INVESTIGATOR'S BROCHURE

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations	Definition
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
$AlPO_4$	aluminum phosphate
ALT	alanine aminotransferase
ANOVA	analysis of variance
APD_{90}	action potential duration at 90% repolarization
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{inf}	area under the curve from zero to infinity
AUC_{24}	area under the plasma concentration-time curve from 0 to 24 hours
AUC_{last}	area under the plasma concentration-time curve from 0 to the time of last measurement
AV	atrioventricular
BID	twice daily
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CHO	Chinese hamster ovary
C	Caesarean
CI	confidence interval
CL	clearance
CL_{cr}	creatinine clearance
CL_P	plasma clearance
CL_r	renal clearance
C_{max}	maximum plasma concentration
CNS	central nervous system
COX	cyclooxygenase
CPS	capsular polysaccharide
CRM_{197}	cross-reactive material 197
CTC	Common Toxicity Criteria
CV	cardiovascular
CVA	cerebrovascular accident
CYP	cytochrome P450
DVT	deep vein thrombosis
EC_{50}	median effective concentration
ECG	electrocardiogram
e-diary	electronic diary
EEG	electroencephalogram
F	bioavailability
F_0	maternal/paternal generation
F_1	first generation
FBE	free base equivalent
f_e	fraction of drug excreted
f_u	fraction of drug unbound
FIH	first-in-human
FMO	flavin-containing monooxygenase
GABA	gamma amino butyric acid
GBS	group B streptococcus
GBS6	group B streptococcus 6-valent polysaccharide conjugate vaccine
GD	gestation day
GGT	gamma-glutamyltransferase
GI	gastrointestinal
GLP	Good Laboratory Practice
HAAG	human α_1-acid glycoprotein

Abbreviations	Definition
HDPE	high density polyethylene
HEK	human embryonic kidney
hERG	human ether-á-go-go-related gene
HPLC	high-performance liquid chromatography
HSA	human serum albumin
IB	investigator's brochure
IC_{50}	50% inhibitory concentration
IC_{90}	minimum concentration that inhibits growth in 90% of strains of a species (for antiviral or antibacterial compounds)
I_{Kr}	hERG current
IM	intramuscular
IP	intraperitoneal
IRC	internal review committee
IV	intravenous
Ki	inhibition constant
MAE	medically attended adverse event
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRHD	maximum recommended human dose
msec	milliseconds
MTD	maximum tolerated dose
NEC	not elsewhere cited
NF	National Formulary
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NOS	not otherwise specified
NSAID(s)	nonsteroidal anti-inflammatory drug(s)
NSTD	non-severely toxic dose
NZW	New Zealand White
PCA	patient-controlled analgesia
PF-06877053	GBS6 with $AlPO_4$
PF 06877054	GBS6
PG(s)	prostaglandin(s)
P-gp	P-glycoprotein
PID	pain intensity difference
PK	pharmacokinetic
QD	once daily
QID	4 times daily
QT	time from the beginning of the QRS complex to the end of the T wave in the electrocardiogram
QTc	QT interval, corrected for heart rate.
QTca	QT interval corrected for heart rate using analysis of covariance
QTc_B	QT interval calculated using Bazett's correction factor
QTc_F	QT interval calculated using Fridericia's correction factor
QTc_V	QT interval data analyzed using Vanderwater's method
RTU	ready-to-use
SAE	Serious adverse event
SAR	Serious adverse reaction
SC	subcutaneous
STD	severely toxic dose
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	apparent terminal half-life
Tdap	tetanus, diphtheria, and acellular pertussis vaccine
TID	3 times daily
TK	toxicokinetic

Abbreviations	Definition
T_{max}	time of occurrence of C_{max}
UDS	unscheduled DNA synthesis
USP	United States Pharmacopeia
V_{ss}	volume of distribution at steady state
Vz/F	volume of distribution derived from $t_{1/2}$, z
WHO	World Health Organization

2. SUMMARY

2.1. Background

Pfizer is developing an investigational vaccine to prevent disease caused by multiple serotypes of the encapsulated bacteria *Streptococcus agalactiae* (also known as group B streptococcus [GBS]). GBS causes serious, life-threatening disease and there is a significant unmet medical need for a vaccine to prevent GBS disease in infants who, because of the timing and rapidity of disease onset, are too young to be actively immunized against this disease. The vaccine, referred to as GBS 6-valent polysaccharide conjugate vaccine (GBS6, PF-06760805), is being developed for the prevention of GBS disease due to vaccine serotypes in infants by active immunization of pregnant women. Further background is presented in Section 3 of this Investigator's Brochure. Populations of adults (such as those at high risk for GBS disease), may also be considered for further development of GBS6.

2.2. Vaccine Component

GBS6 contains capsular polysaccharides (CPSs) of the 6 most common serotypes (Ia, Ib, II, III, IV, and V) responsible for the great majority of GBS disease worldwide;[1] see also Section 3 and Section 5.1). The CPSs are individually conjugated to the cross-reactive material 197 (CRM_{197}) carrier protein, a nontoxic variant of diphtheria toxin and the carrier protein in Prevnar 13®. [redacted] Pfizer assessed 6 different formulations of GBS6, 3 dose levels of GBS6 (5, 10, or 20 µg CPS/serotype conjugate/dose) with or without $AlPO_4$, 0.25 mg elemental aluminum per 0.5 mL dose), in the clinic to determine the optimal candidate. The GBS6 20 µg CPS/serotype conjugate/dose without $AlPO_4$ has been selected for future studies.

2.3. Nonclinical Studies

Nonclinical studies demonstrated a strong functional immune response in mice and rhesus macaques after vaccination with GBS polysaccharide conjugates. The GBS6 active vaccine components elicited anti-GBS polysaccharide antibodies that mediated opsonophagocytic killing activity and were transferred across the placenta of mice. Nonclinical proof of principle for maternal immunization was obtained in a mouse maternal antibody transfer and neonatal protection model, which demonstrated that active immunization of the dam prior to delivery, protected the pups from a lethal challenge dose of GBS bacteria administered shortly after birth (see Section 5.1).

Administration of IM injections (1 dose every 2 weeks) for a total of 3 doses of GBS6 or GBS6 with $AlPO_4$ to SD rats in a repeat-dose toxicity study was tolerated without evidence of systemic toxicity and resulted in a functional antibody response to each of the 6 serotypes in the vaccines (see Section 5.3). Microscopic inflammatory changes at the injection site and increased cellularity in germinal centers of the draining lymph node were consistent with those observed with administration of other vaccines or $AlPO_4$-containing vaccines. When 4 IM injections (2 doses prior to mating and 2 doses during gestation) of GBS6 or GBS6 with $AlPO_4$ were administered to female SD rats or NZW rabbits in fertility and developmental toxicity studies, maternal functional antibodies were present for the 6 serotypes in the 2 vaccines and there were no vaccine-related effects on fertility in the females or embryo/fetal or postnatal development their offspring. Given the lack of adverse findings in rats and

rabbits related to GBS6 or GBS6 with $AlPO_4$ administration, the nonclinical studies conducted support the proposed clinical studies for GBS6.[2]

2.4. Clinical Development of GBS6

2.4.1. Phase 1/2 First-in-Human Study (C1091001)

GBS6 was evaluated in a Phase 1/2 first-in-human (FIH) study in healthy nonpregnant women and men 18 to 49 years of age in the United States. GBS6 was safe and well -tolerated and elicited robust immune responses that persisted through 6 months after vaccination at all dose levels and formulations. No meaningful difference in the GBS serotype IgG immune response was observed between GBS6 doses or formulations. No safety risks were identified beyond reactogenicity through 6 months. The safety findings from this FIH study are similar to those of other investigational GBS vaccines and of other licensed vaccines recommended for use in pregnancy. Data from this study provided support for continuing evaluation of GBS6 in pregnant women and later phase trials.[3] The study design and safety and immunogenicity results are described in Section 6.2.1 and Section 6.2.2, respectively.

2.4.2. Phase 1/2 Study in Healthy Nonpregnant Women and Pregnant Women and their Infants (C1091002)

A Phase 1/2, randomized, placebo-controlled, observer-blinded study in healthy nonpregnant and pregnant women and their infants is ongoing. This study is evaluating the safety, tolerability, and immunogenicity of 3 different dose levels of GBS6 formulated with or without $AlPO_4$ administered in a single dose regimen to pregnant women 18 to 40 years of age. This study is being conducted in 3 stages, beginning with a small cohort of nonpregnant women (Stage 1) who received the highest tolerated dose in the first in human study formulated with and without $AlPO_4$ prior to initiation in pregnant women. Stage 1 booster subjects willing and eligible to participate returned to receive a booster dose of GBS6 approximately 2 years after the primary dose of investigational product. Stage 2 commenced following a review of safety and immunogenicity profile of GBS6 and evaluated the 3 ascending dose levels of GBS6 formulated with or without $AlPO_4$ in healthy pregnant women. Stage 2 used a sentinel-cohort design with cohort progression and dose escalation taking place after a safety review. The final GBS6 dose and formulation to take into Stage 3 and further development was selected after safety and immunogenicity review of Stage 2 data. An additional cohort of healthy pregnant women (Stage 3) will receive the selected GBS6 dose/formulation to provide an expanded safety and immunogenicity data set. This study is the first evaluation of GBS6 in pregnant women, the transfer of anticapsular antibody to their infant subjects, and the kinetics of antibody transfer in the infant subjects. [redacted] Data from this study will be used to progress the development of GBS6 into Phase 3. A planned interim analysis of Stage 2 data with a data cutoff of 9 July 2021 was conducted. Safety results from this interim analysis are provided in Section 6.2.1. The GBS6 20 µg/serotype dose without $AlPO_4$ has been selected for use in Stage 3 and in future licensure studies.

2.4.3. Phase 2, Open-Label Booster Vaccination Trial in Healthy Adults (C1091007)

A Phase 2, open-label trial, an extension to the FIH C1091001 study, evaluated the safety, tolerability, and immunogenicity of a single booster vaccine dose of GBS6 20µg with or without $AlPO_4$, administered approximately 2 years or more after a primary GBS6 dose, to healthy adult males and nonpregnant women. A single booster vaccination of GBS6 was safe, well tolerated, and elicited robust immune responses with both dose formulations. This study demonstrated that a booster vaccination of GBS6 may be of benefit for healthy adults after the primary series, including in those subjects with low antibody levels prior to the first dose. These data are important to inform GBS6 dosing strategies in pregnant women with subsequent pregnancies. The study design and safety and immunogenicity results are described in Section 6.2.1.

2.4.4. Phase 2b Study To Evaluate GBS6 Co-administered with Tdap in Healthy Nonpregnant Women (C1091005)

A Phase 2b, placebo-controlled, randomized, observer-blinded trial designed to evaluate the safety, tolerability, and immunogenicity of GBS6 when administered concomitantly with tetanus, diphtheria, and acellular pertussis vaccine (Tdap) in healthy nonpregnant women 18 through 49 years of age. Because Tdap vaccination is recommended for all pregnant women, C1091005 will evaluate the concomitant administration of GBS6 and Tdap to ensure there is no immune interference. FSFV was achieved on 12 August 2022 and 306 participants were randomized by the LSFV date of 12 October 2022. An interim analysis assessing 1 month post dose is planned for 24 MAR 2023 and the CSR is anticipated to be completed on 11 Sep 2023. Data from this study will be used to progress the development of GBS6 into Phase 3.

3. INTRODUCTION

3.1. Background

There is a long history of success in protecting pediatric and adult populations against diseases caused by encapsulated bacteria using vaccines that target the capsular polysaccharide and generate functional antibody.[4] Likewise, maternal immunization has been demonstrated to be a safe and highly effective method to prevent serious infectious diseases in young infants.[5,6] The use of GBS6 for maternal immunization has the potential to serve as a mechanism to ensure that protective antibody levels are circulating in the infant at the time of birth and protect them against GBS disease.[7,8] Pregnant women may also benefit directly from GBS6 for prevention of GBS peripartum disease.[9,10] Other populations, such as adults of advanced age or with particular risk factors may be considered for GBS6 evaluation in the future.

3.2. GBS Disease Epidemiology

3.2.1. GBS Disease

GBS is an encapsulated, gram-positive coccus that colonizes the lower intestinal and rectovaginal tract. There are 10 serotypes of GBS (Ia, Ib, II, III, IV, V, VI, VII, VIII, and IX), each differentiated by the chemical polysaccharide structure of its capsule. All GBS serotypes have been found to cause disease, but there is variability in their global prevalence and virulence.[11,12] In a review of global infant GBS disease, 5 serotypes (Ia, Ib, II, III, and V) accounted for >85% of disease in all regions with serotype data, causing 96% and 98% of disease in the Americas and Africa, respectively.[1] [13,14] Pfizer has independently confirmed that these 6 serotypes (Ia, Ib, II, III, IV and V) are largely responsible for at least 98% for GBS disease in infants and older adults(see Section 5.1).[15]

Disease due to GBS has been reported in individuals of all ages; however, it is most frequently found in infants younger than 3 months of age and the elderly, especially older adults with comorbid conditions.[1,16,17] Among infants, GBS may cause serious disease, including sepsis, meningitis, and pneumonia; less common manifestations include skin and soft tissue, bone, and joint infections.[18] Pregnant women are uniquely susceptible to GBS disease as well, with clinical manifestations including ascending infections ranging from relatively benign urinary tract infections to chorioamnionitis (which may result in stillbirth or preterm delivery) and puerperal sepsis (which can be fatal).[19,20] Bacteremia (with or without a focus), meningitis, cellulitis, bone and joint infections, pneumonia, and urinary tract infections are also disease manifestations of GBS infections in older nonpregnant adults.[16,21,22,23]

3.2.2. GBS Disease in Nonpregnant Adults

As adults age they are at increased risk for GBS disease, as are adults of all ages with certain comorbid conditions such as diabetes mellitus, malignancies, heart failure, renal disease, and neurologic conditions.[16,17,24] According to the Centers for Disease Control and Prevention (CDC) Active Bacterial Core surveillance (ABCs) system, the annual US incidence of invasive GBS in 2018 was 22.2 3 cases/100,000 in adults 65 to 74 years of age, 35.4/100,000 in adults 75 to 84 years of age, and 44.5/100,000 in adults ≥85 years of age.[25] GBS may cause invasive (bacteremia, bone and joint infections) or noninvasive (cellulitis,

nonbacteremic pneumonia, and urinary tract infections) disease. Because there are challenges in determining a specific bacterial etiology for noninvasive disease manifestations (eg, cellulitis), the burden of noninvasive GBS disease in nonpregnant adults is not well understood. However, given increases in the size of the population that is ≥65 years of age and/or with chronic conditions (eg, type II diabetes), the burden of invasive and noninvasive GBS disease in adults is expected to increase.[21,22,23]

3.2.3. GBS Disease in Infants

GBS is a leading cause of invasive bacterial infection in infants younger than 3 months and a significant global cause of infant morbidity and mortality.[1,26] Serious GBS disease, including sepsis, meningitis, and pneumonia, is associated with mortality rates of 6% to 14% in high-income countries (HICs) and 6.7% to 47% in various low- and middle-income countries (LMICs).[9,14,26,27,28] In surveillance conducted from 1998 to 2007 in the United States, GBS was found to be the most common cause of meningitis in children <2 months of age, the group at highest risk for bacterial meningitis.[29] In one study of children who survived GBS meningitis as infants, 44% of the children were found to have some level of neurologic sequelae. Severe sequelae, such as cognitive delay, cerebral palsy, blindness, and hearing loss, were found in 19% of the children.[30]

GBS disease in infants is often classified as early-onset disease (EOD), which occurs within the first week of life, and late-onset disease (LOD), with most infections occurring between Day 7 and Day 90 (and a median age of approximately 30 days in most studies).[1,12,31] Although there is overlap in clinical syndromes and serotype prevalence in EOD and LOD, there are some features that are more prominent in each. The most common clinical syndrome in EOD is sepsis/bacteremia without a focus (present in 83% to 97% of EOD cases in surveillance from the United States, United Kingdom, and South Africa), whereas LOD is more likely to be associated with a defined focus of infection.[17,27,31] Meningitis is more common in LOD, accounting for 21% to 59% of LOD cases.[17,27,31] Serotype III is relatively more prominent in LOD than are other serotypes.[17,27,31] Infants with suspected invasive GBS disease require a full clinical evaluation (eg, lumbar puncture, blood cultures) to assess the extent of involvement, guide treatment with intravenous antibiotics, and determine the appropriate level of hospital care. The course of GBS disease in infants can be severe, requiring intensive care treatment and cardiorespiratory support. Even with appropriate treatment, there is the potential for death or lifelong disability, making GBS disease a serious medical condition with an unmet medical need that impacts the infant, the family, the public health sector, and the community.

There are a number of factors that are known to increase the risk of EOD; these are generally related to the potential for vertical transmission of GBS from the mother to her newborn during the intrapartum period.[32] Risk factors for EOD include rectovaginal GBS colonization identified late in pregnancy and GBS bacteriuria, believed to be a marker for heavy colonization. Other factors that increase EOD risk include prolonged rupture of membranes prior to delivery, preterm delivery, young maternal age, and previous history of an infant with GBS disease.[32] The major reservoir for GBS carriage in women is the rectovaginal tract, and colonization rates among pregnant and nonpregnant women have been reported to be between 10% and 40% globally.[32,33,34,35,36] The risk of EOD in infants born to

a GBS-colonized mother is >25-fold higher than when the mother is not colonized, and data suggest that without intervention 1% to 2% of newborns born to colonized mothers will develop EOD.[32,37] Factors associated with LOD are less well defined, as the source of the infecting organism may include not only vertical transmission, but also horizontal transmission from other colonized contacts. In studies of LOD, a higher incidence can be found in infants who are black, or born prematurely, and these may represent risk factors.[17] Infants born to women infected with human immunodeficiency virus (HIV) have an increased risk of GBS disease both in high-income and low-income countries.[38,39] This increased susceptibility is believed to be due to low concentrations of naturally acquired maternal antibody to GBS capsule and reduced transplacental antibody transfer.[38]

The reported burden of infant GBS disease varies across regions, and may be influenced by host factors (such as HIV or malaria), by access to antenatal and pediatric health care, and by public health interventions to prevent GBS disease. Furthermore, in many parts of the world, the resources for an accurate microbiological diagnosis, and reporting of cases of GBS disease, are limited, resulting in significant underreporting of disease.[40] Rates are generally higher in resource-limited parts of the world, compared to countries with high gross national income. The global estimated incidence of infant GBS disease is 0.49 per 1000 live births, with the highest incidence in Africa (1.12 per 1000 live births), followed by Europe (0.53 per 1000 live births) and the Americas (0.52 per 1000 live births).[41, 42] In the United States, the incidence of GBS disease in infants decreased significantly since 1990, after intensive public health interventions were introduced (see Section 3.3). Despite these interventions, invasive GBS disease remains the most common cause of neonatal early-onset sepsis and a significant cause of late-onset sepsis among young infants in the United States.[43] In other HICs where maternal screening interventions are applied more selectively, infant GBS rates between 0.3 and 0.7 cases/1000 live births have been reported.[31,44] As of 2019, the most recent year for which complete (non-preliminary) data are publicly available, Active Bacterial Core surveillance (ABC) surveillance estimated that the rates of EOD and LOD in the US were 0.19 per 1,000 live births and 0.33 per 1,000 live births, respectively, for a combined incidence of 0.52 per 1,000 live births. These rates have remained relatively steady over the last 15 years.

Some of the highest rates of GBS disease and highest case fatality rates are found in infant populations in LMICs in regions such as Central America, the Caribbean, and Africa.[1,14,25,27,28,45] Surveillance conducted in South Africa in 3 secondary/tertiary hospitals in Johannesburg, from November 2012 to February 2014, found the rate of infant invasive GBS disease to be 2.38 cases/1000 live births.[27] The rates of GBS disease in other African nations have been estimated at 1.3/1000 live births (Gambia) and 1.8/1000 live births (Malawi).[46,47] The significance of the burden is compounded by the rates of long-term neurological sequelae that may be associated with GBS disease.[27]

Additionally, while an association between GBS colonization and stillbirths and other adverse obstetric outcomes has been described, the true burden of this association is unknown.[14,48,49,50] A recent review and meta- analysis of GBS-associated stillbirths found GBS to be an important potential cause of stillbirth however, the number of studies and the sample sizes were small. This review which evaluated studies conducted after 2000 concluded that 1% of stillbirths in HICs and 4% in Africa were associated with GBS.[51]

Understanding the full perinatal and infant burden of disease attributable to GBS is hampered by limitations in the capture of cases and by the lack of consistent definitions, particularly for early deaths and stillbirths, and often a diagnostic evaluation for a specific etiology is not done. This remains an area for further standardization and research.[48,52,53]

3.3. Current Strategies to Prevent Infant GBS Disease

Young infants are particularly vulnerable to the devastating consequences of GBS disease, even in the face of appropriate treatment; therefore, preventing infection would be the most effective approach to reducing disease and its associated sequelae. Studies conducted in the 1980s found that antibiotics administered during labor and delivery interrupted transmission of GBS from colonized mothers to their infants, thereby reducing EOD.[37,54] These data led to US guidelines for intrapartum antibiotic prophylaxis (IAP) and screening for GBS carriage during pregnancy, introduced in the late 1990s, expanded in 2002 and 2010, and further updated in 2019.[55] Current guidelines call for routine GBS screening during the 36th to 37th week of pregnancy and IAP for GBS-positive mothers, or in the presence of other significant risk factors (eg, amniotic rupture of membranes ≥18 hours).[55] It is notable that the number of cases of EOD in the United States has decreased from a high of 1.7 cases/1000 live births in the early 1990s to 0.19 cases/1000 live births in 2019. The incidence of LOD (0.33 cases/1000 live births in 2019) in the United States has not been reduced by these guidelines, as the route of GBS infection in infants with LOD is not directly related to exposure during the intrapartum period and may involve other factors.[32,56] Since the majority of cases of bacterial meningitis in children in the United States are associated with GBS, specifically LOD, the incidence of bacterial meningitis in young infants has remained relatively constant in the United States (65.2/100,000 children <2 months of age in 1998-2001 and 62.5/100,000 children <2 months of age in 2002-2007).[29] GBS disease in pregnant and postpartum women also has not been reduced through the introduction of IAP in the United States, as may be expected given the short course of administration during the intrapartum period only.

In other HICs, a risk-based approach to IAP has been implemented in the absence of universal screening, out of concerns regarding overuse of antibiotics and program costs. The risk-based approach was less effective in preventing EOD than the screening approach by as much as 50%, as seen in one study.[57] In fact, some of the countries using the risk-based approach, such as the United Kingdom and the Netherlands, have experienced a trend of increasing infant GBS disease rates in recent years.[31,44]

While there has been some success in the United States with the current approach, it places a significant burden on the health care system. Individuals may not present for screening, their results may not be available when they present in labor, or the test result may be falsely negative (possible reasons include a sampling error or acquisition of carriage between screening and labor). In one study, 61% of women with full-term infants who developed GBS EOD had negative screening results late in pregnancy.[58] As noted above, risk-based IAP approaches are less effective than IAP combined with universal screening.[57] Neither risk-based applications of IAP nor universal GBS screening combined with IAP is completely effective in preventing EOD. IAP is intrusive (involving placement of intravenous access), challenging to implement under certain circumstances (eg, precipitous delivery) and, as noted above, is ineffective in preventing LOD. Moreover, IAP results in

unnecessary exposure to antibiotics, promotes the development of antimicrobial resistance, and disrupts the maternal and infant microbiome with potential long-term consequences.[32,59] Importantly, many countries around the world do not have the means, or infrastructure, to implement IAP at all.

3.4. Rationale for Development of GBS6 and Maternal Immunization to Prevent GBS

3.4.1. Rationale for a Vaccine Approach to Prevent GBS Disease

A vaccine offers a feasible and sustainable approach to prevent GBS disease in infants for countries with limited resources, and an added benefit above current GBS prevention strategies in high-resource countries.[7,8,60] It has the potential to prevent both EOD and LOD, and is not dependent on administration of IAP or antenatal GBS screening.

The concept that antibody to CPS of GBS can protect against infant GBS disease, supporting a vaccine approach to prevention, comes from data generated in the late 1970s. Researchers observed that immunoglobulin G (IgG) antibody directed against the GBS serotype III CPS was present in a proportion of US women.[61] This antibody was measured in sera collected at delivery from pregnant women colonized with GBS serotype III whose infants went on to develop EOD due to serotype III GBS, and in sera from GBS serotype III–colonized pregnant women whose infants did not develop EOD (case controls).[61] A correlation was found between low maternal IgG antibody concentration to the serotype III CPS and infant susceptibility to EOD due to serotype III. This suggested that this antibody can be transferred across the placenta and protect the infant against serotype-specific GBS disease.[61] Subsequently, the correlation between maternal serotype III IgG and a lower risk of serotype III GBS EOD was confirmed in another US study, and in studies conducted in Europe and South Africa.[62,63,64,65] A correlation between maternal serotype Ia anticapsular IgG and lower rates of EOD due to serotype Ia GBS has also been demonstrated in US, European, and South African studies.[62,64,65,66] A similar trend with serotype V IgG has also been reported.[62]

The amount of IgG antibody that has been postulated as protective ranges from 0.5 to 10 μg/mL among the various populations, serotypes, study methods, and assays used to measure antibody. The protective level is likely to be dependent on the associated functional opsonophagocytic activity (OPA) of the antibody, since the mechanism of clearance of GBS from the host is anticipated to be through opsonophagocytosis, similar to removal of *Streptococcus pneumoniae.*[67] This also plays a role in preventing acquisition of GBS carriage.[68]

There is a long history of success in protecting infants and adults against diseases caused by encapsulated bacteria using capsular polysaccharide conjugate vaccines.[4] Polysaccharide conjugate vaccines induce T-cell–dependent antibody responses targeting the CPSs. A number of polysaccharide conjugate vaccines have been developed and licensed by Pfizer (HibTITER®, Prevnar®, Prevnar 13), and other manufacturers (eg, ActHIB, PedvaxHIB, Menveo, Hiberix). These vaccines have been recommended for use in pediatric and/or adult immunization programs in many countries around the world. They have a generally favorable safety profile and induce protective antibody demonstrated in prelicensure efficacy studies and/or through established immune correlates of protection with postlicensure demonstration of effectiveness.[4,69,70]

Active immunization of infants to prevent infant GBS disease, even with a polysaccharide conjugate vaccine, is not an appropriate strategy in the case of GBS disease. This is because the time of highest risk is very early in life, and transmission may occur prior to delivery, with rapid development of disease (often EOD develops within 12-24 hours after delivery).[17,60,71] However, maternal immunization could serve as a mechanism to help ensure that protective antibody levels are circulating in the infant at the time of birth.[7,60,71] During the third trimester of pregnancy, IgG is actively transported across the placenta and provides a means for protective antibody to be transferred from a mother to her newborn.[72,73] The efficiency of antibody transfer depends on placental integrity, maternal total IgG level, gestational age at delivery, and IgG subclass.[74] Polysaccharide conjugate vaccines are ideally suited for maternal immunization, because a single vaccination in adults typically elicits robust and relatively rapid IgG responses with functional activity directed against CPS vaccine serotypes. Transfer of this antibody across the placenta will be expected to provide protection against disease due to the GBS serotypes in infants of vaccinated mothers. Clinical data from other investigational GBS polysaccharide conjugate vaccines (see Section 3.5) and Pfizer's nonclinical data (see Section 5.1) provide support that GBS6 has the potential for use in maternal immunization to prevent infant GBS disease.

In addition to disease prevention through placenta transfer of antibody to the infant, immunization of pregnant women may also provide a direct benefit against peripartum or postpartum GBS infections.[10,19] Other adult populations at higher risk of GBS disease may benefit from vaccination with GBS6 to elicit opsonophagocytic antibody, based on experience with other polysaccharide conjugate vaccines, such as Prevnar 13. However, there is less known about protective levels of antibody in these adult populations.

3.4.2. Maternal Immunization

The use of maternal immunization to prevent disease in infants born to vaccinated mothers is not a new concept.[5] In many parts of the world, tetanus toxoid vaccine has been used for a number of years to immunize pregnant women, inducing antibodies that cross the placenta and prevent neonatal tetanus.[5,75]

Immunization of pregnant women with influenza vaccine is recommended in the United States and elsewhere.[76,77] These recommendations are primarily designed to prevent disease in the mother, but evidence suggests that this approach may also mitigate the rate, severity, and other negative impacts of influenza disease in her infant.[78,79] The current US recommendations for influenza vaccine in pregnant women (at any time in their pregnancy based on the appropriate season) were issued by the US Advisory Committee on Immunization Practices (ACIP) in 2004.[77,80] Rates of maternal influenza immunization have increased since 2009, with increased public awareness of serious complications of influenza H1N1 in previously healthy pregnant women. Safety surveillance conducted to date has demonstrated no unusual patterns of pregnancy complications or fetal outcomes.[6,78,81]

More recently, maternal immunization with pertussis-containing vaccines (tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine [Tdap]) has been implemented to help prevent pertussis in infants too young to be eligible for active immunization.[82,83] In 2012, the ACIP recommended the use of Tdap in pregnant women in the United States between 27 and 36 weeks' gestation; this was further updated with a recommendation for use of Tdap with

each pregnancy.[84,85] This recommendation has had increasing adoption, and one recent study found that among insured women from 6 states who had live births in 2013 in the United States, 41.7% had received Tdap.[86] The United Kingdom and other European countries have also implemented maternal immunization recommendations for Tdap. To date, these vaccines have demonstrated an acceptable safety profile with single and repeat dosing.[86,87,88,89,90] In 2013, approximately 60% of pregnant women in the United Kingdom had received Tdap; no pertussis cases were observed in infants whose mothers were vaccinated during pregnancy, and the overall rates in infants have declined.[83,91]

There is increasing appreciation for maternal immunization as a useful tool to help address the global burden of infant morbidity and mortality. With success of currently marketed vaccines for maternal immunization to prevent influenza and pertussis, acceptance of this approach to prevent disease in infants and pregnant women is likely to grow. Maternal immunization therefore represents a promising approach to prevention of GBS disease in young infants and one that can be practically implemented in regions with the highest burden.[10,92]

3.5. Prior Clinical Experience With Investigational GBS Polysaccharide Conjugate Vaccines

3.5.1. Investigational GBS Polysaccharide Conjugate Vaccines

There is extensive clinical experience with different investigational GBS polysaccharide and polysaccharide conjugate vaccines using either tetanus toxoid or CRM_{197} protein carriers, in studies conducted over the past 30 years. This experience includes studies in men, nonpregnant women, and pregnant women, with demonstration of an acceptable safety profile and antibody responses that cross the placenta. In total, data are available from investigational GBS conjugate vaccine studies involving ≥2000 subjects.[8,60] This includes >600 nonpregnant women and >500 pregnant women subjects in studies of an investigational GBS CRM_{197} conjugate vaccine.[60] These investigational vaccines were found to be immunogenic and well tolerated with no safety concerns, providing a reassuring background for the clinical development of GBS6. Additionally, insights gained from these programs will be applied to the GBS6 program as appropriate.[60,93]

3.5.2. Clinical Experience With Investigational GBS Polysaccharide and Polysaccharide Conjugate Vaccines

Based on studies finding correlation between anticapsular antibody and lower relative risk of infant GBS disease (described above), vaccines containing GBS CPS were developed to elicit protective serotype-specific immune responses. These vaccines were evaluated in healthy adults and in a study of pregnant women in the 1970s and 1980s. Results from clinical studies with investigational vaccines containing unconjugated GBS polysaccharides demonstrated suboptimal response rates and were not pursued further.[94,95]

Conjugate technology to generate a T-cell–dependent immune response was then applied to create a vaccine containing serotype III CPS conjugated to the immunogenic tetanus toxoid protein in order to induce more robust antibody response. The serotype III CPS conjugate vaccine at different doses was evaluated in a single dose regimen in the clinic in nonpregnant women 18 to 40 years of age. The group receiving the conjugate vaccine had higher levels of

serotype III antibody within 2 weeks after vaccination than the same dose of unconjugated vaccine, and a higher proportion of subjects with 4-fold rises in antibody were also observed with the conjugate vaccine.[96] Investigational GBS monovalent and bivalent vaccines composed of CPS of serotypes Ia, Ib, II, III, or V conjugated to tetanus toxoid were also developed (dose levels of 2.4 to 63 µg CPS/serotype) and studied in nonpregnant healthy volunteers. The GBS conjugate vaccines were generally safe and well tolerated, and elicited IgG and OPA responses that peaked in the 2 to 8 weeks after vaccination and declined over time, remaining above baseline after 2 years.[8,96,97,98,99,100,101]

The GBS serotype III CPS tetanus toxoid conjugate vaccine was further evaluated in a study of 30 pregnant women.[102] Following vaccination at 30 to 32 weeks' gestation, levels of serotype III IgG were elevated in the cord blood of vaccine recipients (n = 20) compared to controls (n = 10).[102] Serotype III IgG and OPA responses were demonstrated in the infants at 2 months of age. The vaccine was well tolerated and no safety concerns were identified in the pregnant women or their infants.

More recently, another investigational GBS polysaccharide conjugate vaccine has been developed (Novartis, transferred to GlaxoSmithKline [GSK]), and evaluated in a series of Phase 1 and Phase 2 clinical trials in nonpregnant and pregnant women. The investigational trivalent GBS vaccine contained serotype Ia, Ib, and III CPSs conjugated to the CRM_{197} protein.[103]

A Phase 1b study was conducted in 678 nonpregnant women in Belgium to assess the safety and IgG responses of various formulations of the investigational trivalent GBS vaccine given as a single dose or 2 doses separated by a 1-month interval. The formulations varied by dose level (5 and 20 µg CPS/serotype conjugate/dose) and by inclusion of aluminum hydroxide or MF59 adjuvant.[103] No safety concerns were identified and the investigational trivalent GBS vaccines elicited IgG responses to the vaccine serotypes. There was no clear difference in IgG responses with the various adjuvants or doses of CPS/serotype in the vaccine formulations in this study.

In a subsequent Phase 1b/2 study in South Africa, a cohort of 60 nonpregnant women were enrolled to receive a 2-dose series of the trivalent GBS vaccine containing aluminum hydroxide at the 20-µg CPS/serotype/dose level or placebo (2:1 randomization).[104] This was followed by enrollment of a cohort of 320 pregnant women who received a single-dose regimen of vaccine containing no aluminum hydroxide at dose levels of 5, 2.5, and 0.5 µg CPS/serotype/dose or saline placebo (1:1:1:1) at 28 to 35 weeks' gestation.[104] The vaccine elicited IgG to the vaccine serotypes in the vaccine recipients. The nonpregnant women vaccinated with a 2-dose series of the aluminum-containing 20-µg CPS/serotype conjugate dose formulation had higher IgG geometric mean concentrations (GMCs) 1 month after vaccination compared to the pregnant women receiving the 5-µg CPS/serotype conjugate/dose formulation without aluminum. As this seems somewhat inconsistent with the finding in the Phase 1b study, it is considered important to evaluate doses ≥5 µg CPS/serotype and inclusion of aluminum in both nonpregnant and pregnant women.

Safety and immunogenicity data are available from 2 other studies conducted with the investigational trivalent GBS vaccine in pregnant women, one in Belgium and Canada and

the other in South Africa and Malawi.[105,106] The study in South Africa and Malawi included pregnant women with and without HIV infection.[106] A single vaccination (5 µg of CPS/serotype conjugate dose without aluminum hydroxide) was administered between the 24th and 35th weeks of pregnancy in the studies. An additional study of 75 pregnant women in the United States and follow-up revaccination studies have been/are being conducted, but data have not yet been presented (NCT02628886).

The investigational trivalent GBS vaccine demonstrated an acceptable safety profile in the 3 studies in pregnant women, with reported serious adverse events consistent with events that might be observed in pregnant women and young infants.[104,105,106] The investigational trivalent GBS conjugate vaccine was immunogenic for all 3 vaccine serotypes, and antibody was transferred across the placenta to the infants of pregnant vaccine recipients. The HIV-infected women and their infants had lower antibody responses to the vaccine serotypes than HIV-uninfected women.[106] Antibody levels waned in infants over the first 3 months of life. as would be expected with decay of maternal antibody.[104,106] Two of the studies included an assessment of vaccine responses in the infants after they received their diphtheria vaccine, and one after the pneumococcal conjugate vaccine series; no interference in infant responses to the vaccines was reported.[104,105]

3.6. Summary

GBS6 has been developed to prevent GBS disease in young infants by active immunization of pregnant women. GBS6 contains the six most prevalent CPS serotypes (Ia, Ib, II, III, IV and V), accounting for ~98% of disease-causing isolates globally.[2] It is based on the well-established platform of vaccines composed of CPSs conjugated to the CRM_{197} protein that target the polysaccharide capsules of encapsulated bacteria. GBS6 offers benefits beyond the currently existing approaches to prevent infant GBS disease, with greater feasibility of implementation in LMICs, and the potential to expand protection against disease (such as LOD). Based on Pfizer's nonclinical data with GBS6 conjugates, and previous clinical experience with other investigational GBS polysaccharide conjugate vaccines, GBS6 is expected to induce protective IgG and functional immune responses to serotypes causing the great majority of GBS disease in infants globally. The use of GBS6 for maternal immunization with placental antibody transfer serves as a mechanism to ensure that protective antibody levels are circulating in the infant at the time of birth to protect him or her against GBS disease for the period of highest risk. The vaccine may also prevent maternal GBS colonization, that is a known risk factor invasive GBS disease in newborns, and could thus potentially impact transmission both prior to delivery and after the baby is born. Pregnant women may also benefit directly from GBS6 for prevention of GBS peripartum disease. Other populations such as adults of advanced age or with particular risk factors may be considered for GBS6 evaluation in the future.

4. PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

5. NON-CLINICAL STUDIES

5.1. Nonclinical Pharmacology

GBS6 is composed of GBS CPSs corresponding to each of six serotypes (Ia, Ib, II, III, IV, and V) individually conjugated to CRM_{197} using optimized conjugation conditions.

GBS produce capsular polysaccharides that shield it from the host immune response and allow the pathogen to establish invasive infections.[107] Specifically, the terminal sialic acid moiety prevents C3 deposition in the absence of type-specific antibody and thus abrogates activation of the alternative complement pathway.[108,109]

In the presence of CPS antibodies, opsonophagocytosis is the primary mechanism of clearing GBS from the host[110,111] and GBS6 exploits this weakness by raising a protective immune response against capsular polysaccharides of the prevalent serotypes. This approach is precedented by effective licensure of capsular polysaccharide conjugate vaccines against *Streptococcus pneumoniae*, *Haemophilus influenzae,* and *Neisseria meningitidis* serogroups A, C, W, and Y.

A number of publications, as well as a comprehensive meta-analysis of GBS disease surveillance publications, predict that polysaccharide conjugates of the six most prevalent GBS serotypes (Ia, Ib, II, III, IV, and V) would provide coverage for >98% of neonatal disease globally.[112] A recent analysis by Pfizer of global isolates obtained from infant invasive disease cases (<1 year of age) confirmed this, showing that at least 98% of the total isolates could be typed to one of the six documented major types.[113,114,115,116,117,118] GBS6 is therefore expected to protect against more than 98% of cases of infant GBS disease.

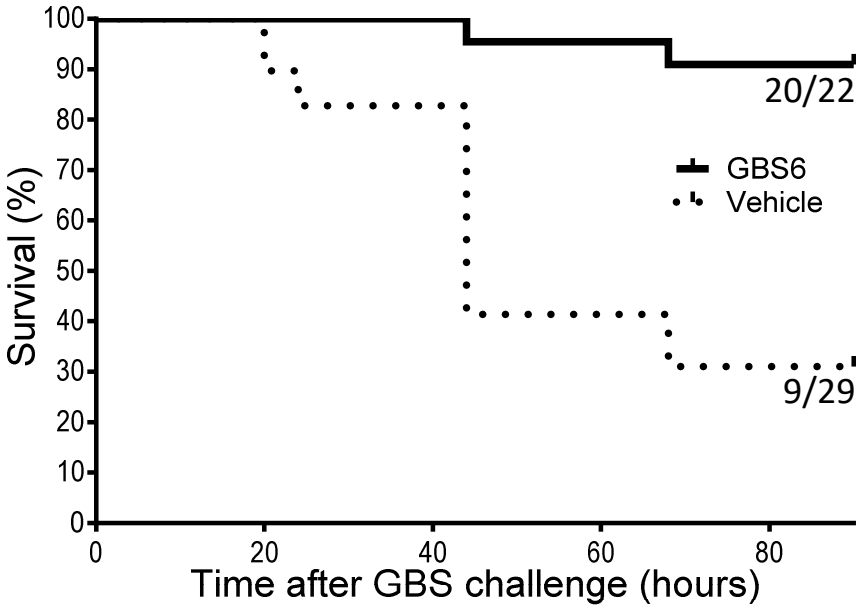
The functional antibodies elicited by the GBS6 may provide several levels of protection: they could potentially prevent the mother from becoming colonized with GBS prior to delivery,[68] protect the mother from GBS infection, [119] and be transferred to the growing fetus, starting in the second and peaking in the third trimester of pregnancy. This placental transfer is the primary mechanism for protection of the fetus or infant from GBS infection and disease. The process of in utero antibody transfer is an active transport of IgG antibodies. The IgG1 antibody subclass is most efficiently transferred followed by IgG4, IgG3, and IgG2.[72] IgM, IgA, and IgE are not transferred. Whereas serum levels of IgE and IgA are generally low, serum IgM concentrations can be significant and can contribute to the killing activity measured in OPA assays.

Therefore, the immune responses observed in mice and nonhuman primates were quantified using a hexaplex direct Luminex immunoassays (dLIA) and six different OPA assays. The OPA assays with six clinical strains, representing the six GBS serotypes in GBS6, measure functional antibodies, while the dLIA measure polysaccharide-specific IgG or IgM binding antibody levels. The Luminex antibody assays used in the GBS6 clinical studies have been calibrated with human reference serum standards derived from GBS6 vaccinees .

Pfizer developed a murine model to demonstrate that the CPS antibodies elicited by GBS6 can confer protection to the offspring born from vaccinated mice.[120] In this model, female mice that have not been pre-exposed to GBS, and thus require several vaccine doses, were

immunized with vehicle control, monovalent CPS conjugate vaccine (10 µg/dose) or GBS6 (5 µg/dose for each conjugate) at Week 0 and 3. During Week 5 the animals were mated and the last immunization occurred at Week 6, i.e. approximately Day 3 of the 21-day pregnancy. Administration of either the monovalent vaccines or GBS6 conferred significant protection of the pups against a lethal dose of the corresponding GBS serotypes 24-48 hours after birth, demonstrating development of a functional bacterial-killing immune response in the mother followed by sufficient maternal antibody transfer to achieve protective levels at birth in the offspring (Figure 1).

Figure 1. Protection of Neonatal Mice against GBS Infection by Active Immunization of Dams



Survival of pups after a challenge at time 0 with a lethal dose of $1.0x10^5$ Colony Forming Units of serotype III GBS. Dams were immunized prior to and during pregnancy with either phosphate-buffered saline (dotted line), or 5 µg GBS6 (straight line), each with $AlPO_4$. Ratios indicate actual number of pups surviving after 96 hours and the number of challenged pups. Similar protection was obtained upon immunization against other GBS serotypes contained in GBS6.

5.1.1. Secondary Pharmacodynamics

Secondary pharmacodynamic studies were not conducted and are generally not considered necessary to support the development and licensure of vaccines for infectious disease.[121,122]

5.1.2. Safety Pharmacology

Safety pharmacology studies were not conducted and are generally not considered necessary to support the development and licensure of vaccines for infectious disease.[121,122]

5.1.3. Pharmacodynamic Drug Interactions

Nonclinical studies evaluating pharmacodynamic drug interactions were not conducted and are generally not needed for vaccines for infectious disease.[121,122]

5.2. Pharmacokinetics and Product Metabolism in Animals

Pharmacokinetic studies have not been conducted for candidate GBS6 formulations. Such studies are not considered necessary for vaccine products (World Health Organization)[121,122].

5.3. Toxicology

5.3.1. Brief Summary

The nonclinical toxicity studies conducted for the GBS6 (PF-06760805) program included a [redacted] GLP-compliant fertility and developmental toxicity studies in rats and rabbits as outlined in Table 1.

[redacted] When GBS6 or GBS6 with $AlPO_4$ were administered to female SD rats or NZW rabbits in fertility and developmental toxicity studies, there were no vaccine-related effects on fertility in the females or embryo/fetal or postnatal development their offspring. Functional antibody response to each of the 6 serotypes in the vaccines occurred in each of these studies.

[redacted] In the fertility and developmental toxicity studies, the administration of 2 doses prior to mating and 2 doses during gestation ensured exposure of the female to the vaccine and antigen-specific antibodies throughout the gestation and lactation periods, and the fetus/offspring to maternal antibodies.[123]

The IM route of exposure was selected for these studies since it is the intended route of clinical administration. The use of rats and rabbits as test species is consistent with the WHO guidances on nonclinical evaluation of vaccines and vaccine adjuvants,[121,122] which recommend that vaccine toxicity studies be conducted in a species that exhibits an immune response to the vaccine antigens. Rats and rabbits showed a functional antibody response to the 6 polysaccharide serotypes in GBS6 in the absence or presence of $AlPO_4$. In addition, rats and rabbits are known to be sensitive to developmental toxicants, and historical data and experience exist at the Test Facilities used to conduct these studies.

Twenty (20) µg polysaccharide for each polysaccharide serotype conjugate (120 µg total polysaccharide) in 0.5 mL is the highest dose that is planned to be evaluated in the clinic; rats received this dose as two 0.25 mL IM injections on each dosing day. This dose volume is consistent with the volume that has been used to evaluate the toxicity of other marketed vaccines in rats.[124] Rabbits received this dose as one 0.5 mL IM injection on each dosing day.

As candidate GBS6 formulations with and without $AlPO_4$ will be evaluated in the clinic, the repeat-dose toxicity study in rats and the fertility and developmental toxicity studies in rats

and rabbits evaluated GBS6 formulations at the highest planned clinical dose of each antigen with and without $AlPO_4$.

Table 1. Overview of Toxicity Testing Program[a]

Study	Study Number/ GLP Compliance	Test Article	Dose[b] (µg)	Total Volume (mL)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reproductive and Developmental Toxicity				
Nonpivotal Studies				
Investigational Fertility and Early Embryonic Development Study of PF-06877053 by IM Injection in Female SD Rats (3 doses)	20123898/ No	Saline Control	0	0.5 (2 x 0.25 mL)[g]
		GBS6 with $AlPO_4$[c,d,e]	20	0.5 (2 x 0.25 mL)[g]
		GBS6 with $AlPO_4$[c,d,e]	20	0.5 (2 x 0.25 mL)[g]
		GBS6 with $AlPO_4$[c,d,e]	20	0.5 (2 x 0.25 mL)[g]
Preliminary Fertility and Early Embryonic Development Study of PF-06877053 by IM Injection in Female NZW Rabbits (3 doses)	AB21917/ No	Saline Control	0	0.5[h]
		GBS6 with $AlPO_4$[c,d,e]	20	0.5[h]
Pivotal Studies				
Combined Fertility and Developmental Study of PF-06877054 and PF-06877053 by IM Injection in Female SD Rats (4 doses)	20125238/ Yes	Saline Control	0	0.5 (2 x 0.25 mL)[i]
		Vehicle Control[c,d]	0	0.5 (2 x 0.25 mL)[i]
		GBS6[c,e]	20	0.5 (2 x 0.25 mL)[i]
		GBS6 with $AlPO_4$[c,d,e]	20	0.5 (2 x 0.25 mL)[i]
Combined Fertility and Developmental Study of PF-06877054 and PF-06877053 by IM Injection in Female NZW Rabbits (4 doses)	AB21918/ Yes	Saline Control	0	0.5[j]
		Vehicle Control[c,d]	0	0.5[j]
		GBS6[c,e]	20	0.5[j]
		GBS6 with $AlPO_4$[c,d,e]	20	0.5[j]

Table 1. Overview of Toxicity Testing Program[a]

Study	Study Number/ GLP Compliance	Test Article	Dose[b] (μg)	Total Volume (mL)

.

a. GLP-compliant studies were conducted in an OECD mutual acceptance of data (MAD) compliant member state.
b. Amount of each CPS/0.5 mL, each individually conjugated to CRM_{197}.
c. The final amount of aluminum in the formulation was 0.5 mg/mL as $AlPO_4$.
d. Contained 20 μg (0.5 mL of 40 μg CPS/mL) of each of the capsular polysaccharide serotypes Ia, Ib, II, III, IV, and V, with each individually conjugated to CRM_{197}.
e. Animals received two 0.25 mL injections (0.25 mL in each quadriceps muscle) for a total dose volume of 0.5 mL on each dosing day (Days 1, 15, and 29).
[redacted]
g. Animals received one 0.5 mL injection (alternating quadriceps muscles) on each dosing day (35 and 21 days prior to mating and Gestation Day 10).
h. Animals received two 0.25 mL injections (0.25 mL in each quadriceps muscle) for a total dose volume of 0.5 mL on each dosing day (21 and 8 days prior to mating and Gestation Days 6 and 20).
j. Animals received one 0.5 mL (alternating quadriceps muscles) injection on each dosing day (35 and 21 days prior to mating and Gestation Days 10 and 24).

5.3.2. Single-Dose Toxicity

Single-dose toxicity studies with candidate GBS6 formulations have not been conducted.

5.3.3. [redacted]

5.3.4. Genotoxicity

Genotoxicity studies with candidate GBS6 formulations have not been conducted. Genotoxicity testing is generally not considered necessary to support the development and licensure of vaccines for infectious disease.[121,122]

5.3.5. Carcinogenicity

Carcinogenicity studies with candidate GBS6 formulations have not been conducted. Carcinogenicity testing is generally not considered necessary to support the development and licensure of vaccines for infectious disease.[121,122]

5.3.6. Reproductive and Developmental Toxicity

The reproductive and developmental toxicity of GBS6 formulations with and without $AlPO_4$ were evaluated in rats and rabbits in fertility and developmental toxicity studies. Preliminary studies in both species were conducted to confirm a dosing regimen that would be suitable for the definitive studies. After a suitable dosing regimen was identified, definitive GLP-compliant fertility and developmental toxicity studies in rats and rabbits were conducted.

5.3.6.1. An Investigational Fertility and Early Embryonic Development Study of PF-06877053 by Intramuscular Injection in Female Rats (20123898)

GBS6 with $AlPO_4$ was administered by 2 IM injections (0.25 mL in each quadriceps muscle; total of 0.5 mL/dosing day) to nulliparous female SD rats (22/group) at the highest dose of antigens being assessed in the clinic (20 µg CPS/serotype conjugate/dose) for a total of 3 doses using one of the following 3 schedules to evaluate potential effects on fertility and early embryonic development: 1) 21 and 8 days prior to cohabitation with untreated males and on GD 6; 2) 35 and 21 days prior to cohabitation with untreated males and on GD 6; or 3) 35 and 21 days prior to cohabitation with untreated males and on GD 10. A concurrent saline control group (22 females) was administered 0.9% sterile saline 35, 21, and 8 days prior to cohabitation with untreated males and on GD 6, for a total of 4 doses. Females were followed through mid-gestation and C-sections were performed on GD 14.

Regardless of the dosing regimen, there were no GBS6 with $AlPO_4$-related effects on body weight, body weight gain, or food consumption before mating or during the gestation phase. There were no GBS6 with $AlPO_4$-related effects on any estrous cycling or mating or fertility parameters. At the GD 14 C-sections, there were no GBS6 with $AlPO_4$-related effects on any ovarian, uterine, or litter parameters; all values were within the historical range of the Test Facility.

In conclusion, GBS6 with $AlPO_4$ administered twice before the start of mating (35 and 21 or 21 and 8 days prior to cohabitation) and once during gestation (GD 6 or 10) at the highest anticipated clinical dose, 20 µg CPS/serotype conjugate/dose, did not result in any maternal toxicity nor any effects on estrous cycling, mating or fertility, or any ovarian and uterine parameter in the F_0 female rats or in early embryonic development or survival in the F_1 offspring.

5.3.6.2. A Combined Fertility and Developmental Study of PF-06877054 and PF-06877053 by Intramuscular Injection in Female Rats (20125238)

GBS6 formulations, with and without $AlPO_4$, were administered by 2 IM injections (0.25 mL in each quadriceps muscle; total of 0.5 mL/dosing day) to nulliparous female SD rats (49/group) at the highest dose of antigens being assessed in the clinic (20 µg CPS/serotype conjugate/dose) for a total of 4 doses (21 and 8 days prior to mating with untreated males and on GDs 6 and 20) to assess potential toxicity of the vaccine on fertility and pre- and postnatal development. 0.9% sterile saline and the vehicle control article were administered to concurrent groups of 49 females/group using the same dosing regimen.

There were no GBS6- or GBS6 with $AlPO_4$-related deaths. All F_0 female rats survived to scheduled euthanasia, with the exception of one vehicle control-dosed F_0 female found dead on GD 25 with 15 conceptuses in utero whose death was attributed to dystocia, one GBS6dosed F_0 female found dead on Day 9 postpartum with no adverse clinical signs, and one GBS6 with $AlPO_4$-dosed F_0 female euthanized on Day 4 postpartum after exhibiting adverse clinical signs. None of these deaths were considered vehicle or test article related as they were single occurrences in each group. There were no GBS6- or GBS6 with $AlPO_4$related clinical observations or effects on body weight, body weight gain, or food consumption before mating or during the gestation phase in the F_0 females. There were no GBS6- or GBS6 with $AlPO_4$-related effects on any estrous cycling or mating or fertility parameters.

There were no GBS6- or GBS6 with $AlPO_4$-related effects on any ovarian, uterine, or litter parameters, including embryo-fetal survival, fetal body weights or external, visceral, or skeletal malformations or variations. There also were no effects of GBS6 or GBS6 with $AlPO_4$ administration on postnatal F_1 offspring development, including postnatal growth, effects on acoustic (auditory) startle or pupil constriction, or survival.

Administration of GBS6 or GBS6 with $AlPO_4$ to F_0 females resulted in the presence of functional antibodies to each of the 6 serotypes in each vaccine. Functional antibodies to one or more of the 6 serotypes were also present in some of the offspring (fetuses and/or pups) of F_0 females administered GBS6 or GBS6 with $AlPO_4$.

In conclusion, administration of GBS6 or GBS6 with $AlPO_4$ to female rats twice before the start of mating (21 and 8 days prior to cohabitation) and twice during gestation (GDs 6 and 20) at the highest anticipated clinical dose, 20 µg CPS/serotype conjugate/dose, did not result in any maternal toxicity nor any effects on estrous cycling, mating or fertility, or any ovarian or uterine parameters in the F_0 female rats or in development or survival in the F_1 offspring.

5.3.6.3. A Preliminary Fertility and Early Embryonic Development Study of PF-06877053 by Intramuscular Administration in Female Rabbits (AB21917)

GBS6 with $AlPO_4$ was administered by IM injection (0.5 mL in alternating quadriceps/dosing day) to nulliparous female NZW rabbits (15 /group) at the highest dose of antigens being assessed in the clinic (20 µg CPS/serotype conjugate/dose) 35 and 21 days prior to mating with untreated males, and on GD 10, for a total of 3 doses, to evaluate potential effects on fertility and early embryonic development. A concurrent control group

(15 females) received 0.9% saline using the same dosing regimen. Females were followed through mid-gestation and C-sections were performed on GD 14.

All F_0 female rabbits survived to scheduled euthanasia. There were no GBS6 with $AlPO_4$-related clinical signs or effects on body weight gain or food consumption. Similarly, there were no GBS6 with $AlPO_4$-related effects on mating performance, fertility, or early embryonic development.

In conclusion, GBS6 with $AlPO_4$ administered twice before the start of mating (35 and 21 days prior to mating) and once during gestation (GD 10) at the highest anticipated clinical dose, 20 μg CPS/serotype conjugate/dose, did not result in any effects on mating, fertility, or any ovarian or uterine parameters in the F_0 females, or early embryonic development or fetal survival.

5.3.6.4. A Combined Fertility and Developmental Study (Including Teratogenicity and Postnatal Investigations) of PF-06877054 and PF-06877053 by Intramuscular Administration in the Rabbit (AB21918)

GBS6 formulations, with and without $AlPO_4$, were administered by IM injection (0.5 mL/dosing day in alternating quadriceps) to nulliparous female NZW rabbits (44/group) at the highest dose of antigens being assessed in the clinic (20 μg CPS/serotype conjugate/dose) 35 and 21 days prior to mating with untreated males and on GDs 10 and 24, for a total of 4 doses, to assess potential toxicity of the vaccines on fertility and pre- and postnatal development in female rabbits. Concurrent saline control and vehicle control (containing $AlPO_4$) groups (44 females) were dosed using the same dosing regimen. This study consisted of two phases, a C-section phase, and a littering phase (22 females/group/phase). All F_0 female rabbits survived to scheduled euthanasia, except for two animals. A saline control female was euthanized along with her litter of 9 pups on Day 16 postpartum after being found in moribund condition. The cause of the moribund condition was not established. A GBS6 with $AlPO_4$-dosed female was euthanized on Day 0 postpartum with complete litter loss (14 stillborn kits). The GBS6 with $AlPO_4$-dosed female showed clinical signs as well as decreased food consumption and body weight loss during the last 3 days of gestation. This death was considered incidental as it was a single occurrence in this group. There were no GBS6- or GBS6 with $AlPO_4$-related clinical observations or effects on body weight, body weight gain, or food consumption before mating or during the gestation phase in the F_0 females. There also were no GBS6- or GBS6 with $AlPO_4$-related effects on any mating or fertility parameters.

There were no GBS6- or GBS6 with $AlPO_4$-related maternal macroscopic observations, nor any effects on any ovarian, uterine, or litter parameters, including embryo-fetal survival, fetal body weights, or external, visceral, or skeletal malformations or variations. There also were no effects of GBS6 or GBS6 with $AlPO_4$ administration on postnatal F_1 offspring development, including postnatal growth, effects on acoustic (auditory) startle or pupil constriction, macroscopic observations, or survival.

Administration of GBS6 or GBS6 with $AlPO_4$ to F_0 females resulted in the detection of functional antibodies to each of the 6 serotypes in each vaccine. Functional antibodies to each of the 6 serotypes were also detected in most of the fetuses of F_0 females administered

GBS6 or GBS6 with $AlPO_4$, and functional antibodies to one or more of the 6 serotypes were detectable in some of the kits at the end of the lactation period.

In conclusion, administration of GBS6 or GBS6 with $AlPO_4$ to female rabbits twice before the start of mating (35 and 21 days prior to cohabitation) and twice during gestation (GD 10 and GD 24) at the highest anticipated clinical dose, 20 µg CPS/serotype conjugate/dose, did not result in any maternal toxicity nor any effects on mating, fertility, or any ovarian or uterine parameters in the F_0 female rabbits or in development or survival in the F_1 offspring.

5.3.7. Local Tolerance

[redacted]

5.3.8. Other Toxicity Studies

5.3.8.1. Phototoxicity

Phototoxicity studies with candidate GBS6 formulations have not been conducted.

5.3.8.2. Antigenicity

[redacted] was evaluated in [redacted] fertility and developmental toxicity studies in rats and rabbits (Section 5.3.6). IM administration of GBS6 or GBS6 with $AlPO_4$ to rats and rabbits resulted in a functional antibody response to each of the 6 polysaccharide conjugate serotypes.

5.3.8.3. Immunotoxicity

Immunotoxicity studies with candidate GBS6 formulations have not been conducted.

5.3.8.4. Mechanistic Studies

Mechanistic studies with candidate GBS6 formulations have not been conducted.

5.3.8.5. Dependence

Dependence studies with candidate GBS6 formulations have not been conducted.

5.3.8.6. Studies on Metabolites

Stand-alone studies with administration of metabolites of candidate GBS6 formulations have not been conducted.

5.3.8.7. Studies on Impurities

Stand-alone studies with administration of impurities of candidate GBS6 formulations have not been conducted.

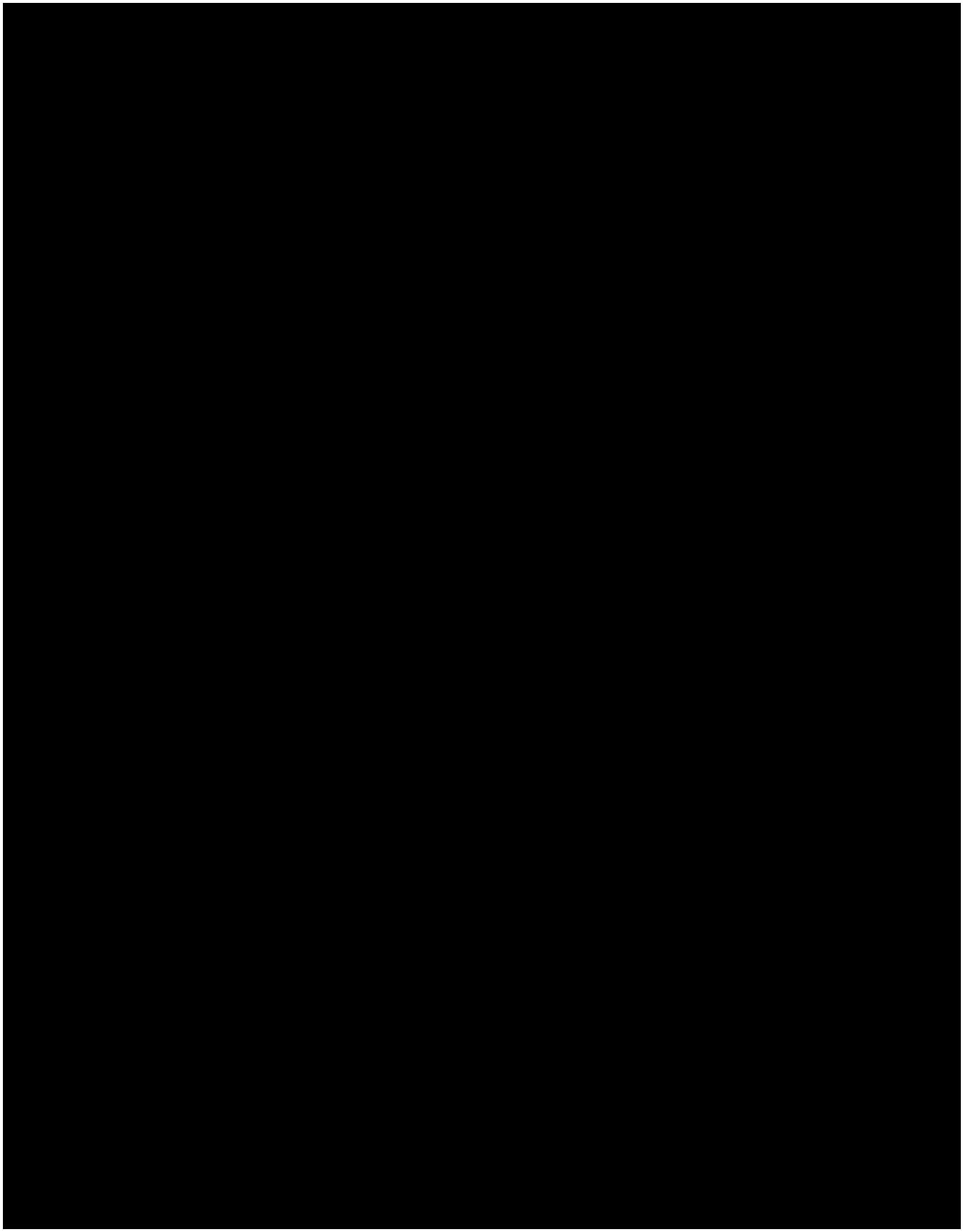
5.3.8.8. Other Studies

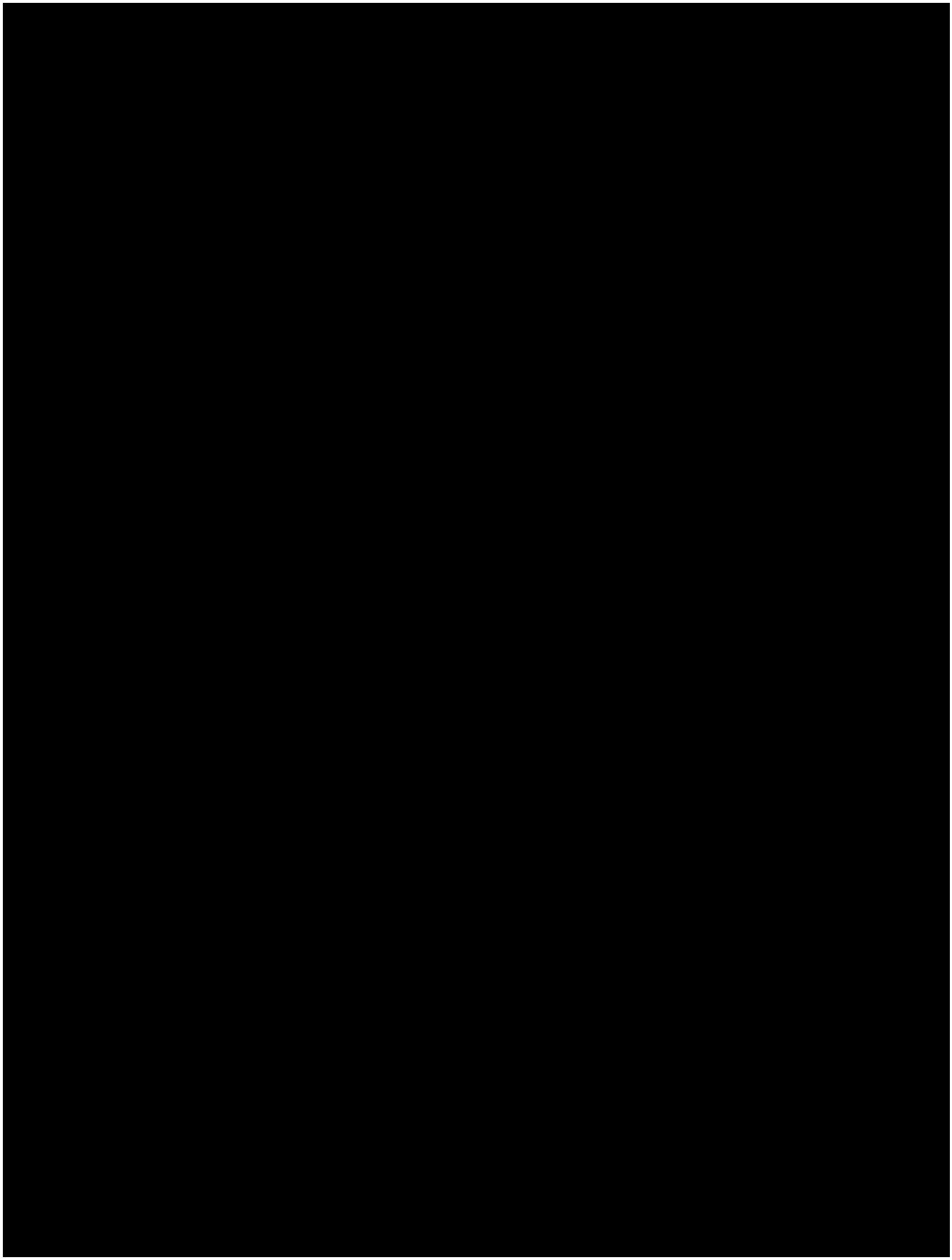
No other studies with candidate GBS6 formulations have been conducted.

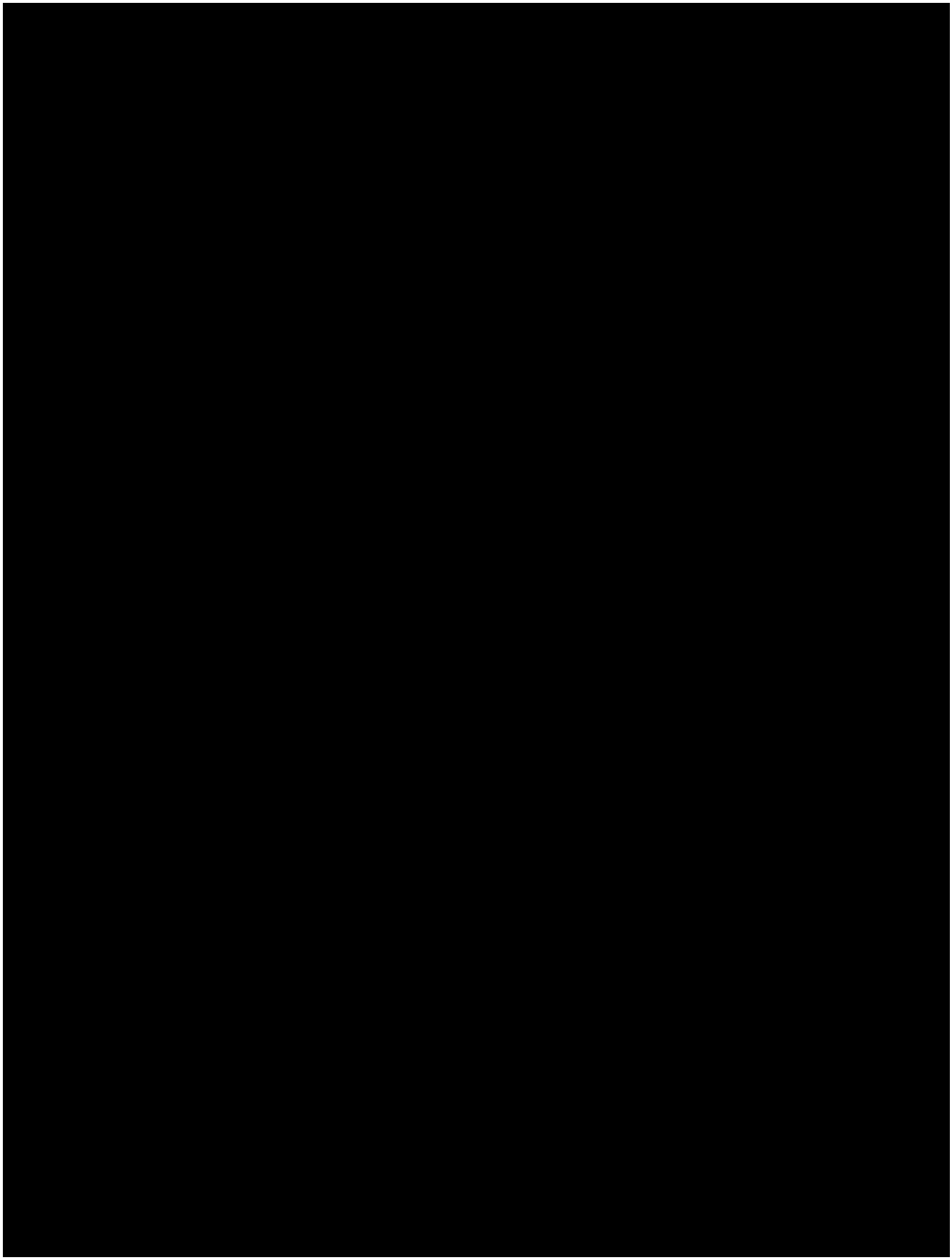
5.3.8.9. Target Organ Toxicity

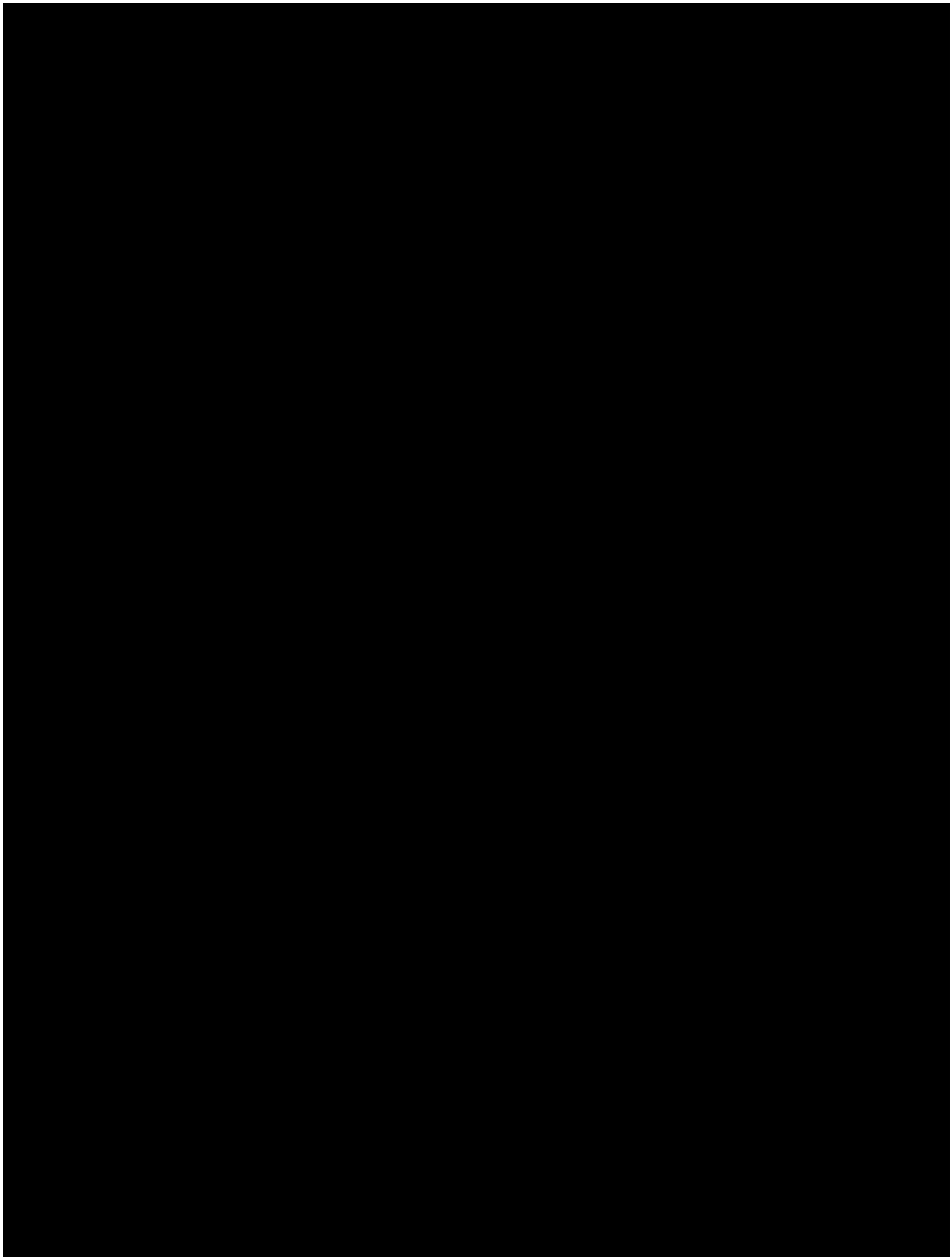
In fertility and developmental toxicity studies in rats and rabbits, there were no vaccine-related effects on female fertility or development of the fetuses/offspring.

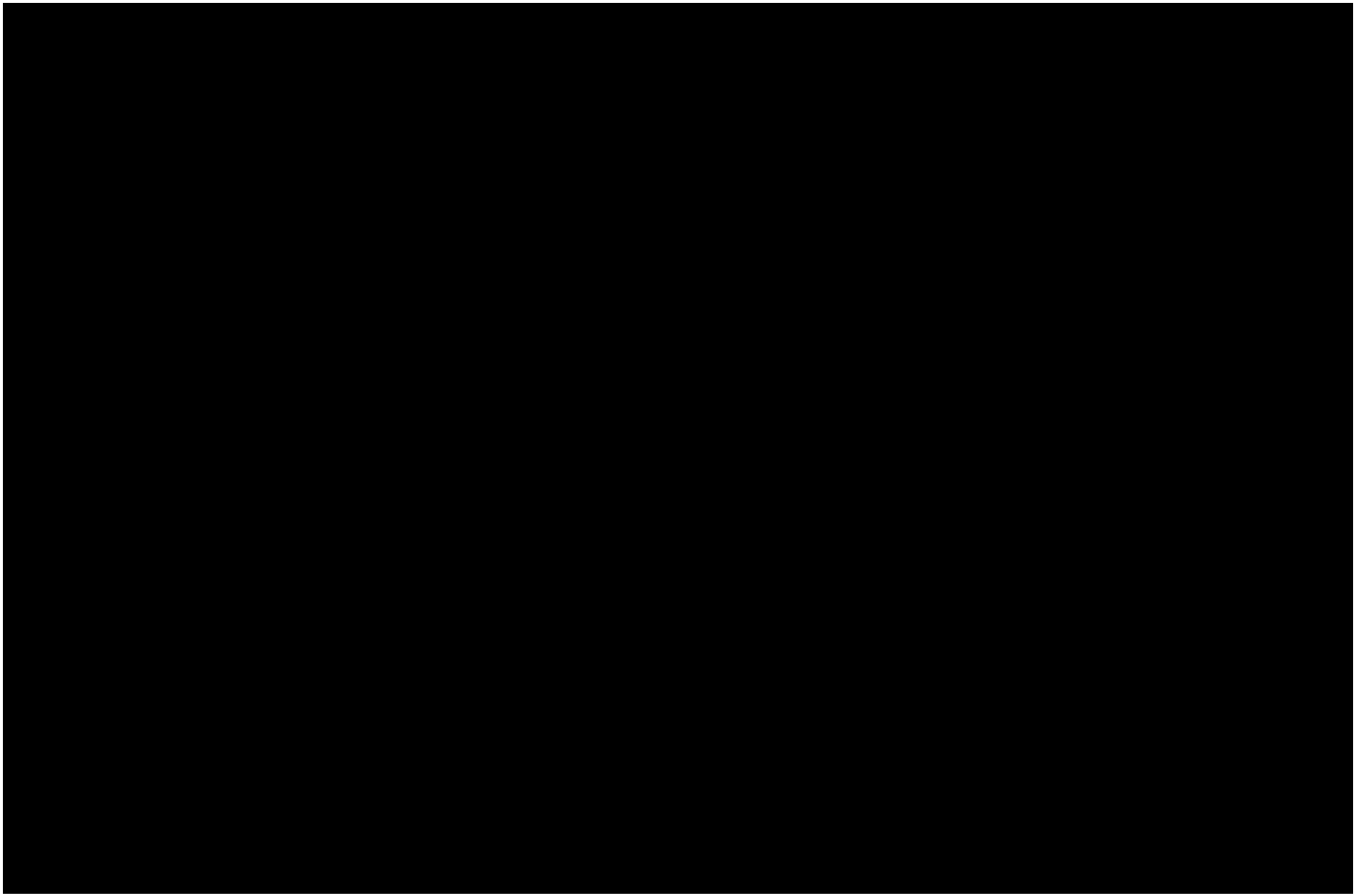
6. EFFECTS IN HUMANS

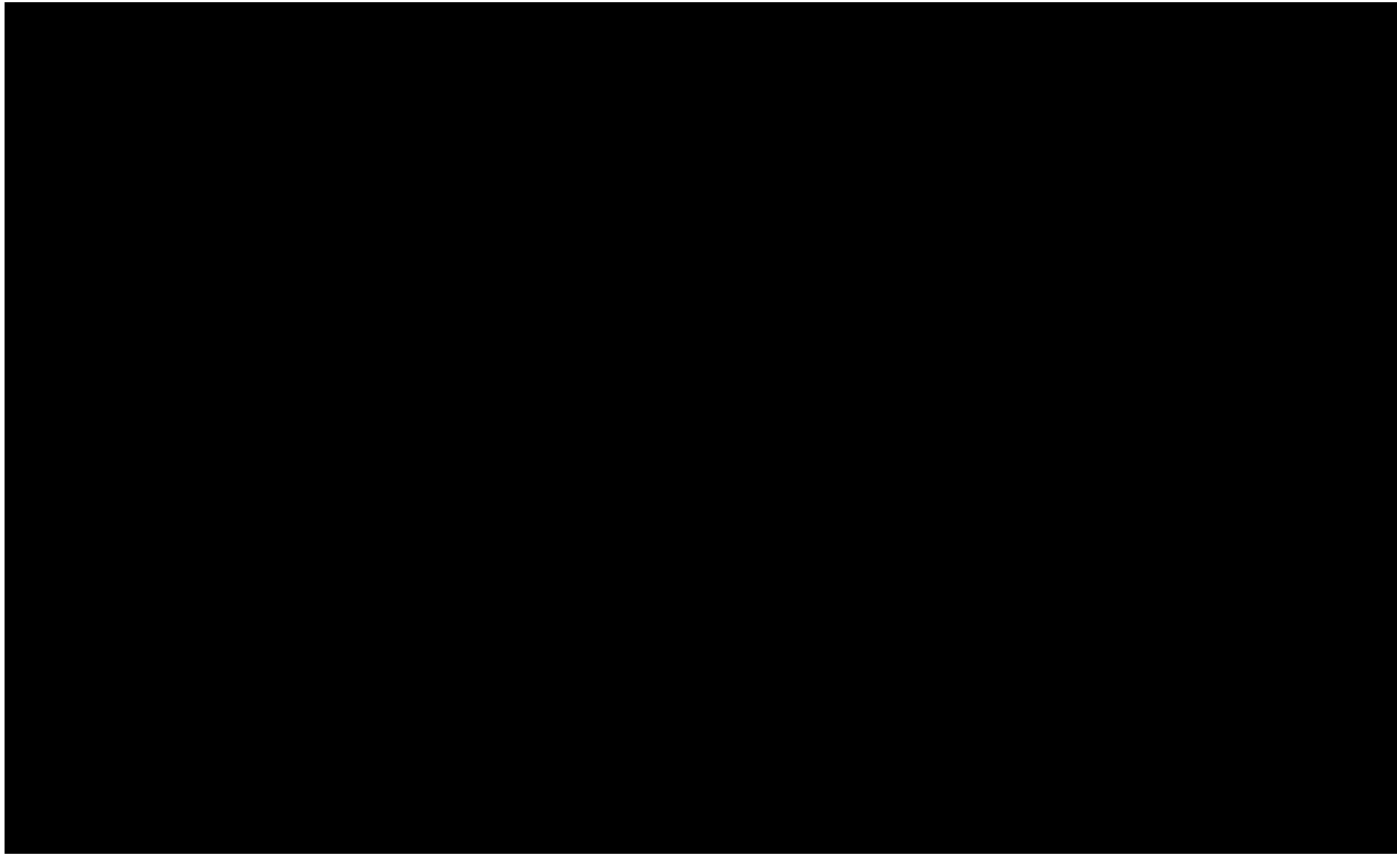


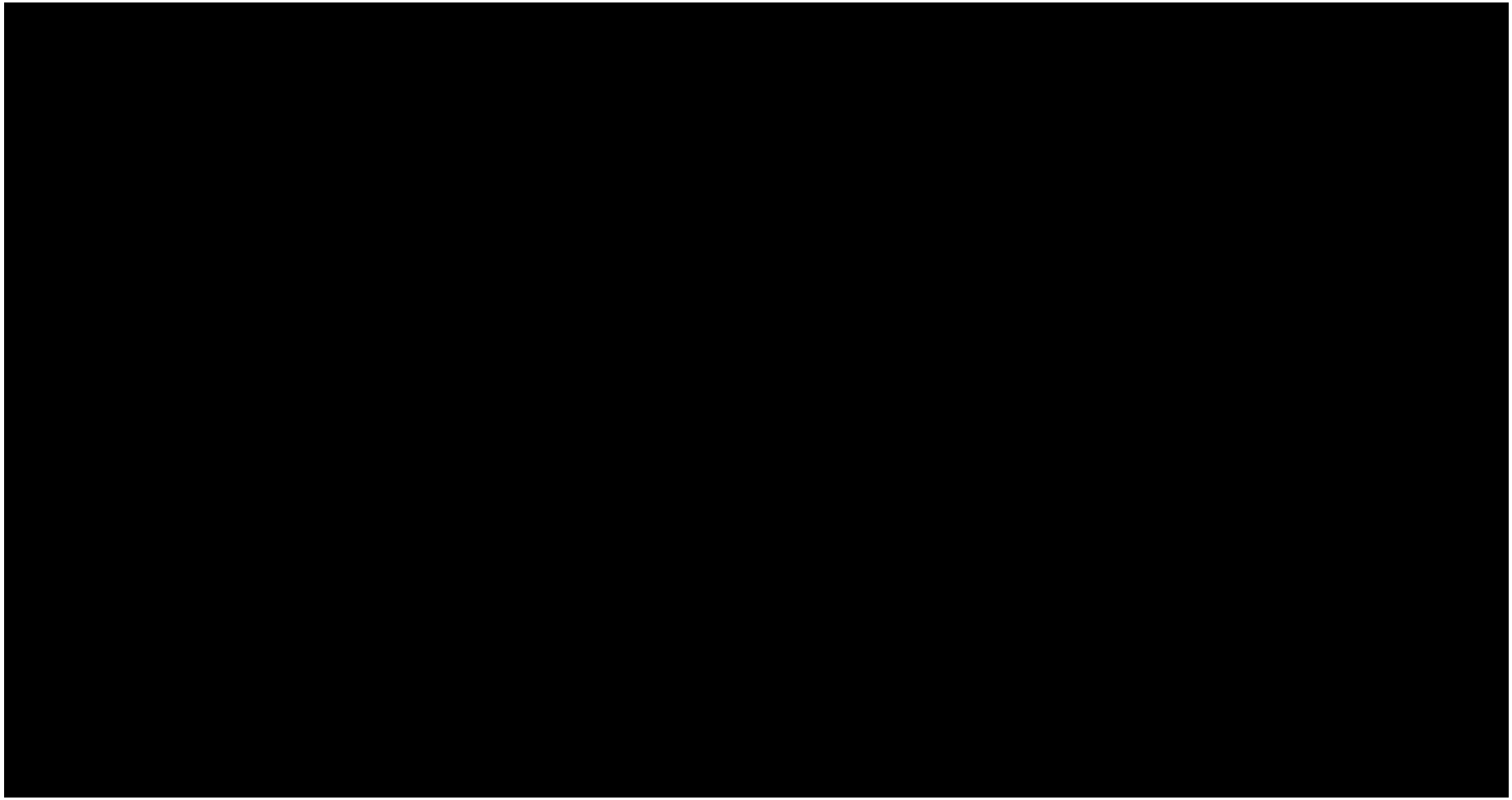


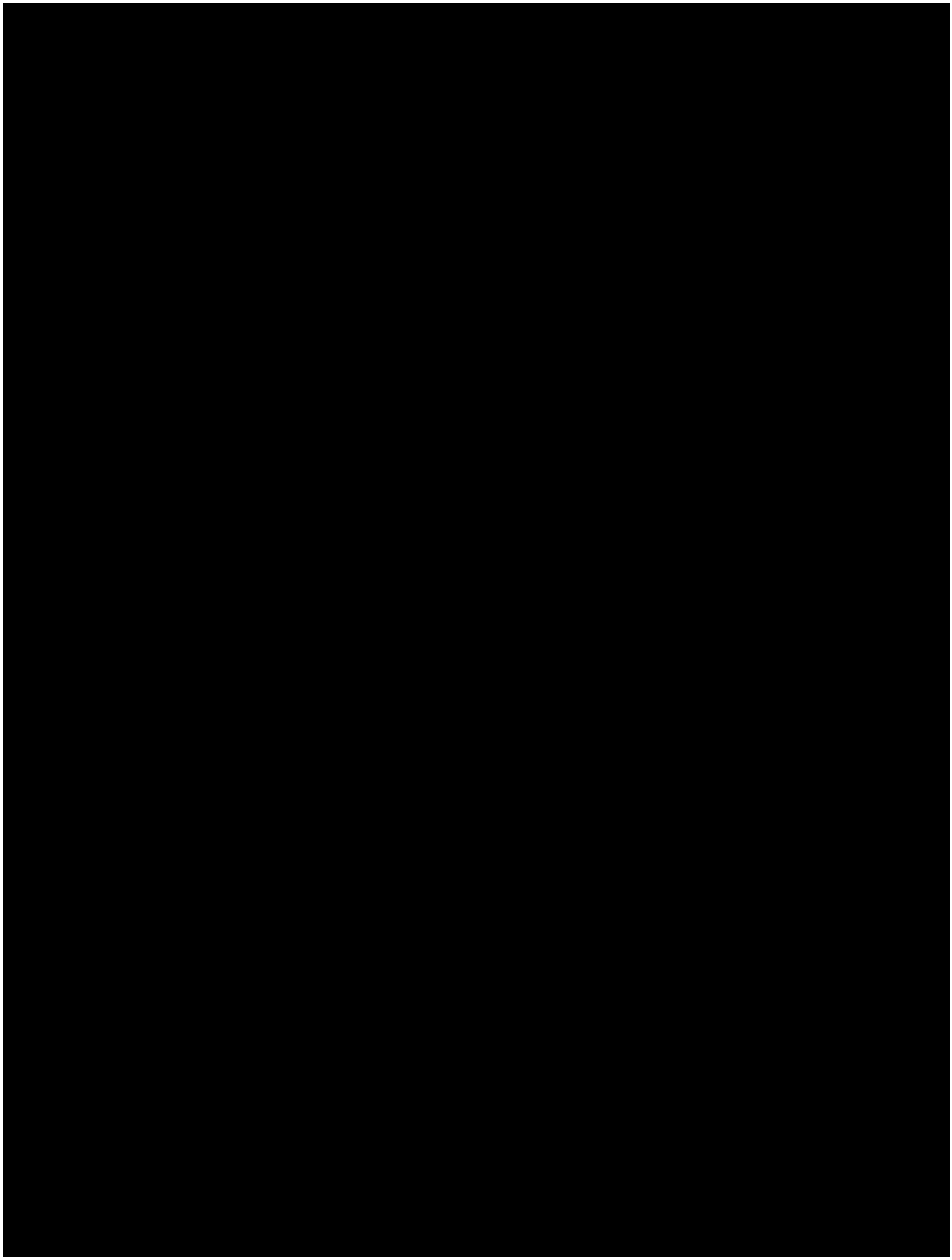


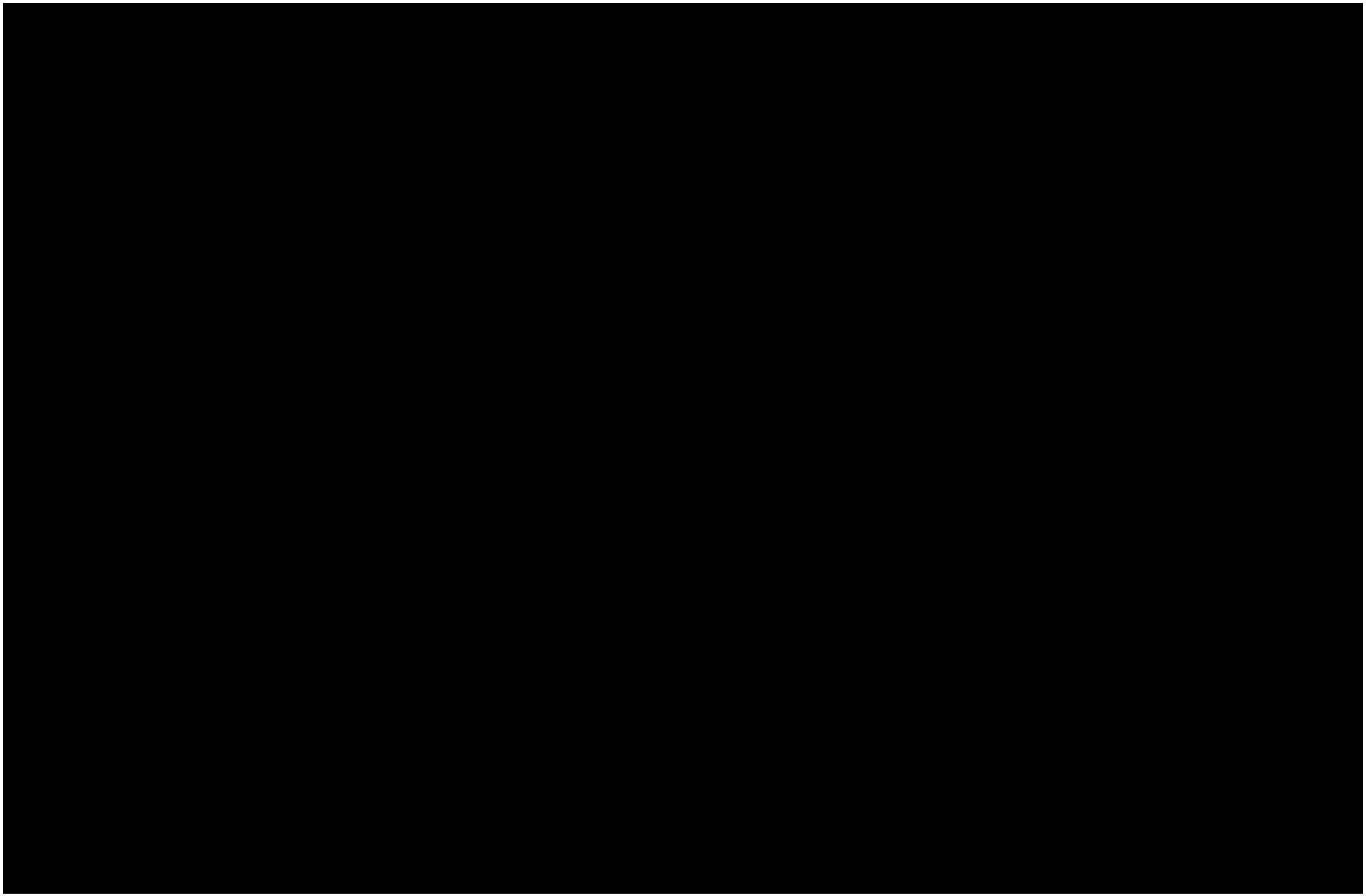


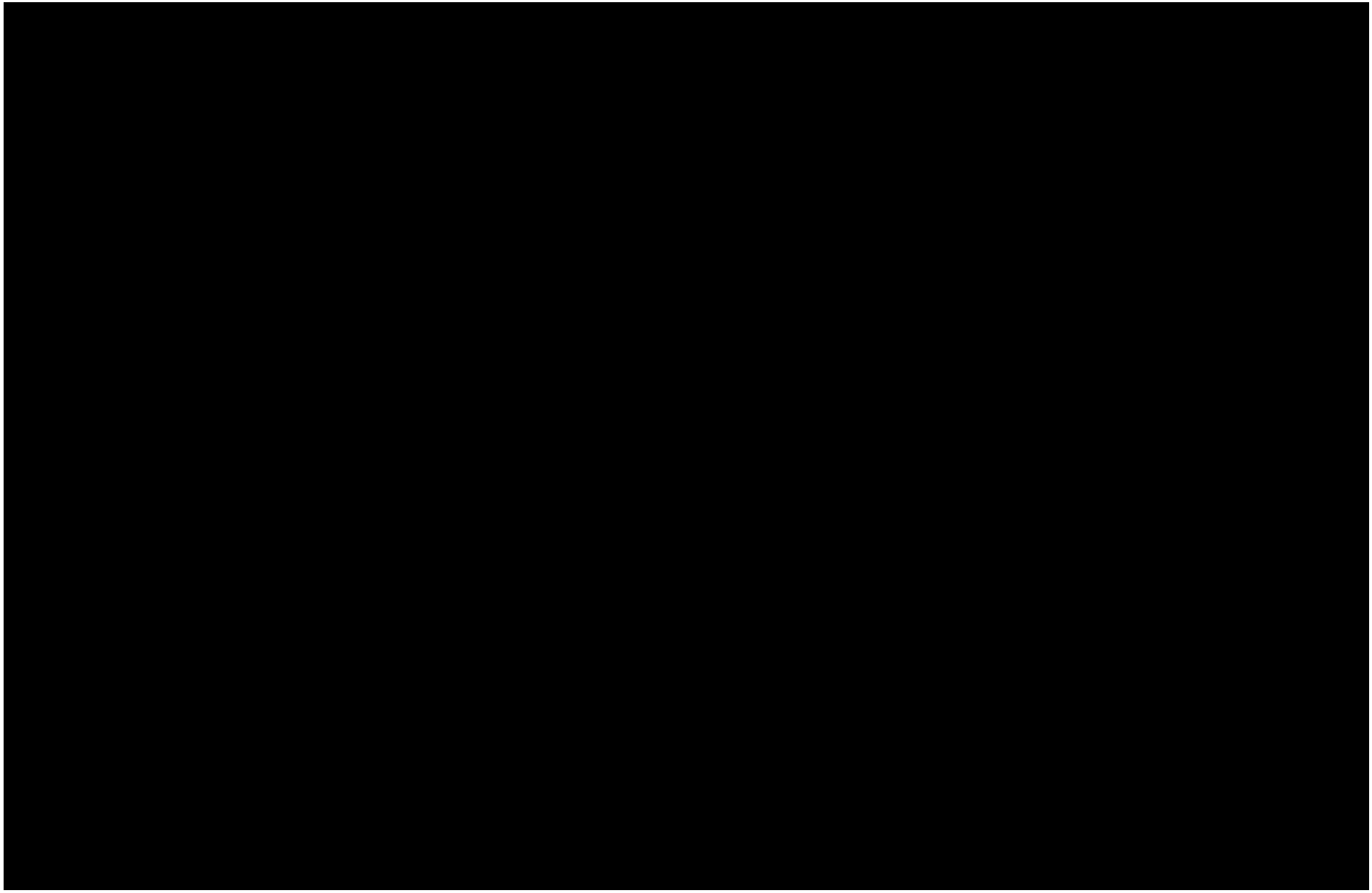


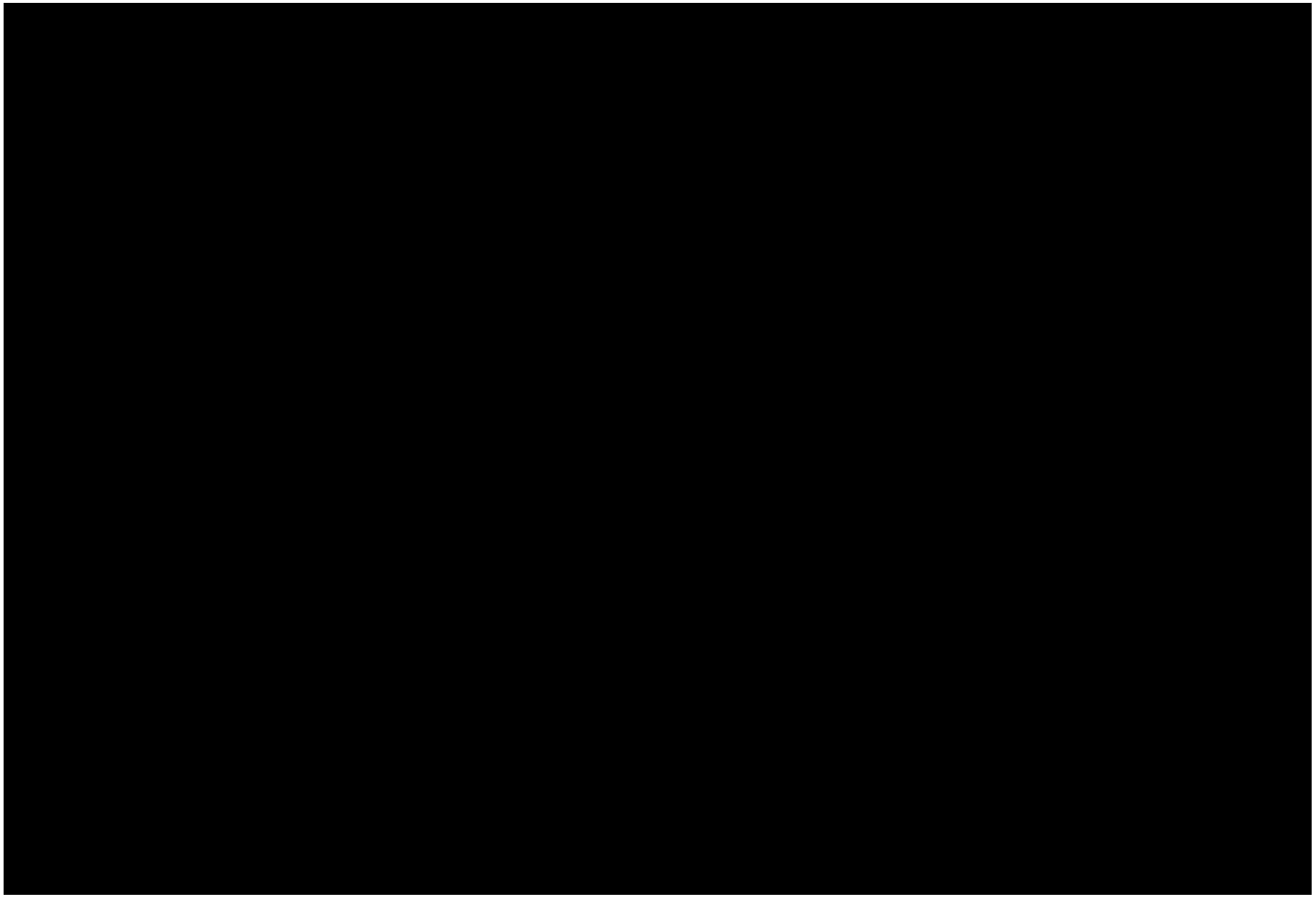


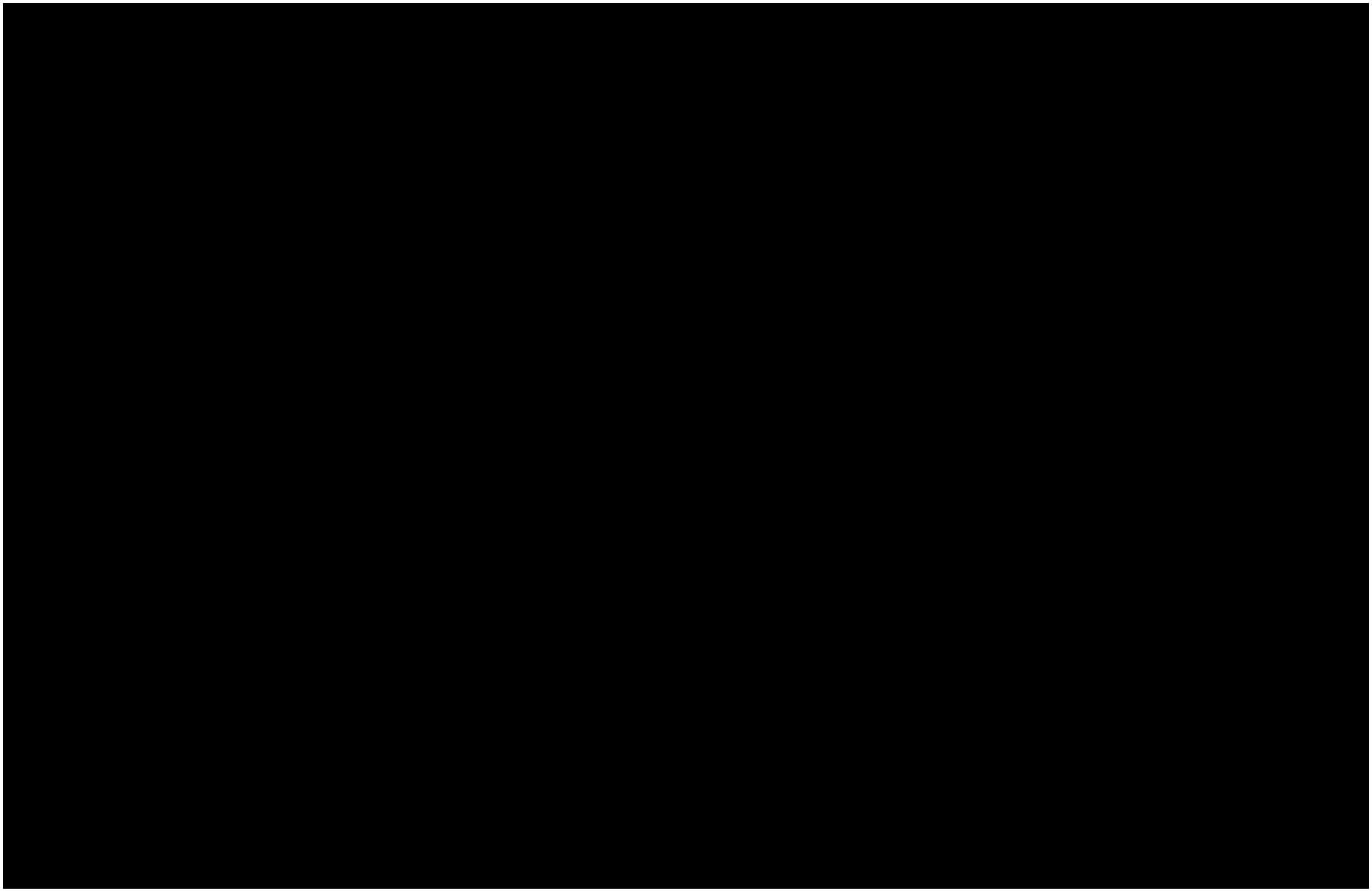


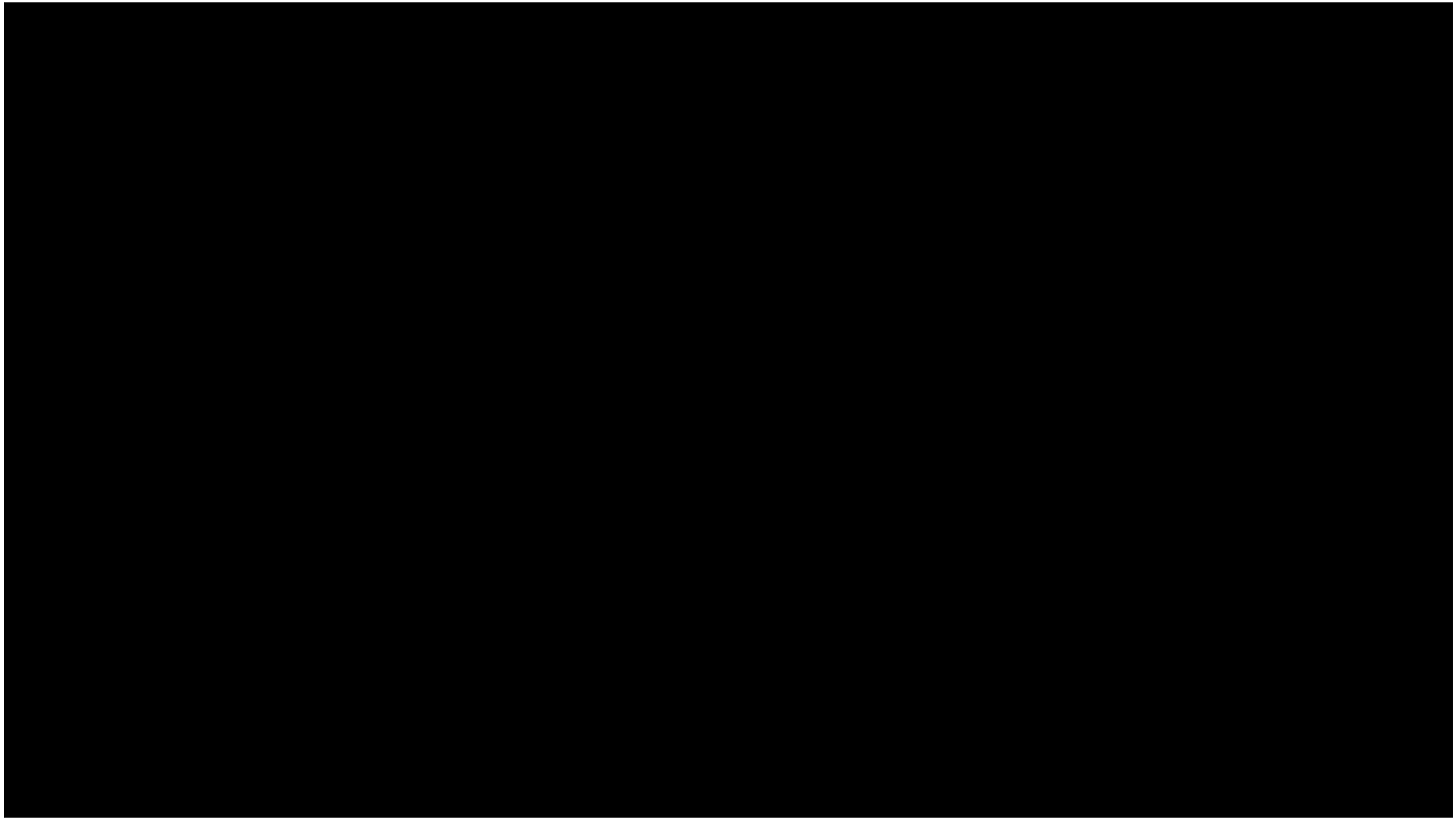


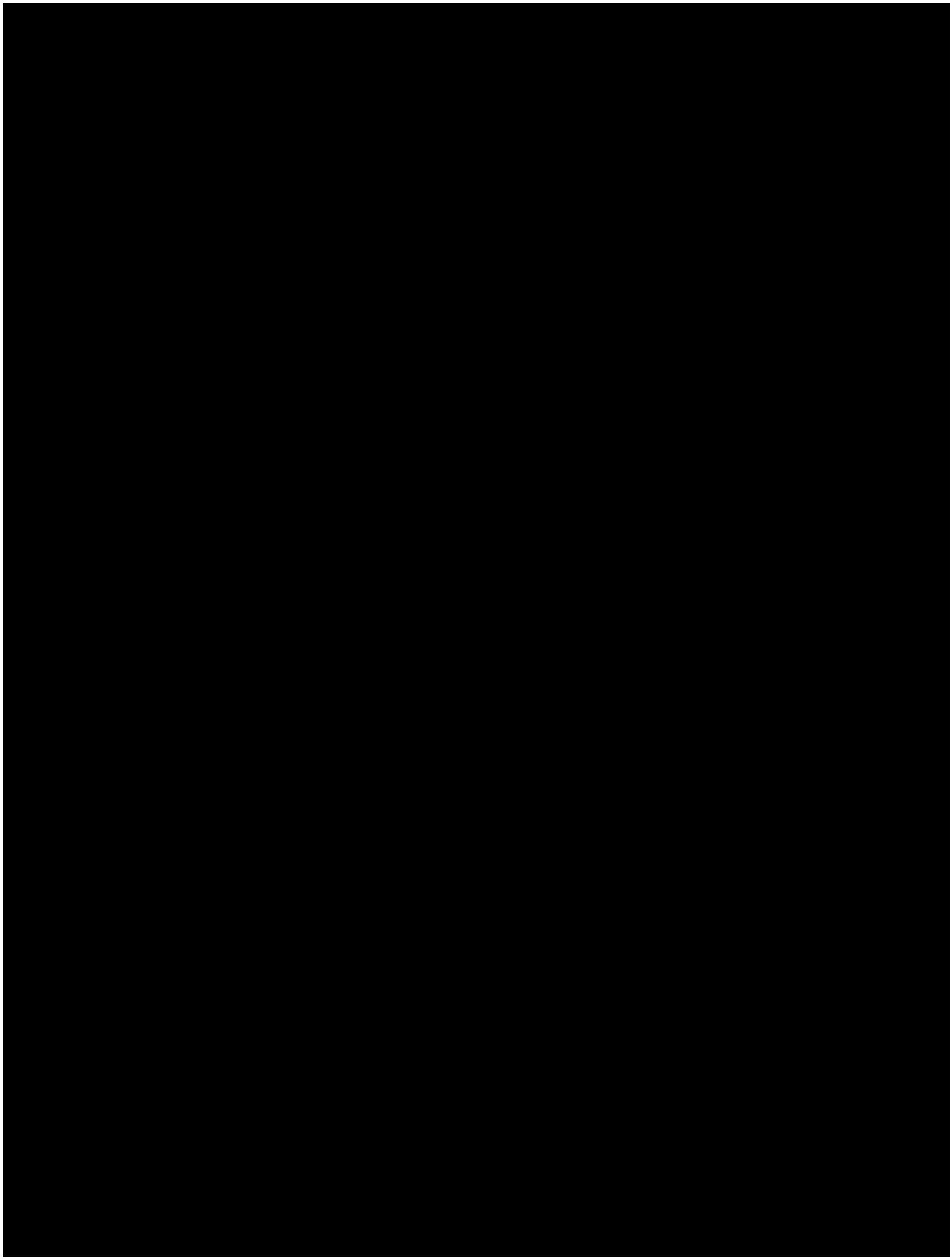


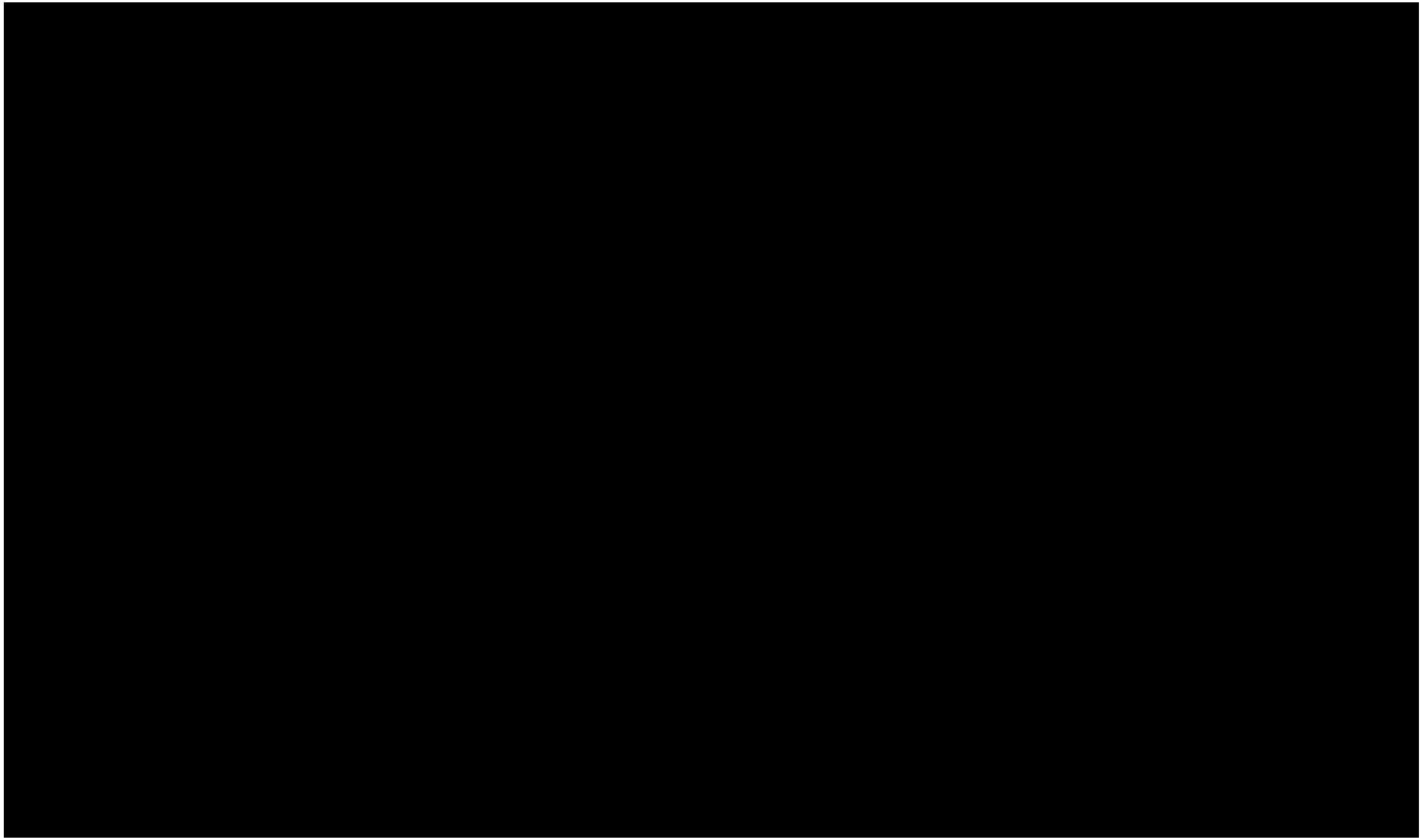


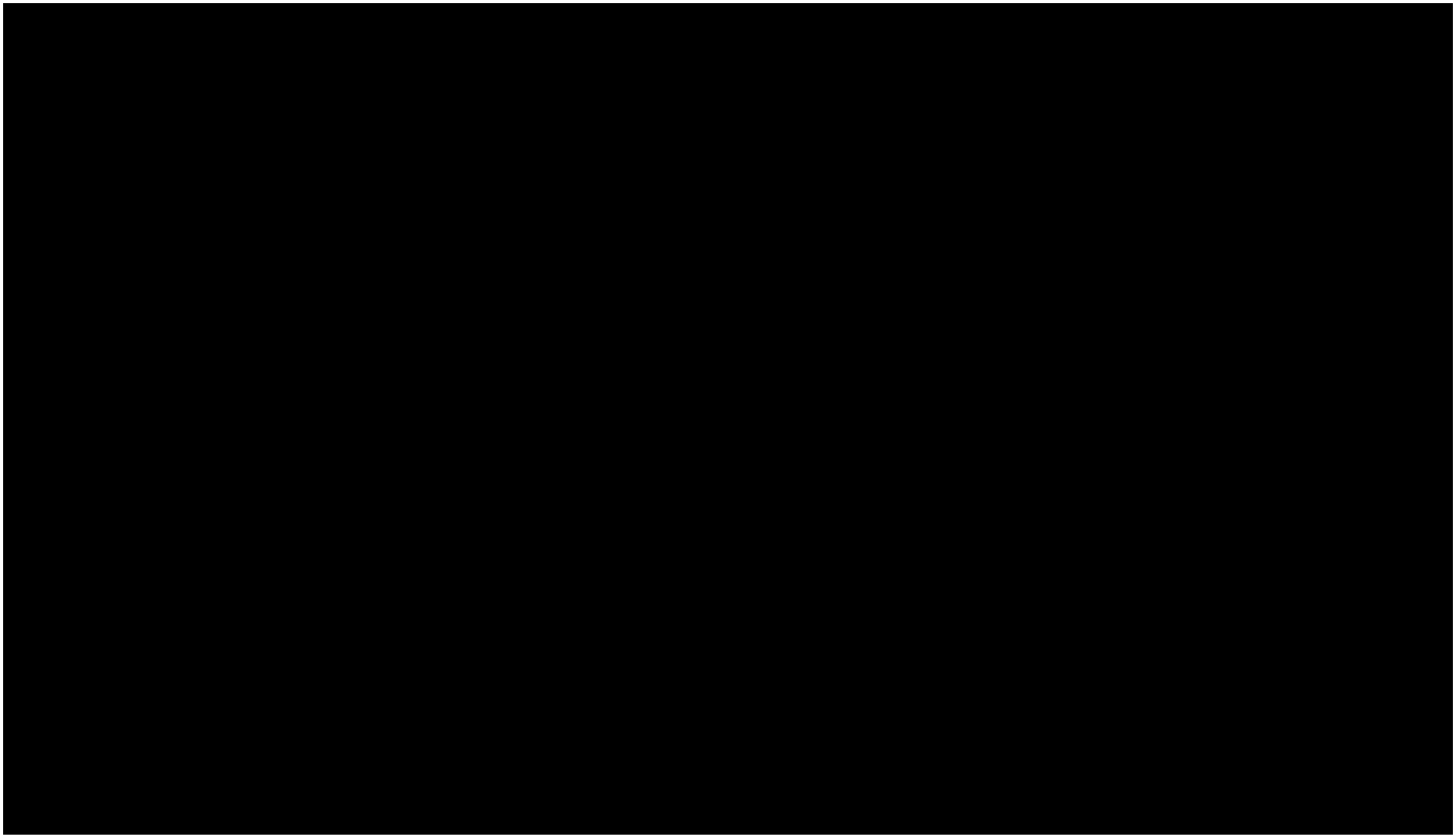


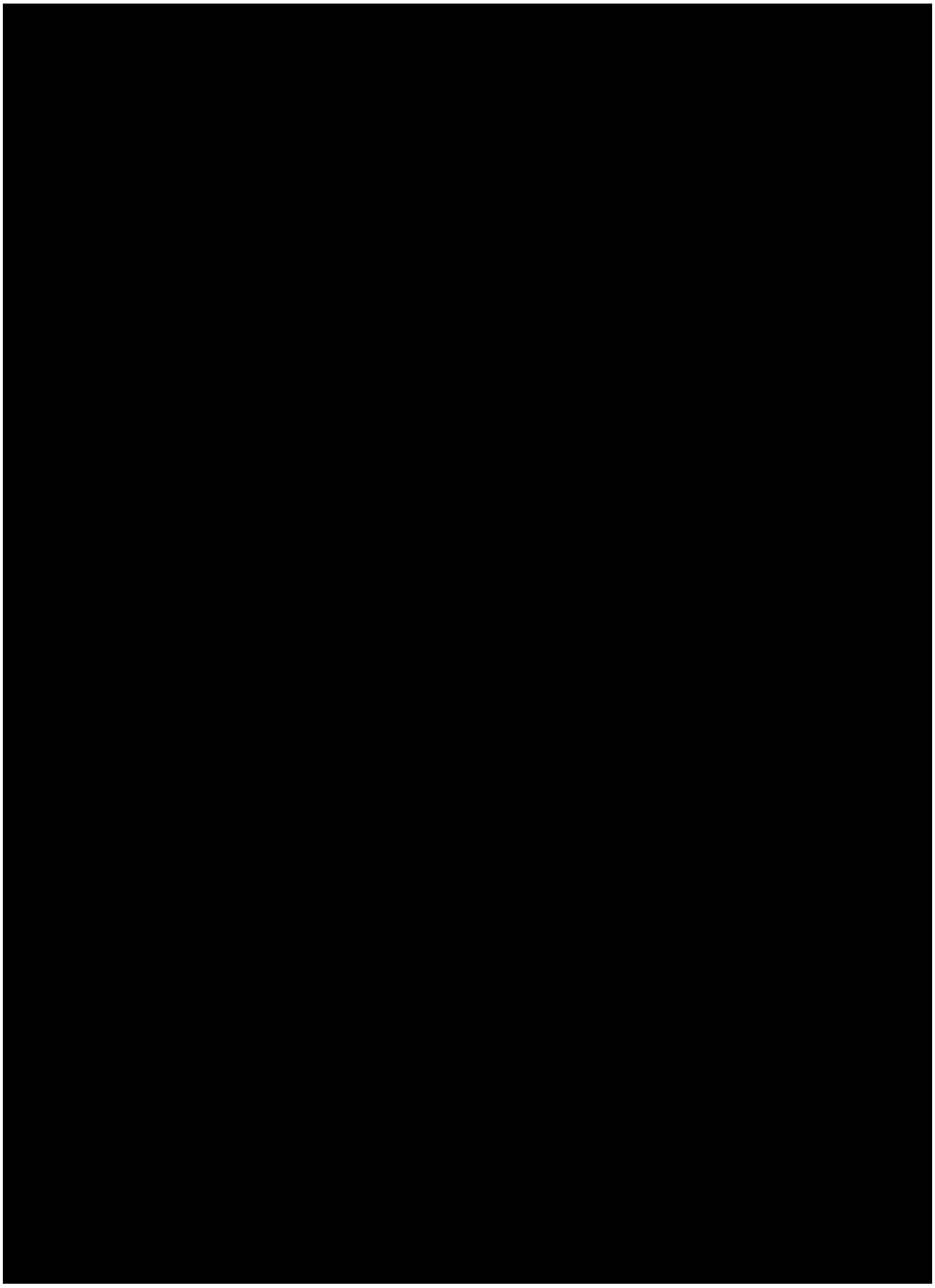


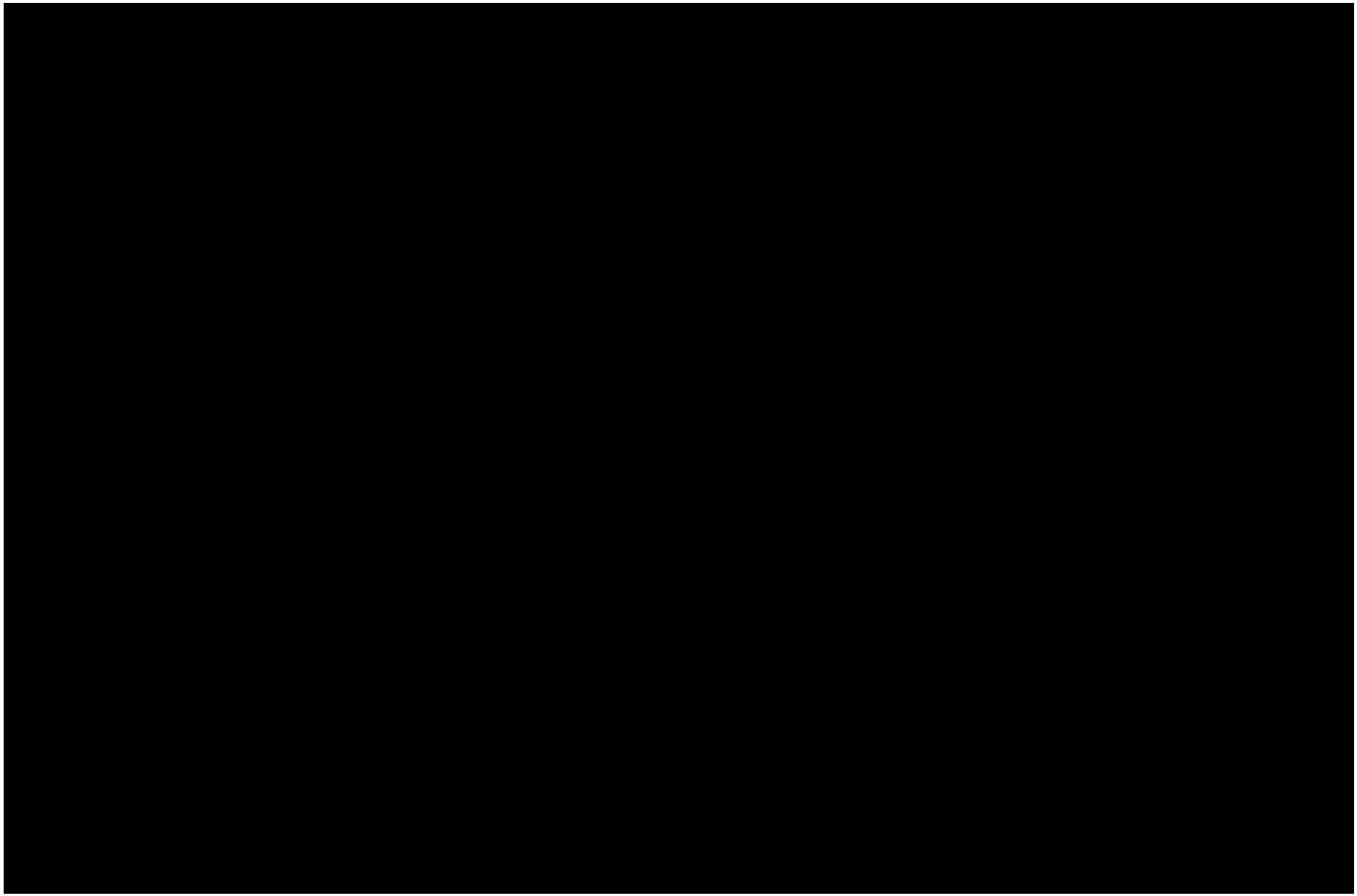


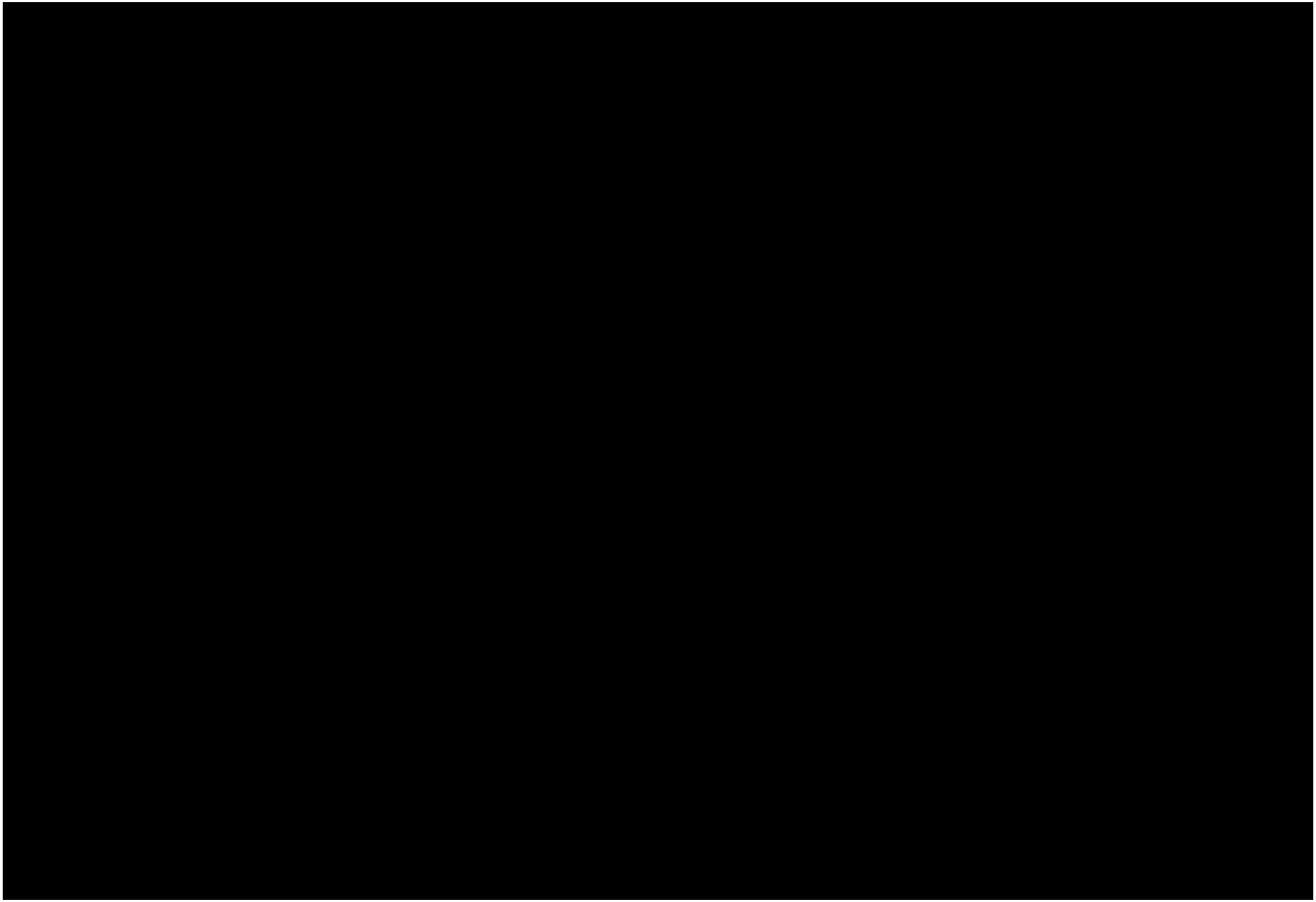


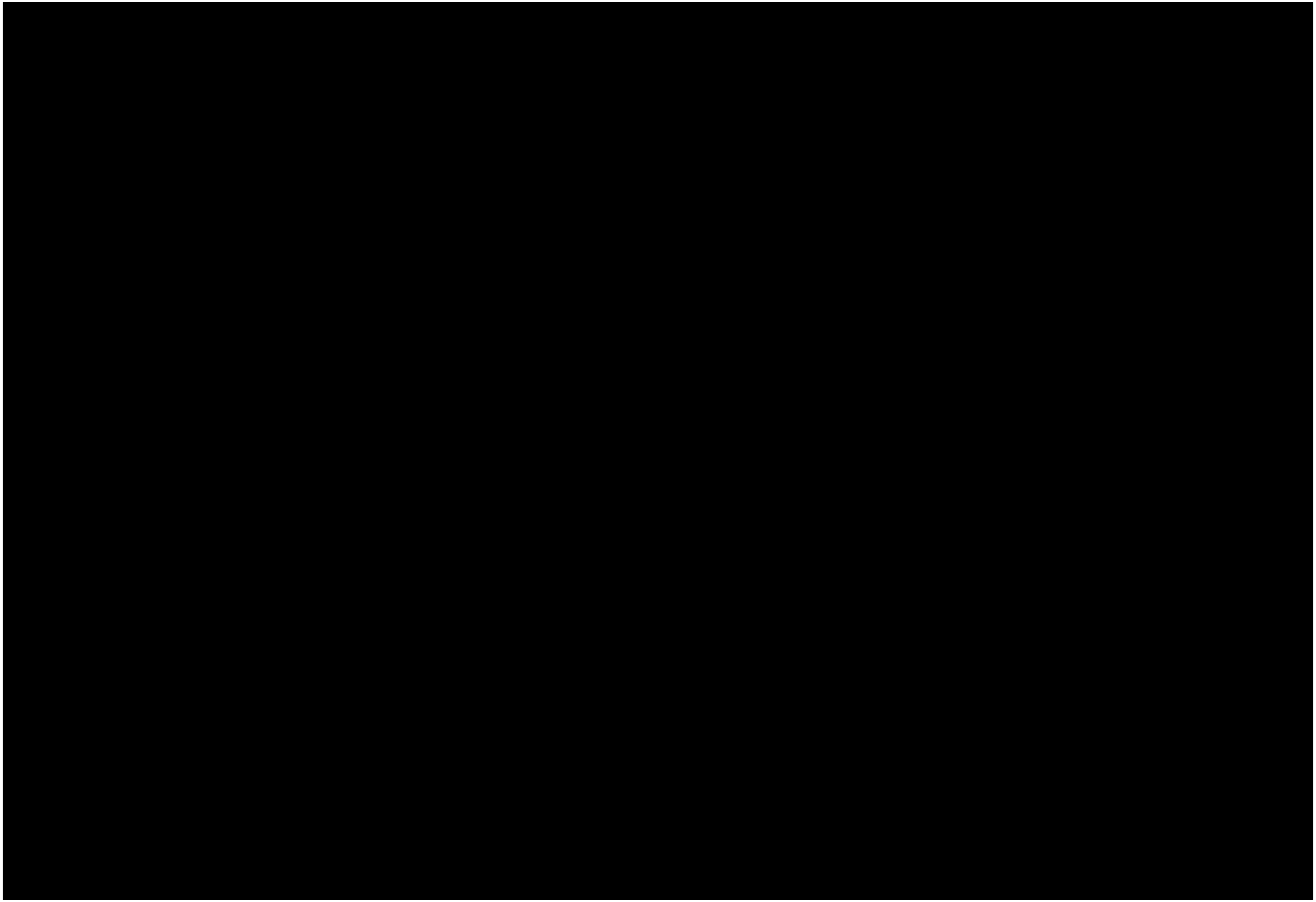


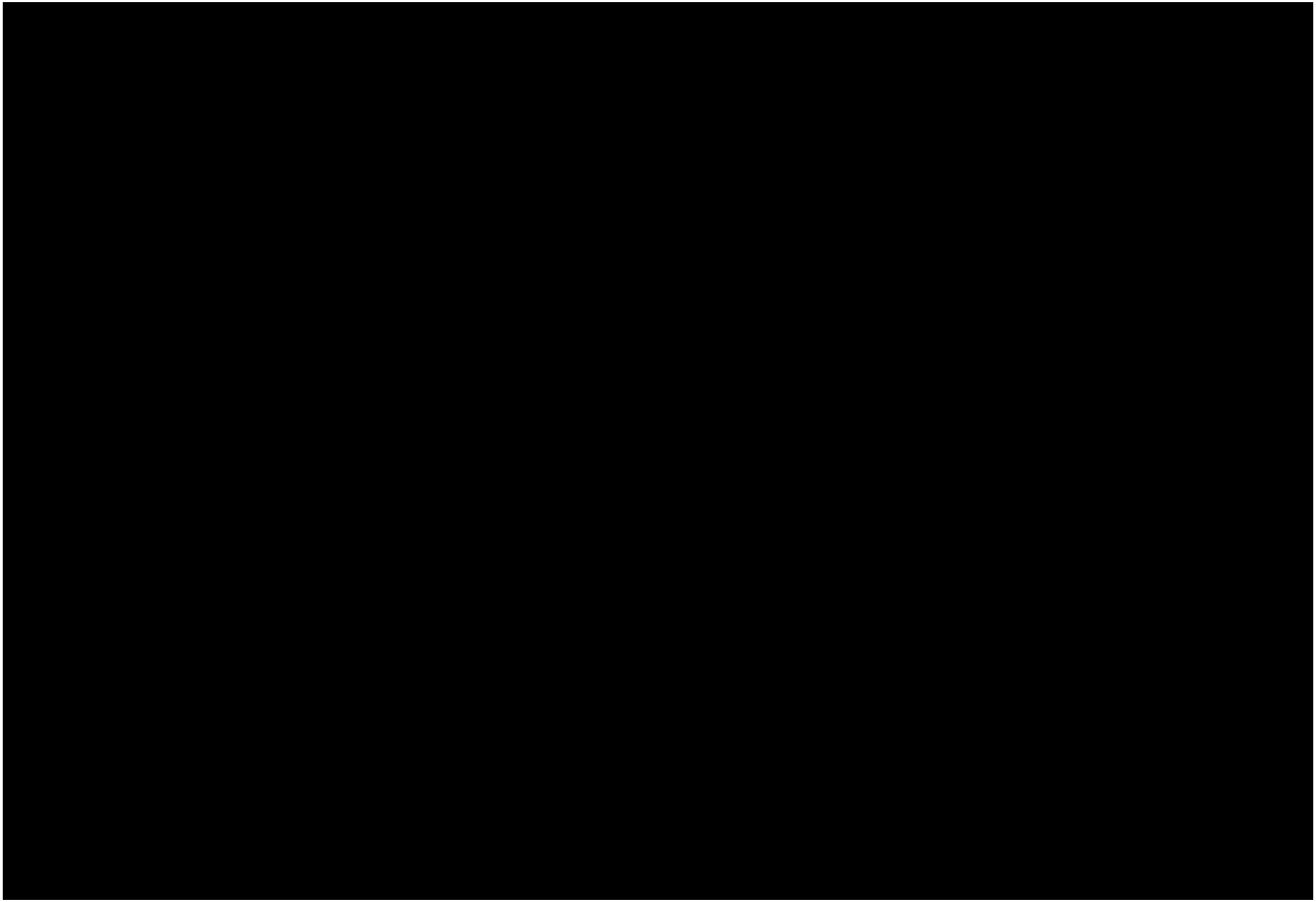


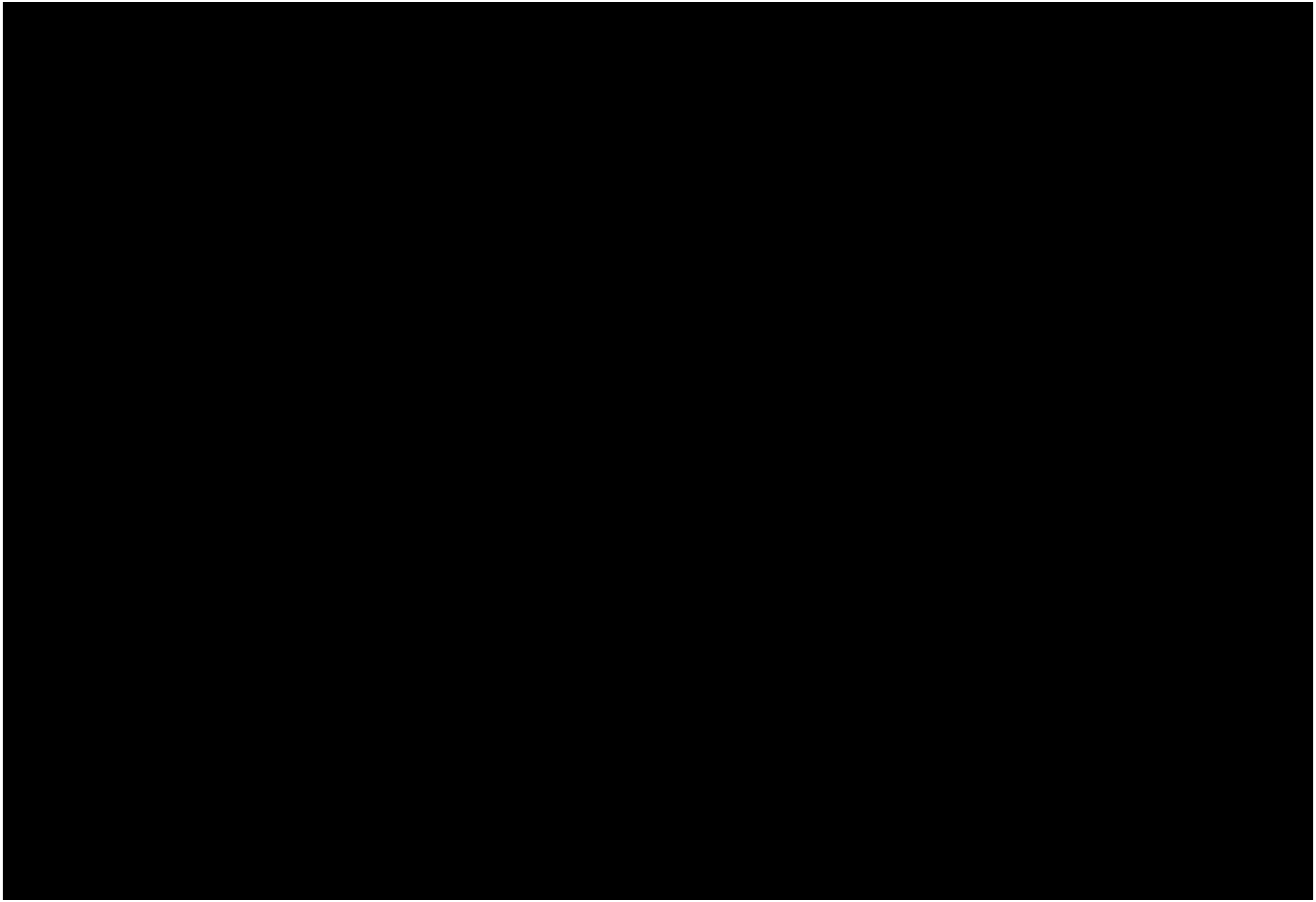


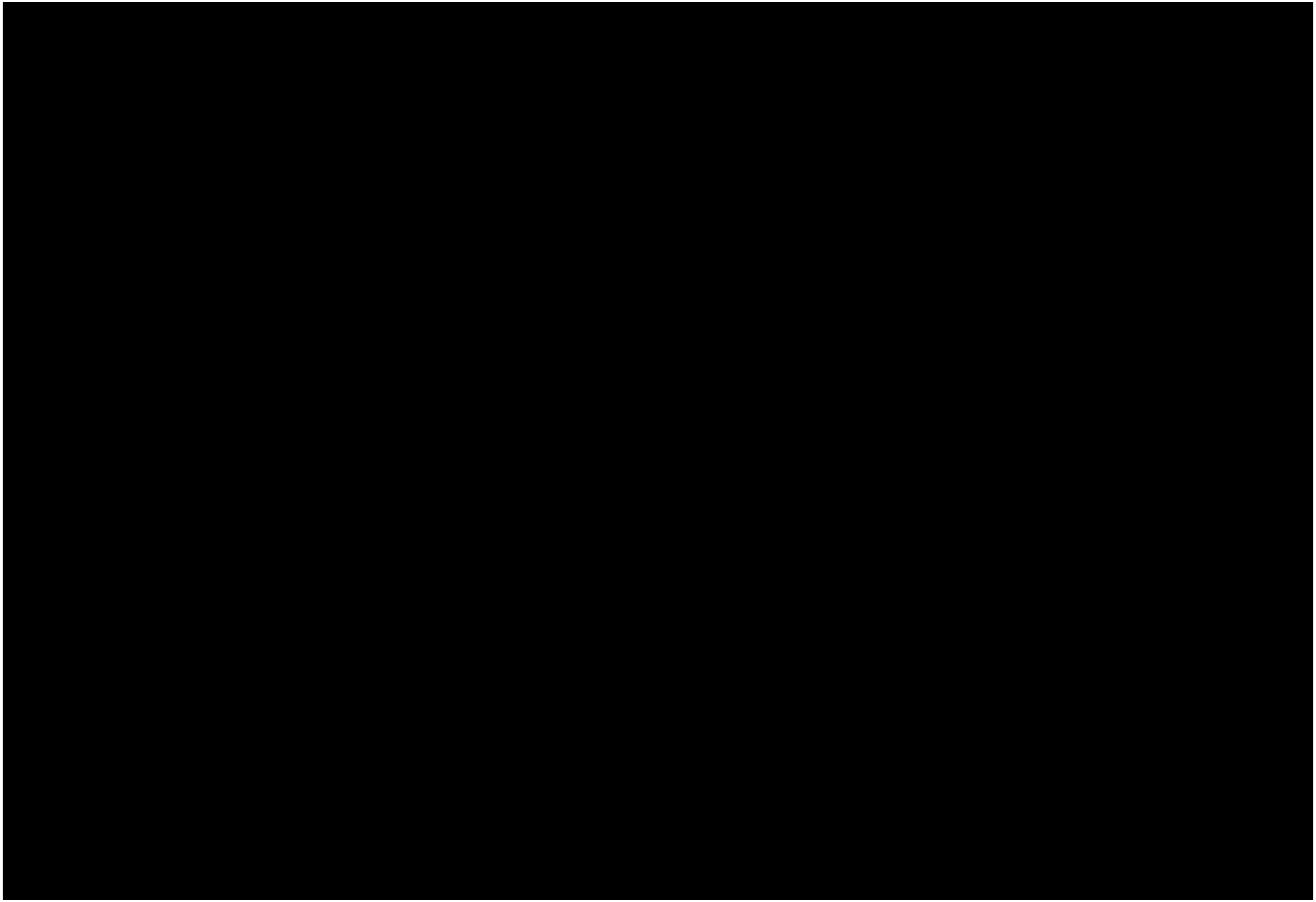


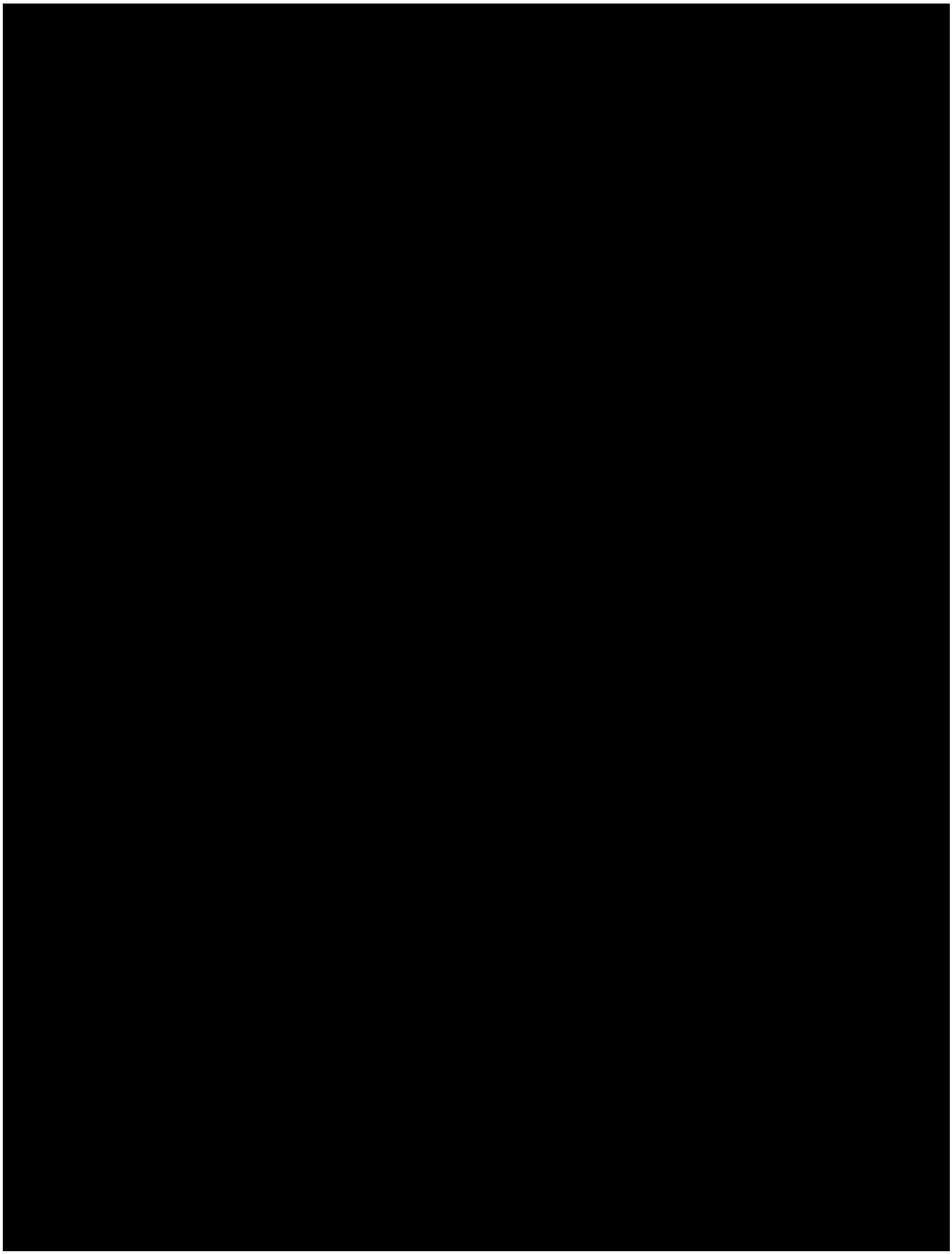


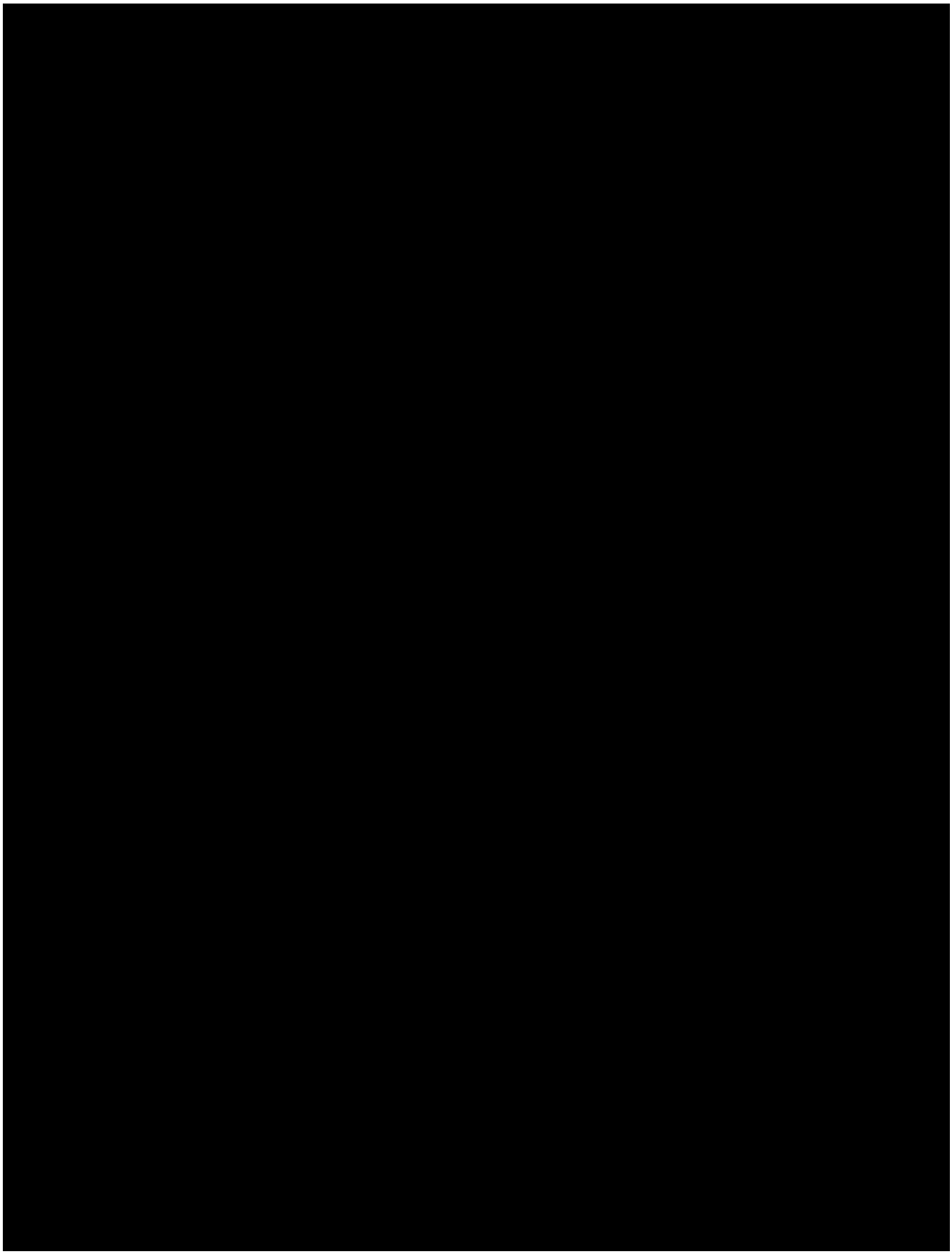


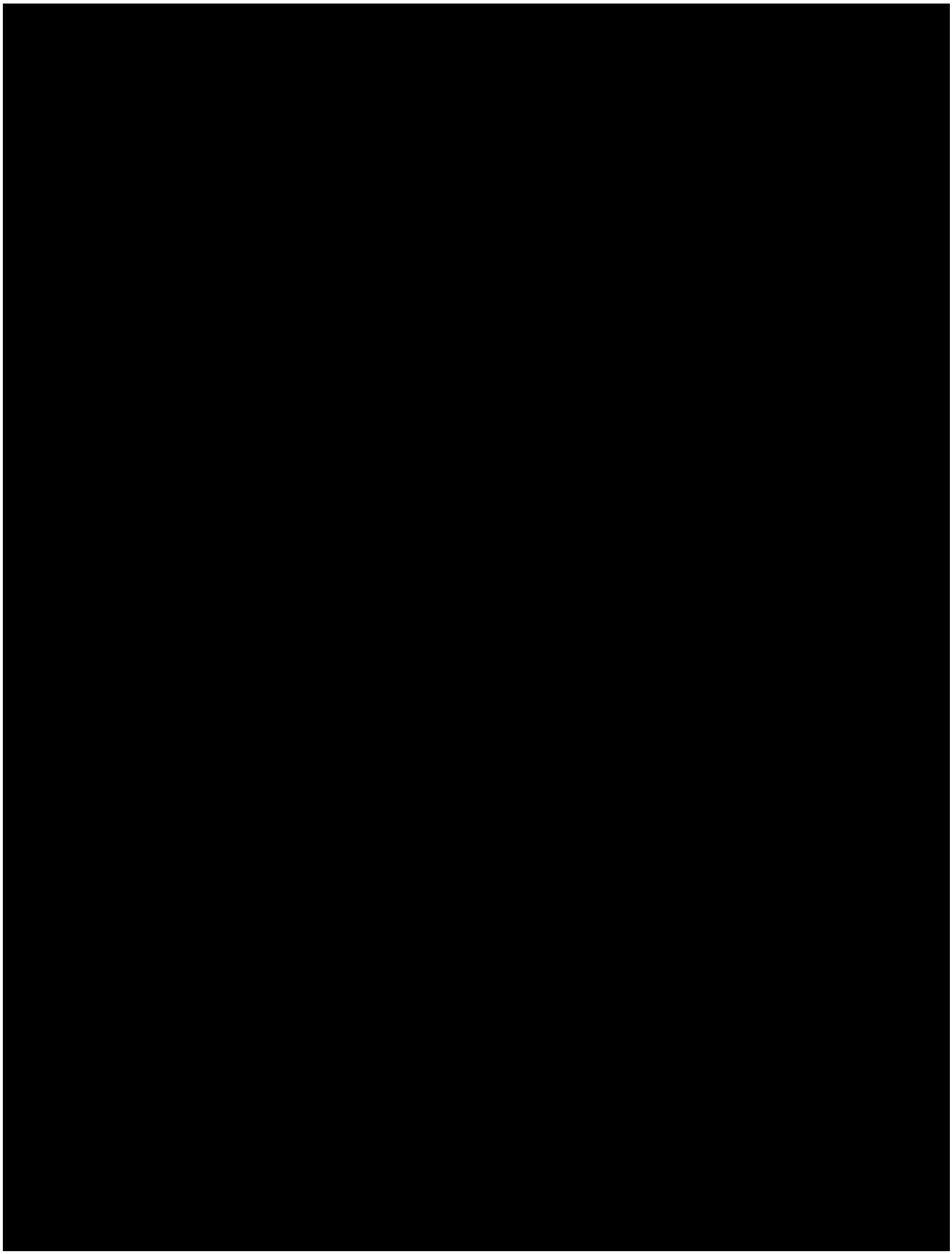


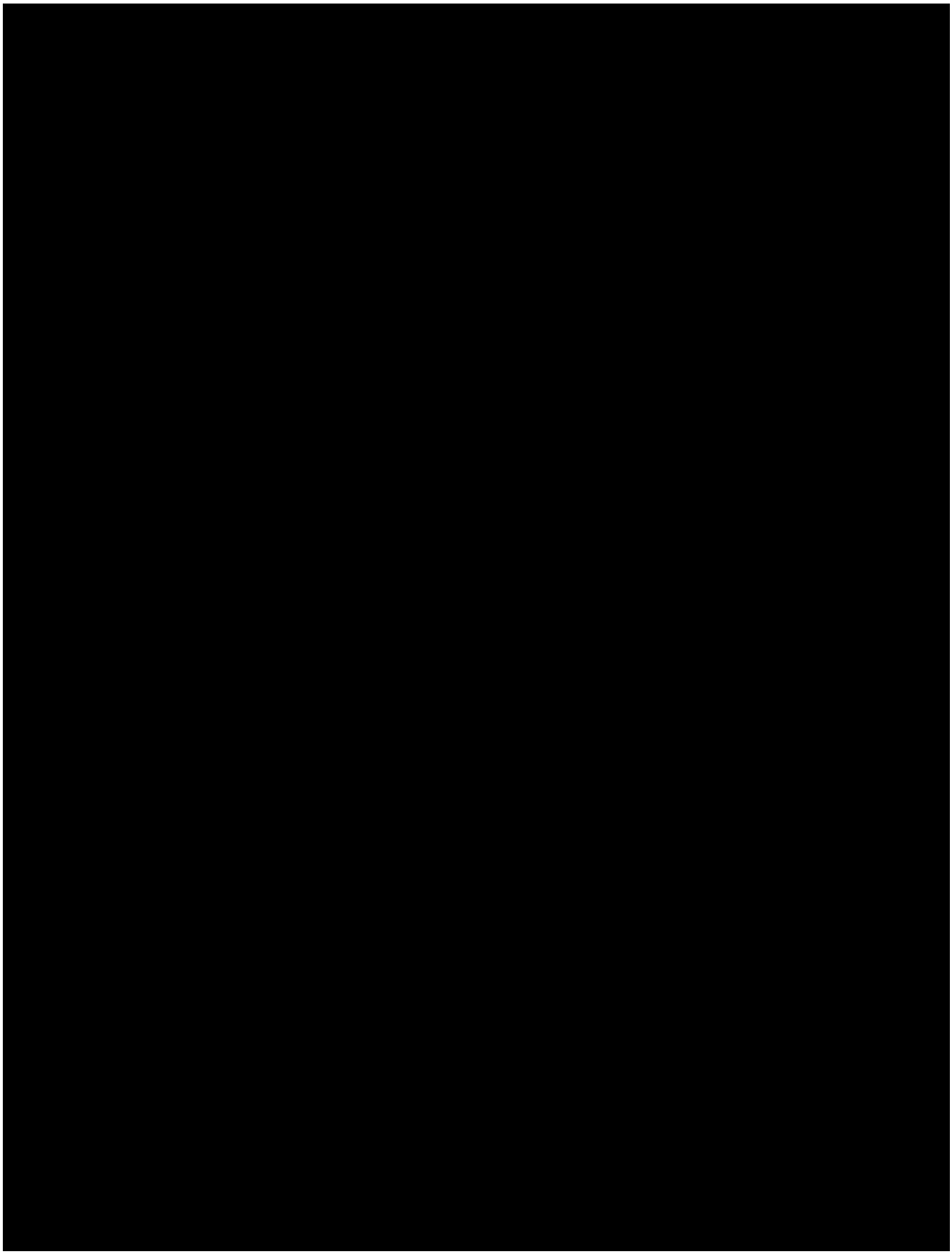


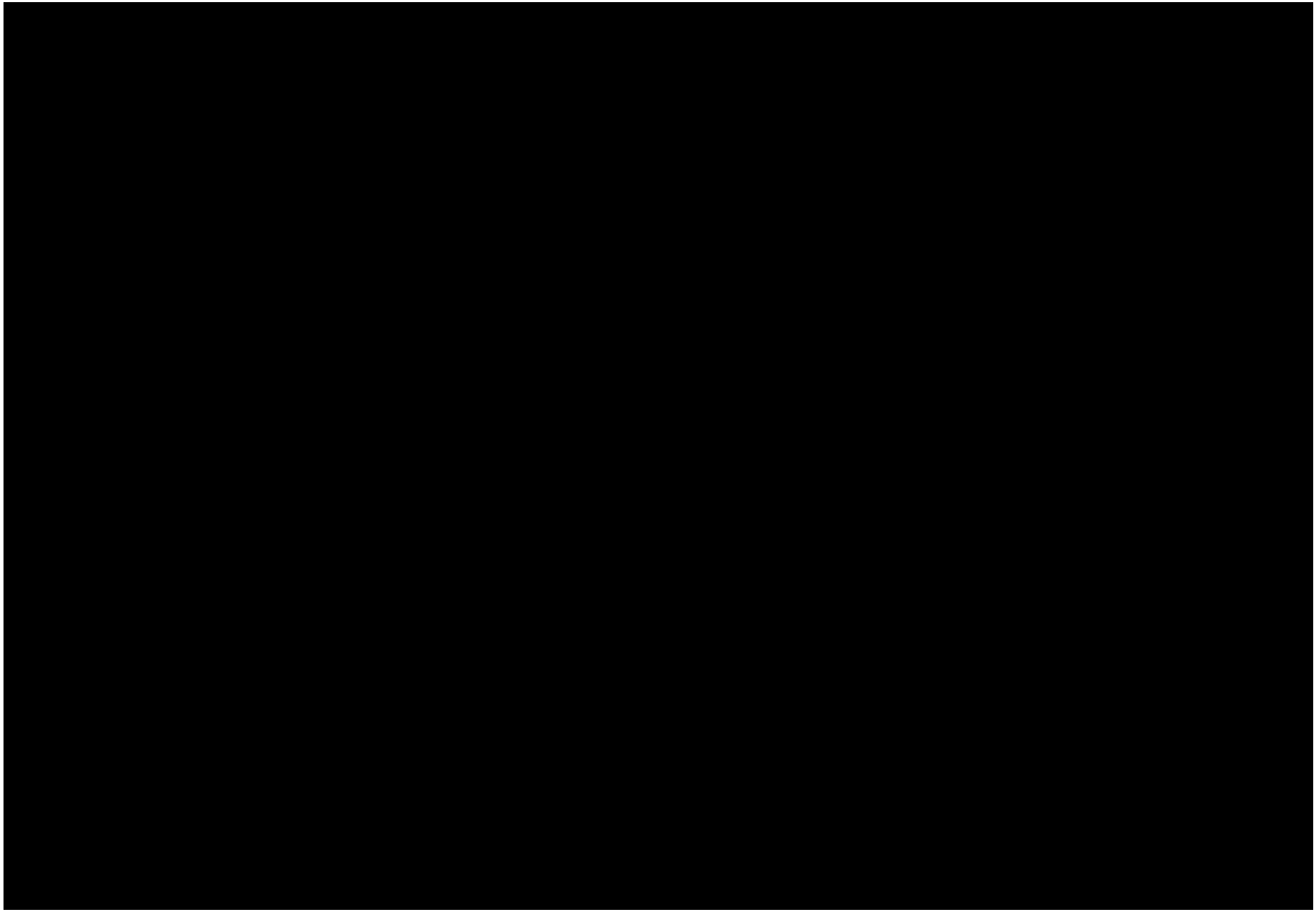


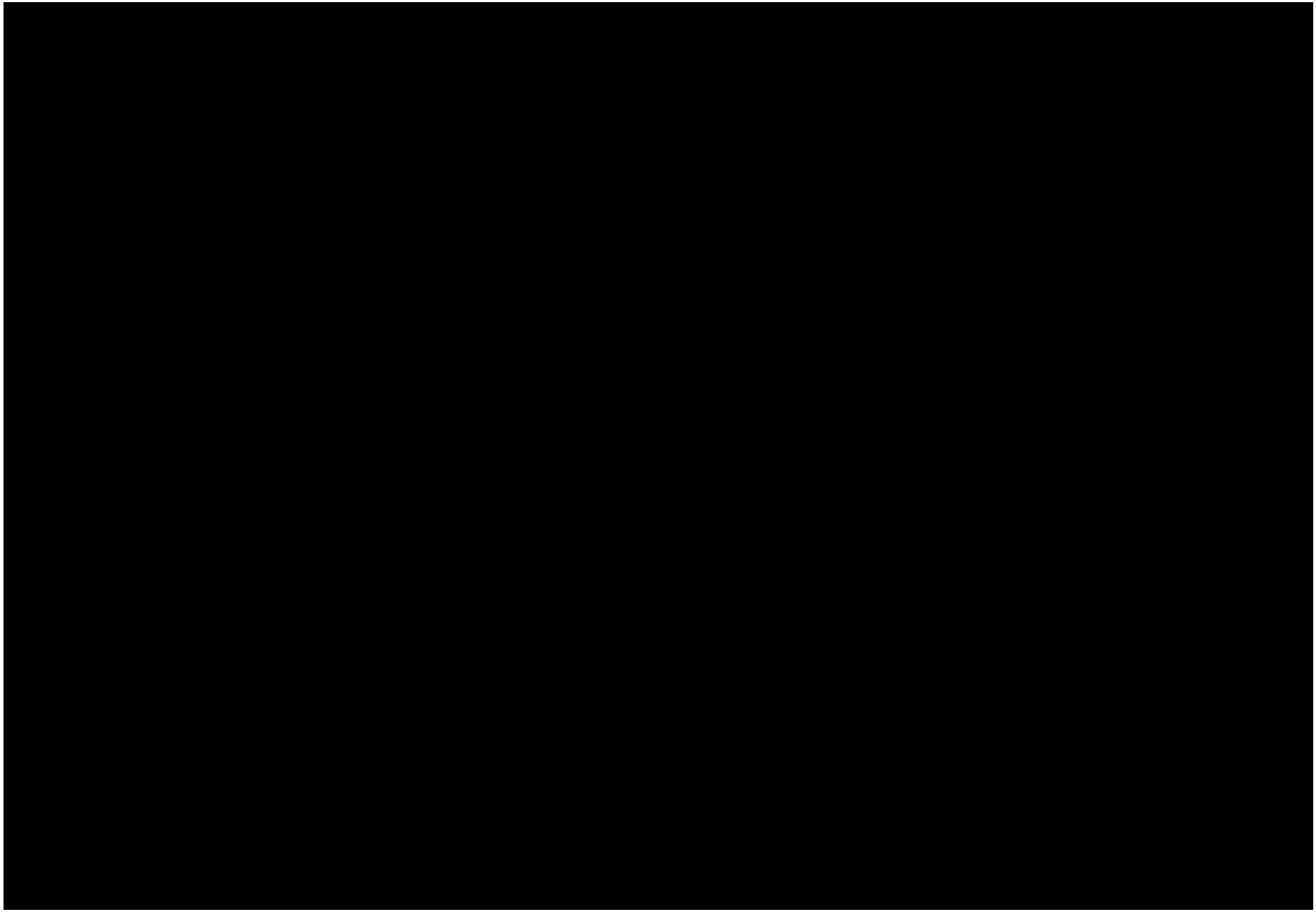


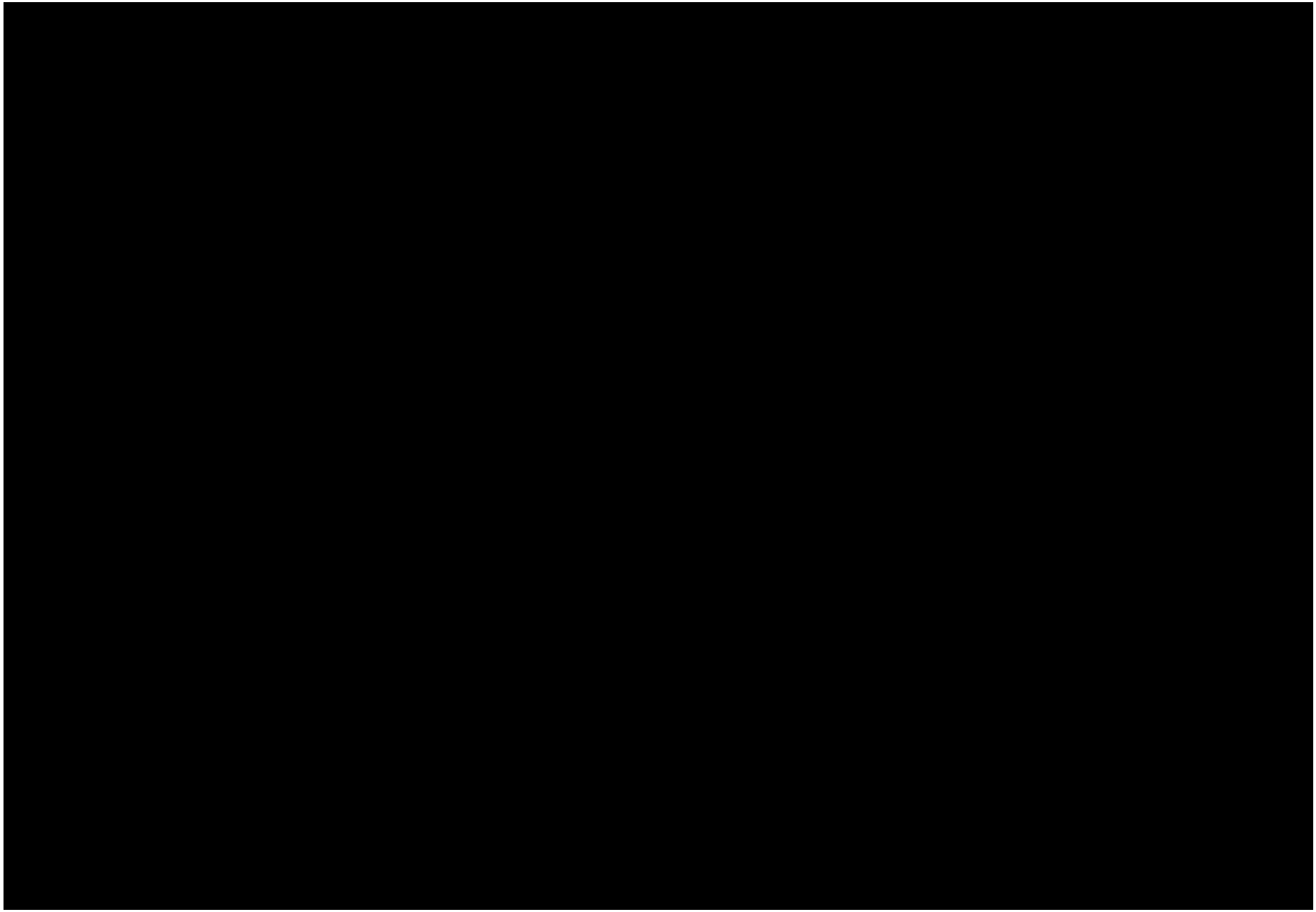


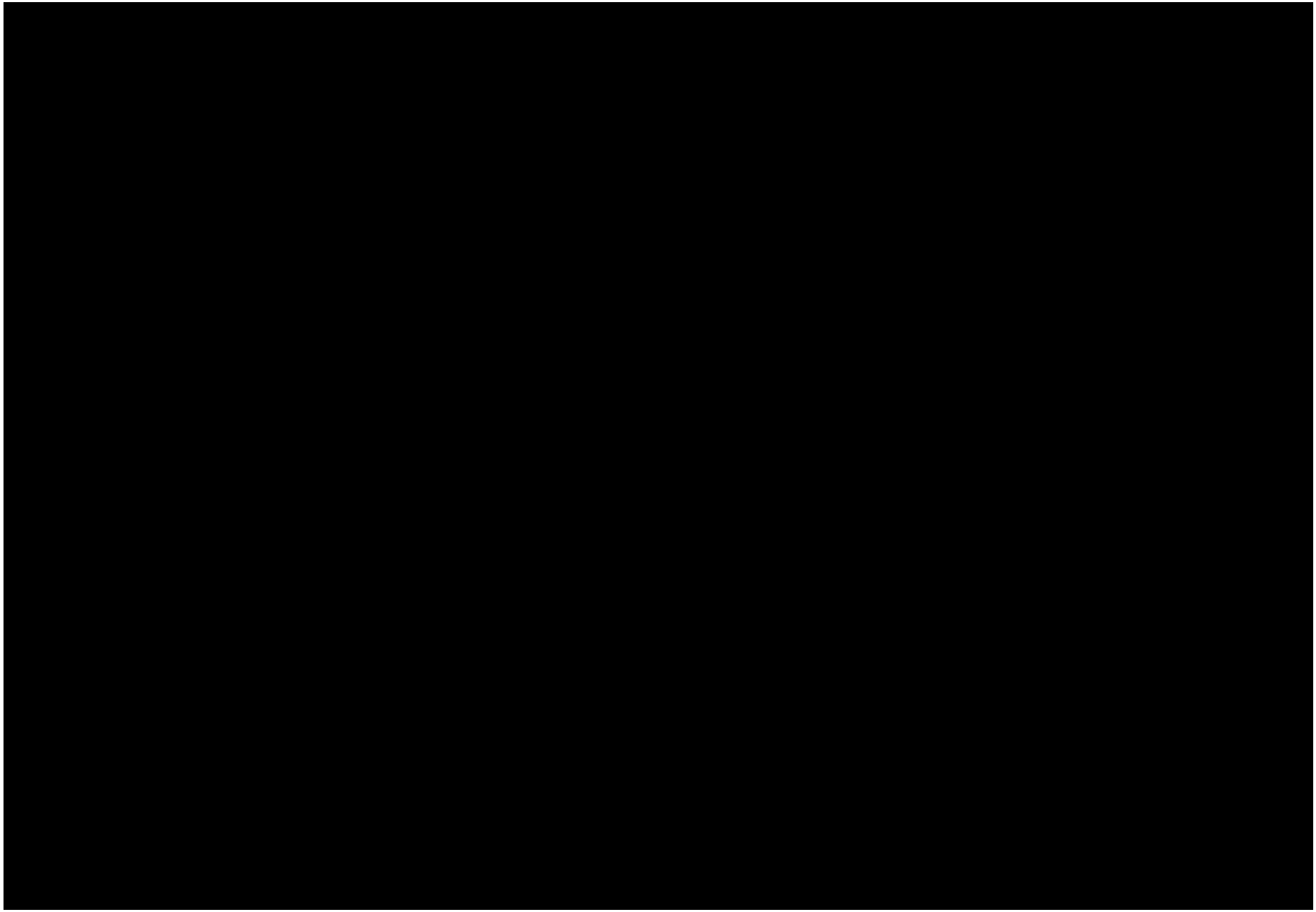


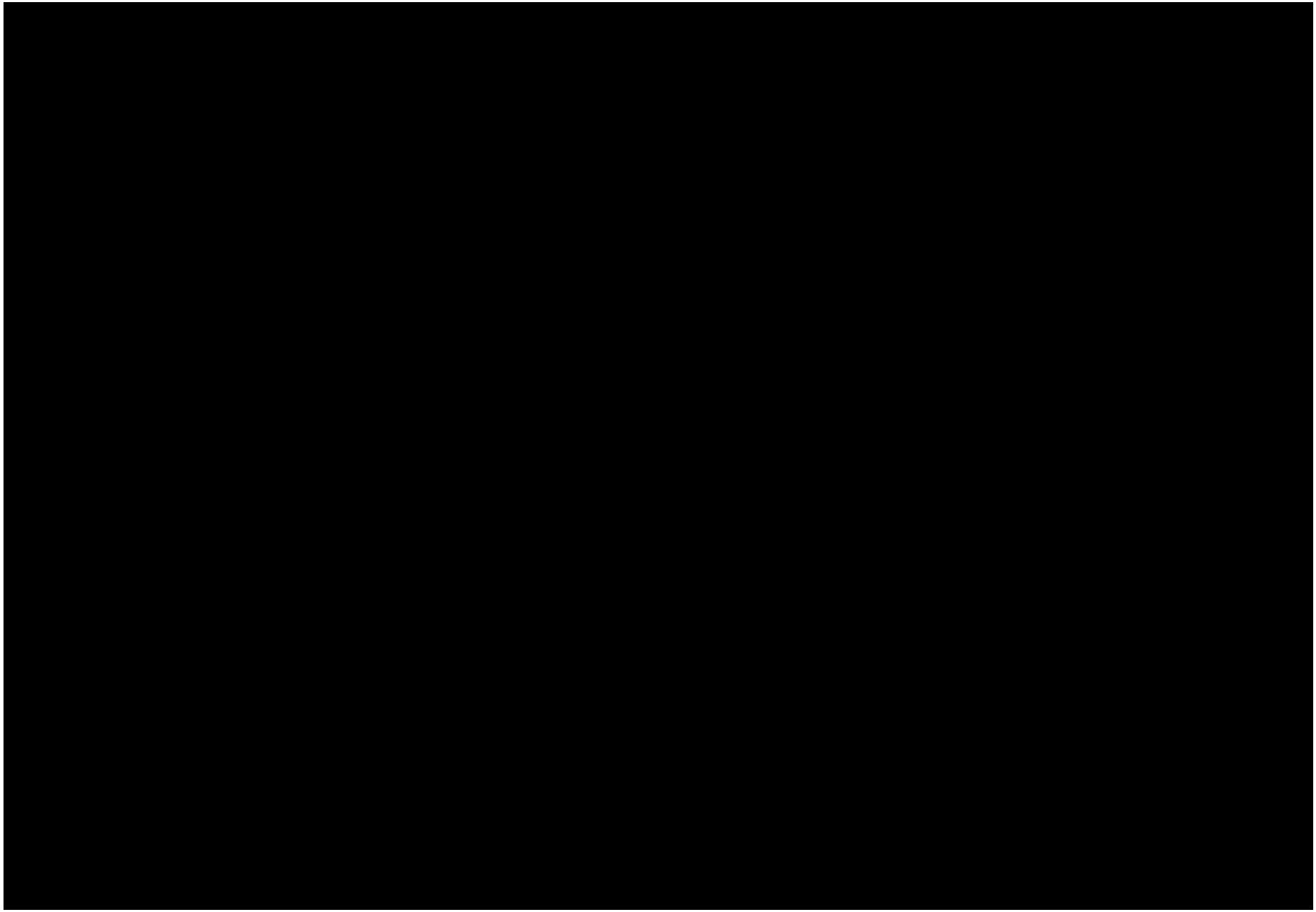


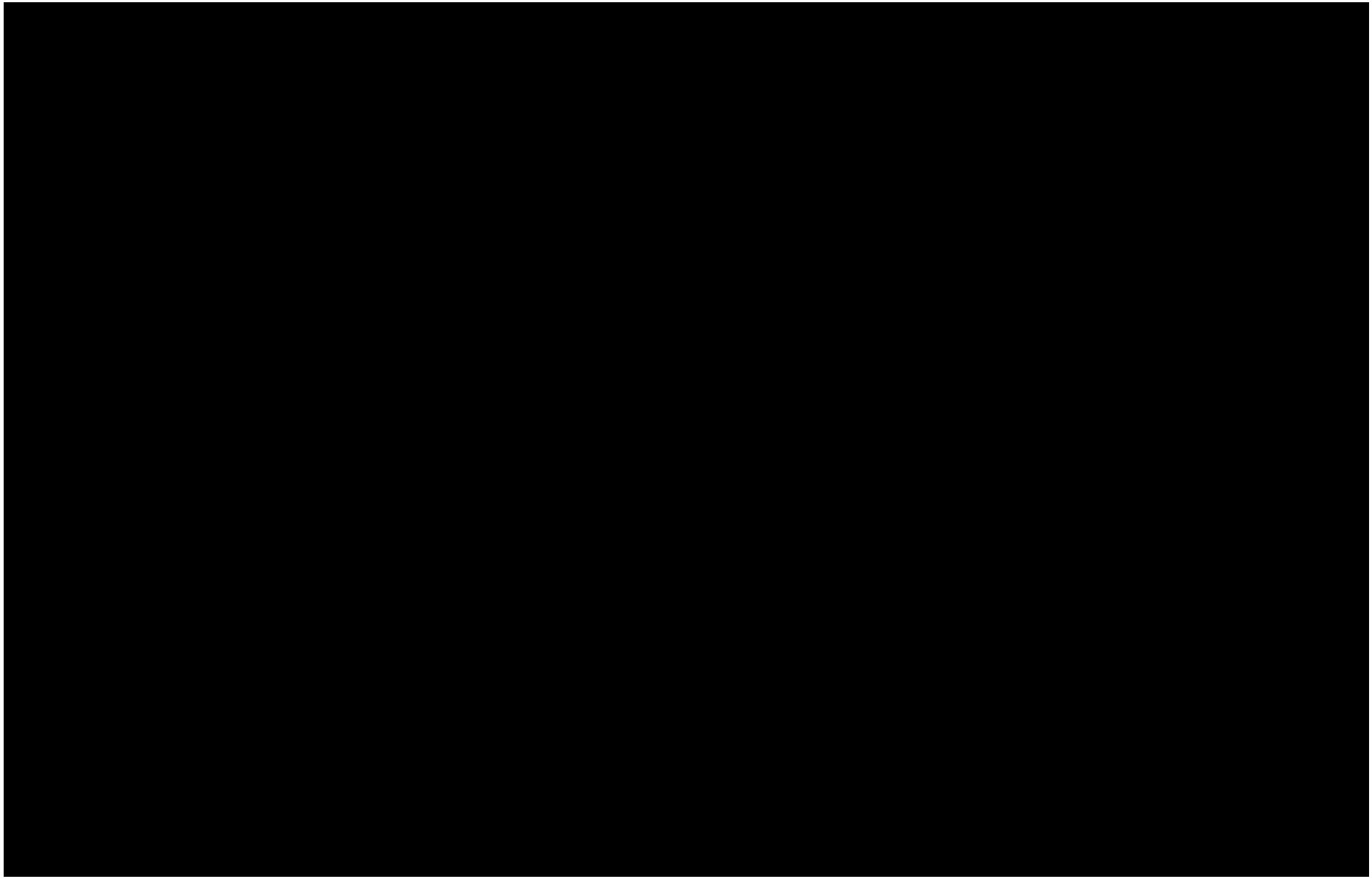












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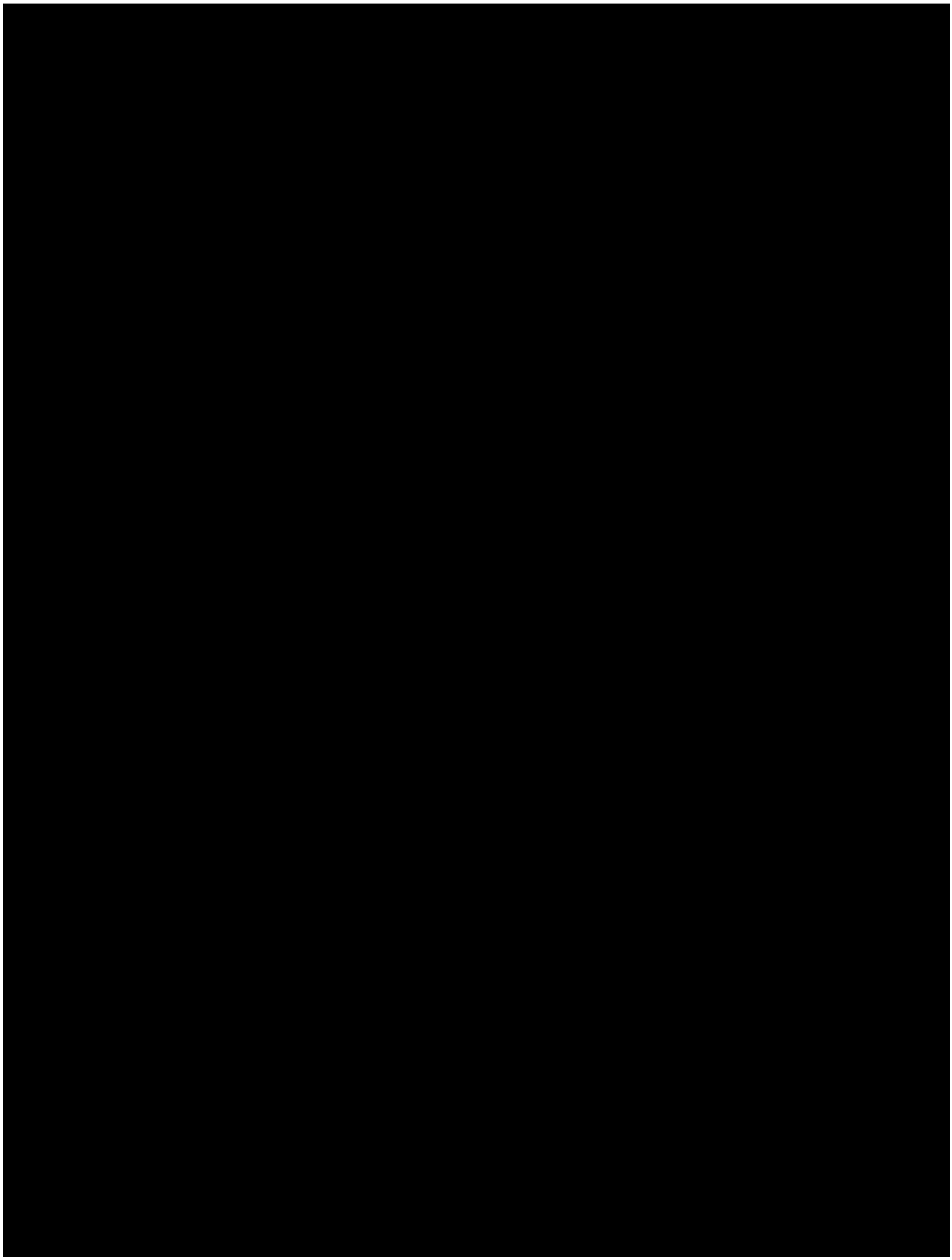

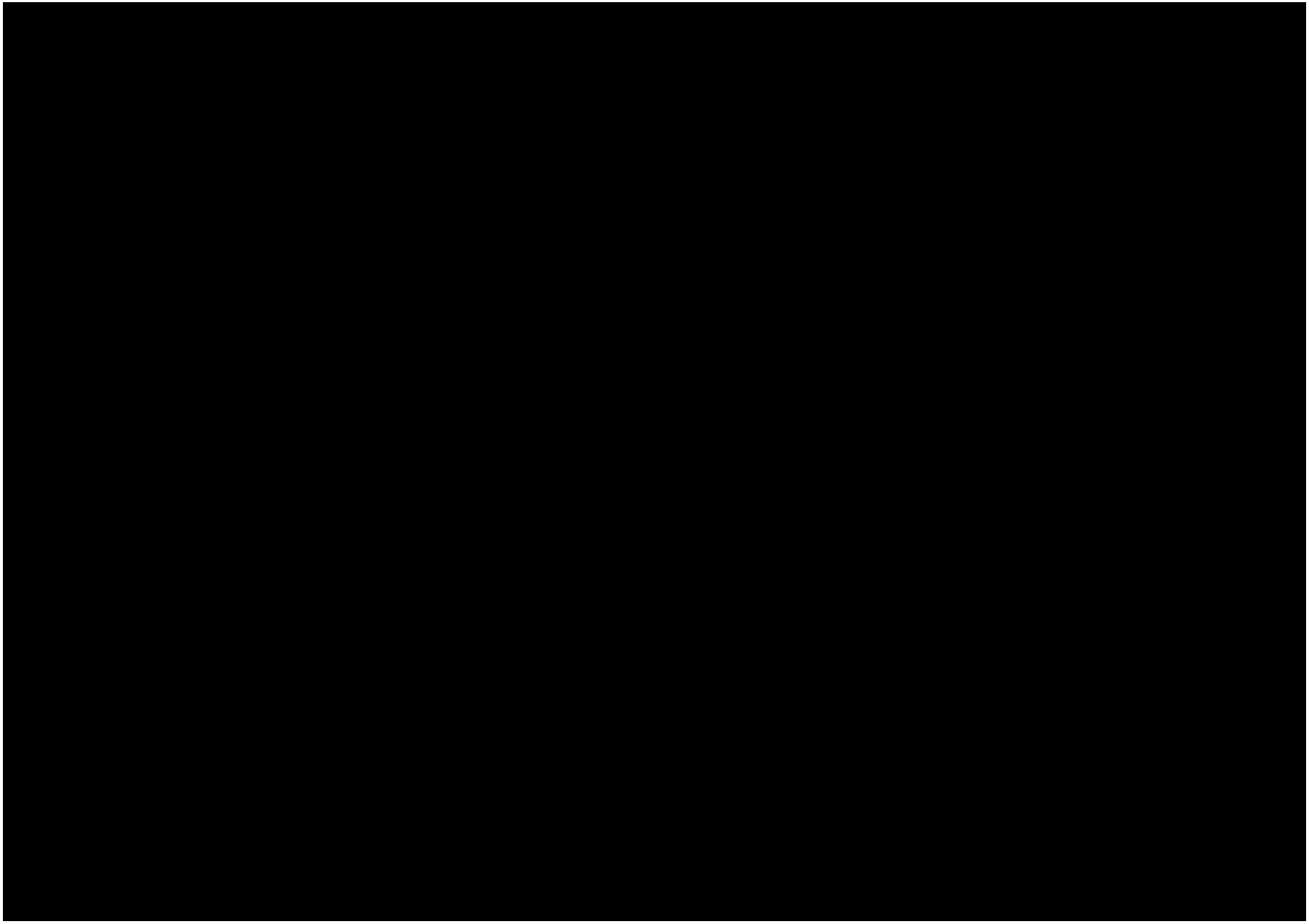

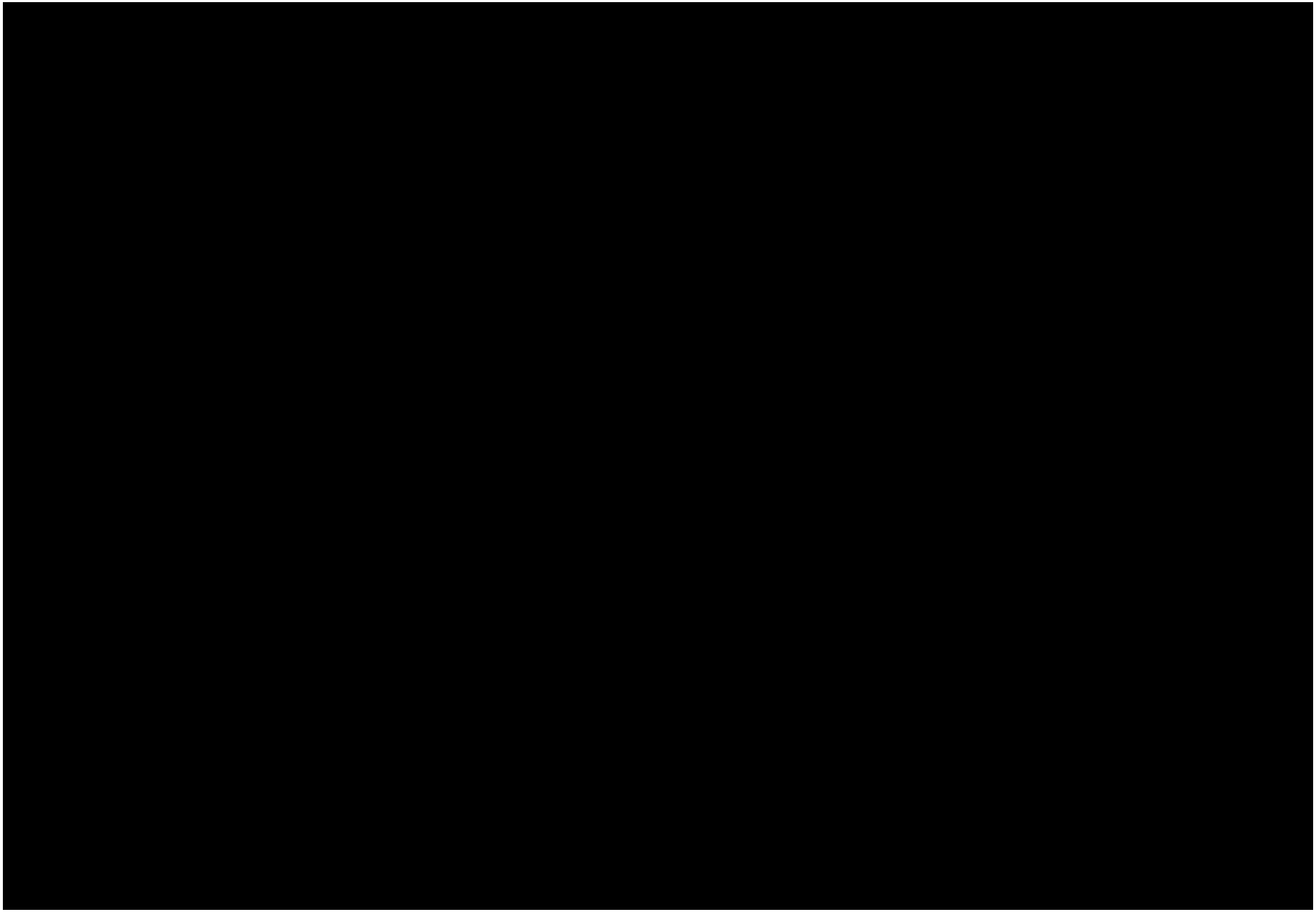

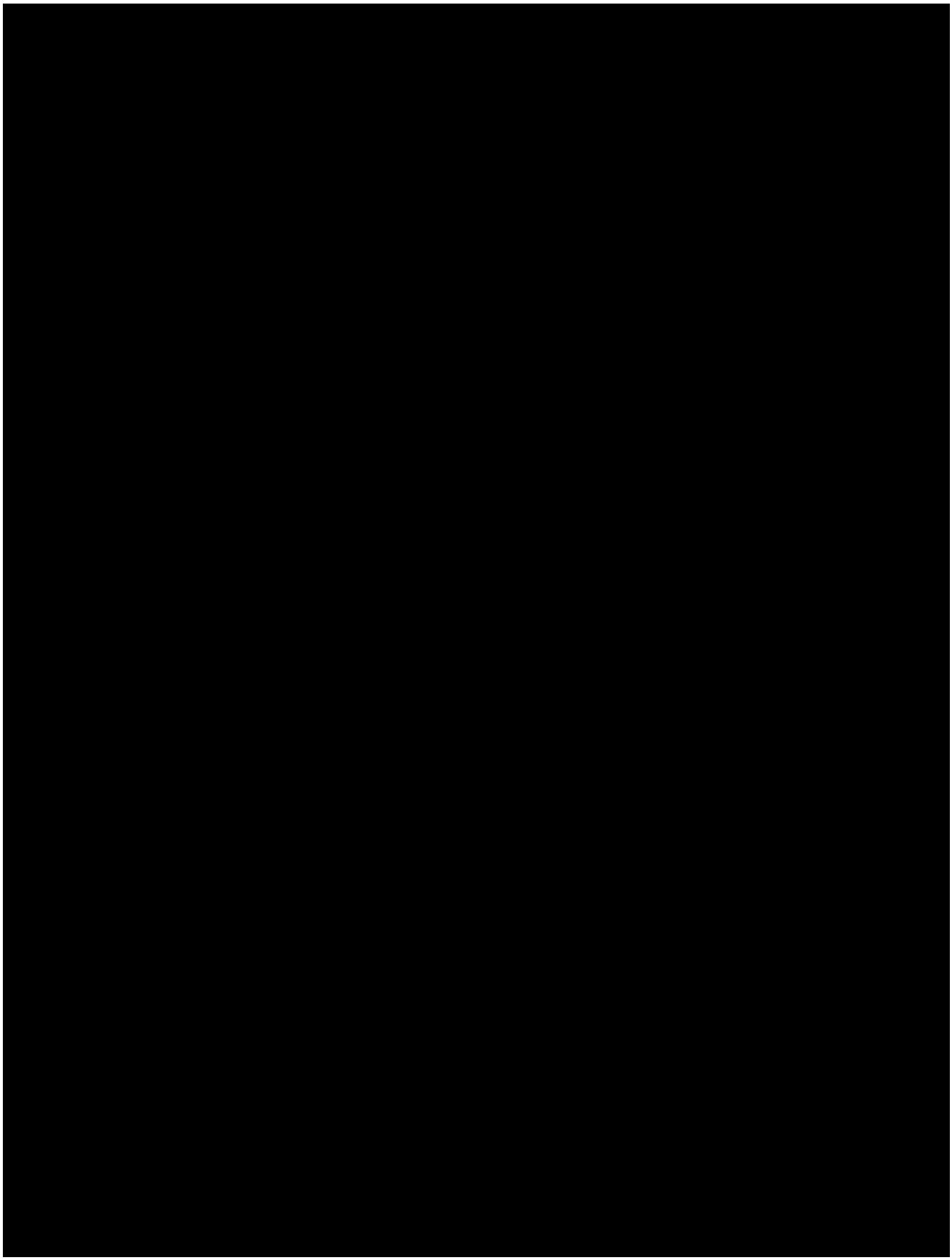

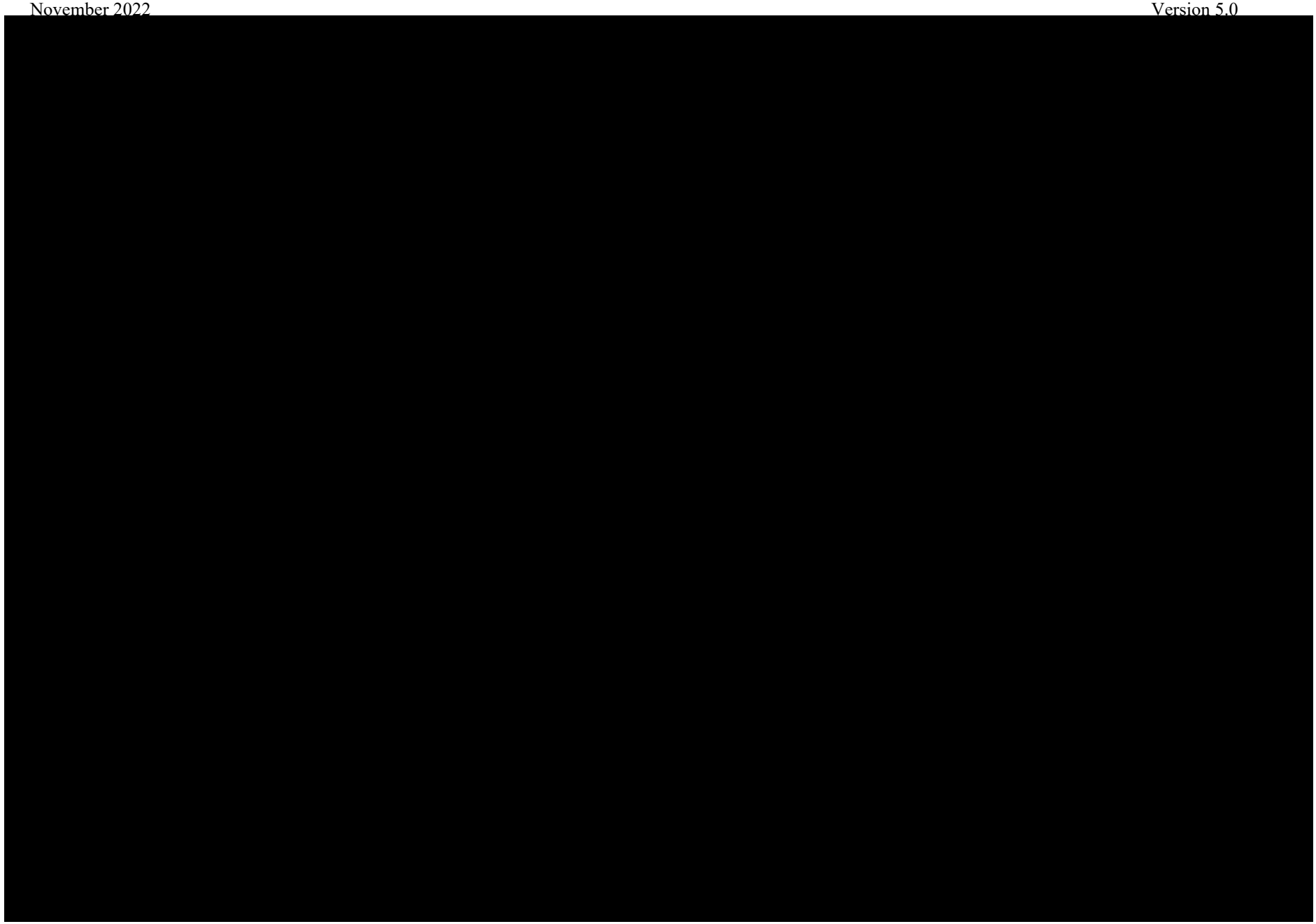

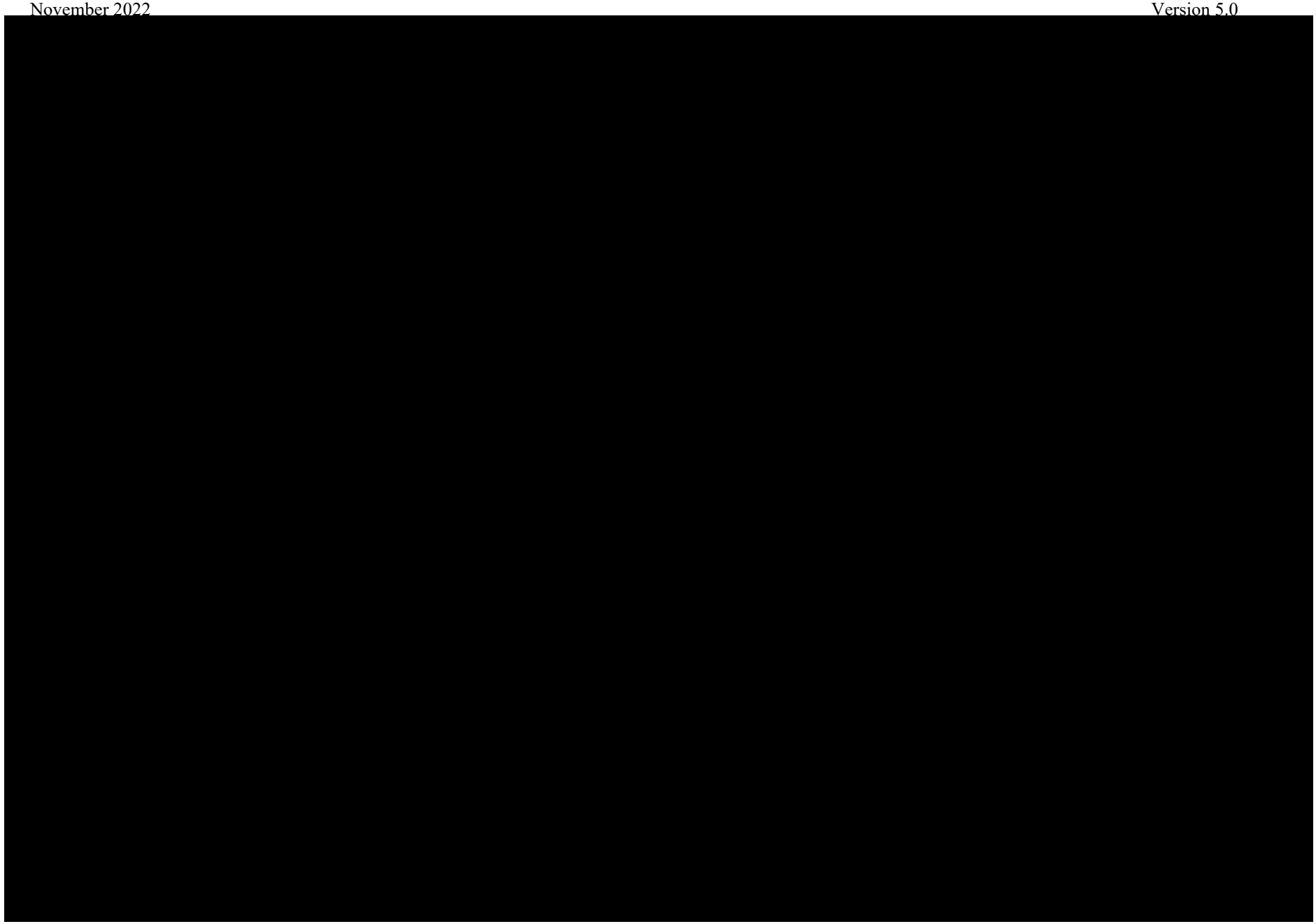

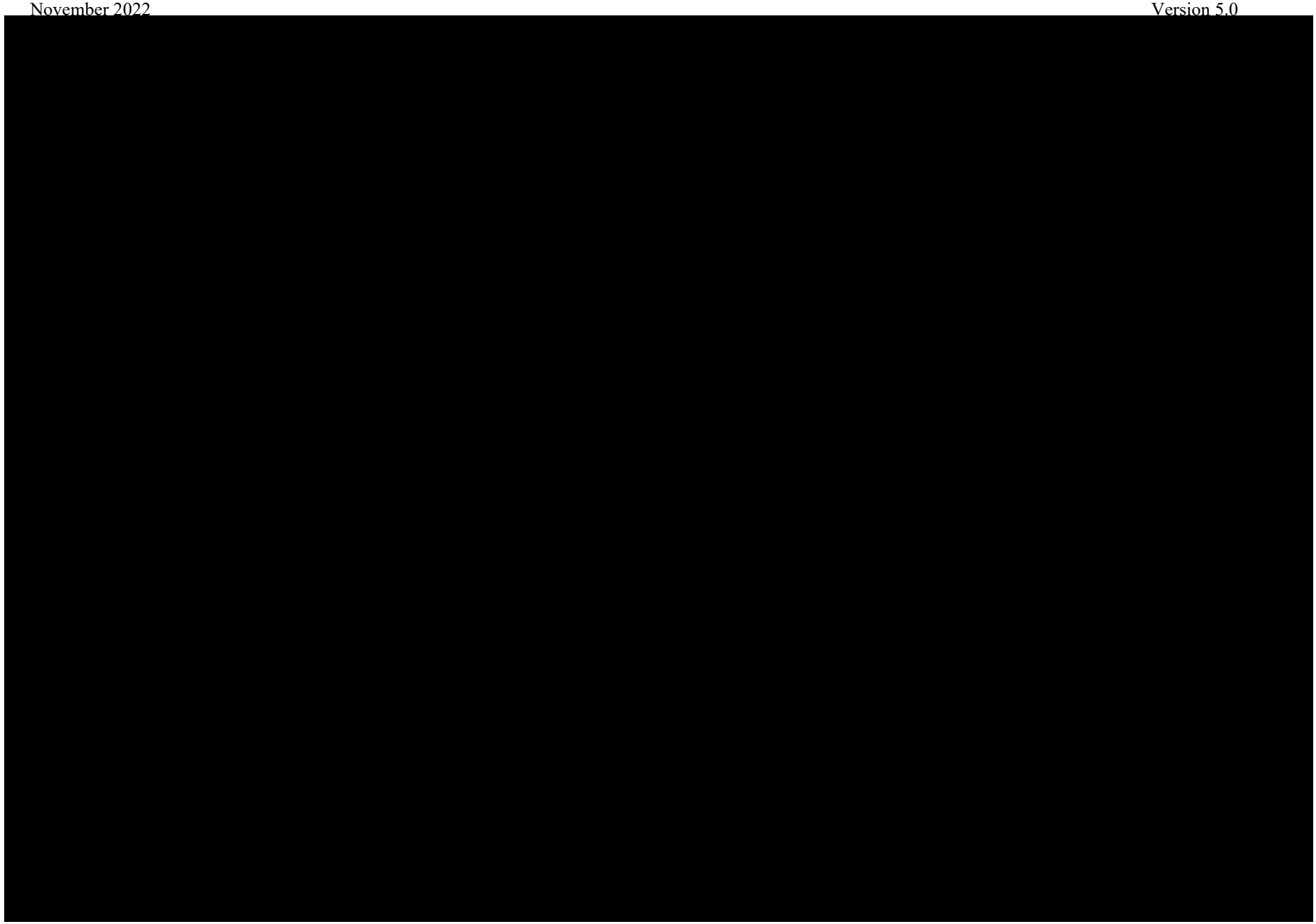

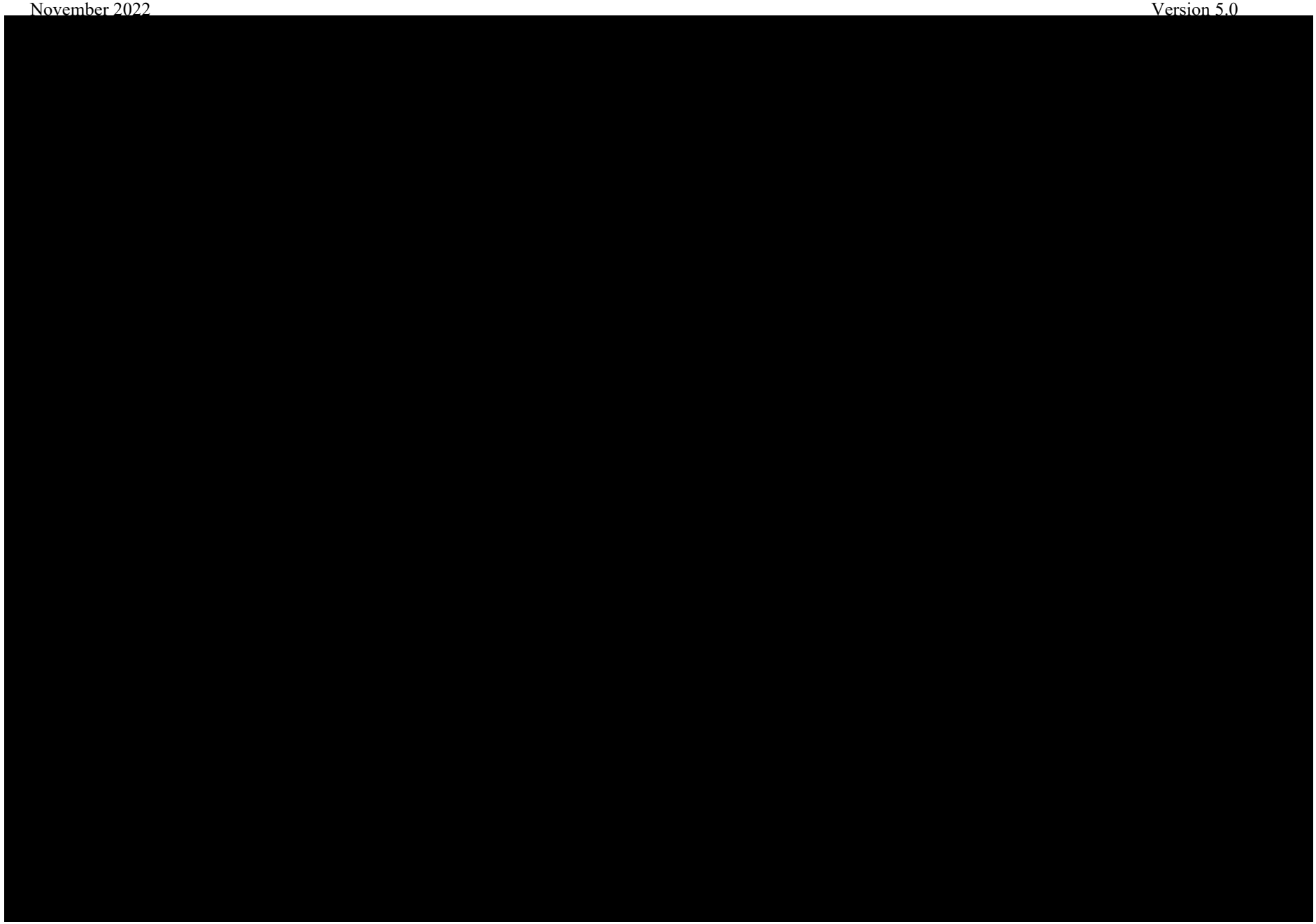

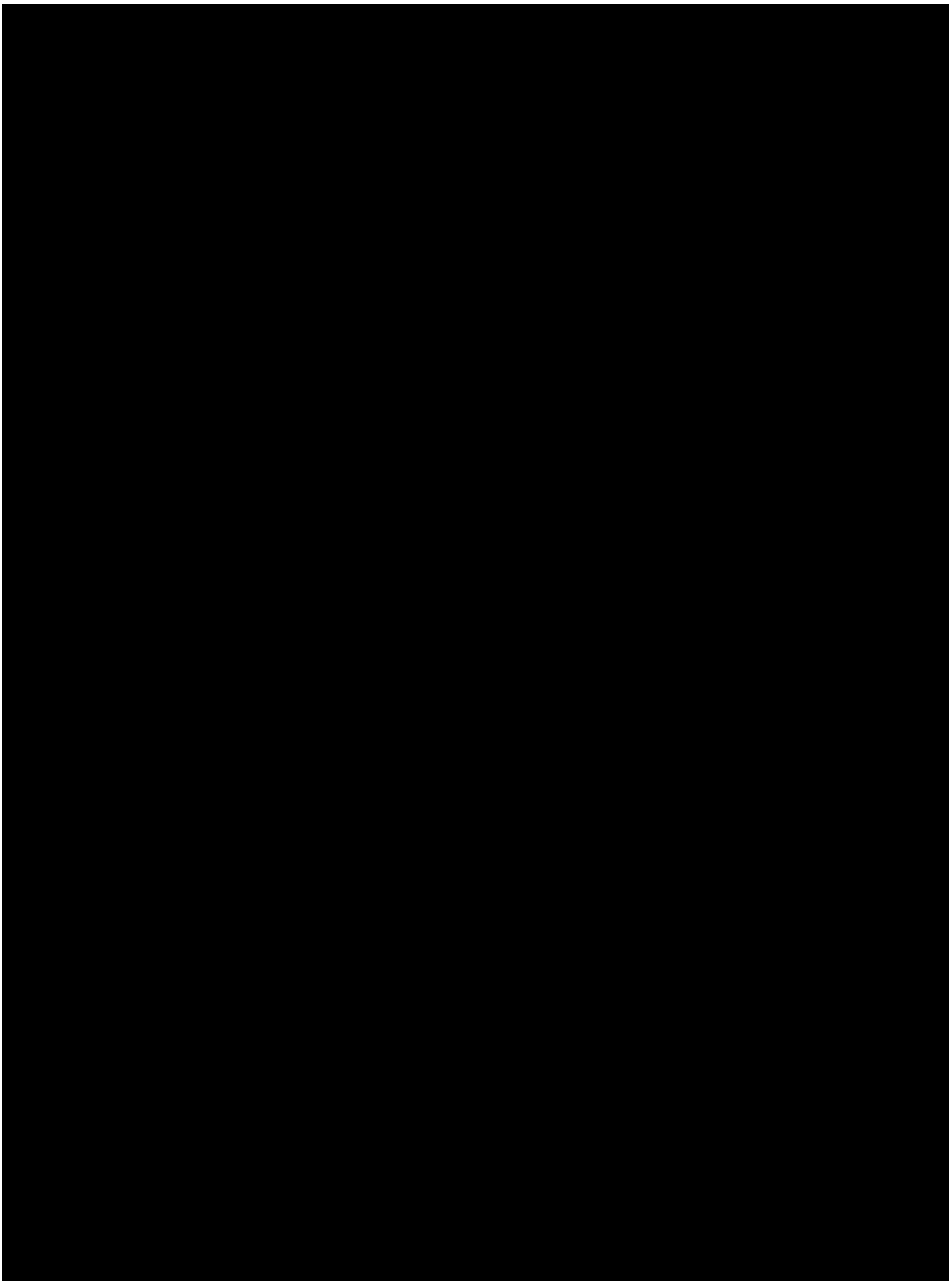

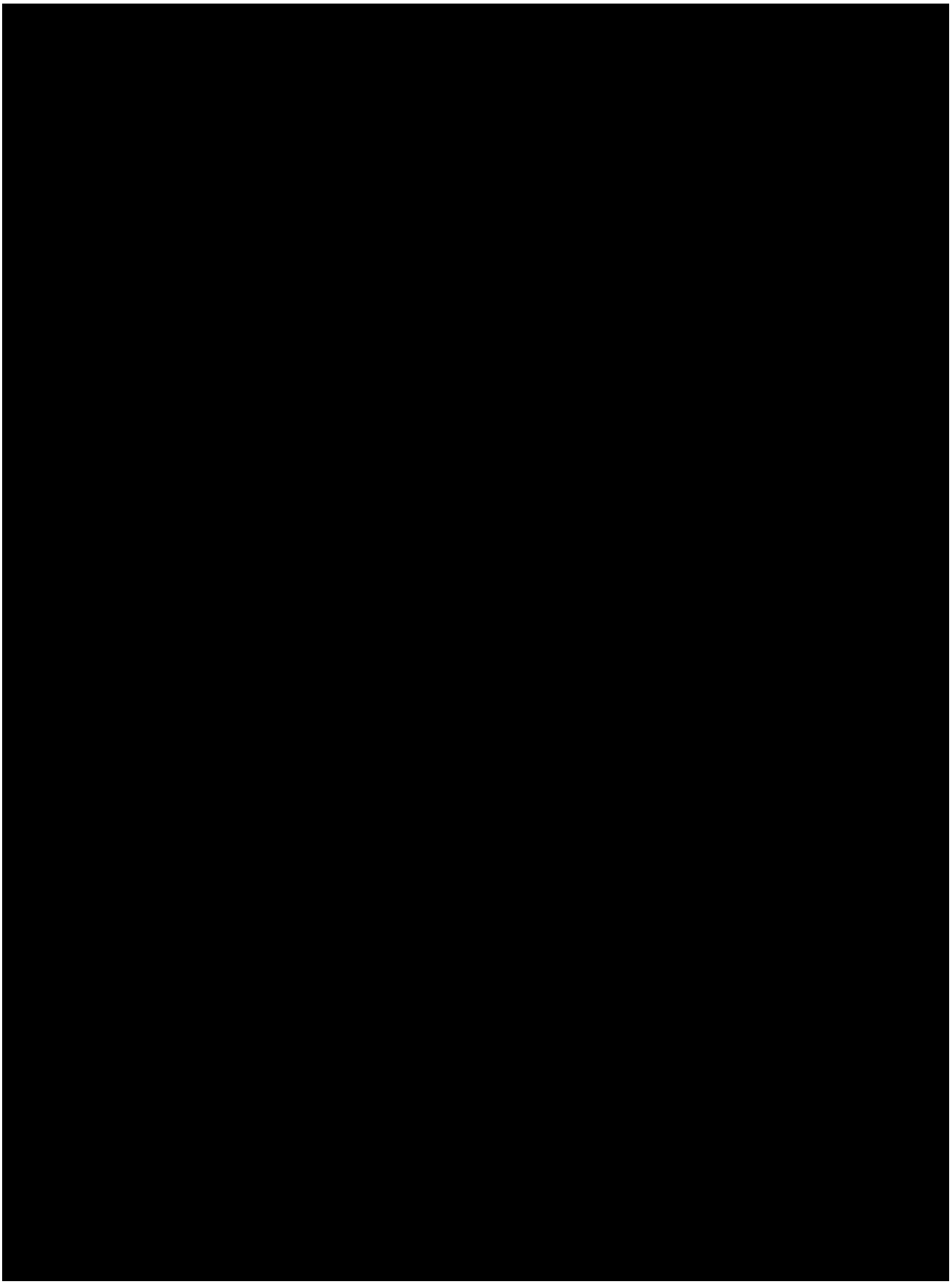

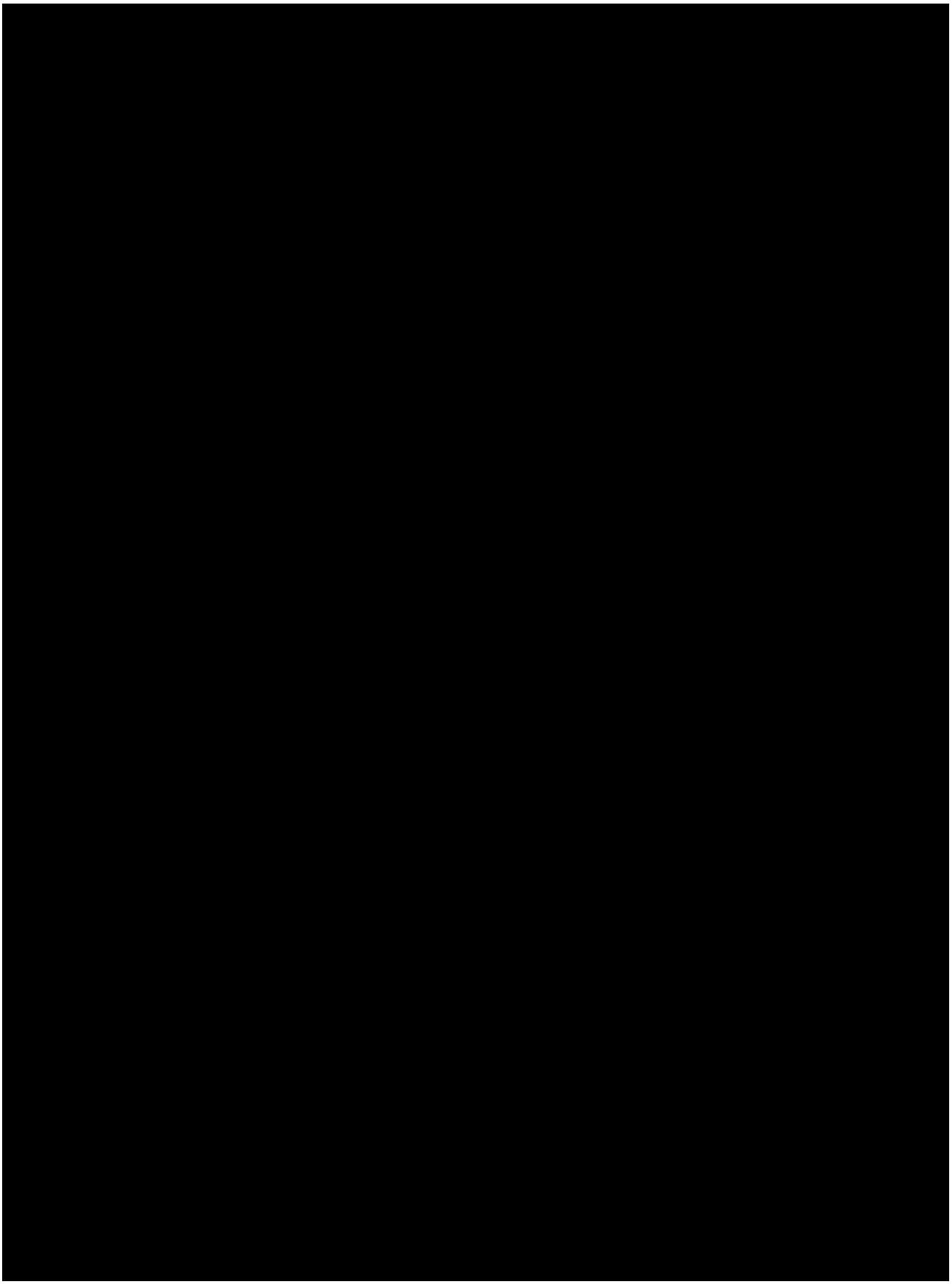

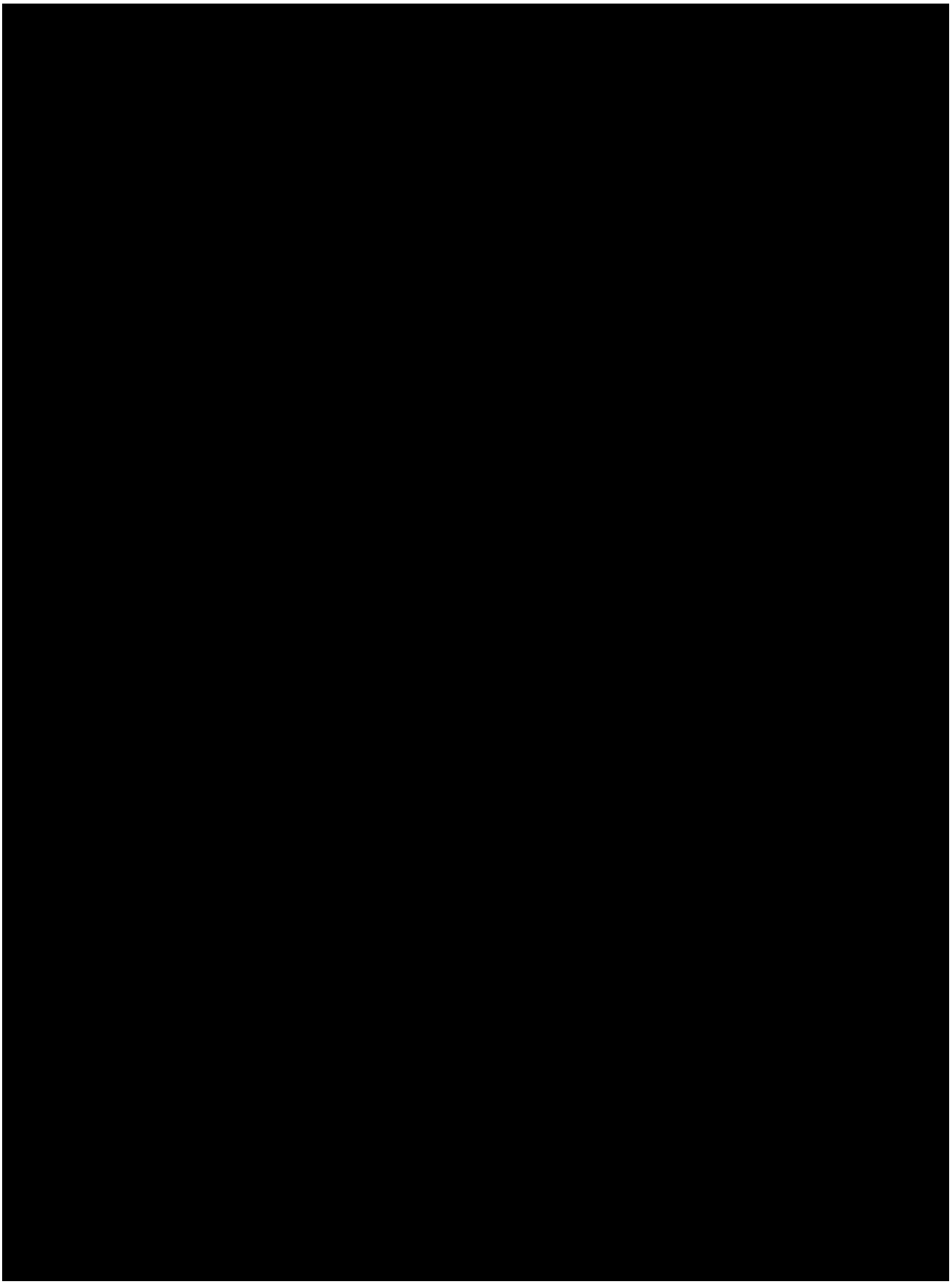

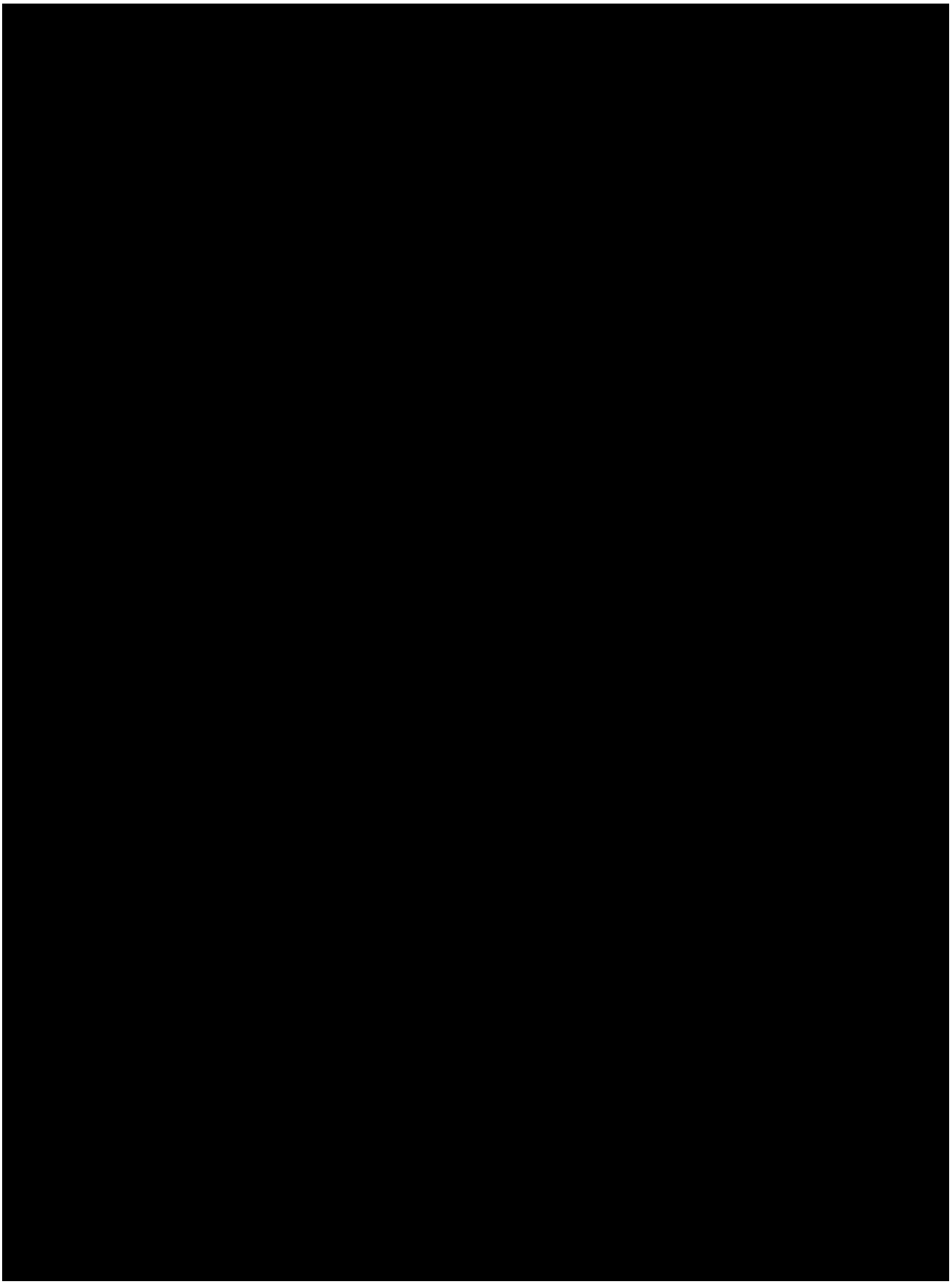

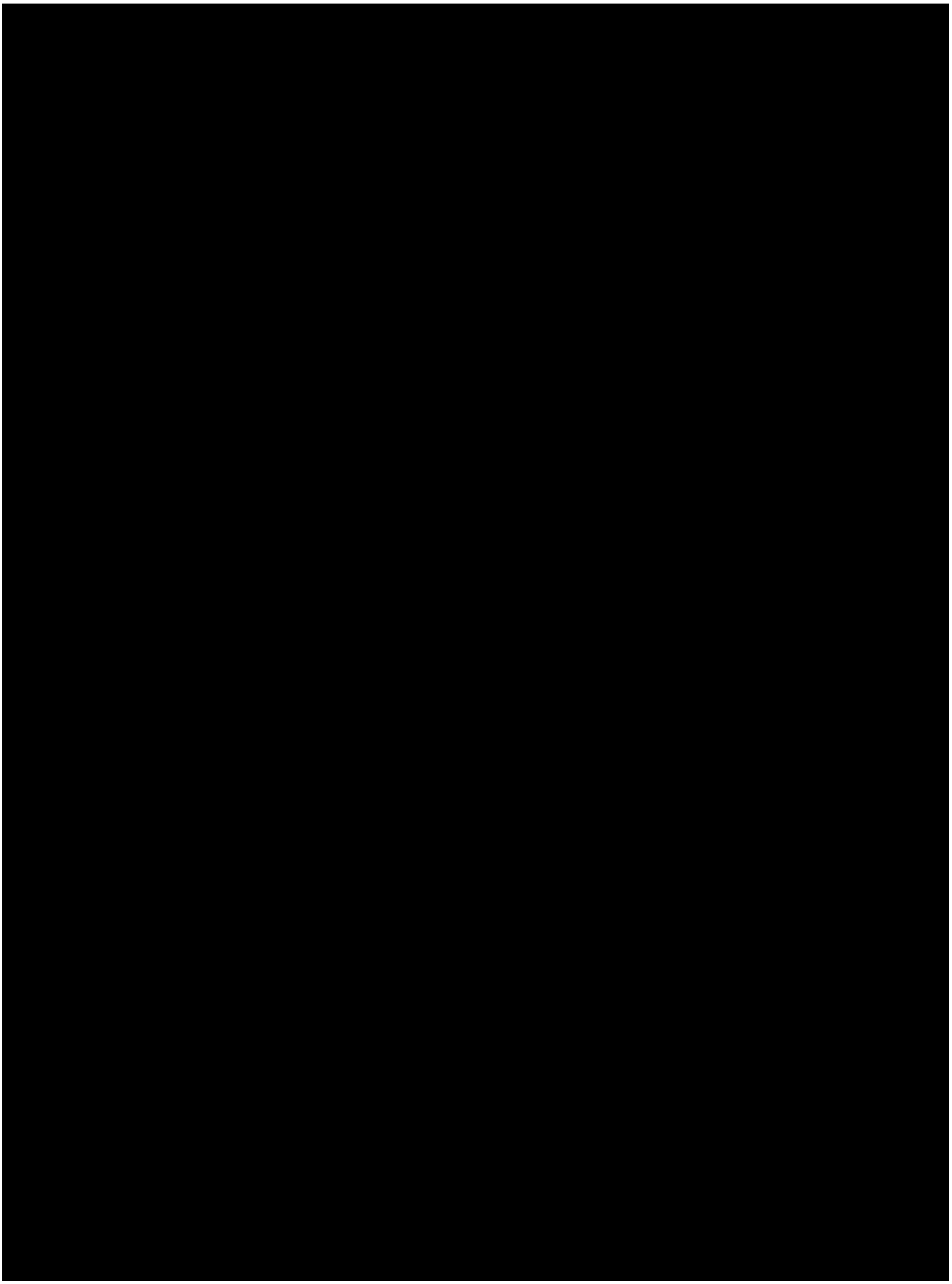

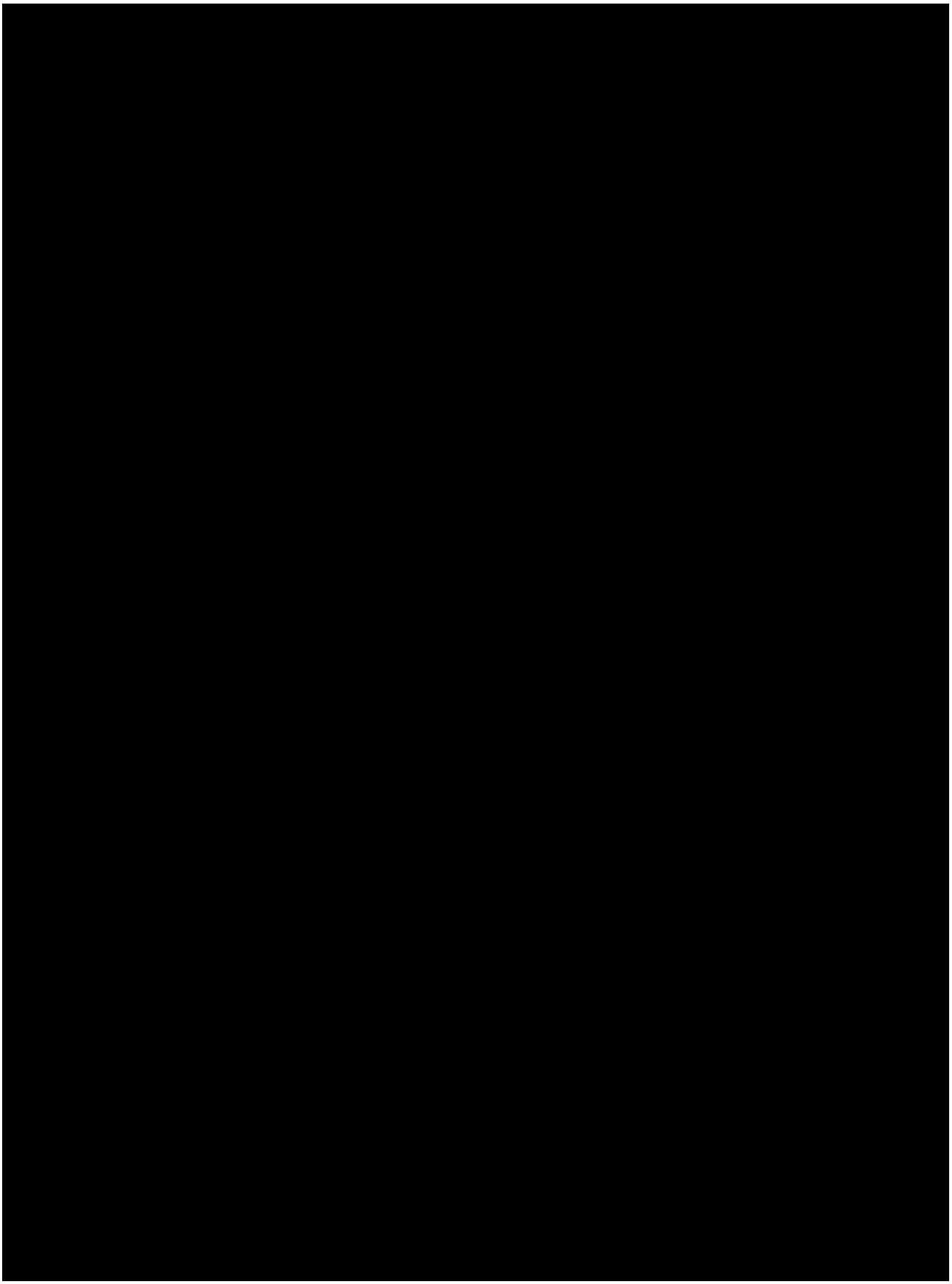

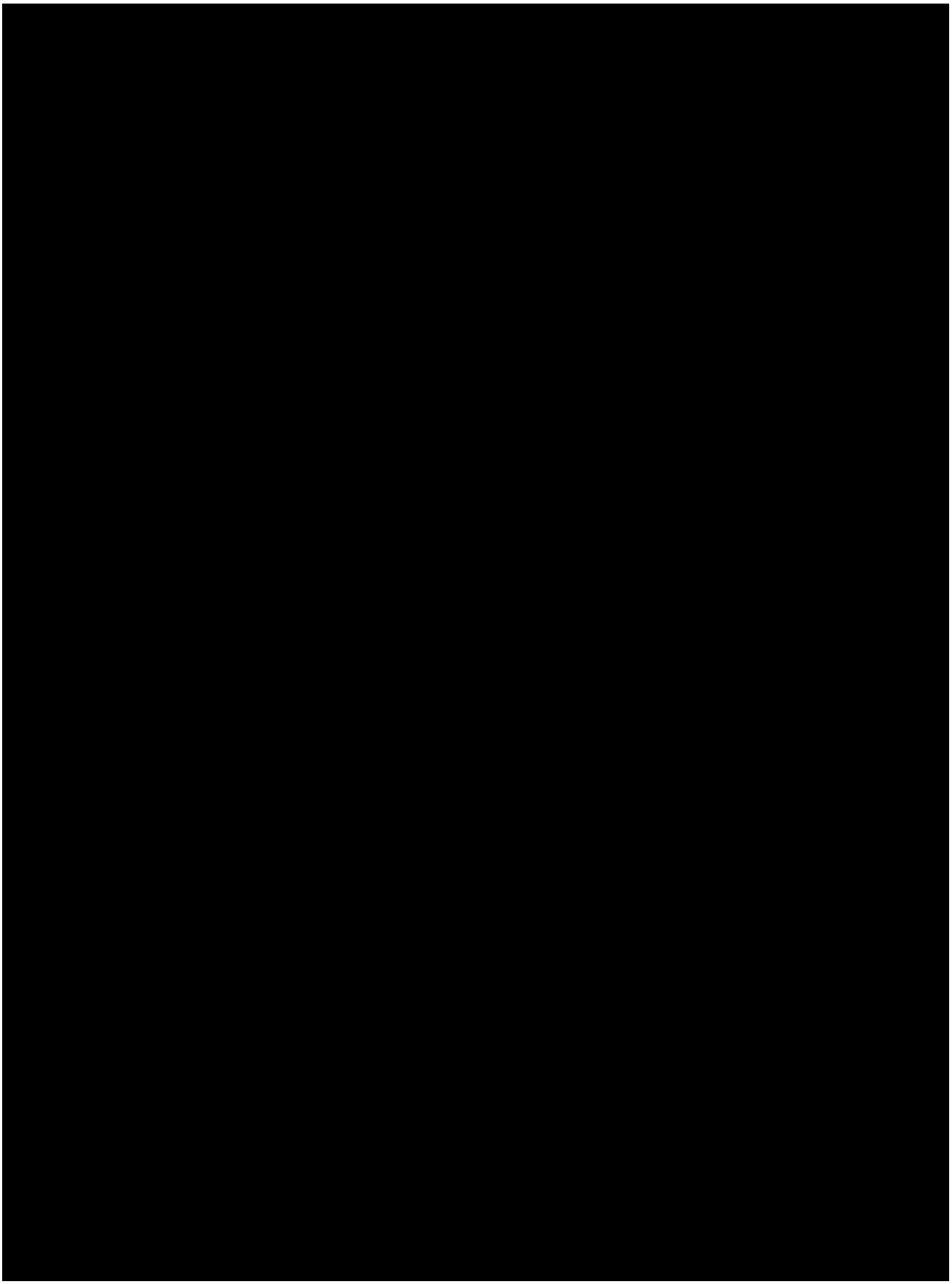

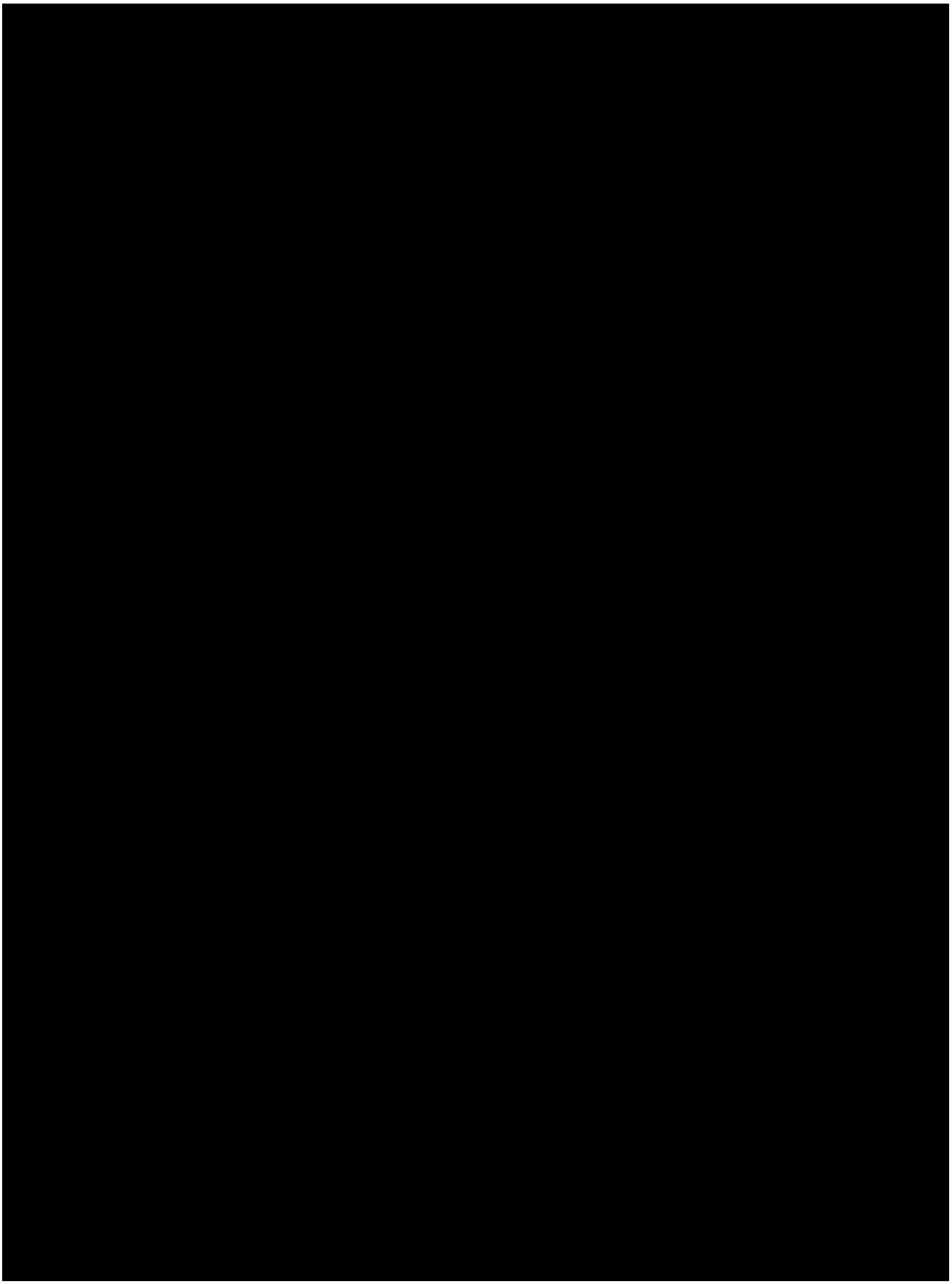

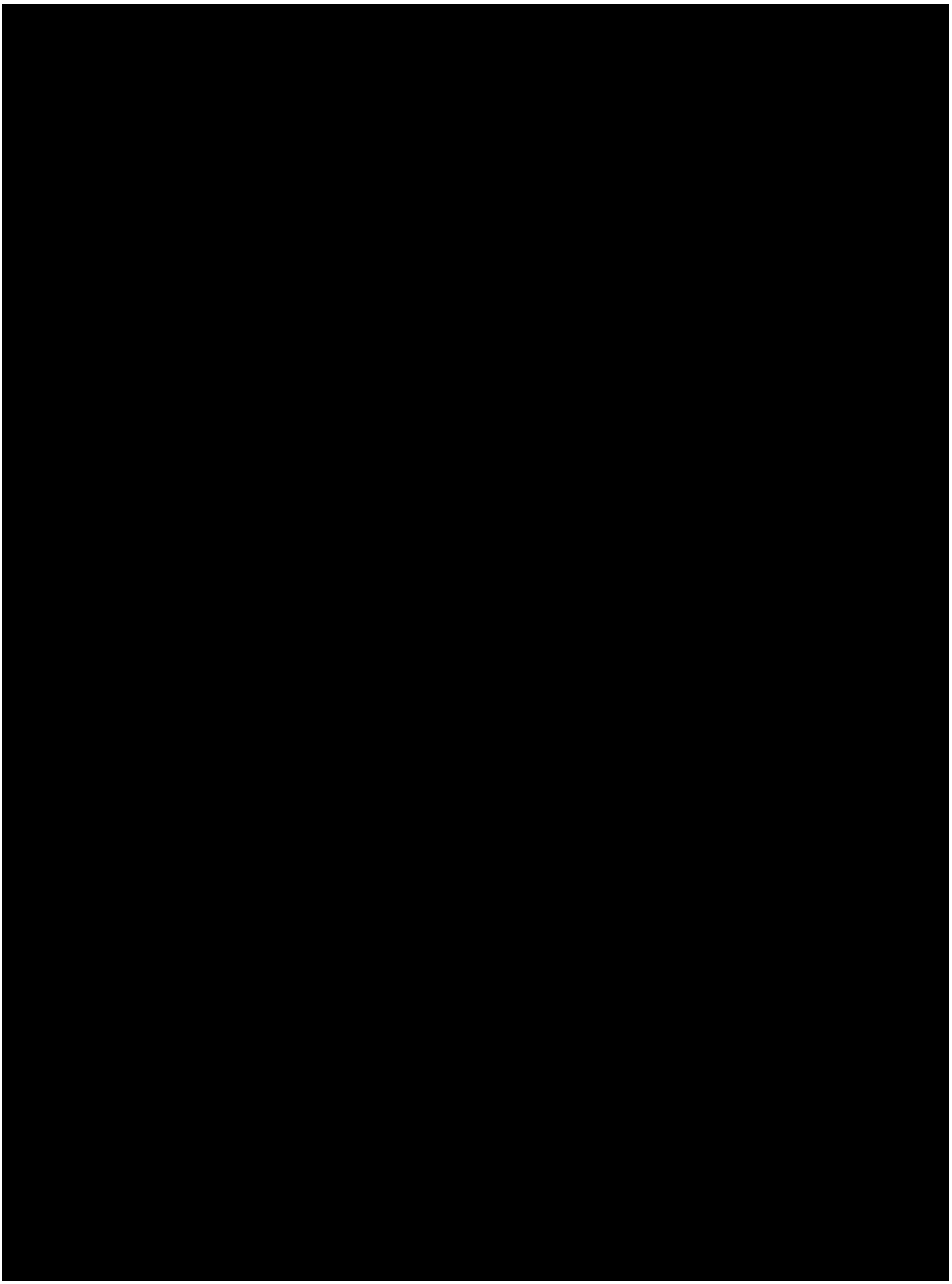

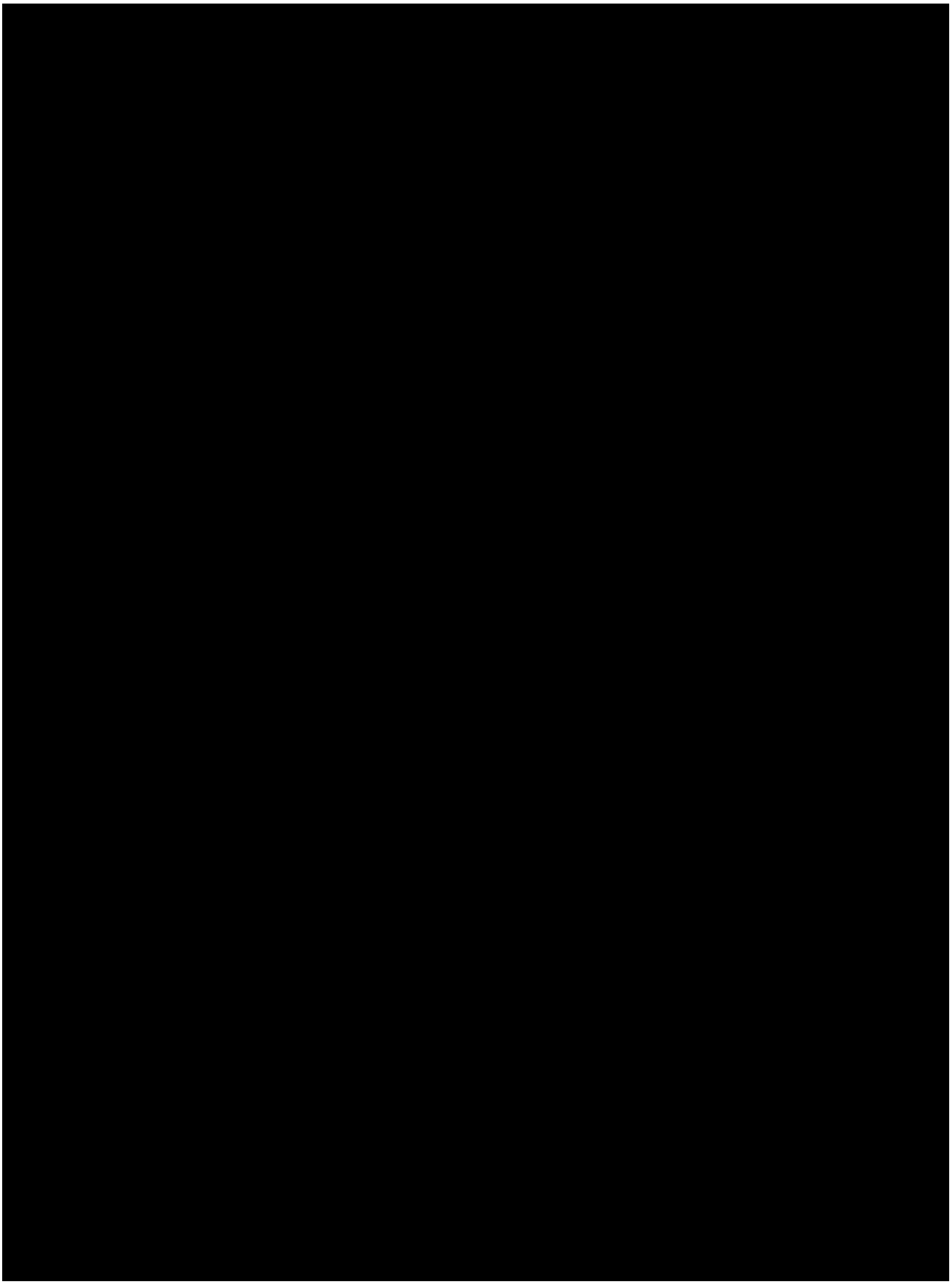

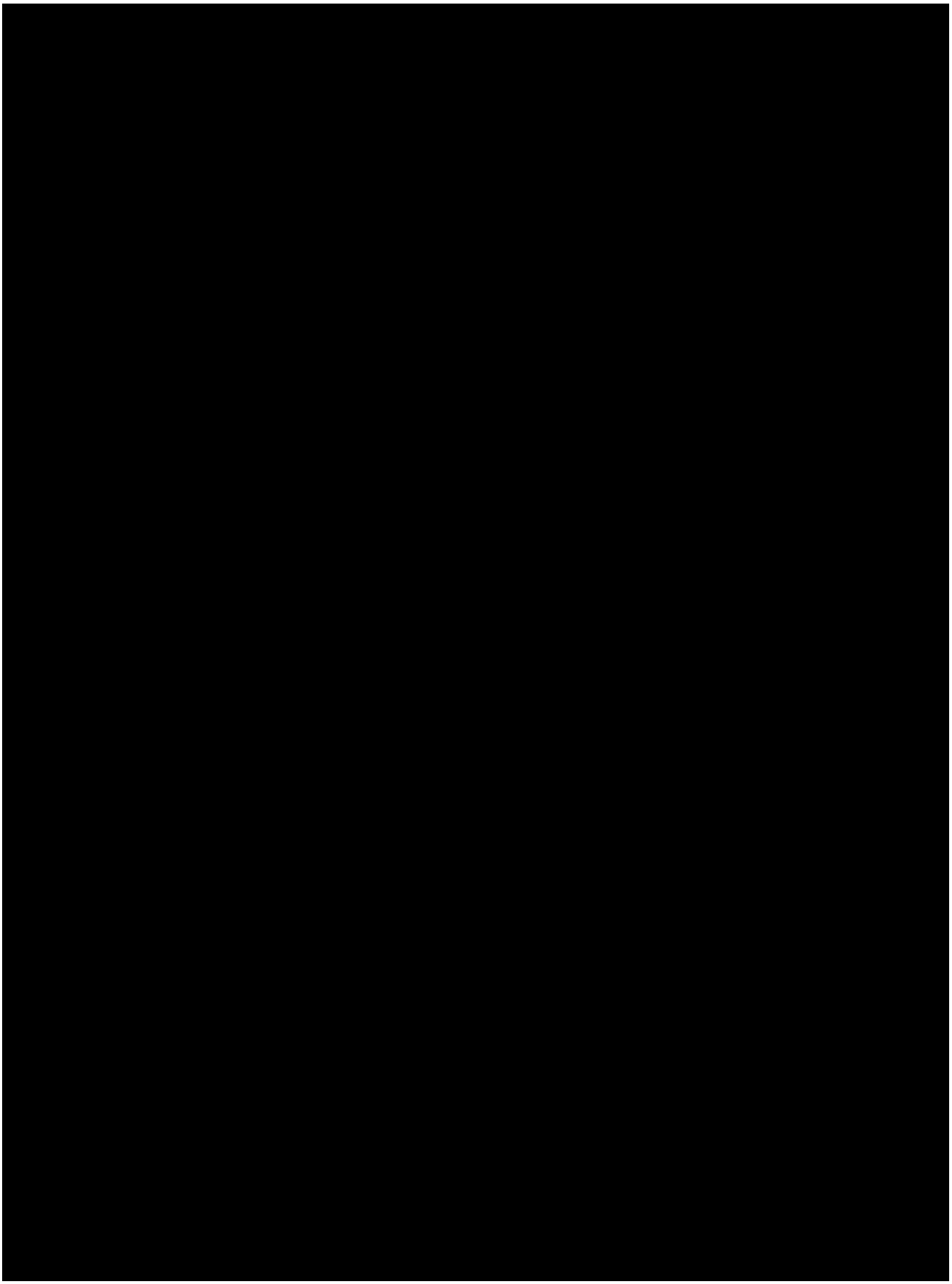

7. SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

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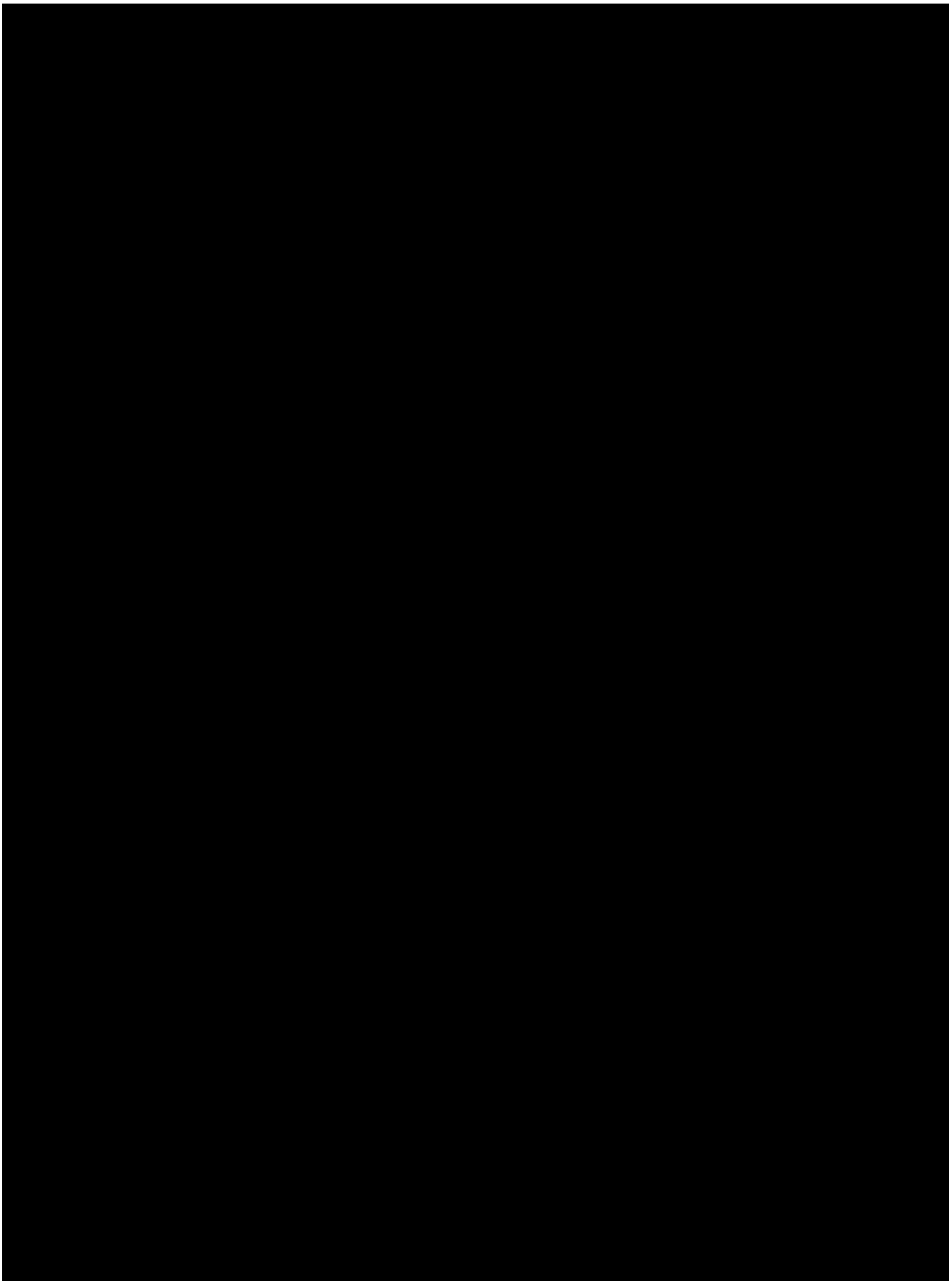

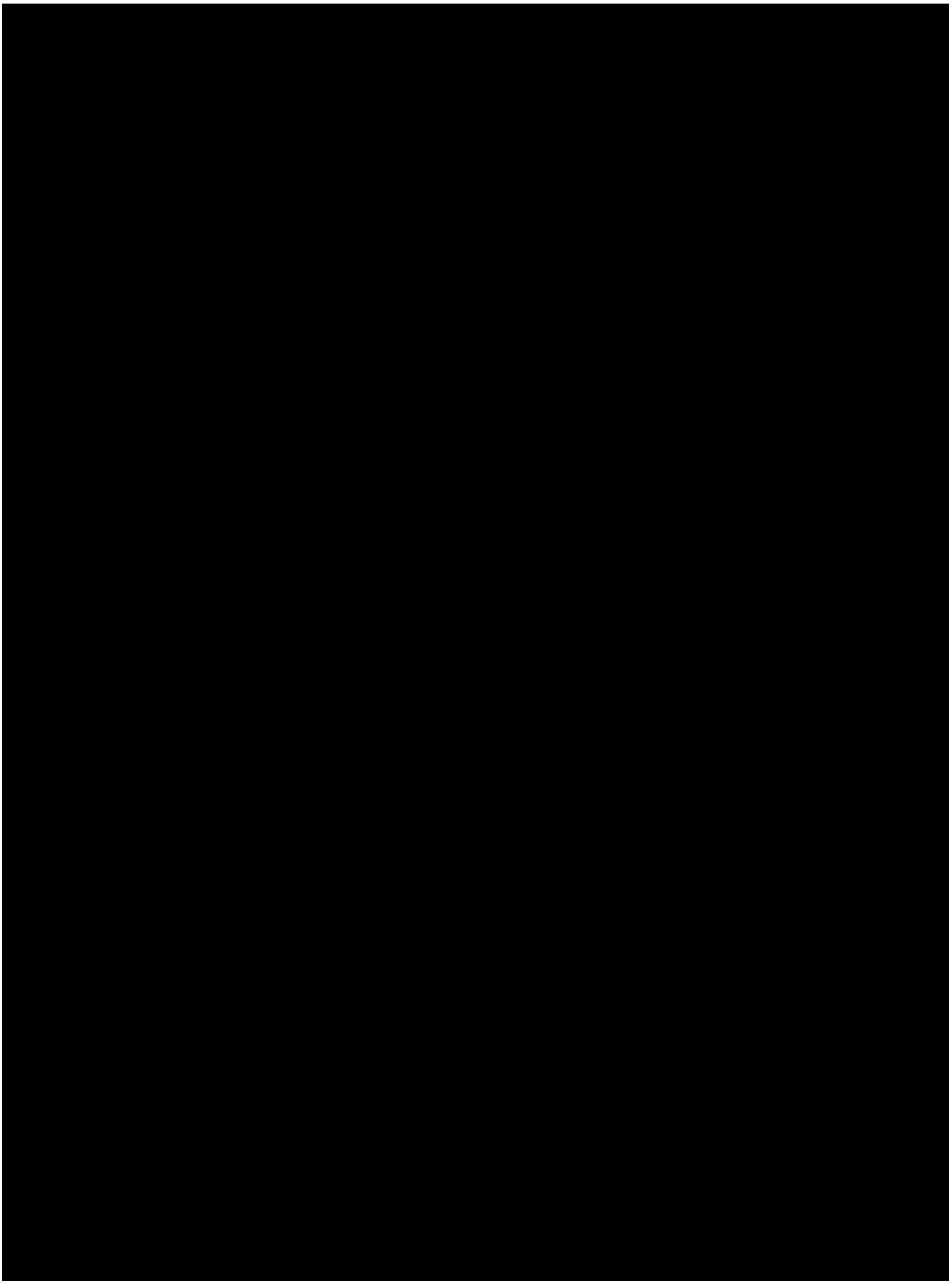

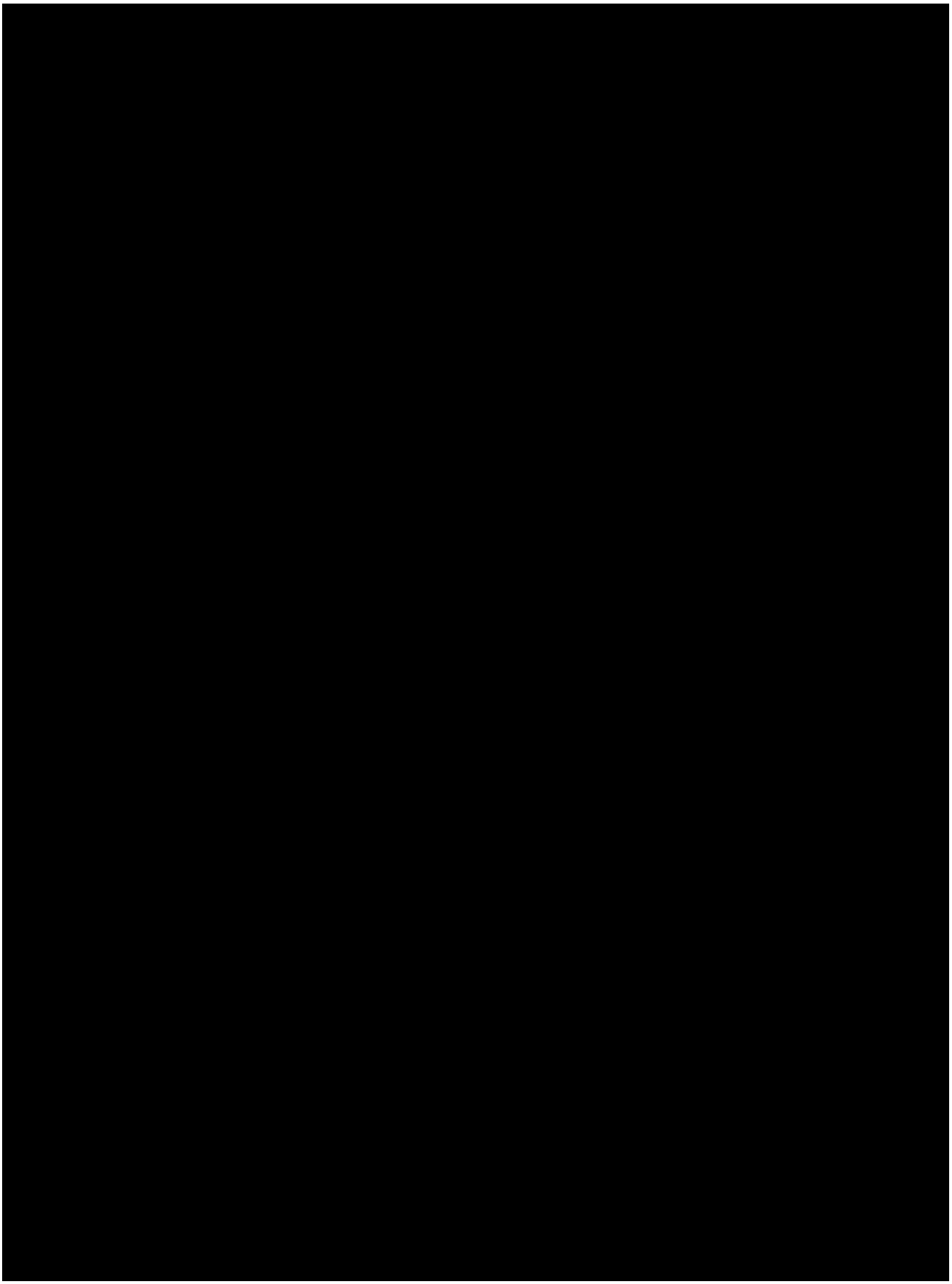

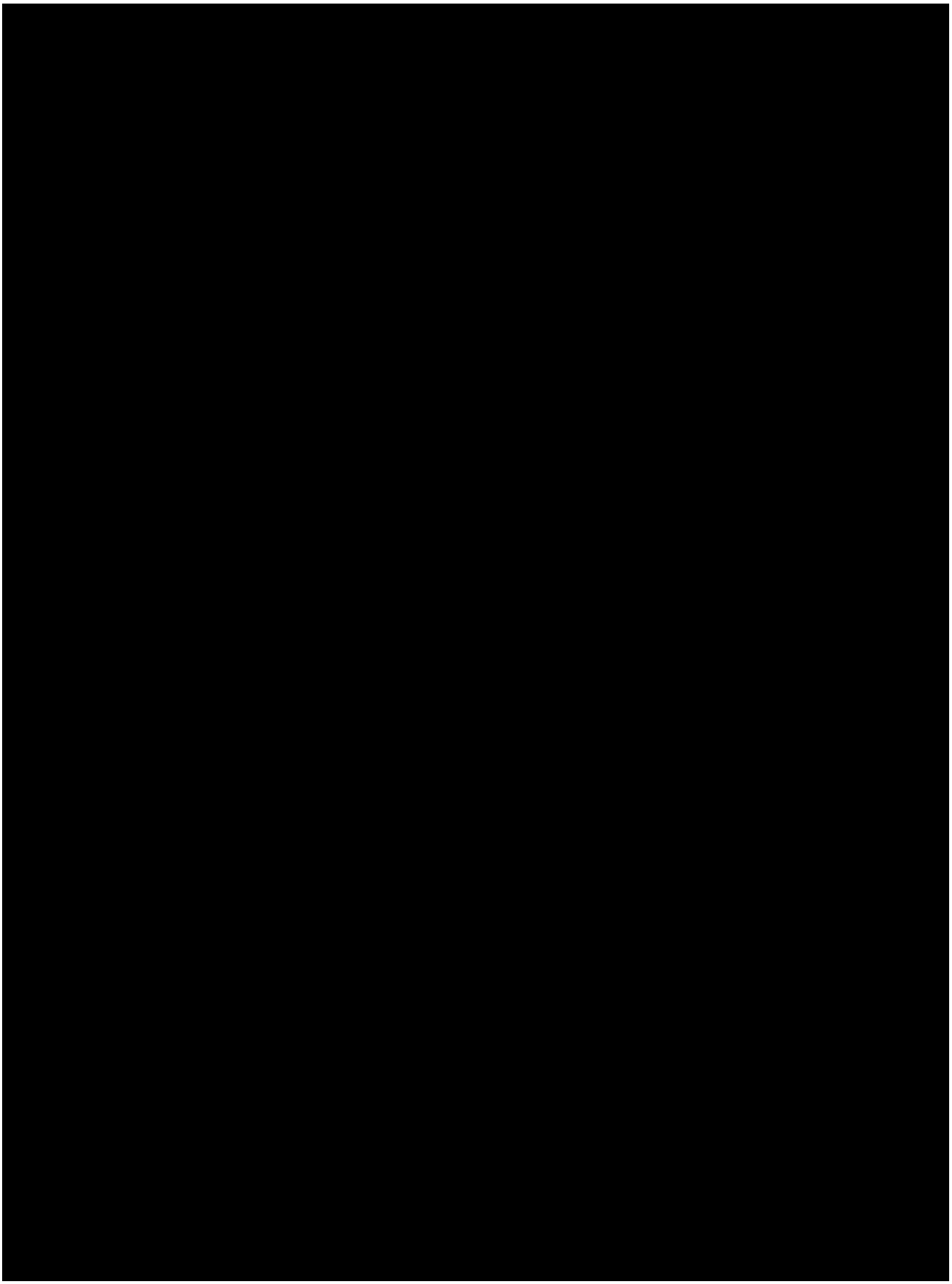

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