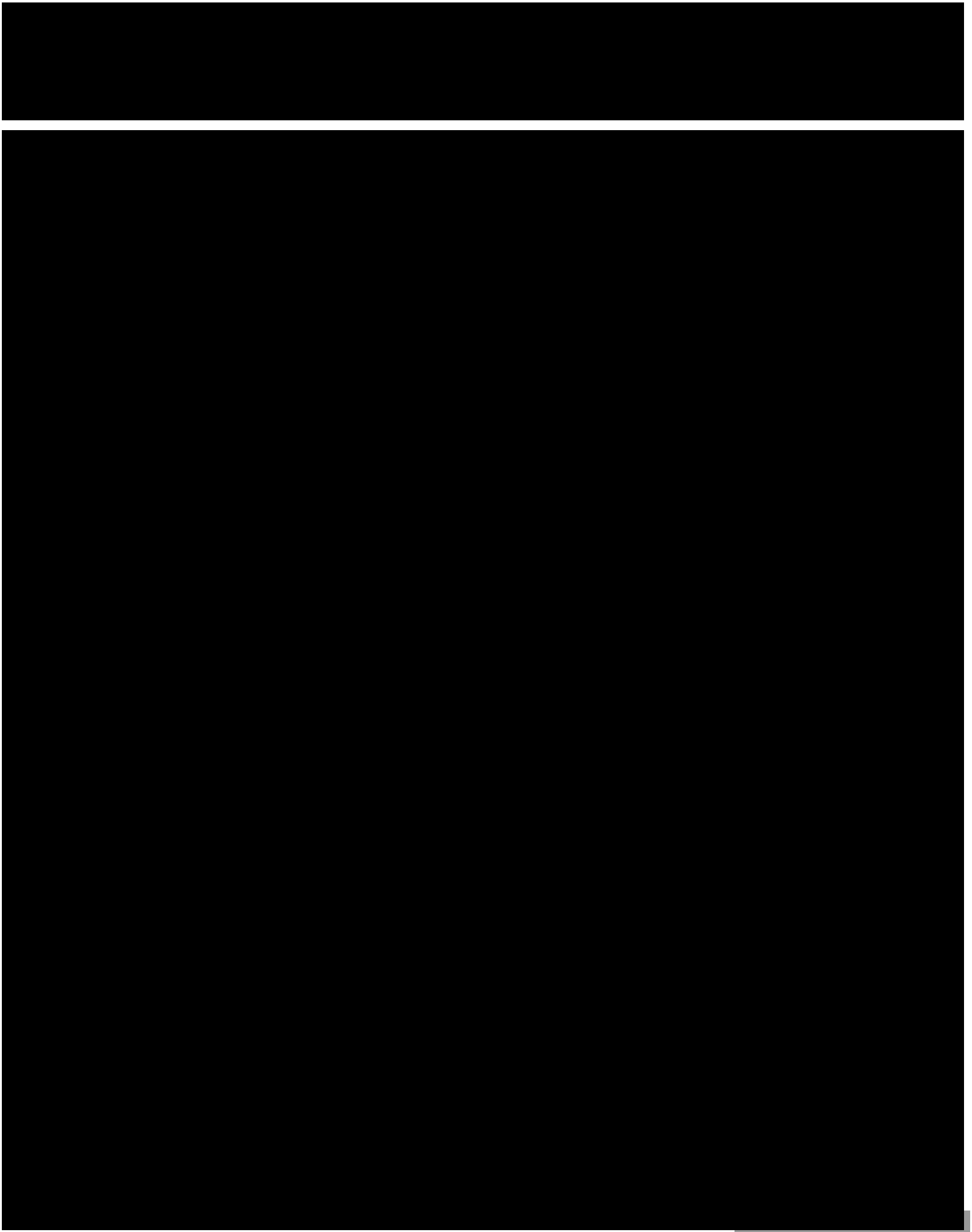

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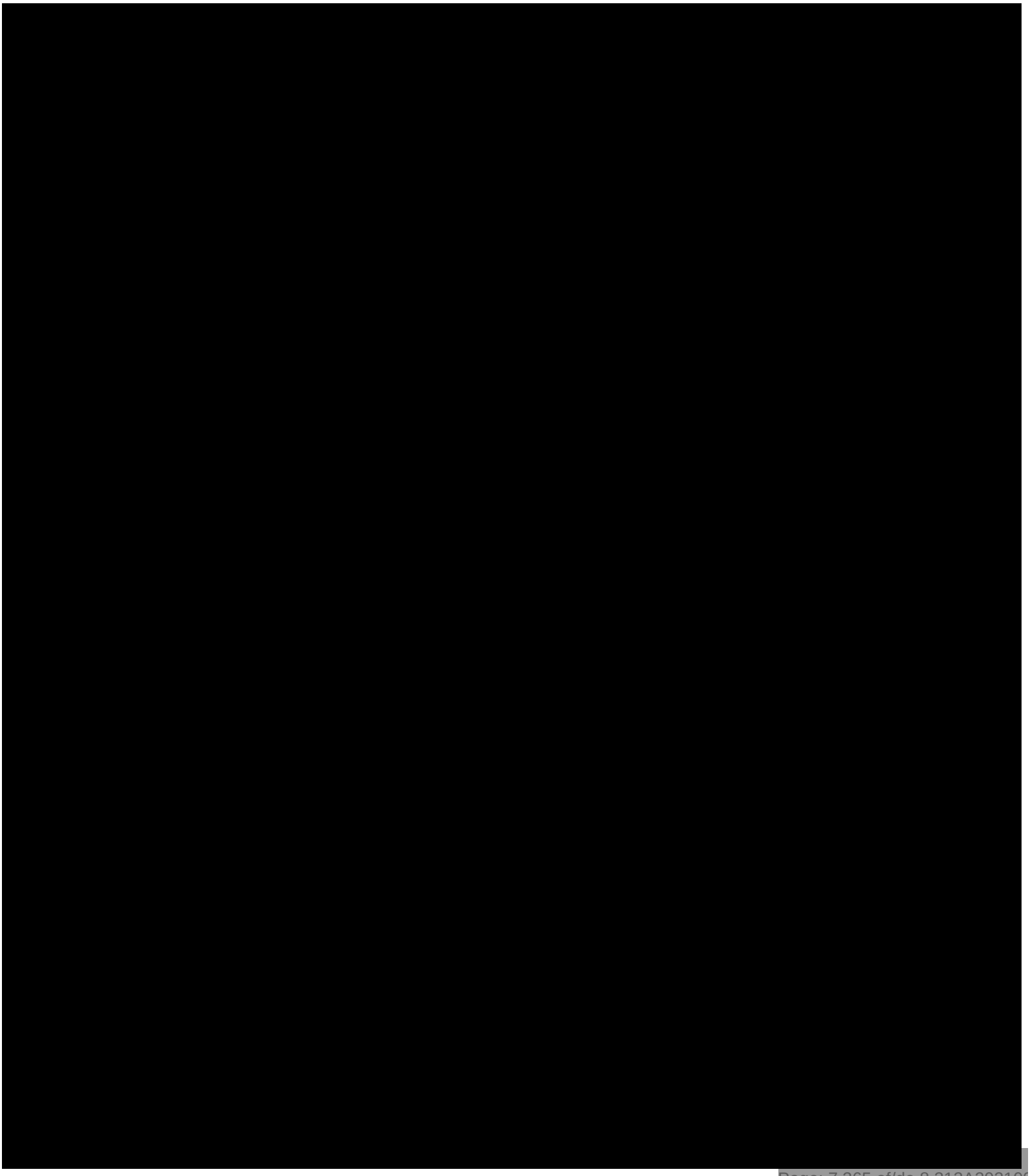

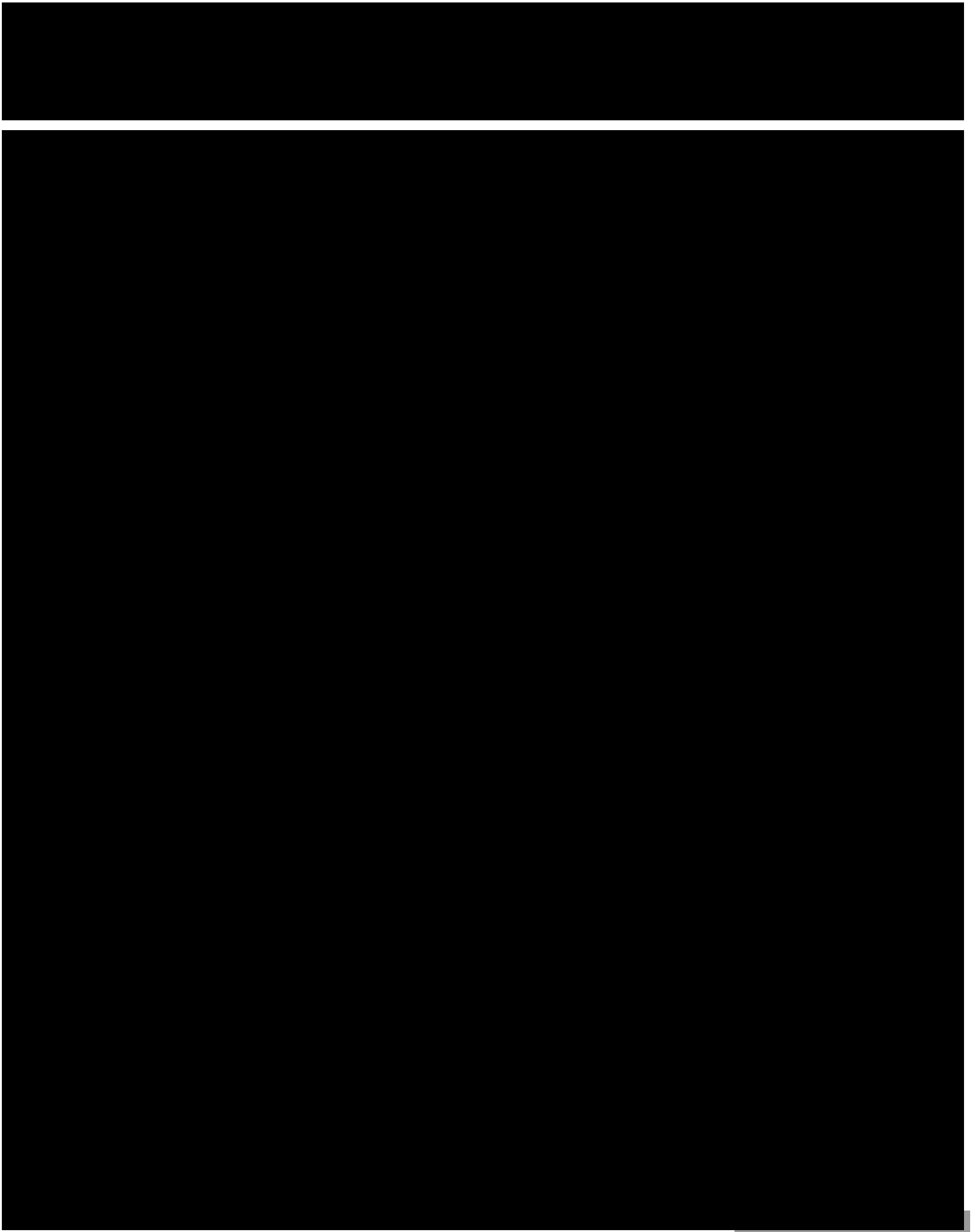

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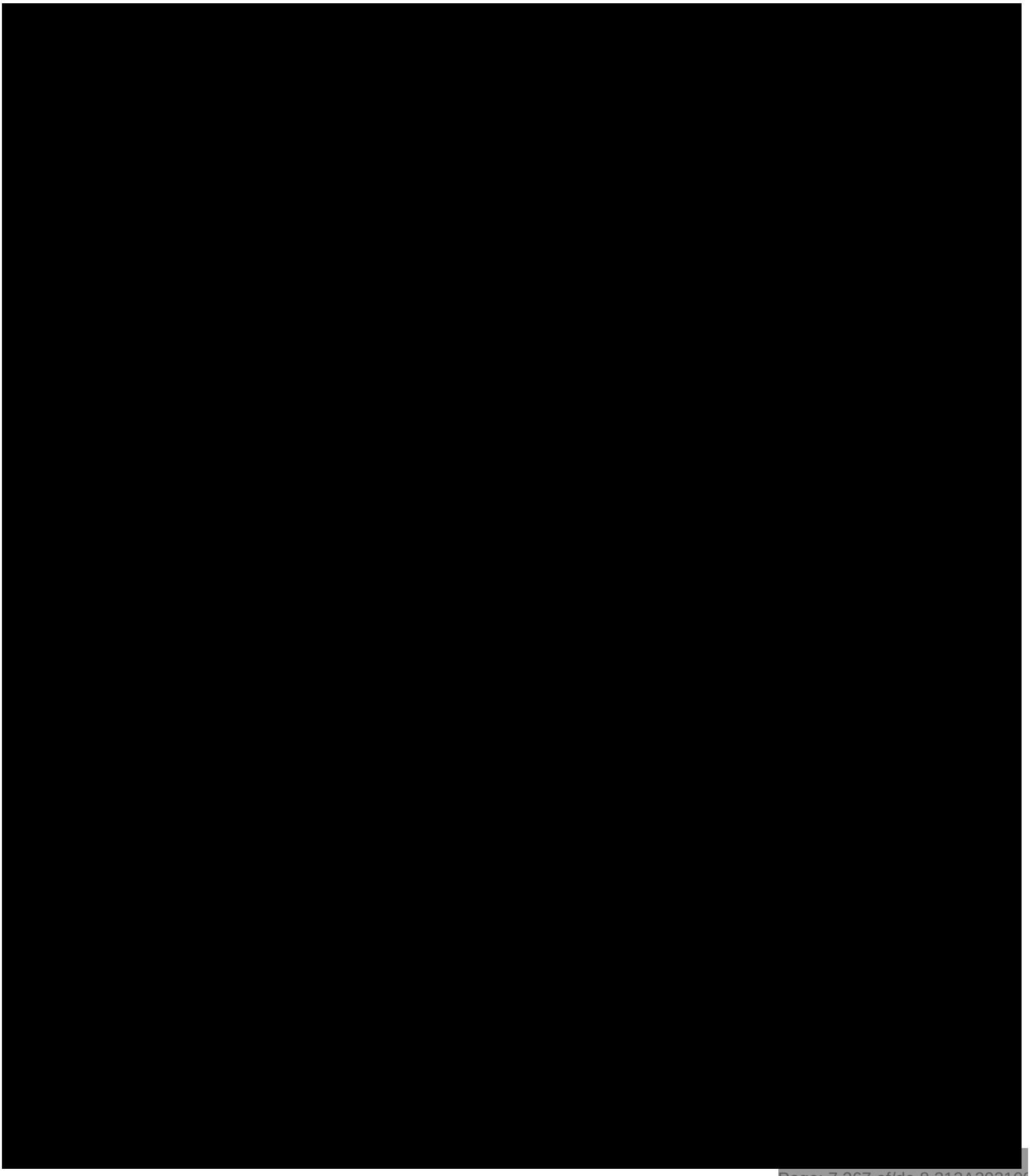

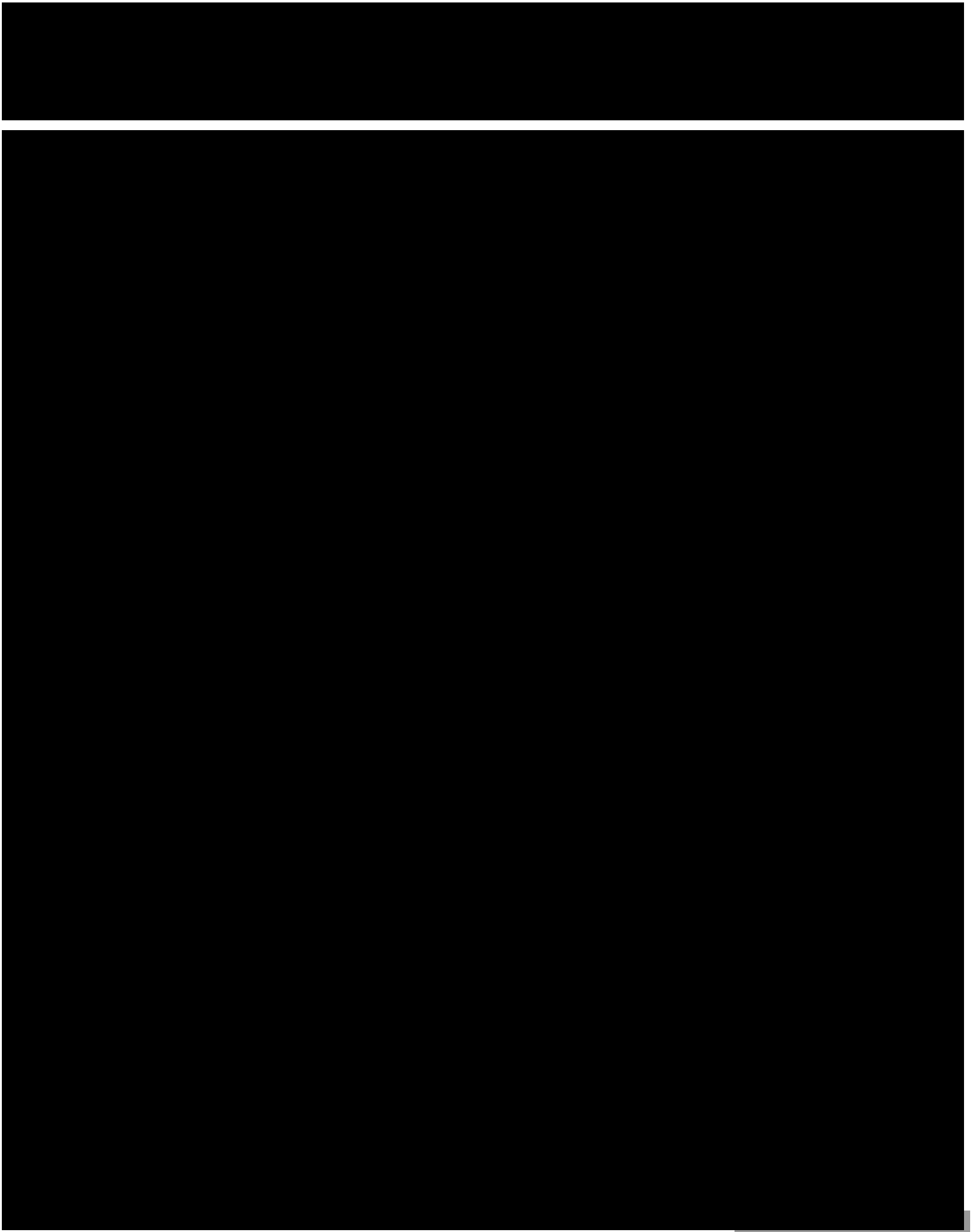

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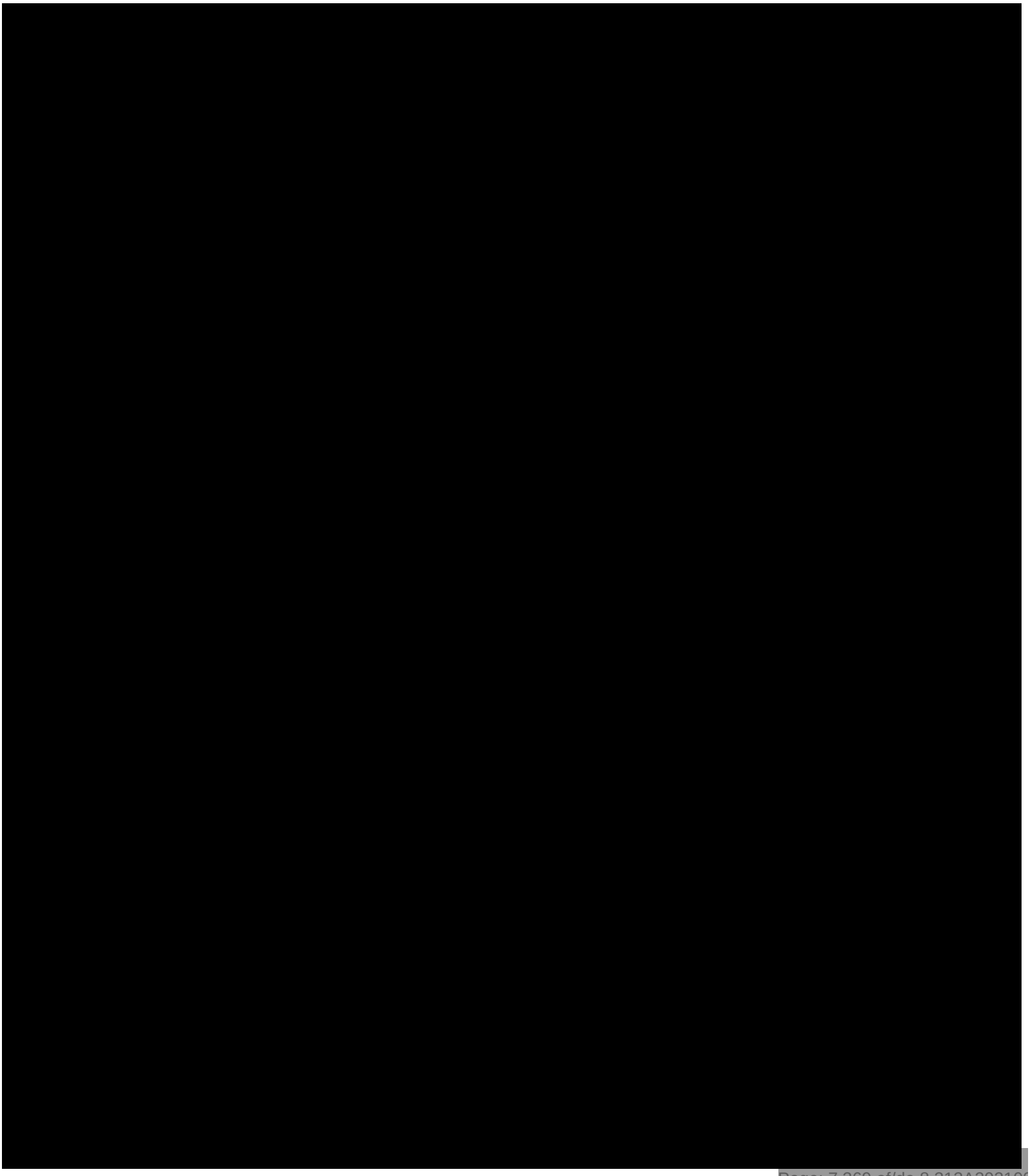

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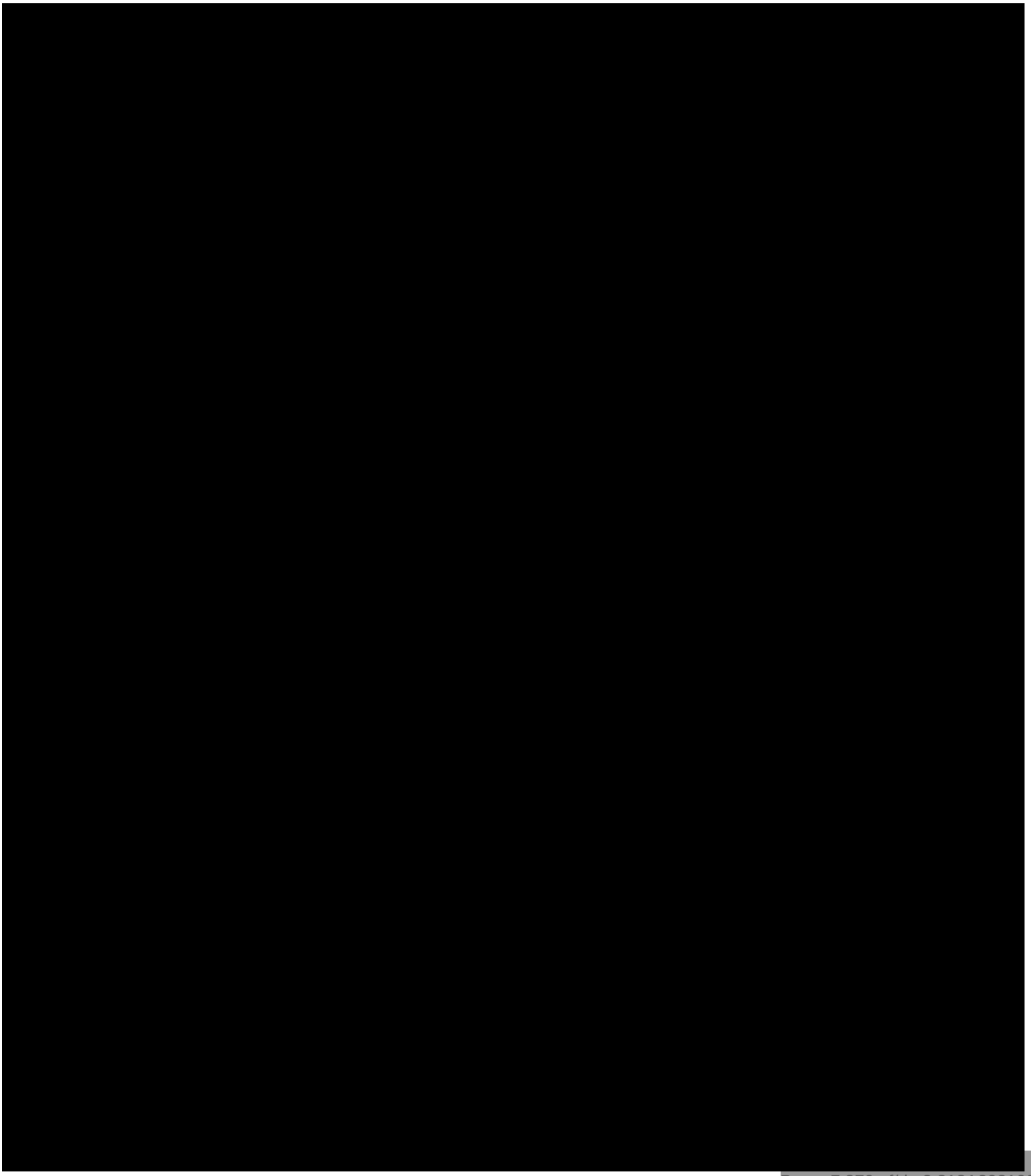

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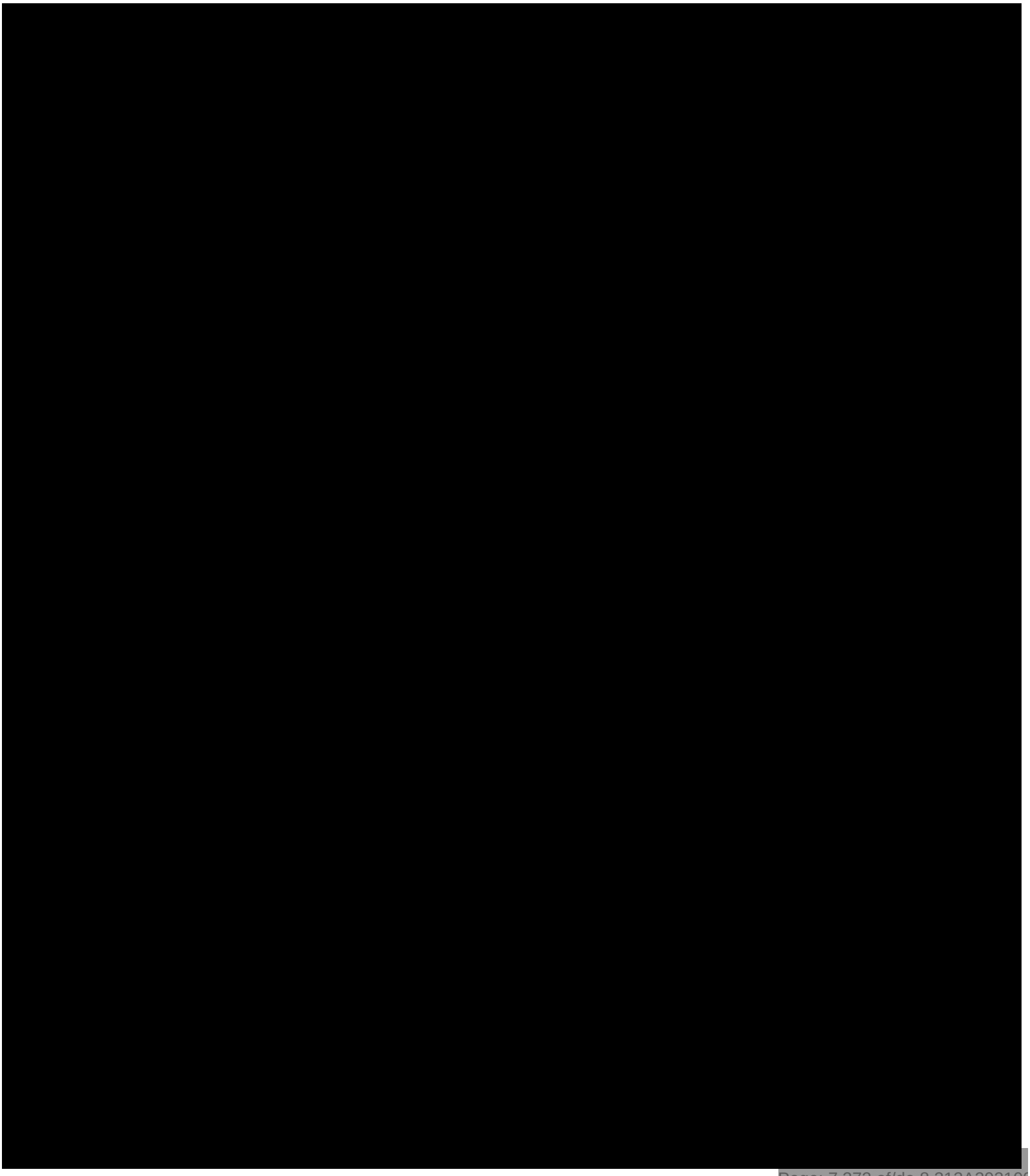

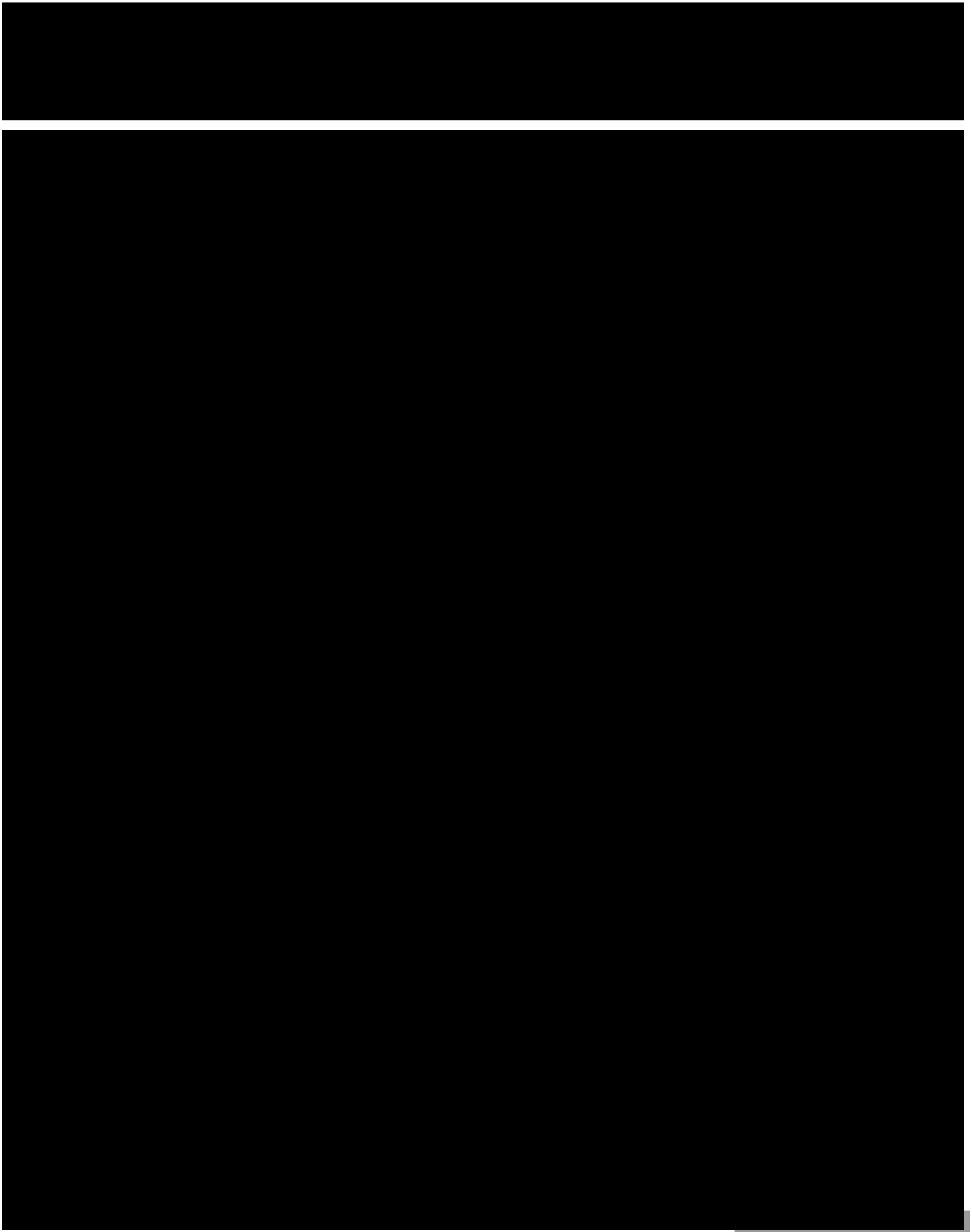

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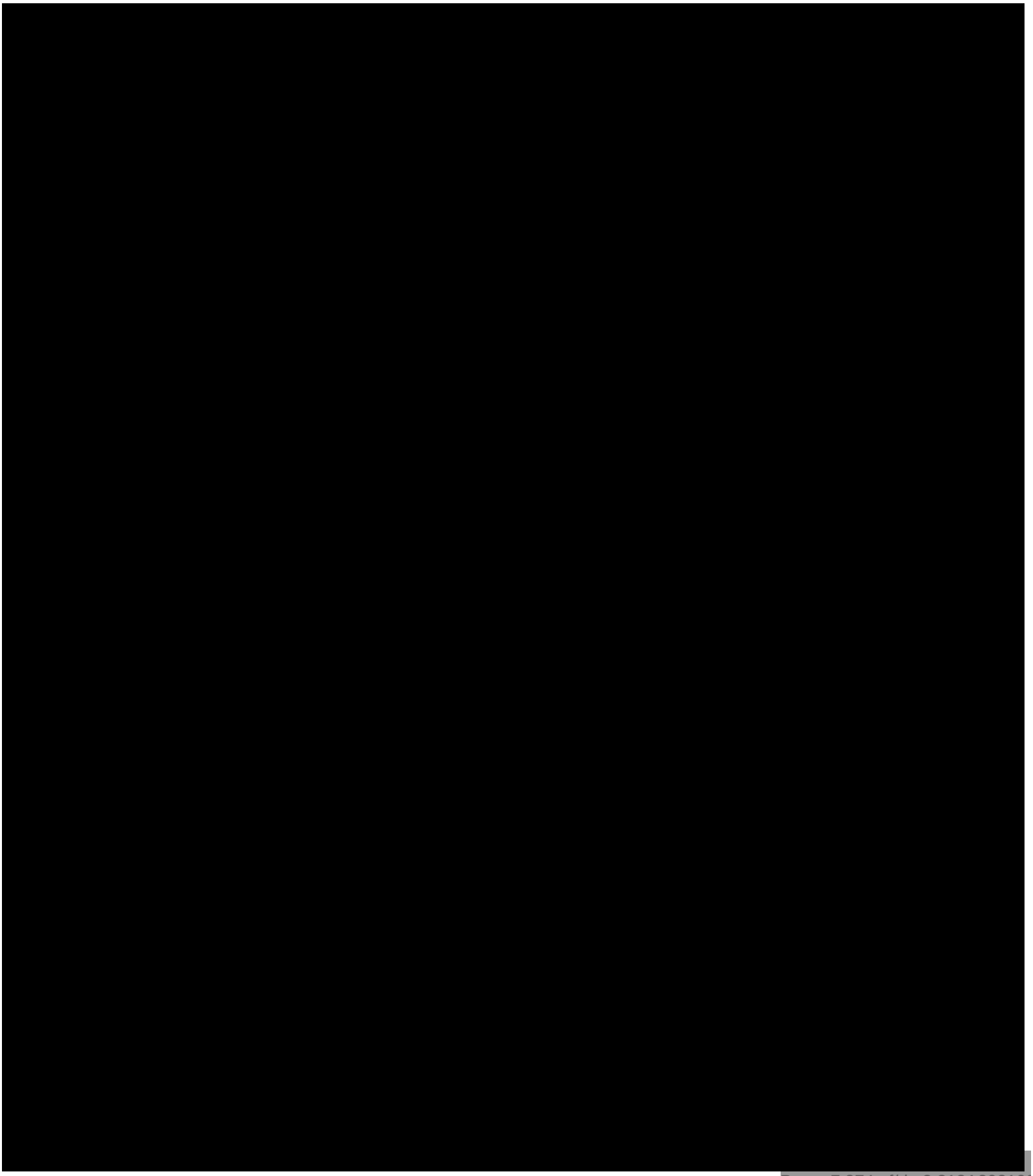

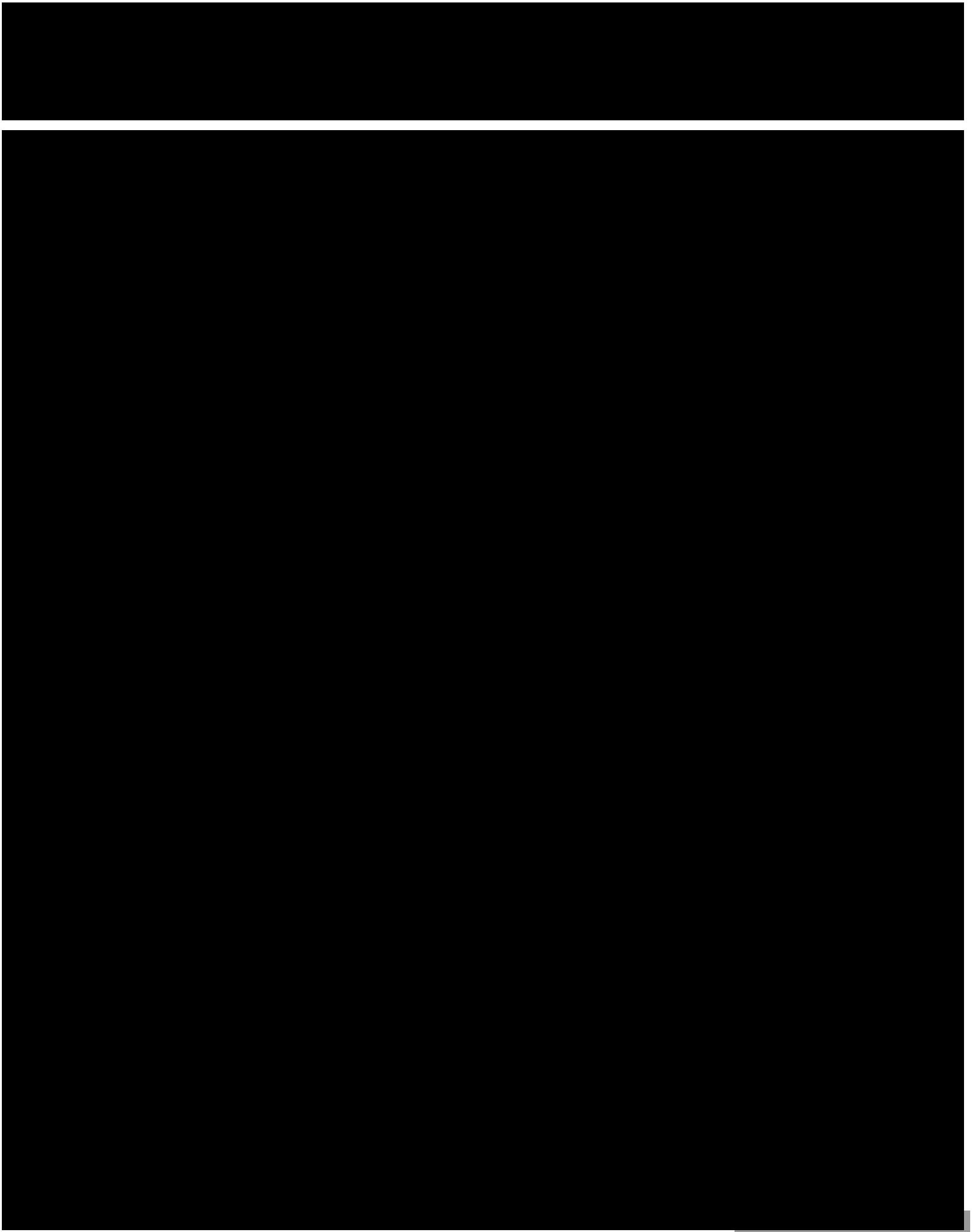

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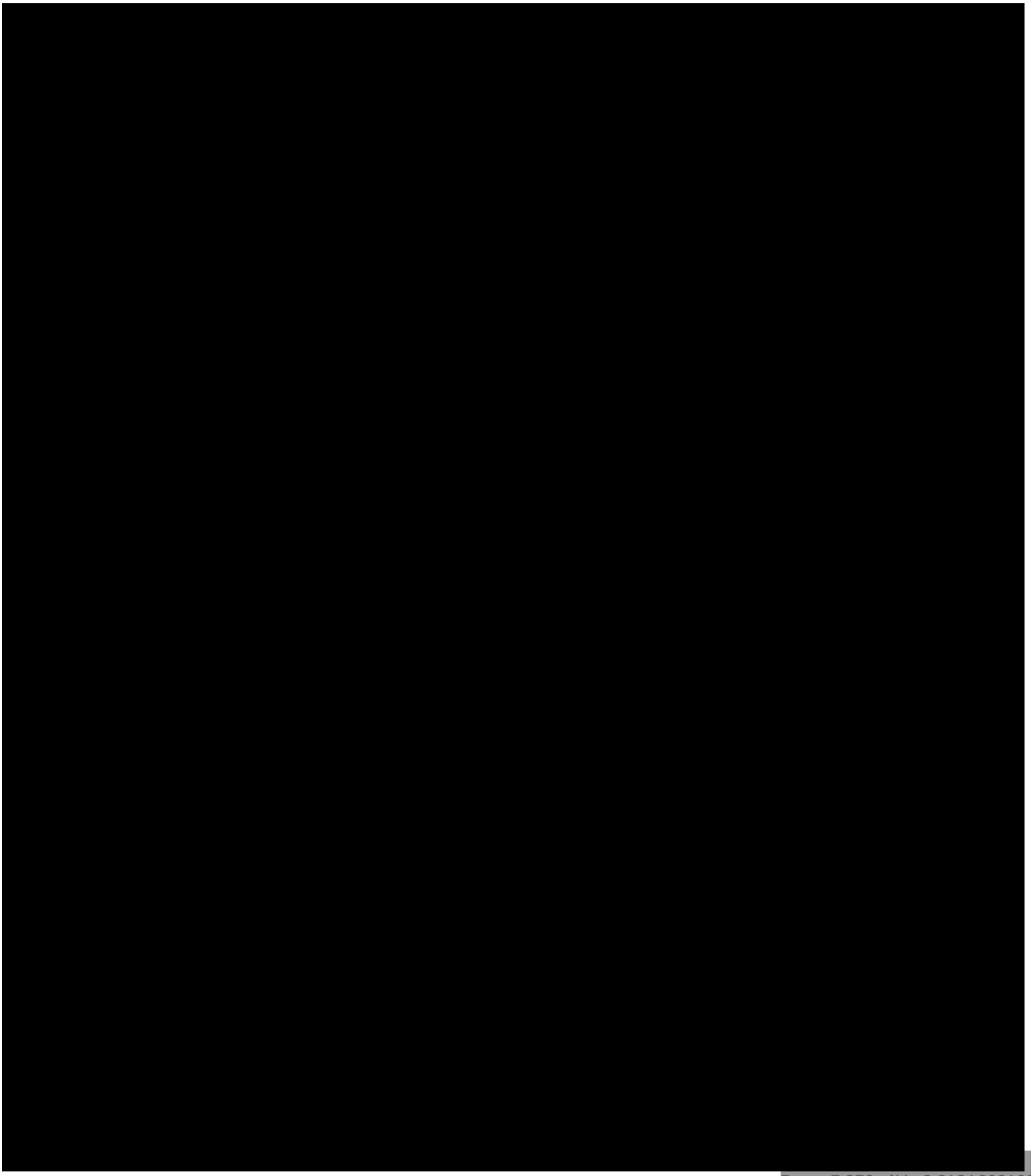

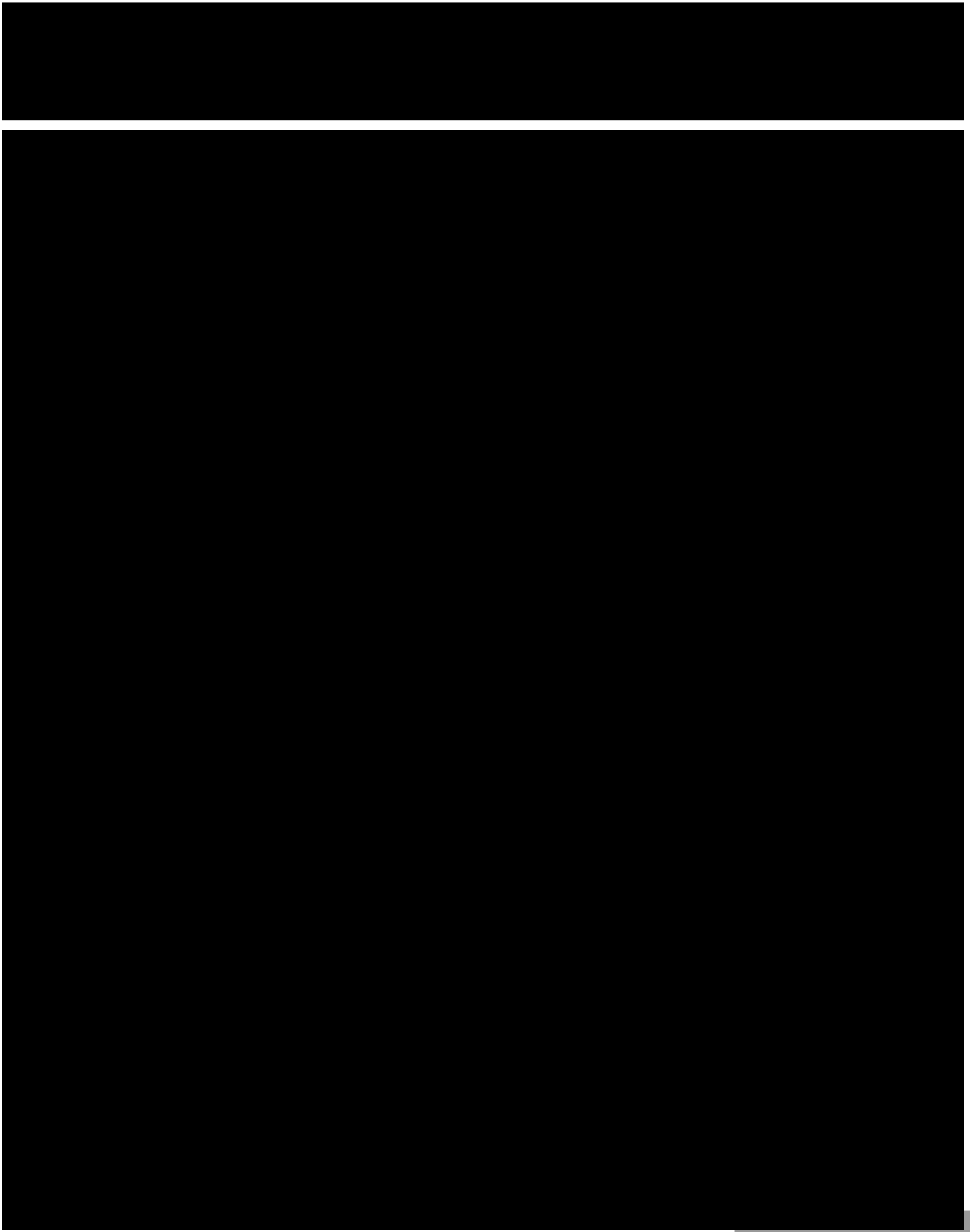

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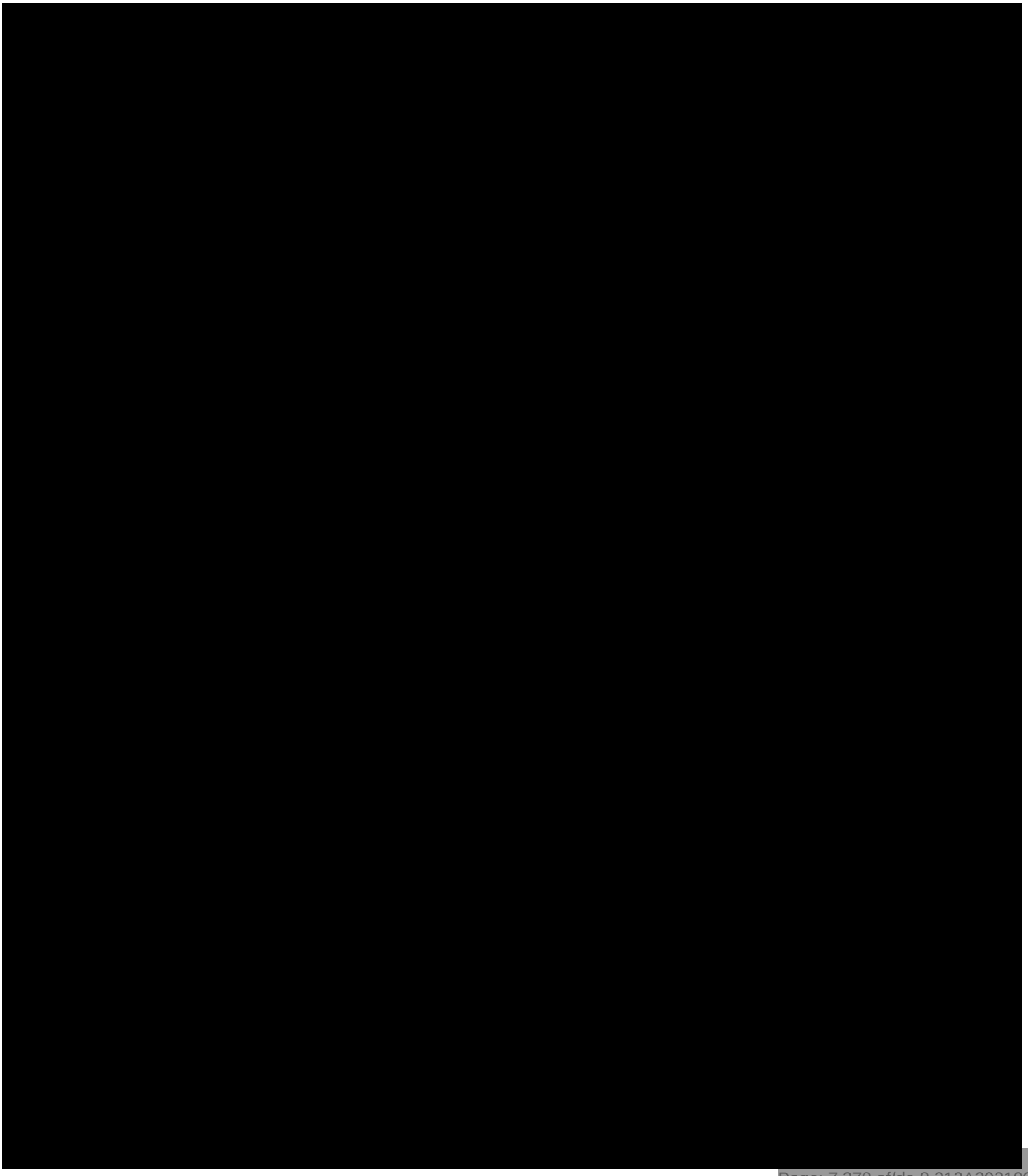

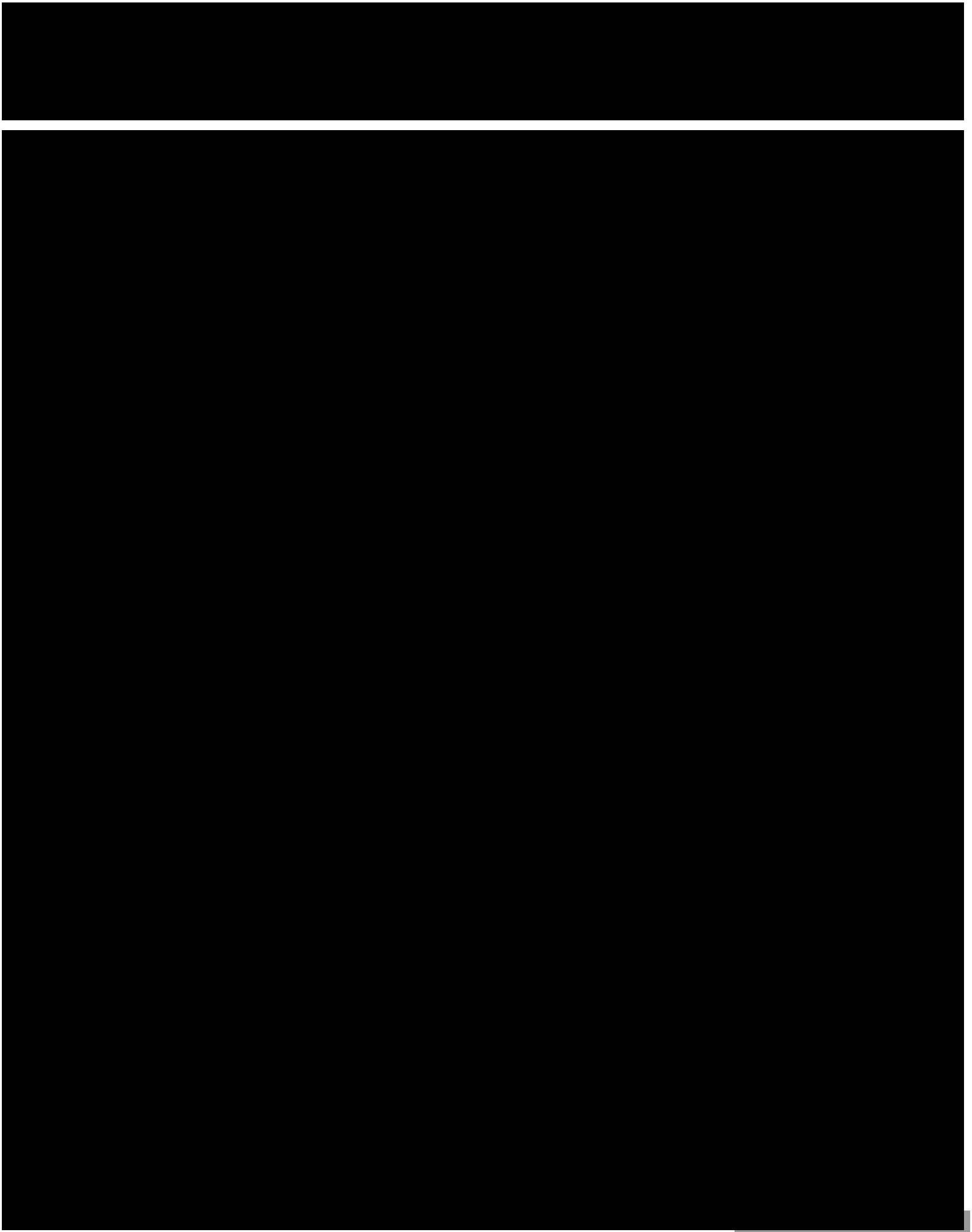

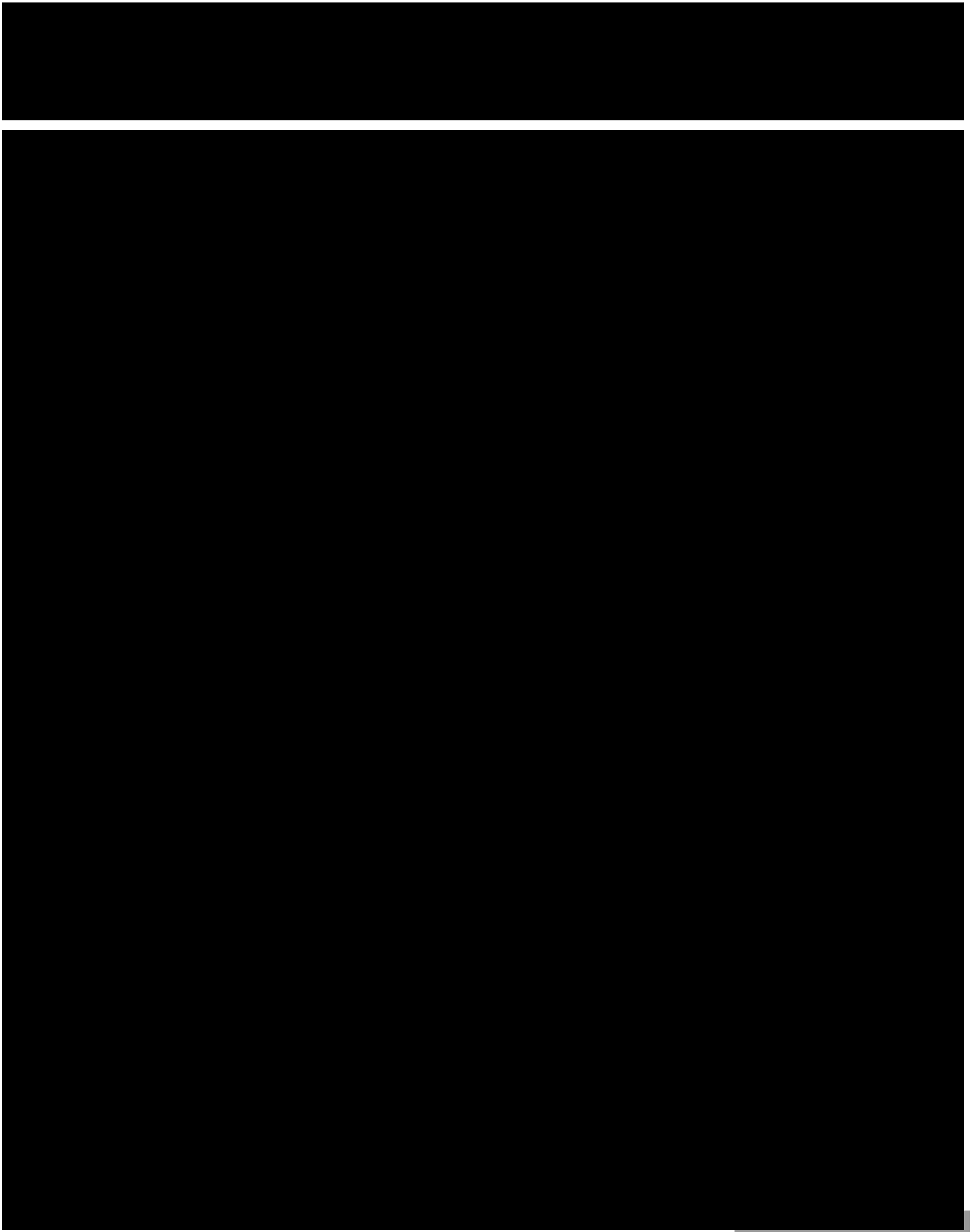

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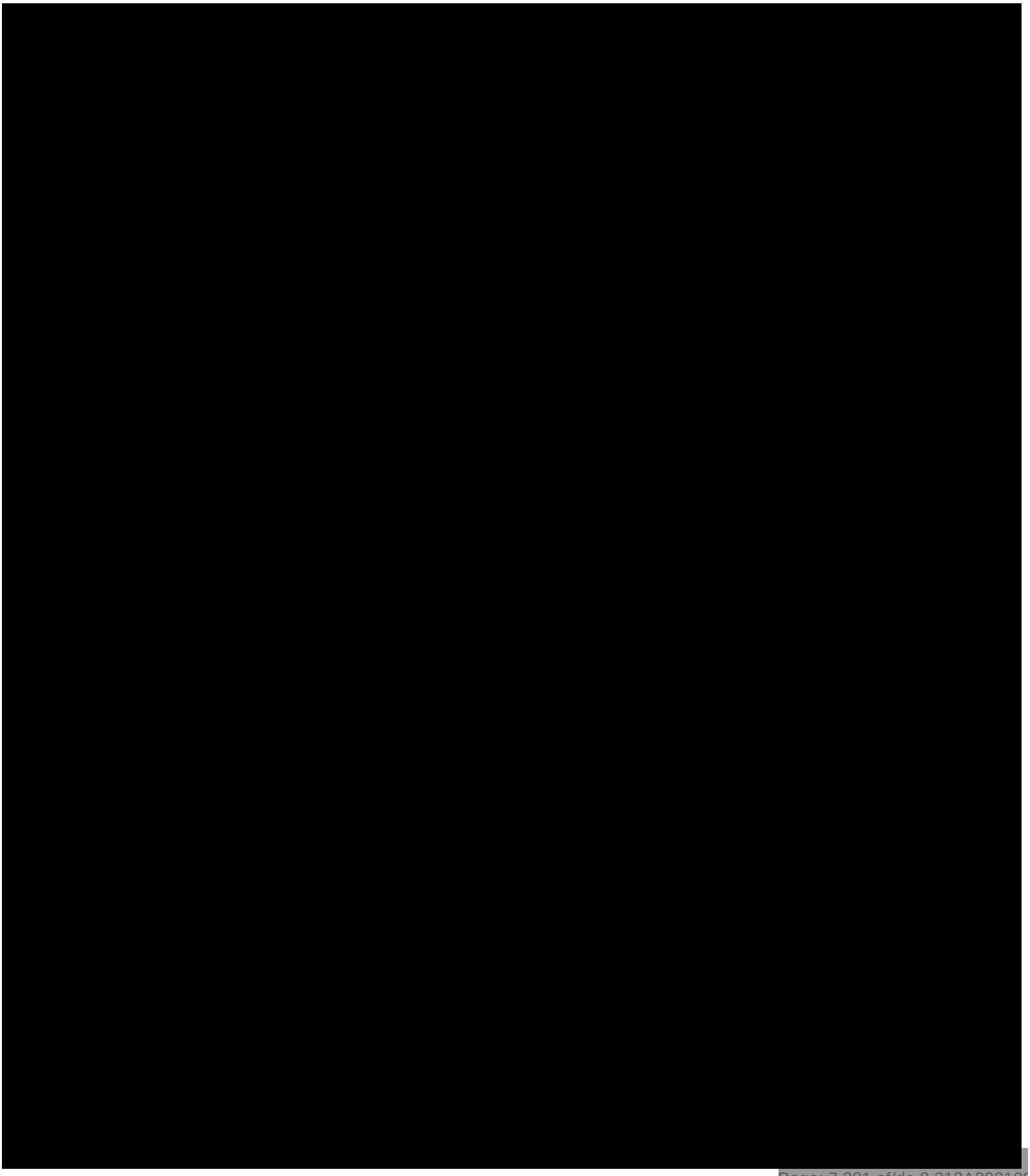

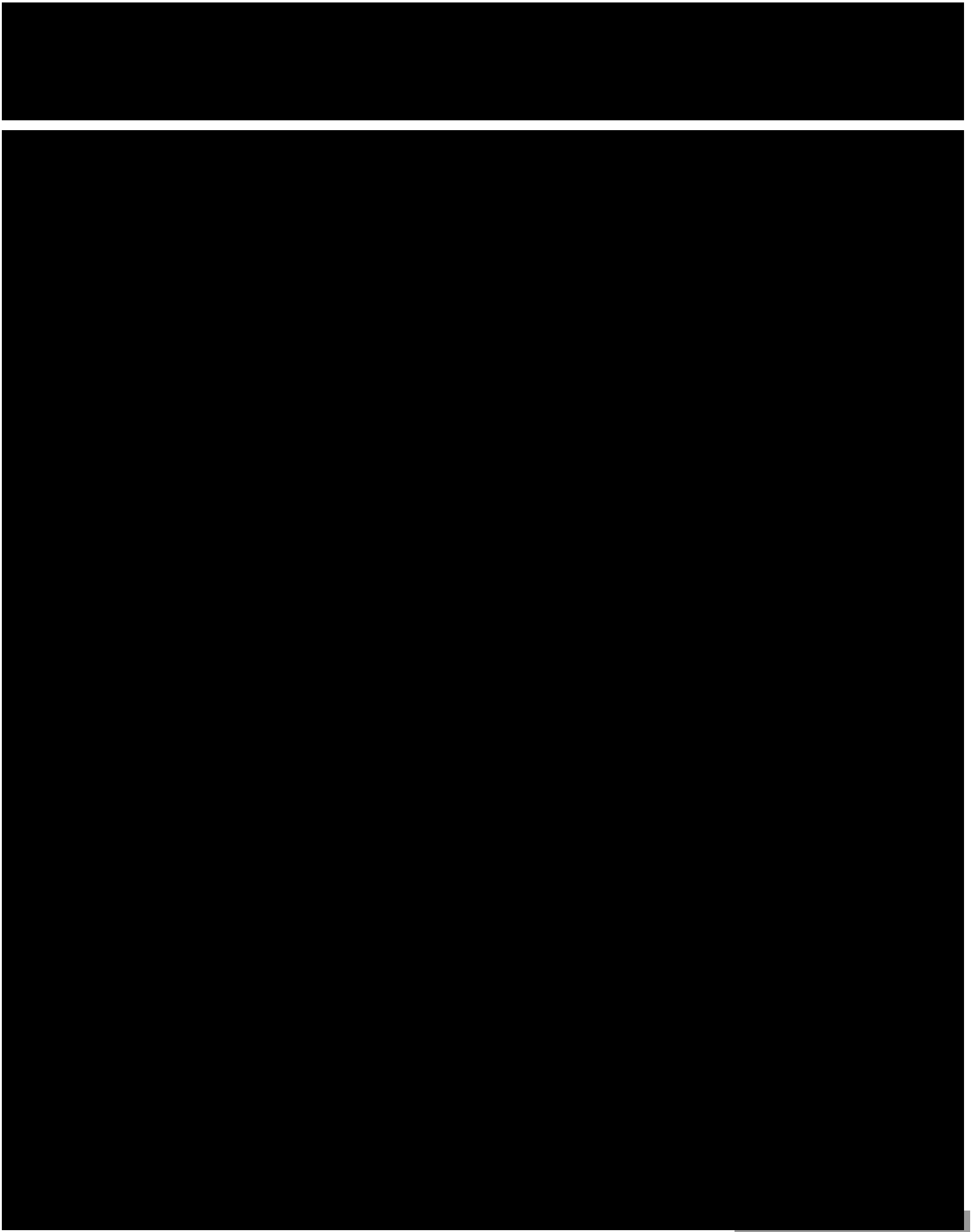

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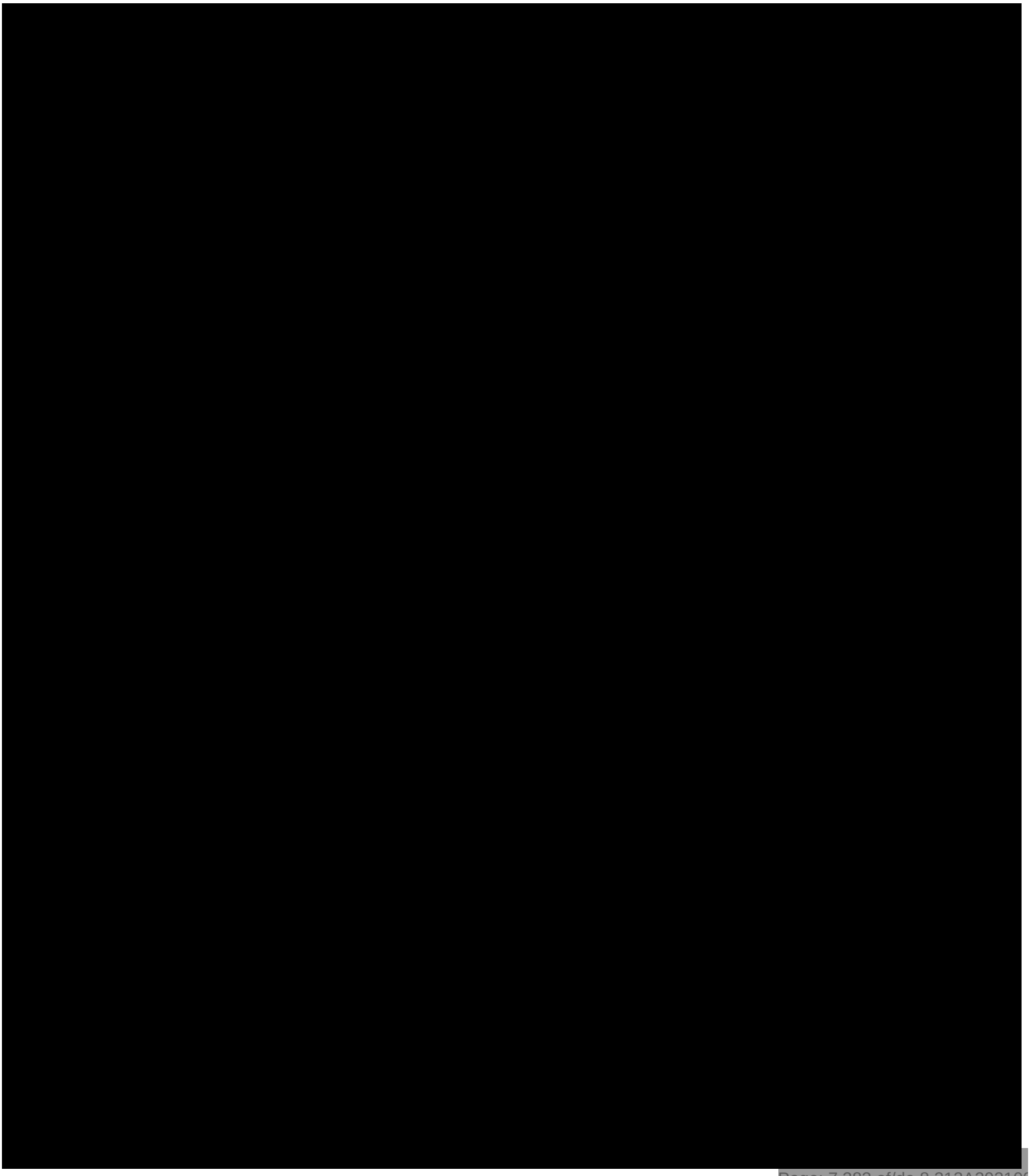

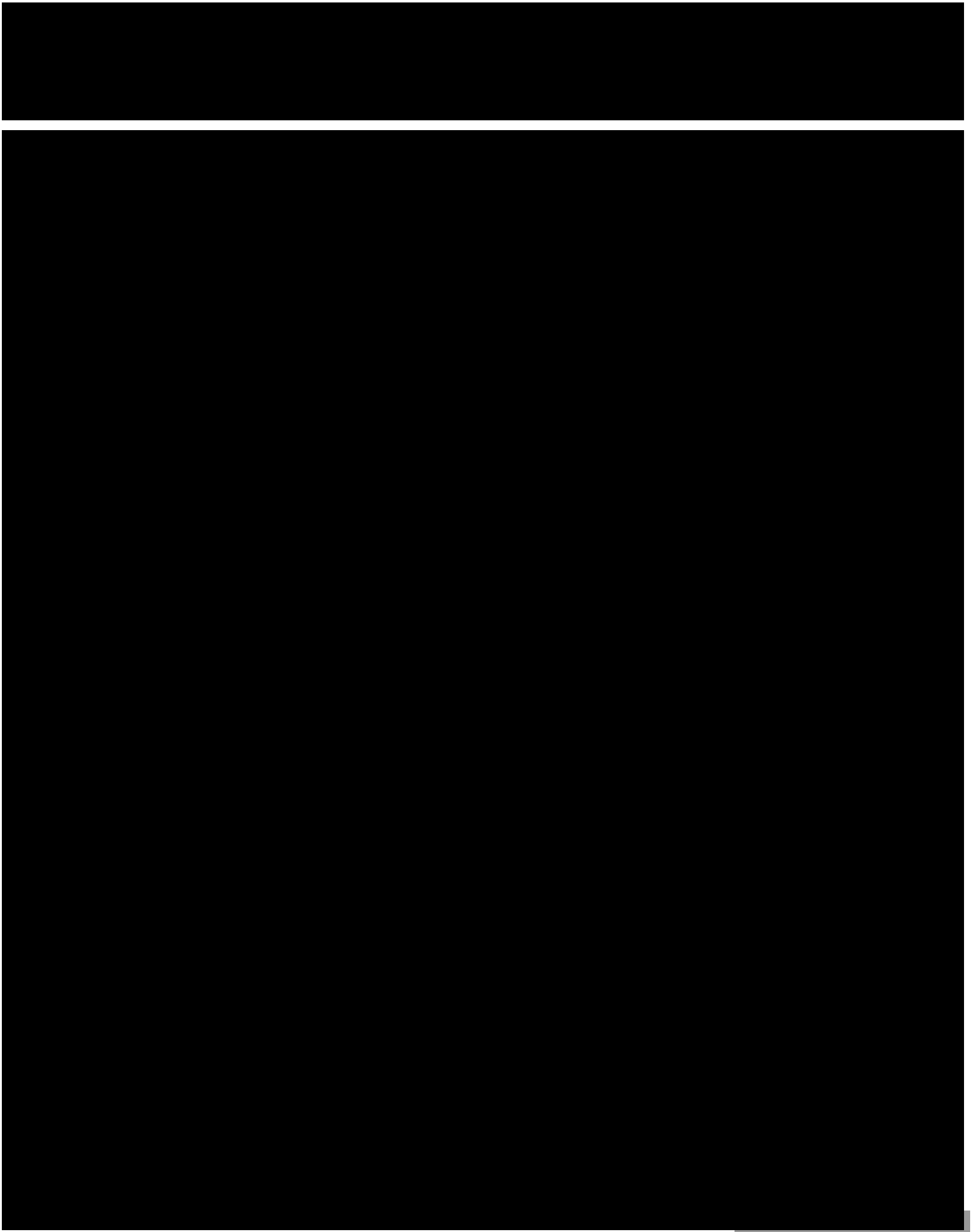

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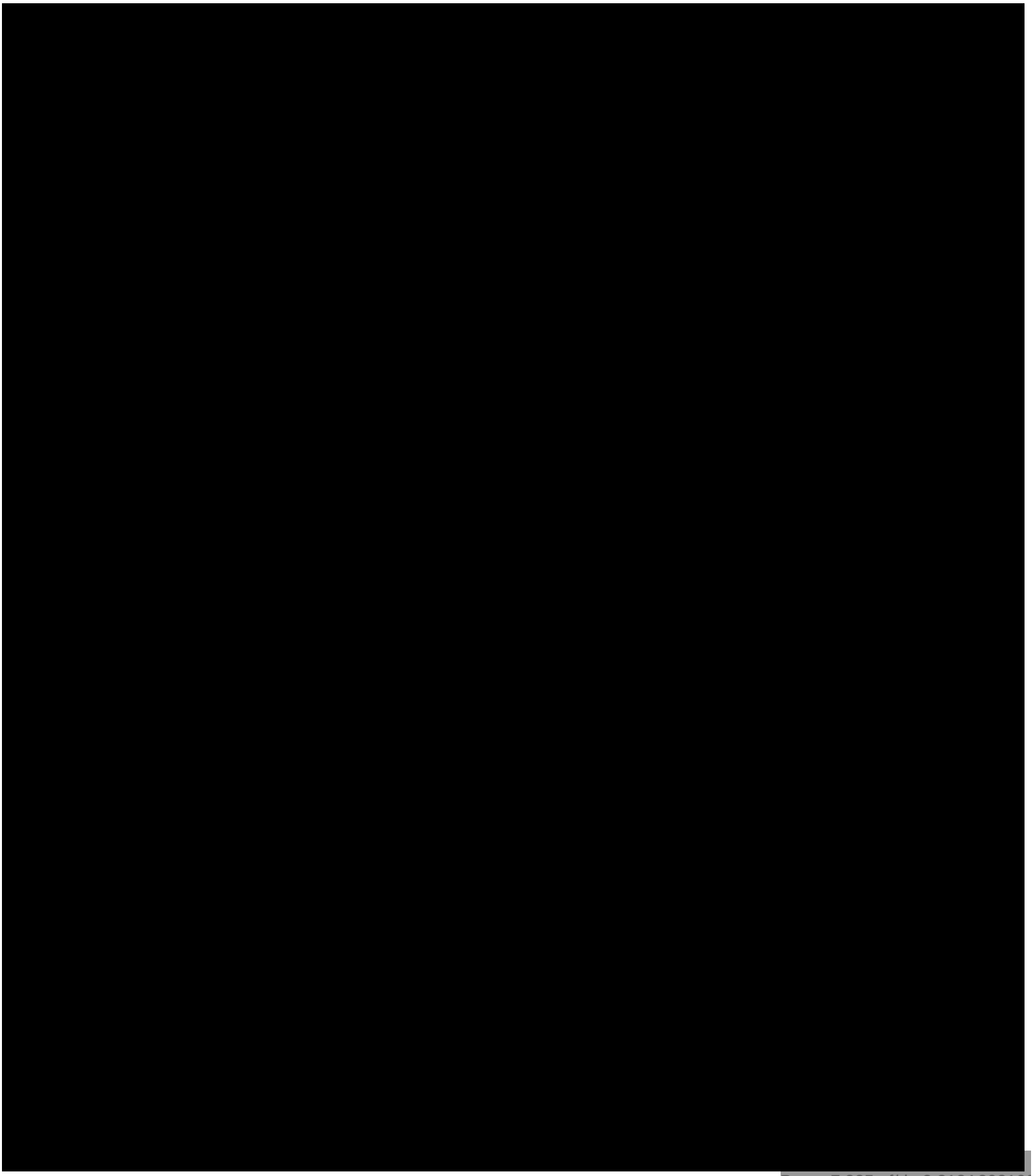

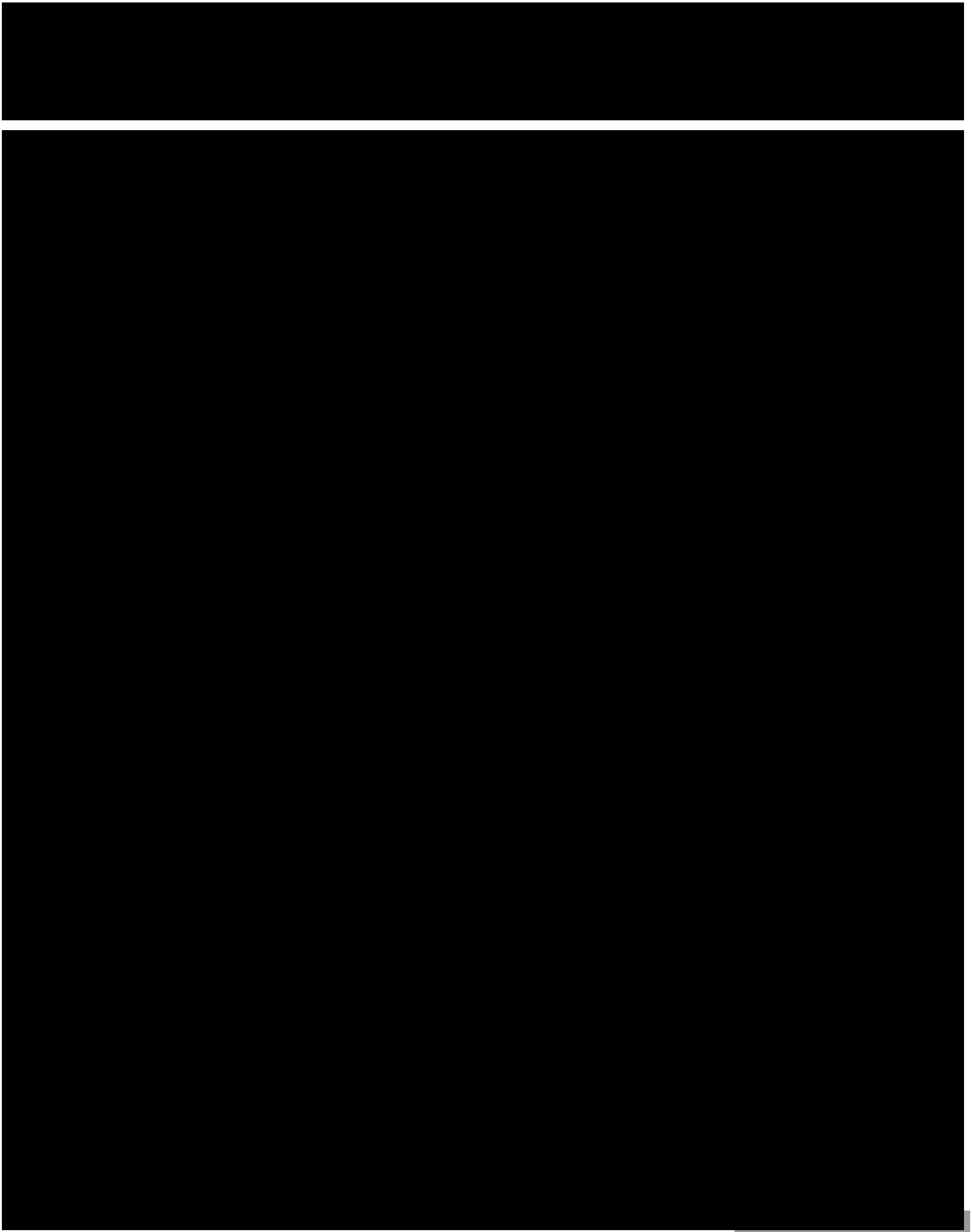

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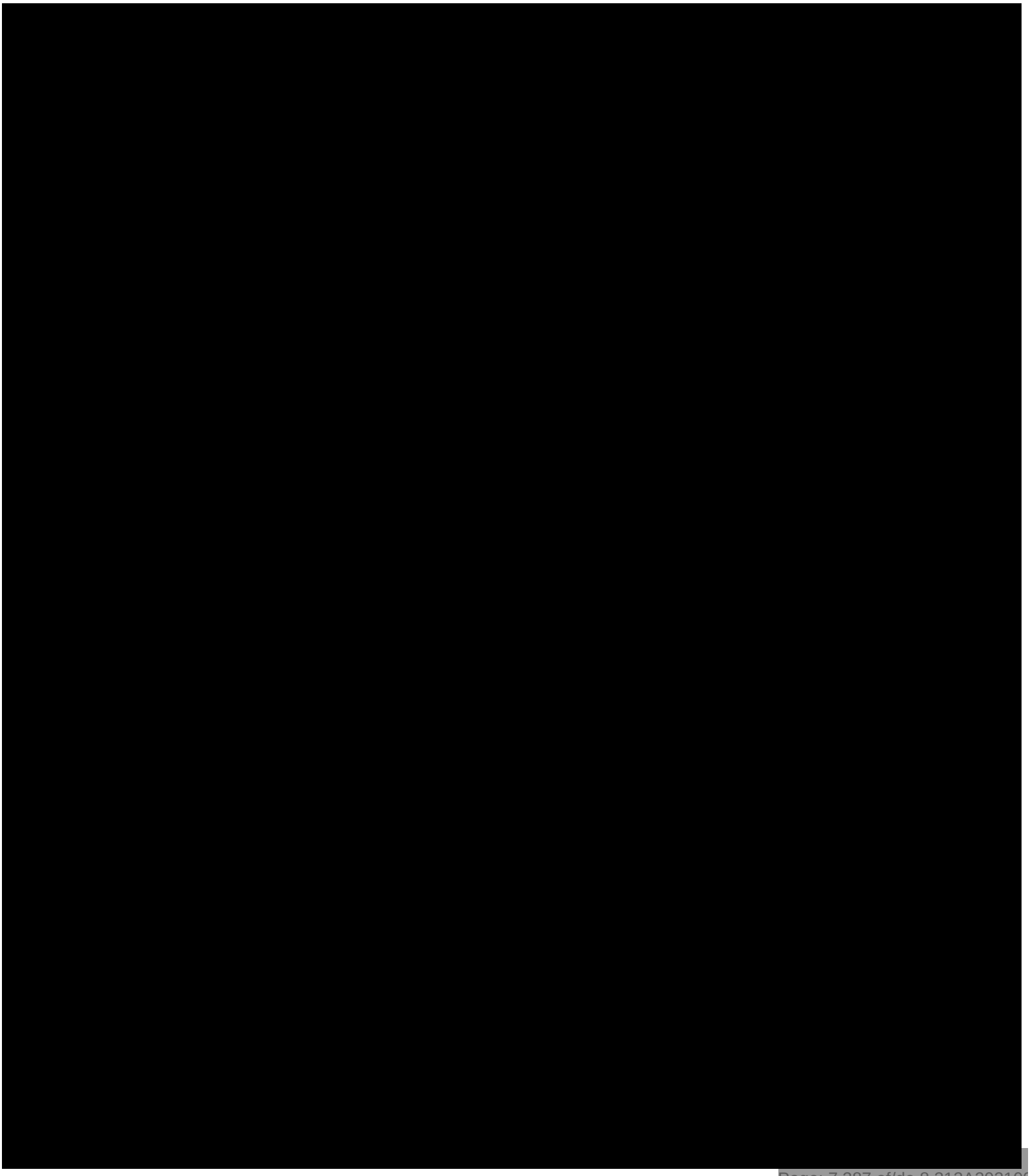

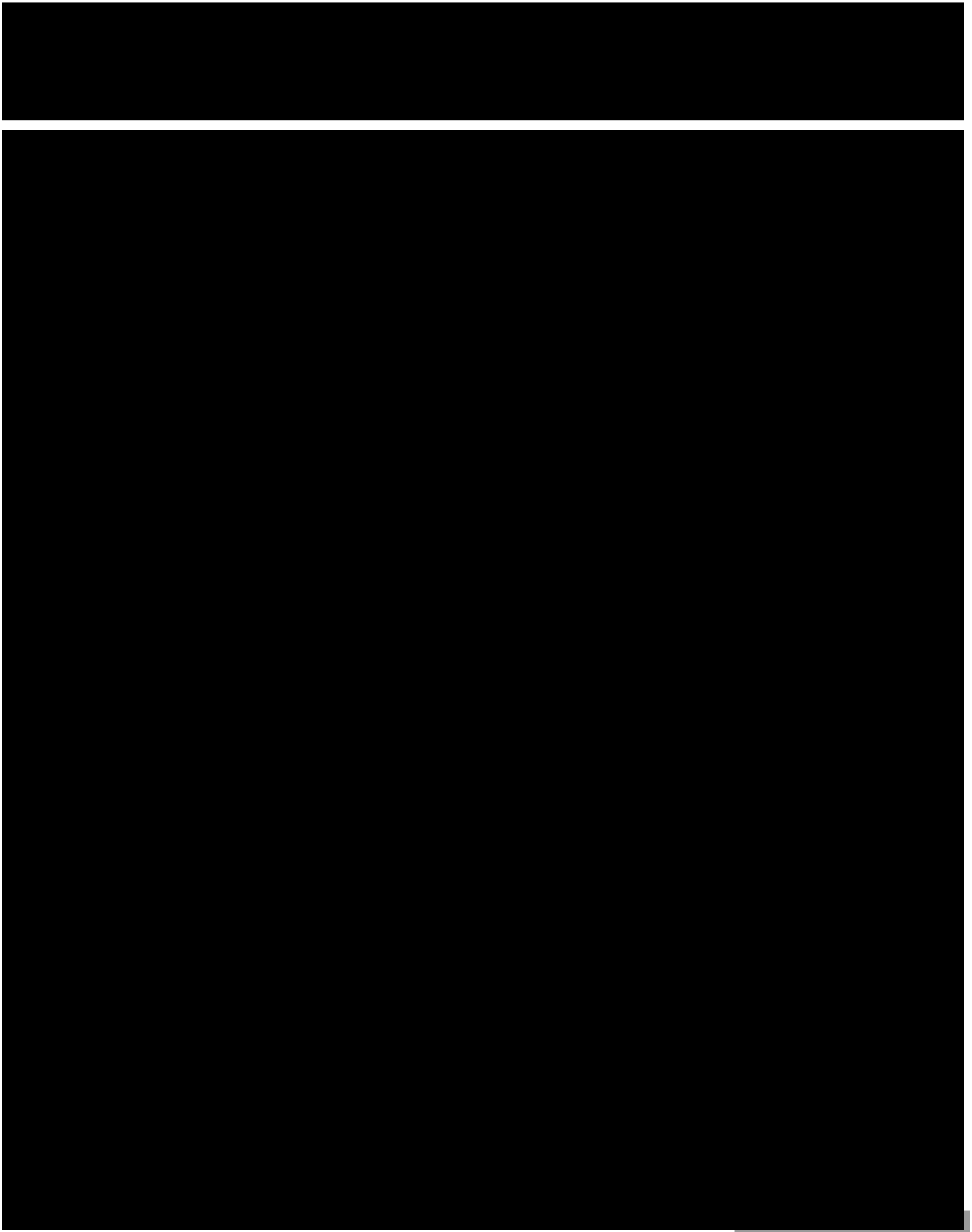

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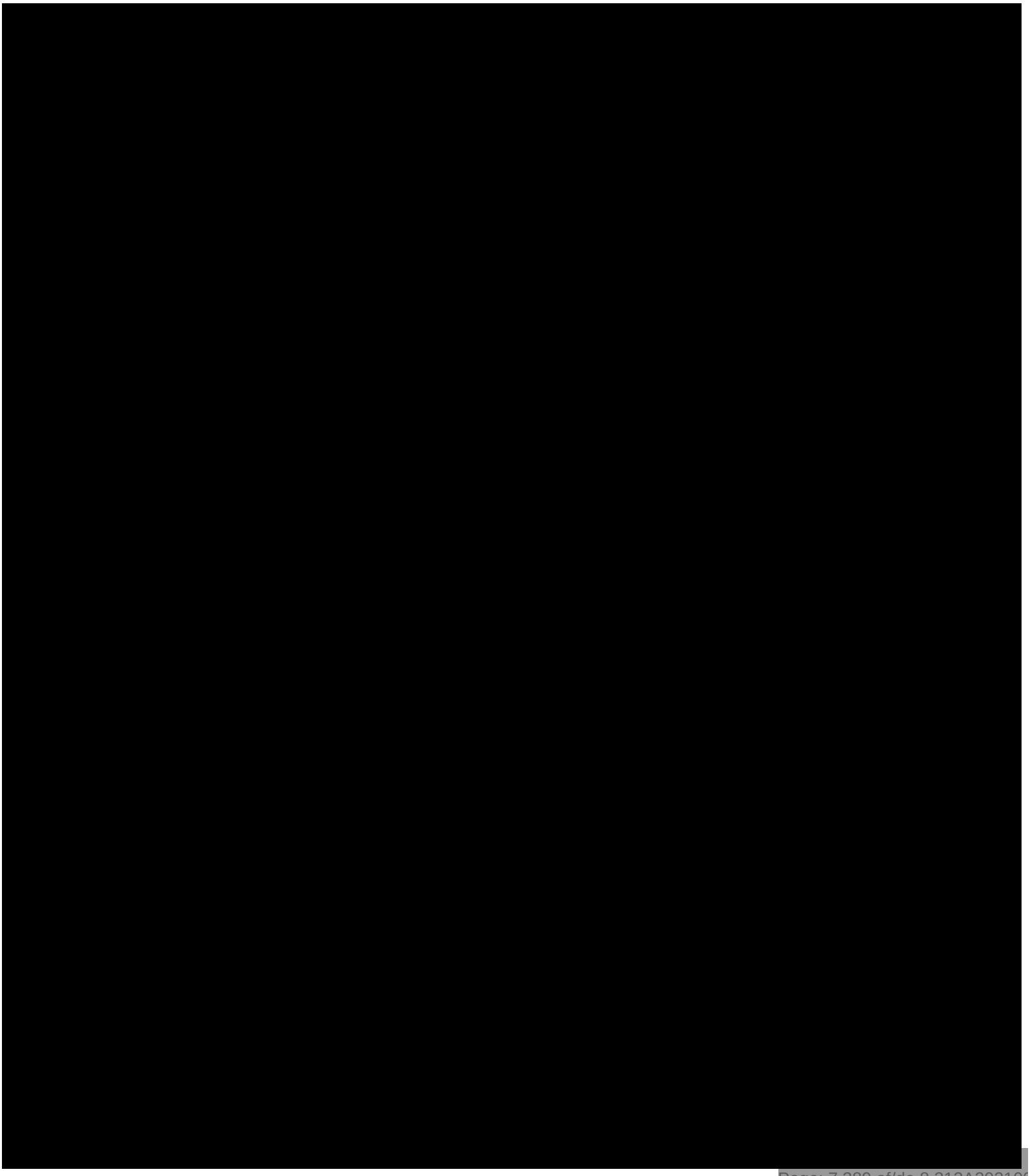

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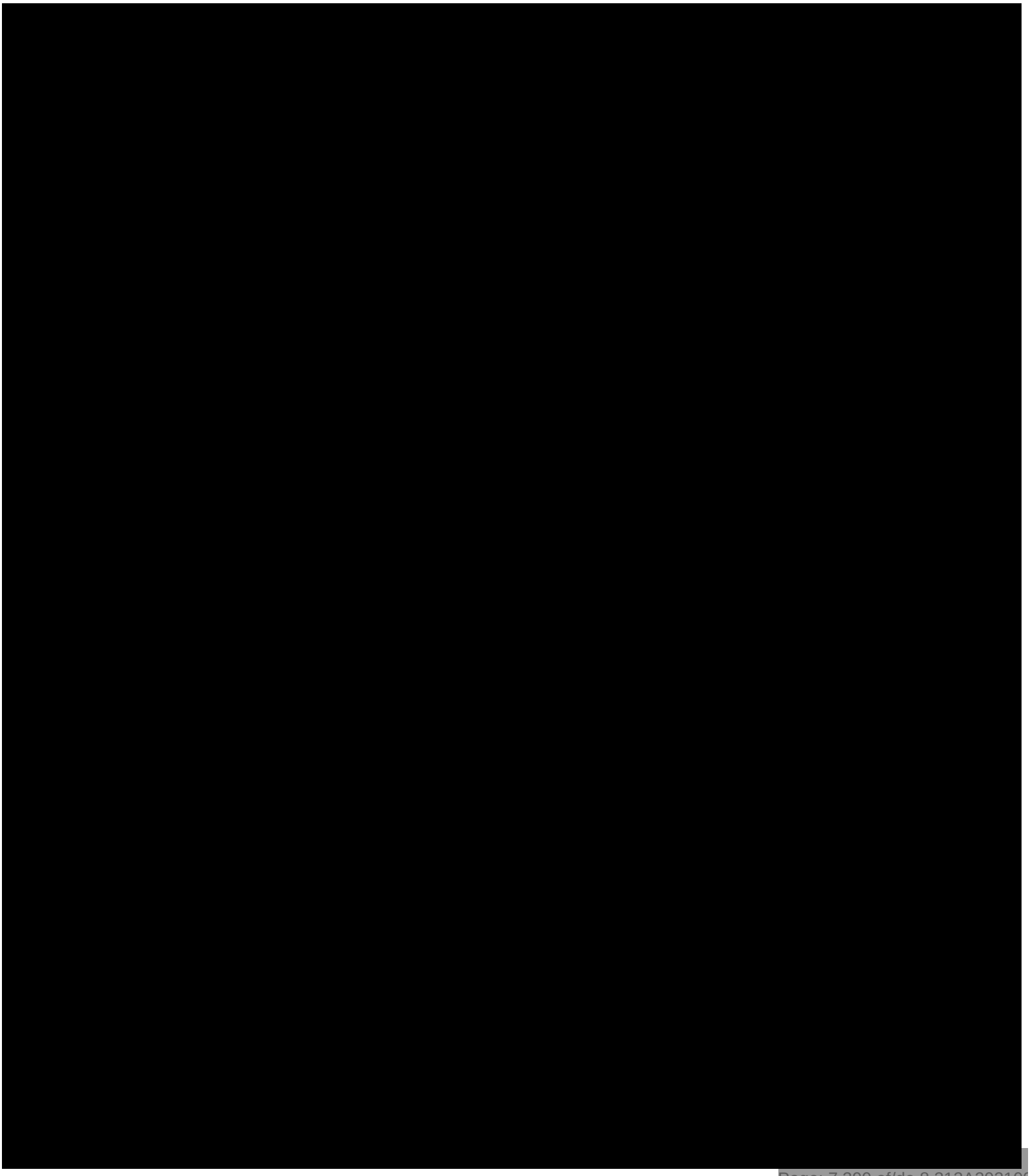

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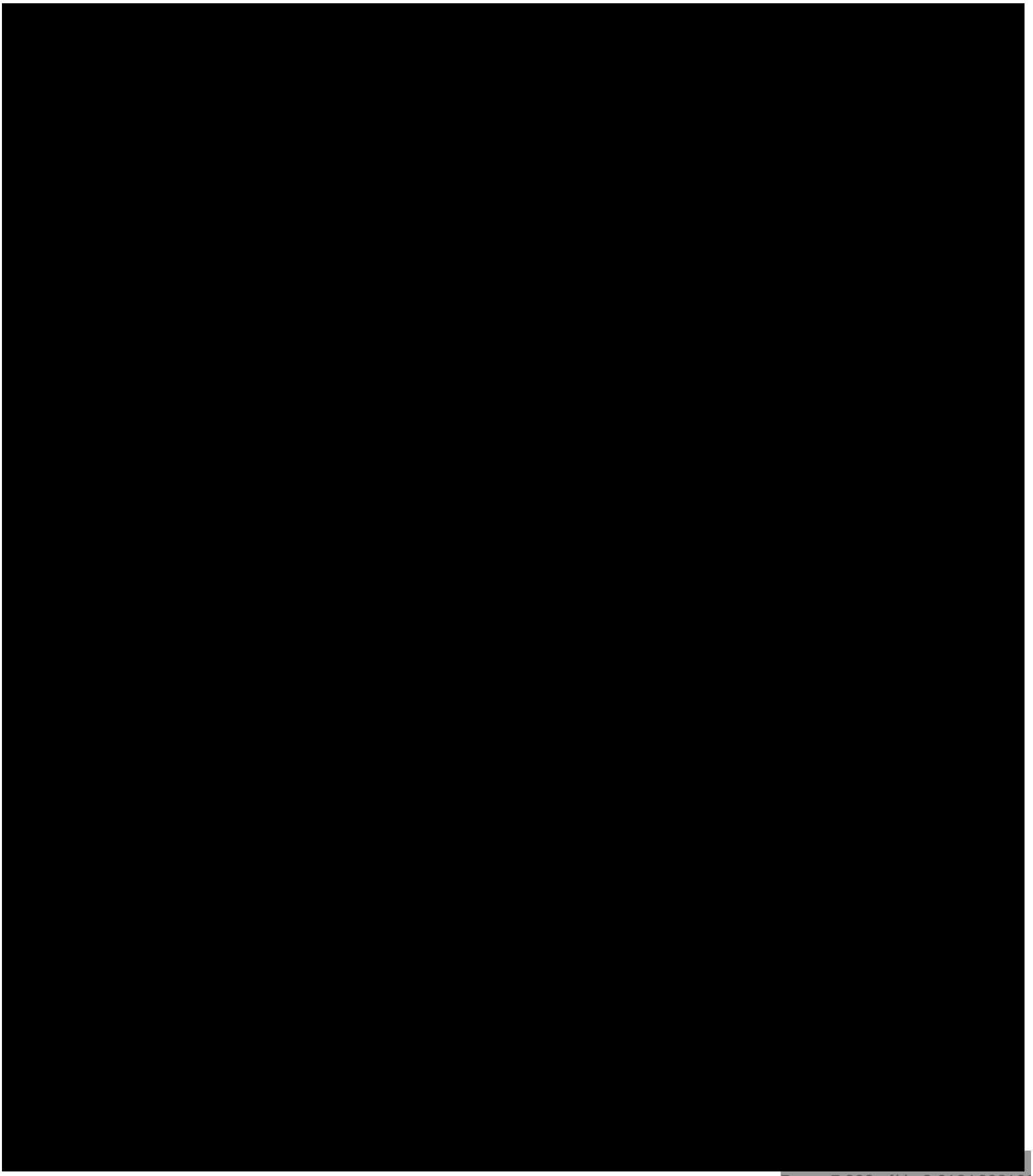

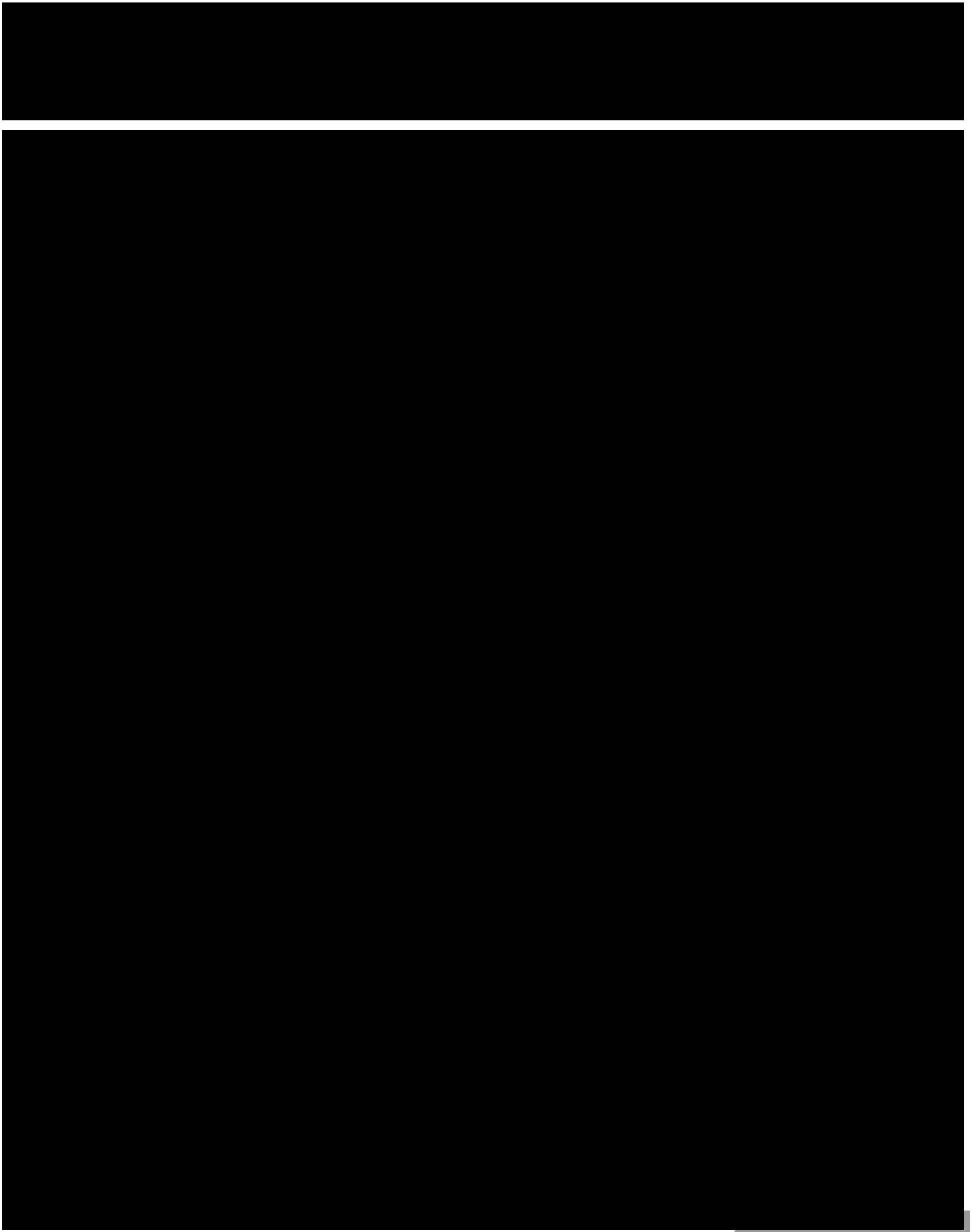

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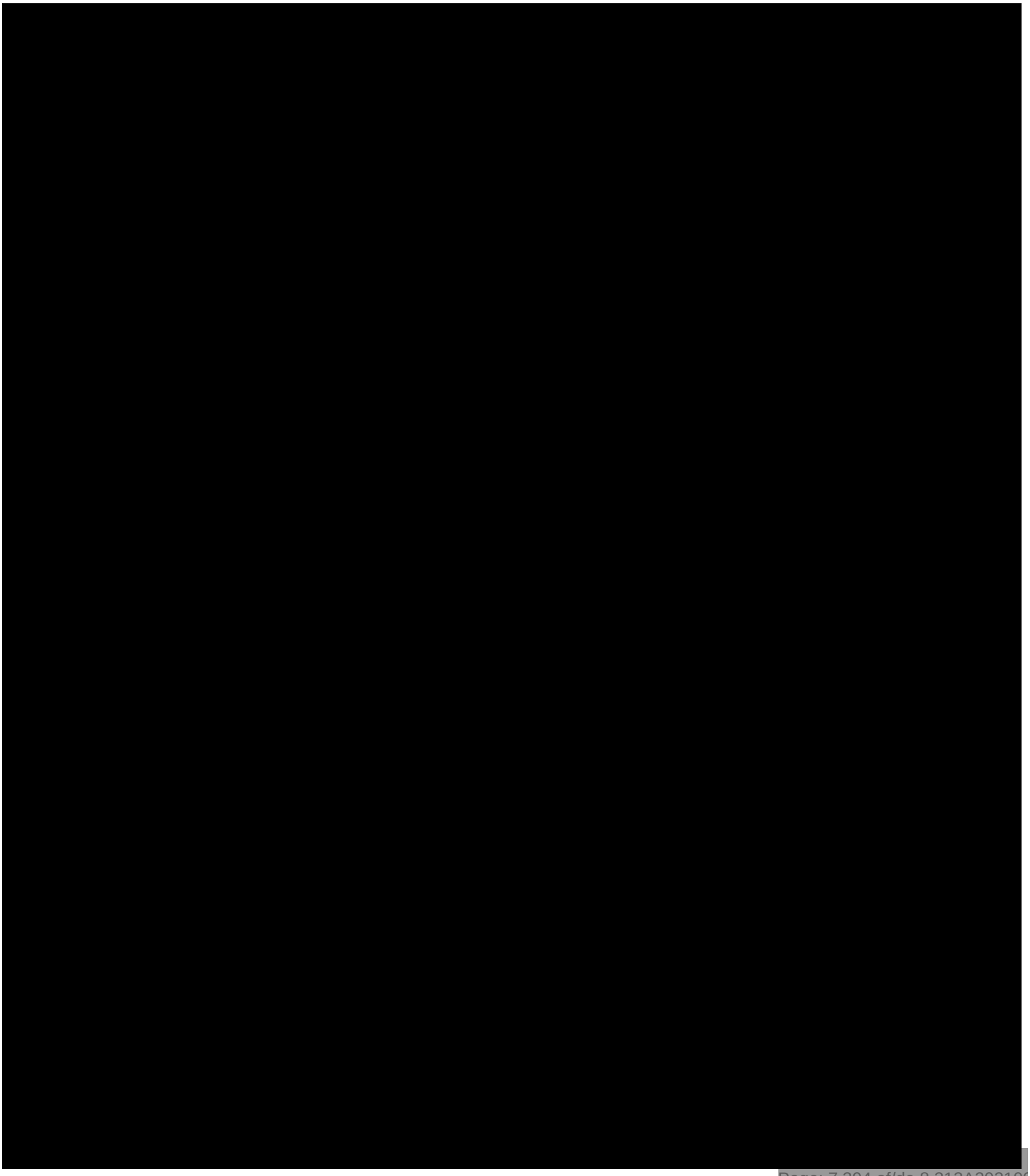

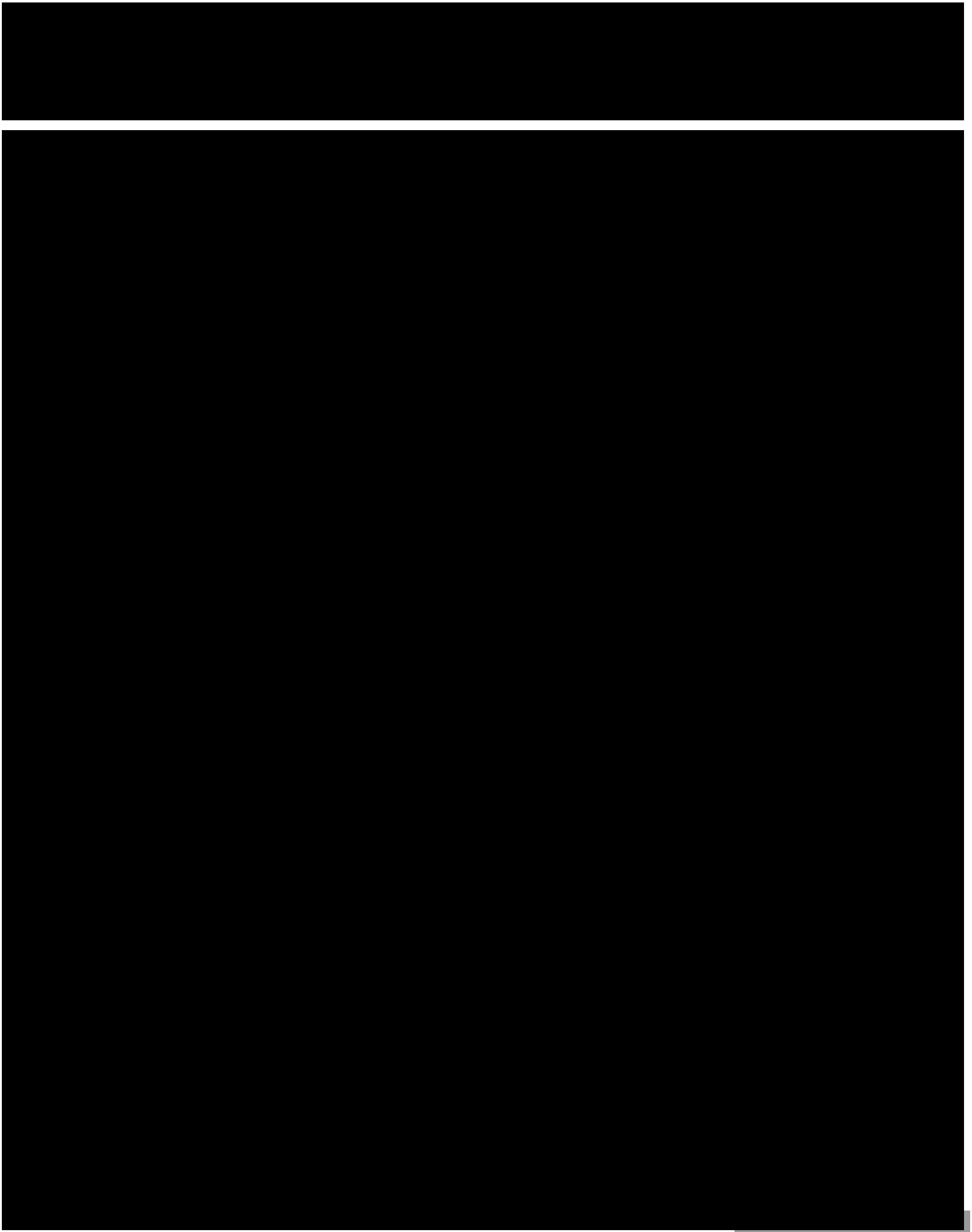

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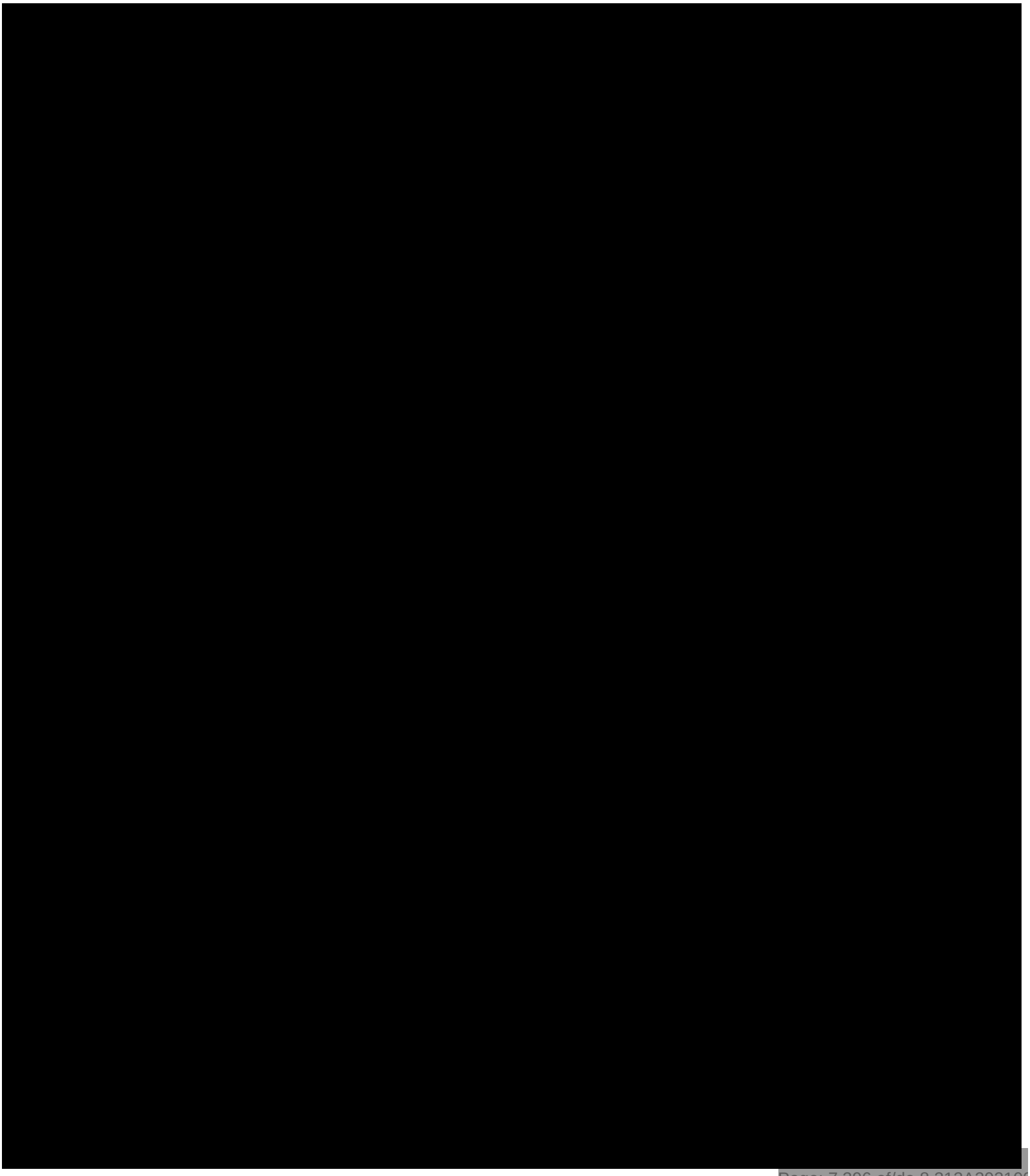

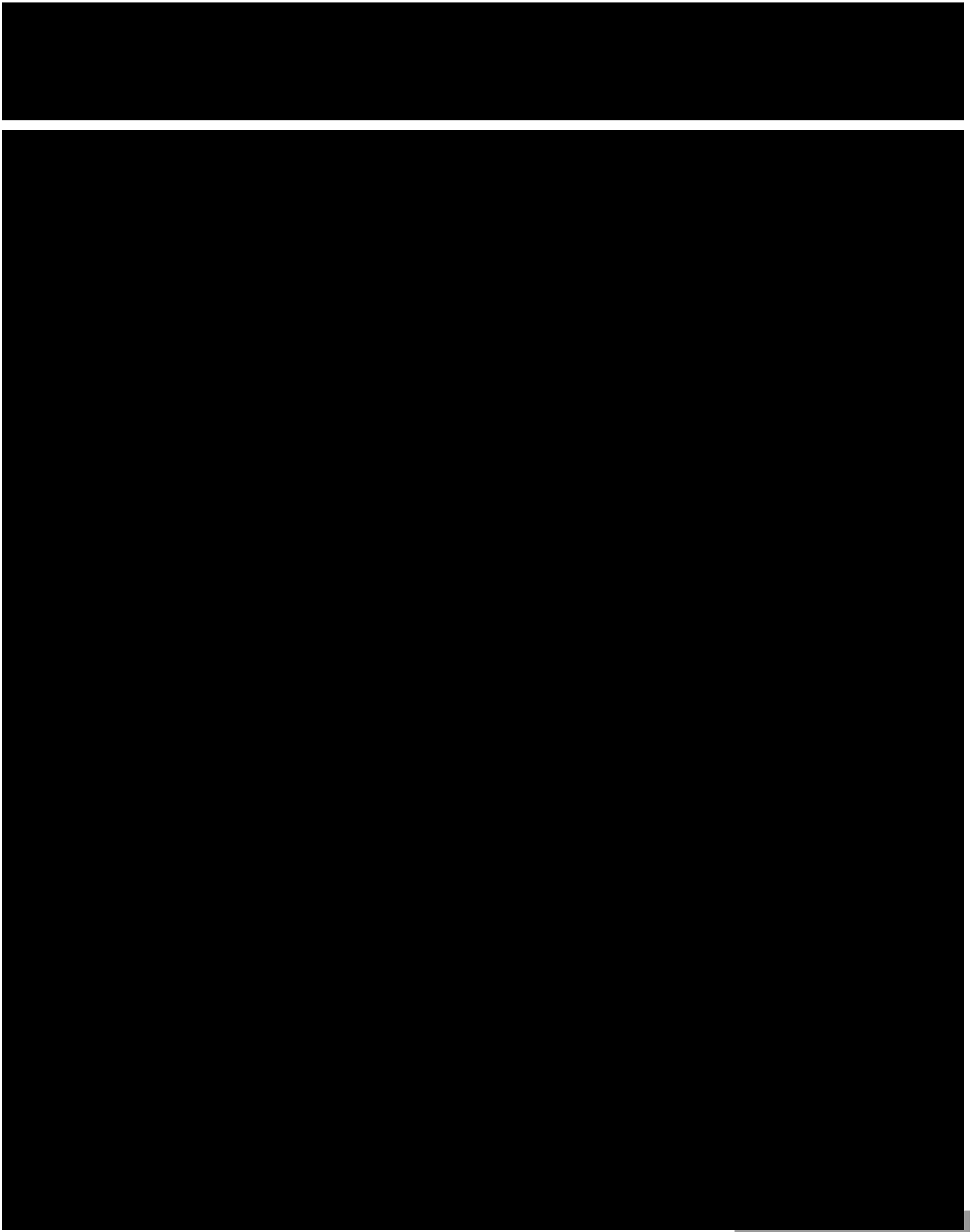

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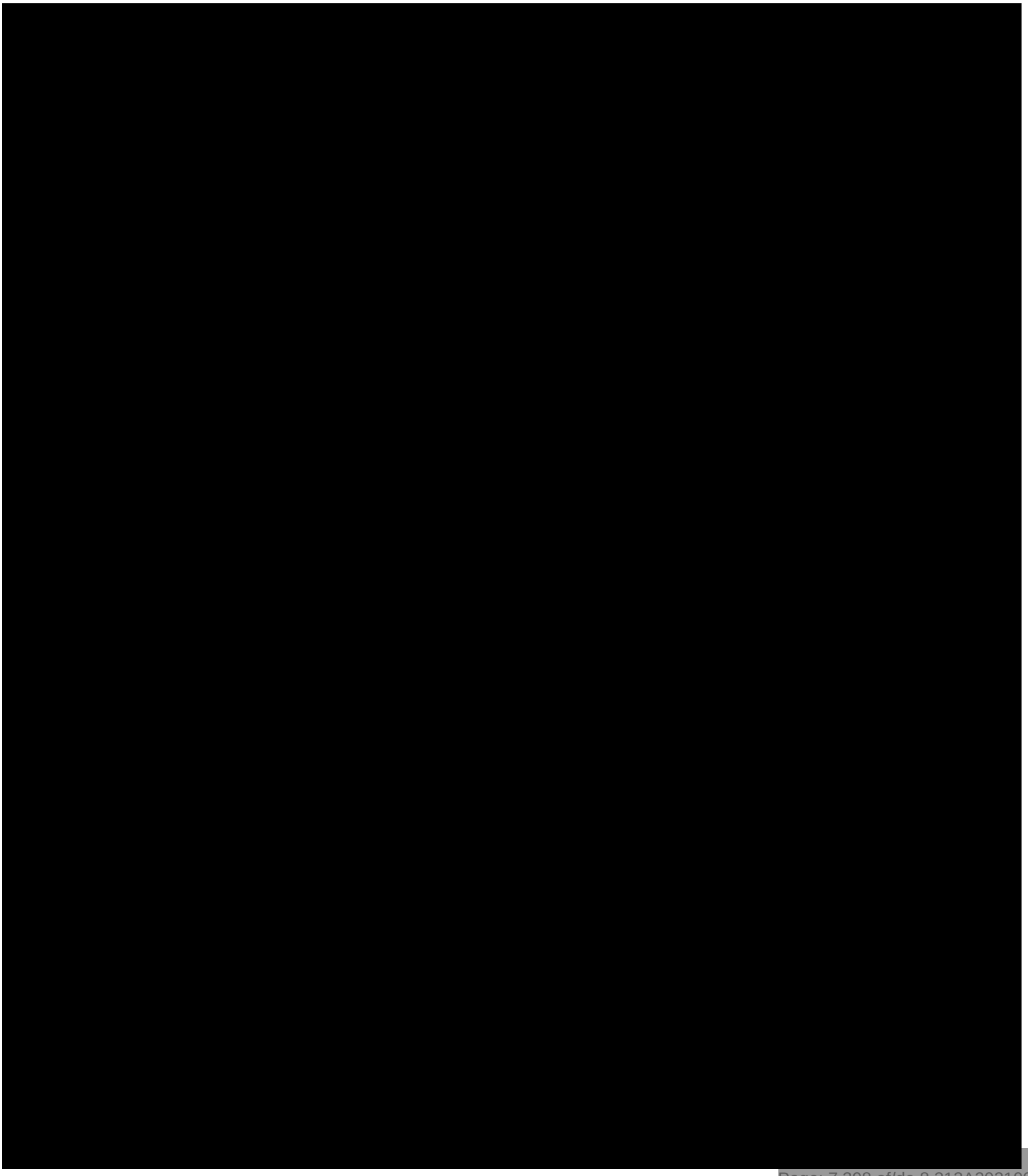

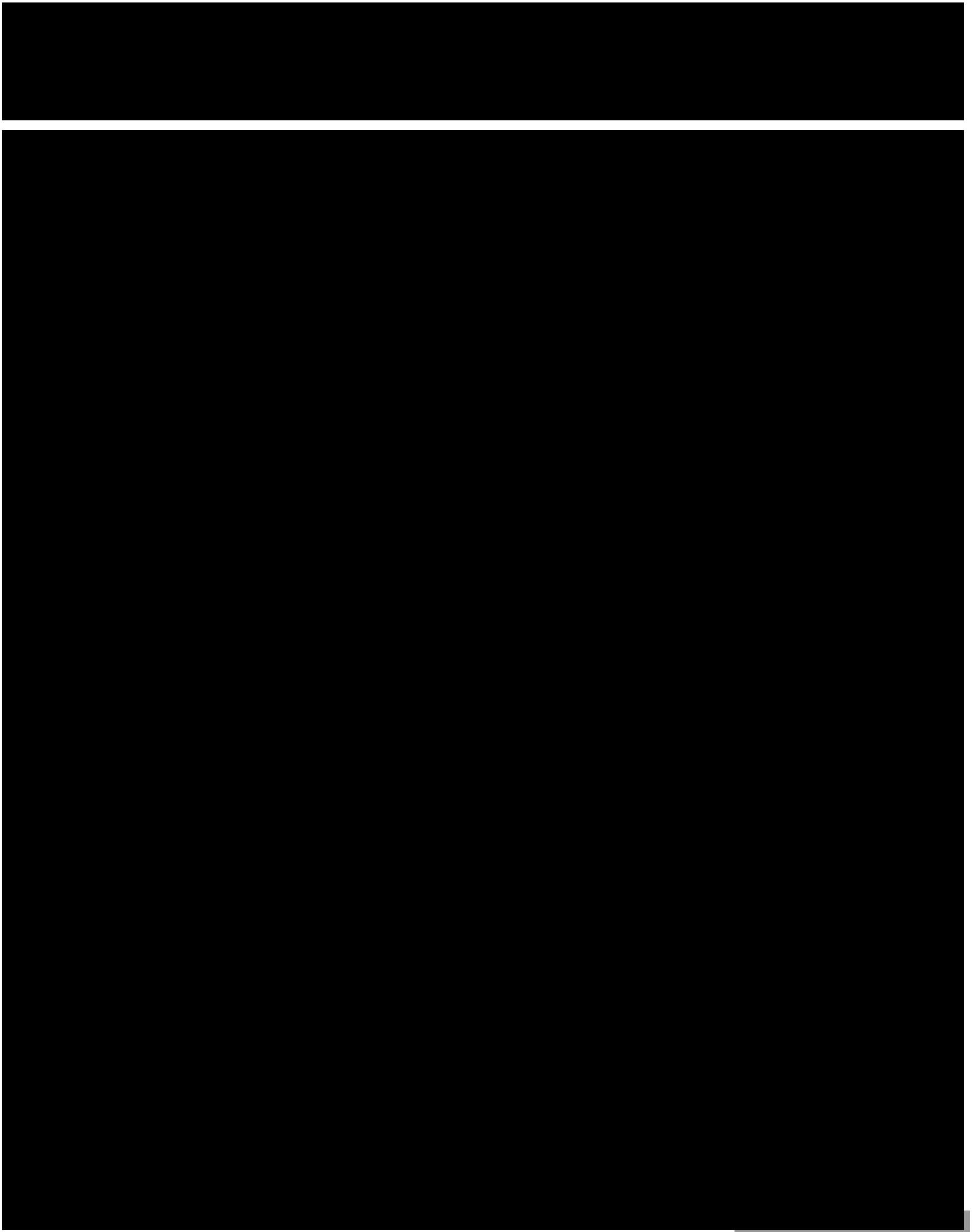

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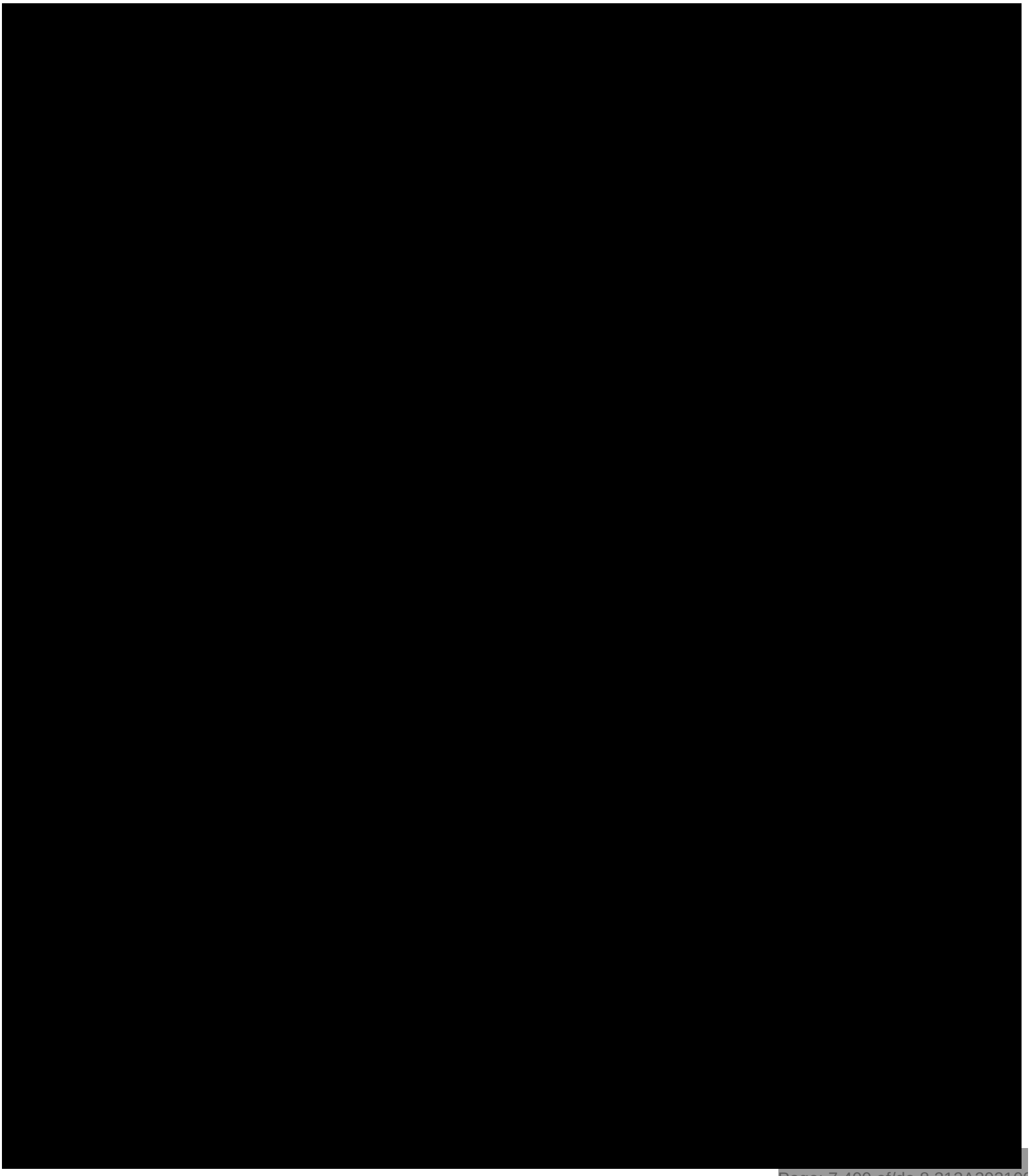

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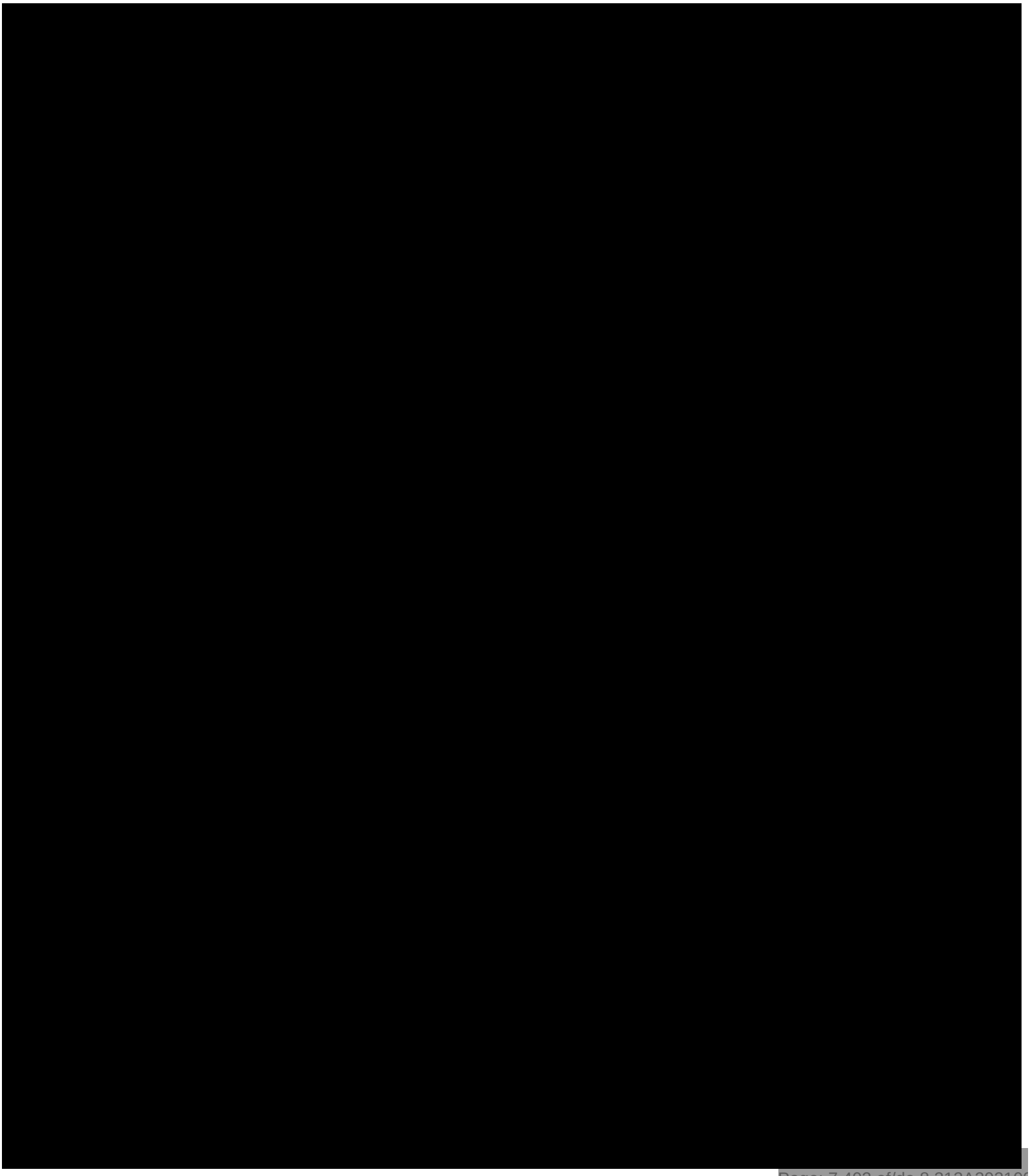

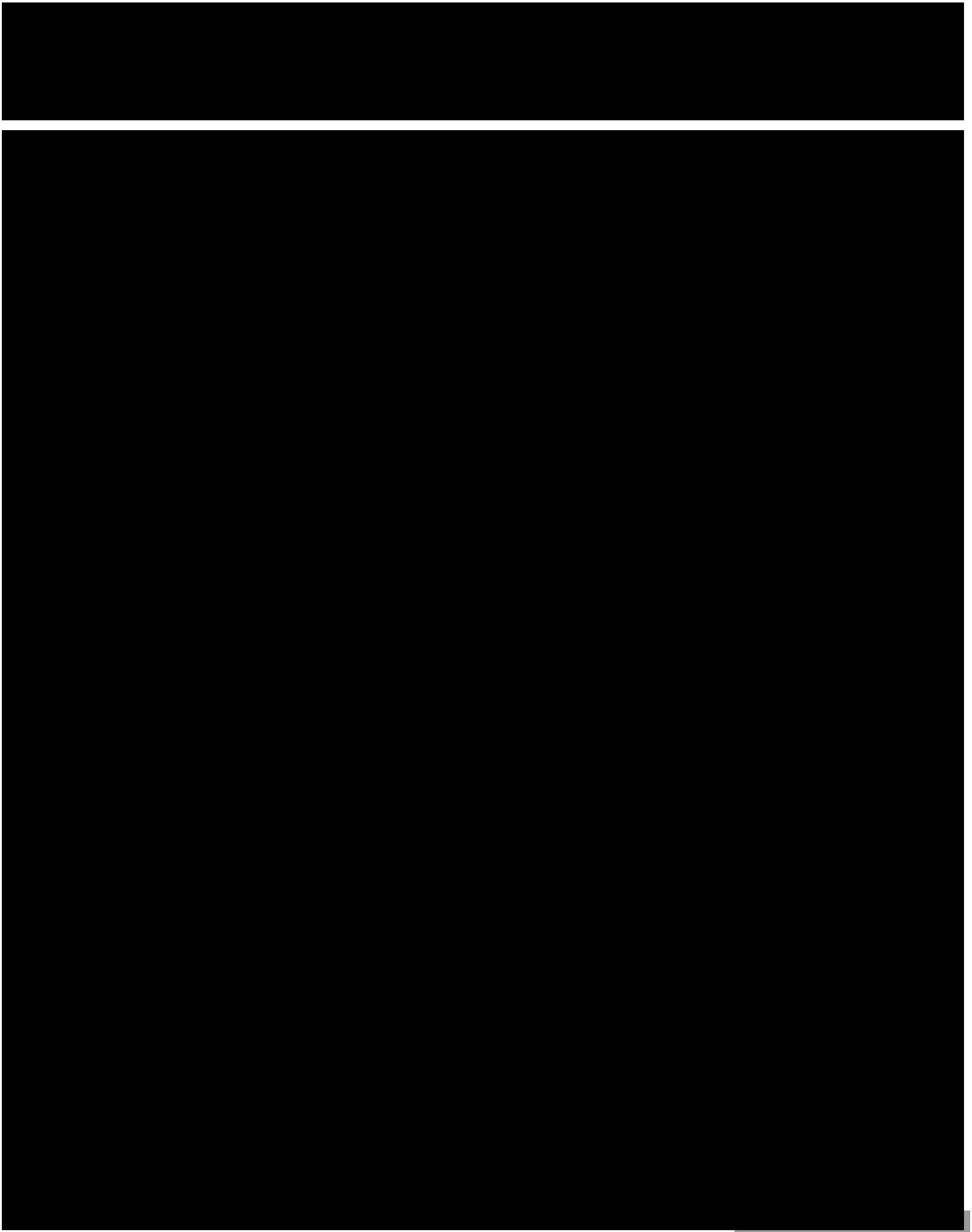

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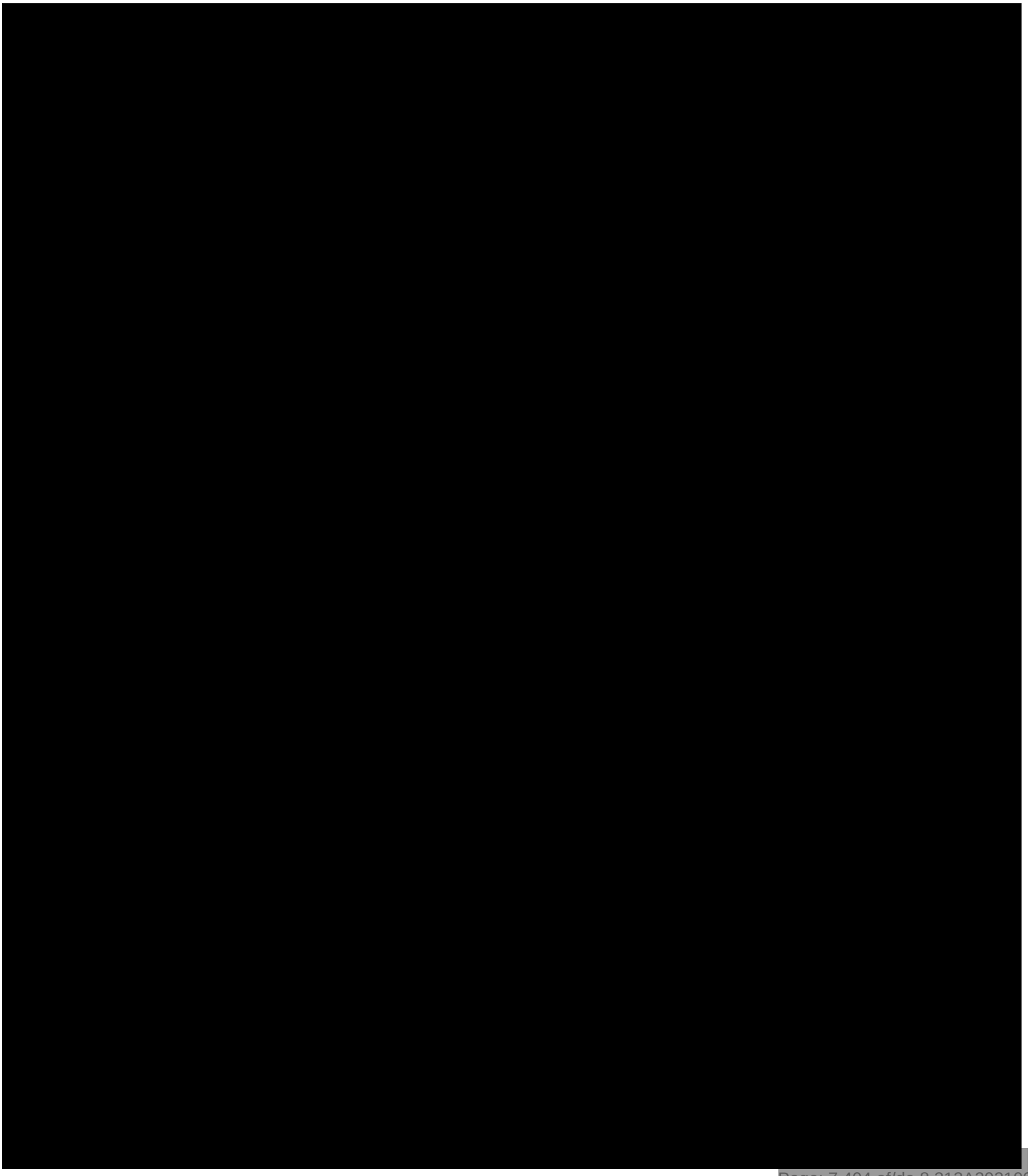

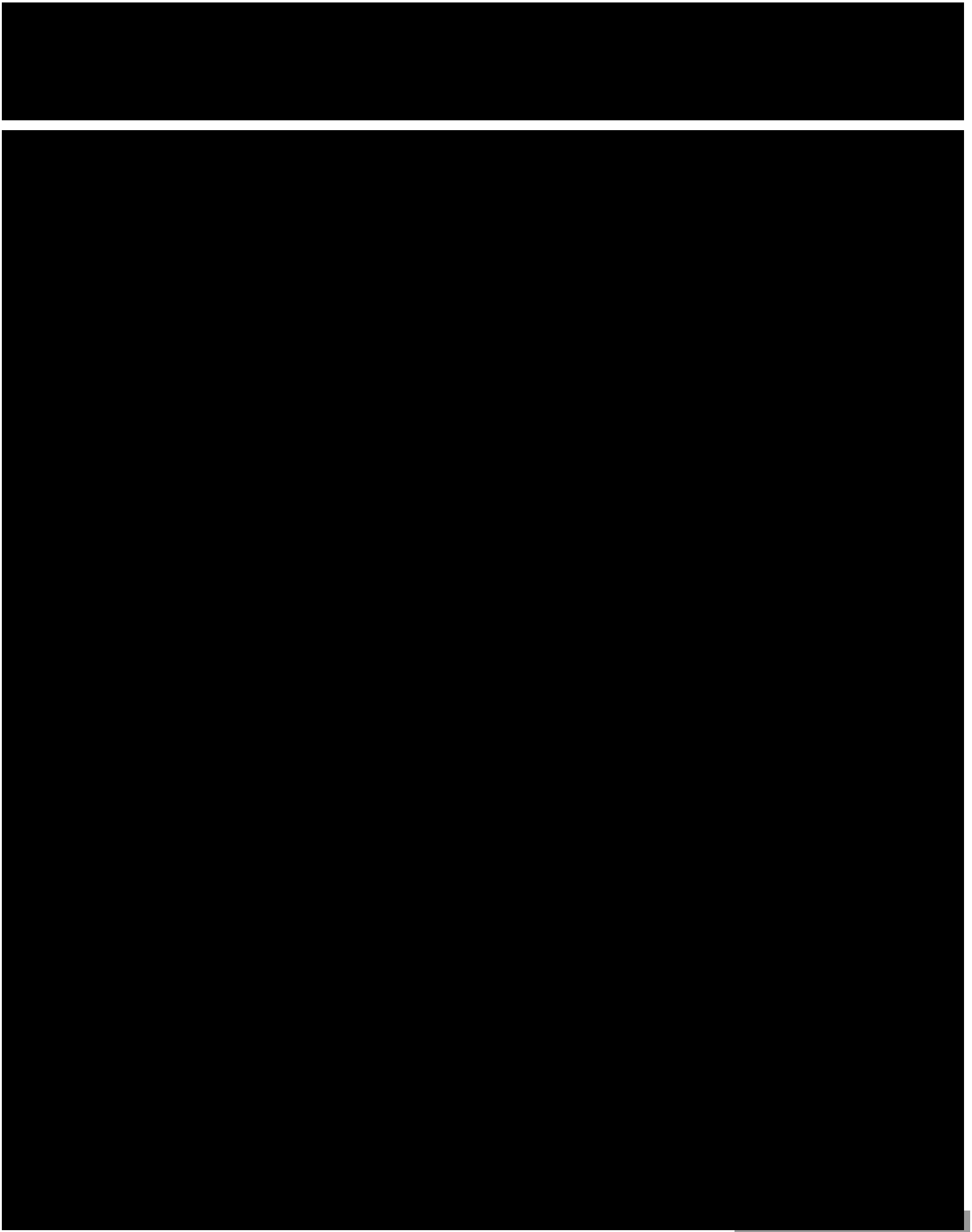

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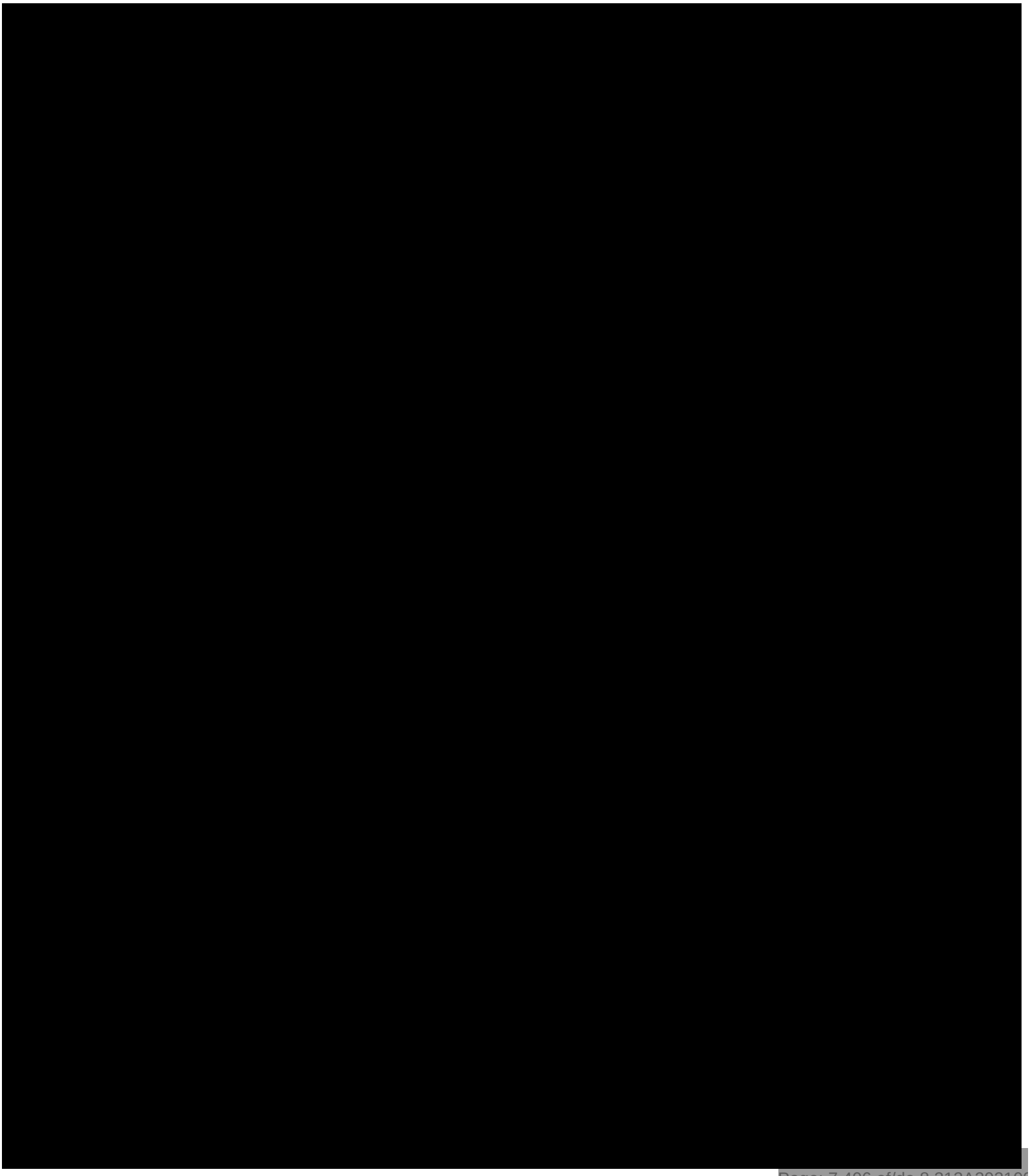

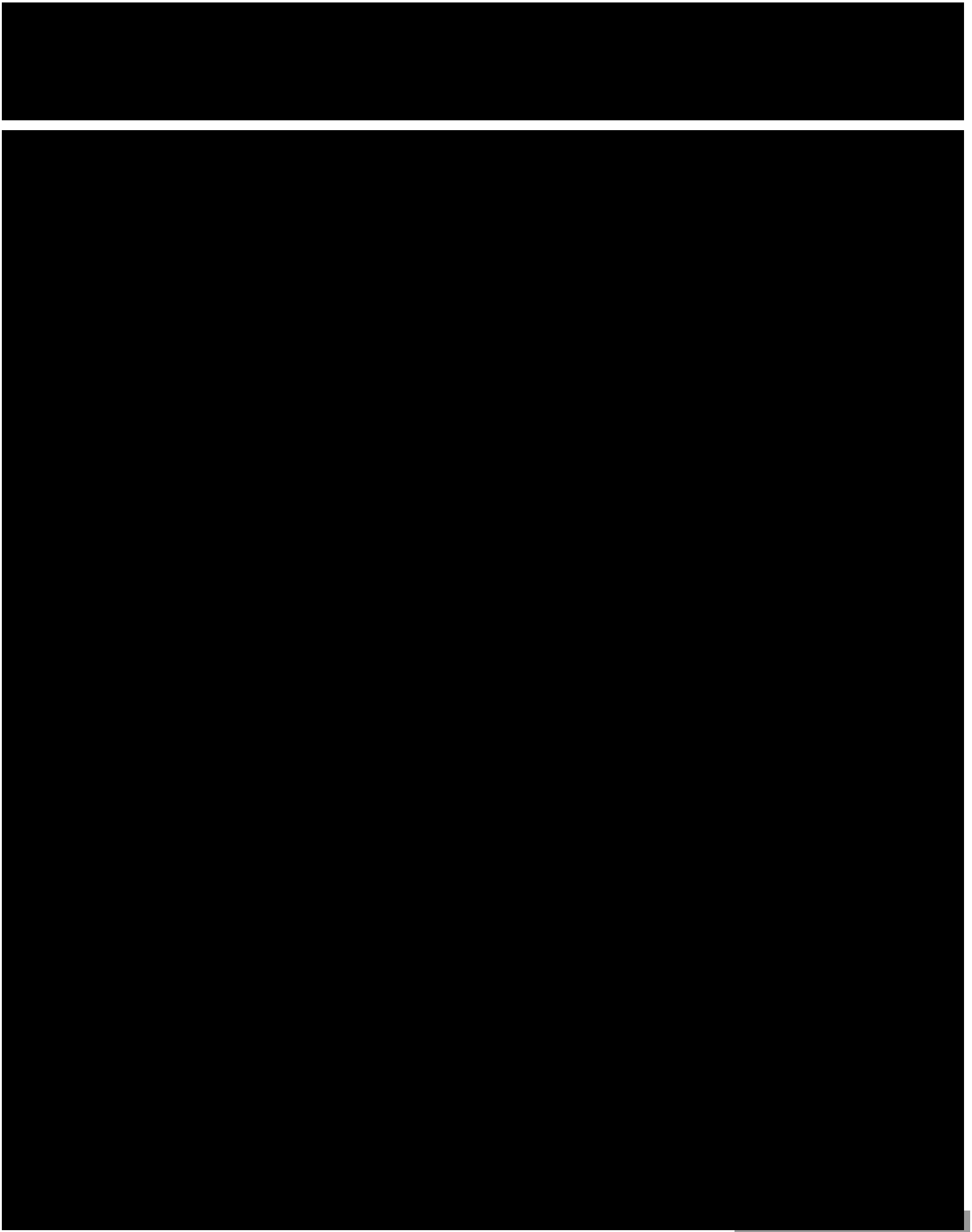

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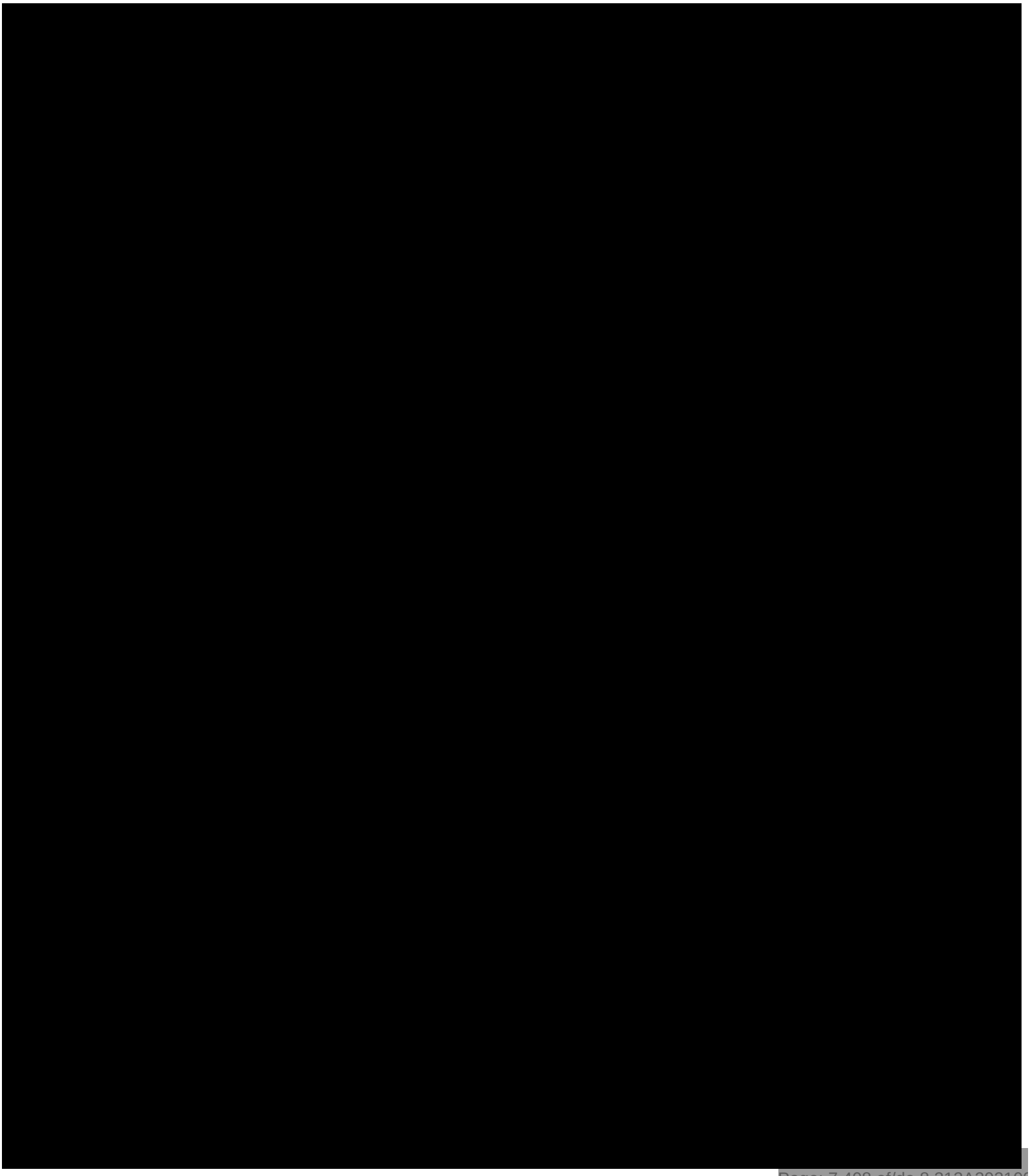

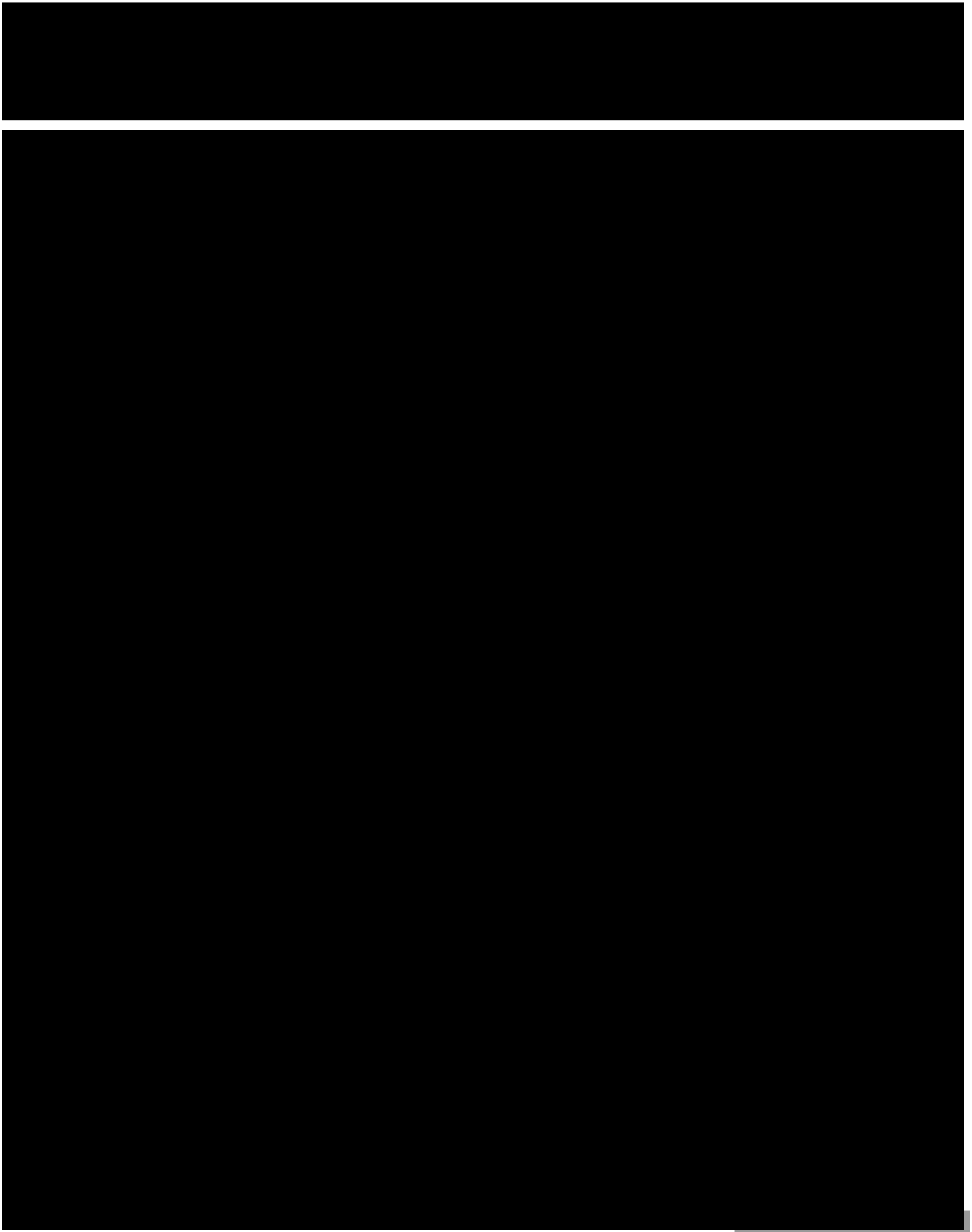

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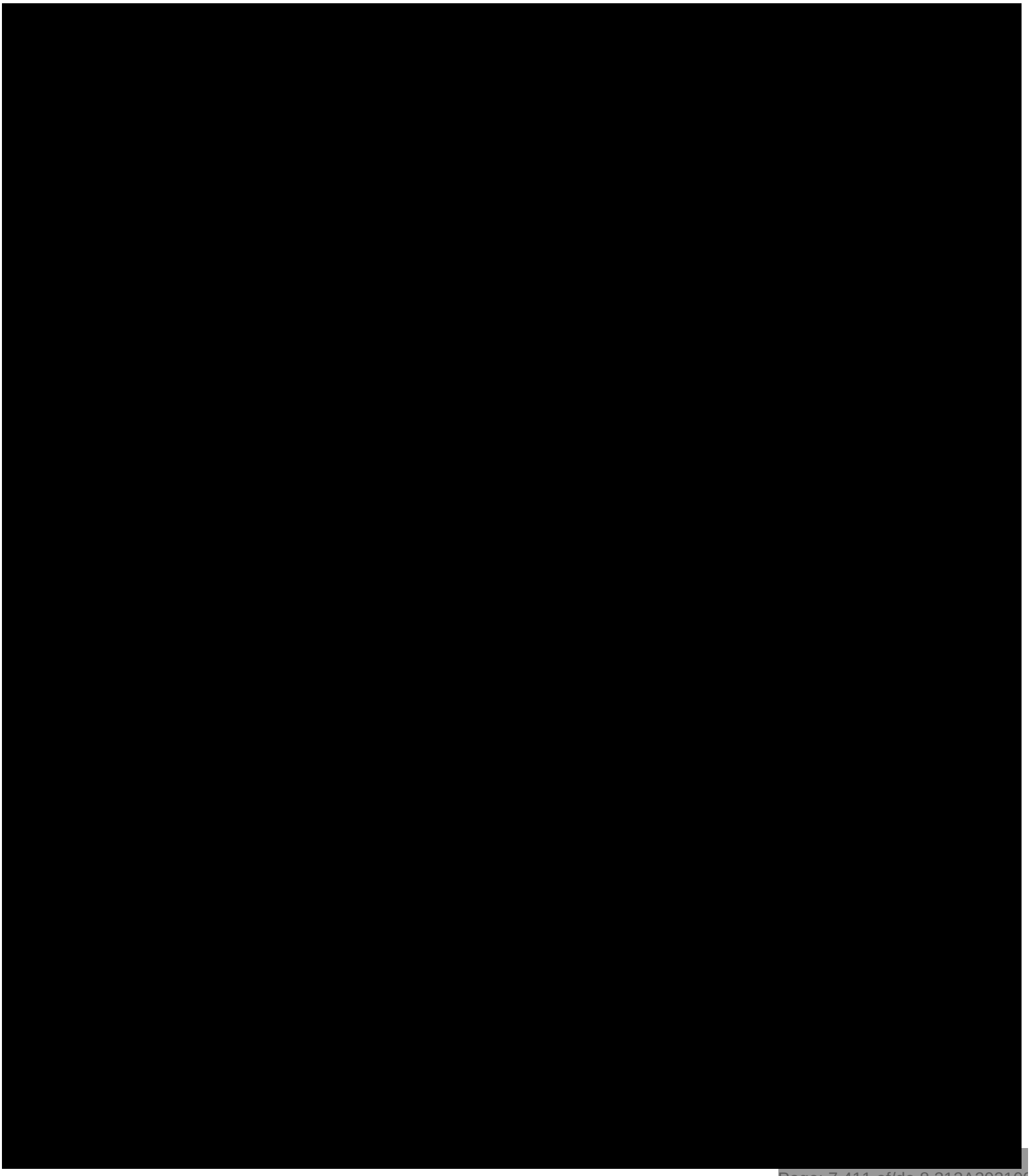

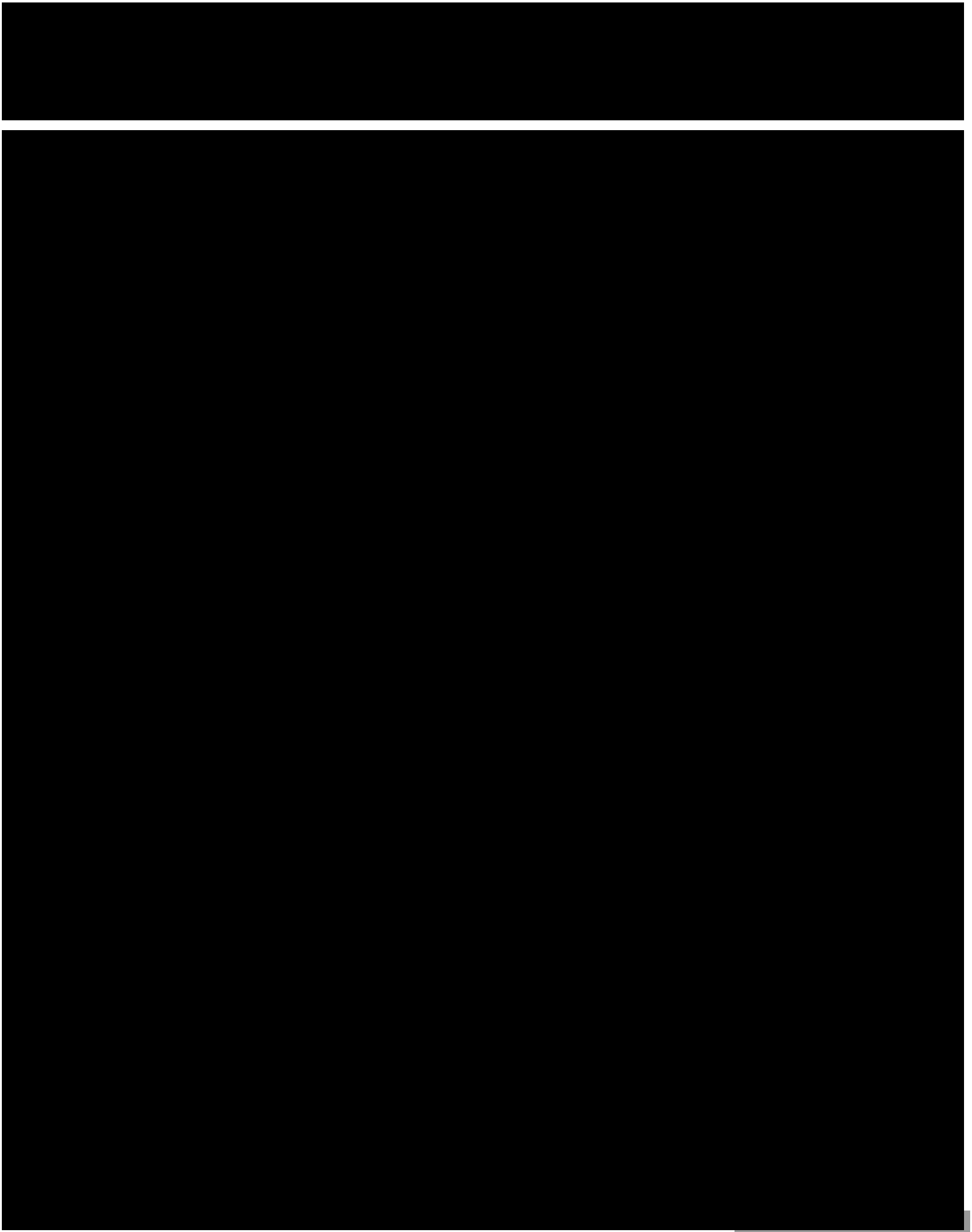

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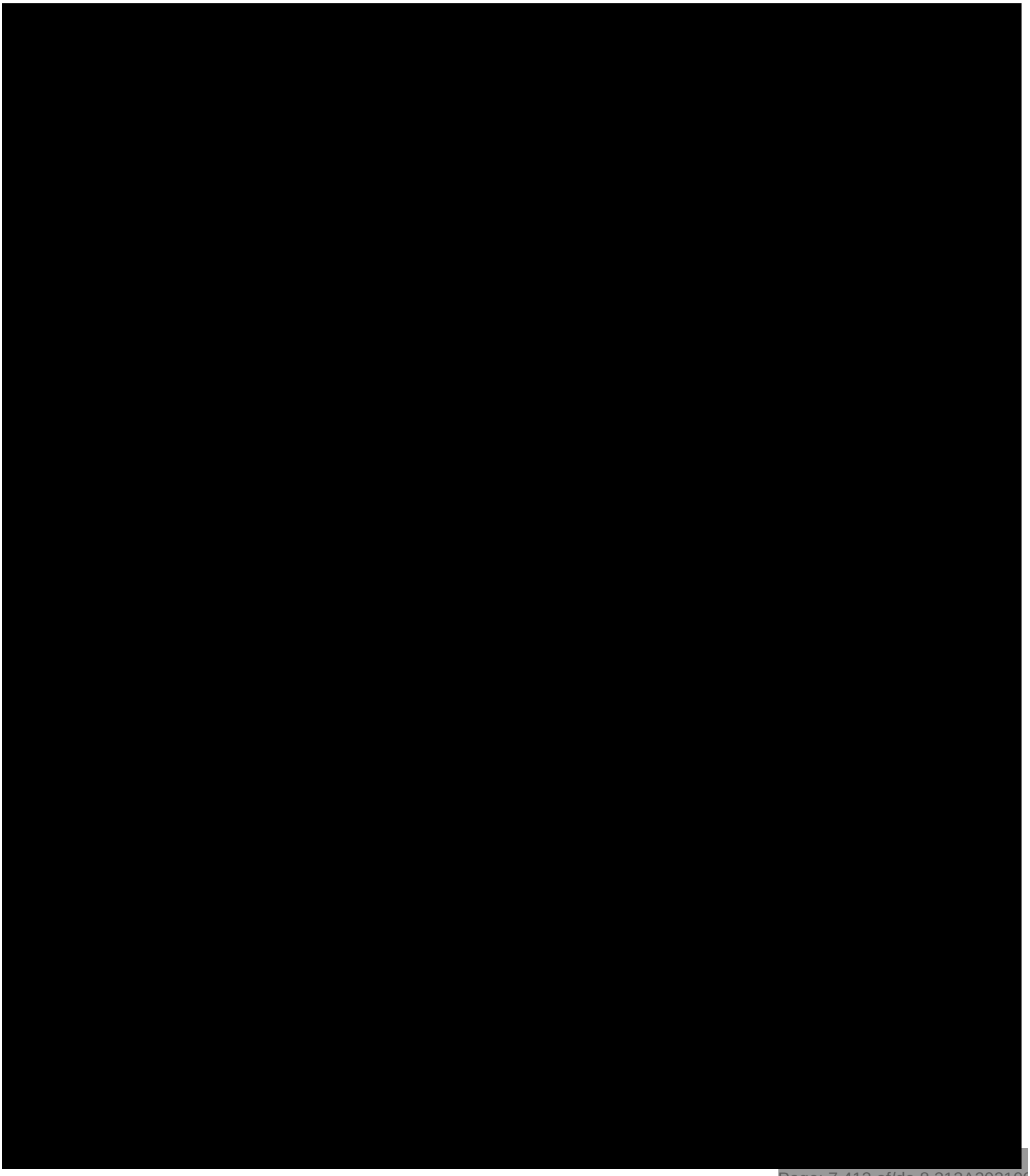

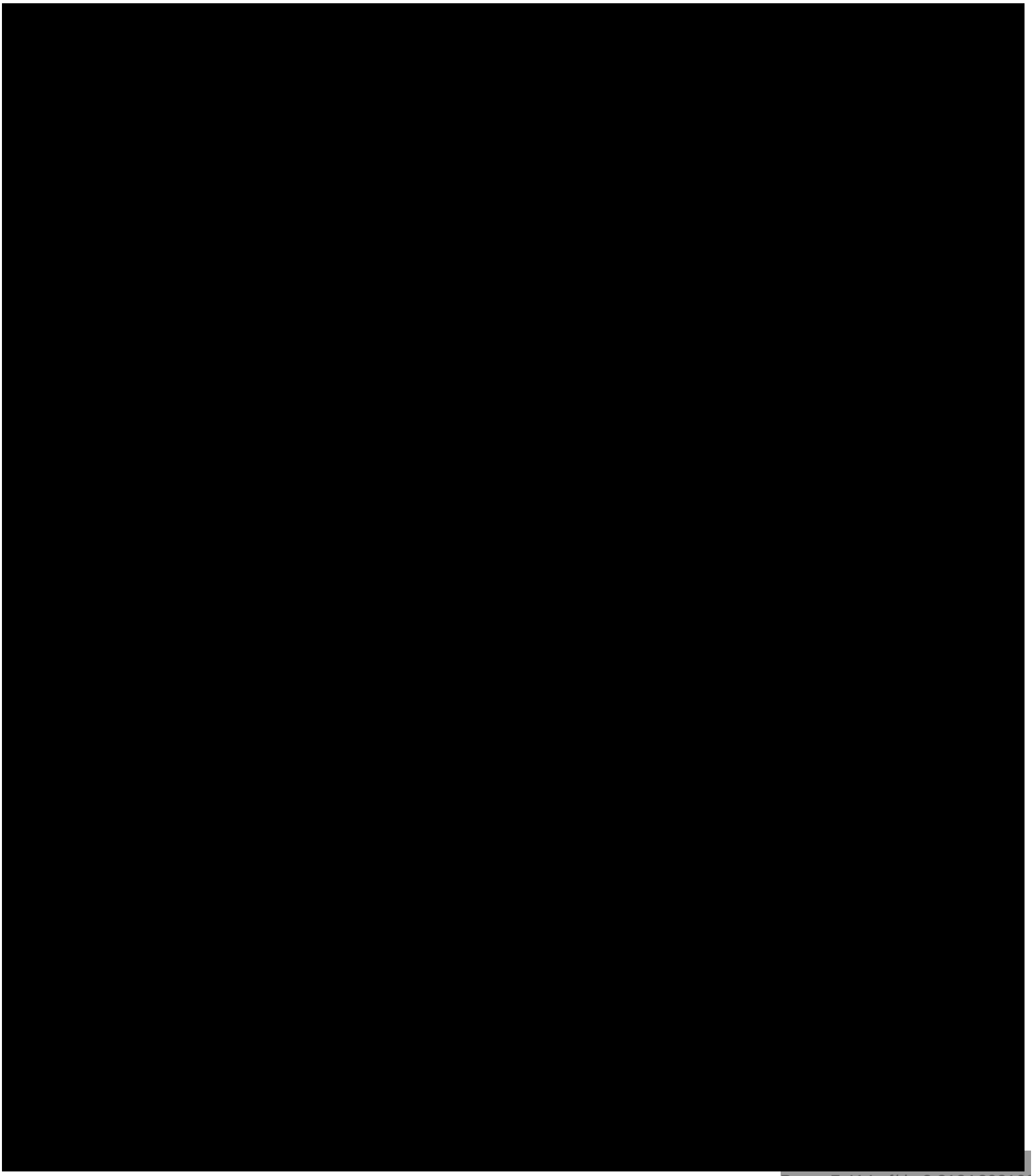

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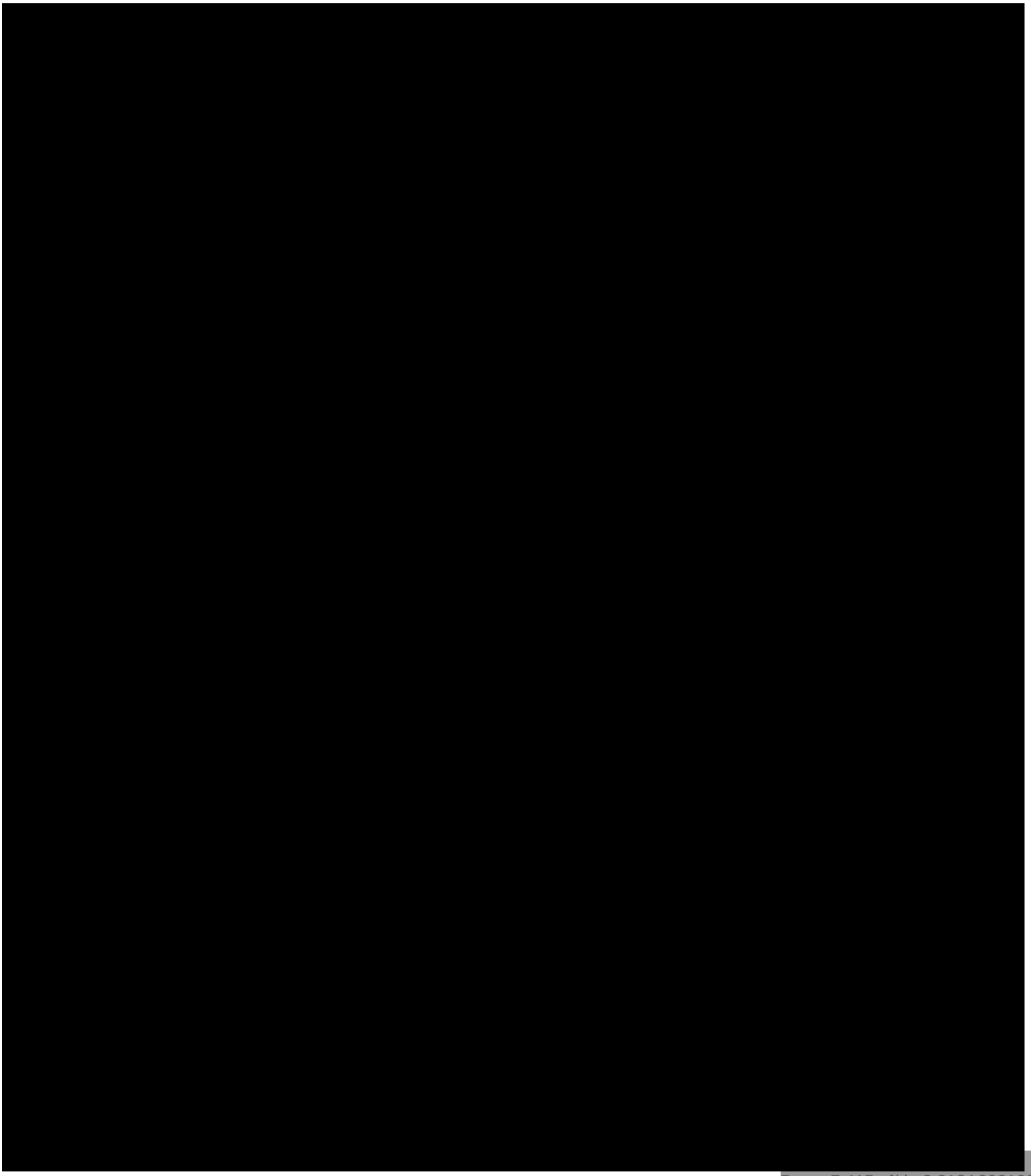

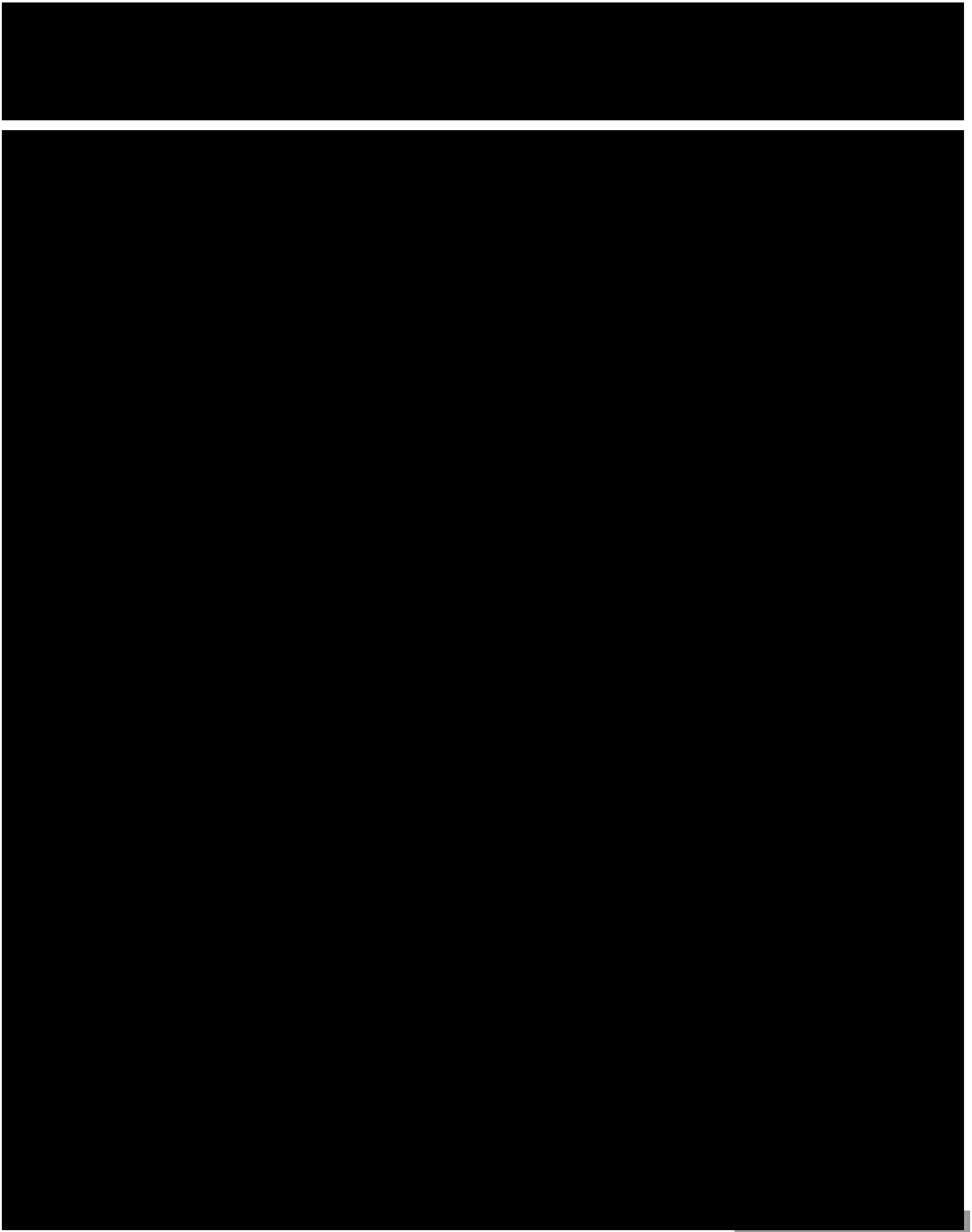

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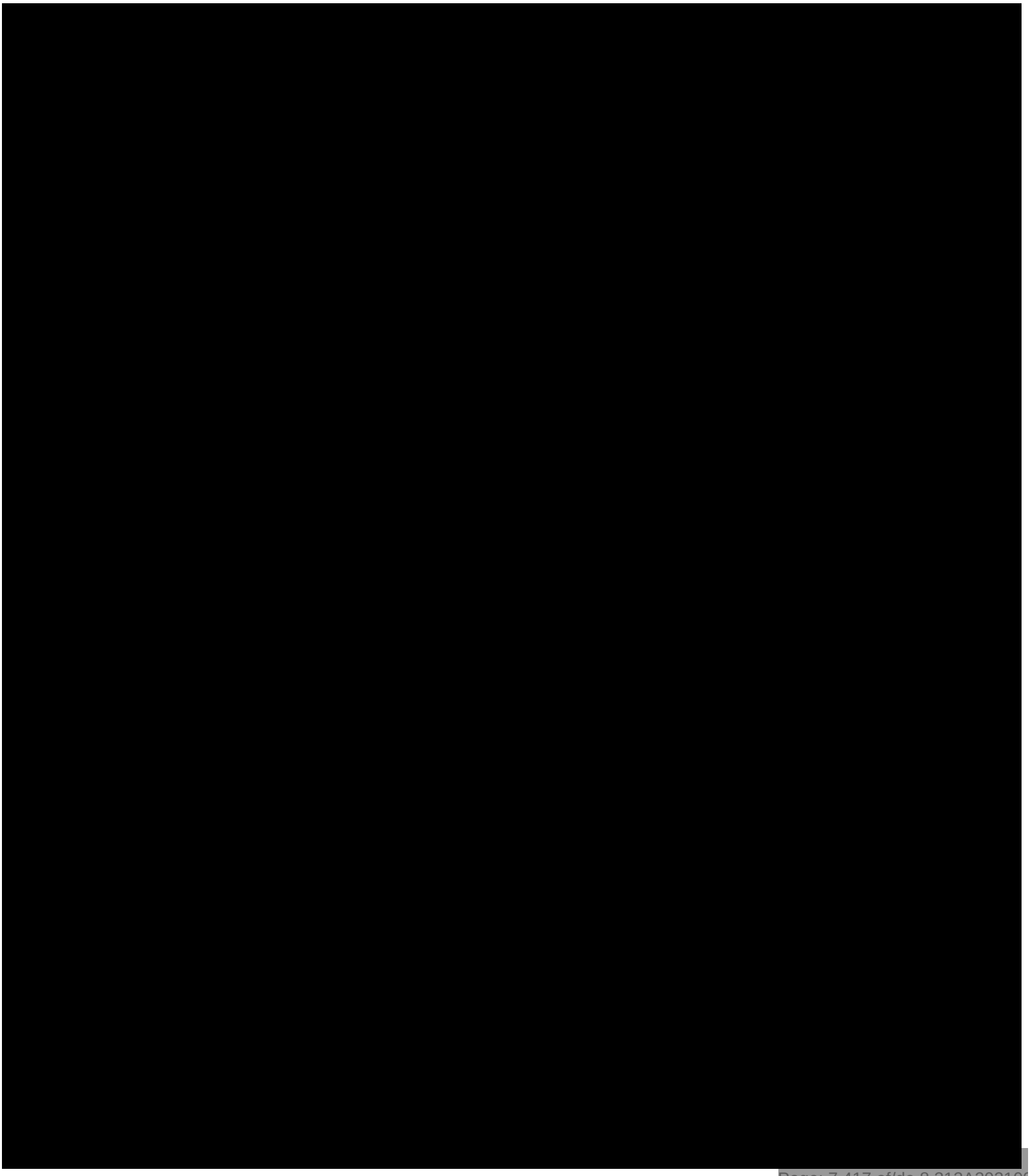

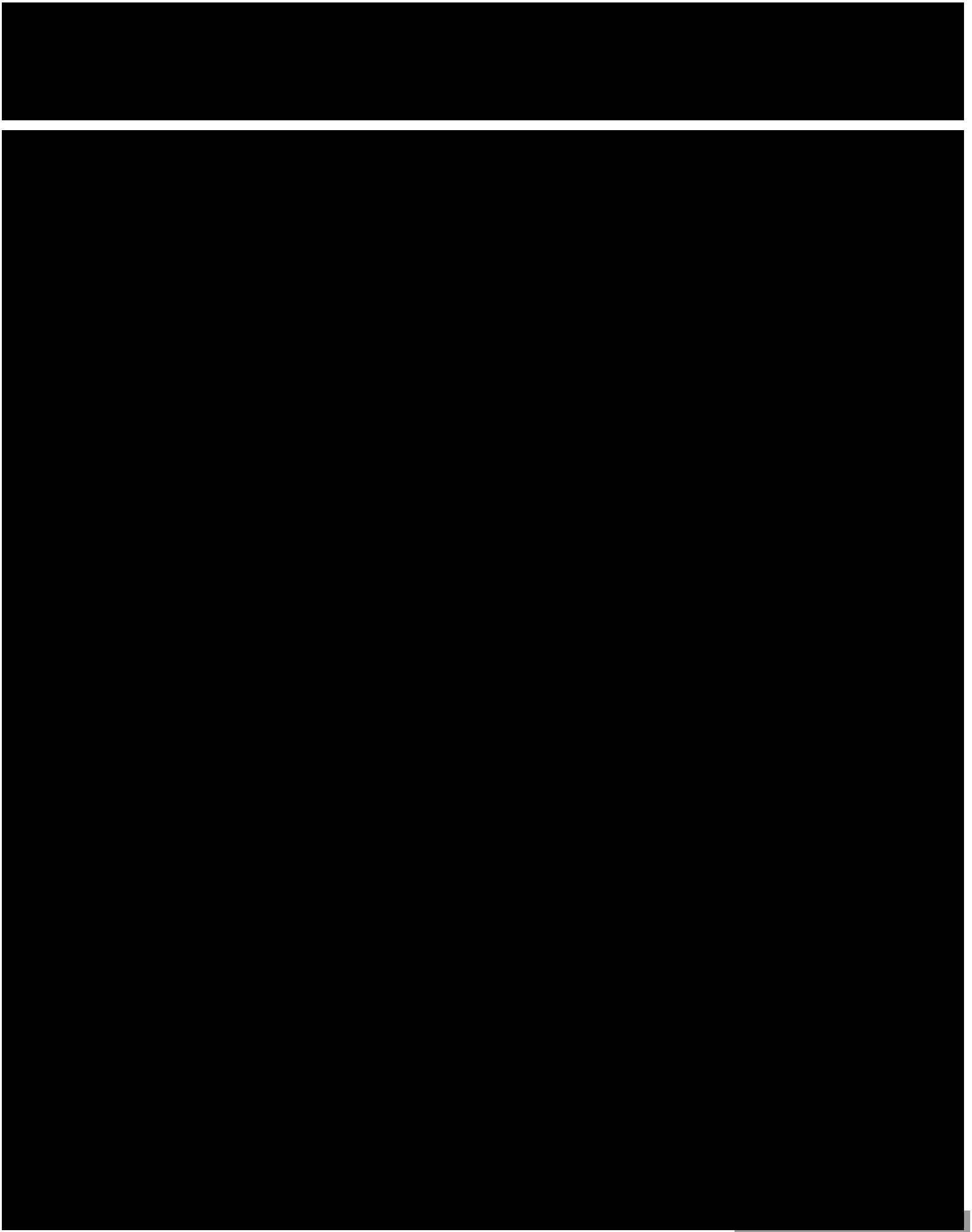

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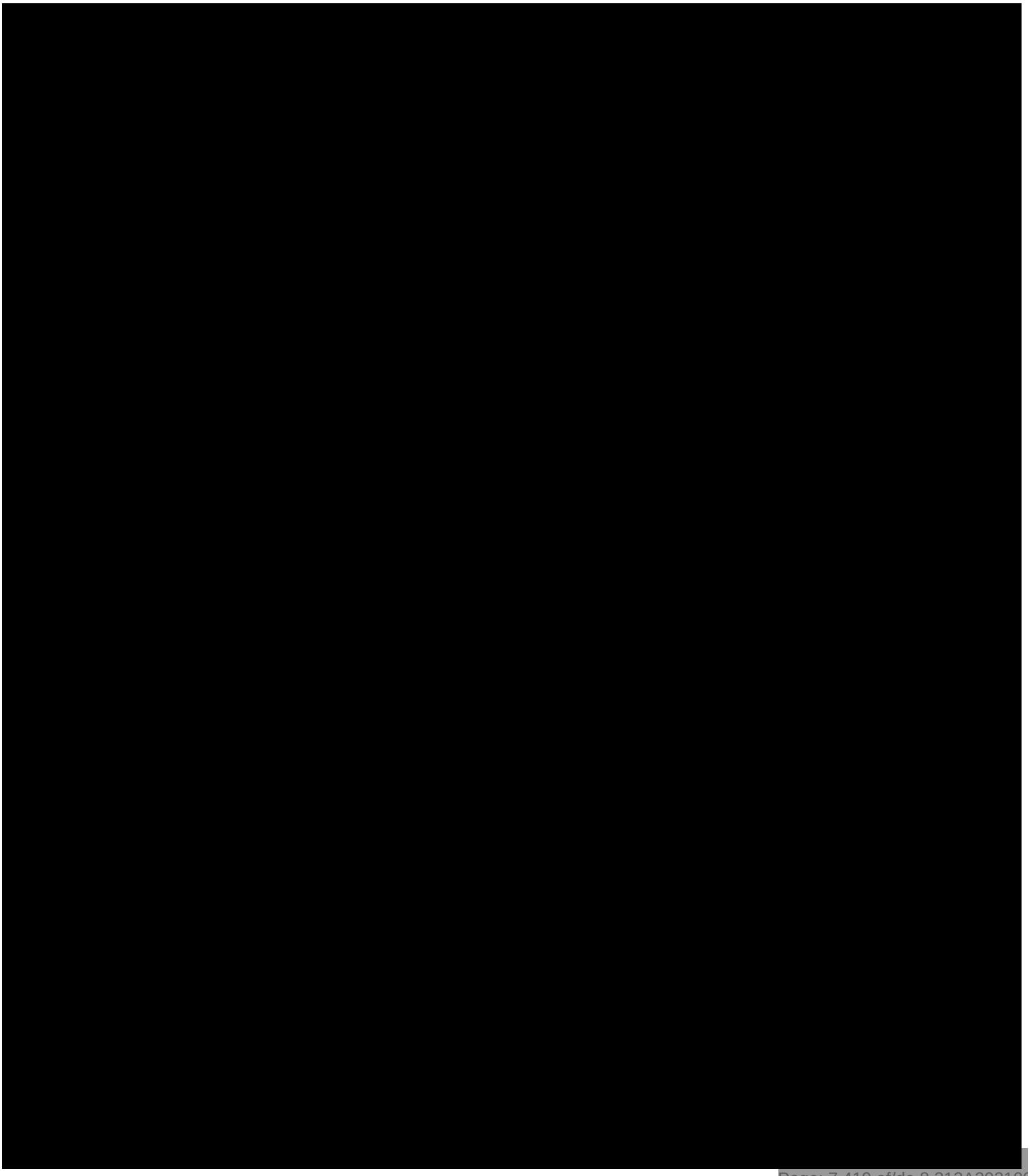

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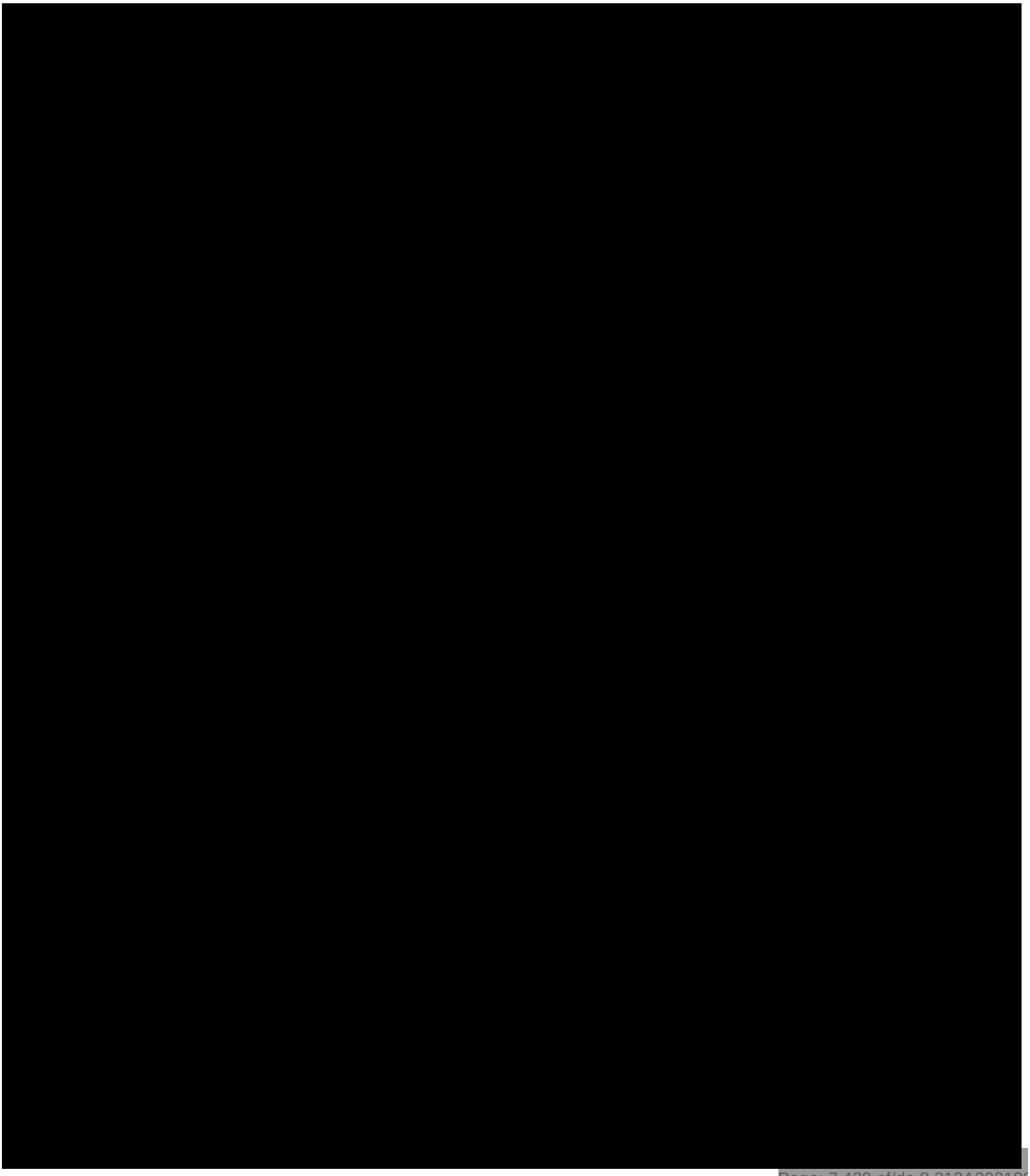

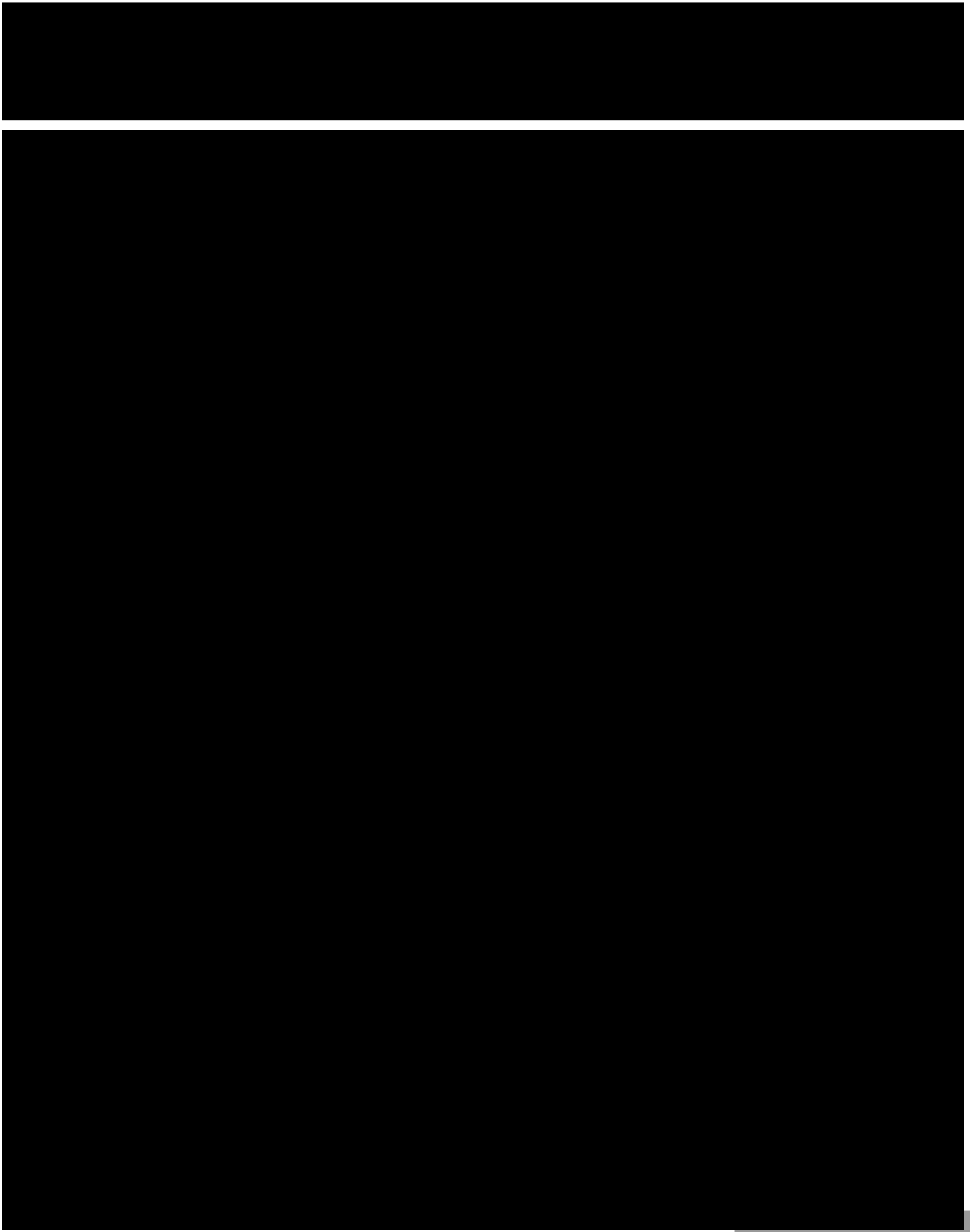

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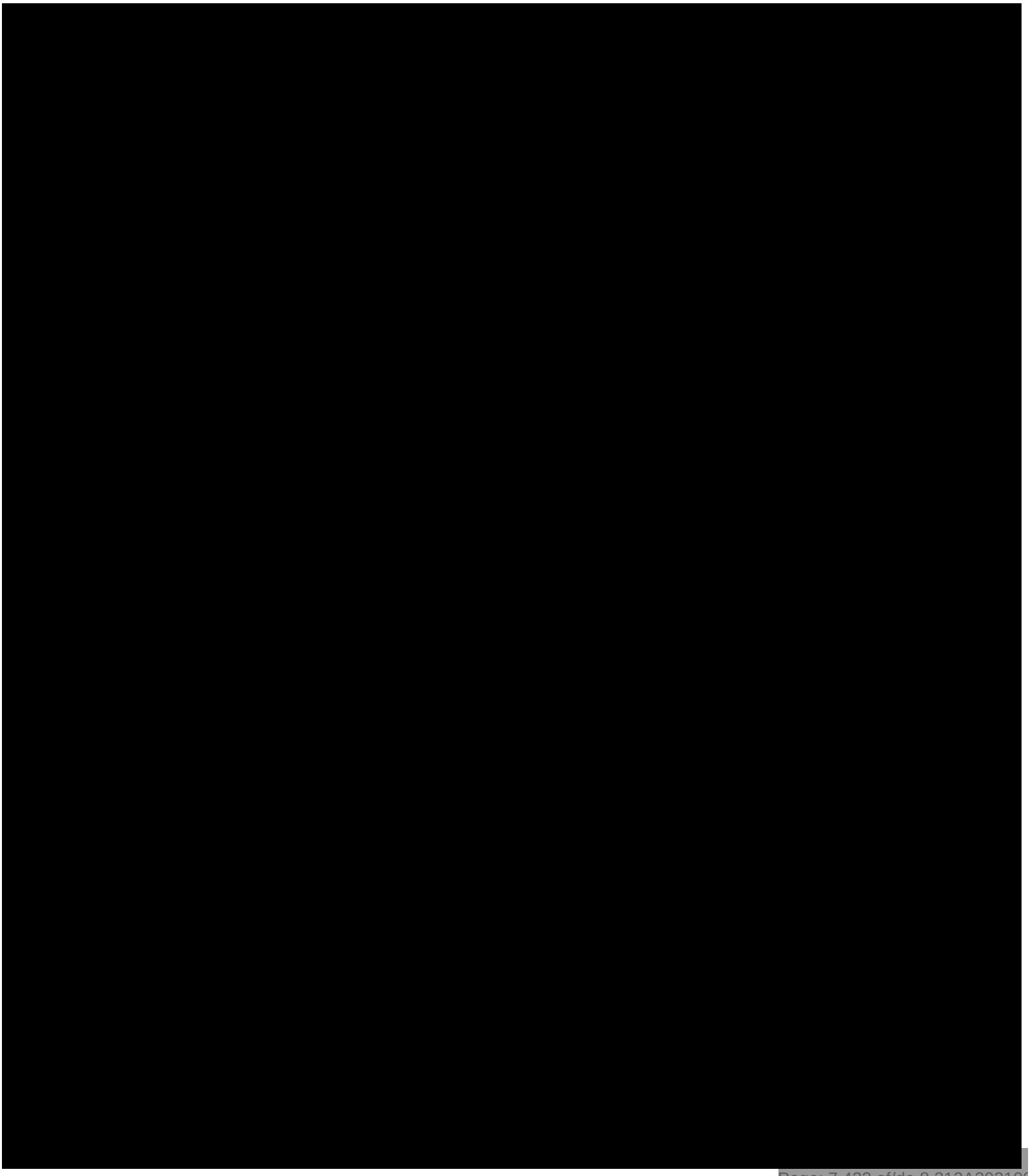

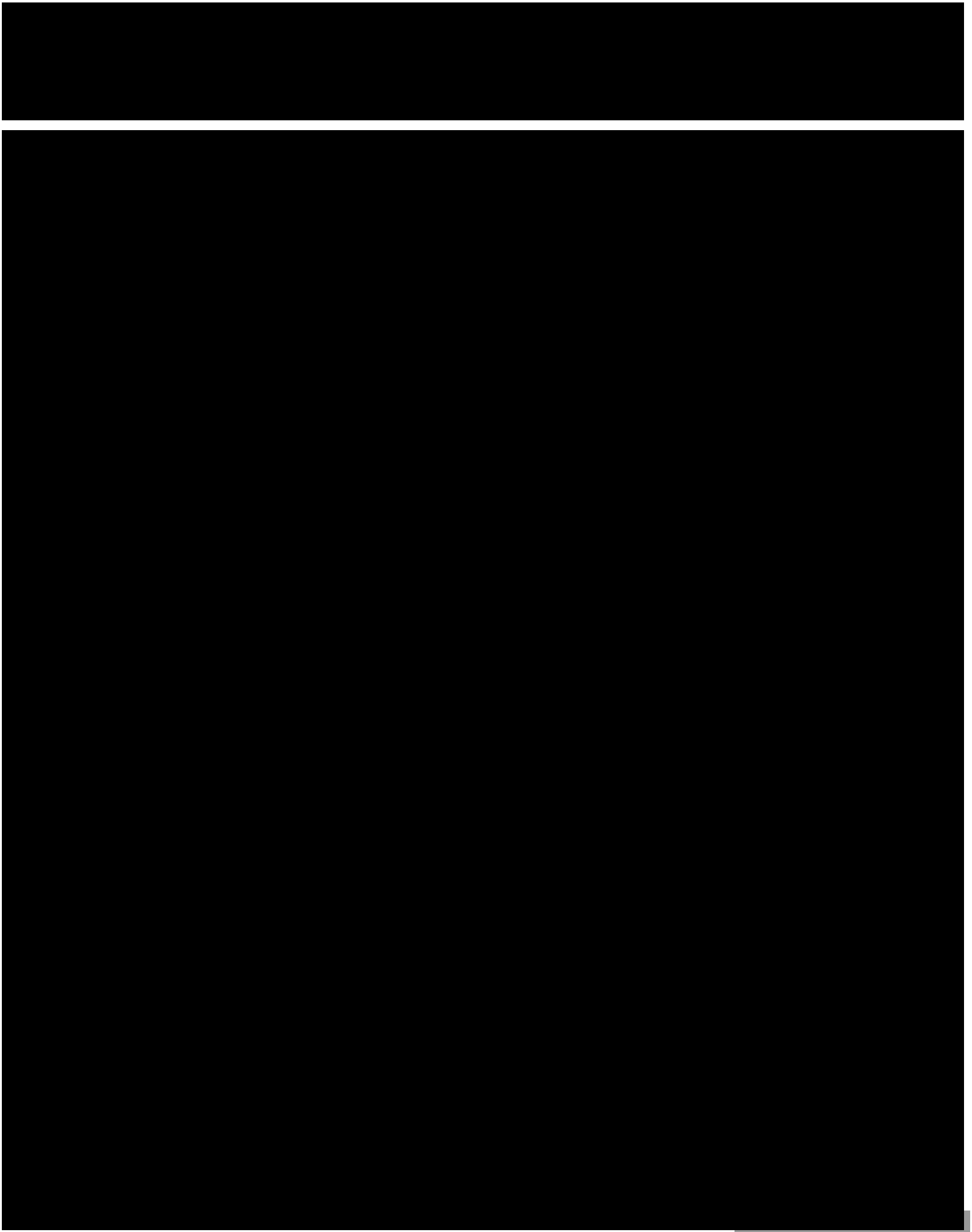

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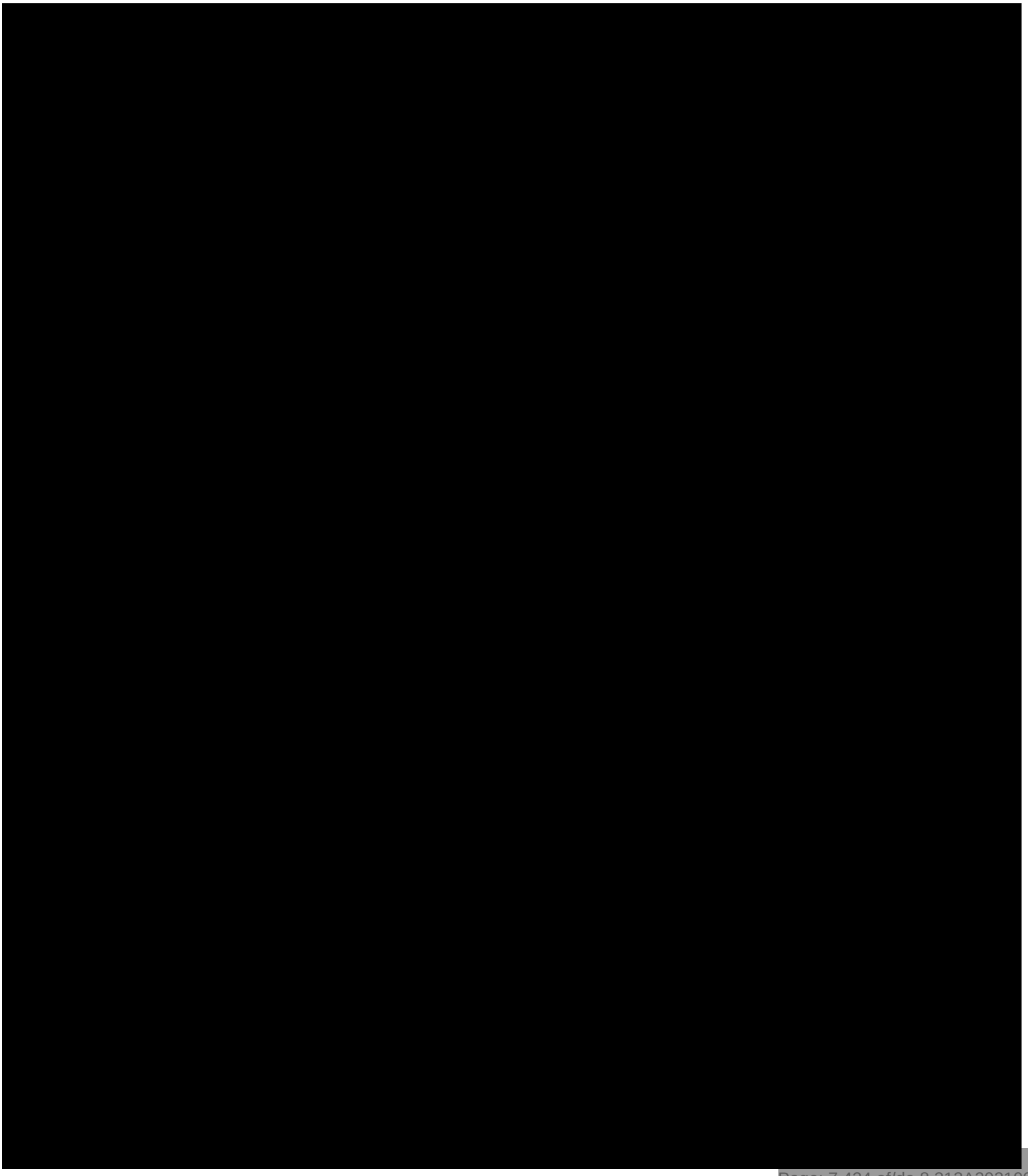

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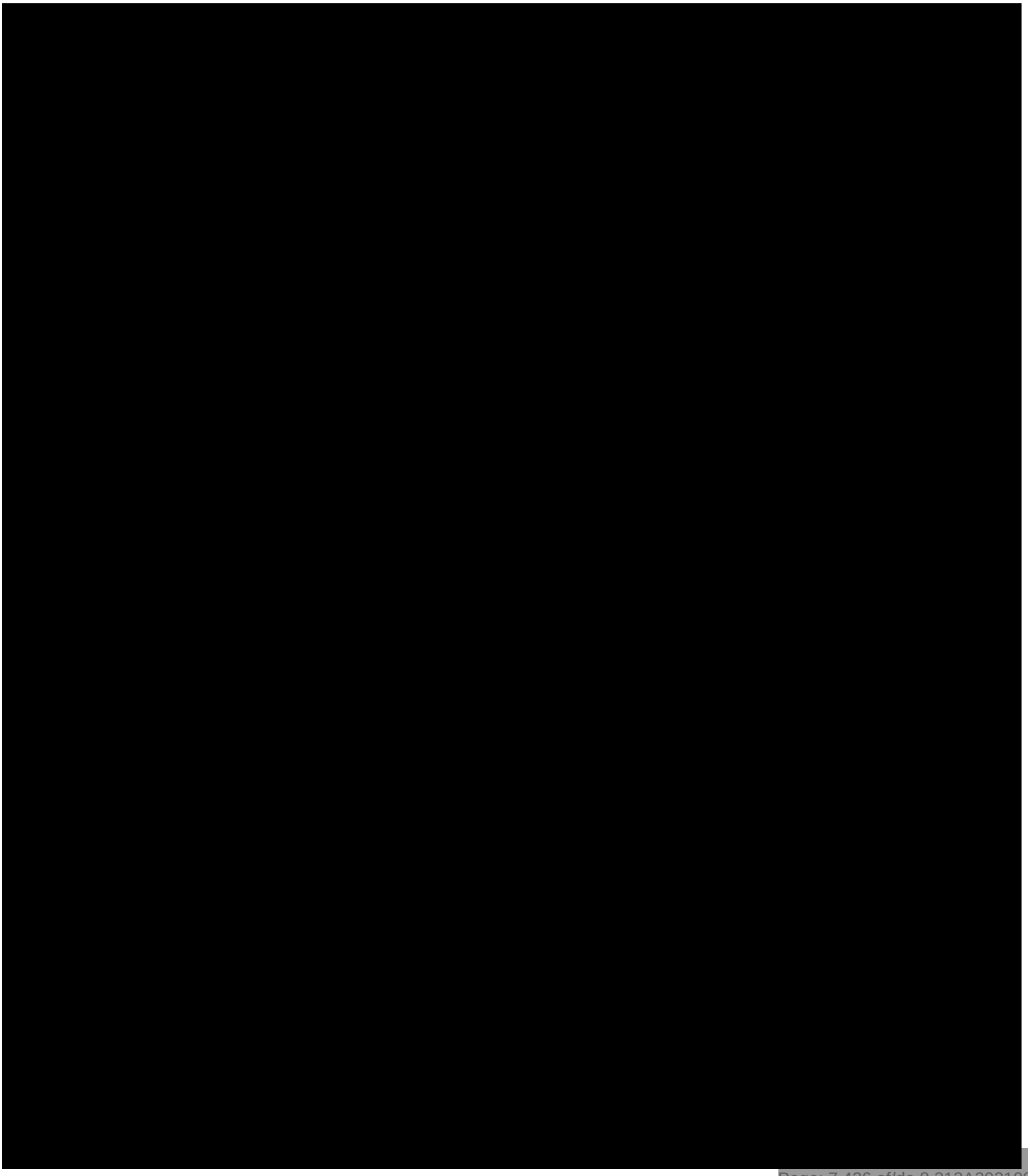

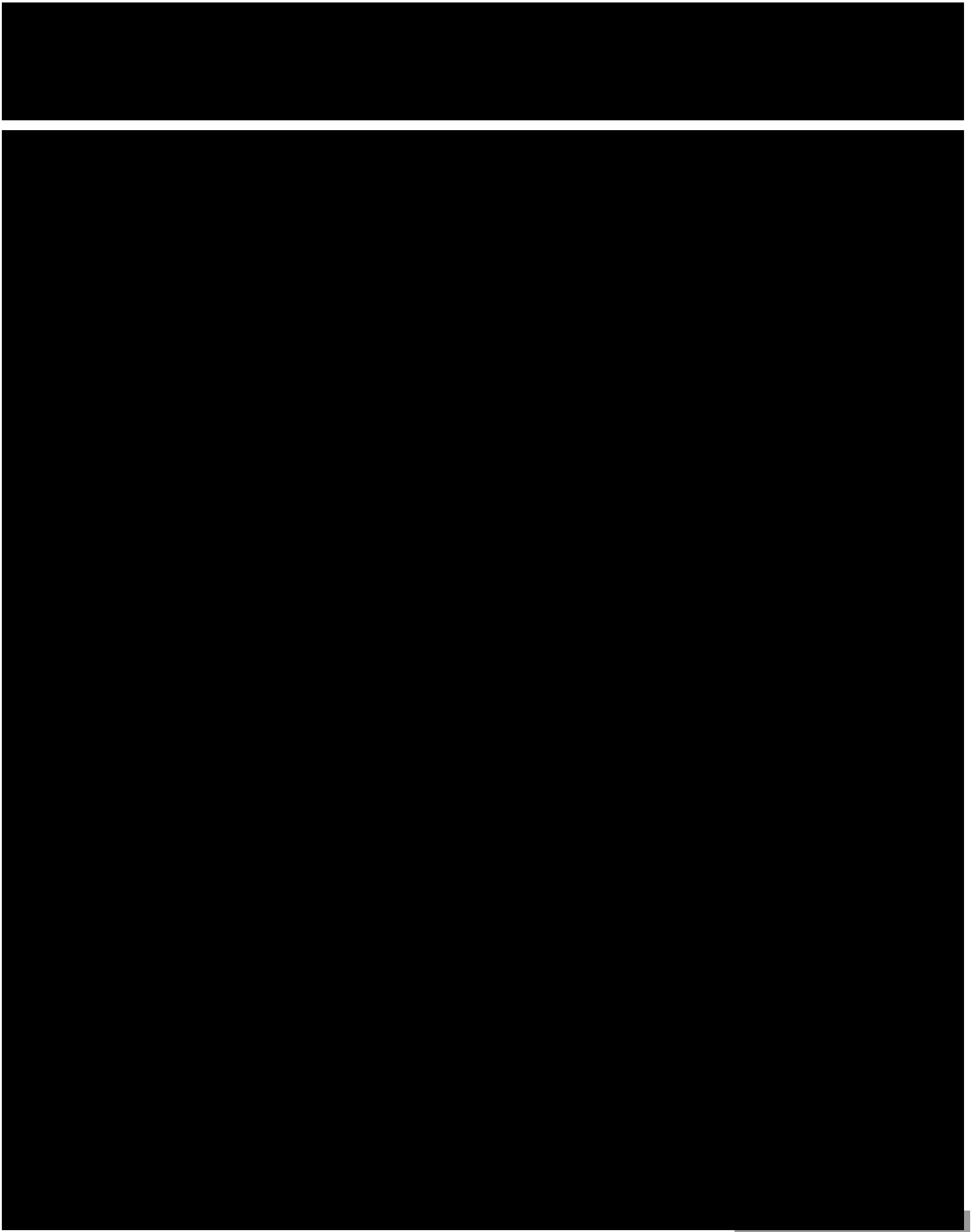

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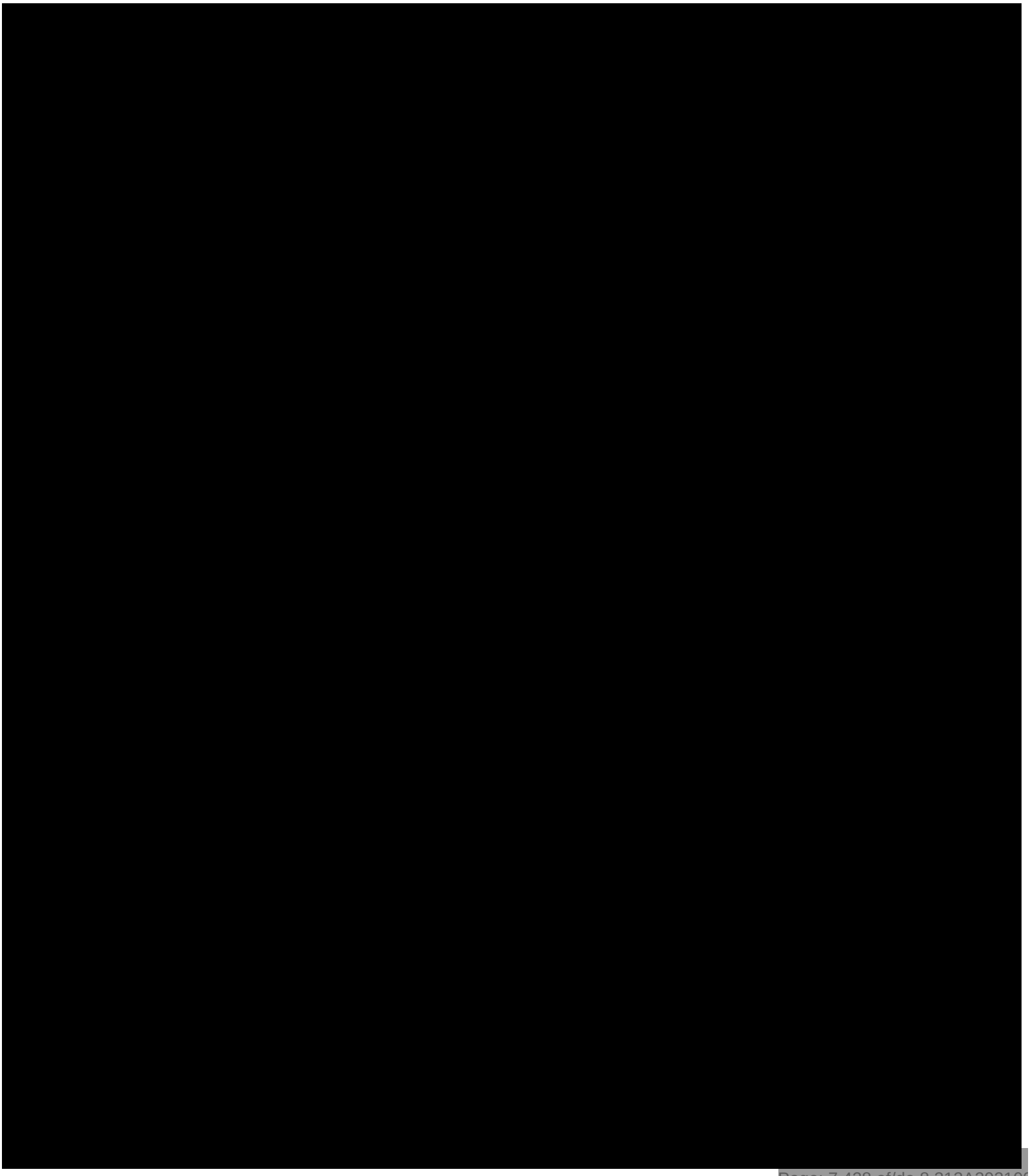

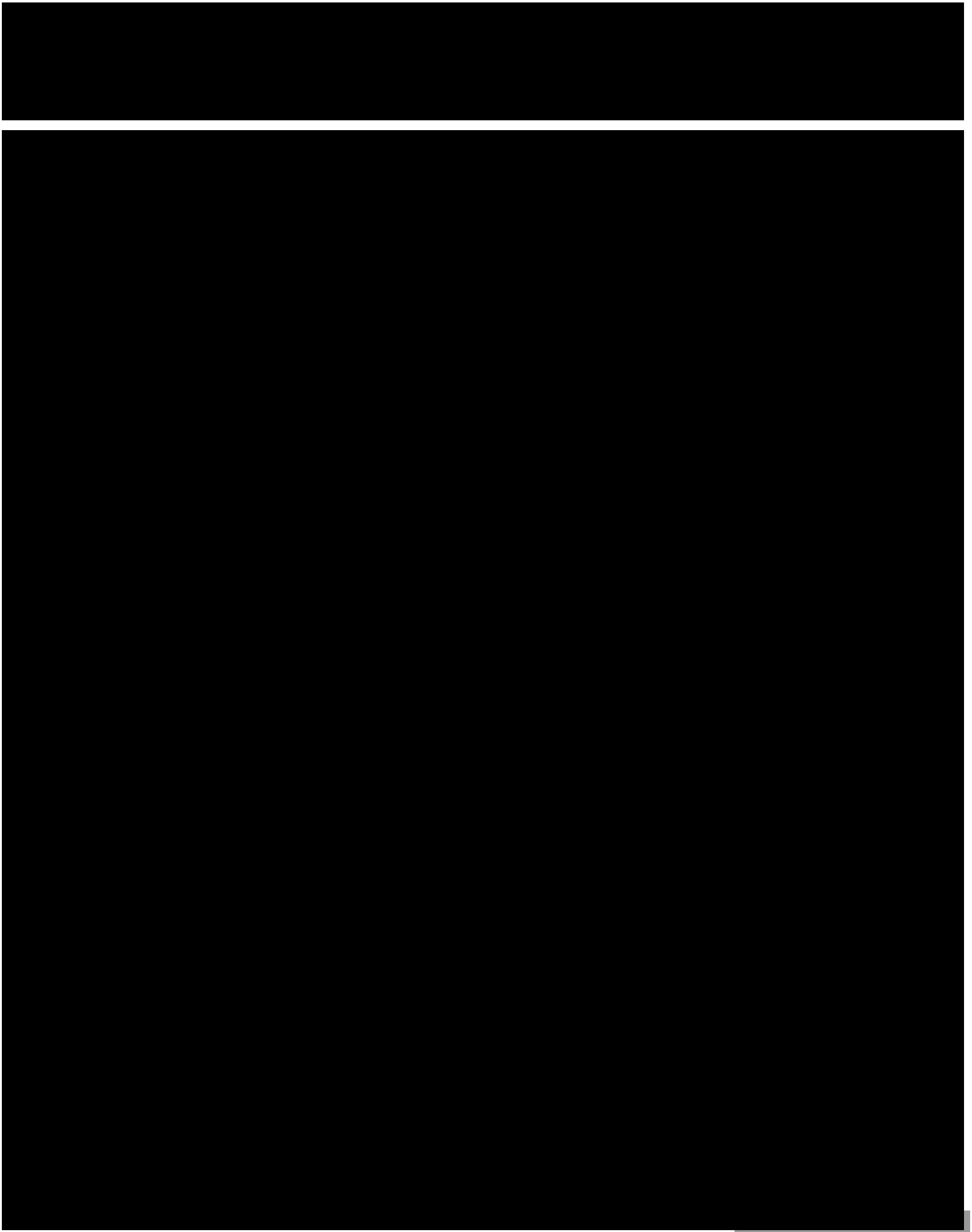

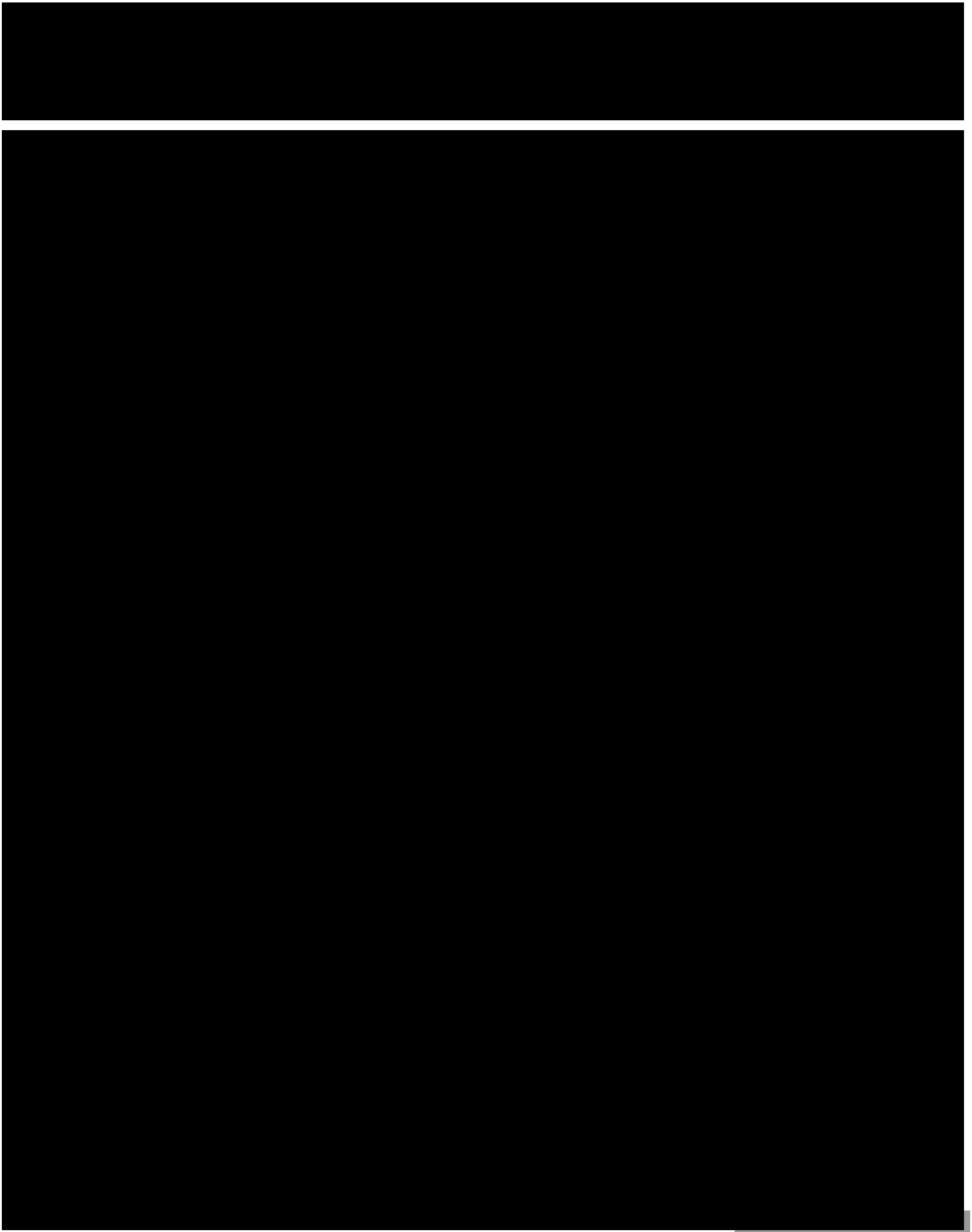

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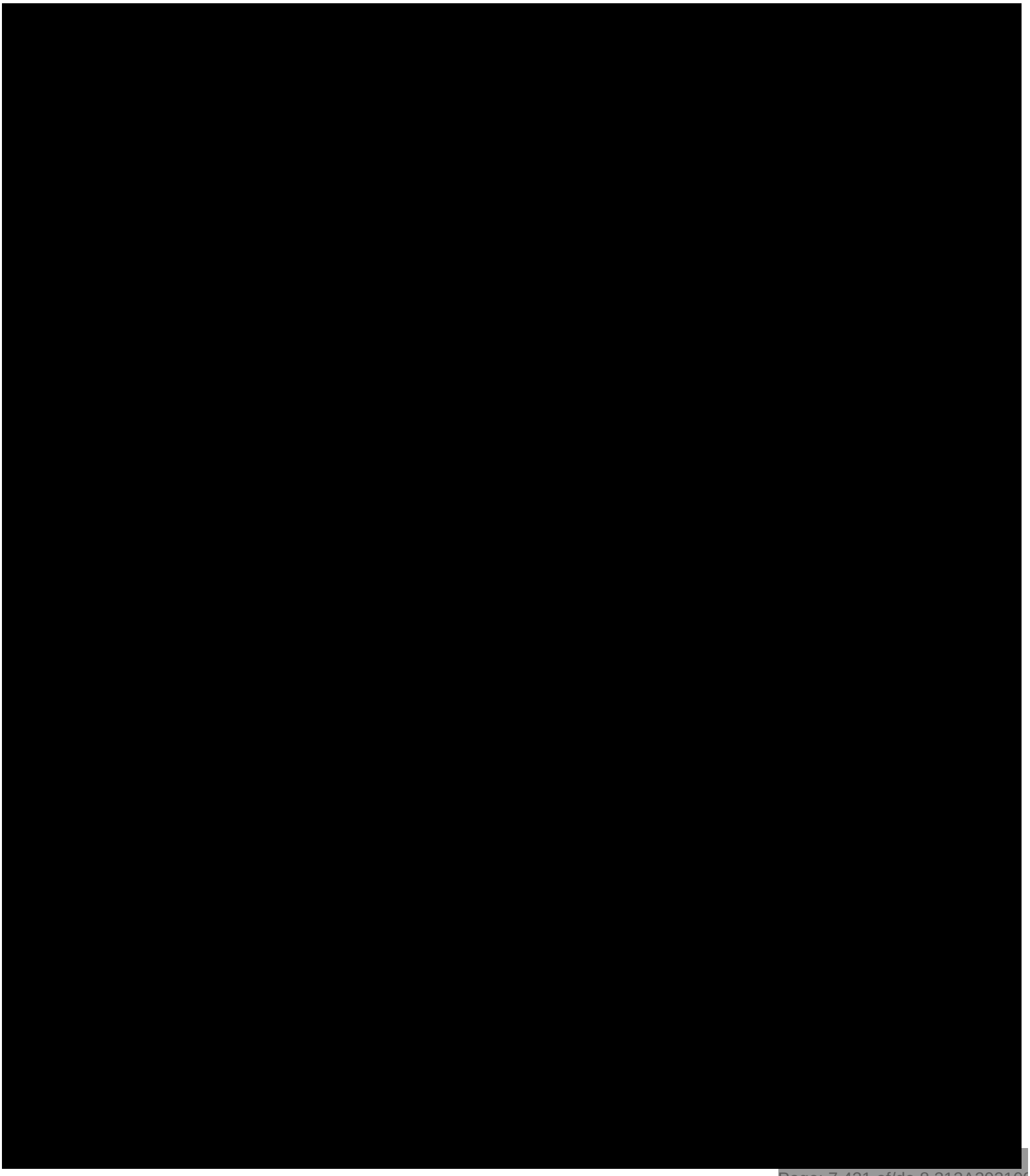

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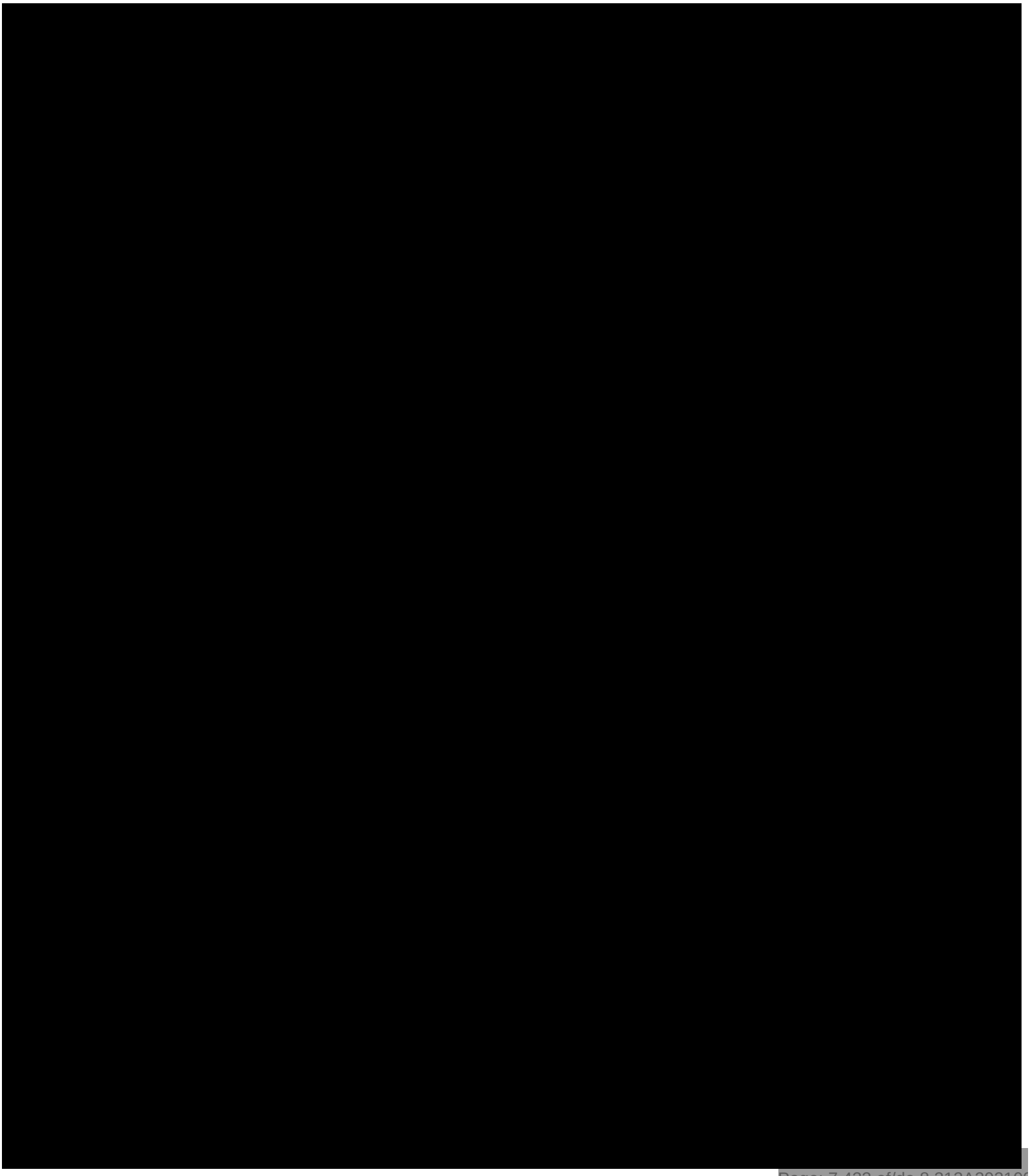

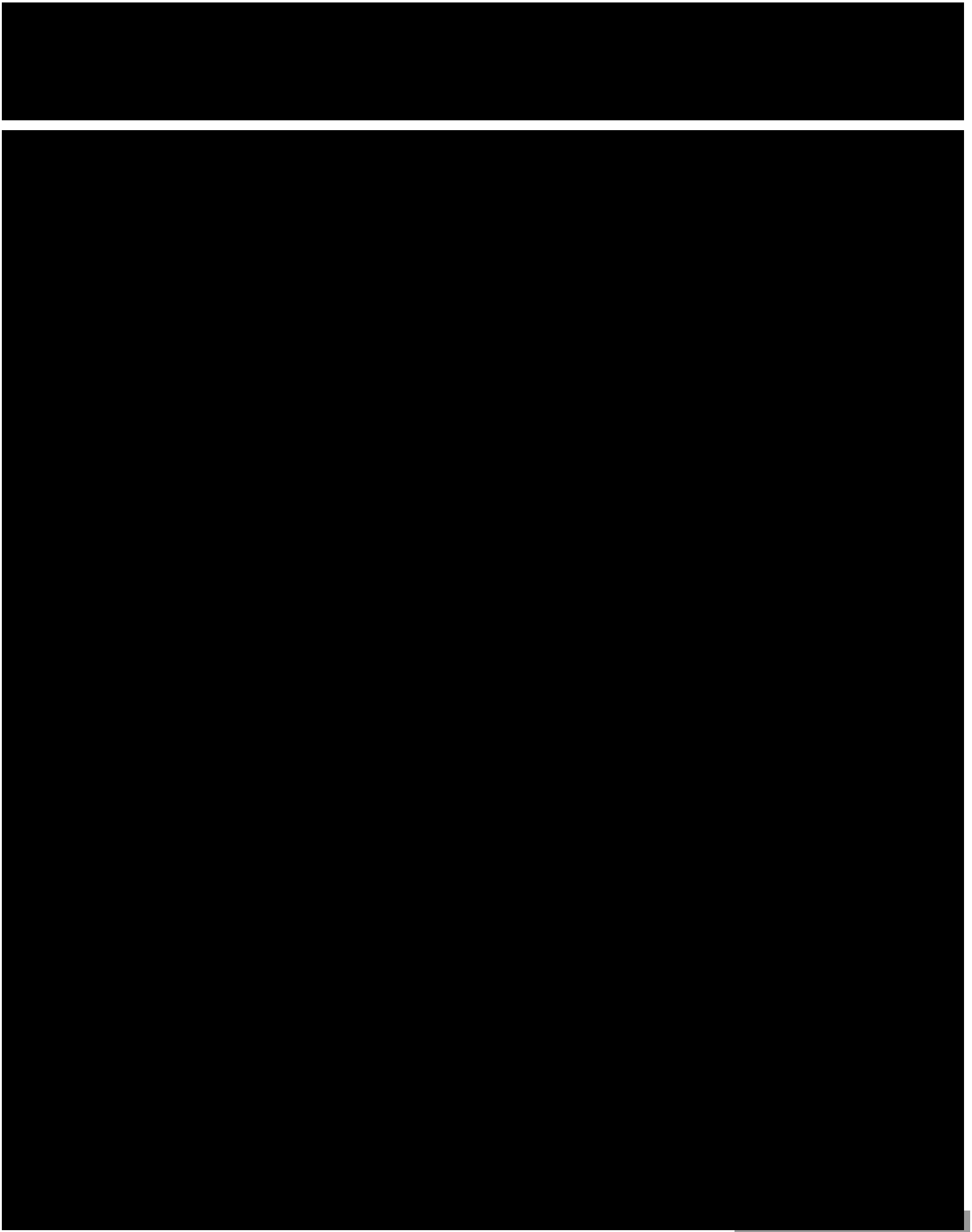

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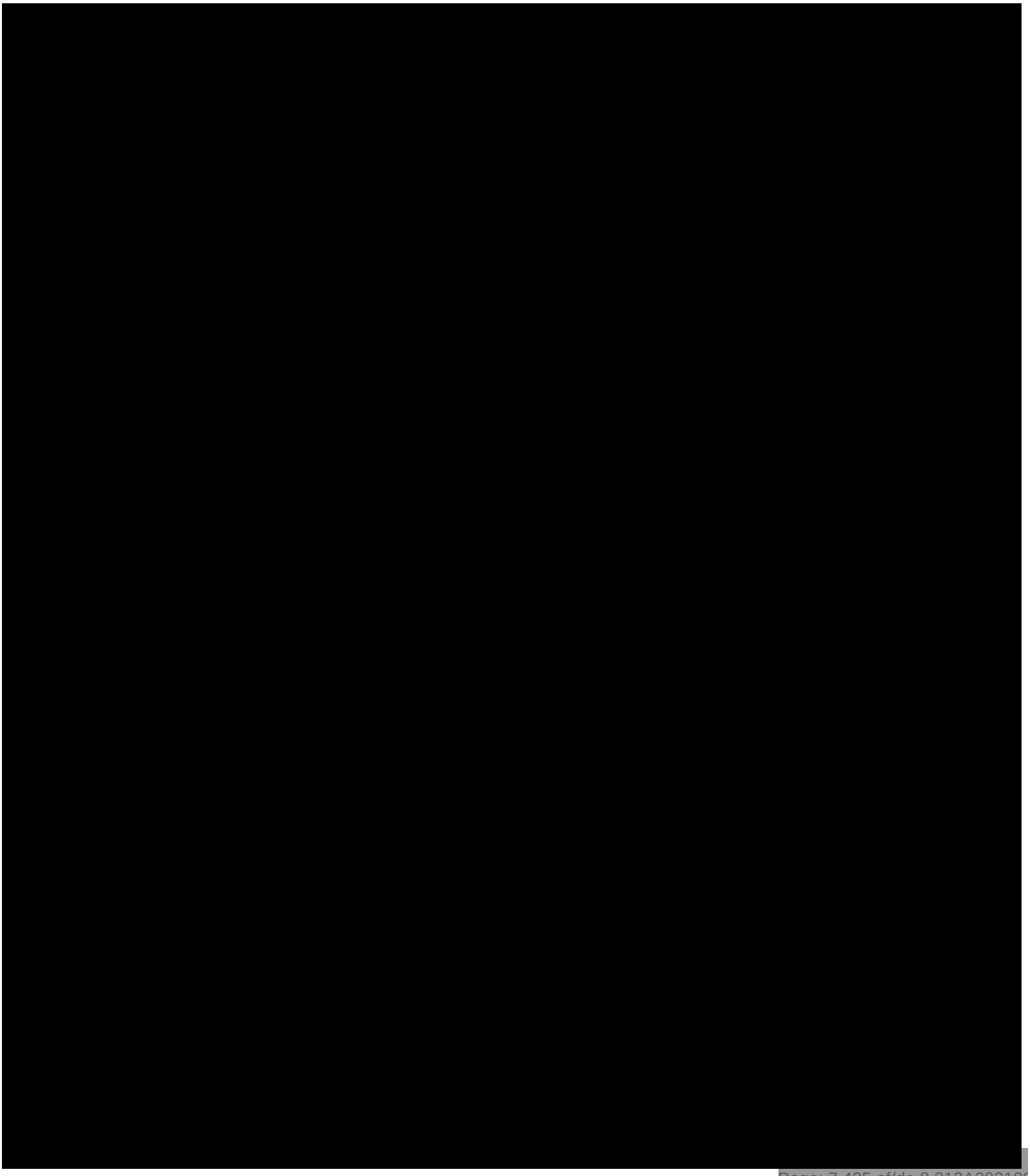

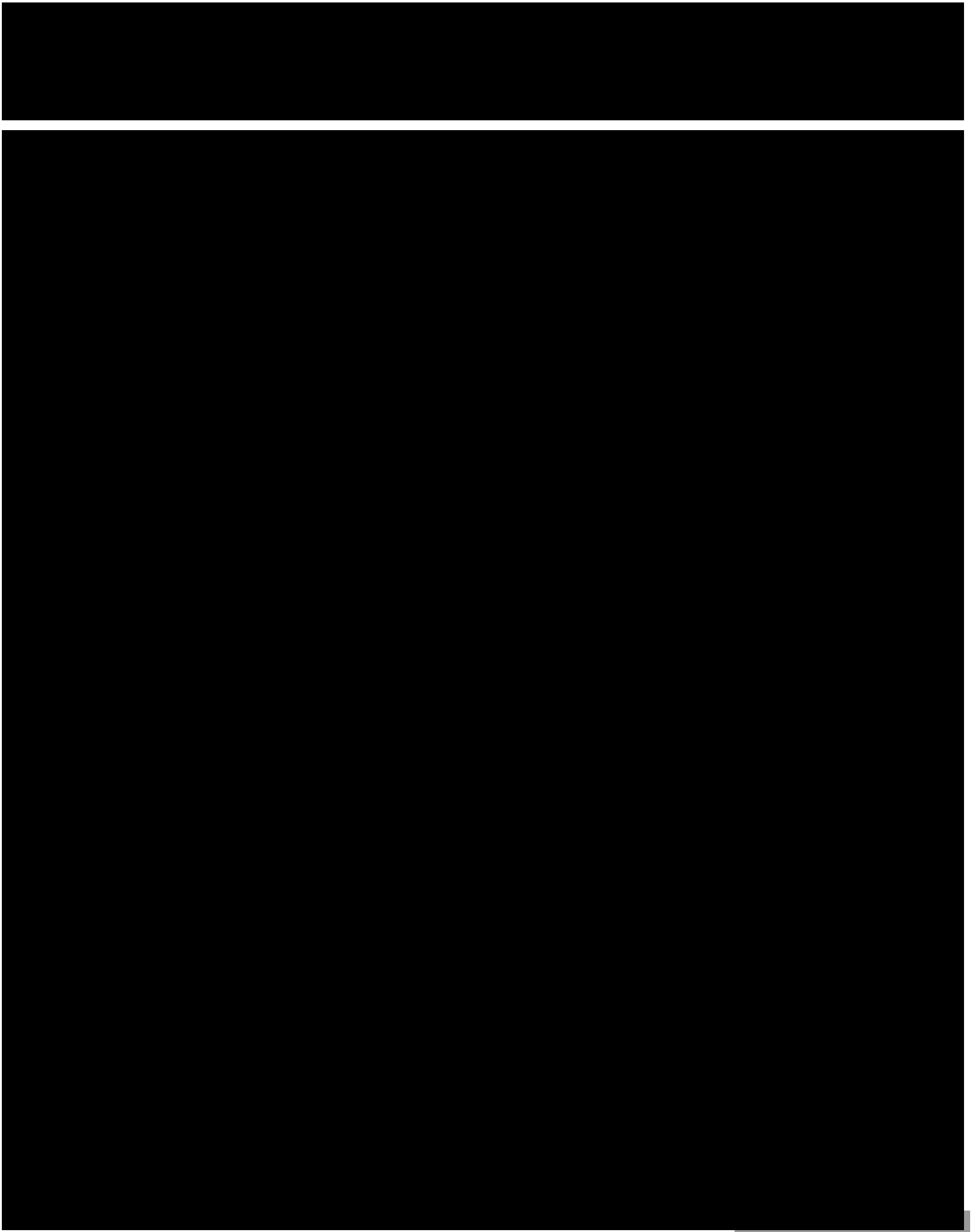

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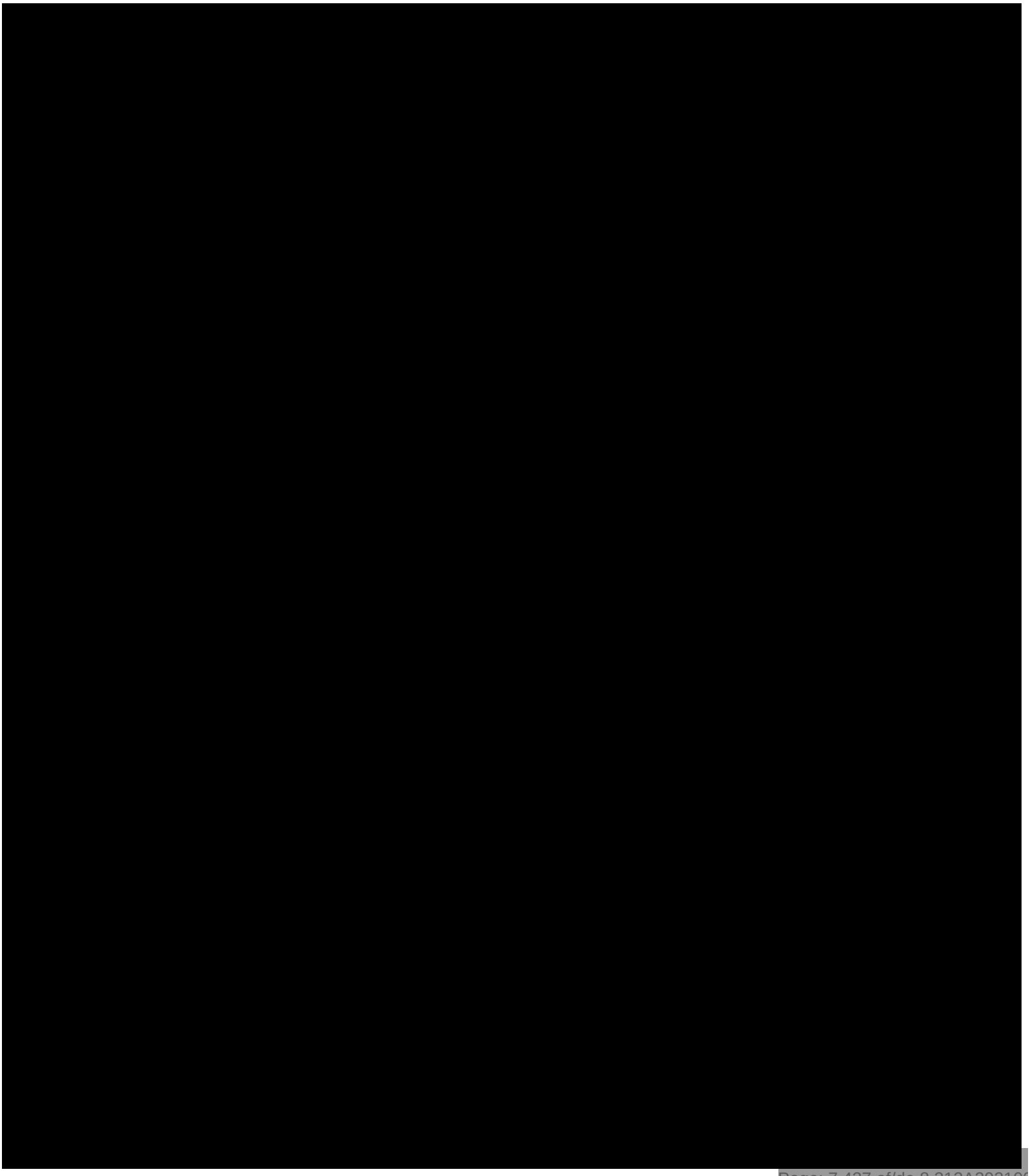

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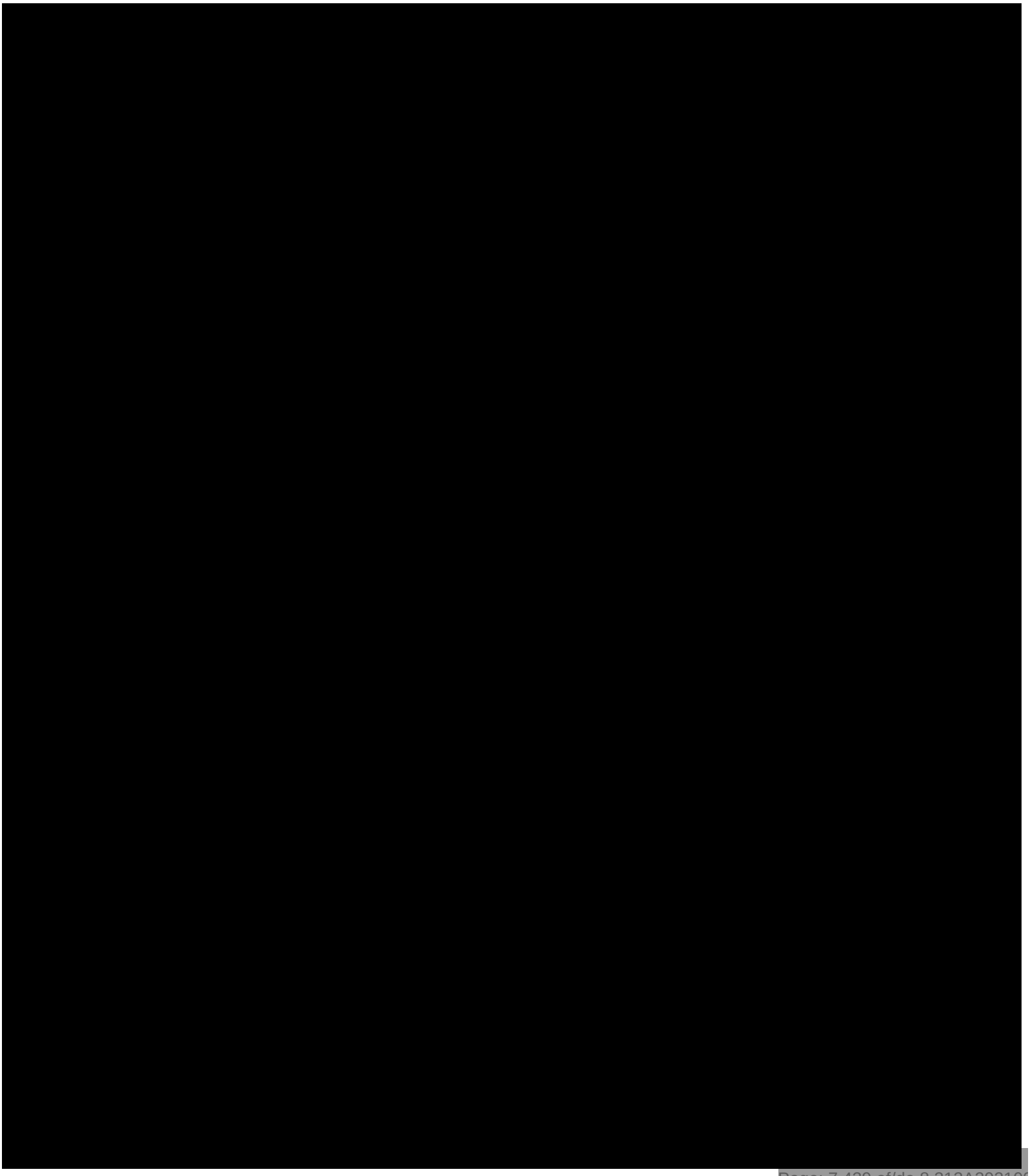

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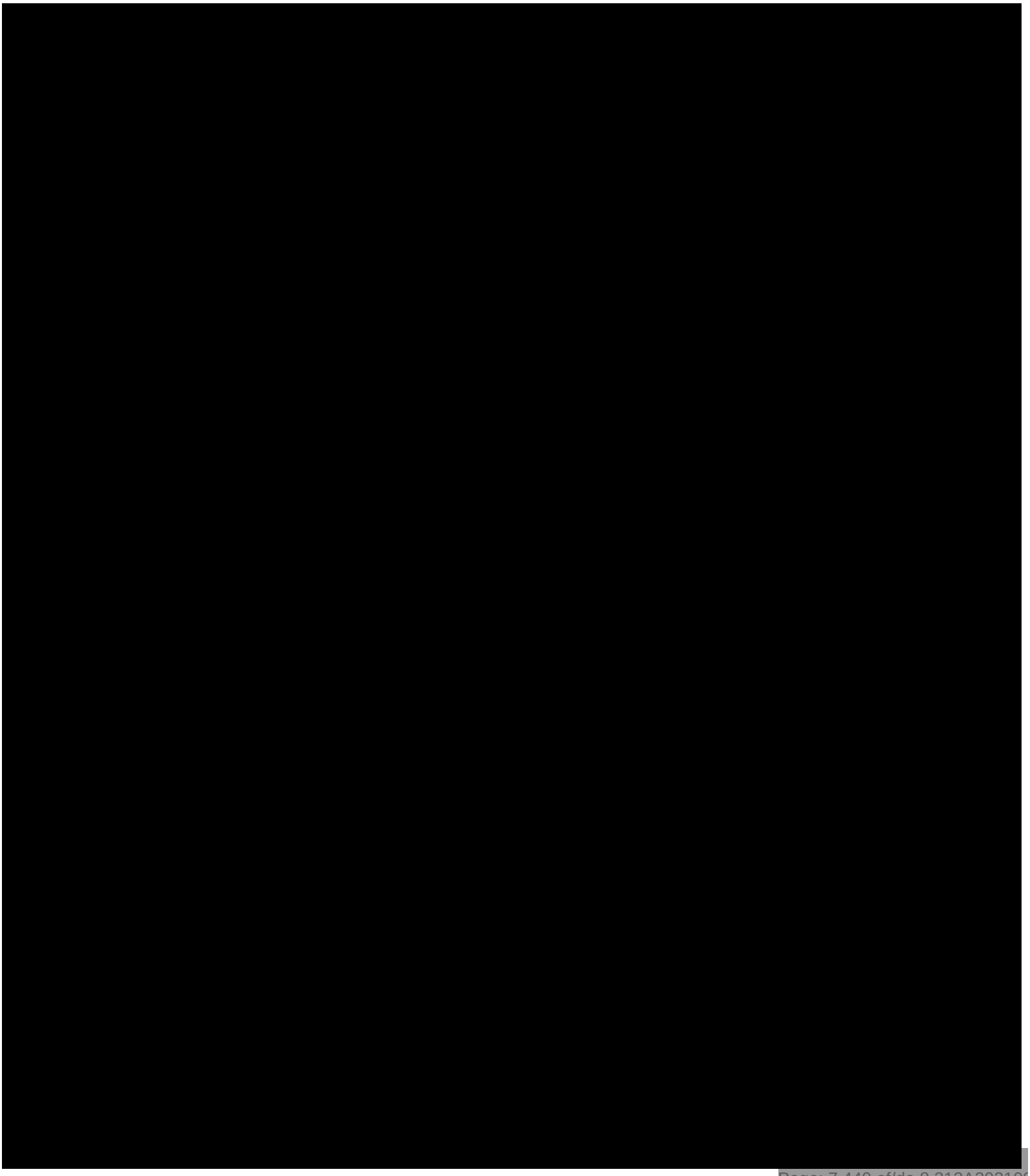

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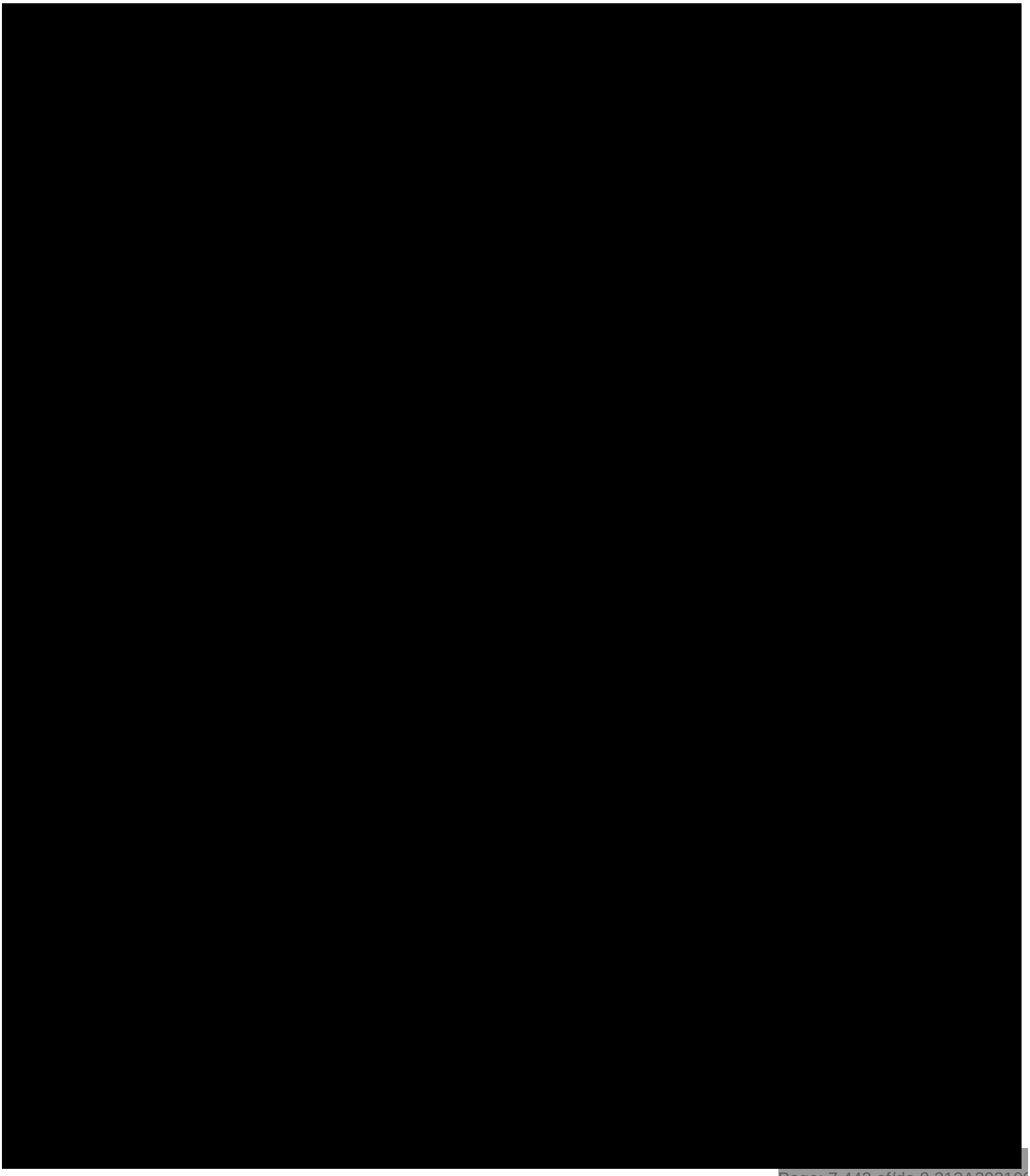

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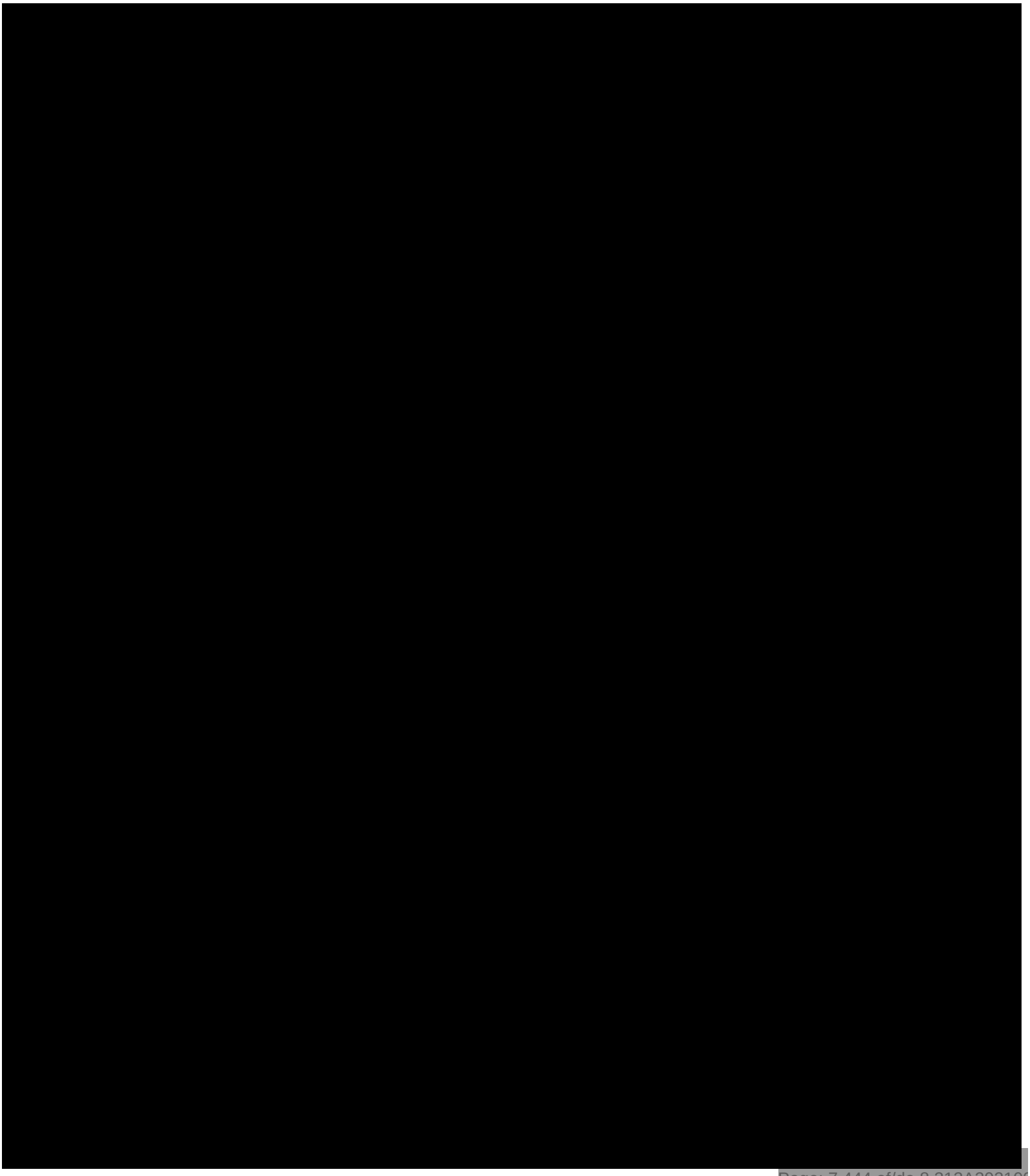

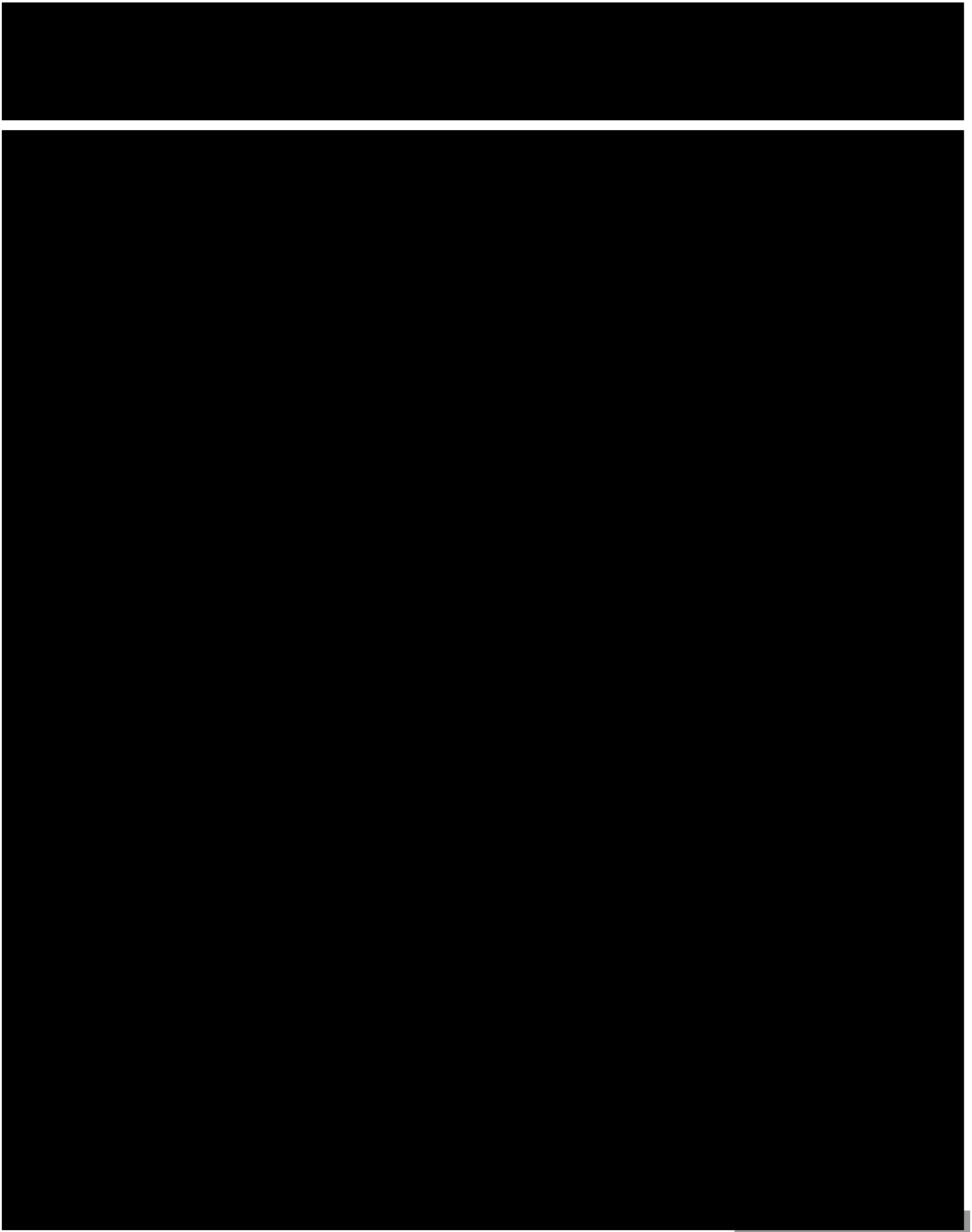

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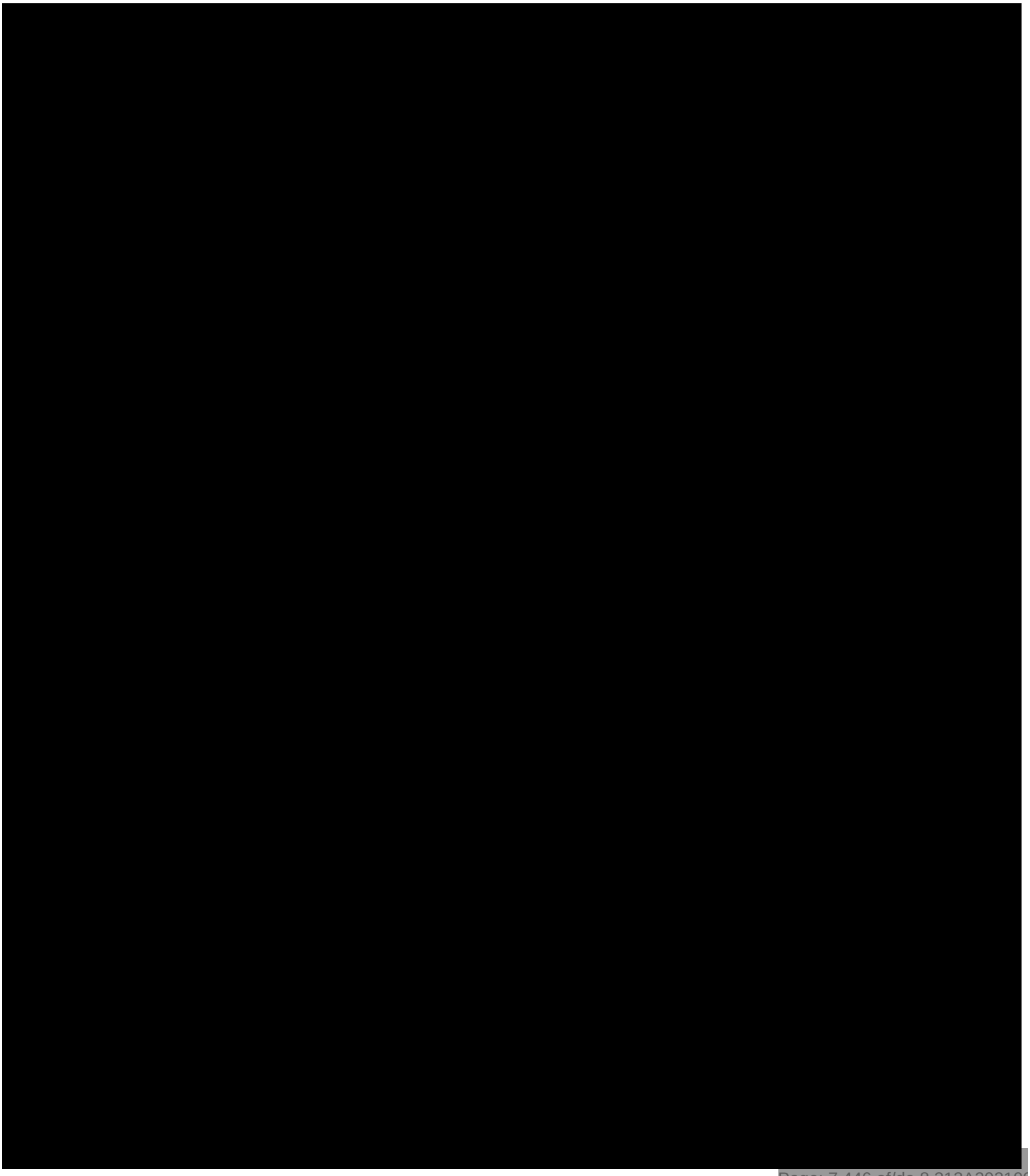

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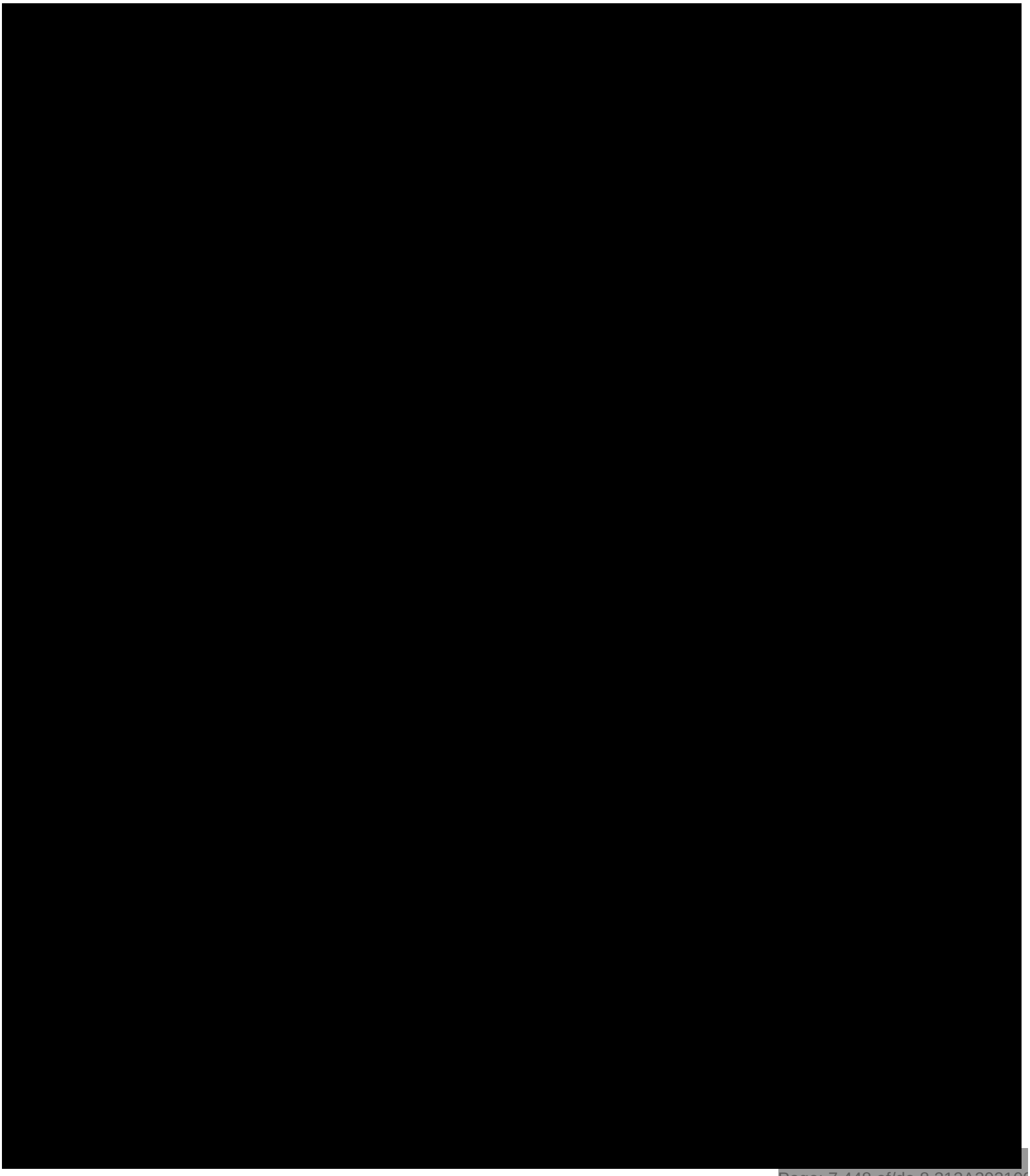

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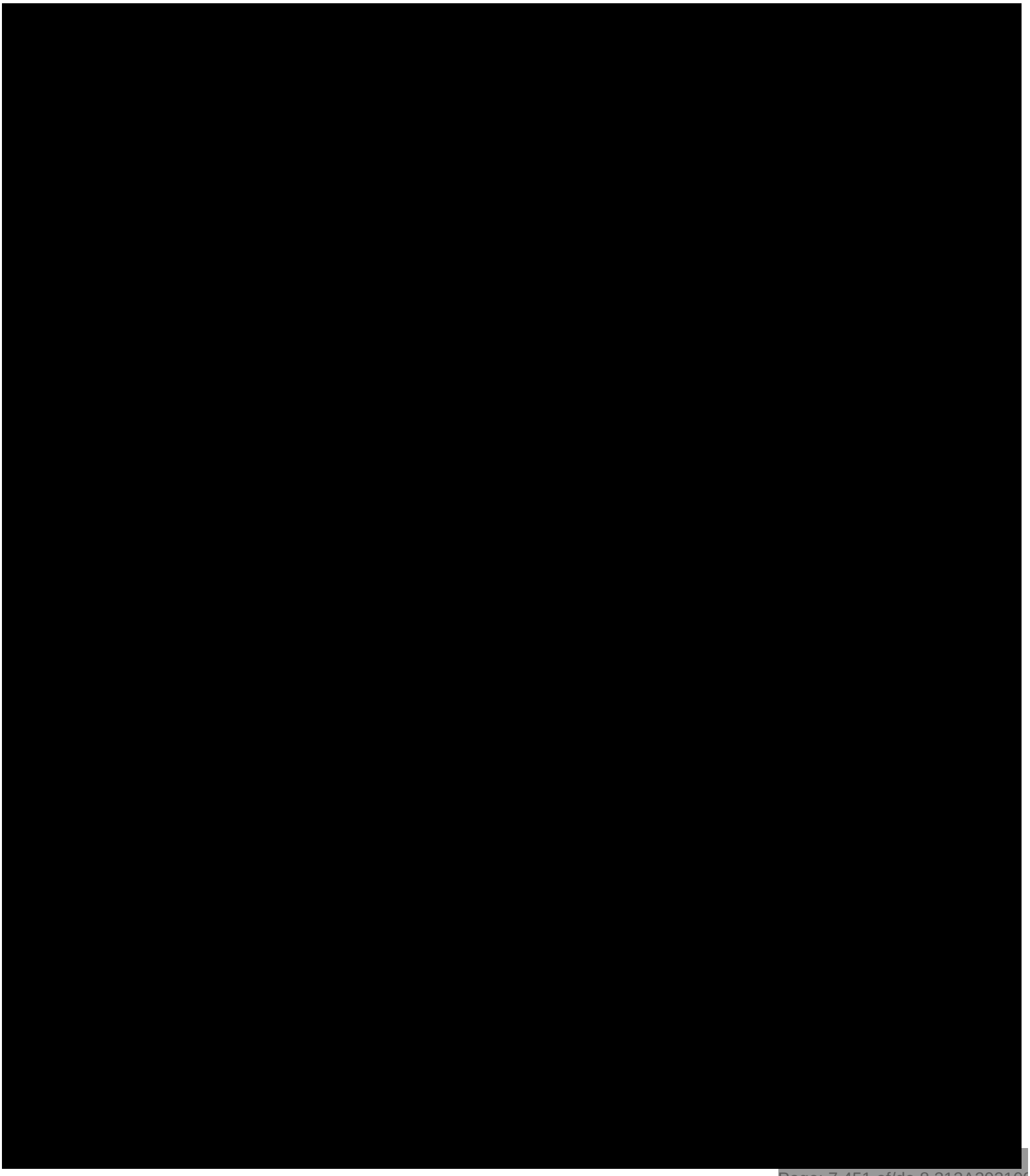

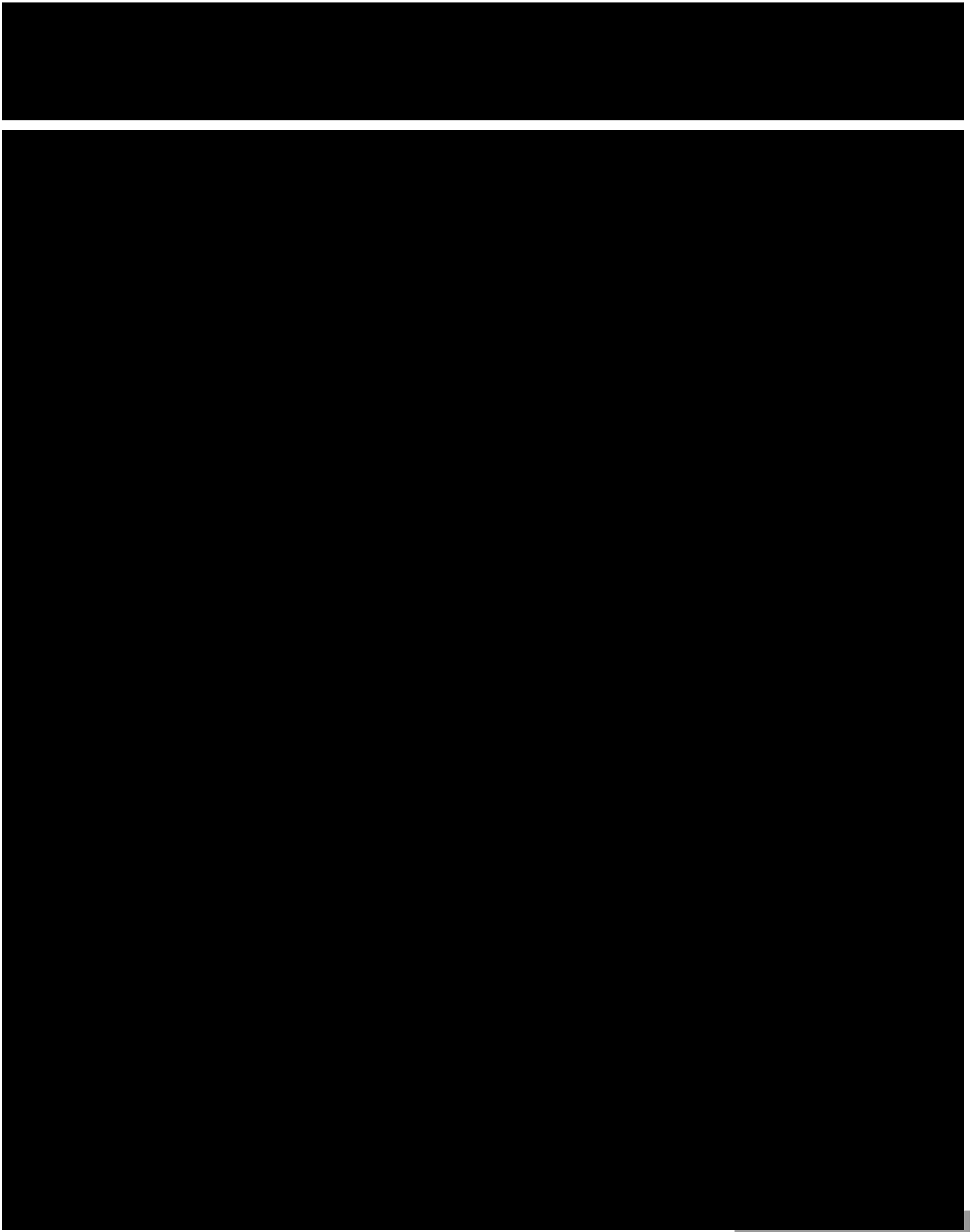

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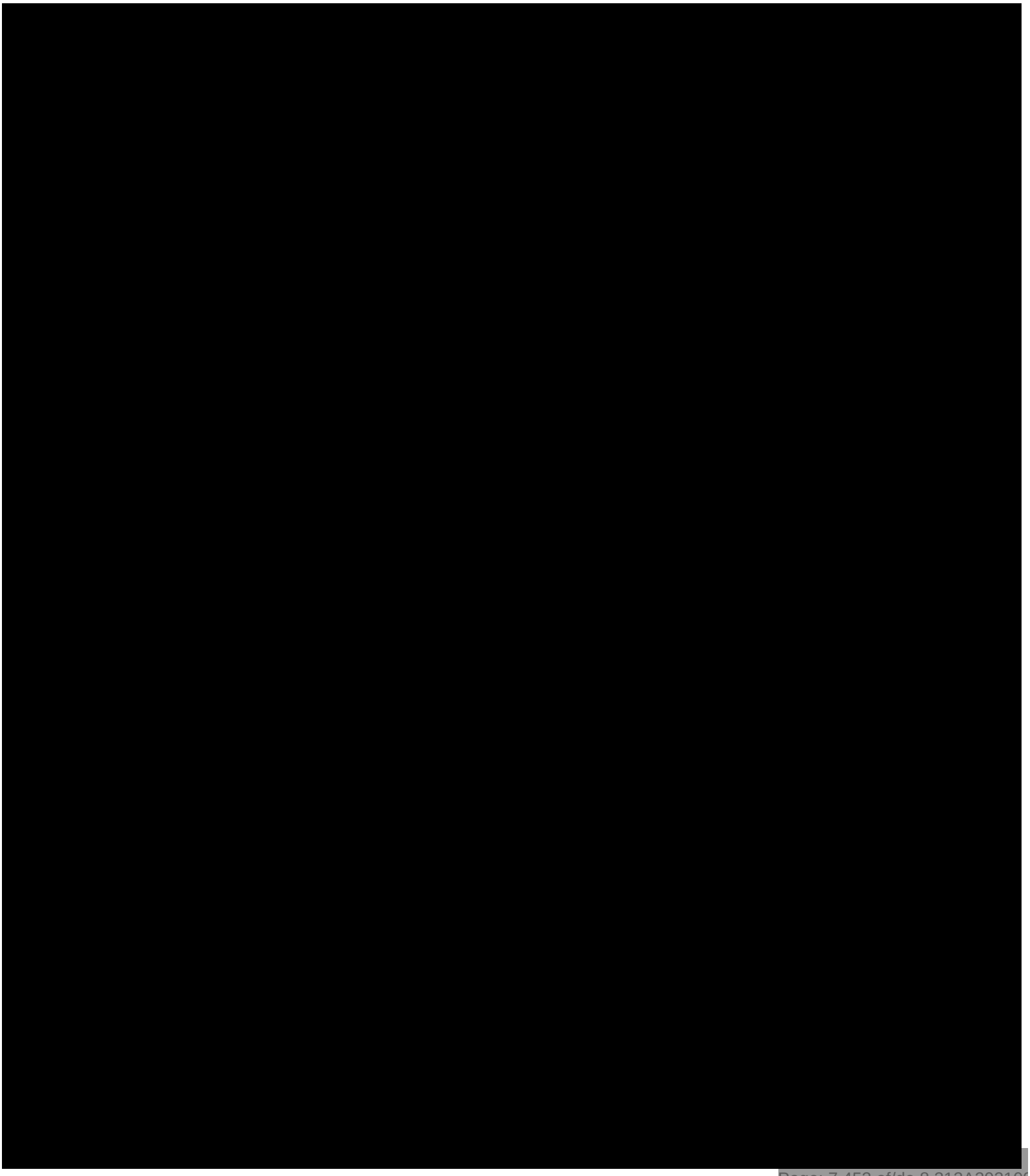

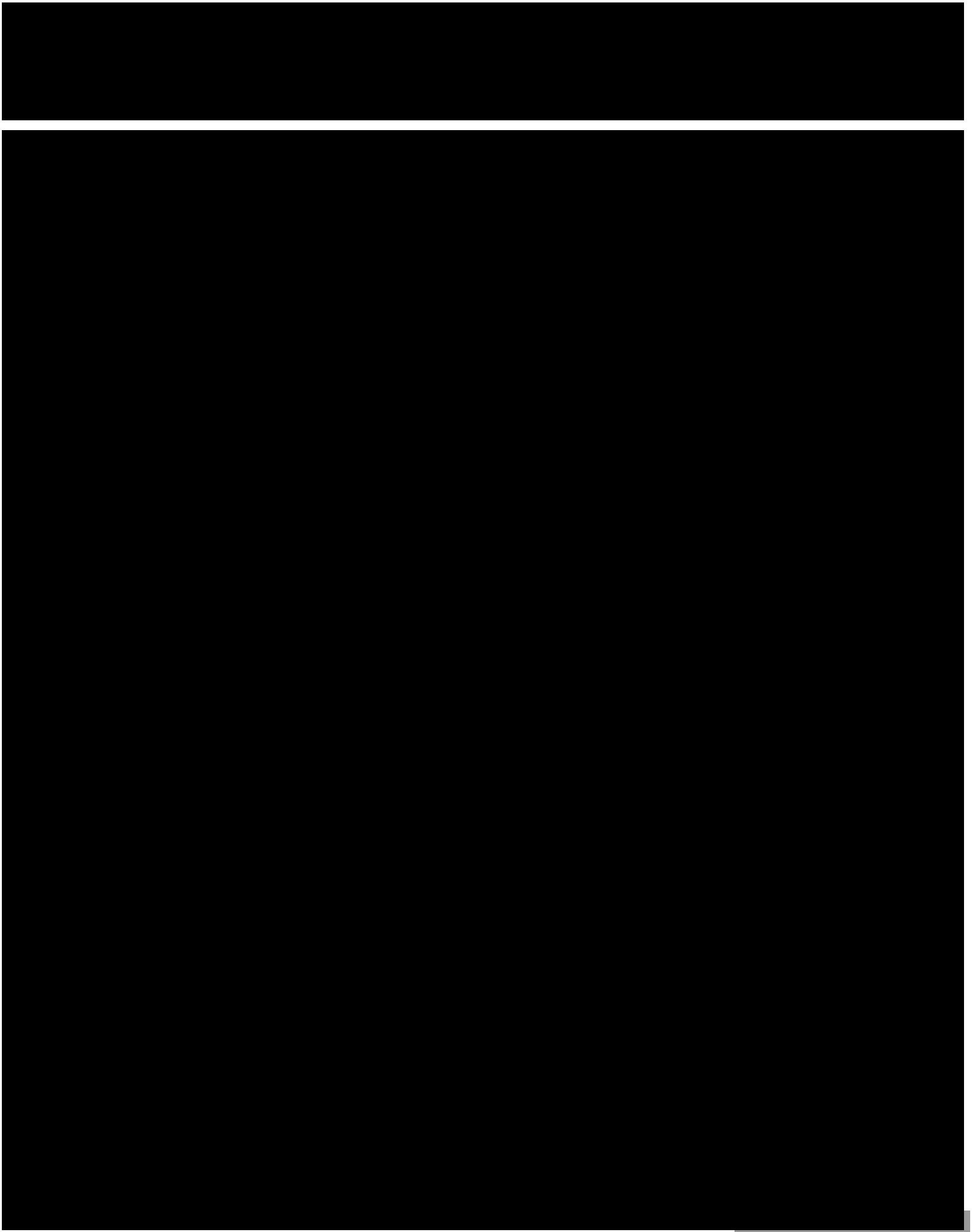

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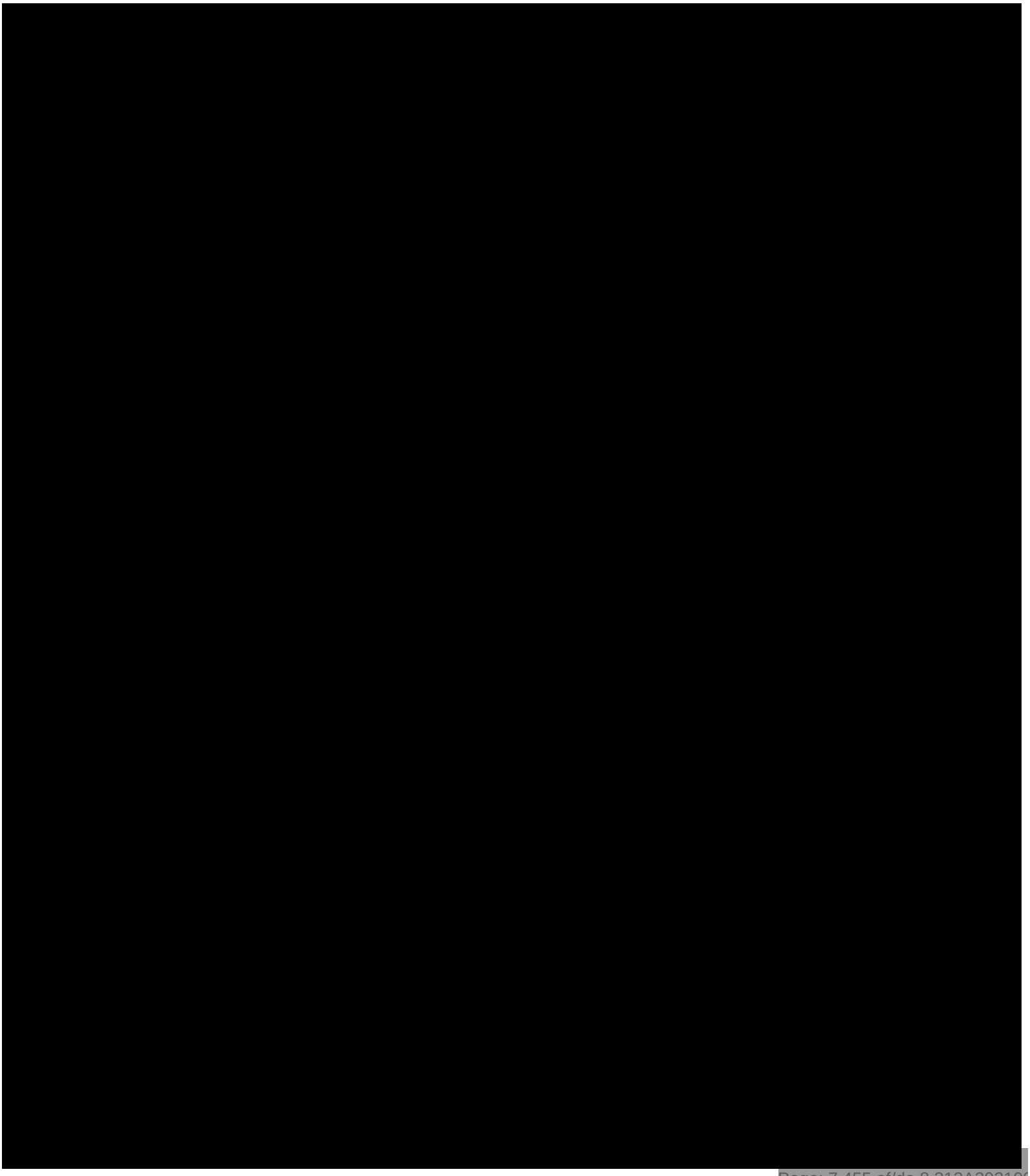

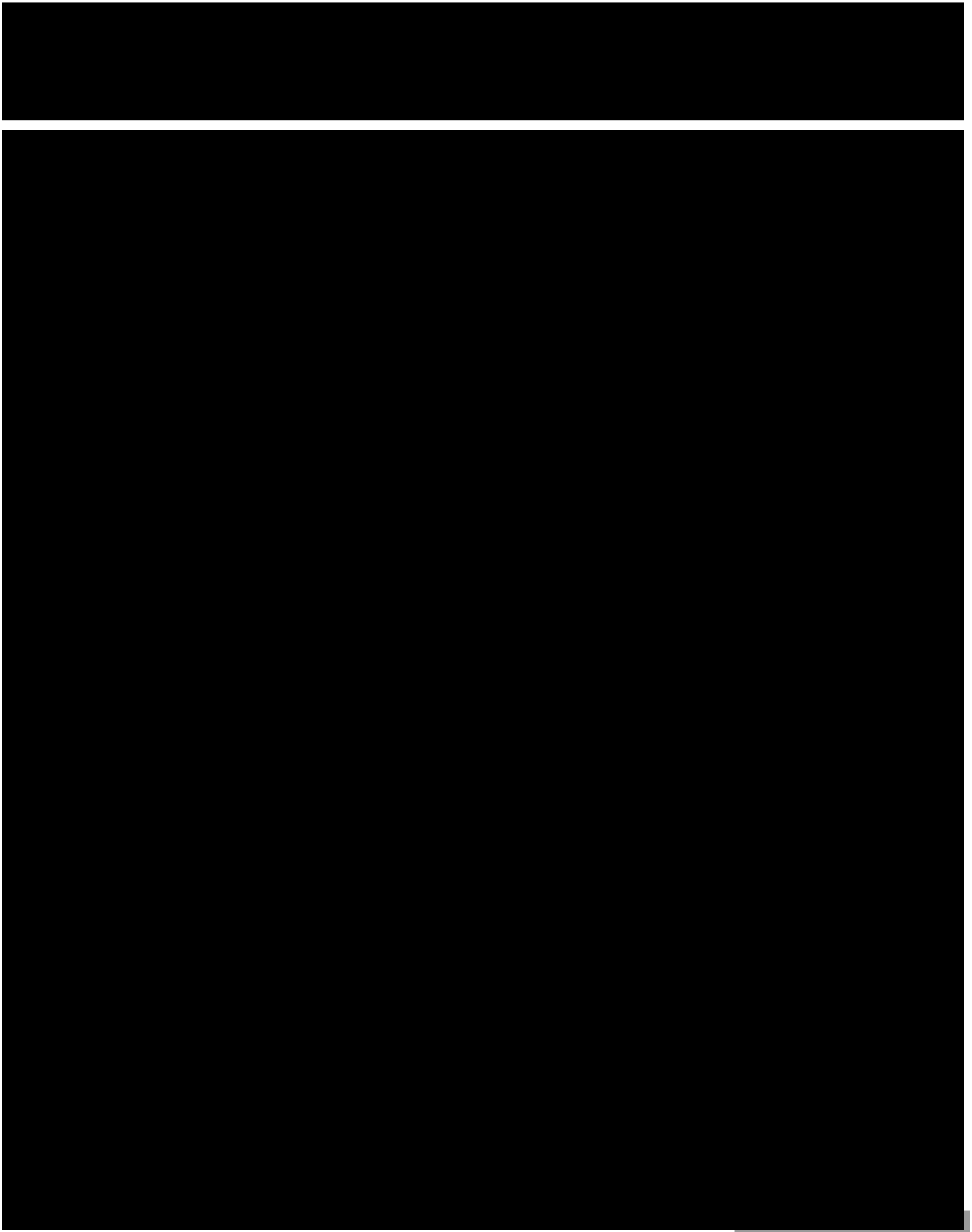

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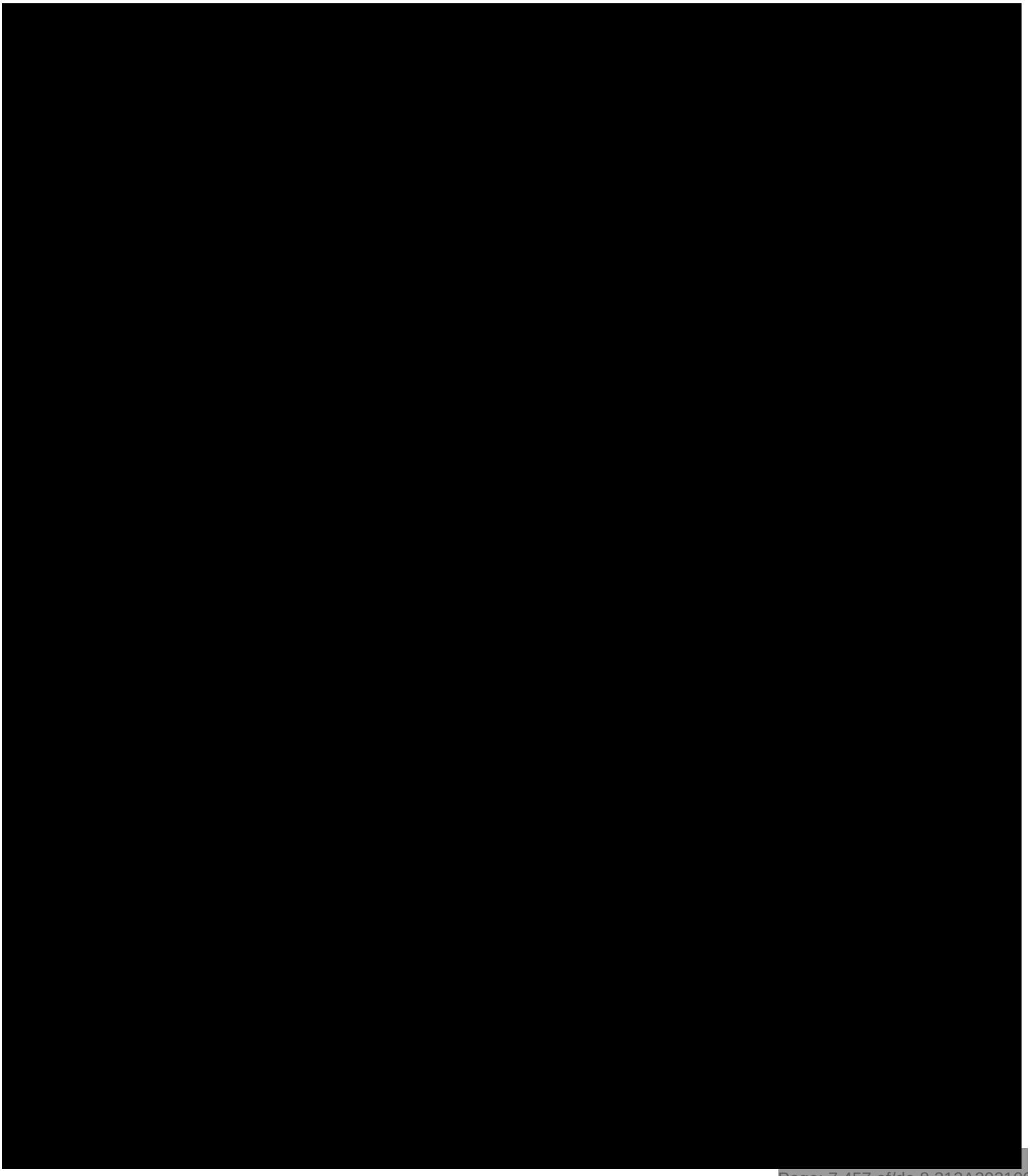

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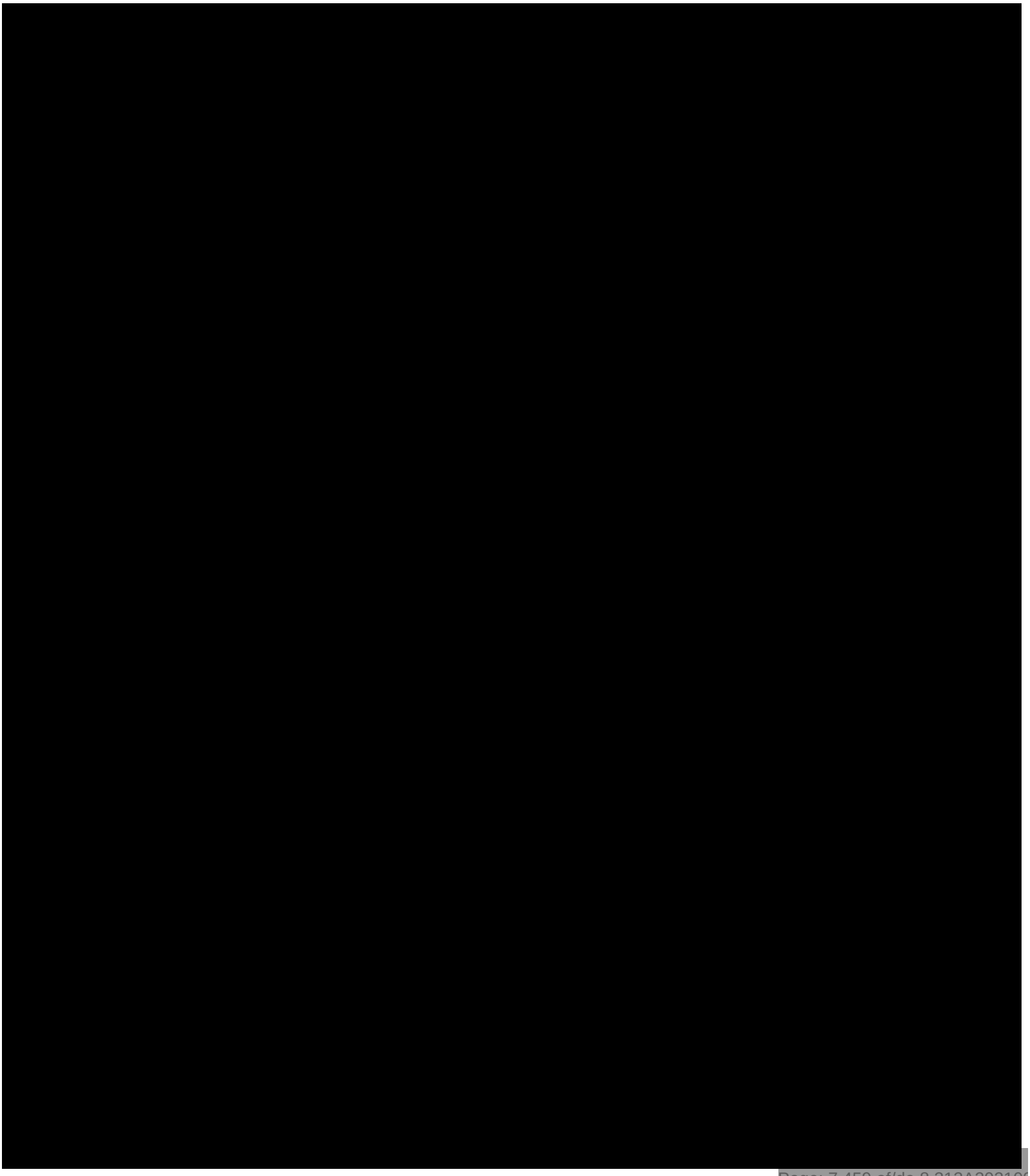

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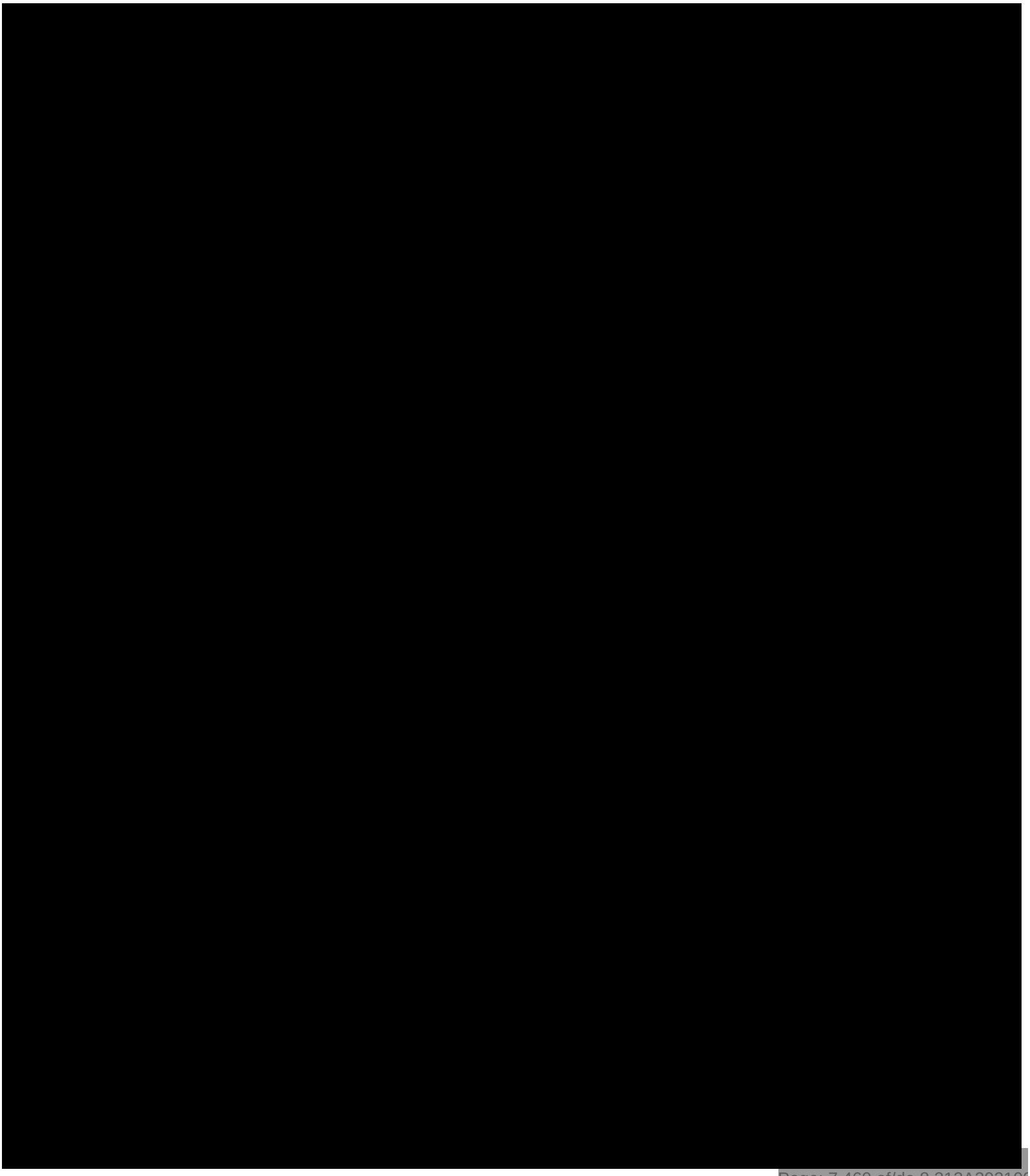

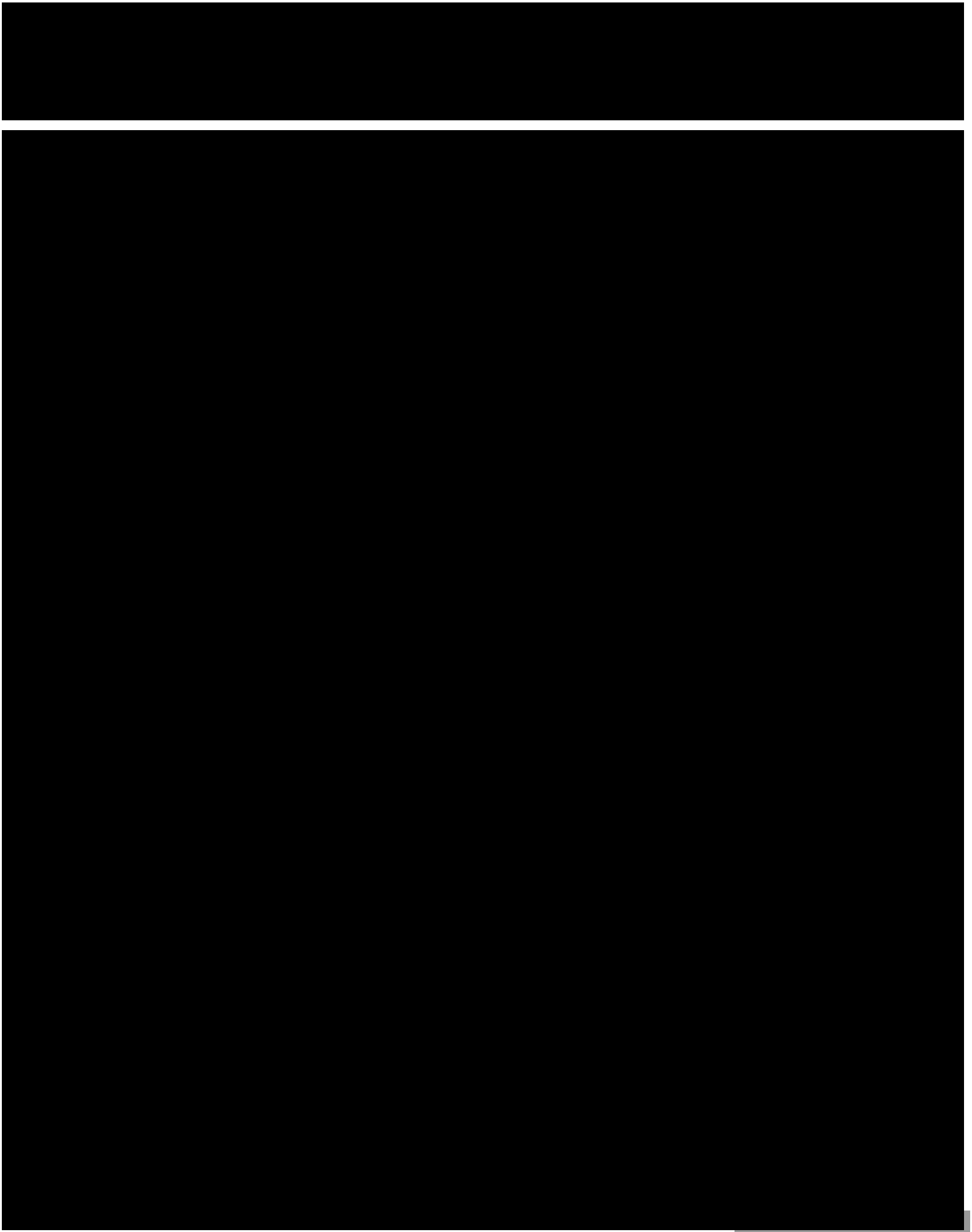

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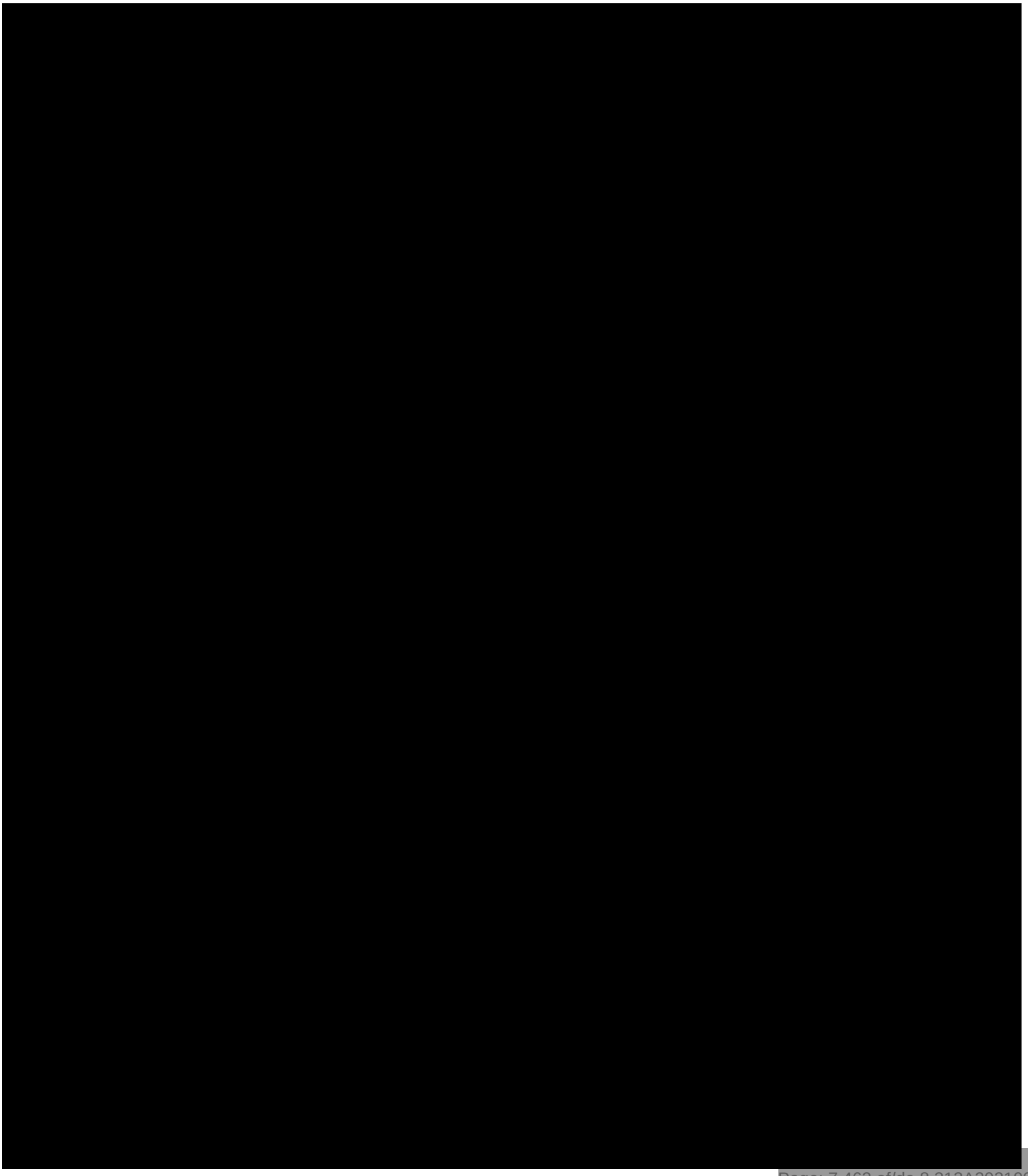

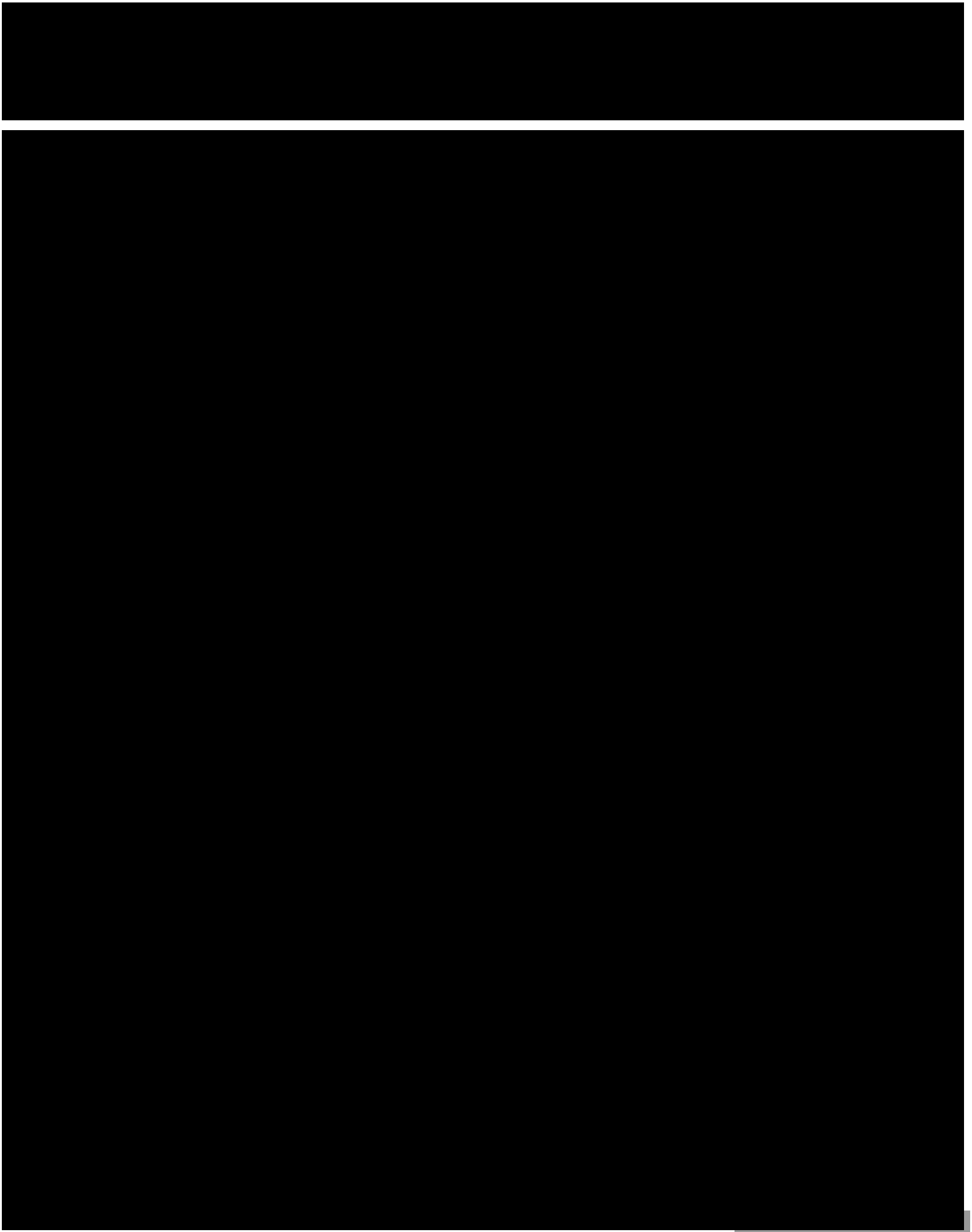

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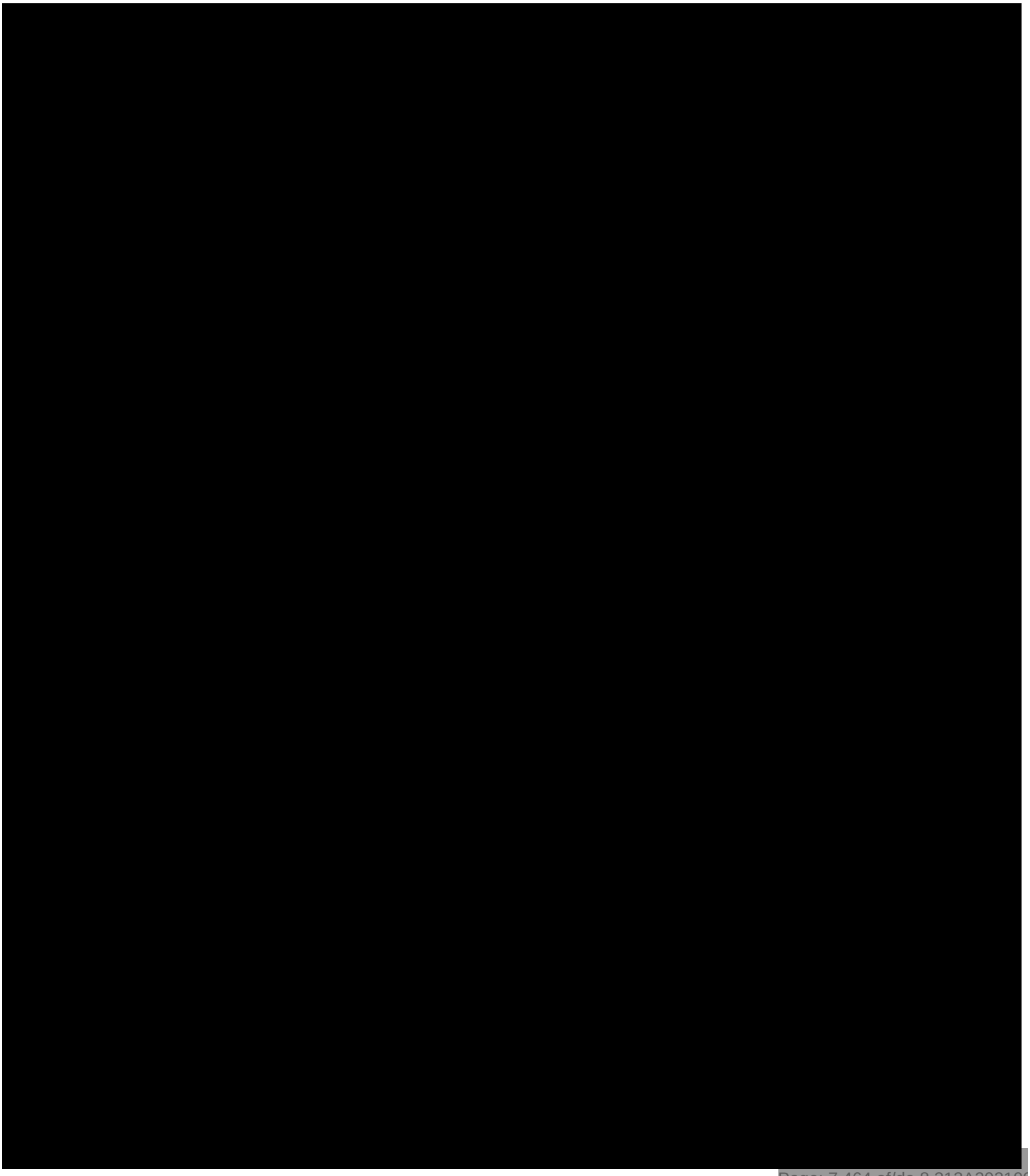

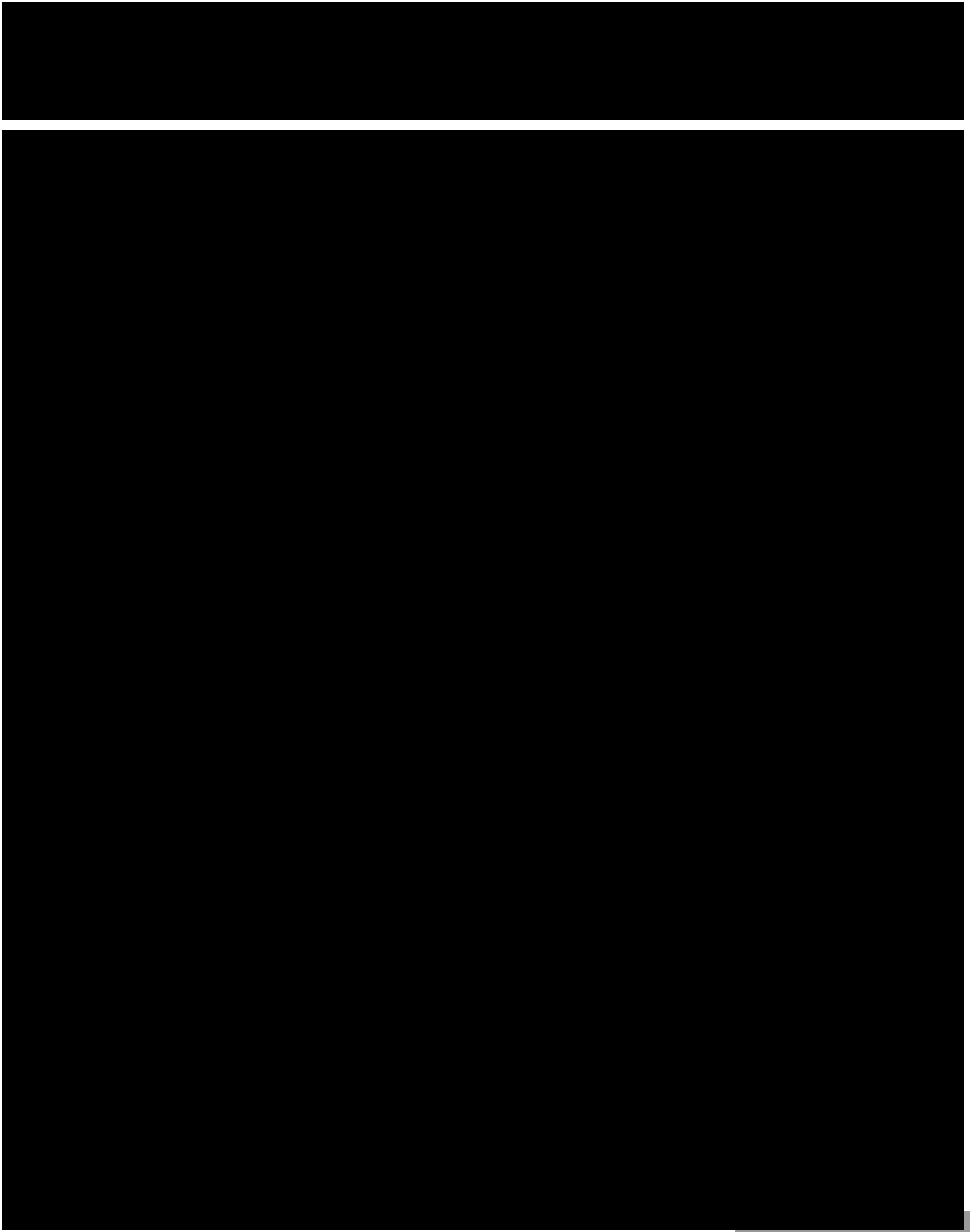

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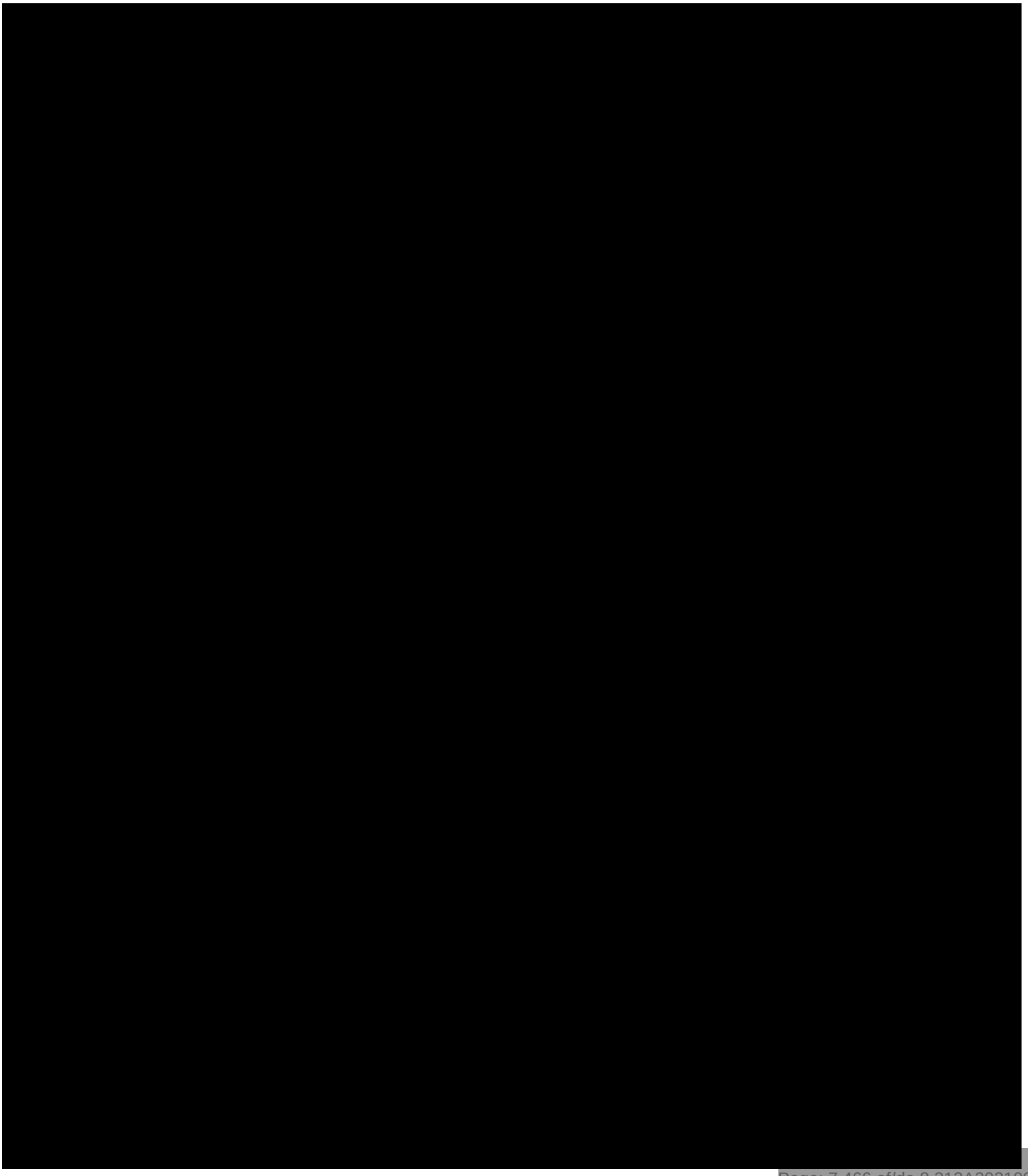

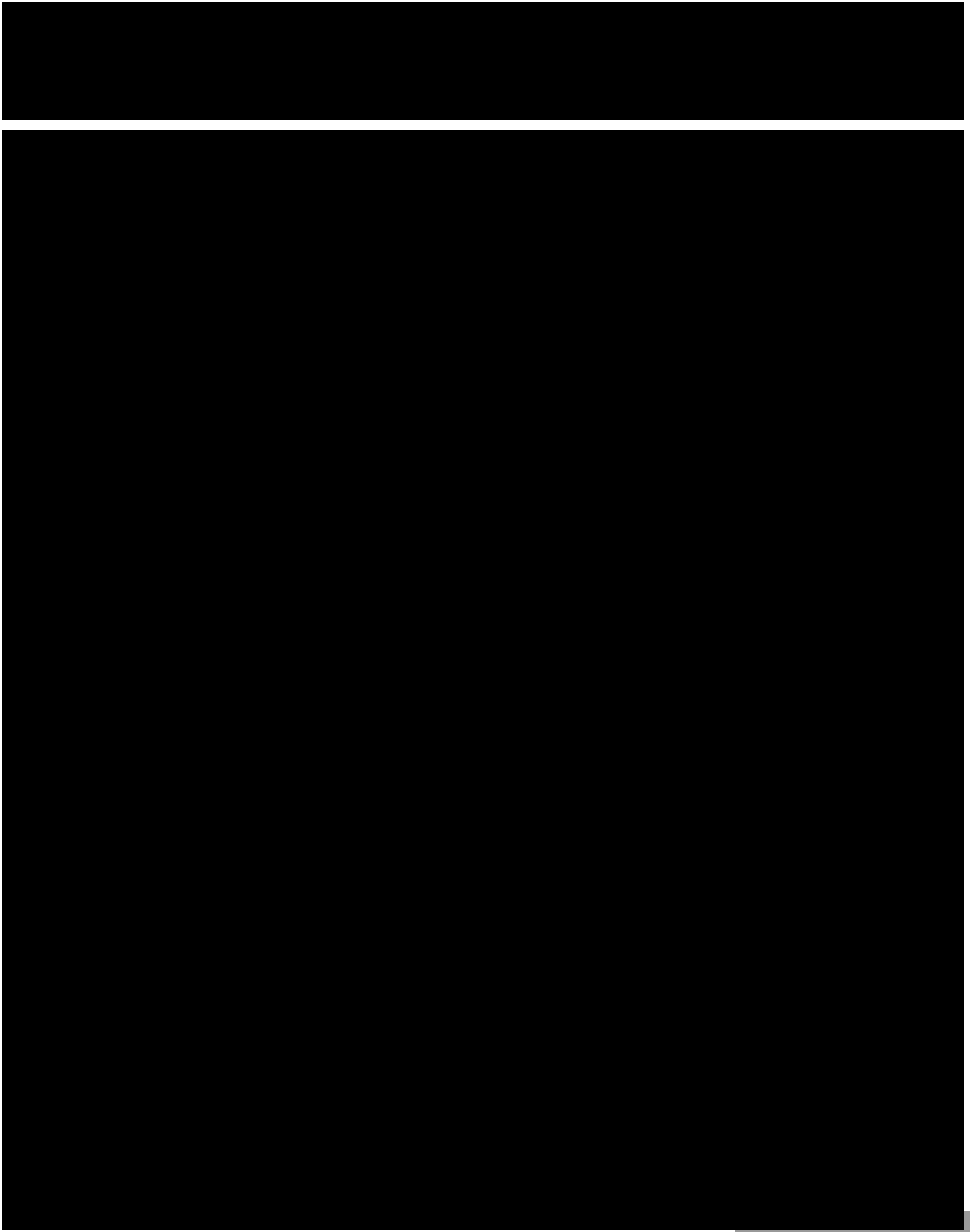

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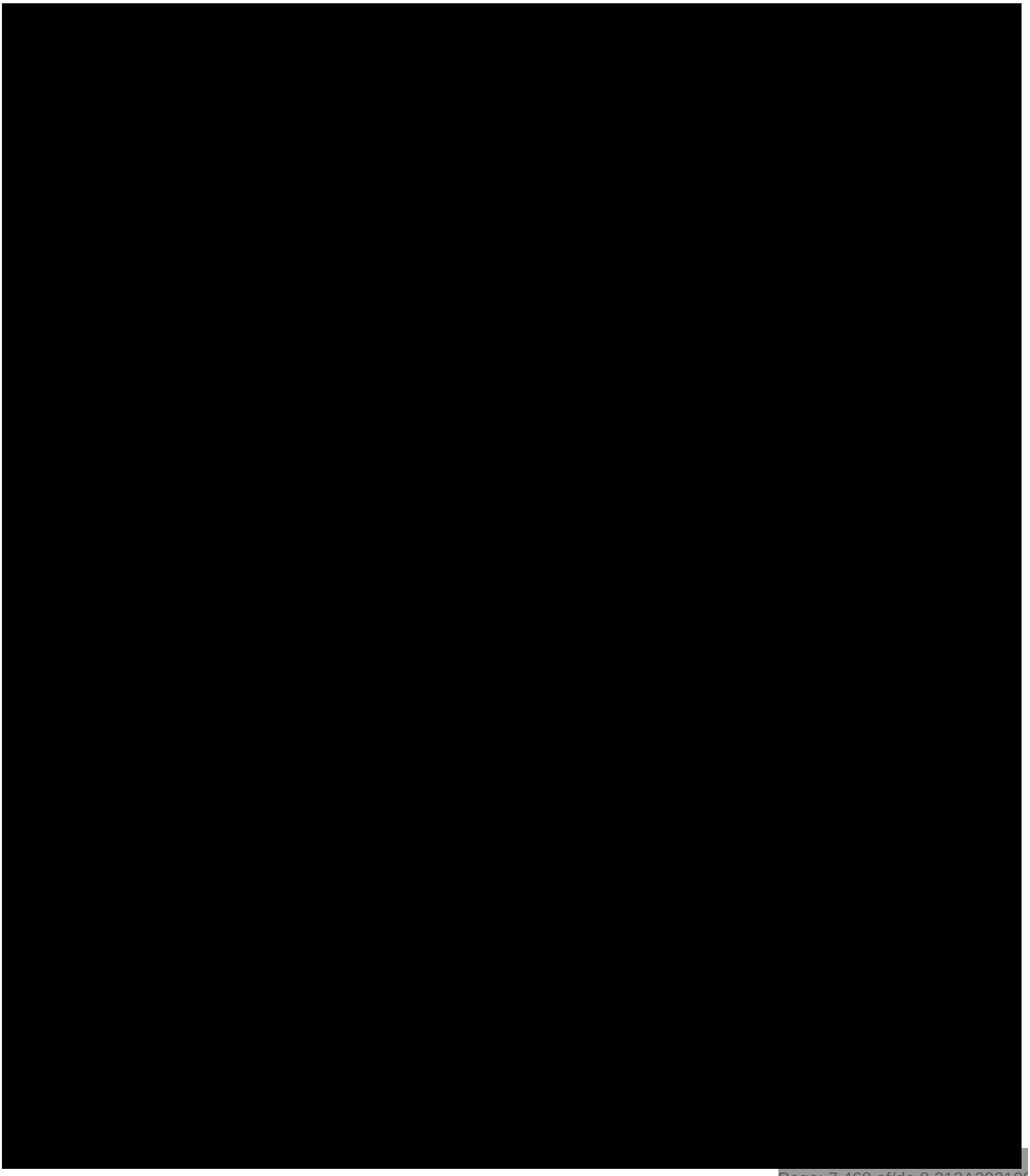

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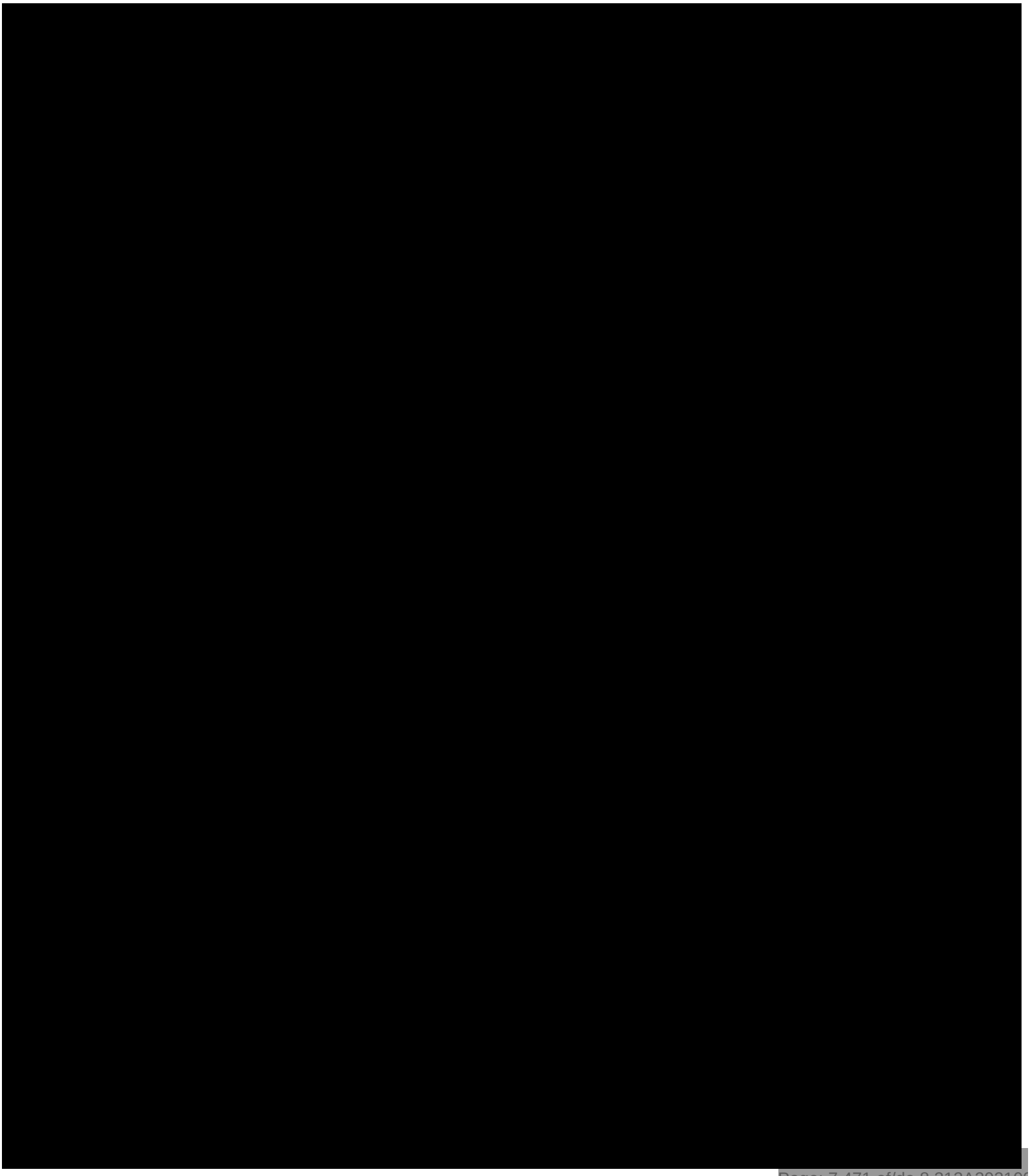

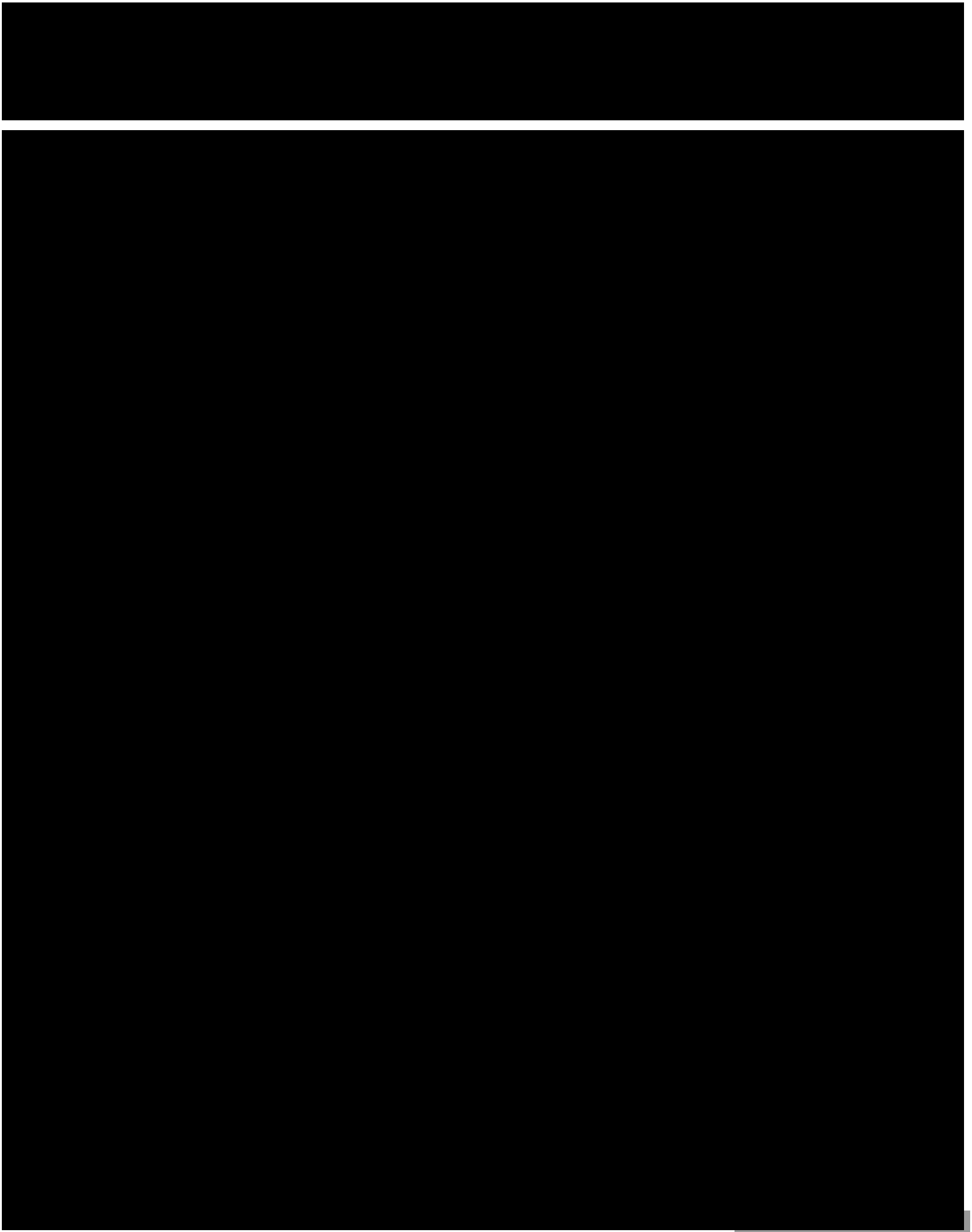

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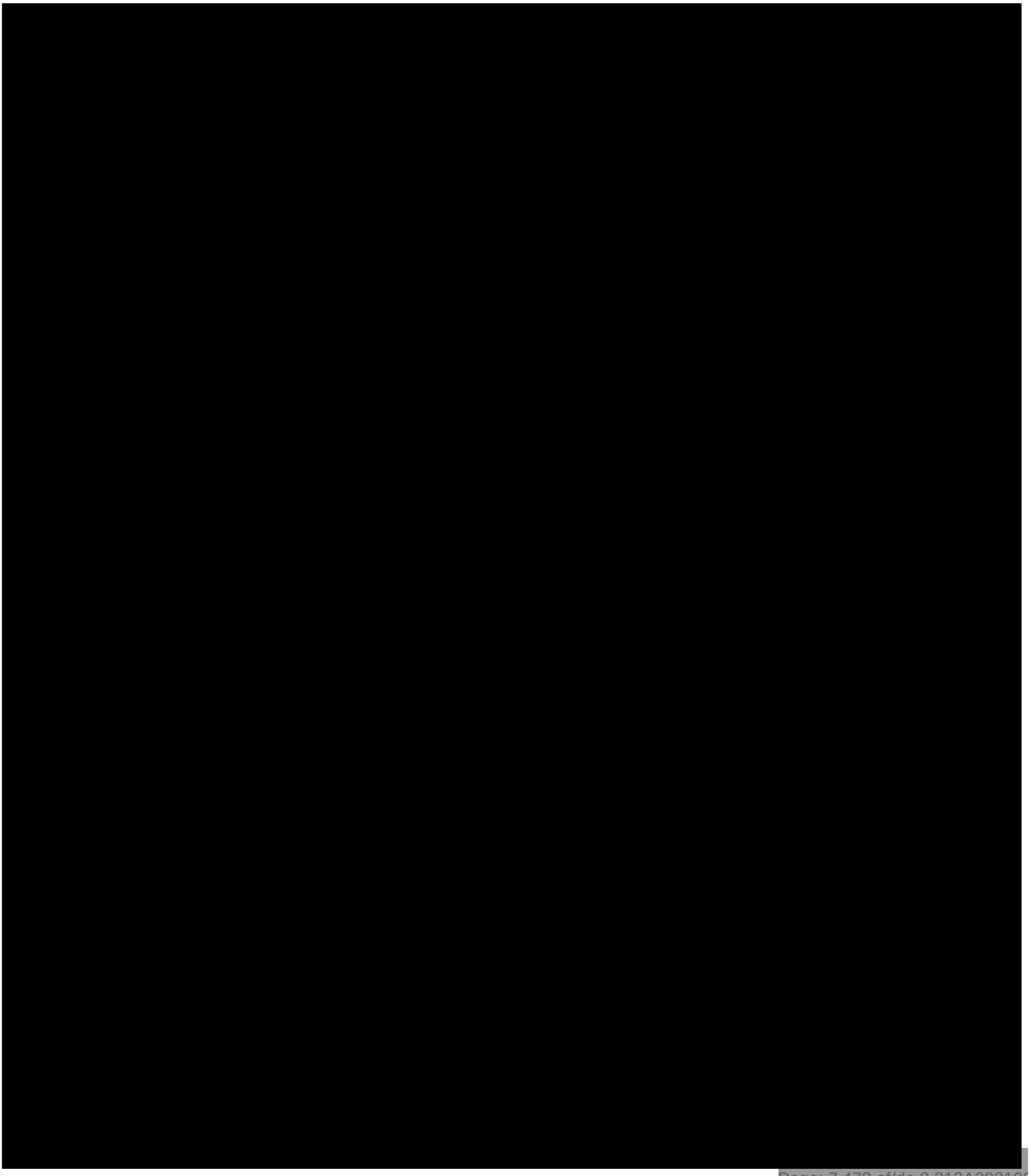

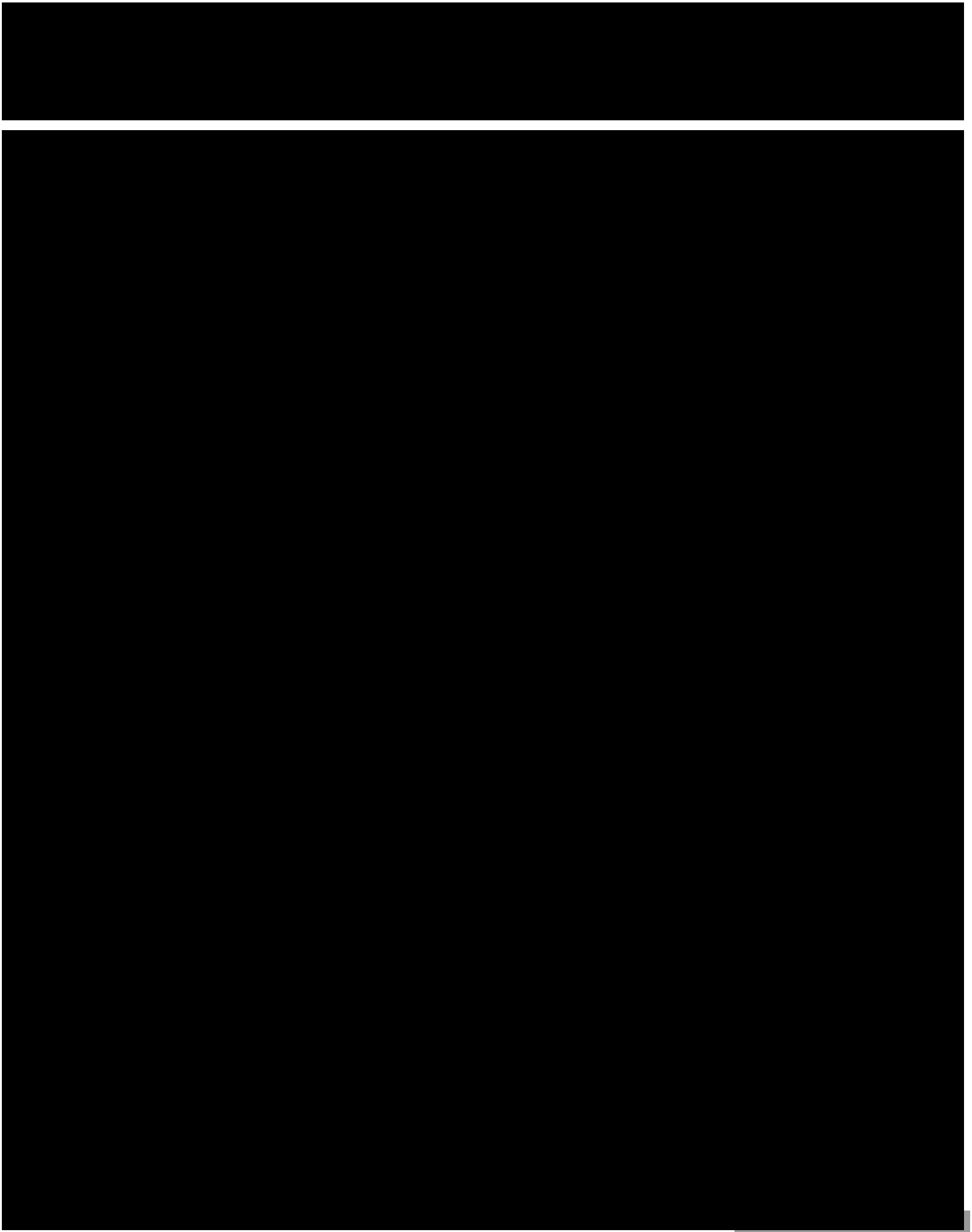

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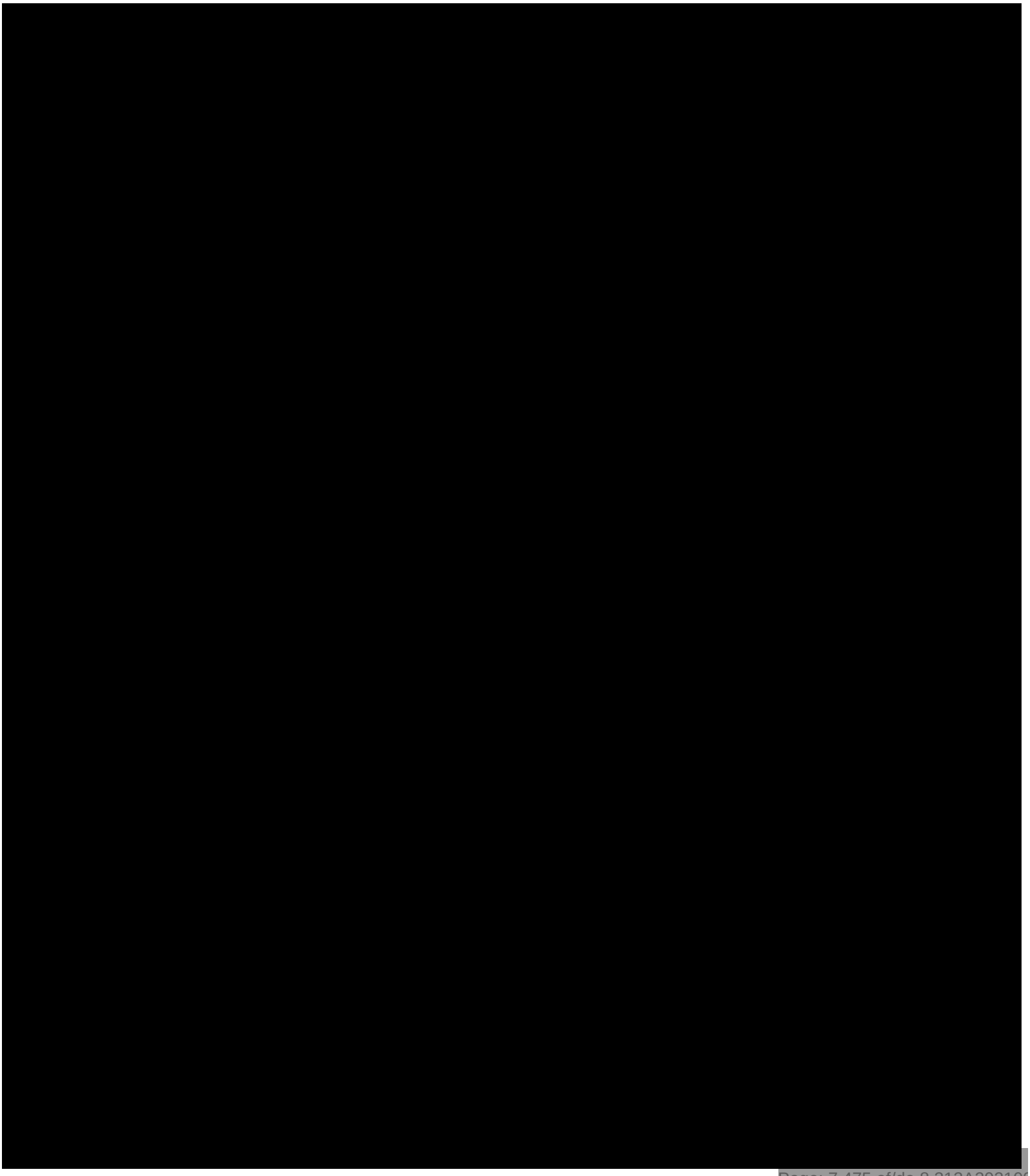

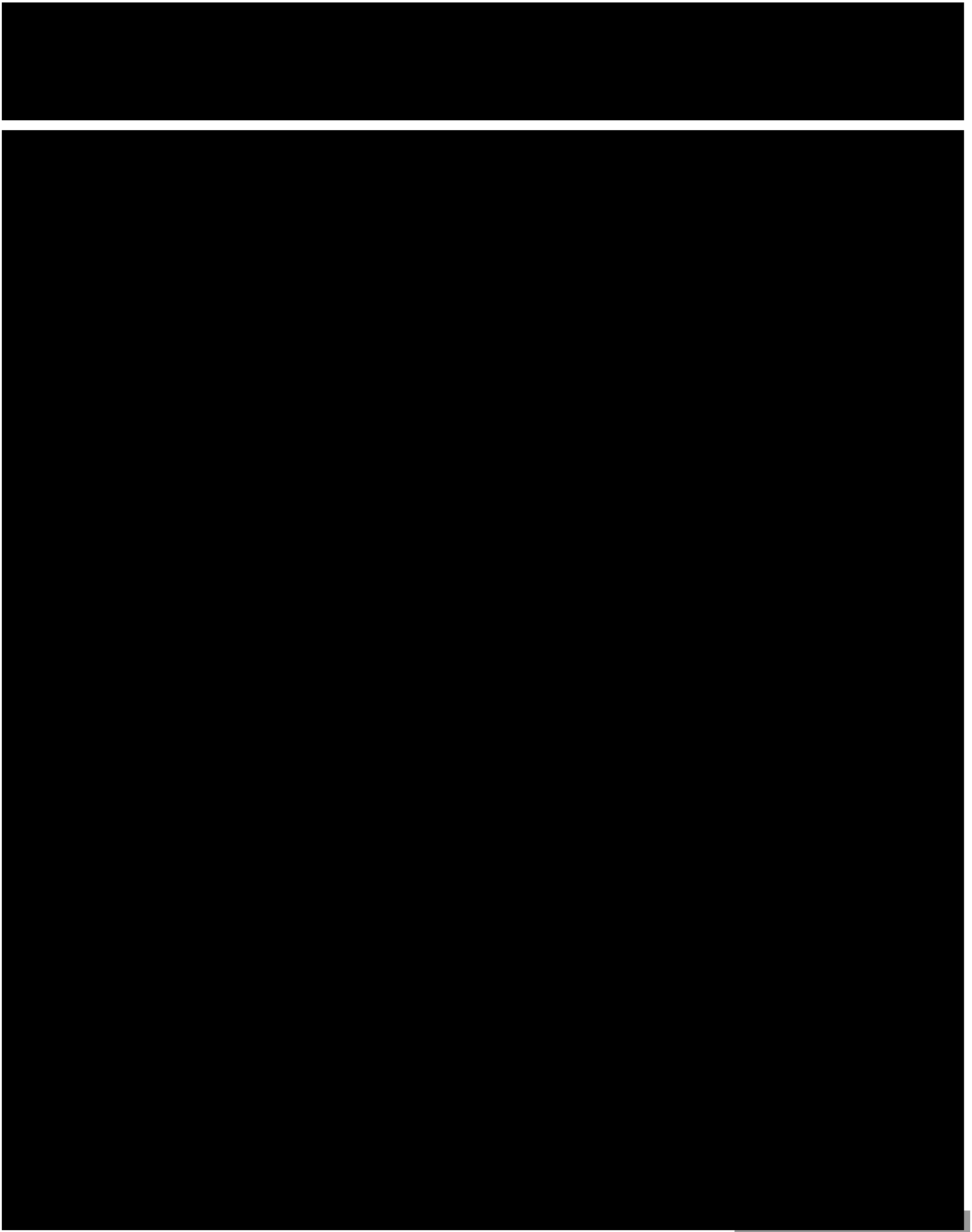

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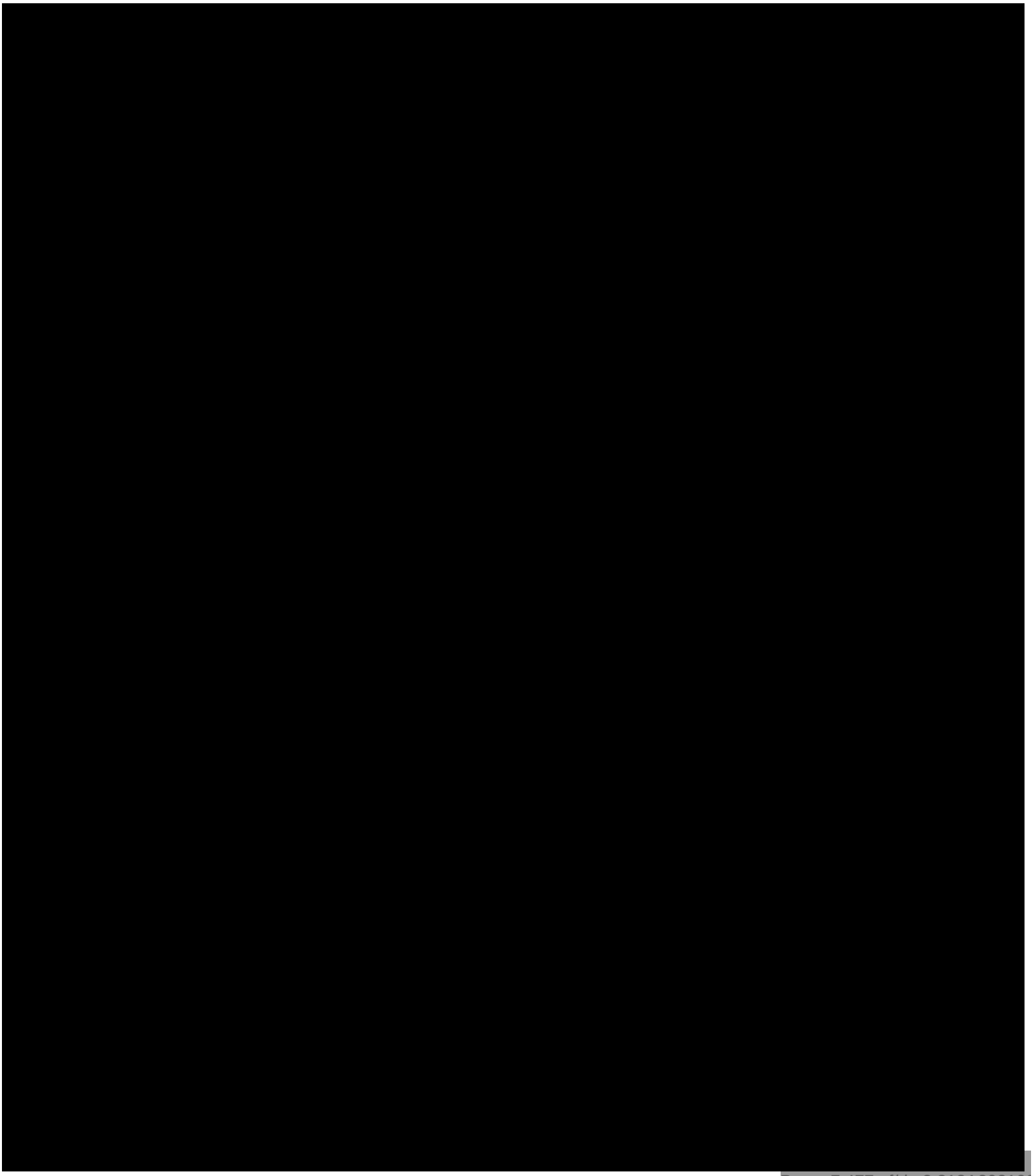

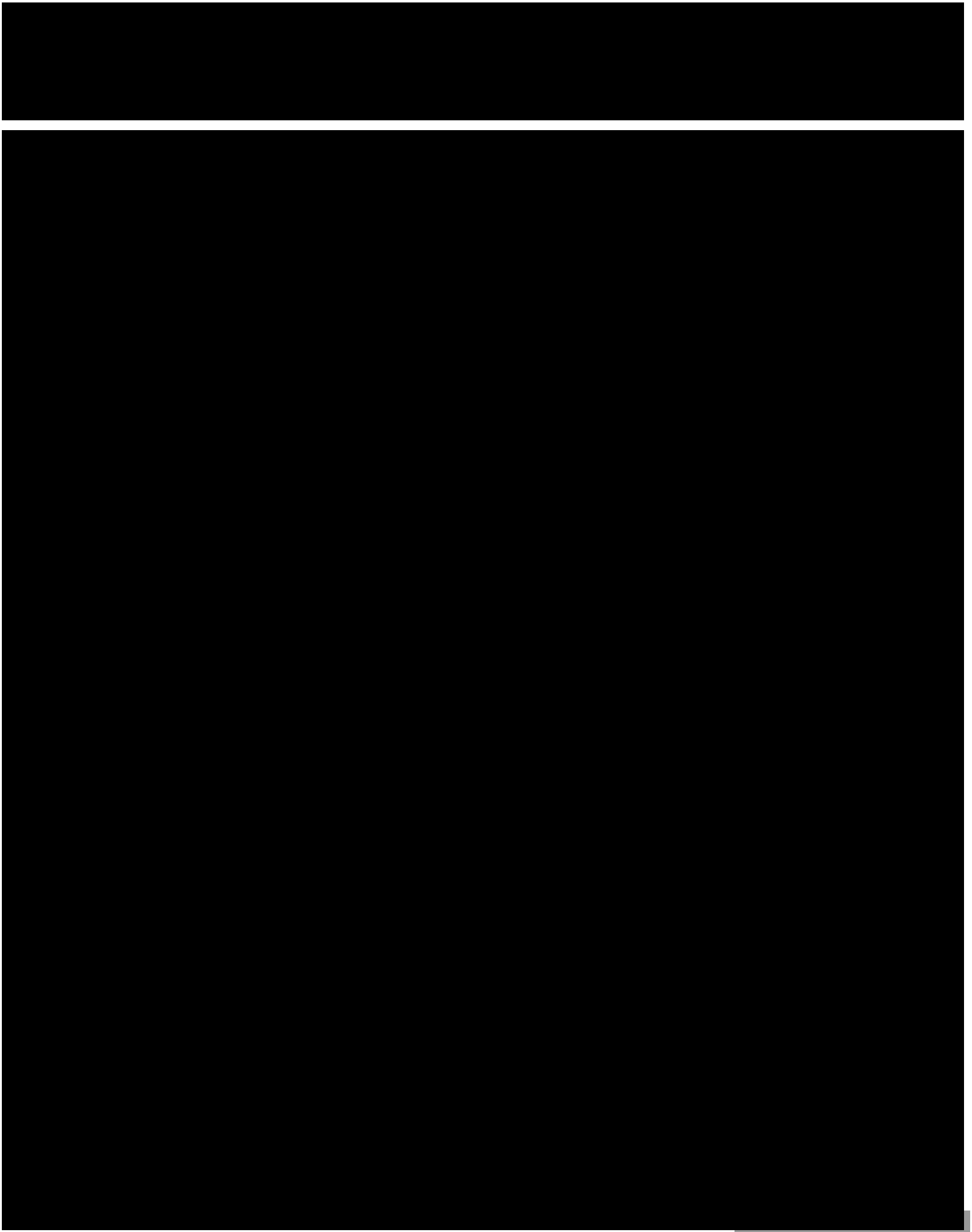

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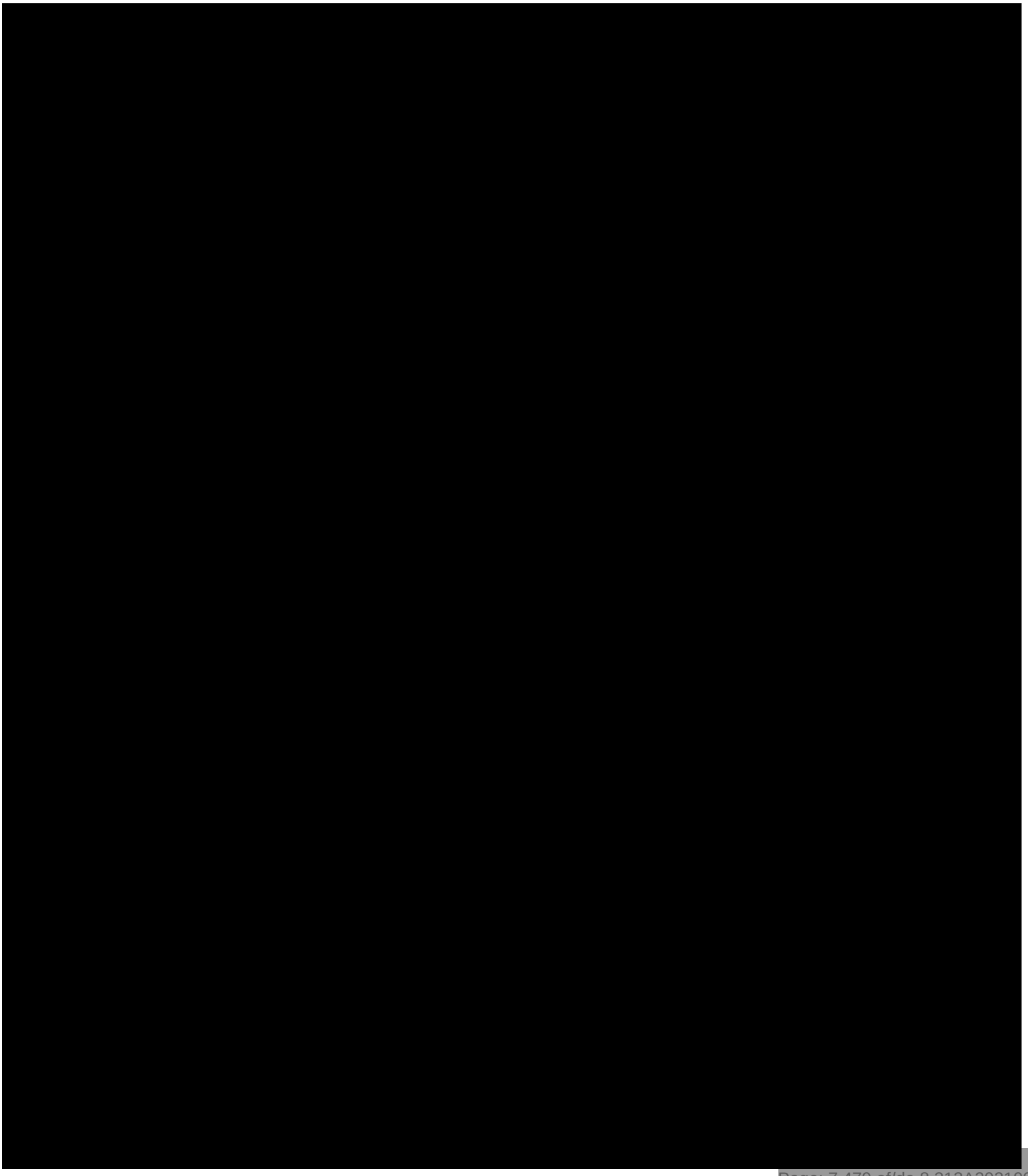

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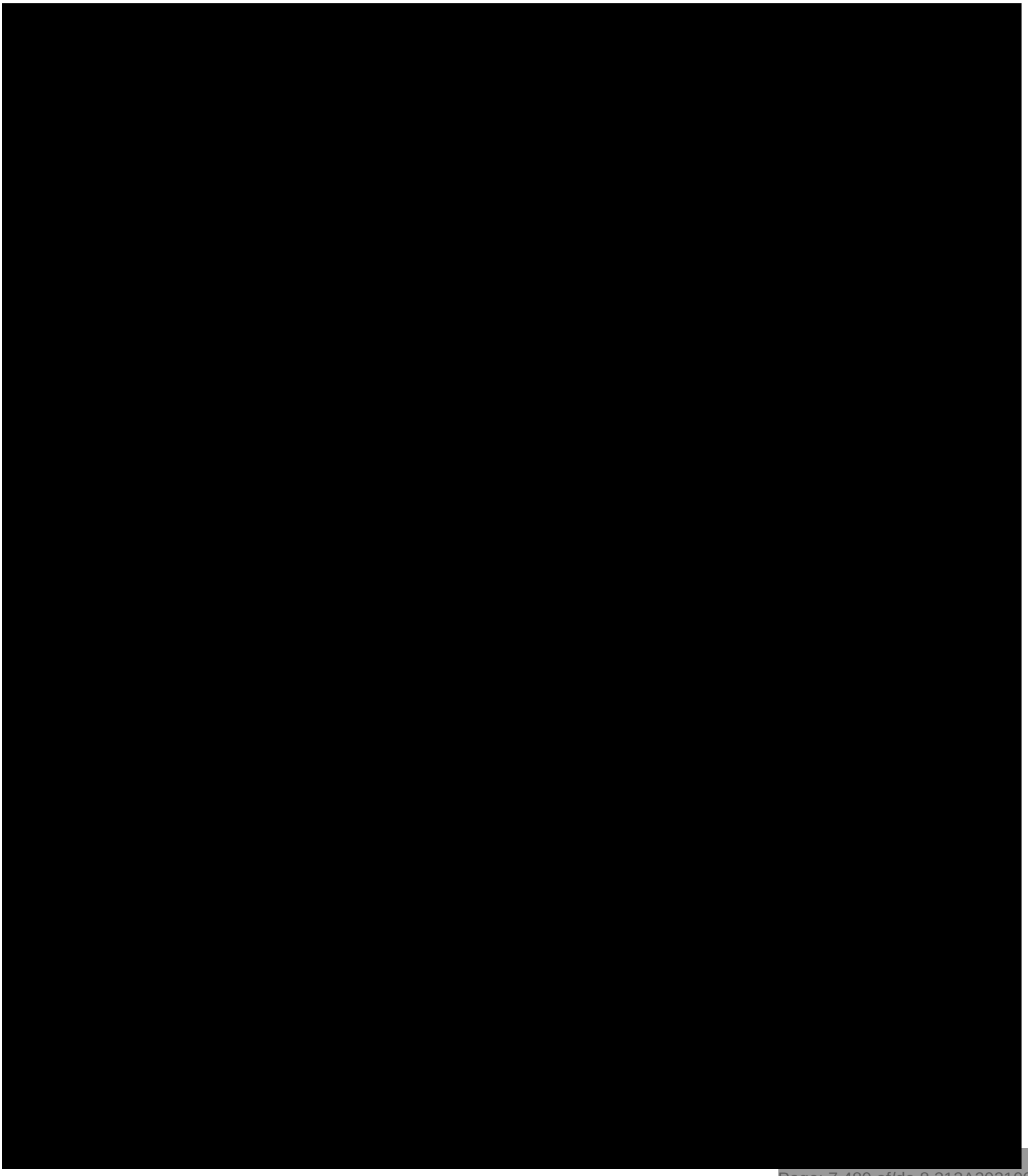

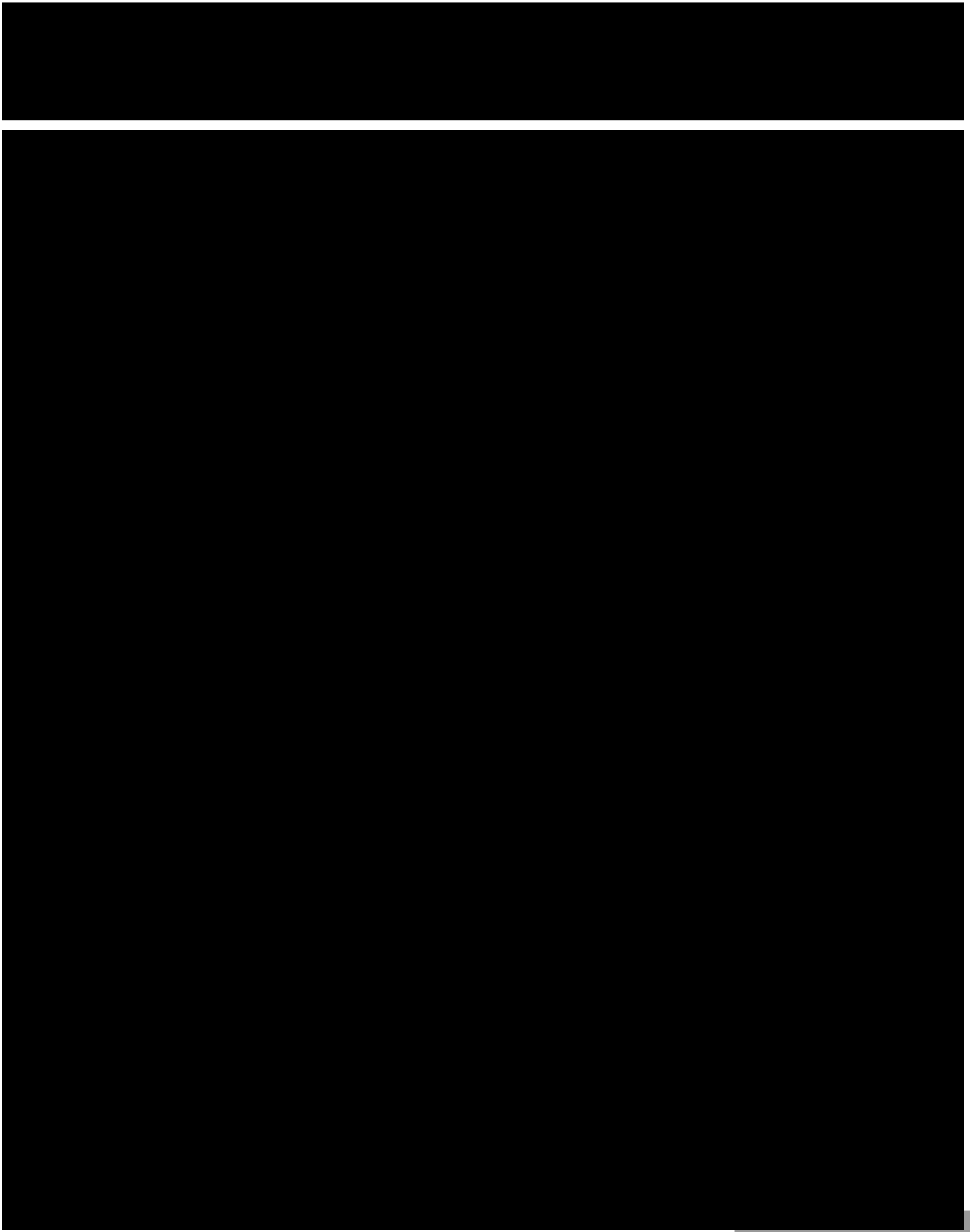

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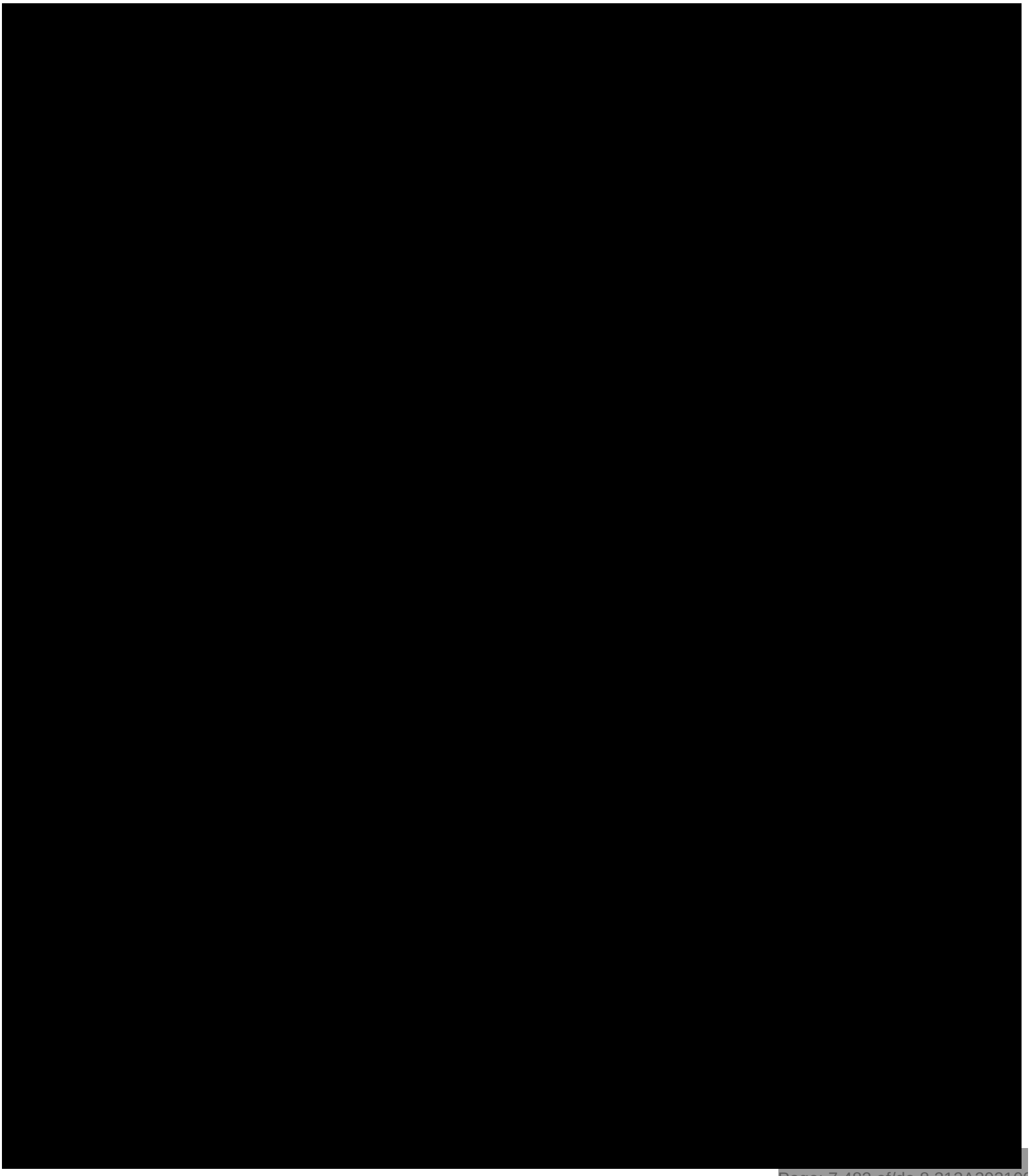

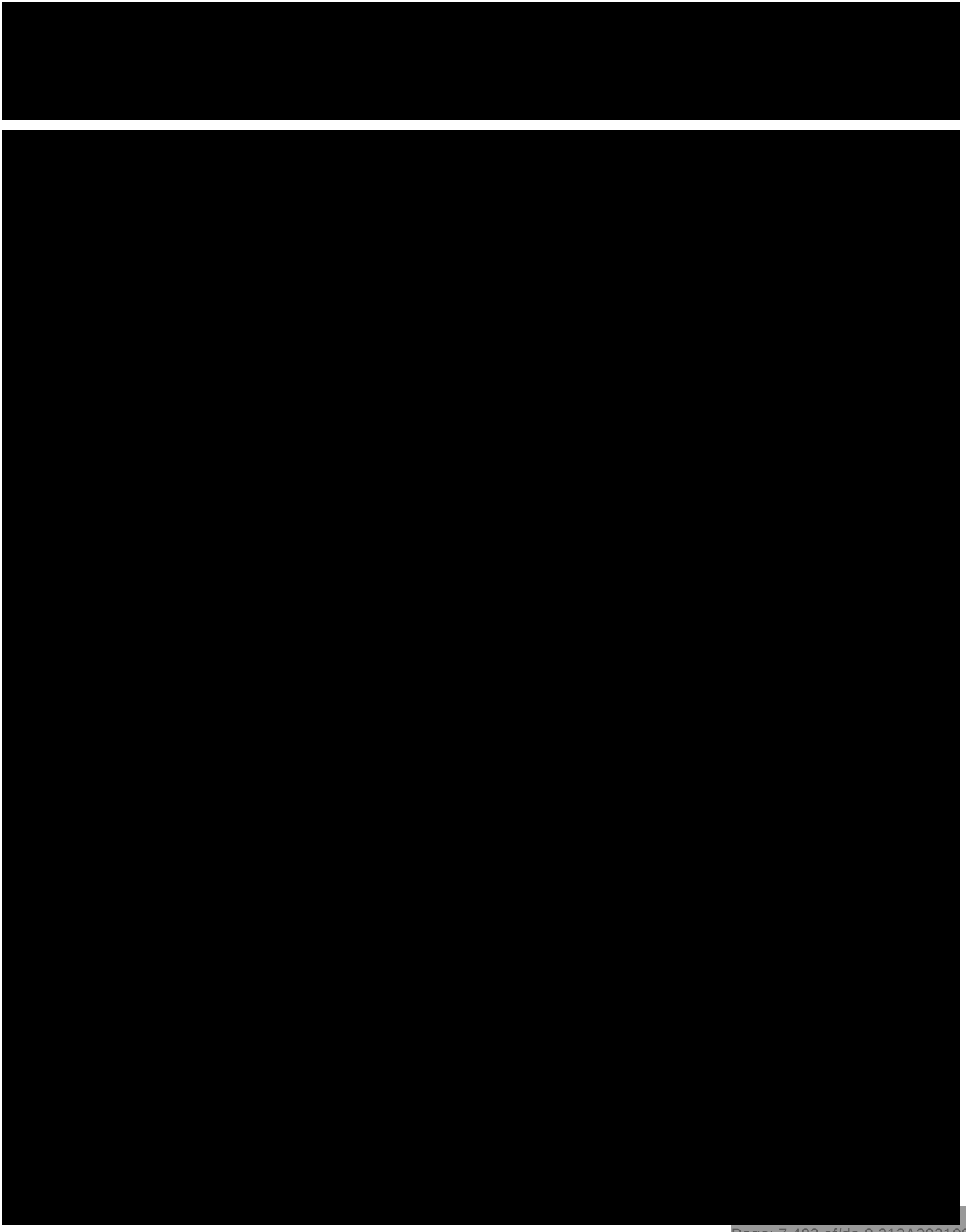

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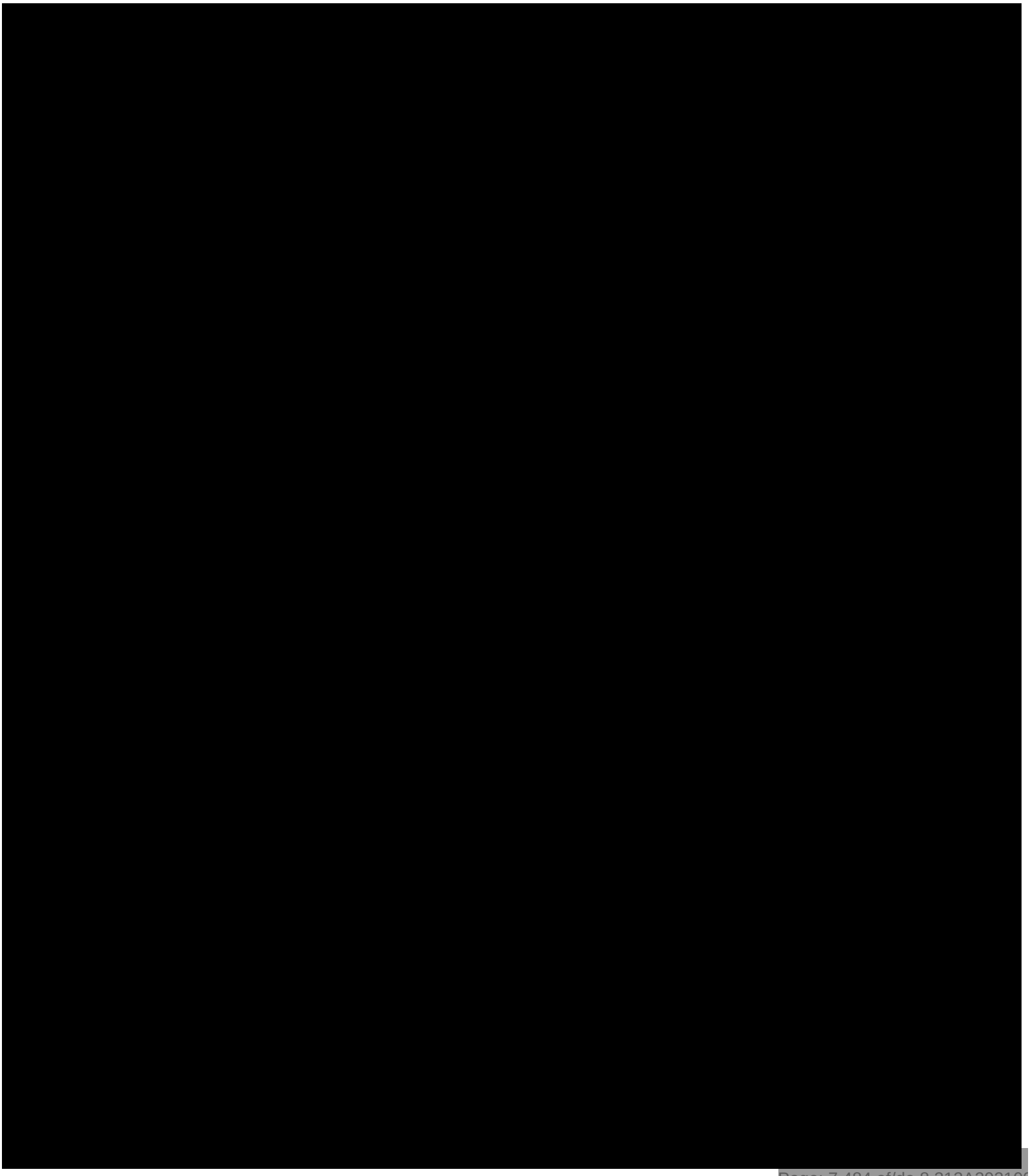

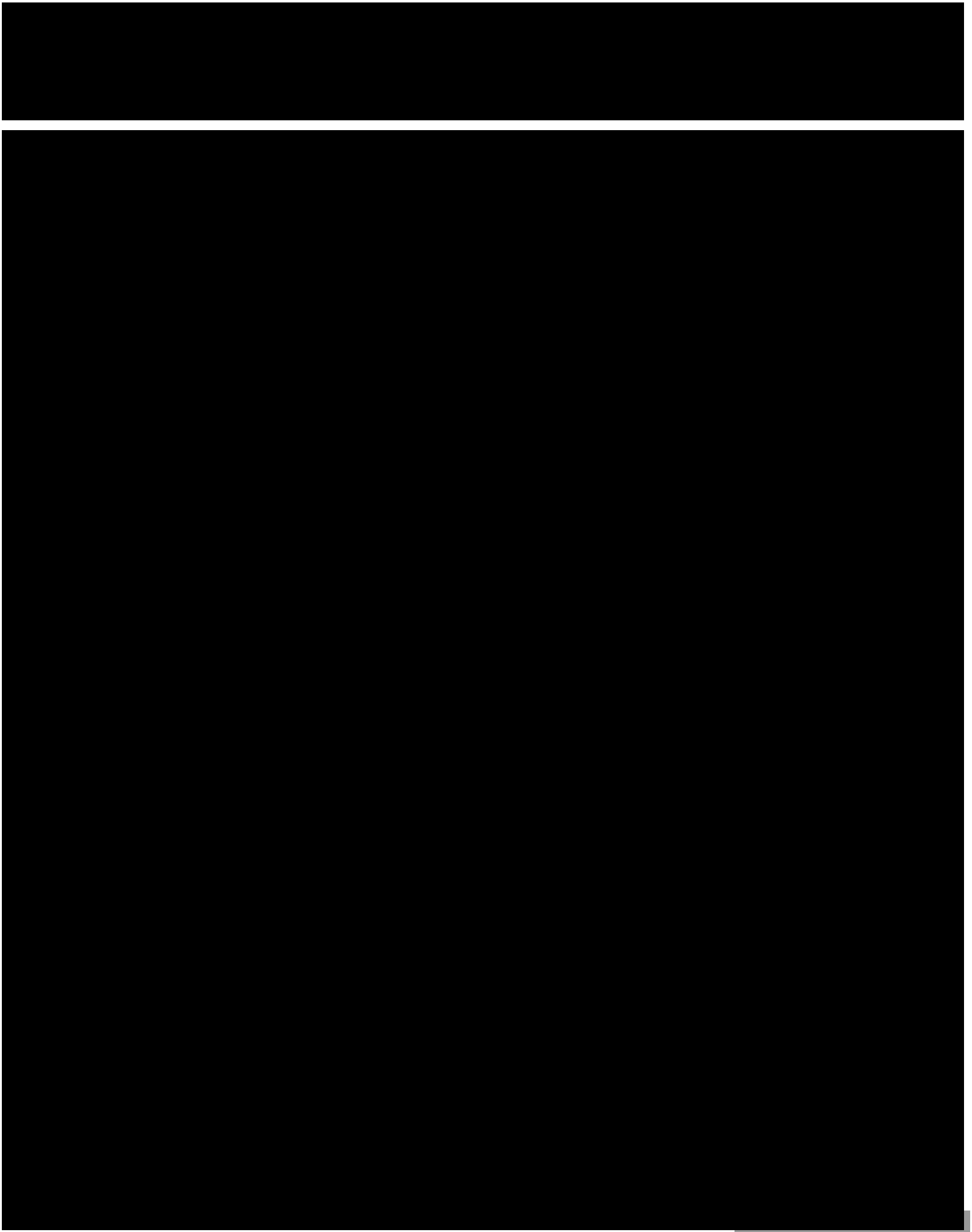

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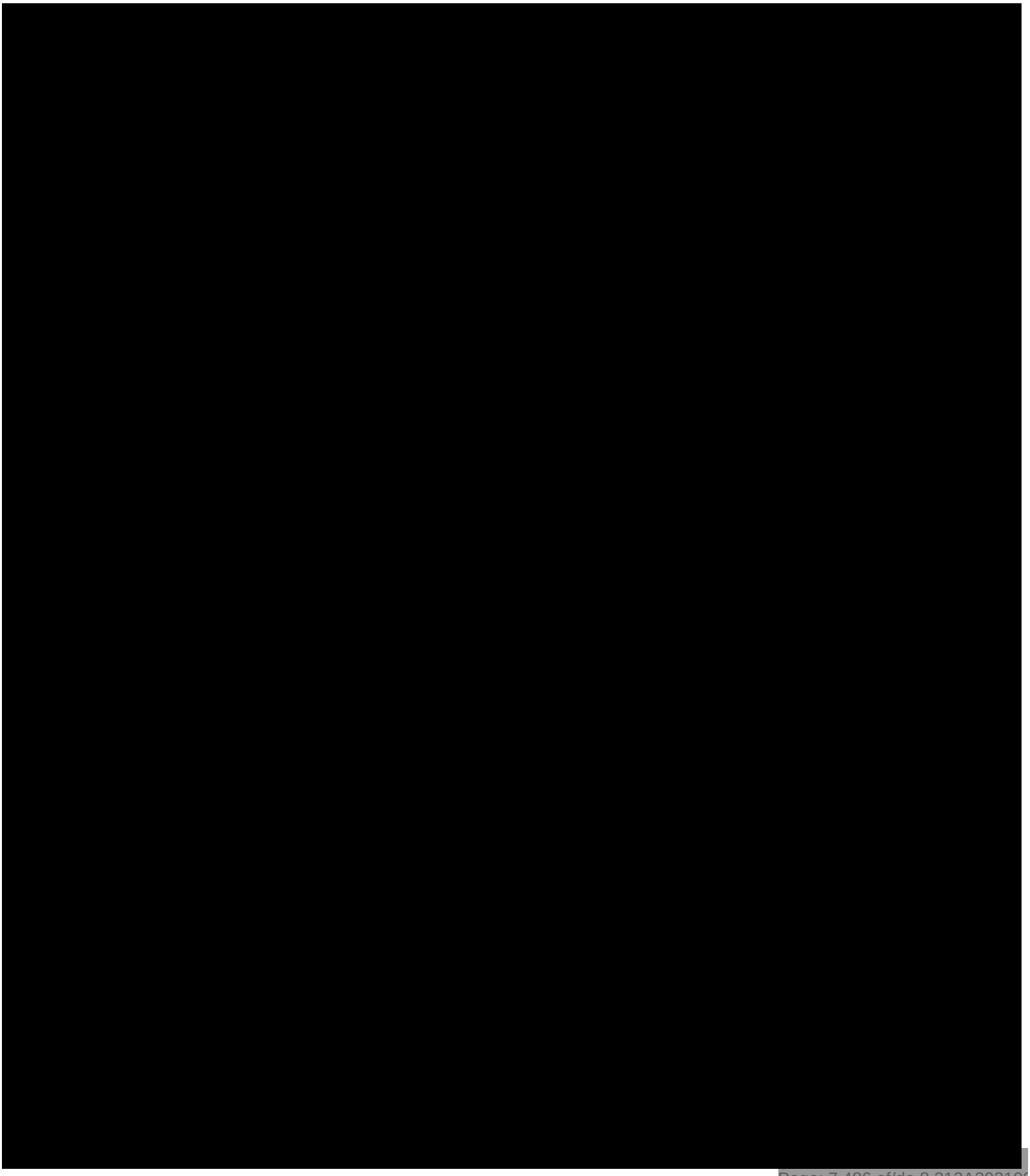

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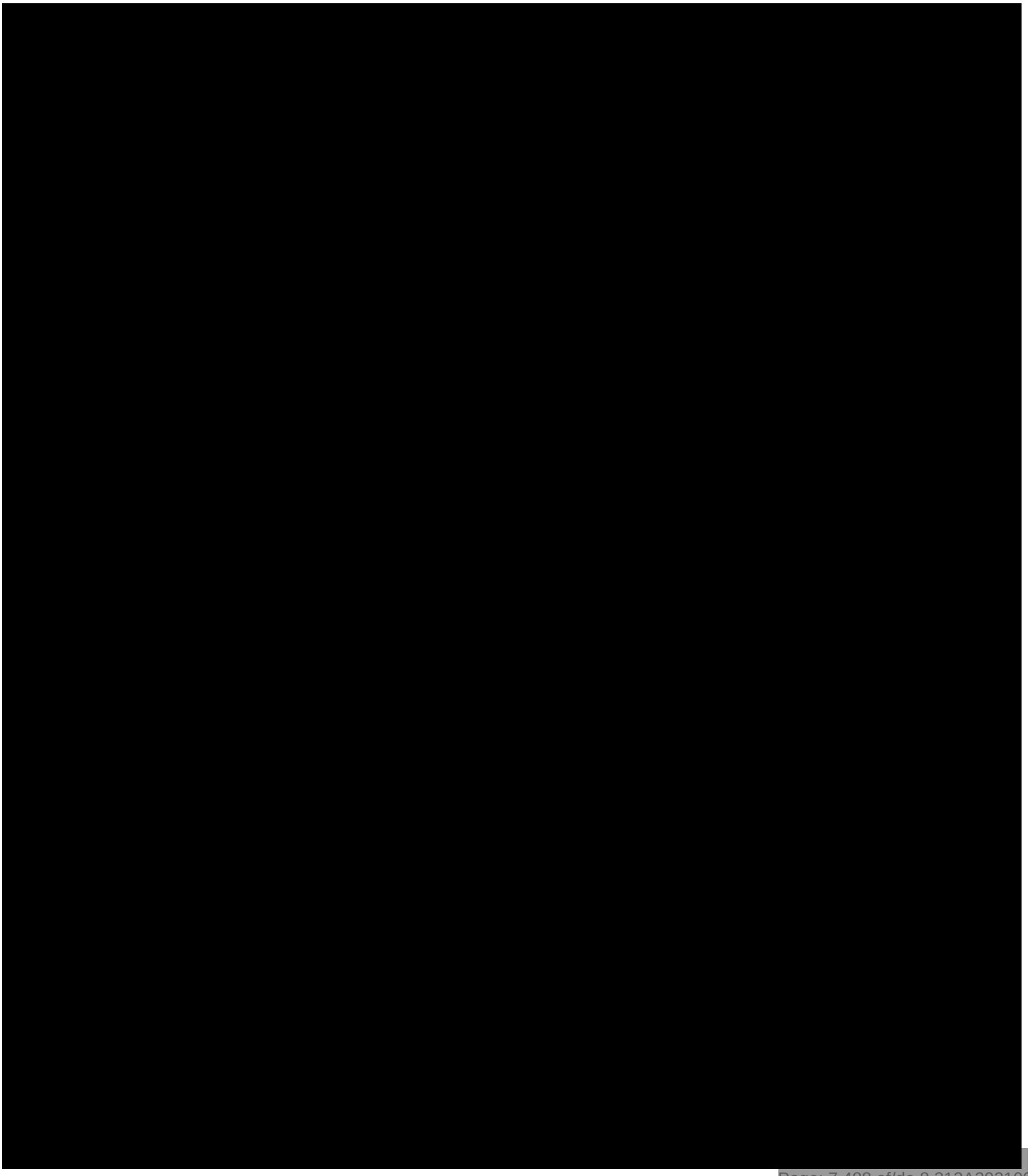

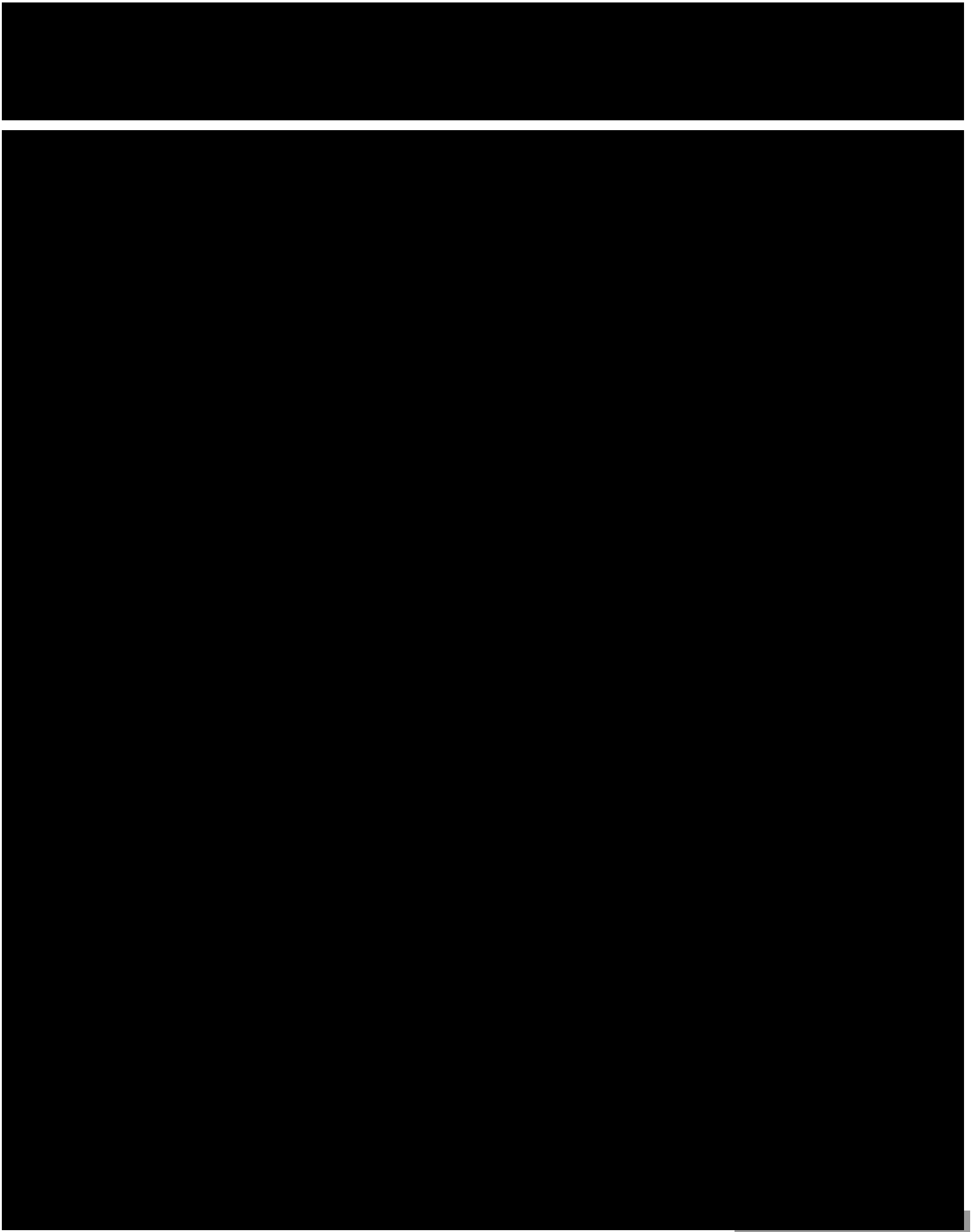

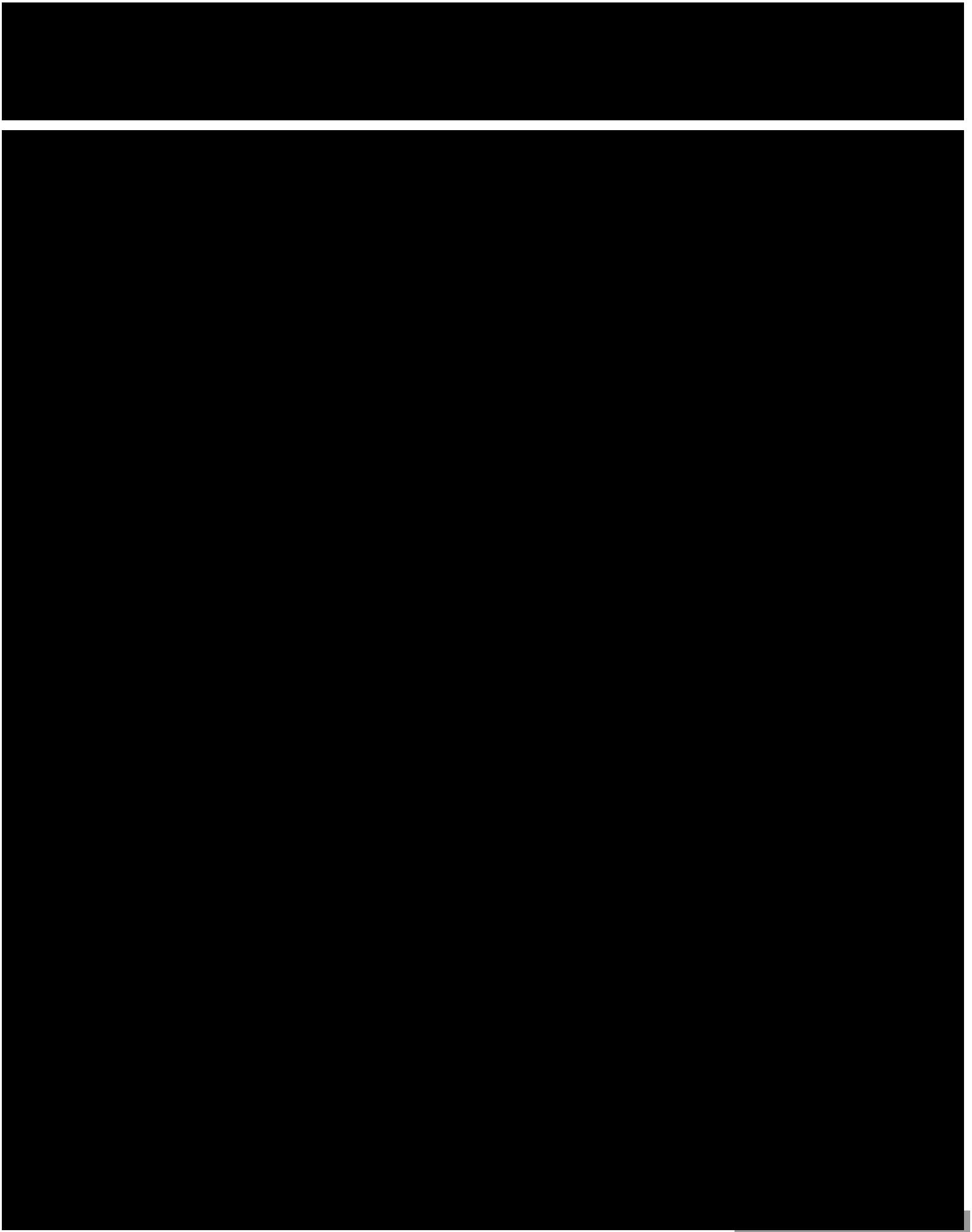

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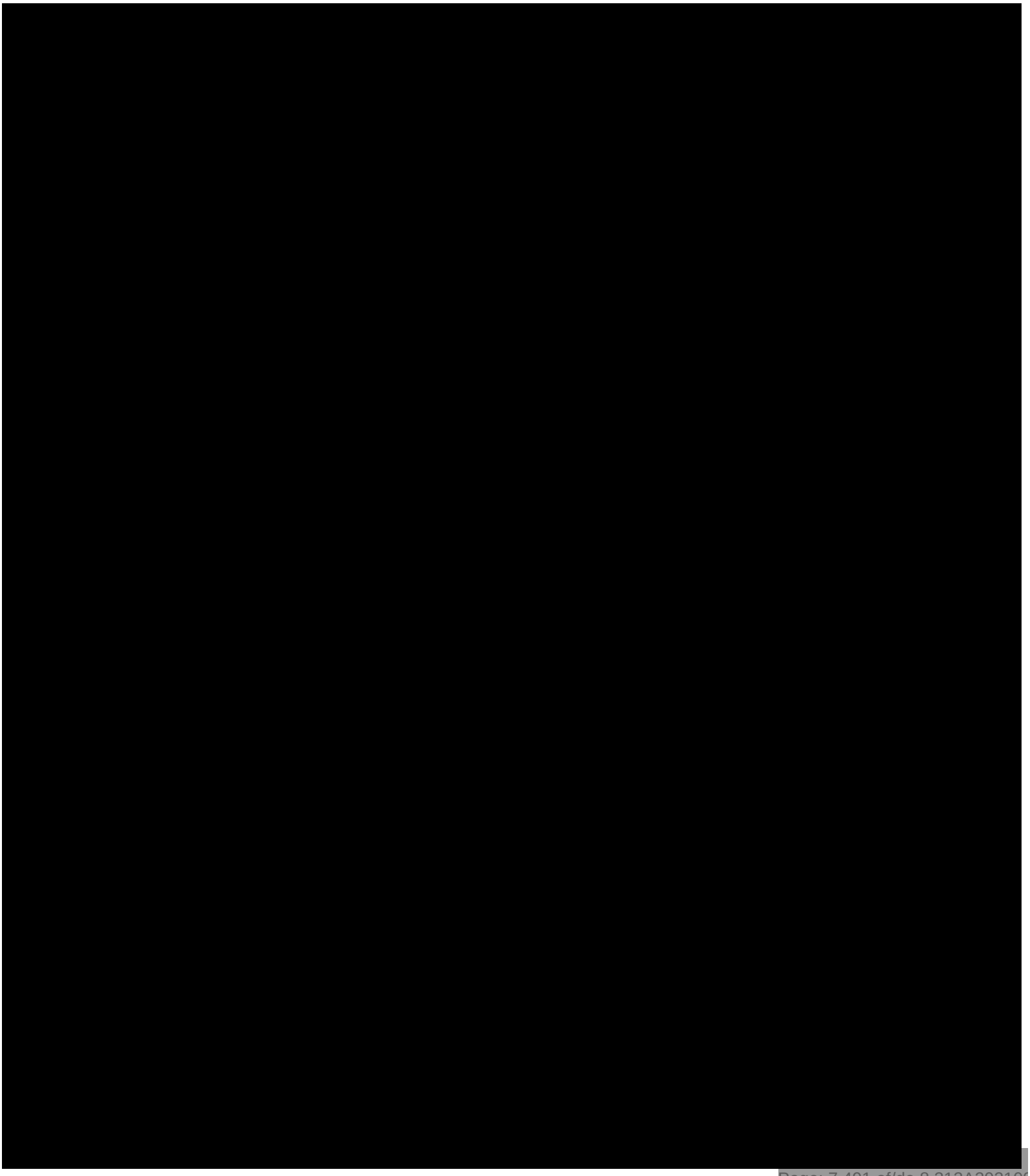

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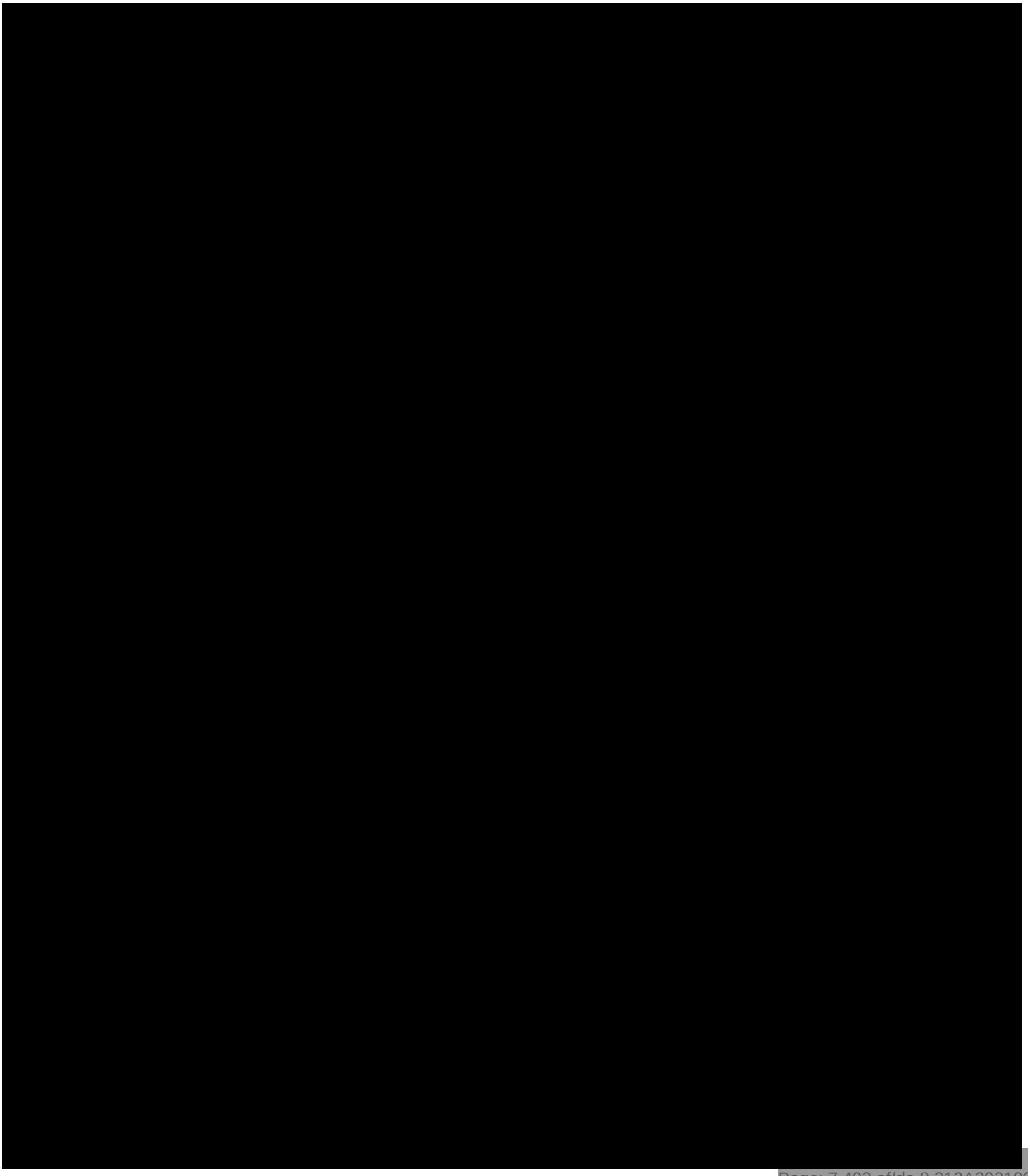

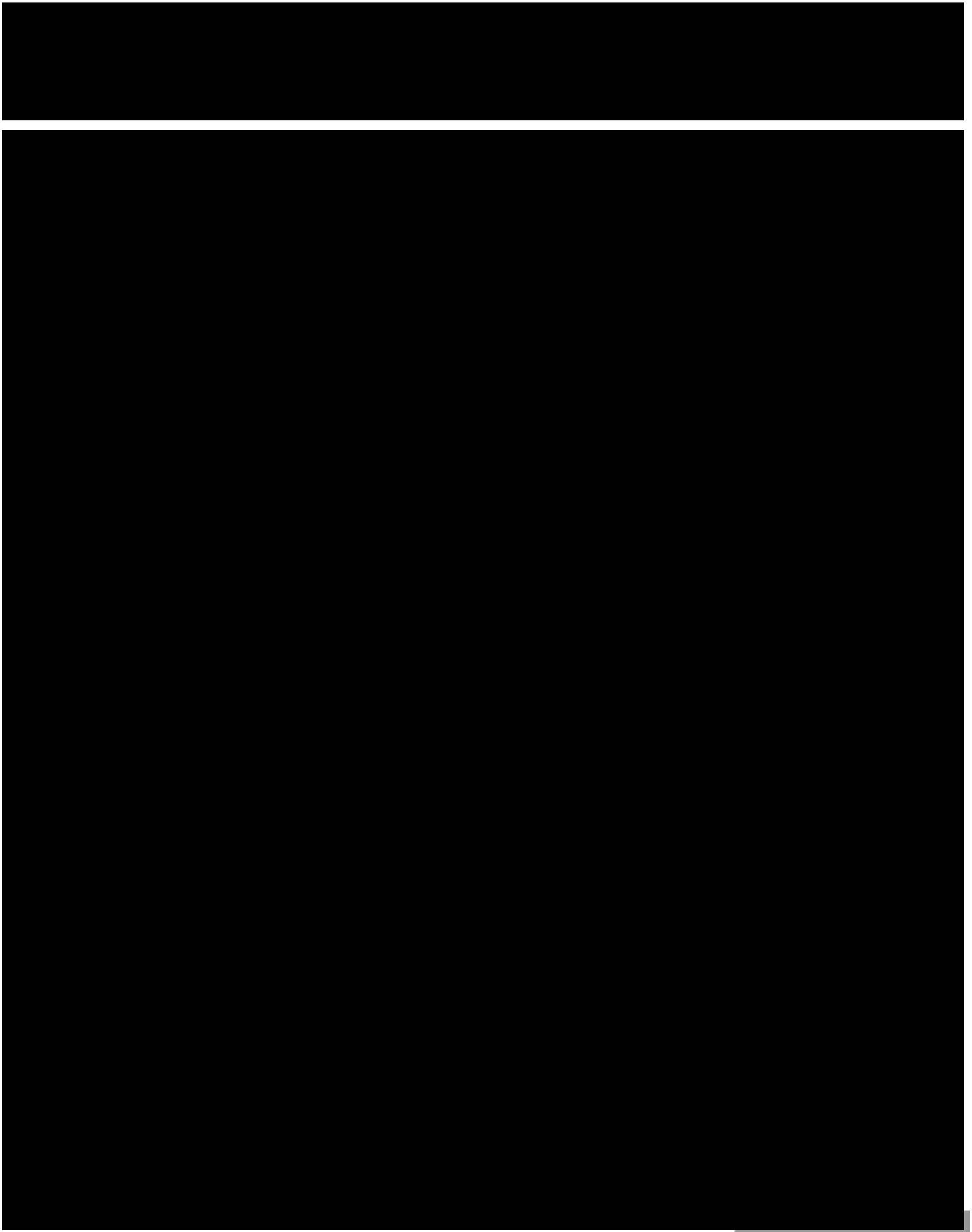

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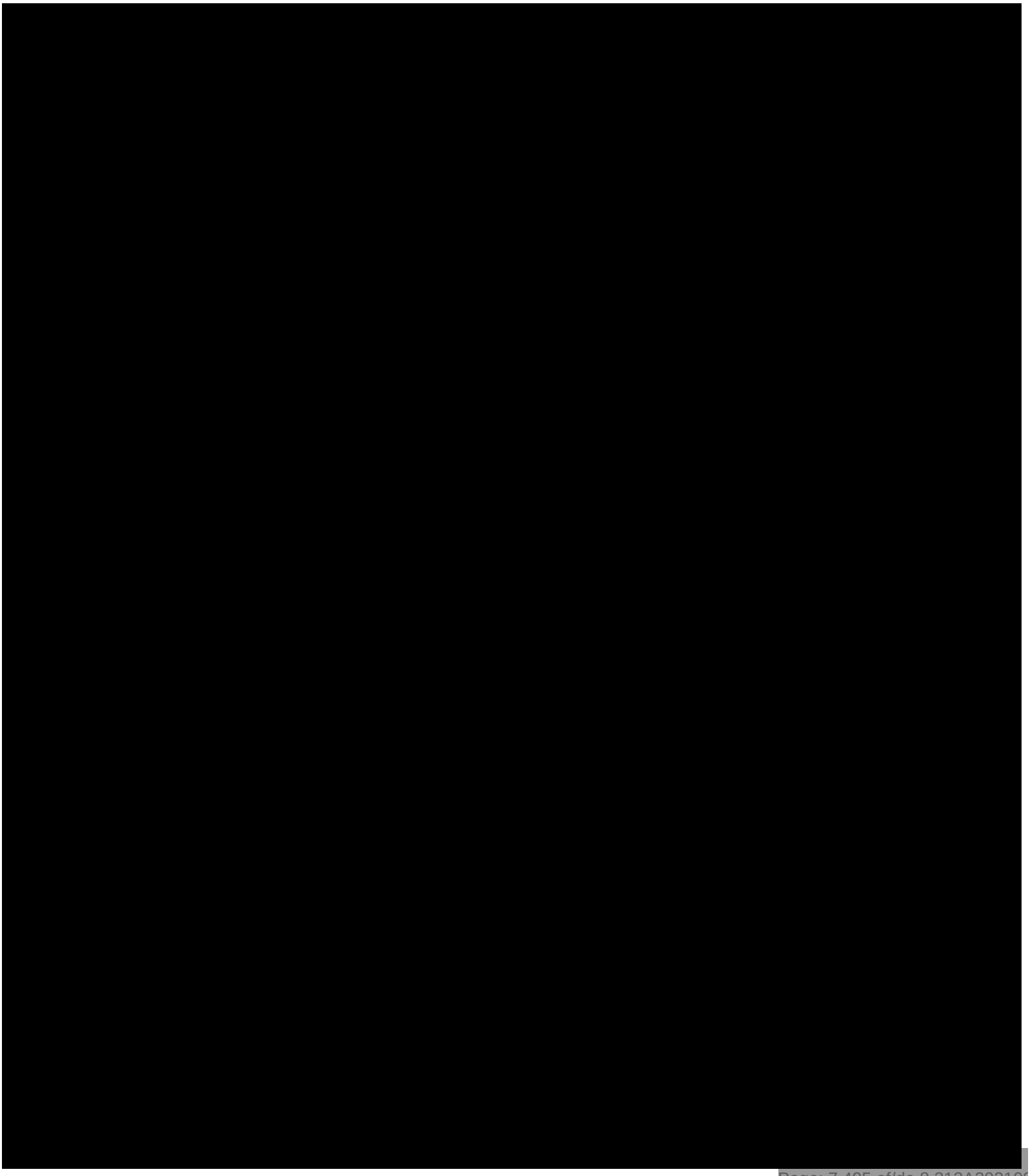

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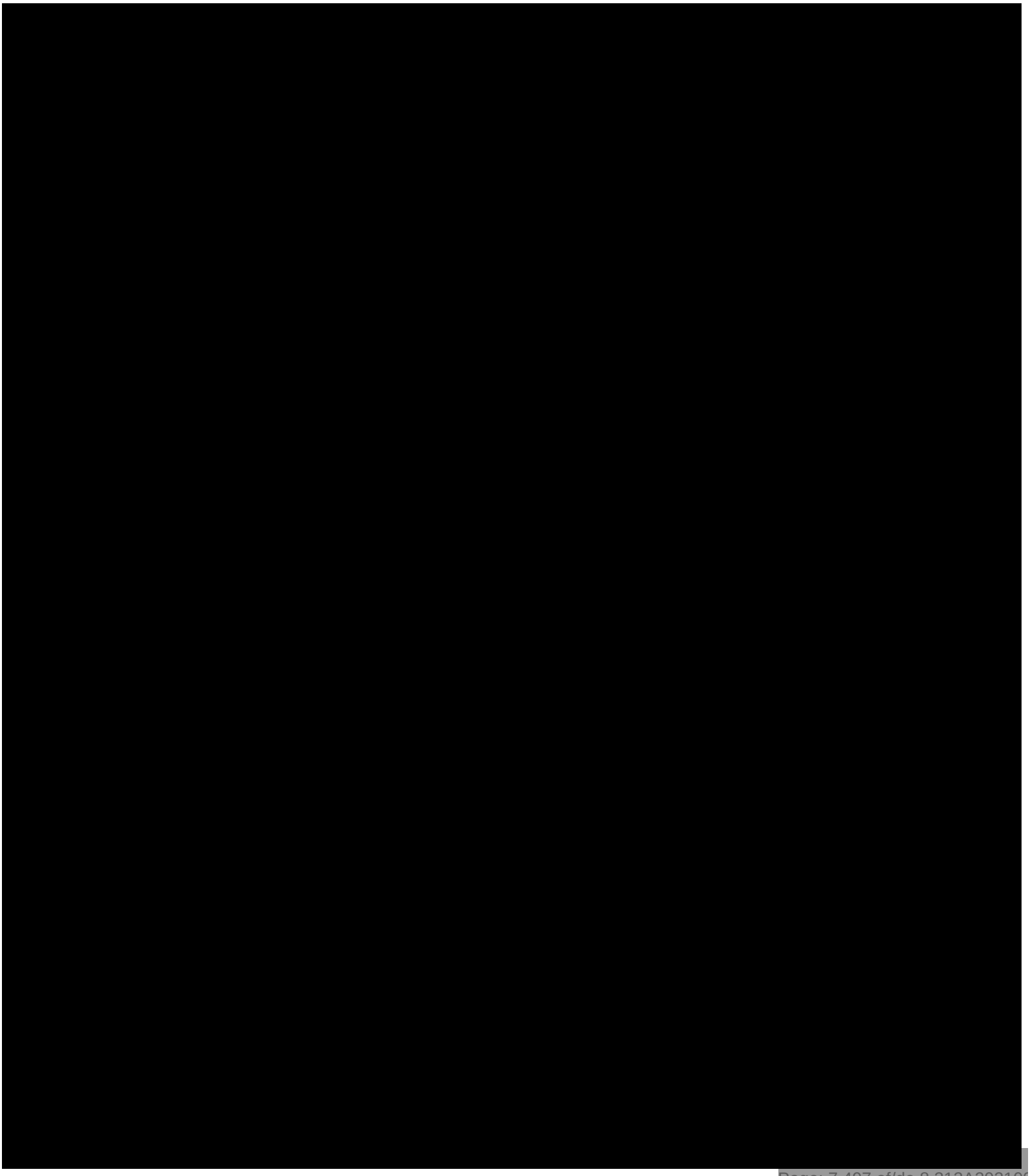

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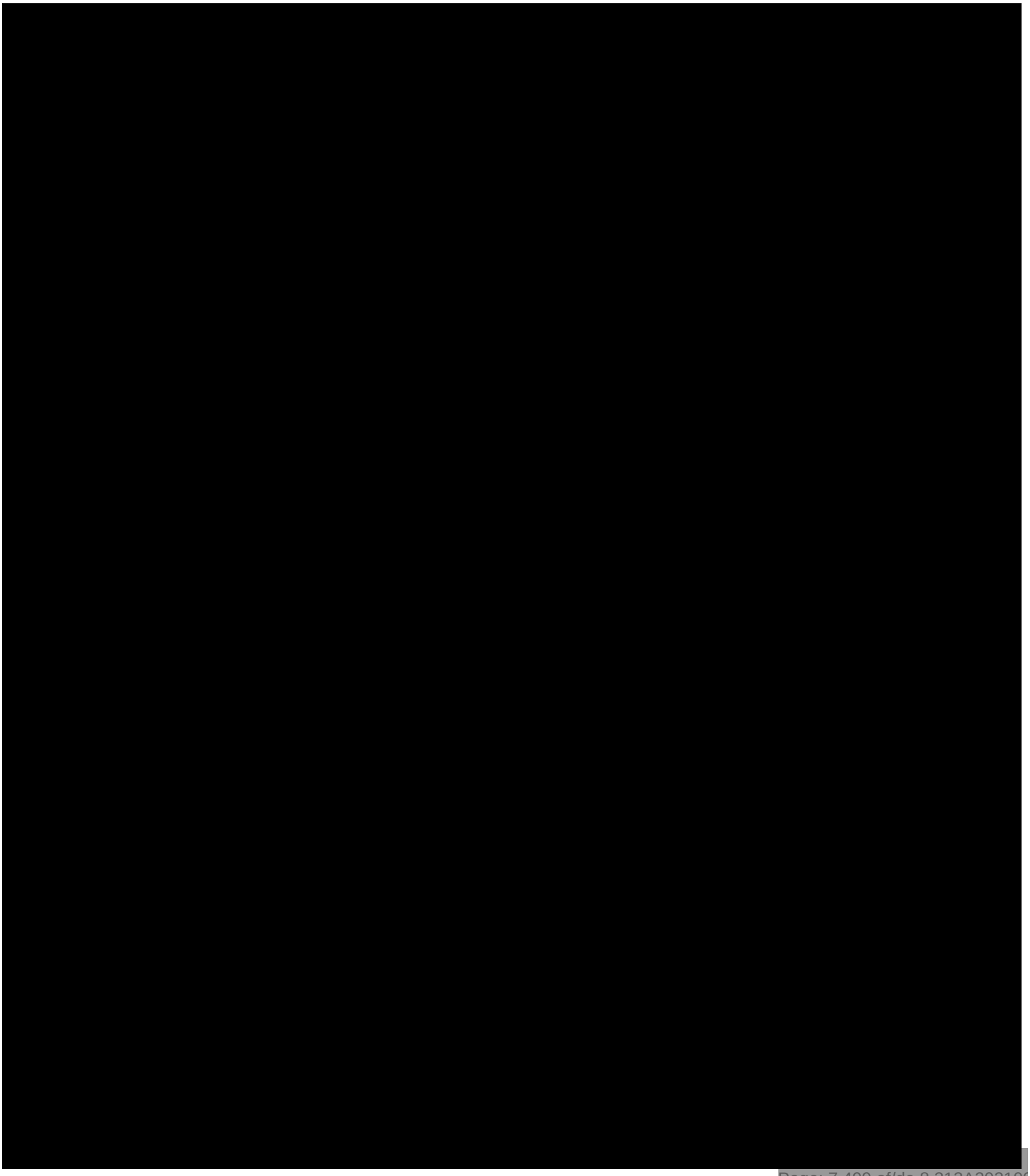

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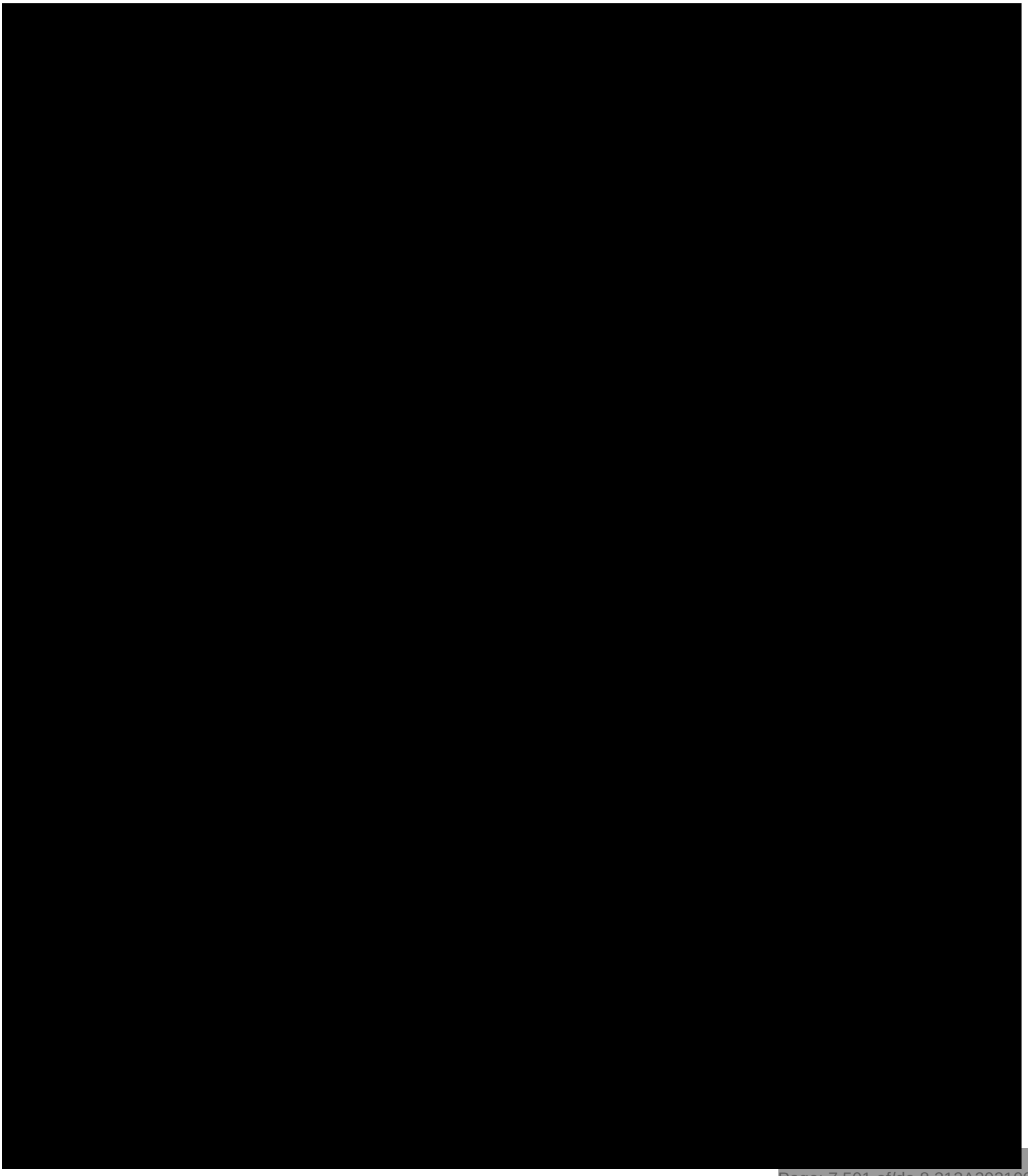

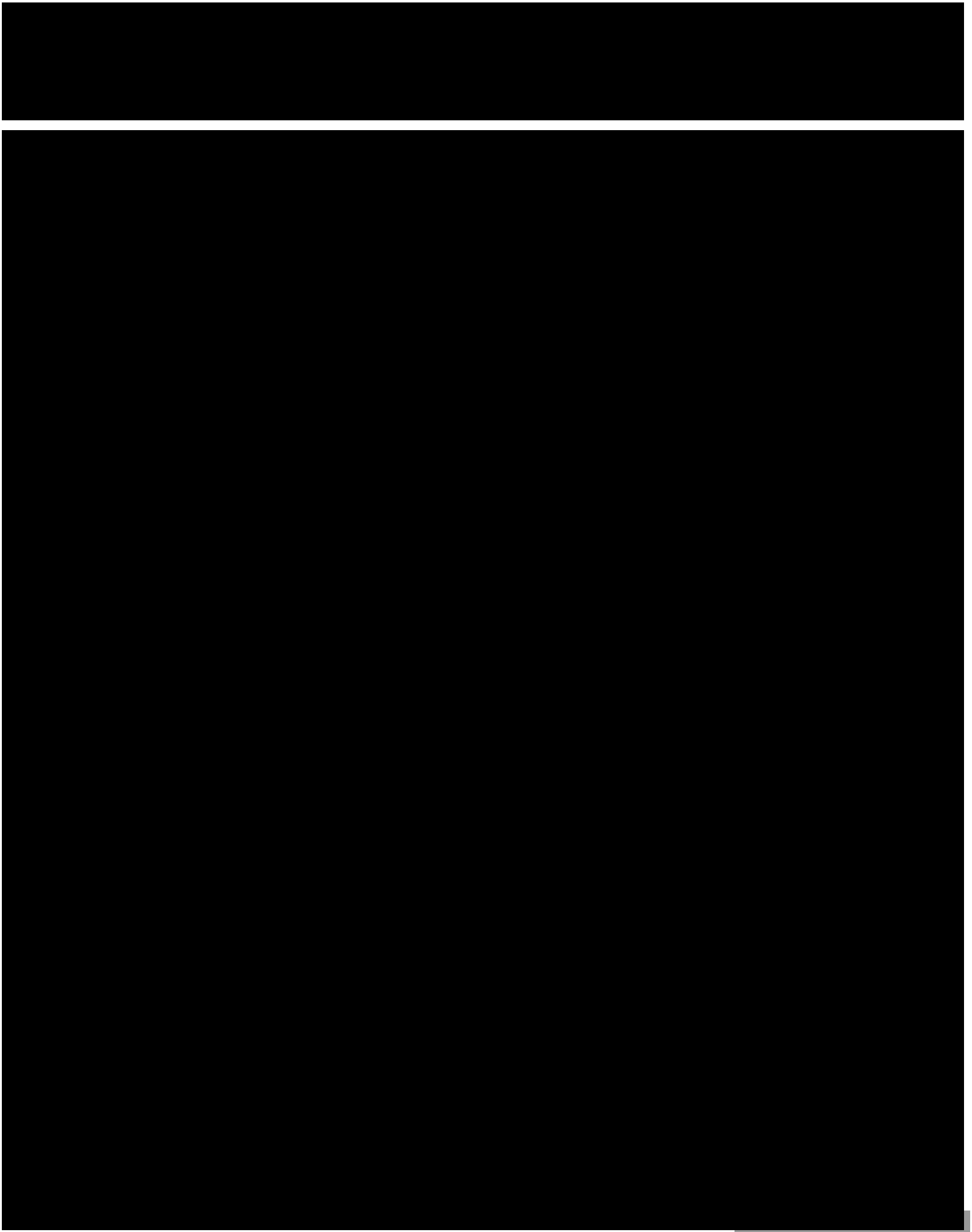

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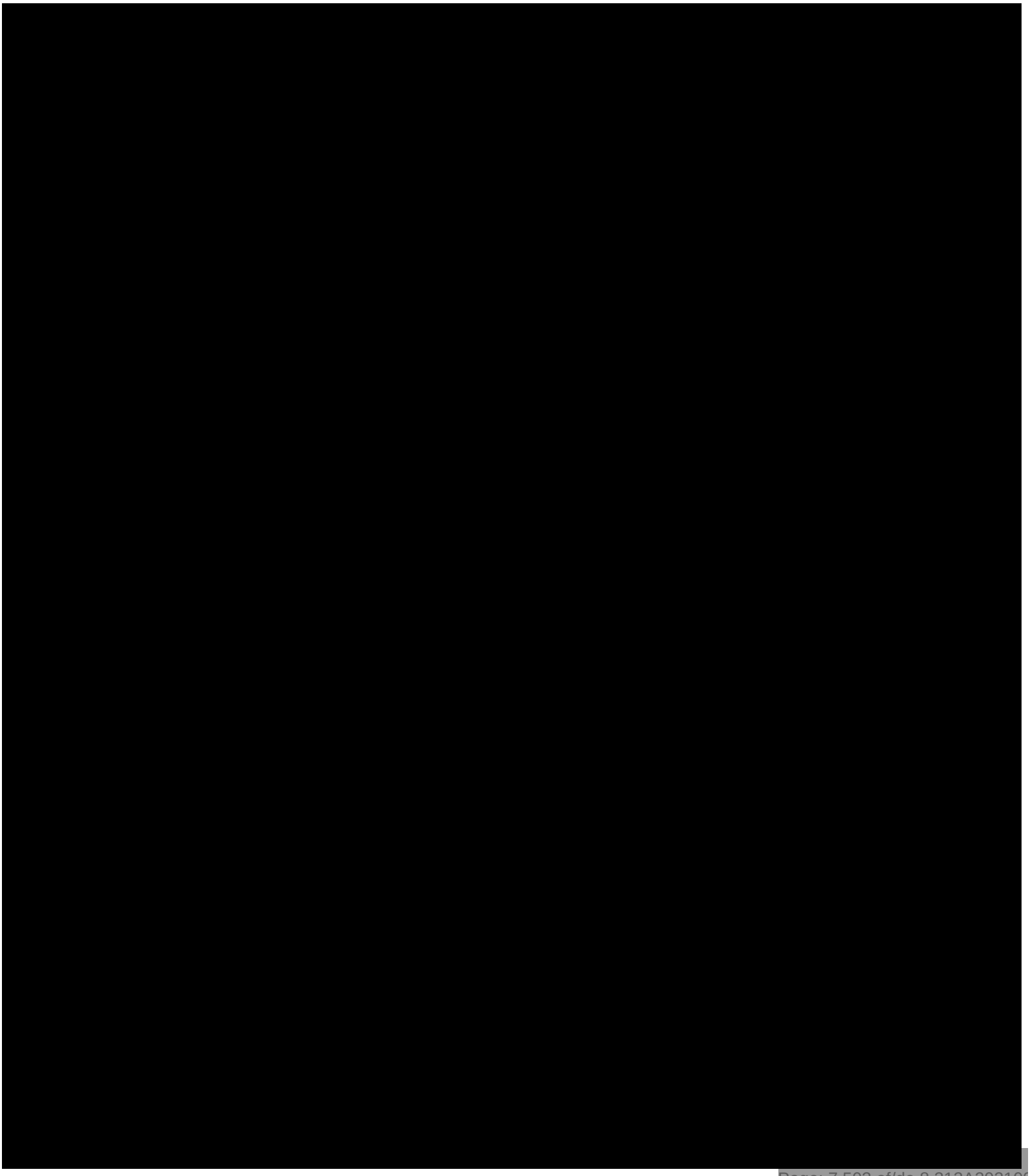

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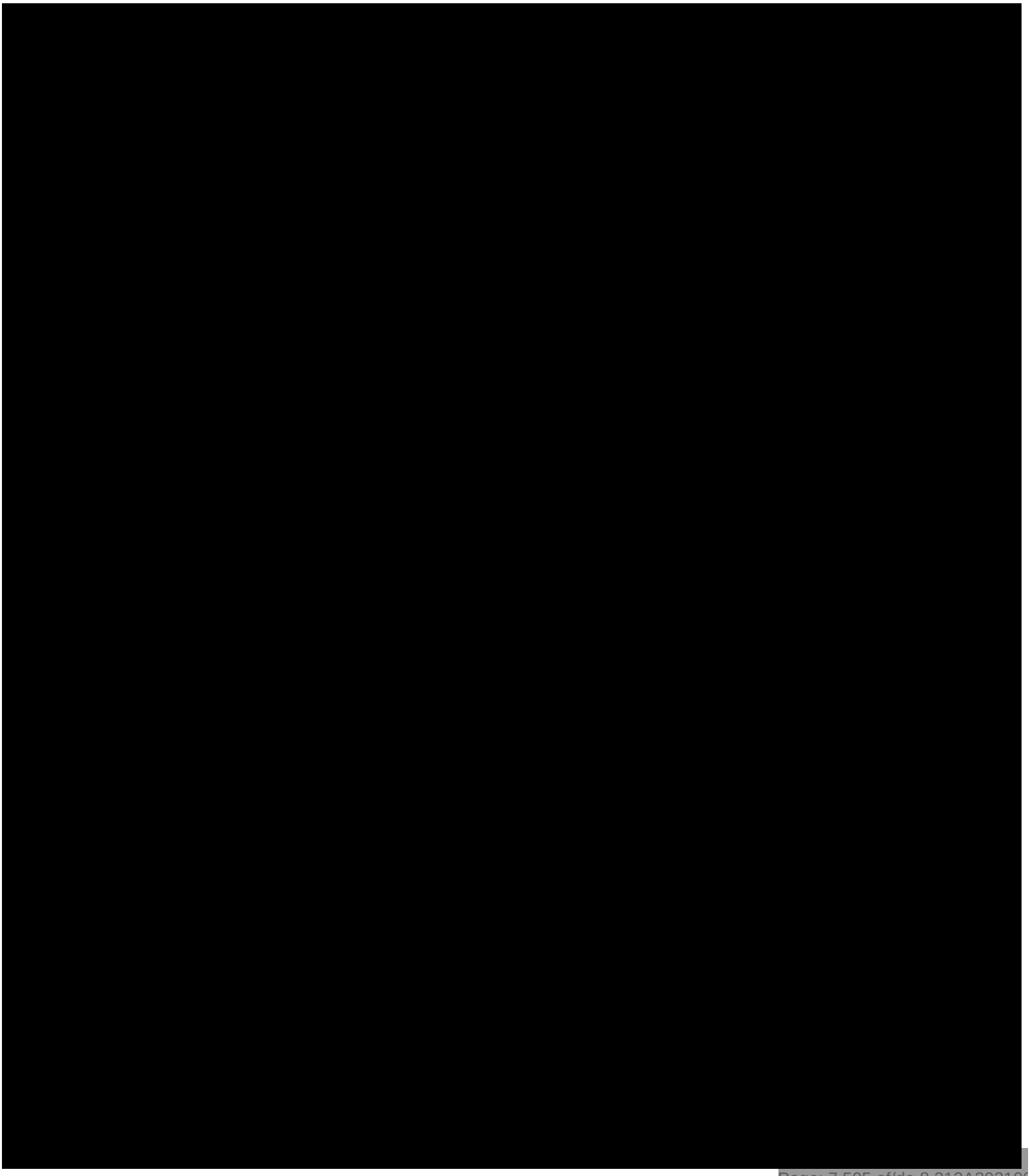

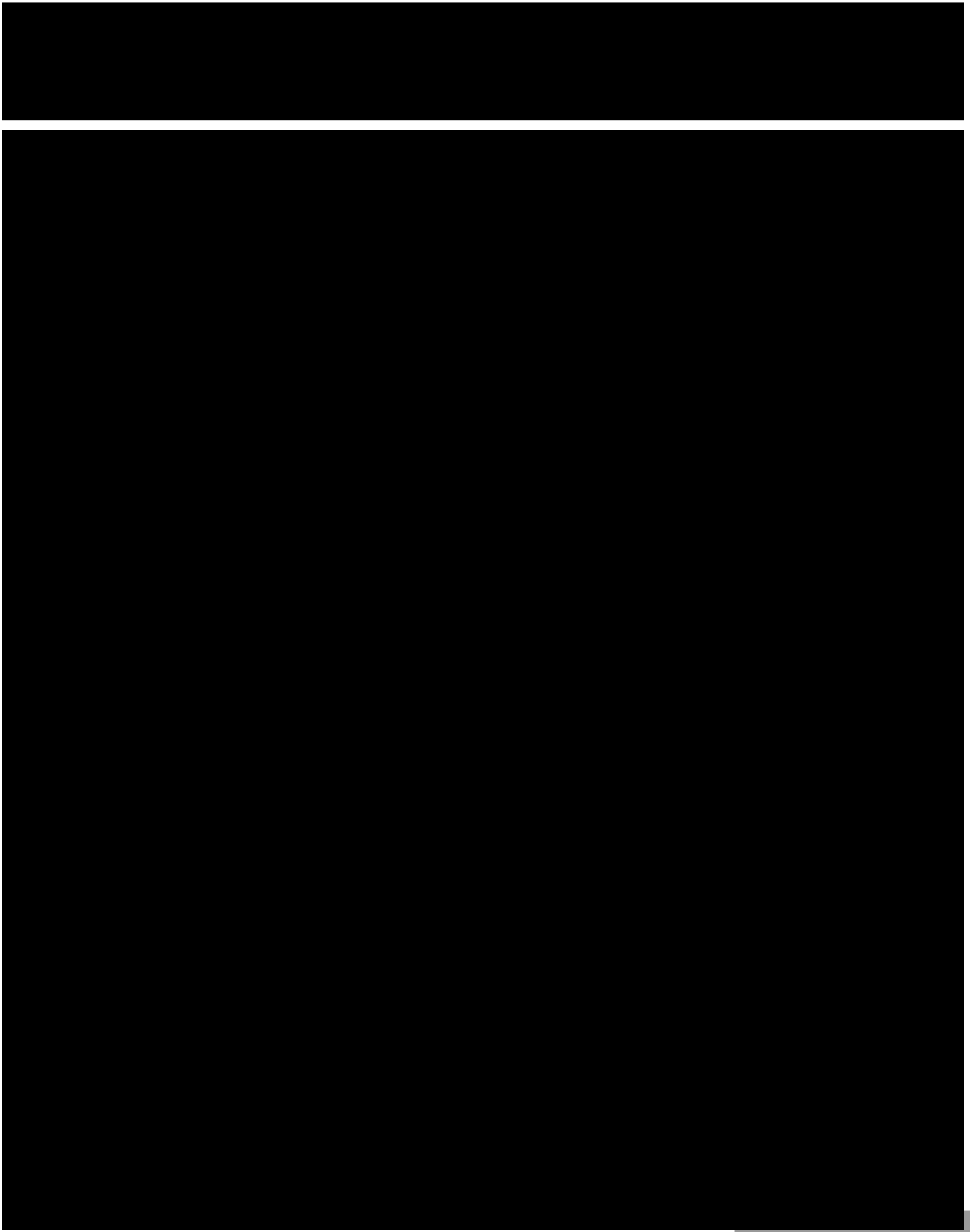

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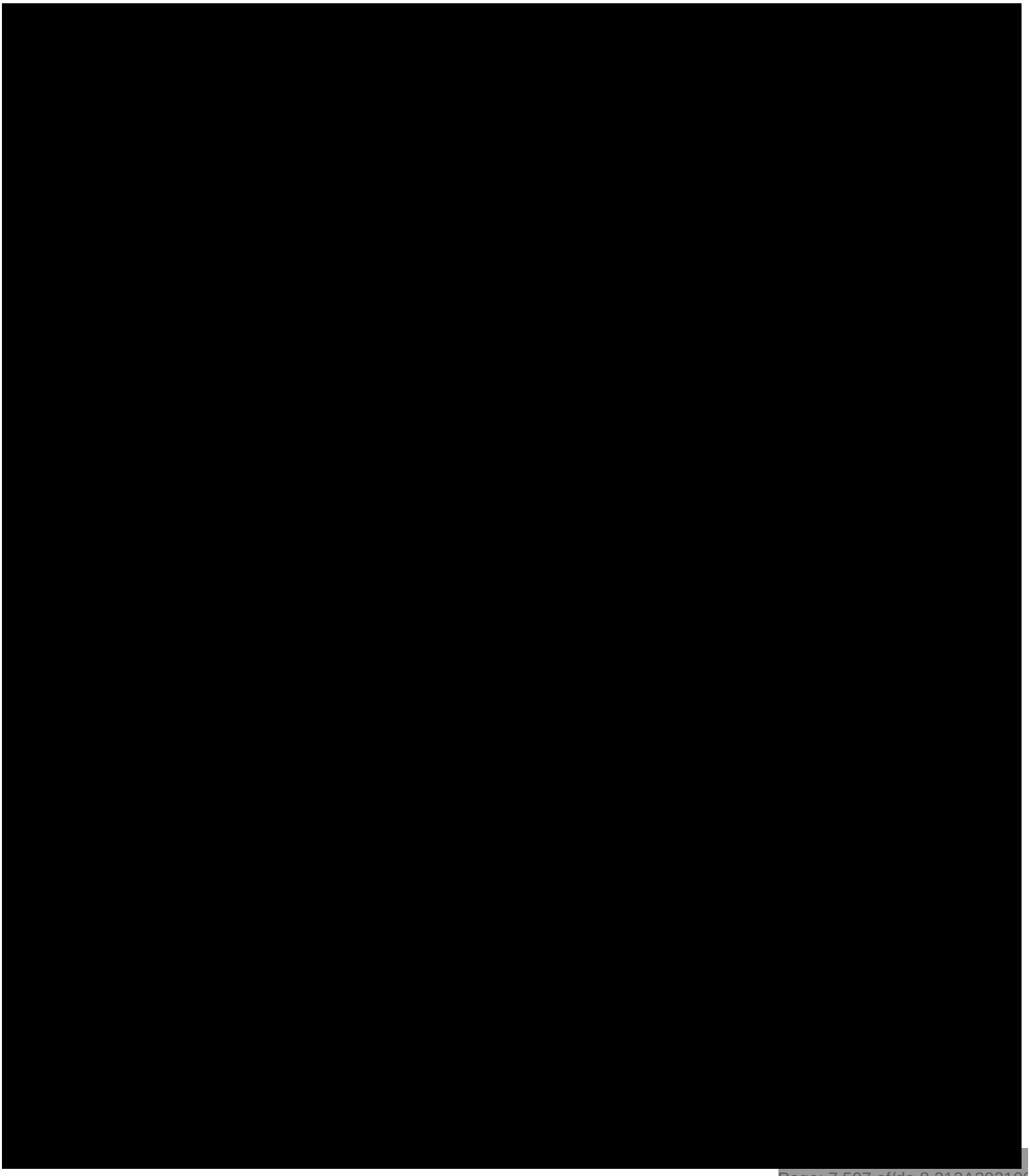

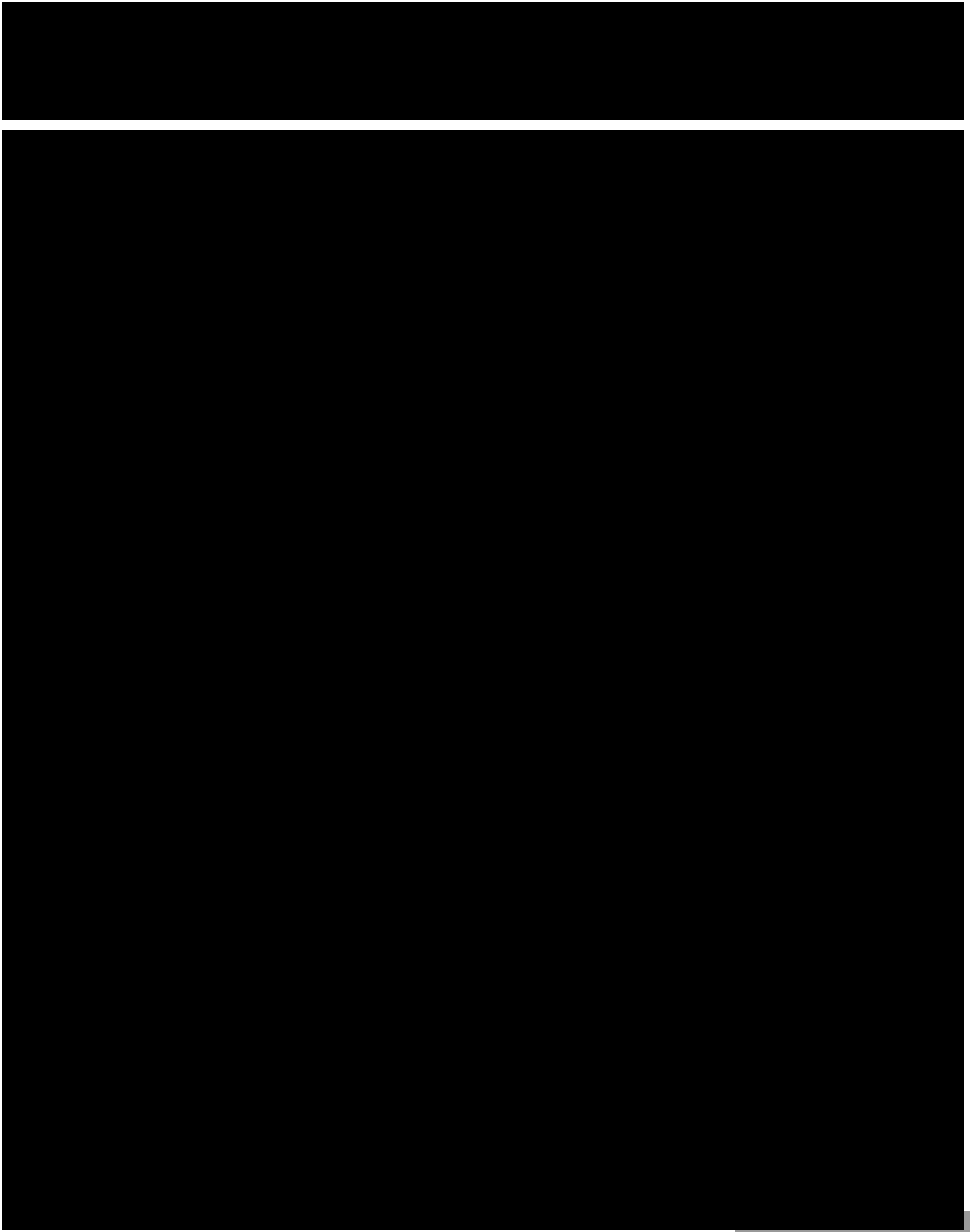

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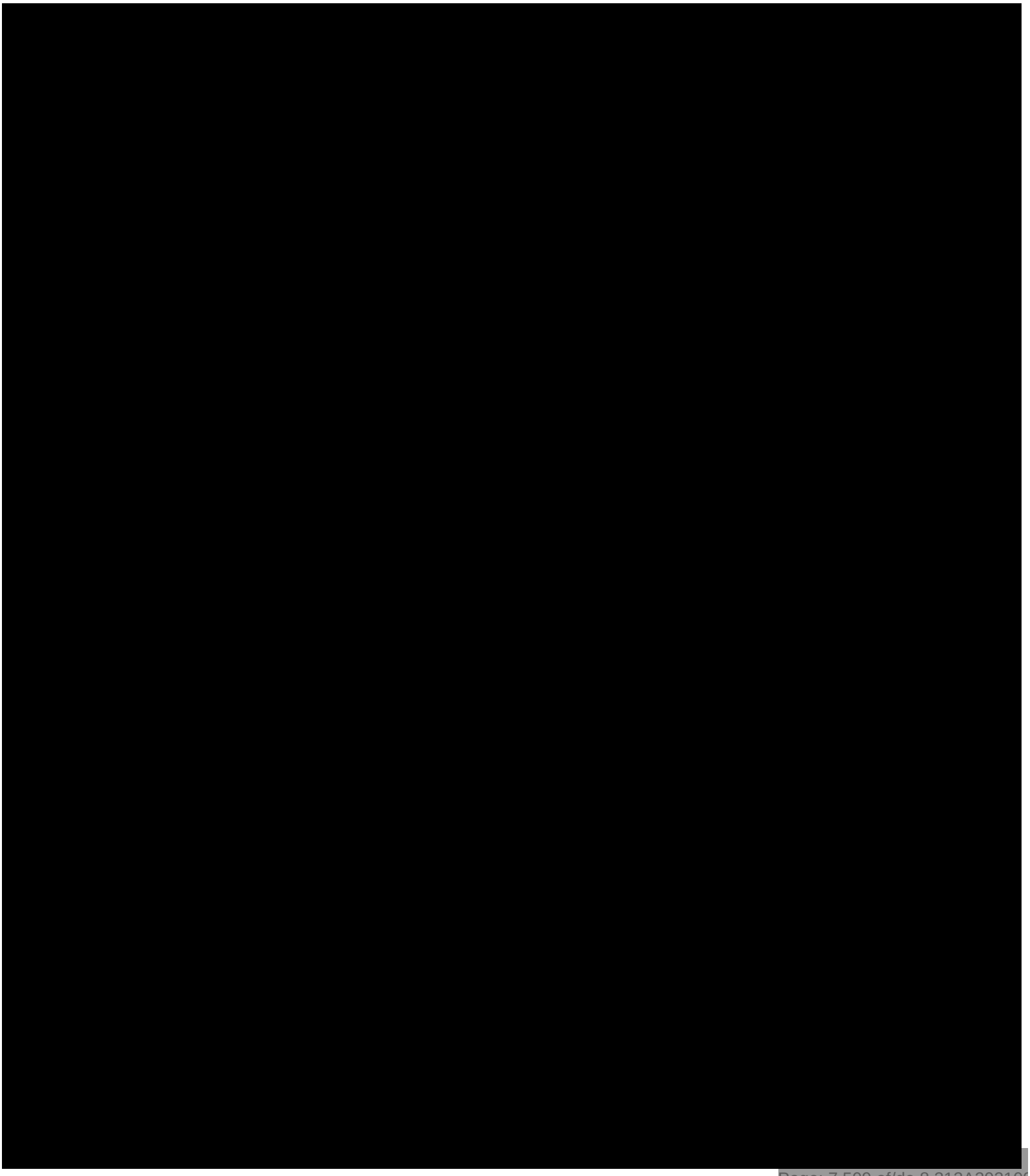

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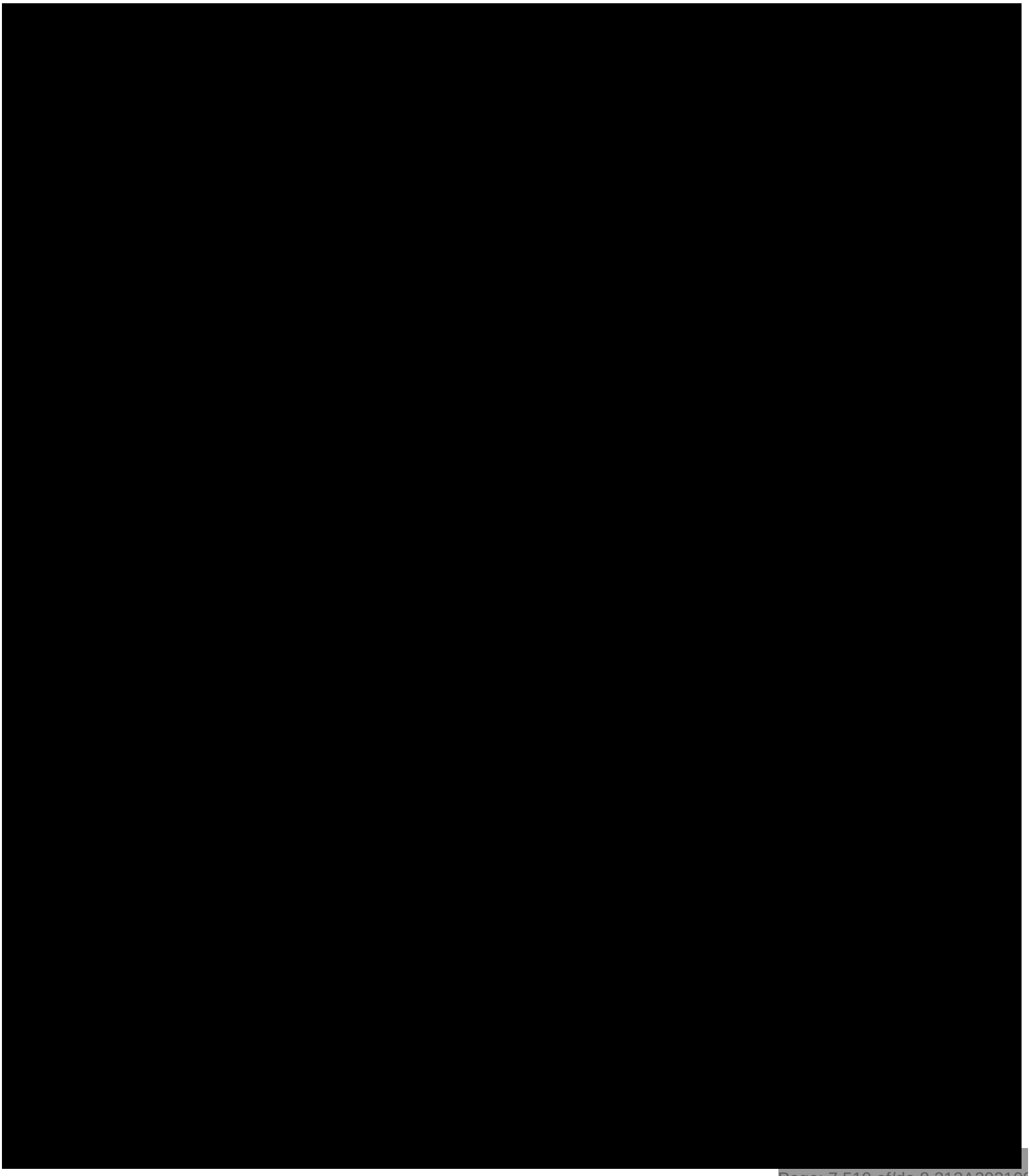

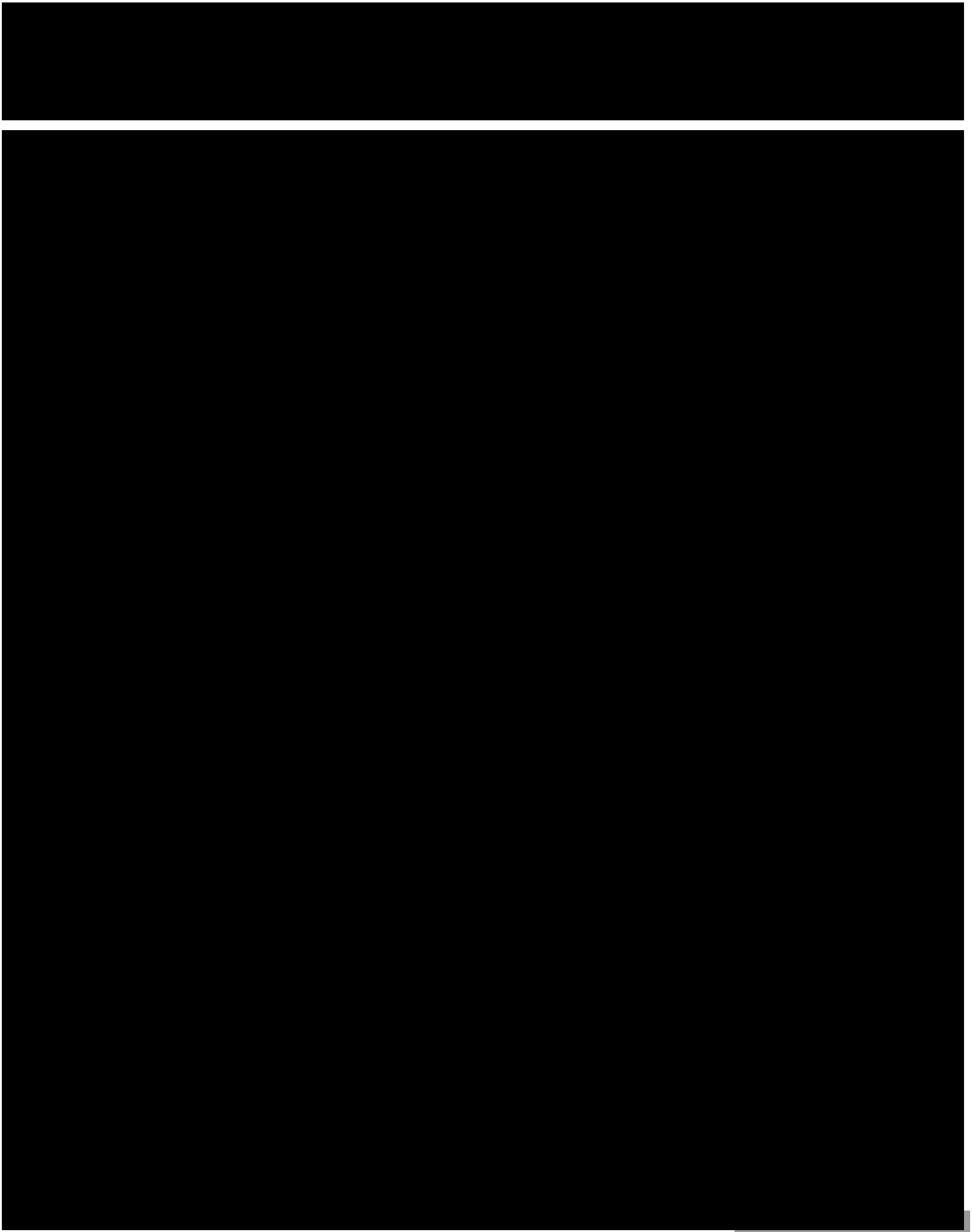

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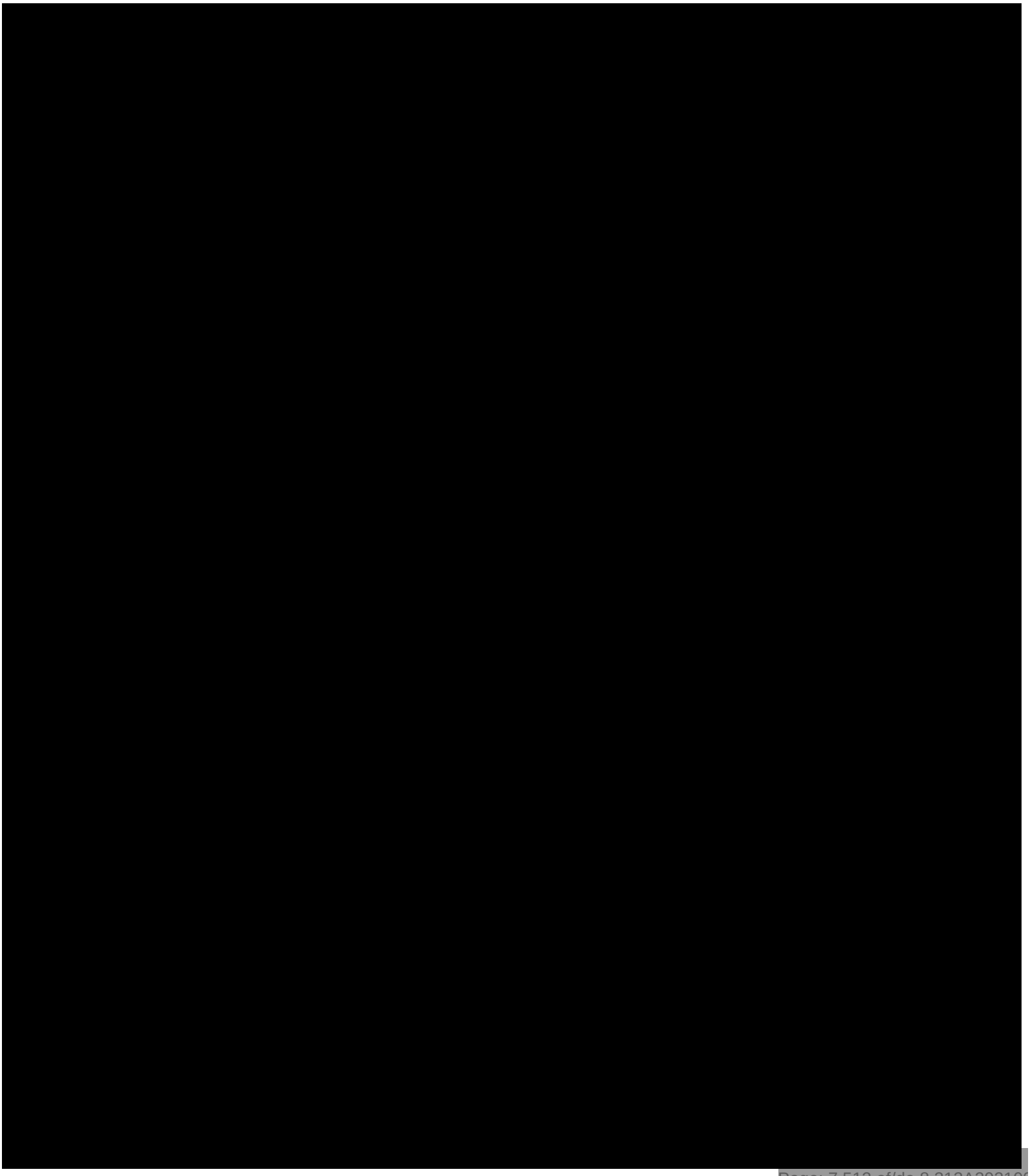

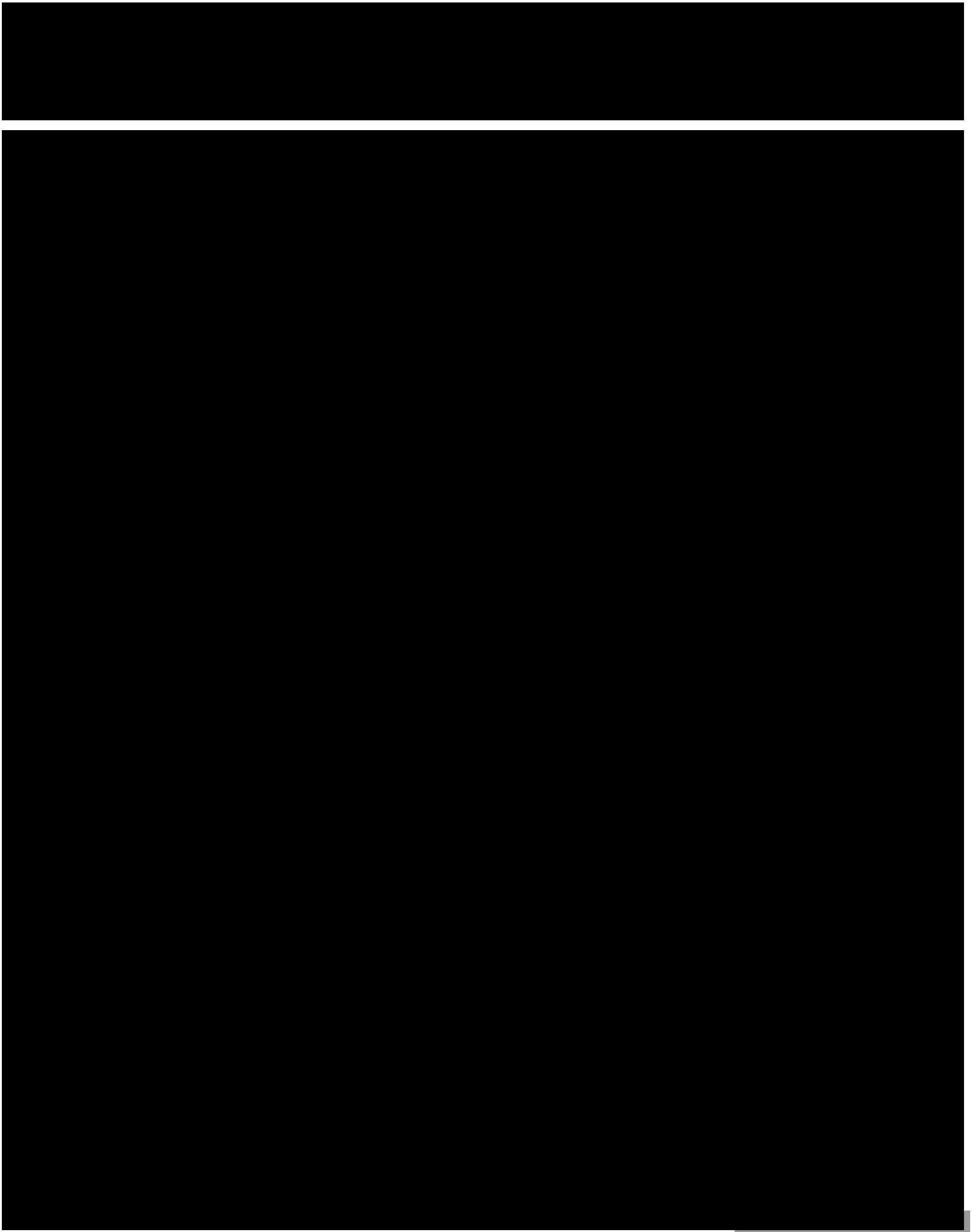

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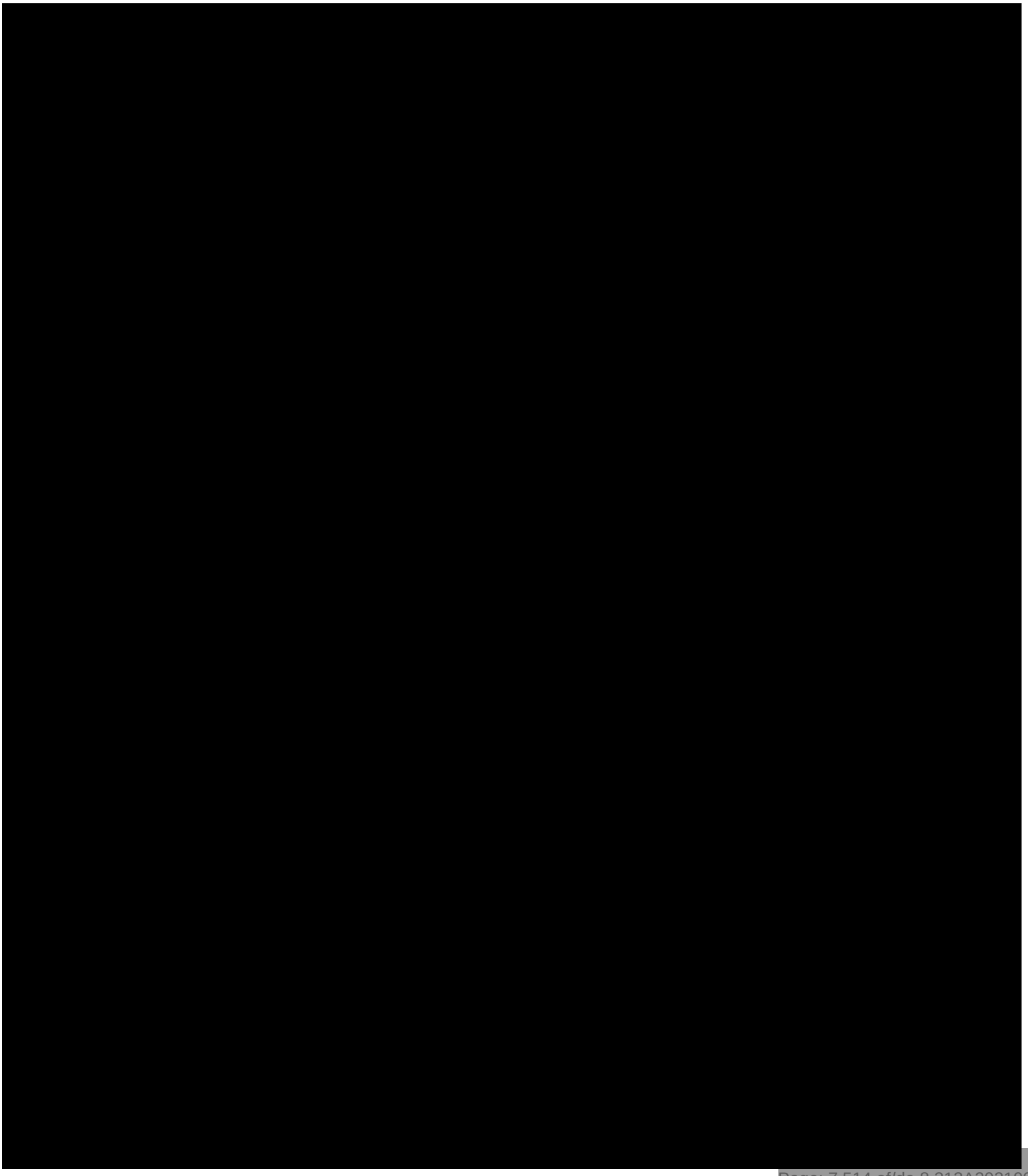

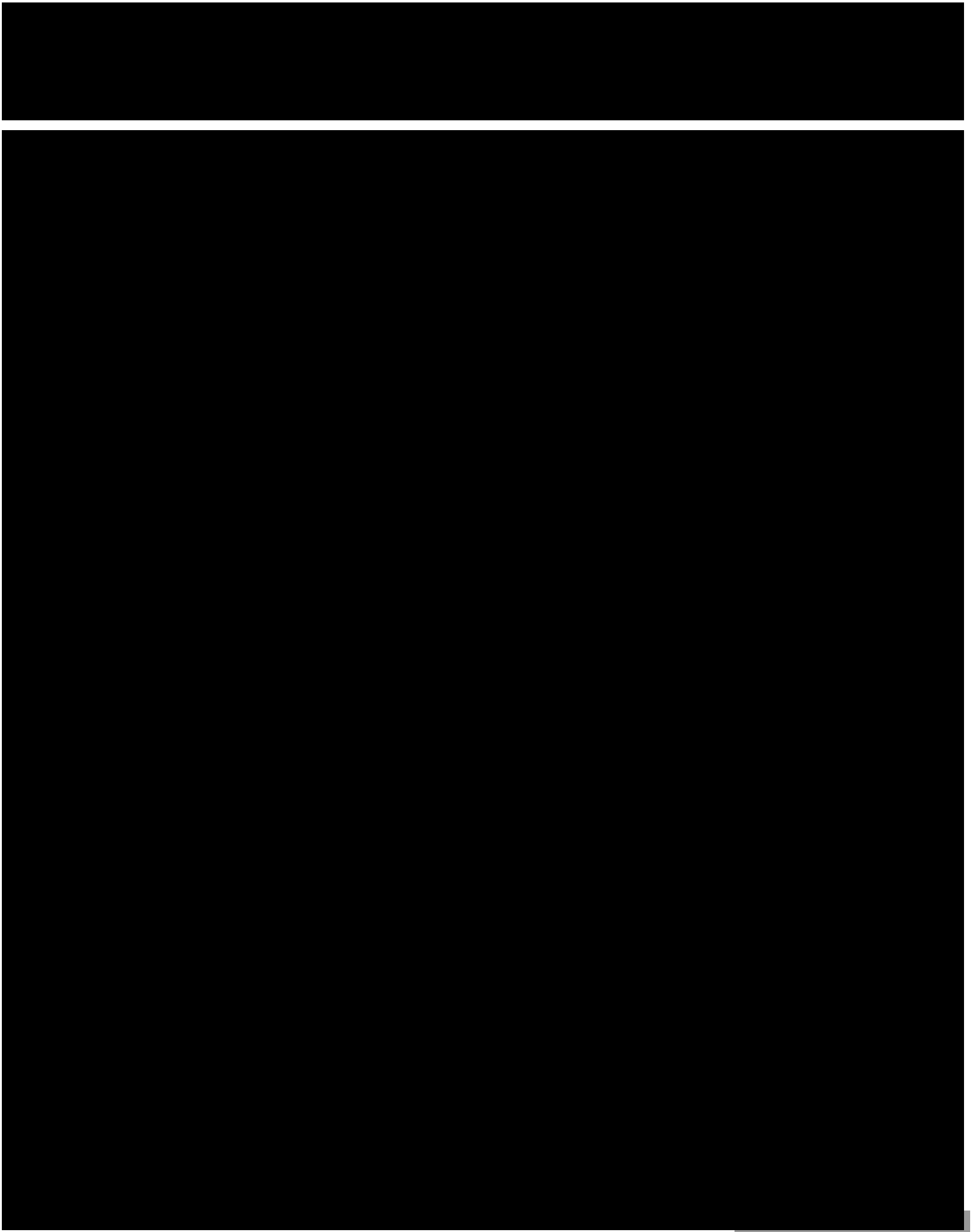

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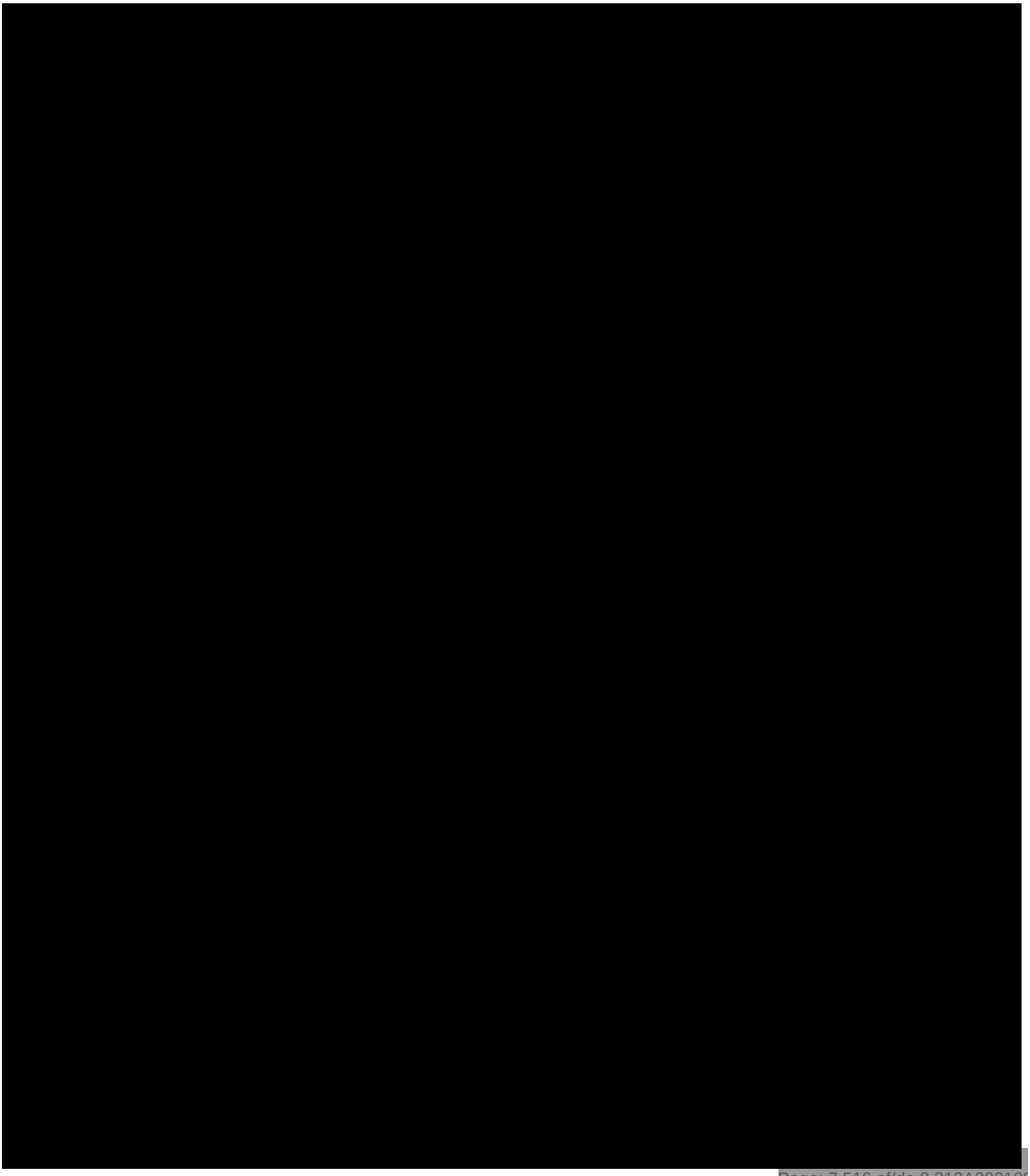

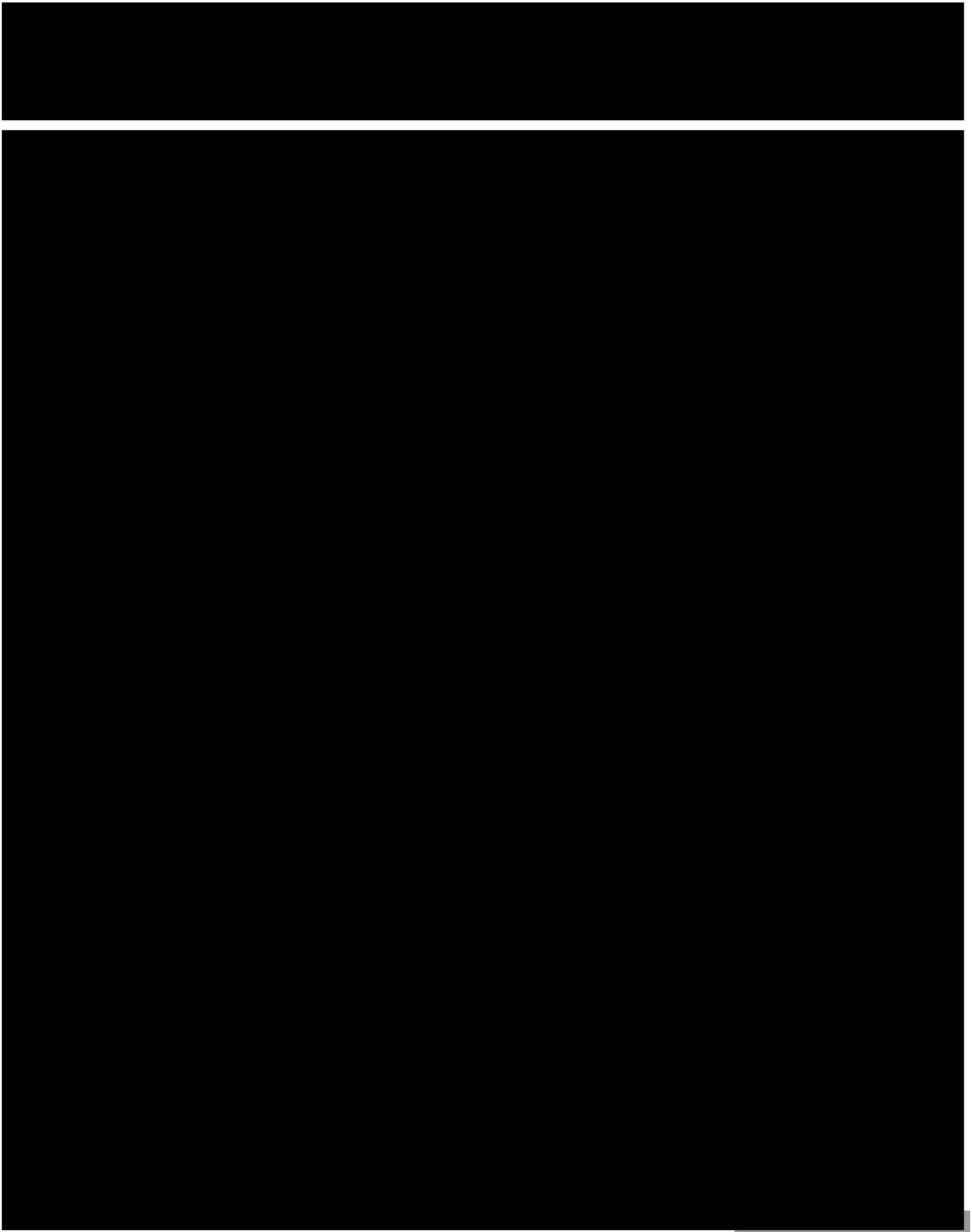

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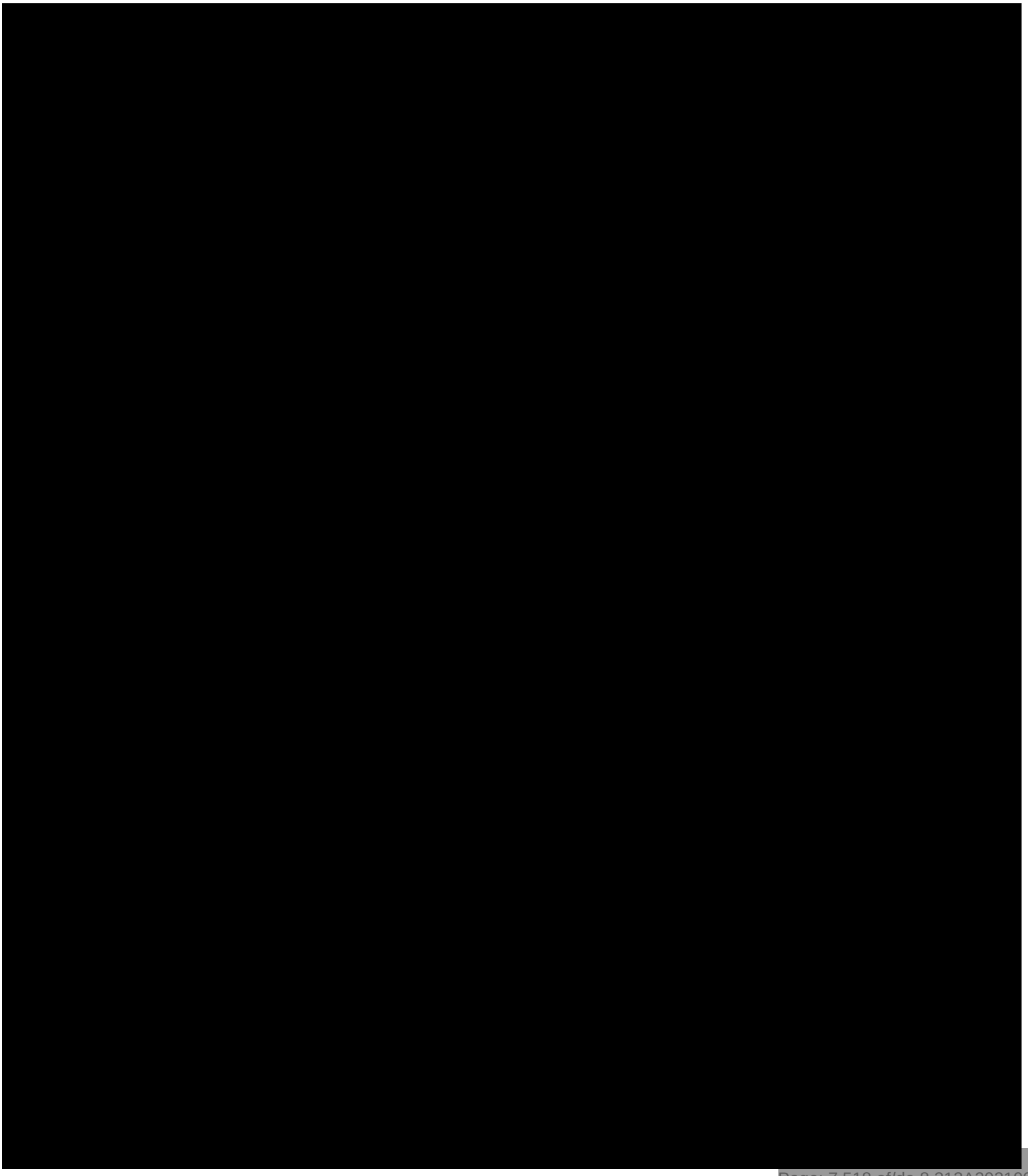

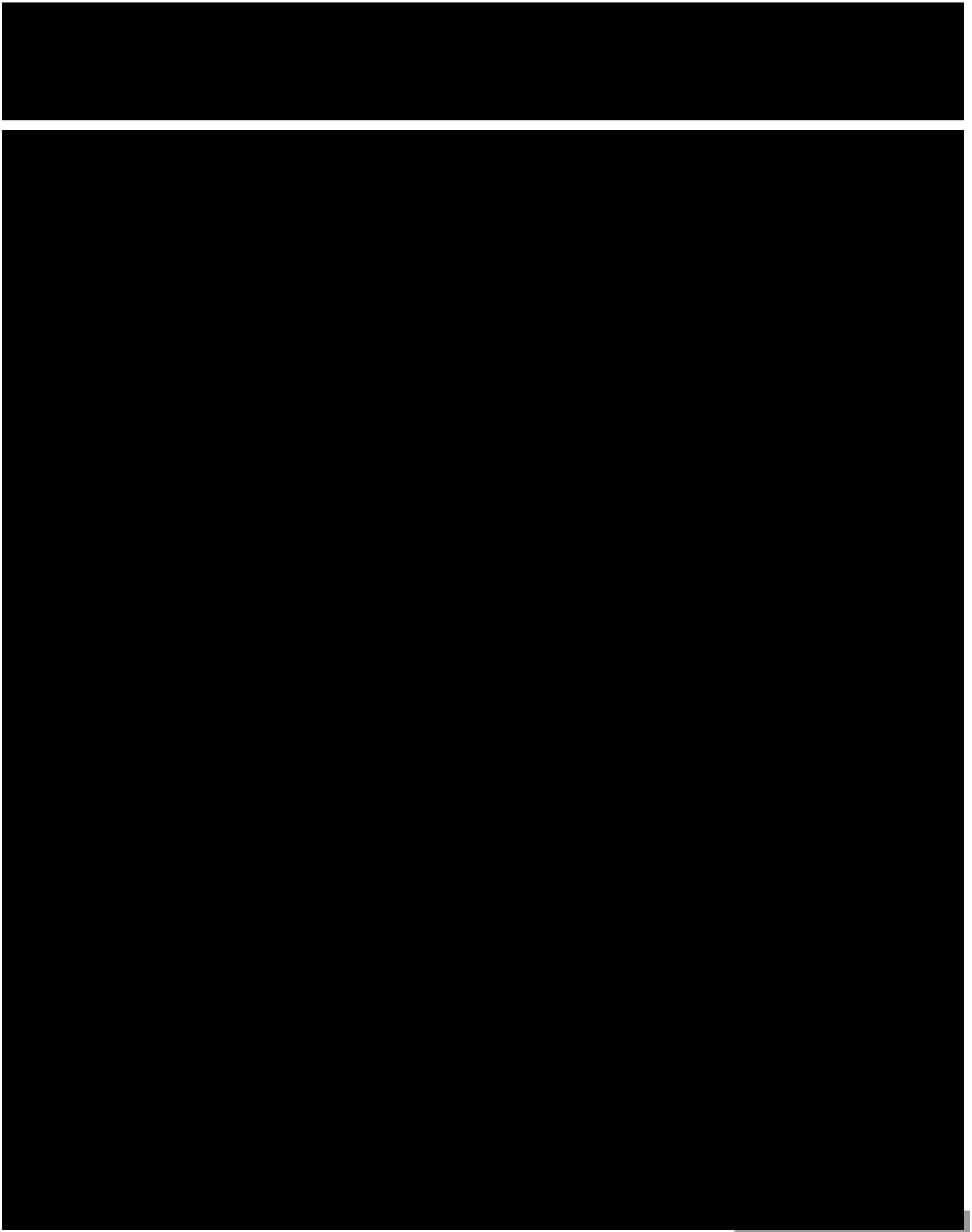

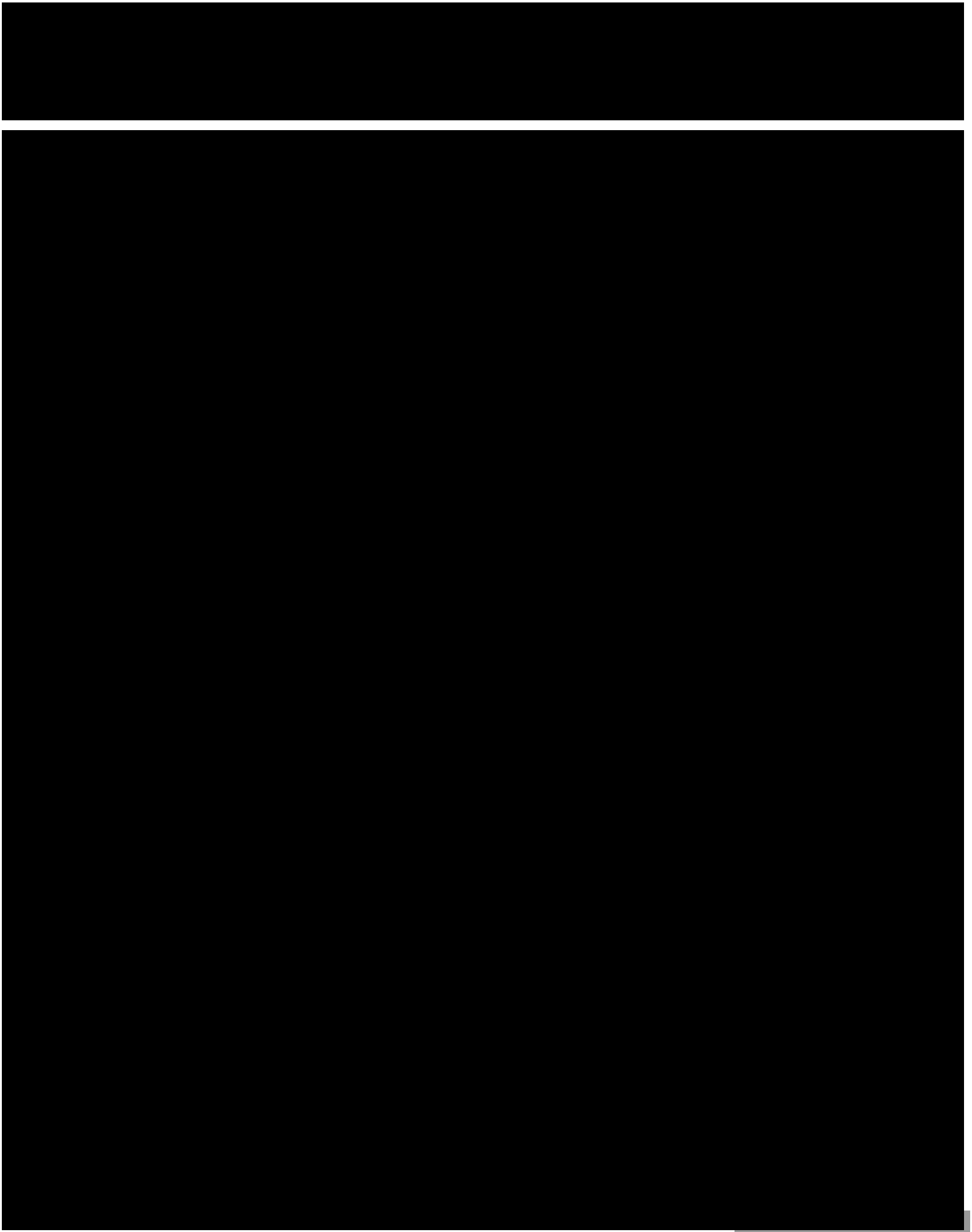

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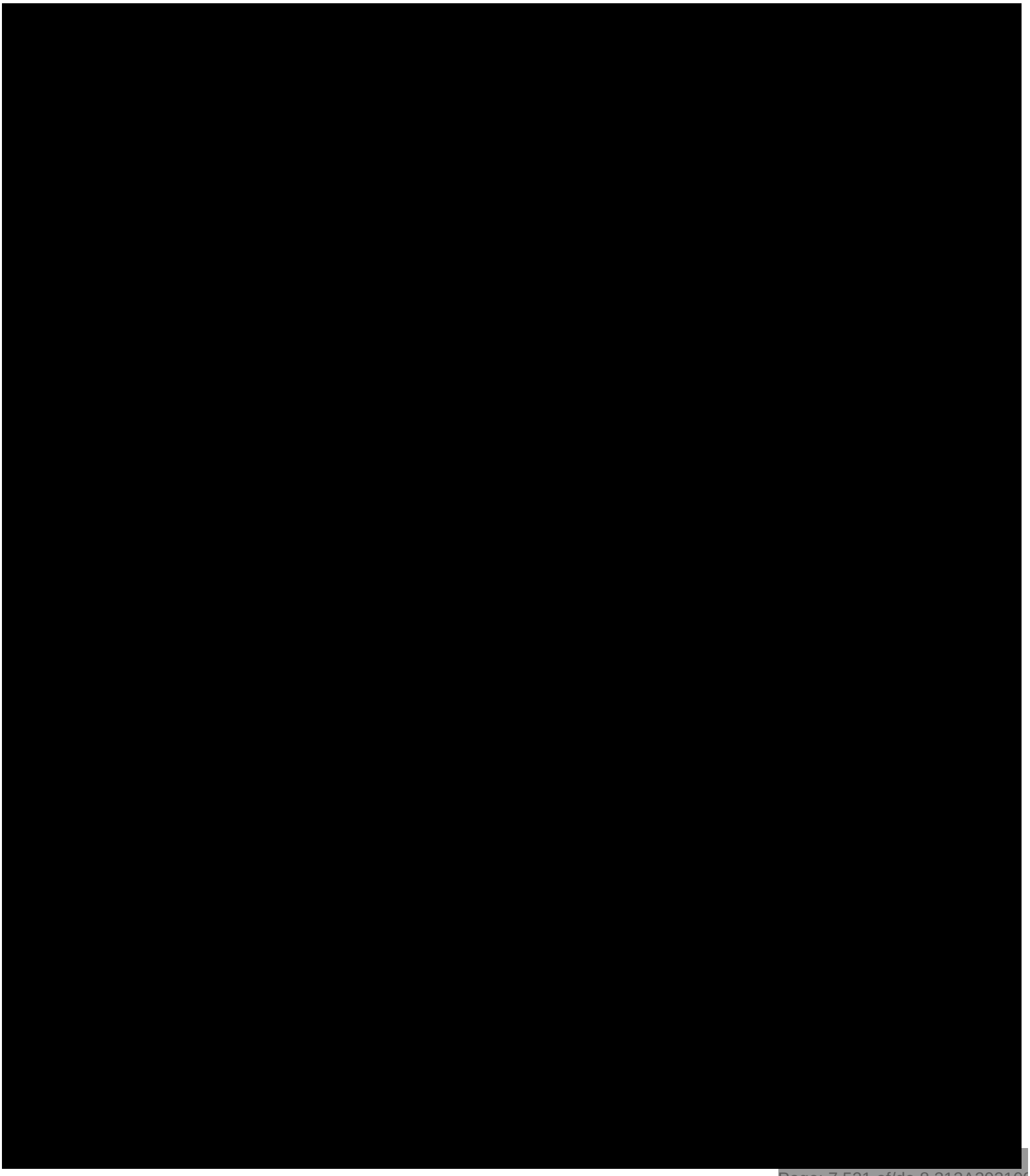

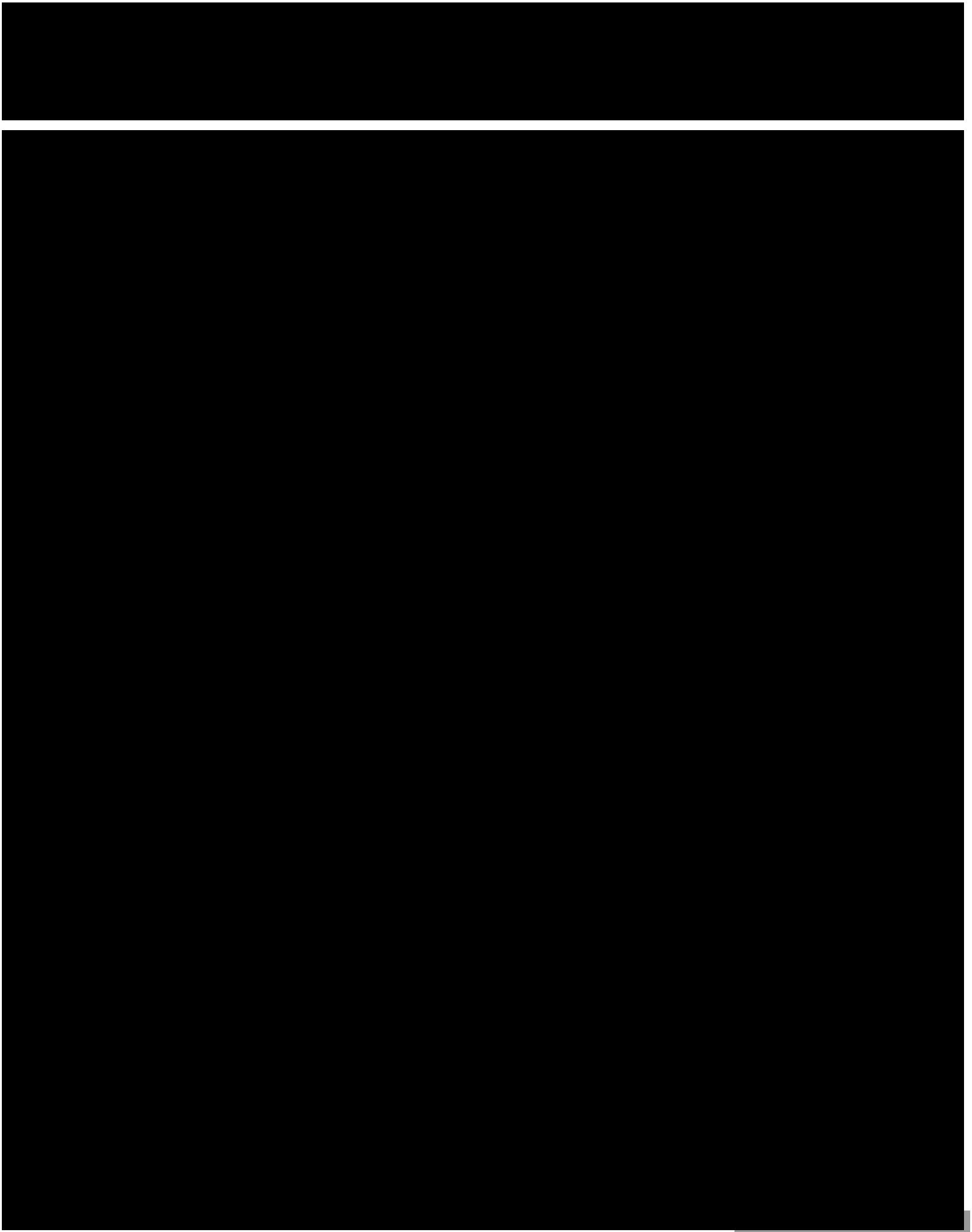

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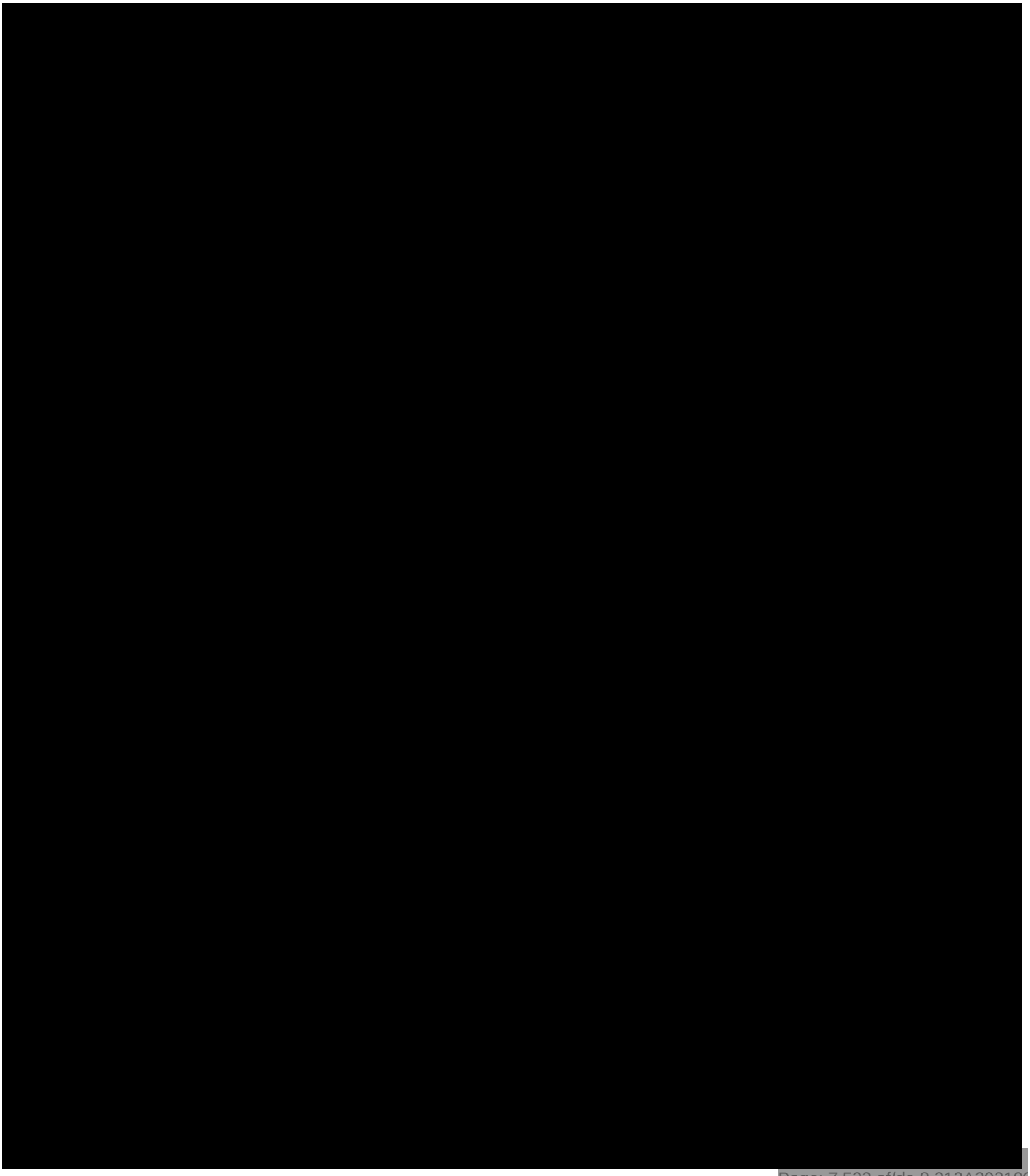

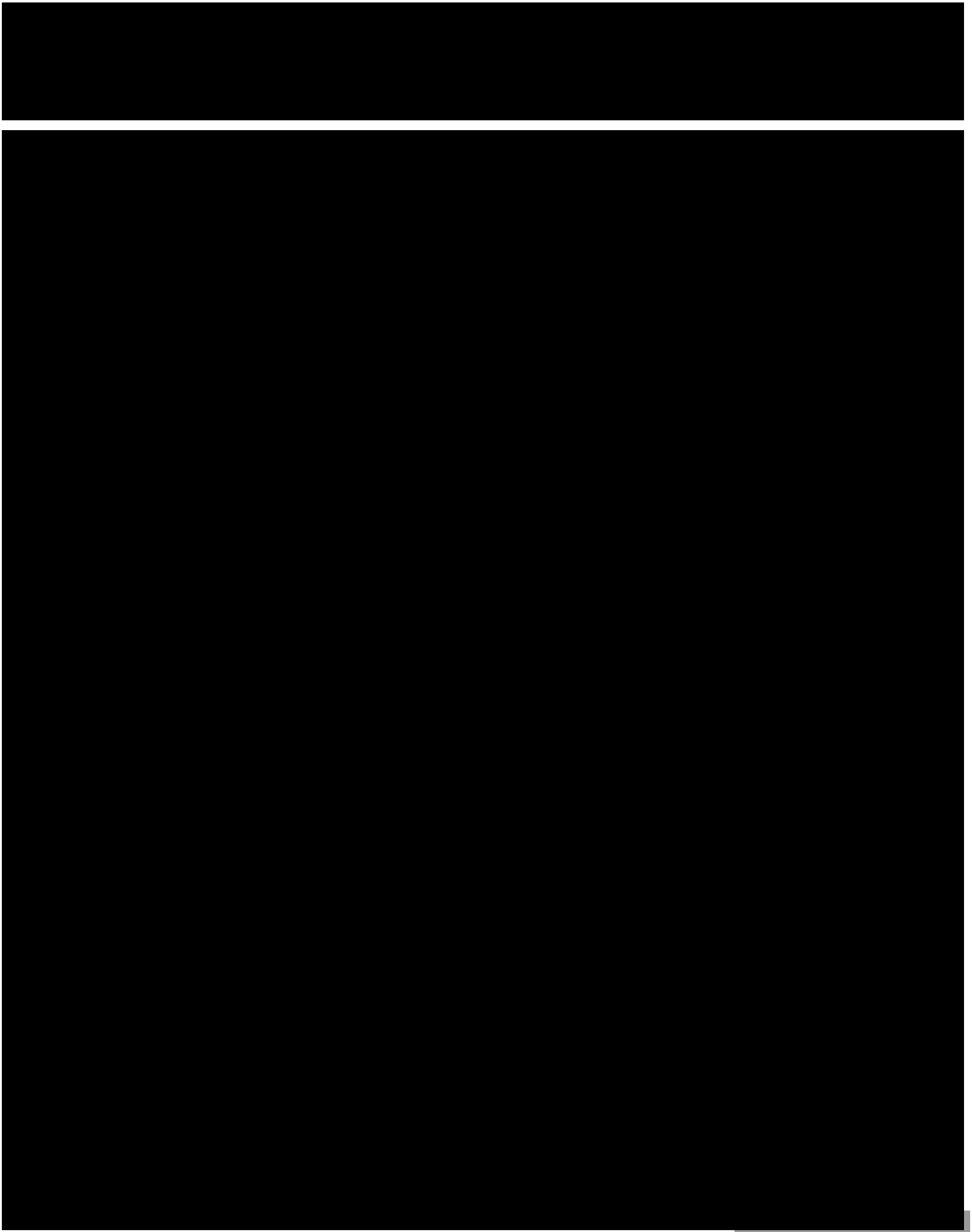

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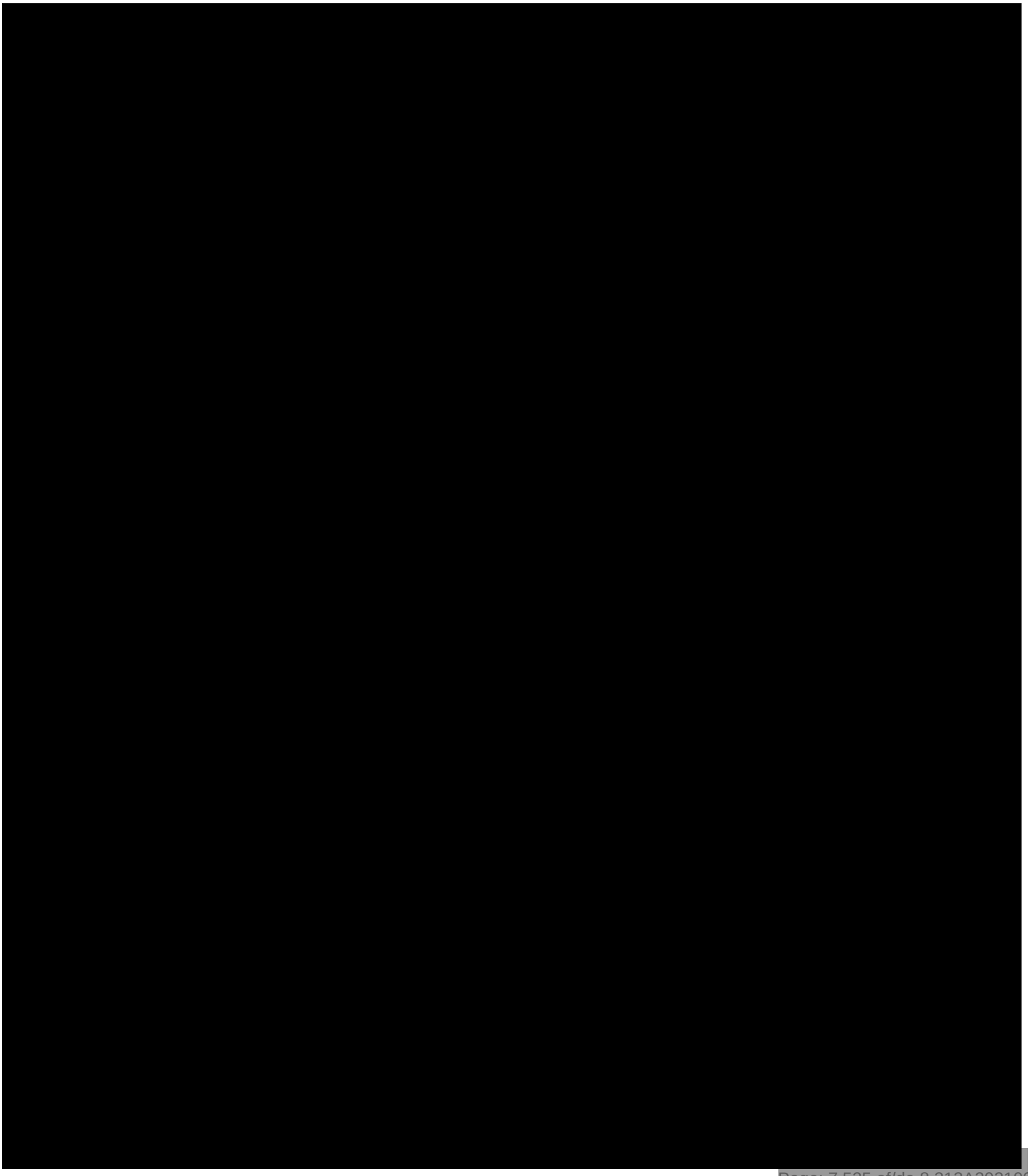

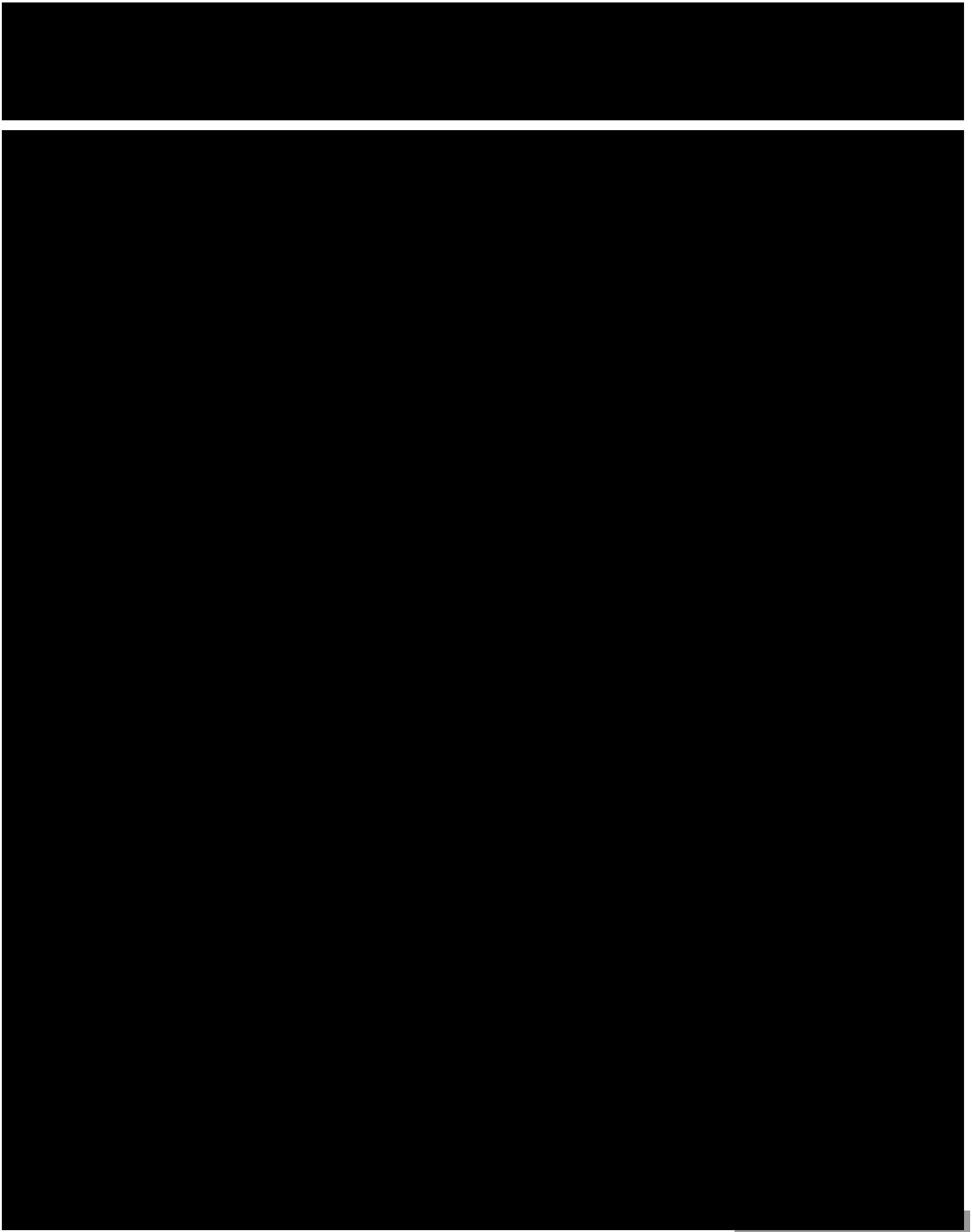

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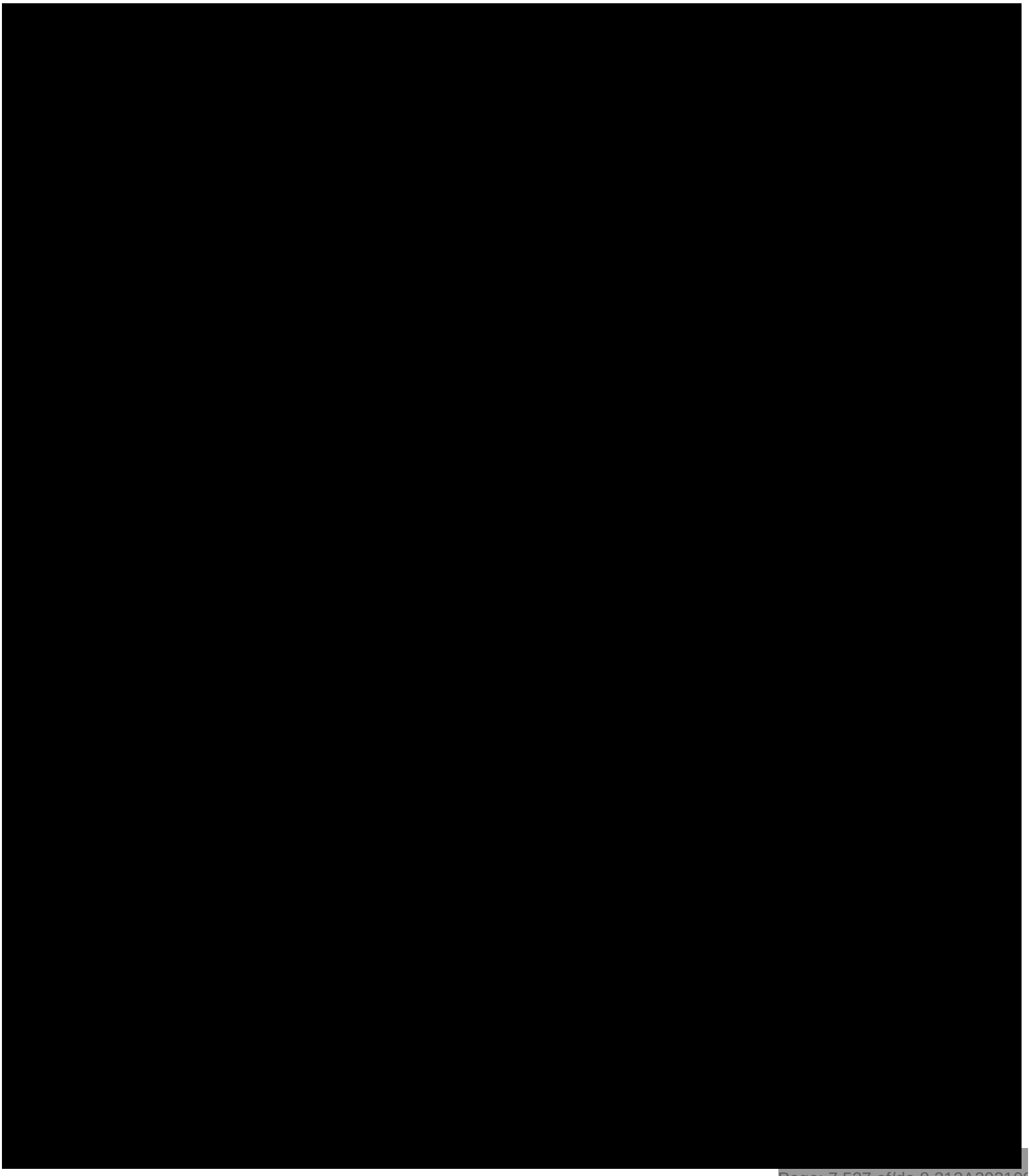

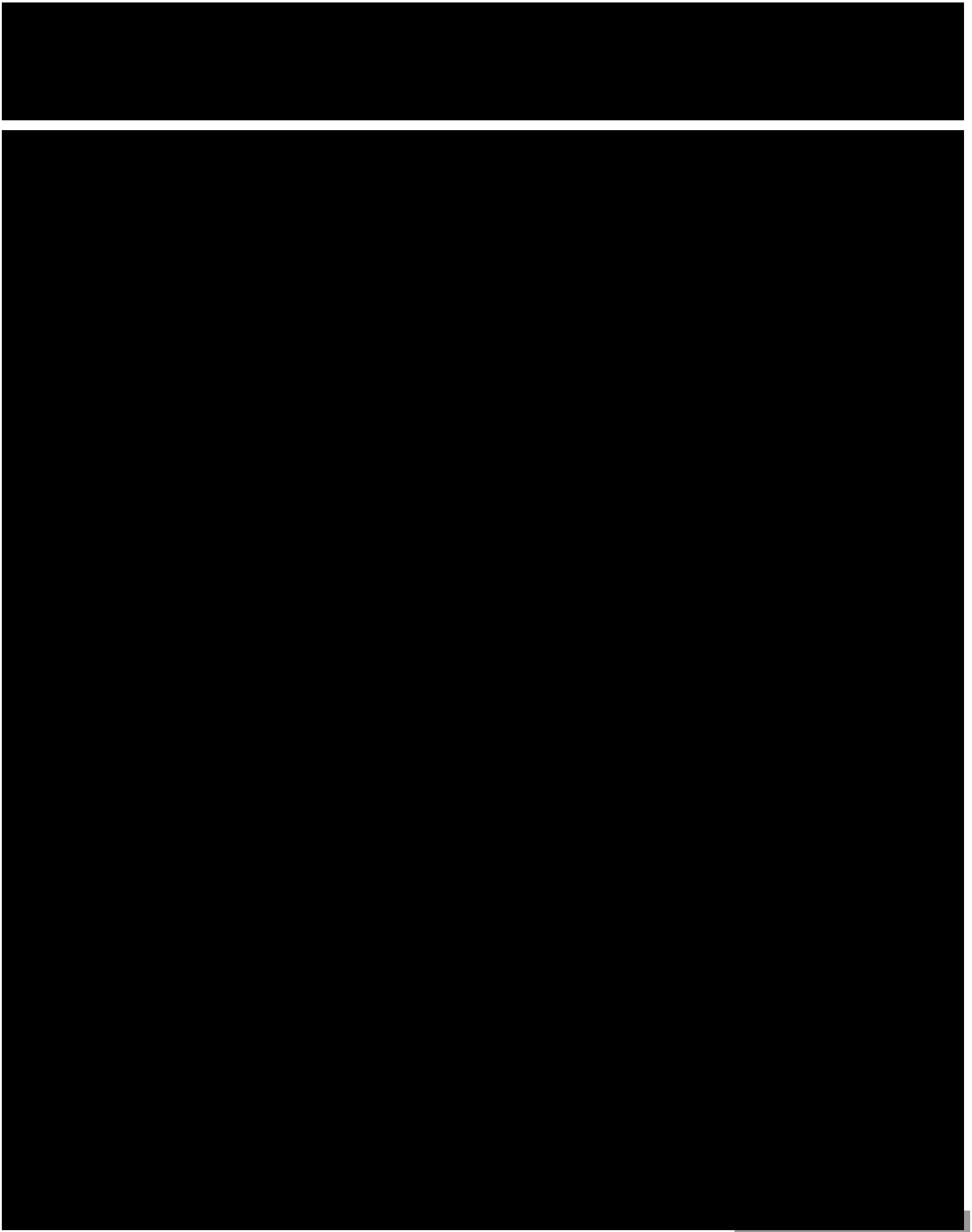

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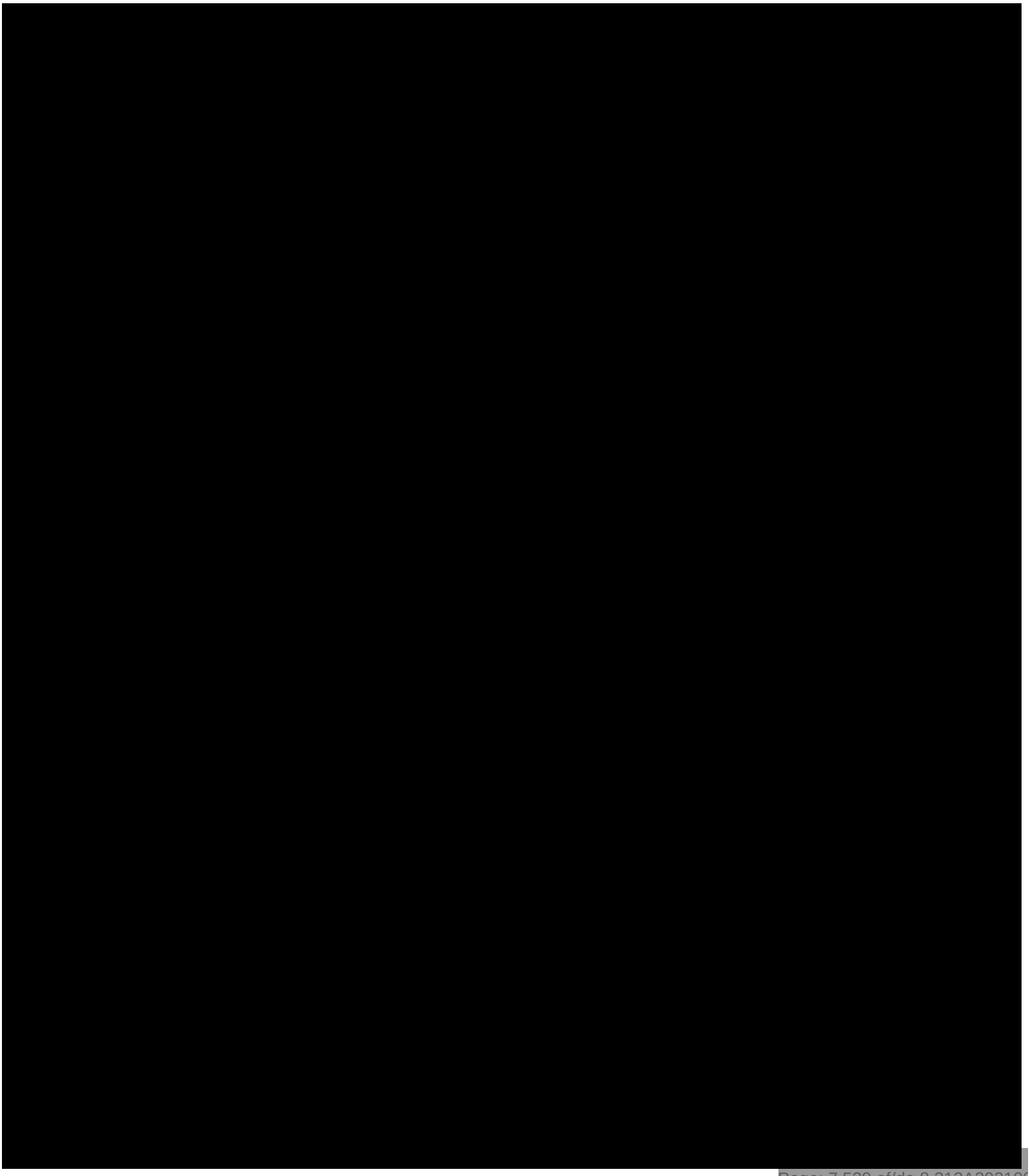

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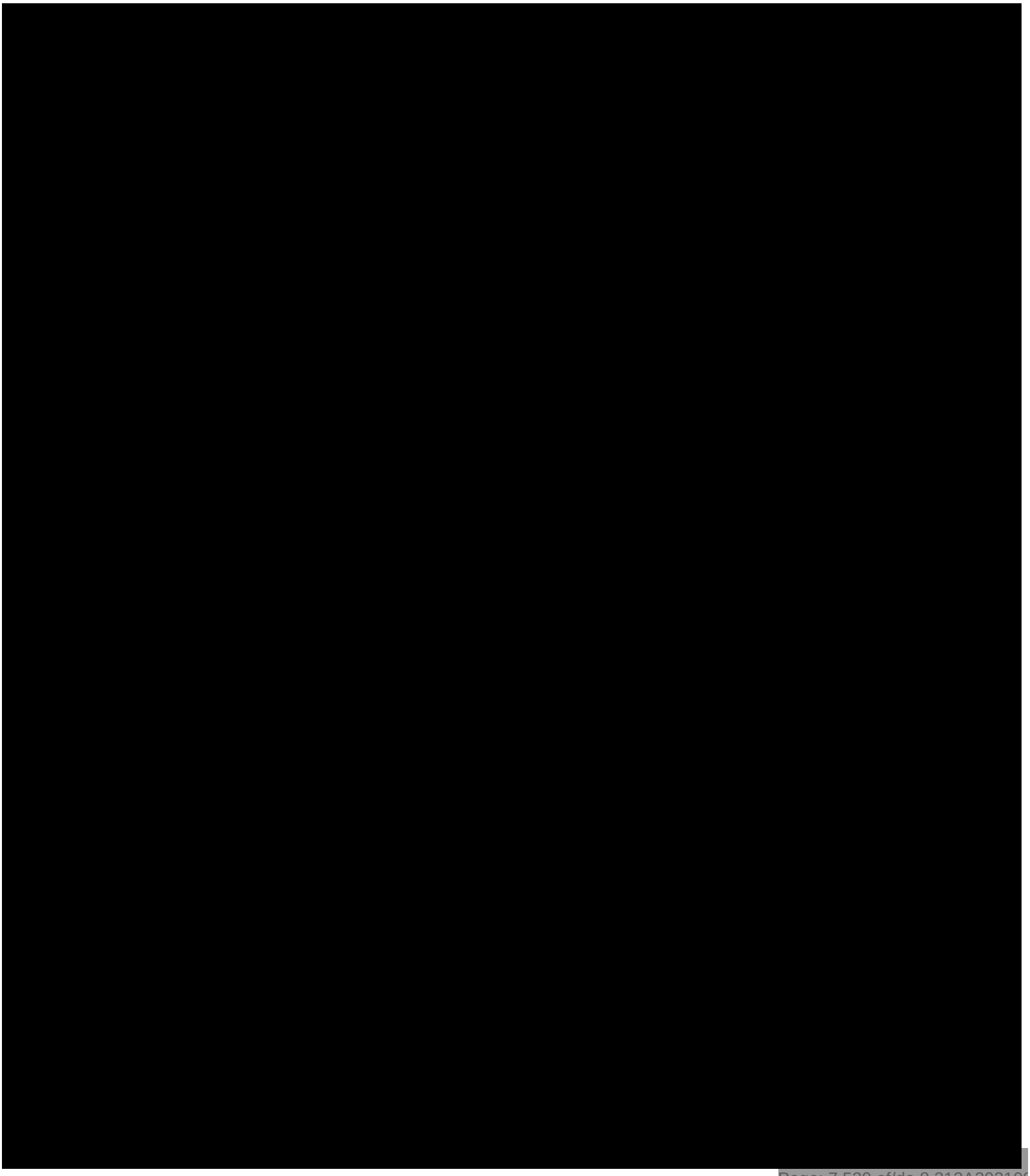

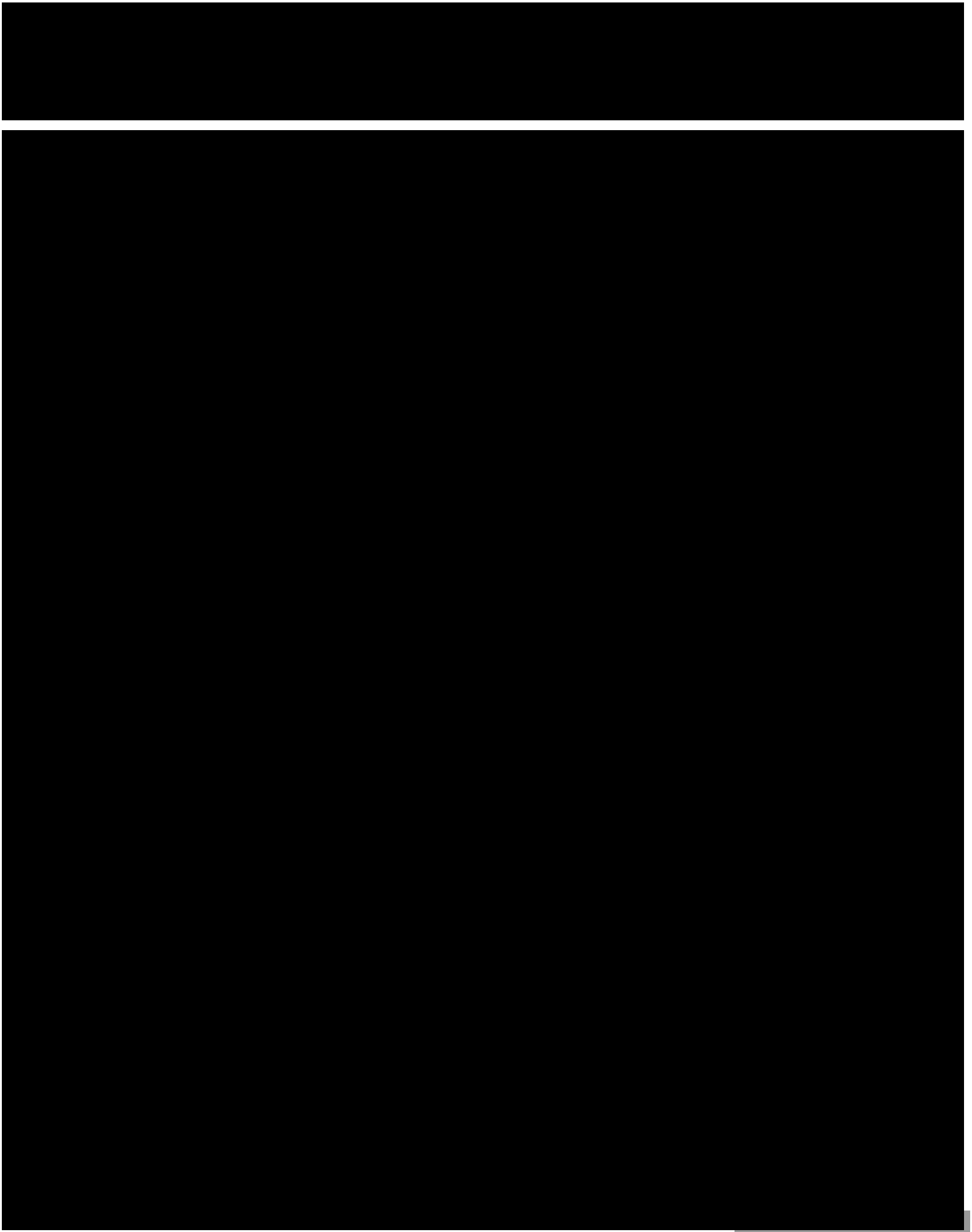

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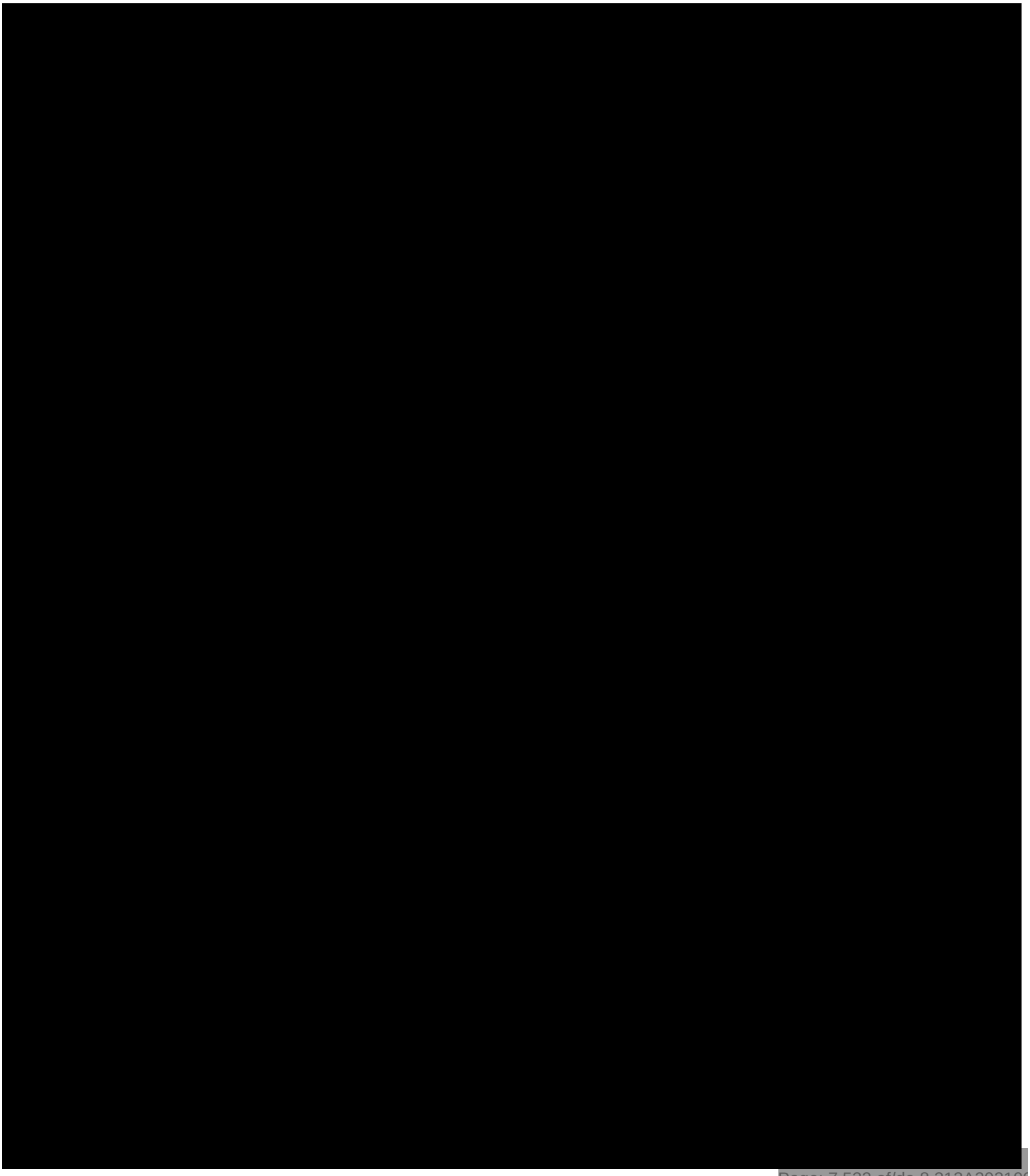

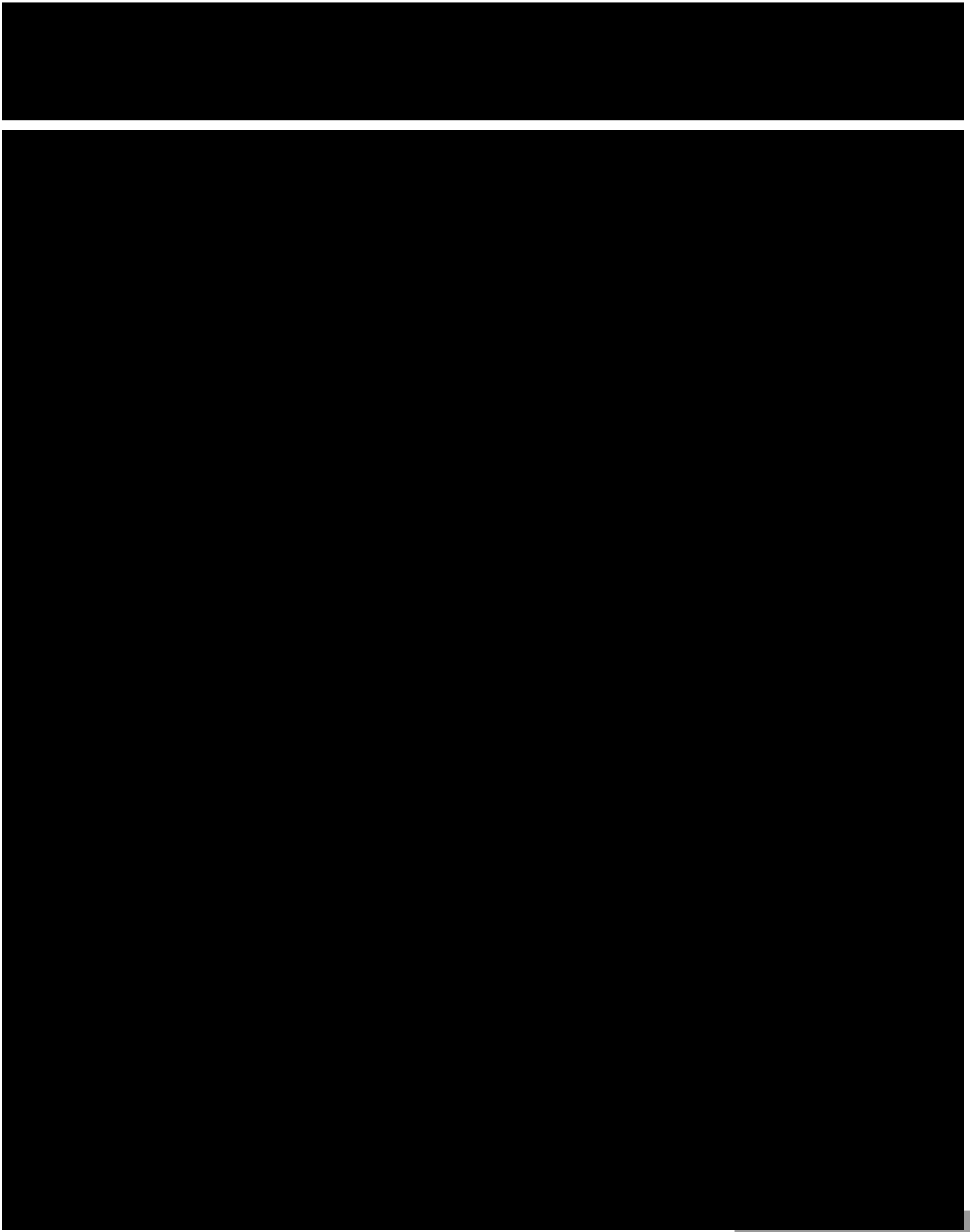

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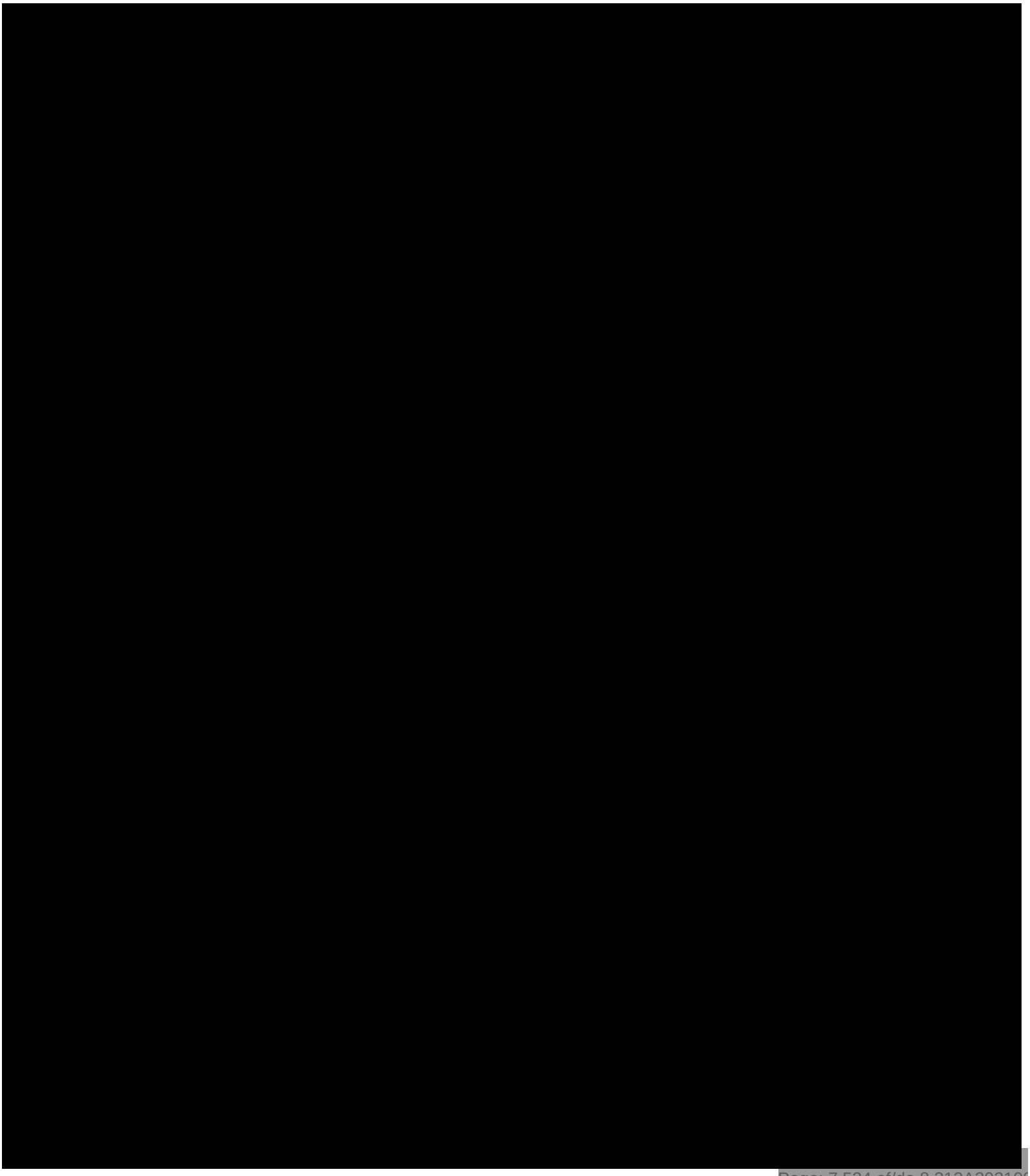

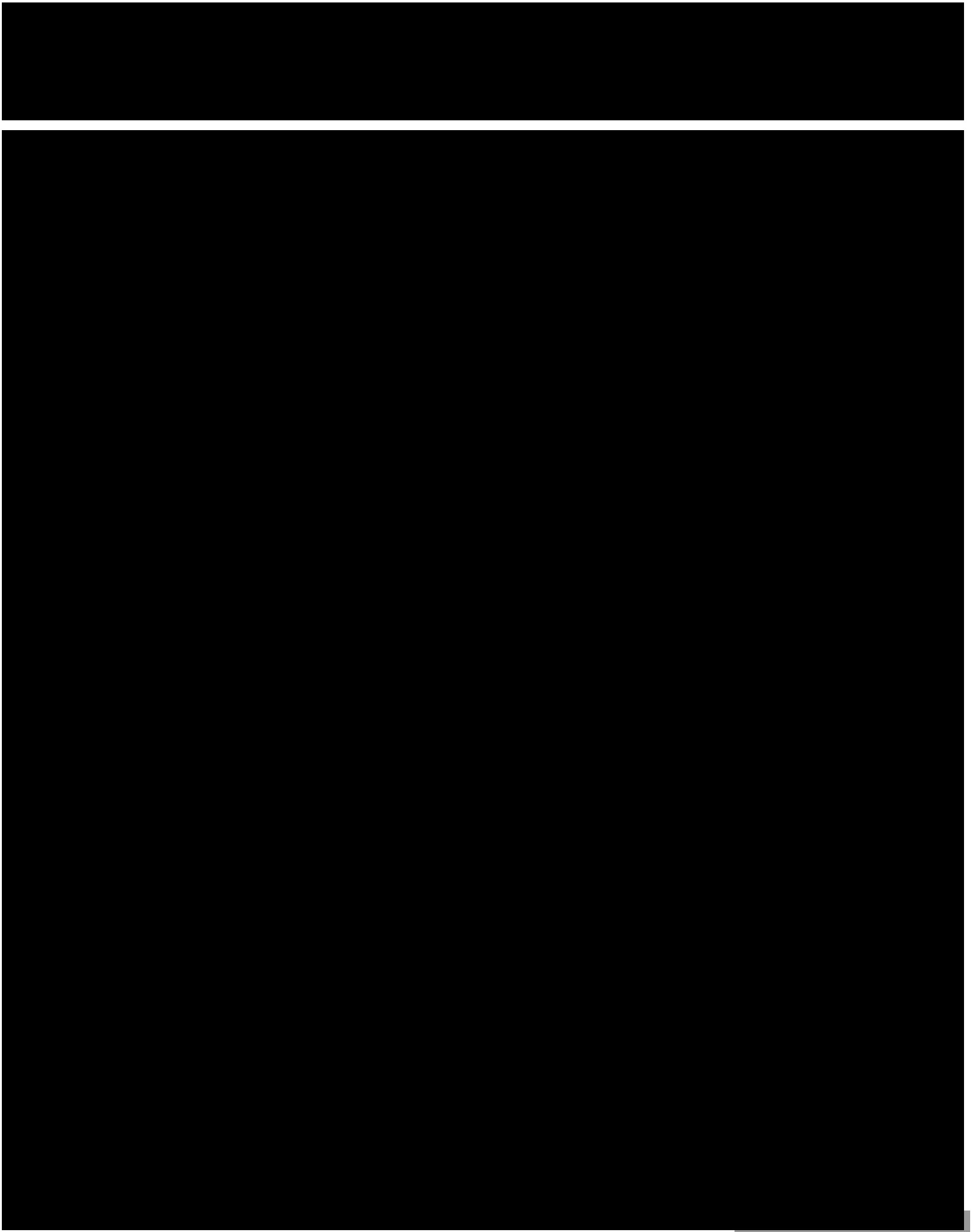

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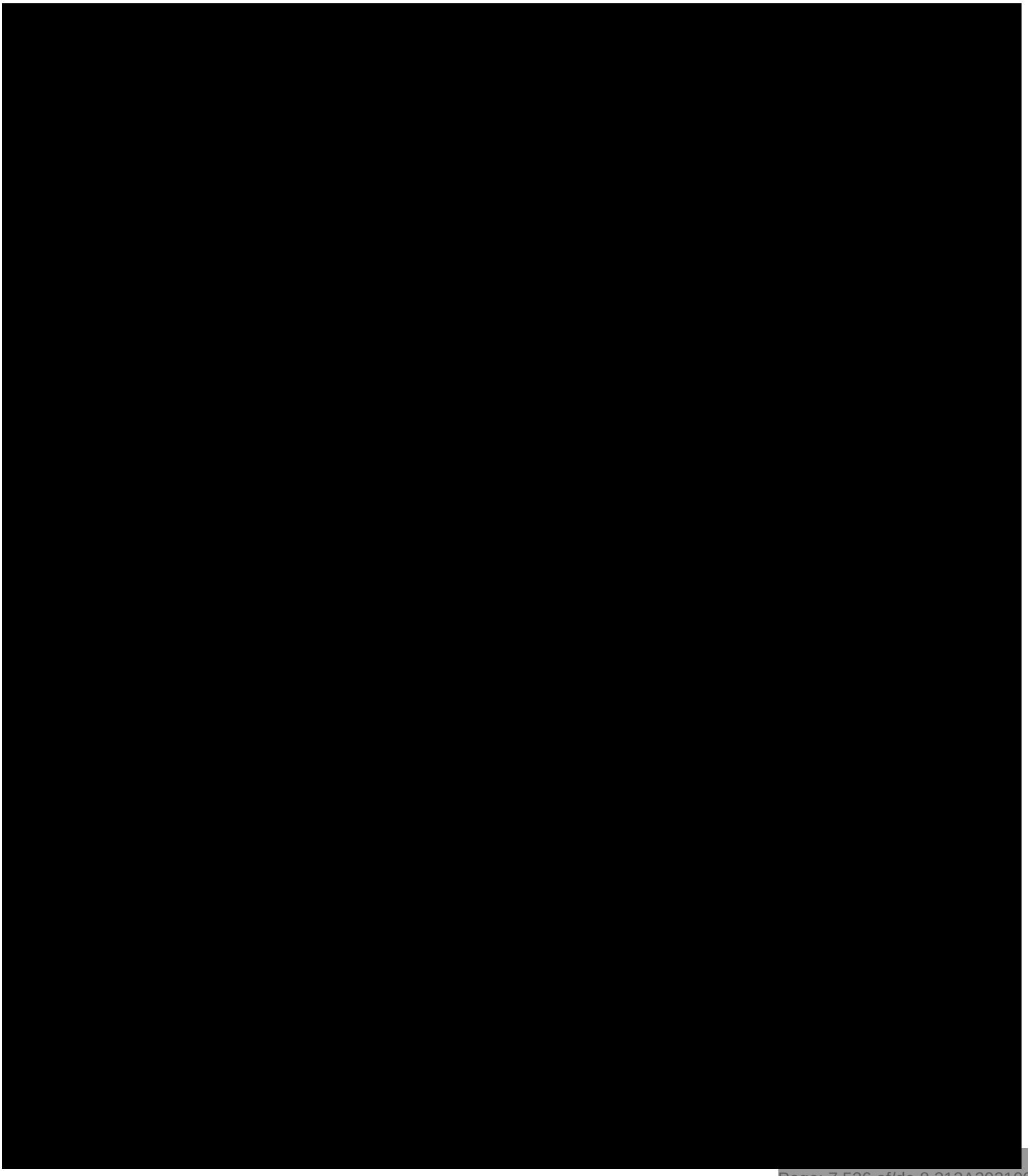

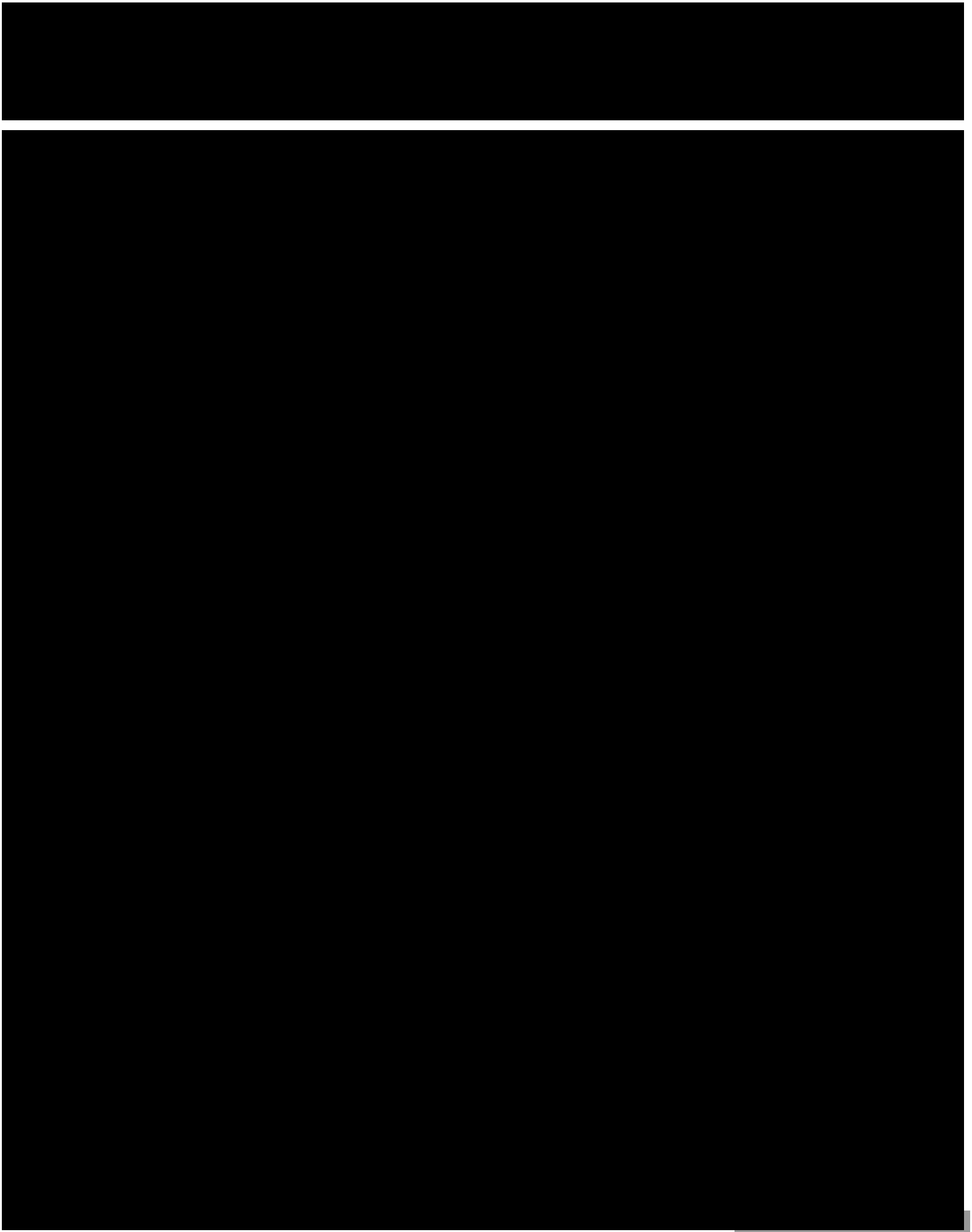

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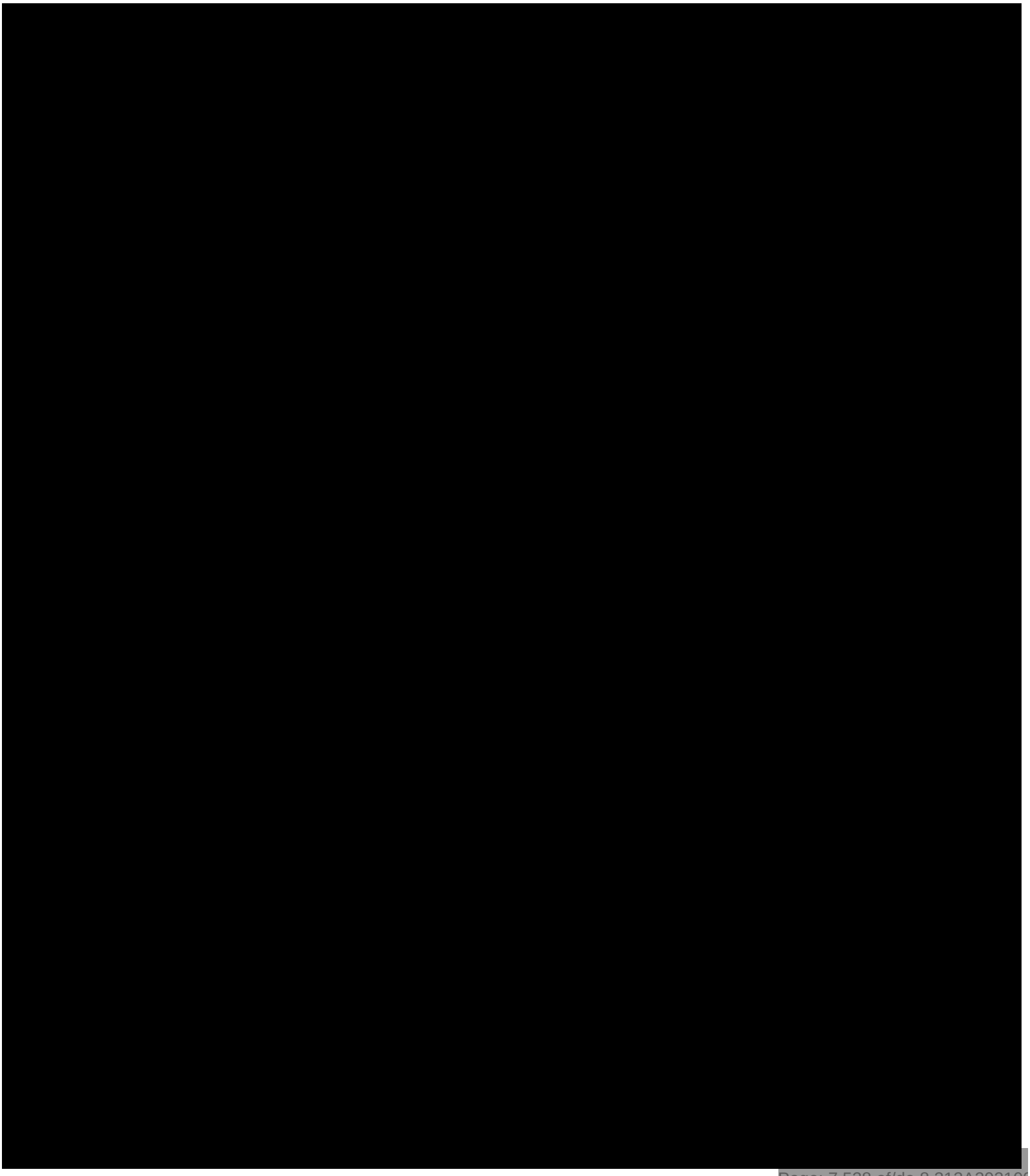

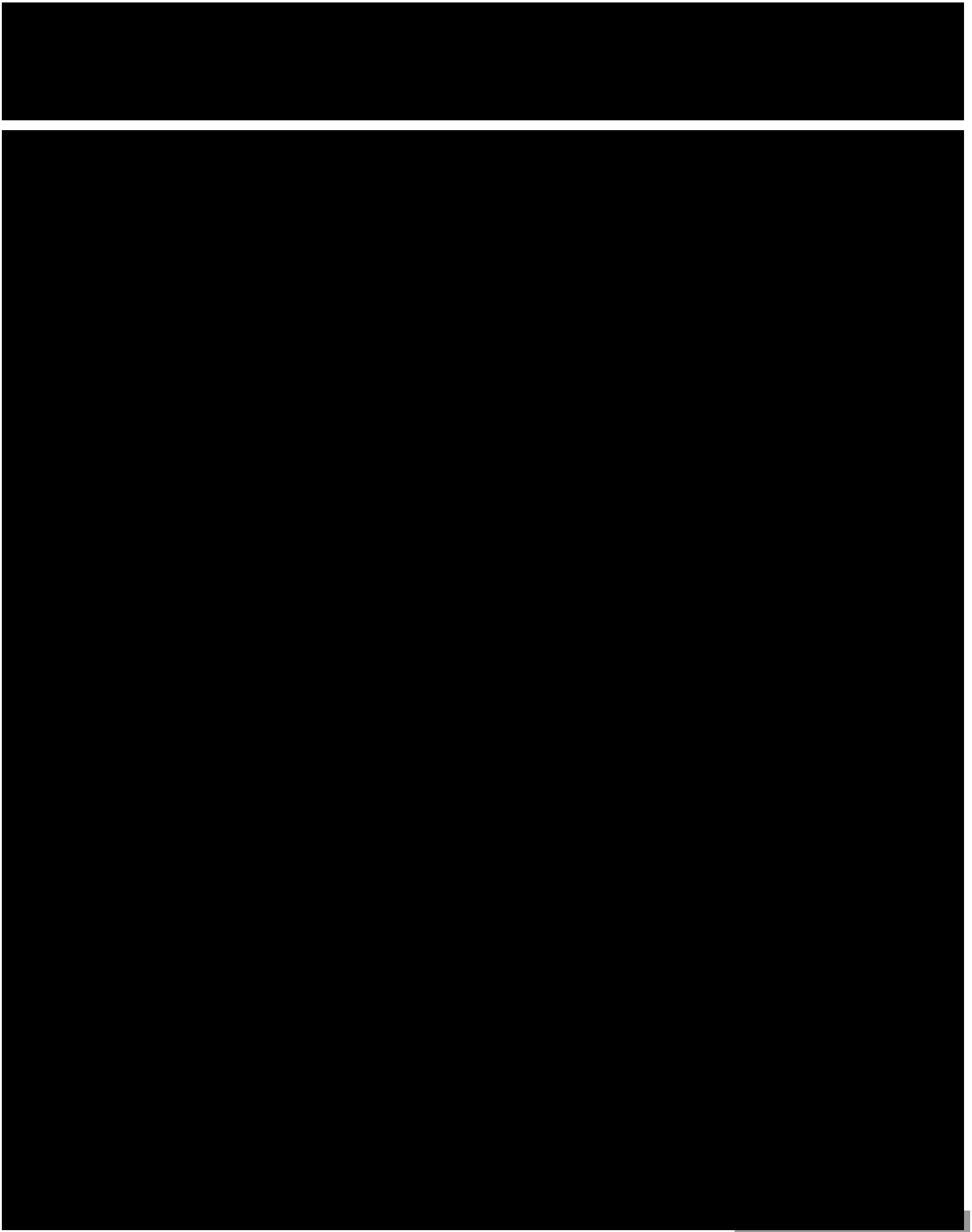

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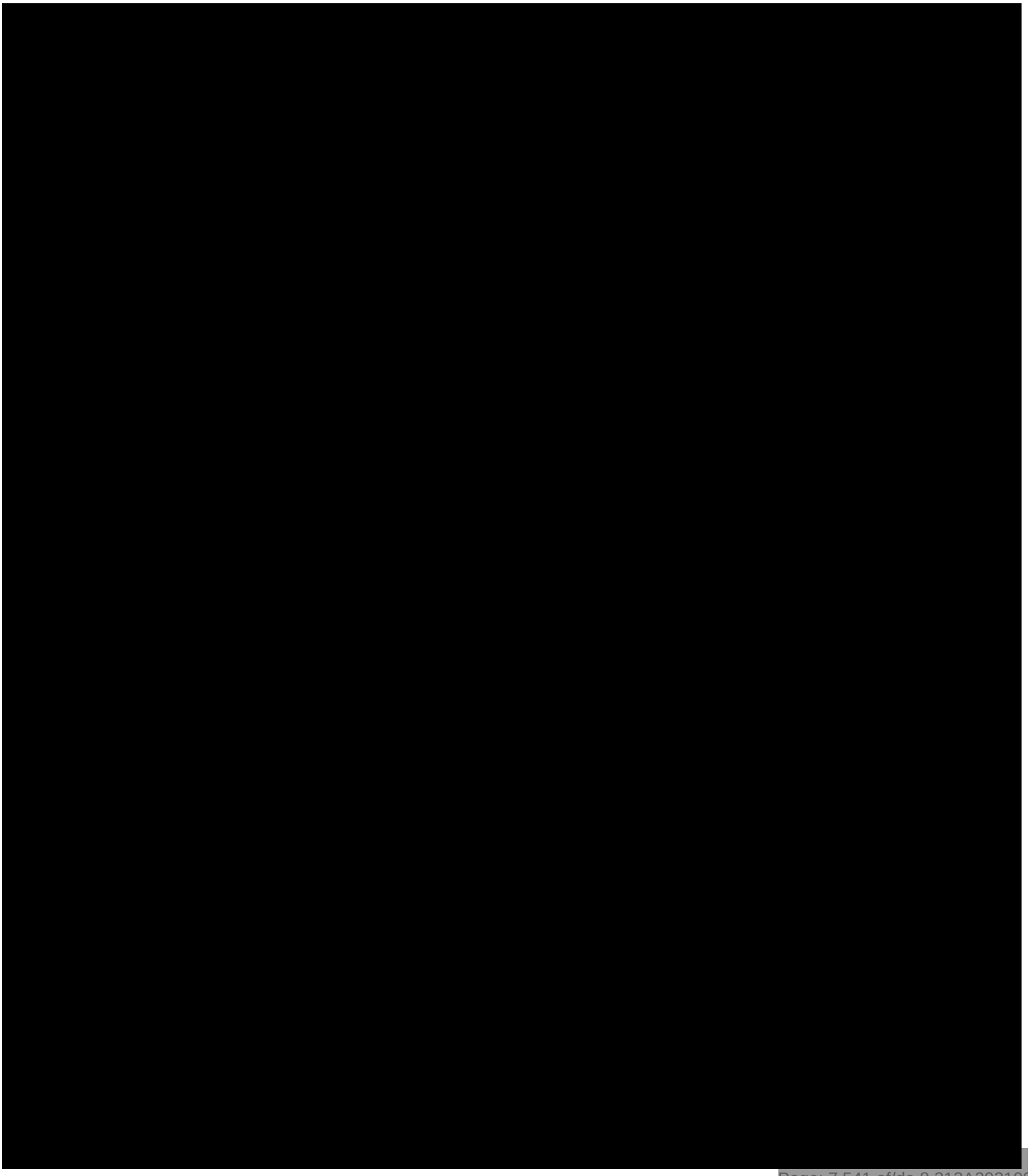

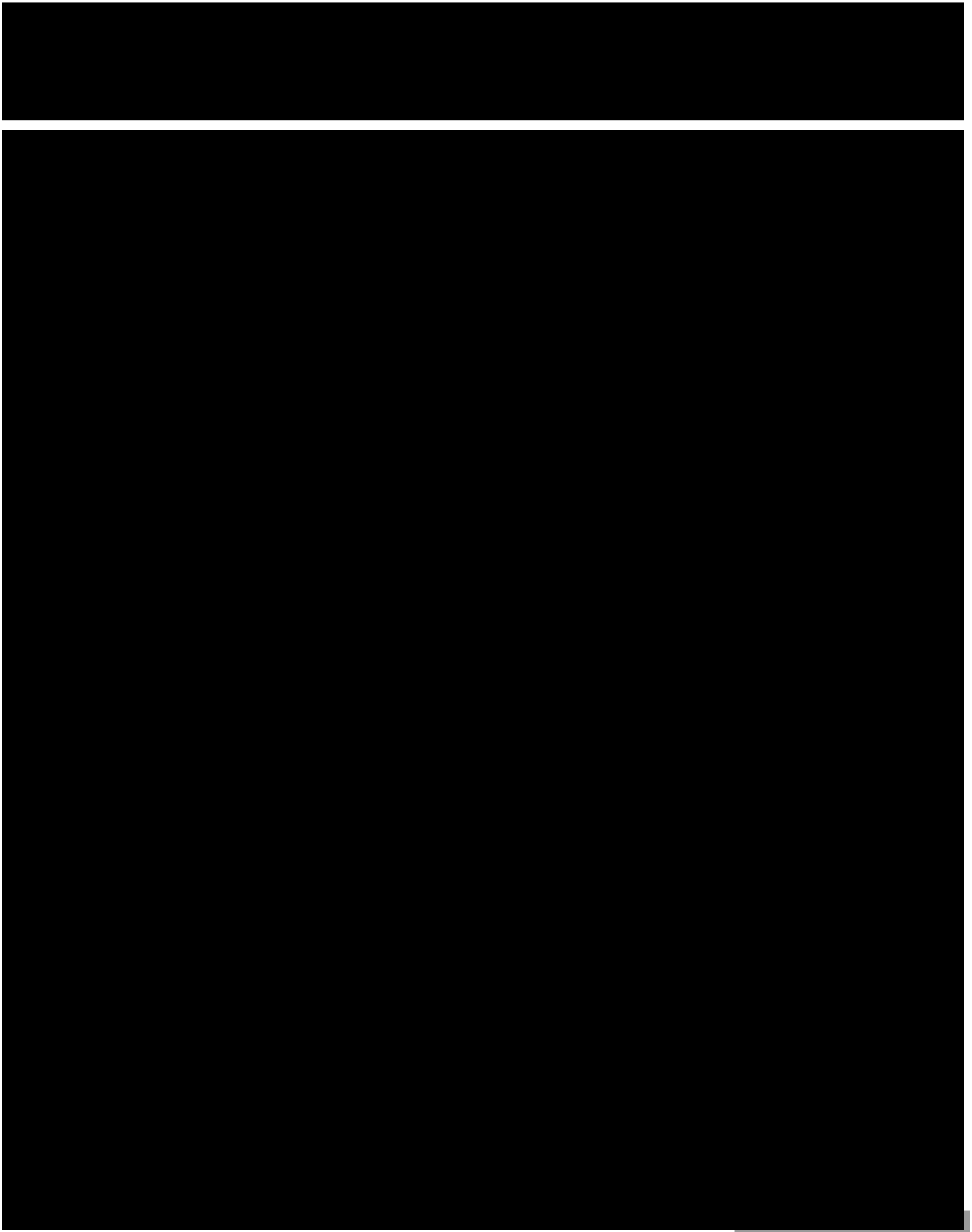

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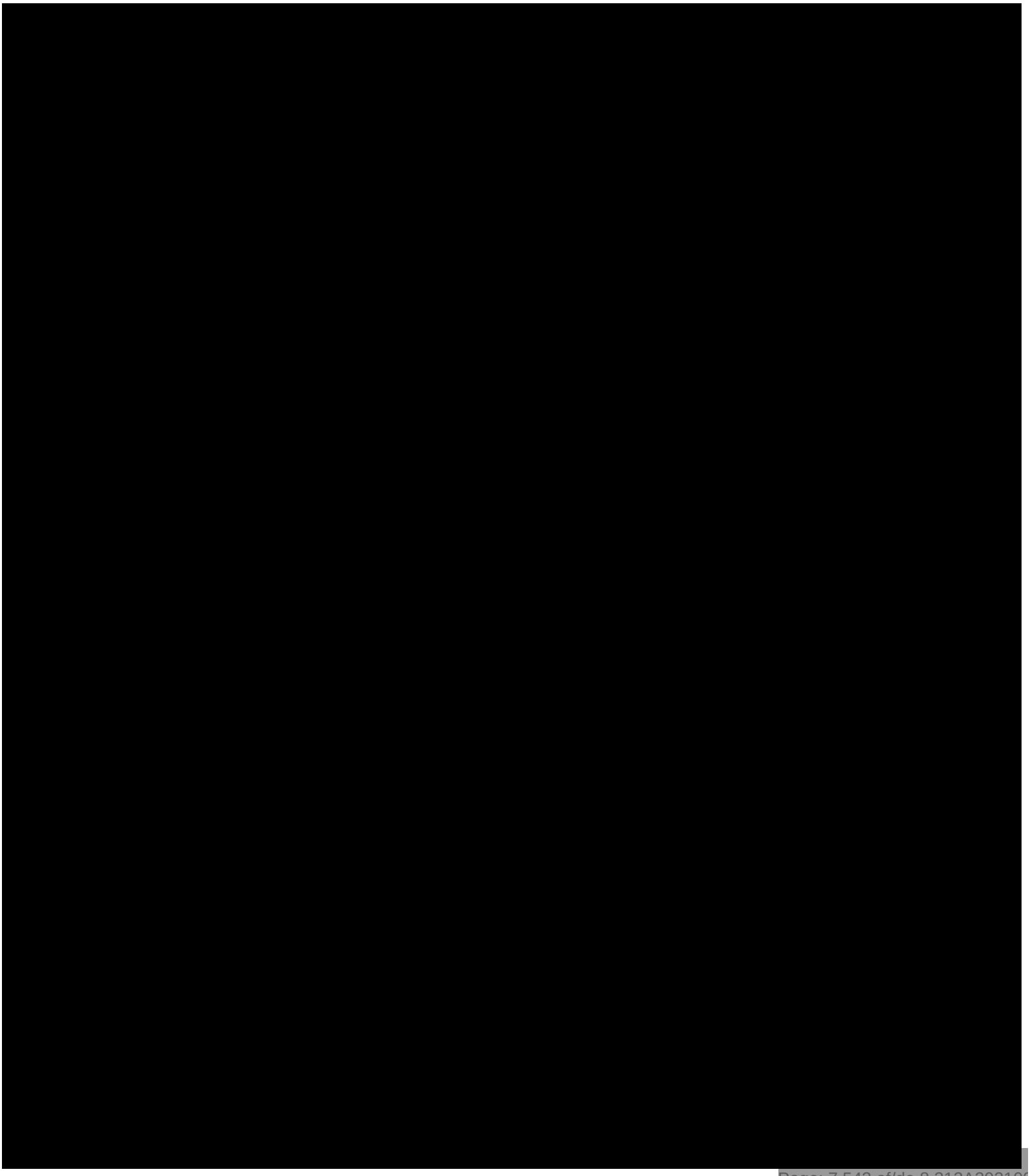

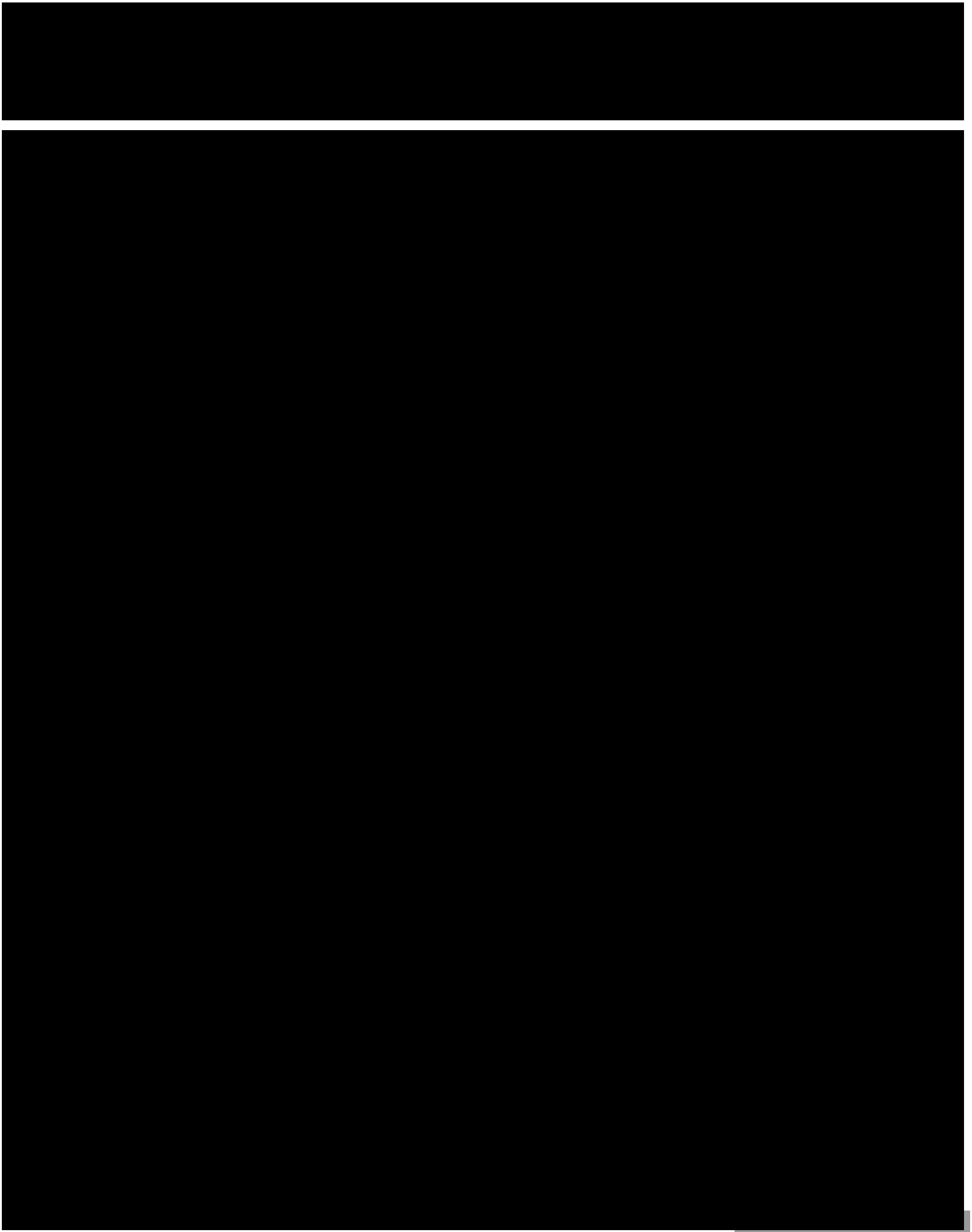

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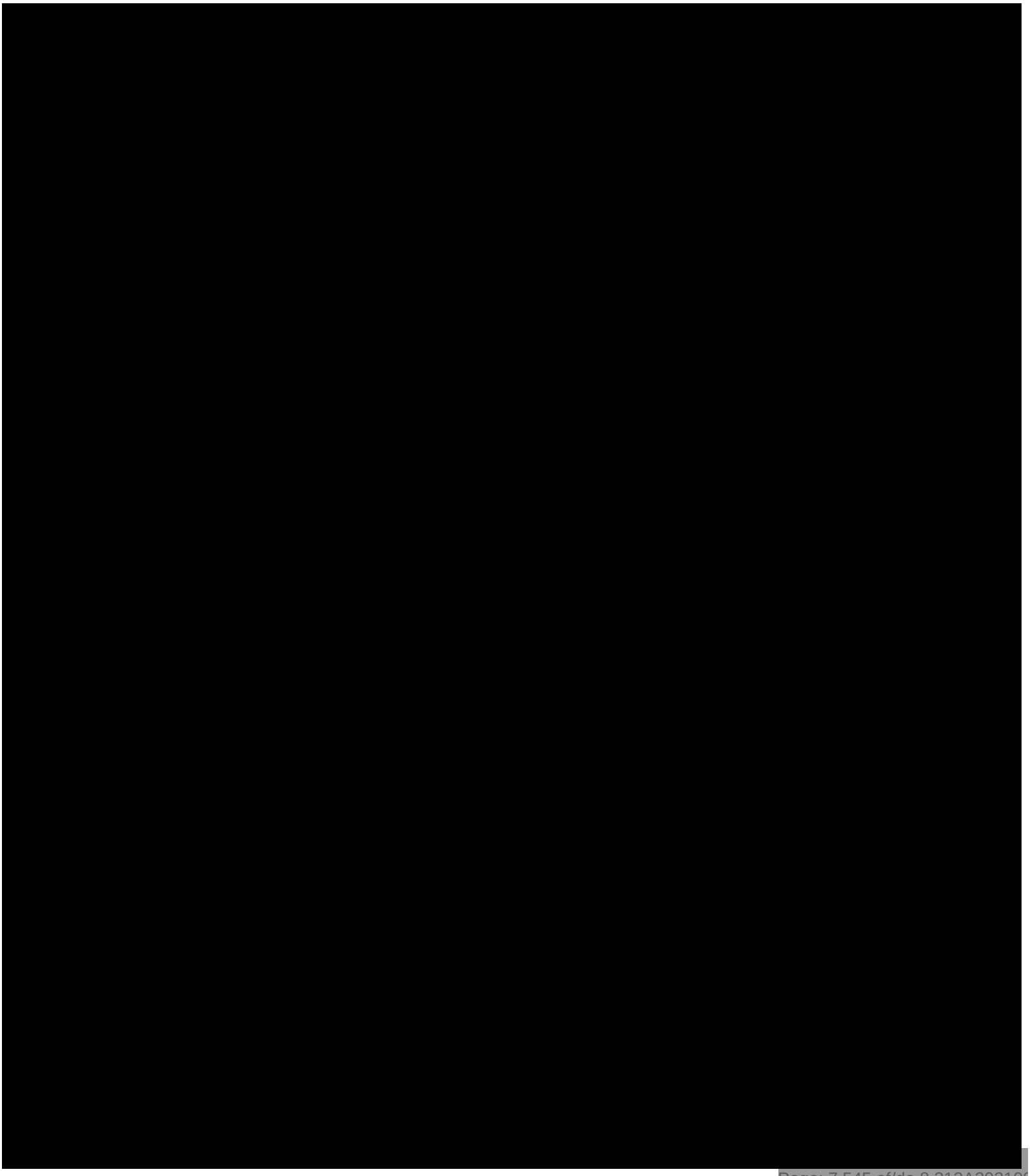

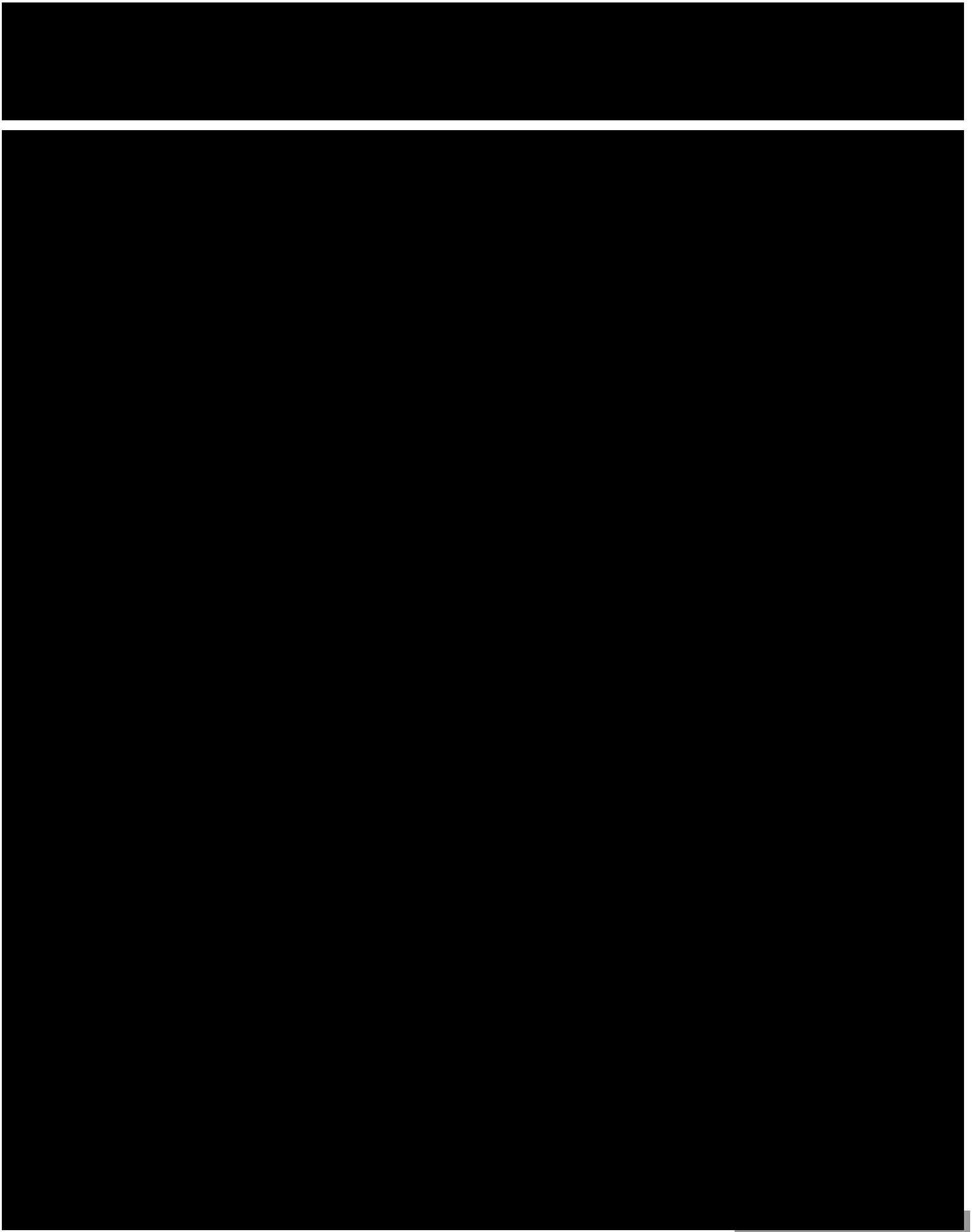

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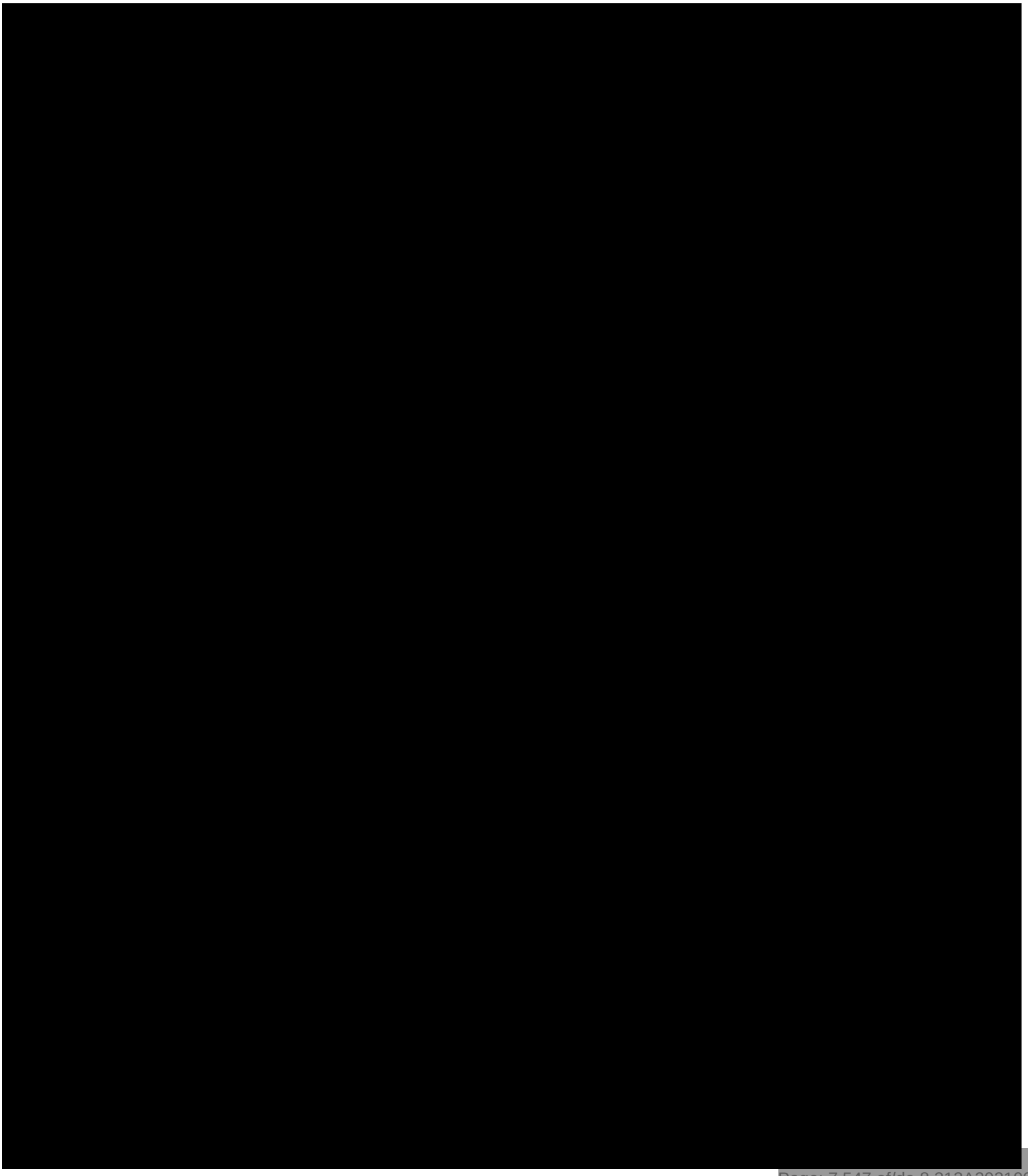

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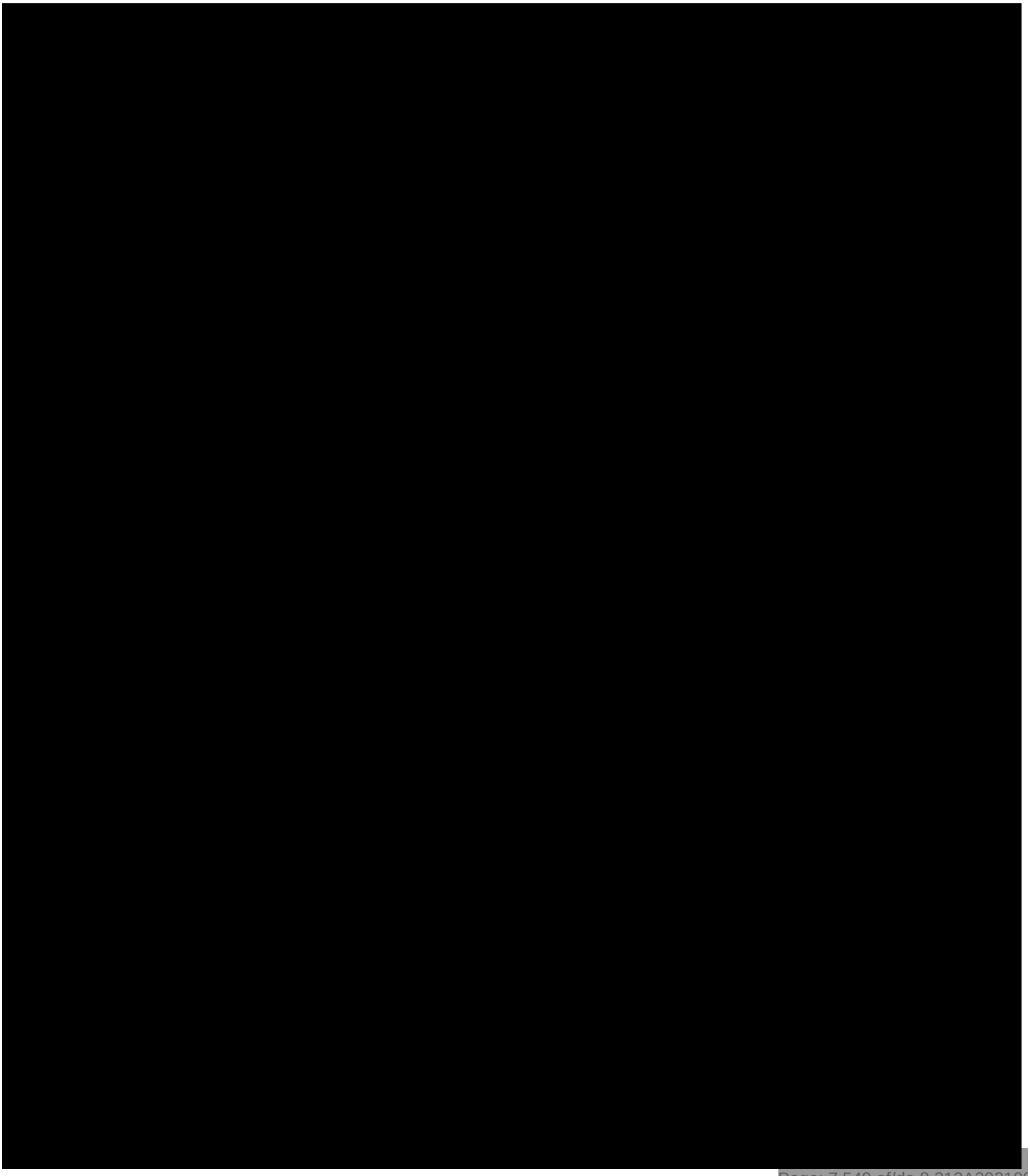

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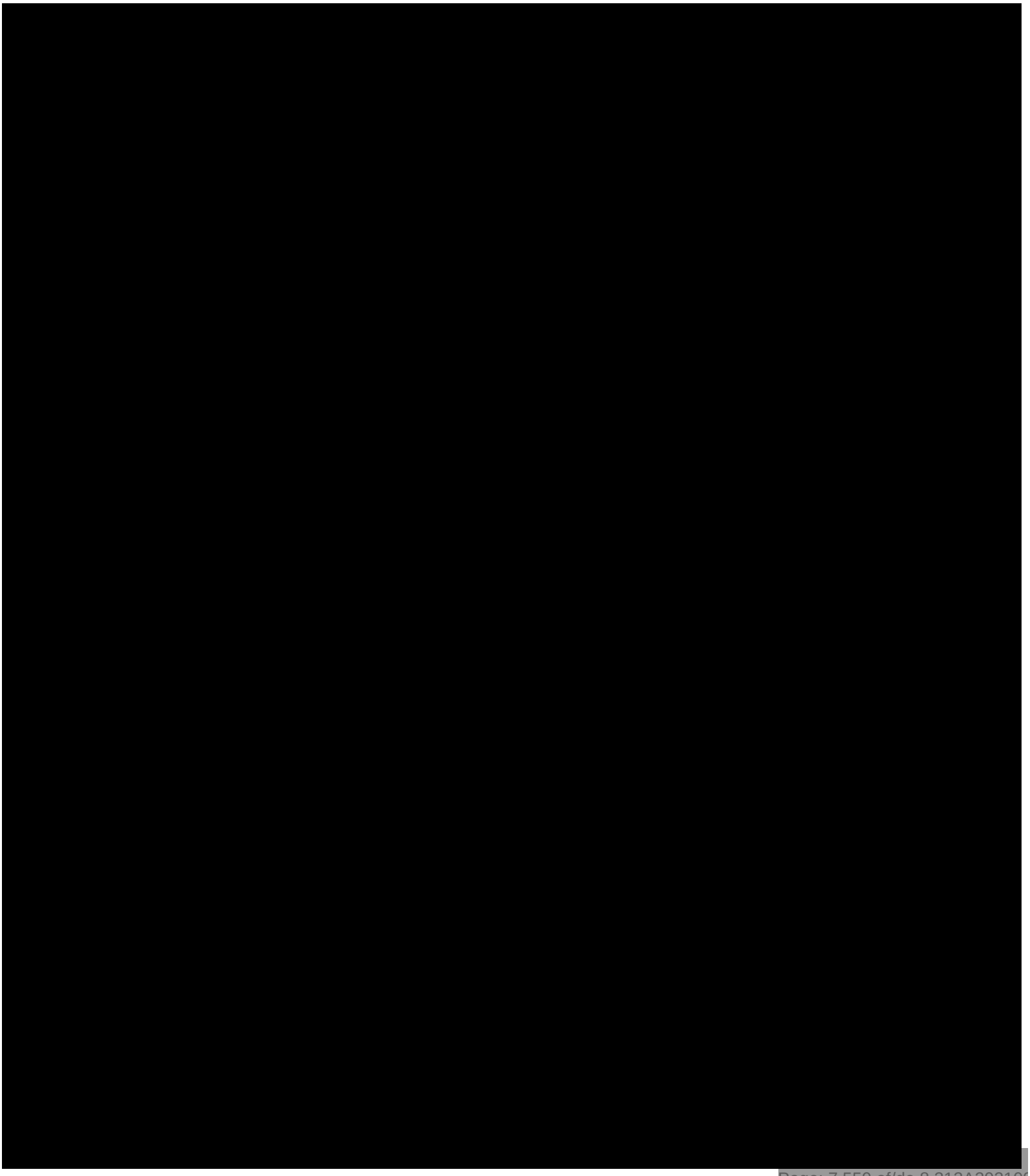

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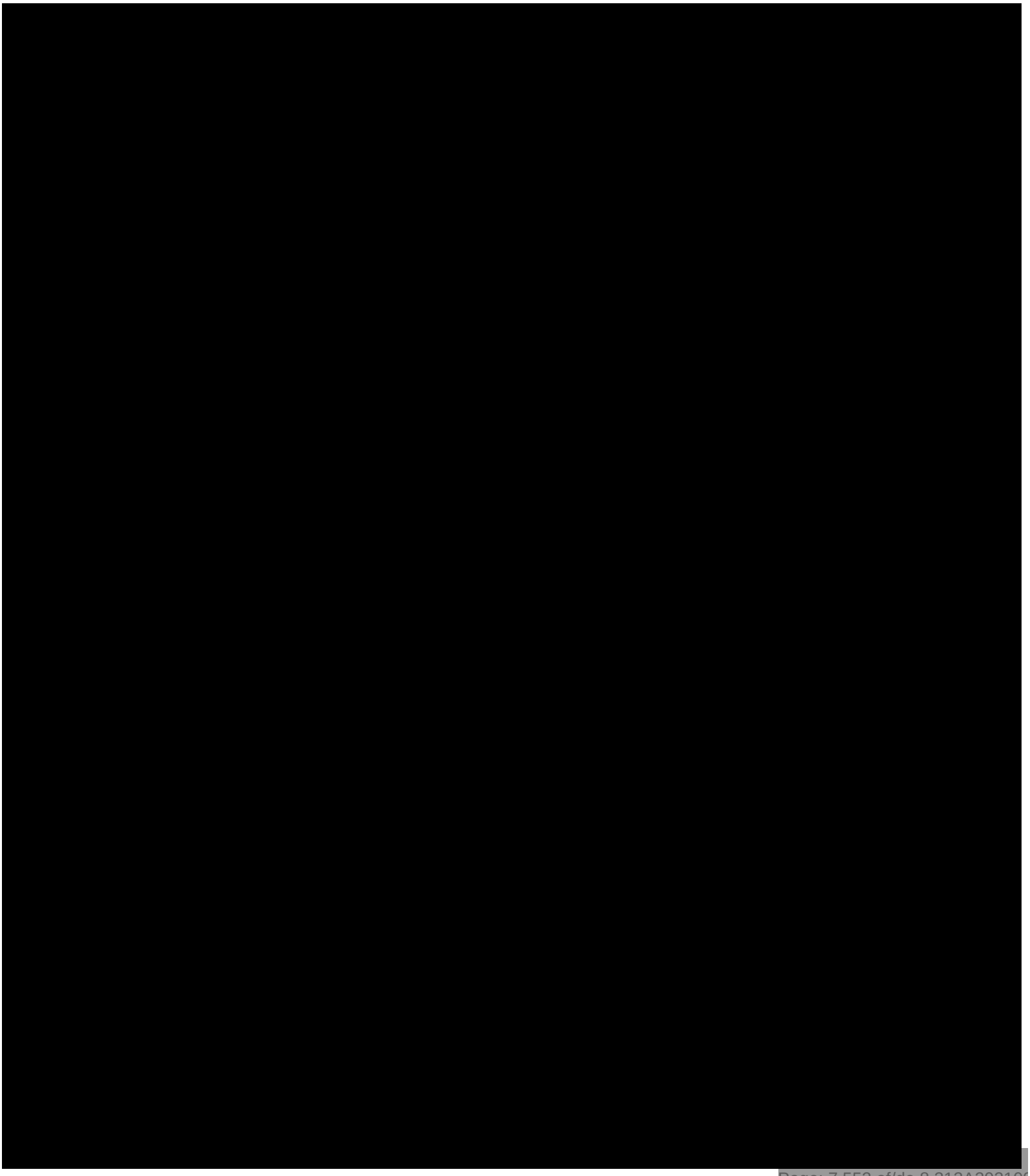

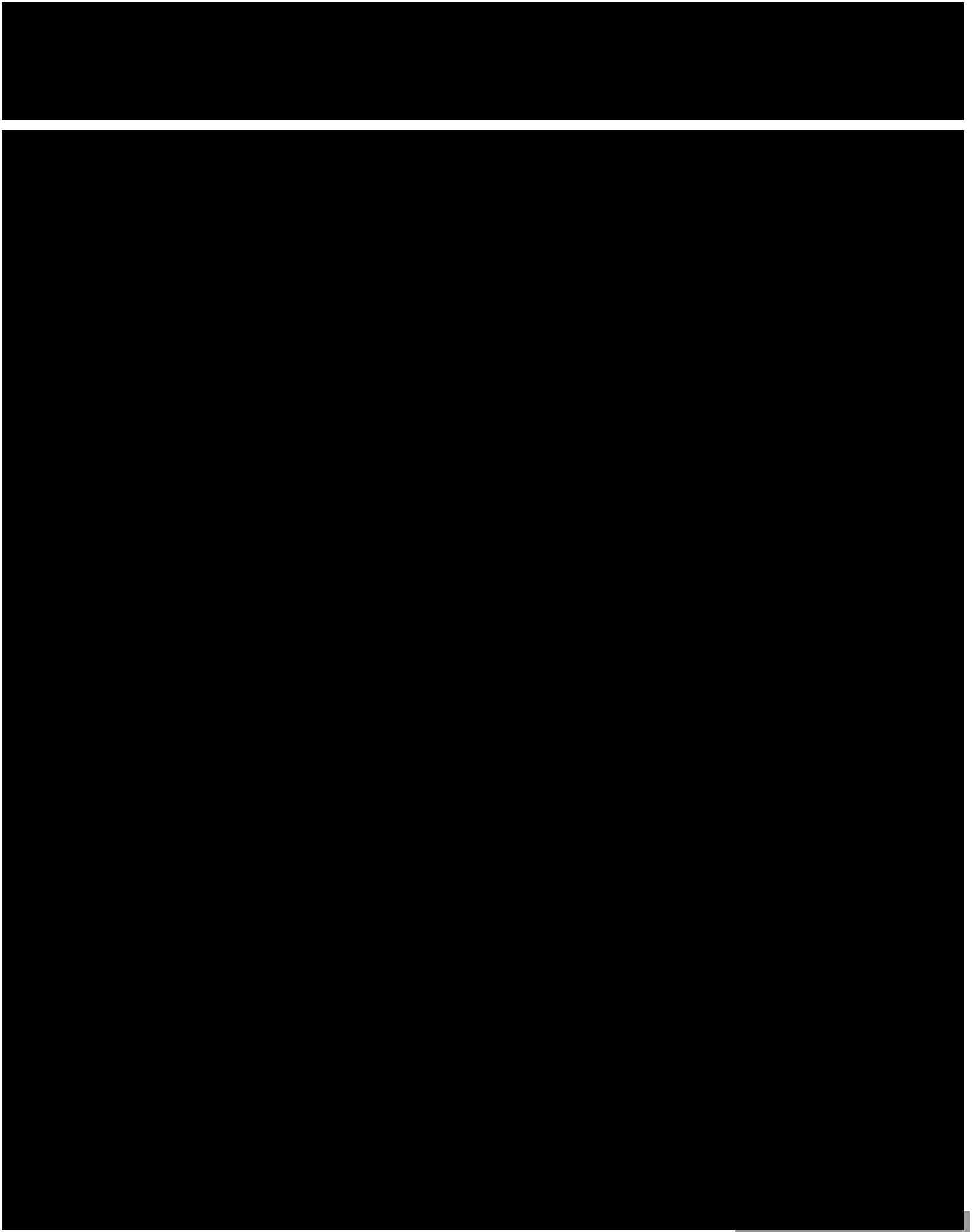

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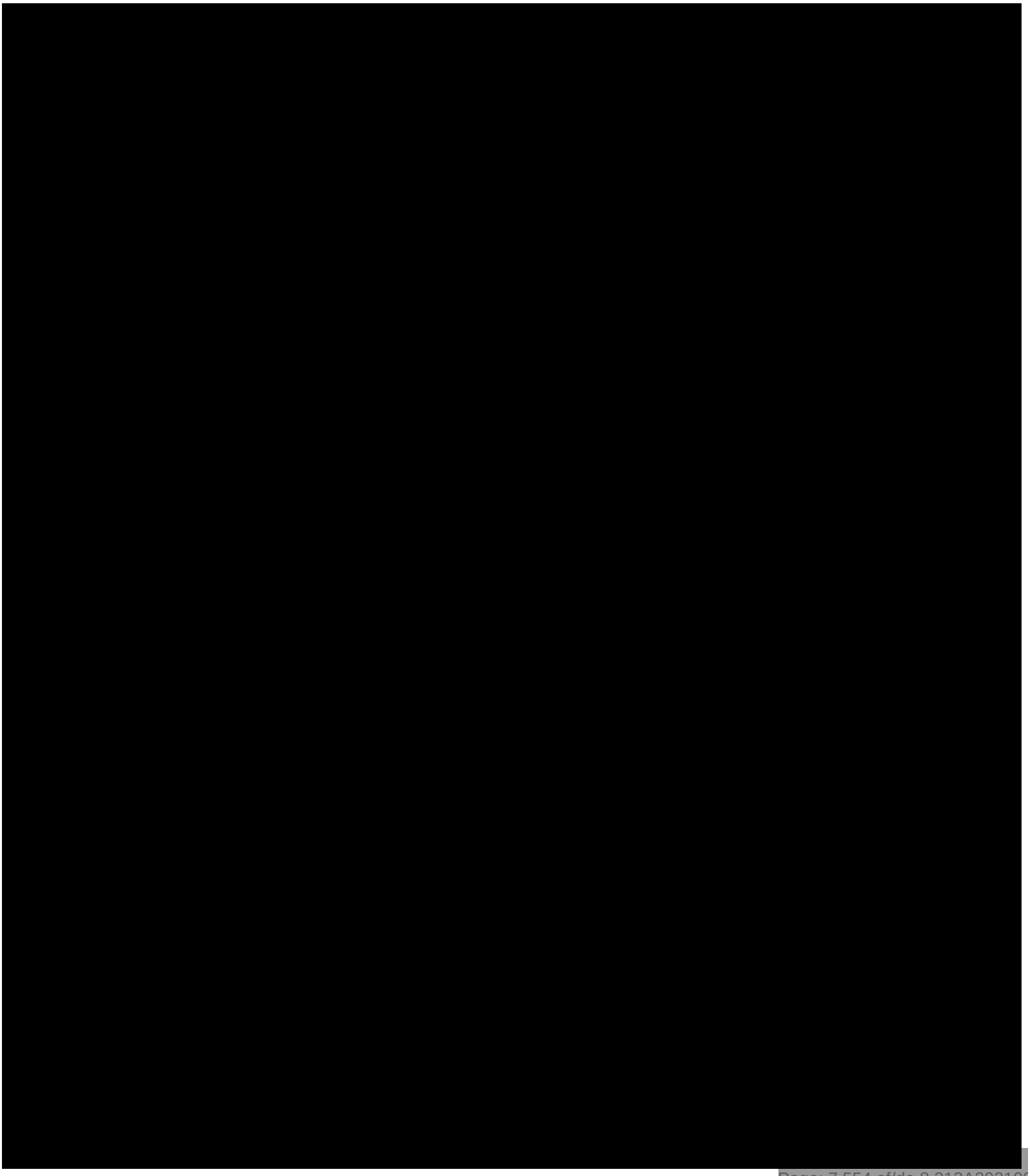

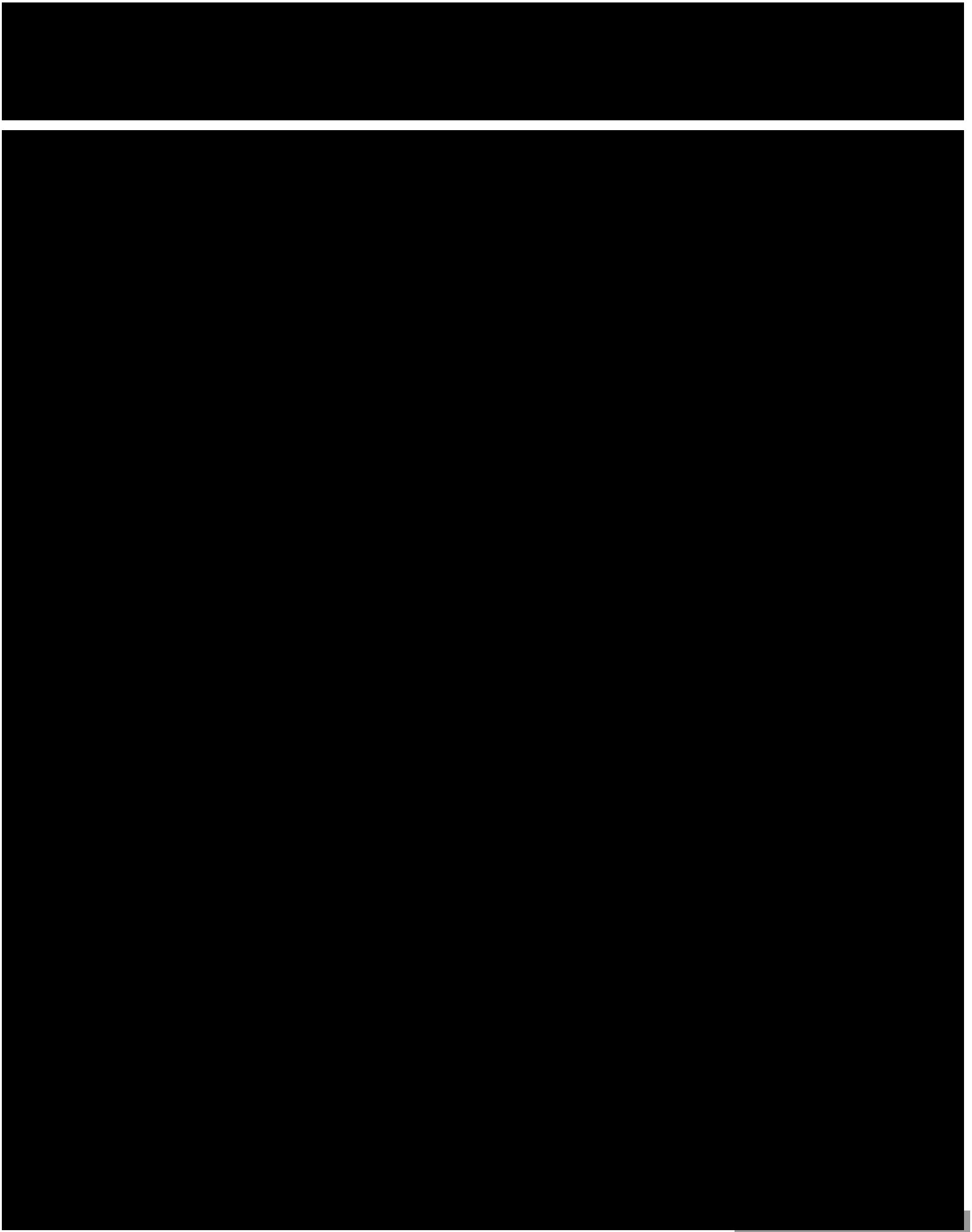

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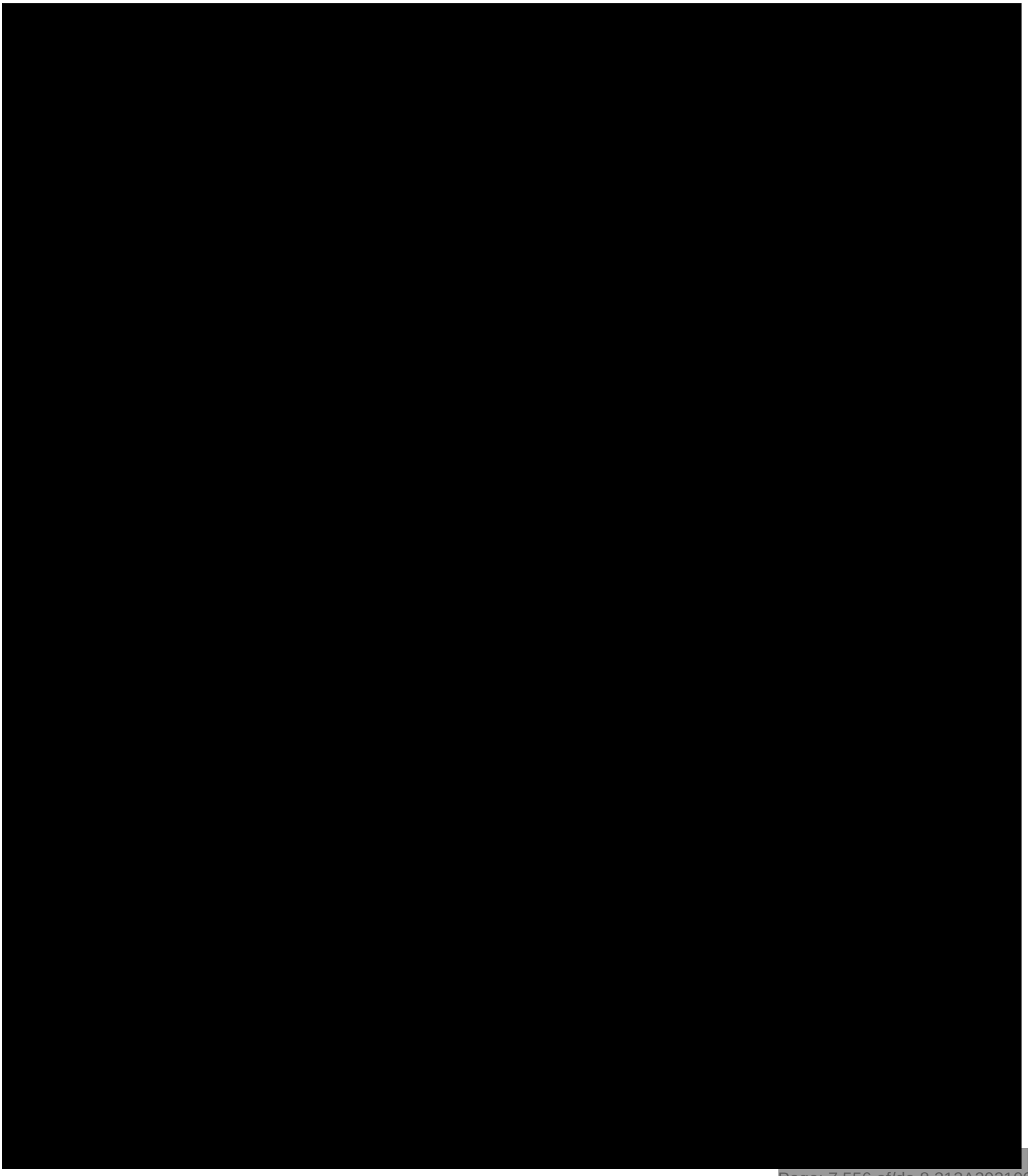

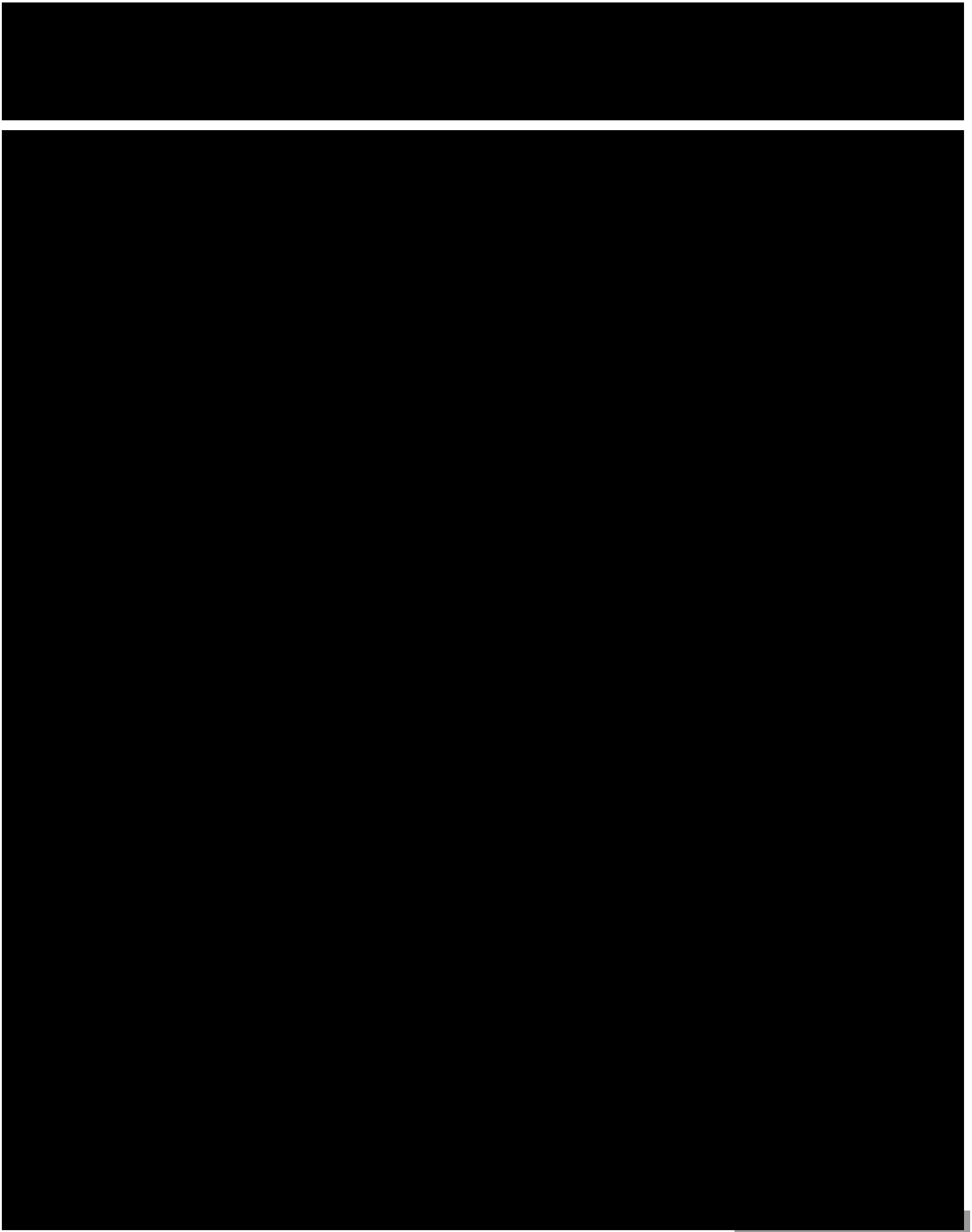

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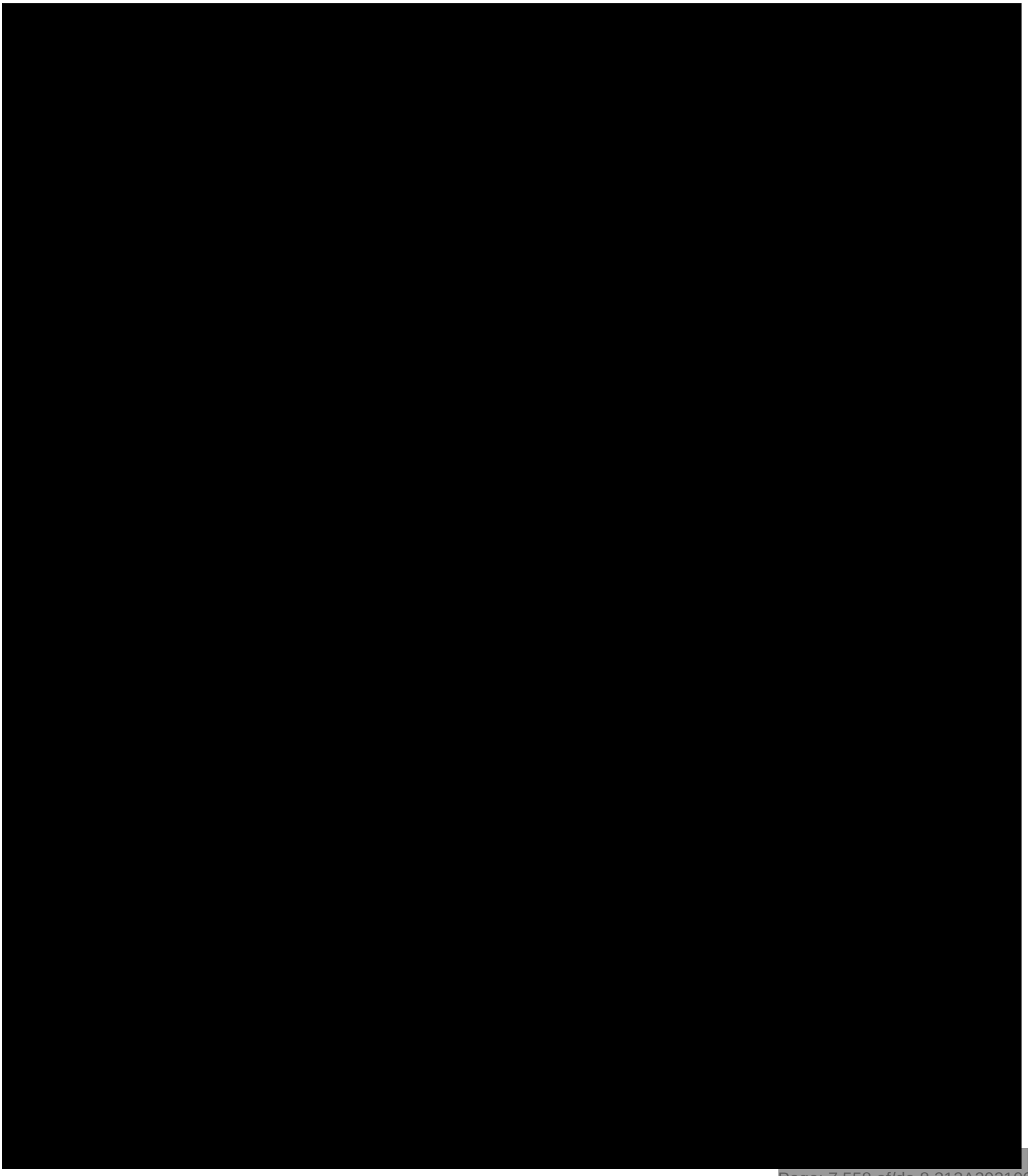

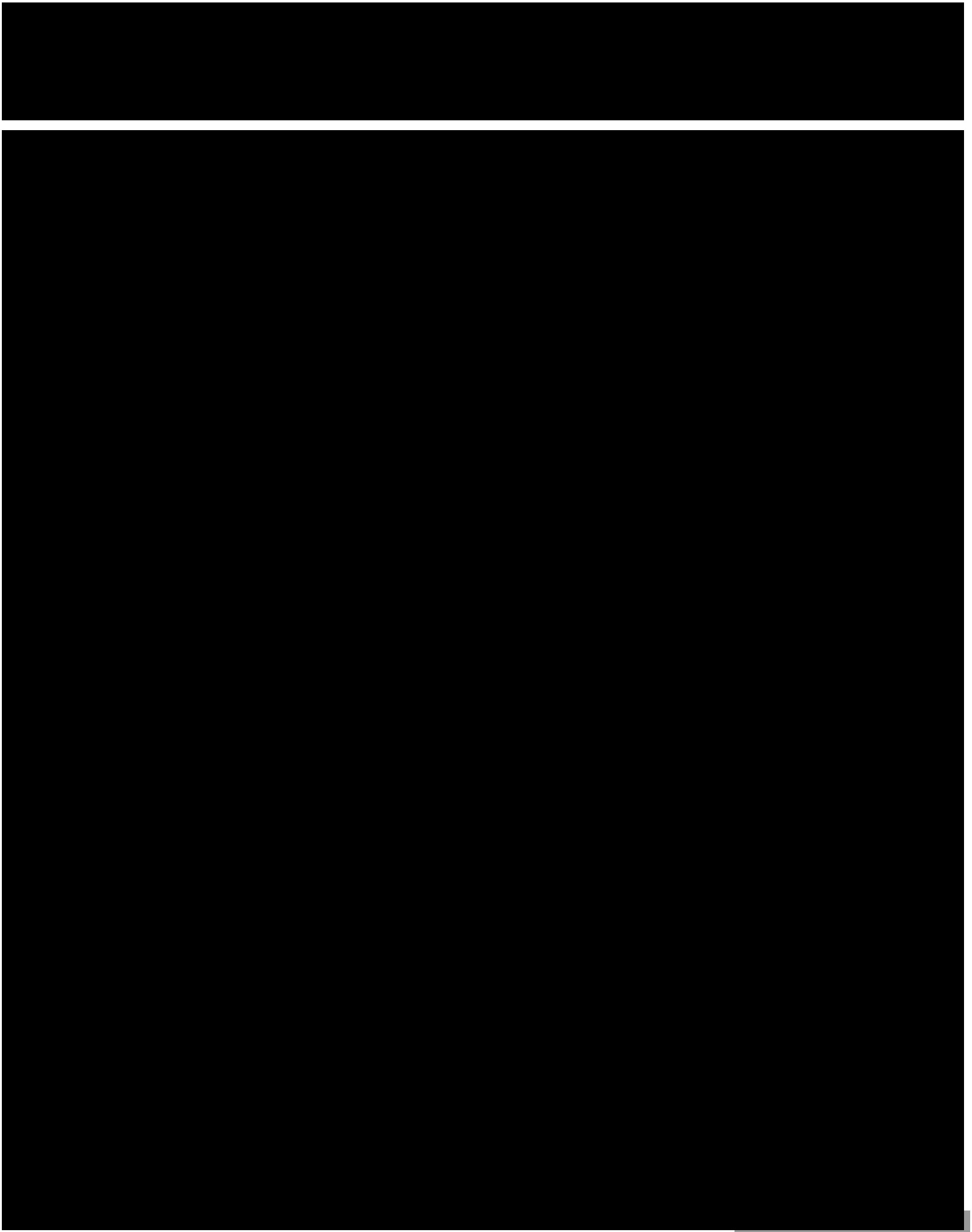

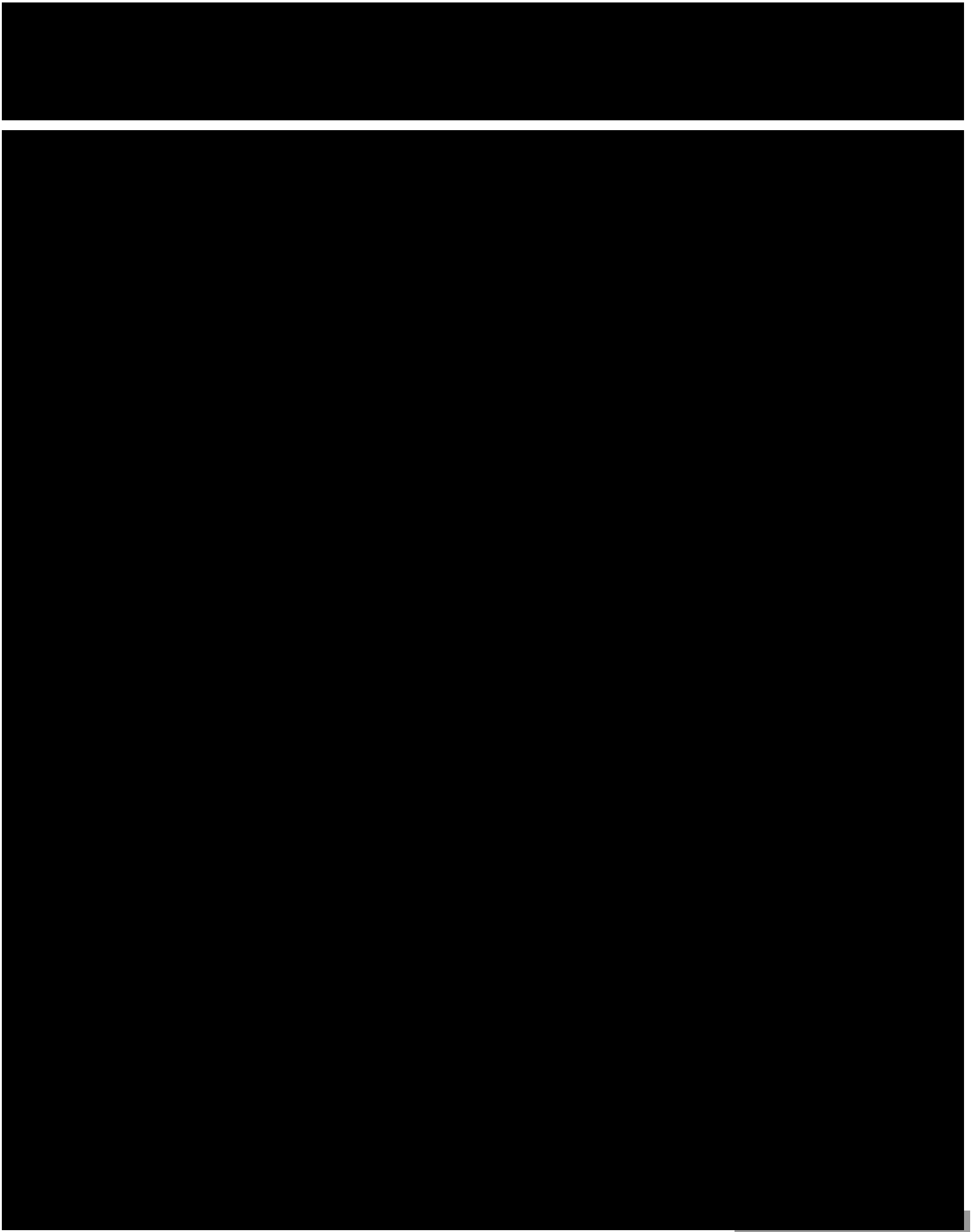

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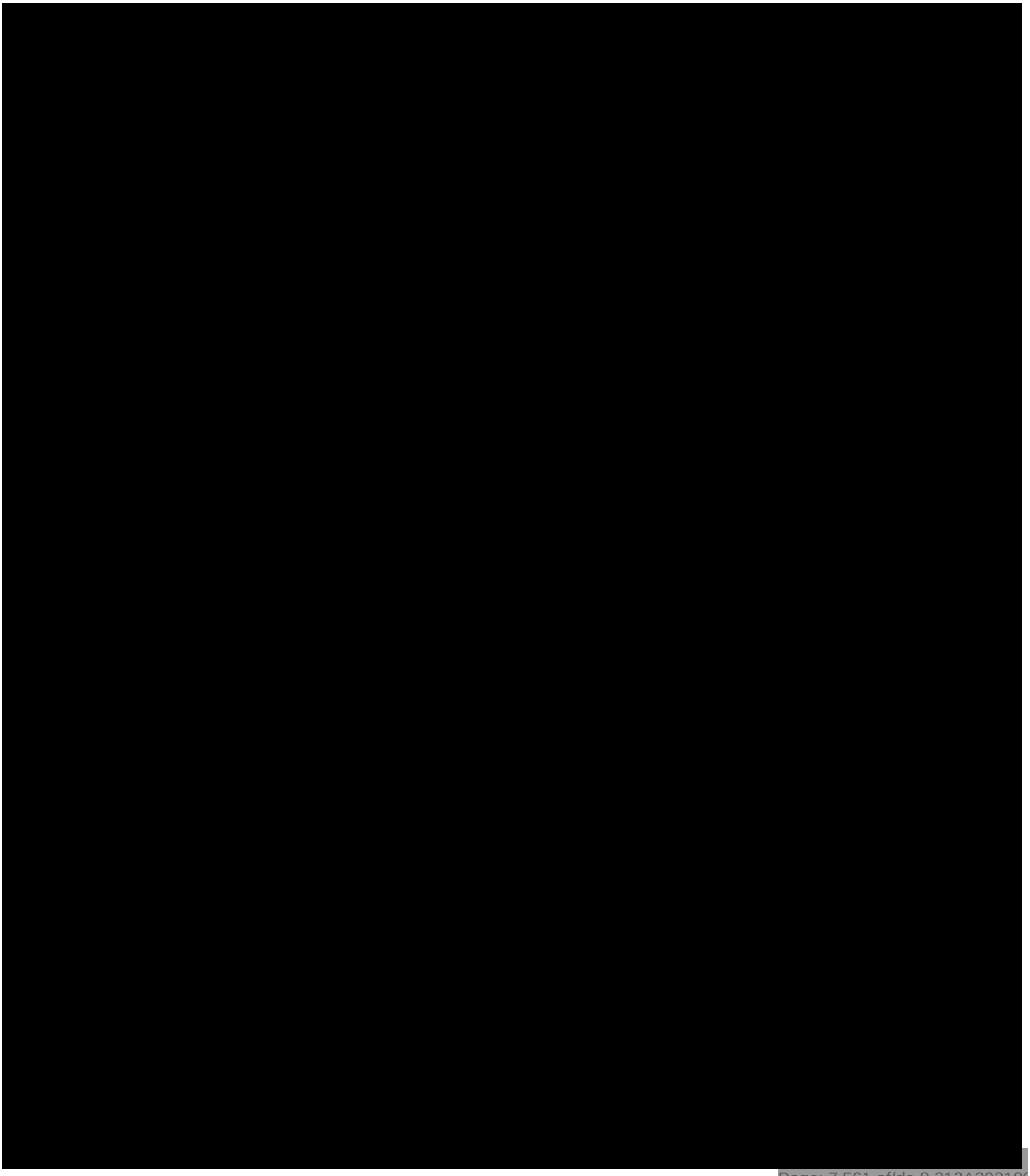

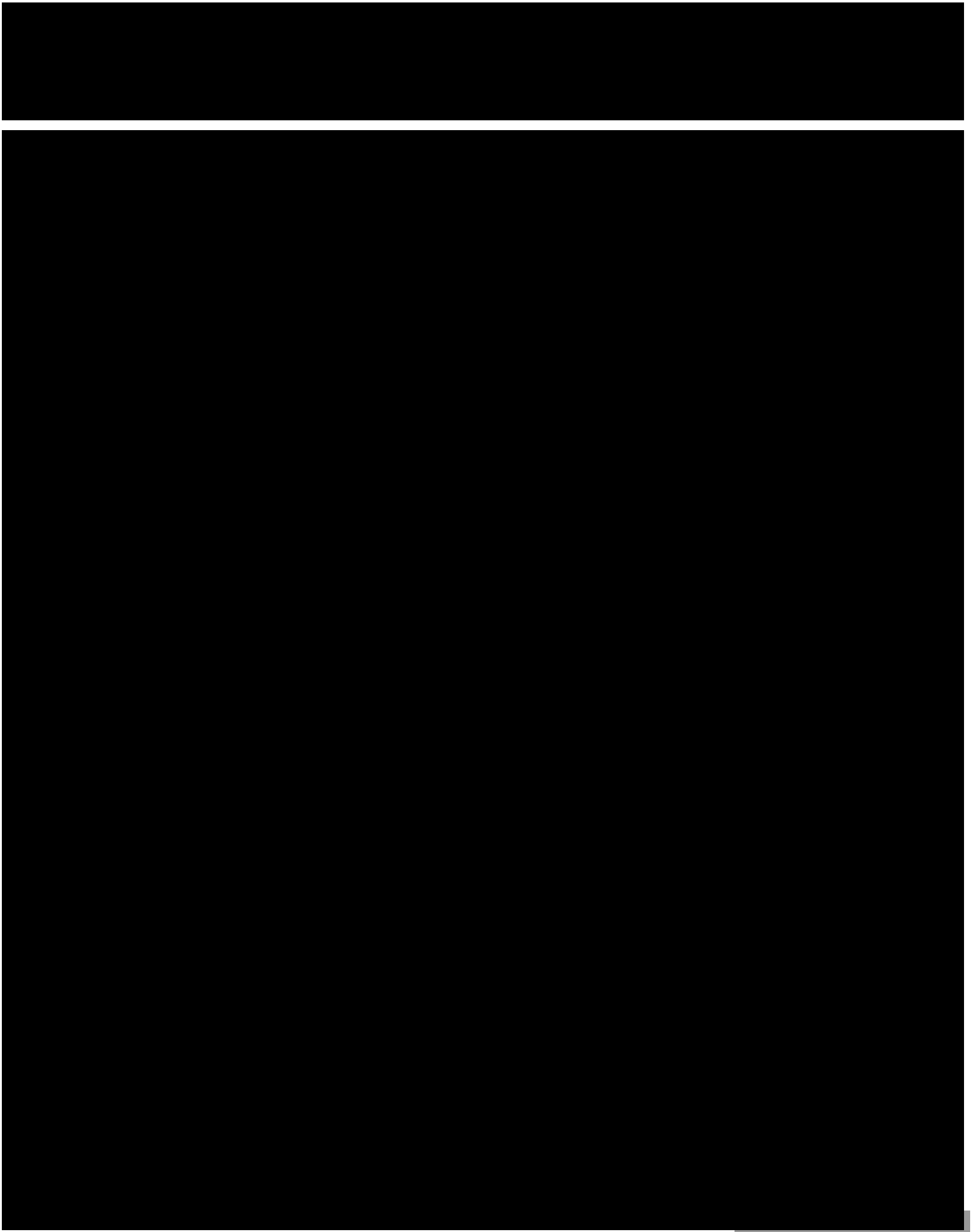

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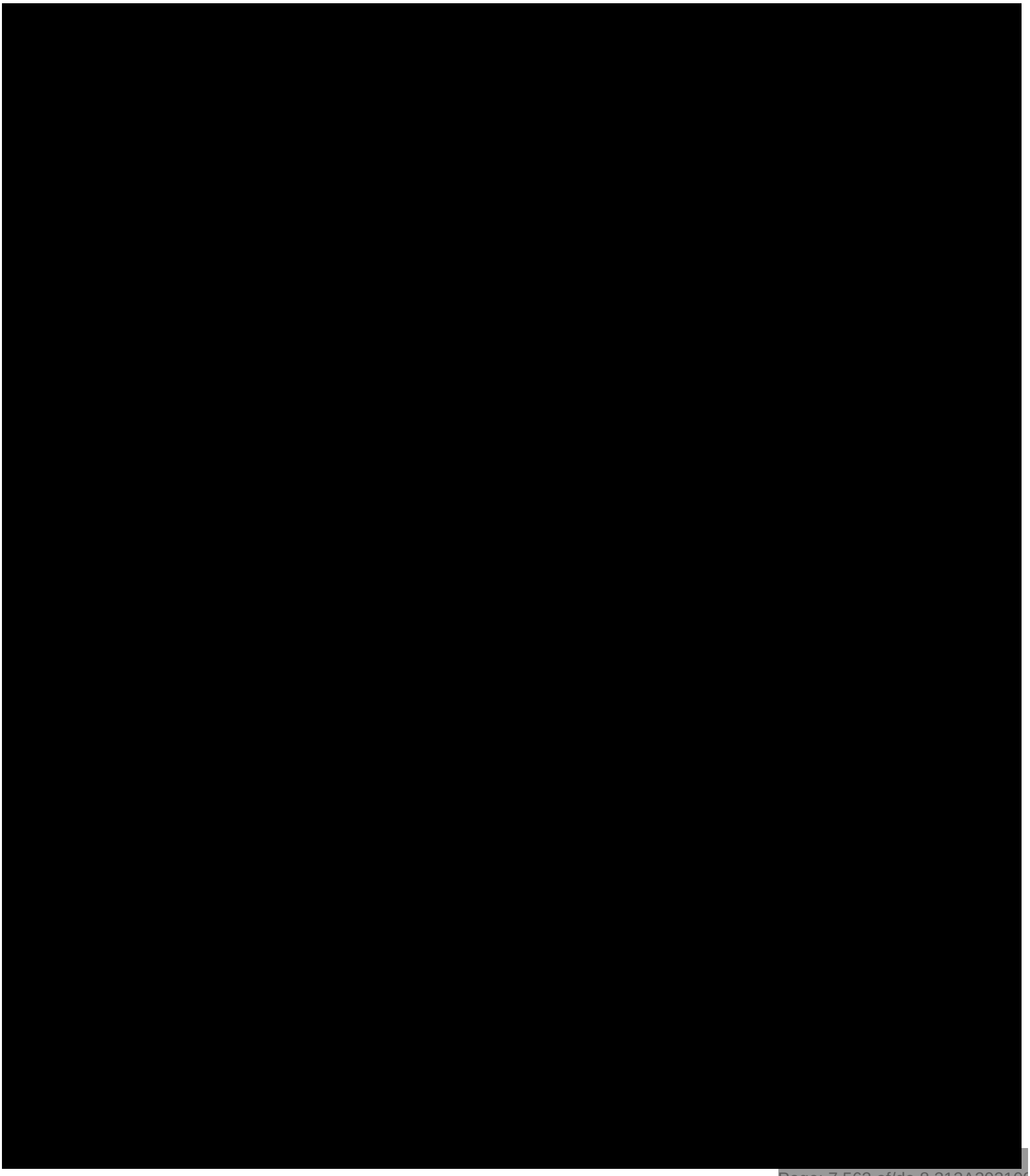

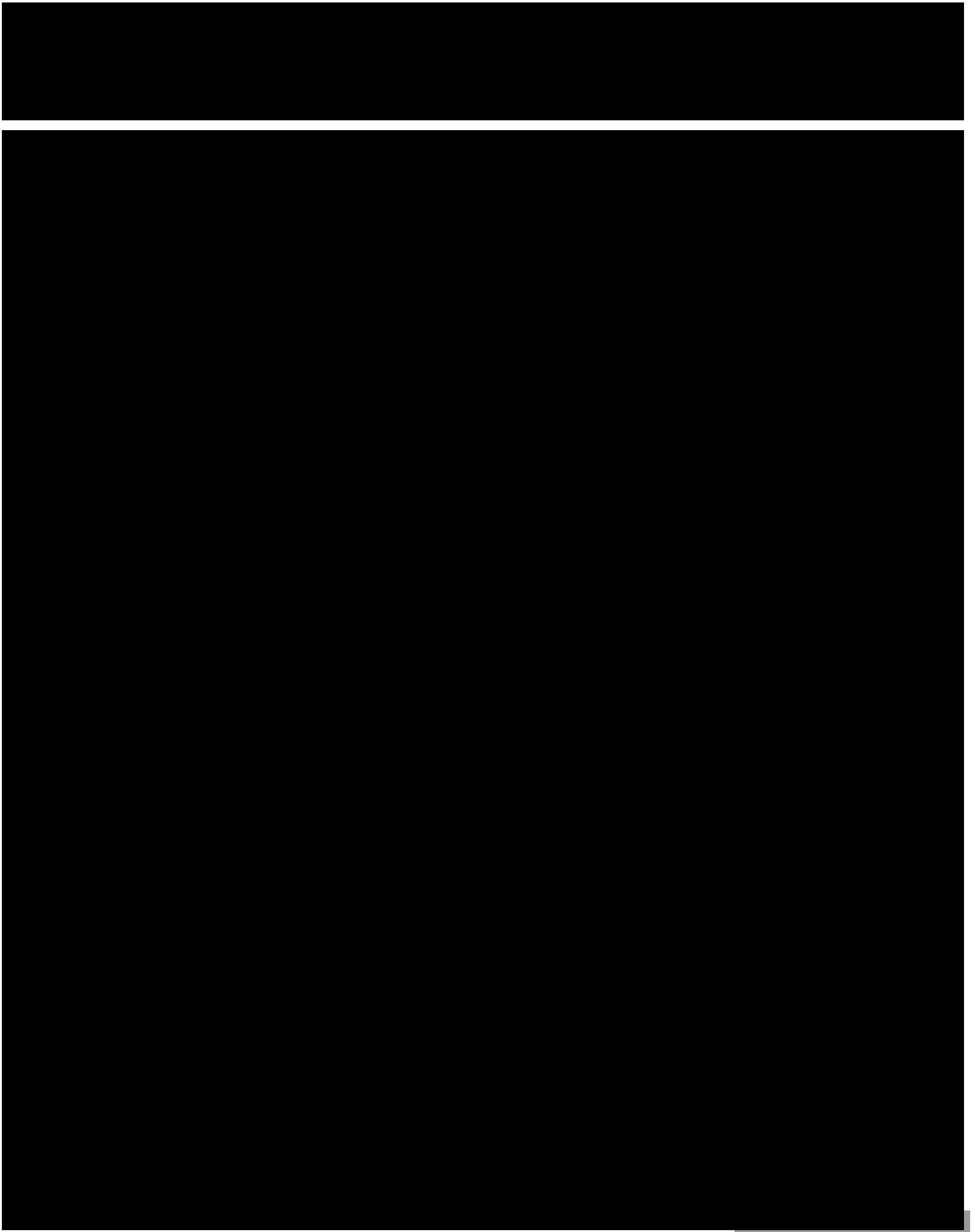

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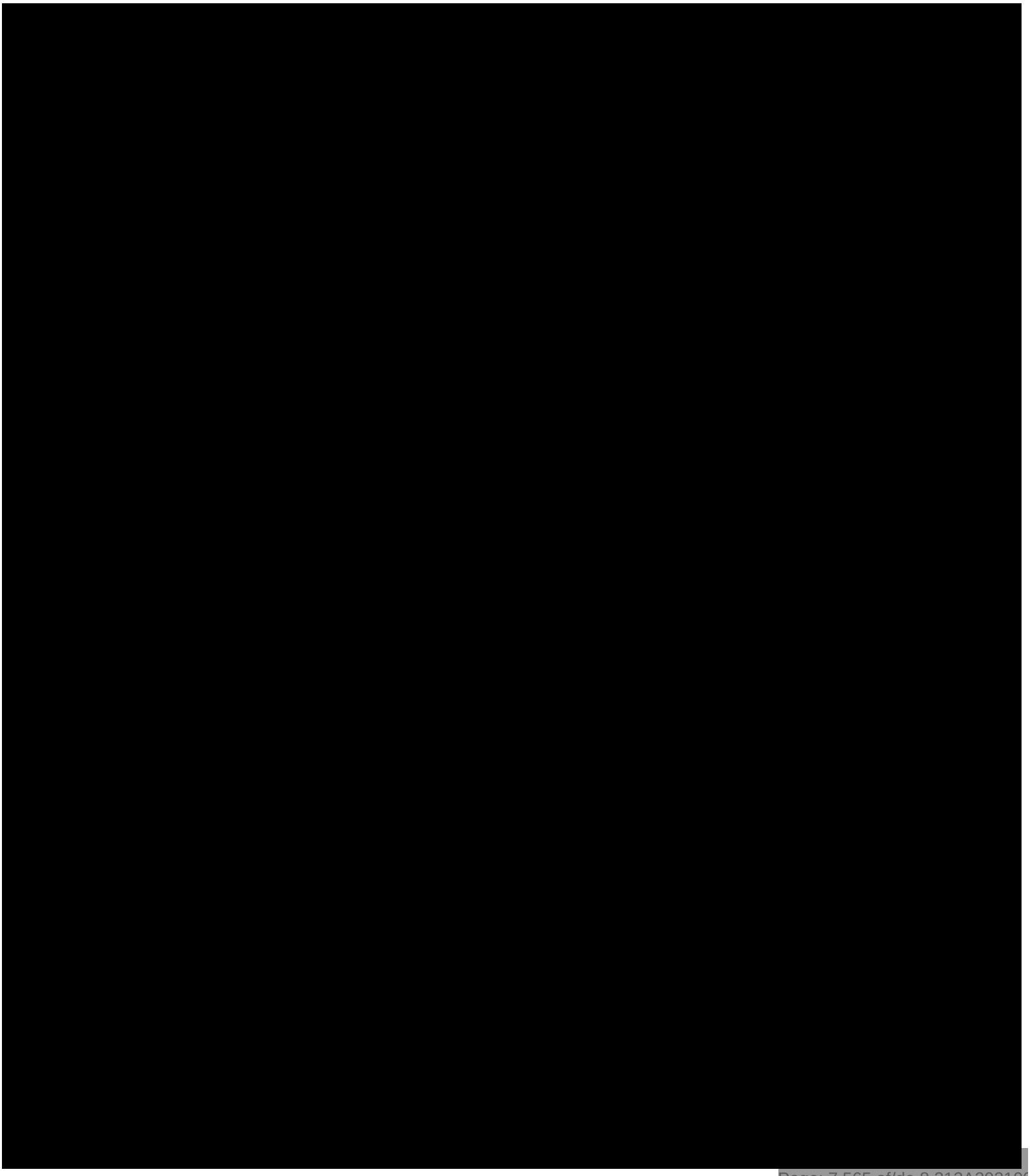

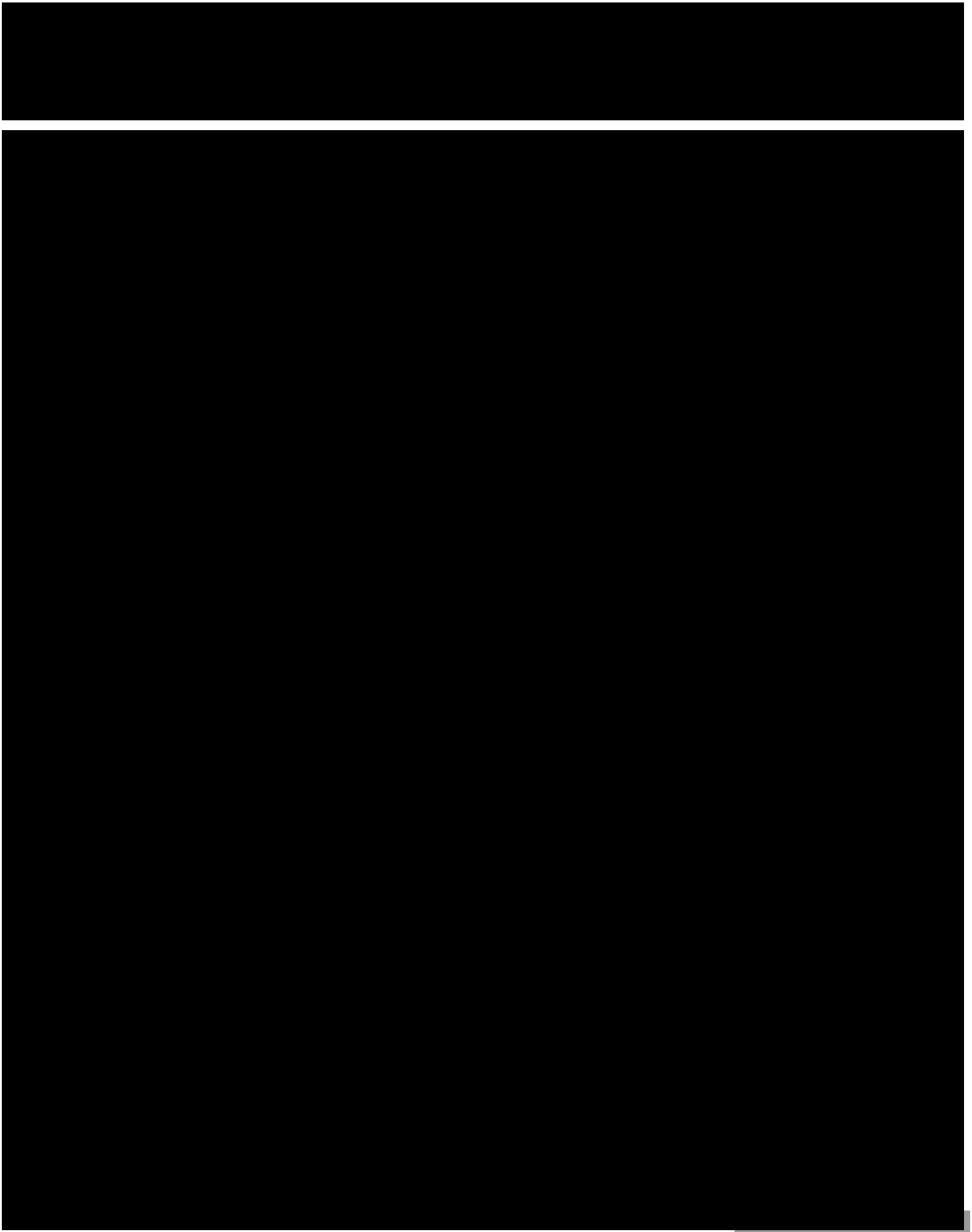

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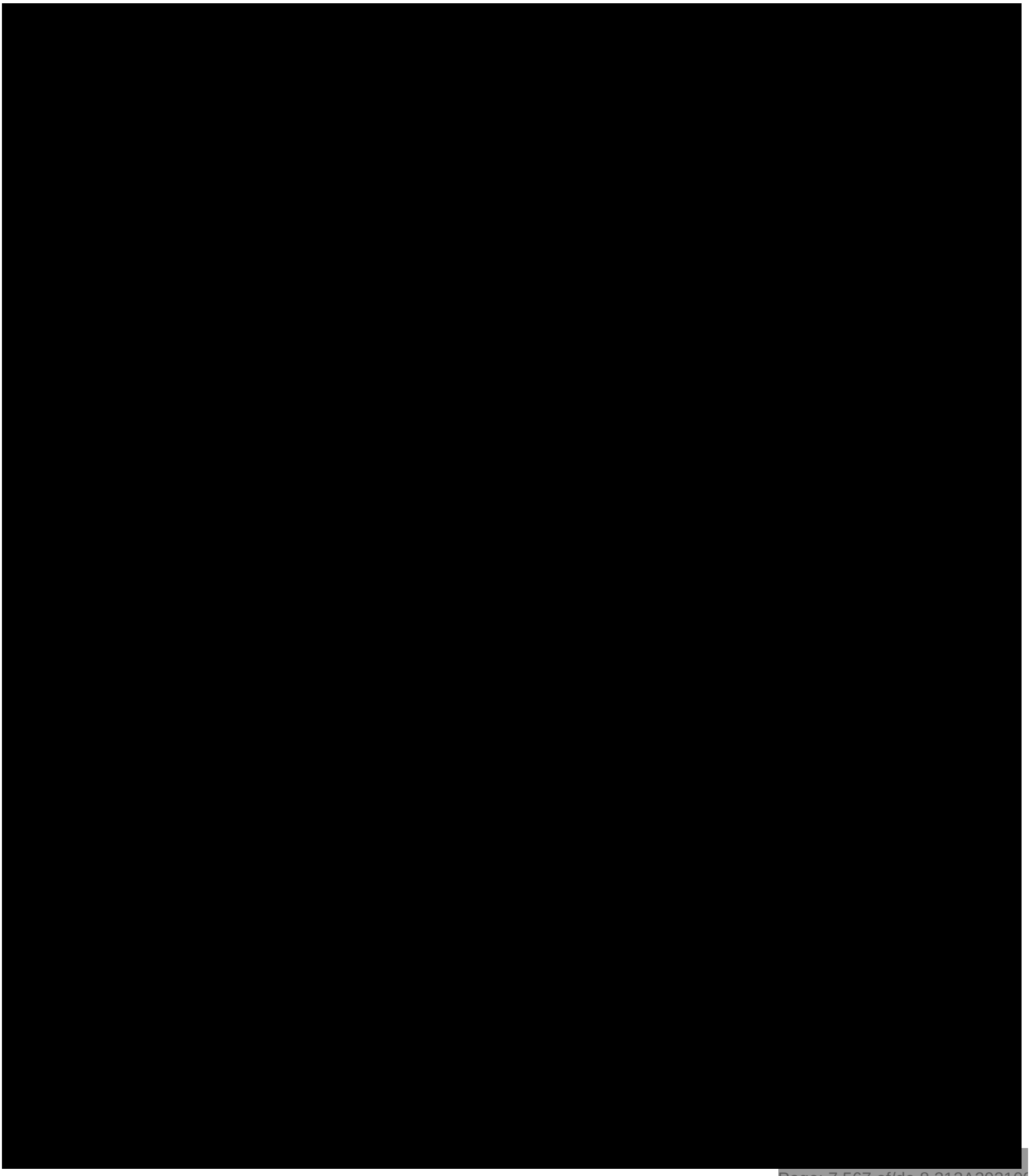

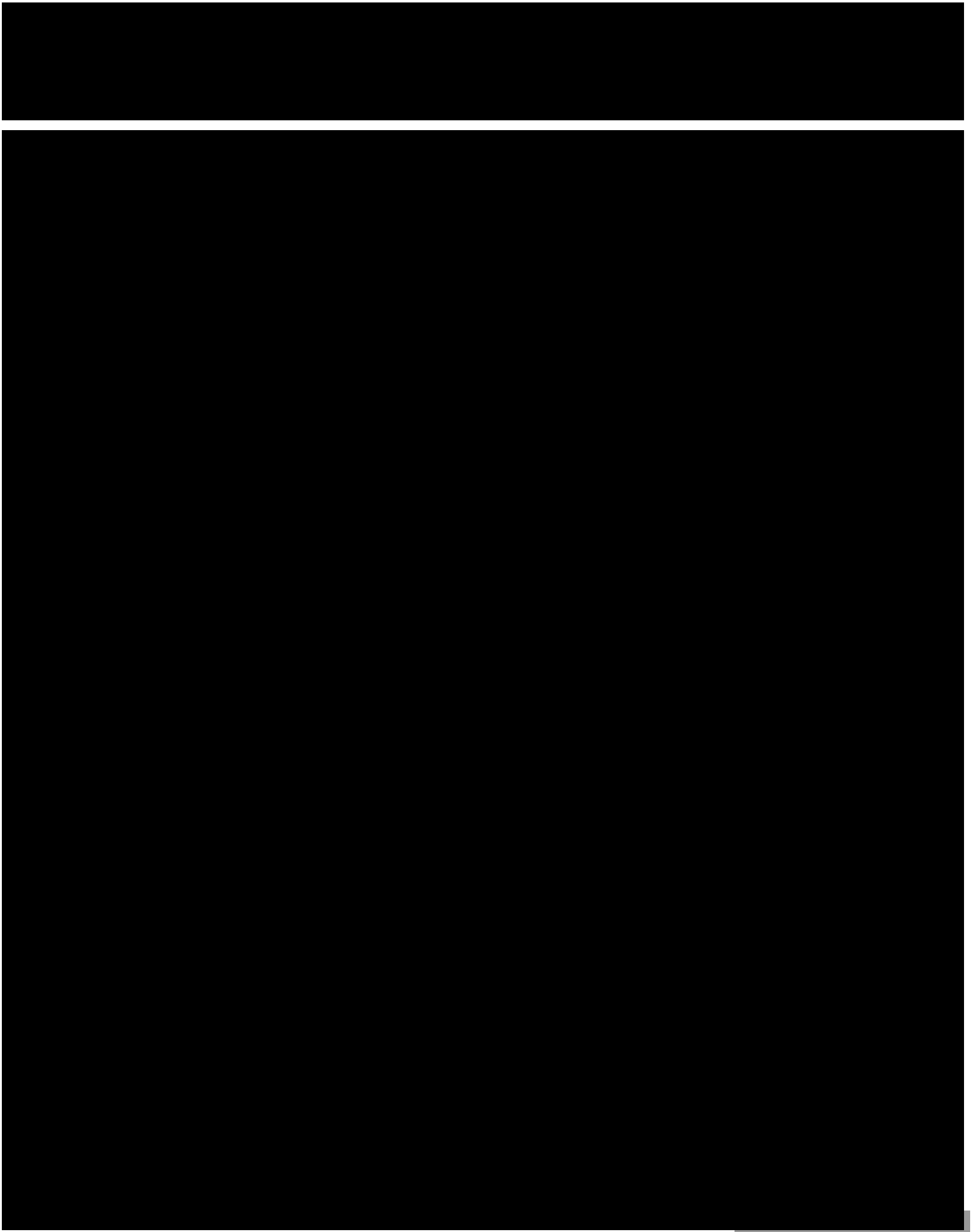

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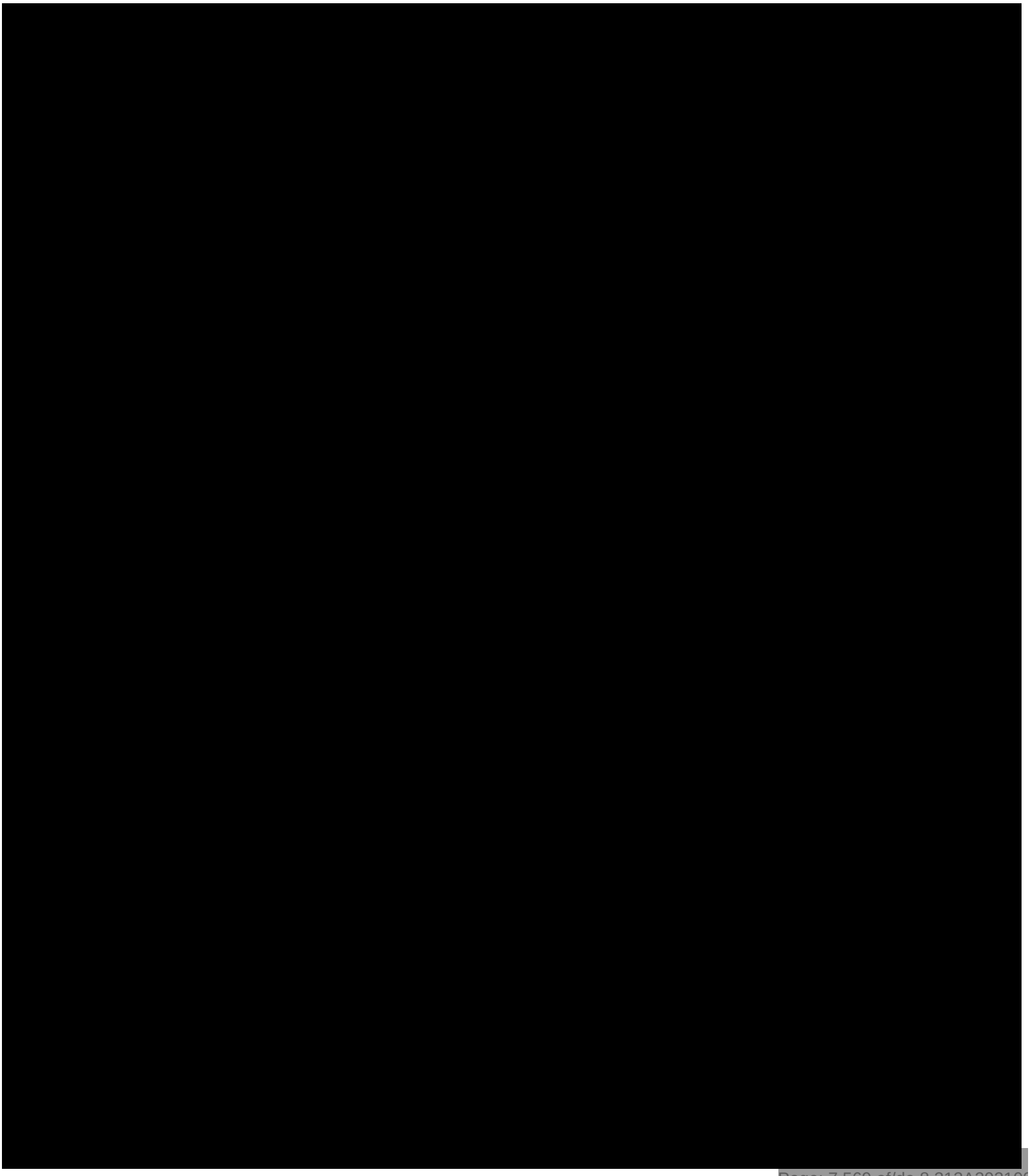

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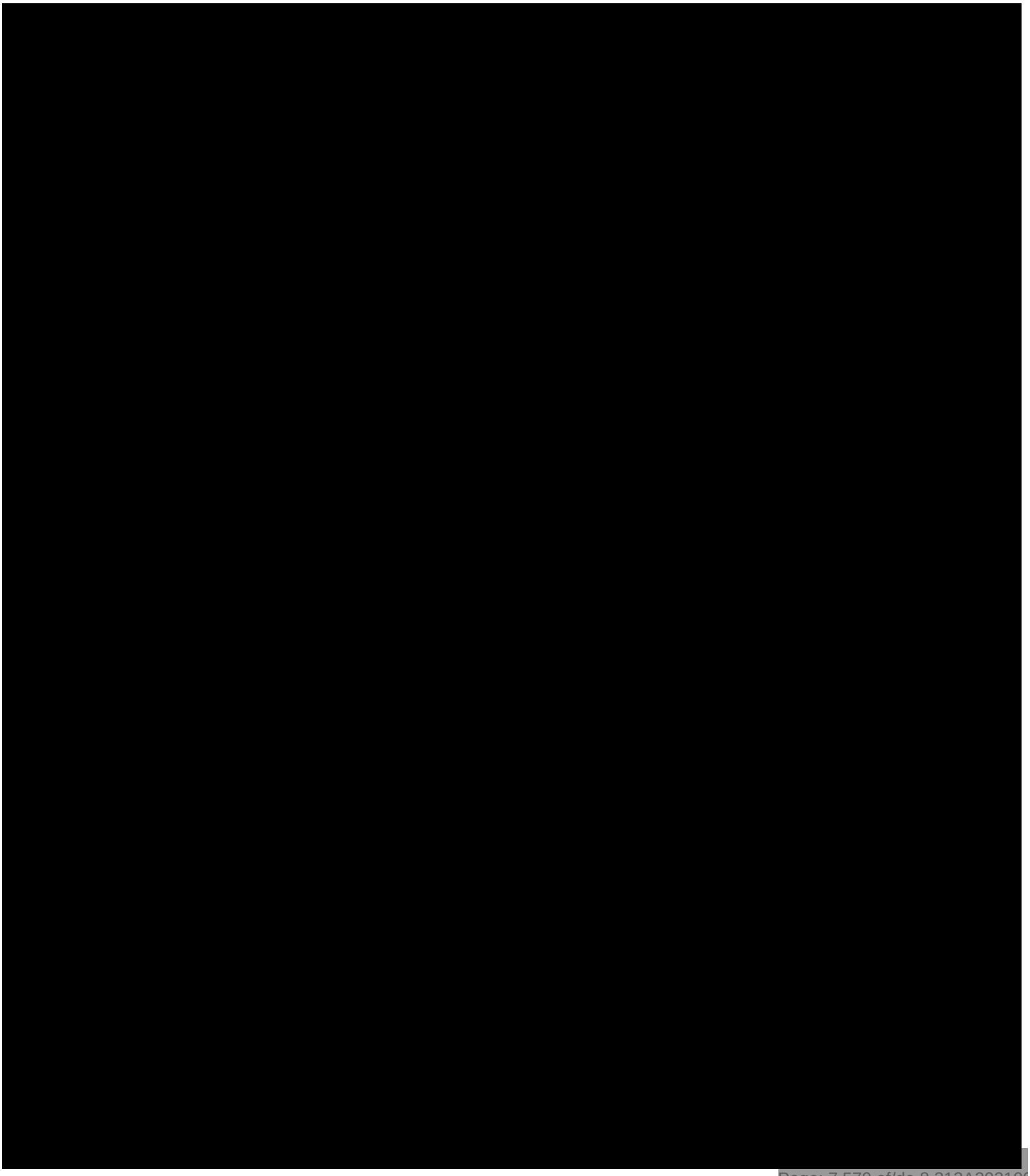

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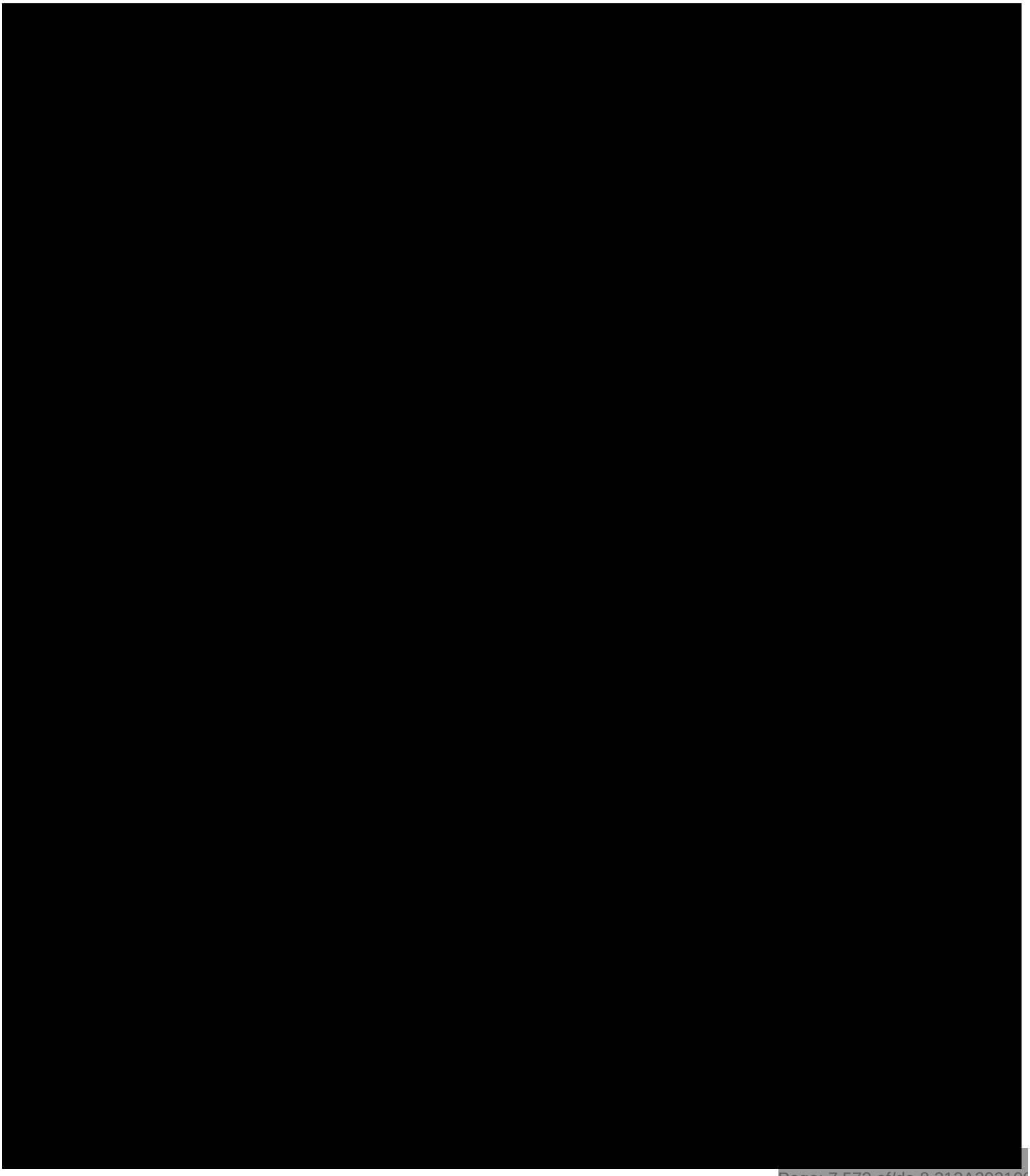

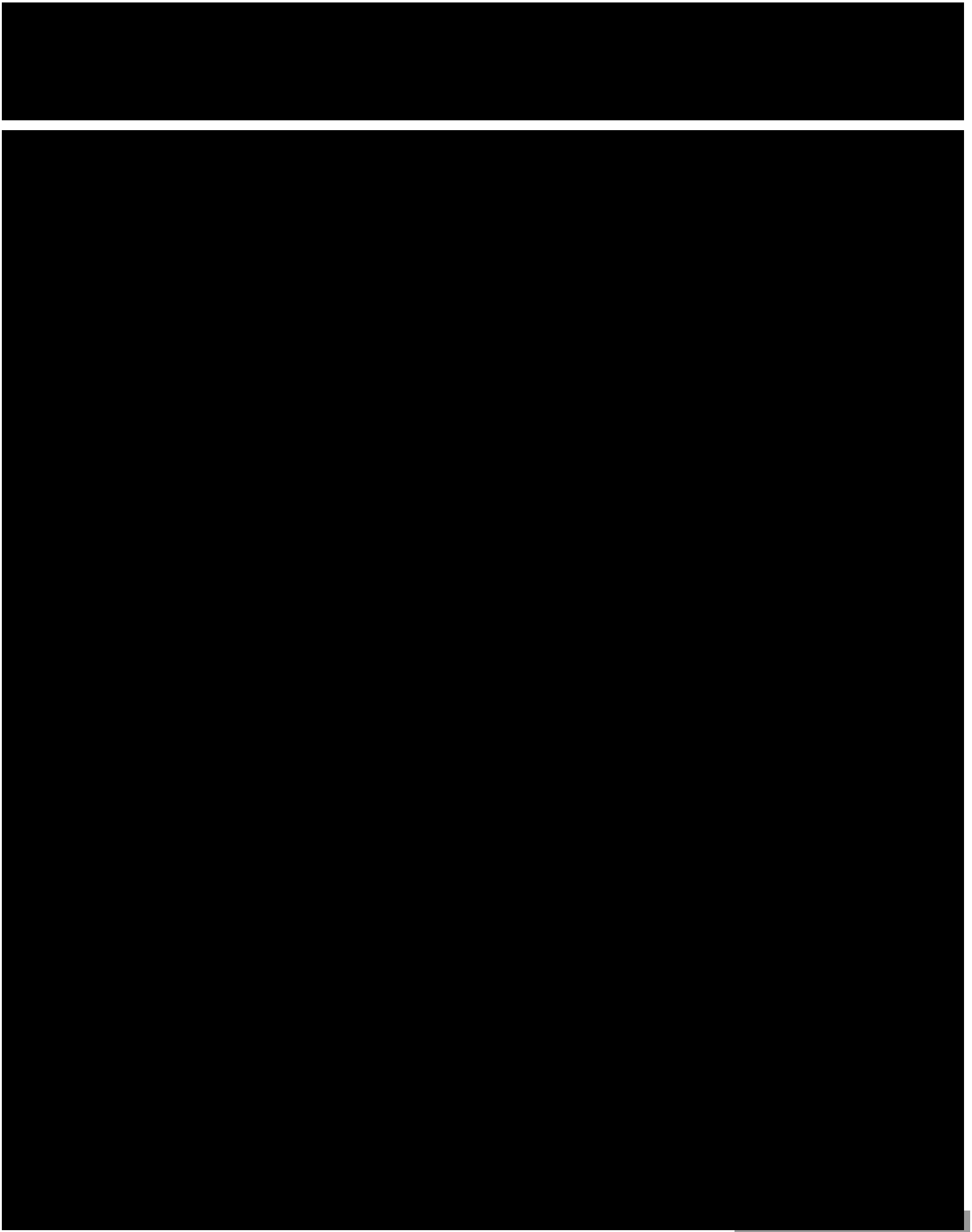

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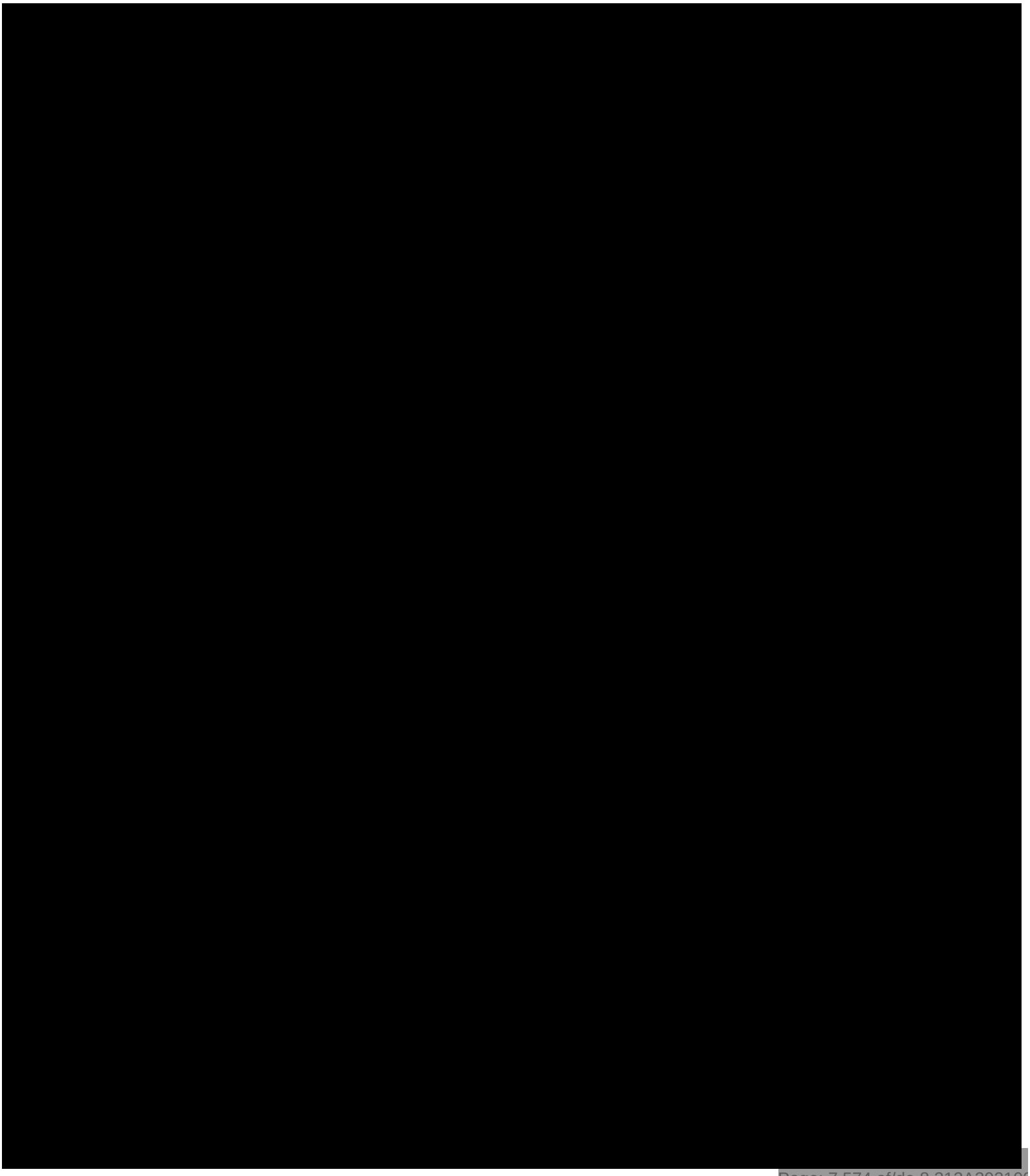

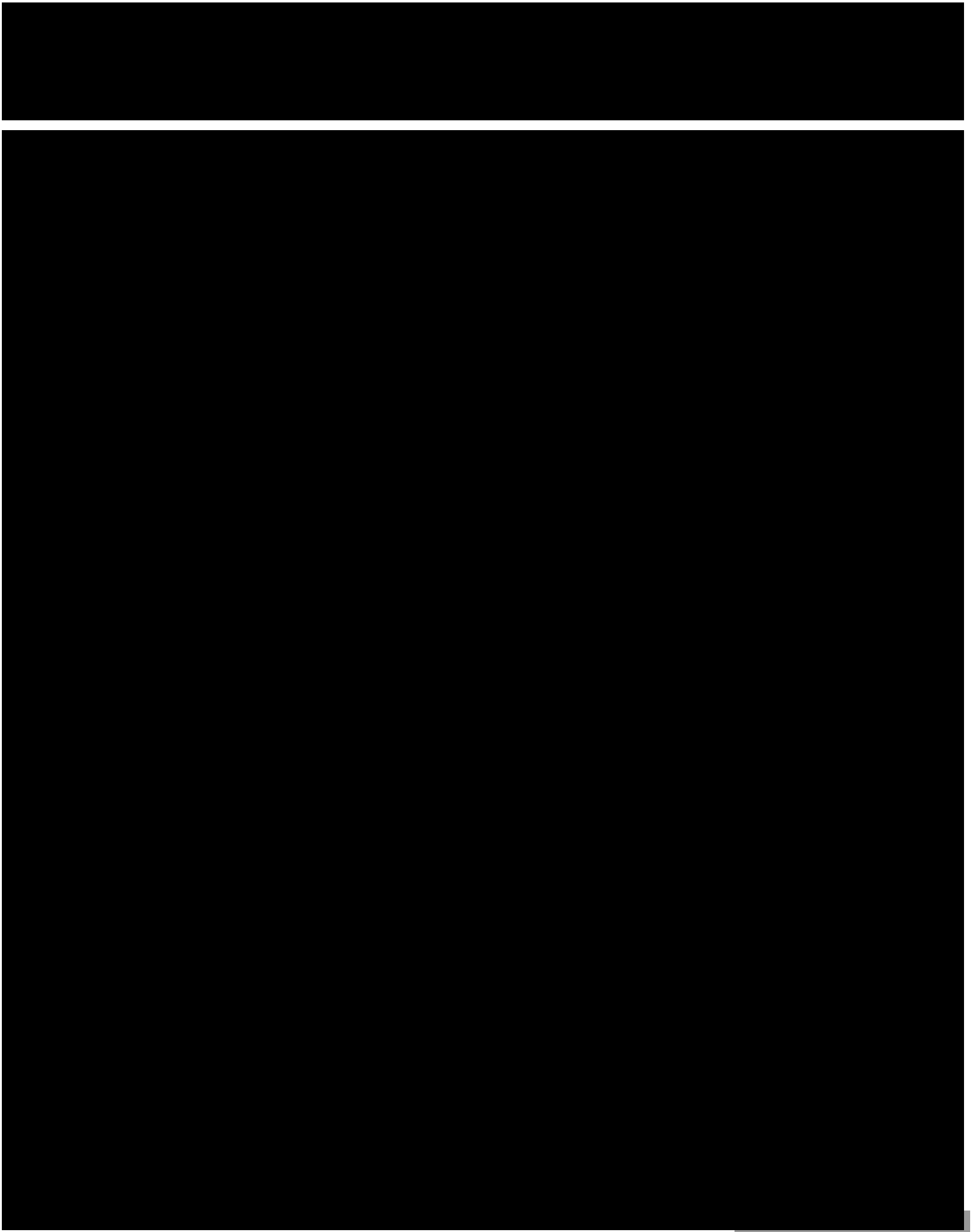

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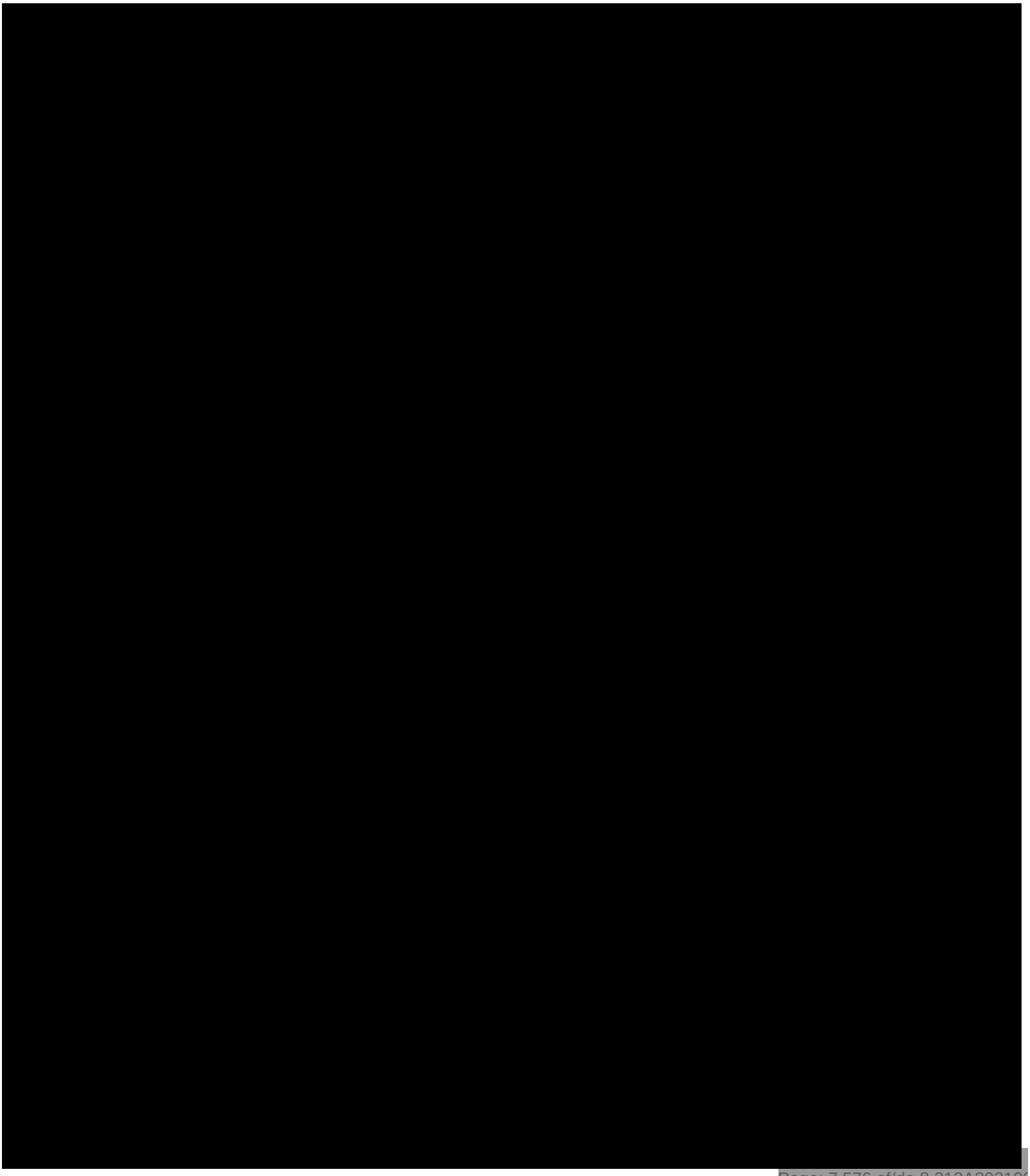

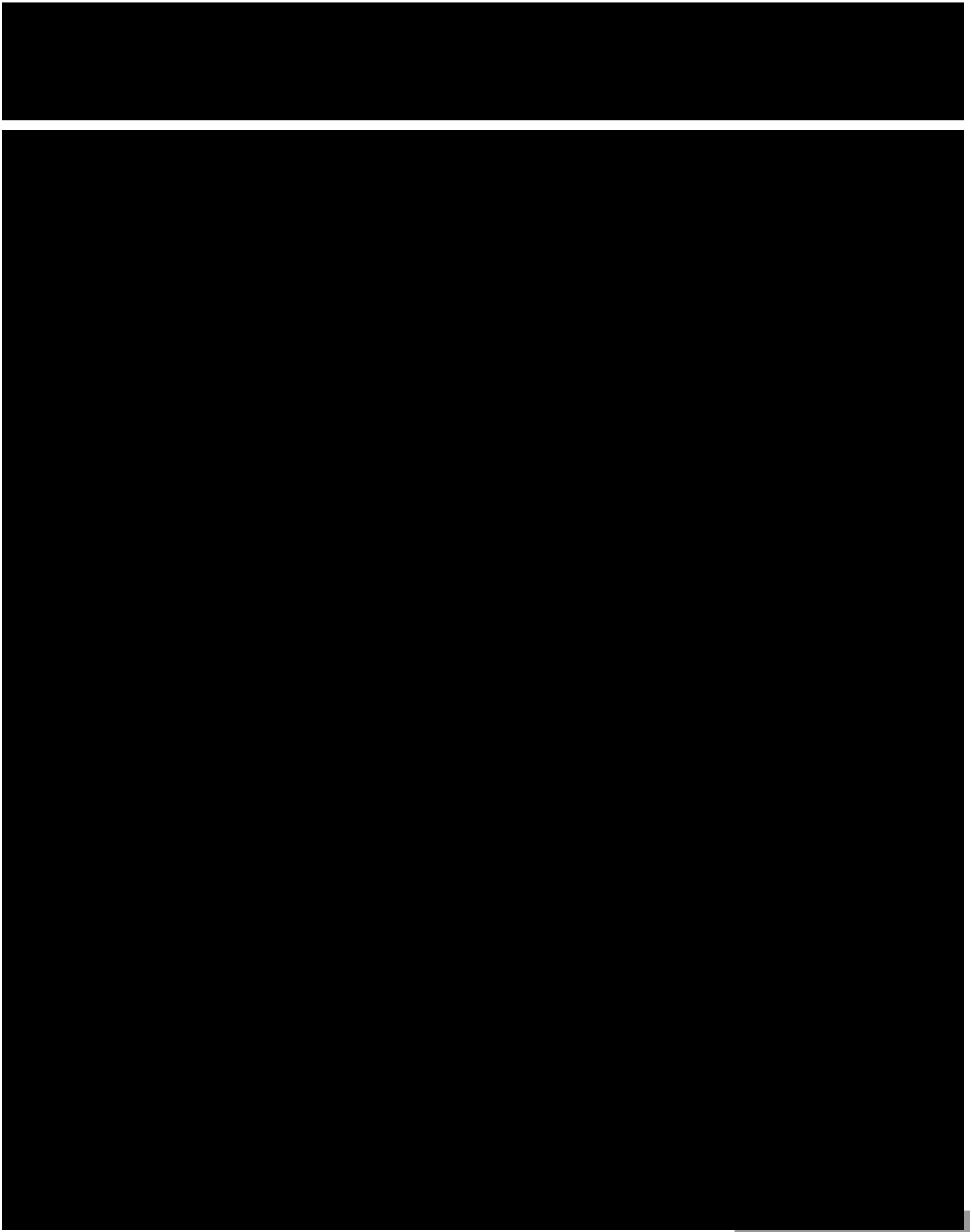

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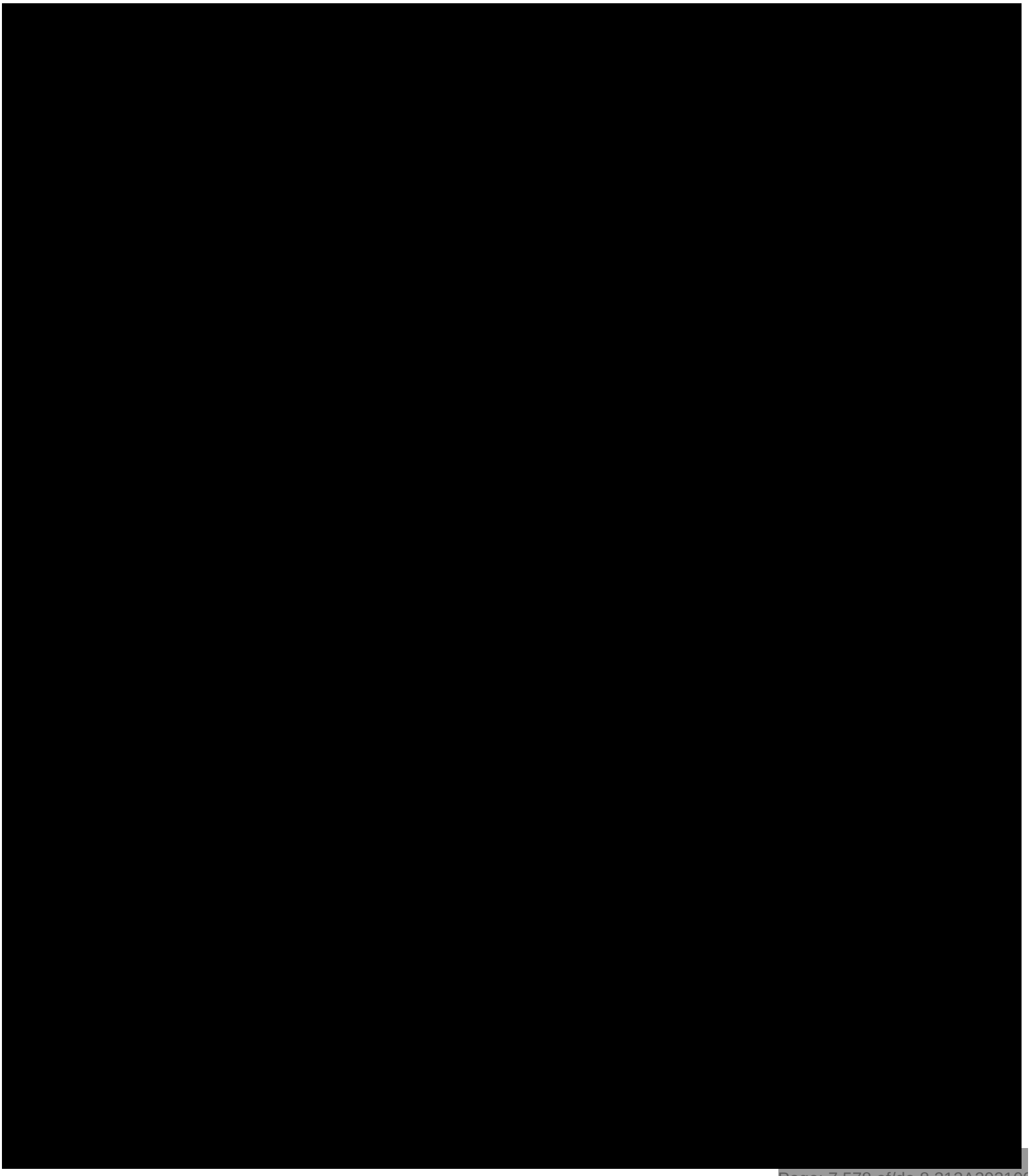

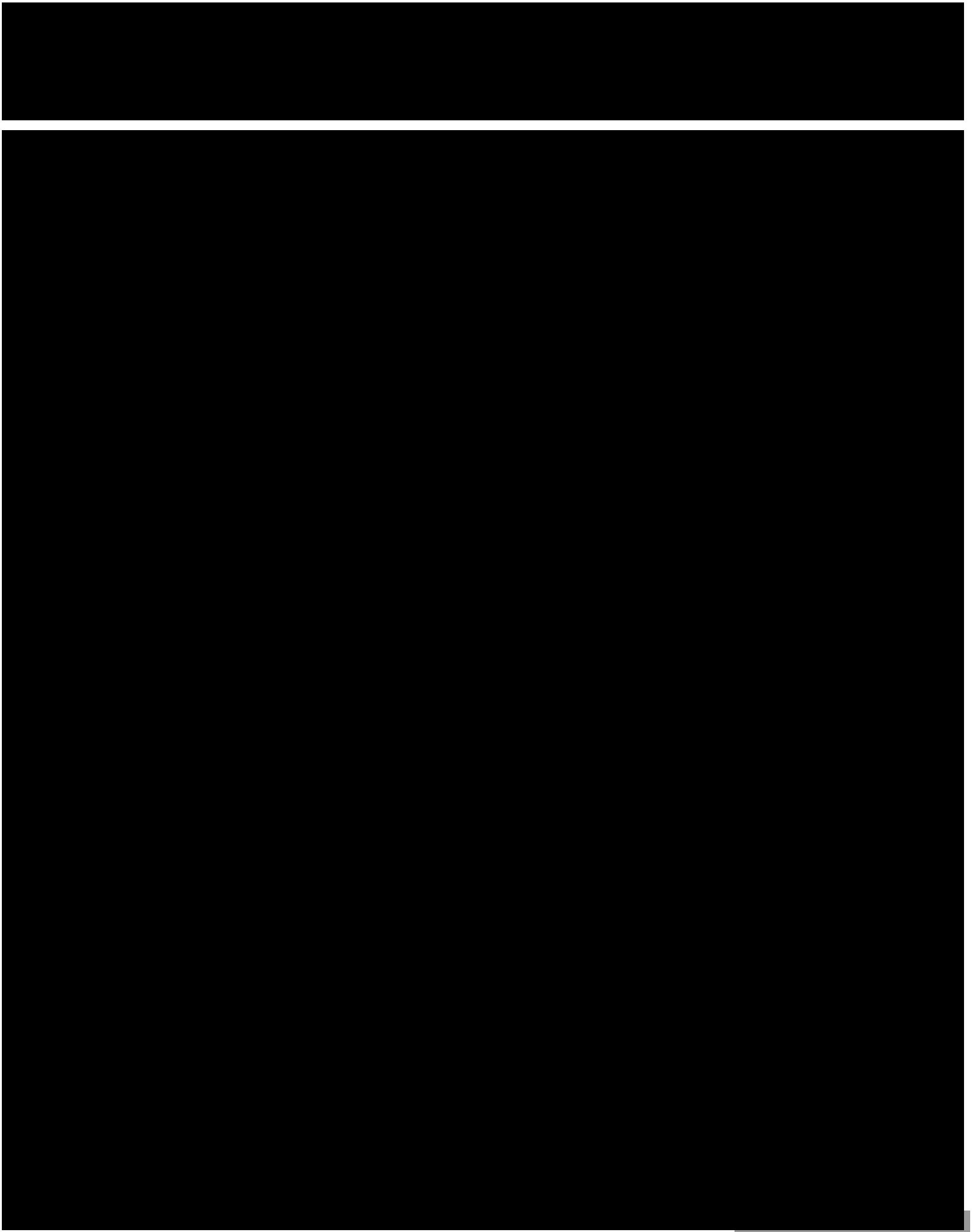

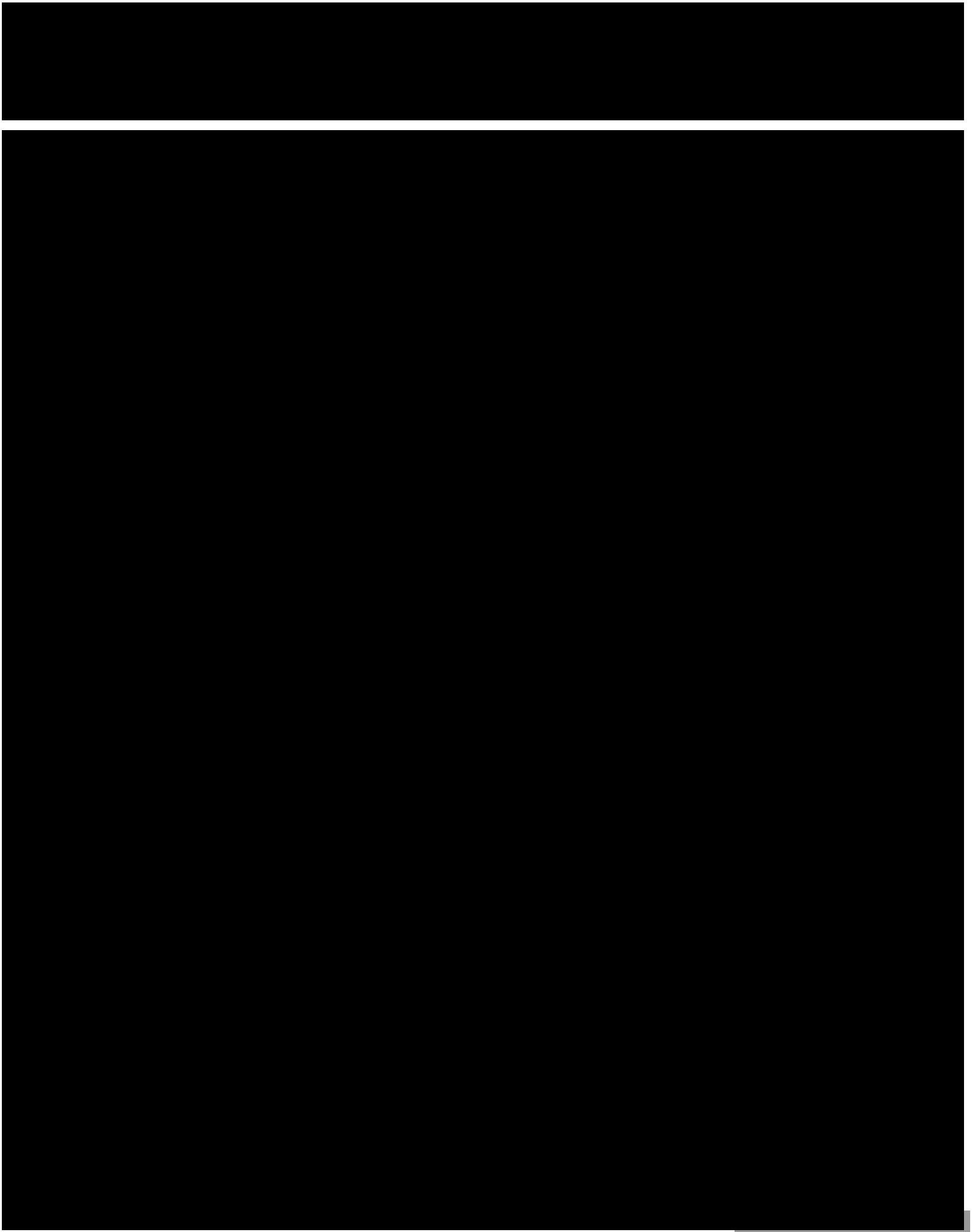

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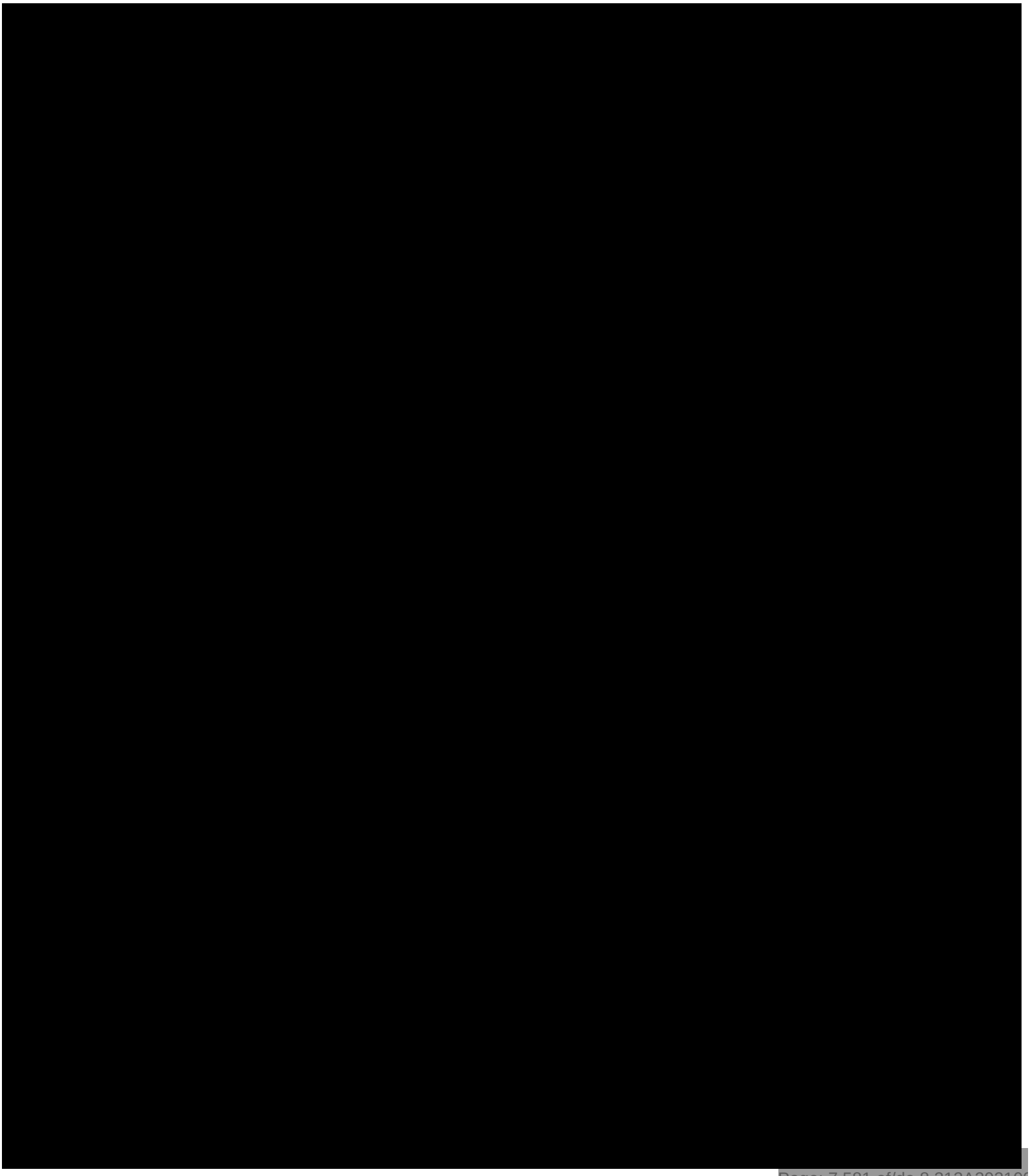

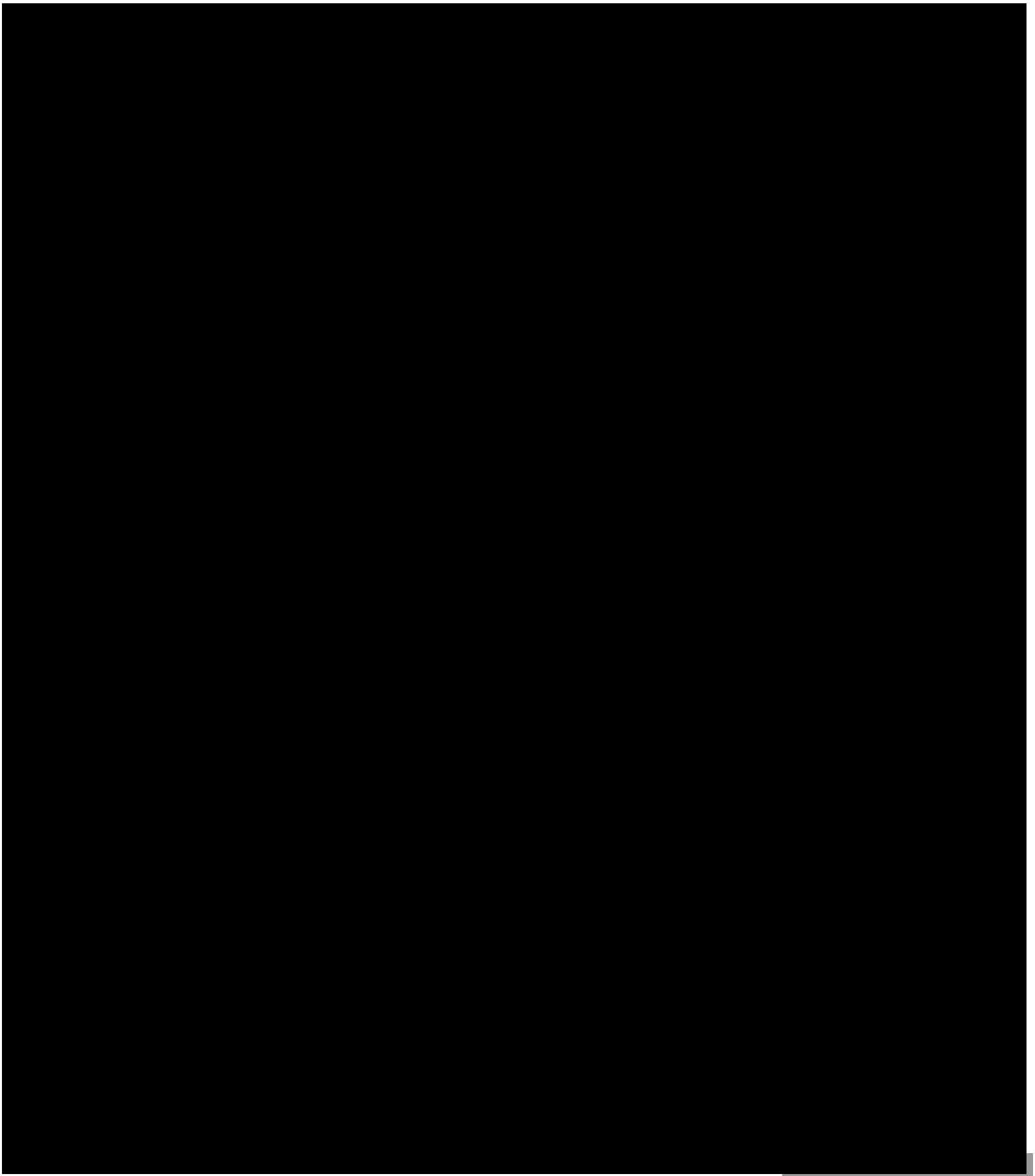

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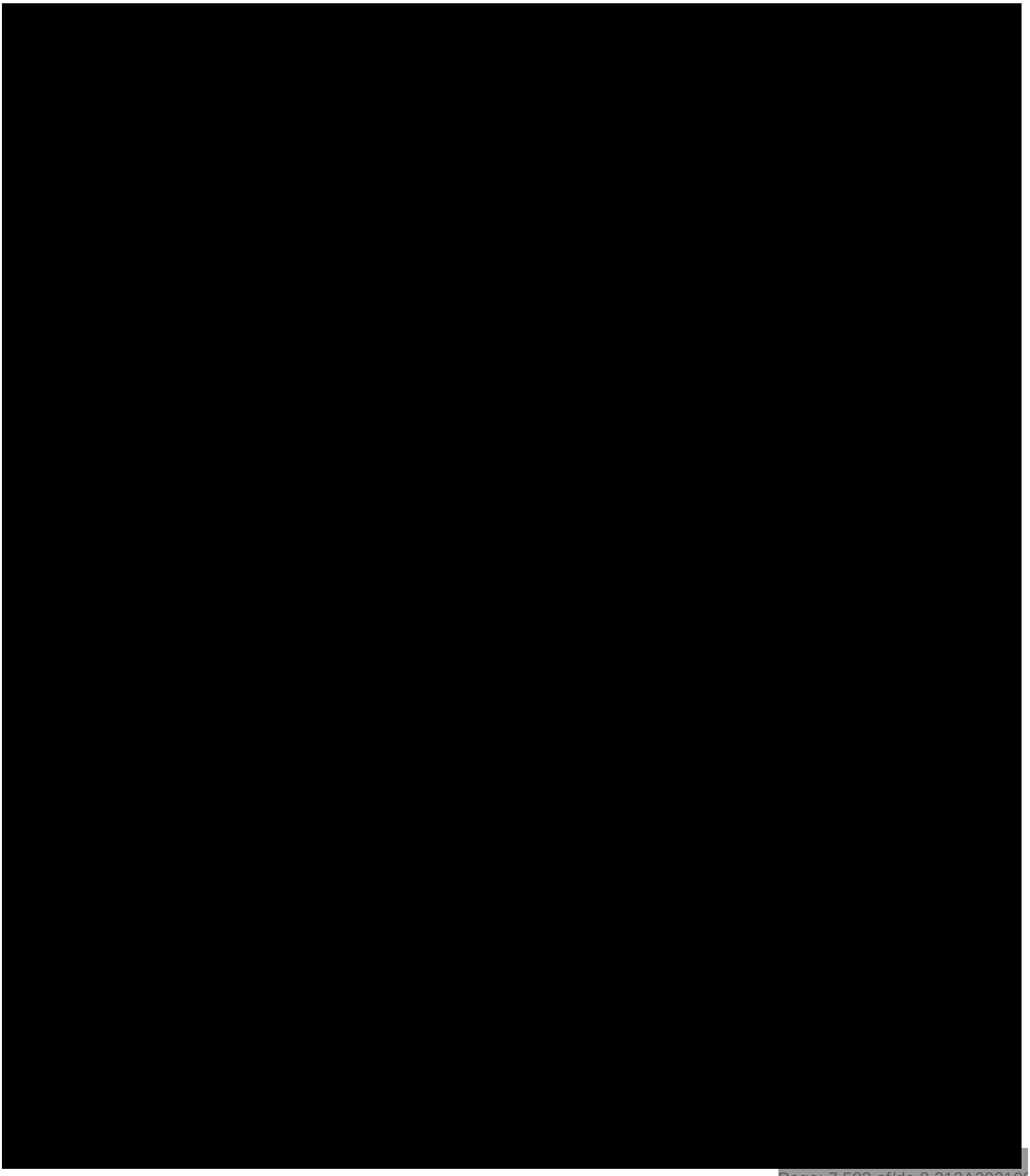

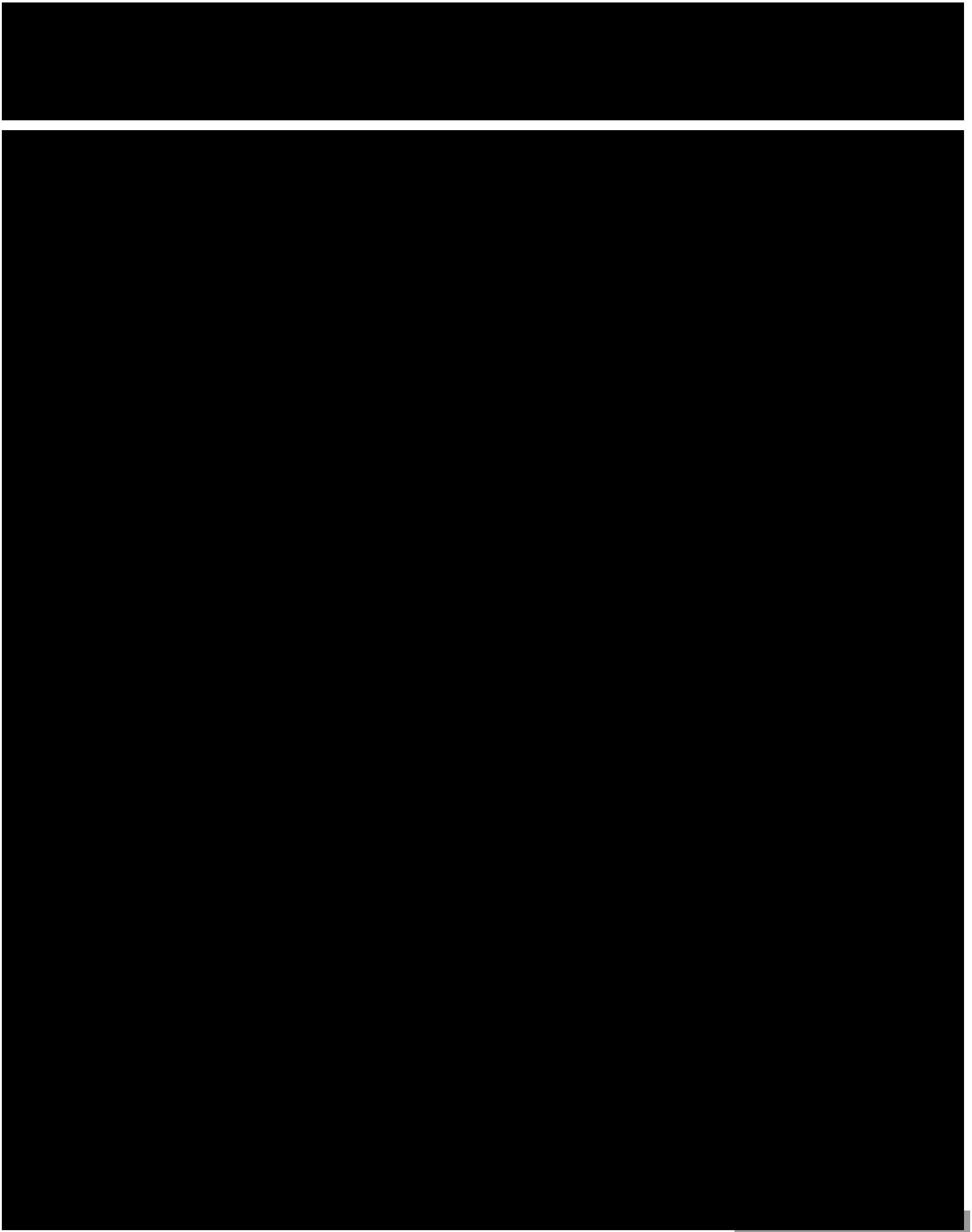

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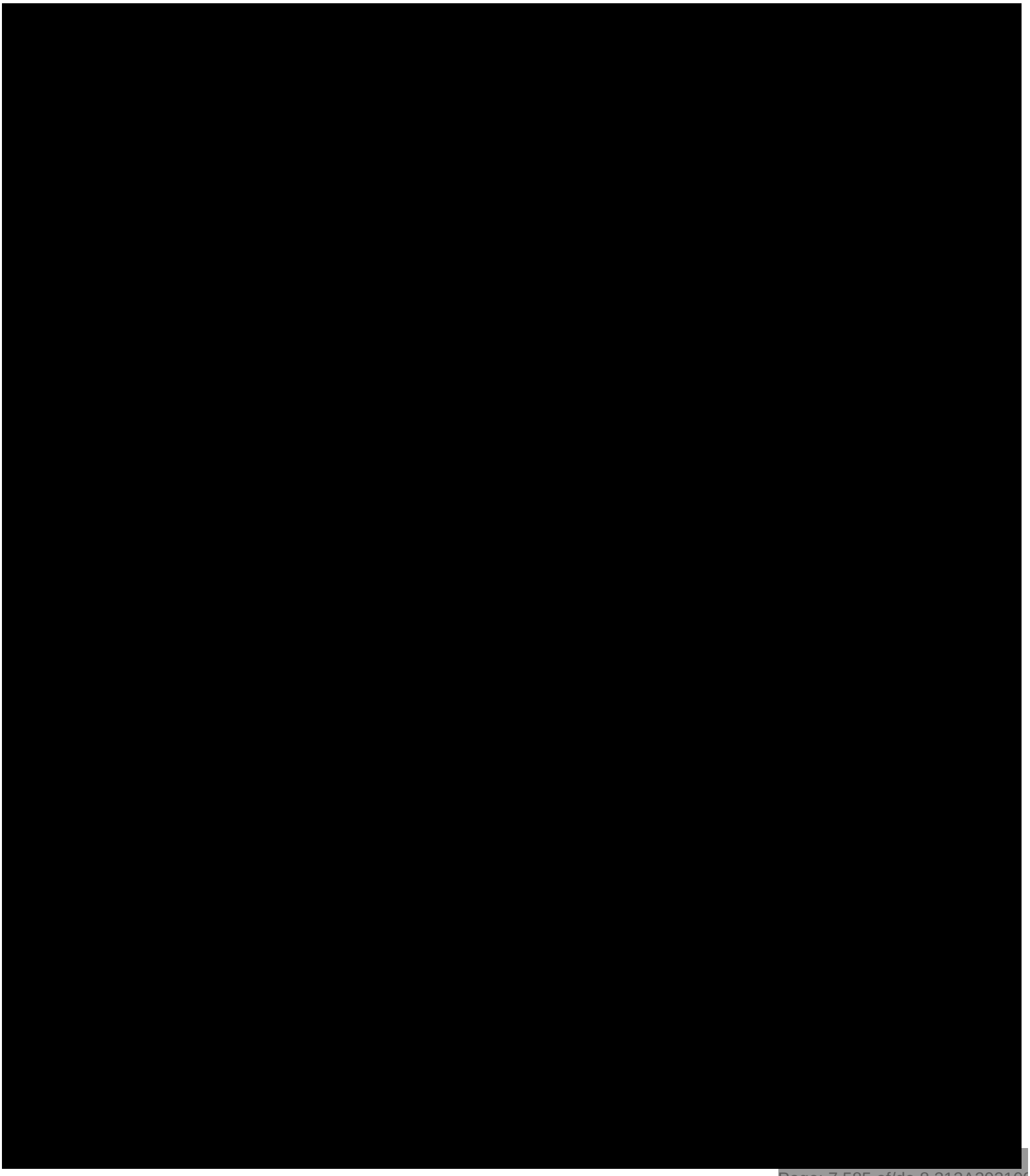

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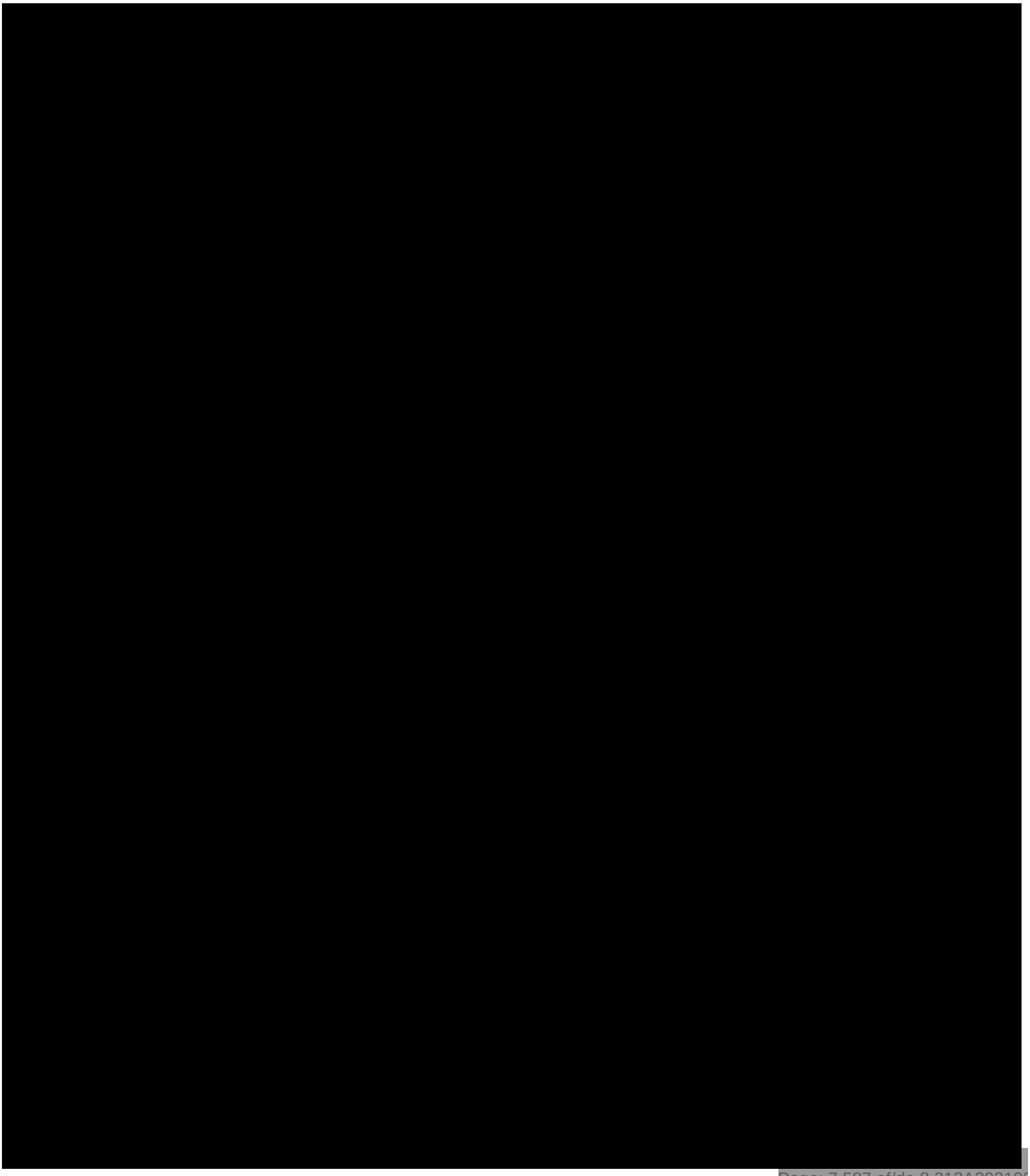

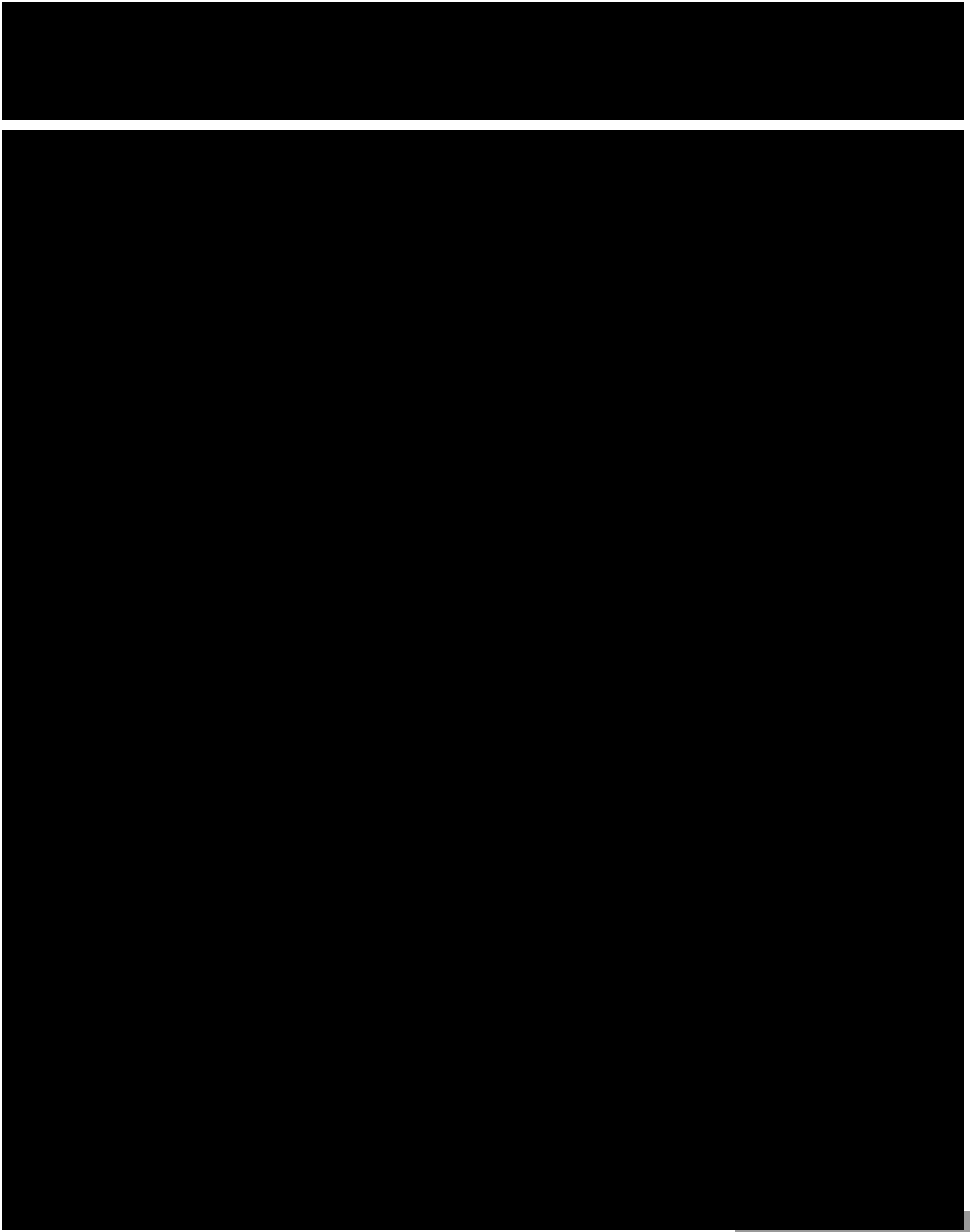

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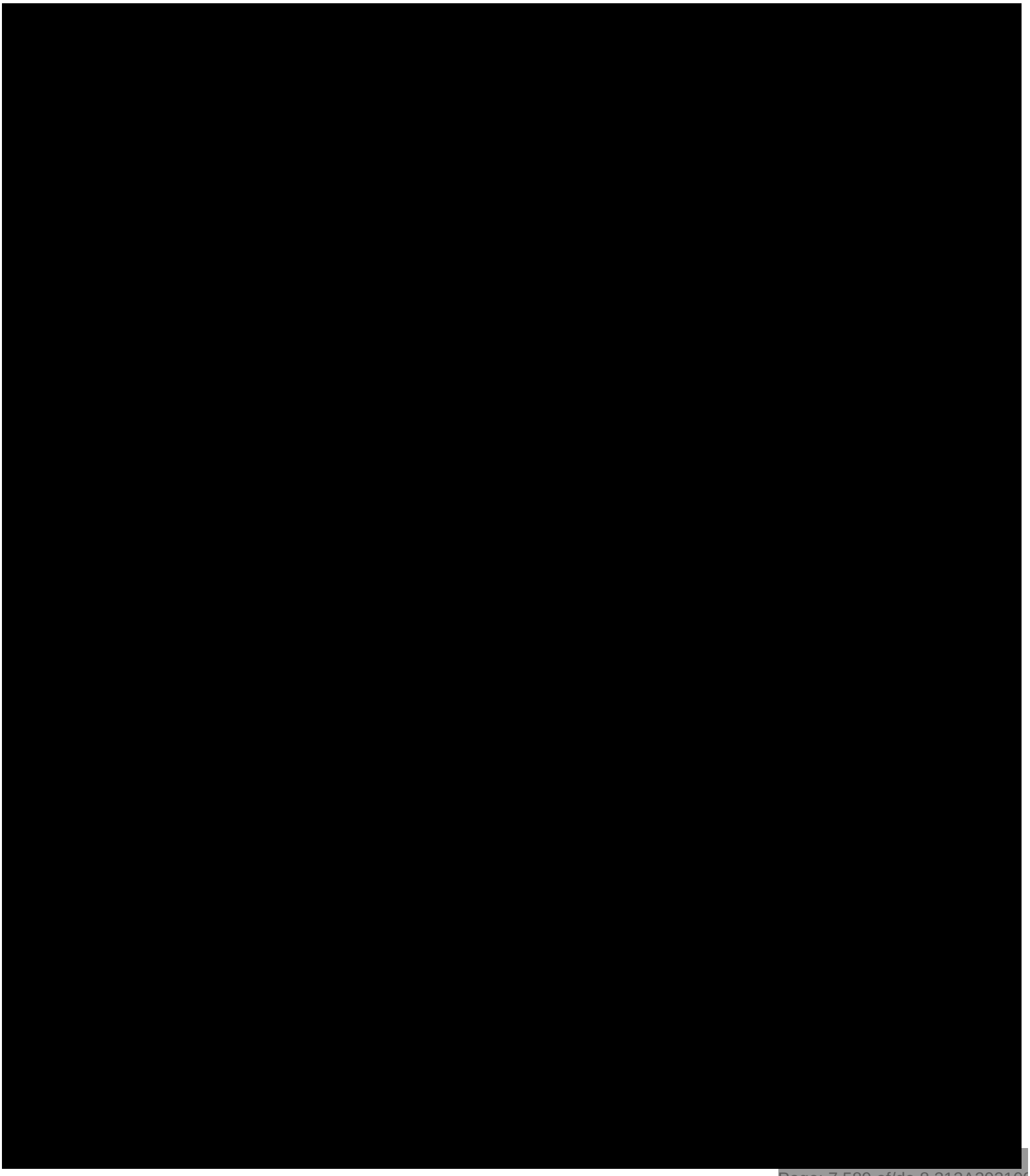

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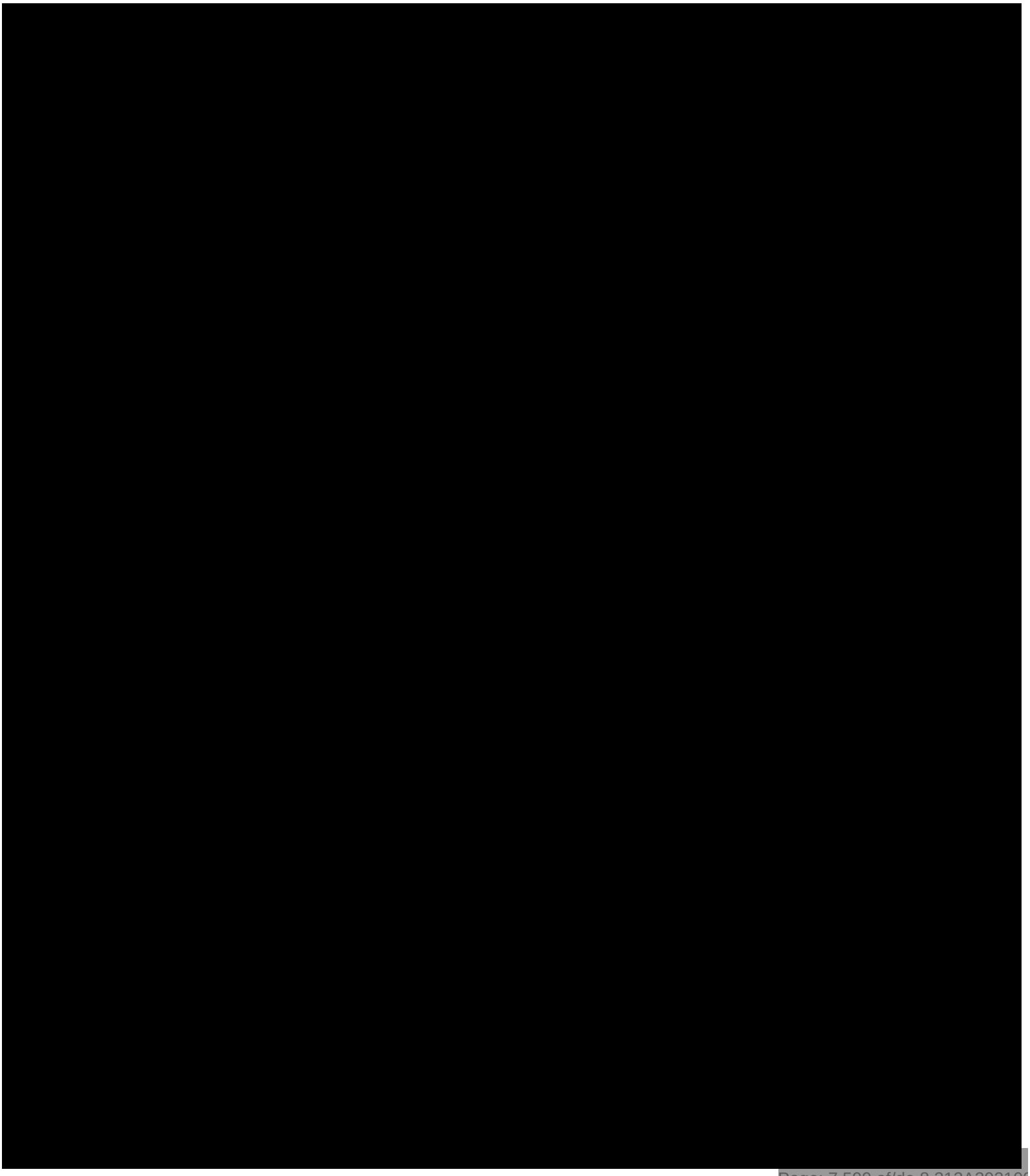

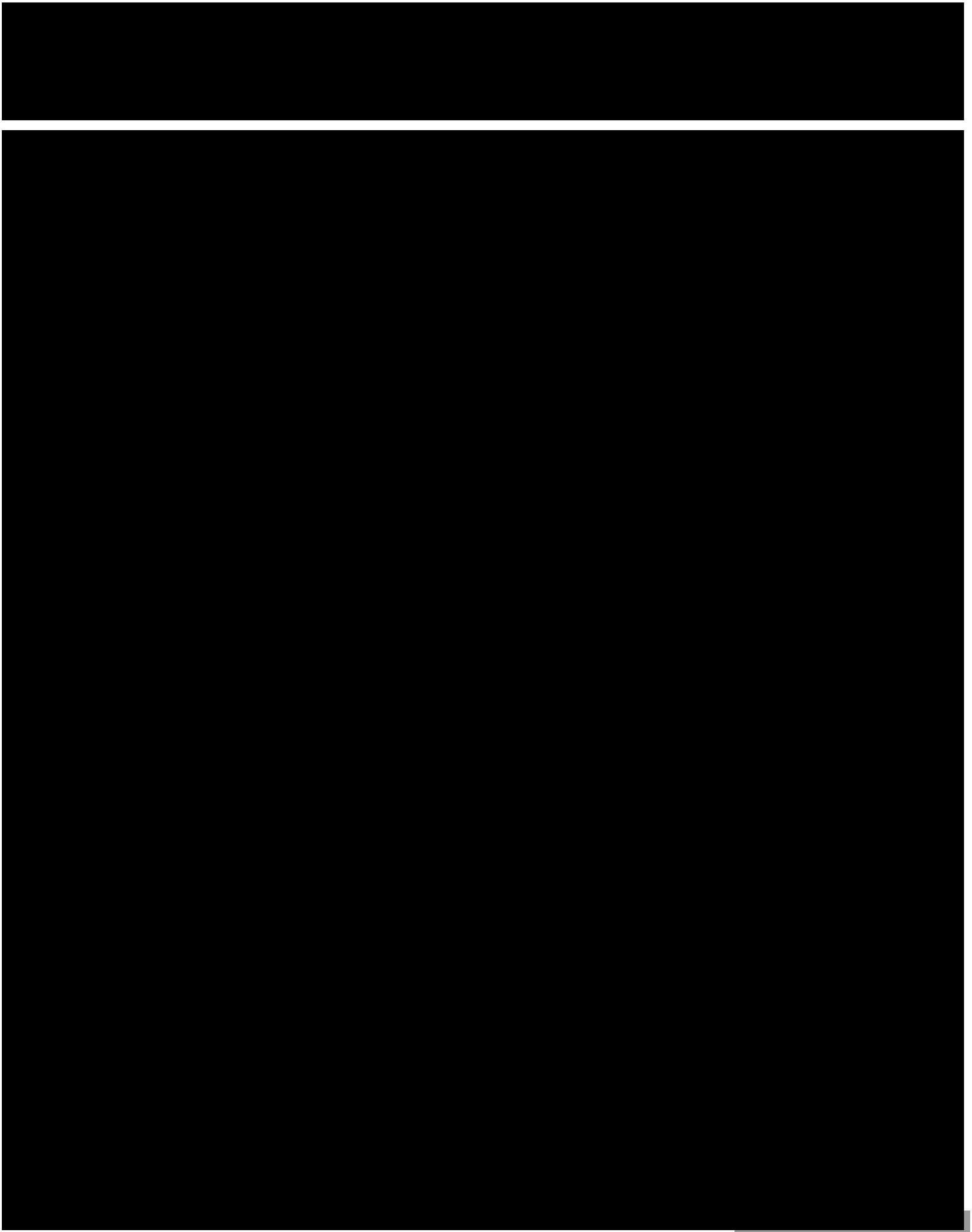

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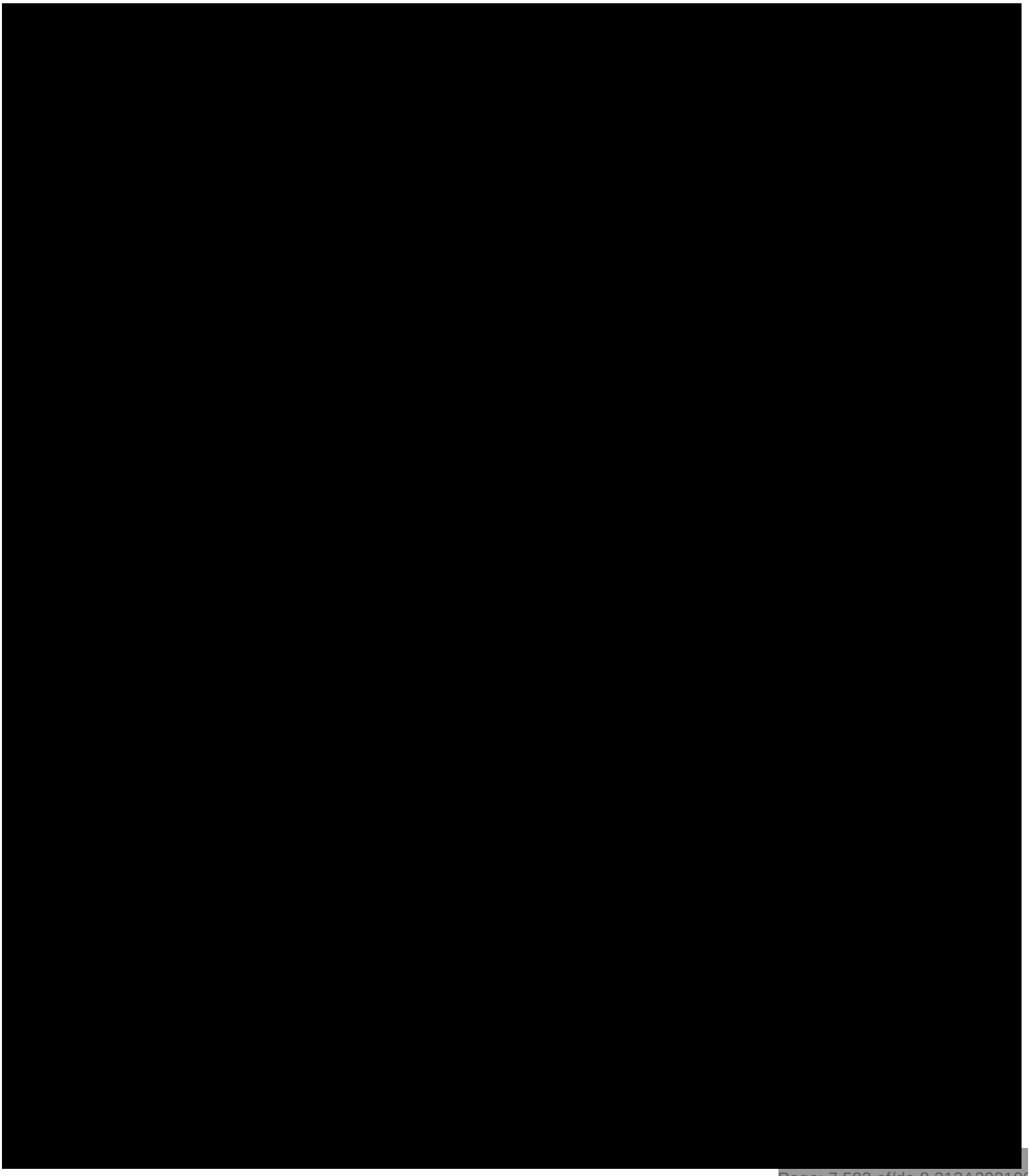

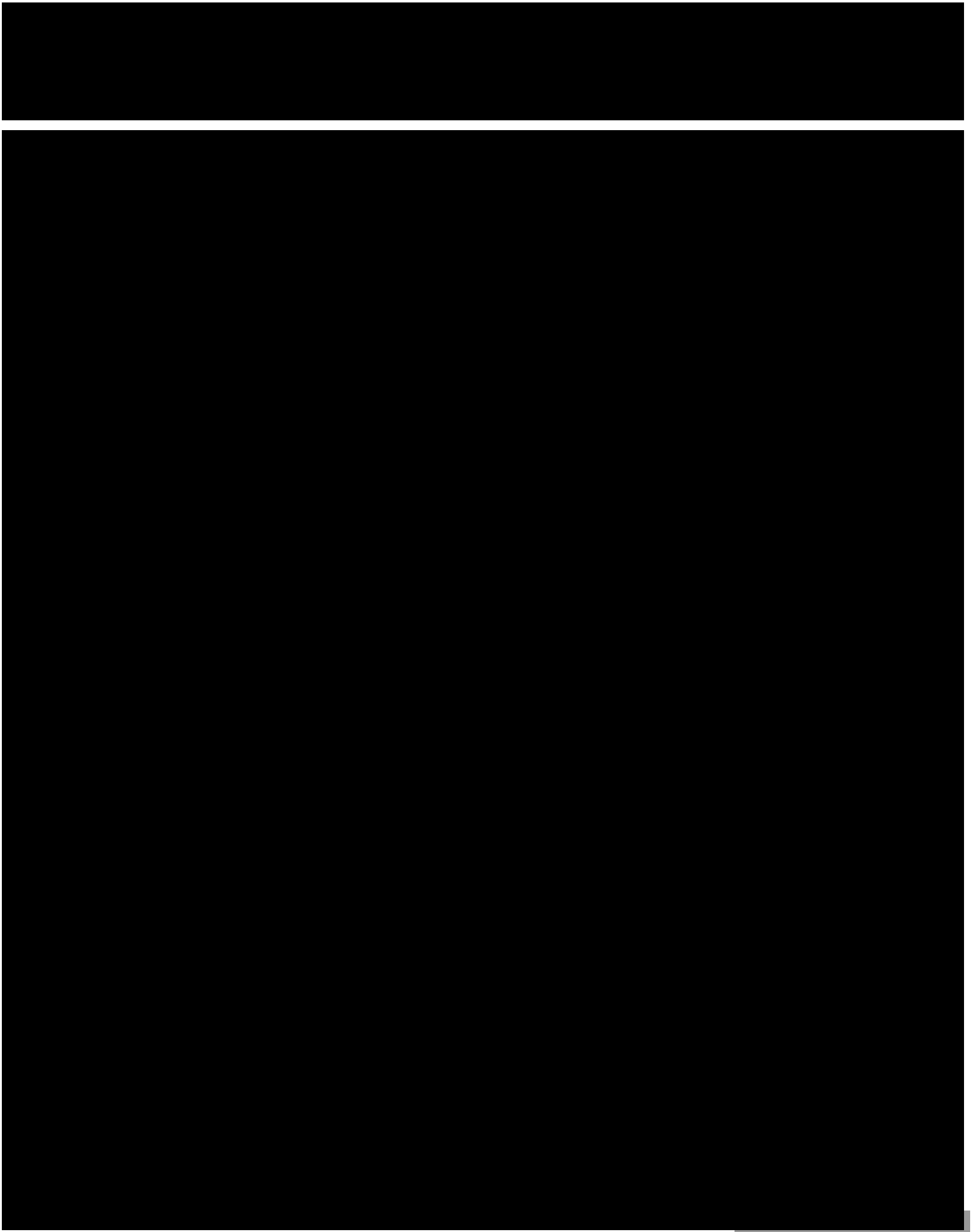

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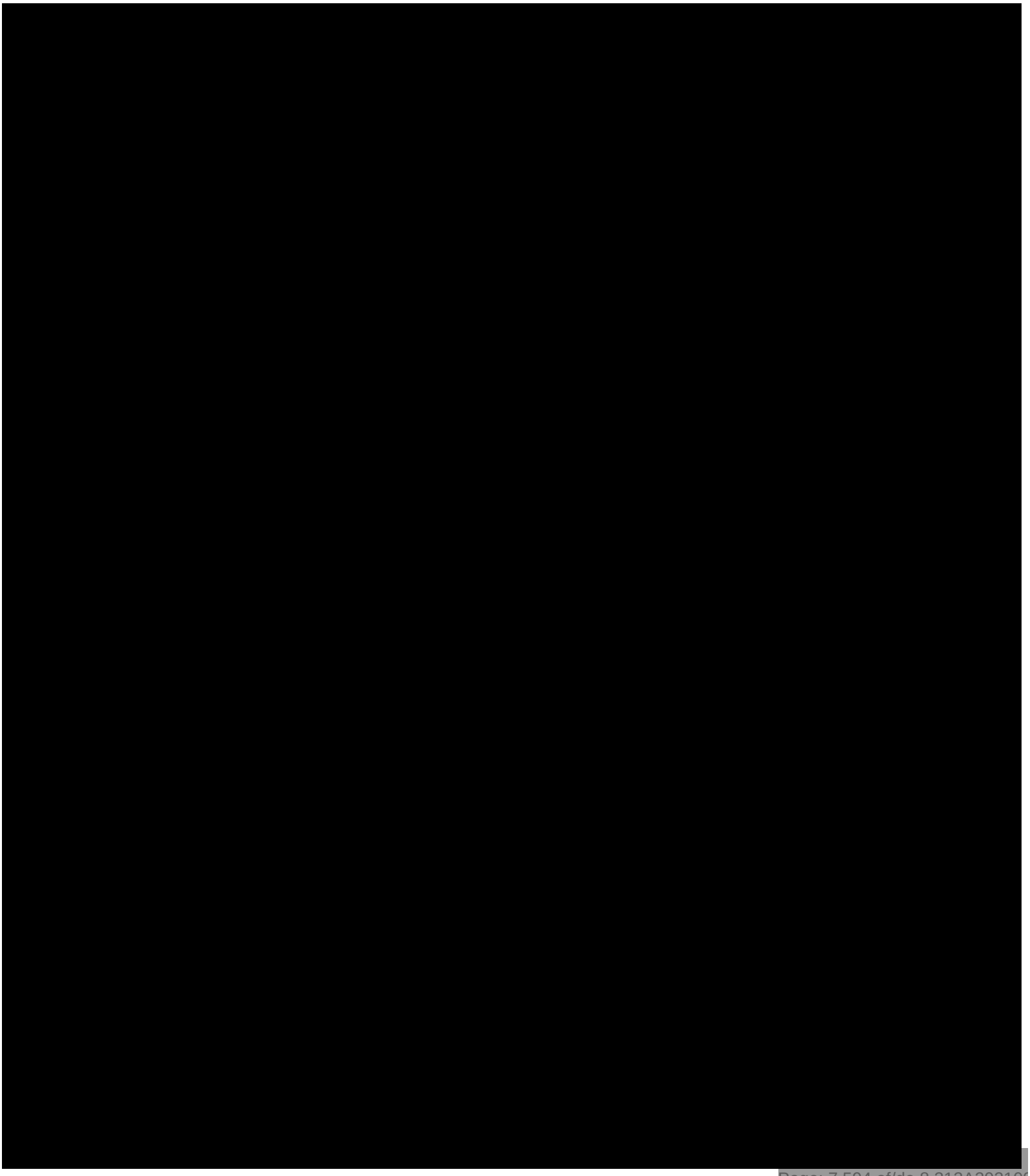

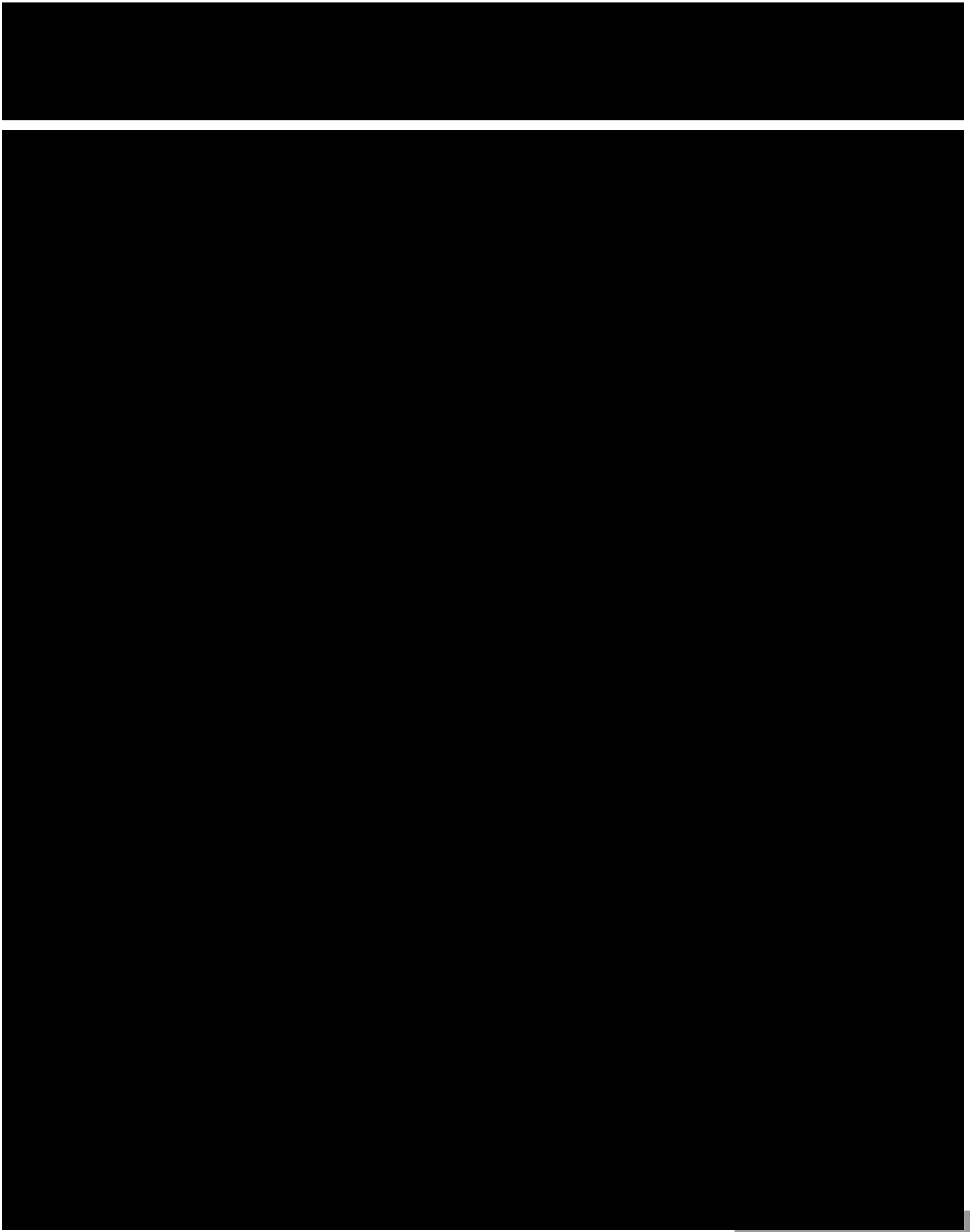

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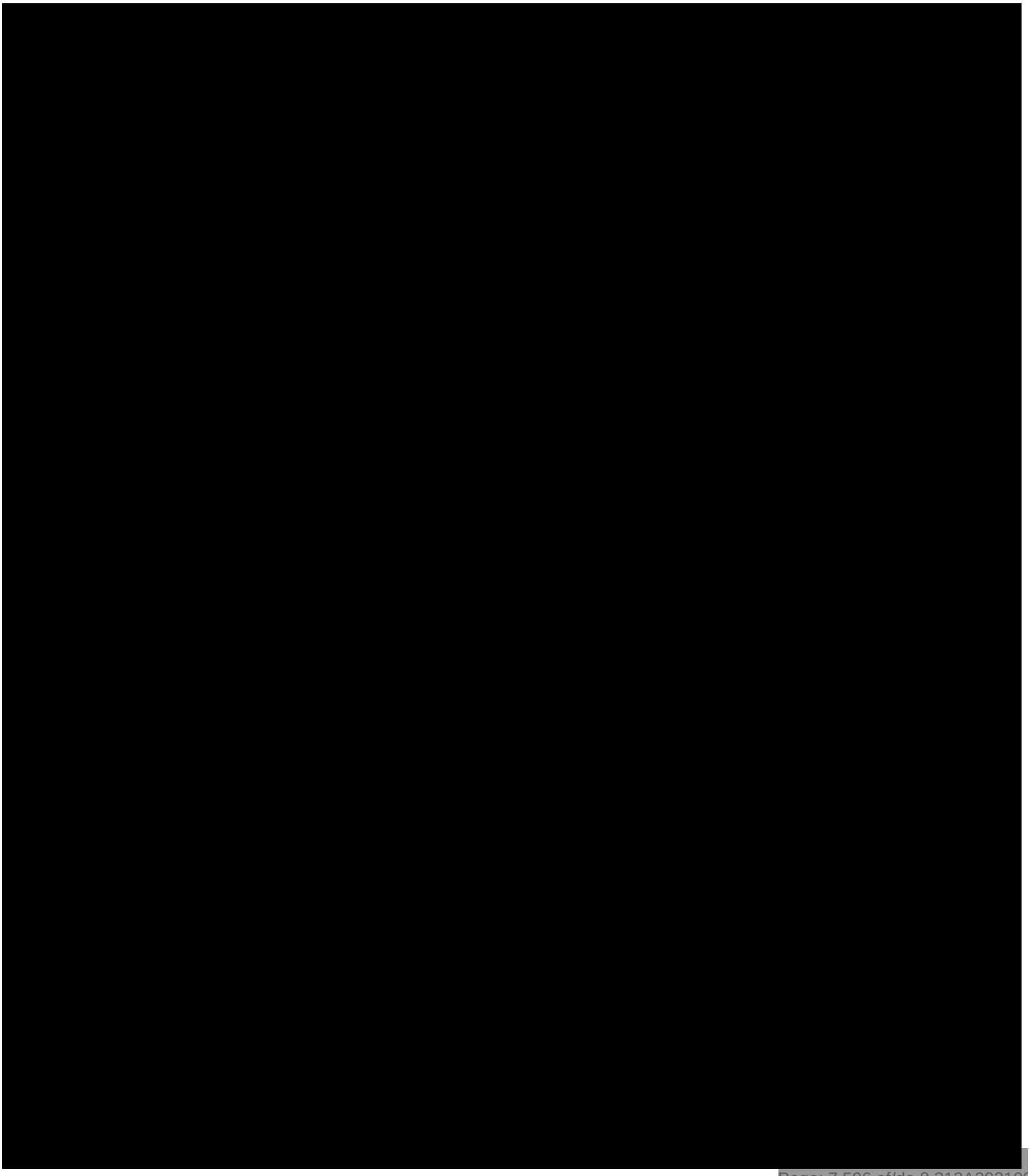

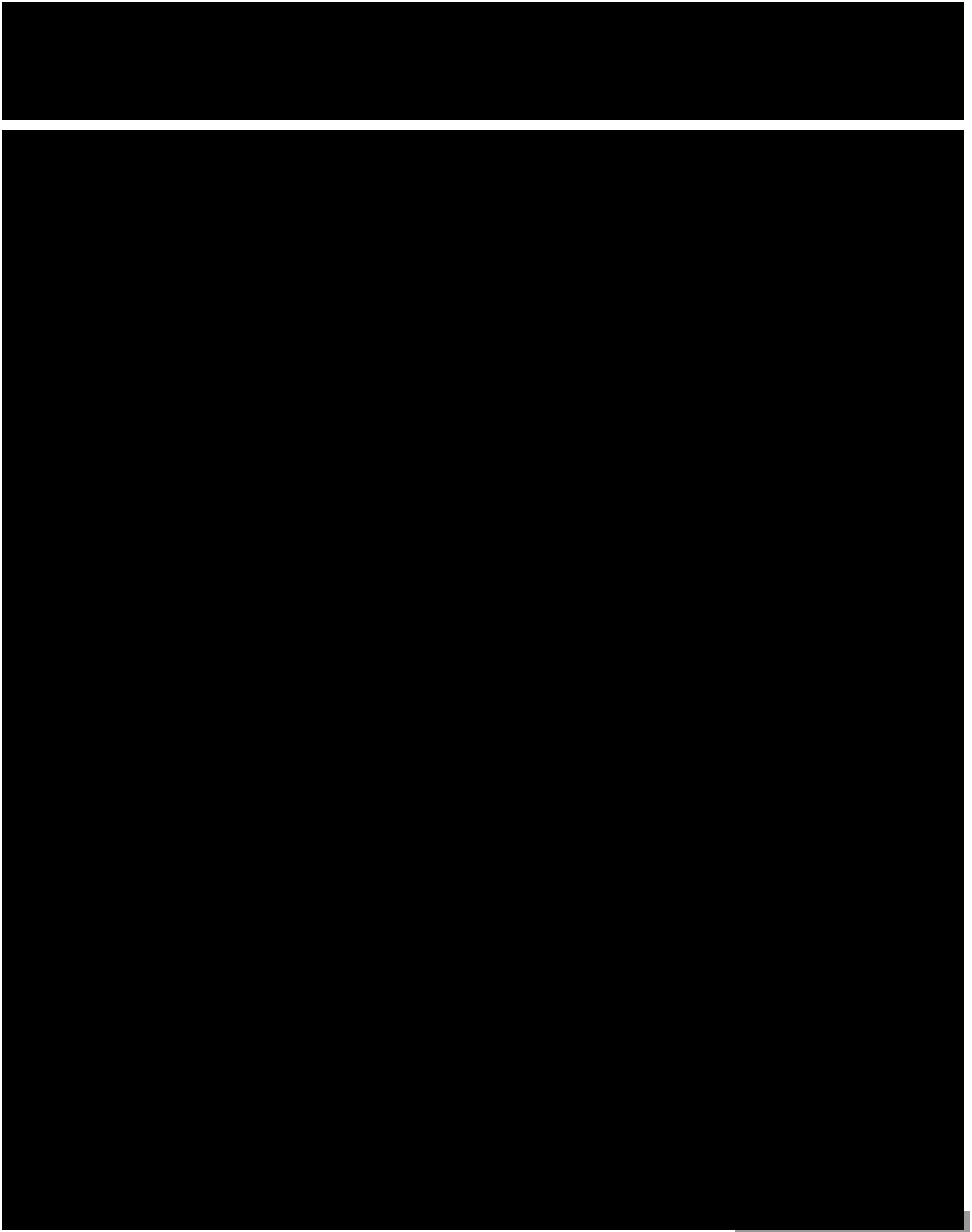

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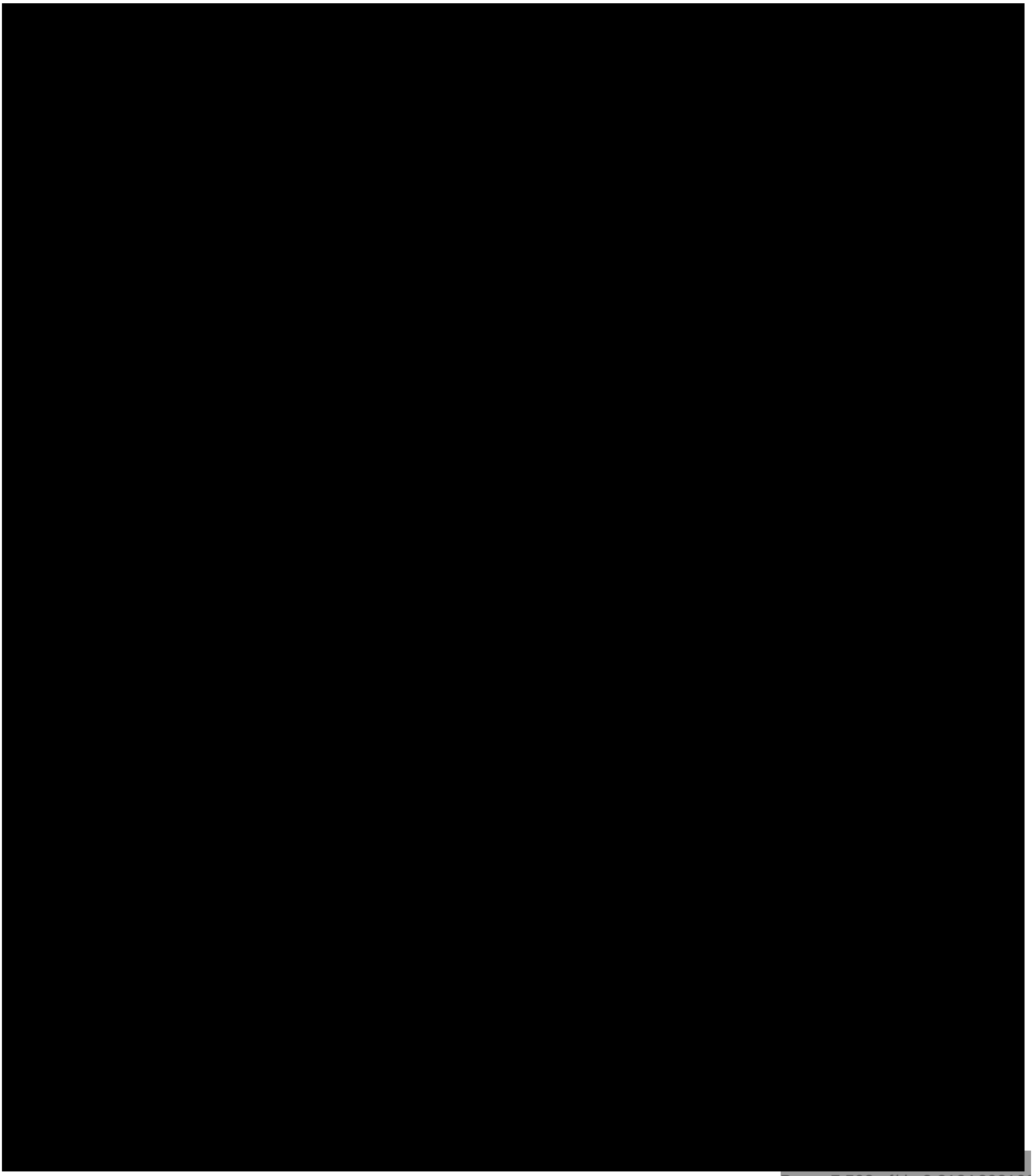

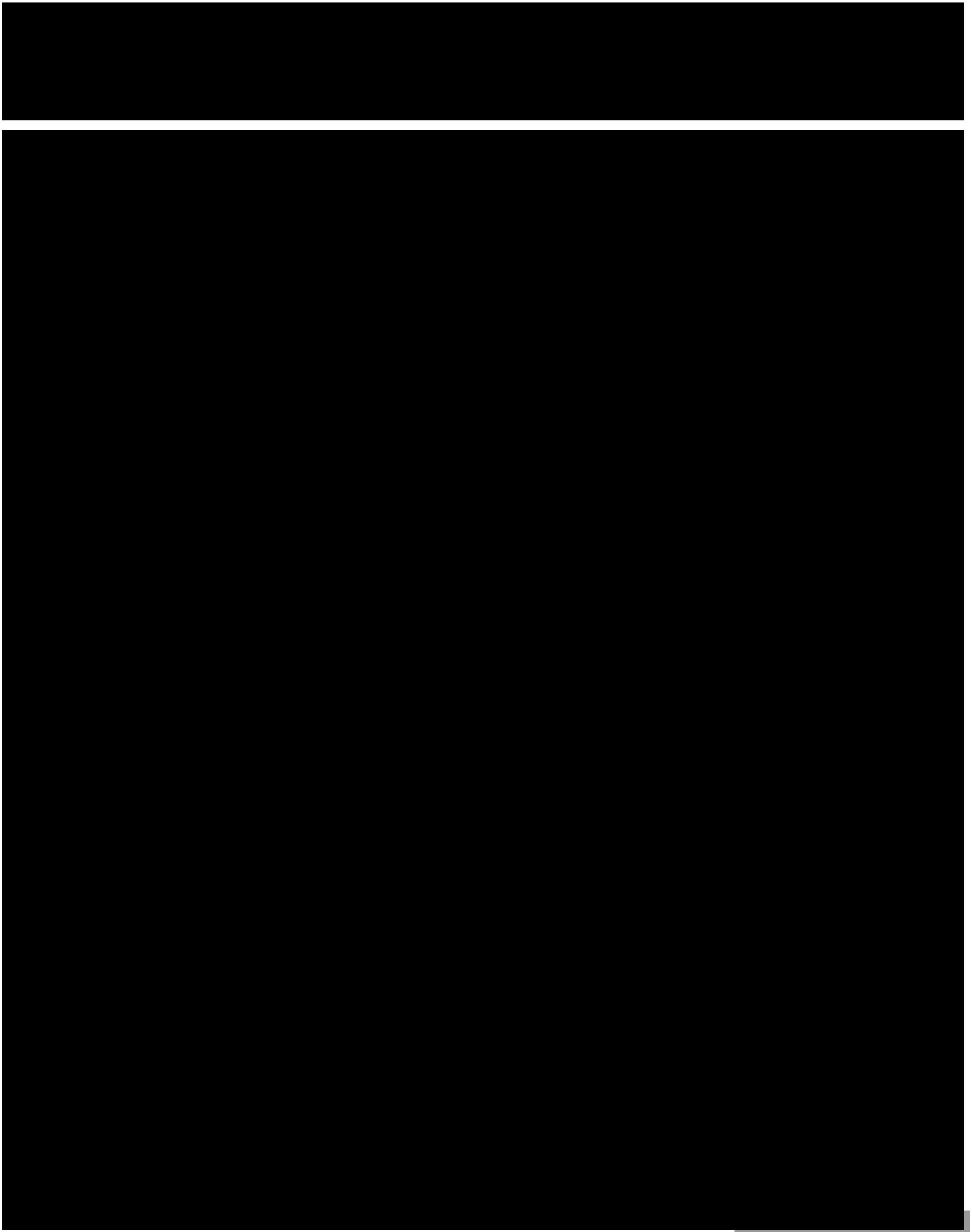

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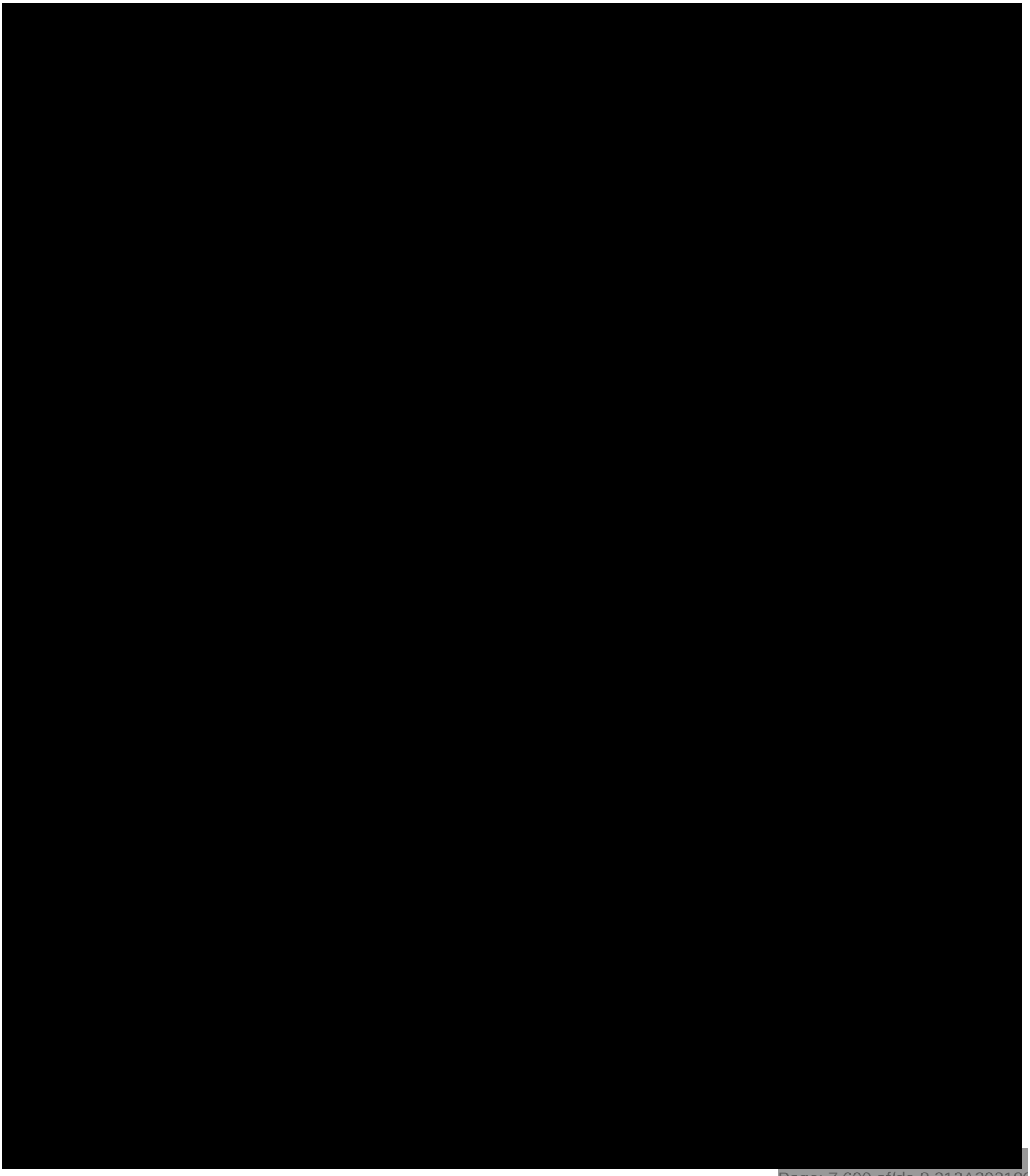

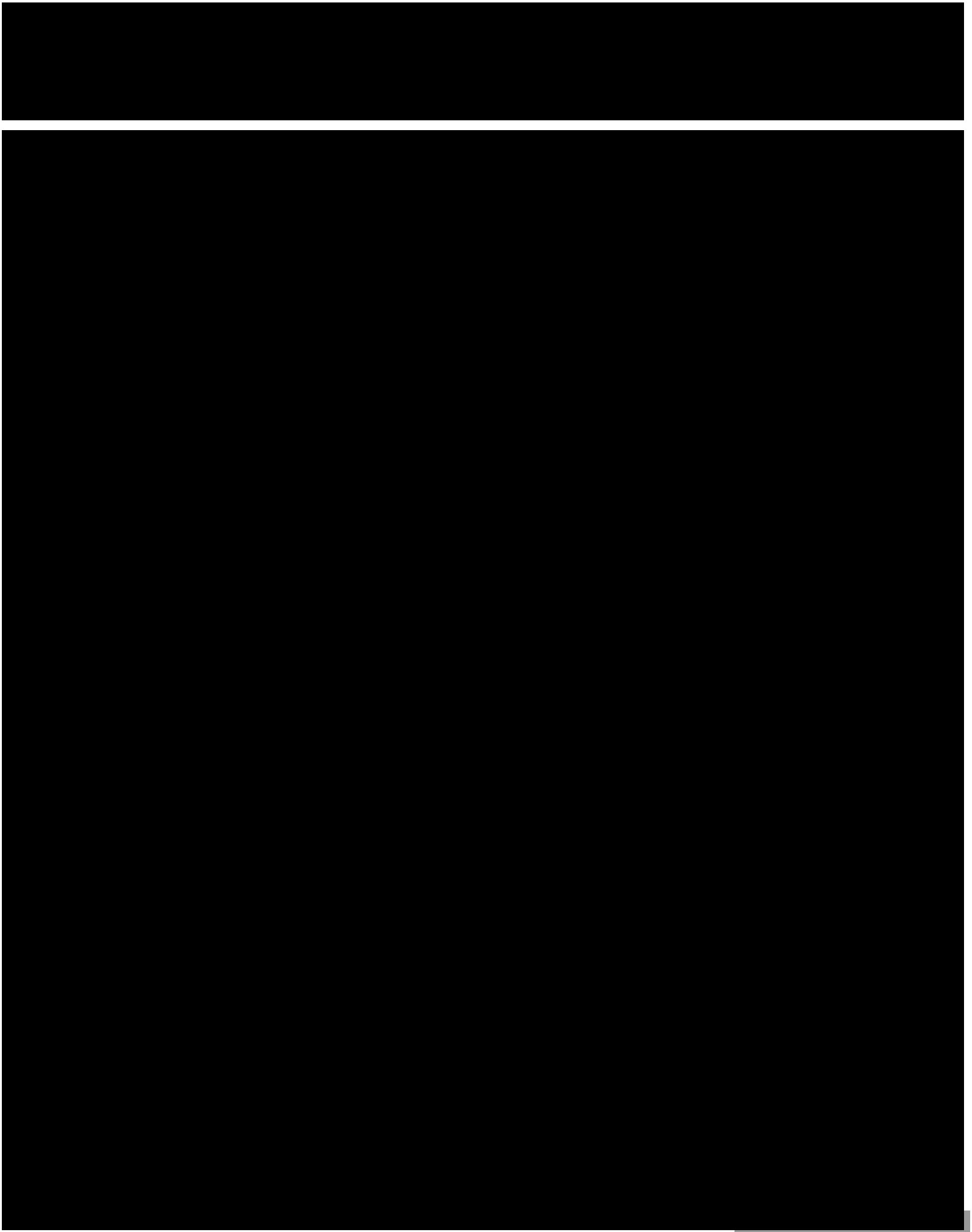

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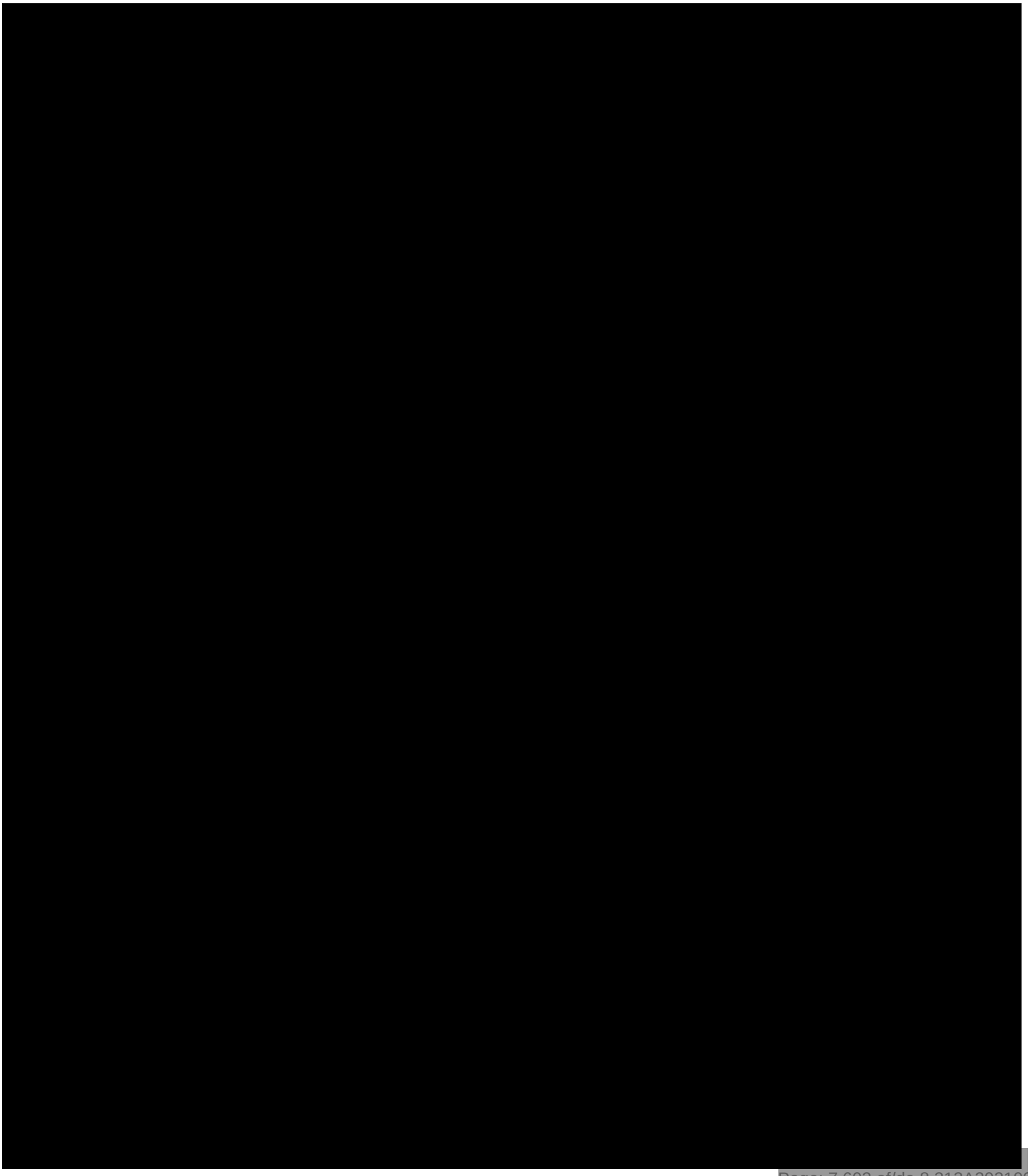

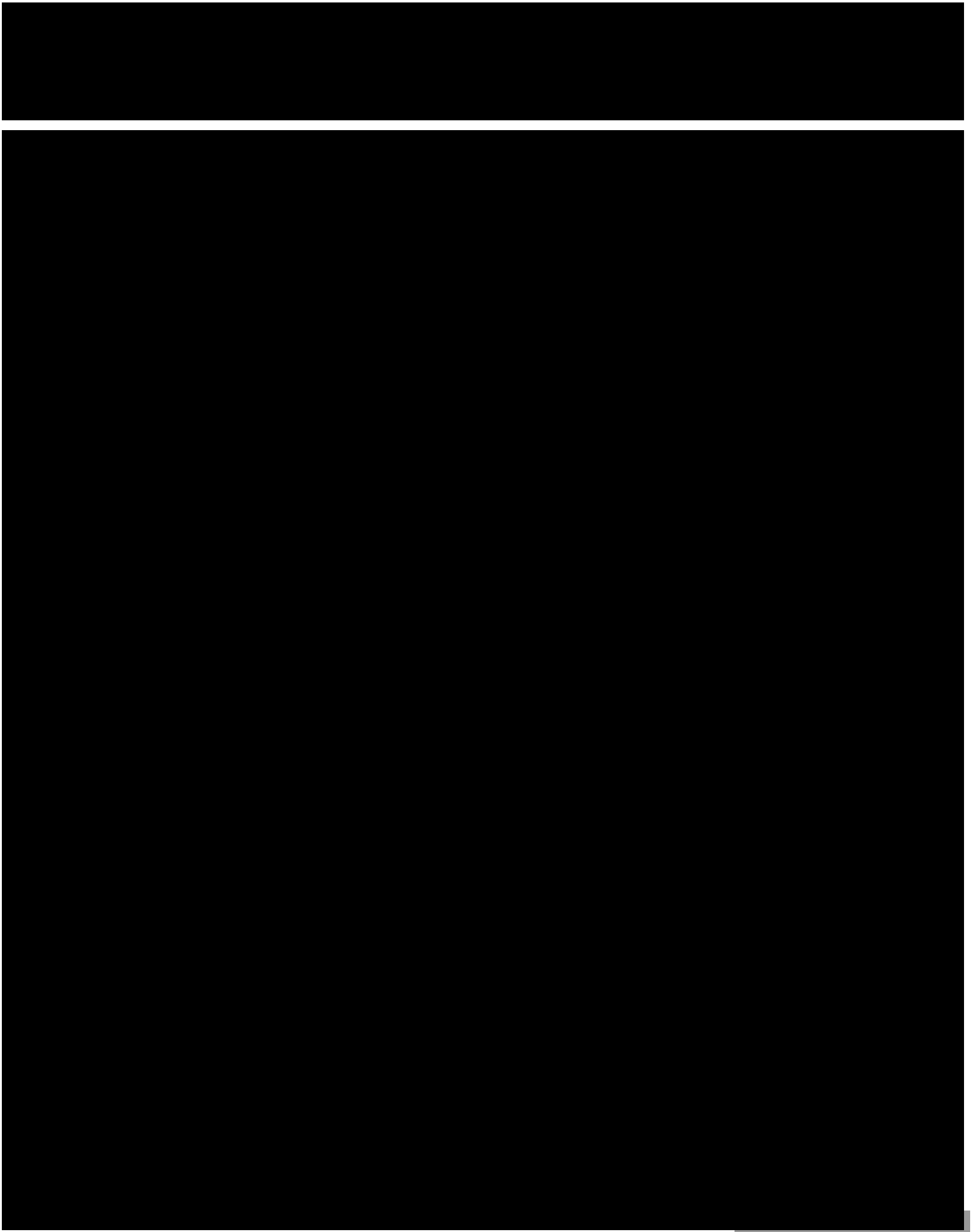

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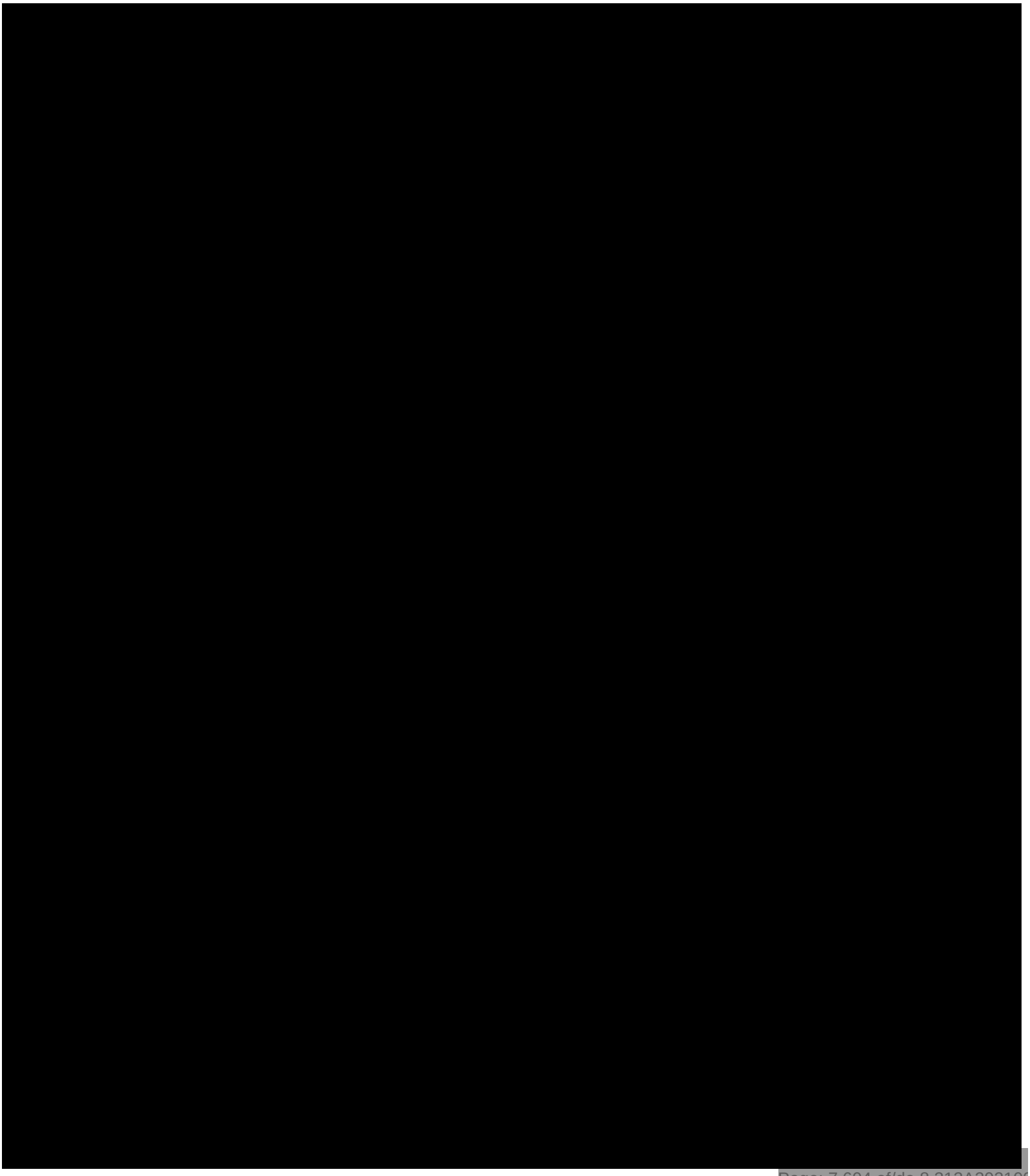

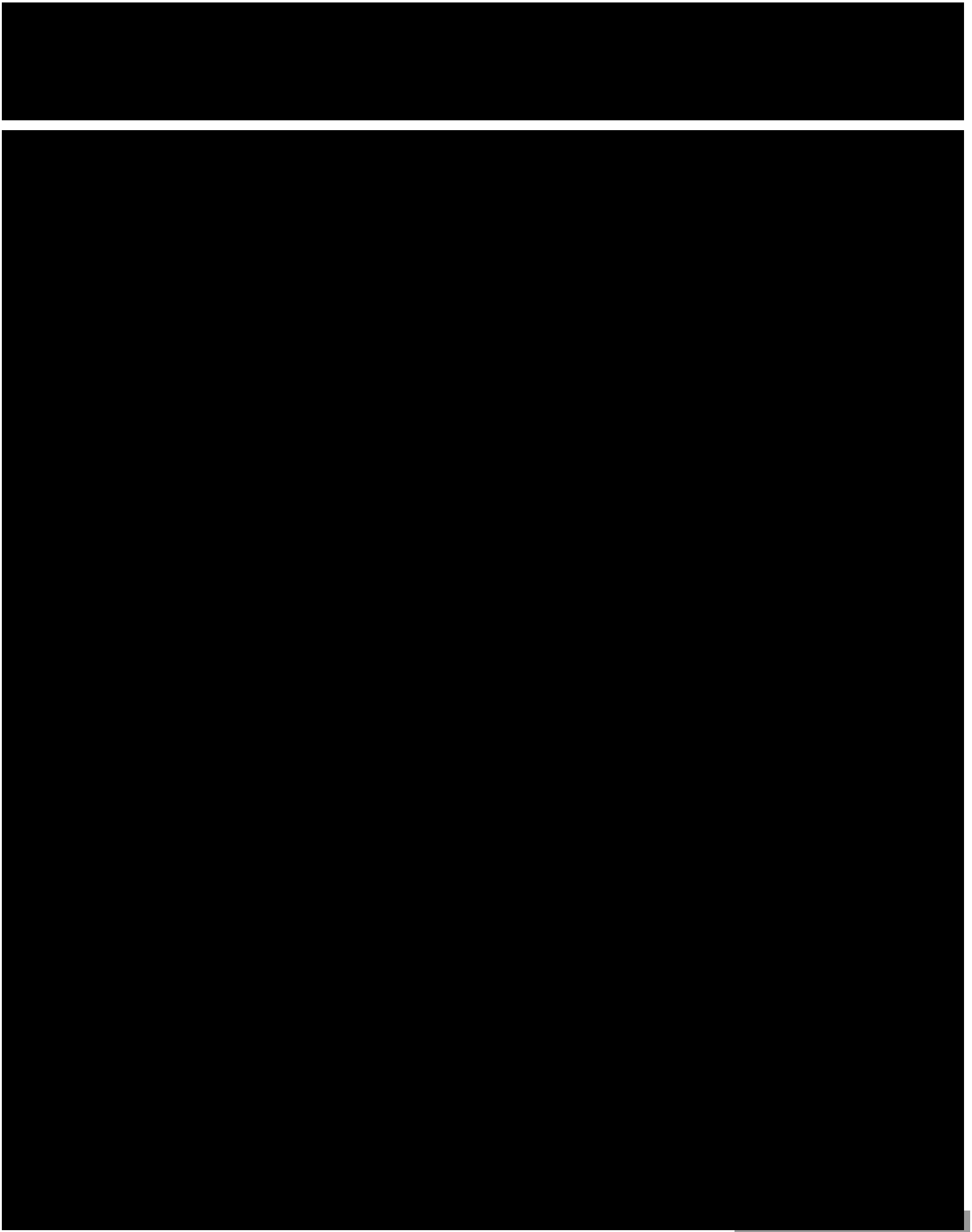

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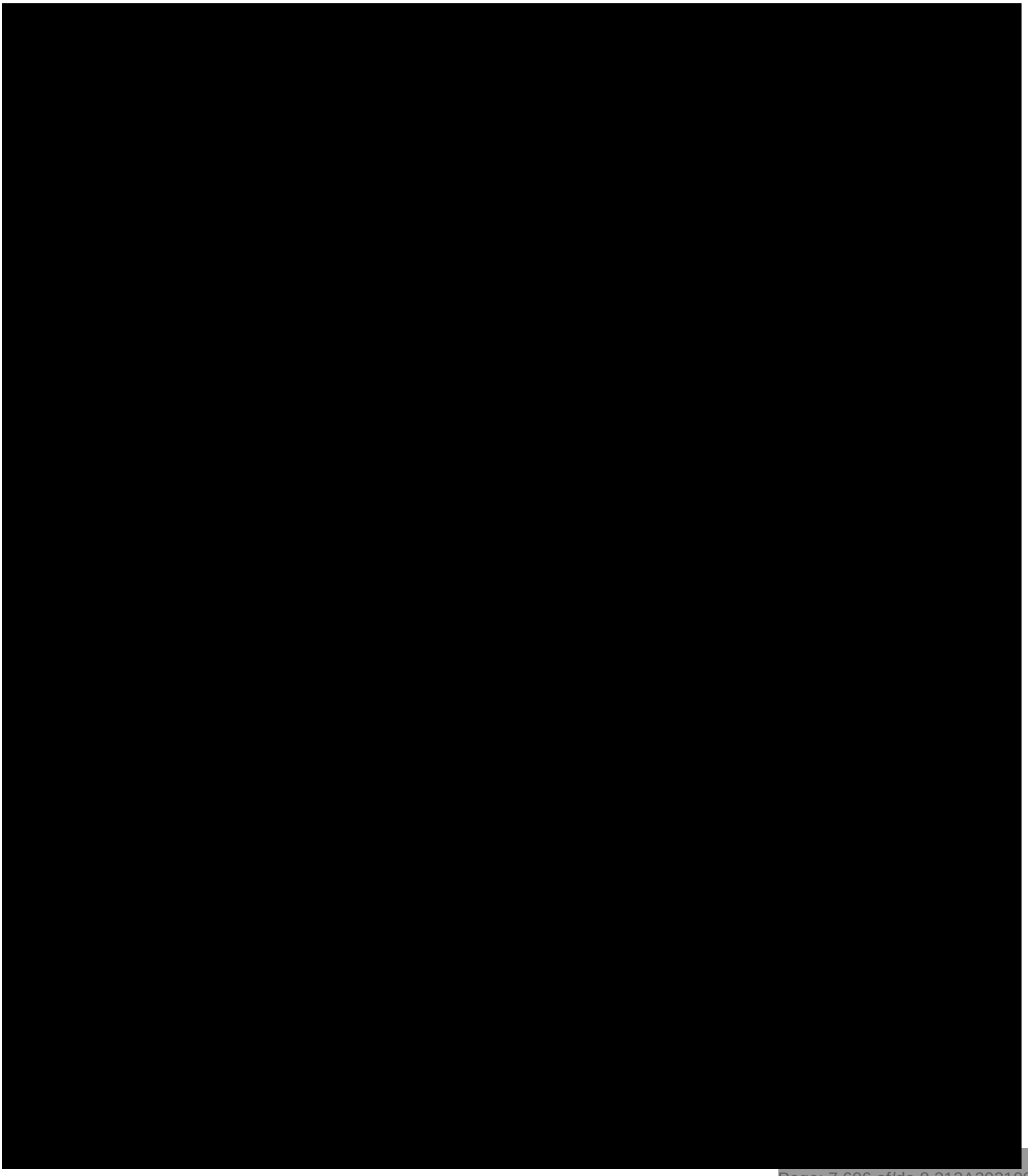

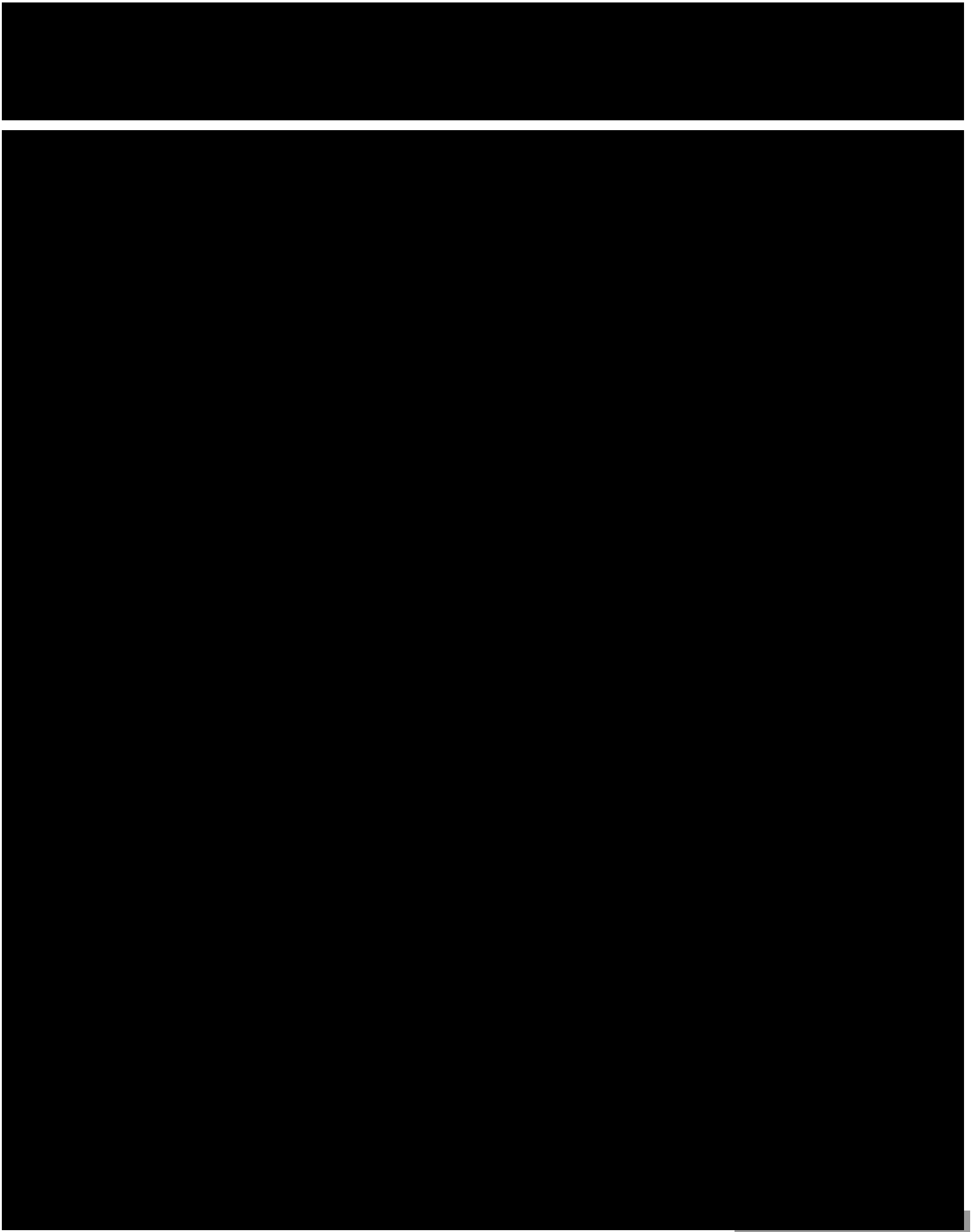

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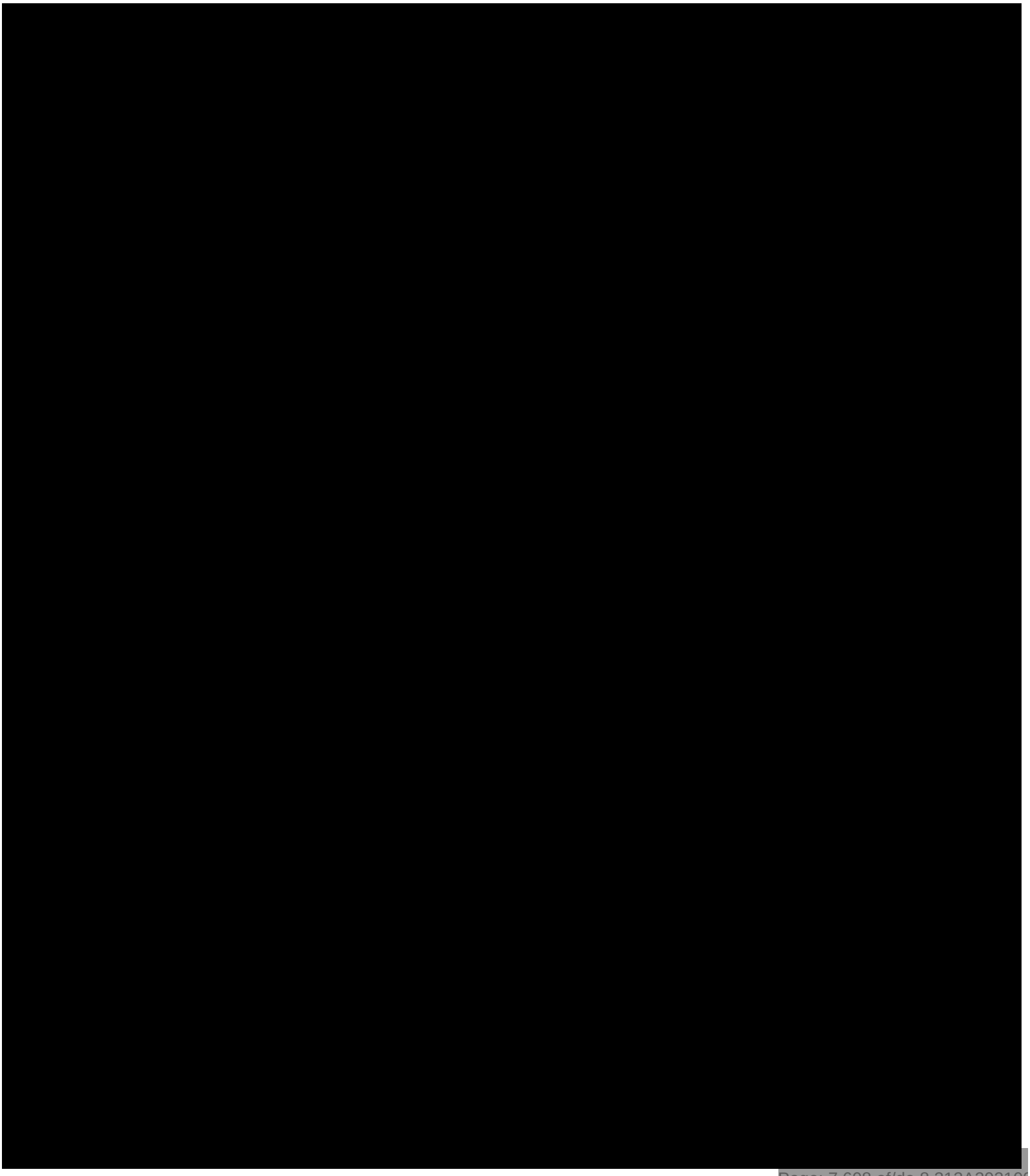

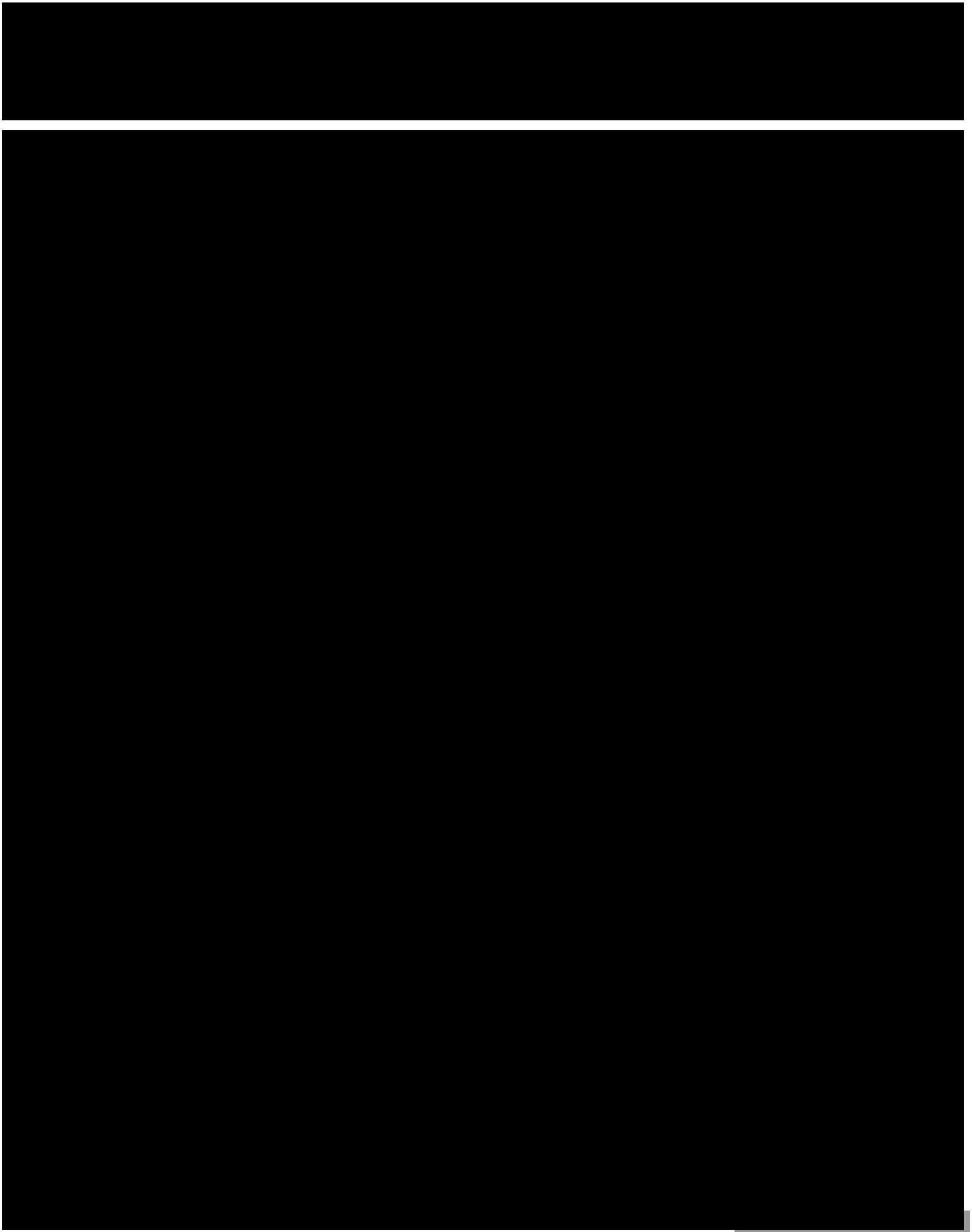

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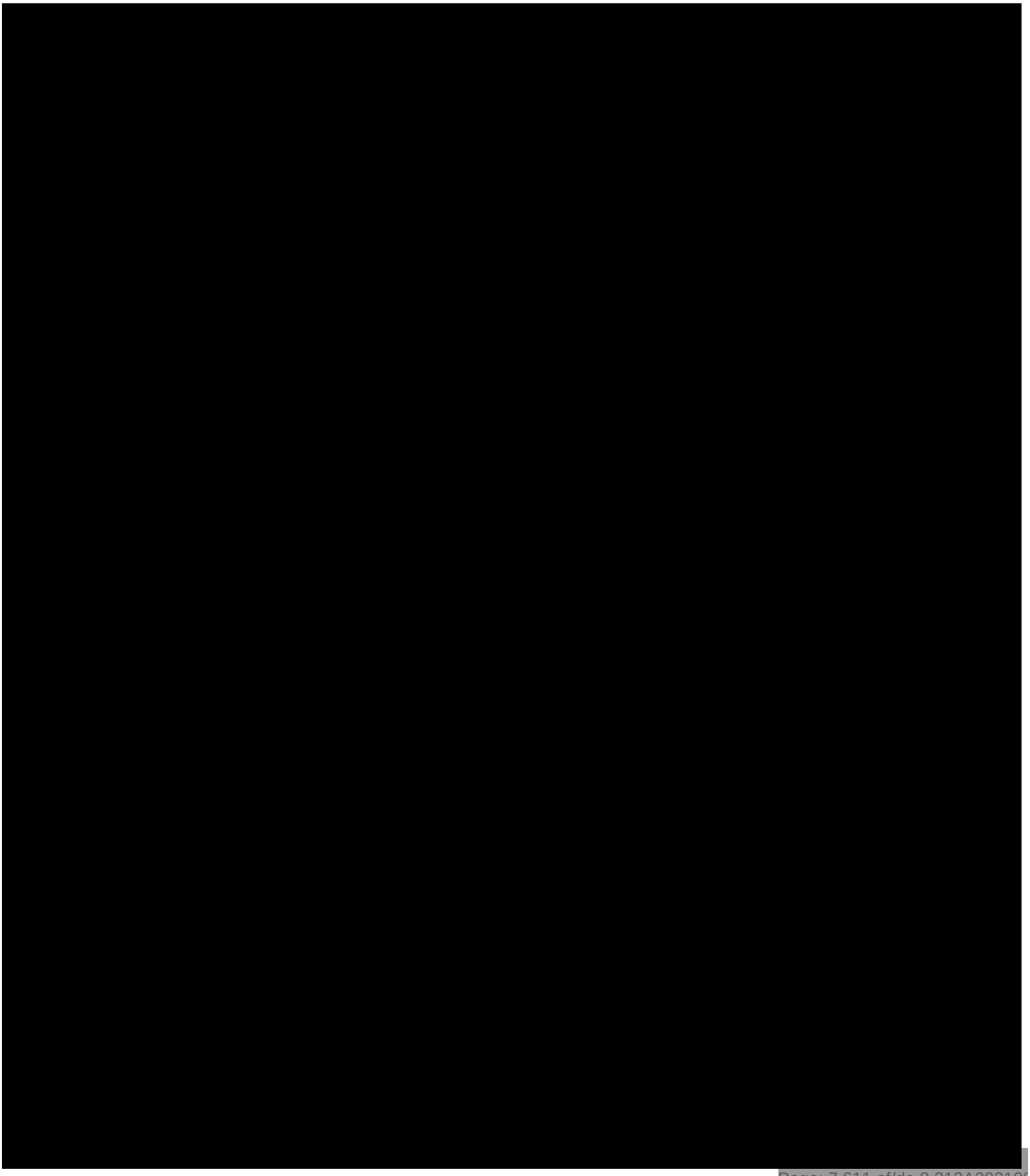

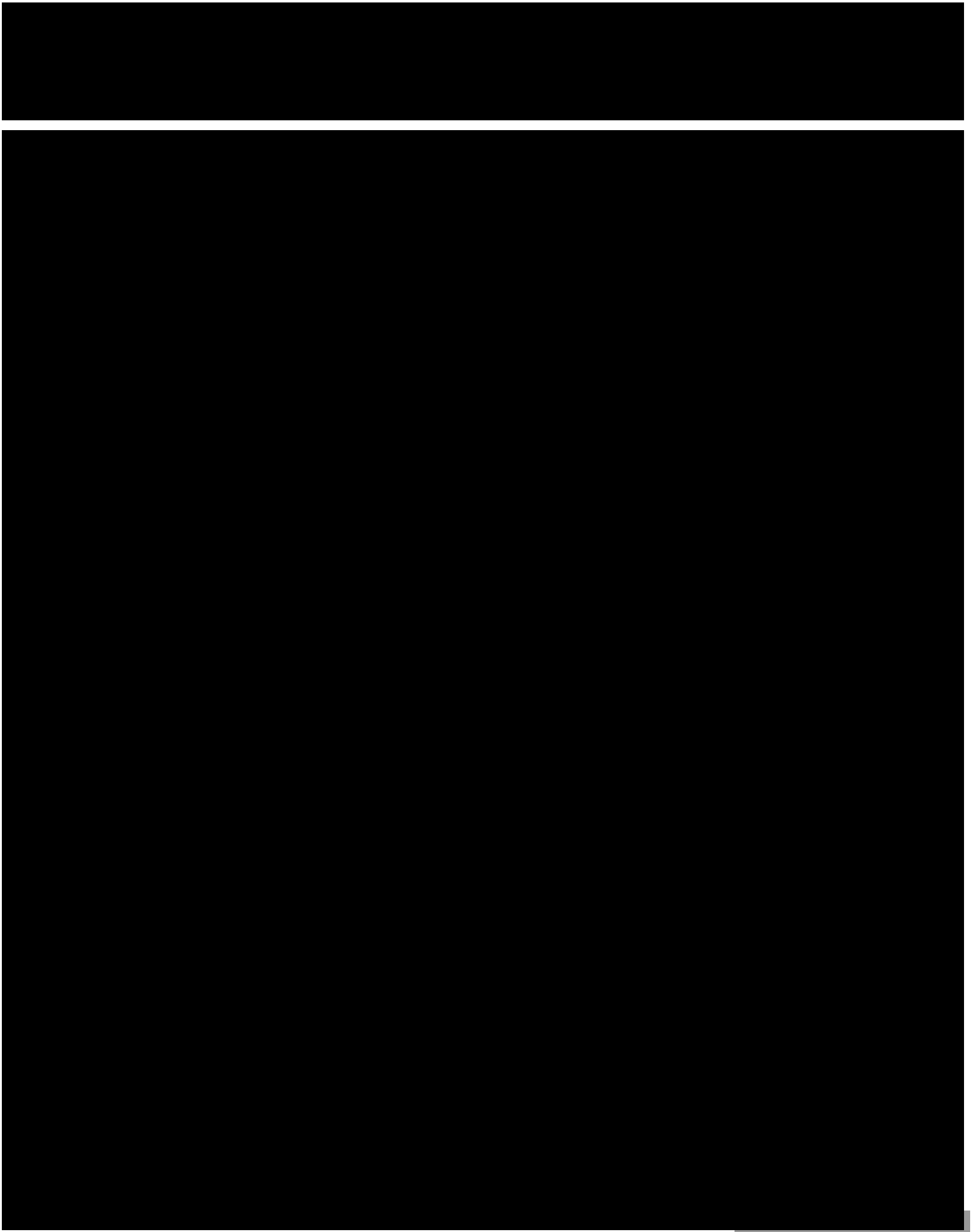

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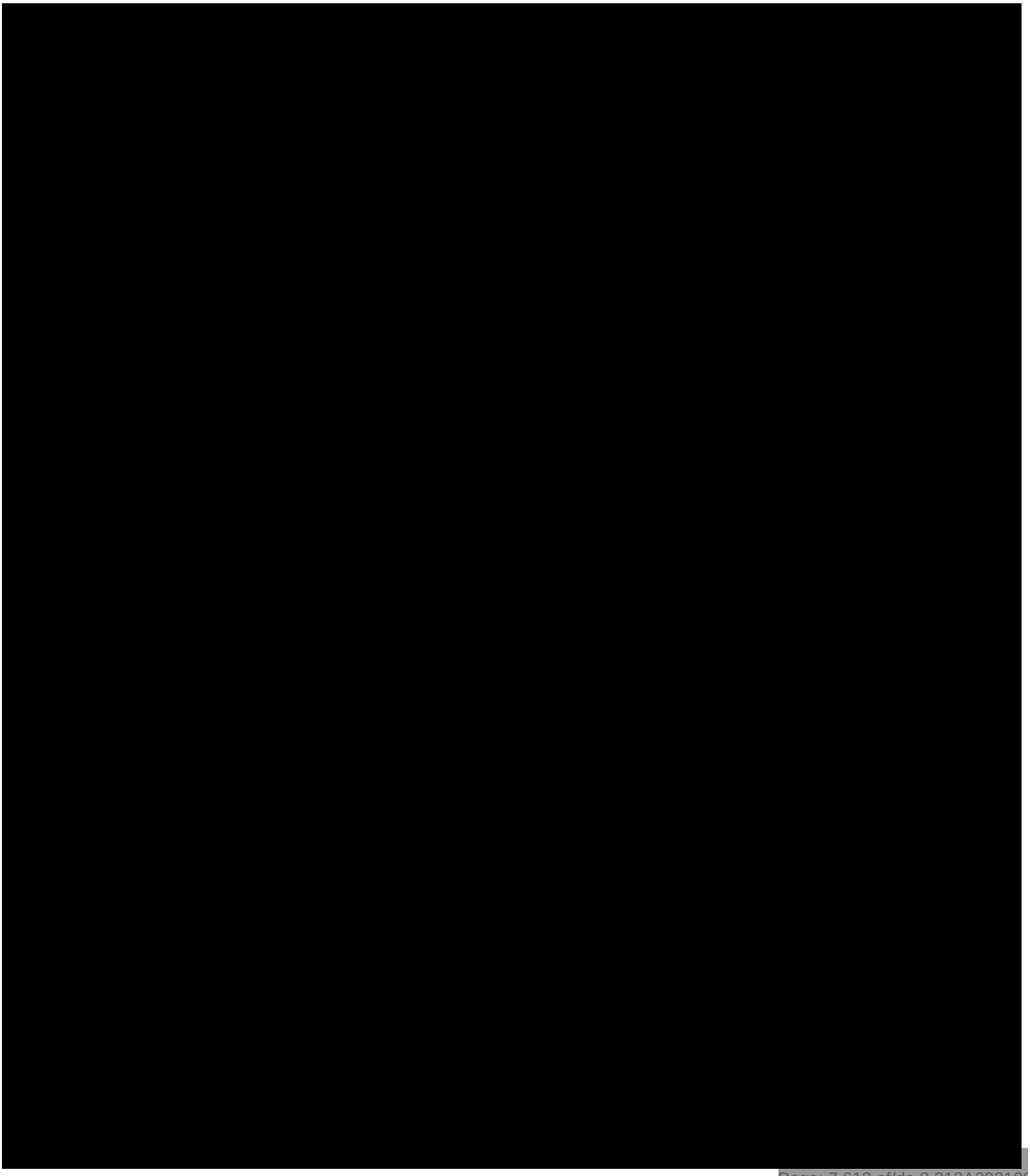

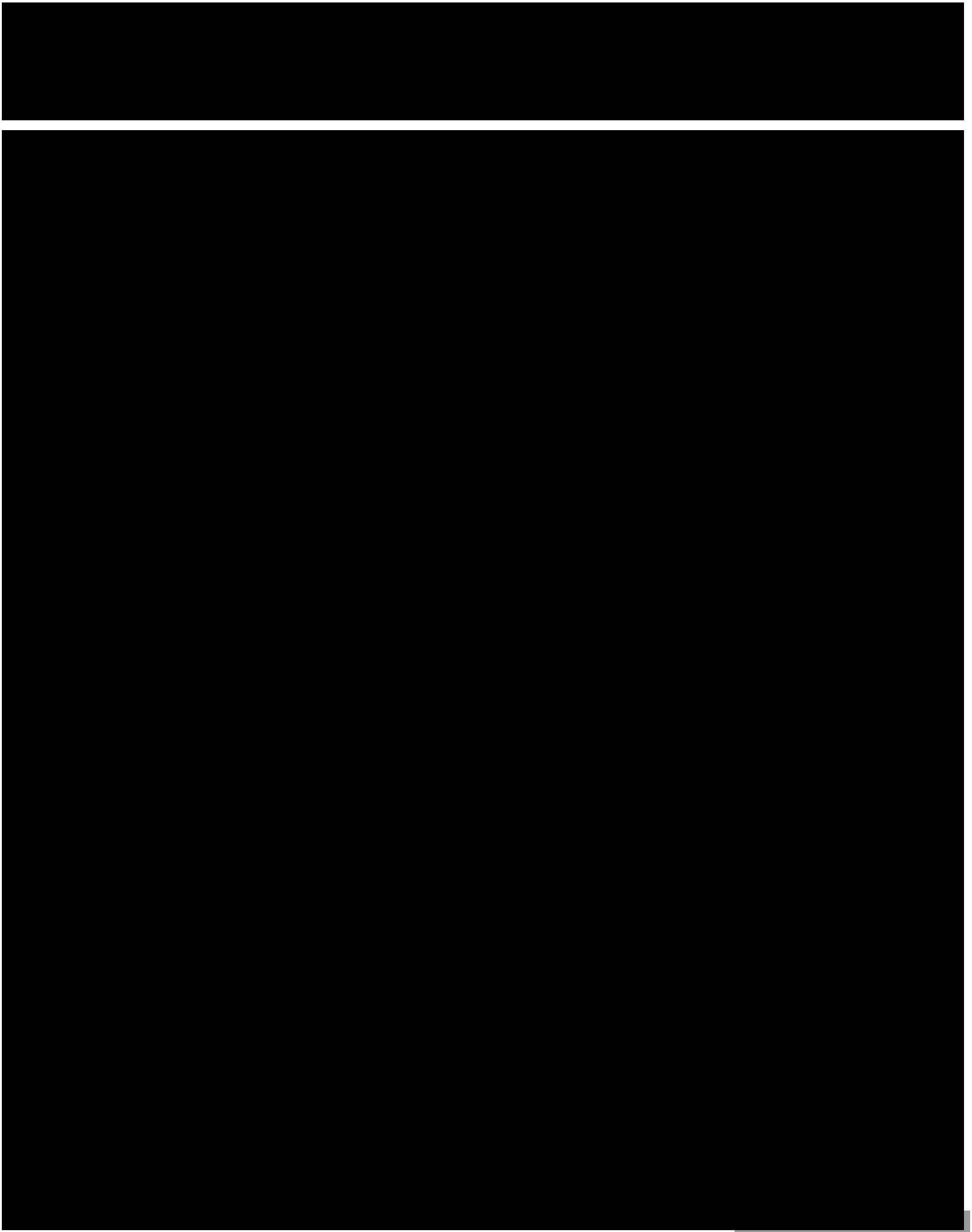

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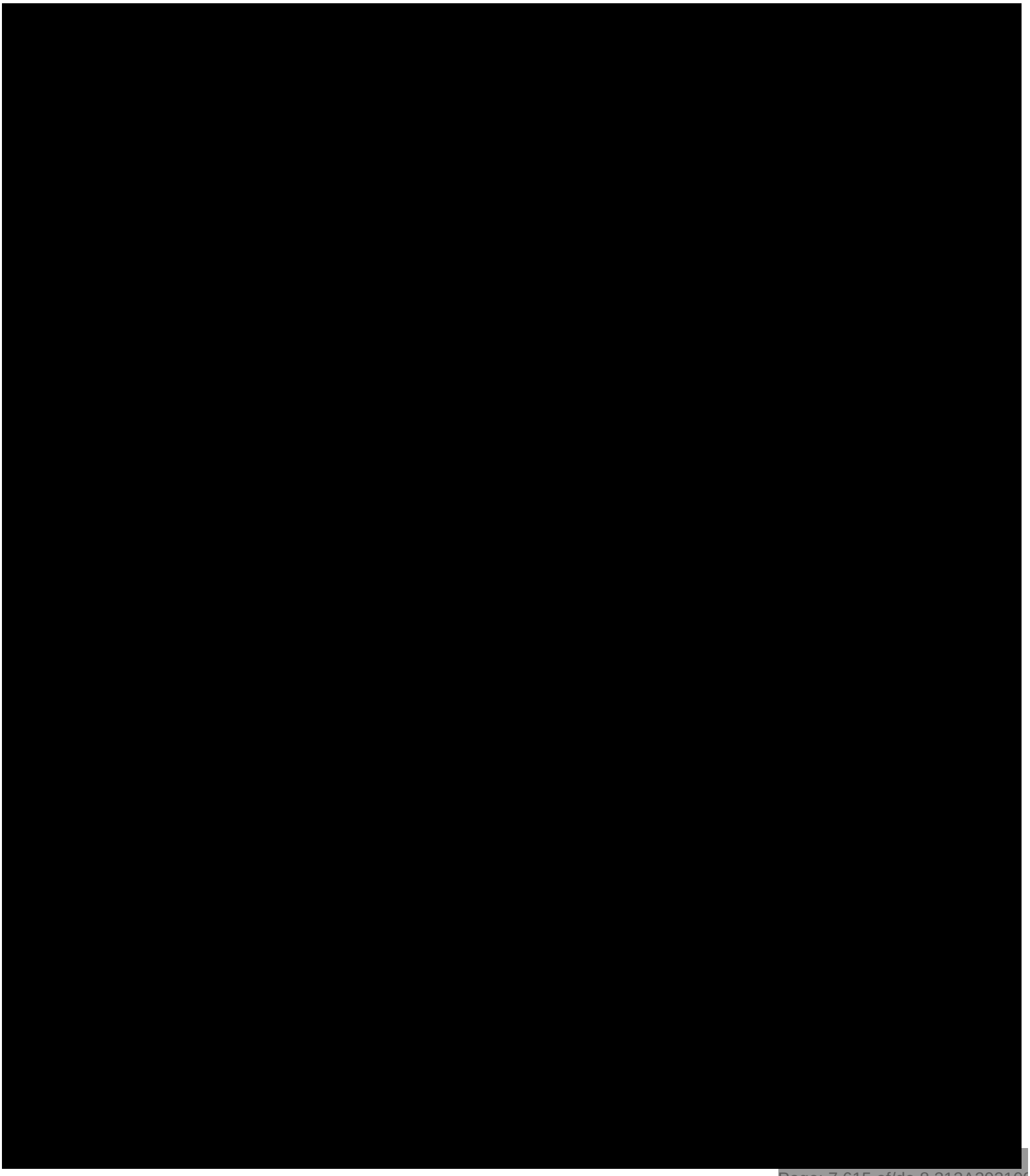

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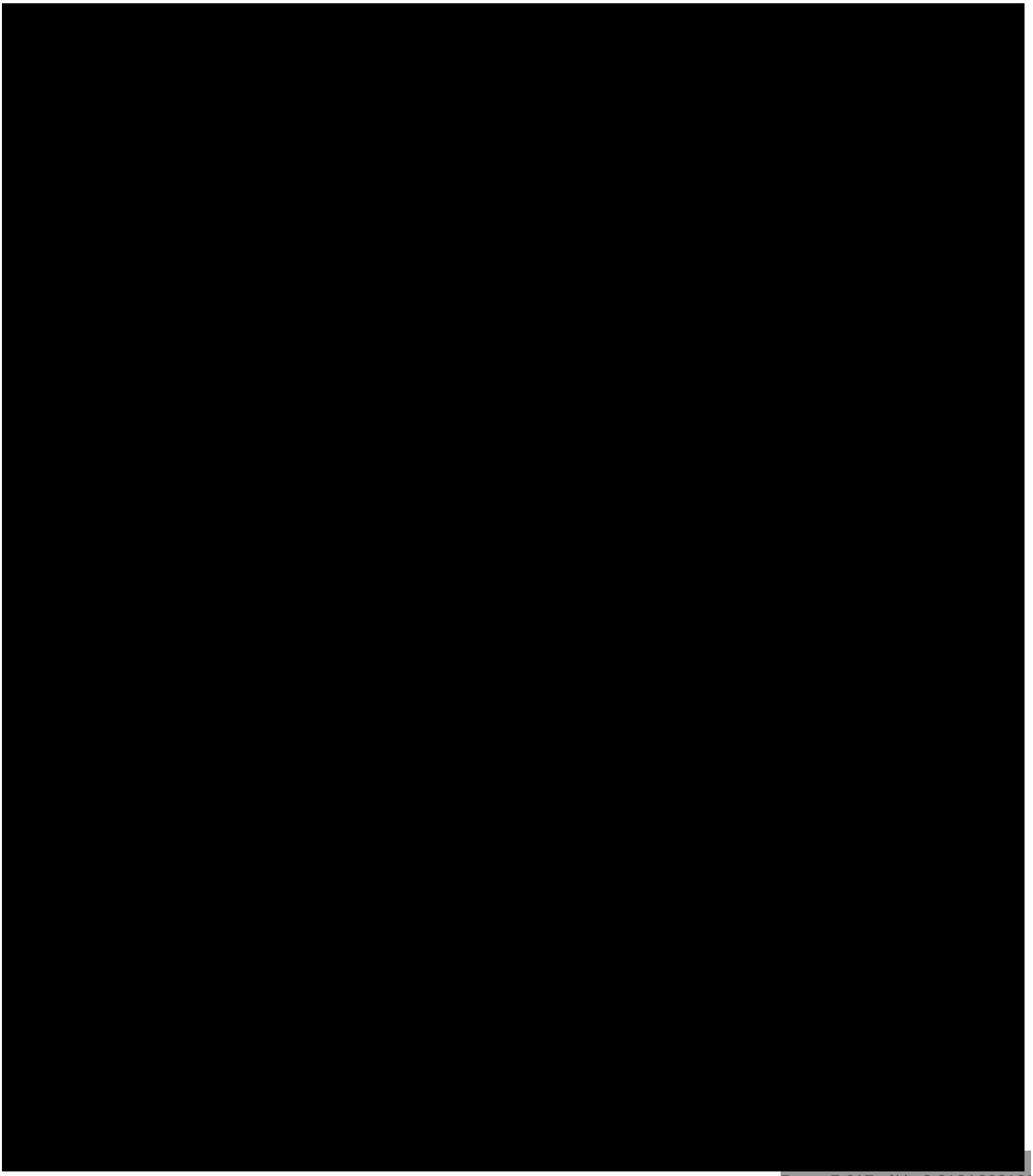

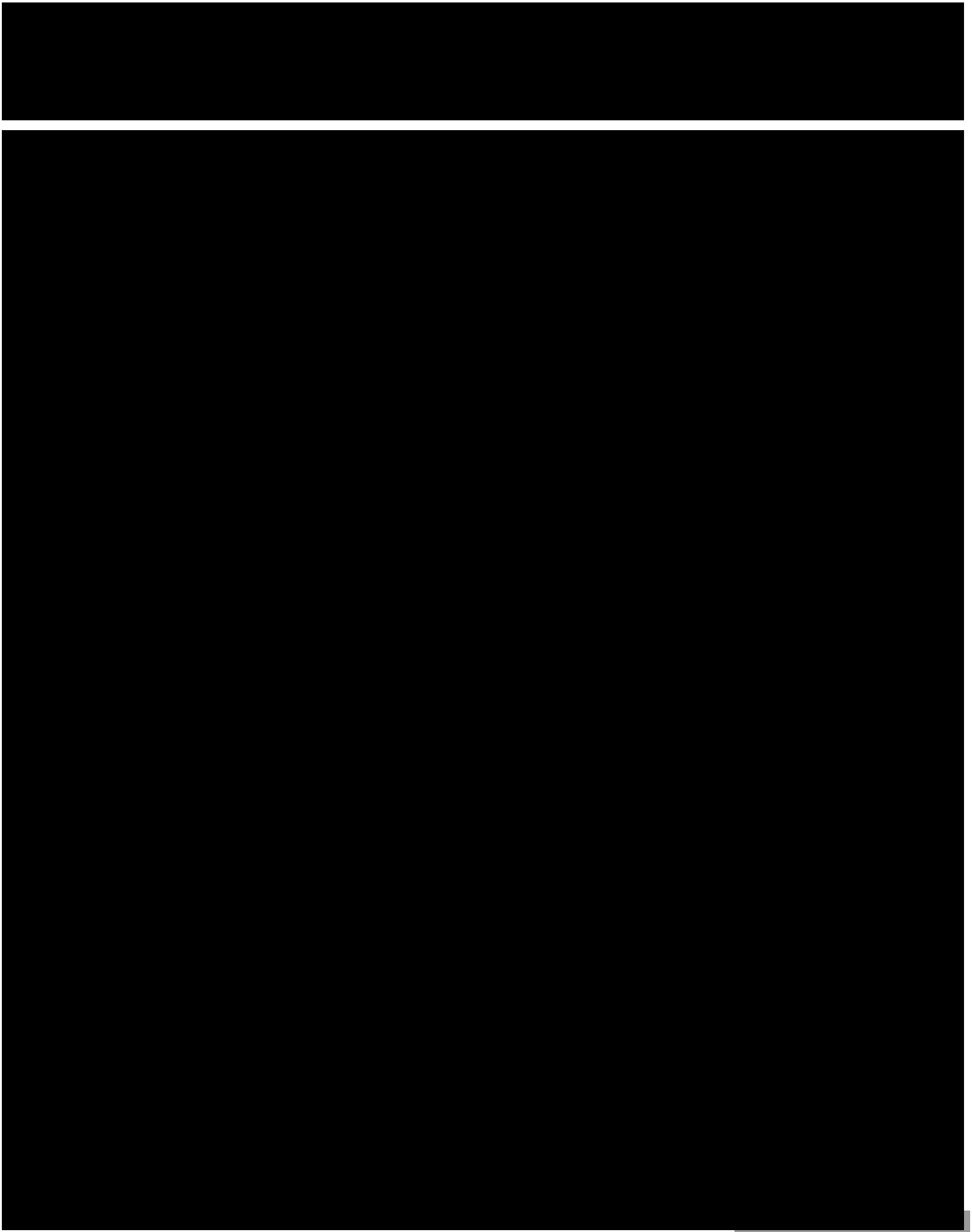

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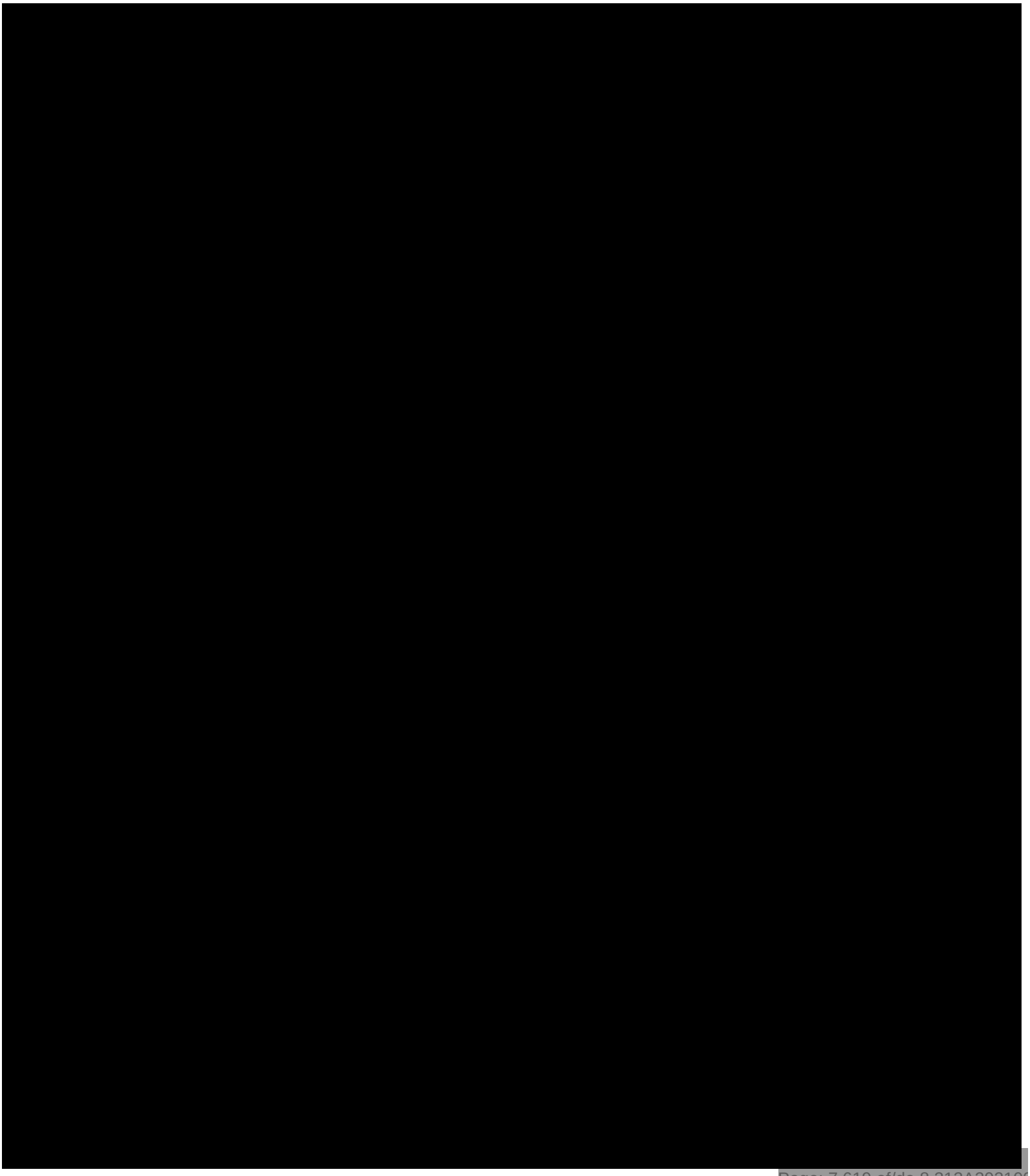

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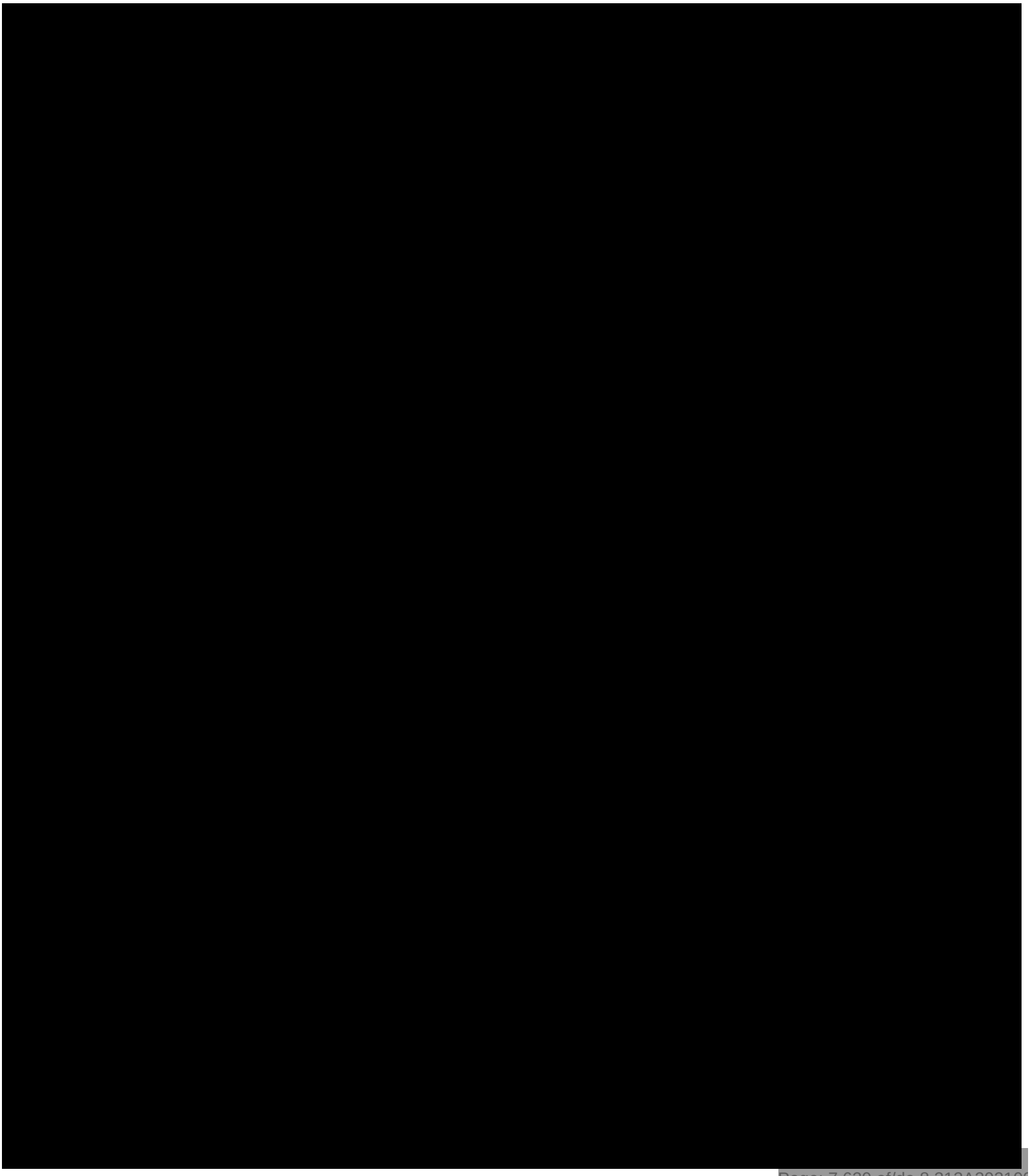

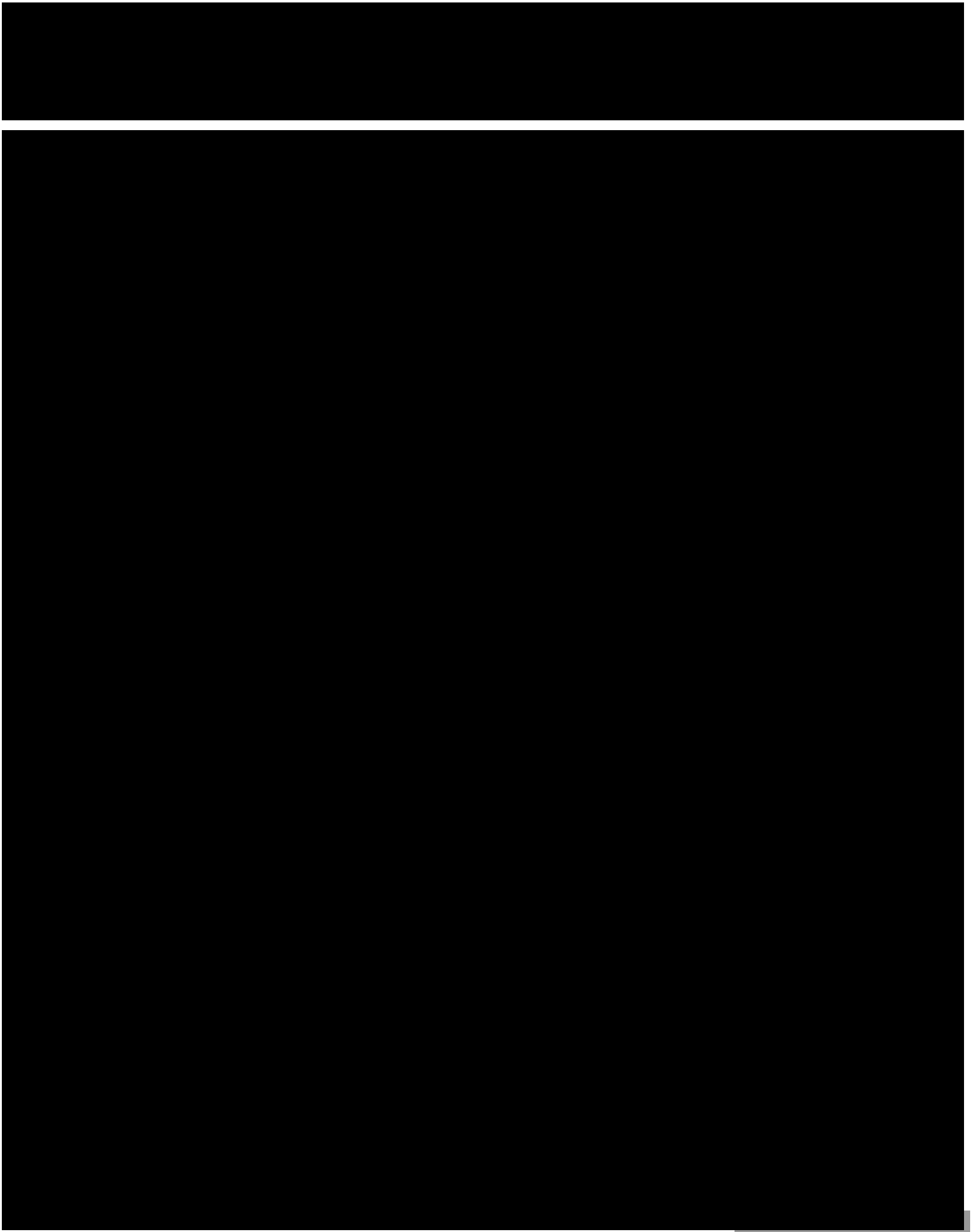

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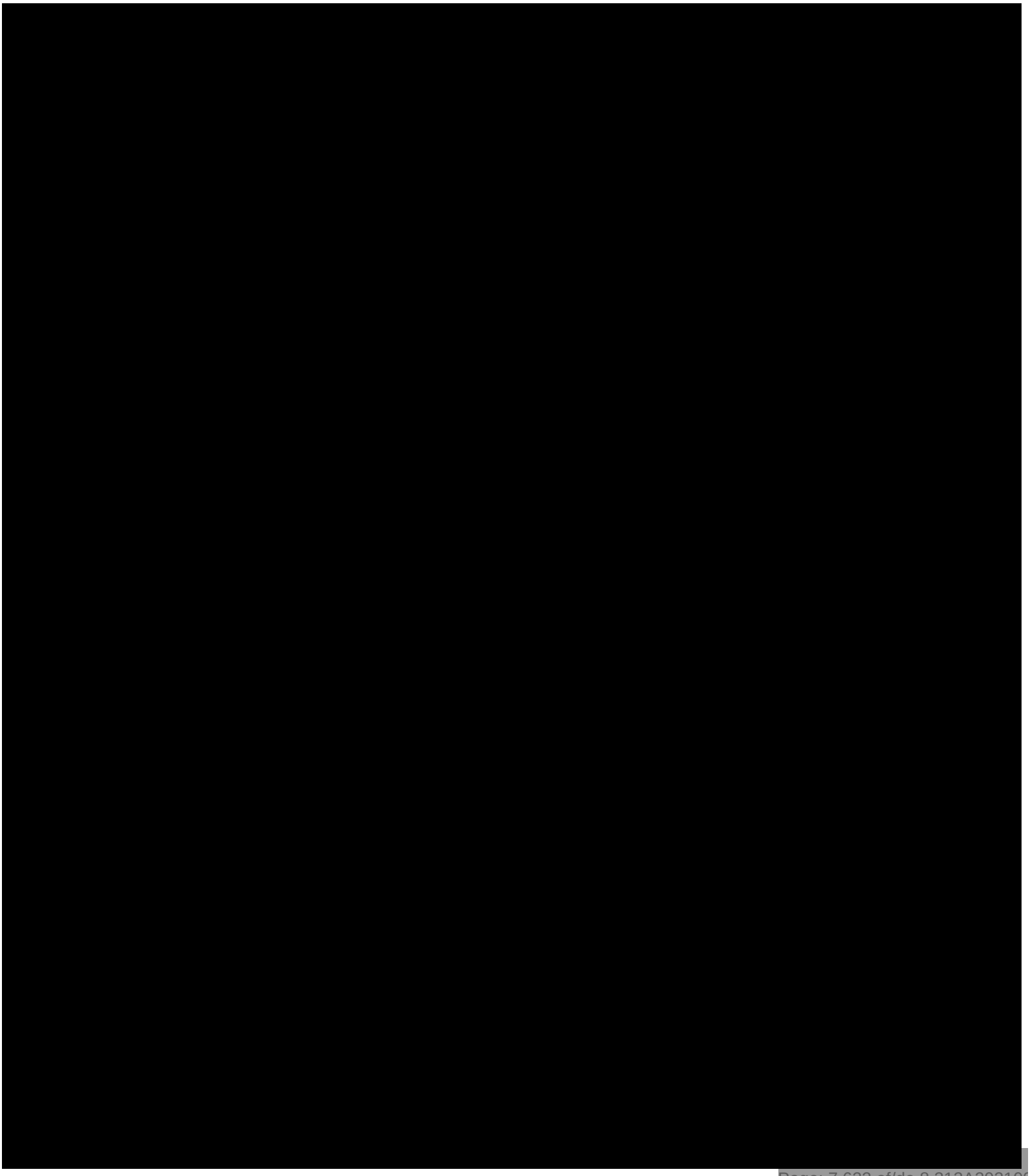

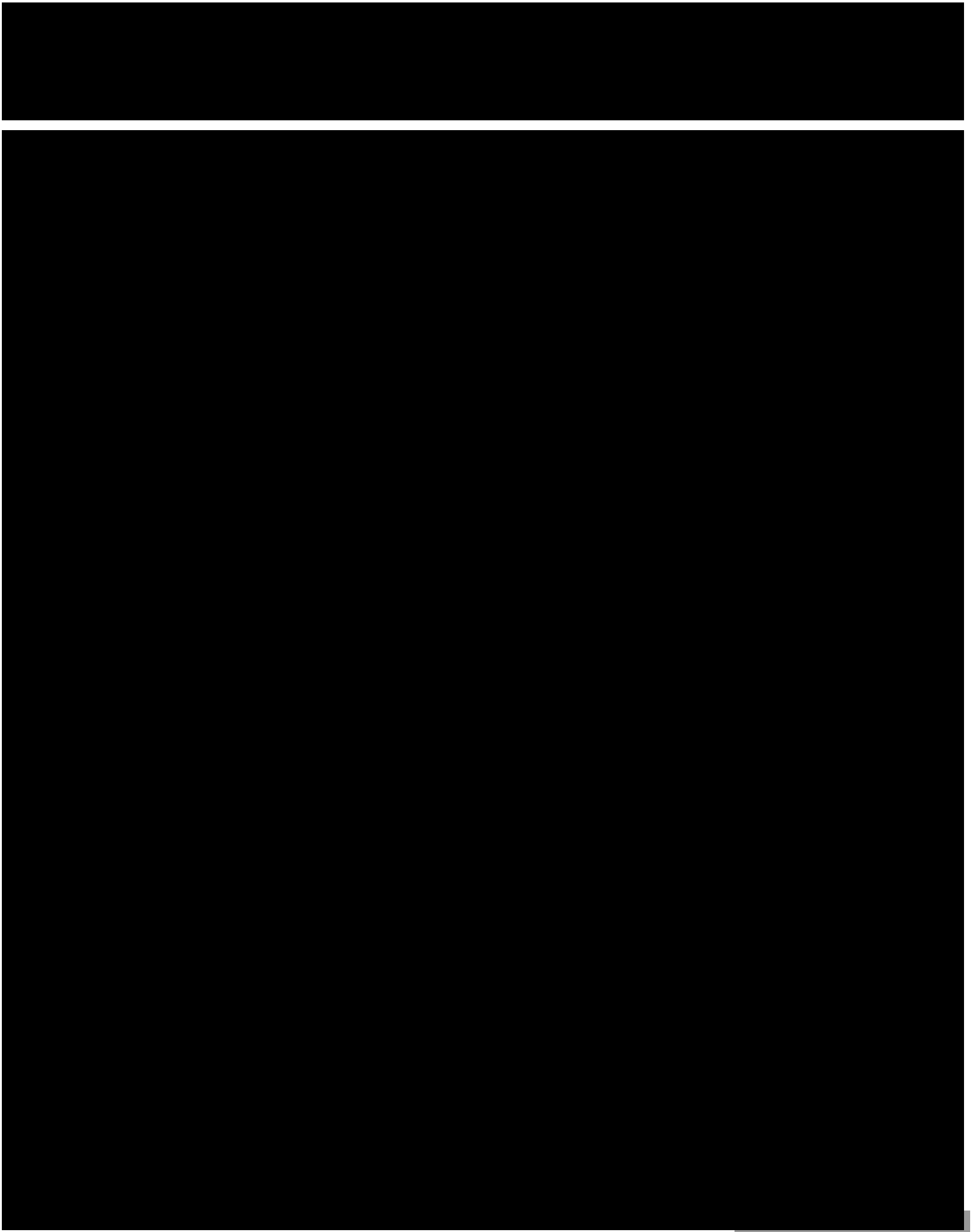

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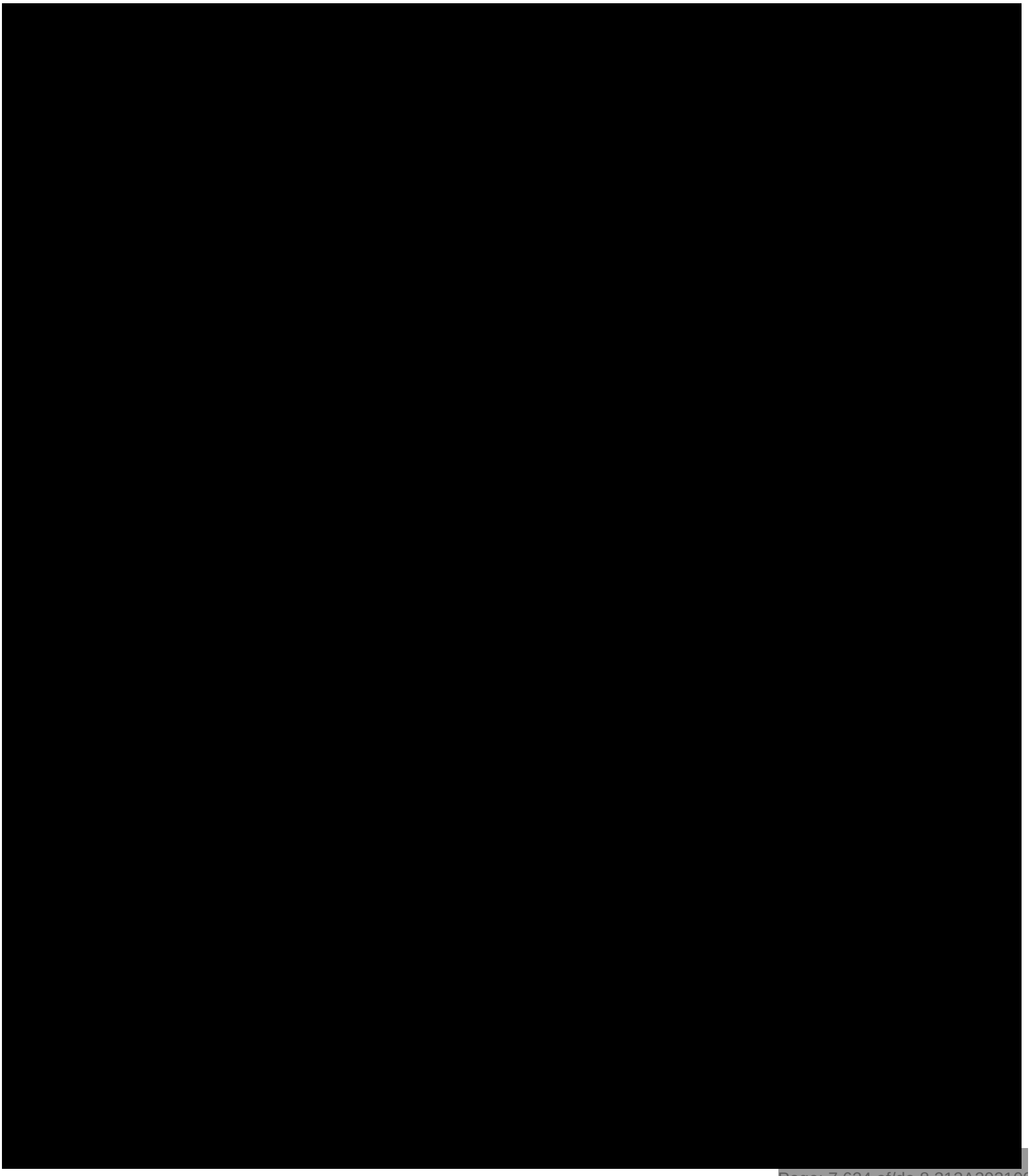

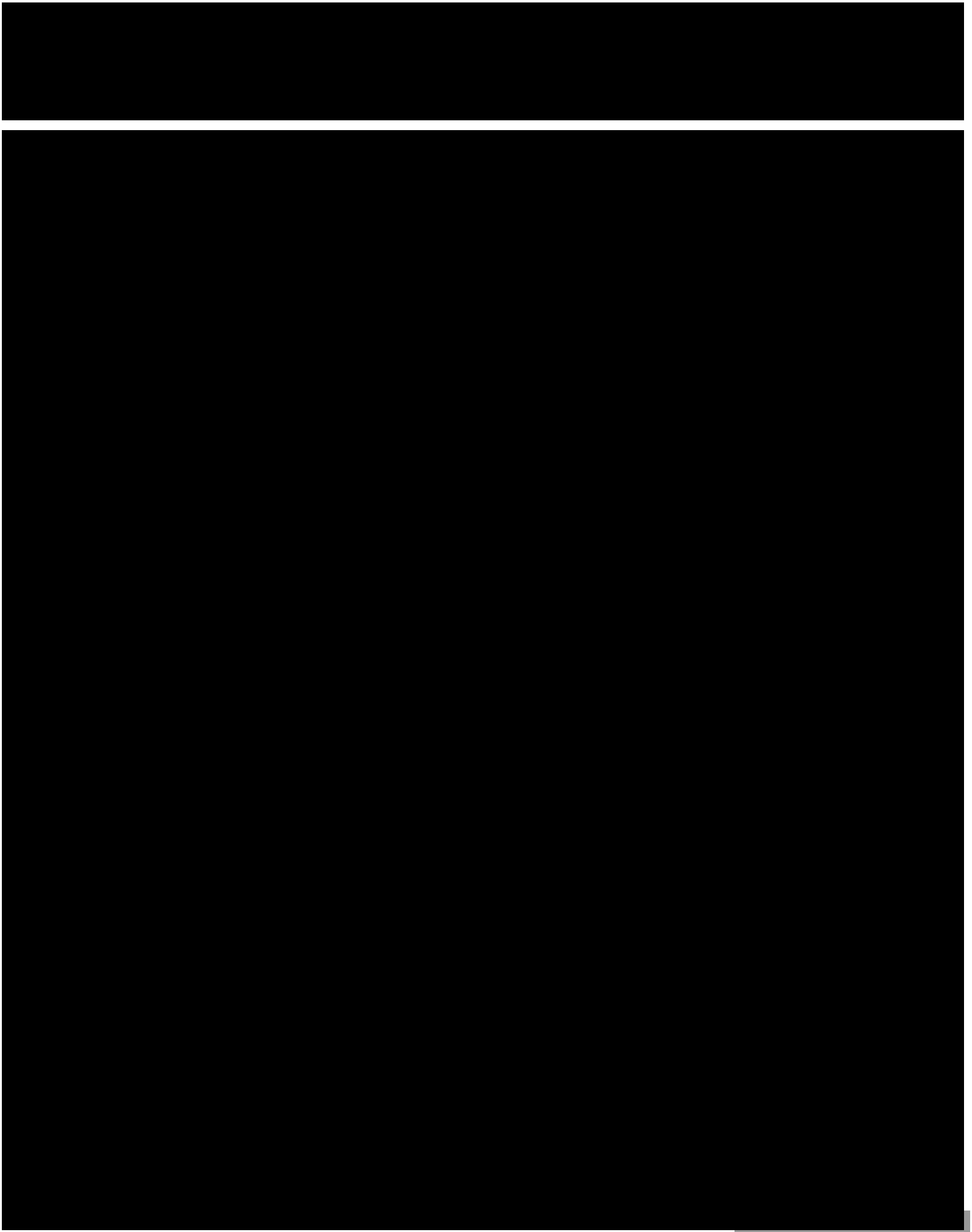

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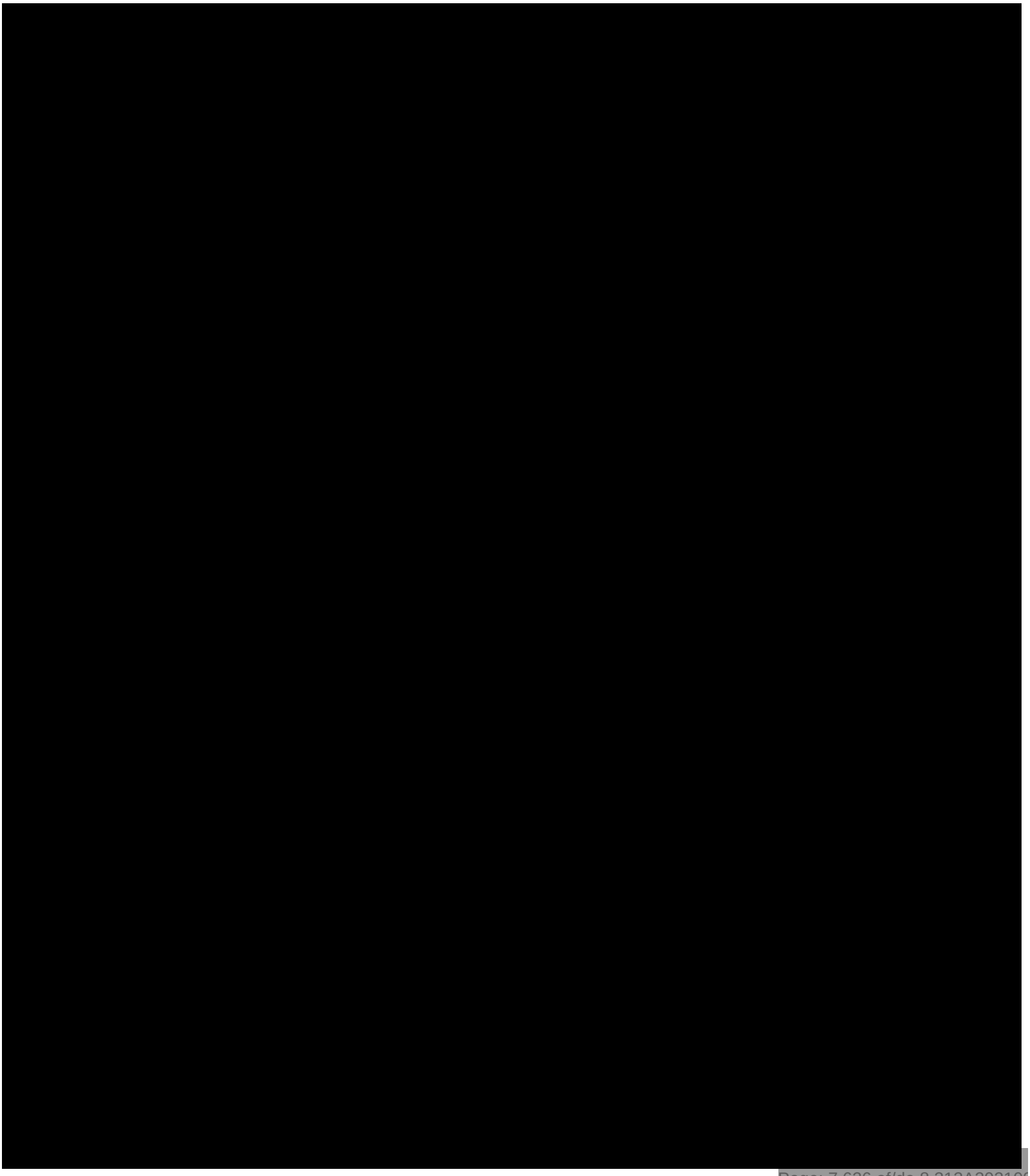

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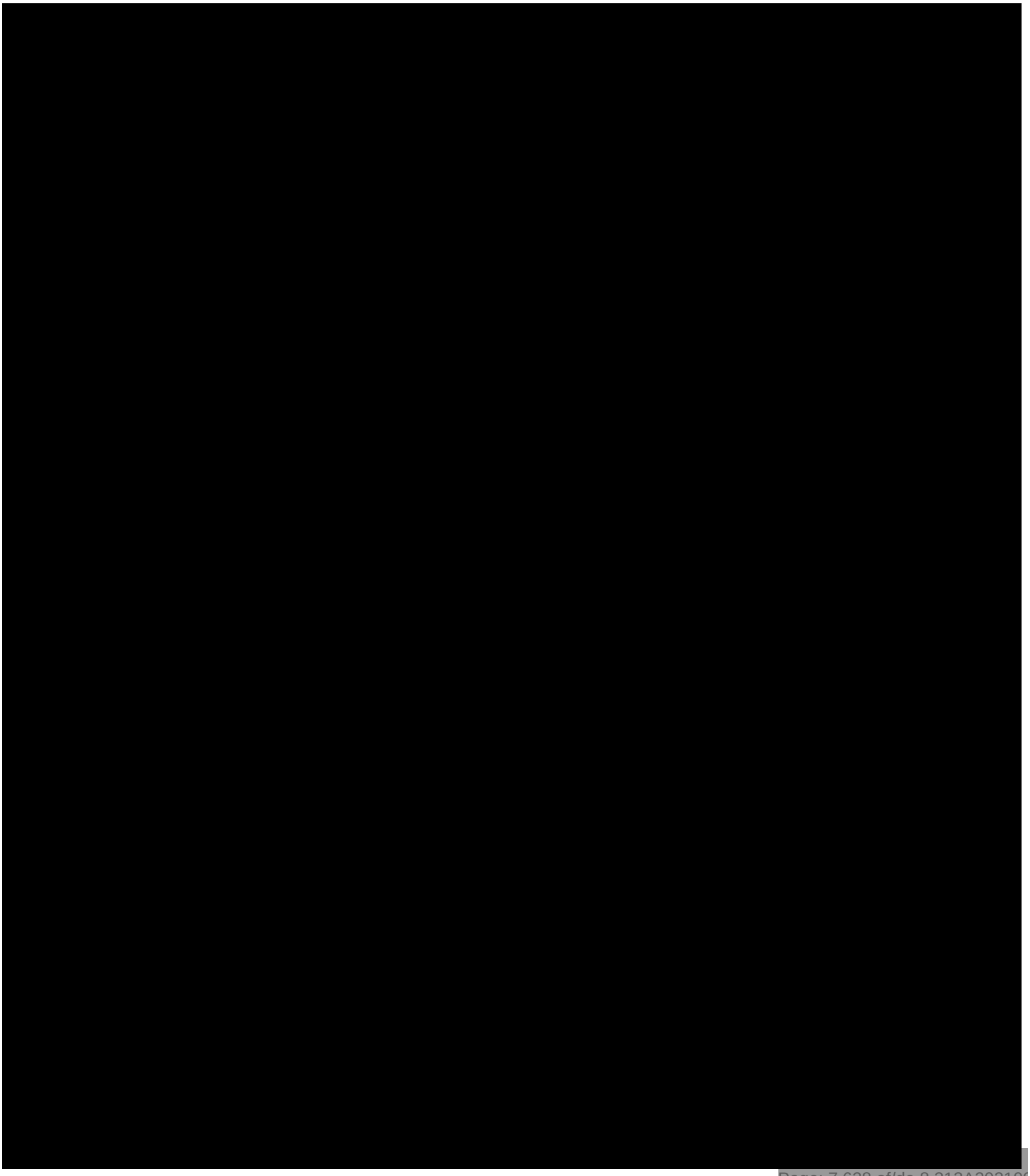

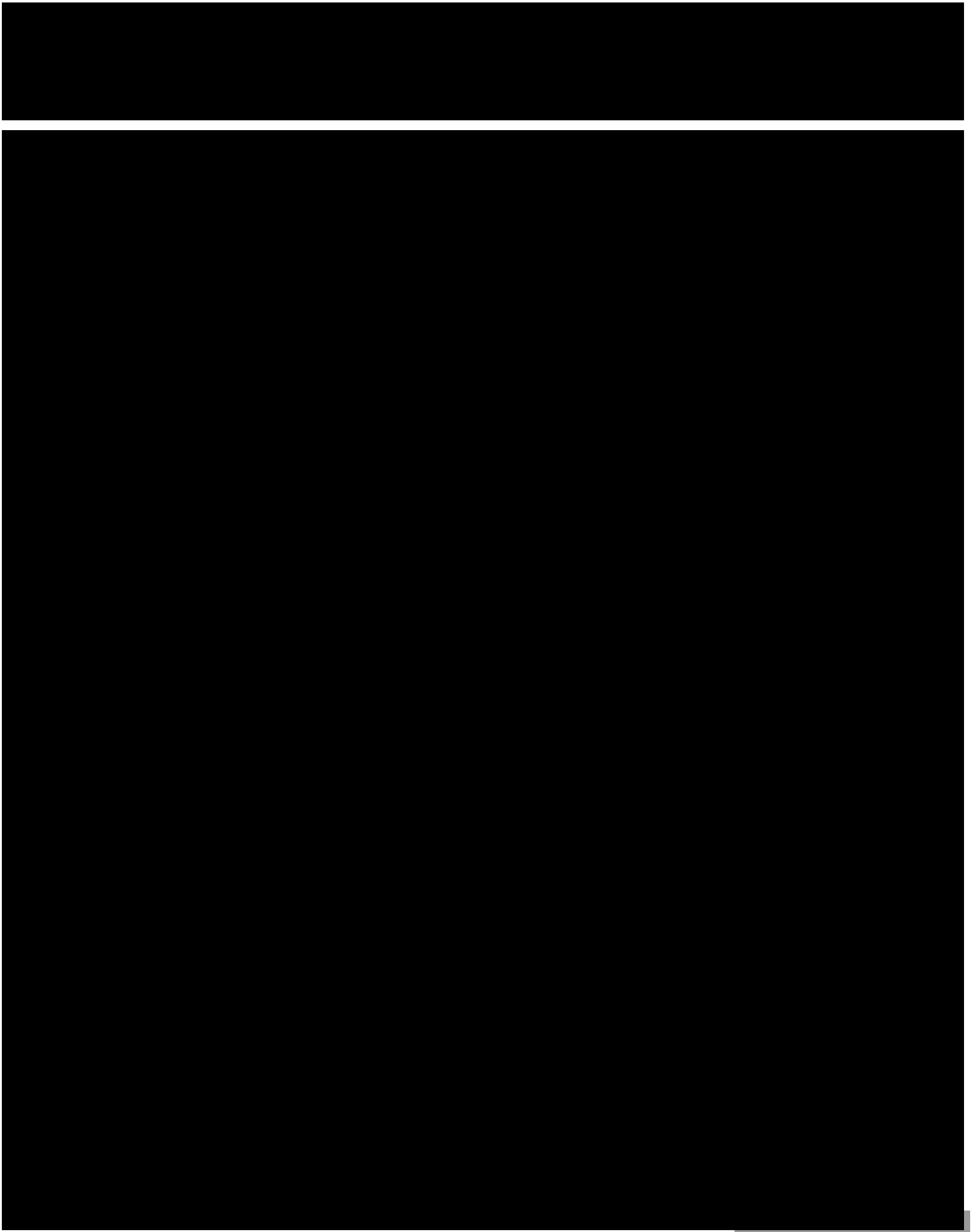

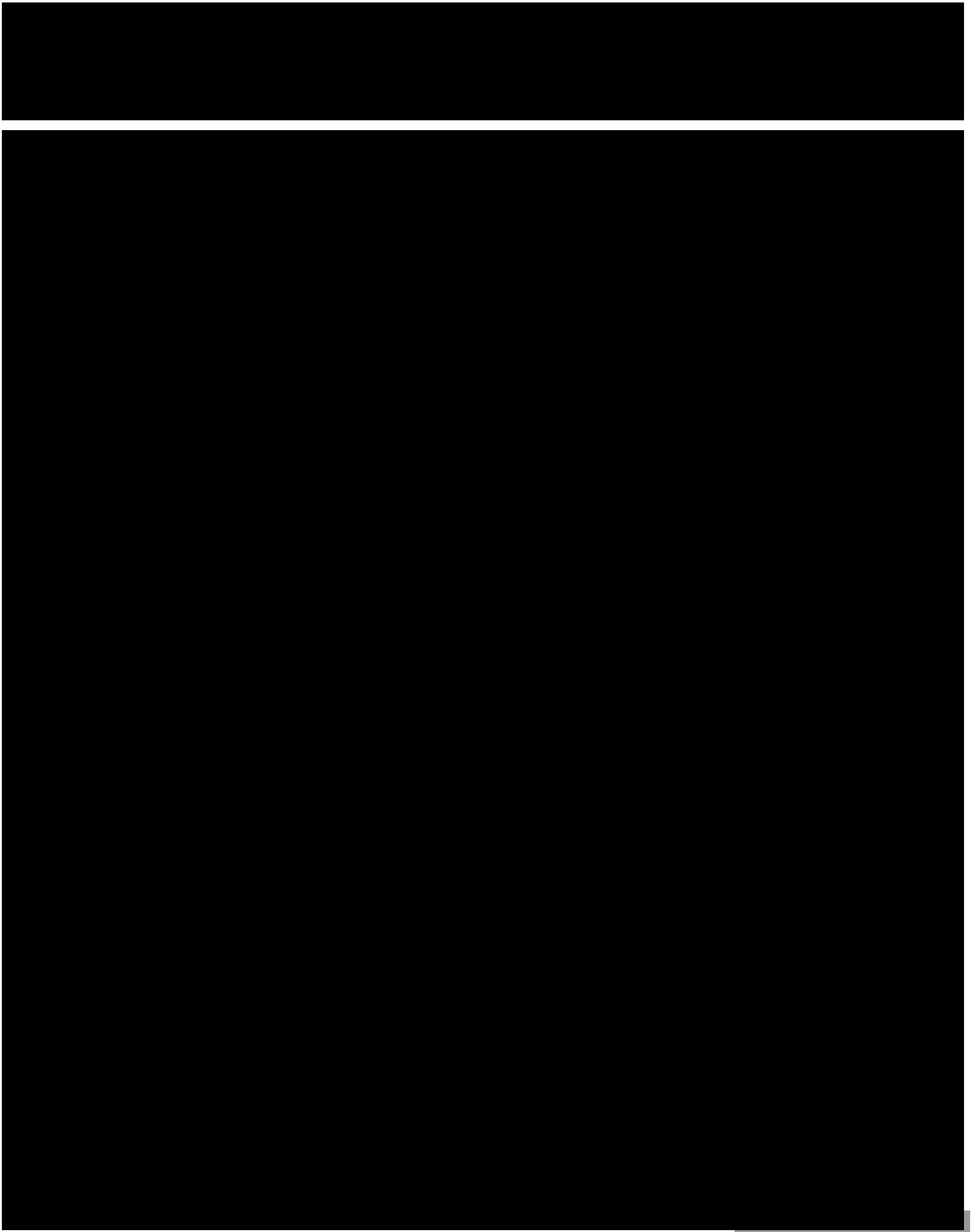

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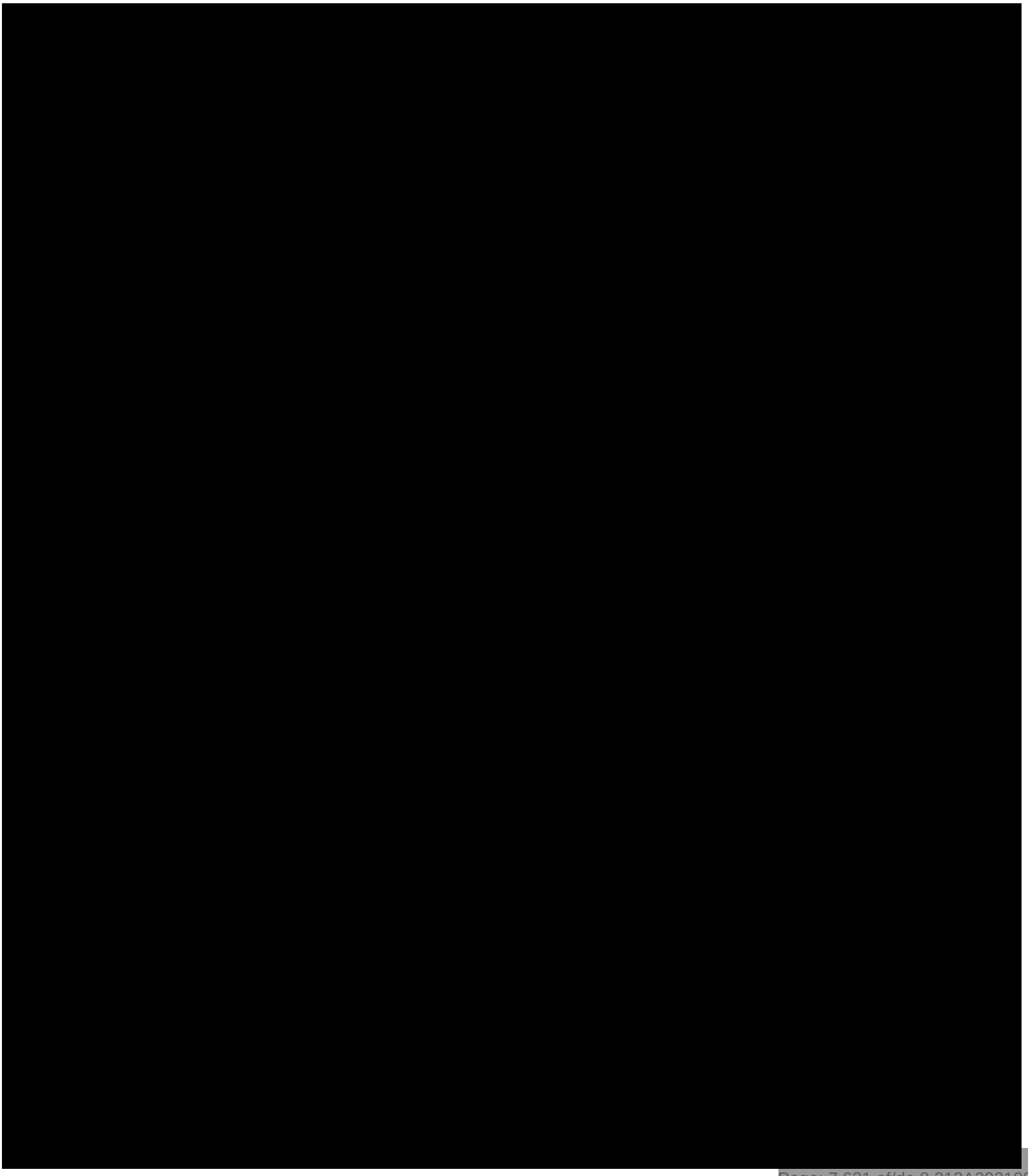

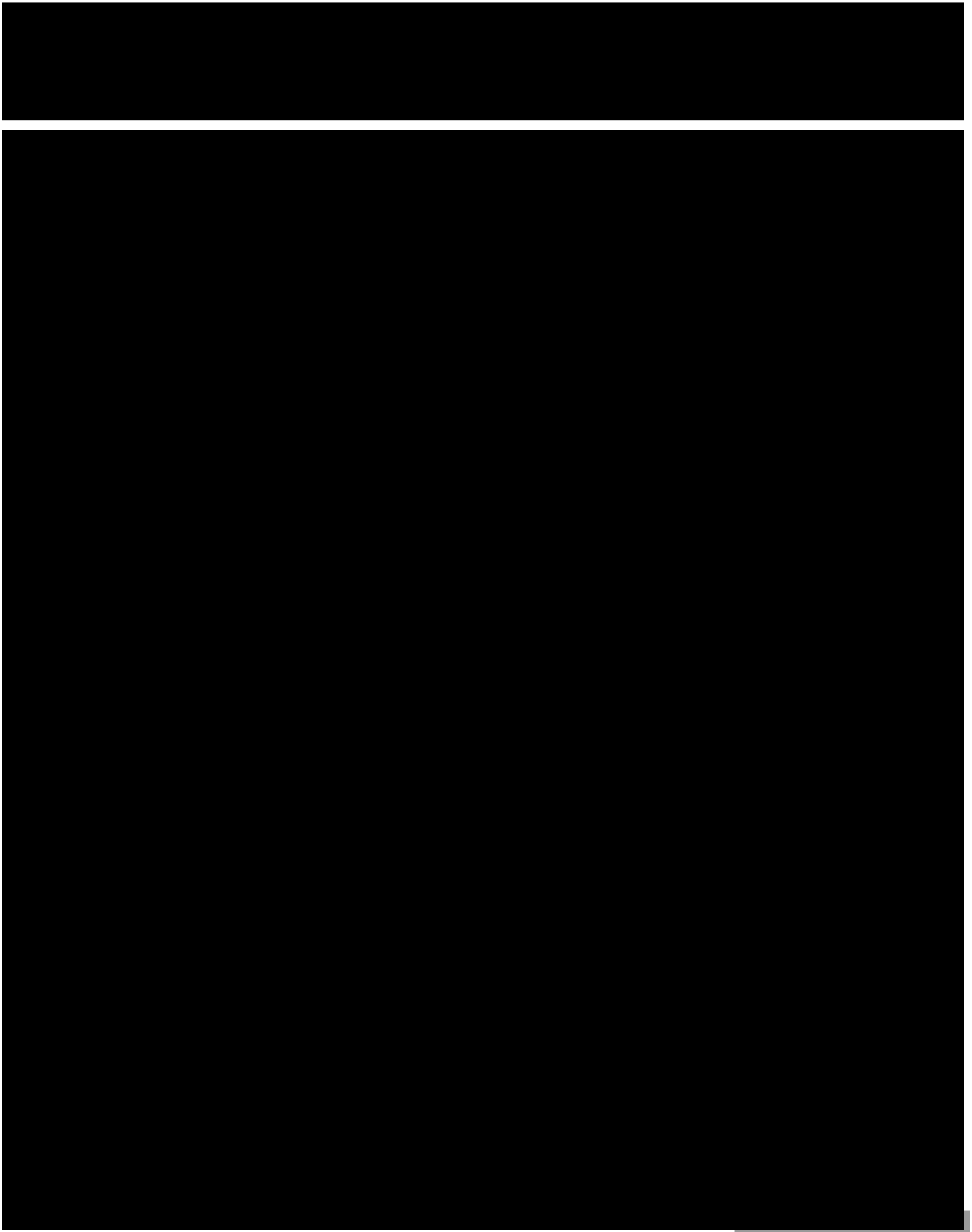

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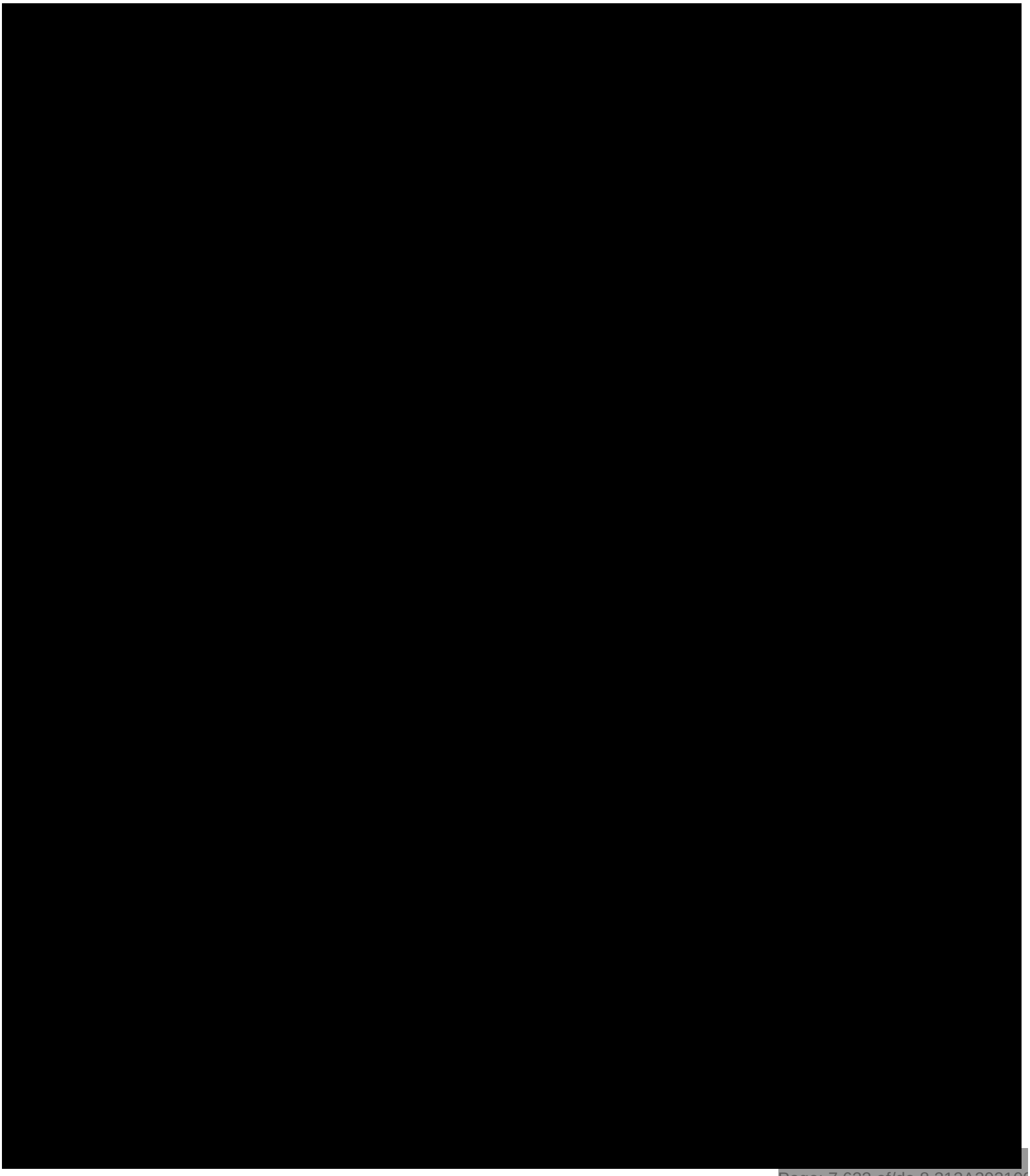

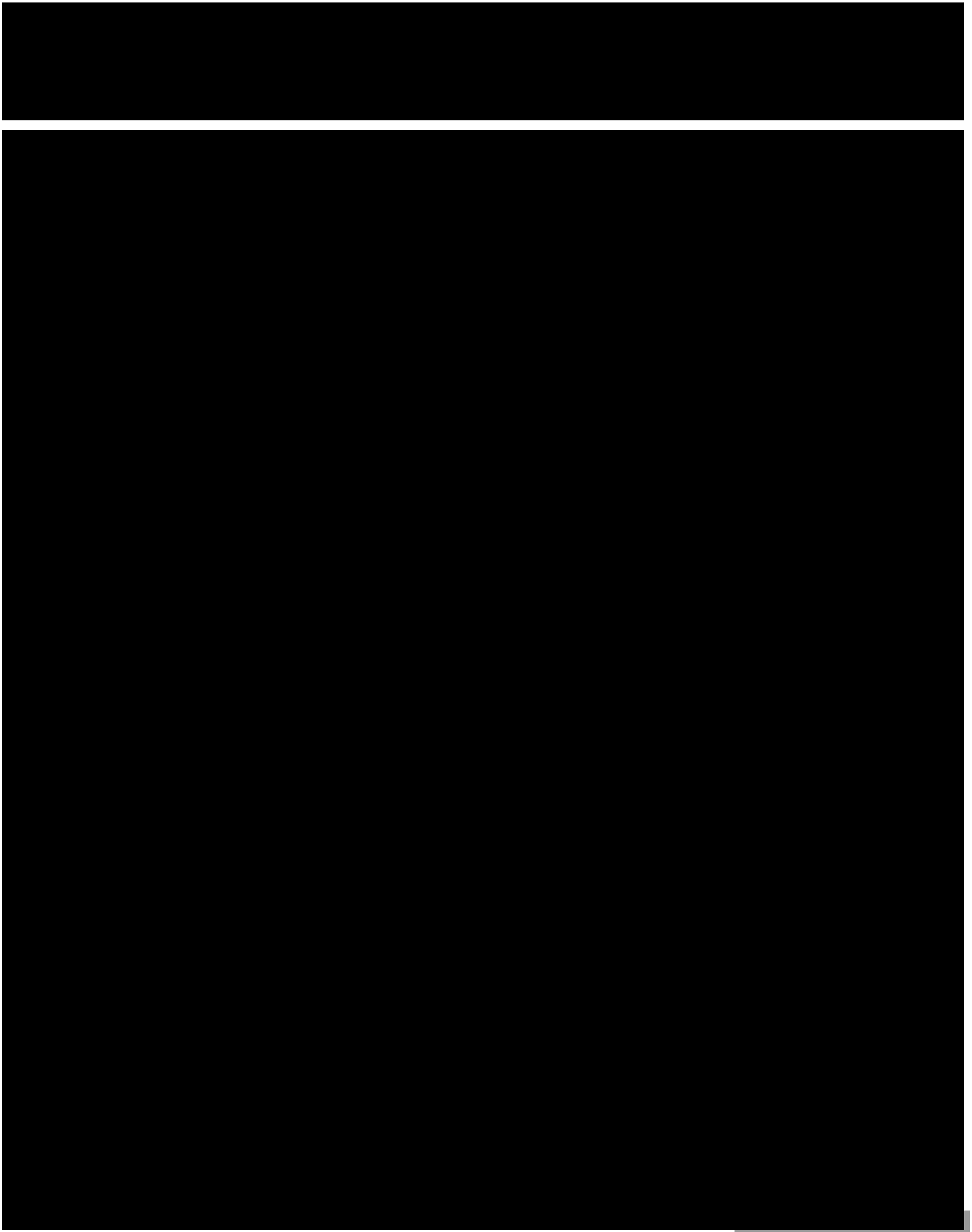

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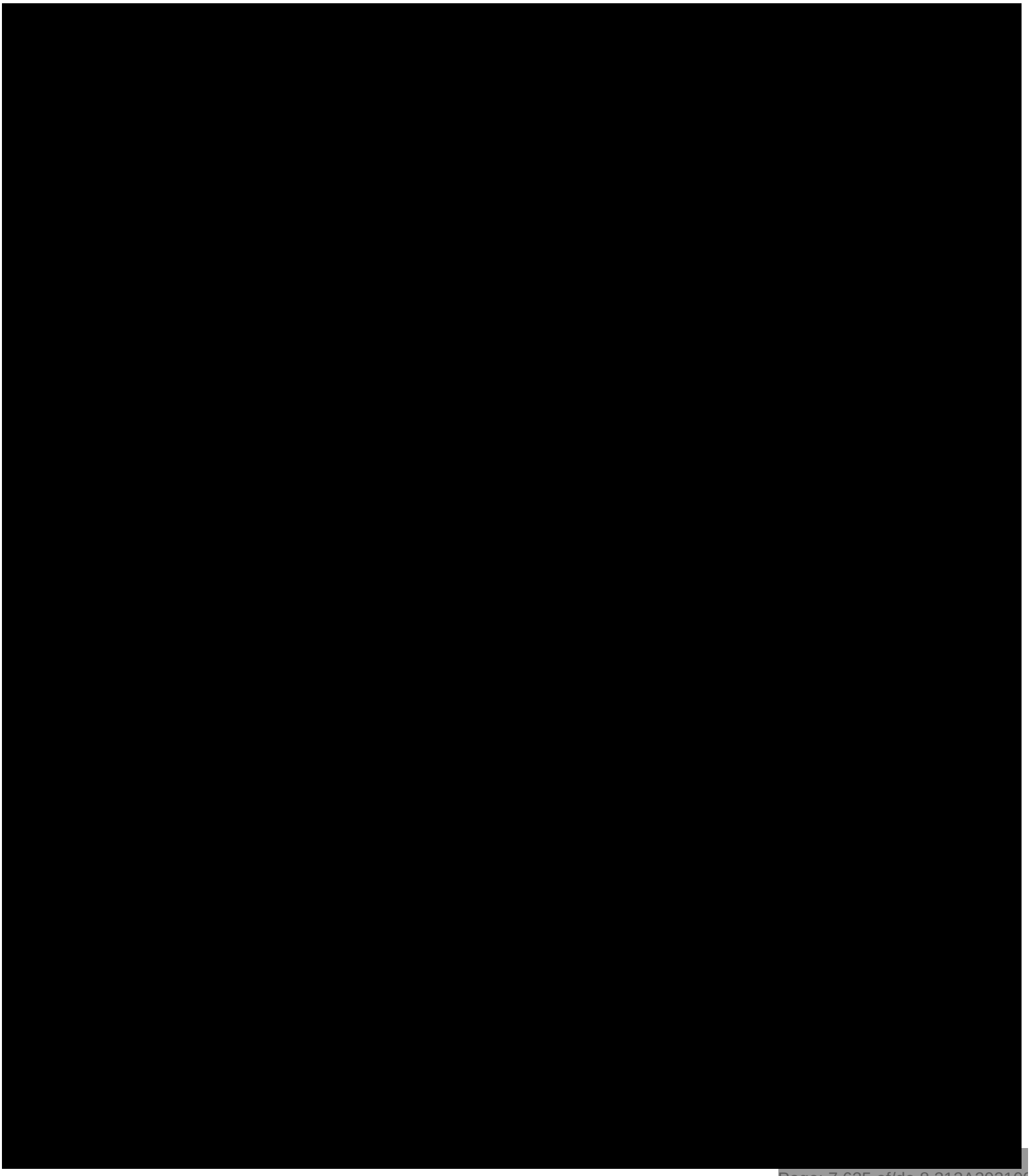

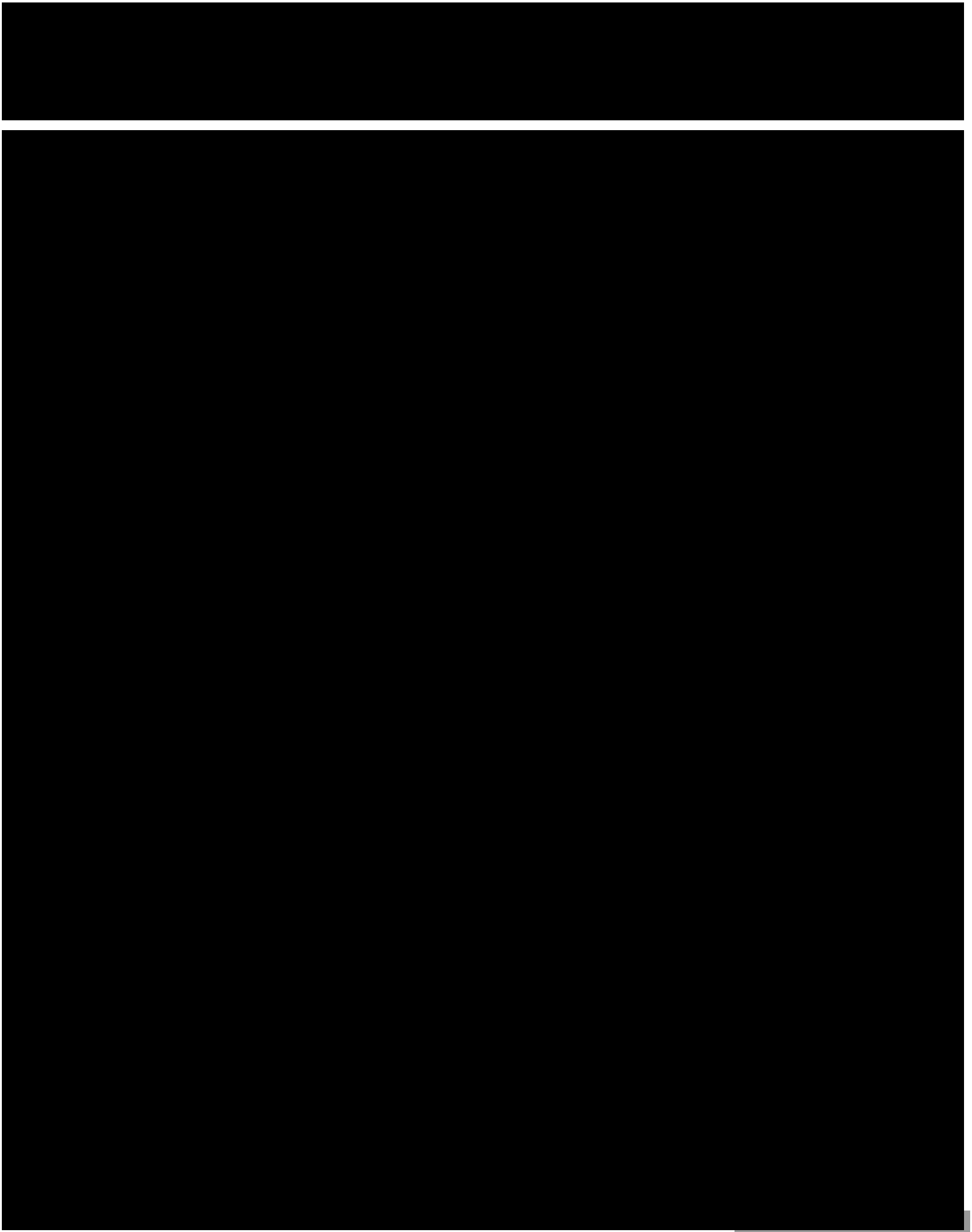

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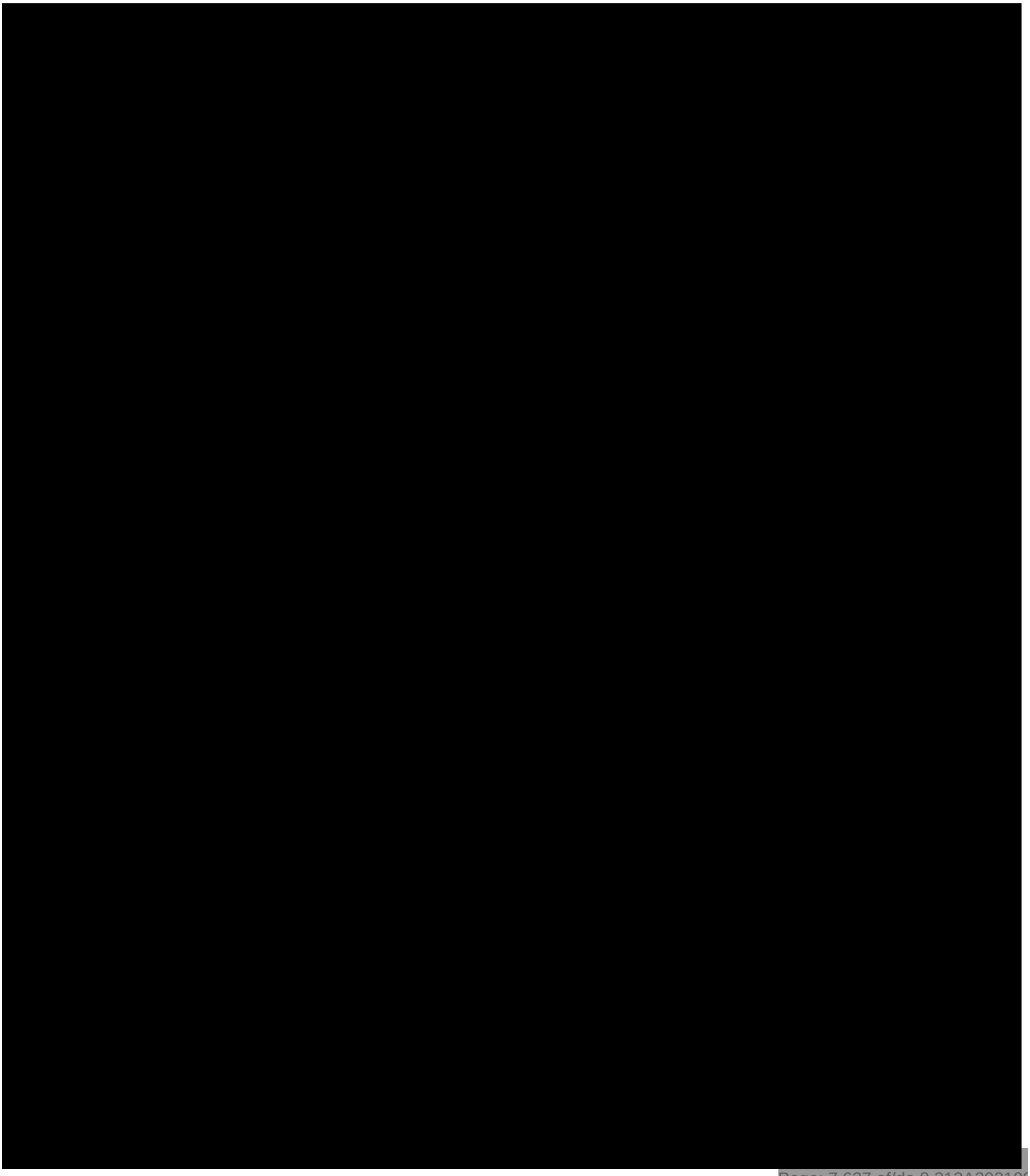

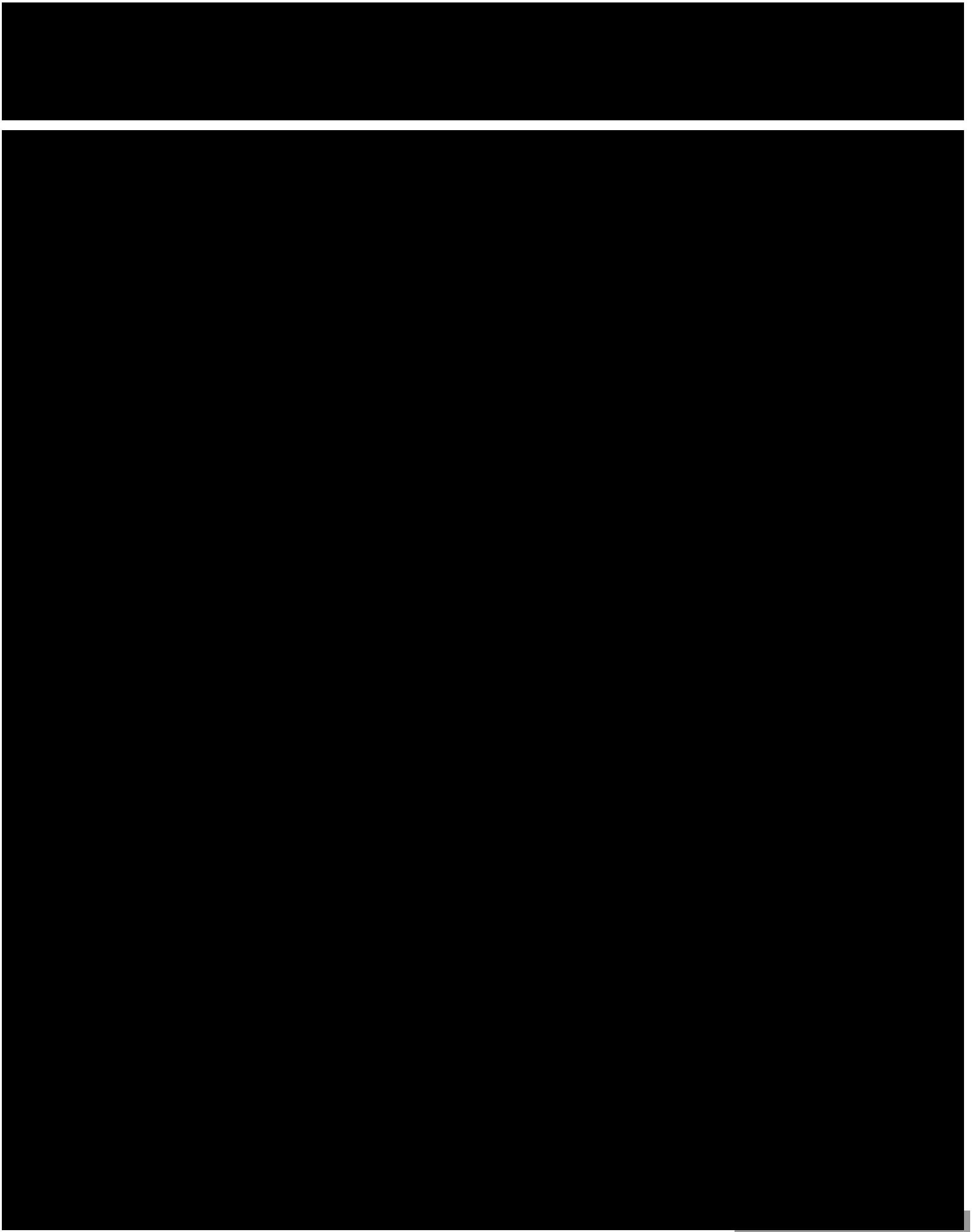

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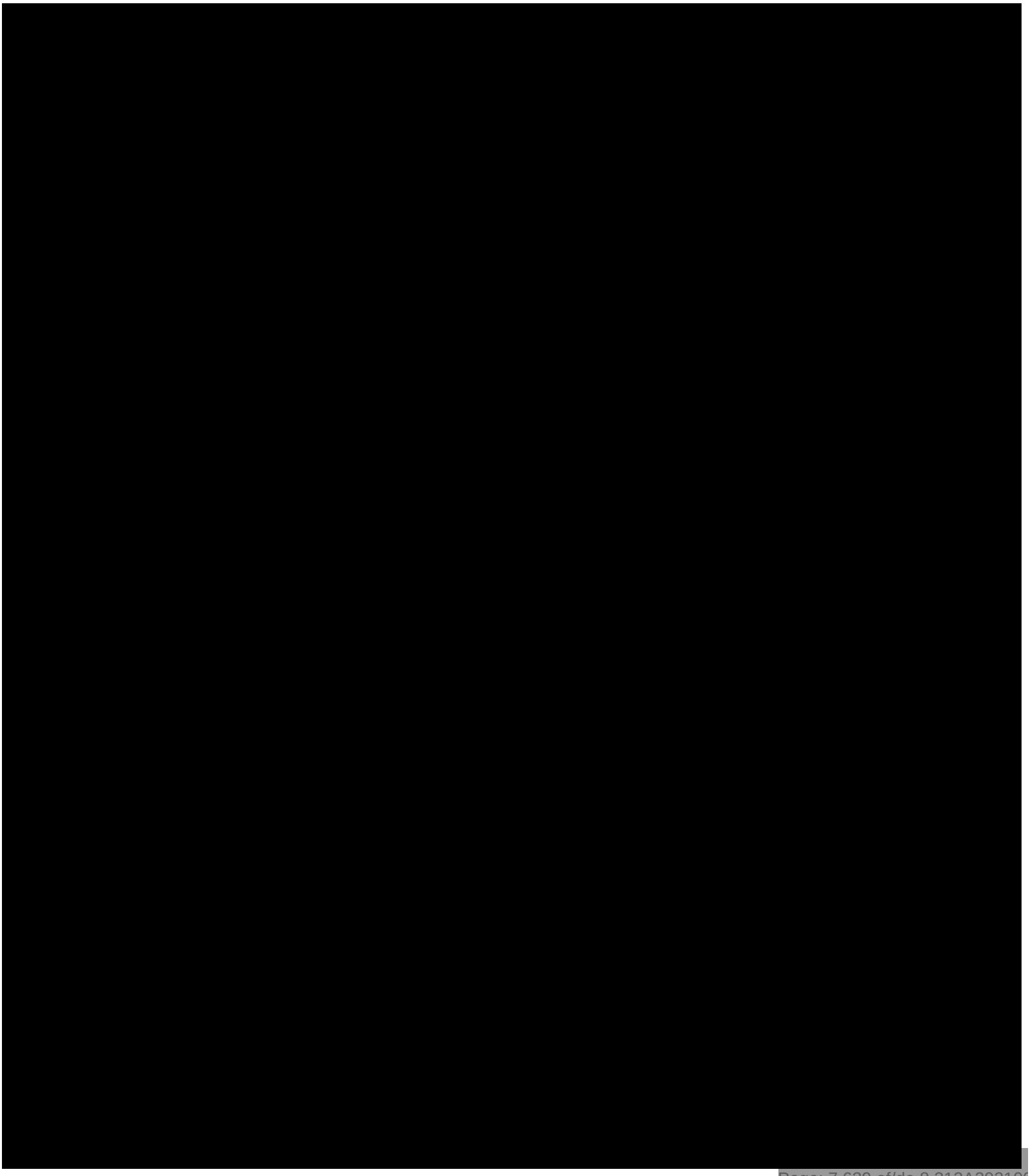

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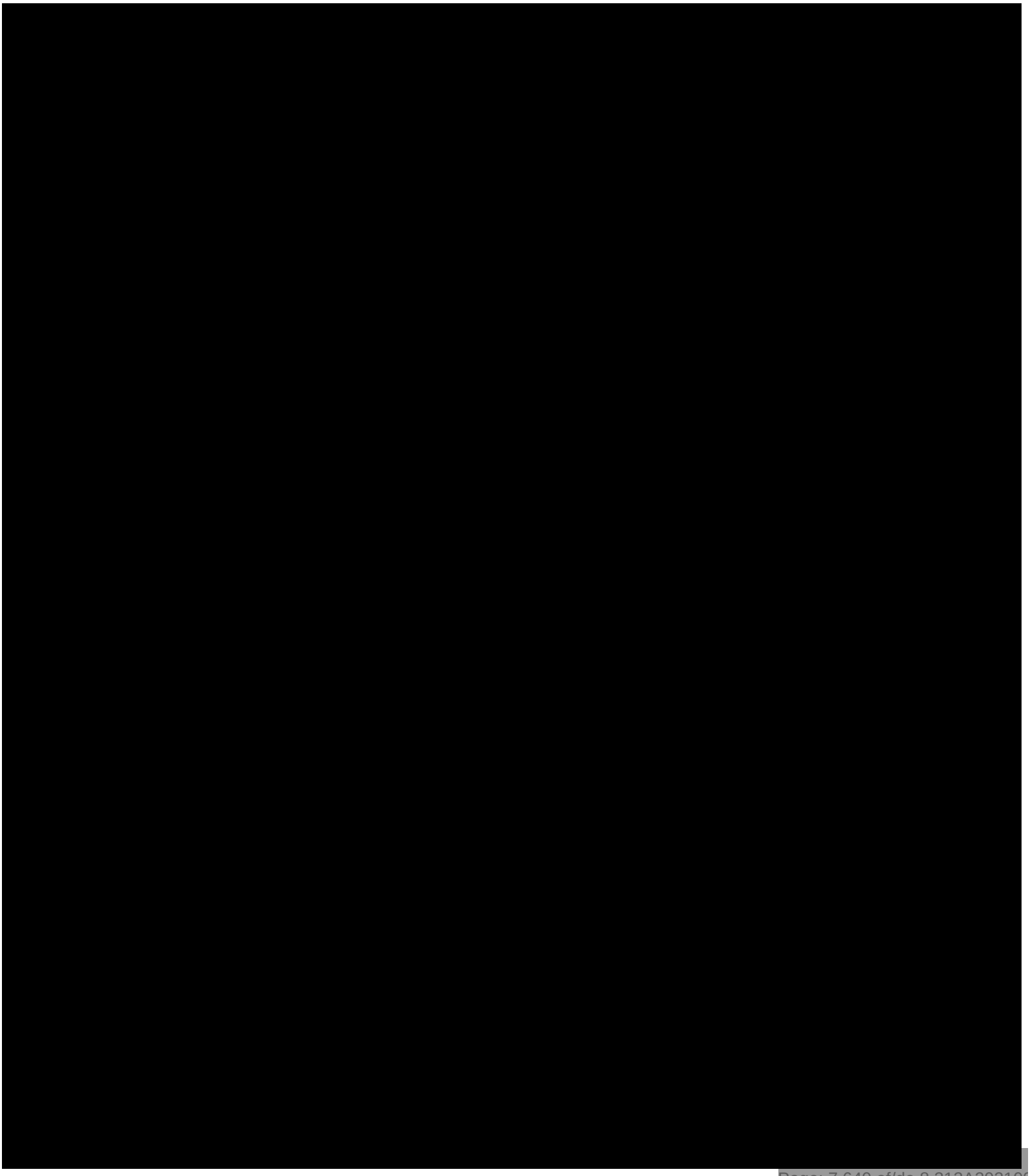

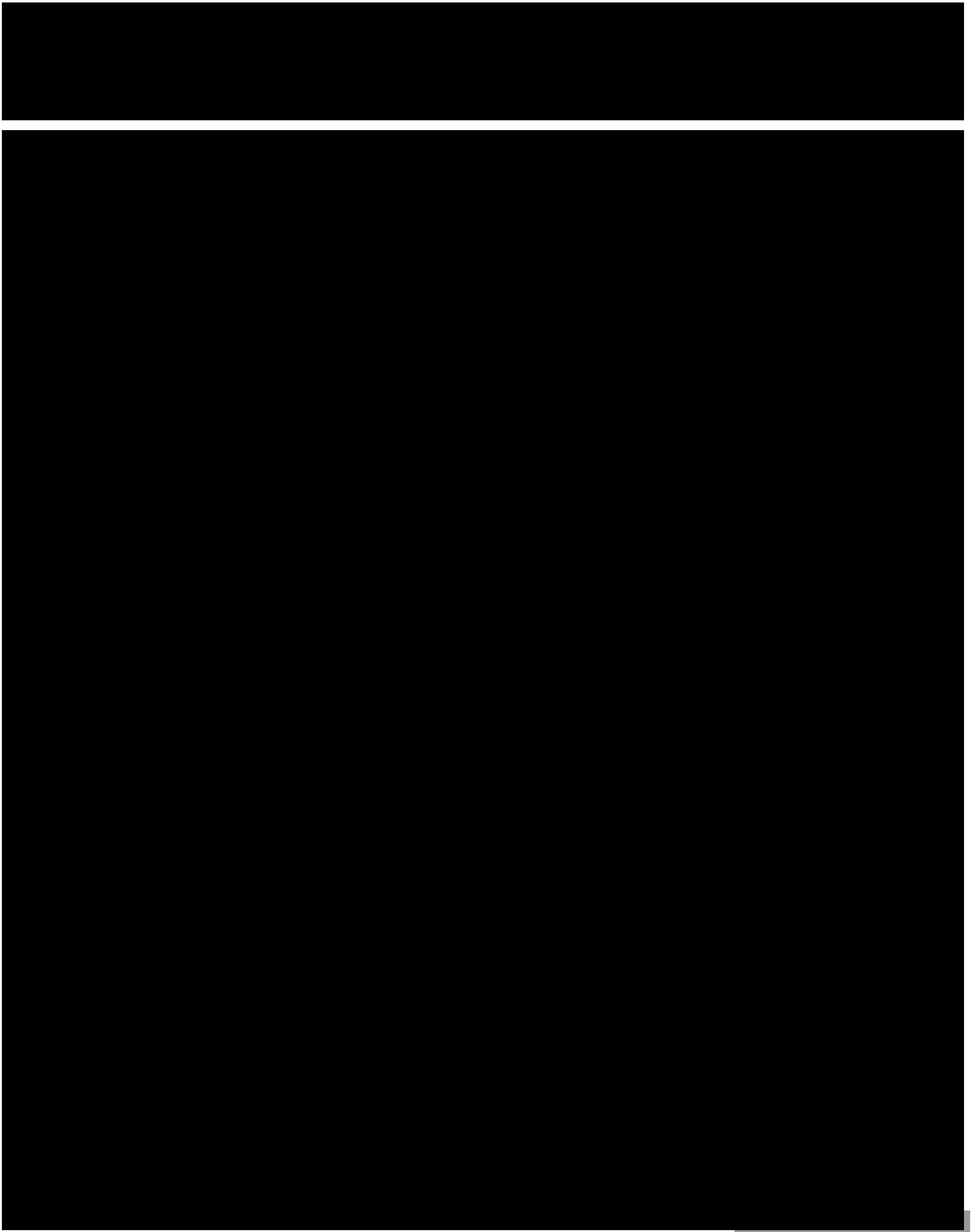

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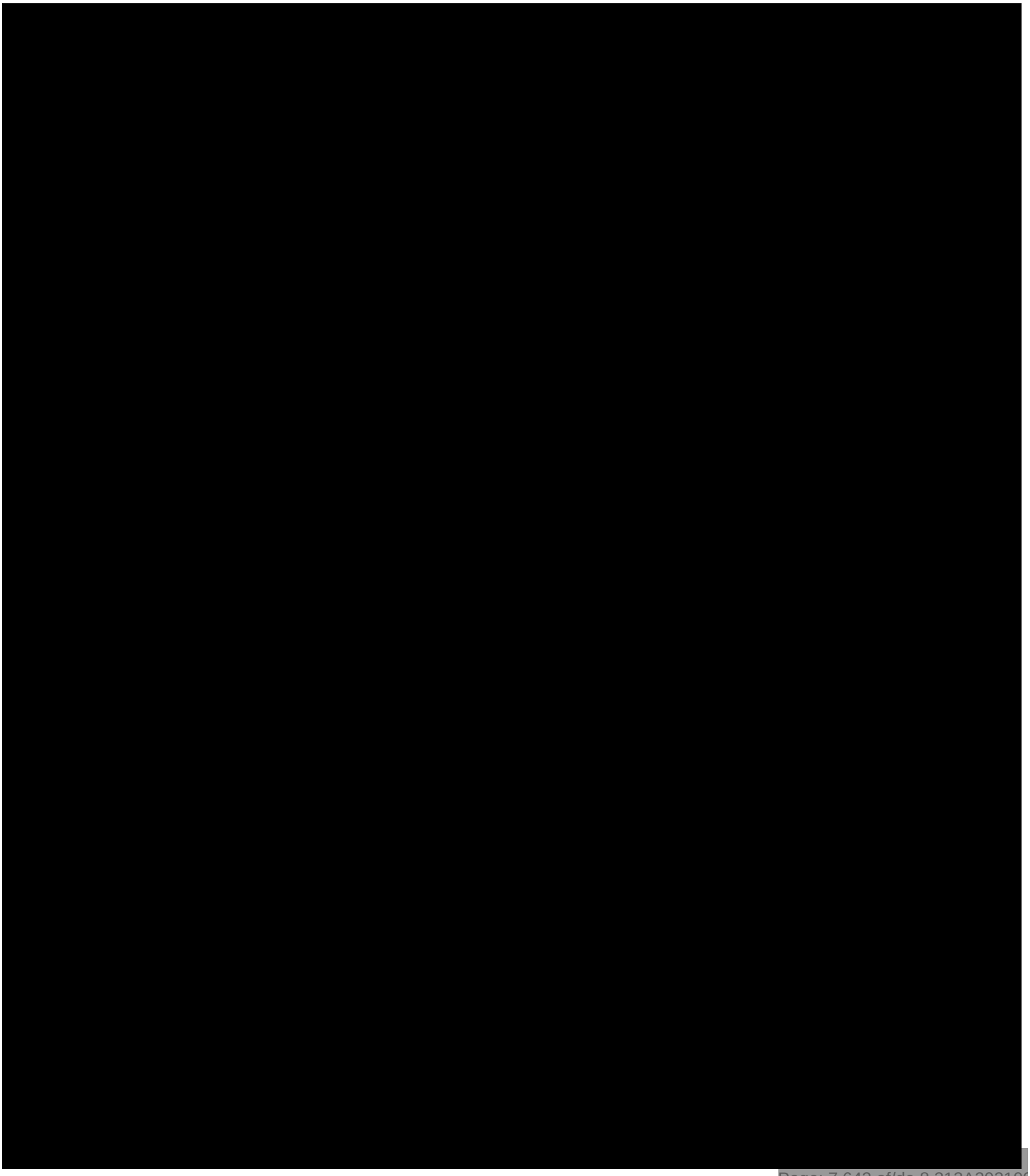

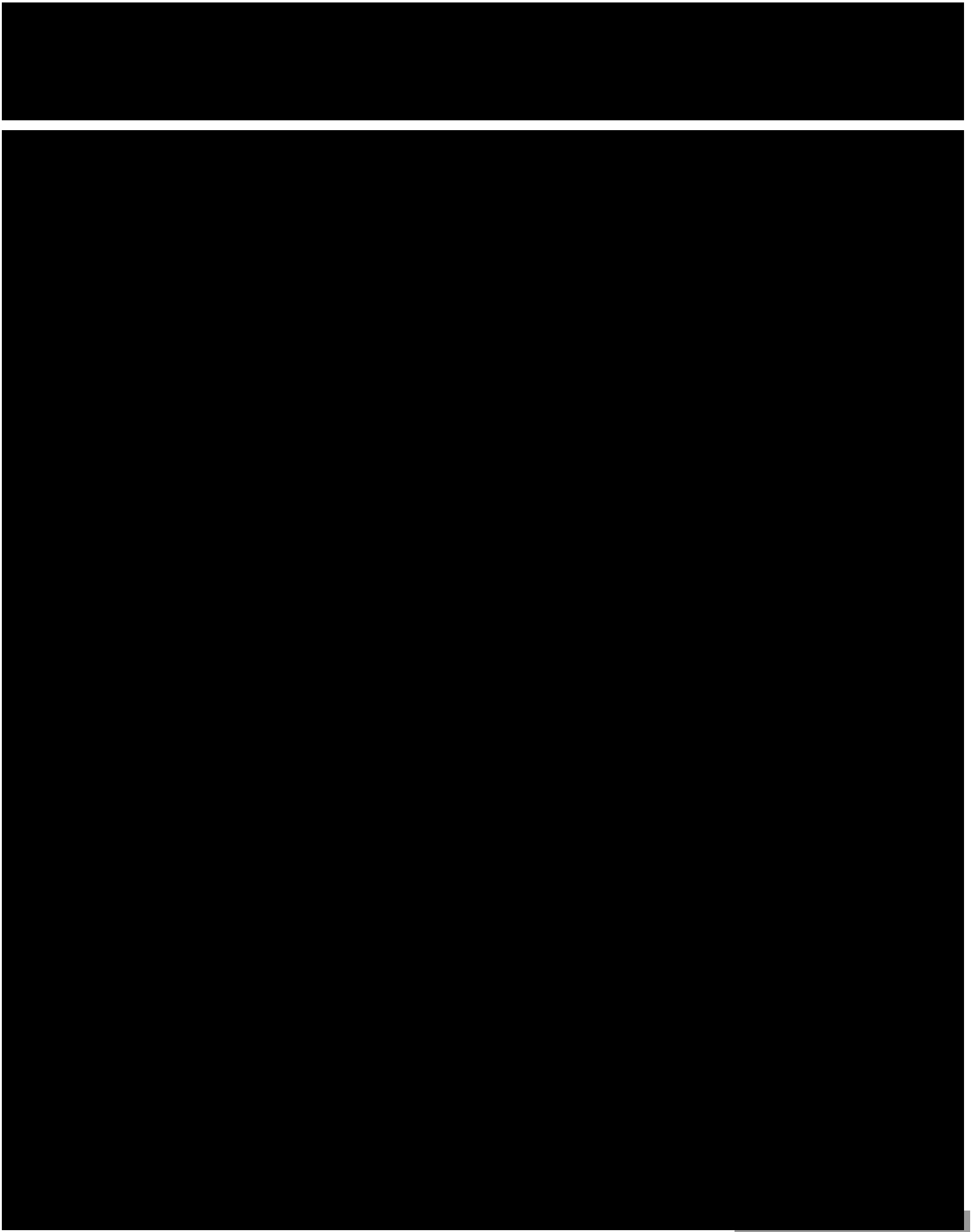

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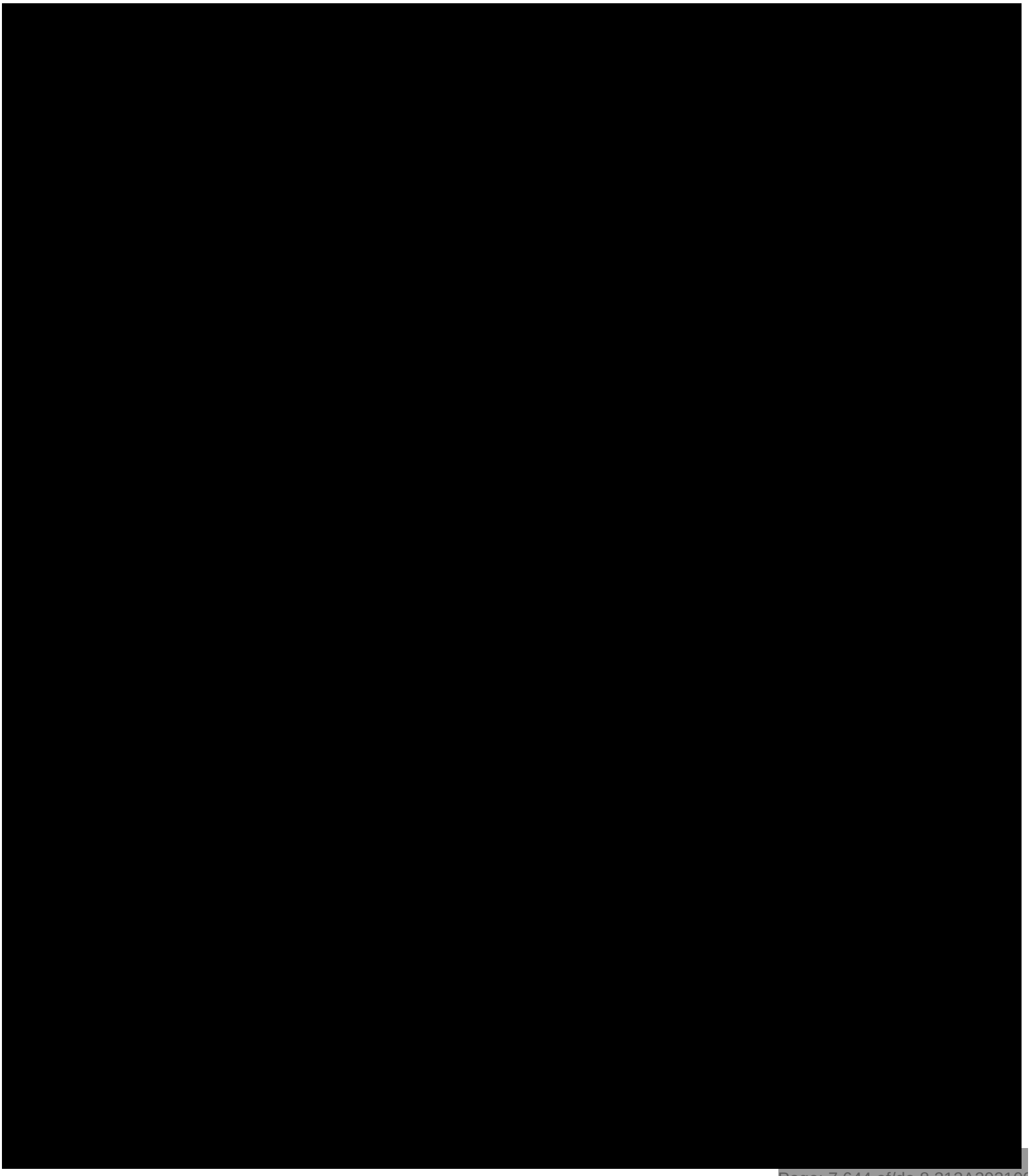

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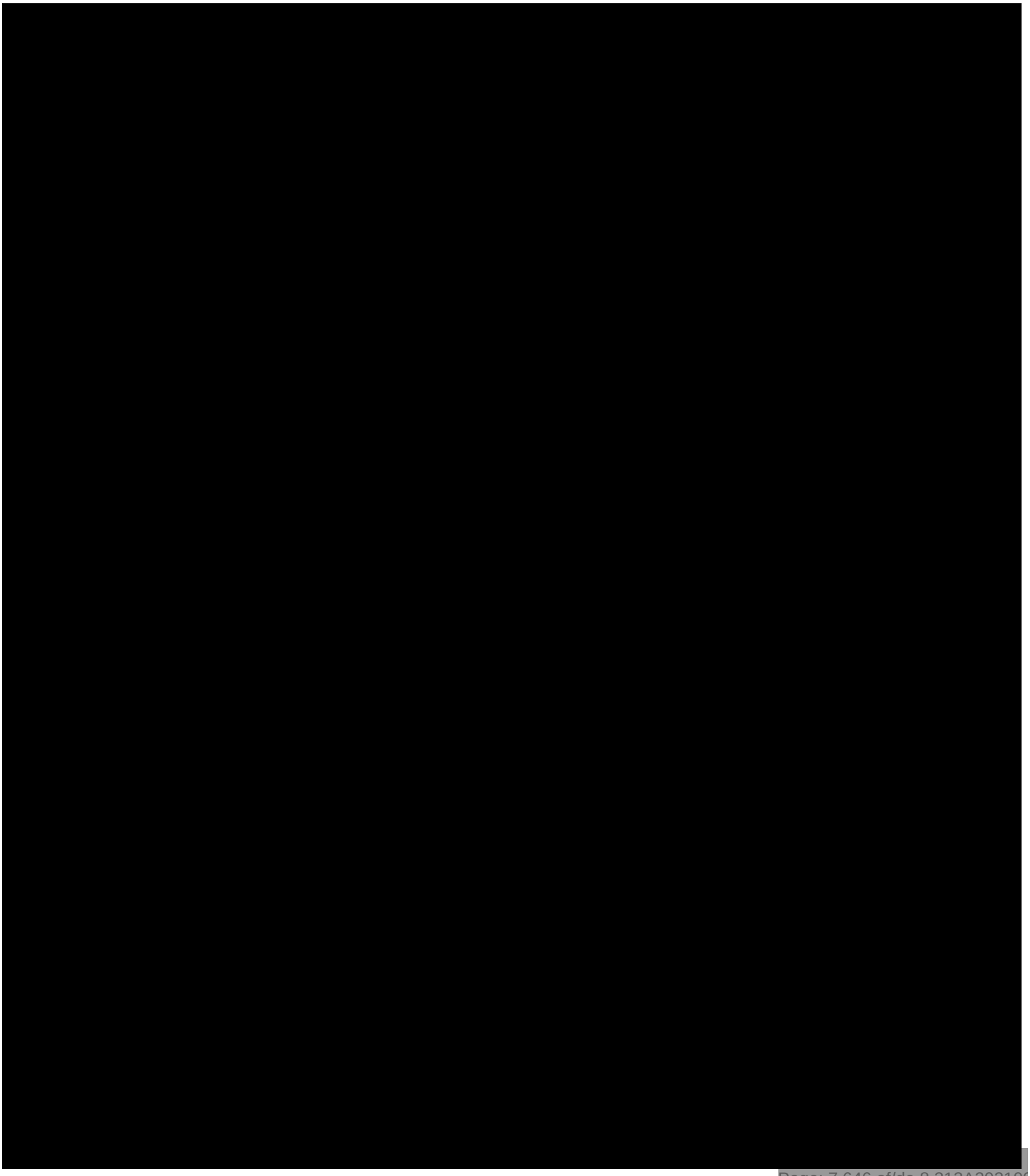

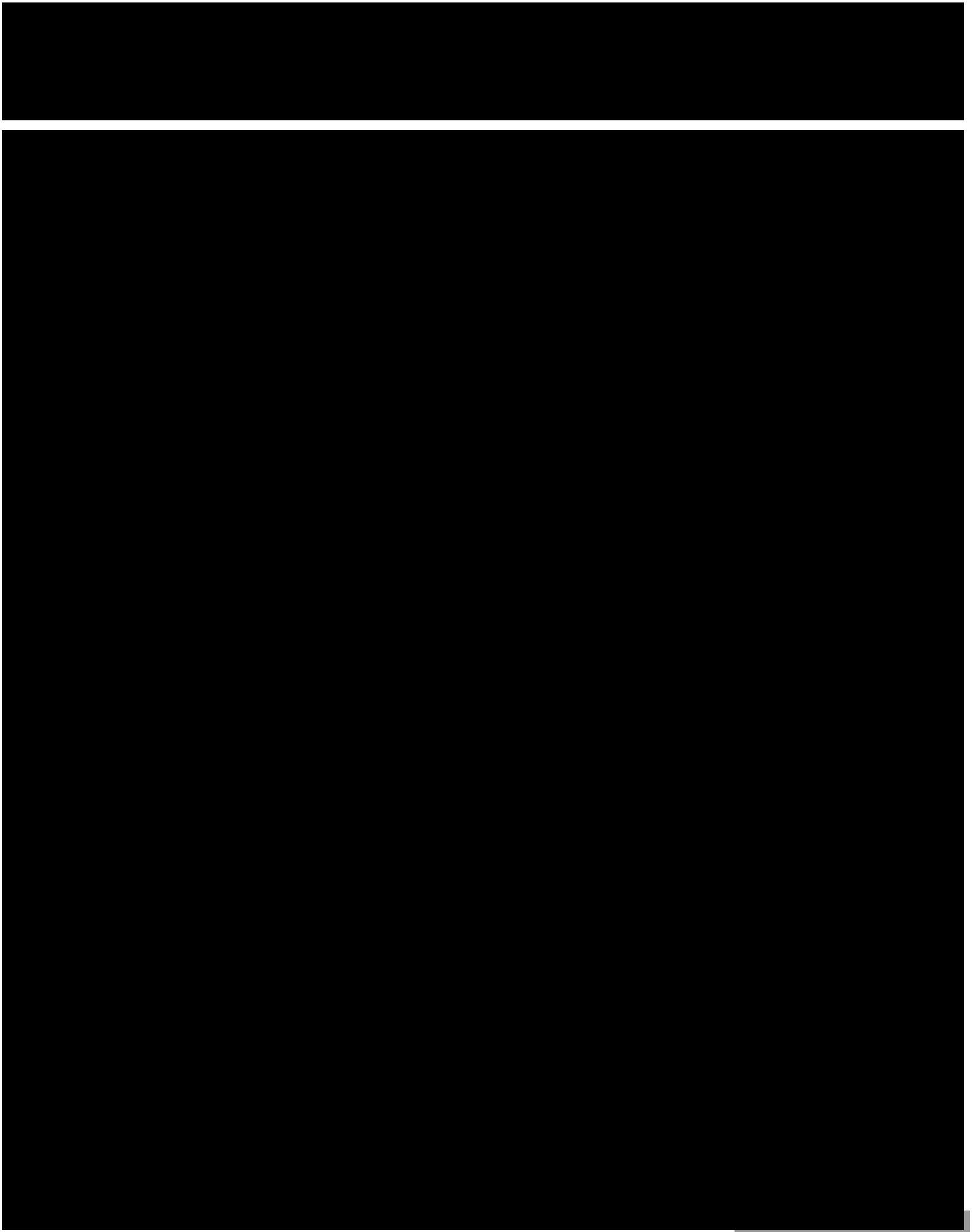

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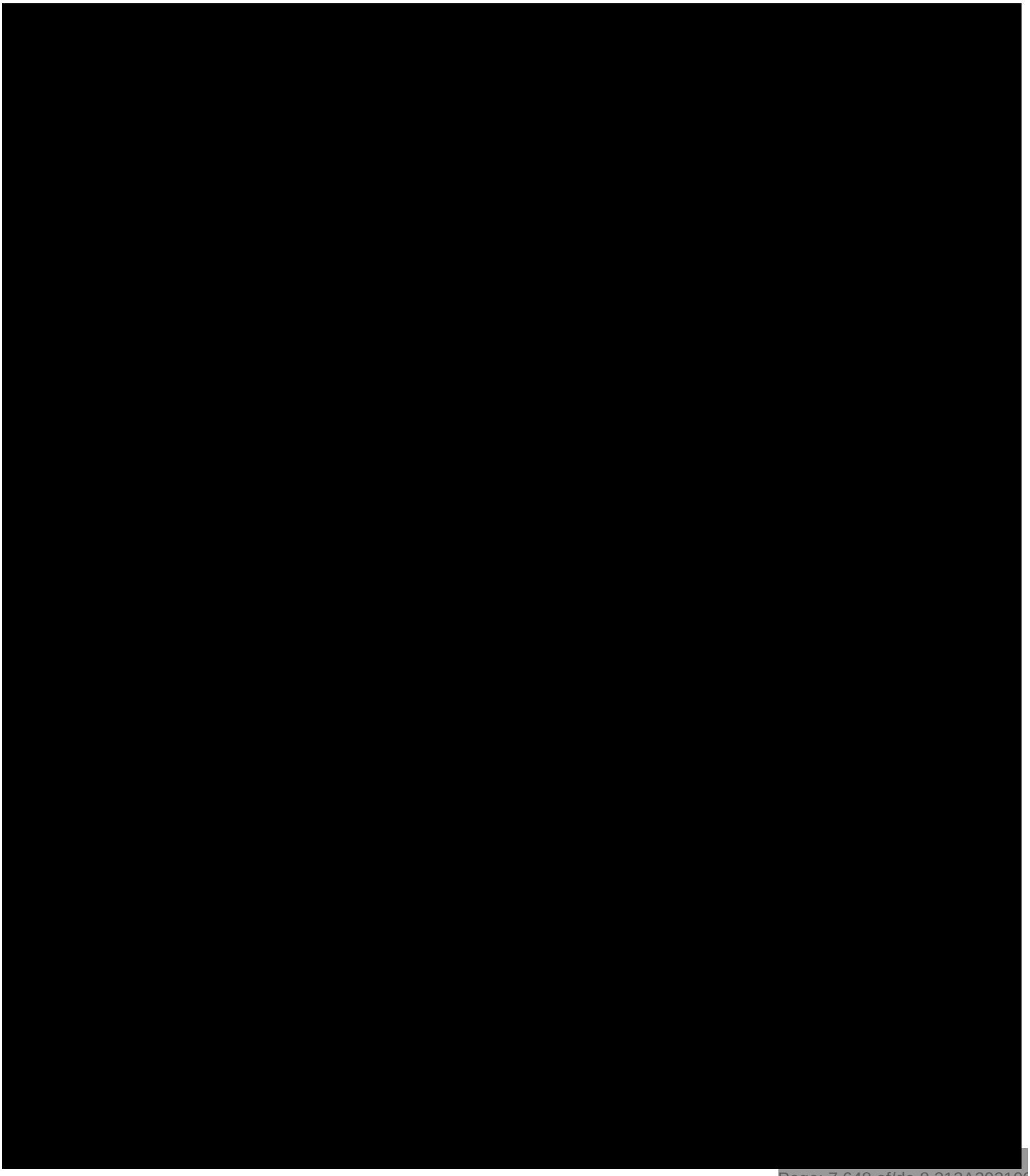

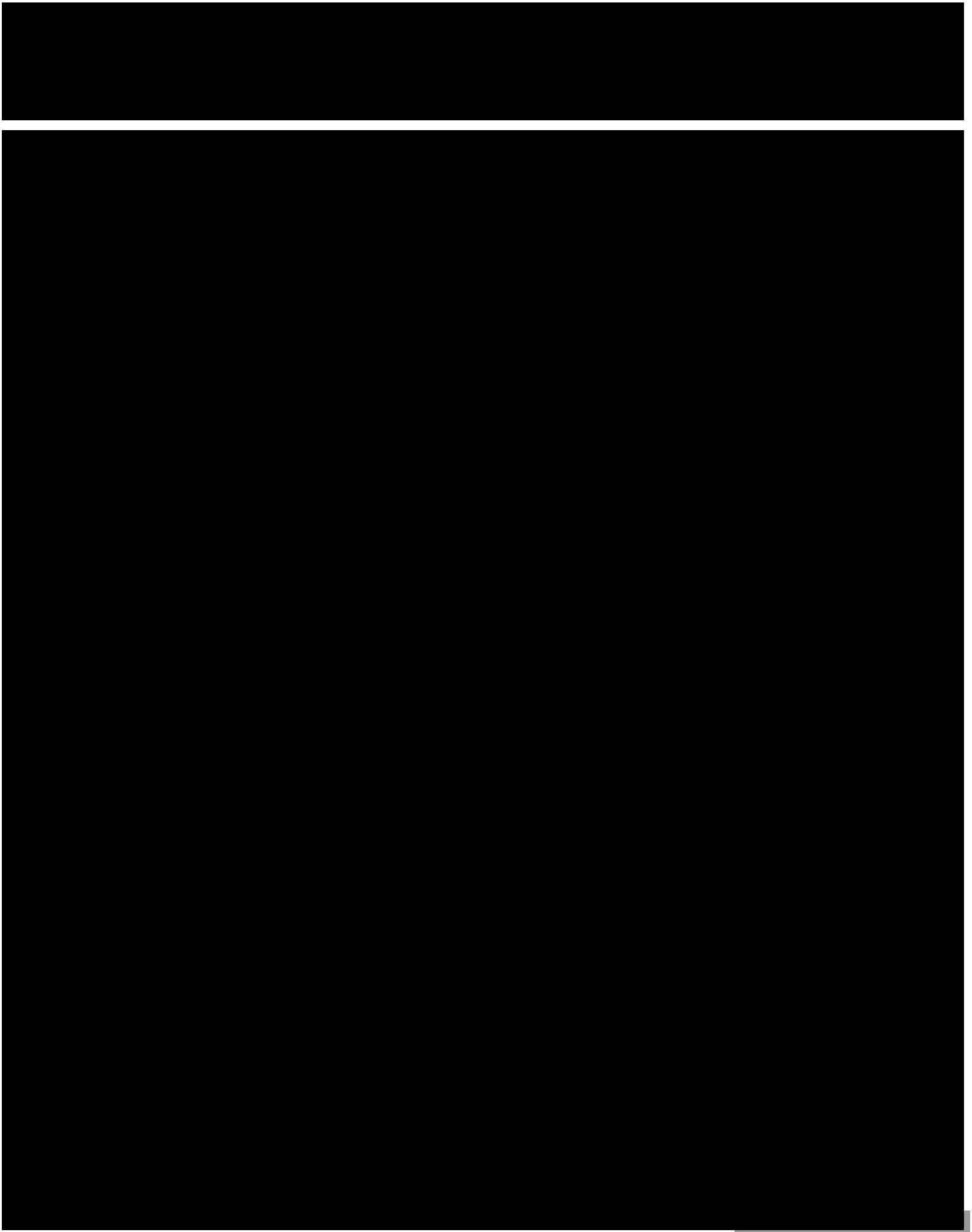

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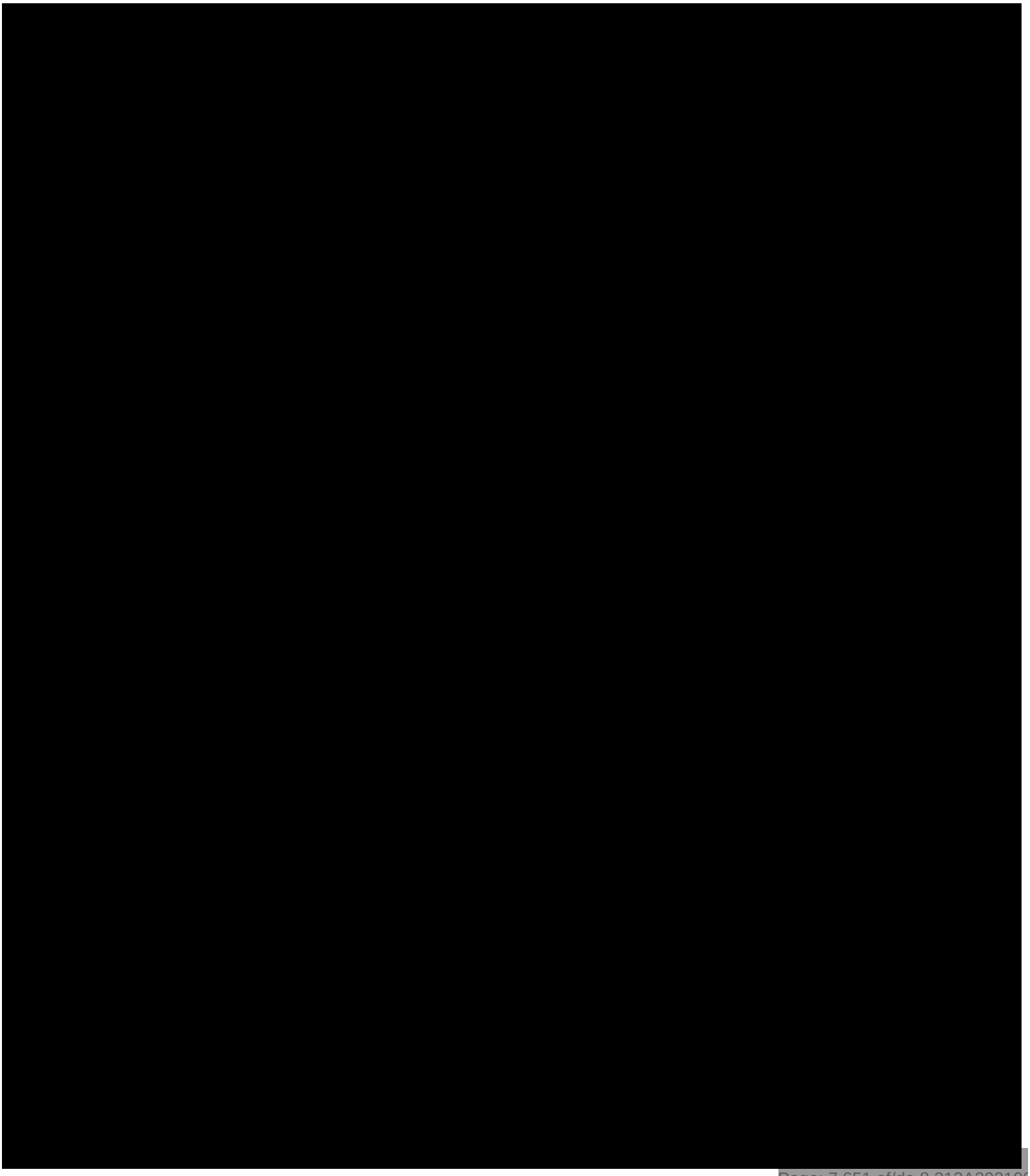

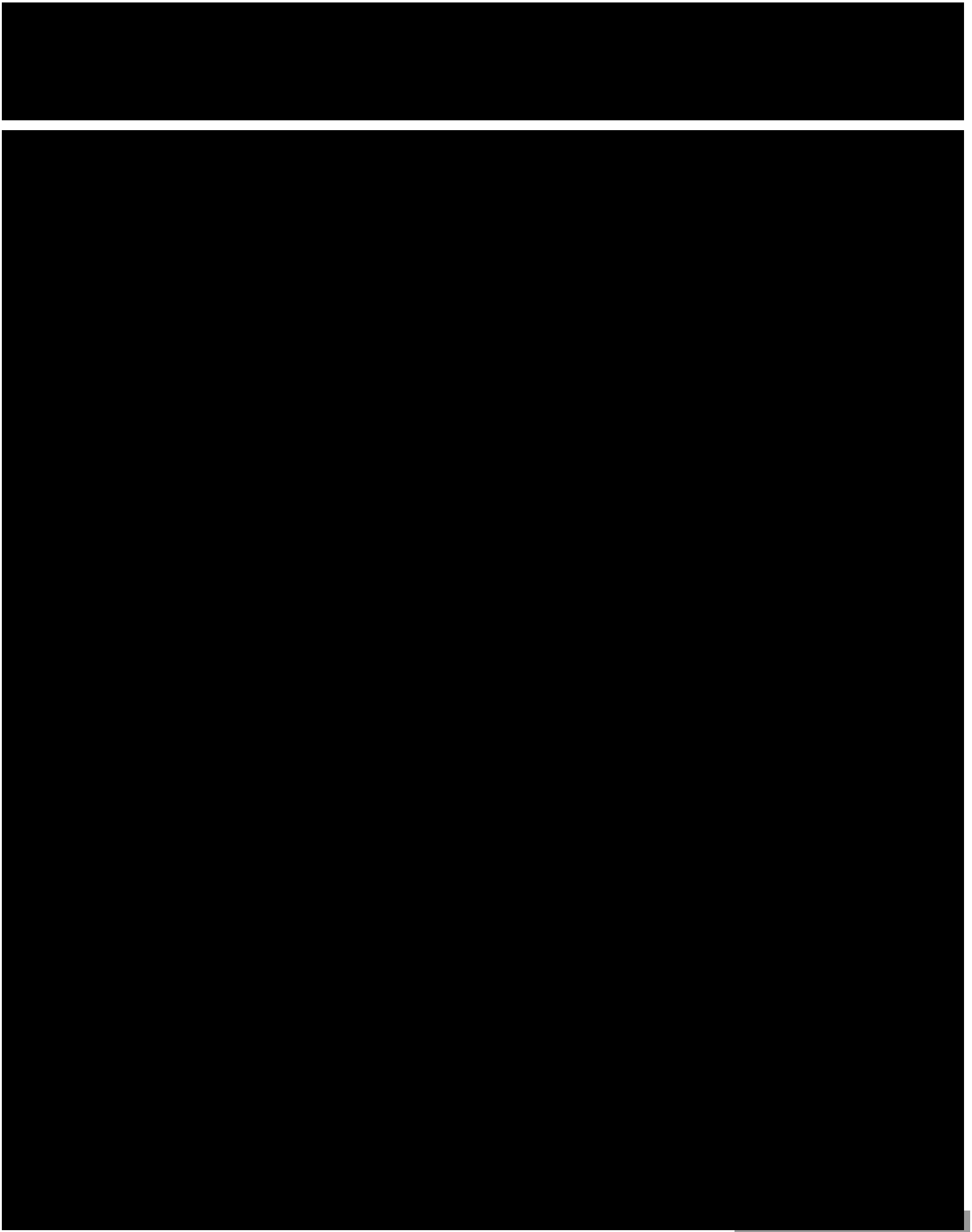

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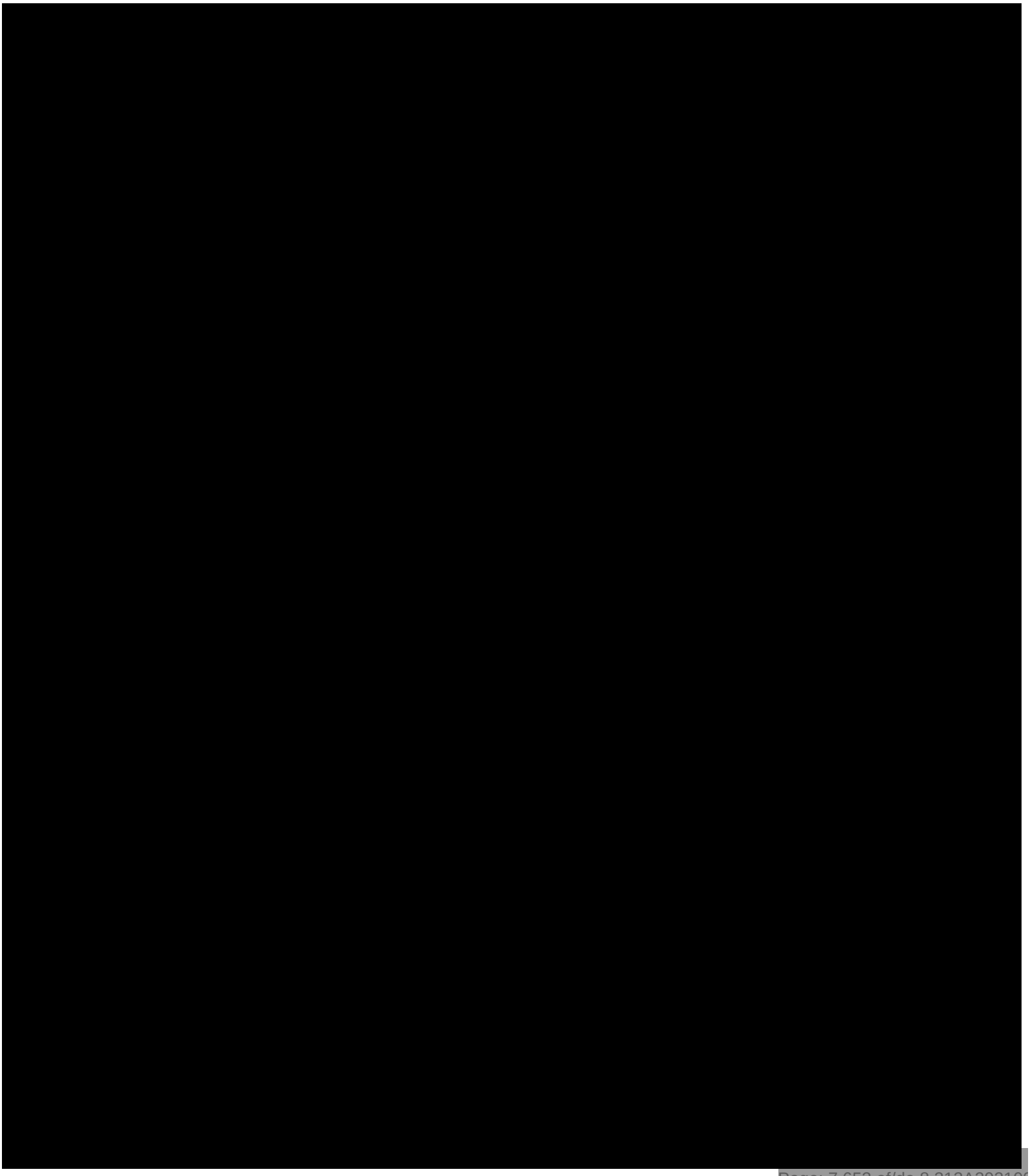

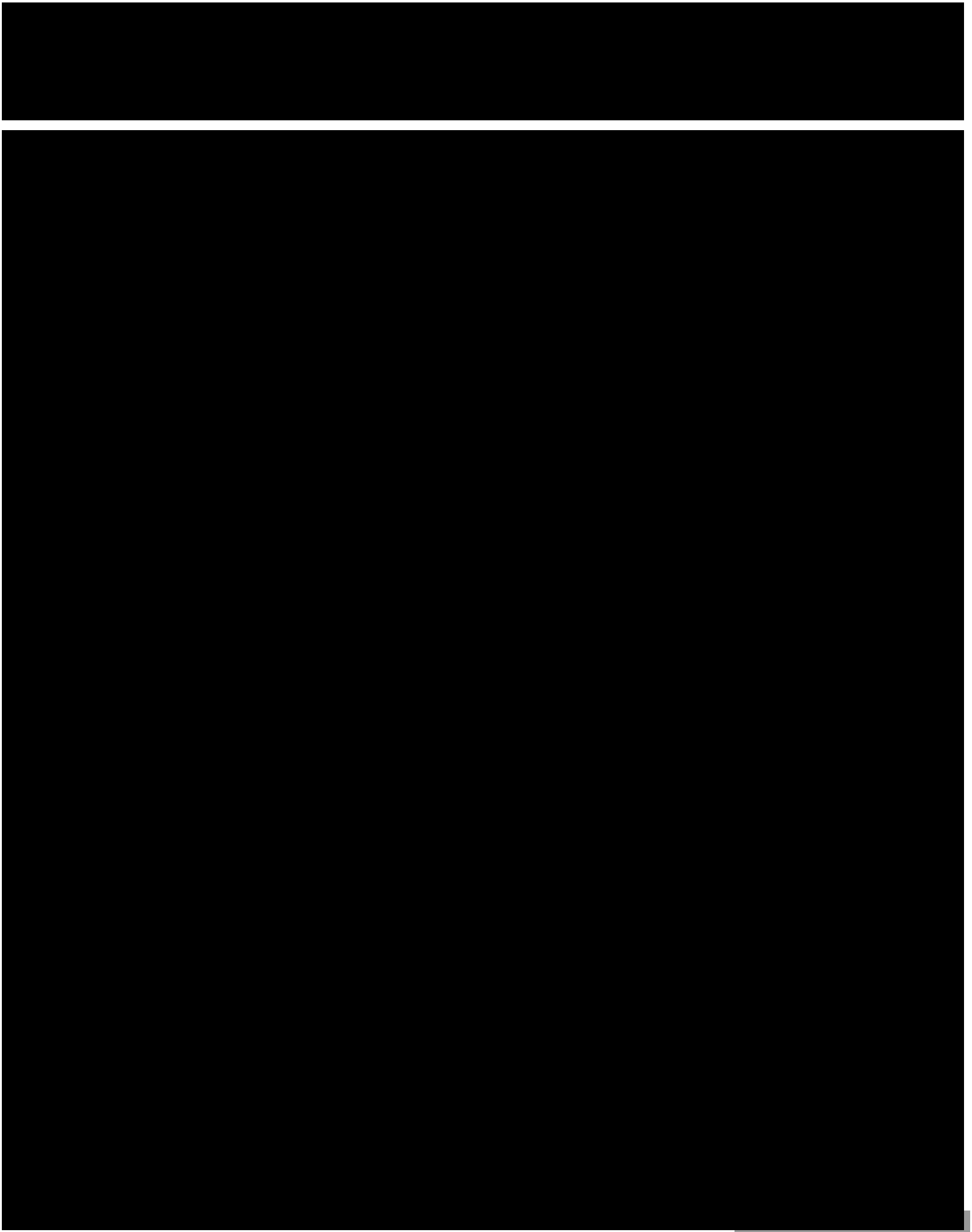

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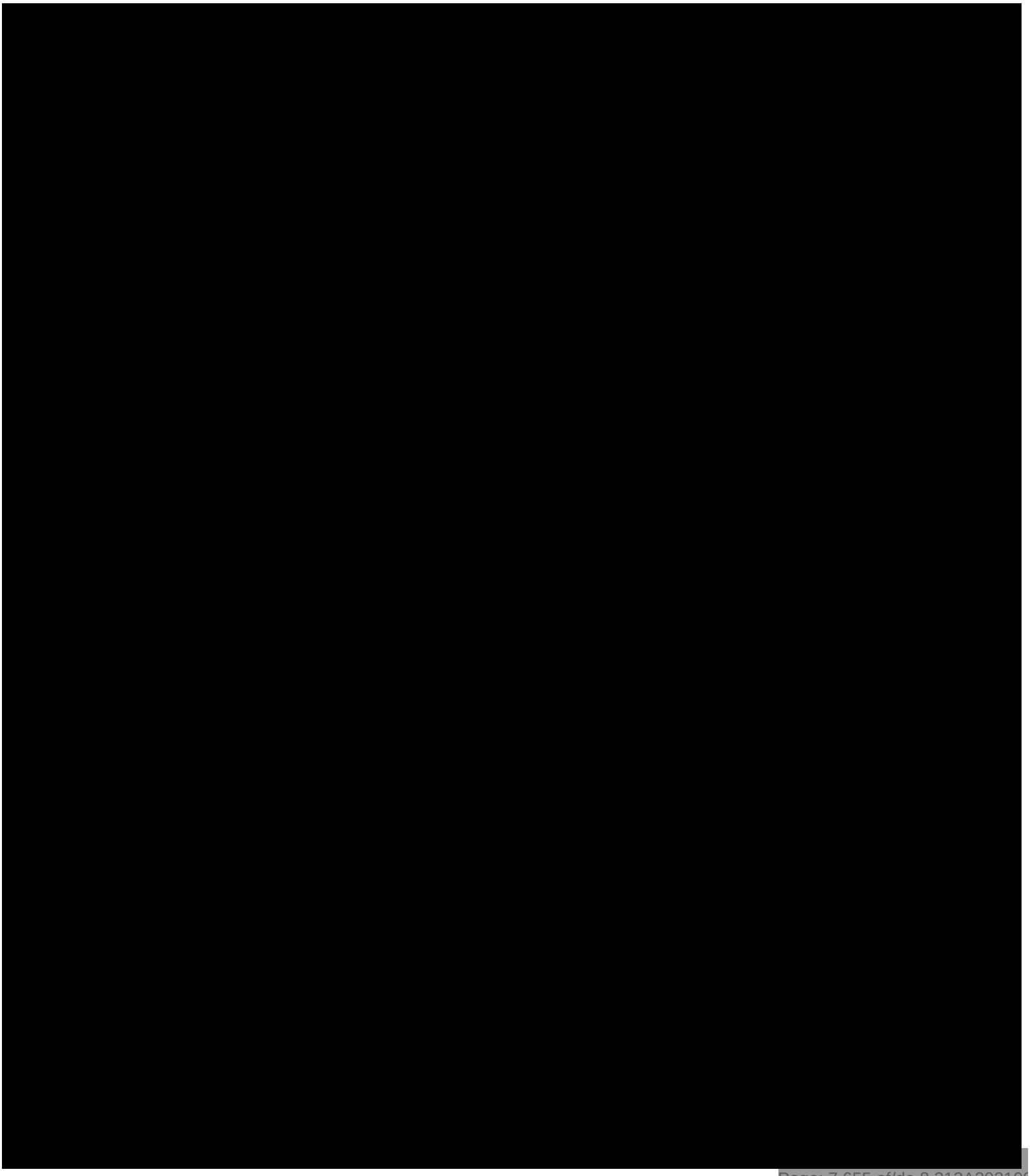

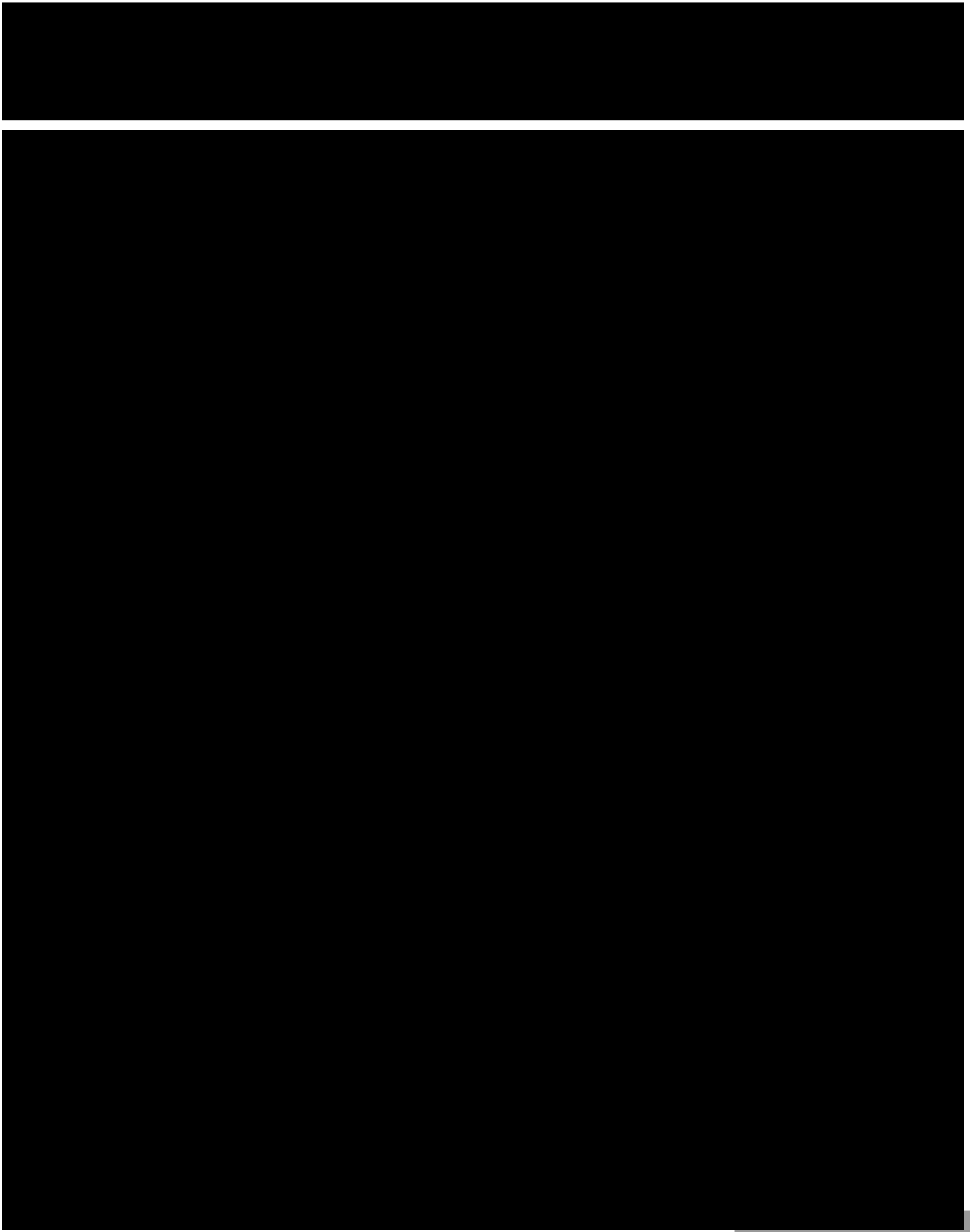

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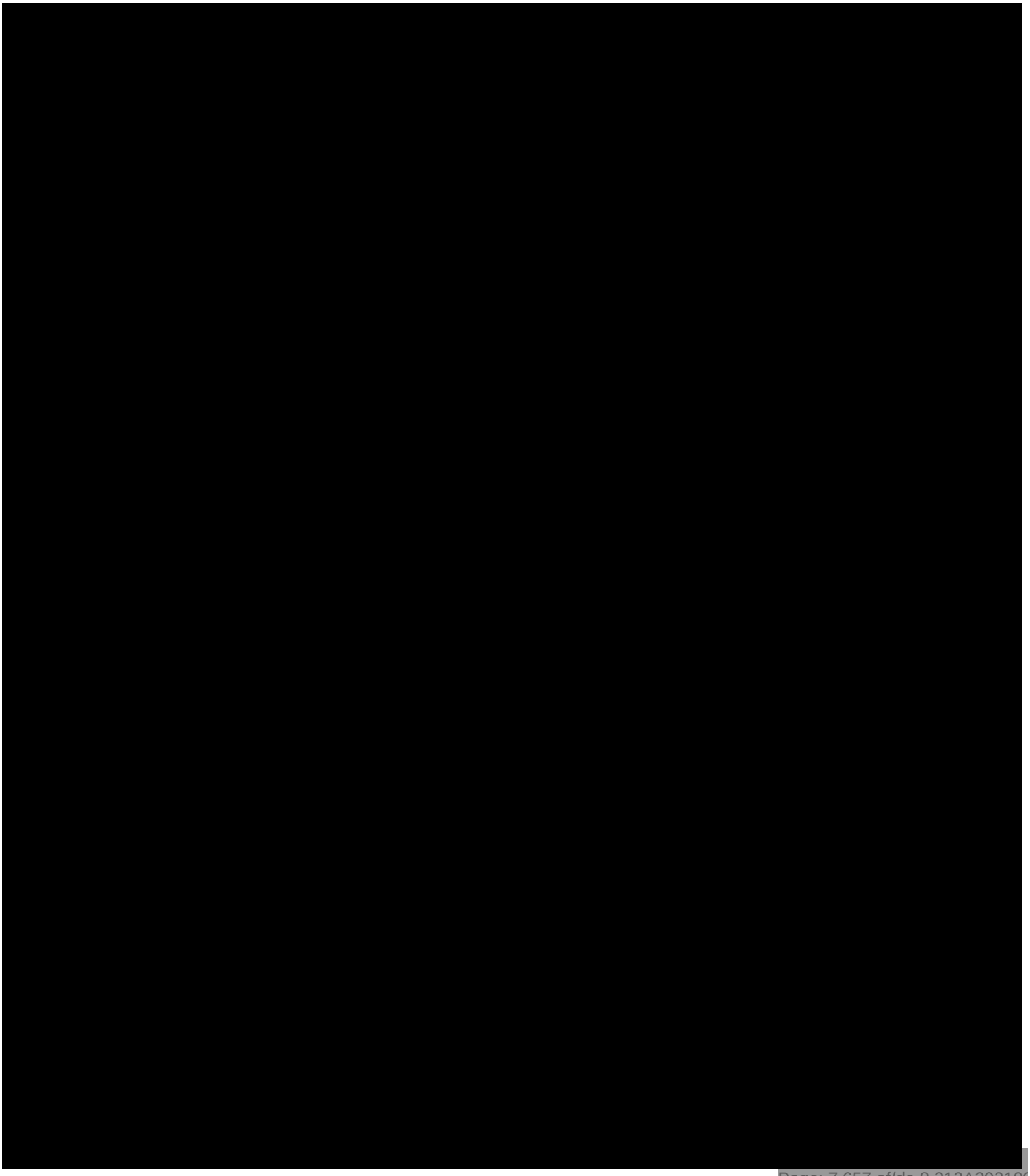

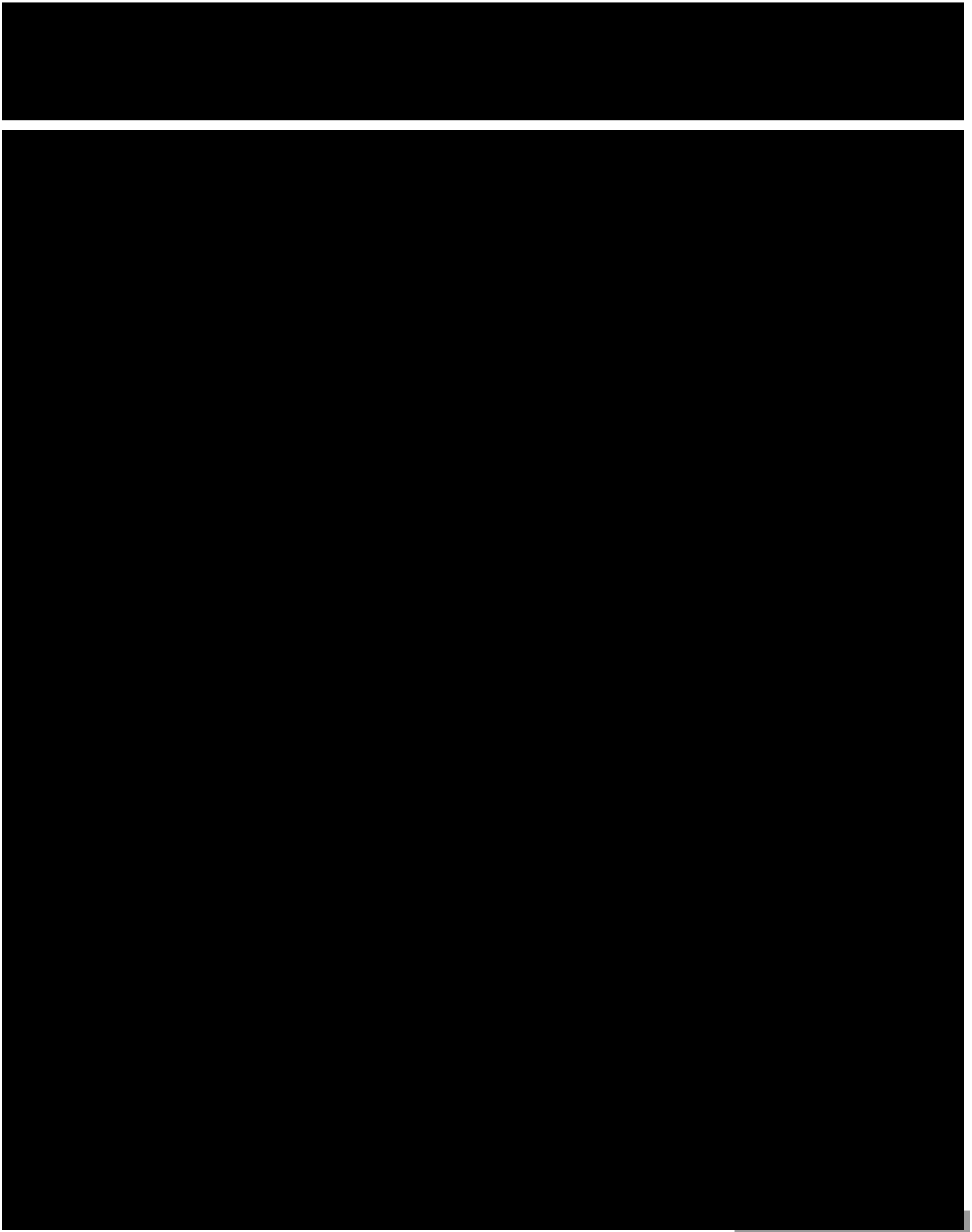

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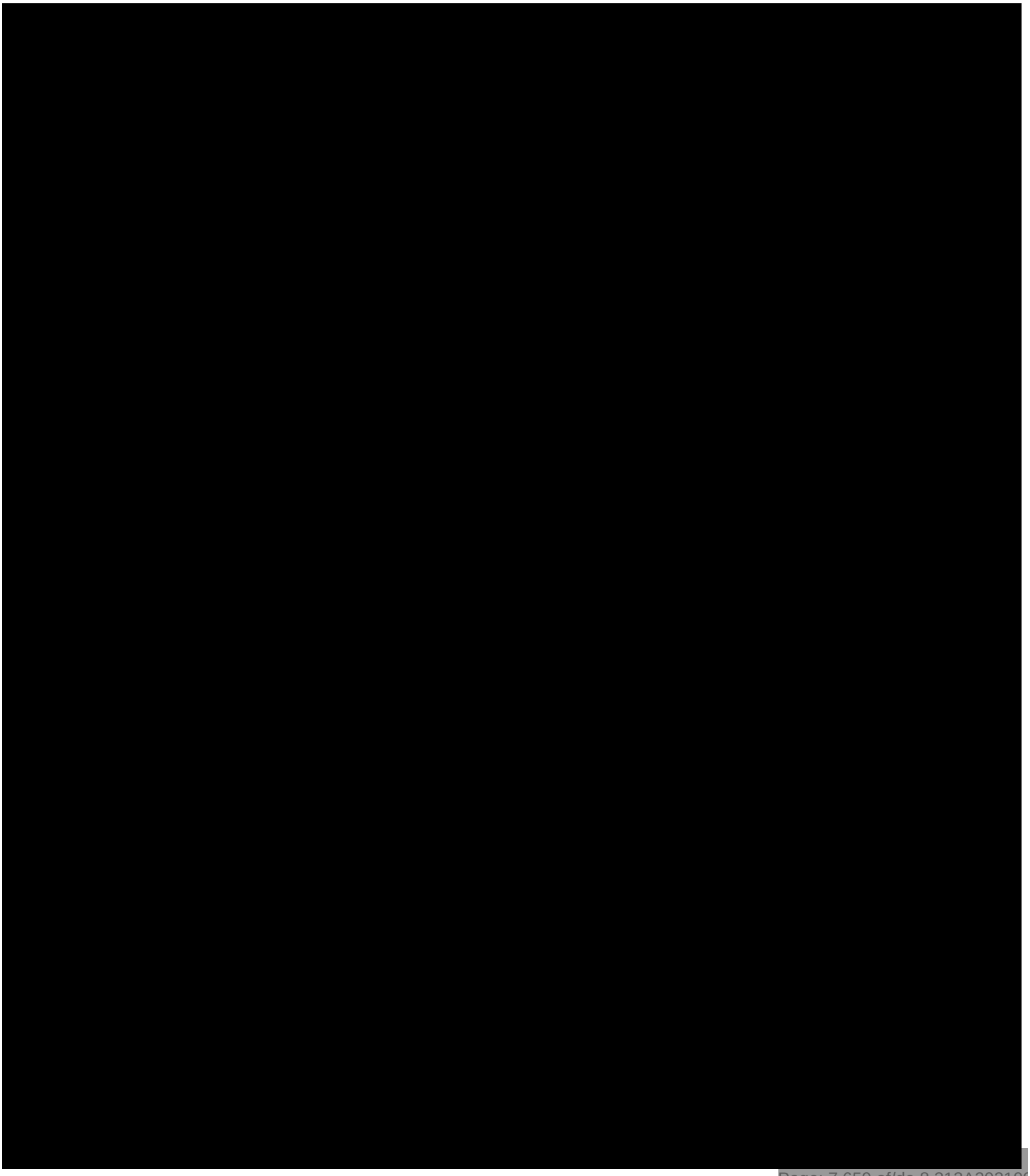

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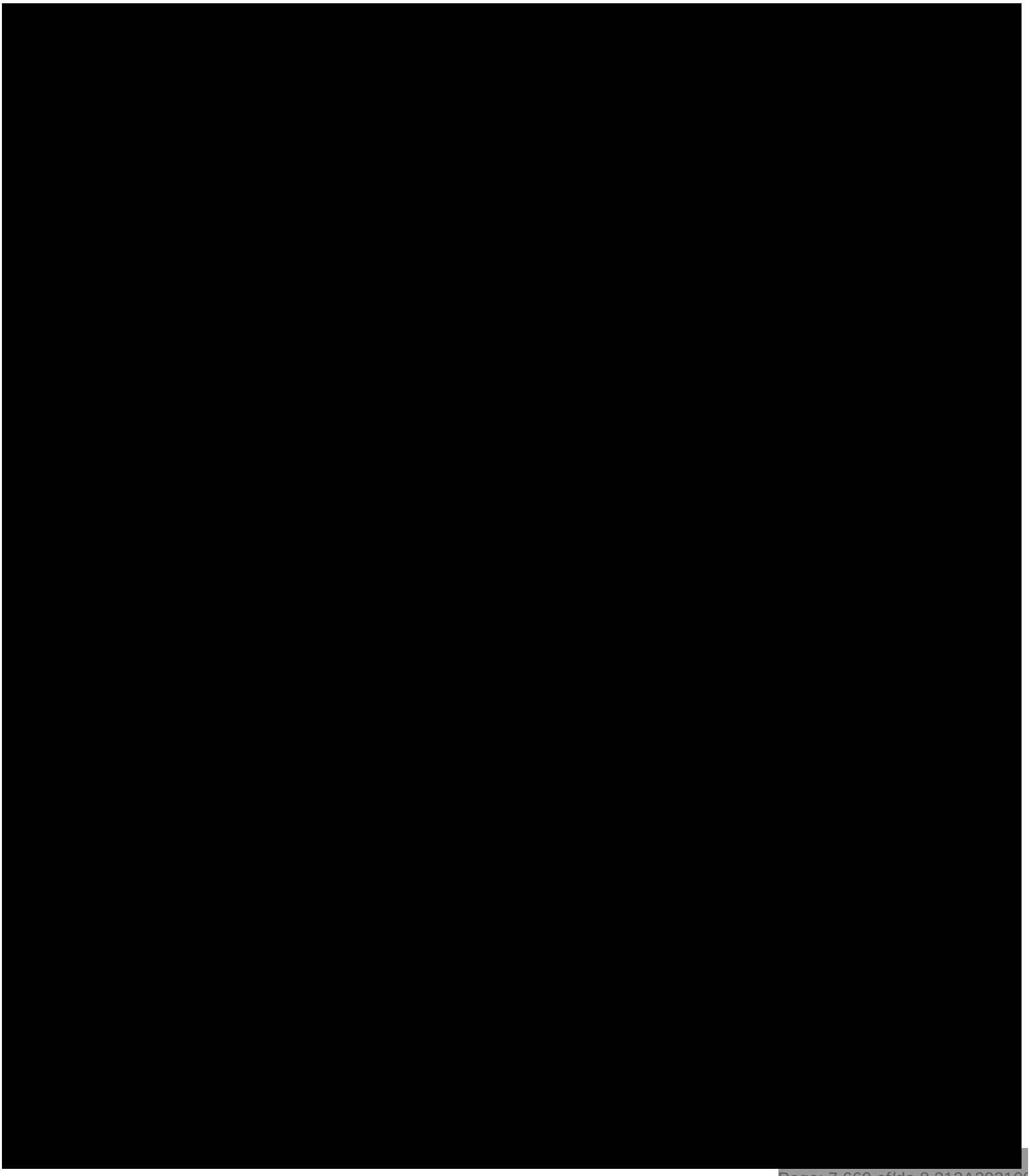

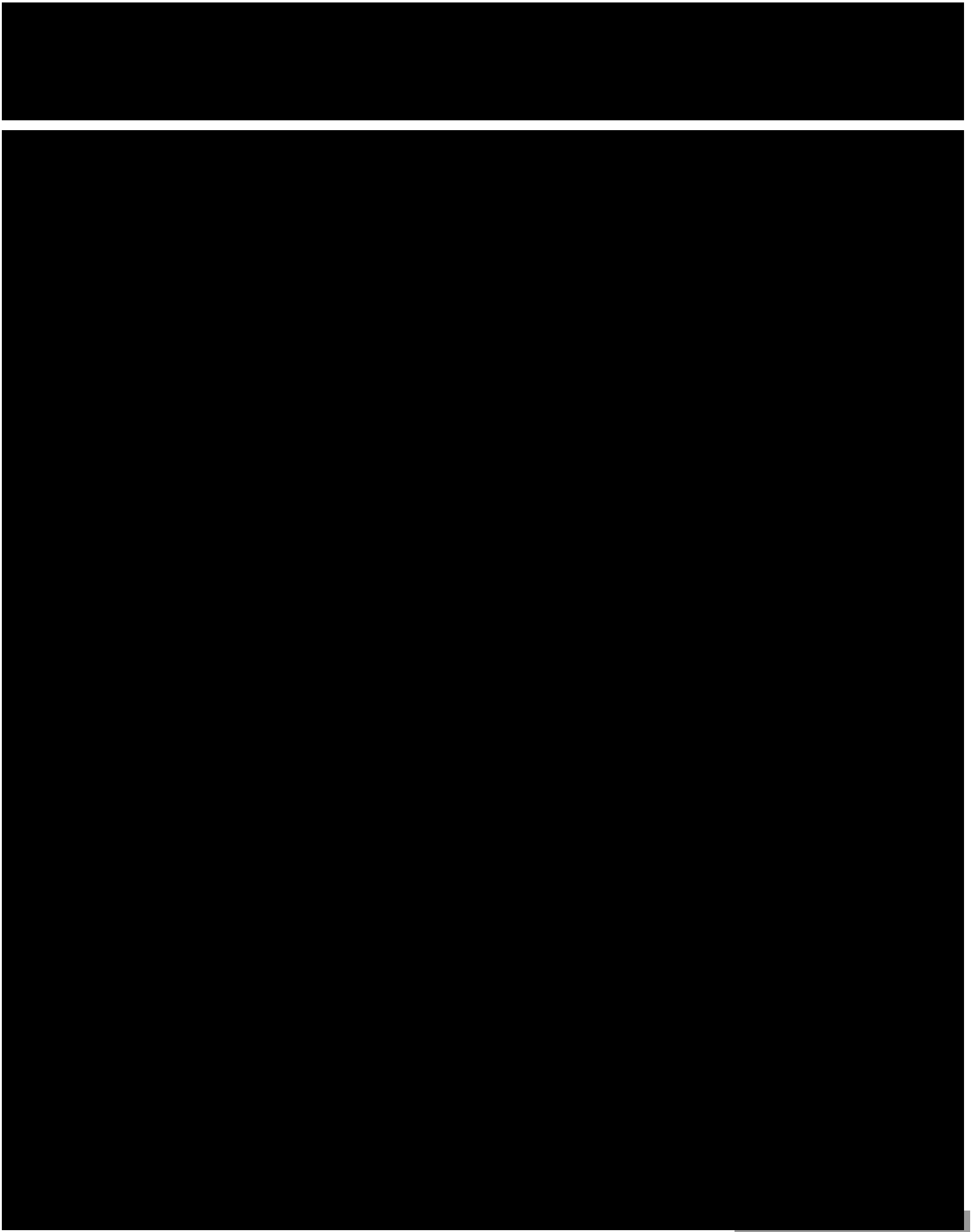

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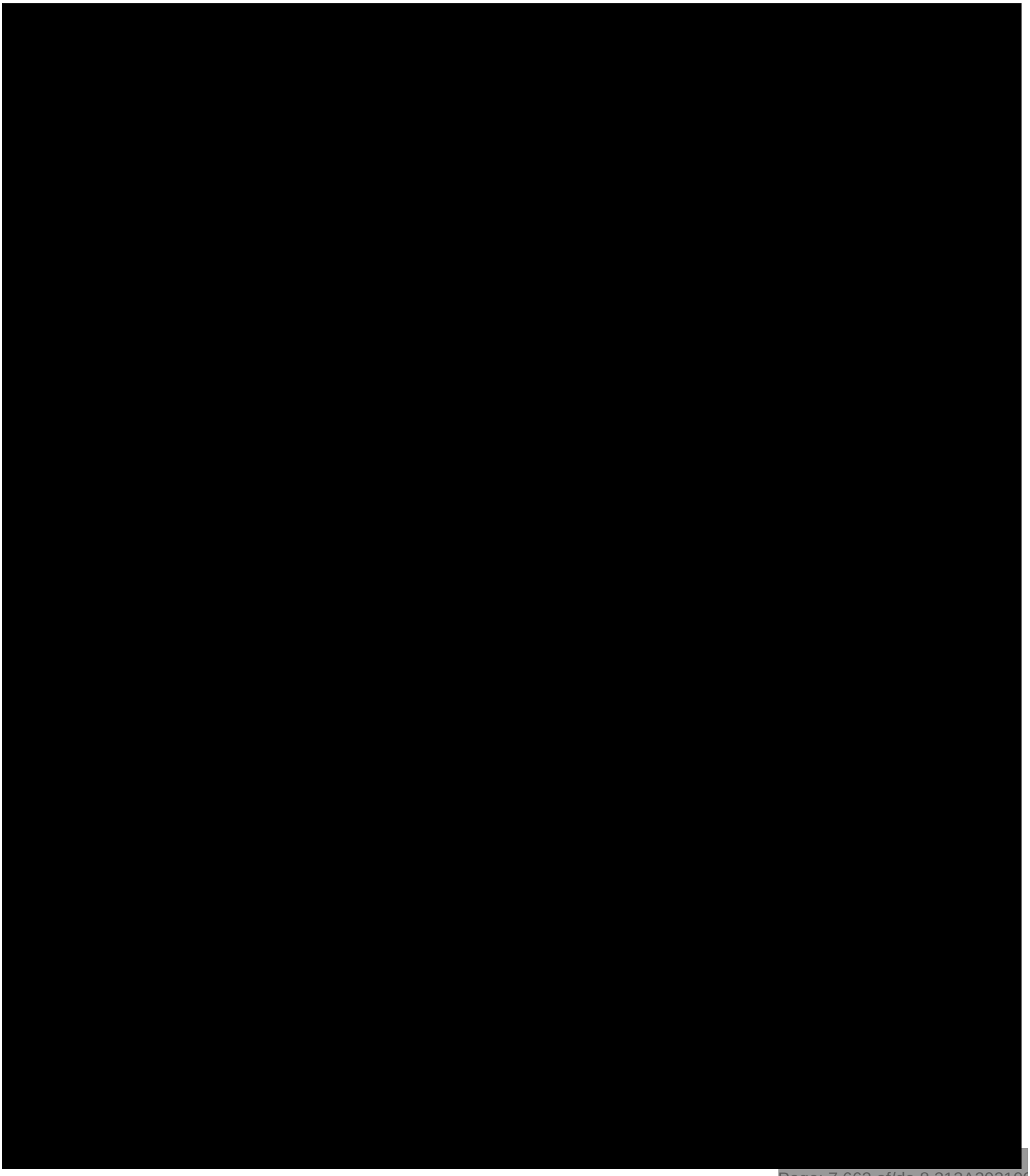

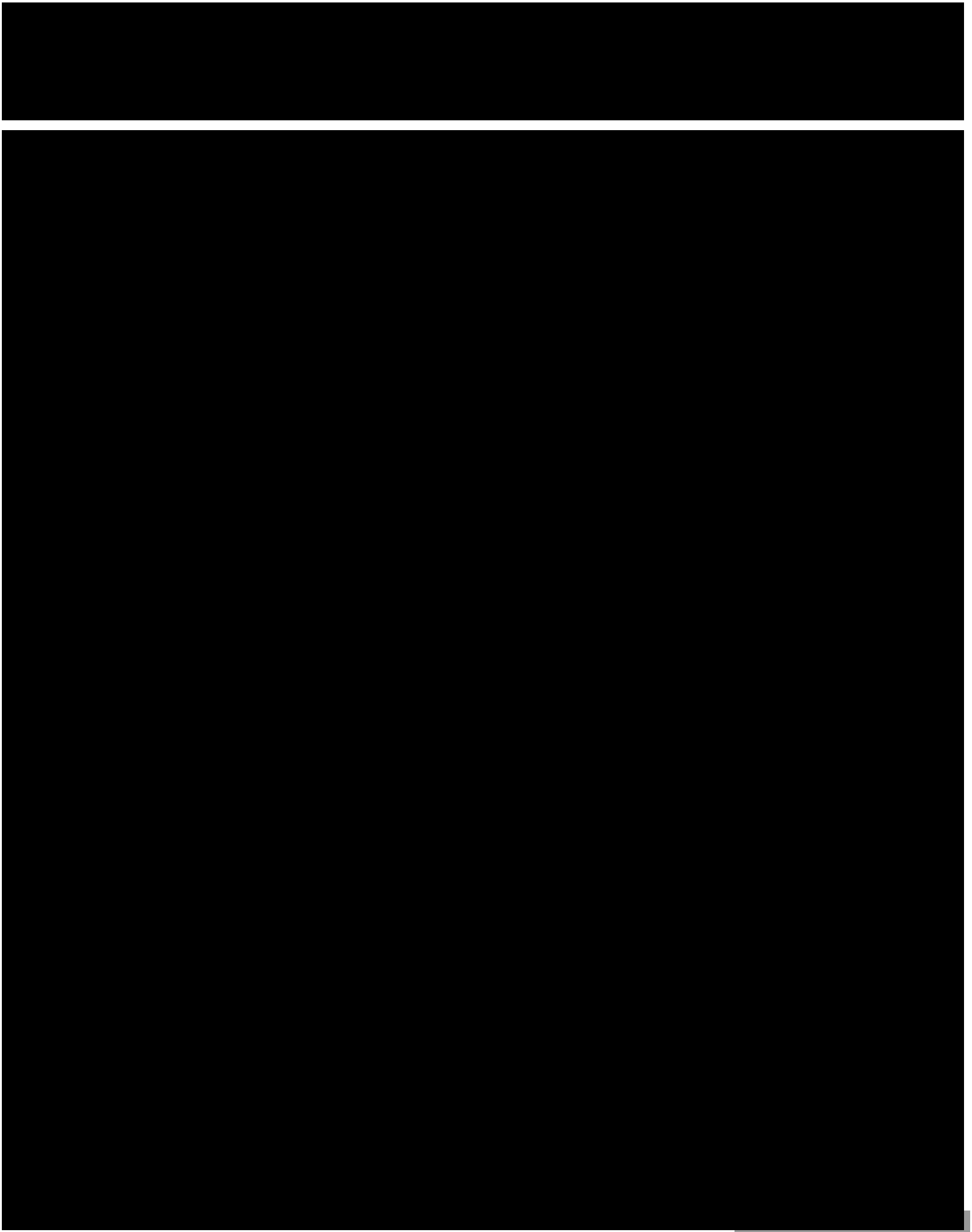

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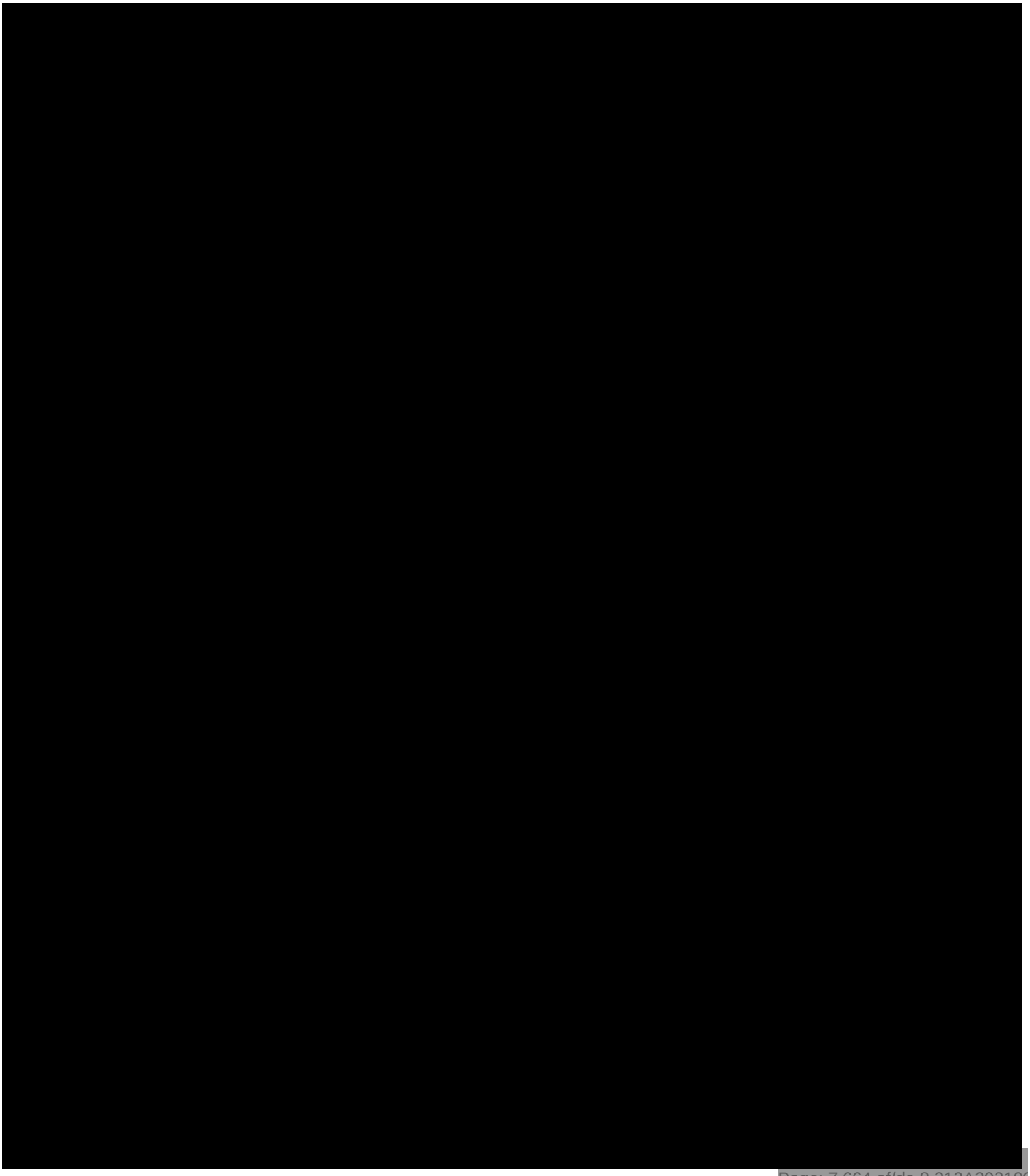

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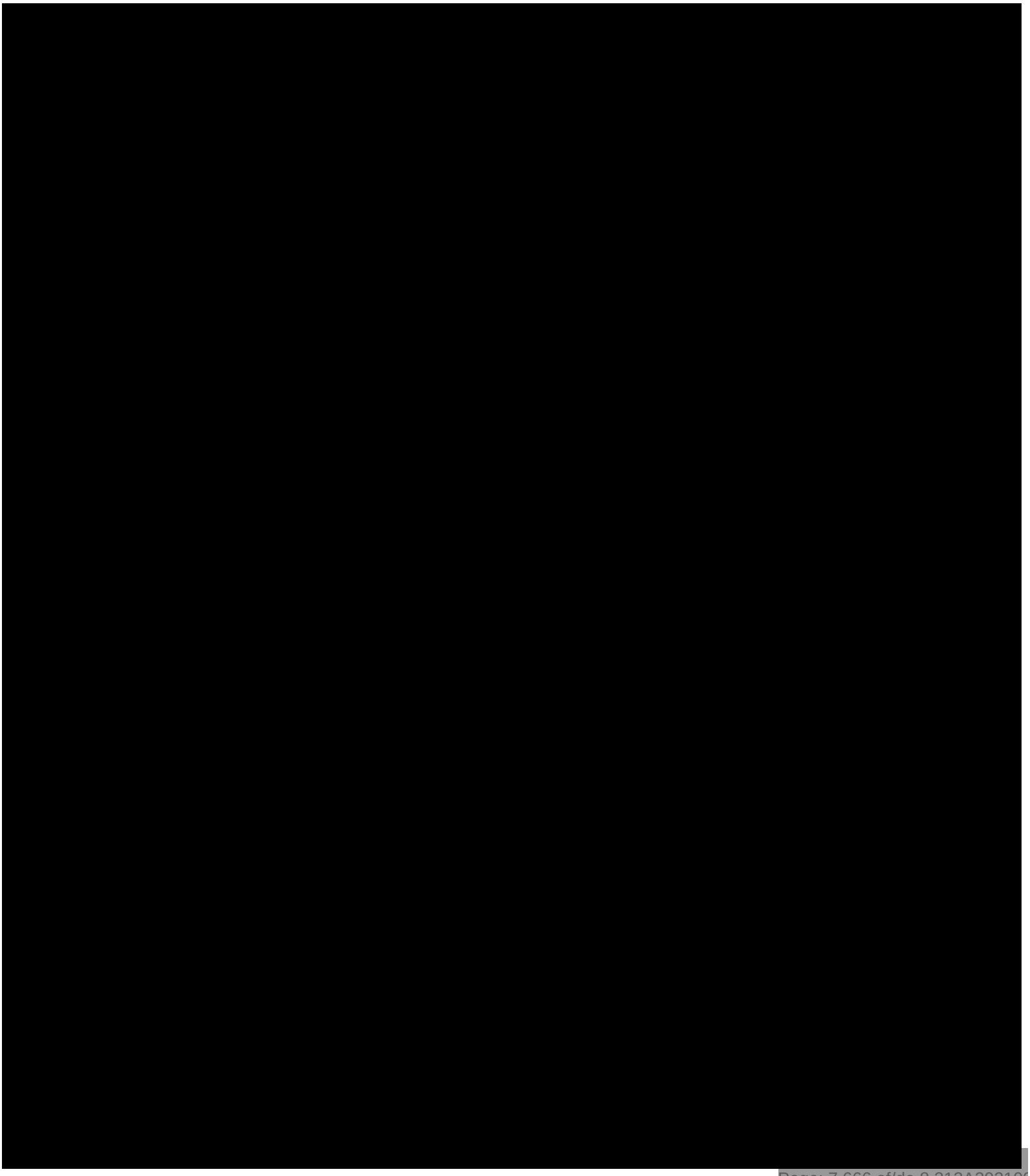

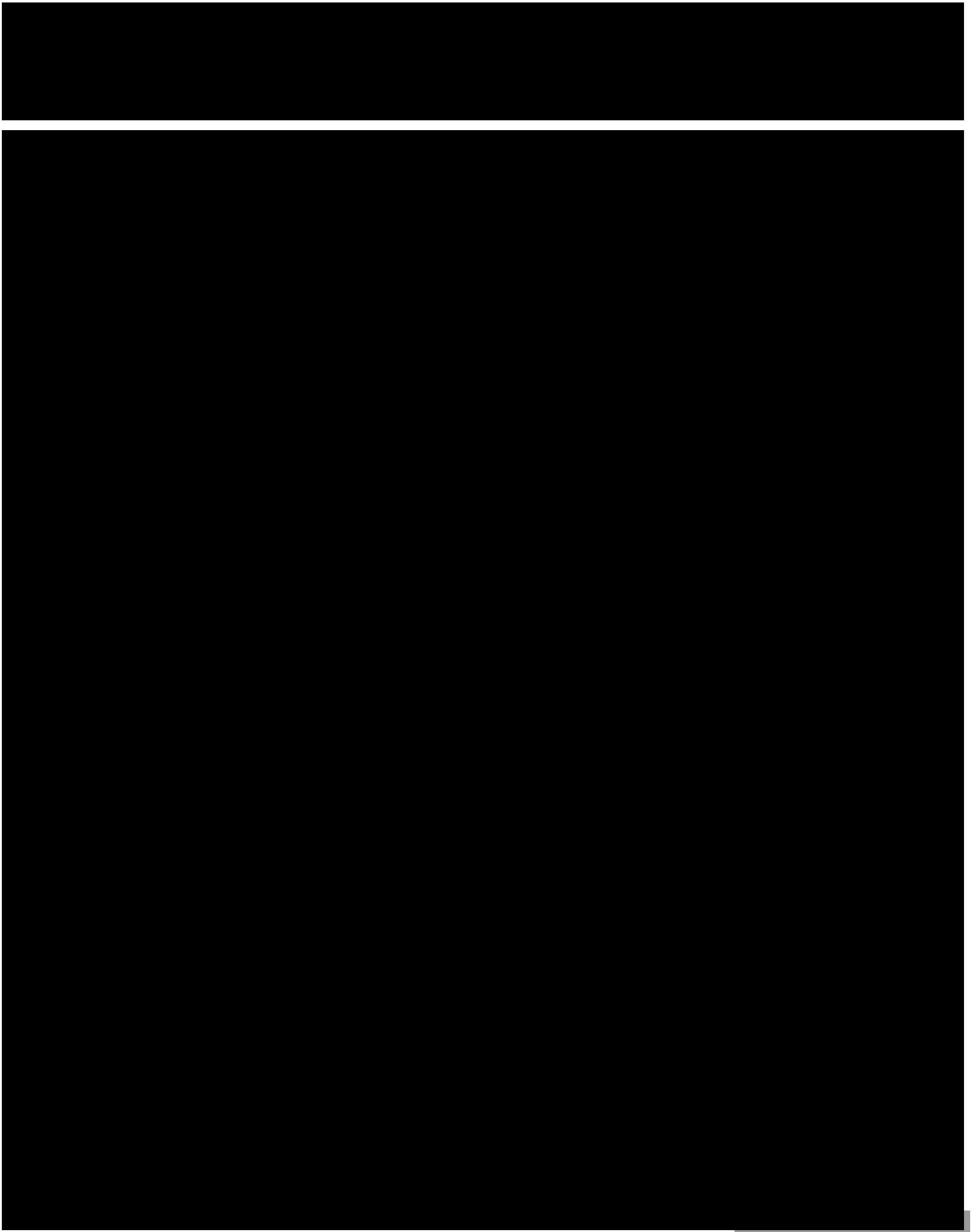

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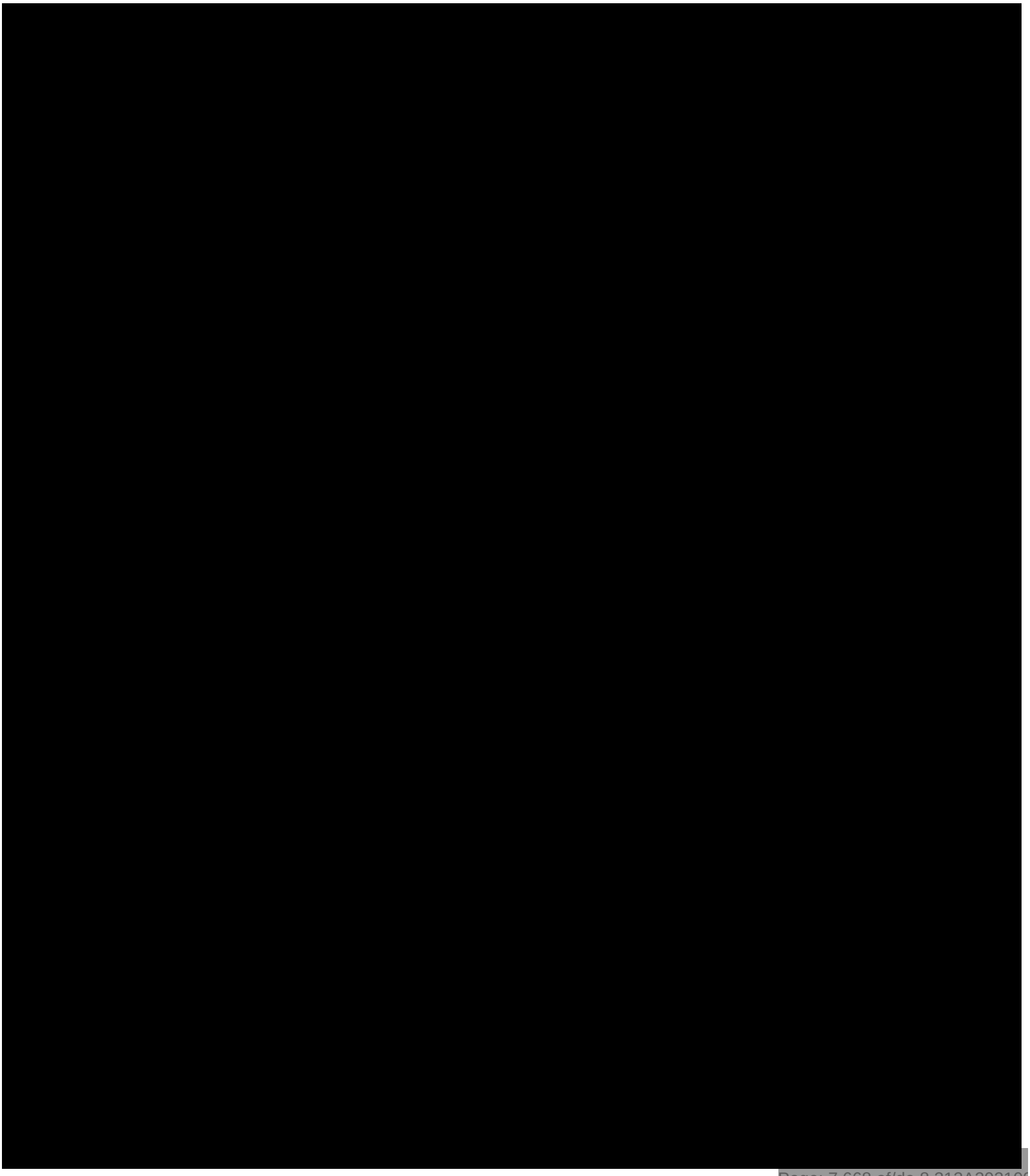

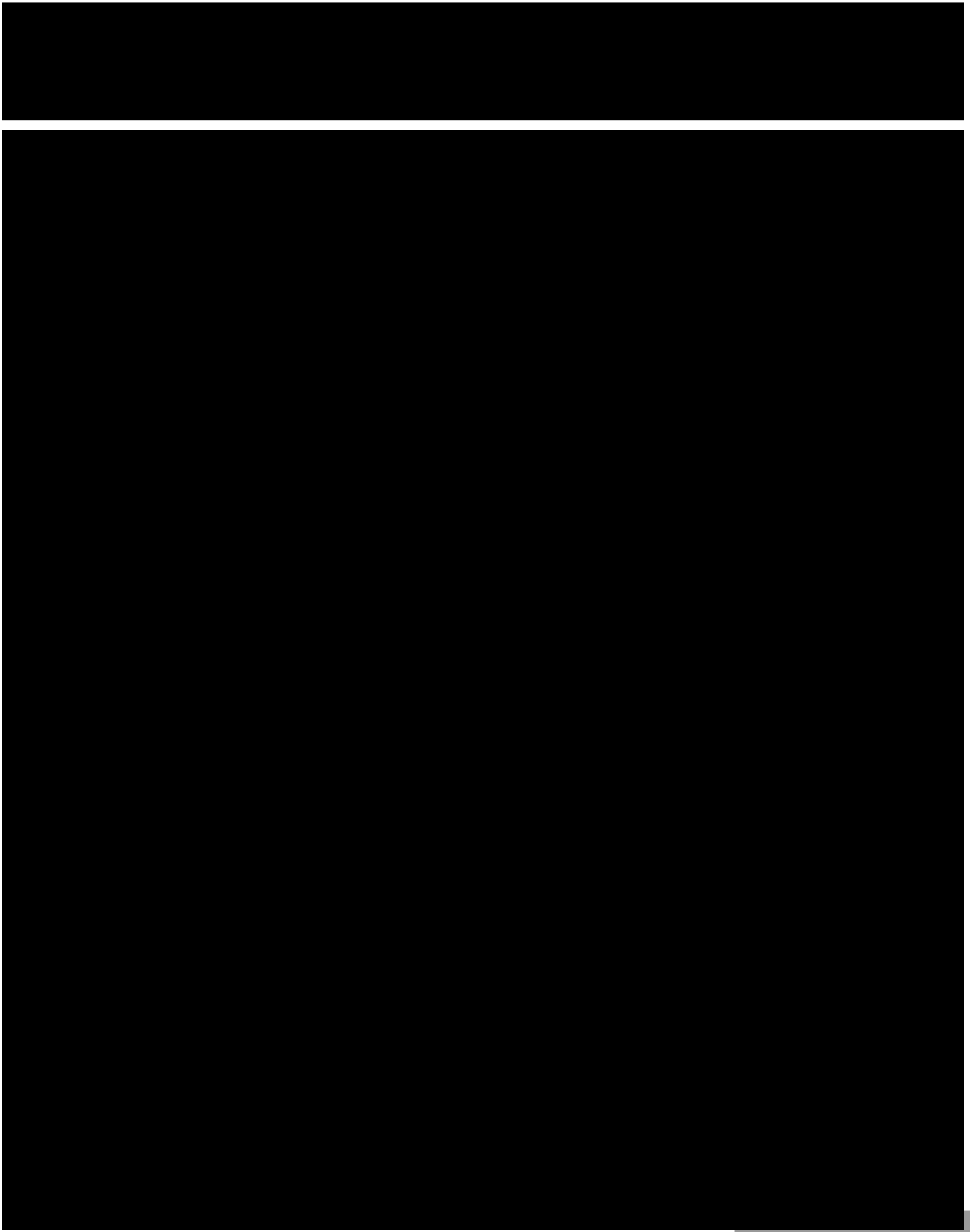

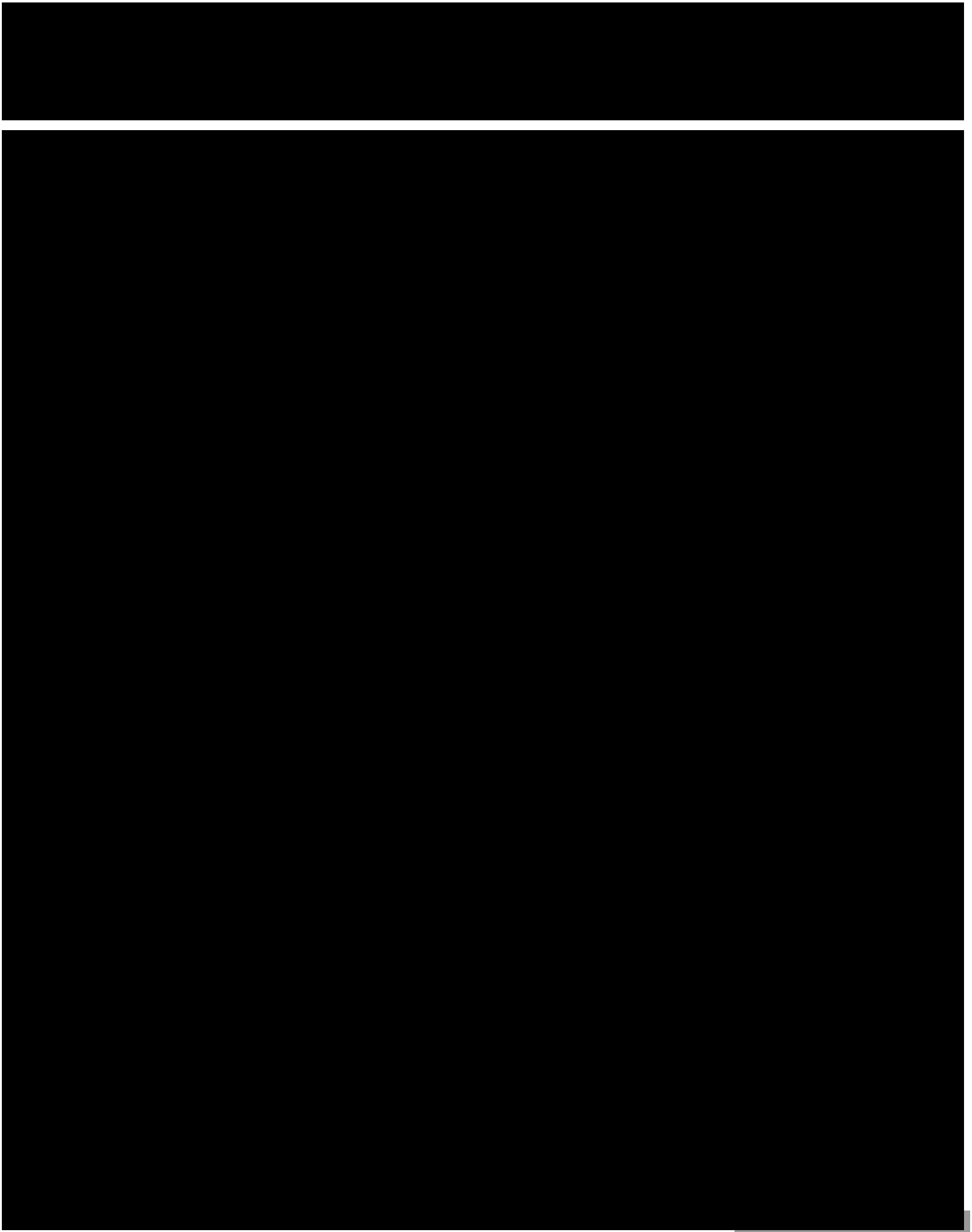

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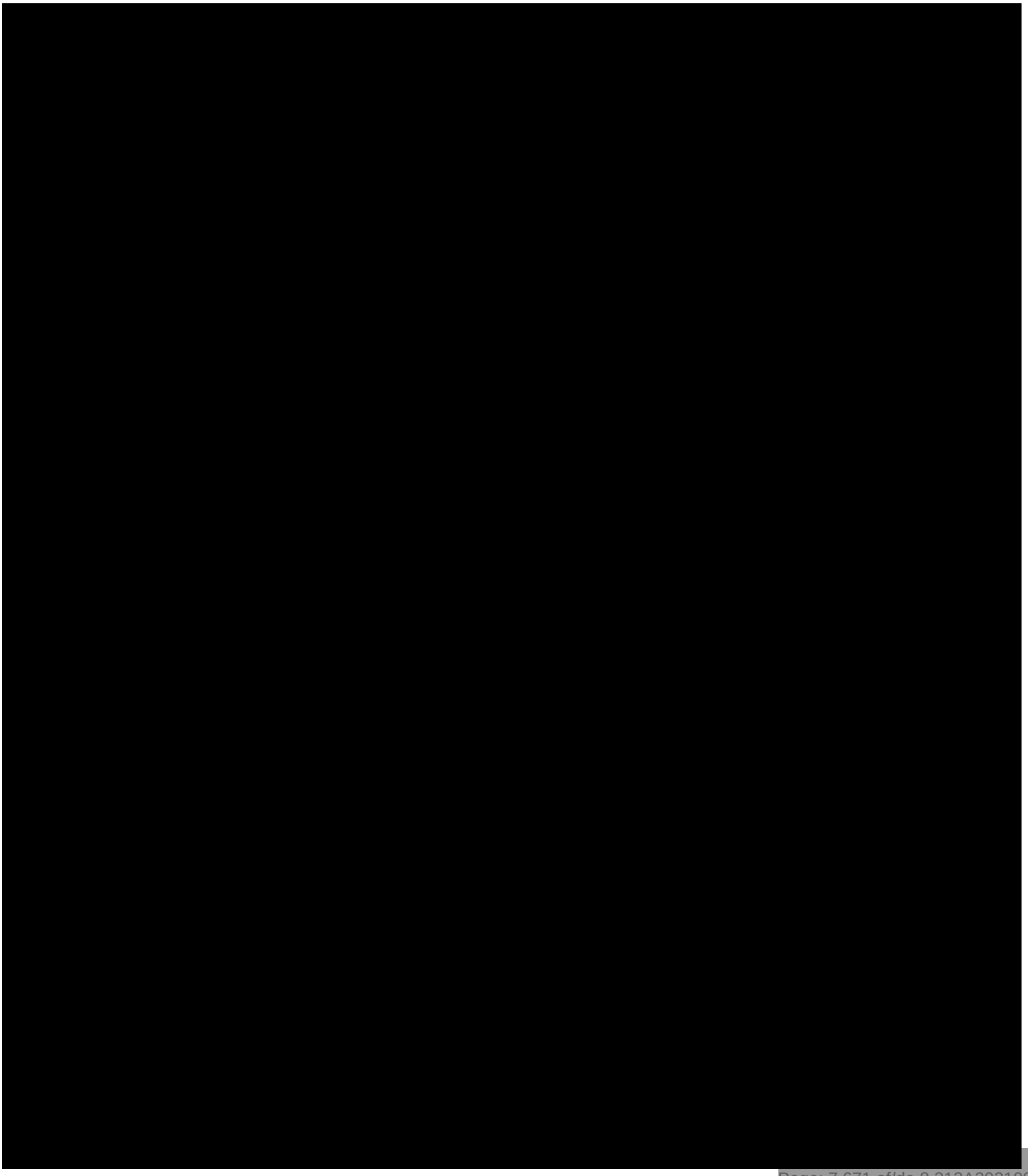

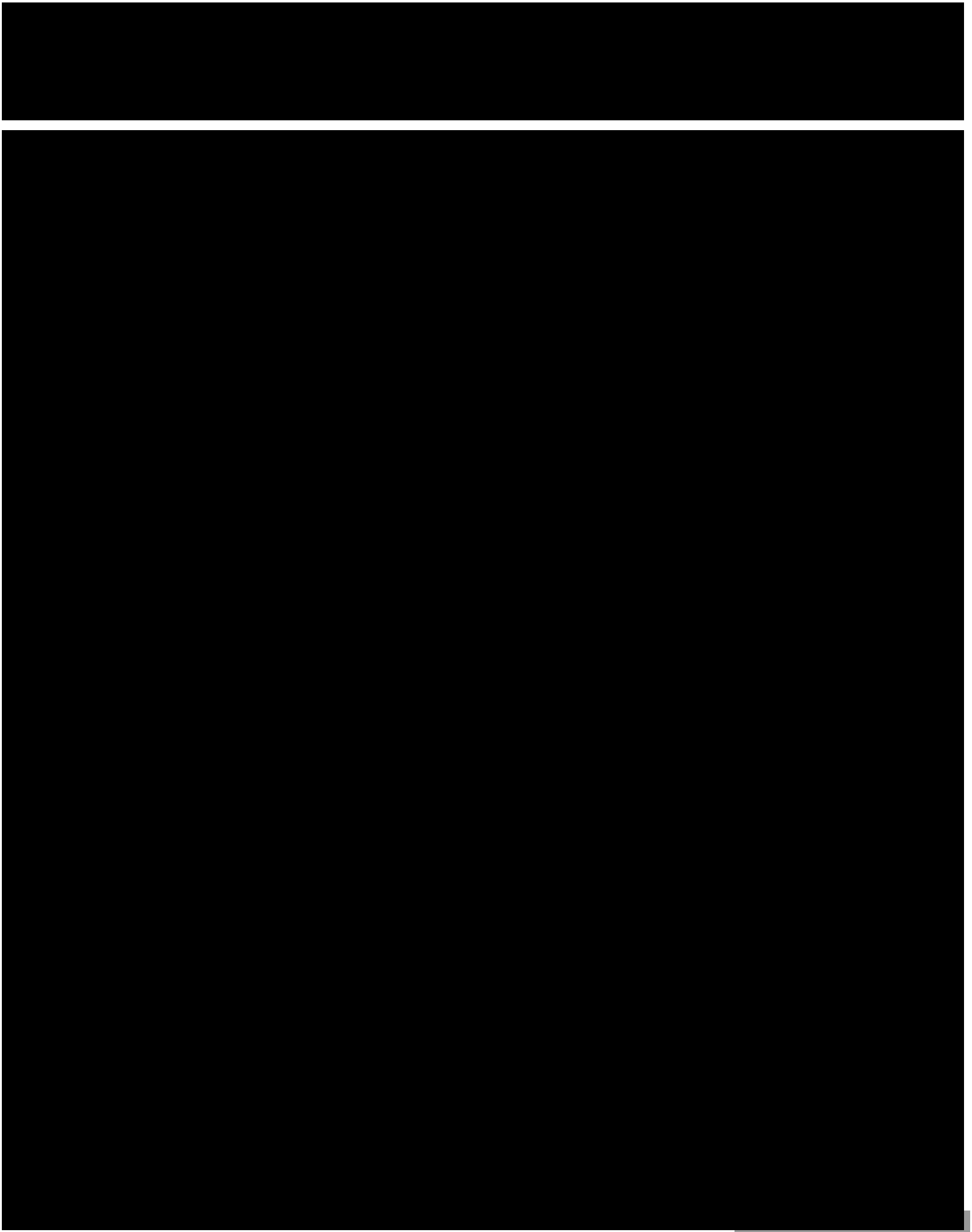

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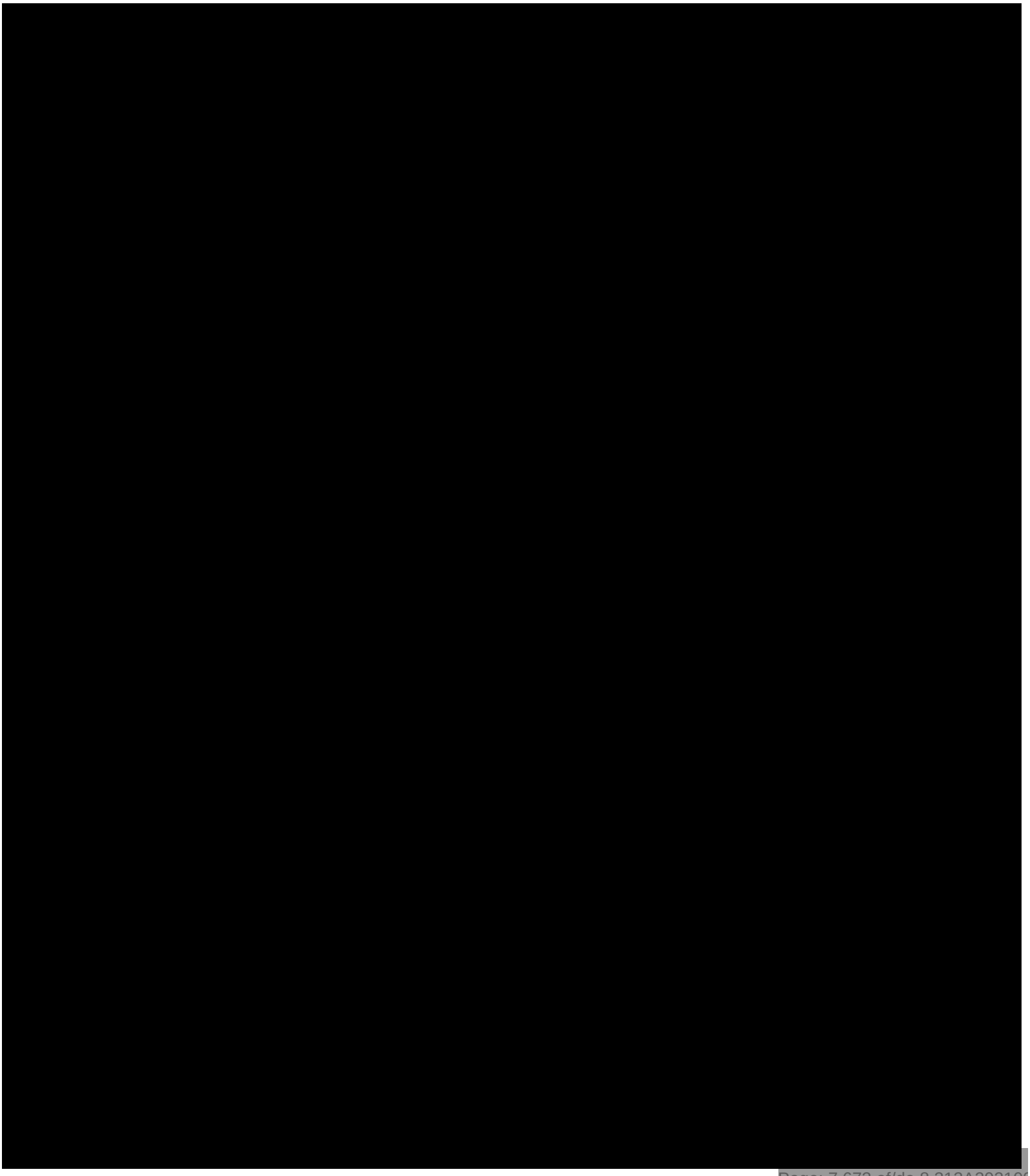

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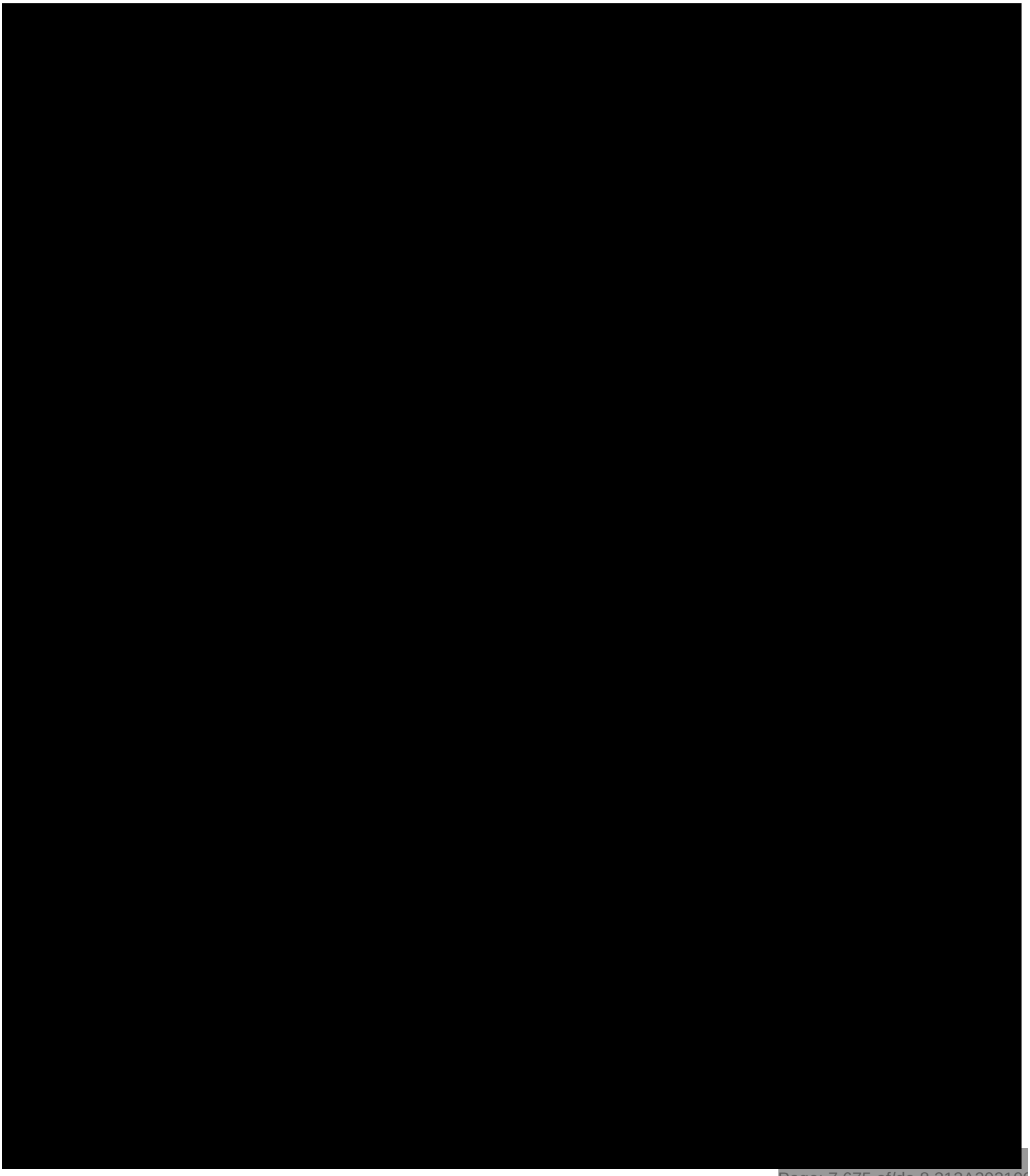

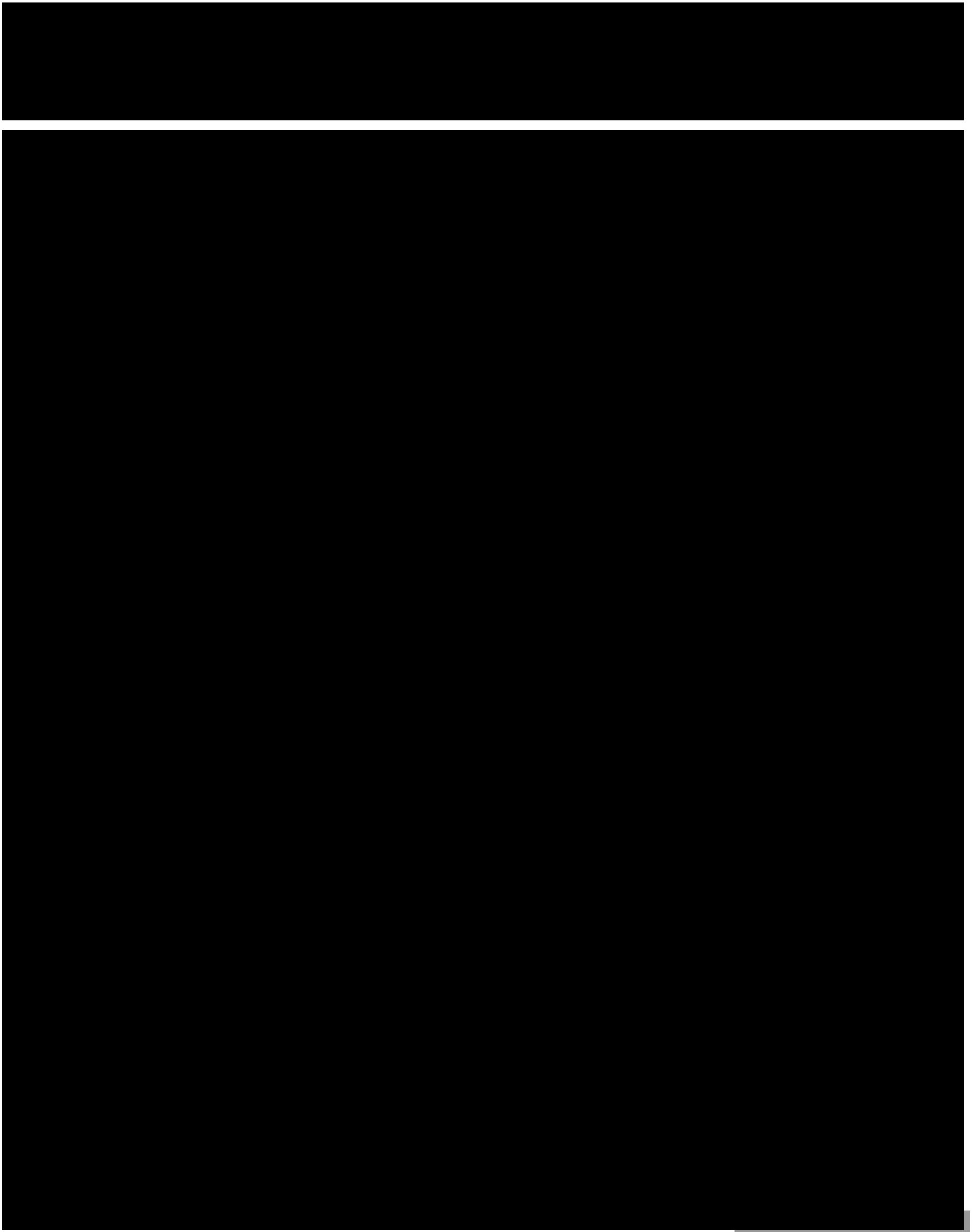

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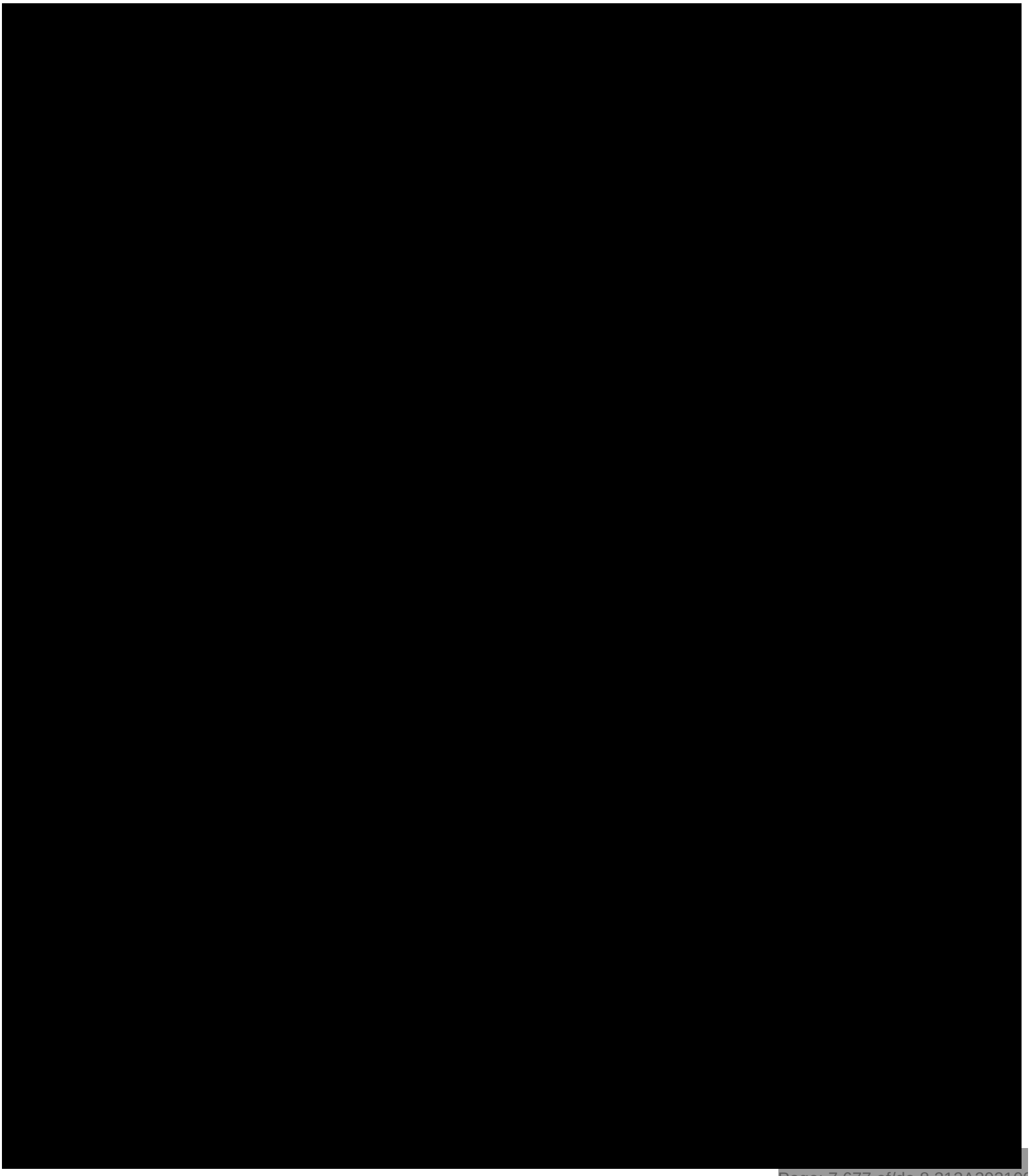

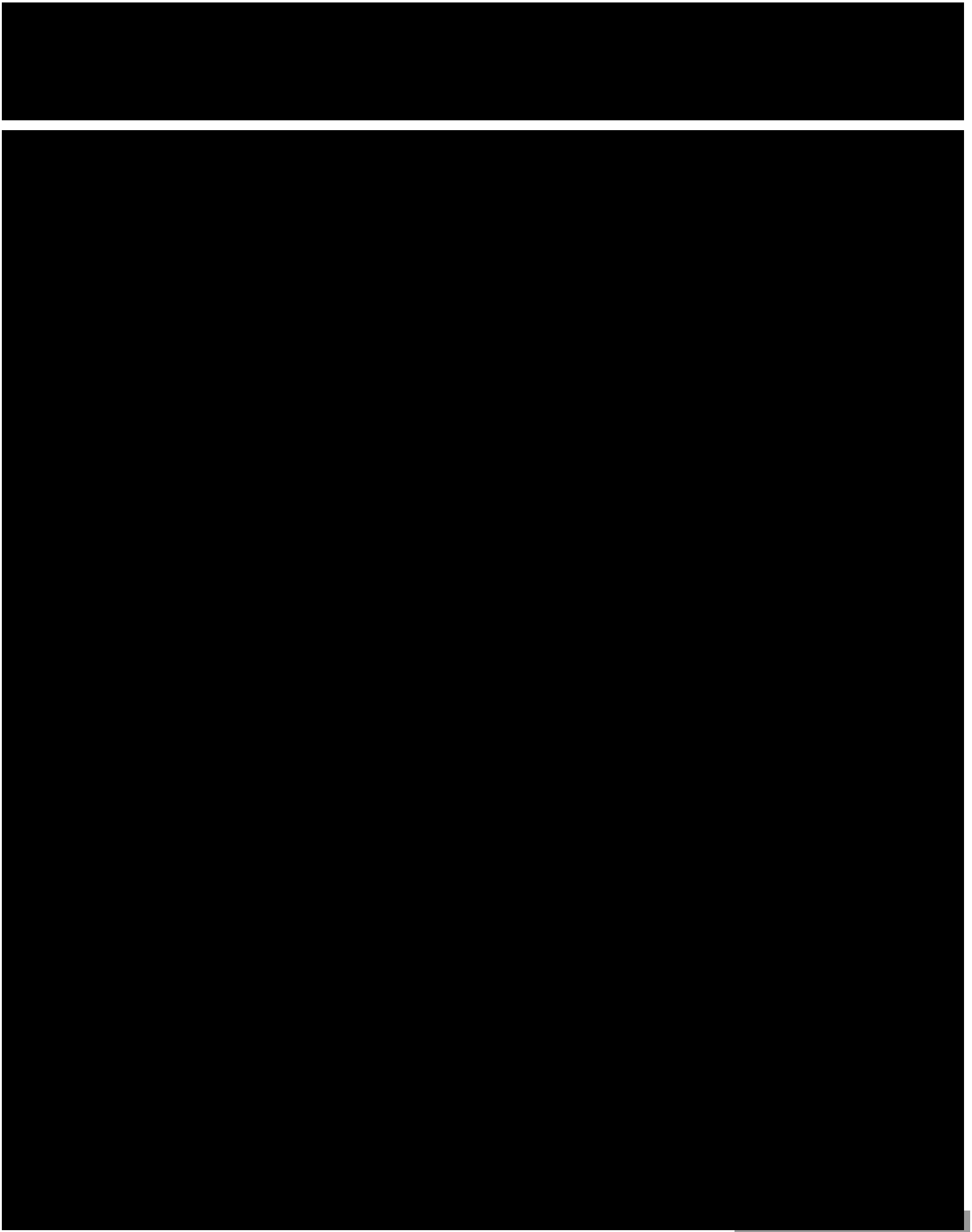

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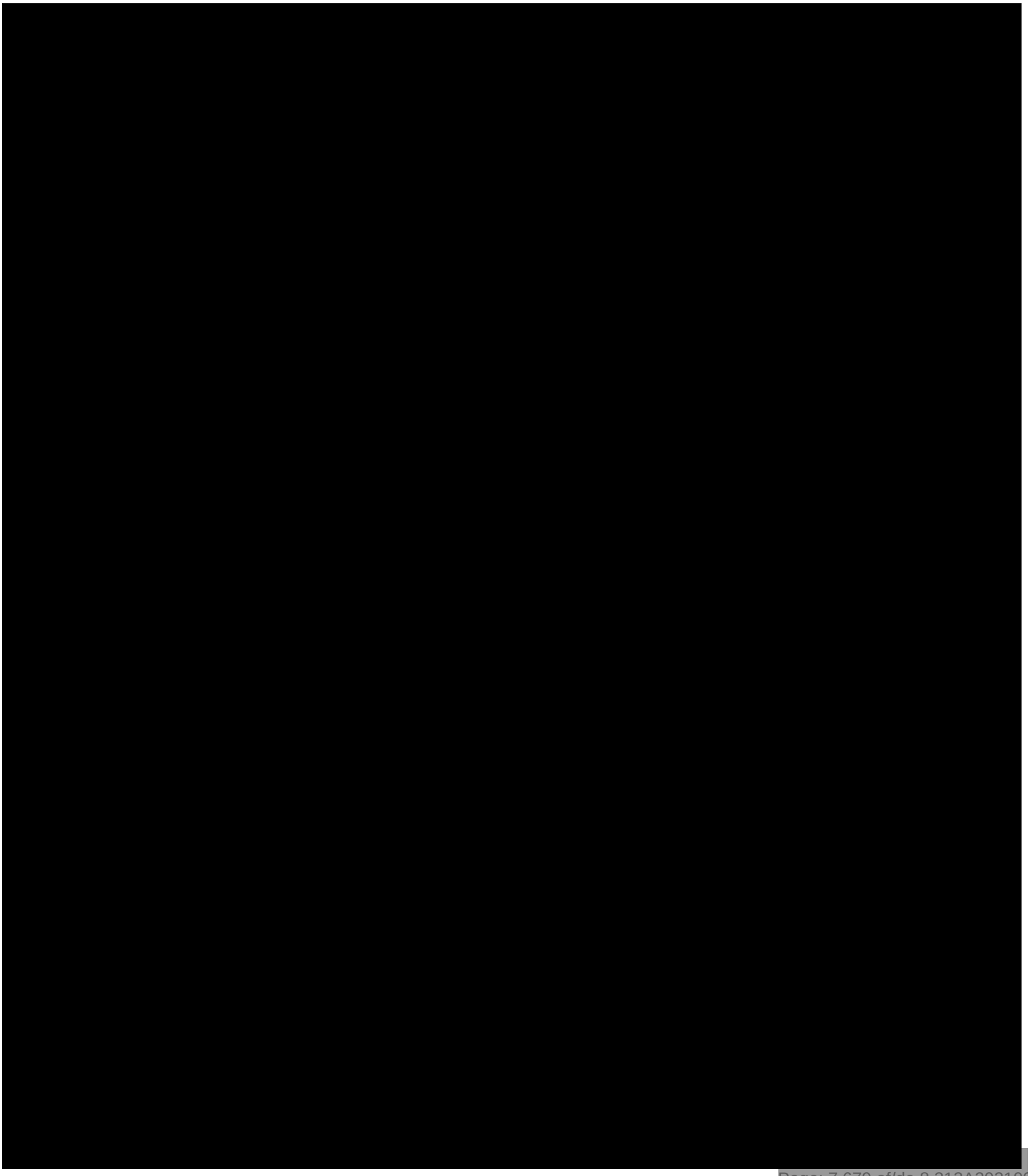

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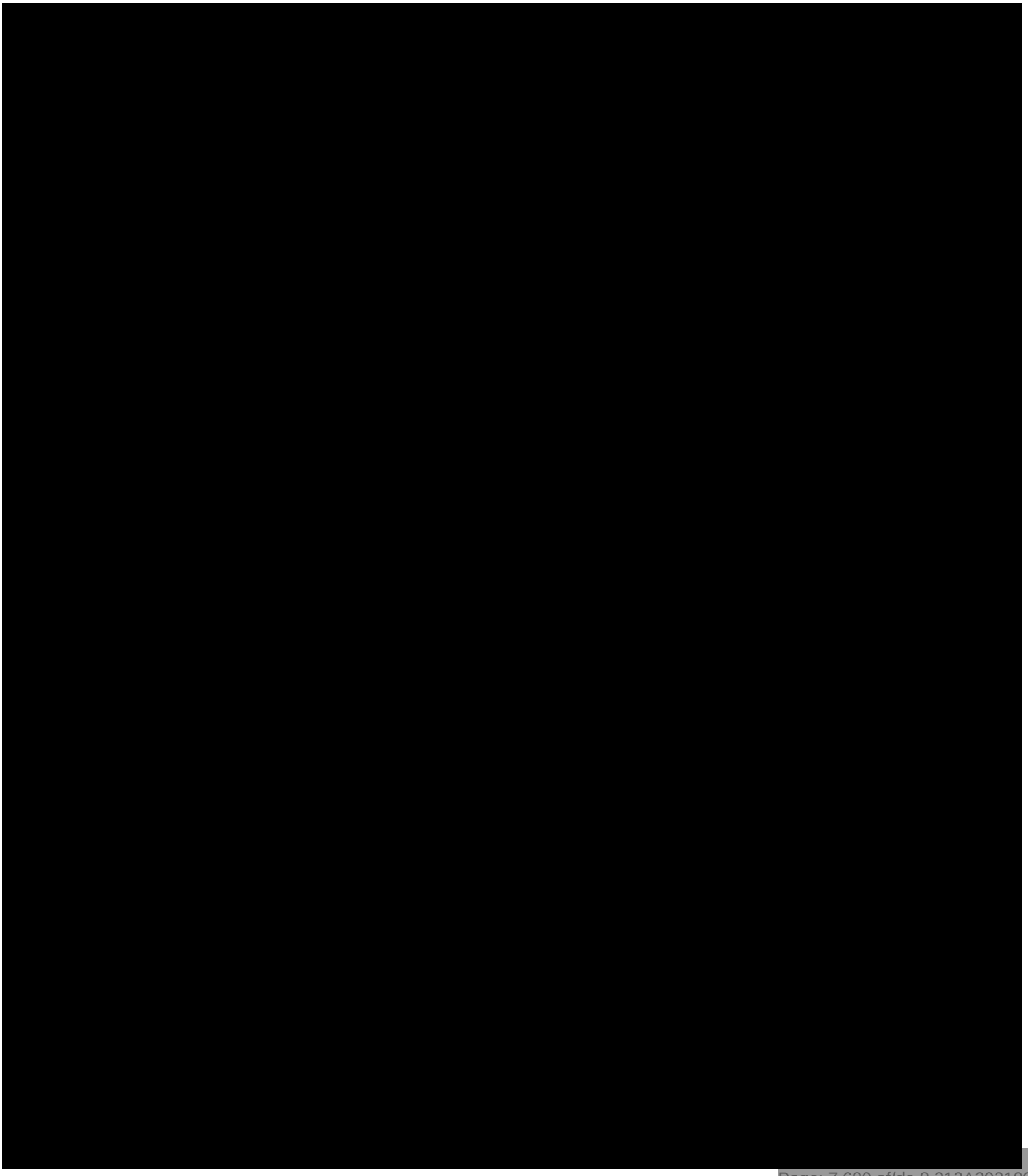

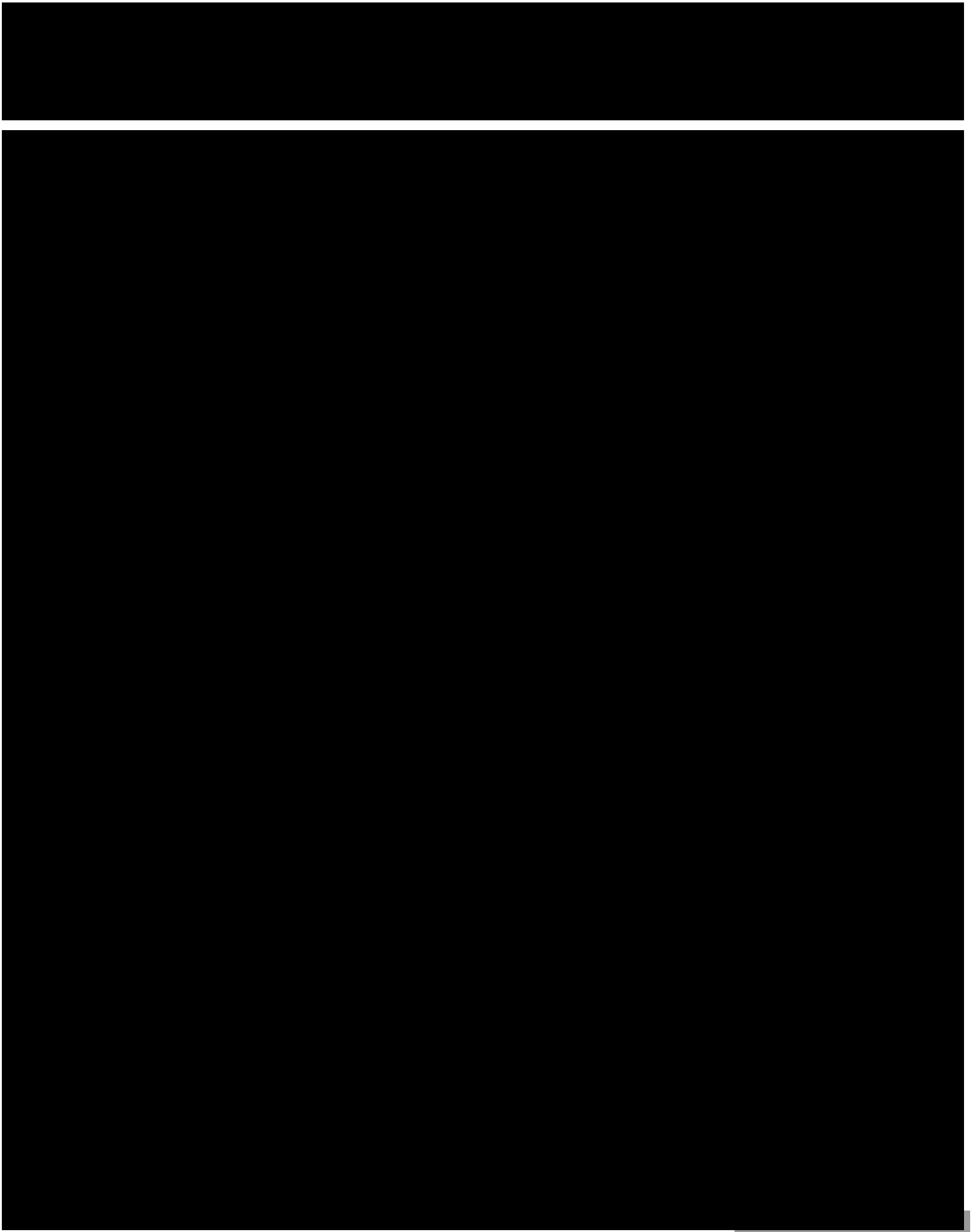

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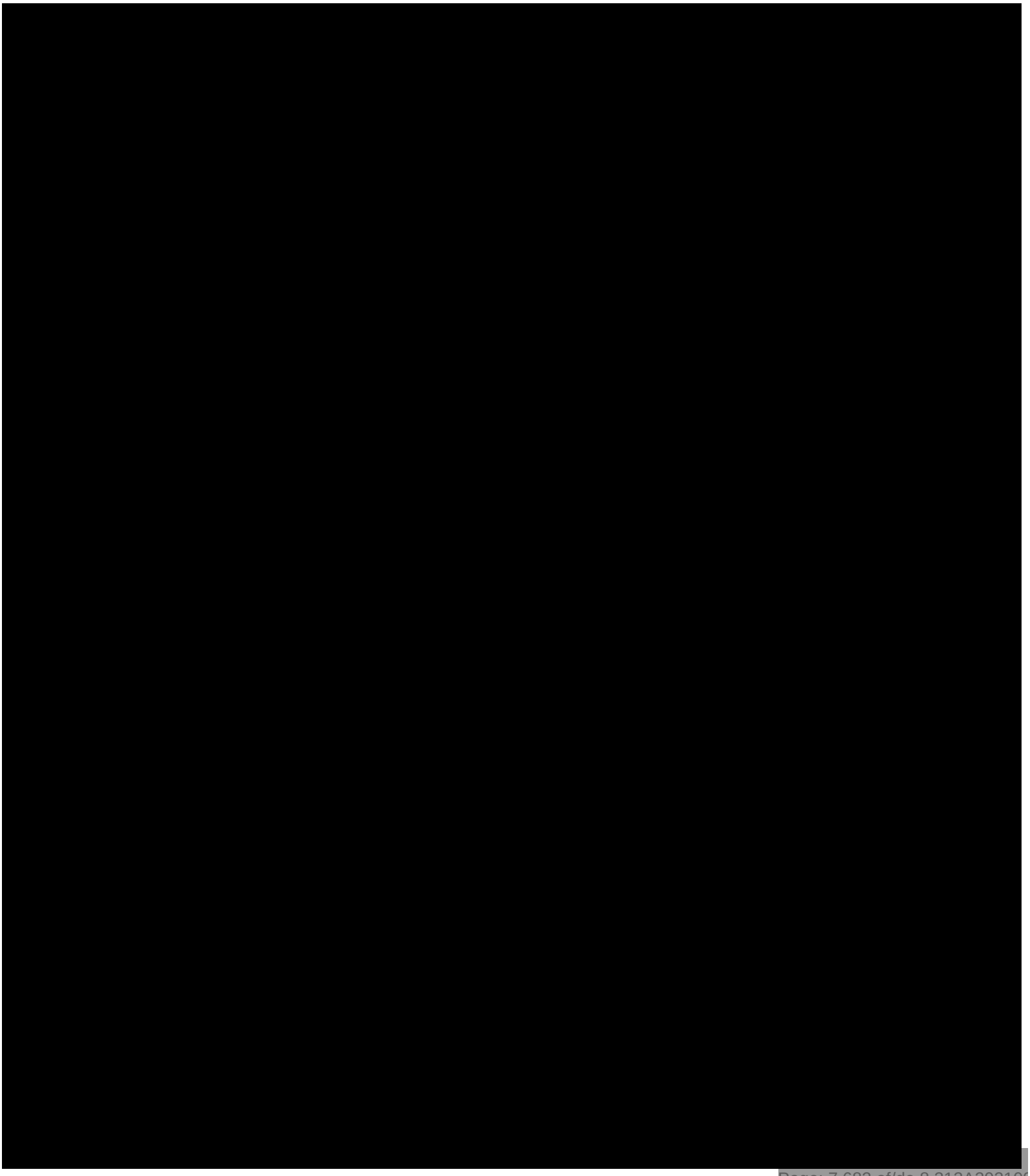

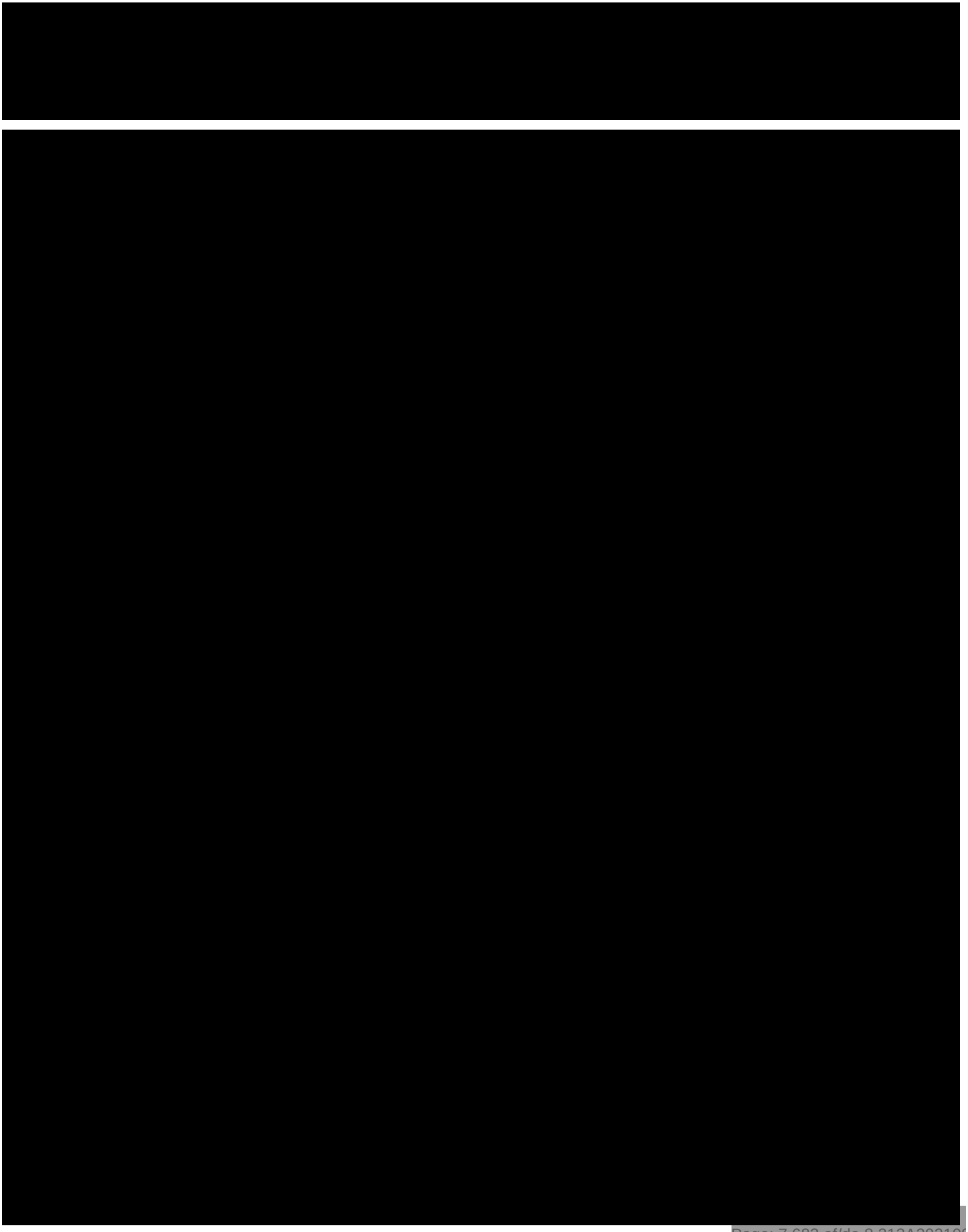

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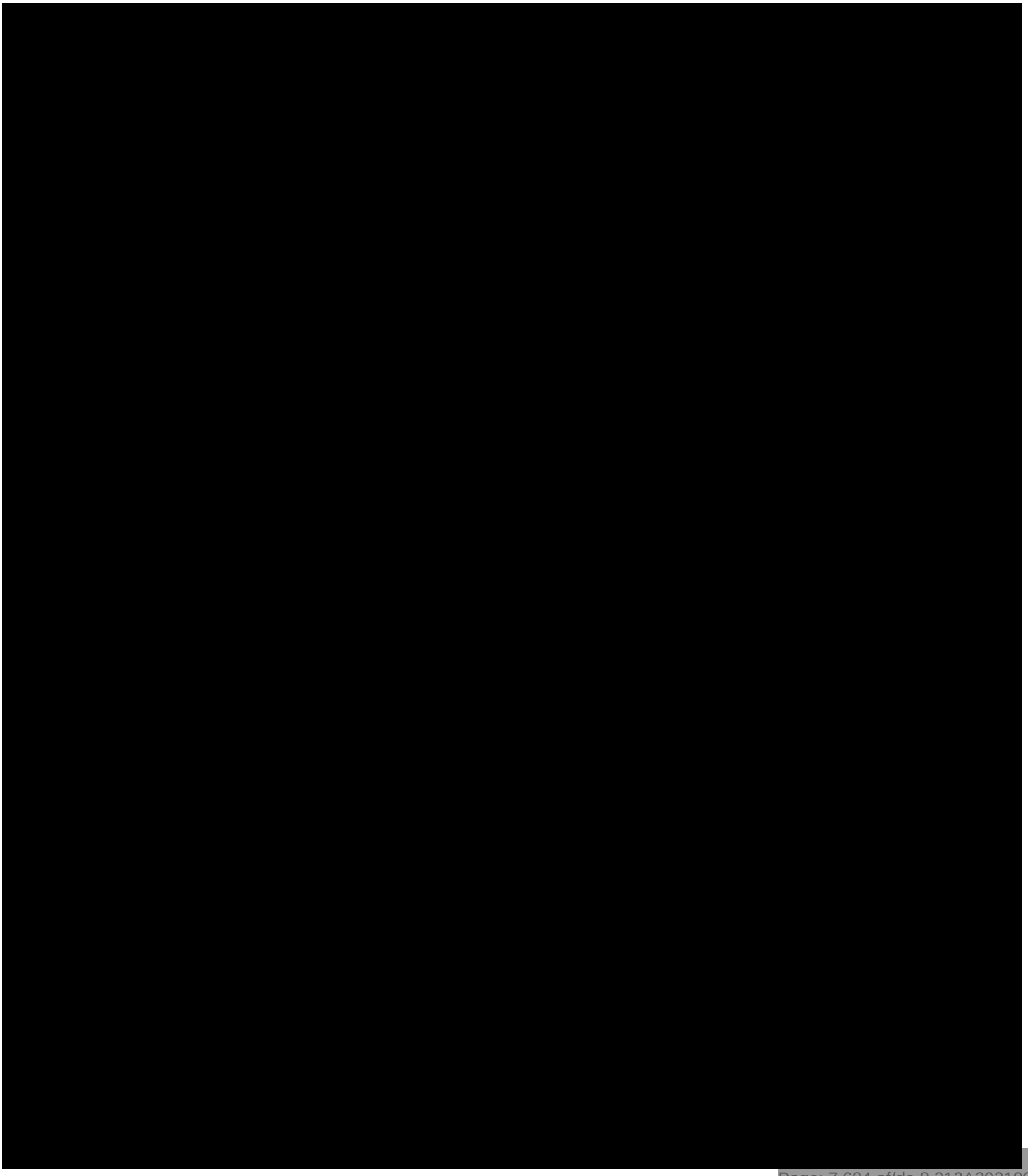

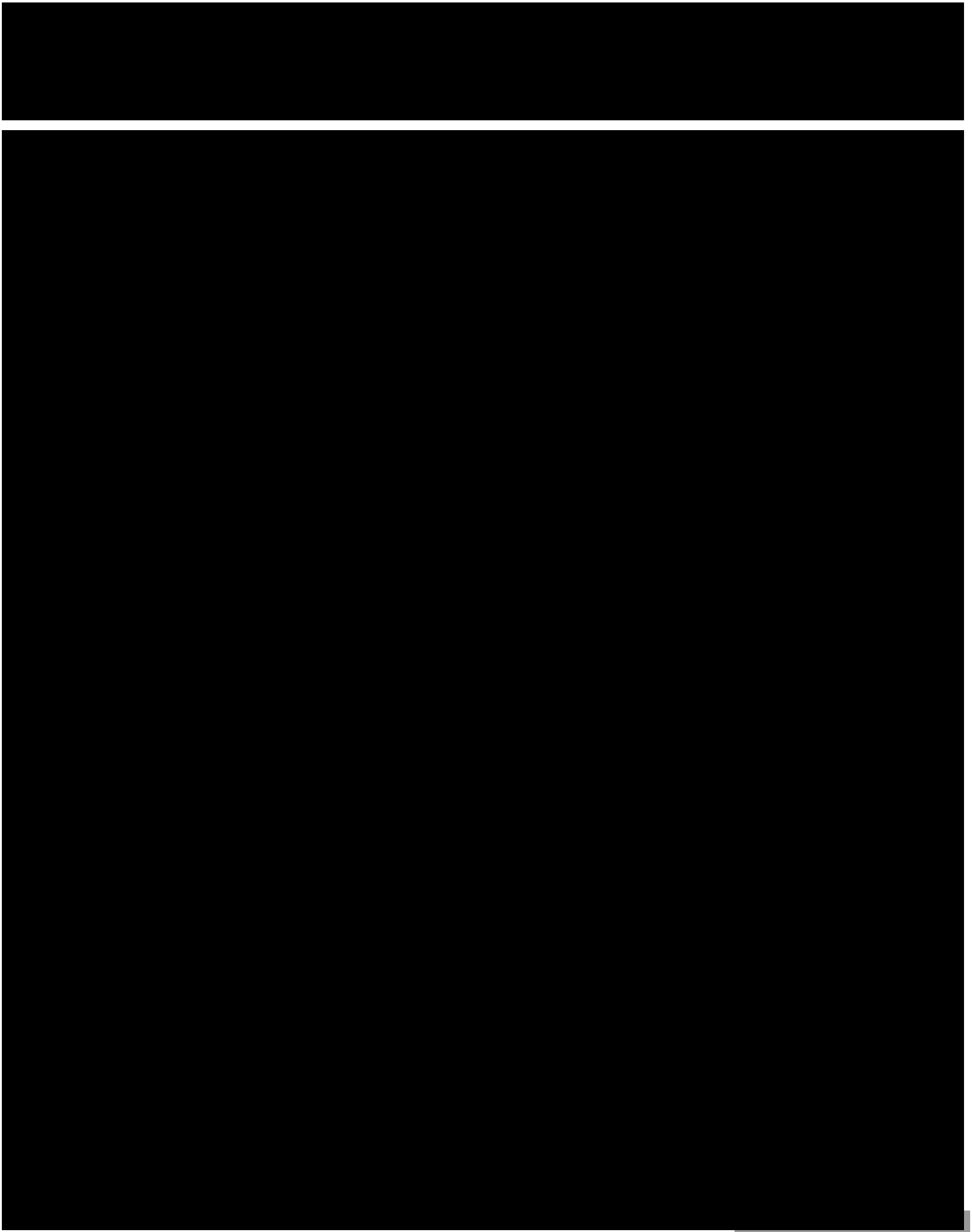

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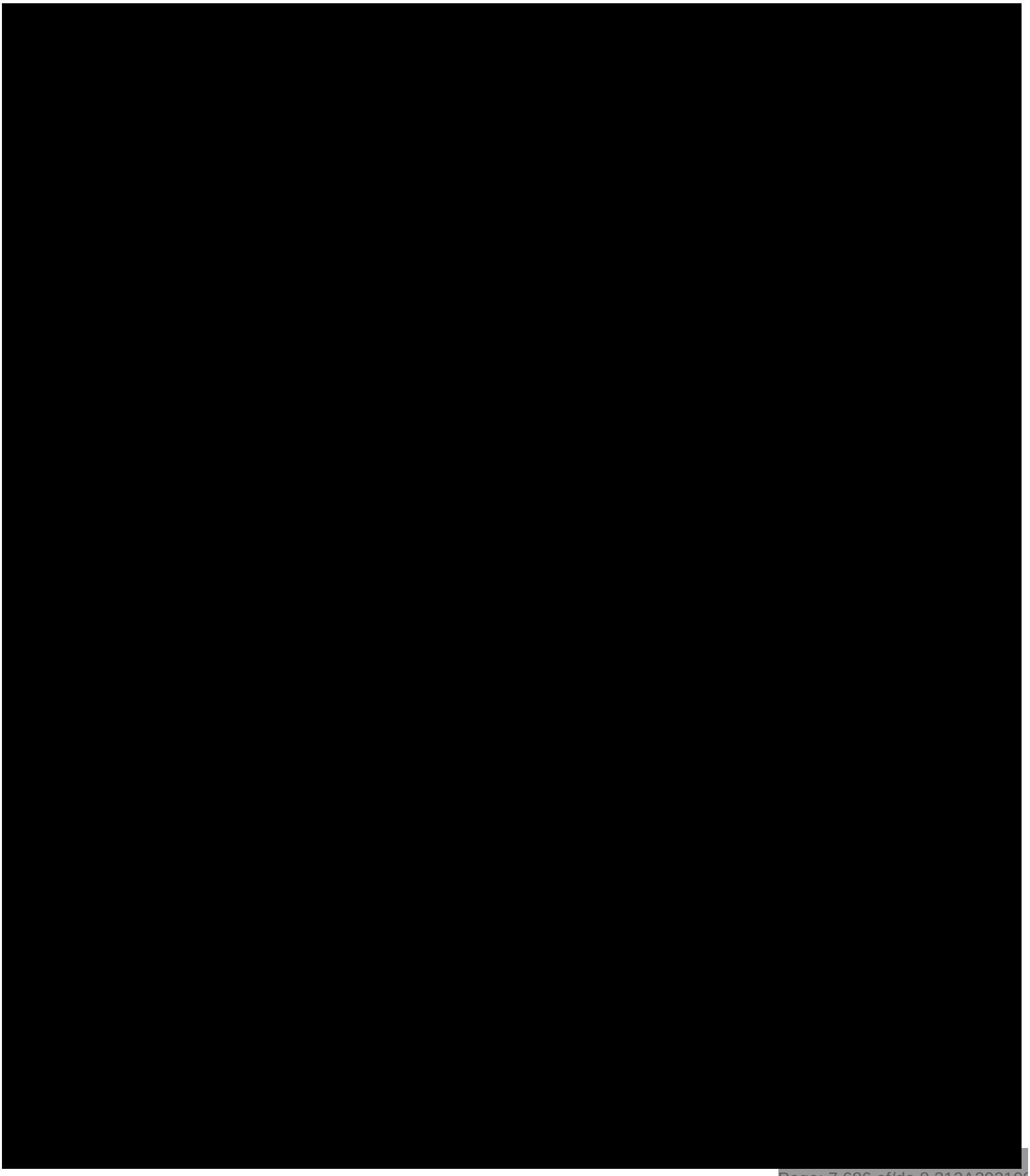

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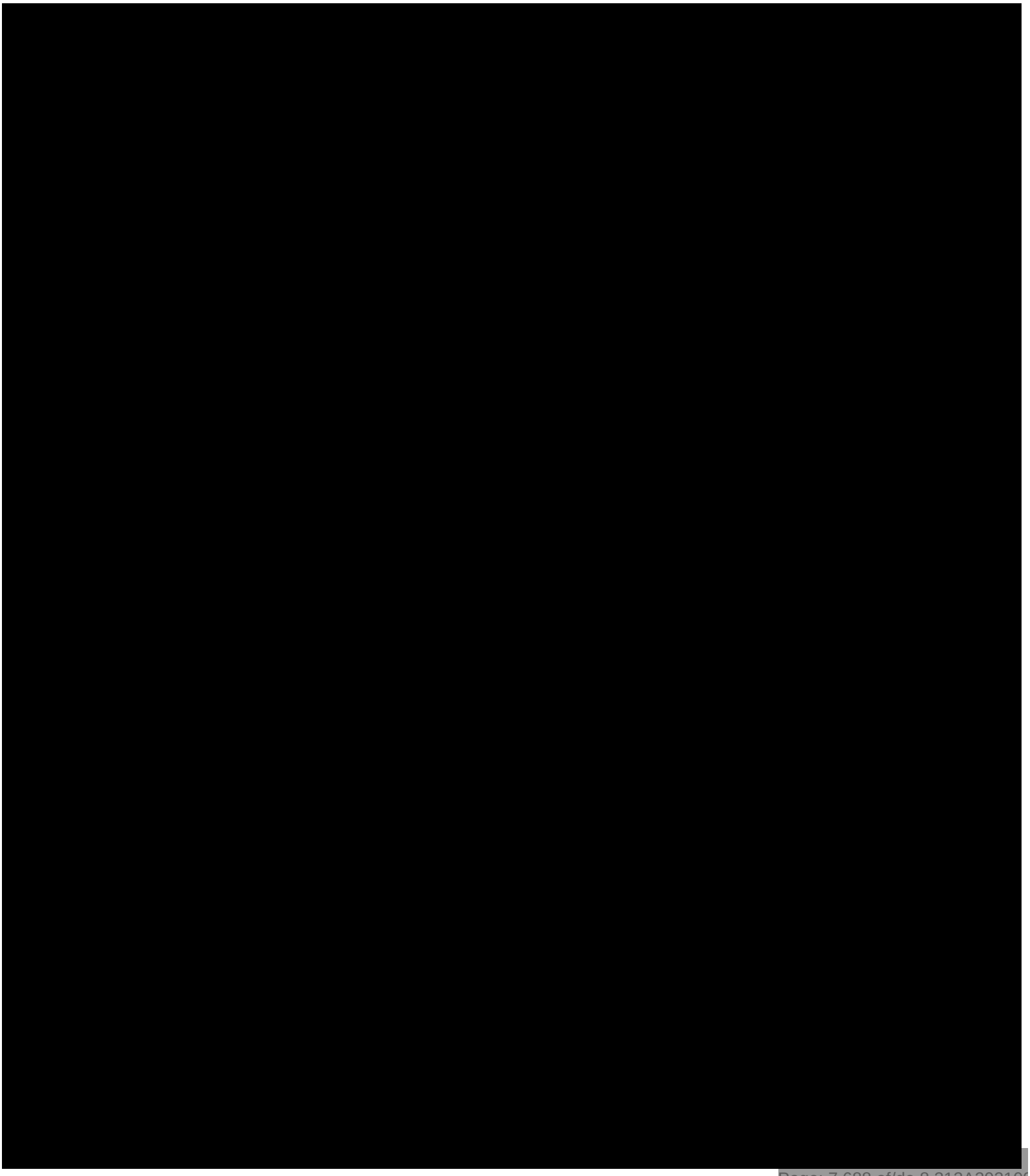

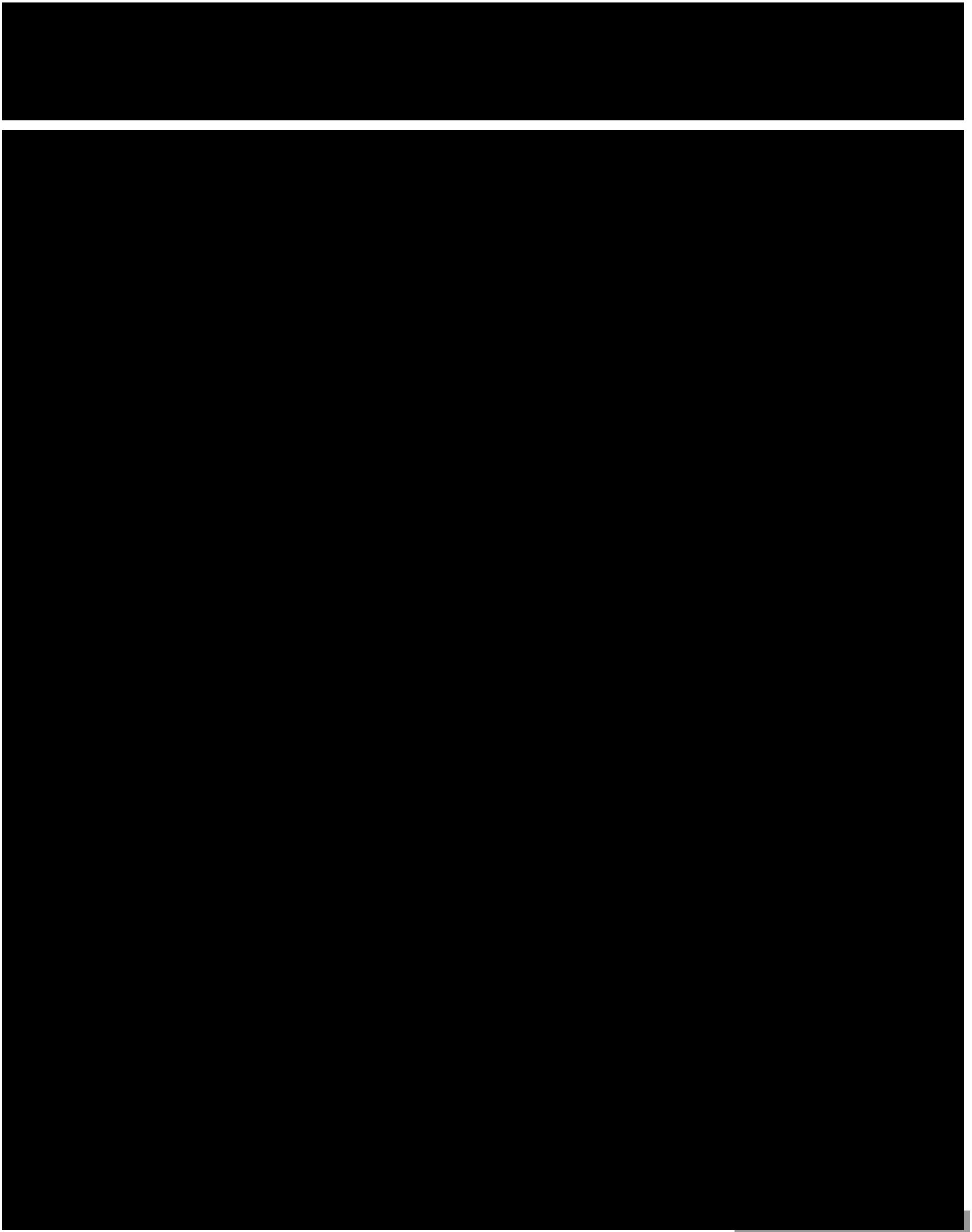

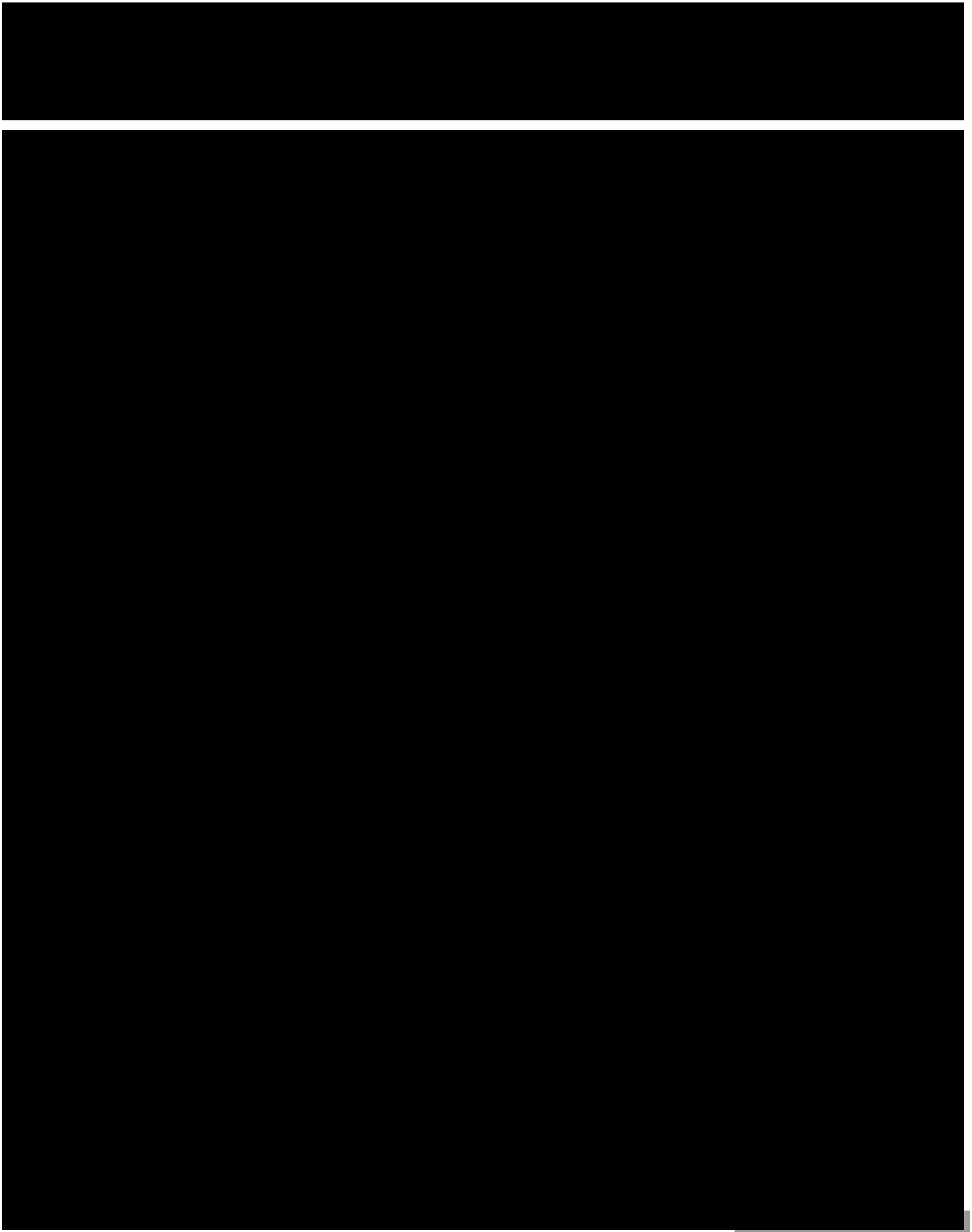

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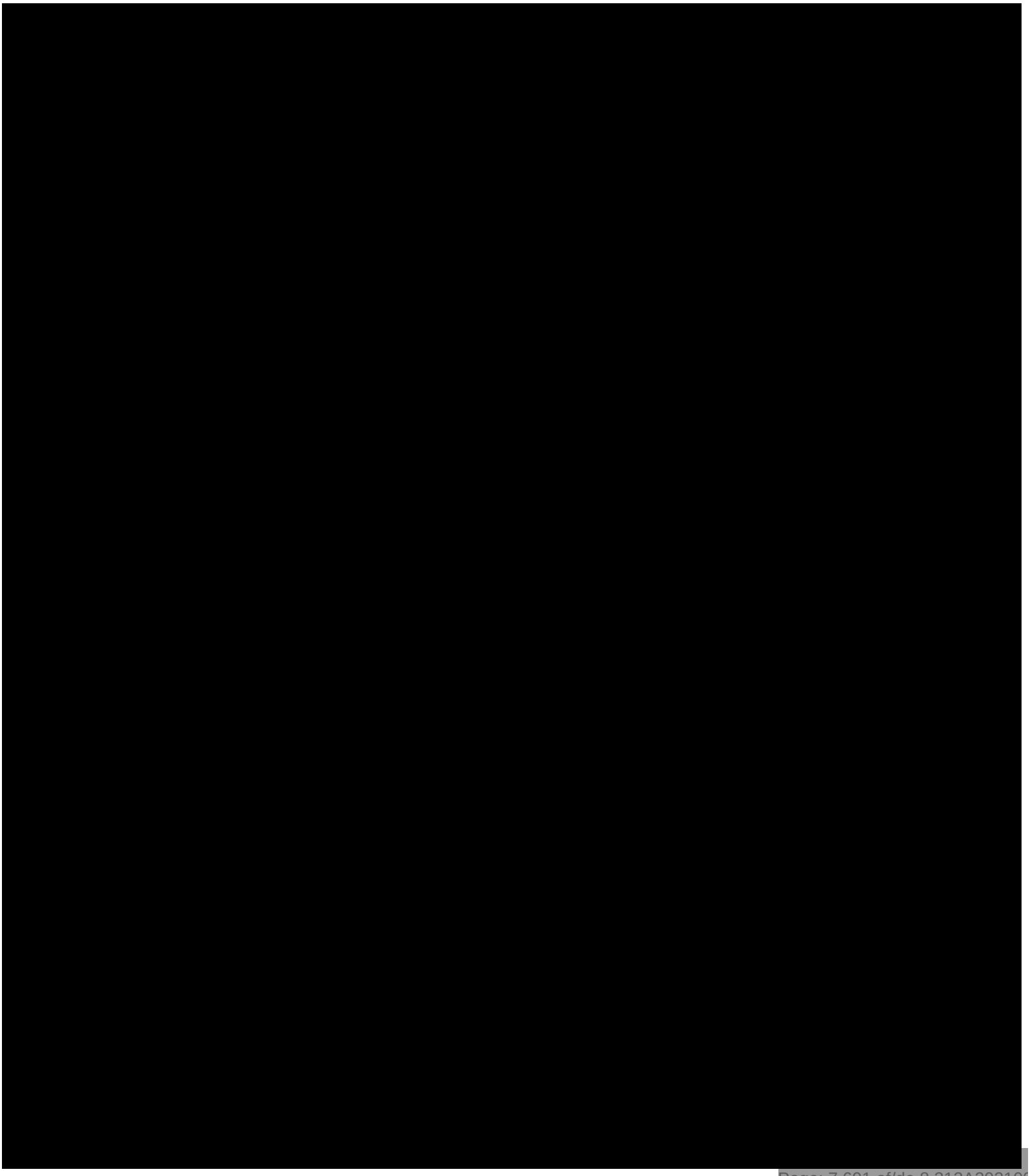

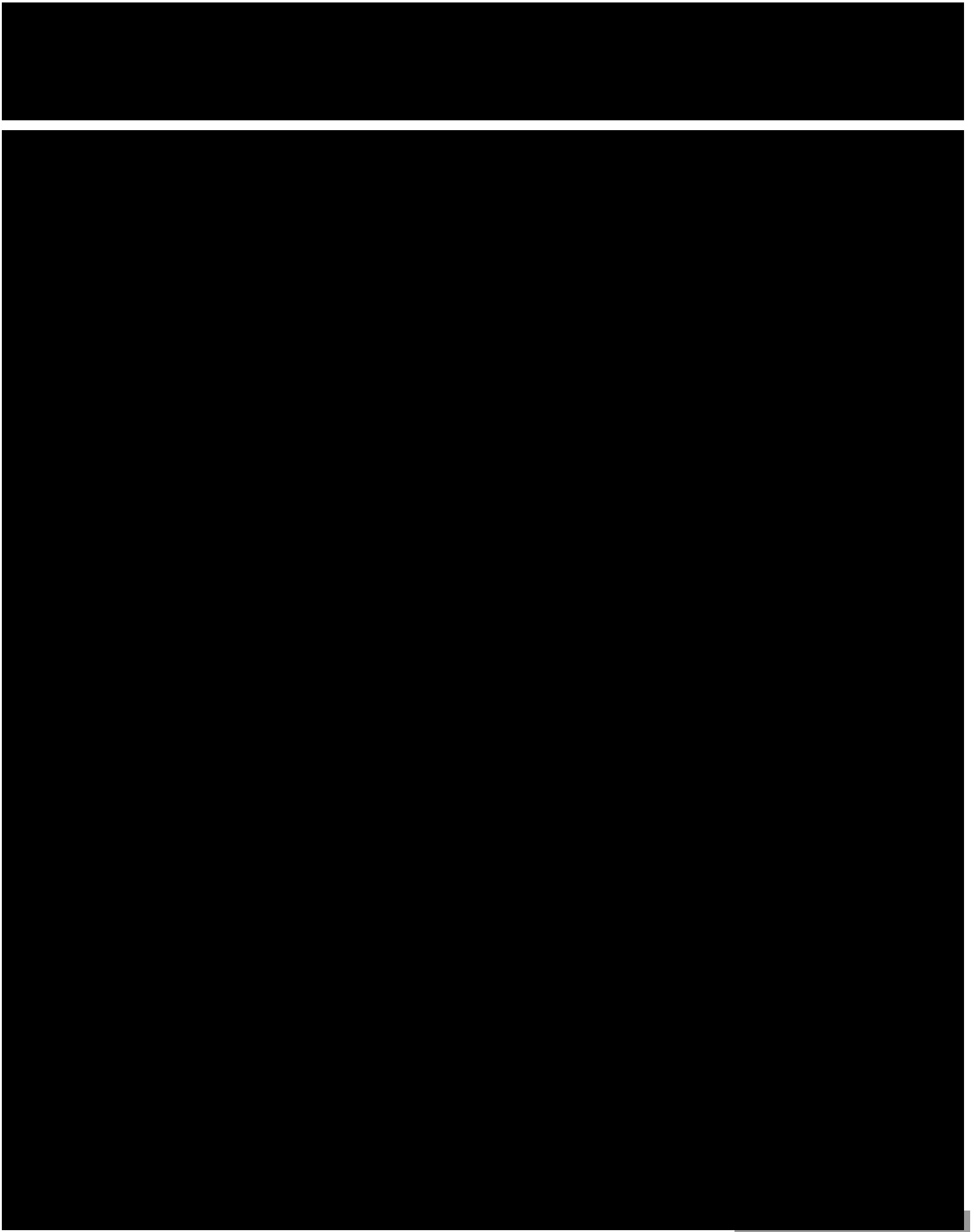

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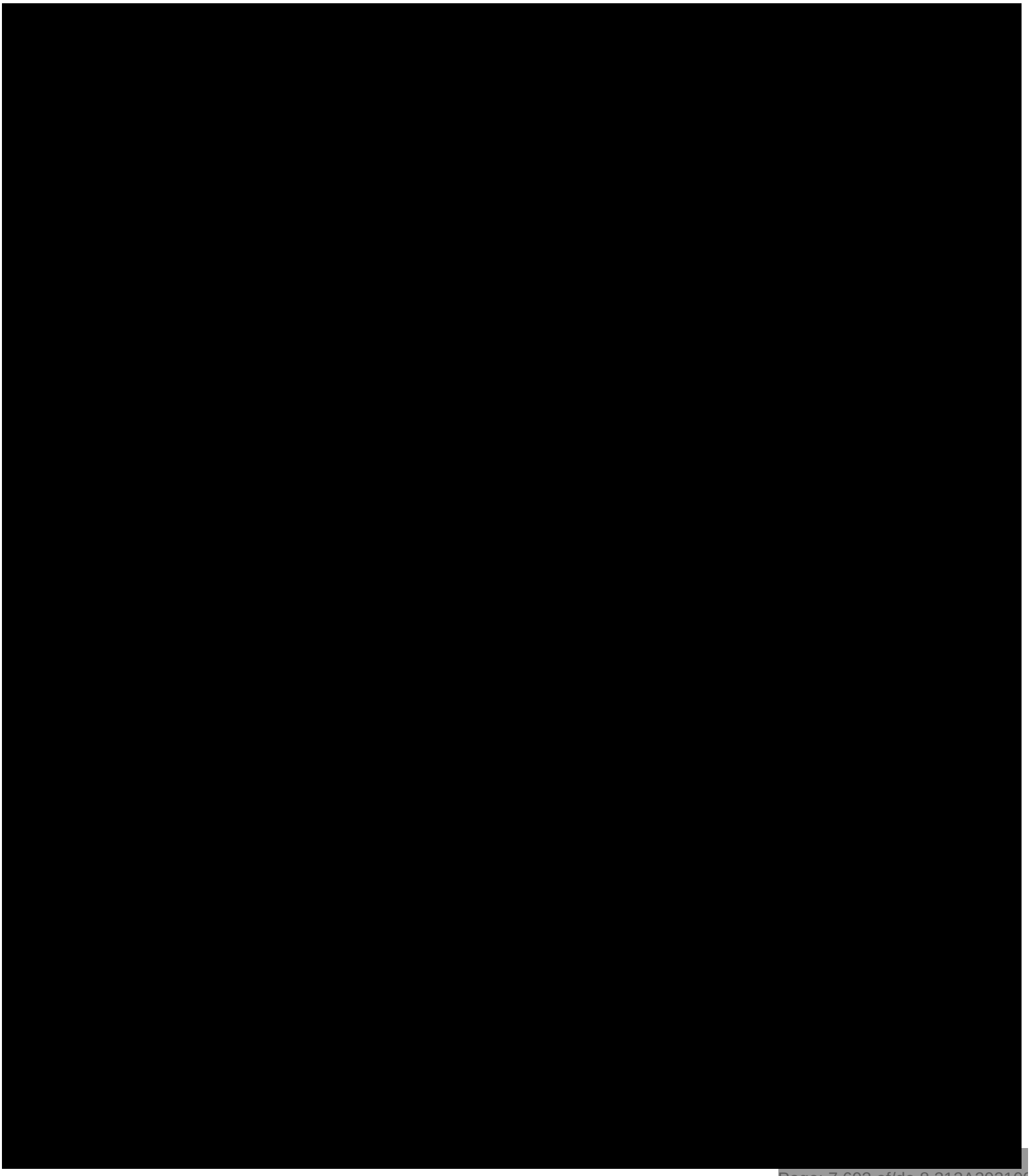

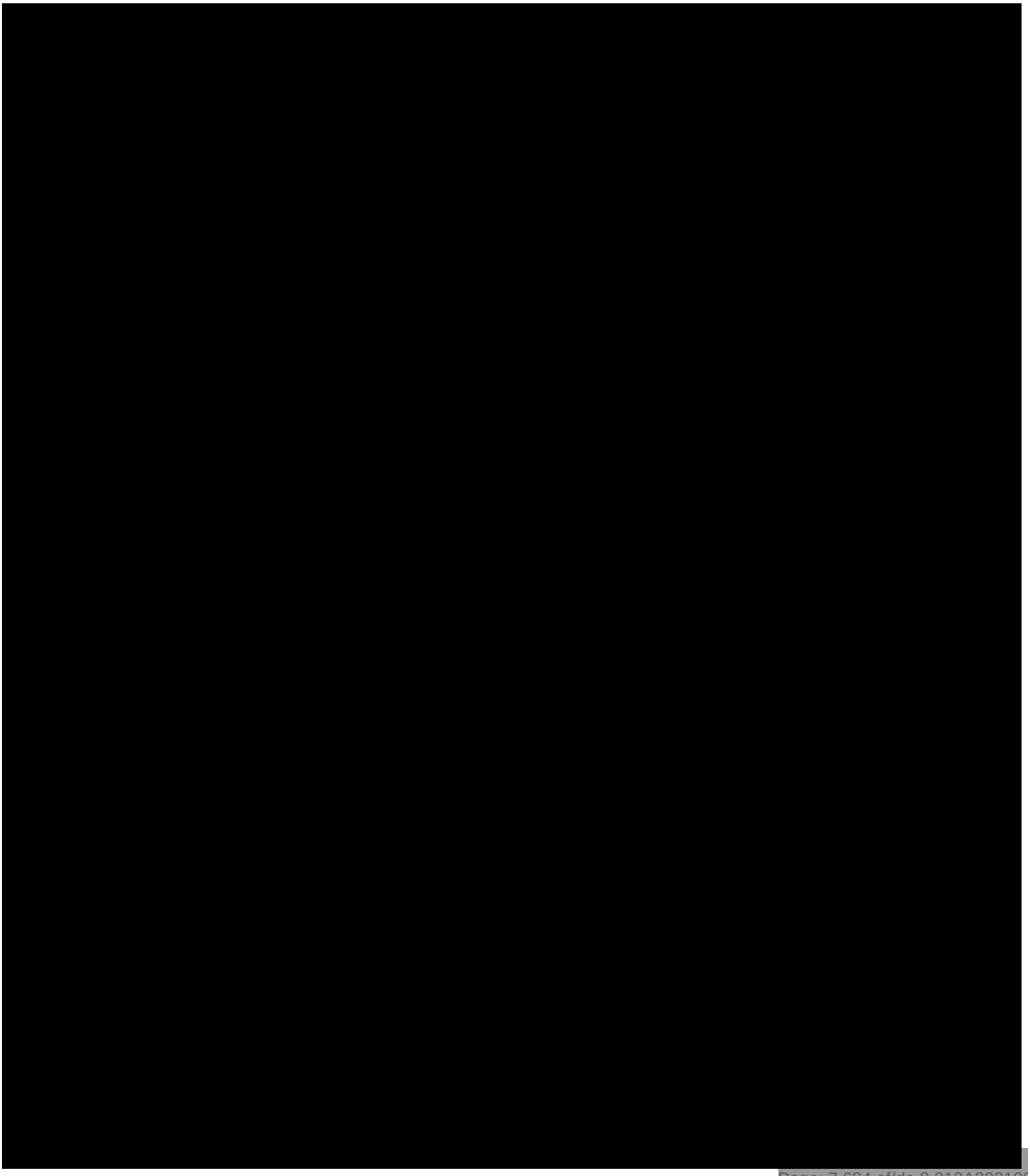

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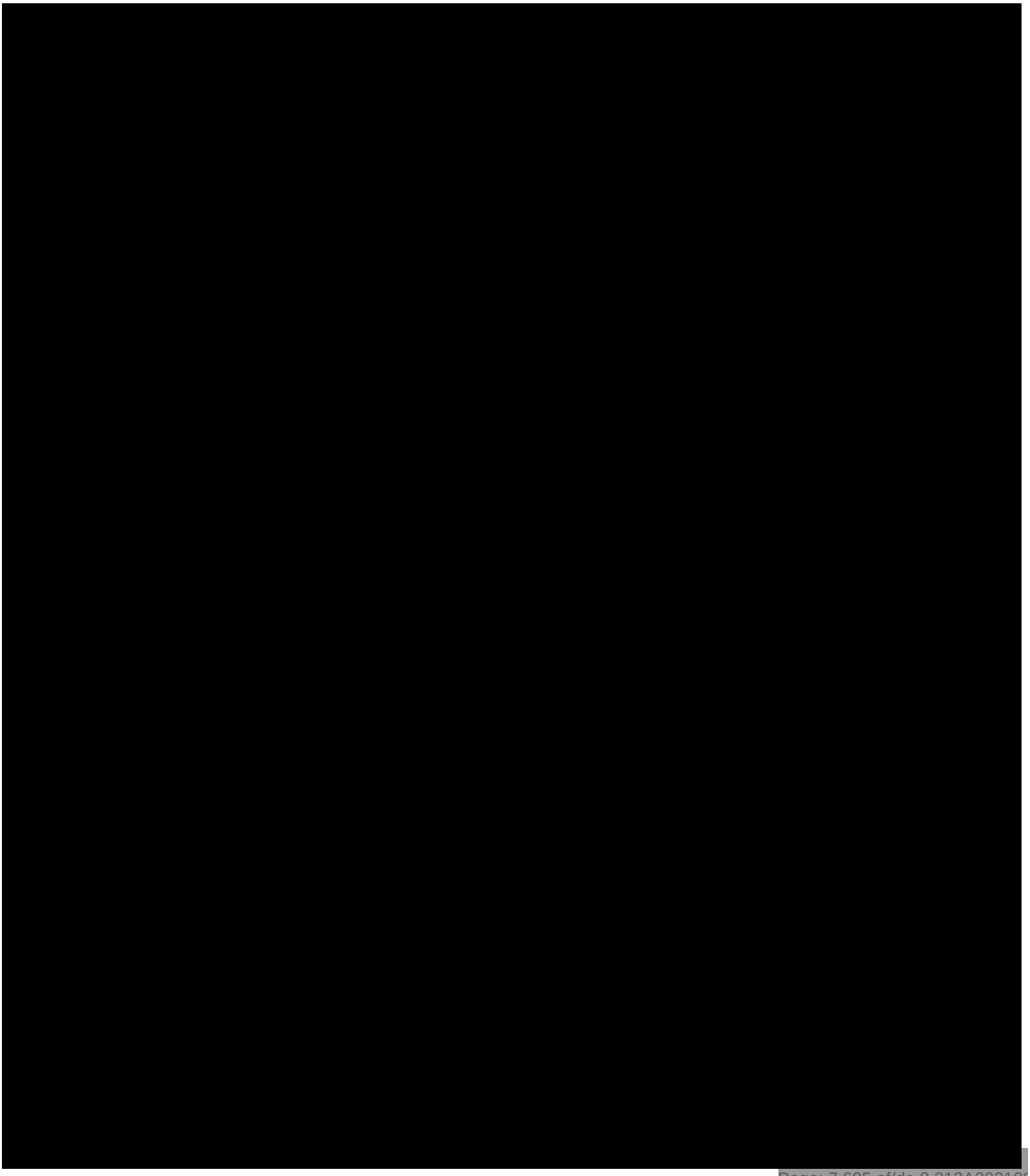

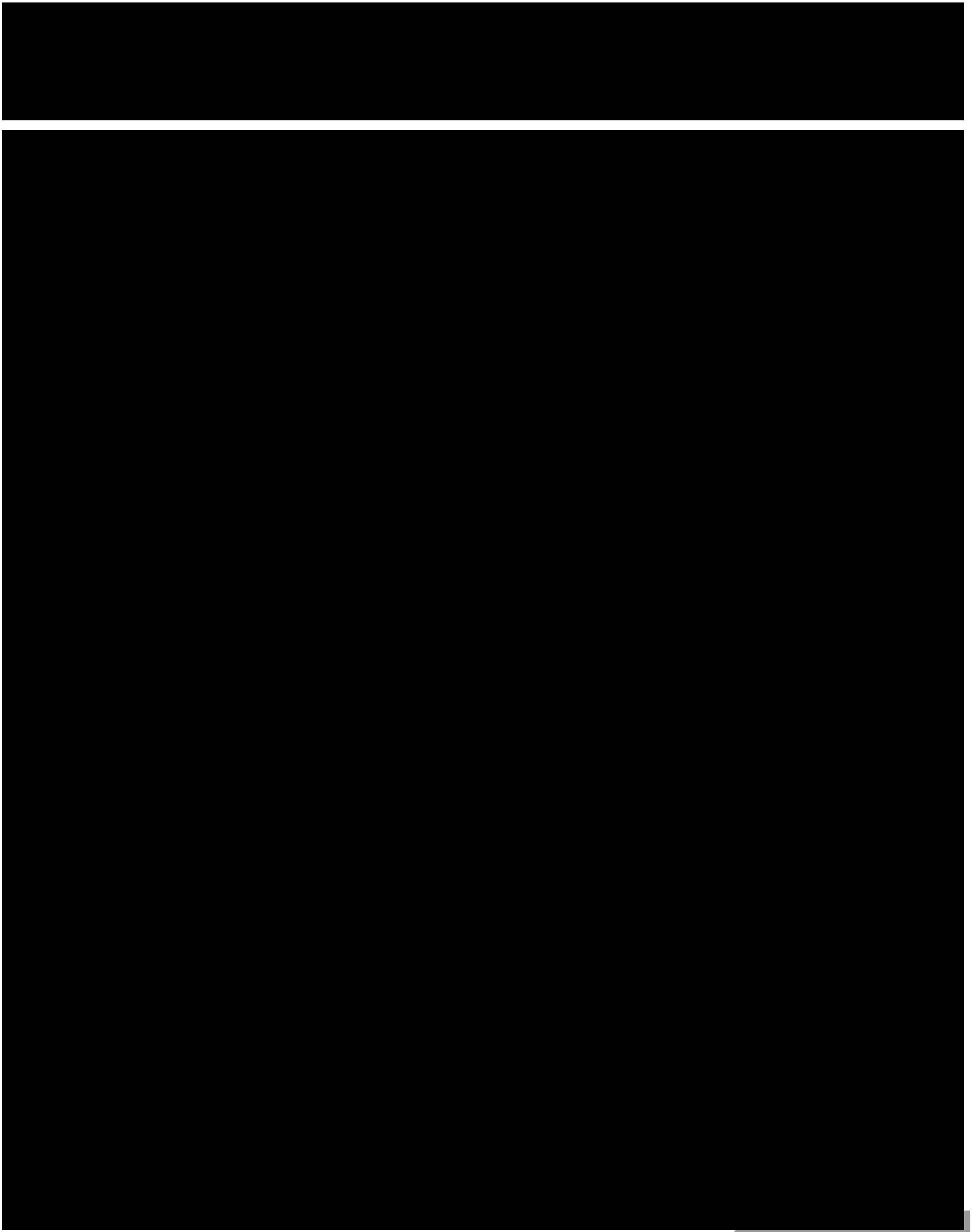

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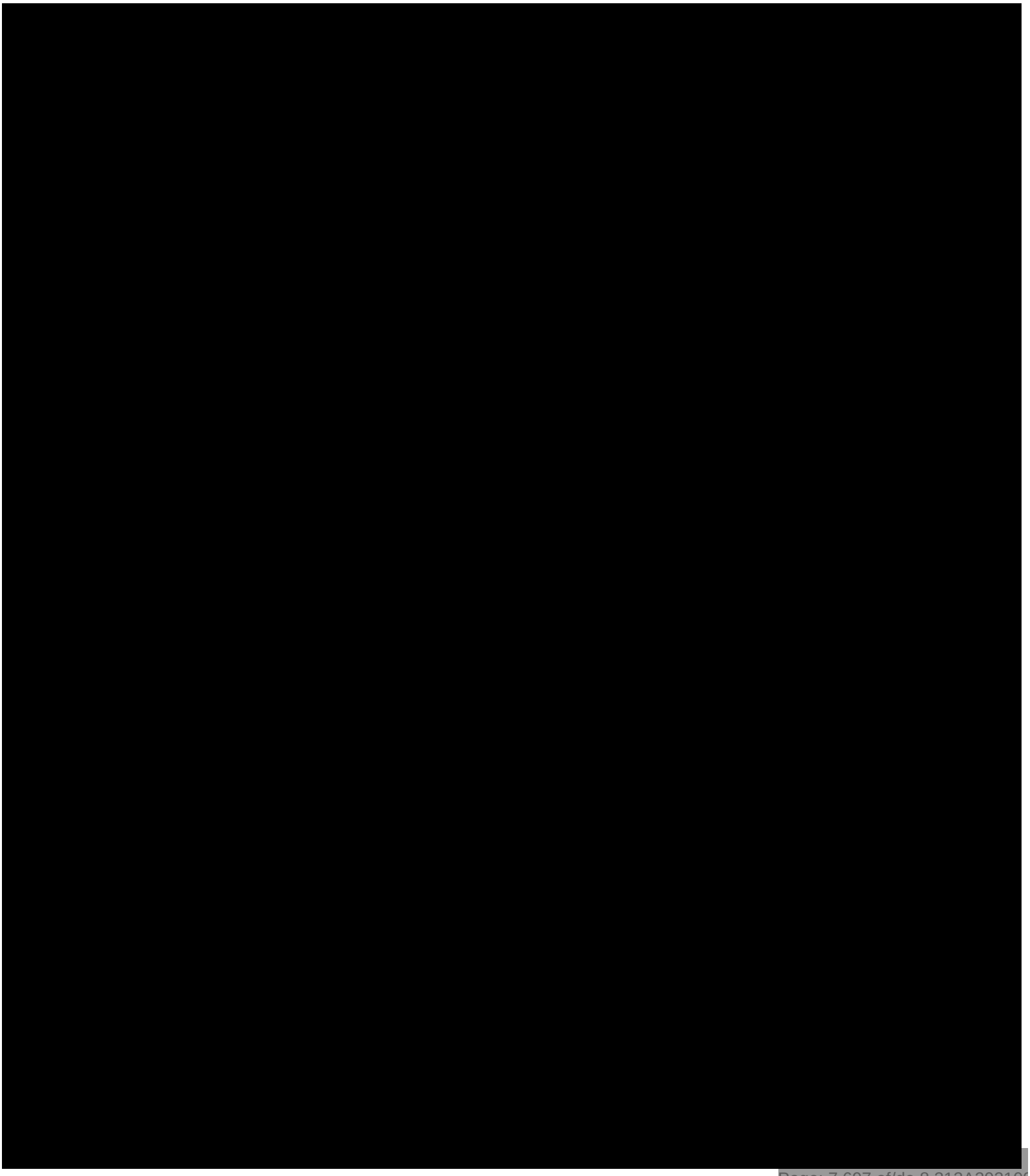

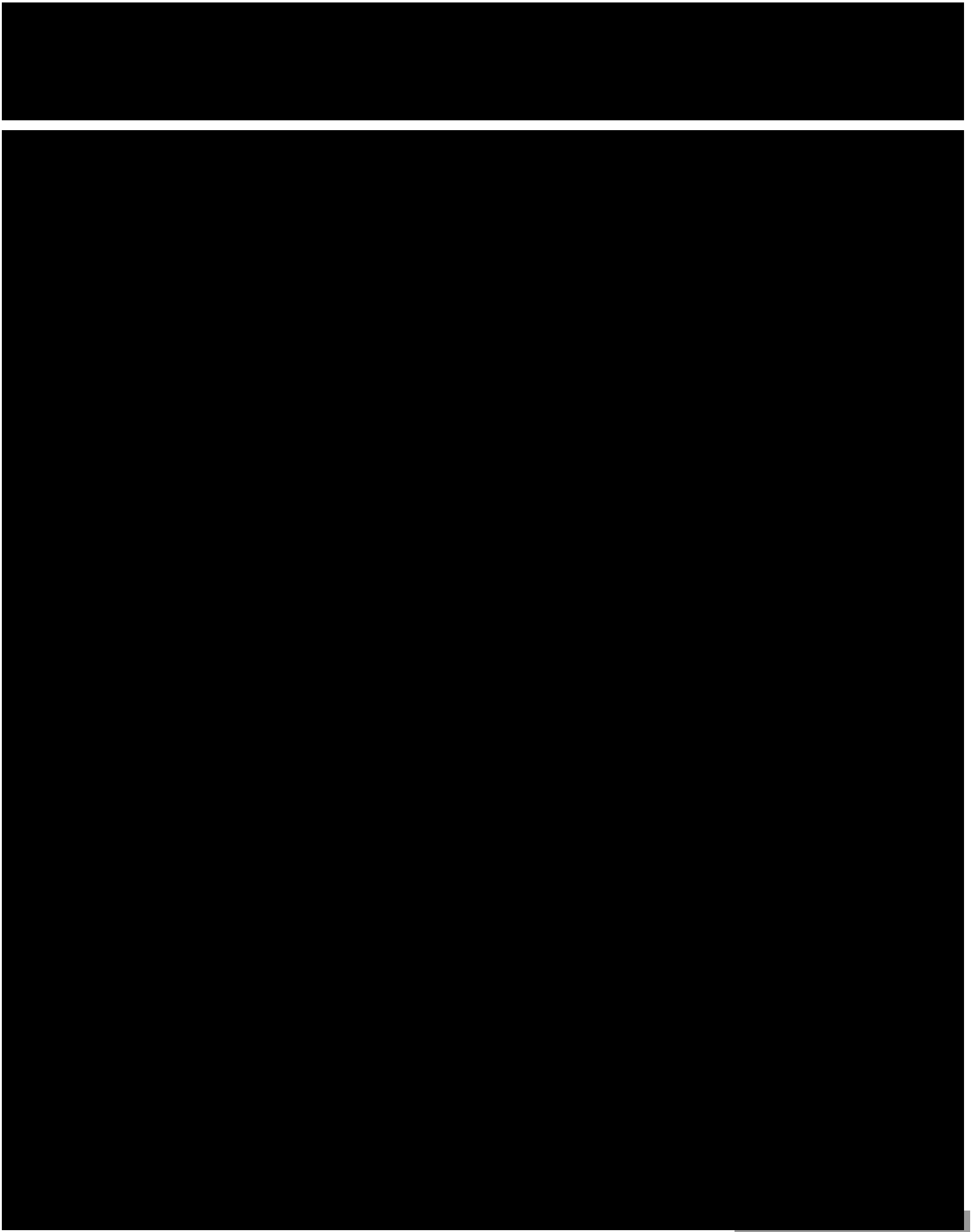

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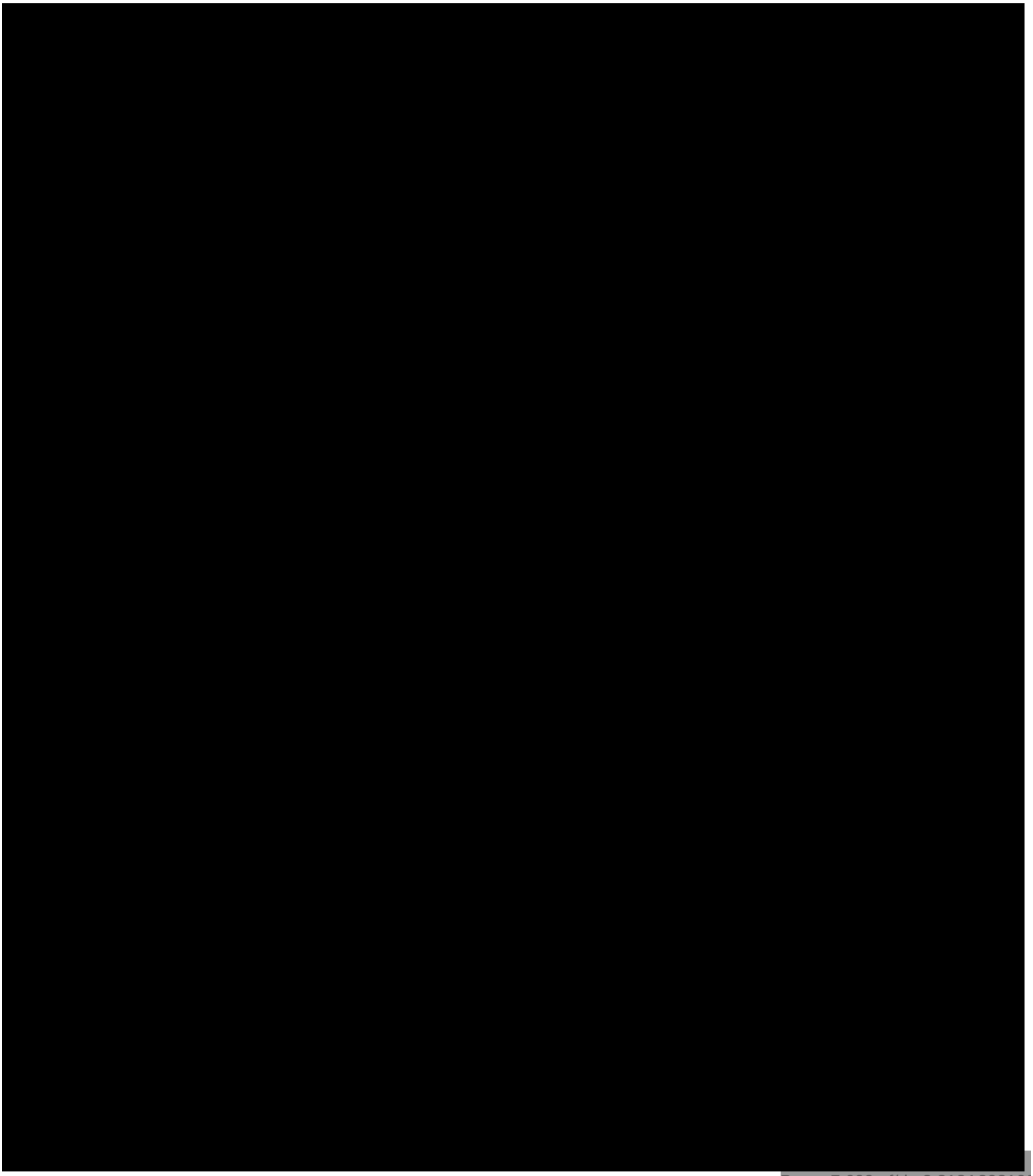

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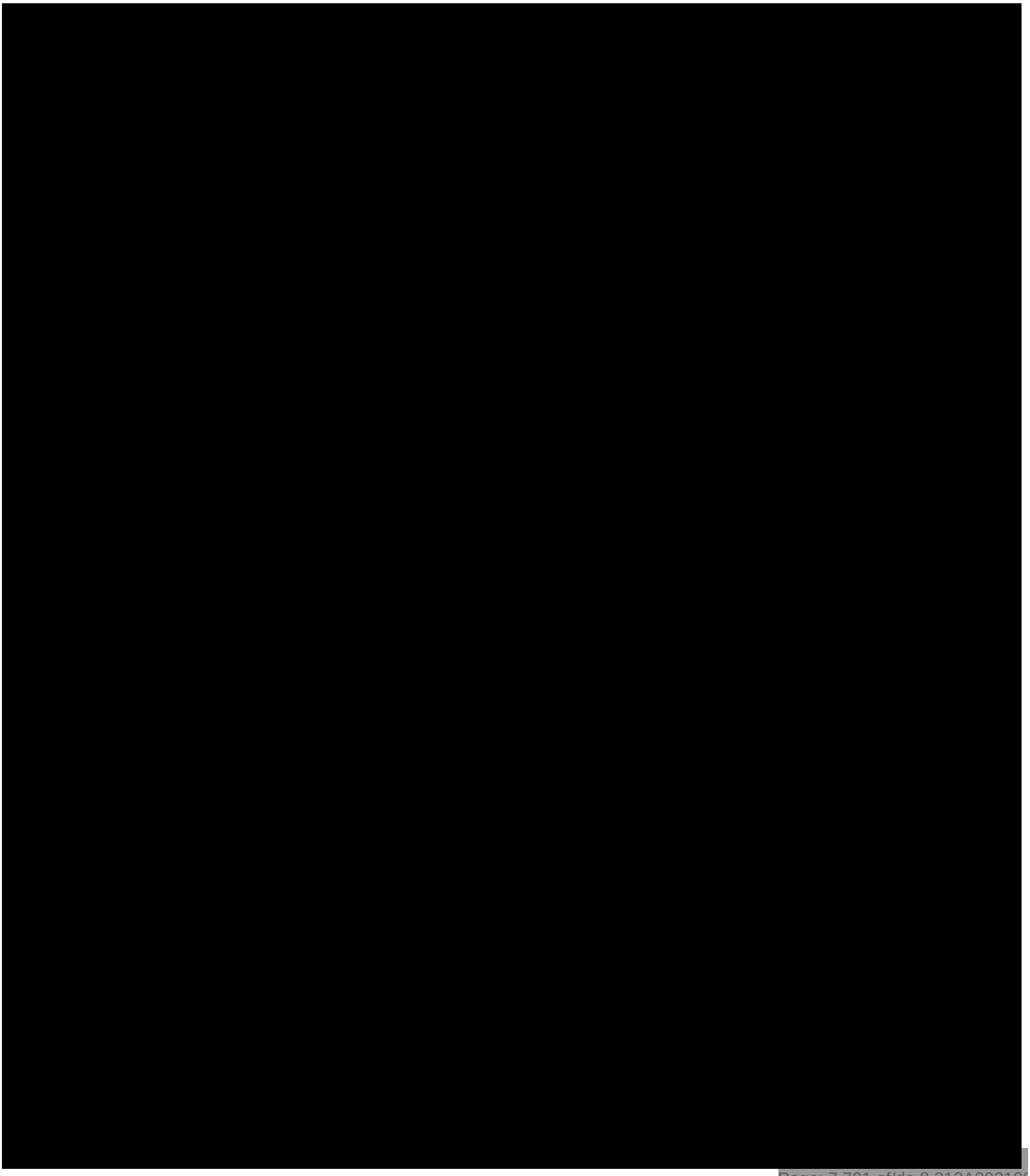

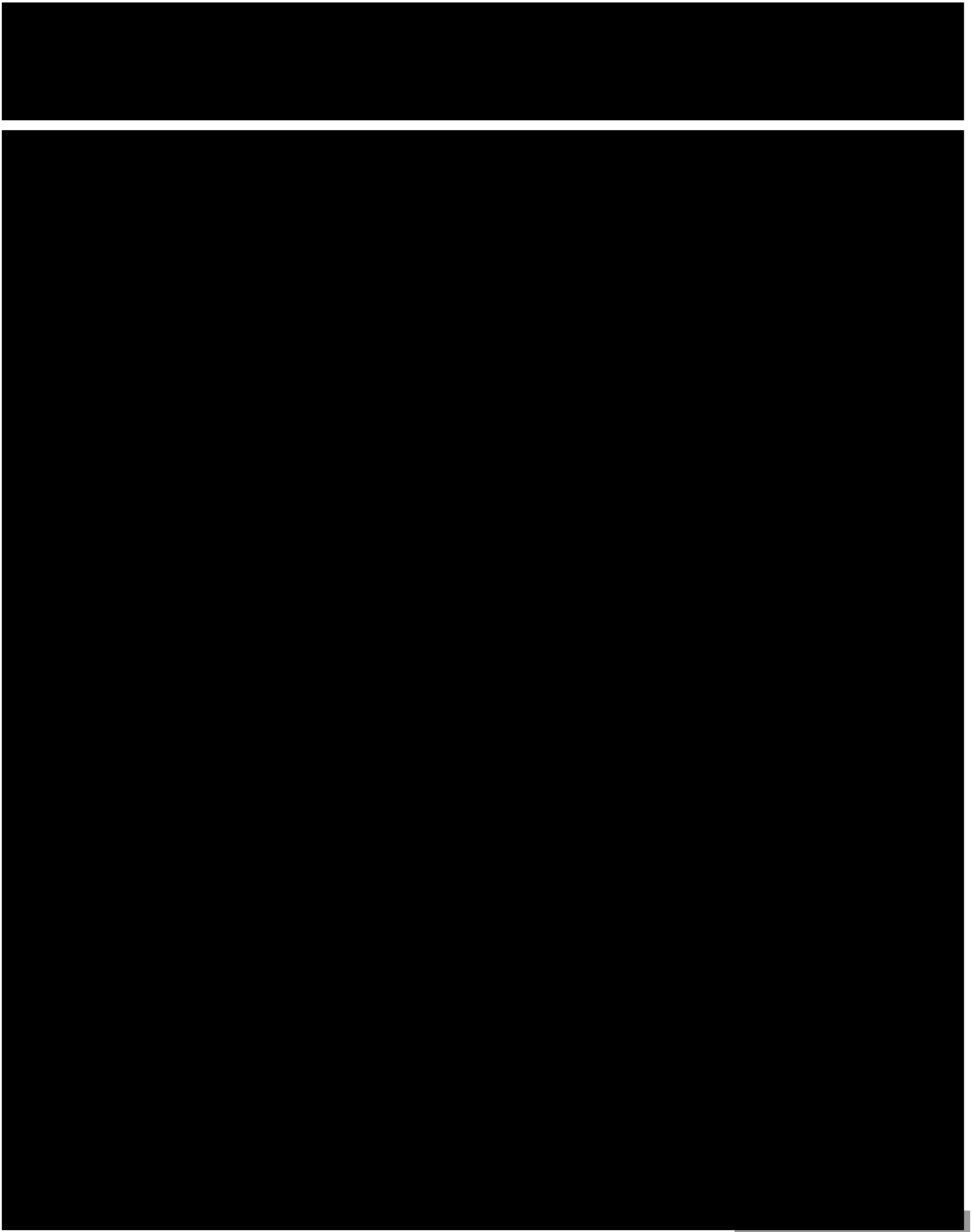

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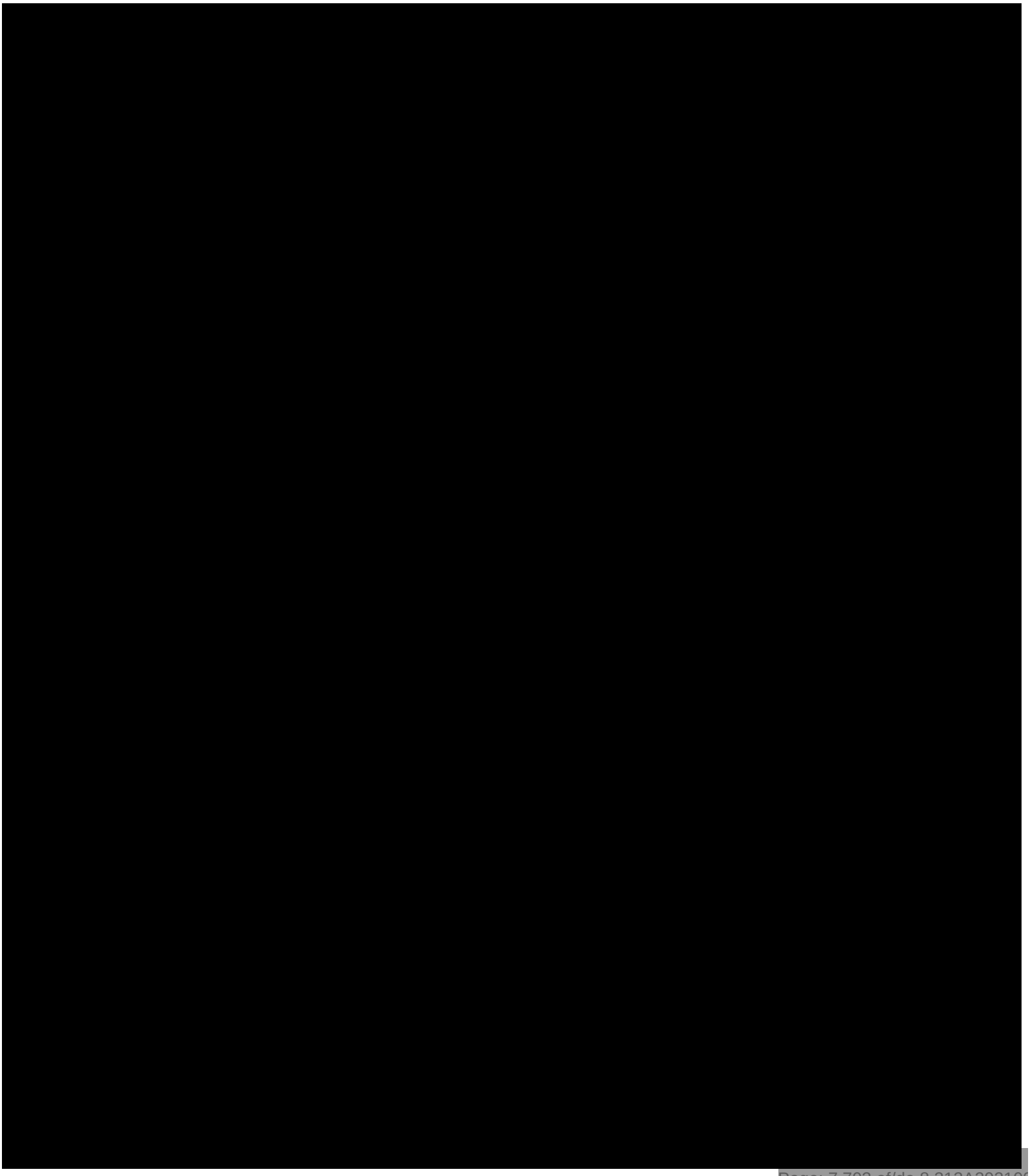

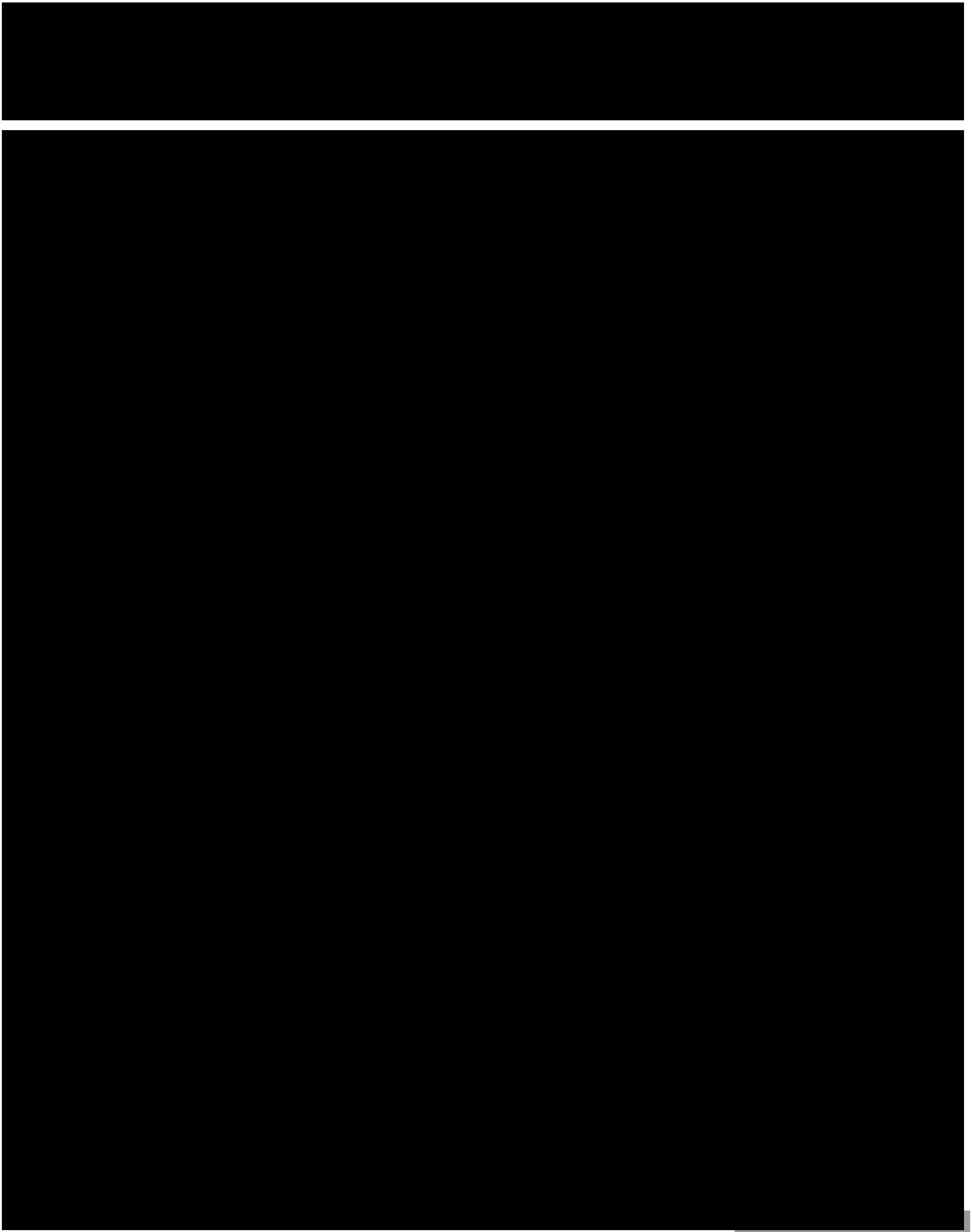

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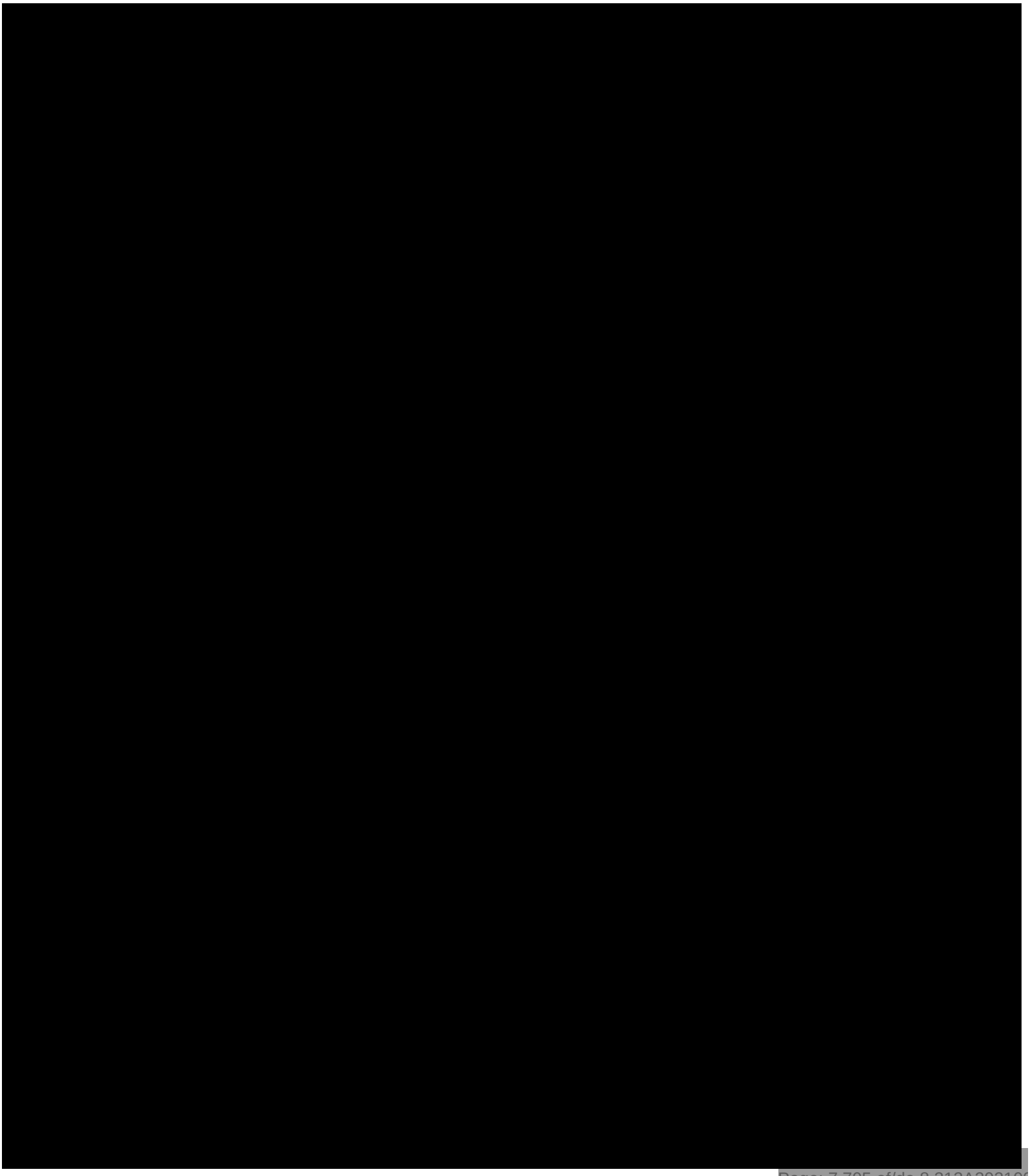

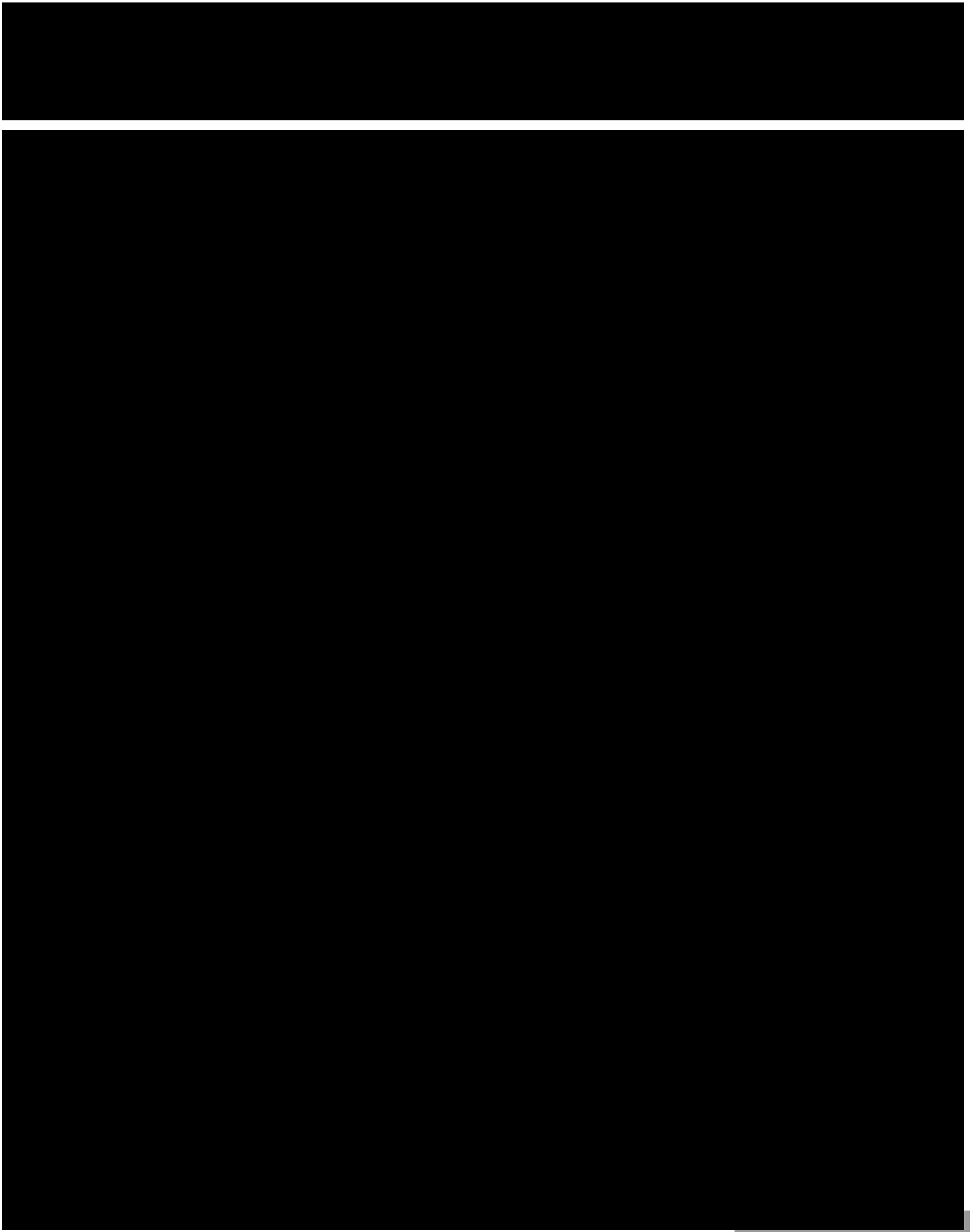

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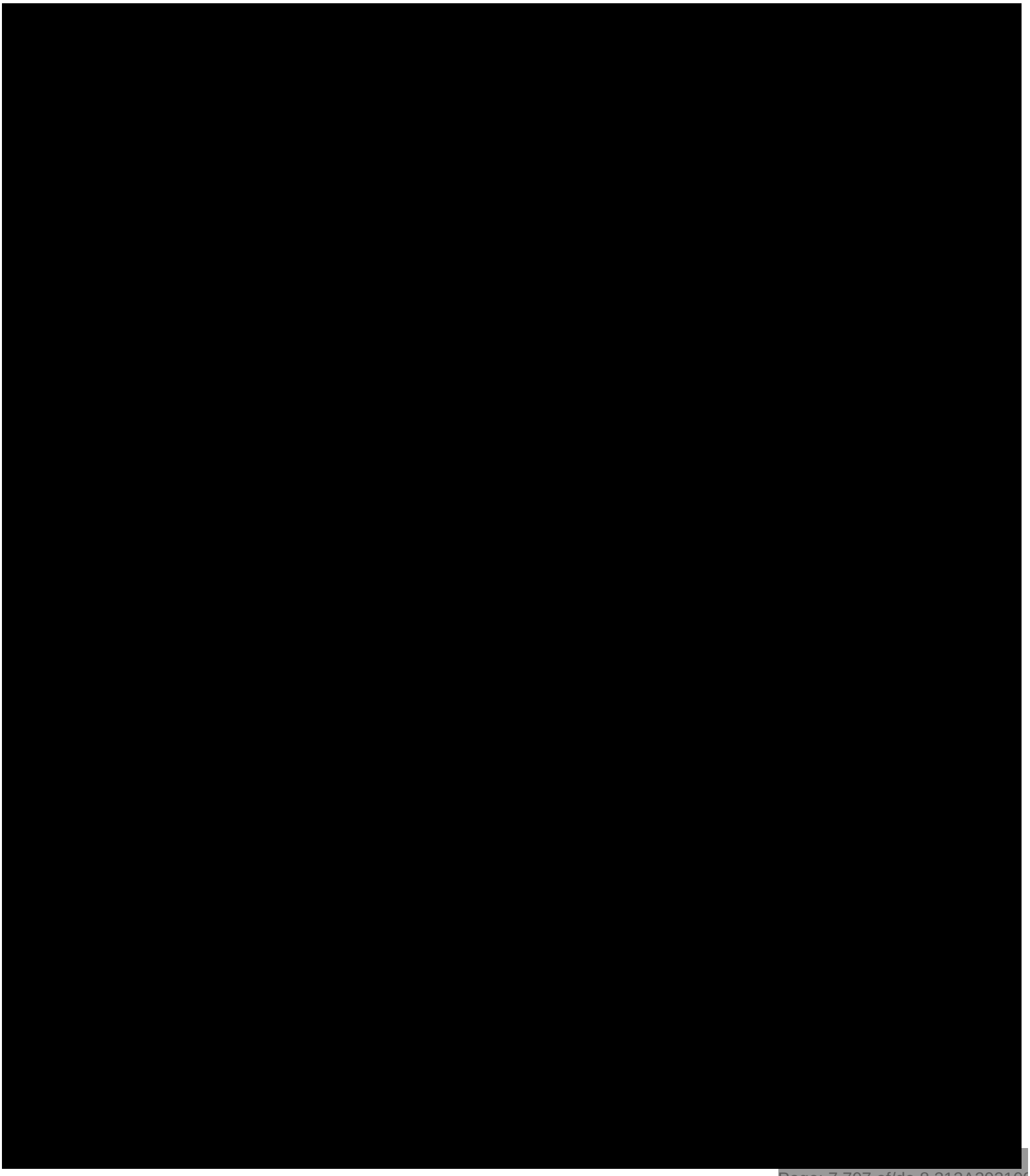

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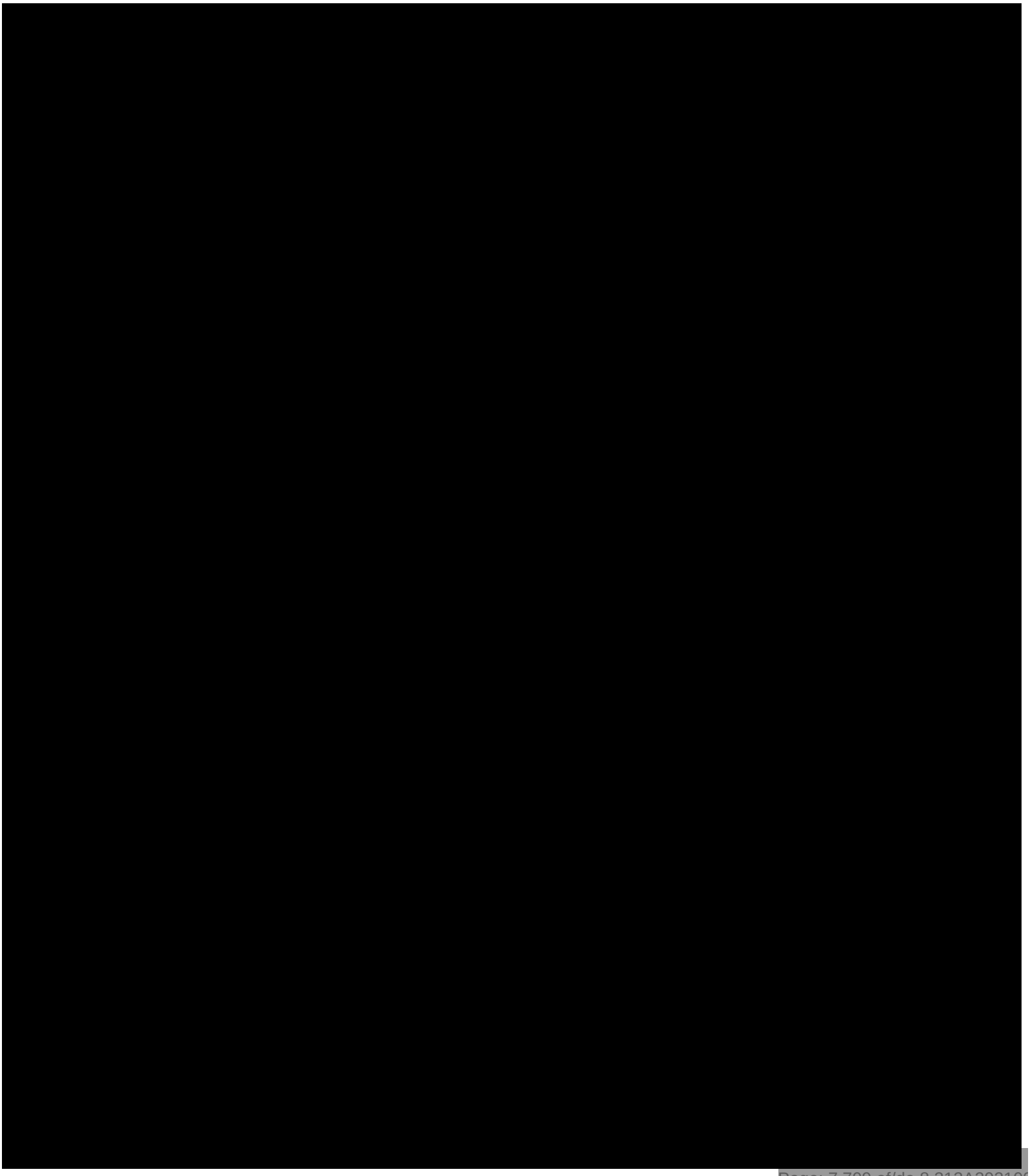

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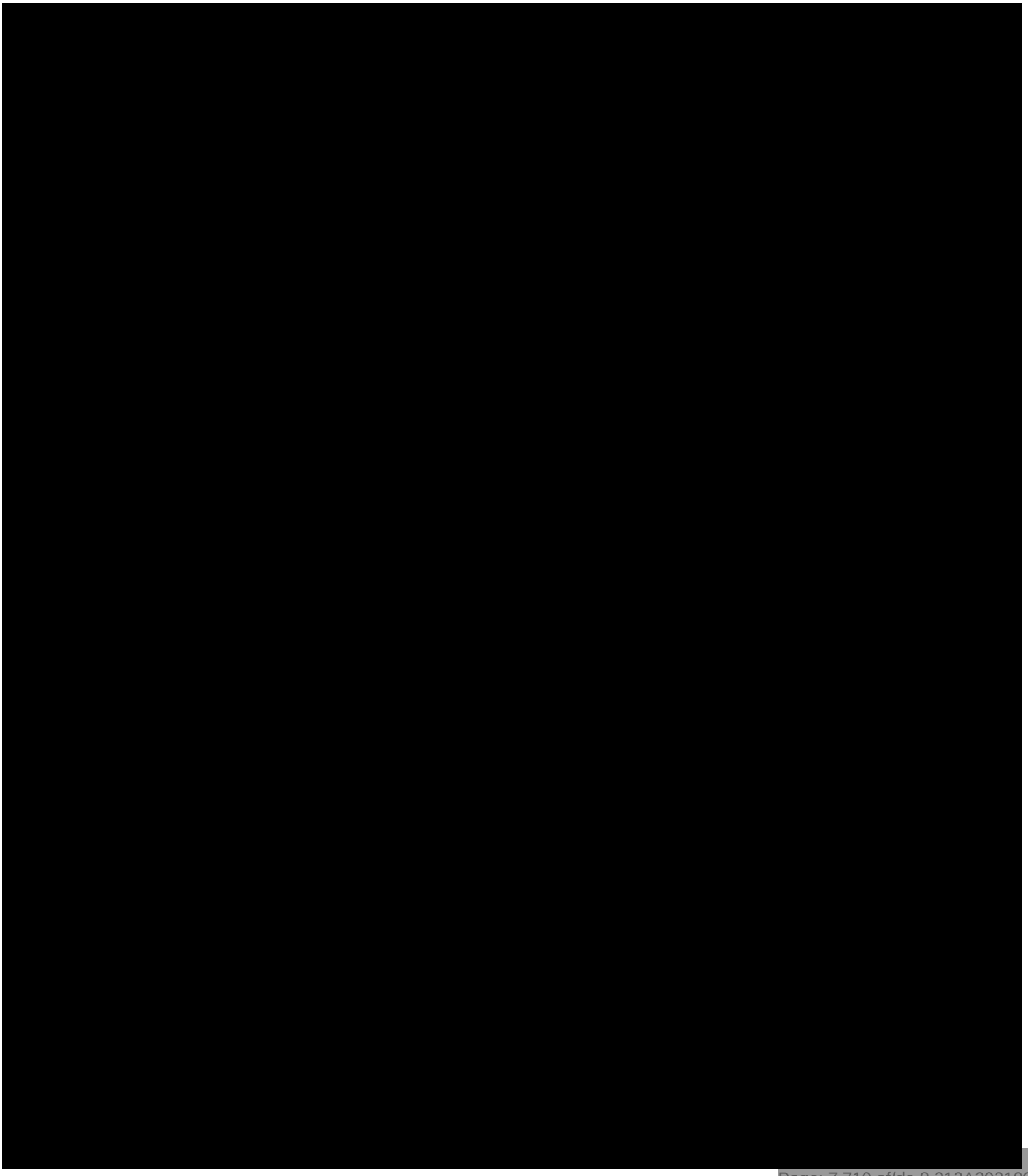

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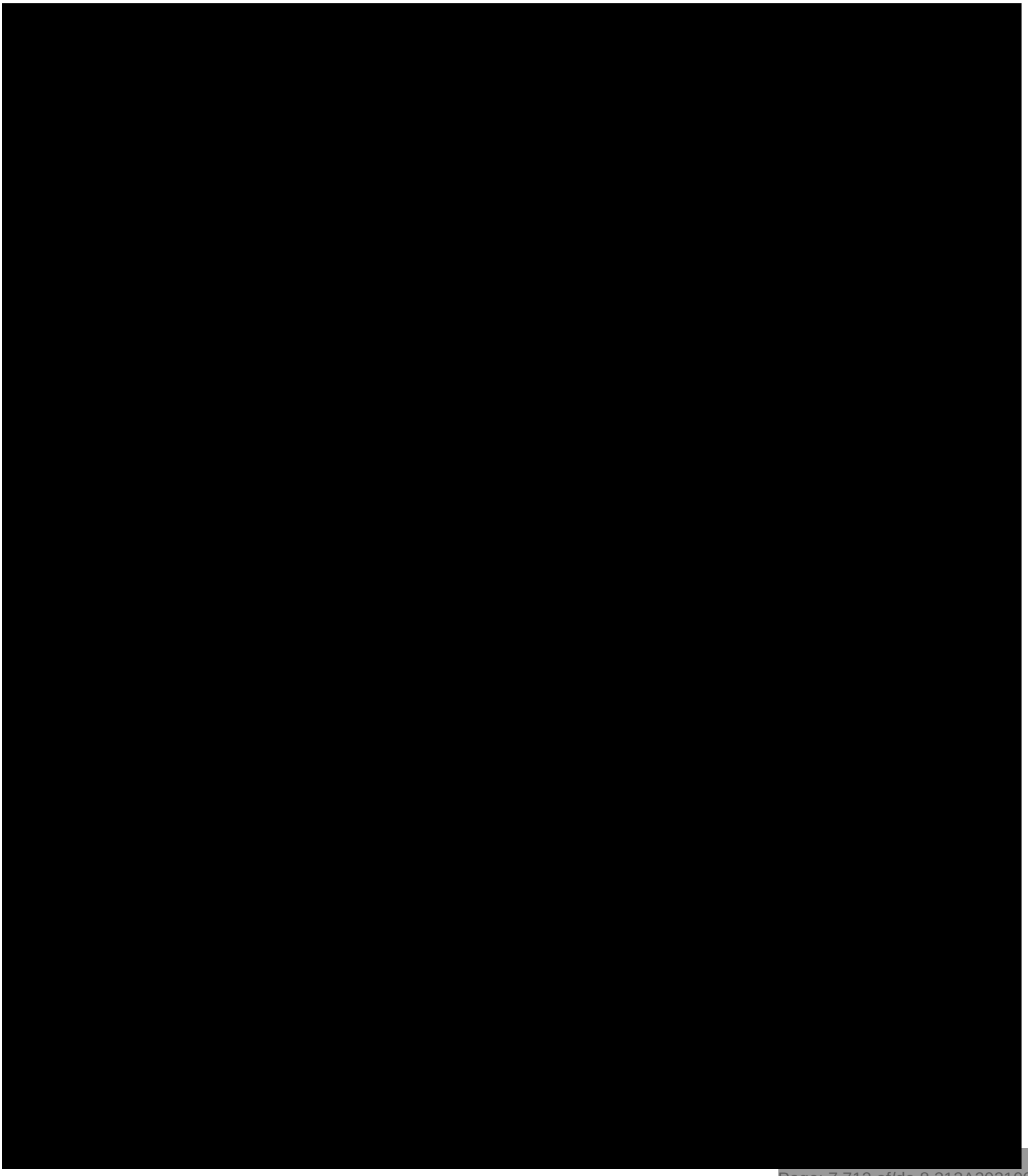

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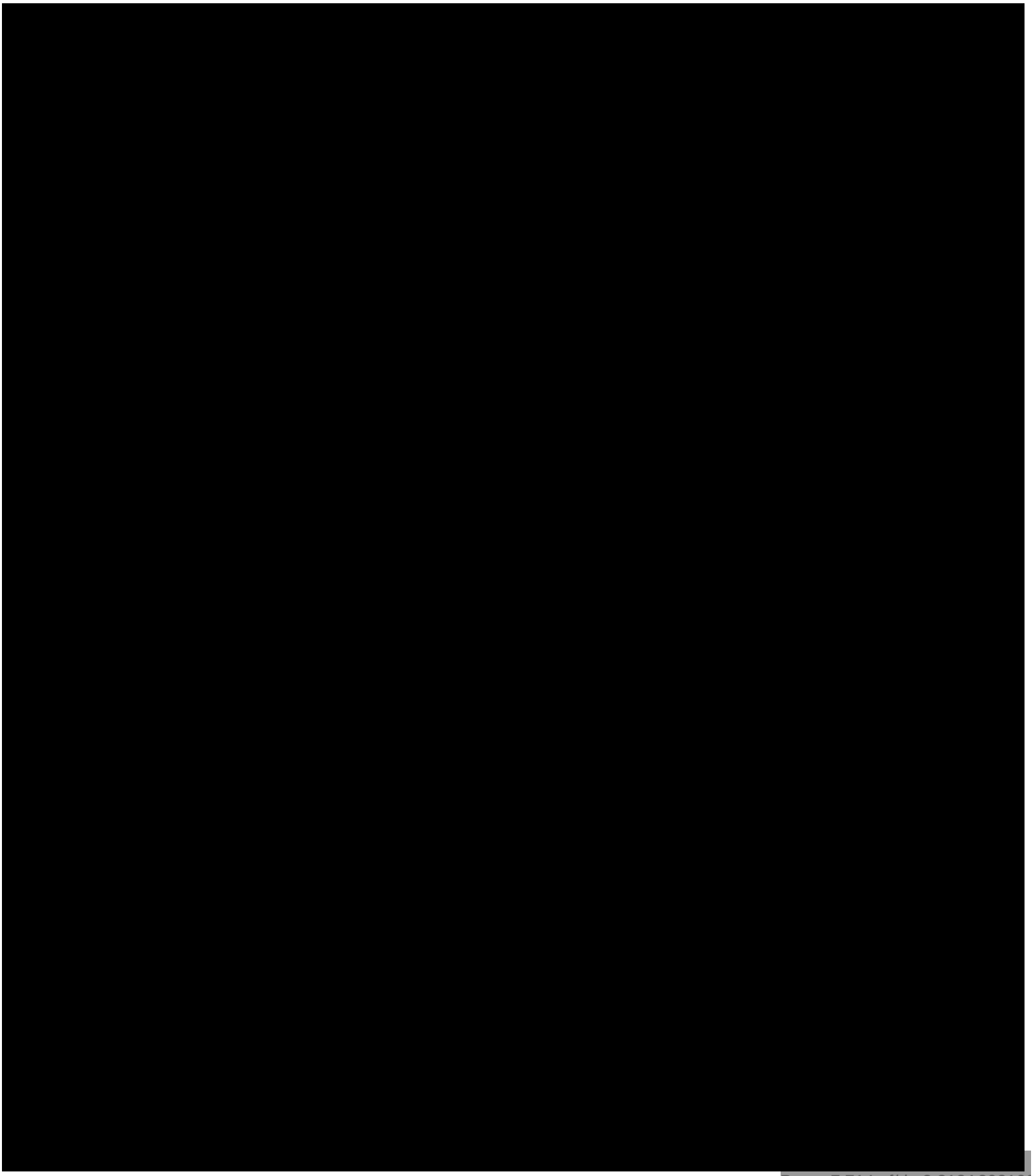

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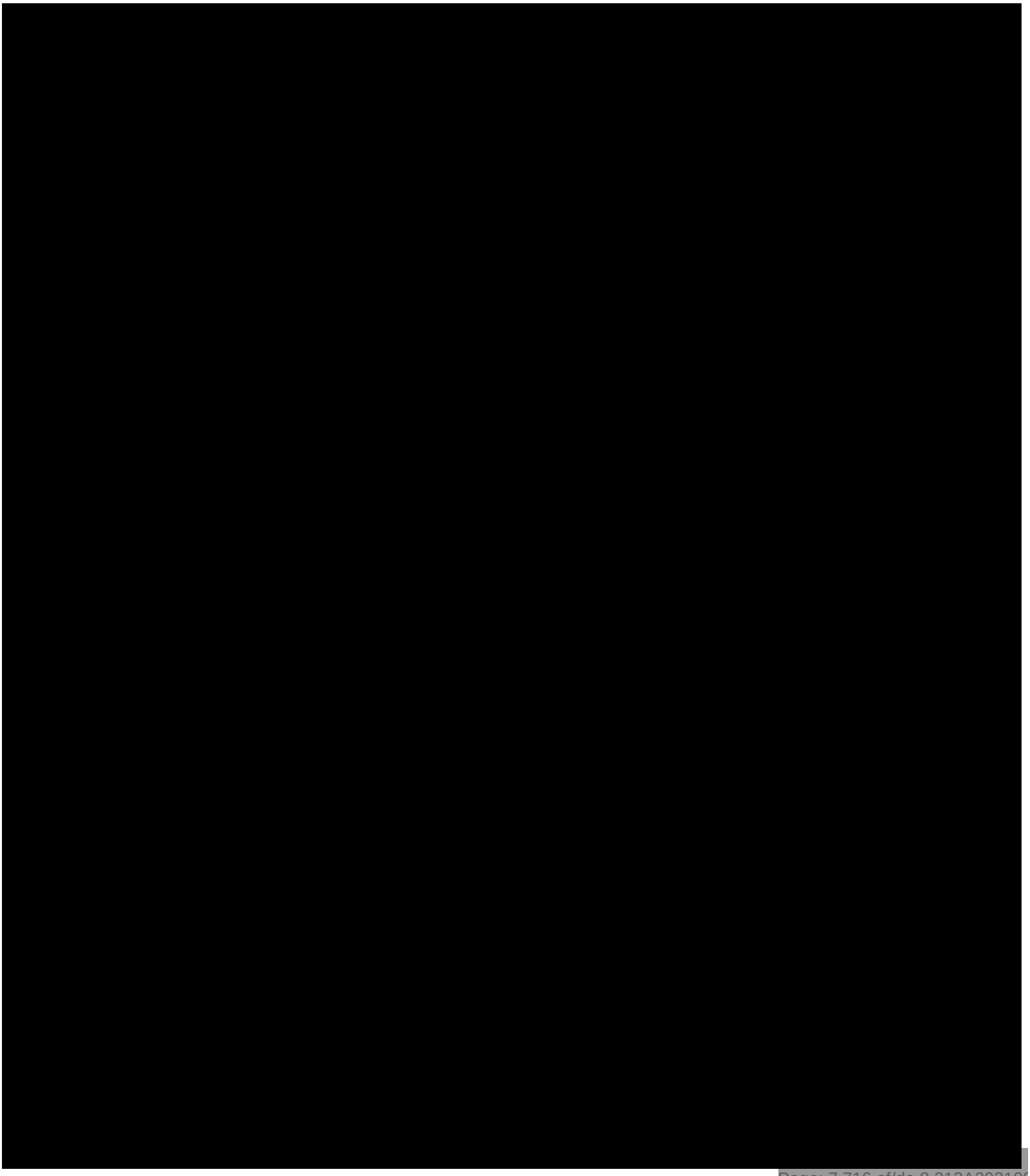

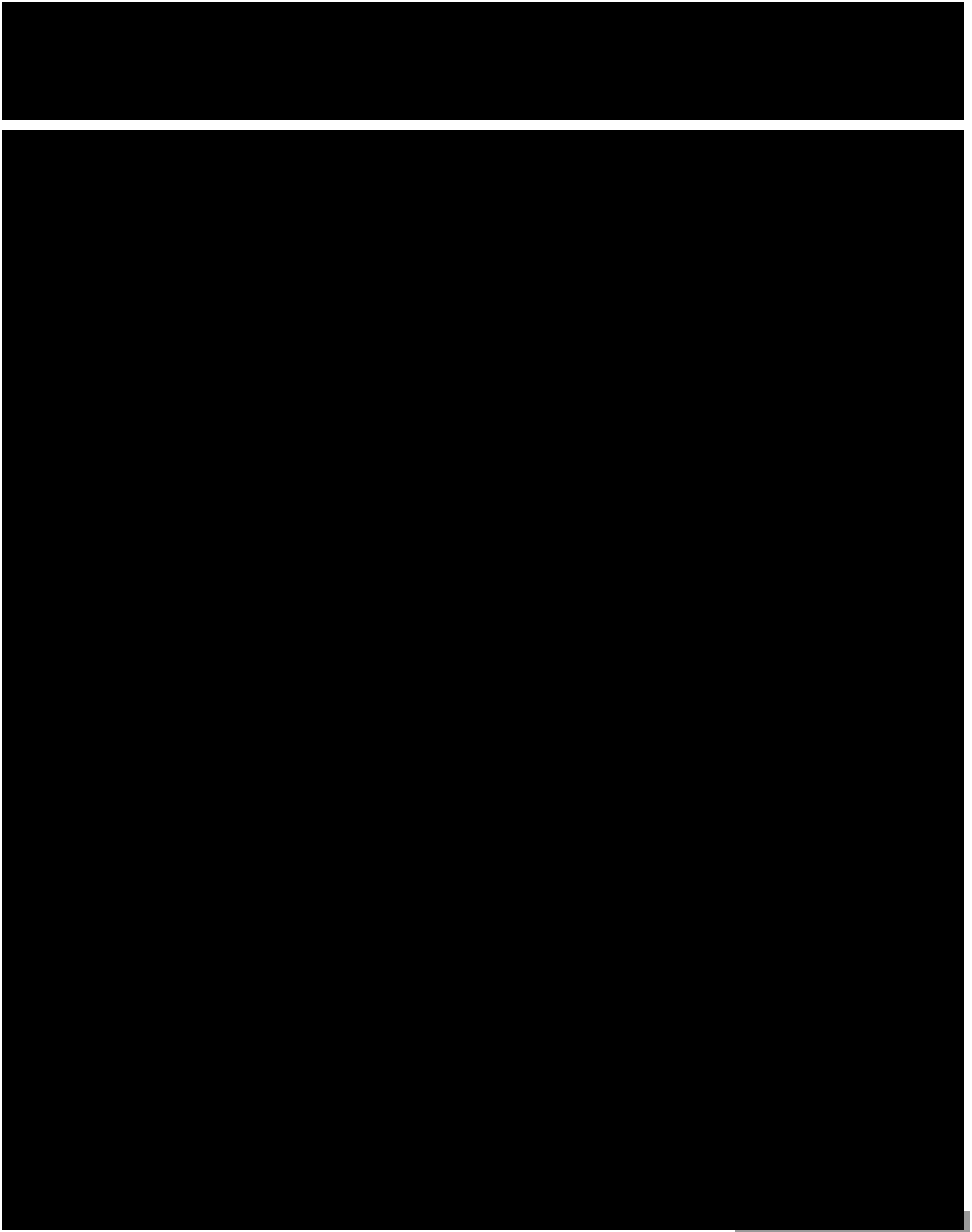

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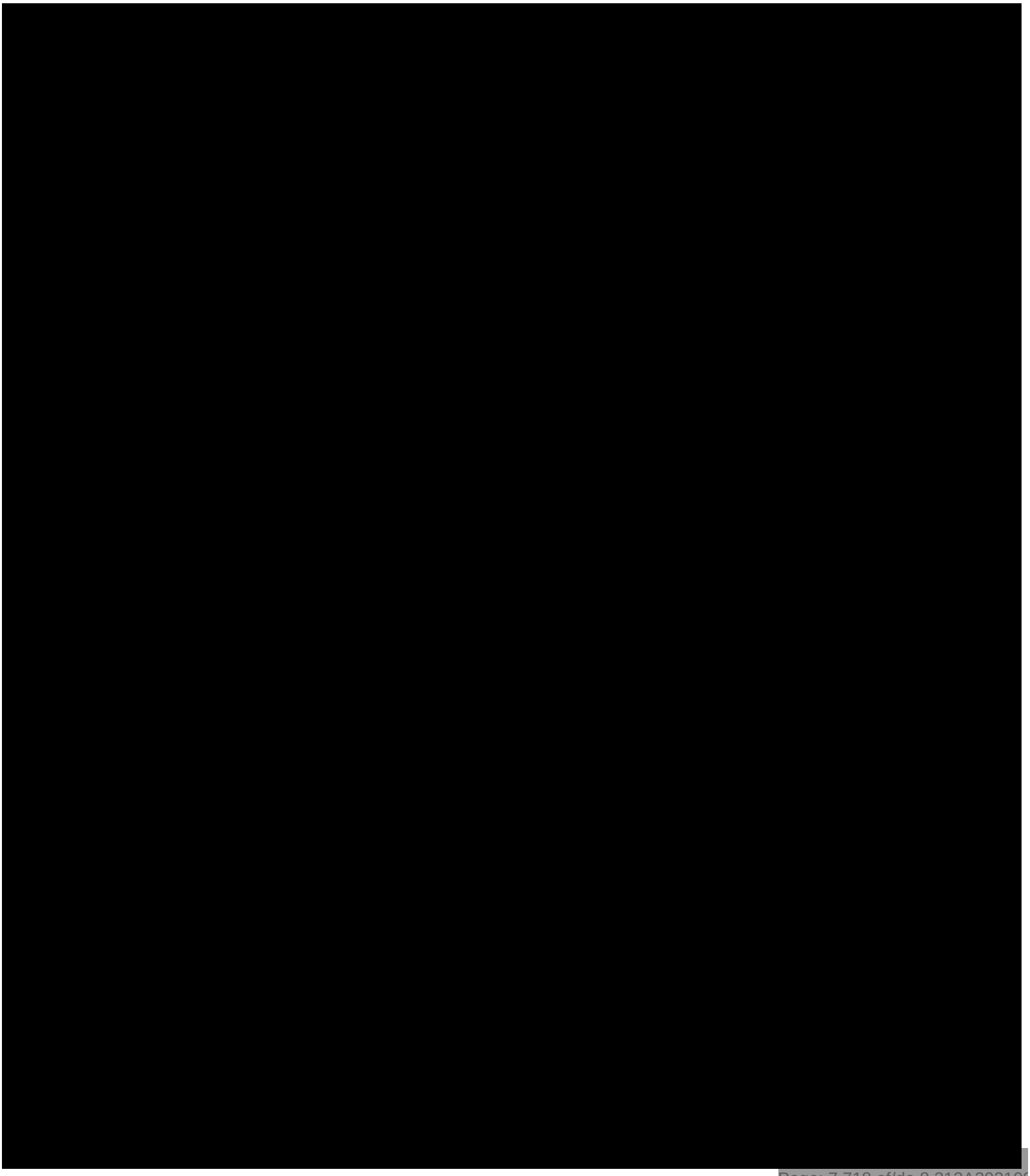

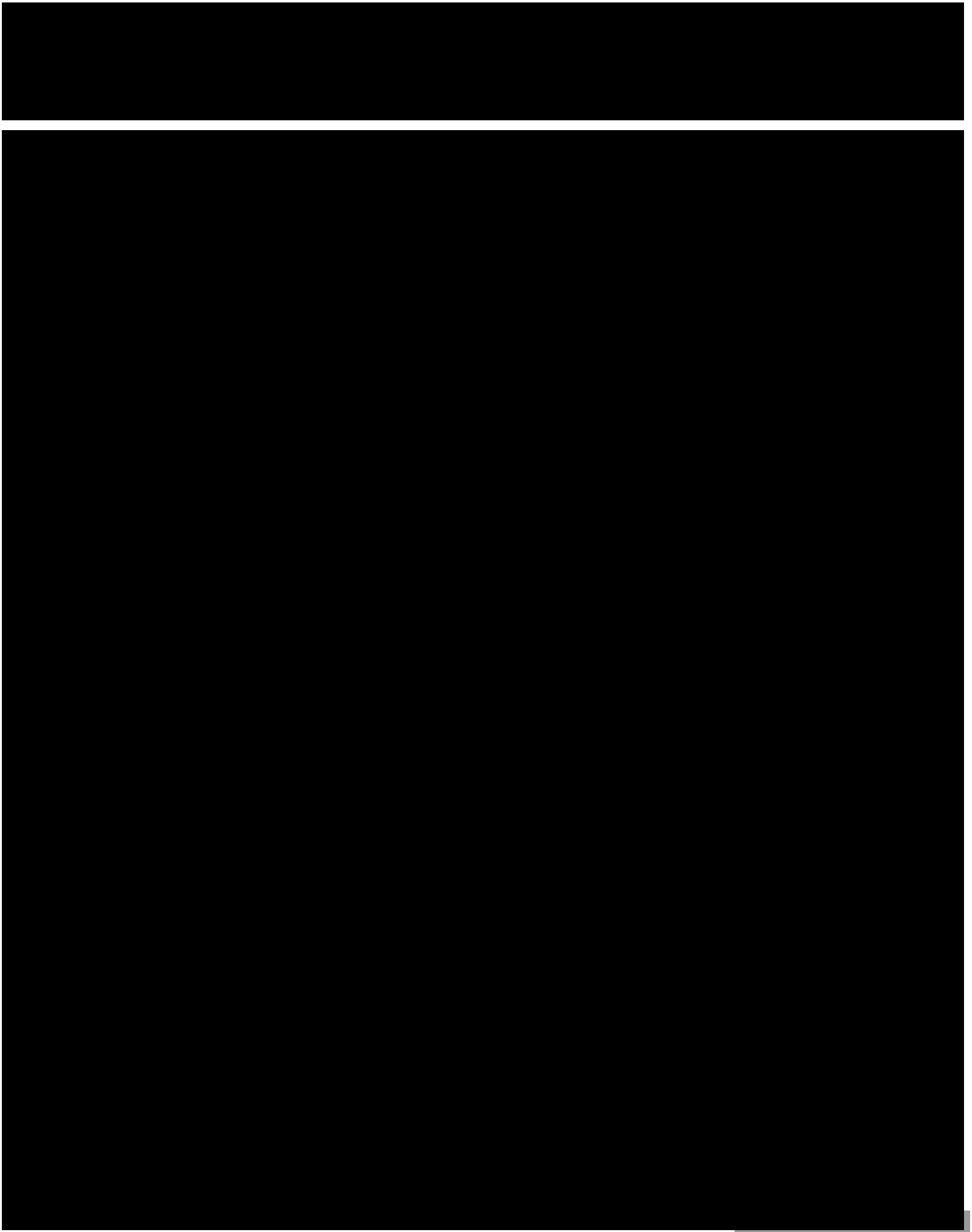

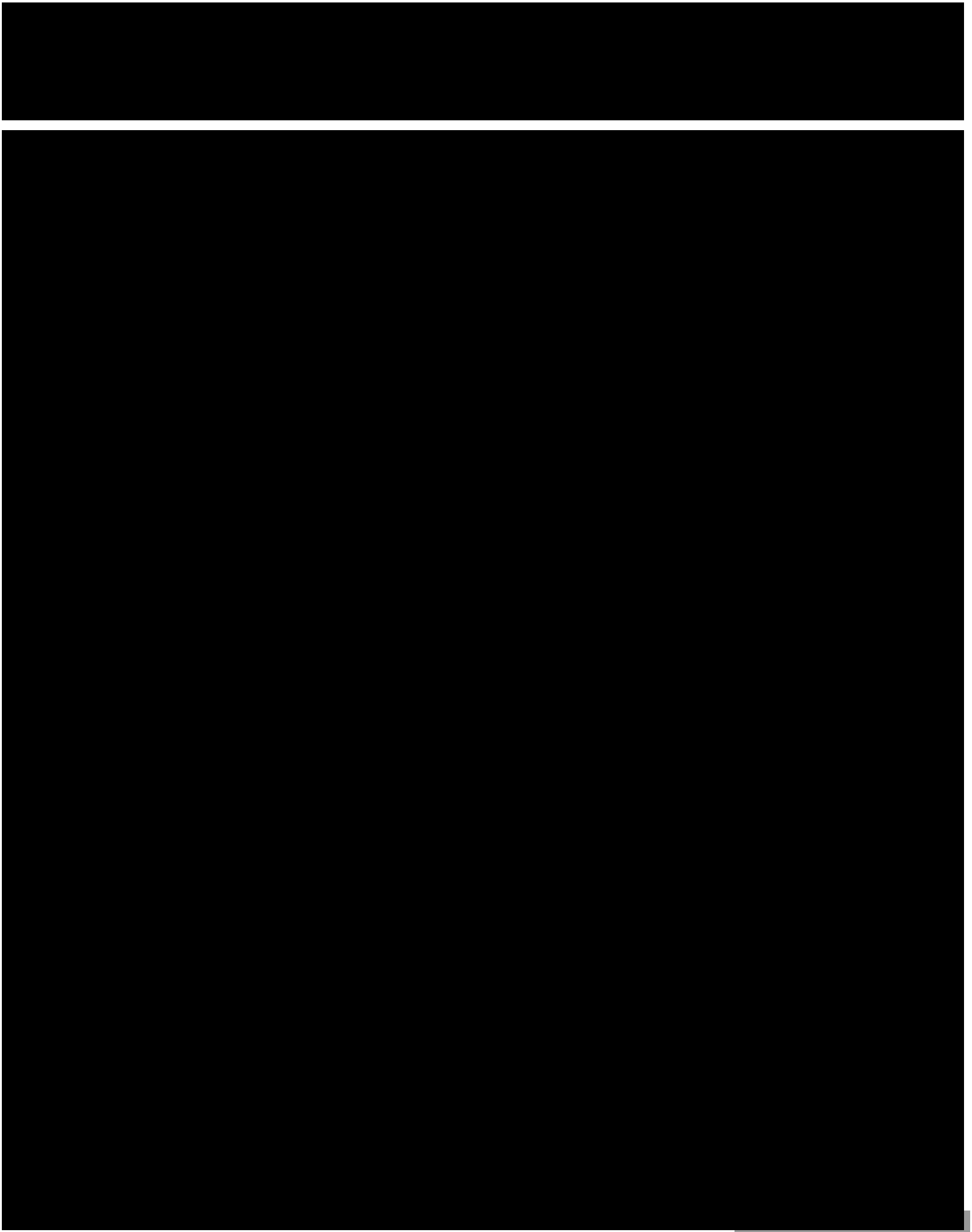

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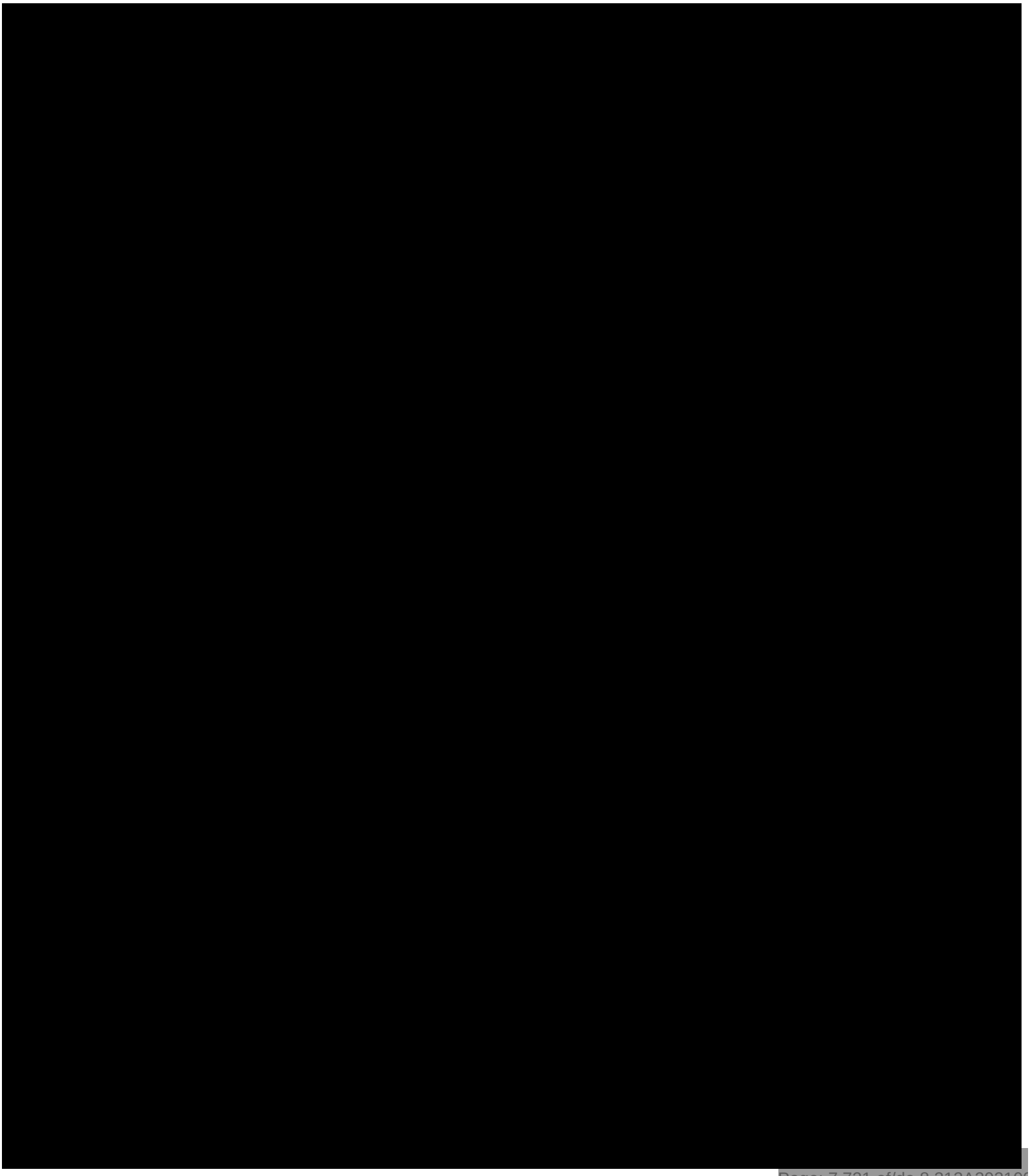

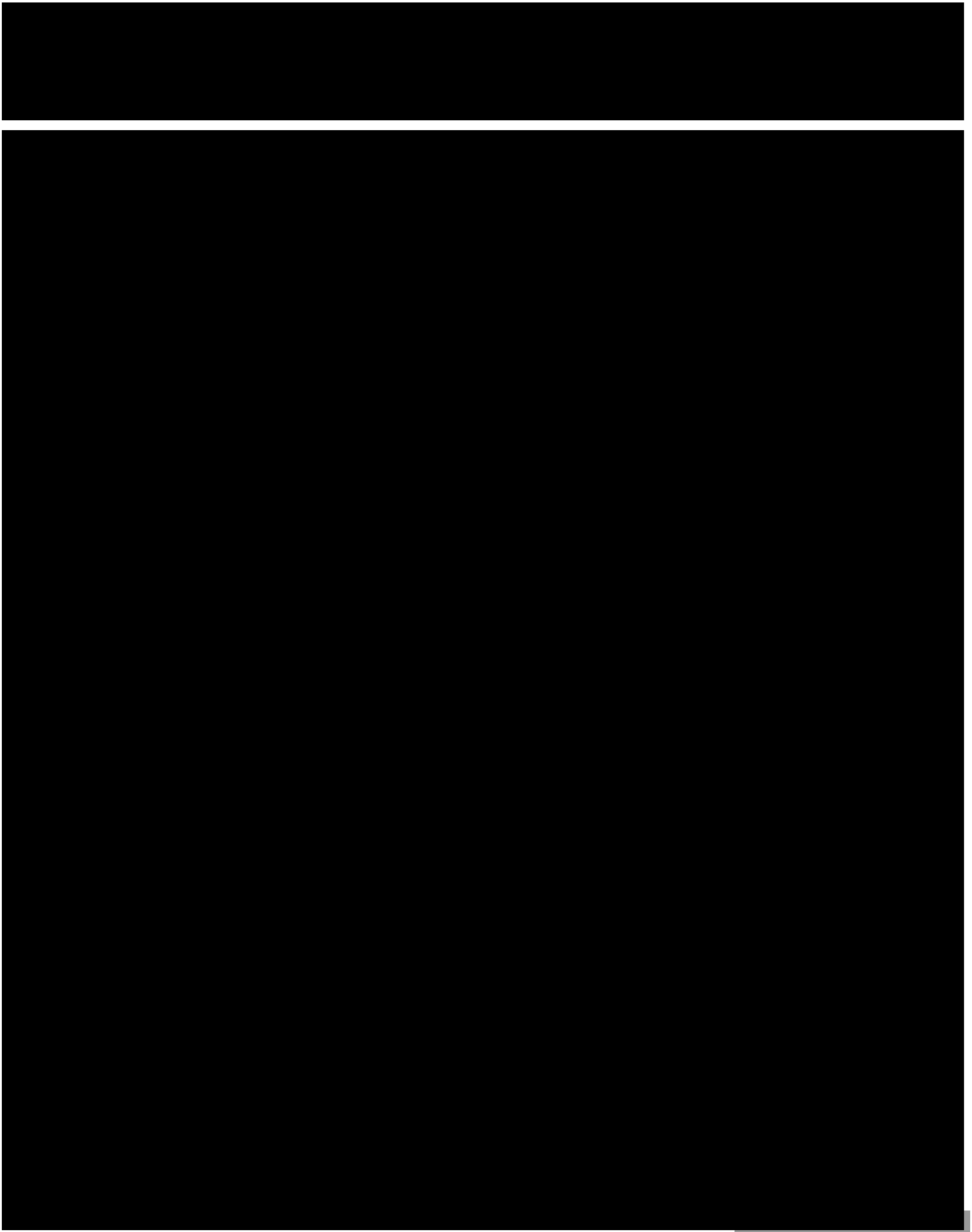

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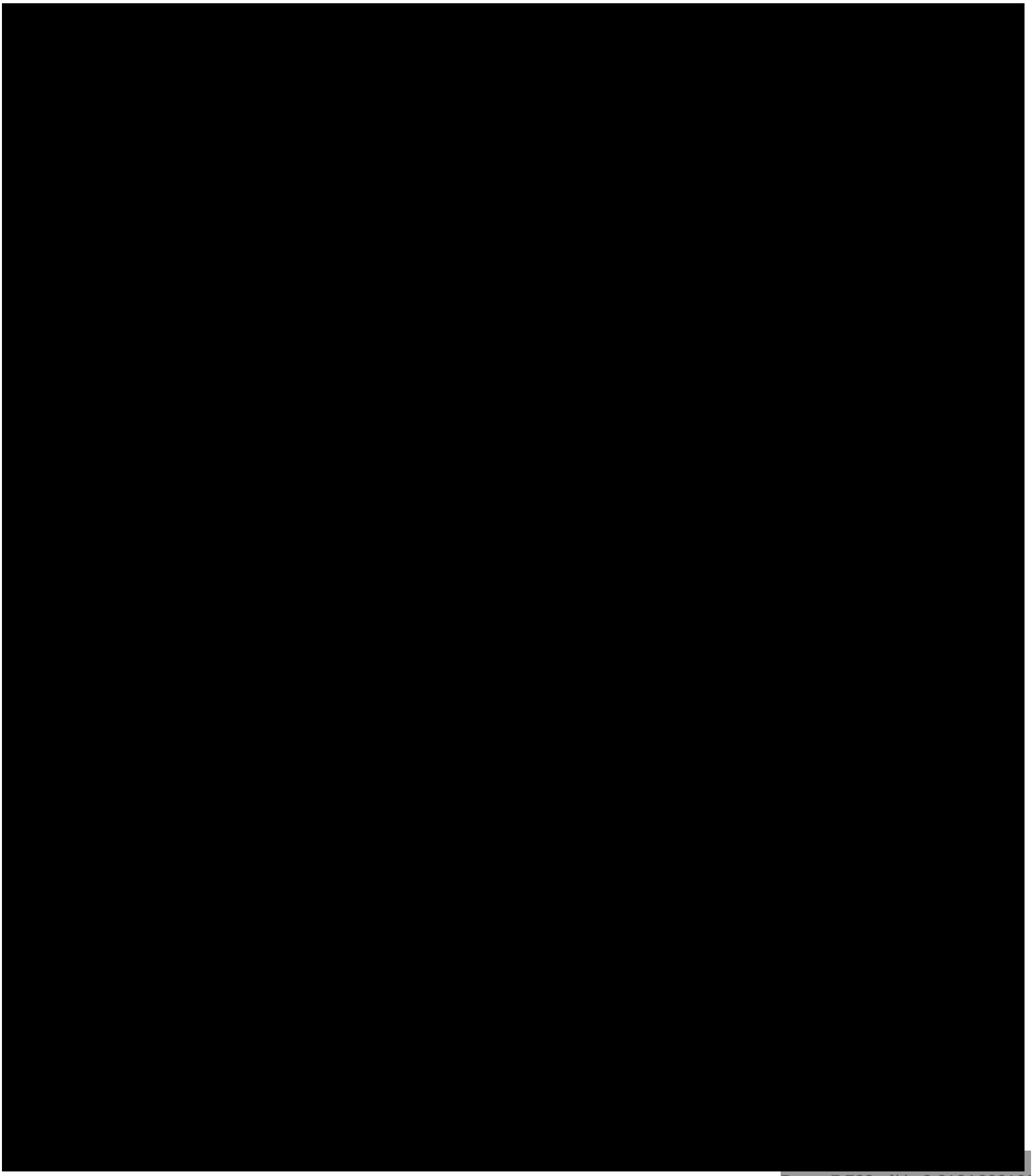

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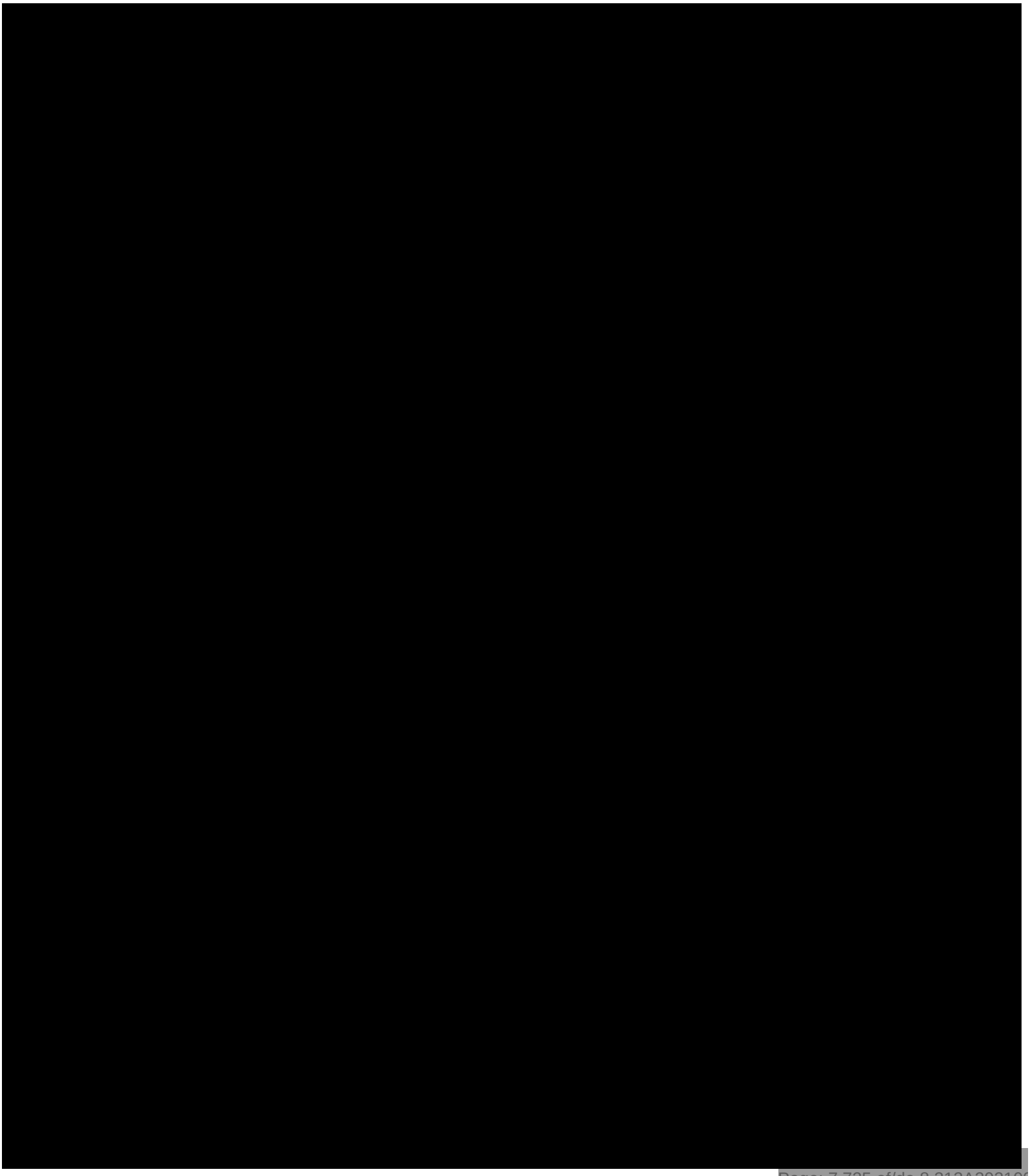

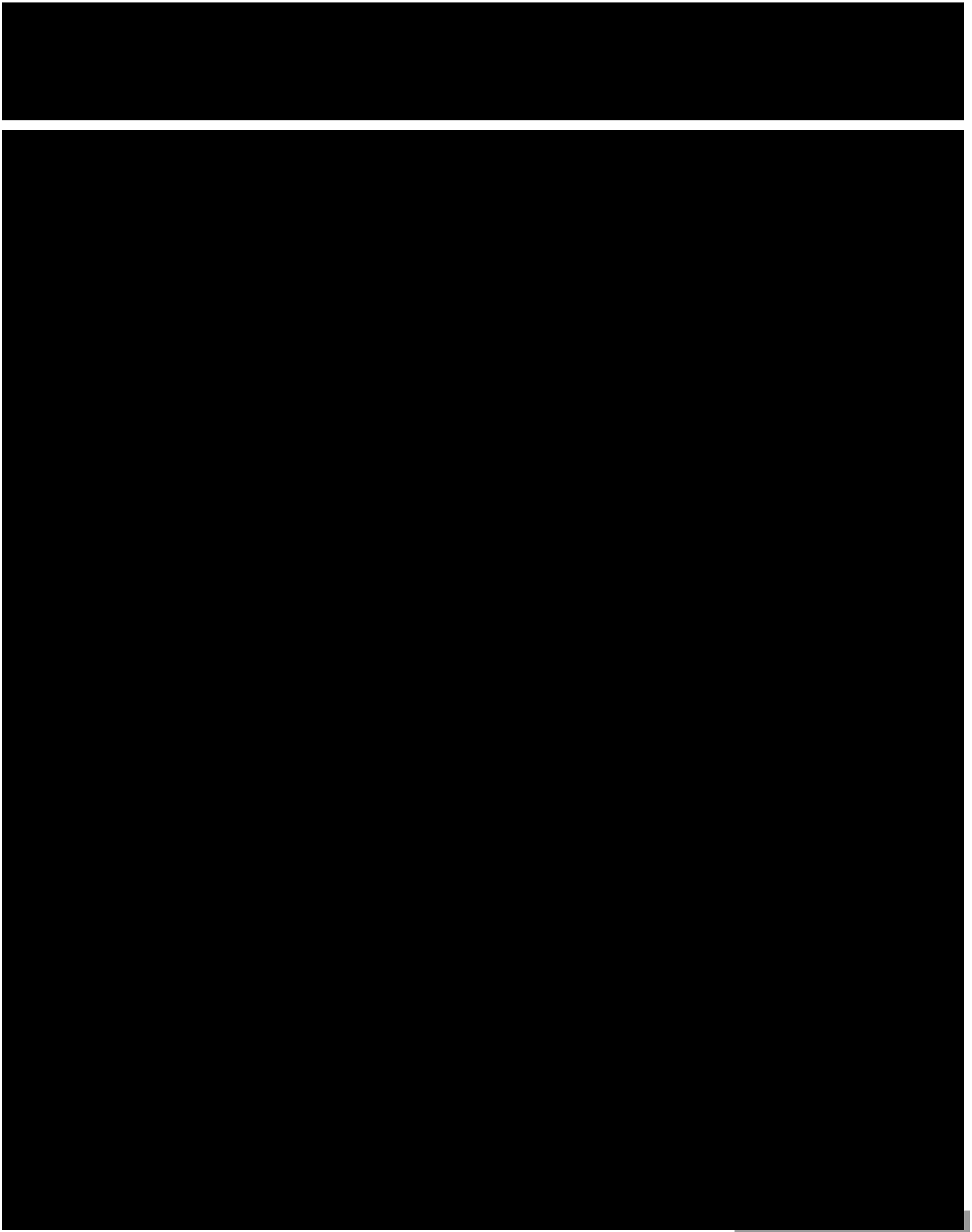

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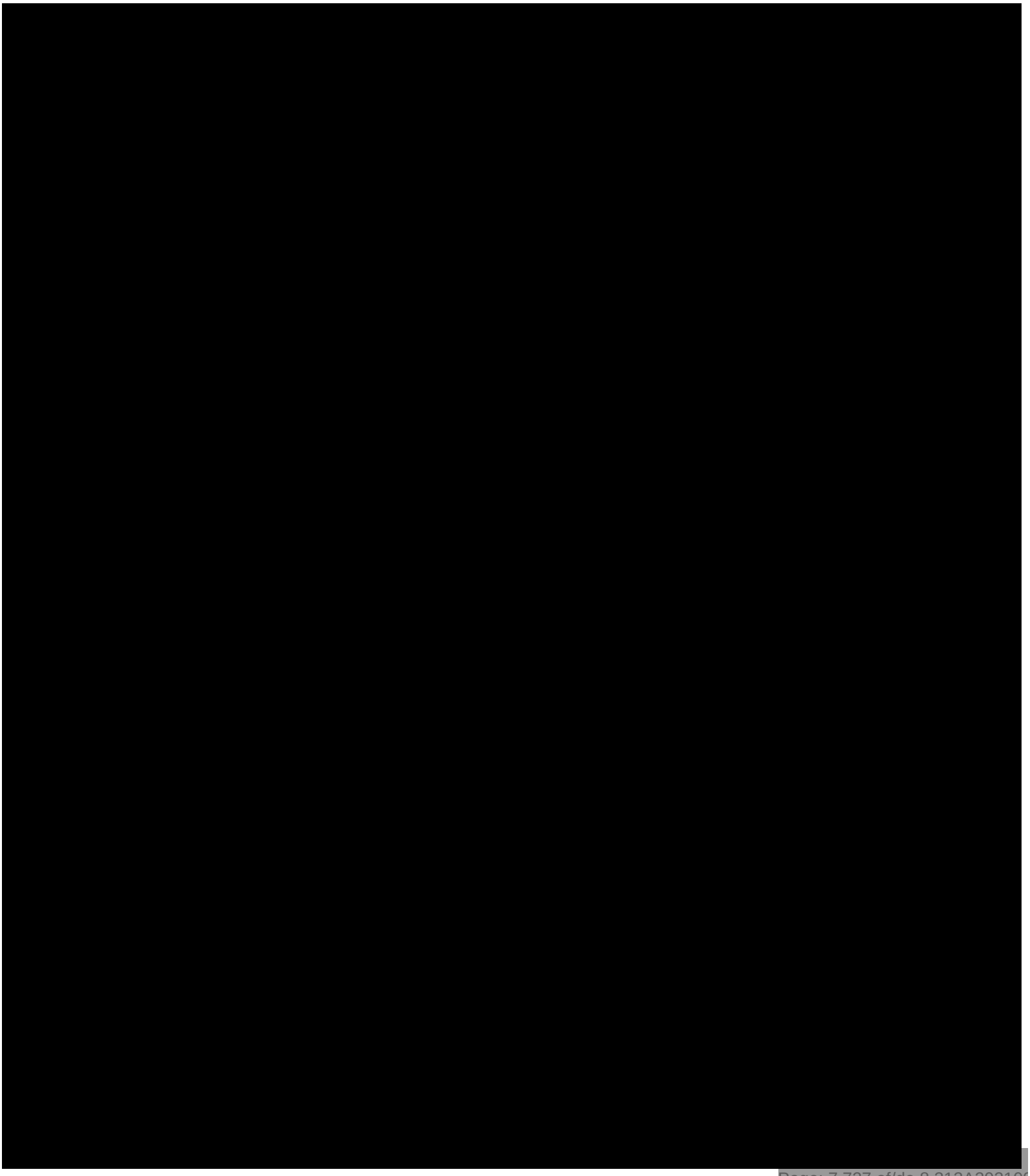

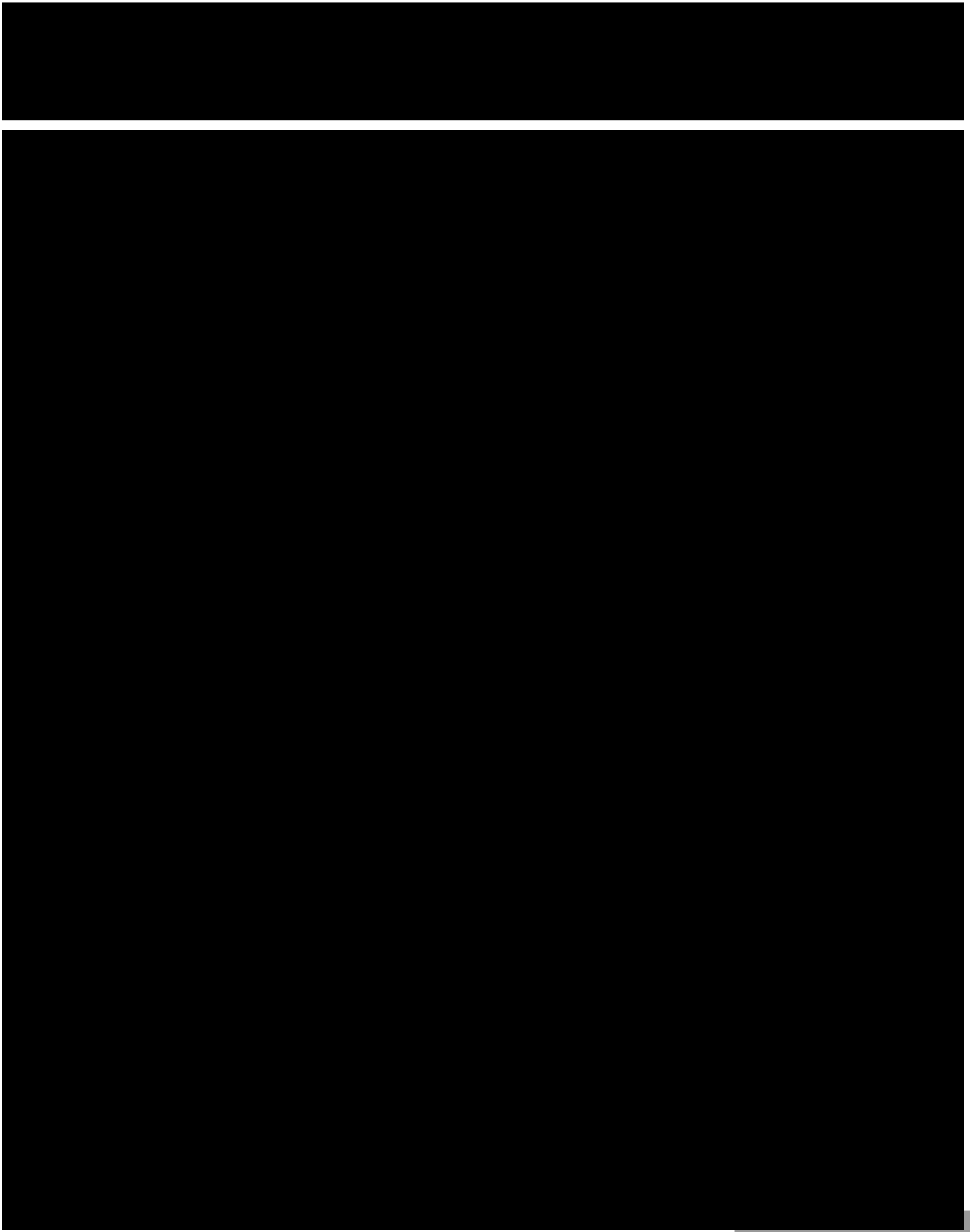

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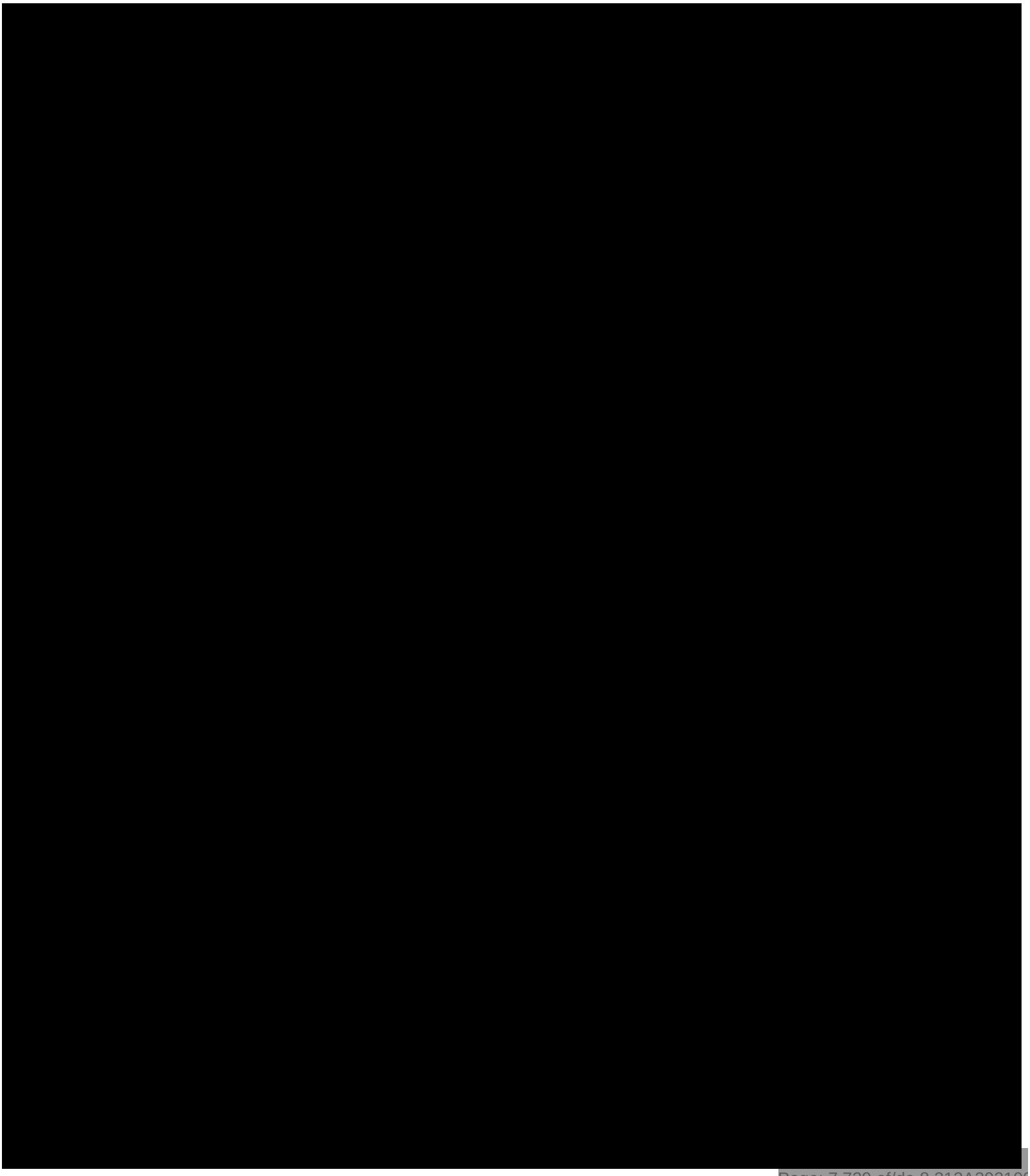

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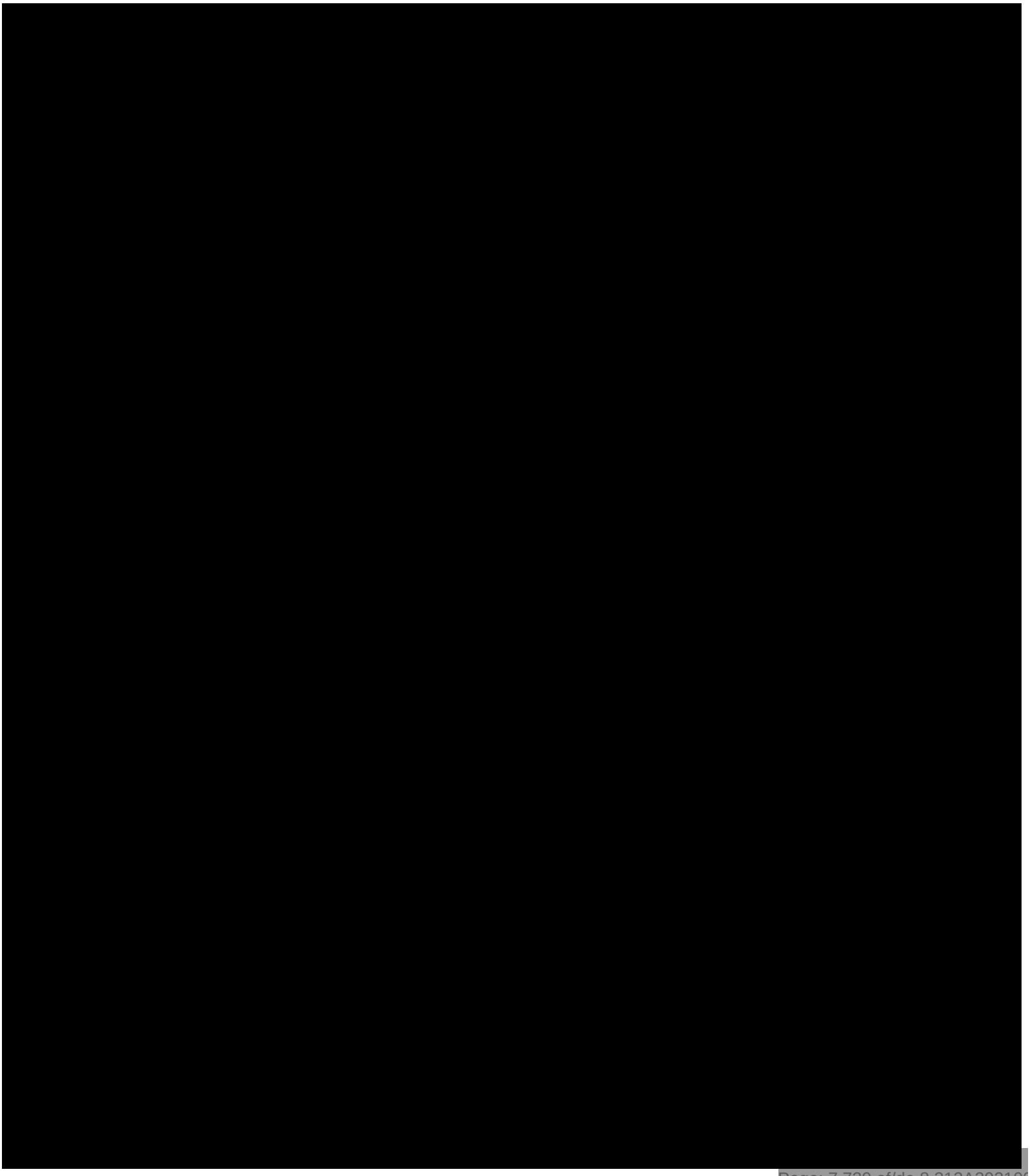

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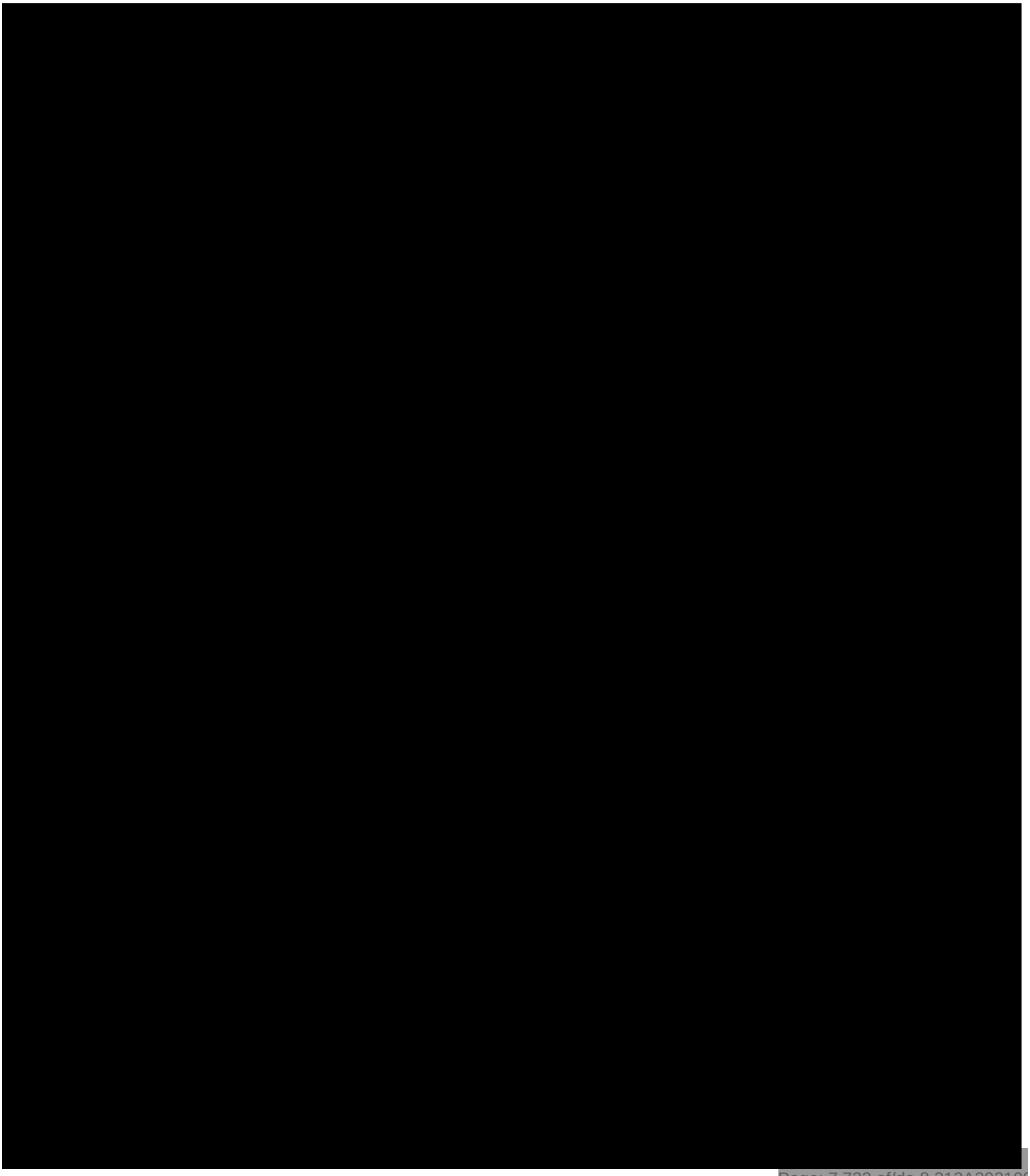

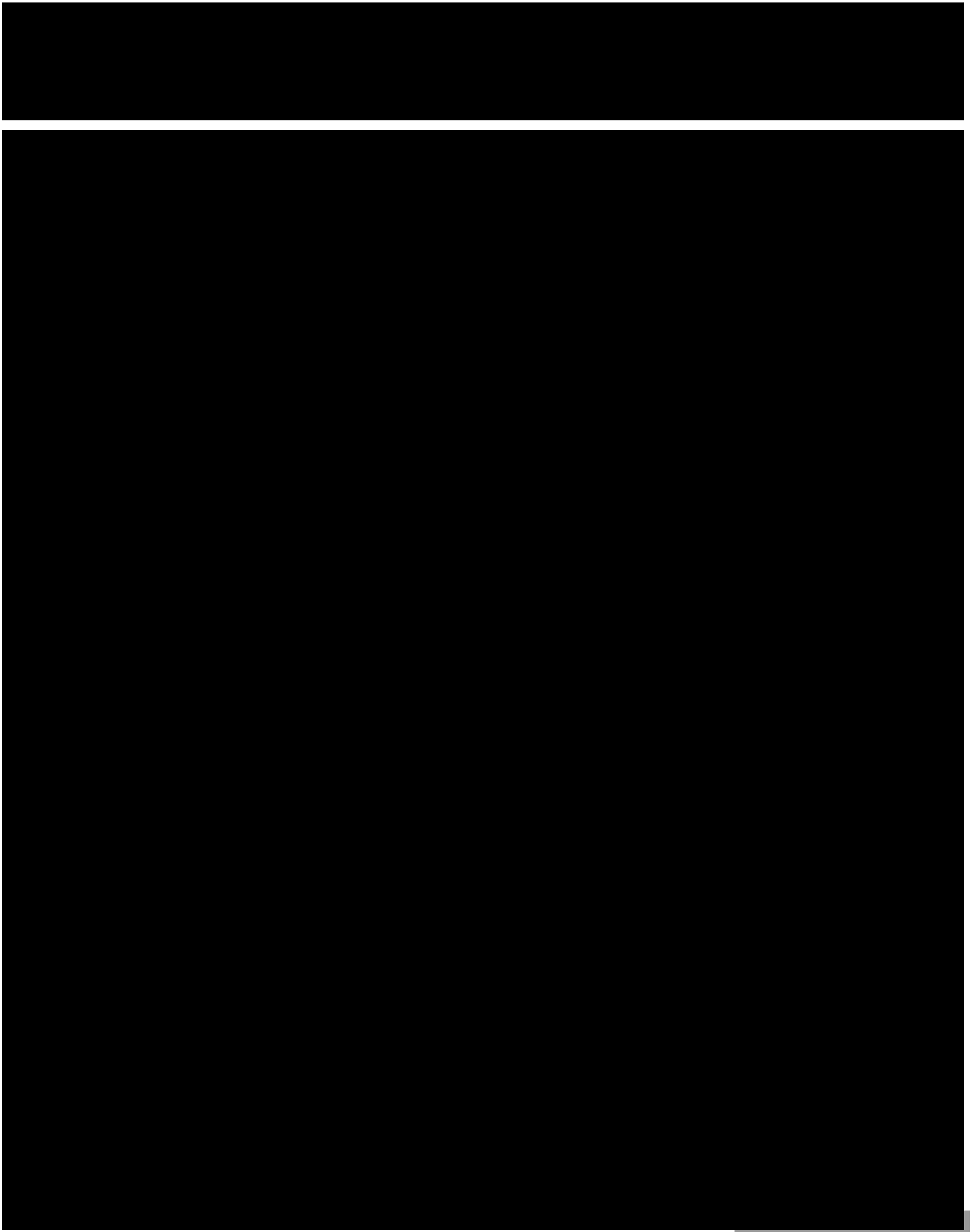

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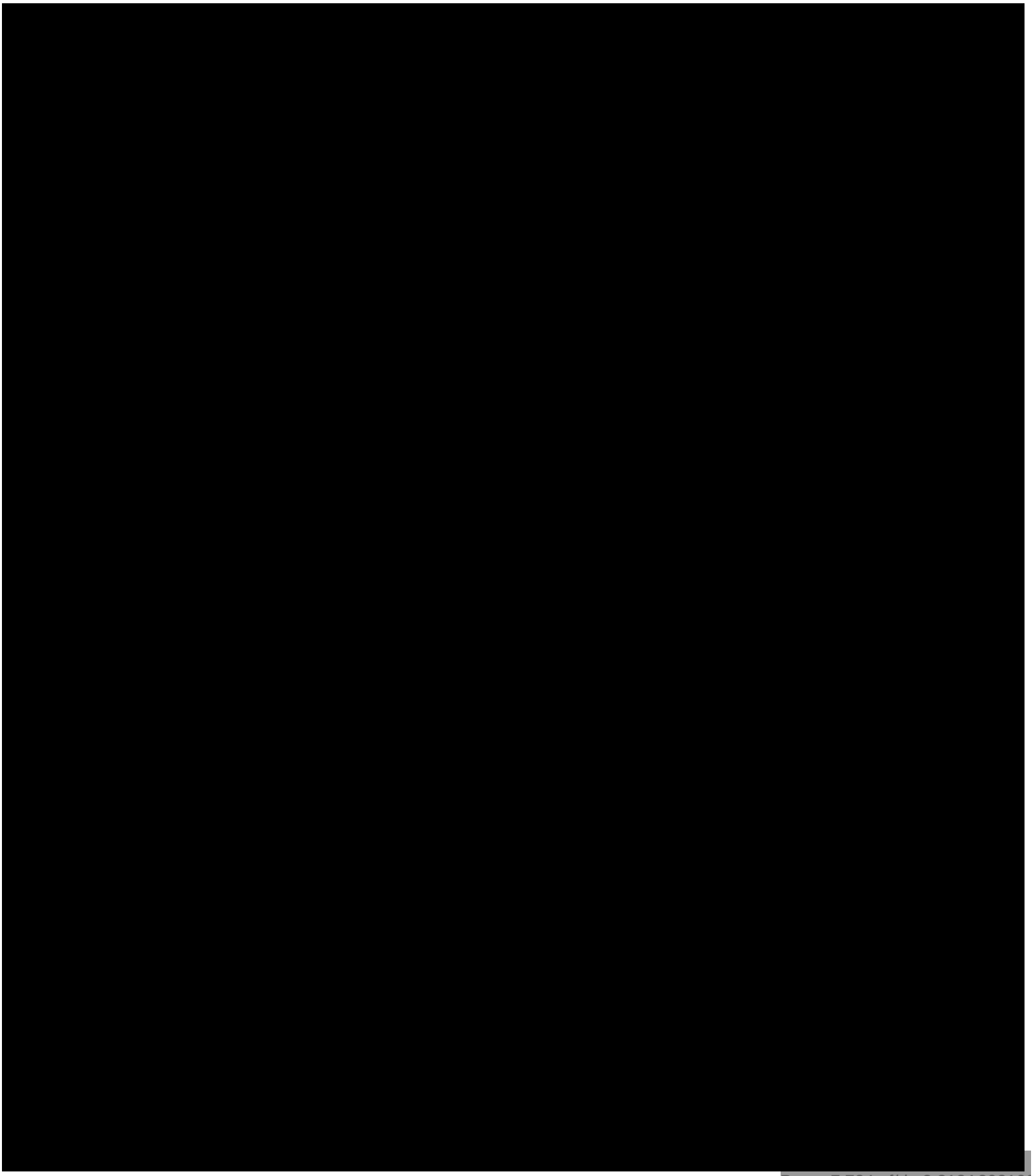

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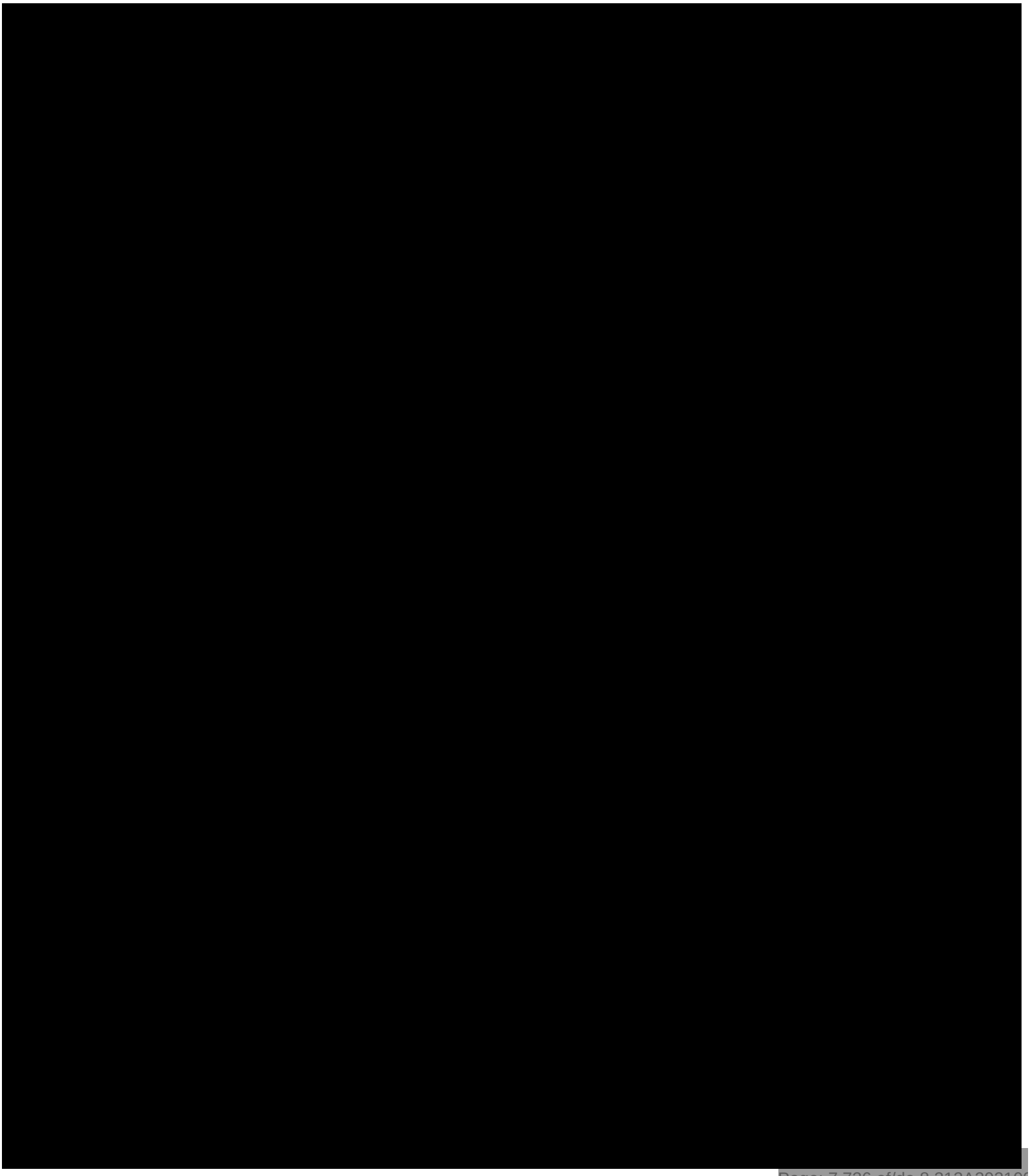

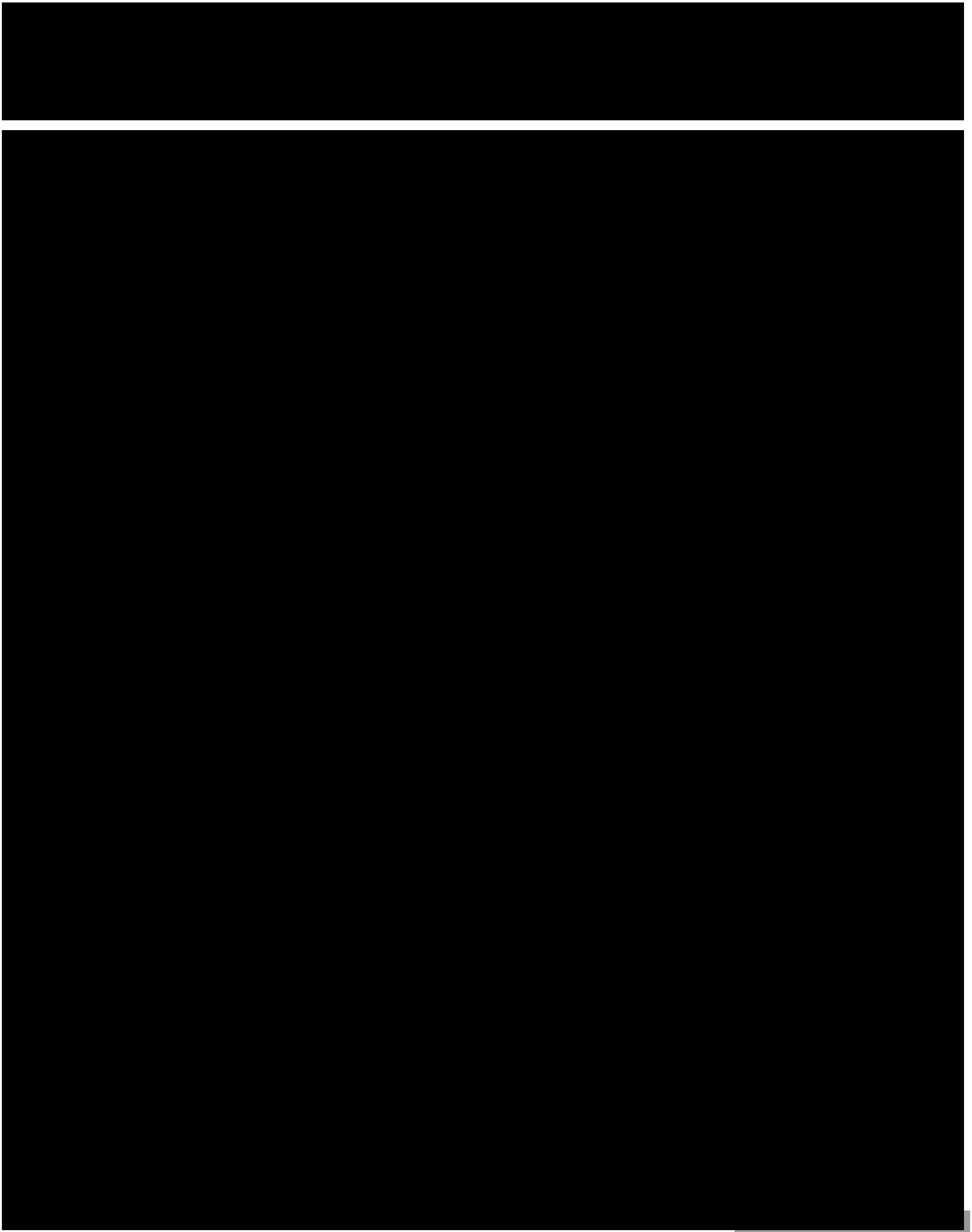

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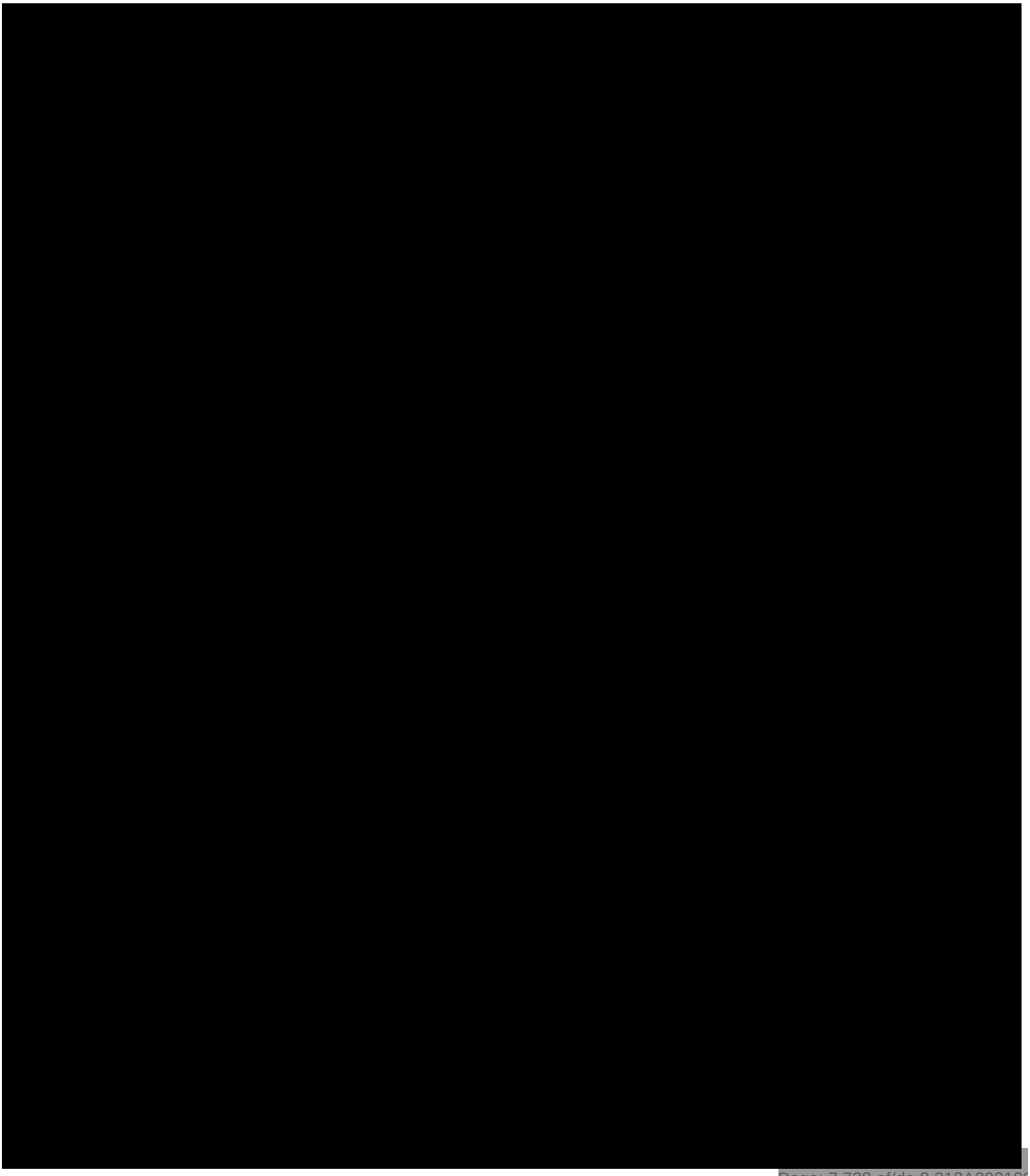

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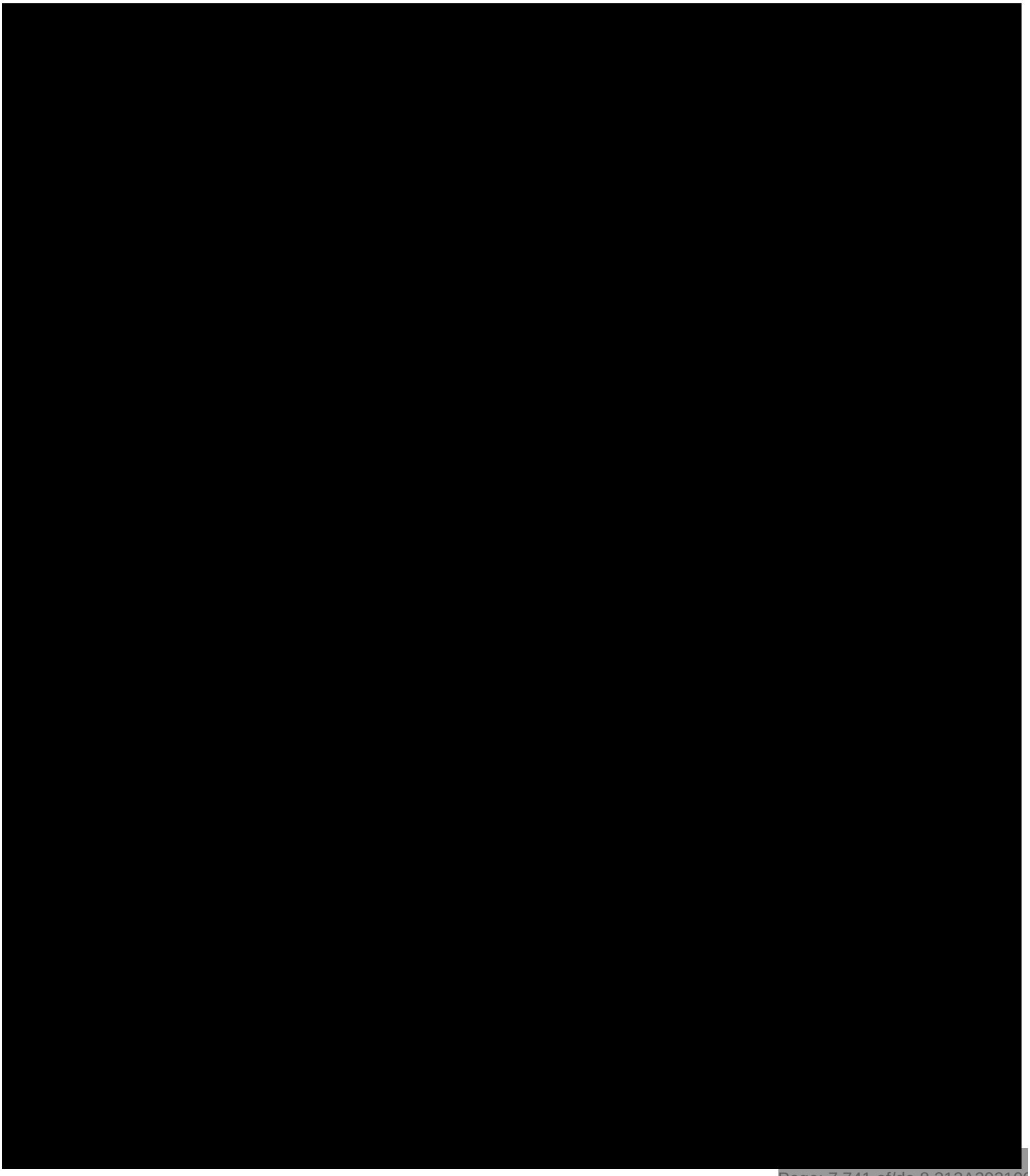

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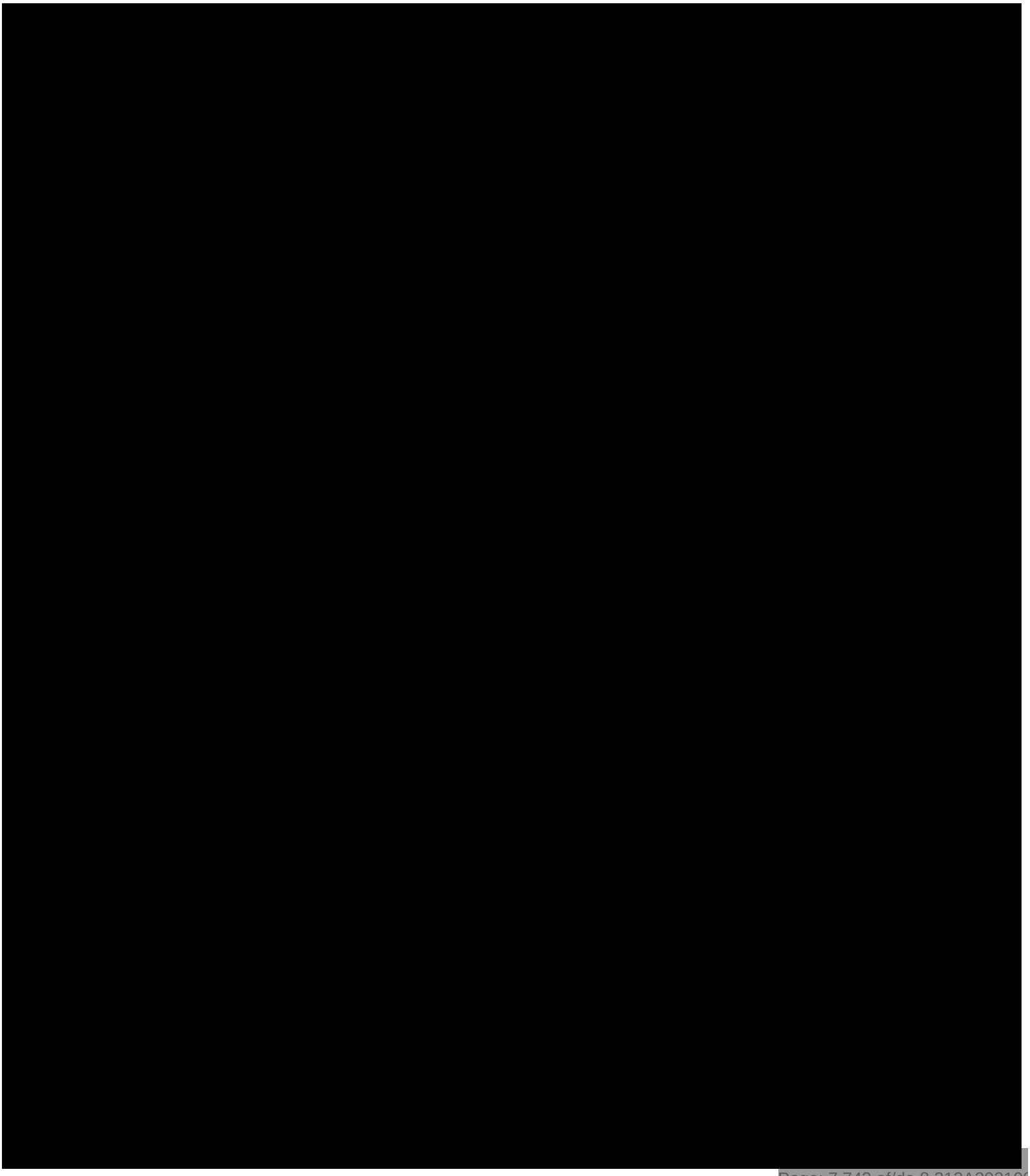

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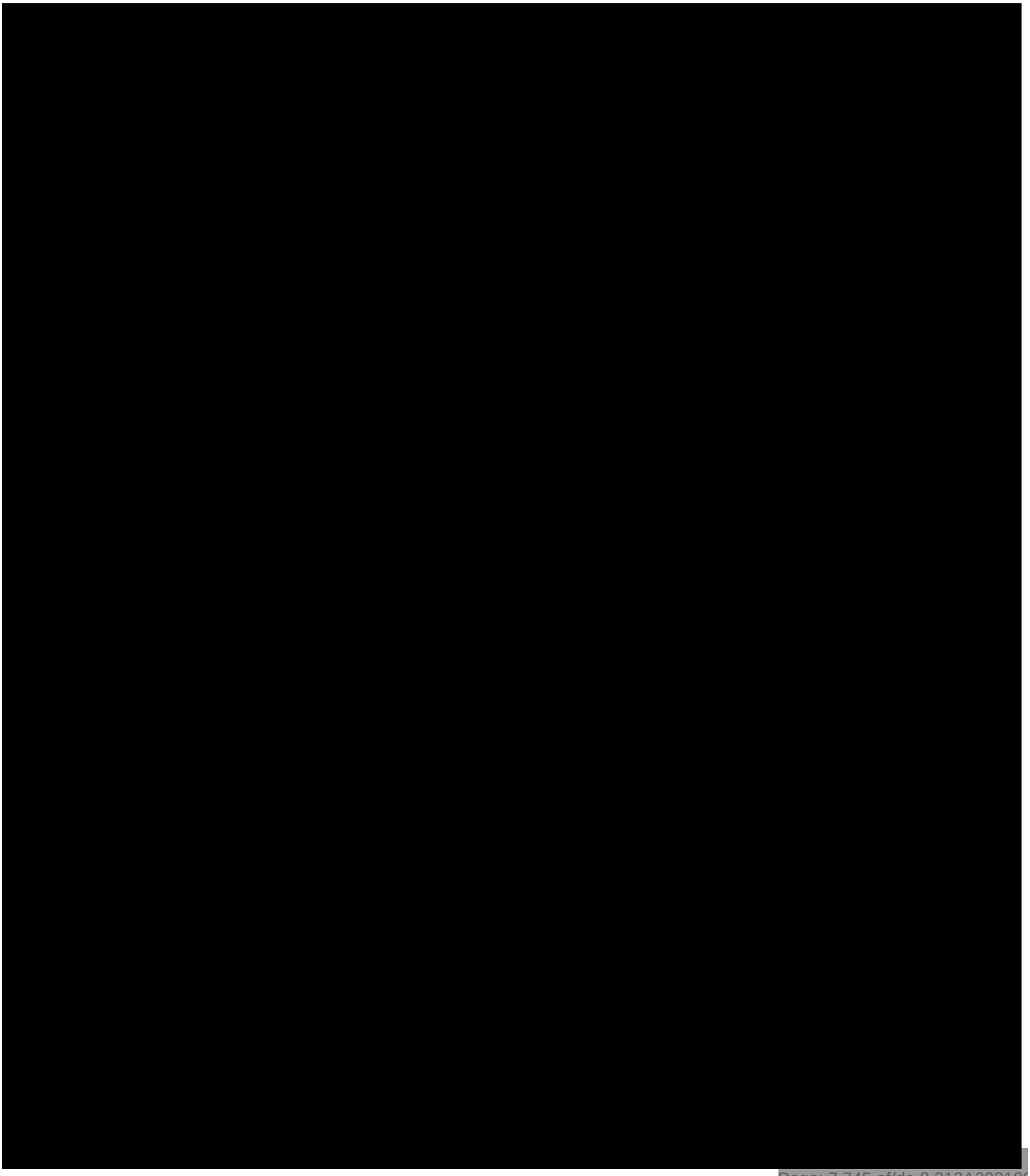

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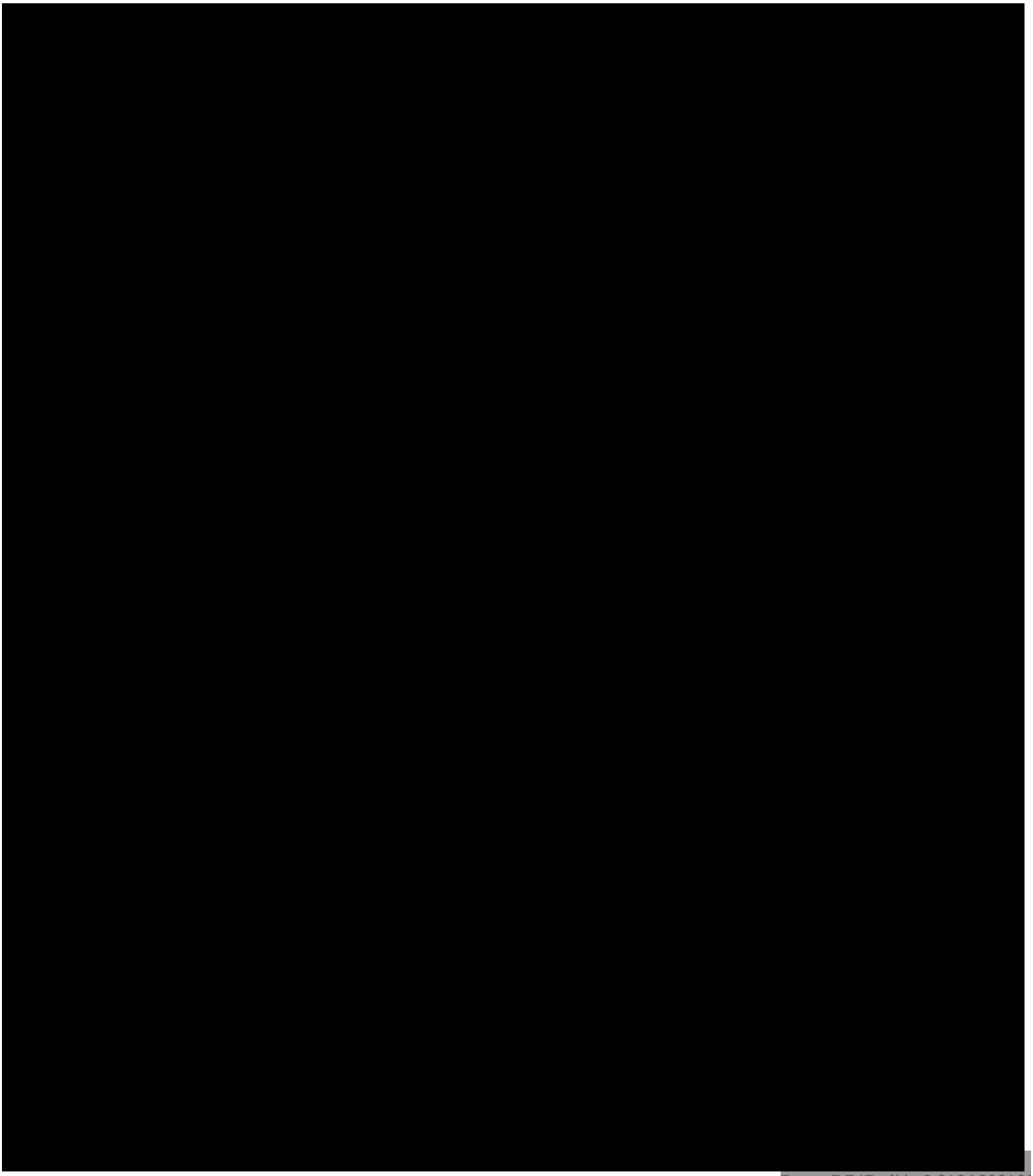

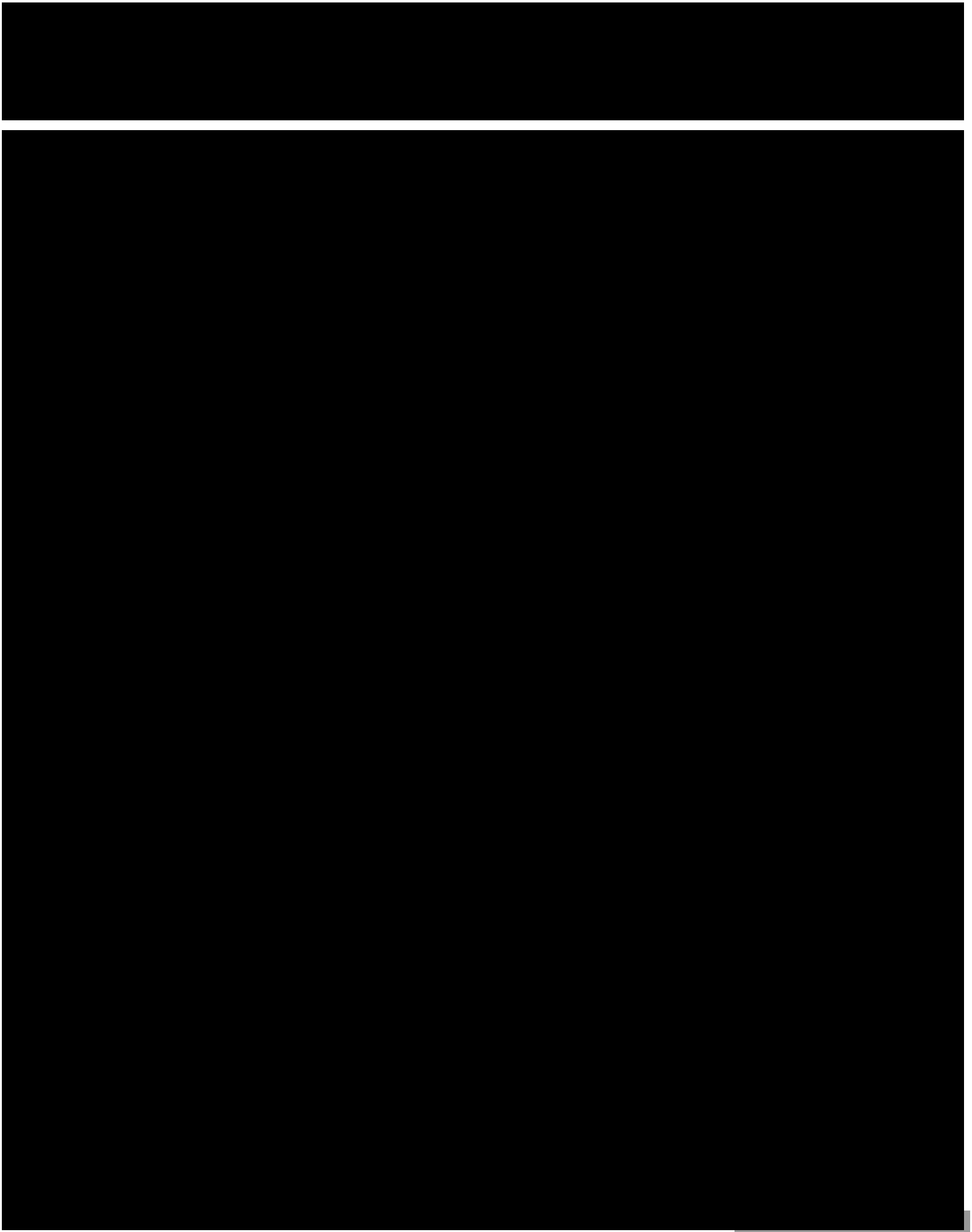

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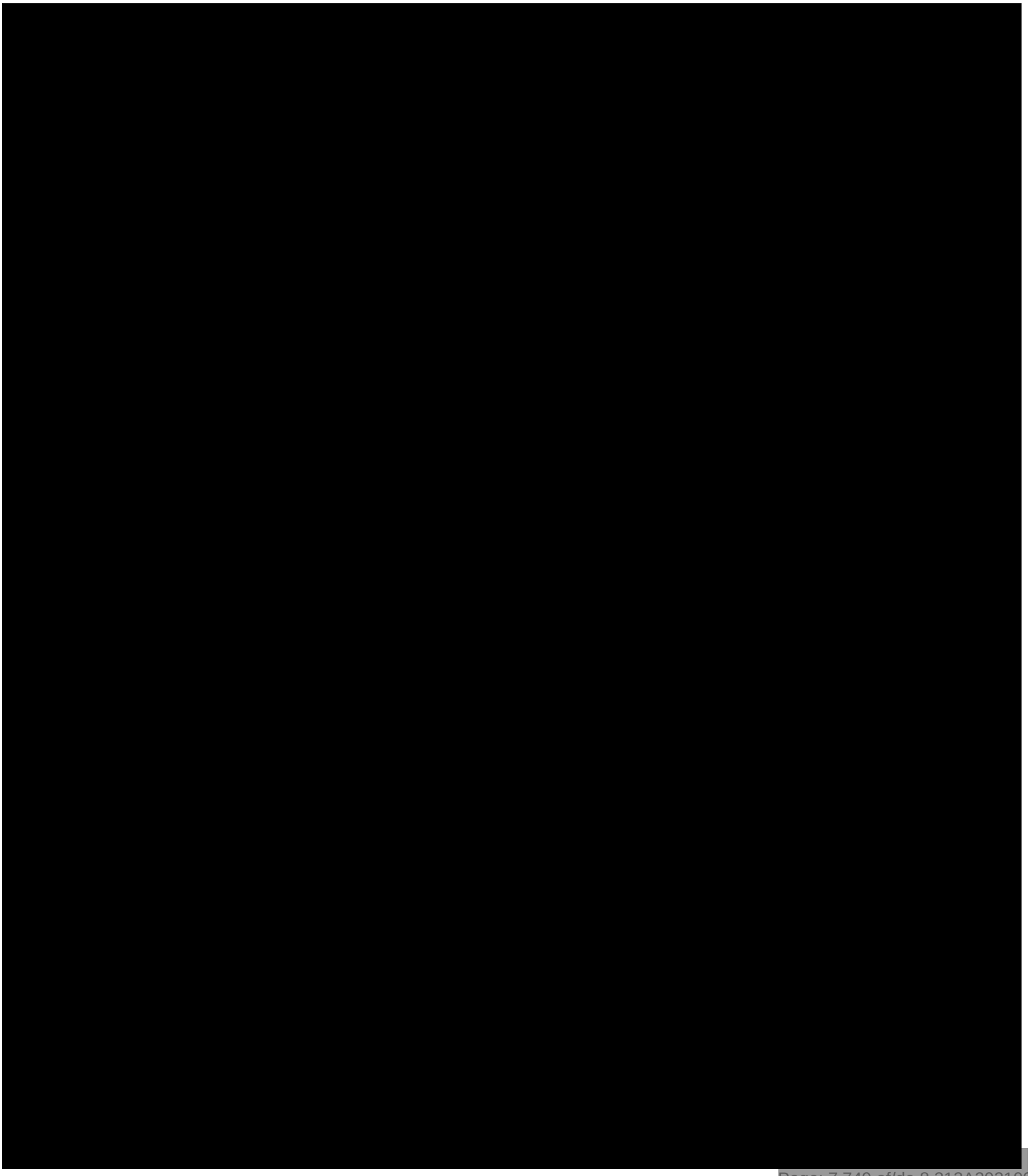

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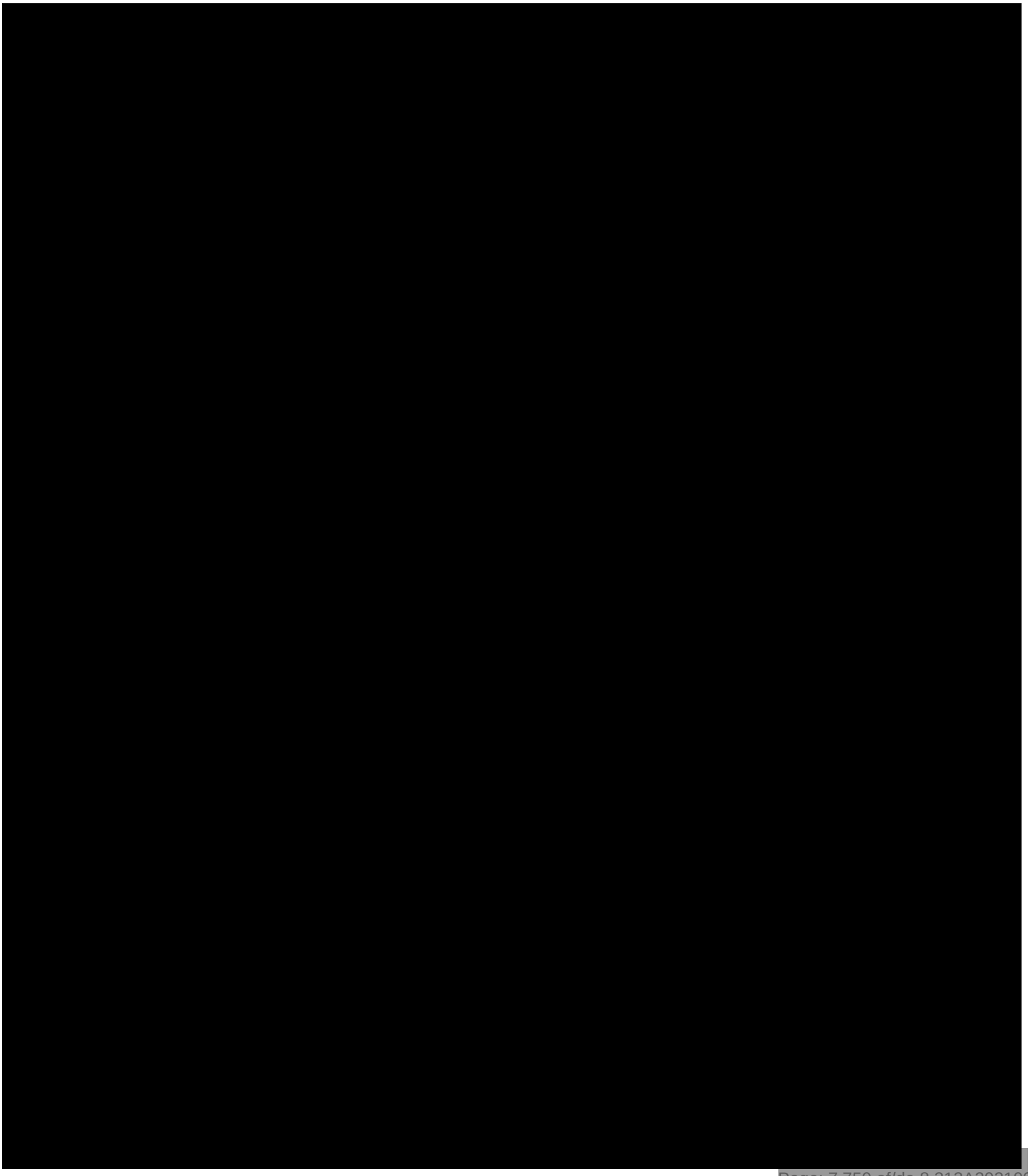

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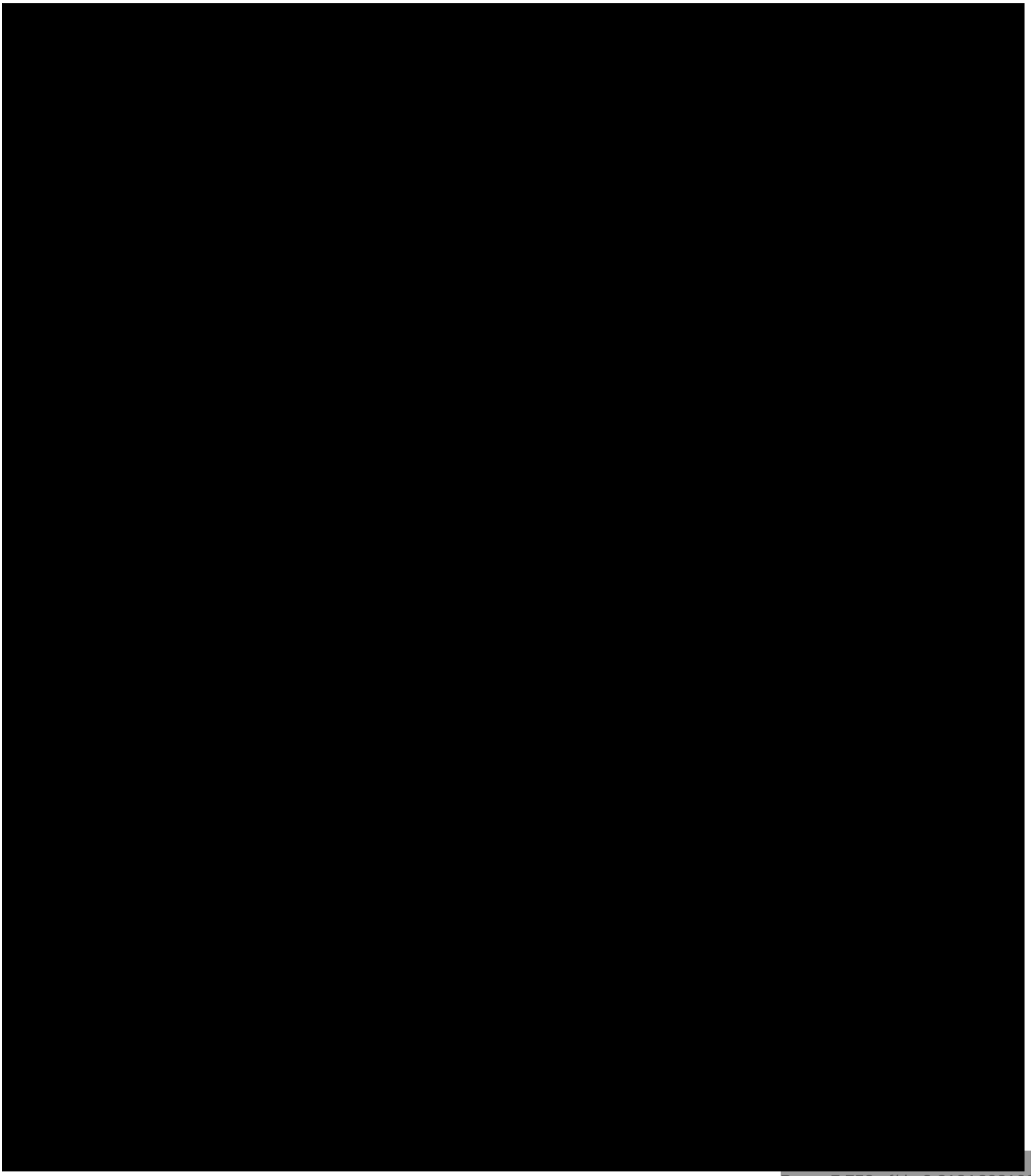

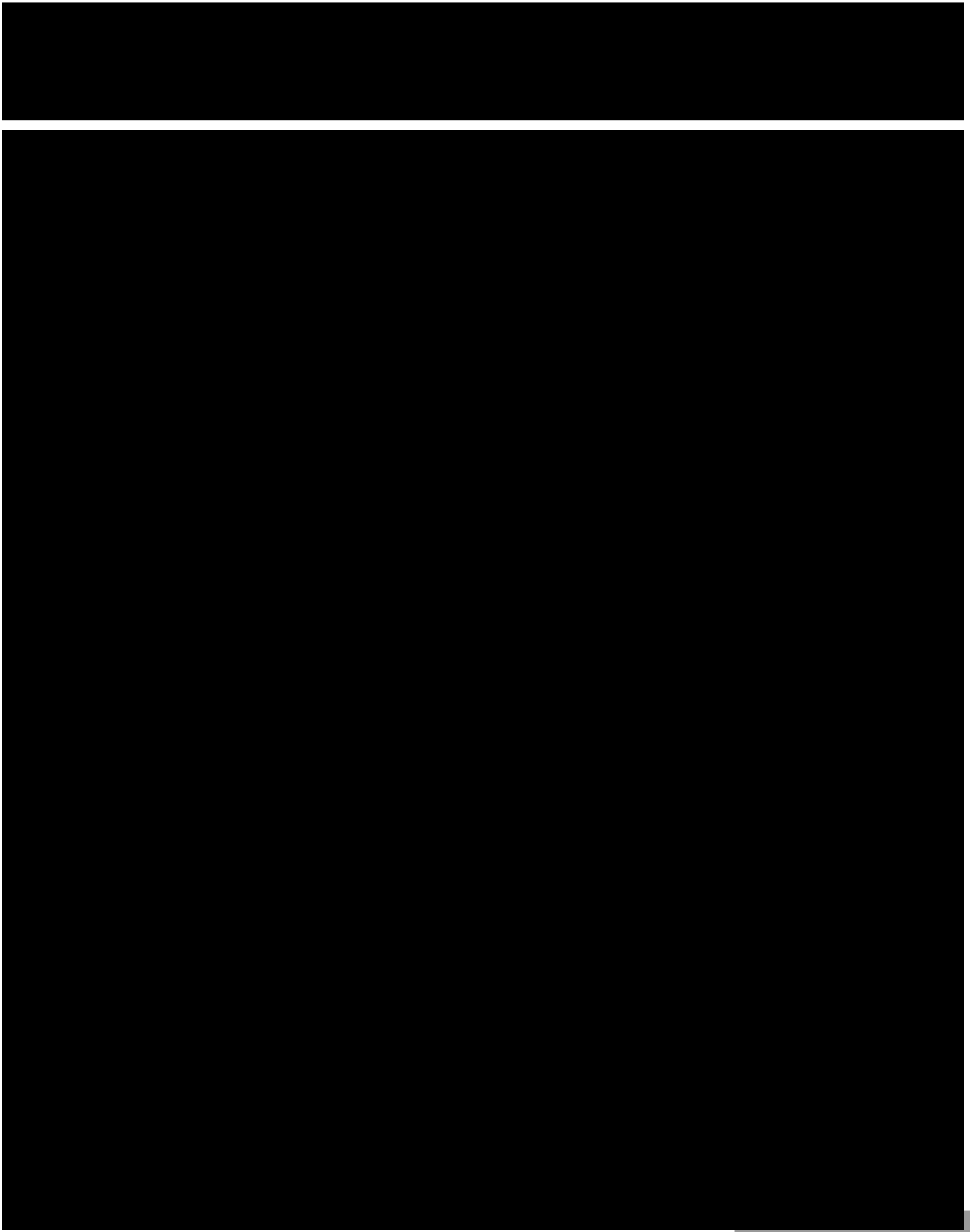

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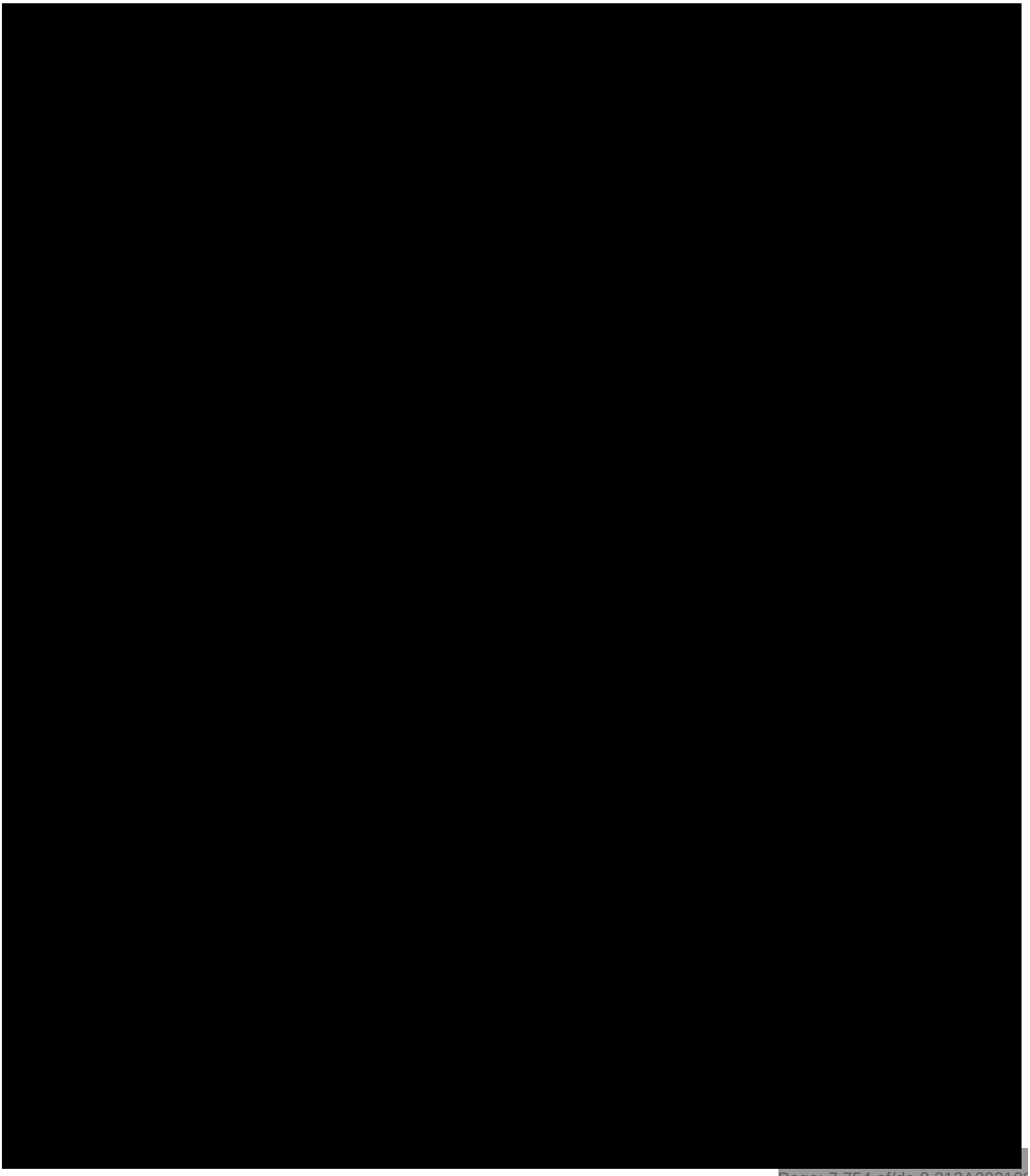

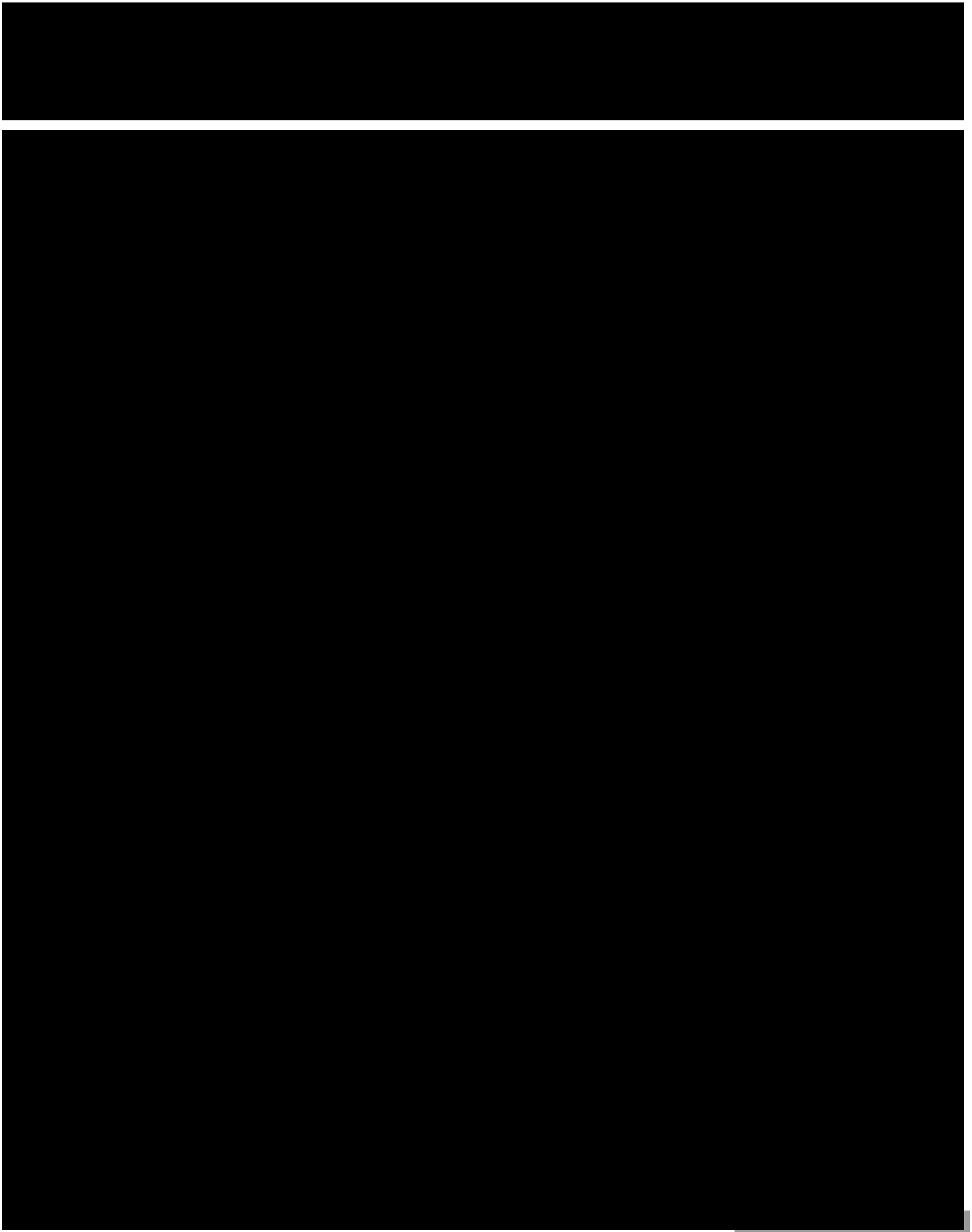

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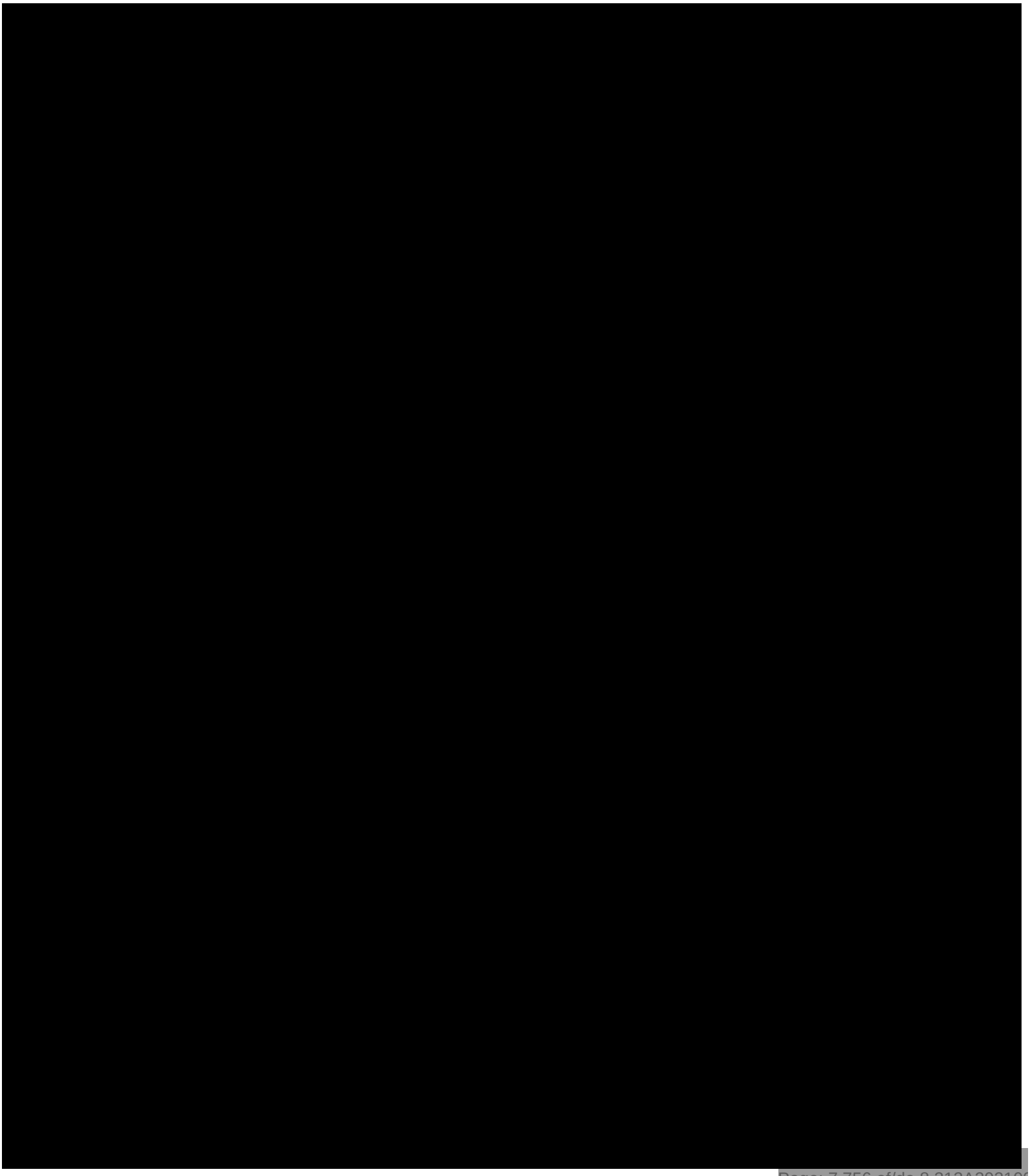

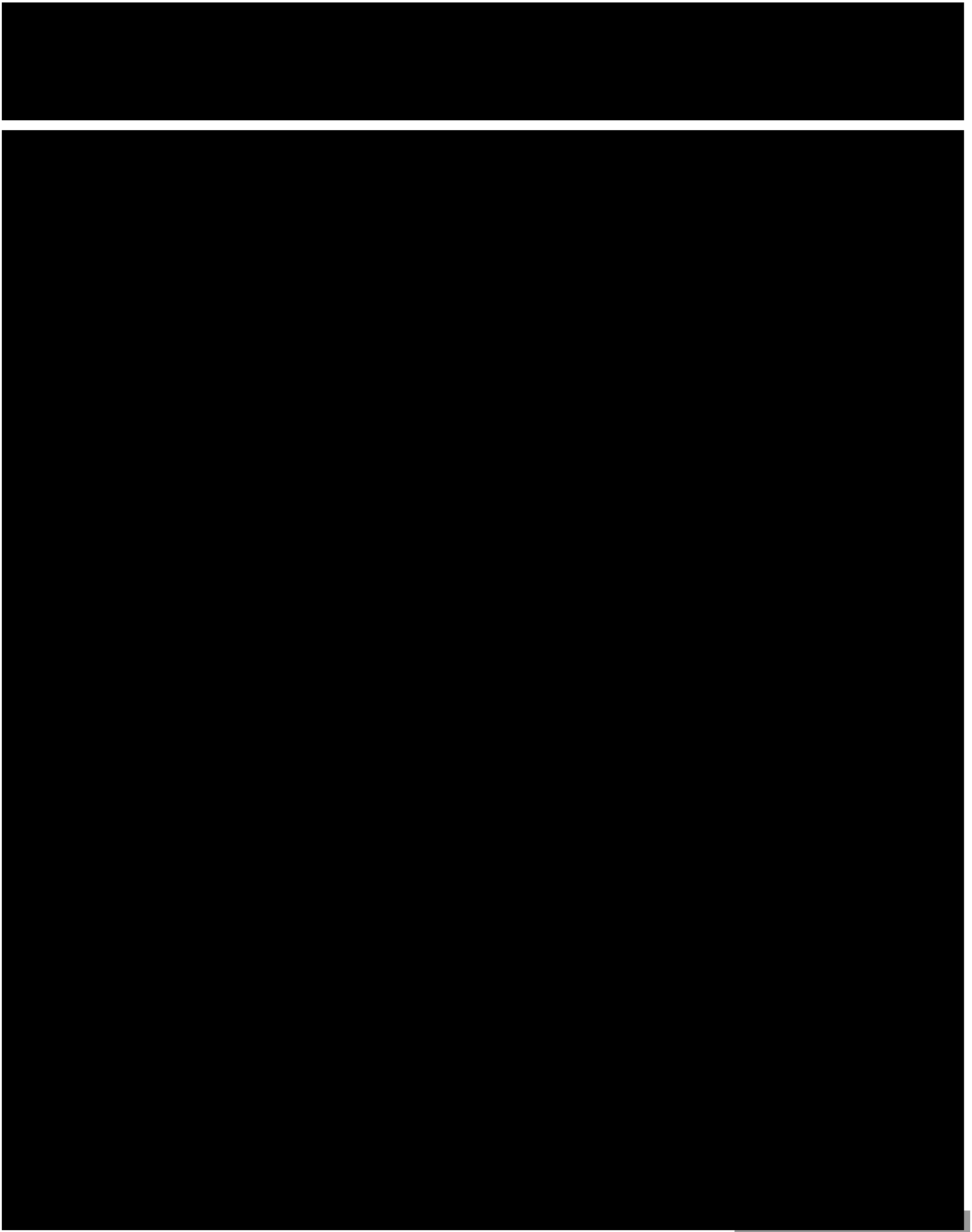

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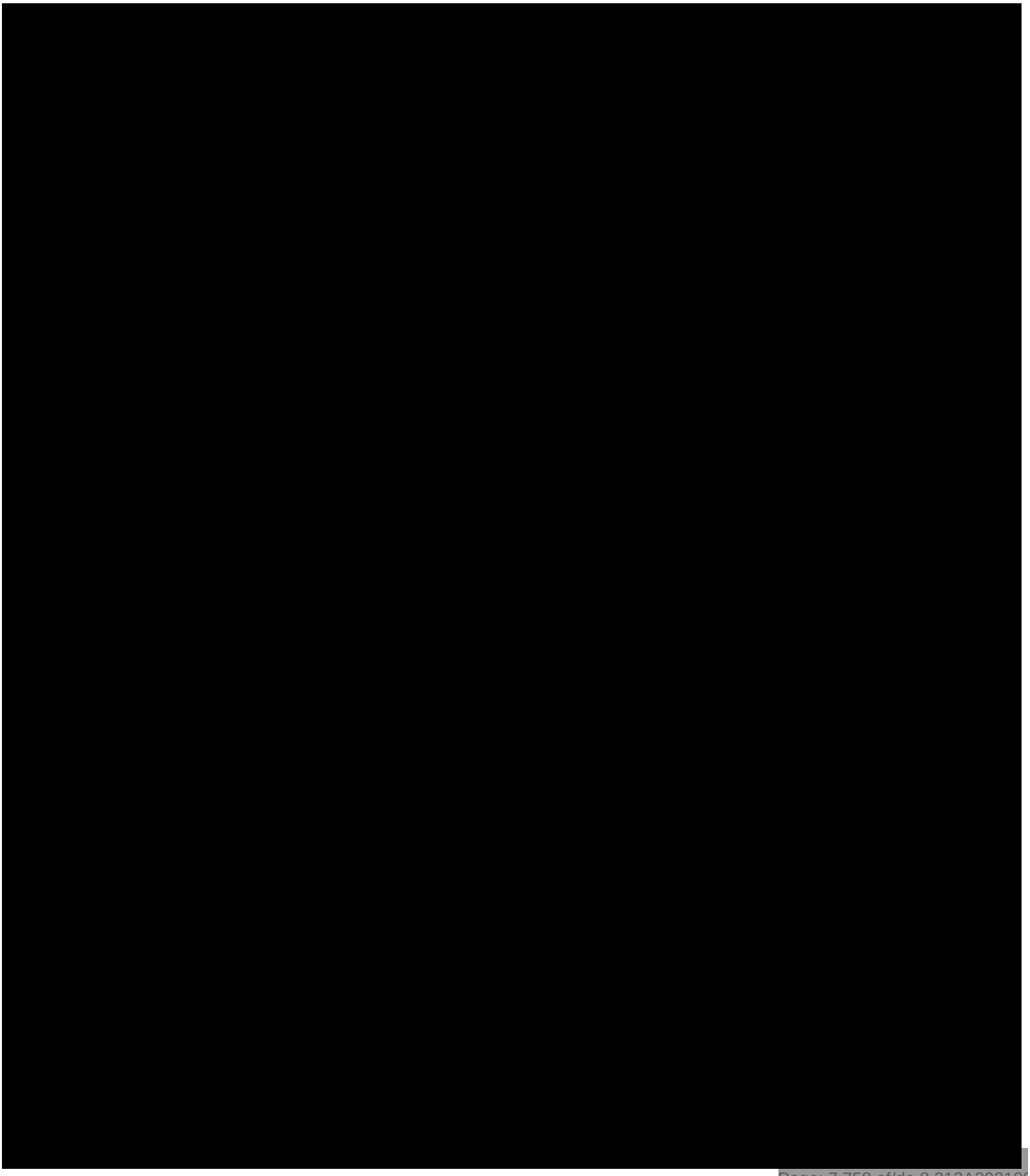

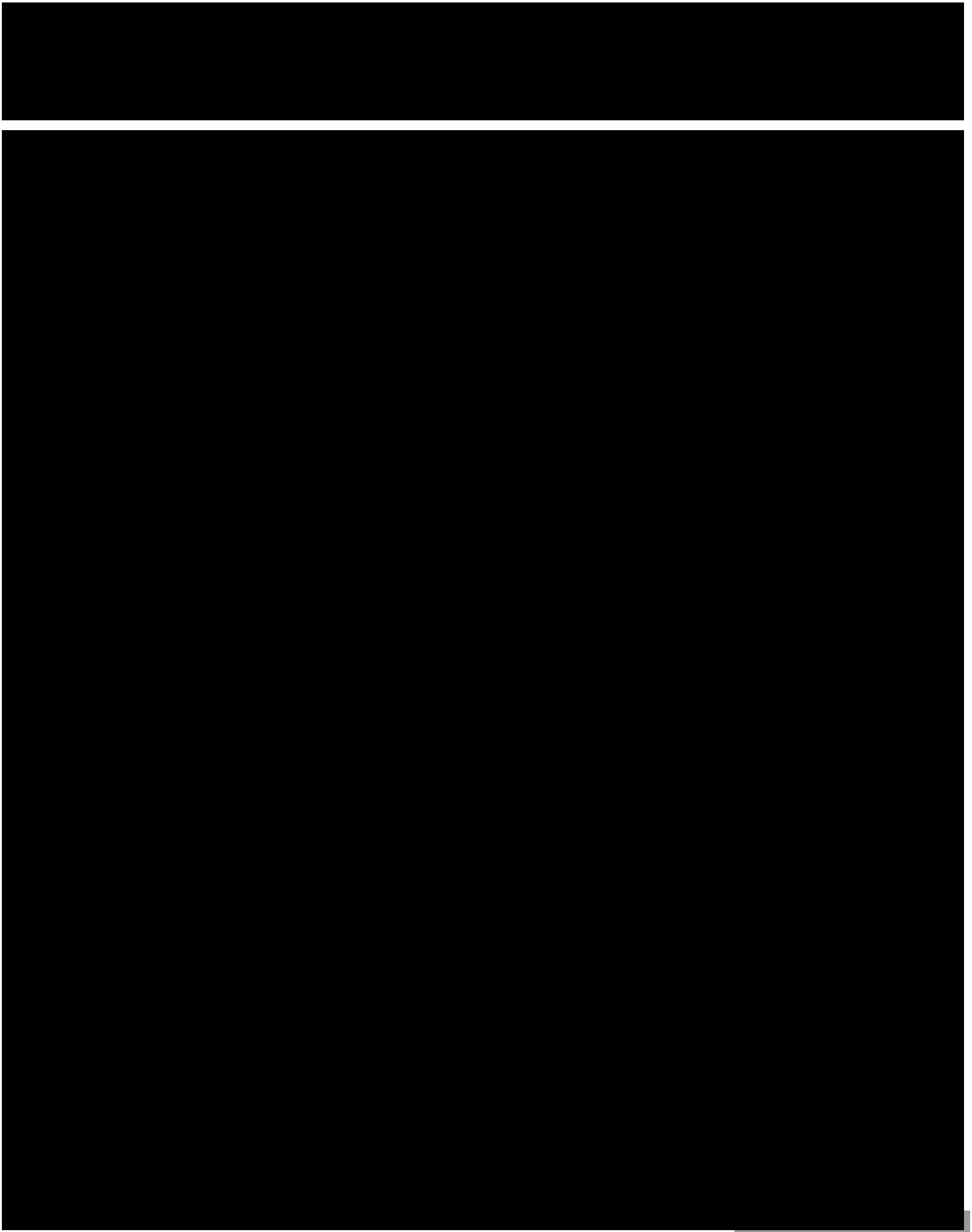

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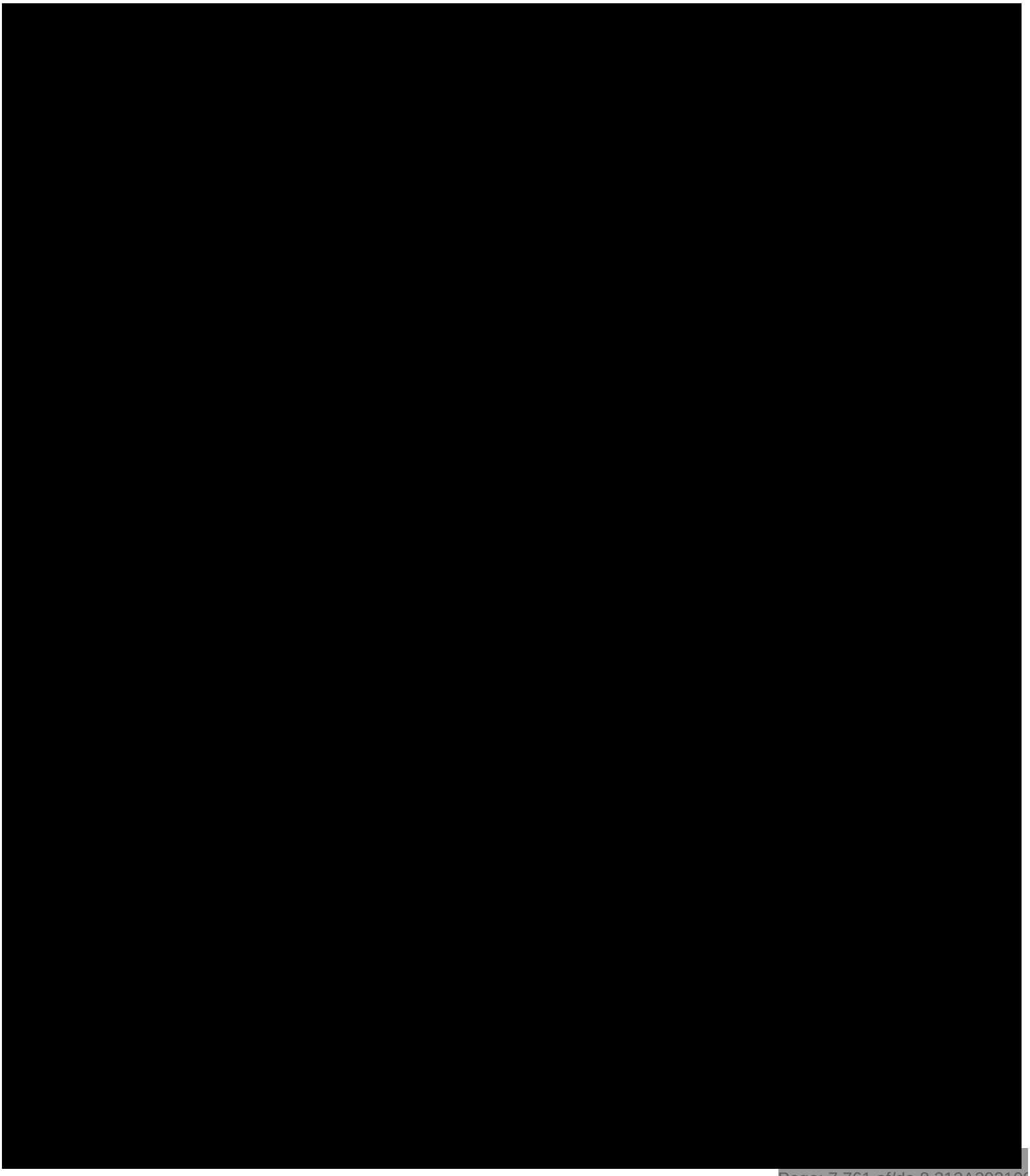

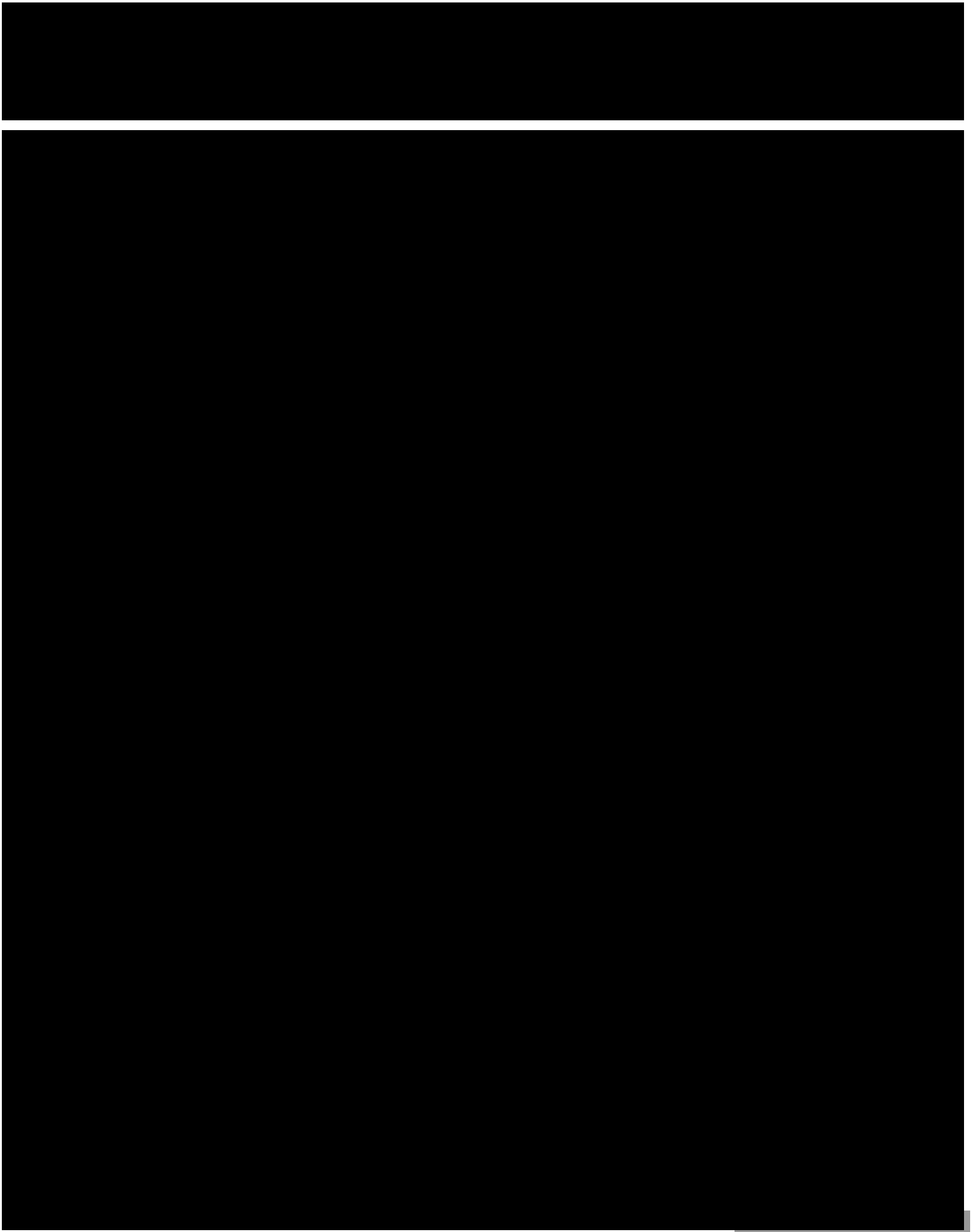

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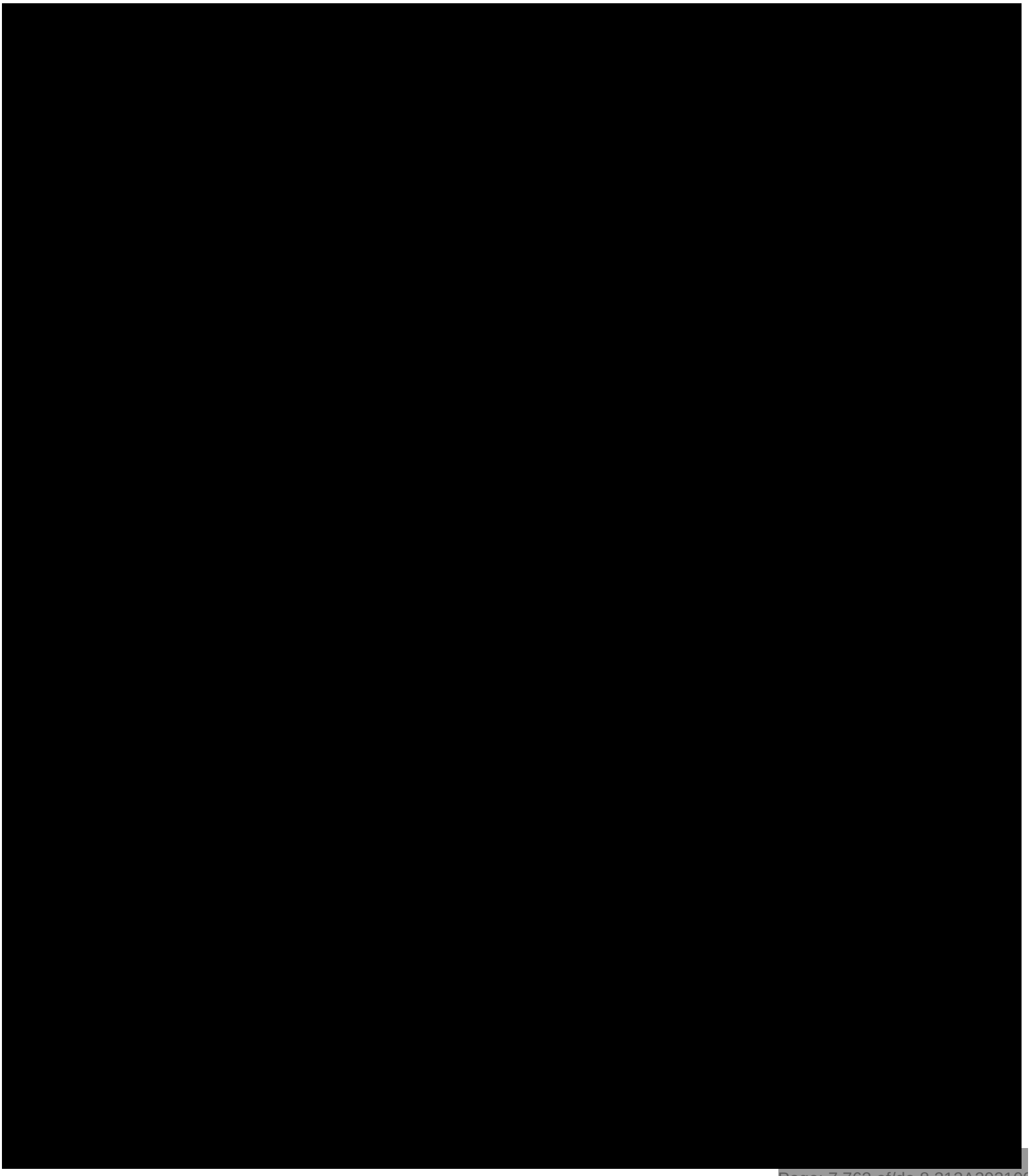

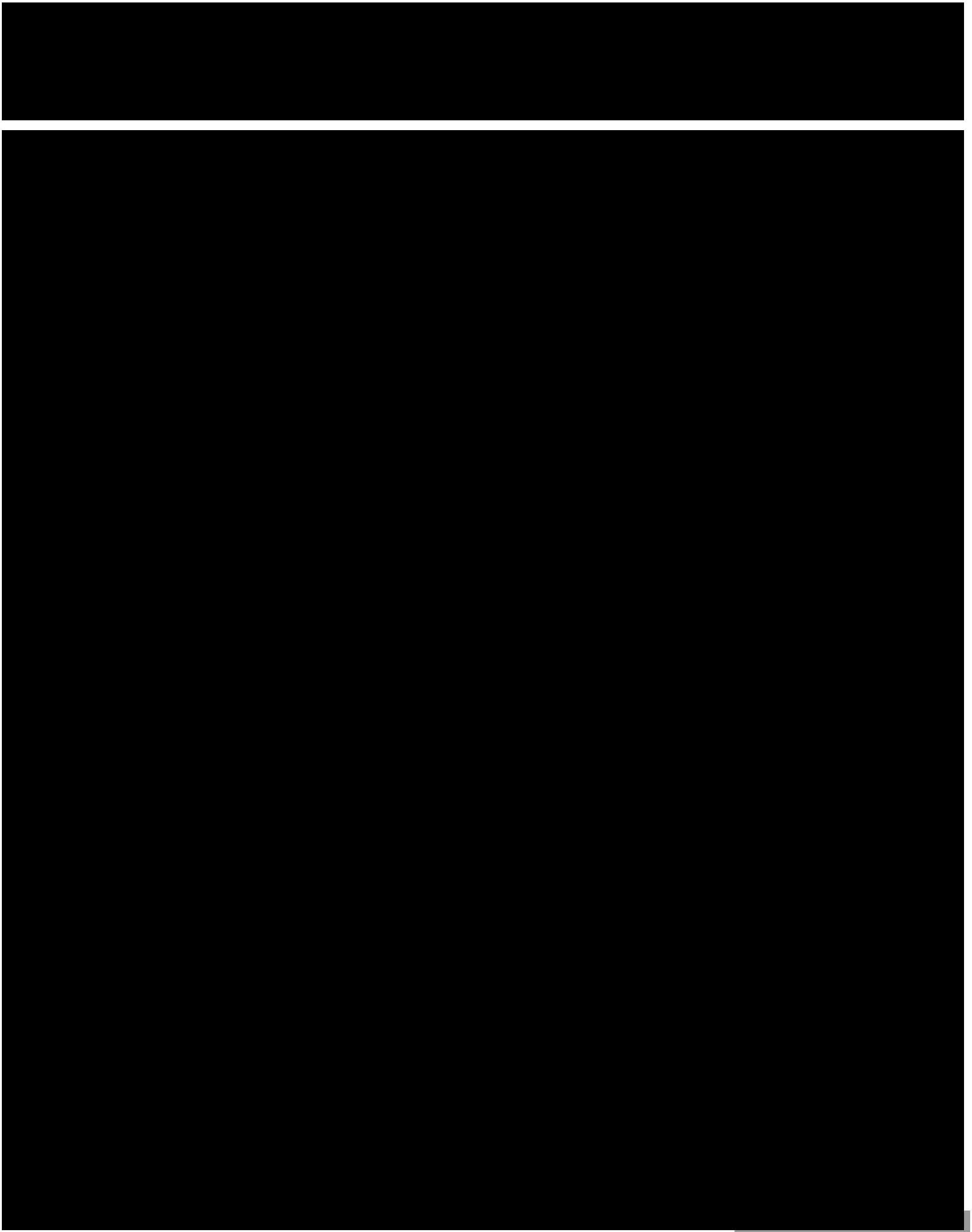

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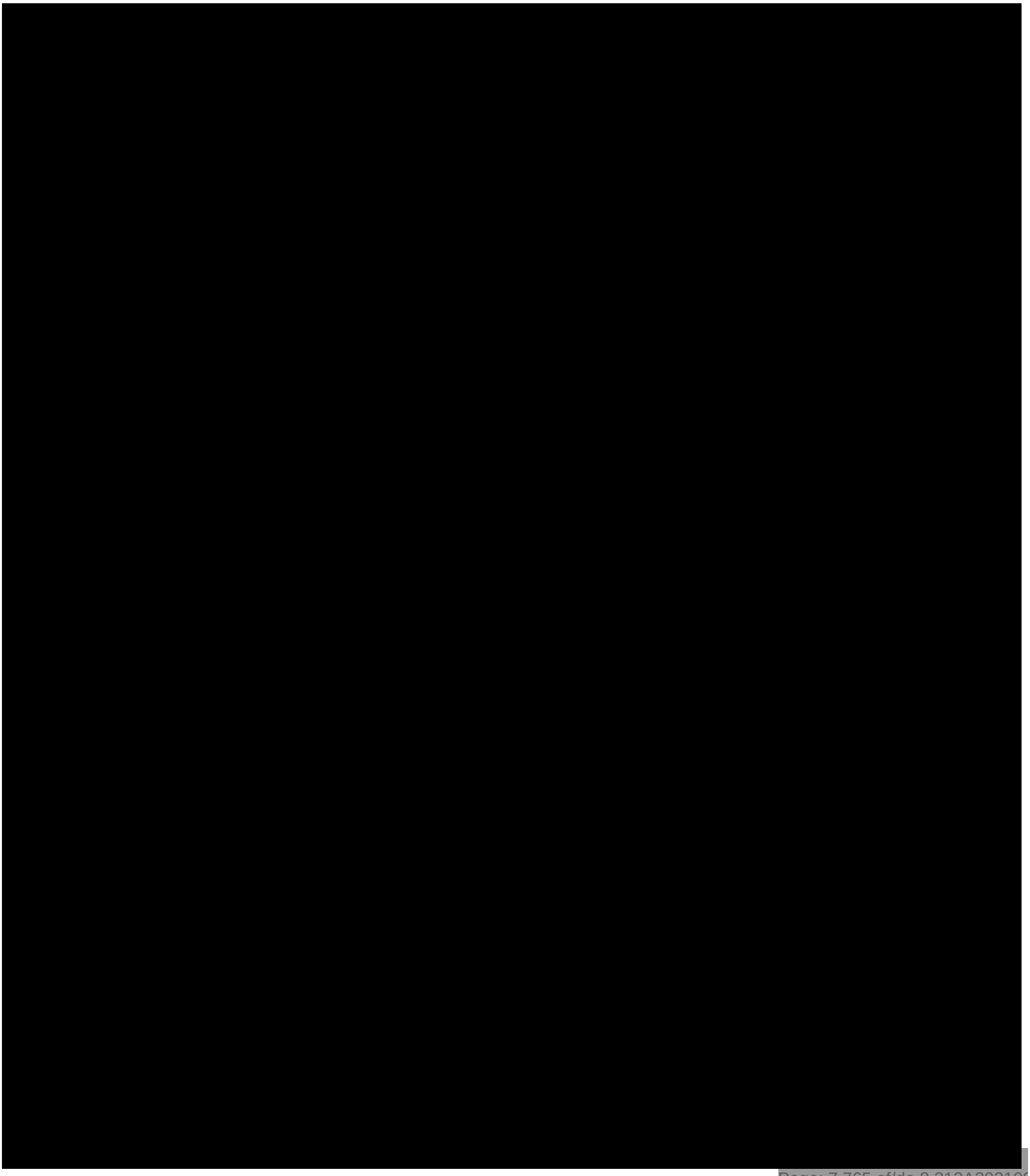

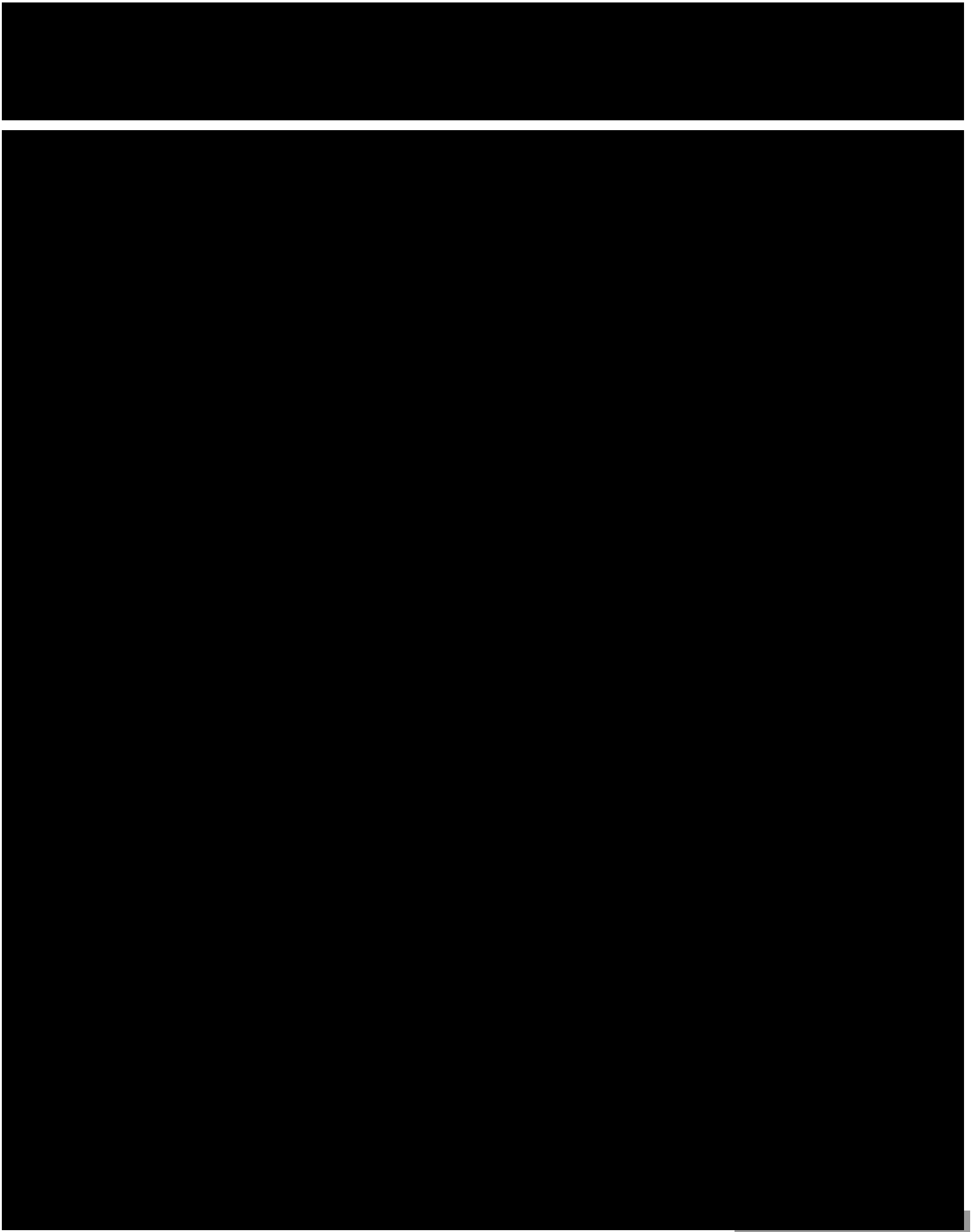

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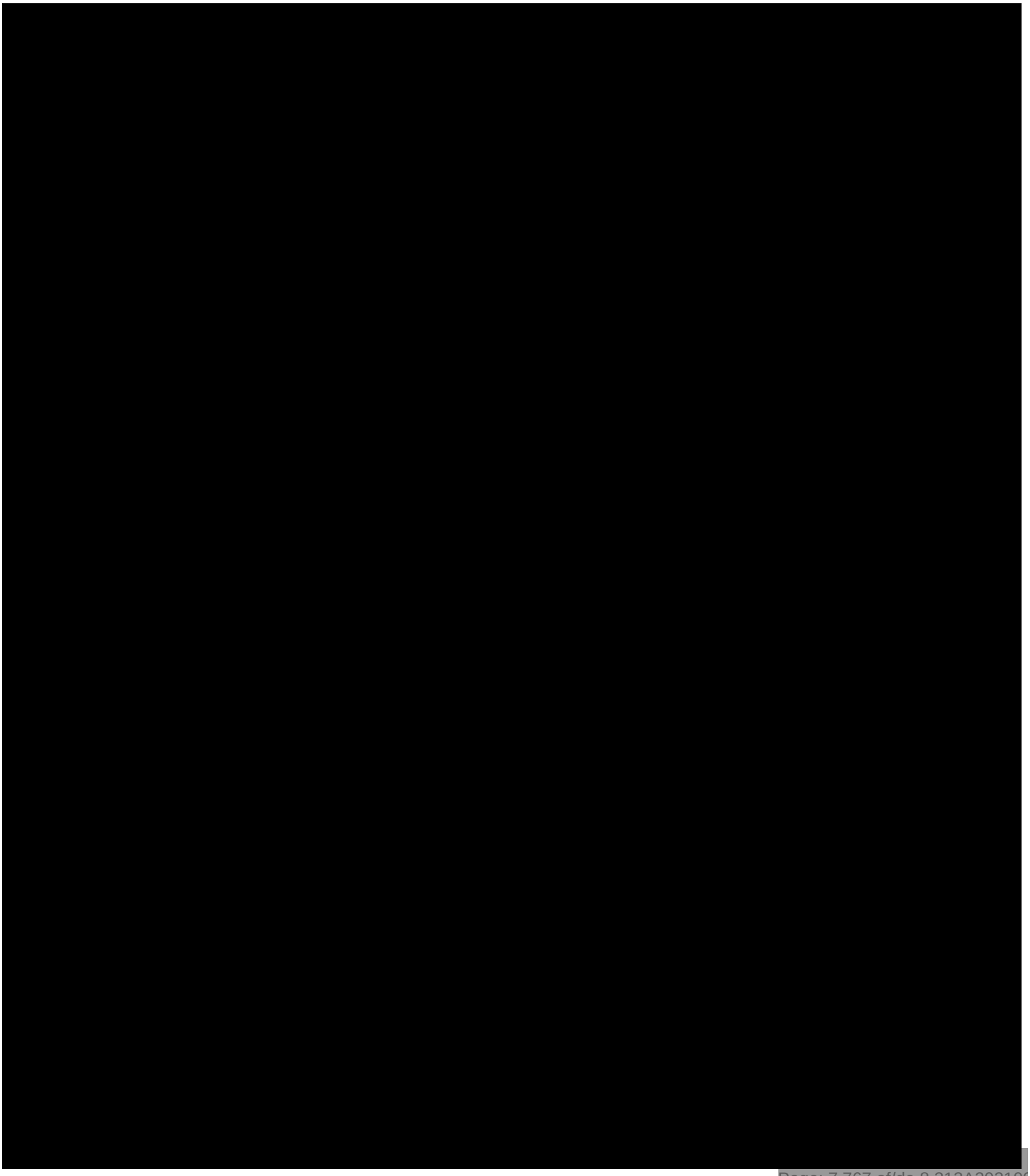

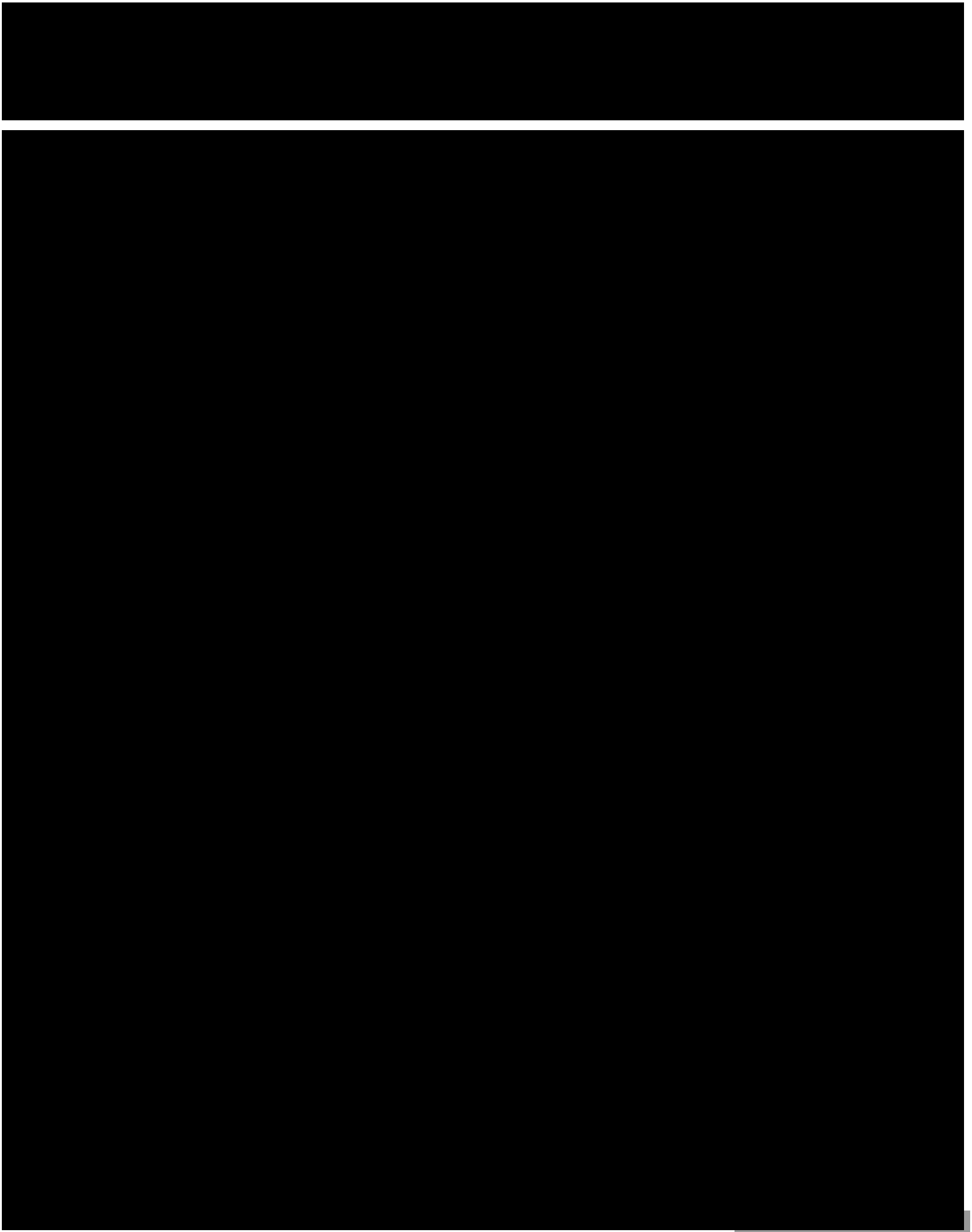

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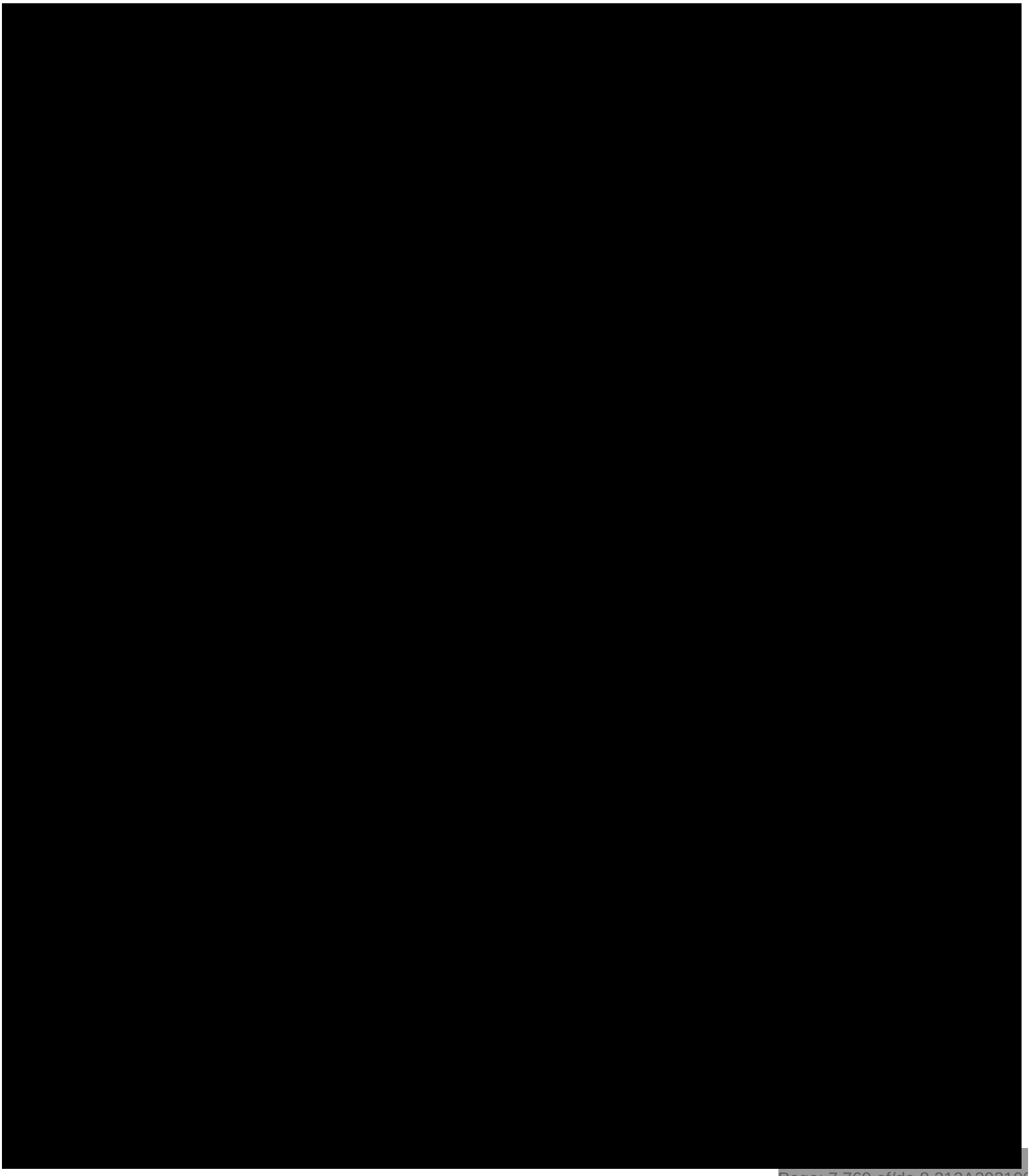

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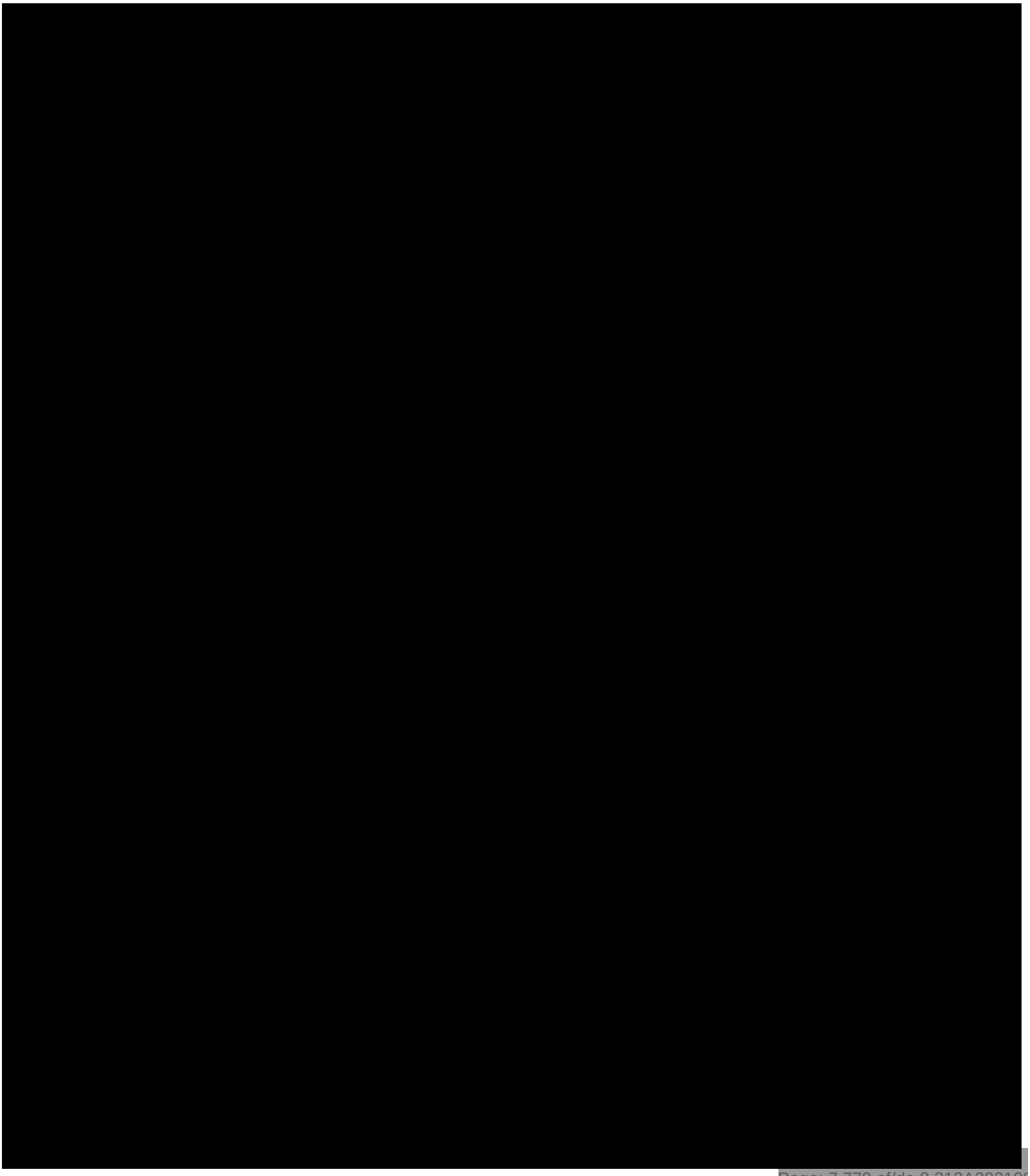

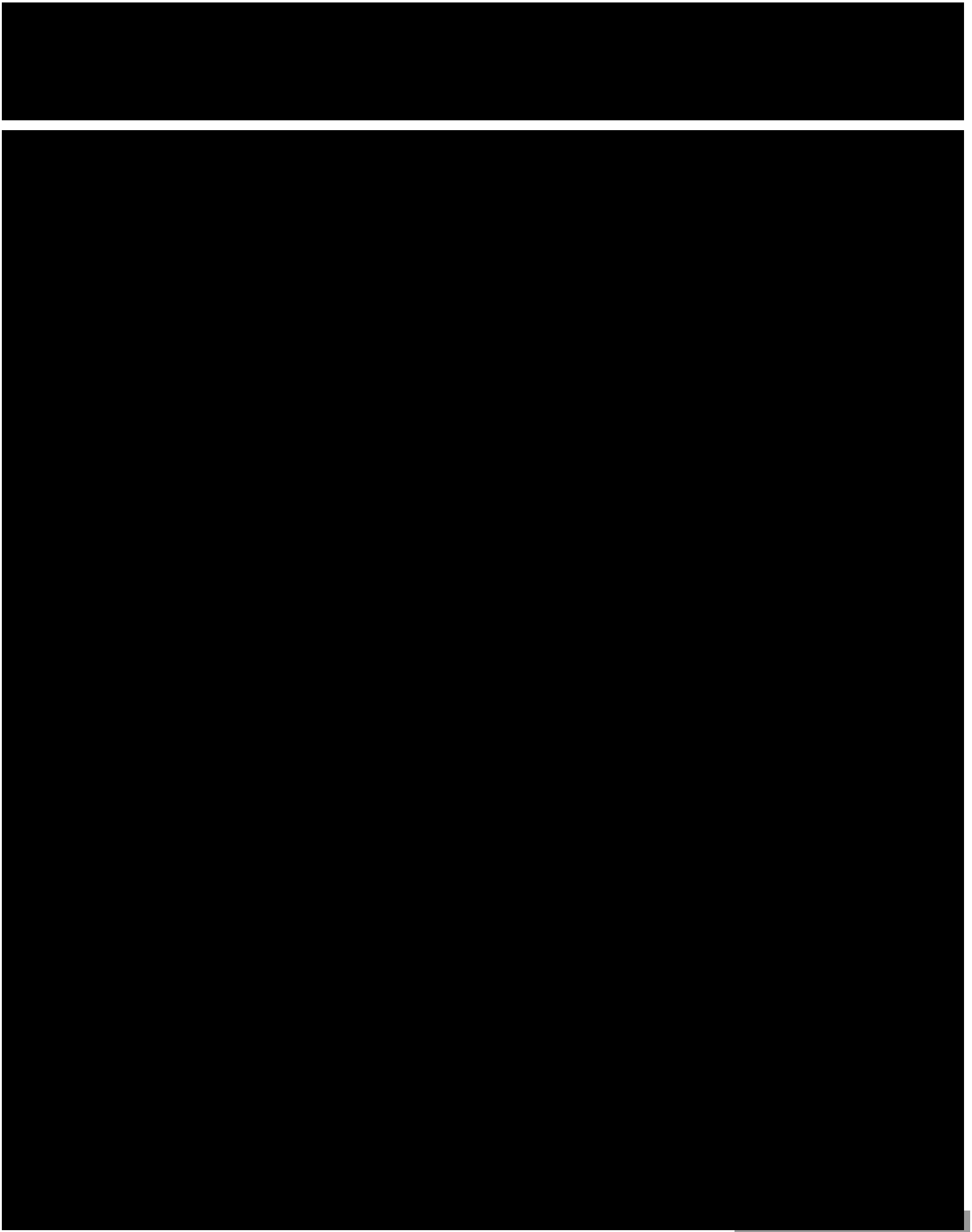

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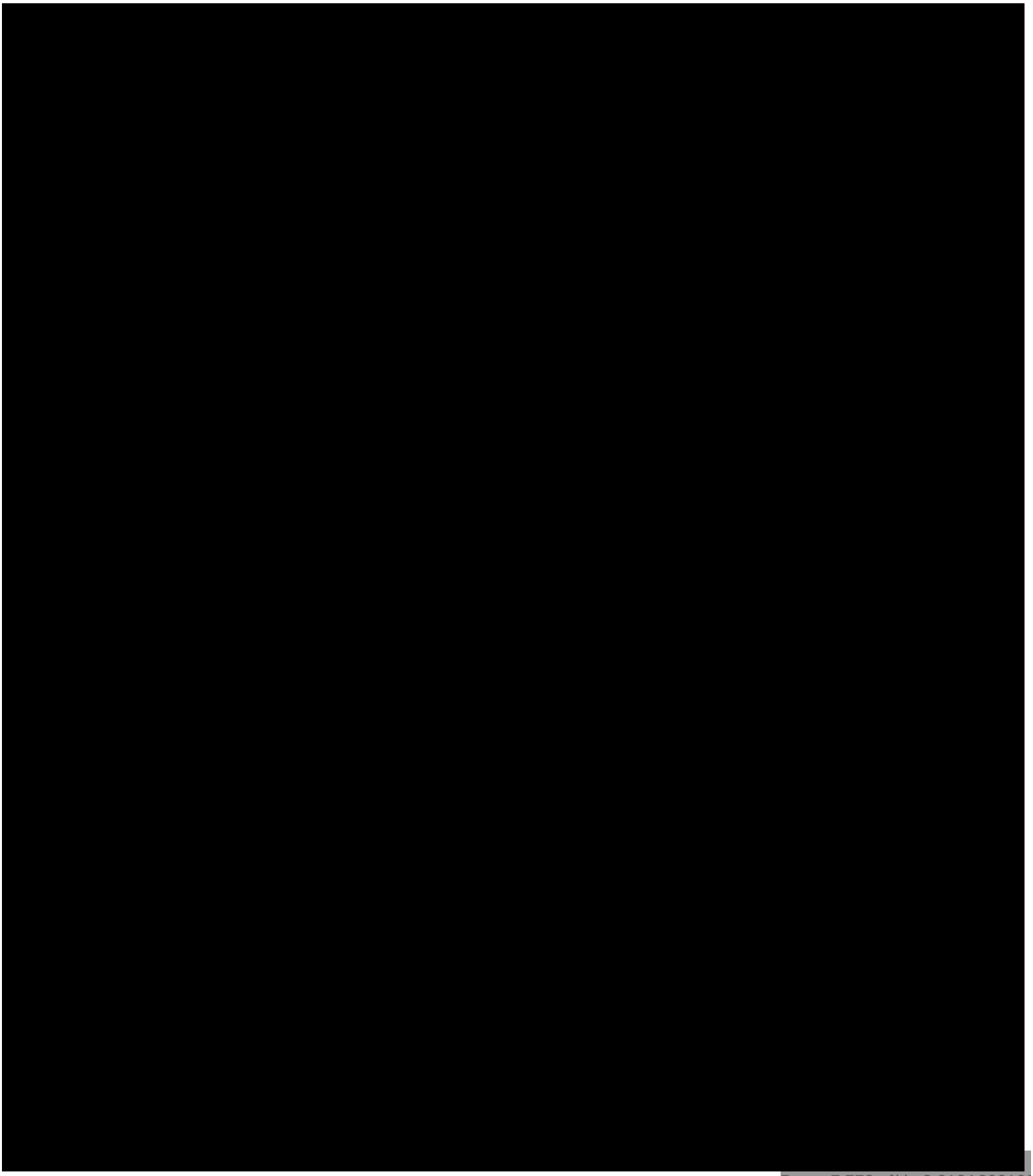

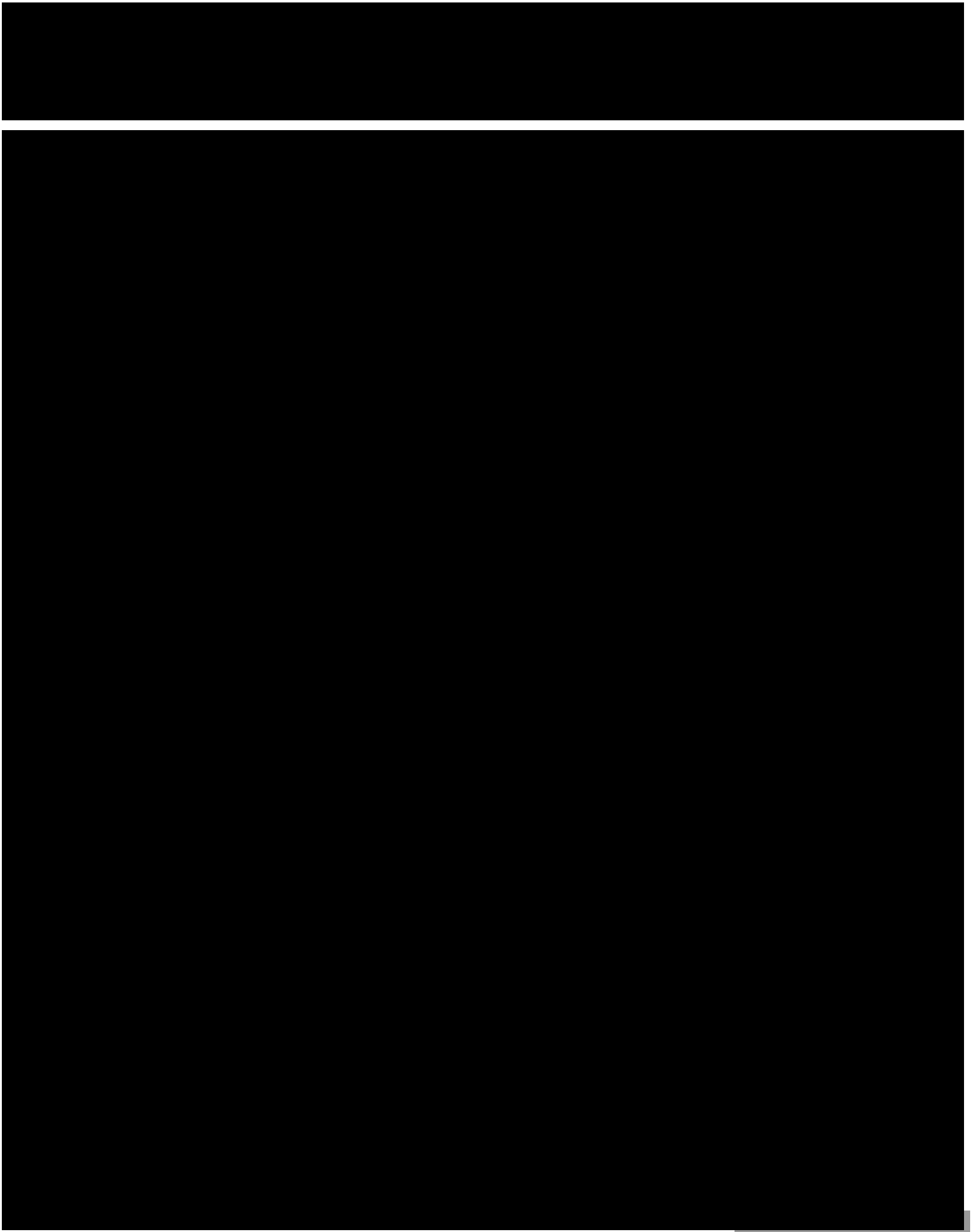

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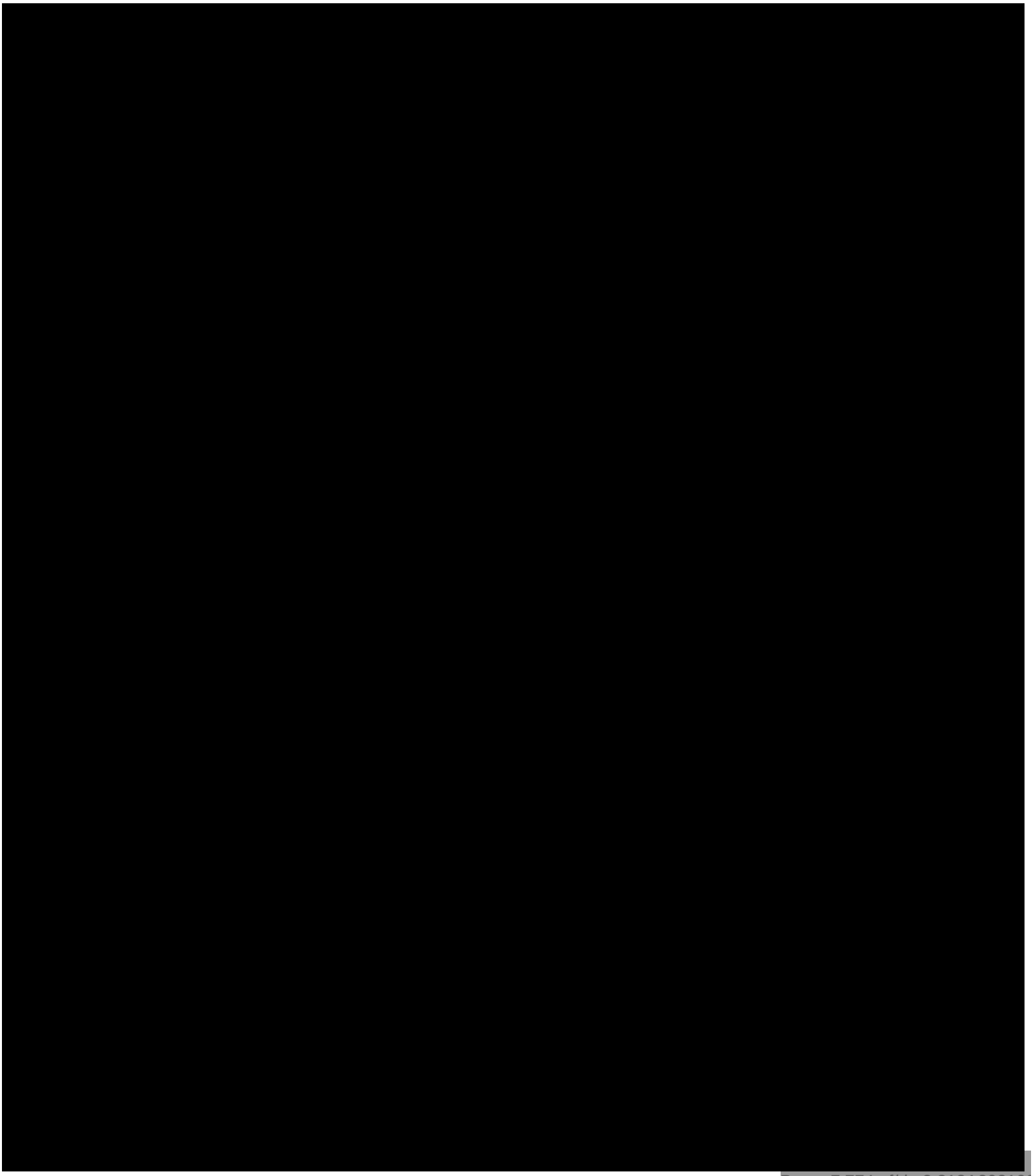

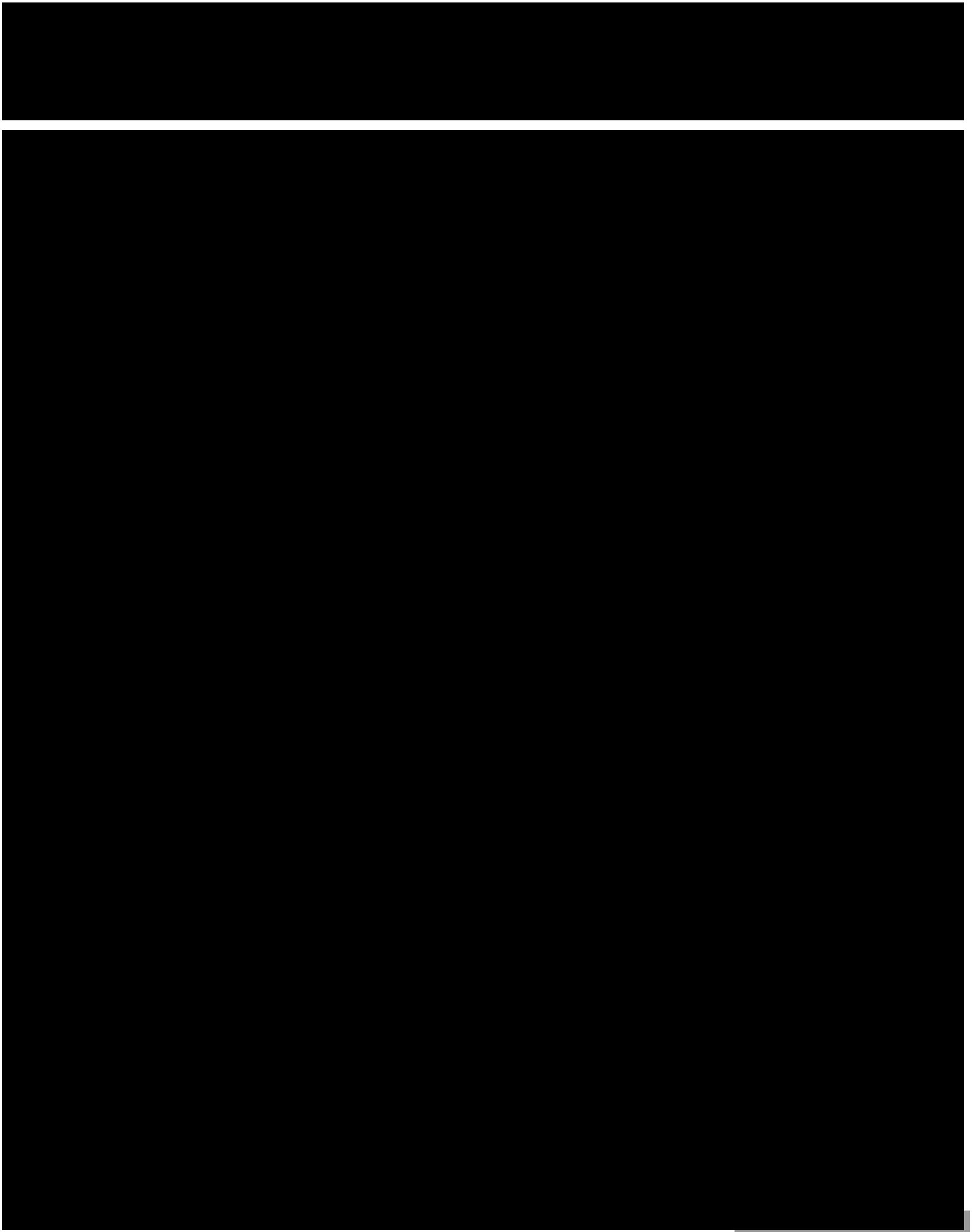

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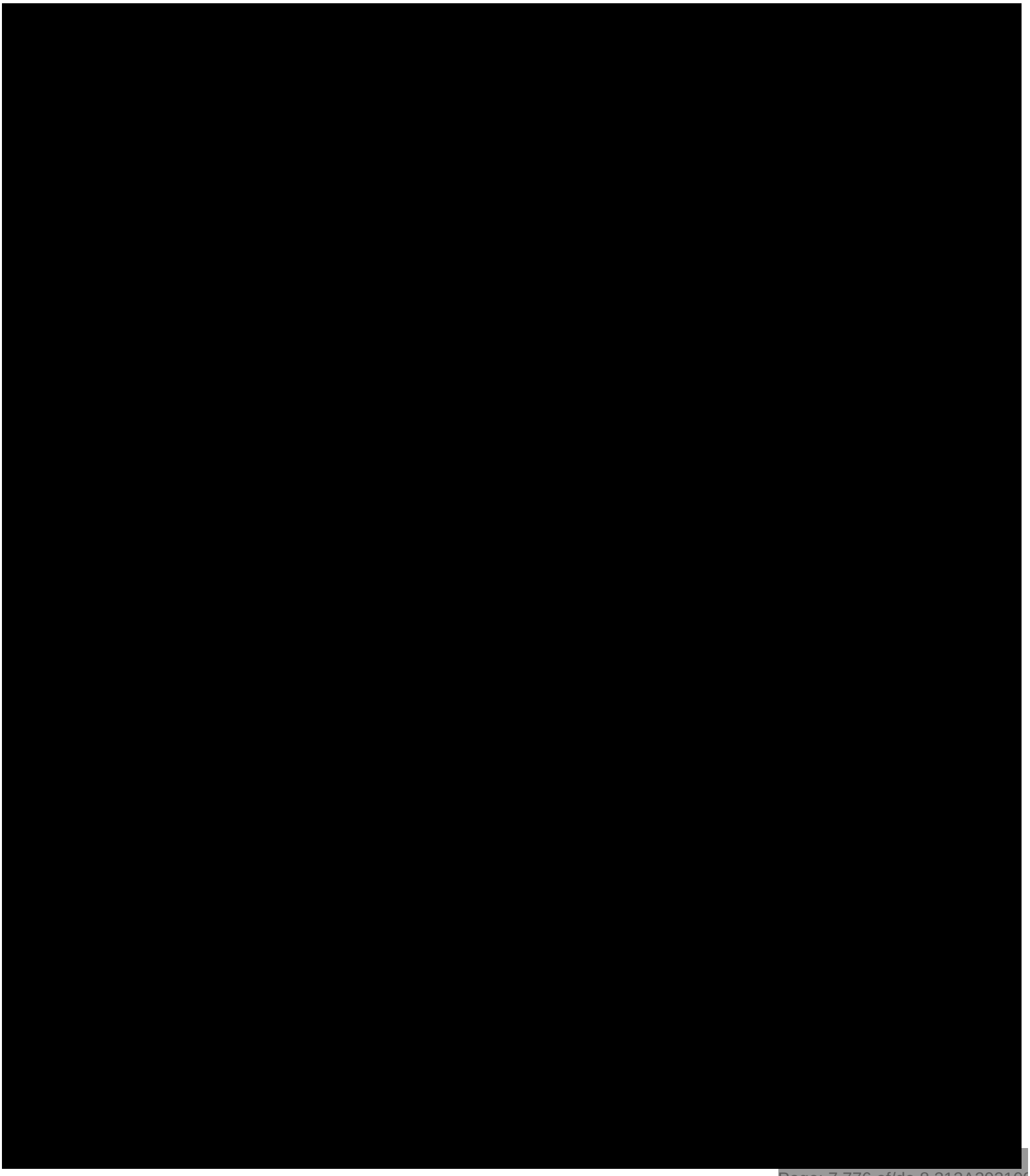

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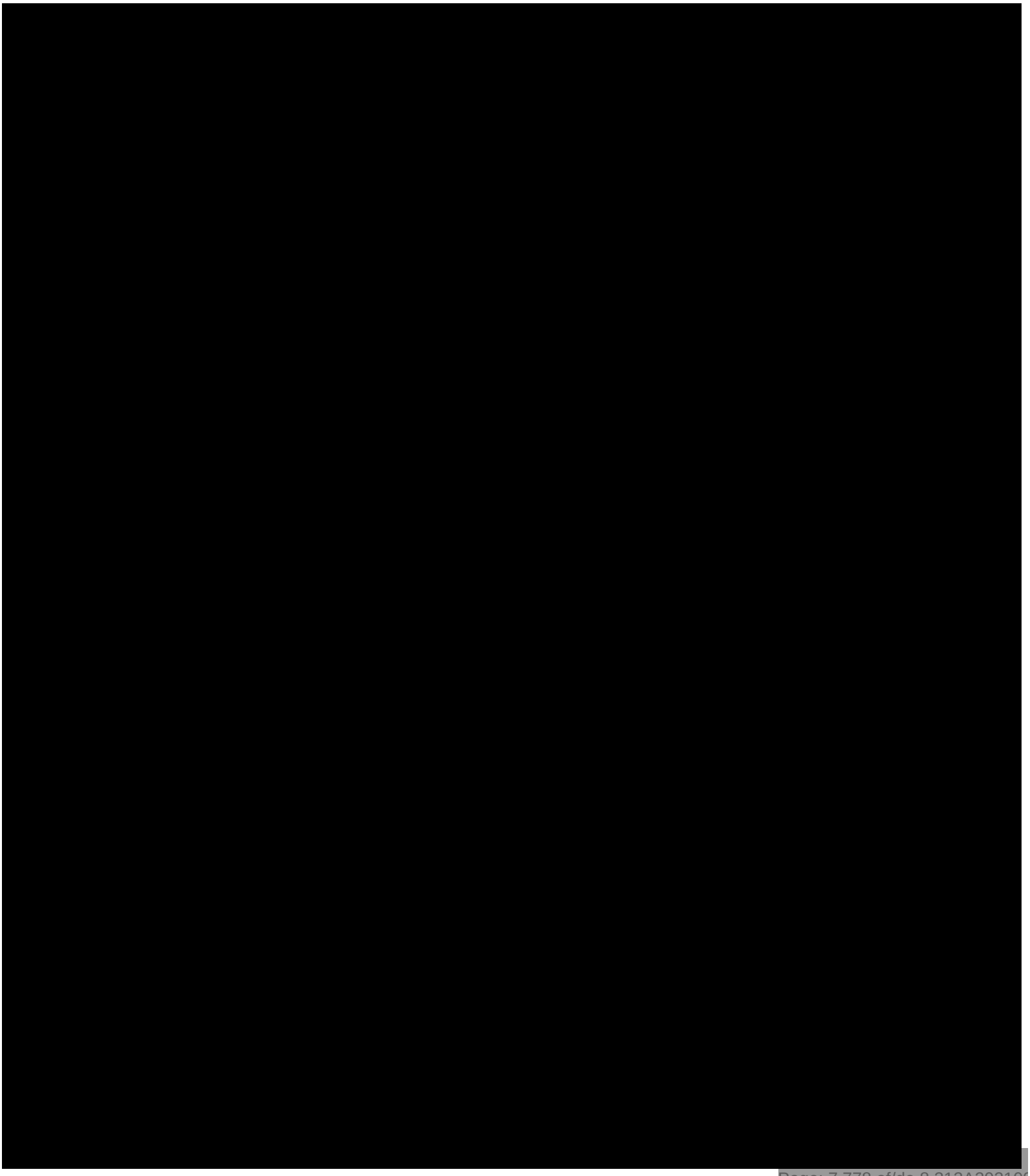

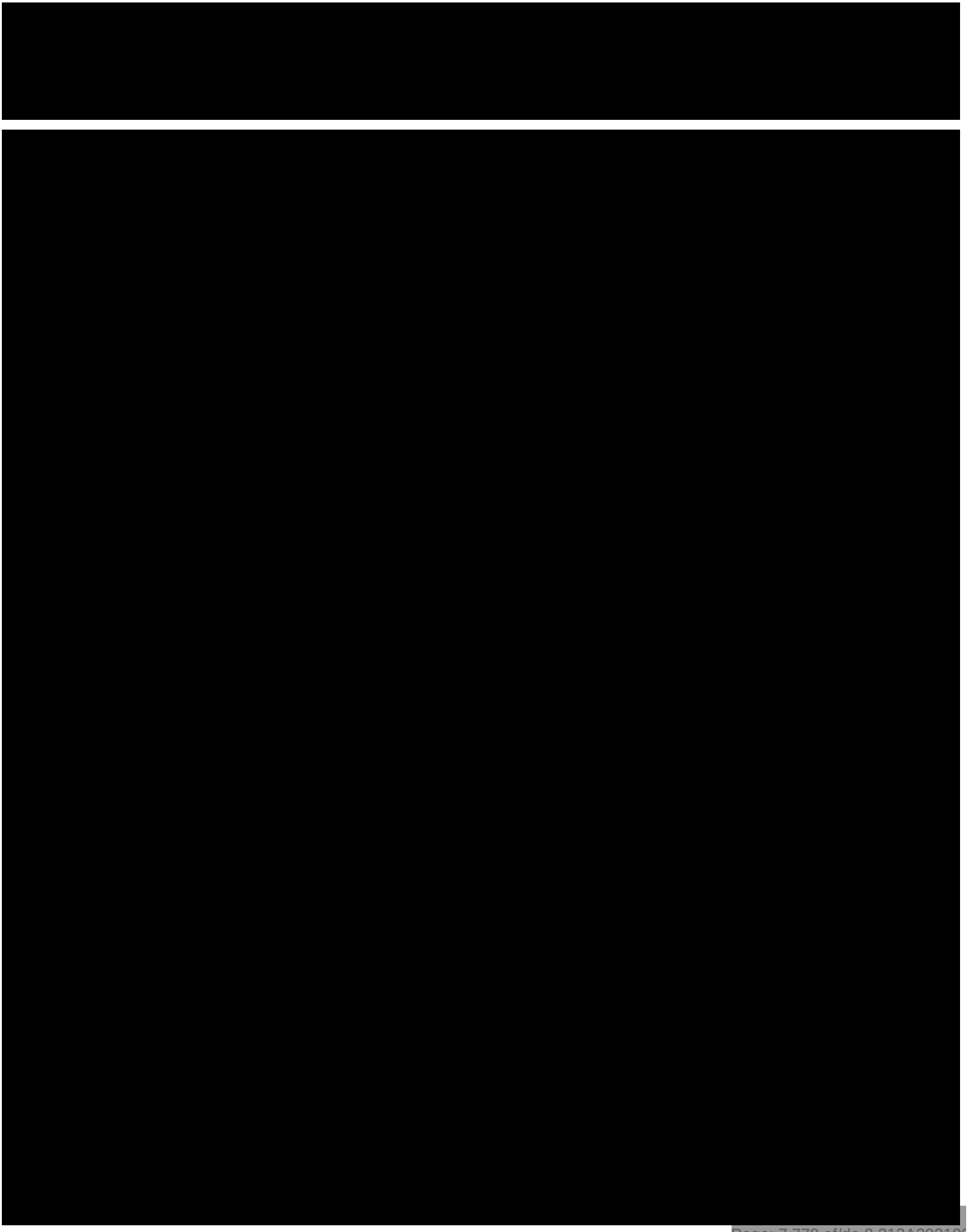

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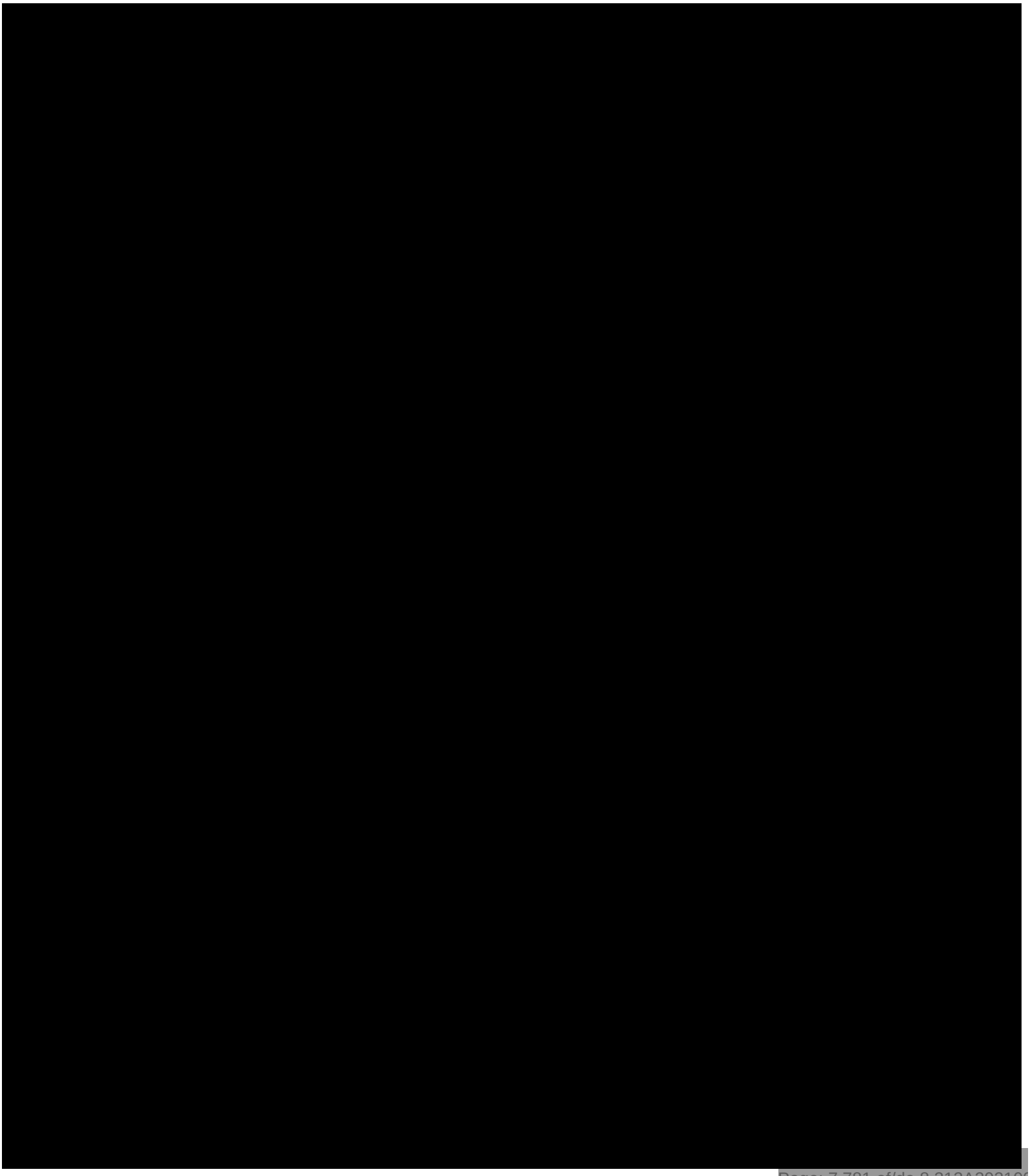

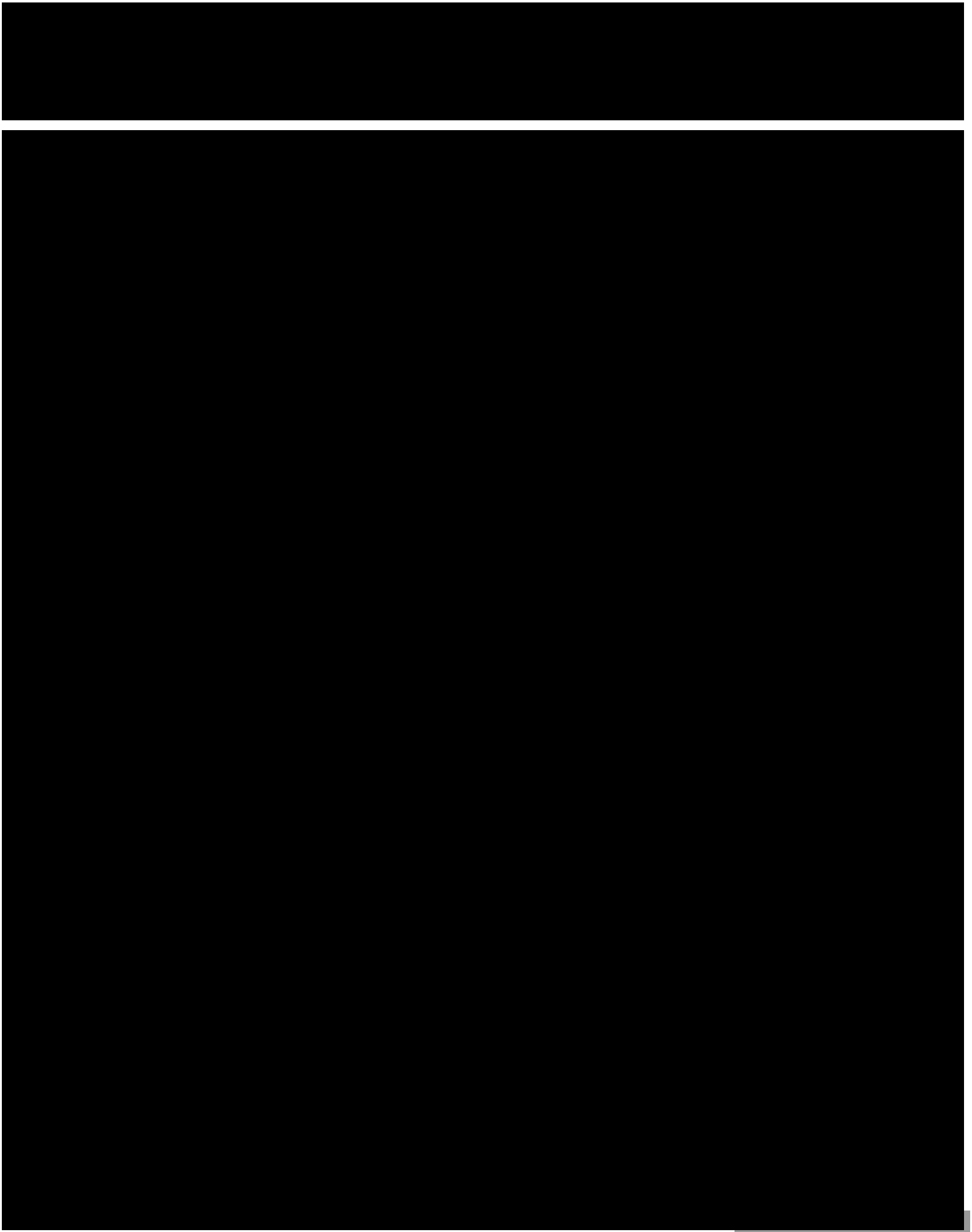

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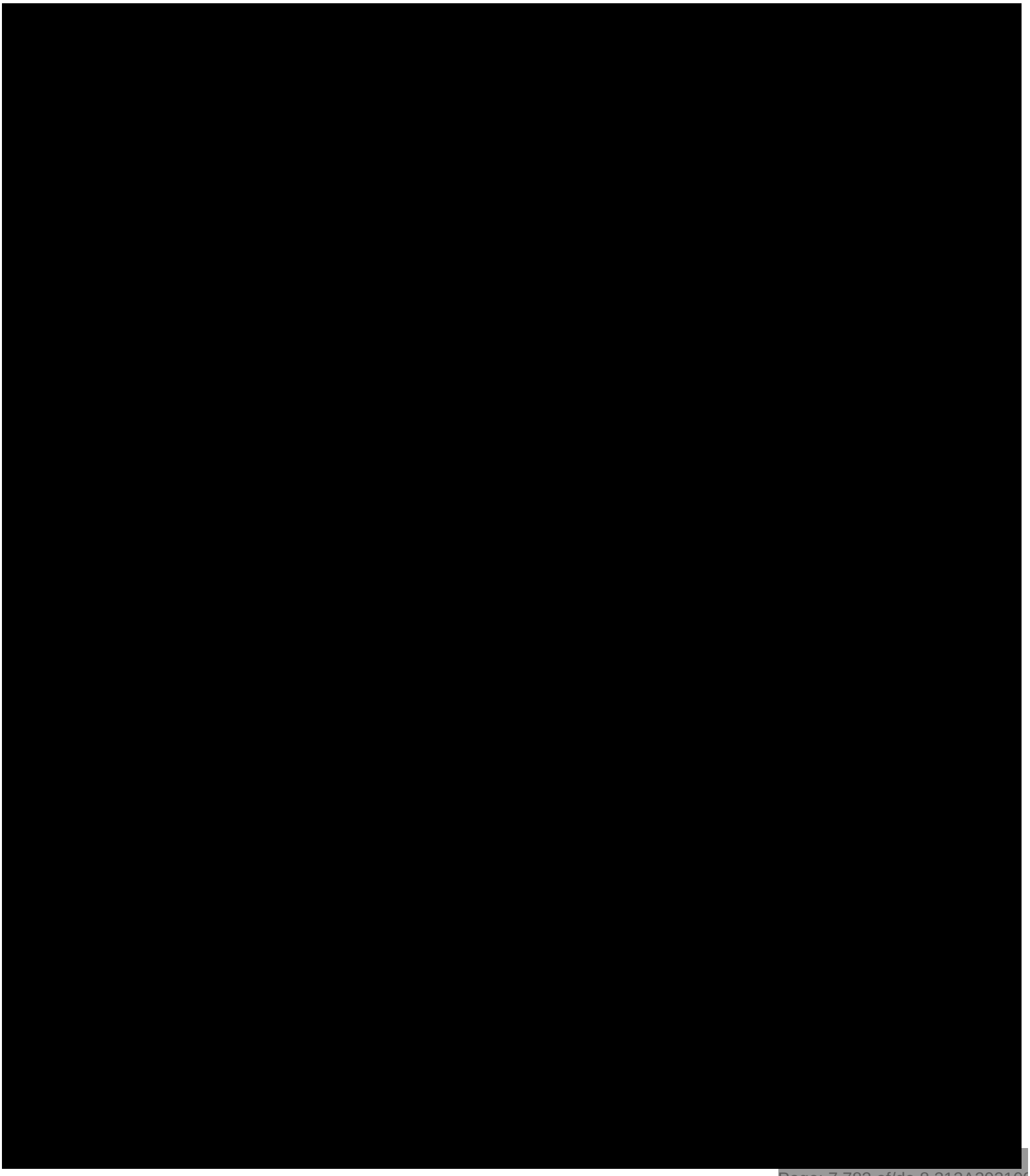

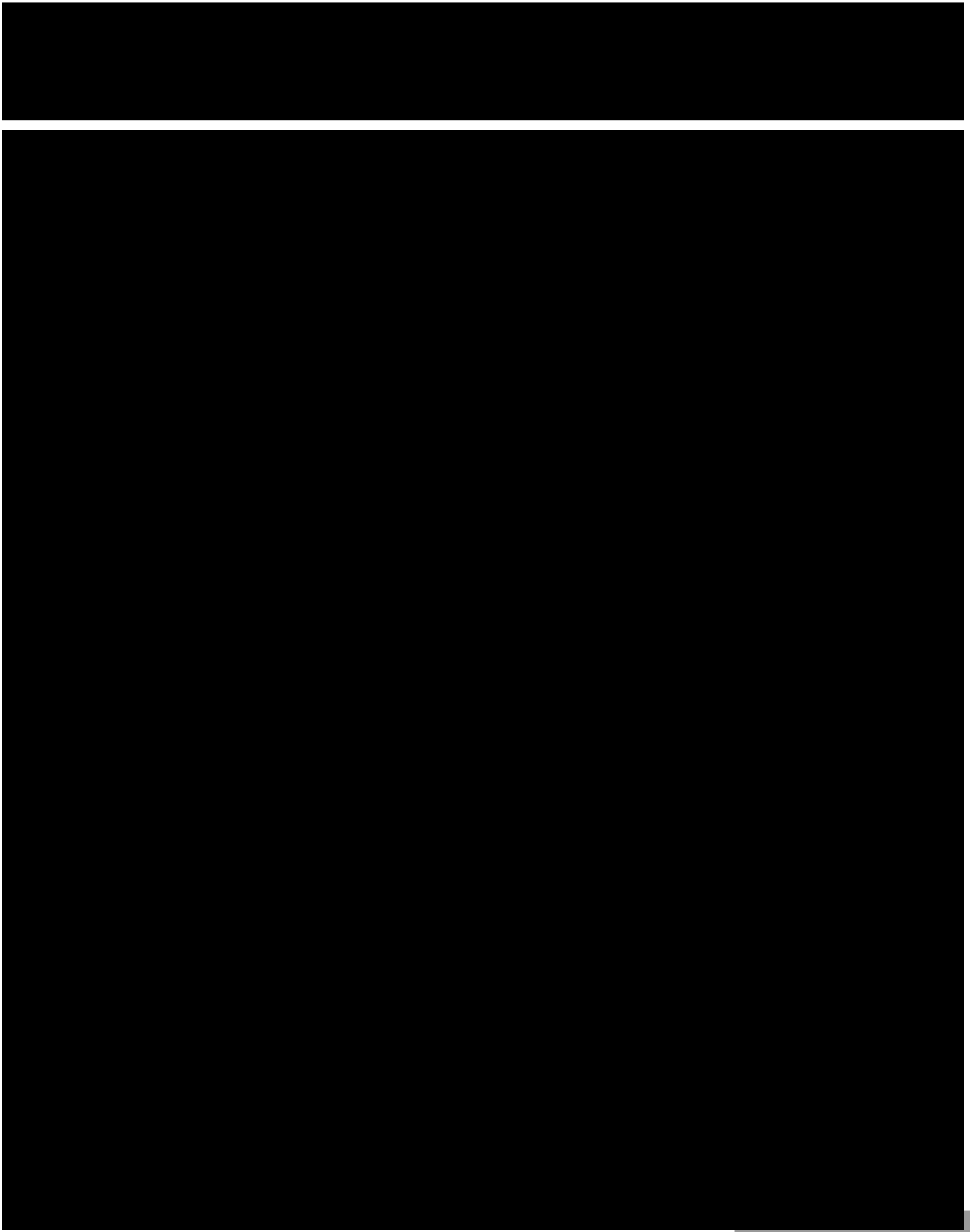

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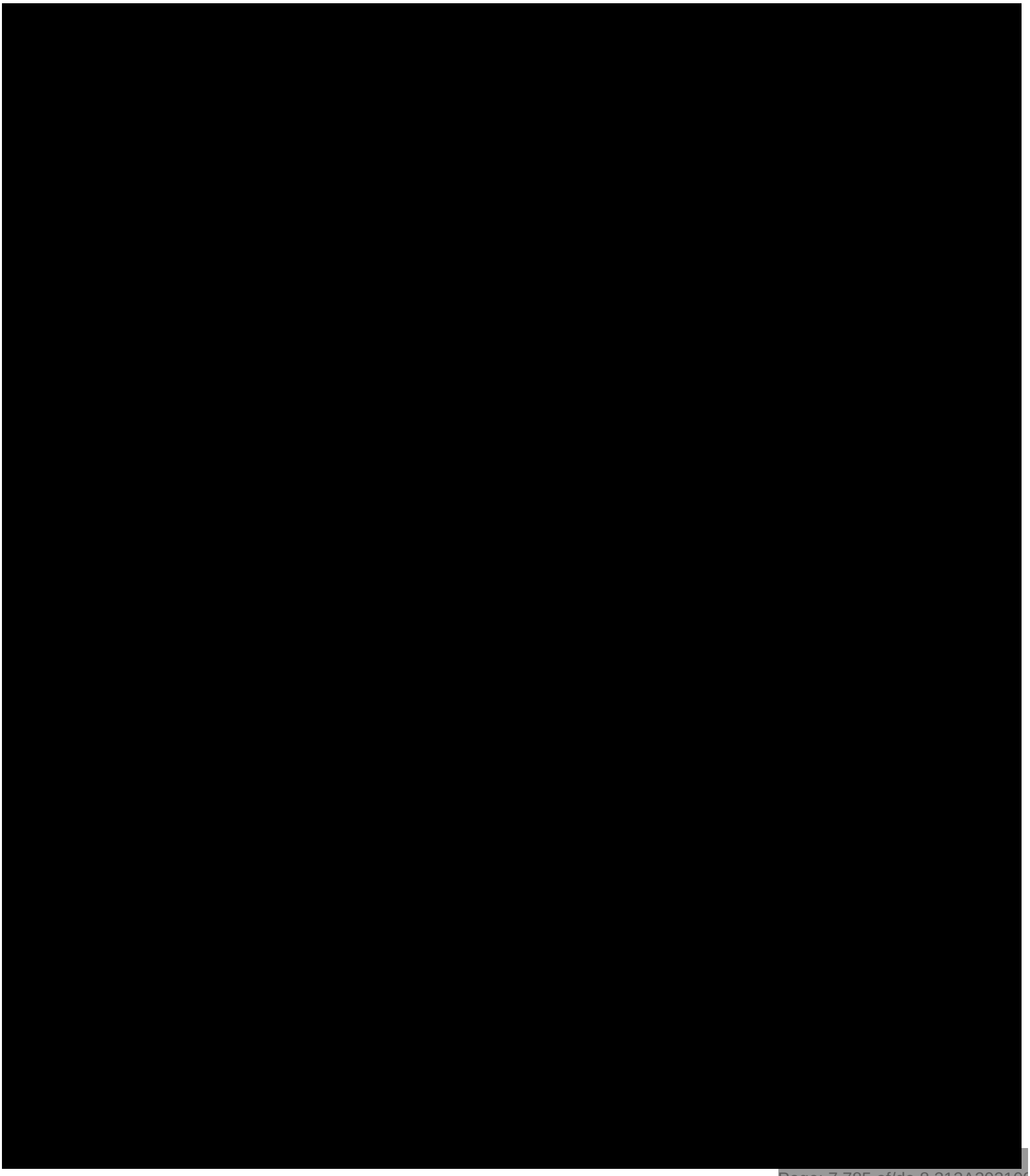

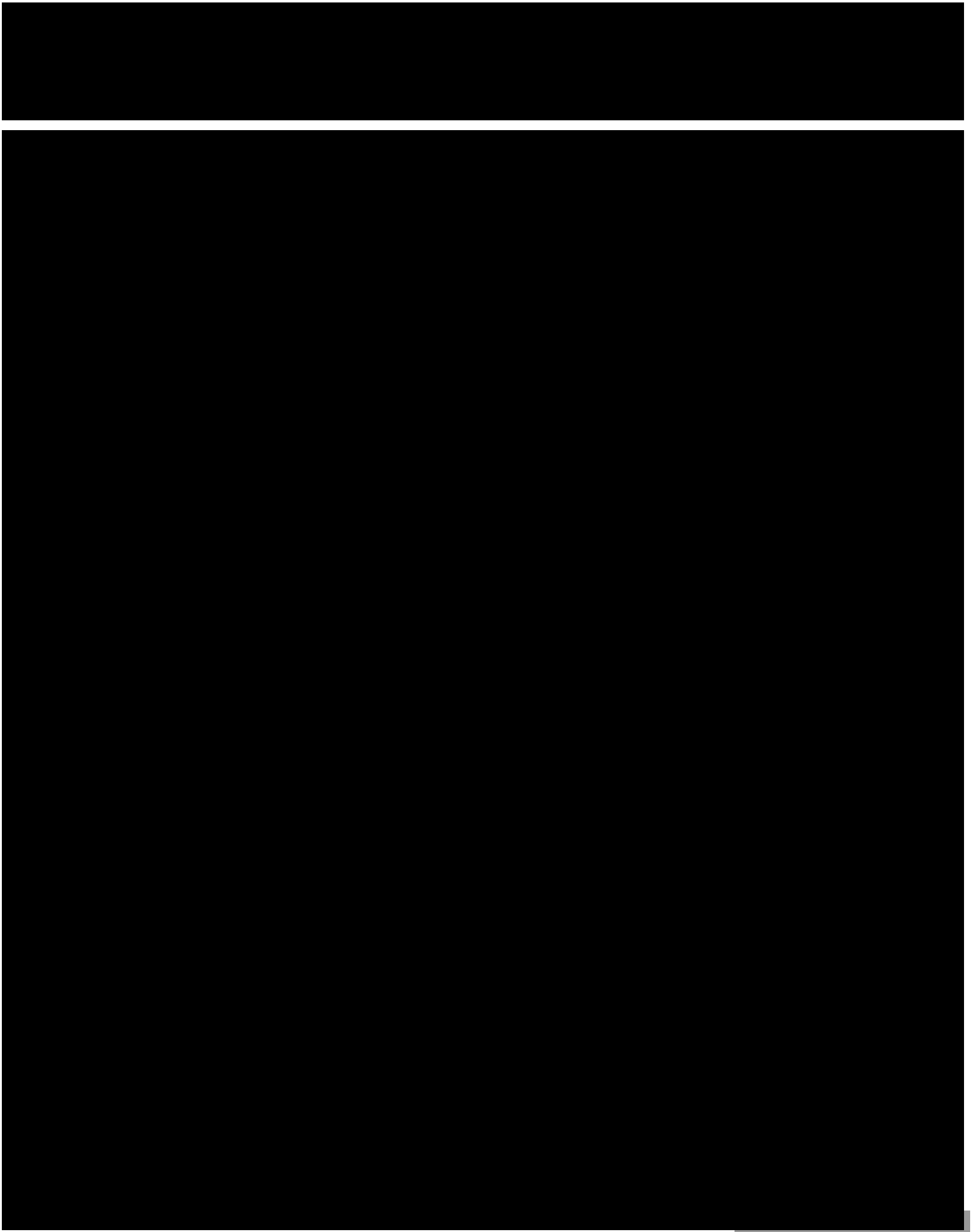

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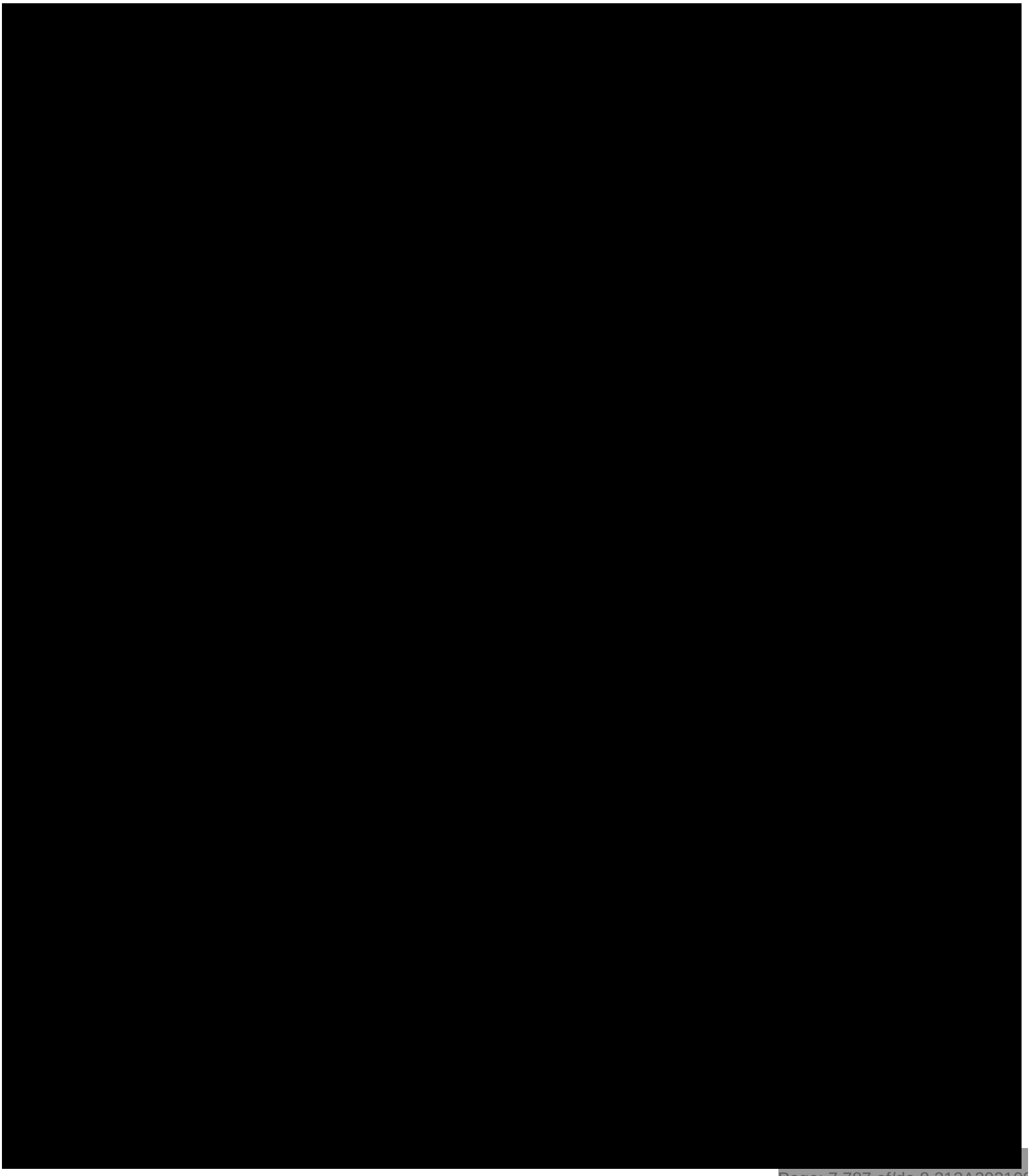

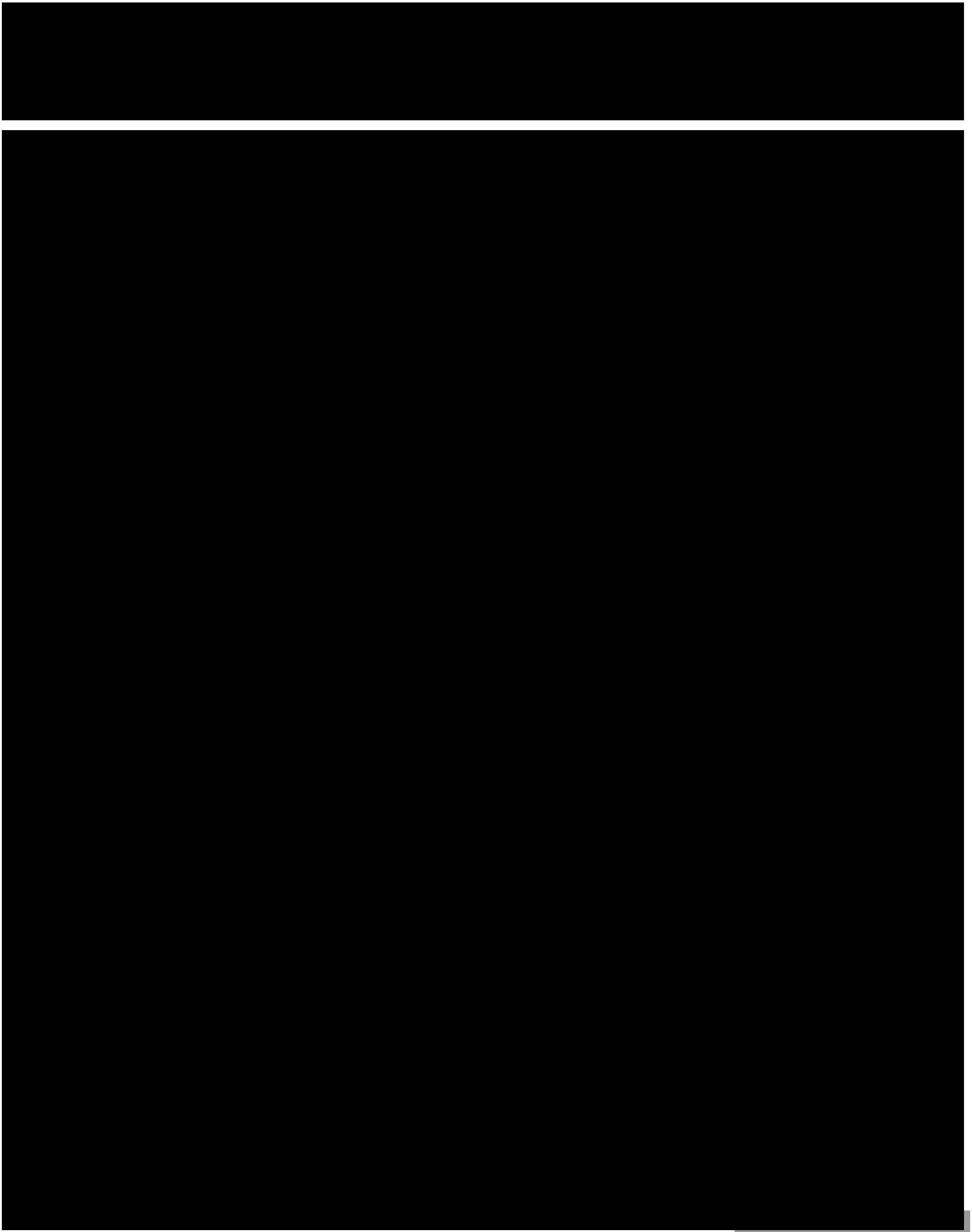

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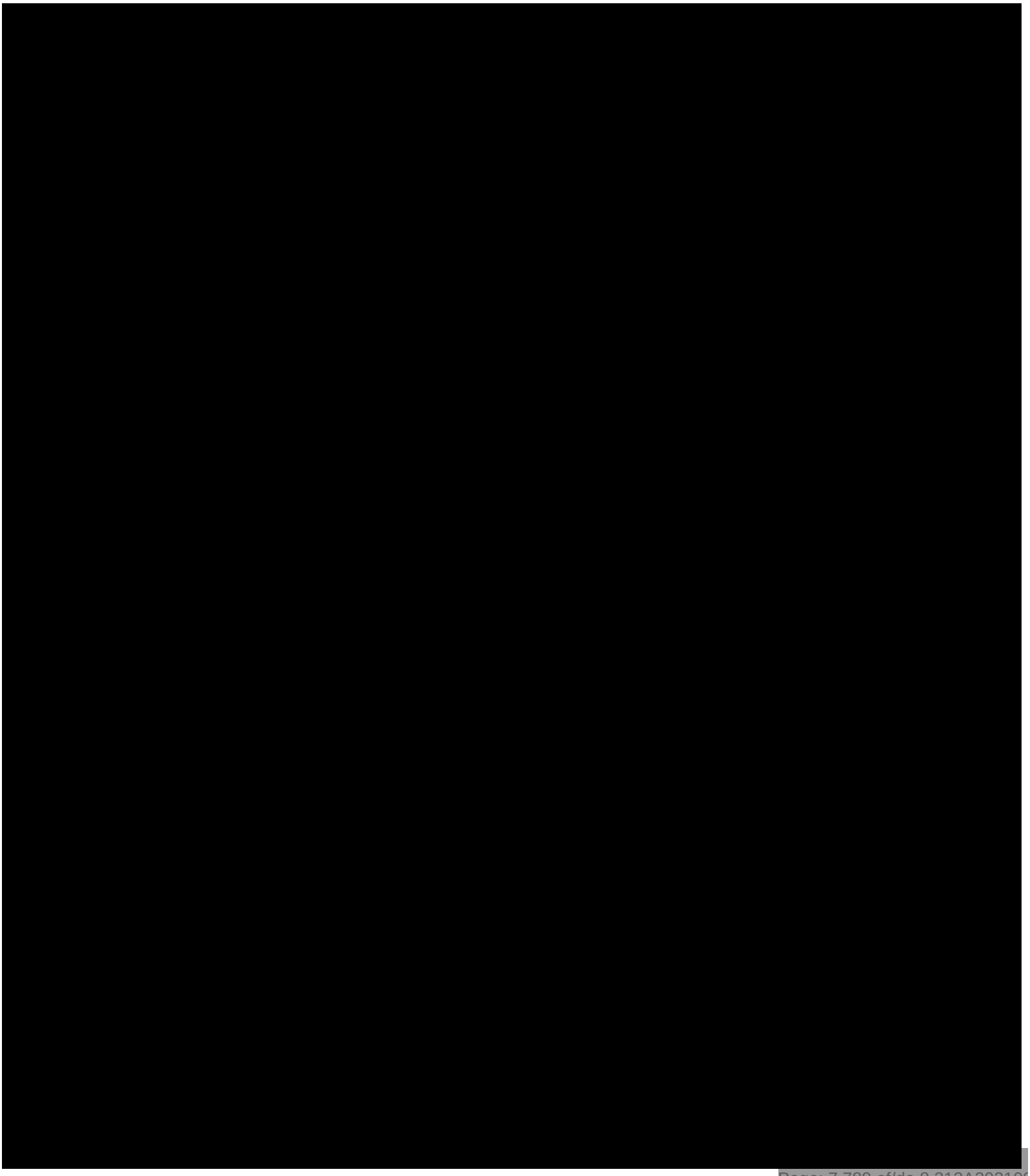

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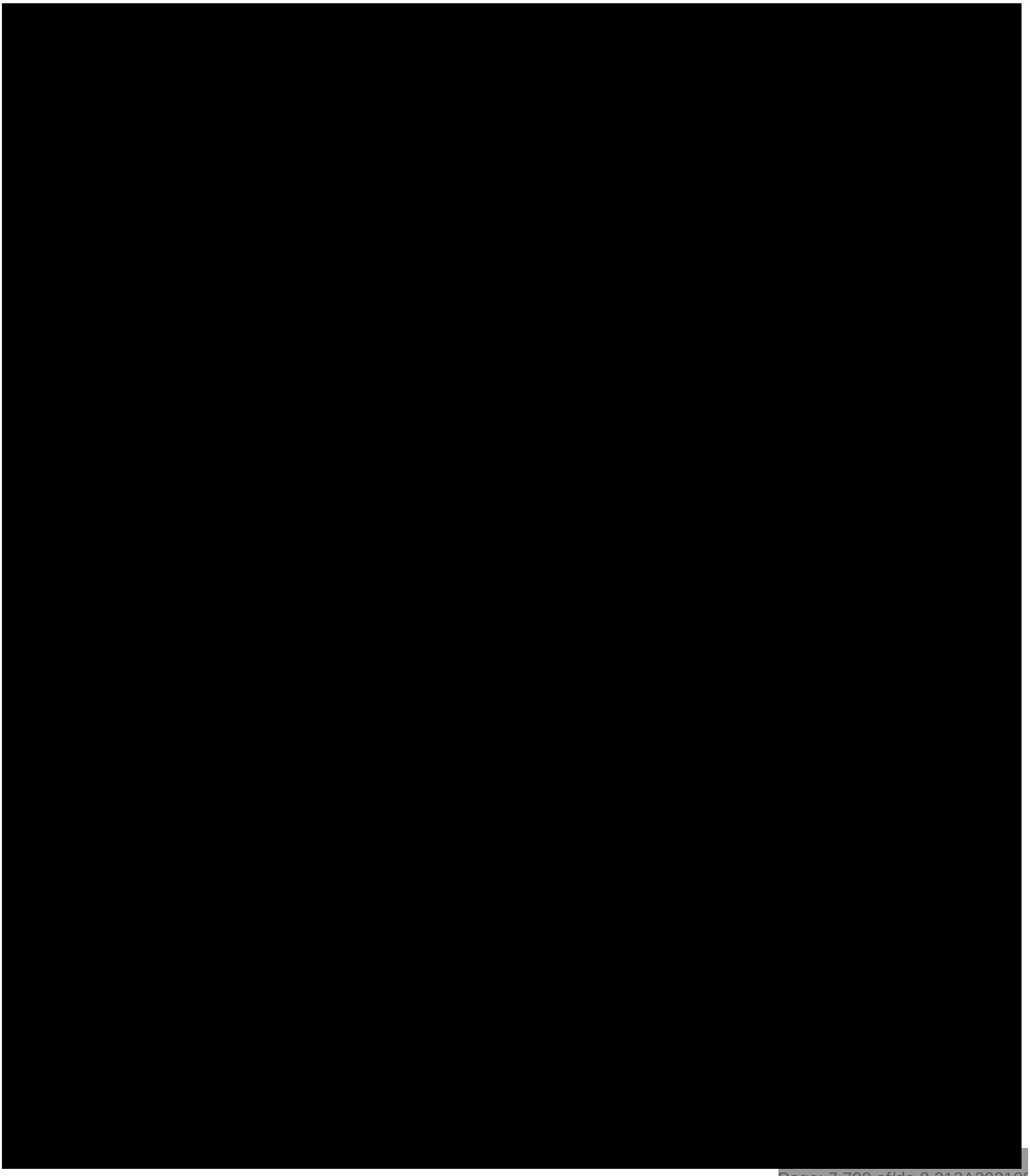

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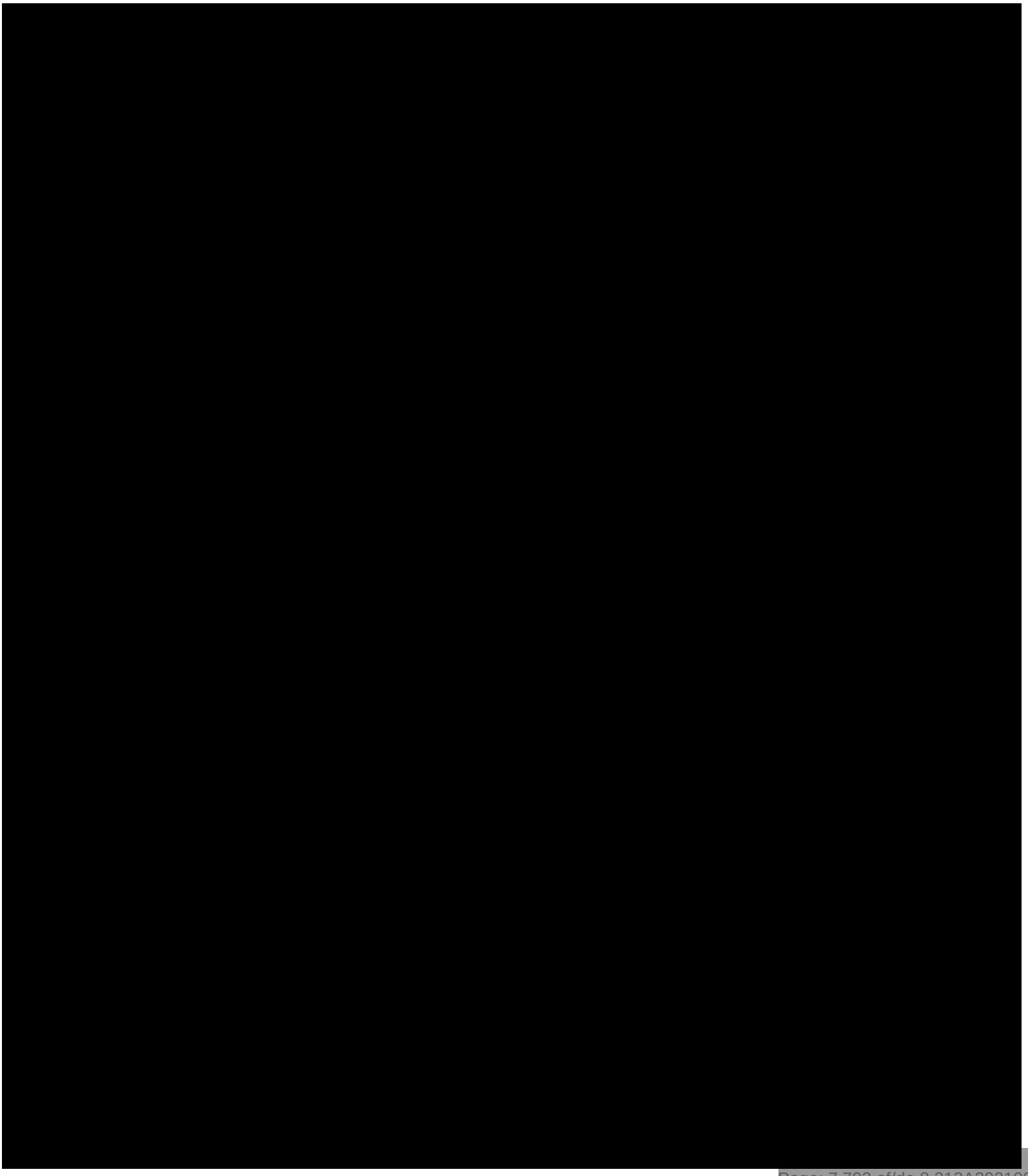

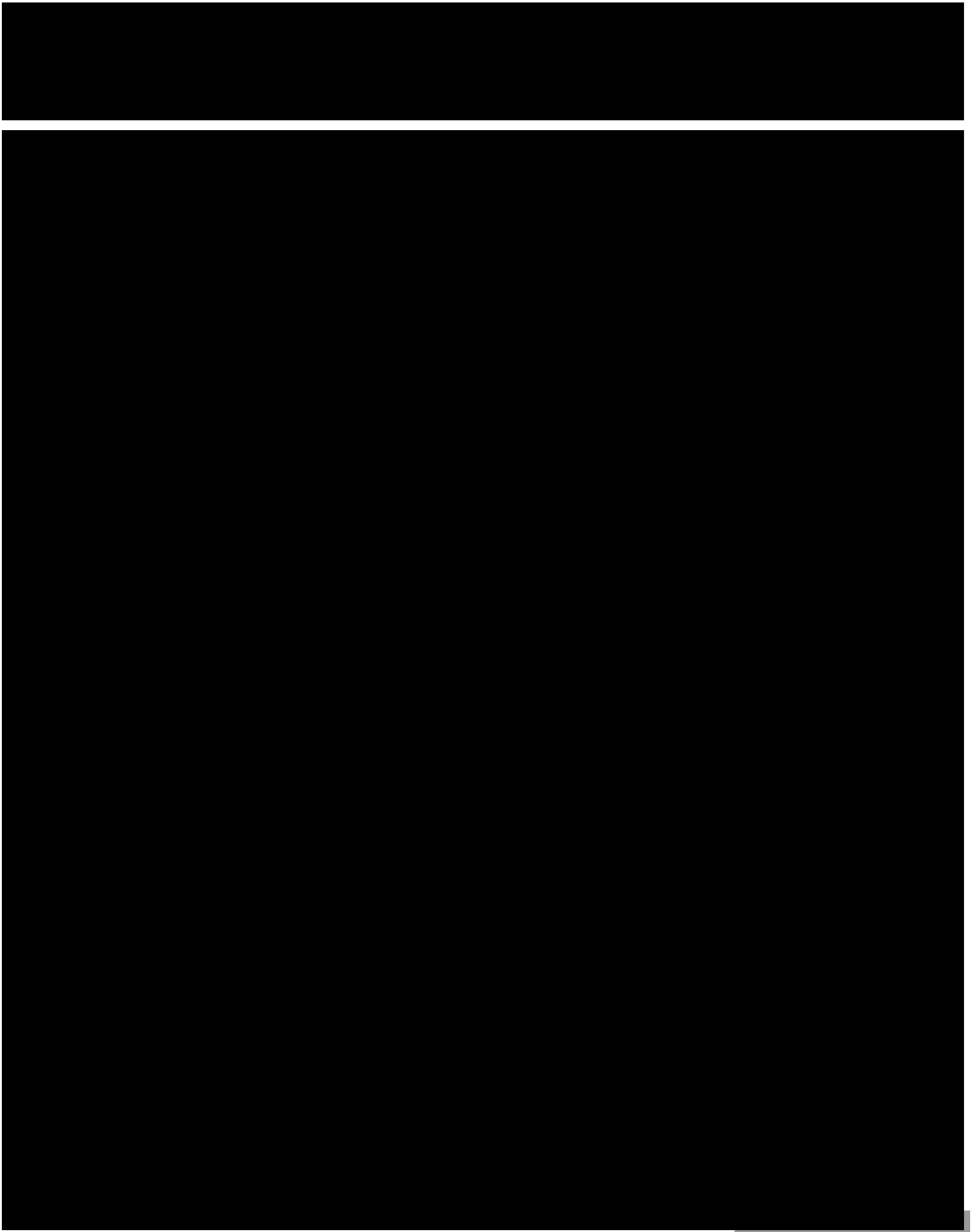

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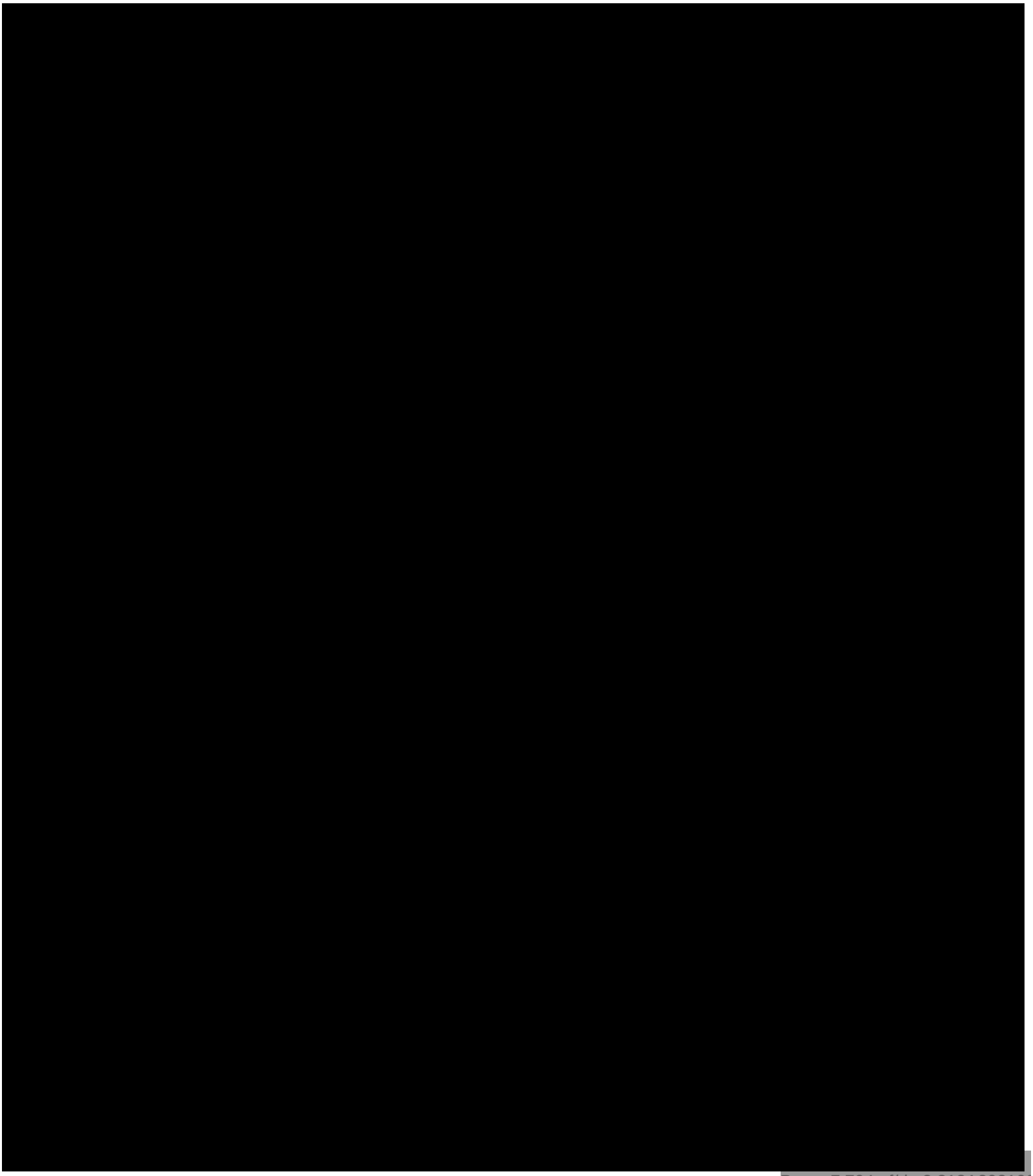

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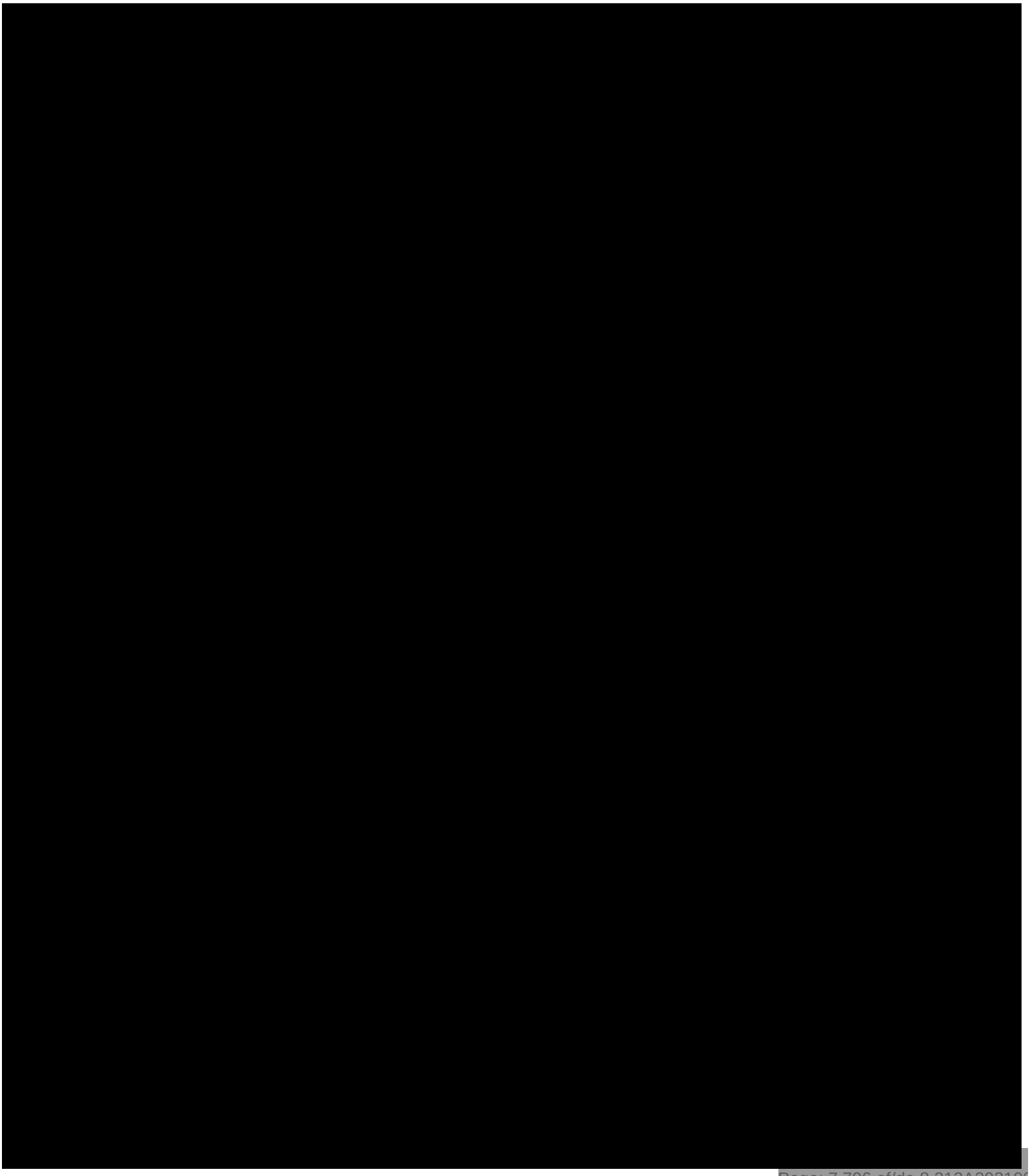

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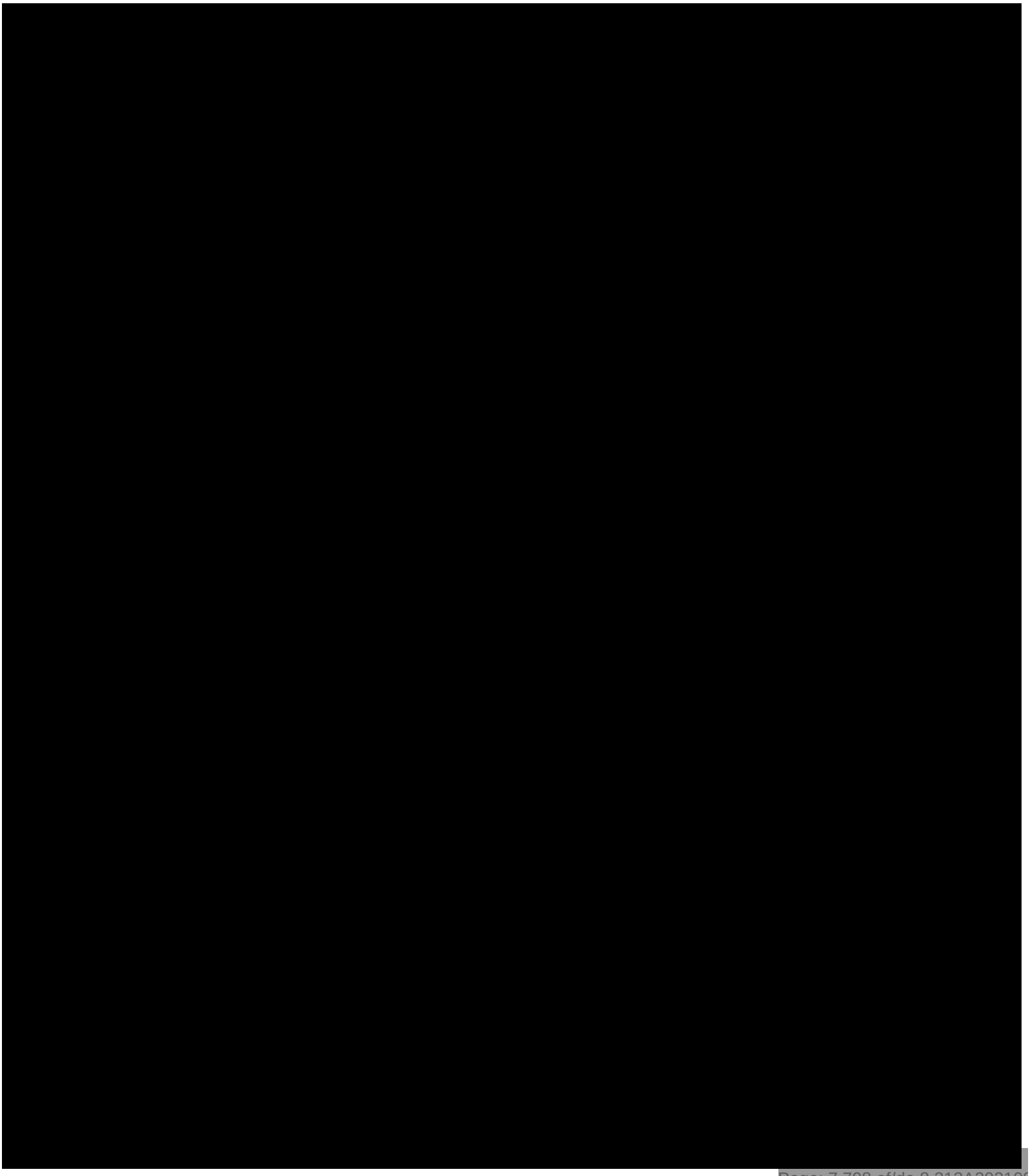

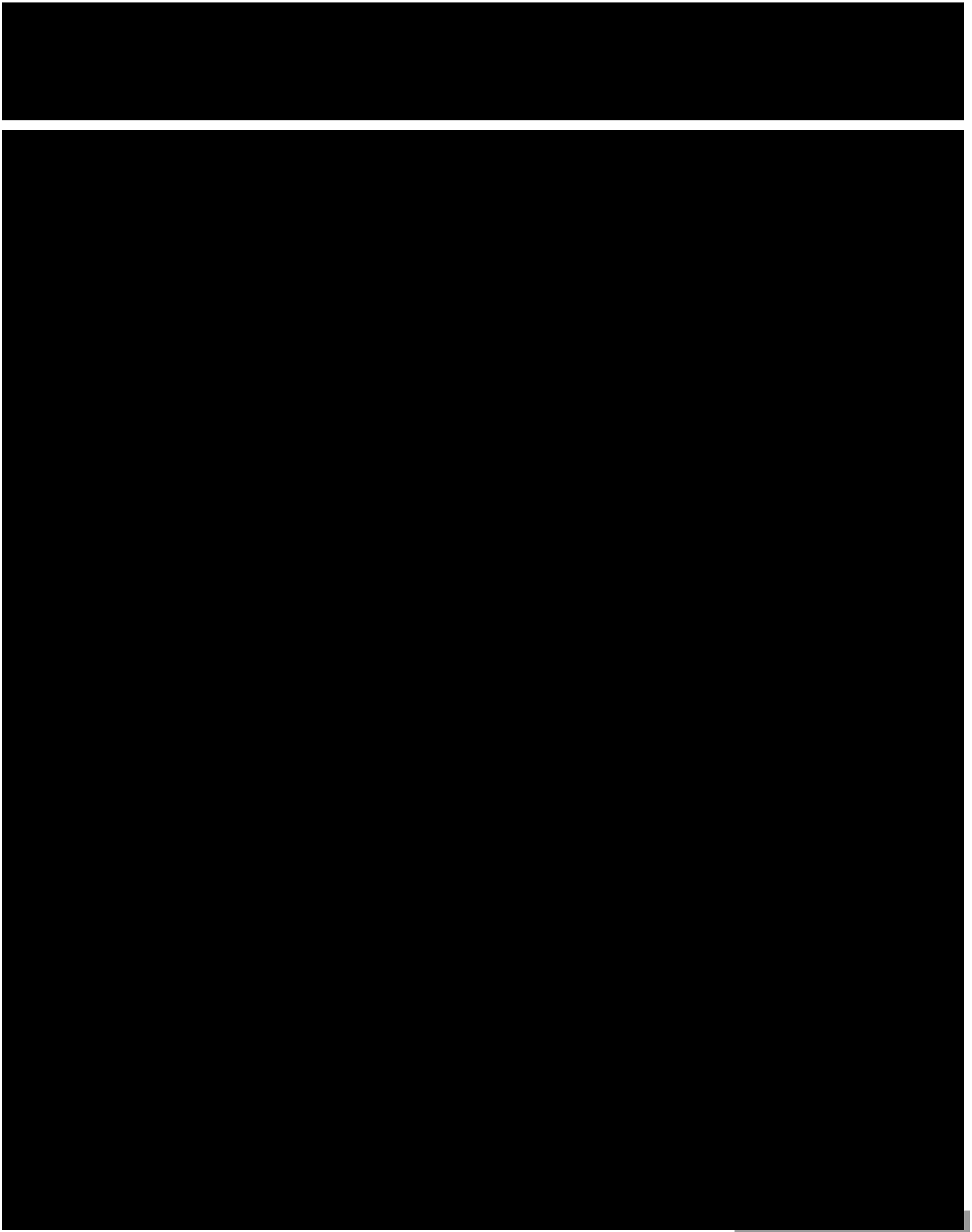

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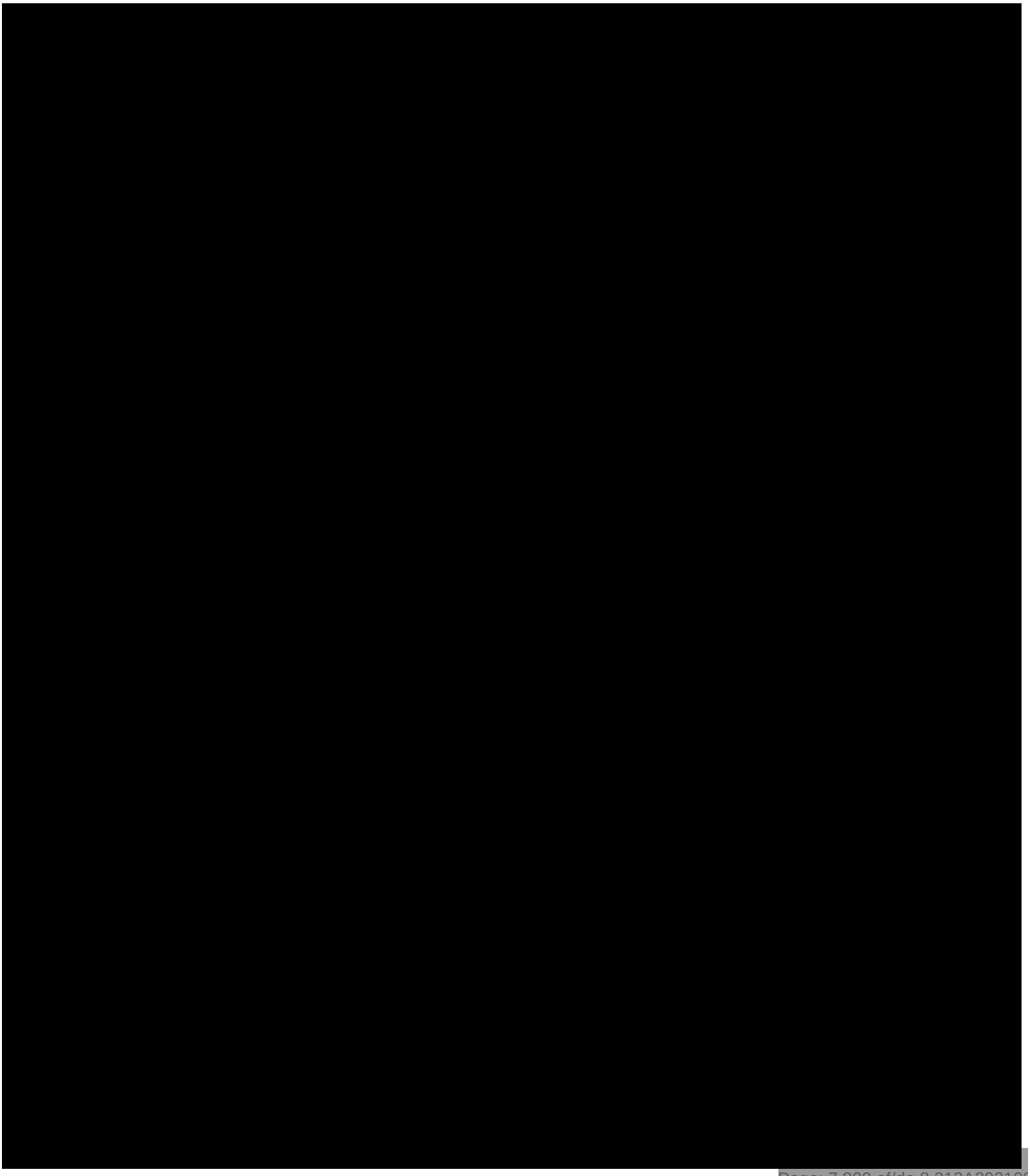

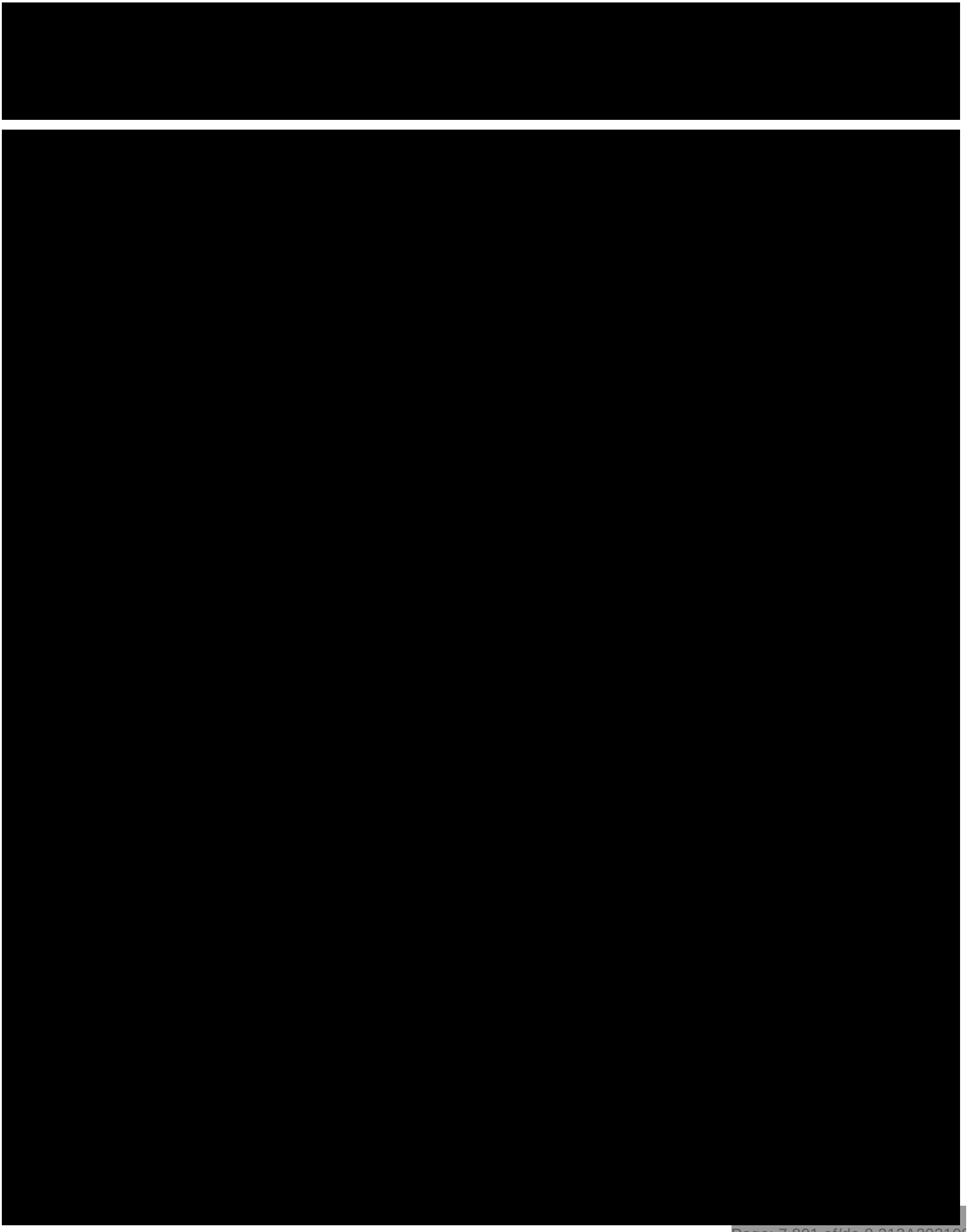

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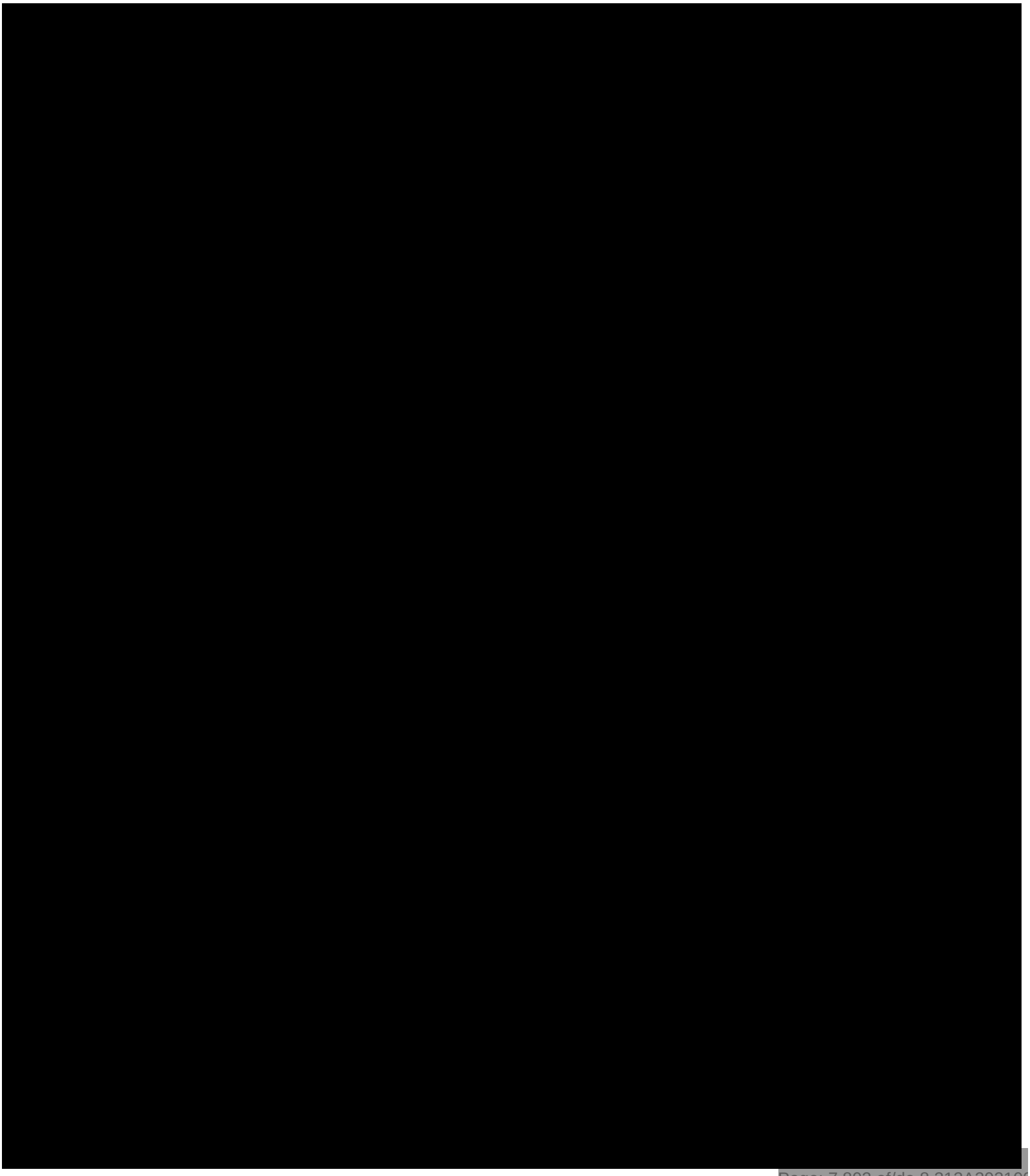

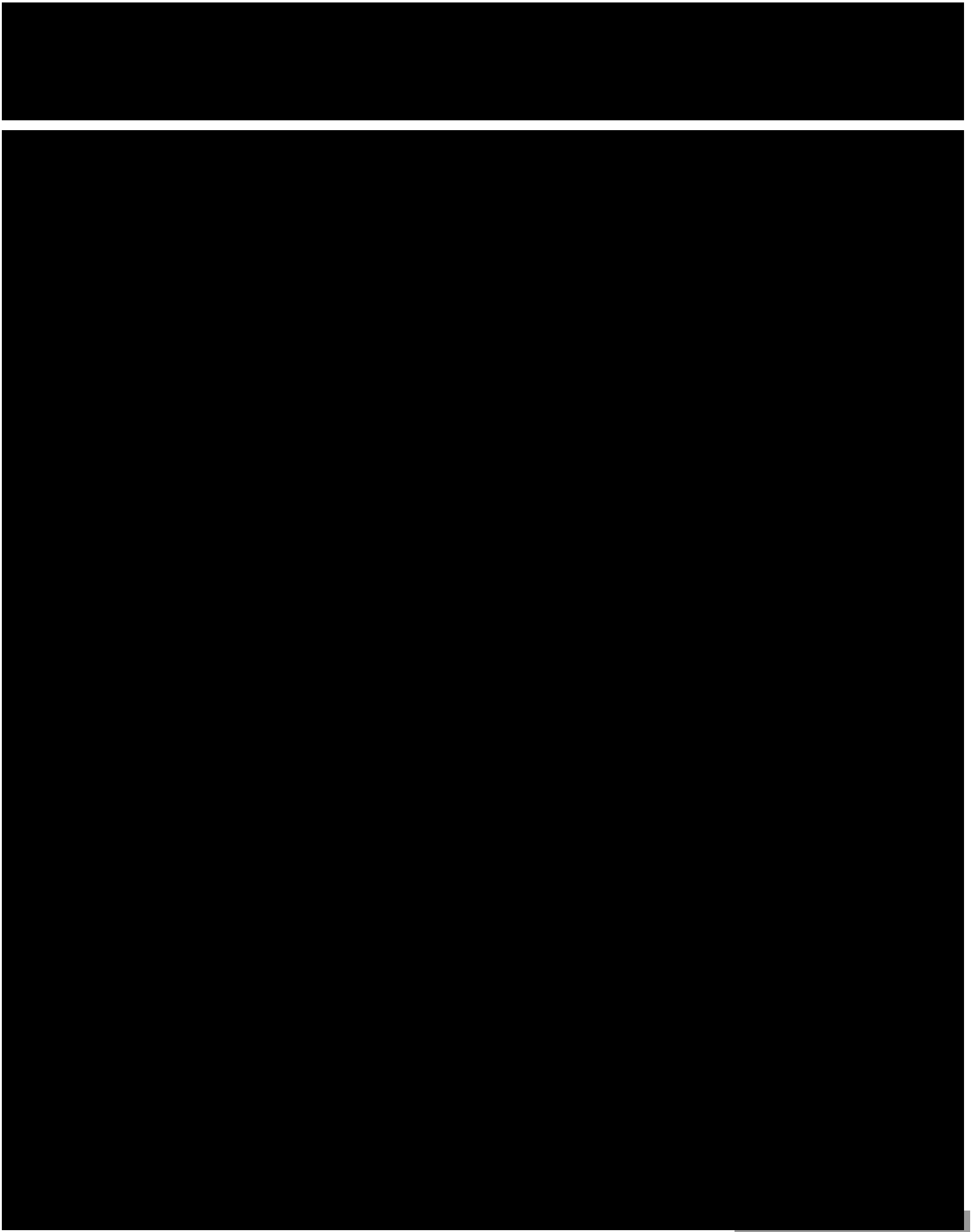

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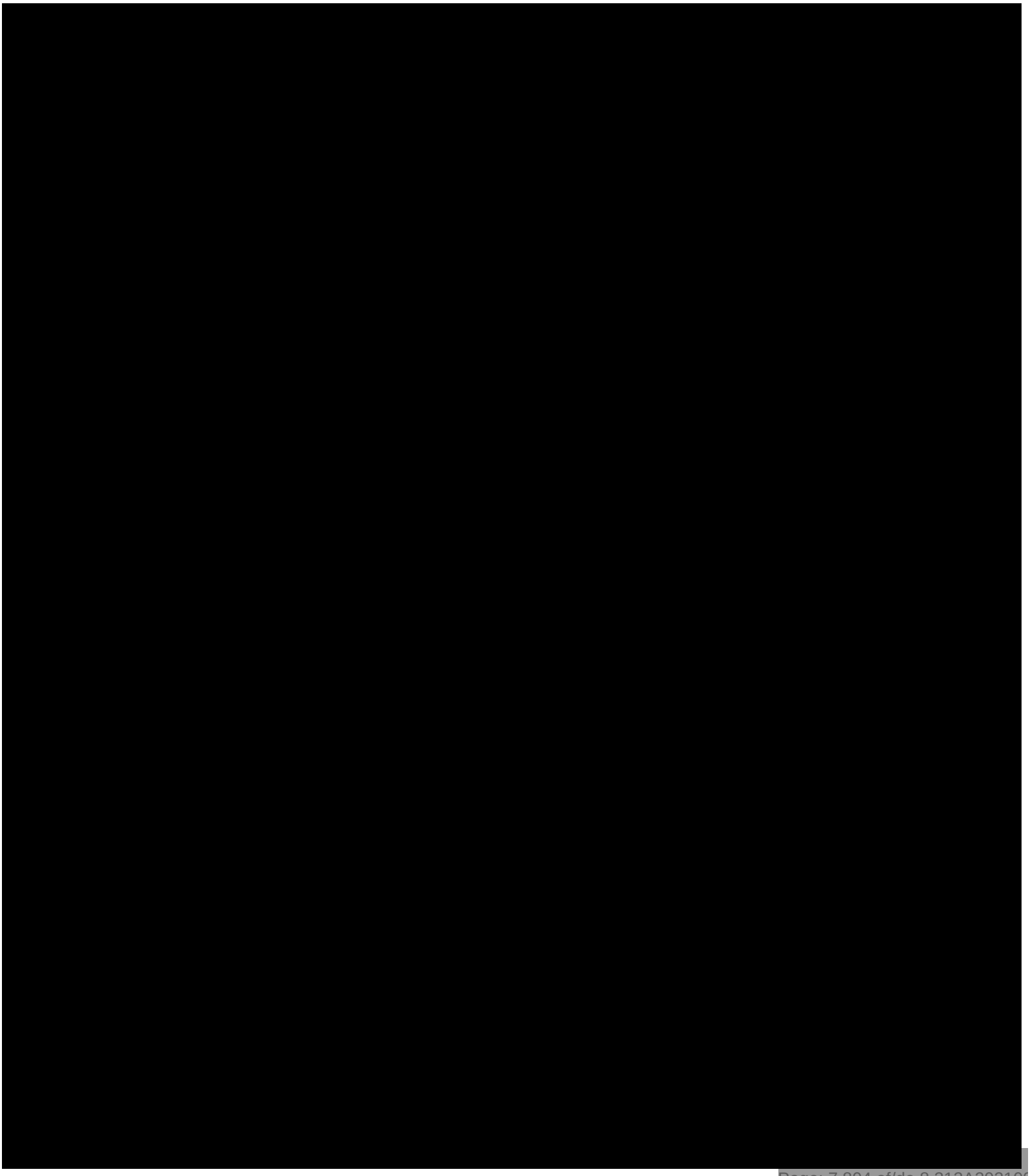

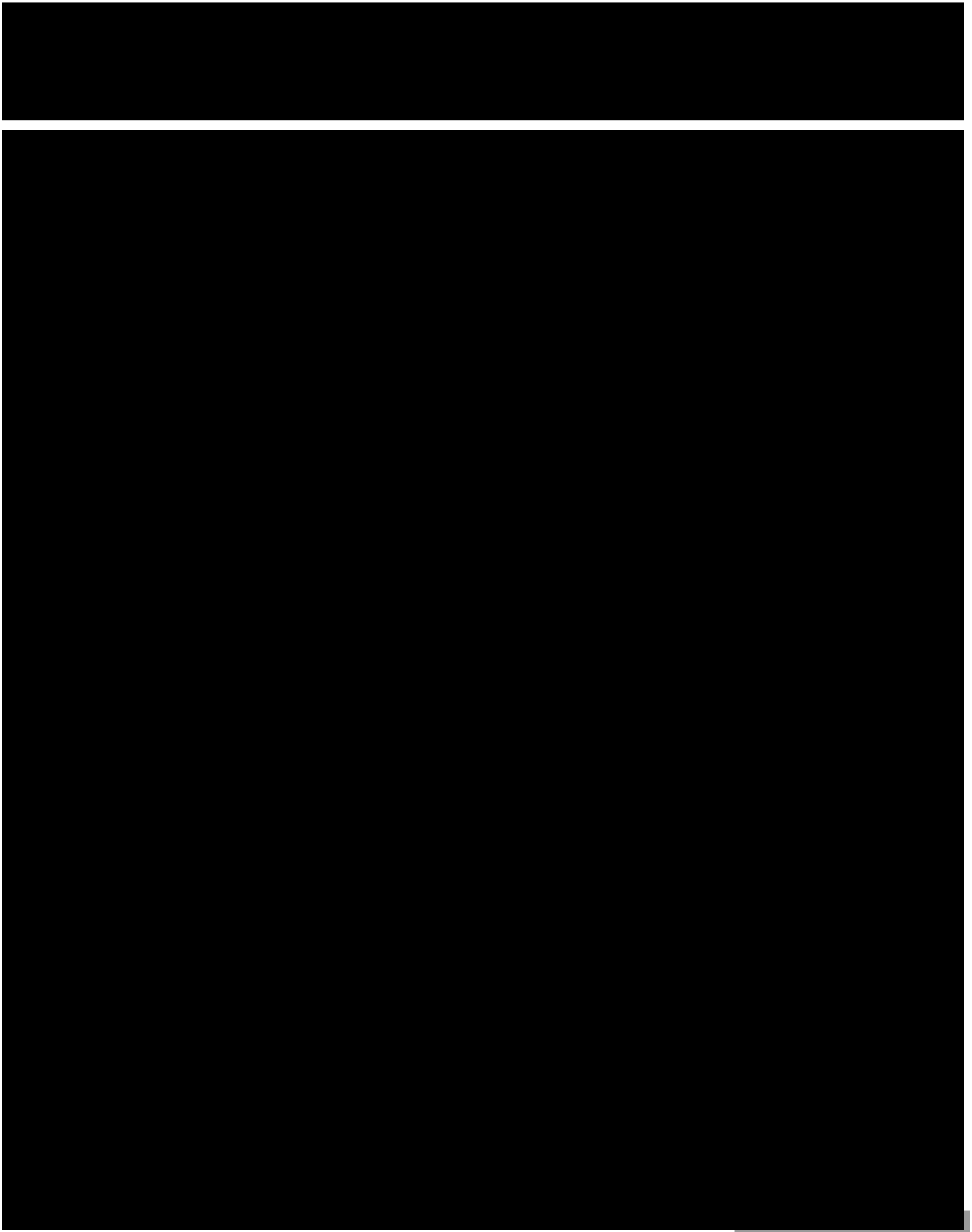

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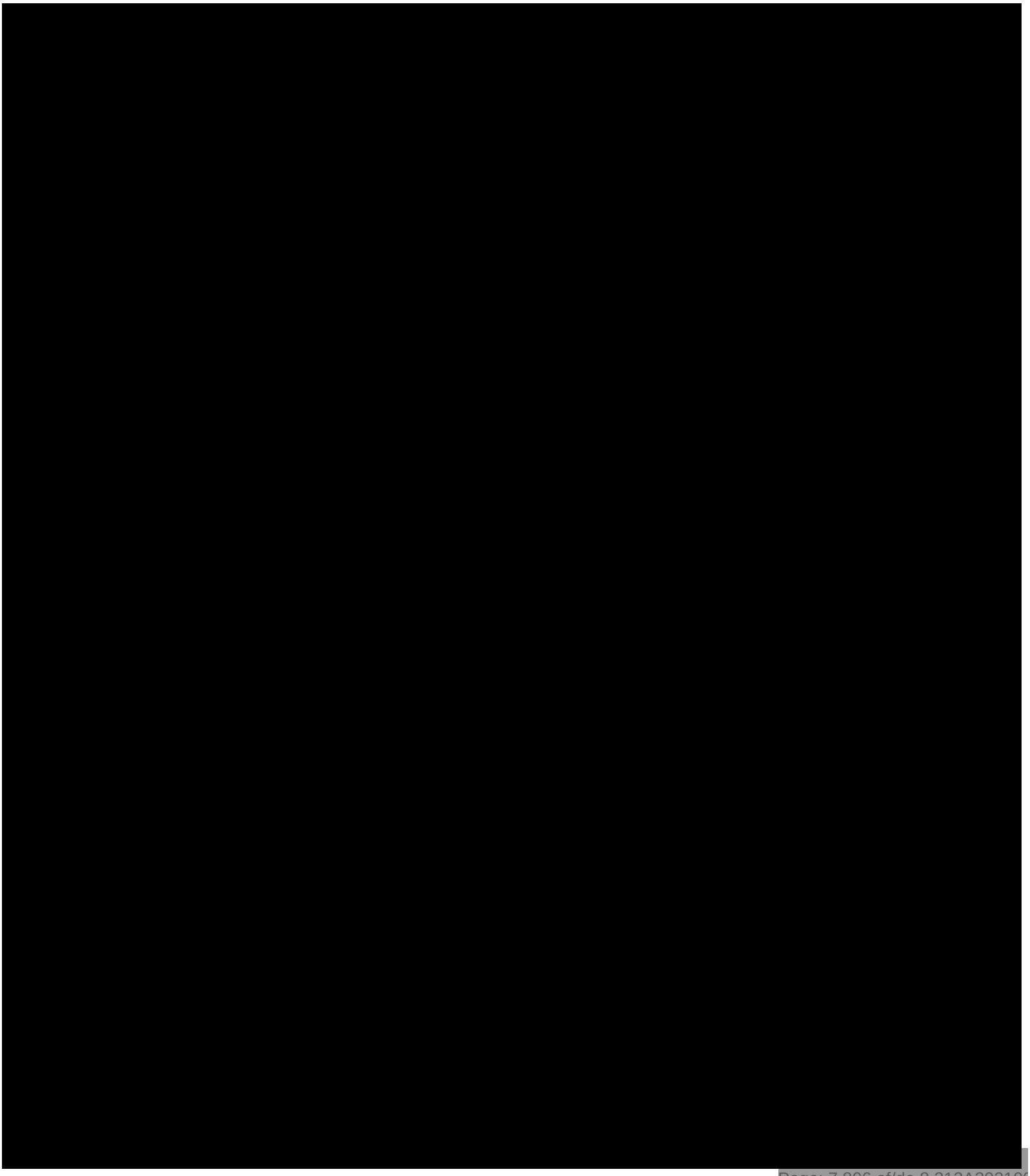

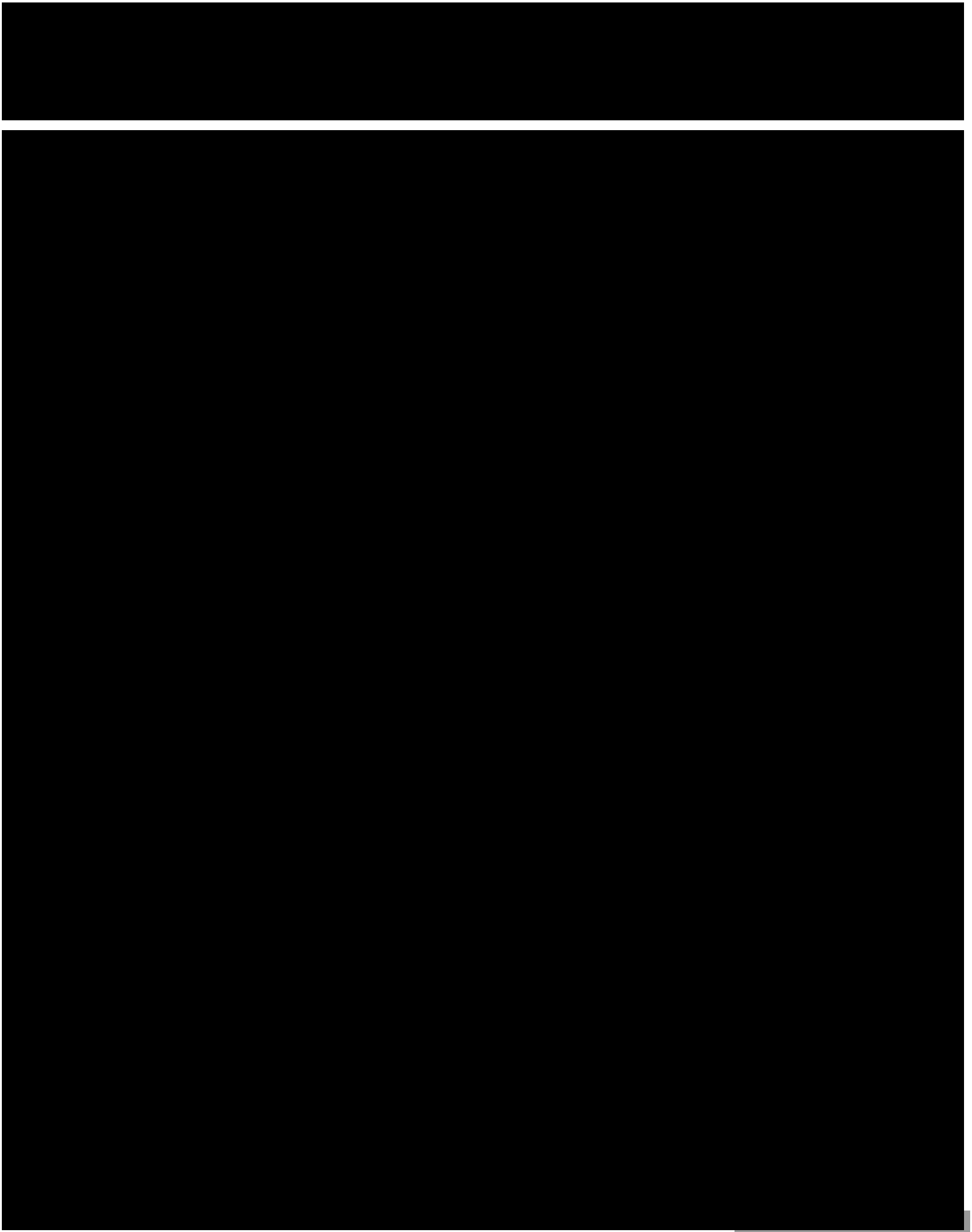

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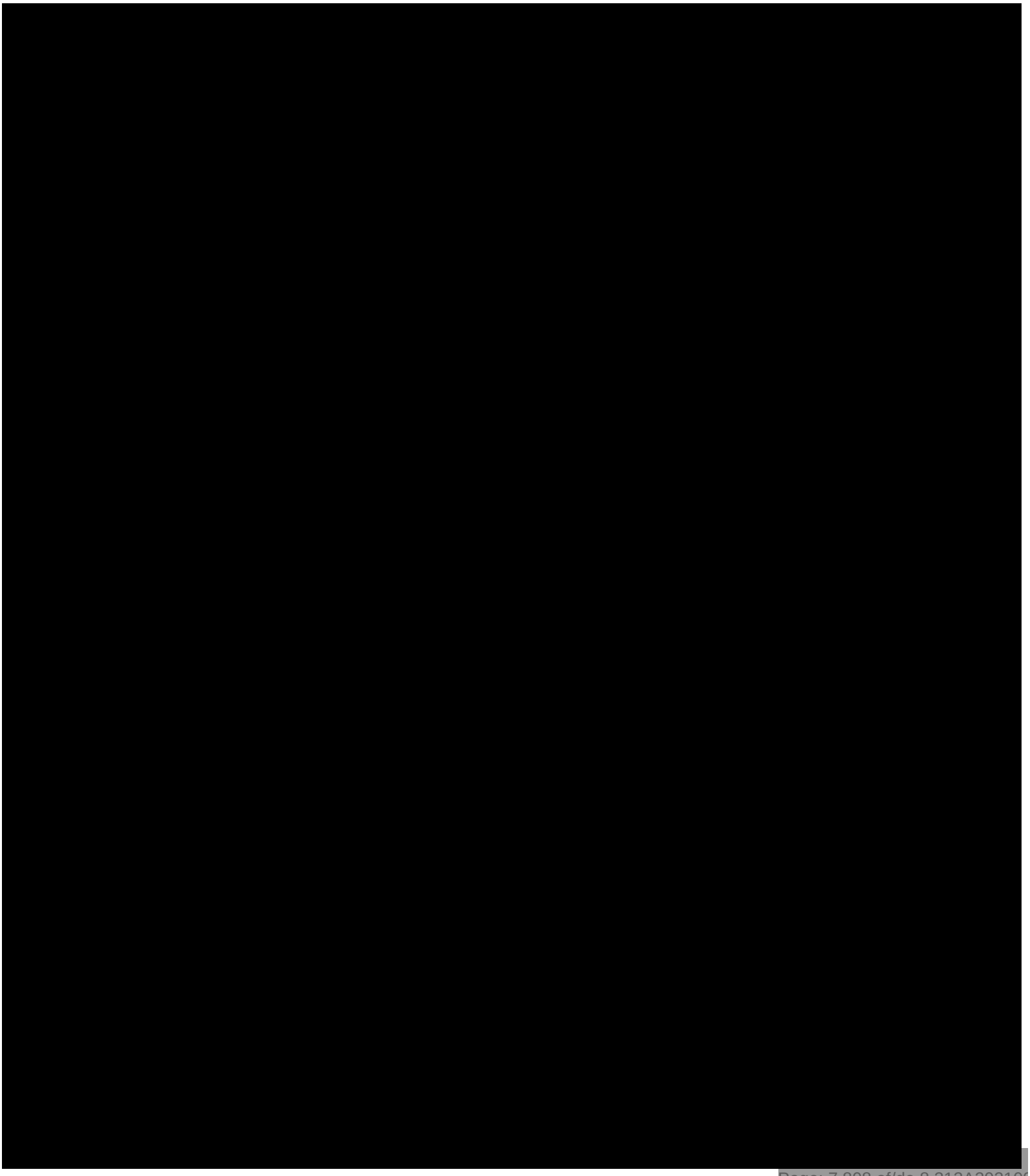

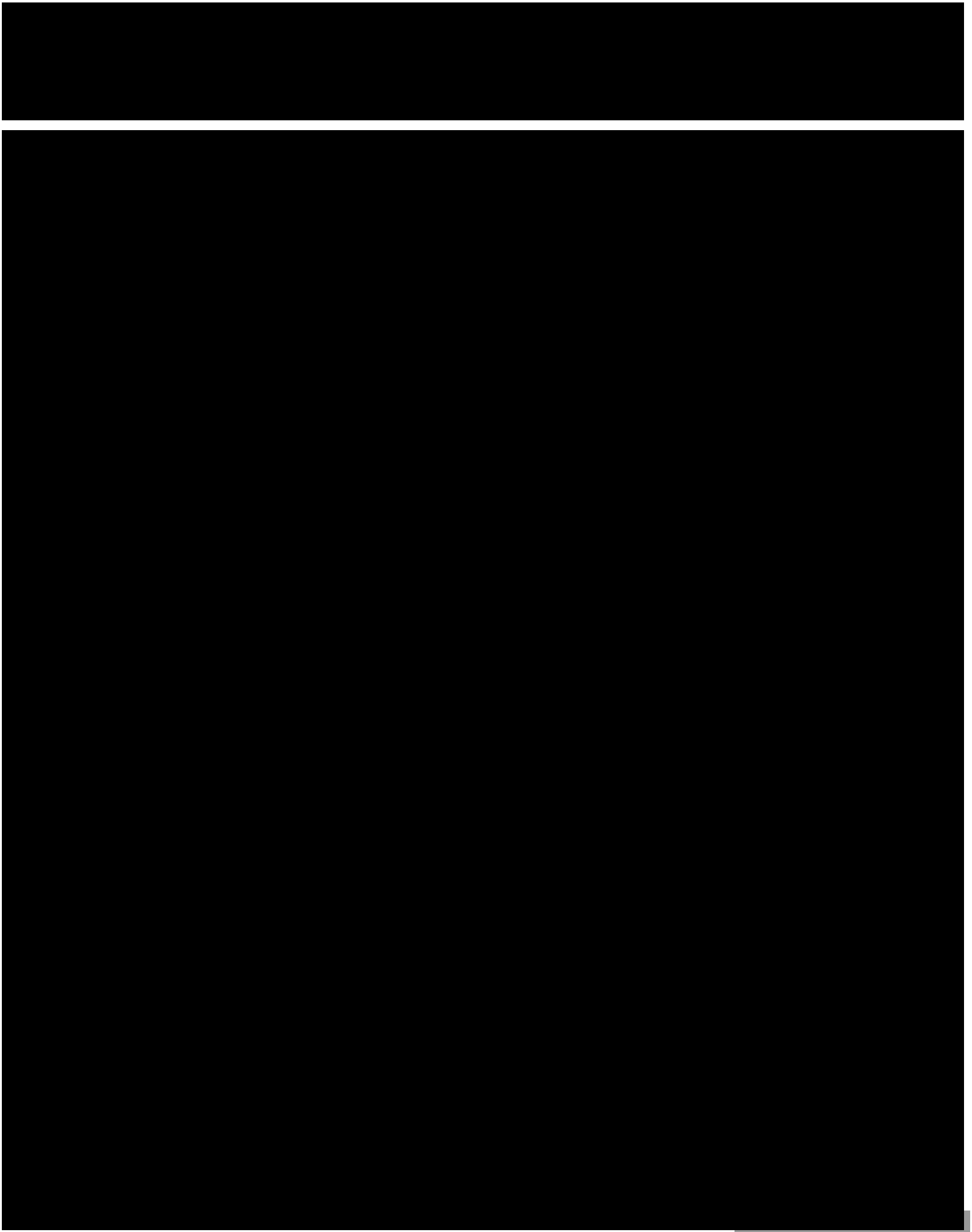

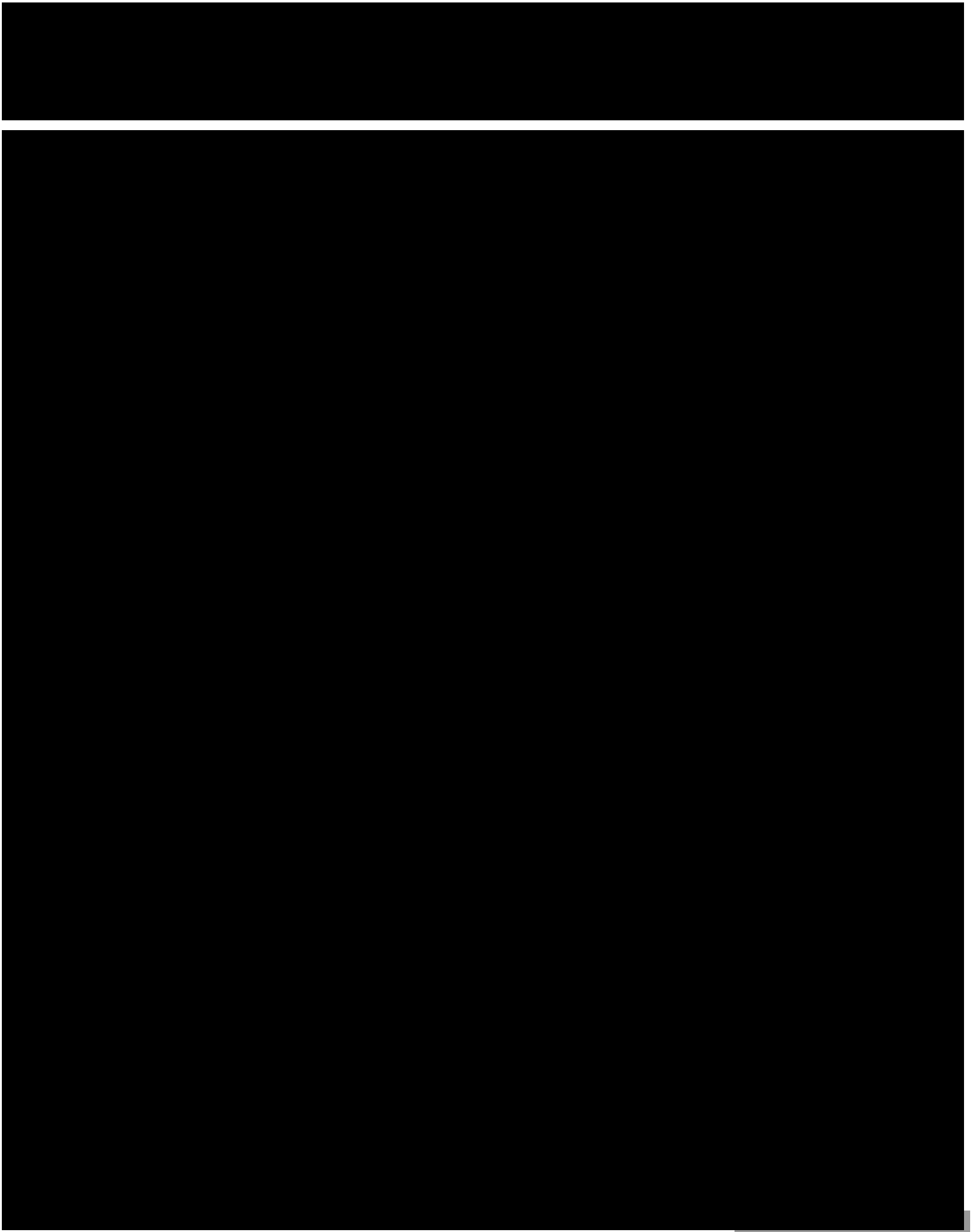

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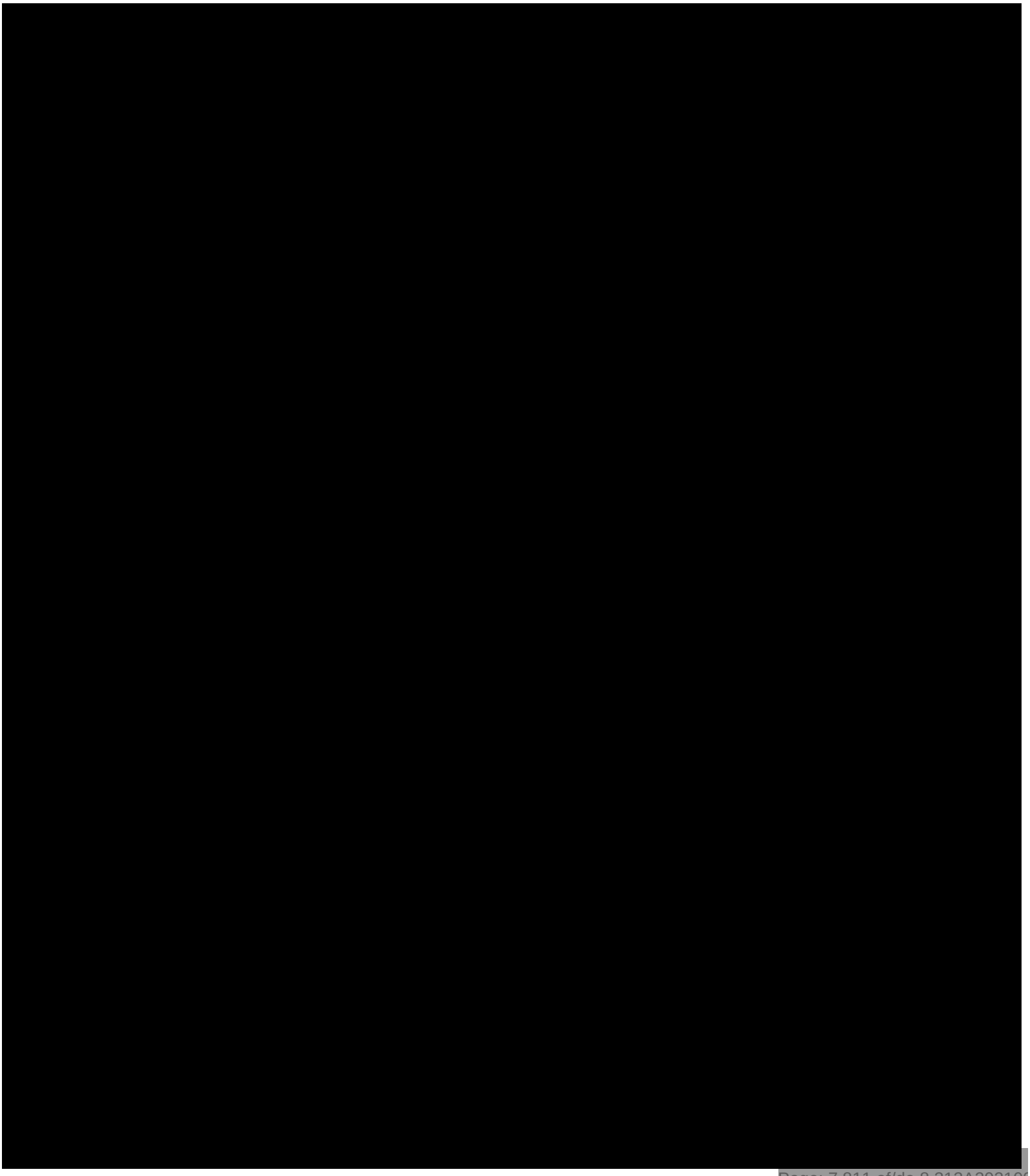

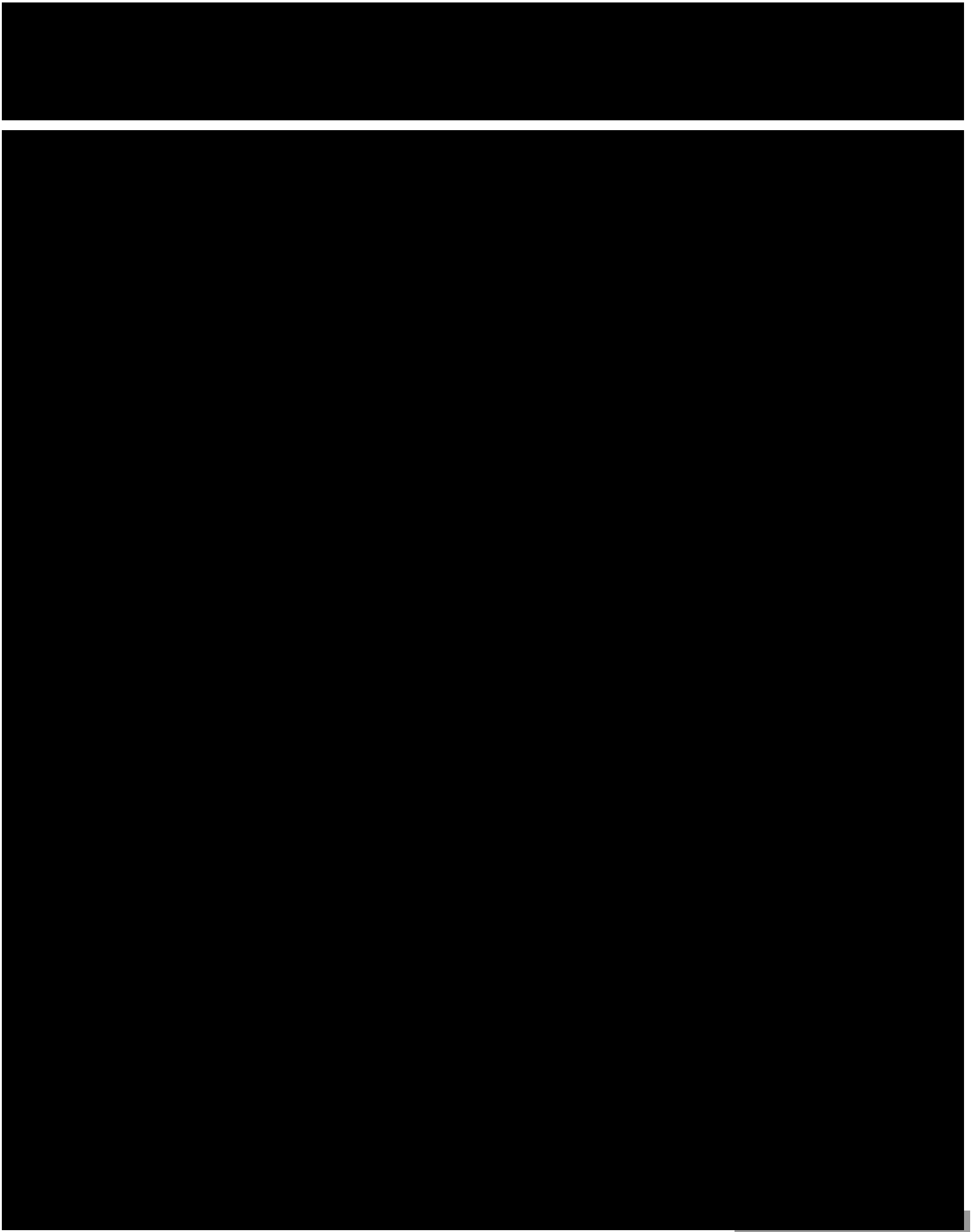

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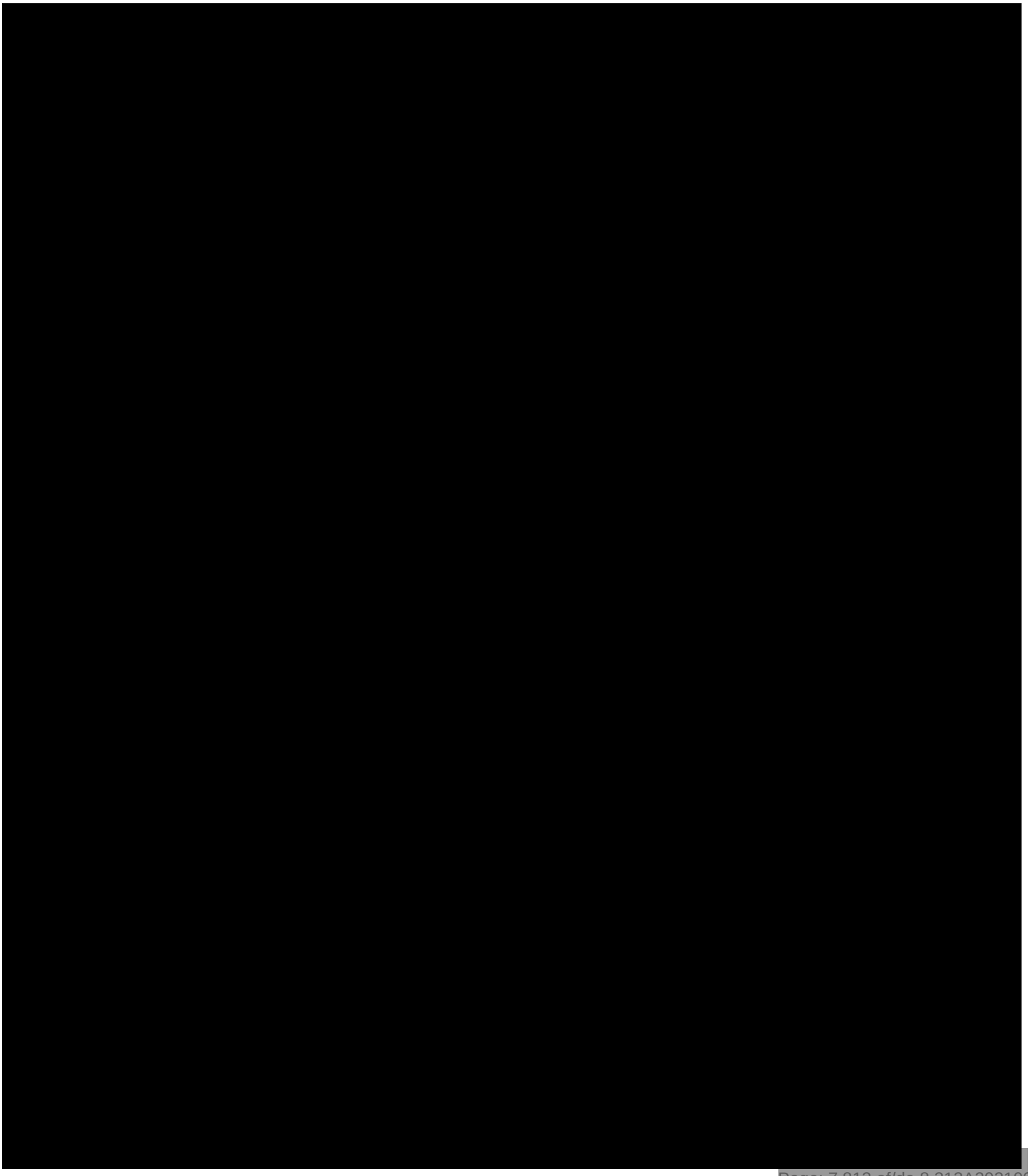

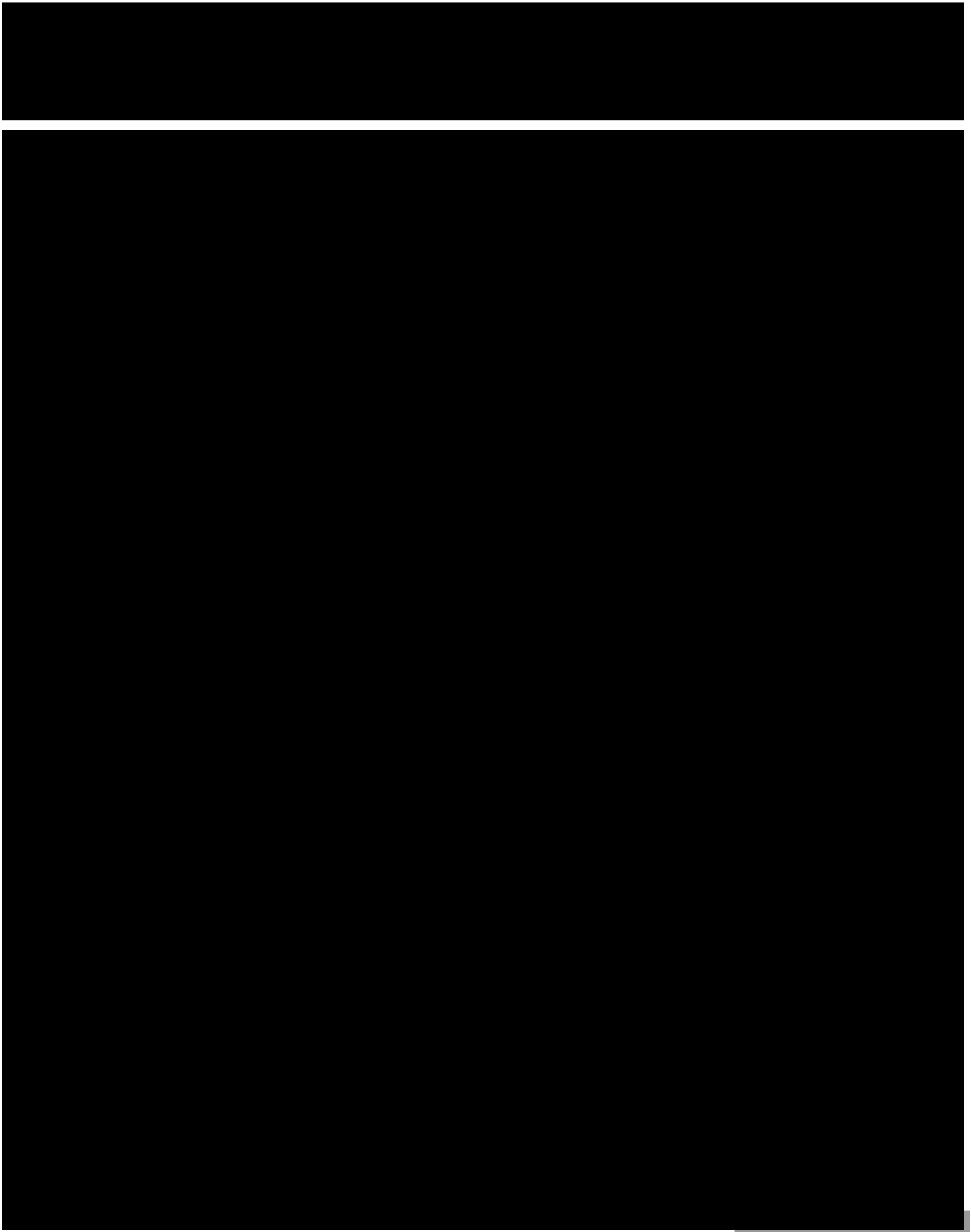

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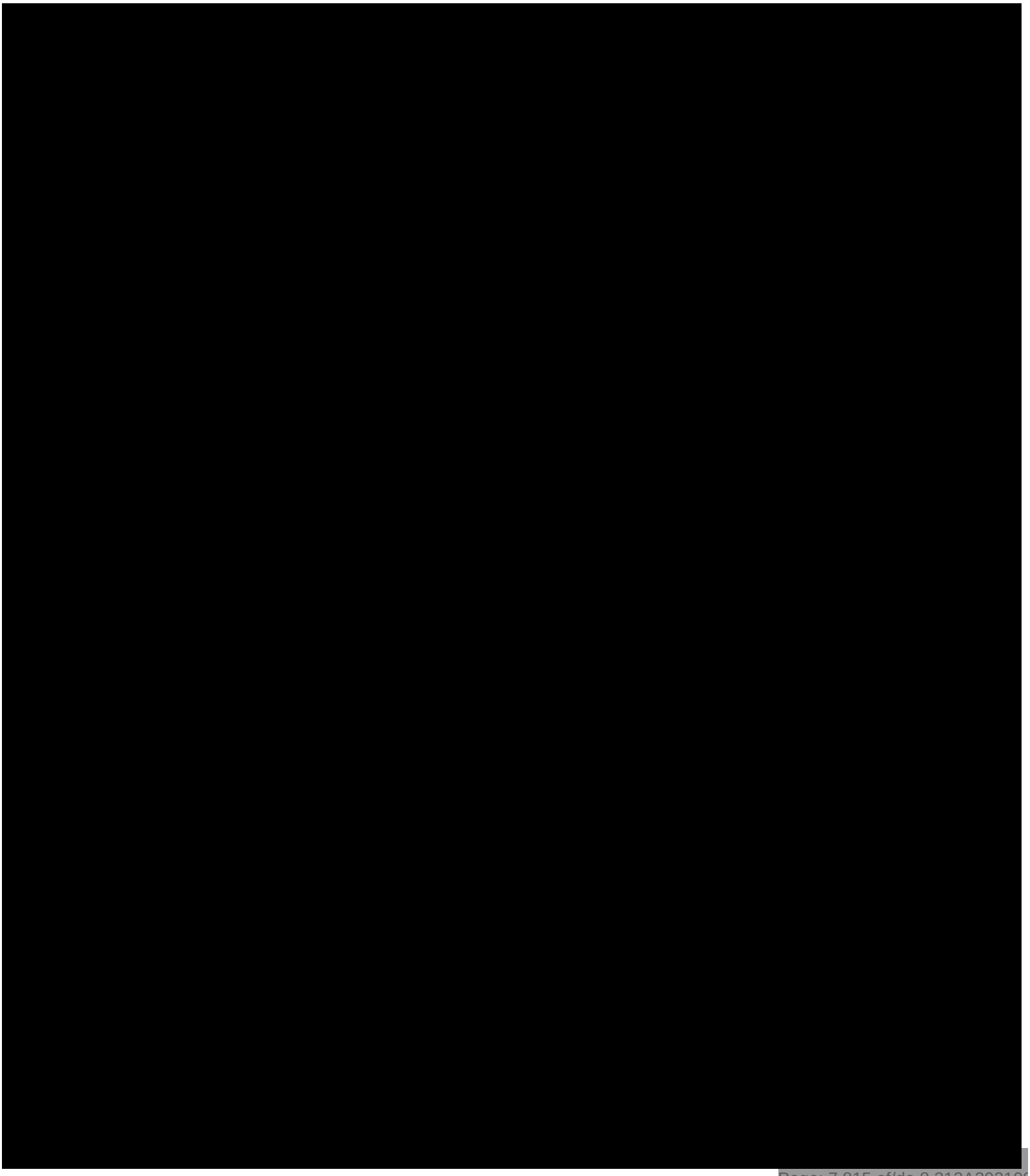

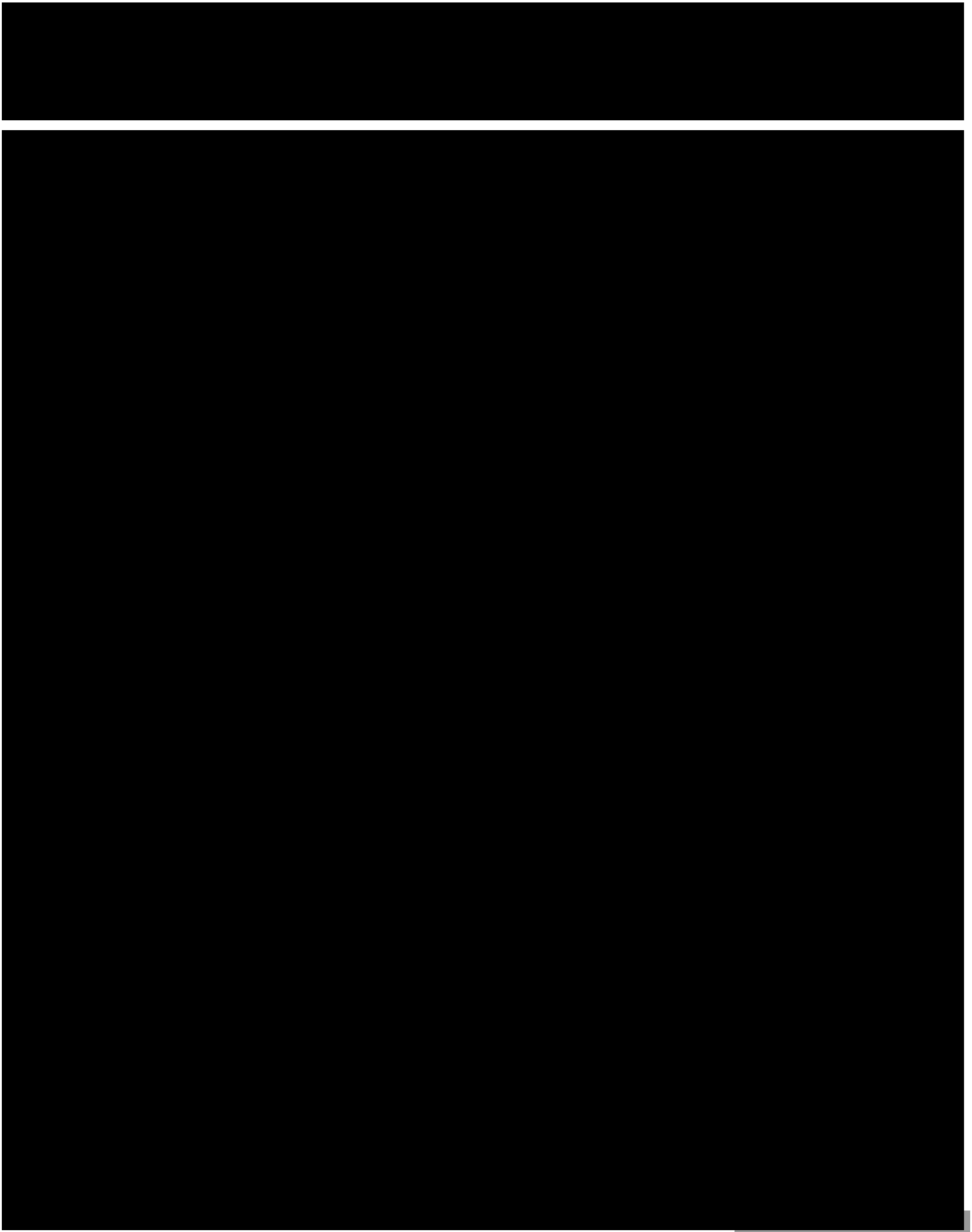

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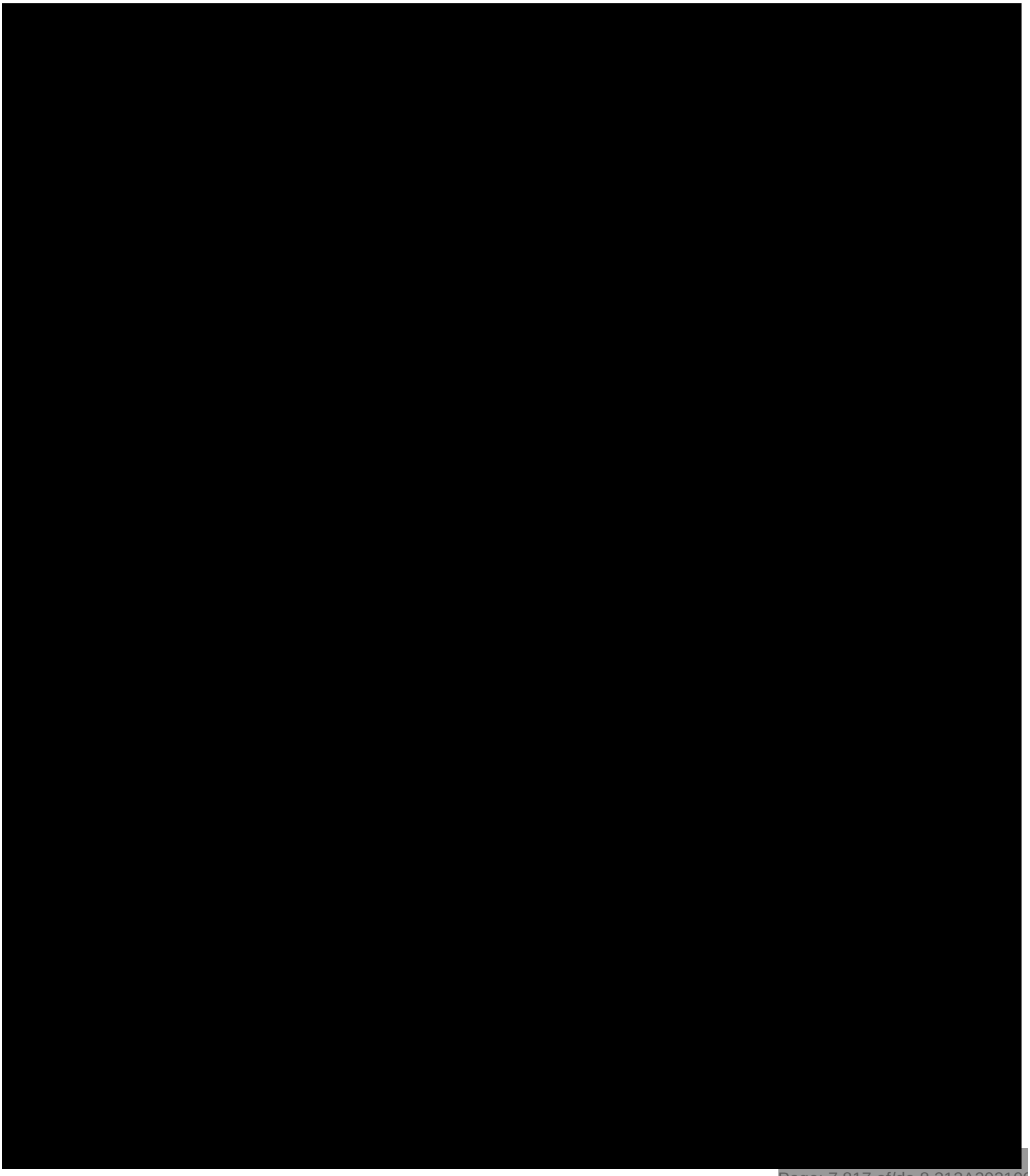

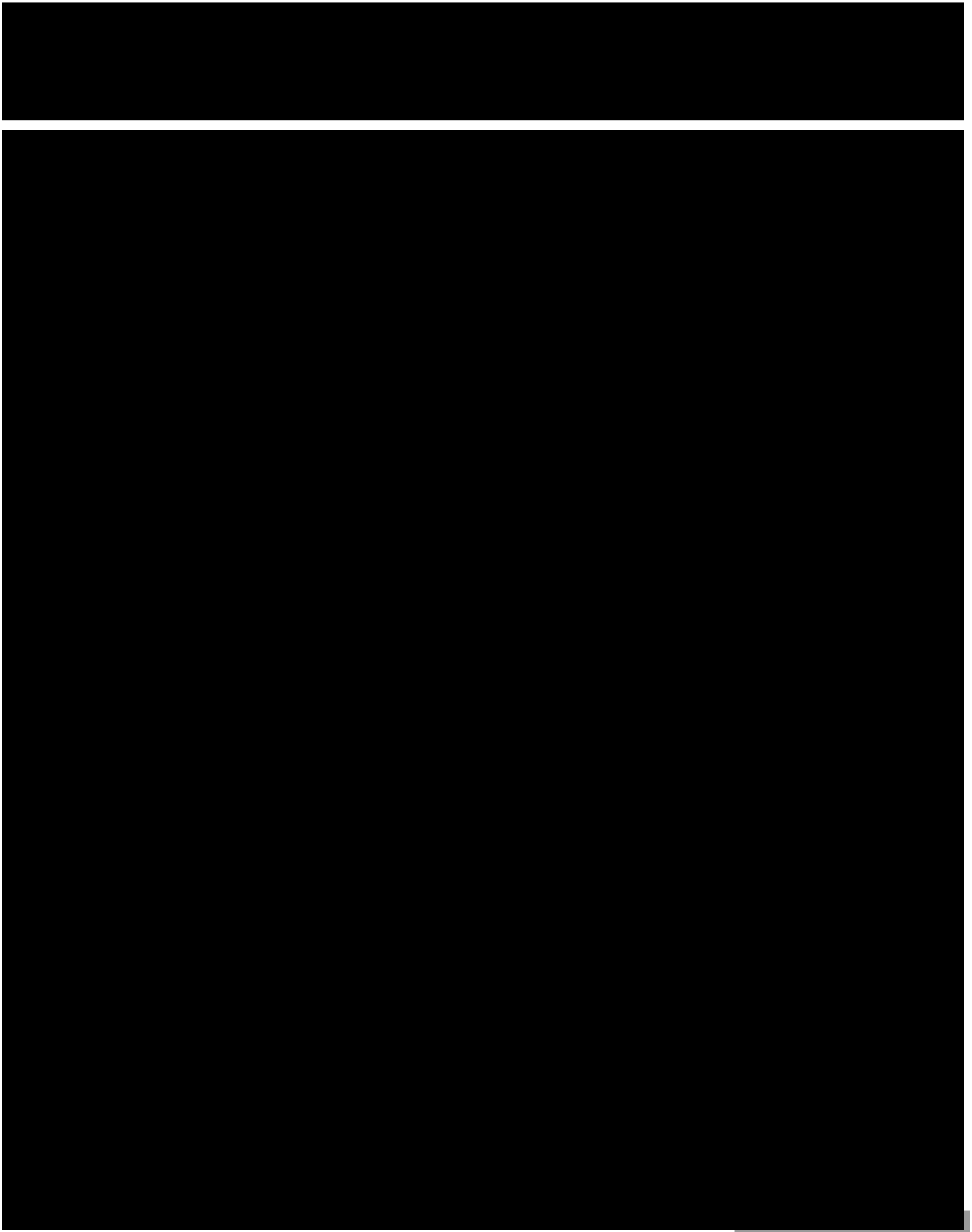

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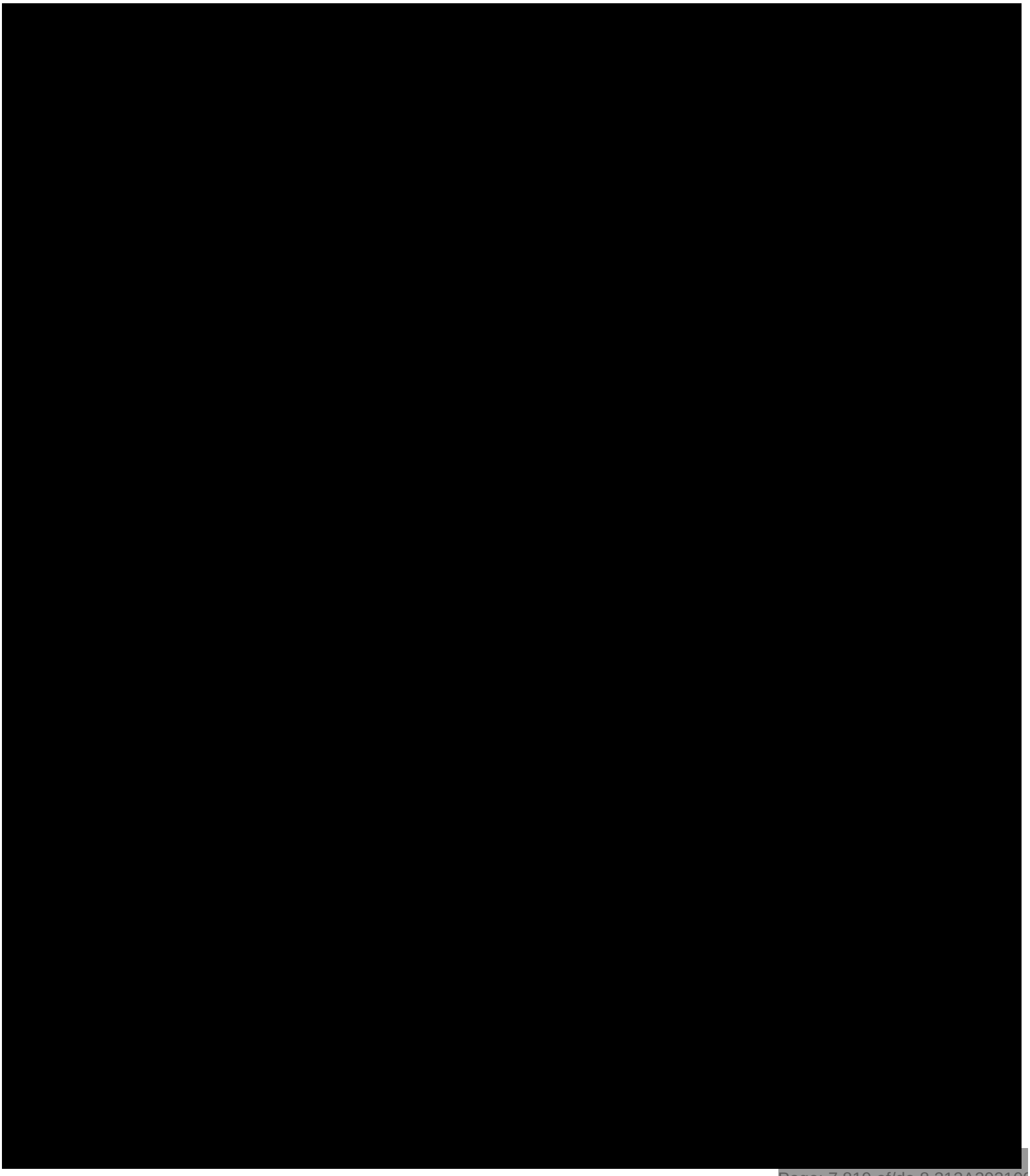

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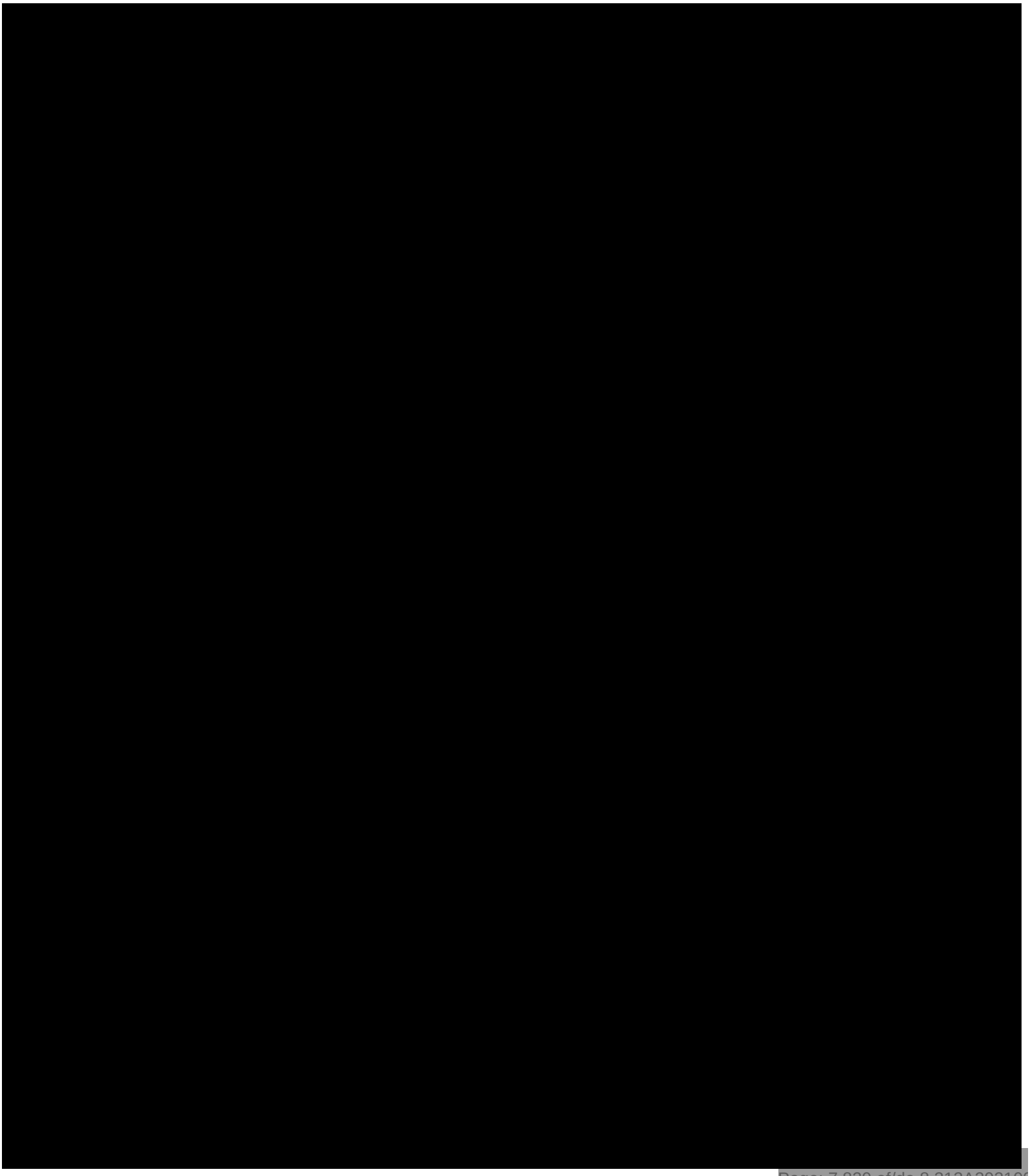

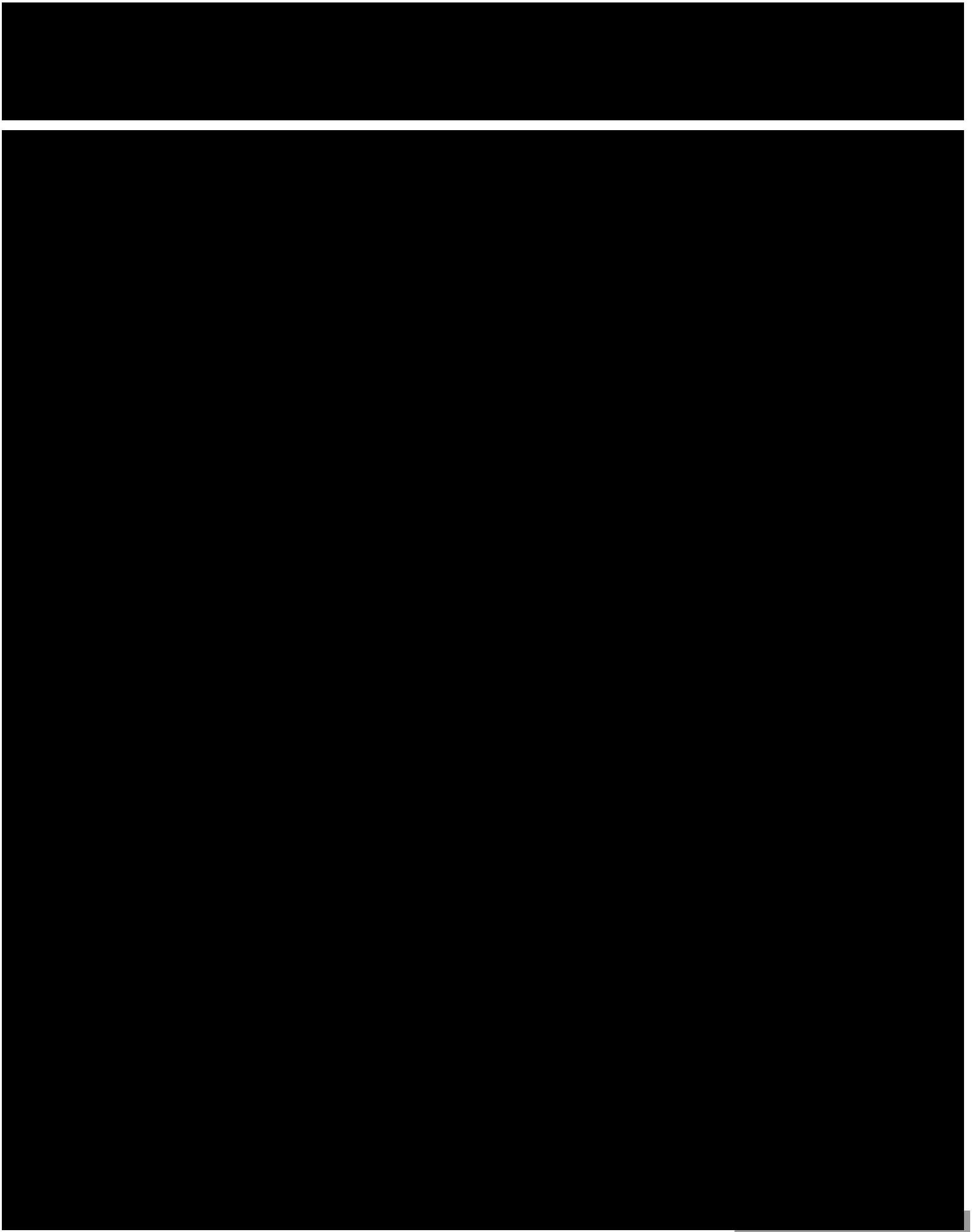

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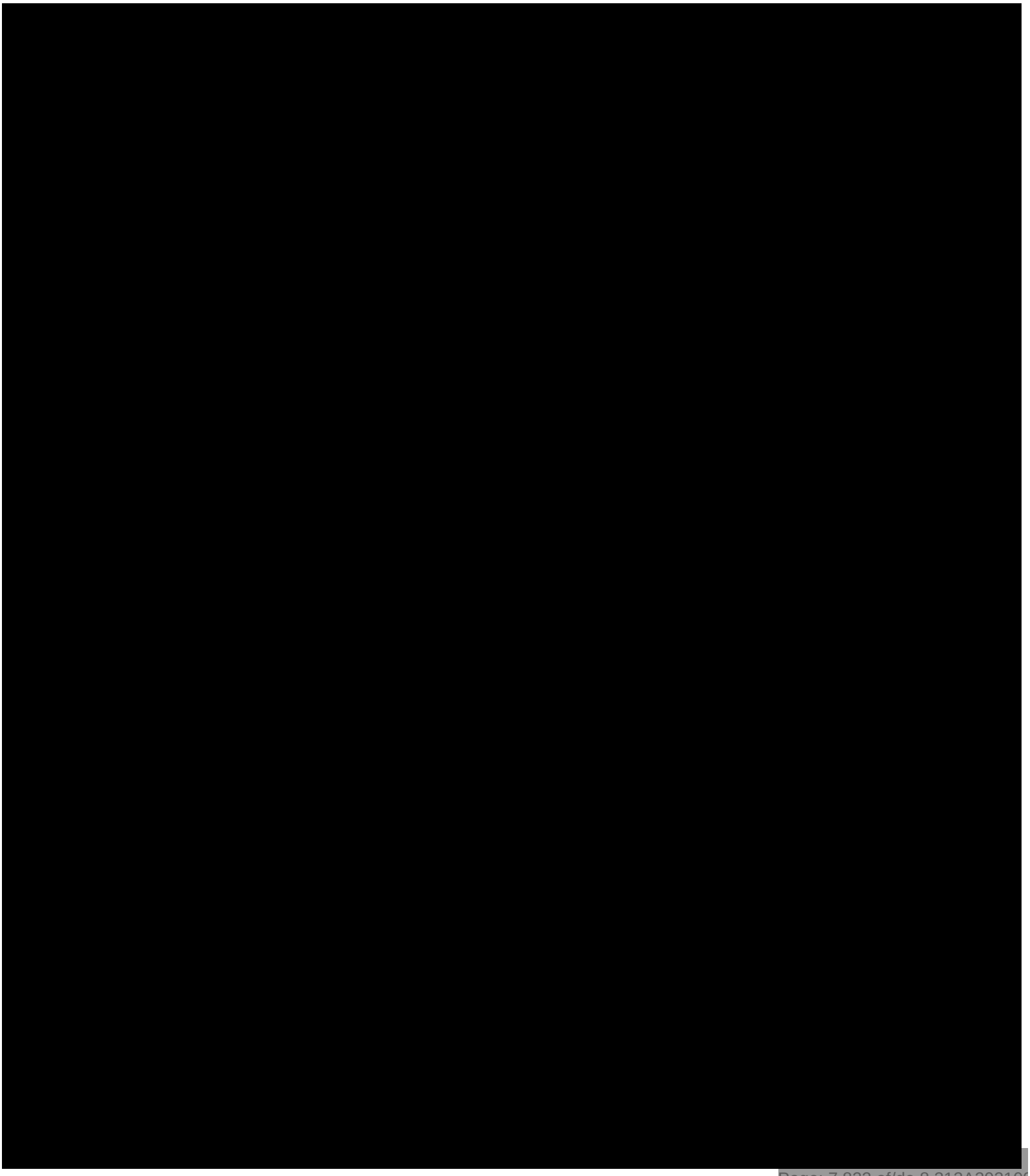

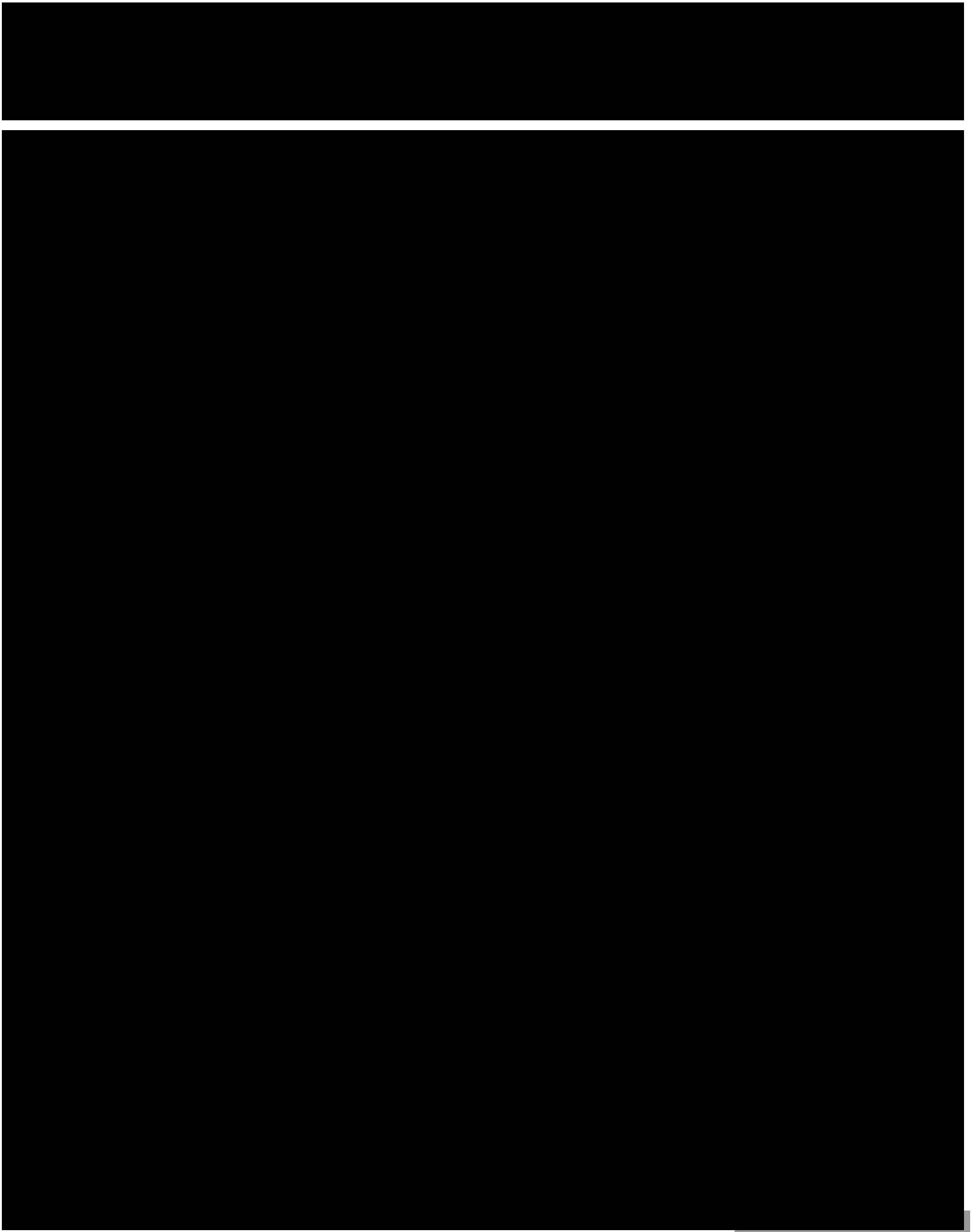

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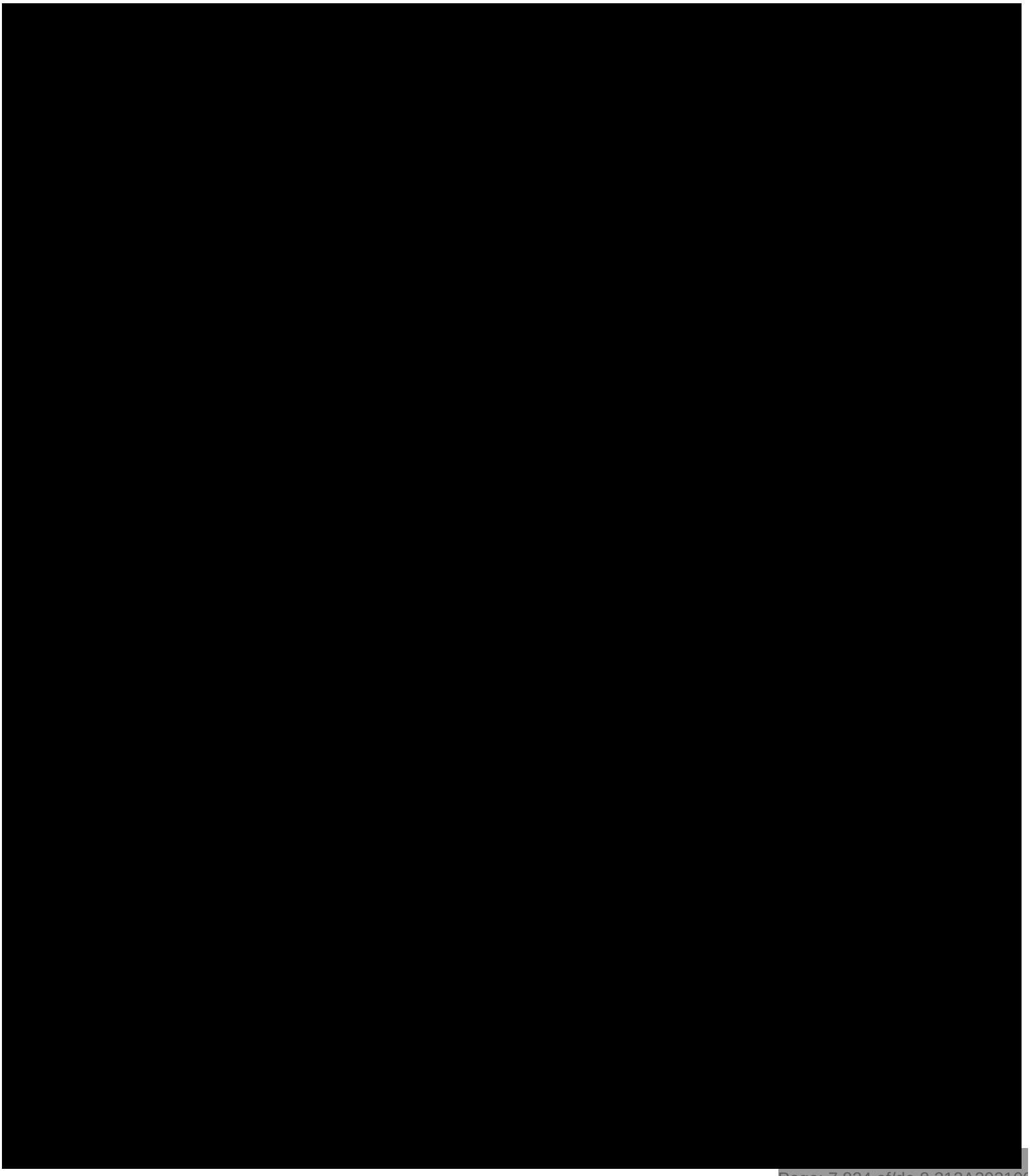

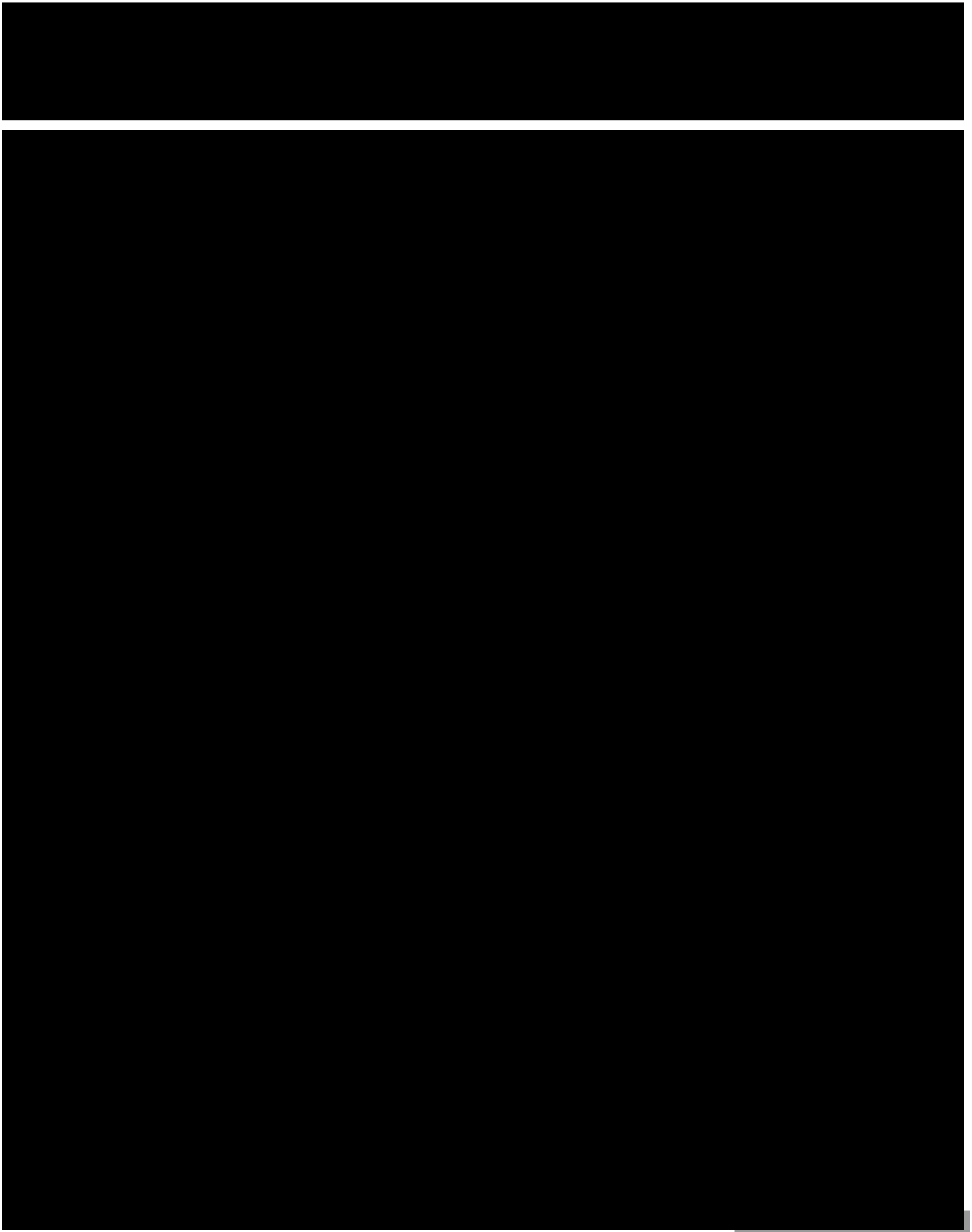

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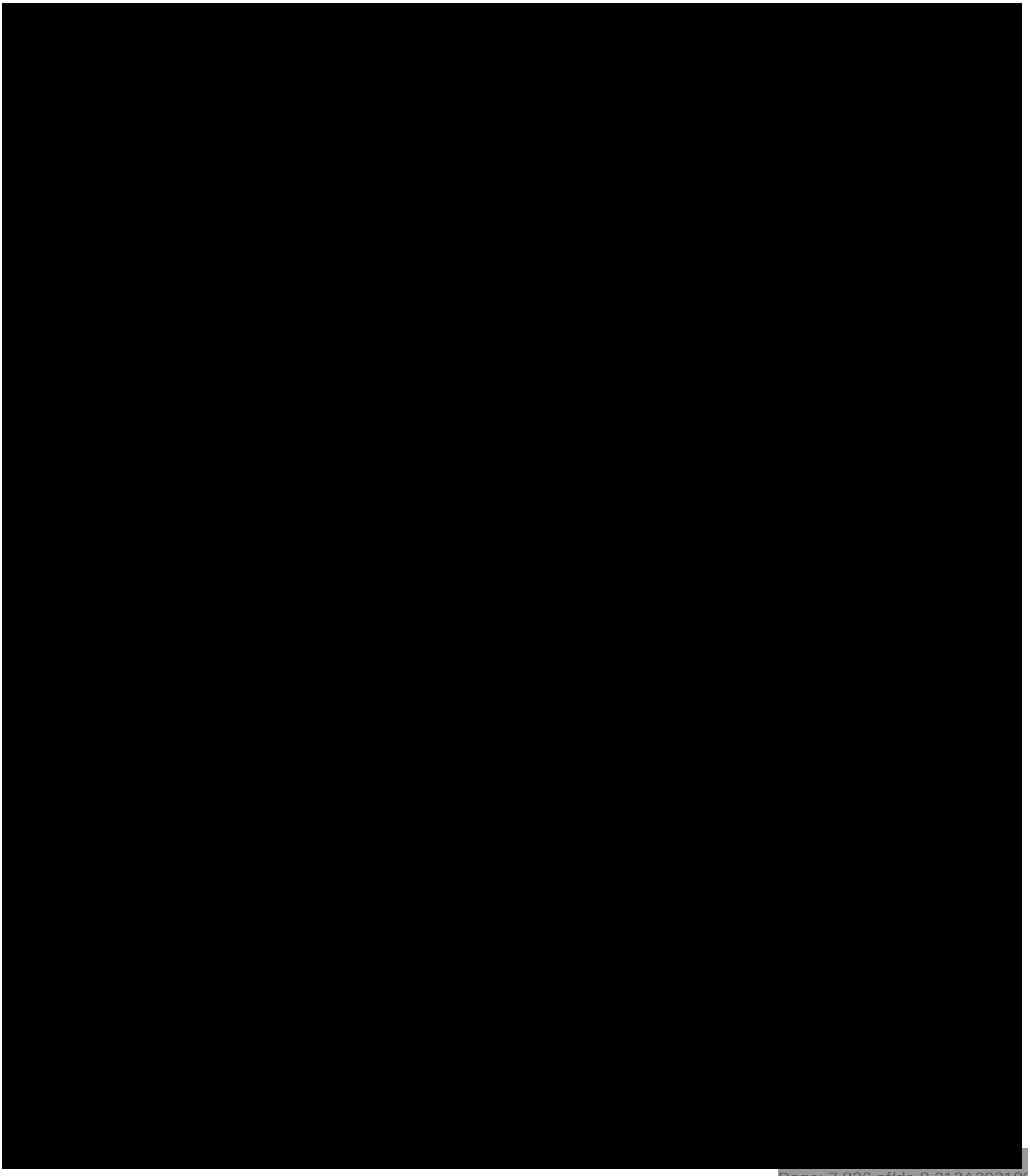

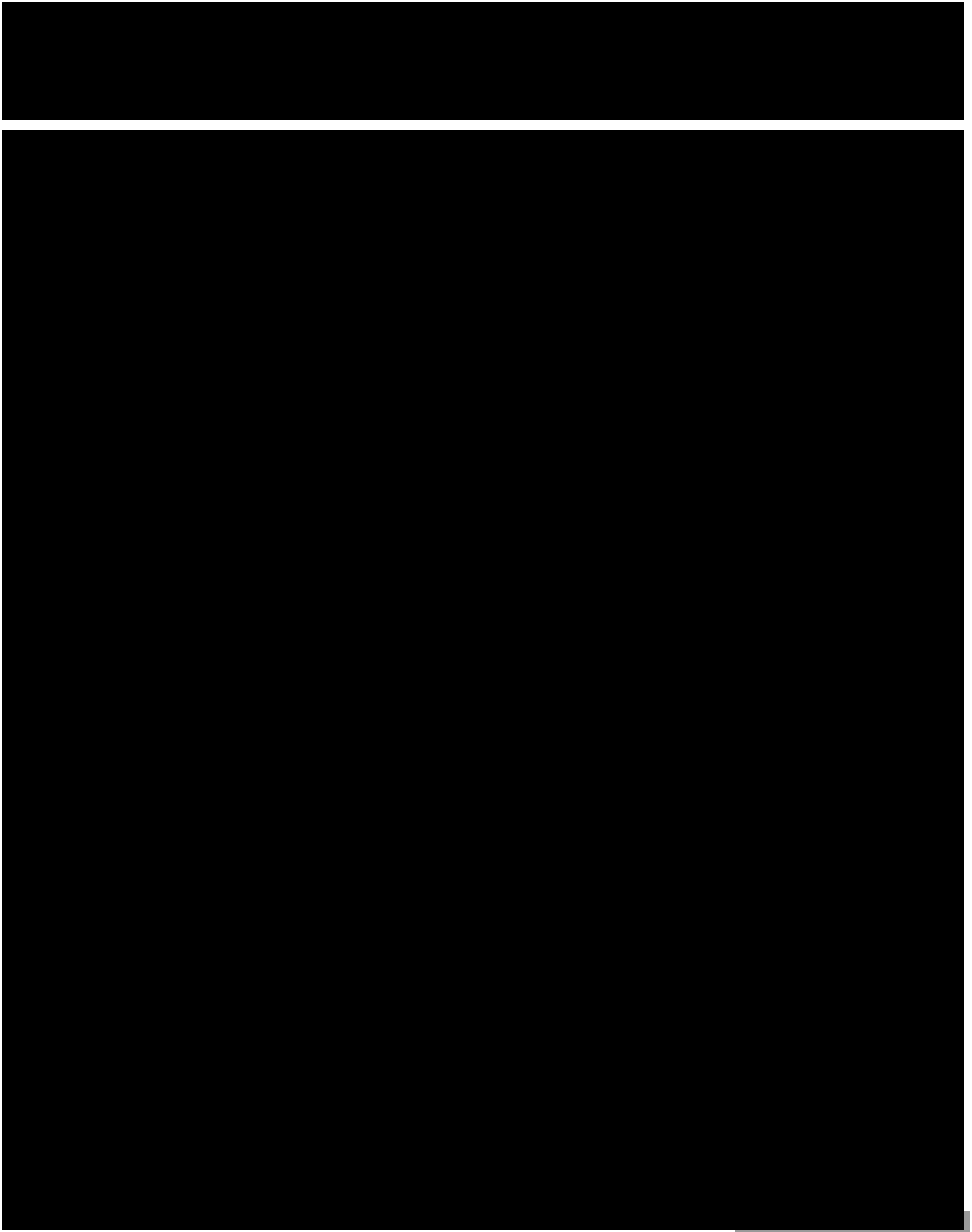

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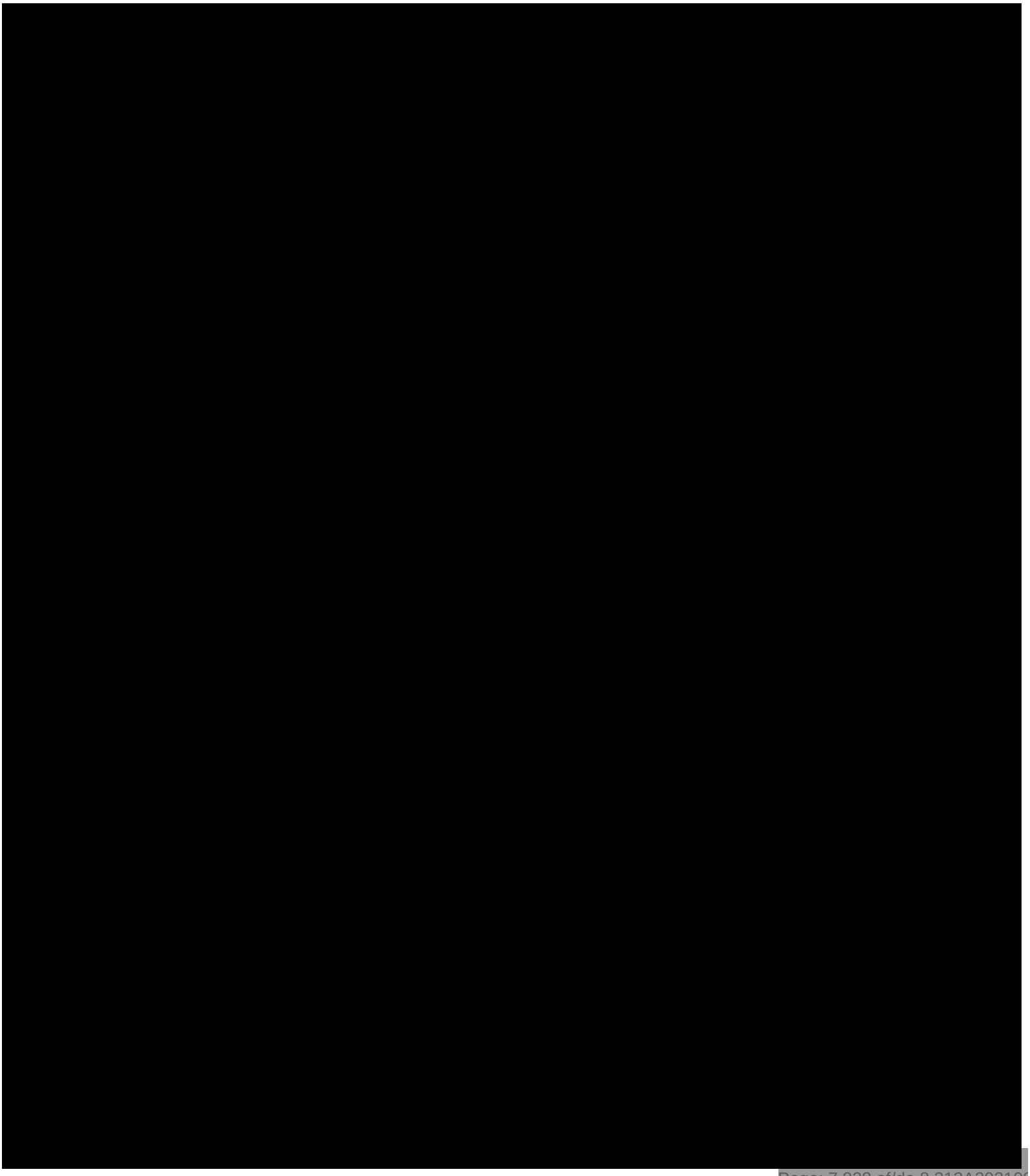

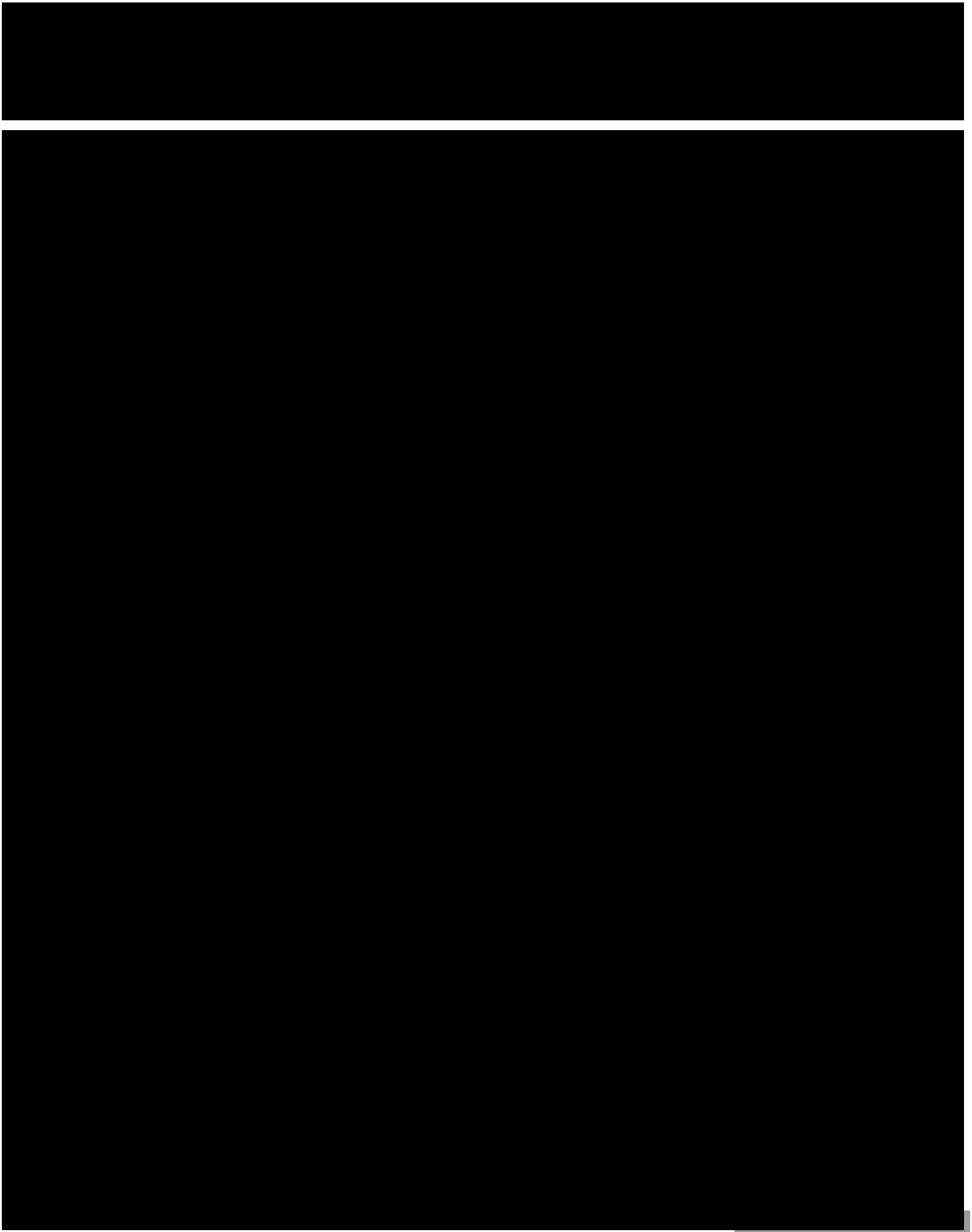

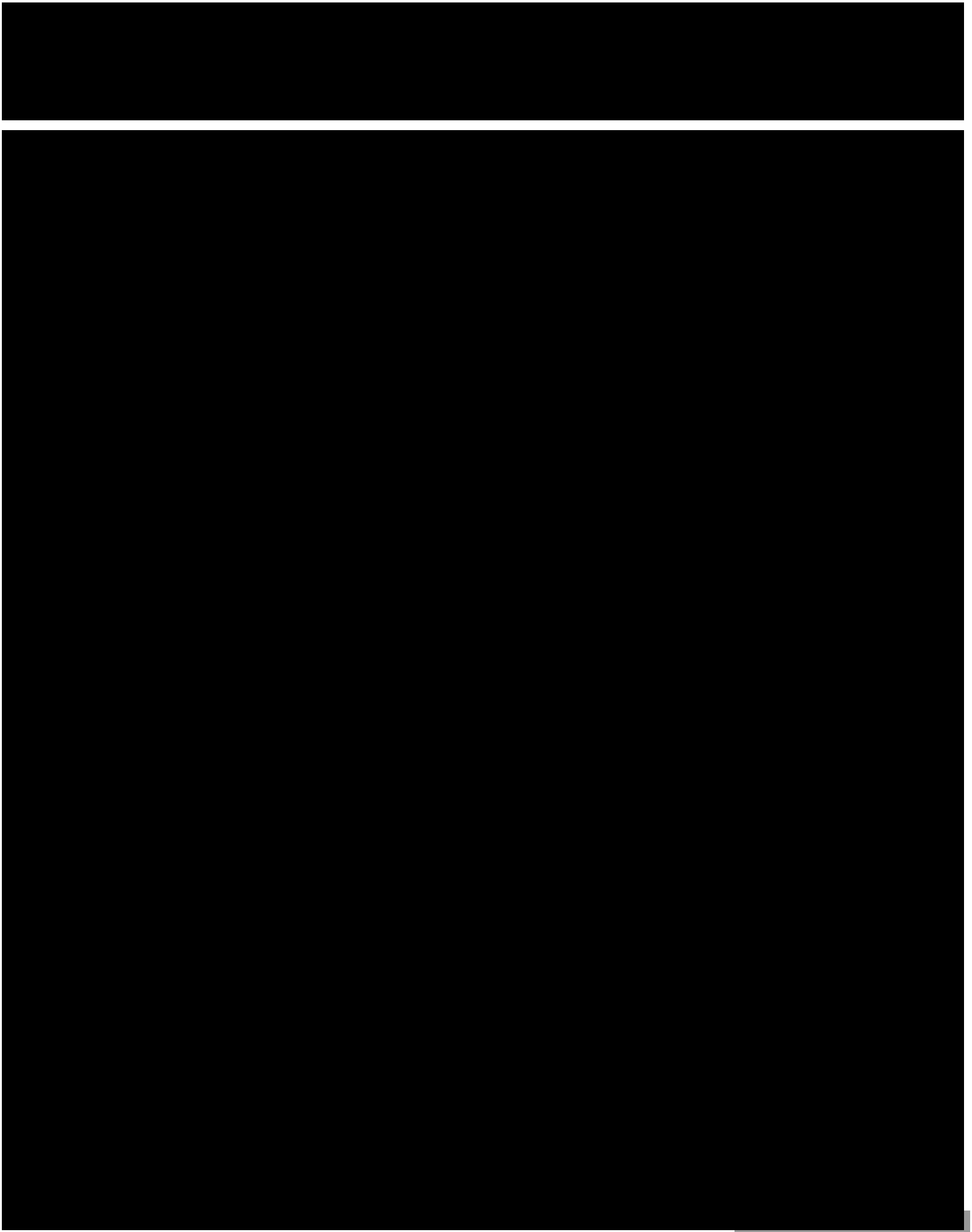

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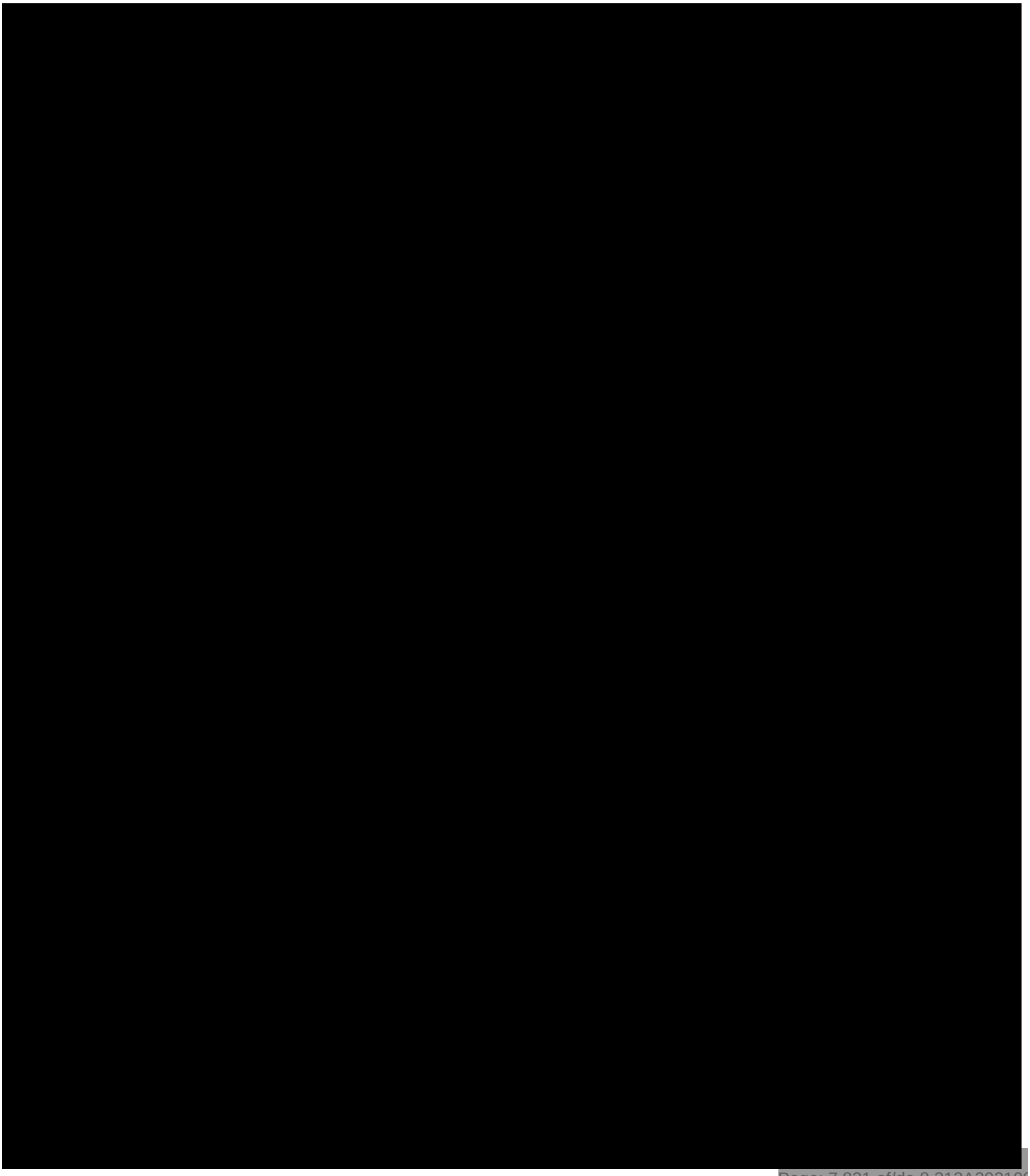

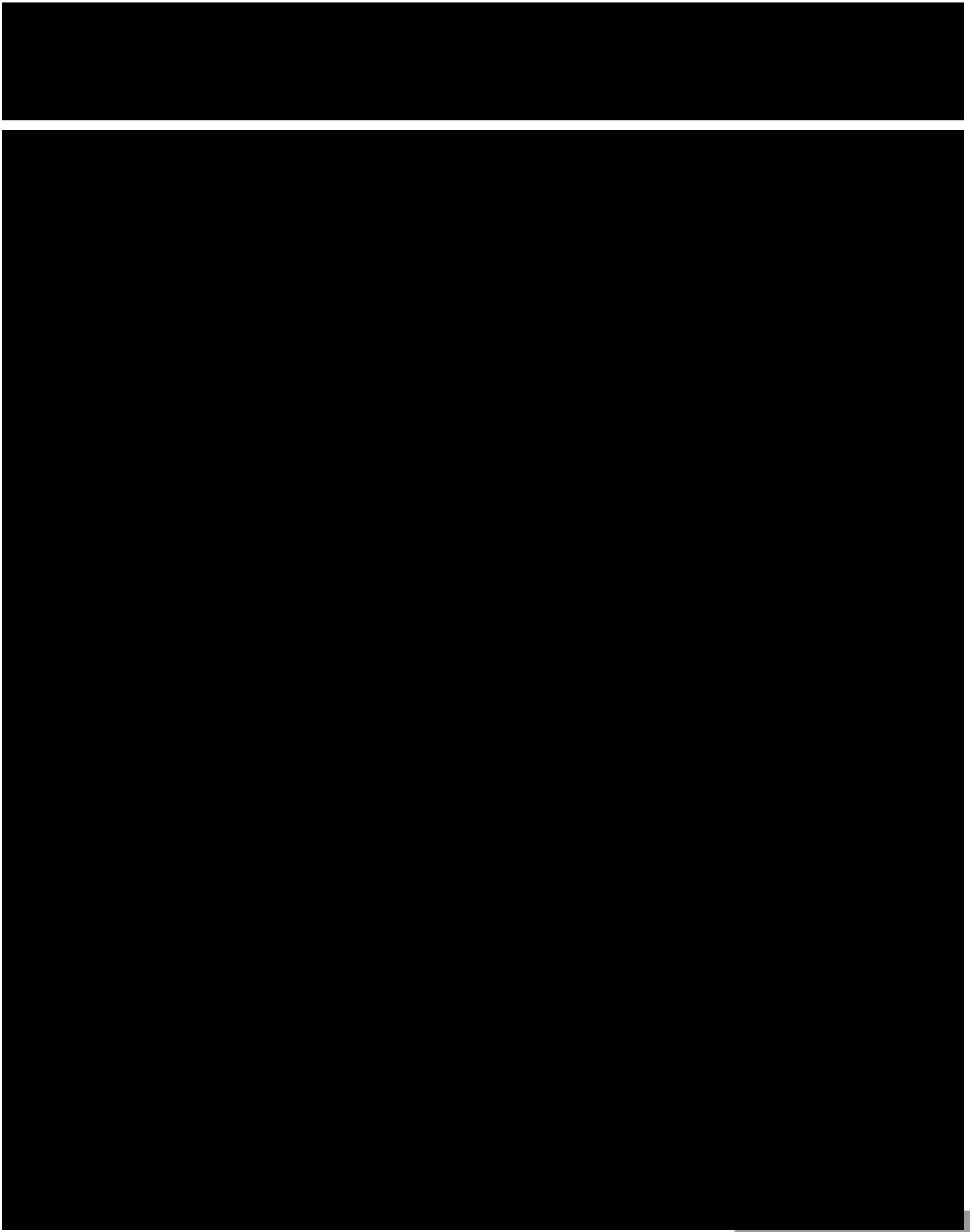

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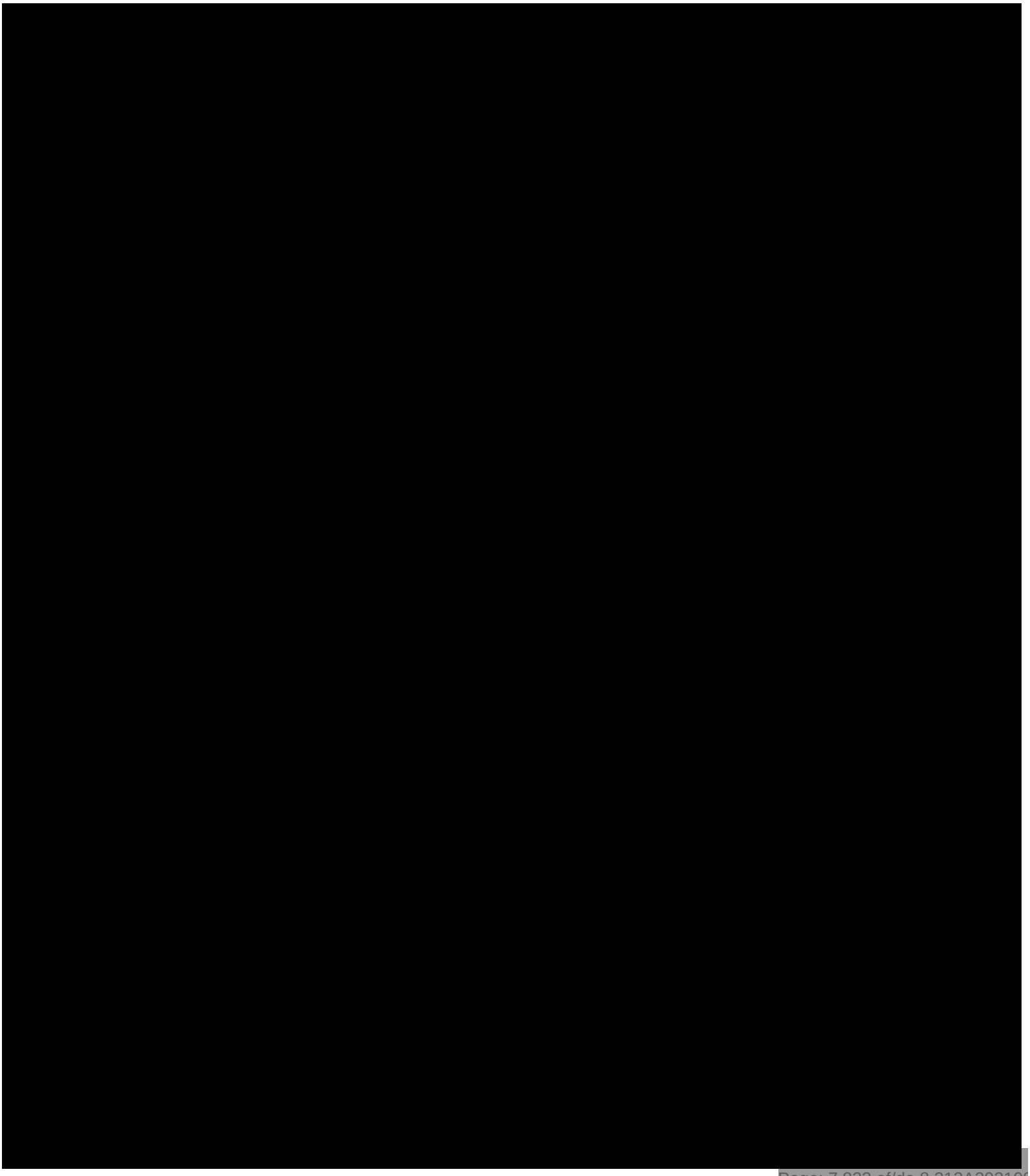

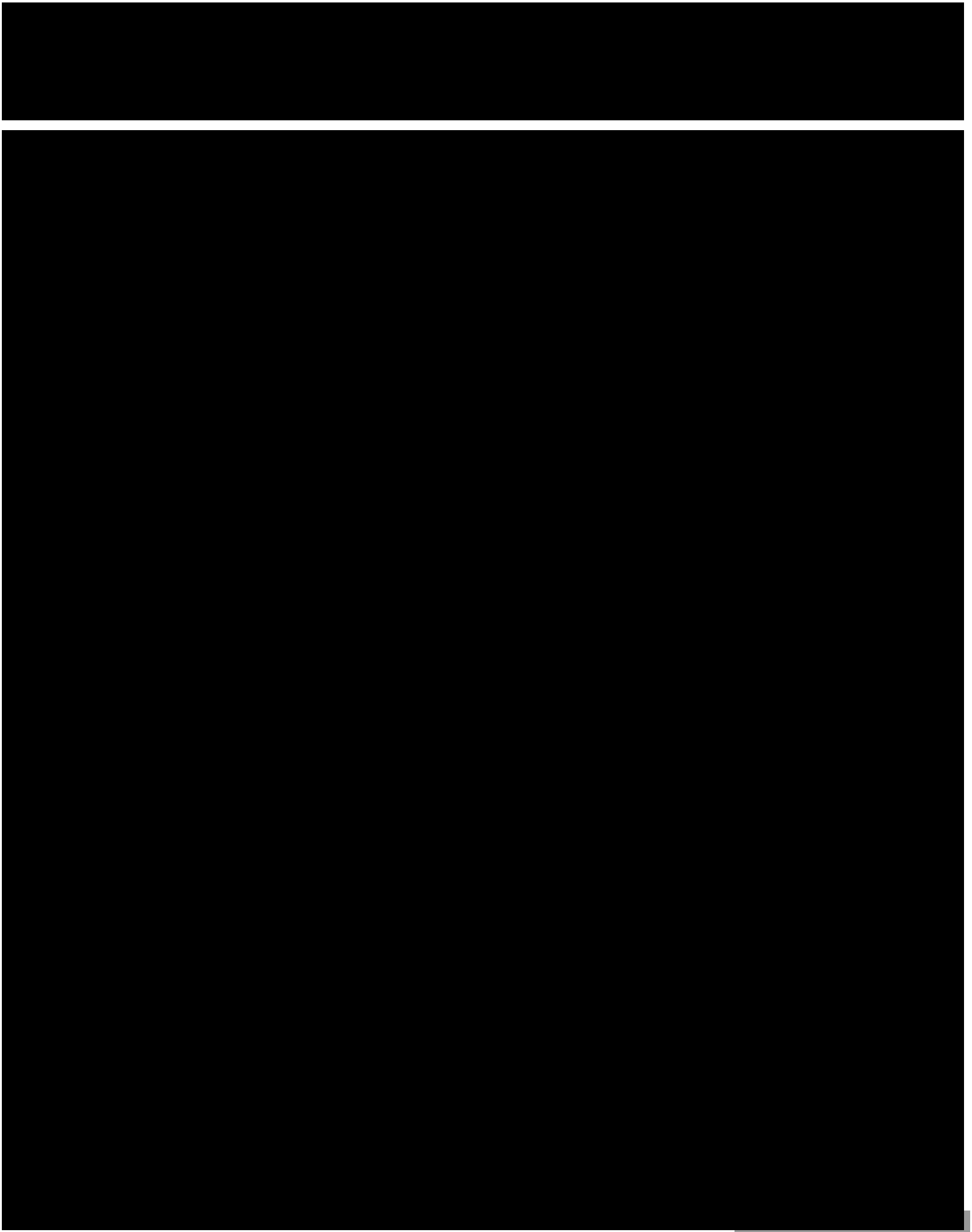

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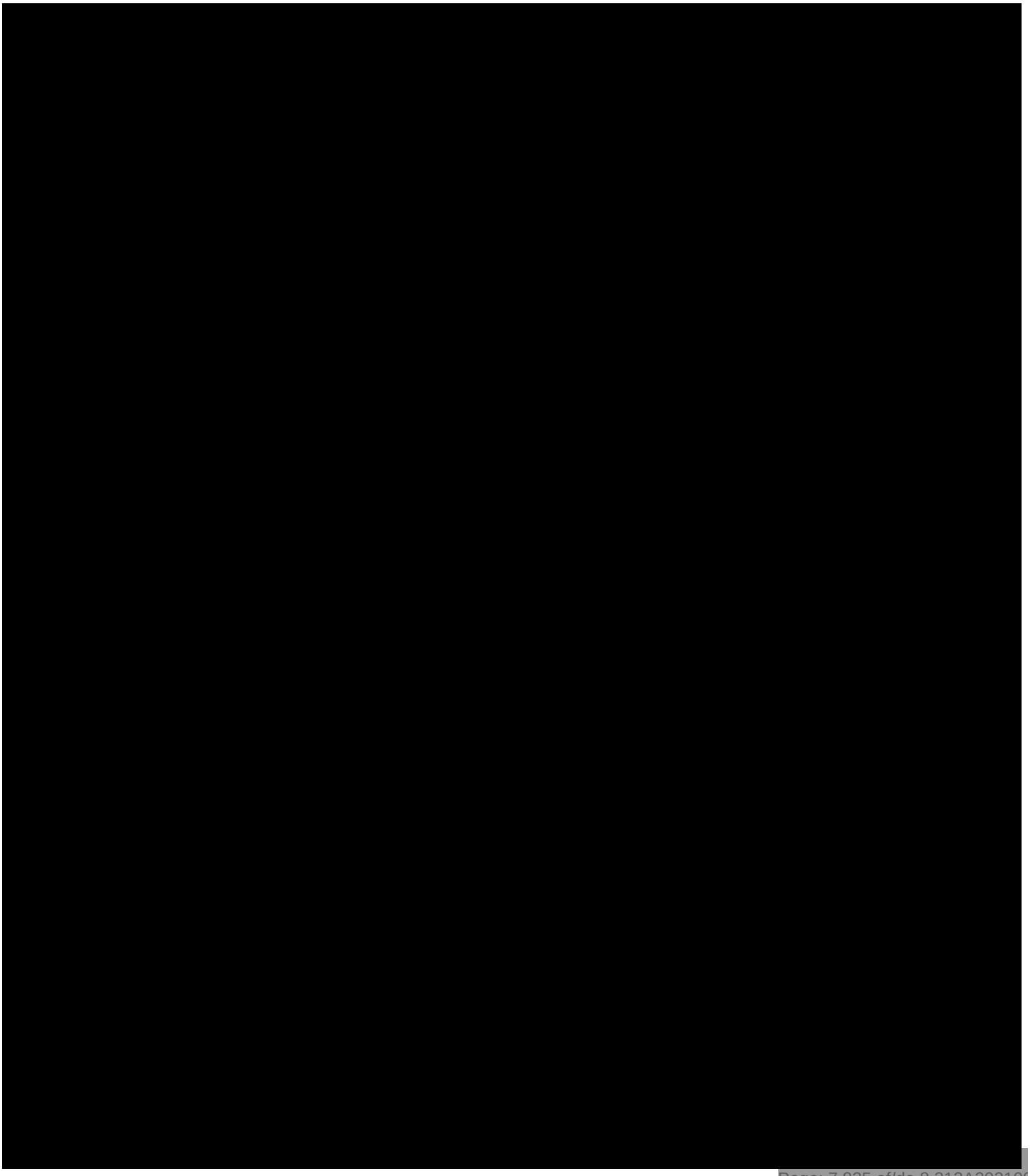

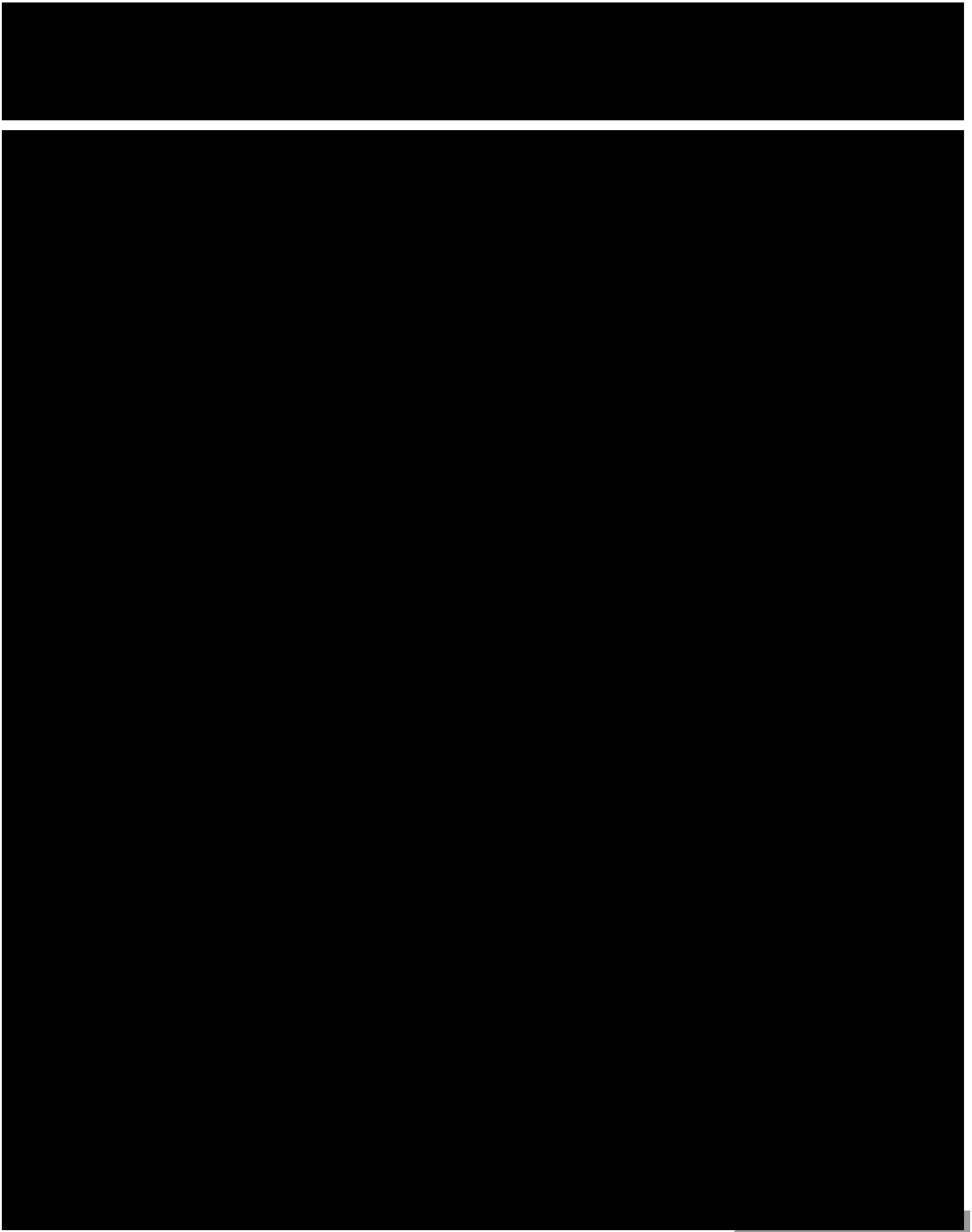

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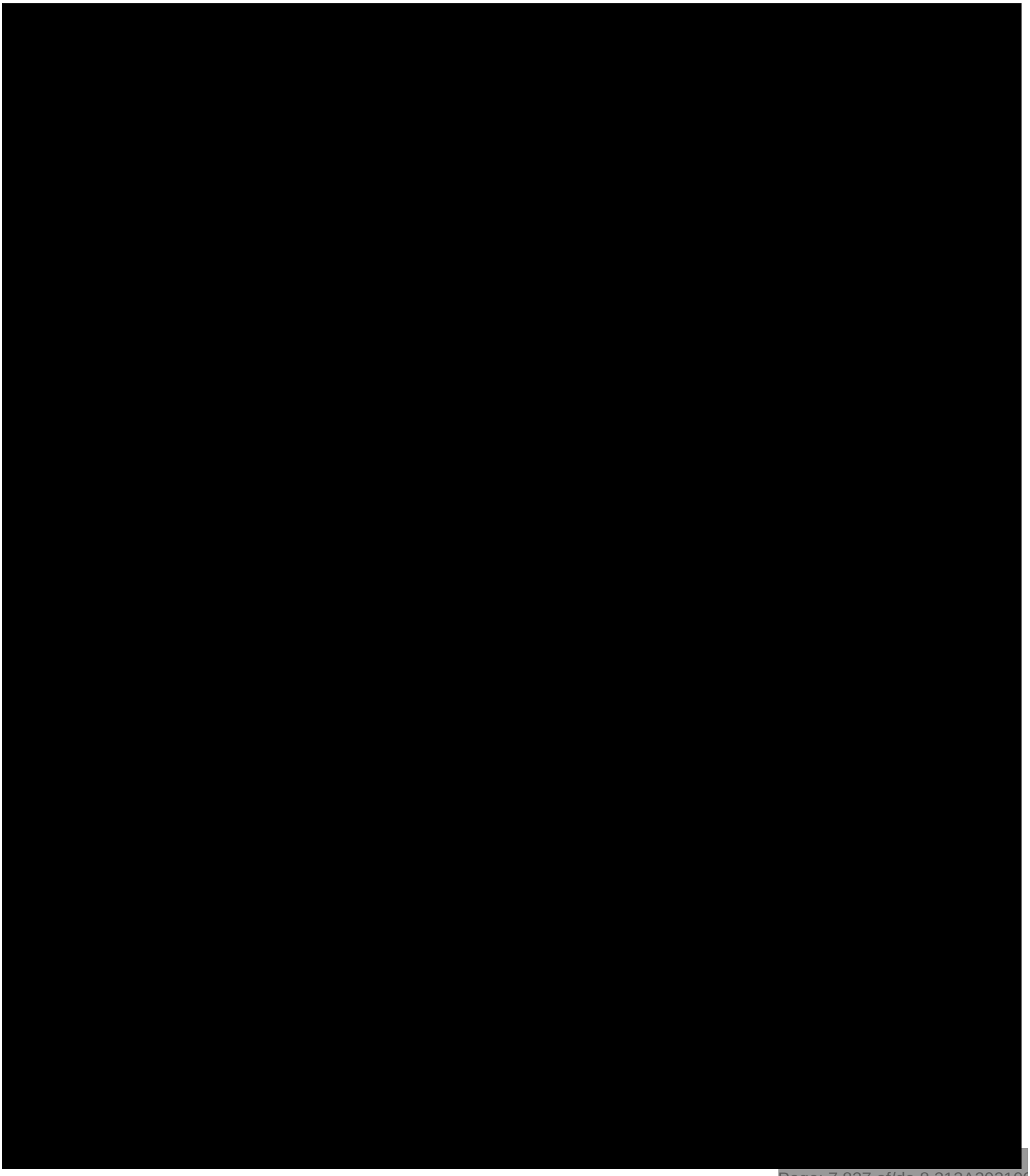

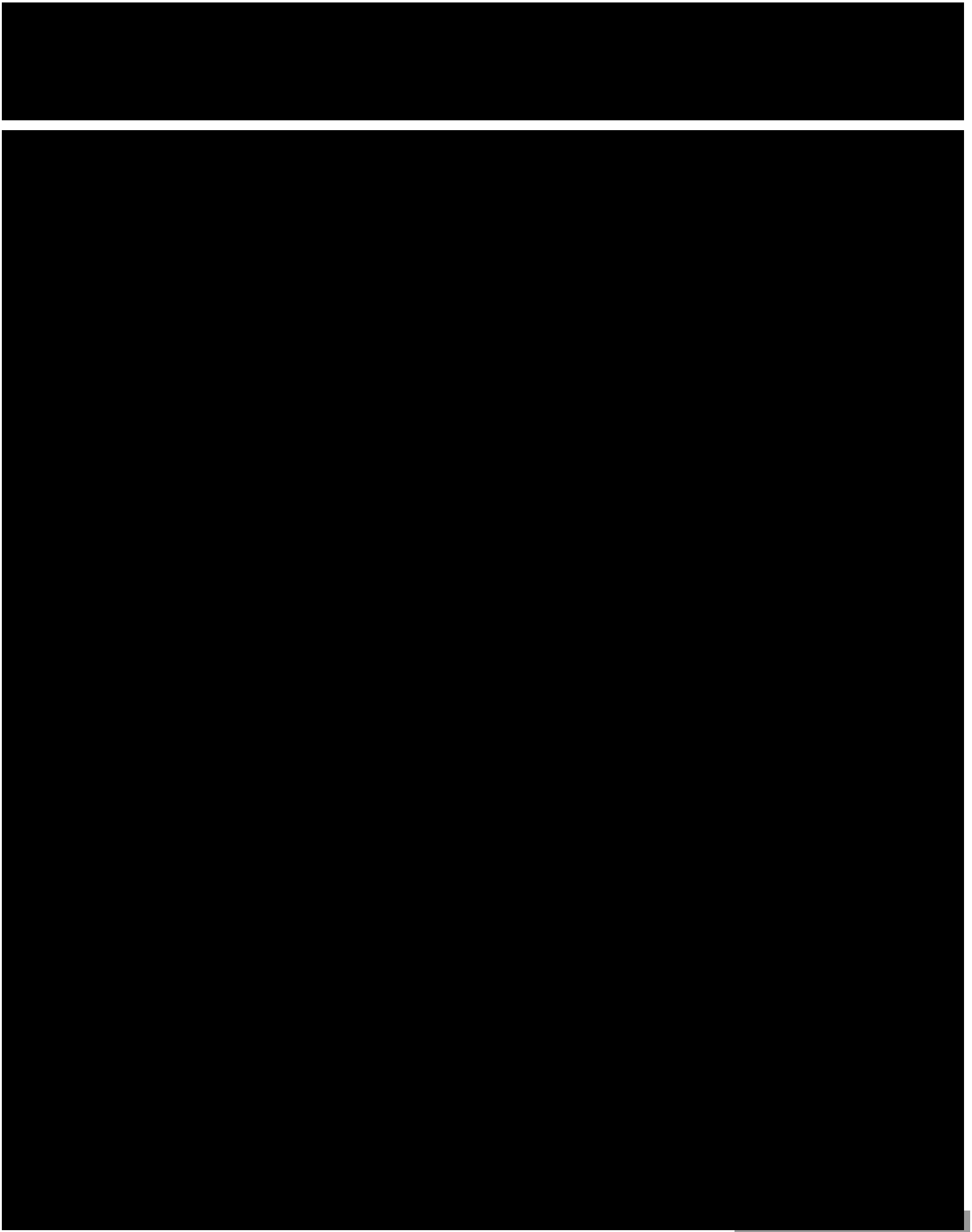

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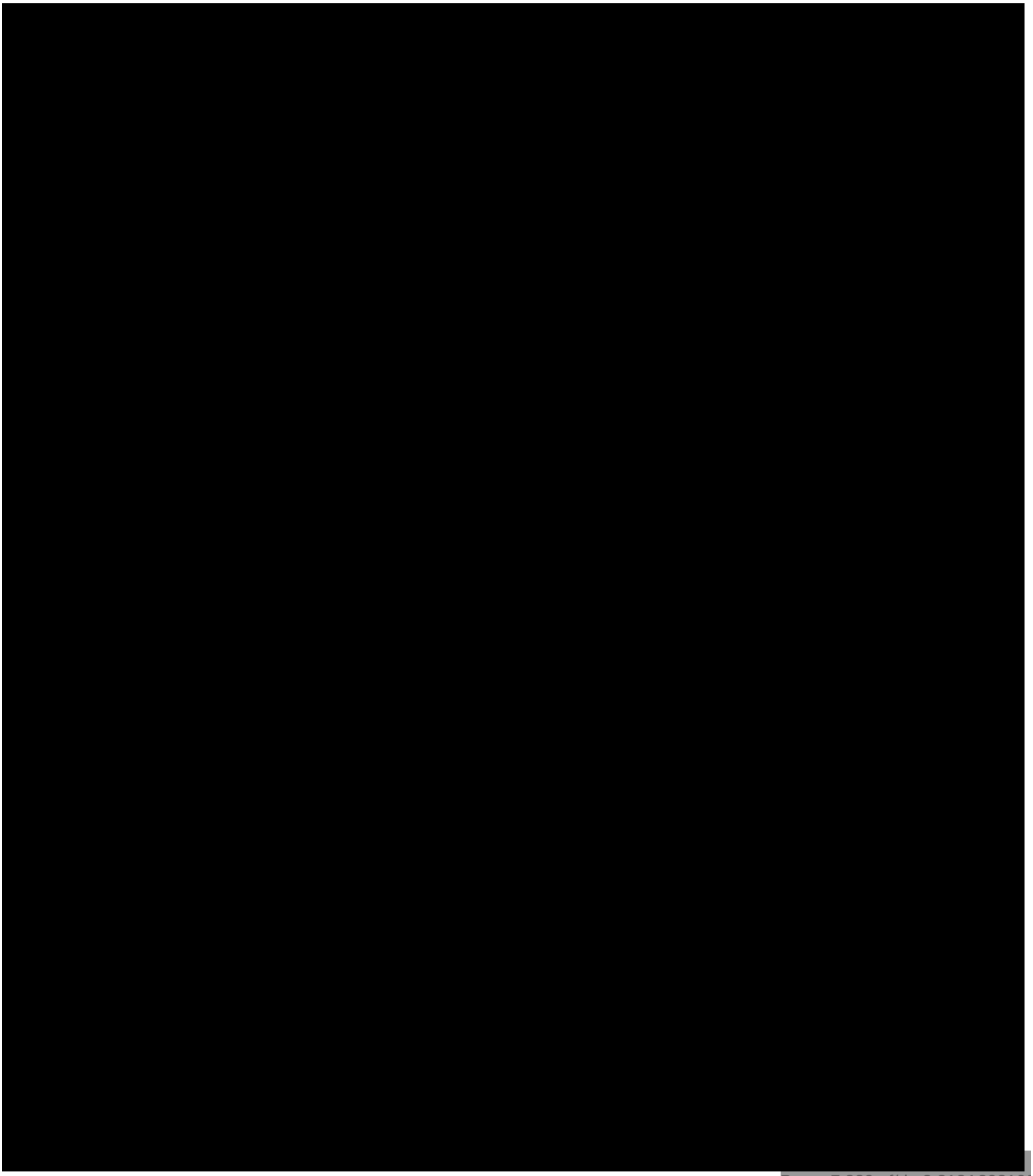

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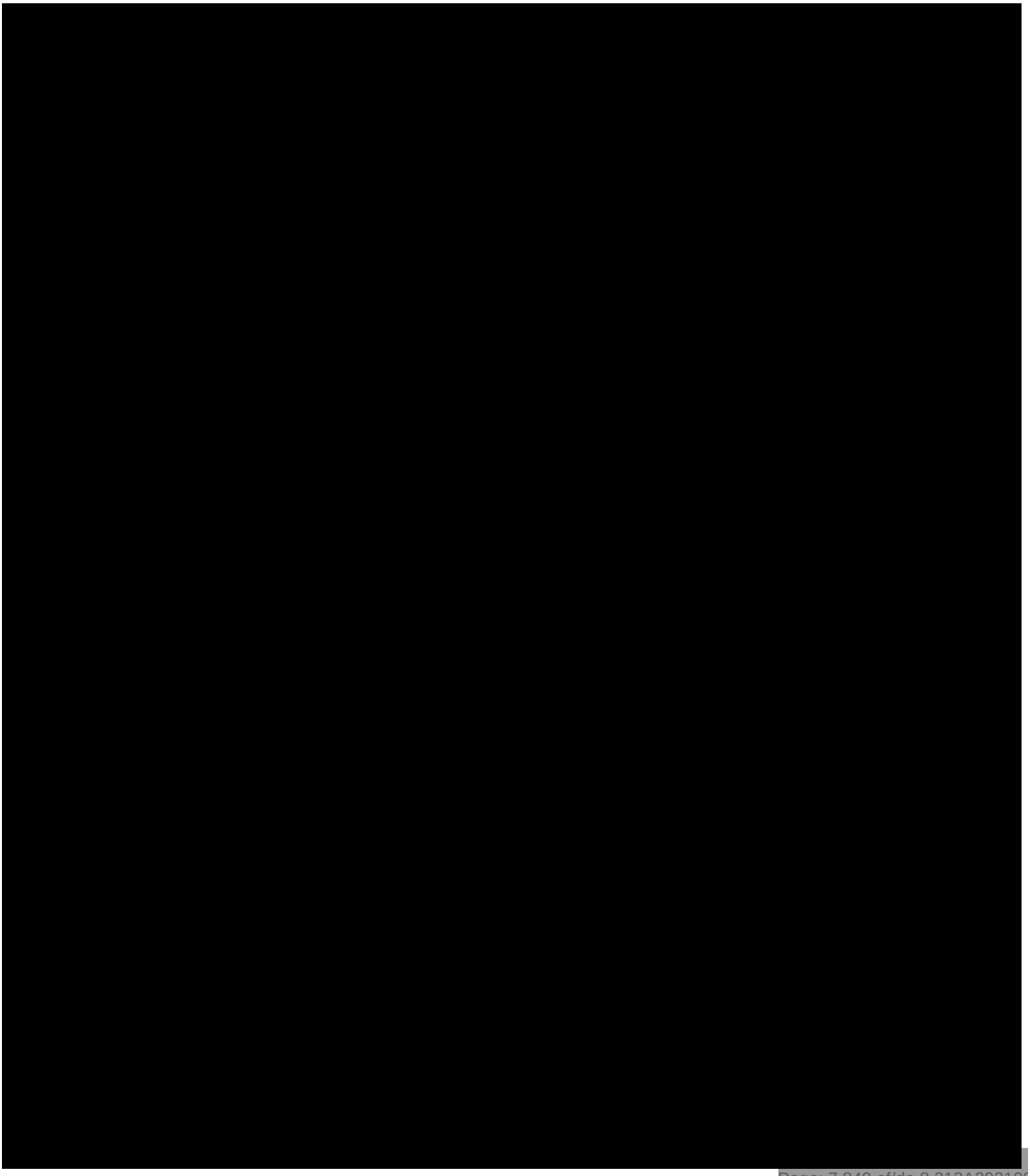

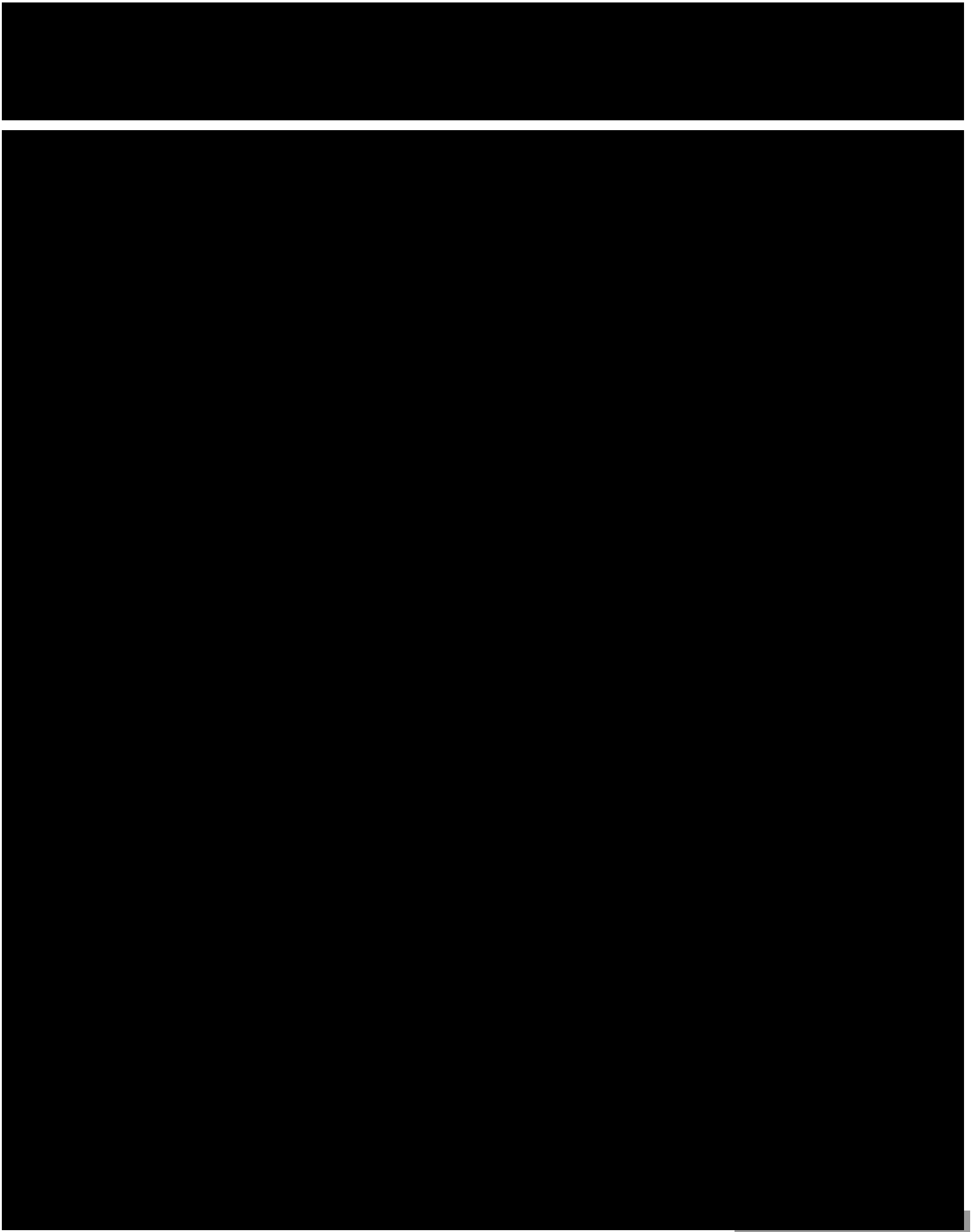

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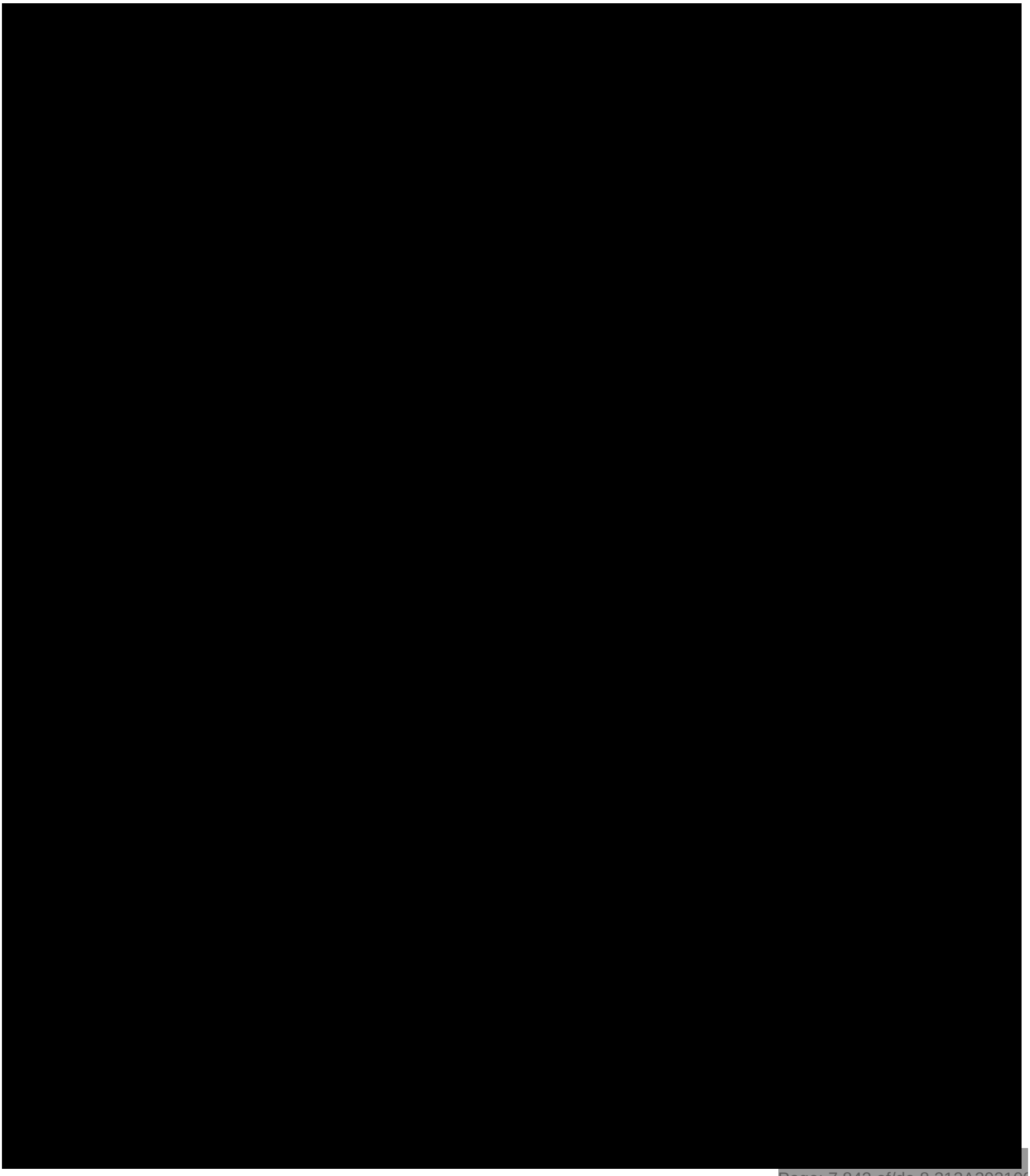

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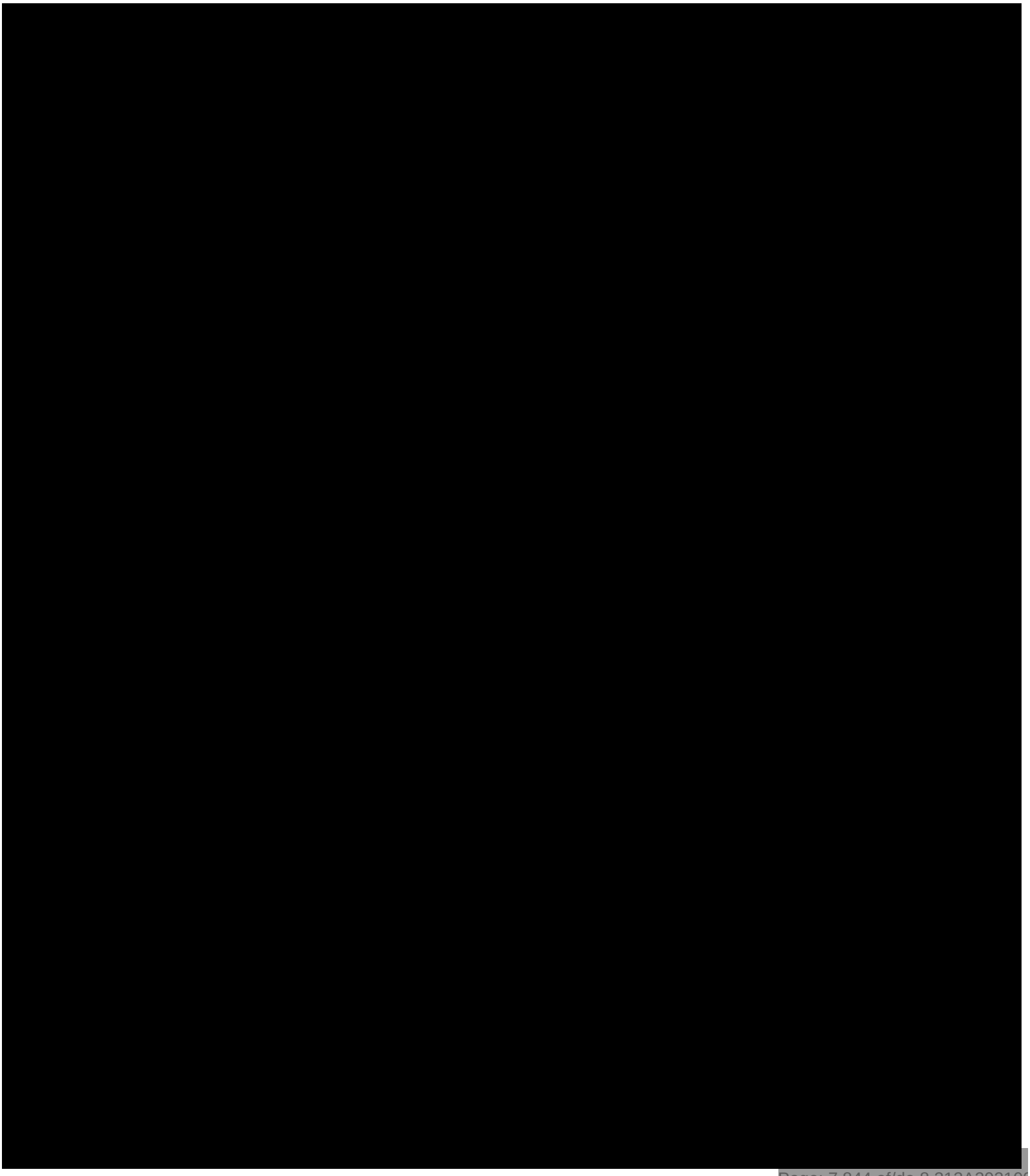

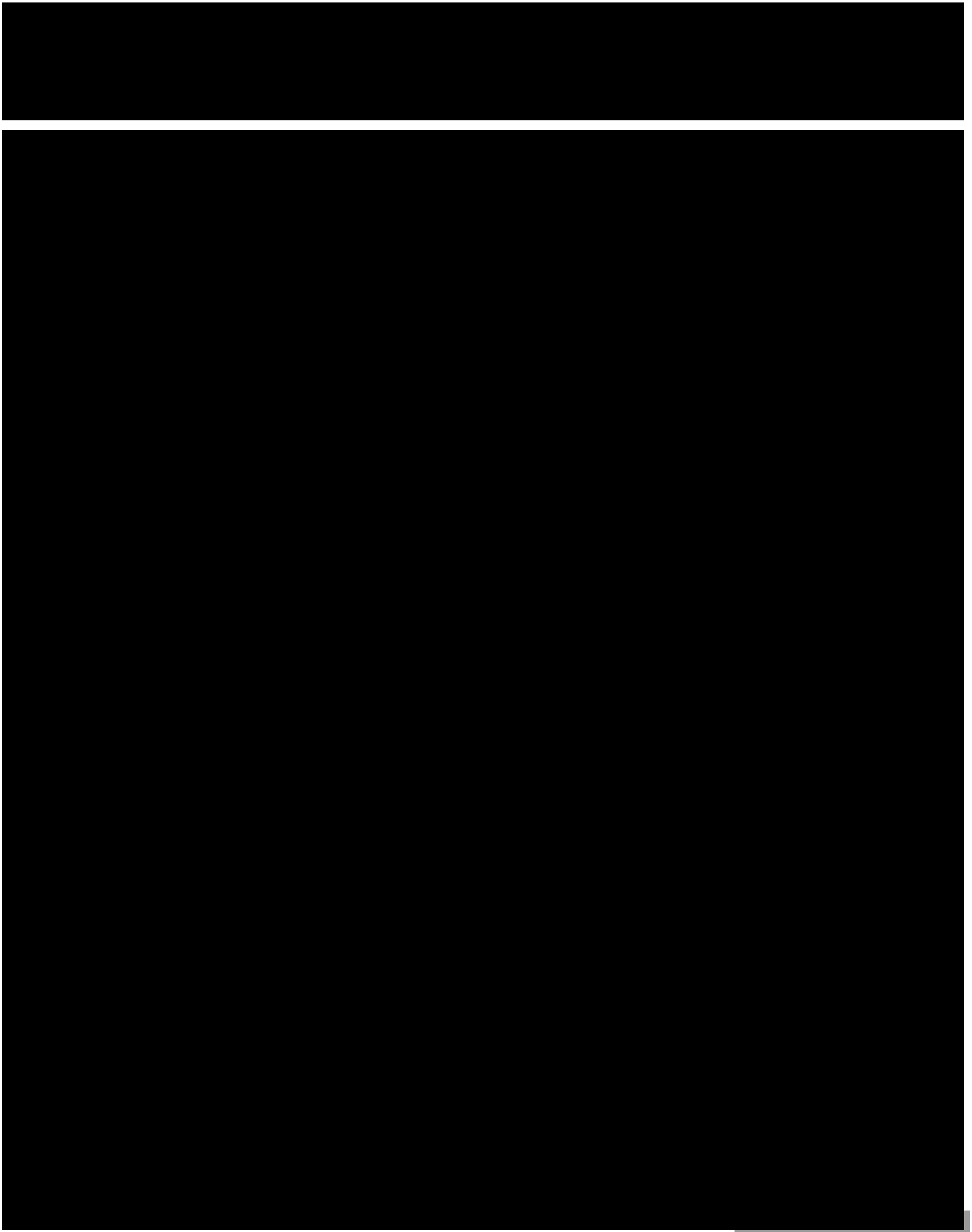

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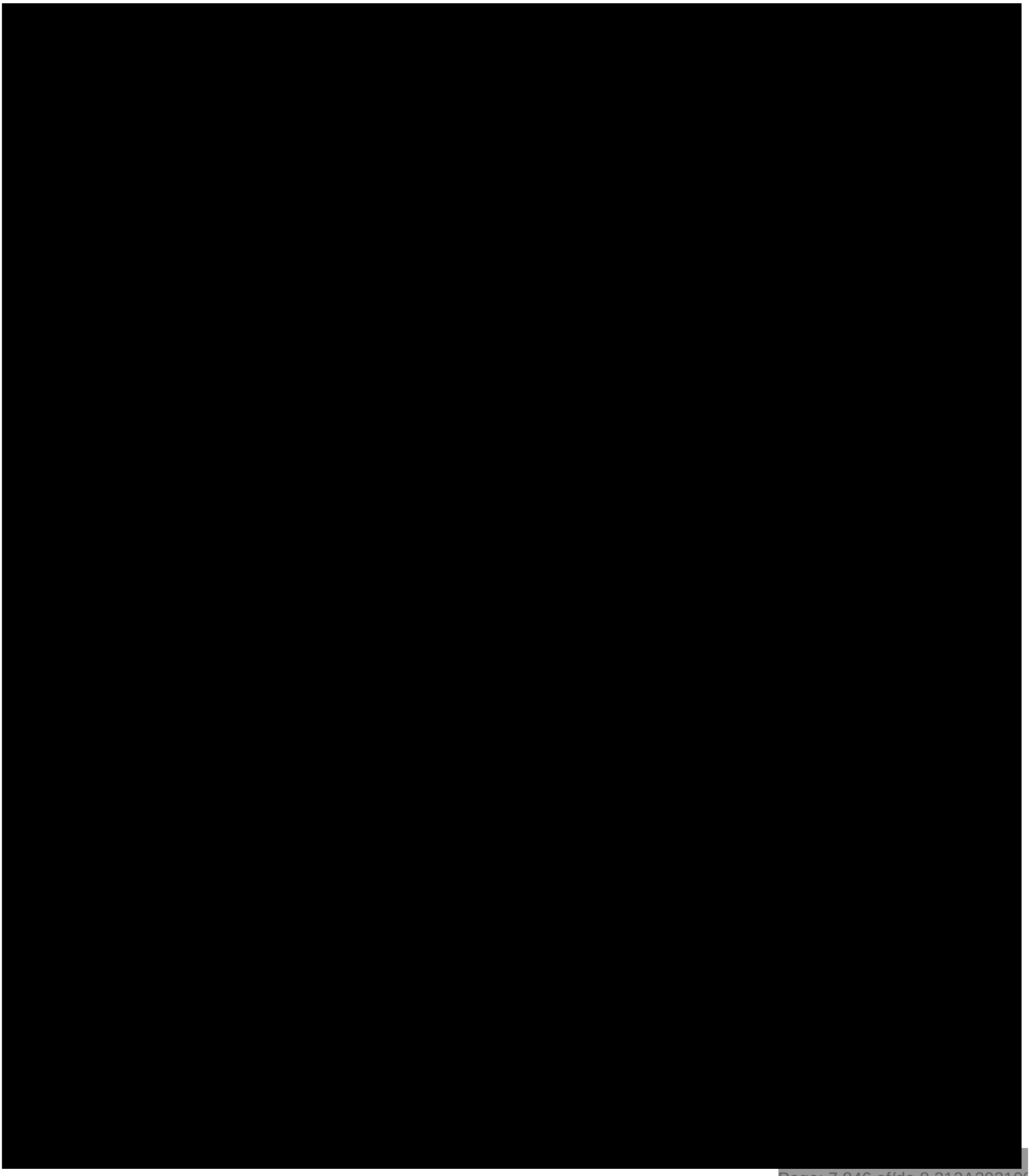

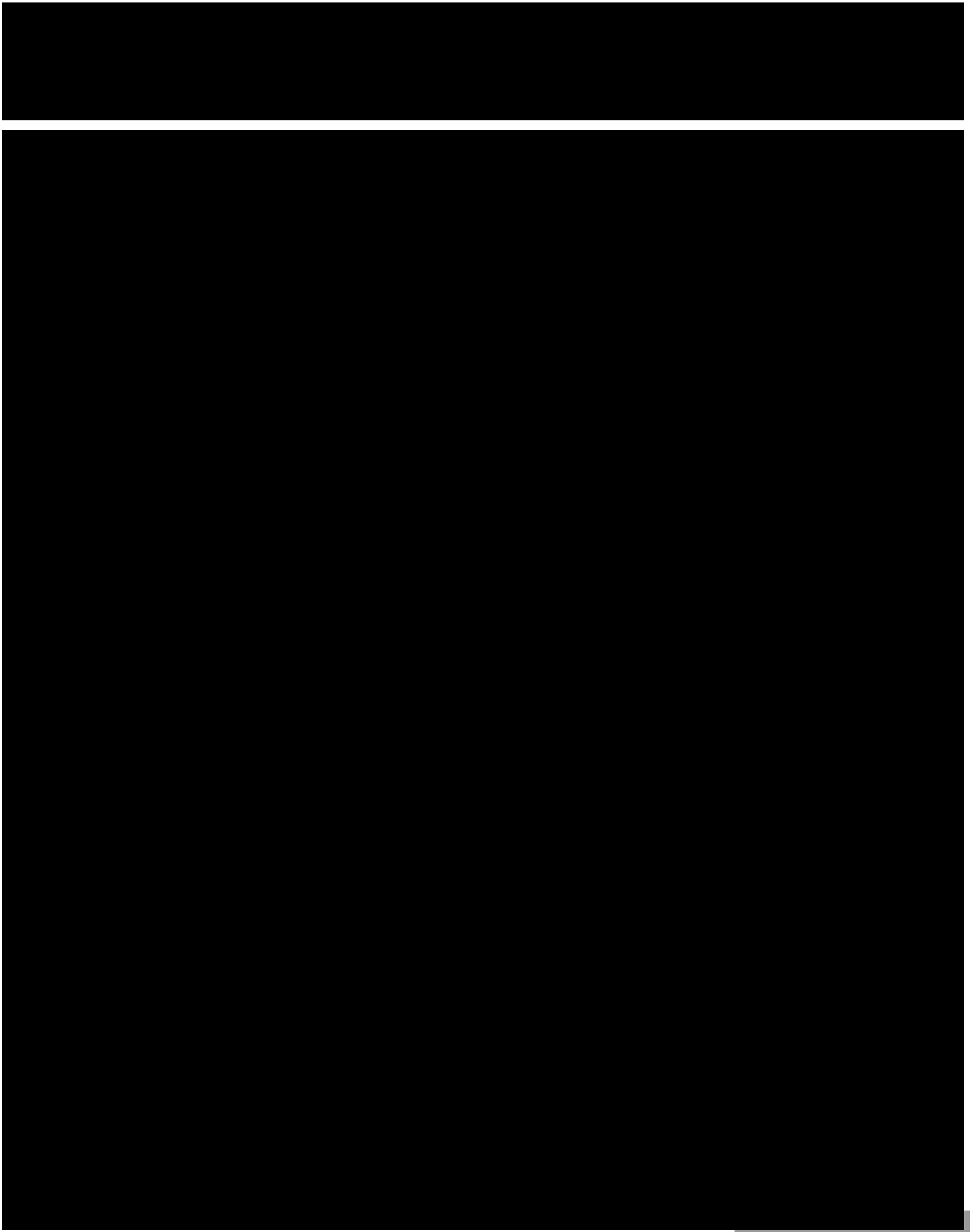

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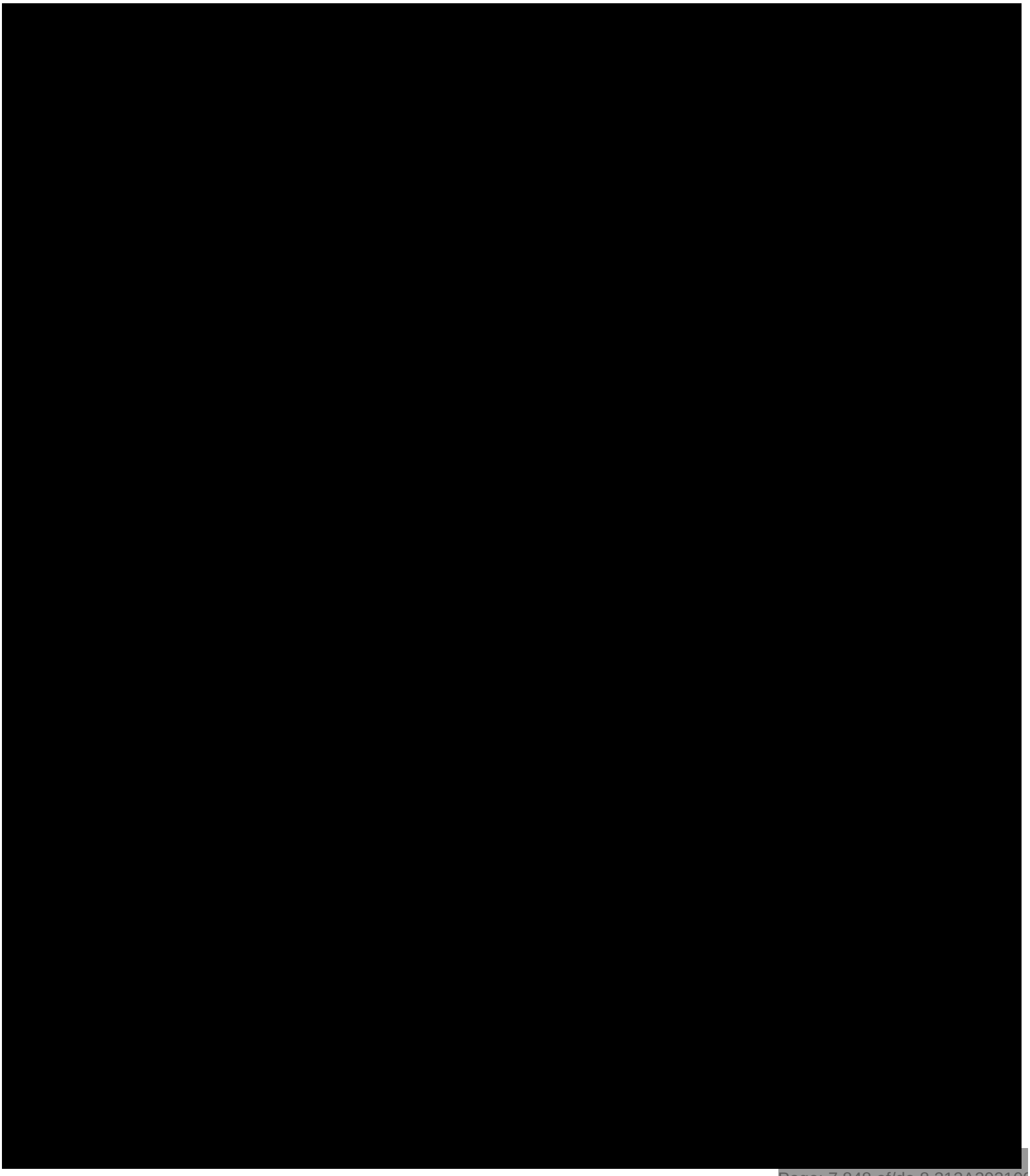

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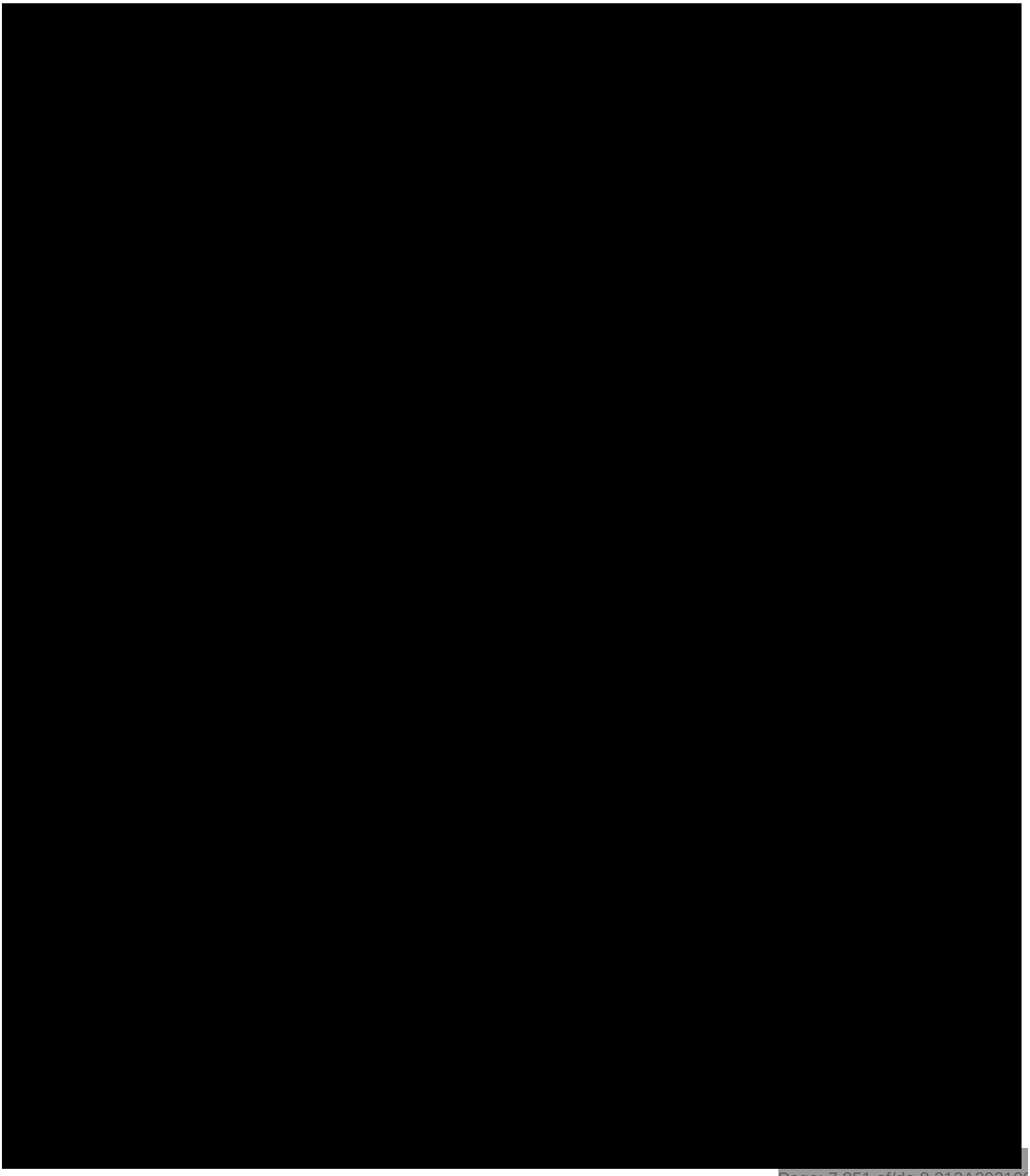

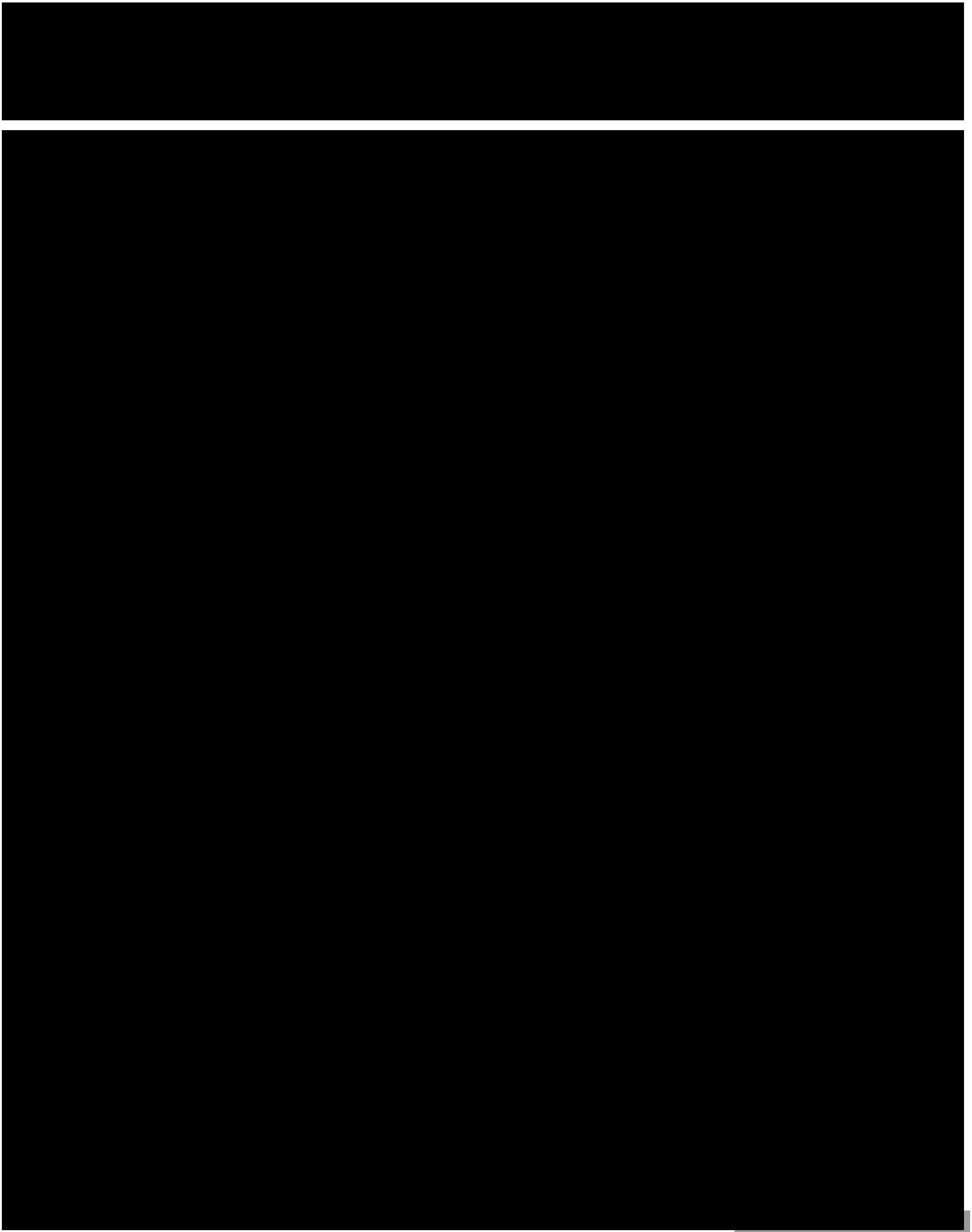

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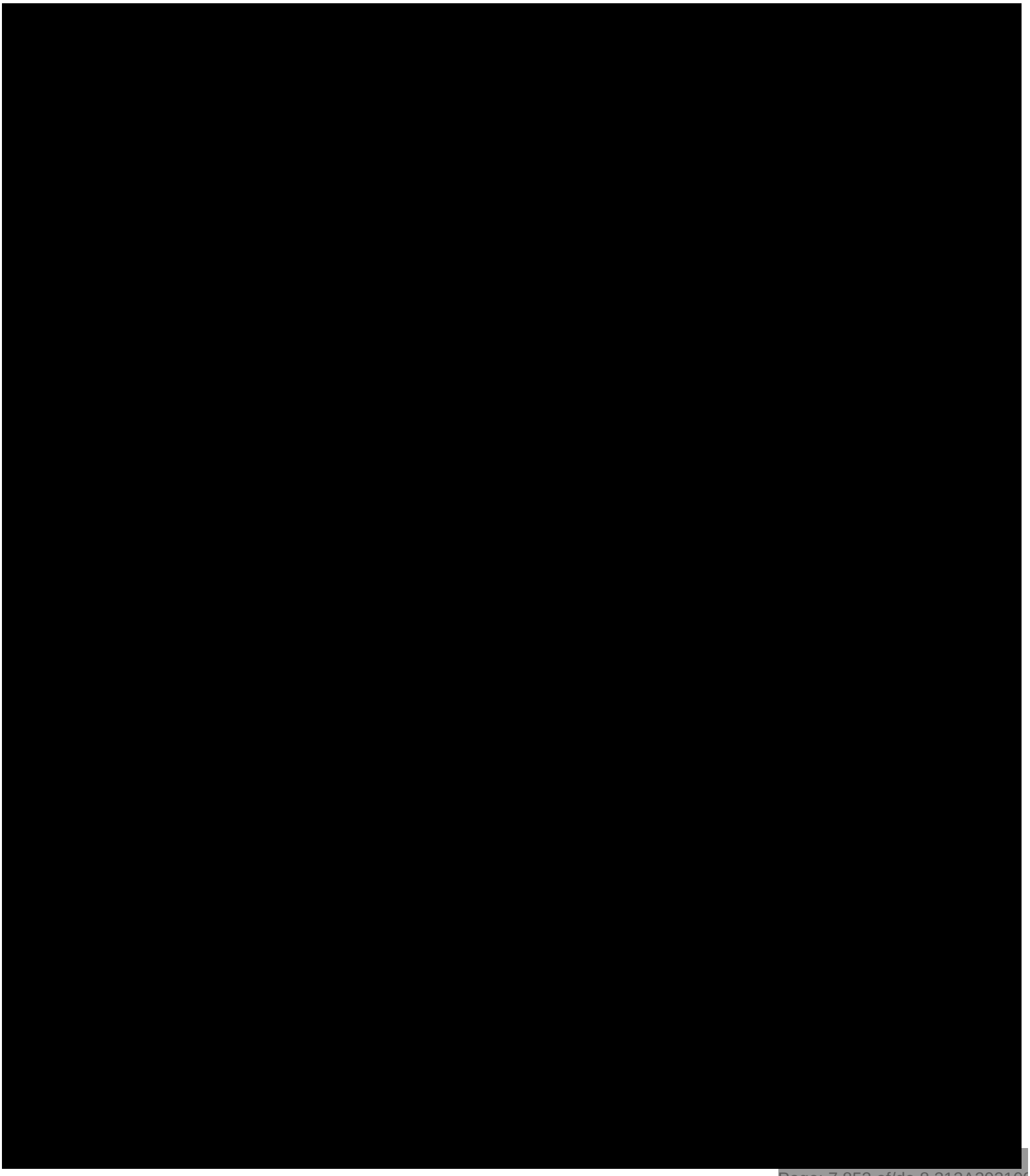

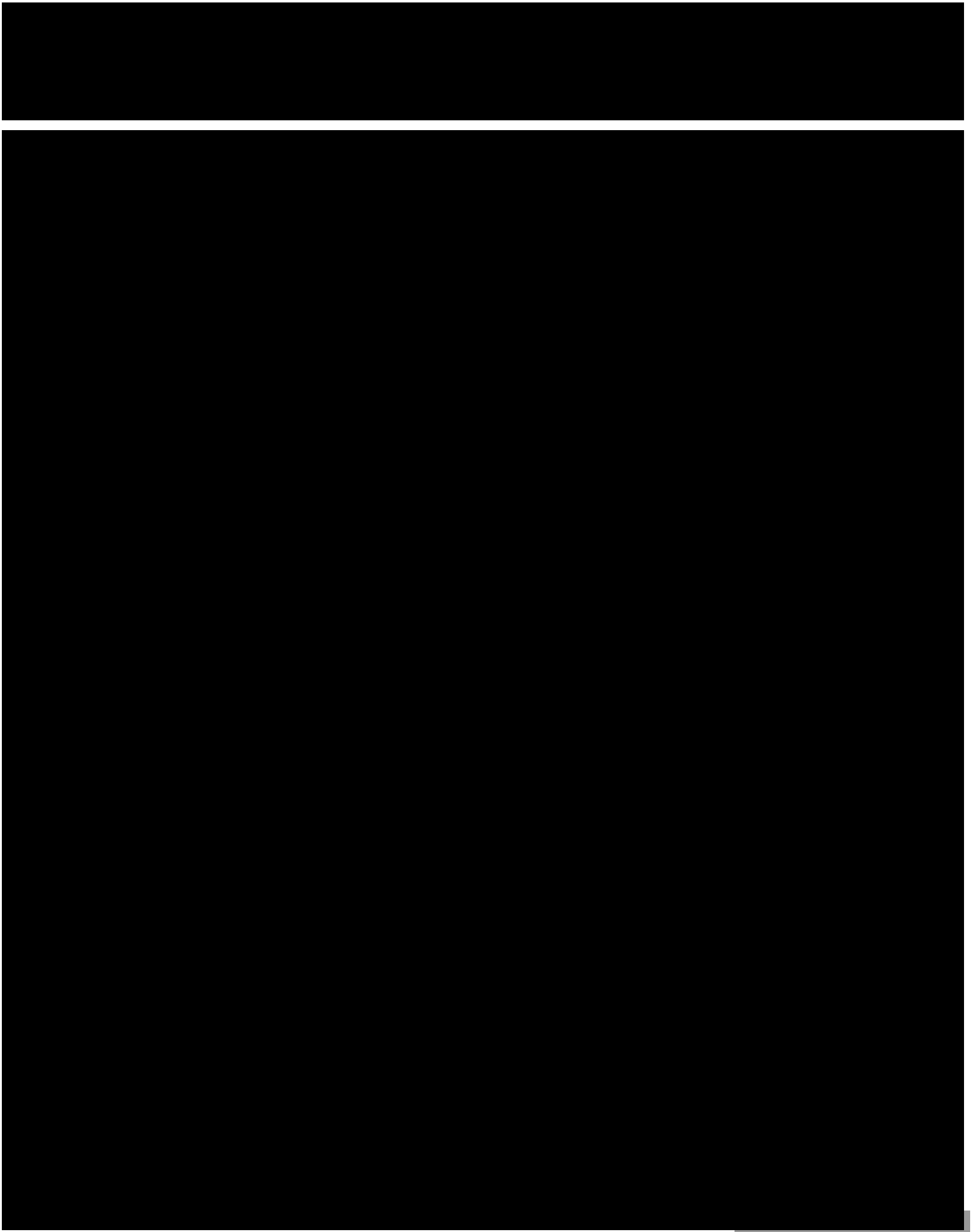

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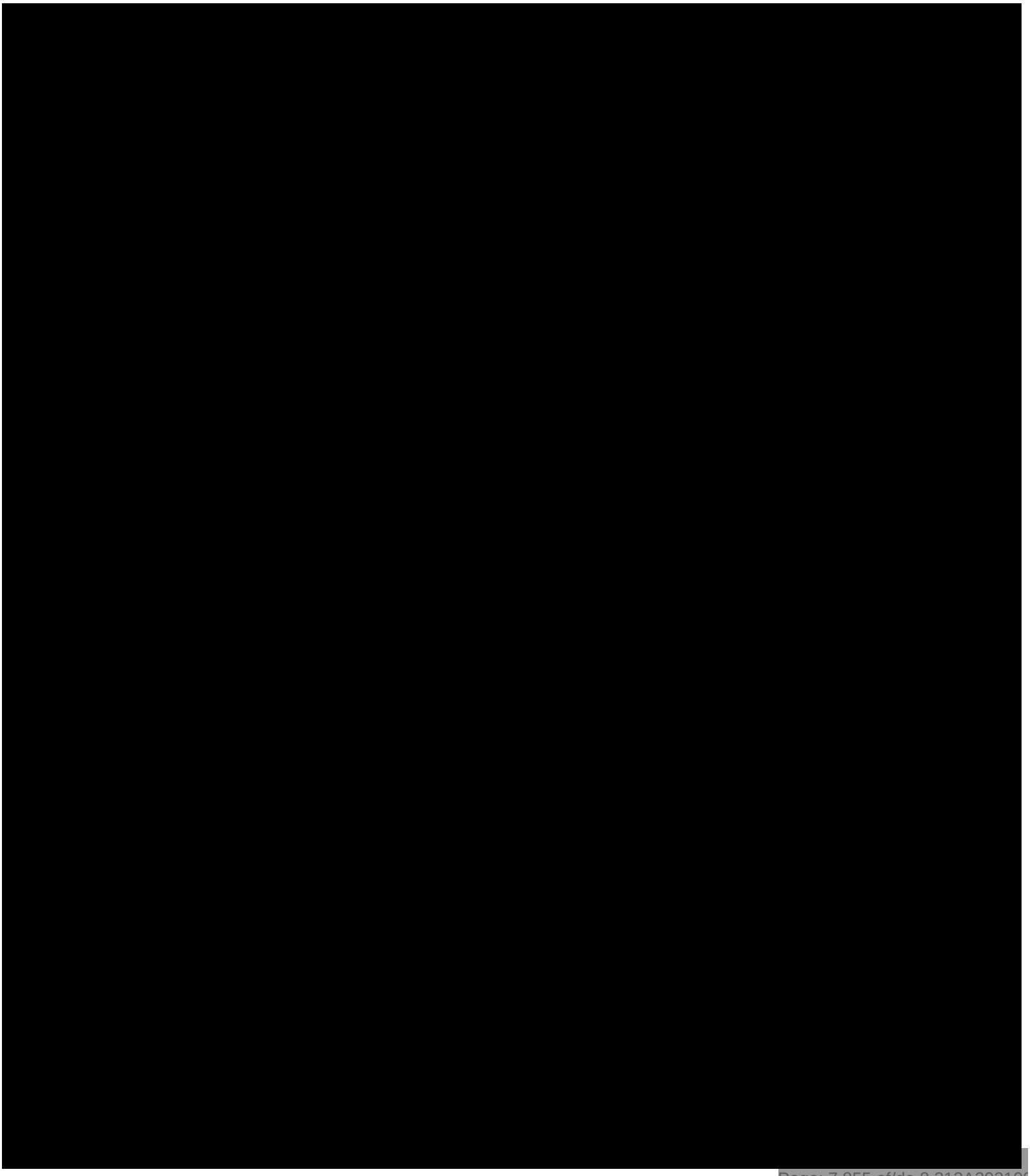

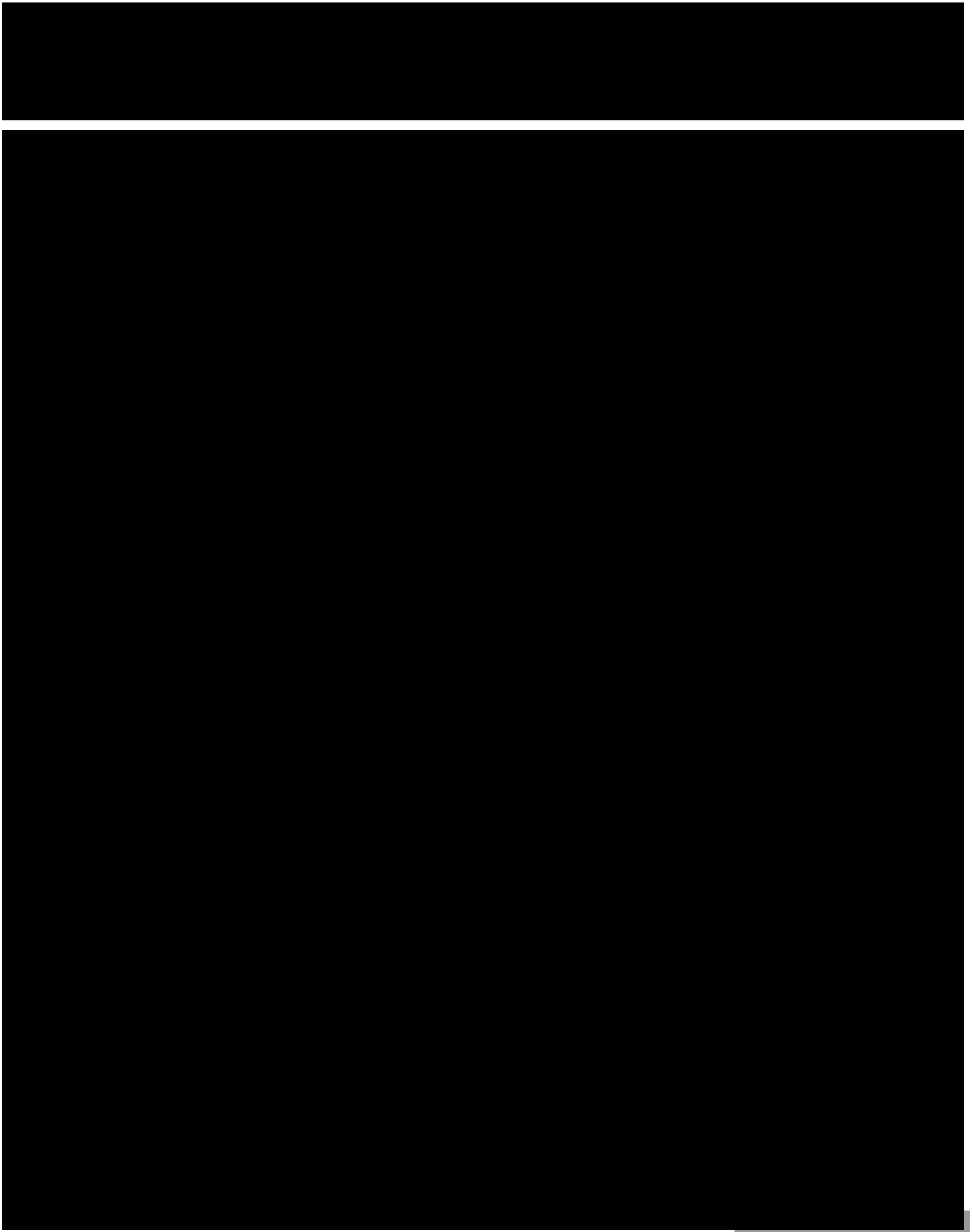

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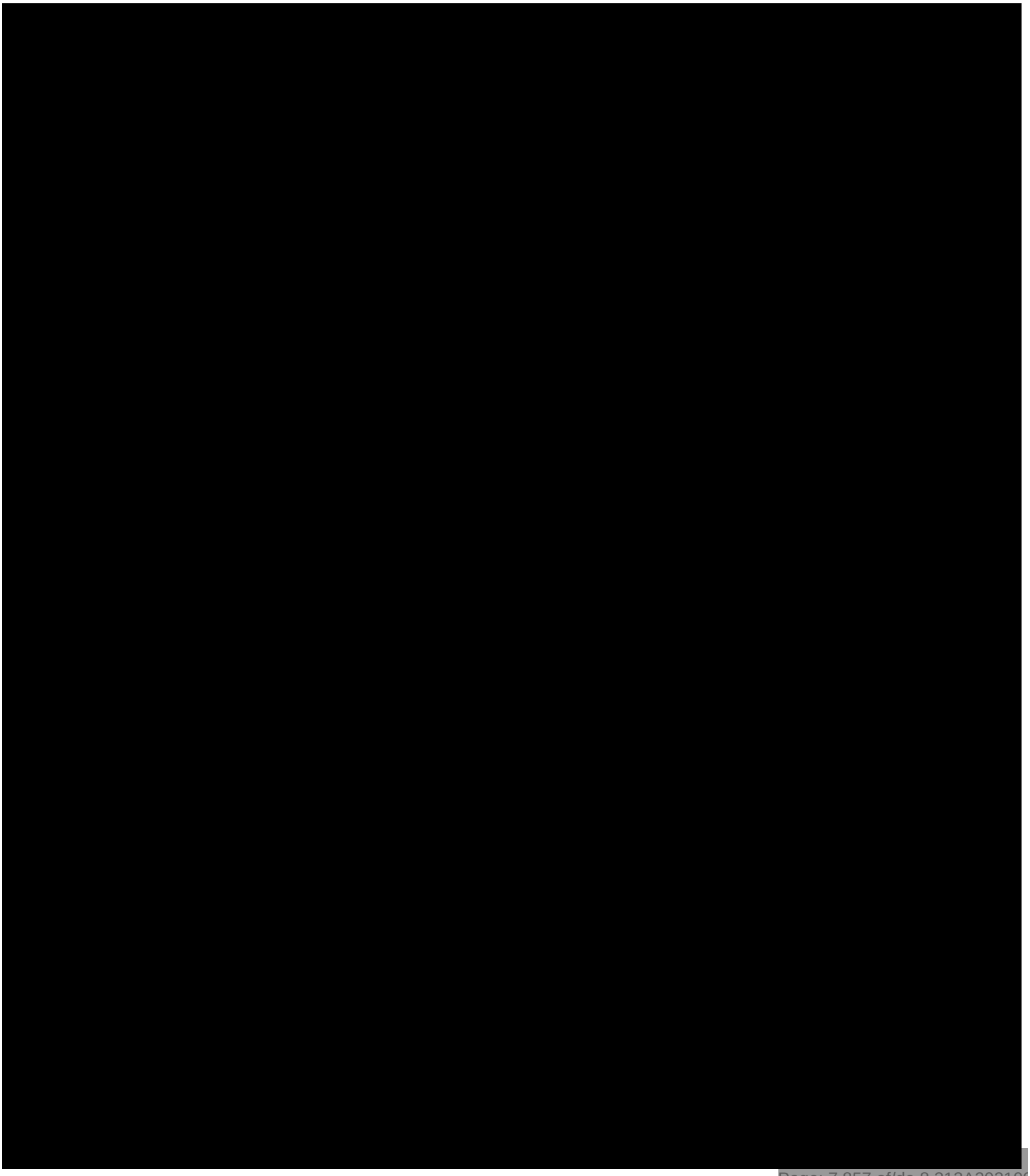

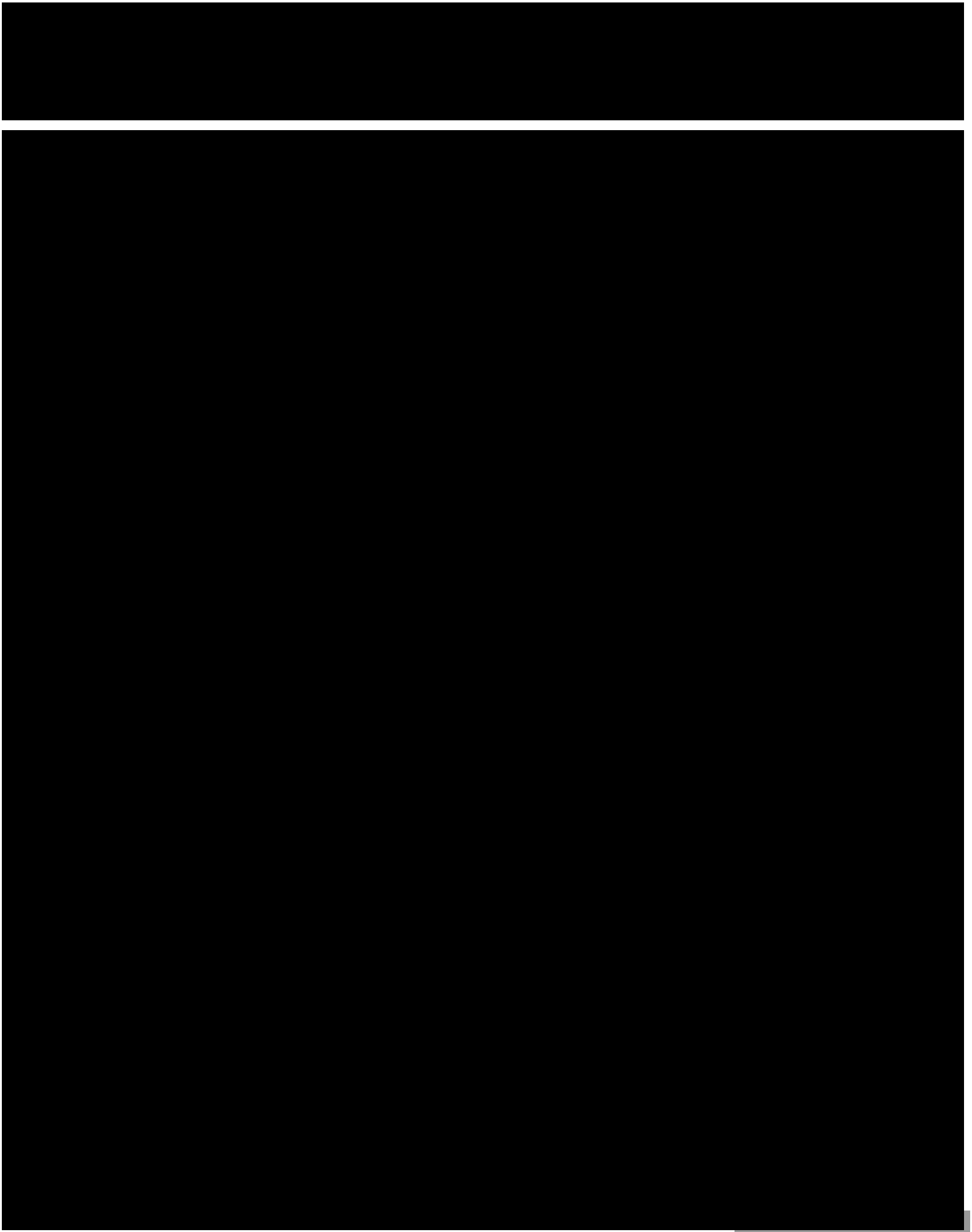

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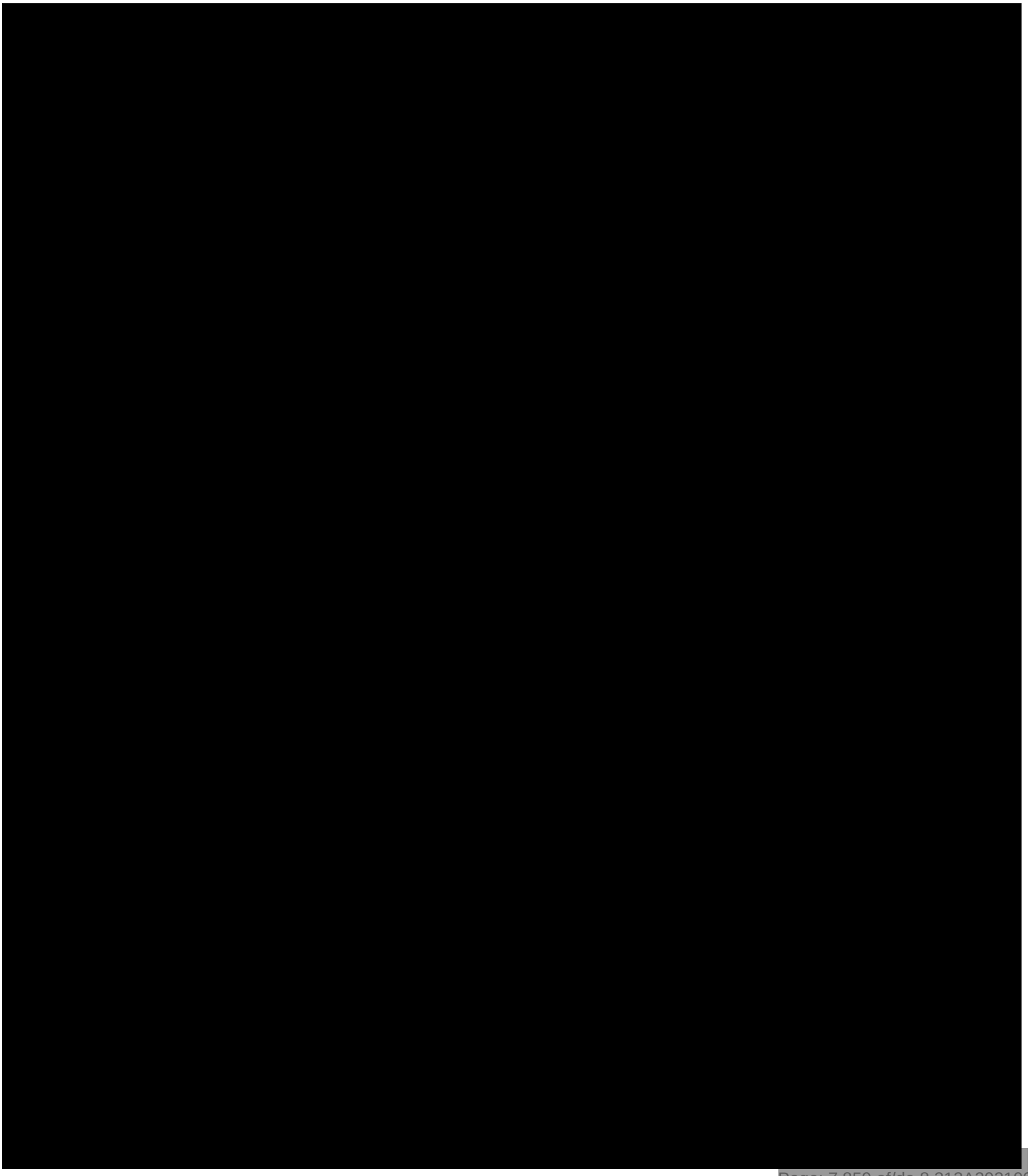

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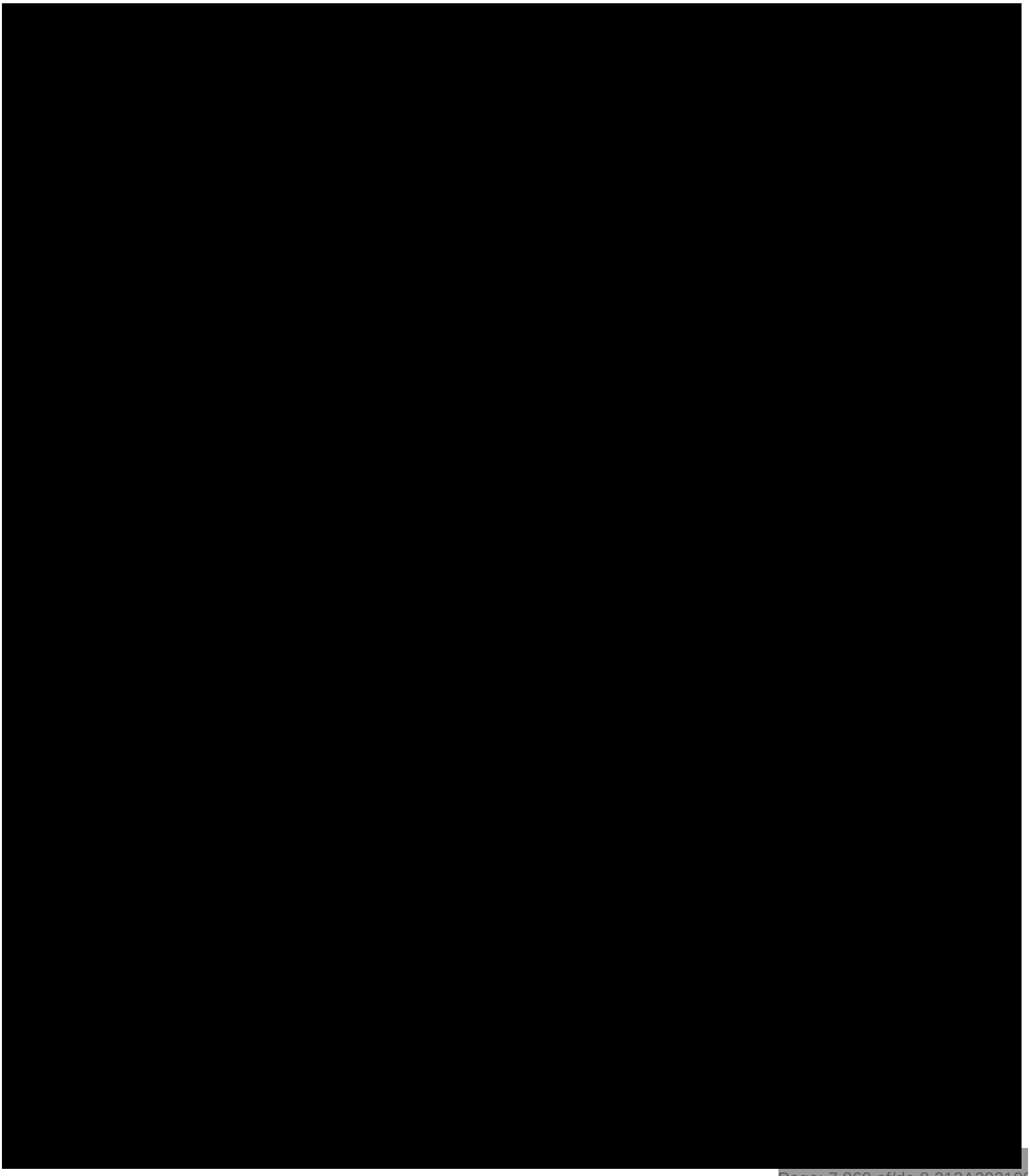

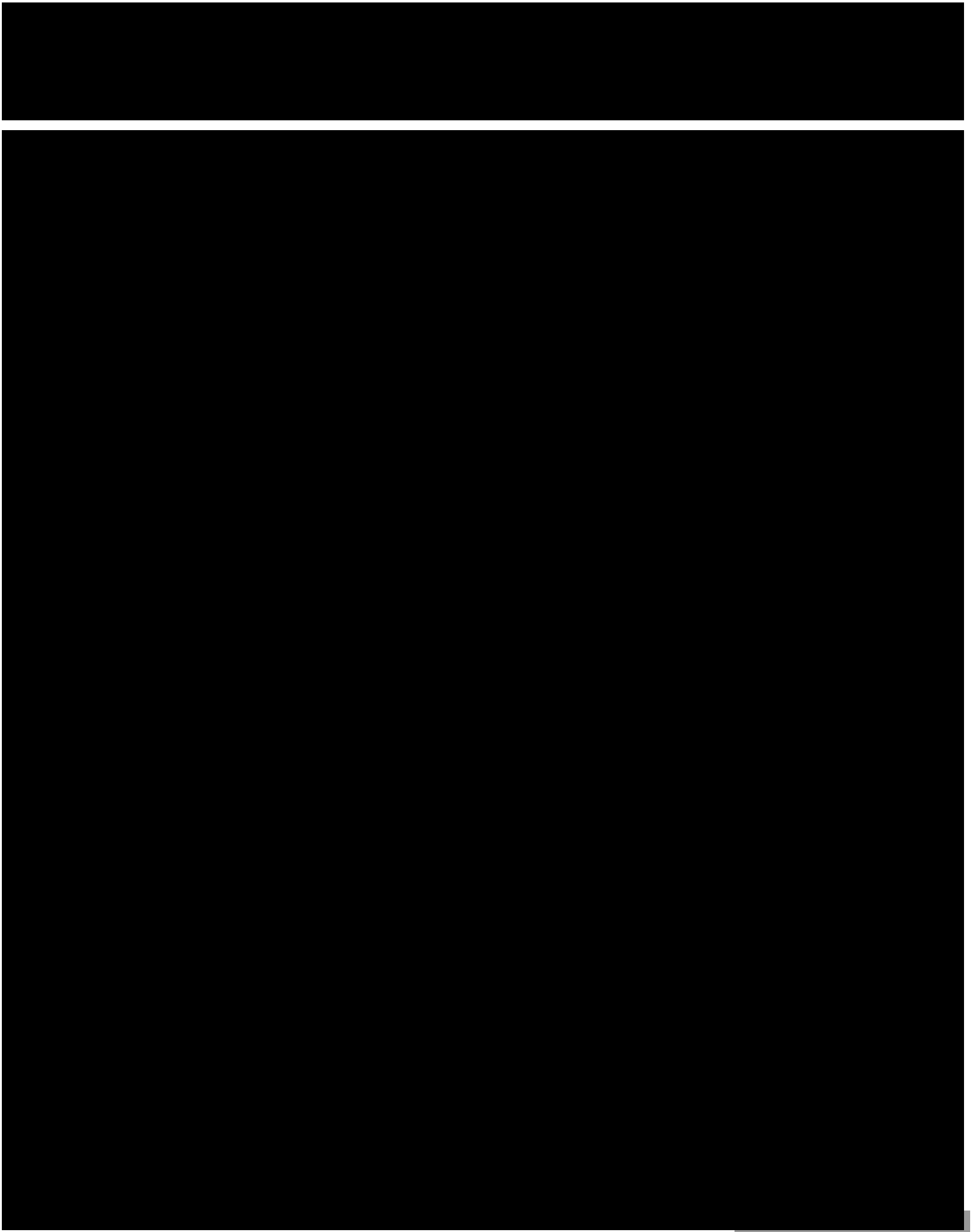

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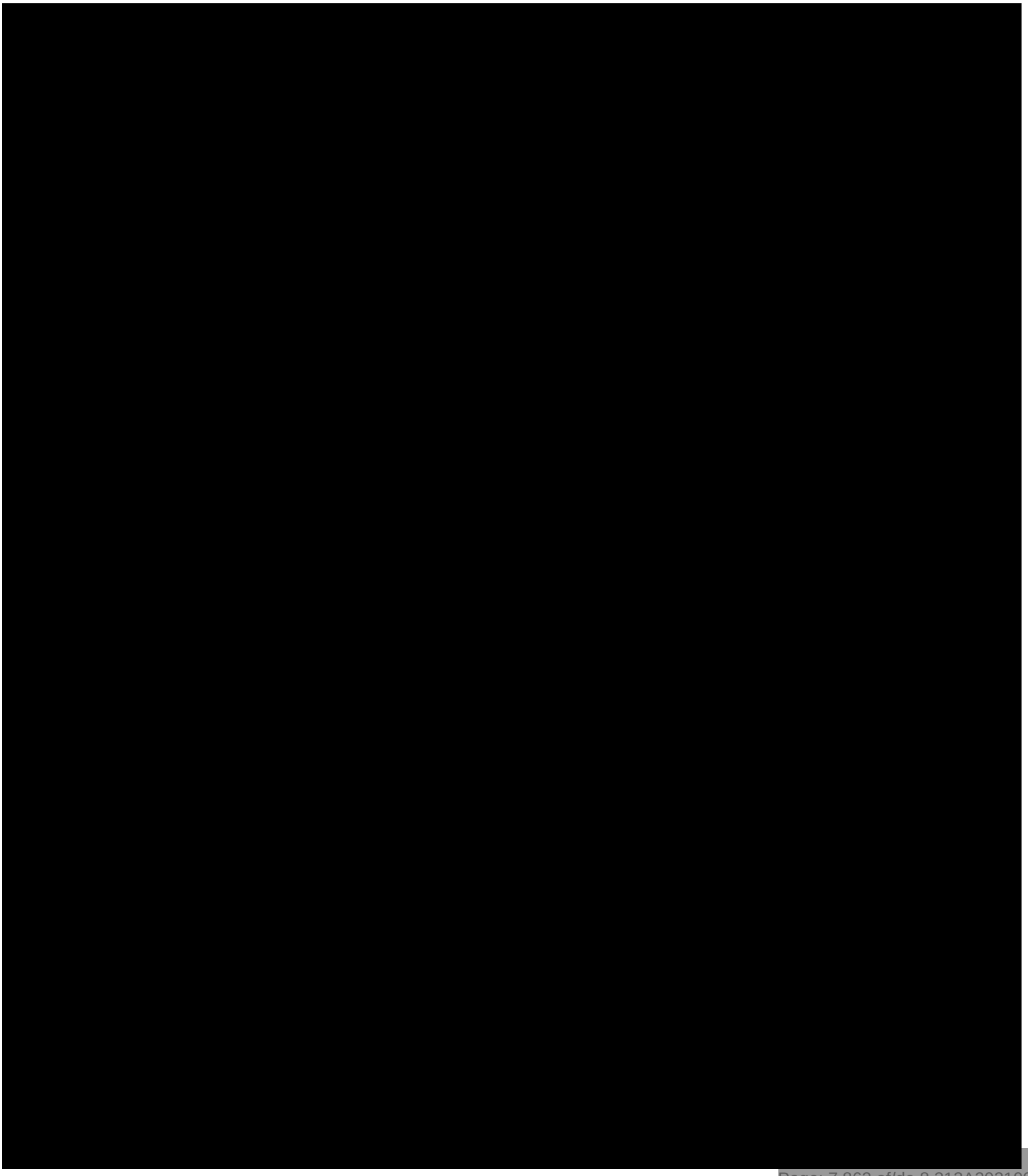

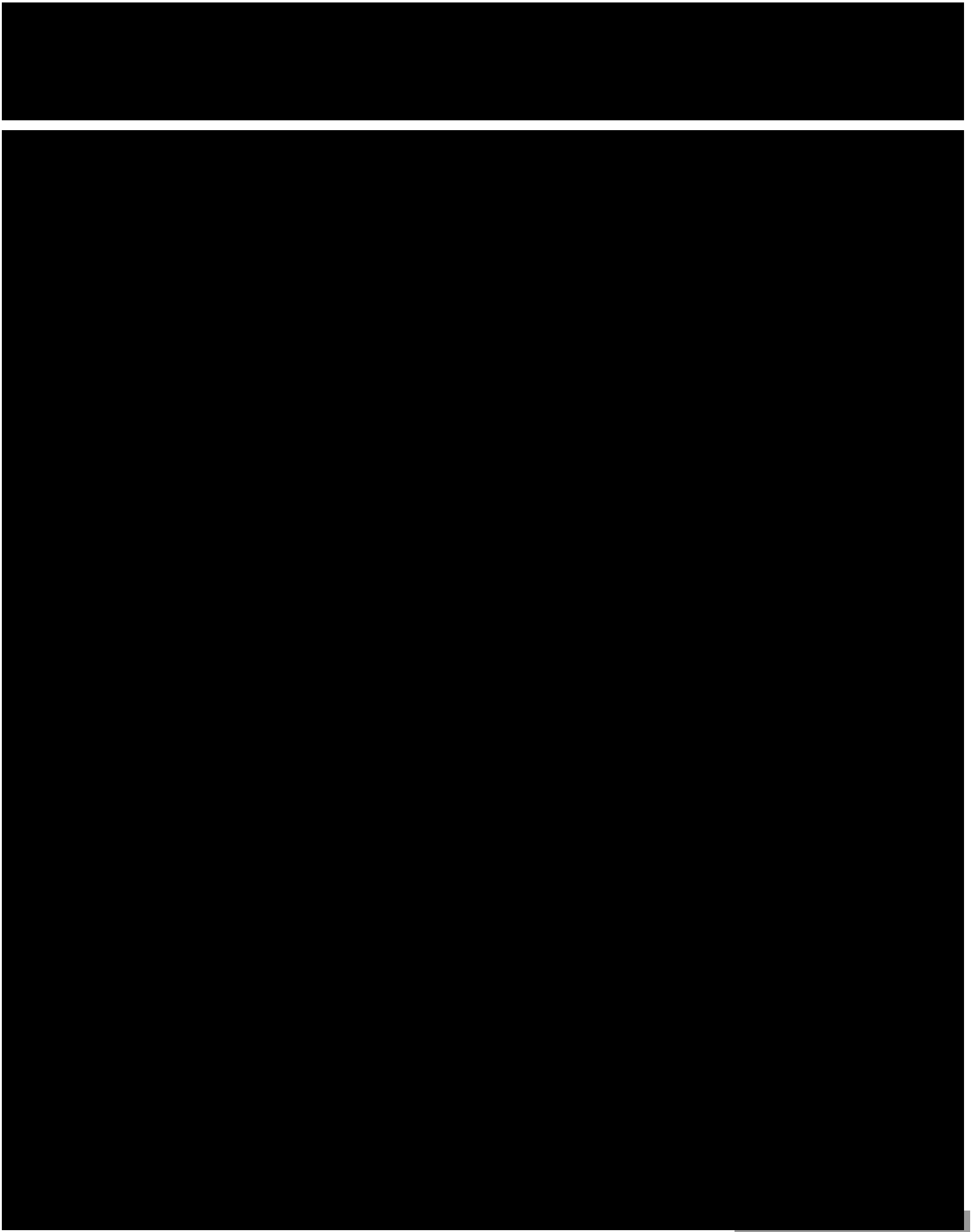

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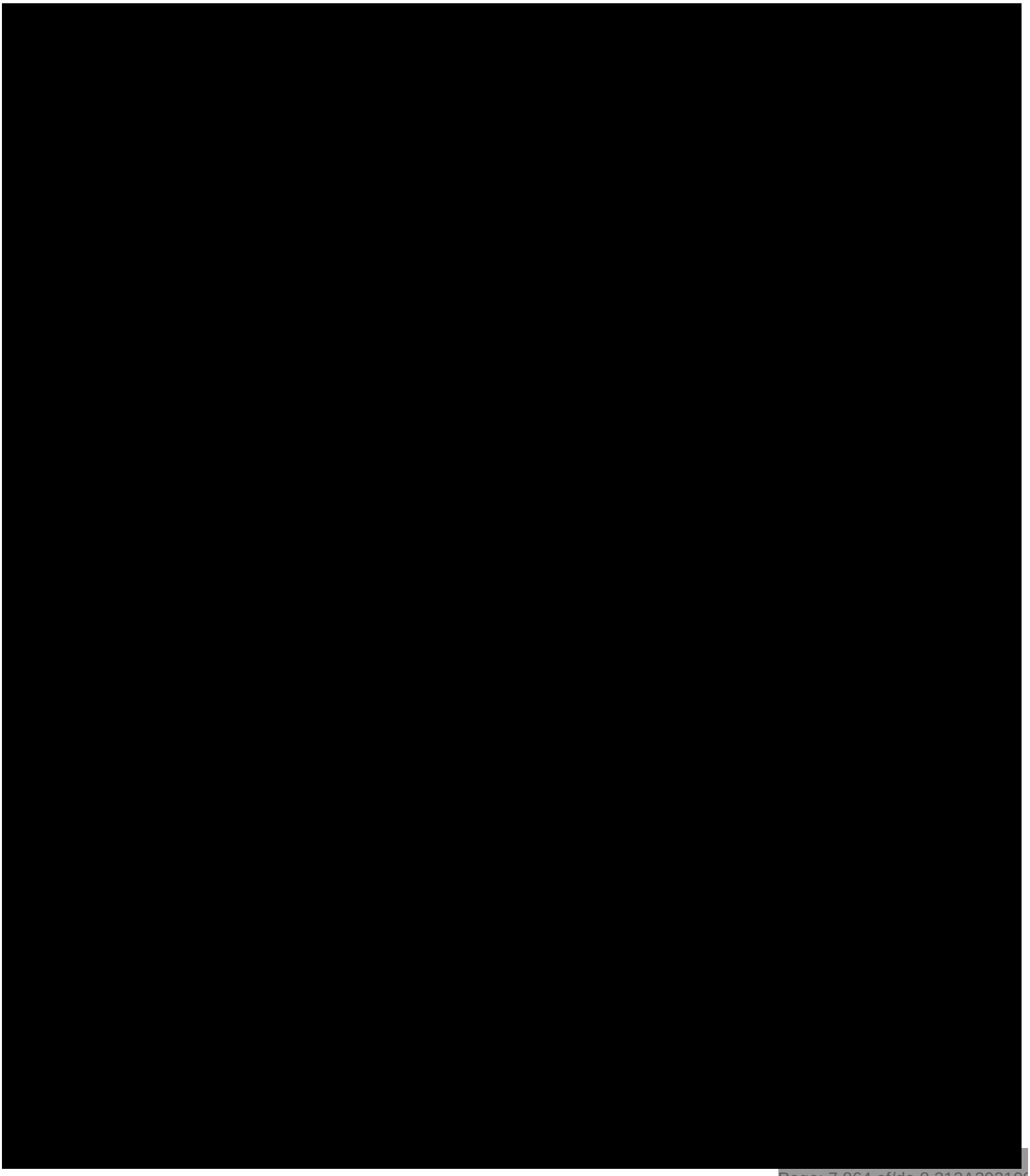

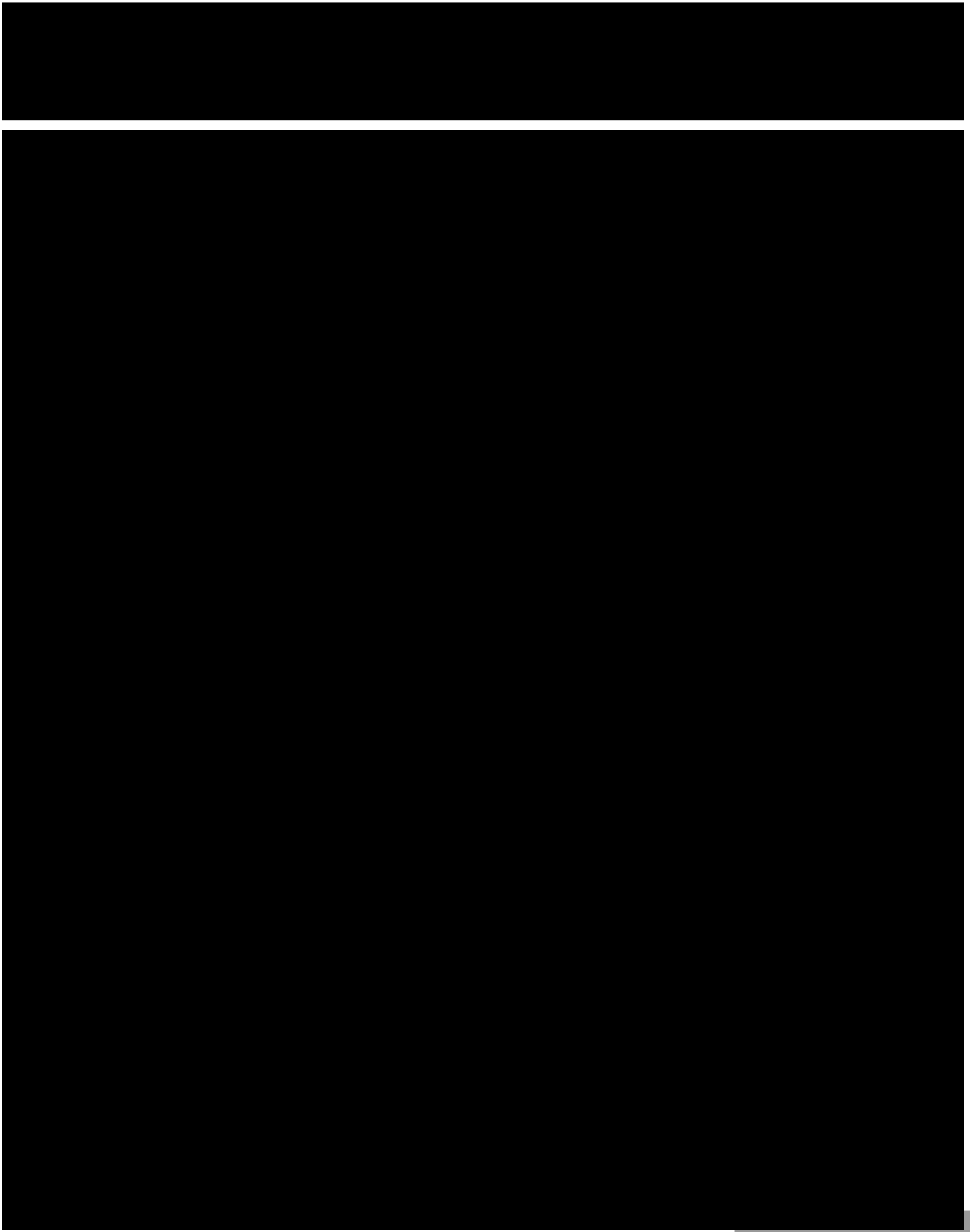

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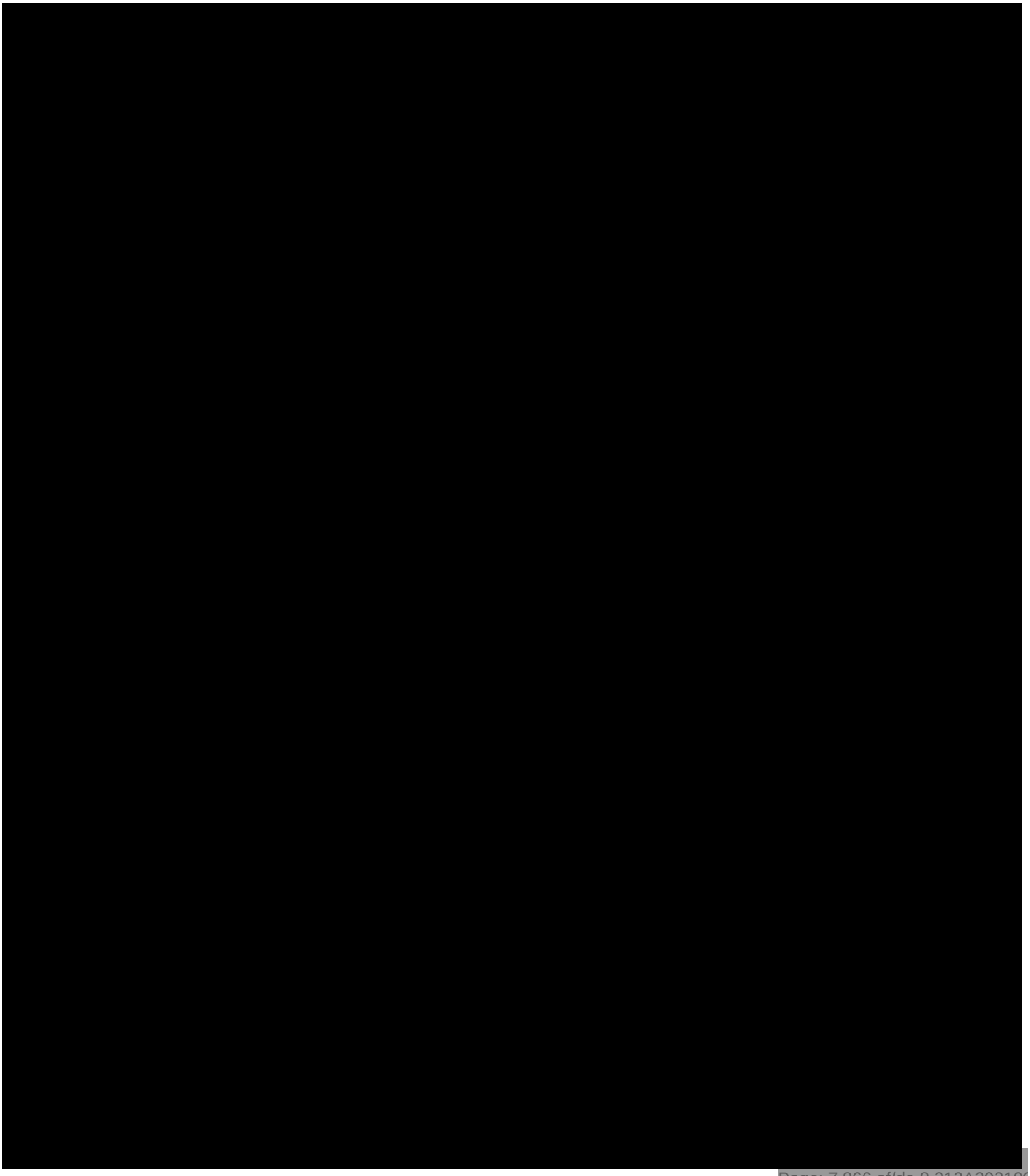

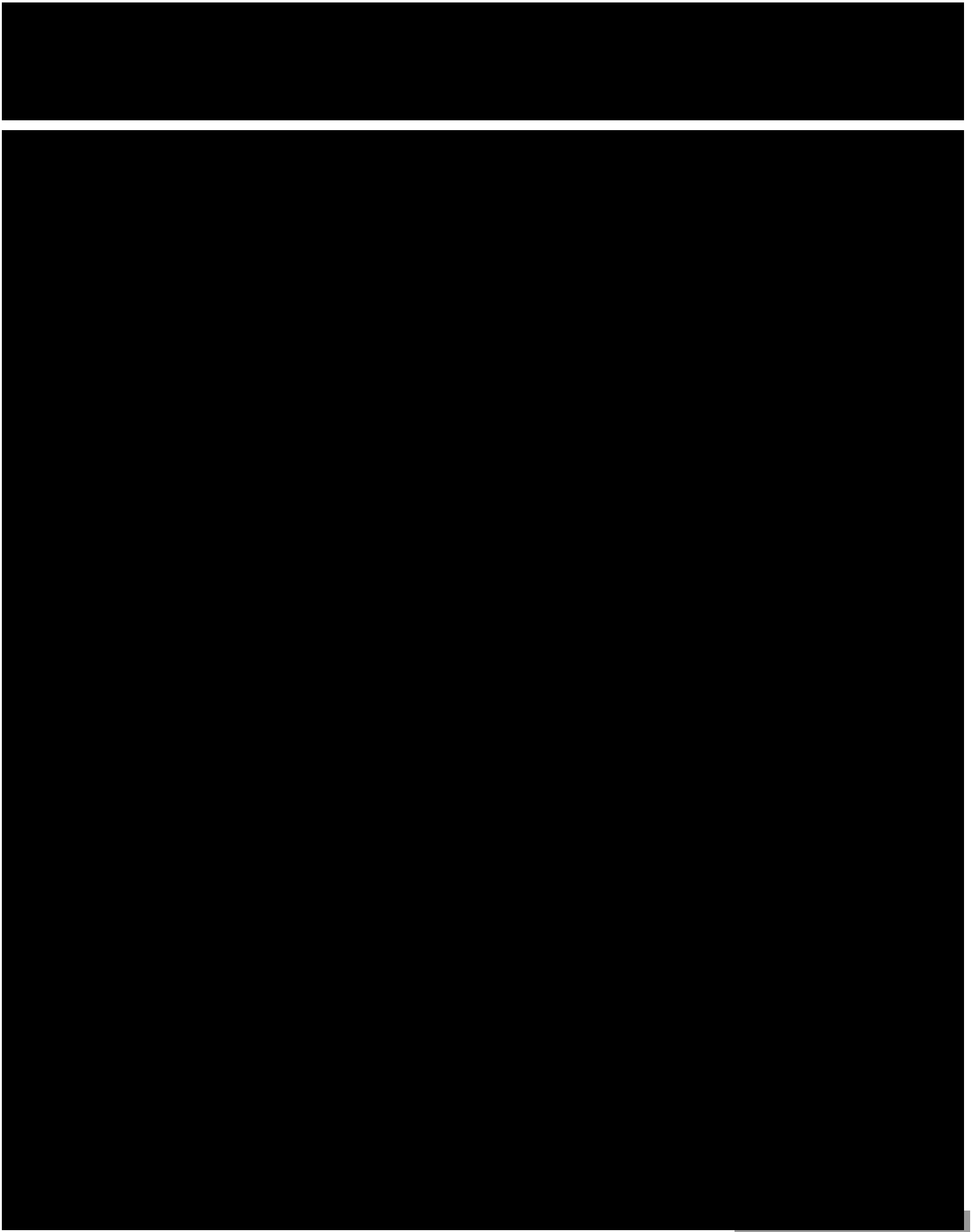

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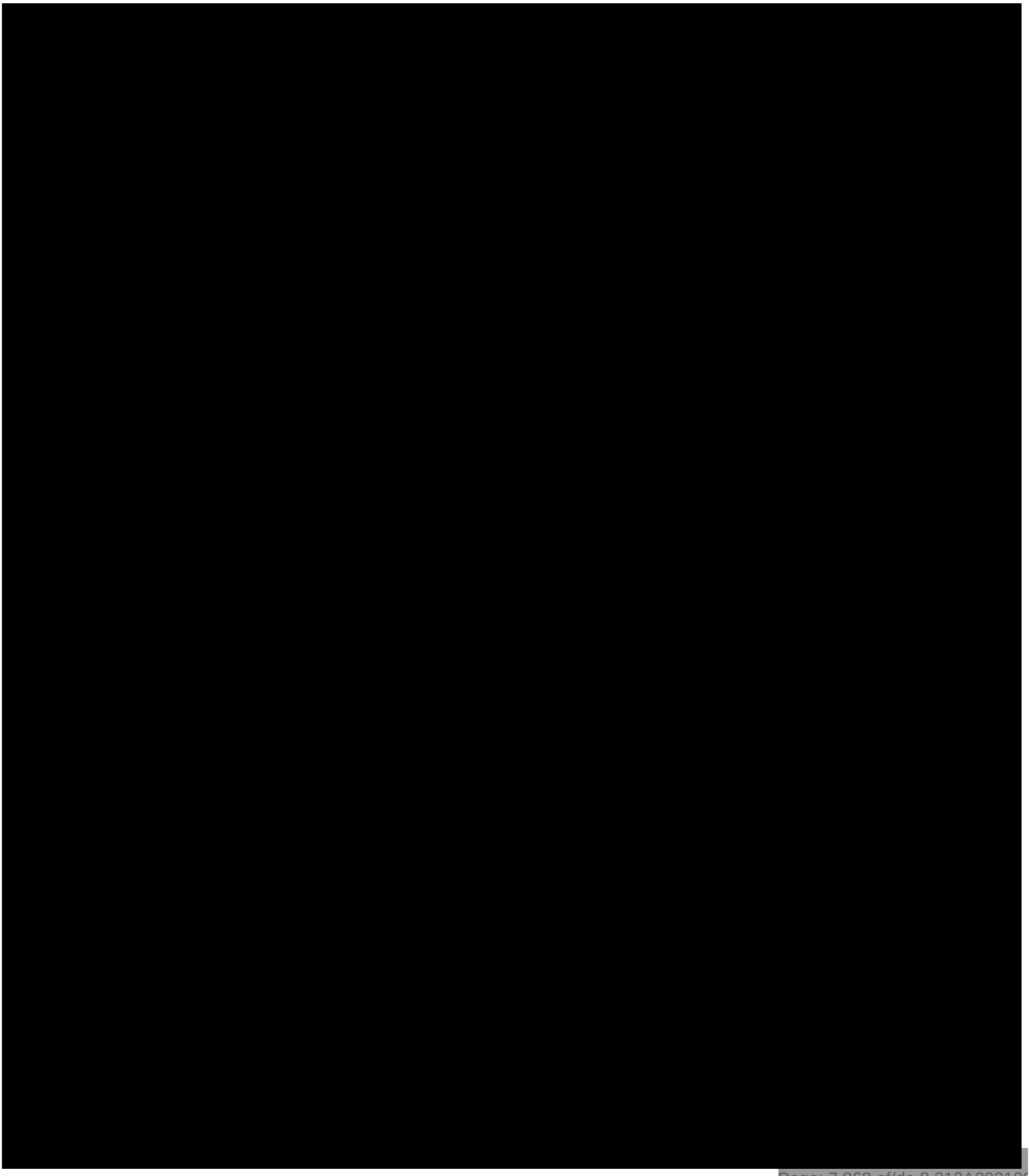

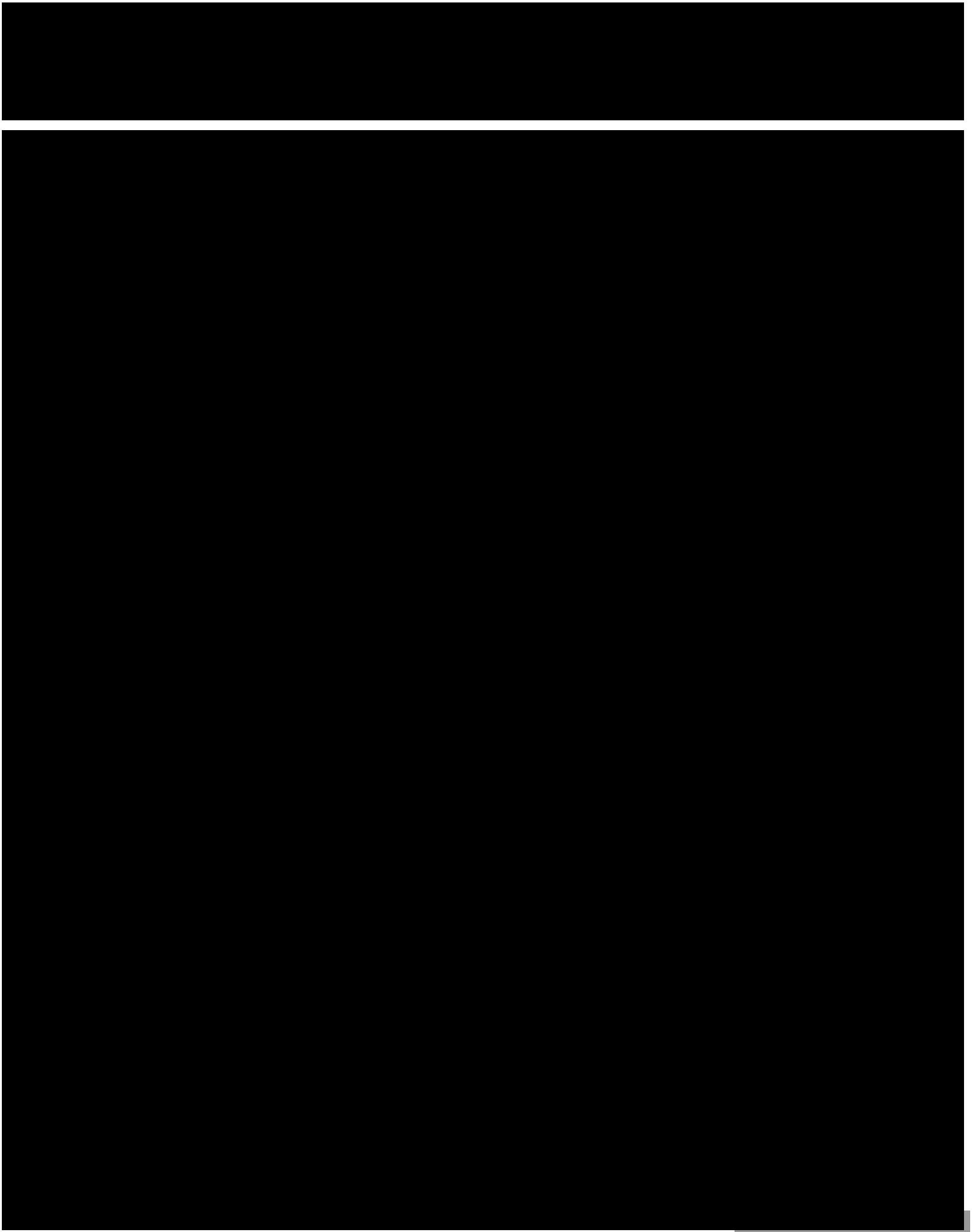

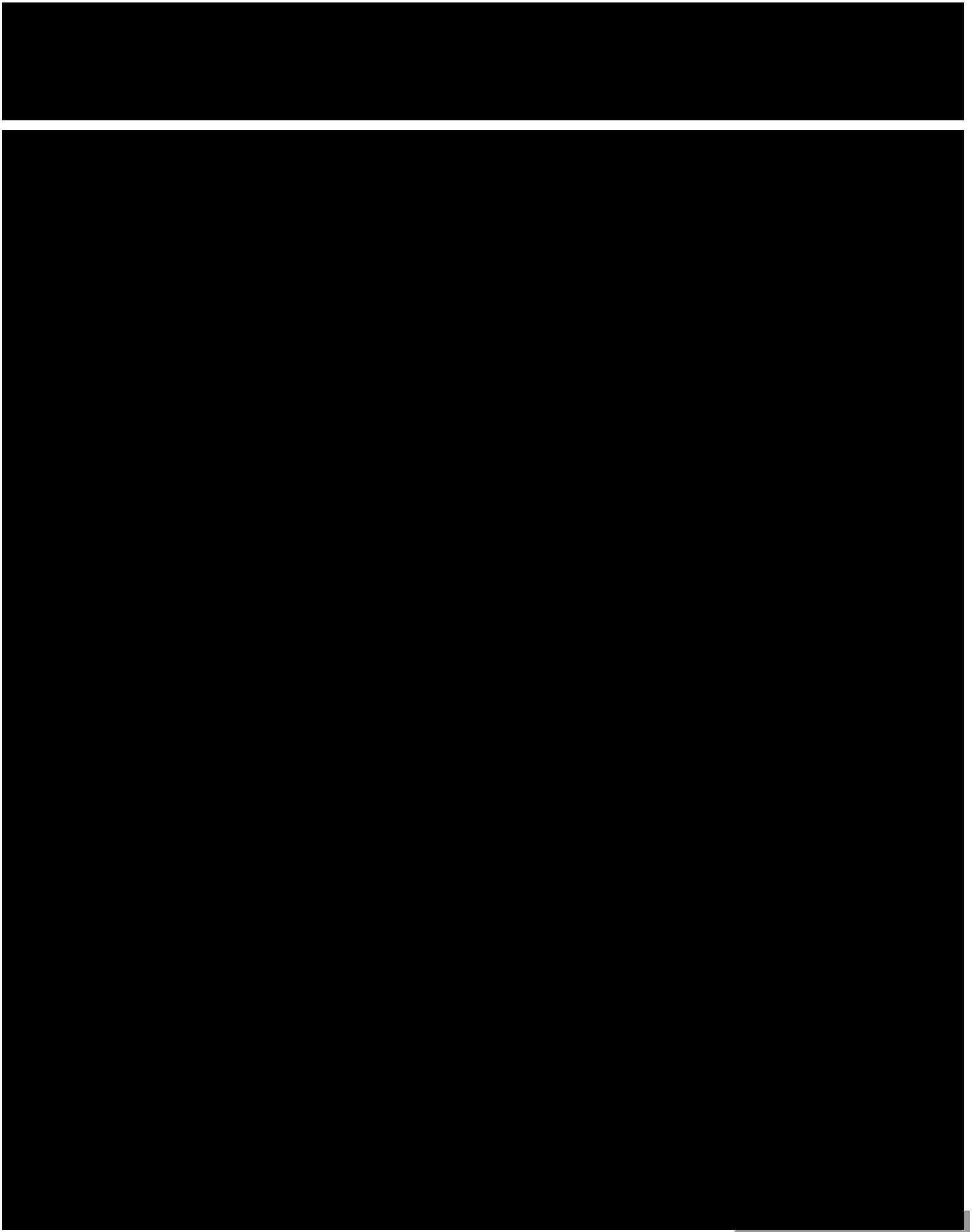

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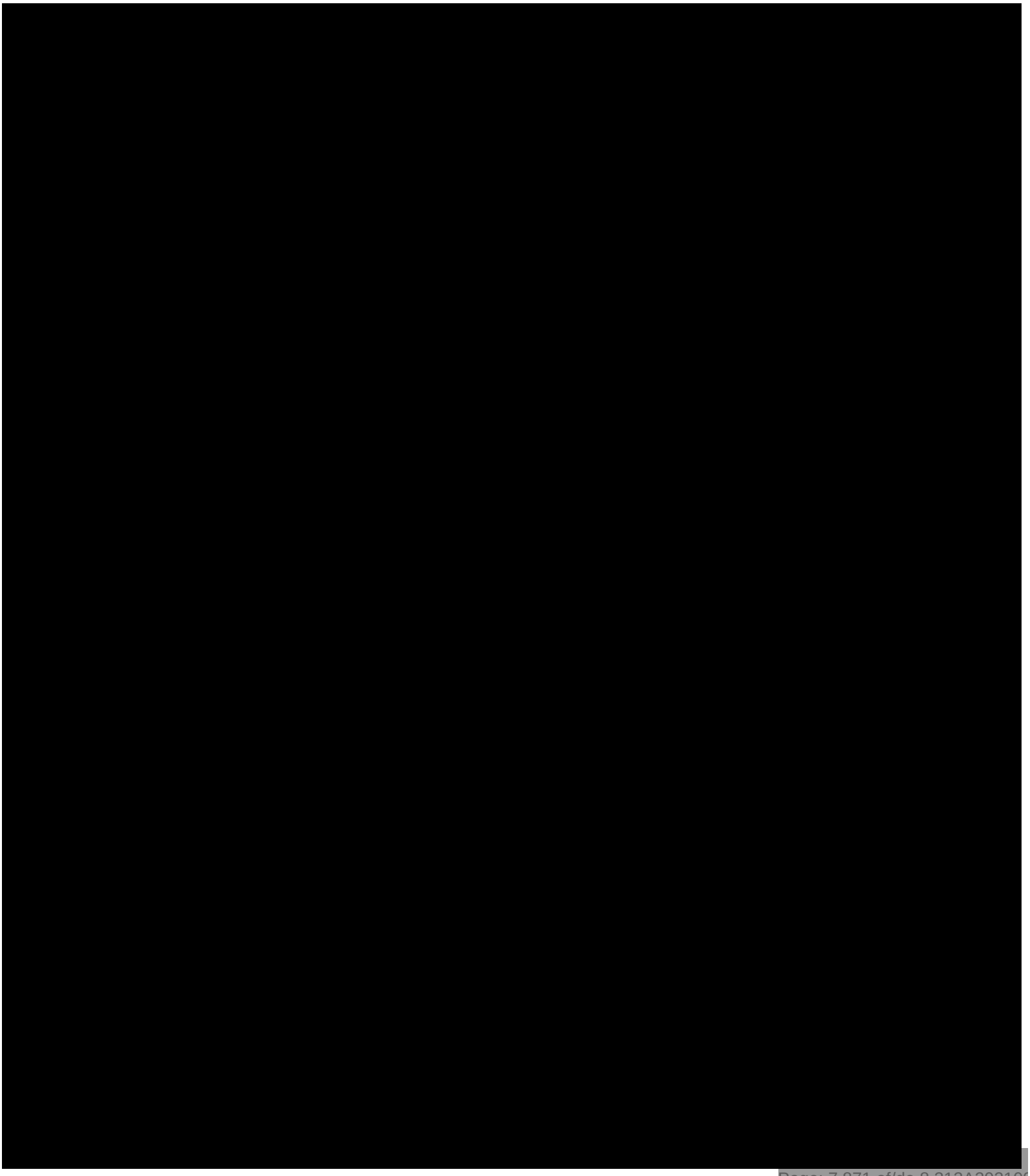

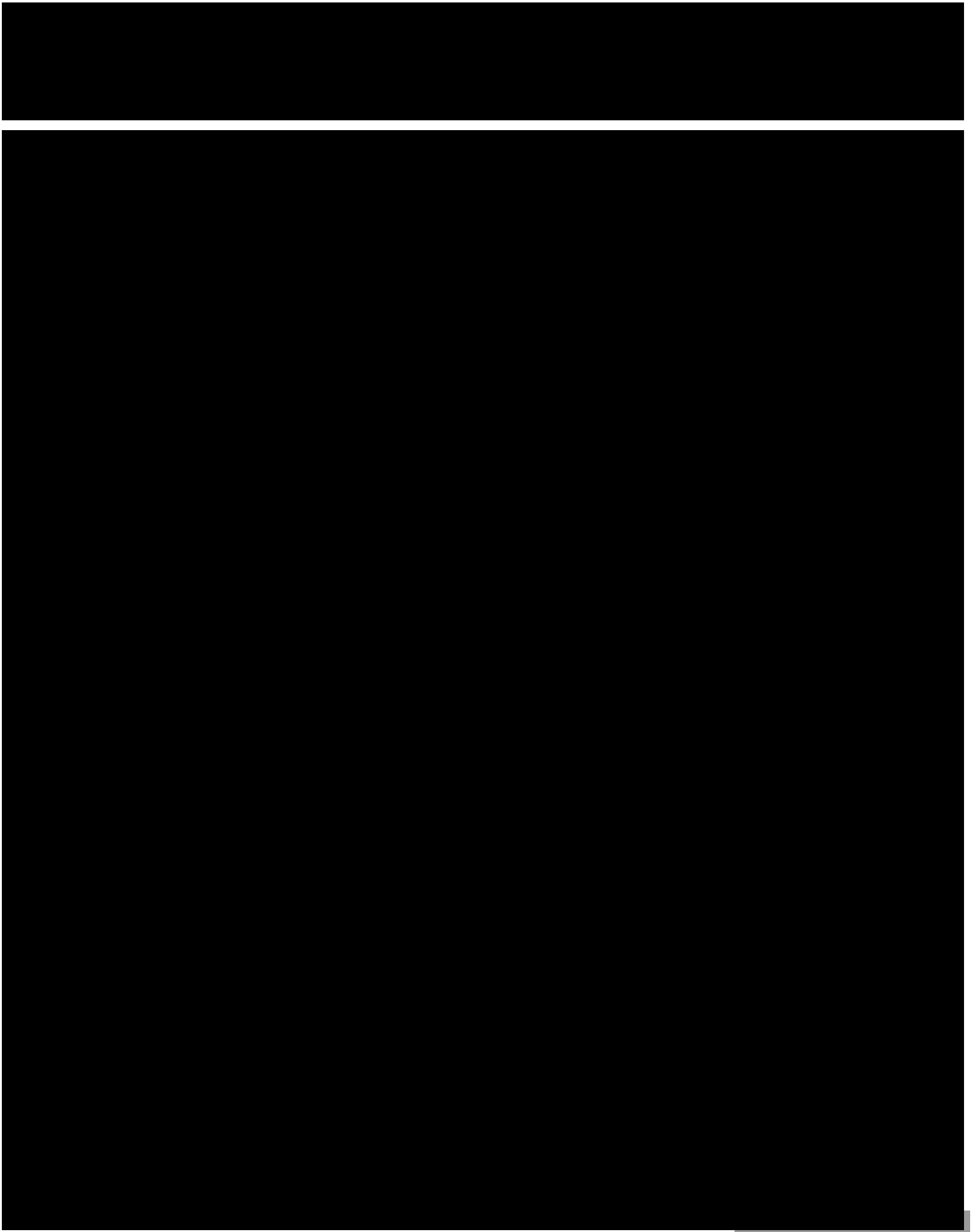

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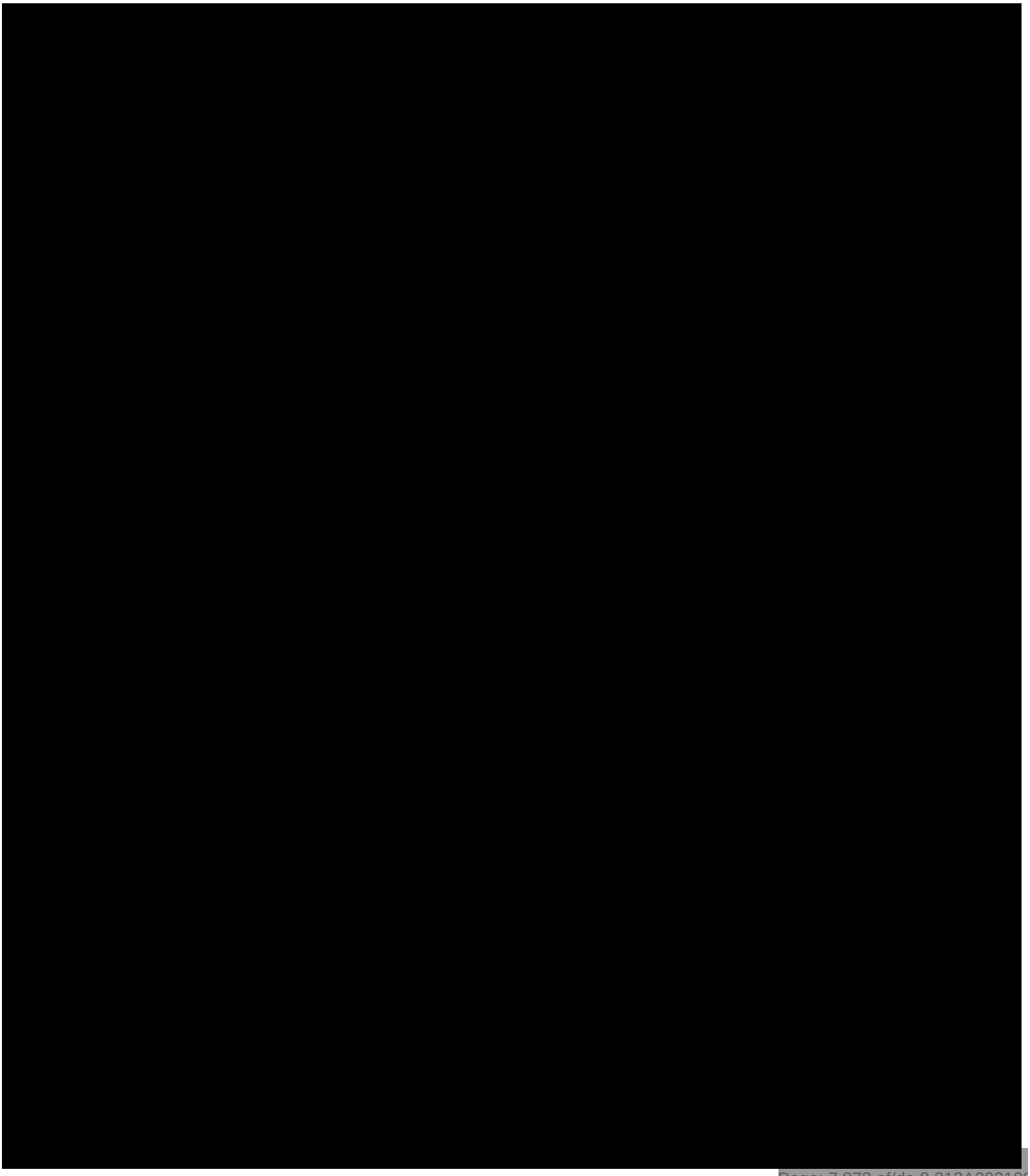

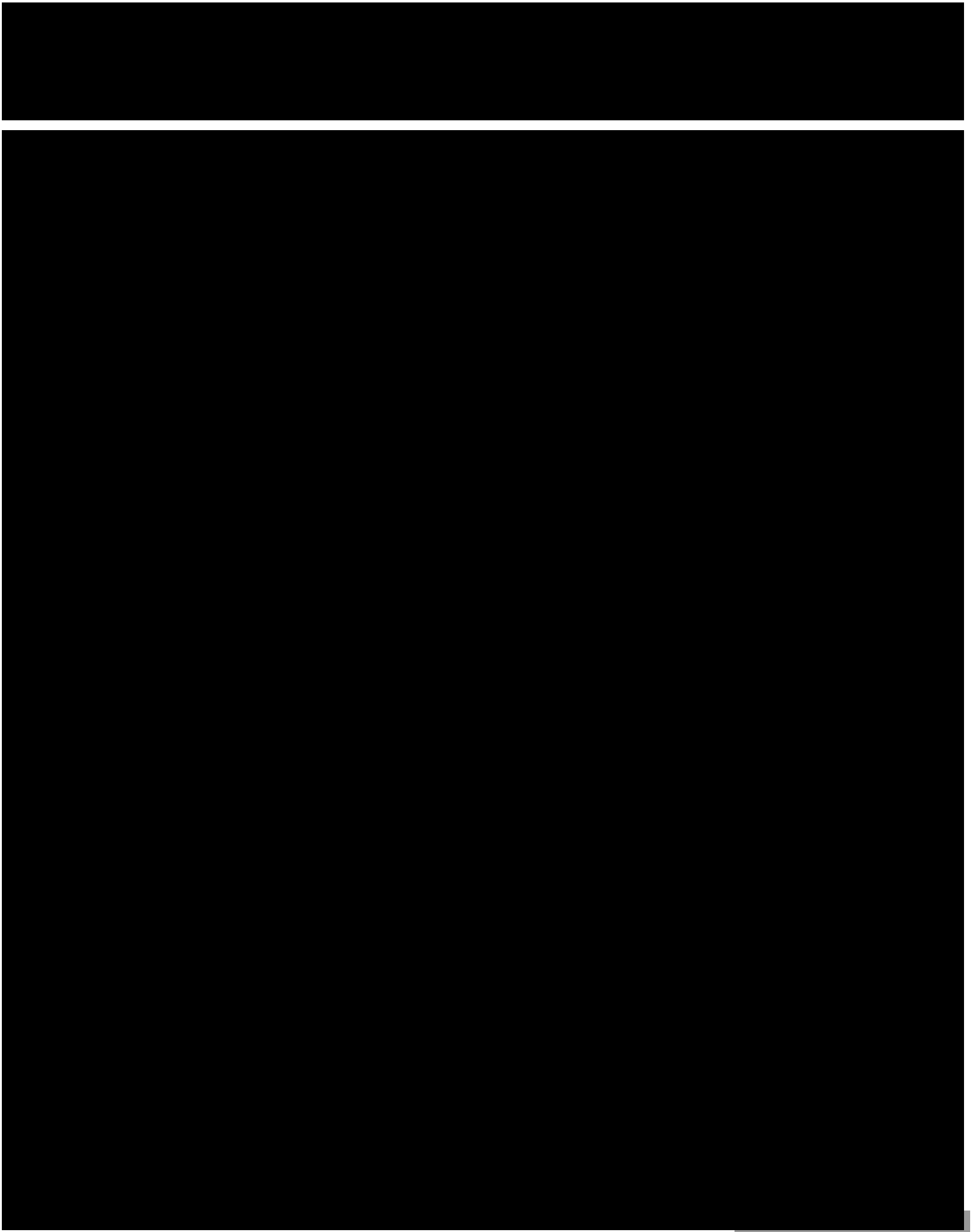

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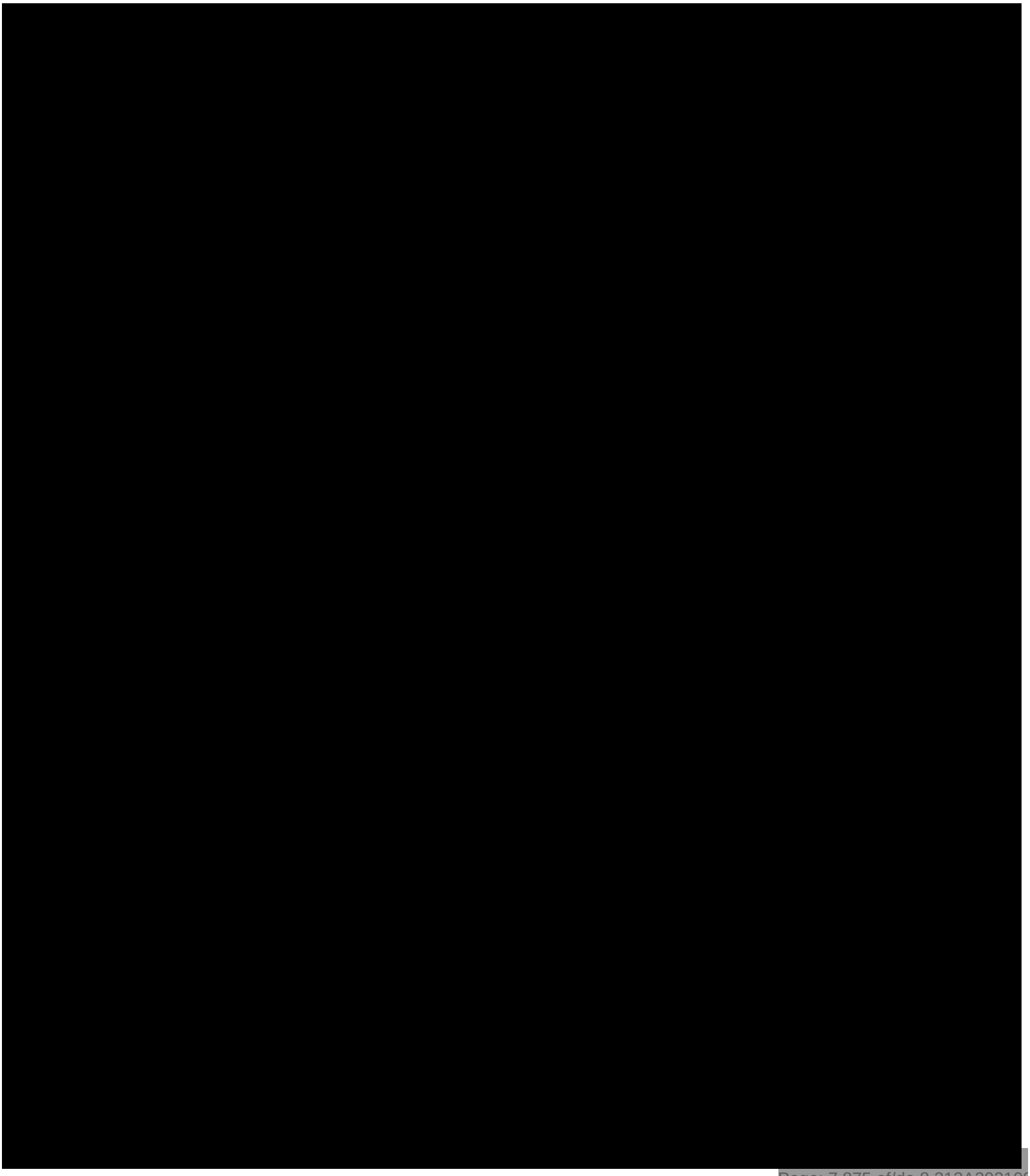

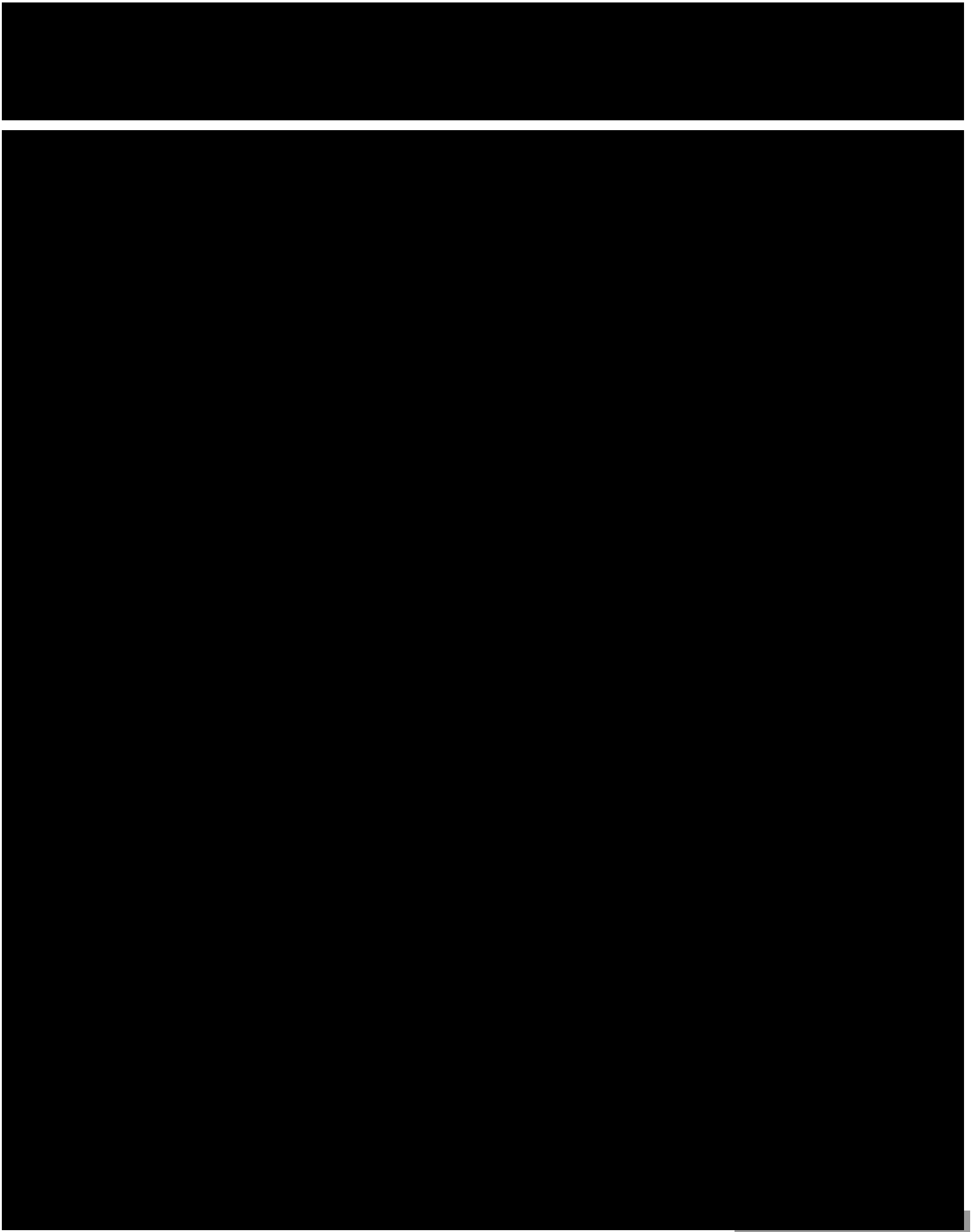

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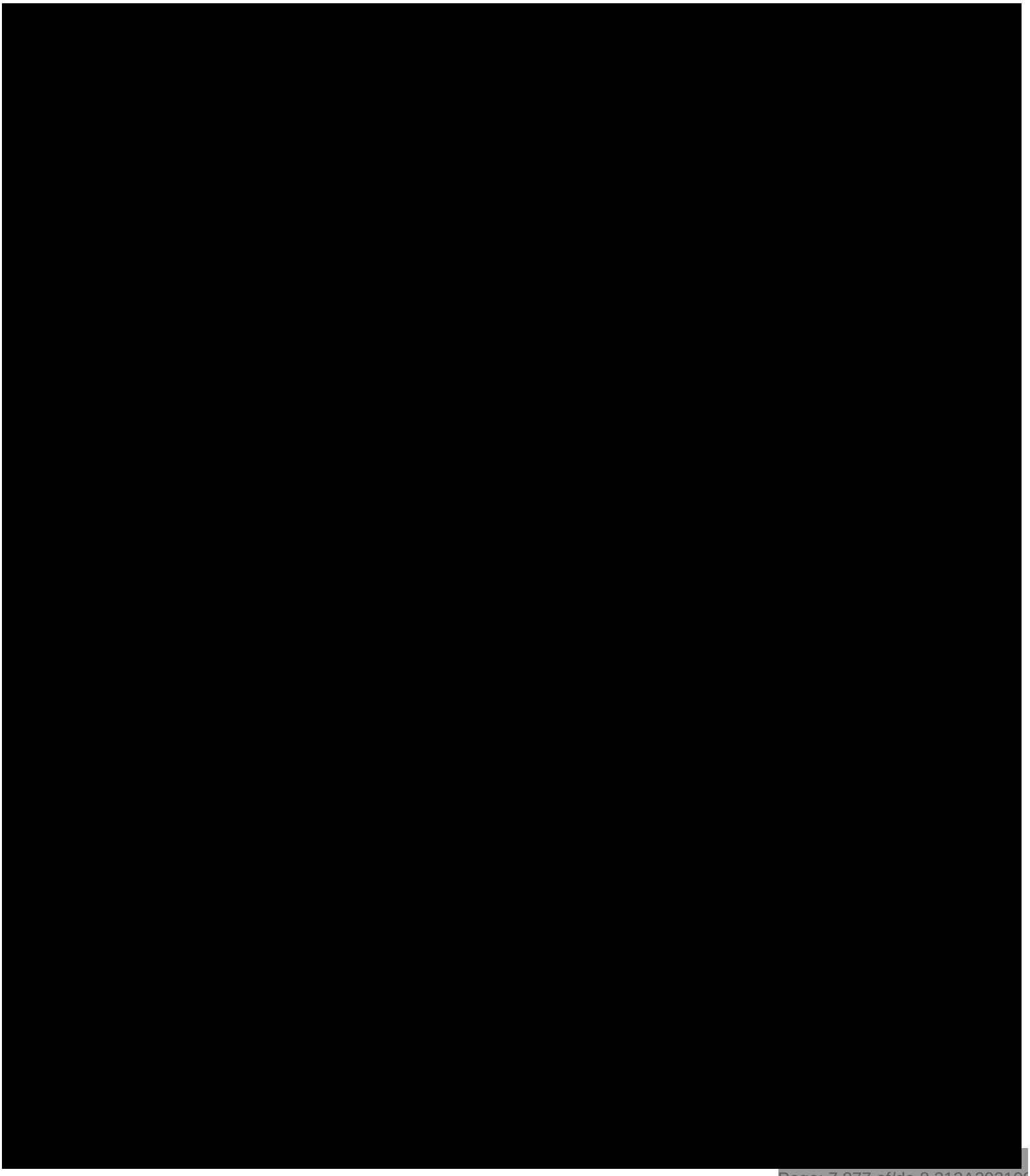

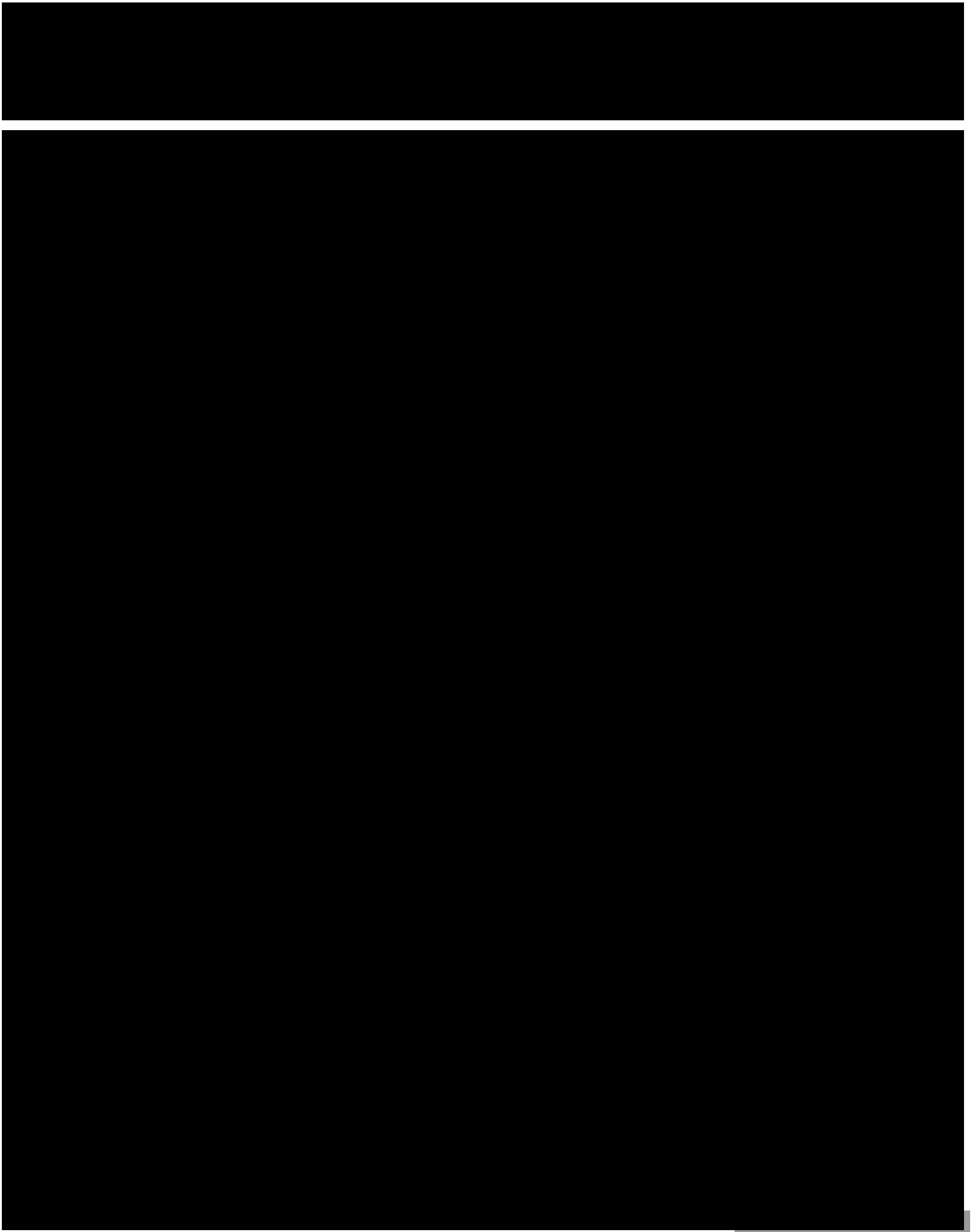

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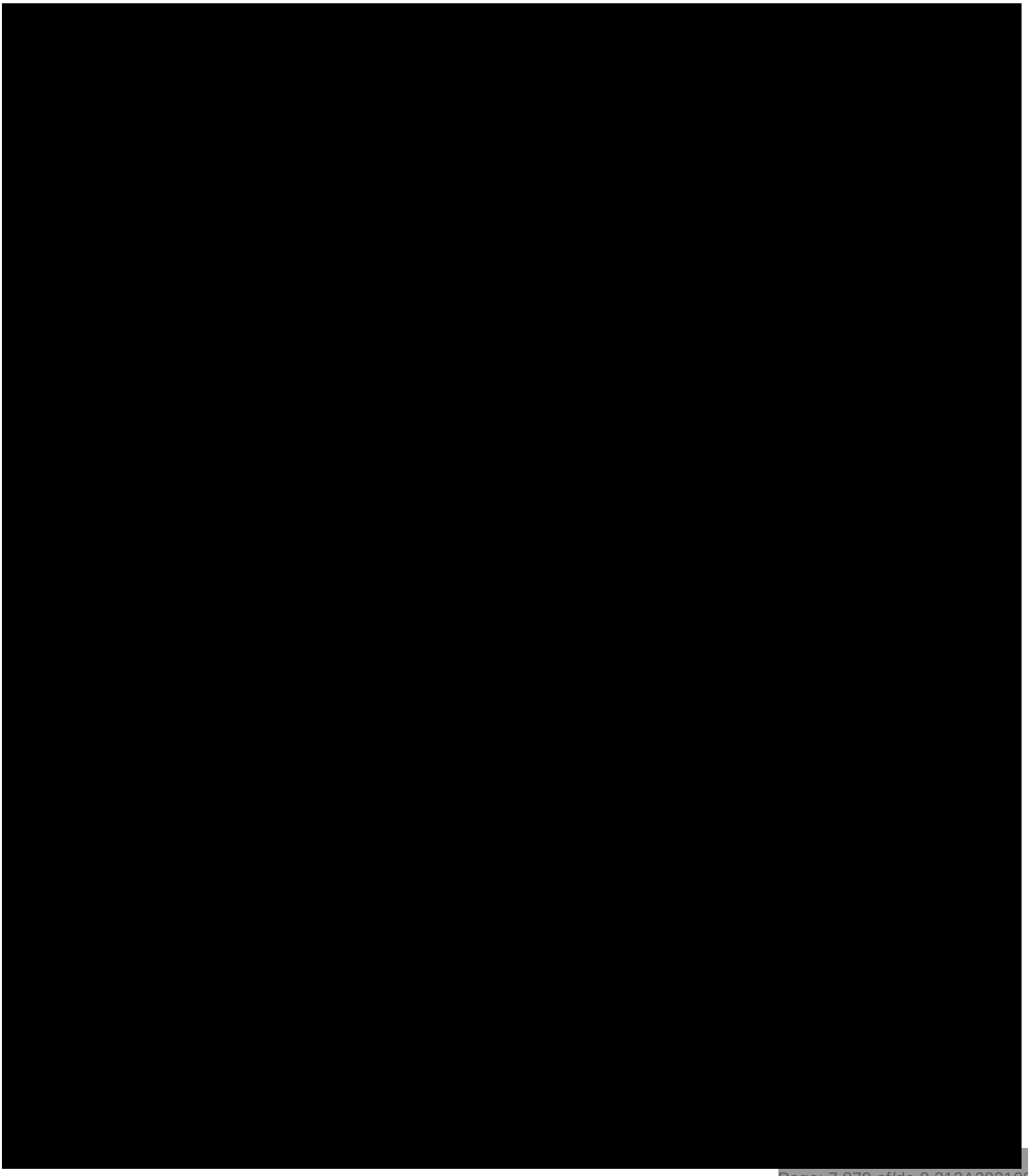

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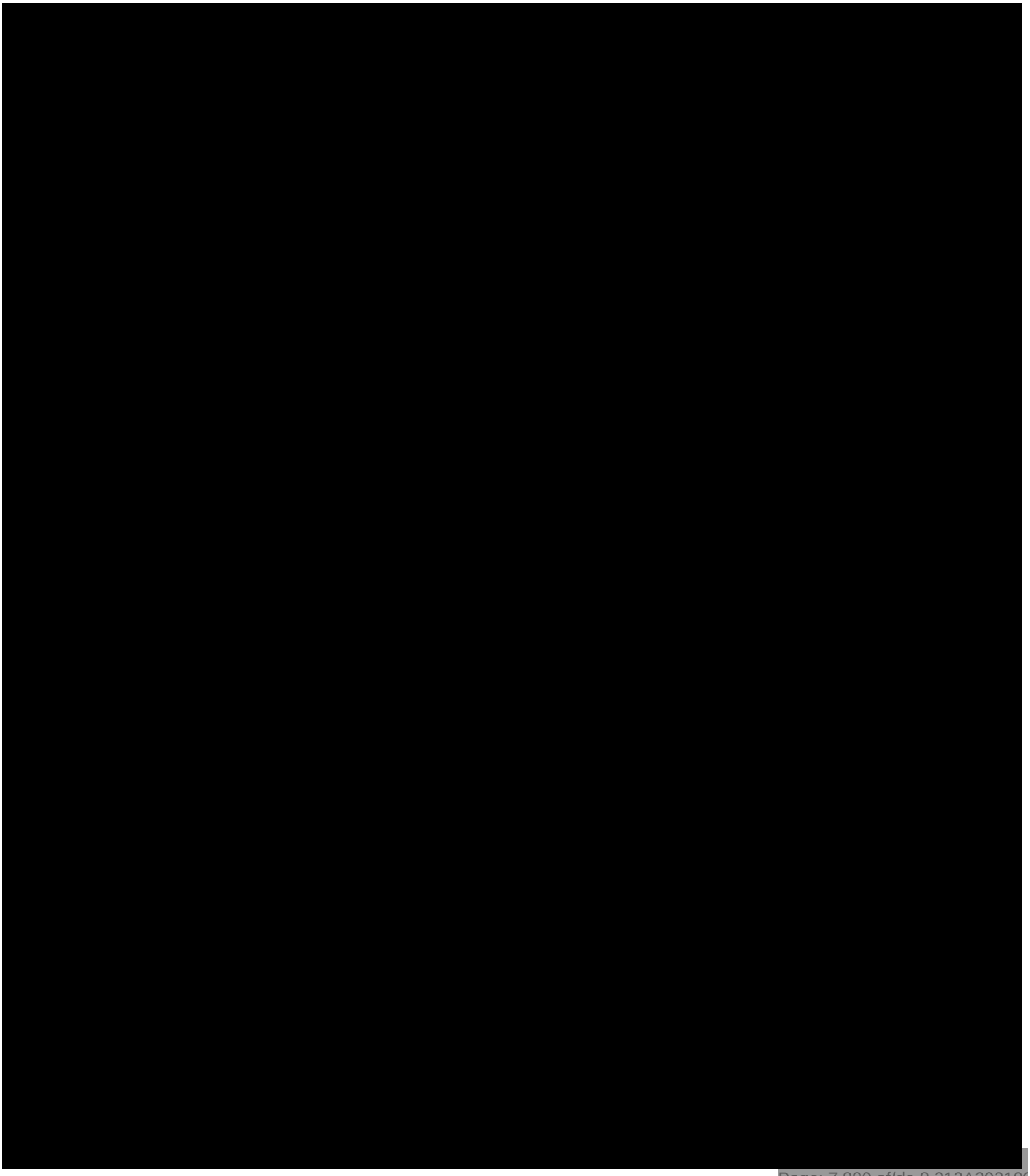

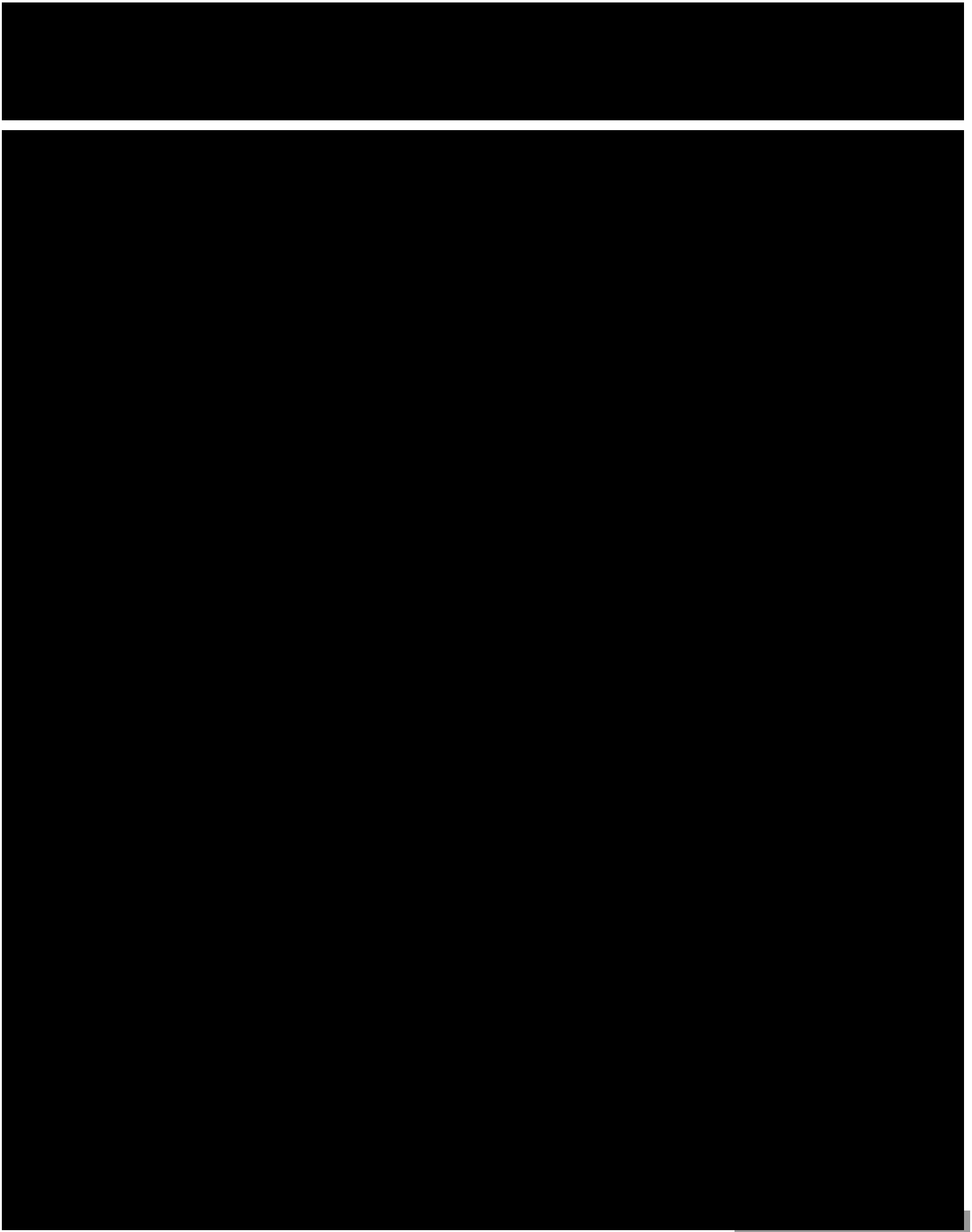

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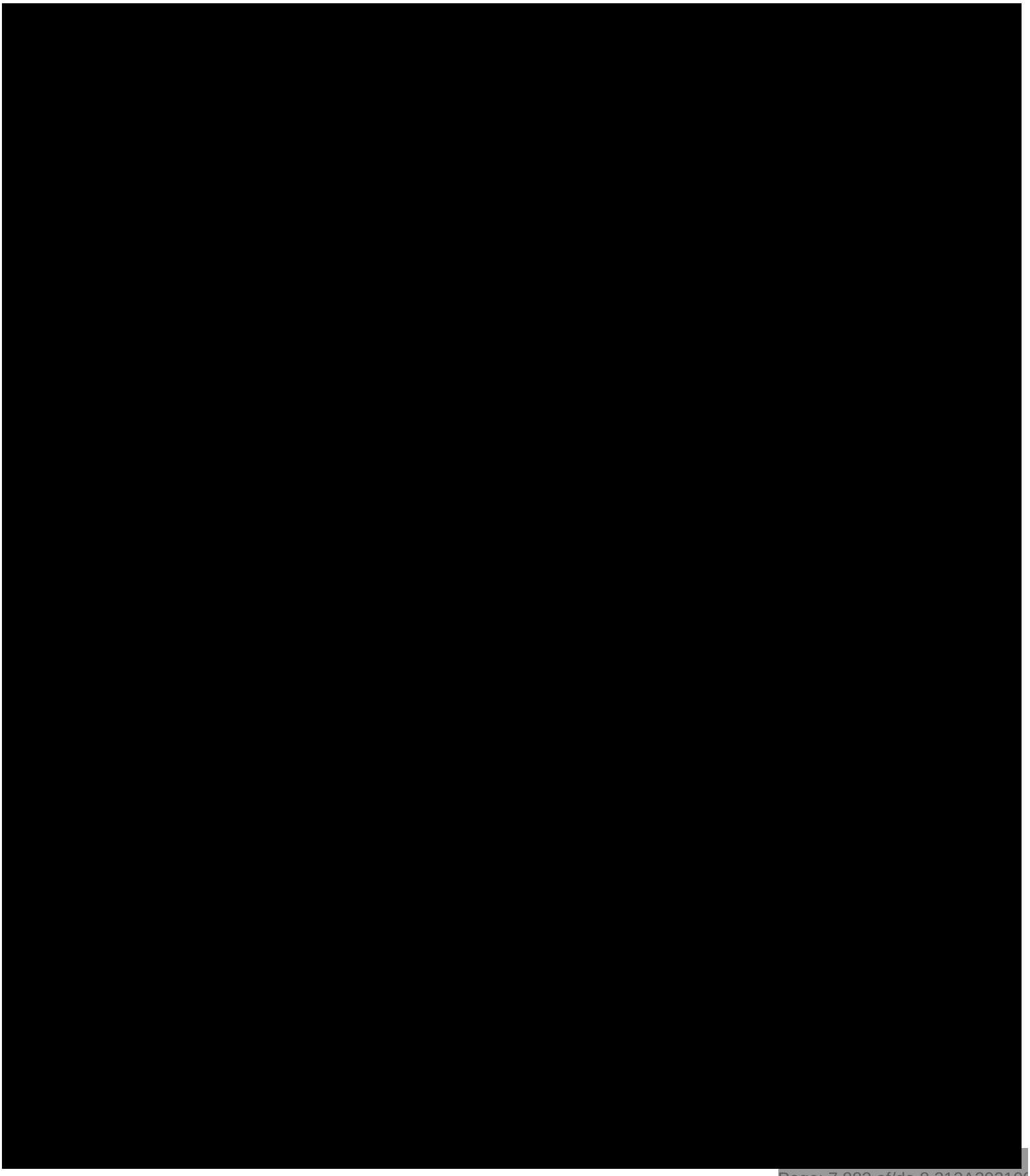

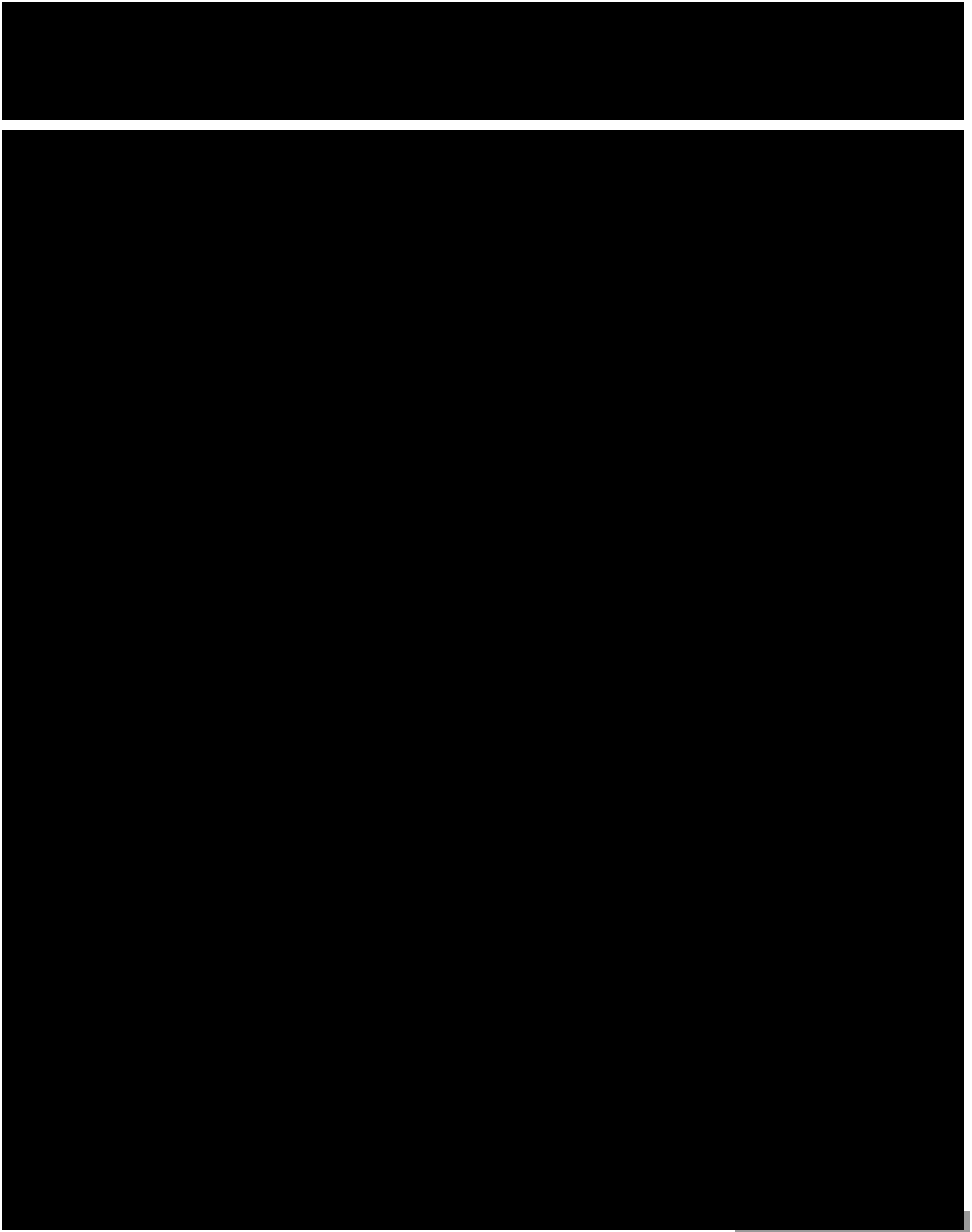

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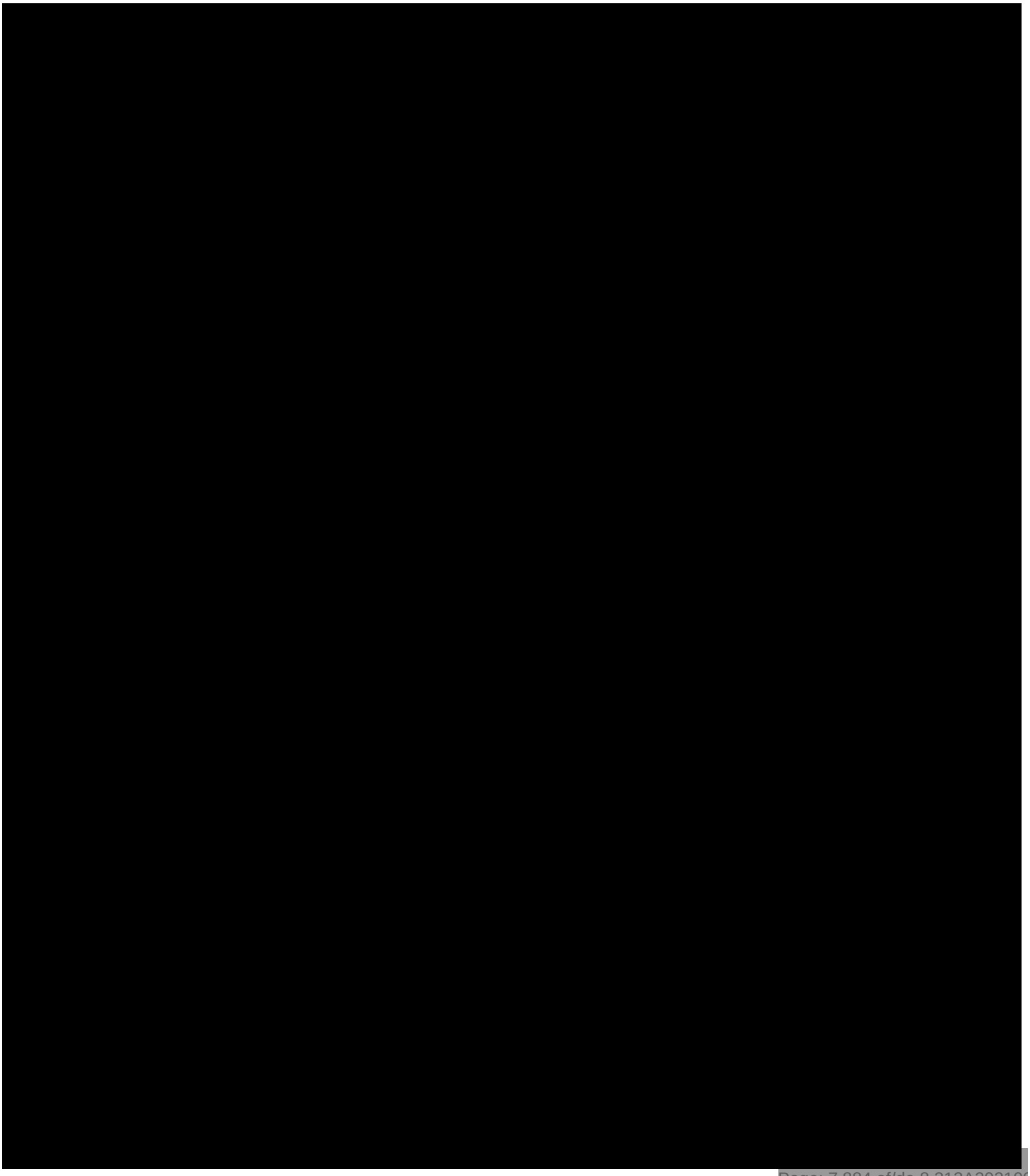

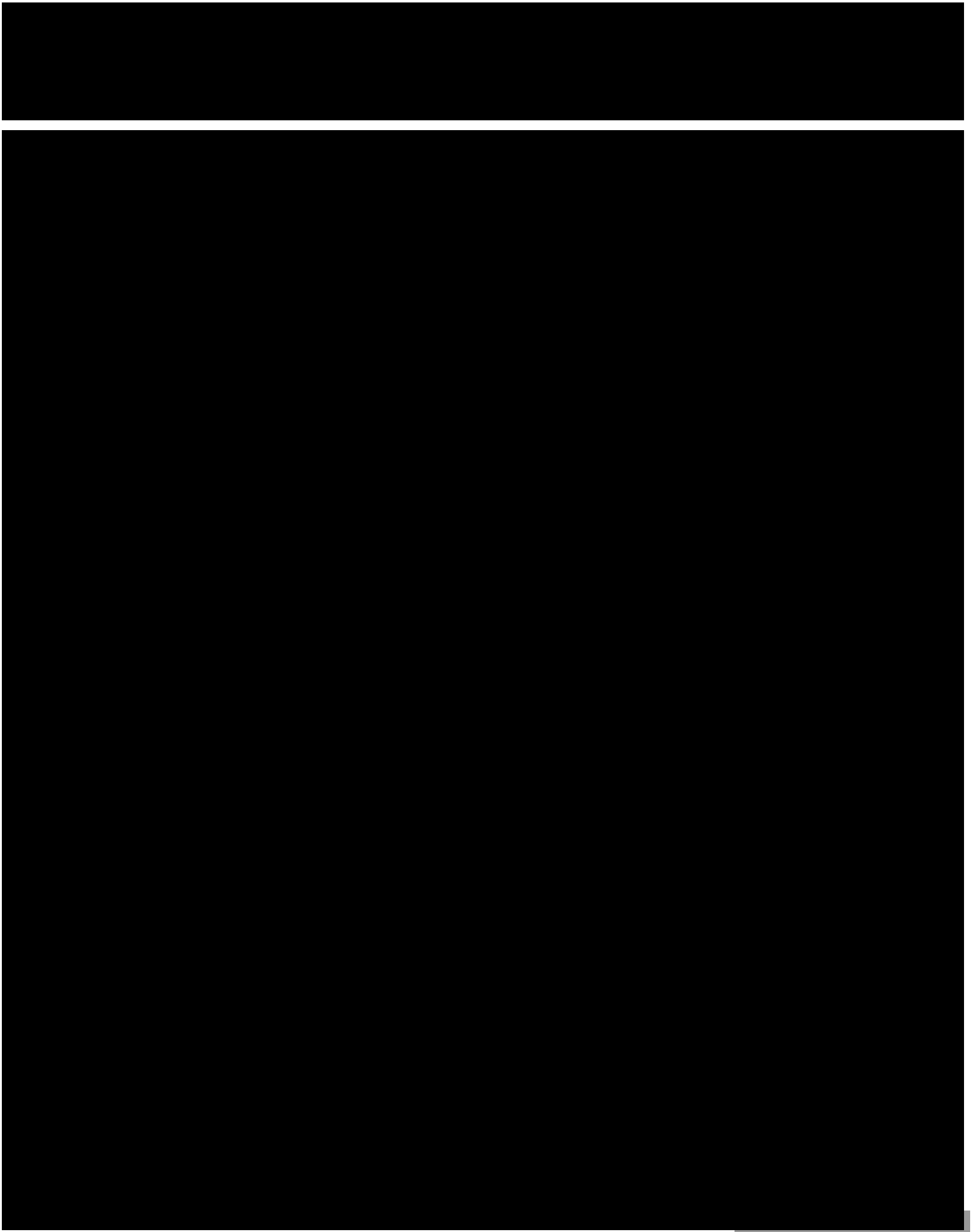

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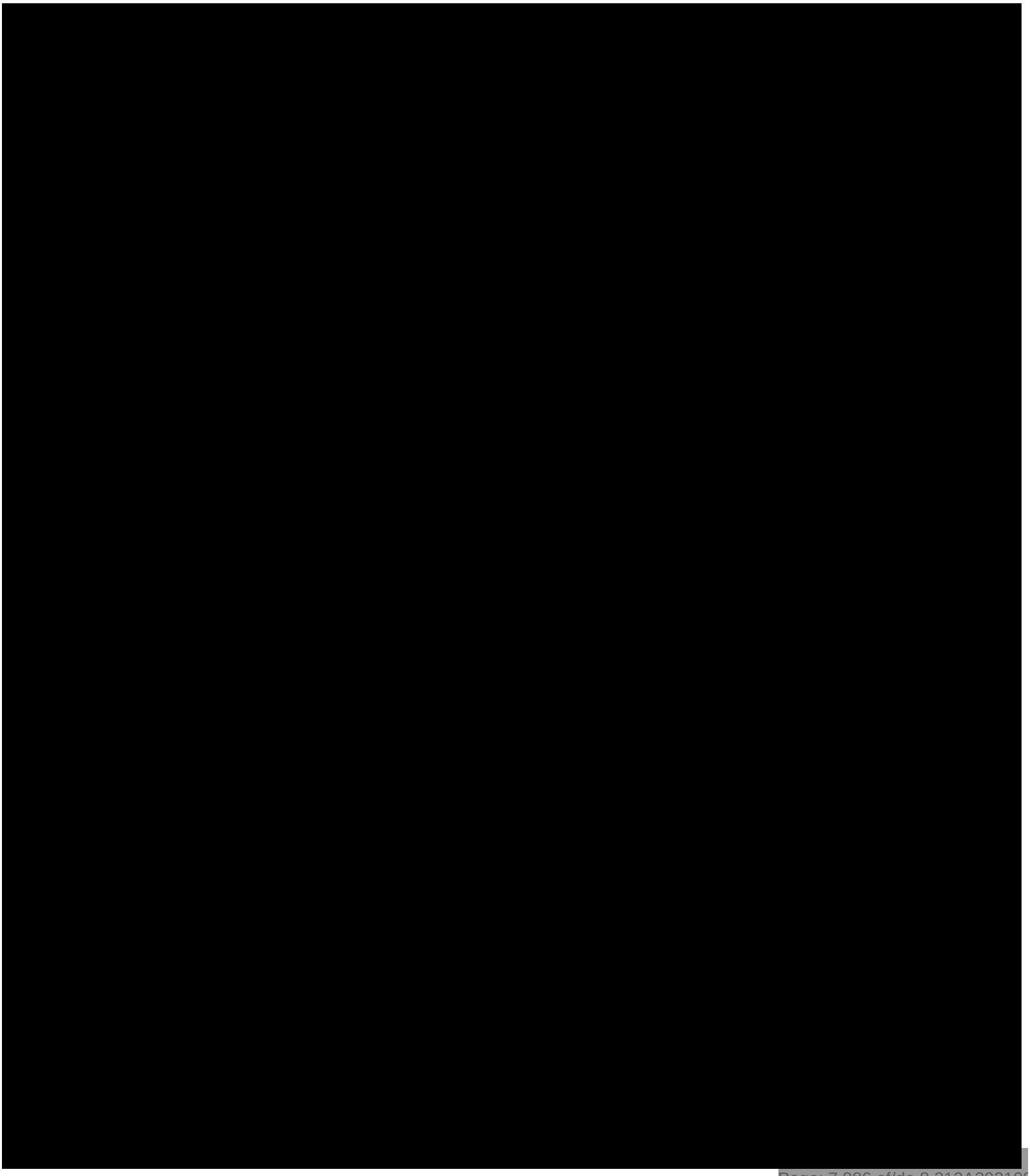

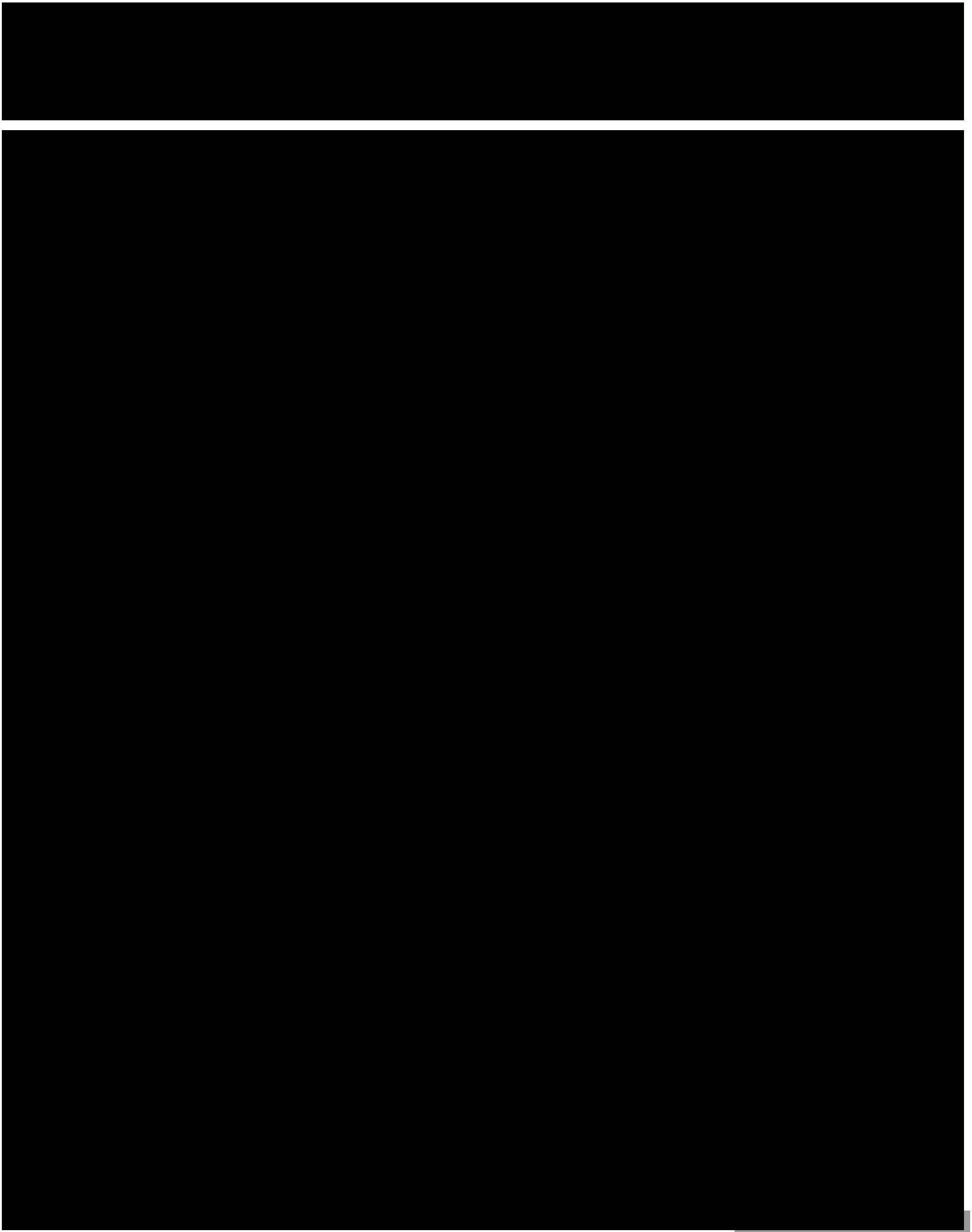

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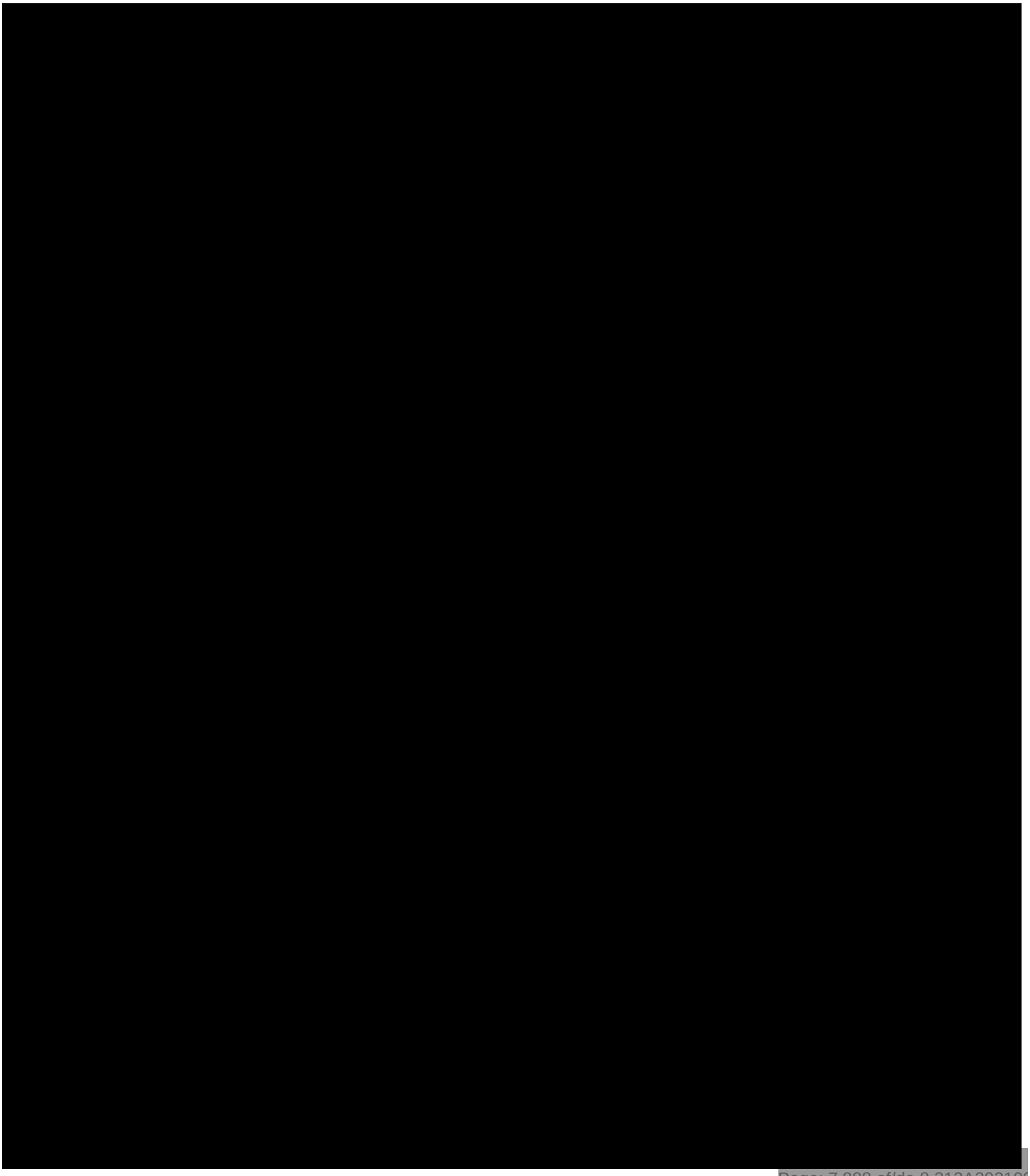

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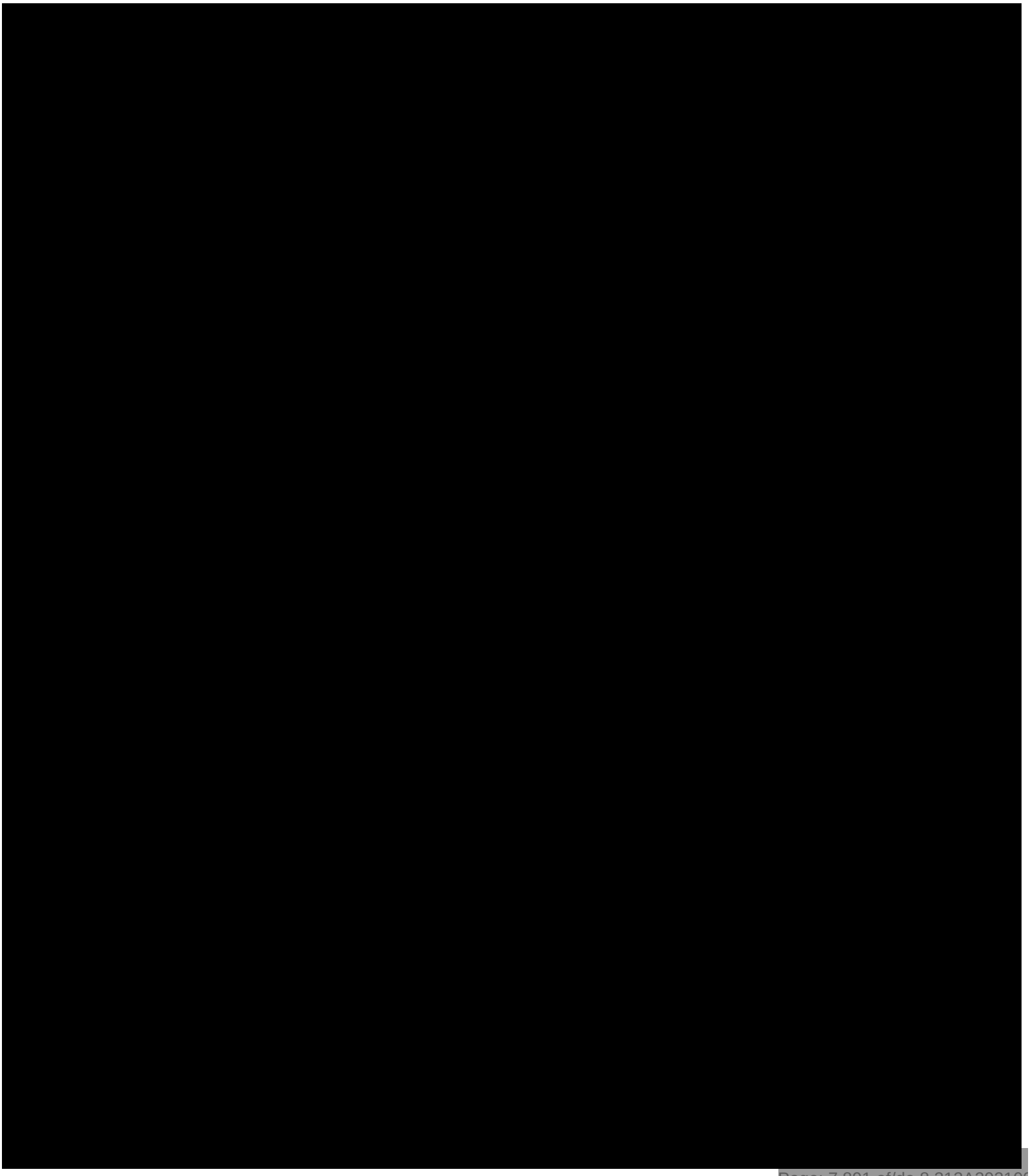

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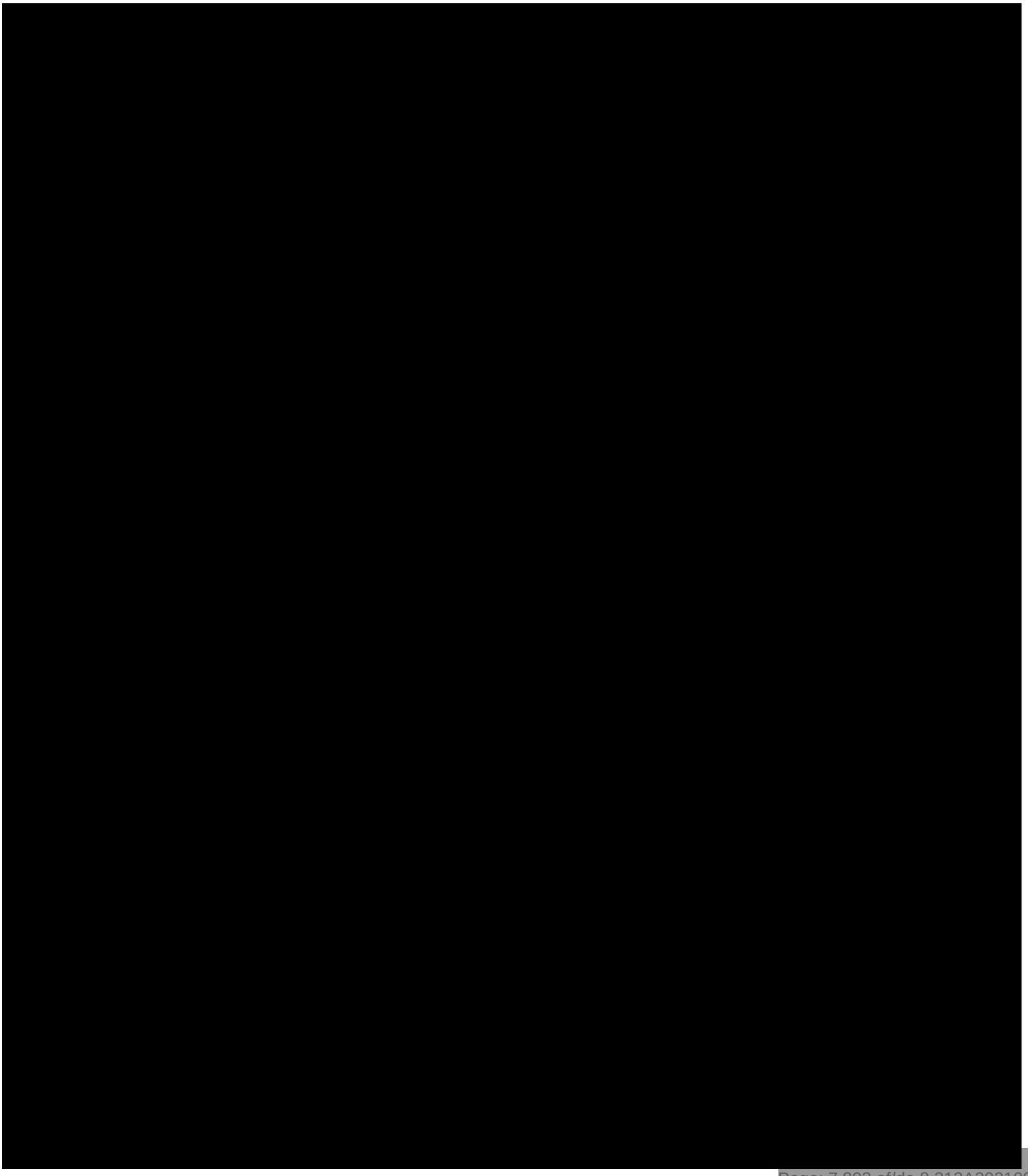

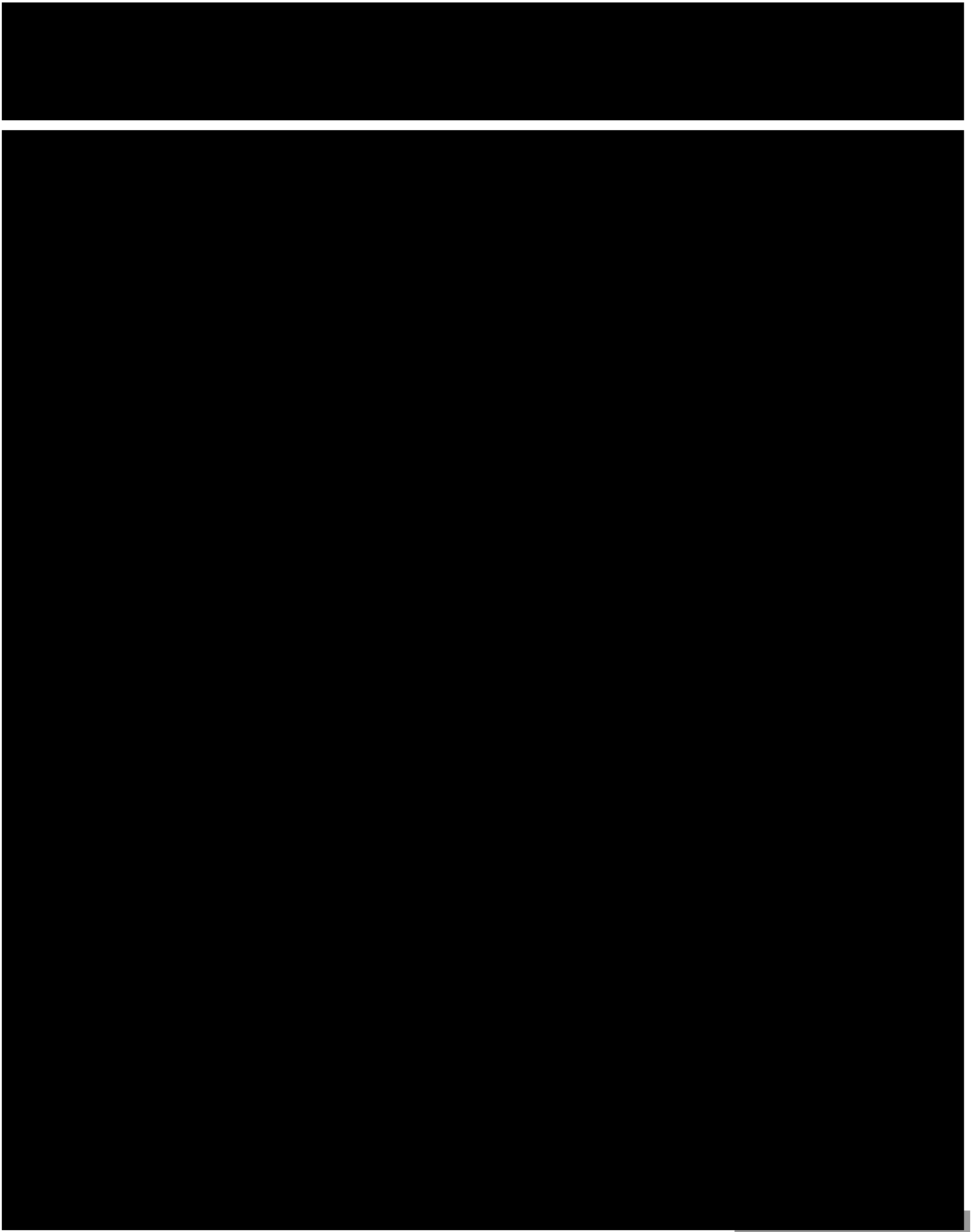

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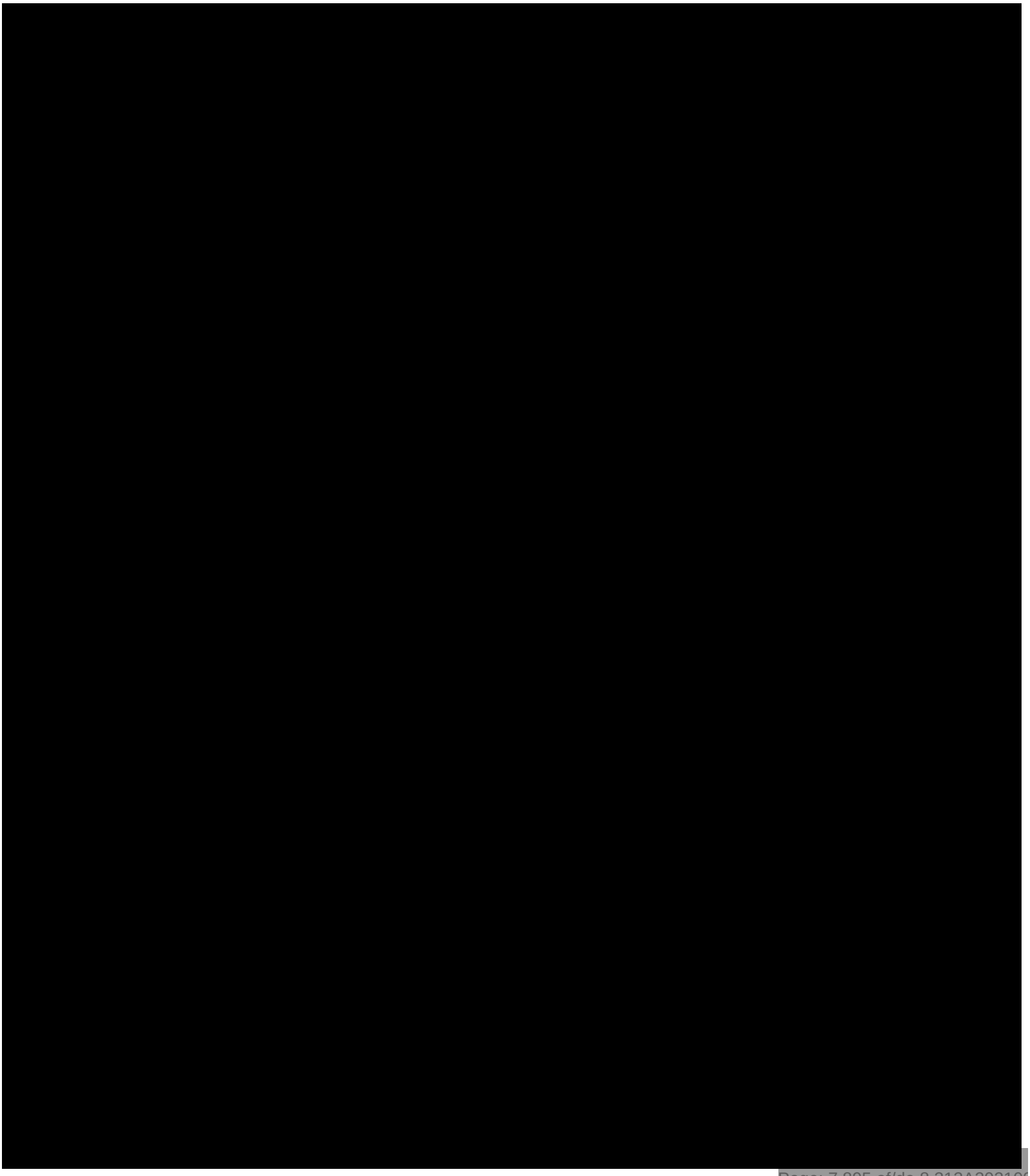

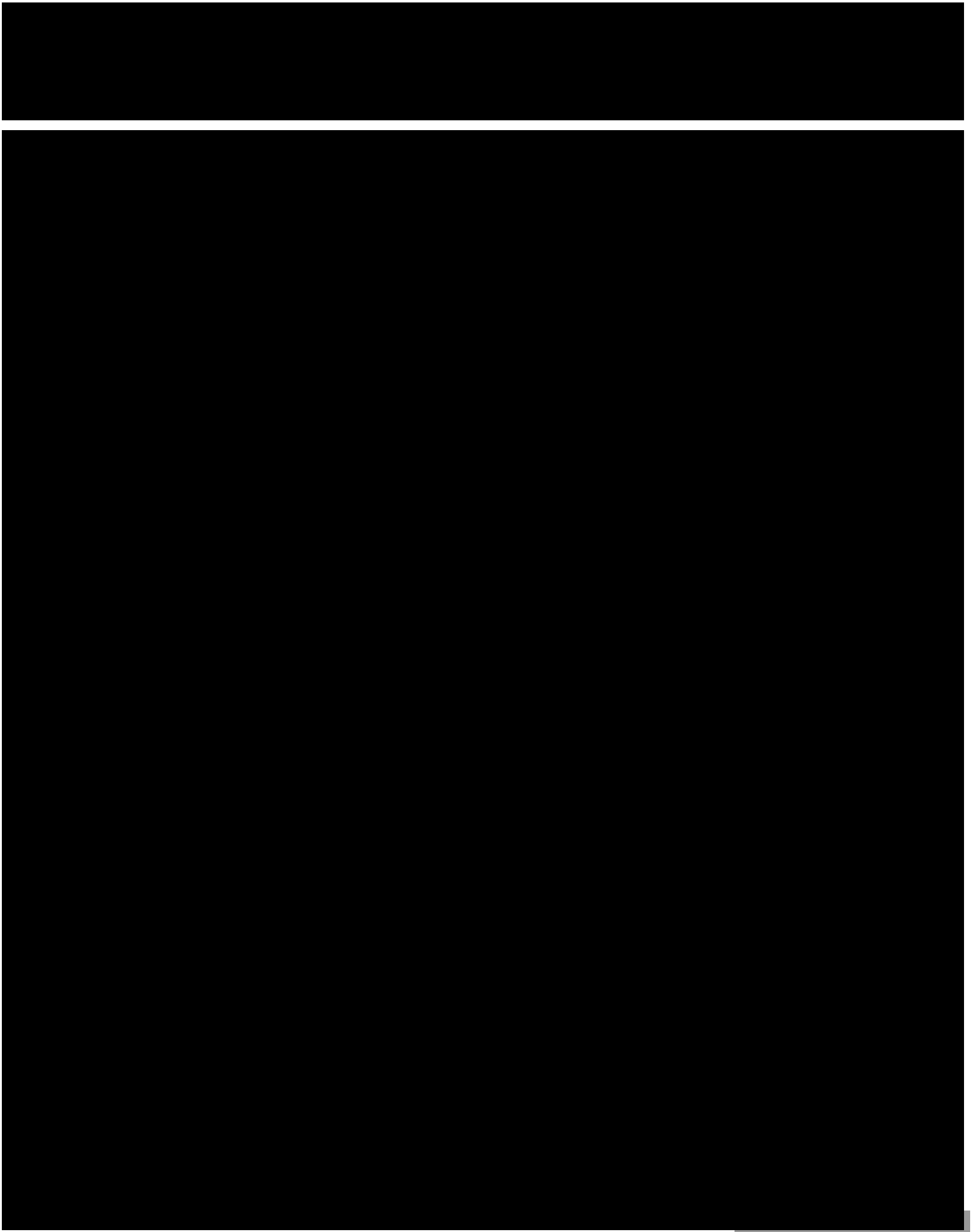

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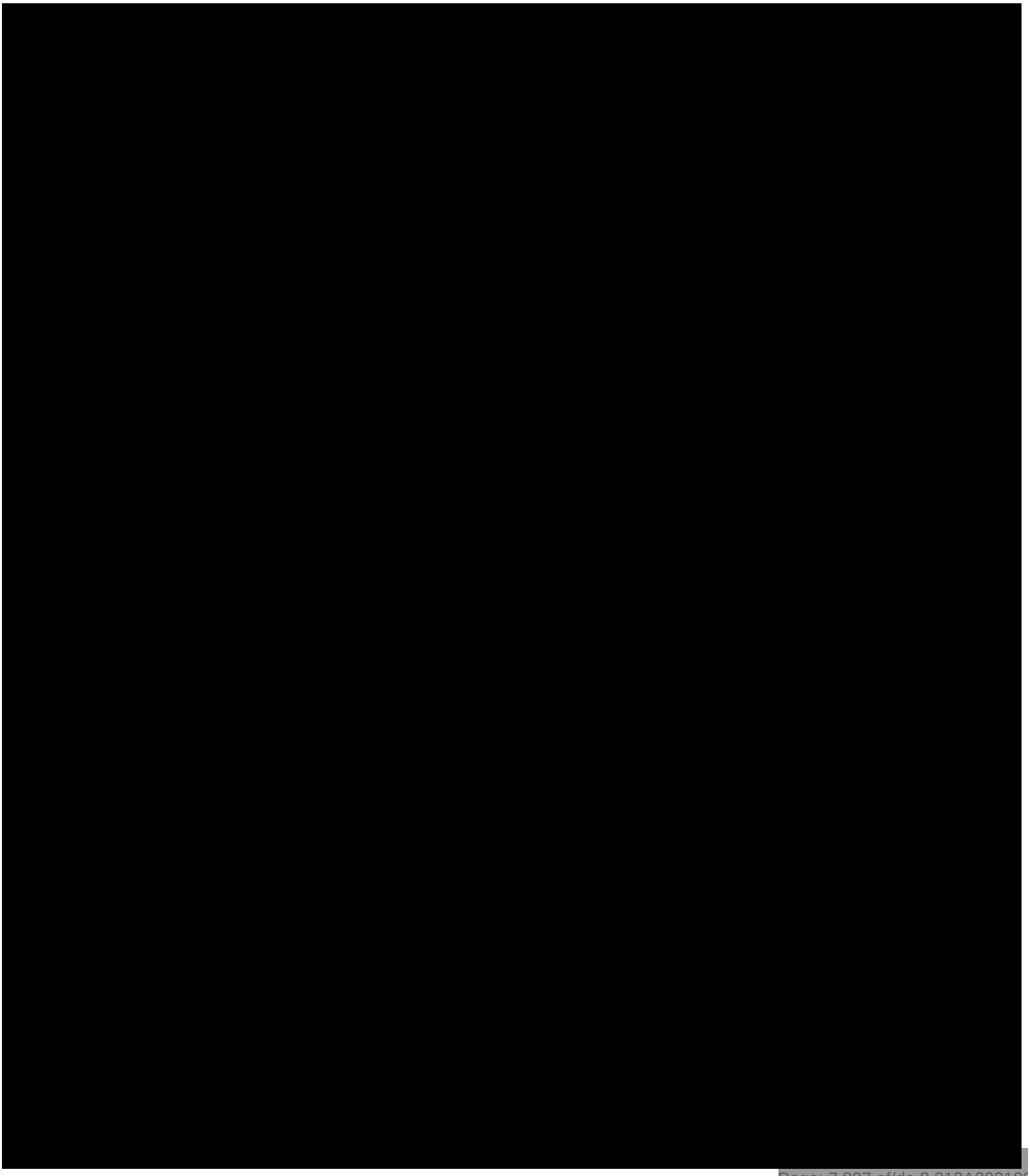

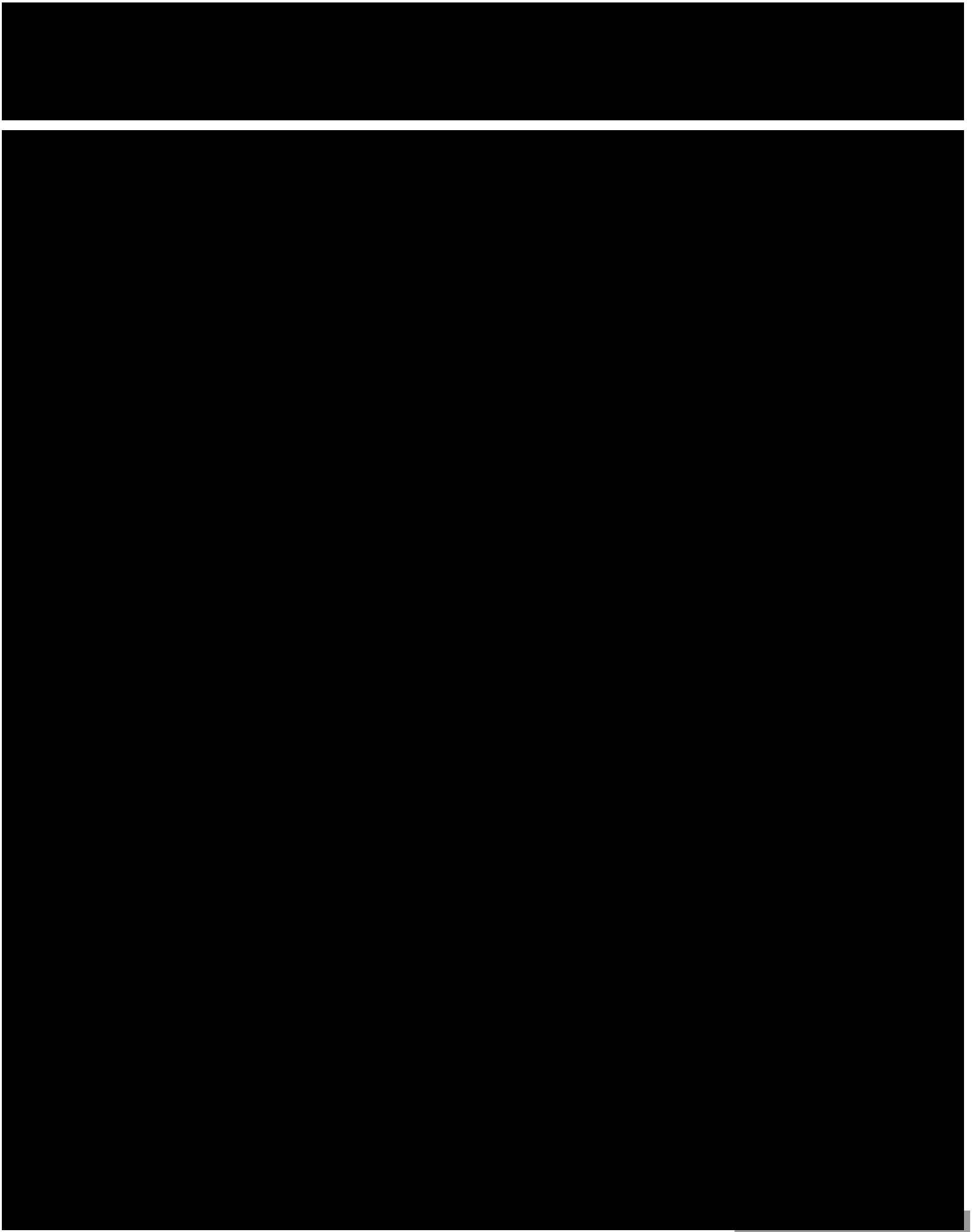

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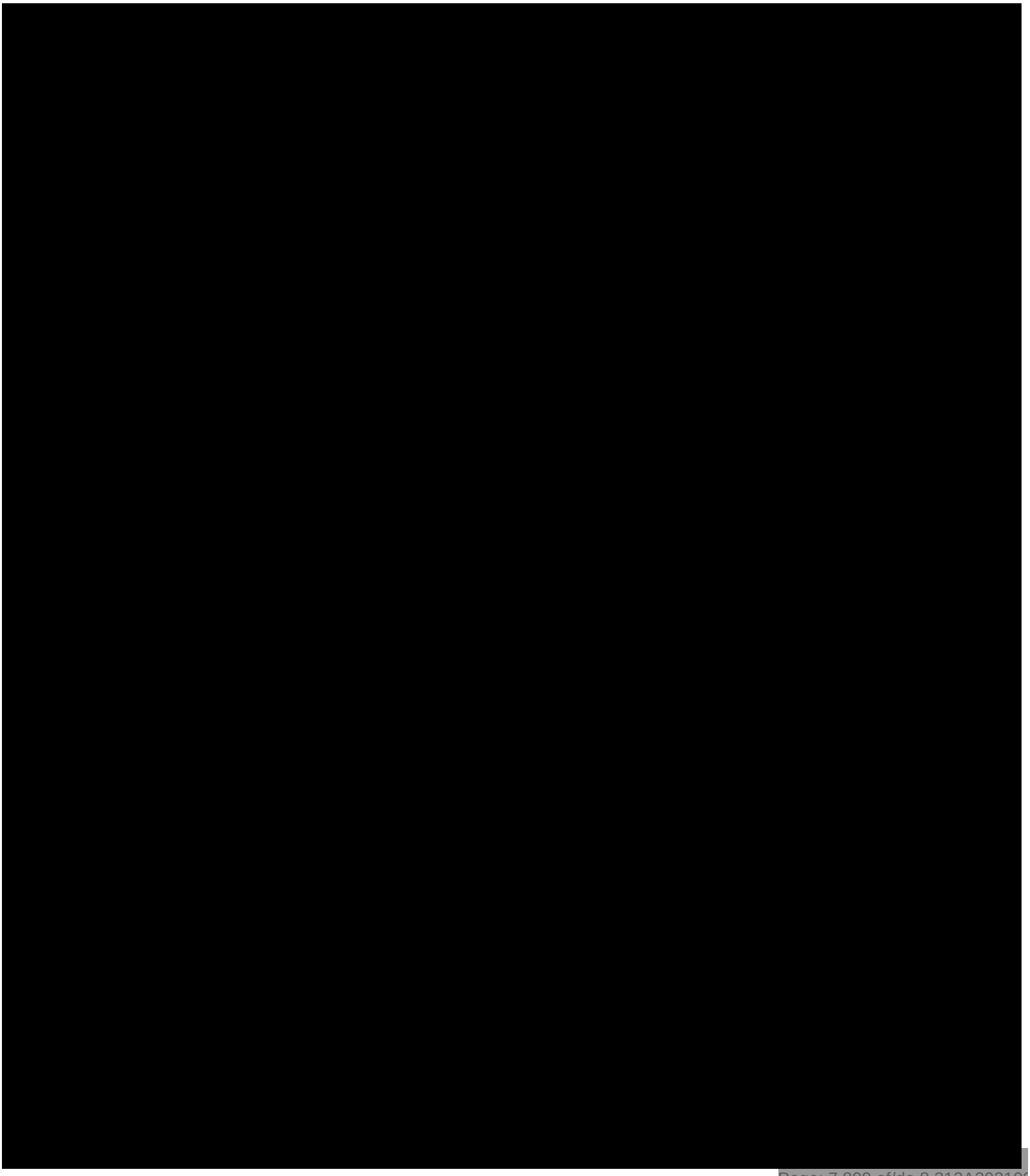

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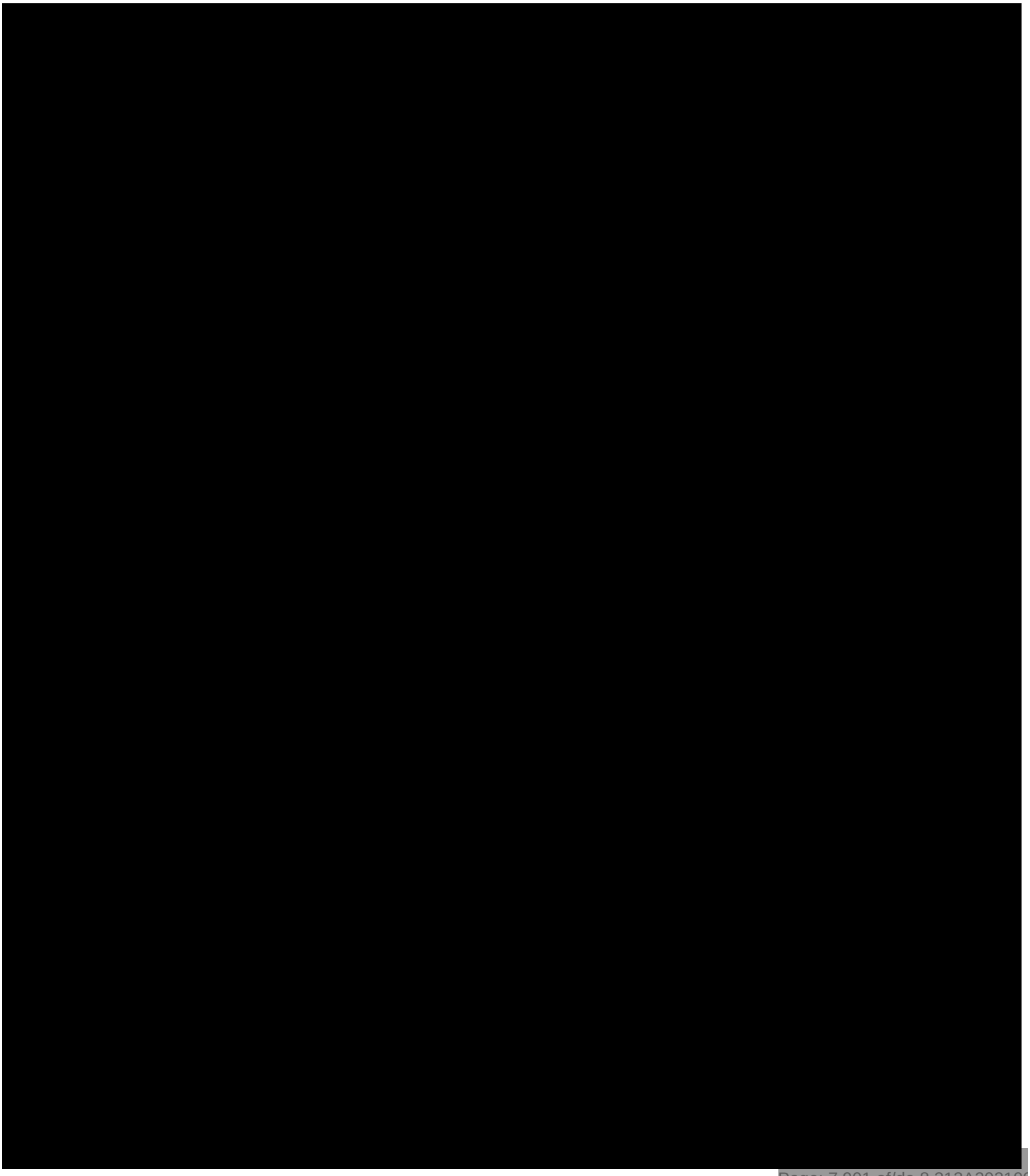

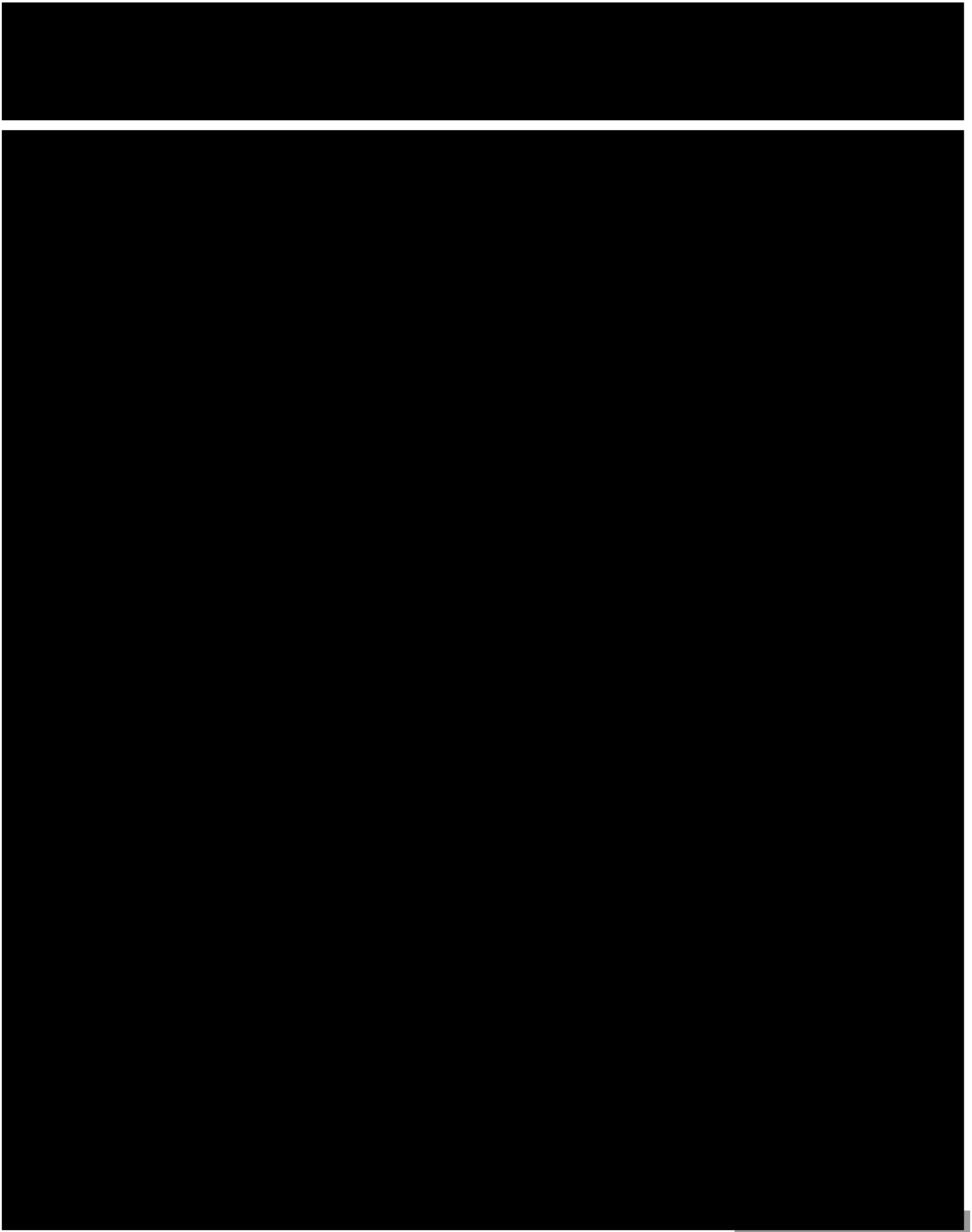

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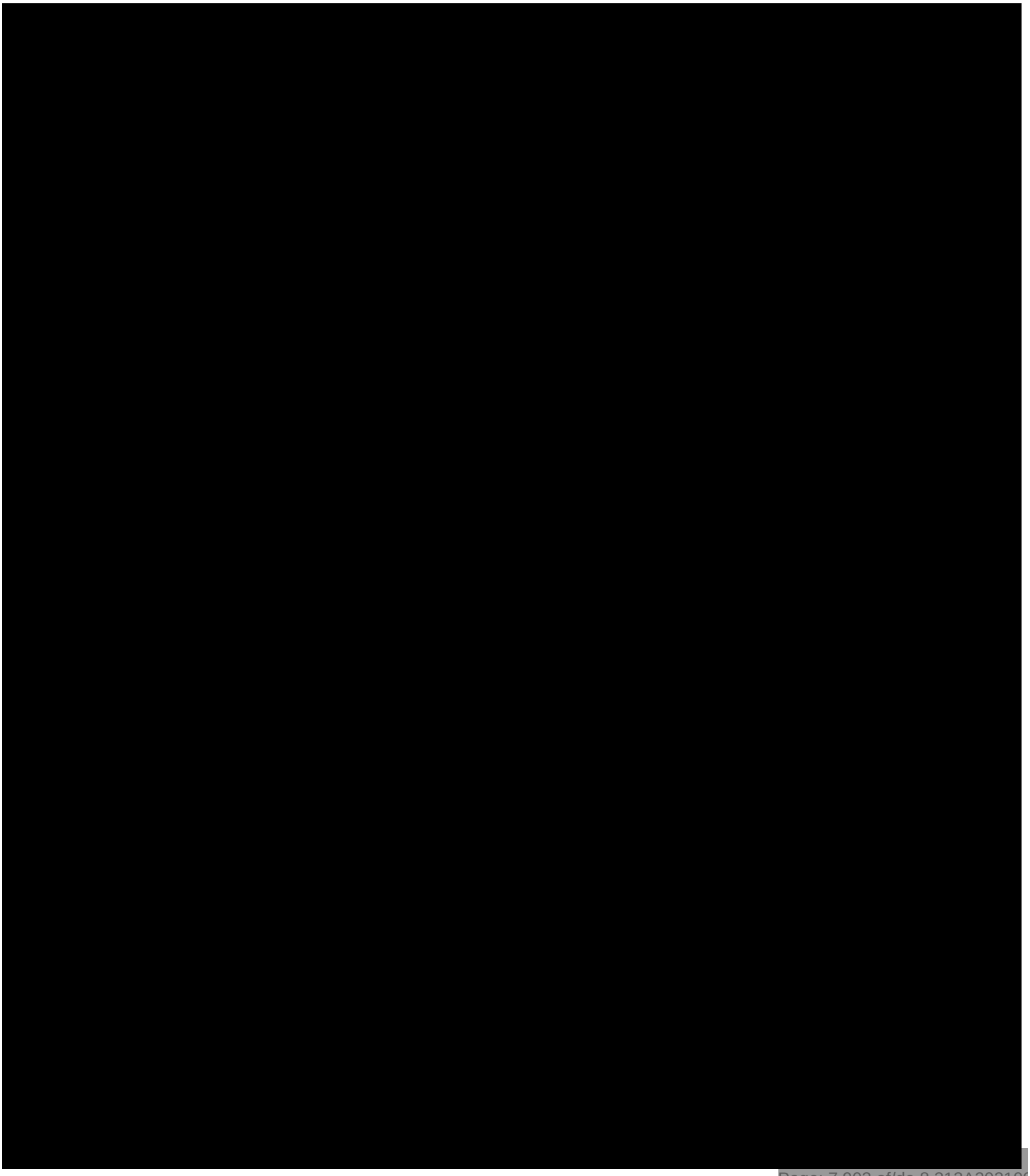

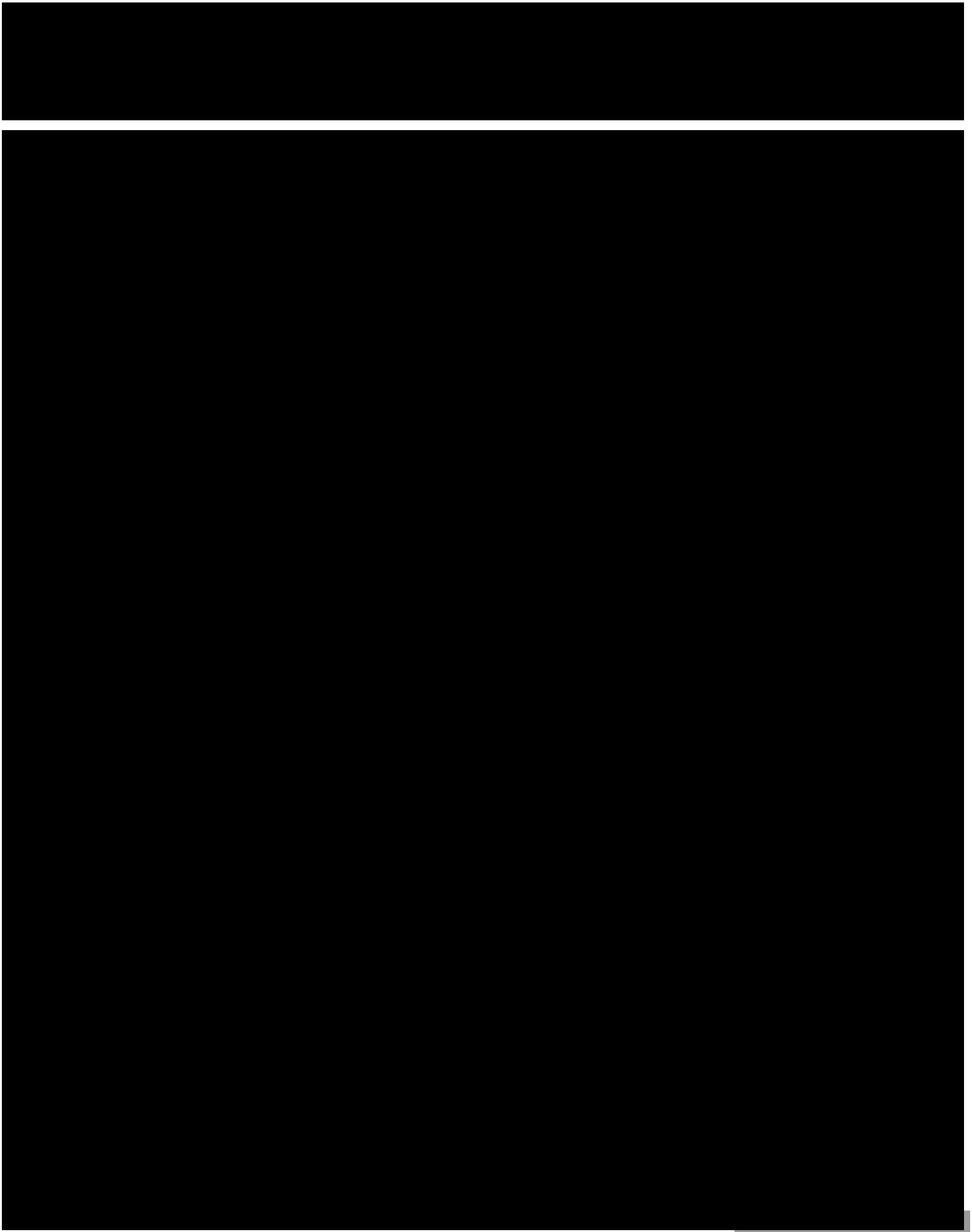

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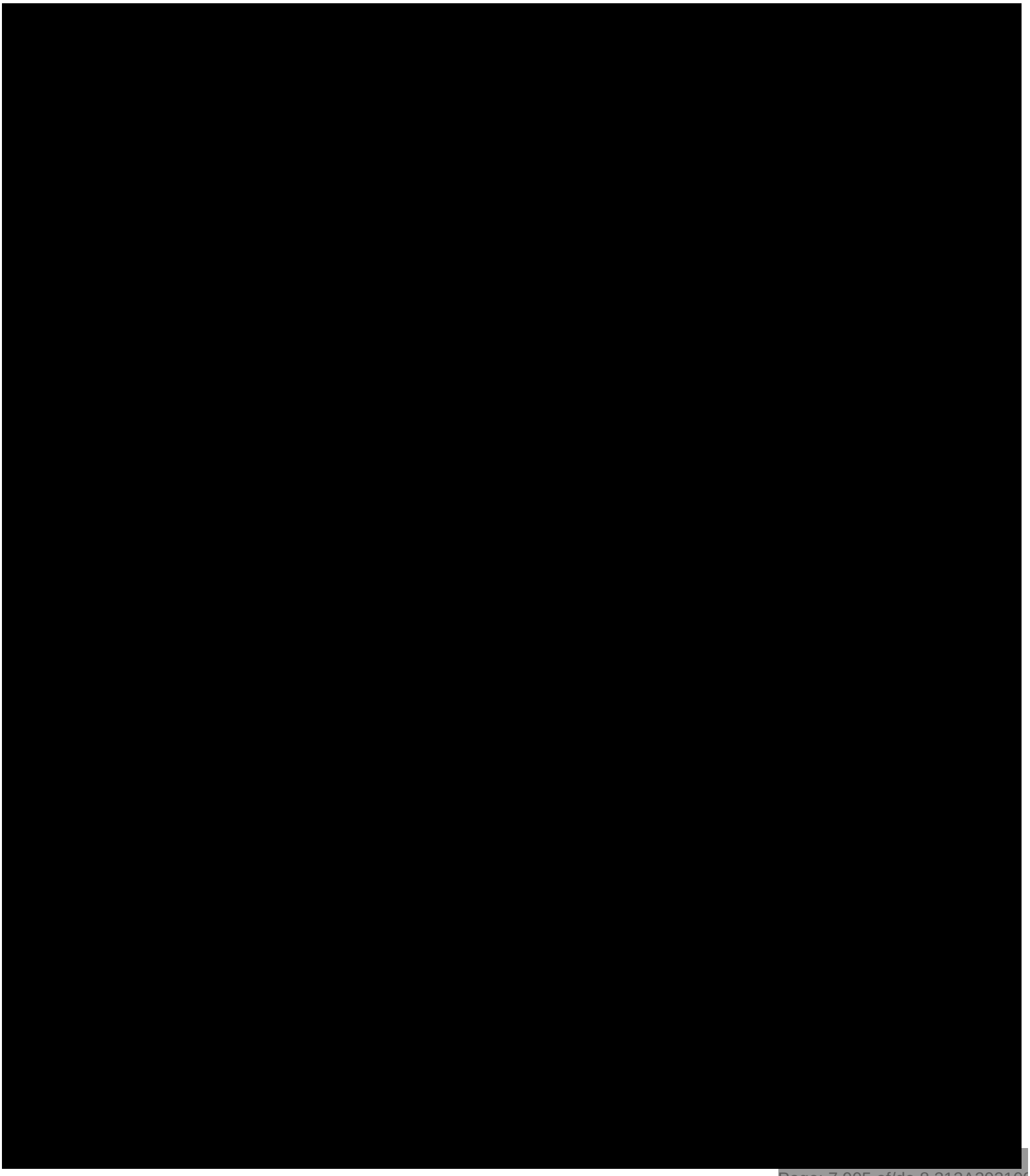

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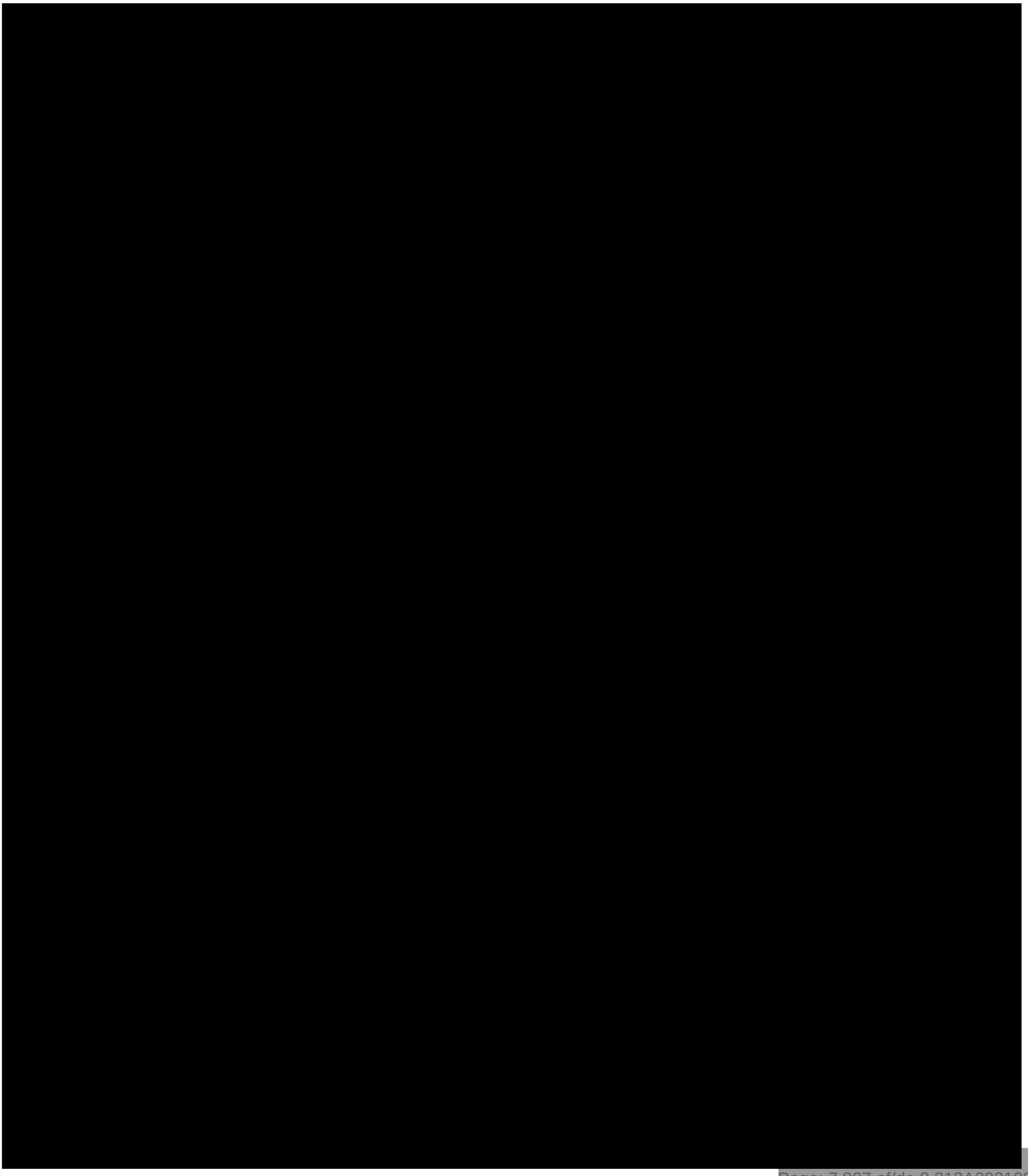

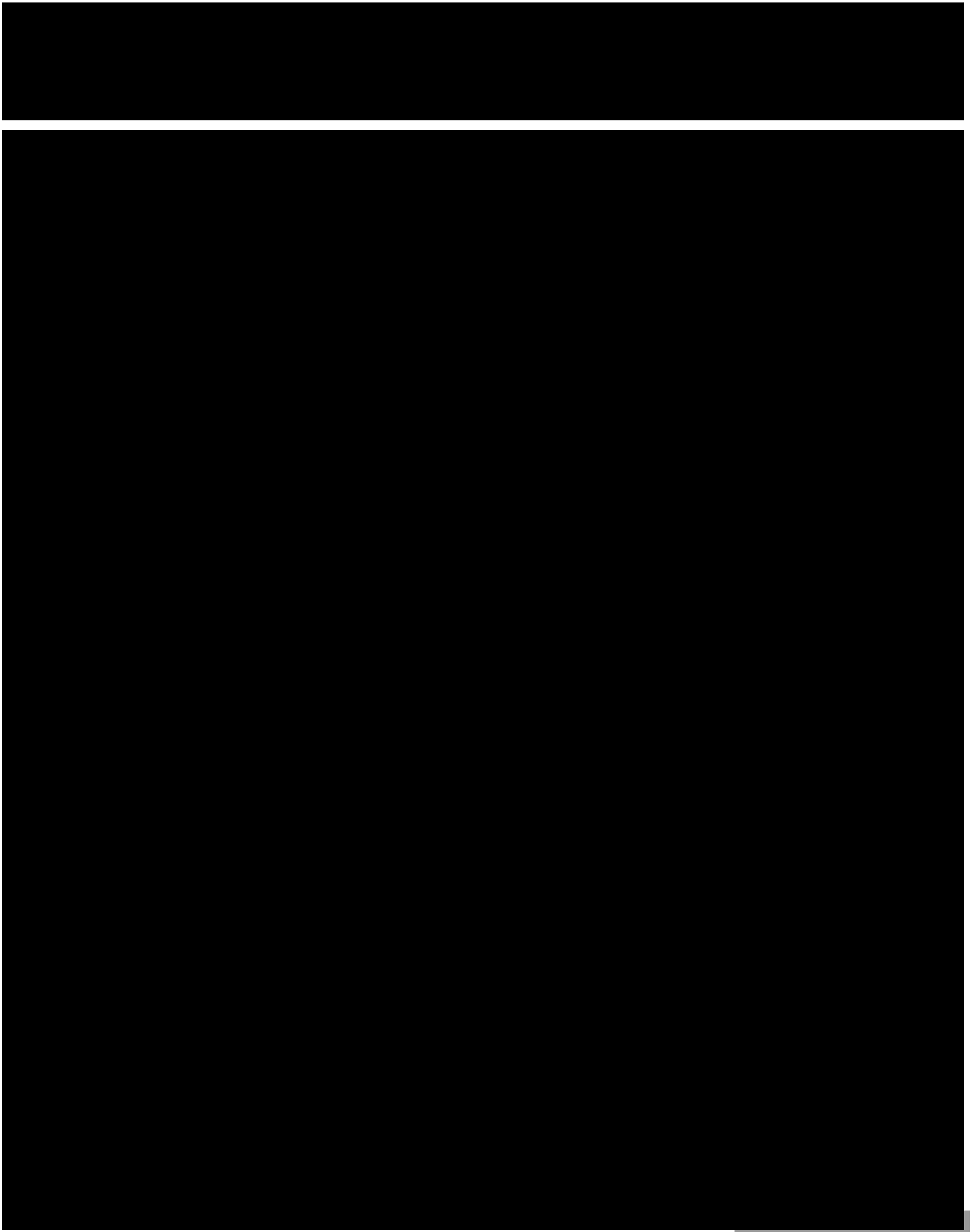

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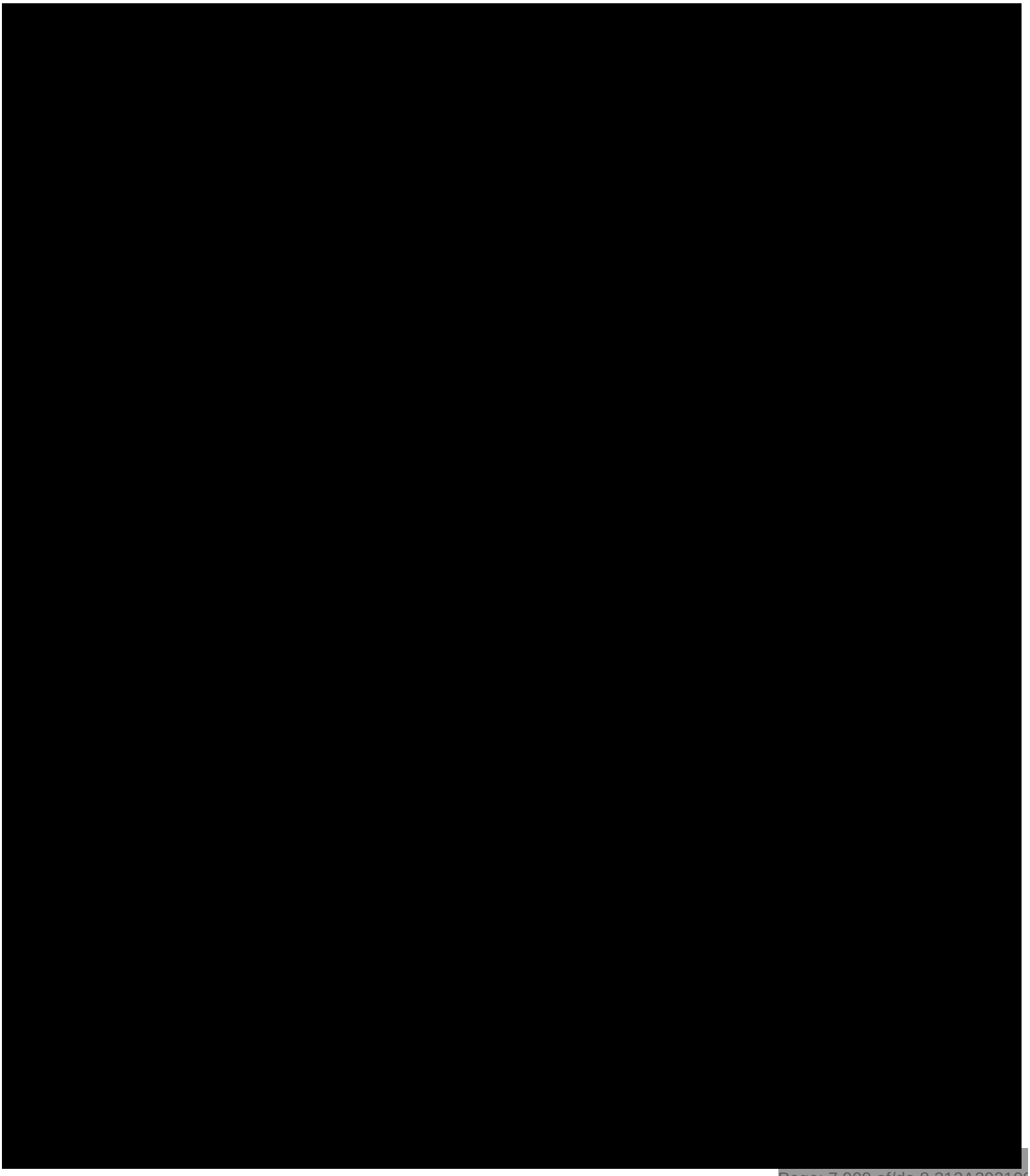

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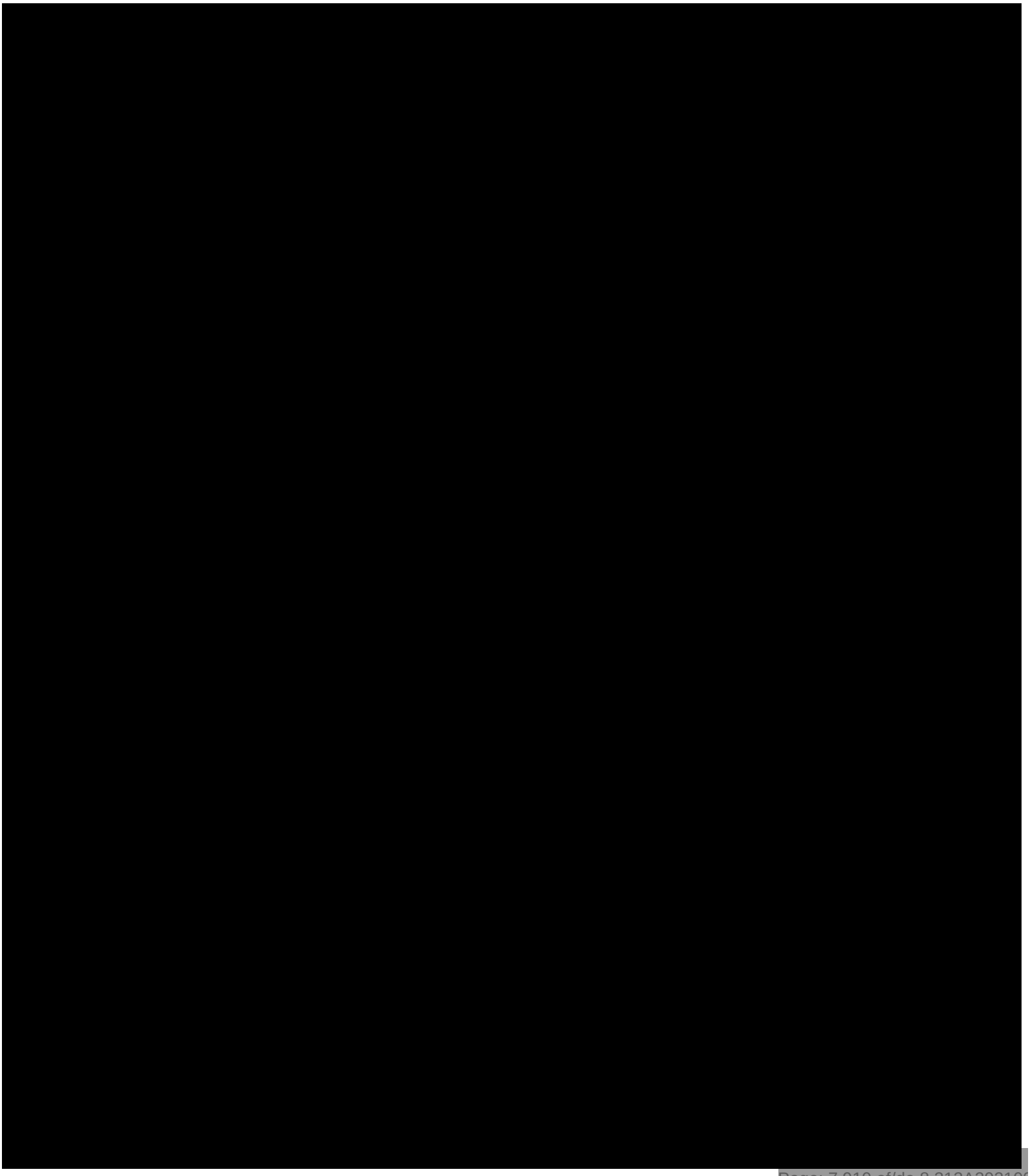

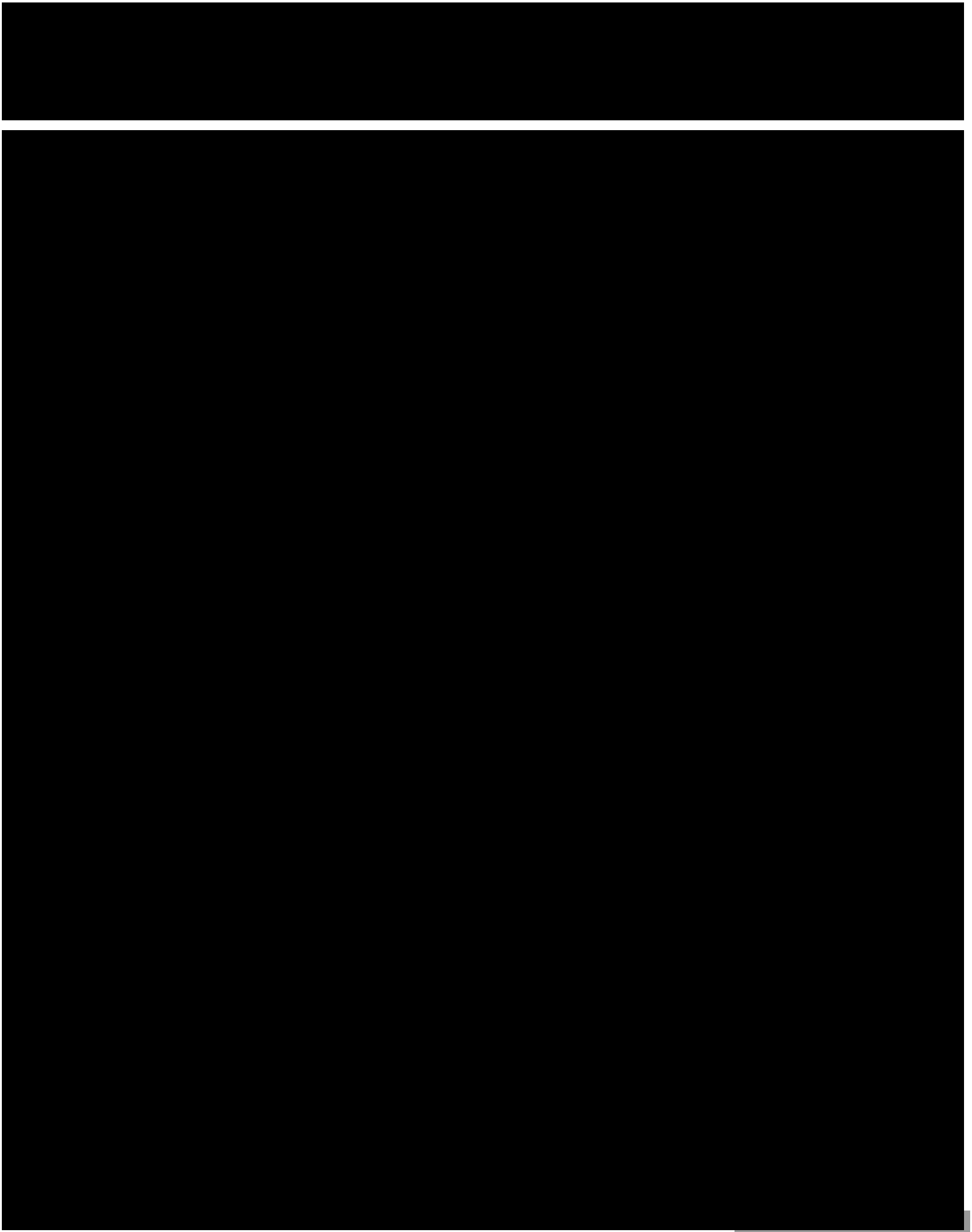

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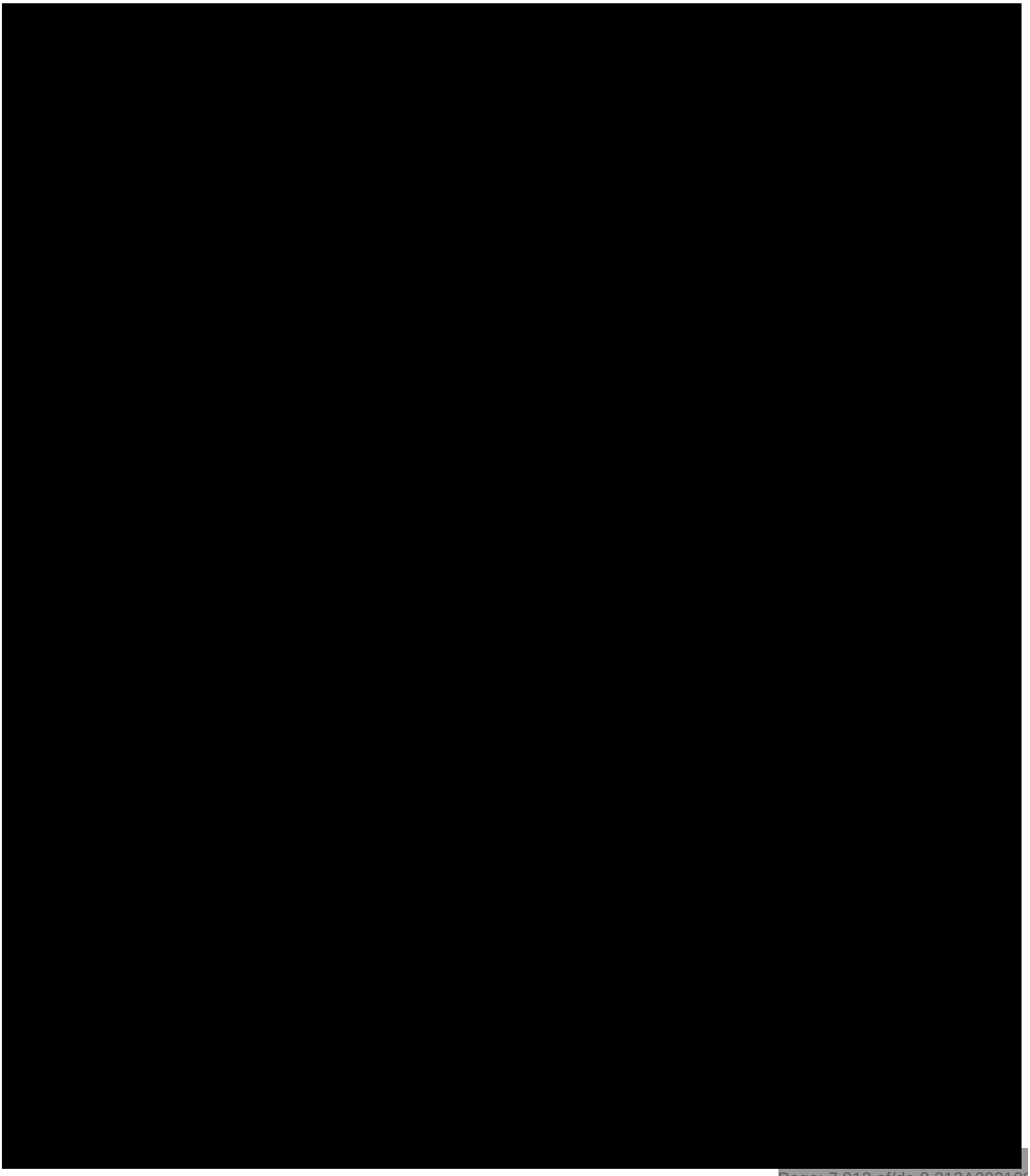

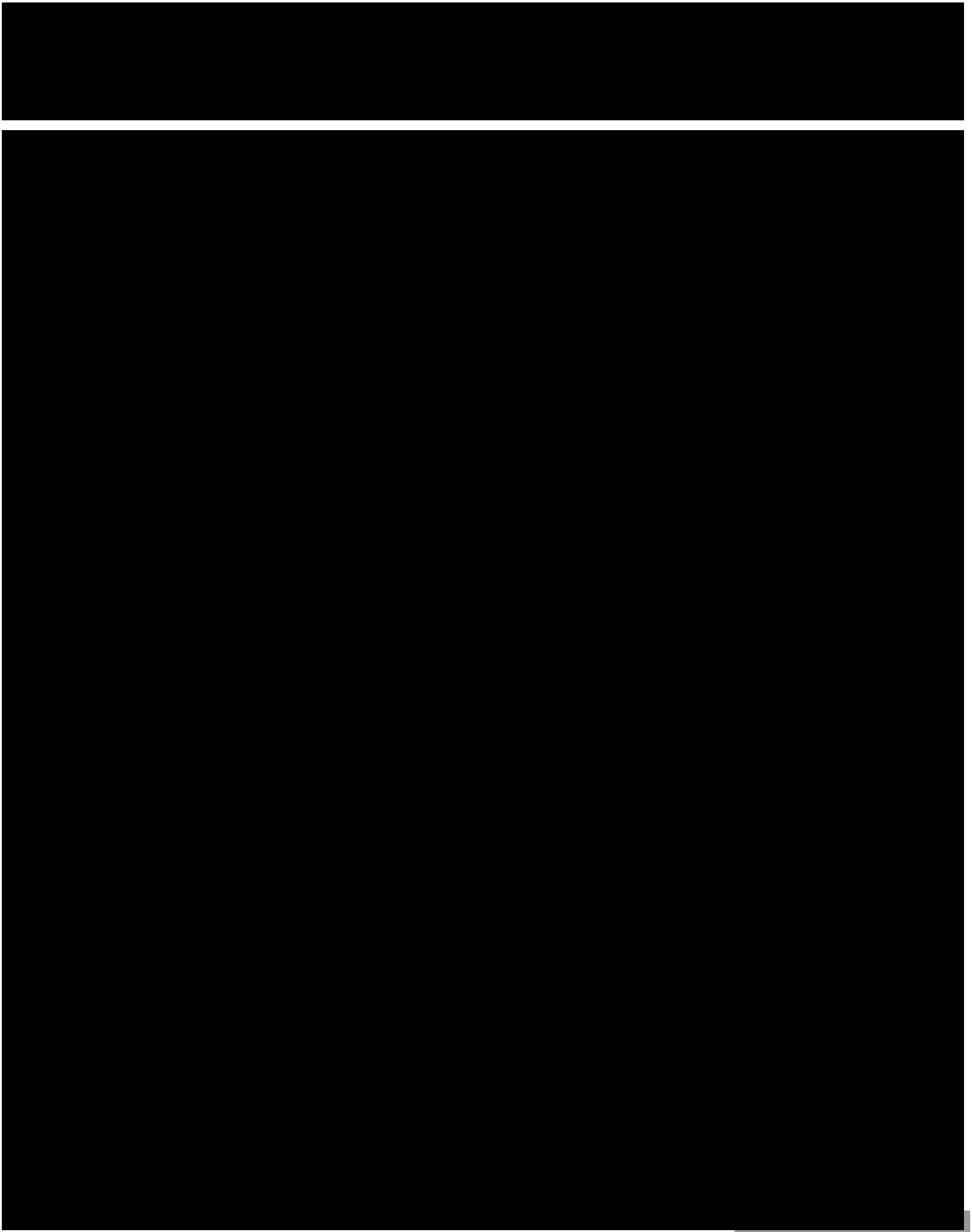

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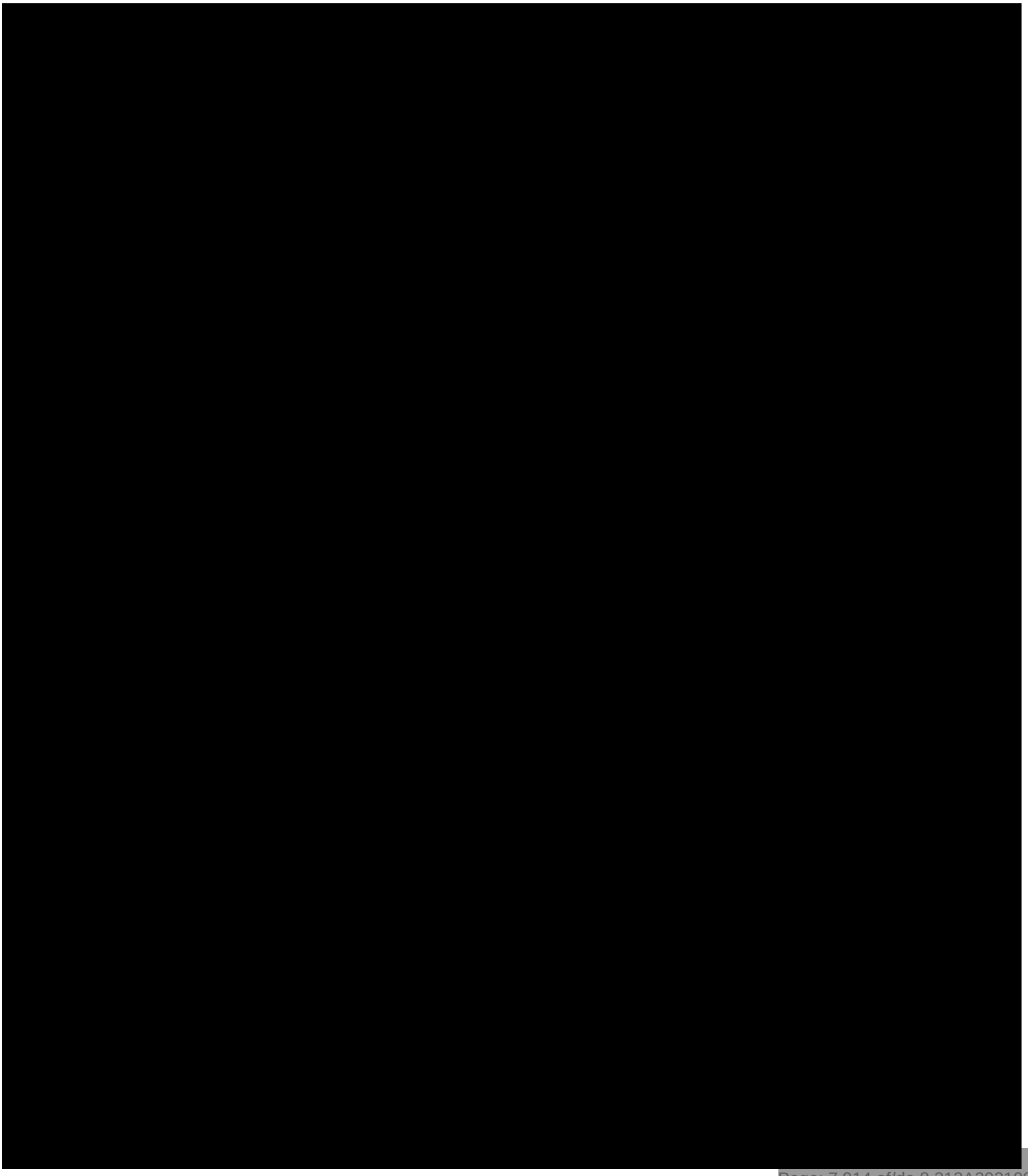

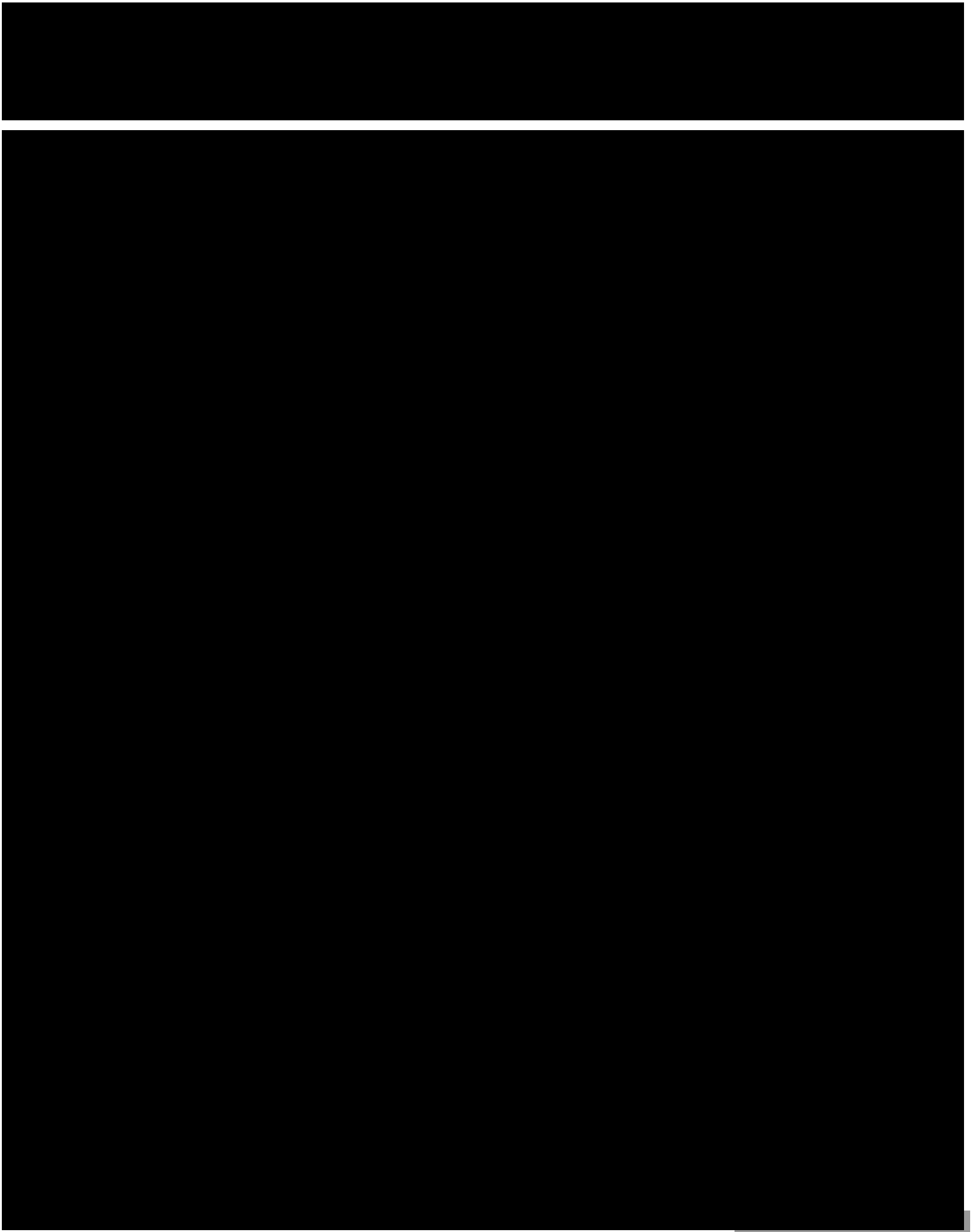

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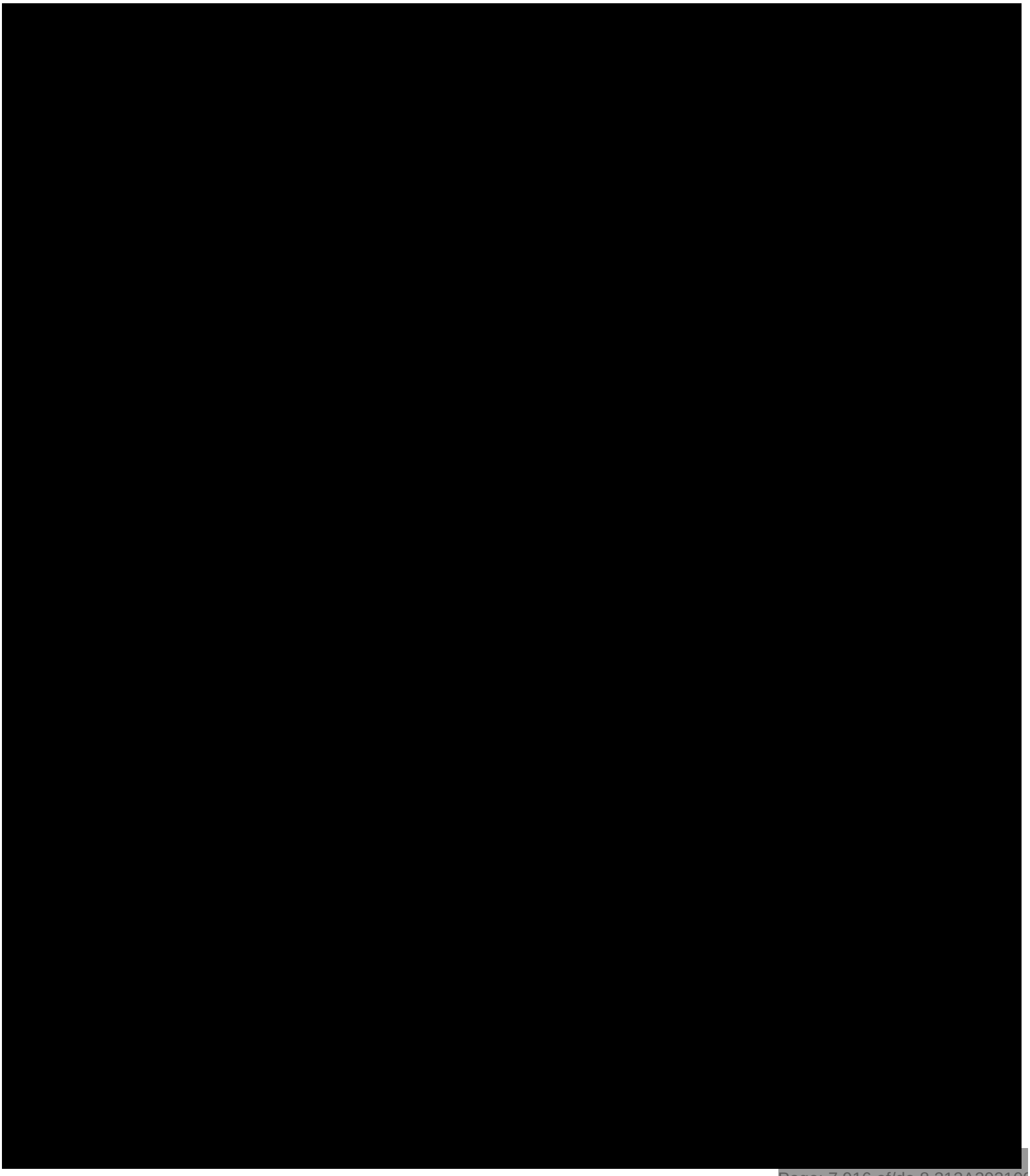

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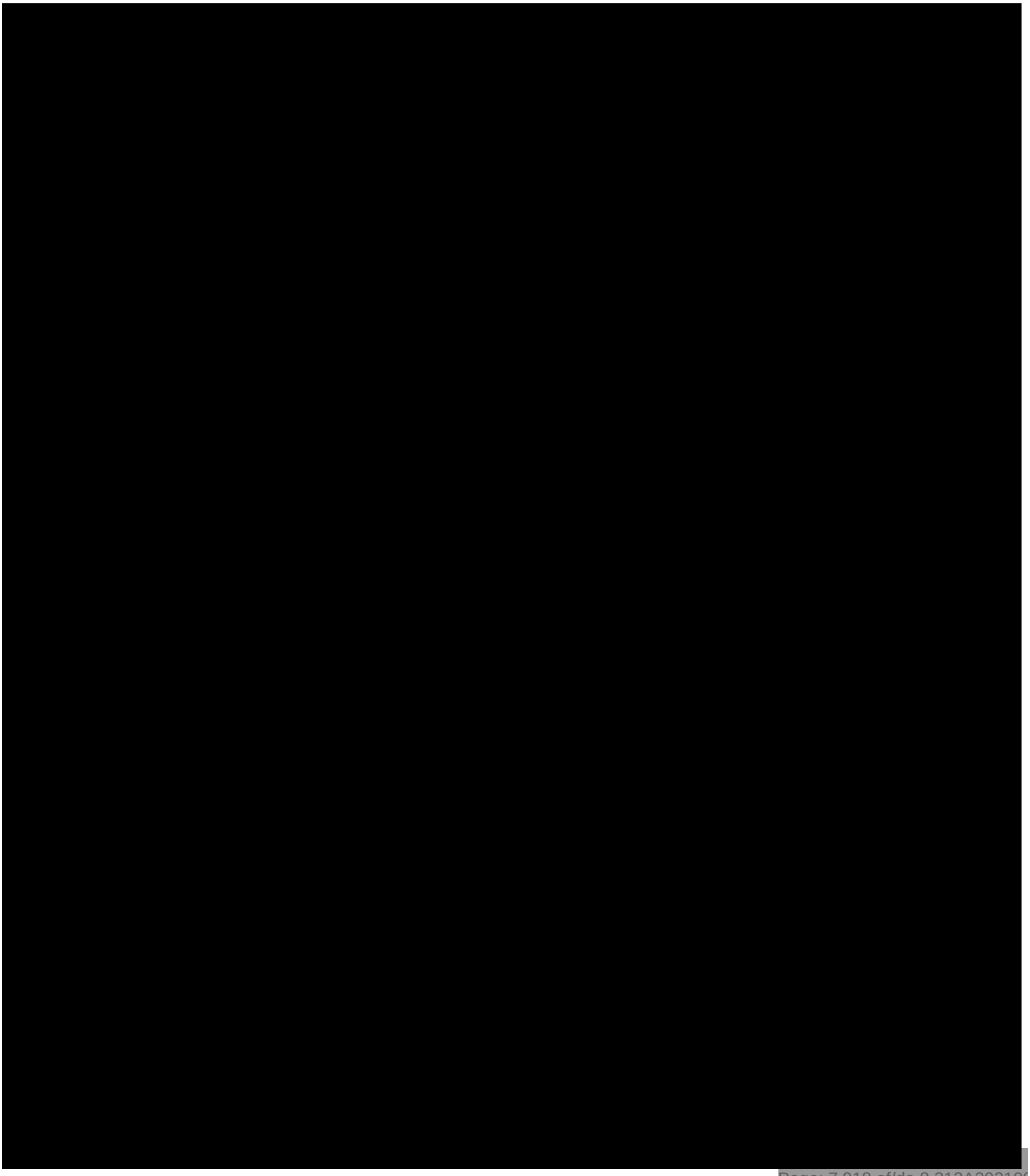

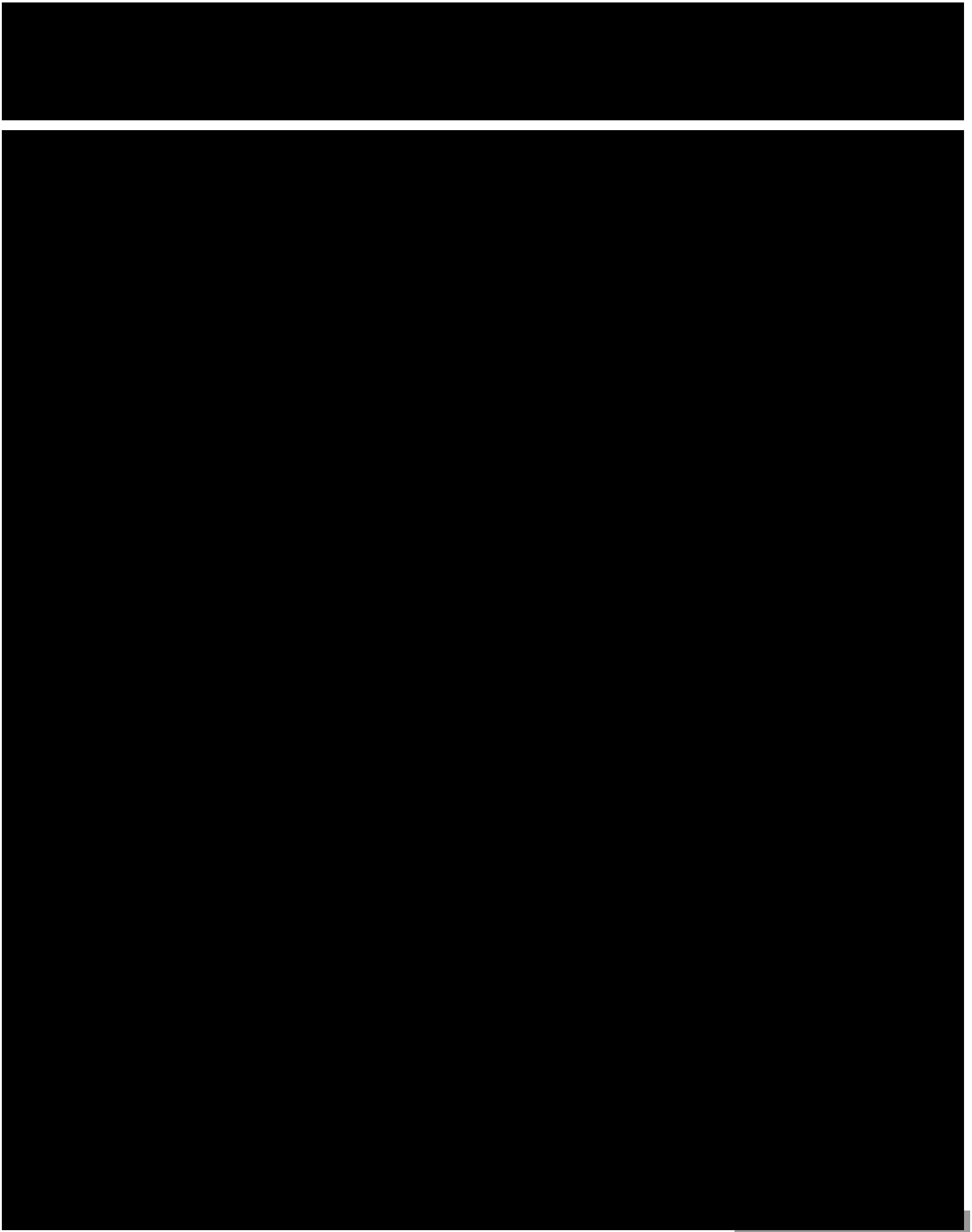

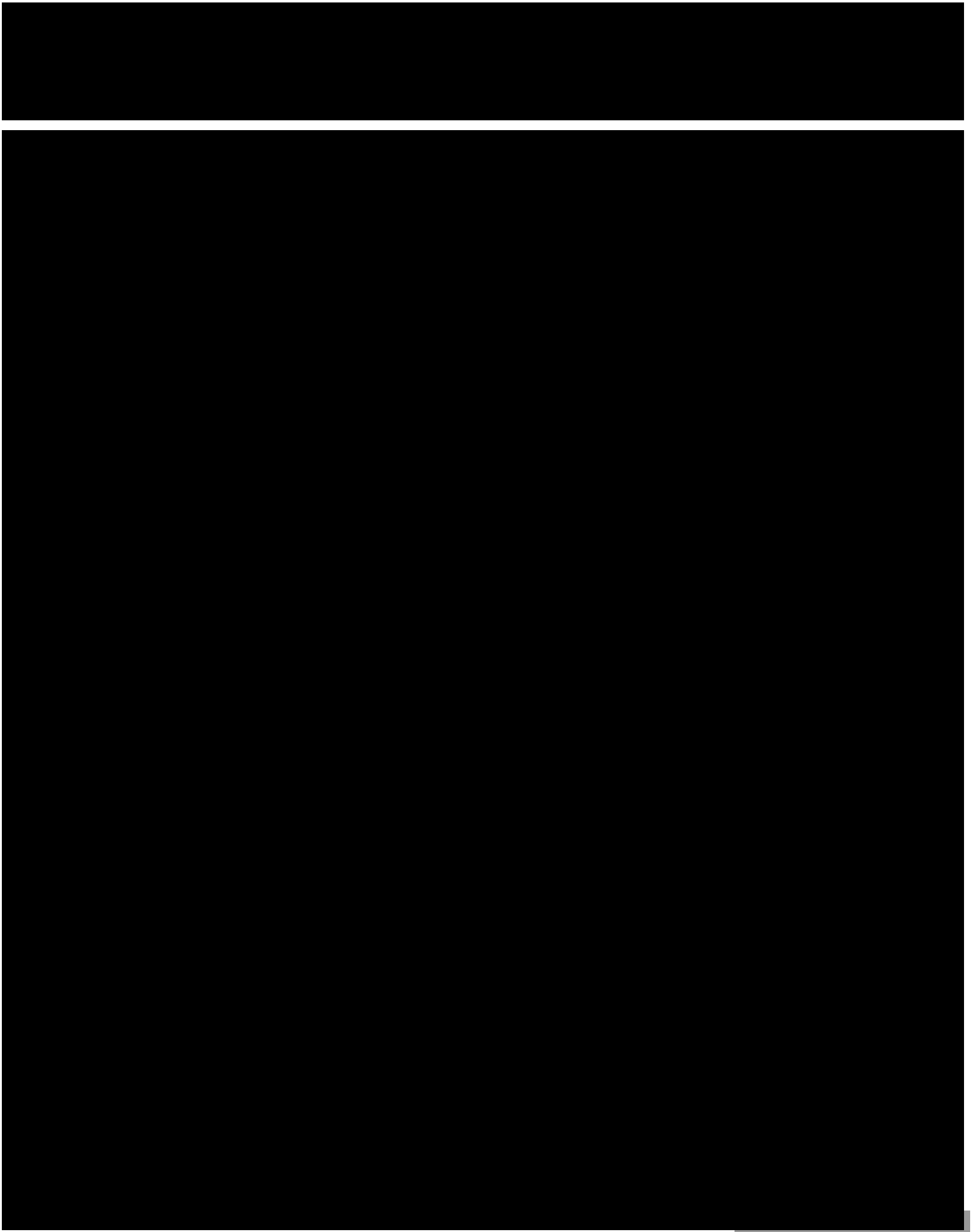

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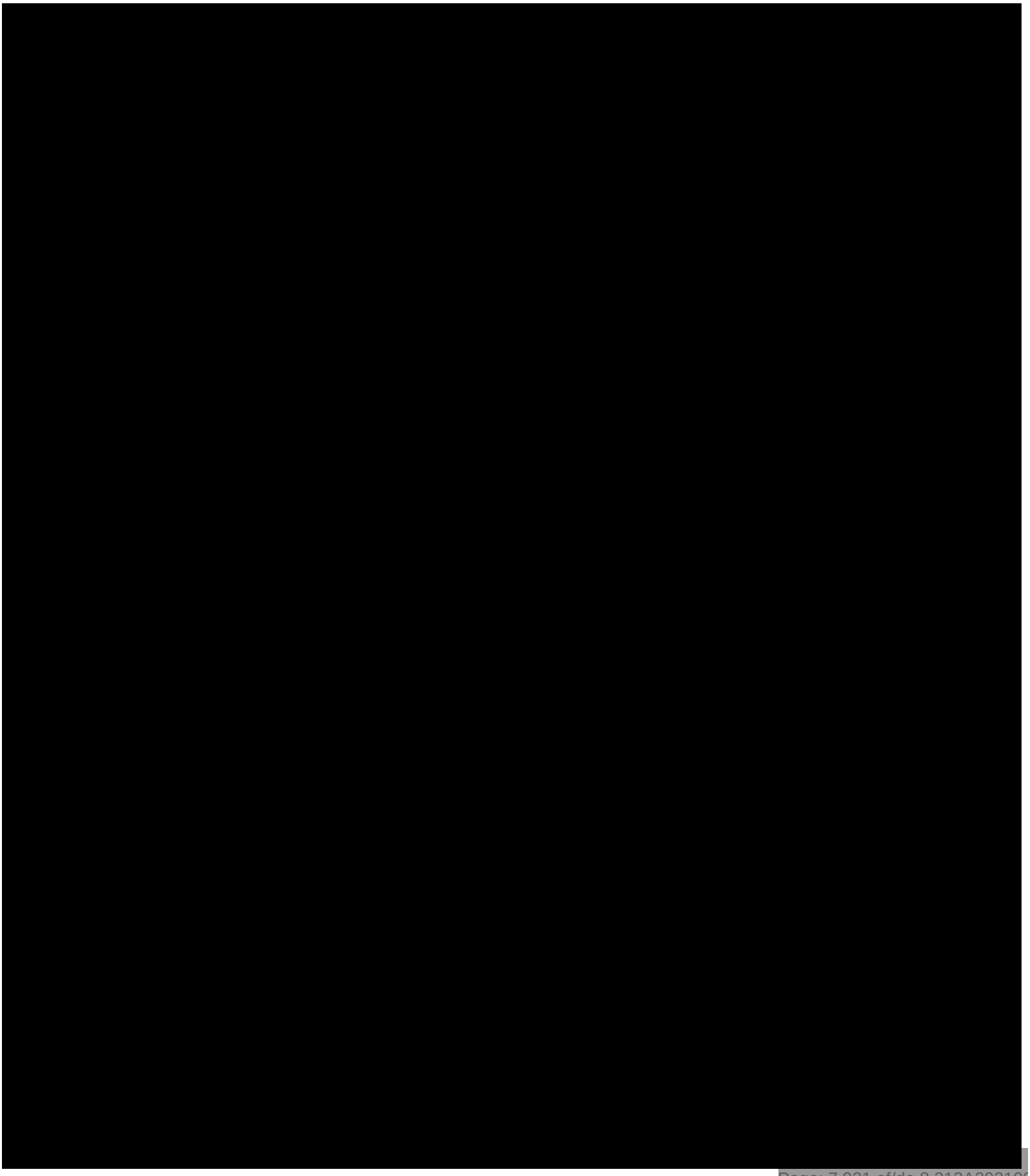

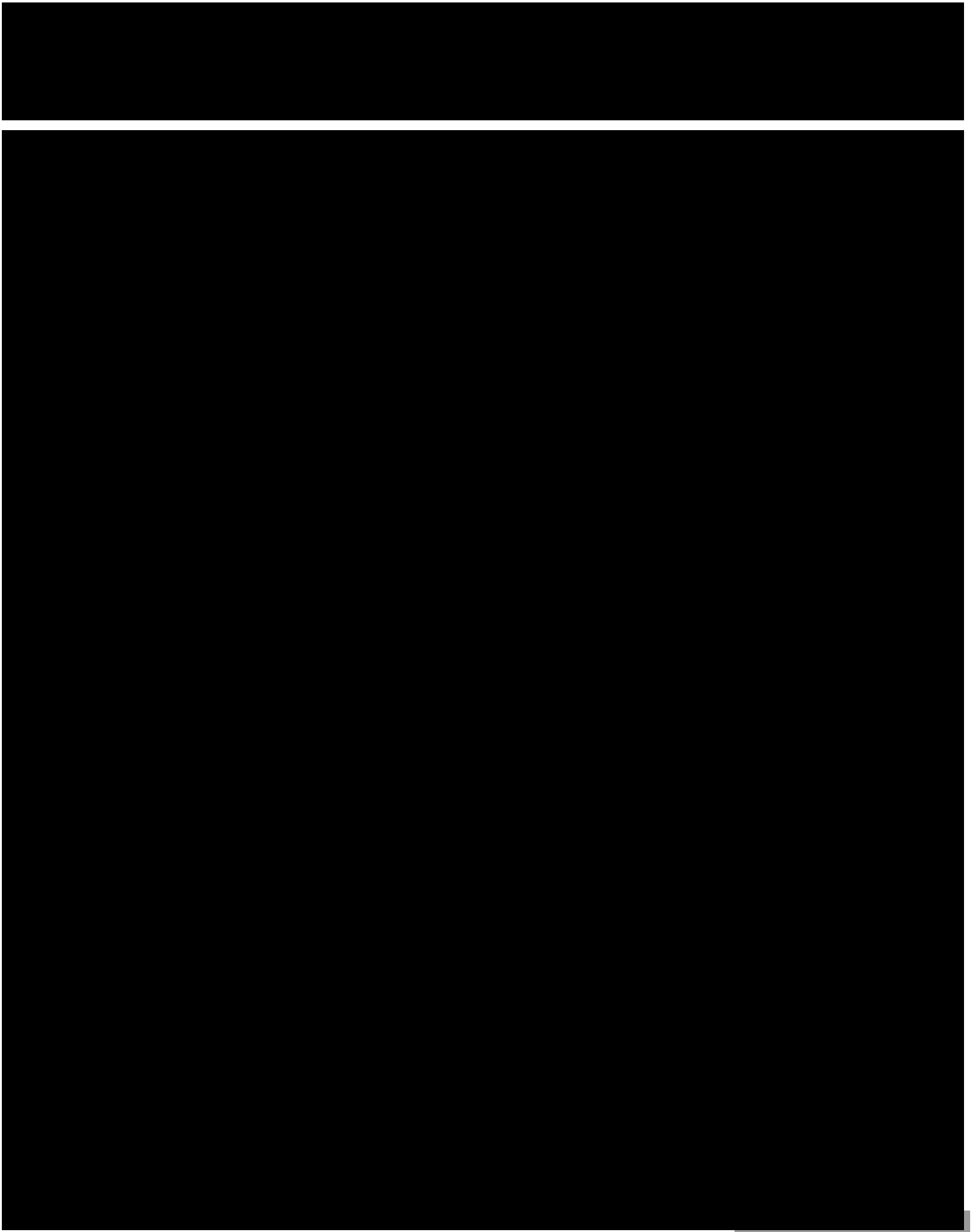

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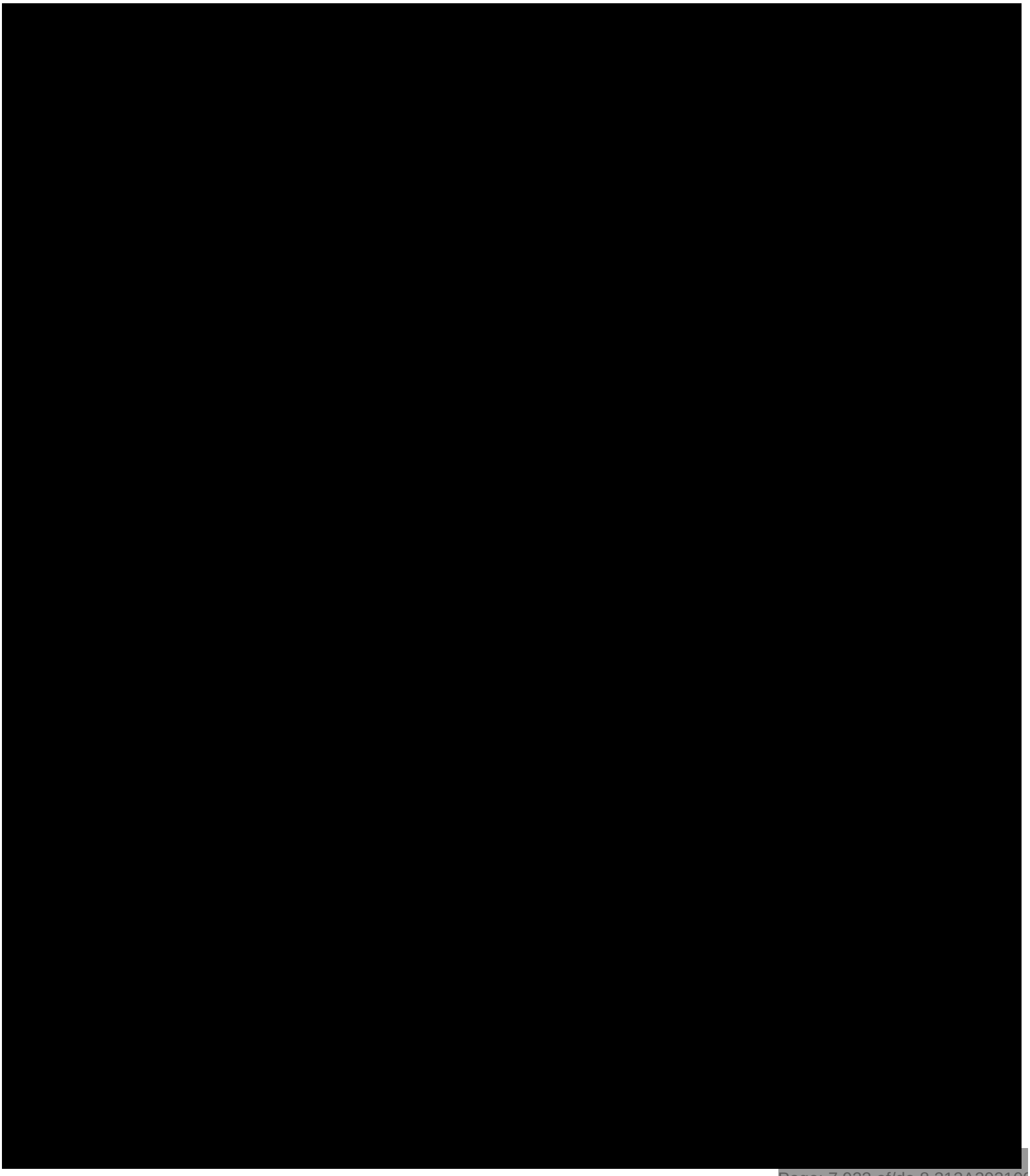

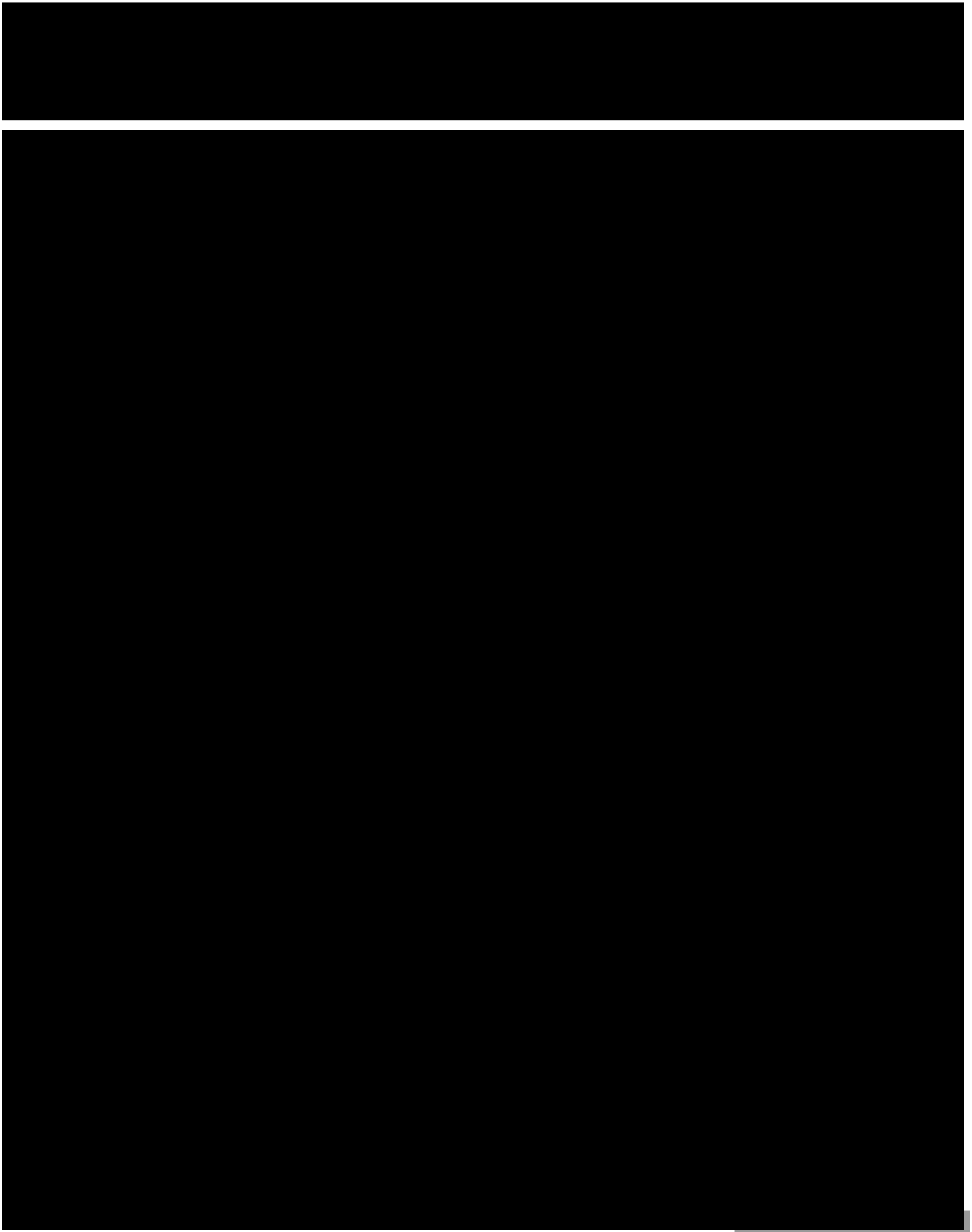

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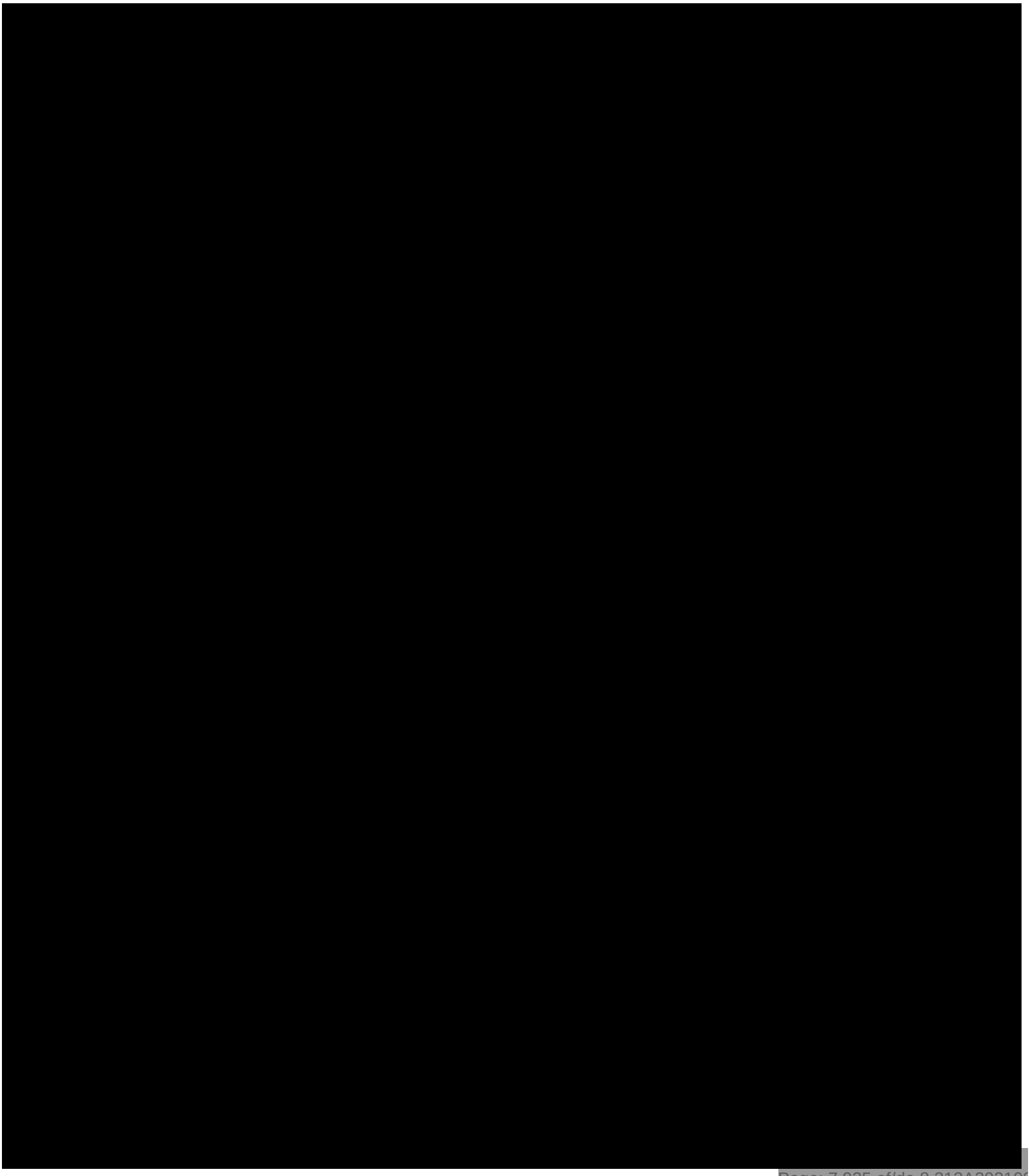

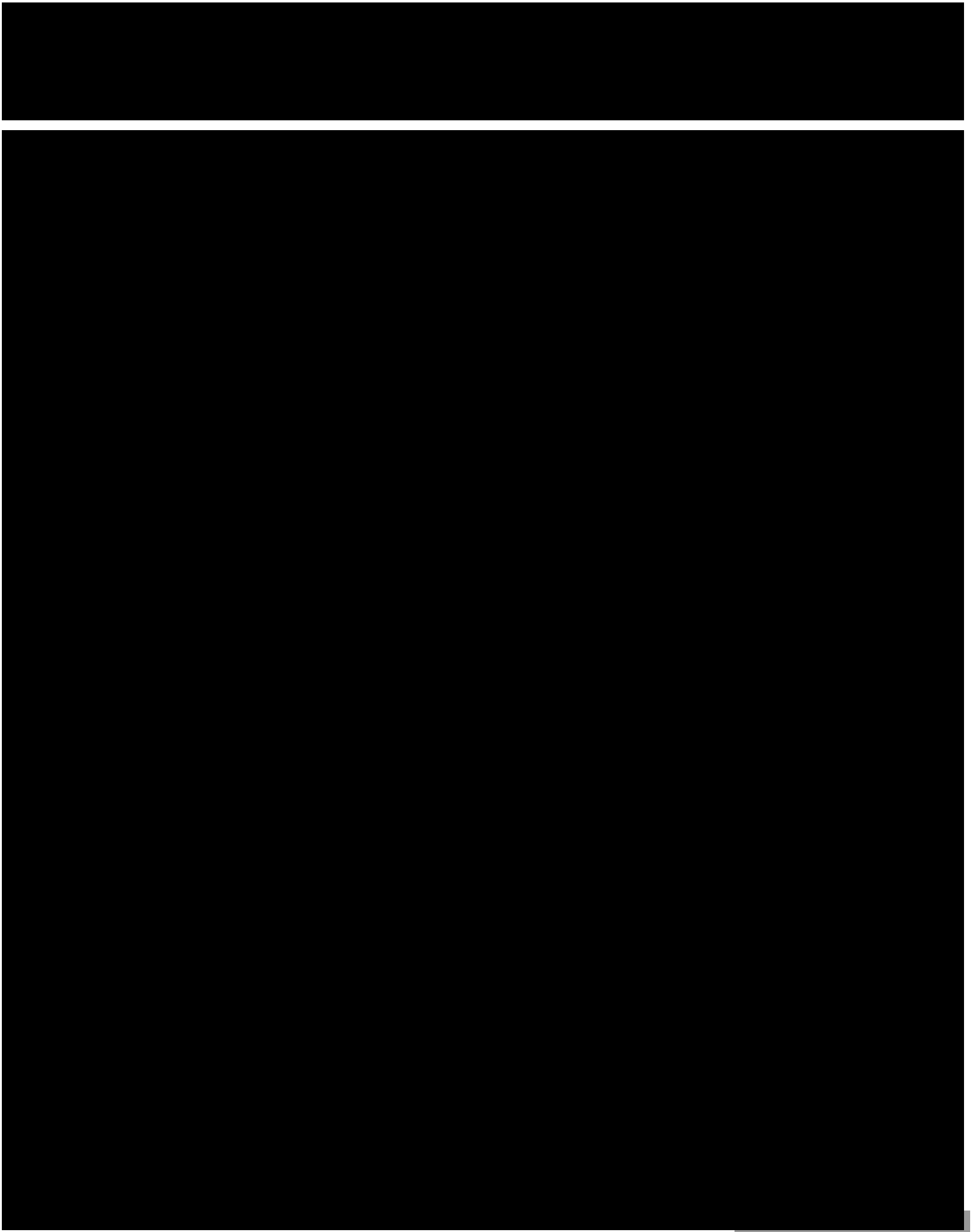

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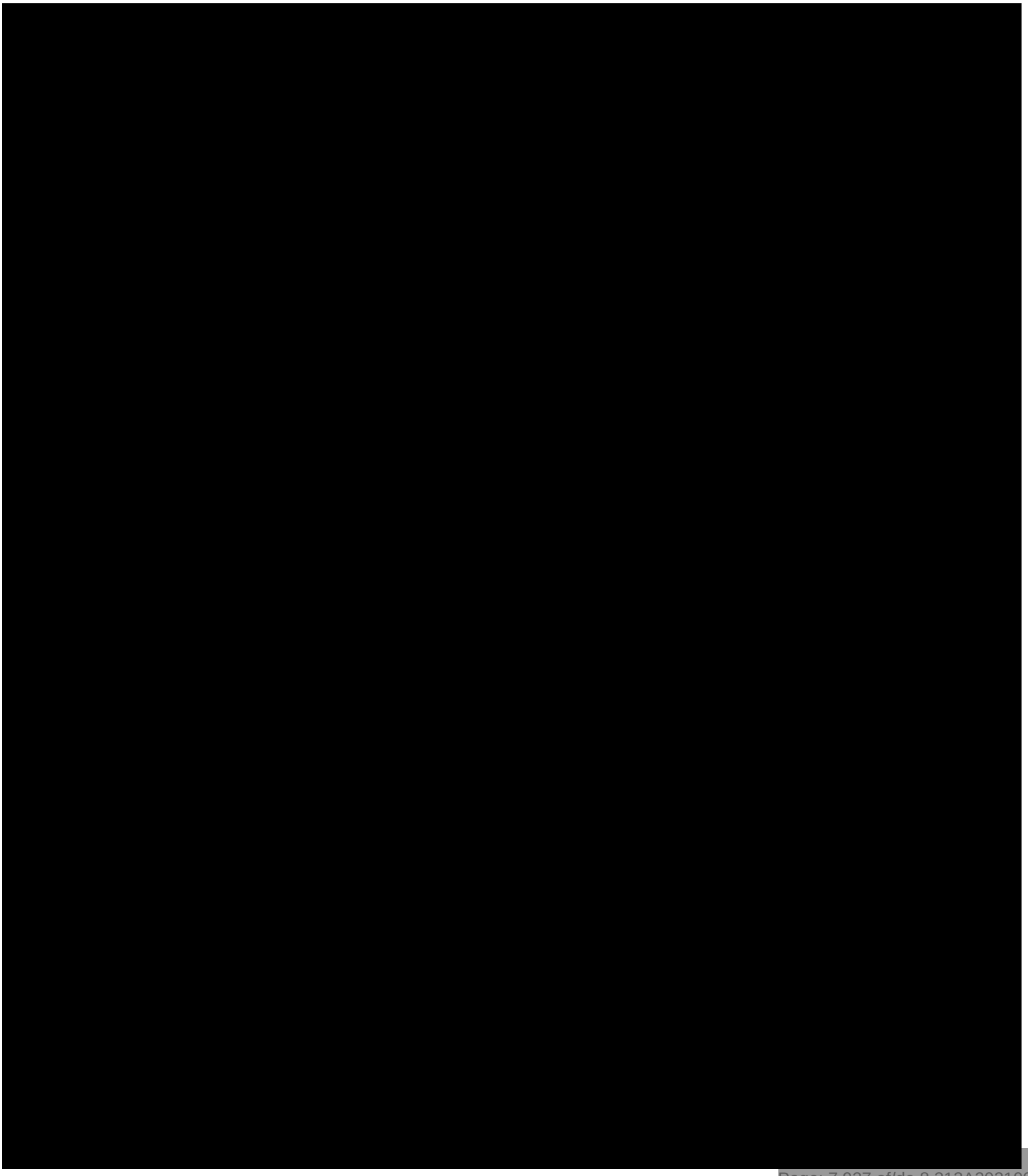

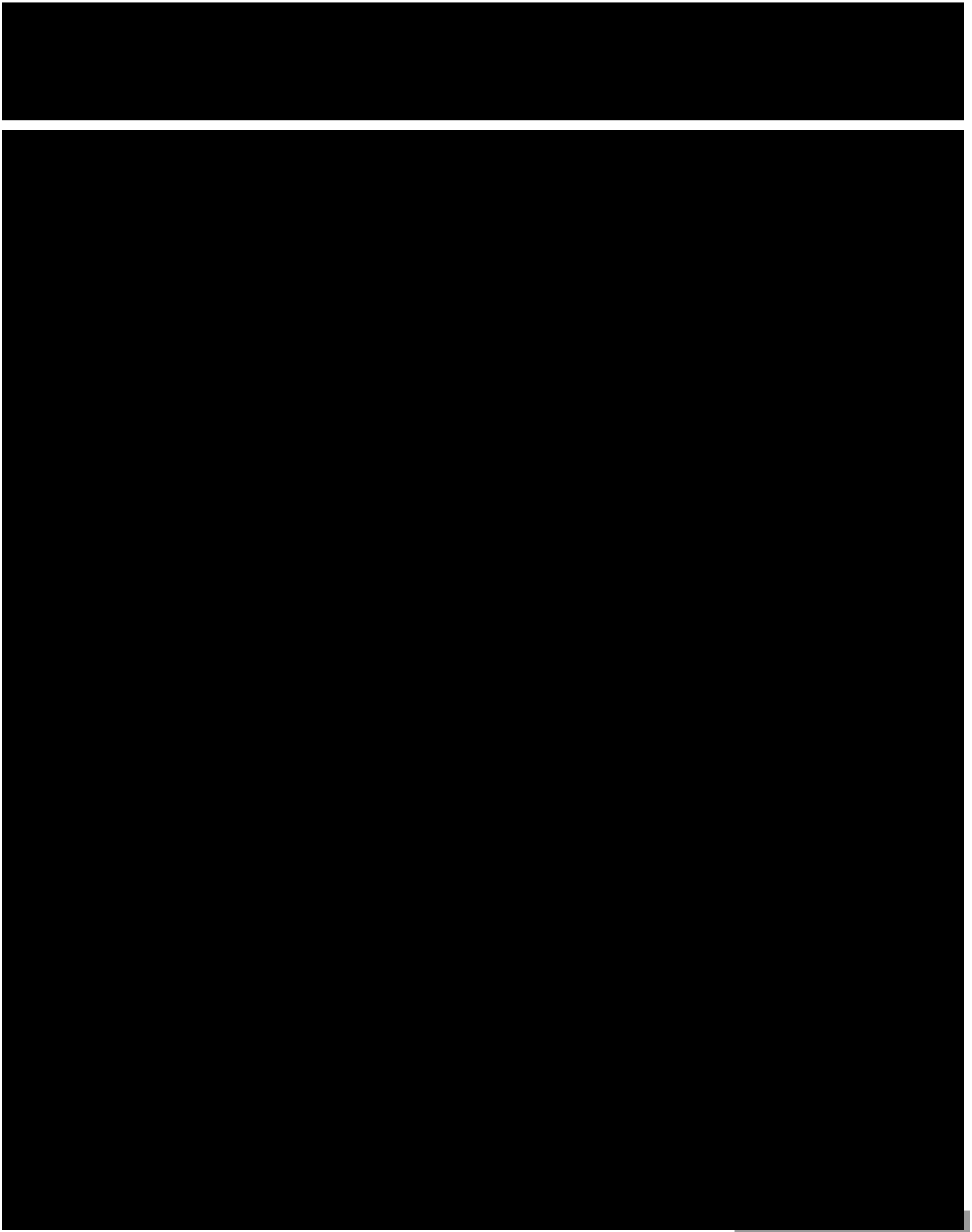

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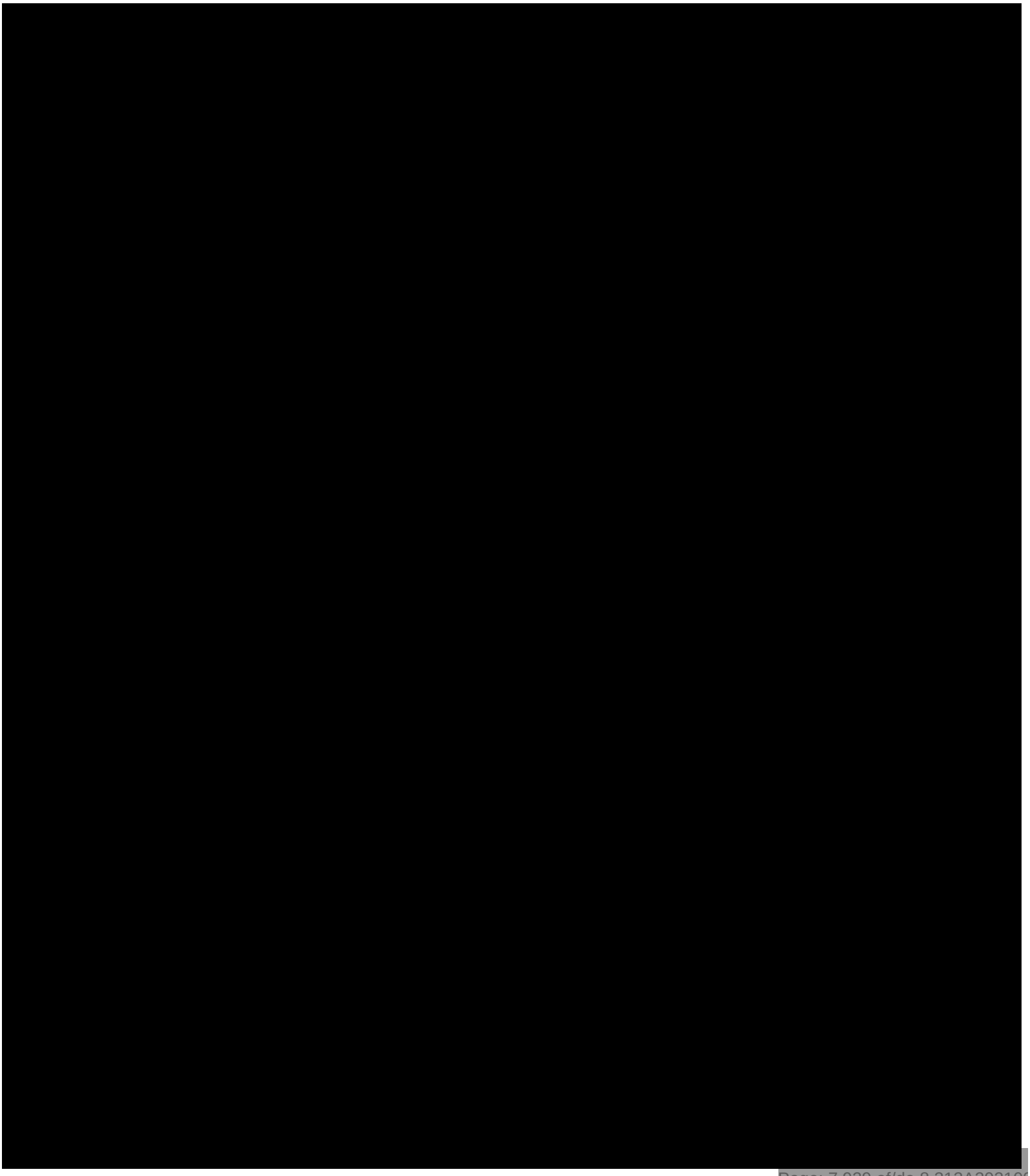

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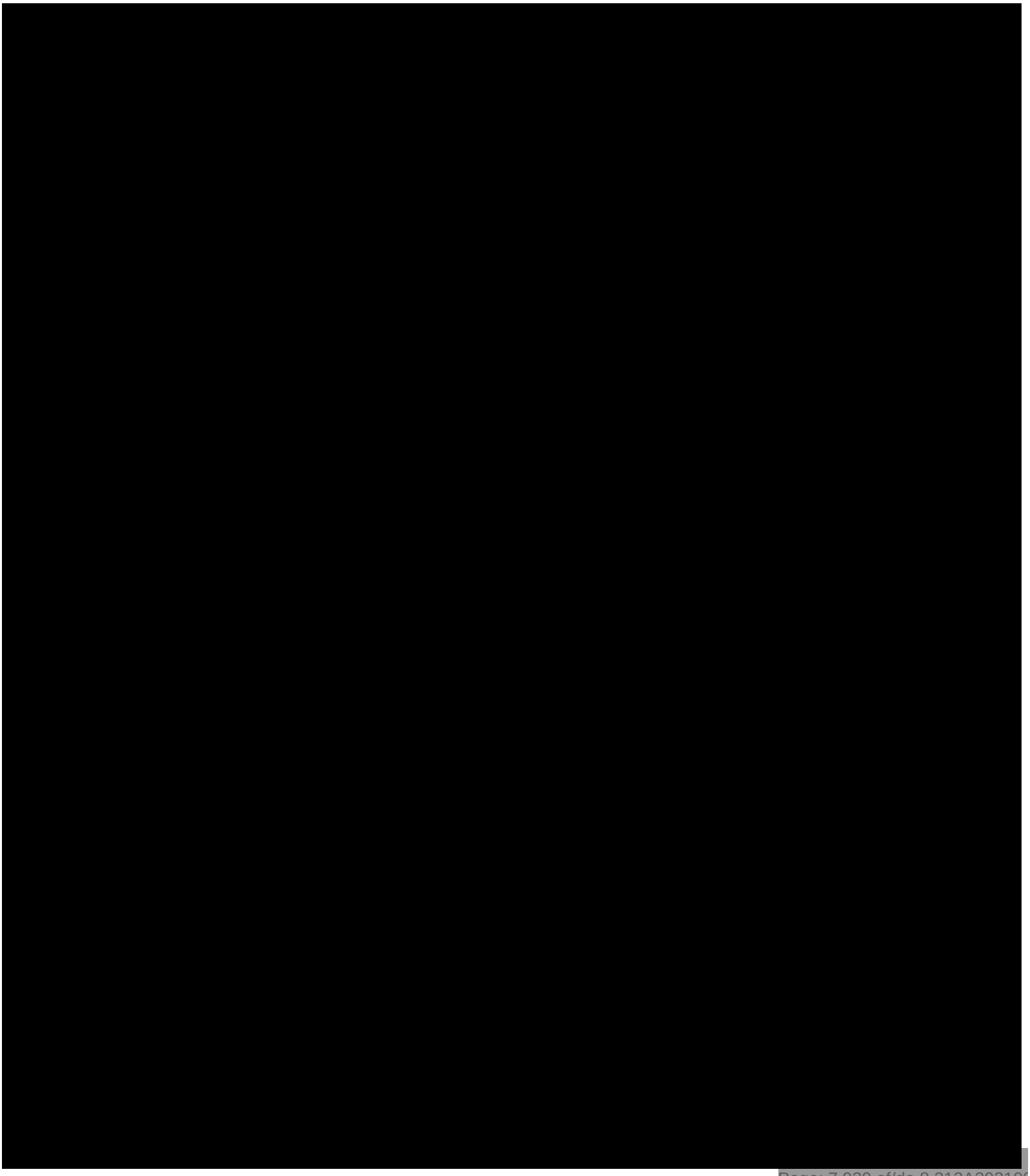

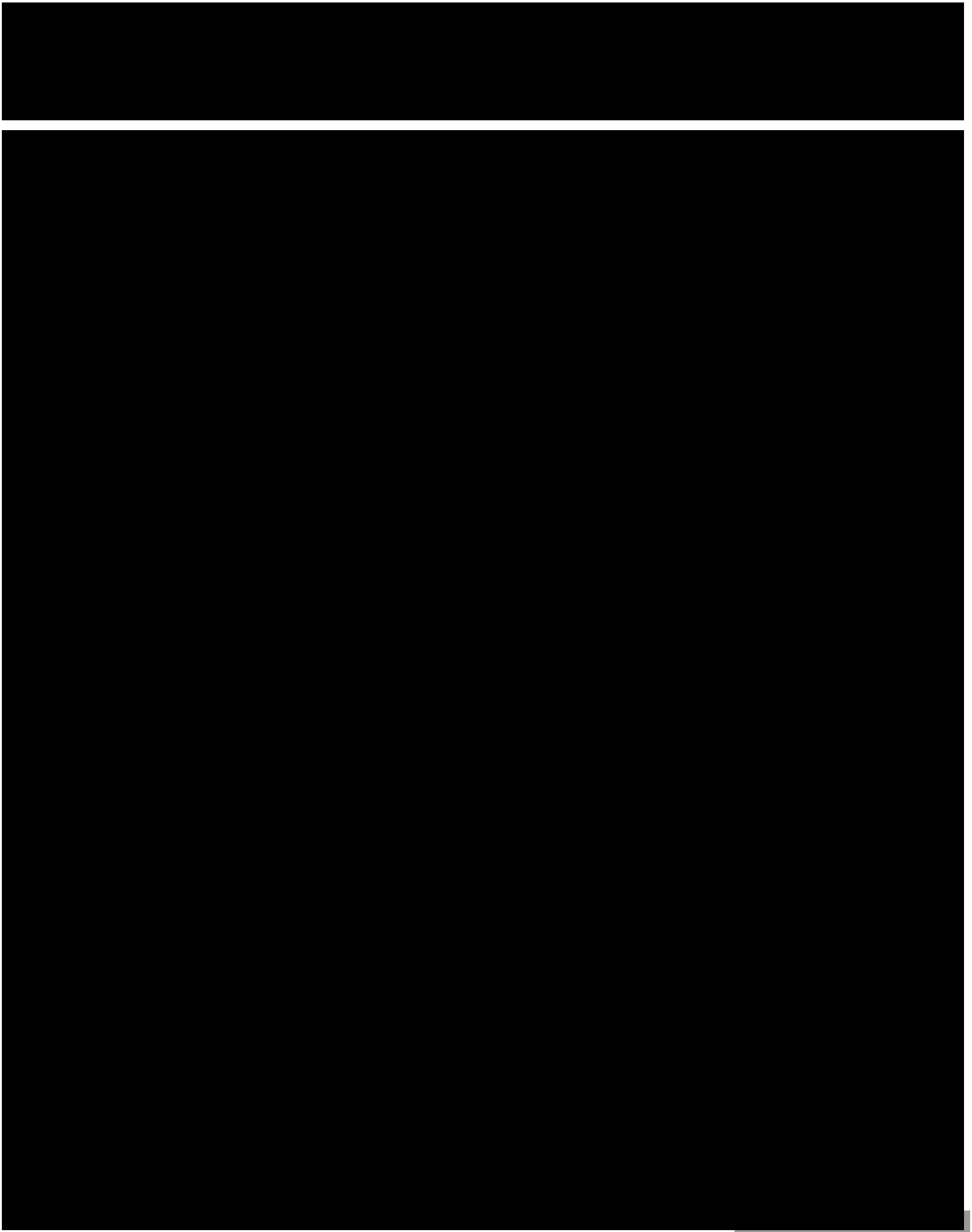

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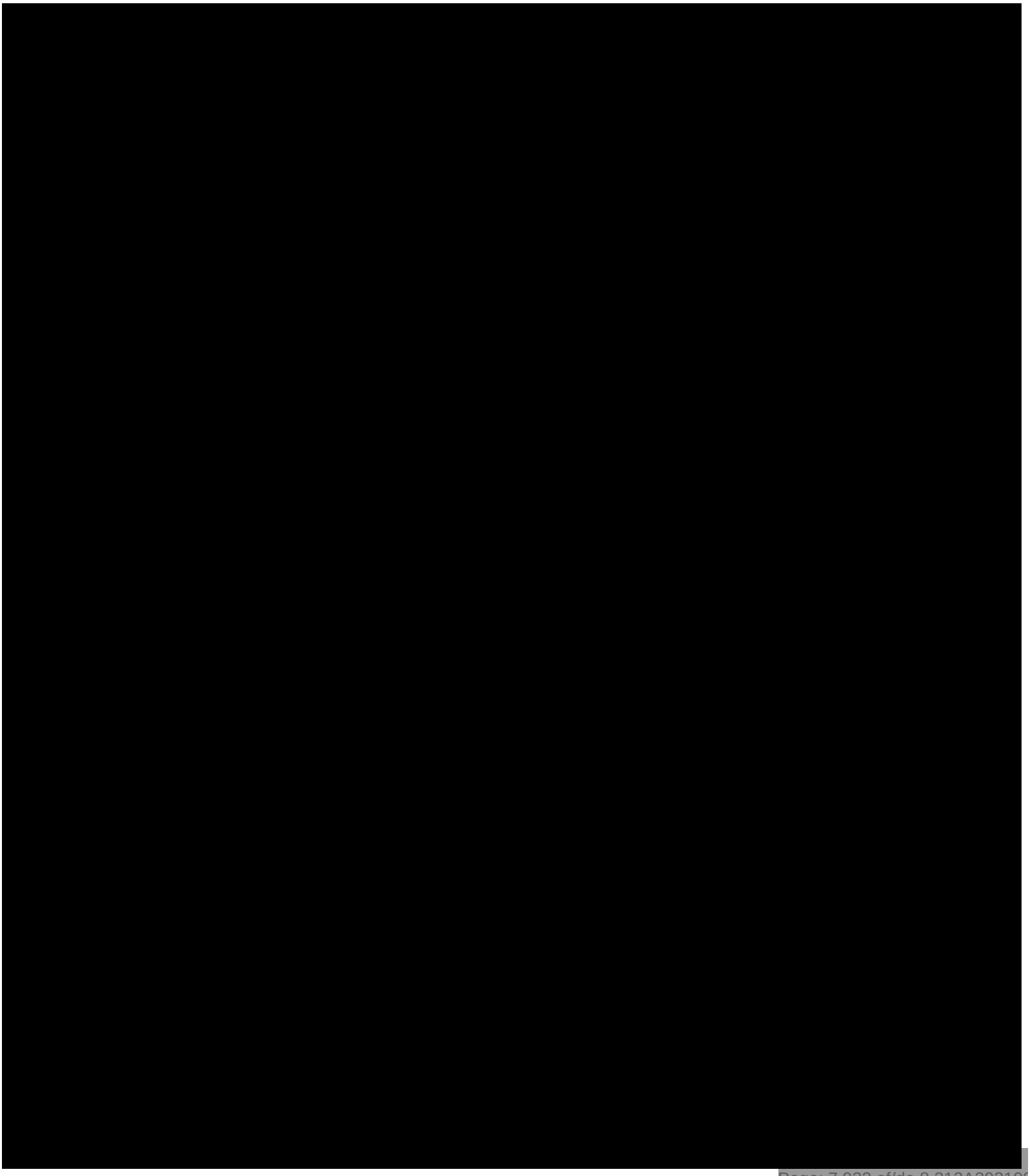

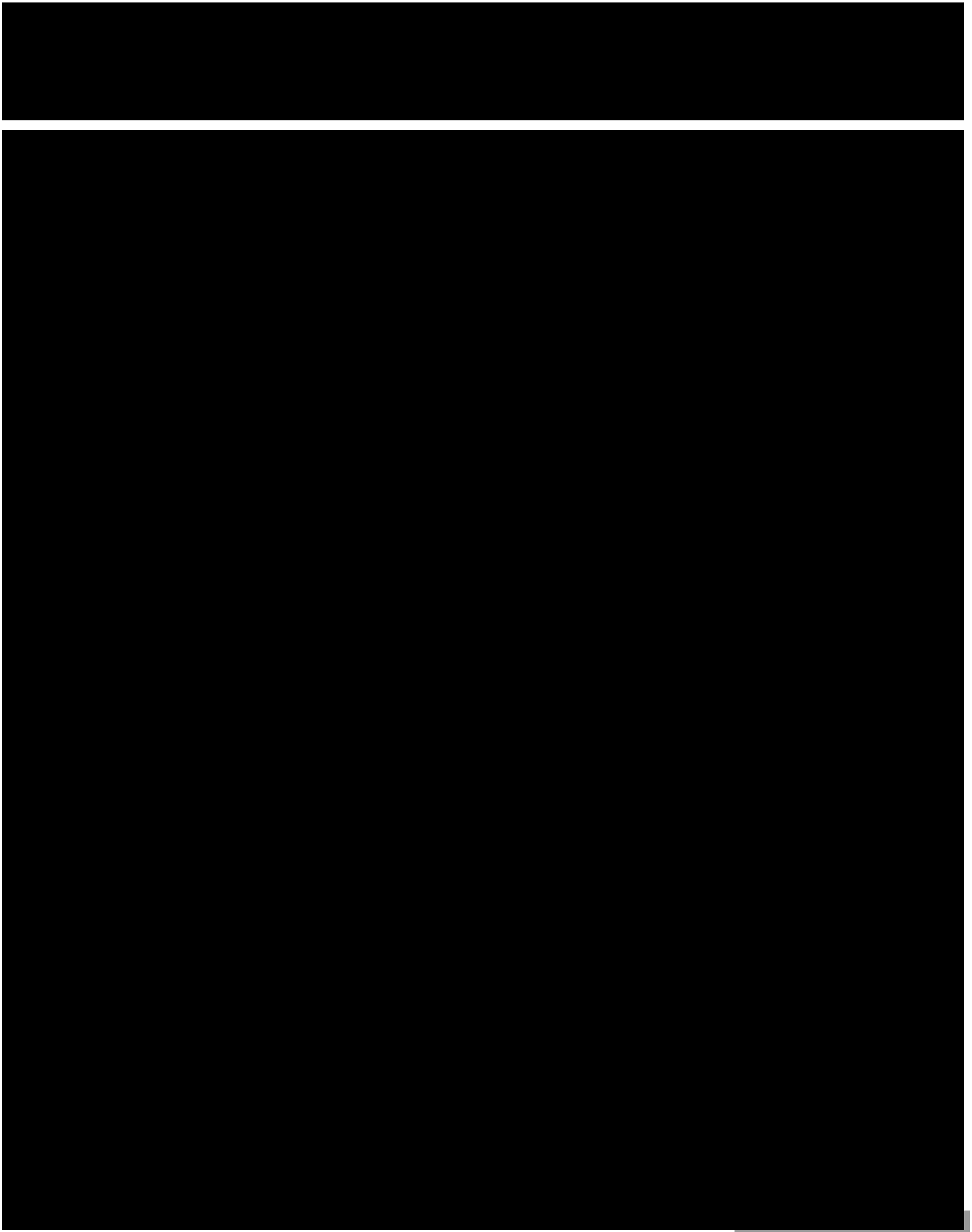

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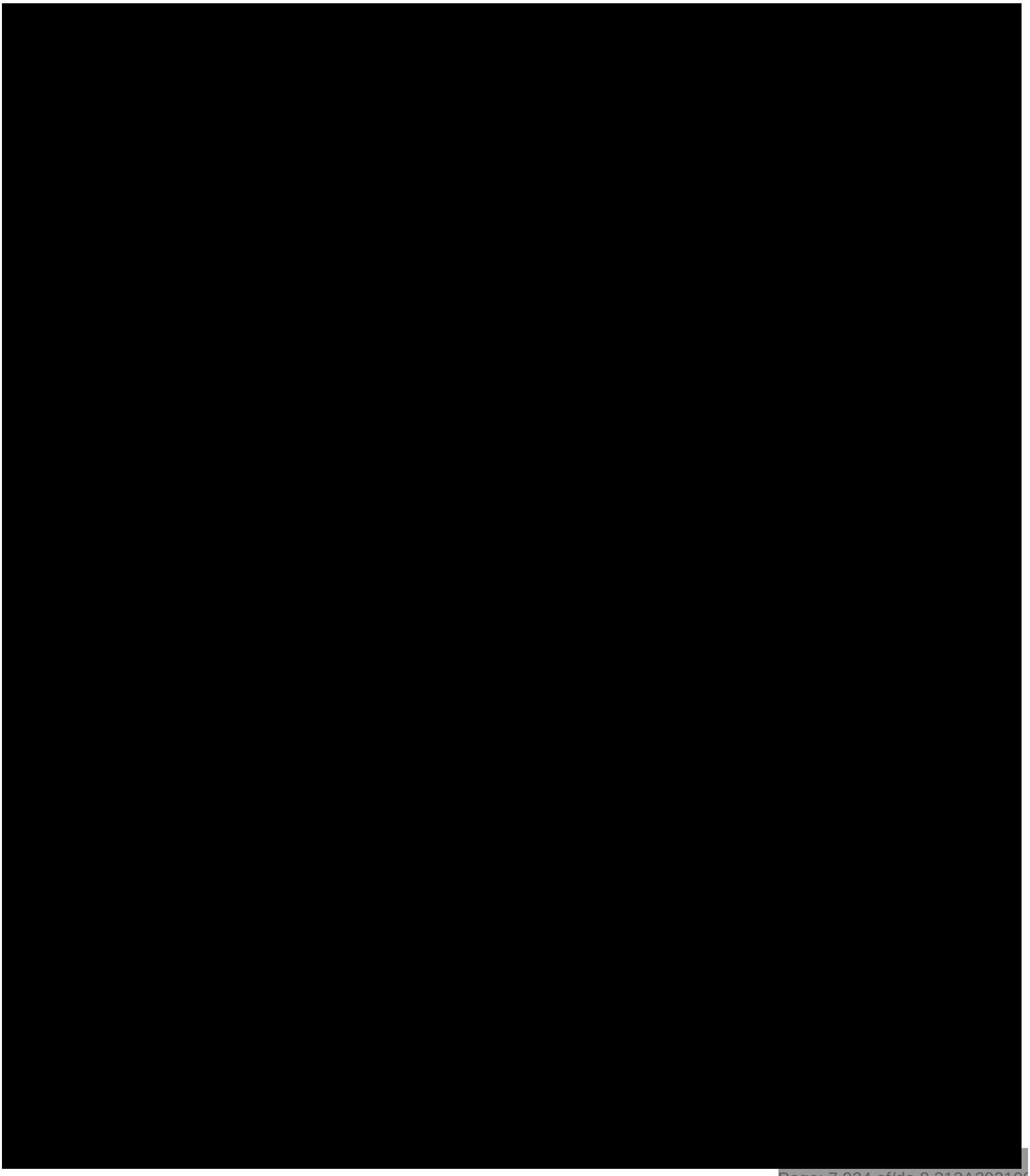

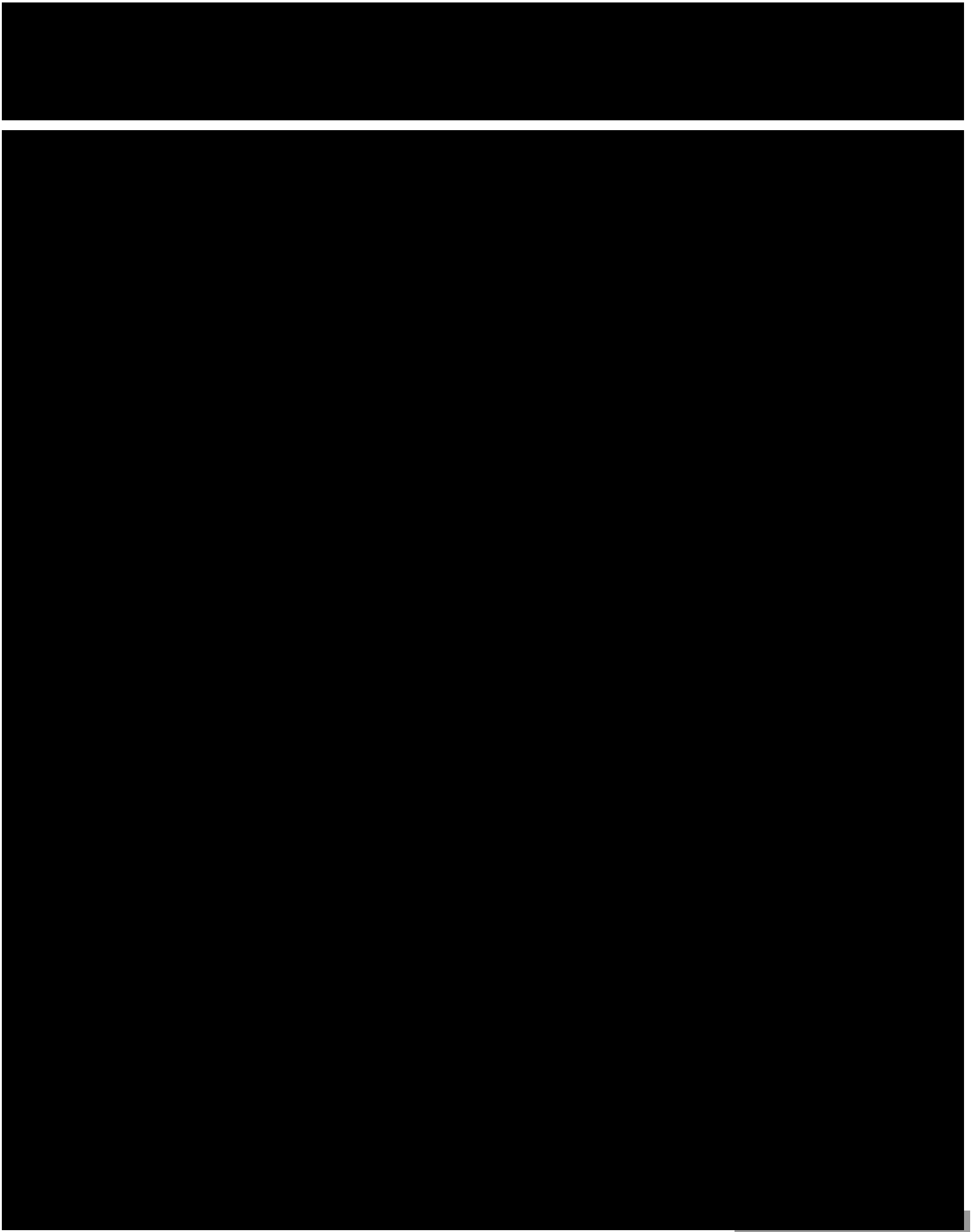

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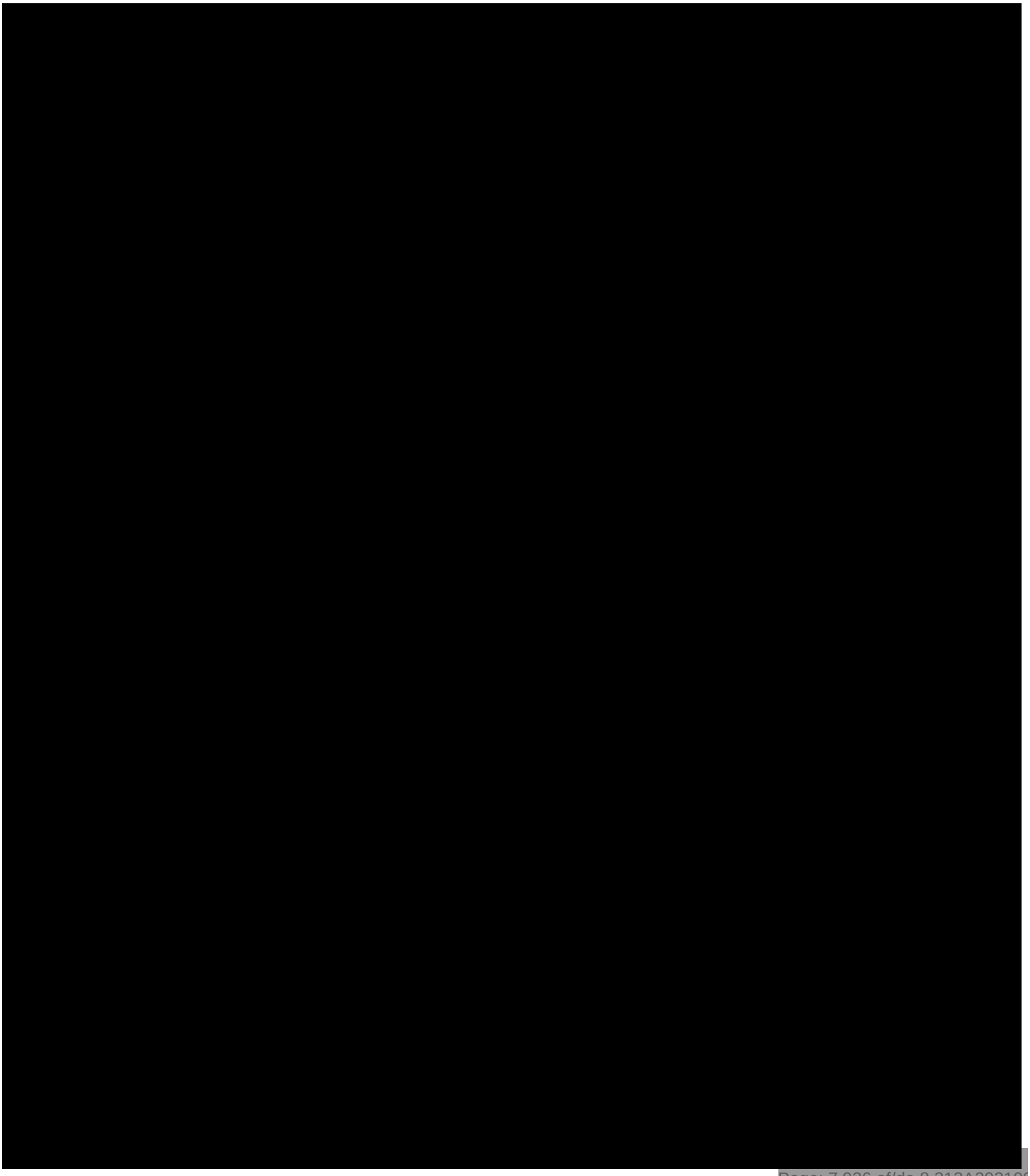

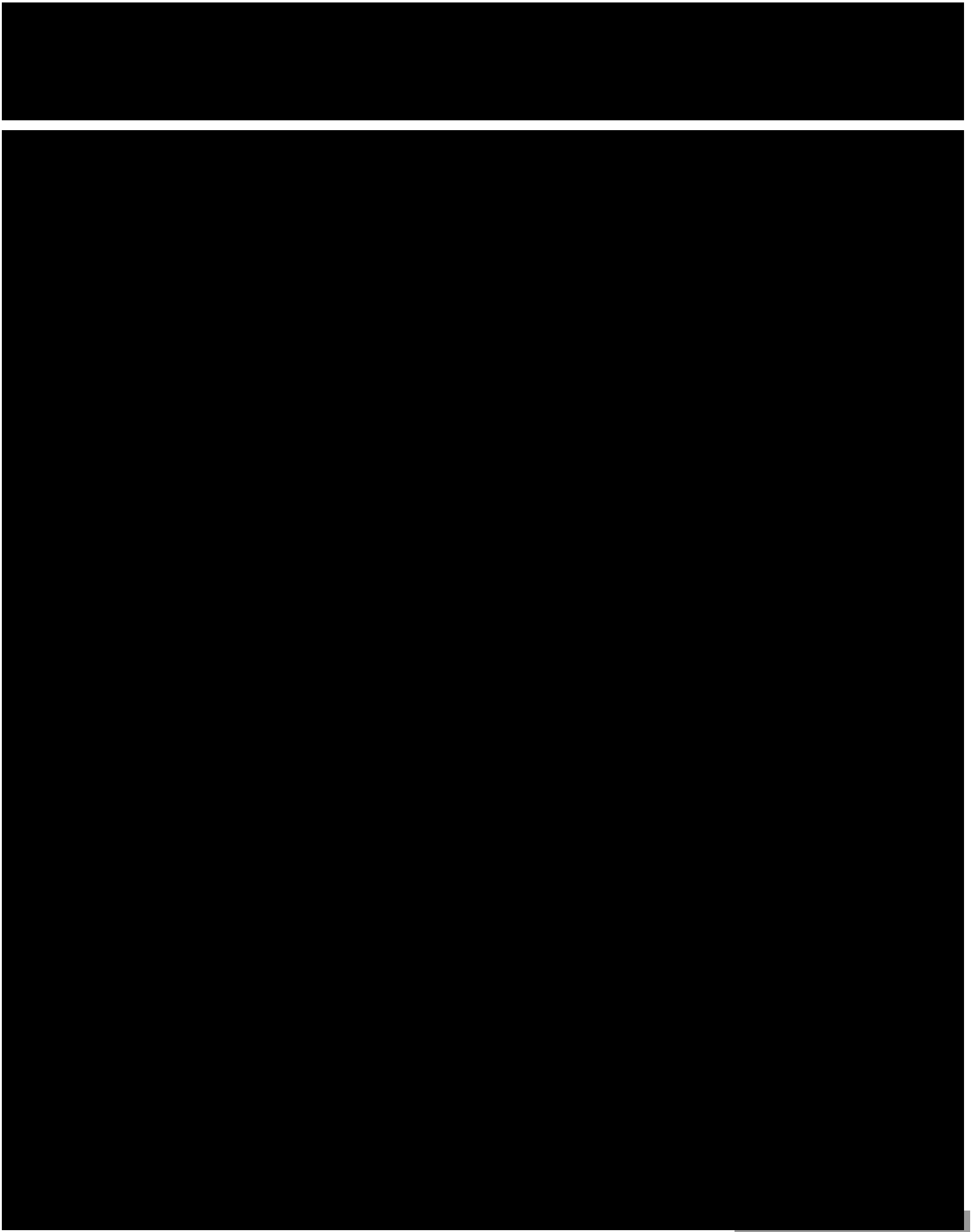

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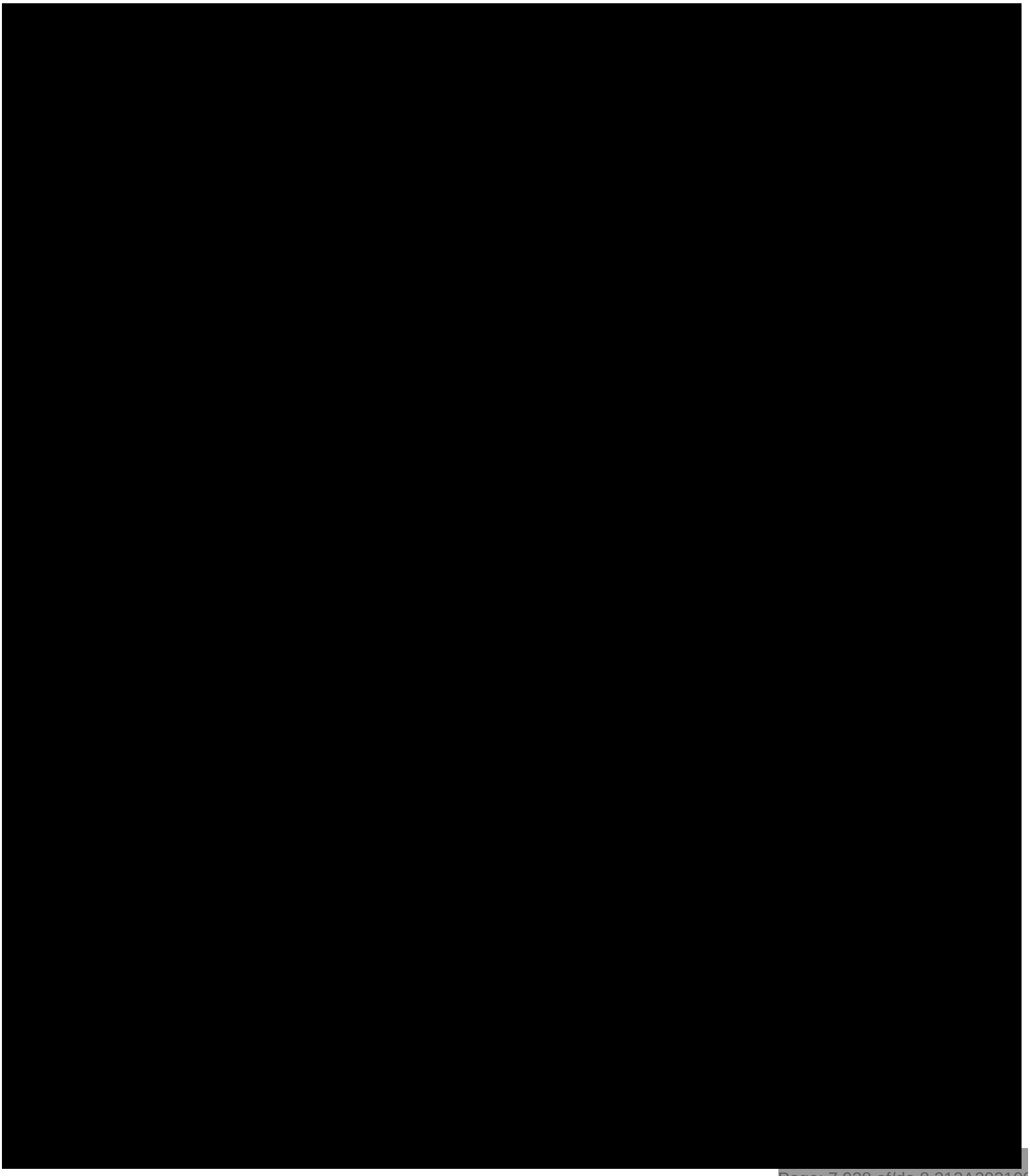

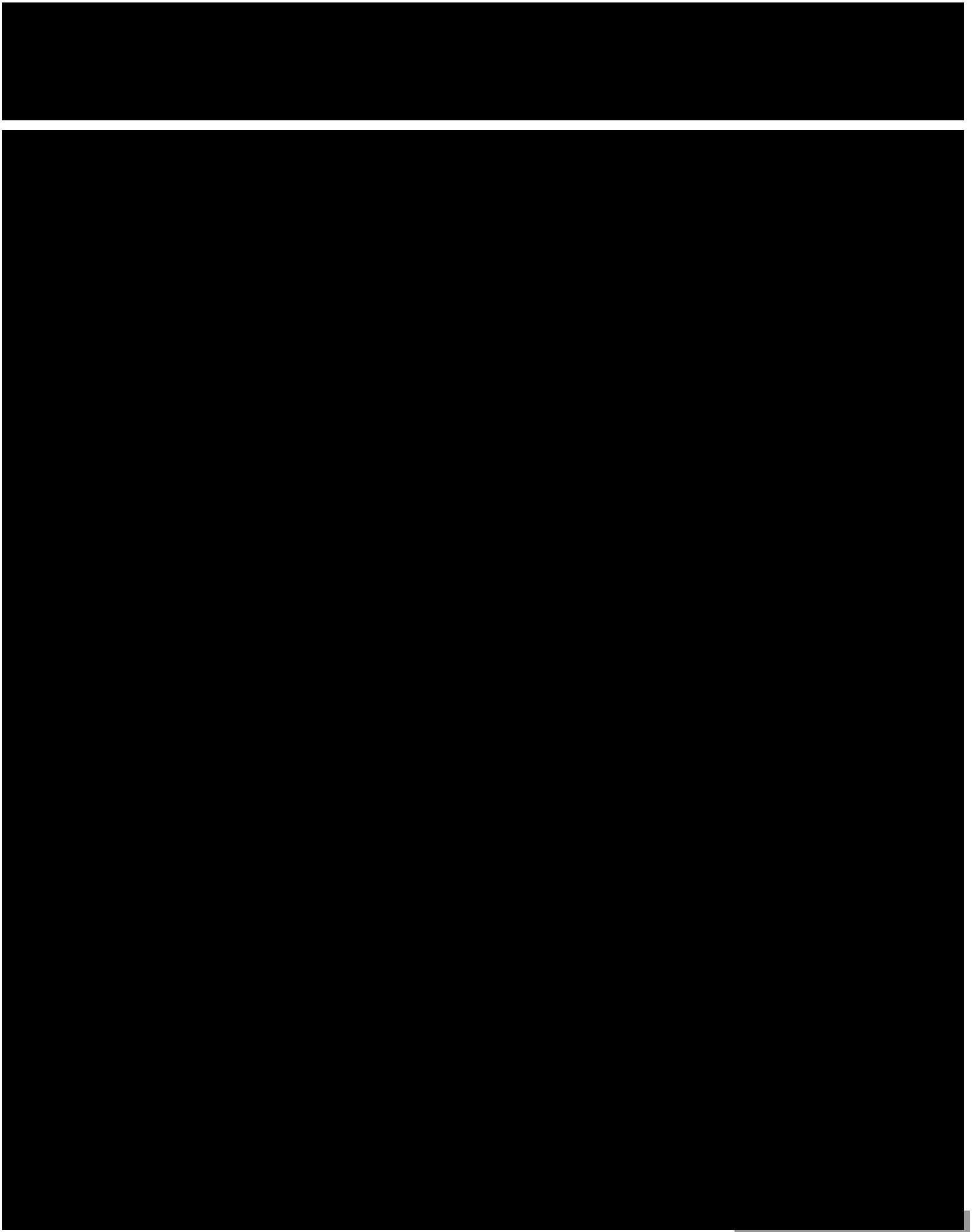

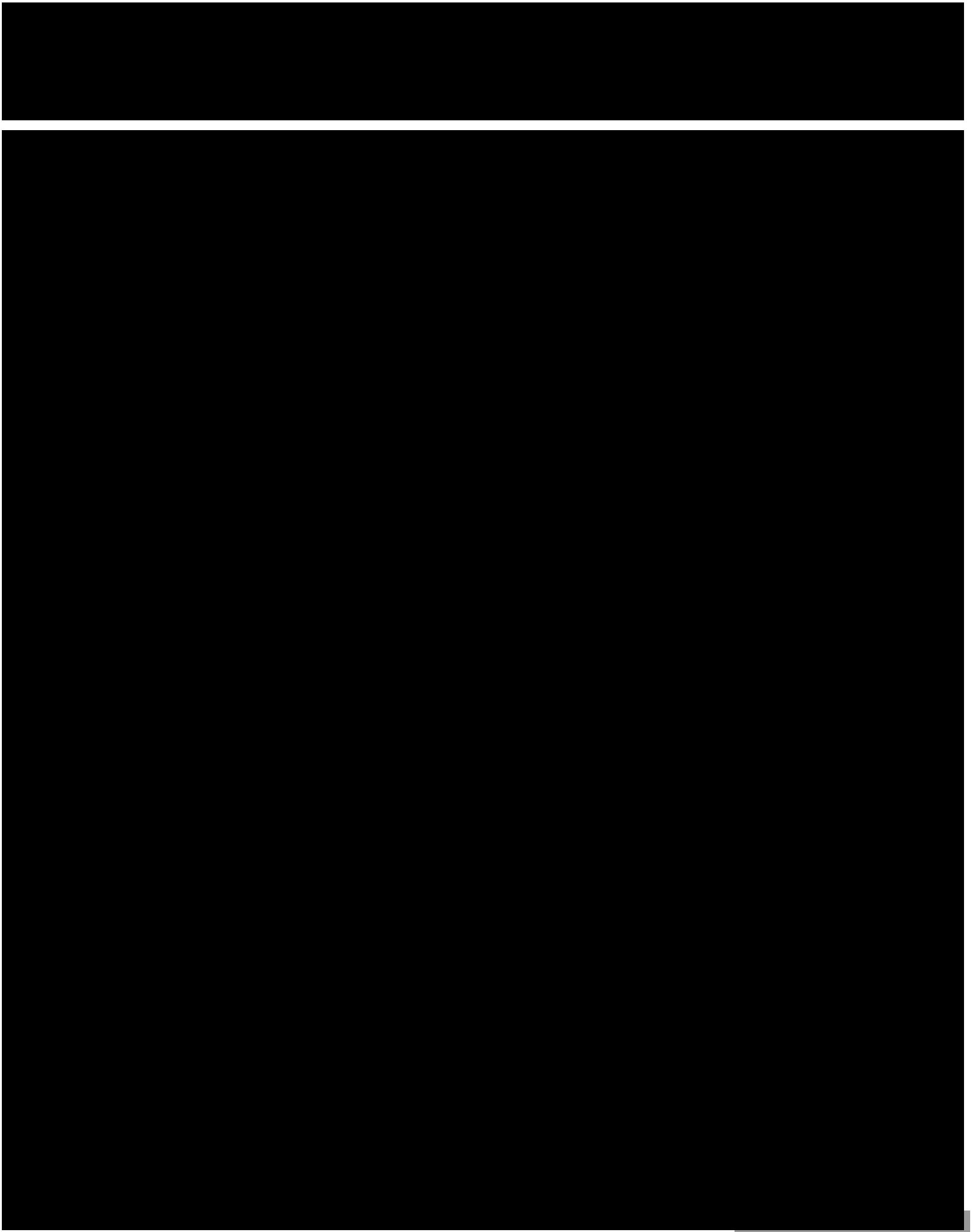

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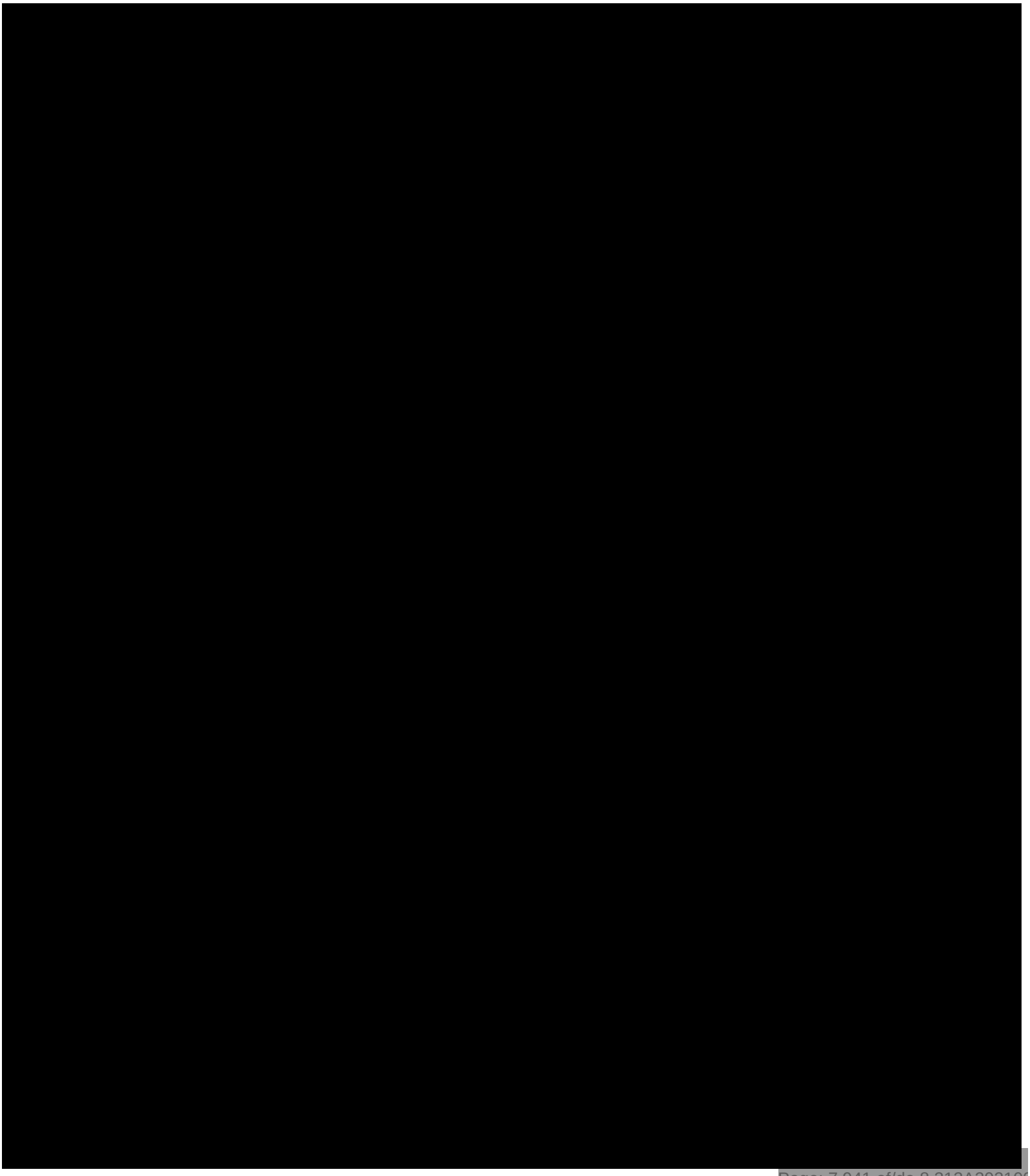

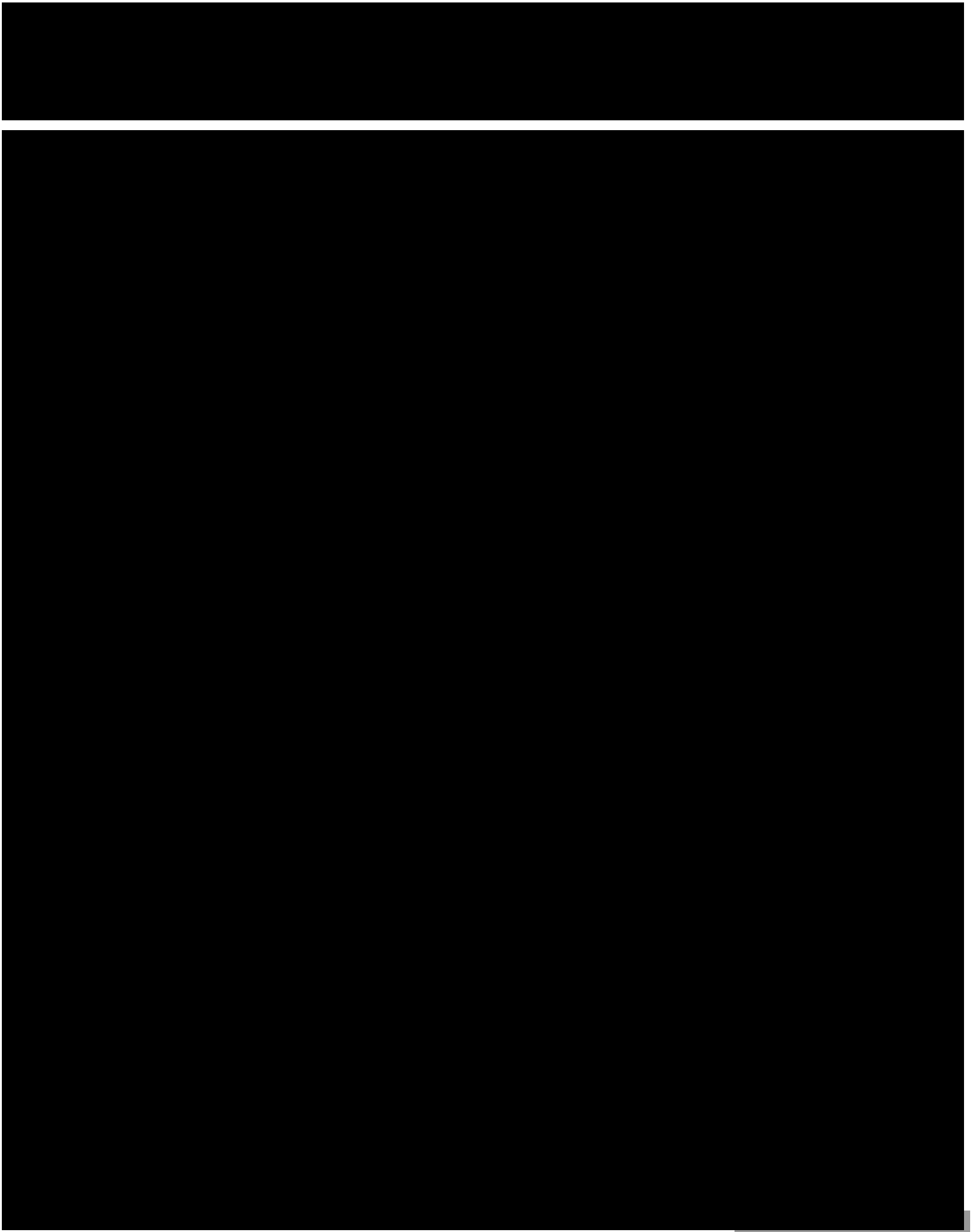

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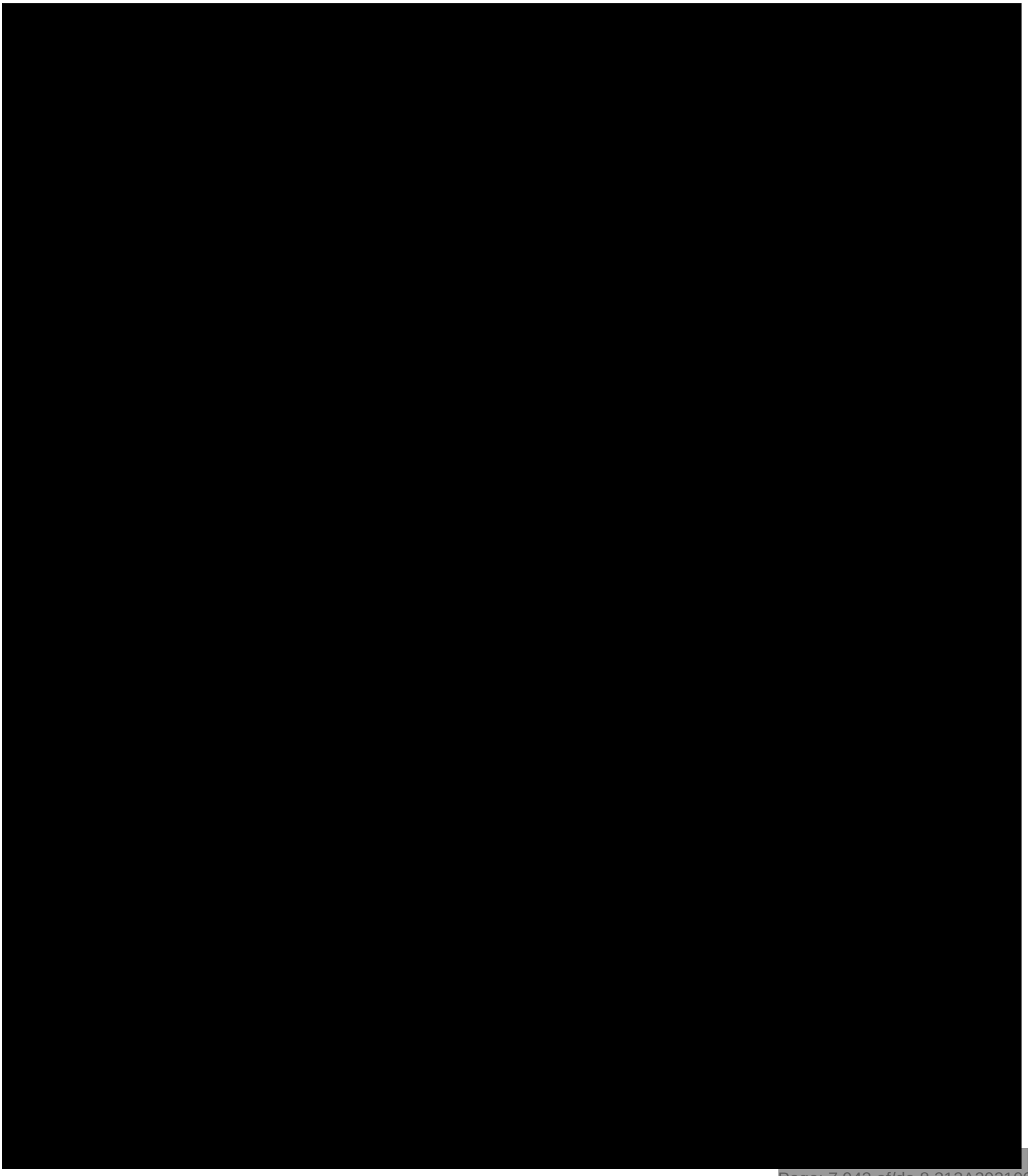

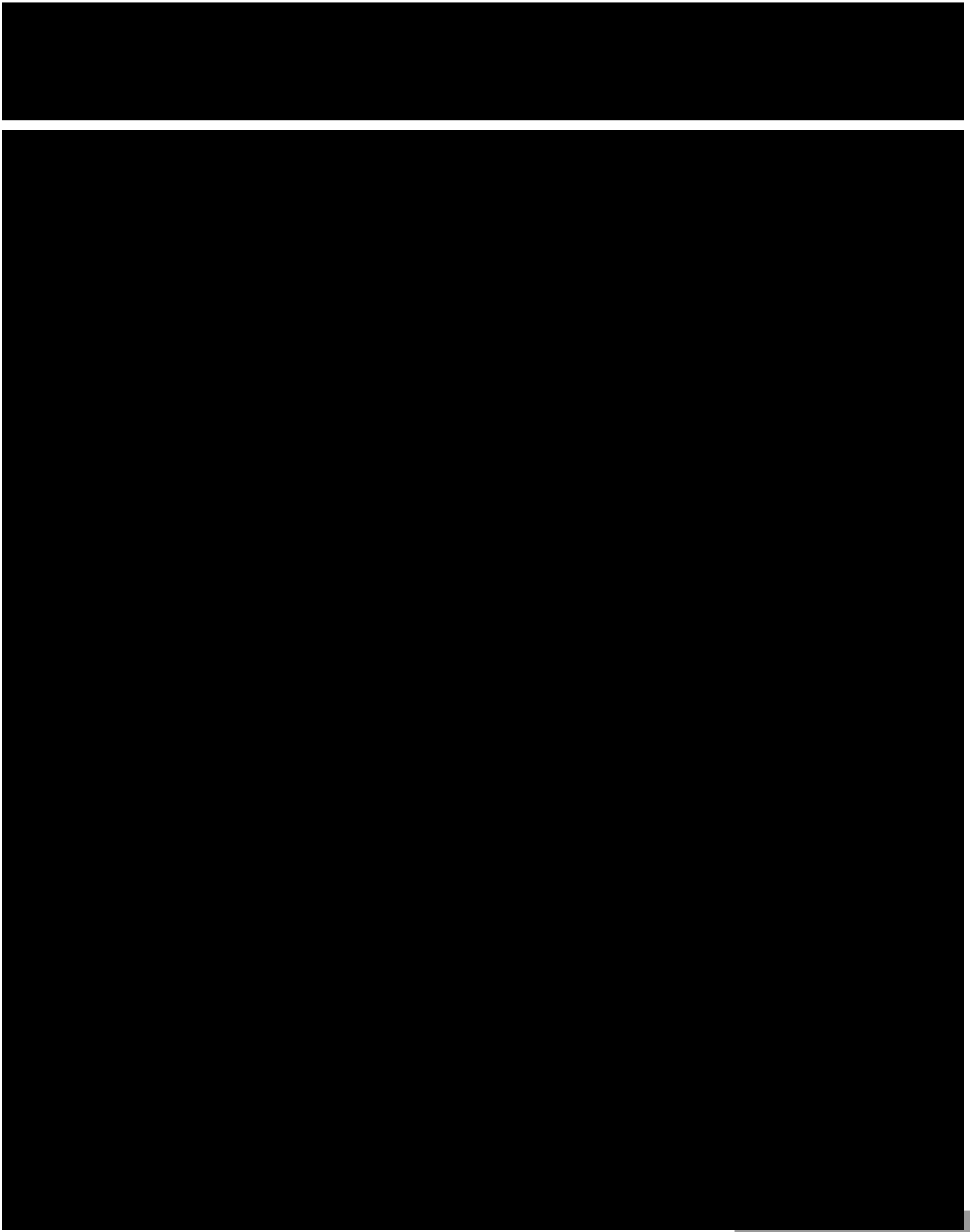

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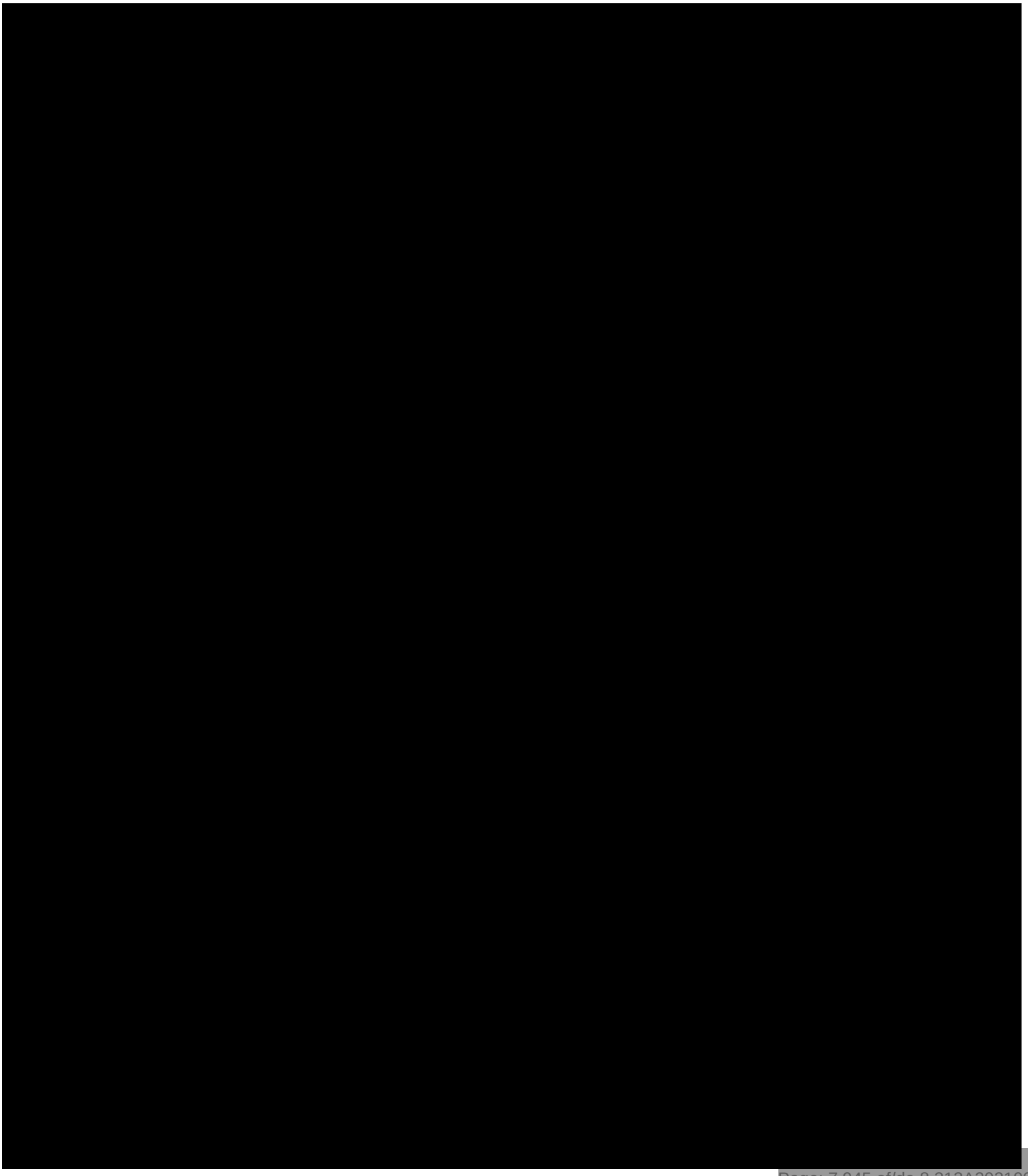

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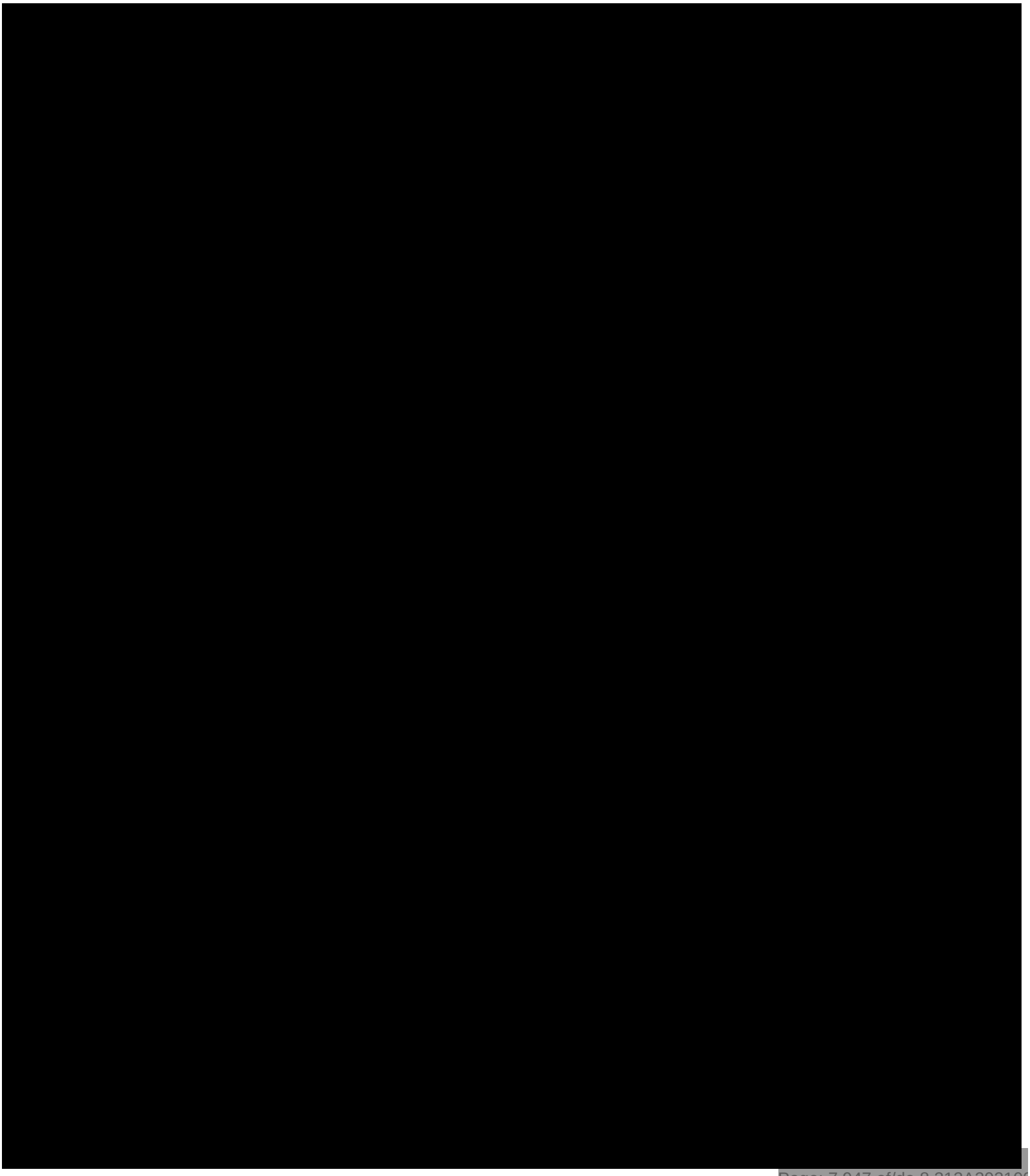

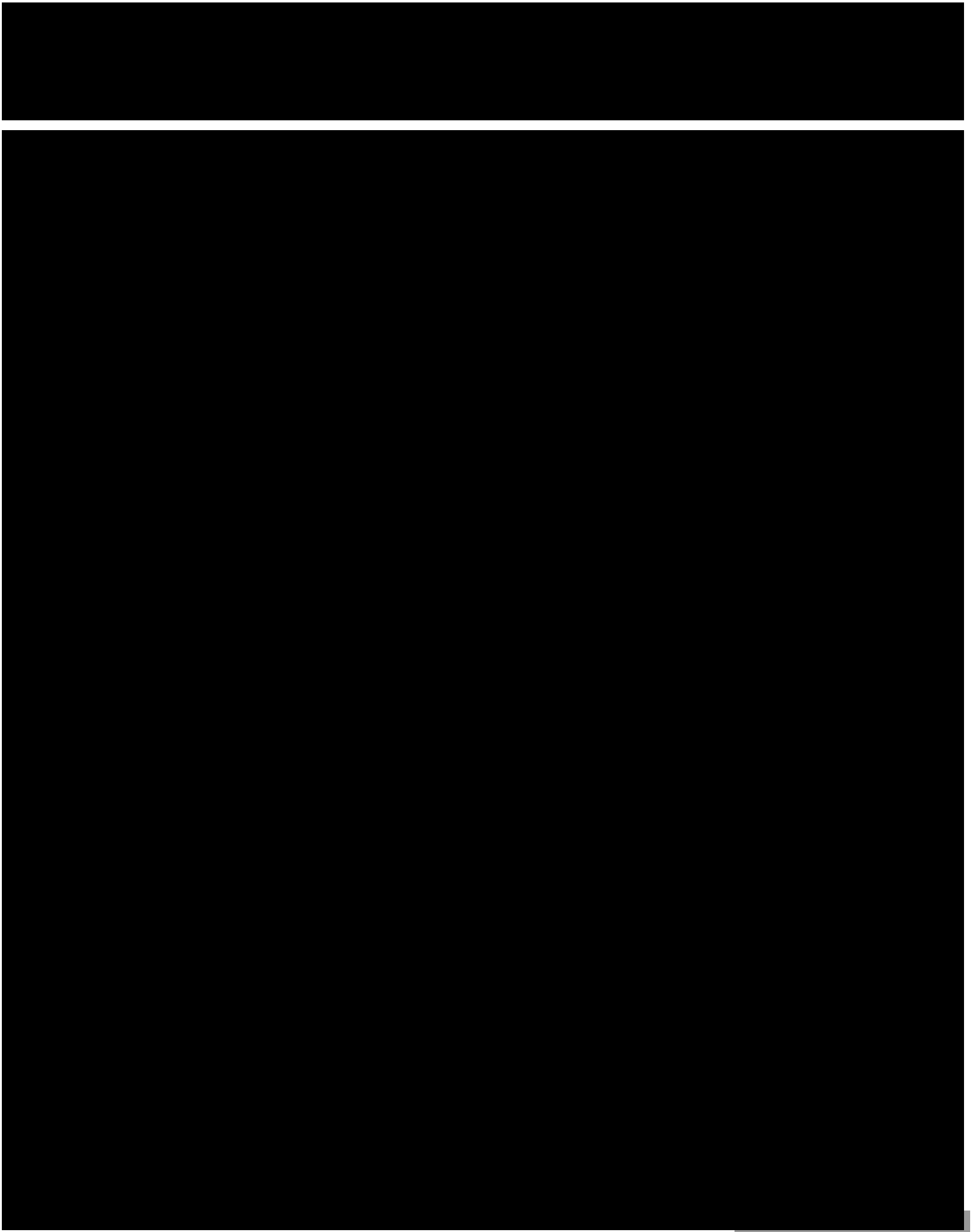

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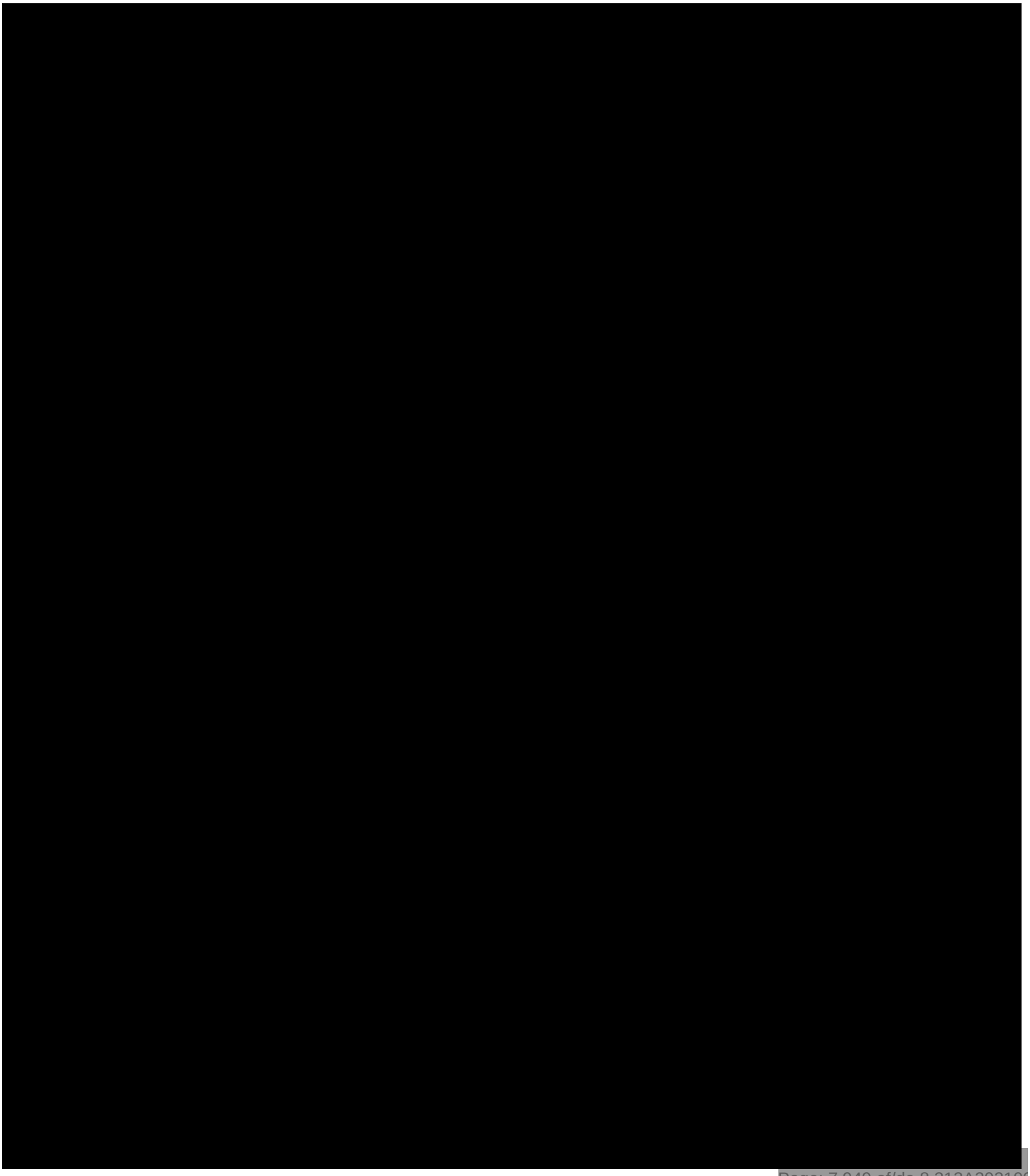

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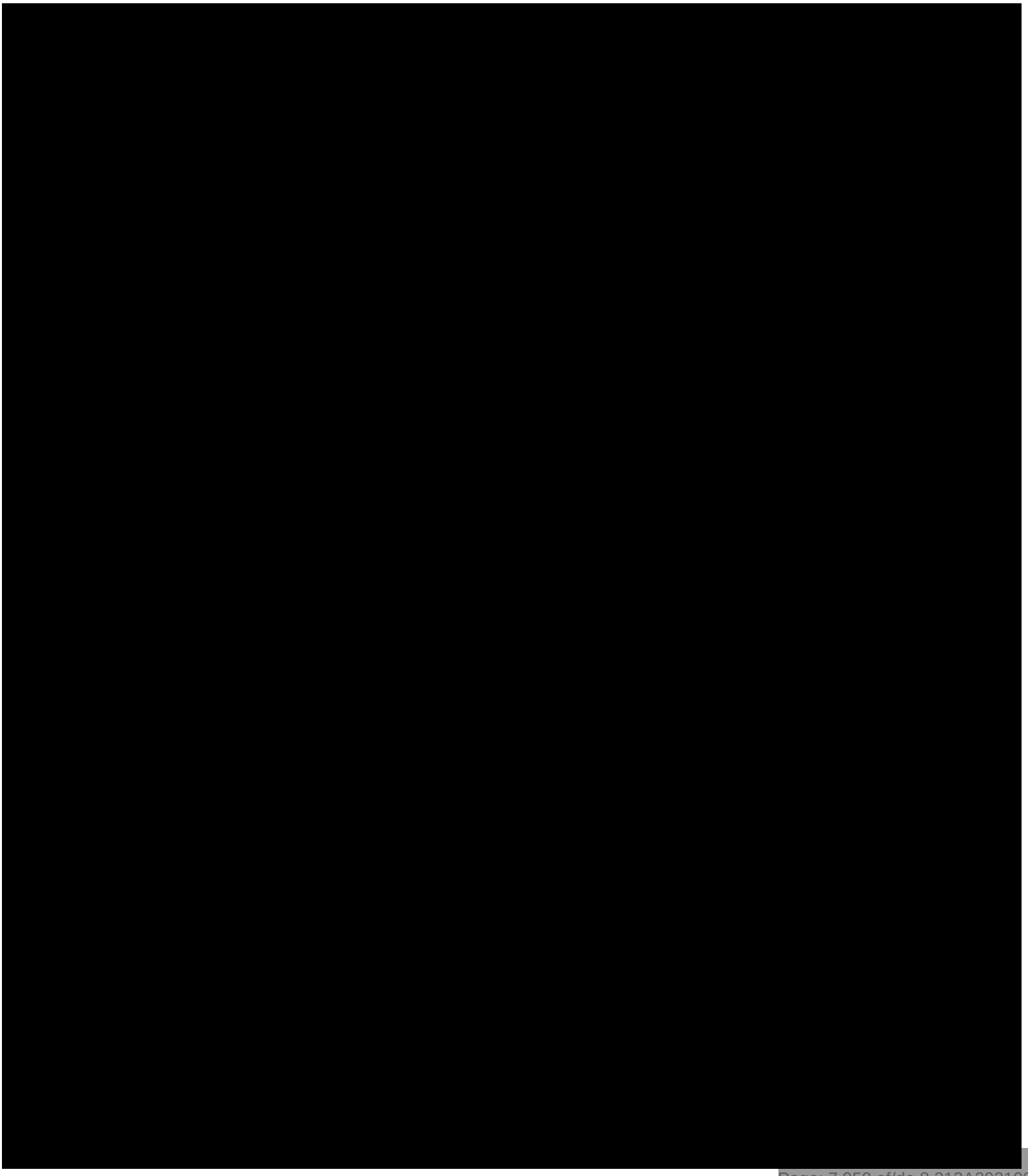

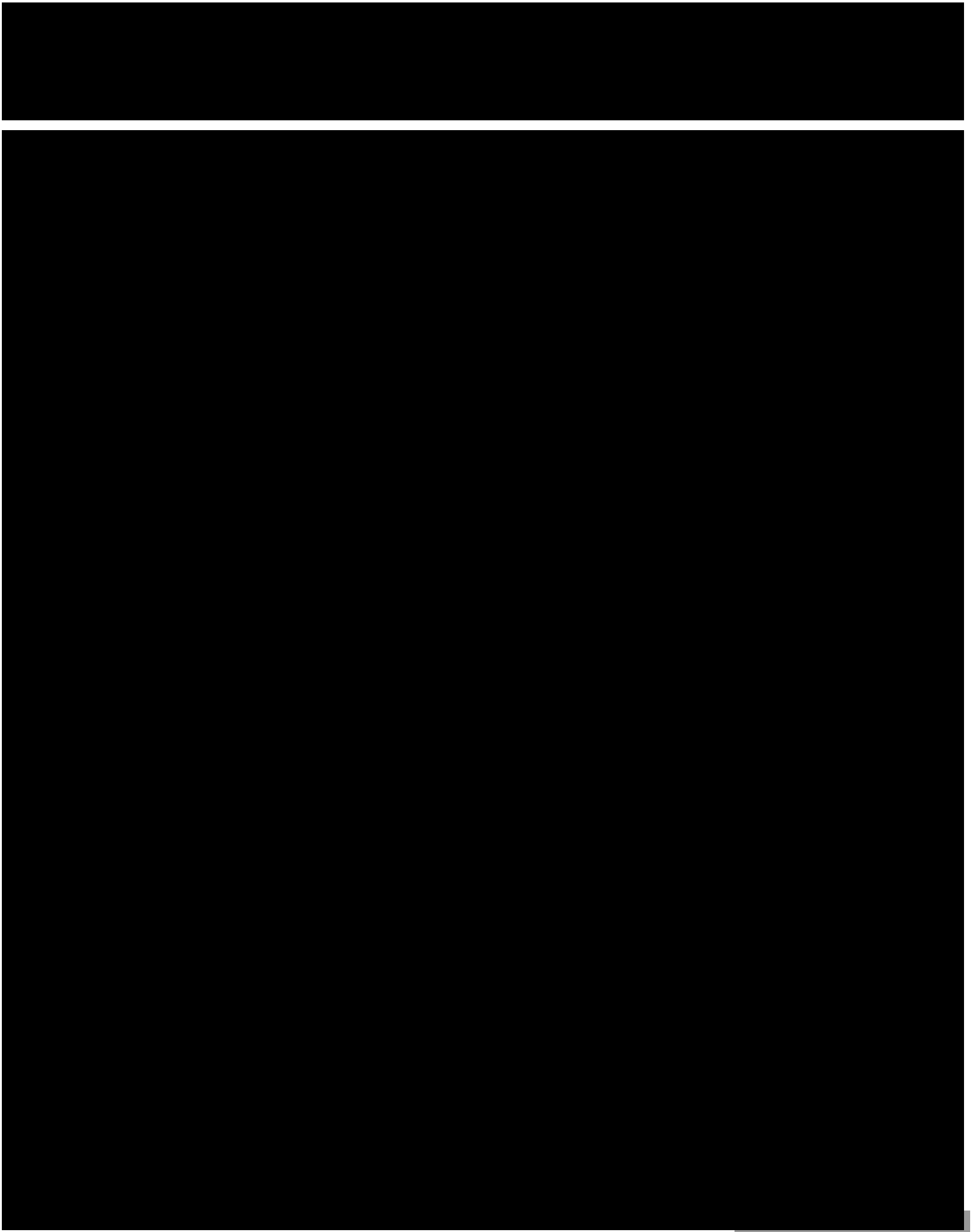

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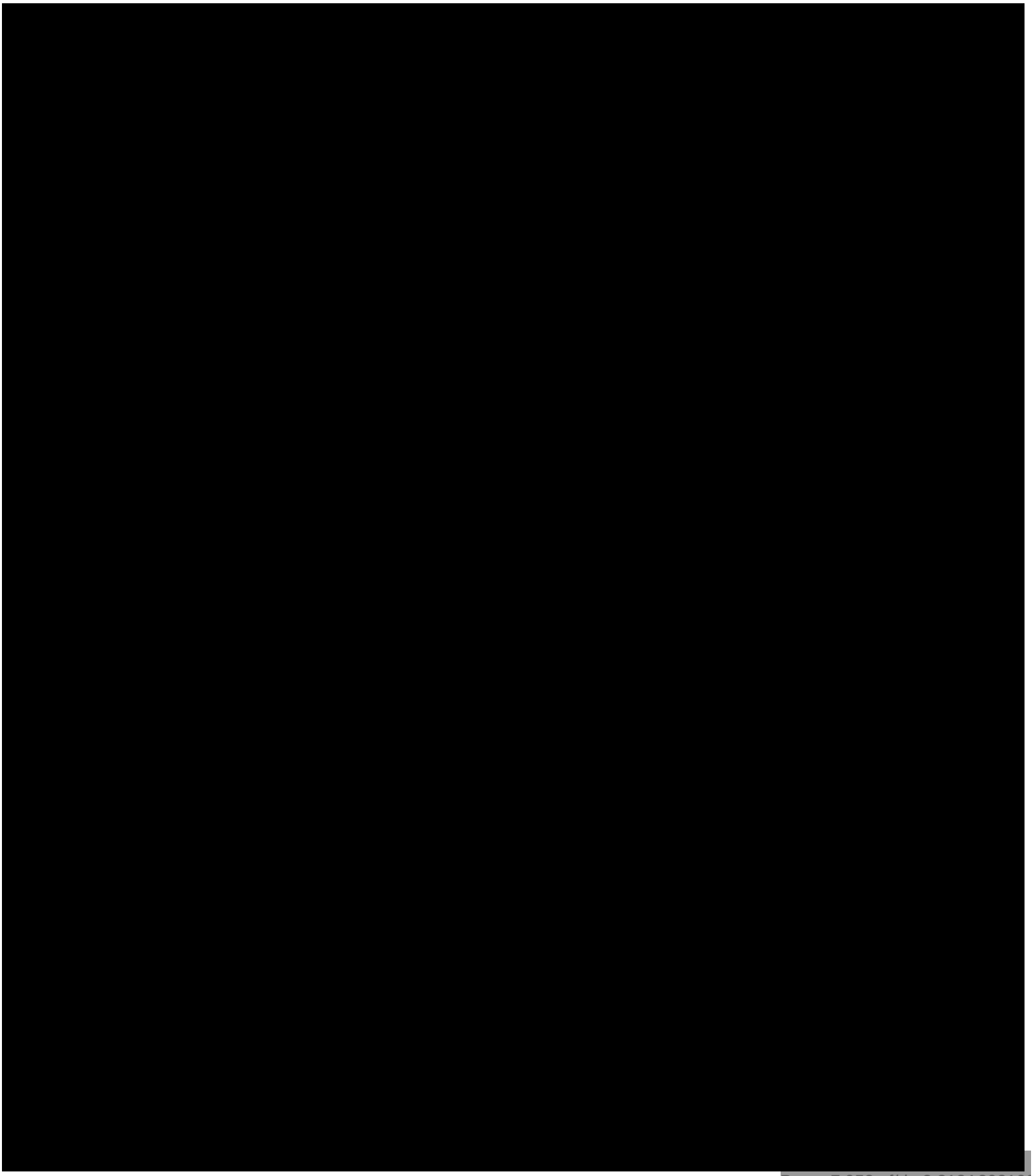

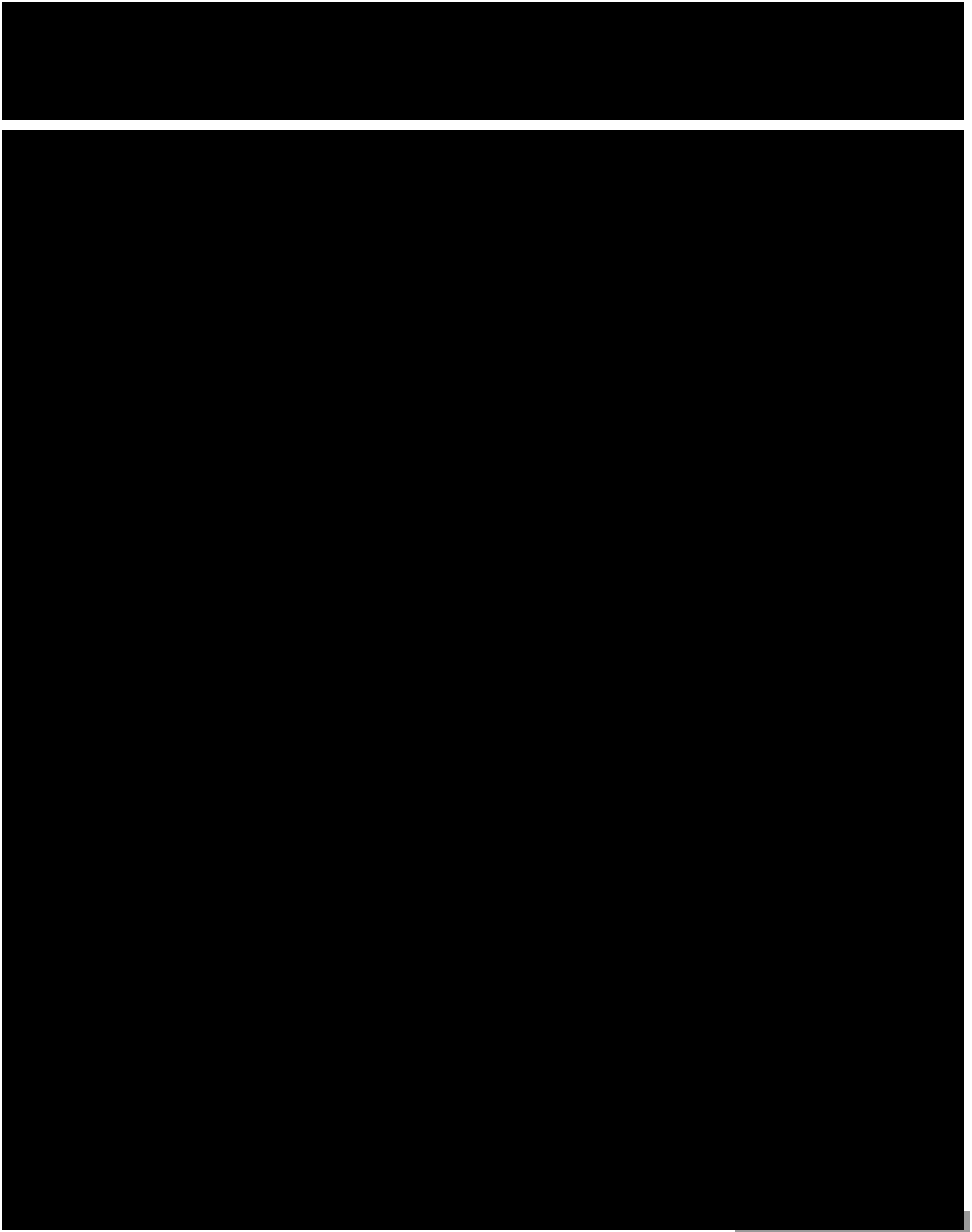

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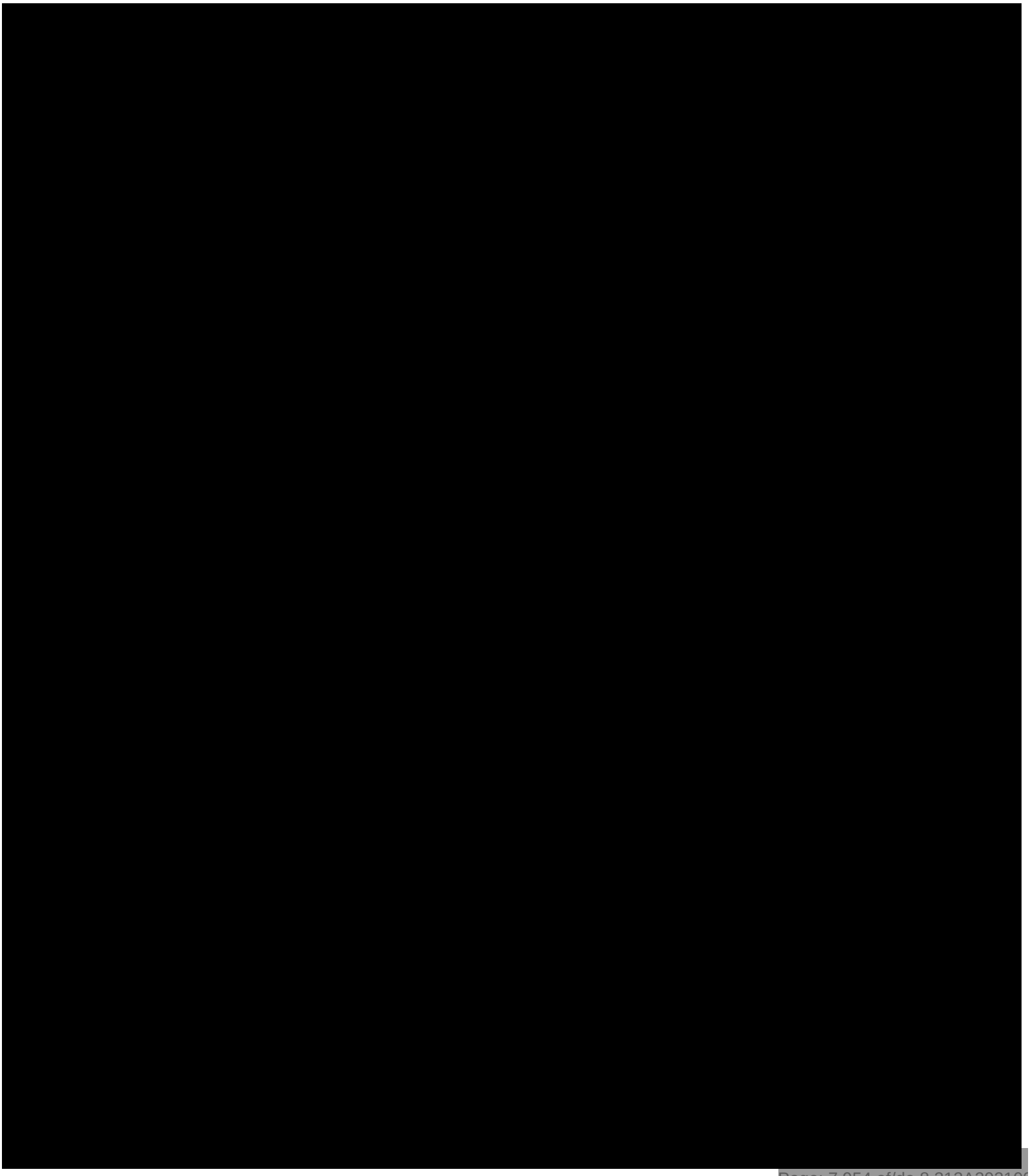

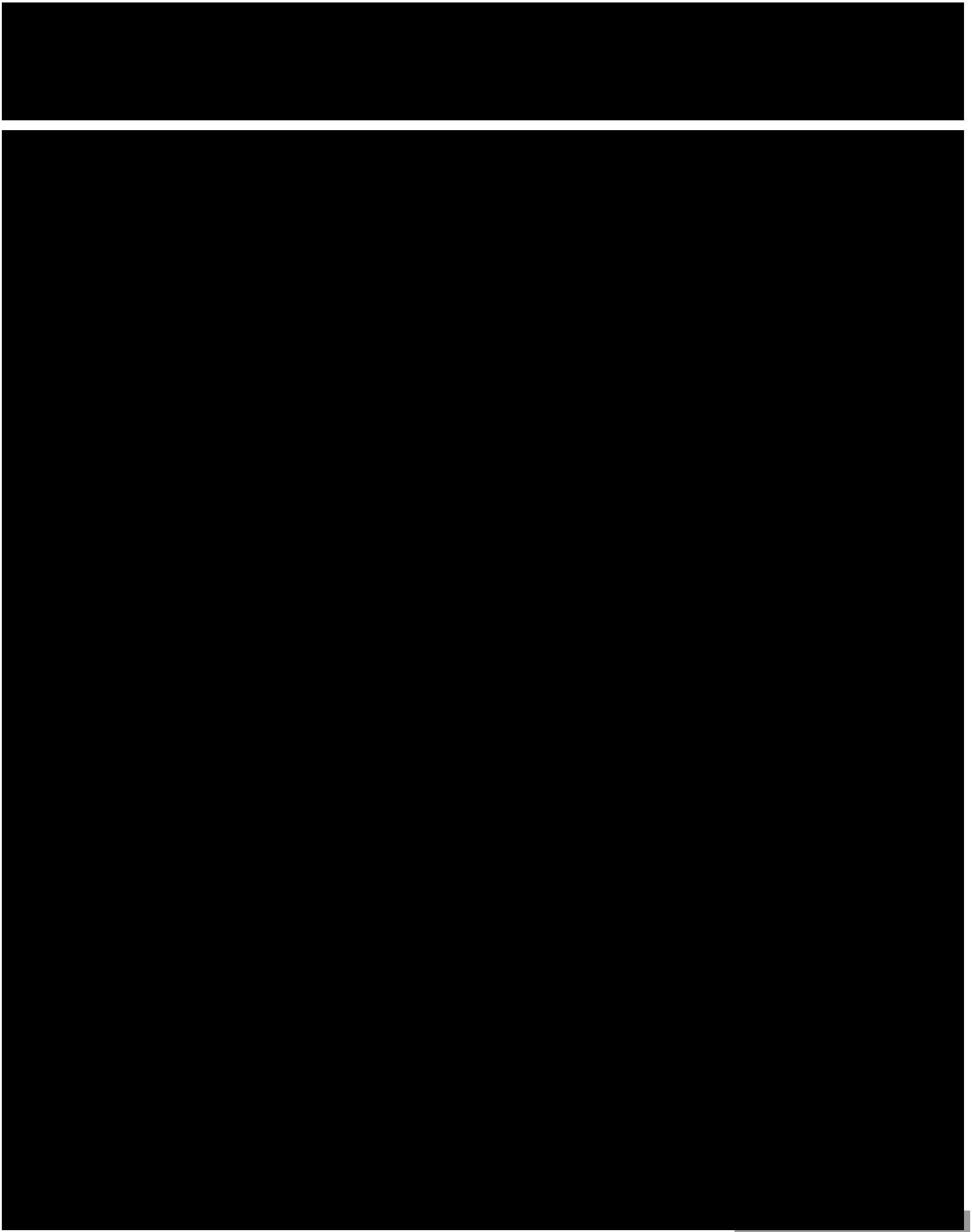

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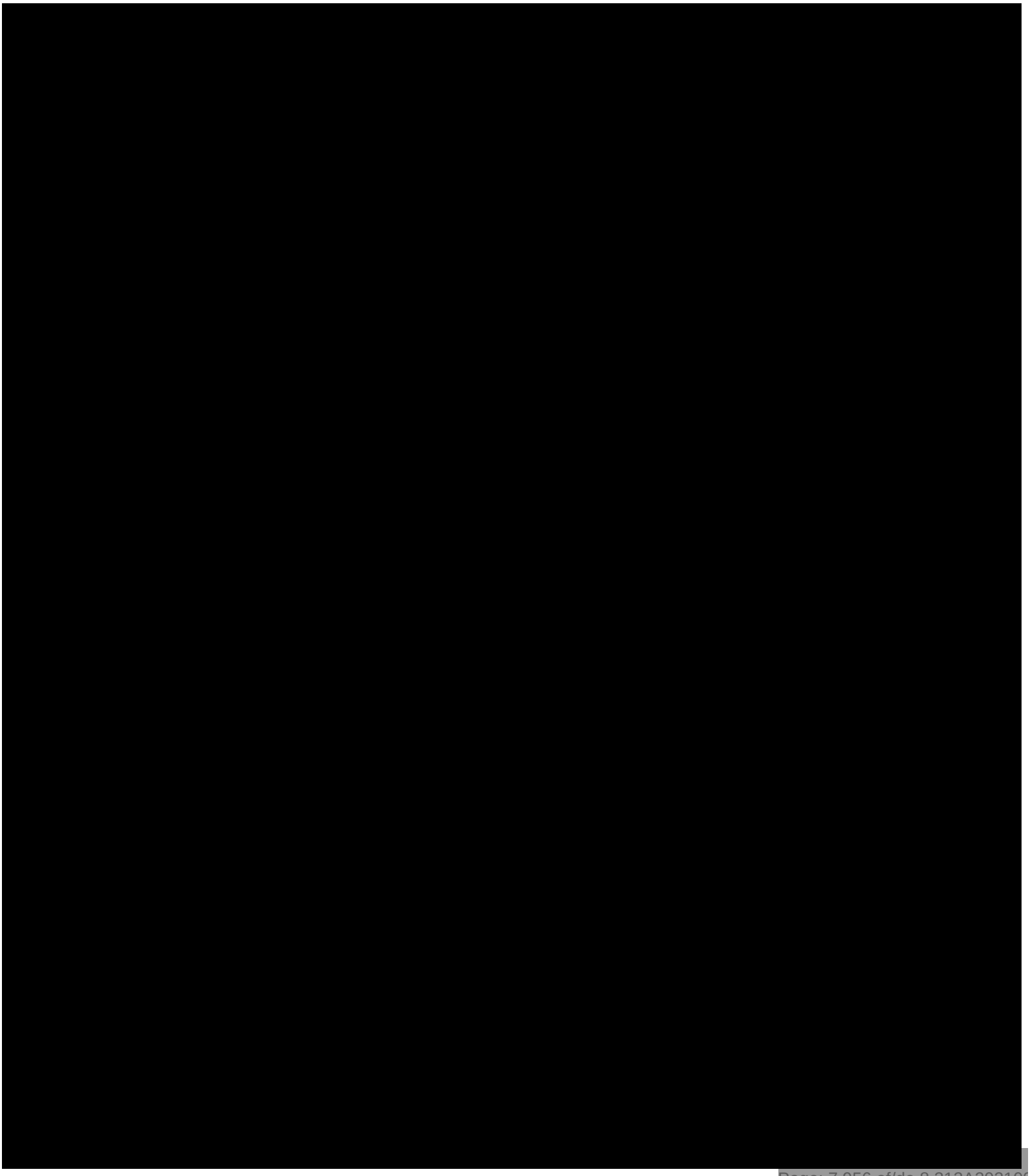

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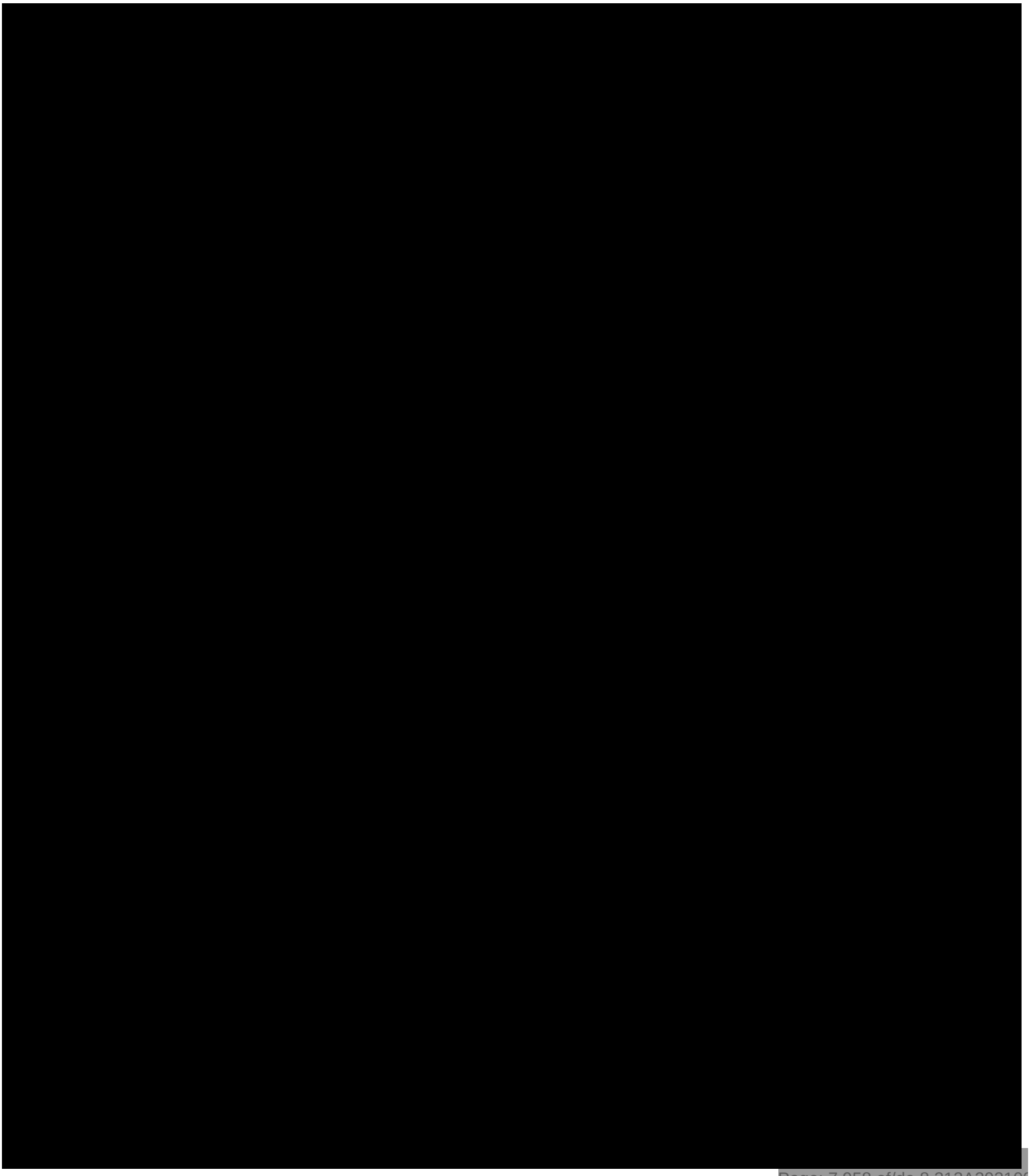

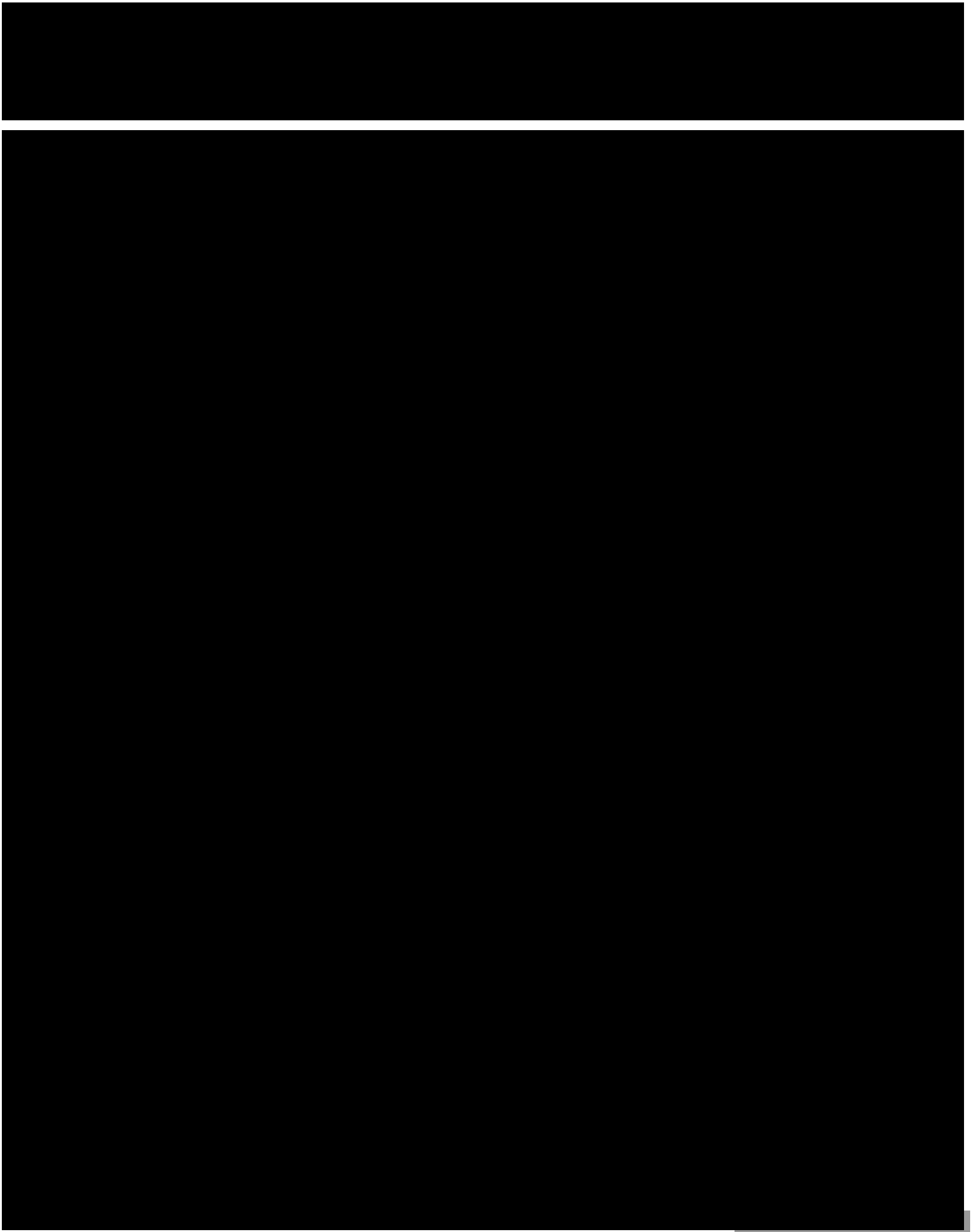

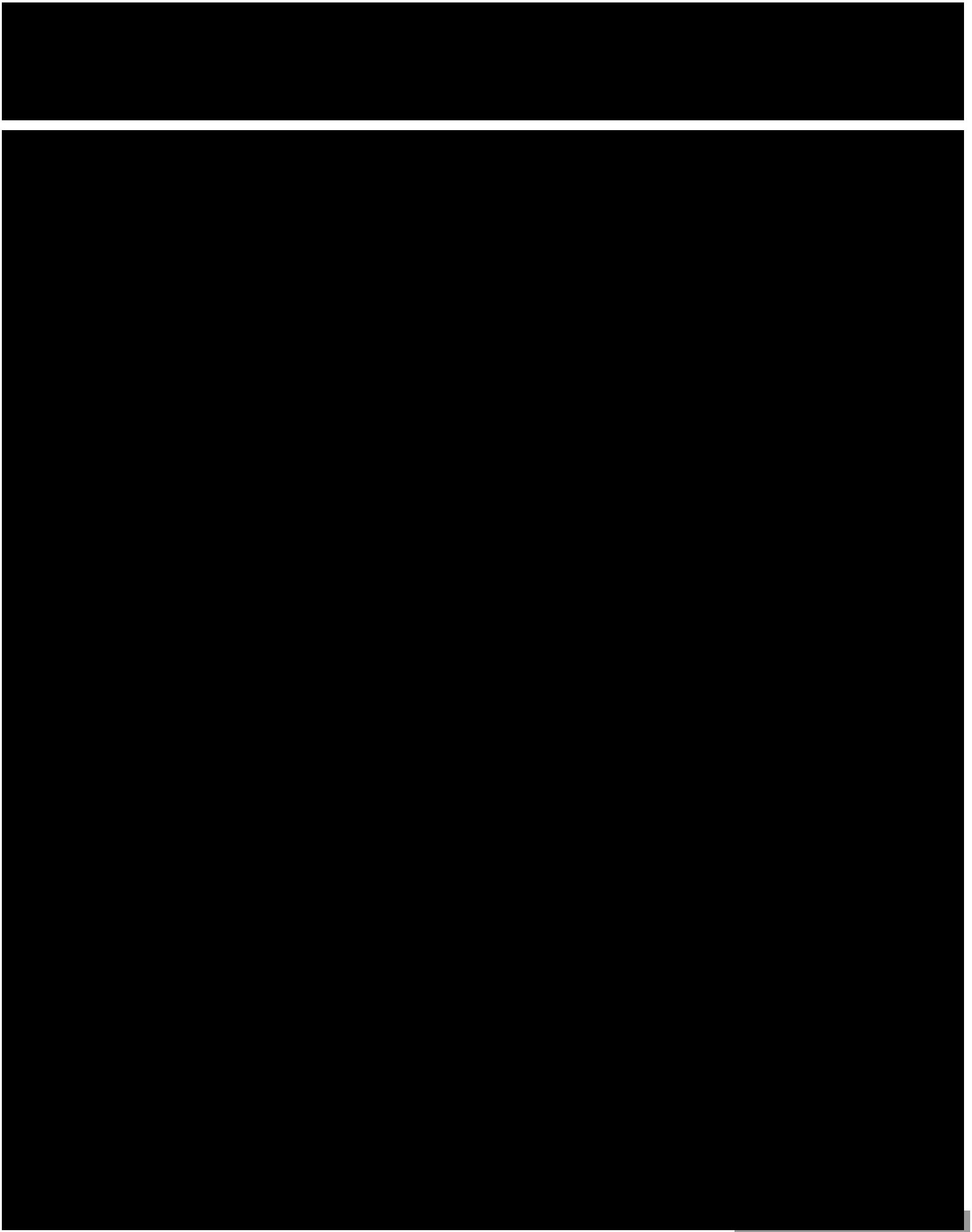

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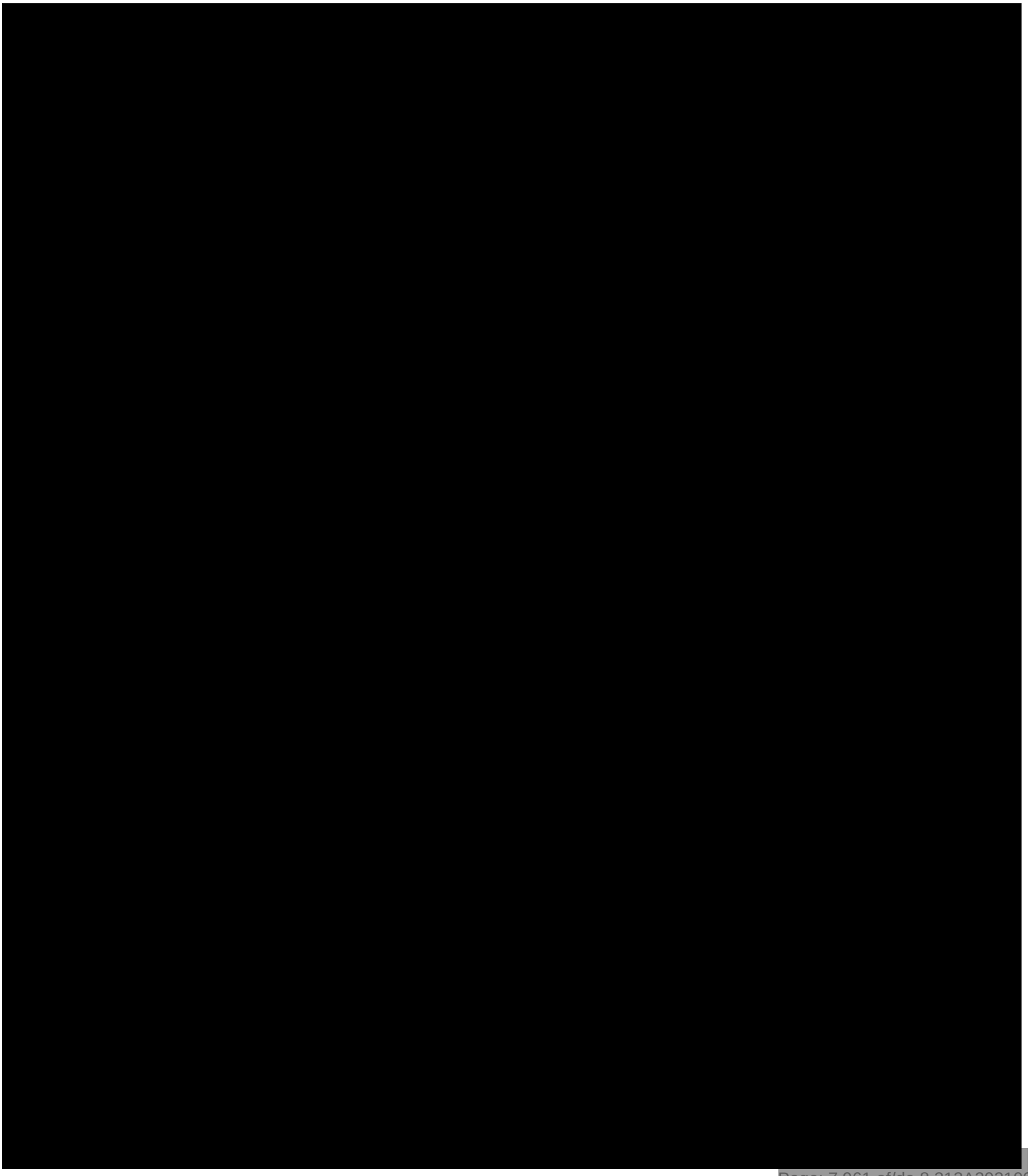

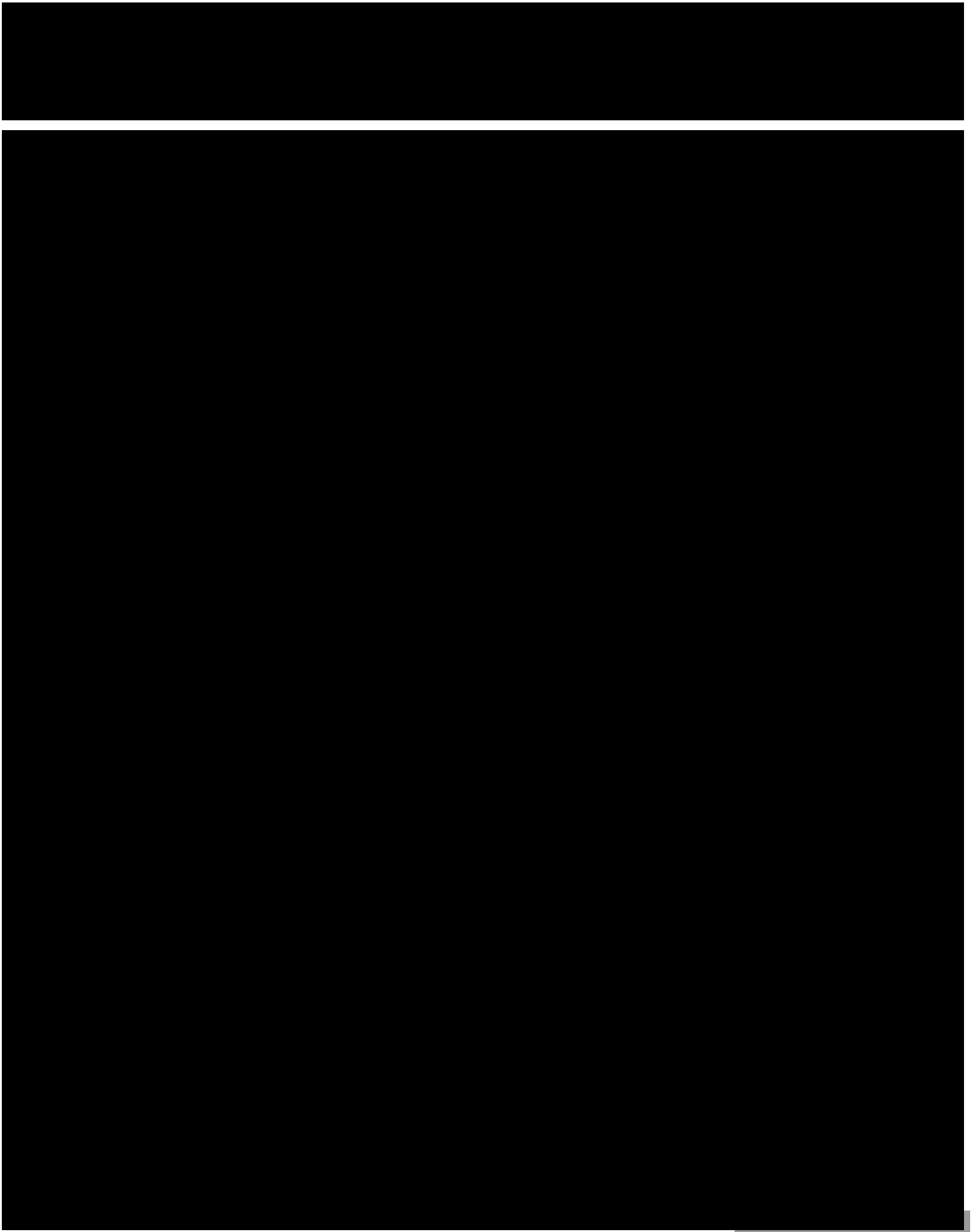

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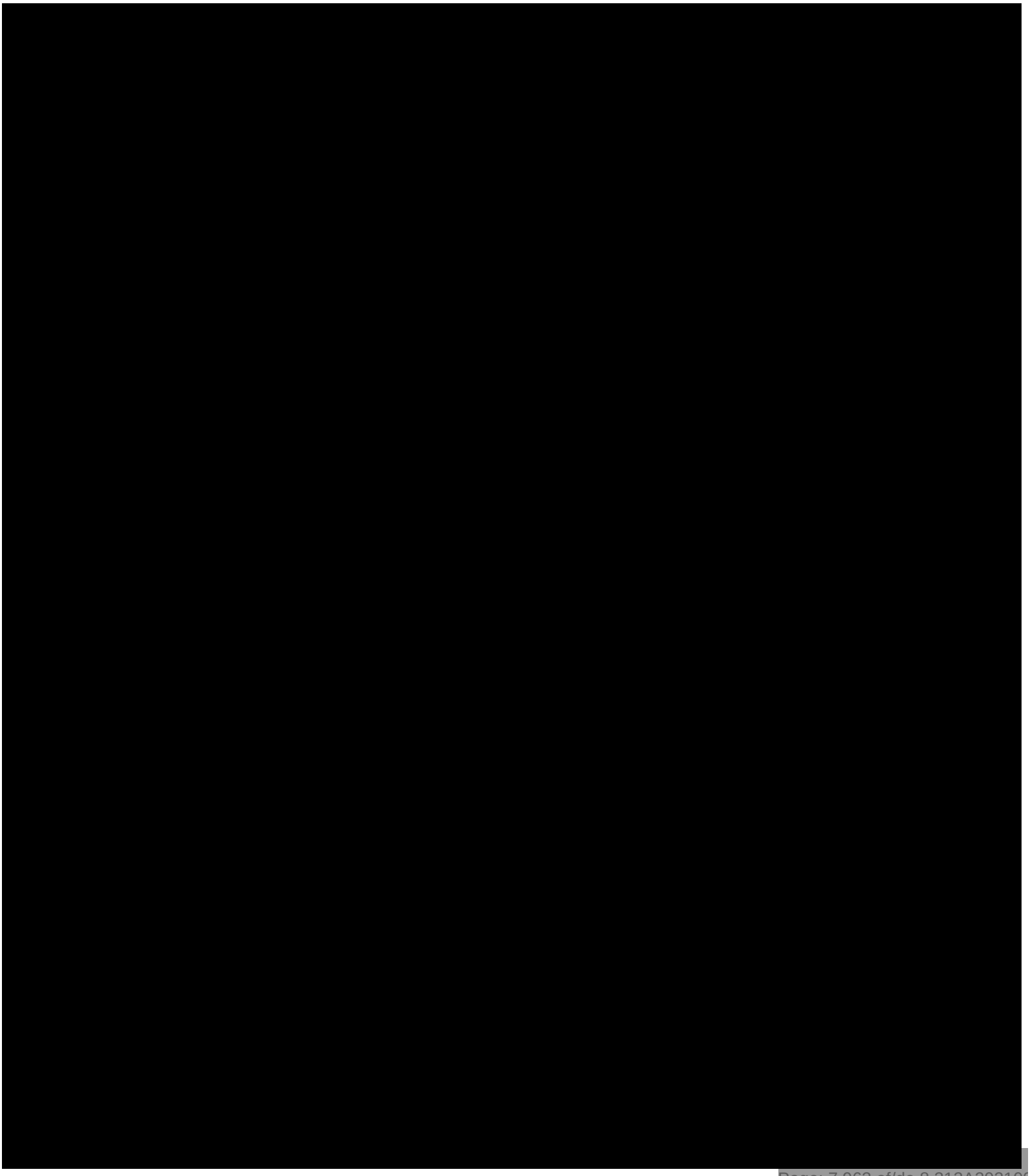

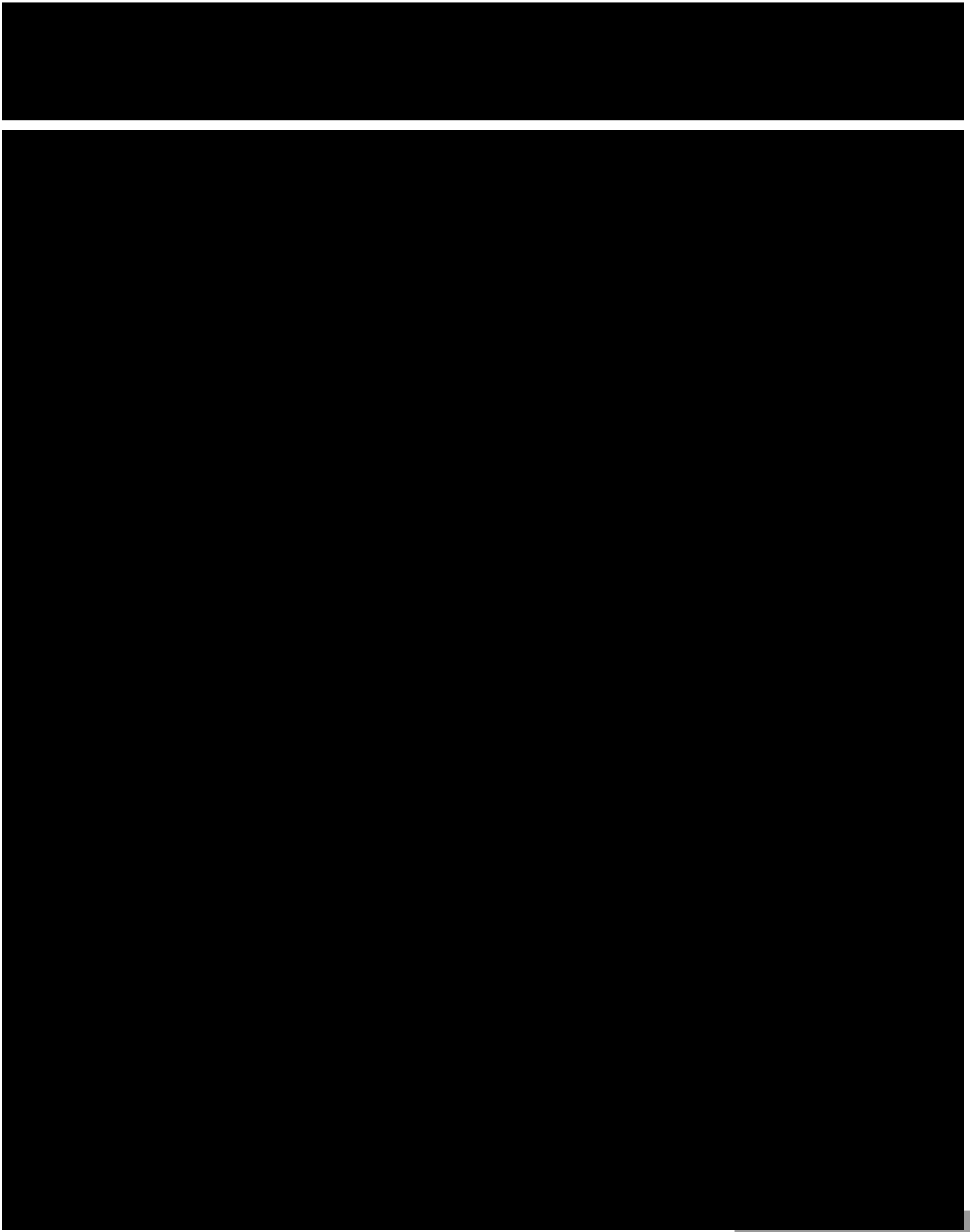

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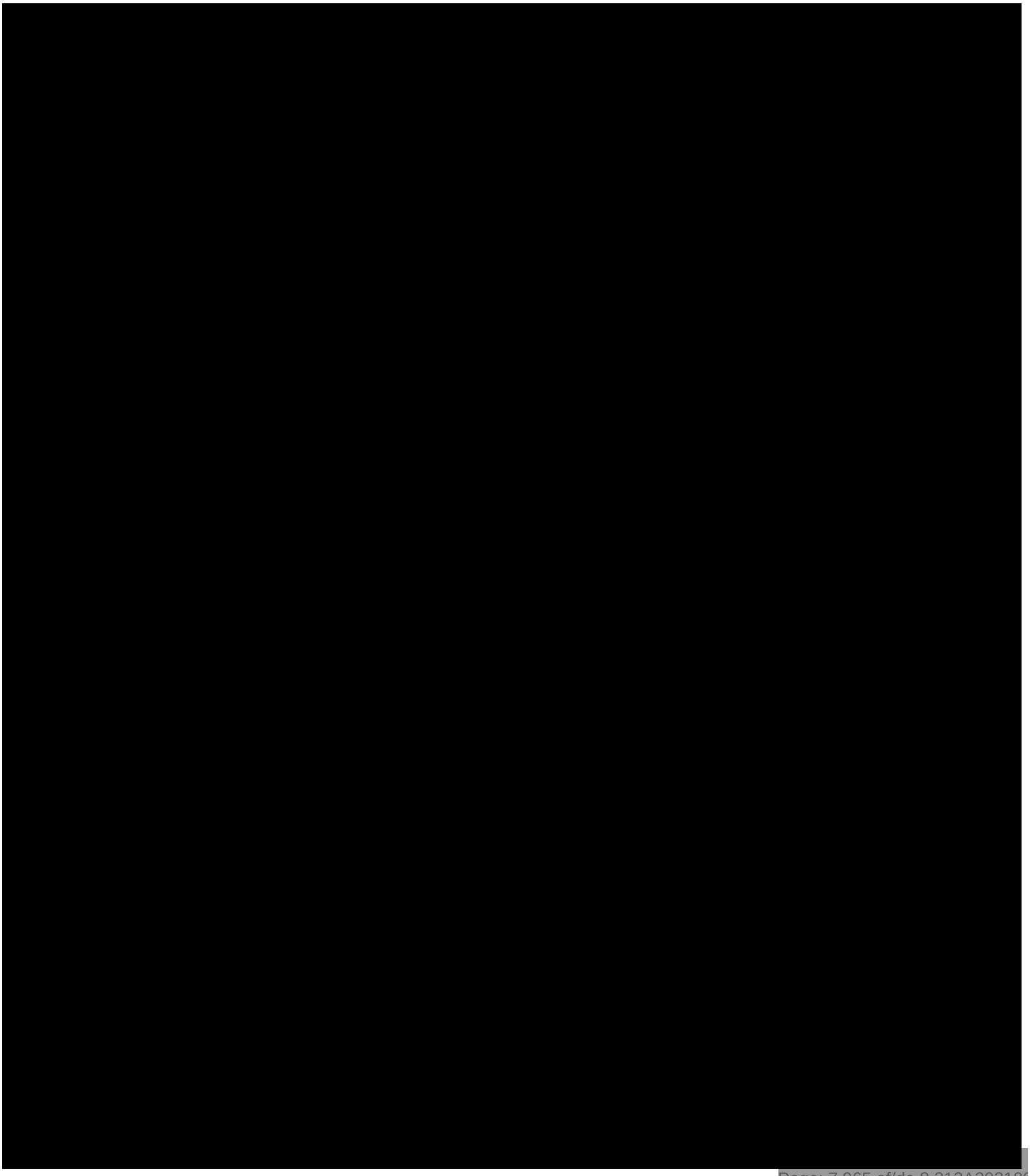

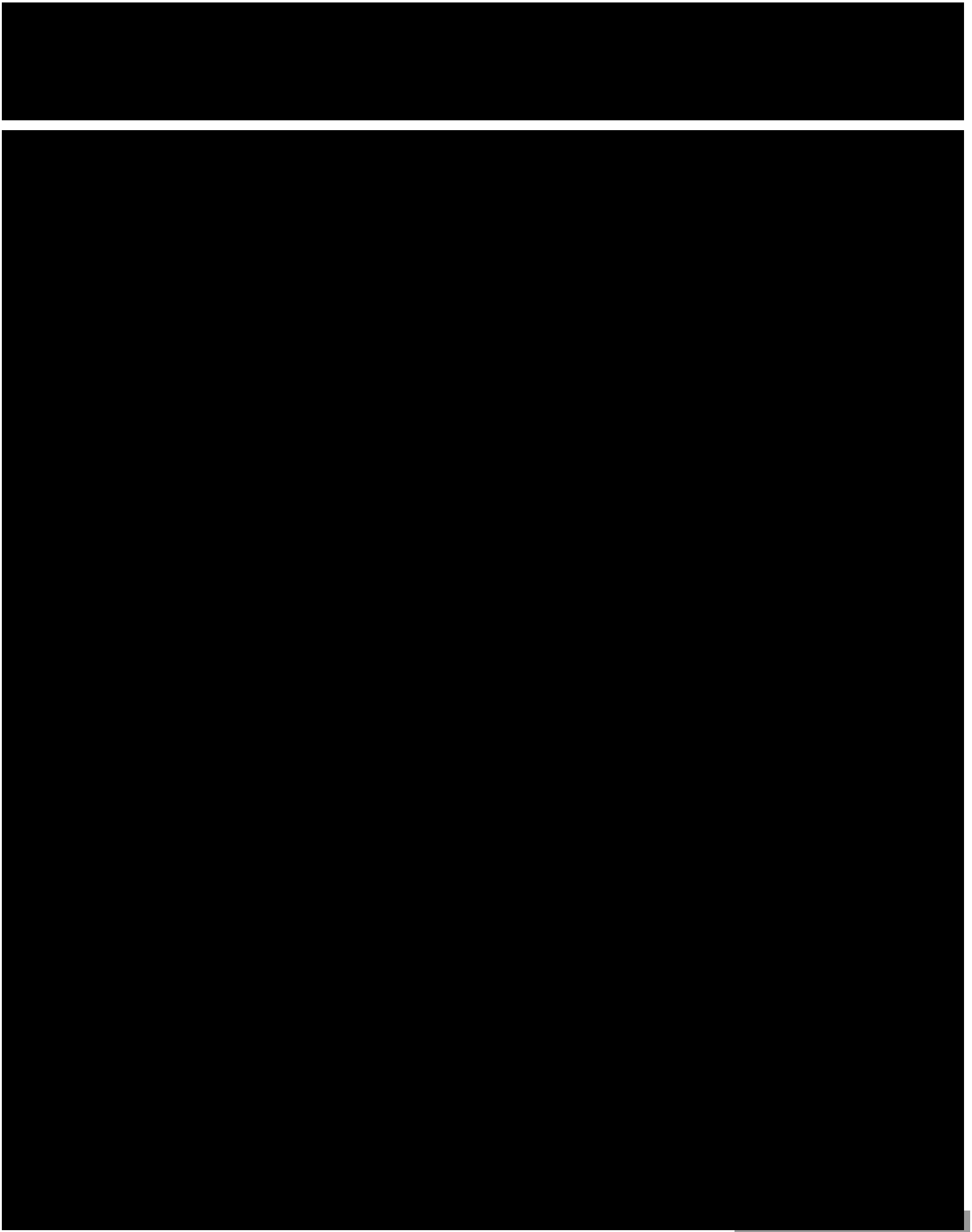

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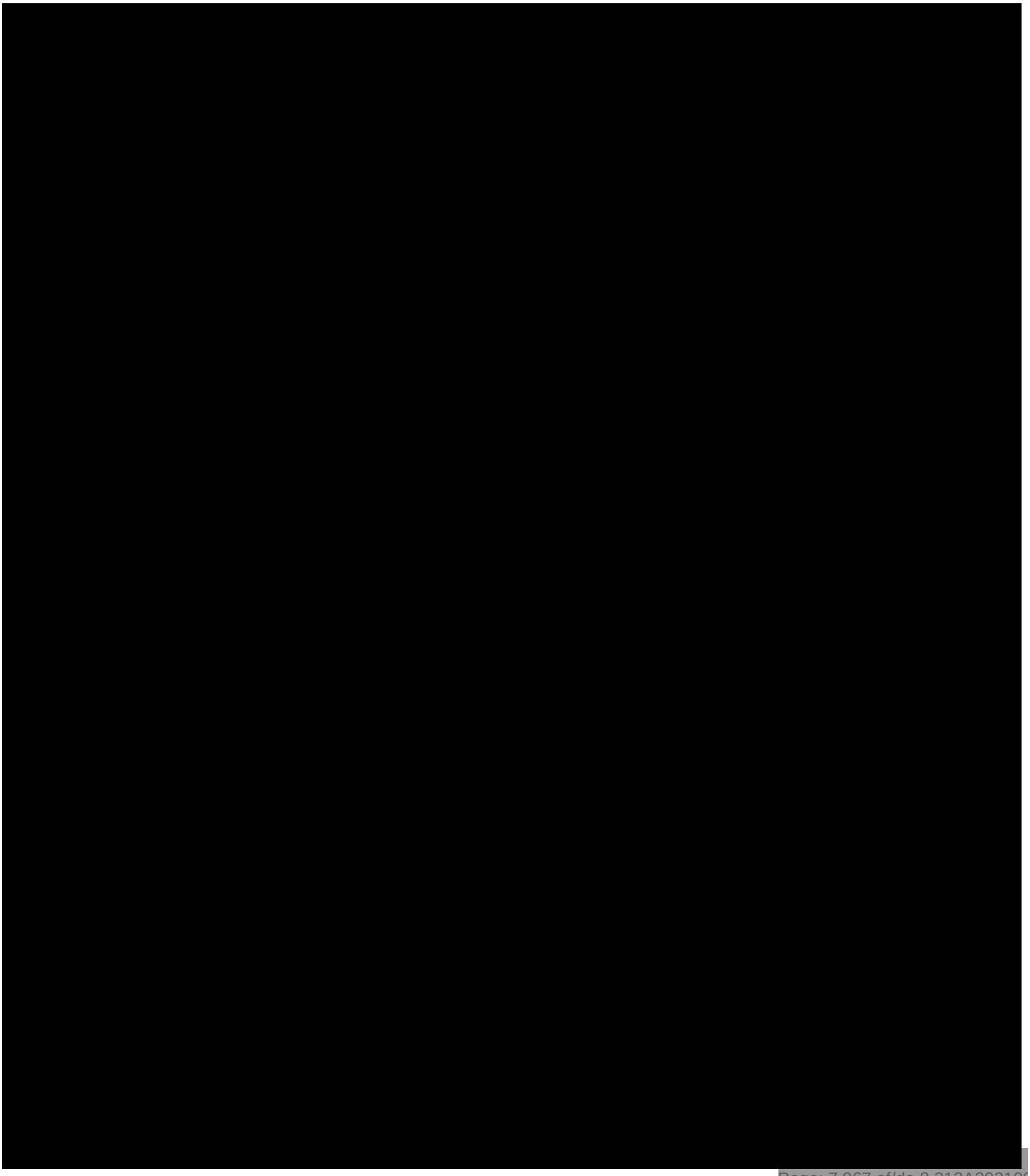

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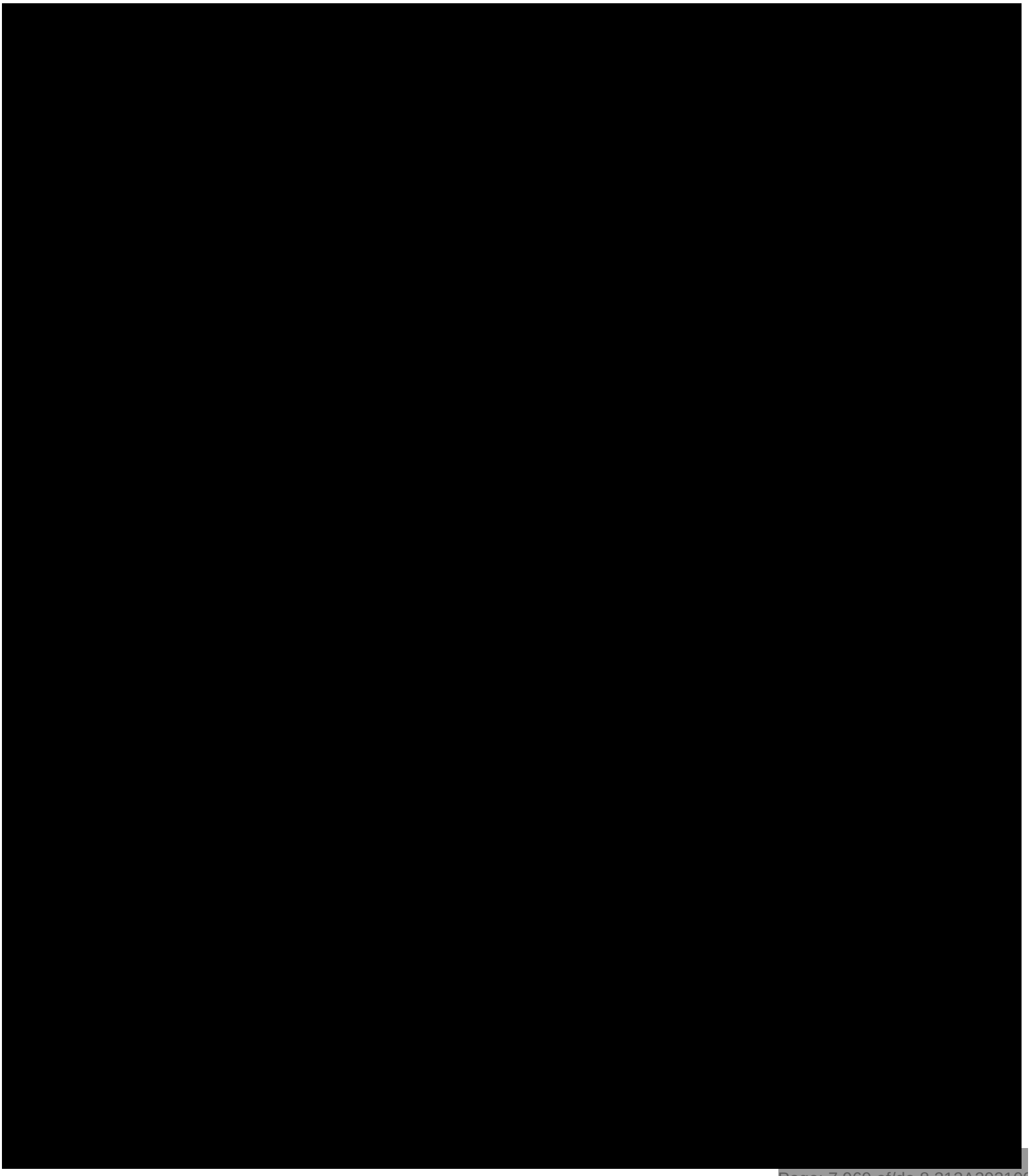

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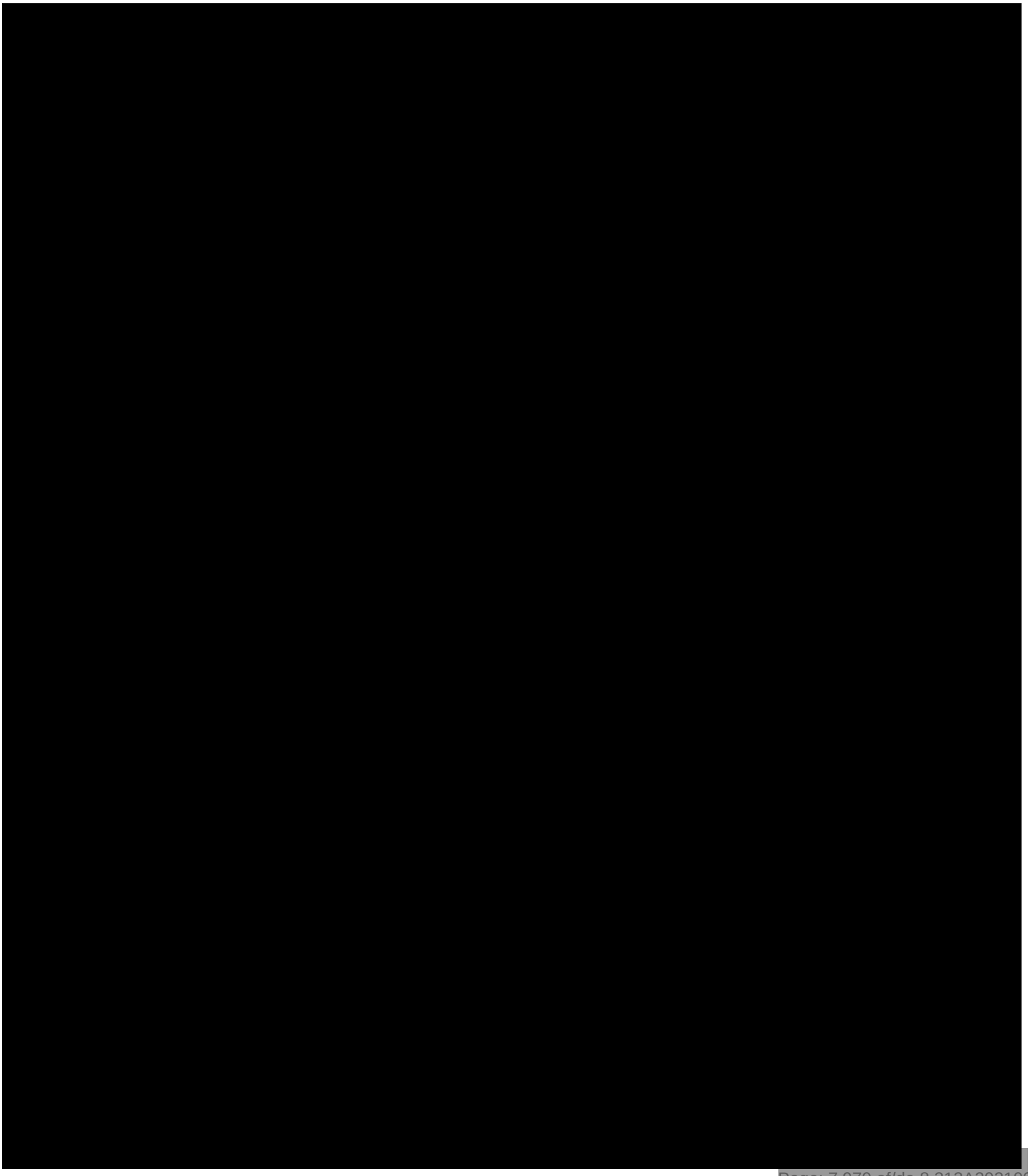

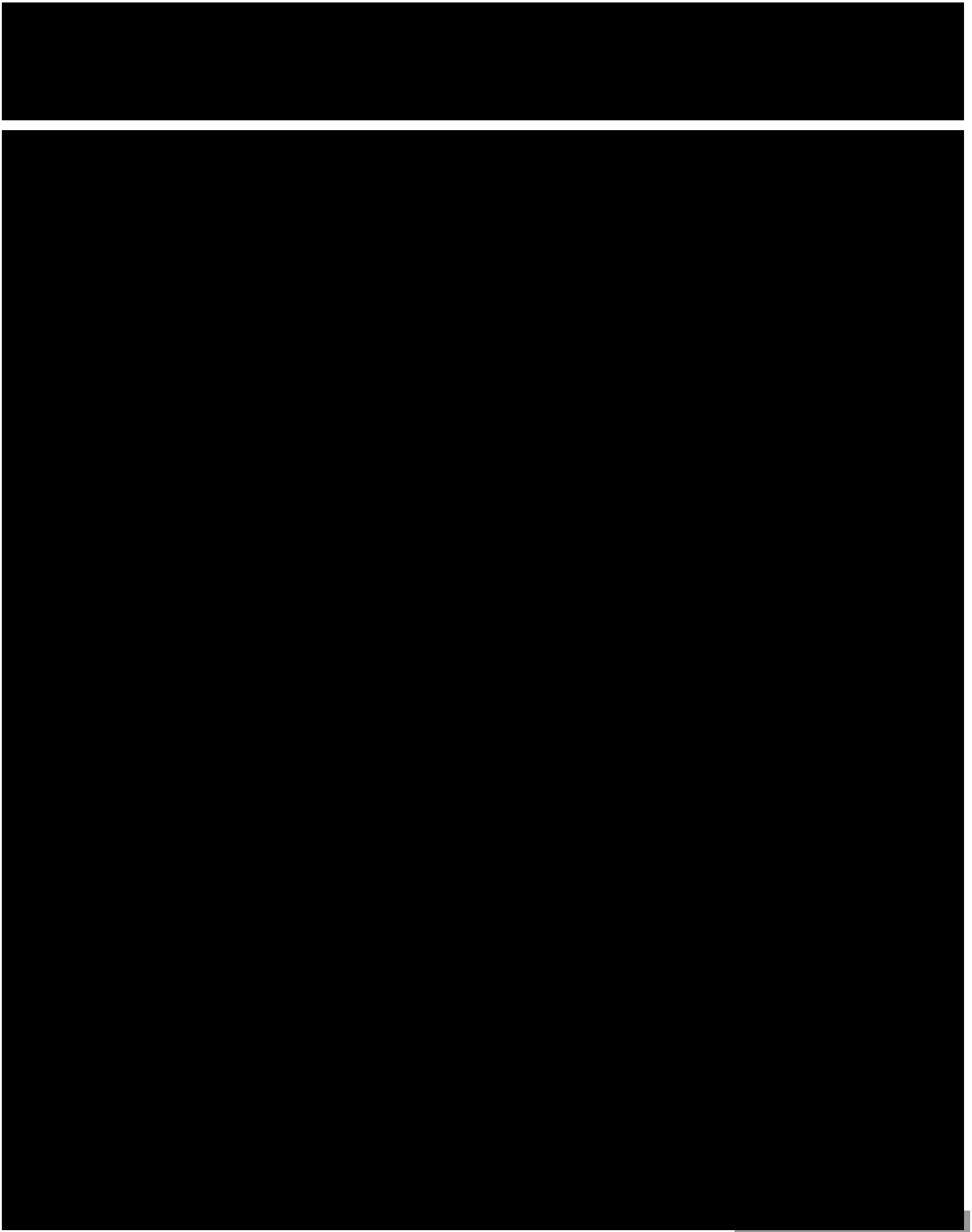

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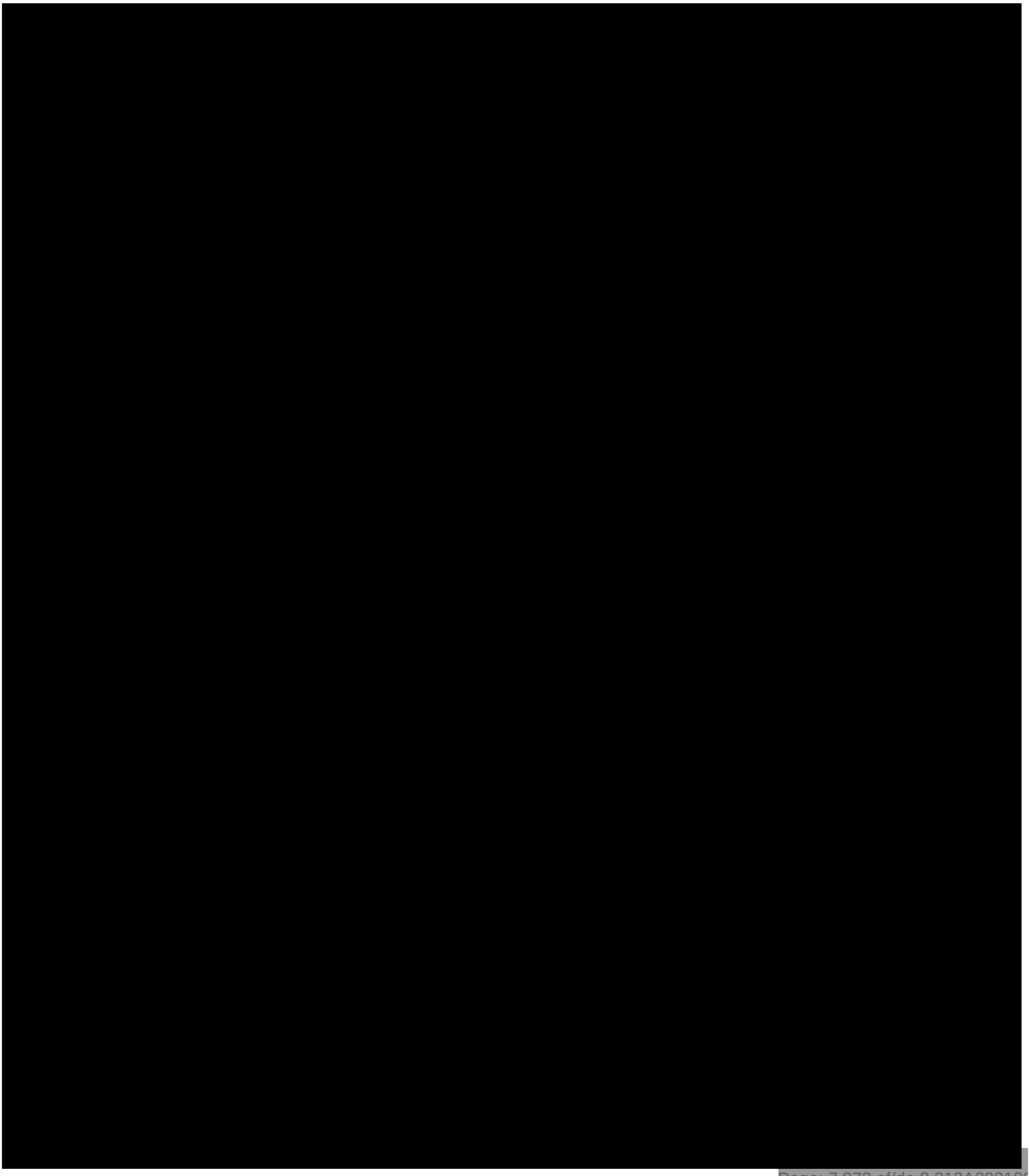

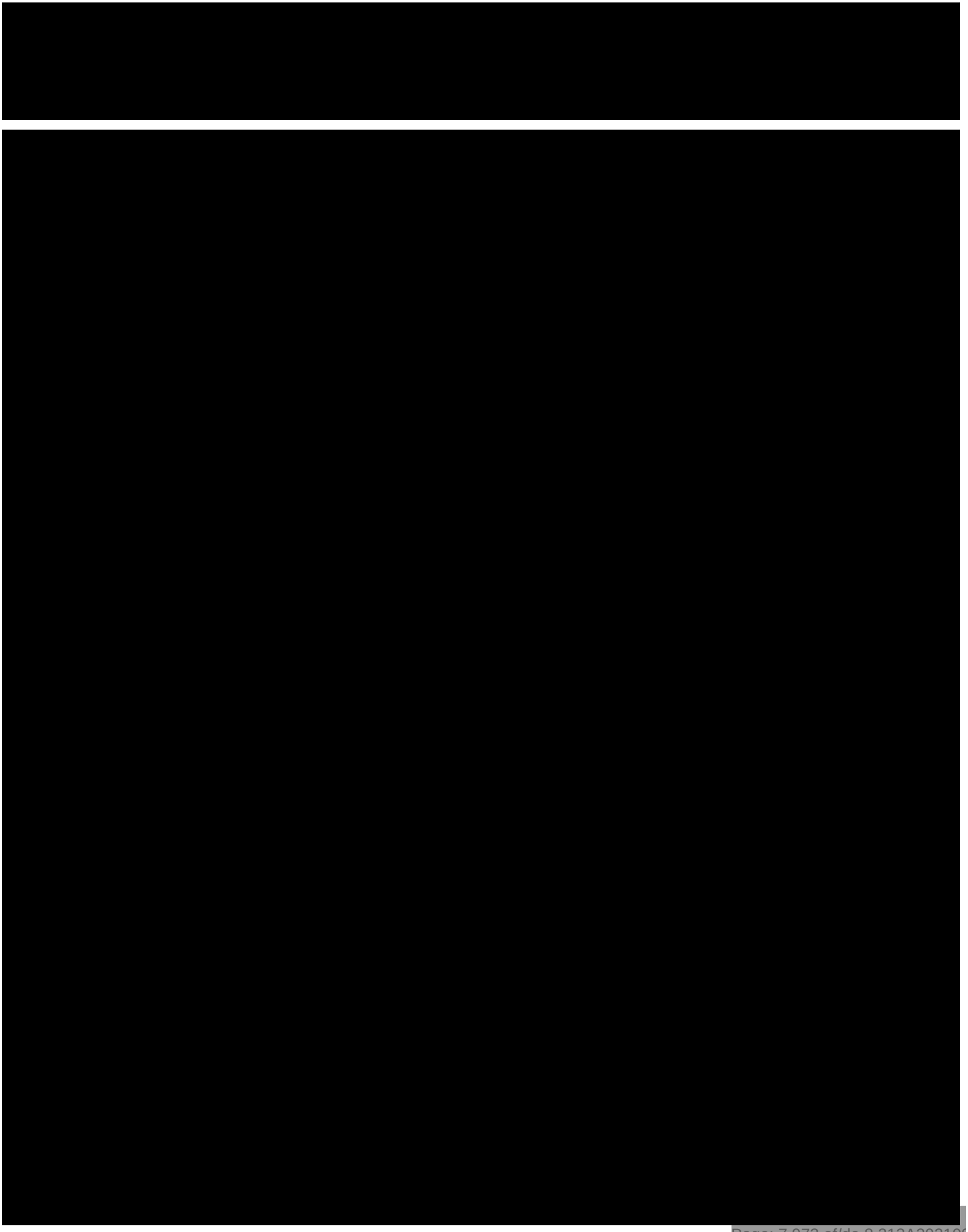

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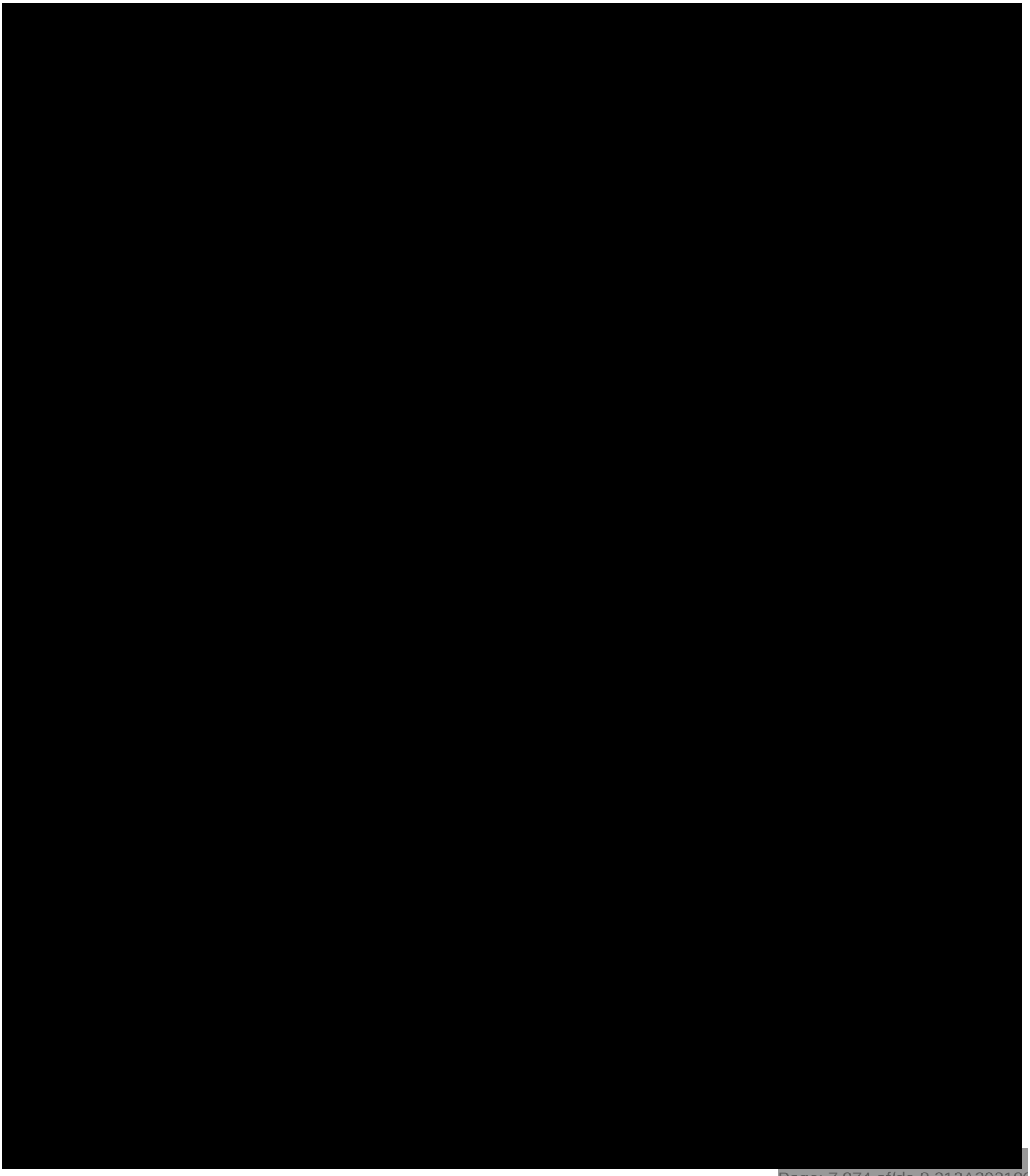

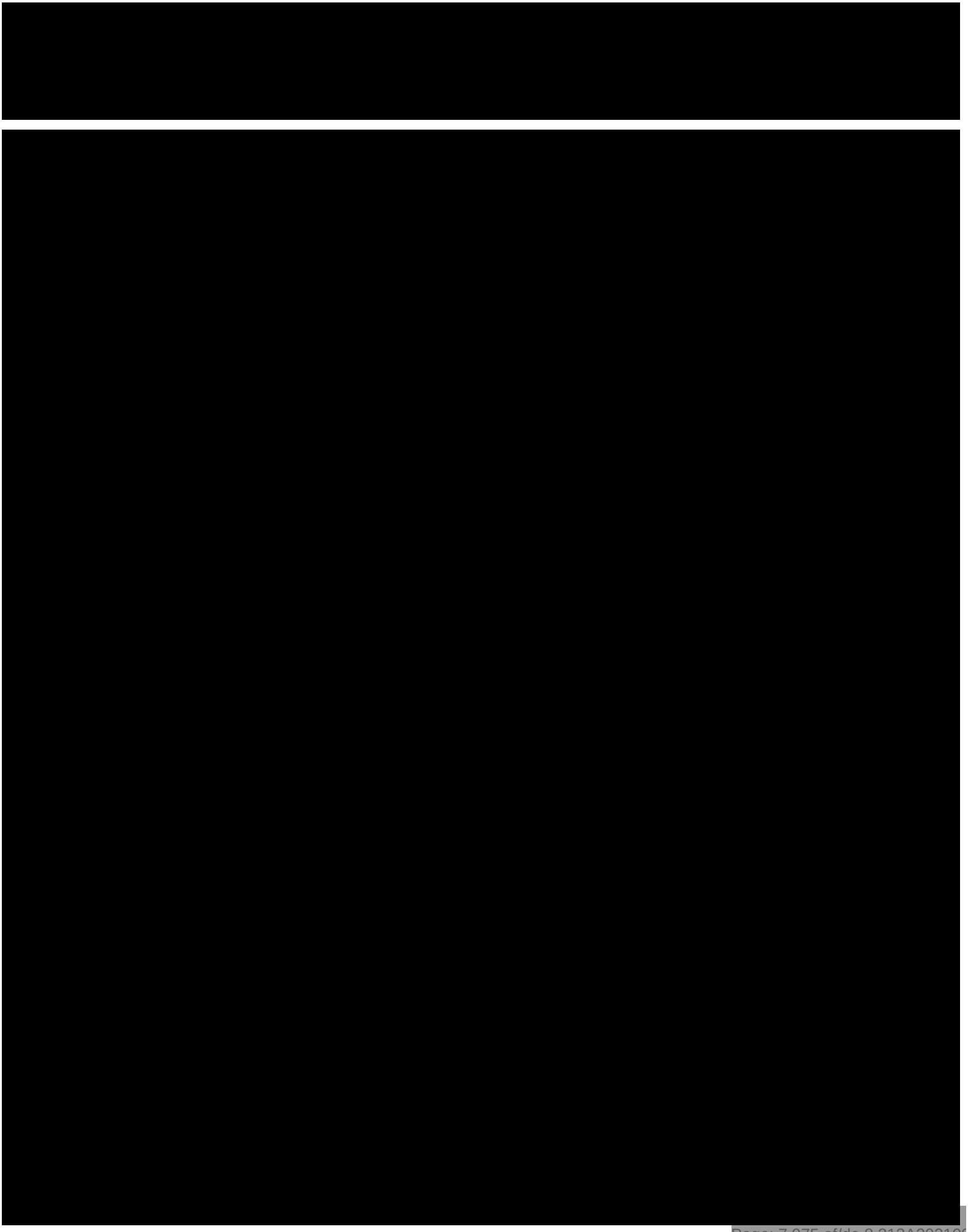

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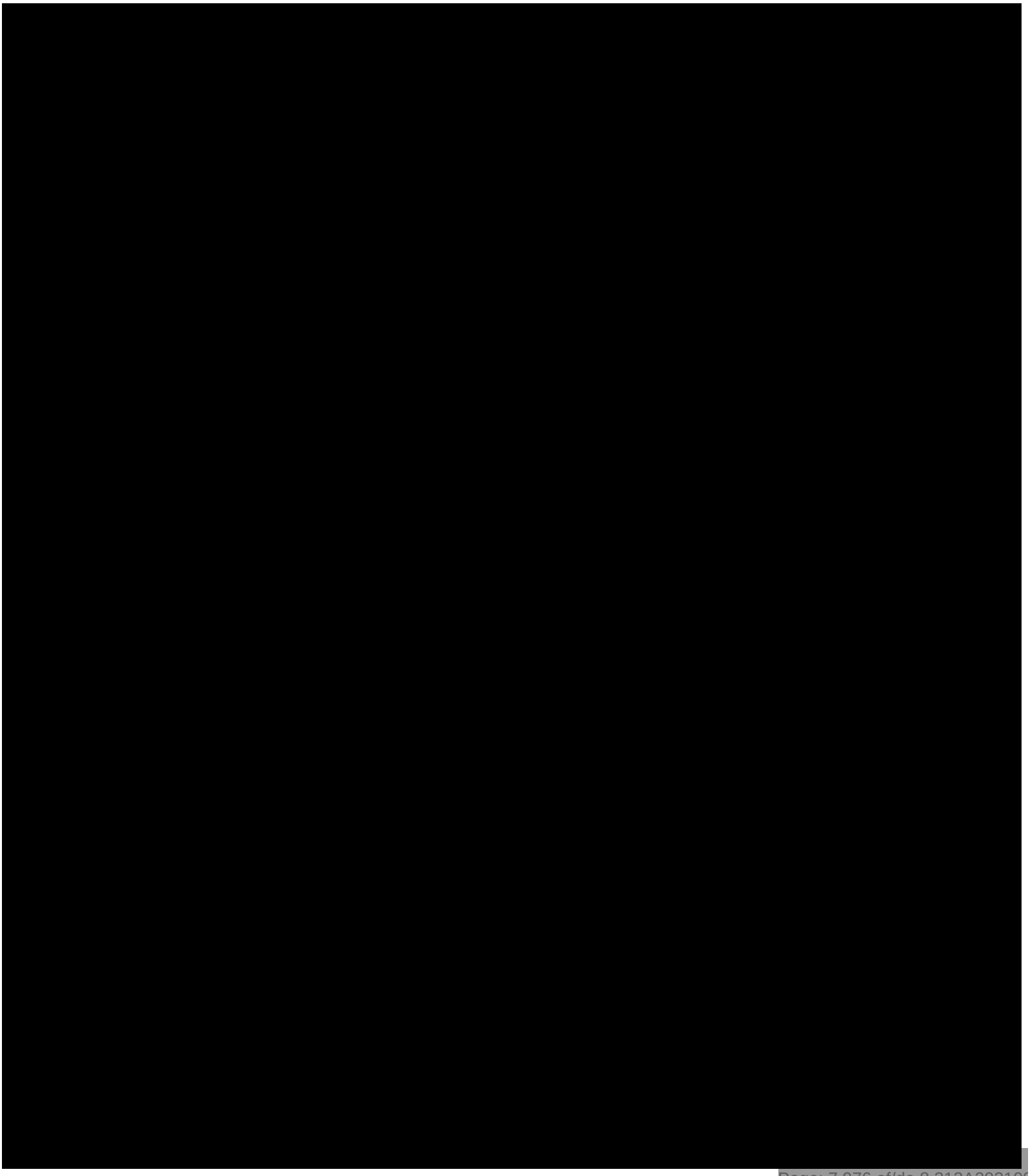

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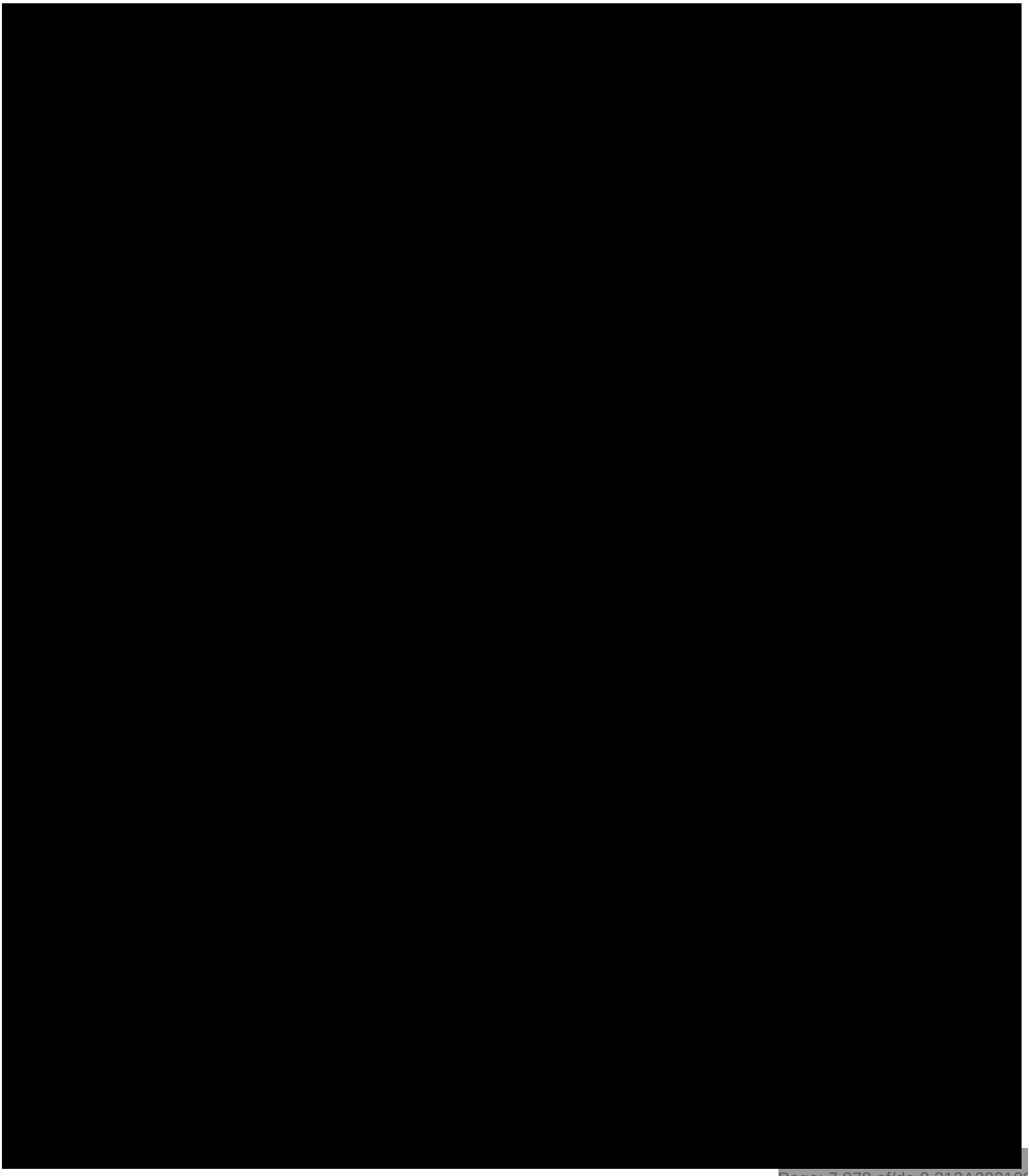

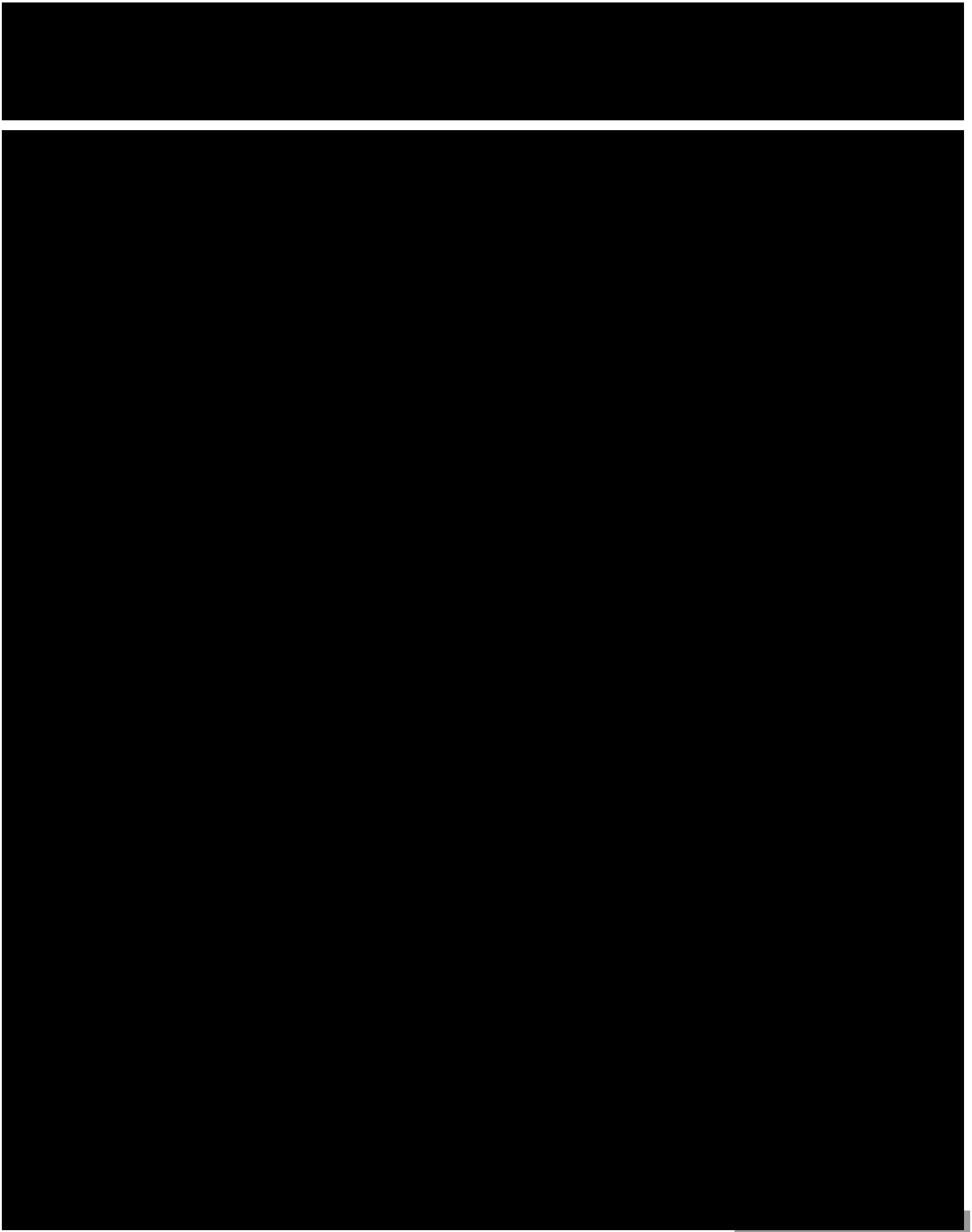

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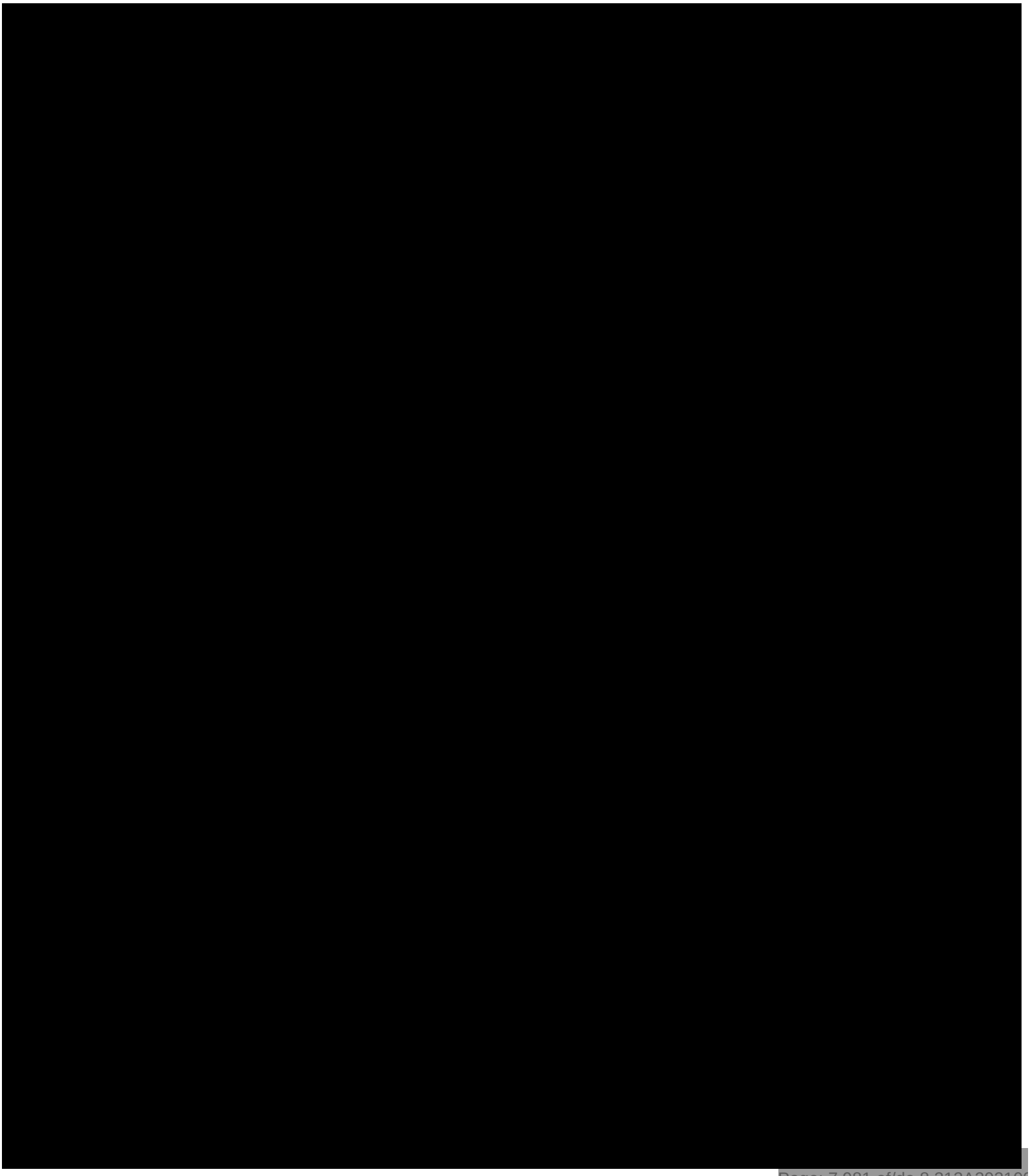

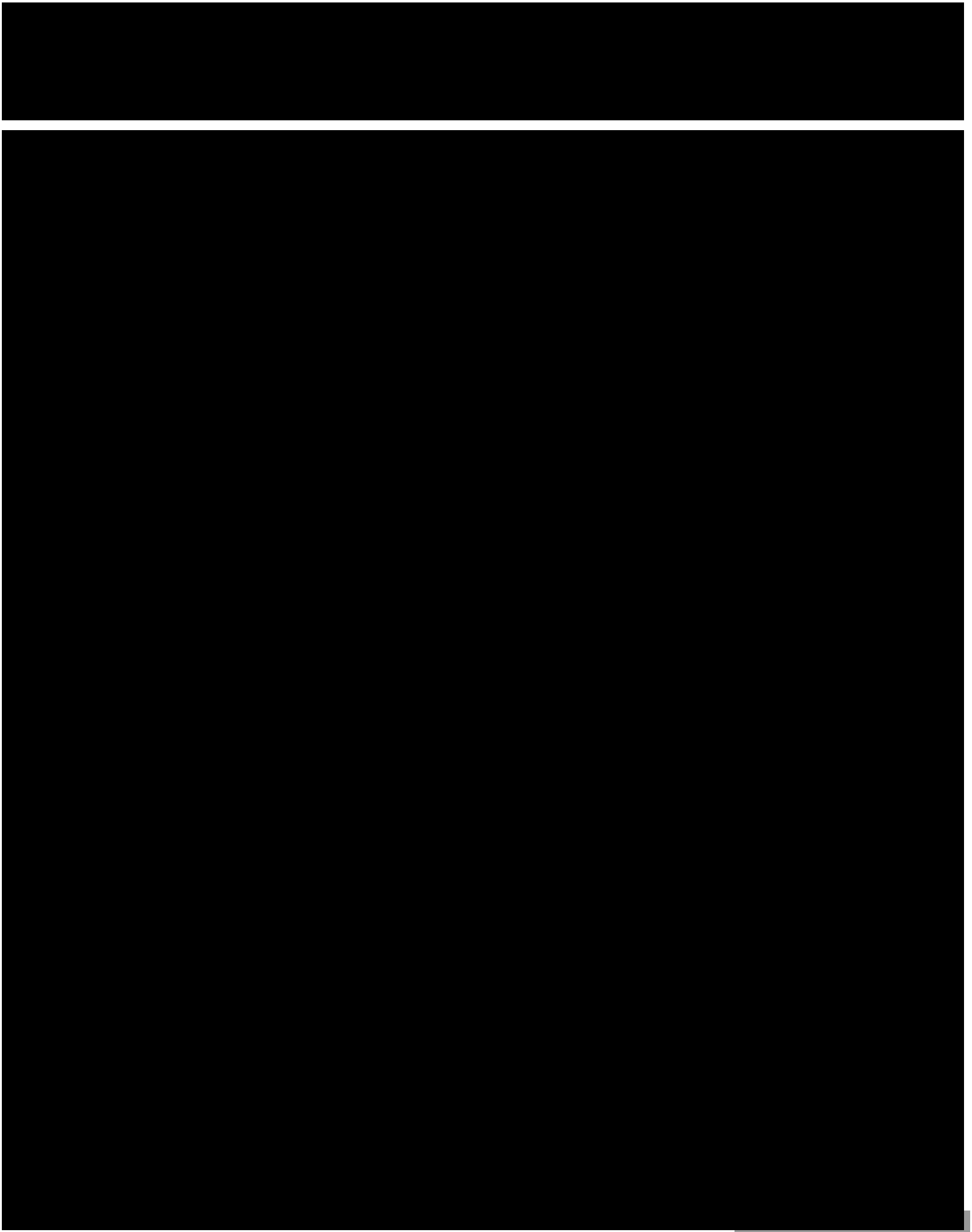

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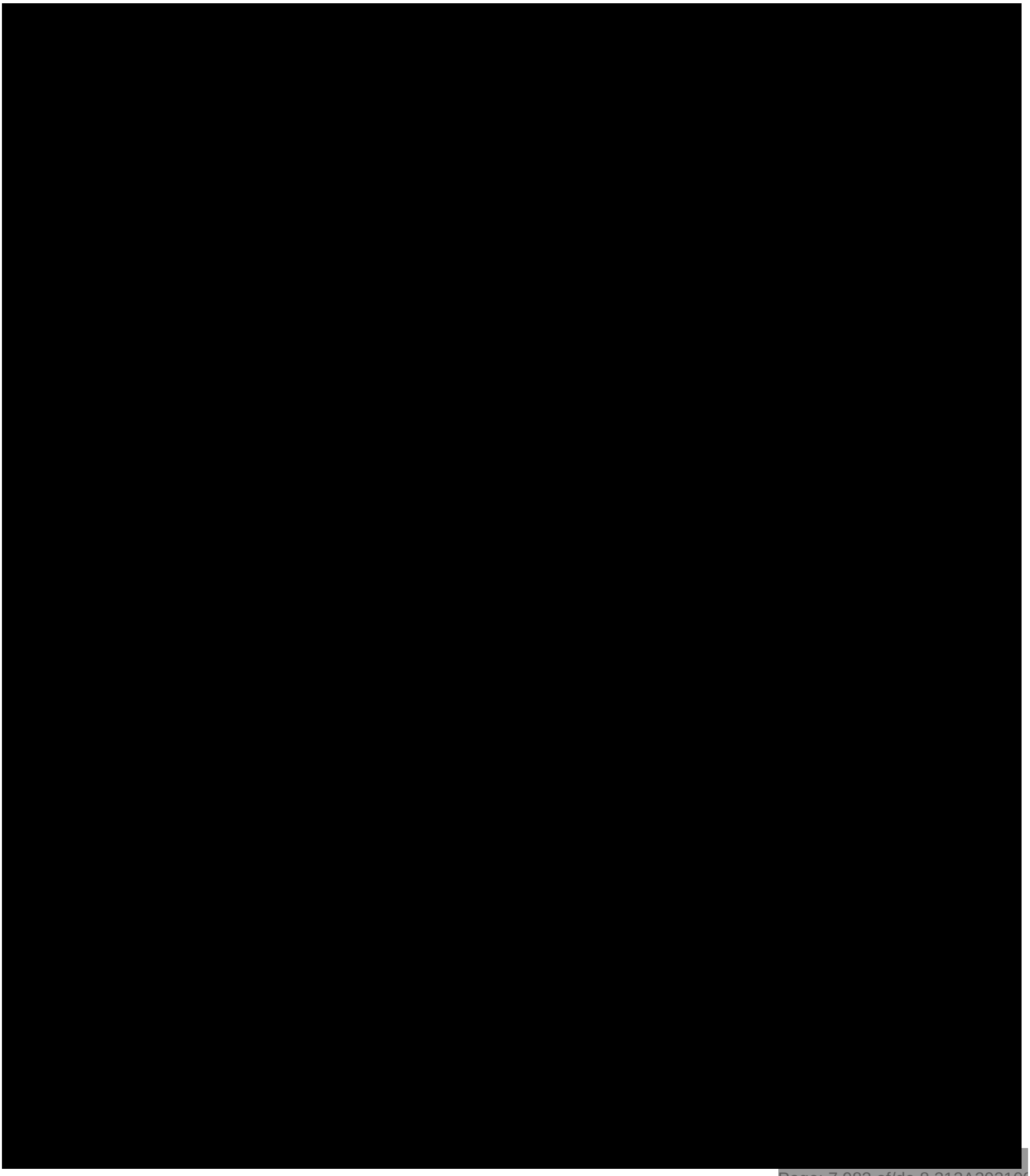

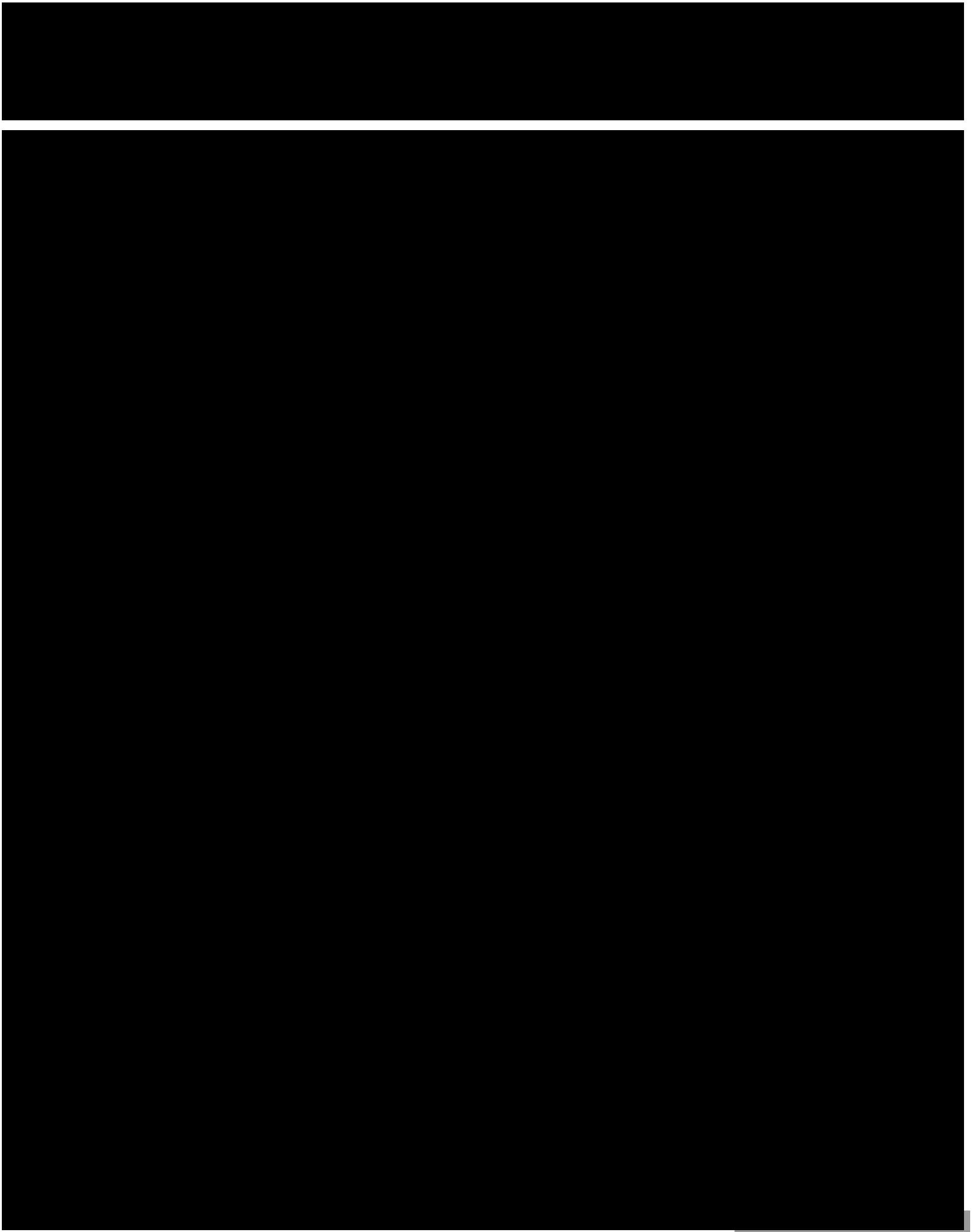

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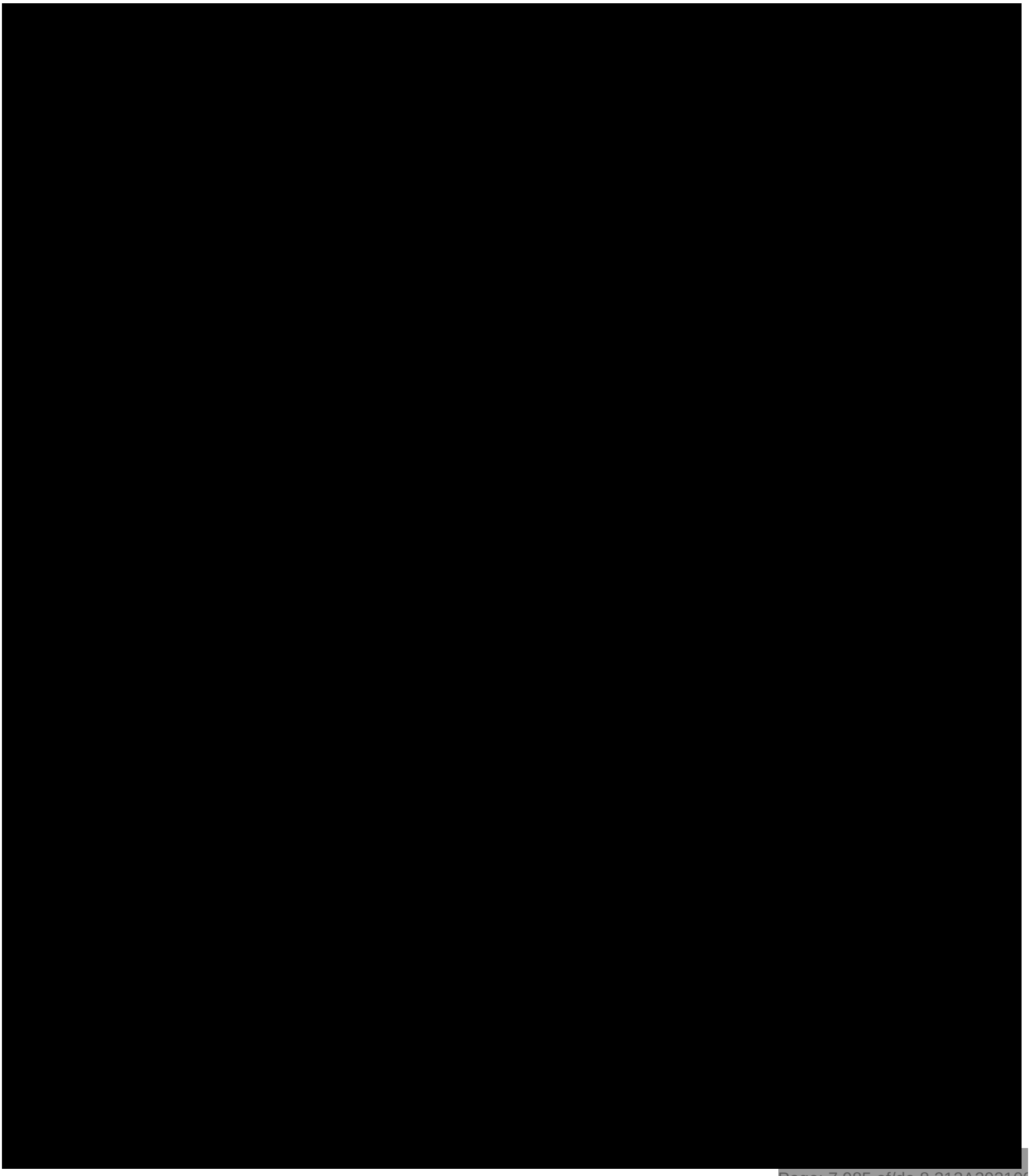

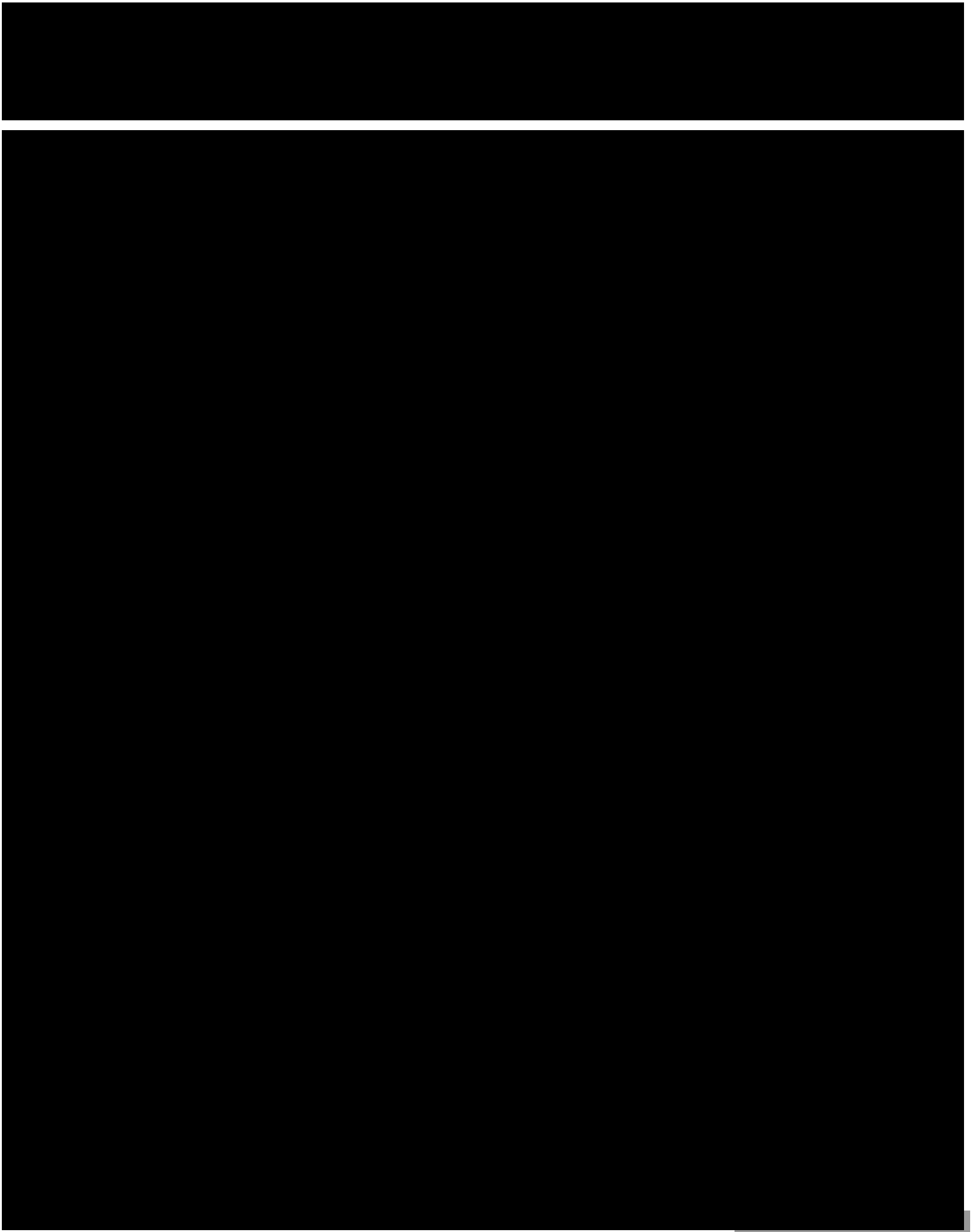

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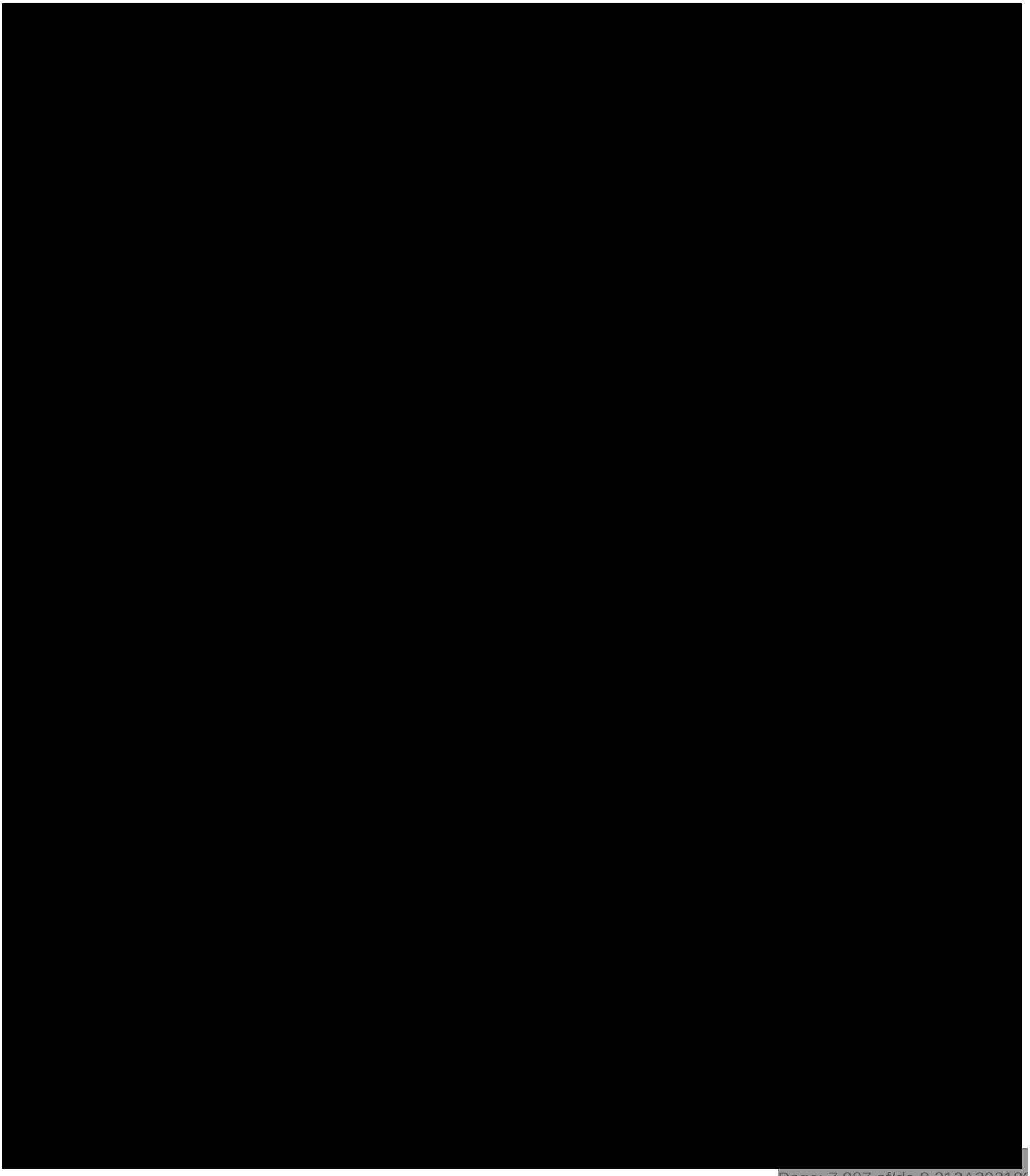

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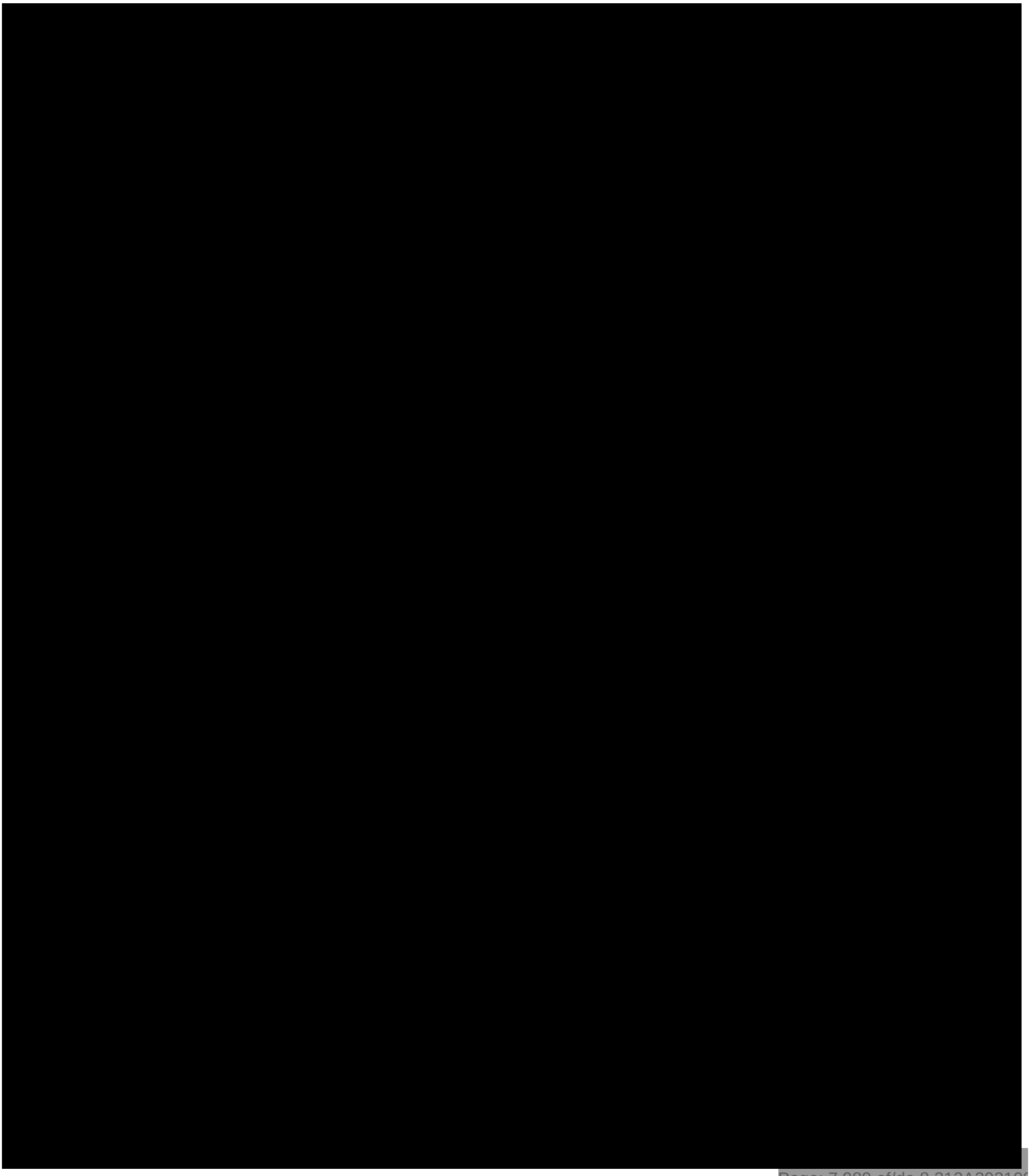

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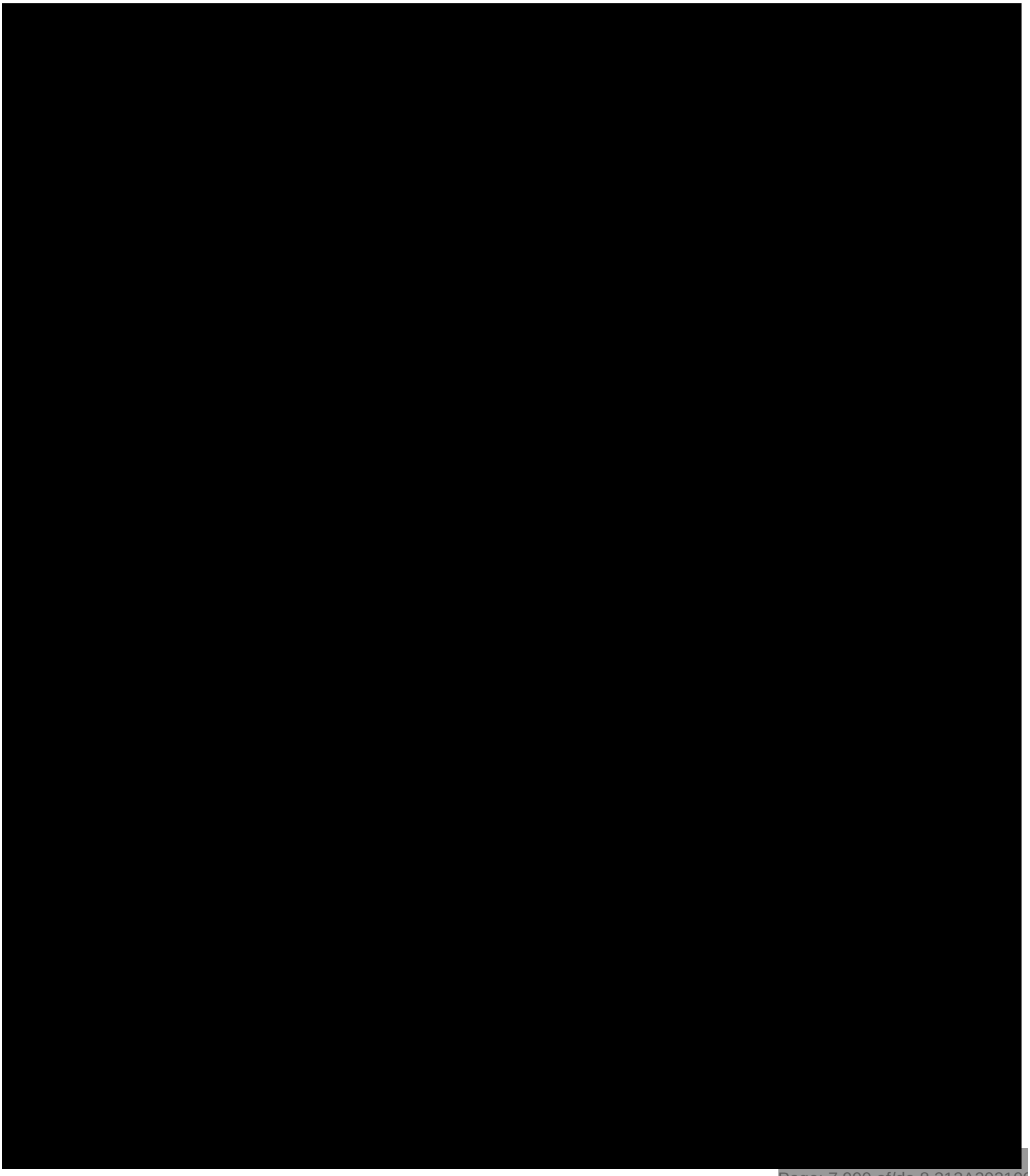

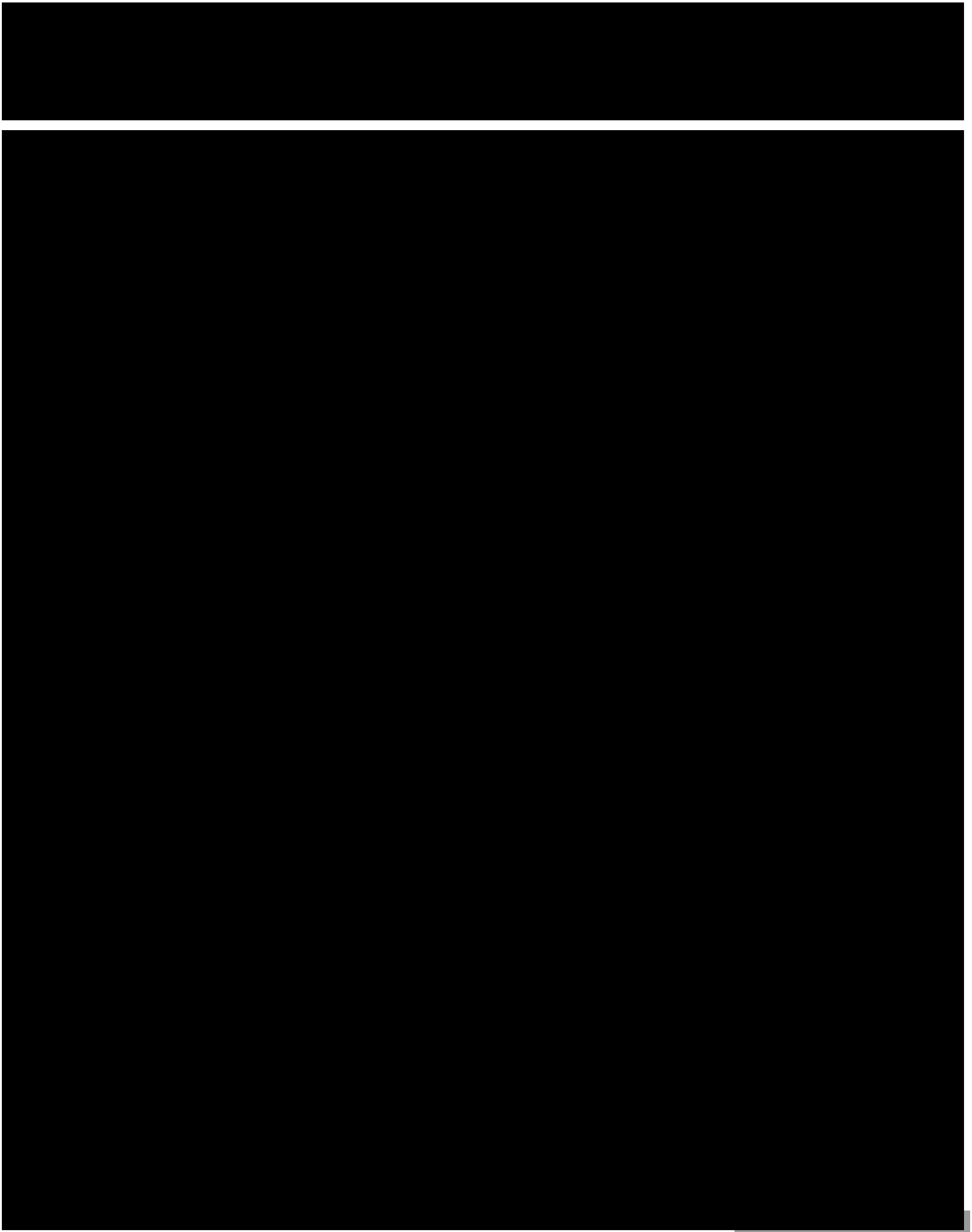

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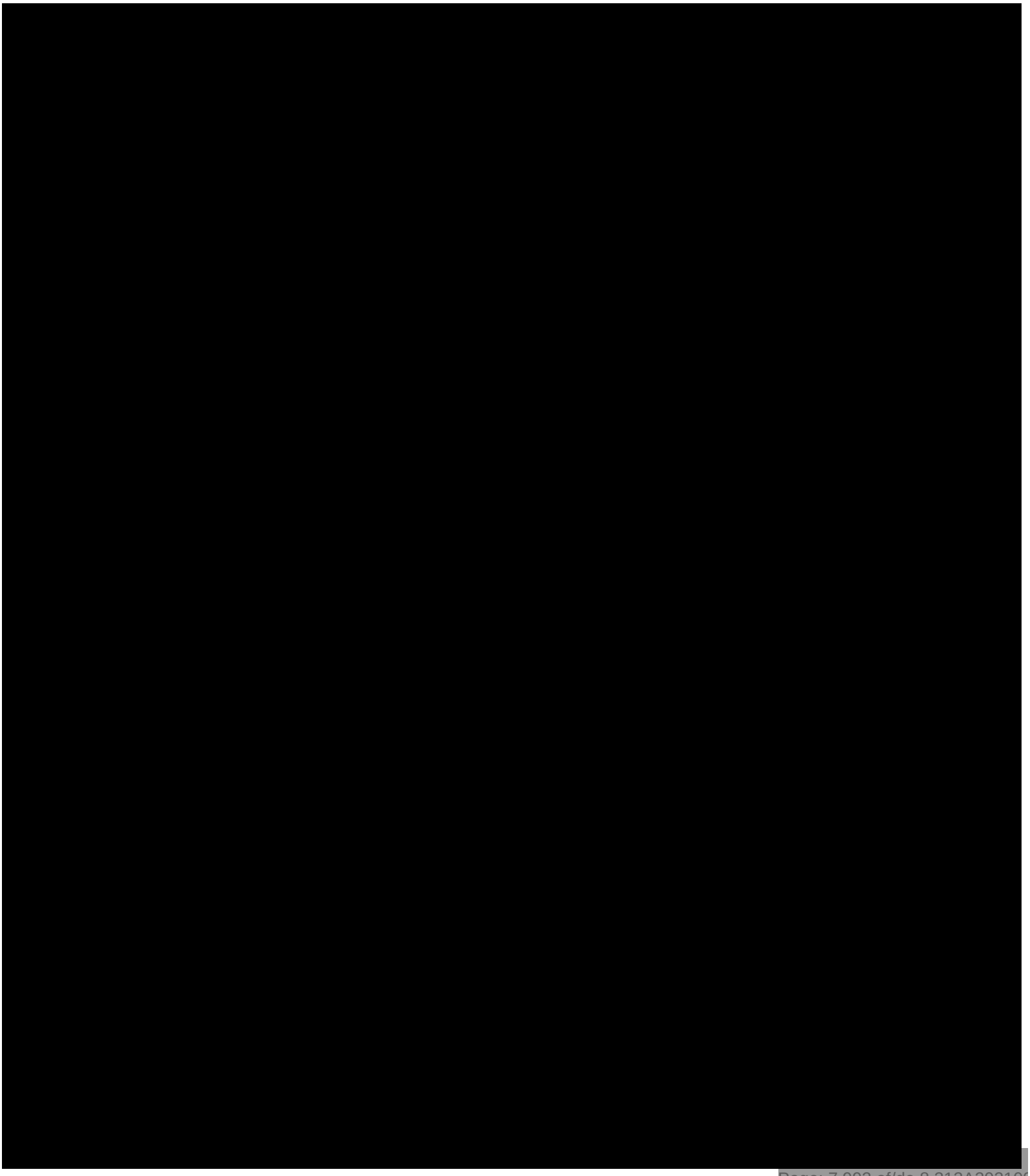

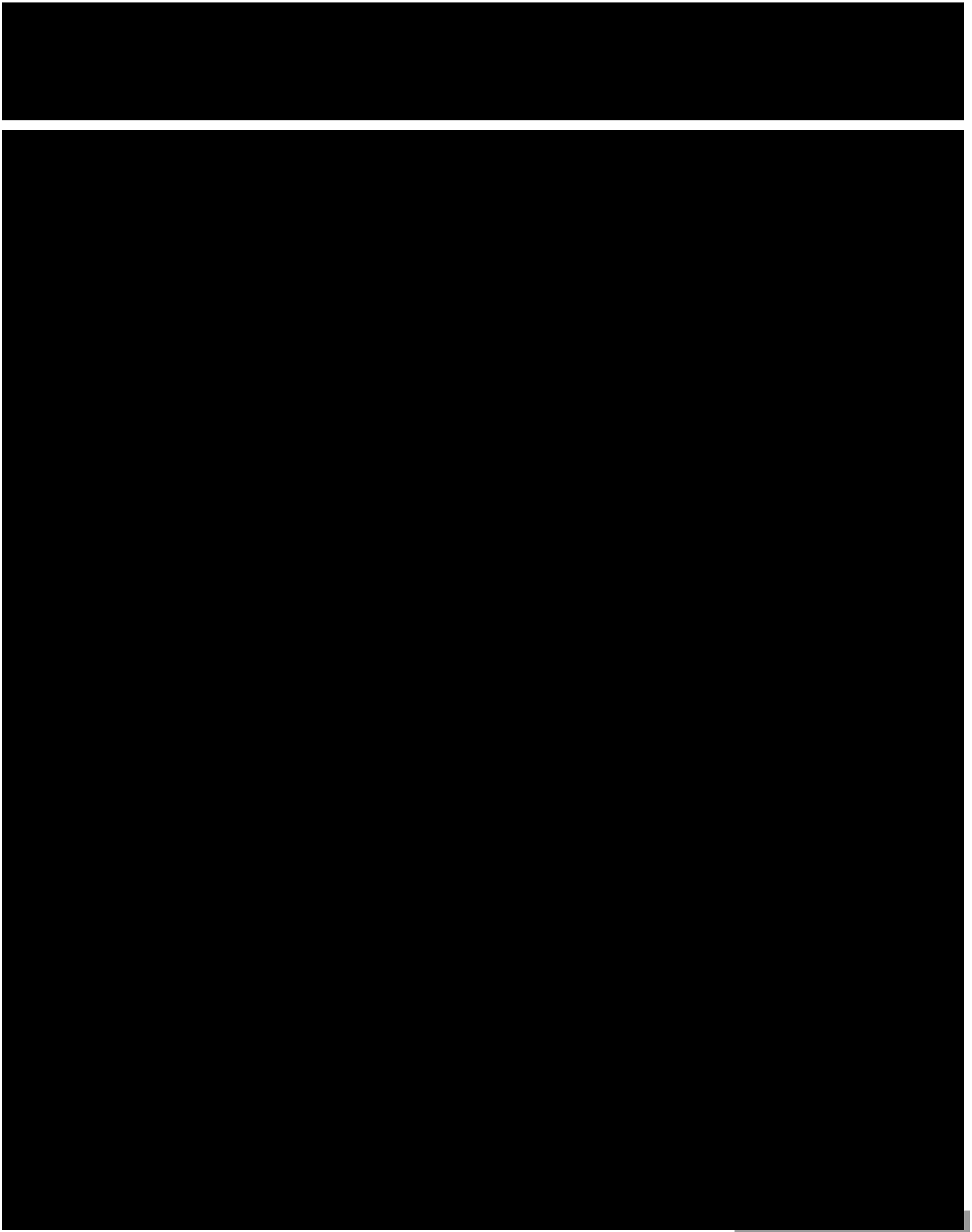

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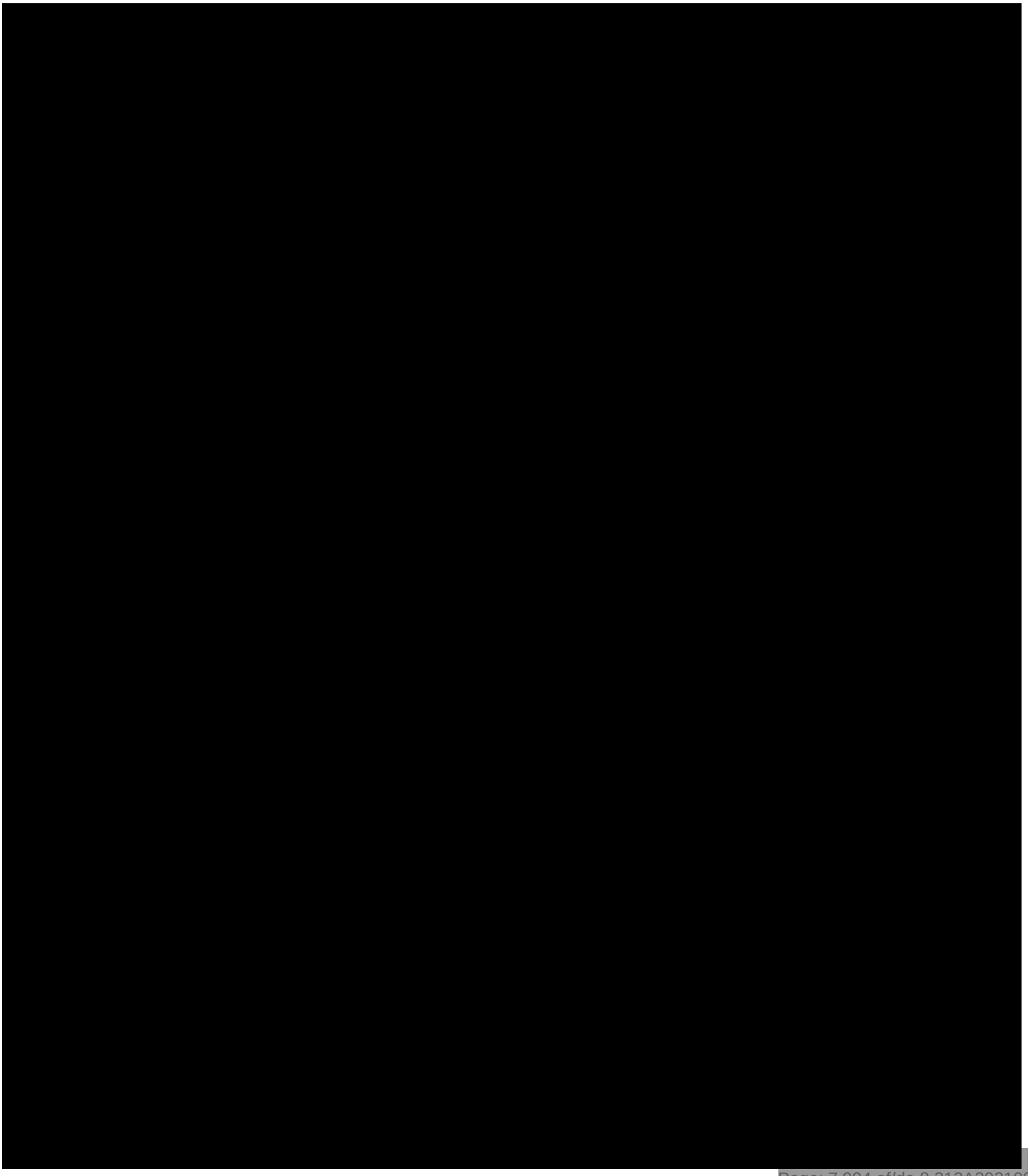

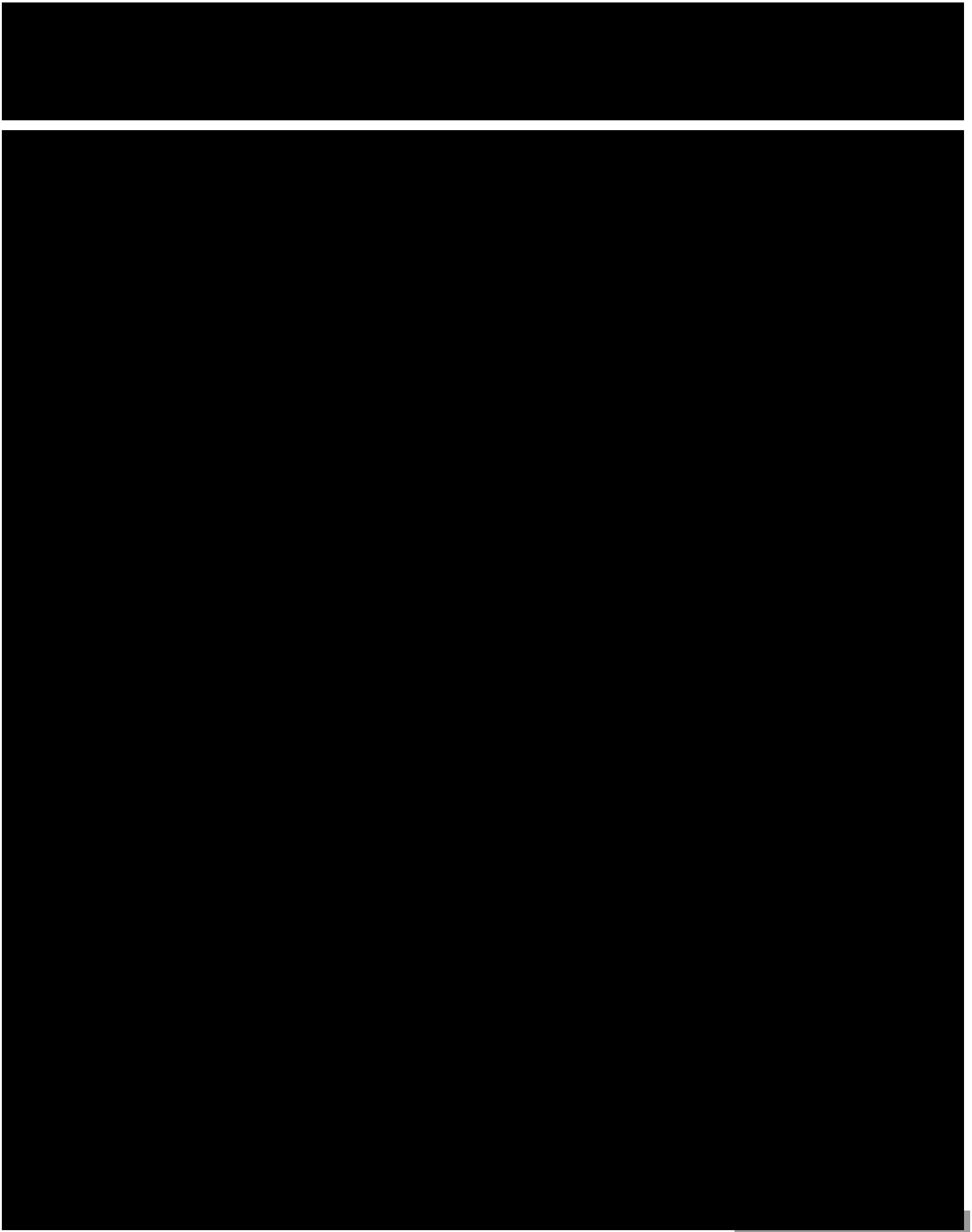

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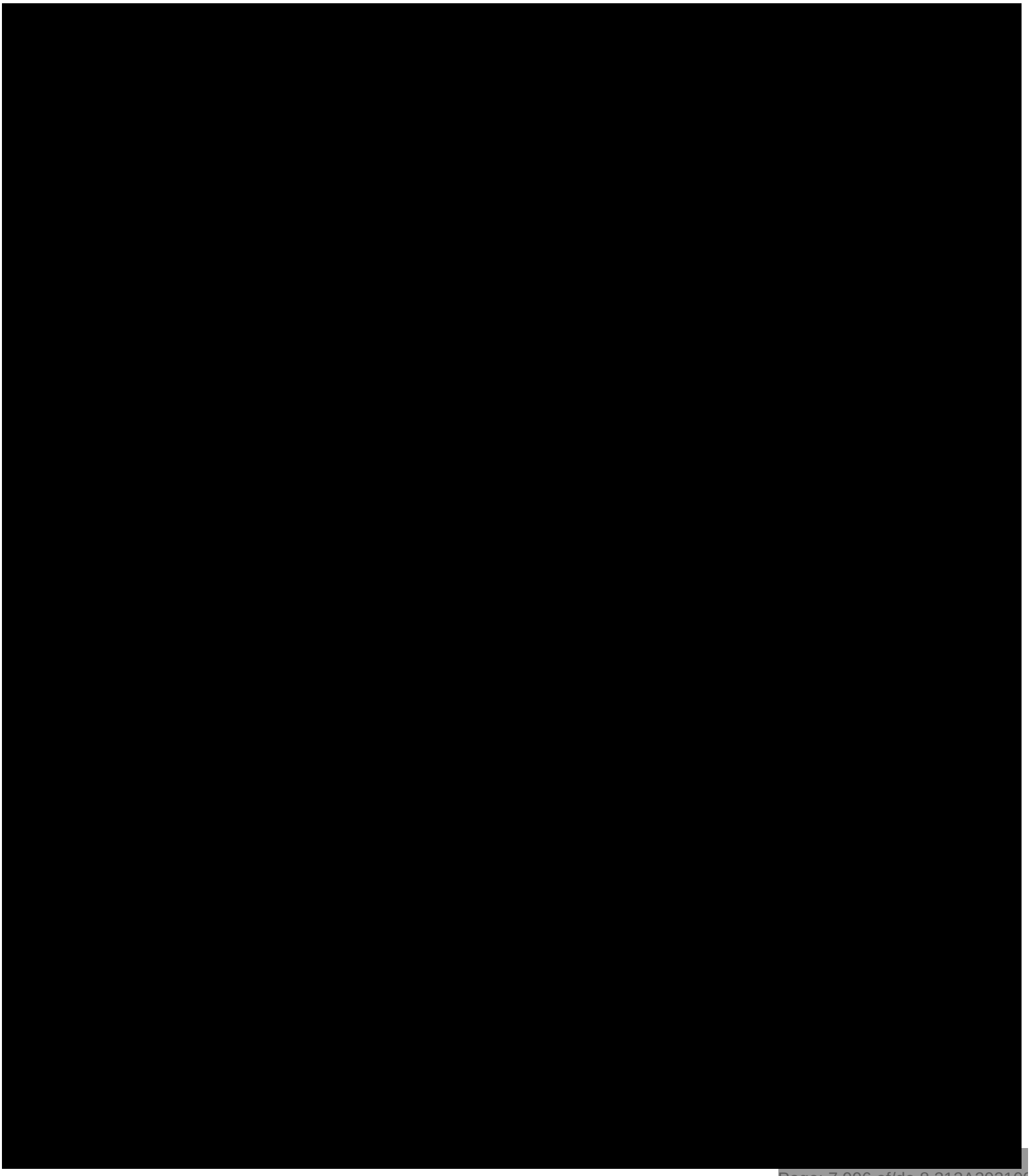

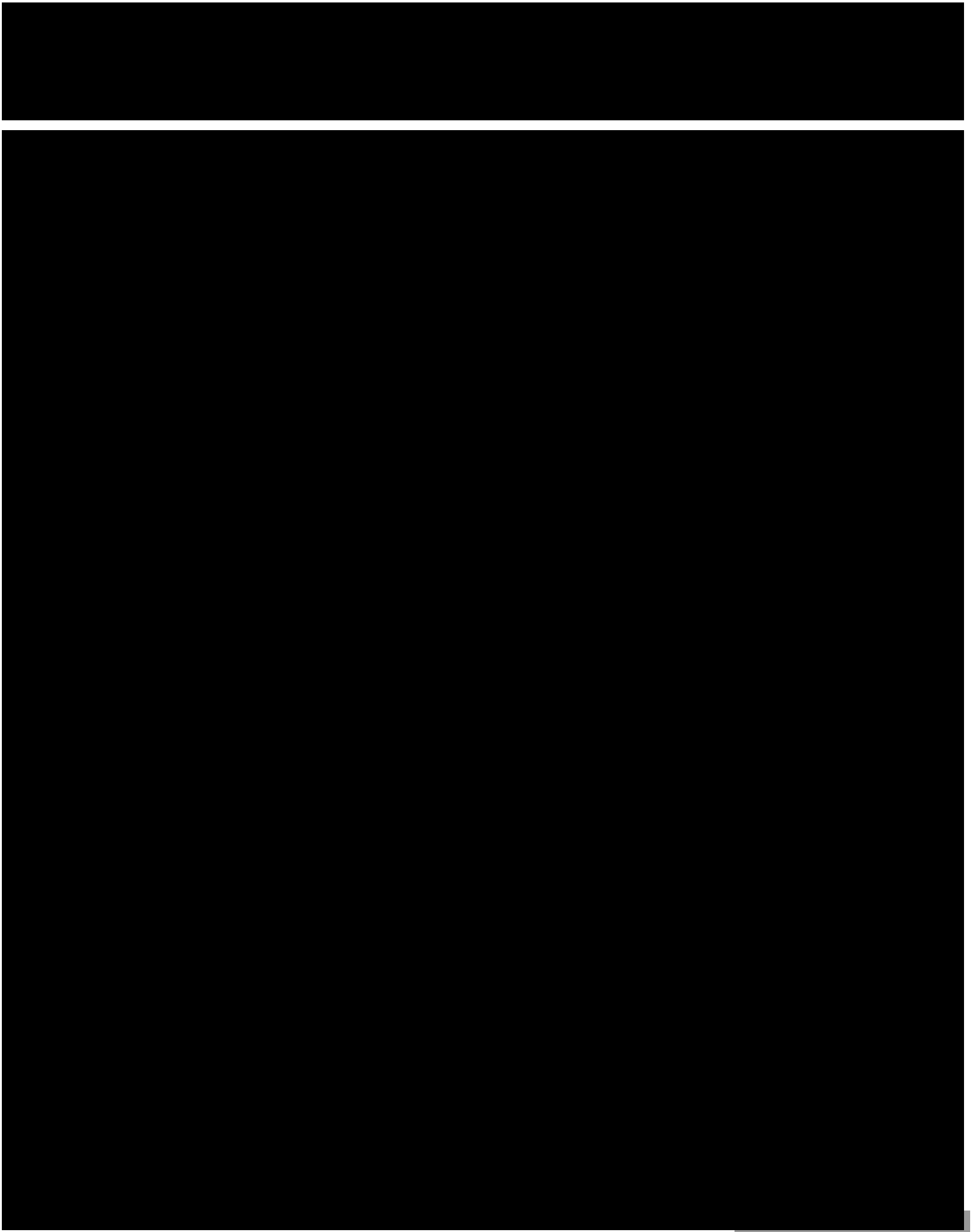

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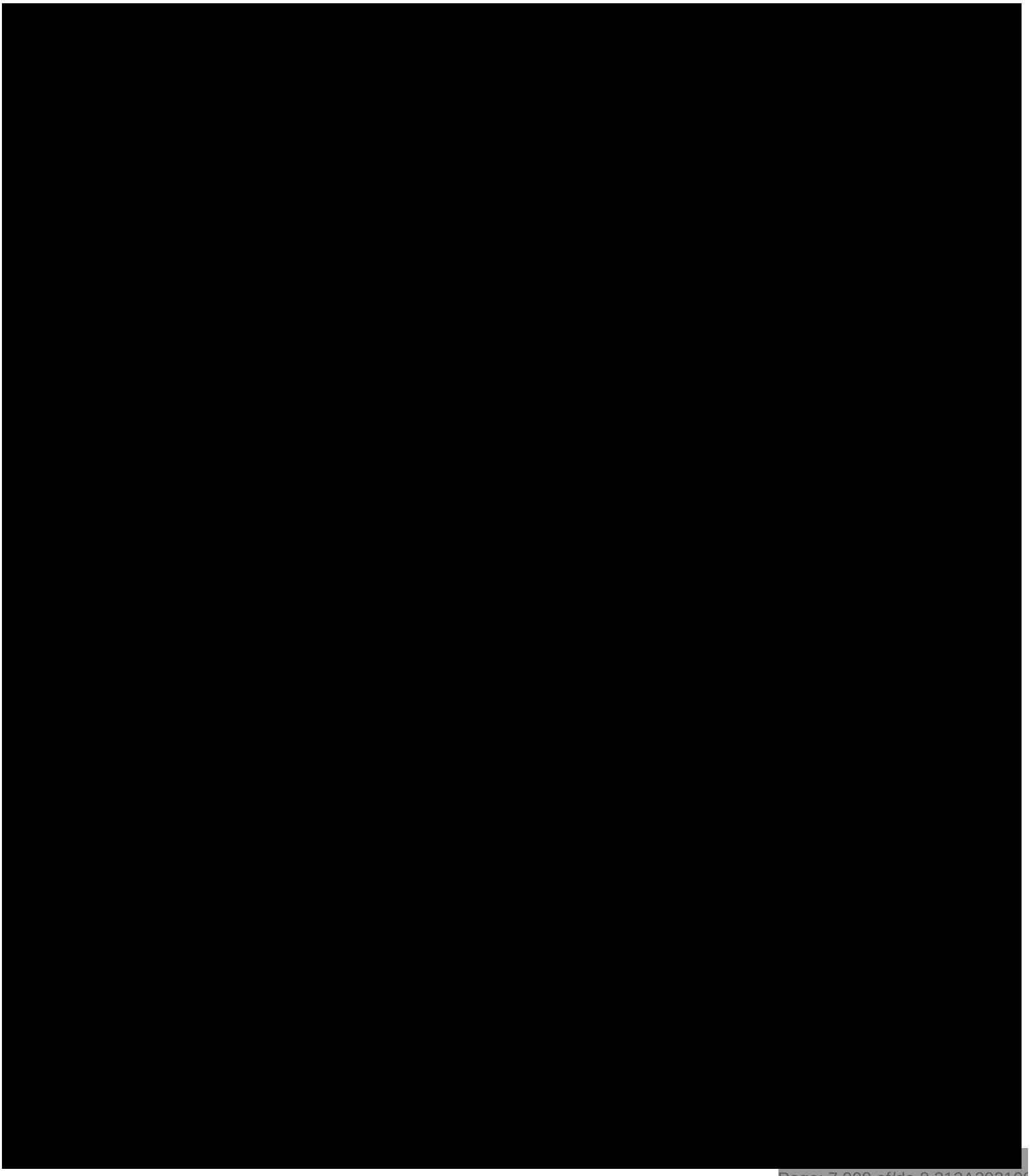

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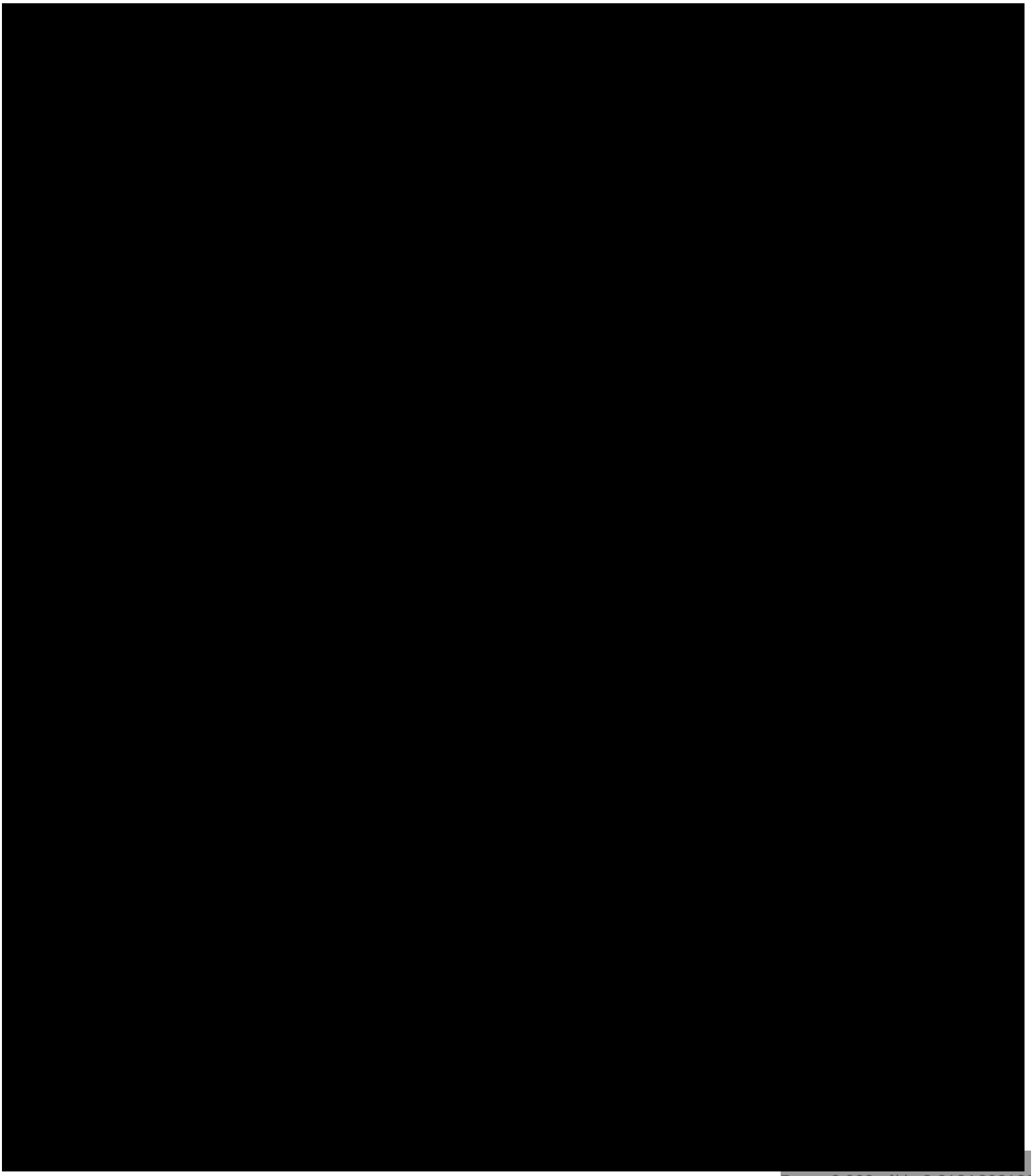

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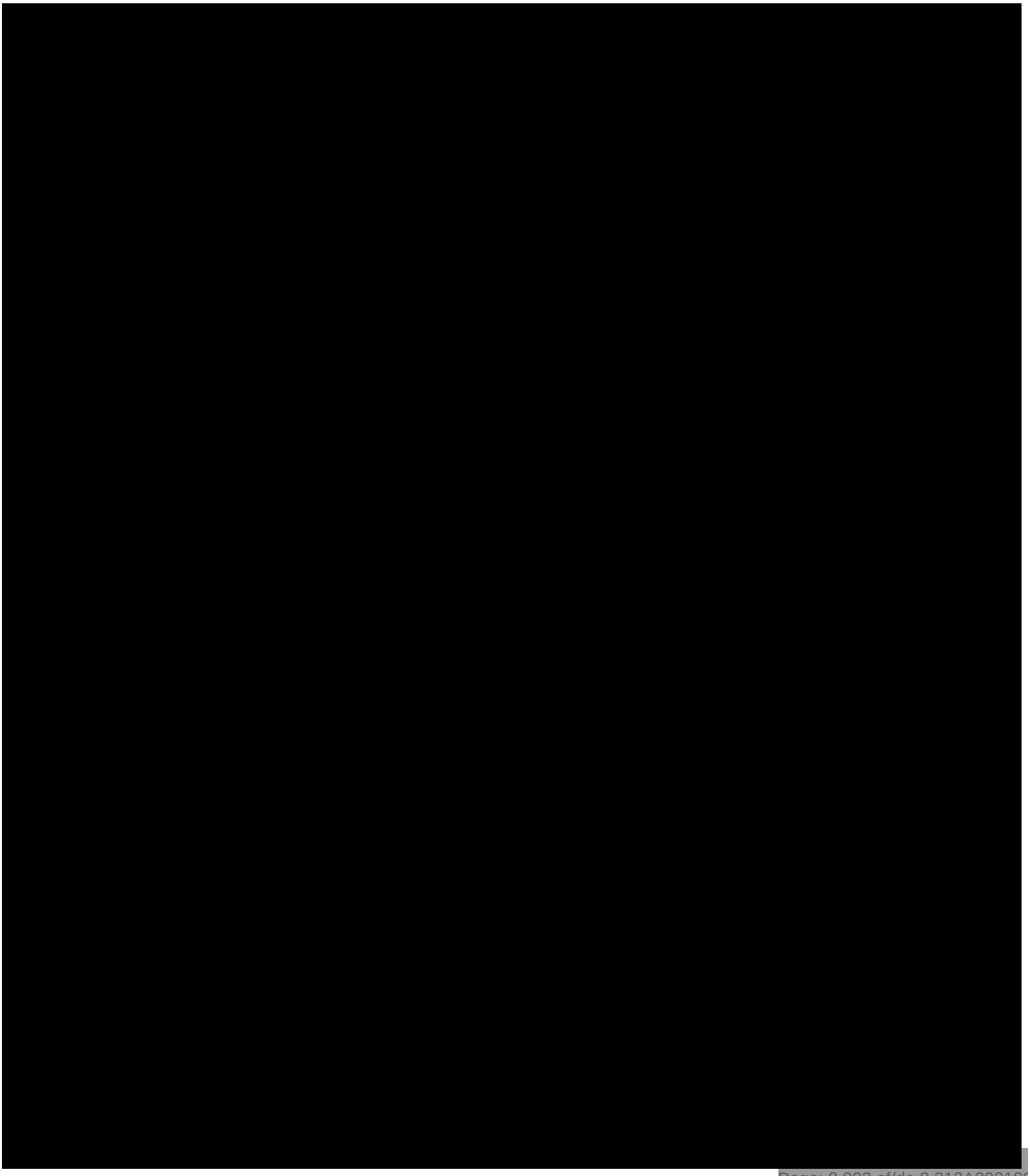

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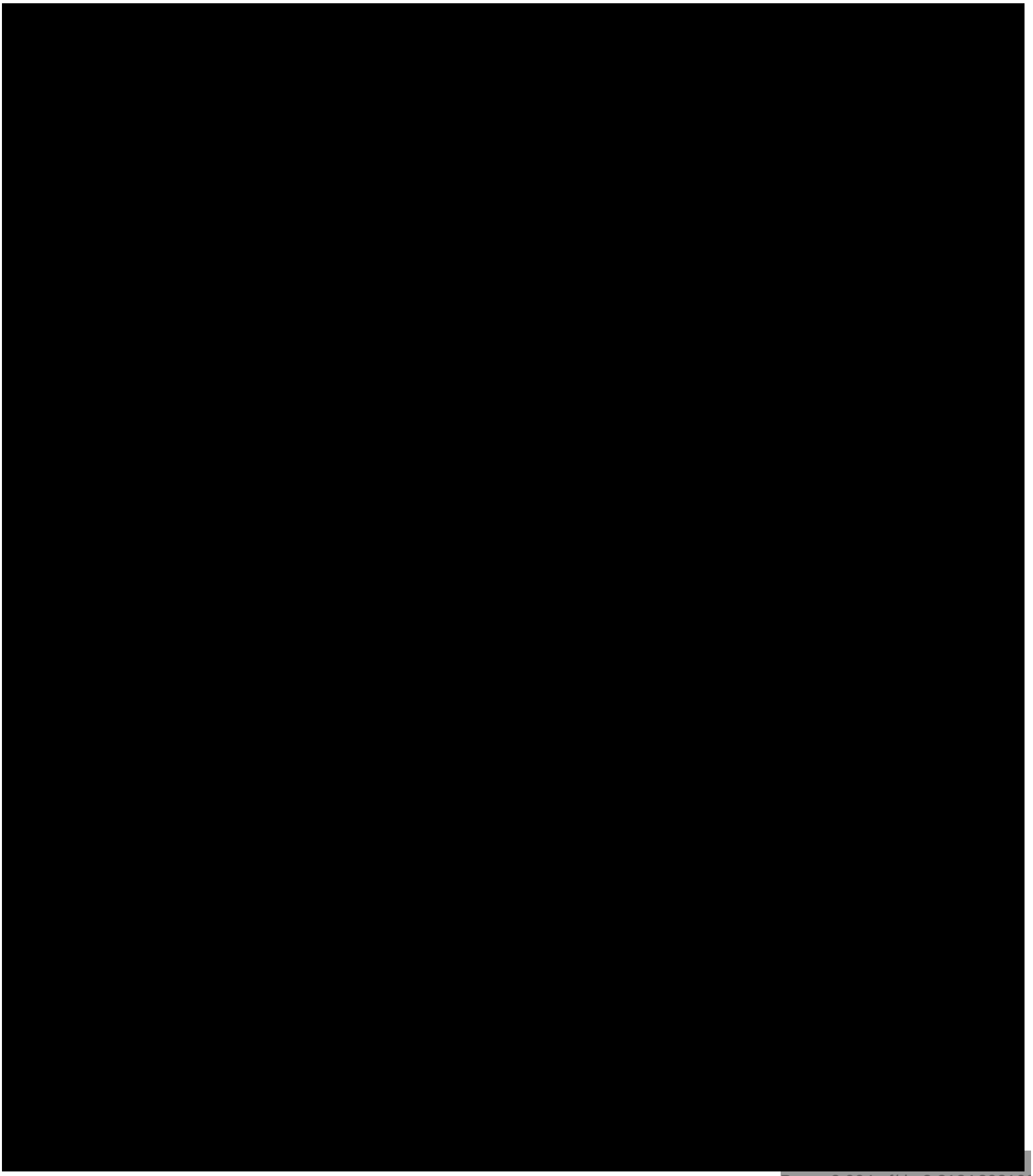

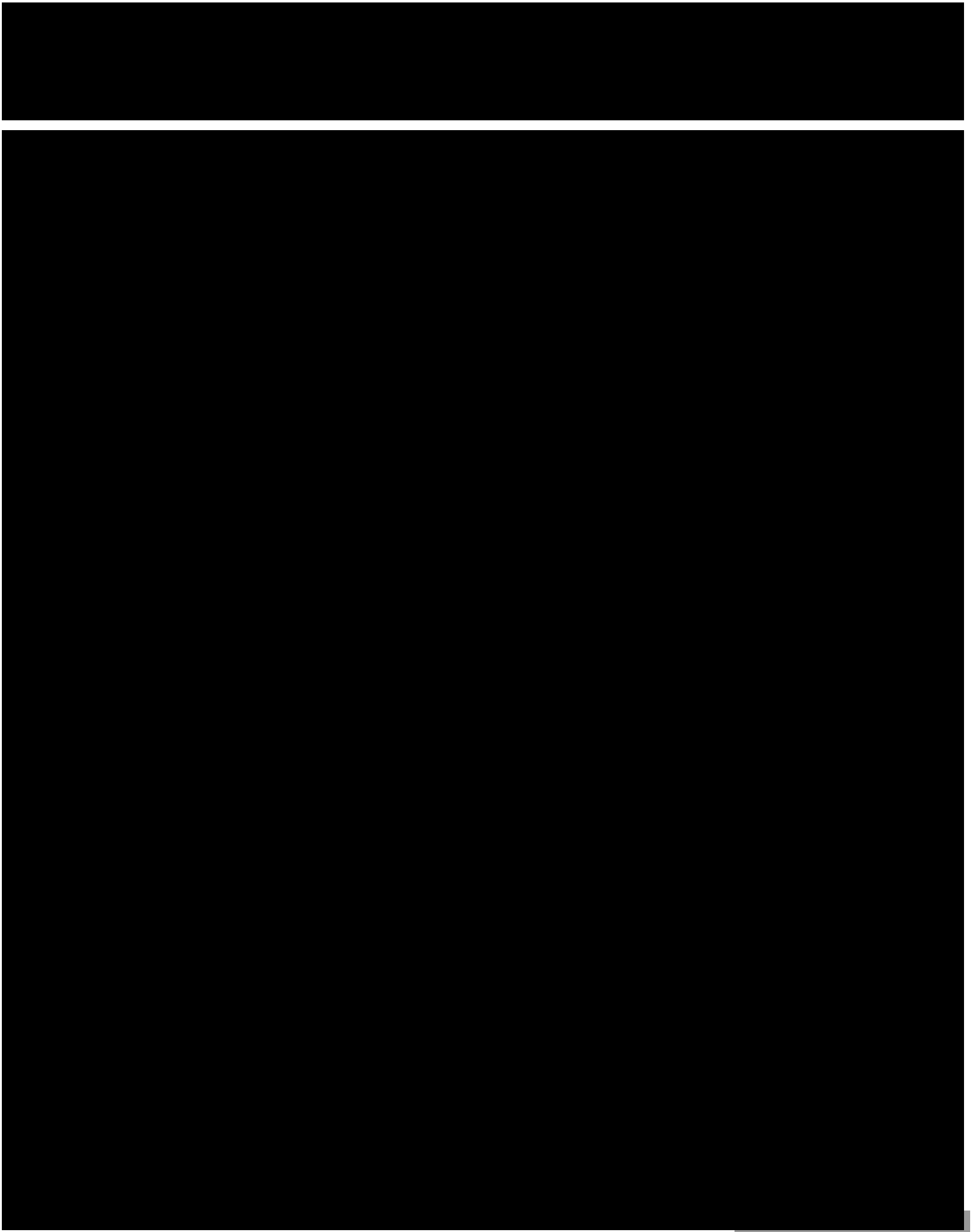

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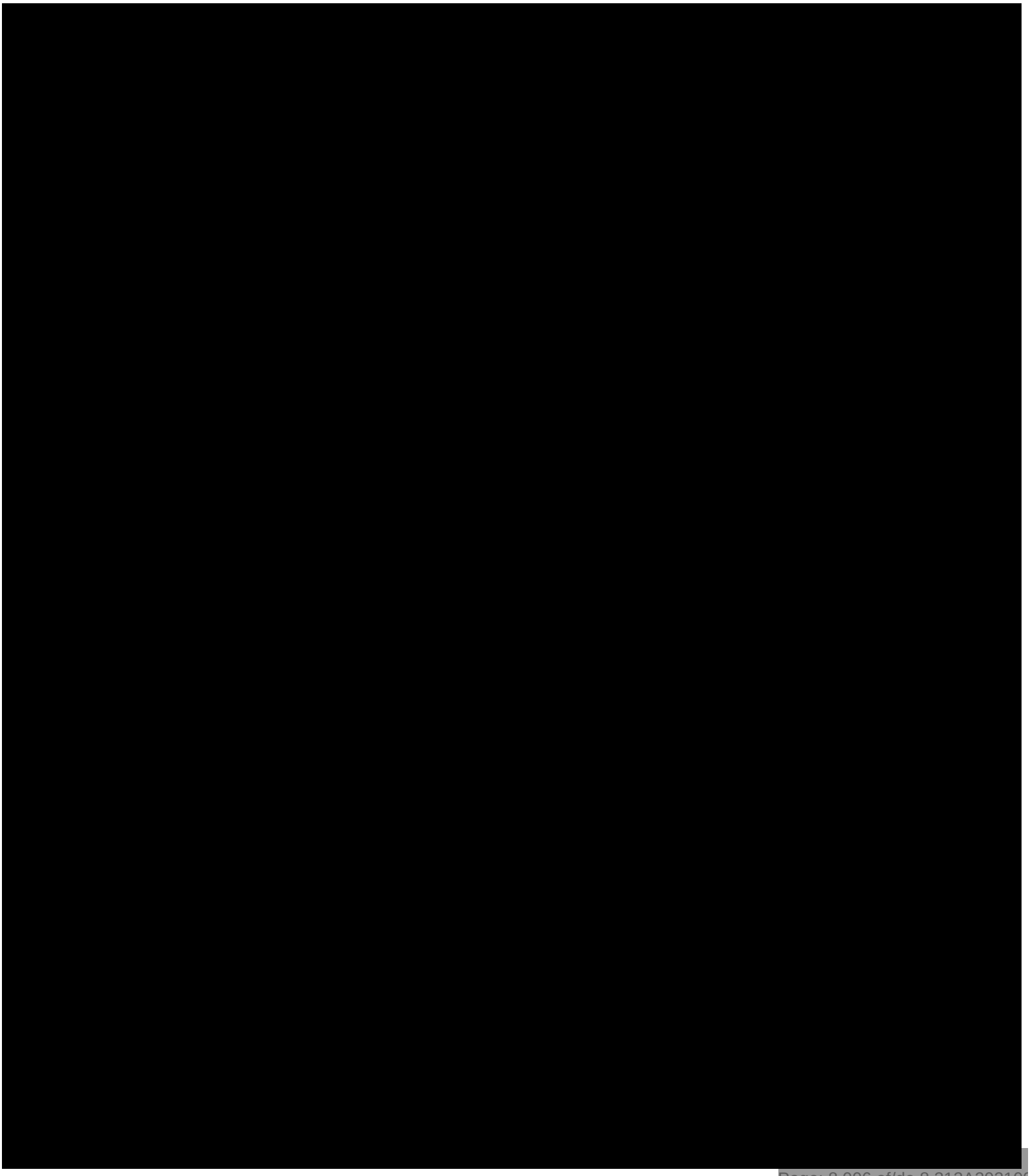

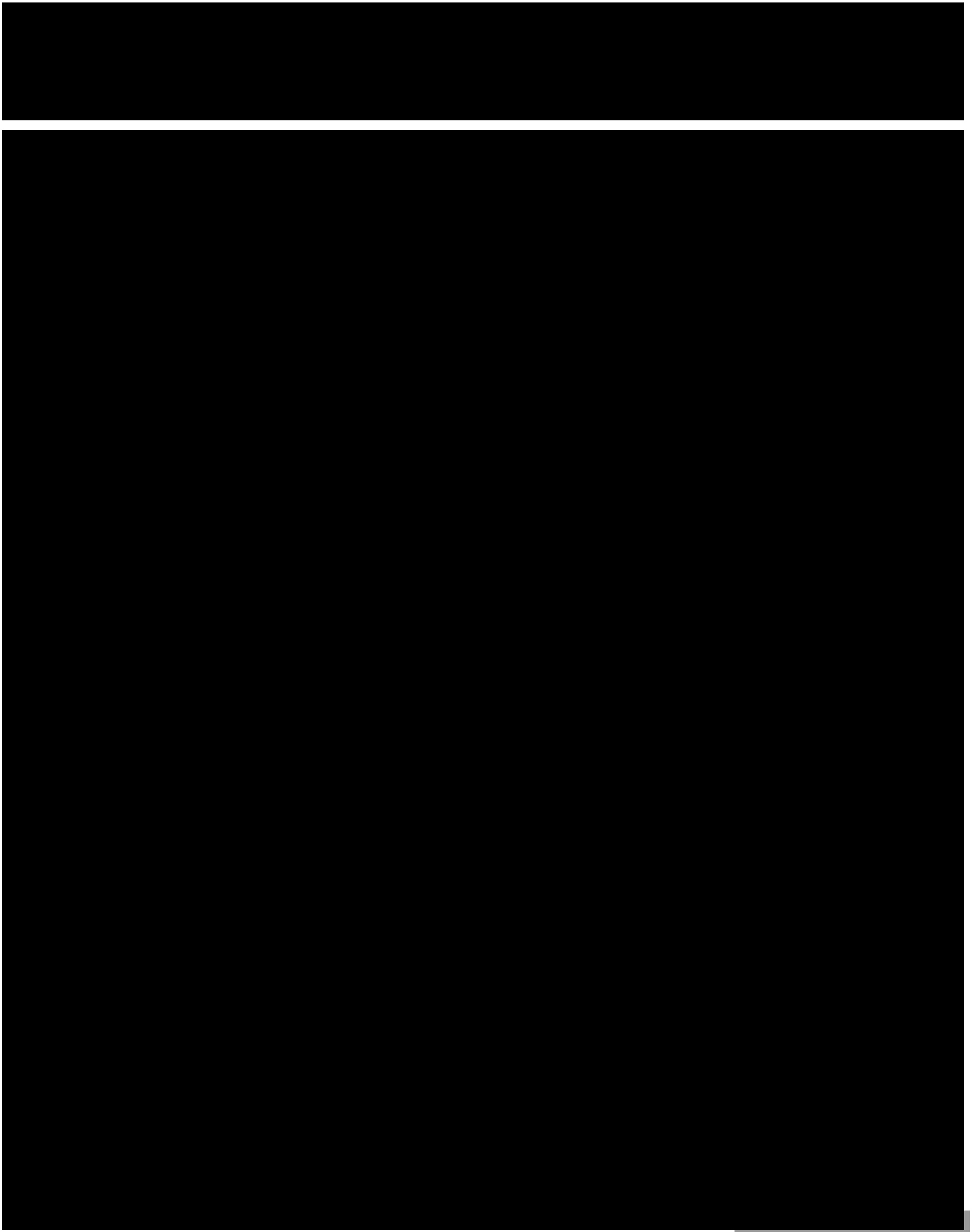

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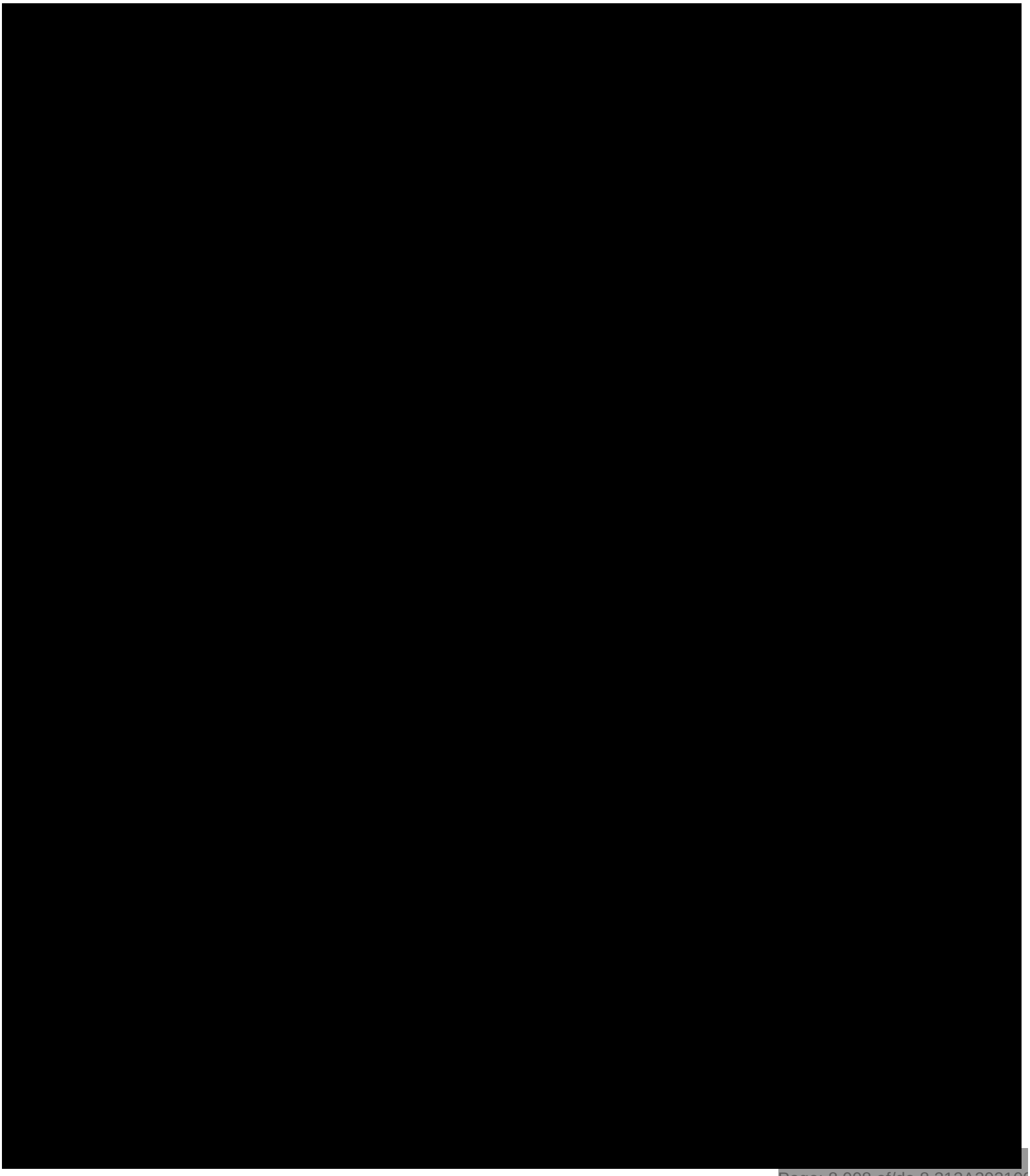

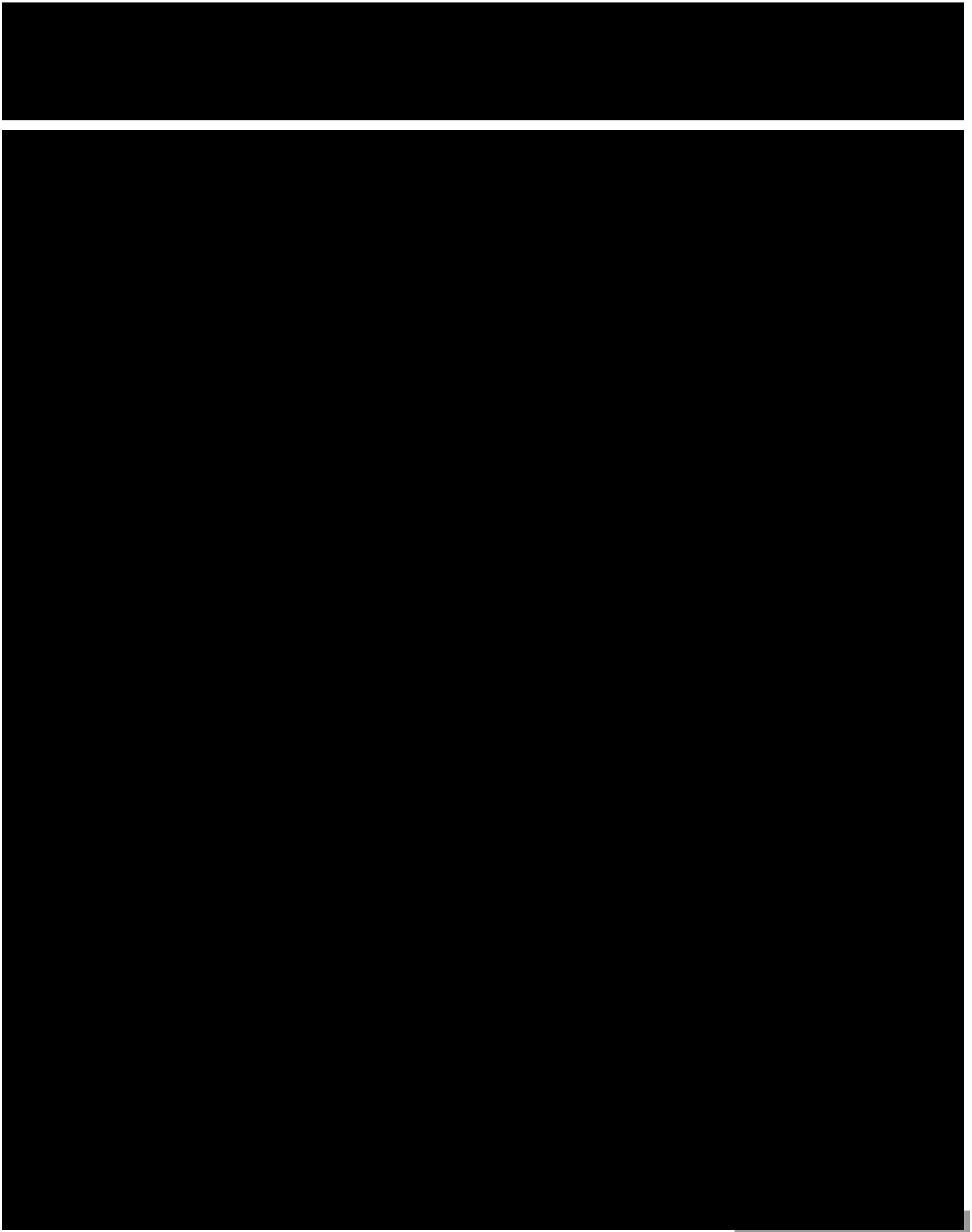

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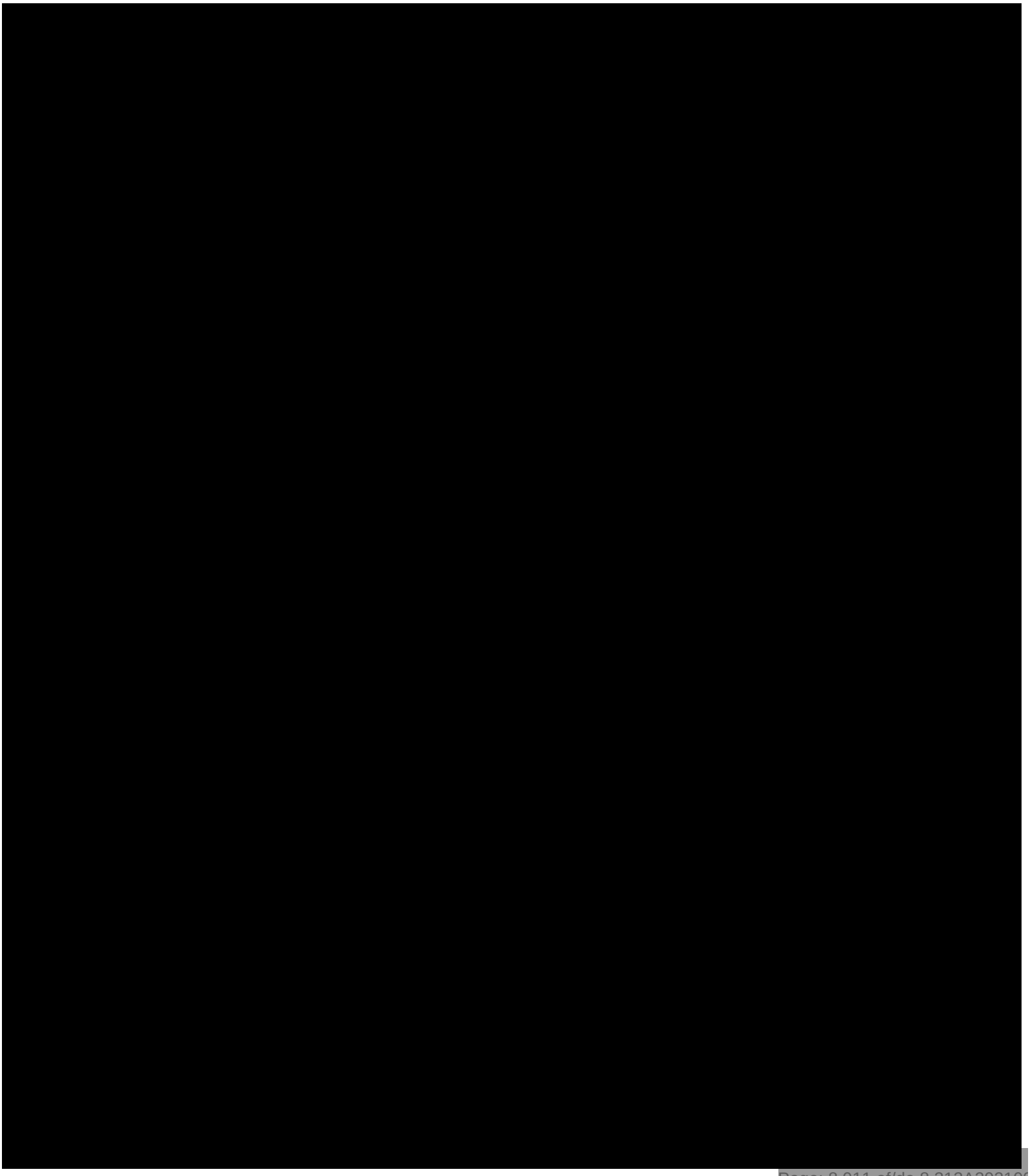

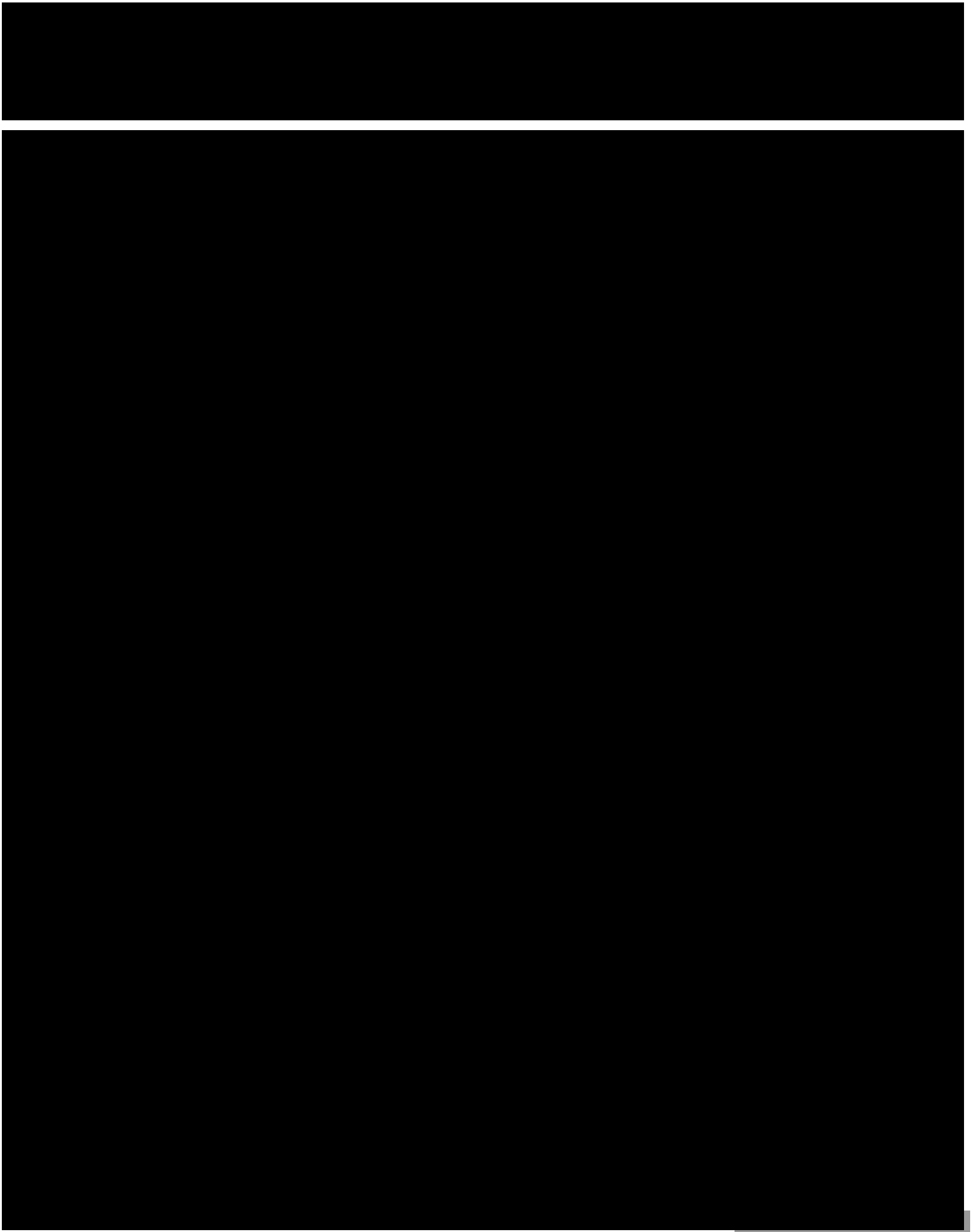

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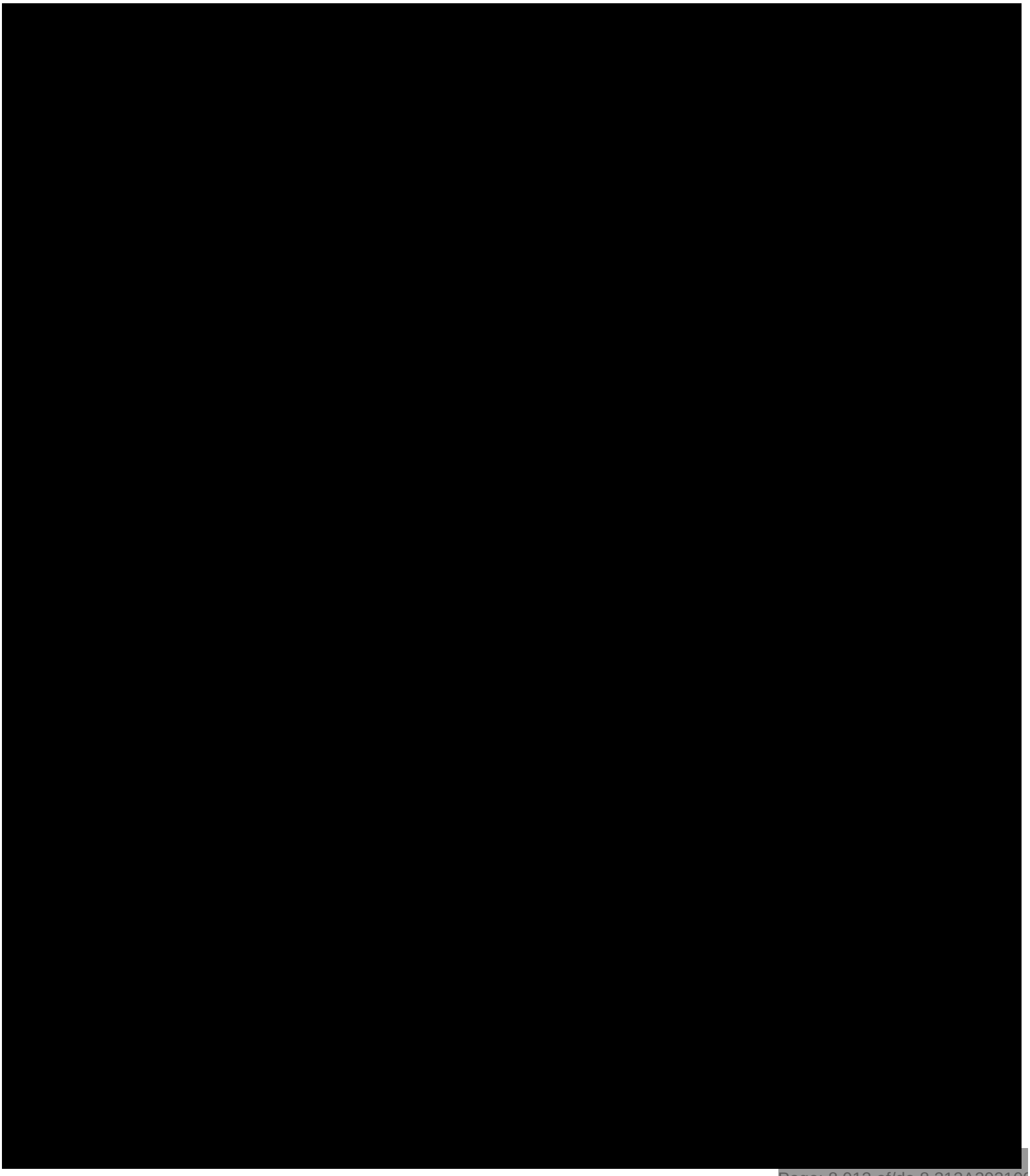

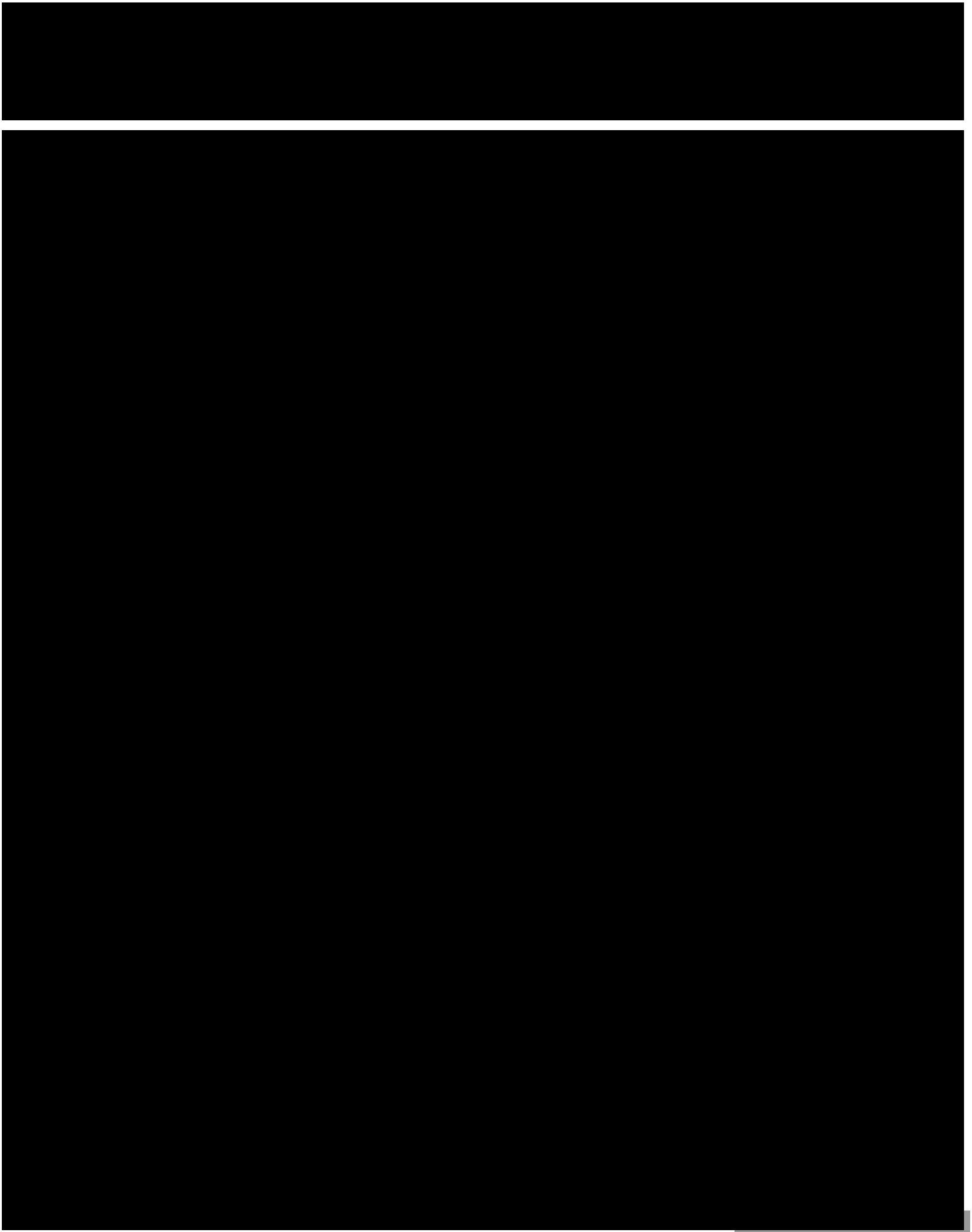

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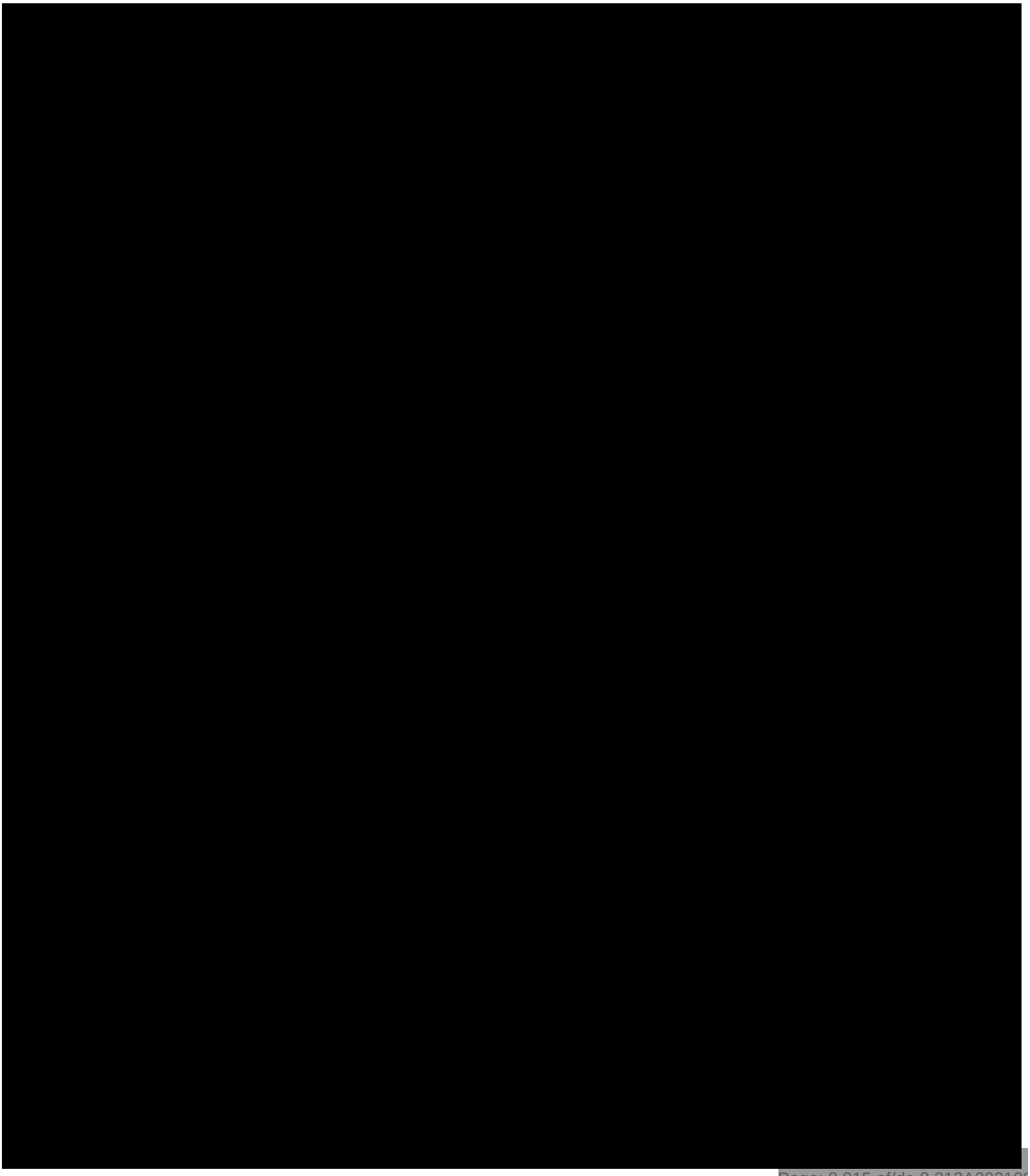

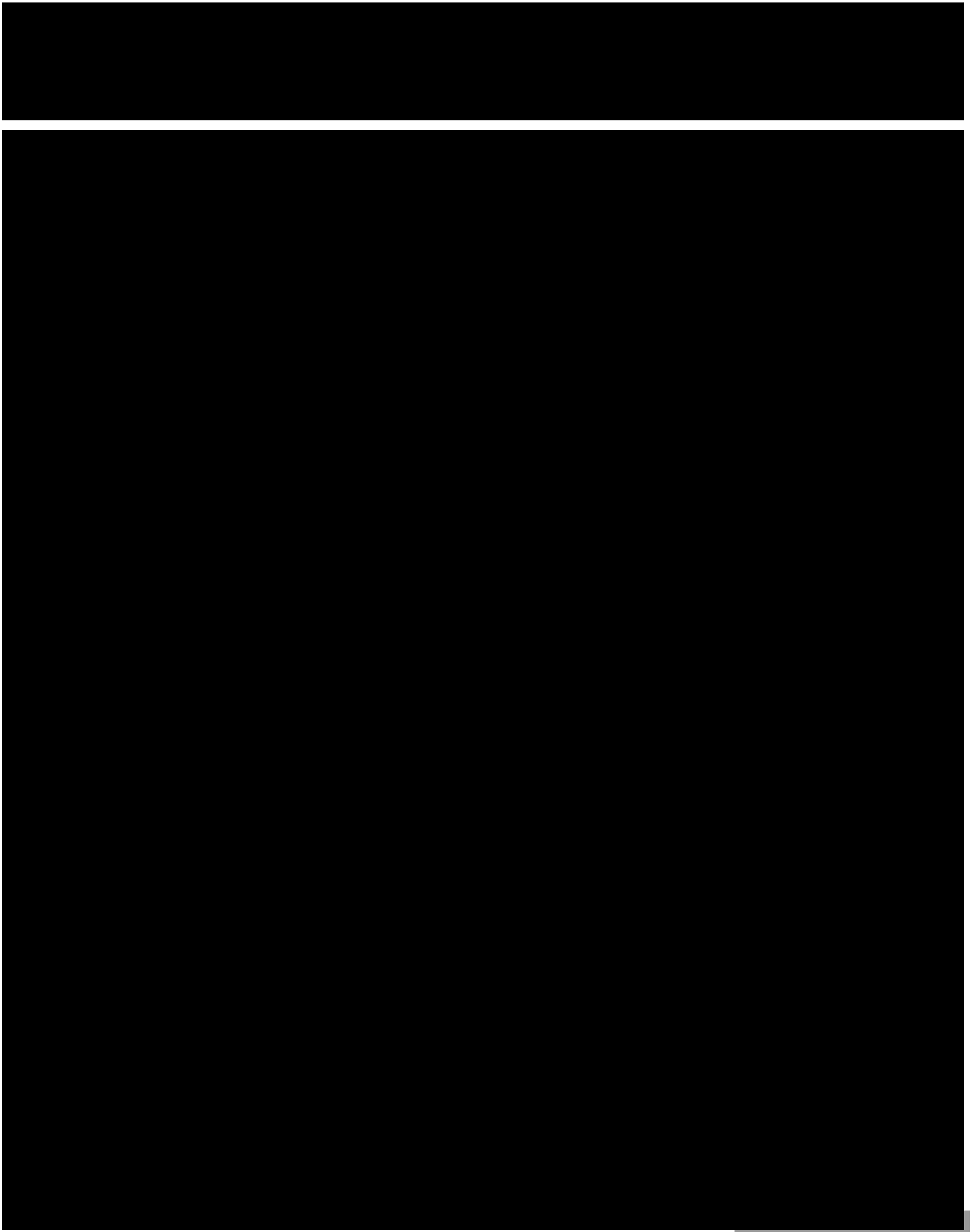

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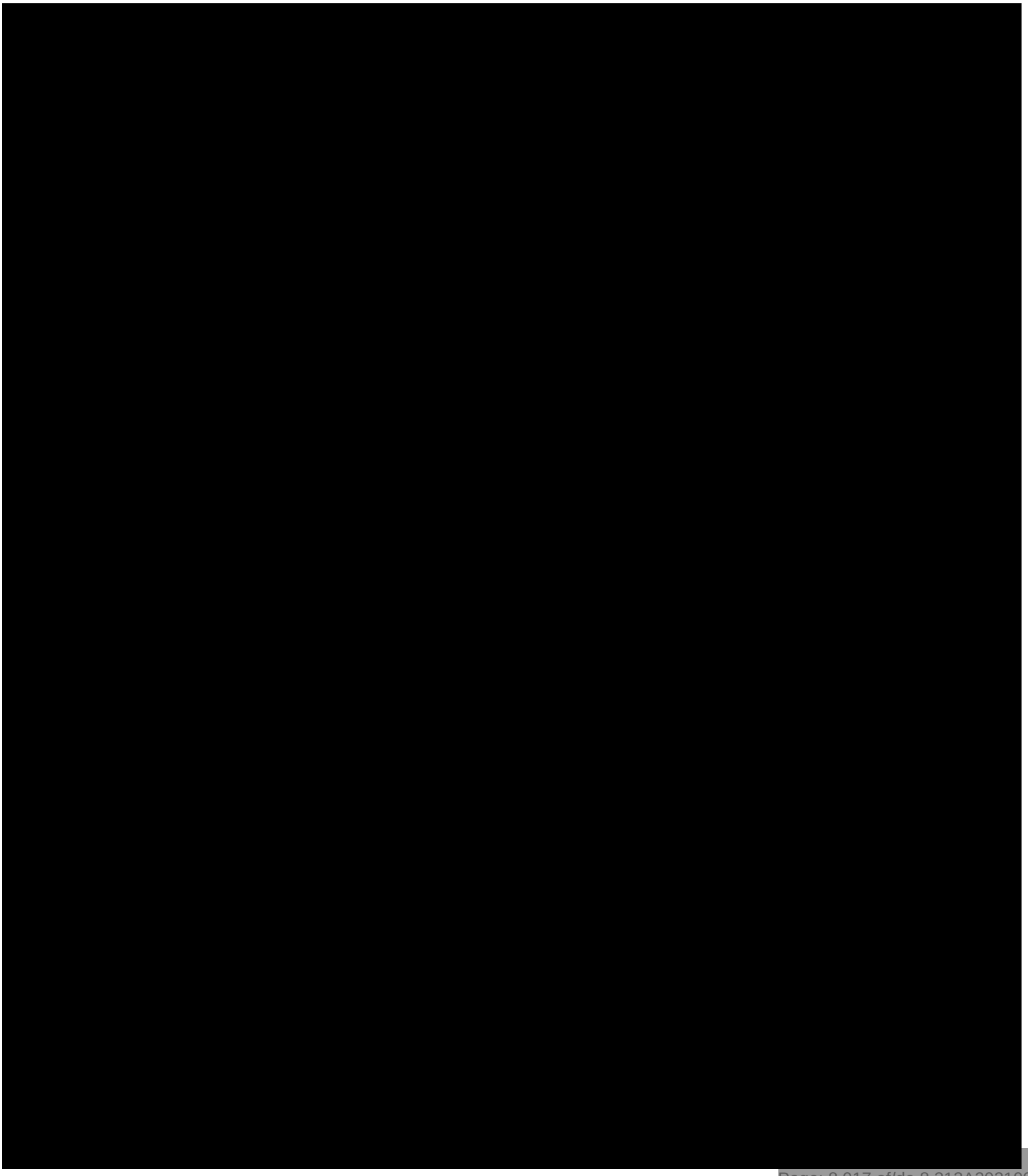

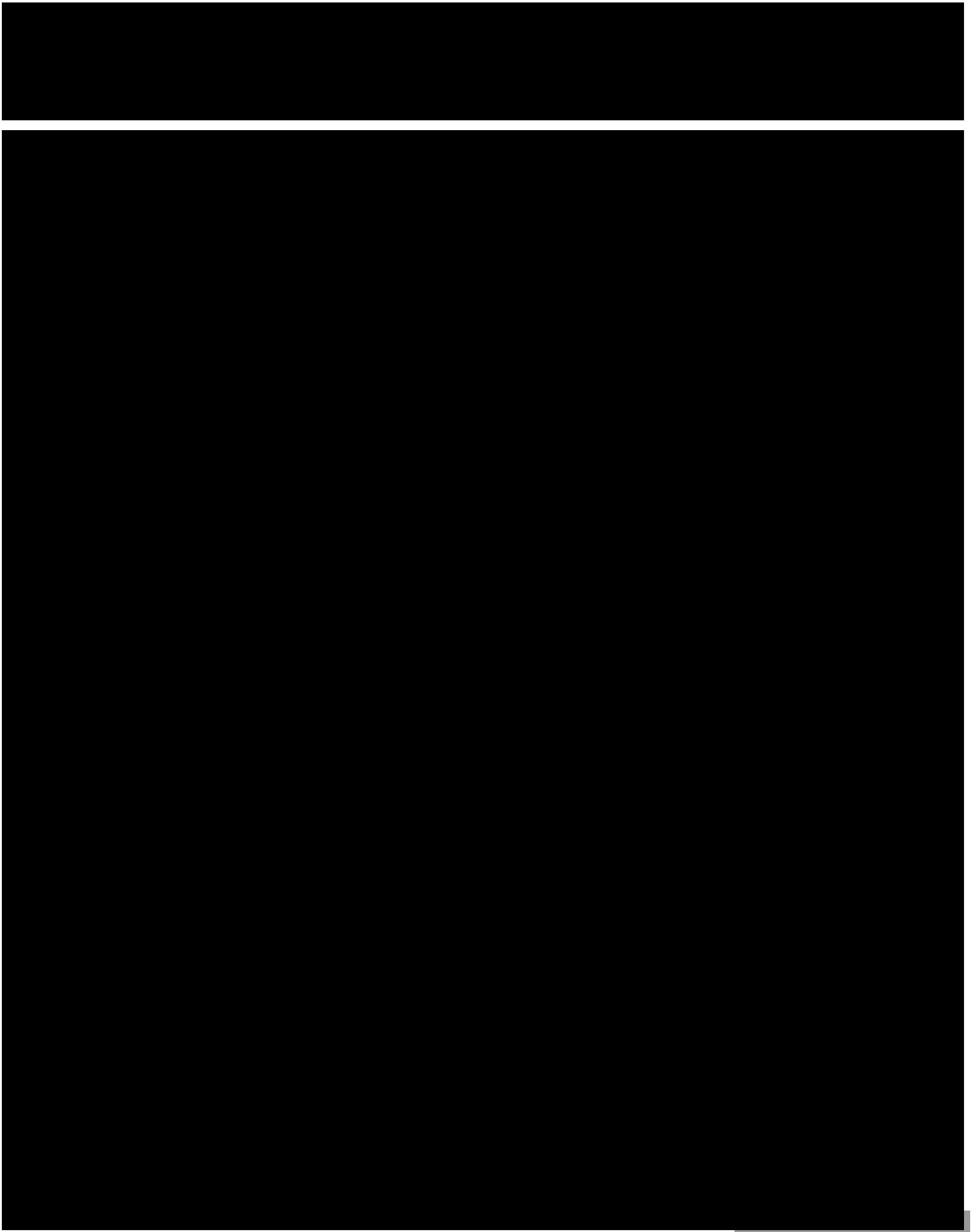

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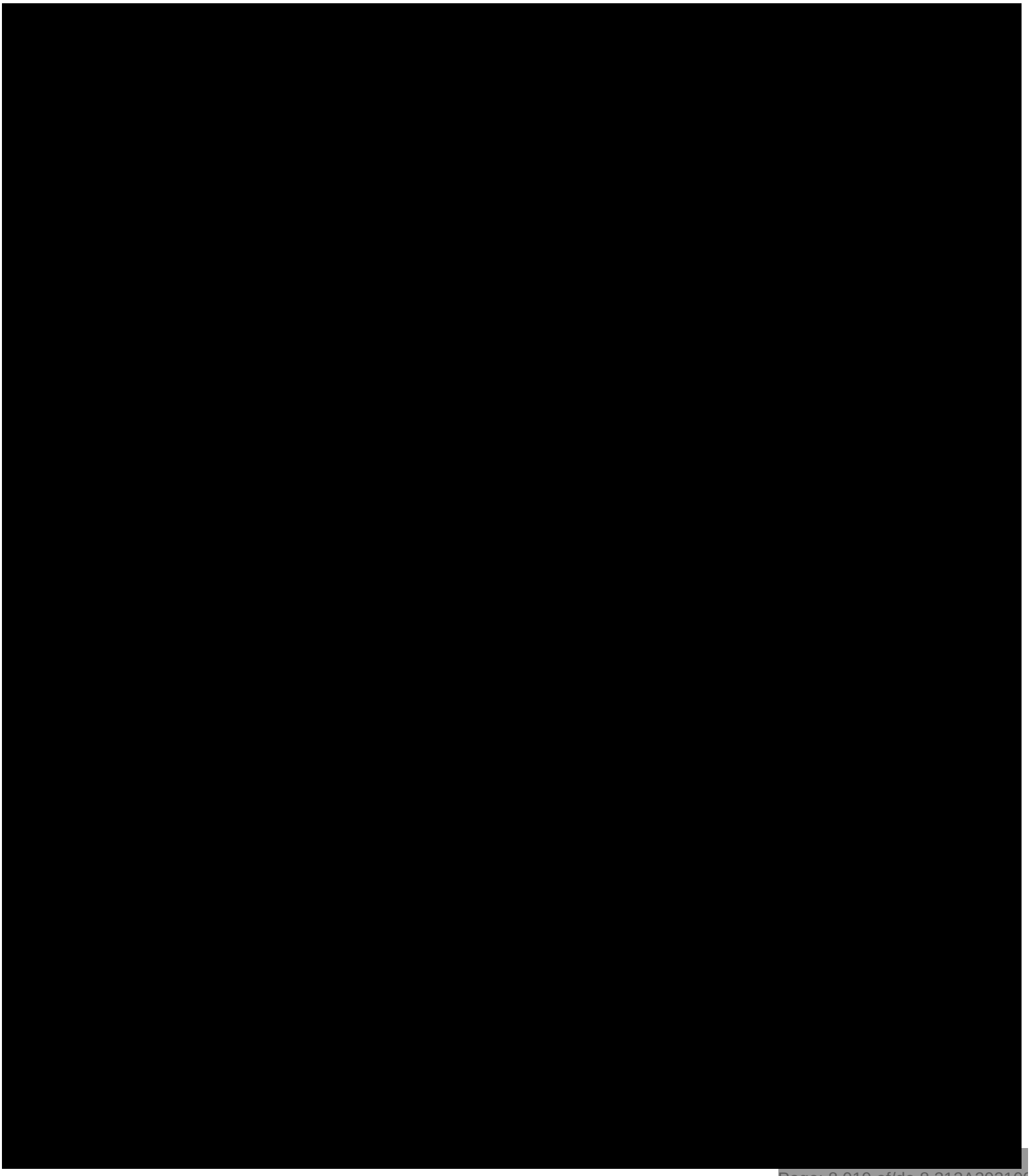

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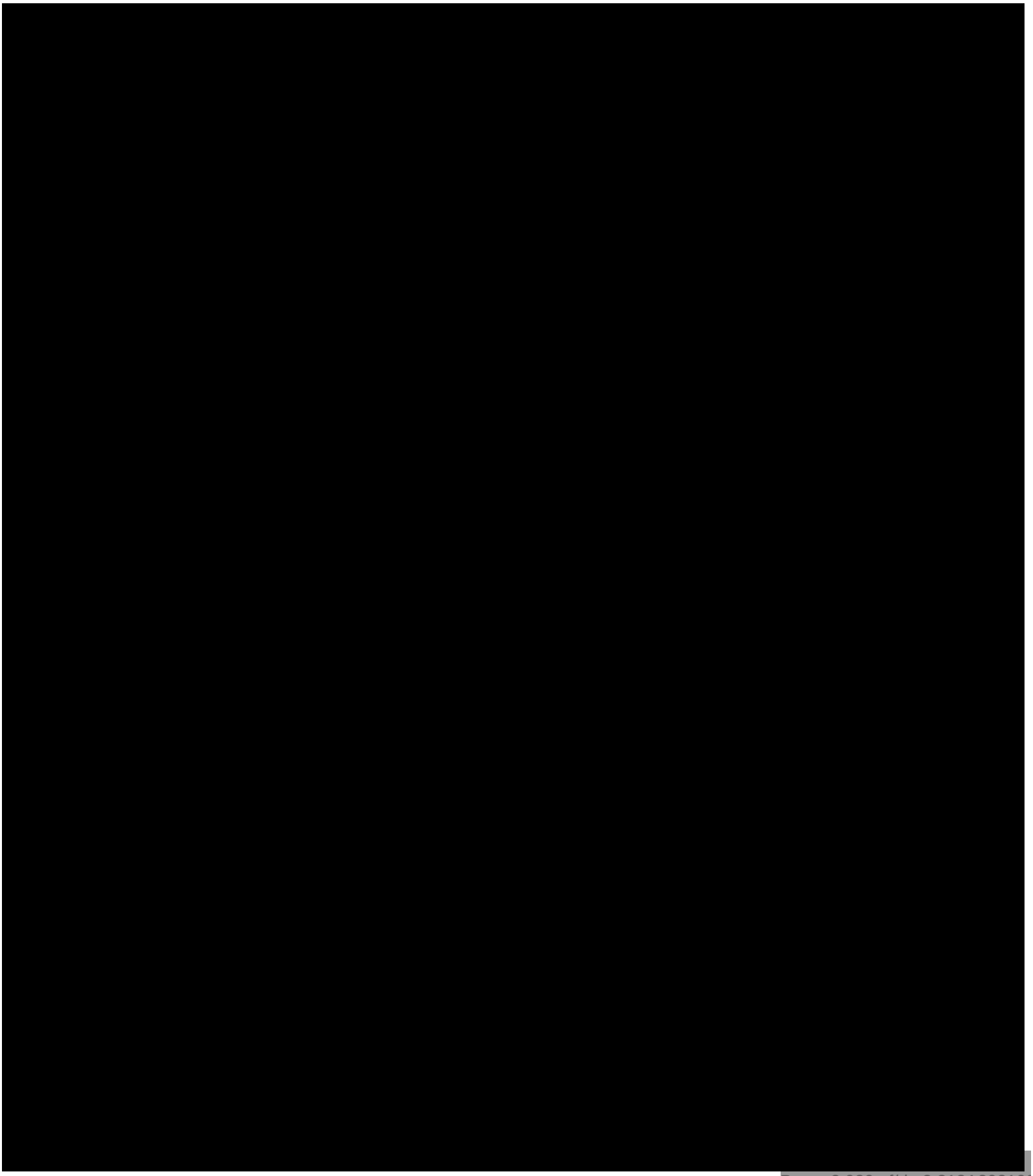

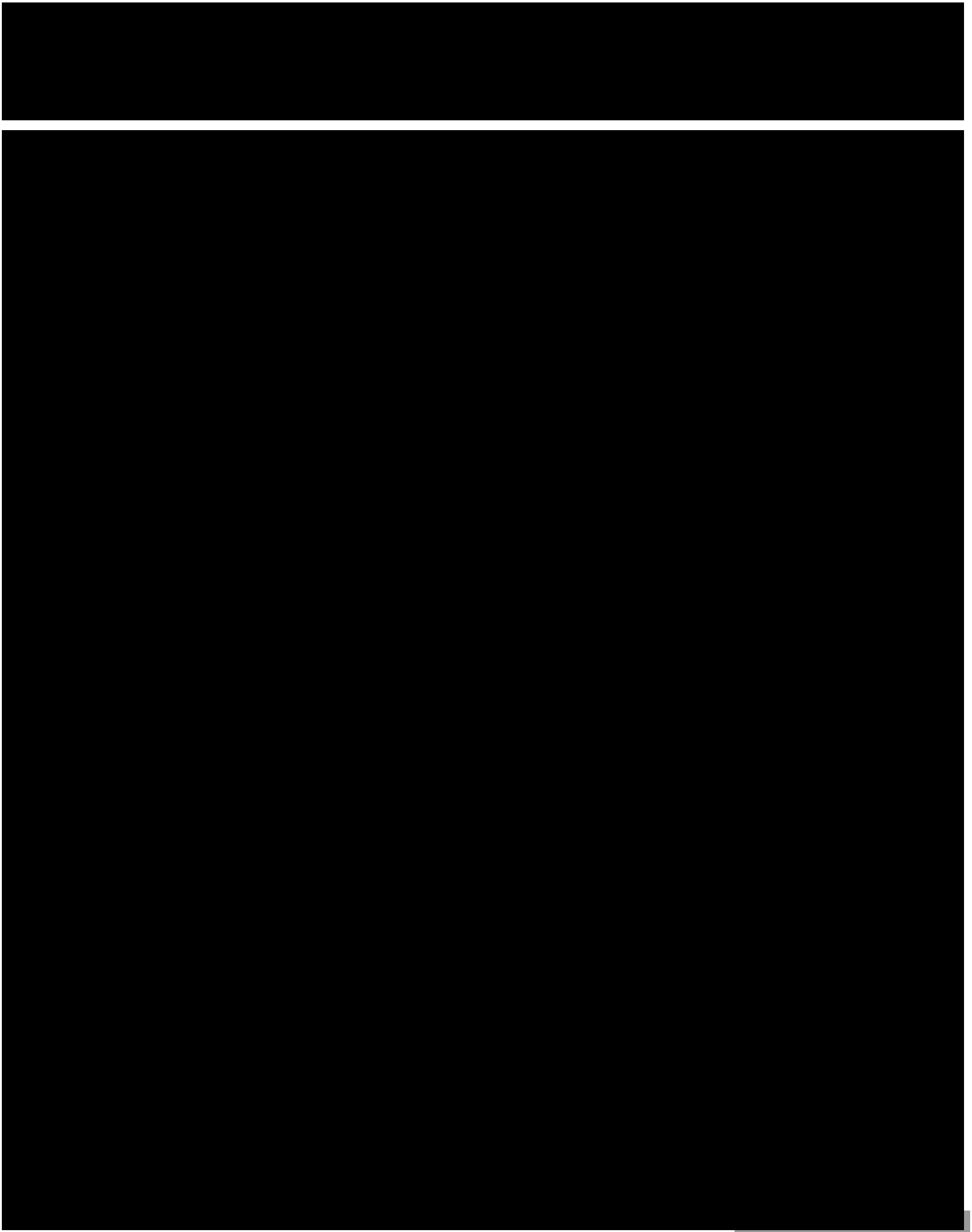

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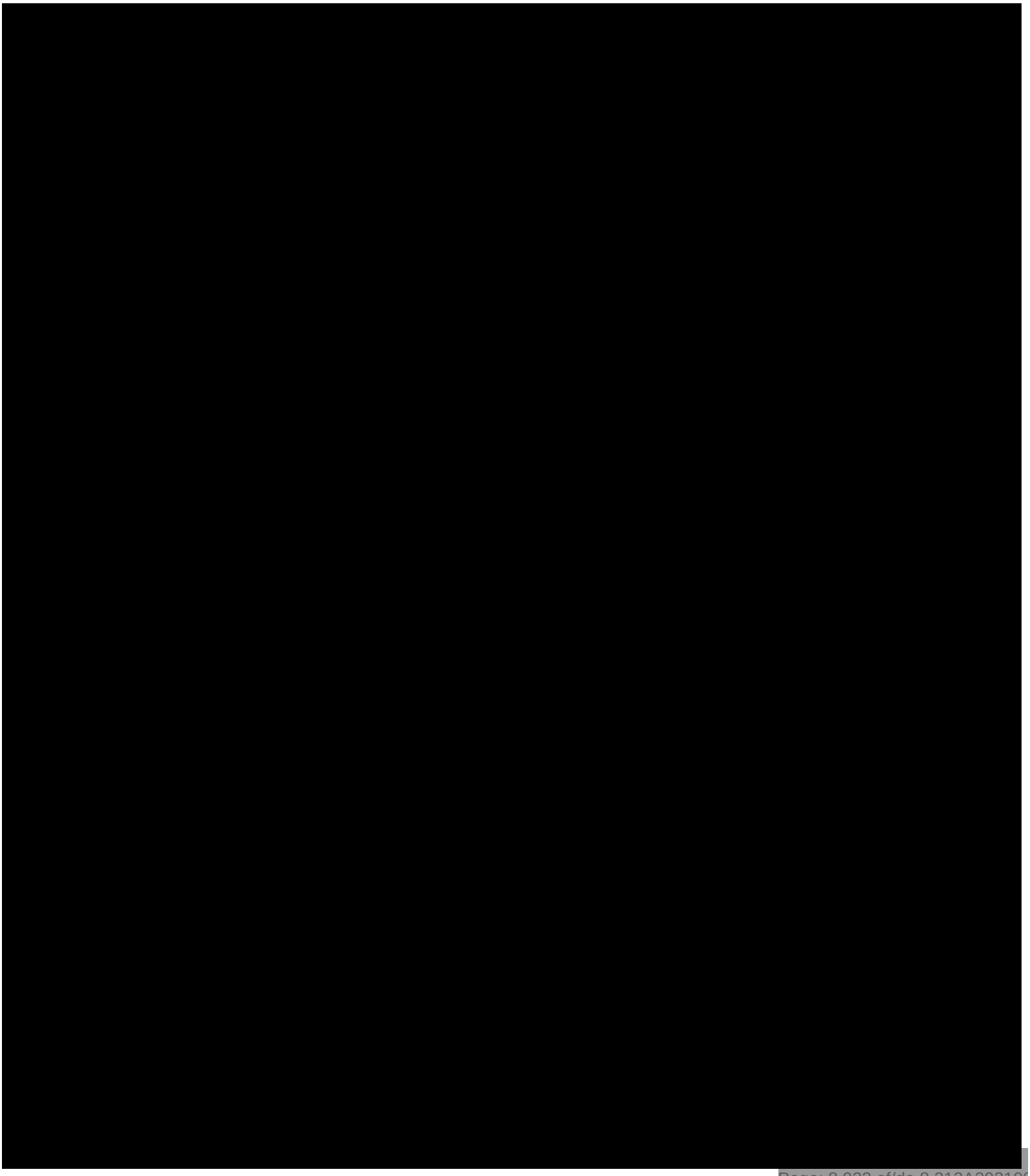

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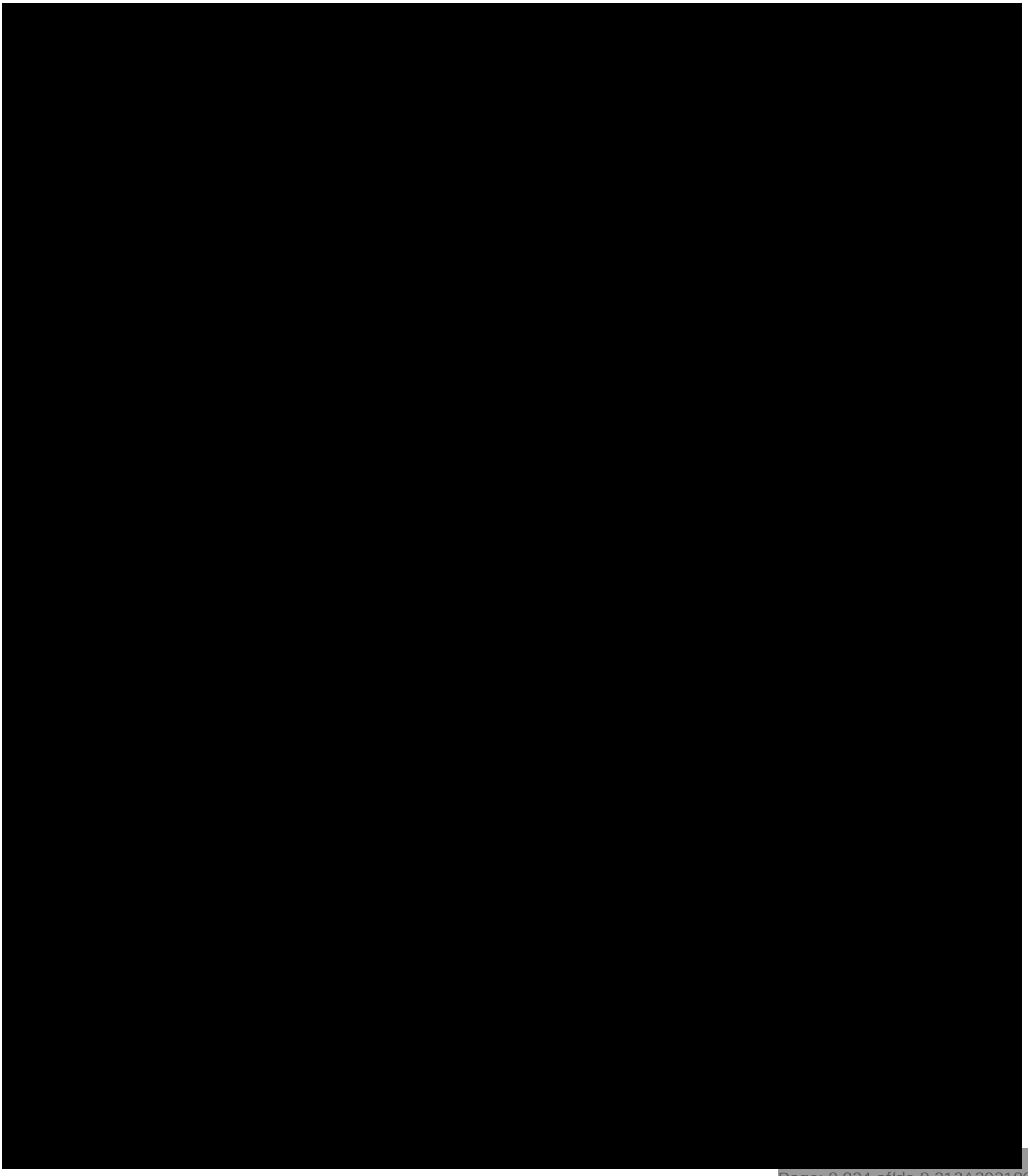

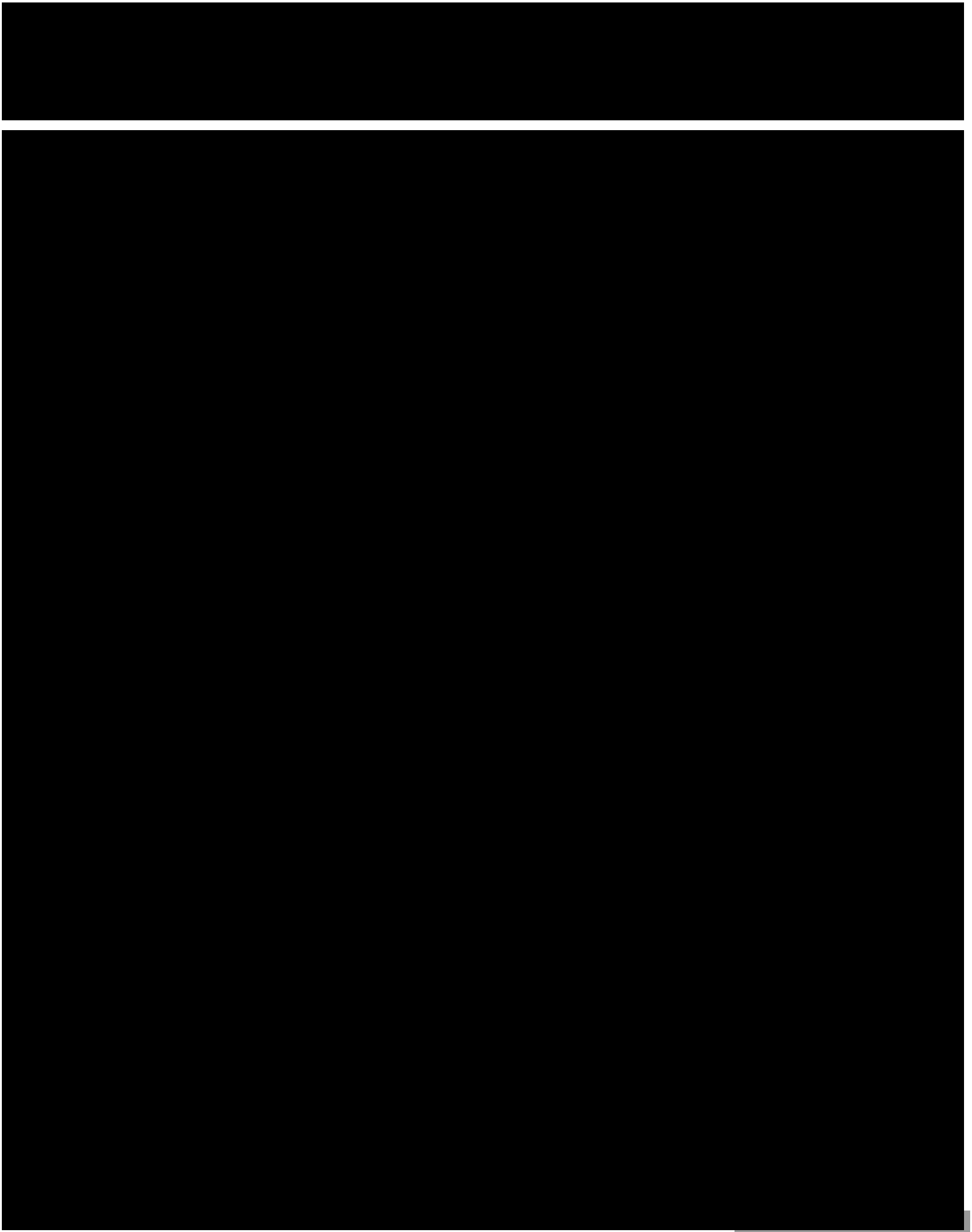

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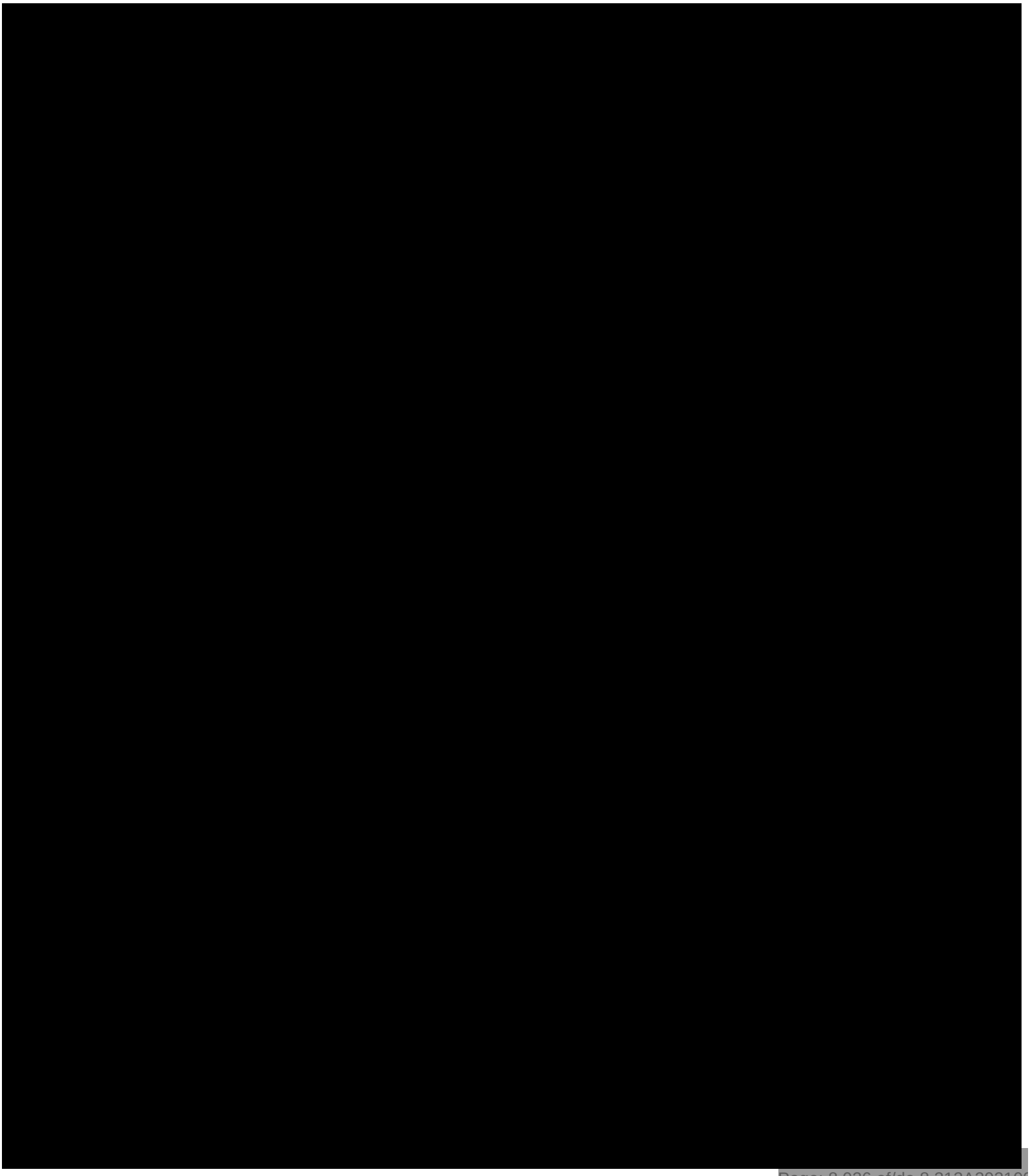

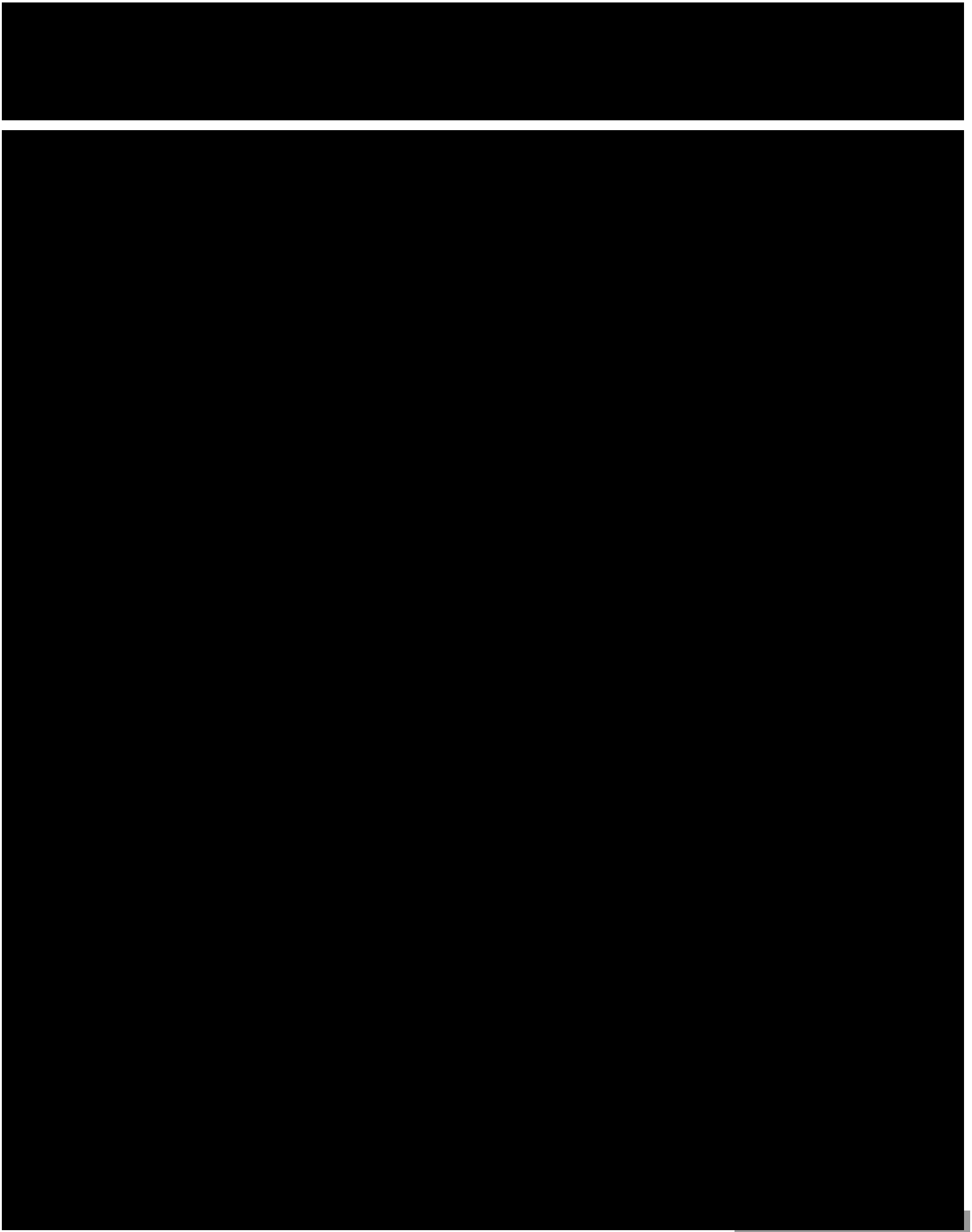

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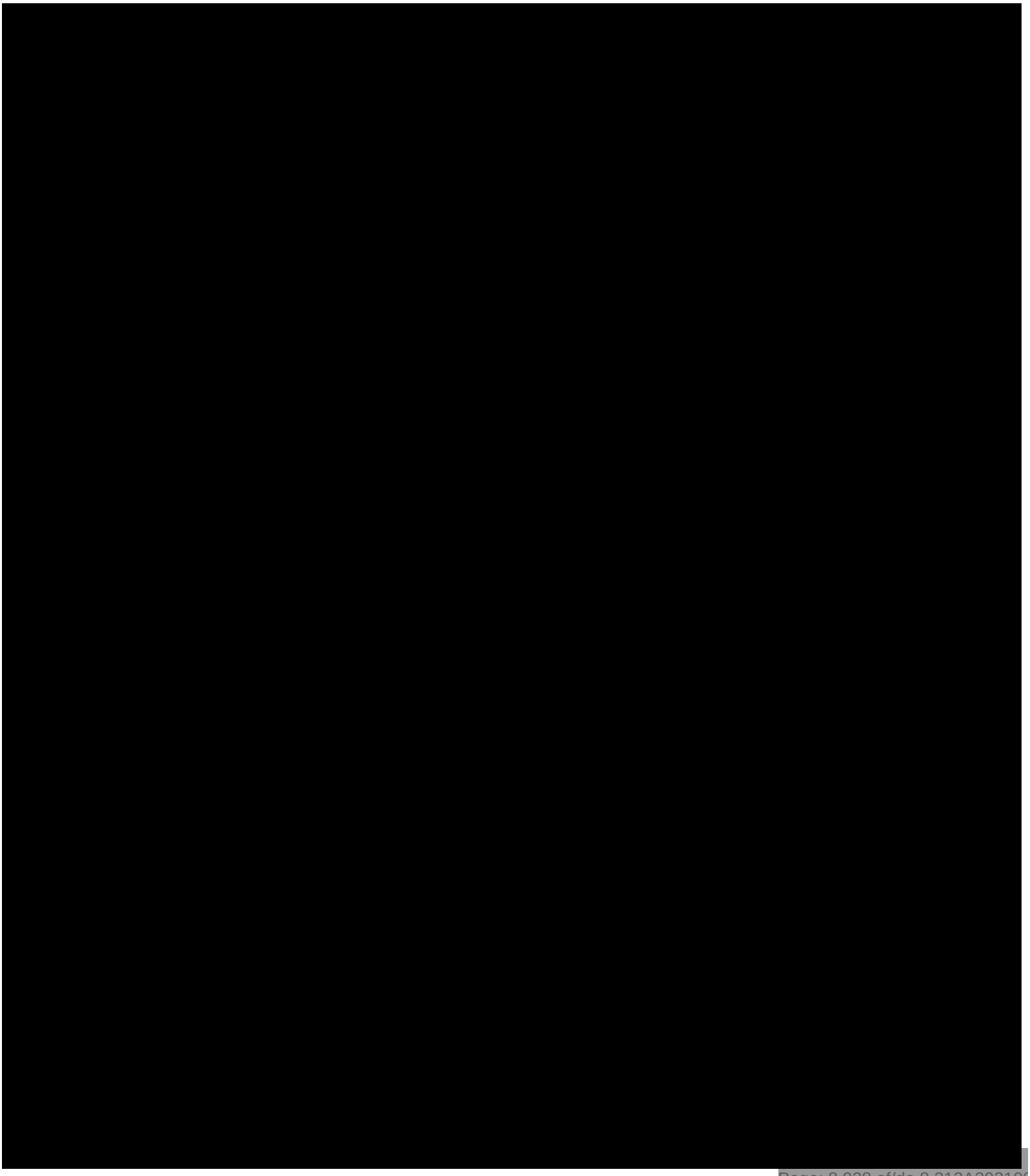

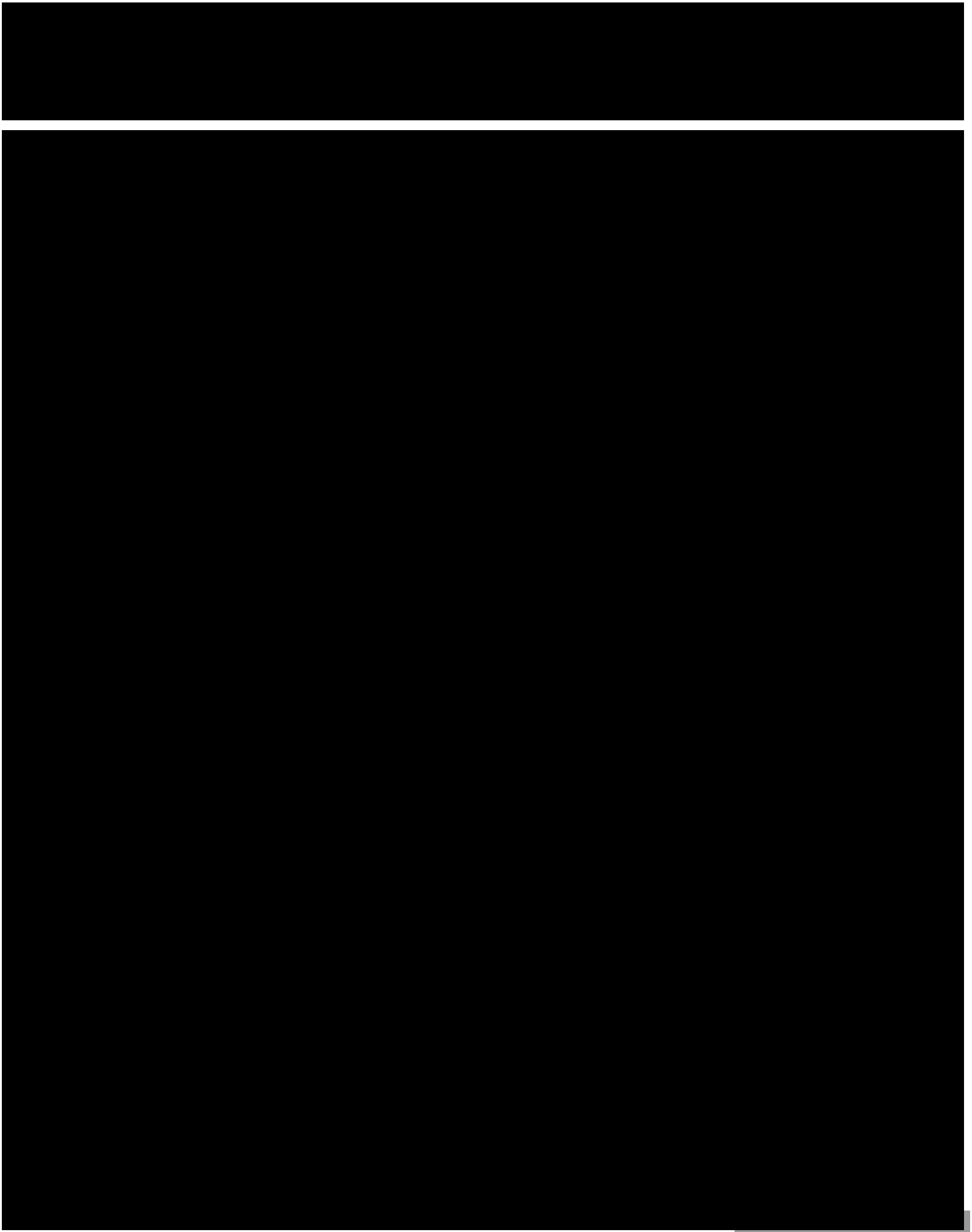

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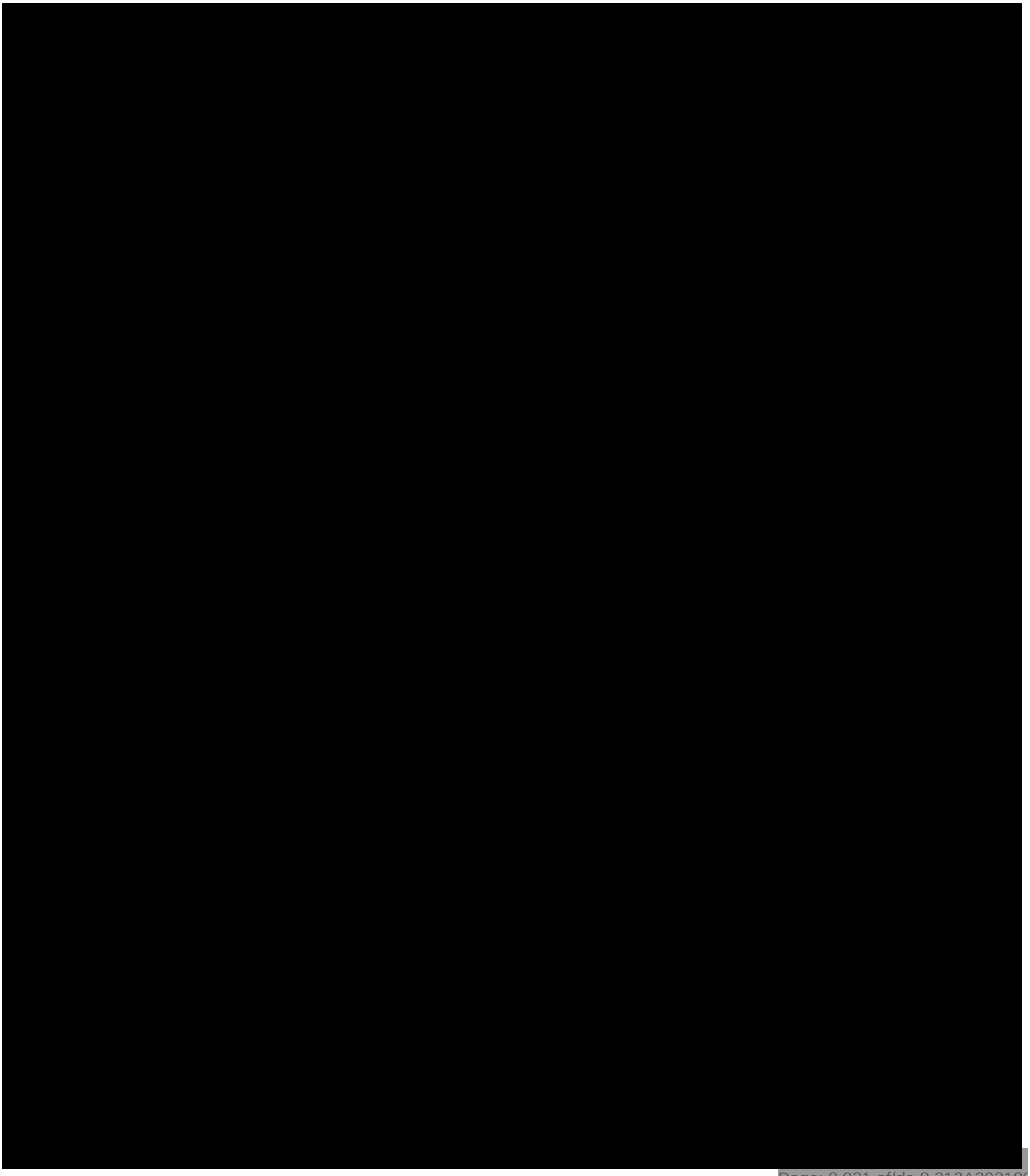

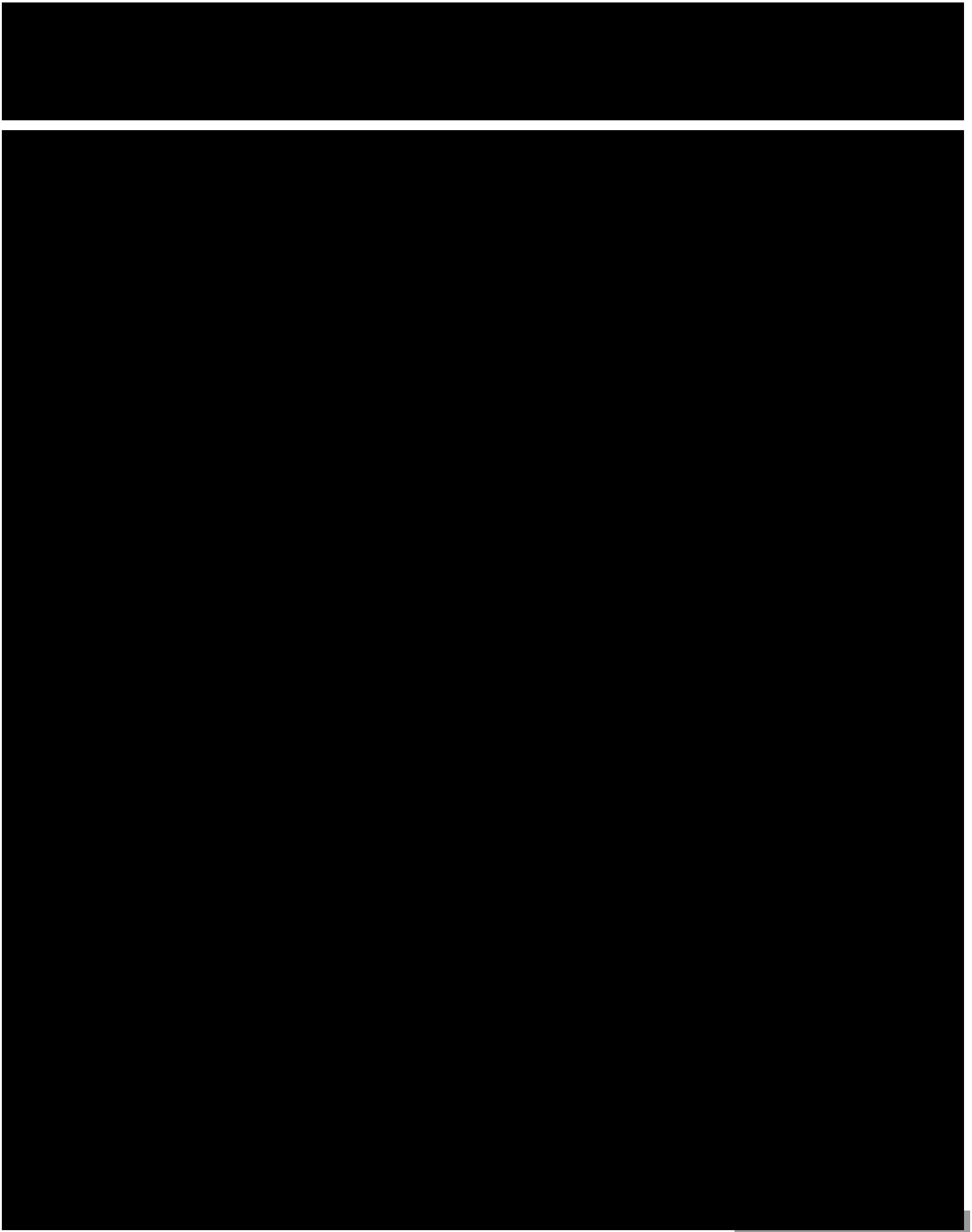

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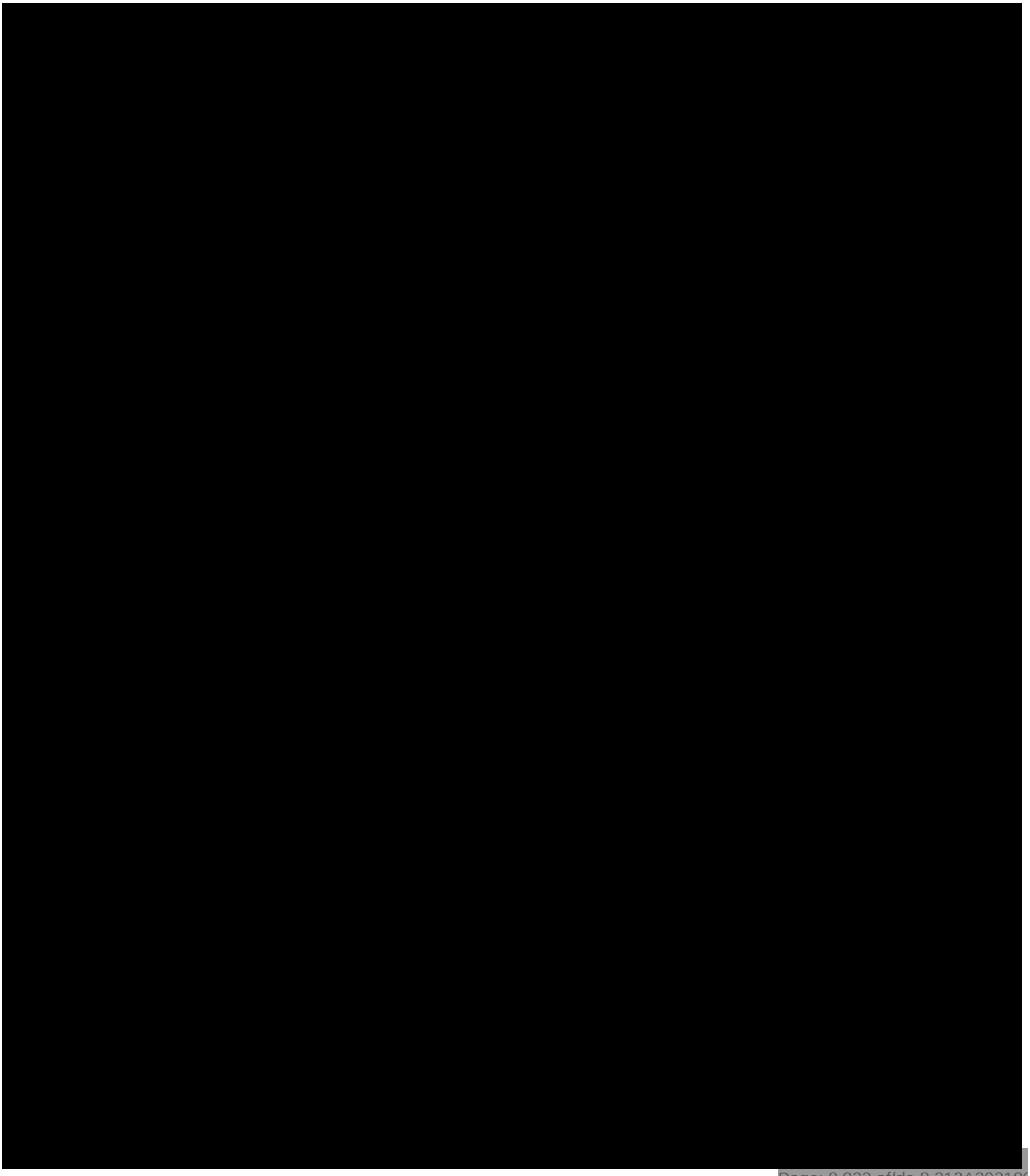

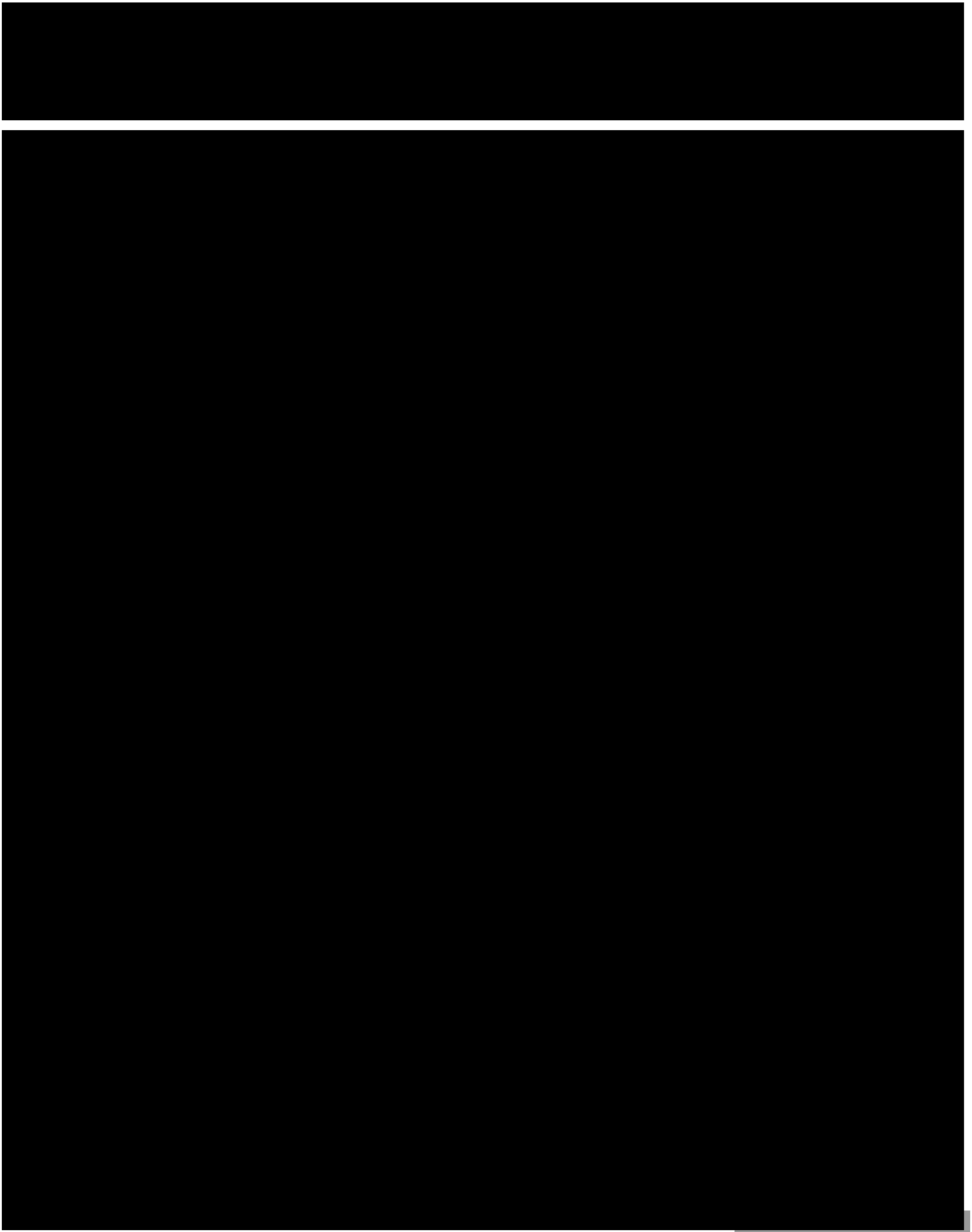

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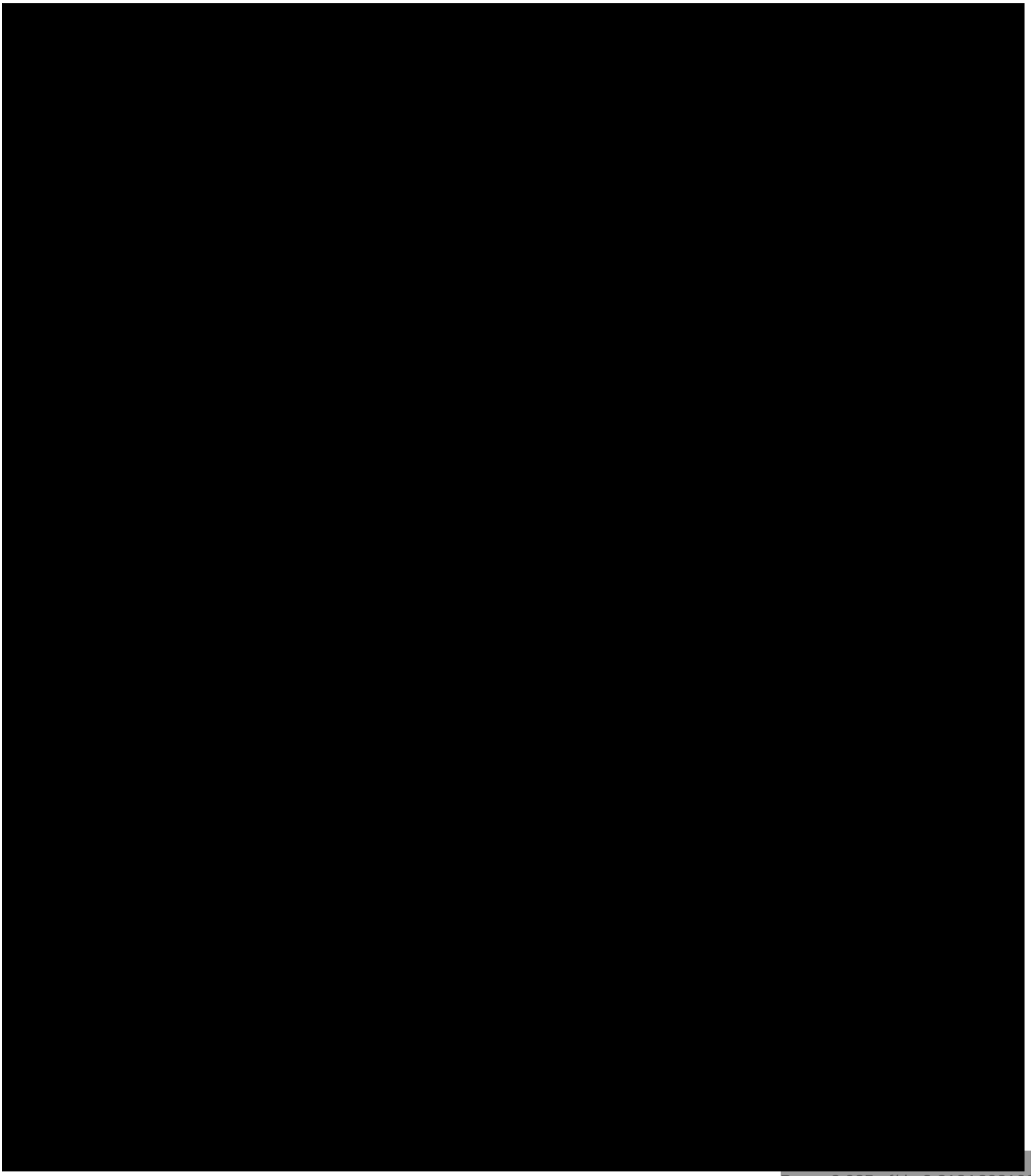

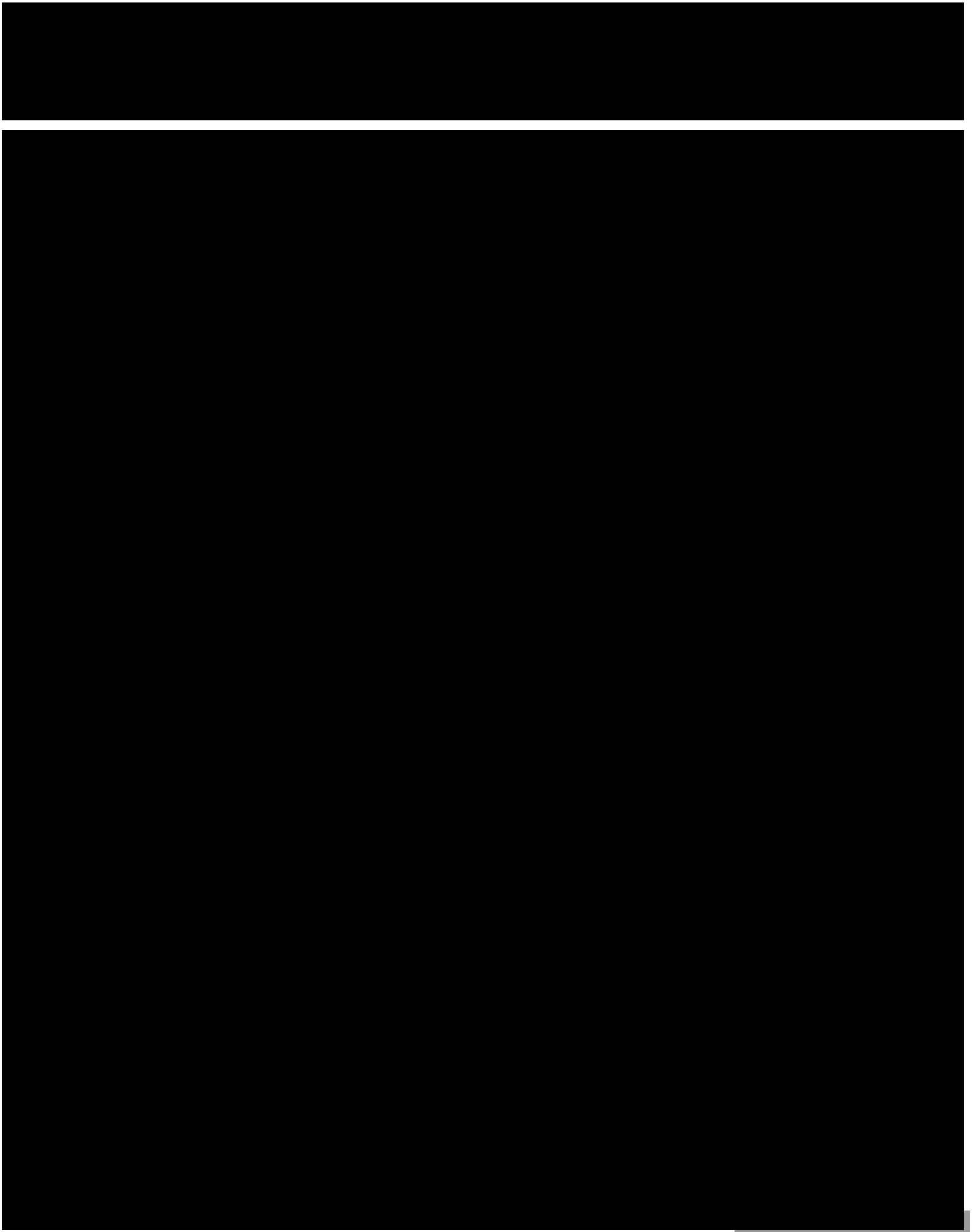

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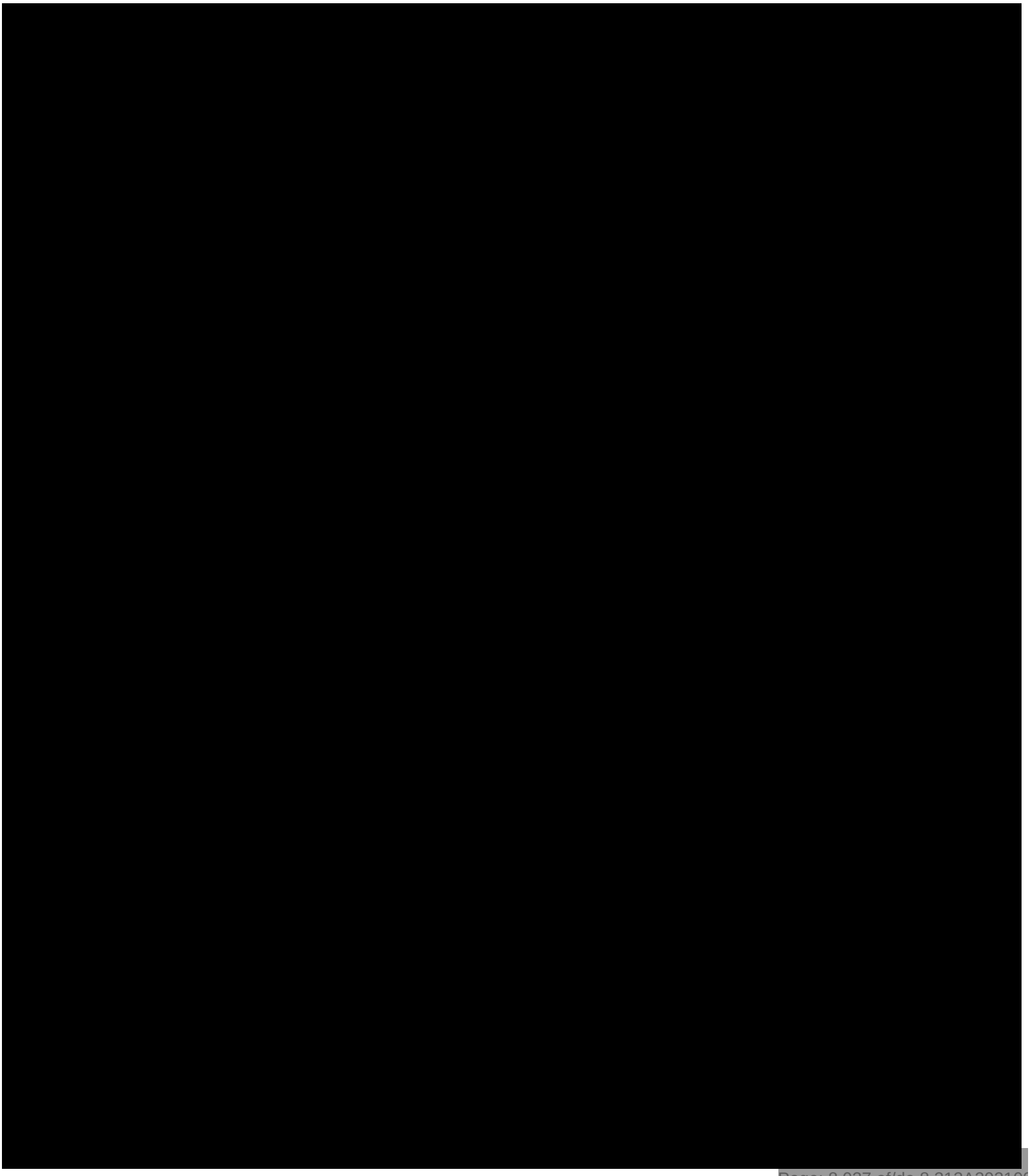

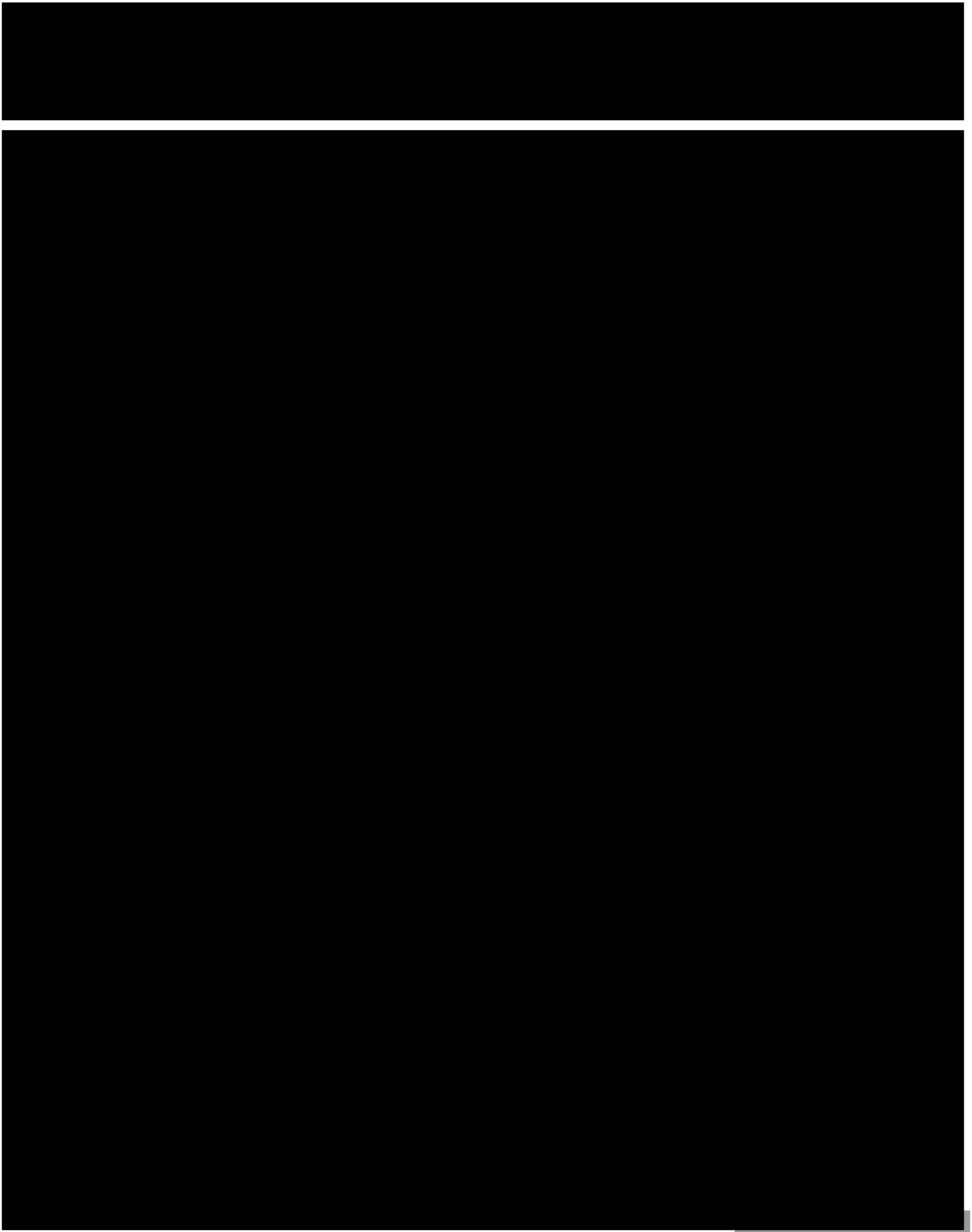

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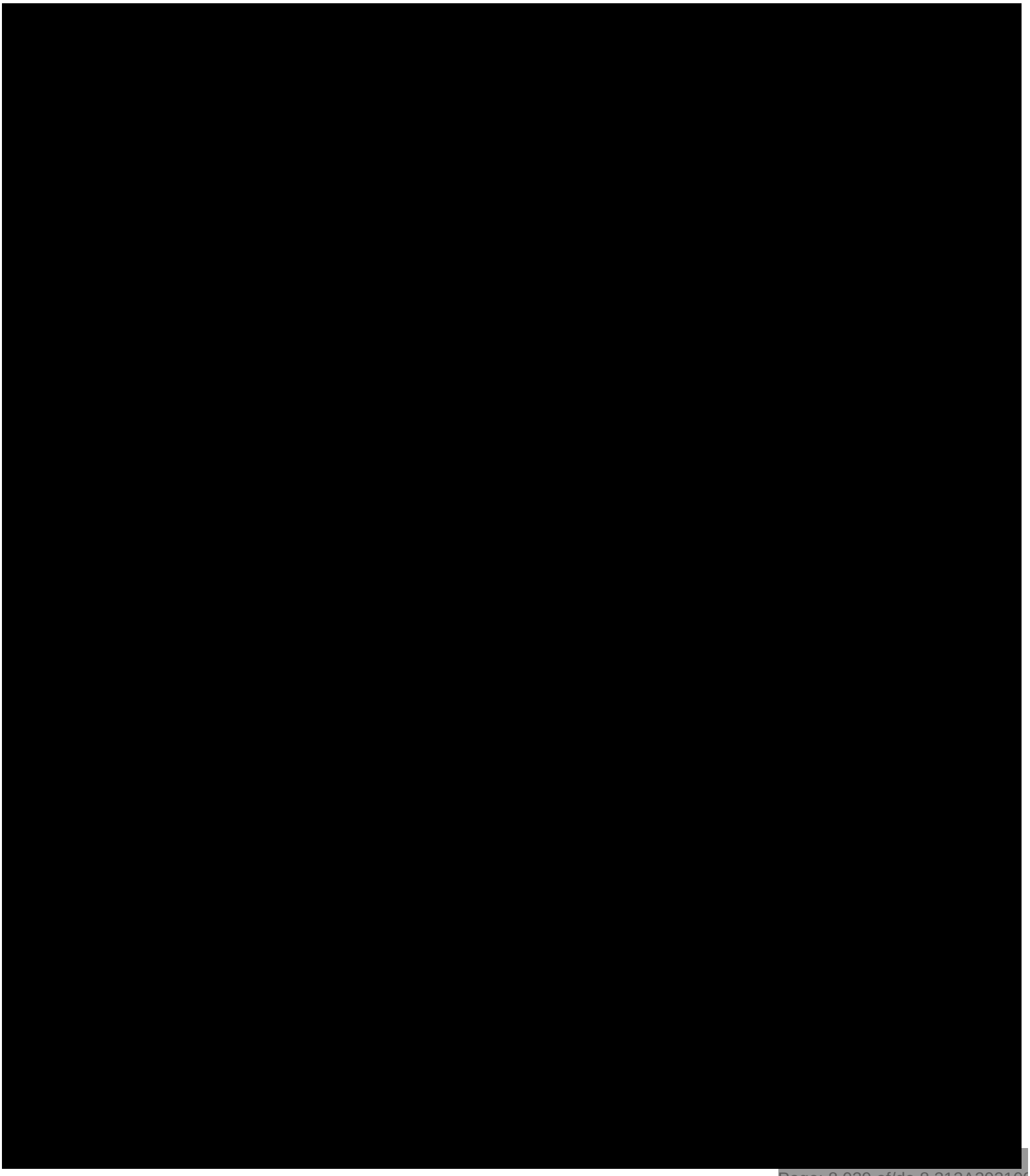

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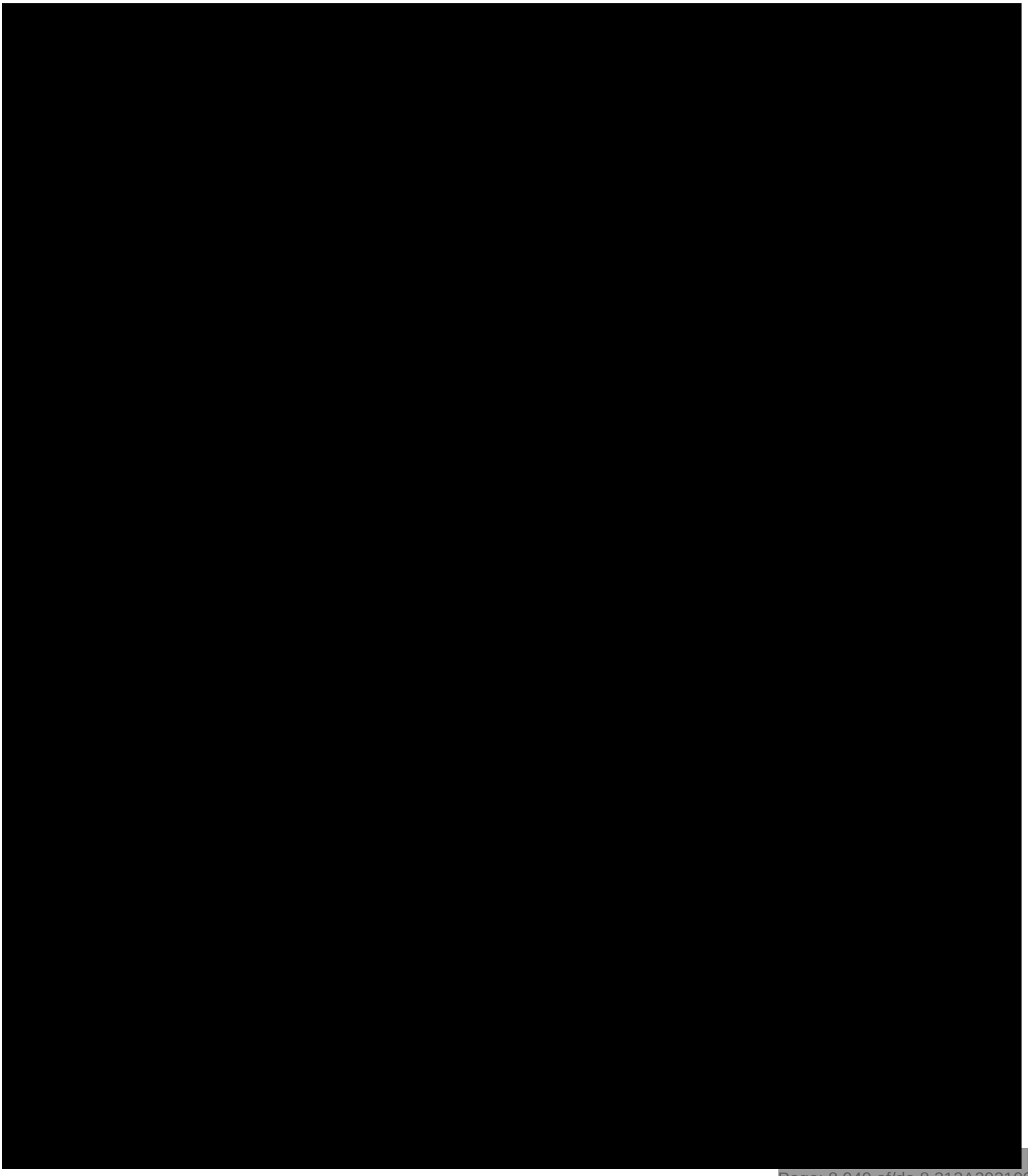

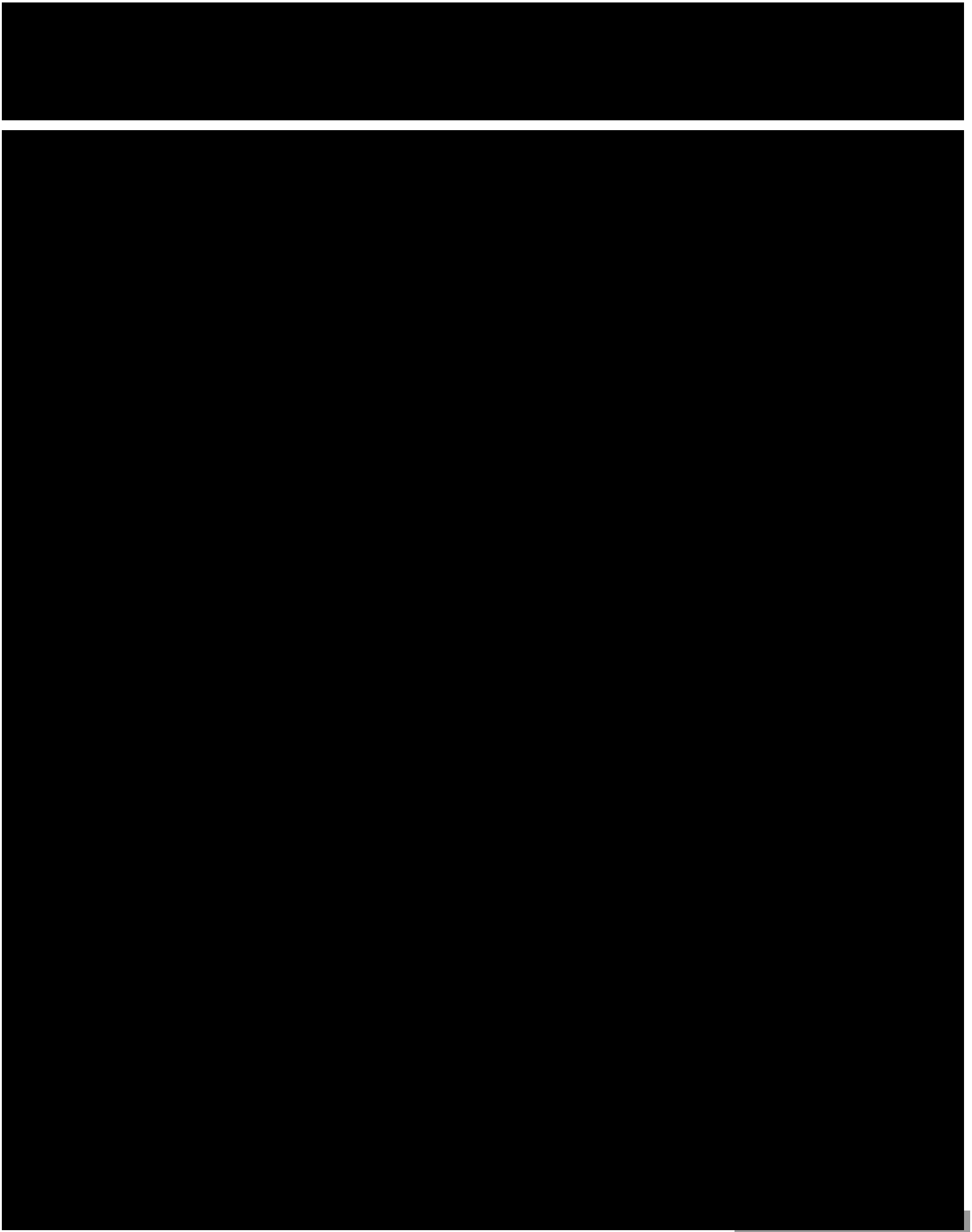

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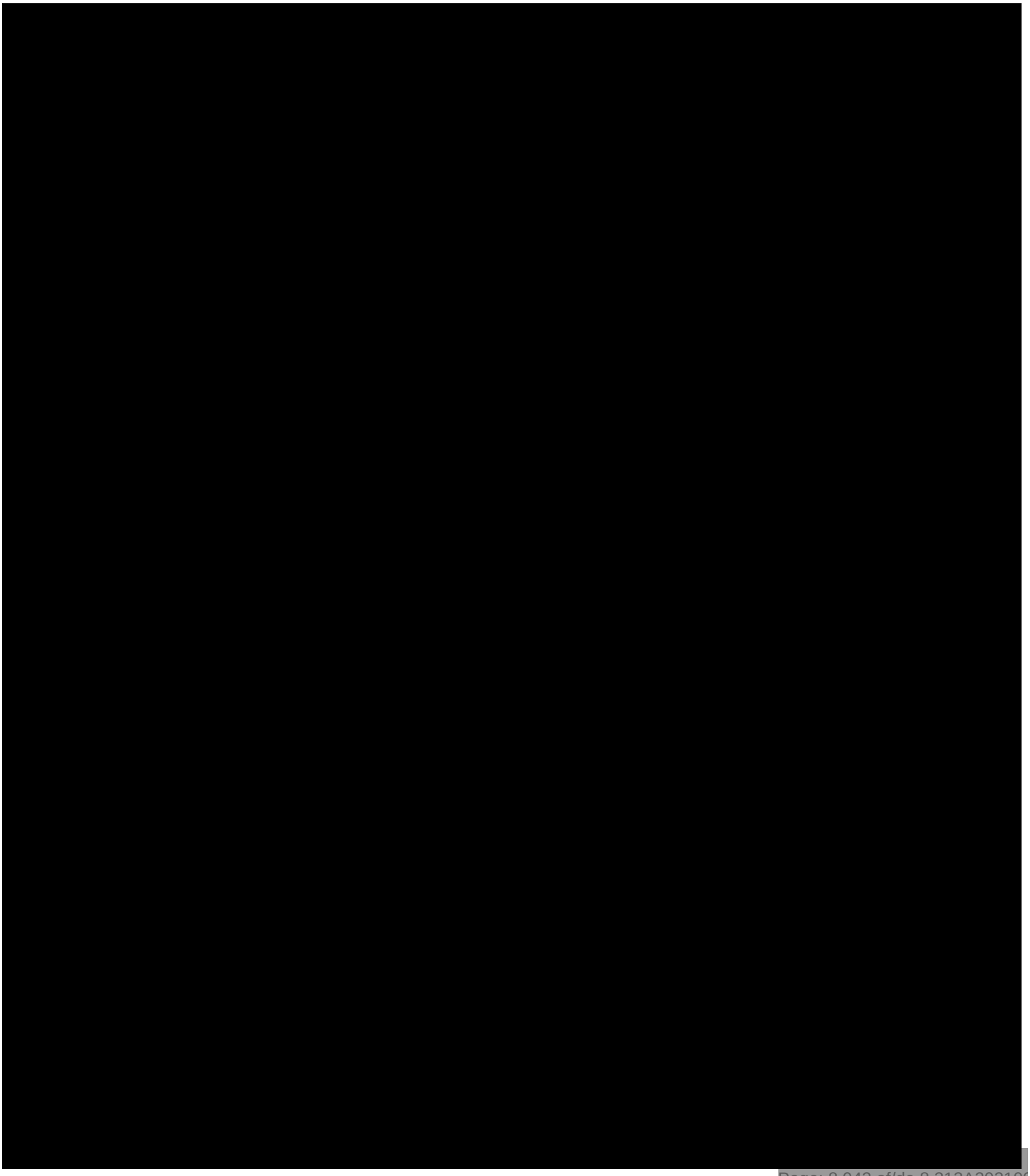

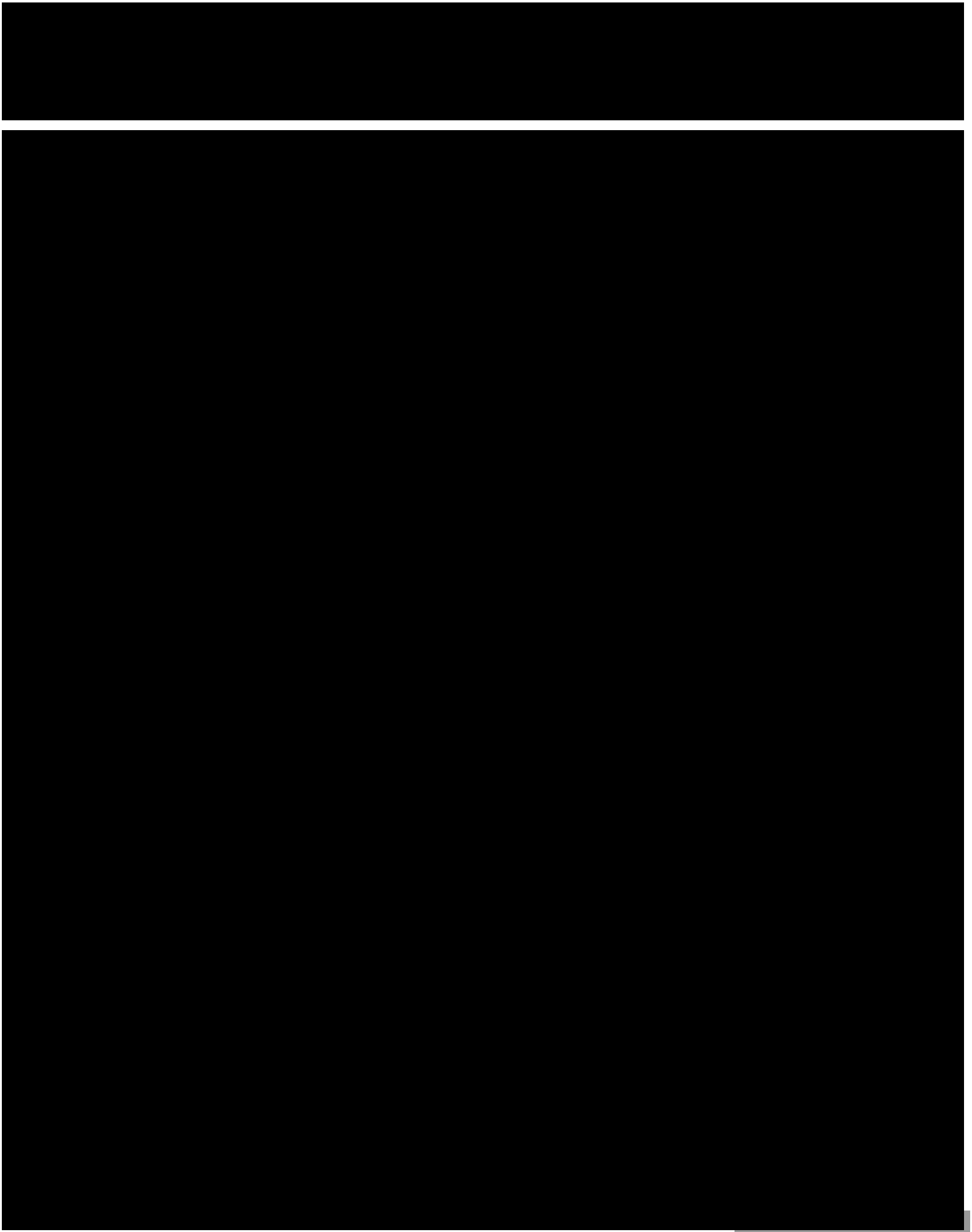

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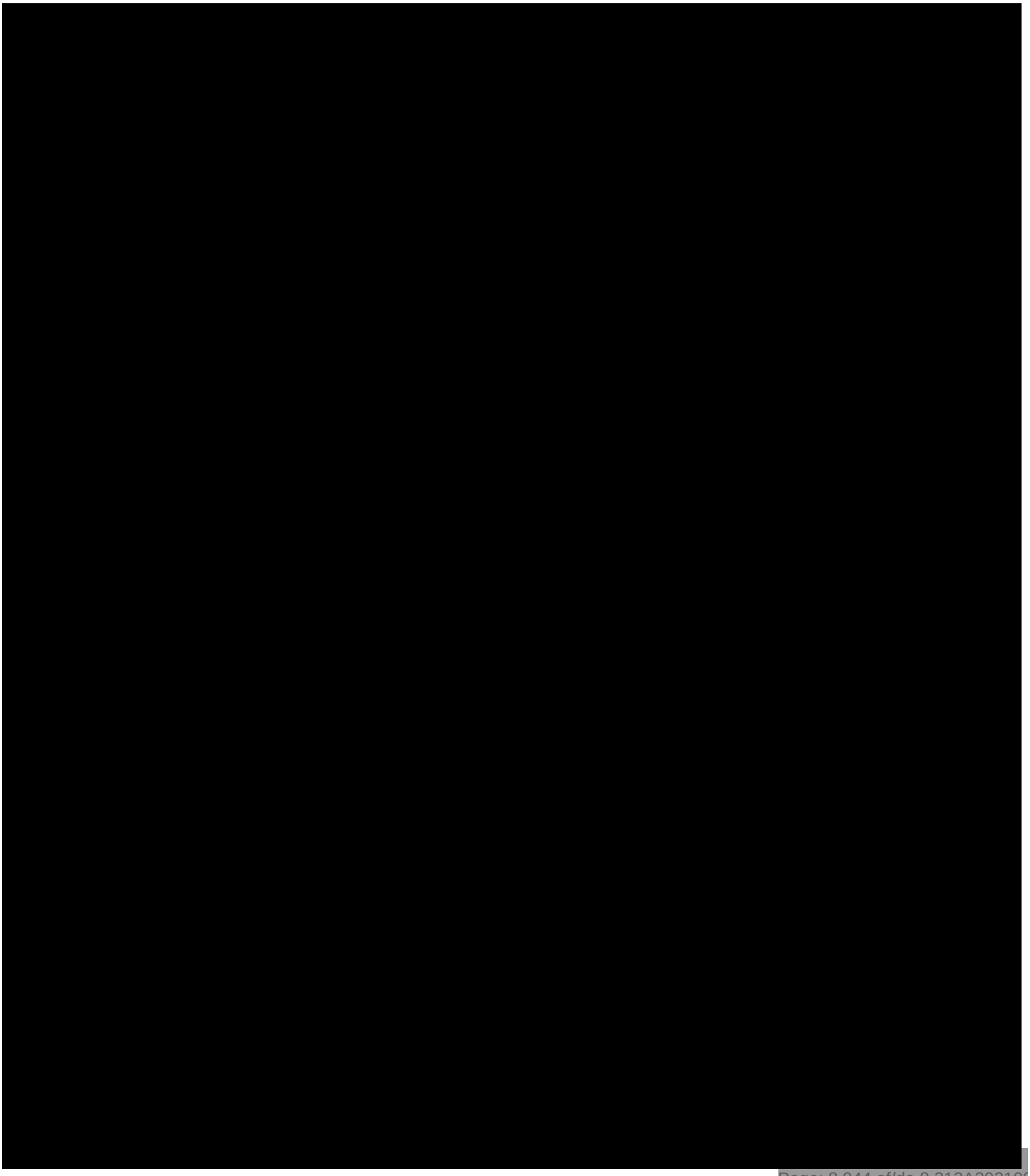

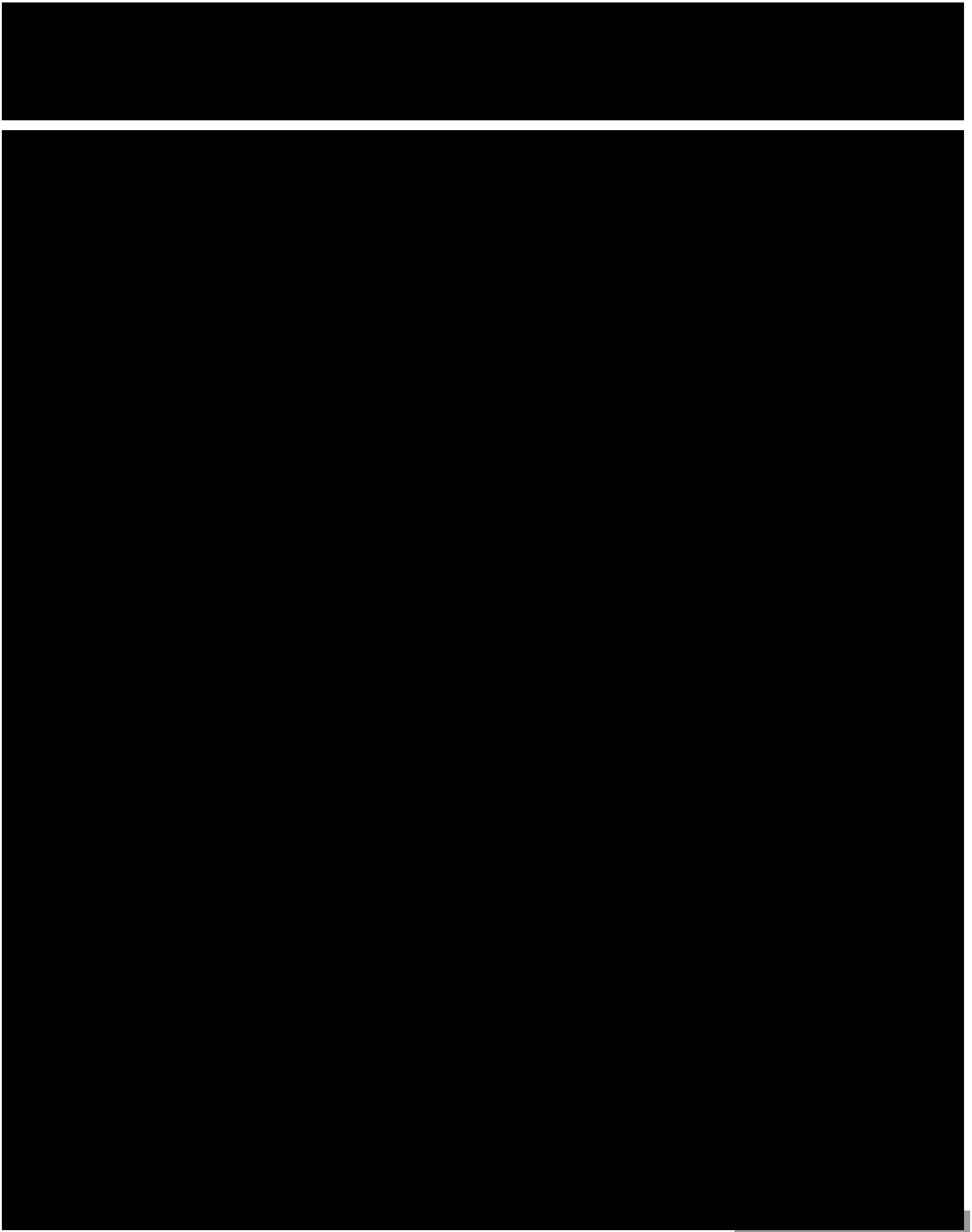

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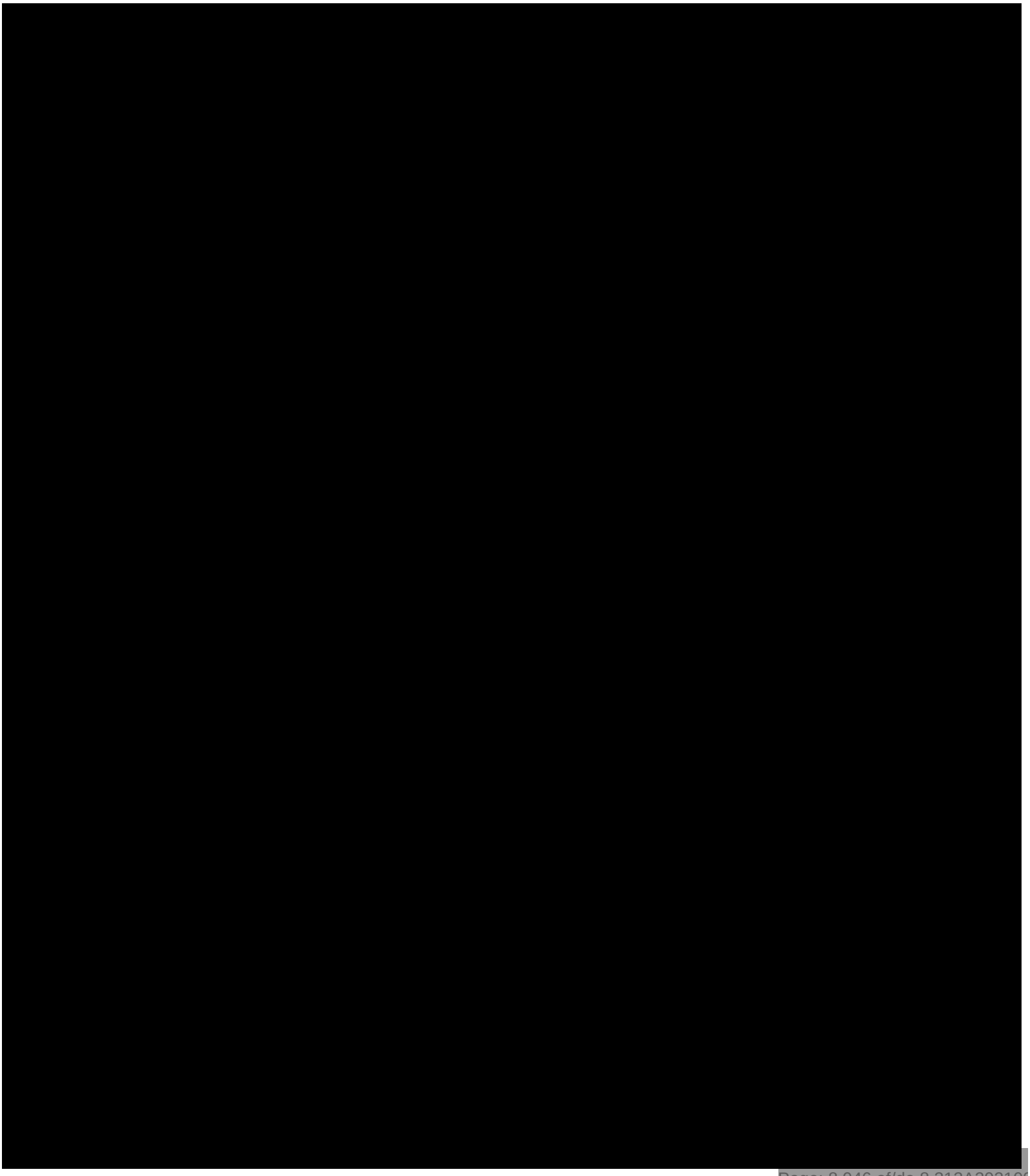

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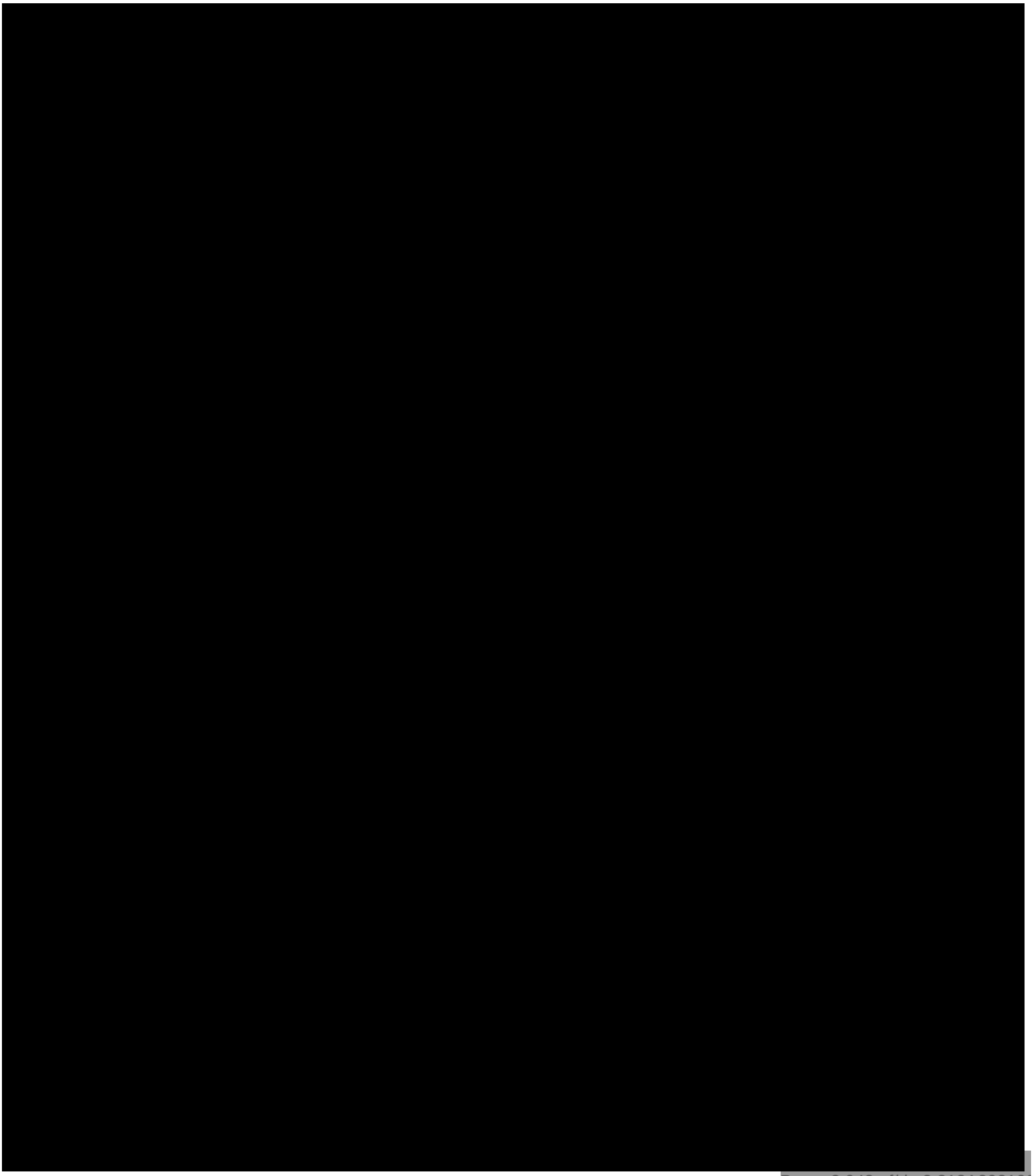

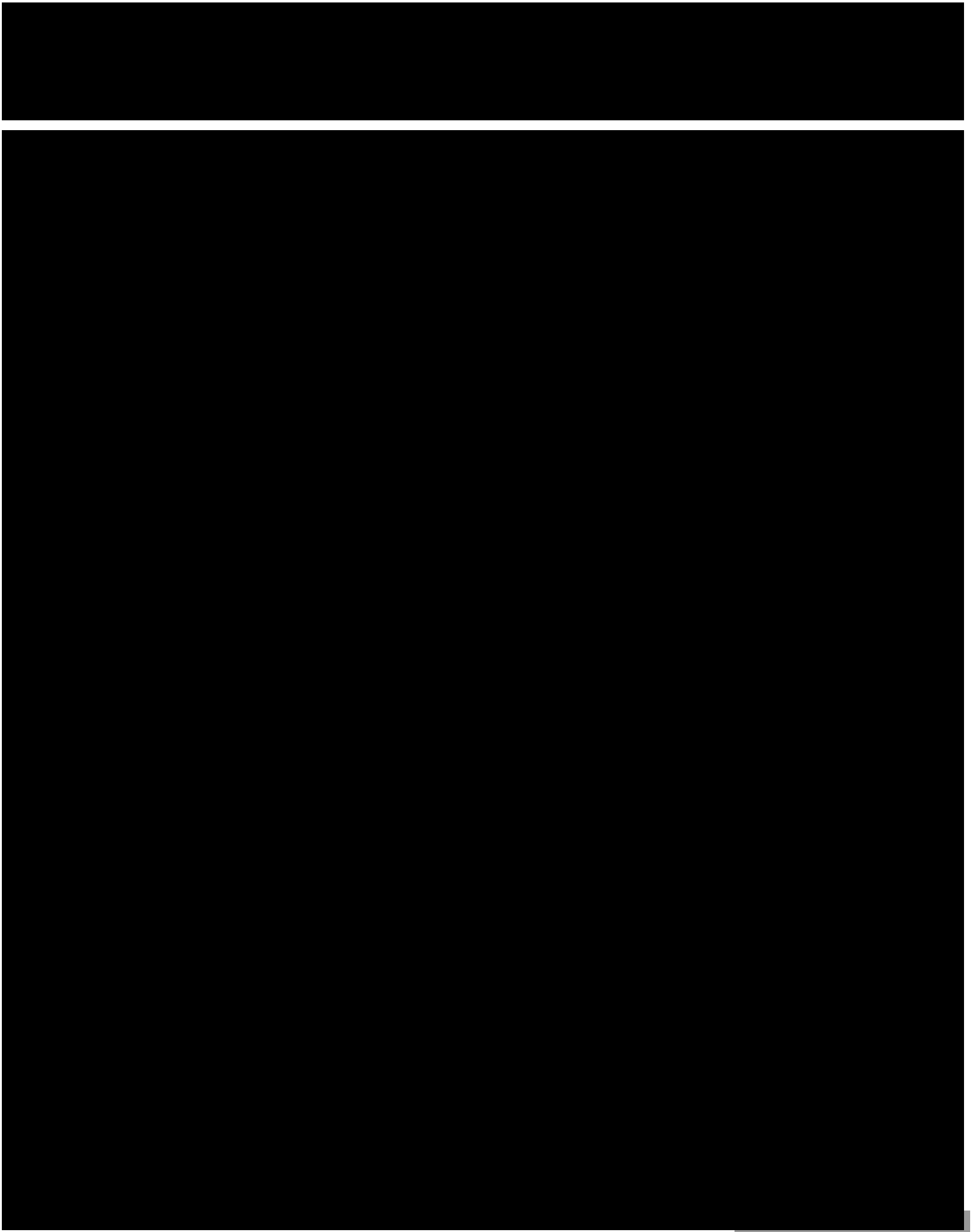

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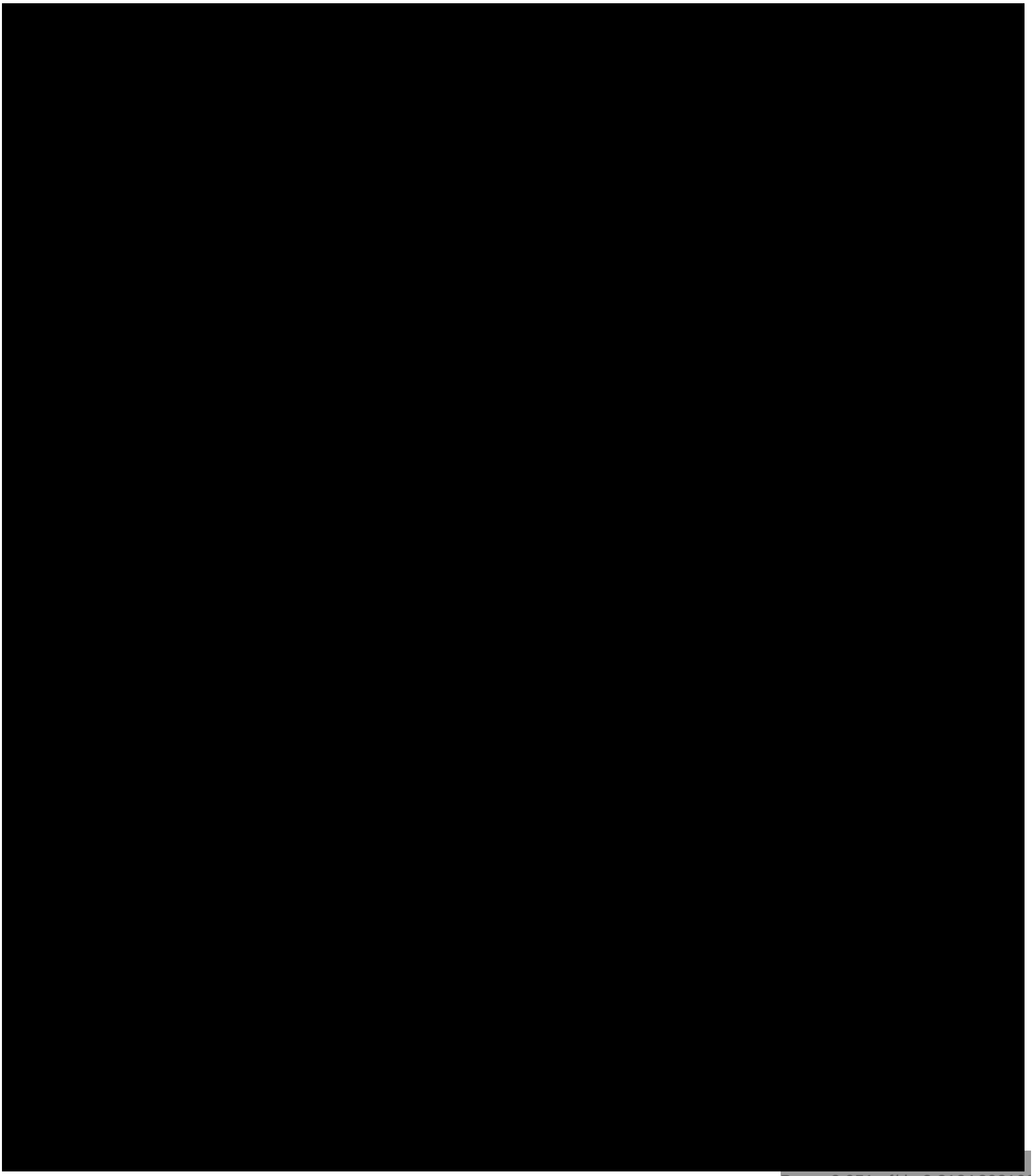

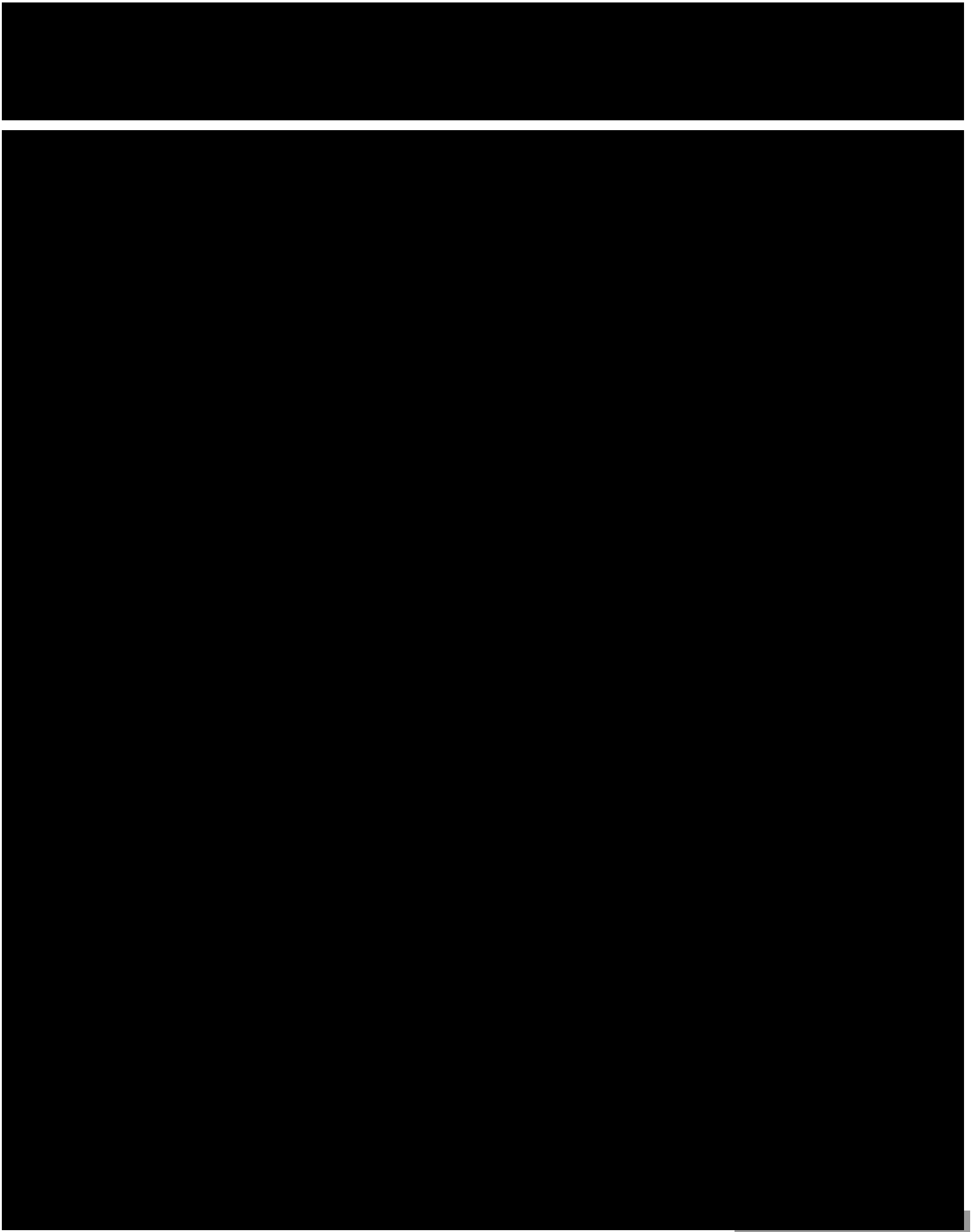

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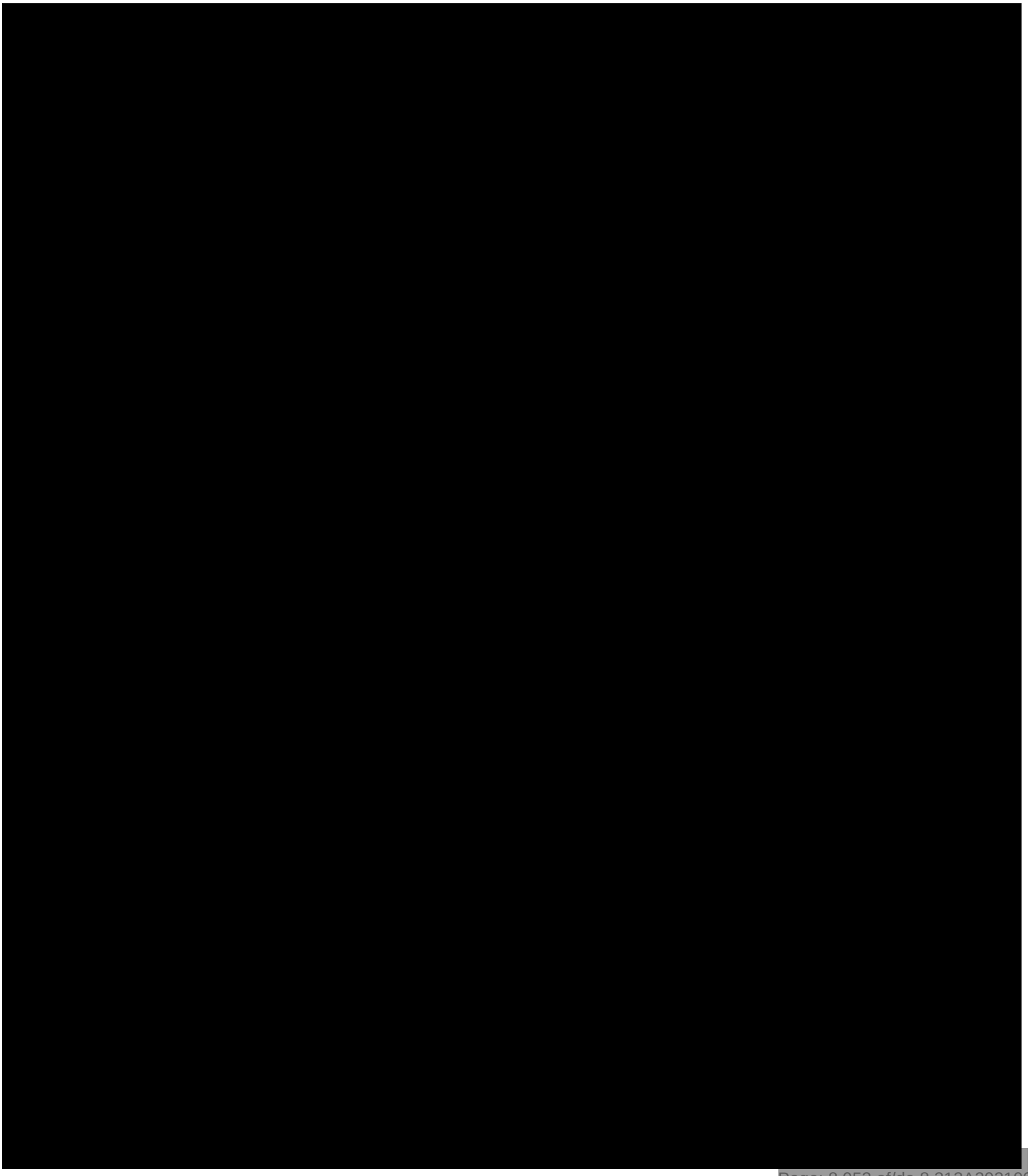

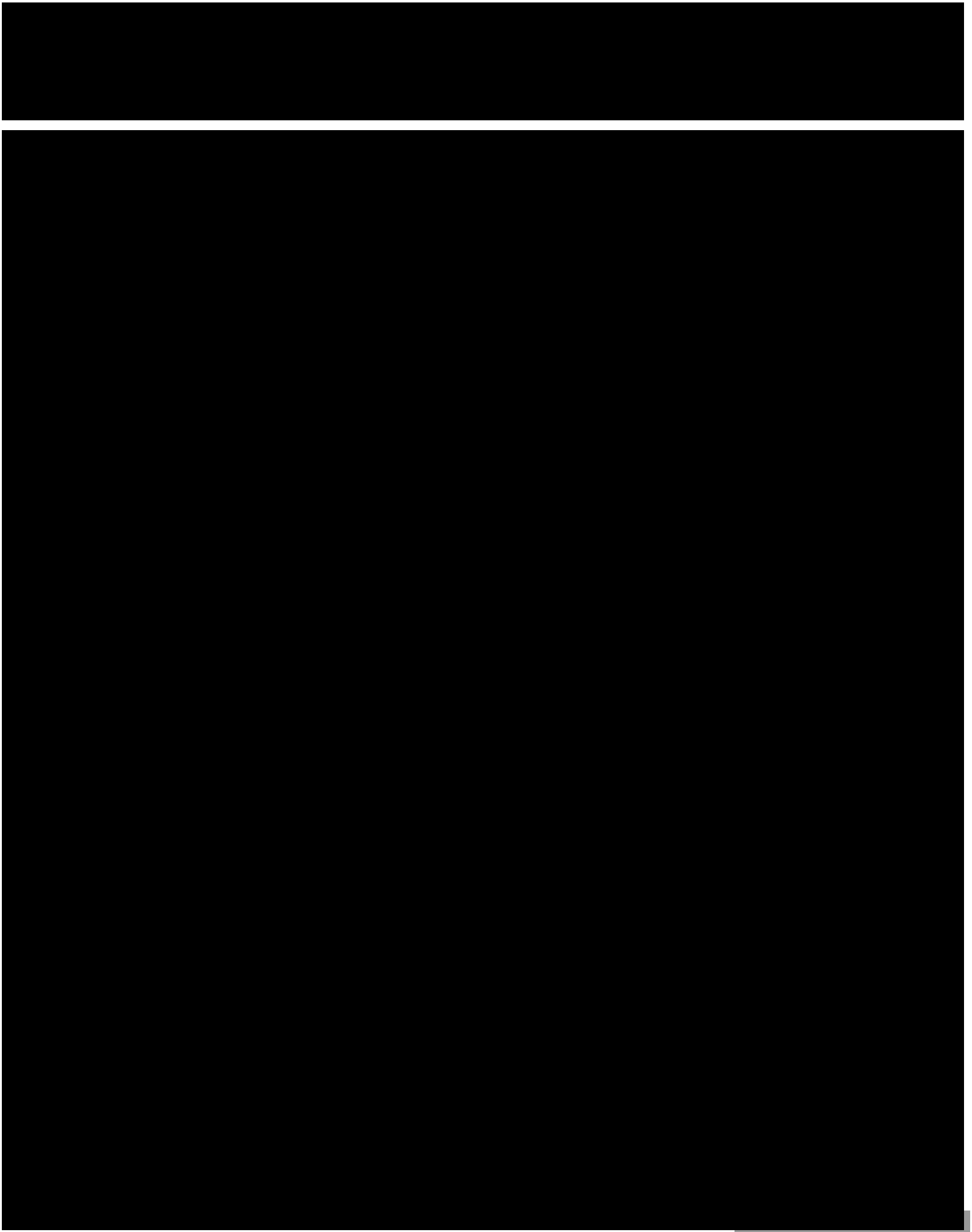

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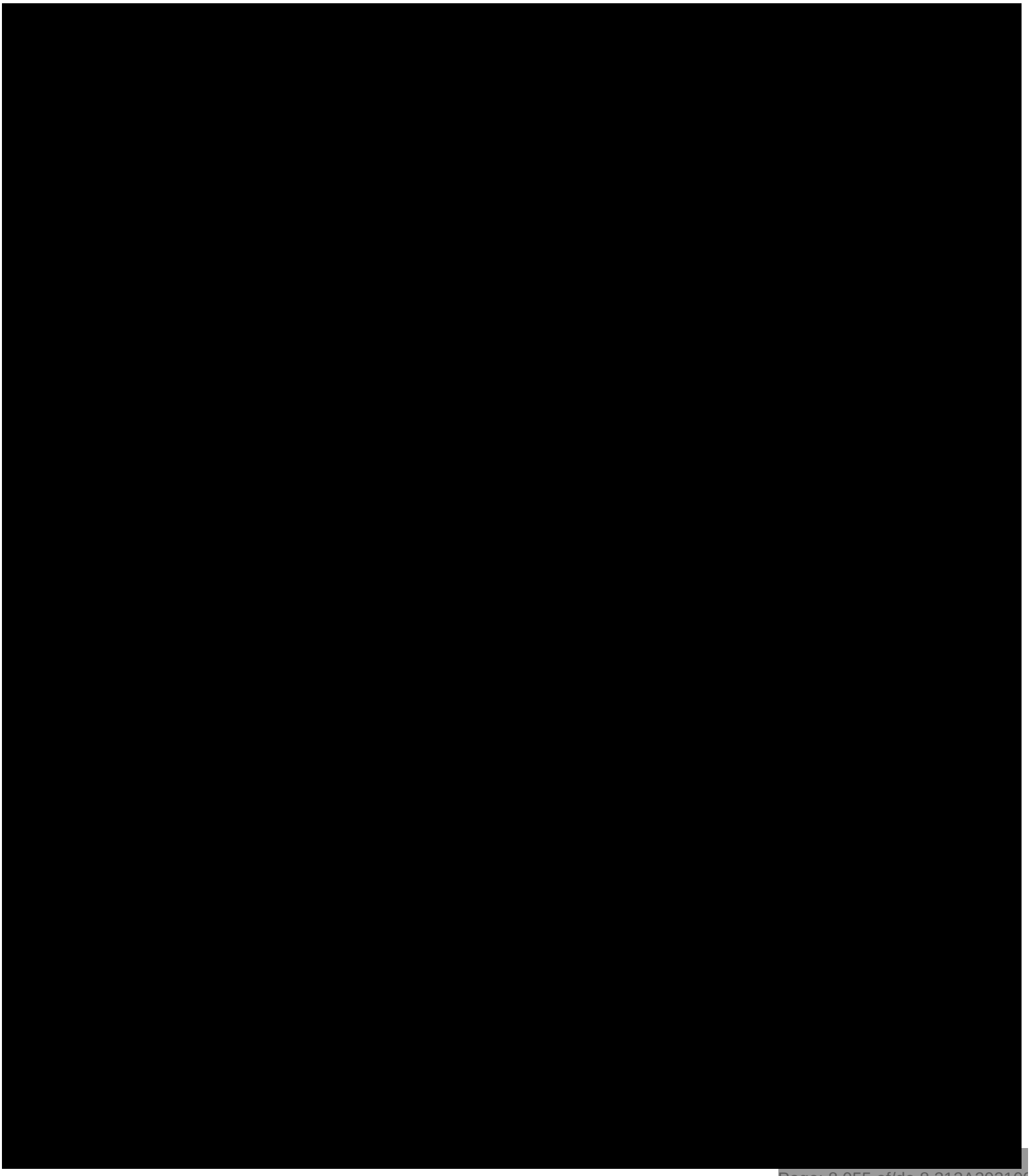

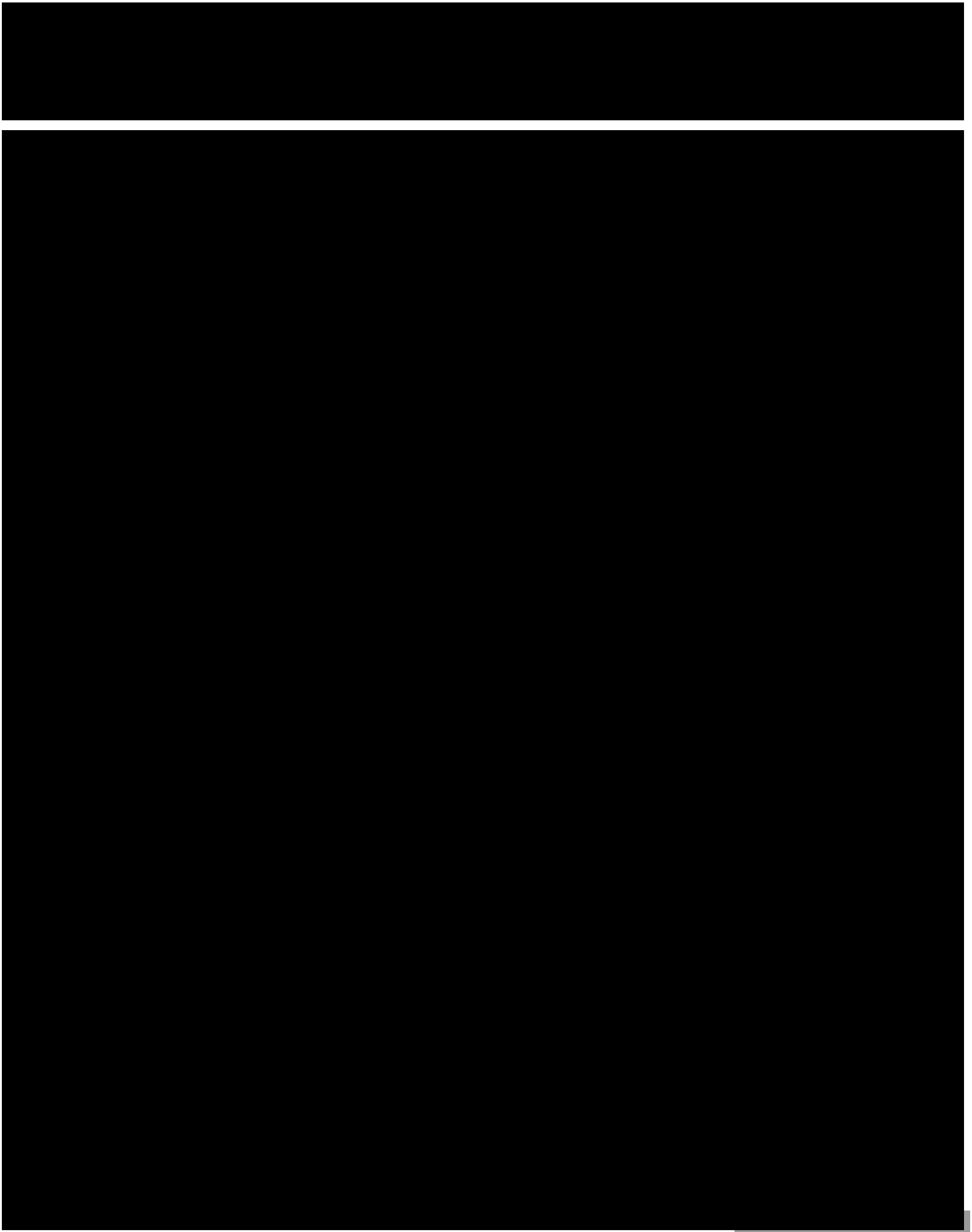

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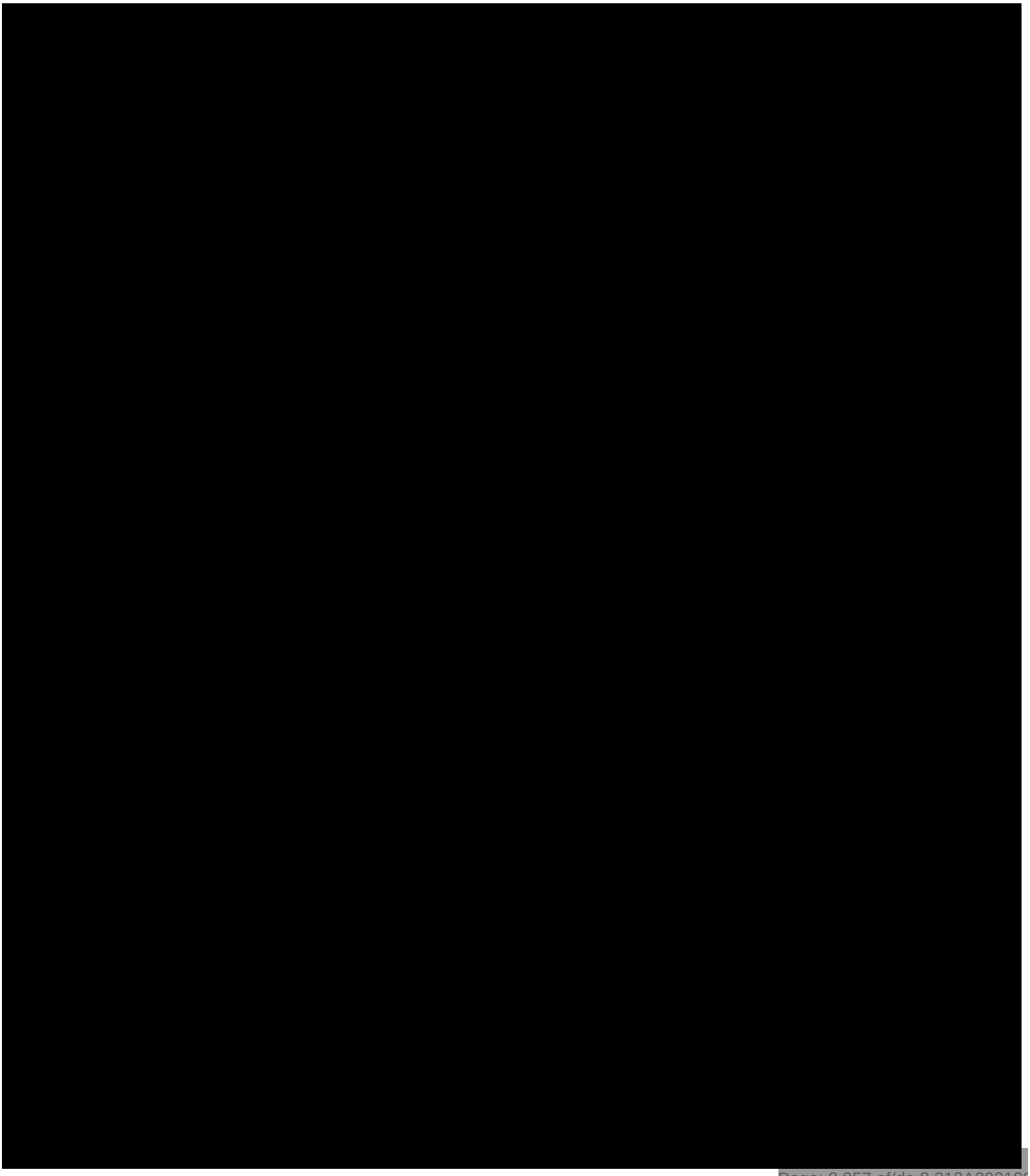

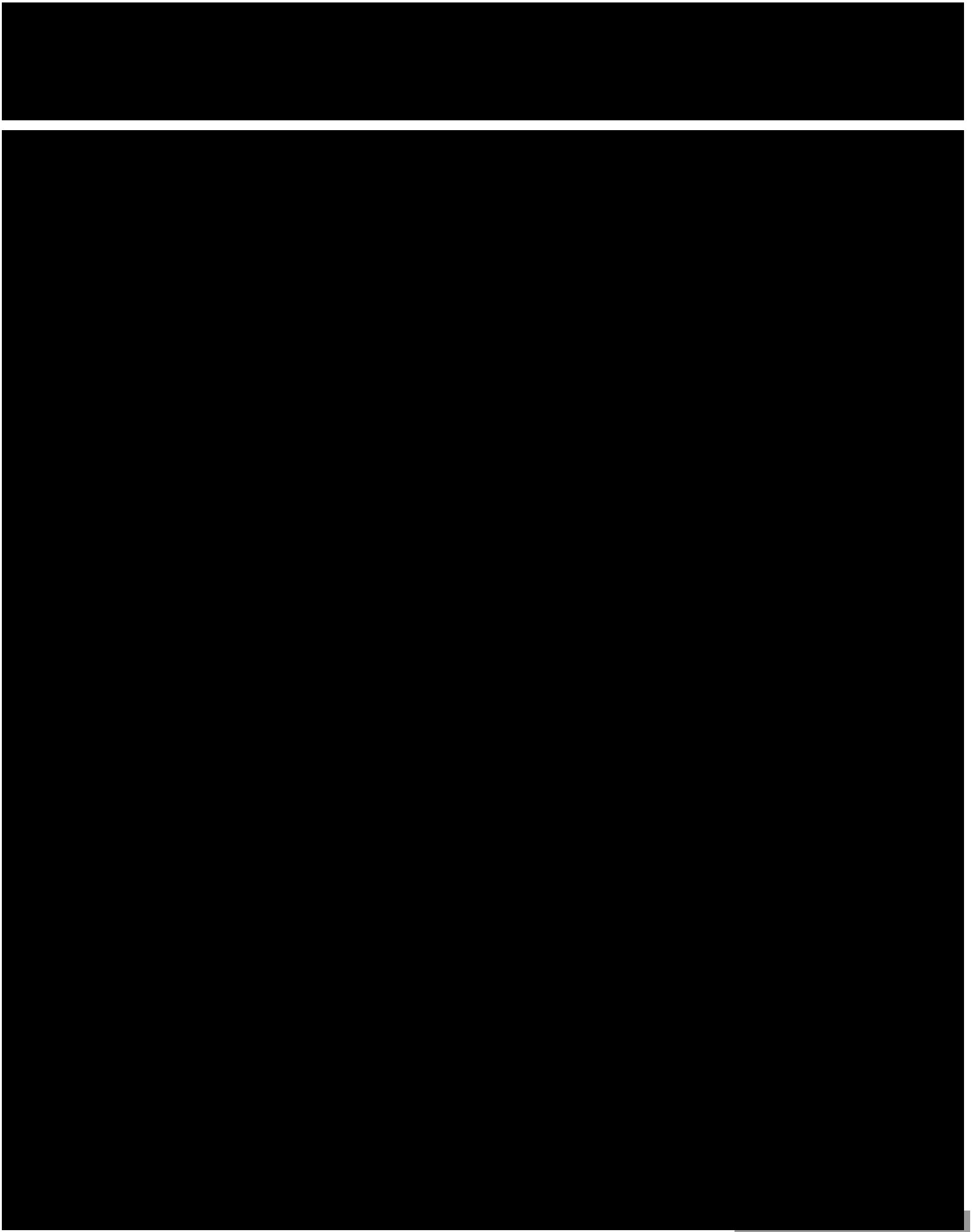

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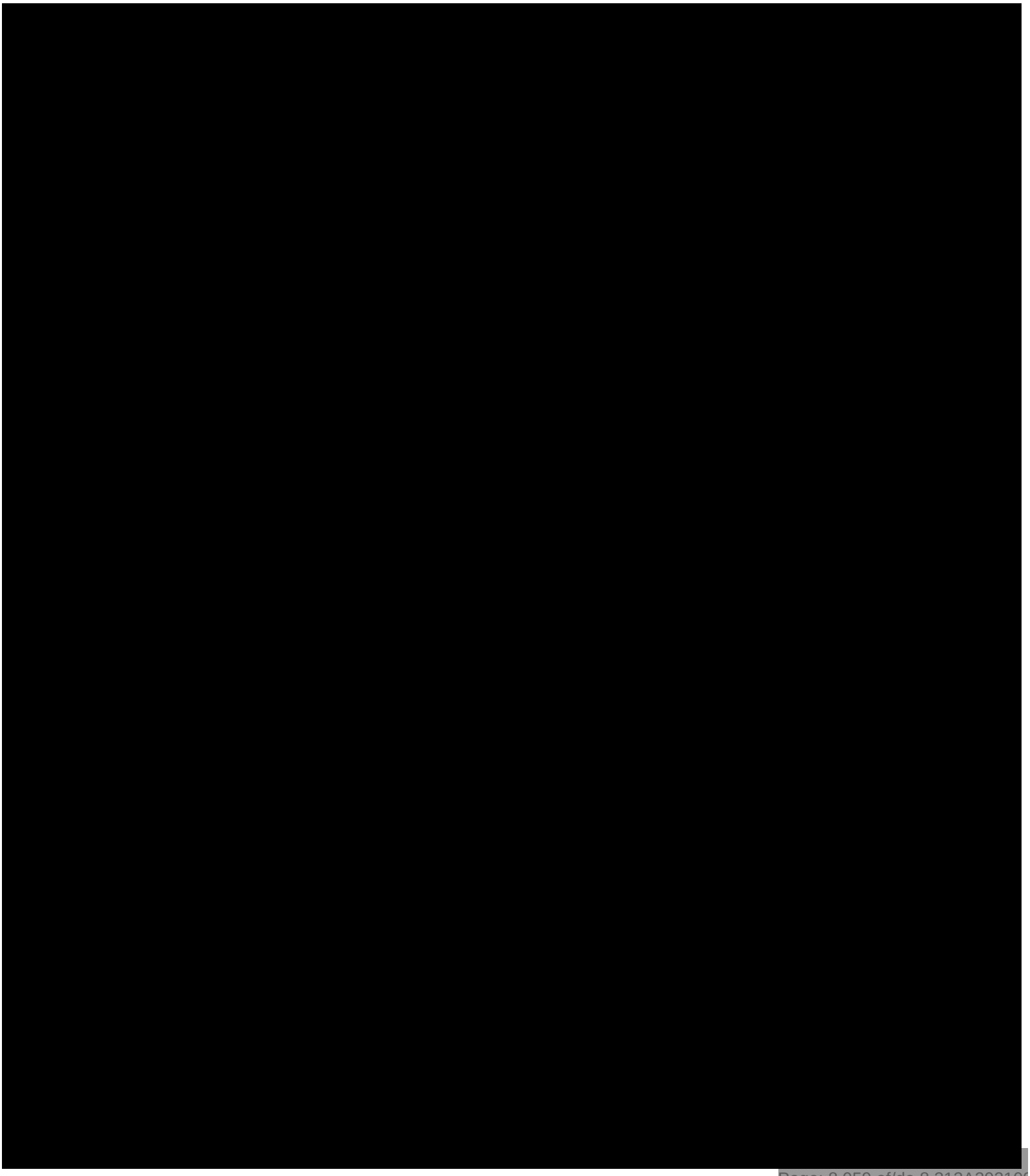

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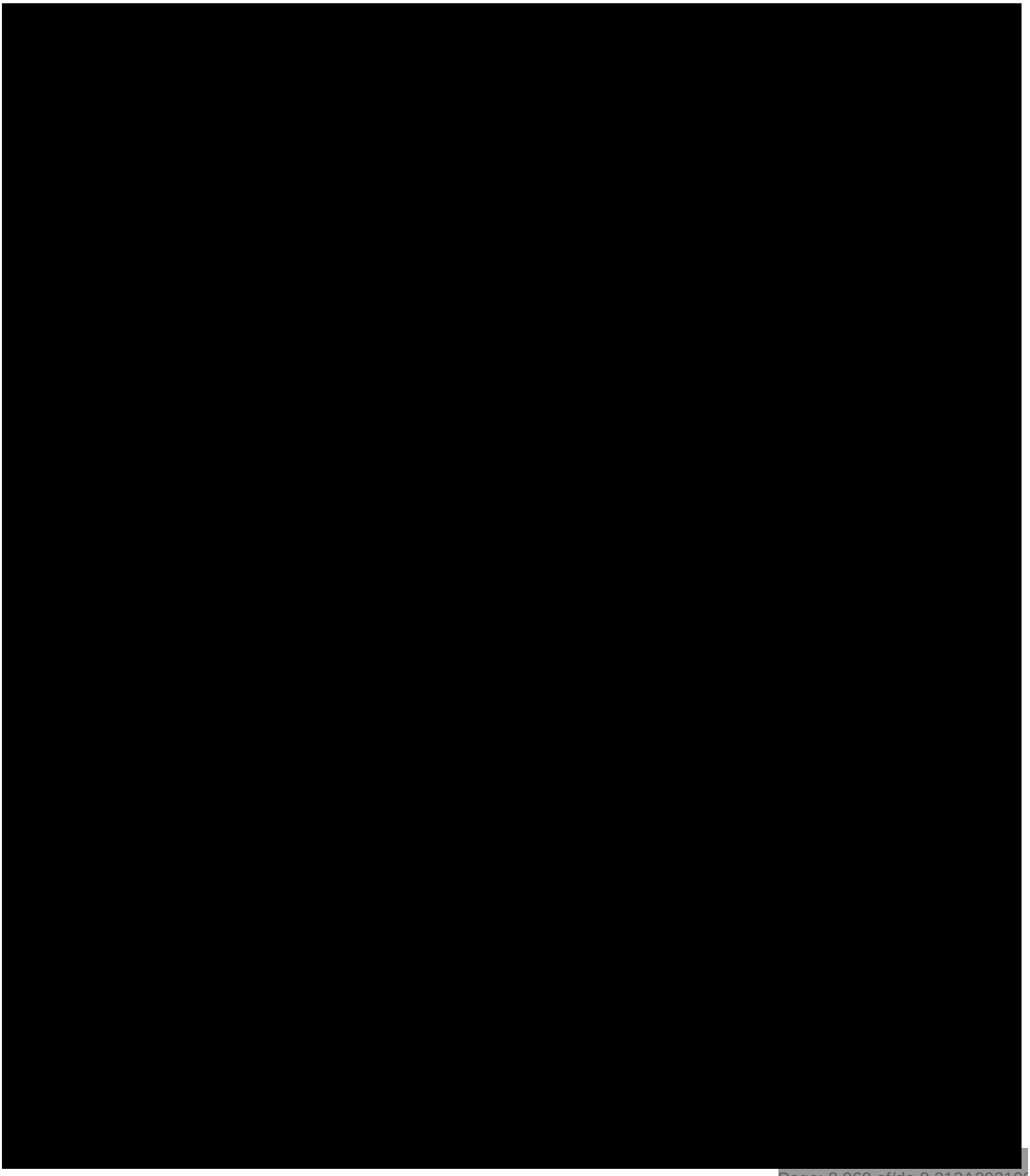

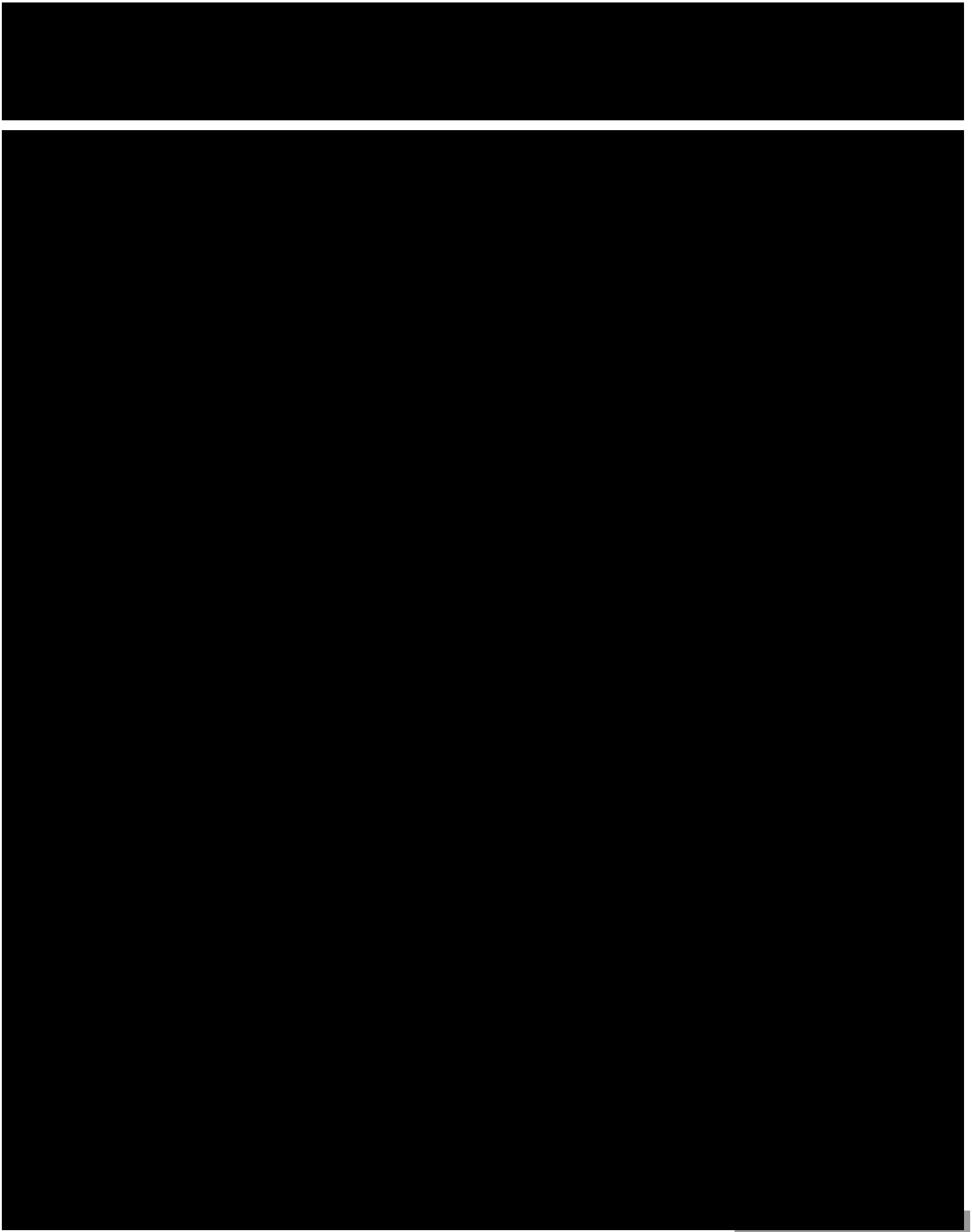

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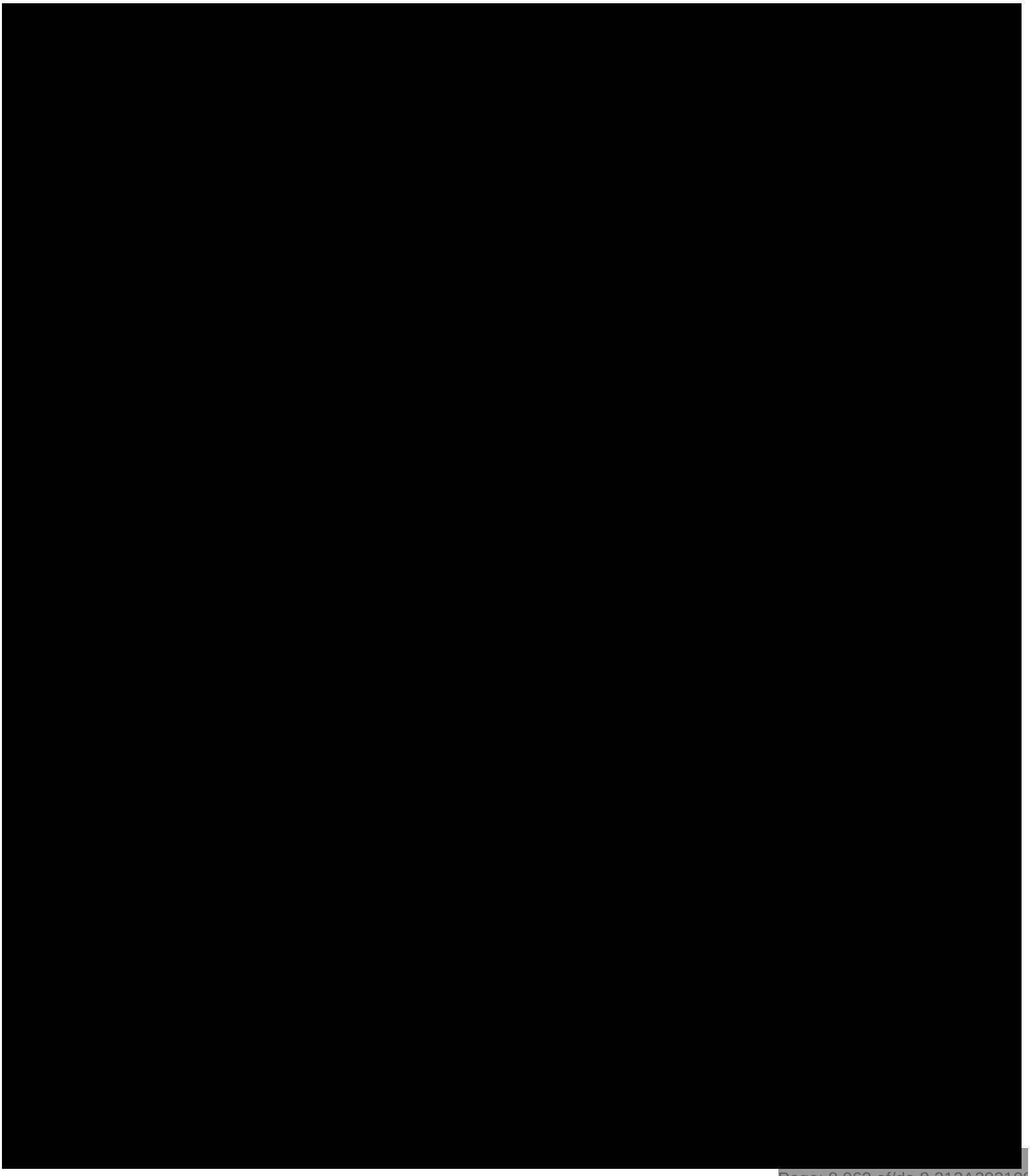

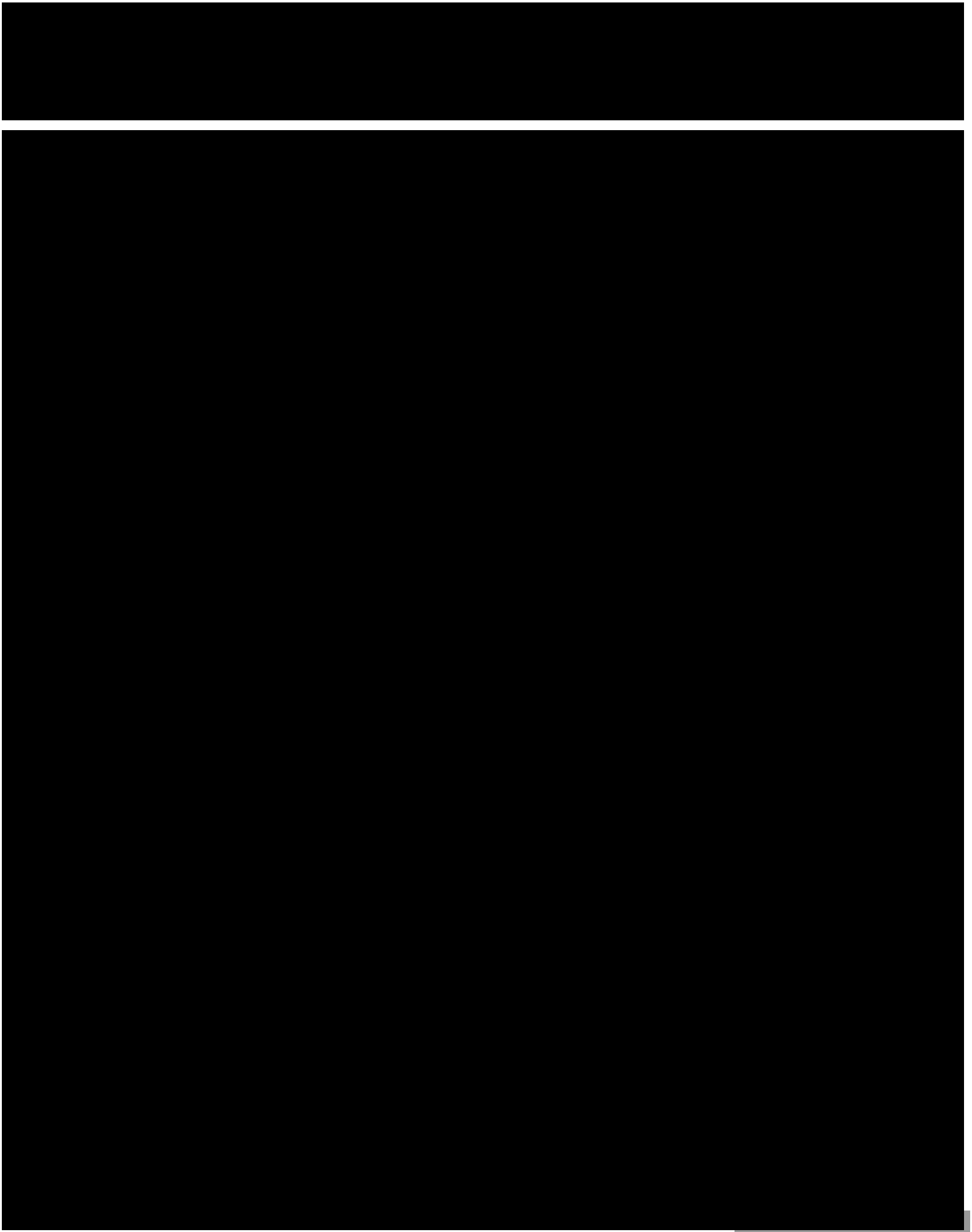

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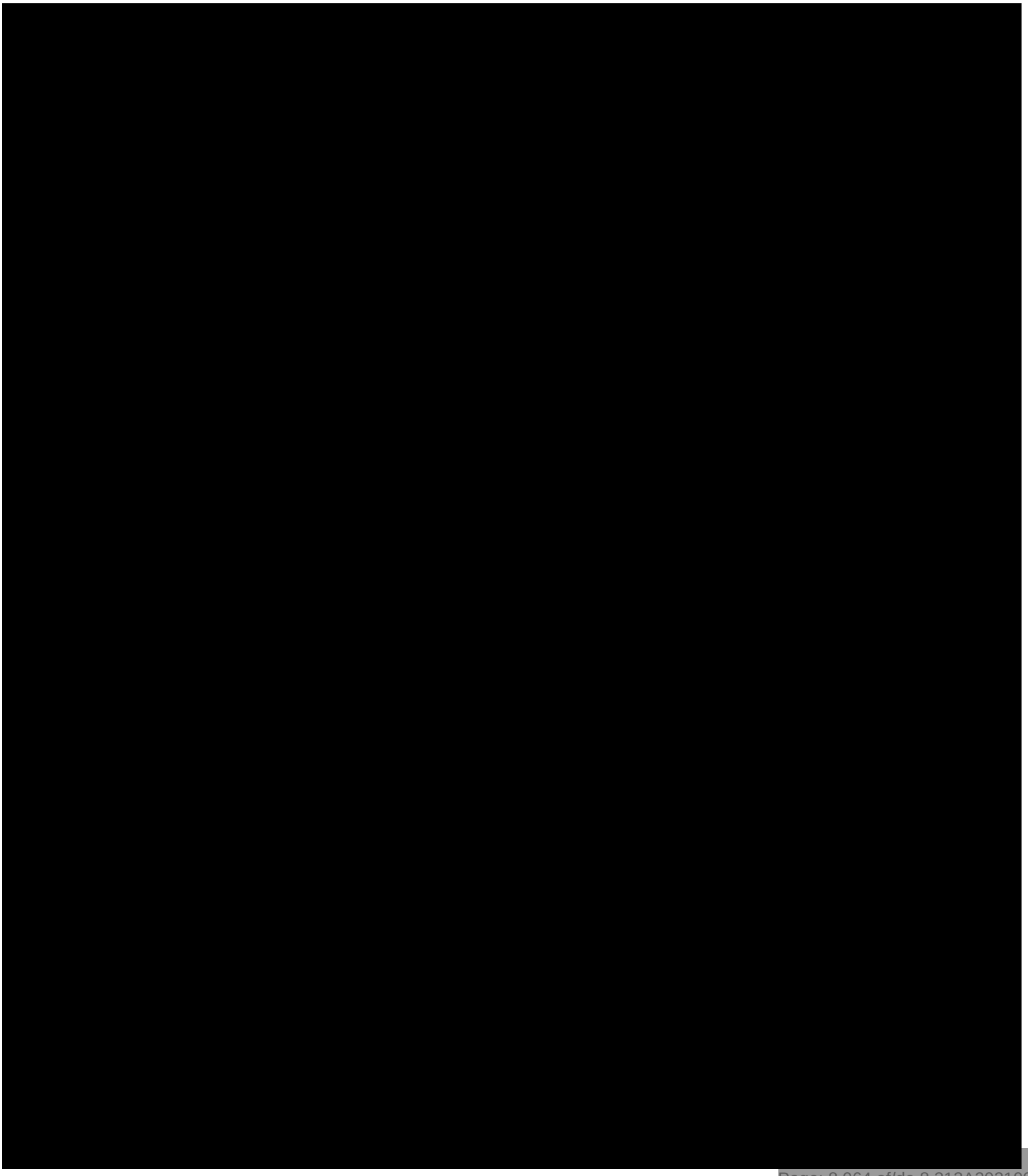

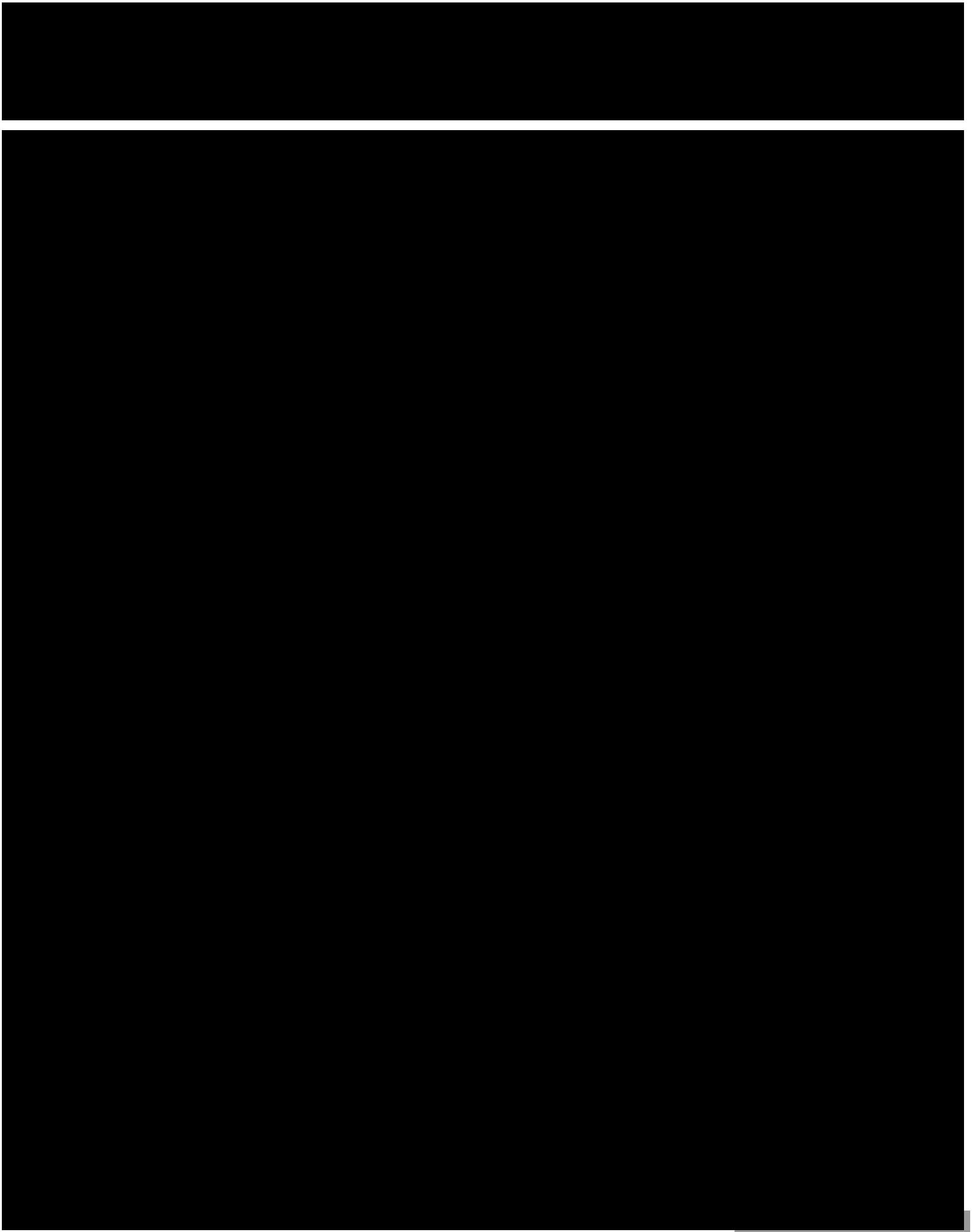

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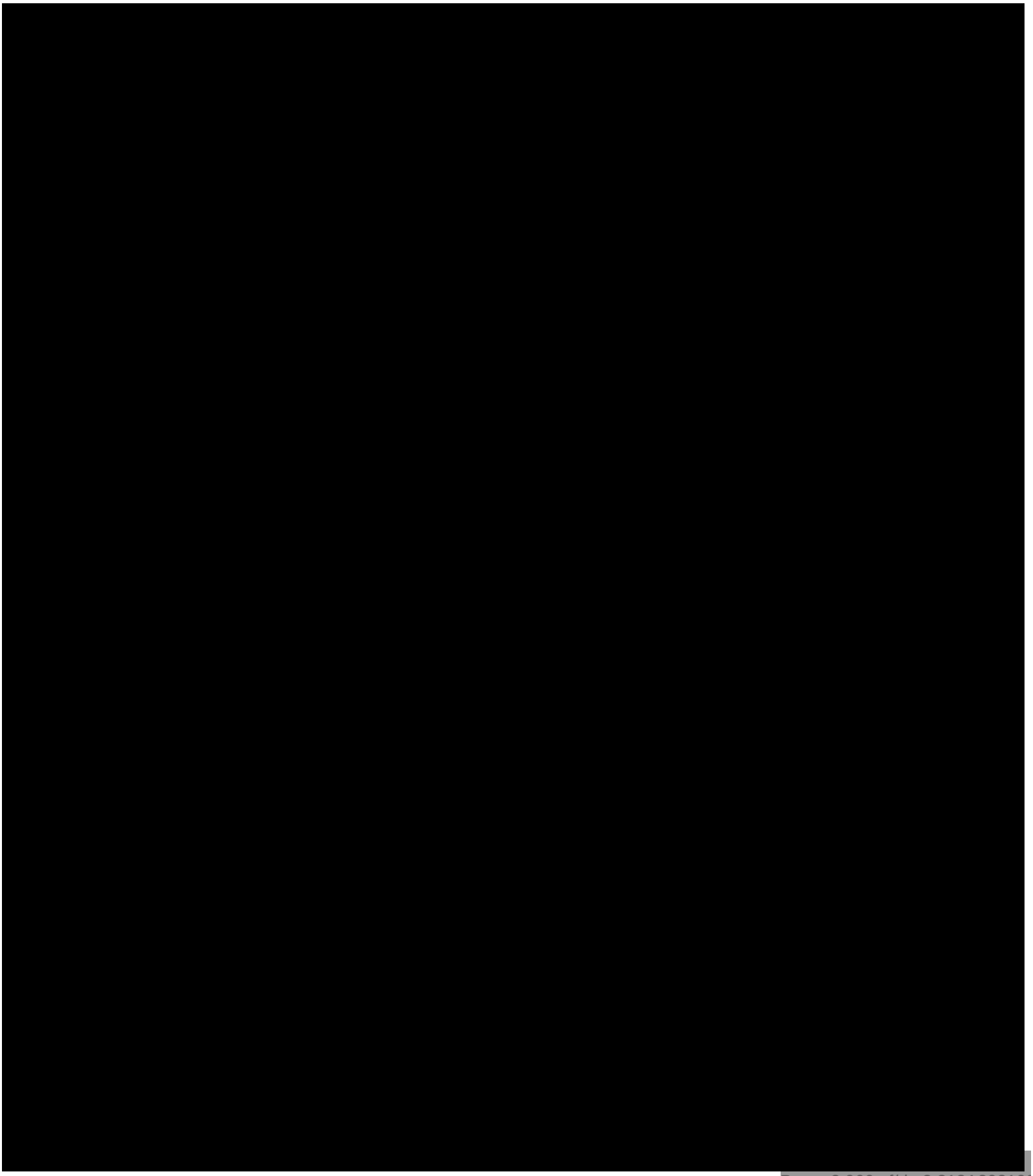

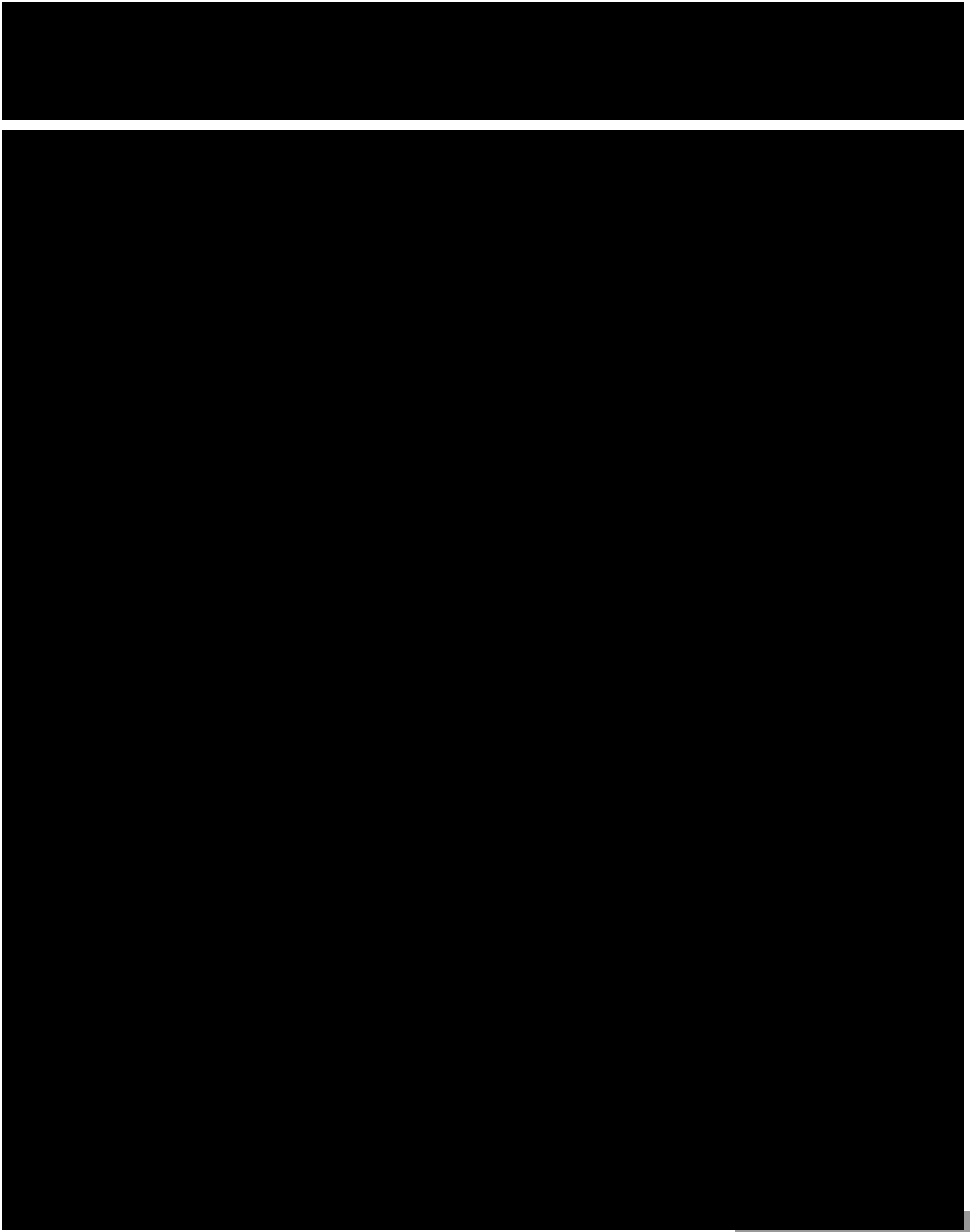

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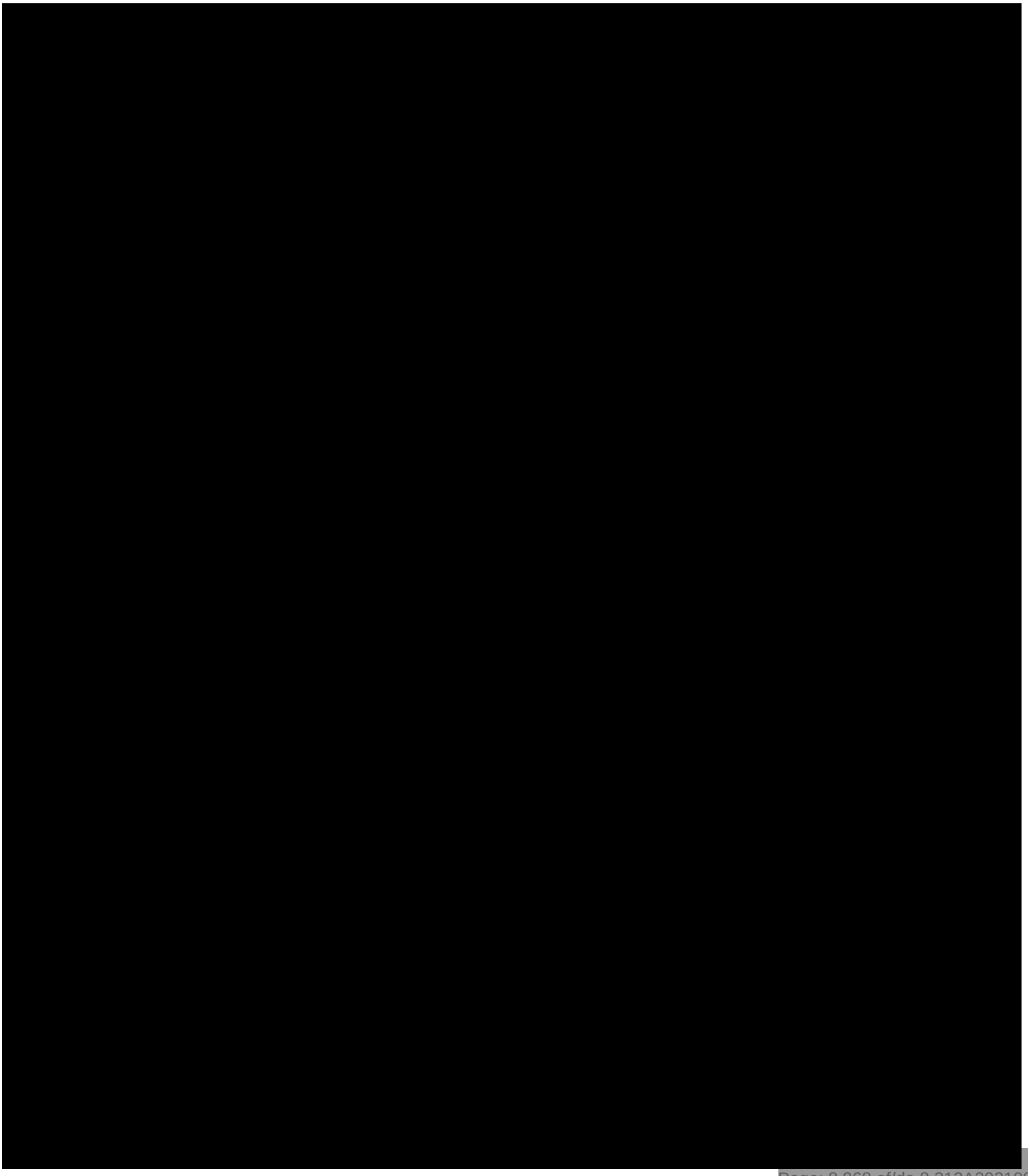

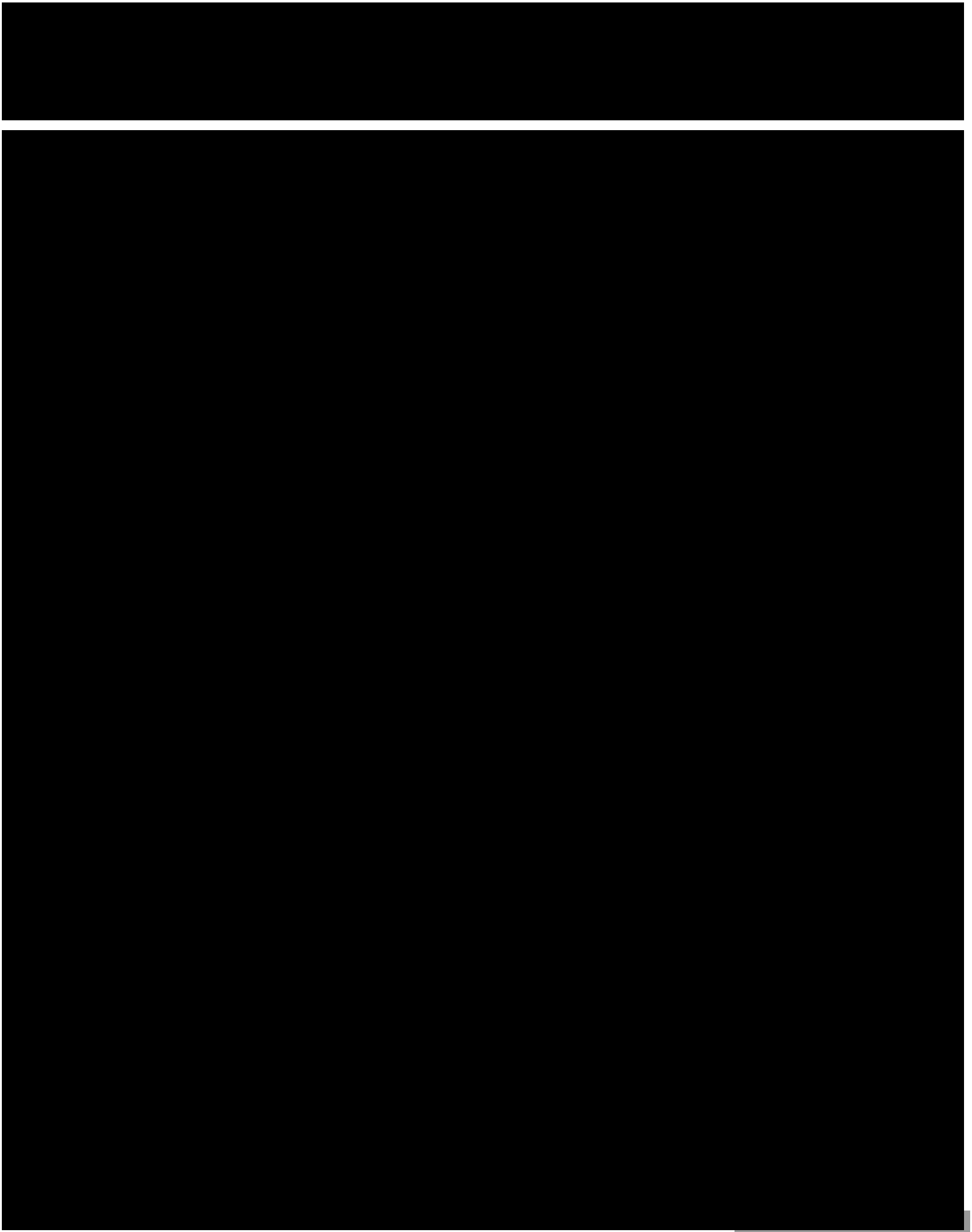

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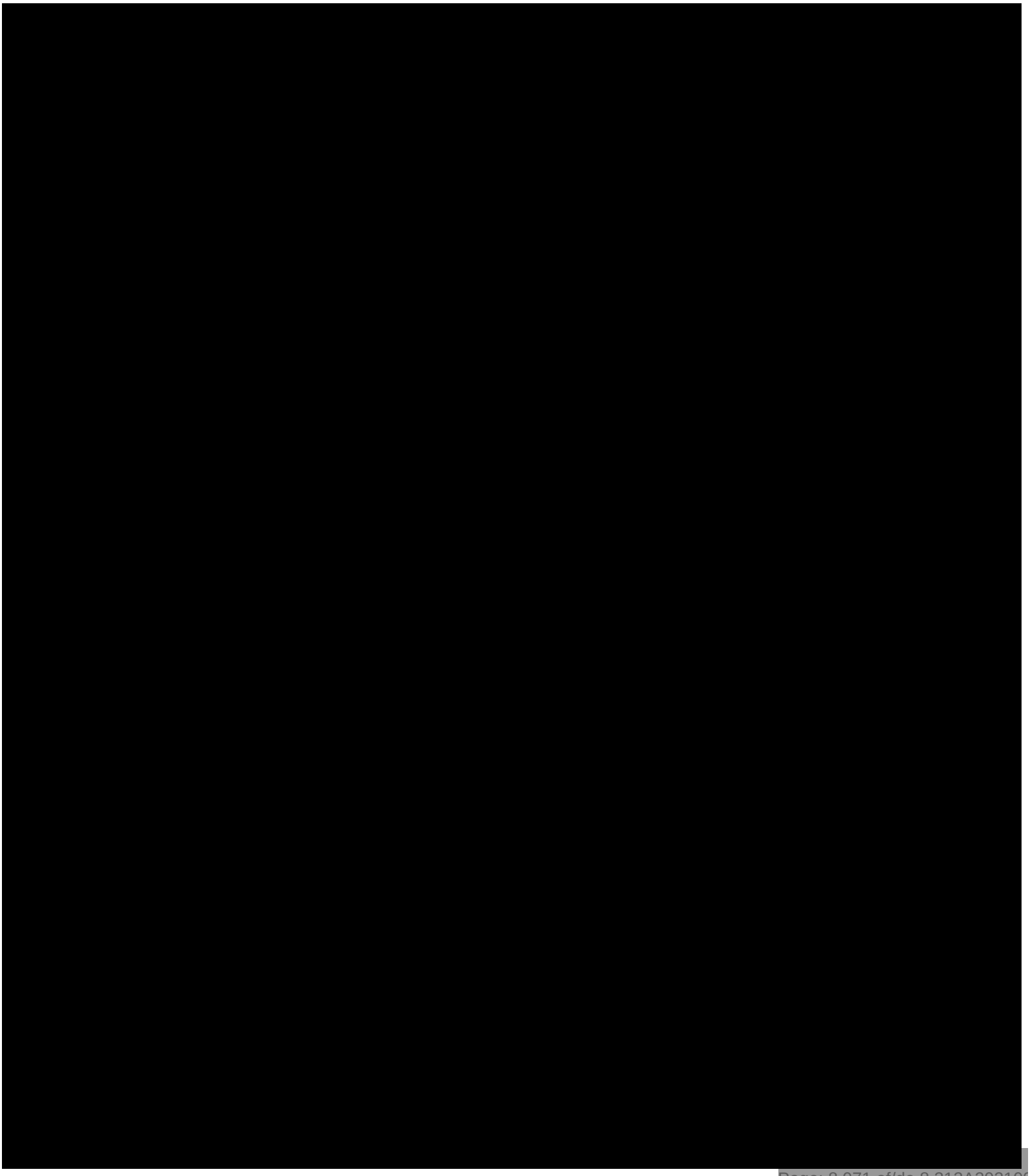

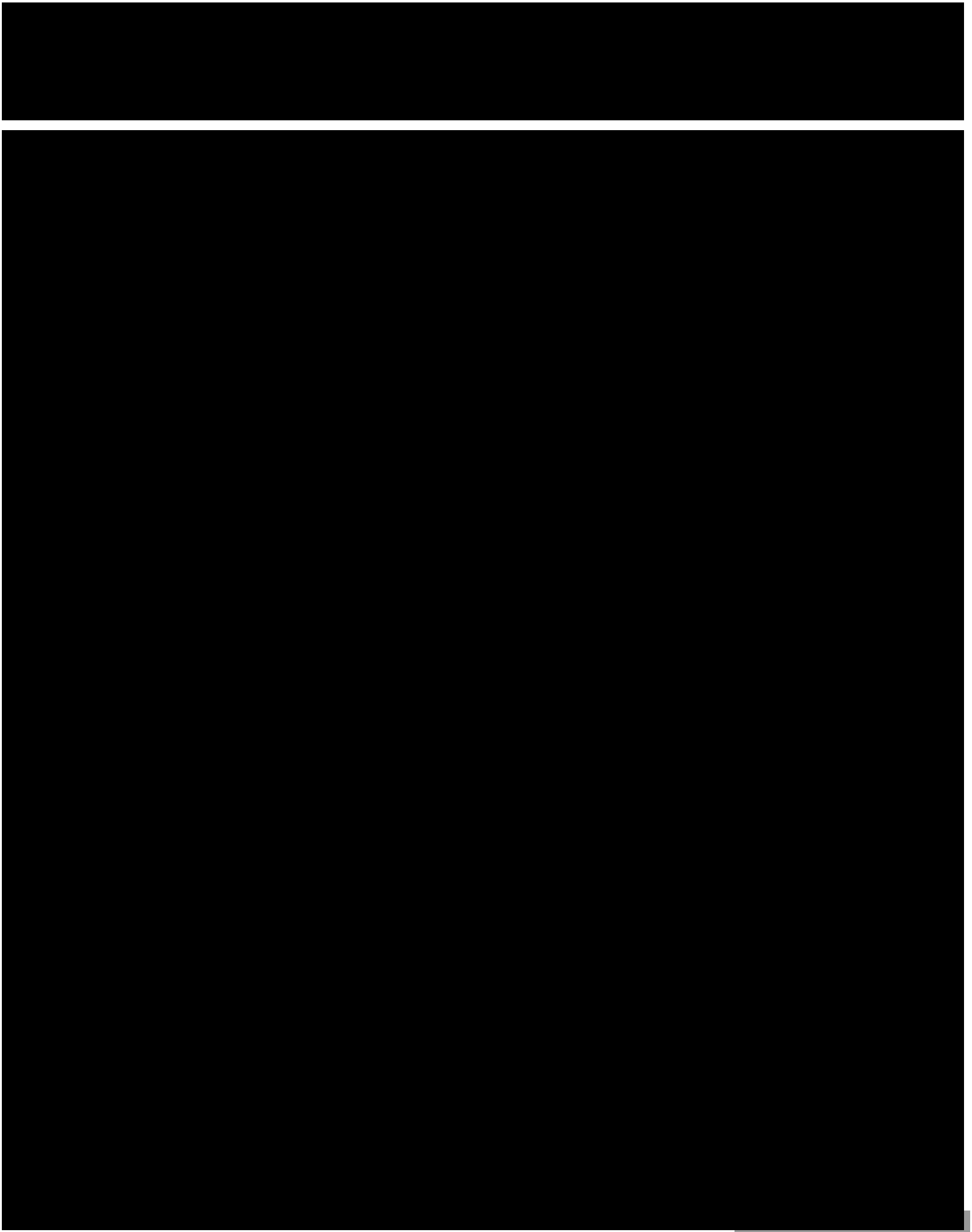

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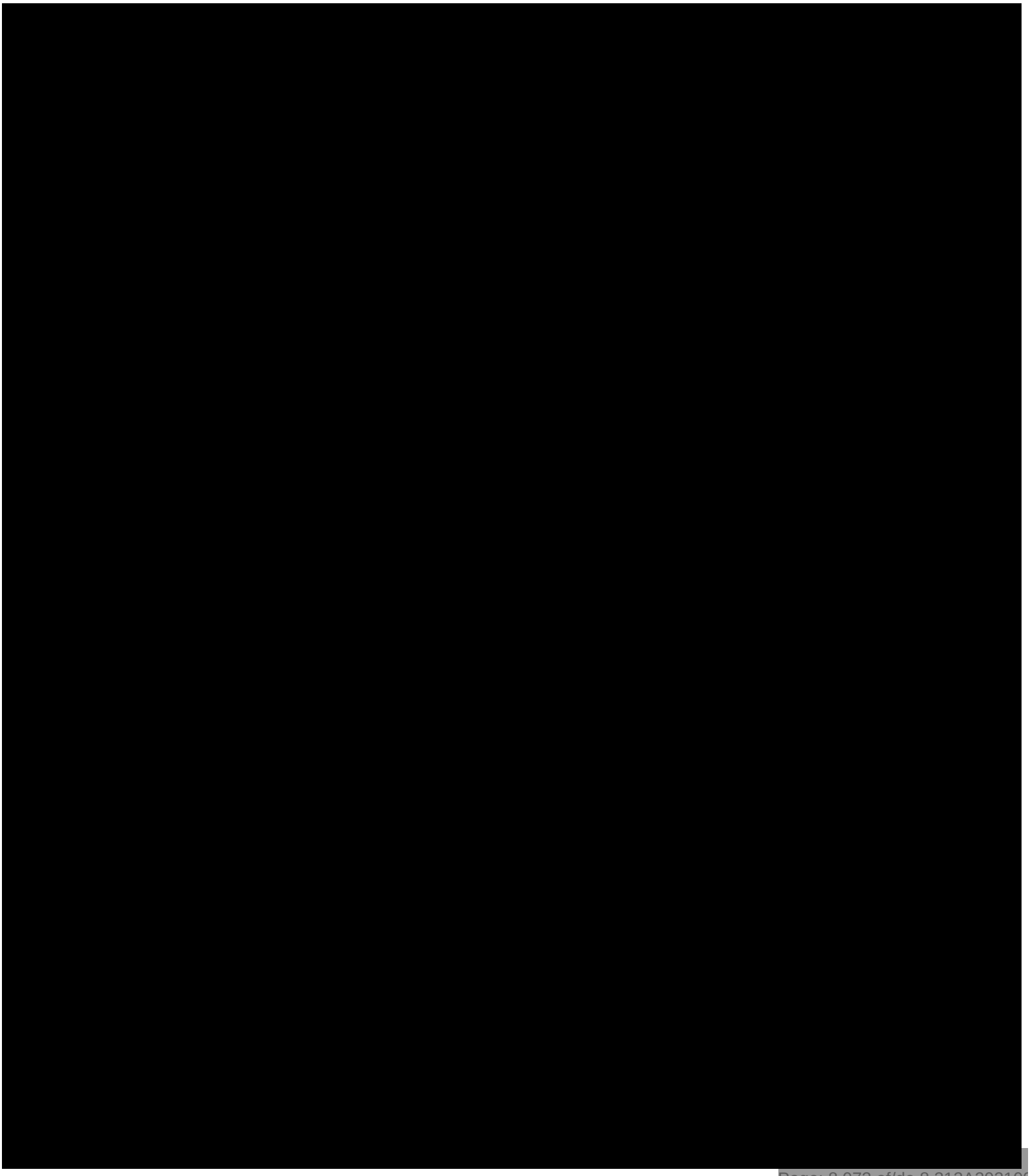

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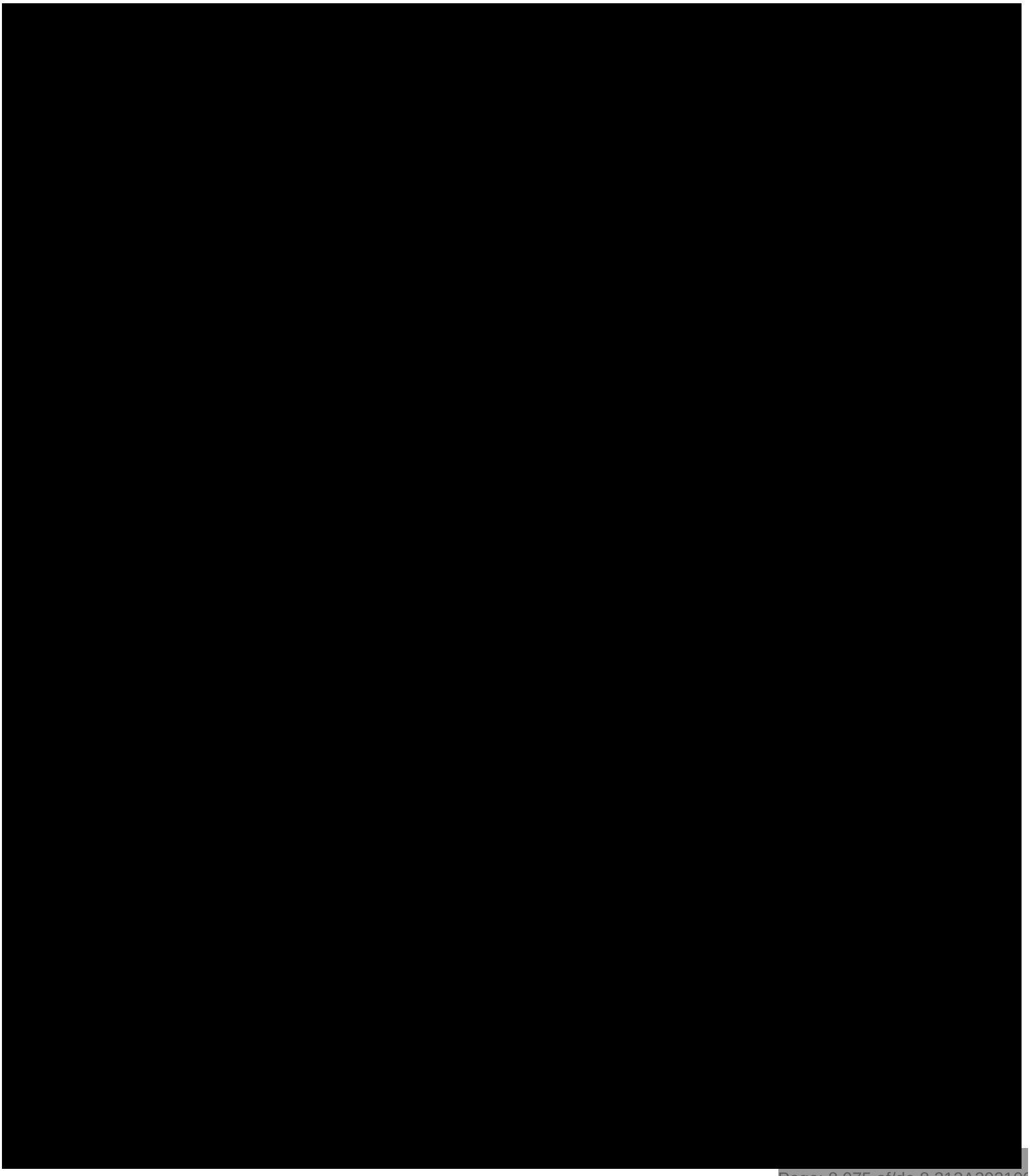

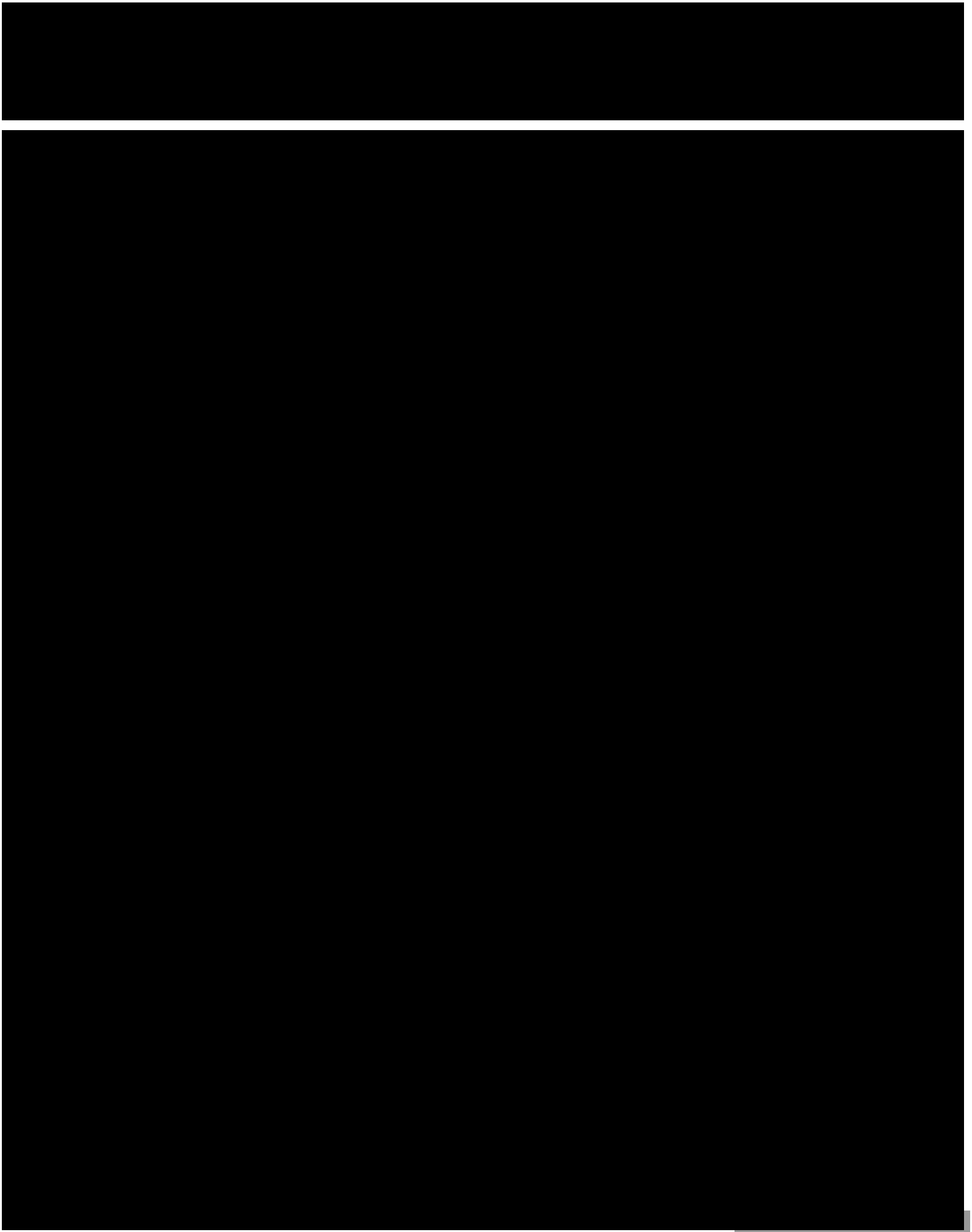

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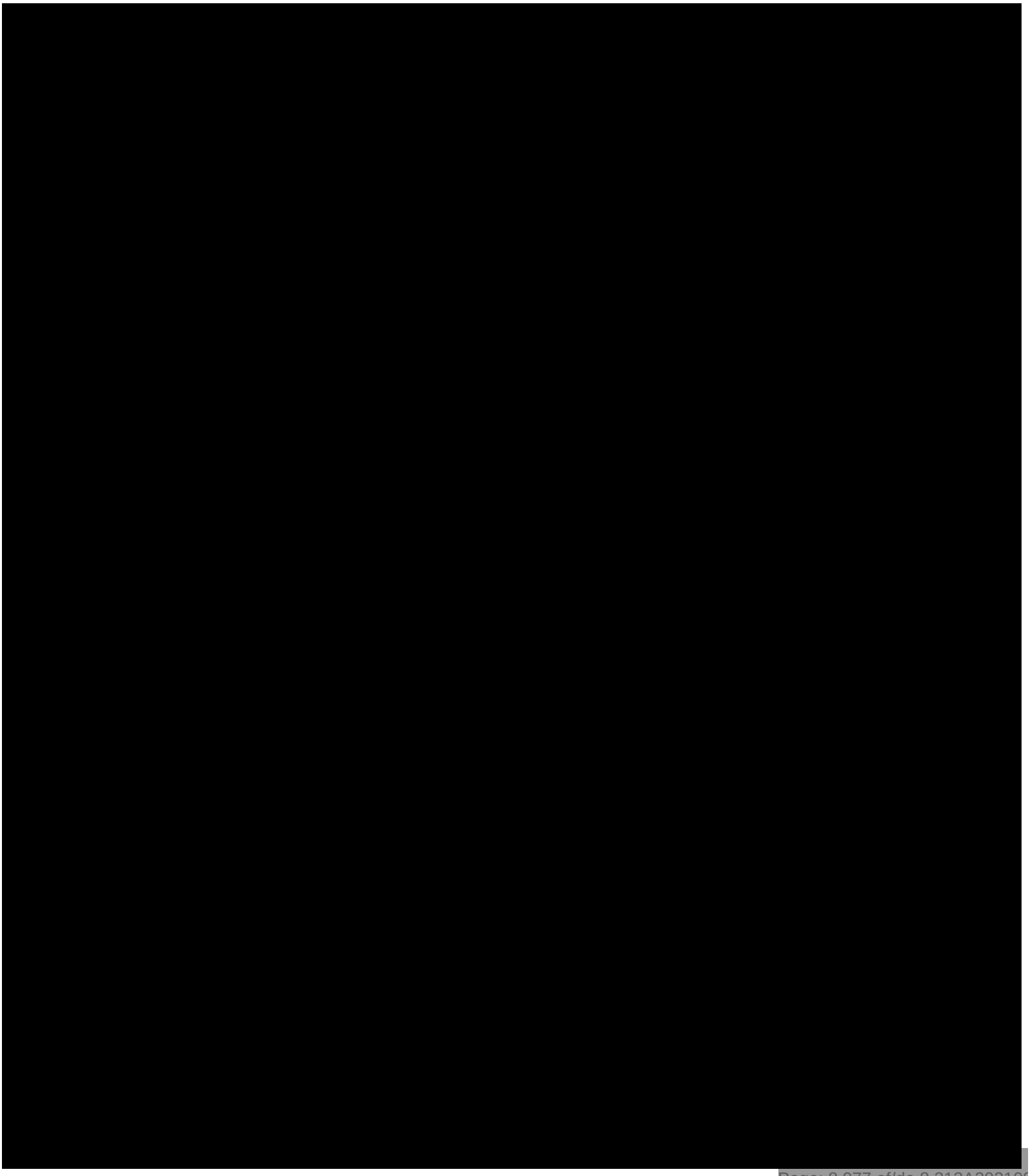

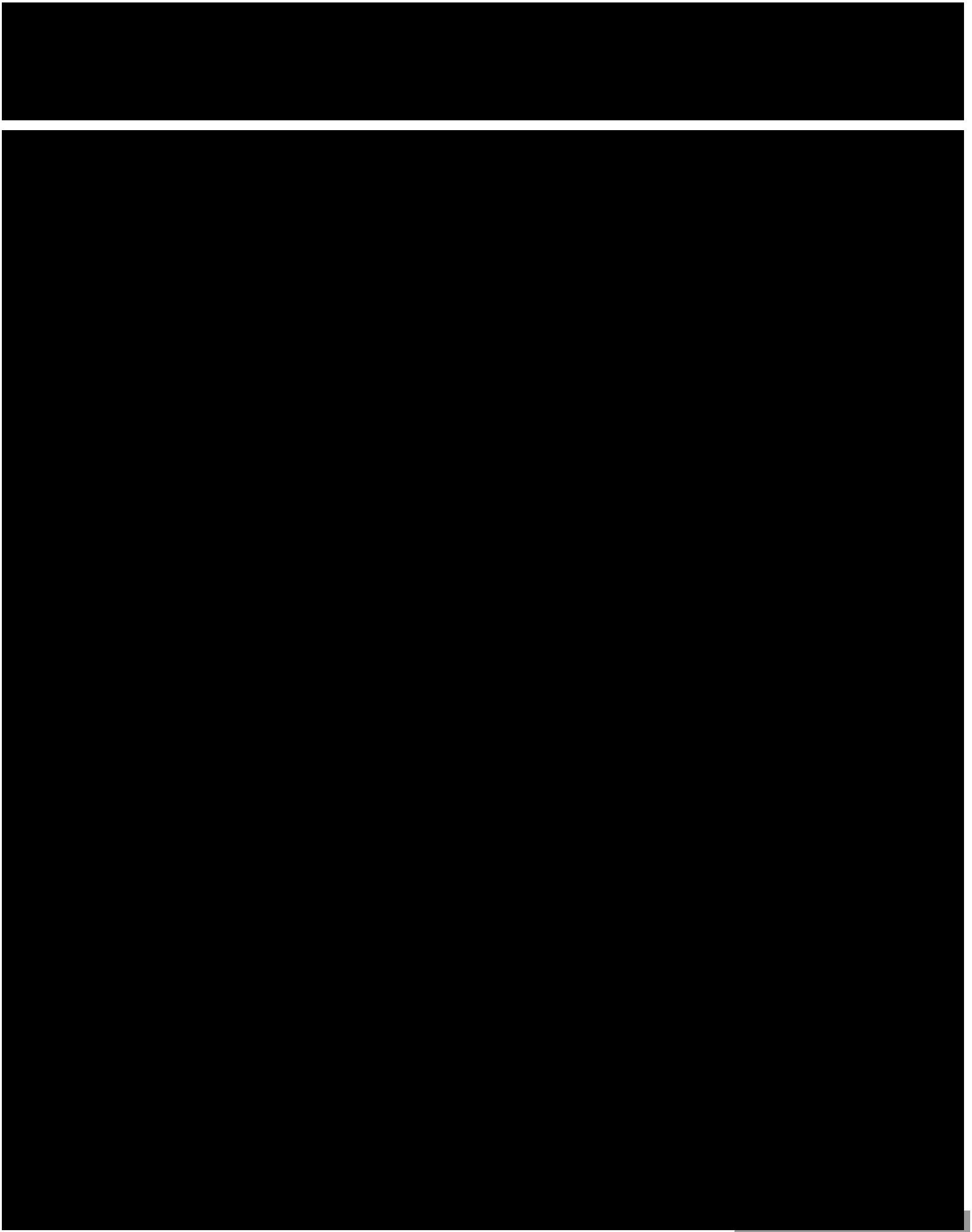

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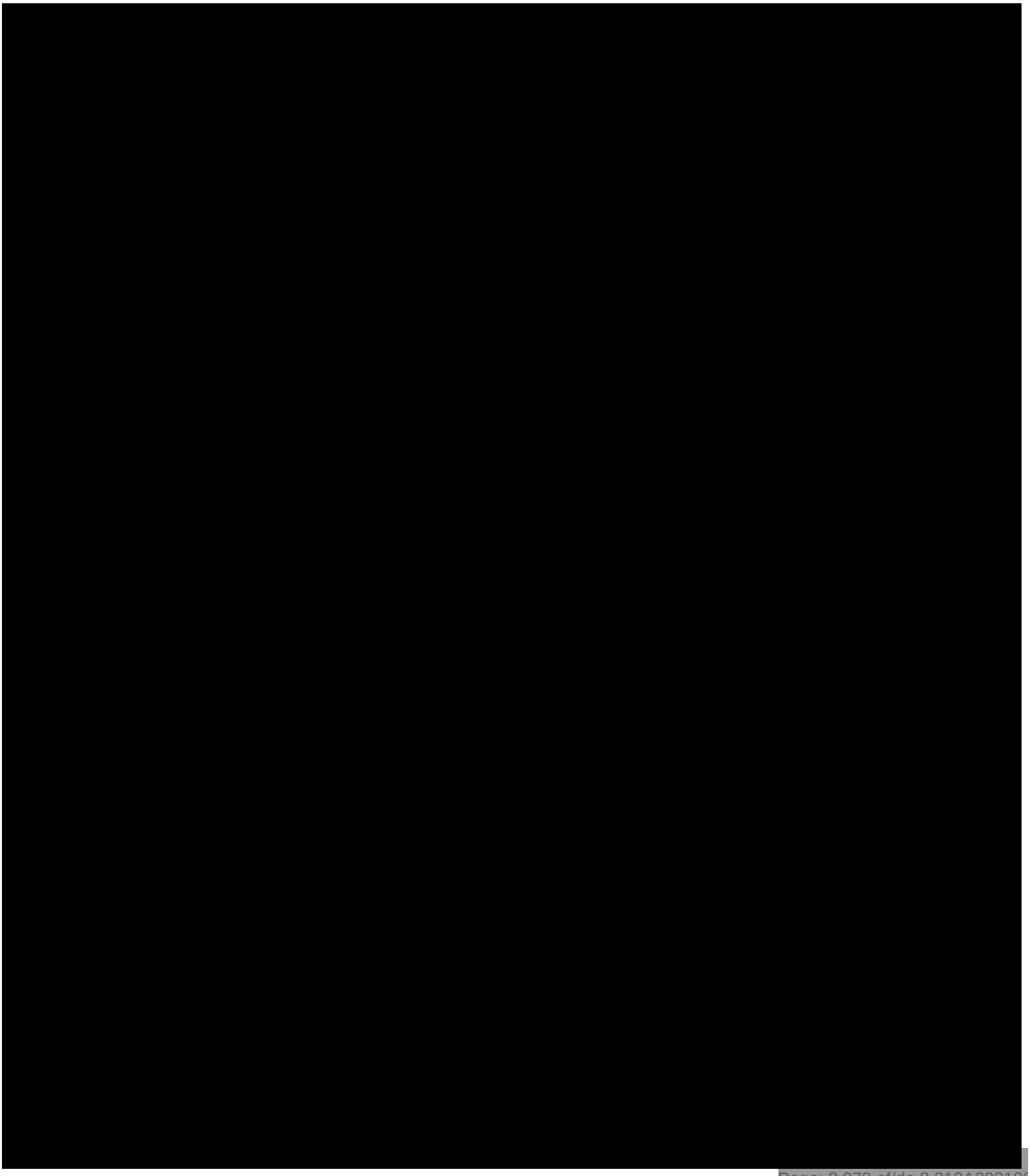

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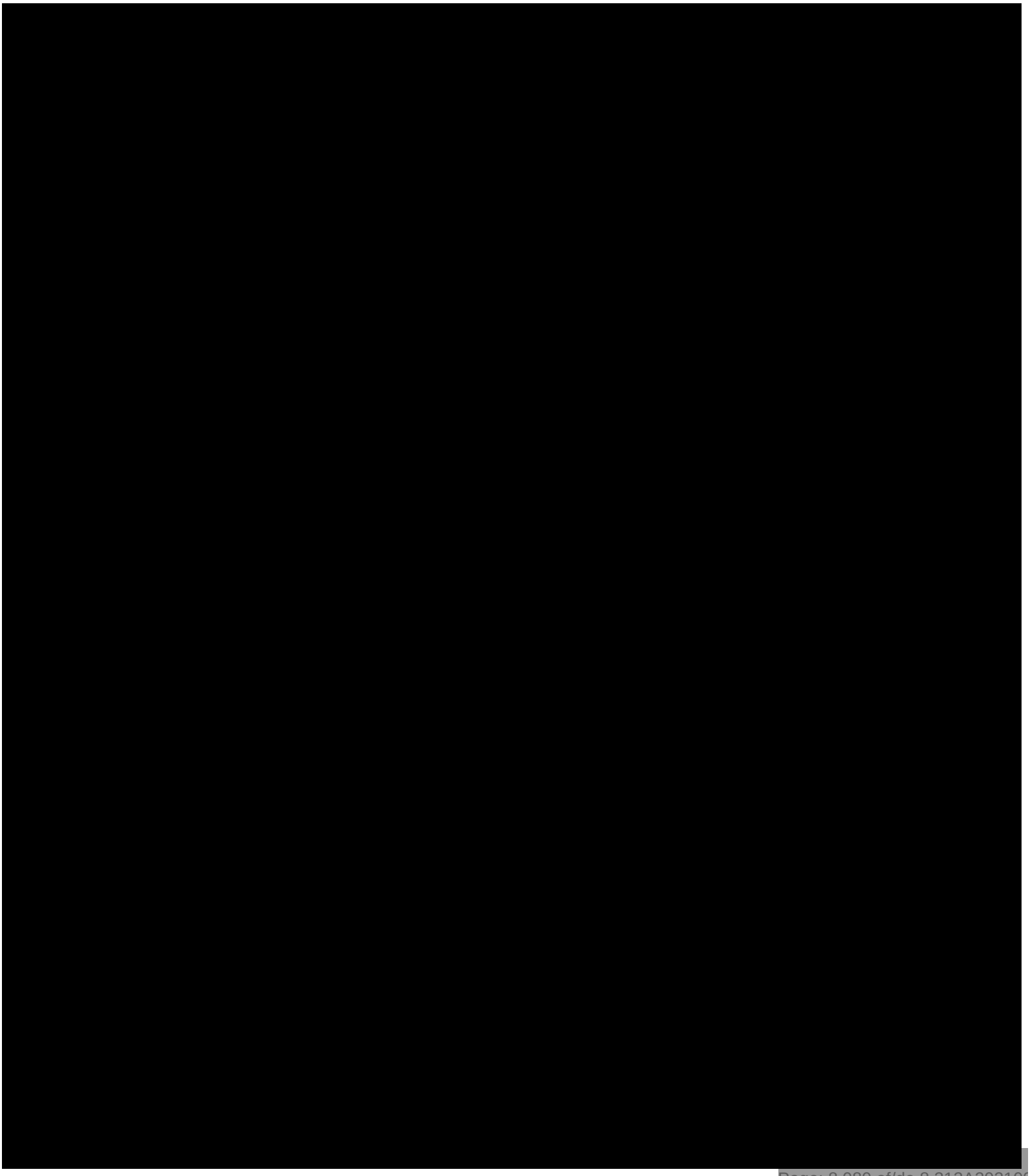

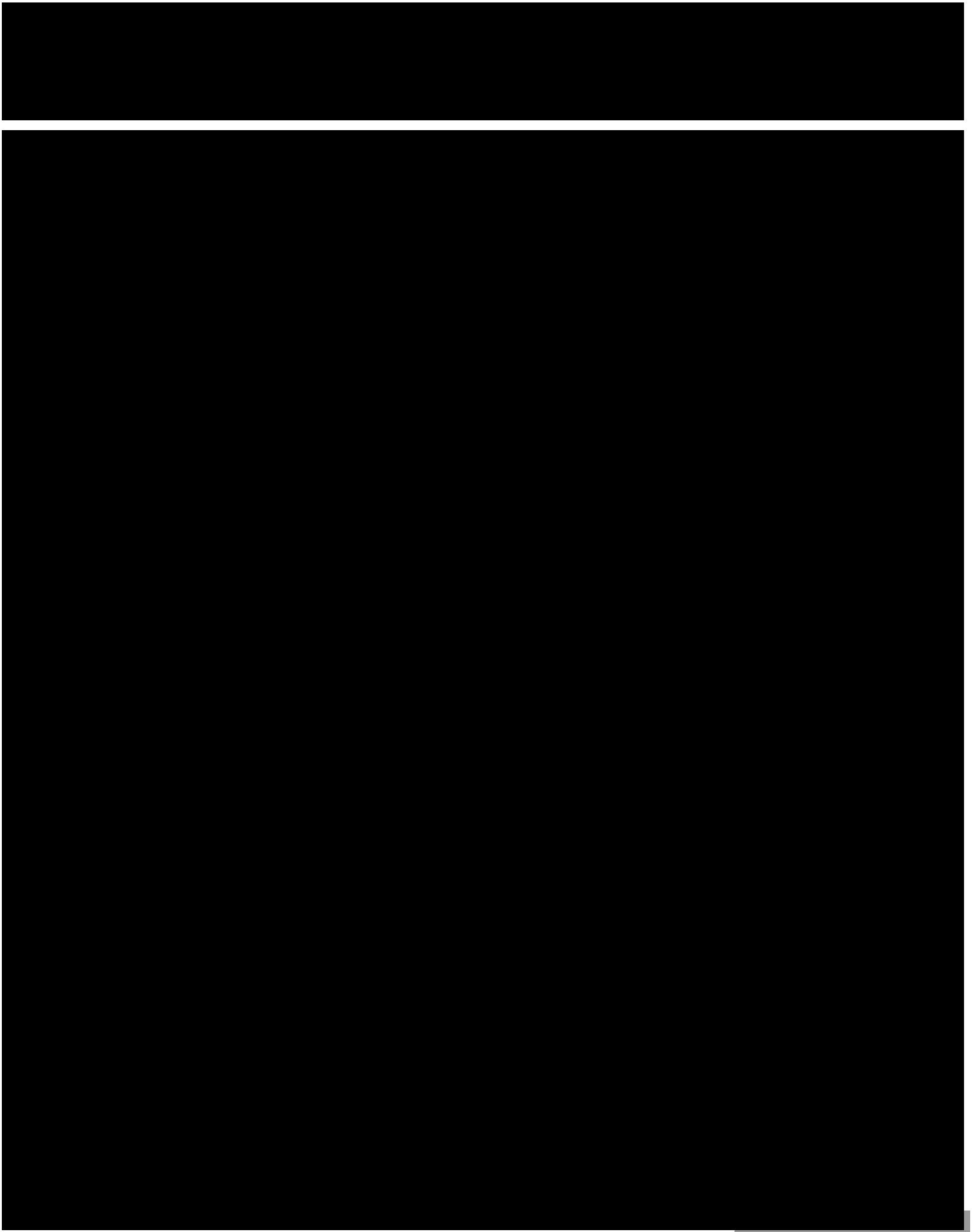

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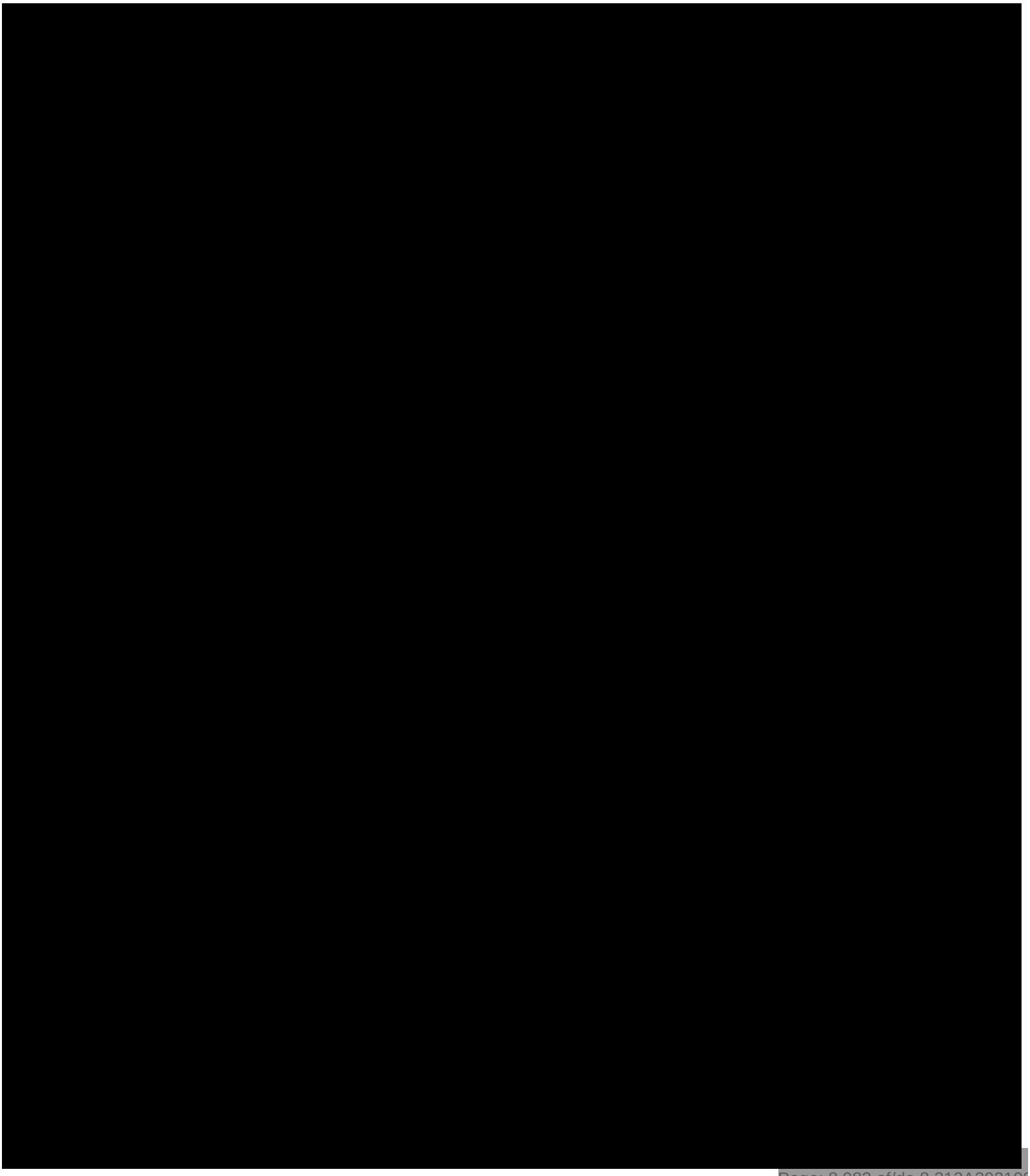

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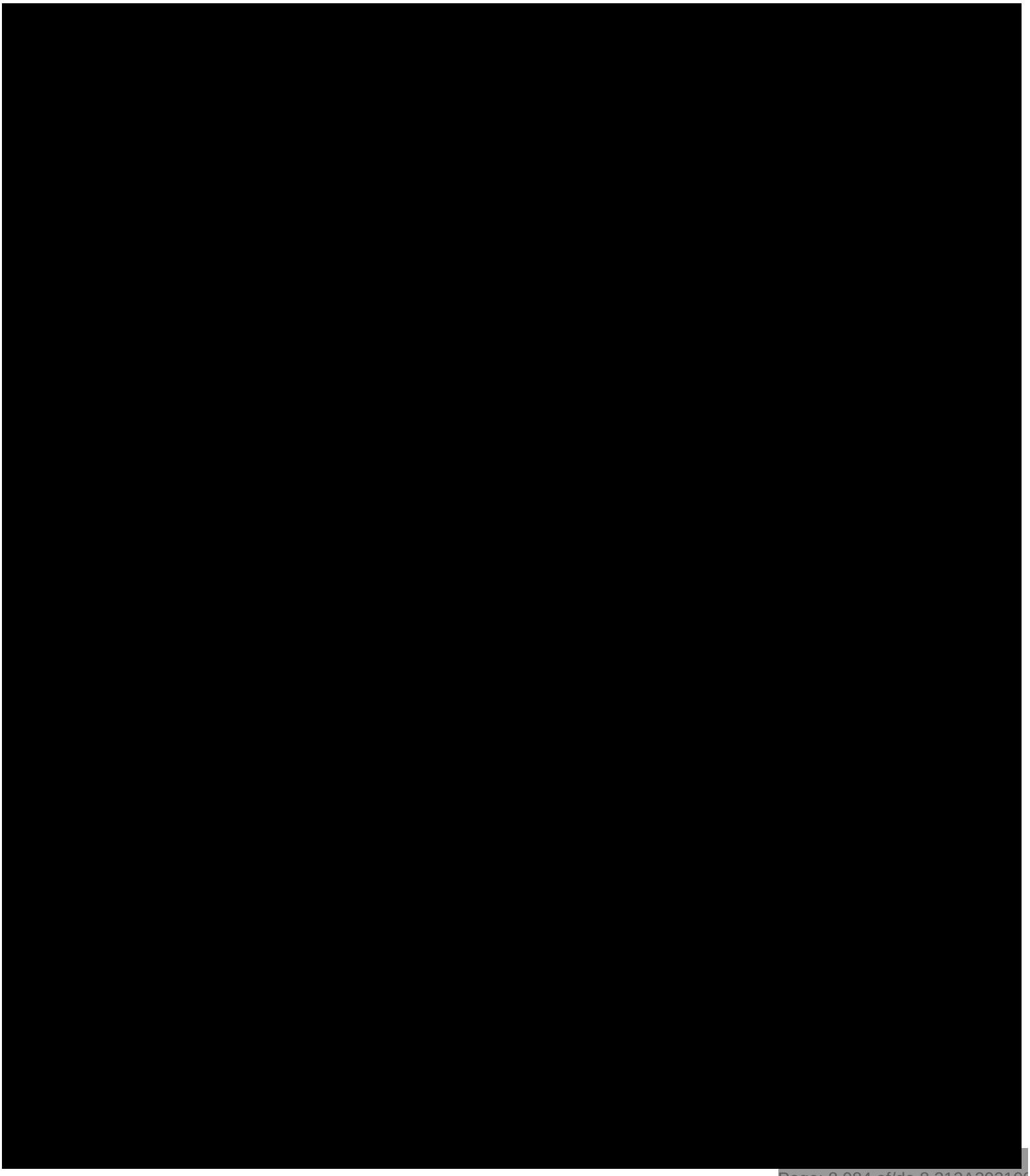

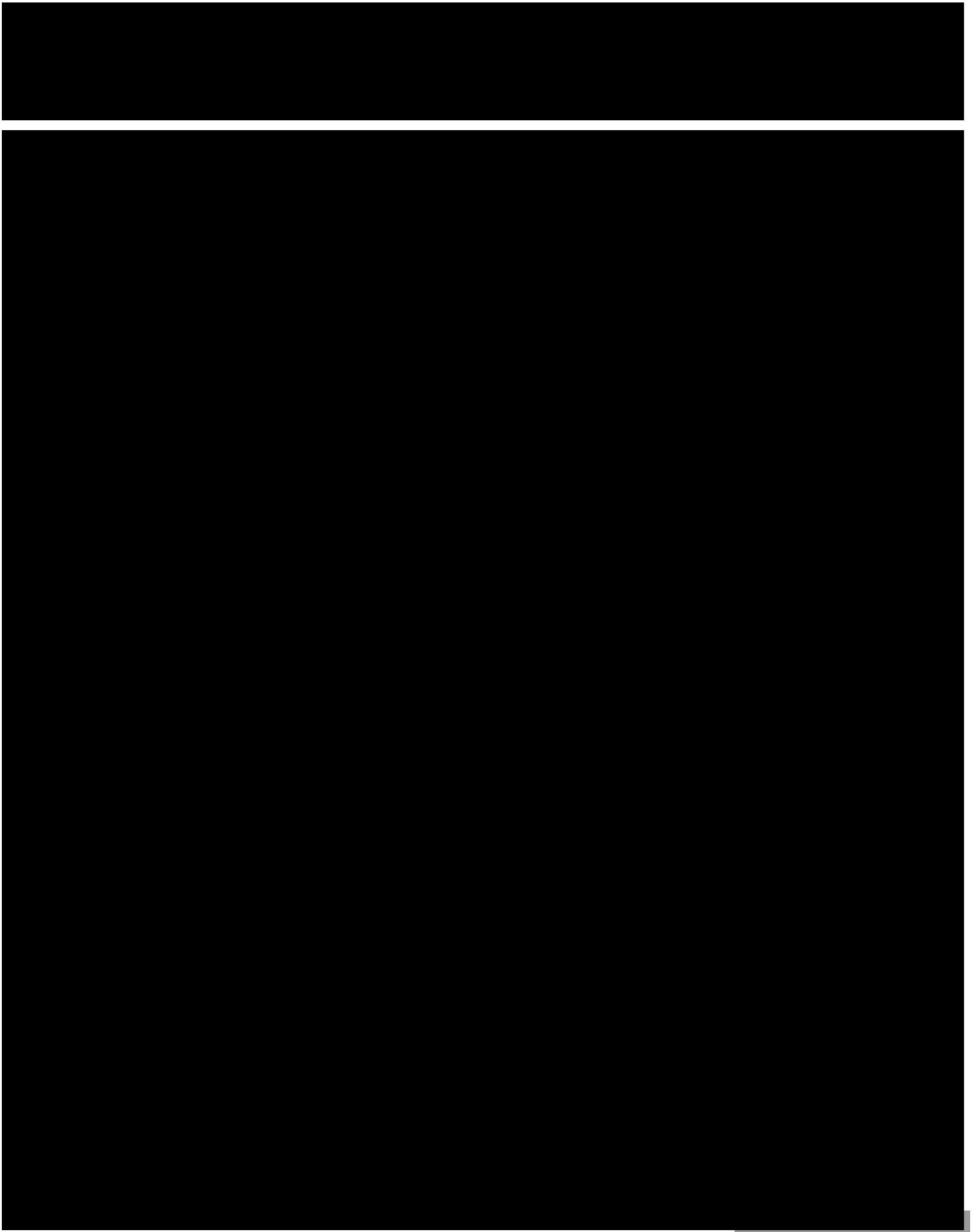

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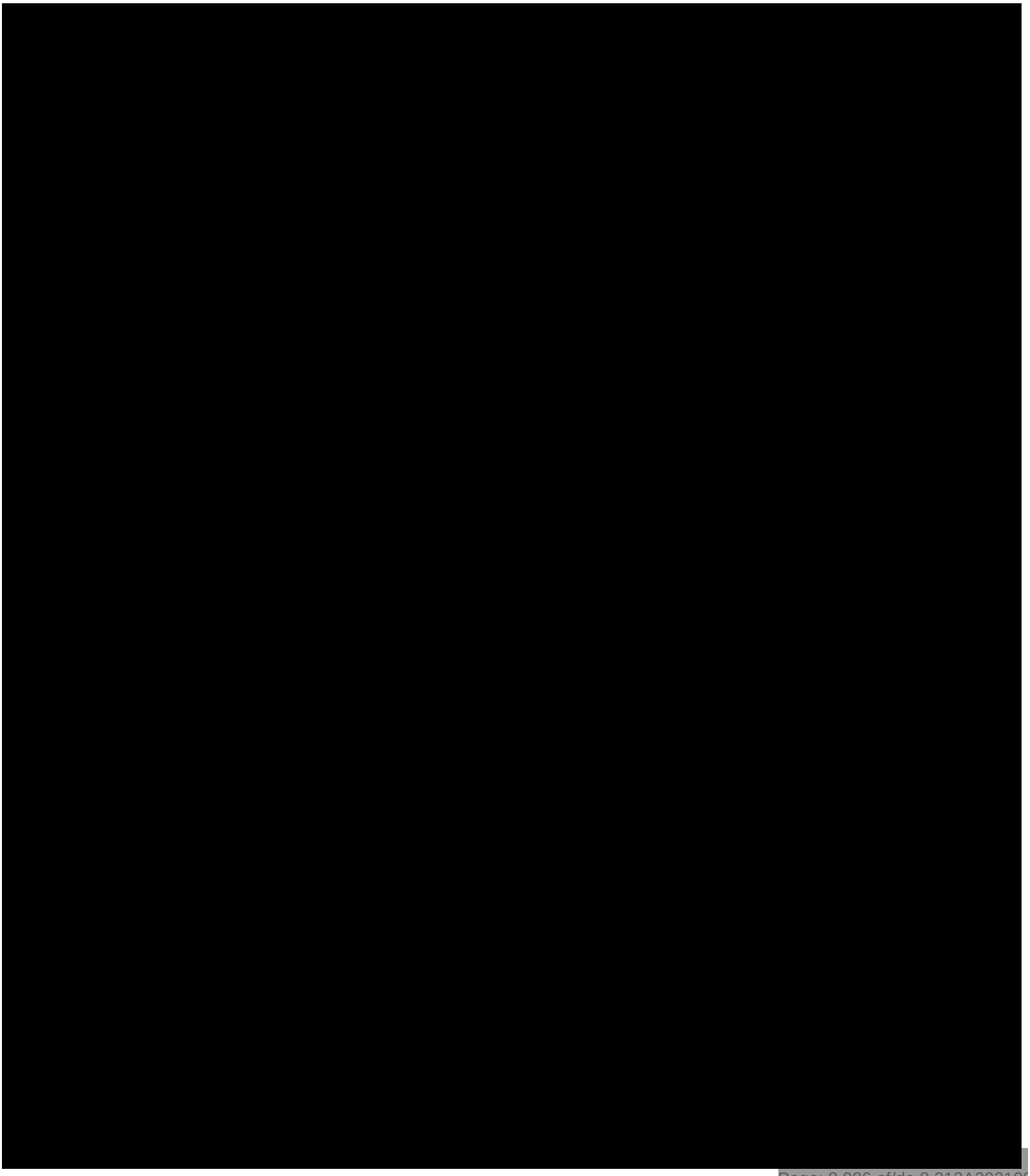

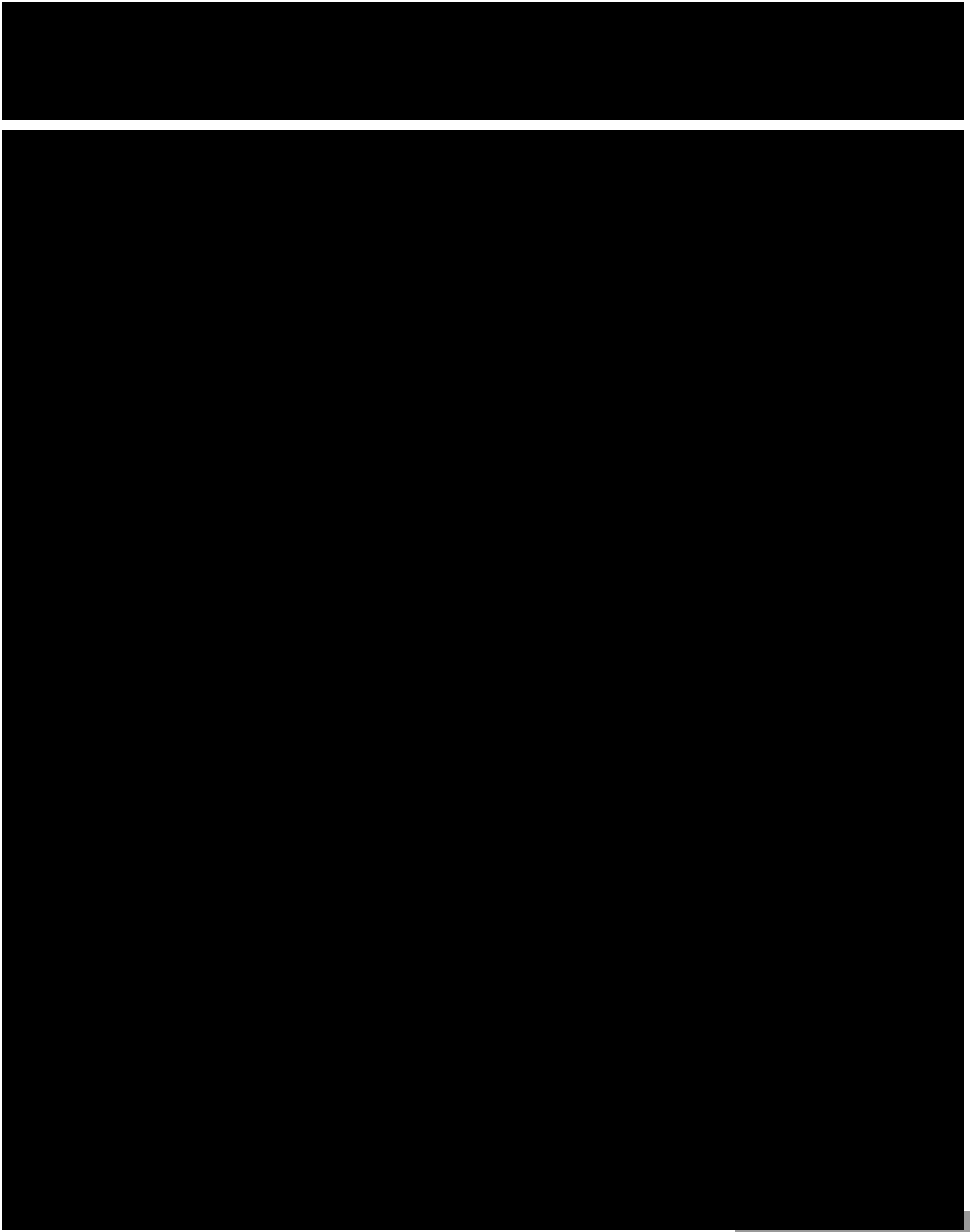

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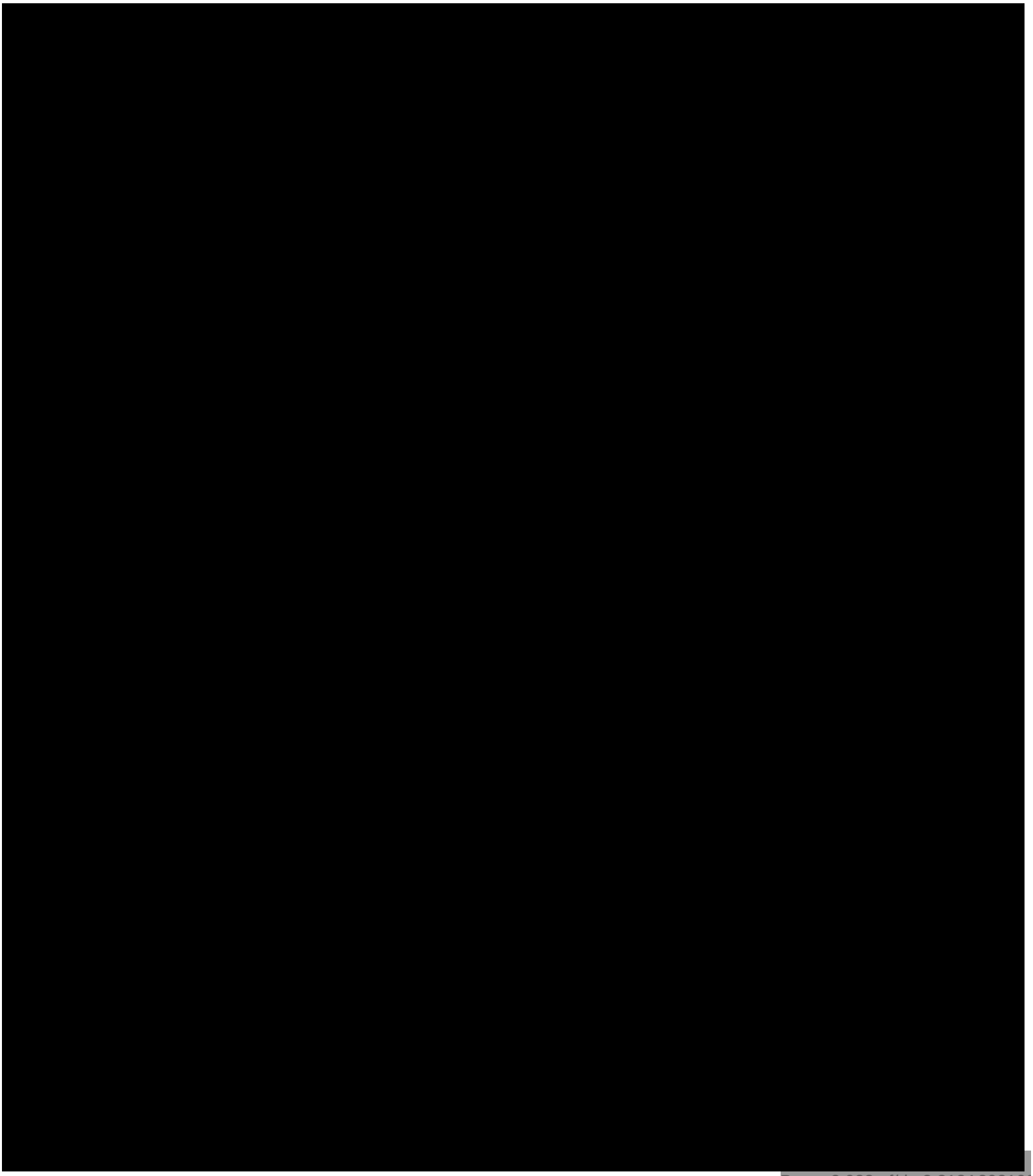

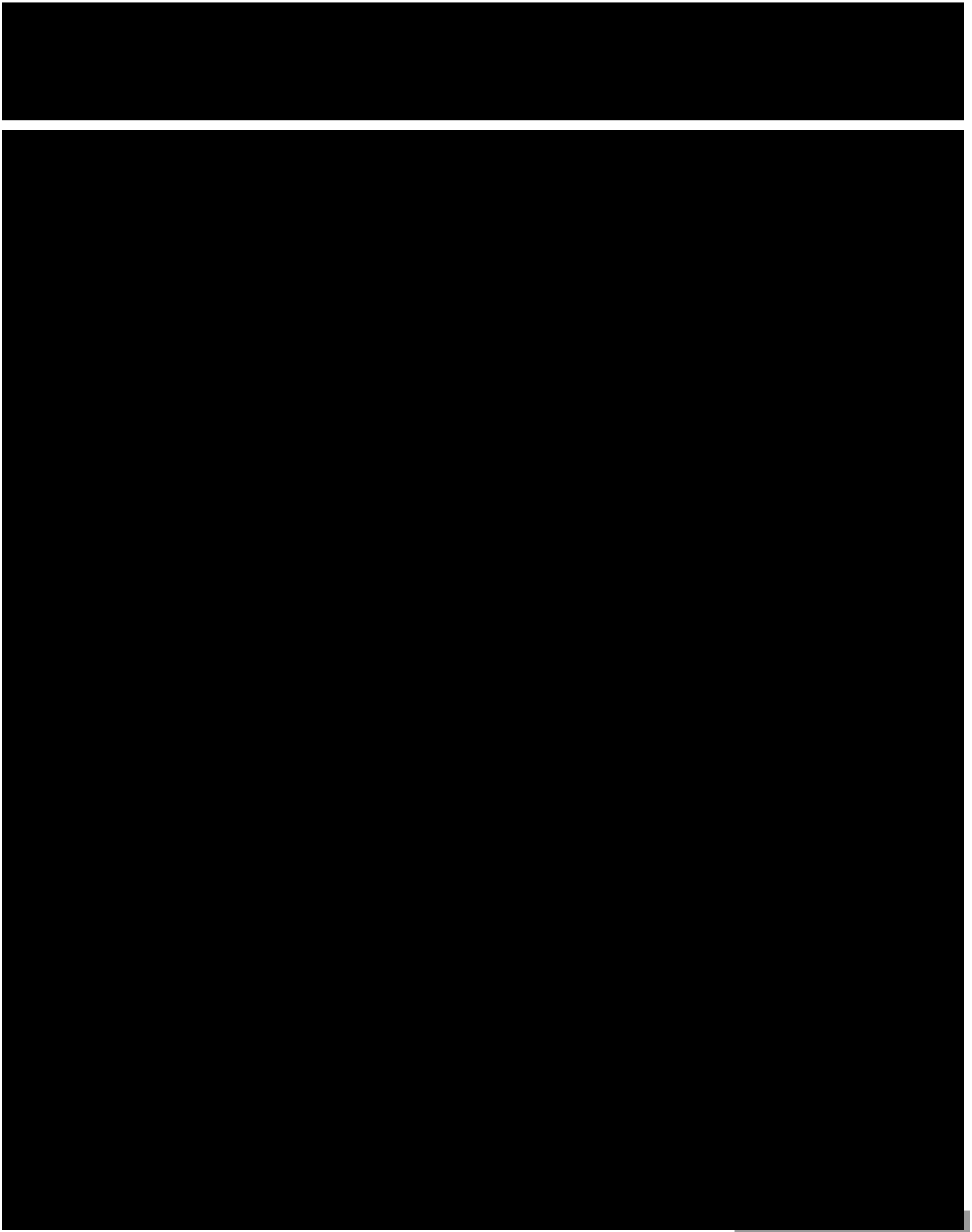

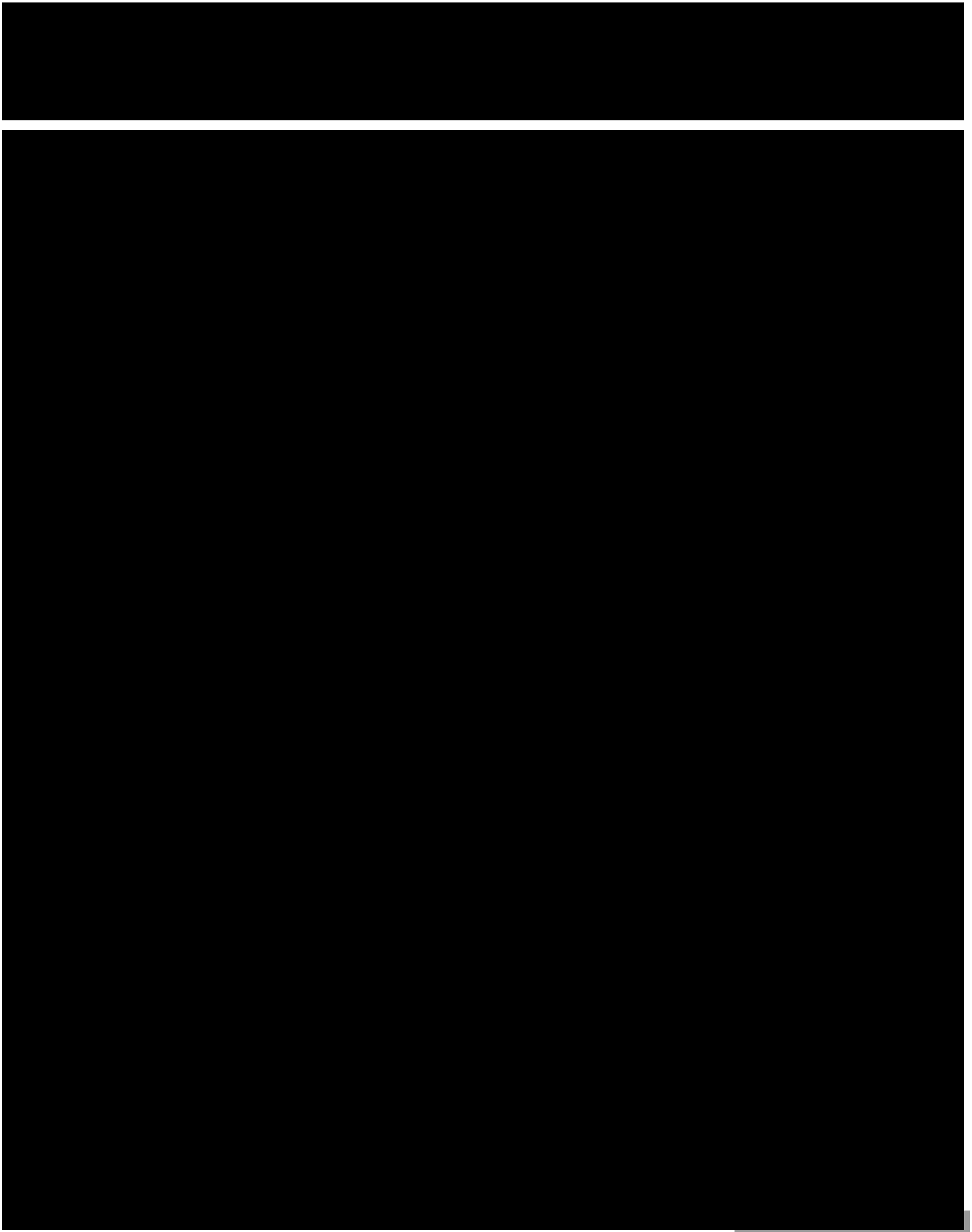

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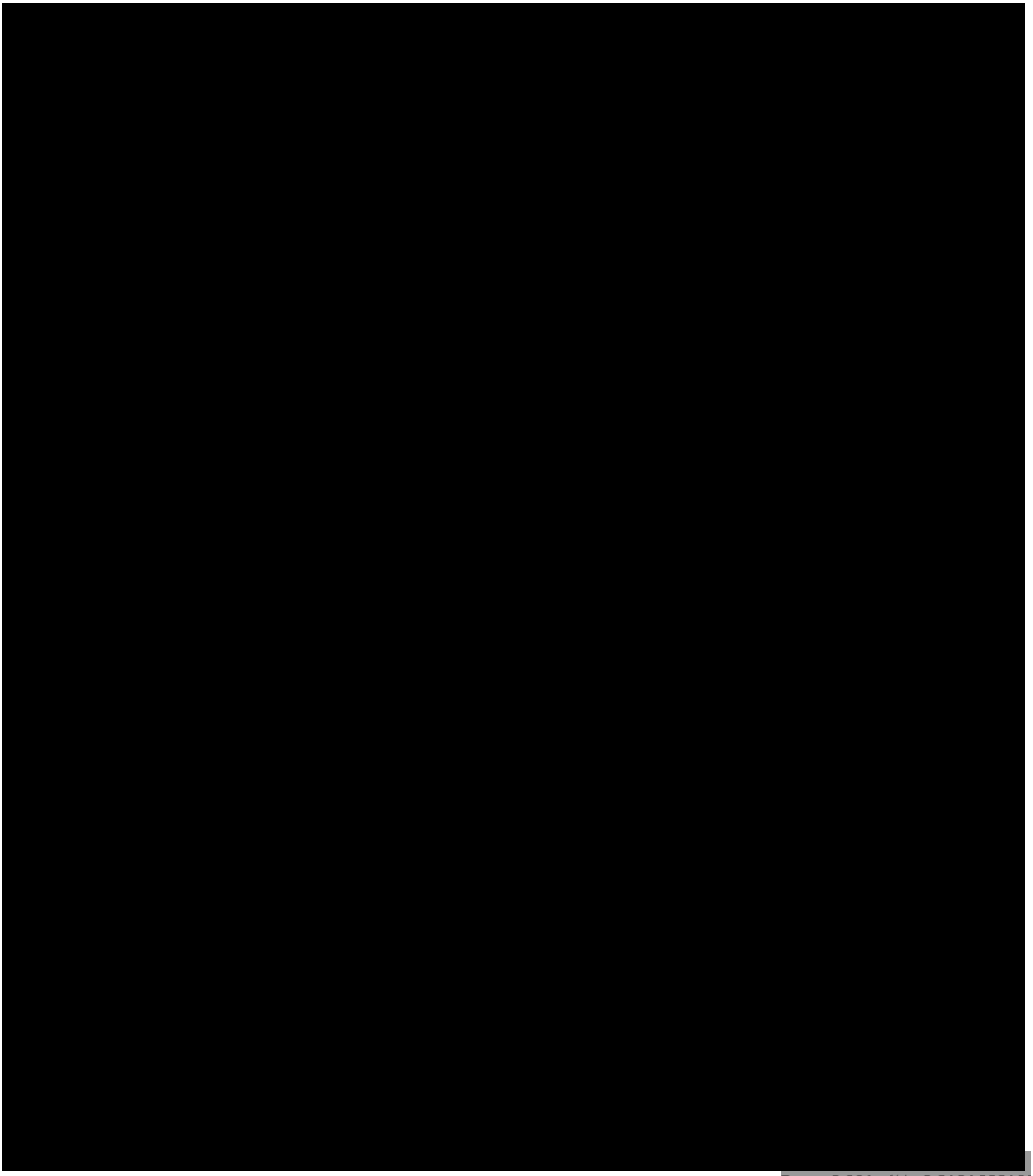

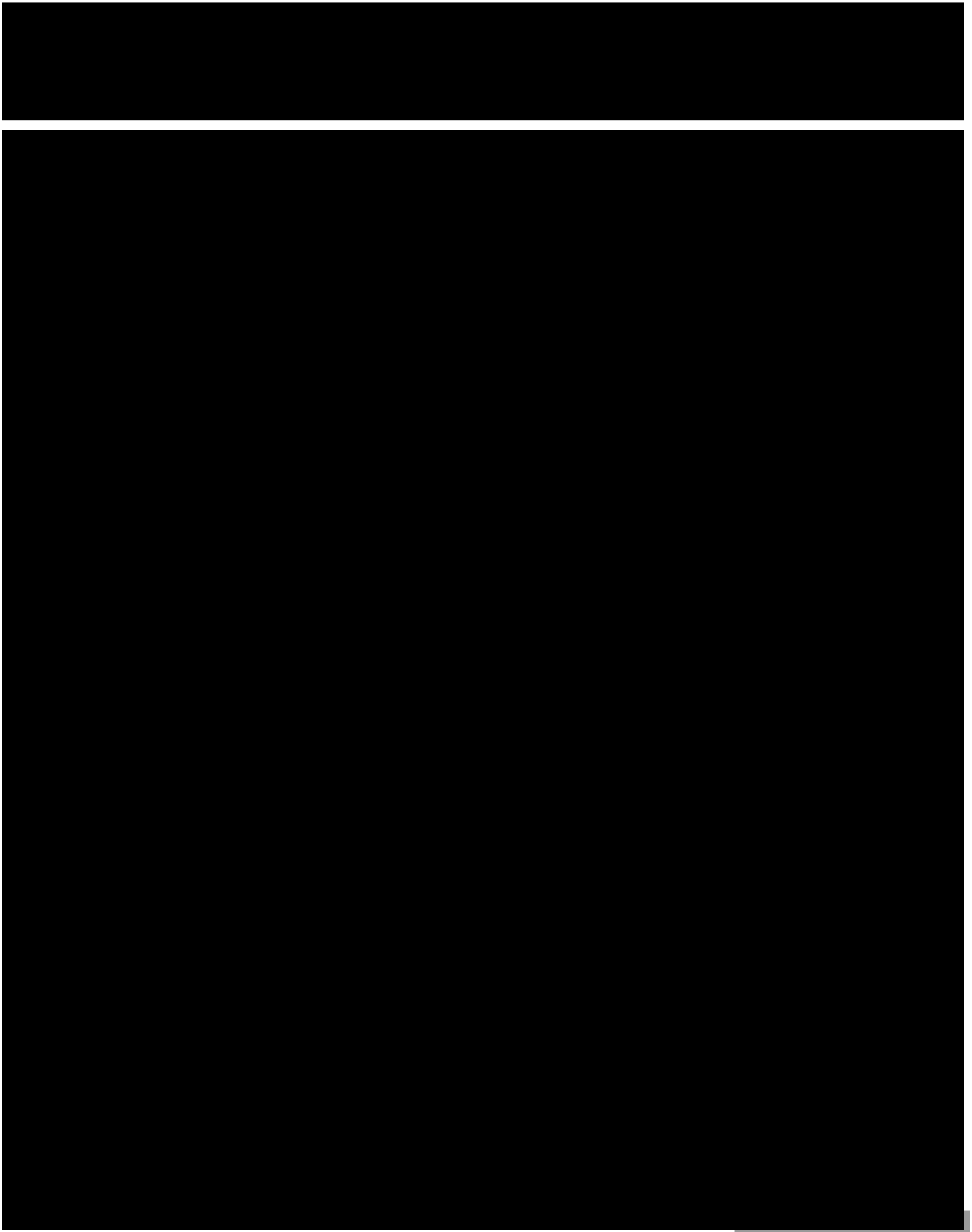

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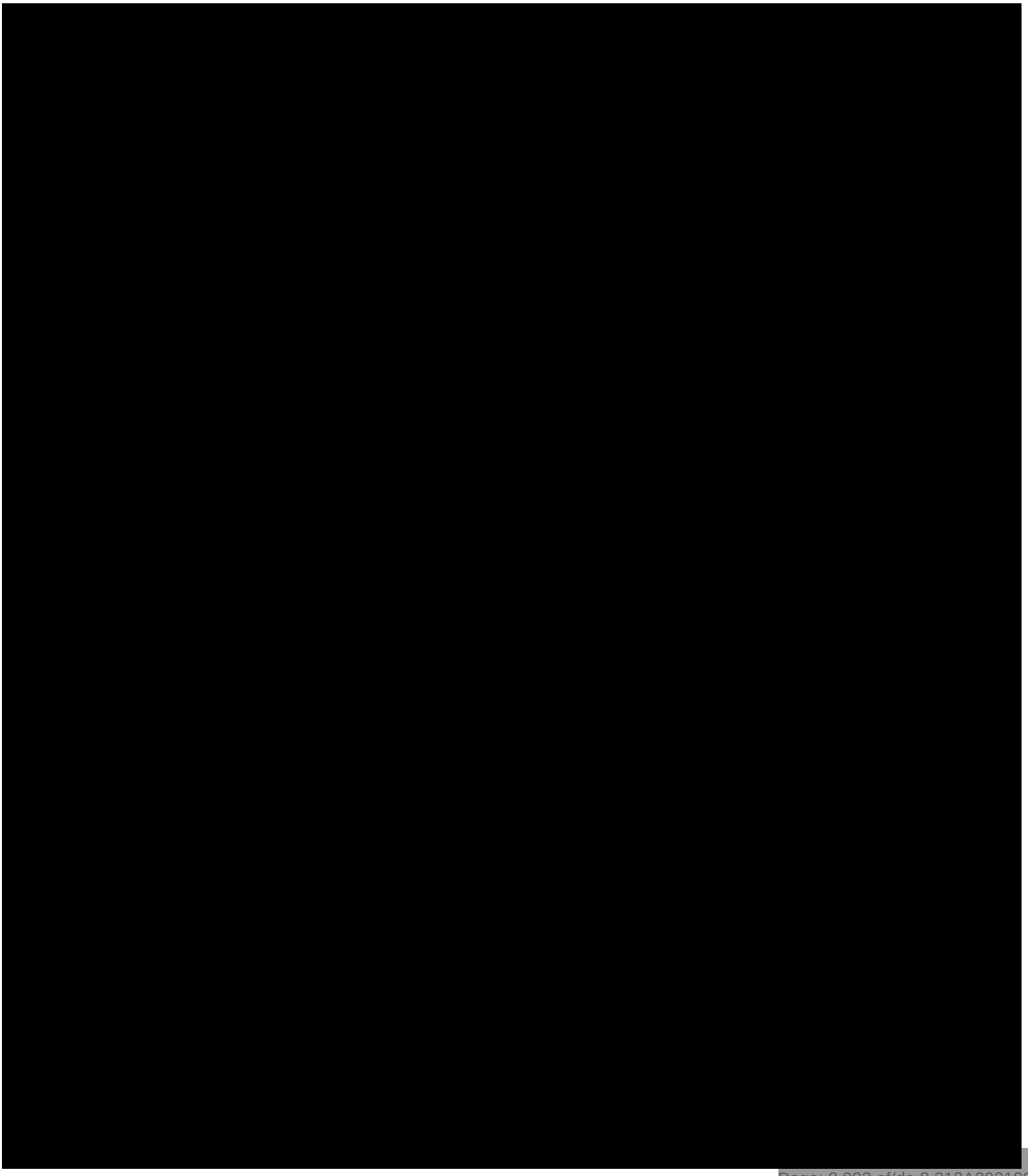

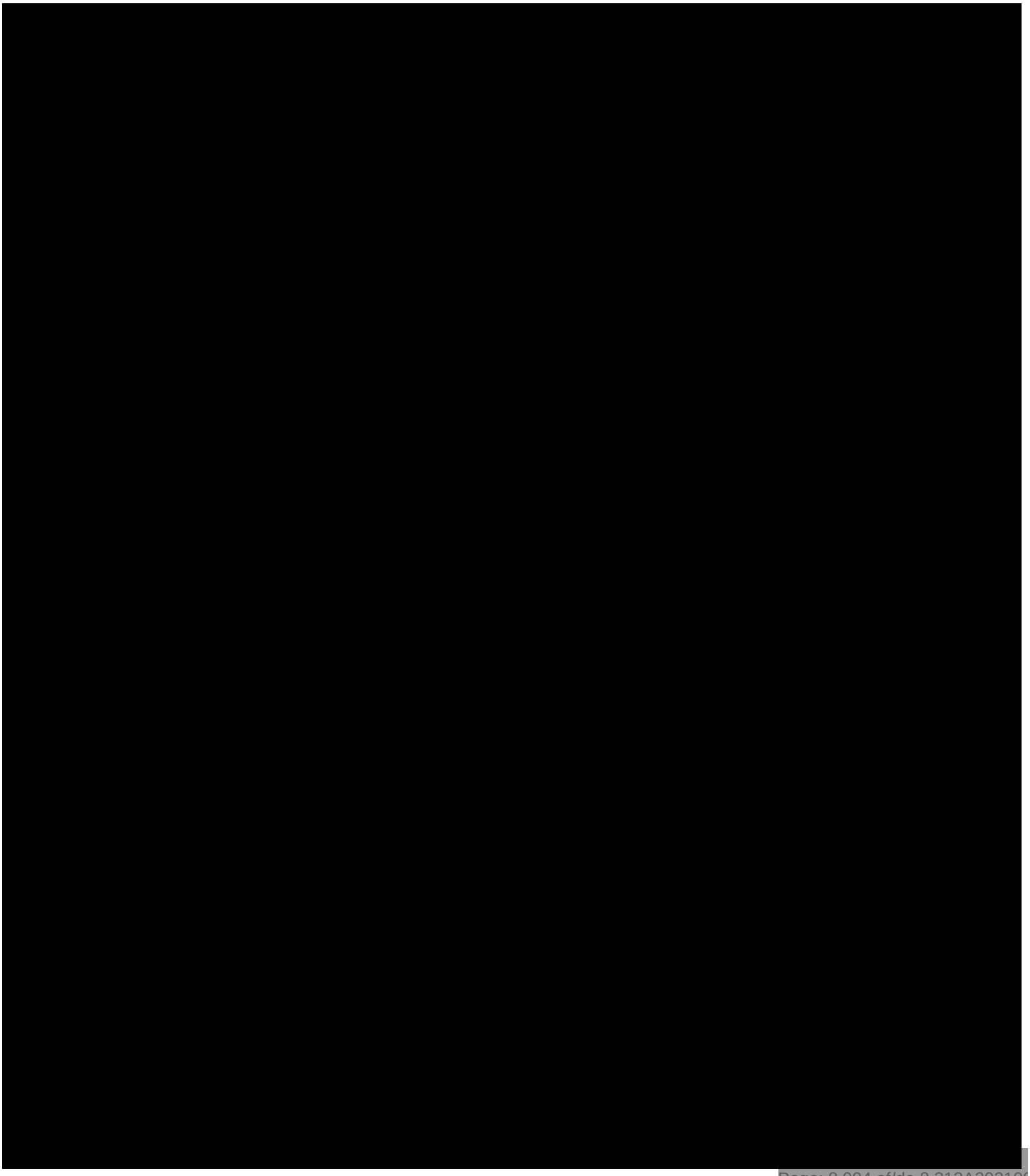

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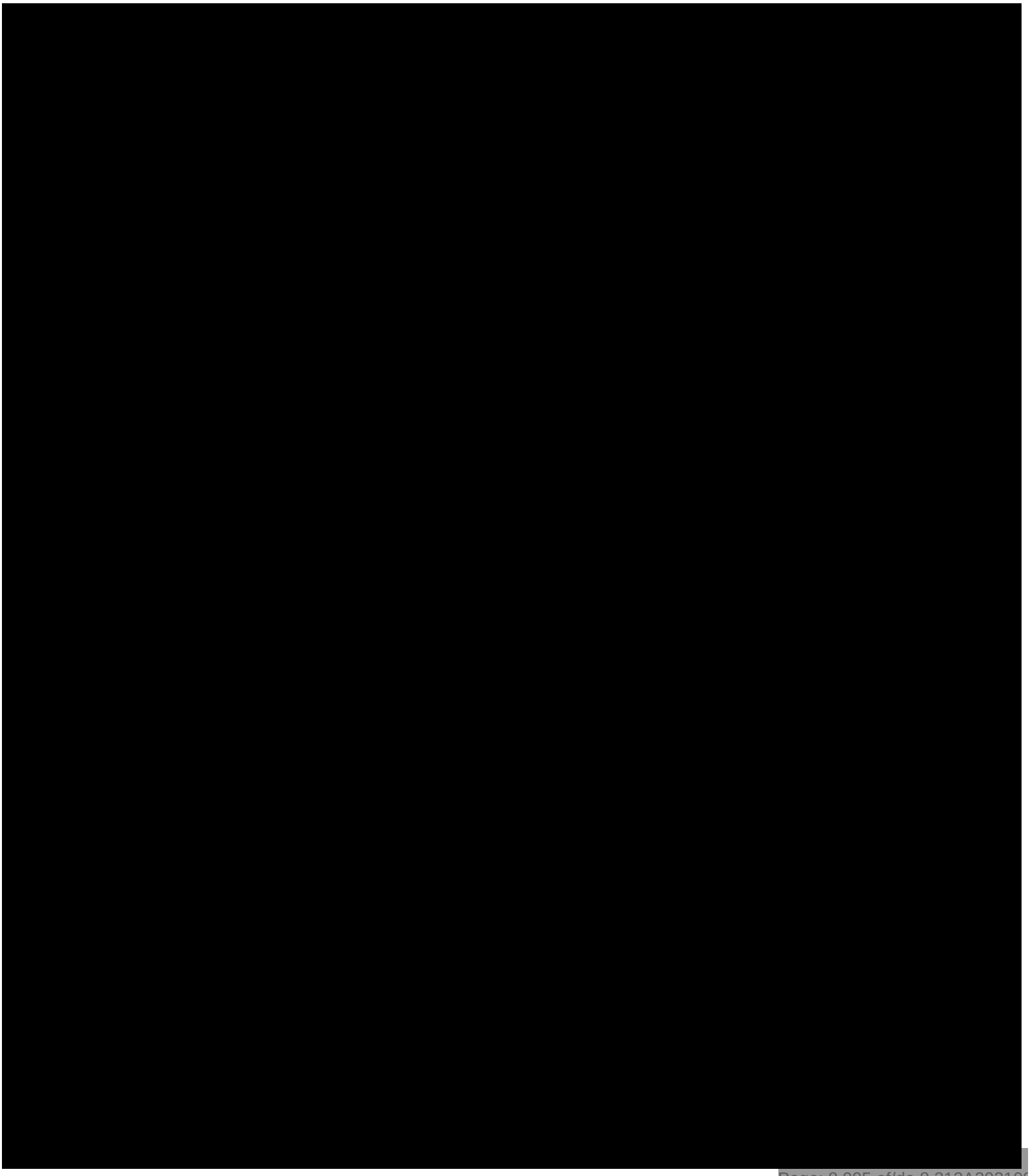

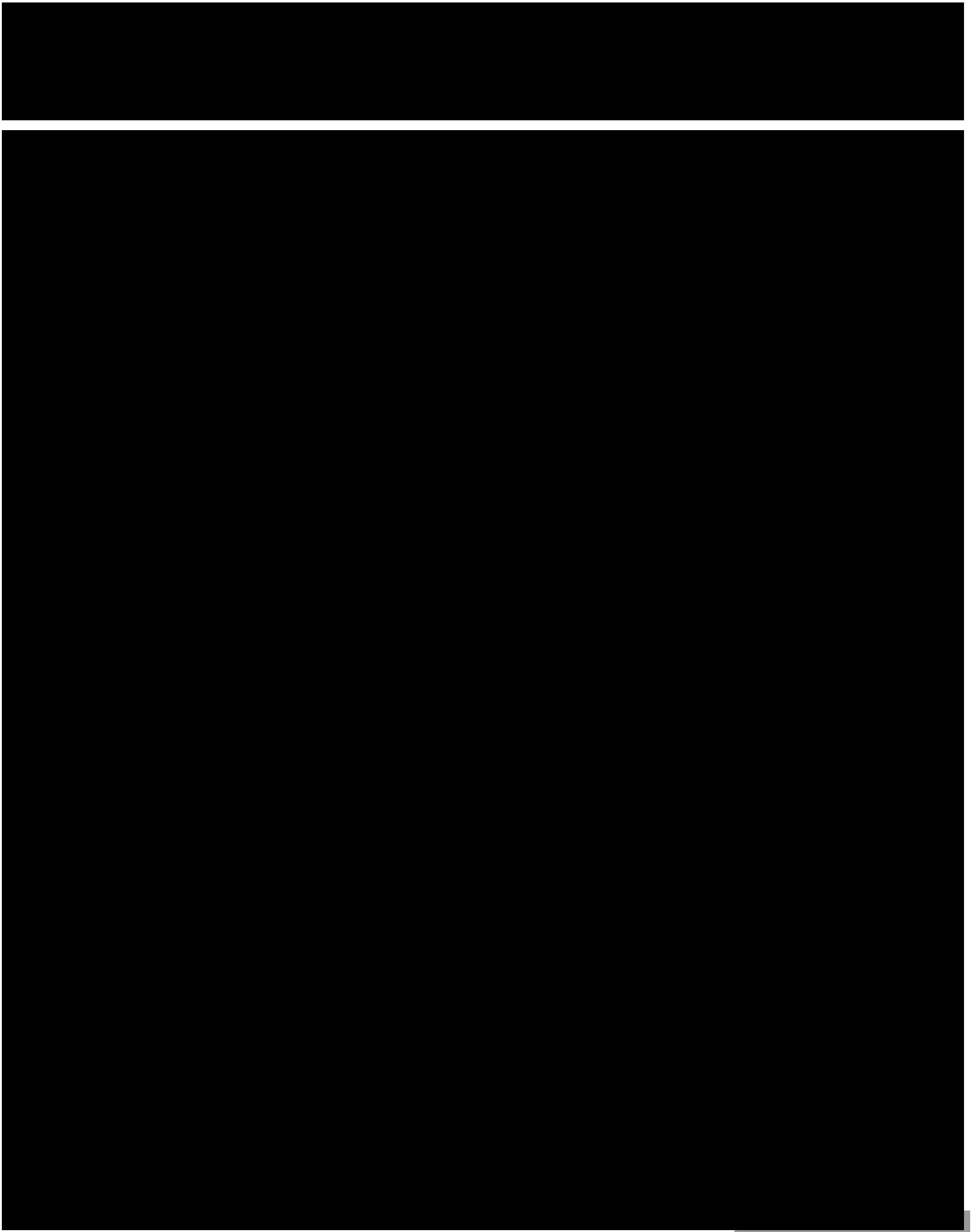

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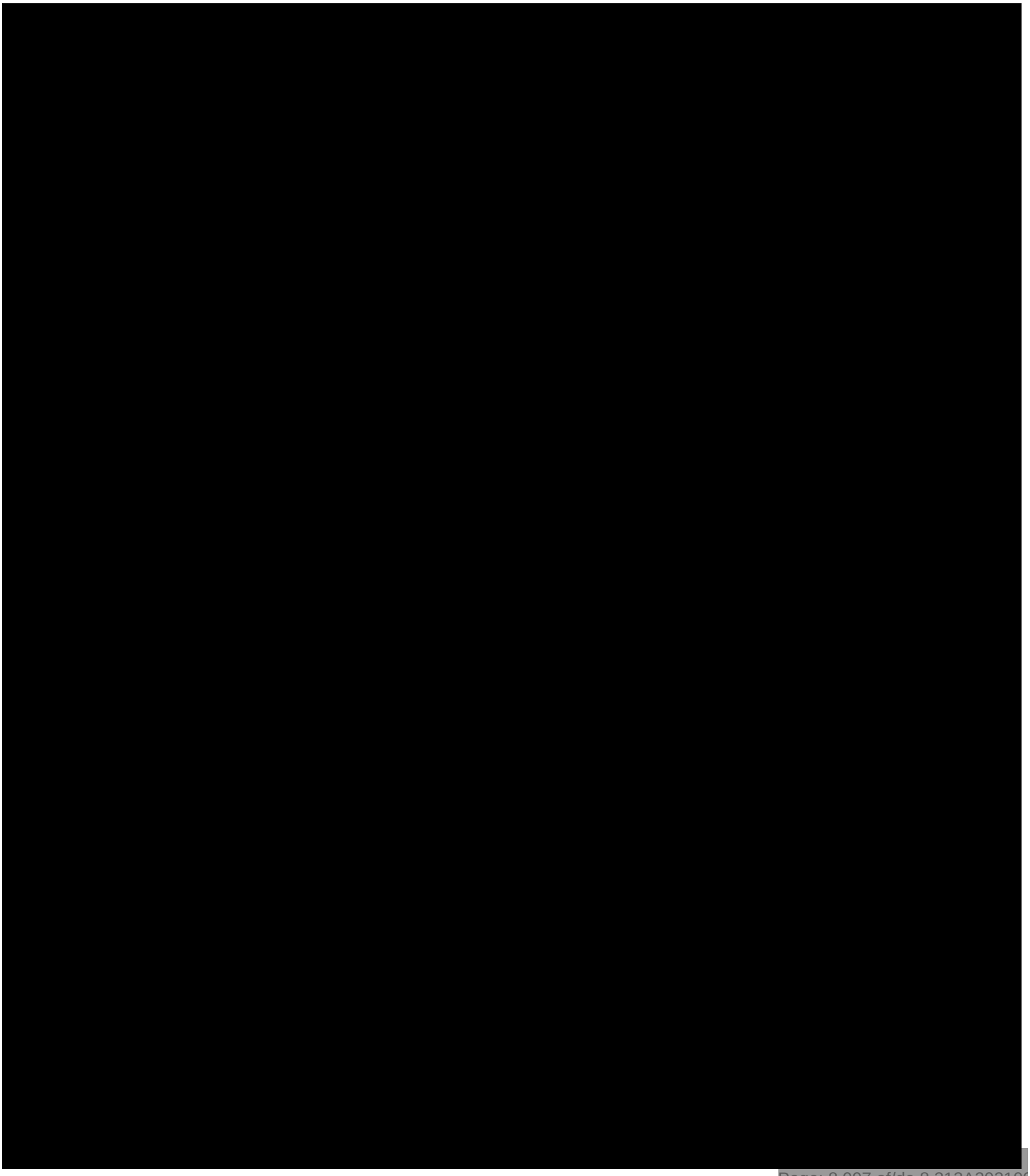

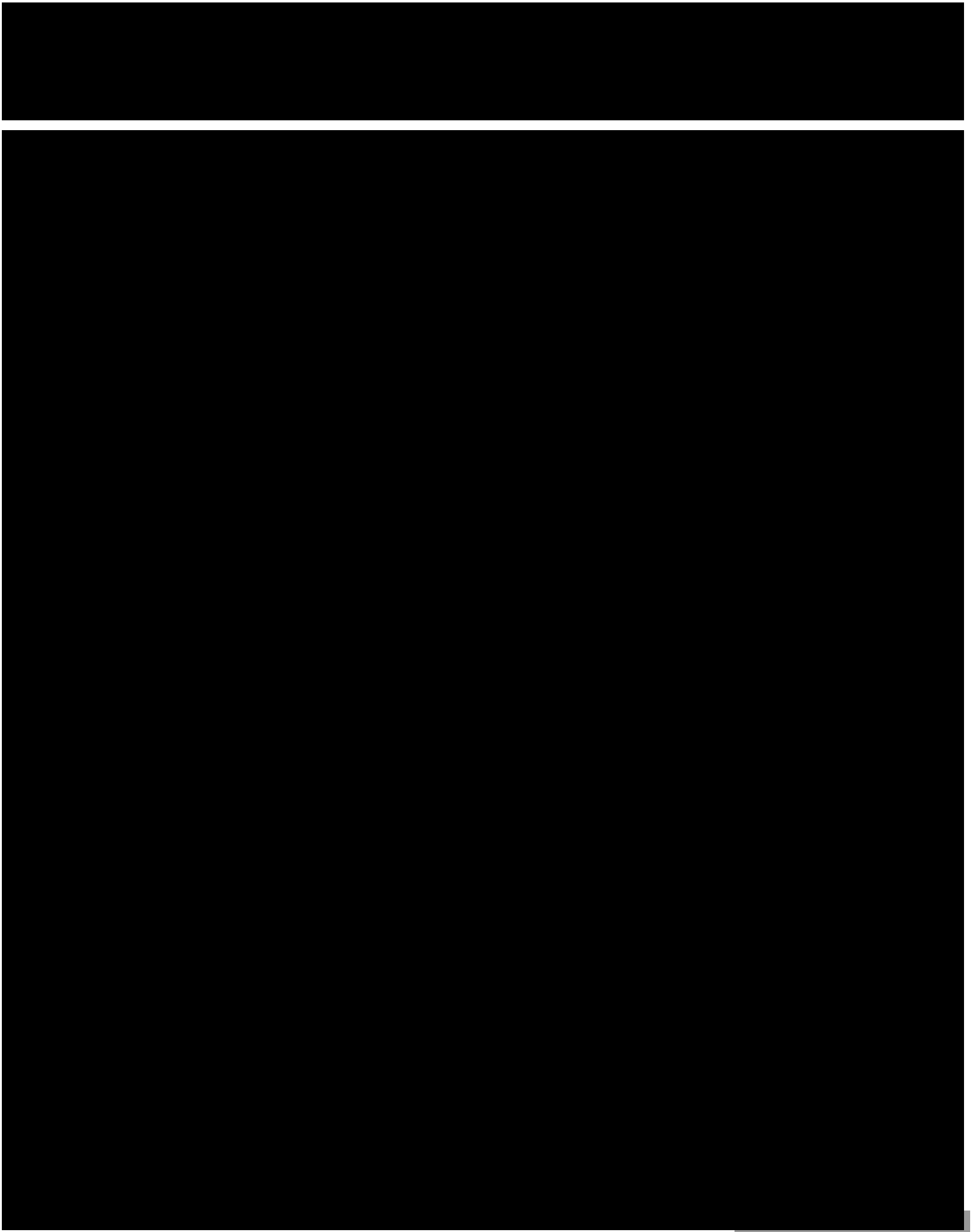

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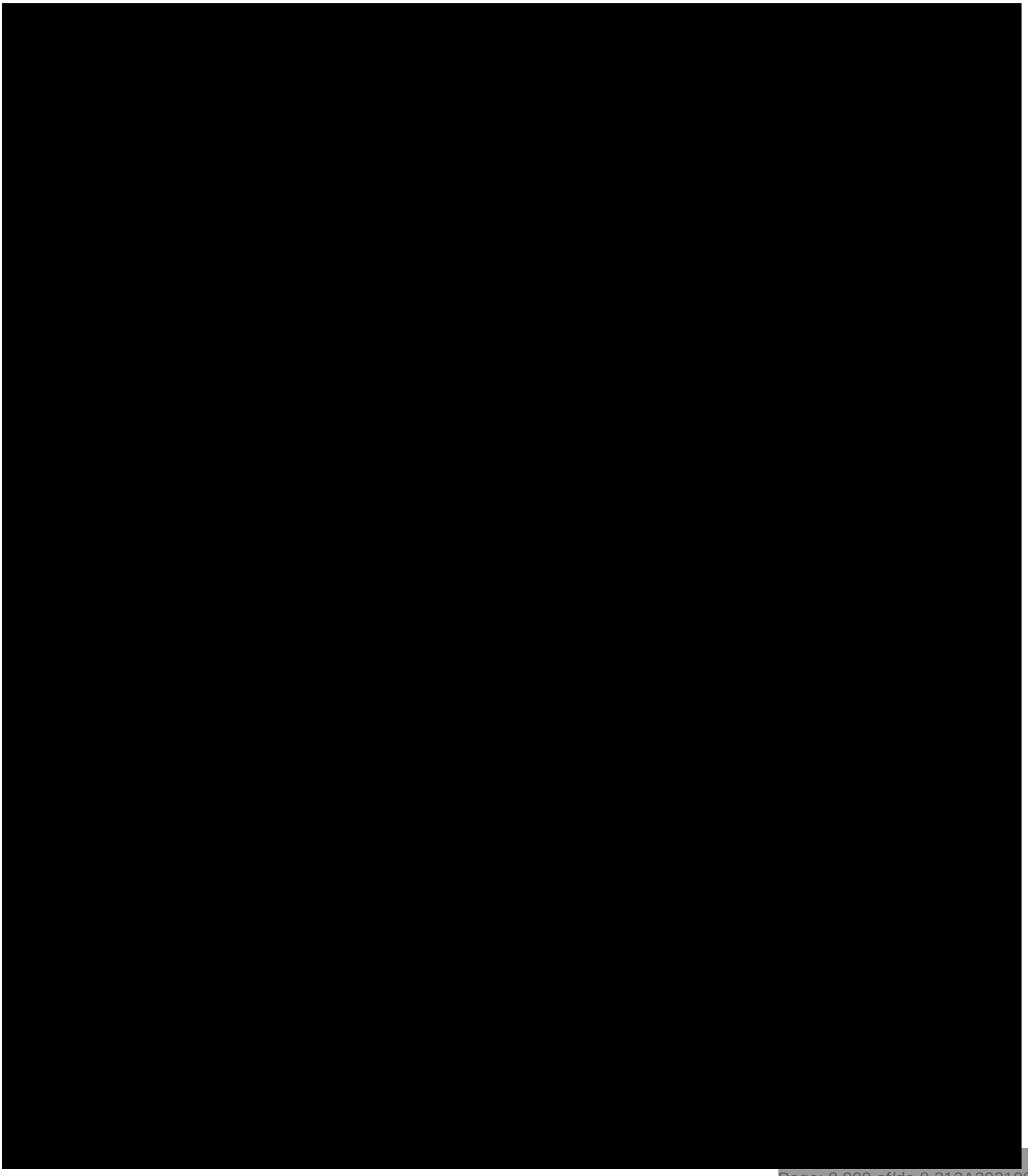

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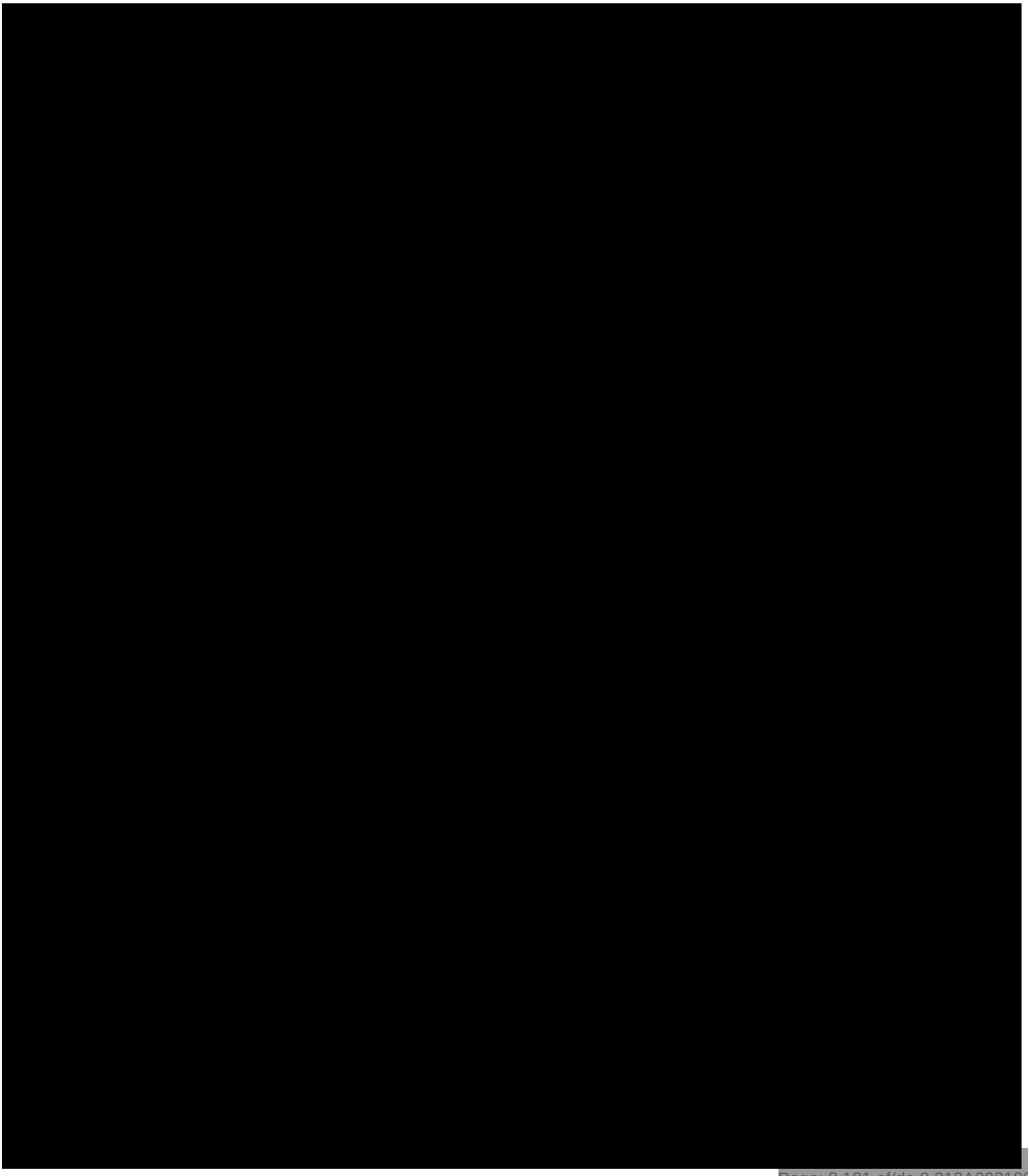

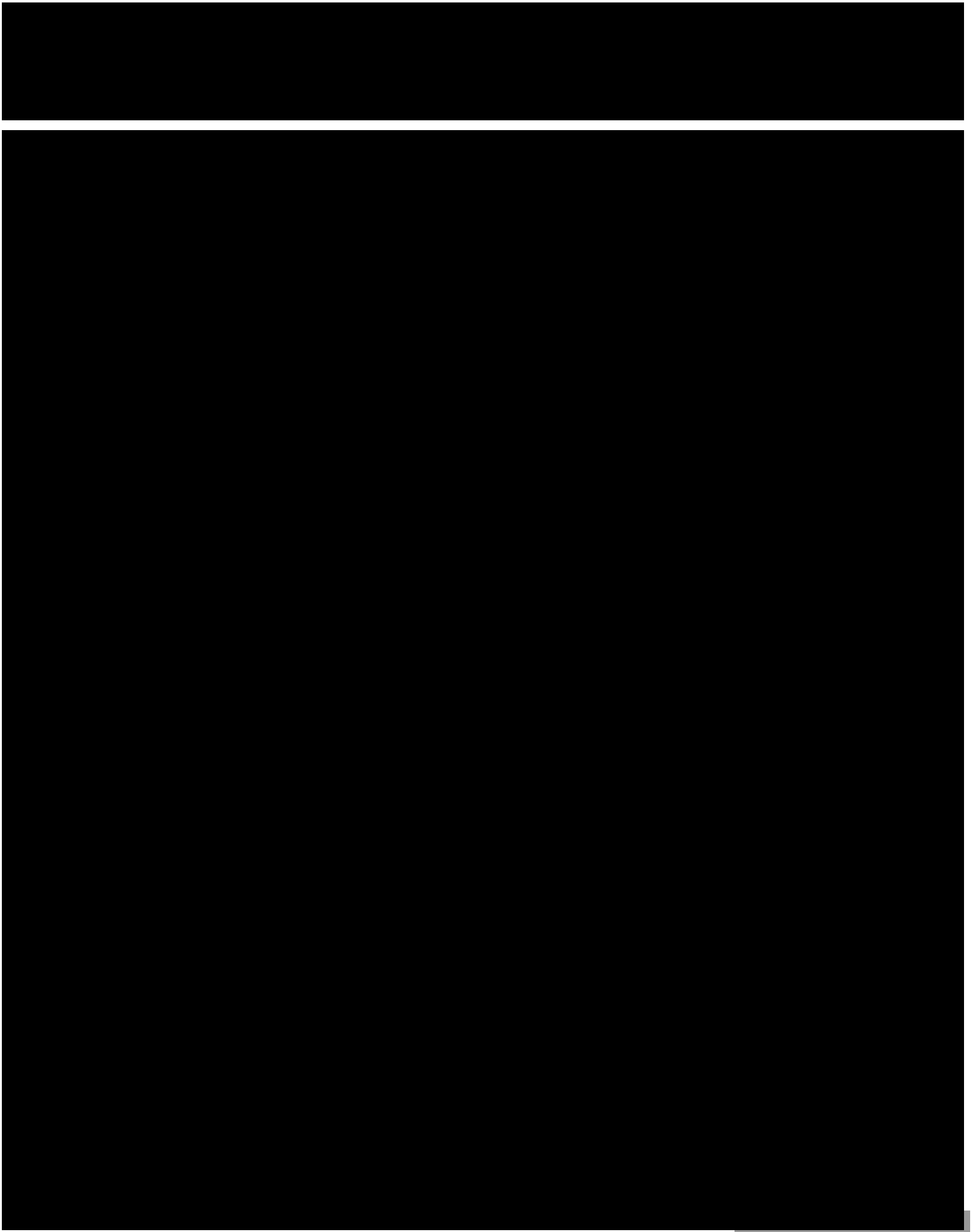

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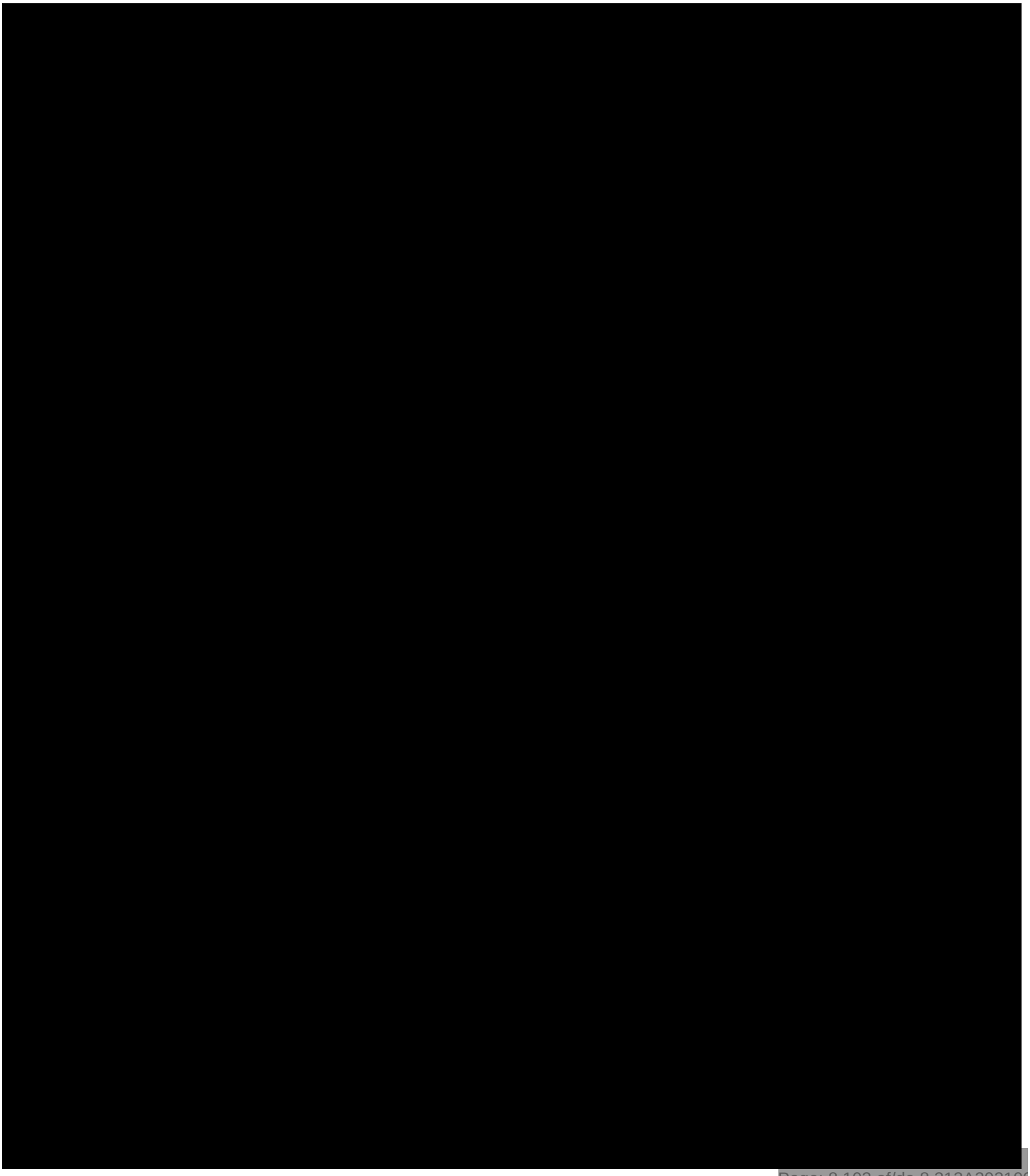

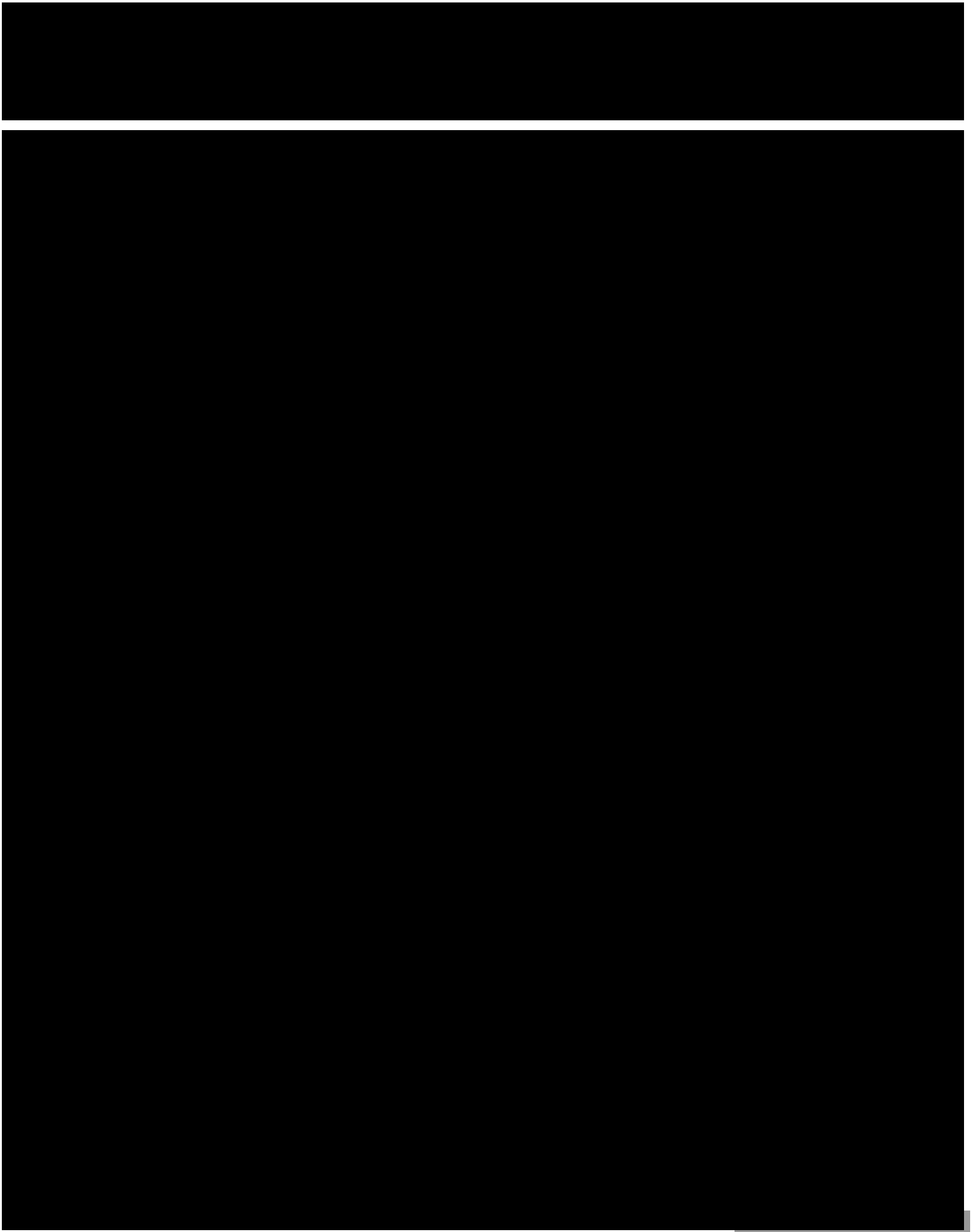

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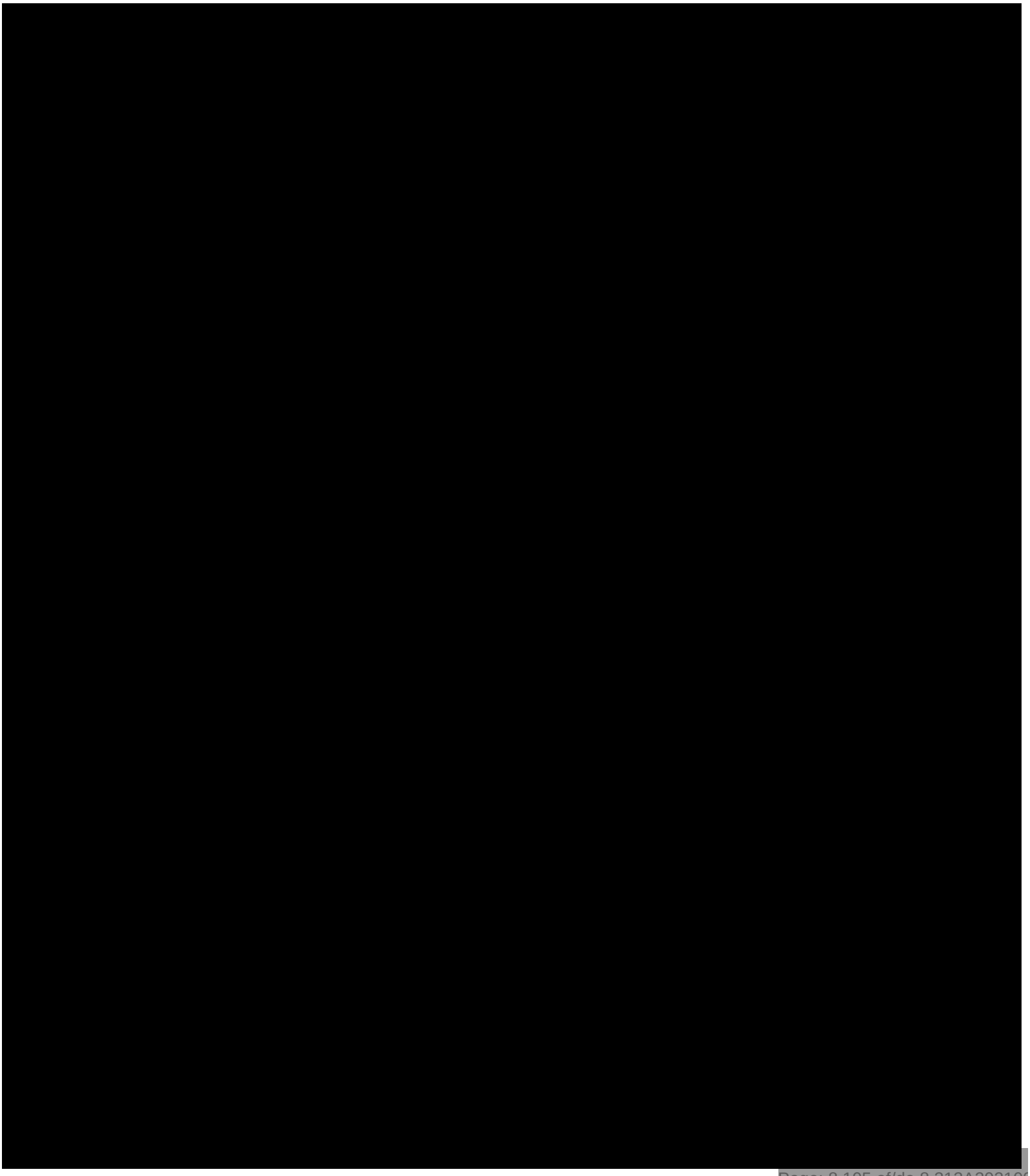

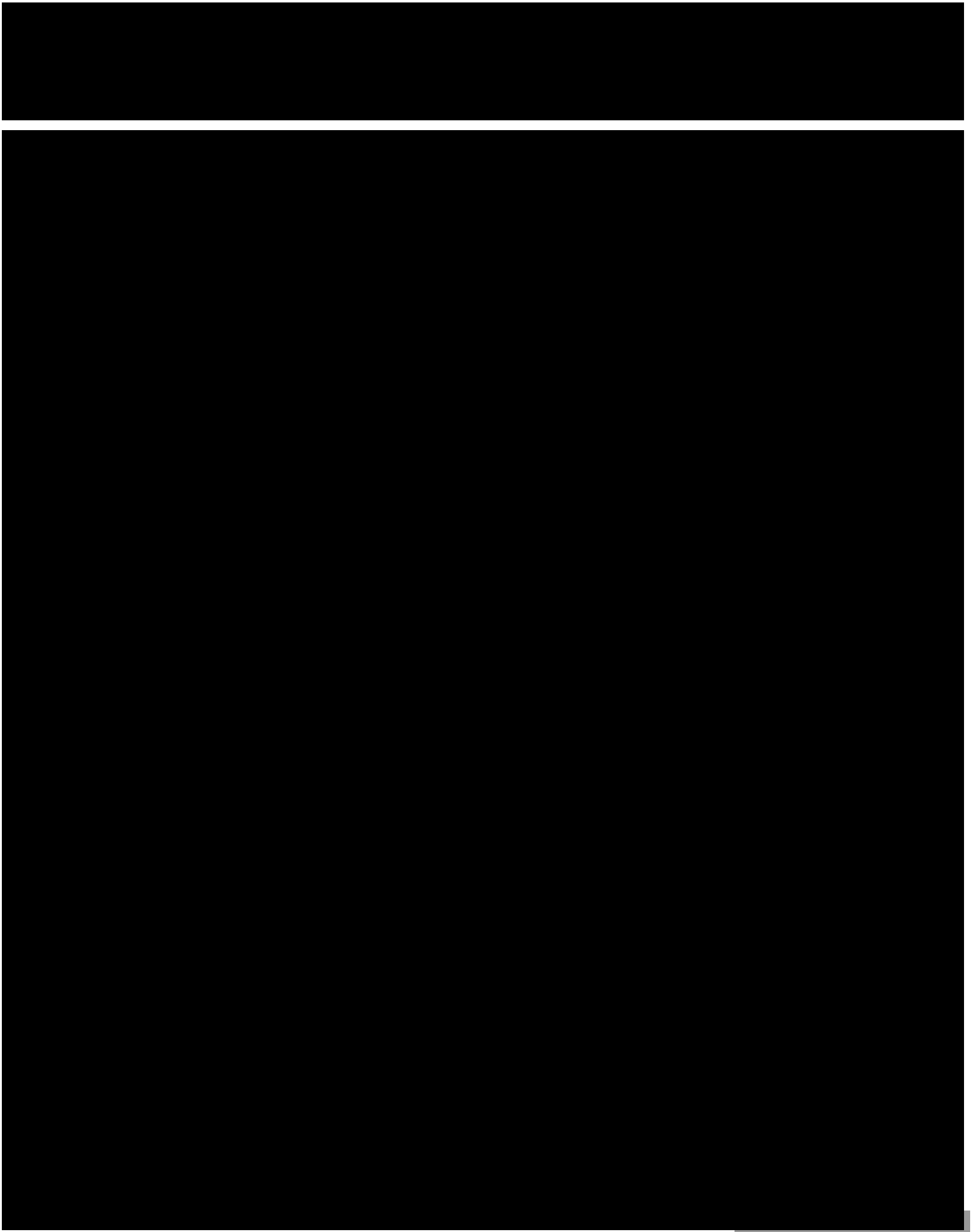

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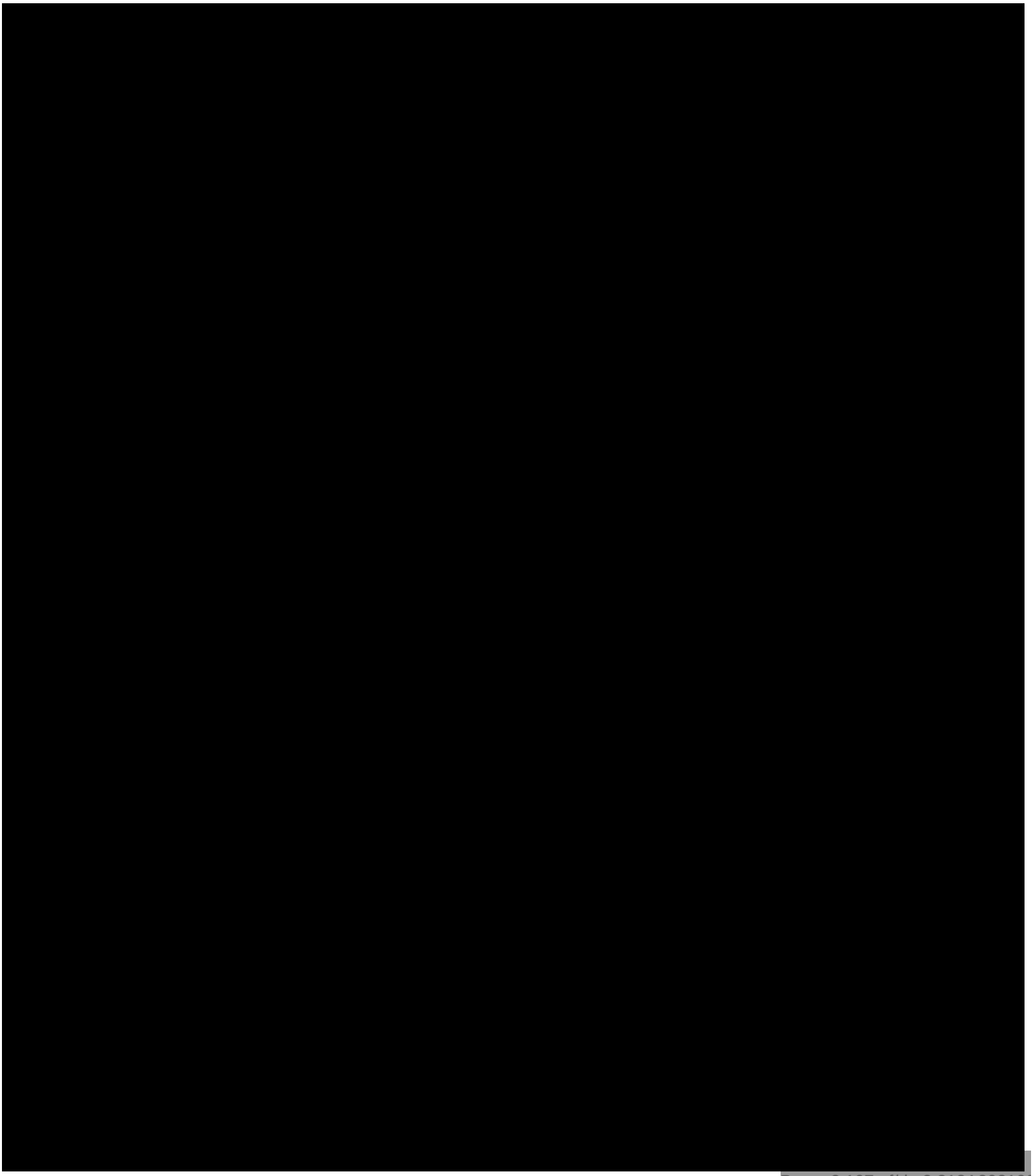

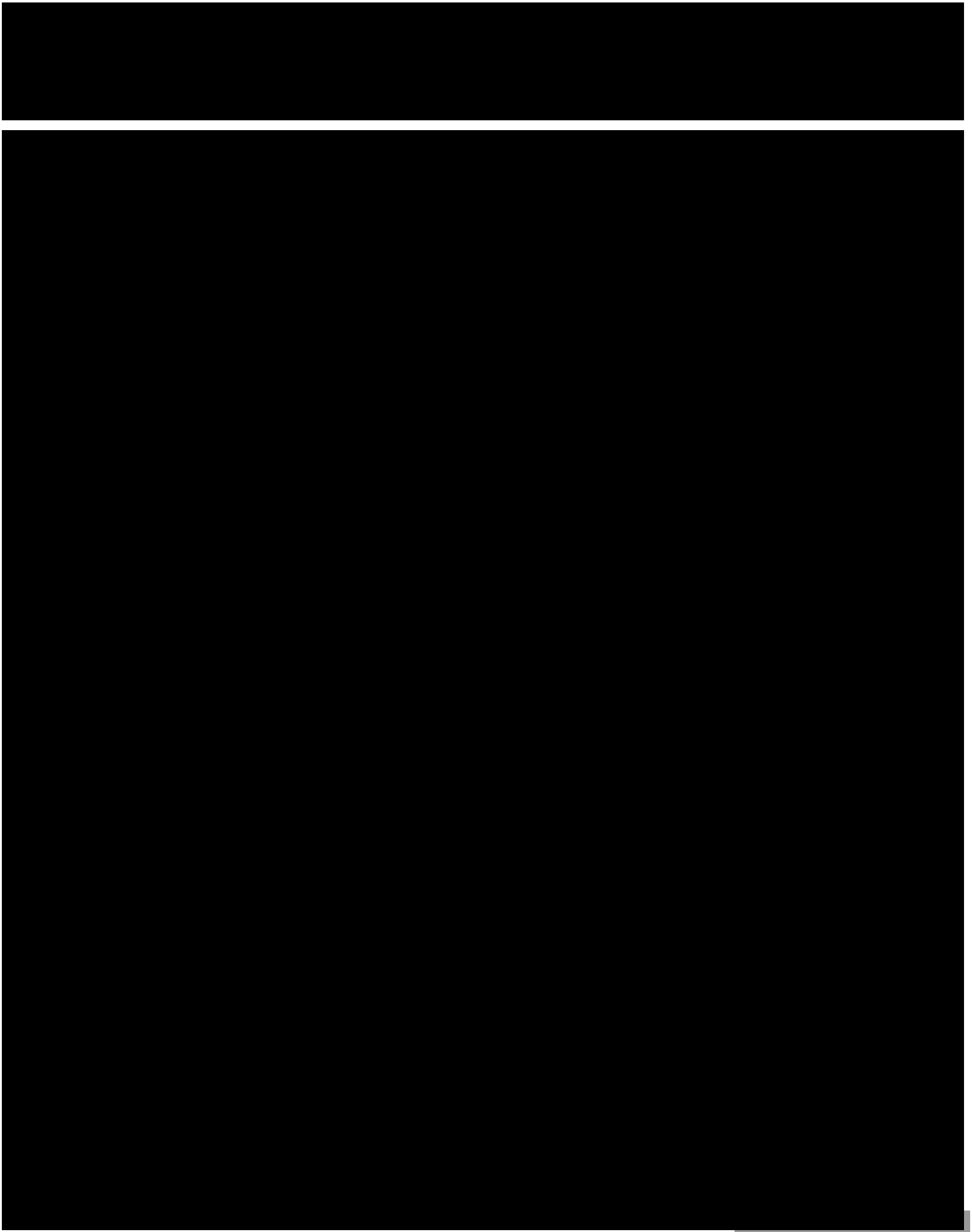

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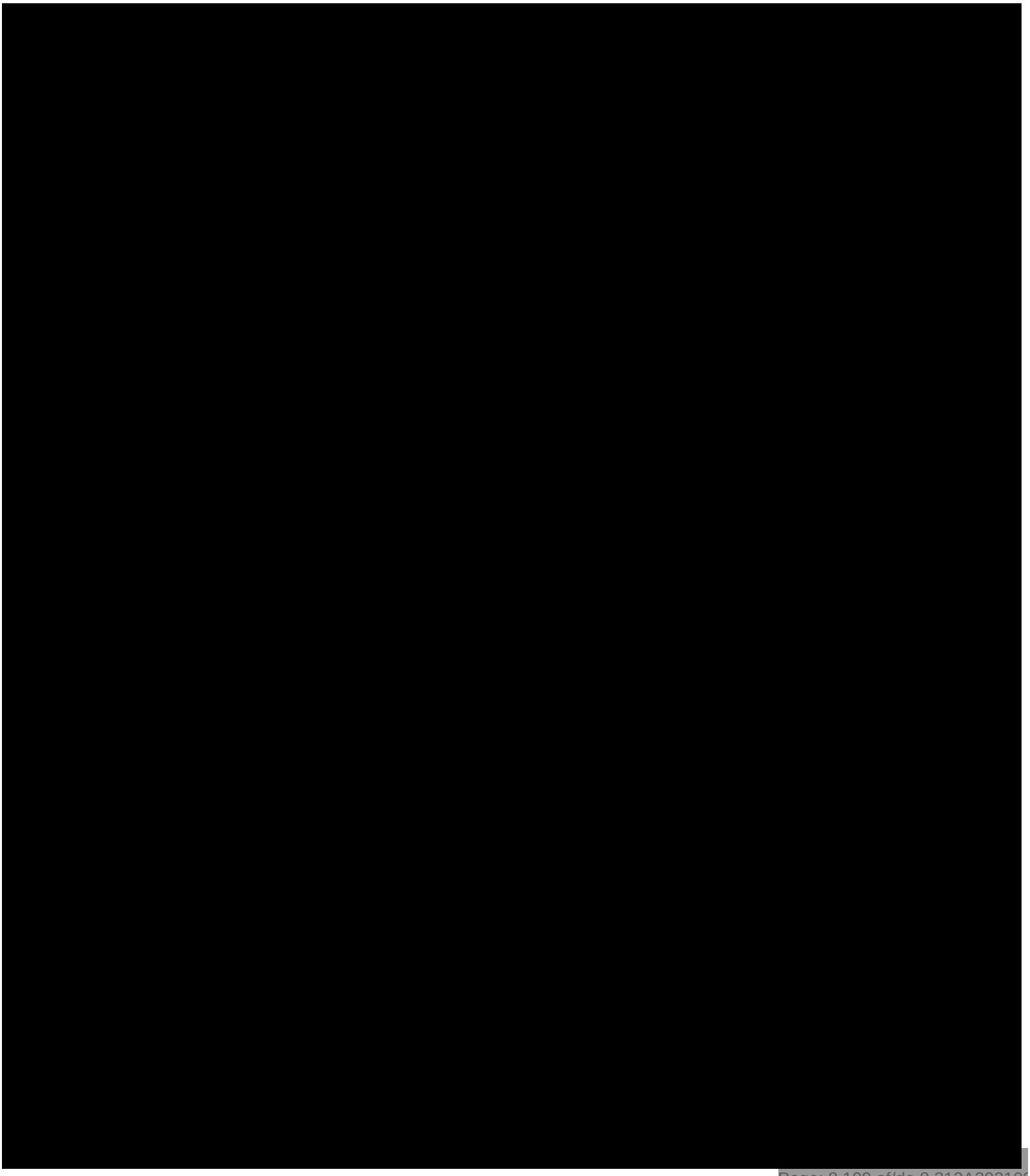

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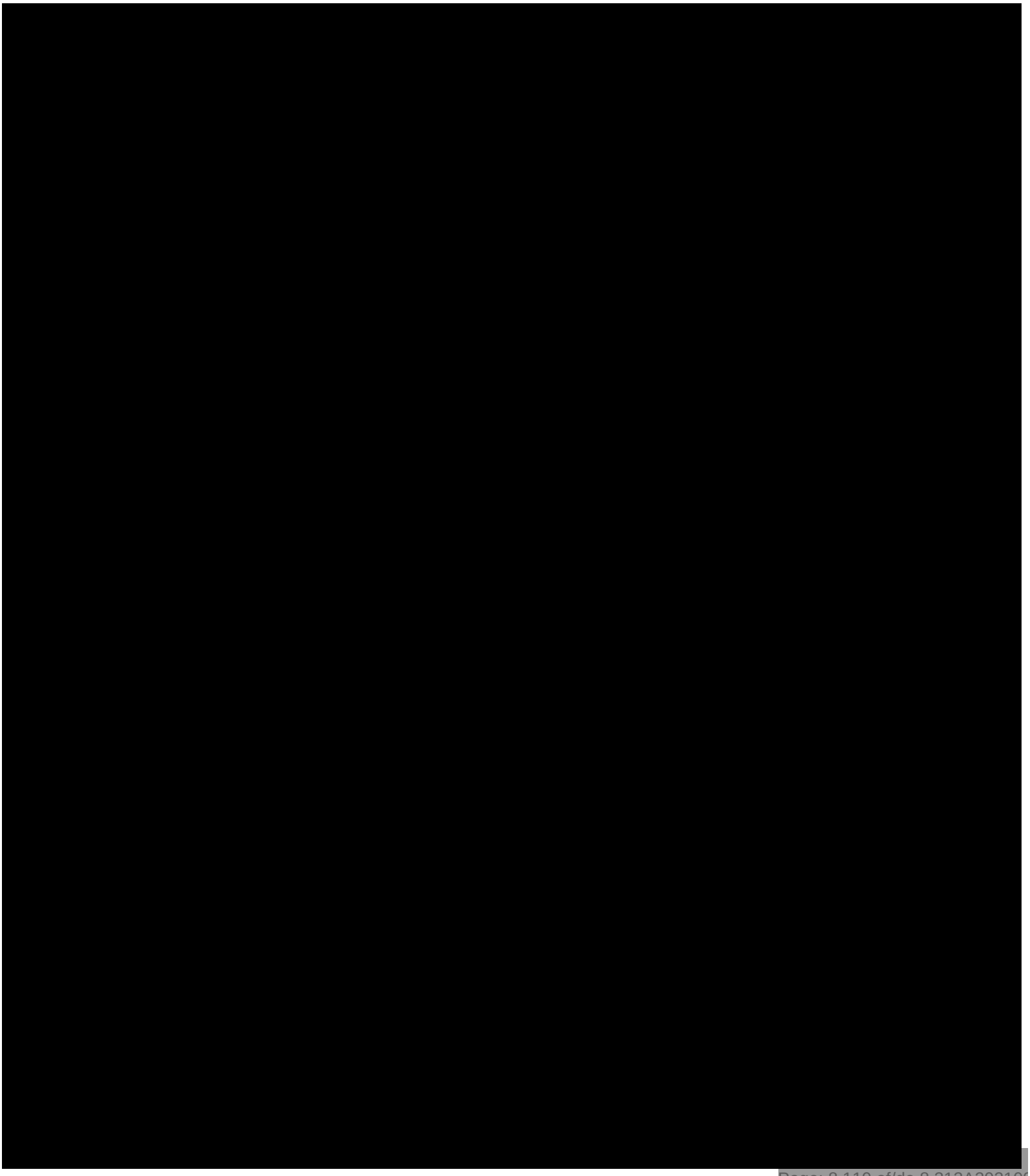

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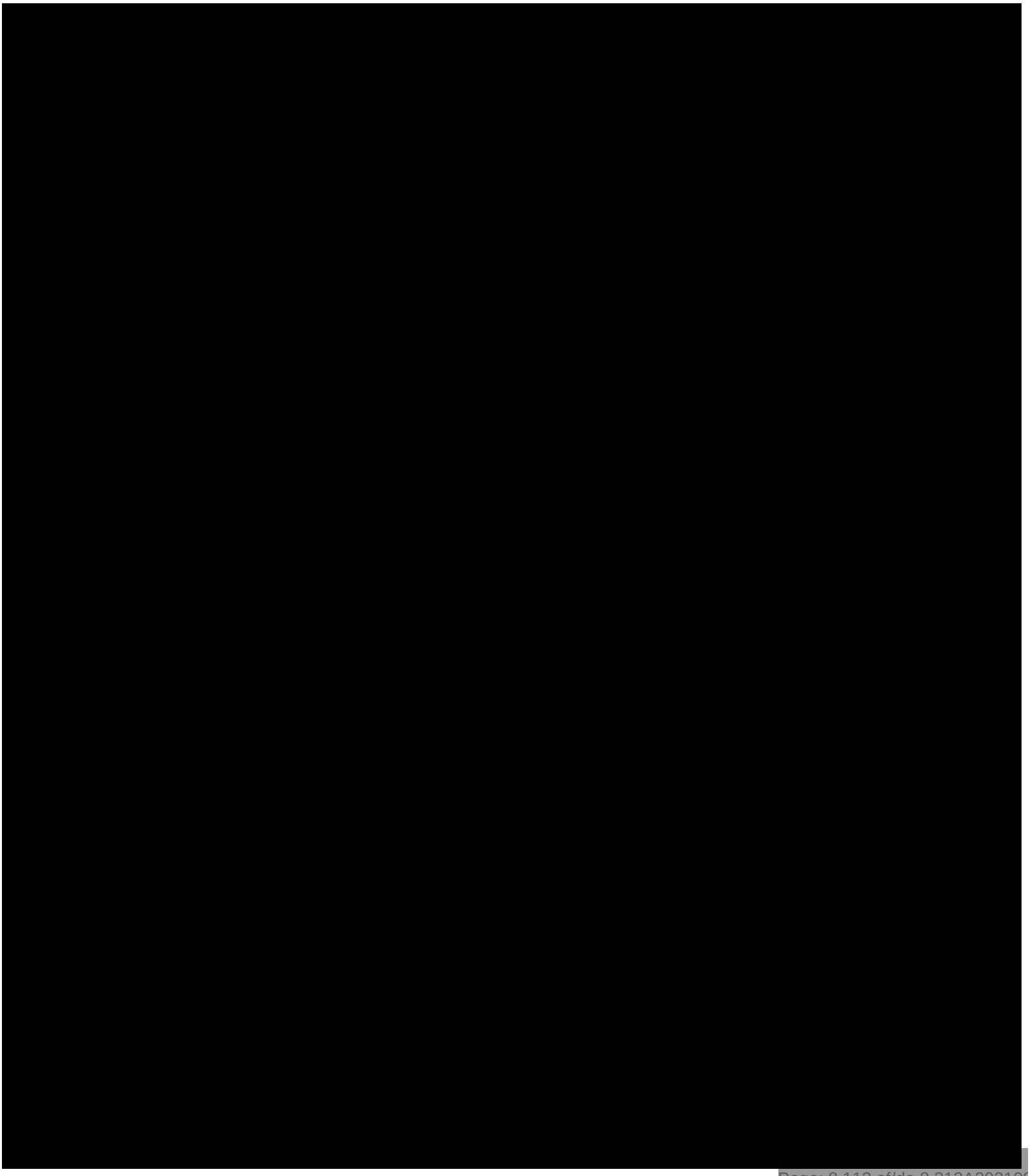

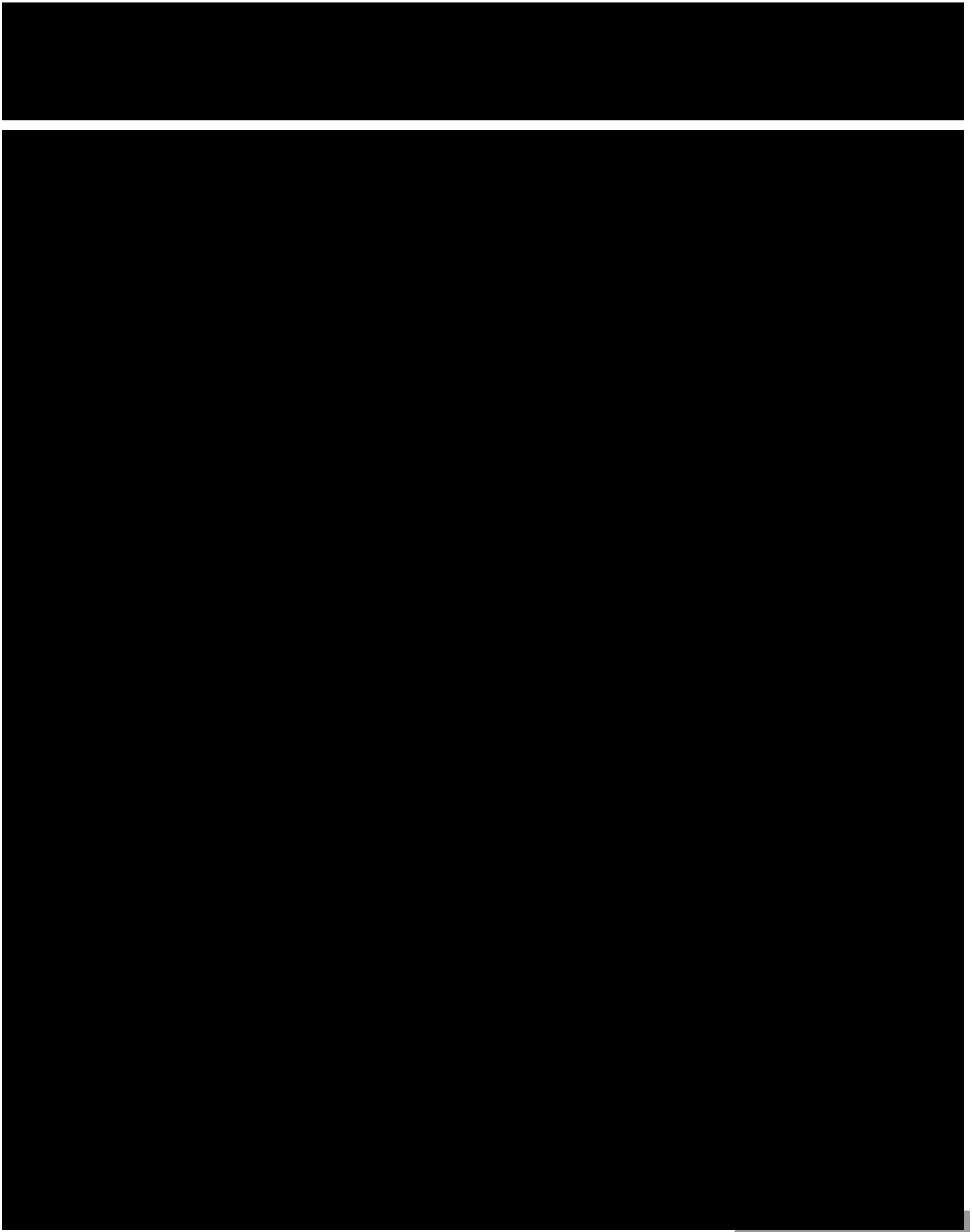

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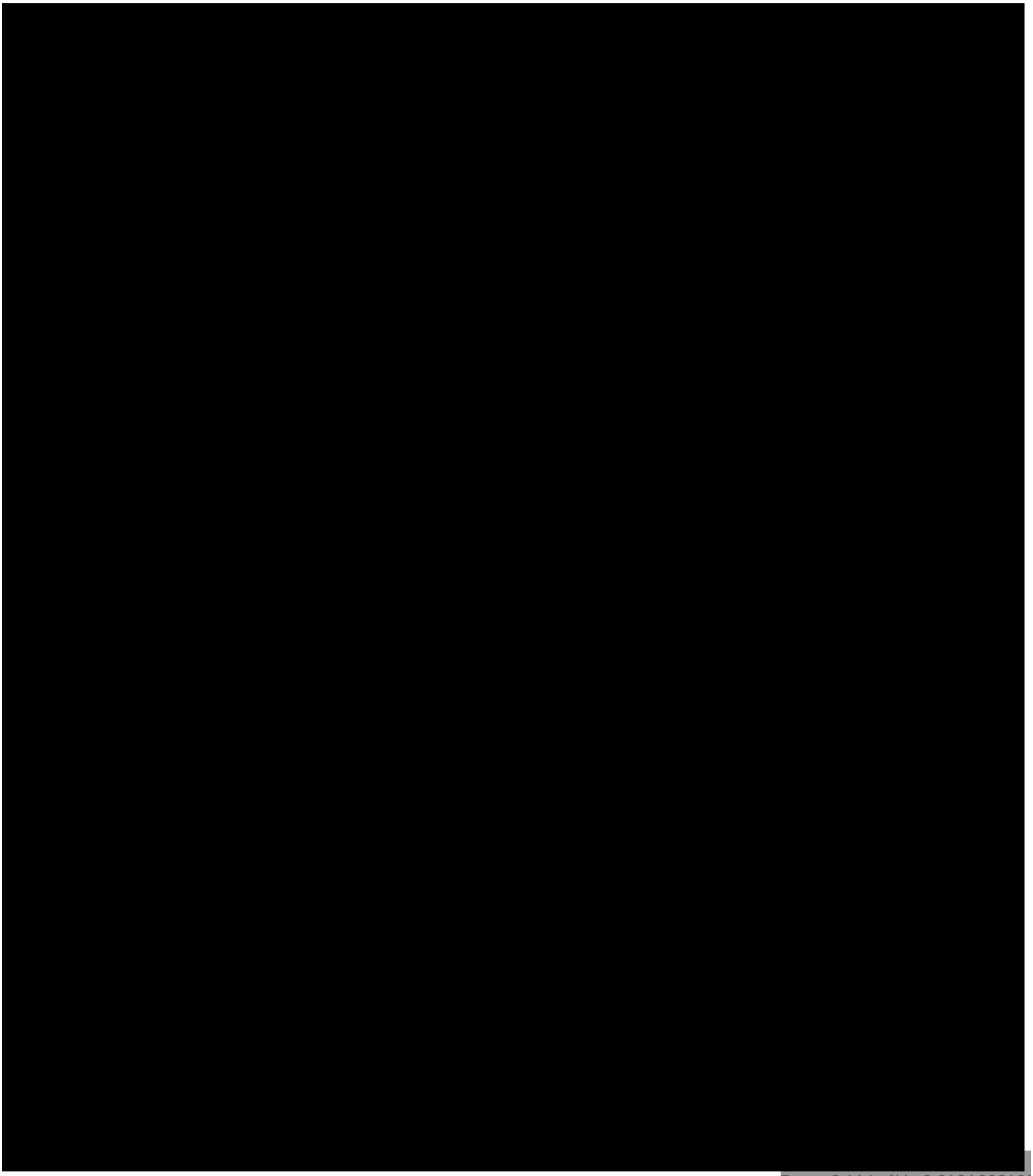

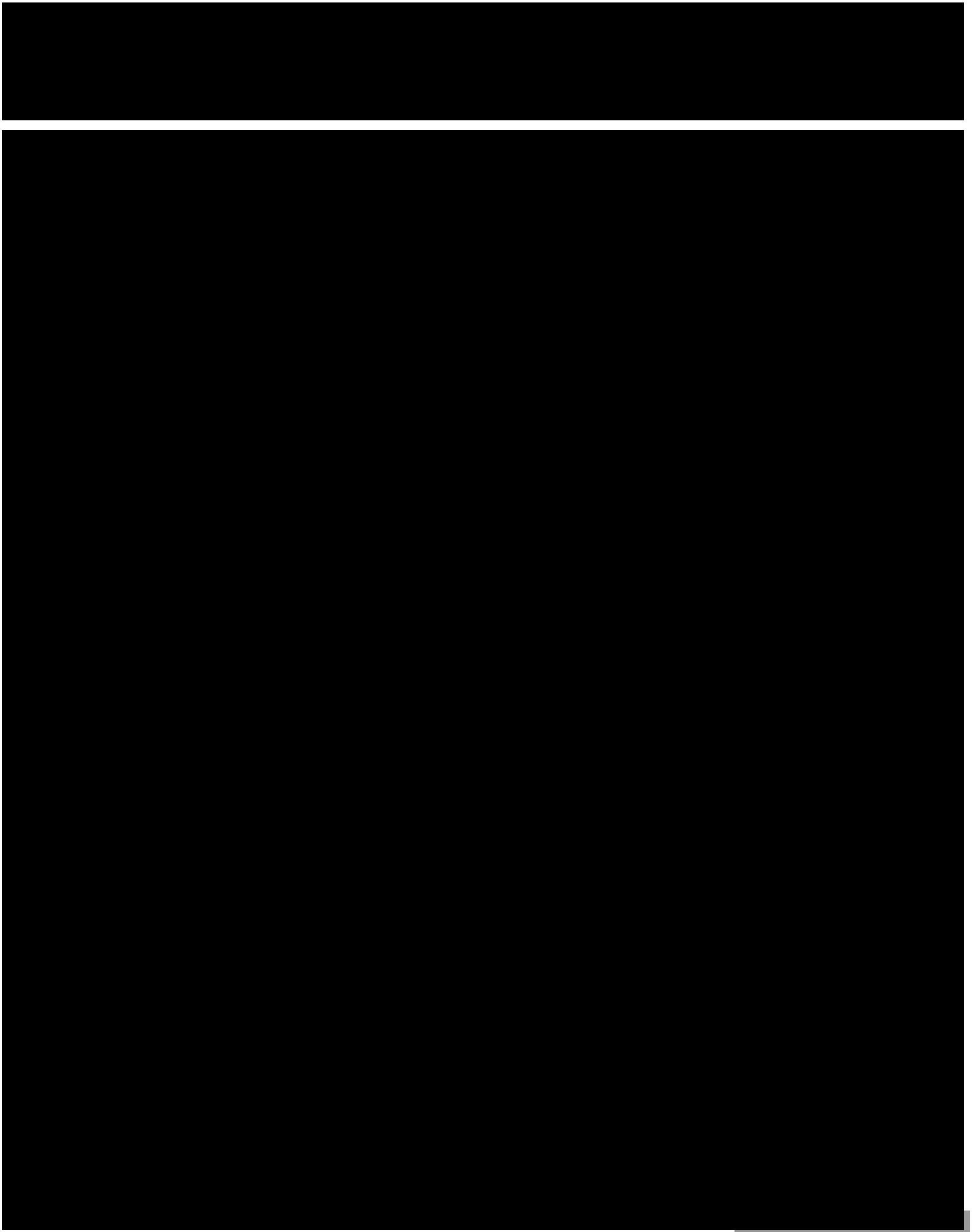

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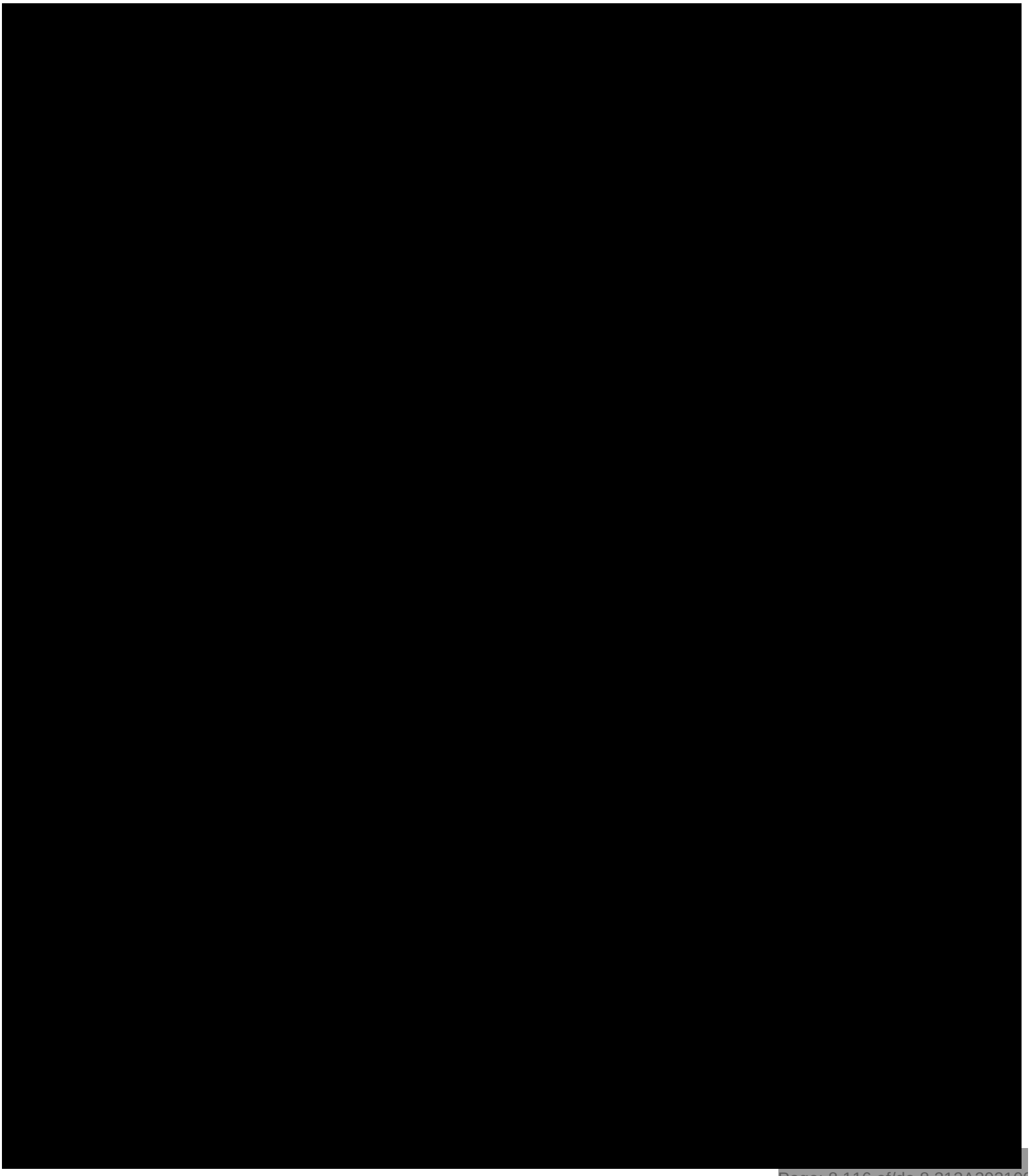

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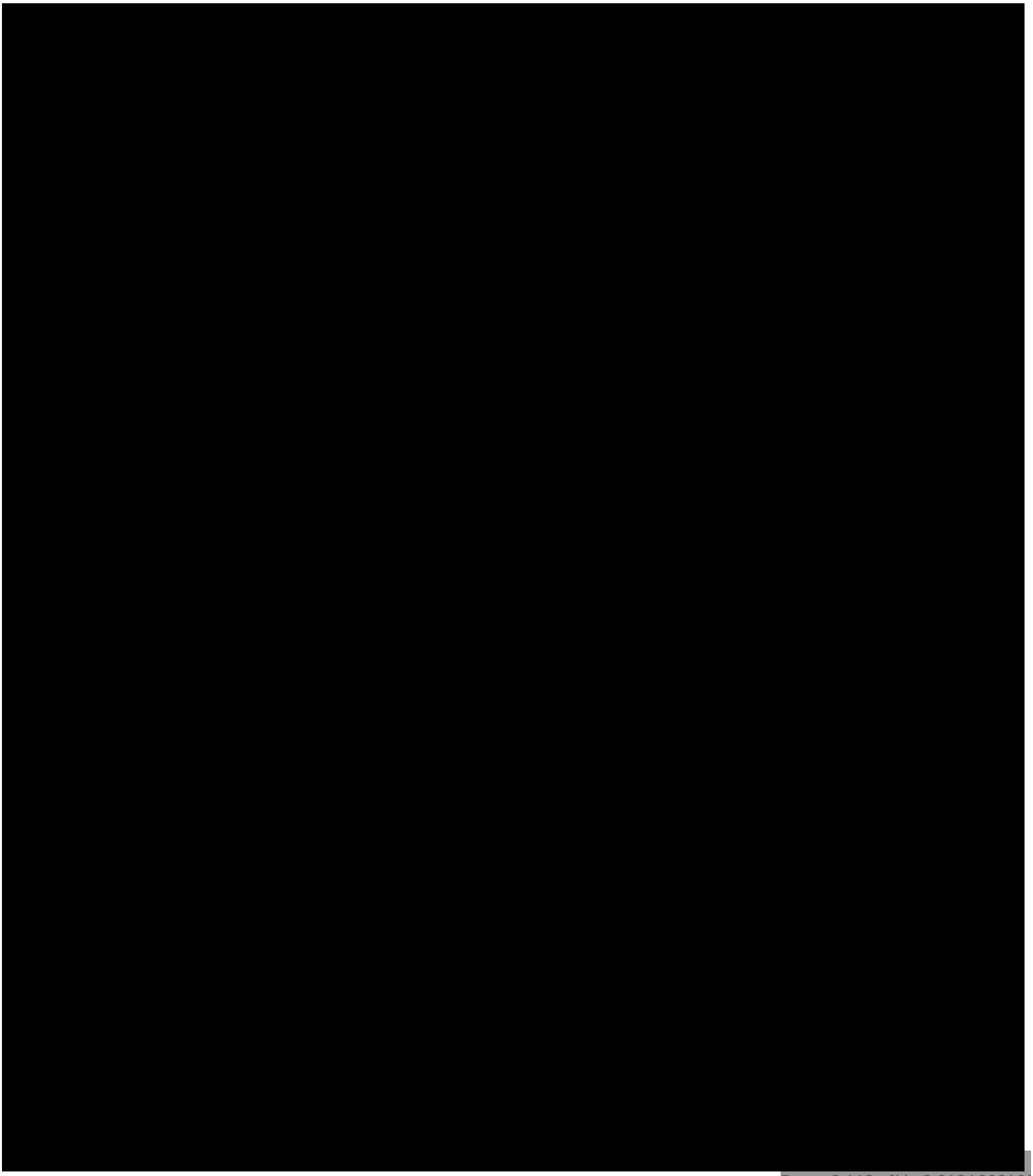

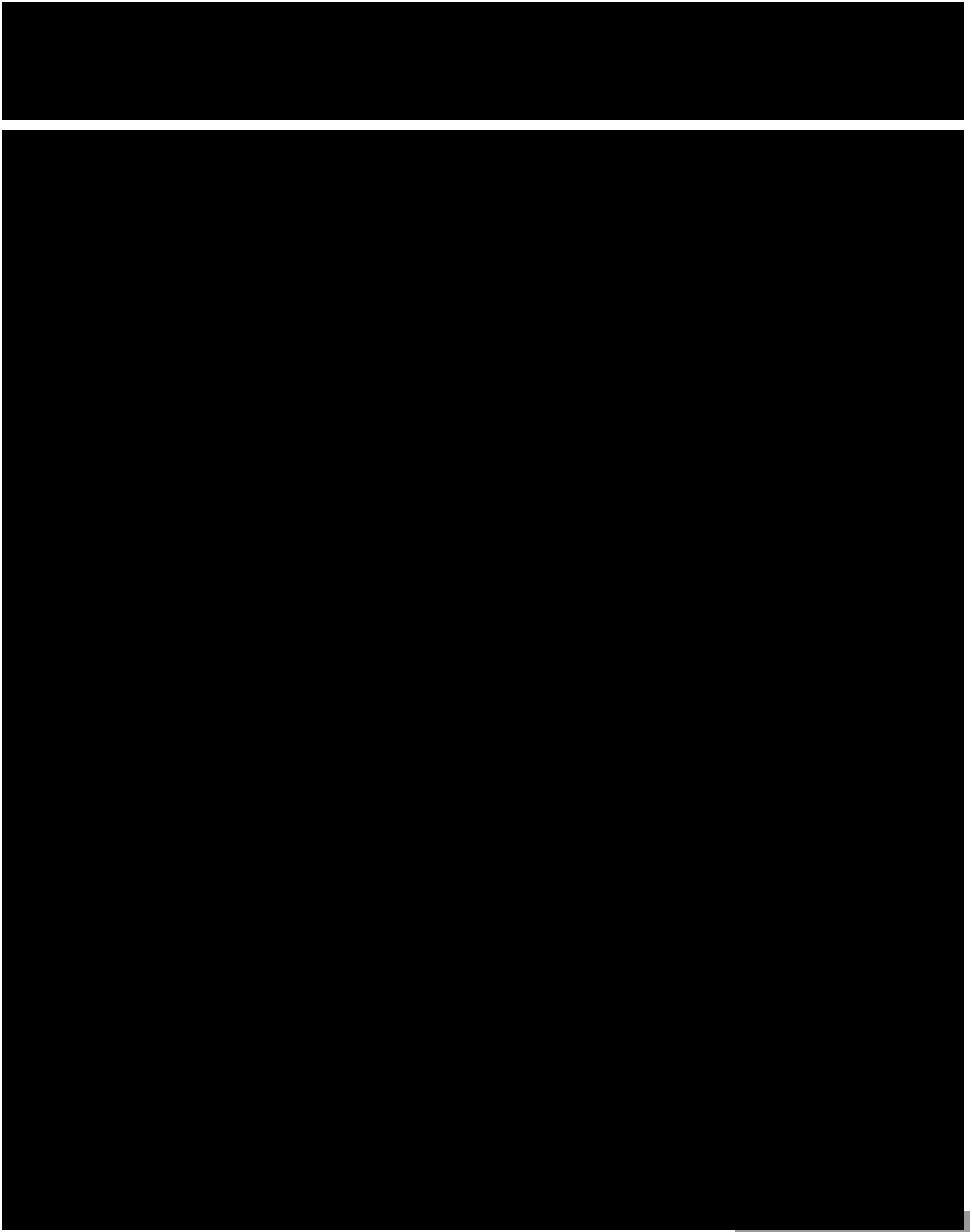

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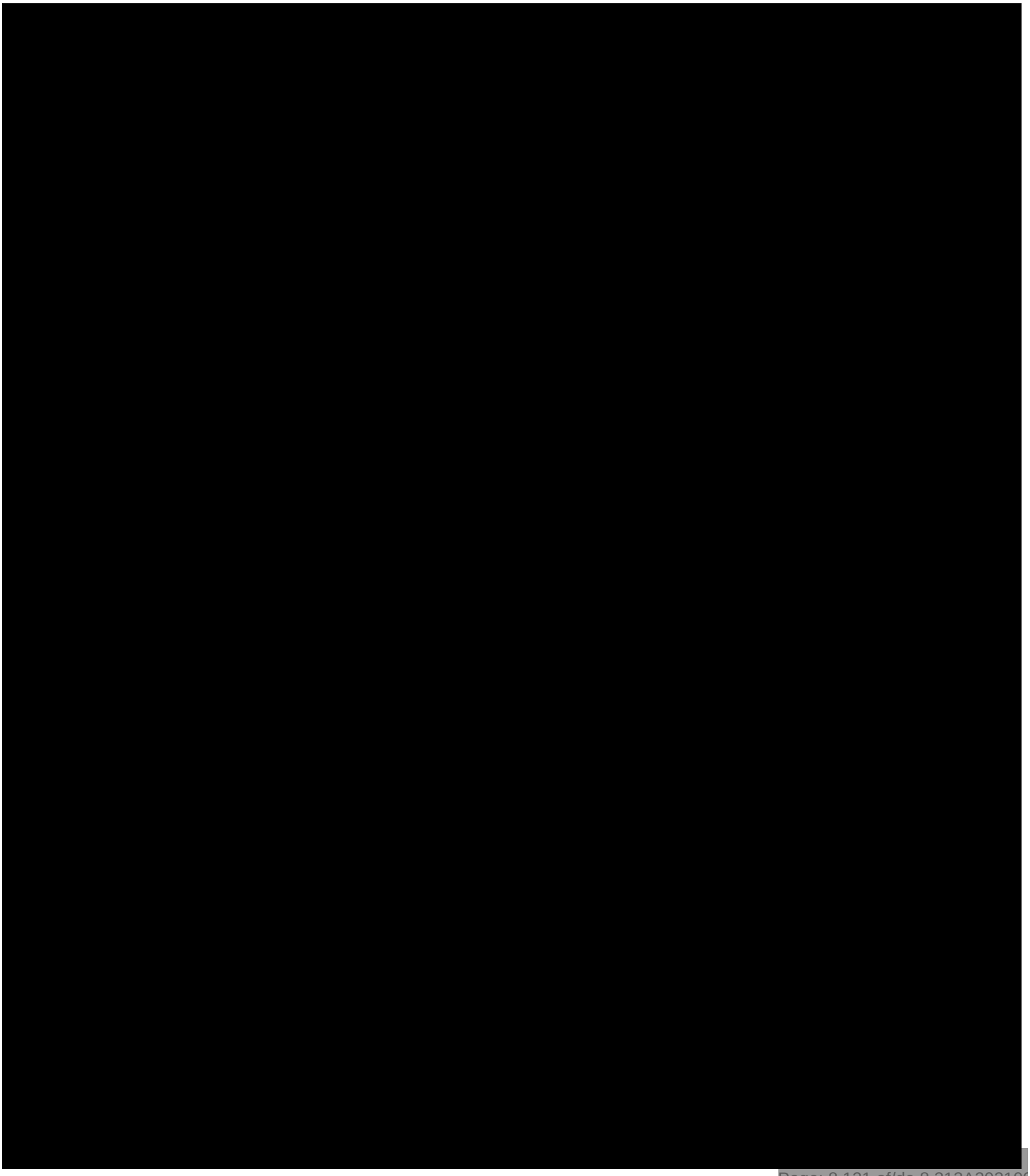

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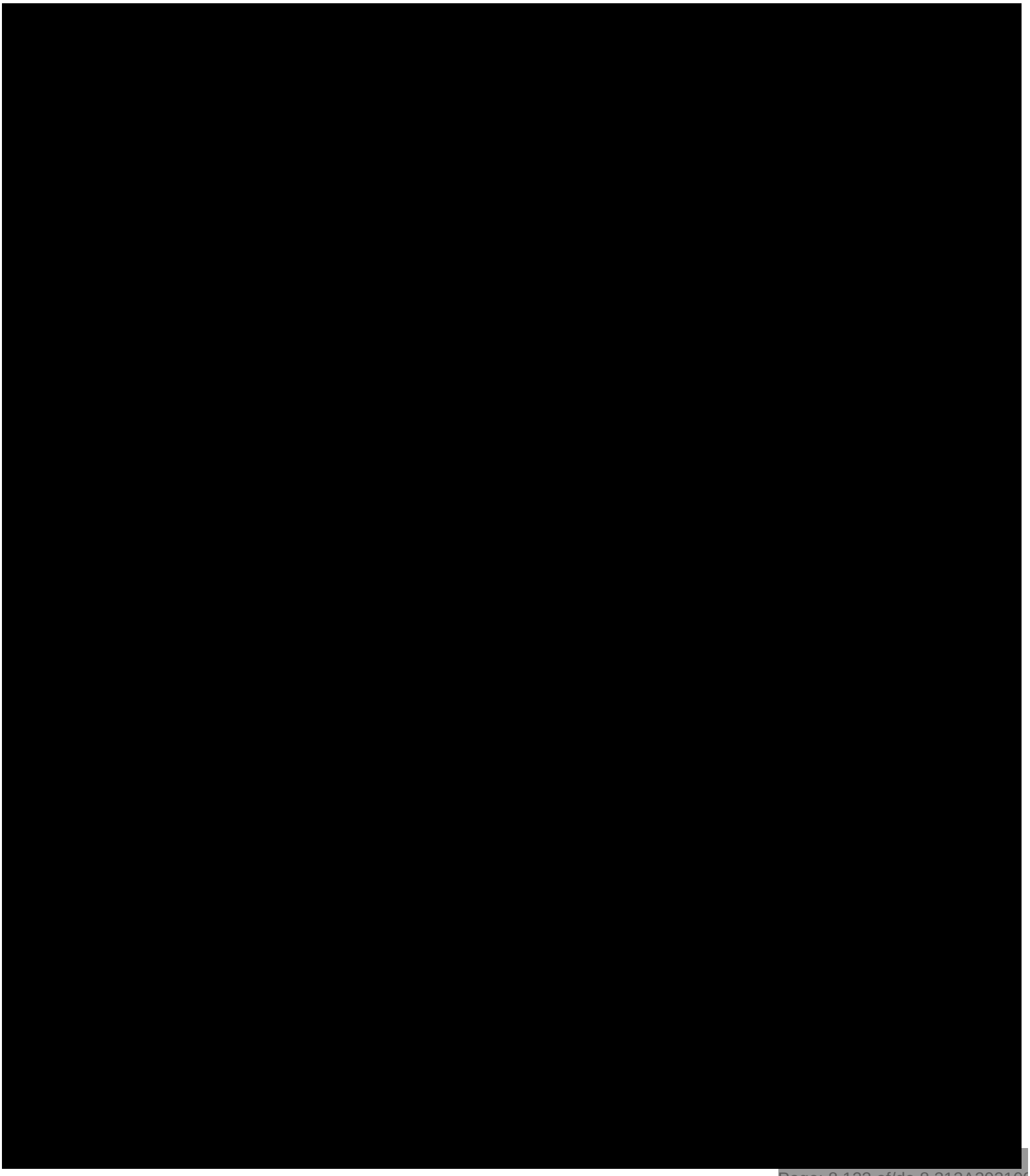

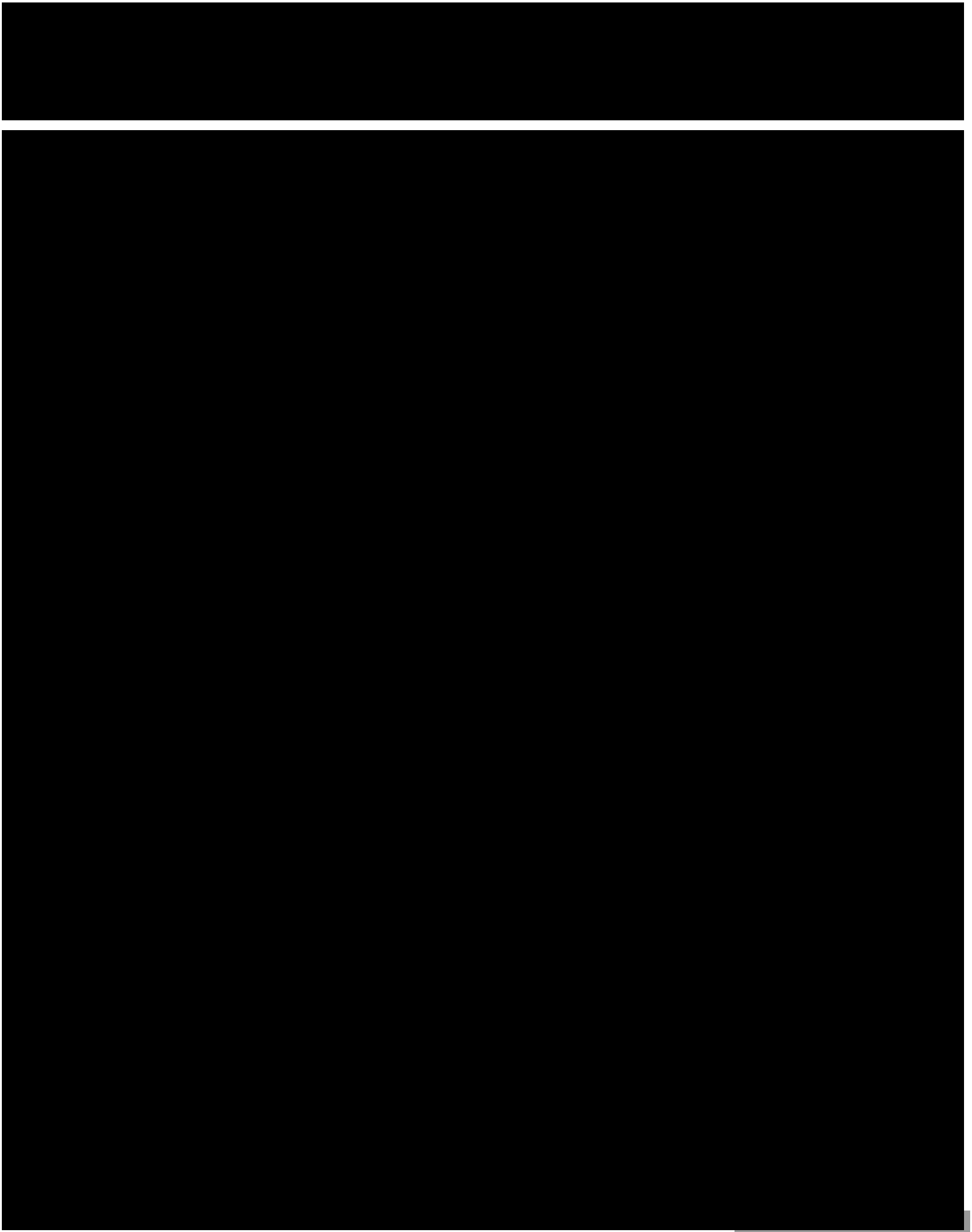

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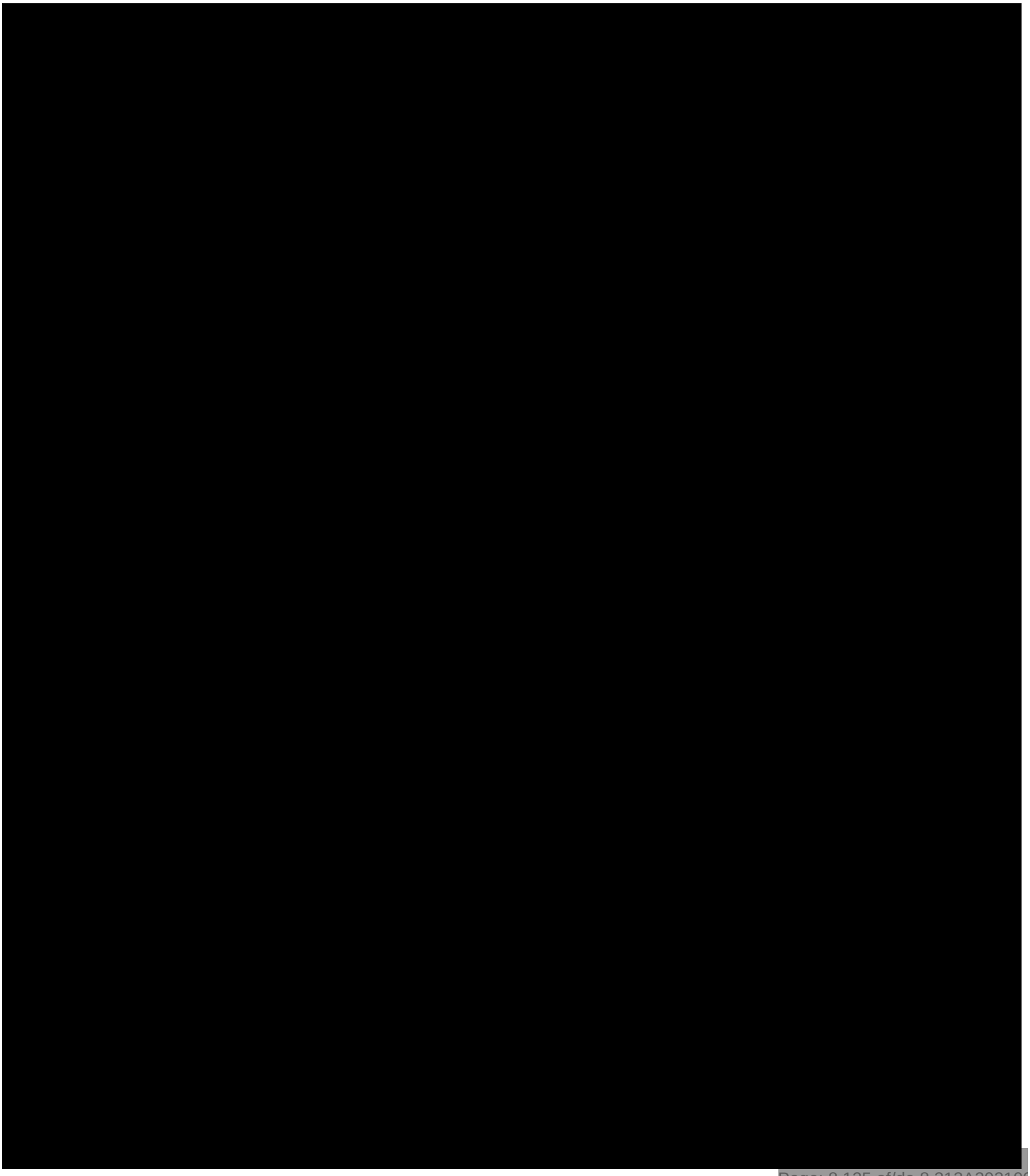

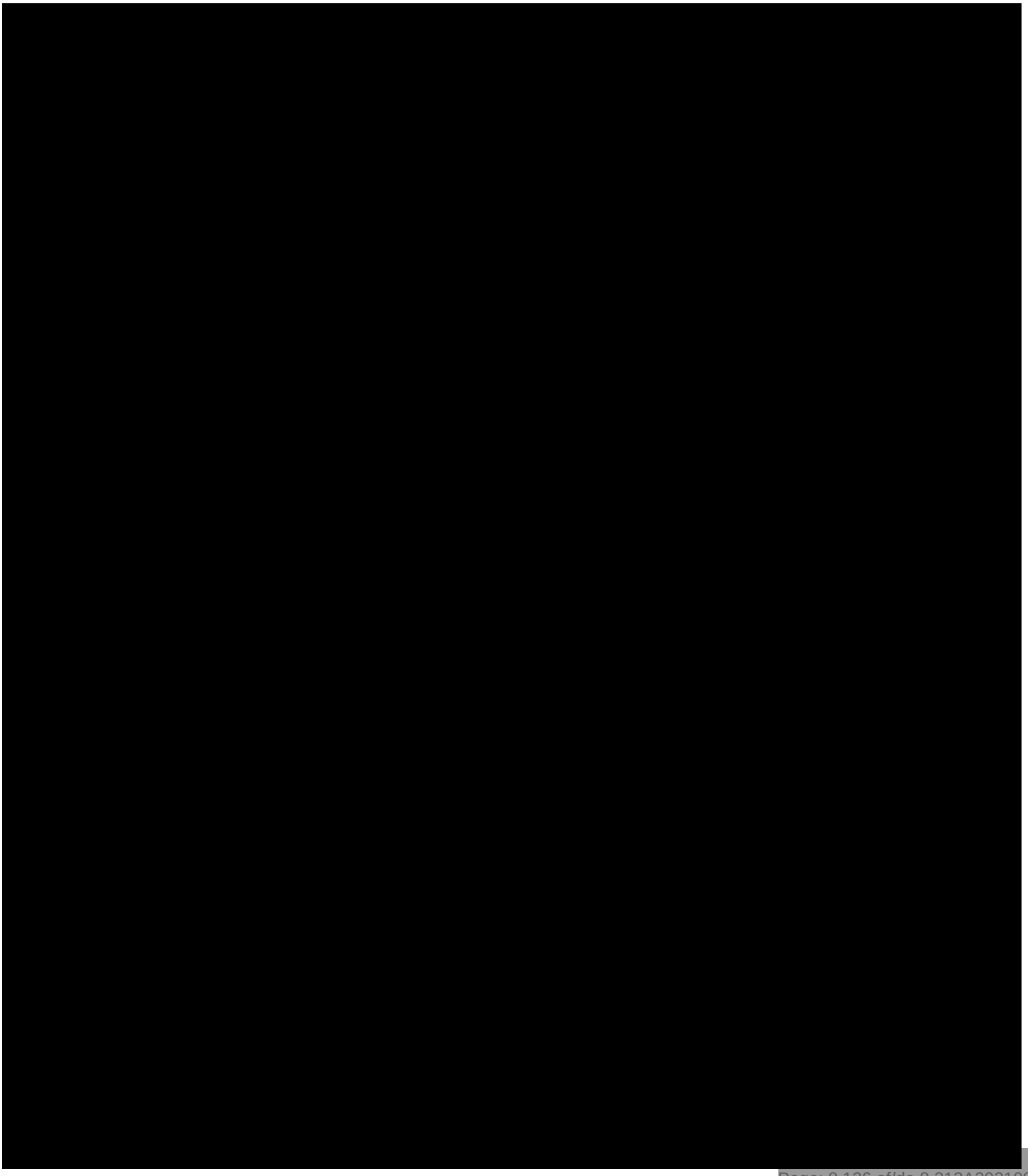

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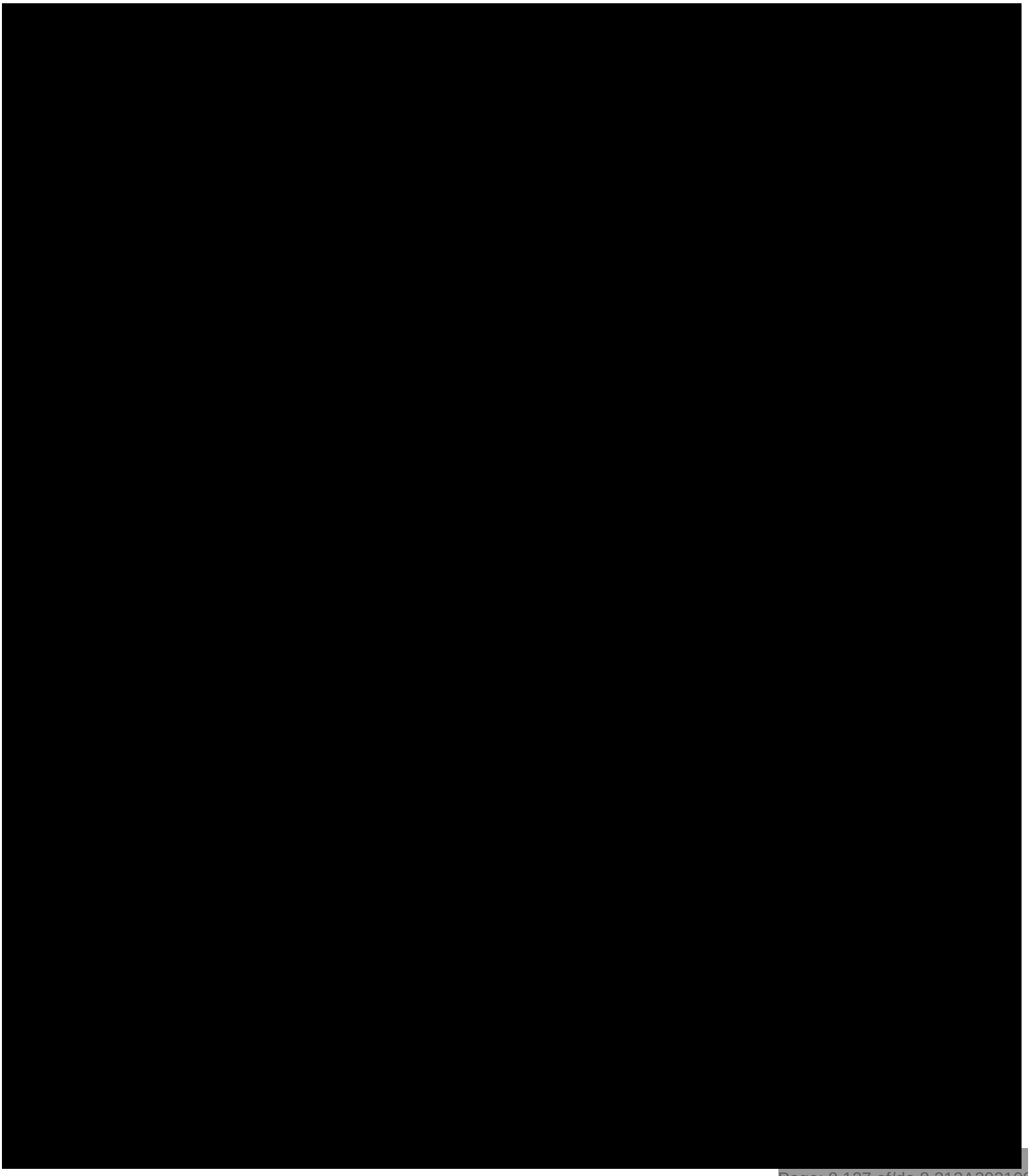

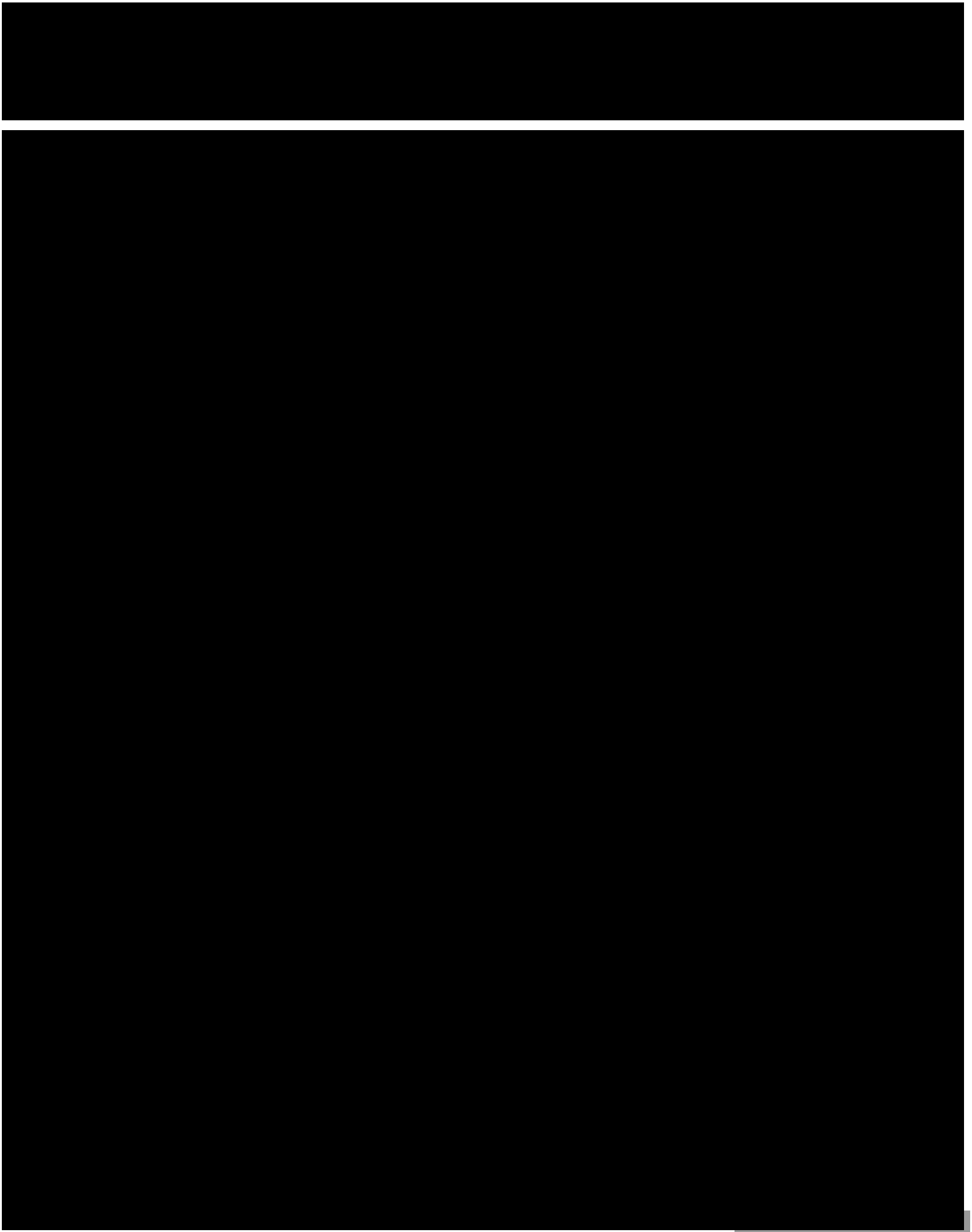

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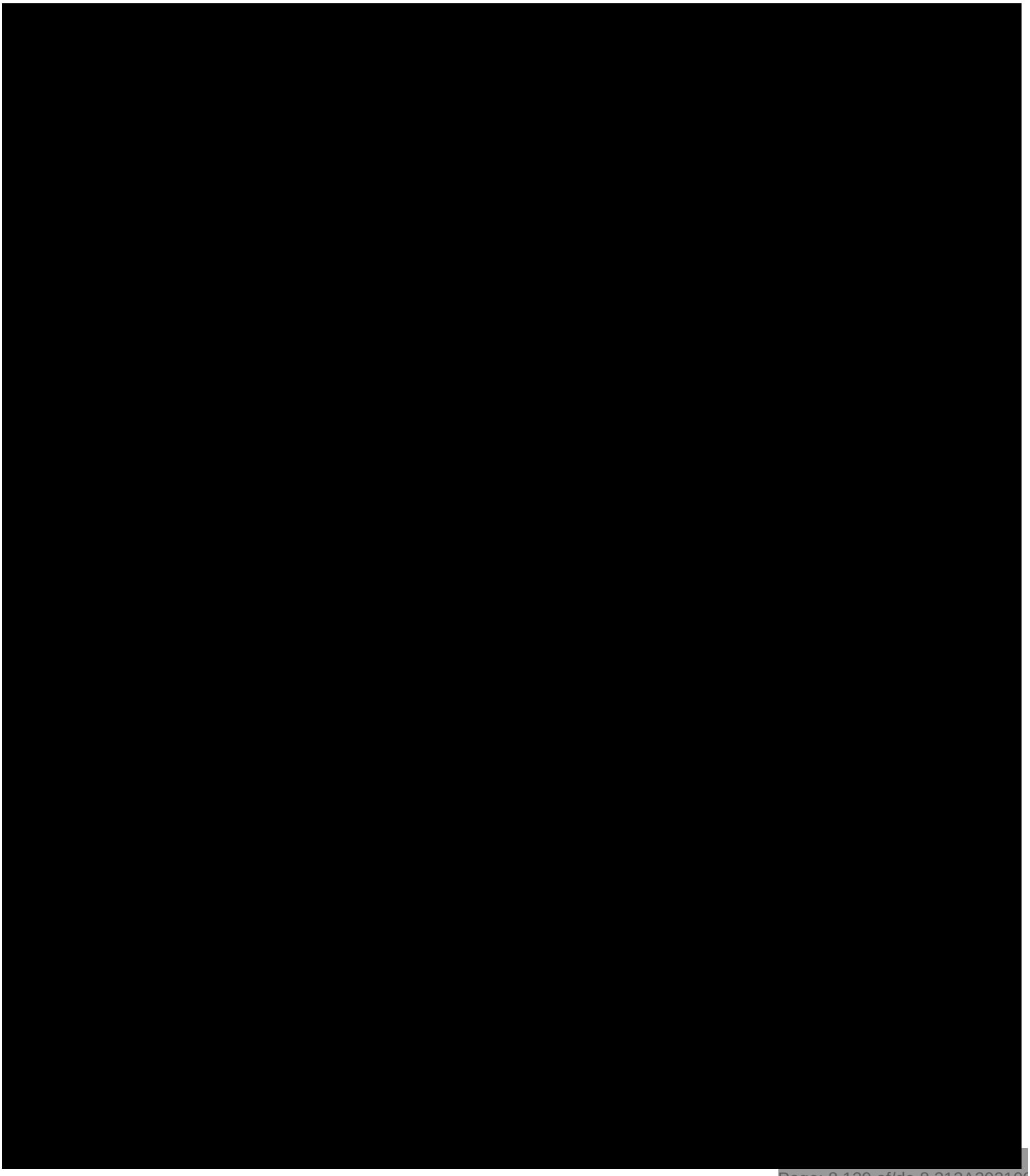

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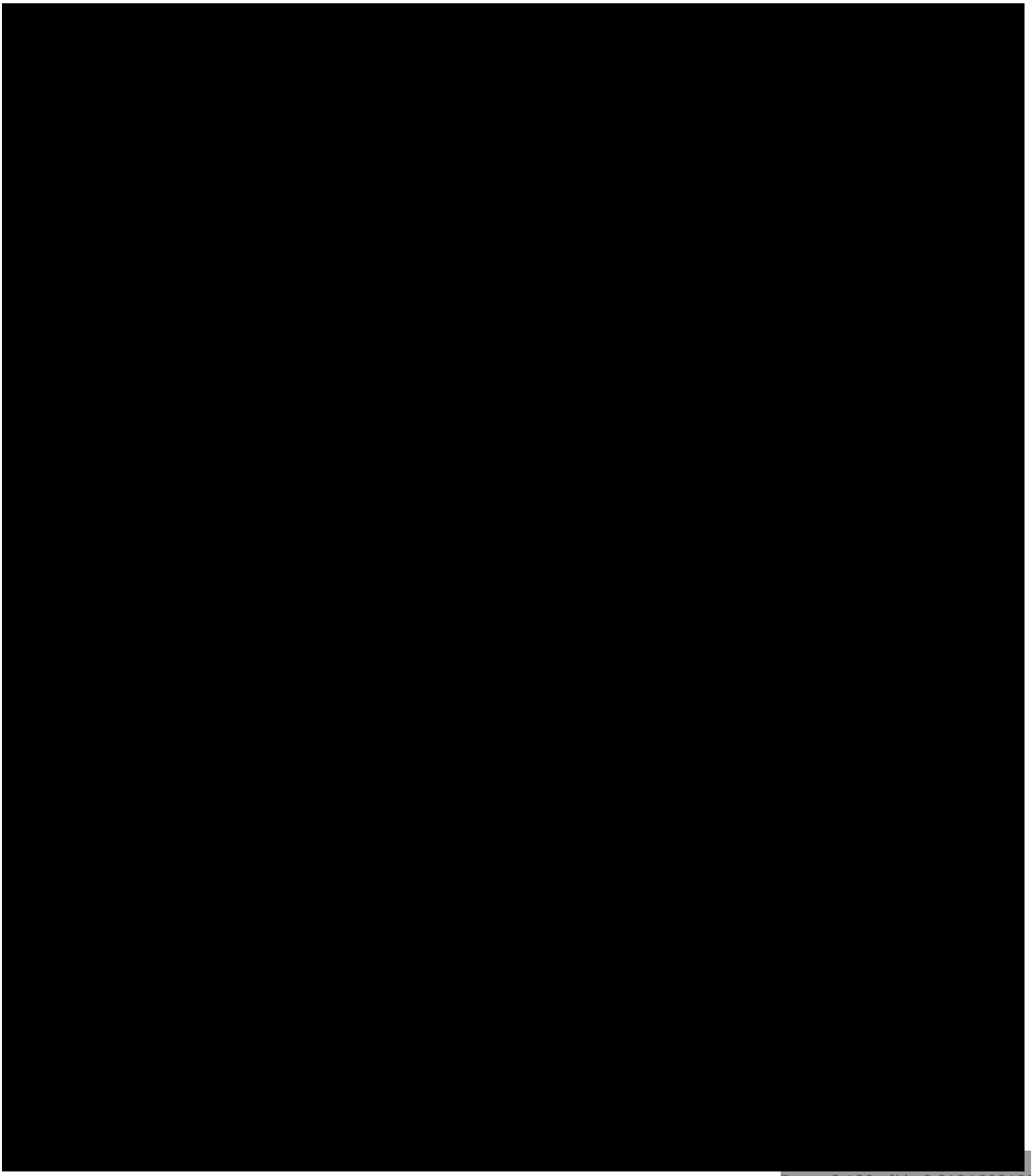

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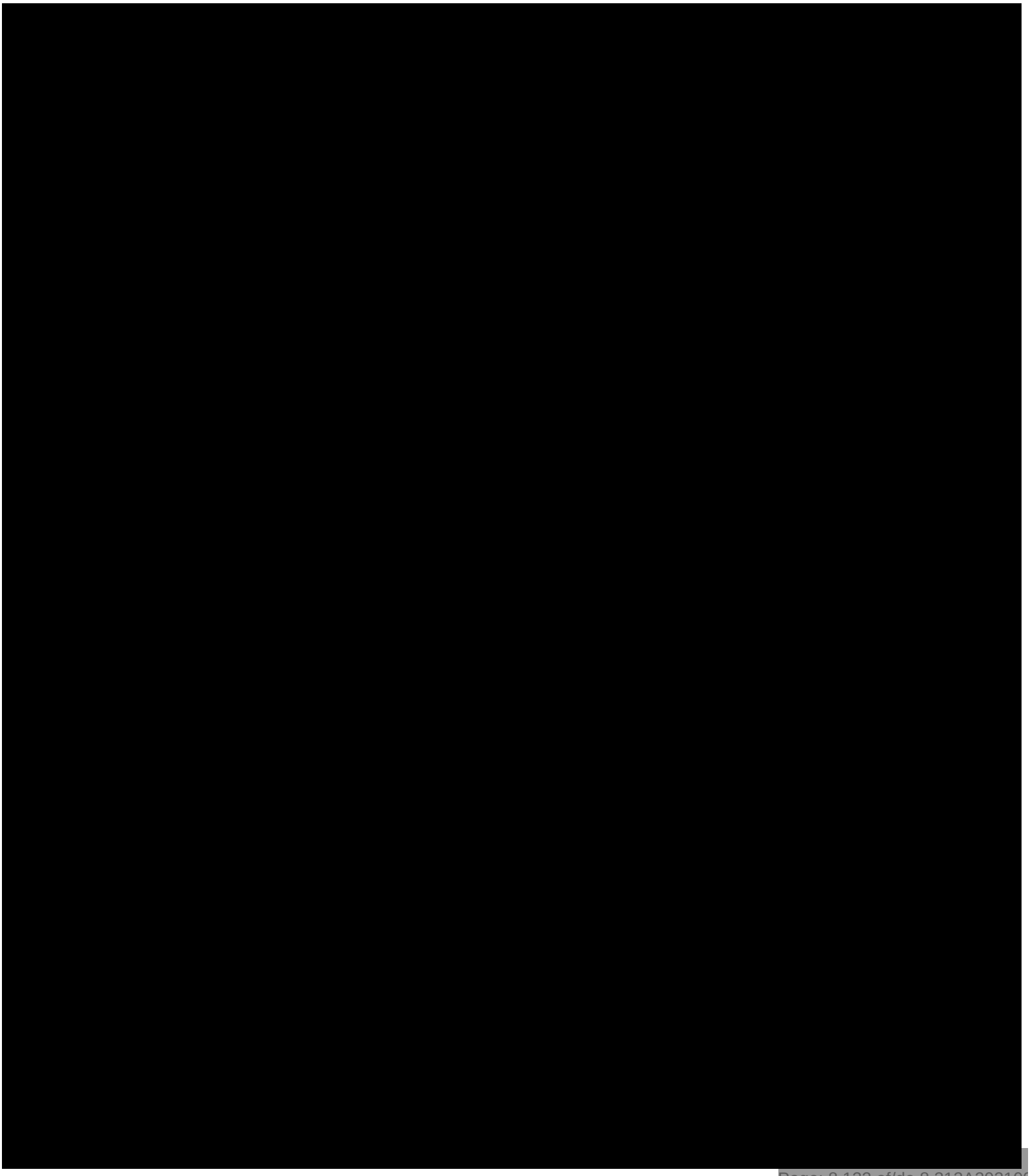

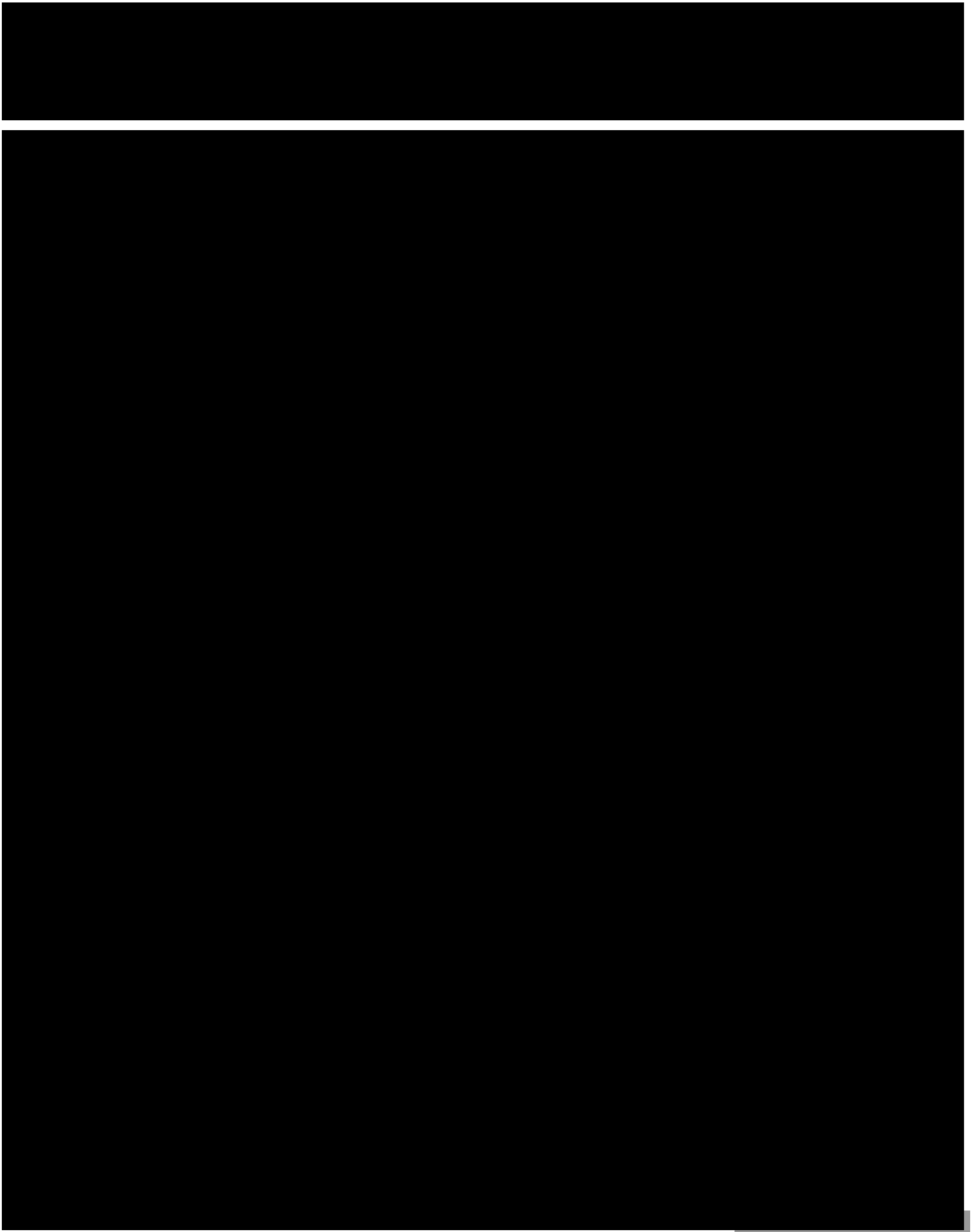

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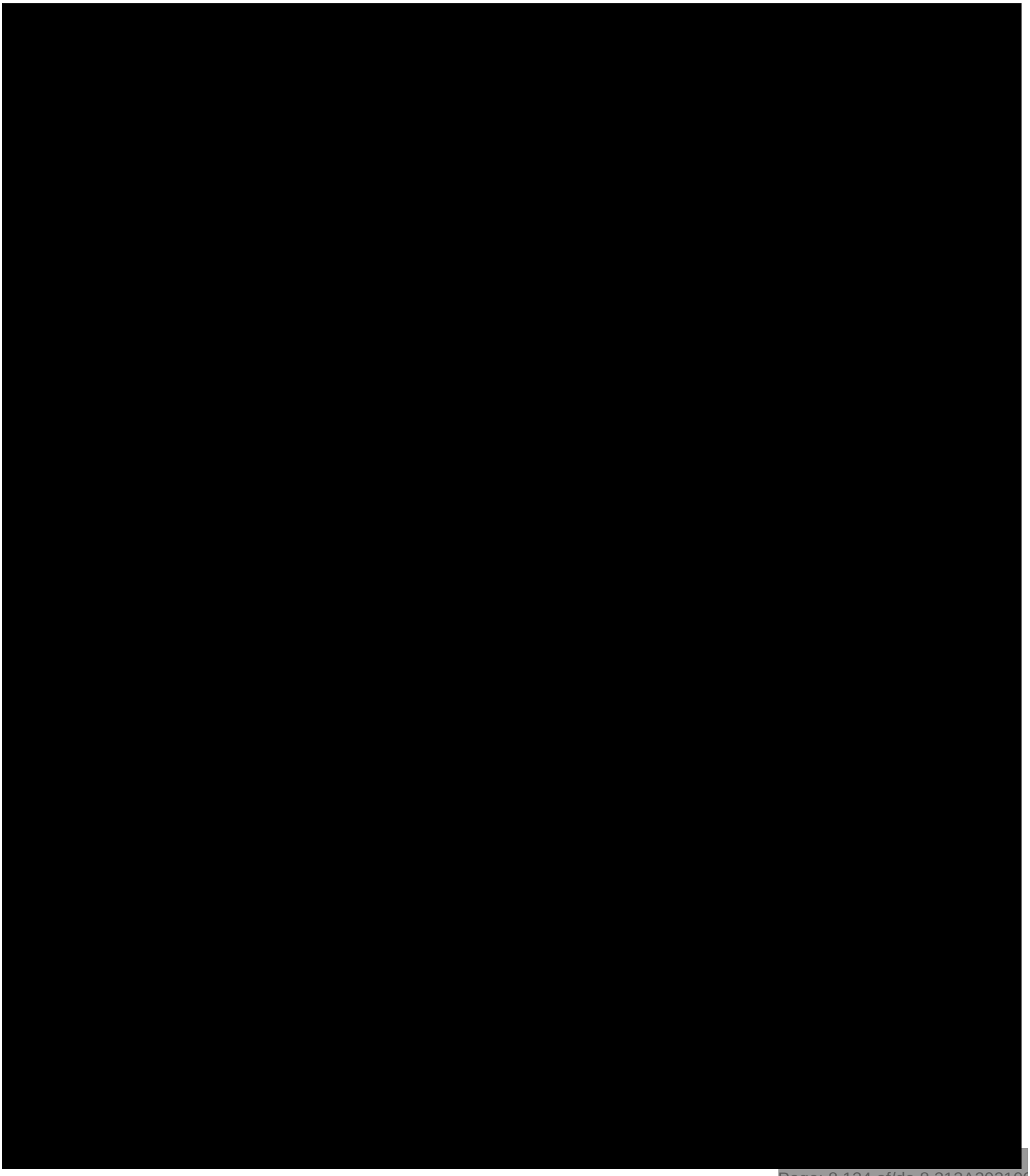

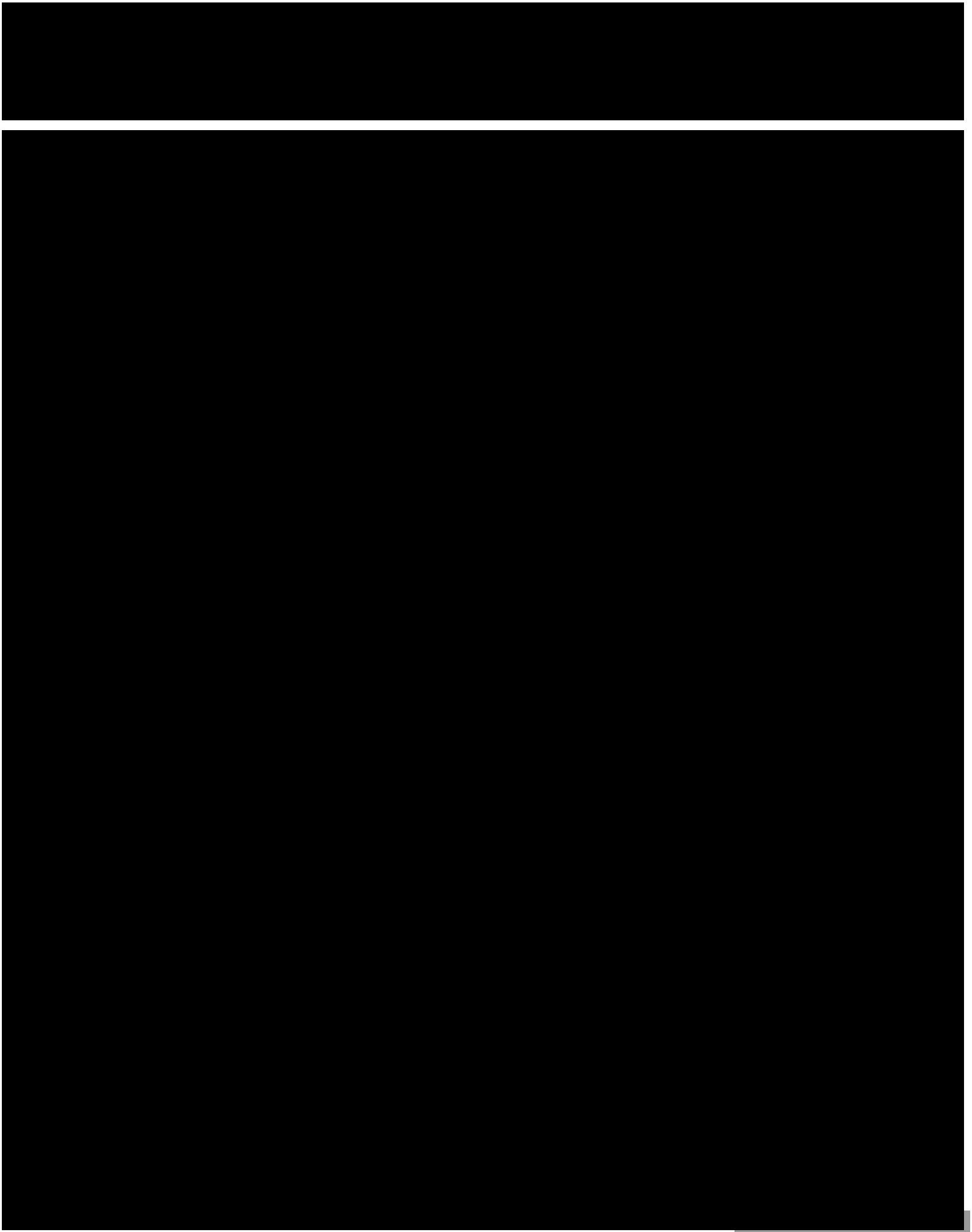

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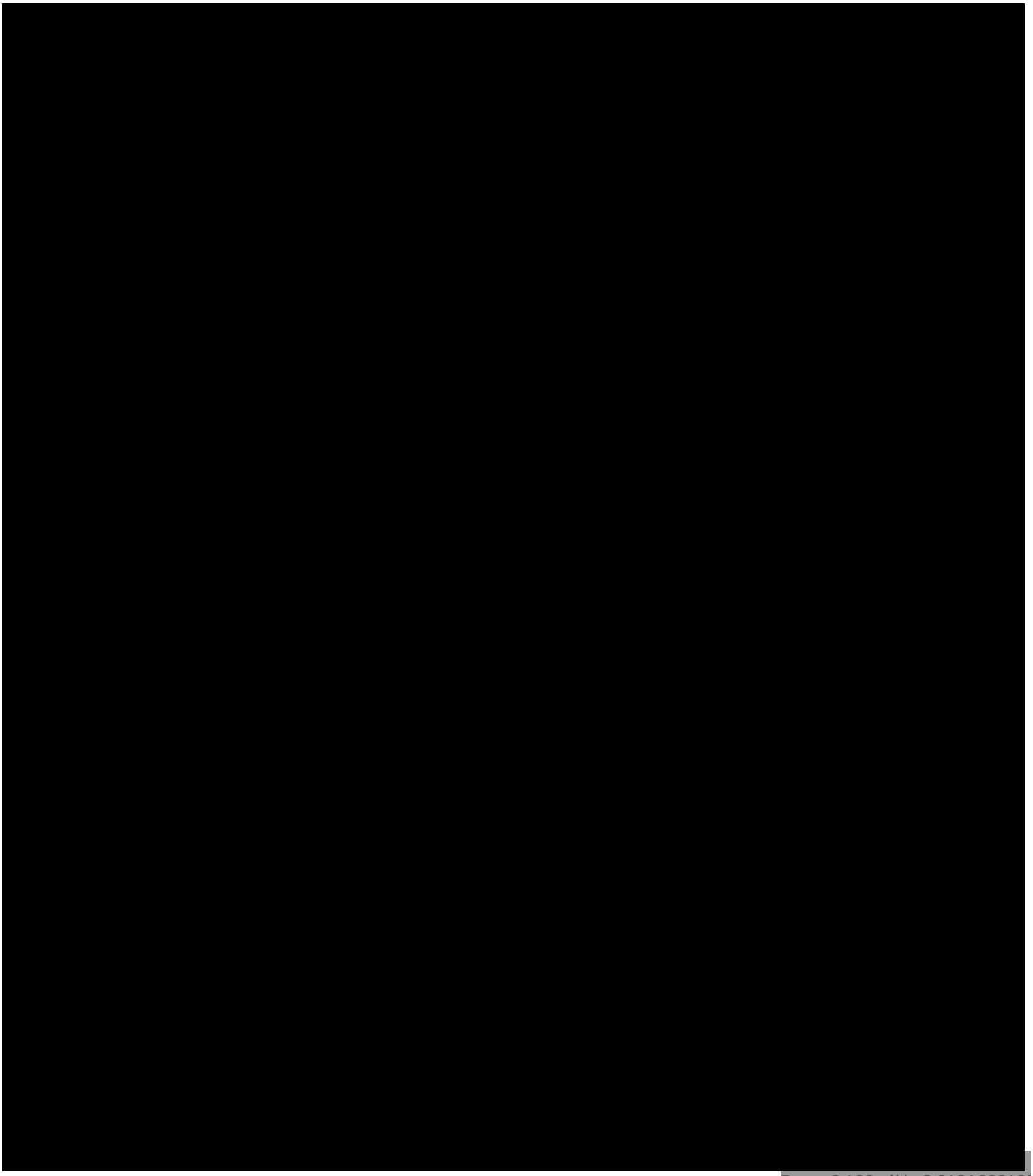

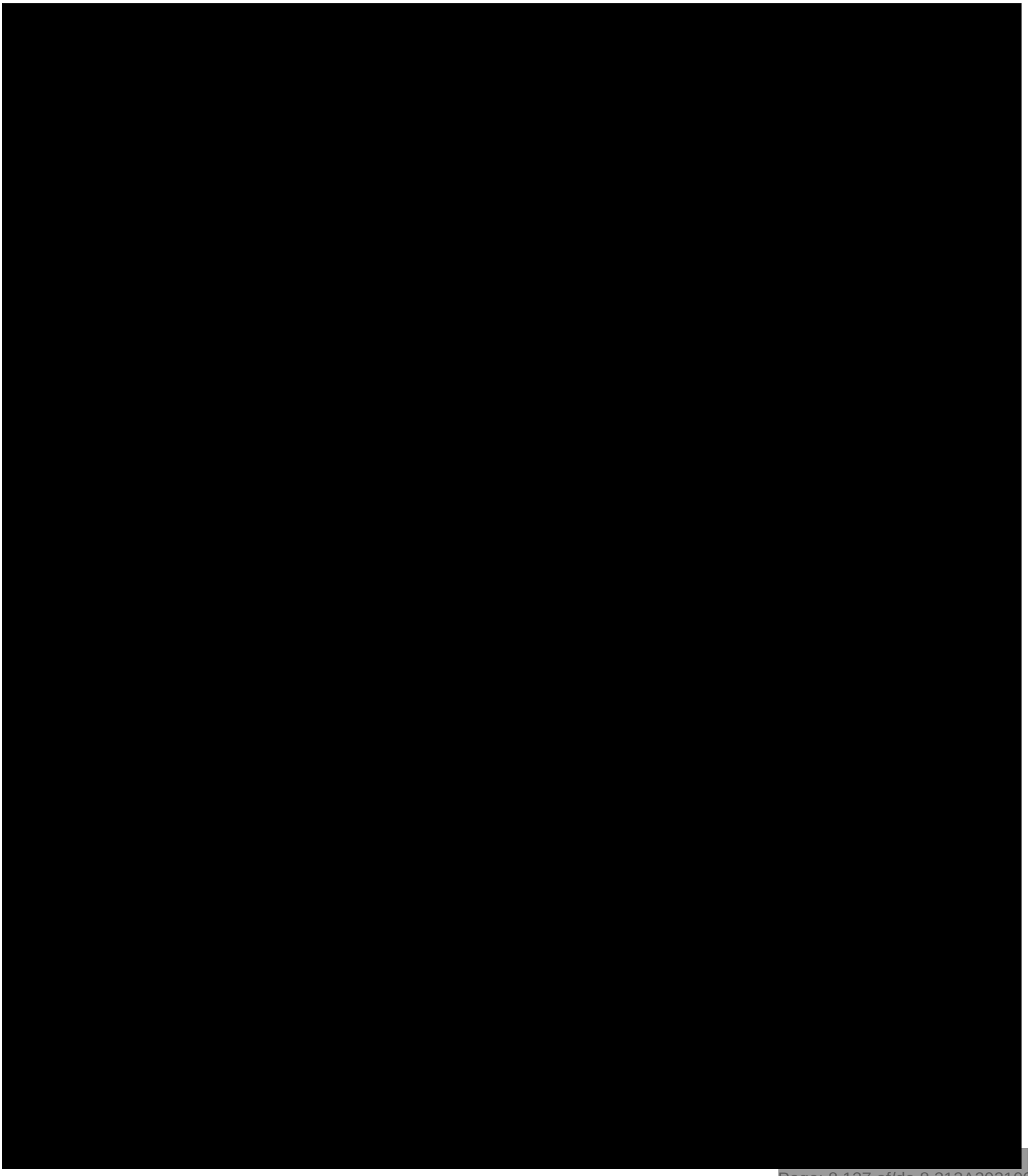

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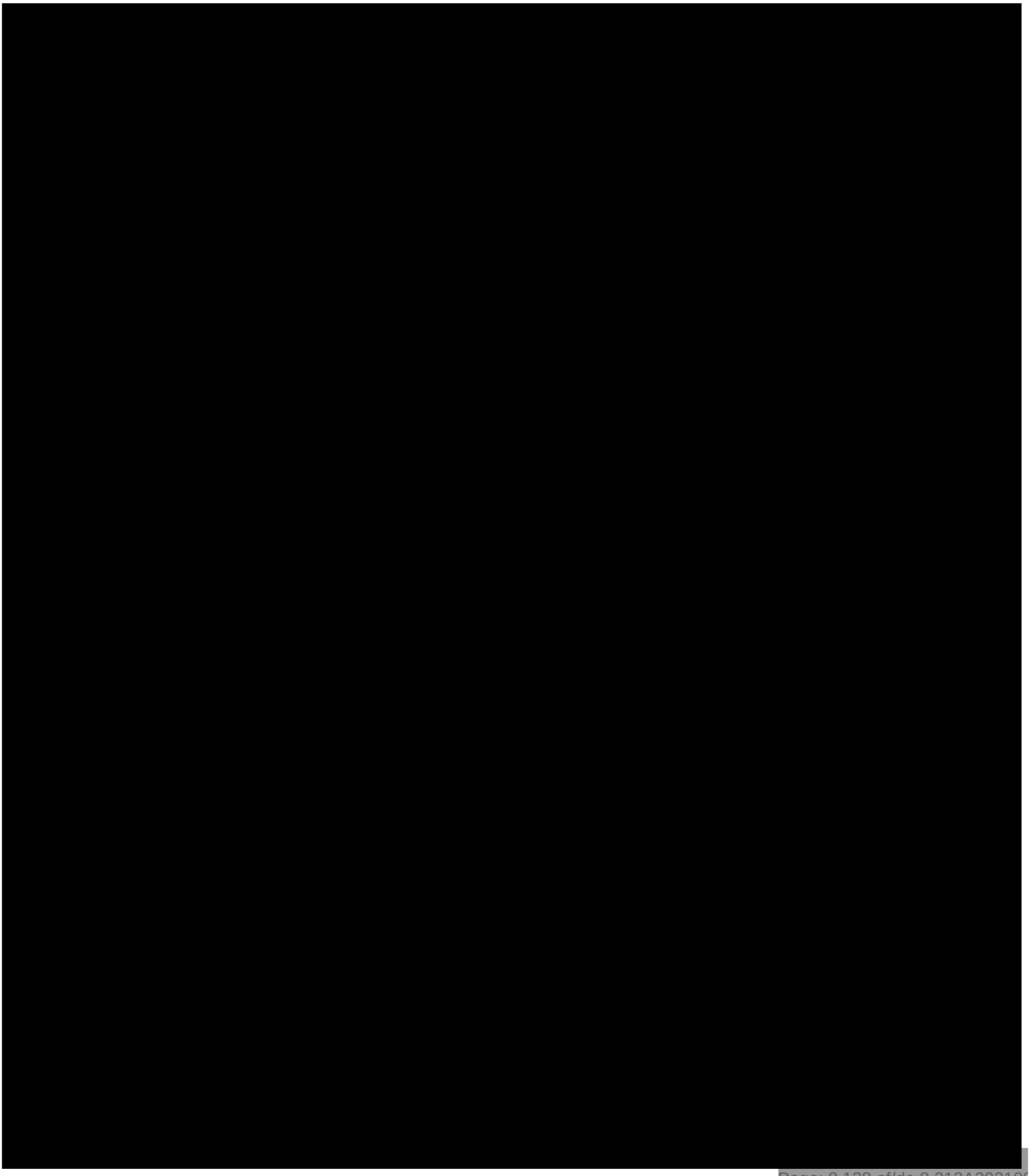

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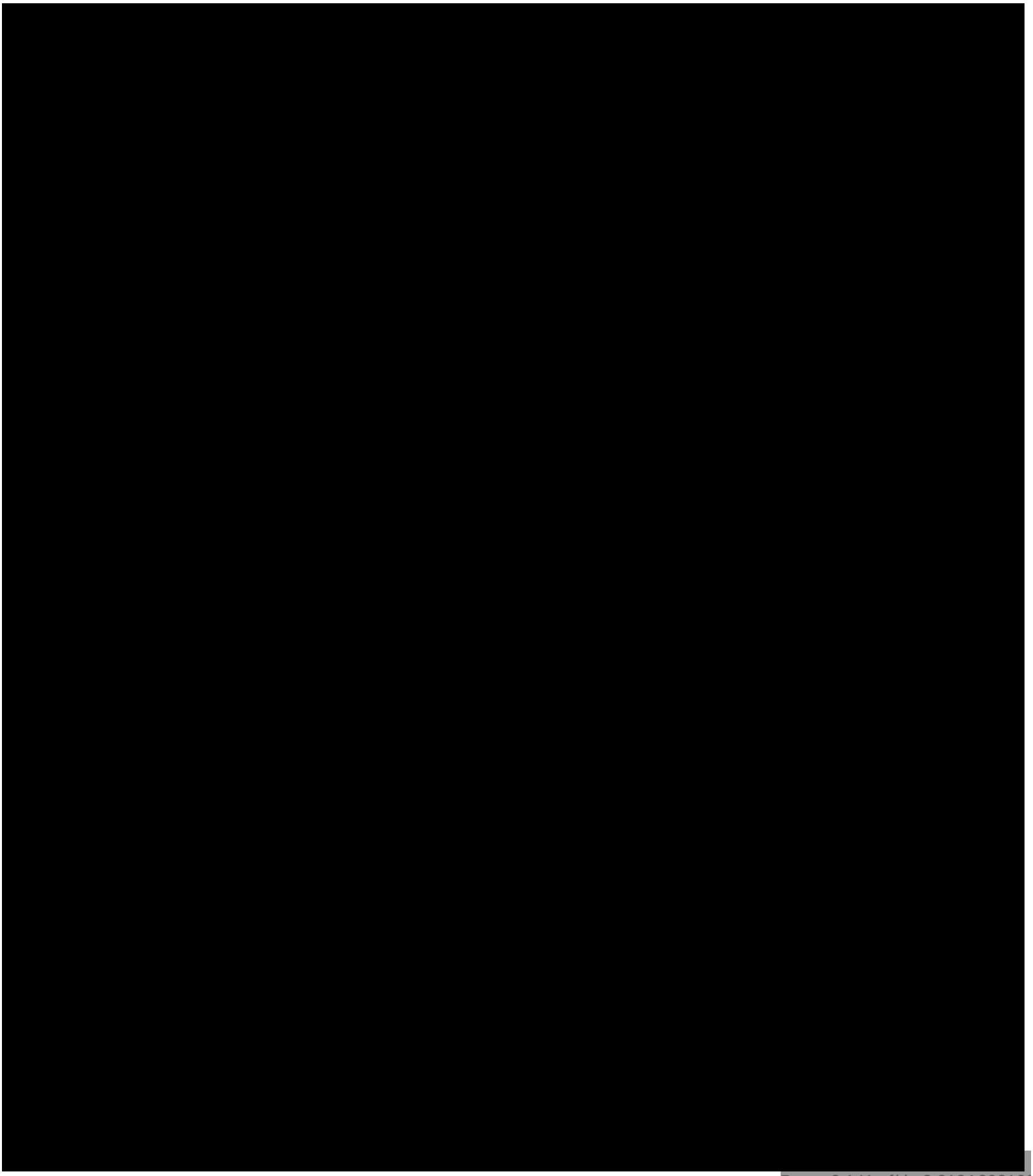

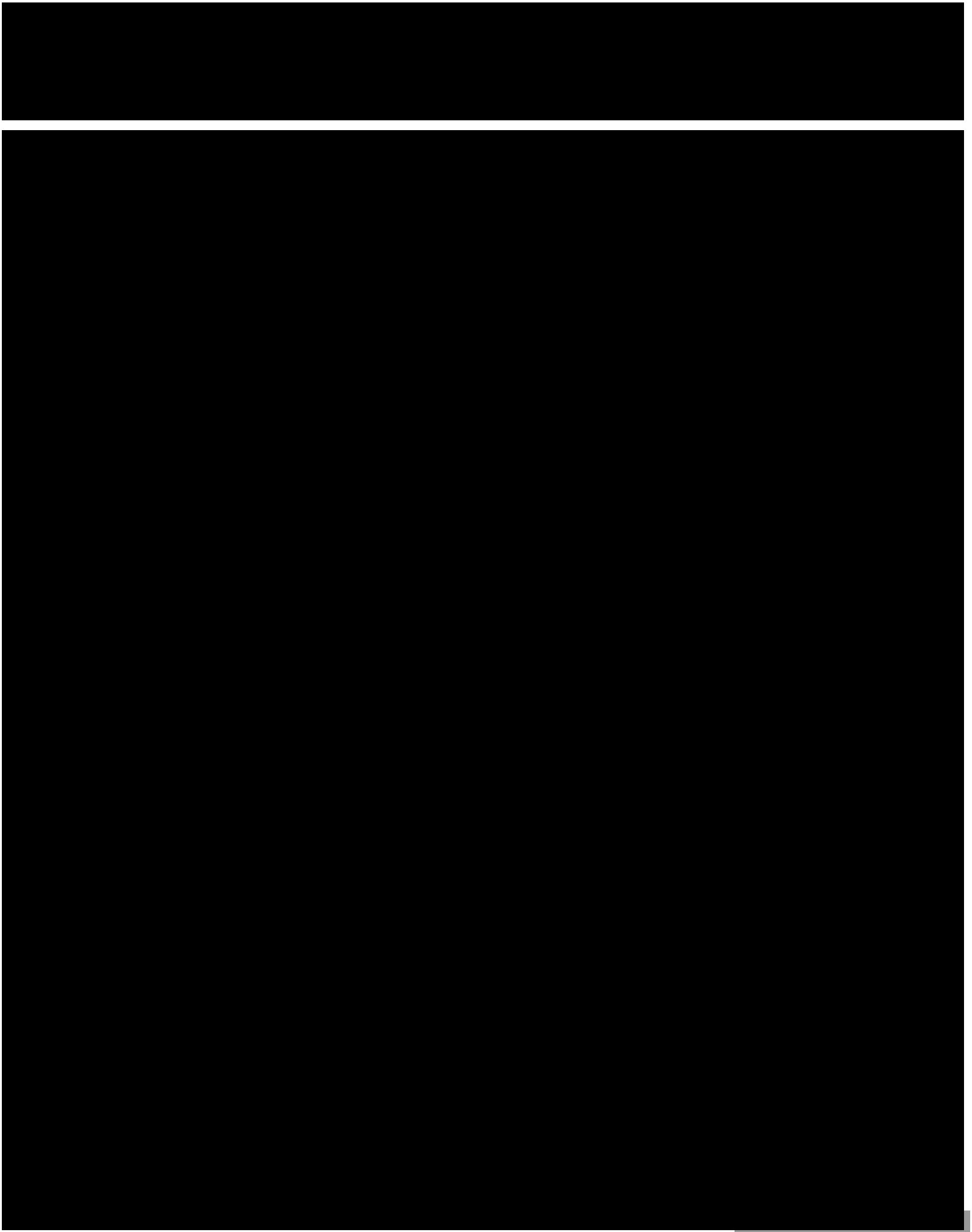

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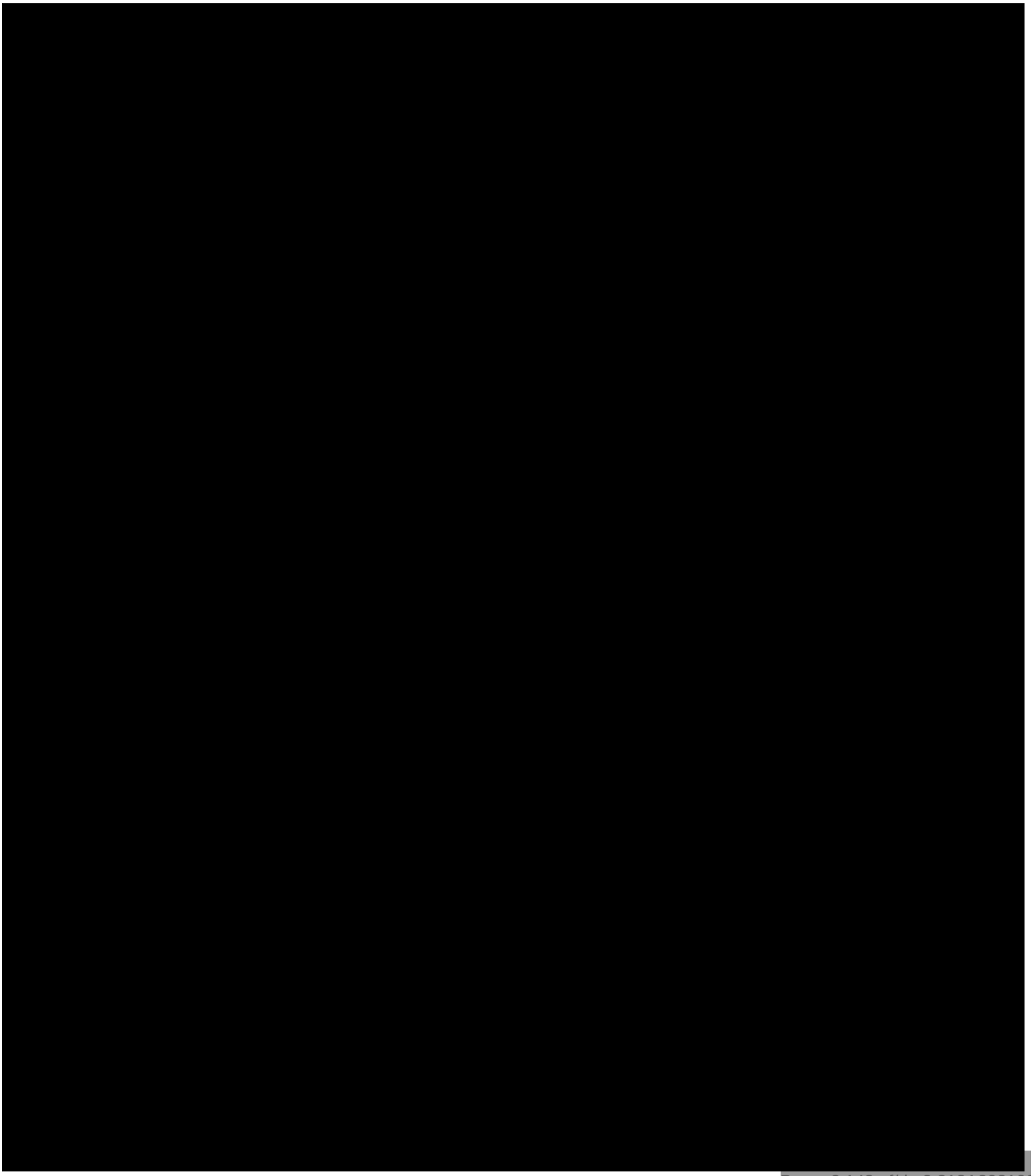

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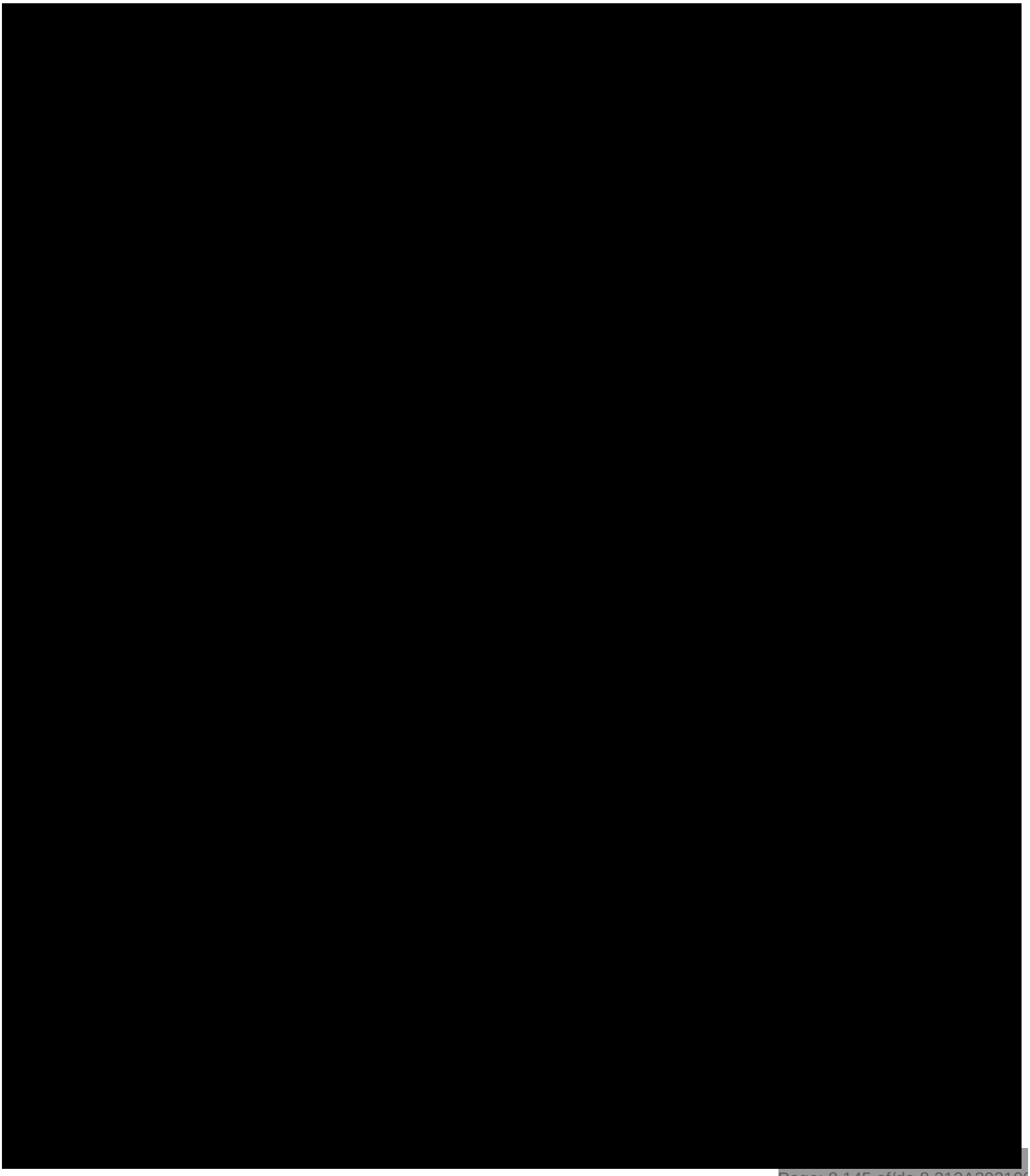

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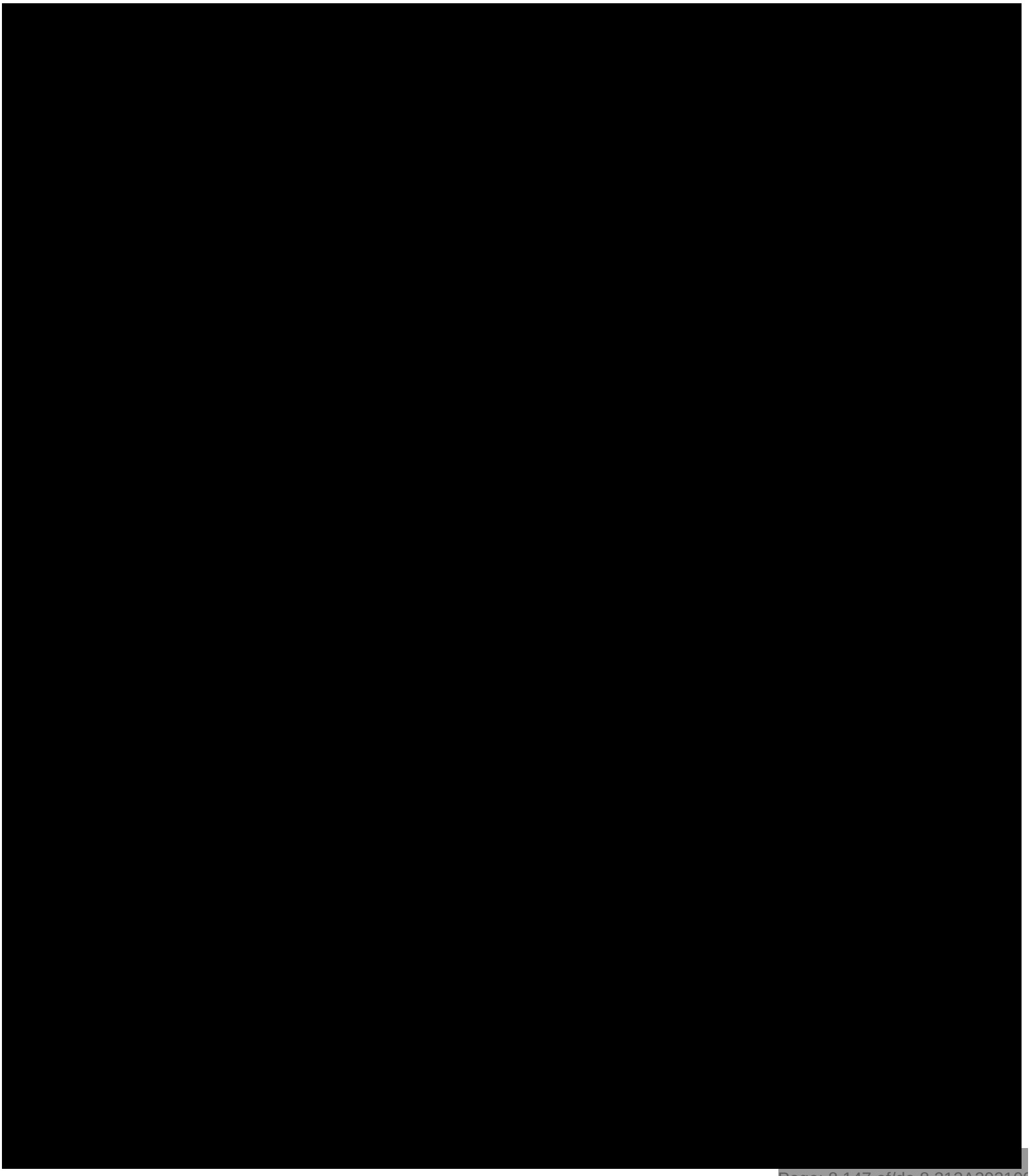

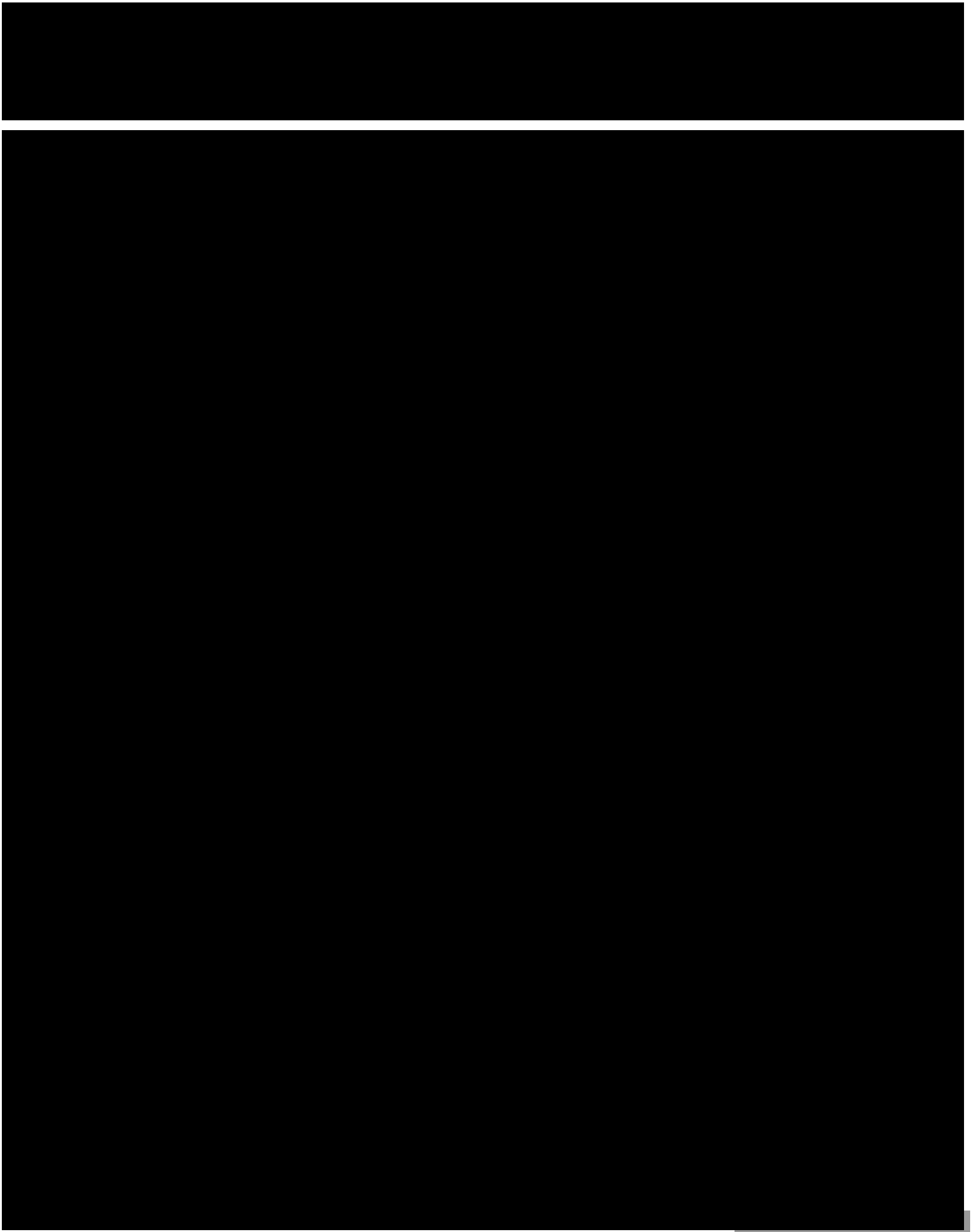

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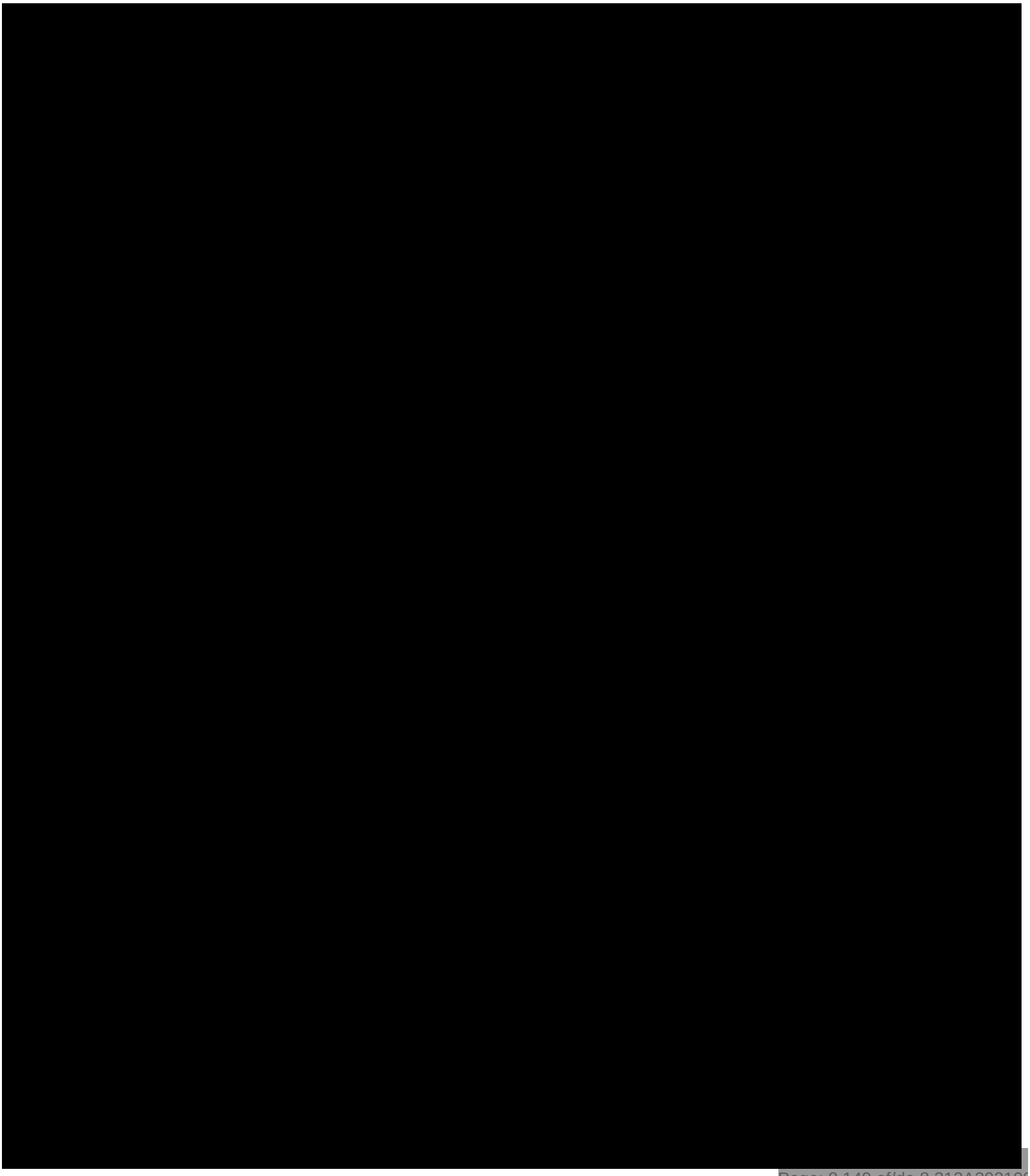

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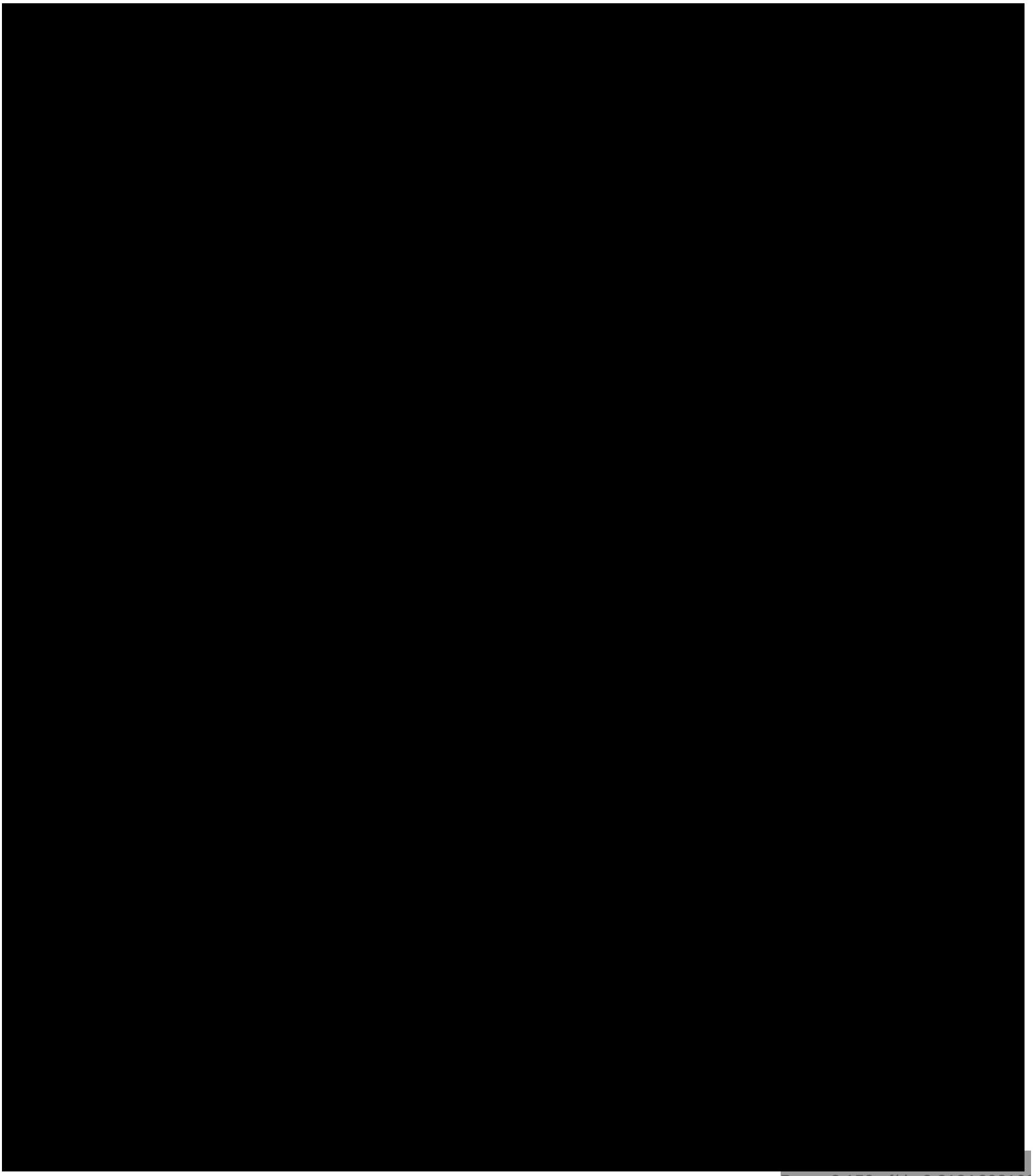

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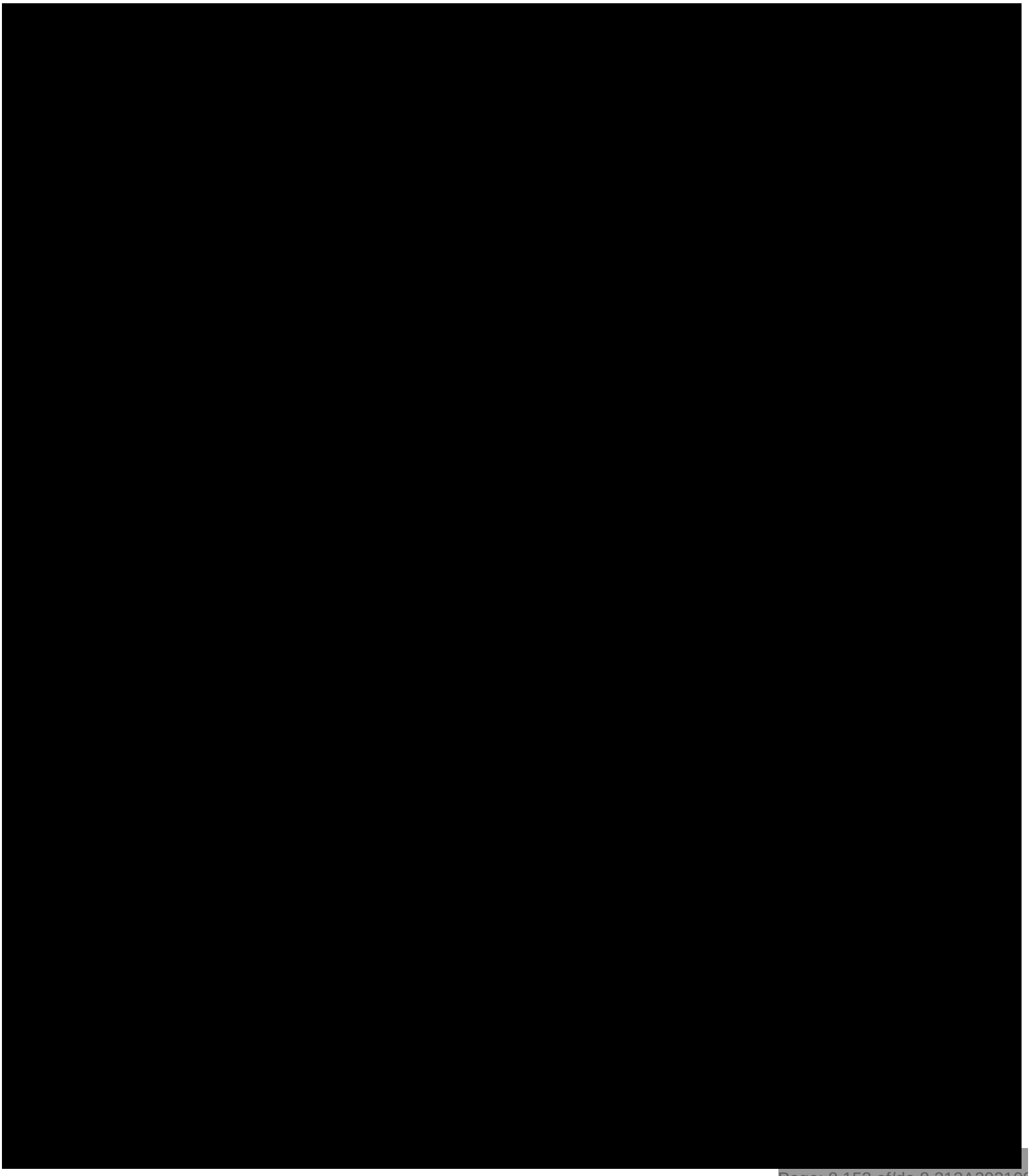

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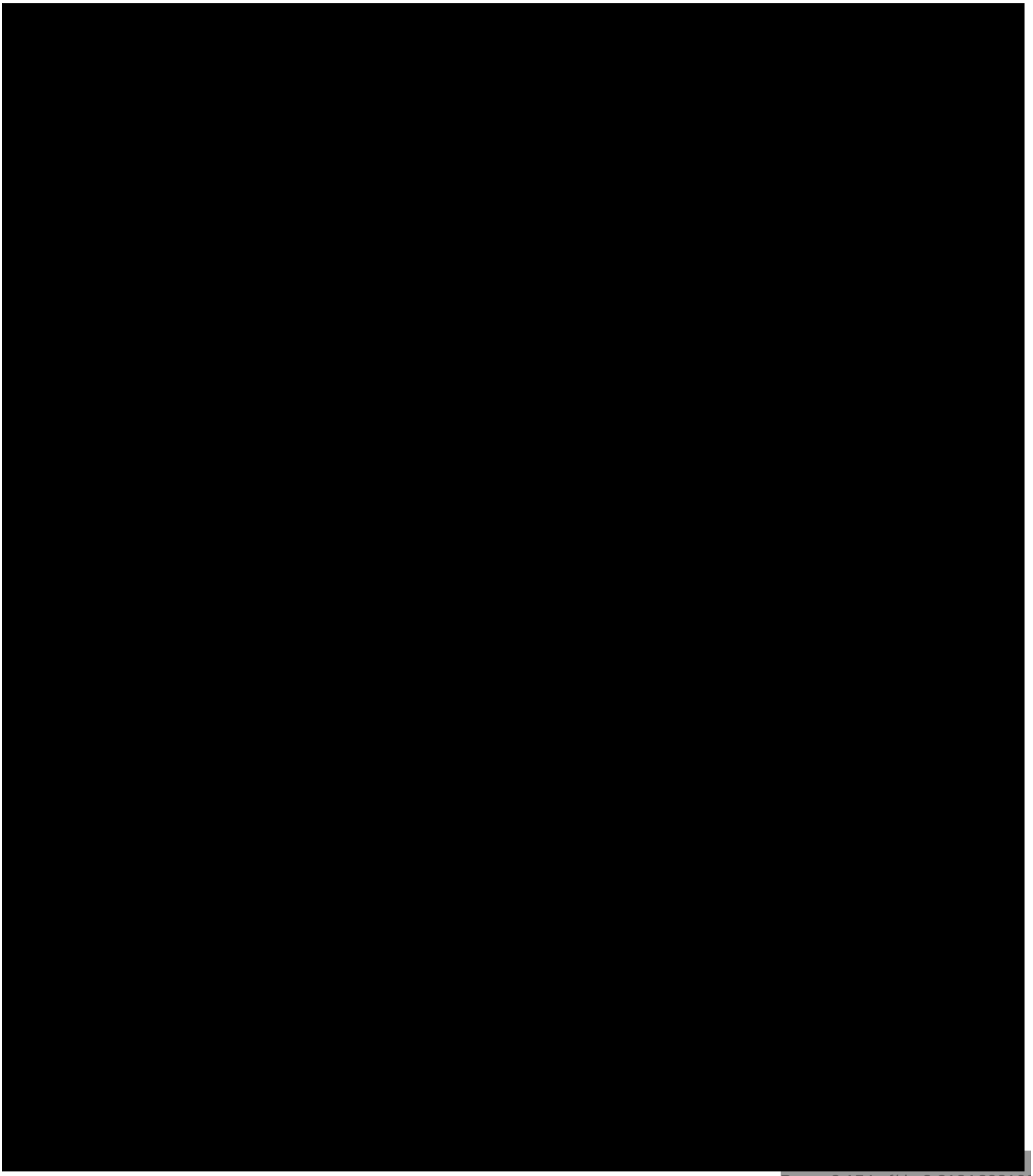

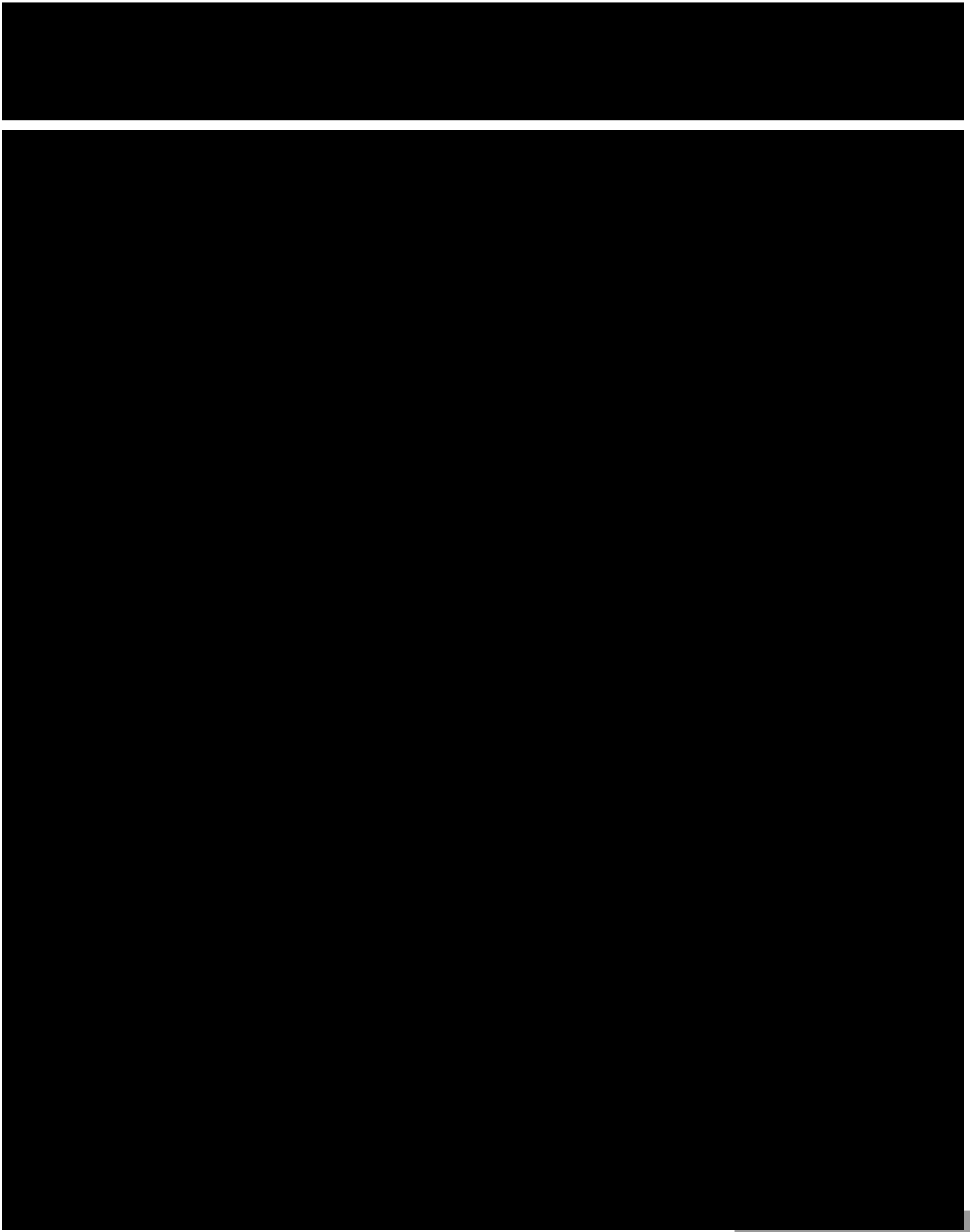

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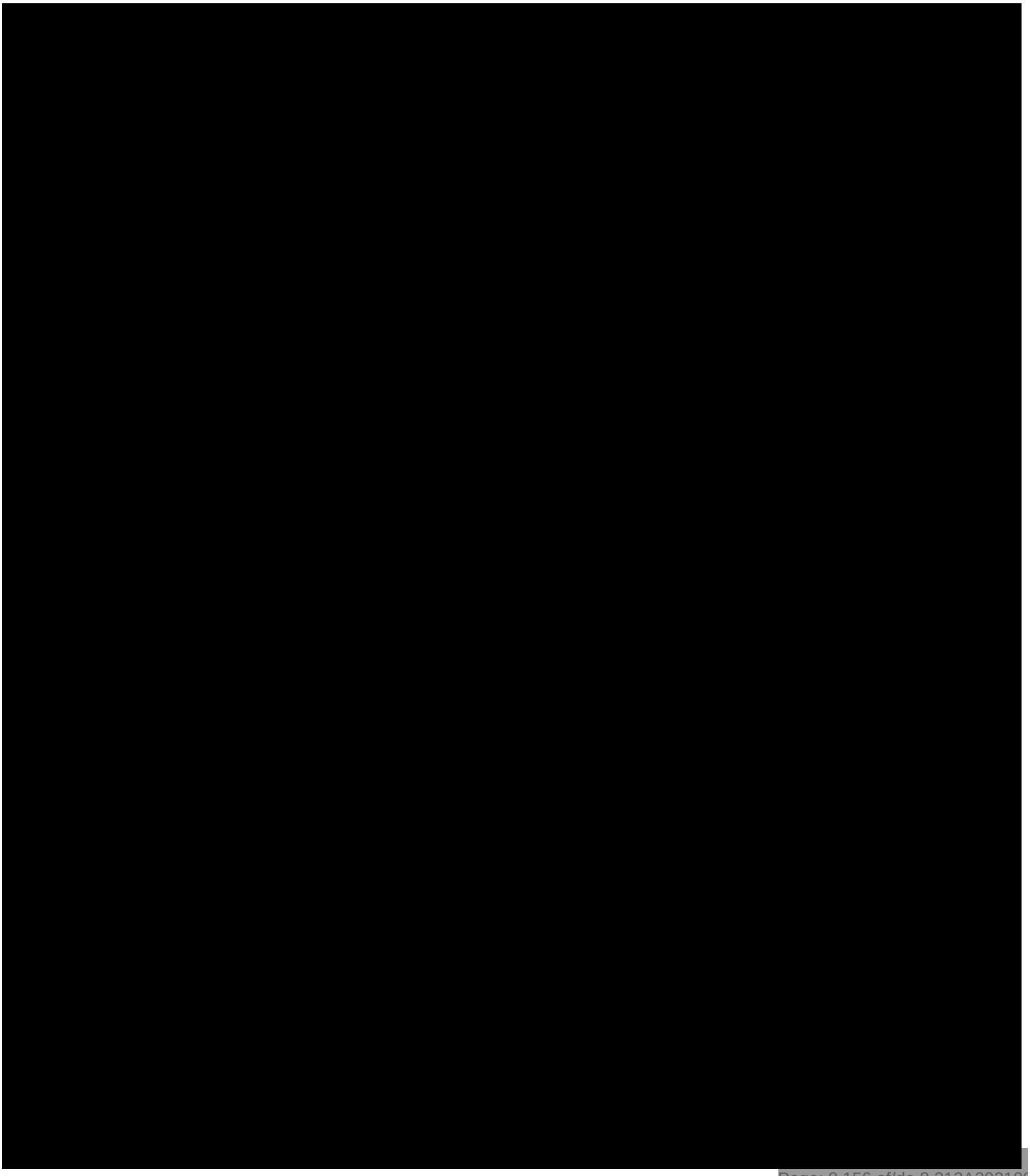

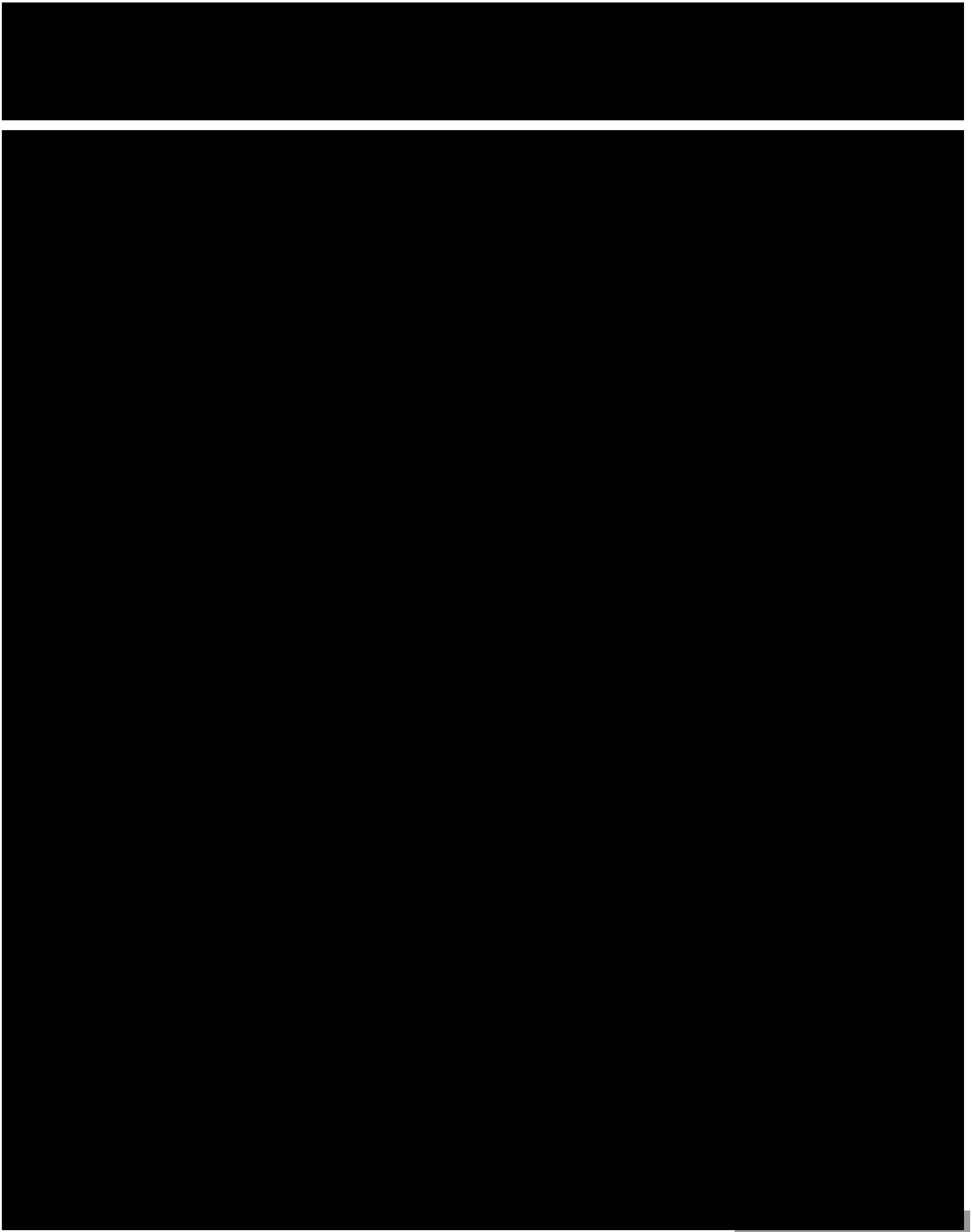

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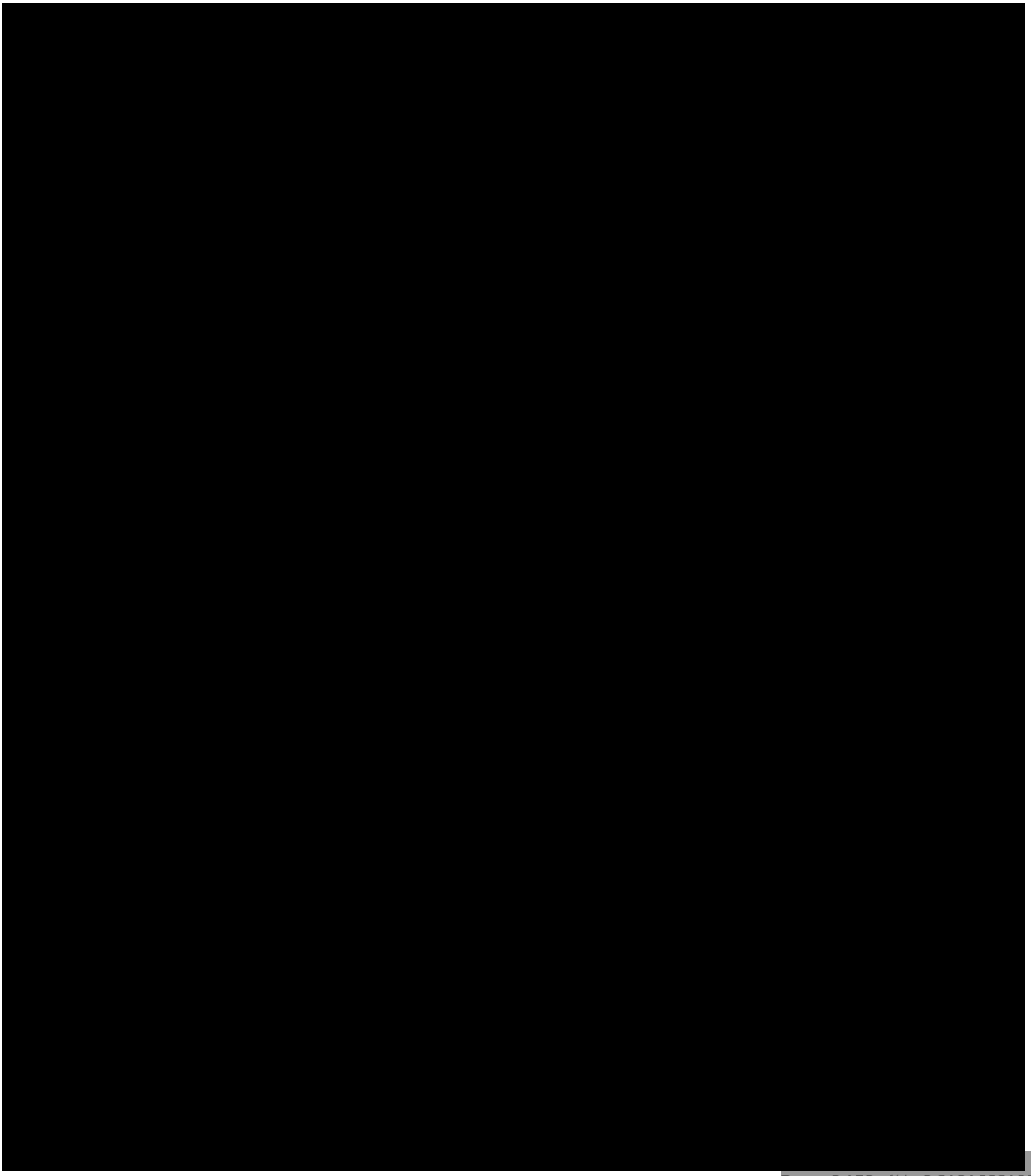

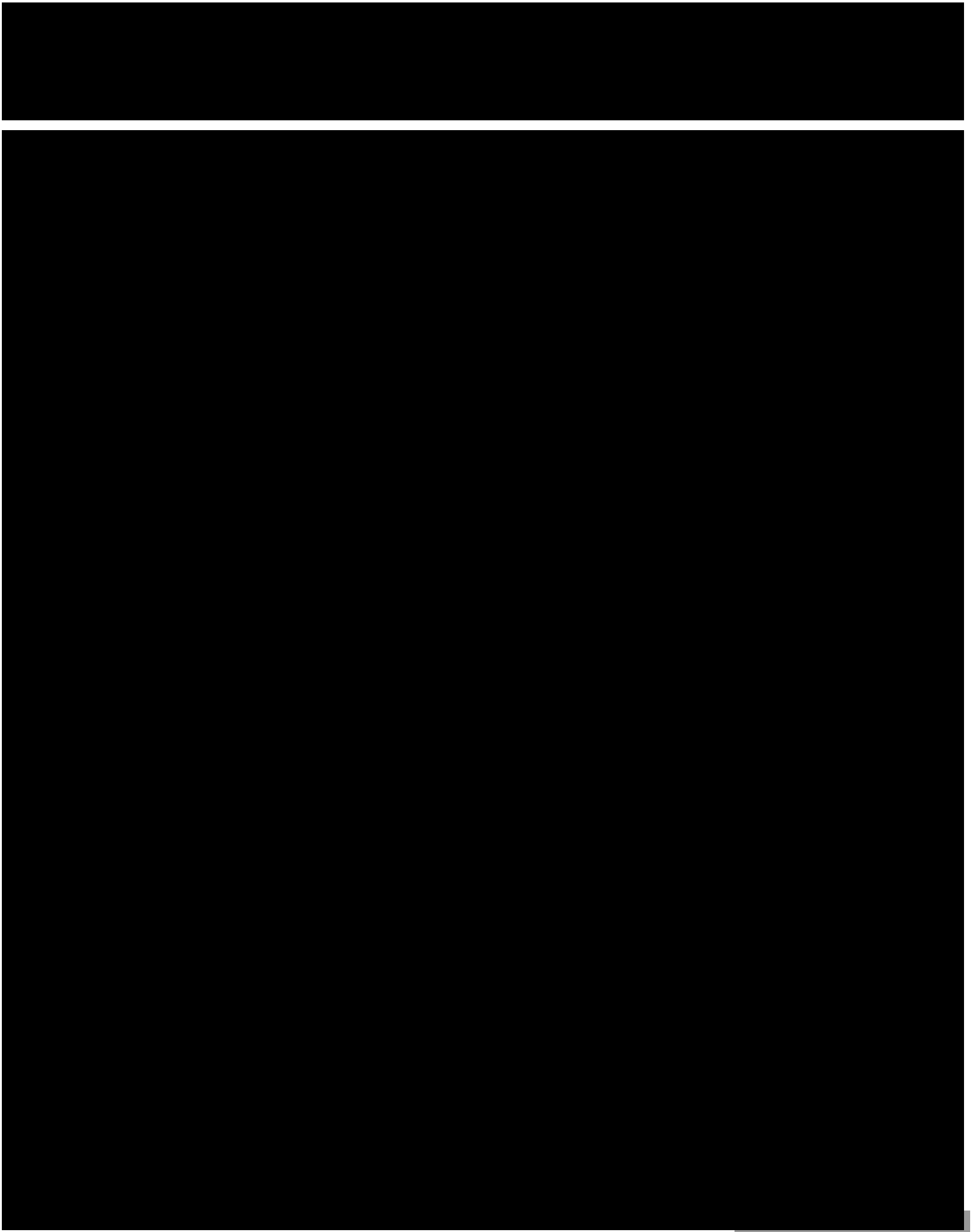

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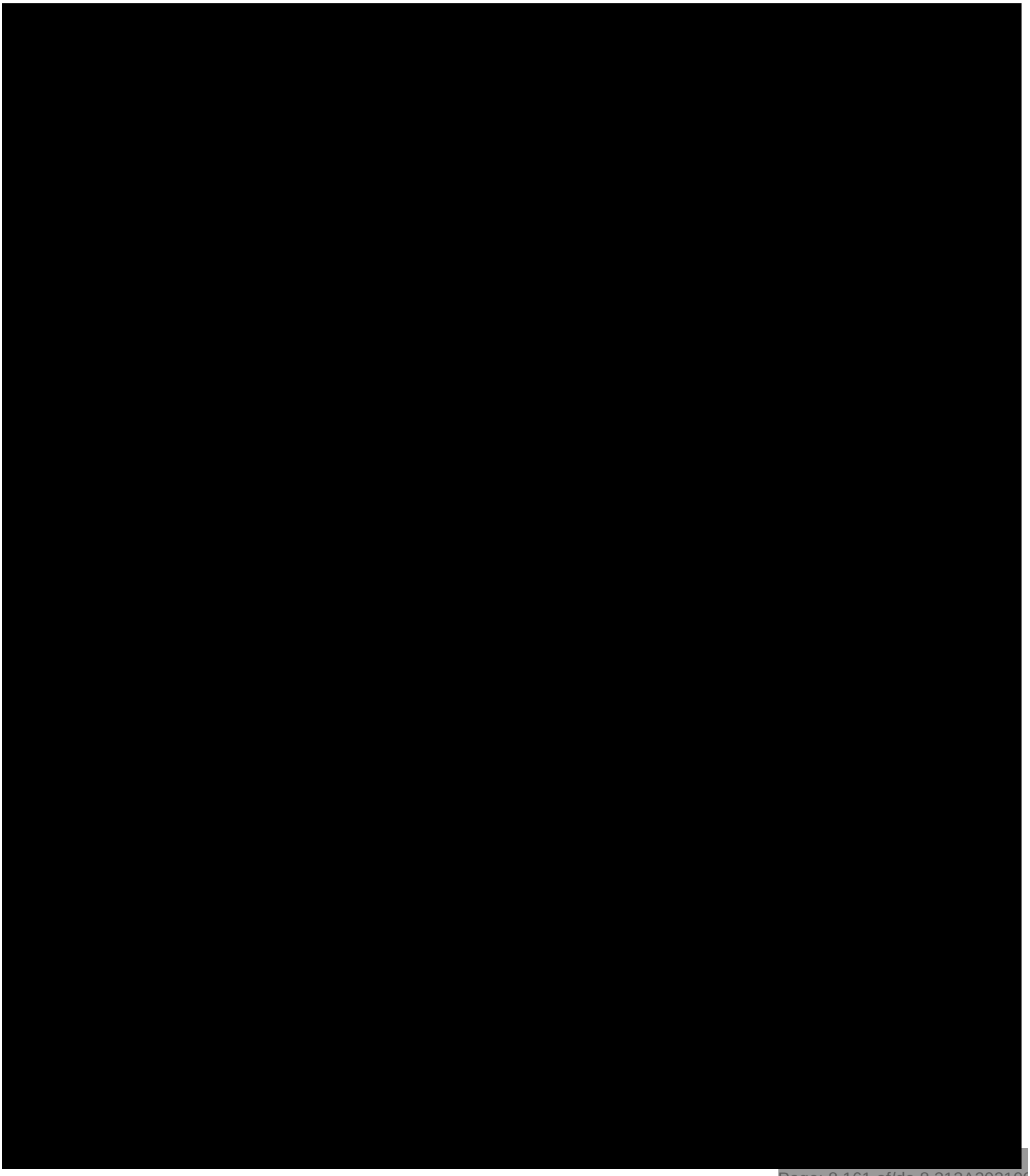

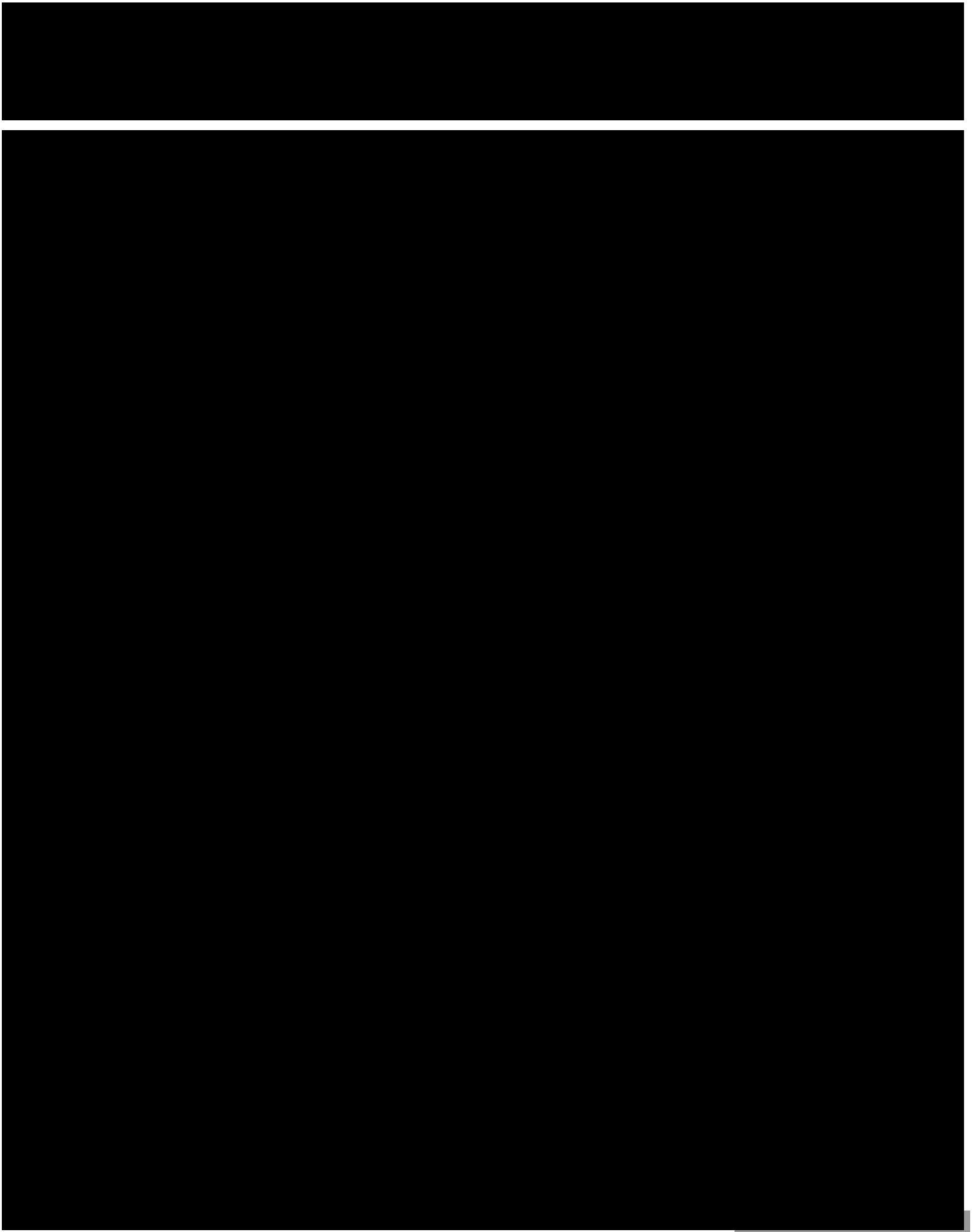

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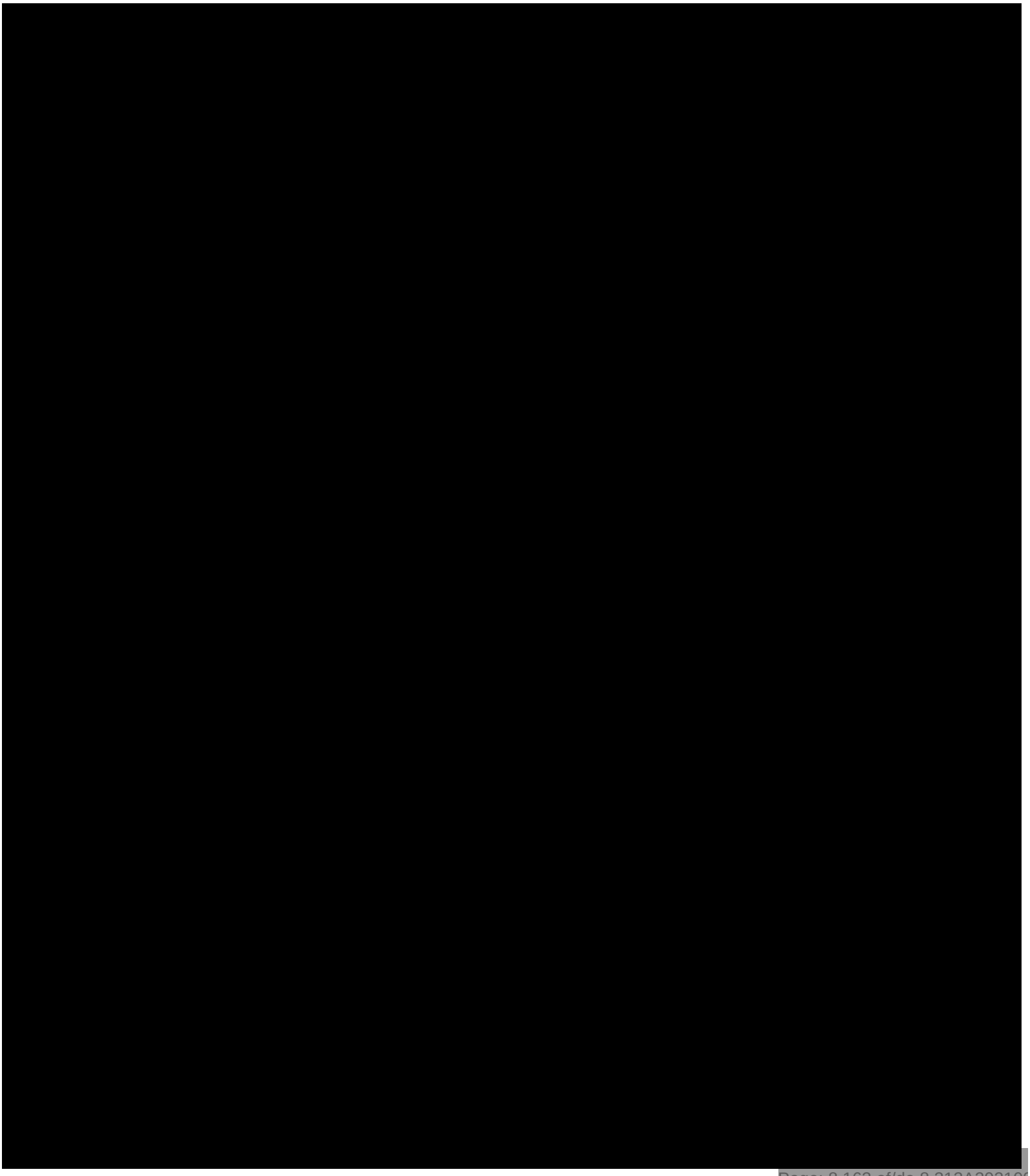

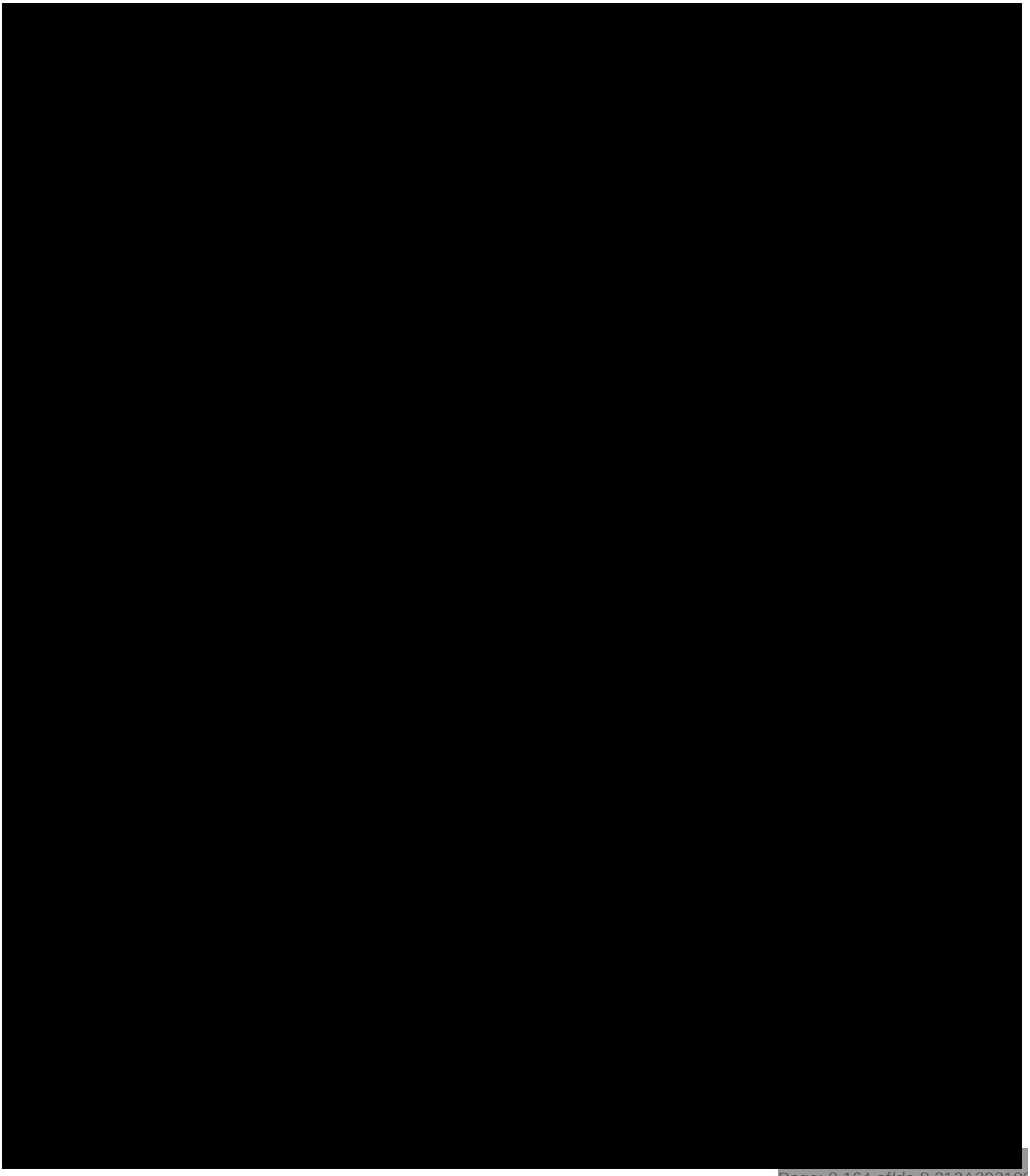

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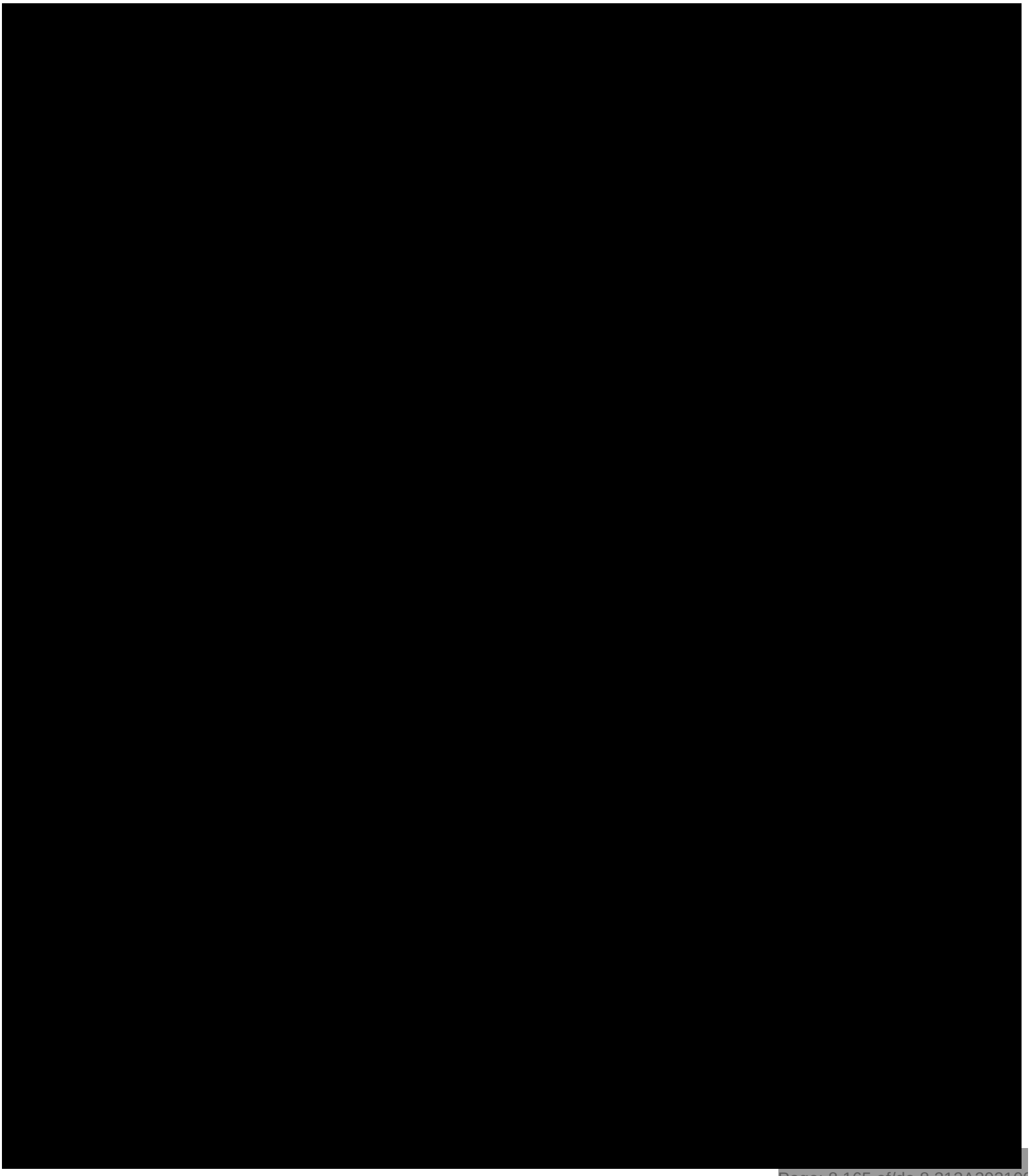

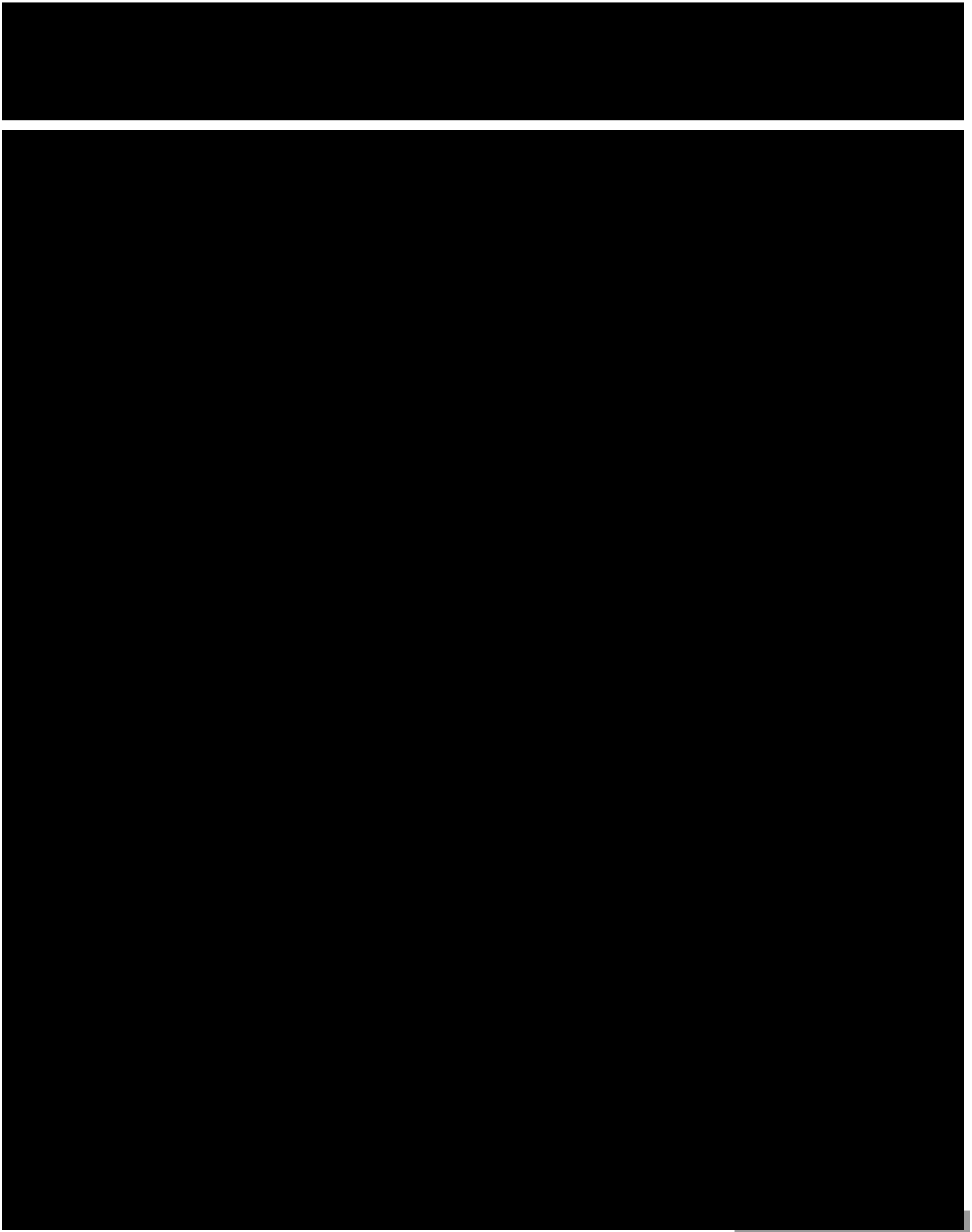

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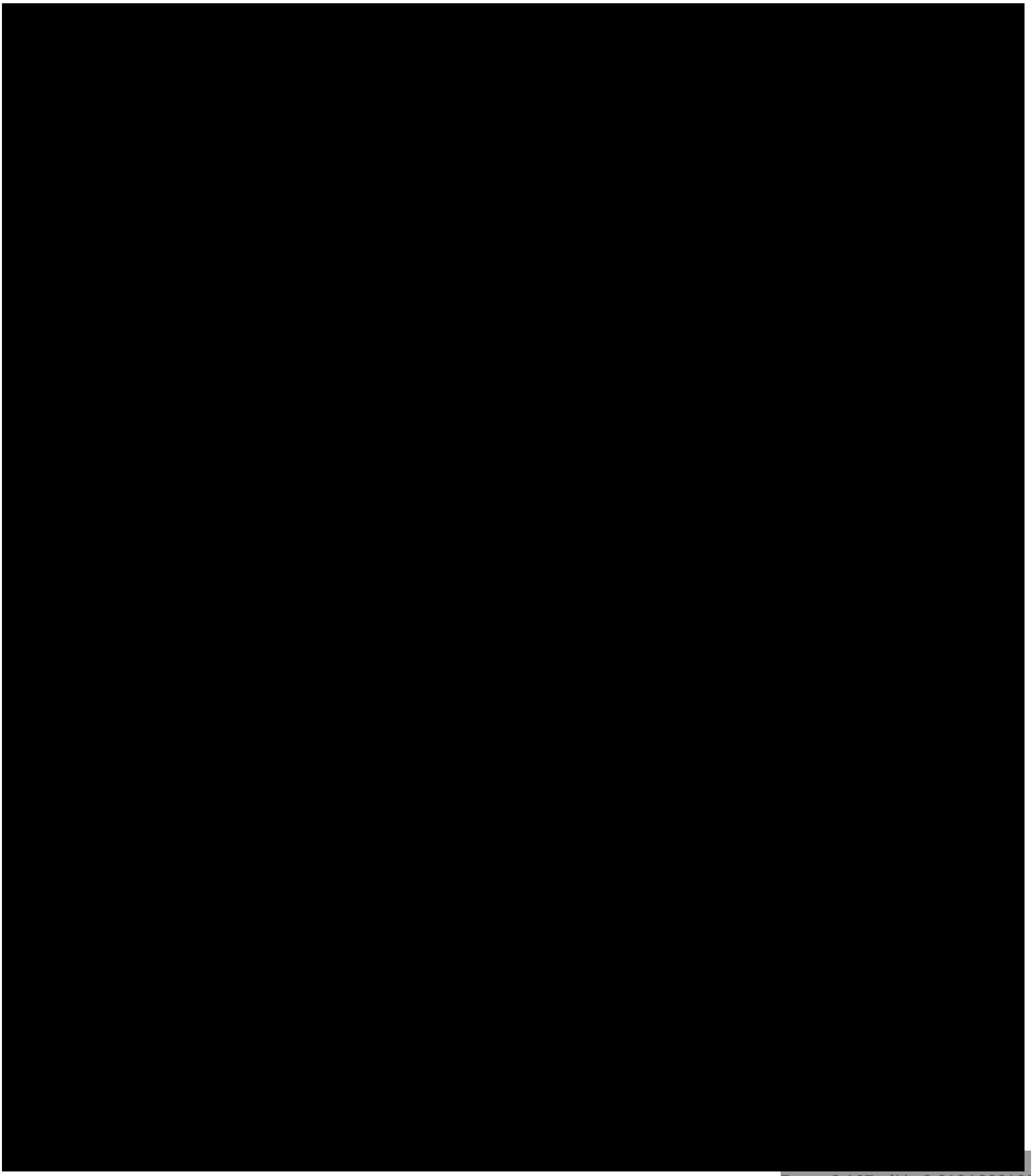

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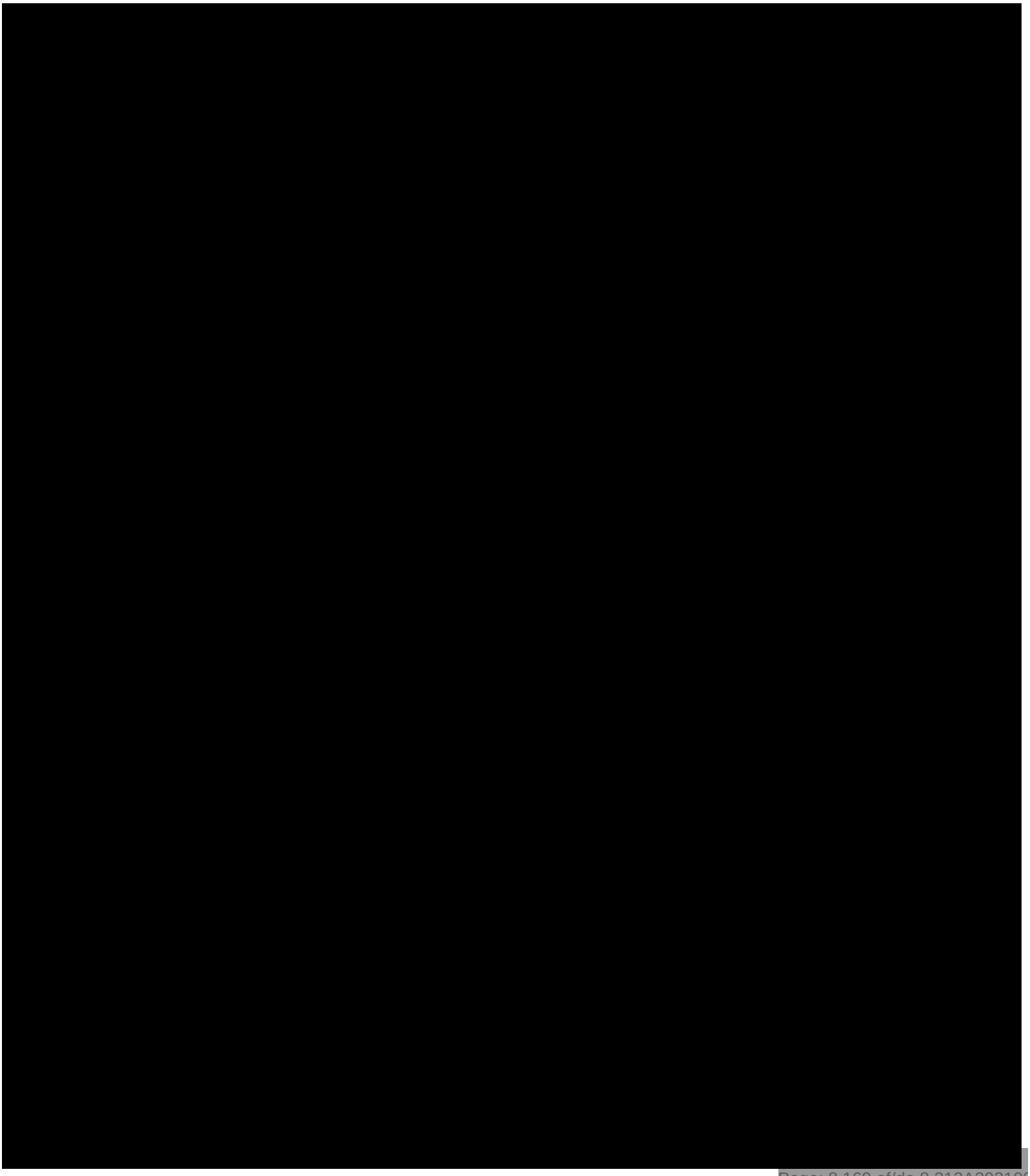

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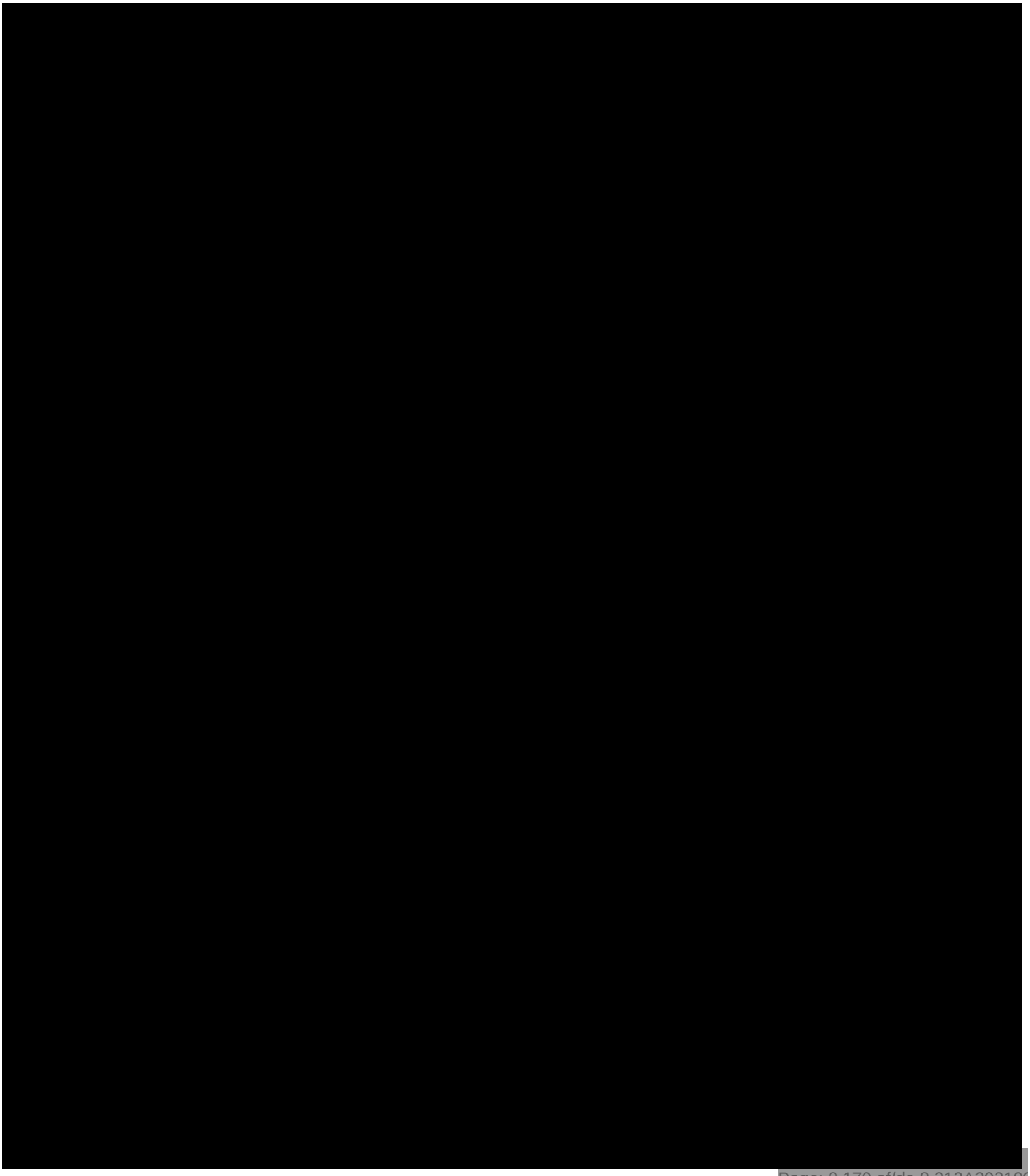

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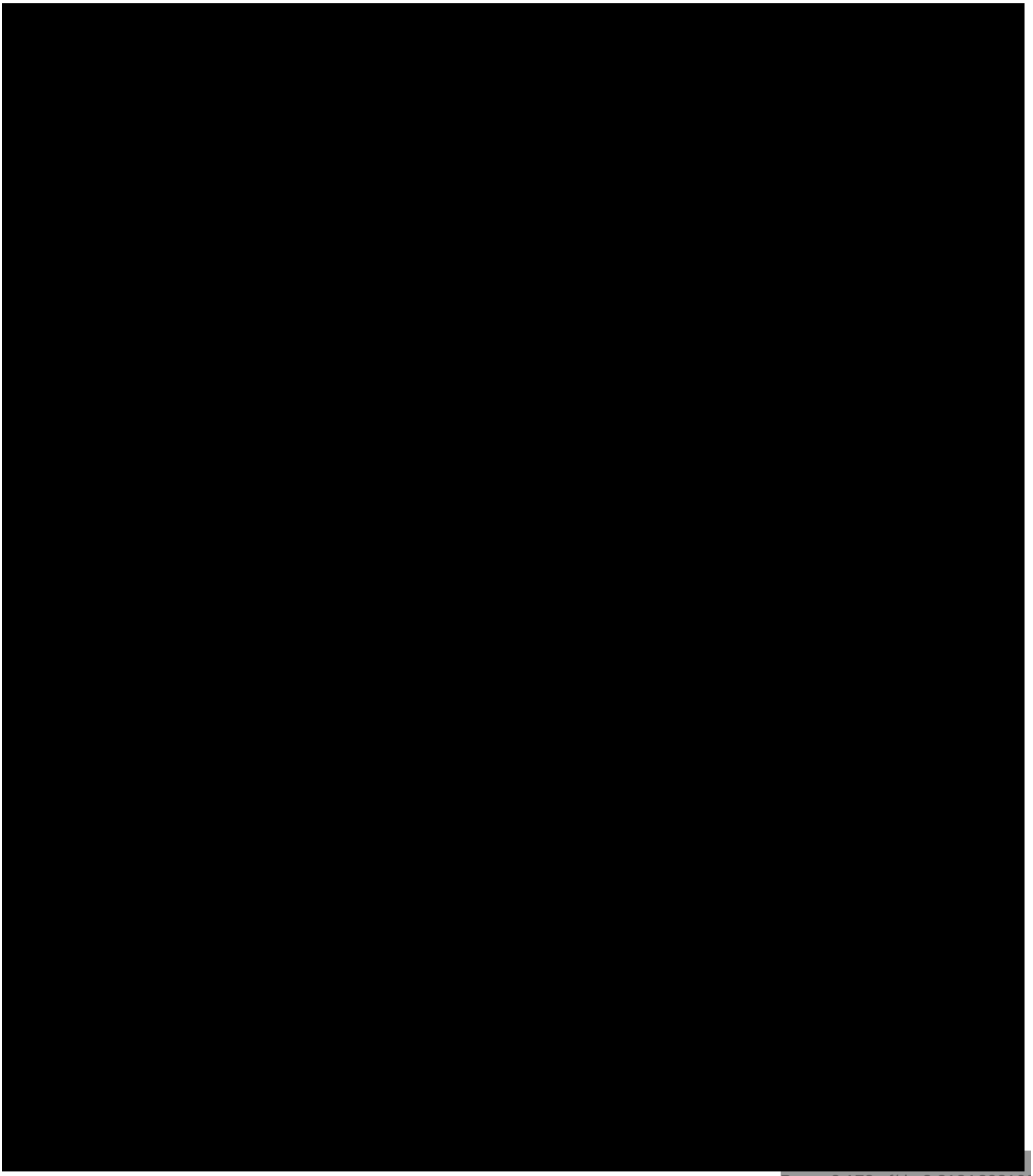

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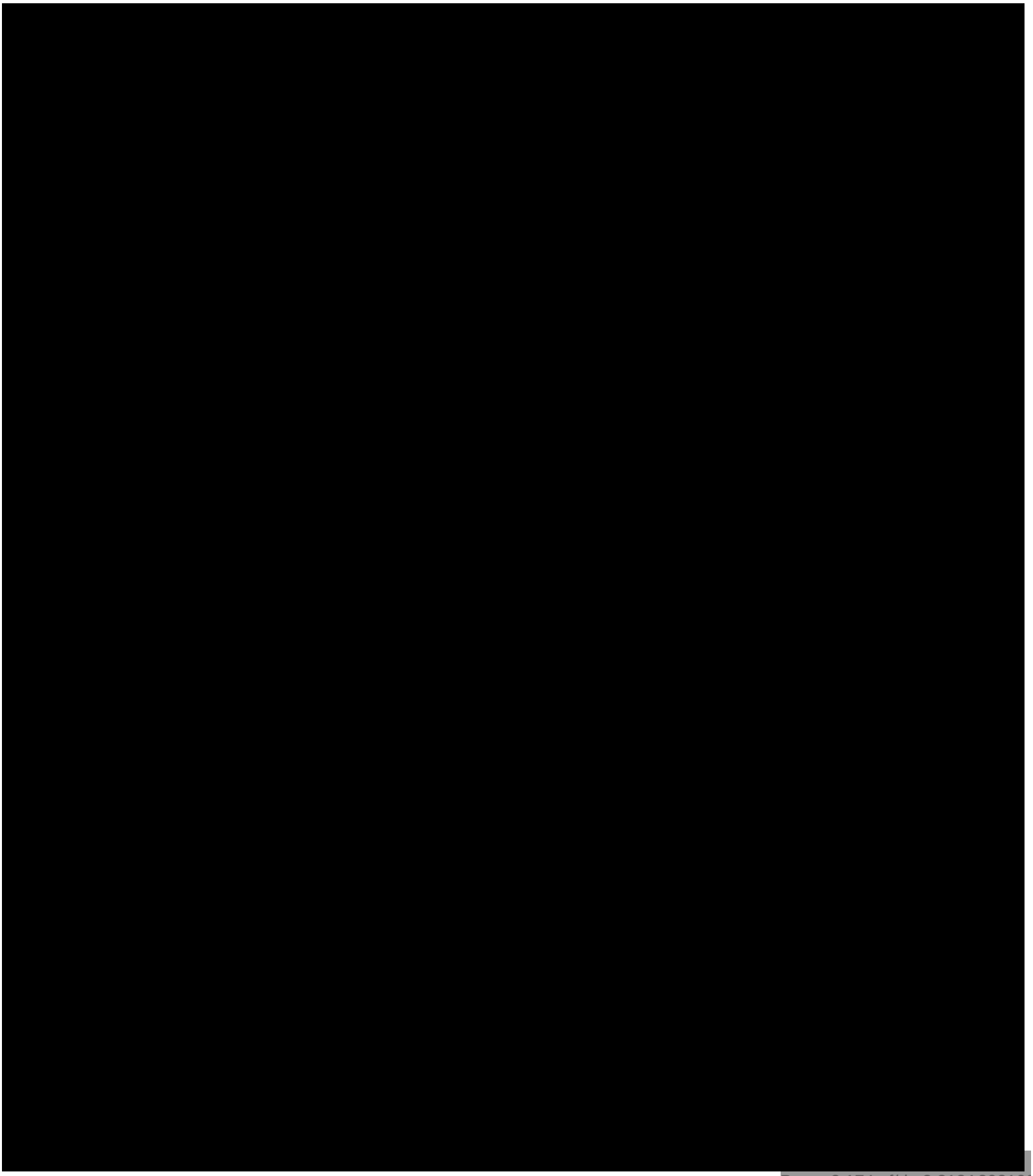

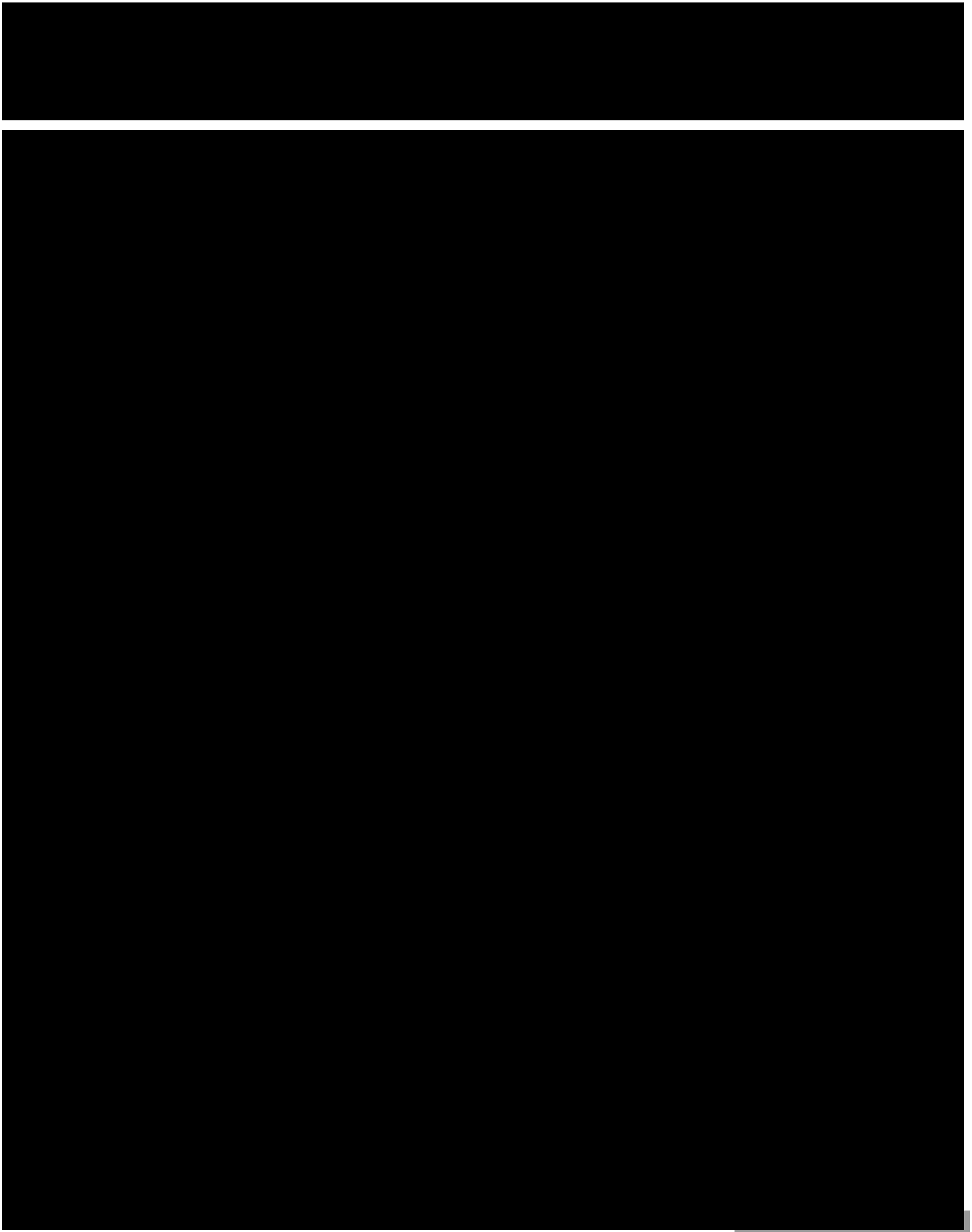

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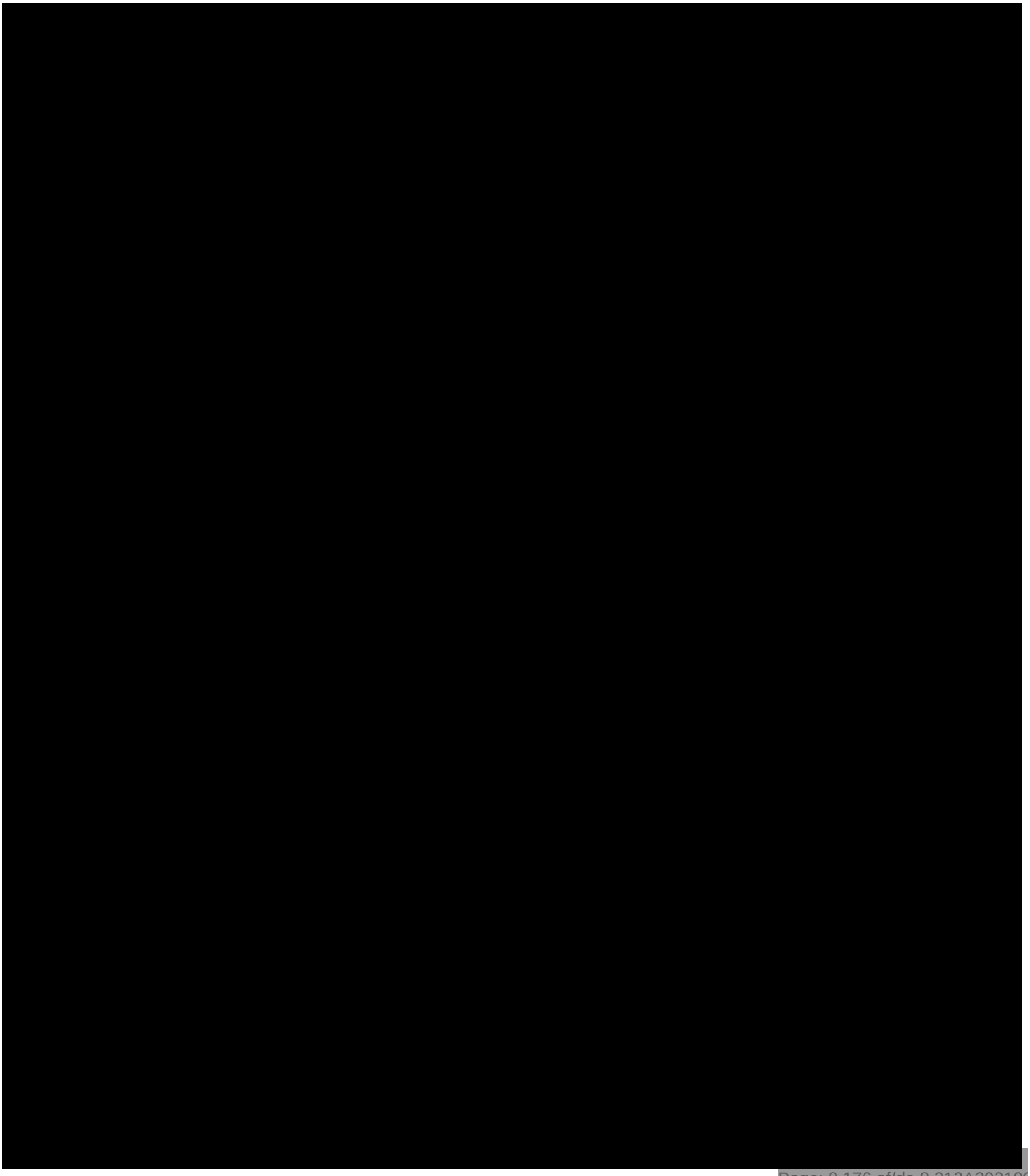

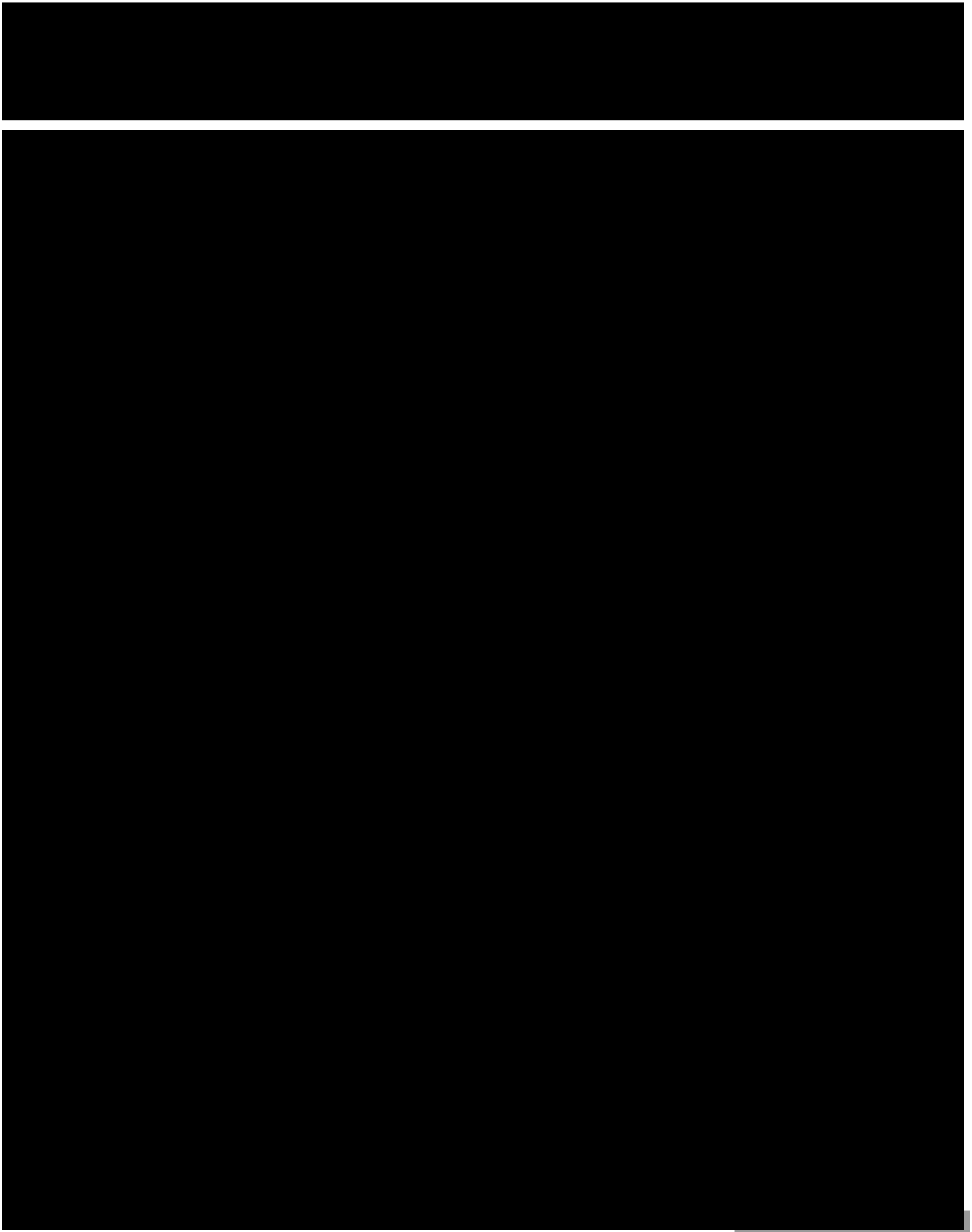

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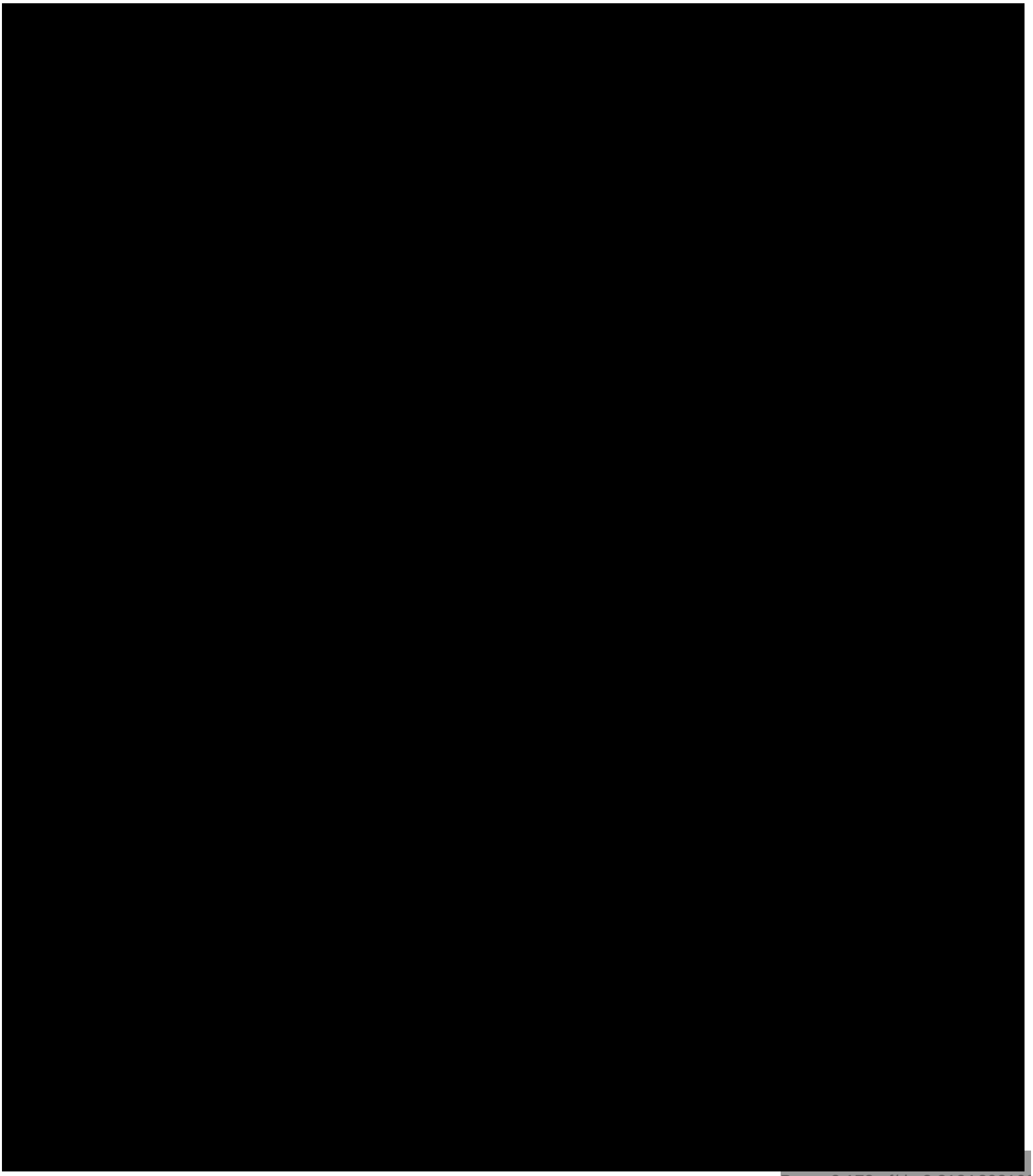

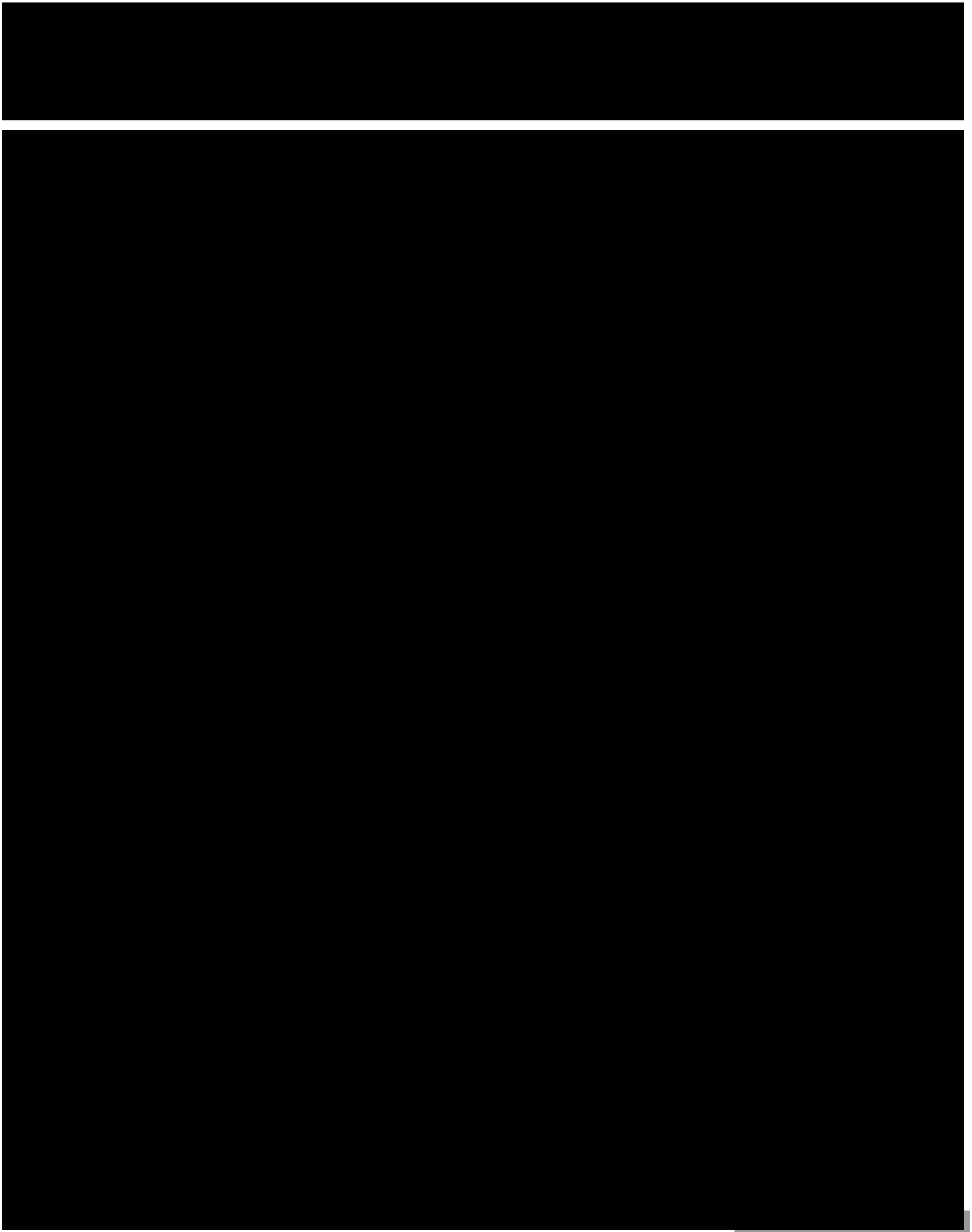

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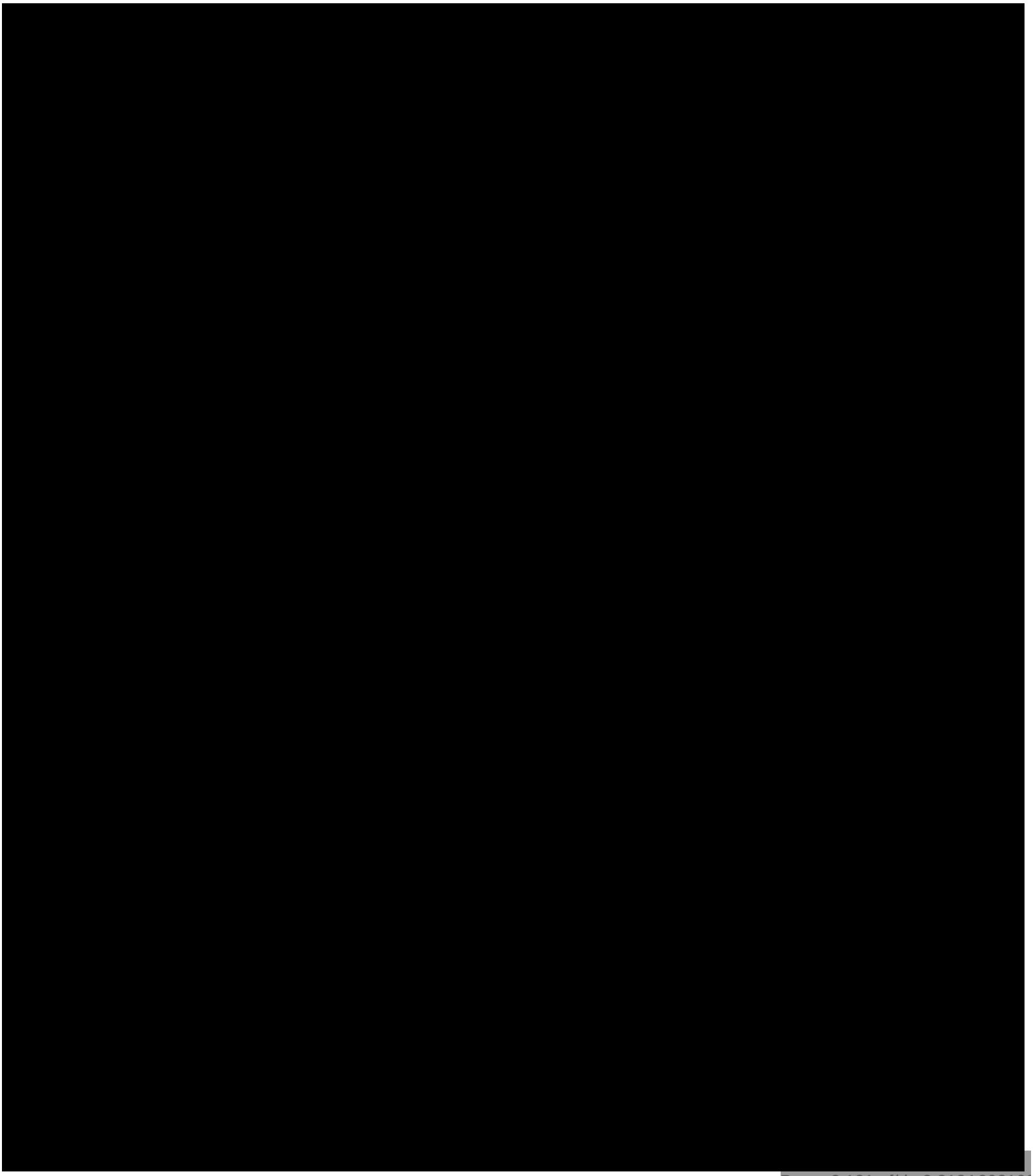

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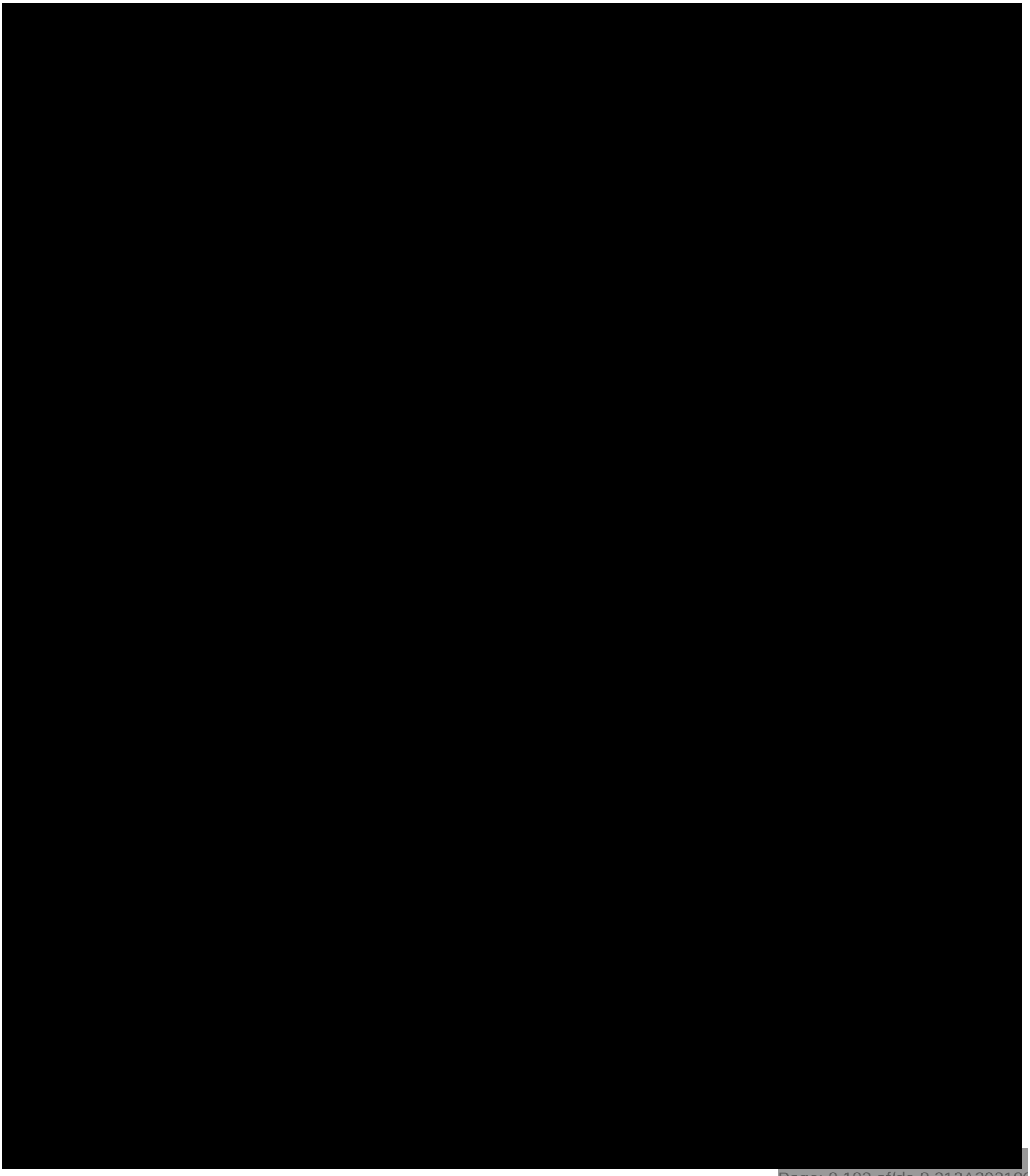

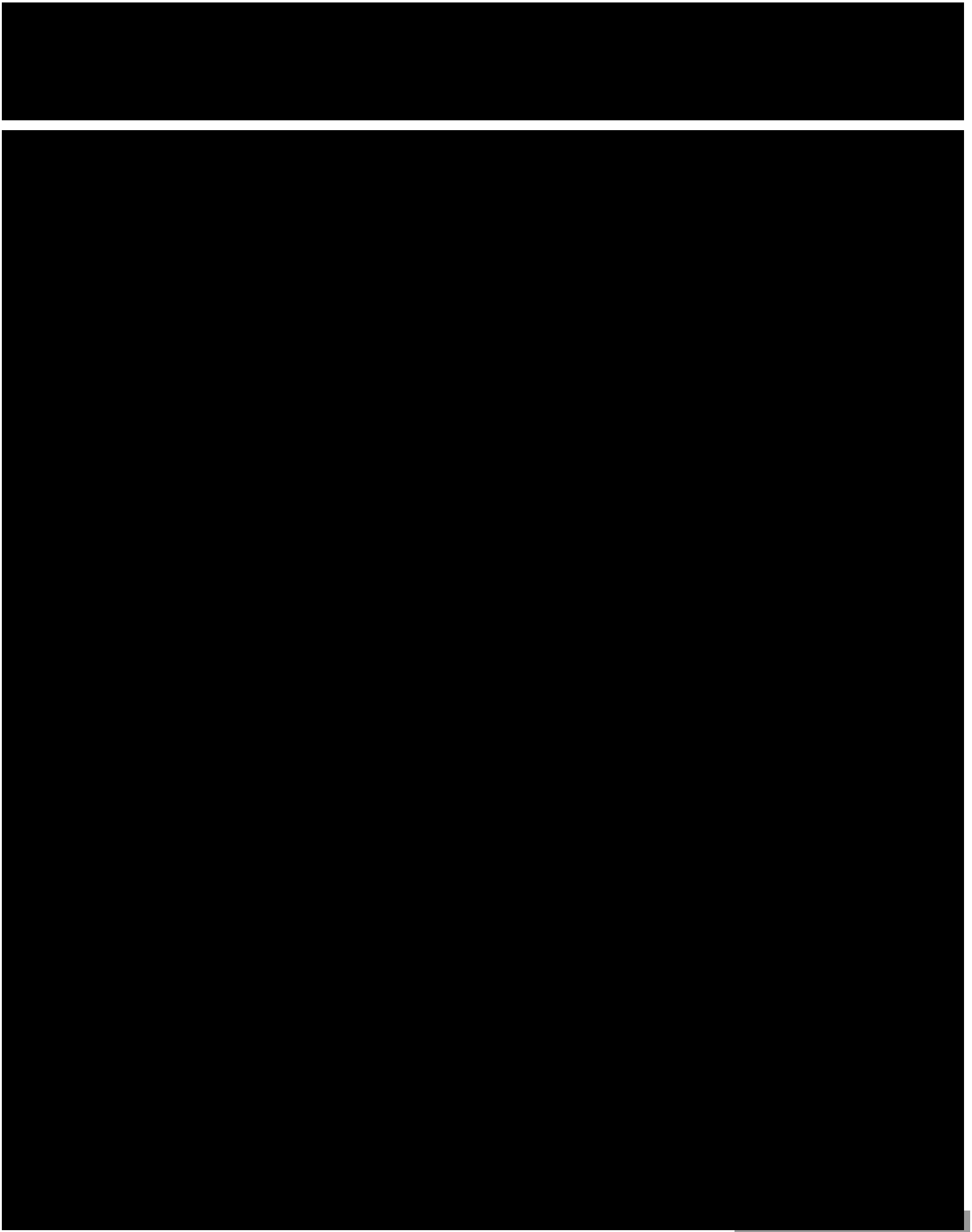

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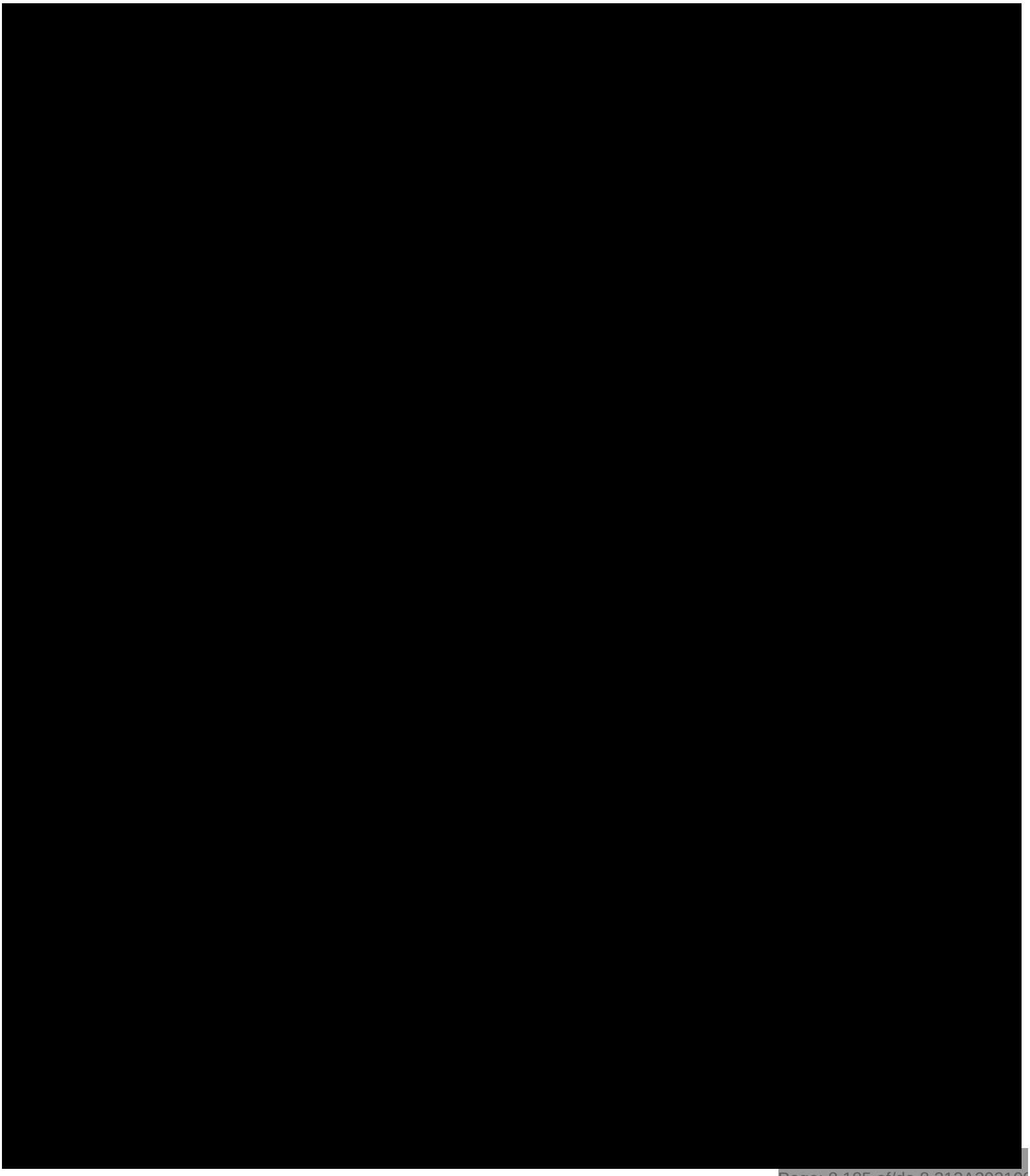

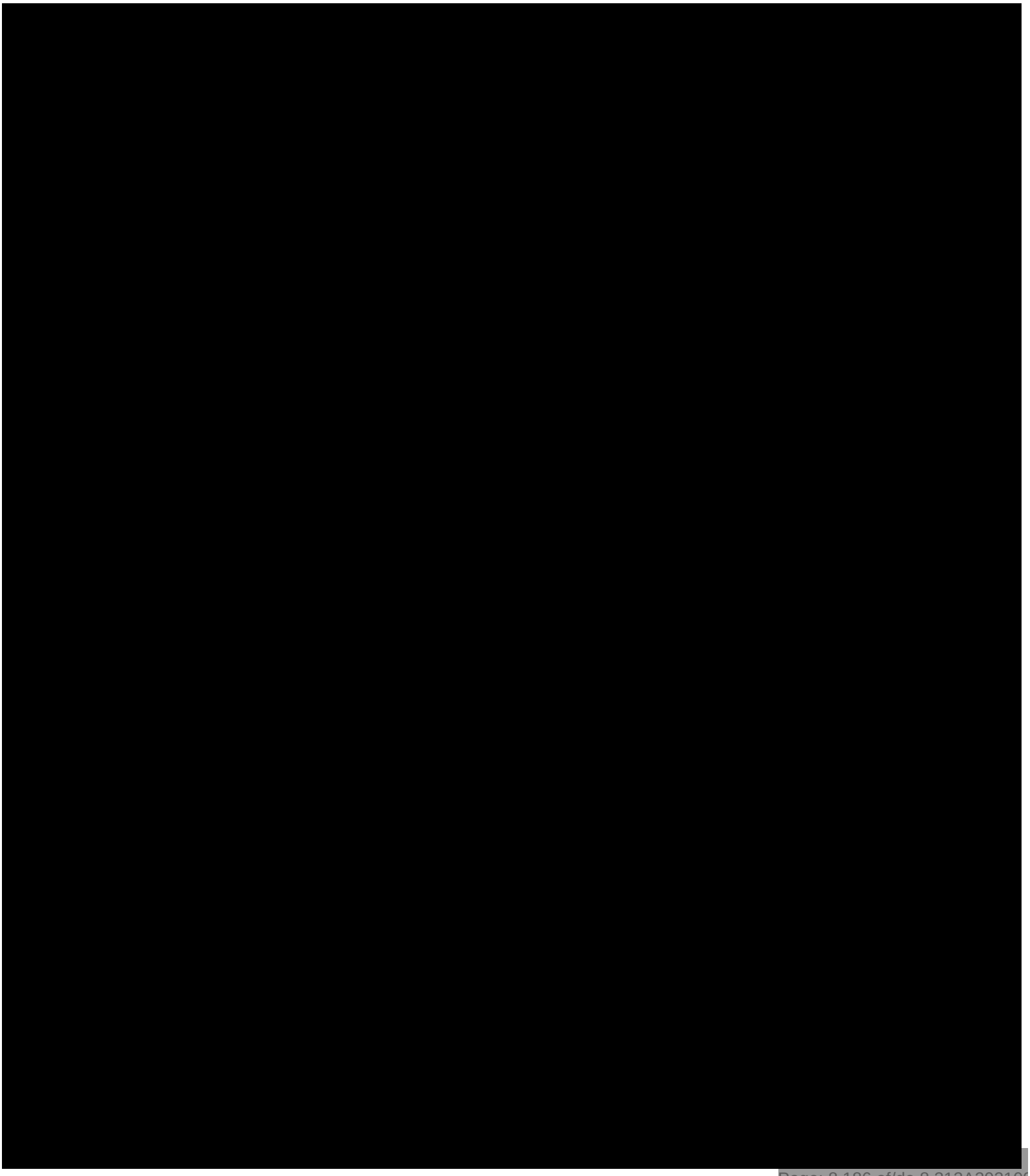

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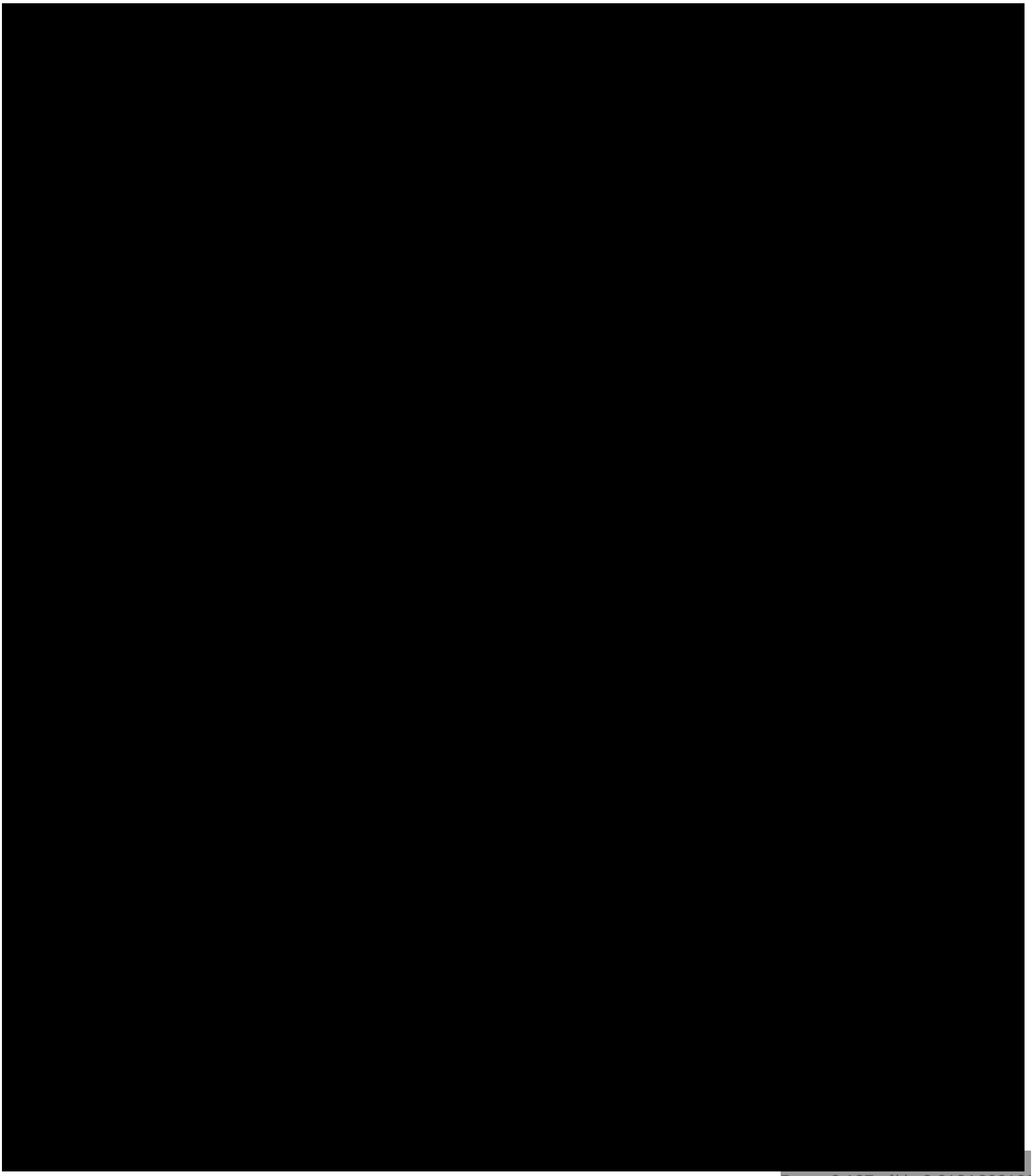

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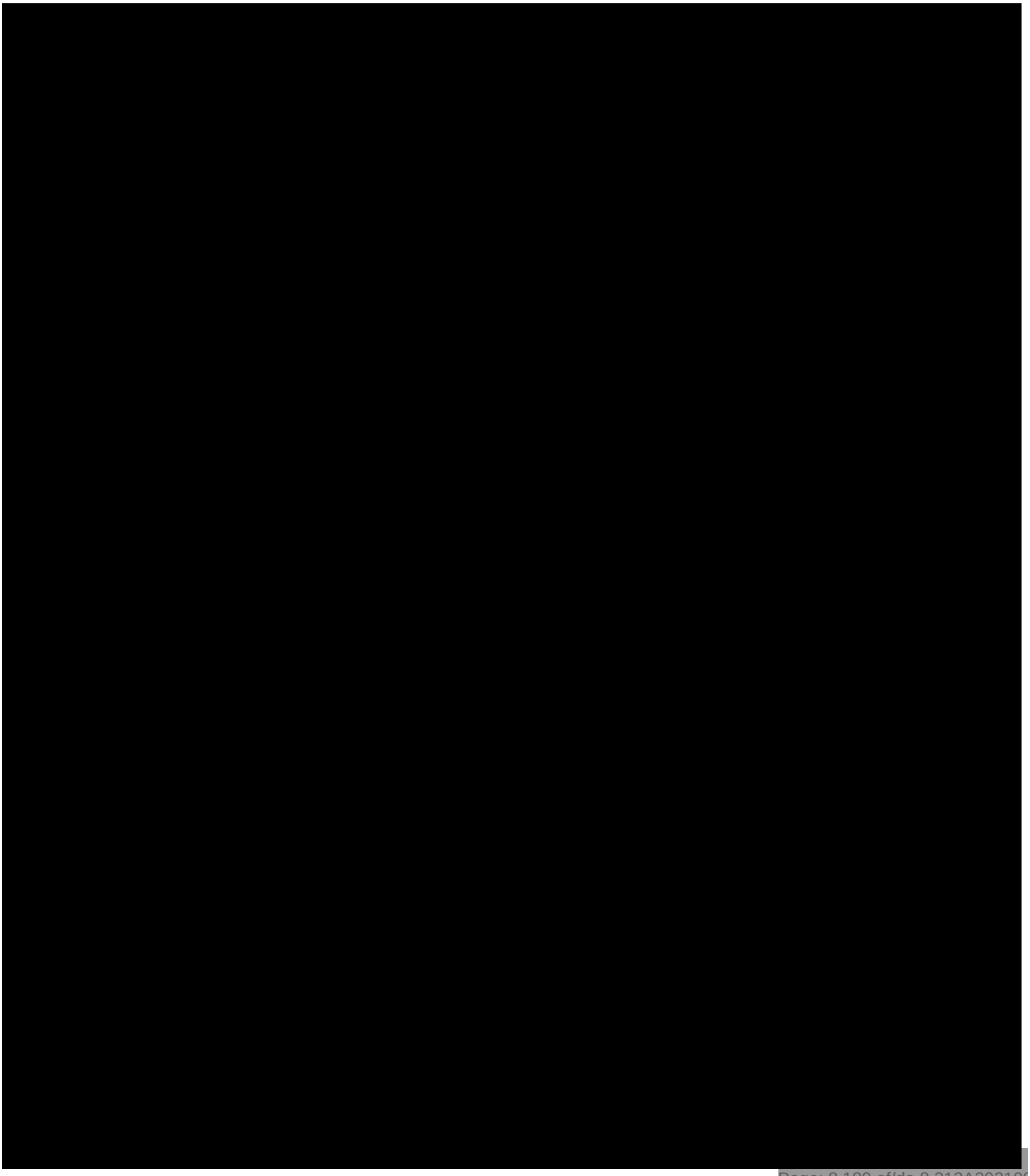

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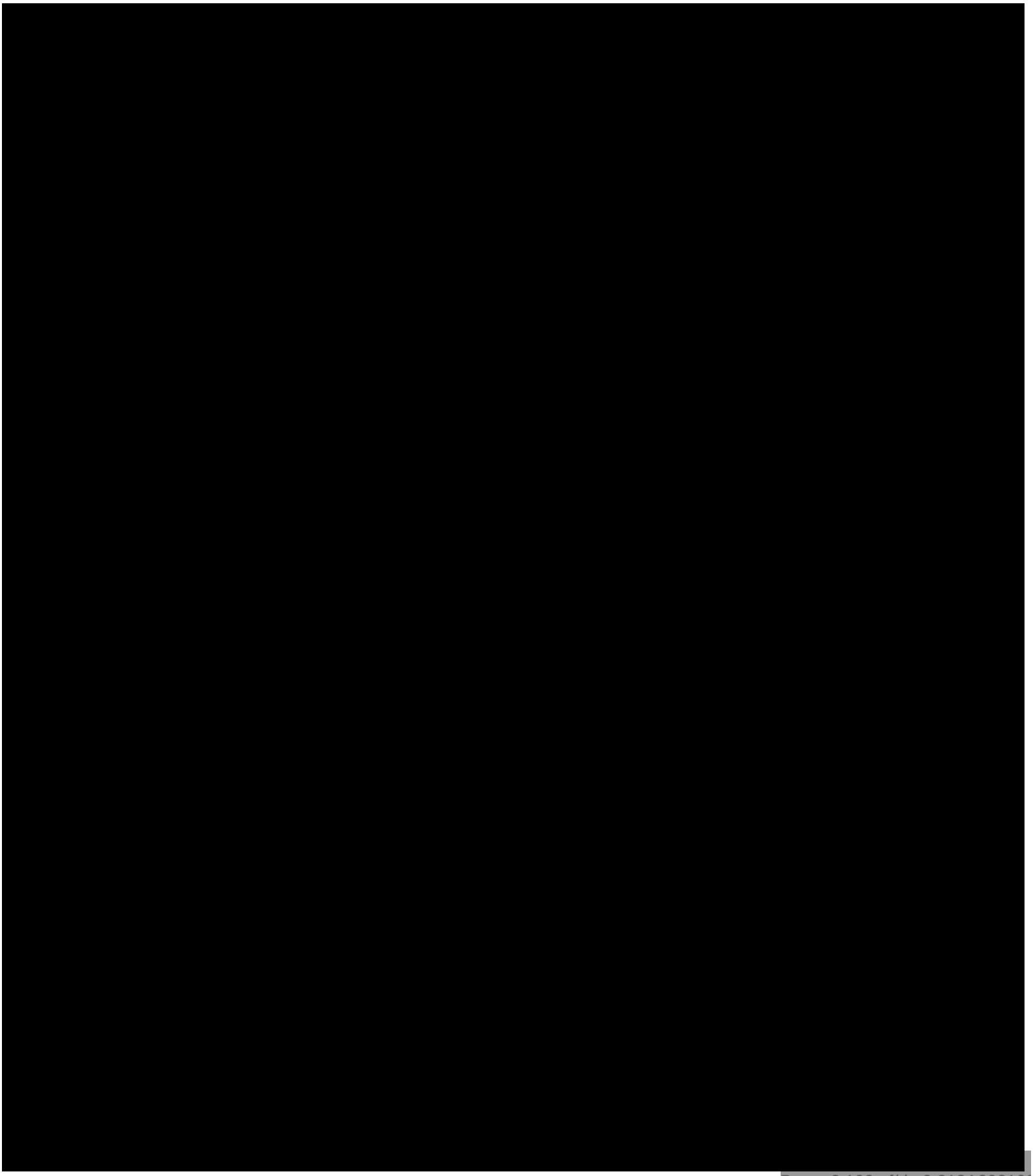

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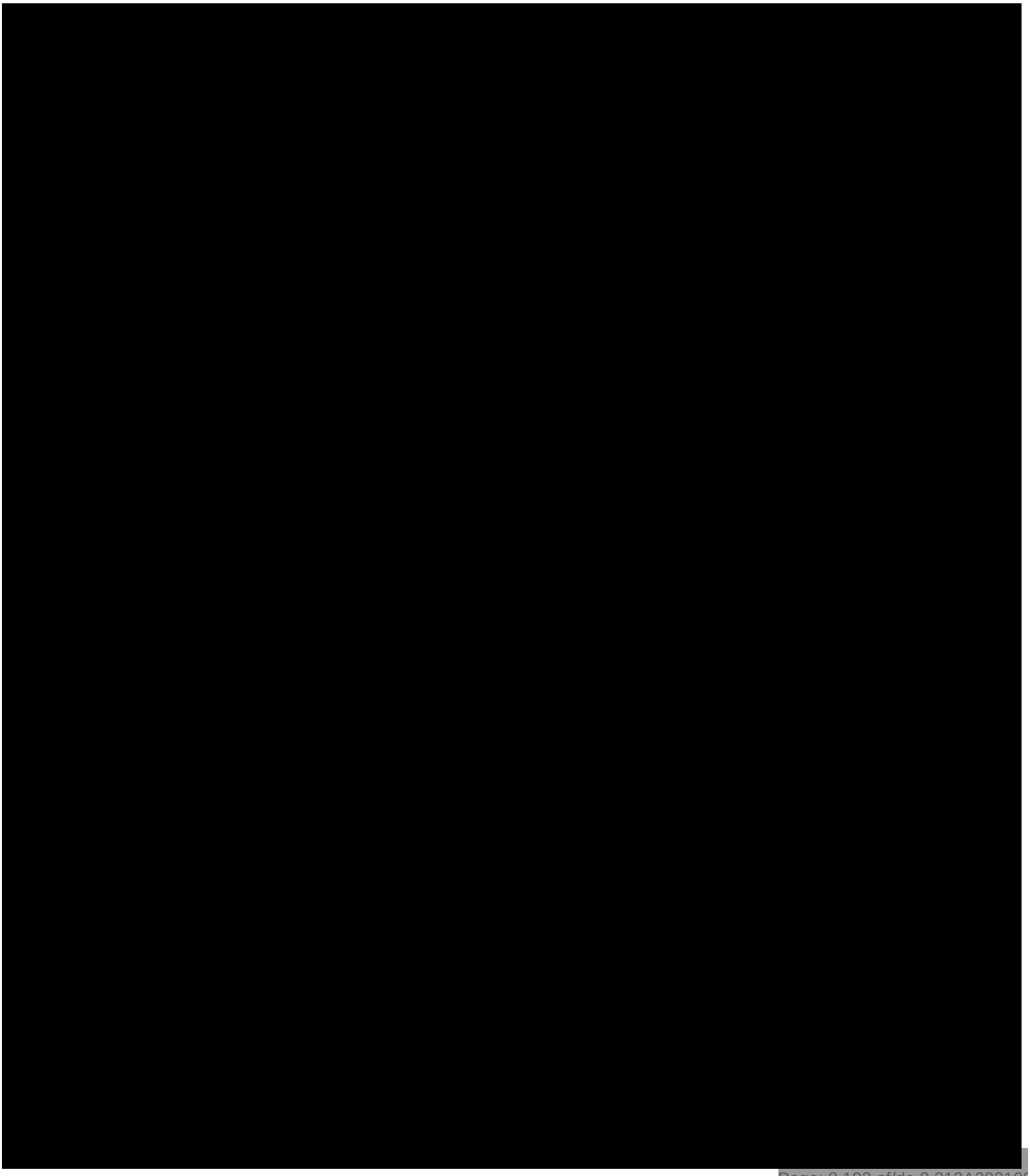

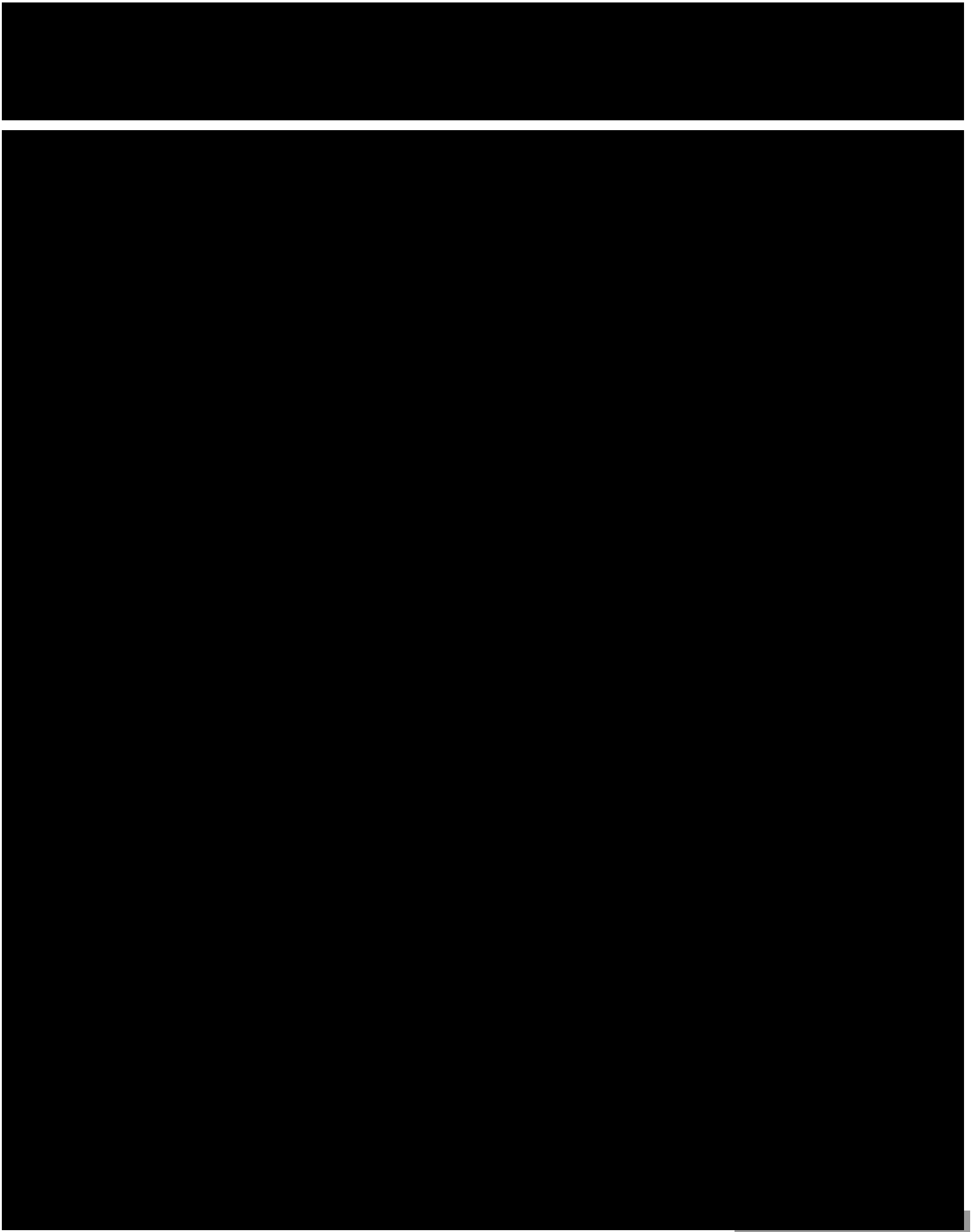

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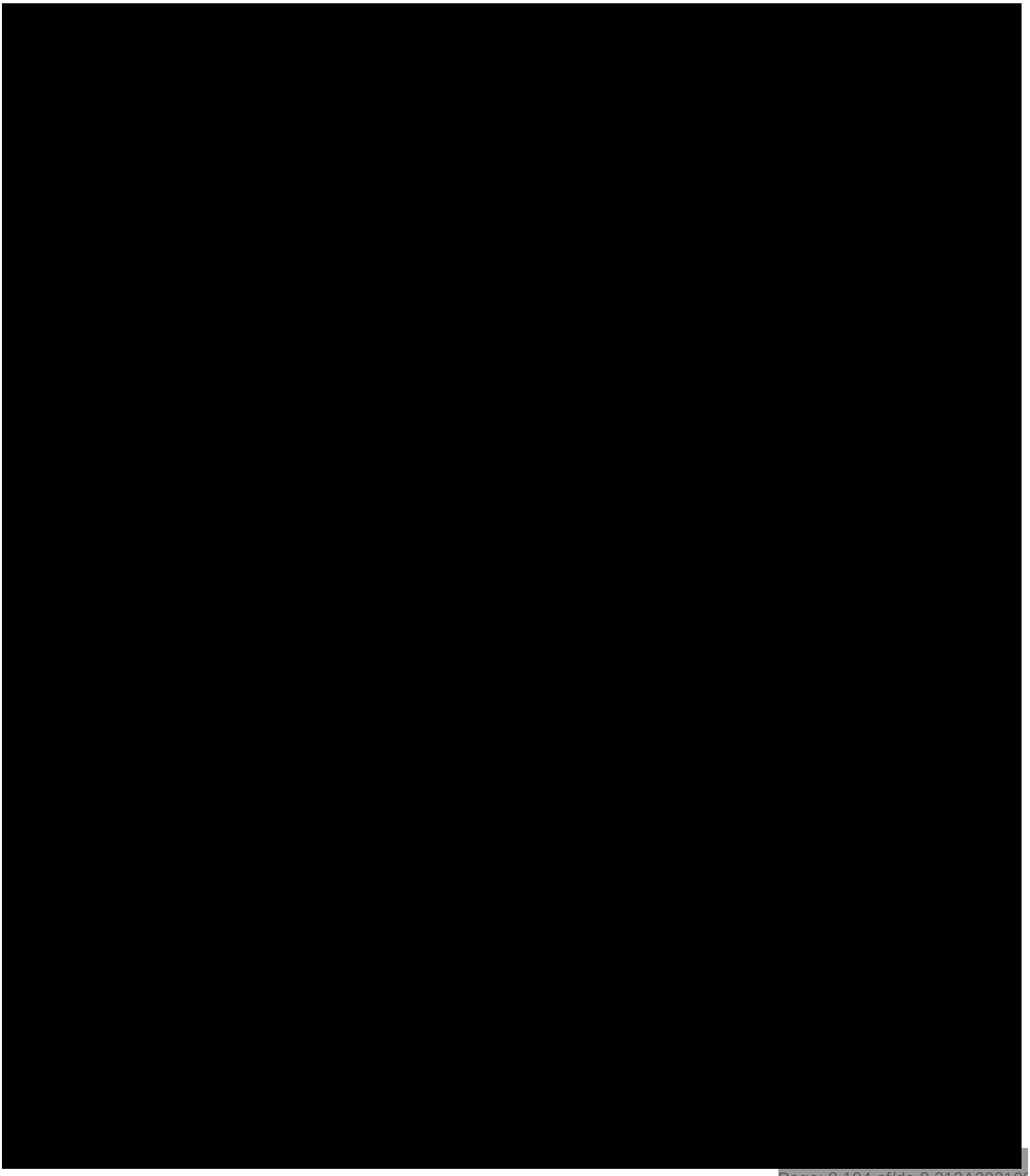

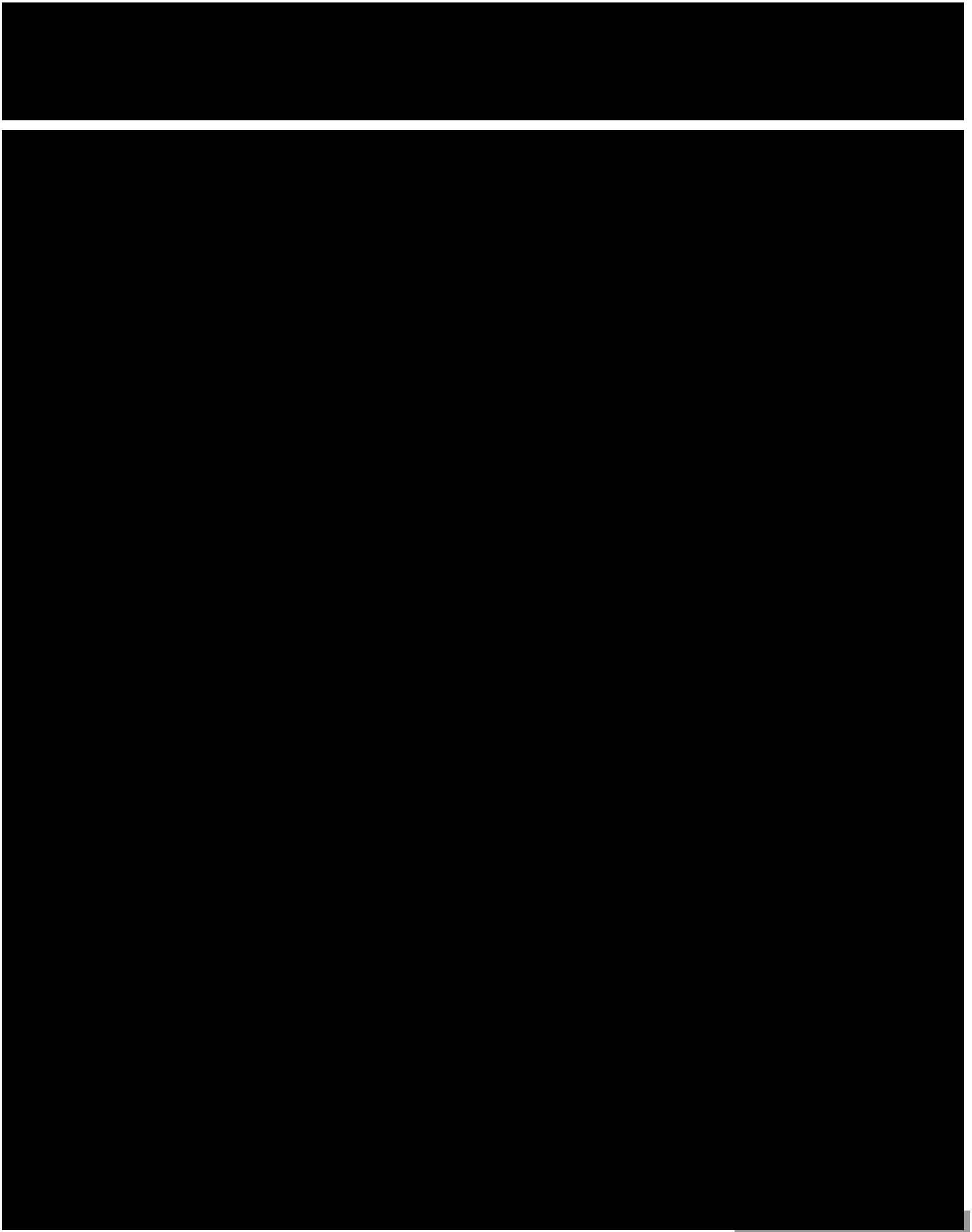

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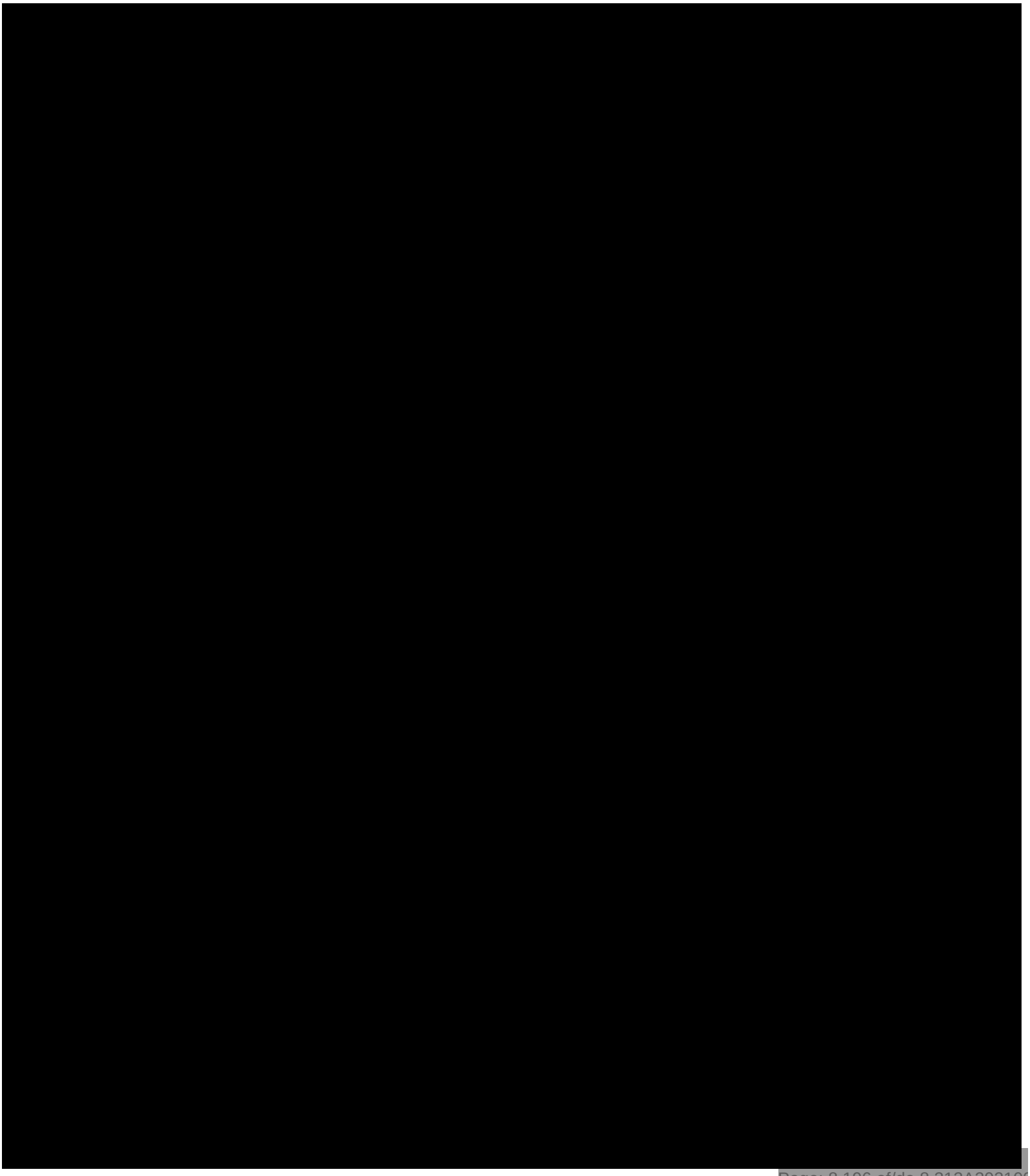

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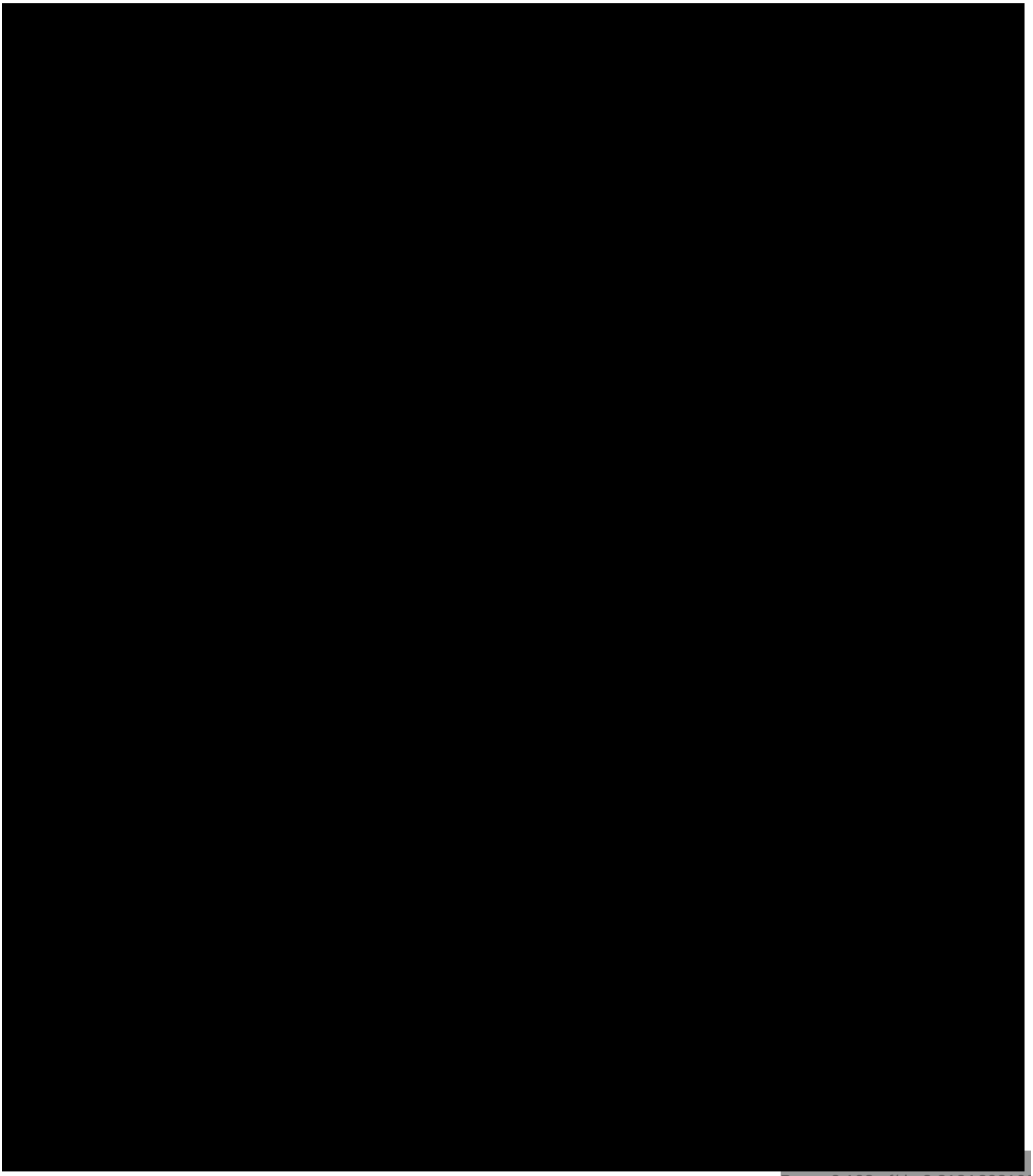

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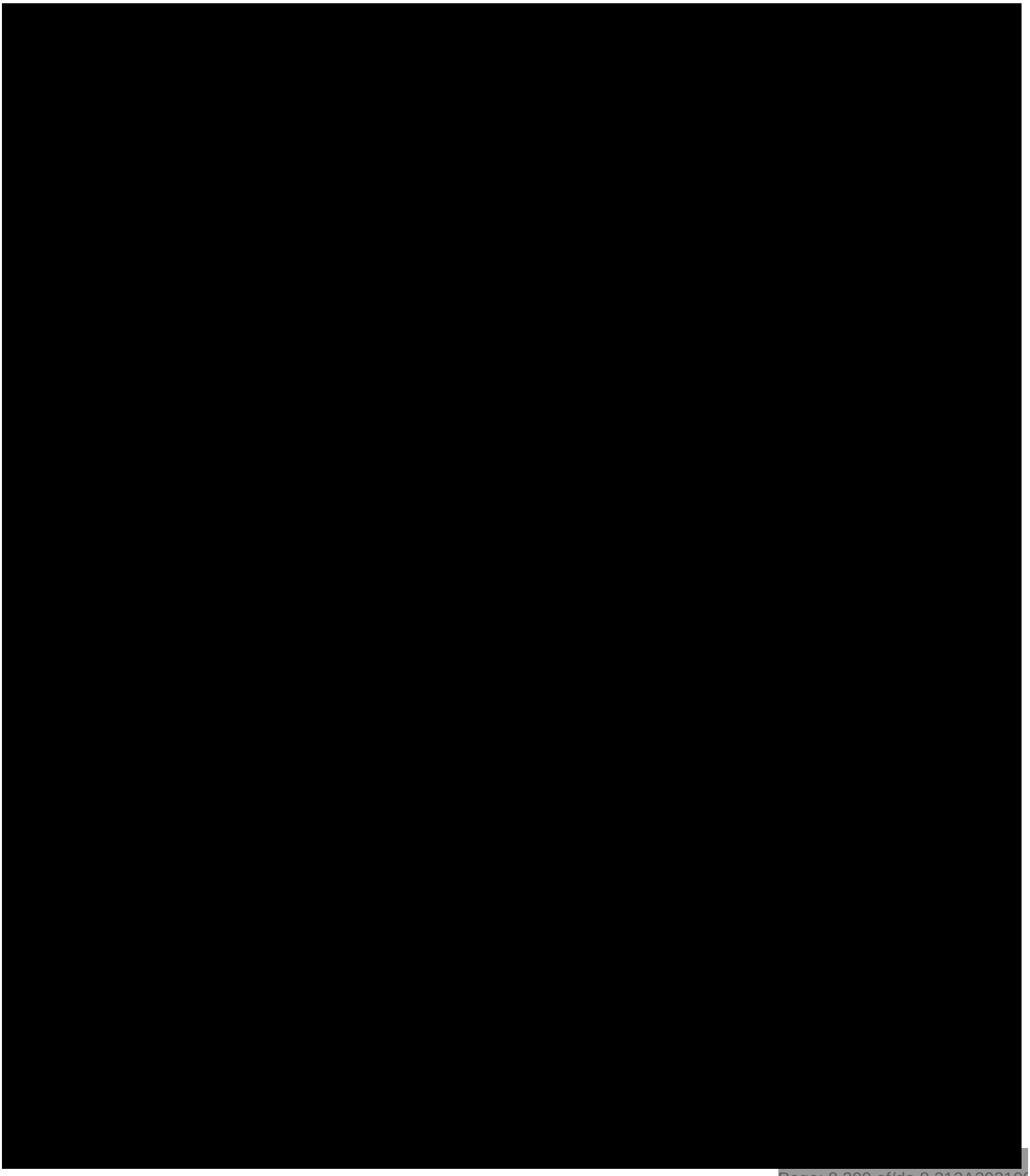

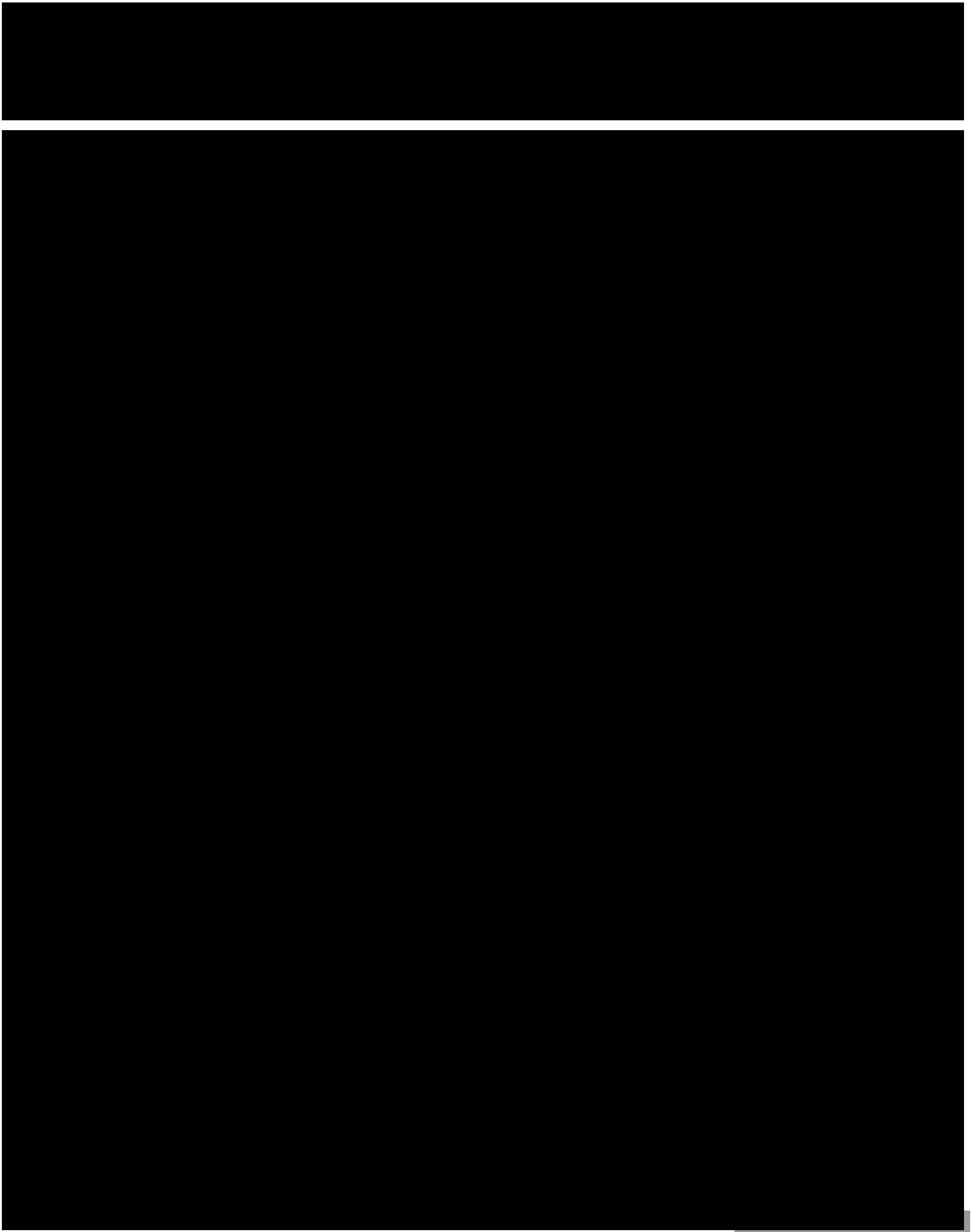

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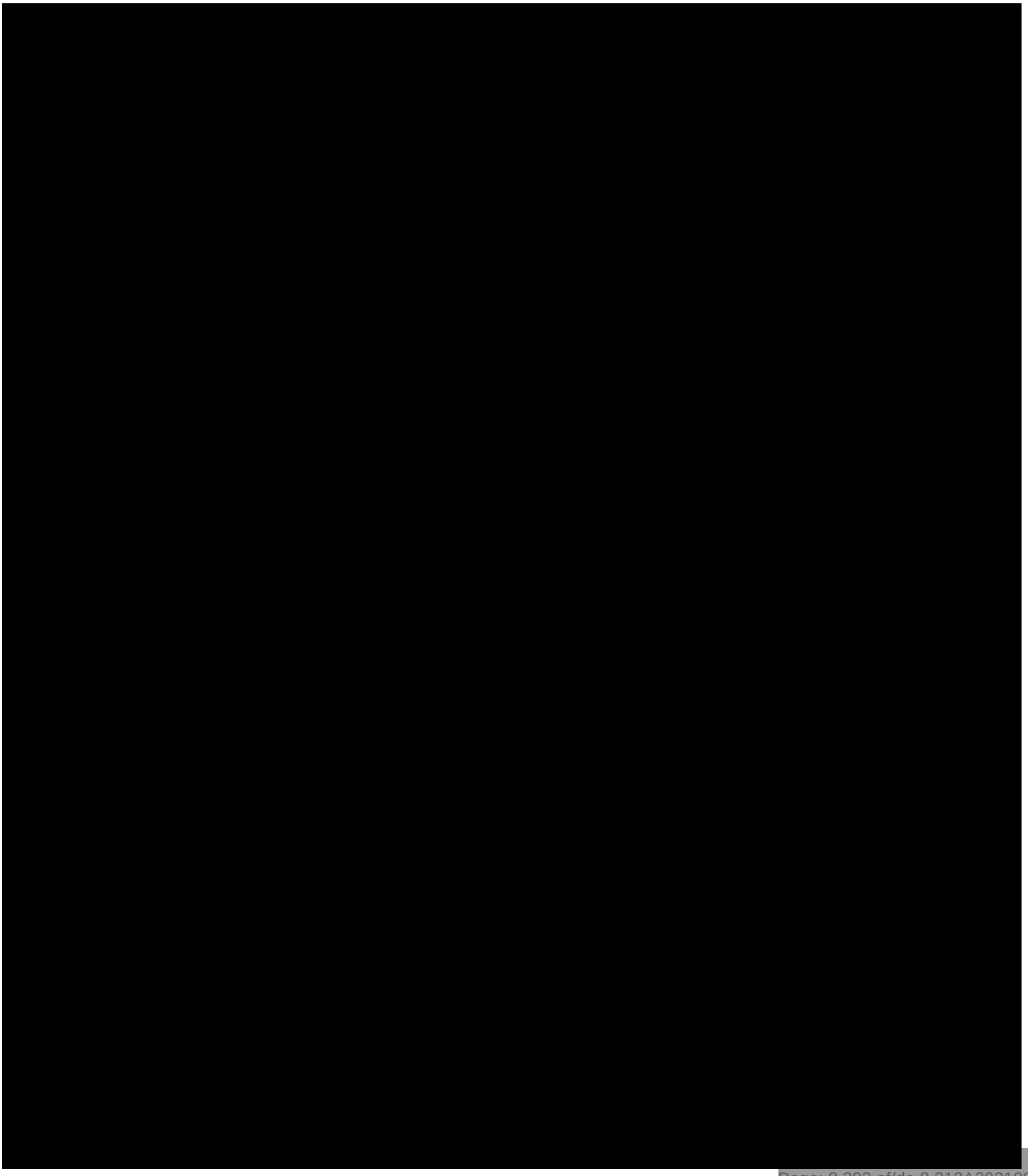

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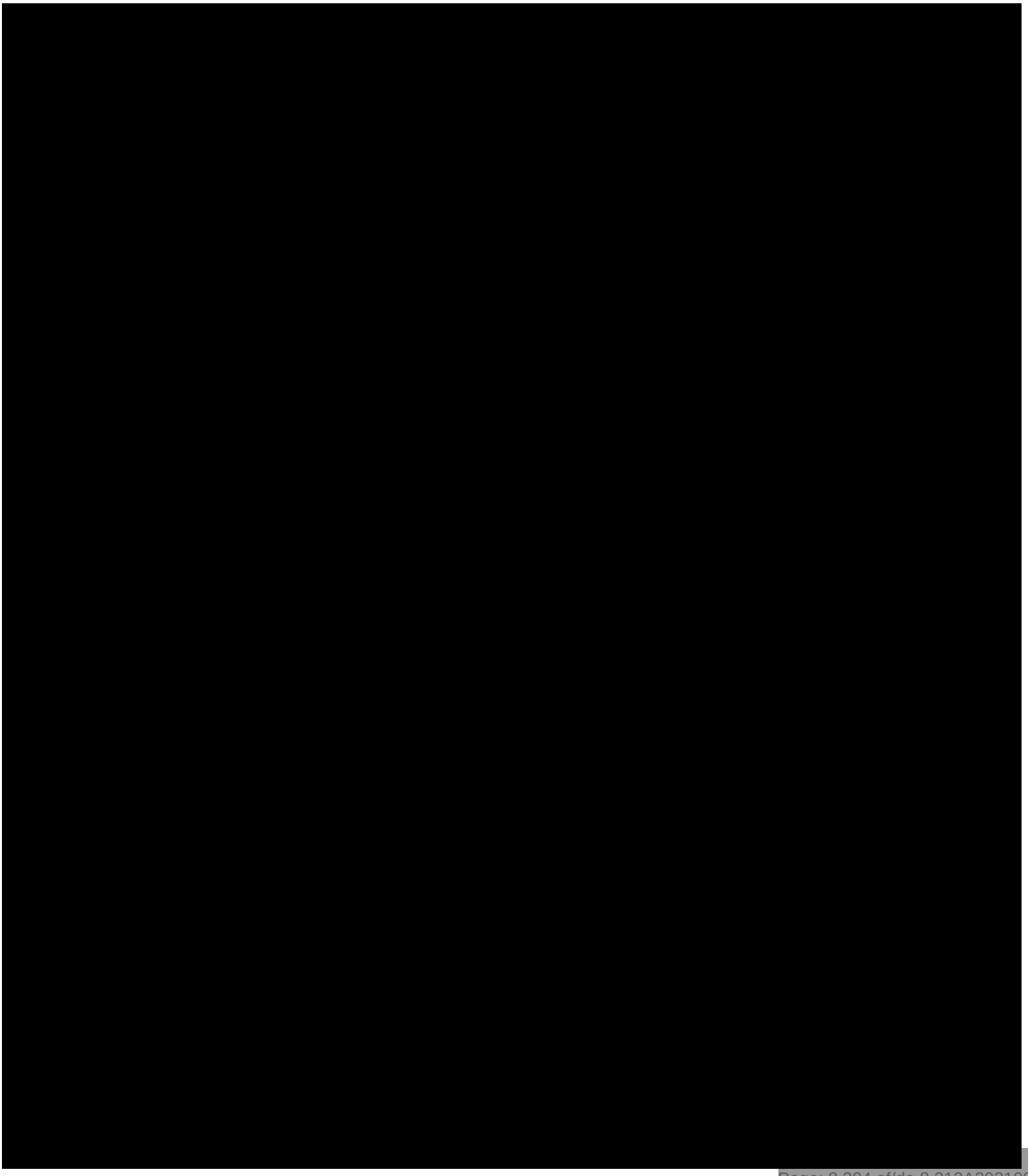

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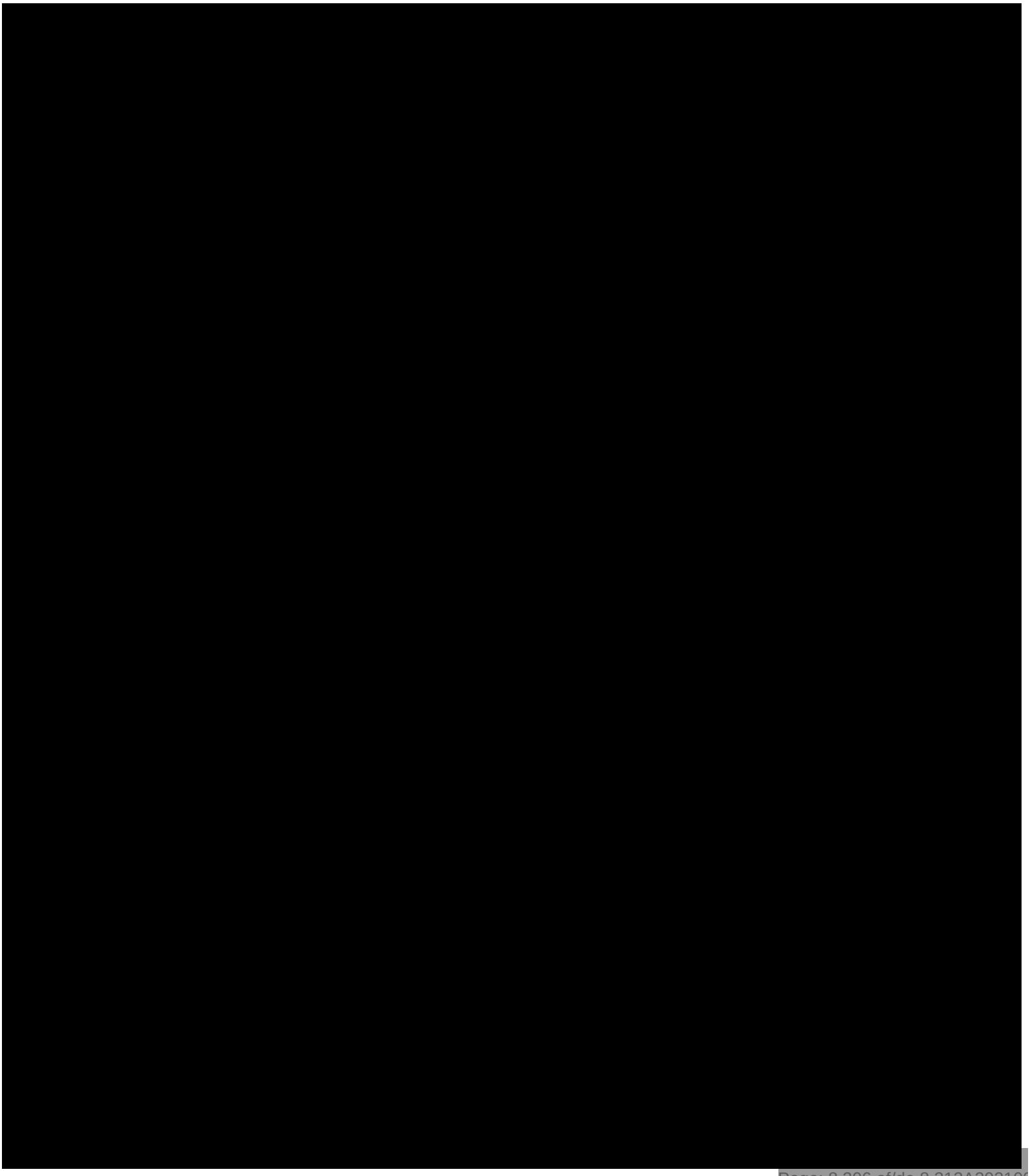

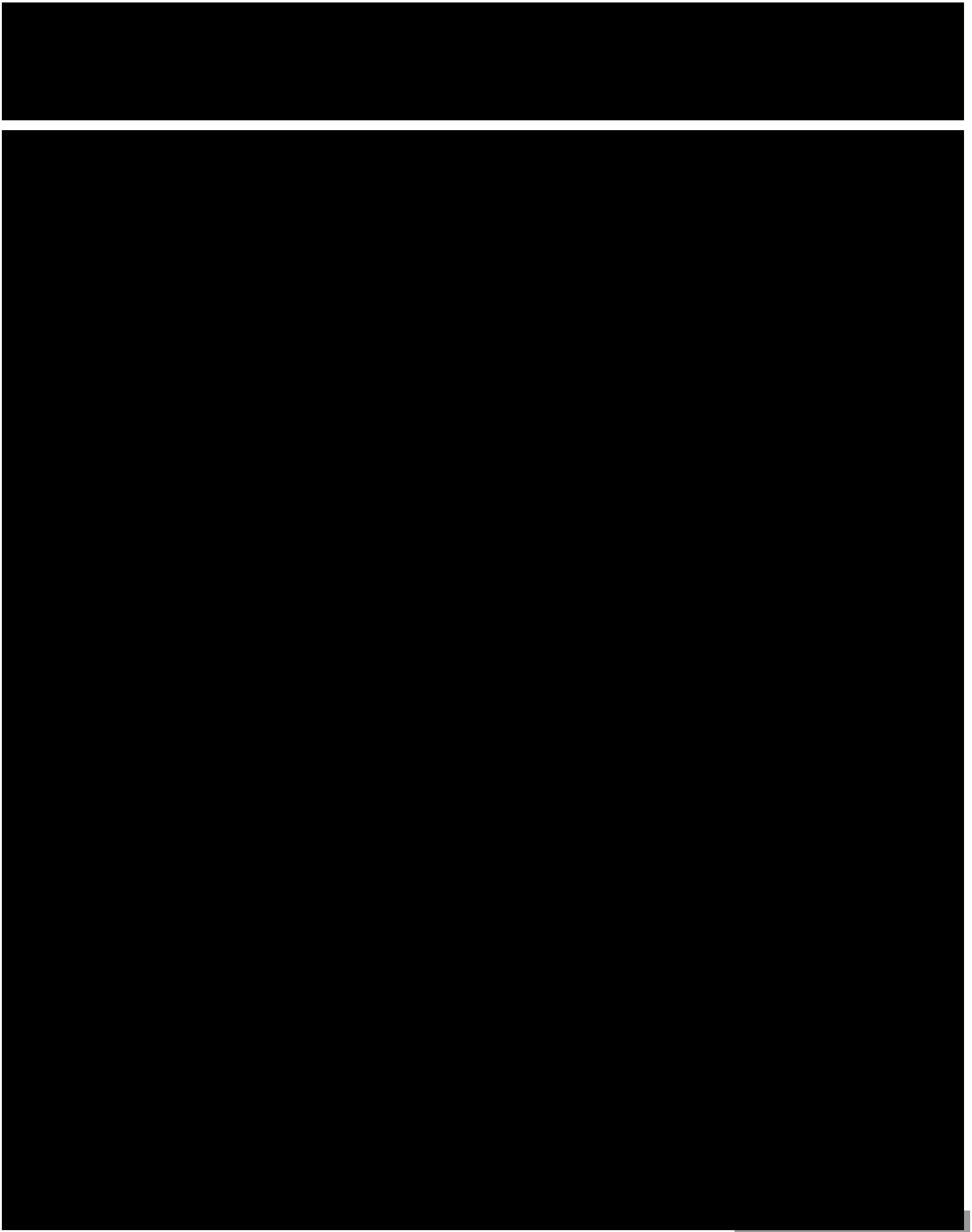

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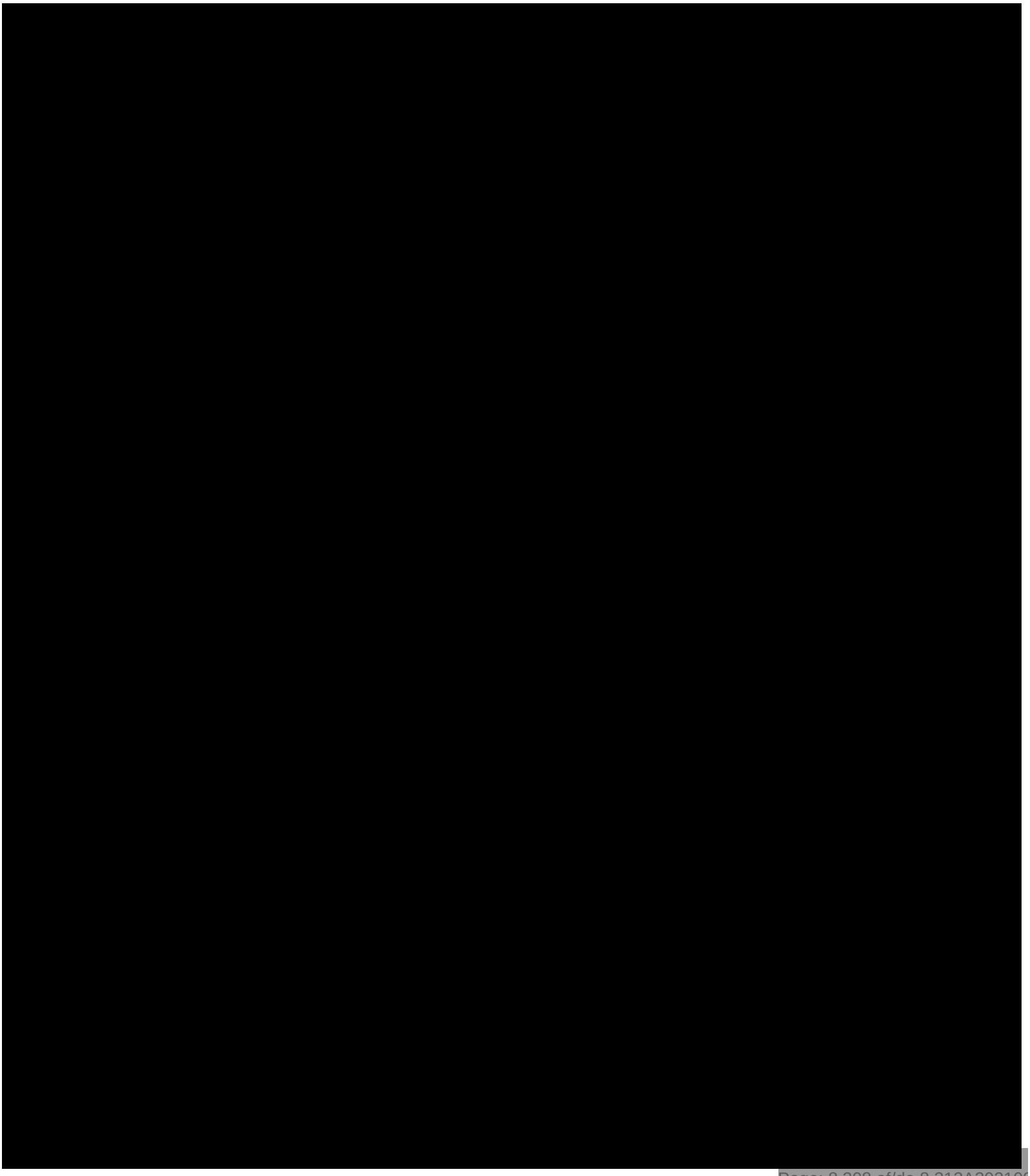

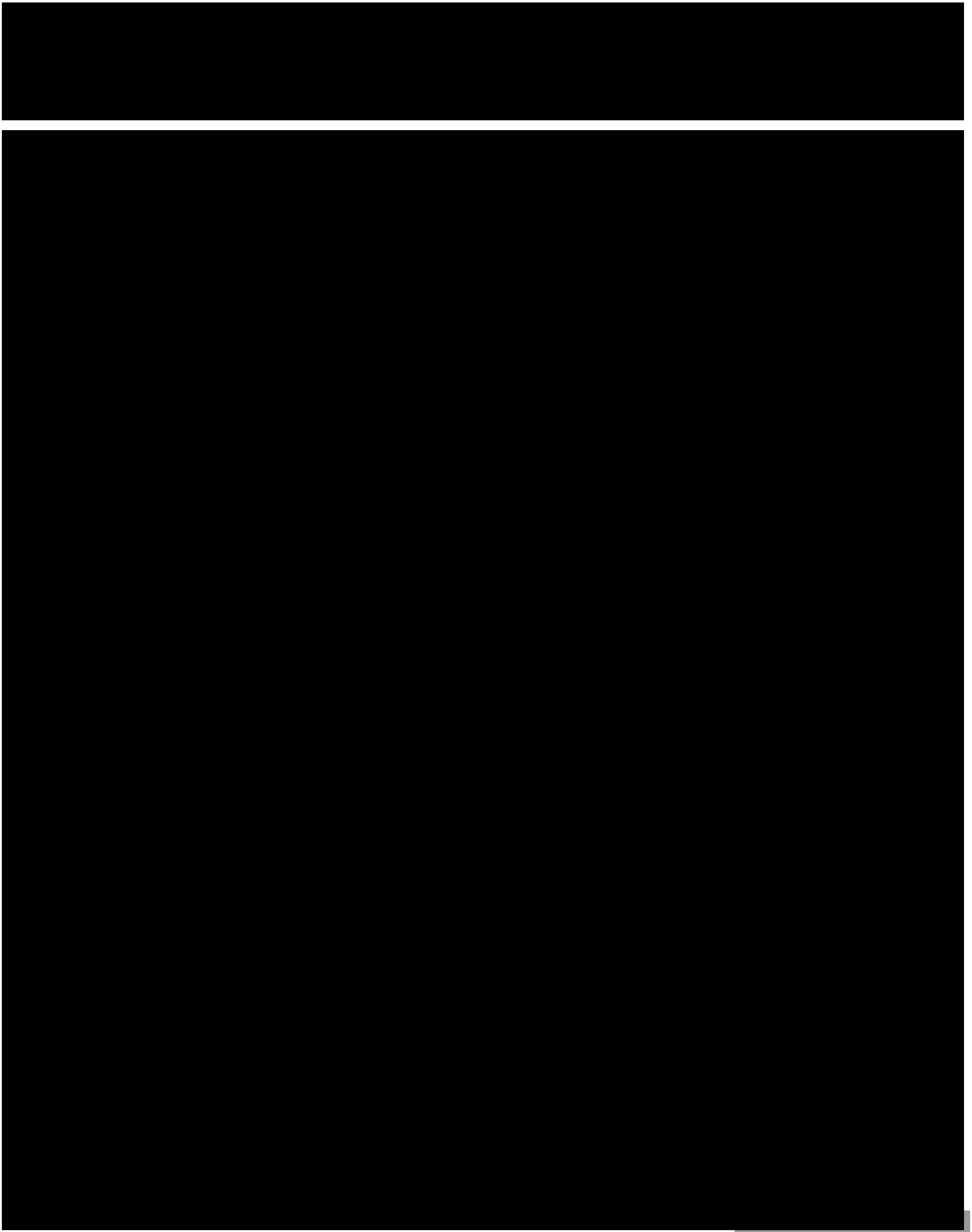

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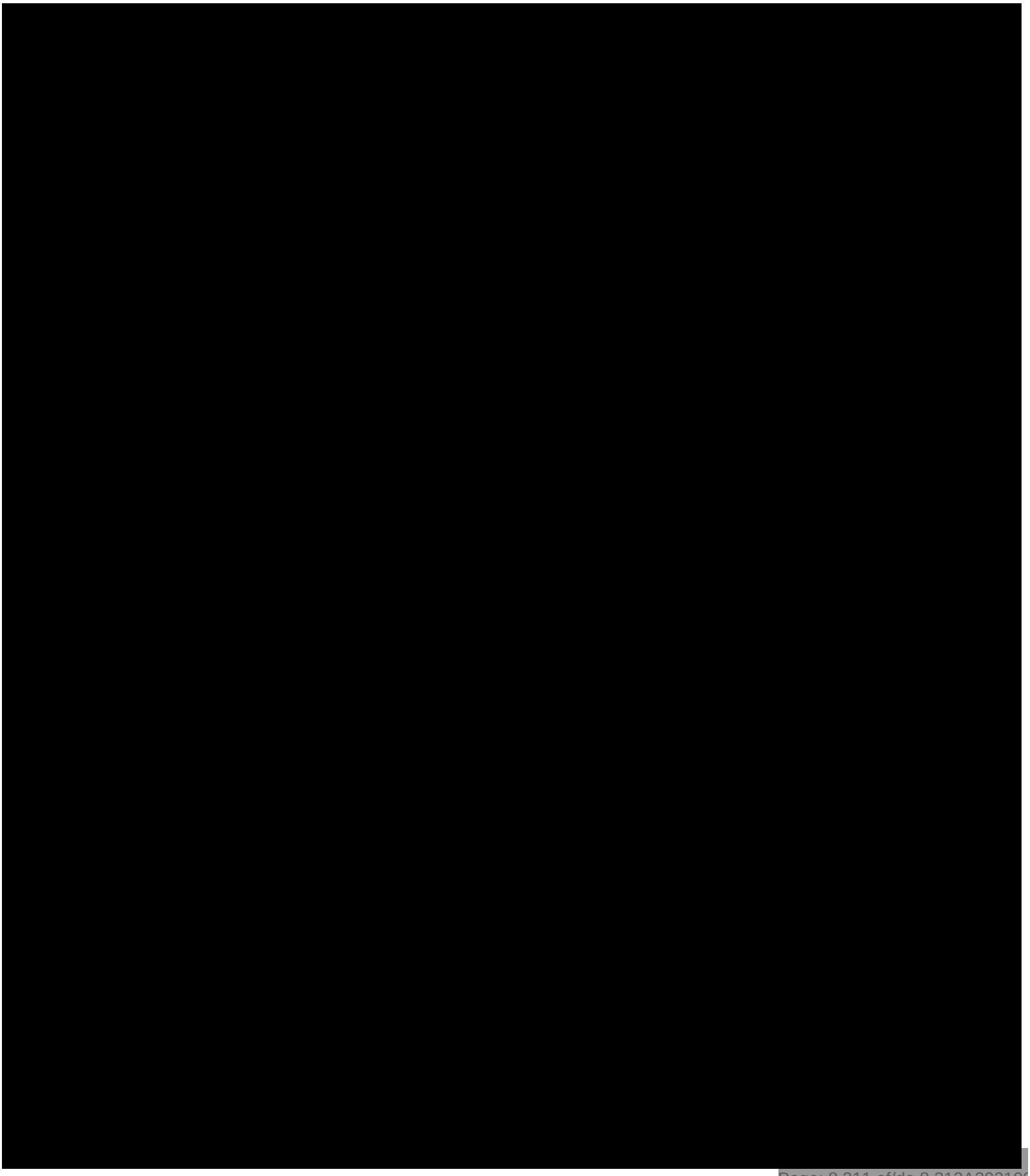

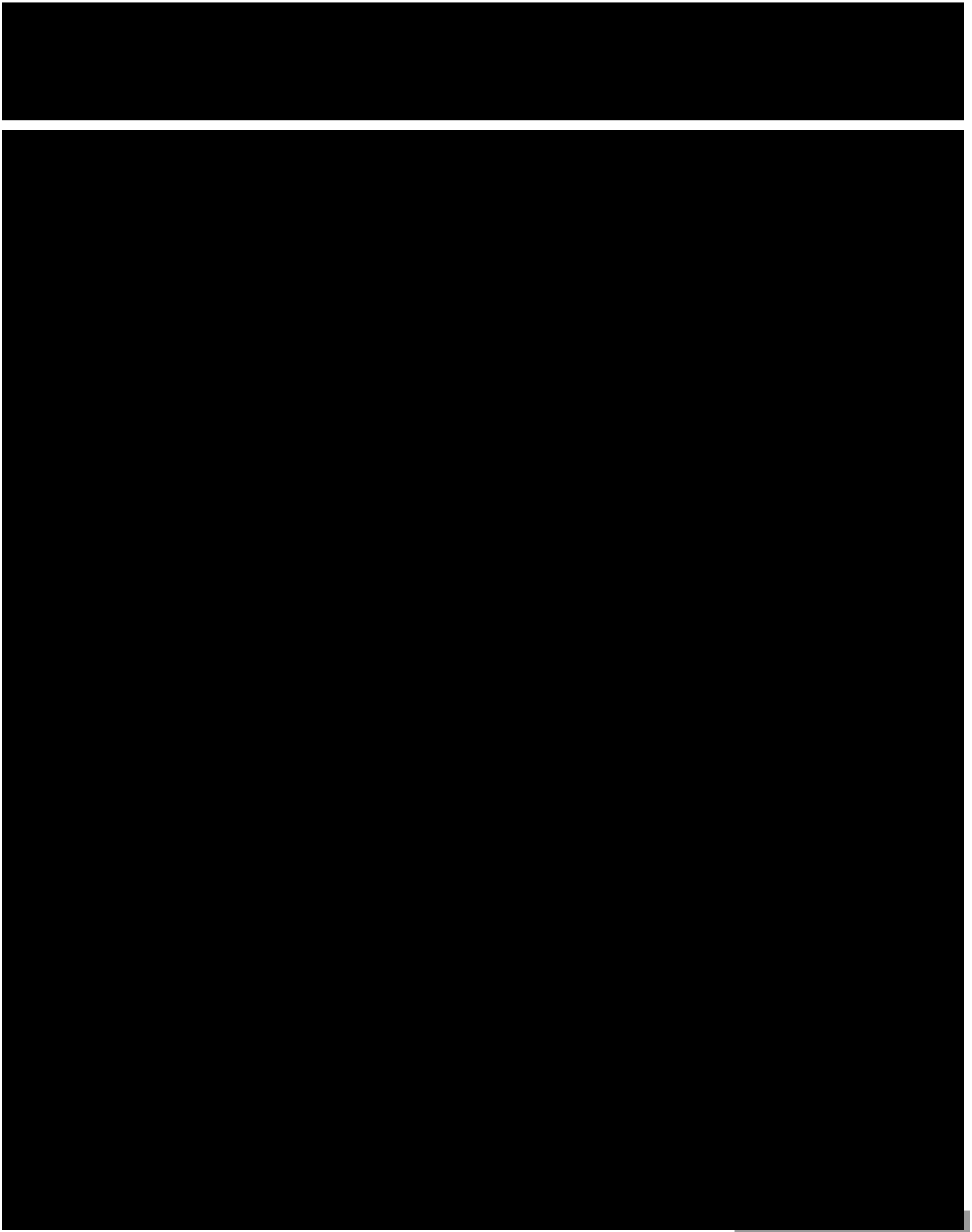

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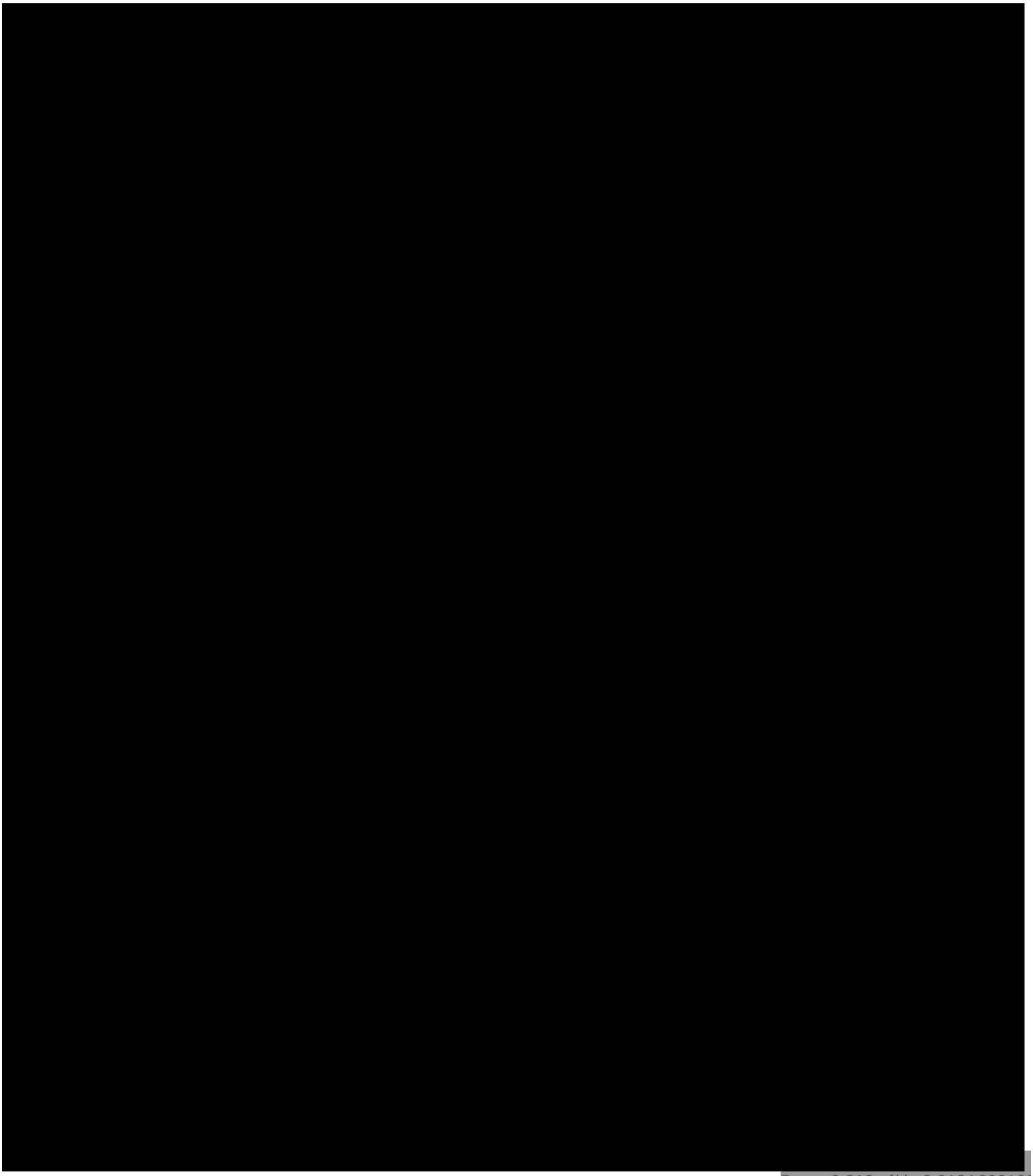

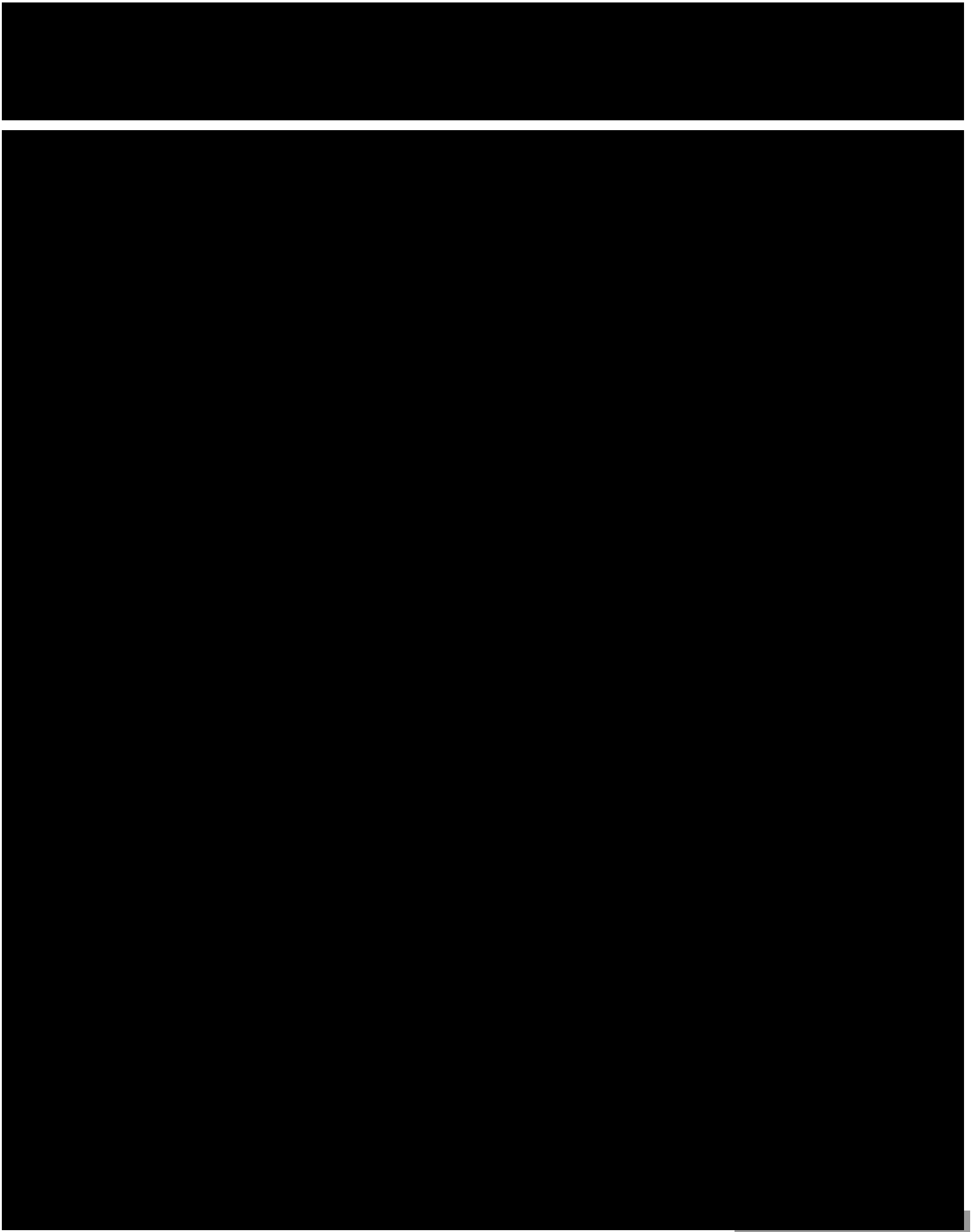

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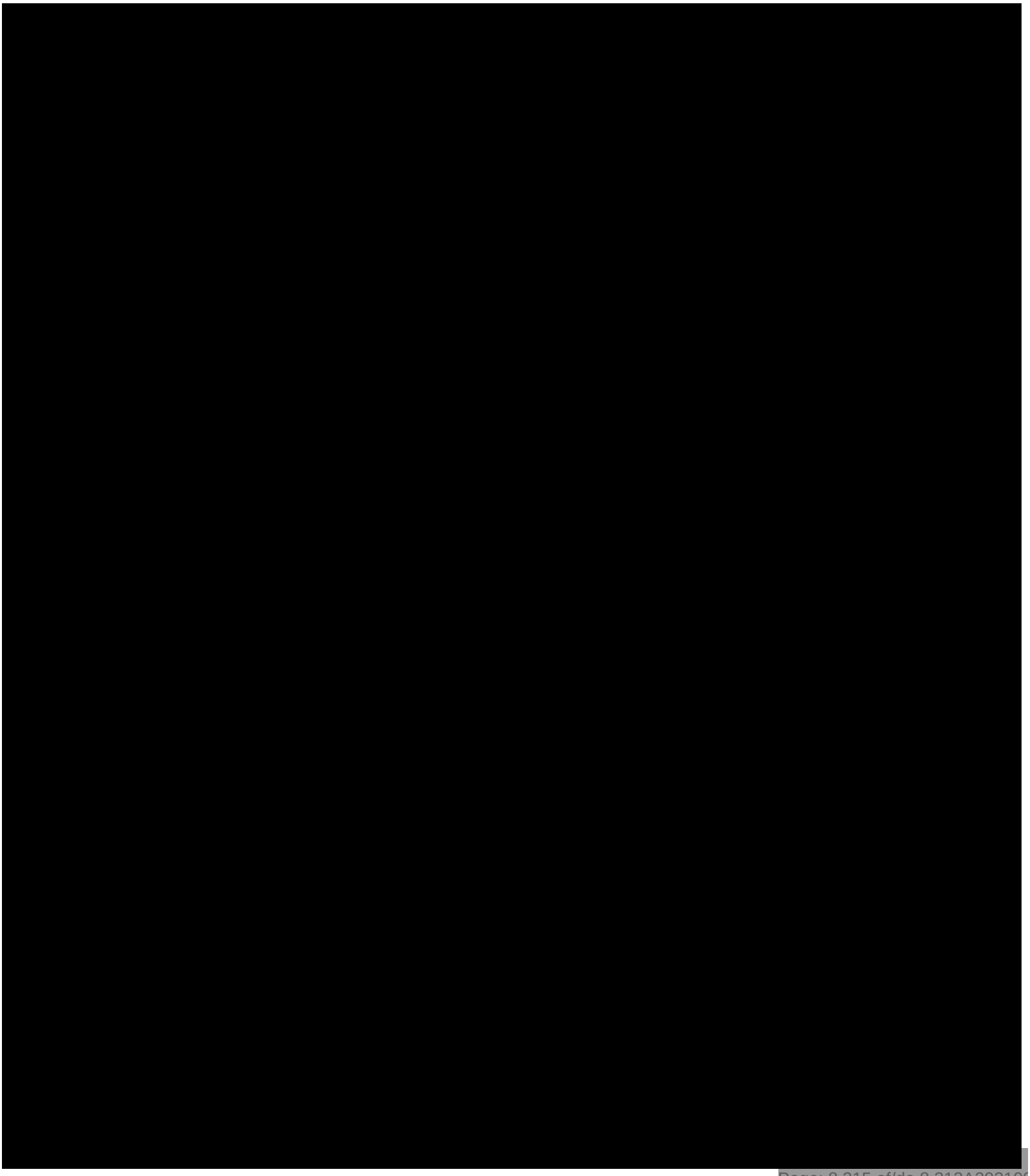

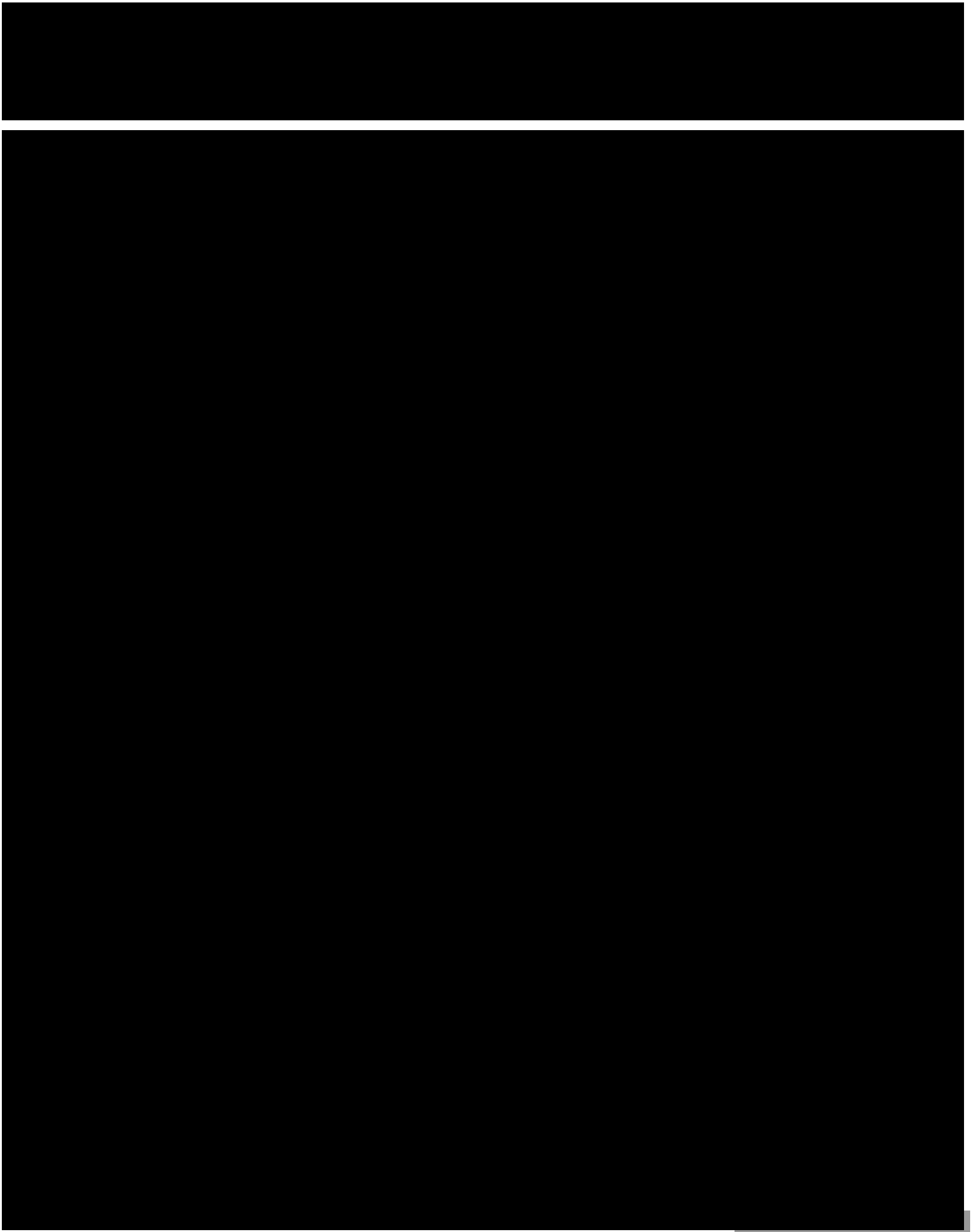

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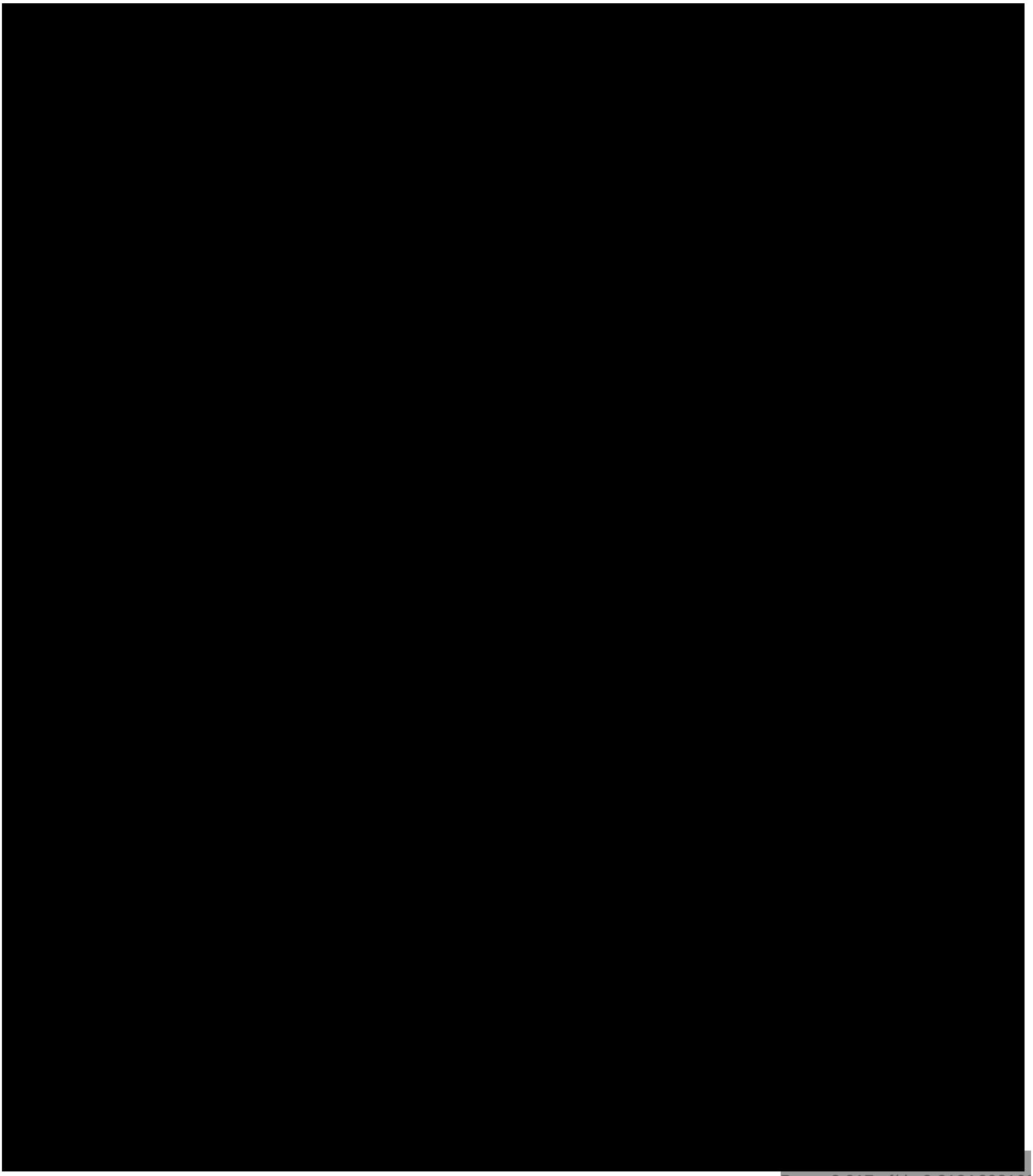

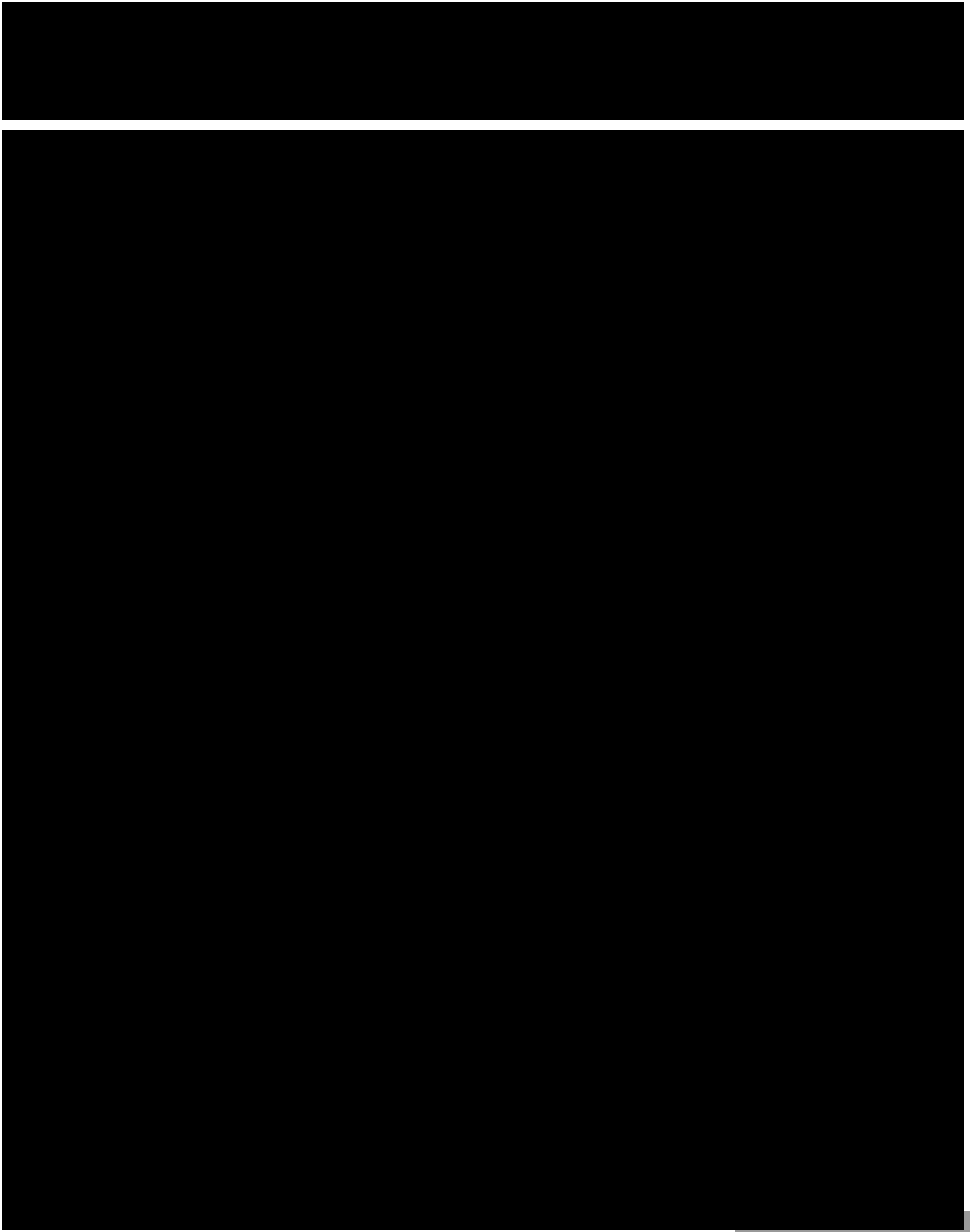

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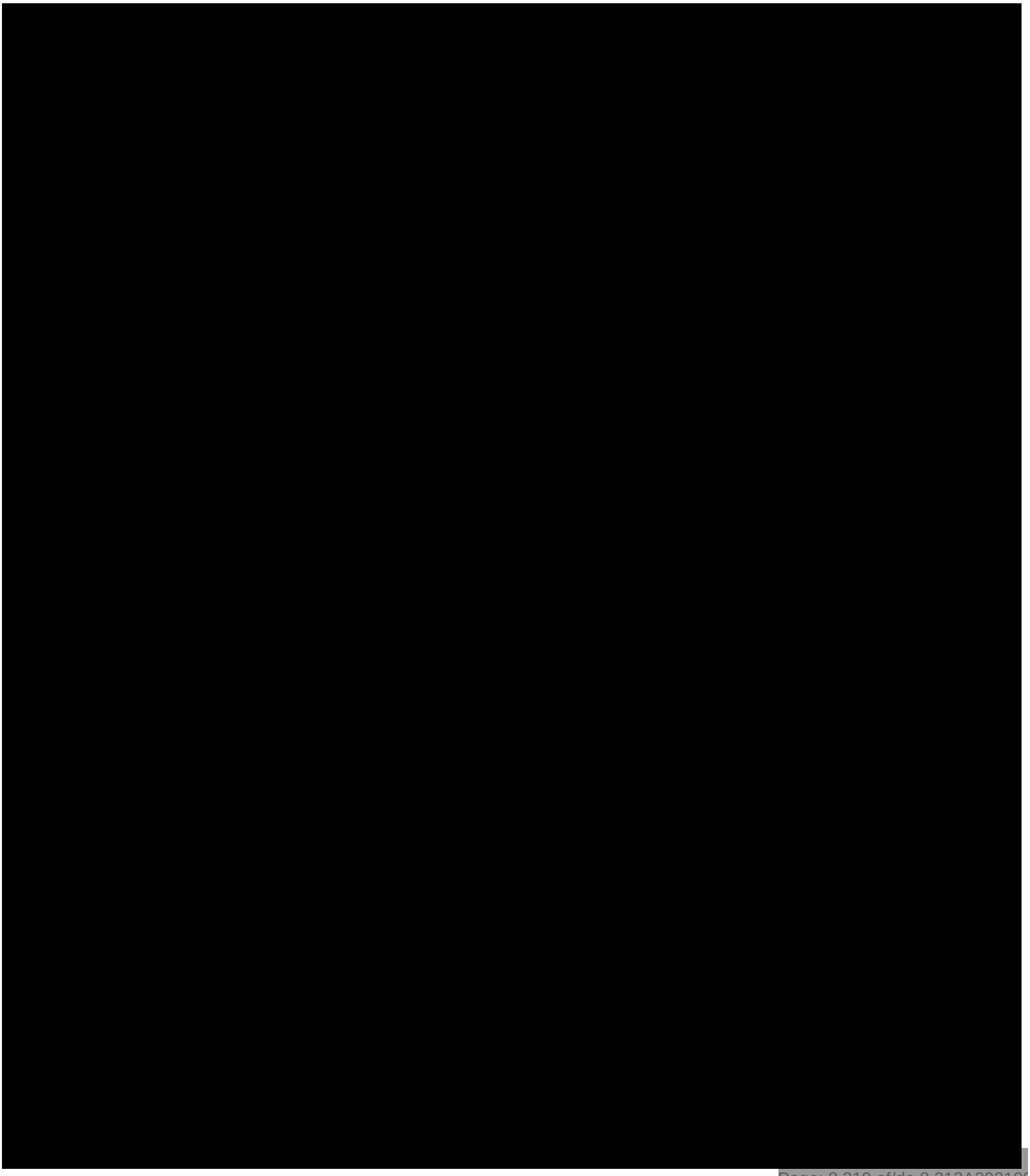

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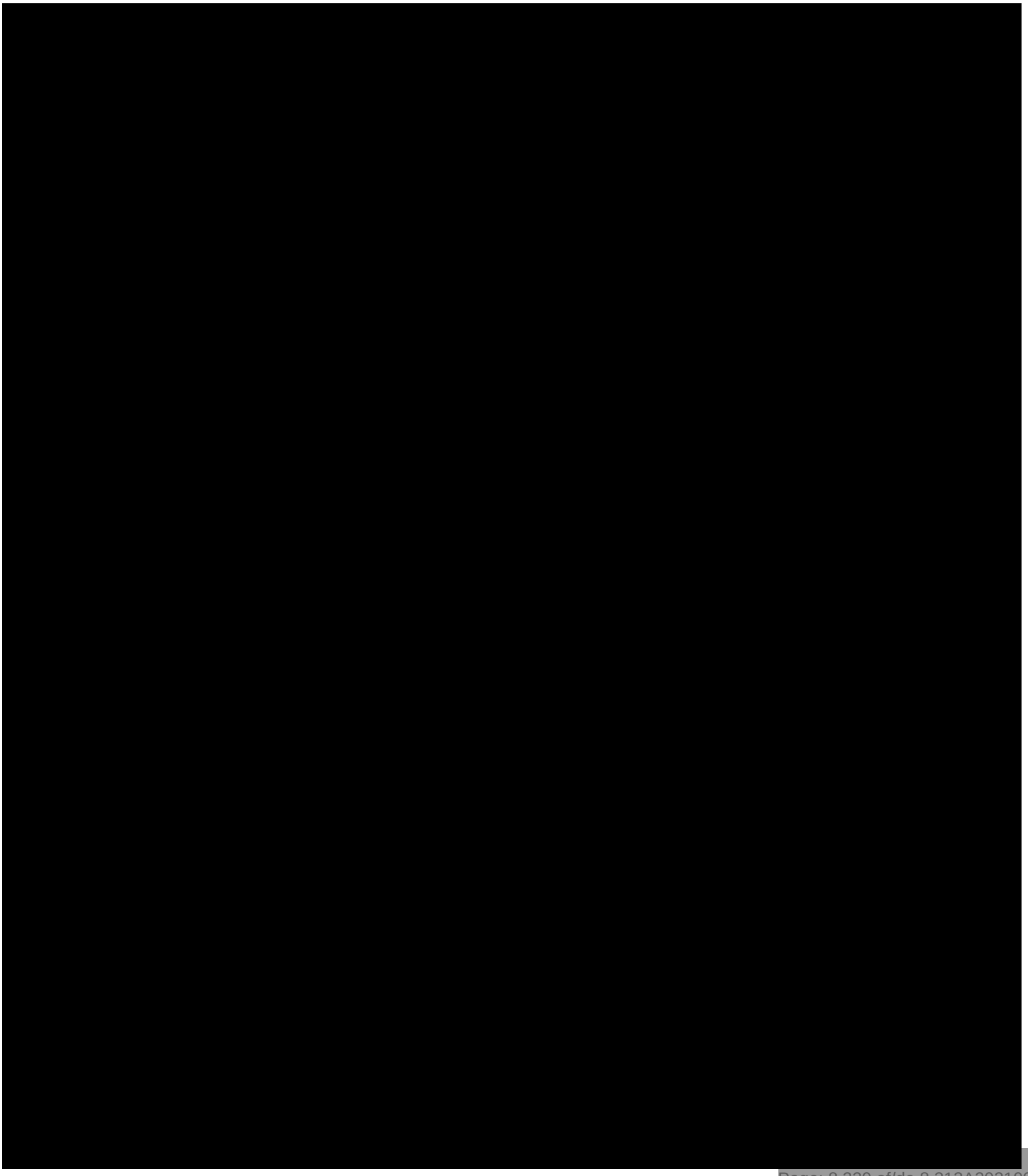

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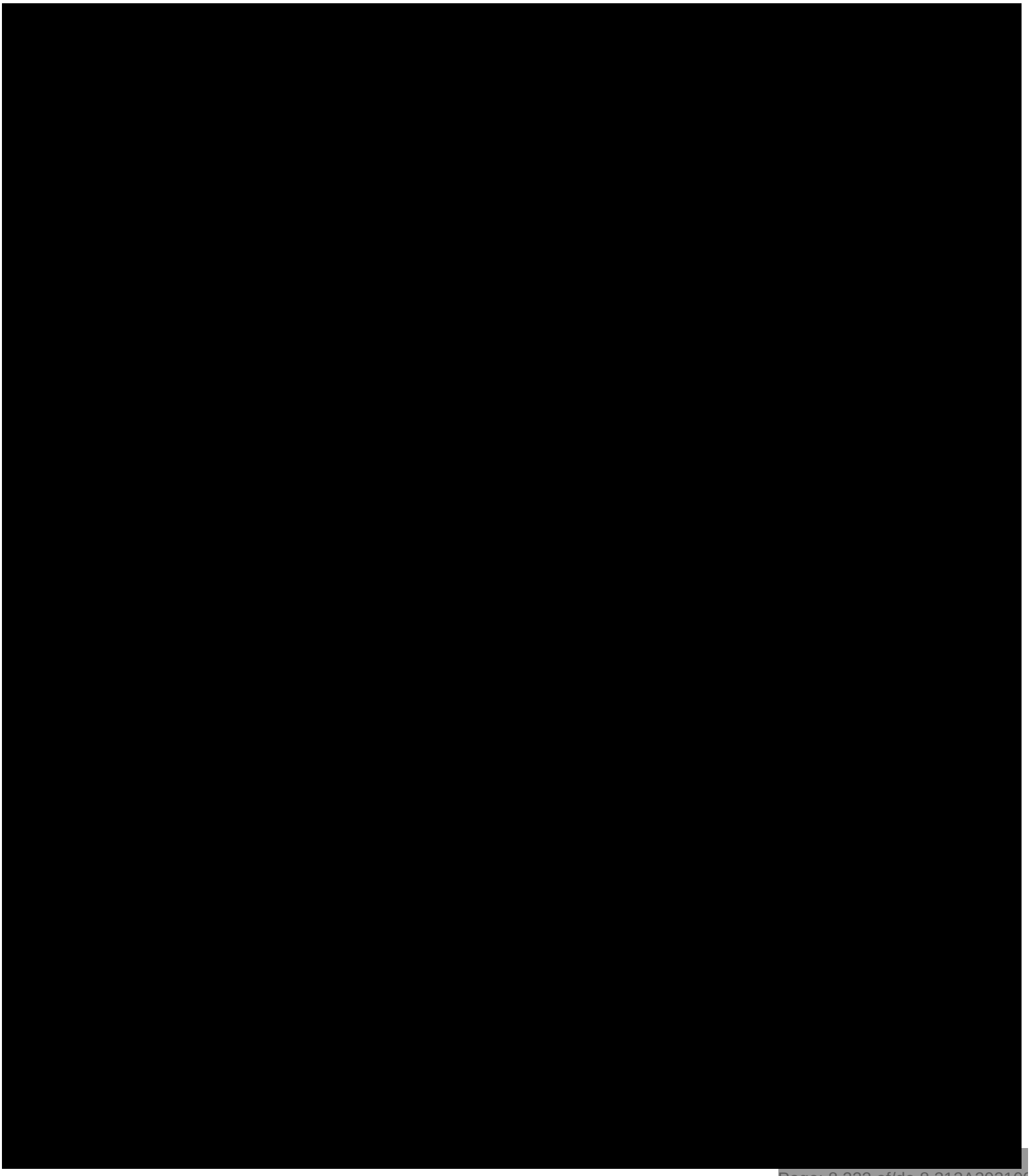

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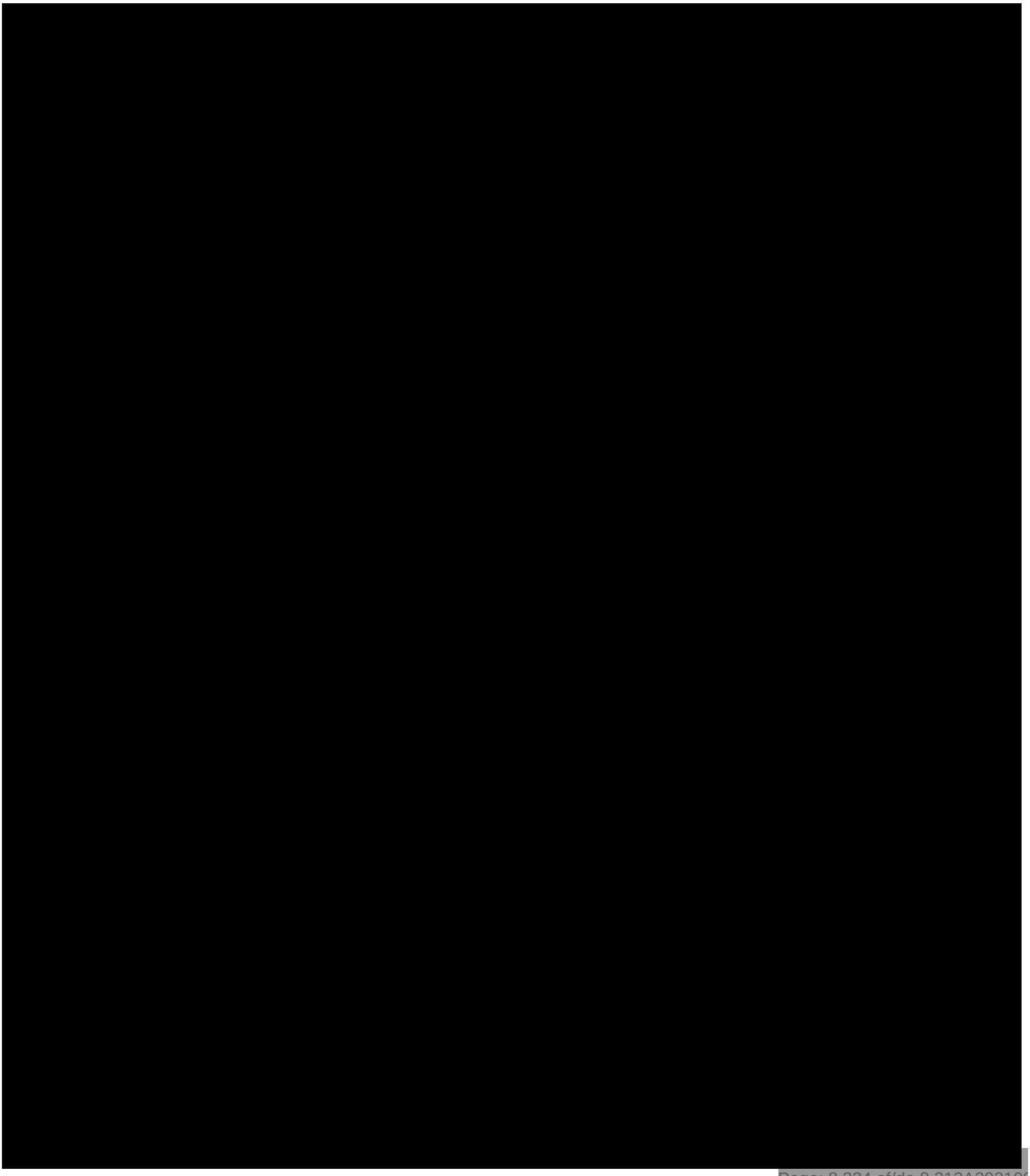

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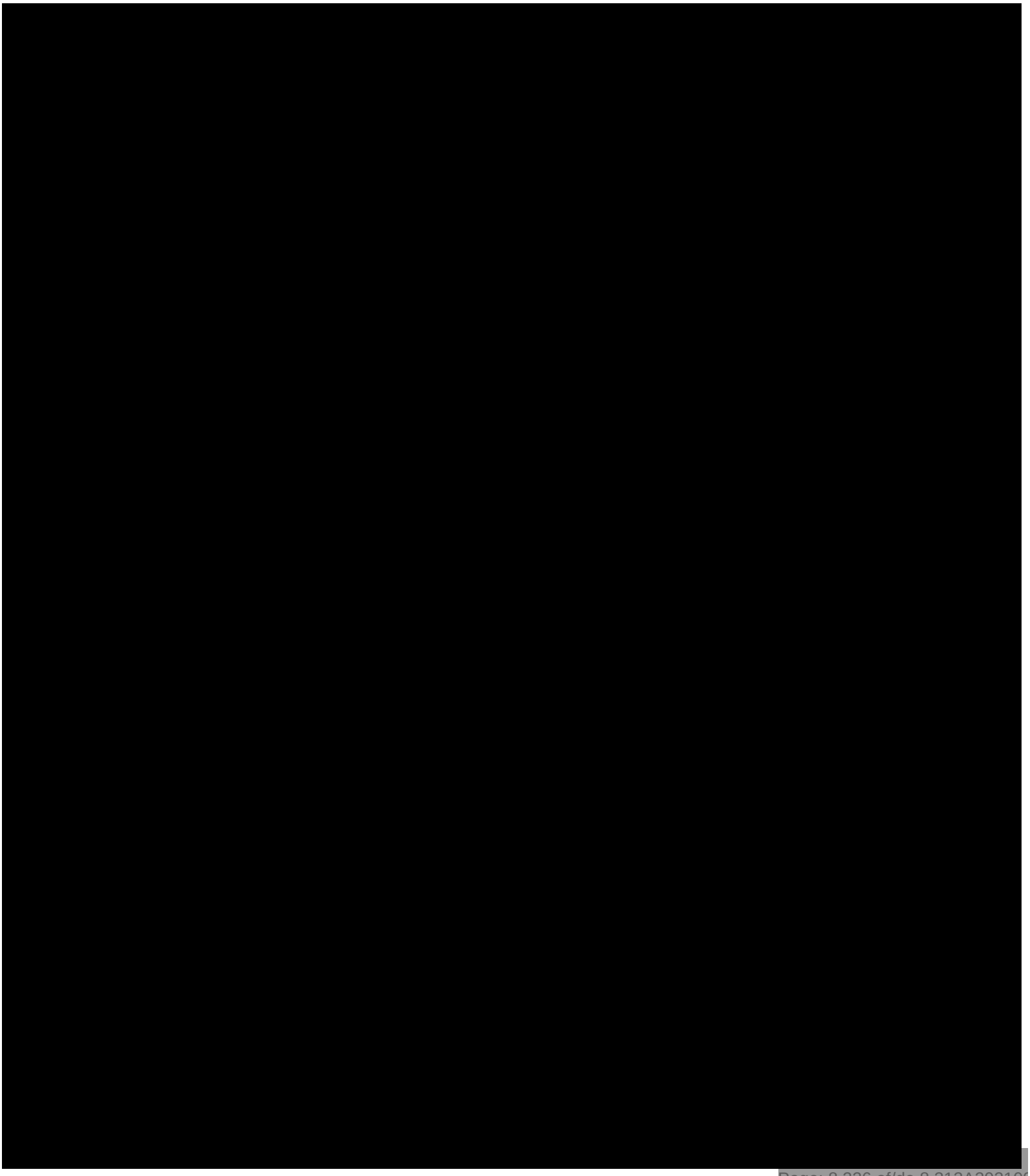

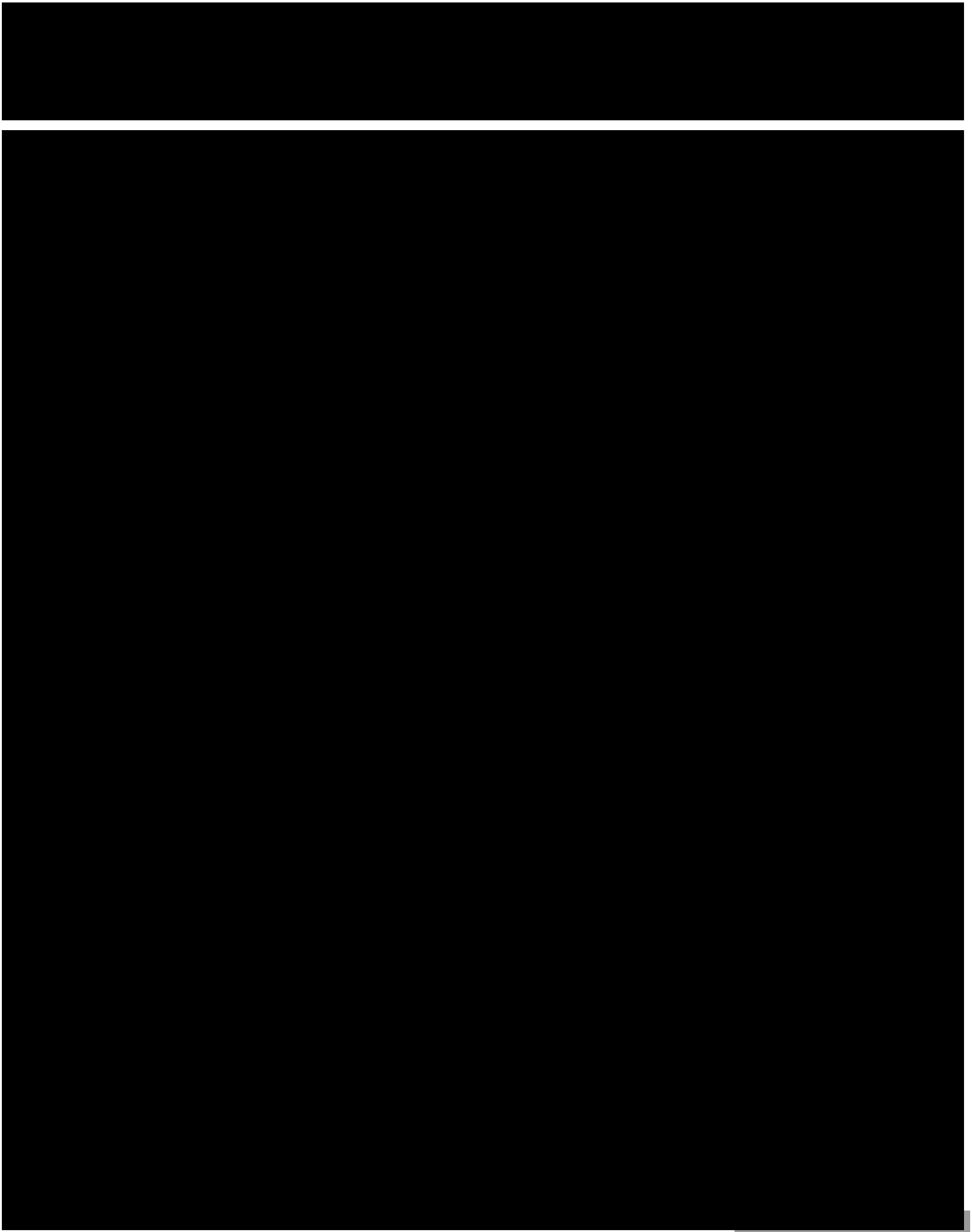

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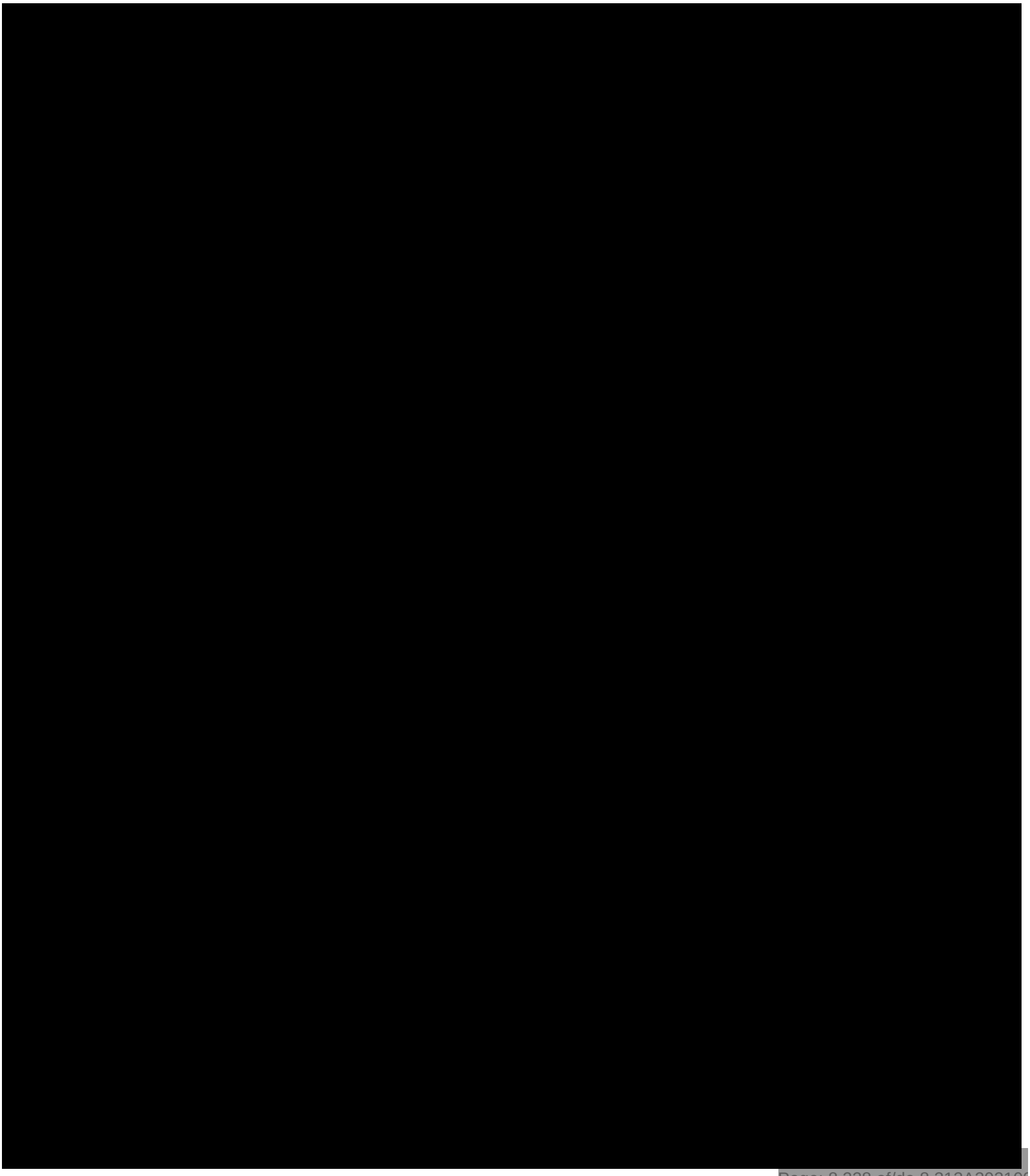

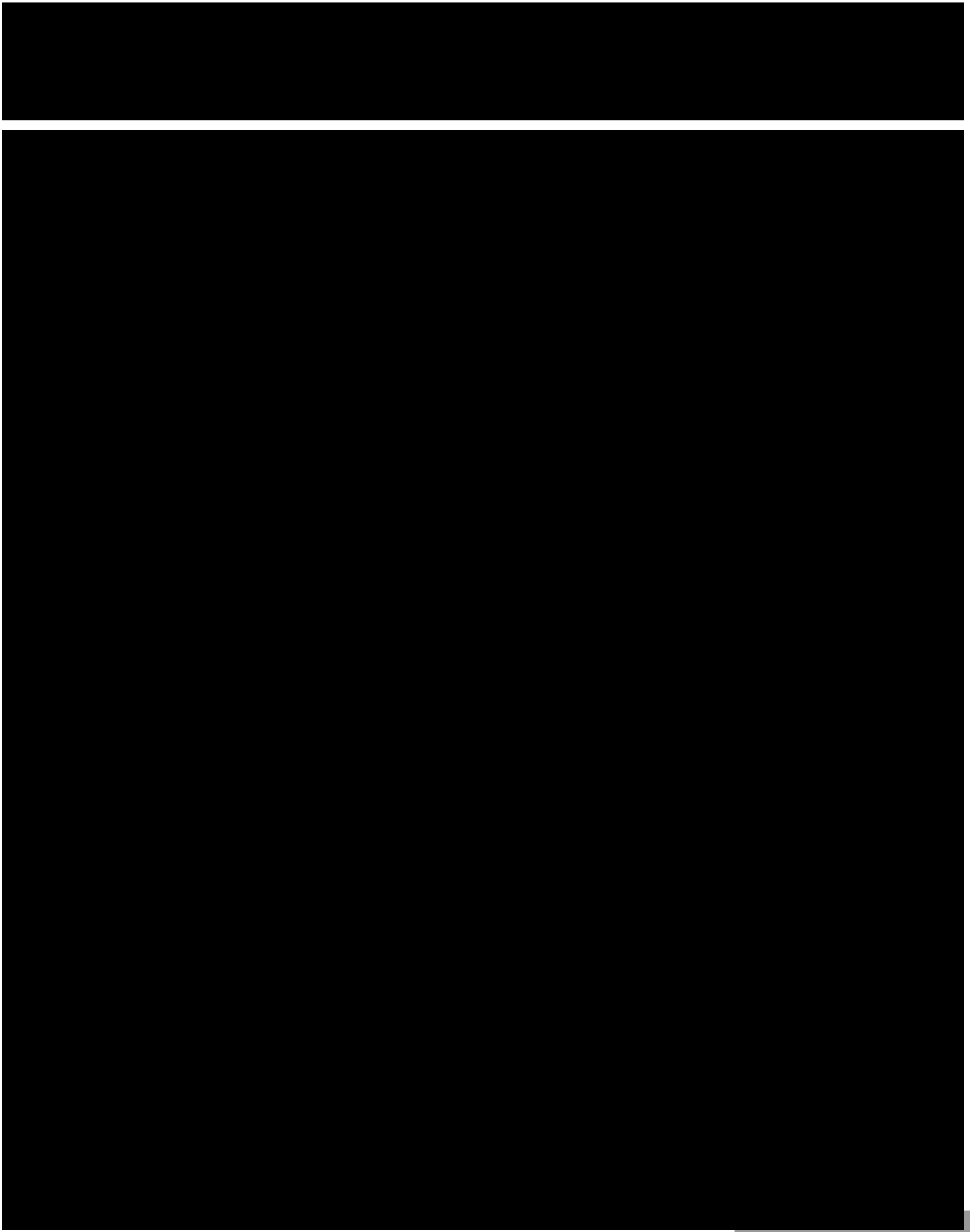

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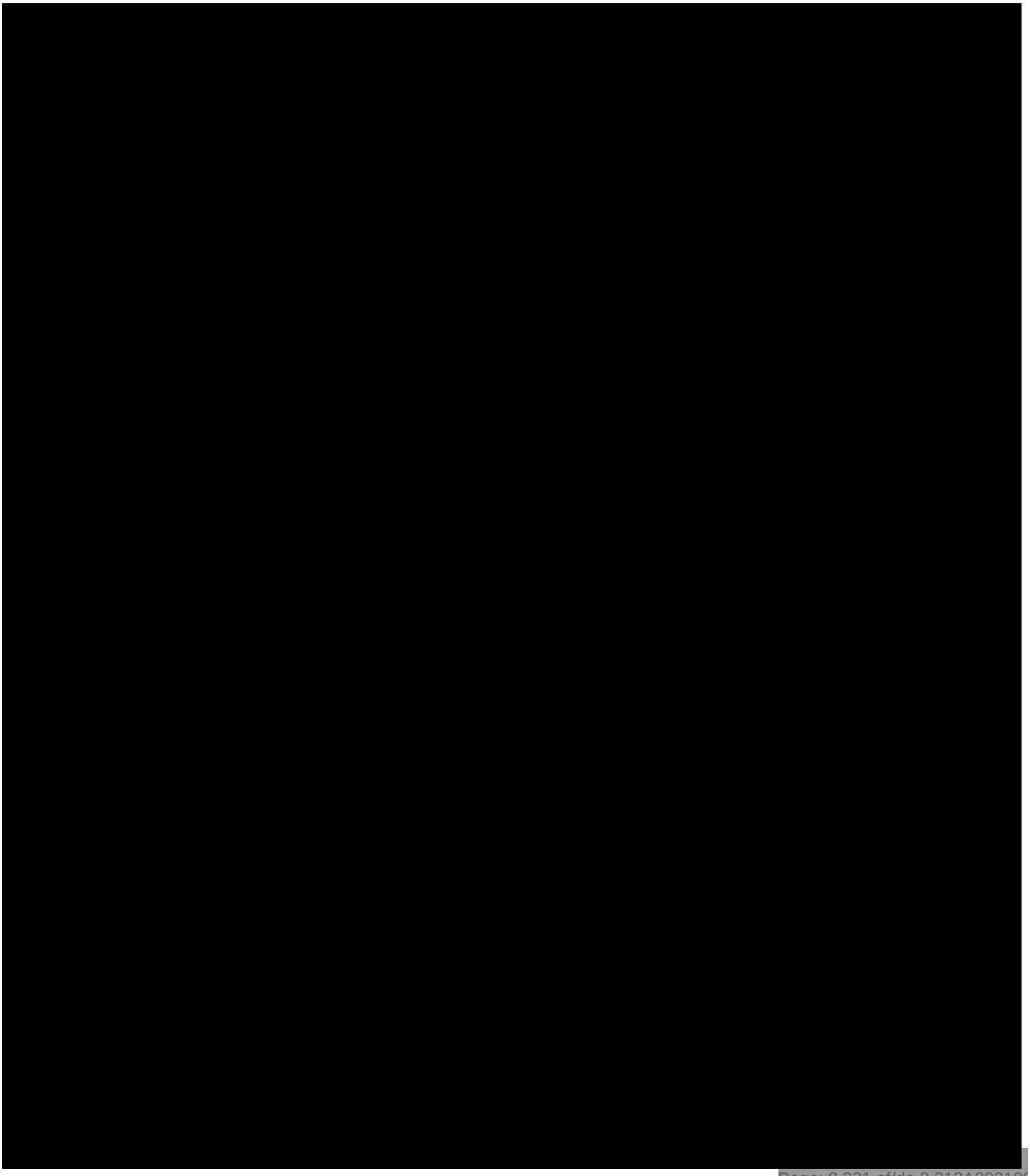

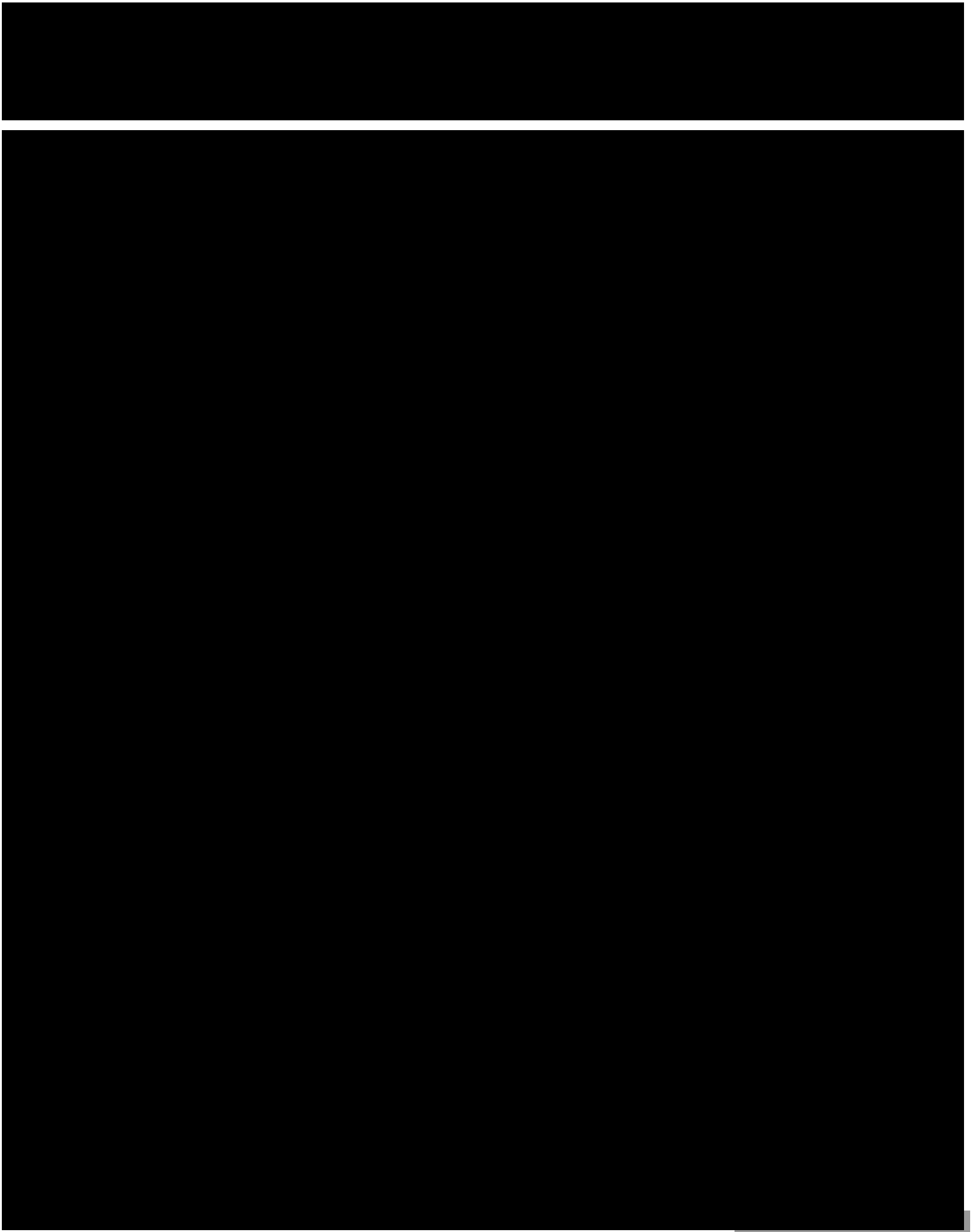

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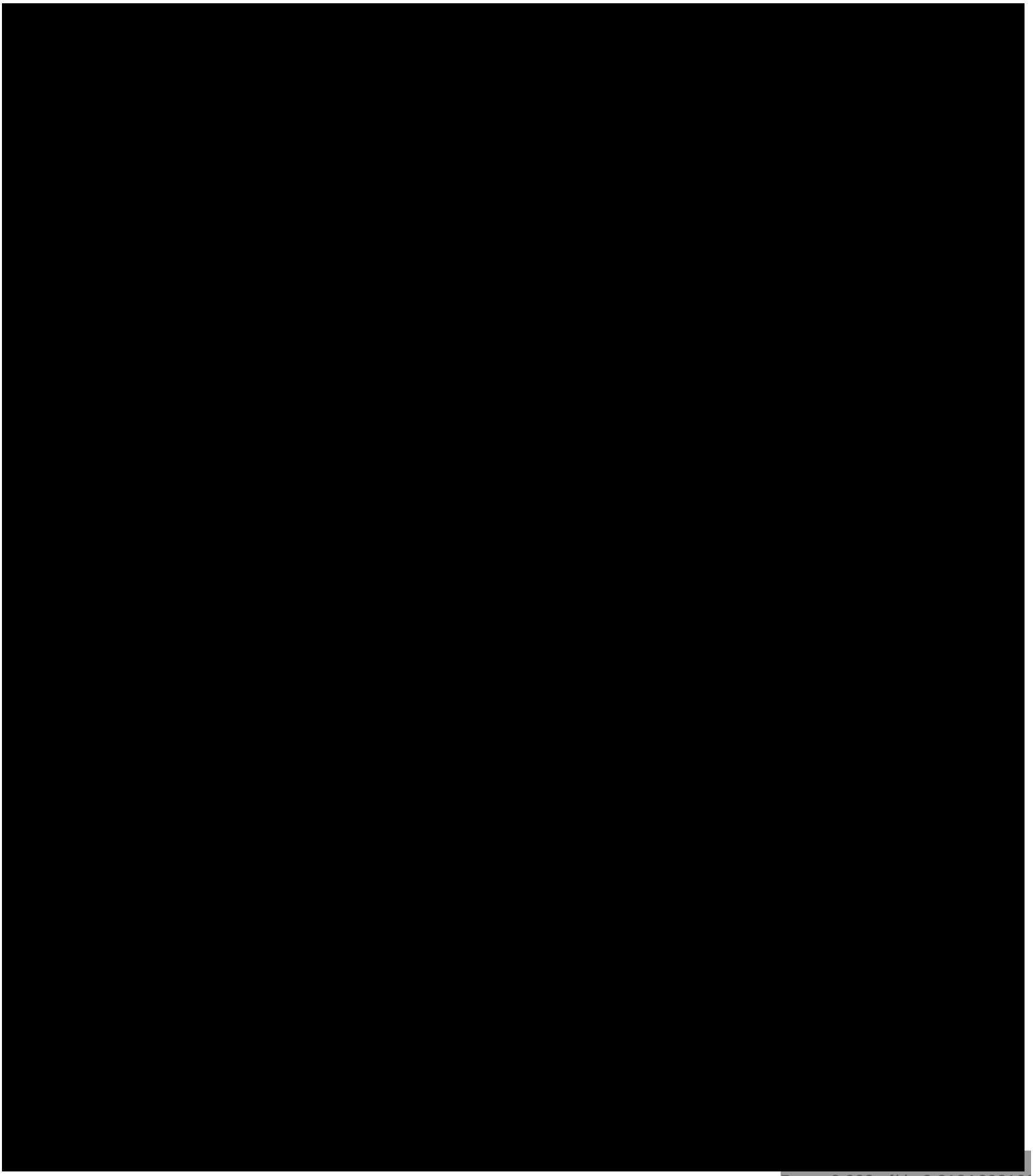

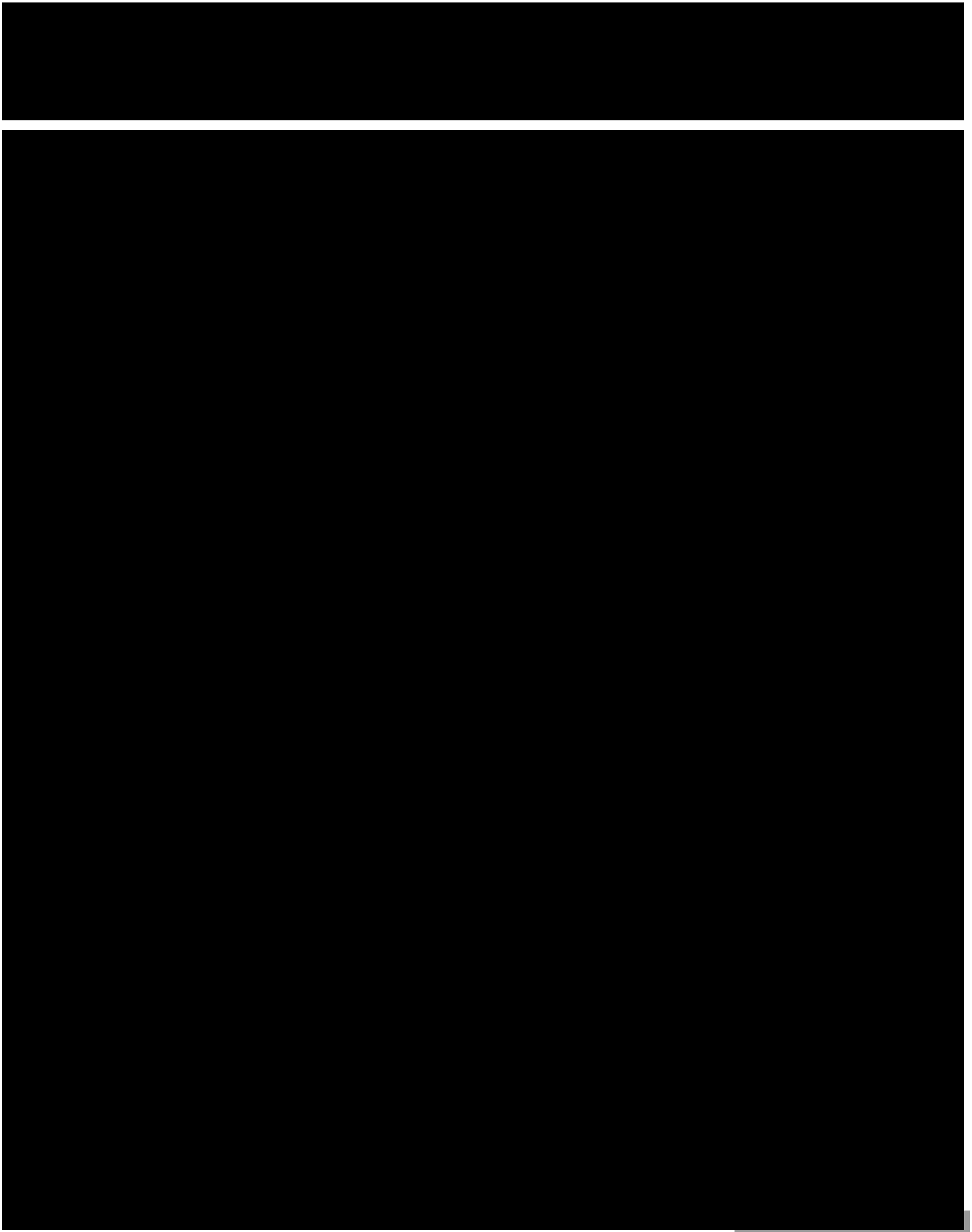

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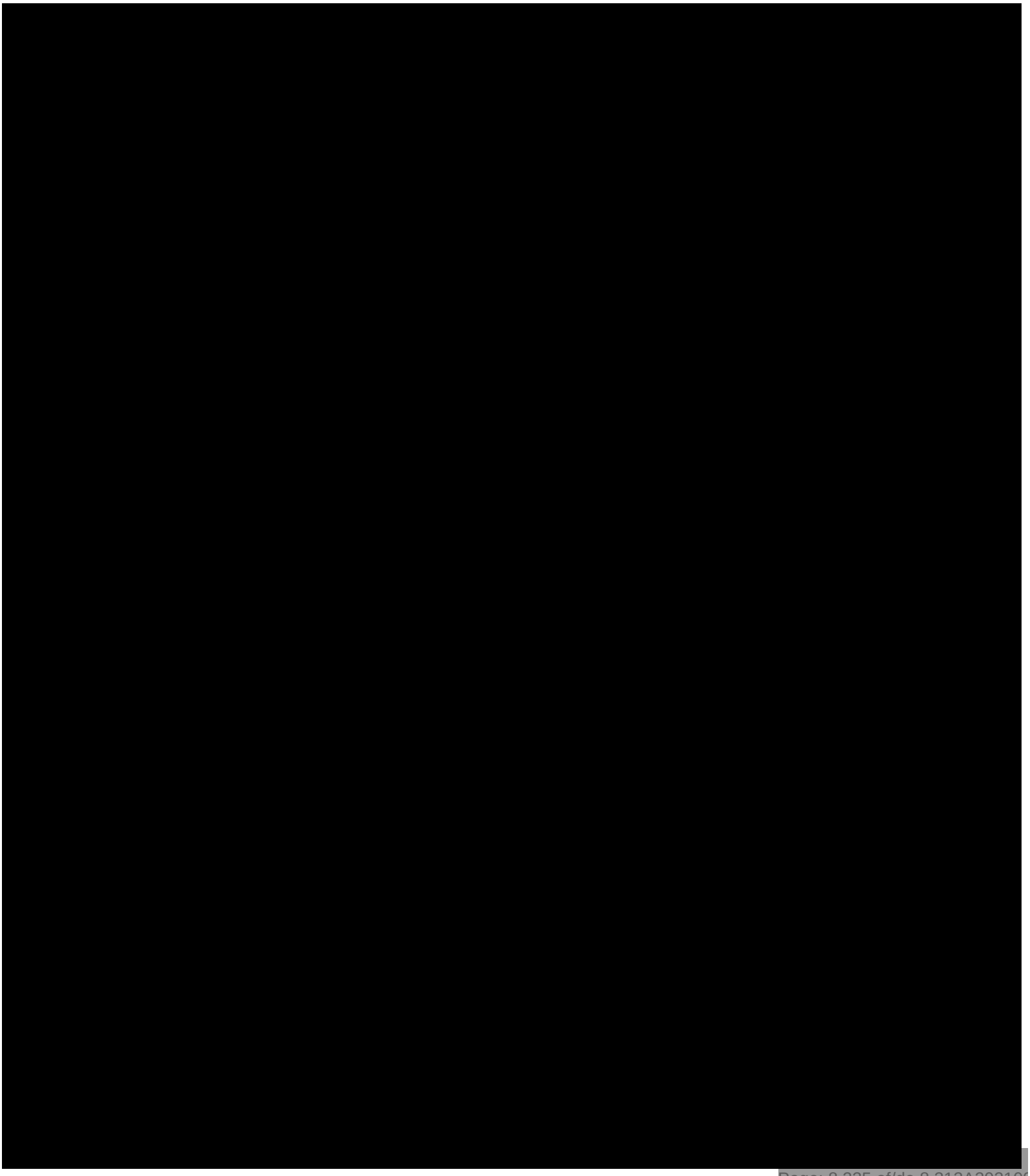

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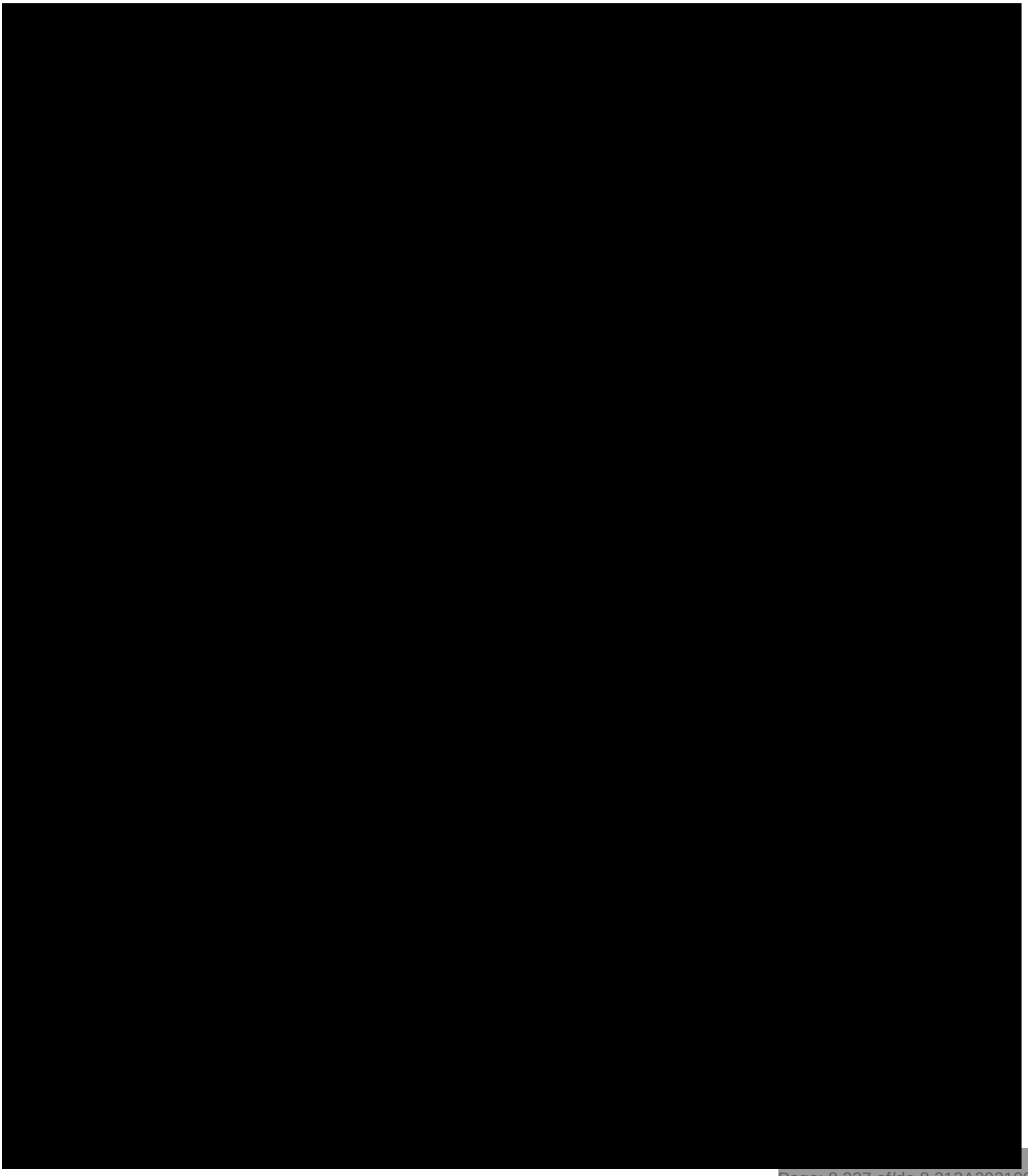

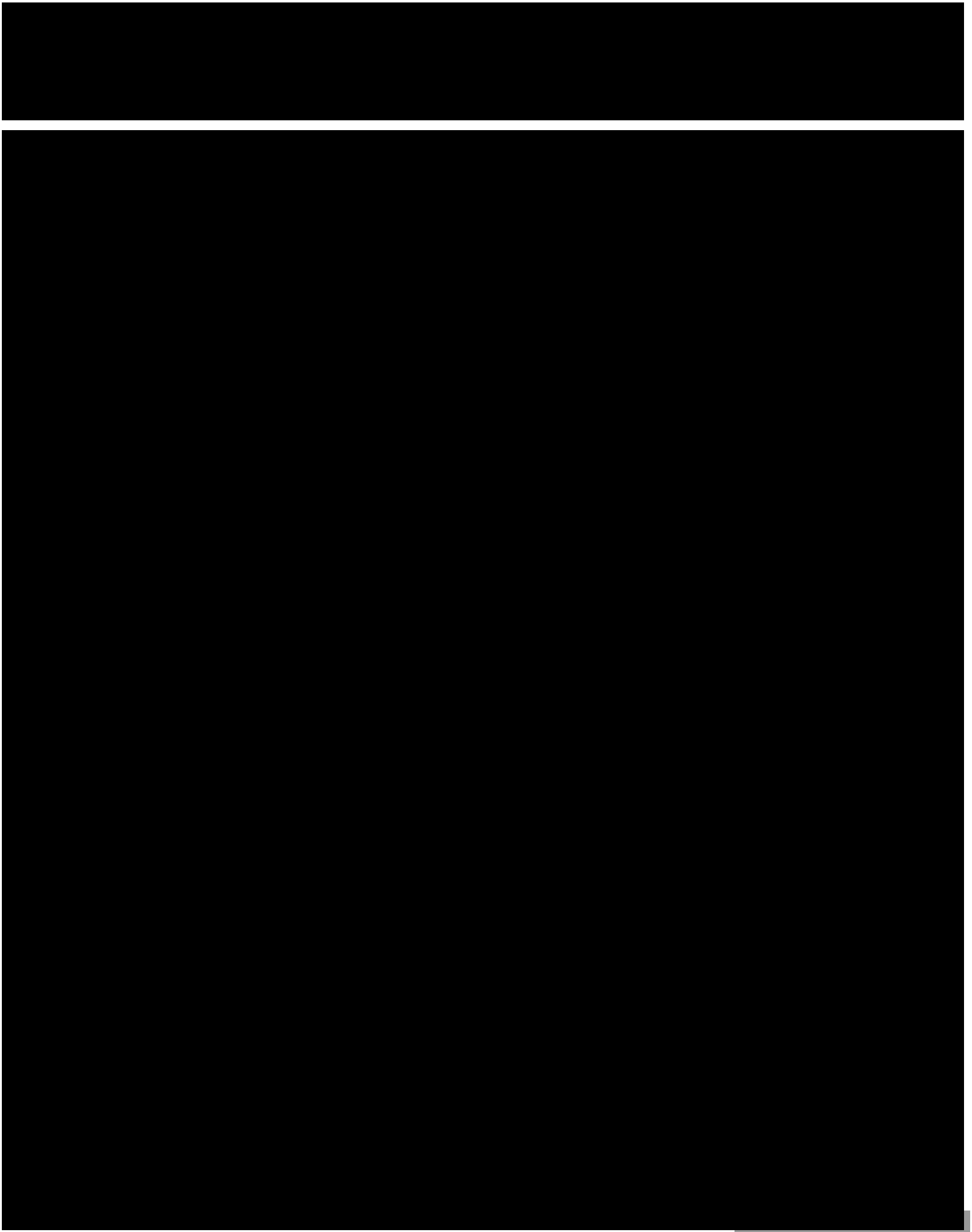

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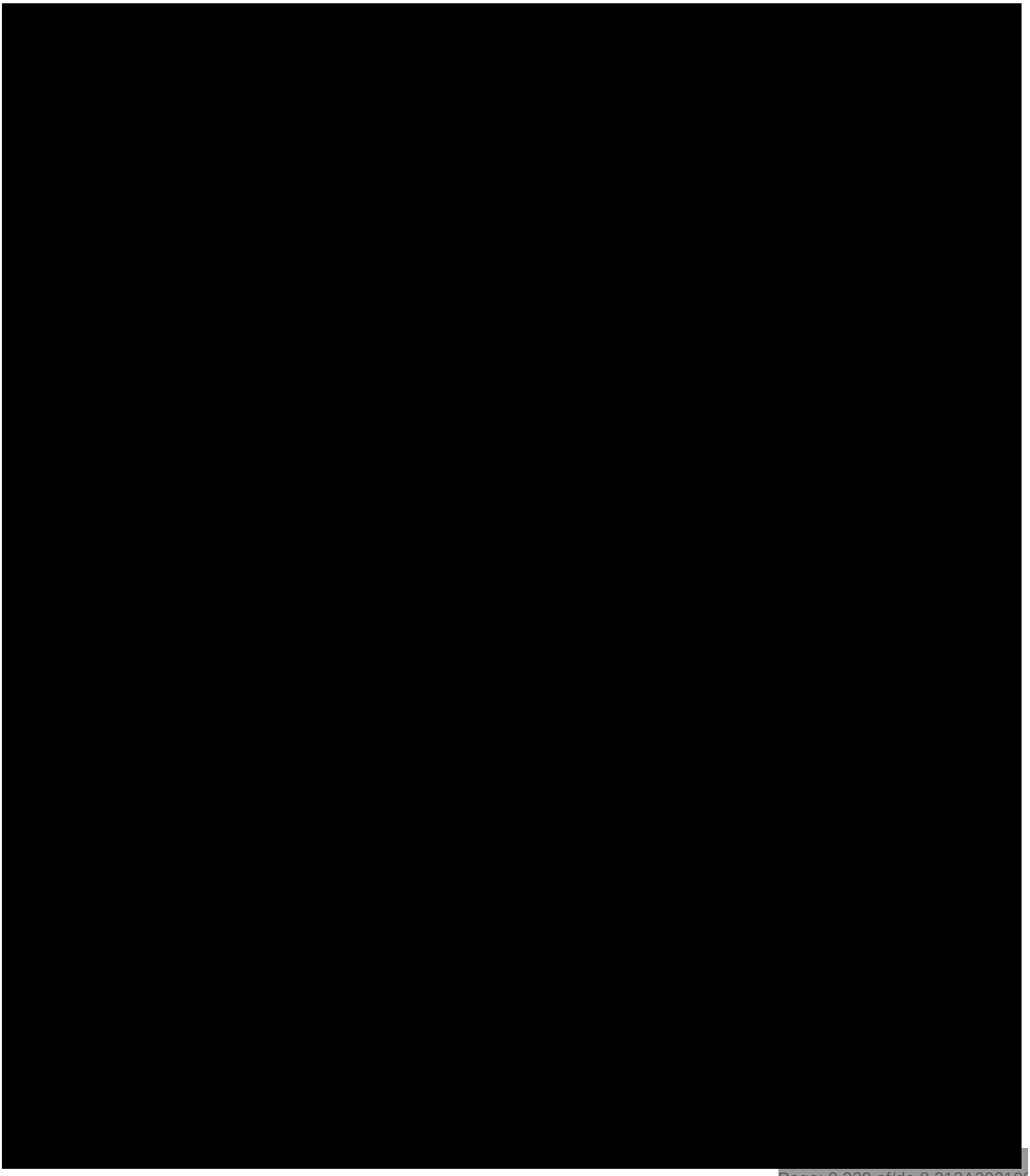

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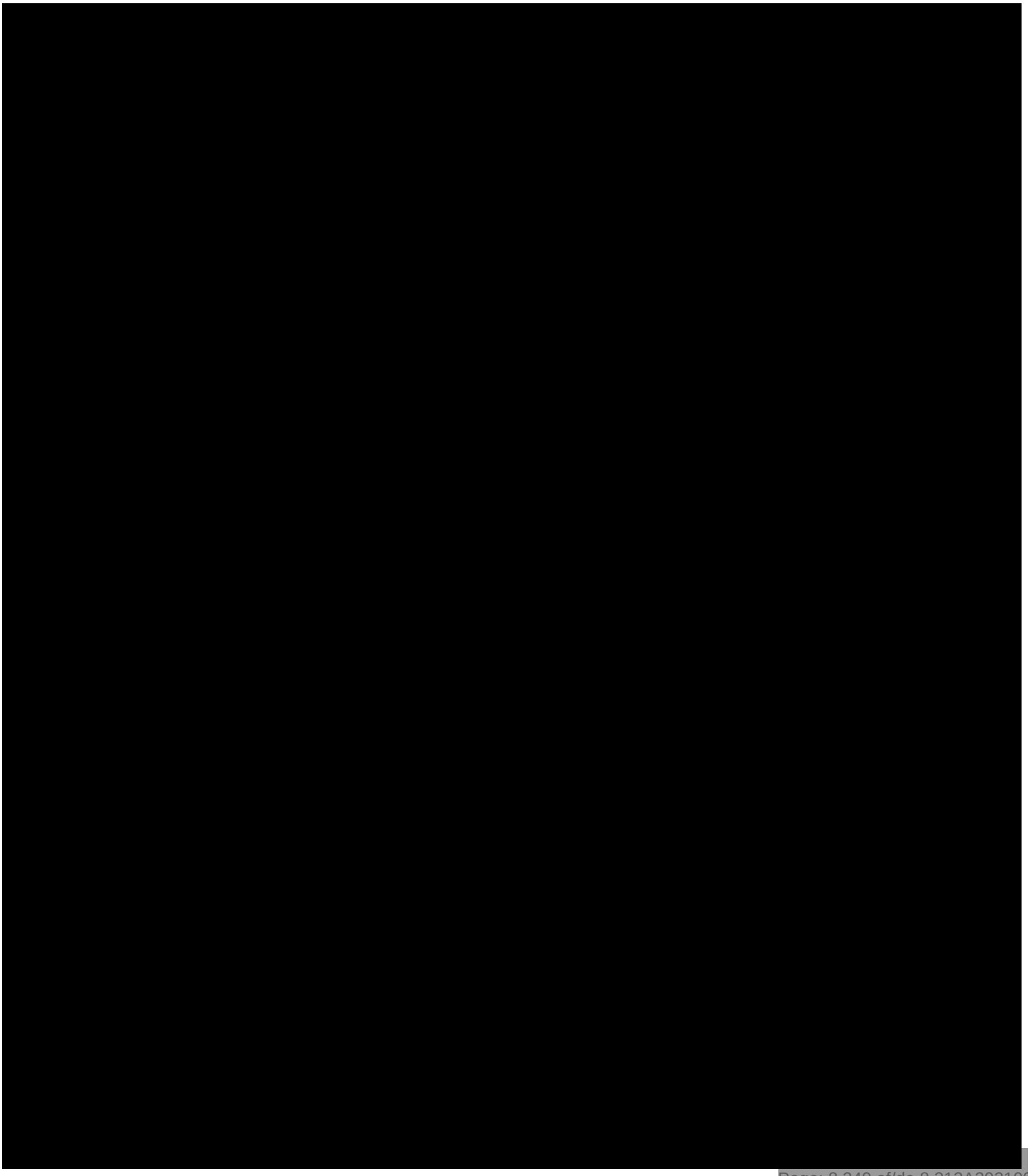

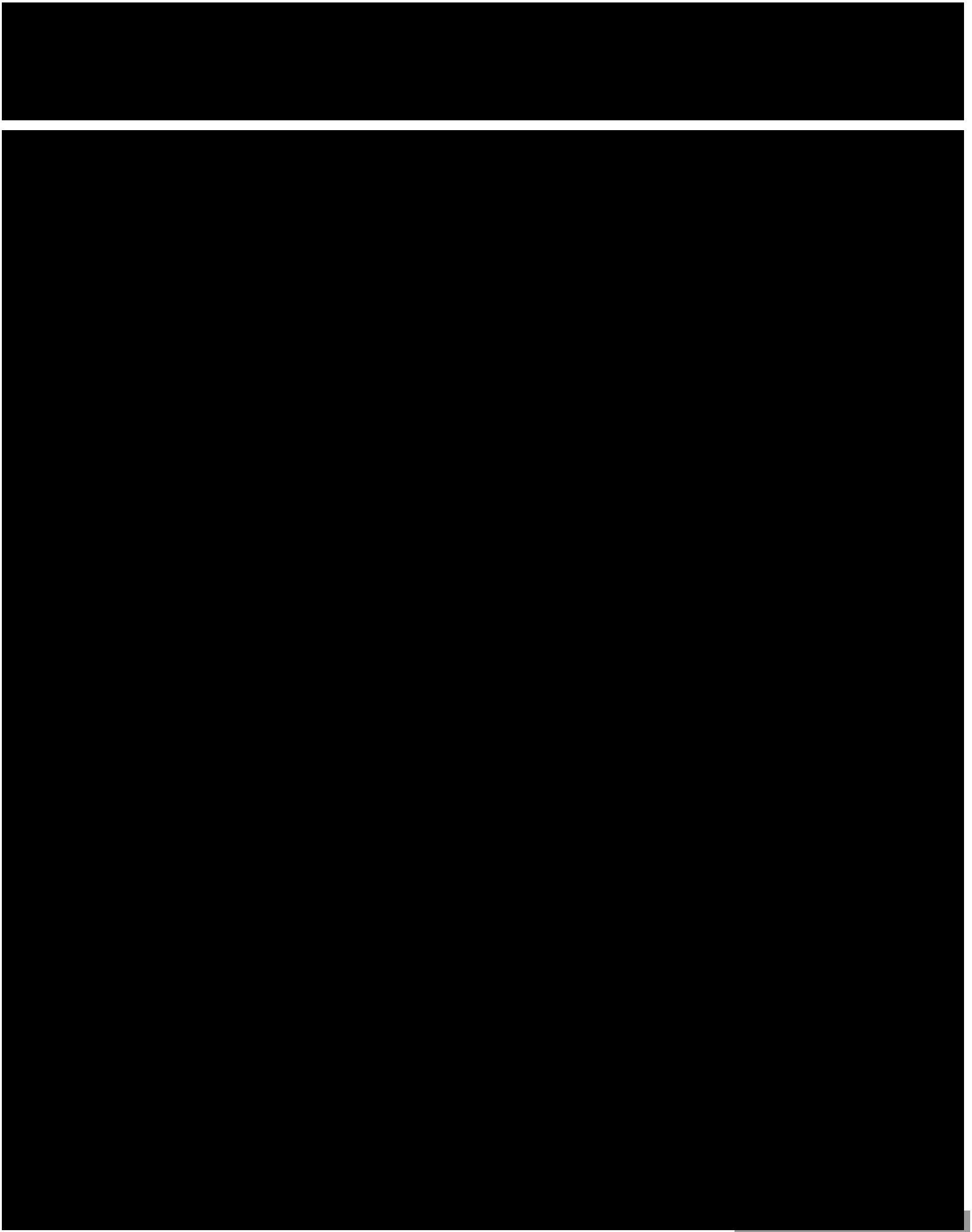

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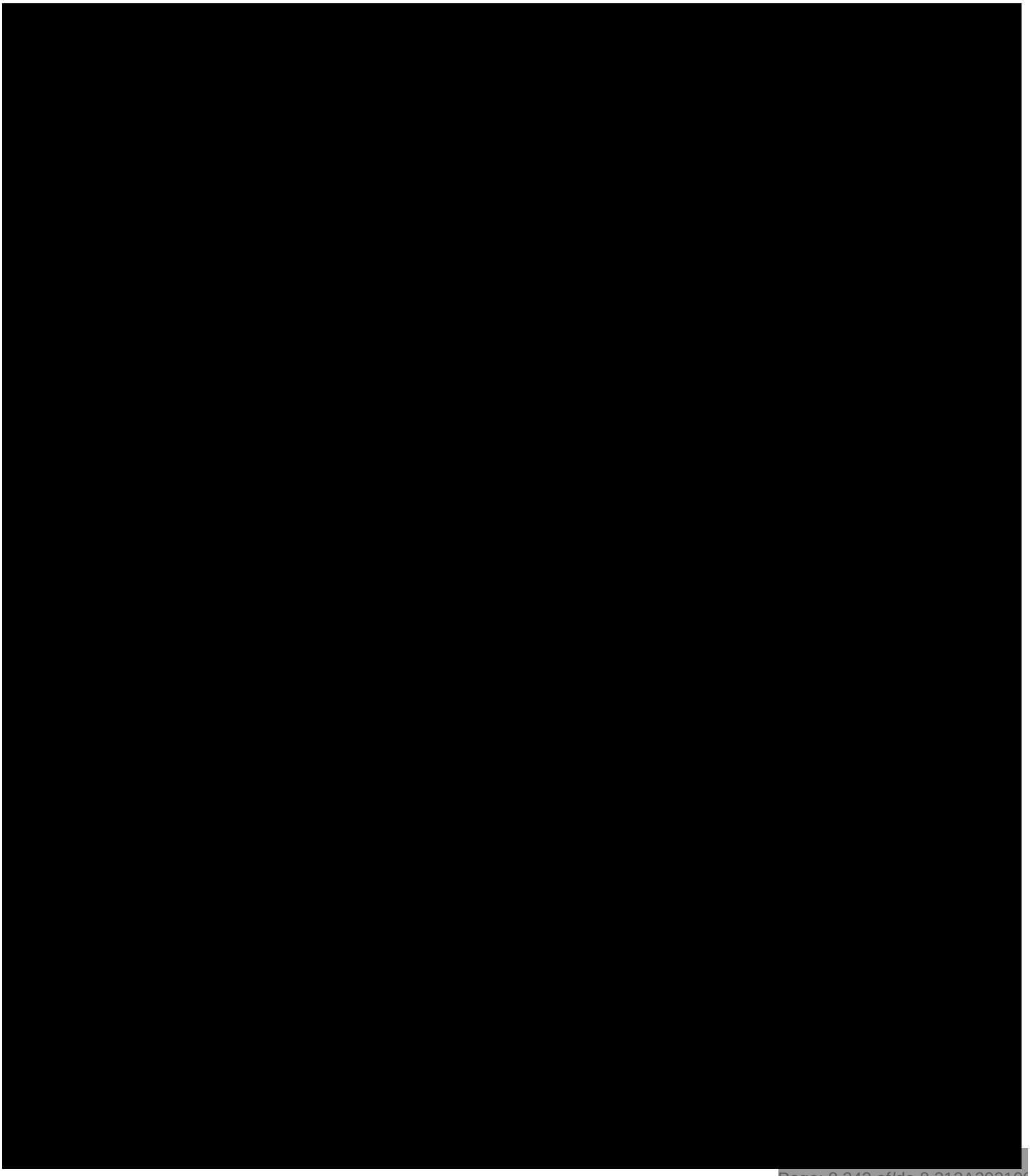

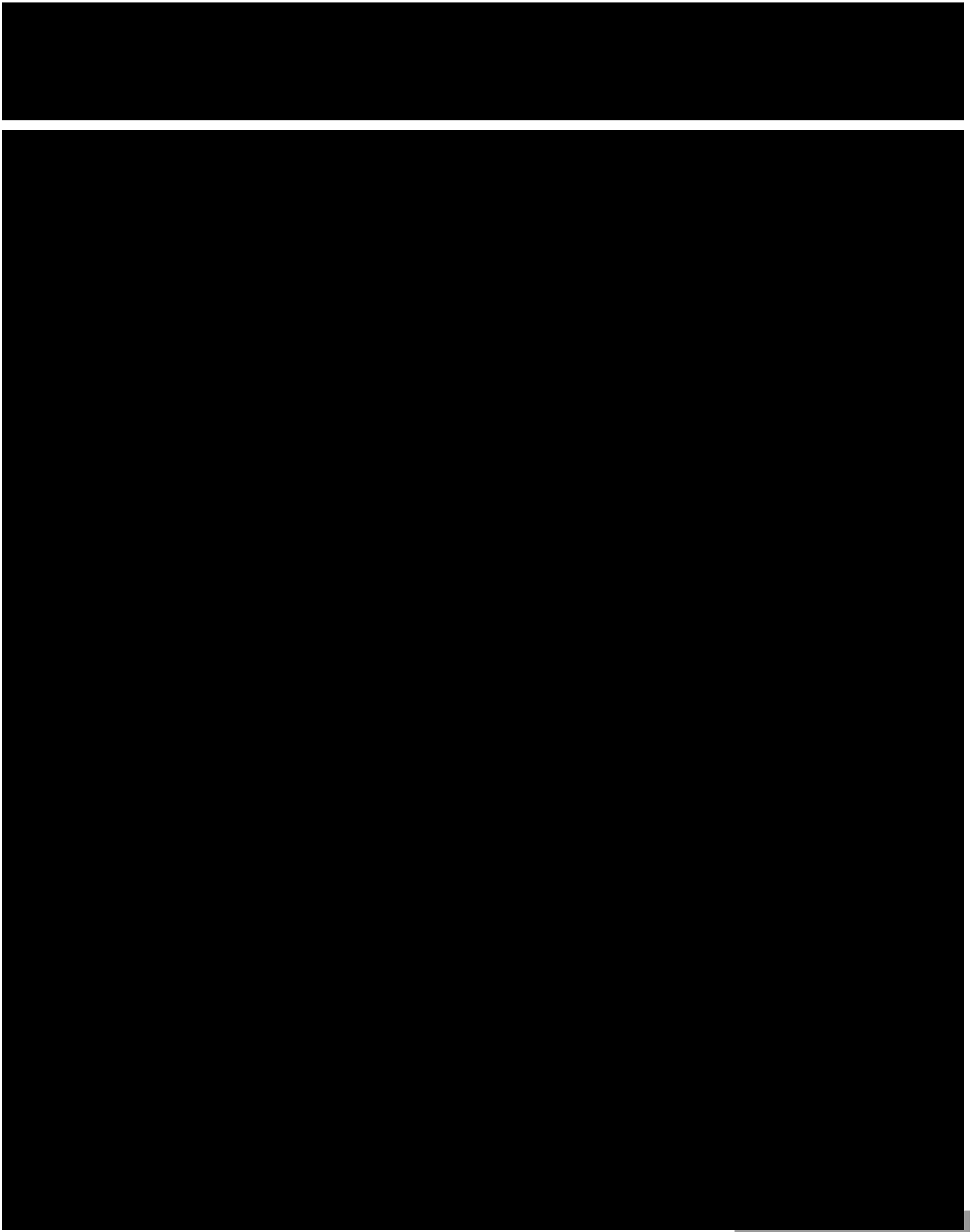

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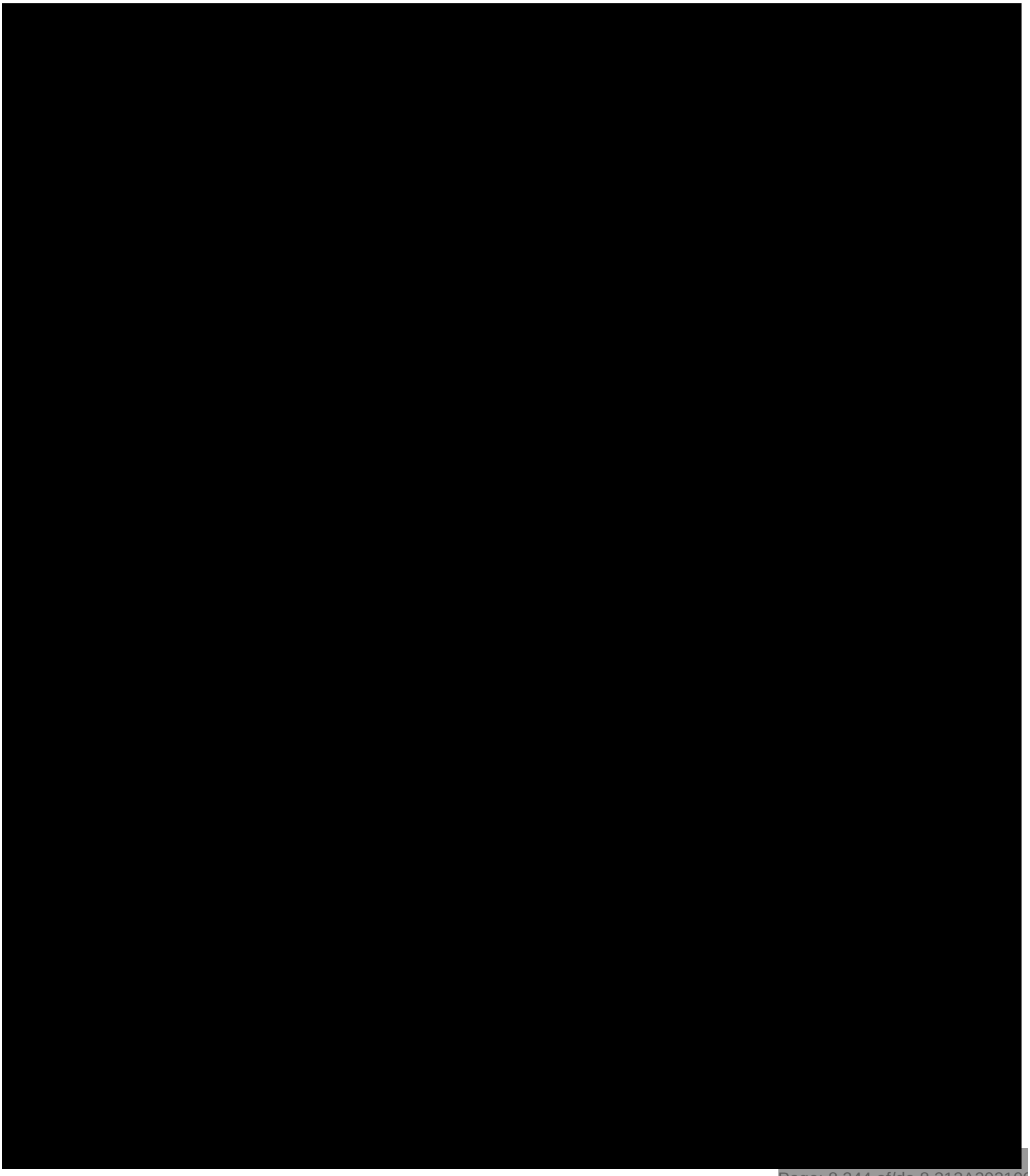

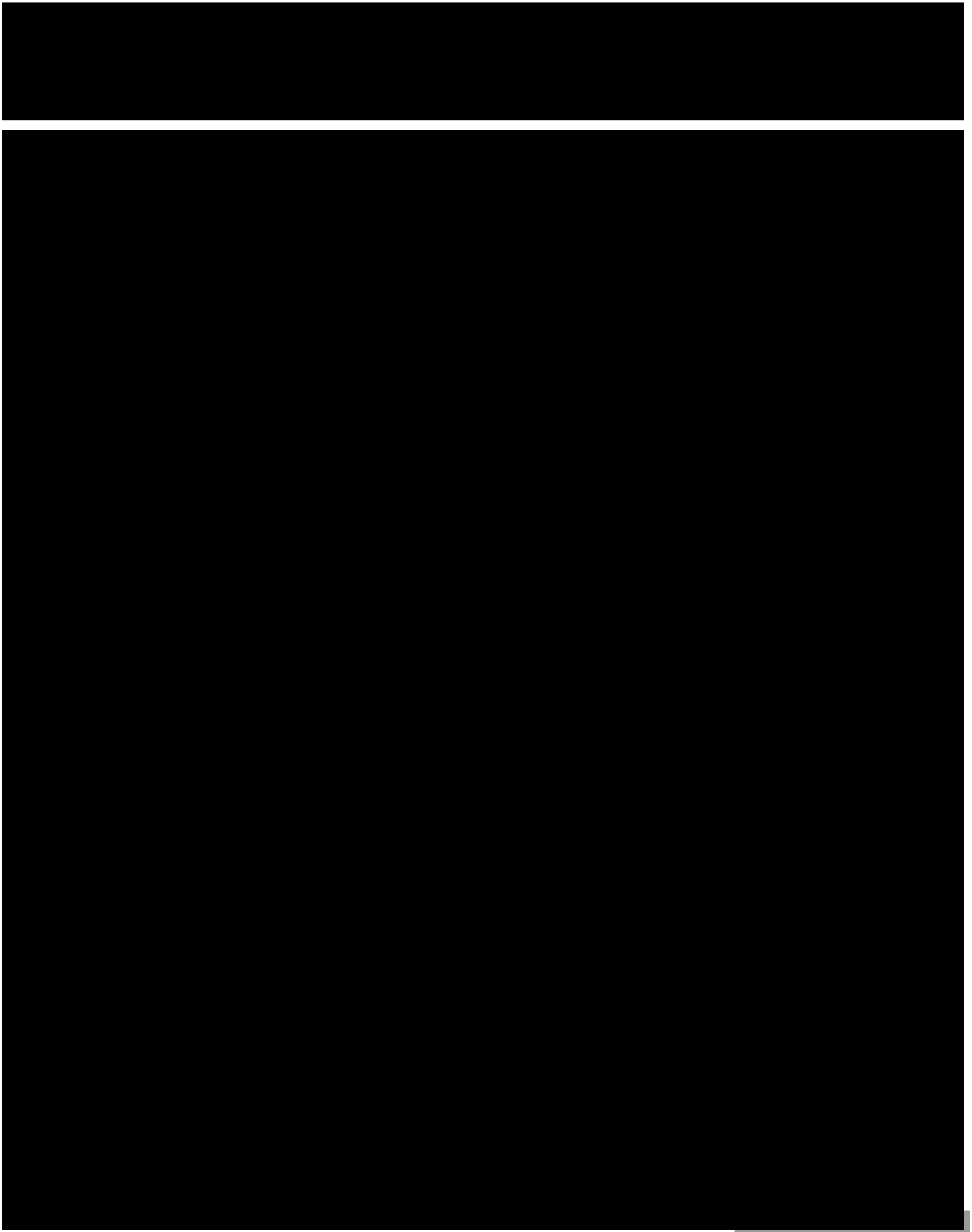

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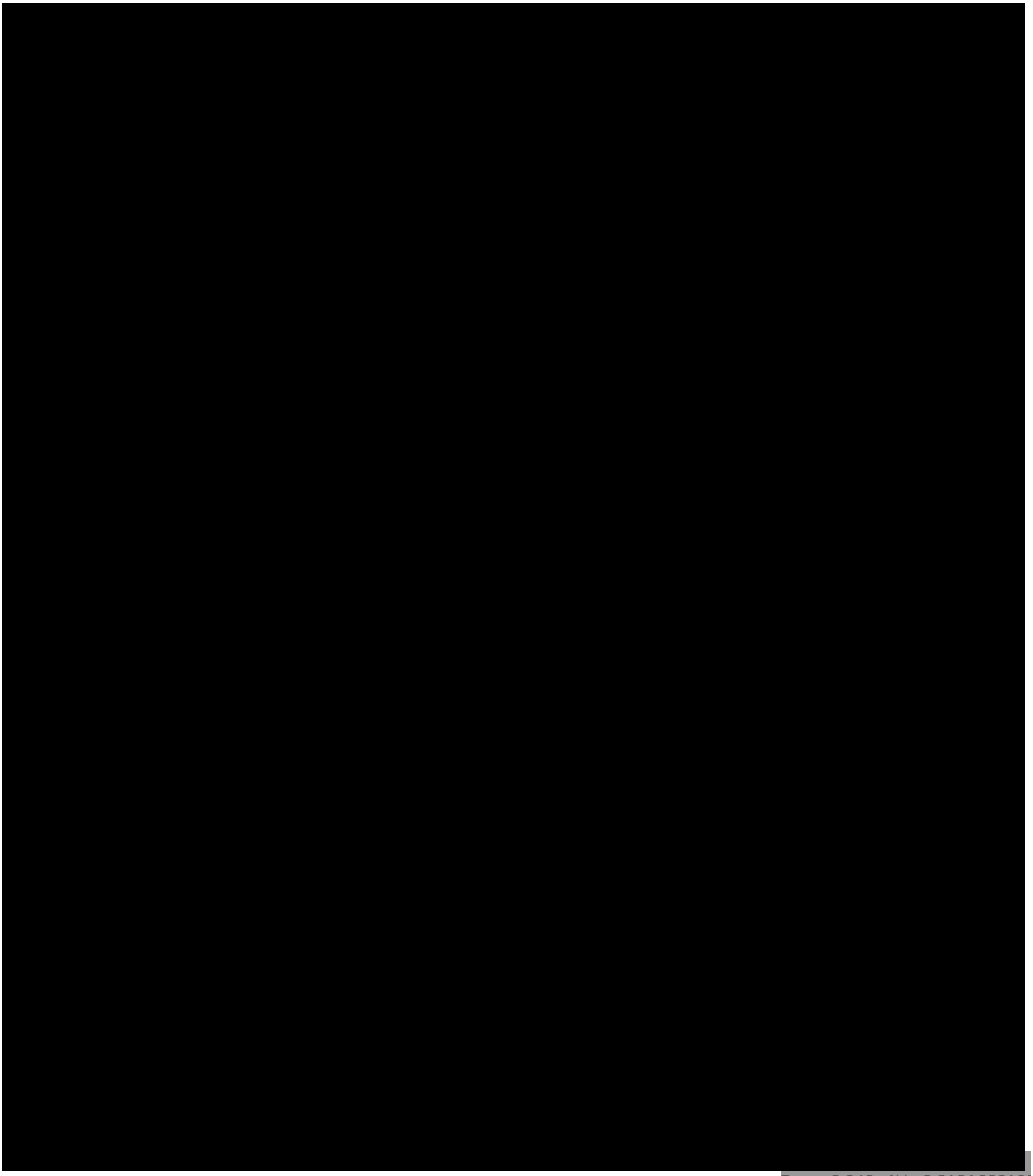

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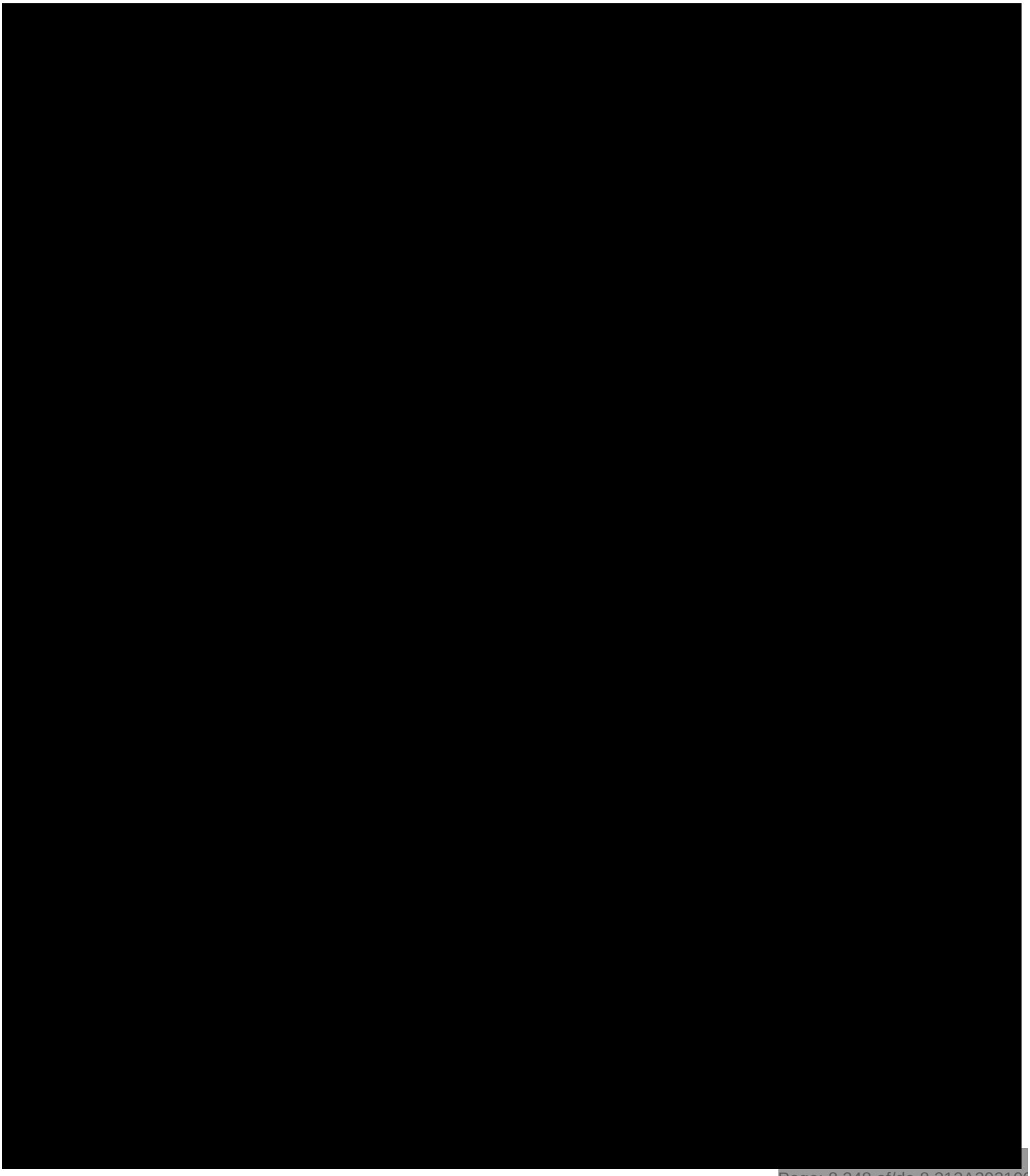

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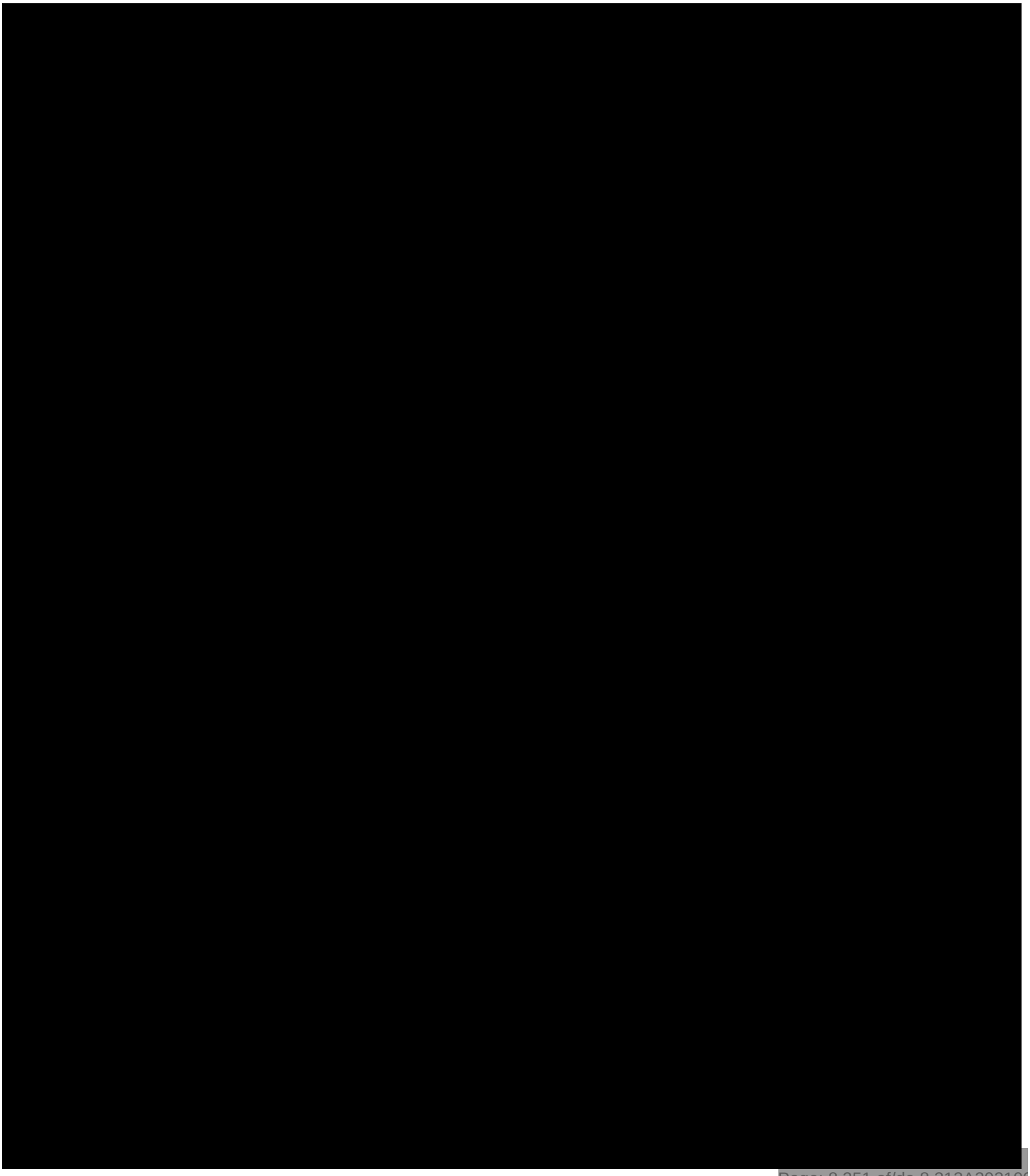

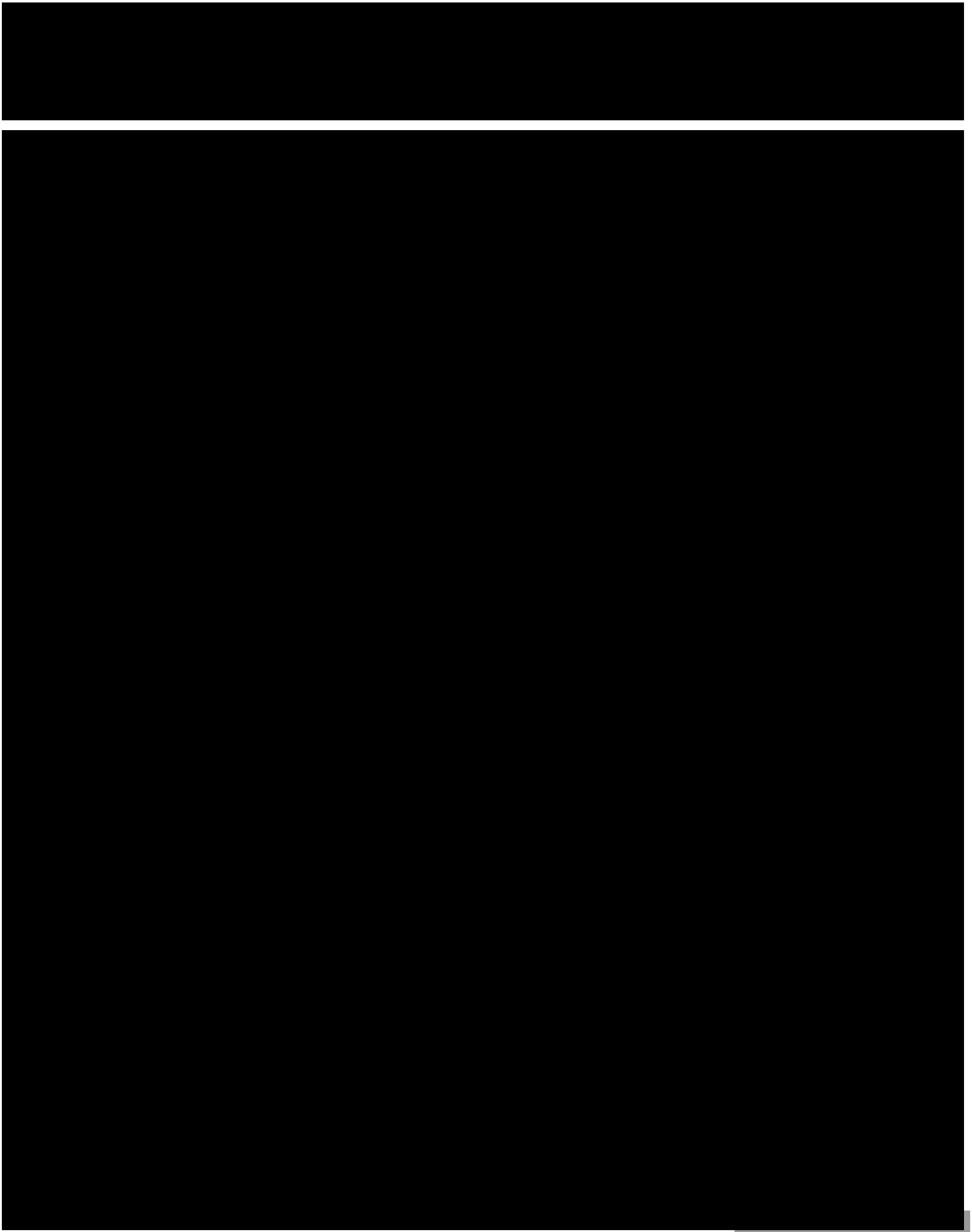

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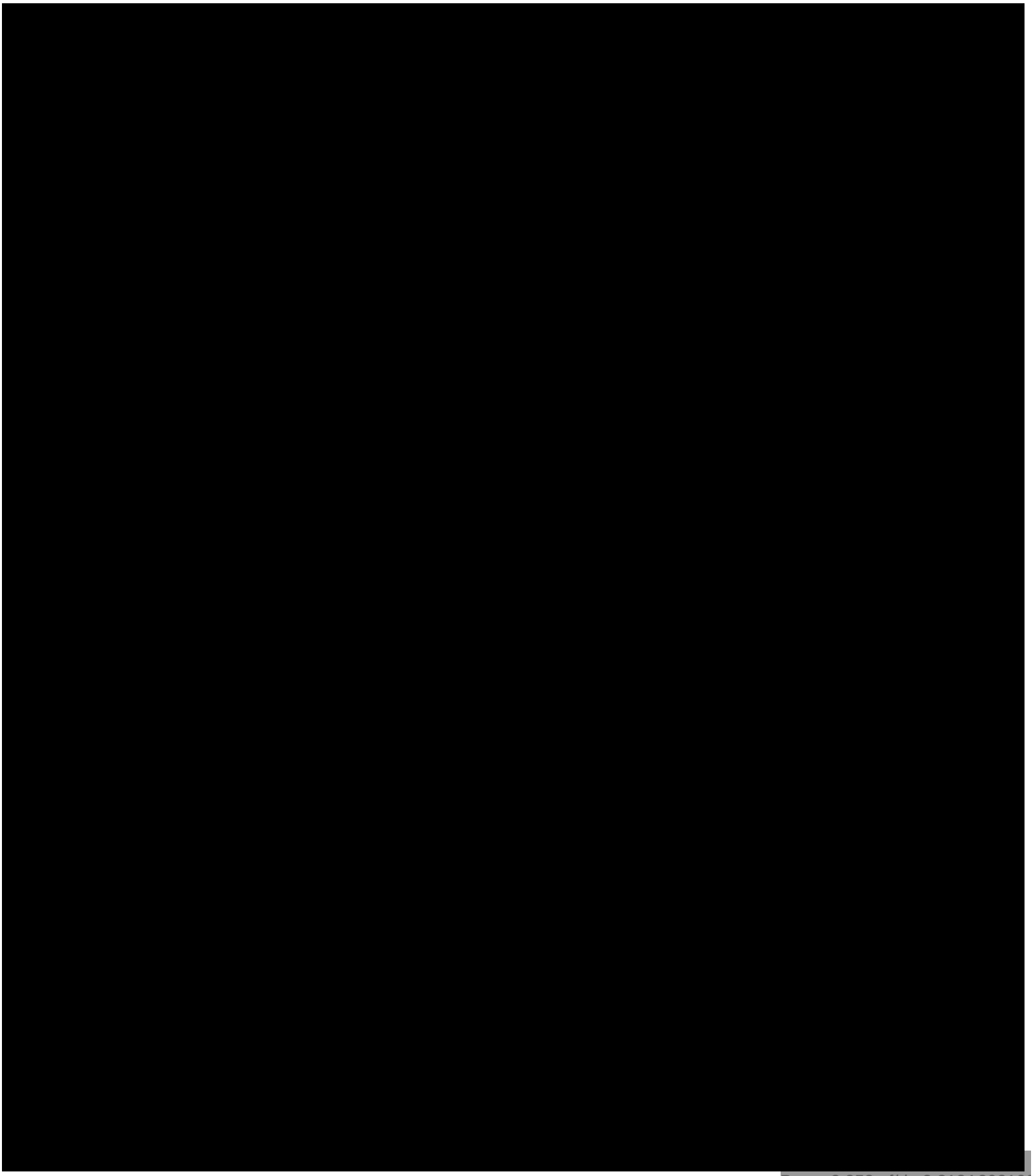

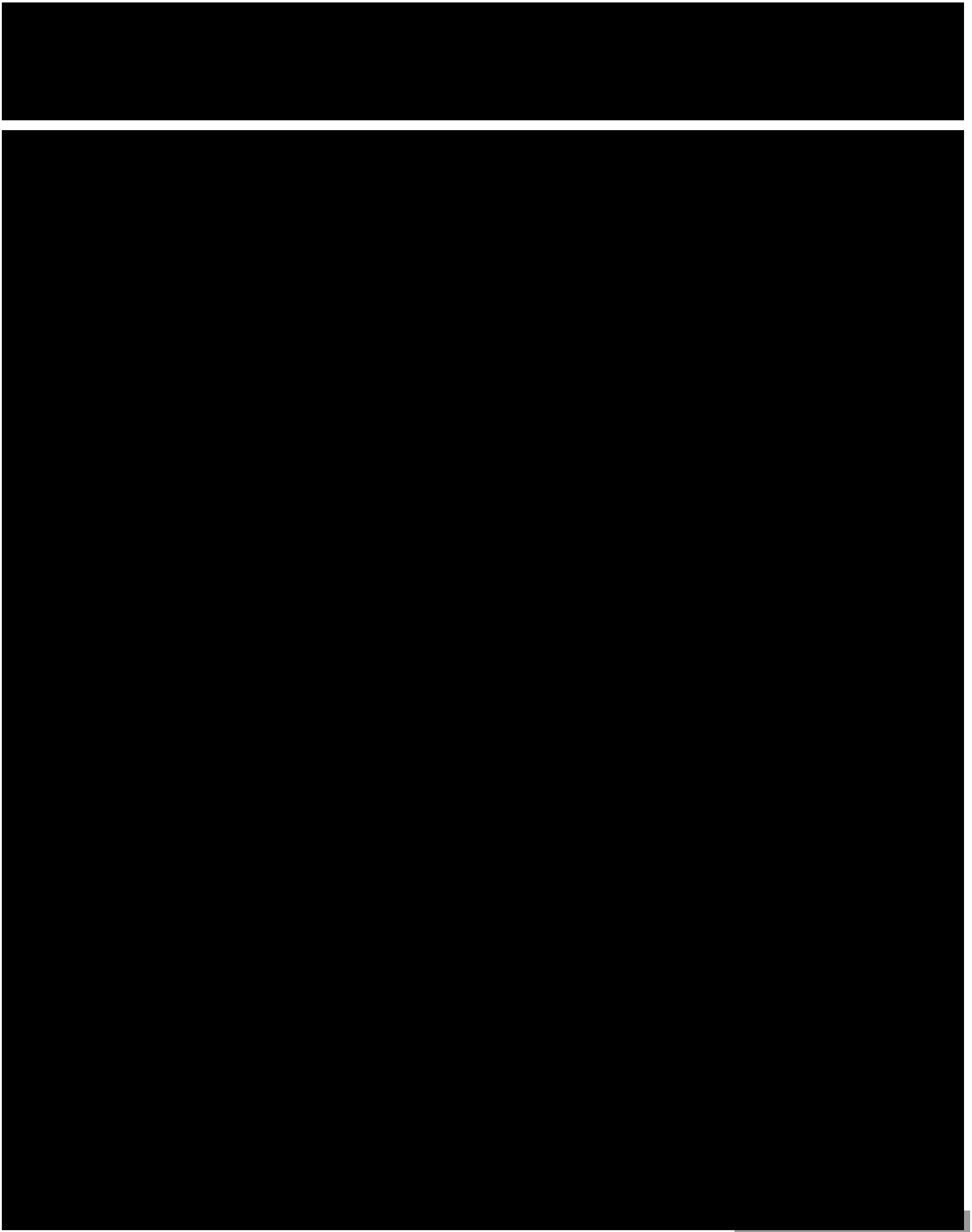

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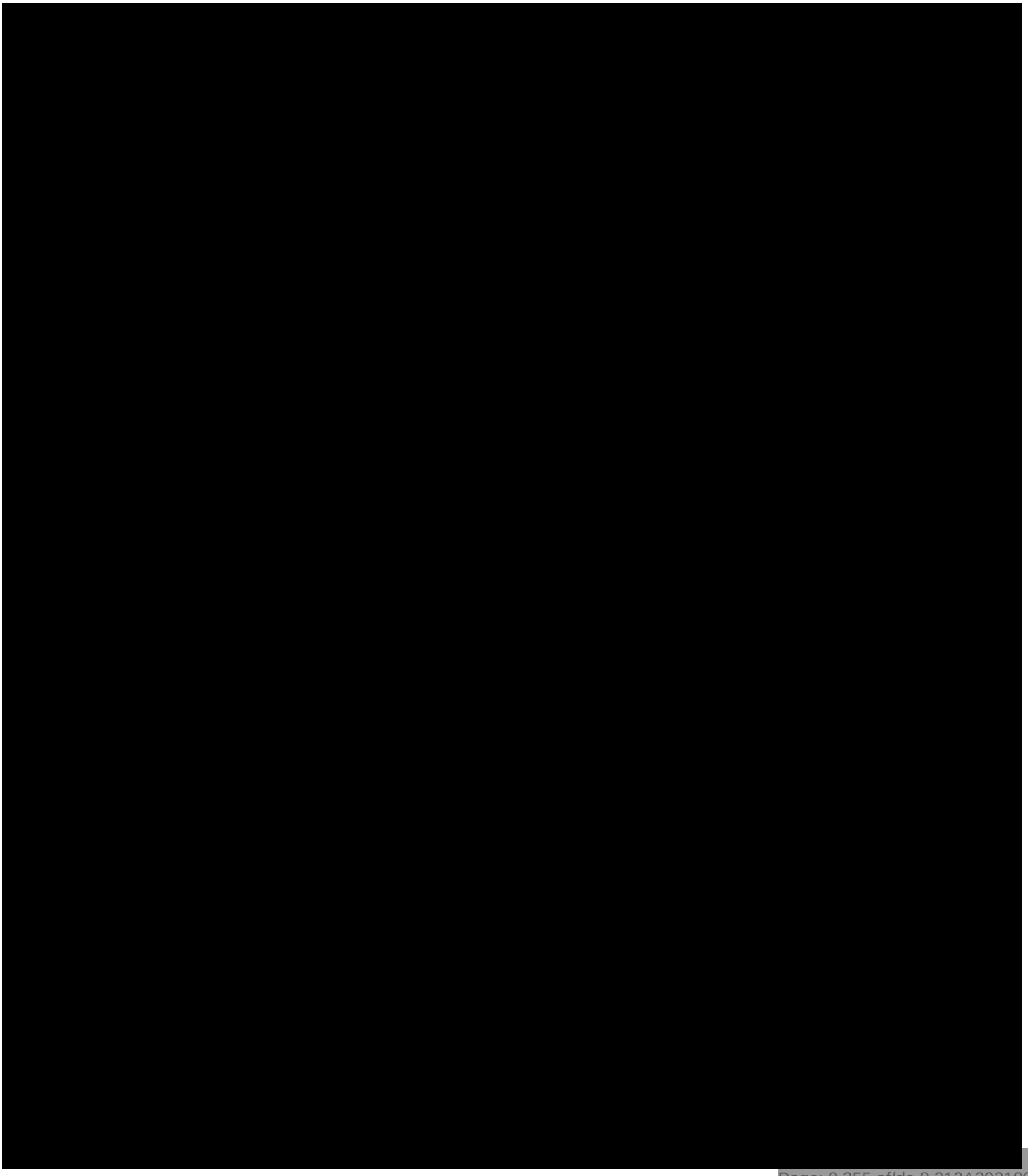

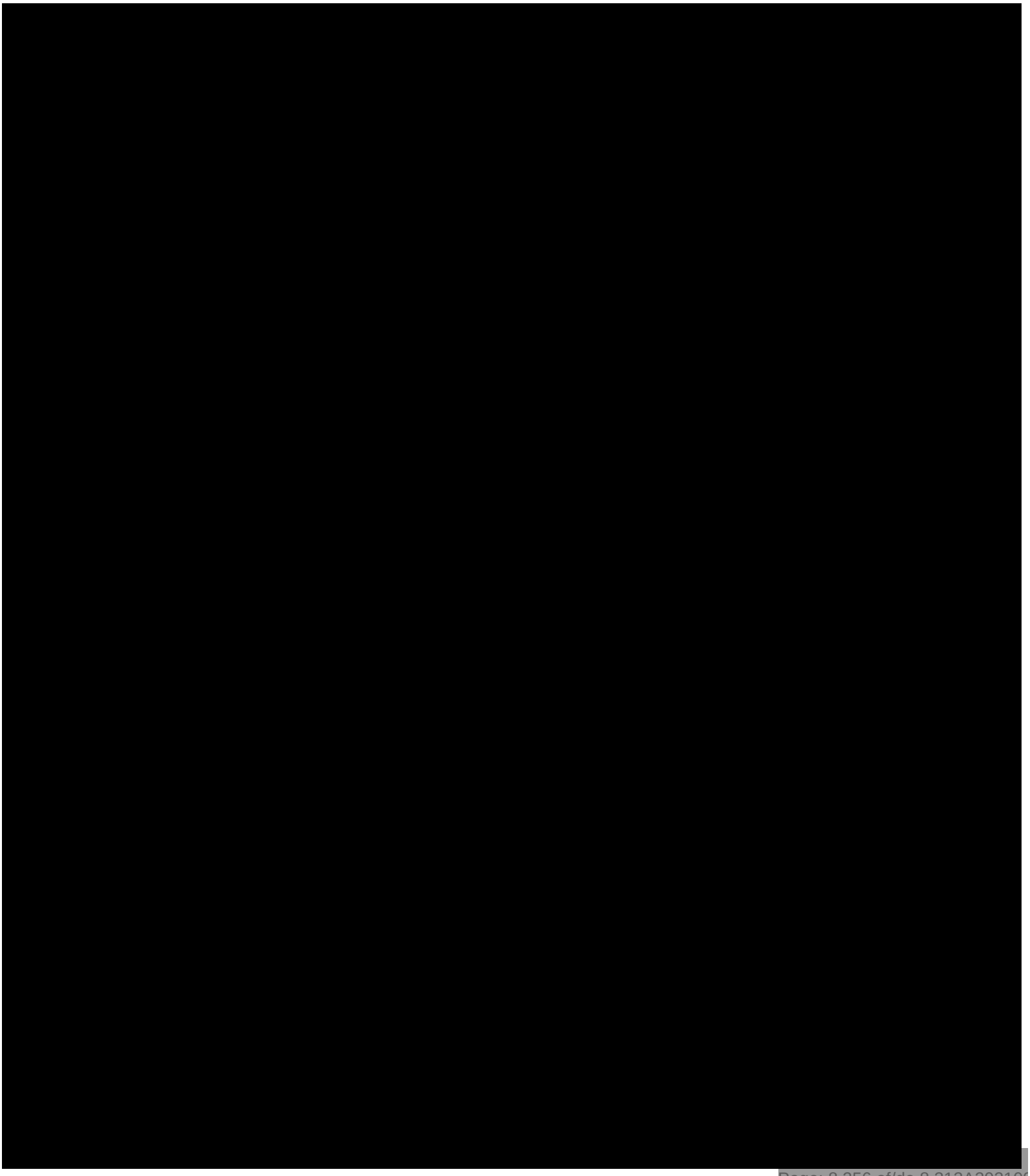

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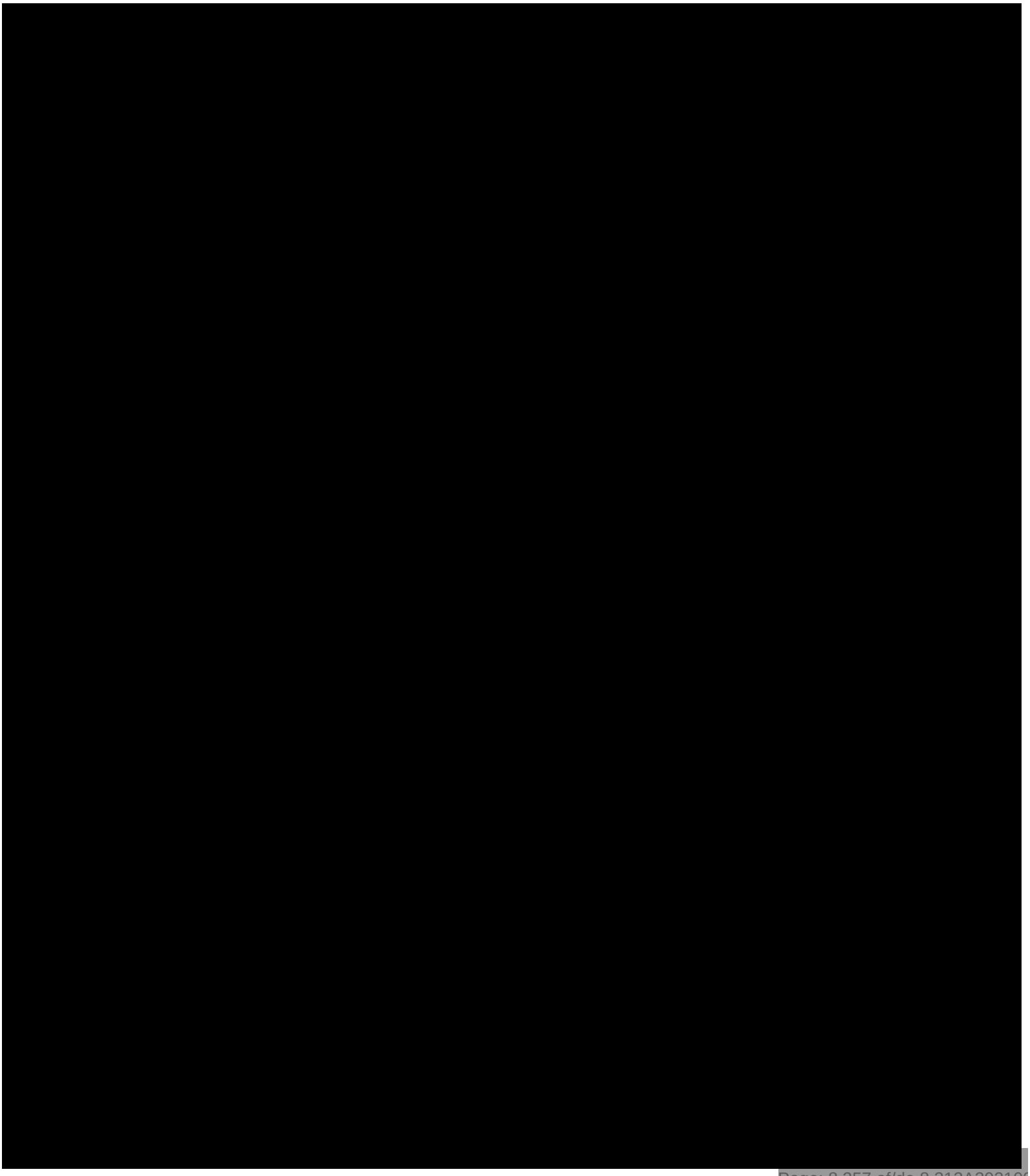

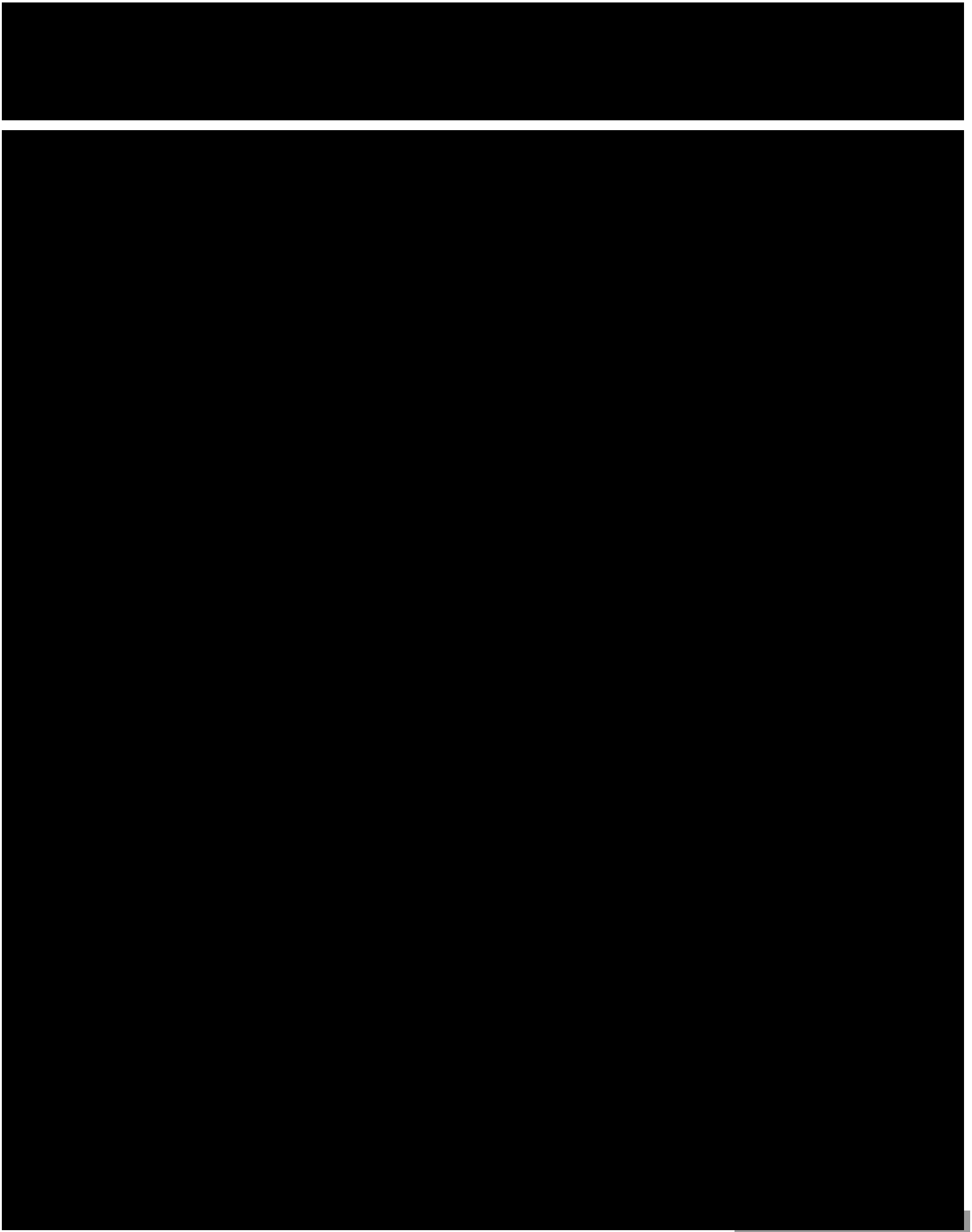

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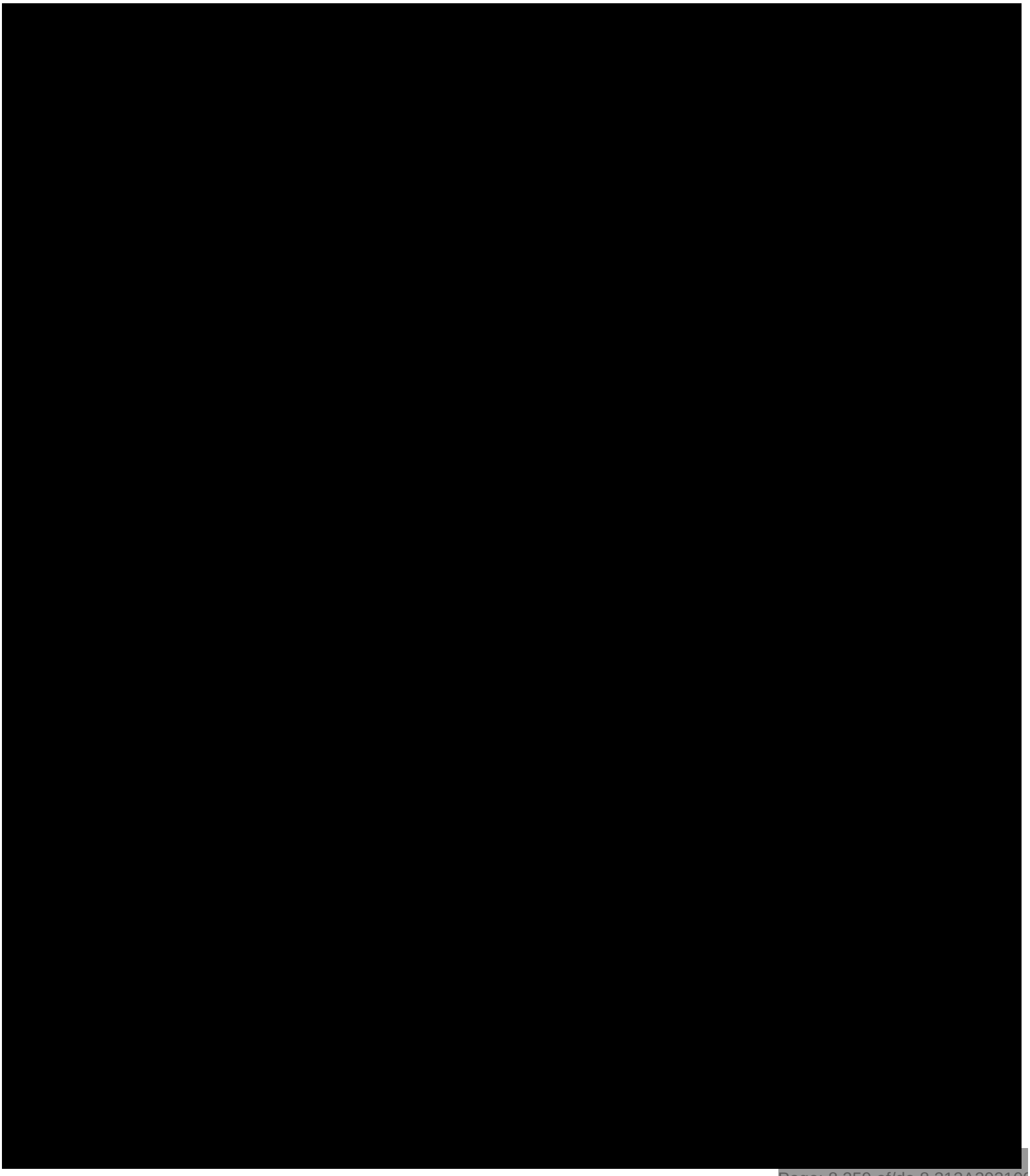

Lignes directrices sur les modifications apportées au *Règlement sur les aliments et drogues* relativement aux drogues utilisées dans le traitement de la COVID-19 : Aperçu

- Aperçu
- Préparation d'une présentation
- Licences d'établissement de produits pharmaceutiques et bonnes pratiques de fabrication
- Propriété intellectuelle
- Exigences postérieures à la mise en marché
- Prépositionnement des drogues contre la COVID-19
- Scénarios de présentation, documents de référence et principales personnes-ressources

Les présentes lignes directrices s'appliquent aux promoteurs de présentations de drogue nouvelle contre la COVID-19, de même qu'aux promoteurs qui cherchent à obtenir un Avis de conformité (AC) pour les drogues contre la COVID-19 qui ont reçu une autorisation temporaire en vertu de l'*arrêté d'urgence concernant l'importation, la vente et la publicité de drogues à utiliser relativement à la COVID-19* (arrêté d'urgence IVPD). Elles s'appliquent également aux nouvelles licences d'établissement de produits pharmaceutiques contre la COVID-19 en vertu du *Règlement sur les aliments et drogues*.

Ce document aidera les fabricants à préparer une présentation pour obtenir un Avis de conformité pour une drogue contre la COVID-19 en vertu du *Règlement*. Il décrit également le processus à suivre pour satisfaire aux exigences réglementaires après la mise en marché.

Sur cette page

- Contexte
- Portée et application
- Objectifs de la politique
- Énoncés de politique
- Explication des principaux termes
- Remarque sur les lignes directrices en général

Contexte

La pandémie de COVID-19 constitue un risque immédiat et important pour la santé et la sécurité des Canadiens. Pour répondre aux besoins connexes en matière de santé publique au Canada, la ministre de la Santé a pris différents arrêtés d'urgence afin d'accélérer et de faciliter l'accès aux drogues, aux instruments médicaux et aux aliments à des fins diététiques spéciales. La ministre a utilisé le pouvoir qui lui est accordé en vertu de l'article 30.1 de la *Loi sur les aliments et drogues* pour prendre ces arrêtés d'urgence.

L'arrêté d'urgence IVPD est entré en vigueur le 16 septembre 2020 et prévoyait :

- une voie d'autorisation facultative et accélérée pour l'importation, la vente et la publicité de drogues à utiliser relativement à la COVID-19
- des exigences modifiées pour les demandes de licence d'établissement de produits pharmaceutiques (LEPP) pour ces drogues
- la mise en place d'un mécanisme de placement des drogues contre la COVID-19 dans les établissements canadiens avant l'autorisation de vendre au Canada (prépositionnement).

L'arrêté d'urgence IVPD prendra fin un an après son entrée en vigueur. Après cette date, les drogues autorisées en vertu de l'arrêté d'urgence IVPD ne seraient plus légalement autorisées pour la vente au Canada, sauf si des mesures de transition étaient mises en œuvre.

L'arrêté d'urgence IVPD a accordé une autorisation d'urgence temporaire pour les drogues contre la COVID-19 afin de lutter contre la pandémie. L'autorisation n'était pas un AC. Pour recevoir un Avis de conformité, une présentation doit être faite en vertu du titre 8 du *Règlement sur les aliments et drogues*.

Le *Règlement* a été modifié afin d'y inclure de nouvelles exigences pour faciliter le processus réglementaire afin que les nouvelles drogues contre la COVID-19 reçoivent un AC au moyen d'une présentation de drogue nouvelle (PDN). Les modifications maintiennent certains des mécanismes mis en place dans le cadre de l'arrêté d'urgence IVPD, continuant ainsi à fournir aux Canadiens un accès rapide à des drogues contre la COVID-19 sûres et efficaces. Les présentes lignes directrices expliquent les exigences modifiées fournies dans ces modifications du *Règlement*.

Pour en savoir plus sur ces mesures et sur l'arrêté d'urgence IVPD, consultez les points suivants :

- Note explicative
- *Arrêté d'urgence concernant l'importation, la vente et la publicité de médicaments à utiliser relativement à la COVID-19*
- Exigences en matière de renseignements et de présentation relatives aux drogues autorisées en vertu de l'Arrêté d'urgence : Ligne directrice
- Partie II de la *Gazette du Canada* pour les modifications au *Règlement sur les aliments et drogues*

Portée et application

COVID-19 signifie maladie à coronavirus 2019. Les présentes lignes directrices s'appliquent :

- aux produits pharmaceutiques autorisés en vertu de l'arrêté d'urgence
- aux fabricants qui prévoient déposer une demande d'AC pour une drogue désignée pour la COVID-19 au sens de l'article C.08.001.2
- aux établissements demandant une LEPP liée aux drogues contre la COVID-19
- au mécanisme de prépositionnement introduit dans l'arrêté d'urgence IVPD.

Une « drogue désignée pour la COVID-19 » est une drogue nouvelle dont l'objet et les conditions d'utilisation recommandés par le fabricant sont liés à la COVID-19. Aux fins du présent document, les drogues contre la COVID-19 comprennent également les drogues désignées pour la COVID-19.

Pour obtenir des conseils sur l'obtention d'une autorisation pour des désinfectants, des désinfectants pour les mains et des produits de santé vétérinaires, les fabricants devraient consulter les lignes directrices suivantes :

- Gestion des présentations et des demandes de drogues.
- Gestion des présentations de désinfectants assimilés aux drogues
- Médicaments antiseptiques à usage humain
- Produits de santé animale : À Propos du Programme de Notification PSA

Les modifications apportées aux titres 1, 1A, 2 et 8 de la partie C du *Règlement* sont décrites dans les présentes lignes directrices. Les modifications introduisent des dispositions semblables à celles que l'on trouve dans l'arrêté d'urgence IVPD concernant les exigences relatives aux autorisations de produits pharmaceutiques, aux demandes de LEPP et au prépositionnement des produits avant autorisation. L'intégration de ces

mesures dans le *Règlement* vise à donner aux Canadiens un accès continu et rapide à des drogues sûres et efficaces contre la COVID-19.

Objectifs de la politique

L'objectif du *Règlement* modifié est de permettre un mécanisme d'accès continu et rapide à des drogues sûres et efficaces contre la COVID-19. L'examen, l'autorisation et la surveillance de ces drogues seront effectués en vertu du *Règlement*.

Les modifications apportées au *Règlement* offrent les avantages suivants :

- continuer à offrir un accès à des drogues sûres, efficaces et de grande qualité contre la COVID-19
- permettre que la vente et la publicité des drogues contre la COVID-19 qui ont été autorisées en vertu de l'arrêté d'urgence IVPD continuent après l'expiration de celui-ci
- permettre aux fabricants de drogues nouvelles contre la COVID-19 pour lesquelles aucune autorisation n'a été demandée dans le cadre de l'arrêté d'urgence IVPD de demander une autorisation en vertu du *Règlement* avec des exigences semblables à celles prévues en vertu de l'arrêté d'urgence IVPD
- maintenir les obligations réglementaires postérieures à la mise en marché imposées aux détenteurs d'autorisation, aux fabricants et aux importateurs après l'expiration de l'arrêté d'urgence IVPD
- continuer de permettre l'importation rapide et le placement dans les installations canadiennes (prépositionnement) d'une drogue prometteuse contre la COVID-19, pour laquelle un contrat d'approvisionnement du gouvernement fédéral est en place, avant que cette drogue ne reçoive une autorisation de mise en marché au Canada
- poursuivre une approche agile qui autorise les activités réglementées pour les drogues contre la COVID-19 pour les LEPP.

En vertu du *Règlement* modifié :

1) Santé Canada n'accorde un AC pour une drogue contre la COVID-19 que s'il est déterminé que les avantages et les risques du produit sont étayés par des preuves de l'innocuité, de l'efficacité et de la qualité constante de la drogue.
2) Les incertitudes ou les mesures d'atténuation des risques liés à la drogue dans le contexte du besoin de santé publique en raison de la COVID-19 sont gérées au moyen de modalités.
3) Comme pour toutes les drogues, Santé Canada évalue et surveille l'innocuité et l'efficacité de toutes les drogues contre la COVID-19 pour lesquelles un AC a été délivré. Au besoin, Santé Canada prend des mesures immédiates, y compris des mesures de conformité et

d'application de la loi et la suspension ou l'annulation d'un avis de conformité, pour protéger la santé et la sécurité des Canadiens.

Énoncés de politique

Les fabricants de drogues contre la COVID-19 peuvent obtenir un AC en vertu du *Règlement* en tirant parti de certaines options et des exigences modifiées reportées de l'arrêté d'urgence IVPD.

Ces modifications au *Règlement* permettent de déposer plus tôt une présentation de drogues pour traiter ou prévenir la COVID-19 au moyen d'un processus de « présentation en continu ». Il incombe aux fabricants de remplir les documents requis et de fournir les données probantes nécessaires à Santé Canada. Les présentations de drogues contre la COVID-19 seront classées par ordre de priorité en fonction des besoins en santé publique.

Les décisions d'autorisation sont fondées sur les documents présentés dans la demande. Santé Canada tiendra compte de la nécessité de la drogue pour répondre aux besoins urgents en santé publique liés à la COVID-19.

Les fabricants qui ont une autorisation valide délivrée en vertu de l'arrêté d'urgence IVPD peuvent déposer une présentation de drogue nouvelle (PDN) en vertu du *Règlement*. La vente du médicament peut se poursuivre pendant l'examen de la présentation, à condition qu'elle ait été déposée dans le délai de 90 jours. (Voir la section « Délais pour déposer une présentation en vertu du *Règlement* afin d'obtenir un avis de conformité ».) Lorsqu'une indication élargie pour la COVID-19 a été autorisée en vertu de l'arrêté d'urgence IVPD pour une drogue commercialisée, le fabricant peut présenter un supplément à une présentation de drogue nouvelle (SPDN) pour ajouter la nouvelle indication relative à la COVID-19. Les SPDN n'ont pas accès à des exigences modifiées en matière de présentation, y compris la capacité de présenter une demande incomplète (présentation en continu).

Selon cette approche, les fabricants qui ont obtenu au départ une autorisation en vertu de l'arrêté d'urgence IVPD peuvent présenter une PDN contenant les mêmes données que celles qui figuraient dans la demande soumise dans le cadre de l'arrêté d'urgence, ainsi que toute mise à jour nécessaire. Le cas échéant, les nouvelles données disponibles devraient être incluses dans la PDN. Pour faciliter un examen accéléré, le promoteur doit fournir un résumé de la trousse de présentation soulignant les changements. Les drogues contre la COVID-19 sont examinées dans un délai accéléré au-delà des normes de rendement habituelles. Par conséquent, la Politique d'examen prioritaire ne s'applique pas.

Les fabricants dont l'autorisation en vertu de l'arrêté d'urgence IVPD a été révoquée ou qui n'ont jamais présenté de demande peuvent également présenter une PDN en s'appuyant sur les exigences modifiées du *Règlement* pour les médicaments contre la COVID-19.

Explication des principaux termes

Drogue désignée contre la COVID-19 : Selon la définition de l'article C.08.001.2, il s'agit d'une « drogue nouvelle » au sens de l'article C.08.001. Par conséquent, elle est assujettie aux exigences du titre 8 de la partie C du *Règlement sur les aliments et drogues*, notamment :

- les dispositions existantes concernant la PDN et les suppléments à des PDN (SPDN) qui exigent un AC (voir C.08.002(1) et C.08.003(1)) pour permettre la vente d'une drogue nouvelle
- les résultats de la présentation en vertu de l'article C.08.004
- les dispositions relatives à la suspension en vertu de l'article C.08.006.

Aux fins du présent document, les drogues désignées pour la COVID-19 seront collectivement appelées drogues contre la COVID-19.

Drogue : D'après la *Loi sur les aliments et drogues*, sont compris parmi les drogues les substances ou mélanges de substances fabriqués, vendus ou présentés comme pouvant servir :

- au diagnostic, au traitement, à l'atténuation ou à la prévention d'une maladie, d'un désordre, d'un état physique anormal ou de leurs symptômes, chez l'être humain ou les animaux
- à la restauration, à la correction ou à la modification des fonctions organiques chez l'être humain ou les animaux
- à la désinfection des locaux où des aliments sont gardés

Remarque sur les lignes directrices en général

Les lignes directrices aident l'industrie et les professionnels de la santé à se conformer aux lois et aux règlements en vigueur. Elles fournissent également des conseils au personnel de Santé Canada sur la façon de réaliser des mandats et d'atteindre les objectifs fixés de façon équitable, uniforme et efficace.

Les lignes directrices sont des outils administratifs n'ayant pas force de loi, ce qui permet une certaine souplesse d'approche. Toutefois, pour être acceptables, les autres approches des principes et pratiques décrits dans le présent document doivent s'appuyer sur une justification adéquate. Ces autres approches devraient être examinées préalablement en consultation avec le programme concerné pour veiller à ce qu'elles respectent les exigences des lois et des règlements applicables.

Comme toujours, Santé Canada se réserve le droit de demander des renseignements ou du matériel supplémentaires, ou de définir des conditions dont il n'est pas explicitement question dans le présent document, afin de

nous aider à évaluer adéquatement l'innocuité, l'efficacité ou la qualité d'un produit thérapeutique donné. Nous nous engageons à justifier de telles demandes et à documenter clairement nos décisions.

Le présent document devrait être lu en parallèle avec l'avis d'accompagnement et les sections pertinentes des autres lignes directrices applicables.

Lignes directrices sur les exigences modifiées relatives aux drogues utilisées pour la COVID-19 : Préparation d'une présentation

- Aperçu
- Préparation d'une présentation
- Licences d'établissement de produits pharmaceutiques et bonnes pratiques de fabrication
- Propriété intellectuelle
- Exigences postérieures à la mise en marché
- Prépositionnement des drogues contre la COVID-19
- Scénarios de présentation, documents de référence et principales personnes-ressources

Sur cette page

- Scénarios de présentation
- Exigences modifiées
- Format et structure pour le dépôt
- Contenu et exigences de dépôt
- Plan de gestion des risques
- Étiquetage
- Avis de conformité (AC) pour une drogue contre la COVID-19
- Numéro d'identification du médicament (DIN)
- Avis de mise en marché
- Transparence
- Normes de rendement
- Frais

Scénarios de présentation

Le gouverneur en conseil a présenté des modifications au *Règlement* afin de prévoir un mécanisme pour que les drogues contre la COVID-19 soient autorisées par la délivrance d'un AC, en fonction des exigences modifiées qui ont été transférées de l'arrêté d'urgence IVPD.

Le tableau 1 donne un aperçu des exigences modifiées pour les drogues contre la COVID-19 dans le *Règlement*.

Le type de présentation « vérification de la conformité de la PDN » a été créé pour les PDN qui demandent une approbation en fonction des exigences énoncées aux paragraphes C.08.002(2.1), C.08.002(2.2) ou C.08.002(2.3) du *Règlement*. Pour utiliser l'une ou l'autre des autres exigences, le fabricant doit faire les déclarations exigées à l'alinéa C.08.002(2.4)a) et satisfaire à l'exigence de l'alinéa C.08.002(2.4)b). Pour satisfaire aux exigences du paragraphe C.08.002(2.1), le fabricant doit également faire la déclaration exigée à l'alinéa C.08.002(2.1)a) et satisfaire à l'exigence de l'alinéa C.08.002(2.1)b). Les fabricants devraient s'assurer que toutes les déclarations requises sont faites dans le module 1.2.3, « Formulaires de certification et d'attestation ».

Pour plus de détails, veuillez consulter les scénarios de présentation. Le type de soumission de vérification de la conformité de la PDN signifie PDN [COVID].

Tableau 1 : Aperçu des exigences modifiées pour les présentations de drogues contre la COVID-19

	Type de présentation	**Exigences modifiées disponibles**	**Modalités et conditions**
Drogue nouvelle ayant les mêmes données que celles qui ont été déposées en vertu de l'arrêté d'urgence (et peut-être des données supplémentaires)	PDN	C.08.002(2.1) : preuve à l'appui C.08.002(2.2) : ébauche d'étiquette C.08.002(2.3) : présentation en continu	Oui, seulement si C.08.002(2.1) est utilisé

	Type de présentation	Exigences modifiées disponibles	Modalités et conditions
Nouvelle drogue contre la COVID-19 (non déposée antérieurement en vertu de l'arrêté d'urgence IVPD)	PDN	C.08.002(2.1) : preuve à l'appui C.08.002(2.2) : ébauche d'étiquette C.08.002(2.3) : présentation en continu	Oui, seulement si C.08.002(2.1) est utilisé
Ajout d'une indication supplémentaire pour la COVID-19 à une drogue commercialisée	SPDN	Aucune	Non
Suppléments à des présentations de drogue nouvelle après l'autorisation de la PDN	SPDN	Aucune	Oui, seulement si reportées de la PDN C.08.002 (2.1) et peut inclure (C.01.014.21(1)(b)) supplémentaire

Délais pour déposer une présentation en vertu du *Règlement* afin d'obtenir un avis de conformité

Les modifications au *Règlement* prévoient qu'une autorisation en vertu de l'arrêté d'urgence IVPD sera révoquée à moins qu'une présentation ne soit déposée :

- dans les 90 jours suivant l'entrée en vigueur des modifications, si le médicament a été autorisé en vertu de l'arrêté d'urgence IVPD avant l'entrée en vigueur des modifications
- dans les 90 jours suivant la délivrance d'une autorisation en vertu de l'arrêté d'urgence IVPD, si la drogue a été autorisée après l'entrée en vigueur des modifications

Lorsqu'une présentation a été déposée dans ces délais, la drogue contre la COVID-19 peut continuer d'être vendue en vertu de l'autorisation de l'arrêté

d'urgence IVPD jusqu'à ce que la présentation ait été approuvée, rejetée ou retirée. C'est le cas même après que l'arrêté d'urgence IVPD prendra fin.

Si un fabricant ne dépose pas une présentation en vertu du *Règlement* dans les délais prescrits, il devra attendre que le produit soit autorisé en vertu du *Règlement* pour reprendre la vente.

Exigences modifiées

Les fabricants de drogues contre la COVID-19 auront la possibilité de se conformer en vertu du *Règlement* à des exigences semblables à celles de l'arrêté d'urgence IVPD, telles qu'elles sont énoncées aux paragraphes C.08.002(2.1) à (2.3). Pour utiliser ces autres exigences, les fabricants doivent inclure une déclaration indiquant que l'objet et les conditions d'utilisation précisés dans la PDN ne se rapportent qu'à la COVID-19.

Les fabricants devraient s'assurer que toutes les déclarations requises sont faites dans le module 1.2.3, « Formulaires de certification et d'attestation ». Les fabricants sont également encouragés à indiquer dans une lettre de présentation les exigences modifiées qu'ils ont l'intention de respecter.

Les exigences modifiées comprennent :

- la capacité de déposer une présentation en continu (C.08.002(2.3))
- l'exemption de présenter des rapports détaillés sur les tests effectués pour établir l'innocuité et l'efficacité clinique de la drogue nouvelle en vertu des alinéas C.08.002(2)g) et h)
    - toutefois, le fabricant doit fournir une preuve suffisante que les avantages de la drogue l'emportent sur les risques, compte tenu des incertitudes et des besoins en matière de santé publique en raison de la COVID-19 (C.08.002(2.1)b))
- l'exemption de l'obligation prévue à l'alinéa C.08.002(2)j.1) de fournir une maquette d'étiquette si le fabricant fournit une ébauche de l'étiquette
    - la présentation doit également comprendre tout encart et document fourni sur demande qui contient des renseignements supplémentaires sur l'utilisation de la drogue (C.08.002(2.2))
- l'exemption de l'obligation, en vertu de l'alinéa C.08.002(2)o), de procéder à une évaluation pour déterminer s'il existe une probabilité que la drogue nouvelle soit prise pour une autre drogue en raison d'une ressemblance entre les noms de marque
    - communément appelé l'évaluation du nom de marque

Les options offertes aux paragraphes C.08.002(2.1), C.08.002(2.2) et C.08.002(2.3) ne s'appliquent que si le fabricant a satisfait aux exigences énoncées au paragraphe C.08.002(2.4).

Santé Canada a l'intention d'évaluer les exigences des paragraphes C.08.002(2.1), C.08.002(2.2), C.08.002(2.3) et C.08.002(2.4) en matière de contrôle.

Conformément au paragraphe C.08.002(2.5), le règlement modifié ne s'applique pas si le fabricant demande un avis de conformité pour une drogue contre la COVID-19 sur la base d'une comparaison directe ou indirecte entre la drogue contre la COVID-19 et une autre drogue contre la COVID-19 (par exemple, une présentation de drogue générique ou biosimilaire). Les présentations seront évaluées en vertu du paragraphe C.08.002(2.5) avant qu'une présentation reçoive une date de dépôt.

L'innocuité et l'efficacité : C.08.002(2.1) comme solution de rechange aux alinéas C.08.002(2)g) et C.08.002(2)h)

Le *Règlement* a été modifié pour permettre aux fabricants qui demandent l'approbation d'une drogue contre la COVID-19 de déposer une présentation avec un autre ensemble de données lorsque cela est justifié en fonction des besoins urgents en santé publique découlant de la COVID-19. Au fur et à mesure que d'autres produits répondent aux besoins en santé publique découlant de la COVID-19, les fabricants devraient discuter des exigences en matière de données avec Santé Canada avant de déposer leur présentation. Un ensemble de données fondé sur l'article C.08.002(2.1) ne peut être approprié que dans certaines circonstances.

Après discussion avec Santé Canada, un fabricant peut déposer une PDN pour une drogue contre la COVID-19 sans se conformer aux exigences énoncées aux alinéas C.08.002(2)g) et C.08.002(2)h). Pour ce faire :

- le fabricant doit indiquer que la PDN concerne une drogue contre la COVID-19 (C.08.002(2)(2.1)(a))
- la PDN doit contenir suffisamment de données probantes établissant l'innocuité, l'efficacité et la qualité pour que les avantages de la drogue nouvelle l'emportent sur les risques (C.08.002(2)(2.1)b))

Les fabricants devraient faire la déclaration exigée dans le module 1.2.3, « Formulaires de certification et d'attestation ». Les fabricants sont encouragés à préciser dans une lettre de présentation que la PDN s'appuie sur le paragraphe C.08.002(2.1) du *Règlement* pour faciliter le traitement.

Un fabricant qui s'en remet au paragraphe C.08.002(2.1) pour fournir des données probantes établissant l'innocuité et l'efficacité sera assujetti aux conditions qui pourraient être imposées à un AC délivré pour une drogue contre la COVID-19. (Voir l'alinéa C.01.014.21(1)b).) Dans le contexte du besoin en matière de santé publique lié à la COVID-19, le fabricant doit inclure dans la PDN suffisamment de données probantes établissant l'innocuité, l'efficacité et la qualité démontrant que les avantages de la drogue l'emportent sur les risques. Santé Canada examine la PDN et

appliquera des conditions à l'autorisation pour obliger le fabricant à tenir compte des risques et des incertitudes après l'autorisation.

Si le fabricant dispose d'un ensemble complet de données pour appuyer la PDN, il peut choisir de ne pas se fier au paragraphe C.08.002(2.1).

Pour de plus amples renseignements, veuillez consulter les documents d'orientation suivants :

- Exigences en matière de données probantes pour les vaccins contre la COVID-19
- Exigences en matière de données probantes pour les drogues contre la COVID-19

Étiquettes des produits

L'article C.08.002(2.2) prévoit une exemption de l'exigence de l'alinéa C.08.002(2)j.1) de fournir une maquette des étiquettes de la drogue.

Toutefois, la présentation doit contenir une ébauche de chaque étiquette à utiliser avec la drogue nouvelle. Cela comprend tout encart dans l'emballage et tout document qui contient des renseignements supplémentaires sur l'utilisation de la drogue nouvelle.

Les fabricants sont encouragés à préciser dans une lettre de présentation que la PDN s'appuie sur le paragraphe C.08.002(2.2) du *Règlement* pour faciliter le traitement.

Présentations en continu

L'article C.08.002(2.3) reprend la capacité du fabricant de déposer une présentation en continu, comme le permet l'arrêté d'urgence IVPD. Il est reconnu que les présentations peuvent ne pas être complètes au moment du dépôt initial. Santé Canada commencera son examen à l'aide des renseignements fournis par le fabricant et acceptera de nouvelles données probantes lorsqu'elles seront disponibles jusqu'à ce que la présentation soit jugée complète. Un fabricant peut déposer une PDN pour une drogue nouvelle contre la COVID-19 sans inclure certaines des données autrement requises en vertu :

- des alinéas C.08.002(2)e) à C.08.002(2)k), C.08.002(2)m) et C.08.002(2)n)
- de l'alinéa C.08.002(2.1)b) ou
- Du paragraphe C.08.002(2.2)

Ce processus d'examen en continu peut réduire le temps qu'il faut pour autoriser ces drogues nouvelles essentielles tout en maintenant des normes appropriées d'innocuité, d'efficacité et de qualité.

Pour déposer une présentation en continu, le fabricant doit inclure tous les formulaires applicables et les autres éléments administratifs. La PDN doit également comprendre un plan indiquant les parties manquantes de la présentation. Ce plan doit préciser comment et quand les renseignements ou les documents manquants seront fournis au ministre pendant la période d'examen. (Voir le paragraphe C.08.002(2.3).)

Les fabricants sont encouragés à préciser dans une lettre de présentation que la PDN s'appuie sur le paragraphe C.08.002(2.3) du *Règlement* pour faciliter le traitement. Comme pour les autres PDN en vertu du titre 8, la date de dépôt désigne la date à laquelle :

- Santé Canada juge que la PDN est complète d'un point de vue administratif
- tous les éléments et formulaires requis pour le traitement ont été remplis et soumis à Santé Canada

La date de dépôt peut différer de la date de réception originale si la présentation est considérée comme incomplète d'un point de vue administratif à ce moment-là. Les données ou les renseignements fournis par la suite dans une présentation en continu seront considérés comme des renseignements sollicités dans le cadre de la PDN et ne changeront pas la date de dépôt de la présentation.

Des renseignements suffisants doivent être fournis dans un délai raisonnable. Le ministre examine la PDN en fonction des exigences et prend une décision, conformément à l'article C.08.004 du *Règlement*.

Le plan devrait contenir :

- une liste des données non cliniques, cliniques et de qualité à fournir (prévues et en cours)
- un délai pour la disponibilité de ces données cliniques et de qualité
- un délai pour le dépôt de ces données cliniques et de qualité aux fins d'examen

Si les renseignements manquants décrits dans le plan sont présentés sous forme de trousses multiples, le plan doit clairement préciser les renseignements qui seront contenus dans chaque trousse de données. Par exemple :

- L'ensemble de données A sera soumis le JJ/MM/AAAA et contient les résultats des études XX, YY et ZZ
- L'ensemble de données B sera soumis le JJ/MM/AAAA et contient les résultats des études MM, NN et OO

Les réunions préalables à la présentation donnent l'occasion de discuter du plan en détail. Ces réunions devraient servir à :

- établir le contenu et l'échéancier de la présentation
- déterminer les données qui seront soumises au moment du dépôt de la présentation
- déterminer les données qui seront fournies à une date ultérieure

La lettre de présentation devrait renvoyer au plan. Si des changements doivent être apportés à l'étiquetage pour refléter les nouveaux renseignements, il faut inclure des copies annotées et épurées des étiquettes de la drogue.

Santé Canada :

- examinera la présentation pour s'assurer qu'elle comprend le plan détaillé
- évaluera les renseignements fournis par le fabricant
- acceptera les nouvelles données probantes dès qu'elles seront prêtes jusqu'à ce que l'examen de la demande soit terminé

Toute donnée ou information subséquente envoyée plus tard est considérée comme de l'information sollicitée dans le cadre de la PDN si les données ou l'information sont fournies conformément au plan ou en réponse à la demande de Santé Canada. Les renseignements ou les données fournis autrement peuvent être considérés comme des renseignements non sollicités.

Santé Canada ne délivrera pas d'AC tant que le ministre n'est pas convaincu que la PDN est conforme aux exigences de l'article C.08.002.

Détails sur les activités de réglementation et les transactions pour les drogues désignées contre la COVID-19

Comme il a été mentionné précédemment, les exigences modifiées introduites par des modifications au *Règlement* ne sont disponibles que pour une PDN. Le type de présentation « vérification de la conformité de la PDN » a été créé pour les PDN qui s'appuient sur les dispositions des paragraphes C.08.002(2.1), C.08.002(2.2) ou C.08.002(2.3) du *Règlement*. Le fabricant doit sélectionner le type de présentation « vérification de la conformité de la PDN » dans le modèle de transaction réglementaire approprié du Processus d'inscription réglementaire (PIR) lorsqu'il soumet sa PDN. Les types de présentation « vérification de la conformité de la PDN » sont décrits comme « présentation de drogue avec exigences modifiées pour les drogues désignées contre la COVID-19 ».

Pour déposer une PDN qui ne bénéficie d'aucune des exigences modifiées mentionnées dans les trois paragraphes ci-dessus, un fabricant doit sélectionner le type de PDN ordinaire quand il soumet sa PDN.

Réunions préalable à la présentation

Les fabricants sont encouragés à communiquer régulièrement avec Santé Canada. Des consultations précoces et continues avec Santé Canada aident à assurer le respect des exigences réglementaires.

Avant de déposer une PDN, les fabricants sont encouragés à demander une réunion préalable à la présentation pour discuter de tous les aspects de leur présentation. À cette réunion, Santé Canada s'attend à ce que vous décriviez votre plan de présentation et indiquiez comment et quand vous fournirez au ministre les renseignements ou les documents manquants, le cas échéant (paragraphe C.08.002(2.3)).

Pour demander une réunion préalable à la présentation avec la direction appropriée, consultez les documents d'orientation sur les sujets suivants :

- Gestion des présentations et des demandes de drogues
- Gestion des présentations réglementaires pour les médicaments vétérinaires

Pour obtenir les coordonnées pertinentes, veuillez consulter les principales personnes-ressources.

Format et structure pour le dépôt

Pour connaître les procédures générales de dépôt des demandes, veuillez consulter les documents d'orientation sur les sujets suivants :

- Gestion des présentations et des demandes de drogues
- Gestion des présentations réglementaires pour les médicaments vétérinaires

Les présentations de drogues pour usage humain devraient être formatées, structurées et déposées comme indiqué dans les documents suivants :

- Document d'orientation sur la préparation des activités de réglementation en format eCTD
- Organisation et placement de documents pour le module canadien 1
- Document d'orientation sur le processus d'inscription réglementaire (PIR)

Les fabricants qui ne peuvent pas se conformer aux exigences de formatage peuvent communiquer avec le Bureau des présentations et de la propriété

intellectuelle pour obtenir d'autres options et des conseils. Veuillez envoyer un courriel à hc.ereview.sc@canada.ca.

Les présentations de médicaments vétérinaires devraient être formatées, structurées et déposées conformément aux documents d'orientation suivants :

- Préparation des activités de réglementation en format autre que le format eCTD
- Processus d'inscription réglementaire (PIR)

Les fabricants qui ne peuvent se conformer aux exigences de formatage peuvent communiquer avec la Direction des médicaments vétérinaires par courriel à hc.vdd.skmd.so-dgps.dmv.cp.sc@canada.ca.

Les présentations faites en vertu du *Règlement* doivent être indépendantes de toute demande faite dans le cadre de l'arrêté d'urgence IVPD. À tout le moins, elles doivent contenir les mêmes données que celles qui ont été incluses dans la demande soumise en vertu de l'arrêté d'urgence IVPD, ainsi que les mises à jour requises. Le promoteur doit inclure toutes les données sur lesquelles il se fonde pour appuyer sa PDN.

Les présentations déposées en vertu du *Règlement* pour lesquelles une demande a déjà été déposée en vertu de l'arrêté d'urgence IVPD recevront le même numéro de dossier que la demande relative à l'arrêté d'urgence IVPD. Les fabricants doivent identifier ce numéro de dossier dans la correspondance pertinente.

Contenu et exigences de dépôt

Pour la trousse d'information clinique et non clinique, vous n'aurez peut-être pas besoin d'inclure autant de renseignements que pour une trousse de données dans une présentation de drogue type. Cela est contrebalancé par des renseignements supplémentaires, qui doivent être fournis dans le cadre des présentations en continu ainsi que par les modalités d'autorisation.

Exigences et renseignements non cliniques

Des renseignements non cliniques clés peuvent être nécessaires pour :

- démontrer le potentiel d'efficacité clinique dans les conditions d'utilisation proposées
- appuyer l'innocuité de la drogue contre la COVID-19

Toutes les principales études devraient être menées conformément aux bonnes pratiques de laboratoire.

Pour en savoir davantage, veuillez consulter les lignes directrices suivantes :

- Données d'études non cliniques en laboratoire à l'appui des demandes et des présentations de drogues : respect des bonnes pratiques de laboratoire

Exigences et renseignements cliniques

Un fabricant peut présenter une PDN en se fondant sur les exigences modifiées des paragraphes C.08.002(2.1) à (2.3). Tous les renseignements connus doivent être fournis pour appuyer l'innocuité et l'efficacité de la drogue contre la COVID-19. Cela comprend toutes les données disponibles sur les essais cliniques et les documents de synthèse sur l'innocuité et l'efficacité.

Pour de plus amples renseignements, veuillez consulter les documents d'orientation suivants :

- Exigences en matière de données probantes pour les vaccins contre la COVID-19
- Exigences en matière de données probantes pour les drogues contre la COVID-19

Informations et exigences de qualité (chimie et fabrication)

Pour de plus amples renseignements sur le respect des exigences en matière de demande et d'information, veuillez consulter la liste des documents d'orientation. En vertu de l'article C.08.002(2.3) du *Règlement*, le fabricant peut fournir les renseignements et le matériel normalement exigés en vertu des alinéas (2)e), f) et m) sur une base continue. Le fabricant doit préciser dans son plan comment et quand il fournira les renseignements manquants à Santé Canada.

Pour de plus amples renseignements, veuillez consulter les documents d'orientation suivants :

- Exigences en matière de données probantes pour les vaccins contre la COVID-19
- Exigences en matière de données probantes pour les drogues contre la COVID-19

Présentations comparatives pour les produits pharmaceutiques subséquents

En vertu des voies de présentation abrégée de drogue nouvelle (PADN) et de PDN du *Règlement sur les aliments et drogues*, les fabricants de produits pharmaceutiques subséquents (drogues génériques et produits biosimilaires) peuvent demander un AC sur la base d'une comparaison avec une drogue qui a déjà reçu un AC.

Les fabricants doivent démontrer la similitude avec une drogue de référence autorisée (par exemple, dans le cas des drogues génériques, un produit de référence canadien au sens de l'article C.08.001.1). Pour ce faire, il dépose une présentation comparative qui repose, en partie, sur les preuves préalablement autorisées de l'innocuité et de l'efficacité de la drogue de référence. Le fabricant peut alors présenter un ensemble de données réduit dans la soumission.

Les modifications n'étendent pas les exigences modifiées prévues aux nouveaux paragraphes C.08.002(2.1), (2.2) et (2.3) aux cas où les fabricants demandent un AC pour une drogue contre la COVID-19 sur la base d'une comparaison directe ou indirecte entre cette drogue et une autre drogue contre la COVID-19.

Le *Règlement* ne permet pas le dépôt de présentations comparatives tout en profitant de l'une ou l'autre des exigences modifiées, même si le consentement du fabricant du produit de référence est fourni. Par conséquent, les présentations comparatives devraient être déposées sous forme de PADN ou de PDN comparative.

Santé Canada appliquera le paragraphe C.08.002(2.5) du *Règlement* au traitement des demandes comparatives visant à obtenir une approbation en se fondant sur les nouveaux paragraphes C.08.002(2.1), (2.2) et (2.3) ne recevront pas de date de dépôt. Quand il semble que le dépôt d'une présentation n'est pas possible, le fabricant recevra une décision préliminaire écrite et aura la possibilité de présenter des observations en réponse. Si, à la suite de l'examen des observations, Santé Canada est d'avis que la présentation ne peut être déposée, le fabricant en sera avisé, et la présentation ne sera pas traitée davantage.

Il est interdit aux fabricants de produits pharmaceutiques subséquents de soumettre une présentation sur la base d'une comparaison directe ou indirecte avec une drogue contre la COVID-19 pour laquelle une autorisation a été délivrée en vertu de l'arrêté d'urgence IVPD (C.08.003.01(2)). Veuillez noter que le paragraphe C.08.003.01(2) ne vise pas à empêcher le dépôt d'une présentation contenant de nouvelles données provenant d'essais cliniques comparant l'efficacité de la drogue nouvelle à une drogue existante. Veuillez également noter que l'article C.08.003.01 n'empêche pas le dépôt d'une présentation ou d'un supplément sur la base d'une comparaison avec une drogue contre la COVID-19 qui a reçu un AC (C.08.003.01(3)).

Les fabricants qui ont l'intention de présenter une demande d'AC pour une drogue contre la COVID-19 en se fondant sur une comparaison avec une autre drogue contre la COVID-19 sont encouragés à communiquer avec Santé Canada pour une réunion préalable à la présentation.

Une présentation de drogue contre la COVID-19 devrait contenir tous les renseignements disponibles pour aider Santé Canada à évaluer l'innocuité, l'efficacité et la qualité de la drogue. L'information devrait comprendre des preuves de son efficacité pour les espèces ciblées, la sécurité des animaux, la sécurité humaine et la qualité.

Dans le cas des drogues utilisées chez les animaux d'élevage, il faut fournir de l'information sur l'innocuité des résidus de drogue dans la viande et d'autres produits alimentaires provenant de l'animal traité destiné à la consommation humaine.

Plan de gestion des risques

Les fabricants doivent soumettre un plan de gestion des risques (PGR) pour une drogue contre la COVID-19. Si un PGR a été déposé dans le cadre de la demande d'arrêté d'urgence IVPD, un PGR mis à jour contenant les données postcommercialisation les plus récentes, les mesures de réduction des risques et les activités de pharmacovigilance doit être soumis.

Le PGR devrait mettre l'accent sur les risques pour la sécurité mis à jour du produit dans le contexte de l'utilisation contre la COVID-19 afin de s'assurer que :

- le profil avantage-risque du produit est géré de manière optimale tout au long de son cycle de vie
- les lacunes au titre des connaissances au moment de l'autorisation sont décrites et les risques sont davantage quantifiés et caractérisés au fil du temps

Il doit :

- décrire les risques pour la sécurité du produit associés à l'utilisation contre la COVID-19
- décrire les activités de pharmacovigilance et les activités de réduction des risques utilisées pour identifier, caractériser, prévenir ou réduire au minimum les risques
- contenir une évaluation de l'efficacité de ces mesures de réduction des risques

Pour obtenir des renseignements sur la portée des PGR, veuillez consulter le document d'orientation suivant :

- Présentation des plans de gestion des risques et des engagements en matière de suivi

Pour les drogues contre la COVID-19 soumises pour autorisation, le PGR devrait comprendre les éléments suivants :

- une section des spécifications de sécurité sur les risques cernés, les risques et les renseignements manquants pour le produit (par exemple, les populations spéciales pour lesquelles il y a peu d'information ou qui ont été exclues des essais cliniques), en mettant l'accent sur les risques chez les patients atteints de la COVID-19, le cas échéant
- un plan de pharmacovigilance sur les activités particulières à entreprendre pour cerner et signaler les problèmes de sécurité, y compris la déclaration accélérée des effets indésirables, la déclaration périodique et les études en cours ou prévues pour quantifier et caractériser ces risques (p. ex., registres, études de cohortes rétrospectives)
- un plan de réduction des risques pour gérer les risques pour la sécurité, y compris les mesures courantes de réduction des risques (par exemple, l'étiquetage) et des mesures supplémentaires au-delà de celles considérées comme routinières (comme du matériel éducatif pour les professionnels de la santé ou les patients, ou un programme d'accès ou de distribution restreint), au besoin
- un plan visant à mesurer l'efficacité d'autres activités de réduction des risques

Un PGR qui a été examiné et accepté dans le cadre de la présentation d'une drogue contre la COVID-19 devrait être mis en œuvre. Si le fabricant a déposé une demande en vertu de l'exigence du paragraphe C.08.002(2.1), tous les éléments d'un PGR qui sont essentiels à l'utilisation sécuritaire et efficace du produit pourraient être identifiés comme des modalités et doivent être mis en œuvre.

Un addenda canadien qui démontre que le PGR répond aux exigences réglementaires canadiennes doit accompagner le PGR de base. Des renseignements sur ces exigences sont fournis dans les documents d'orientation et avis récents suivants :

- Exigences en matière de données probantes pour les vaccins contre la COVID-19
- Exigences en matière de données probantes pour les drogues contre la COVID-19
- Avis de clarification aux fabricants et aux promoteurs de médicaments : Considérations propres au contexte canadien dans les plans de gestion des risques

Si vous avez des questions au sujet du type de renseignements requis sur la qualité, l'innocuité et l'efficacité, veuillez communiquer avec la direction appropriée de Santé Canada. Veuillez consulter les principales personnes-ressources pour obtenir les coordonnées pertinentes.

Étiquetage

Les fabricants d'une drogue contre la COVID-19 doivent se conformer à toutes les exigences d'étiquetage applicables de la *Loi sur les aliments et drogues* et des parties A et C du *Règlement* :

- A.01.014
- A.01.015
- A.01.60.1 à A.01.068
- A.01.065
- C.01.004 à C.01.011
- C.01.401
- C.03.202
- C.03.203
- C.03.206 à C.03.209
- C.04.019 et C.04.020

Les dispositions réglementaires existantes sur l'étiquetage des médicaments vétérinaires s'appliquent également.

Les fabricants qui déposent une PDN pour une drogue contre la COVID-19 en utilisant les exigences modifiées peuvent être invités à inclure une mise en garde sur les étiquettes intérieures et extérieures. Cette déclaration peut être affichée sur n'importe quel panneau. Les données présentées à l'appui de la PDN et les modalités connexes que le ministre inscrira sur le DIN dicteront cela.

Les exigences d'étiquetage en langage clair pour les maquettes d'étiquettes et les trousses d'évaluation du nom commercial ne s'appliquent pas (C.08.002(2)(j.1) et C.08.002(2)(o)).

Bien qu'ils soient exemptés de ces exigences, les fabricants sont fortement encouragés à remplir et à présenter un dossier d'évaluation du nom commercial et à fournir des maquettes d'étiquettes :

- au moment du dépôt de la PDN (si disponible) ou
- au plus tôt après le dépôt de la PDN

Les fabricants peuvent également déposer ces documents après l'obtention de l'AC.

Santé Canada peut appliquer les modalités d'étiquetage au besoin. Nous demanderons au commanditaire de soumettre une évaluation du nom commercial et des maquettes d'étiquettes d'emballage finales à un moment convenu si le promoteur choisit d'utiliser les exigences d'étiquetage modifiées prévues par le *Règlement*.

Les fabricants qui ne sont pas en mesure de fournir un dossier complet d'évaluation du nom commercial au moment du dépôt de la demande ou le plus tôt possible après le dépôt de la PDN peuvent fournir un dossier où des exercices de simulation sont omis.

L'étiquetage en langage clair et les composantes de présentation ou de consonance semblable ne sont pas nécessaires en ce qui concerne l'étiquetage des médicaments vétérinaires.

Consultez la liste des documents d'orientation pour d'autres directives sur l'étiquetage.

Dépôt d'un supplément à une PDN pour une drogue contre la COVID-19

Un fabricant d'une drogue contre la COVID-19 qui détient une autorisation pour une drogue nouvelle en vertu de l'arrêté d'urgence IVPD peut déposer une PDN en vertu de l'article C.08.002 du *Règlement*. Une fois que le fabricant reçoit un AC pour la drogue contre la COVID-19, il peut déposer un supplément à cette présentation de drogue nouvelle (SPDN) pour tout changement postérieur à l'AC. Le cas échéant, le fabricant peut également être en mesure d'intégrer le changement dans sa PDN.

Consultez les documents d'orientation suivants sur les changements après l'AC :

- Document cadre (Médicaments pharmaceutiques, biologiques et radiopharmaceutiques à usage humain seulement)
- Document sur l'innocuité et l'efficacité (Pour les produits biologiques, pharmaceutiques et radiopharmaceutiques à usage humain seulement)
- Changements survenus après l'avis de conformité (AC) : Document sur la qualité

Avis de conformité (AC) pour une drogue contre la COVID-19

Pour que Santé Canada délivre un AC (C.08.004) pour la vente d'une drogue contre la COVID-19, la PDN doit satisfaire aux exigences de l'article C.08.002. Dans le cas des drogues qui se fondent sur les exigences modifiées de l'article C.08.002 (2.1), la PDN doit contenir suffisamment de preuves pour appuyer la conclusion selon laquelle les avantages de la drogue l'emportent sur les risques lorsqu'elle est utilisée de la façon indiquée. Les données probantes tiennent compte des incertitudes entourant la drogue dans le contexte des besoins en santé publique liés à la COVID-19.

Numéro d'identification du médicament (DIN)

Lorsque le fabricant d'une drogue contre la COVID-19 qui était précédemment autorisée en vertu de l'arrêté d'urgence IVPD présente une PDN pour obtenir un AC, le DIN attribué en vertu de l'arrêté d'urgence IVPD demeure actif jusqu'à ce que la PDN ait été approuvée, rejetée ou retirée. Cela garantit le maintien de toutes les obligations réglementaires associées au DIN.

Une fois qu'un AC est délivré pour une drogue contre la COVID-19, Santé Canada peut attribuer les mêmes chiffres pour le DIN en vertu de l'article C.01.014.2 que ceux qui ont été attribués en vertu de l'article 7 de l'arrêté d'urgence IVPD.

Si la présentation soumise en vertu du *Règlement* est rejetée ou retirée, le DIN sera révoqué à ce moment-là.

Les fabricants devraient consulter la Ligne directrice : Exigences réglementaires associées à une identification numérique attribuée à une drogue (DIN) pour obtenir de plus amples renseignements sur les DIN.

Conditions d'utilisation d'un DIN pour une drogue contre la COVID-19 fondées sur les exigences modifiées du paragraphe C.08.002(2.1)

Santé Canada peut, à tout moment, imposer ou modifier les conditions d'un DIN (C.01.014.21(1)b)) d'une drogue contre la COVID-19 quand le fabricant s'est fié au paragraphe C.08.002(2.1) pour obtenir un AC. Si le fabricant a utilisé d'autres dispositions seulement, le pouvoir sur les conditions ne s'applique pas.

Ce pouvoir permet à Santé Canada de délivrer un AC pour une drogue contre la COVID-19 tout en imposant des conditions supplémentaires auxquelles le détenteur du DIN doit se conformer. Ces modalités sont utilisées pour assurer une surveillance appropriée, gérer les incertitudes ou atténuer les risques. Toutefois, les conditions d'un DIN pour une drogue contre la COVID-19 utilisant la souplesse de présentation prévue au paragraphe C.08.002(2.1) seront fondées sur ce qui est nécessaire lorsqu'une présentation n'est pas en mesure de satisfaire aux exigences habituelles en matière de données. Voici des exemples de conditions prévues :

- des mesures précises de pharmacovigilance et de gestion et d'atténuation des risques
- des renseignements supplémentaires sur la qualité
- une confirmation de l'efficacité
- les mesures prises pour prévenir ou atténuer une pénurie de drogues

Les conditions figurent sur le DIN et y demeurent, peu importe les SPDN (suppléments à une présentation de drogue nouvelle) subséquents. Il y a

exception si le ministre supprime les conditions dans le cadre du processus (SPDN).

Les modalités peuvent également s'appliquer aux drogues autorisées sur la base d'une comparaison avec une drogue contre la COVID-19, lorsque l'AC du produit de comparaison s'appuyait sur ces assouplissements en matière de présentation (C.01.014.21(1.1)b)). Cela garantit que tout engagement postérieur à la mise en marché d'un produit de référence peut également être imposé sur les AC émis sur la base d'une comparaison.

Les conditions peuvent être imposées ou modifiées en tout temps sur un DIN pour une drogue contre la COVID-19 (C.01.014.21(1.1)a)) qui a été déposée de l'une des façons suivantes :

- une PDN en vertu de l'article C.08.002 s'appuyant sur les assouplissements en matière de données mentionnés au paragraphe C.08.002(2.1)
- un supplément à une PDN pour cette drogue nouvelle.

Elles peuvent également être imposées ou modifiées en tout temps sur un DIN pour une drogue contre la COVID-19 (C.01.014.21(1.1)b)) autorisée sur la base d'une comparaison directe ou indirecte avec une autre drogue contre la COVID-19 (voir l'alinéa C.01.014.21(1.1)a)) et déposée comme suit :

- une PDN déposée en vertu de l'article C.08.002
- une présentation abrégée de drogue nouvelle (PADN) déposée en vertu de l'article C.08.002.1
- un supplément à une présentation de drogue nouvelle ou une présentation abrégée de drogue nouvelle déposée en vertu de l'article C.08.003.

Santé Canada discutera des conditions avec le promoteur avant de les imposer. Toutes les conditions sont exécutoires en vertu de l'article 21.7 de la Loi.

Les conditions ne s'appliquent pas à toutes les drogues, y compris les drogues contre la COVID-19, autorisées par les voies existantes de la PDN et des SPDN si le fabricant :

- est en mesure de satisfaire à toutes les exigences en matière de données (C.08.002(2)g) et h))
- n'a pas invoqué l'article C.08.002(2.1).

Soumettre des renseignements pour respecter les conditions

Les renseignements sur le respect des conditions doivent être présentés à titre de renseignements sollicités avec une lettre de présentation. Le sujet

devrait indiquer « Renseignements sollicités, respect des conditions pour la drogue contre la COVID-19 ». Des documents justificatifs doivent être fournis.

Santé Canada examinera la documentation pour déterminer si les conditions ont été respectées. Une fois que nous serons convaincus que le fabricant s'est conformé à toutes les conditions, nous l'indiquerons dans une lettre et ferons référence au numéro de dossier ou de contrôle original.

Avis de mise en marché

Un avis de mise en marché d'une drogue autorisée en vertu de l'arrêté d'urgence IVPD ne constitue pas un avis de mise en marché d'une drogue en vertu du *Règlement*. C'est le cas même si les mêmes chiffres ont été attribués à la drogue que le DIN utilisé en vertu de l'arrêté d'urgence IVPD et du *Règlement*.

Le fabricant d'une drogue contre la COVID-19 autorisée en vertu du *Règlement* doit aviser Santé Canada lorsqu'il vend pour la première fois la drogue contre la COVID-19 en vertu d'un AC. Le fabricant doit remplir, signer, dater et retourner le formulaire de notification de drogue (FND) fourni par Santé Canada dans les 30 jours suivant la date de la première vente. Toutes les pages du FND doivent être retournées à Santé Canada.

Le DIN attribué en vertu de l'arrêté d'urgence IVPD sera révoqué une fois que le même DIN sera attribué à la drogue en vertu du *Règlement*. Notre Base de données sur les produits pharmaceutiques indiquera que le DIN est « approuvé » jusqu'à ce que le fabricant soumette un FND rempli, après quoi le DIN sera « mis sur le marché ».

Si le fabricant n'a pas déposé de maquettes d'étiquettes au cours de l'examen, il doit présenter les maquettes finales ou les étiquettes imprimées finales quand la drogue contre la COVID-19 est commercialisée ou lancée.

Pour plus d'informations sur les avis de mise en marché ou les avis d'interruption de vente, consultez le document suivant :

- Lignes directrices : Exigences réglementaires associées à une identification numérique attribuée à une drogue (DIN)

Changements dans la propriété des produits, fusions et rachats ou contrats de licence

Les présentations proposant des changements administratifs doivent être déposées dans les présentations administratives (abrégées) de drogue nouvelle (PADN).

Si les promoteurs proposent des changements d'étiquetage en même temps que les changements administratifs proposés, ils doivent déposer ces changements dans une PADN « étiquetage seulement » pour obtenir l'autorisation de Santé Canada. Ils doivent le faire avant d'apporter des changements aux matériaux d'étiquetage sur le marché.

Consultez le document d'orientation suivant pour de plus amples renseignements :

- Traitement administratif des présentations et des demandes concernant les médicaments destinés aux humains ou les désinfectants

Avis de cessation de la vente

Le fabricant d'une drogue contre la COVID-19 doit présenter un avis de cessation de la vente à Santé Canada dans les 30 jours suivant la cessation permanente de la vente de la drogue contre la COVID-19 au Canada. La date de cessation de la vente est la dernière fois que le fabricant vend sa drogue, et non la dernière fois qu'il est vendu au détail.

Pour obtenir des renseignements et des procédures générales sur l'avis de cessation de la vente, les détenteurs d'autorisation doivent consulter :

- Lignes directrices : Exigences réglementaires associées à une identification numérique attribuée à une drogue (DIN)

Pour de plus amples renseignements sur les exigences supplémentaires sur la façon de déclarer une cessation de la vente, consultez la section sur les pénuries ou la cessation de la vente.

Transparence

Santé Canada continuera de communiquer des renseignements à jour sur la COVID-19 en vertu du *Règlement sur les aliments et drogues* modifié.

Vous trouverez les renseignements suivants en ligne :

- Portail des vaccins et traitements contre la COVID-19
- les présentations de drogues contre la COVID-19 qui ont été acceptées pour examen dans les listes des Présentations de médicaments et de produits de santé en cours d'examen (PCE)
- Sommaires des décisions réglementaires (SDR) et sommaires des motifs de décision (SMD) pour les drogues contre la COVID-19 dans le Registre des médicaments et des produits de santé
- Les renseignements cliniques utilisés pour faire approuver les drogues contre la COVID-19 peuvent être consultés sur le portail de

renseignements cliniques de Santé Canada ou dans le Registre des médicaments et des produits de santé.
- Mesures et résultats d'inspection des médicaments dans la base de données Inspections des médicaments et des produits de santé

De plus, sur demande, Santé Canada continuera de fournir aux intervenants externes les plans de gestion des risques approuvés les plus à jour pour les vaccins contre la COVID, et ce, dans leur intégralité.

Veuillez également consulter les documents d'orientation suivants :

- Diffusion publique des renseignements cliniques

Normes de rendement

Santé Canada compte accorder la priorité aux demandes concernant des drogues contre la COVID-19. Les présentations de drogues seront classées par ordre de priorité et examinées en fonction des besoins en santé publique.

Le temps requis pour examiner une présentation dépendra de la présentation elle-même, du volume de données à évaluer et de la capacité du fabricant de présenter les données conformément au plan, le cas échéant. Les normes de rendement publiées s'appliqueront aux présentations liées des drogues contre la COVID-19, autres que les présentations en continu, faites en vertu du *Règlement*.

Les présentations en continu ne seront pas assujetties à des normes de rendement (en d'autres termes, des frais aux fabricants en raison de normes de rendement qui ne sont pas respectées). Cela est expliqué dans la section Frais ci-après.

Pour de plus amples renseignements, veuillez consulter les documents d'orientation suivants :

- Gestion des présentations et des demandes de drogues
- Gestion des présentations réglementaires pour les médicaments vétérinaires

Frais

Frais de présentation

Les frais d'évaluation préalable à la mise en marché seront remboursés pour les présentations soumises en vertu du *Règlement sur les aliments et drogues* en vue d'obtenir l'approbation d'une drogue contre la COVID-19, à condition :

- qu'une demande ait déjà été déposée en vertu de l'arrêté d'urgence IVPD pour la même drogue et
- qu'aucune présentation n'ait été déposée antérieurement en vertu du *Règlement sur les aliments et drogues* pour cette drogue

Une fois qu'une drogue a reçu un Avis de conformité en vertu du *Règlement*, les frais actuels liés au droit de vendre une drogue s'appliquent.

Quand aucune demande n'a été déposée en vertu de l'arrêté d'urgence IVPD, les frais suivants s'appliqueront aux présentations de drogue contre la COVID-19 déposées en vertu du *Règlement* :

- les frais d'évaluation existants seront facturés pour les présentations
- les mesures d'atténuation existantes pour les petites entreprises sont disponibles pour les présentations de drogue contre la COVID-19 et comprennent :
  - l'exonération complète des frais d'évaluation pour la première présentation de drogue de l'entreprise à Santé Canada
  - une réduction de 50 % de tous les autres frais d'évaluation ainsi qu'une réduction de 25 % des frais de DIN et de LEPP

Veuillez consulter le document d'orientation suivant :

- Frais pour l'examen des présentations et des demandes de médicaments à usage humain et de désinfectants assimilés à une drogue

Les présentations assorties de frais sont associées à des normes de rendement. Des pénalités peuvent s'appliquer :

- Les normes de rendement publiées s'appliqueront, mais on s'attend à ce que la plupart des présentations de drogue contre la COVID-19 soient gérées et examinées efficacement.
- Les présentations en continu ne seront pas assujetties à des normes de rendement (en d'autres termes, la remise de 25 % aux fabricants en raison de normes de rendement non respectées ne s'appliquera pas).

Lignes directrices sur les modifications apportées au Règlement sur les aliments et drogues relativement aux drogues utilisées dans le traitement de la COVID-19 : Licences d'établissement de produits pharmaceutiques et bonnes pratiques de fabrication

- Aperçu
- Préparation d'une présentation
- Licences d'établissement de produits pharmaceutiques et bonnes pratiques de fabrication
- Propriété intellectuelle
- Exigences postérieures à la mise en marché
- Prépositionnement des drogues contre la COVID-19
- Scénarios de présentation, documents de référence et principales personnes-ressources

Sur cette page

- Licences d'établissement de produits pharmaceutiques pour des drogues contre la COVID-19
- Demande de LEPP nouvelle ou modifiée pour une drogue contre la COVID-19
- Conditions de la LEPP
- Suspension et annulation de la LEPP
- Normes de rendement de la LEPP
- Frais de licence d'établissement de produits pharmaceutiques
- Transition des LEPP émises ou modifiées en vertu de l'arrêté d'urgence IVPD
- Bonnes pratiques de fabrication

Licences d'établissement de produits pharmaceutiques pour des drogues contre la COVID-19

Le titre 1A de la partie C du *Règlement* s'applique aux drogues contre la COVID-19. Une personne doit détenir une licence d'établissement de produits pharmaceutiques (LEPP) autorisant toute activité menée à l'égard des drogues contre la COVID-19.

Vous trouverez les renseignements suivants en ligne :

- l'interprétation du *Règlement* sur les exigences en matière de LEPP dans le Document d'orientation sur les licences d'établissement de produits pharmaceutiques (GUI-0002)
- vos responsabilités liées au processus de demande de LEPP et à la façon dont Santé Canada gère les demandes de LEPP dans le document Gestion des demandes et du rendement en matière de licences d'établissement de produits pharmaceutiques (GUI-0127)

Pour en savoir plus sur les licences d'établissement de produits pharmaceutiques et la COVID-19, consultez notre page Les licences d'établissement de produits pharmaceutiques et la COVID-19.

Si vous avez des questions au sujet des exigences relatives aux LEPP ou des demandes de LEPP pour les drogues contre la COVID-19, veuillez nous envoyer un courriel à hc.del.questions-leppp.sc@canada.ca. Inscrivez le terme « COVID-19 » dans la ligne d'objet de votre courriel pour obtenir une réponse plus rapide.

Demande de LEPP nouvelle ou modifiée pour une drogue contre la COVID-19

Les nouvelles demandes de licence d'établissement de produits pharmaceutiques (LEPP) (C.01A.005(1)) ou les demandes de modification (C.01A.006(1) (1.1)) pour une drogue contre la COVID-19 peuvent être présentées en vertu du *Règlement*. Suivre le processus standard et utiliser la version la plus récente du formulaire de demande (FRM-0033).

Lorsque vous présentez une demande de LEPP nouvelle ou modifiée pour une drogue contre la COVID-19, assurez-vous d'inclure les renseignements suivants :

- la ligne objet « drogue contre la COVID-19 » dans le courriel de demande, qui indique qu'il s'agit d'une demande hautement prioritaire
- une déclaration dans le corps du courriel de demande ou de la lettre de présentation indiquant que la demande de LEPP concerne une drogue contre la COVID-19 présentée en vertu des paragraphes C.01A.005(2) ou C.01A.006(1.1) du *Règlement*
- le nom de la drogue.

Envoyez votre formulaire de demande rempli par courriel à hc.el.applications-le.sc@canada.ca.

Pour de plus amples renseignements sur les exigences de la LEPP, veuillez consulter les documents d'orientation suivants :

- Licences d'établissement de produits pharmaceutiques (GUI-0002)
- Comment démontrer la conformité des établissements étrangers avec les bonnes pratiques de fabrication des médicaments (GUI-0080)
- Gestion des demandes et du rendement en matière de licences d'établissement de produits pharmaceutiques (GUI-0127)

Délivrance d'une LEPP pour une drogue contre la COVID-19

Santé Canada émet ou modifie des LEPP conformément au titre 1A de la partie C du *Règlement*.

Les demandes de LEPP liées à la COVID-19 présentées en vertu du *Règlement* sont traitées rapidement. Les délais pour l'examen accéléré sont déterminés au cas par cas. Les documents présentés dans la demande et le volume d'information à évaluer sont des facteurs qui déterminent la rapidité avec laquelle nous pouvons examiner la demande.

Pour obtenir de plus amples renseignements sur l'octroi d'une LEPP ou d'une LEPP modifiée, veuillez consulter :

- Document d'orientation sur les licences d'établissement de produits pharmaceutiques (GUI-0002)

Conditions de la LEPP

À tout moment, Santé Canada peut imposer des conditions ou modifier les conditions applicables aux LEPP pour une drogue contre la COVID-19 présentée en vertu du *Règlement*. Les décisions d'imposer ou de modifier les modalités sont fondées sur le besoin d'atténuer ou de gérer une surveillance supplémentaire pour des raisons fondées sur le risque. Ces motifs comprennent les éléments de preuve disponibles, la nécessité médicale et les activités menées.

La capacité d'imposer ou de modifier les modalités donne à Santé Canada la souplesse nécessaire pour faciliter l'accès rapide aux drogues contre la COVID-19 tout en atténuant les risques.

Les conditions imposées précédemment sur une LEPP délivrée en vertu de l'arrêté d'urgence IVPD pour une drogue contre la COVID-19 continueront de s'appliquer en vertu du *Règlement*, au besoin.

Toute personne qui détient une LEPP doit mener les activités pouvant faire l'objet d'une licence conformément à la licence et aux conditions qui lui sont imposées.

Les détenteurs d'une LEPP qui ne se conforment pas aux conditions imposées sur leur permis seront assujettis à des mesures de conformité et d'application de la loi en cas de contravention à l'article 21.7 de la *Loi sur les aliments et drogues*. Ces mesures seront conformes au cadre législatif et aux principes énoncés dans notre Politique de conformité et d'application de la loi pour les produits de santé (POL-0001).

Suspension et annulation de la LEPP

Santé Canada peut suspendre ou annuler une LEPP en tout ou en partie pour l'une ou l'autre des raisons énoncées aux articles C.01A.016 à C.01A.017.1 afin de prévenir un risque pour la santé et la sécurité du consommateur relativement à une drogue contre la COVID-19. Lorsqu'une LEPP est suspendue ou annulée, le détenteur de la LEPP doit cesser toutes les activités suspendues ou annulées.

Pour plus d'informations sur la suspension et l'annulation de la LEPP, consultez :

- Document d'orientation sur les licences d'établissement de produits pharmaceutiques (GUI-0002)

Normes de rendement de la LEPP

Les demandes de LEPP liées à des drogues contre la COVID-19 seront classées comme prioritaires et examinées en fonction des critères suivants :

- besoin en santé publique
- documents présentés dans la demande
- volume d'information à évaluer.

Pour de plus amples renseignements sur la norme de rendement, veuillez consulter le document d'orientation sur :

- Gestion des demandes et du rendement en matière de licences d'établissement de produits pharmaceutiques (GUI-0127)

Frais de licence d'établissement de produits pharmaceutiques

Les frais de LEPP seront remboursés pour les demandes présentées en vertu de l'arrêté d'urgence IVPD jusqu'au 16 septembre 2021. Par la suite, les frais de LEPP s'appliqueront à l'examen des demandes de LEPP présentées pour une drogue contre la COVID-19.

Veuillez consulter le document d'orientation suivant :

- Frais pour l'examen des demandes de licence d'établissement de produits pharmaceutiques pour usage humain et vétérinaire

Des frais s'appliquent pour l'examen des types de demandes de LEPP suivants :

- une demande de LEPP nouvelle ou rétablie
- une demande de modification visant à ajouter un immeuble national à une LEPP
- une demande de révision annuelle d'une LEPP

Les frais de LEPP sont calculés à l'aide des composantes suivantes :

- Composante nationale : les frais exigés pour chaque bâtiment énuméré dans la licence ou la demande en fonction de l'activité la plus en amont de ce bâtiment.
- Composante des bâtiments étrangers : les frais exigés pour chaque bâtiment étranger unique (ou bâtiment à l'extérieur du Canada) sur la licence ou la demande

Les frais peuvent être annulés ou réduits pour les demandes déposées par :

- une petite entreprise
- un établissement de soins de santé financé par des fonds publics
- toute direction générale ou tout organisme du gouvernement du Canada ou d'une province ou d'un territoire

Transition des LEPP émises ou modifiées en vertu de l'arrêté d'urgence IVPD

Les demandes qui ont été présentées en vertu de l'article 20 de l'arrêté d'urgence IVPD avant son expiration, mais qui n'ont pas été traitées continueront d'être examinées comme si elles avaient été présentées en vertu des paragraphes C.01A.005(2) ou C.01A.006(1.1) du *Règlement sur les aliments et drogues*. Pour ces demandes, les frais de LEPP ne s'appliquent pas.

Notification

Les détenteurs de LEPP qui souhaitent conserver leur licence, ou une partie de leur licence, pour une drogue contre la COVID-19 en vertu du *Règlement* doivent aviser Santé Canada avant l'expiration de l'arrêté d'urgence IVPD. Nous recommandons de le faire au moins 30 jours avant l'expiration de l'arrêté d'urgence IVPD.

Pour conserver une LEPP délivrée en vertu de l'article 20 de l'arrêté d'urgence IVPD, veuillez soumettre les renseignements suivants à Santé Canada :

- inclure la mention « Conserver une LEPP obtenue en vertu de l'arrêté d'urgence pour une drogue contre la COVID-19 » dans la ligne d'objet du courriel de notification
- inclure des détails indiquant que l'avis est soumis pour conserver une LEPP ou une partie d'une LEPP délivrée pour une demande présentée en vertu de l'article 20 de l'arrêté d'urgence IVPD
- inclure le numéro de demande attribué par l'Unité des licences d'établissement de produits pharmaceutiques.

Santé Canada examinera votre avis de conservation et vous informera si des renseignements supplémentaires sont requis.

Le défaut de nous aviser entraînera l'annulation de la LEPP, en tout ou en partie par application de la règle transitoire du *Règlement*.

Bonnes pratiques de fabrication

Pour plus d'informations sur les exigences relatives aux bonnes pratiques de fabrication (BPF), consultez :

- Bonnes pratiques de fabrication des drogues (GUI-0001)

Les exigences en matière de preuves pour appuyer la conformité aux BPF des bâtiments étrangers sont incluses dans les directives suivantes :

- Comment démontrer la conformité des établissements étrangers avec les bonnes pratiques de fabrication des médicaments (GUI-0080)

Si vous n'êtes pas en mesure d'obtenir les documents décrits dans le document GUI-0080 en raison de la pandémie, veuillez nous envoyer un courriel à hc.foreign.site-etranger.sc@canada.ca. Vous devez communiquer avec nous avant d'envoyer votre demande de LEPP. Assurez-vous d'inclure « COVID-19 » dans votre ligne d'objet.

Si vous n'êtes pas en mesure d'organiser une inspection des BPF dans votre établissement en raison de la pandémie, veuillez nous envoyer un courriel à hc.drug.gmp.questions-bpf.medicaments.sc@canada.ca. Nous pourrions envisager des allègements opérationnels et des assouplissements aux délais d'inspection établis en vertu du régime actuel de droits, au cas par cas. Afin de surveiller la conformité, les inspections des BPF seront effectuées au moyen d'une approche fondée sur le risque pour les activités pouvant faire l'objet d'une licence.

La prolongation de certaines mesures d'assouplissement pour la conformité aux LEPP et aux BPF, telles que communiquées dans les bulletins sur les LEPP, se poursuivra jusqu'à nouvel ordre.

Pour en savoir plus sur les bonnes pratiques de fabrication et la COVID-19, consultez notre page sur les Bonnes pratiques de fabrication pendant la pandémie de COVID-19.

Analyse du produit fini

Les détenteurs de LEPP doivent satisfaire à toutes les exigences en matière de mainlevée des produits énoncées dans le *Règlement sur les aliments et drogues*.

Les exigences relatives aux essais de produits finis énoncées à l'article C.02.019 du Règlement ne s'appliquent plus à un distributeur ou à un importateur d'une drogue de l'annexe D (drogues biologiques) contre la COVID-19 s'il fait l'objet d'une demande écrite dans le cadre du programme de mainlevée des lots (C.04.015).

Les détenteurs de permis doivent se conformer aux exigences en matière d'essais dans le titre 2 du *Règlement*. Si vous n'êtes pas en mesure de satisfaire à ces exigences en raison de la pandémie, communiquez avec nous à hc.drug.gmp.questions-bpf.medicaments.sc@canada.ca.

Pour de plus amples renseignements sur les exigences du programme de mise en circulation des lots, veuillez consulter les documents suivants :

- Lignes directrices à l'intention des promoteurs : Programme d'autorisation de mise en circulation des lots de drogues visées à l'annexe D (produits biologiques)
- Bonnes pratiques de fabrication des drogues (GUI-0001)

Lignes directrices sur les modifications apportées au Règlement sur les aliments et drogues relativement aux drogues utilisées dans le traitement de la COVID-19 : Propriété intellectuelle

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- Propriété intellectuelle
- Protection des données
- *Règlement sur les médicaments brevetés (avis de conformité)*
- Certificat de protection supplémentaire

Propriété intellectuelle

Par suite de l'examen, de l'autorisation et de la surveillance des drogues contre la COVID-19 en vertu du *Règlement*, les fabricants peuvent bénéficier des protections en matière de propriété intellectuelle qui sont disponibles à l'égard d'une présentation qui donne lieu à un AC. Ces protections comprennent :

- la protection des données en vertu de l'article C.08.004.1 du *Règlement sur les aliments et drogues*

- la protection en vertu du *Règlement sur les médicaments brevetés (avis de conformité)*
- la protection en vertu du régime du *Certificat de protection supplémentaire*

Protection des données

Les modifications contiennent une disposition d'interprétation qui clarifie l'incidence d'une autorisation en vertu de l'arrêté d'urgence IVPD sur l'admissibilité à la protection des données, mais elles ne modifient pas ces protections.

Le paragraphe C.08.004.1(1) du *Règlement sur les aliments et drogues* prévoit qu'une « drogue innovante » est une drogue qui contient un ingrédient médicinal qui n'a pas été préalablement approuvé dans une drogue par le ministre et qui n'est pas une variante d'un ingrédient médicinal précédemment approuvé. Les modifications introduisent un libellé pour expliquer que, aux fins de la définition de « drogue innovante » au paragraphe C.08.004.1(1) du *Règlement*, un ingrédient médicinal n'est pas considéré comme approuvé dans une drogue en raison d'une autorisation en vertu de l'arrêté d'urgence IVPD. Cette disposition ne vise pas à modifier la portée ou l'interprétation actuelle du terme « approuvé » selon la définition actuelle. Elle explique plutôt l'application prévue de cette définition quand un ingrédient médicinal a été utilisé dans un médicament autorisé en vertu de l'arrêté d'urgence IVPD.

L'interprétation de « drogue innovante » garantit qu'une autorisation accordée en vertu de l'arrêté d'urgence IVPD n'exclut pas l'admissibilité à la protection des données en vertu du *Règlement*.

La protection des données sera évaluée conformément au processus existant, tel que décrit dans le Lignes directrices : La protection des données en vertu de l'article C.08.004.1 du *Règlement sur les aliments et drogues*.

Règlement sur les médicaments brevetés (avis de conformité)

Les modifications apportées au *Règlement sur les aliments et drogues* ne perturbent pas l'application de la *Loi sur les brevets* ni du *Règlement sur les médicaments brevetés (AC)*. Les listes de brevets peuvent être ajoutées au Registre des brevets au moment où la présentation ou le supplément est approuvé en vertu du Règlement, pourvu que les exigences du *Règlement sur les médicaments brevetés (avis de conformité)* soient respectées.

Dans le cas d'une présentation en continu, les données ou les renseignements fournis après la date de dépôt ne changeront pas la date de

dépôt de la présentation. Comme c'est le cas pour les autres demandes, les listes de brevets fournies après la date de dépôt de la présentation doivent respecter les exigences de délai du paragraphe 4(6) du *Règlement sur les médicaments brevetés (avis de conformité)* pour être prises en considération en vue de leur inscription au Registre des brevets.

Le *Règlement sur les médicaments brevetés (AC)* continuera d'être appliqué conformément aux processus existants. Elles sont décrites dans le *Règlement sur les médicaments brevetés (avis de conformité).*

Certificat de protection supplémentaire

Les modifications apportées au *Règlement sur les aliments et drogues* ne perturbent pas l'application de la *Loi sur les brevets* ni du *Règlement sur les certificats de protection supplémentaire*. Par conséquent, un certificat de protection supplémentaire peut être délivré à l'égard d'un brevet pour une drogue approuvée en vertu du *Règlement*, pourvu que les exigences du *Règlement sur les CPS* et de la *Loi sur les brevets* aient été respectées.

Bien qu'elles ne soient pas présentées à cette fin, les dispositions contenues dans ces modifications permettent de déposer plus tôt une PDN, ce qui facilite la tâche des fabricants qui souhaitent déposer leur PDN dans le délai prévu à l'alinéa 106(1)f) de la *Loi sur les brevets* et au paragraphe 6(1).b) établi en vertu du *Règlement sur les CPS* pour être admissible à l'obtention d'un certificat de protection supplémentaire.

Le régime de certificat de protection supplémentaire continuera d'être administré conformément aux lois existantes et au processus décrit dans les Lignes Directrices : Certificats de protection supplémentaire. Les intervenants sont invités à consulter la section 2.2.2 du présent document pour examiner l'interprétation continue de Santé Canada concernant une « demande d'approbation de mise en marché équivalente à une autorisation de vente » aux fins de l'alinéa 106(1)f) de la *Loi sur les brevets* et du paragraphe 6(1).b) du *Règlement sur les CPS*.

Lignes directrices sur les modifications apportées au Règlement sur les aliments et drogues relativement aux drogues utilisées dans le traitement de la COVID-19 : Exigences postérieures à la mise en marché

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La seule modification liée à la réglementation post-commercialisation est le nouveau pouvoir (permanent) du ministre d'imposer des conditions pour une drogue désignée contre la COVID-19 (C.01.014.21).

Afin d'assurer l'utilisation sûre et efficace d'un produit, des exigences post-commercialisation supplémentaires peuvent être imposées comme condition de l'autorisation. La présentation et la mise en œuvre d'un plan de gestion des risques (PGR) ou de ses éléments constituent un exemple de conditions post-commercialisation de l'autorisation. Autrement, les règlements en vigueur sur la postcommercialisation demeurent les mêmes.

Pour en savoir davantage sur la portée des PGR, consultez les documents suivants :

- Lignes directrices - Présentation des plans de gestion des risques et des engagements en matière de suivi

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- Rapports de synthèse annuels
- Rapports sommaires sur les enjeux
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Exigences en matière de rapports de pharmacovigilance

Déclaration d'effets indésirables

Les effets indésirables doivent être signalés au Programme Canada Vigilance.

Le détenteur d'une autorisation de mise en marché (DAMM) doit présenter un rapport dans les 15 jours suivant la réception des renseignements suivants (C.01.017) :

- effets indésirables graves attendus et inattendus des drogues au Canada
- effets indésirables graves et inattendus à l'étranger
- cas inhabituels où la drogue nouvelle ne produit pas l'effet prévu (C.08.007, C.08.008)

Toutefois, les effets indésirables associés à une drogue contre la COVID-19 sont une priorité. On encourage fortement les DAMM à soumettre sans délai à Santé Canada des rapports sur ce domaine prioritaire. Les DAMM devraient indiquer dans le rapport qu'il s'agit d'une drogue contre la COVID-19.

Pour obtenir des renseignements et des procédures générales sur la façon de signaler les effets indésirables graves d'une drogue, veuillez consulter le document d'orientation suivant :

- Déclaration des effets indésirables des produits de santé commercialisés

Vous pouvez également obtenir plus de renseignements sur la présentation de rapports par voie électronique.

Pour en savoir plus sur la façon de déclarer les effets indésirables associés aux médicaments vétérinaires, les DAMM sont invités à communiquer avec la Direction des médicaments vétérinaires par courriel à hc.pv-vet.sc@canada.ca.

Rapports de synthèse annuels

Une fois par année et à la demande du ministre de la Santé, les DAMM doivent effectuer une analyse critique et concise des effets indésirables et des effets indésirables graves d'une drogue. Ils doivent également préparer un rapport sommaire sur les rapports reçus au cours des 12 mois précédents (C.01.018).

Pour obtenir des renseignements sur la préparation et la présentation d'un rapport de synthèse annuel, veuillez consulter le document d'orientation suivant :

- Préparation et présentation de rapports de synthèse pour les drogues et les produits de santé naturels commercialisés

Rapports sommaires sur les enjeux

Santé Canada peut demander un rapport de synthèse sur un problème (C.01.019) en tout temps. Ce rapport est une analyse critique et concise d'un problème précis de sécurité ou d'efficacité.

Pour obtenir des renseignements sur la préparation et la présentation d'un rapport de synthèse sur un problème, veuillez consulter le document d'orientation suivant :

- Préparation et présentation de rapports de synthèse pour les drogues et les produits de santé naturels commercialisés

Autres bonnes pratiques de pharmacovigilance

Pour plus d'informations sur les exigences en matière de pharmacovigilance, consultez :

- Lignes directrices sur les Bonnes pratiques de pharmacovigilance (BPV) (GUI-0102)

Déclaration des mesures prises à l'étranger

En vertu de l'article C.01.050 du *Règlement*, les détenteurs d'une autorisation doivent aviser Santé Canada des mesures réglementaires prises à l'étranger. Il s'agit notamment du risque grave lié aux rappels, à la suspension ou à la révocation d'autorisations de fabrication ou de mise en marché dans l'une des administrations réglementaires étrangères spécifiées.

Pour de plus amples renseignements sur cette exigence de déclaration, veuillez consulter le document d'orientation suivant :

- Aviser Santé Canada des mesures prises dans les pays étrangers

Autres exigences postérieures à la mise en marché

Tenue des dossiers

En vertu du paragraphe C.01.020(1) du *Règlement,* les fabricants d'une drogue contre la COVID-19 doivent tenir des registres et des rapports de cas en lien avec les articles C.01.017 à C.01.019.

En vertu de l'article C.02.020, les détenteurs de LEPP doivent tenir des dossiers pour chaque drogue contre la COVID-19 qu'ils fabriquent, emballent ou étiquettent, distribuent ou importent.

Pour en savoir plus, consultez :

- Bonnes pratiques de fabrication des drogues (GUI-0001)

Pénuries ou cessation de vente

Dans le cas des drogues pour usage humain, les détenteurs d'une autorisation devraient consulter les articles C.01.014.9 et C.01.014.10 et le Guide pour la déclaration de pénuries et de cessations de la vente de drogues. Le guide contient des renseignements supplémentaires et des procédures générales sur la façon de signaler les pénuries de drogues et les interruptions de la vente.

Pour plus de détails sur les pénuries, voir l'Arrêté d'urgence concernant la prévention et l'atténuation de pénuries de drogues liées à la COVID-19.

Pour de plus amples renseignements sur la déclaration des pénuries, les détenteurs d'autorisation de médicaments vétérinaires doivent communiquer avec la Direction des médicaments vétérinaires par courriel à hc.vdd.vetdrugs-medsvet.dmv.sc@canada.ca.

Conformité et application de la loi

Santé Canada surveille la conformité, entreprend des activités d'application de la loi et s'efforce de prévenir la non-conformité. Lorsqu'il prend des mesures de conformité et d'application de la loi, Santé Canada tient compte d'un certain nombre de facteurs tout en respectant le cadre législatif et les principes de notre Politique de conformité et d'application pour les produits de santé (POL-0001).

Pour de plus amples renseignements, consultez la liste des documents d'orientation.

Lignes directrices sur les modifications apportées au Règlement sur les aliments et drogues relativement aux drogues utilisées dans le traitement de la COVID-19 : Prépositionnement des drogues contre la COVID-19

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Une drogue prometteuse contre la COVID-19 peut être importée au Canada avant d'avoir reçu une autorisation de mise en marché au Canada. Cette importation et ce placement précoces dans les installations canadiennes sont appelés « prépositionnement ». Cela facilite la distribution immédiate de la drogue dès qu'elle est autorisée, ce qui la rend accessible aux Canadiens le plus tôt possible.

Ce mécanisme peut être utilisé pour importer au Canada une drogue prometteuse contre la COVID-19 si l'administratrice en chef de la santé publique (ACSP) de l'Agence de la santé publique du Canada a avisé le ministre de la drogue contre la COVID-19 qui doit faire l'objet d'un prépositionnement.

Pour avoir le droit d'importer une drogue contre la COVID-19 pour un prépositionnement, plusieurs conditions doivent être respectées :

- Le gouvernement du Canada a conclu un marché d'approvisionnement pour cette drogue.
- Aucune autorisation n'a été délivrée pour la drogue.
- Le fabricant a déposé une présentation en vue de l'autorisation de la drogue.
- L'importateur de la drogue qui doit faire l'objet d'un prépositionnement possède une licence d'établissement de produits pharmaceutiques valide au Canada.
- L'ACSP a fourni au ministre les renseignements exigés en vertu de l'article C.08.009.03.
- Le détenteur d'une LEPP a fourni au ministre les renseignements exigés en vertu du paragraphe C.08.009.03(2), notamment :
- La preuve démontrant que le ou les bâtiments étrangers où la drogue contre la COVID-19 est fabriquée, emballée, étiquetée ou testée satisfont aux exigences applicables des dispositions des titres 2 à 4 de la partie C du *Règlement*.

Importation et distribution d'une drogue ayant fait l'objet d'un prépositionnement

À la suite de l'examen des renseignements fournis par l'ACSP et l'importateur, le ministre de la Santé envoie une lettre à l'ACSP pour lui indiquer si les exigences relatives au prépositionnement ont été respectées. Pour faciliter l'importation de la drogue prépositionnée au Canada, une copie de cette lettre doit accompagner le produit de l'autre côté de la frontière.

La personne qui importe une drogue contre la COVID-19 en vue d'un prépositionnement doit avoir une licence d'établissement de produits pharmaceutiques (LEPP), mais elle n'a pas besoin que l'activité d'importation soit autorisée par la LEPP. Toutefois, le détenteur de la LEPP responsable de l'importation de la drogue contre la COVID-19 faisant l'objet d'un prépositionnement sera assujetti à certains articles des titres 2 à 4 de la partie C du *Règlement* concernant l'entreposage, la distribution, le contrôle de la qualité et le rappel rapide.

Une drogue contre la COVID-19 faisant l'objet d'un prépositionnement ne peut pas être distribuée avant d'être autorisée au Canada. Elle peut toutefois être déplacée vers une autre installation d'entreposage, à condition que le ministre ait été avisé par l'ACSP de l'adresse municipale de cette installation.

Une fois que la drogue a reçu une autorisation de mise sur le marché au Canada, toutes les exigences de la LEPP s'appliquent à l'importation et à la distribution subséquentes.

Les drogues contre la COVID-19 faisant l'objet d'un prépositionnement qui ne reçoivent pas d'autorisation de mise en marché en vertu du *Règlement* doivent être détruites ou retournées au fabricant.

Pour obtenir des conseils sur la façon de respecter les exigences réglementaires relatives à la tenue de dossiers, à l'entreposage et à la distribution des drogues contre la COVID-19 faisant l'objet d'un prépositionnement, veuillez consulter :

- Bonnes pratiques de fabrication des drogues (GUI-0001)

Les exigences en matière de preuves à l'appui de la conformité aux BPF sont incluses dans le document d'orientation suivant :

- Comment démontrer la conformité des établissements étrangers avec les bonnes pratiques de fabrication des médicaments (GUI-0080)

Pour en savoir plus sur les bonnes pratiques de fabrication et la COVID-19, consultez les Bonnes pratiques de fabrication pendant la pandémie de COVID-19.

Transition des drogues en prépositionnement de l'arrêté d'urgence IVPD au *Règlement*

Les drogues contre la COVID-19 qui satisfont aux exigences des articles 27 à 30 de l'arrêté d'urgence IVPD sont réputées avoir été prépositionnées en vertu du *Règlement*.

Tout renseignement fourni en vertu des articles 27 à 30 de l'arrêté d'urgence IVPD avant son expiration, mais qui n'a pas été jugé avoir satisfait à toutes les exigences de prépositionnement continuera d'être examiné en vertu du *Règlement.*

Lignes directrices sur les modifications apportées au Règlement sur les aliments et drogues relativement aux drogues utilisées dans le traitement de la COVID-19 : Scénarios de présentation, documents de référence et principales personnes-ressources

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Scénarios de présentation

Veuillez consulter le tableau 1 du présent document d'orientation pour obtenir un résumé des scénarios de présentation.

Scénario 1

Une drogue contre la COVID-19 est autorisée en vertu de l'arrêté d'urgence IVPD (l'autorisation n'a pas été suspendue ni révoquée) et

une présentation est par la suite déposée en vertu du *Règlement sur les aliments et drogues* pour cette drogue.

Les fabricants déposeraient une PDN en vertu du titre 8 du *Règlement*. La présentation doit contenir les mêmes données que celles qui ont été incluses dans la demande soumise en vertu de l'arrêté d'urgence IVPD, ainsi que les mises à jour nécessaires. Cela peut comprendre de nouveaux éléments de preuve qui n'étaient pas disponibles quand la demande a été déposée en vertu de l'arrêté d'urgence IVPD. Les fabricants décriraient dans un résumé les changements apportés à la demande par rapport au dépôt en vertu de l'arrêté d'urgence IVPD.

Pour maintenir la capacité de vendre la drogue contre la COVID-19 autorisée en vertu de l'arrêté d'urgence IVPD, la PDN doit être déposée :

- dans les 90 jours suivant l'entrée en vigueur des modifications, si la drogue a été autorisée en vertu de l'arrêté d'urgence IVPD avant l'entrée en vigueur des modifications
- dans les 90 jours suivant la délivrance d'une autorisation en vertu de l'arrêté d'urgence IVPD, si la drogue a été autorisée après l'entrée en vigueur des modifications

Les fabricants peuvent continuer de vendre la drogue contre la COVID-19 en vertu de l'autorisation de l'arrêté d'urgence IVPD jusqu'à ce que la PDN soit approuvée, rejetée ou retirée. Ce sera le cas même après que l'arrêté d'urgence IVPD prendra fin.

Bon nombre des dispositions réglementaires figurant dans l'arrêté d'urgence IVPD sont disponibles au moment du dépôt d'une présentation en vertu du *Règlement*. Elles sont décrites plus en détail dans :

- Présentations en continu
- Exigences et renseignements cliniques
- Exigences et renseignements non cliniques
- Informations et exigences de qualité (chimie et fabrication)
- Étiquettes des produits
- Étiquetage

Une PDN déposée en vertu du *Règlement* modifié appuierait la délivrance de l'avis de conformité (AC), ainsi que les conditions applicables. De plus amples détails sont fournis dans :

- Délivrance d'un avis de conformité pour une drogue contre la COVID-19
- Conditions d'utilisation d'un numéro d'identification de drogue fondées sur les exigences modifiées du paragraphe C.08.002(2.1)

Pendant que la PDN fait l'objet d'un examen, le DIN attribué en vertu de l'arrêté d'urgence IVPD demeure attribué à la drogue autorisée en vertu de cet arrêté d'urgence. Cela continue d'assurer le respect de toutes les obligations réglementaires associées à la drogue. Les promoteurs sont invités à discuter avec Santé Canada de leurs plans d'emballage, d'étiquetage et de réutilisation d'un DIN.

Scénario 2

Une PDN est déposée pour une drogue contre la COVID-19 pour laquelle aucune demande n'a été déposée en vertu de l'arrêté d'urgence IVPD.

Les fabricants de drogues nouvelles contre la COVID-19 qui n'ont pas présenté de demande en vertu de l'arrêté d'urgence IVPD peuvent présenter une PDN pour faire approuver la drogue en se fondant sur les exigences modifiées en vertu du processus de PDN modifié dans le *Règlement*.

Bon nombre des dispositions réglementaires figurant dans l'arrêté d'urgence IVPD sont disponibles au moment du dépôt d'une présentation en vertu du *Règlement*. Elles sont décrites plus en détail dans :

- Présentations en continu
- Exigences et renseignements cliniques
- Exigences et renseignements non cliniques
- Informations et exigences de qualité (chimie et fabrication)
- Étiquettes des produits
- Étiquetage

Une PDN déposée en vertu du *Règlement* modifié appuierait la délivrance de l'AC, ainsi que les conditions applicables. De plus amples détails sont fournis dans :

- Délivrance d'un avis de conformité pour une drogue contre la COVID-19
- Conditions d'utilisation d'un numéro d'identification de drogue fondées sur les exigences modifiées du paragraphe C.08.002(2.1)

Le fabricant devra attendre de recevoir un AC avant de commercialiser sa drogue.

Scénario 3

Un SPDN pour une drogue commercialisée est déposé lorsqu'une indication élargie pour la COVID-19 a été autorisée en vertu de l'arrêté d'urgence IVPD.

Lorsqu'une indication élargie pour la COVID-19 a été autorisée en vertu de l'arrêté d'urgence IVPD pour une drogue commercialisée, le fabricant peut présenter un supplément à une présentation de drogue nouvelle (SPDN) pour ajouter la nouvelle indication relative à la COVID-19. Le *règlement* modifié, y compris la capacité de soumettre une présentation incomplète (présentation en continu), n'est pas disponible dans ce scénario.

Pour maintenir la capacité de vendre la drogue contre la COVID-19, le SPDN doit être déposé :

- dans les 90 jours suivant l'entrée en vigueur des modifications, si la drogue a été autorisée avant l'entrée en vigueur des modifications
- dans les 90 jours suivant la délivrance d'une autorisation en vertu de l'arrêté d'urgence IVPD, si la drogue a été autorisée après l'entrée en vigueur des modifications

Les fabricants peuvent continuer de vendre la drogue contre la COVID-19 en vertu de l'autorisation de l'arrêté d'urgence IVPD jusqu'à ce que le SPDN soit approuvé, rejeté ou retiré (même après l'expiration de l'arrêté d'urgence IVPD). Les fabricants sont encouragés à déposer les SPDN avant que l'autorisation de l'arrêté d'urgence IVPD ne cesse d'avoir effet.

Le fabricant doit inclure tous les renseignements connus disponibles sur l'utilisation de la drogue approuvée pour la COVID-19.

Scénario 4

Une présentation visant à obtenir l'approbation d'un produit pharmaceutique subséquent sur la base d'une comparaison directe ou indirecte avec une drogue contre la COVID-19 (par exemple, une présentation comparative).

Les présentations subséquentes visant à obtenir l'approbation d'une drogue contre la COVID-19 sur la base d'une comparaison directe ou indirecte avec une autre drogue contre la COVID-19 ne sont pas admissibles au *Règlement* modifié. Ces présentations seront déposées sous forme de PADN ou de PDN comparative.

Documents de référence

Documents d'orientation et pages Web sur les demandes d'autorisation :

- Gestion des présentations et des demandes de drogues
- Lignes directrices :Préparation des activités de réglementation en format Electronic Common Technical Document
- Lignes directrices :Préparation des activités de réglementation en format « Électronique autre que le format eCTD »
- Processus d'inscription réglementaire

- Portail commun des demandes électroniques
- Gestion des présentations réglementaires pour les médicaments vétérinaires
- Dépôt des soumissions par voie électronique

Lignes directrices

- Exigences en matière de renseignements et de présentation relatives aux médicaments biologiques biosimilaires.
- Présentations de drogue fondées sur les données de tierces parties (Source documentaire et expérience de commercialisation)
- L'utilisation des examens étrangers par Santé Canada
- Détermination du statut de vente sur ordonnance pour drogues destinées aux humains et aux animaux
- Questions et réponses :La Liste des drogues sur ordonnance
- Exigences réglementaires associées à une identification numérique attribuée à une drogue (DIN)
- Les licences d'établissement de produits pharmaceutiques et la COVID-19
- Bonnes pratiques de fabrication pendant la pandémie de COVID-19
- Politique de conformité et d'application de la loi pour les produits de santé (POL-0001)
- Bases de données sur les médicaments et les instruments médicaux
- Feuille de route réglementaire pour les drogues biologiques (annexe D) au Canada

Lignes directrices sur l'innocuité et l'efficacité :

- Données d'études non cliniques en laboratoire à l'appui des demandes et des présentations de drogues :respect des bonnes pratiques de laboratoire
- Préparation de données comparatives de biodisponibilité pour les présentations de drogues dans le format CTD
- *Cochrane Handbook for Systematic Reviews of Interventions* (en anglais seulement)
- Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (en anglais seulement)

Documents d'orientation sur la qualité :

- Préparation des données sur la qualité pour les présentations de drogues dans le format CTD :Produits biologiques ou issus de la biotechnologie
- Préparation des données sur la qualité pour les présentations de drogues dans le format CTD :Produits biothérapeutiques conventionnels

- Lignes directrices : Qualité (chimie et fabrication) :Présentations de drogue nouvelle (PDN) et présentations abrégées de drogue nouvelle (PADN)

Lignes directrices sur l'étiquetage :

- Lignes directrices à intention de l'industrie :Examen des marques nominatives de médicament
- Foire aux questions – Examen des marques nominatives de médicament
- Guide des bonnes pratiques d'étiquetage et d'emballage pour les médicaments sur ordonnance
- Questions et réponses :Le règlement sur l'étiquetage en langage clair pour les médicaments sur ordonnance
- Politique sur l'étiquetage des contenants spéciaux
- Étiquetage des médicaments pharmaceutiques destinés à l'usage des humains
- Lignes directrices et les avis sur les monographies de produit

Documents d'orientation sur les licences d'établissement :

- Document d'orientation sur les licences d'établissement de produits pharmaceutiques (GUI-0002)
- Gestion des demandes et du rendement en matière de licences d'établissement de produits pharmaceutiques (GUI-0127)

Documents d'orientation sur les Bonnes pratiques de fabrication (BPF) :

- Bonnes pratiques de fabrication des drogues (GUI-0001)
- Annexe 2 à l'édition actuelle des Lignes directrices sur les Bonnes pratiques de fabrication Drogues visées à l'Annexe D (drogues biologiques) (GUI-0027)
- Comment démontrer la conformité des établissements étrangers avec les bonnes pratiques de fabrication des médicaments (GUI-0080)
- Bonnes pratiques de fabrication (BPF) des ingrédients pharmaceutiques actifs (IPA) - (GUI-0104)

Document d'orientation sur les bonnes pratiques de laboratoire (BPL) :

- Directive d'homologation : Bonnes pratiques de laboratoire (Dir-9801)

Documents d'orientation sur la surveillance post-commercialisation :

- Aperçu de la Déclaration des effets indésirables des produits de santé commercialisés
- Déclarez une réaction indésirable à un médicament : industrie
- Préparation et présentation de rapports de synthèse pour les drogues et les produits de santé naturels commercialisés

- Lignes directrices sur les Bonnes pratiques de pharmacovigilance (BPV) (GUI-0102)
- Aviser Santé Canada des mesures prises dans les pays étrangers :Document d'orientation à l'intention de l'industrie
- Modifications à la *Loi sur les aliments et drogues* :Guide pour l'application des nouveaux pouvoirs : Pouvoir d'exiger et de communiquer des renseignements, Pouvoir d'exiger la modification d'une étiquette, Pouvoir d'ordonner un rappel
- Format et contenu des évaluations des avantages et des risques après la mise en marché au Canada
- Présentation des plans de gestion des risques et des engagements en matière de suivi
- Guide pour la déclaration de pénuries et de cessations de la vente de drogues
- Politique sur les retraits/rappels de produits de santé (POL-0016)
- Guide pour le retrait de drogues et de produits de santé naturels (GUI-0039)

Lignes directrices : Changements survenus après l'avis de conformité (AC) :

- Document cadre (Médicaments pharmaceutiques, biologiques et radiopharmaceutiques à usage humain seulement)
- Document sur la qualité
- Document sur l'innocuité et l'efficacité (Pour les produits biologiques, pharmaceutiques et radiopharmaceutiques à usage humain seulement)

Lignes directrices sur la publicité :

- Marketing des médicaments et des instruments médicaux

Lignes directrices sur les désinfectants et monographies :

- Gestion des présentations de désinfectants assimilés aux drogues
- Exigences en matière d'innocuité et d'efficacité relatives aux désinfectants assimilés aux drogues pour surfaces
- Désinfectants assimilés aux drogues
- Demande de numéro d'identification du médicament (DIN) pour les désinfectants assimilés aux drogues pendant la pandémie de COVID-19
- Monographie sur les désinfectants pour surfaces dures

Produits pharmaceutiques en vente libre et désinfectants pour les mains (nettoyants antiseptiques pour la peau) – documents d'orientation et monographies :

- Médicaments antiseptiques à usage humain
- Gestion des présentations et des demandes de drogues
- Compendium des monographies

Principales personnes-ressources

Pour que nous puissions accorder la priorité à votre demande, veuillez inclure « drogue contre la COVID-19 » dans la ligne d'objet de votre courriel.

Direction des médicaments biologiques et radiopharmaceutiques
Bureau des affaires réglementaires
Courriel : hc.brdd.ora.sc@canada.ca

Direction des produits thérapeutiques
Division de la gestion de projets réglementaires
Courriel : hc.rpmd-dgpr.sc@canada.ca

Direction des médicaments vétérinaires
Division de la gestion des présentations et du savoir
Courriel : hc.vdd.skmd.so-dgps.dmv.cp.sc@canada.ca

Direction des produits de santé naturels et sans ordonnance
Demandes de renseignements généraux
Courriel : hc.nnhpd-dpsnso.sc@canada.ca

Pour les demandes de renseignements sur la propriété intellectuelle :

Bureau des médicaments brevetés et de la liaison
Courriel : hc.opml-bmbl.sc@canada.ca

Pour les demandes de renseignements sur le format de la demande :

Bureau des présentations et de la propriété intellectuelle
Courriel : hc.ereview.sc@canada.ca

Pour les demandes de renseignements sur la déclaration des effets indésirables :

Programme Canada Vigilance (CVP)

Pour les demandes de renseignements sur les exigences de conformité aux bonnes pratiques de fabrication (BPF) :

Courriel : GMP_Questions_BPF@hc-sc.gc.ca

Pour les demandes de renseignements liées à la licence d'établissement de produits pharmaceutiques (LEPP) :

Courriel : hc.del.questions-leppp.sc@canada.ca