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SUMMARY OF EVALUATION

Applications for registration of thirteen McGhan Gel-Filled Mammary Implants, as listed in the Registration Information, were received by TGA in December 1997. Although the Device Registration Section holds the coordinating role, the evaluation is being performed in cooperation with the TDEC Advisory Panel on Biomaterials. Evaluators are drawn from the Panel, experts in relevant fields and TGA officers. A list of evaluators is included in the Chronological Summary document at Paper B.

The products were not eligible to claim equivalence for any aspects of their materials, manufacture, safety or efficacy as no silicone gel implants have been evaluated for inclusion or registered in the ARTG previously.

The evaluation takes into consideration the requirements described in the DR4, *Australian Medical Device Requirements, Version 4, under the Therapeutic Goods Act 1989, Section 2.11 Breast Prostheses (not Saline or Water)*.

Broadly, the evaluation was grouped into three areas of required expertise, though areas of overlap were inevitable and inter-group consultation occurred.

Design, materials, testing and manufacturing:

The design and materials of the prostheses were fully characterised and documented. Following the initial stage of evaluation further questions on purity of the materials, aspects of shell texturing and gel permeation chromatography were addressed to the sponsor. Also methodology used in determining shell leakage and bleed and details relating to fatigue, ageing and impact testing were sought from the sponsor.

The information provided satisfied the deficiencies. The Panel members responsible for design, materials, testing and manufacturing concluded that there were no outstanding matters for these aspects of the devices.

Labelling and Product Information:

The labels were assessed by TGA officers and found to comply with the Therapeutic Goods Order No. 37.

Both TGA officers and the Clinical review group assessed the Product Information independently. Many similar topics were apparent between the TGA Breast Information Booklet and the Product Information supplied by McGhan. Problems with the device PI included small print, sophisticated language and delegation of responsibility to the patient. The manufacturer proposed a possible review of the information to include patient-friendly language and presentation.

At the time of review, the TGA Booklet was considered to be a more suitable document for patient information.

Sterility:

Therapeutic Goods Administration Laboratories conducted the sterility evaluation. The devices are sterilised by dry heat under cycle parameters of [REDACTED]. The manufacturing environment, pre-sterilisation bioburden, sterilisation parameters, cycle validation and packaging integrity were taken into consideration when assessing the sterility of the product for release. A number of areas of the sterilisation process required

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clarification, including bioburden reduction, environmental monitoring, testing procedures, cycle validation, testing of the biological indicators, monitoring of routine sterilisation cycles. All points raised by TGAL were responded to and acceptable explanations given.

Biocompatibility:

The initial submission reviewed by the Biocompatibility group of the Panel provided study protocols but omitted comprehensive data to enable adequate evaluation. The studies were stated to comprise both *in vitro* and *in vivo* assays as described in the Tripartite Biocompatibility Guidance and ISO 10993-1:2, *Biological Evaluation of Medical Devices – Part 1: Guidance on Selection of Test* on phenyl/phenyl silicone elastomer shell, patch and valve materials, and the silicone gel.

The additional information was submitted upon request to the sponsor and was found to have been performed on individual “finished” device components rather than the finished device. Notwithstanding this, the results of the battery of tests recommended by ISO 10993-1:2 demonstrated that toxicity could not be detected in the parameters measured.

At the time when these devices were tested, immunotoxicity testing of devices fell outside the scope of ISO 10993. It was instigated under the National Toxicological Program in the USA and used for assessing the potential immunotoxicity of silicone materials. Upon request for more complete immunotoxicity testing, it was found that the materials associated with the McGhan gel-filled mammary implants had not been subjected to testing for potential cellular or humoral responses. The additional tests were performed. The majority of parameters assessed was within the expected specification or could be satisfactorily explained. The single outstanding discrepancy is in relation to an unexplained increase in spleen weight in mice treated with the high dose of cohesive gel filler. This abnormality is not associated with a corresponding increase in cell numbers within the spleen or change in the specific activity of the spleen IgM antibody-forming cell. The sponsor is performing an additional study to assess the histology of the spleen for any abnormalities and has confirmed submission of this information during the week of 20 November 2000.

Clinical:

A clinical group, consisting of specialist clinicians in plastic surgery and immunology, reviewed the clinical information submitted in support of the clinical safety and efficacy of the McGhan gel mammary implants. The areas of focus in the clinical evaluation were necessarily broad. The evaluators examined safety and efficacy in terms of local and systemic issues in augmentation and reconstruction, device integrity, capsular contracture, patient disease, cancer detection, general surgical issues and breast-feeding.

The final recommendations of this group are:

1. It is recommended that the Delegate be advised that there are no clinical objections to the entry of McGhan Silicone-filled Mammary Implant Prostheses being entered on to the ARTG.
2. It is recommended that some form of register for breast implants be established in order to establish more accurately the performance of and complication rates for various surgical implanting procedures and implant surface textures.
3. Breast implants should be subject to active post market surveillance.
4. It is recommended that the sponsor review the patient information supplied with this product to ensure its accuracy especially in relation to complication rates.

REGISTRATION REPORT

McGhan Gel-Filled Mammary Prostheses

Sub TGA IN Device Description
File Number

98/3	99427	McGhan Style 110 BIOCELL™ Textured Gel-Filled/Round Moderate Profile Mammary Implant	
98/4	99428	McGhan Style 120 BIOCELL™ Textured Gel-Filled/Round High Profile Mammary Implant	
98/5	99429	McGhan Style 153 BioDIMENSIONAL™ BIOCELL™ Textured Gel-Filled Mammary Implant	
98/6	99430	McGhan Style 410 BioDIMENSIONAL™ BIOCELL™ Textured Cohesive Gel-Filled Mammary Implant	
98/7	99431	McGhan Style 410FM BioDIMENSIONAL™ BIOCELL™ Textured Cohesive Gel-Filled Mammary Implant	
98/8	99432	McGhan Style 150 BioDIMENSIONAL™ BIOCELL™ Textured Expandable Gel/Saline-Filled Mammary Implant with Adjustable Inner Lumen - Standard	
98/9	99433	McGhan Style 150 BioDIMENSIONAL™ BIOCELL™ Textured Expandable Gel/Saline-Filled Mammary Implant with Adjustable Inner Lumen - Low Pole	
98/10	99434	McGhan Style 177 McGhan INTRASHIEL™ Gel/Saline Filled, Double Lumen, Round Mammary Implant - WITHDRAWN	
98/11	99435	McGhan Style 40 INTRASHIEL™ Gel-Filled Round, Standard Profile Mammary Implant	
98/12	99436	McGhan Style 45 INTRASHIEL™ Gel-Filled Round, High Profile Mammary Implant	
98/13	99437	McGhan Style 46 McGhan INTRASHIEL™ Gel/Saline Filled, Double Lumen, Round Mammary Implant - WITHDRAWN	
98/14	99438	CUI Type RLD, DRIE, Round Low Profile Gel-Filled Mammary Implant	
98/15	99439	CUI Type RHD, DRIE, Round High Profile Gel-Filled Mammary Implant	
98/16	99440	CUI Type MLP, Microcell™, DRIE Low Profile Gel-Filled Mammary Implant	
98/17	99441	CUI Type MHP, Microcell™, DRIE High Profile DRIE Gel-Filled Mammary Implant	

Sponsor Device Technologies Australia P/L

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Contact -
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Manufacturer McGhan Ltd
Kilbride Industrial Estate
Arklow County, Wicklow, Ireland

Ent ID: 17503 TD1

Manufact Steps
GMP Status

Manufacturer Biological Laboratories Europe Ltd,
Carrentila, Ballina, Co. Mayo, Ireland,
Manufact Steps TMM (Sterility testing of exposed biological indicators).
GMP Status

Ent ID: 27870 LI1

INTRODUCTION

In December 1997 the sponsor, Helex A Pty Ltd lodged an application for registration on 15 different models of silicone breast implants. However, a change of sponsorship occurred in November 1998 whereby Device Technologies Australia Pty Ltd (Ent ID: 19396) is now the new sponsor. The various models will be sold under two brand names viz: McGhan and CUI. The submission has been compiled to represent all 15 styles of implant as they share the following key features:

- Indications;
- Manufacturer;
- Method of sterilisation;
- Method of manufacturing of basic implant, and
- Shell constituent

The implants are provided as either single lumen or double lumen. The double lumen designs provide a choice of expansion in conjunction with a tissue expander or through expansion of the saline fill in a permanent implant. The styles are grouped into 3 basic groups:

- | | |
|---|---|
| Group 1 (textured and single lumen styles): | Group includes styles 110, 120, 410, 410FM, MLP and MHP. Within the group differences between the products consist of different profiles, shaping and gel type. |
| Group 2 (smooth and single lumen styles): | Group includes styles 40, 45, RLD and RHD. All styles share common characteristics of round shape and responsive gel. Styles offer different profiles (standard, high or low). |
| Group 3 (double lumen style): | Group includes styles 153, 150, 150 LP, 177 and 46. Style 46 is the only smooth style. Style 153 is filled with gel and uses cohesive gel while the other styles are filled with saline and use responsive gel. |

The submission states that styles 110, 120, 153, 410, 410FM, 150, 150LP, MLP and MHP are CE marked. Styles 40, 45, 46, 177, RHD and RLD will be submitted for CE marking in the near future. The sponsor informed TGA in September 1998 that Styles 46 and 177 were obsolete and would not be manufactured in the future. These applications have been withdrawn.

The McGhan and CUI implants are intended for use in cosmetic augmentation mammoplasty or in breast reconstruction following mastectomy. The implants are surgically placed submuscularly or subcutaneously. The implants are composed of silicone elastomer and gel components and have either a smooth or textured surface. McGhan Style 150 was packaged with a 21 gauge needle infusion set to allow the inner lumen of the device to be filled with sterile saline. The manufacturer has redeveloped this accessory and it will be packaged and supplied separate from the prosthesis, thus it requires separate CE marking, and will be subject of a listing application in Australia.

General Description Details:

1.) McGhan Gel-Filled Mammary Implants – Styles 110, 120, 153, 410, 410FM, 150, 40, 45:

The McGhan Styles 110, 120, 153, 410, 410FM, 150, 40, and 45 are Gel-Filled Mammary Implants designed for use in cosmetic augmentation mammoplasty or in breast reconstruction following mastectomy. The implant is surgically placed submuscularly or subcutaneously.

These implants are composed of silicone elastomer and gel components. The implants have either a smooth or a textured surface.

All of the styles incorporate the McGhan INTRASHIEL™ patented low bleed silicone elastomeric barrier which significantly reduces gel diffusion.

Style 110: (McGhan Style 110 BIOCELL™ Textured Gel-Filled/Round Moderate Profile Mammary Implant)

The McGhan style 110 is a BIOCELL™ textured surface, silicone gel-filled mammary implant with an INTRASHIEL™ barrier shell. The style 110 is a single lumen, round device with a moderate profile and a volume ranging from 90 cc to 510 cc.

Style 120: (McGhan Style 120 BIOCELL™ Textured Gel-Filled/Round High Profile Mammary Implant)

The McGhan style 120 is a BIOCELL™ textured surface, silicone gel-filled mammary implant with an INTRASHIEL™ barrier shell. The style 120 is a single lumen round device with a high profile and a volume ranging from 180cc to 650cc.

Style 153: (McGhan Style 153 BioDIMENSIONAL™ BIOCELL™ Textured Gel-Filled Mammary Implant)

The McGhan 153 is a BIODIMENSIONAL™, BIOCELL™ textured surface, silicone, gel-filled mammary implant with an INTRASHIEL™ barrier shell. The Style 153 is a double lumen anatomically shaped implant with a volume ranging from 190cc to 720cc. The inner lumen in the lower pole maintains implant shape and projections. The Style 153 is used in combination with the McGhan Style 133 Tissue Expander as part of the BIODIMENSIONAL™ two stage reconstructions.

Style 410: (McGhan Style 410 BioDIMENSIONAL™ BIOCELL™ Textured Cohesive Gel-Filled Mammary Implant)

The Style 410 is a BIODIMENSIONAL™, BIOCELL™ textured surface silicone gel-filled mammary implant with an INTRASHIEL™ barrier shell. The Style 410 is a single lumen anatomically shaped implant with a volume ranging from 210cc to 620cc and incorporates narrow distribution cohesive gel. The gel remains anatomically distributed within the implant shell.

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Style 410FM: (McGhan Style 410 FM BioDIMENSIONAL™ BIOCELL™ Textured Cohesive Gel-Filled Mammary Implant)

The McGhan Style 410FM is a design modification of the McGhan Style 410. It is a BIODIMENSIONAL™, BIOCELL™ textured surface silicone gel-filled mammary implant with an INTRASHIEL™ barrier shell. The Style 410FM is a single lumen anatomically shaped implant with a volume ranging from 155cc to 670cc and incorporates narrow distribution cohesive gel. The patch is laser etched with lot numbers for improved product traceability and is the same design as the CUI Type MLP/MHP patches. Six orientation dots are included on all products in order to assist in the placement of the product.

Style 150: (McGhan Style 150 BioDIMENSIONAL™ BIOCELL™ Textured Expandable Gel/Saline-Filled Mammary Implant with Adjustable Inner Lumen (Low Pole))

The McGhan Style 150 is a BIODIMENSIONAL™ BIOCELL™ textured surface, silicone gel-filled mammary implant with an INTRASHIEL™ barrier shell. The Style 150 is a double lumen anatomically shaped implant. The adjustable saline-fill inner lumen is surrounded by a silicone gel outer lumen. Two choices in dimensional height and upper pole configurations, the Style 150 full height with a volume ranging from 180/200cc to 720/760cc and the Style 150 short height with a volume ranging from 135/145cc to 625/655cc are available to match the widest range of patient requirements. The short height version of the Style 150 is also referred to as the Style 150 Low Pole (LP).

The BIOCELL™ Sleeve is a sterile delivery sleeve that assists in the placement of textured mammary implants. The use of a sleeve for insertion provides a shell/tissue interface with less friction. It is available from local distributors.

Style 40: (McGhan Style 40 INTRASHIEL™ Gel-Filled/Round High Profile Mammary Implant)

The McGhan 40 is a smooth surfaced silicone-gel-filled mammary implant with an INTRASHIEL™ barrier shell. The Style 40 is a single lumen, round device with a standard profile and a volume ranging from 80cc to 560cc.

Style 45: (McGhan Style 45 INTRASHIEL™ Gel-Filled/Round High Profile Mammary Implant)

The McGhan Style 45 is a smooth surfaced, silicone gel-filled mammary implant with an INTRASHIEL™ barrier shell. The Style 45 is a single lumen, round device with a high profile and a volume ranging from 120cc to 800cc.

2.) CUI Type RLD, RHD, MLP, MHP:

The CUI Type RLD/RHD/MLP/MHP are gel-filled mammary implants designed for use in cosmetic augmentation mammoplasty or in breast reconstruction following mastectomy. The implant is surgically placed submuscularly or subcutaneously.

The implants are composed of silicone elastomer and gel components and have either smooth or textured surface. All of the styles incorporate a DRIE (Diffusion Rate Inhibiting Envelope) technology.

CUI Type RLD: (CUI Type RLD DRIE Low Profile Gel-Filled Mammary Implant)

The CUI Type RLD is a smooth surfaced silicone gel-filled mammary implant with a DRIE barrier shell. The RLD is a single lumen, round device with a low profile and a volume ranging from 100-800cc.

CUI Type RHD: (CUI Type RHD DRIE Round High Profile Gel-Filled Mammary Implant)

The CUI Type RHD is a smooth surfaced silicone gel-filled mammary implant with a DRIE barrier shell. The RHD is a single lumen, round device with a high profile and a volume ranging from 100-600cc.

CUI Type MLP: (CUI Type MLP MicroCell DRIE Low Profile Gel-Filled Mammary Implant)

The CUI Type MLP is a MicroCell textured, silicone gel-filled mammary implant with a DRIE barrier shell. The MLP is a single lumen, round device with a low profile and a volume ranging from 110-380cc.

CUI Type MHP: (CUI Type MHP MicroCell DRIE High Profile Gel-Filled Mammary Implant)

The CUI Type MHP is a MicroCell textured, silicone gel-filled mammary implant with a DRIE barrier shell. The MHP is a single lumen, round device with a high profile and a volume ranging from 100-410cc.

Product Identification:

The name of the manufacturer and the volume of the implant currently appear on each device.

APPLICATION ANALYSIS:

- 1.) Does the device have FDA approval or CE mark? **YES, a number of models have been approved for CE Marking. At time of application, other models were to be submitted and assessed for CE Marking.**

The McGhan Style 110, 120, 410, 410FM, 153 and 150 and the CUI Type MLP and MHP are CE Mark approved according to the European Medical Device Directive (93/42/EEC). The CE Mark ensures entry to all markets within the European Union.

A project to CE Mark the remaining McGhan and CUI Styles is currently ongoing. All styles will be CE Marked by June 1998.

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Table 1 below shows the summary of submission and approval dates for the various styles.

Table 1: Table of Registration Submissions for the McGhan Limited Styles 110, 120, 153, 150, 410, 40, 45 and the CUI Styles RLD, RHD, MLP, MHP

Country	Company	Product	<u>Date Submitted</u>	<u>Status Accepted</u>
Hungary	ML	110/120	12/92	2/94
Hungary	ML	153	1/94	2/94
Czech Rep.	ML	110/120	9/93	1/94
Slovak Rep.	ML	153	10/93	2/94
Norway	ML	110/120	5/94	10/94
Norway	ML	153	5/94	10/94
Norway	ML	410	8/95	2/96
Holland	ML	40/45	10/89	2/93
Hungary	ML	40/45	12/92	2/94
Czech Rep.	ML	40/45	9/93	1/94
Hungary	ML	RLD/RHD	12/92	2/94
Peru	ML	RLD/RHD	12/94	5/95
Hungary	ML	MLP/MHP	12/92	2/94

At the present time the US permits only restricted supply of gel-filled breast implant and approval for general marketing is not available.

- 2) Does the product have significant commercial history? And
- 3) From the implant history, has there been significant problems or regulatory actions against the products?

A. McGhan Styles 110, 120, 153, 410, 410FM, 150, 150 Low Pole, 40, 45:

Silicone based mammary implants have been successfully used in breast augmentation and reconstruction surgery for over 30 years.

Manufacture of the Style 110 and Style 120 gel-filled mammary implants by McGhan Medical Corporation began in 1988. The manufacture was transferred to McGhan Limited in 1989. The devices have been available on the International Market for over six years.

The McGhan Style 153 is a BioDIMENSIONAL™ BIOCELL™ textured gel-filled mammary implant. Its manufacture began in 1991. The Style 153 has been manufactured by McGhan Limited since 1993 and has been available on the international market for just over 5 years.

The McGhan Style 410 is an anatomically shaped narrow distribution gel filled mammary implant designed for breast reconstruction. McGhan Limited has manufactured the Style 410 since 1993.

The McGhan Style 410 is a precursor for the McGhan Style 410FM. As it has been recently launched sales figures are not available.

McGhan Limited has manufactured the Style 150 since 1995. [REDACTED]

The McGhan Style 40 gel-filled smooth mammary implant was one of the original McGhan designs and was first introduced in 1979. The Style 45 implant, which has the same basic design as the Style 40 but differs in profile and in size range was introduced in 1985. Until 1992 McGhan Medical Corporation US manufactured all of these devices. McGhan Limited subsequently took over the manufacture of these devices. [REDACTED]

All of these devices incorporate the patented INTRASHIEL™ silicone elastomer barrier shell, which has been shown to limit the occurrence of gel diffusion.

All product manufactured by McGhan Limited are exported. The products are available throughout Europe and may be sold in Ireland through the local area distributor, which is based in the U.K.

B. CUI Styles MLP/MHP/RLD/RHD:

CUI Corporation originally manufactured the CUI Type RLD and RHD. Manufacture commenced in March 1986 and August 1987 respectively. CUI discontinued manufacture of both devices in July 1991. The manufacturing technology was then transferred to McGhan Limited and full production of Styles RLD and RHD commenced at this facility in January 1992. McGhan Limited initiated the manufacture of the CUI Type MLP and MHP in 1990.

Overseas Regulatory Action and Status:

Gel-filled Mammary Implants manufactured by McGhan Limited are not subject to specific regulatory actions, (bans, moratoriums, etc.) however, gel-filled mammary implants in general are subjected to regulatory action and supply may be restricted or banned in certain countries such as the U.S.A. and France.

In January 1992 the U.S. FDA proposed that gel-filled mammary implants be classified in a Class III category. This requires the manufacturer to submit additional information on the safety and suitability of these devices for long-term use. As a result a voluntary moratorium on the distribution and implantation of these devices was called until the FDA and an advisory panel had time to consider all available information.

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Following the moratorium introduced in the U.S.A., France also introduced legislation to prohibit sale of non-saline filled mammary implants.

4.) Does the device contain "new technology"? NO

5.) Is the device of Human and Animal origin? NO

6.) Does the device/s have a predicate in the ARTG? NO

Equivalence Claim:

As the products have no predicate in the Register there is no base for a claim of equivalence. However it should be noted that McGhan has several saline-filled mammary prostheses which have been approved as low level registrable devices for supply in Australia. A similar shell material from one of the saline filled implants is used in the patch component of the gel-filled prosthesis.

[REDACTED]

[REDACTED]

[REDACTED]

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DESIGN

Design attributes of the various McGhan and CUI Silicone Gel-filled Mammary Prostheses Styles share a number of chemical and structural features. The fundamental differences lie in the size (fill volume), the varying shapes/profiles of the prostheses, the shell surface (textured or smooth) and gel type. [REDACTED]

The materials and general principles of manufacture are common to all Styles within this application.

Three Styles, 150, 150LP and 153 have dual lumens to permit volume expansion with either saline (Styles 150) or tissue expander (Style 153). The procedures for manufacture of the double lumen devices do not significantly differ from the base models. Additional steps [REDACTED]

The gel filling material is one of three types, standard or Responsive gel, narrow distribution/responsive gel and cohesive gel. Chemical constituents of each are the same, however the standard /responsive gel is termed narrow distribution [REDACTED]

[REDACTED] McGhan claim that, in fact, all the gels used are cohesive as specified in the defining clause of ASTM F703. In response to another matter, correspondence from McGhan dated 3/9/99 stated '... a decision has been taken to discontinue use of the gel (referring to Narrow Distribution Cohesive) in favour of the Cohesive version.'

For clarity, the features of the different Styles are presented in Table 4

Example engineering design sheets of single and double lumen Styles are attached to assist in visualisation of the device components, and demonstrate the overall design similarities.

The devices are proposed for the same clinical indications, viz. augmentation or reconstruction mammoplasty.

Table 4:

DESIGN FEATURES OF THE MCGHAN AND CUI STYLE MAMMARY IMPLANTS

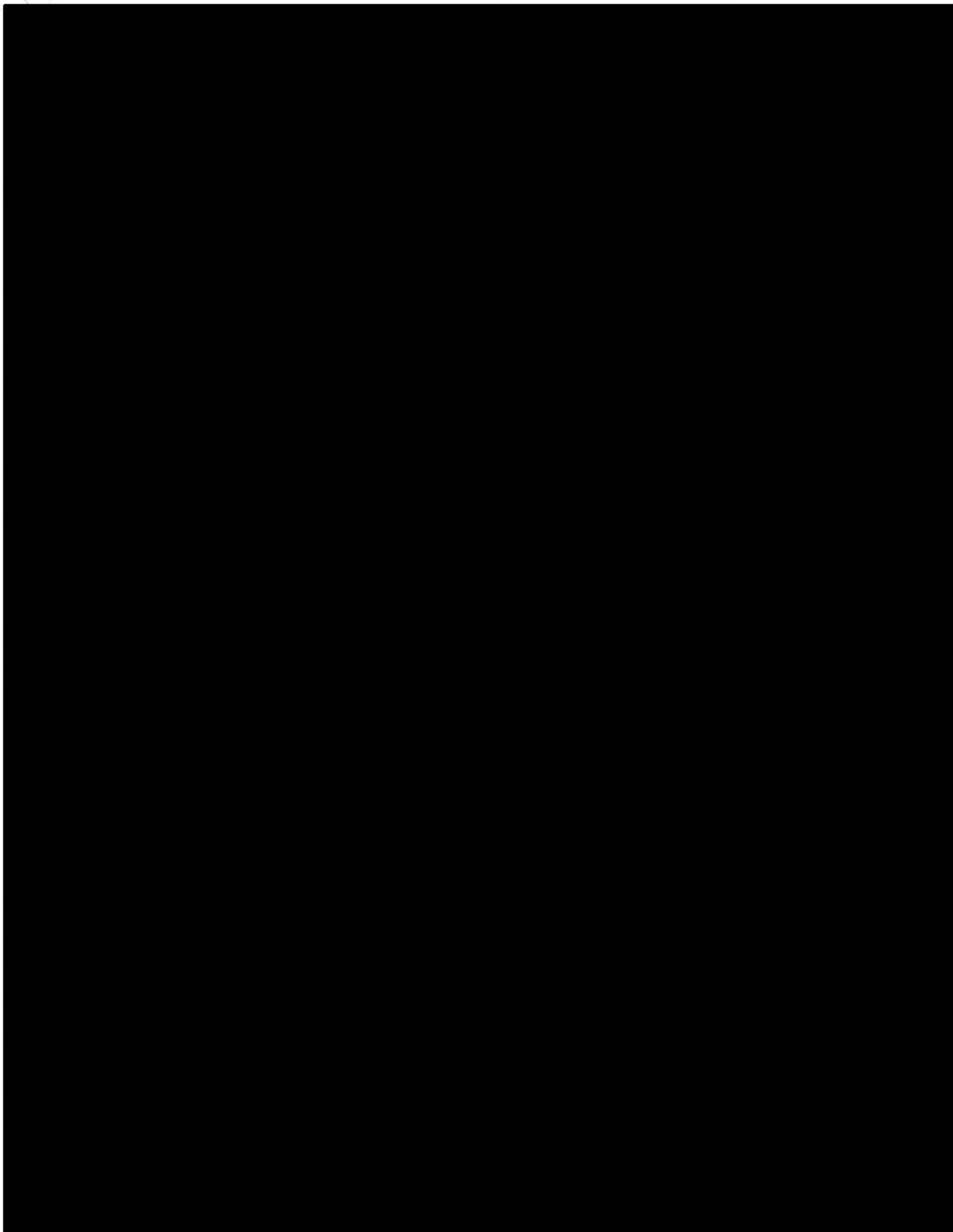
Style McGhan	Shape	Profile	Size Range (cc)	Fill Type ¹		Patch ³	Leaf Valve ⁴	Surface	
110	Round	Moderate	90-510	Responsive Gel		Bilaminate		Textured	
120	Round	High	180-650	Responsive Gel		Bilaminate		Textured	
153	Anatomical	Full Height	190-720	Responsive Gel		Bilaminate	Yes	Textured	
410	Anatomical	Standard	210-610	Cohesive		Bilaminate		Textured	
410FM	Anatomical	Moderate	155-670	Cohesive		Bilaminate		Textured	
150	Anatomical	Full Height	180/200- 720/760*	Narrow Distribution Responsive Gel/Saline		Bilaminate	Yes	Textured	
150LP	Anatomical	Short Height	135/145- 625/655*	Narrow Distribution Responsive Gel/Saline		Bilaminate	Yes	Textured	
40	Round	Standard	80-560	Responsive Gel		Bilaminate		Smooth	
45	Round	High	120-800	Responsive Gel		Bilaminate		Smooth	
CUI									
MLP	Round	Low	110-380	Responsive Gel		Bilaminate		Textured	
MHP	Round	High	100-410	Responsive Gel		Bilaminate		Textured	
RLD	Round	Low	100-800	Responsive Gel		Bilaminate		Smooth	
RHD	Round	High	100-600	Responsive Gel		Bilaminate		Smooth	

¹ Gel: [REDACTED] - Responsive Gel, [REDACTED] ratio of Part A: Part B varies for Gel type - All Cohesive (as defined by ASTM F703)

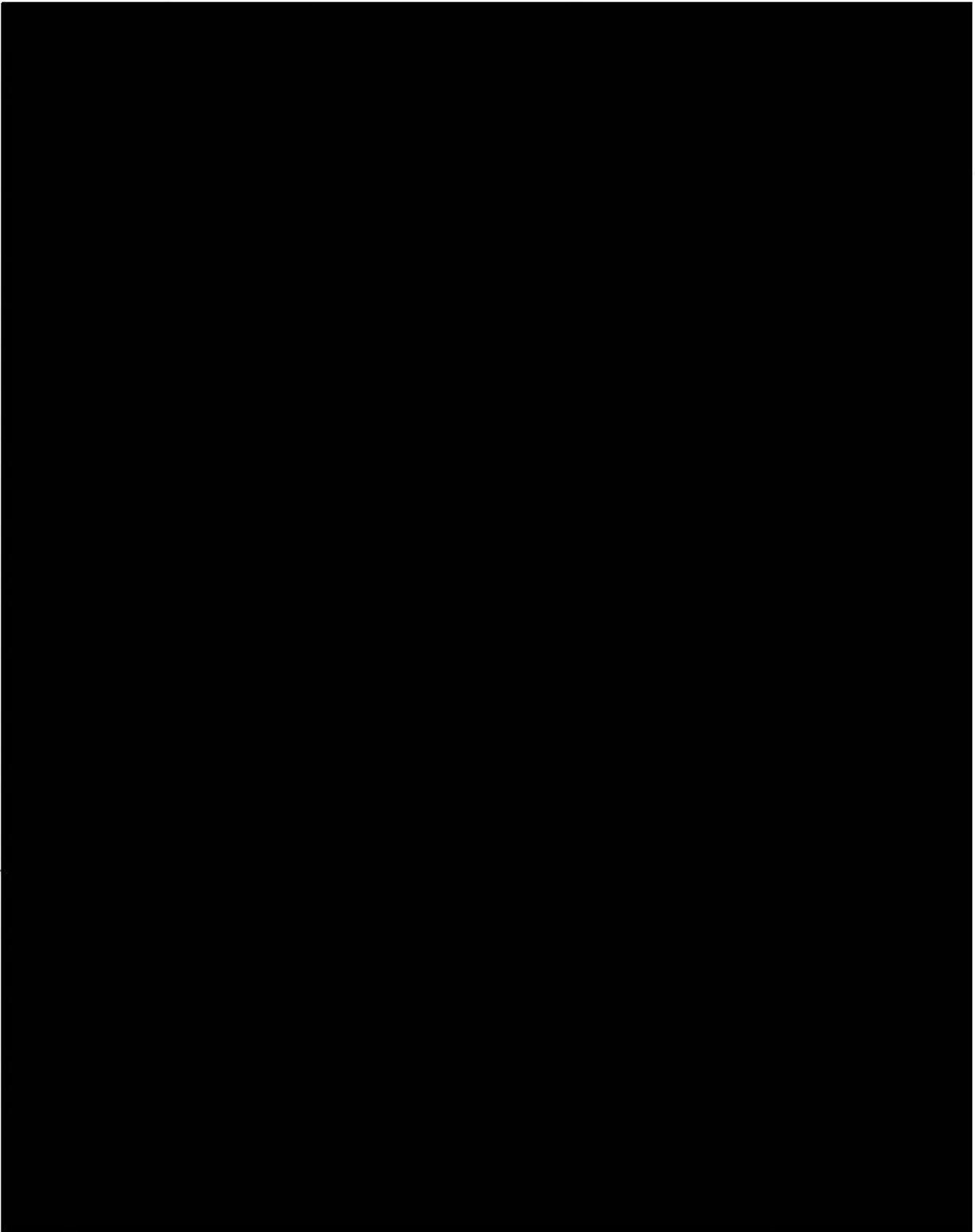
³ The Patch used to close the shell is a bilaminate structure formed from [REDACTED] the latter a barrier sheeting.

⁴ Leaf Valves are used on adjustable prostheses and are formed from [REDACTED] Overlays, discs and circles are also formed from [REDACTED]

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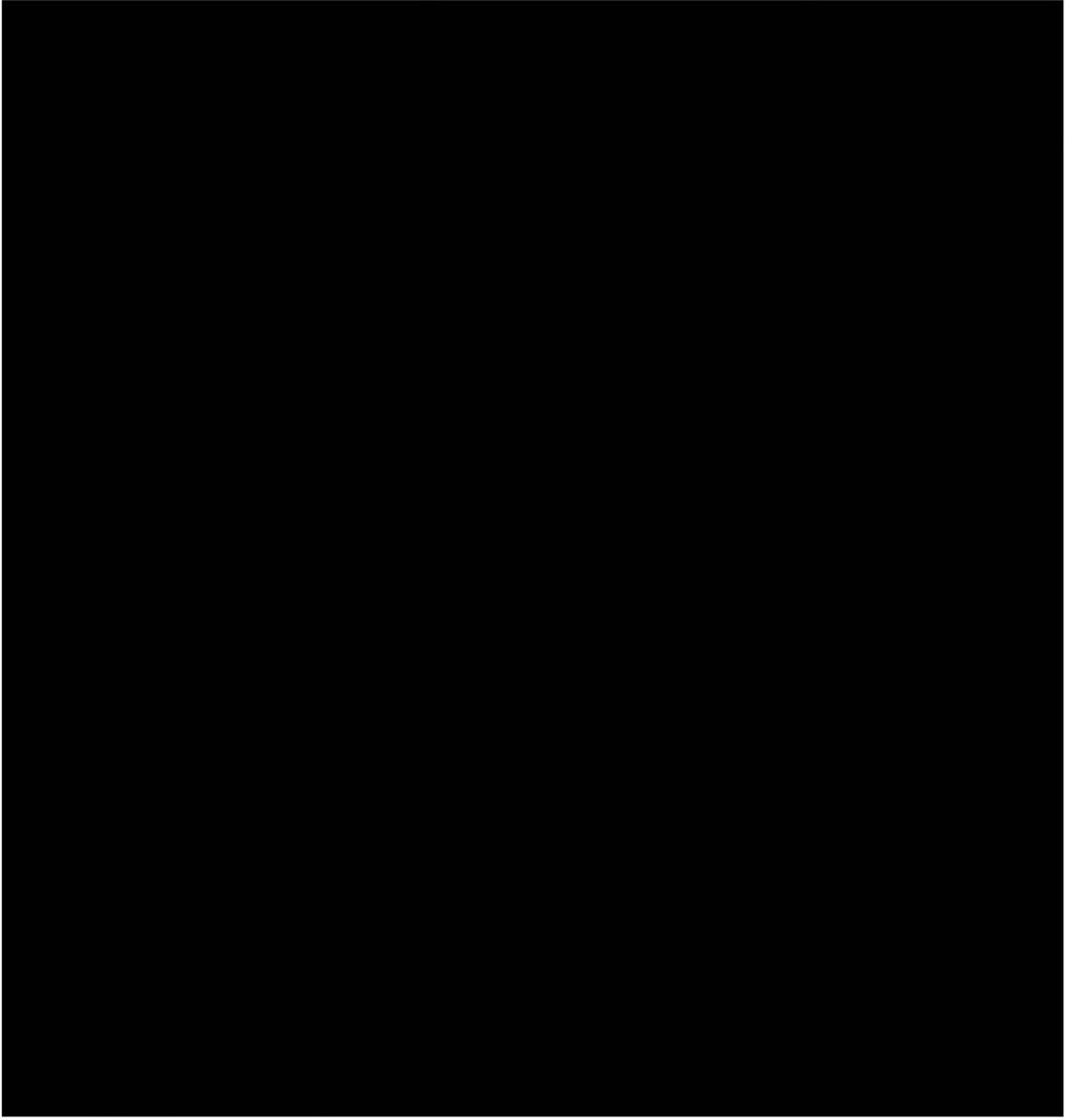


MATERIALS/MANUFACTURING

2. Raw materials control

The manufacturer's Standard Operating Procedure for Incoming Inspection of Controlled Material (all raw materials included in the provided tables) states in point 2.1.3 "Parts are inspected as directed in the relevant Material Specification or Drawing and Q.A. Procedure to ensure the lot complies with the quality requirements of the part." The Materials' Specifications have been provided.

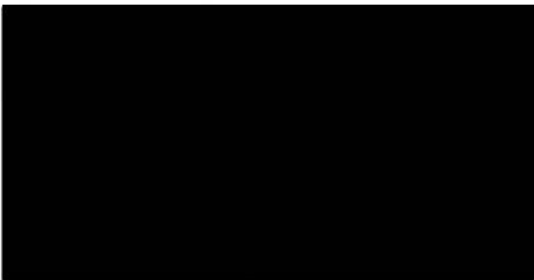
200

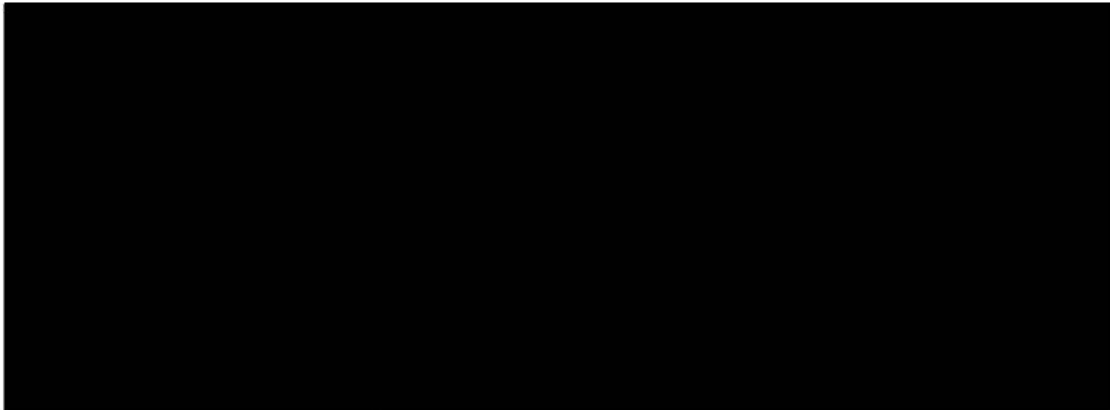


4. Tests performed for the final device.

The breast implants are manufactured in accordance with:

- Pr EN 12180 Non active surgical implants, body contouring implants, specific requirements for mammary implants.
- ASTM F703 Standard Specification for Implantable Breast Prostheses





5. Additional questions from the Panel.

After evaluation of the data submitted, the following questions were forwarded to Sponsor as a part of the S31 letter dated September 1998:

1. *Details of the purities of the individual components in the materials specifications (e.g. on p 655) are required.*

A critical parameter that is not addressed is the procedure to introduce texture,

The quality control and procedural information is required. Please justify why radiopacity information has not been provided.

2. *Details of the shell leakage testing method were not provided*

Similarly, the detailed procedure for assessing accelerated gel bleed (apparently Q4234) should be supplied for assessment.

3. *Data on fatigue, ageing and impact testing on each of the products, which although is not required by ASTM F703-96, is part of the draft ISO/CEN standard and is required for review.*

4. *The GPC data presented on pp 1057-70 in section 3.5.1.3 requires clarification. Please explain and comment as to its significance to safety.*

6. Comments about received responses.

The provided responses (Two volumes – Volume 1 of 4 and Part C Volume 1 of 1 of the “Reply to Section 31 Questions” September 1998) were assessed and discussed during the Panel meeting. The following are final conclusions (from the report of the Panel meeting – 27 October 1998):

- 1 (i) The information provided is acceptable.

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- 1 (ii) The definitions of "batch" and "lot" are noted and are acceptable.
- 1 (iii) The material provided relating to the procedures and size regulation of [REDACTED] is acceptable.
- 1 (iv) The information about radiopacity is acceptable.
- 2. The leakage and bleed information is acceptable.
- 3. The test data on fatigue and impact testing provided are acceptable.
- 4. The explanation given is satisfactory.

7. Final conclusion from the Panel

The final conclusion from the Panel members responsible for materials/manufacturing aspects was that these issues have been addressed appropriately and there are no outstanding items with this product.

Packaging

The primary and outer packaging consist of Polycarbonate [REDACTED] thermoforms [REDACTED] and Tyvek [REDACTED] lids [REDACTED] that are heat/pressure sealed in position. These materials are frequently used as primary packaging materials for devices and have an established history of compatibility. Specifications/engineering drawings of the packaging system, SOPs for primary and secondary packaging have been provided. [REDACTED]

[REDACTED] General material compatibility was an integral part of the assessment in the biological safety/compatibility evaluation. Product or components tested for biological safety were packaged and sterilised in the final packaging. There was no evidence that the packaging was a source of contamination/residues rendering the device material not compatible when assessed against ISO 10993.

The primary packaging is inspected pre-sterilisation and post-sterilisation for cracks, holes, cuts etc, bubbles, holes and creases in the seals.

The secondary packaging is a cardboard box to which the outer label is affixed, thereby sealing the opening.

[REDACTED]

In an accelerated aging study the packaging was shown to maintain the sterility of enclosed prostheses for a period of up to 5 years. The data submitted in support of this claim were reviewed in the Sterility evaluation.

Labelling

The inner and outer package labels for each of the McGhan and CUI Style mammary prostheses have been assessed and found compliant with Therapeutic Goods Order No 37. The Serial number is used to denote Lot or Batch number.

Instructions, patient information, promotional material and service manuals.

Many of the issues raised in the TGA Breast Information Booklet are dealt with in this PI. Other printed documents include multilingual Caution Inserts and the Informed Consent Forms. This latter form provides some information for the patient to peruse prior to signing, but it is obvious the document is not patient-friendly. The print is far too small, the presentation of information is crowded and the language too sophisticated for general population acceptance. The consent paragraph outlines the conditions upon which the patient is taking responsibility: essentially it absolves both manufacturer/sponsor and clinician of any liability.

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The TGA Booklet provides a more realistic level of responsibility. [REDACTED]

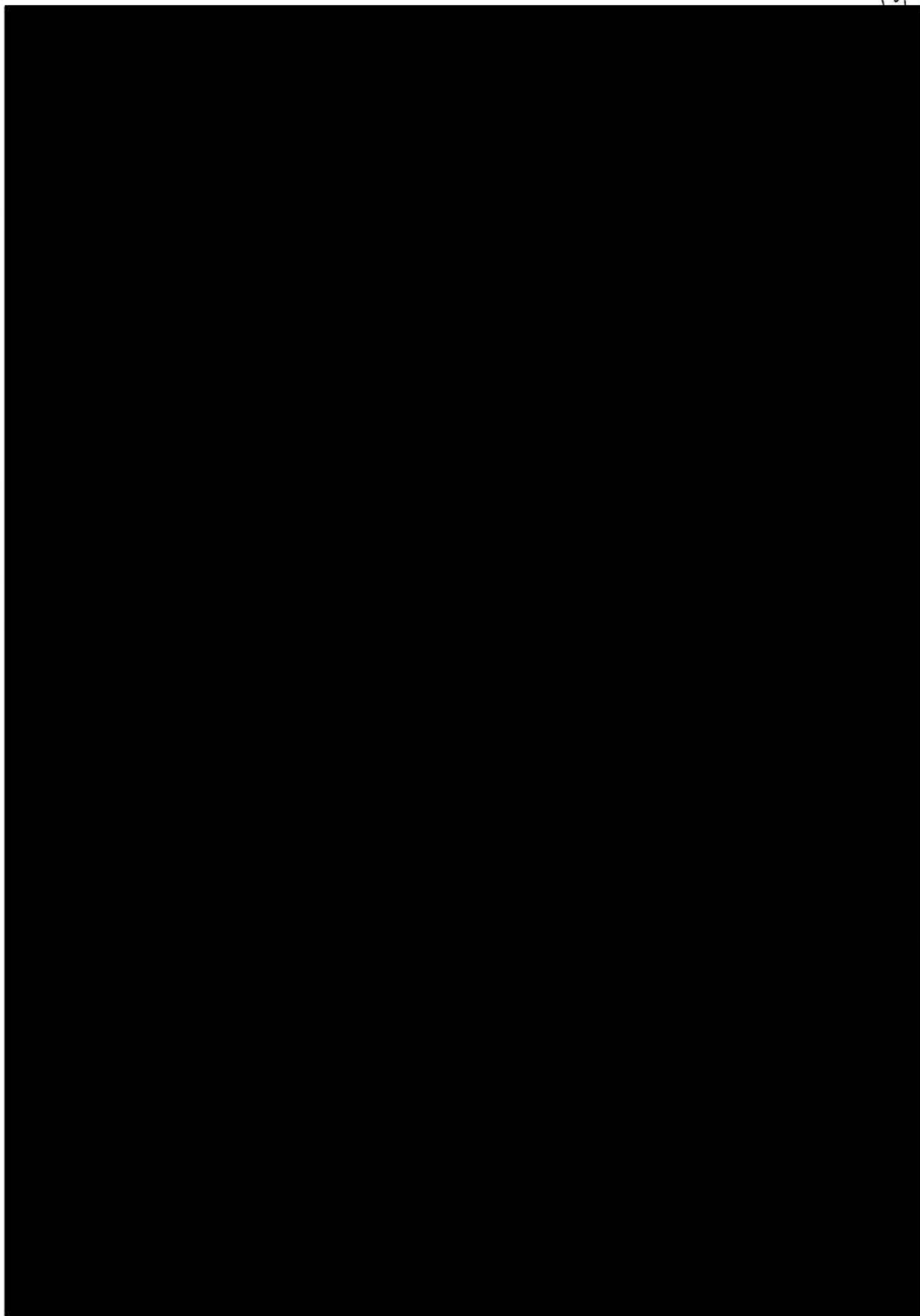
Q In relation to the product information and patient consent material it is noted that the print is far too small, the presentation of information is crowded and the language too sophisticated for general population acceptance. The consent paragraph outlines the conditions upon which the patient is taking responsibility: essentially it absolves both manufacturer/sponsor and clinician of any liability. Please comment.

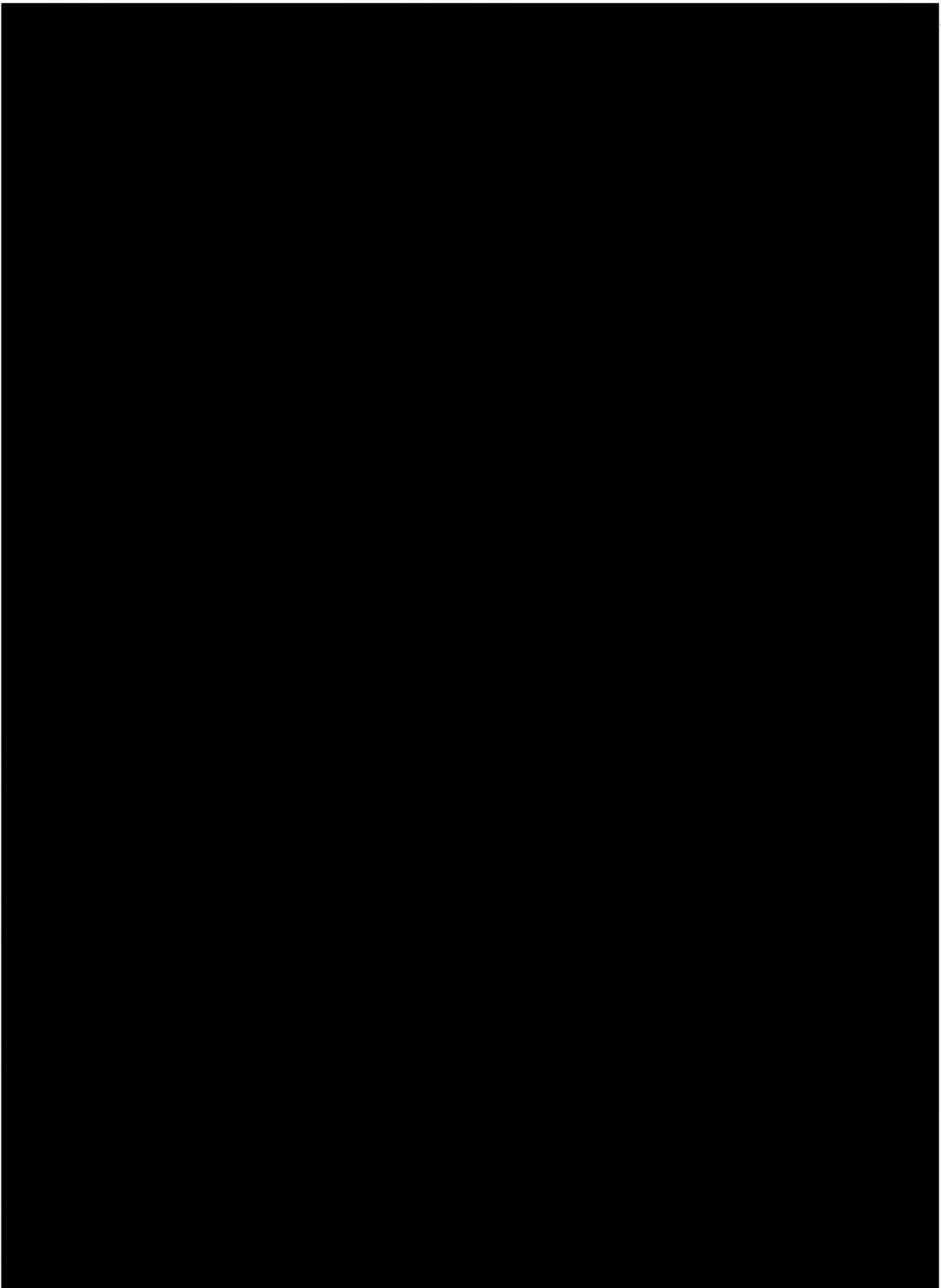
A. The response states that the patient consent material originally submitted was photo-reduced. Also the manufacturer states a possible review of the PI and introducing less sophisticated language and improved presentation. Responsibility for information dissemination, potential for implant-associated problems/expectations and general implant discussion lies between the surgeon and patient.

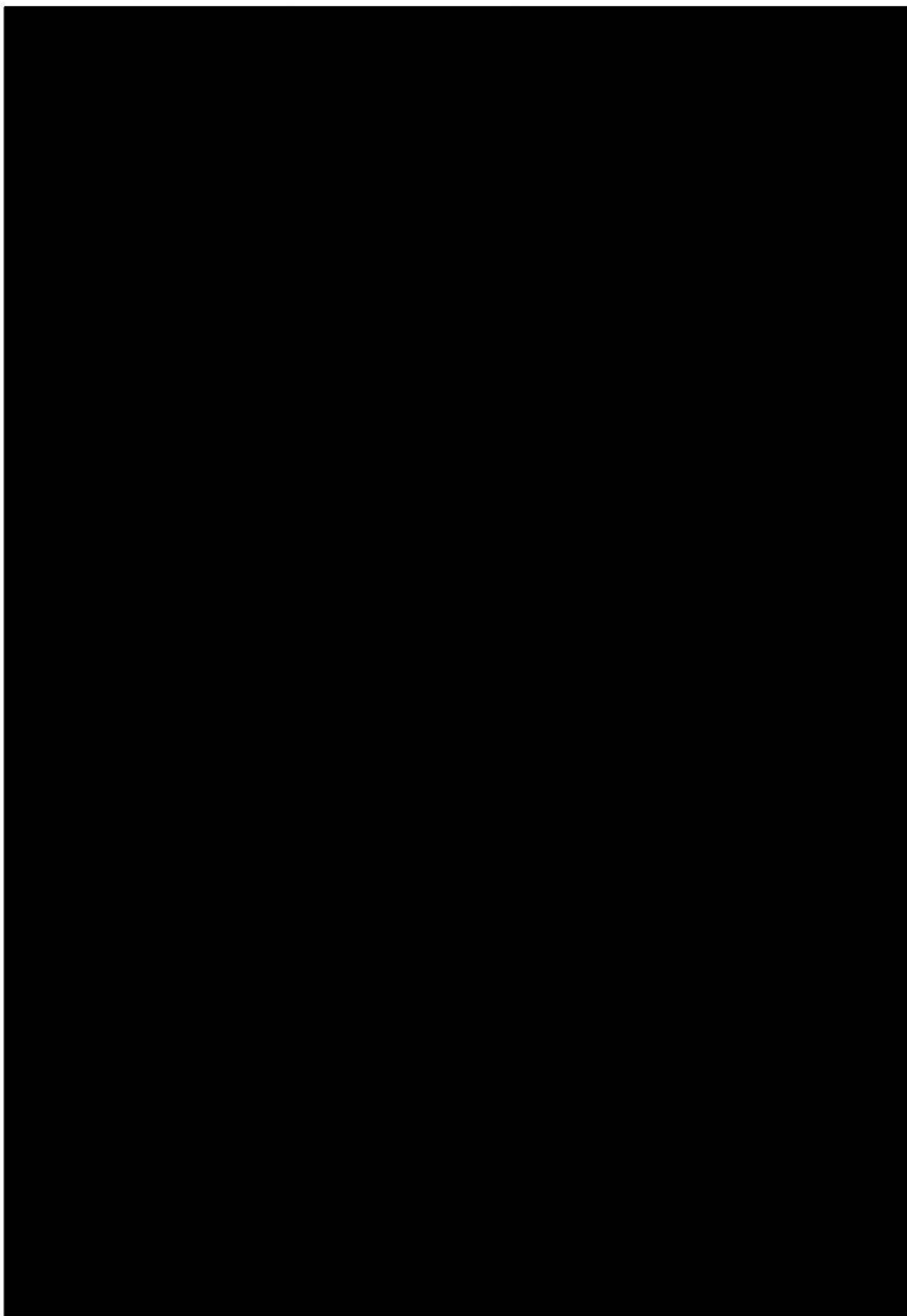
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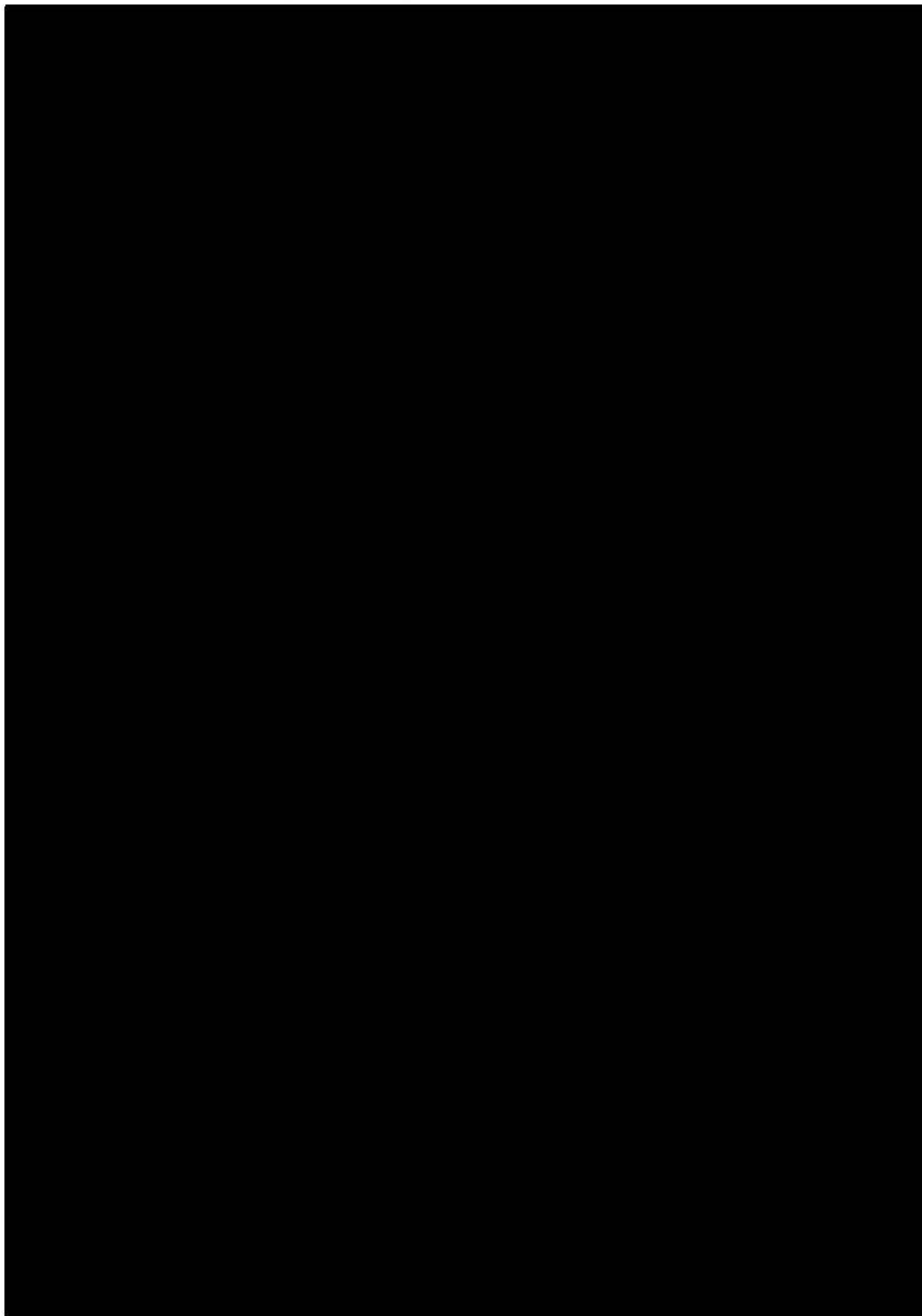


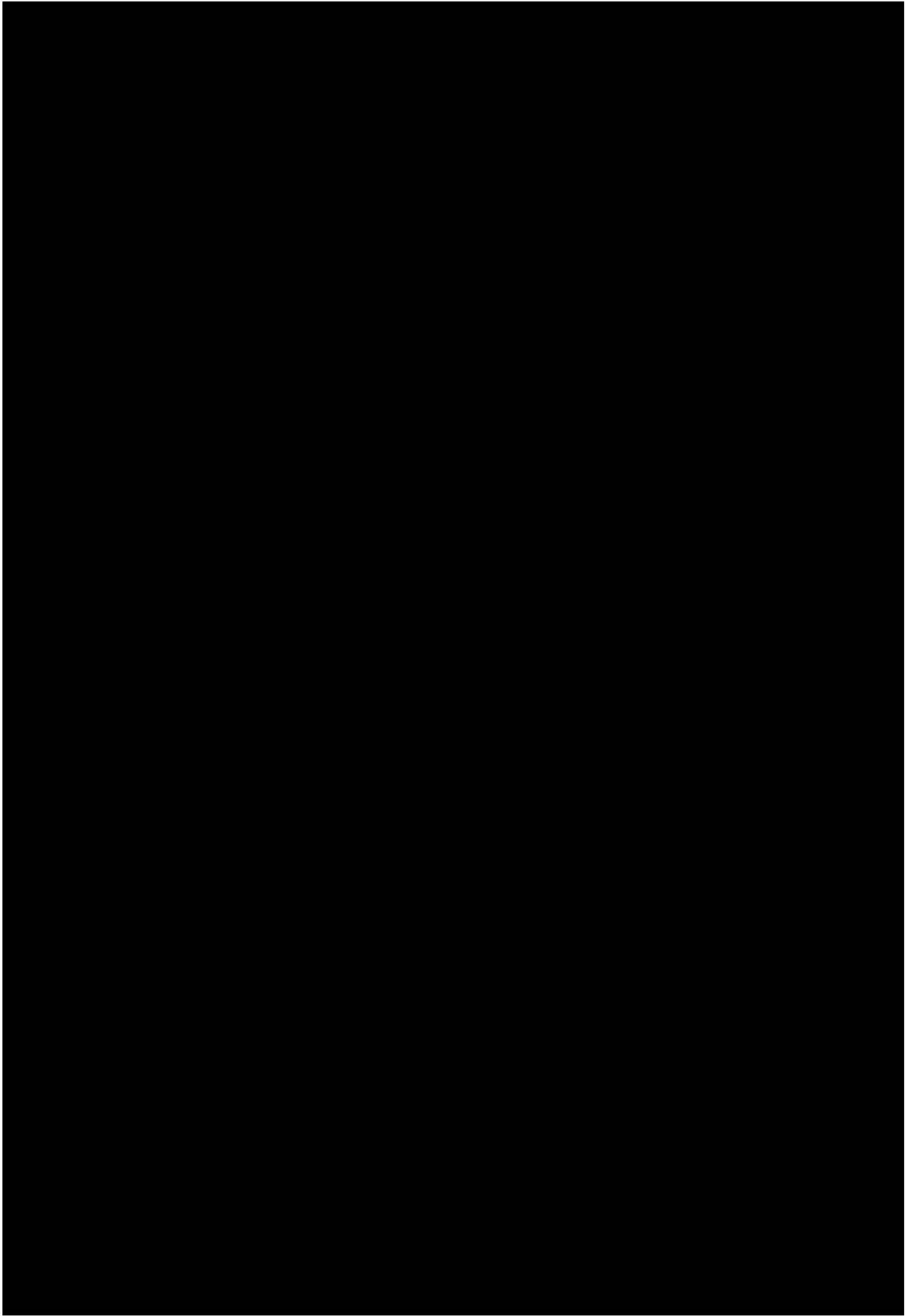


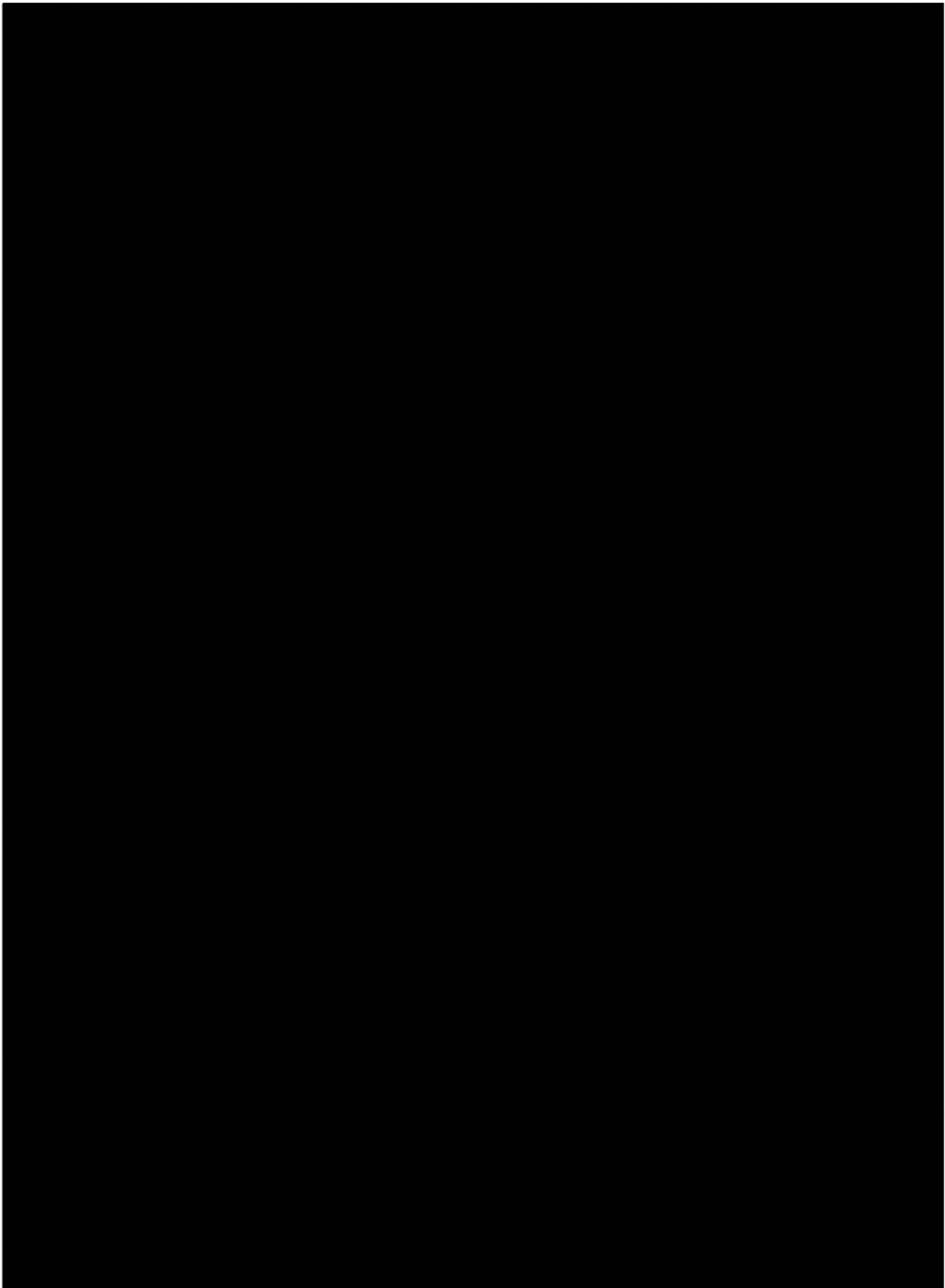
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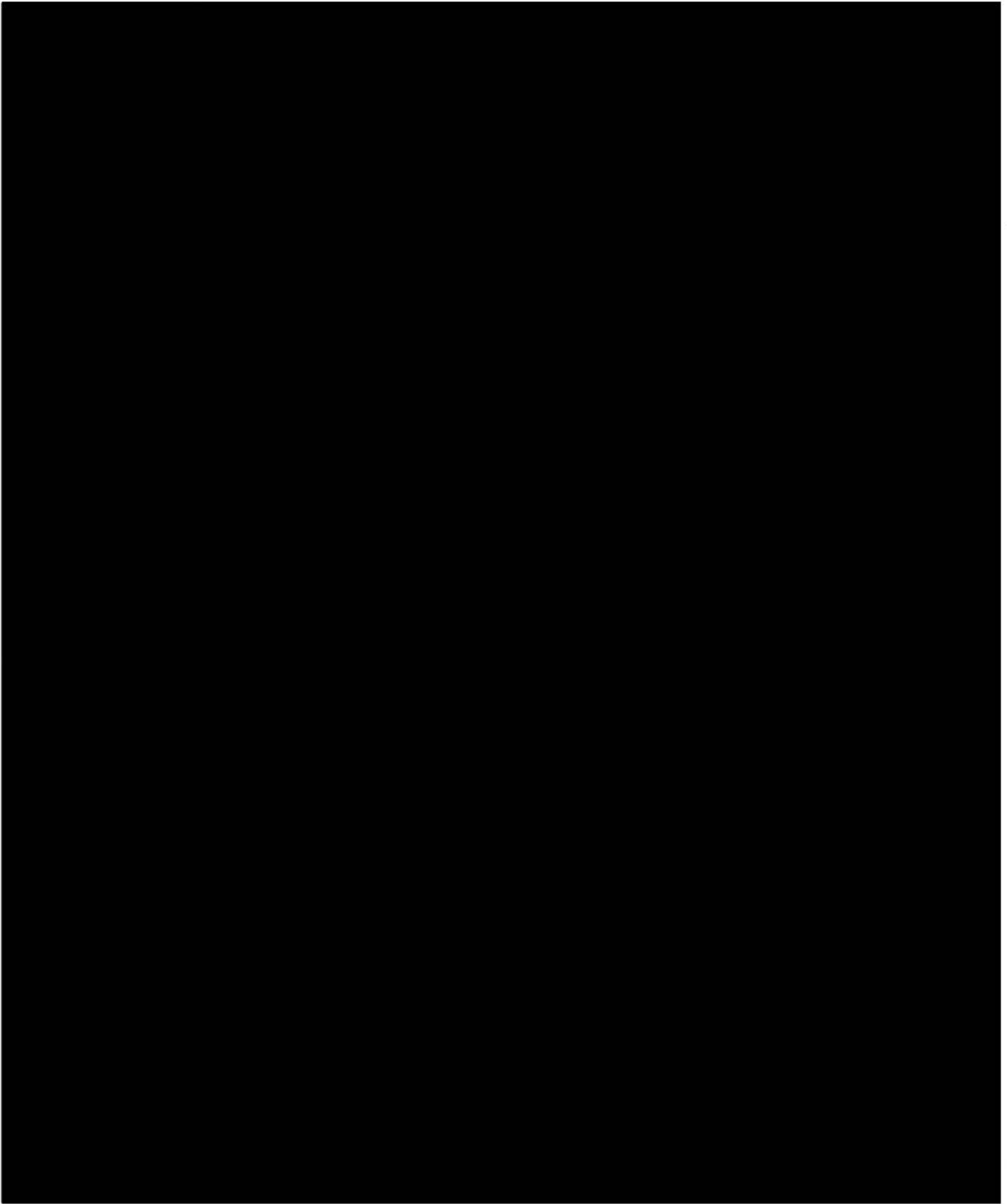
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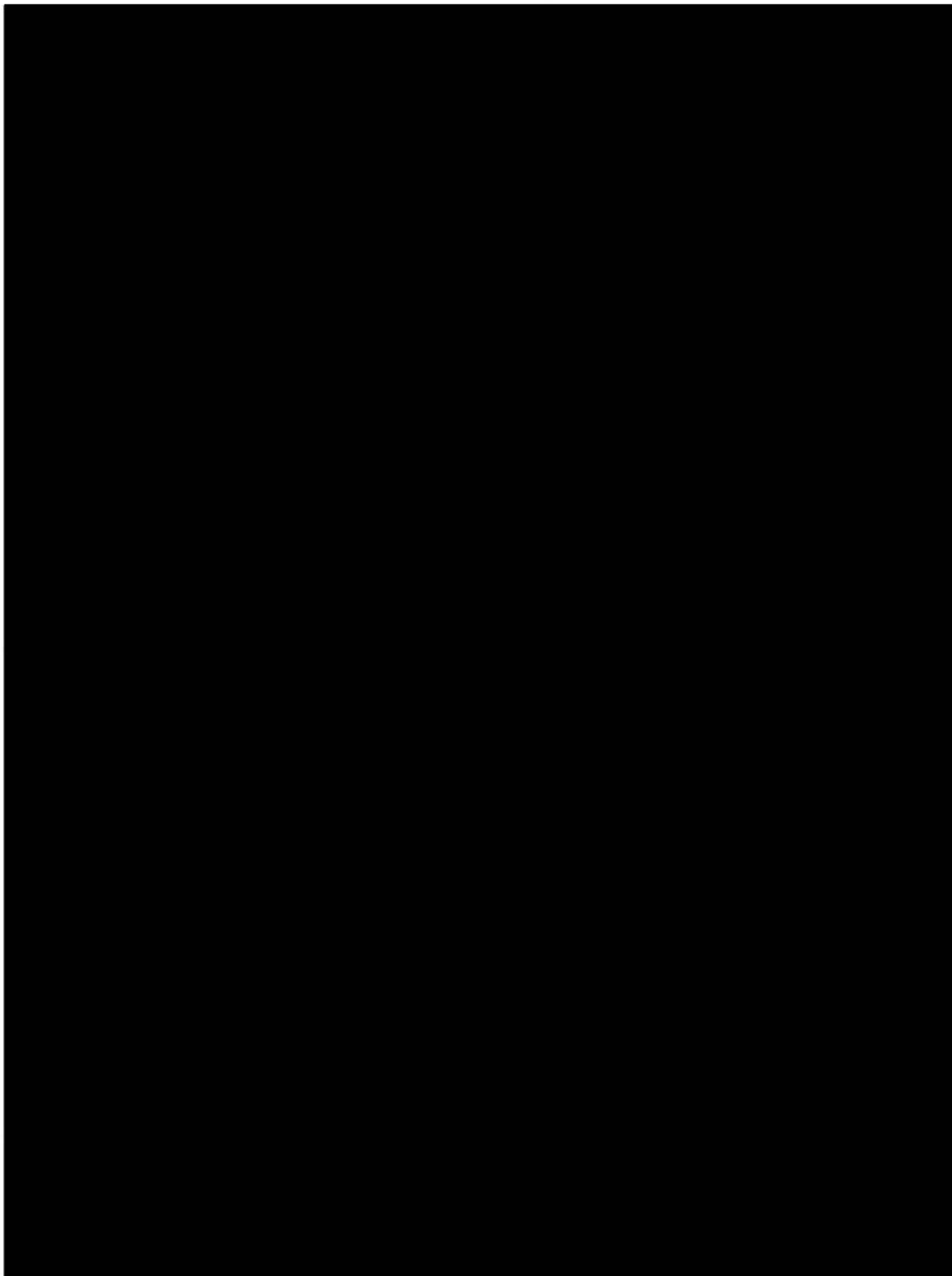
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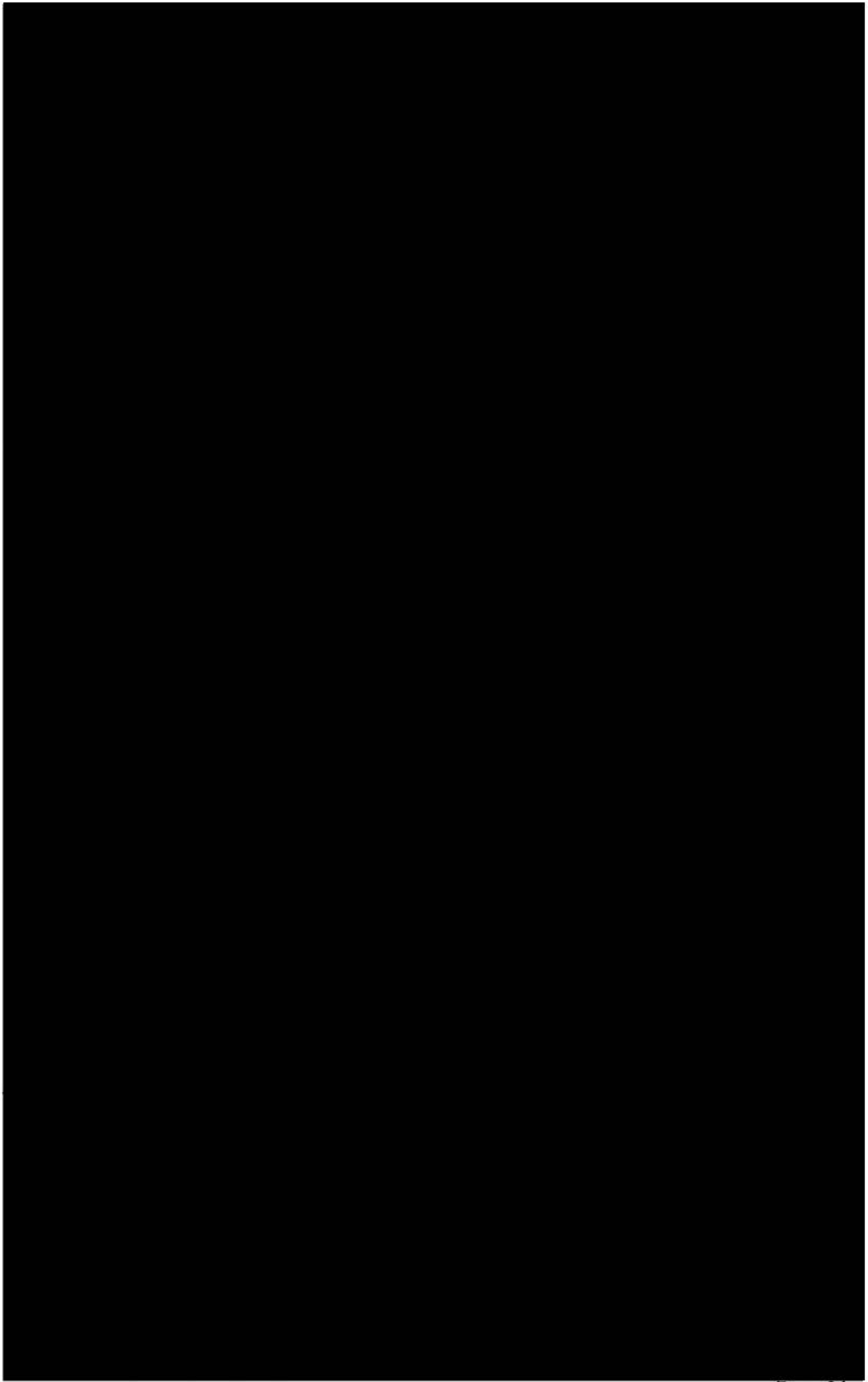


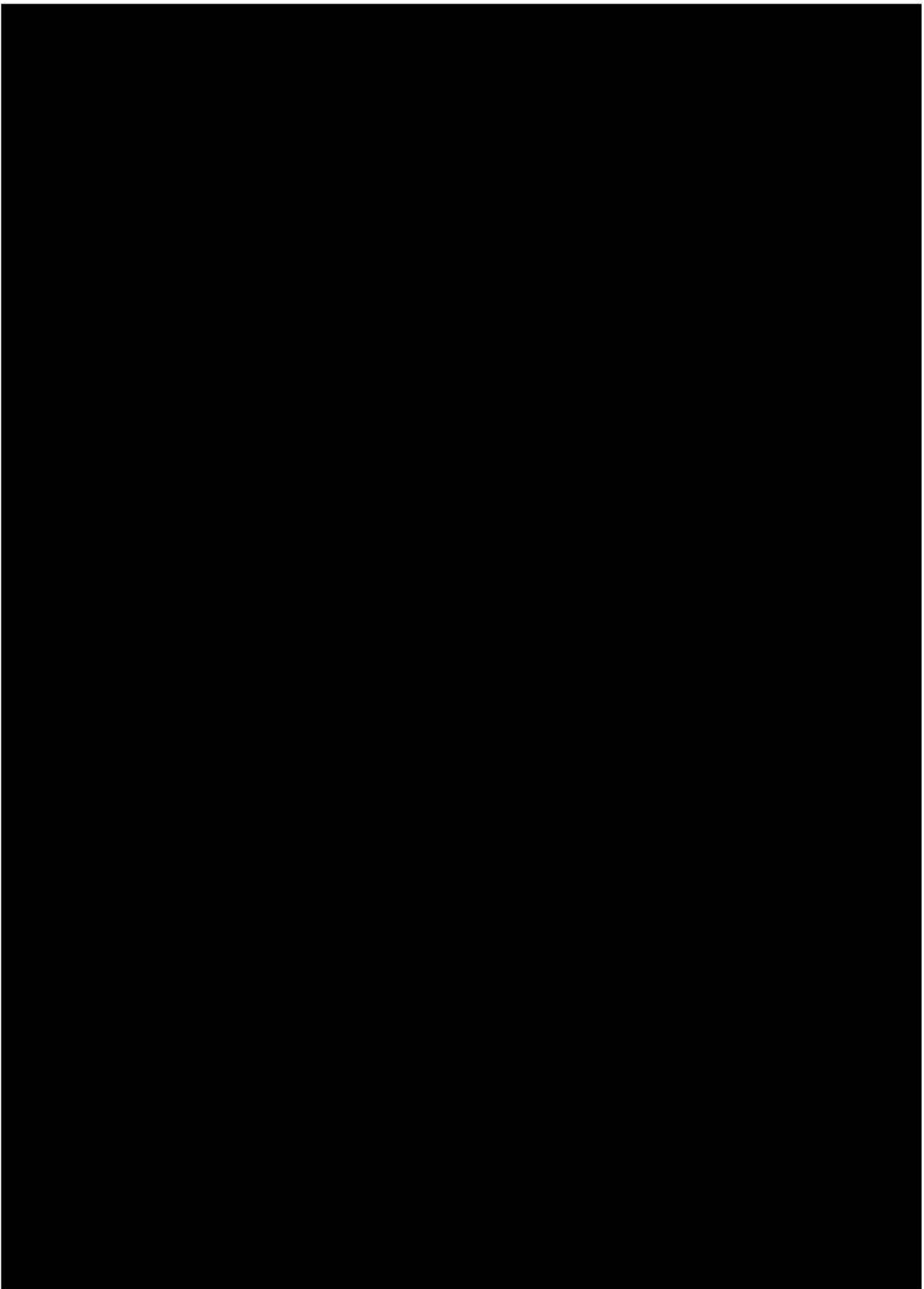


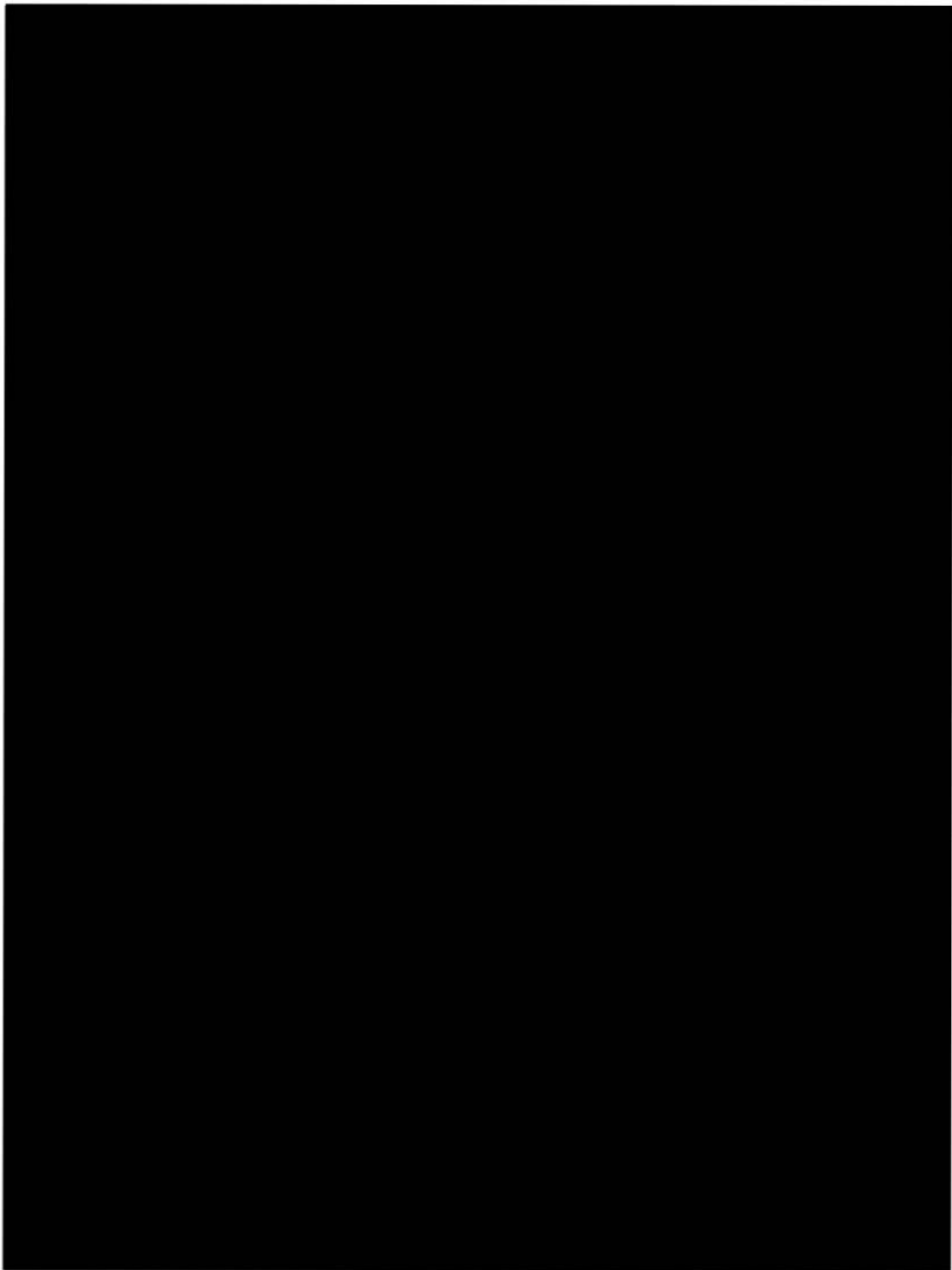


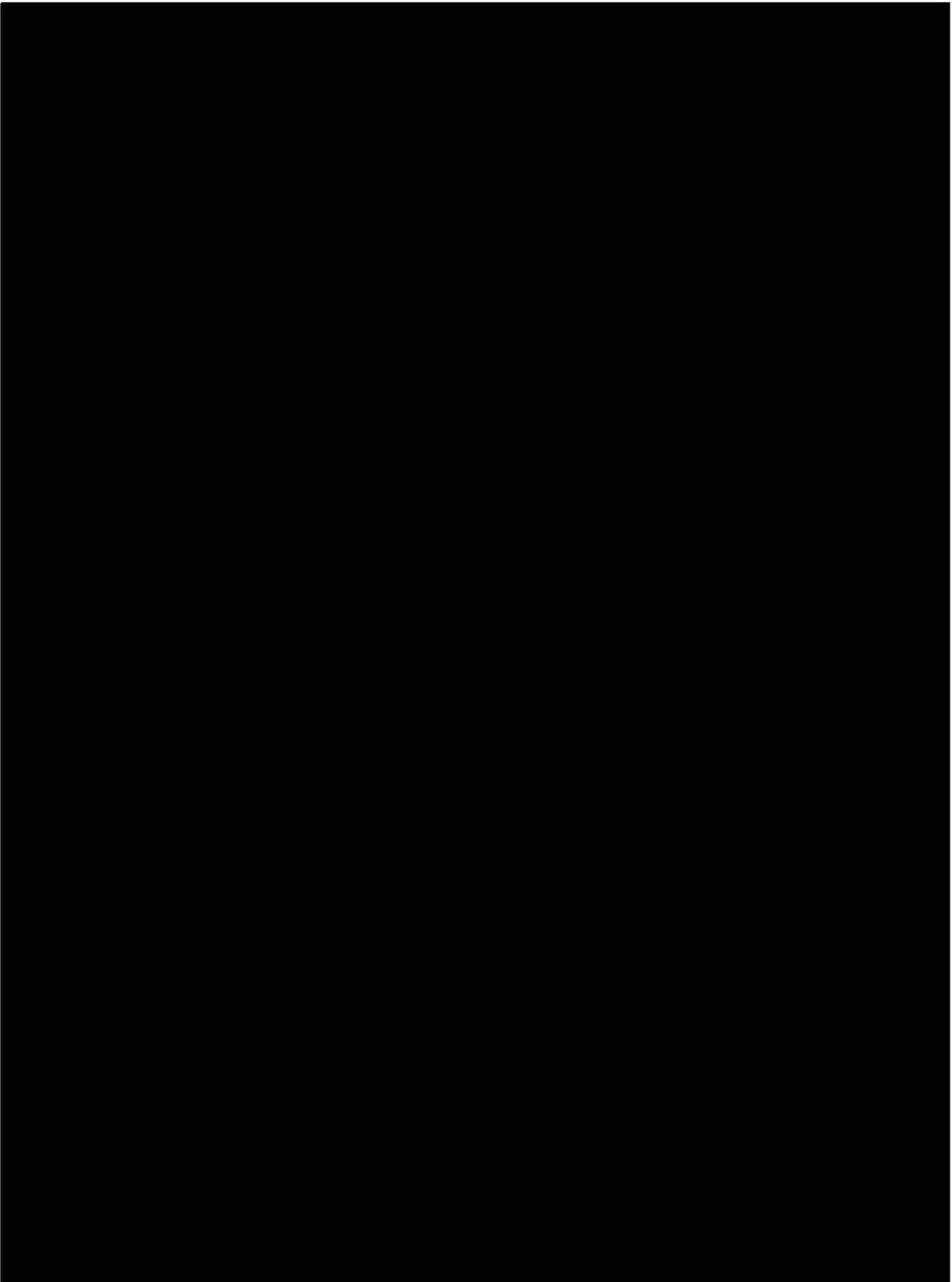


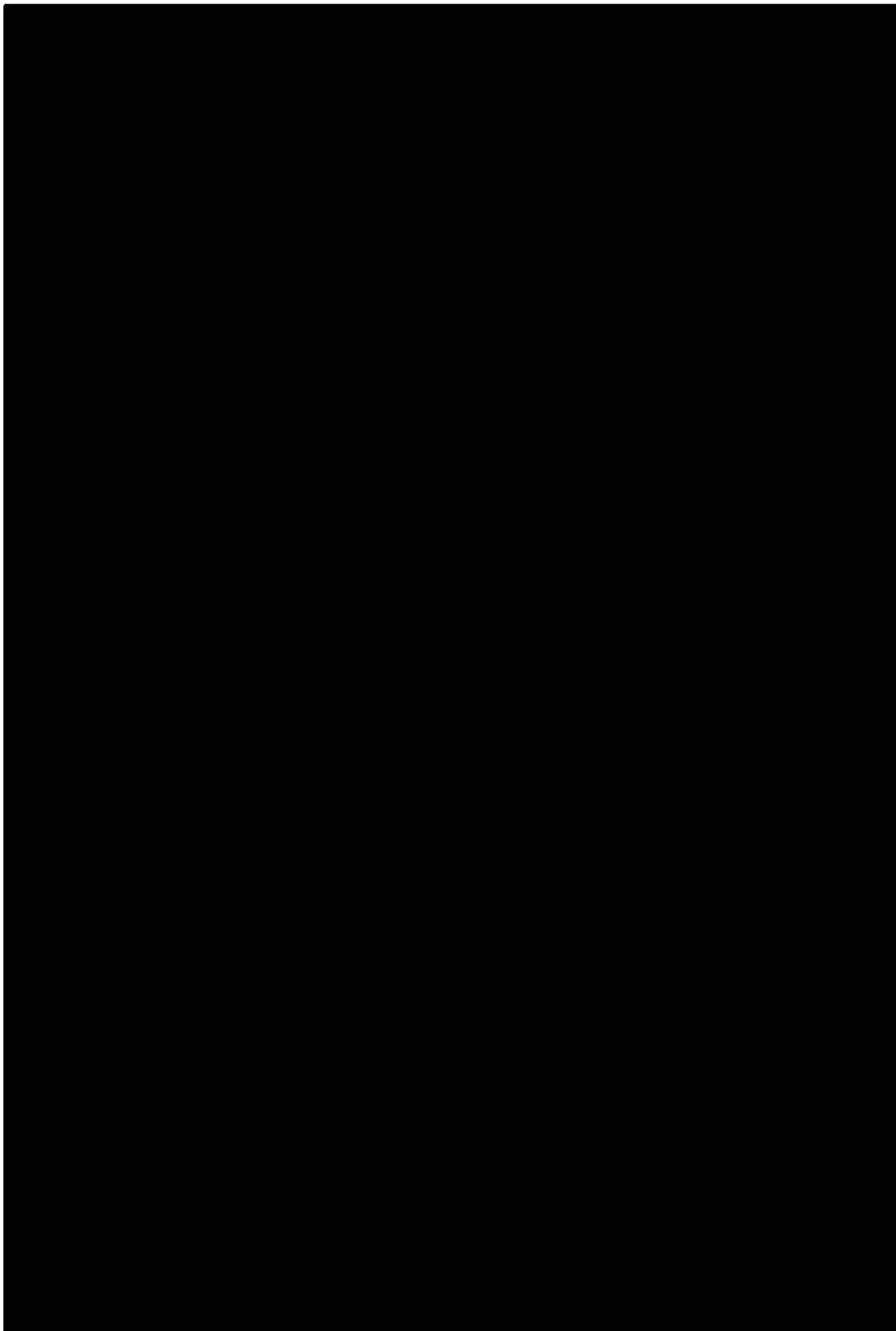


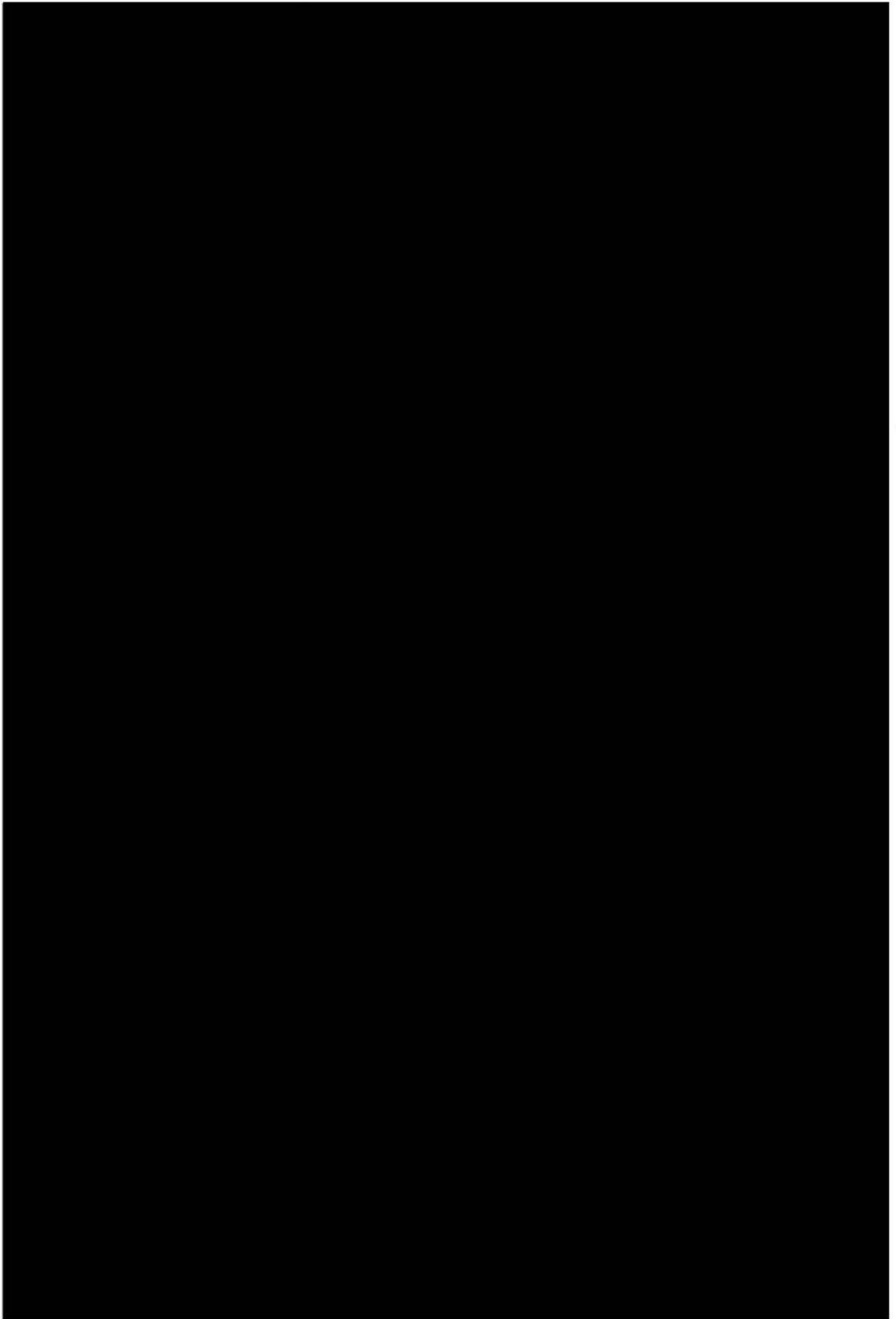


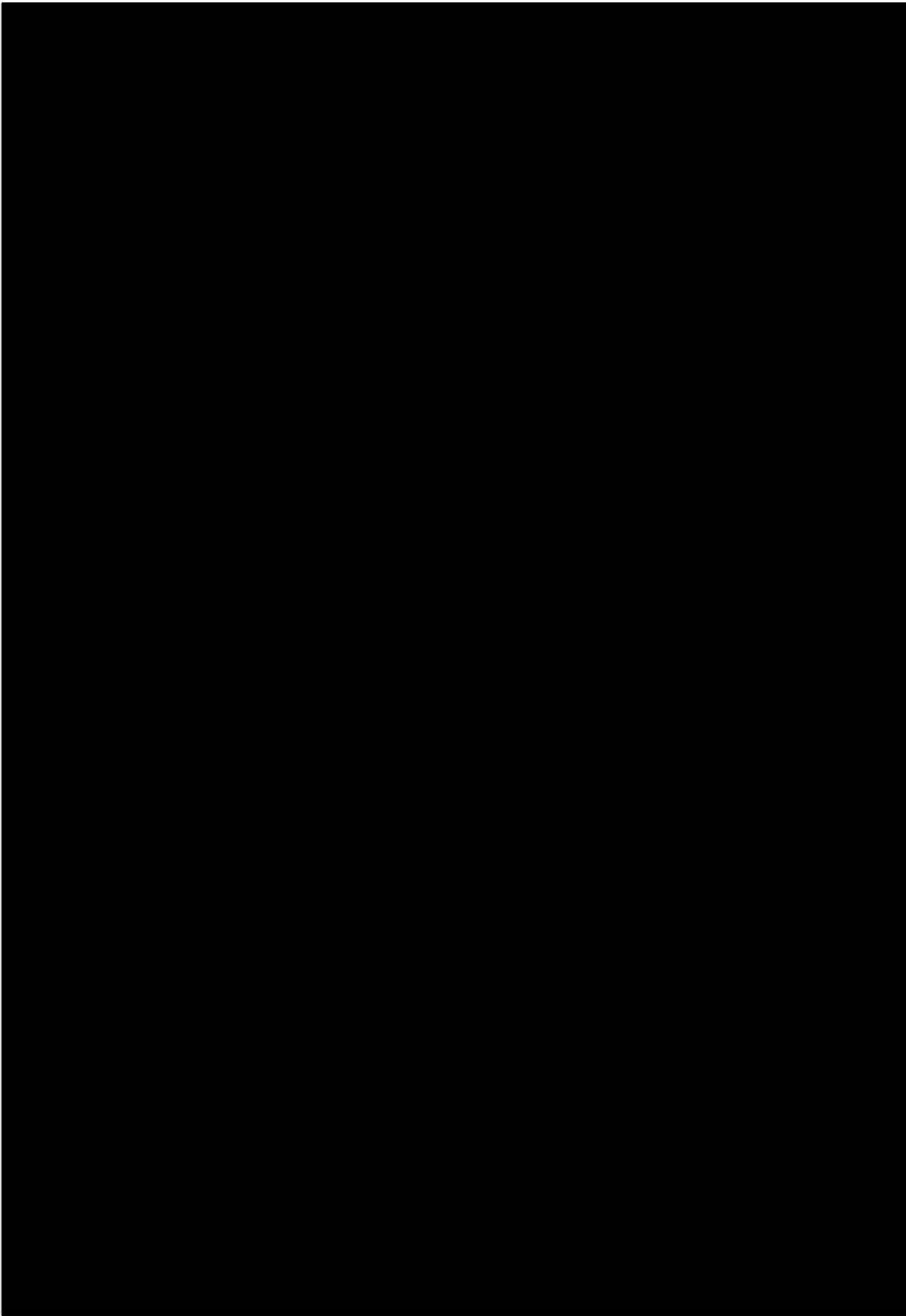


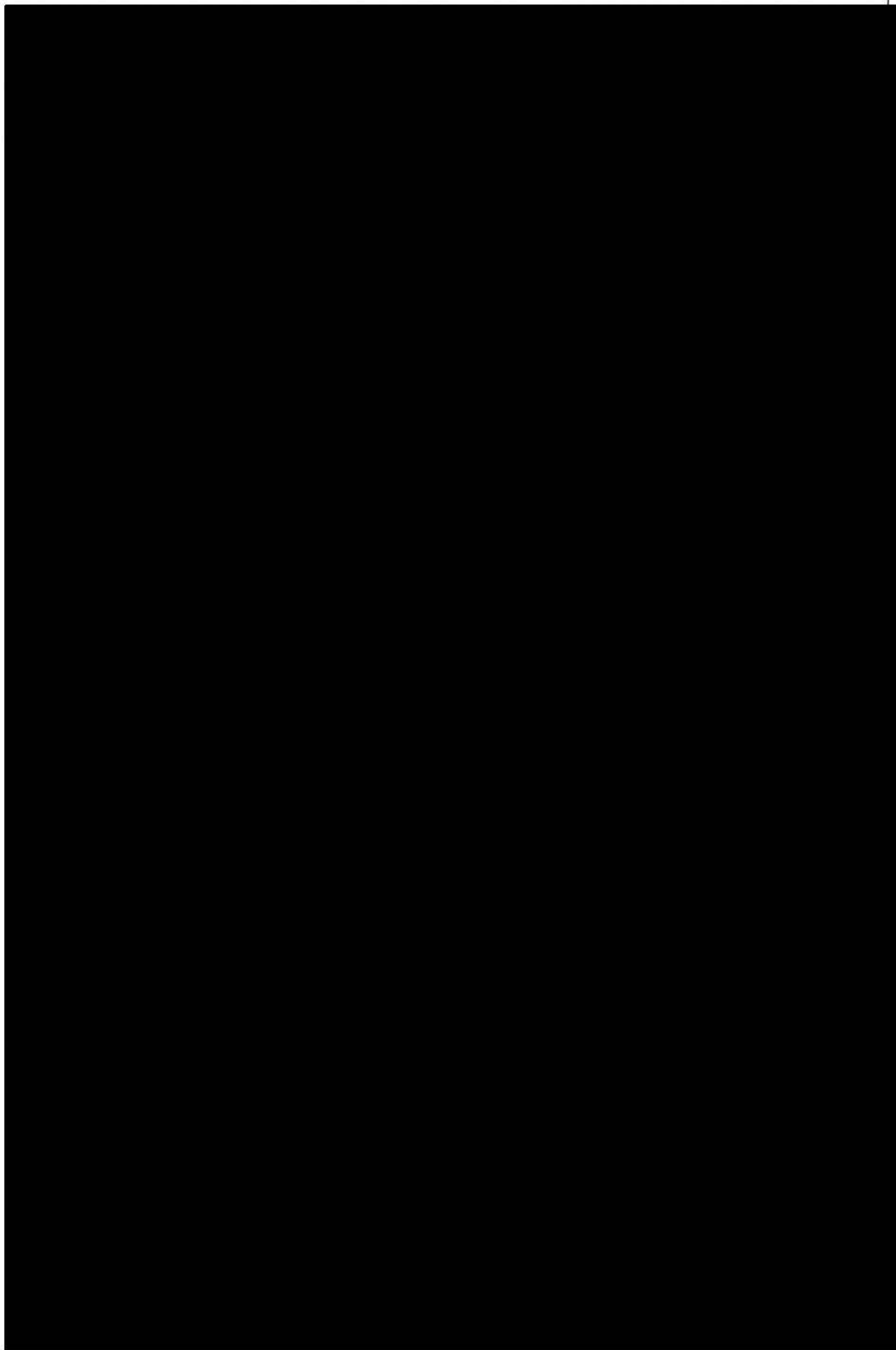


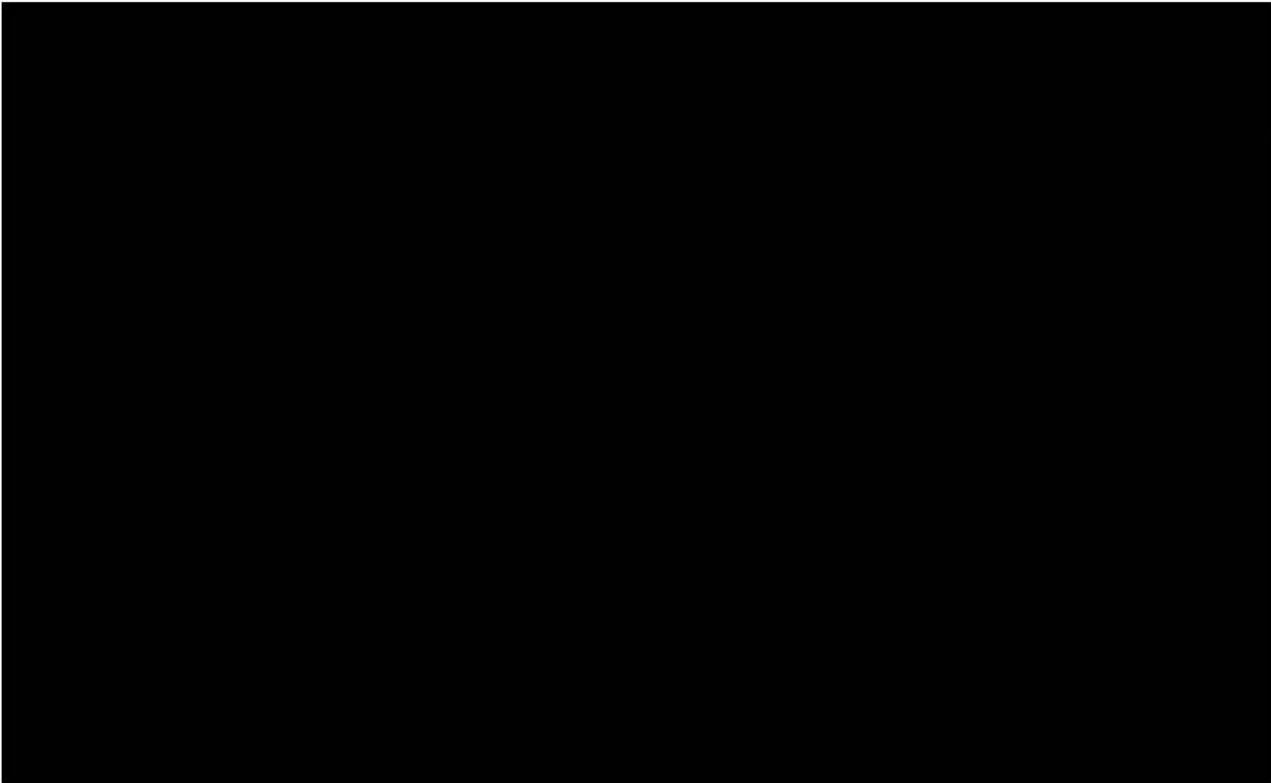


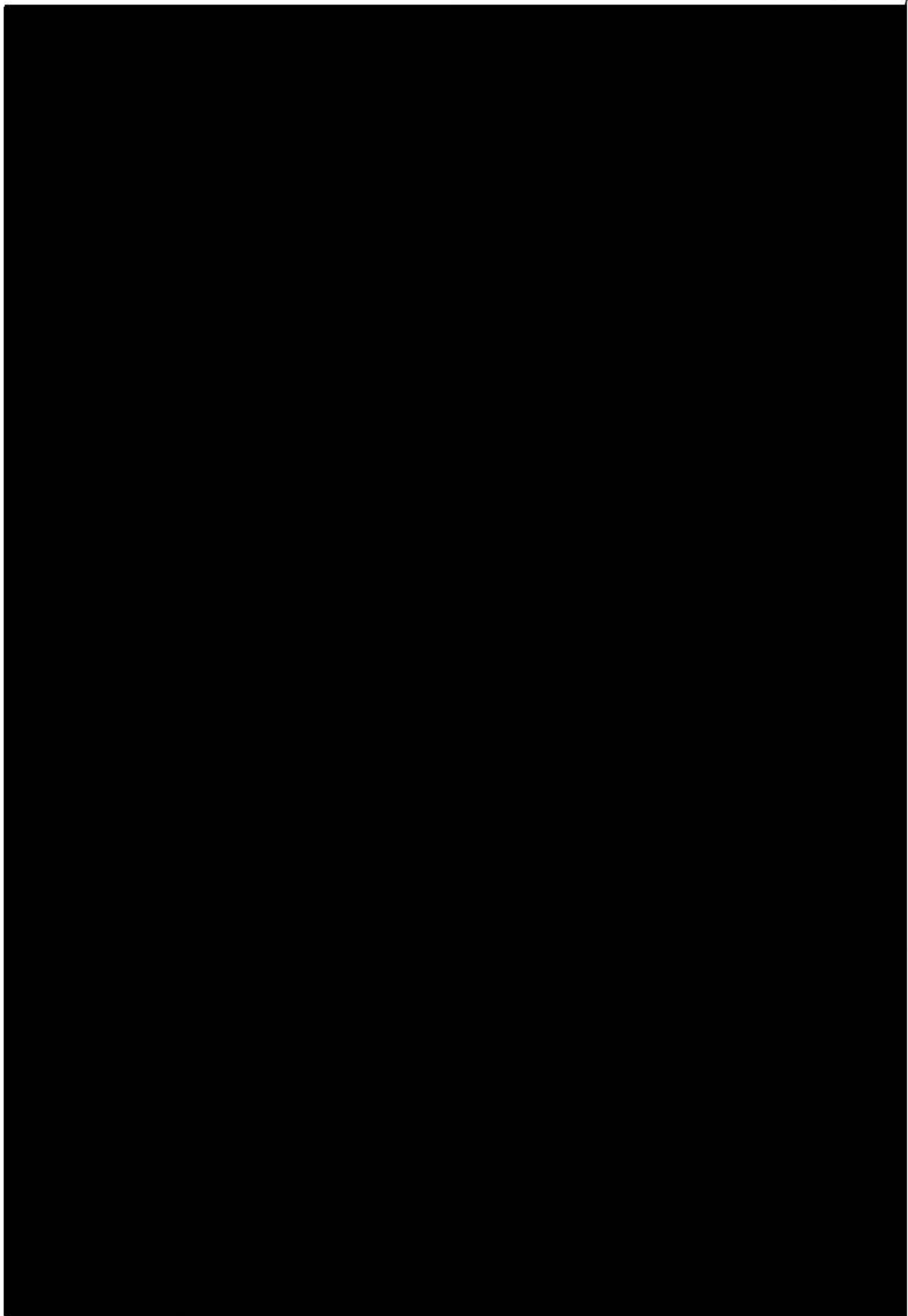


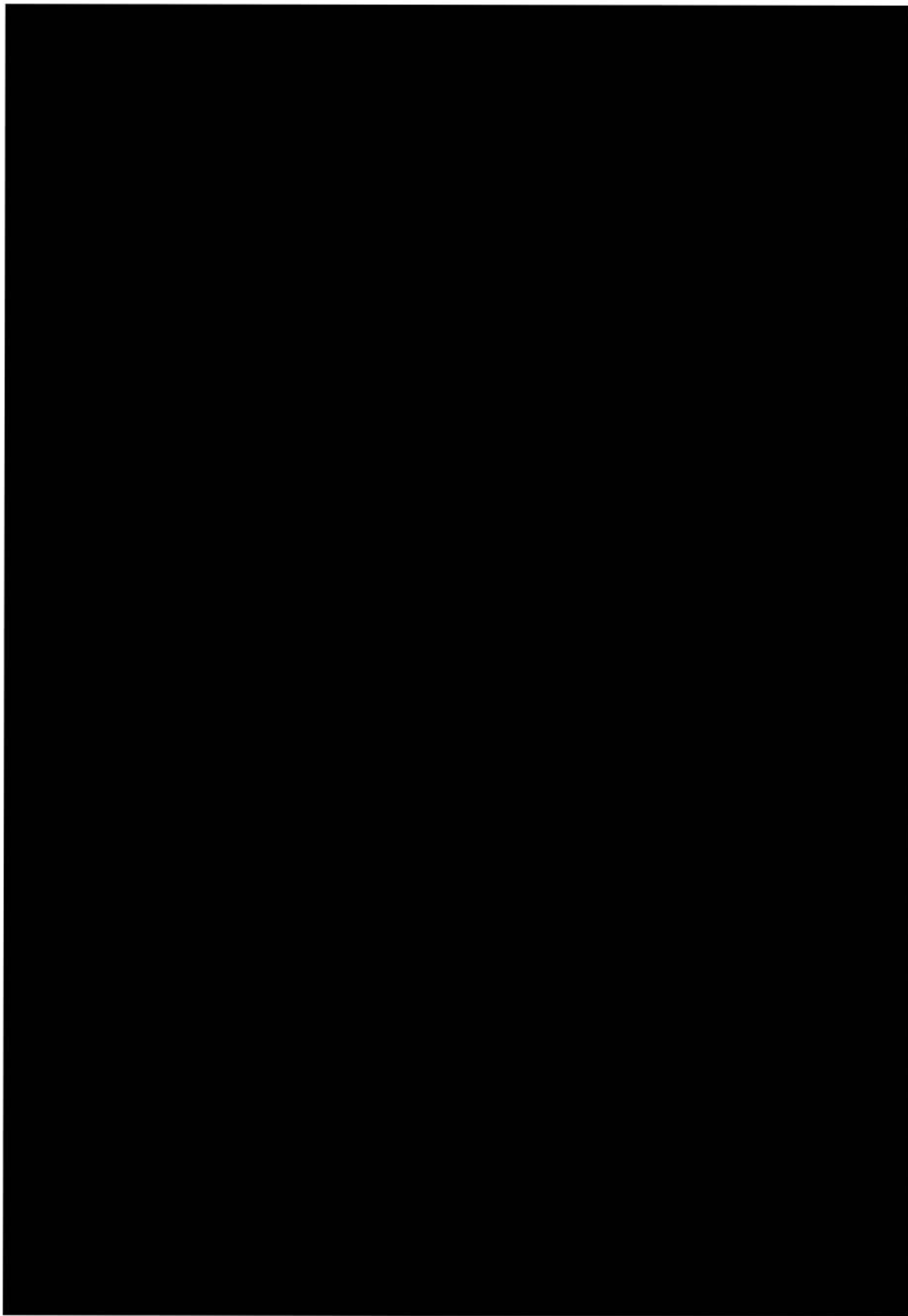




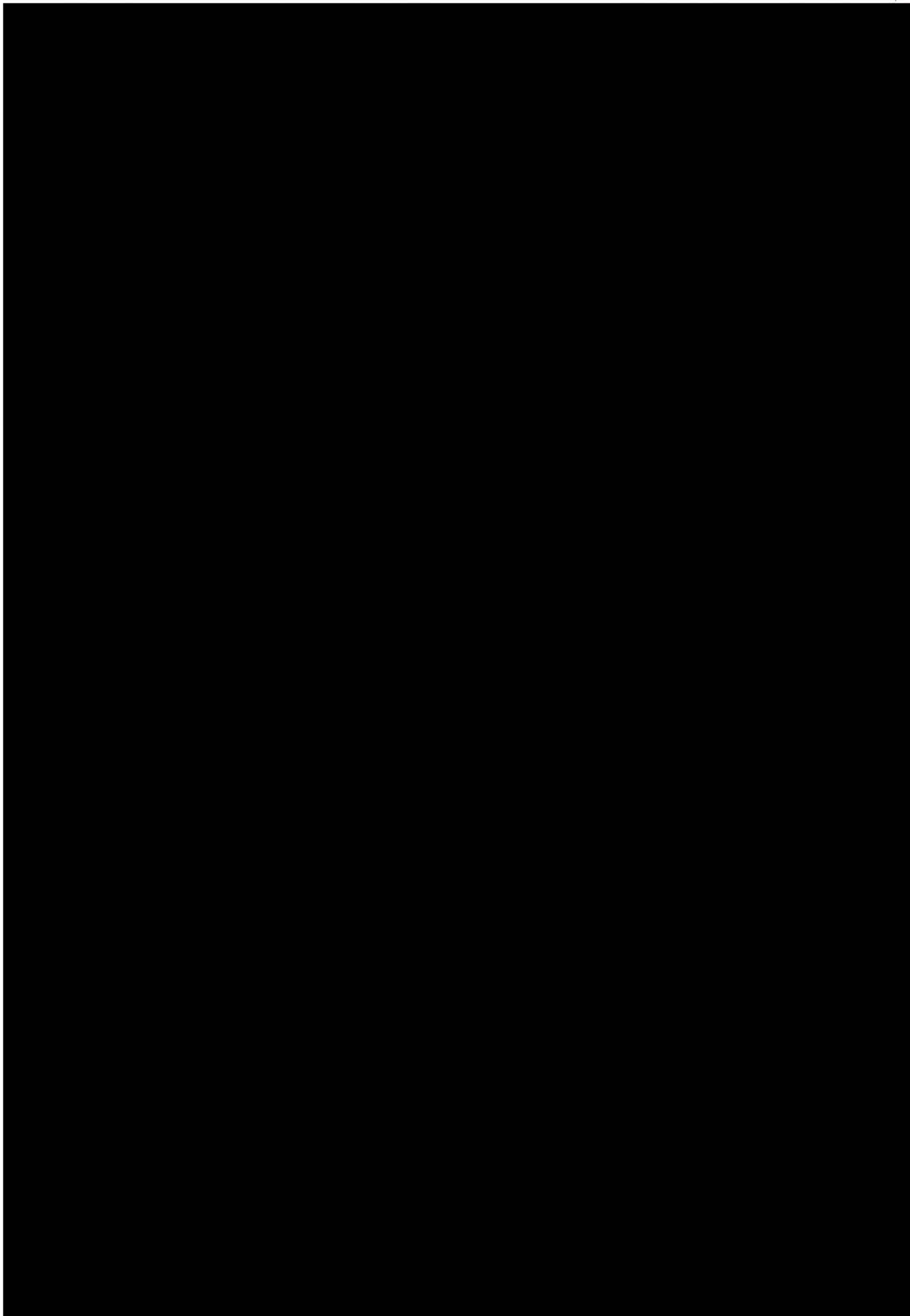


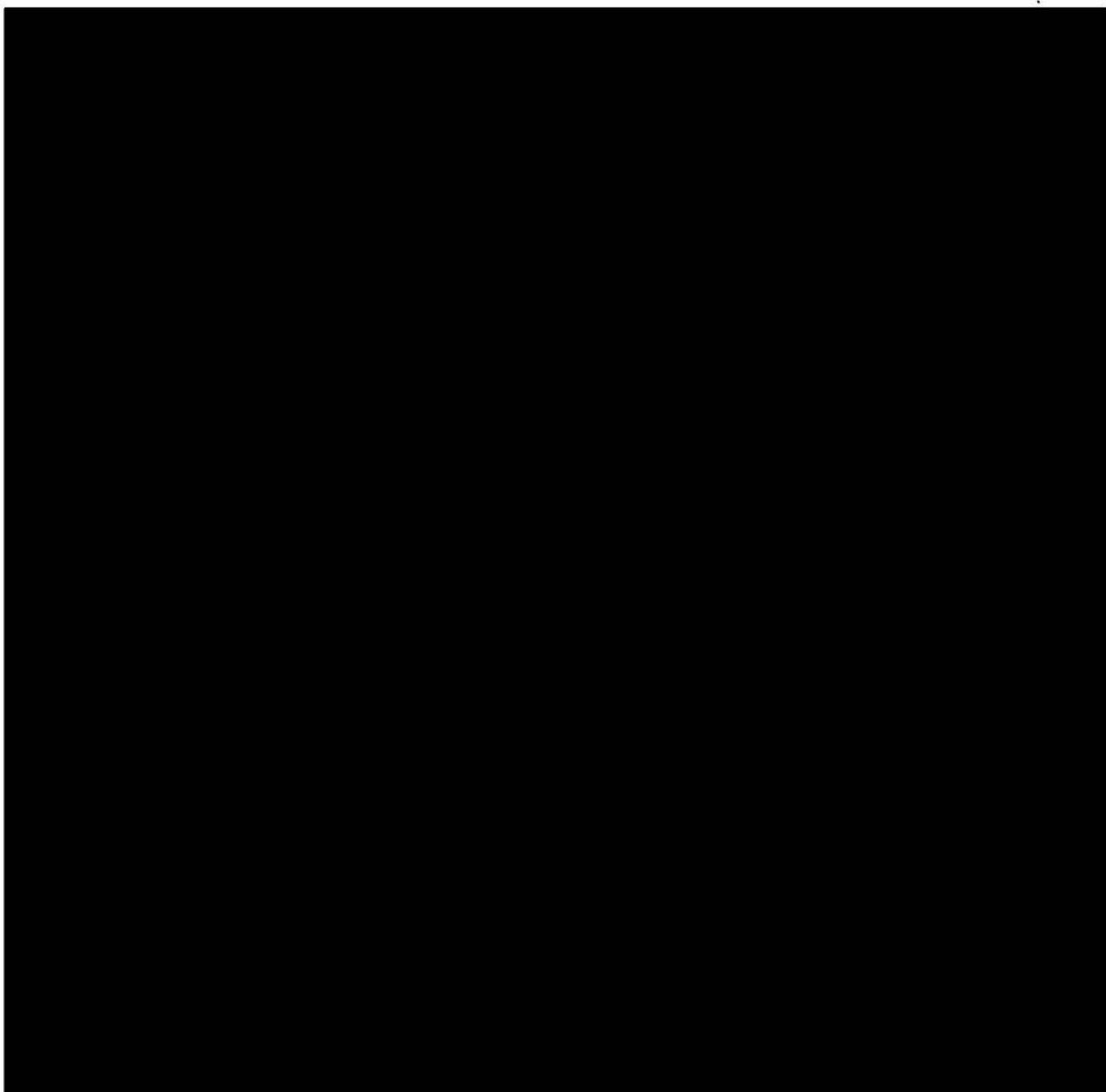


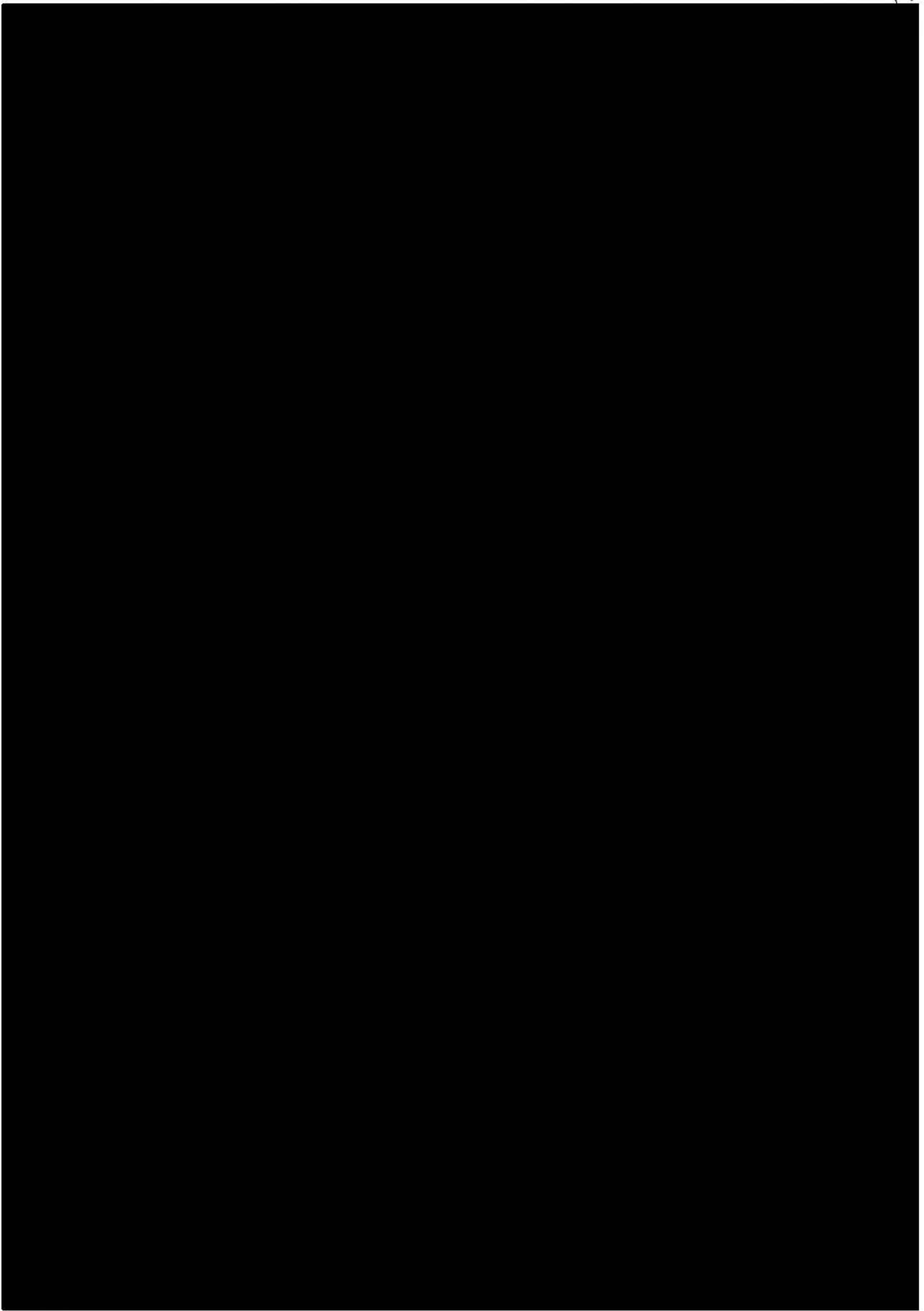


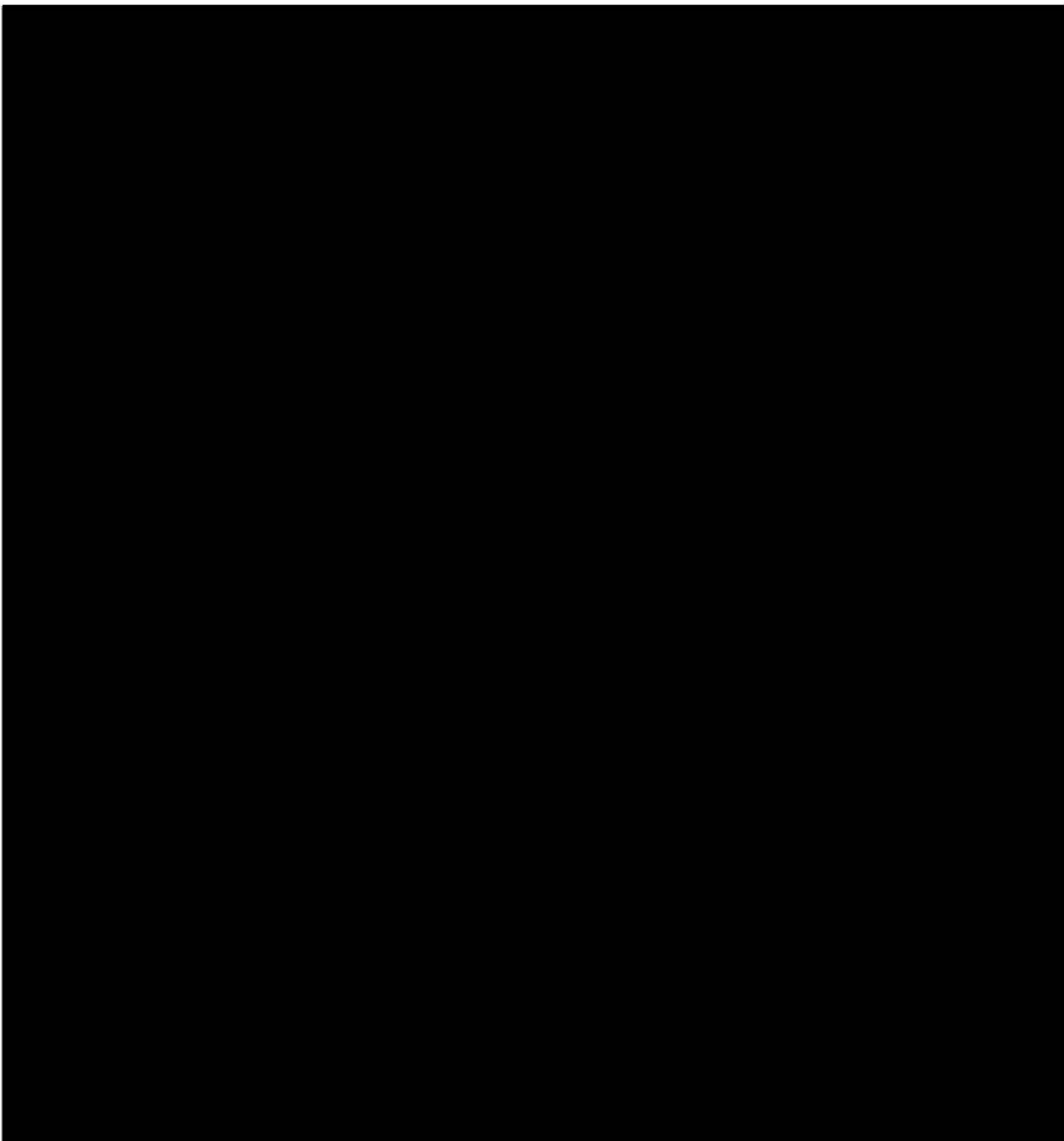




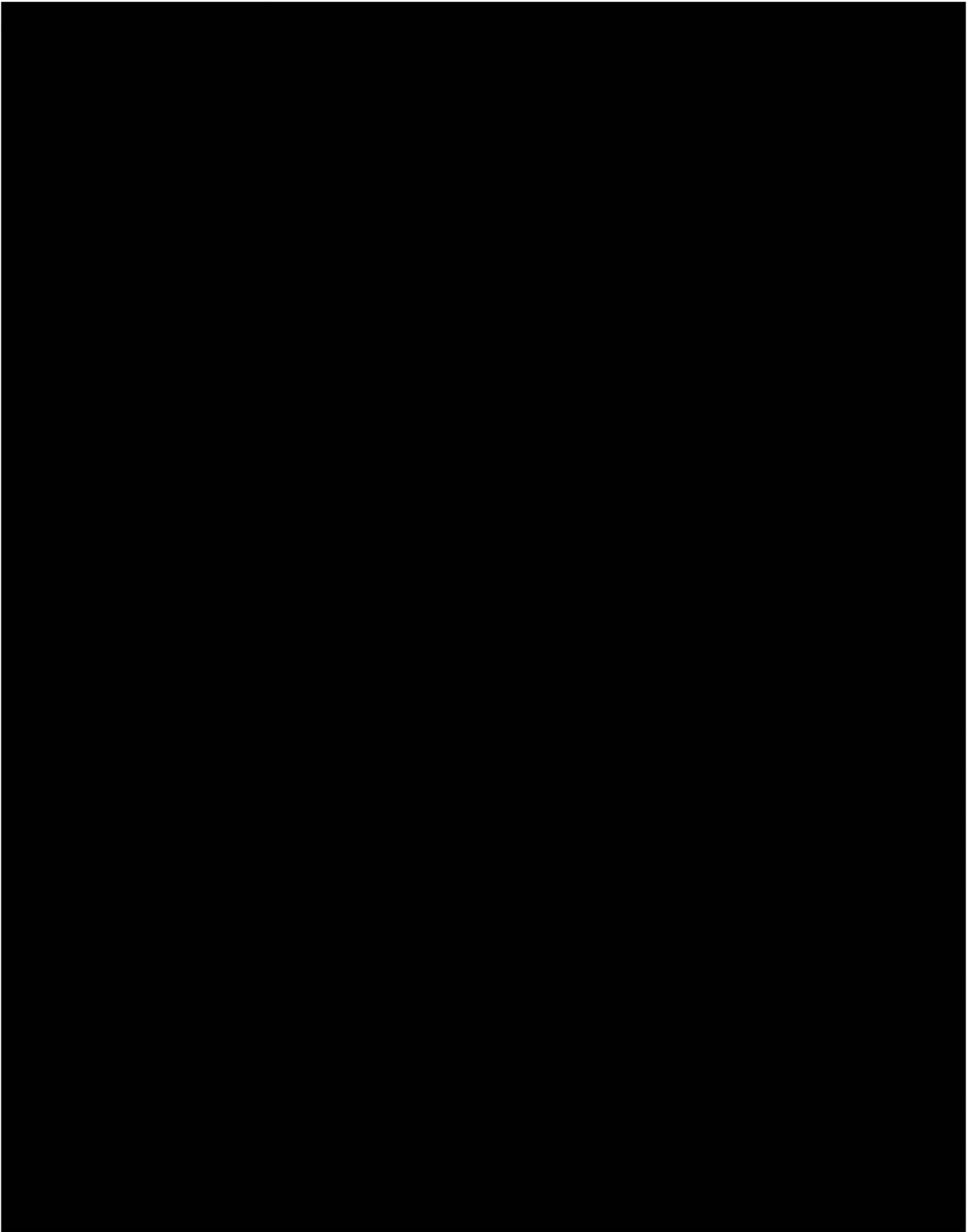


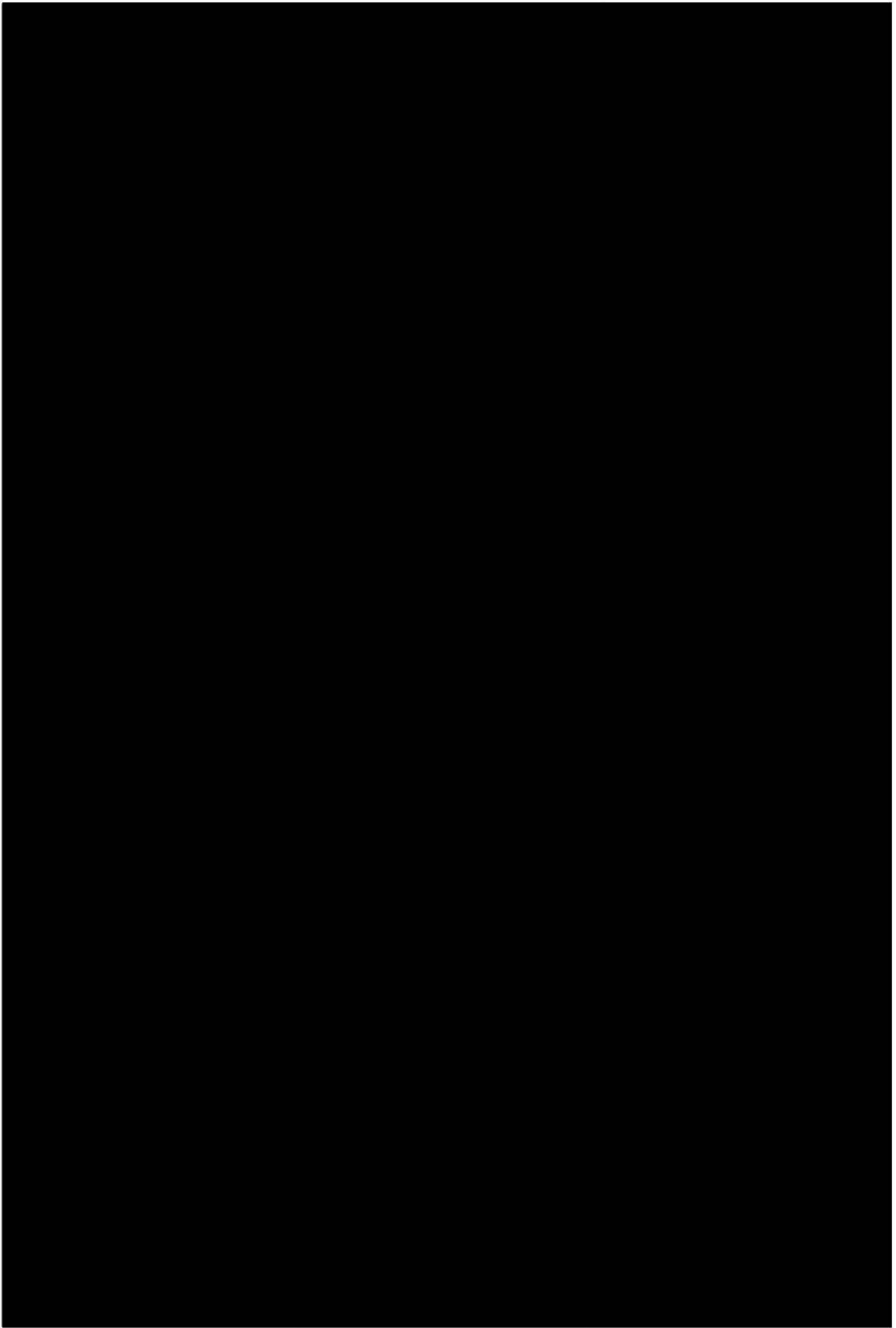


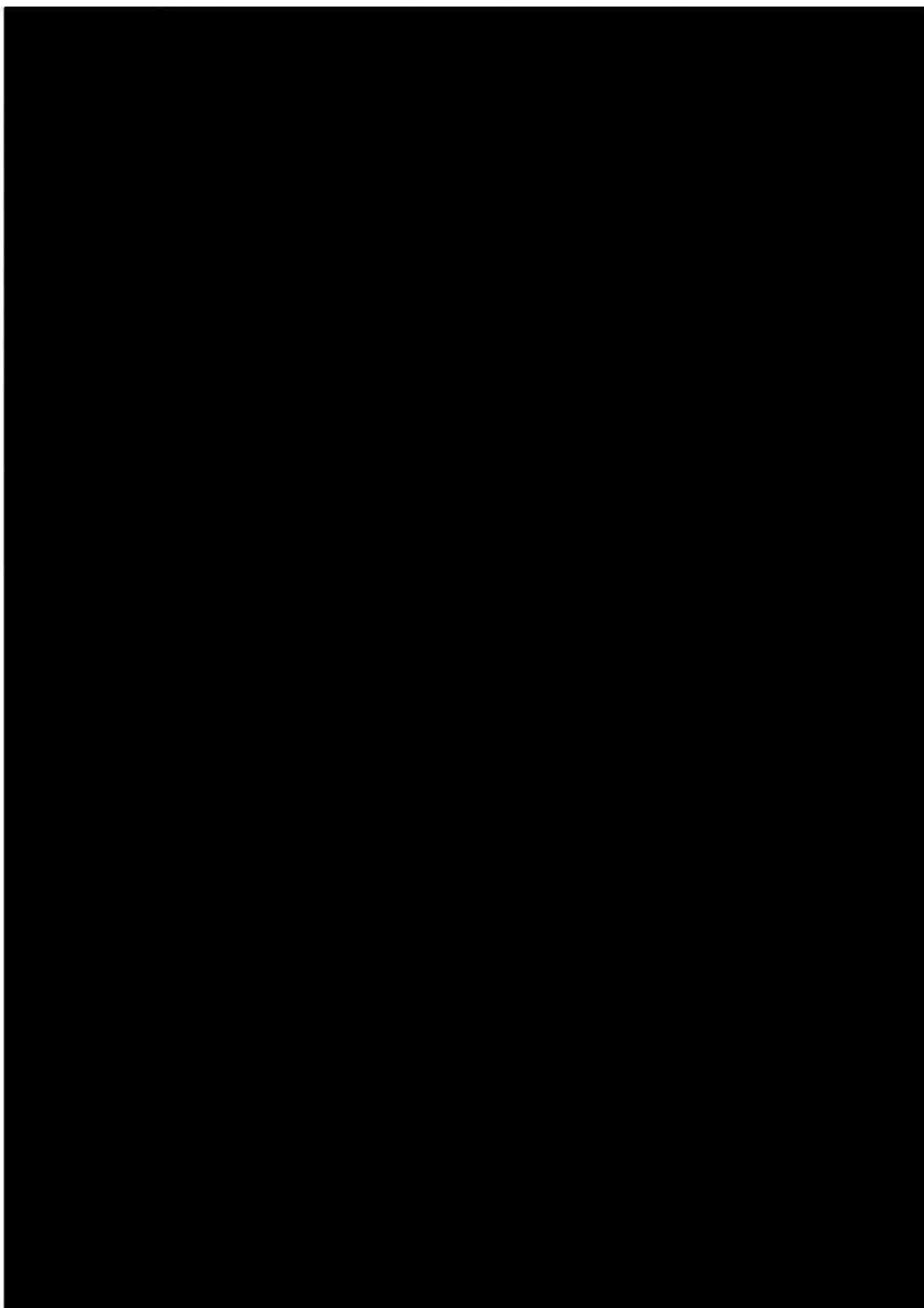


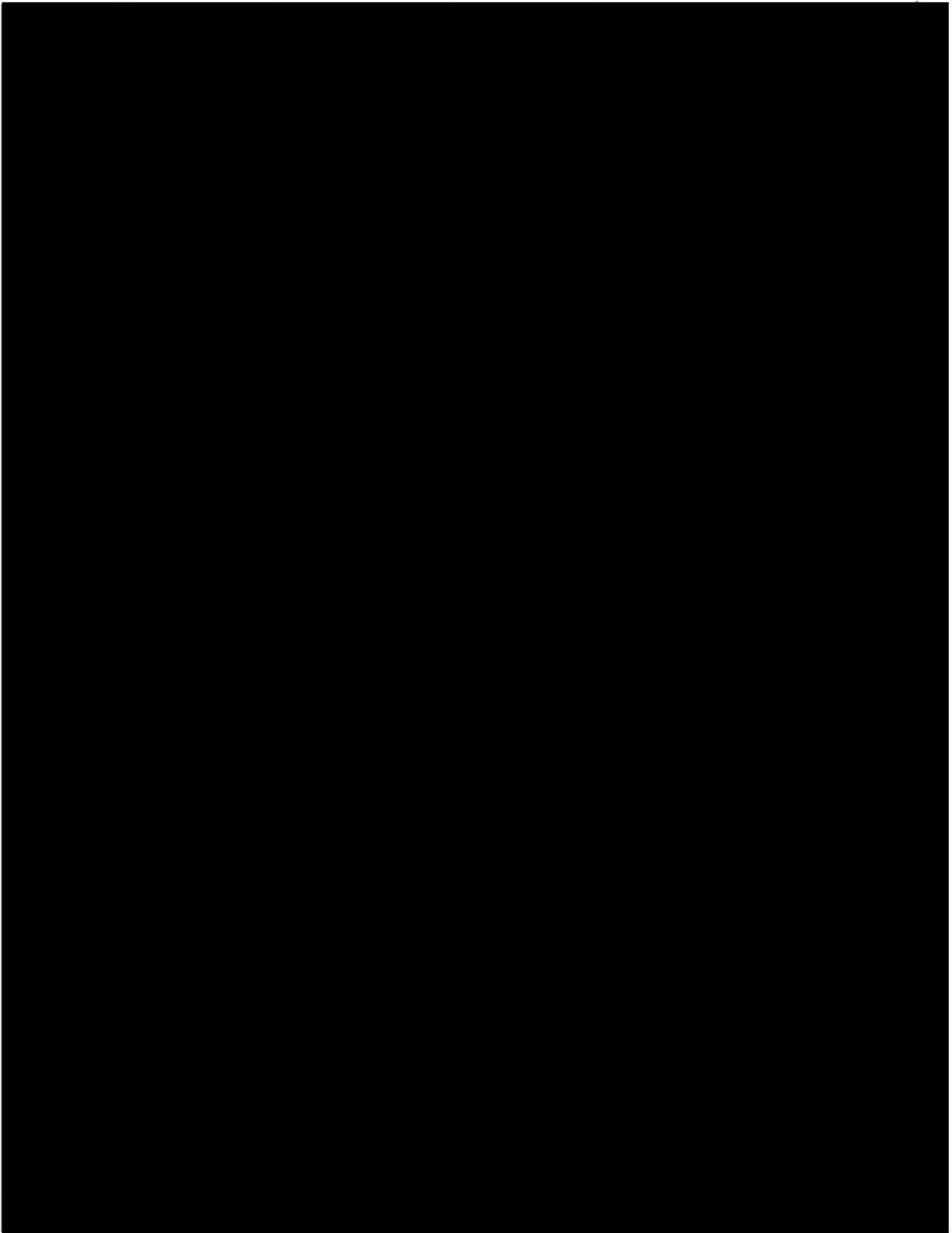






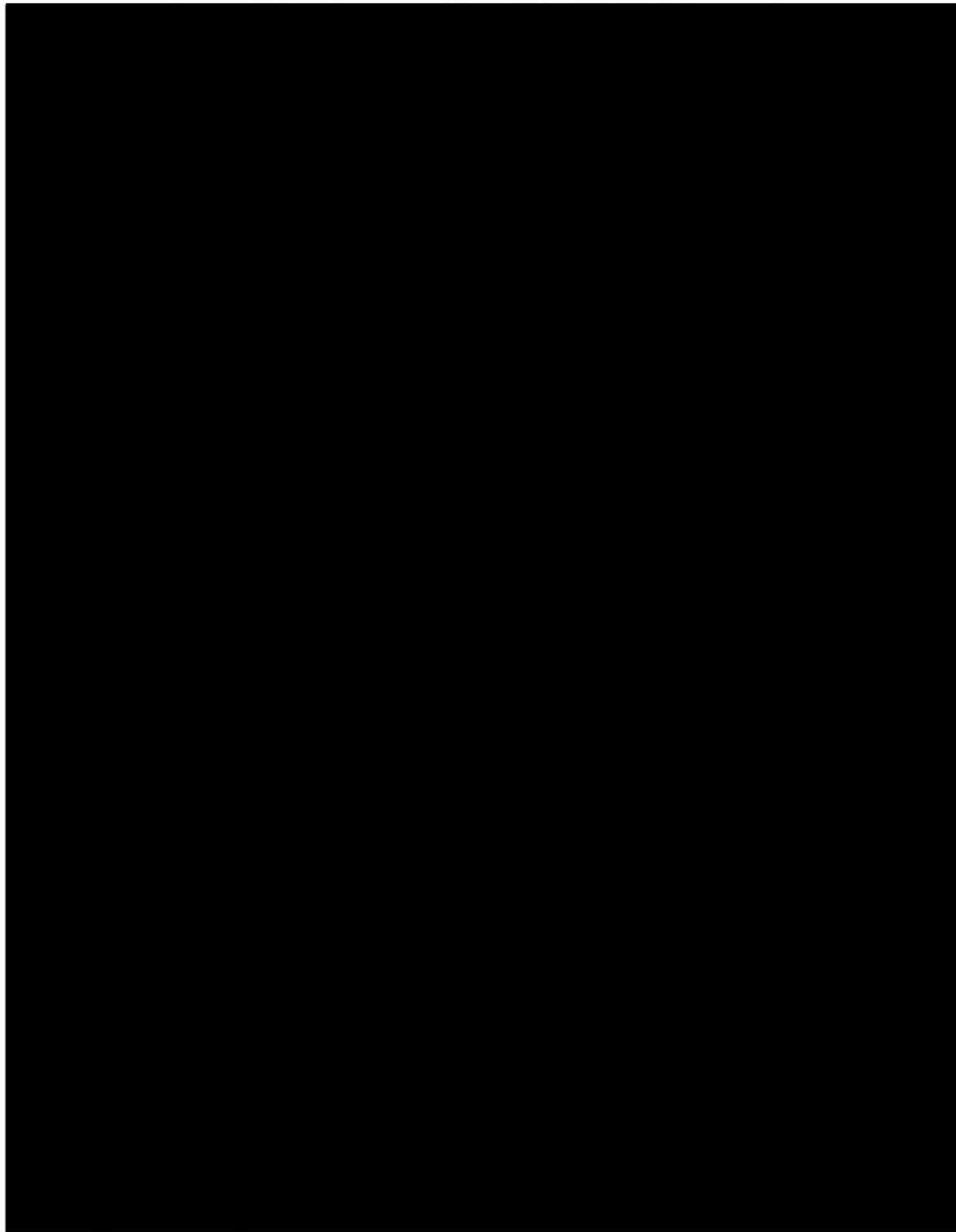


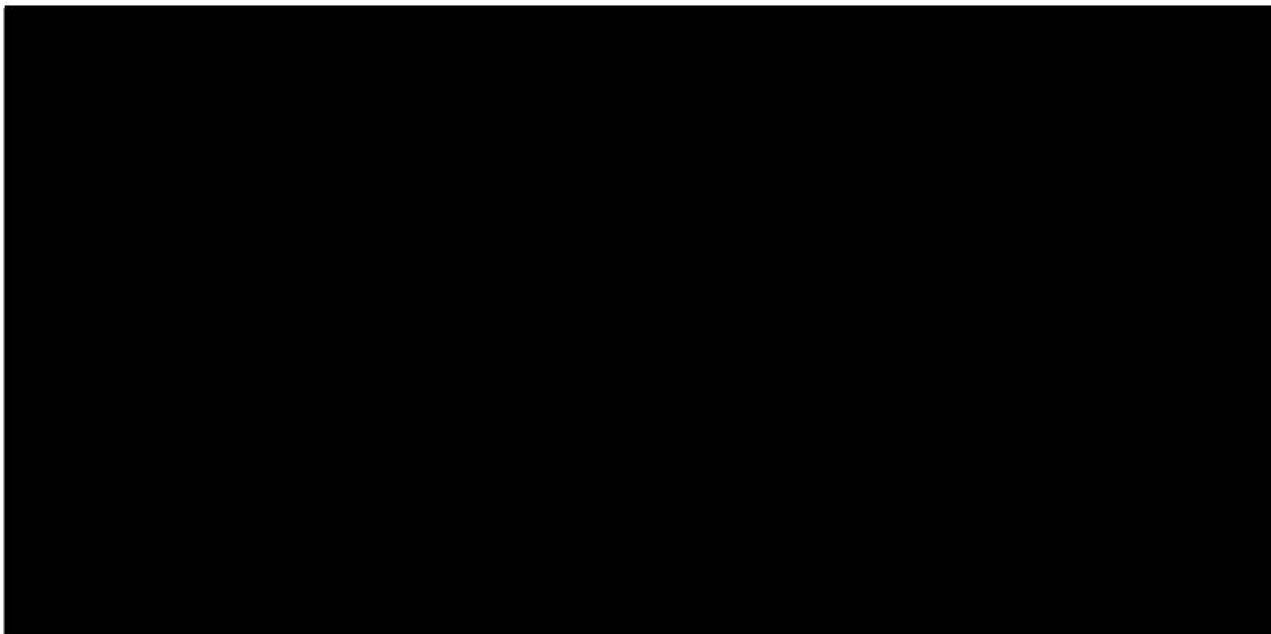






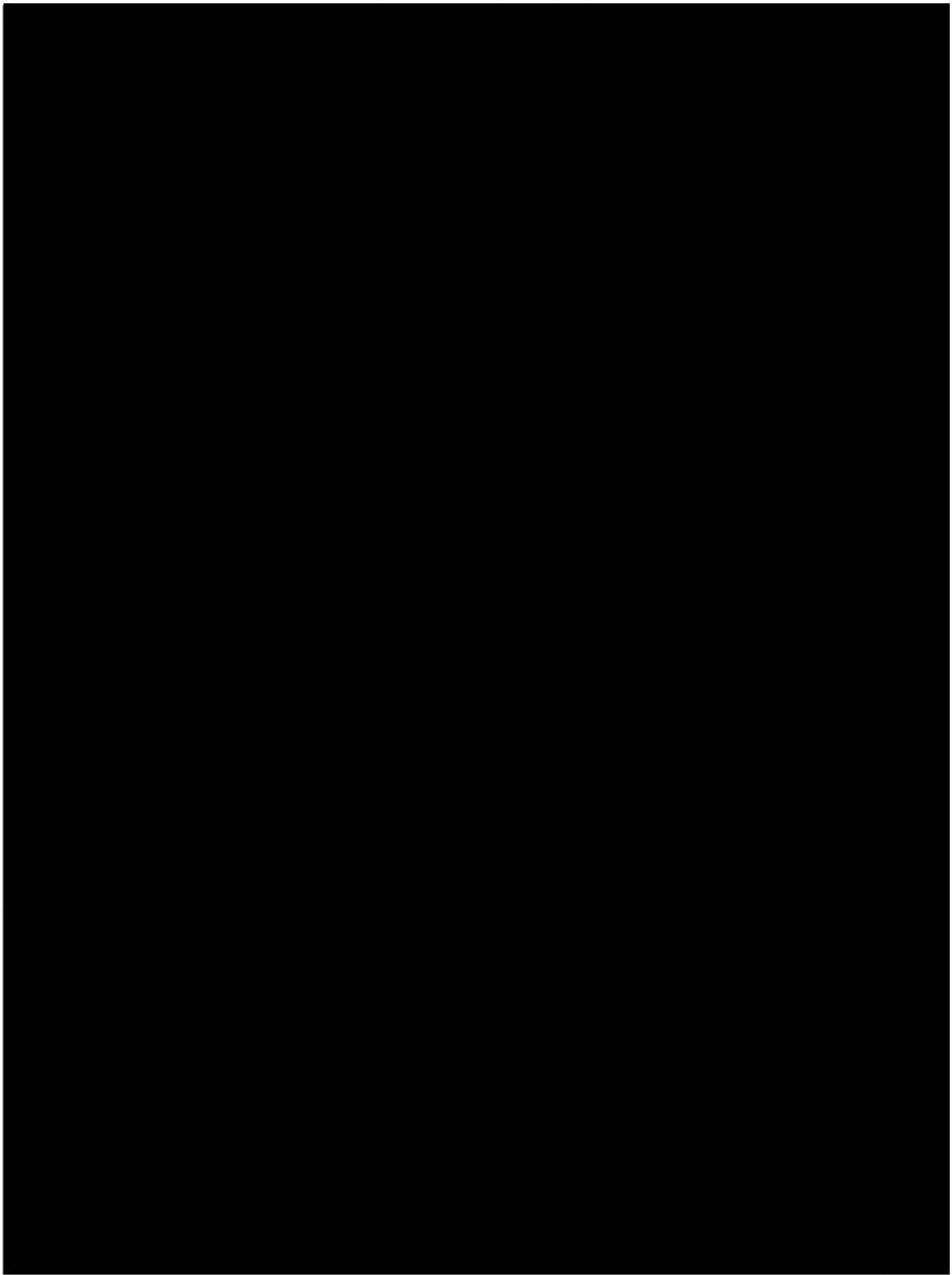
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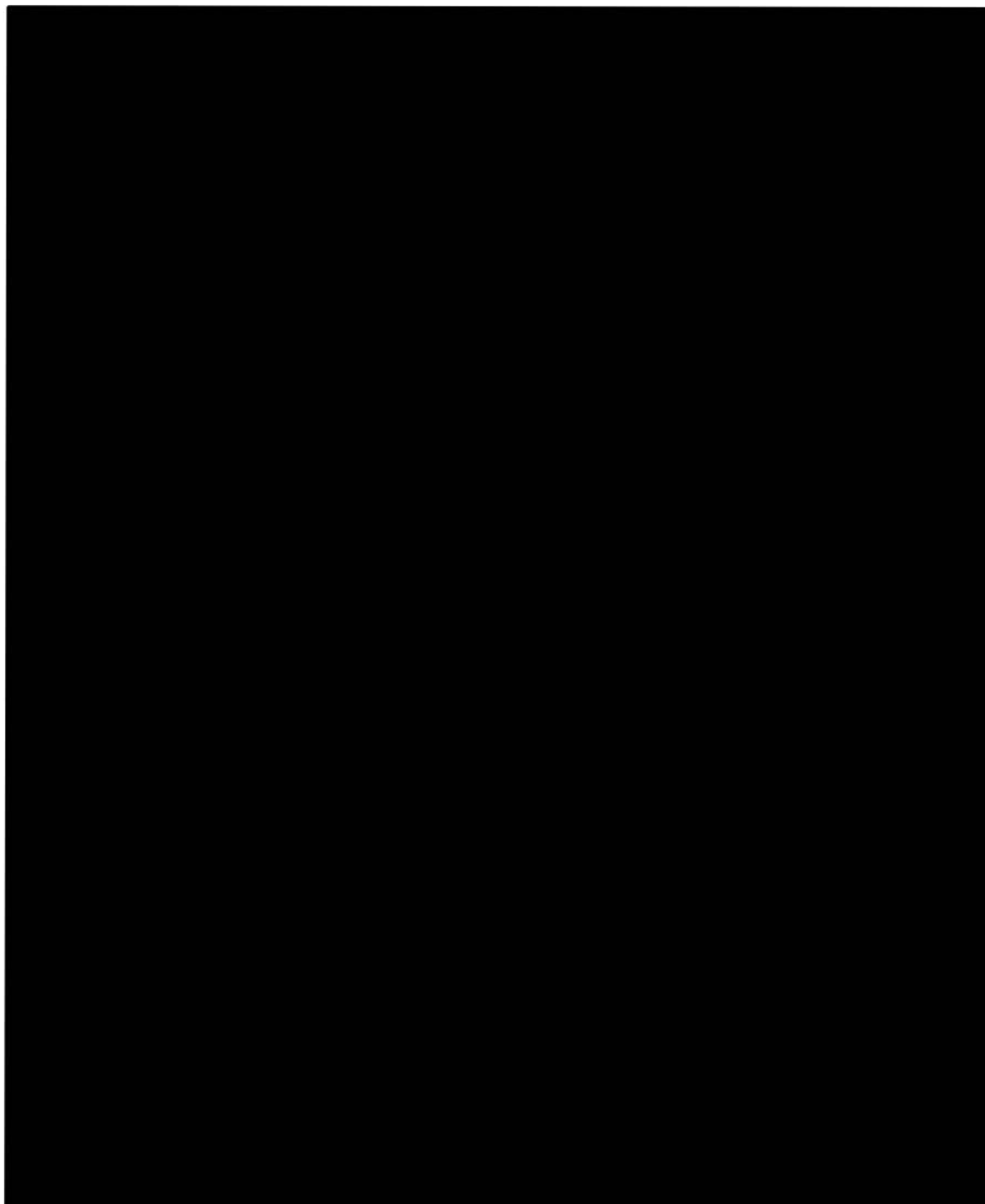
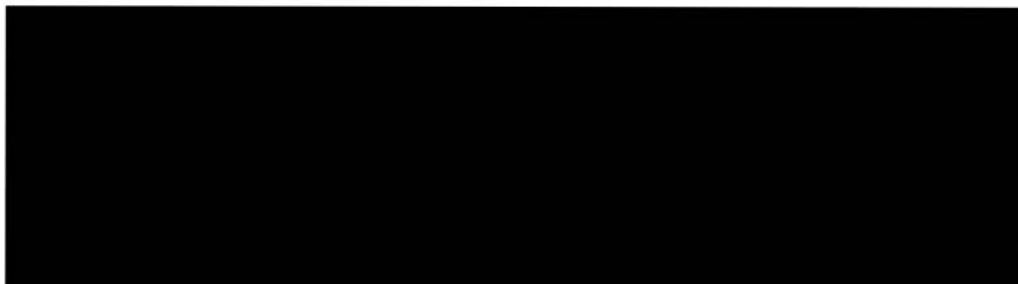


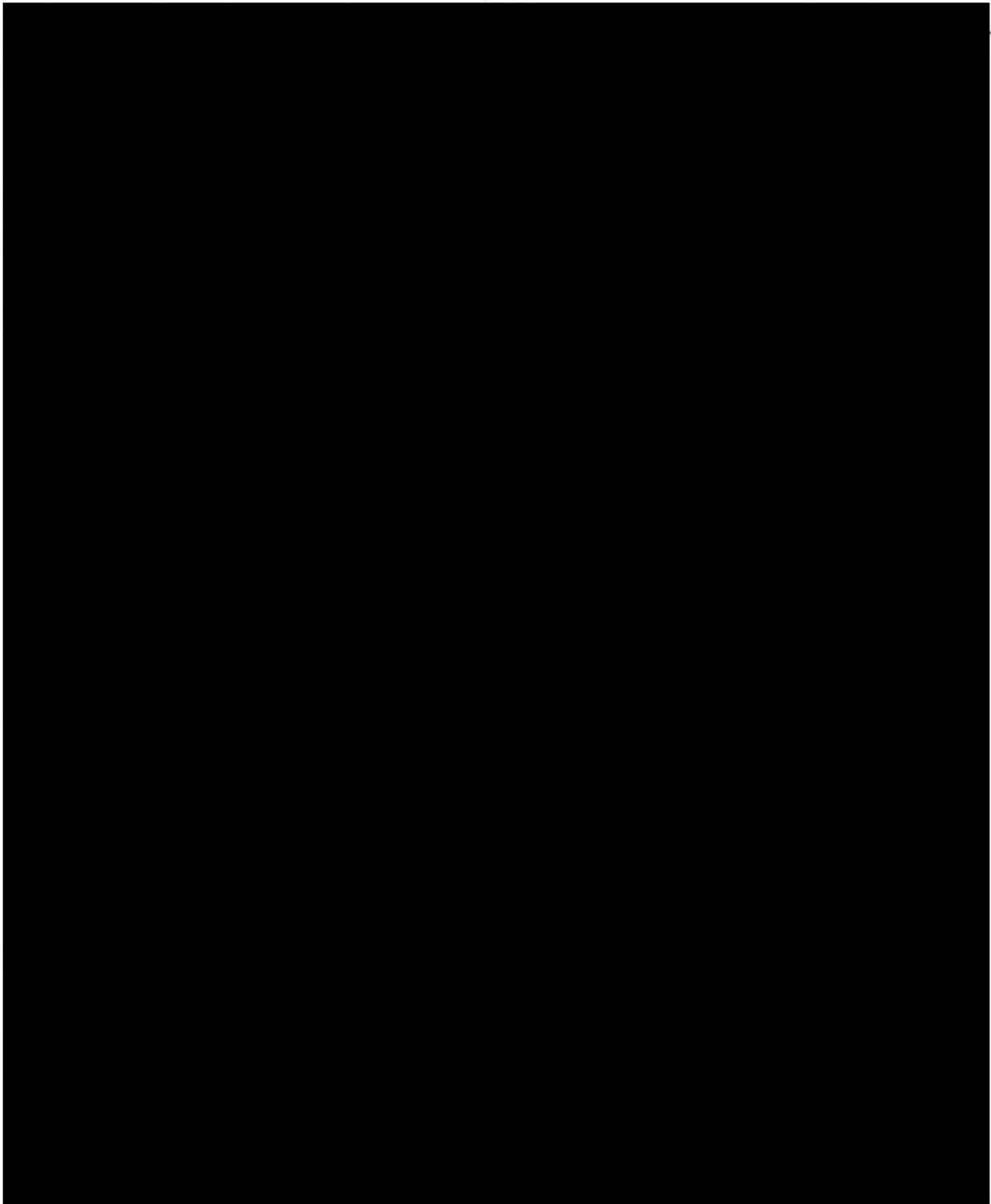


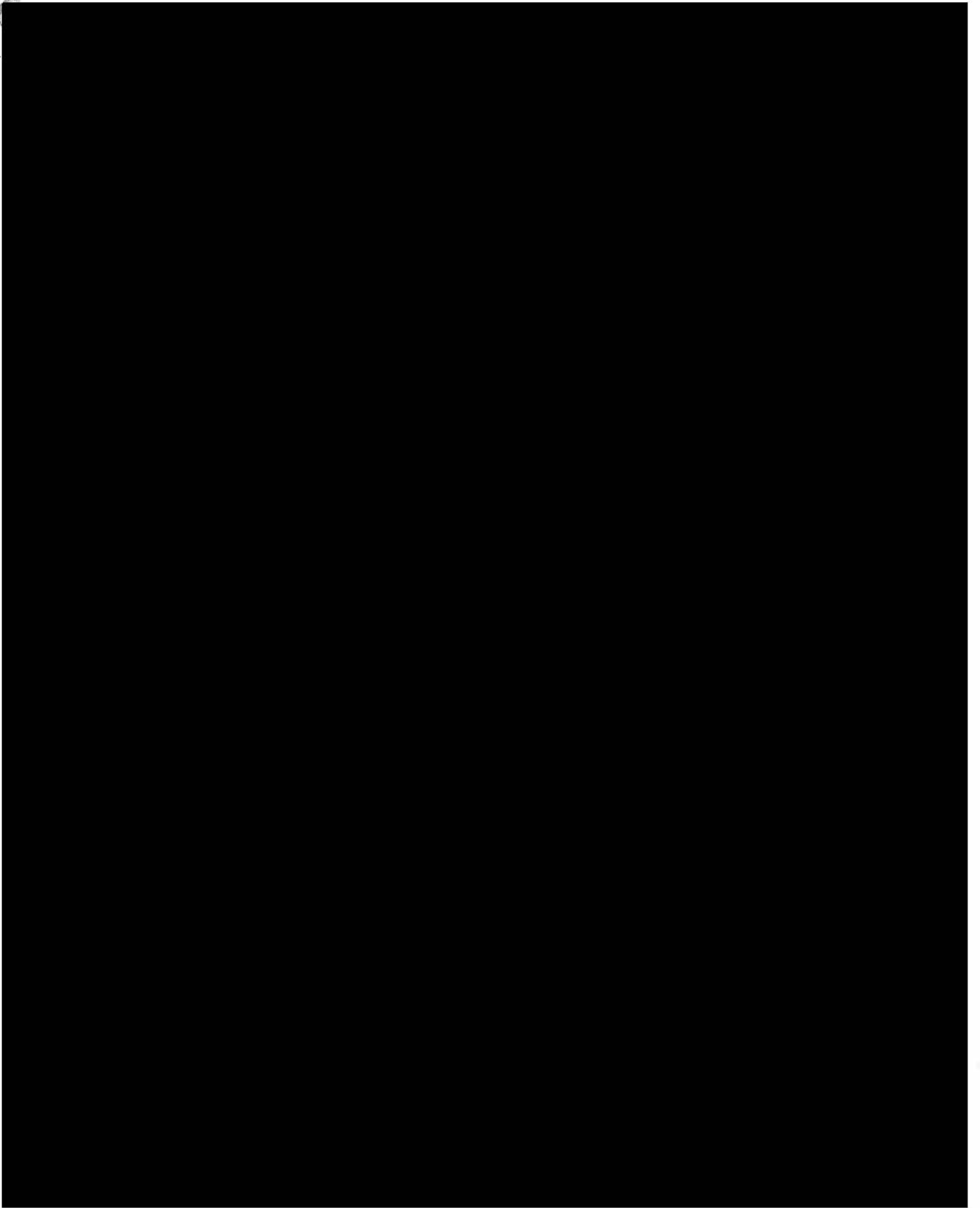
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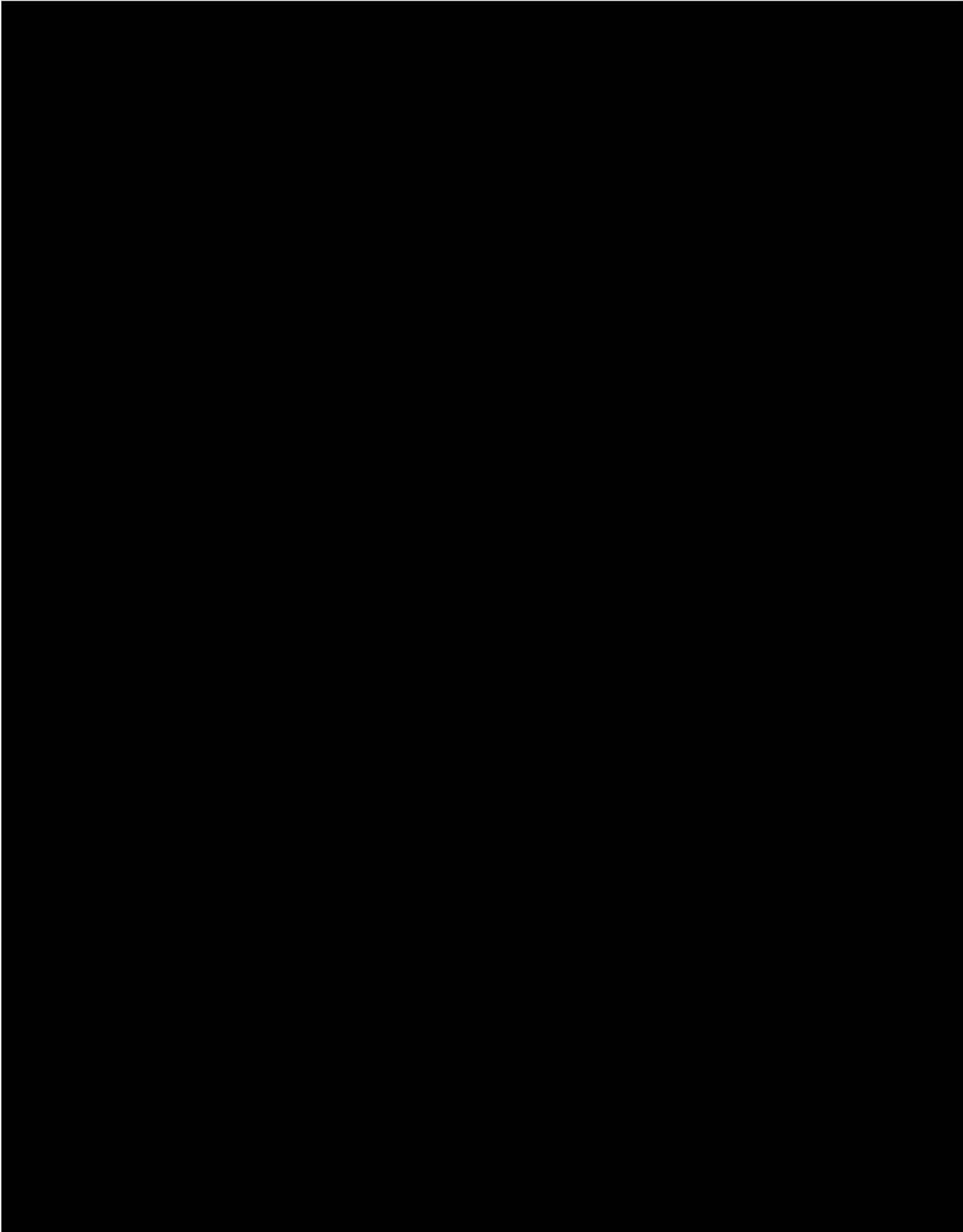
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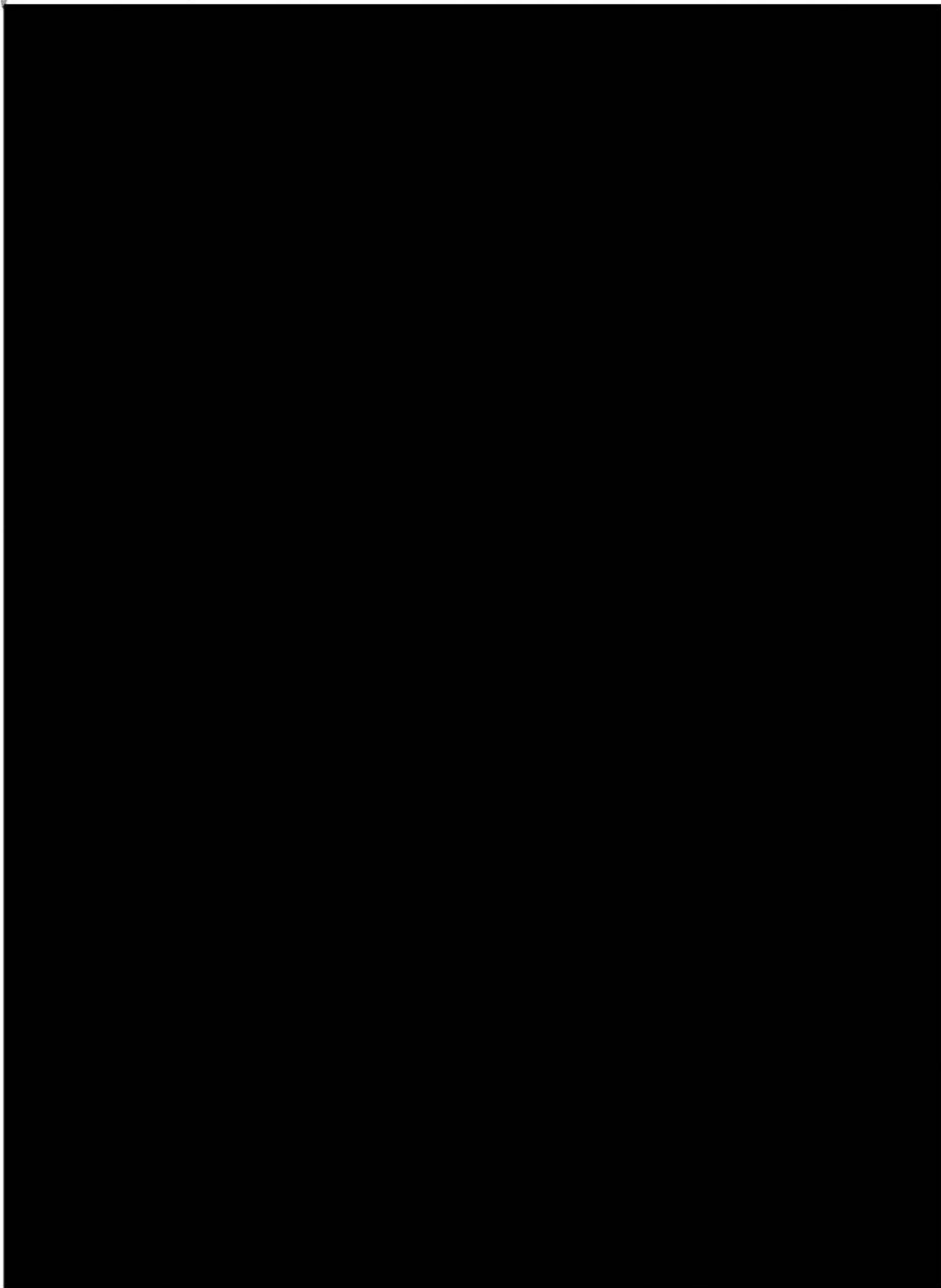


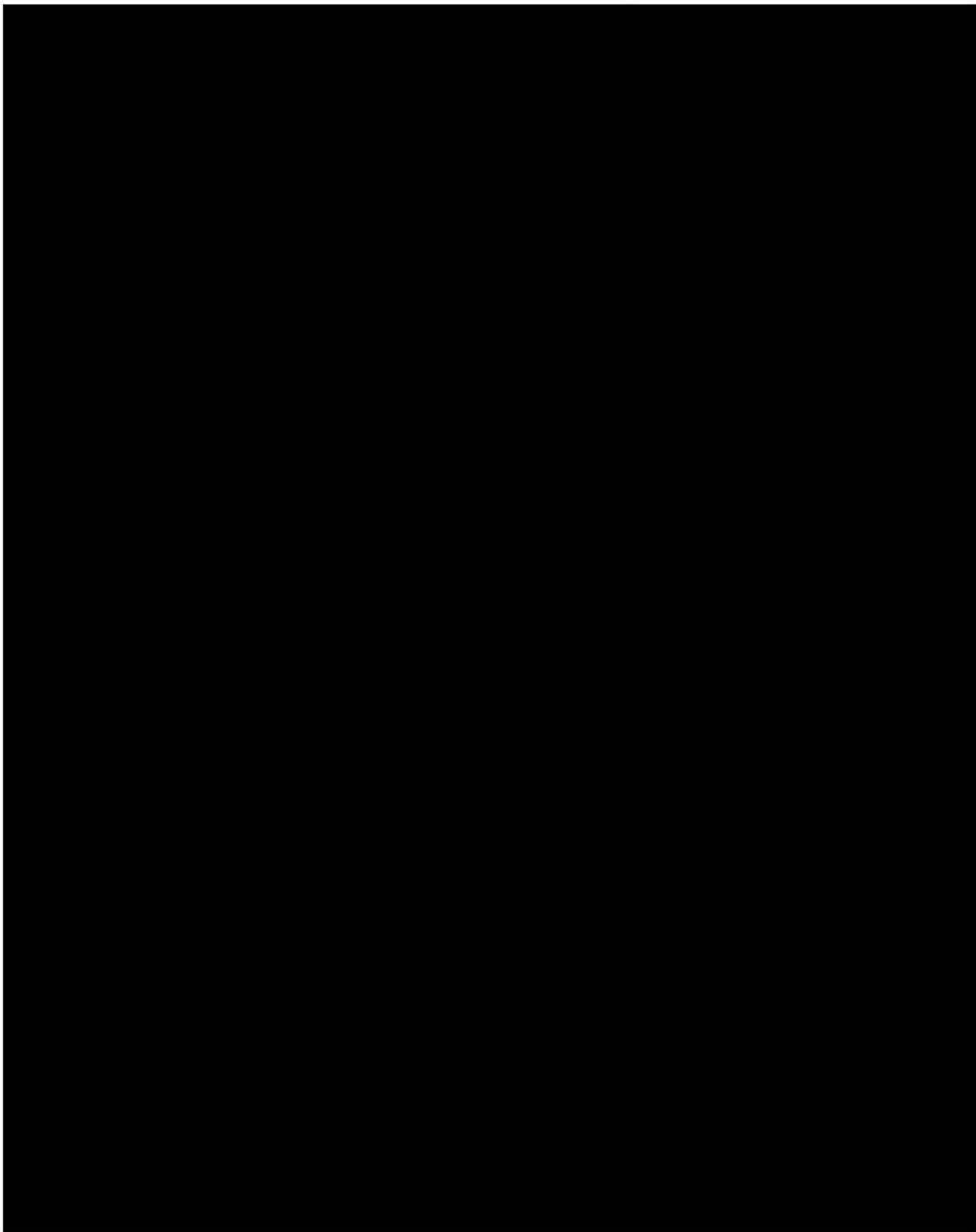


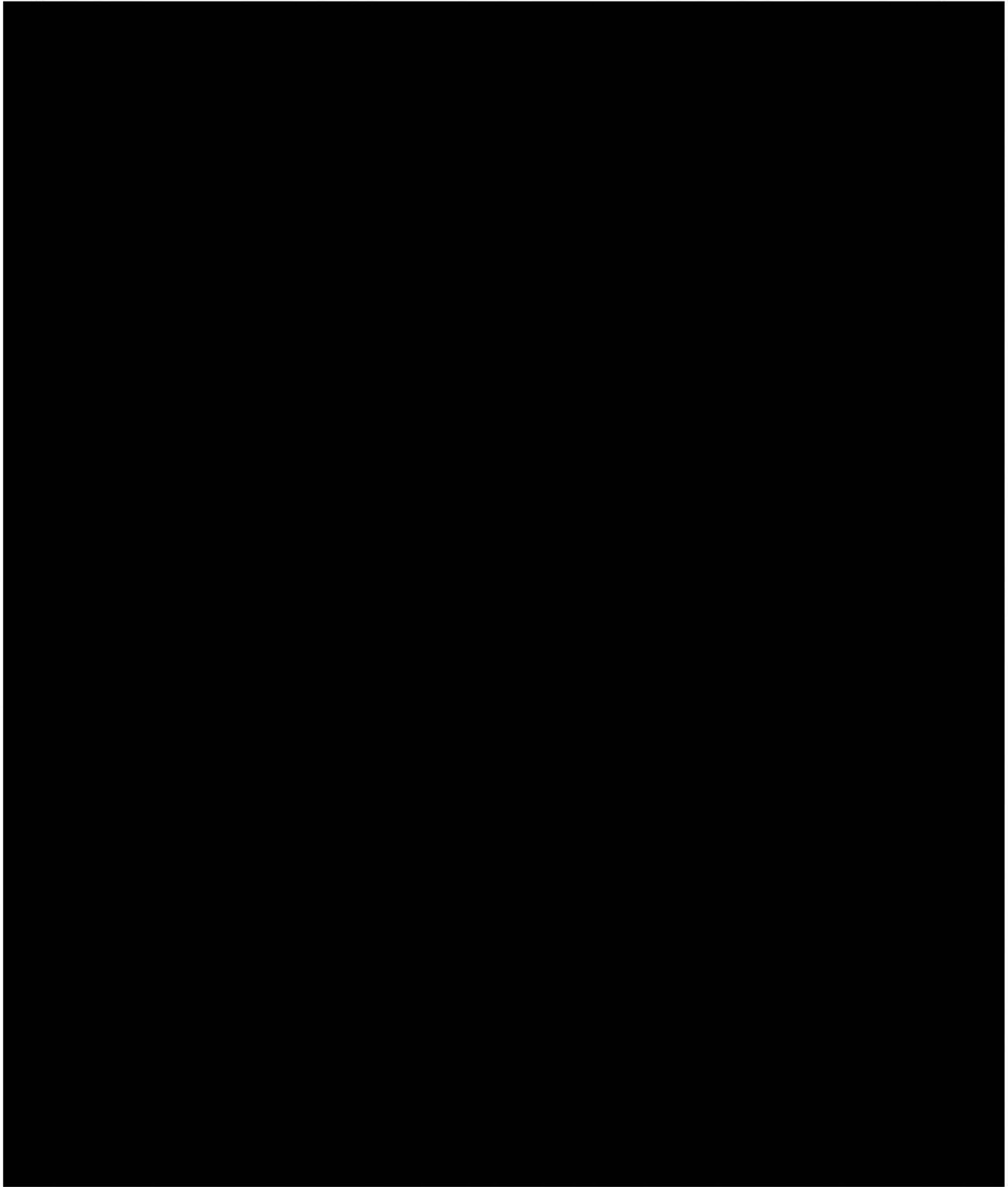




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SUMMARY OF CLINICAL EVALUATION

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INTRODUCTION

The clinical data for this product was evaluated by two specialist clinicians with wide experience in plastic surgery and immunology respectively. The data supplied consisted of some historical clinical data related to silicone breast implants in general and some more recent data on the later model silicone filled implants.

It is necessary to evaluate Silicone Breast Implants for Quality, Safety and Efficacy and evaluation of the clinical data is important in establishing all these criteria.

Breast implants have been available for many years throughout the world and in that time a number of questions have arisen. These questions relate to the incidence of implant rupture, systemic effects of silicone, local effects of silicone leakage and surgical complications. These questions must be addressed to establish the safety of silicone filled breast implants. The question of efficacy of the breast implants is not similar to that which is required of, for example, a pacemaker which must perform complex tasks which at times have a life saving effect on patients. Breast implants perform their task by altering the shape of breasts, either following surgery for other conditions, such as carcinoma, or for simple breast augmentation. The difficulty in assessing the risk benefit for breast implants is that the benefit in most cases is aesthetic with a considerable psychological well being dividend but no straight out health benefit such as with a pacemaker. Against this must be weighed the real risks associated with implantation of silicone filled breast implants.

The task given to the external evaluators was to assess, on the data available, the level of risk associated with the use of silicone filled breast implants and give a view, based on their experience, of whether this product reached an acceptable level of risk benefit.

Because of the complexity of the questions raised in this evaluation, much of the medical literature on this topic was reviewed in addition to the data supplied by the sponsor. This was particularly so when examining the systemic effects of silicone.

SPECIFIC ISSUES ON SAFETY

Systemic Effects of Silicone

Well-defined systemic autoimmune diseases such as rheumatoid arthritis, scleroderma, systemic lupus erythematosus, Sjogren's syndrome and mixed connective tissue diseases have been described in case anecdotes as being associated with silicone breast implants. The difficulty in addressing this issue is that all the studies seeking to investigate this matter have been generic and not related specifically to the implant being evaluated. The sponsor has submitted a report by ENVIRON. The external evaluators also reviewed a number of additional studies from the medical literature and found reassurance that in at least seven case controlled studies no evidence is provided to support an association between silicone breast implants and well defined systemic auto-immune syndromes. The possibility of systemic syndromes, unrelated to the well-defined syndromes, was discussed but there was no real evidence to suggest that such syndromes exist but the possibility was not entirely closed off. It was noted that removal of implants in patients with systemic disorders had no consistent effect on their illness.

The issue of the development of autoantibodies of various types was discussed in the sponsor's submission but did not show a consistent pattern. The question of autoantibodies has not been clarified by more recent literature.

It was the belief of the evaluators that the risk of systemic disease did not constitute an objection to the registration of these silicone filled implants.

Local Effects of Silicone

Breast Cancer

The sponsor's submission reports that there is no increase in the incidence of breast carcinoma in patients with silicone filled breast implants. Recent finding in a number of studies has reinforced this, principally a study from Sweden.

Breast Cancer Detection

It is acknowledged that the presence of silicone filled breast implants makes mammography detection of breast carcinoma more difficult. It is important that radiographers are aware of the presence of breast implants at the time of mammography to ensure that appropriate views are taken.

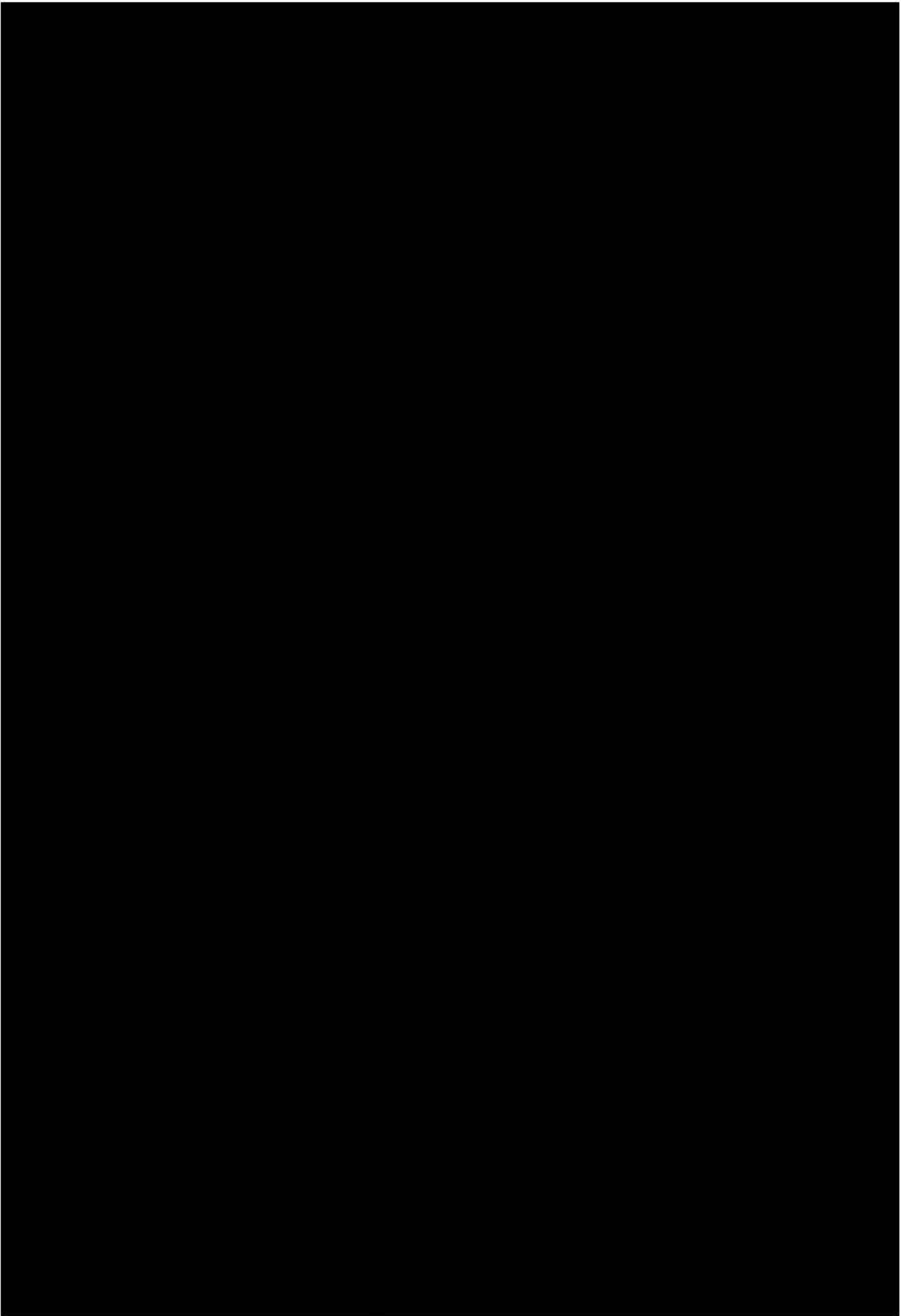
Breast Feeding

The evaluators have found two case reports that allege that silicone in breast milk has interfered with gastrointestinal function of suckling infants. These claims have not been verified in larger studies and have to be seen in the context of the use of silicone in bottle teats and approved use of silicones in paediatric medications.

IMPLANT SPECIFIC LOCAL ISSUES

The sponsor presented data derived from [REDACTED]

[REDACTED] The evaluators felt that complaint data was not ideal in measuring these issues but found the rates reported as acceptably low.





Recommendations

1. It is recommended that the Delegate be advised that there are no clinical objections to the entry of McGhan Silicone-filled Mammary Implant Prostheses being entered on to the ARTG.
2. It is recommended that some form of register for breast implants be established in order to establish more accurately the performance of and complication rates for various surgical implanting procedures and implant surface textures.
3. Breast implants should be subject to active post market surveillance.
4. It is recommended that the sponsor review the patient information supplied with this product to ensure its accuracy especially in relation to complication rates.

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