# CLINICAL PHARMACOLOGY REVIEW

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| BLA: 125118/45 | Submission Date(s): 6/1/2007 |
| Brand Name | Orencia |
| Generic Name | Abatacept |
| Clinical Pharmacology Reviewer | Srikanth C. Nallani, Ph.D. |
| Pharmacometrics Reviewer | Atul V. Bhattaram, Ph.D. |
| Pharmacometrics Team Leader | Jogarao Gobburu, Ph.D. |
| Team Leader | Suresh Doddapaneni, Ph.D. |
| OCP Division | Division of Clinical Pharmacology II |
| OND Division | Anesthesia, Analgesia and Rheumatology Products |
| Sponsor | Bristol-Myers Squibb Company |
| Relevant IND(s) | 9391 |
| Formulation; Strength(s) | Lyophilized powder for intravenous injection; 250 mg/mL |
| Indication | Indicated for reducing signs and symptoms in pediatric and adolescent patients with moderately to severely active juvenile idiopathic arthritis/juvenile rheumatoid arthritis with polyarticular course who have had an inadequate response to one or more DMARDs, such as methotrexate (MTX) or TNF antagonists. ORENCIA may be used as monotherapy or concomitantly with MTX. |
| Proposed Dosage Regimen | For pediatric and adolescent patients with JIA/JRA, ORENCIA should be administered at a dose of 10 mg/kg specifically calculated based on the patient's body weight at each administration, not to exceed a maximum dose of 1000 mg. |

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Concurrence:

Srikanth C. Nallani, Ph.D. 2/20/2008

Atul V. Bhattaram, Ph.D. 2/20/2008

Joga Gobburu, Ph.D. 2/20/2008

Suresh Doddapaneni, Ph.D. 2/20/08

# 1 Executive Summary

## 1.1 Recommendation

From the viewpoint of the Office of Clinical Pharmacology, the information contained in this submission is acceptable, provided that a mutually acceptable agreement can be reached between the Agency and sponsor regarding the language in the package insert.

## 1.2 Phase IV Commitments

None

## 1.3 Summary of CPB Findings

Bristol-Myers Squibb Company submitted Supplement 45 to BLA 125118 on 6/1/2007 seeking a pediatric indication, reducing signs and symptoms of Juvenile Idiopathic Arthritis (JIA)/Juvenile Rheumatoid Arthritis (JRA), for Orencia.

In 2005, Orencia was approved for adult indication of reducing signs and symptoms, inducing major clinical response, slowing the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more DMARDs, such as methotrexate or TNF antagonists. Orencia may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.

The submission consists of clinical safety, efficacy and clinical pharmacology data from a single randomized withdrawal clinical efficacy study IM101033. Study IM101033 was "A Phase 3, Multi-center, Multi-national, Randomized, Withdrawal Study to Evaluate the Safety and Efficacy of Abatacept in Children and Adolescents with Active Polyarticular Juvenile Rheumatoid Arthritis". Pediatric JIA/JRA patients were treated with abatacept 10 mg/kg IV infusion in an open-label design for four months. Subjects that met the criteria "American College of Rheumatology (ACR) Pediatric 30 definition of improvement" in Period A were randomized and treated for six months with either abatacept or placebo into the double-blind phase (Period B). The primary efficacy endpoint, which was evaluated in the double-blind phase (Period B), was the time to disease flare. Pediatric patients from the following situations received an open-label extension with abatacept therapy (10 mg/kg IV infusion); a) subjects who completed the lead-in phase (Period A) without adequate response were given the option to receive treatment; b) subjects who completed the double-blind phase (Period B) without experiencing flare; c) subjects who discontinued from the double-blind phase (Period B) due to flare.

Serum samples for abatacept analysis were only collected adequately in the Period A and B at the following times, but no blood samples were collected in period C. Blood samples were collected on A57, A113, B85, and B169 indicated as Period Days, for analysis of abatacept, anti-abatacept and anti-CTLA4 antibodies. Evaluation of mean change from baseline at above indicated PK sampling time points was carried out for cytokines (soluble interleukin-2 receptor [sIL-2R], IL-6, soluble Intercellular Adhesion Molecule-1 [sICAM-1], E-selectin, tumor necrosis factor-alpha [TNF-α], and matrix metalloproteinase-3 [MMP-3]) whose regular collection is indicated in the protocol.

Population PK analysis evaluated the effect of age, race, gender, glomerular filtration rate, hepatic enzyme levels on the pharmacokinetics of abatacept in pediatric subjects. PK data from pediatric JRA/JIA subjects was pooled with PK data obtained previously from adult rheumatoid arthritis (RA) patients to better explore the effects of the above indicated covariates on abatacept clearance. The concentration-time data for abatacept in JRA/JIA were well described by a linear 2-compartment model. Abatacept clearance and distribution volumes (central and peripheral) increase with baseline body weight. After accounting for the effect of baseline body weight, abatacept clearance was not related to age, gender, or race. The population PK analysis and details of results of the analysis are discussed in Section 4 of the review.

Steady-state serum peak and trough concentrations of abatacept were 217 (57 to 700) and 11.9 (0.15 to 44.6) µg/mL. Steady-steady trough serum concentrations of abatacept were similar in patients that were seropositive or seronegative to abatacept antibodies. Serum levels of abatacept at steady-state were not significantly different in patients receiving different concomitant medications such as methotrexate, corticosteroids or NSAIDs.

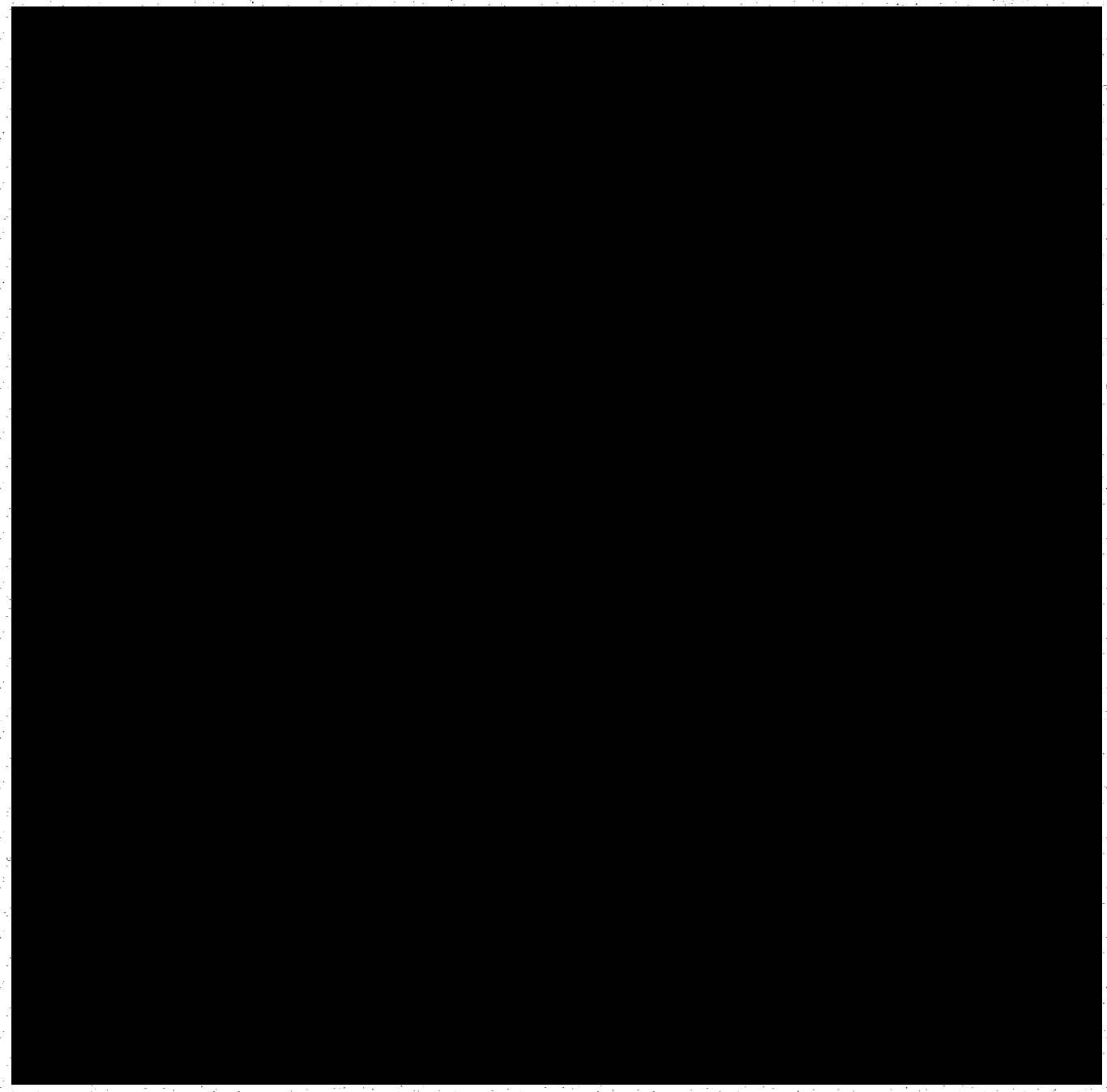
The sponsor proposed labeling changes relevant to clinical pharmacology in section **2 Dosing and Administration, 6.2 Clinical experience in JRA/JIA patients, 12 Clinical Pharmacology, Pharmacokinetics, JRA/JIA patients.**

Currently, Orencia is approved with the following fixed dose regimen in adults:

**Table 1: Dose of ORENCIA in Adult RA**

| Body Weight of Patient | Dose | Number of Vials[a] |
|---|---|---|
| <60 kg | 500 mg | 2 |
| 60 to 100 kg | 750 mg | 3 |
| >100 kg | 1000 mg | 4 |

[redacted]



## 2 QBR

### 2.1 General Attributes

Bristol-Myers Squibb Company submitted BLA 125118 on 6/1/2007 seeking a pediatric indication, reducing signs and symptoms of Juvenile Idiopathic Arthritis/Juvenile Rheumatoid Arthritis, for Orencia.

In 2005, Orencia was approved for adult indication of reducing signs and symptoms, inducing major clinical response, slowing the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs, such as methotrexate or TNF antagonists. ORENCIA may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.

*Mechanism of Action:* ORENCIA or generic name abatacept, is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1 (IgG1). Abatacept is a selective costimulation modulator that inhibits T cell (T lymphocyte) activation by binding to CD80 and CD86, thereby blocking interaction with CD28. This interaction provides a costimulatory signal necessary for full activation of T lymphocytes. Activated T lymphocytes are implicated in the pathogenesis of rheumatoid arthritis (RA) and are found in the synovium of patients with RA.

### 2.2 General Clinical Pharmacology

Single randomized withdrawal clinical efficacy study # IM101033 was conducted in support of the proposed pediatric indication. Study # IM101033 was "A Phase 3, Multi-center, Multi-national, Randomized, Withdrawal Study to Evaluate the Safety and Efficacy of Abatacept in Children and Adolescents with Active Polyarticular Juvenile Rheumatoid Arthritis".

Period A: Pediatric JIA/JRA patients were treated with abatacept 10 mg/kg IV infusion in an open-label design for four months. Subjects that met the criteria "American College of Rheumatology (ACR) Pediatric 30 definition of improvement" in Period A were randomized to either abatacept or placebo into the double-blind phase (Period B).

Period B: Pediatric JIA/JRA patients were treated with abatacept 10 mg/kg or placebo IV infusion in a double-blind design for six months. The primary efficacy endpoint, which was evaluated in the double-blind phase (Period B), was the time to disease flare. The definition of flare was based on the change in the ACR Pediatric core-response variables from the beginning of the double-blind treatment period. Subjects who worsened by 30 percent or more in at least 3 of the 6 core-response variables without improving by 30 percent or more in more than 1 of the 6 core-response variables met the criteria for flare. If Global Assessments were used to define flare, there had to have been a change of at least 2 cm. If the number of active joints and/or joints with limitation of motion was used to define flare, there had to have been a worsening of at least 2 joints.

Period C: Pediatric patients from the following situations received an open-label extension with abatacept therapy (10 mg/kg IV infusion); a) subjects who completed the lead-in phase (Period A) without adequate response were given the option to receive treatment; b) subjects who completed the double-blind phase (Period B) without experiencing flare; c) subjects who discontinued from the double-blind phase (Period B) due to flare.

*PK sampling scheme*

Serum samples for abatacept analysis were only collected adequately in the Period A and B at the following times, but no blood samples were collected in period C.

*Immunogenicity analysis sampling*

Blood samples were collected on A57, A113, B85, and B169 indicated as Period Days, for analysis of anti-abatacept and anti-CTLA4 antibodies.

*Pharmacodynamic endpoints:*

Evaluation of mean change from baseline at above indicated PK sampling time points was carried out for cytokines (soluble interleukin-2 receptor [sIL-2R], IL-6, soluble Intercellular Adhesion Molecule-1 [sICAM-1], E-selectin, tumor necrosis factor-alpha [TNF-α], and matrix metalloproteinase-3 [MMP-3]) whose regular collection is indicated in the protocol.

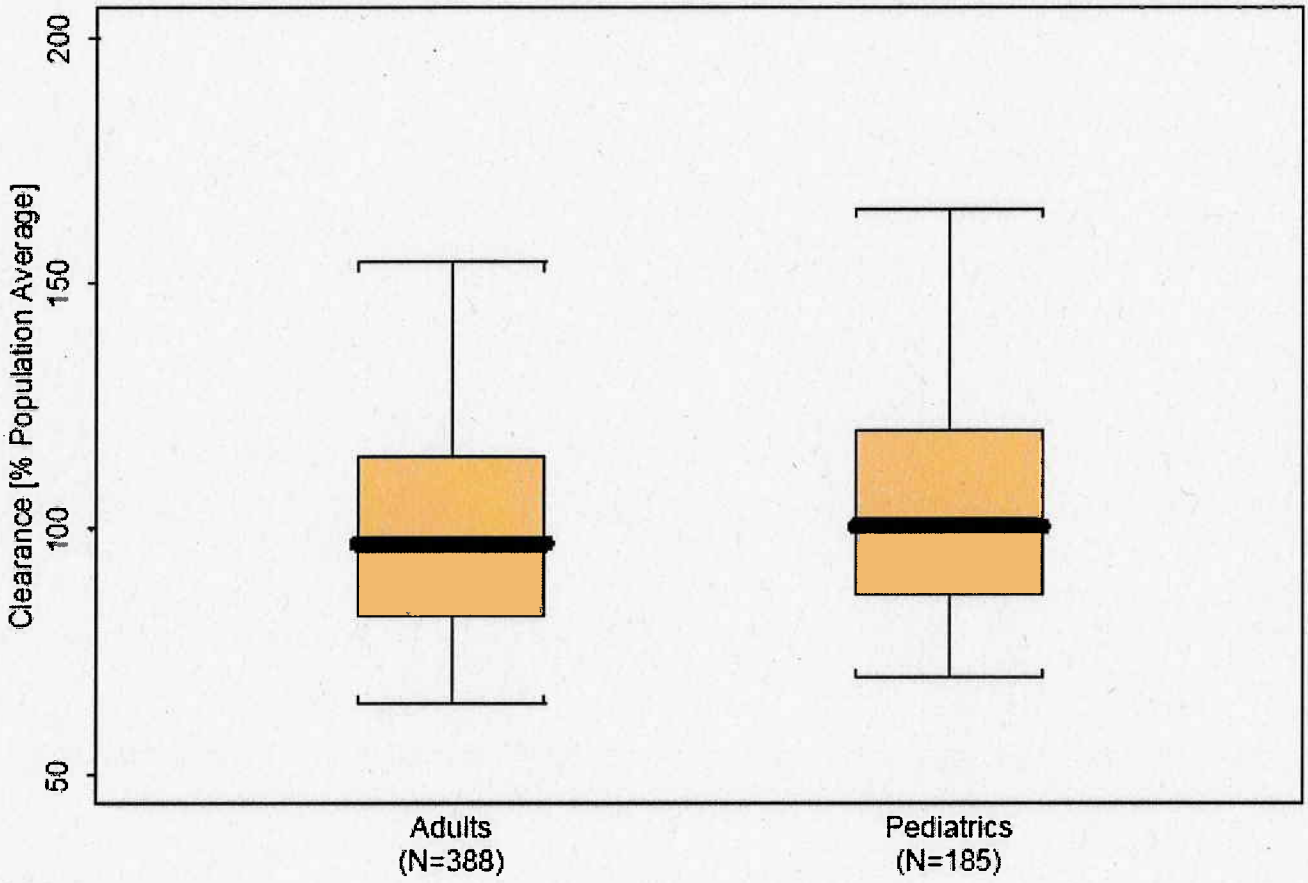
2.3 Intrinsic Factors

***Is dosage adjustment necessary in pediatric patients with regard to age, race, gender, renal or hepatic impairment?***

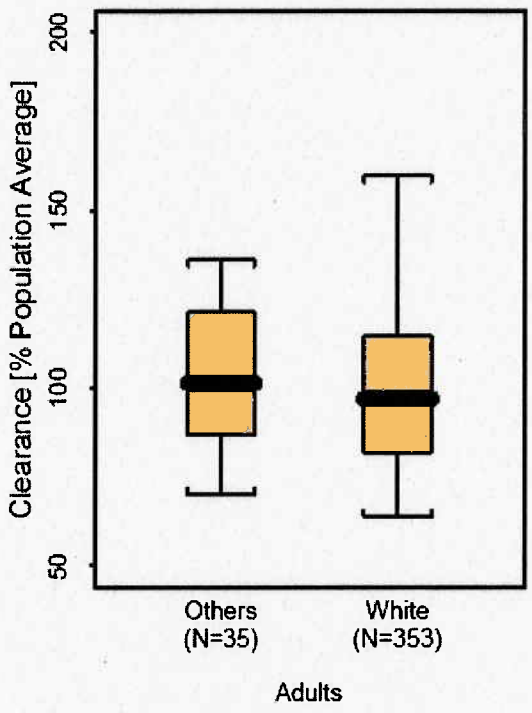
*Dosing adjustment in pediatric subjects is not necessary based on age, race, and gender, renal and hepatic impairment.*

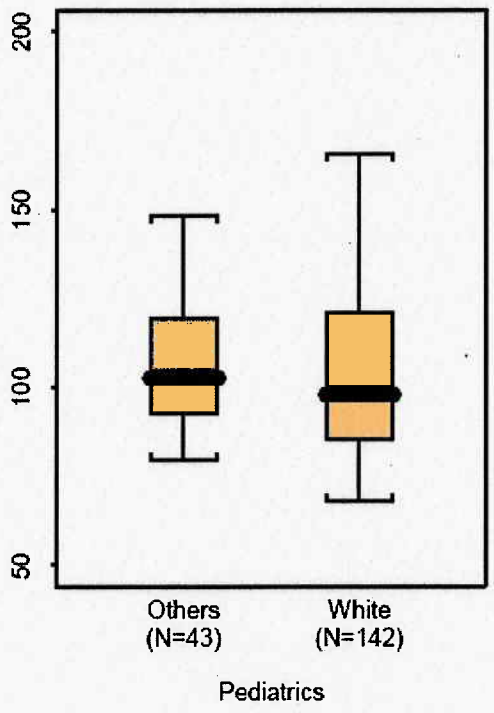
Population PK analysis evaluated the effect of age, race, gender, glomerular filtration rate, hepatic enzyme levels on the pharmacokinetics of abatacept in pediatric subjects. Bodyweight based dosing was investigated for efficacy in the randomized withdrawal clinical efficacy study # 101033. After accounting for the effect of baseline body weight, abatacept clearance was not related to age, gender, or race. The population PK analysis and details of results of the analysis are discussed in Section 4 of the review.

Clearance versus Age Group

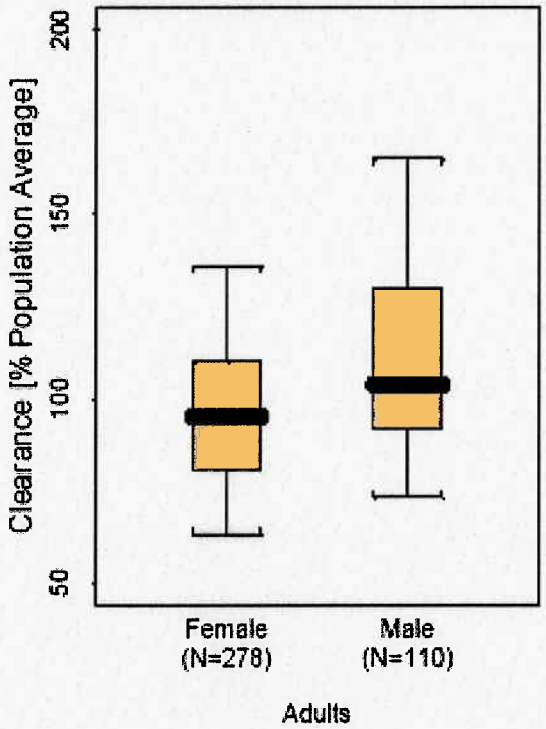

Clearance [% Population Average]
200
150
100
50
Adults
(N=388)
Pediatrics
(N=185)

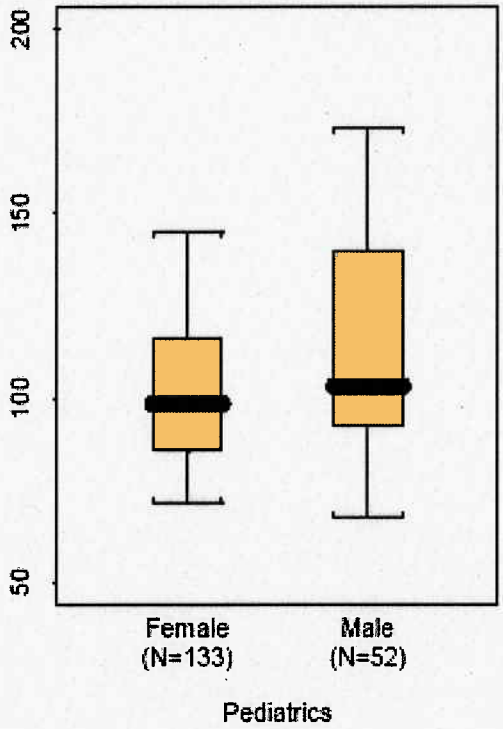
Clearance versus Race




Clearance versus Gender



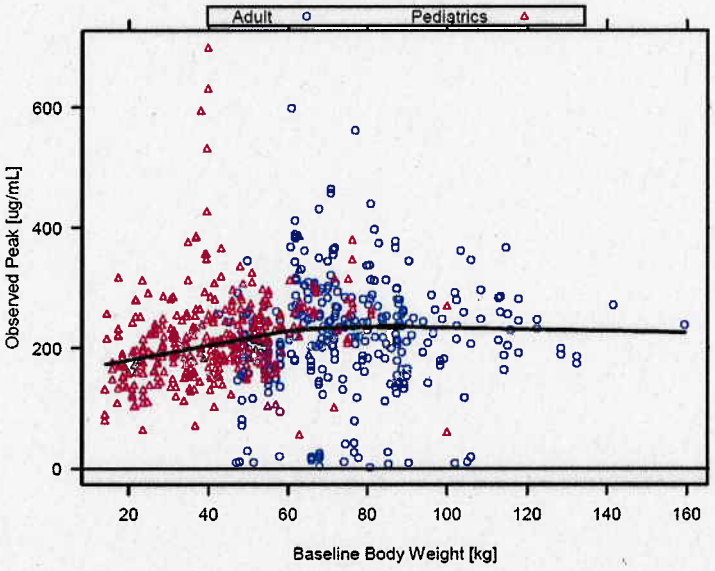
***How does systemic exposure to abatacept in JRA/JIA patients compare to adult RA patients?***

*The abatacept exposure in adult RA subjects and JRA/JIA subjects of the same body weight given the same dose are expected to be the same.*

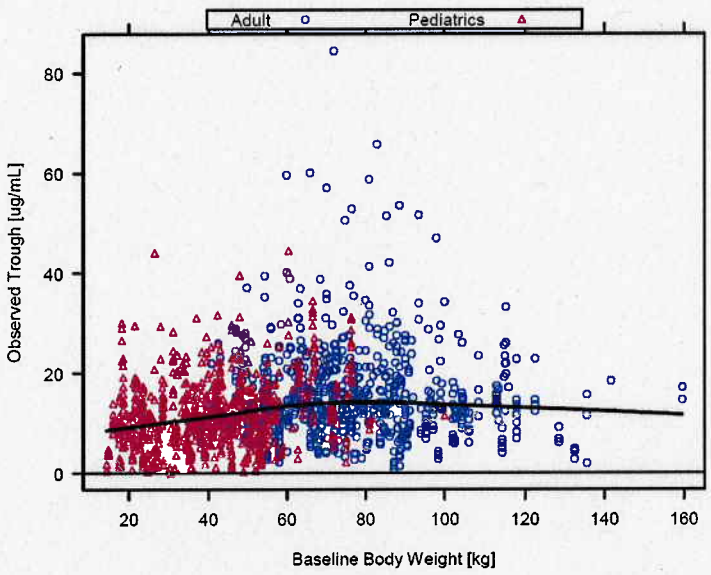
The mean (range) trough serum concentration of abatacept at steady-state were 11.9 (0.15 to 44.6) µg/mL. The peak or end of infusion serum concentrations of abatacept at steady-state were 217.2 (57.8 –to 700) µg/mL in JRA/JIA subjects, while in adults serum abatacept concentrations were about 295 µg/mL (171 – 398 range).

Following administration of abatacept at a dose of 10 mg/kg as an IV infusion, steady state serum concentrations were dependant on bodyweight in pediatric JRA/JIA patients and adult RA patients (See figures below). The relationship between body weight and clearance was less than dose proportional (proportionality factor=0.5). Hence, patients with higher bodyweights are likely to have more drug levels when administered by mg/kg dosing regimen which assumes that if dose is given by bodyweight, the AUC should be similar across various bodyweight ranges. Despite the differences in exposure compared to expected, the response rate of the IM101033 study was comparable to those of the adult RA studies. For the IM101033 study, 64.7% of the total population studied responded (ACR Pediatric 30) during Period A, which is comparable to the 61% and 68% response rate (ACR 20 response at 6 months) of the abatacept groups for the adult RA studies, IM101100 and IM101102. Continued dosing of the JRA/JIA subjects in Period B led to a steady improvement in response, as measured by subjects ascending from ACR Pediatric 30 to ACR 50, 70 and 90 responses, supporting the efficacy of this dosing regimen.

**Abatacept Peak Serum Concentrations for JRA/JIA and Adult RA Subjects versus Baseline Body Weight (10 mg/kg Dose)**




**Abatacept Trough Serum Concentrations for JRA/JIA and Adult RA Subjects versus Baseline Body Weight (10 mg/kg Dose)**




***How does immunogenicity to abatacept affect its Pharmacokinetics?***

*Steady-steady trough serum concentrations of abatacept were similar in patients that were seropositive or seronegative to abatacept antibodies.*

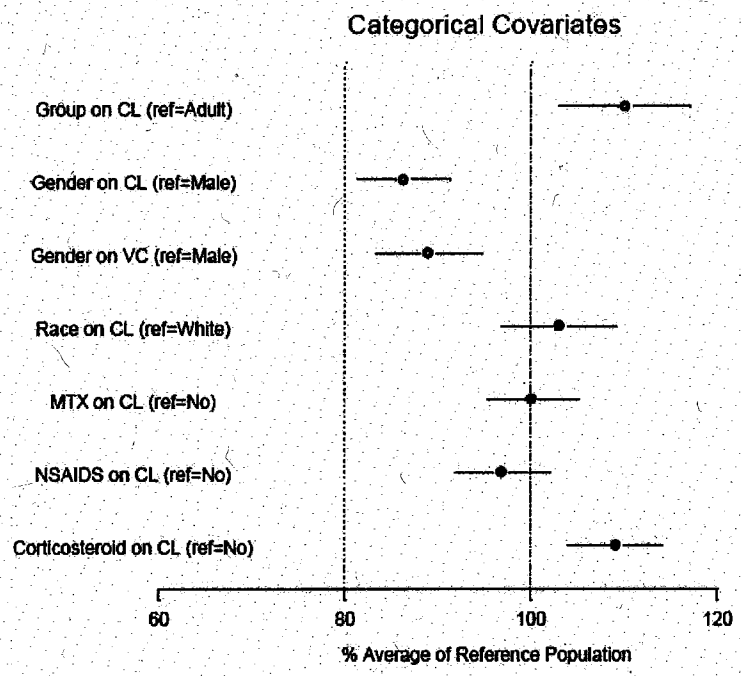
Noteworthy is the fact that neutralizing antibodies can only be detected when serum concentrations of abatacept were ≤ 1 μg/mL. This is a commonly known limitation for the ELISA assay employed in assessing antibodies for therapeutic biological protein products. Presence of antibody response on the PK of abatacept was not evaluated in the population PK analysis. However, the presence of an antibody response was evaluated with regard to the trough plasma levels of abatacept, which did not appear to change with regard to antibody presence.

For subjects randomized to placebo in Period B, serum concentrations of abatacept upon re-initiation of therapy in Period C were comparable to those seen in Period A, even in the presence of an antibody response. Since neutralizing antibodies can only be detected when serum concentrations of abatacept were ≤ 1 μg/mL, the predominant number of samples evaluable for neutralizing antibodies (29 of 30 total samples) were samples collected during Period B in placebo-treated subjects, or following study discontinuation (56 and/or 85 days post-treatment visit). Thirty (30) samples from 25 of the 40 seropositive subjects were evaluable for neutralizing activity. Of these, 13 samples from 10 subjects contained neutralizing antibodies. Eight (8) of the 10 subjects with samples having neutralizing activity (positive for neutralizing activity on Days B85 and/or B169) were placebo-randomized subjects. The remaining 2 subjects were Period A non-responders. Neutralizing activity was observed in Period A post-dose samples at 56 and 85 days in 1 of these subjects, and on Day C85 in the other subject.

2.4 Extrinsic Factors

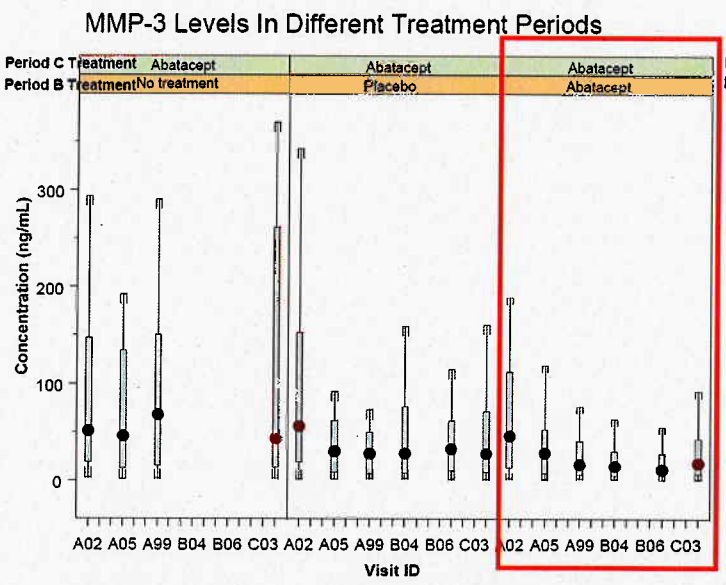
*Trough levels of abatacept at steady-state were not significantly different in patients receiving different concomitant medications such as methotrexate, corticosteroids or NSAIDs.*

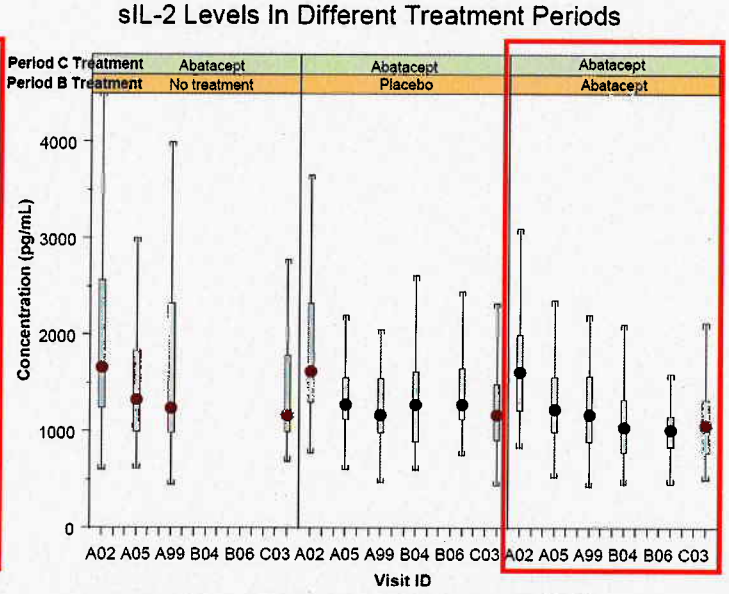
Sponsor evaluated the effect of concomitant medications on the clearance and volume of distribution (central) in the population PK analysis.

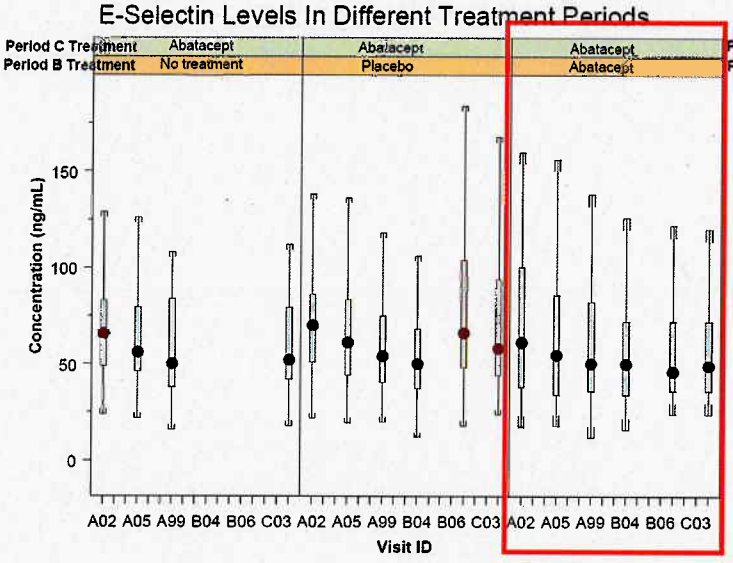


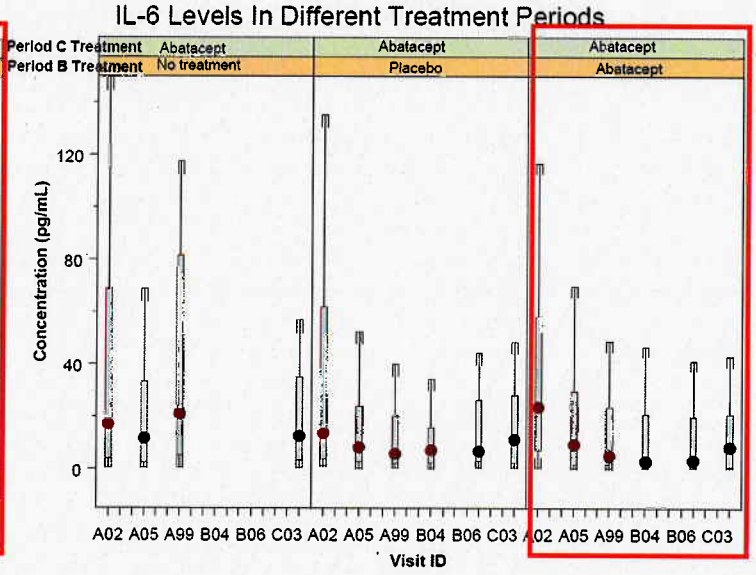

*What are the noted changes in Pharmacodynamic Marker levels with abatacept treatment?*
*Decrease in cytokine levels was noted in pediatric patients receiving abatacept treatment through periods A, B & C, compared to non-responders who discontinued treatment after Period A and Placebo treated patients in Period B.*

The changes from baseline in cytokine levels were with considerable variation. Generally a decrease from baseline in the mean levels of cytokines (sIL-2R, IL-6, E-selectin, and MMP-3) was noted following the abatacept or placebo treatment during the lead-in phase (Period A) and the double-blind phase (Period B). Decrease in cytokine levels was consistently noted in pediatric patients receiving abatacept treatment through periods A & B (Figure in red box below), compared to non-responders who discontinued treatment after Period A and Placebo treated patients in Period B.




## 2.5 General Biopharmaceutics

*Not applicable*

## 2.6 Analytical

Abatacept was quantified in the JRA/JIA serum samples using a validated enzyme-linked immunosorbent assay (ELISA) with a lower limit of quantitation of 1 ng/mL. The range of reliable response for the ELISA is 1 to 30 ng/mL. Samples with concentrations>30 ng/mL are diluted with 10% human serum in buffer into the standard curve range.

## 3 Labeling

Sponsor indicated labeling changes are presented in regular text, reviewer's revisions in the form of additions and deletions are indicated as bold text and strikethrough text, respectively.

# 2 Dosage and Administration

## 2.1 Adult Rheumatoid Arthritis

For adult patients with RA, ORENCIA should be administered as a 30-minute intravenous infusion utilizing the weight range-based dosing specified in Table 1. Following the initial administration, ORENCIA should be given at 2 and 4 weeks after the first infusion and every 4 weeks thereafter. ORENCIA may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.

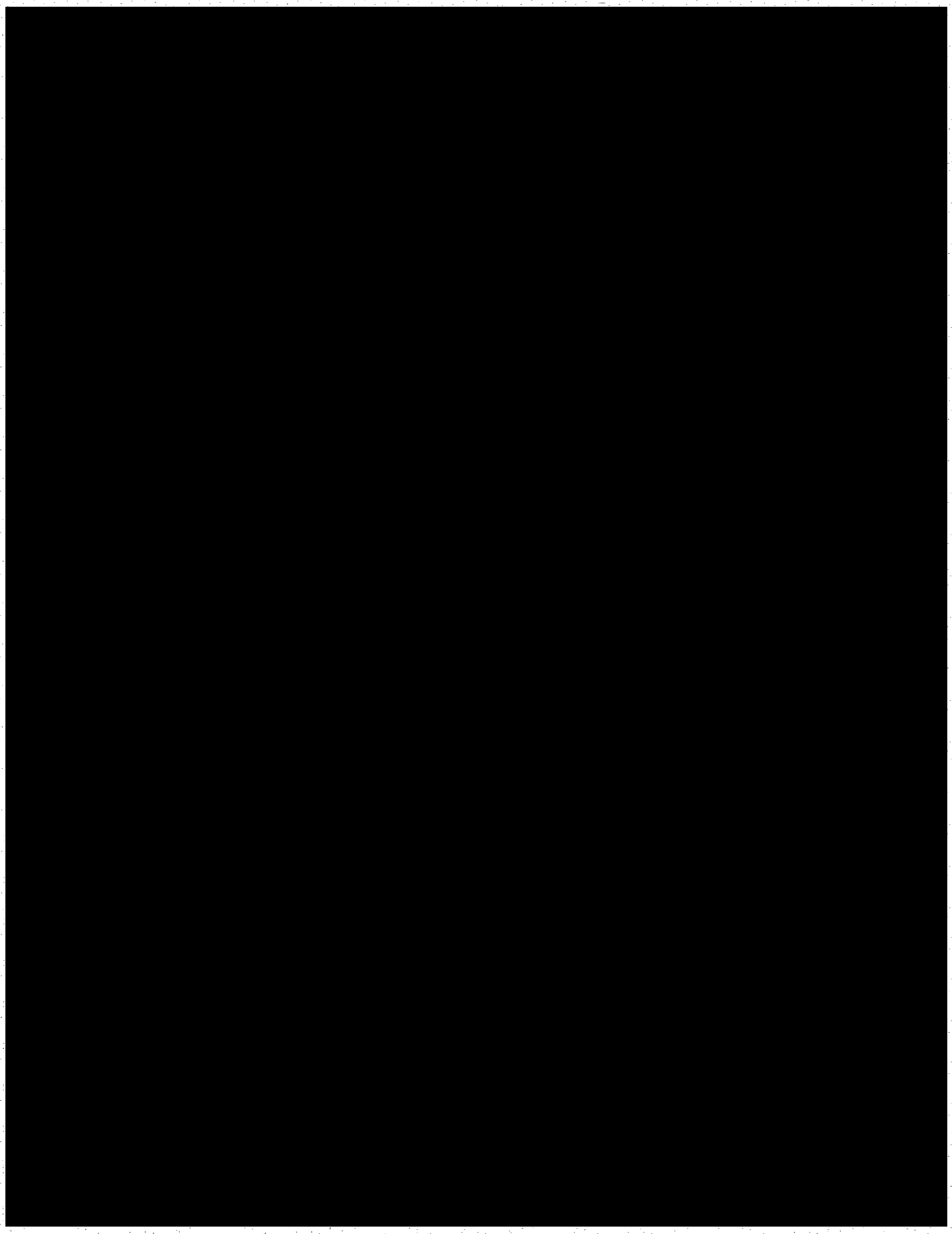
For pediatric and adolescent patients with juvenile idiopathic arthritis (JIA)/juvenile rheumatoid arthritis (JRA), a dose specifically calculated based on each patient's body weight is used [see *Dosage and Administration (2.2)*].

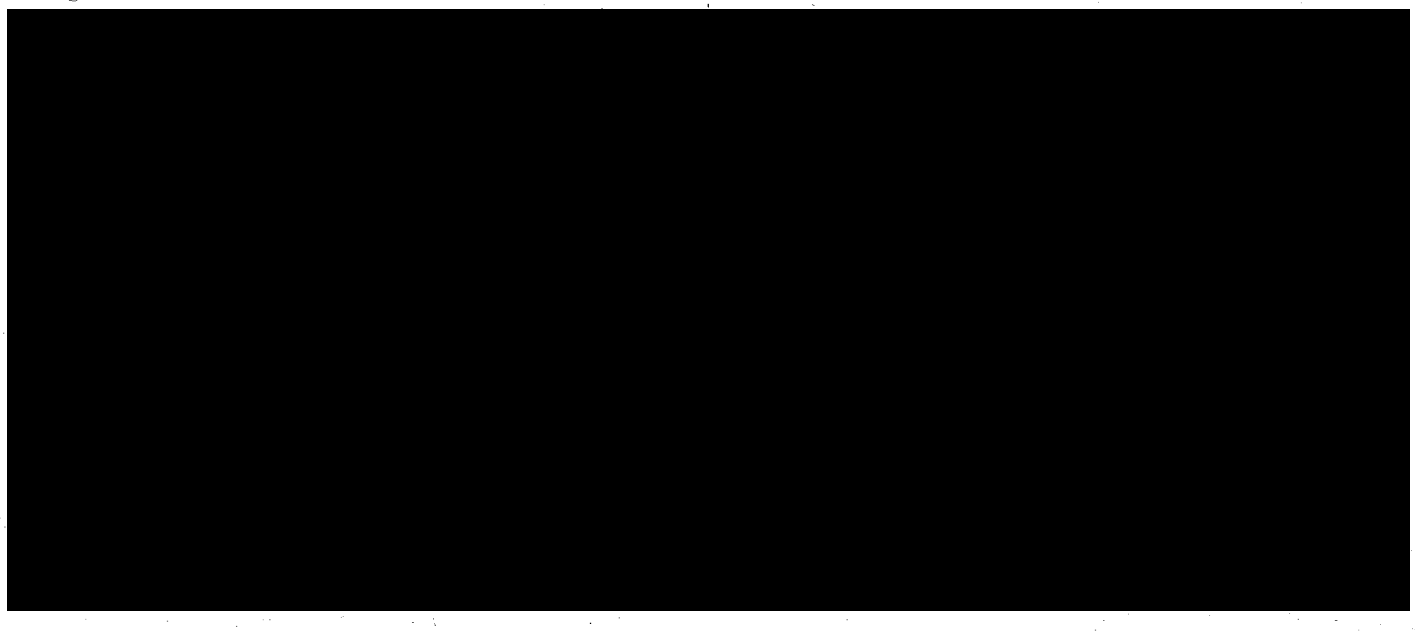
**Table 1: Dose of ORENCIA in Adult RA**

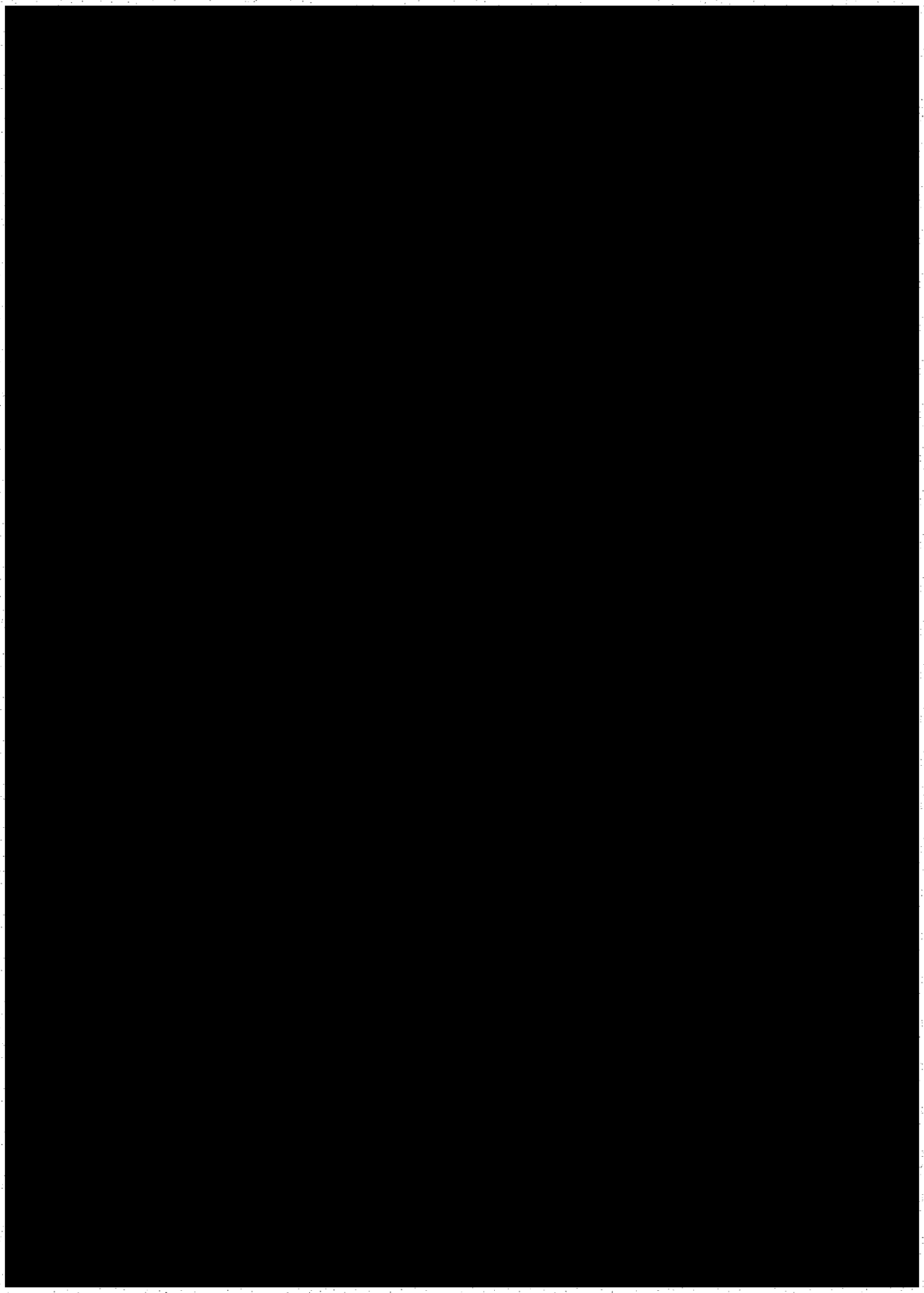
| Body Weight of Patient | Dose | Number of Vials[a] |
|---|---|---|
| <60 kg | 500 mg | 2 |
| 60 to 100 kg | 750 mg | 3 |
| >100 kg | 1000 mg | 4 |

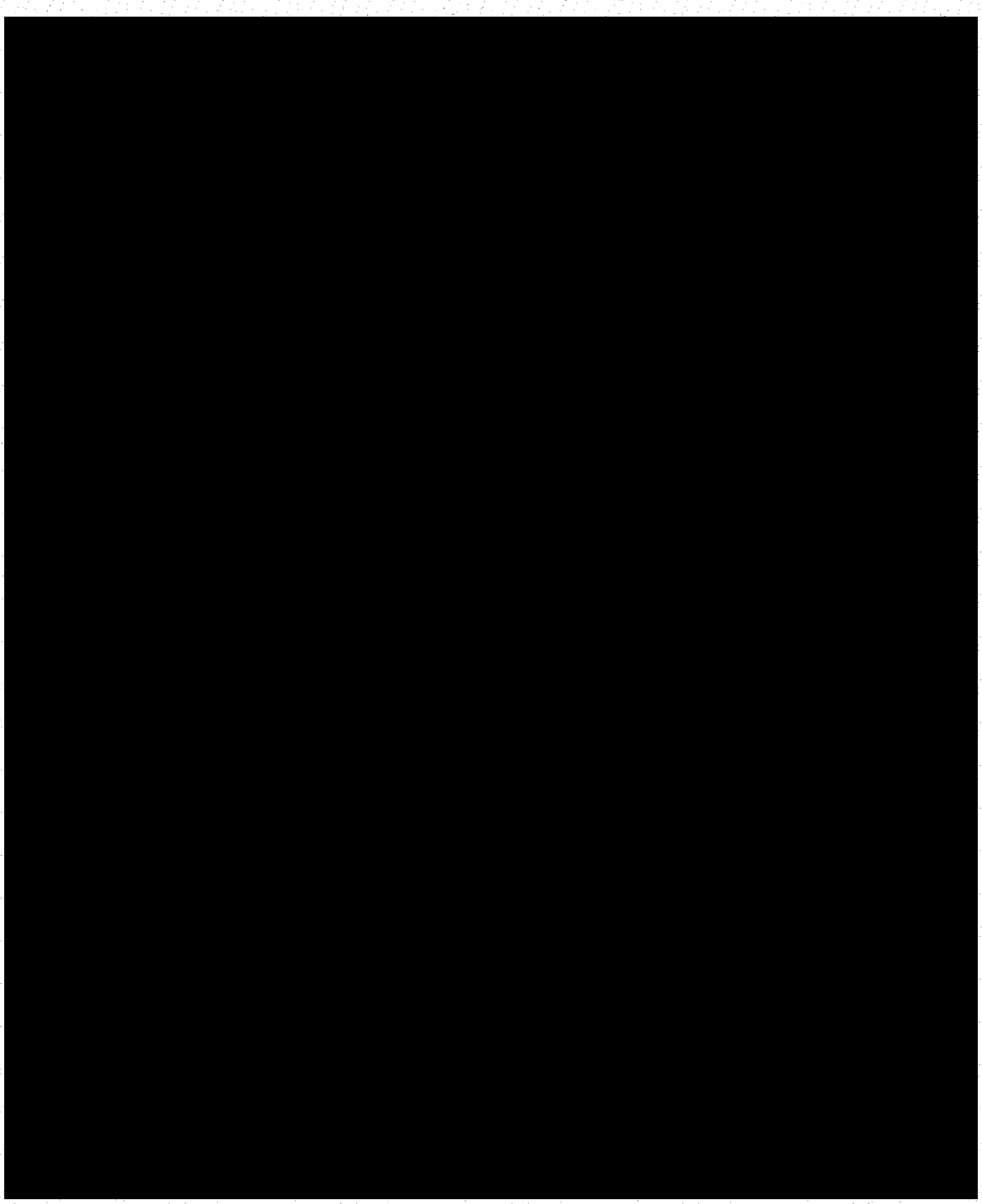
[a] Each vial provides 250 mg of abatacept for administration.

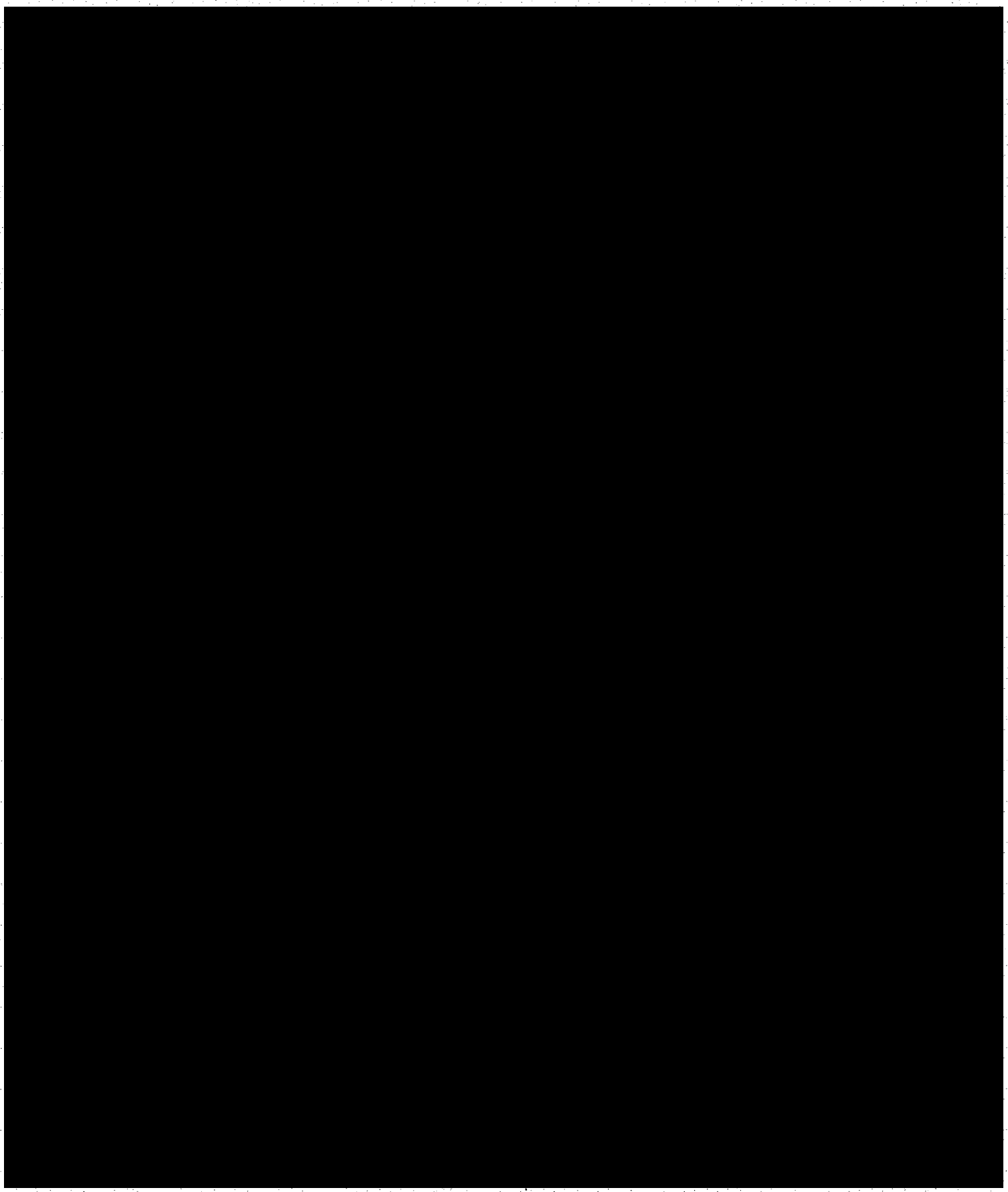
[redacted]

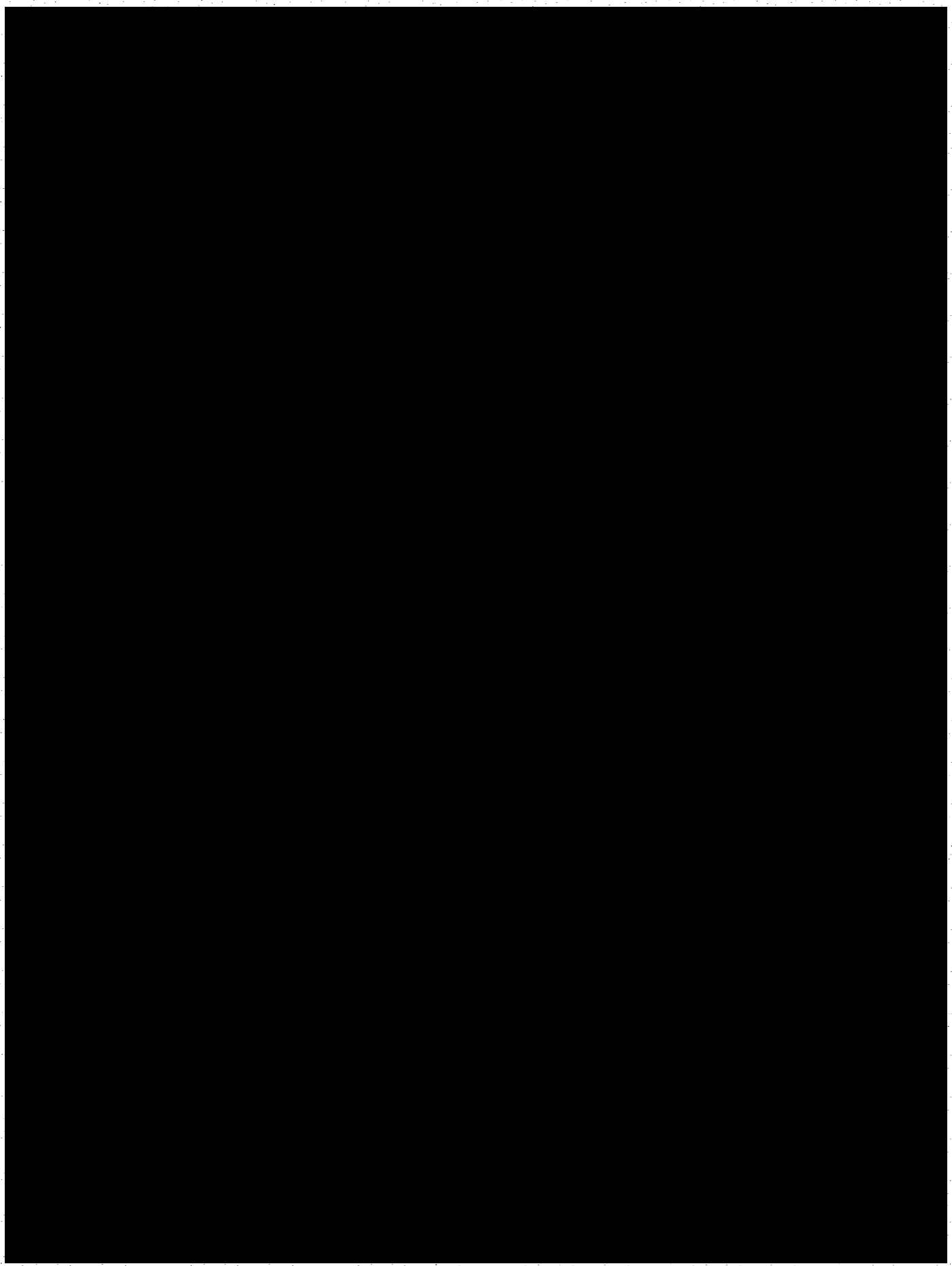


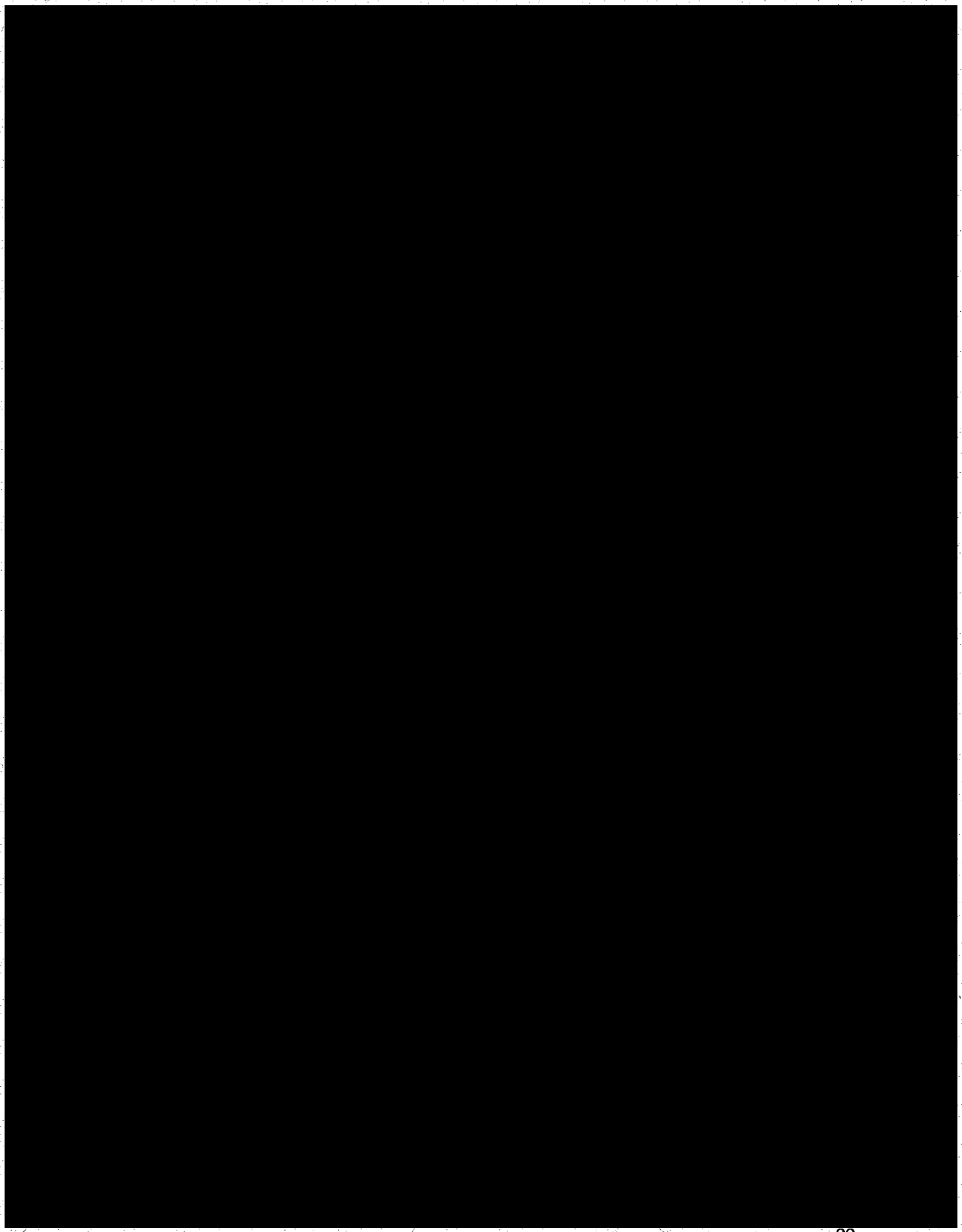


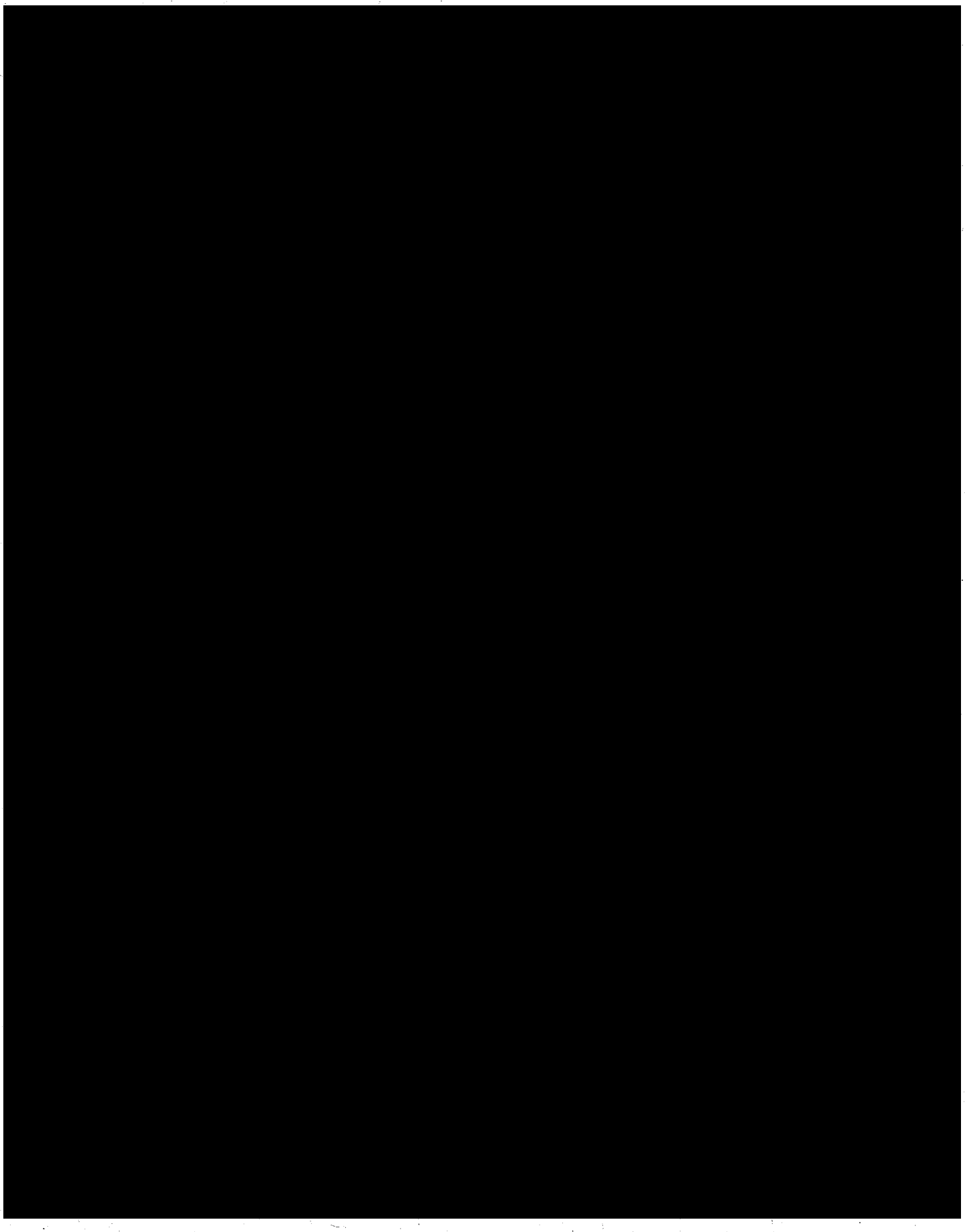


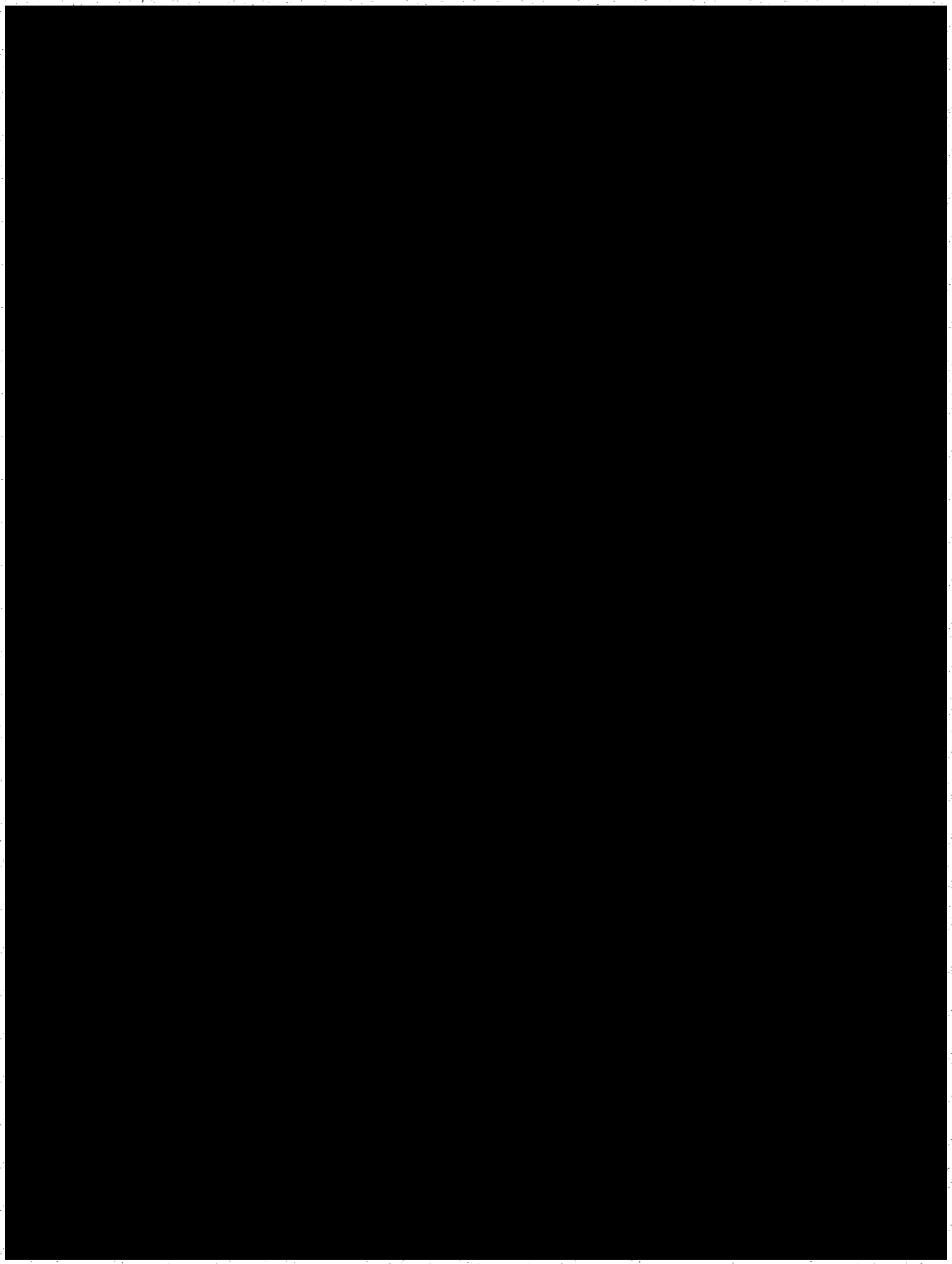


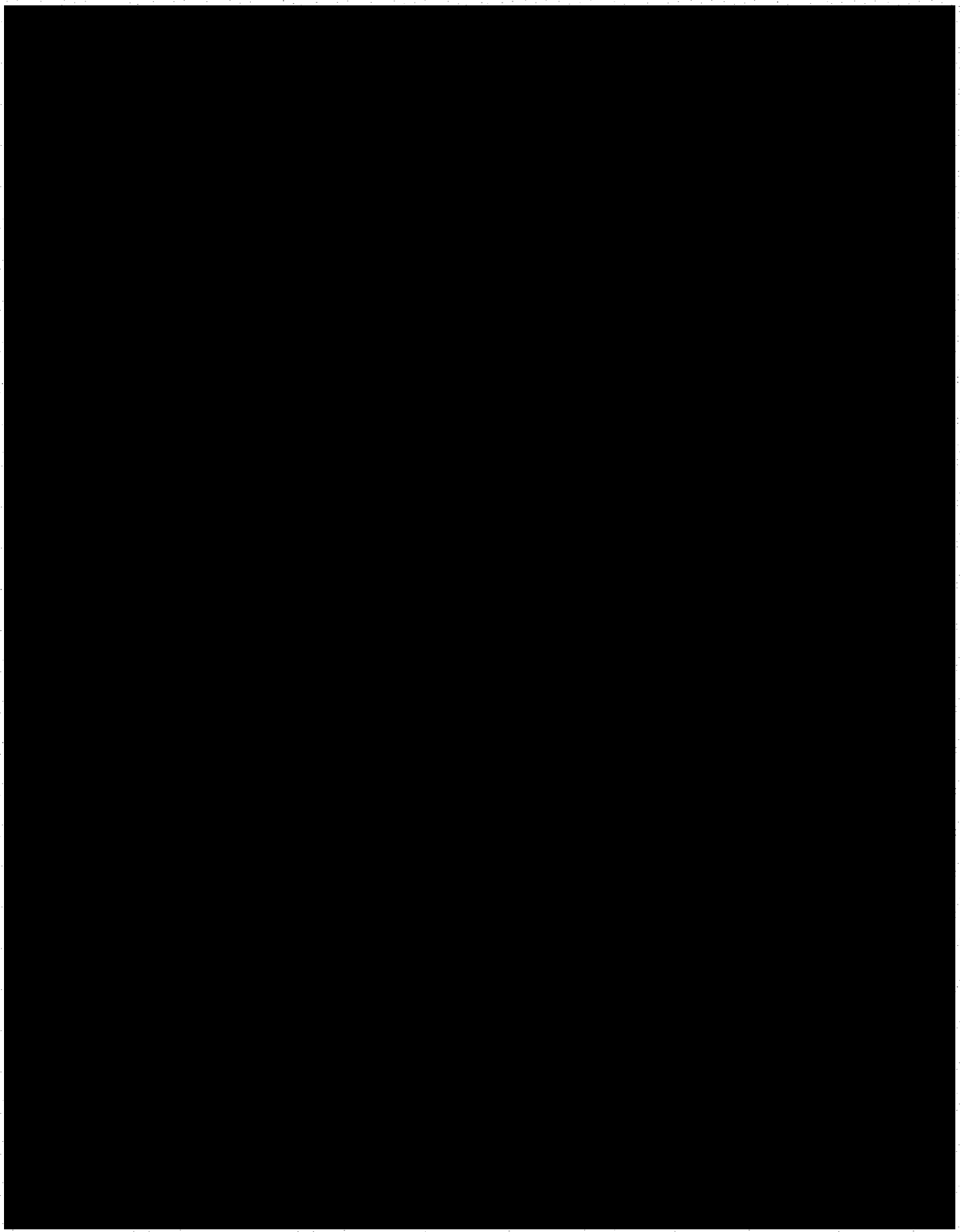


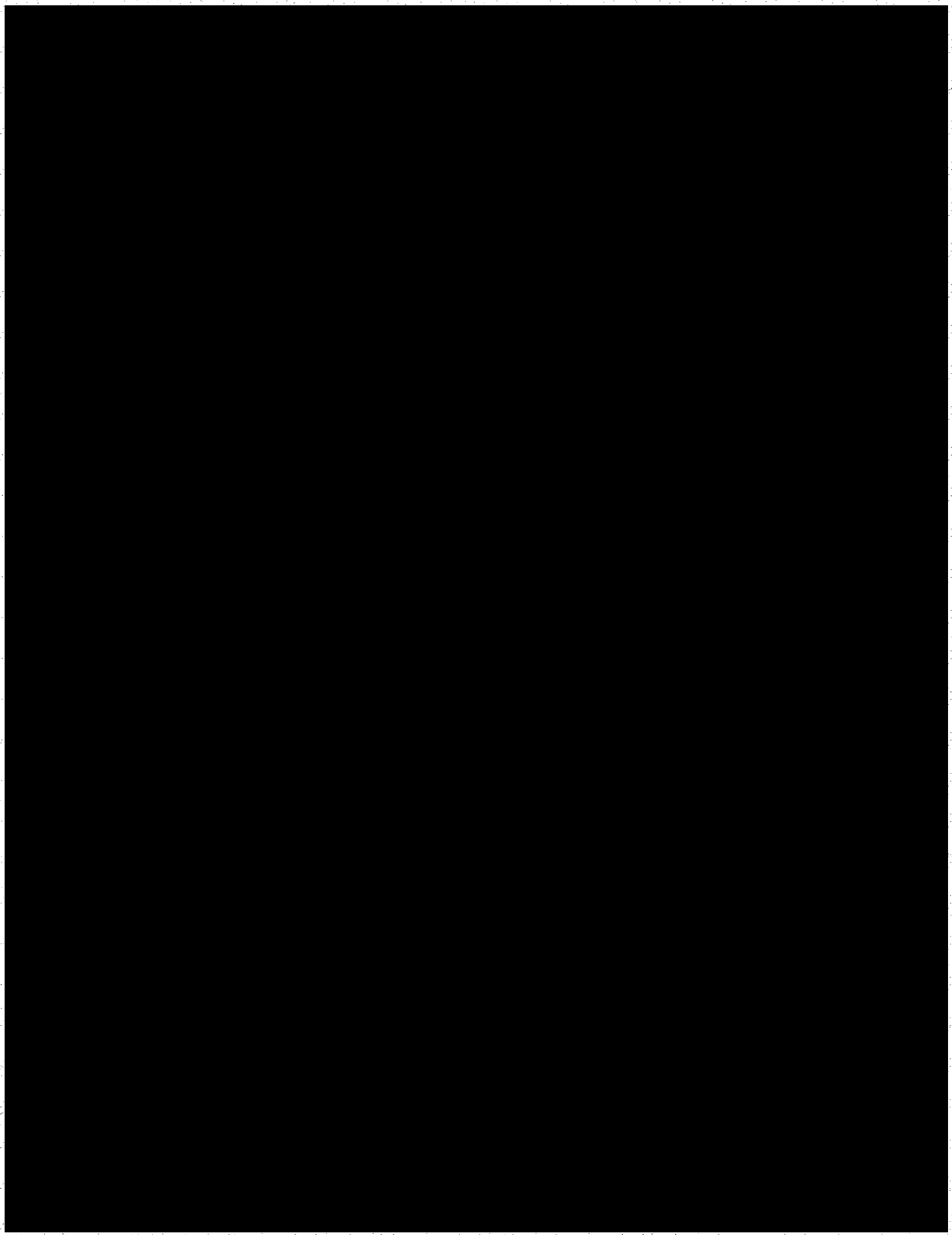


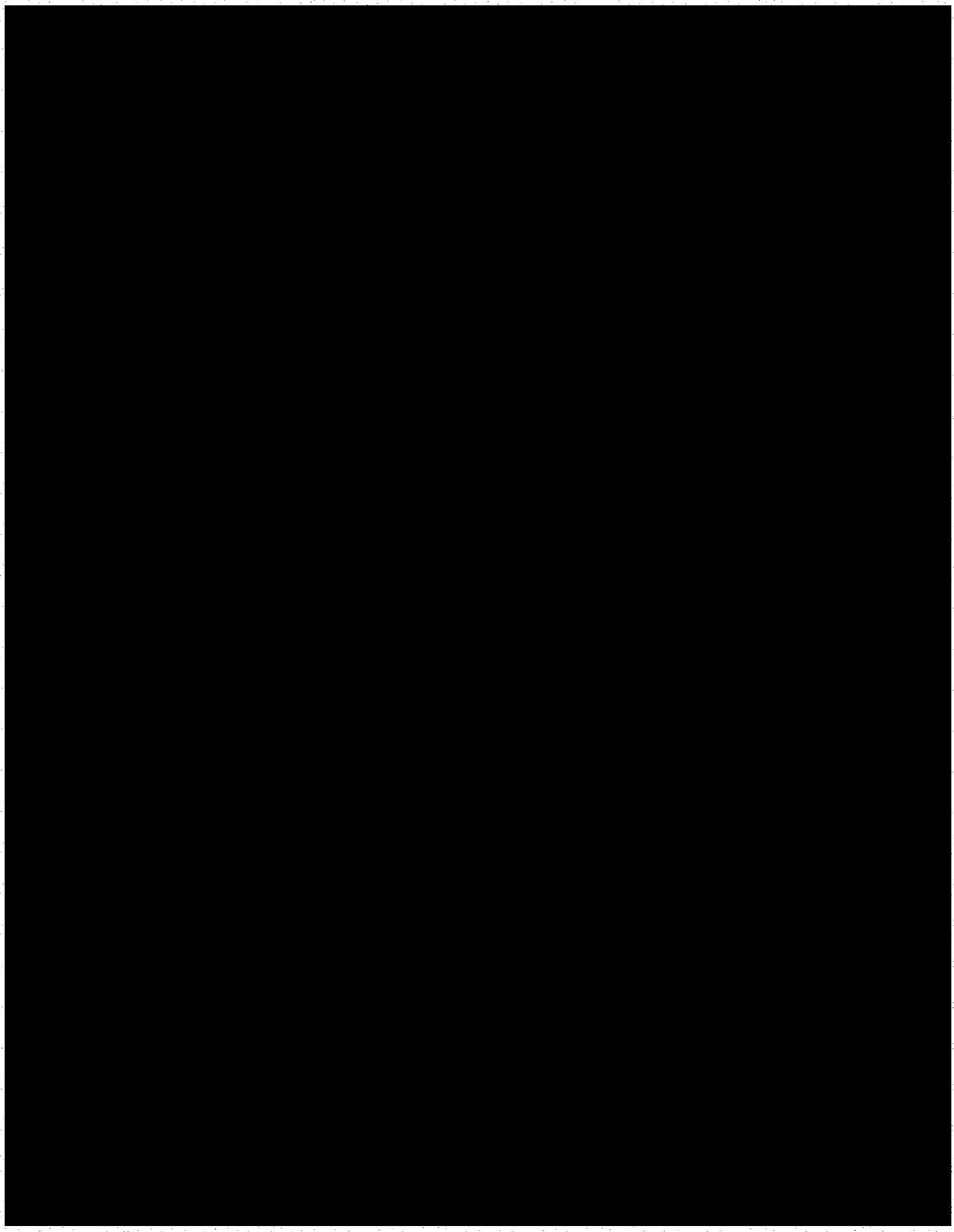


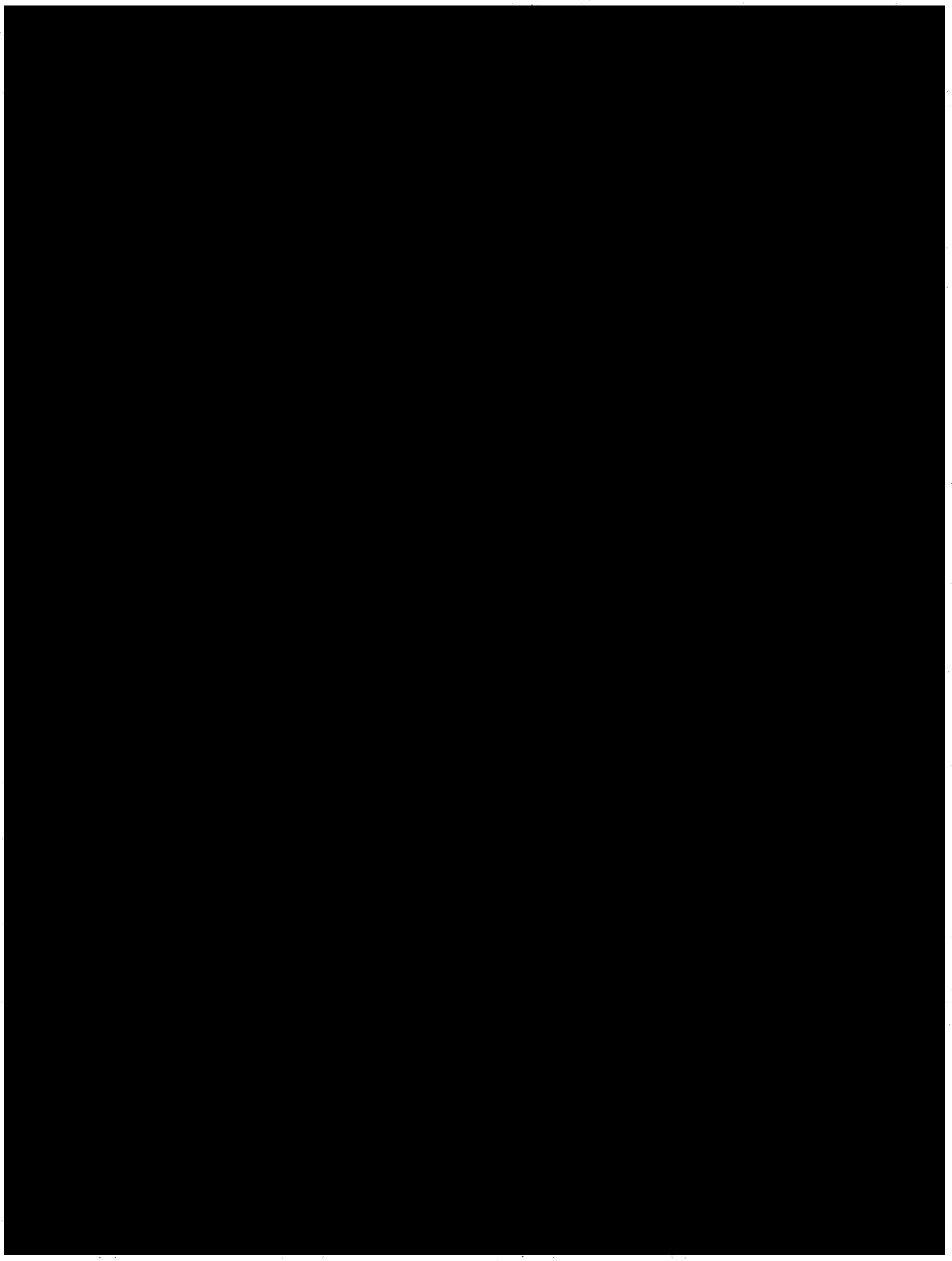


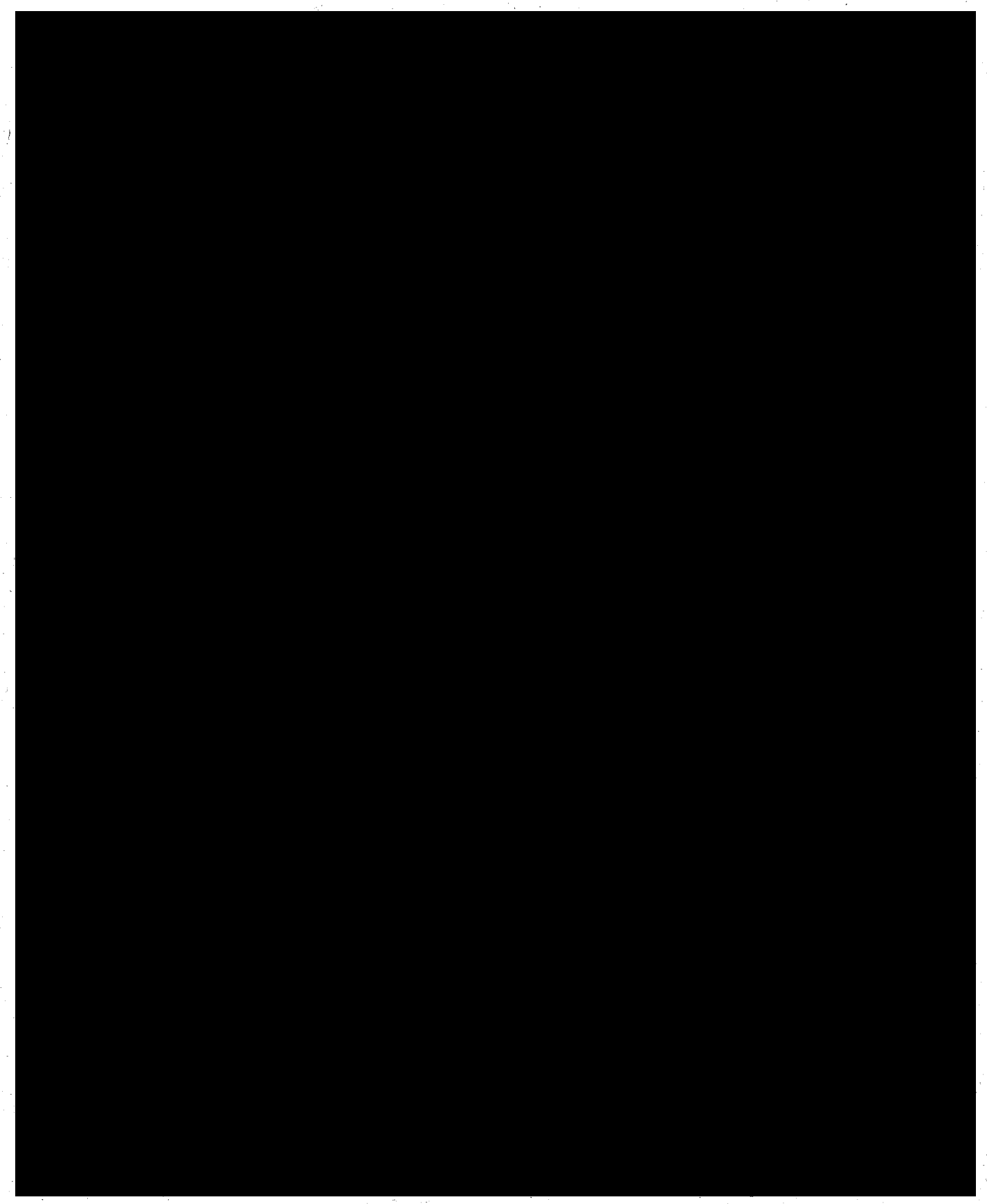


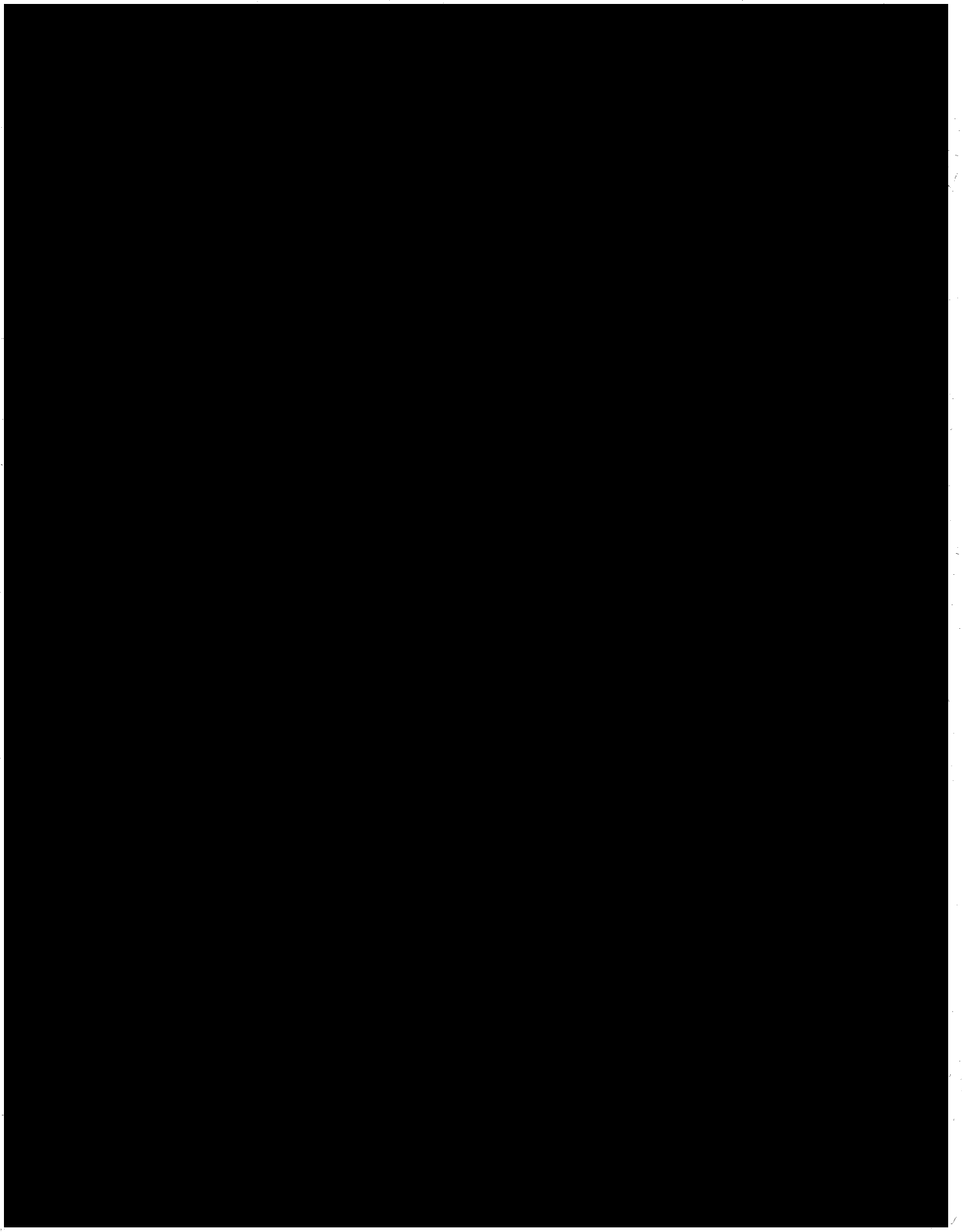


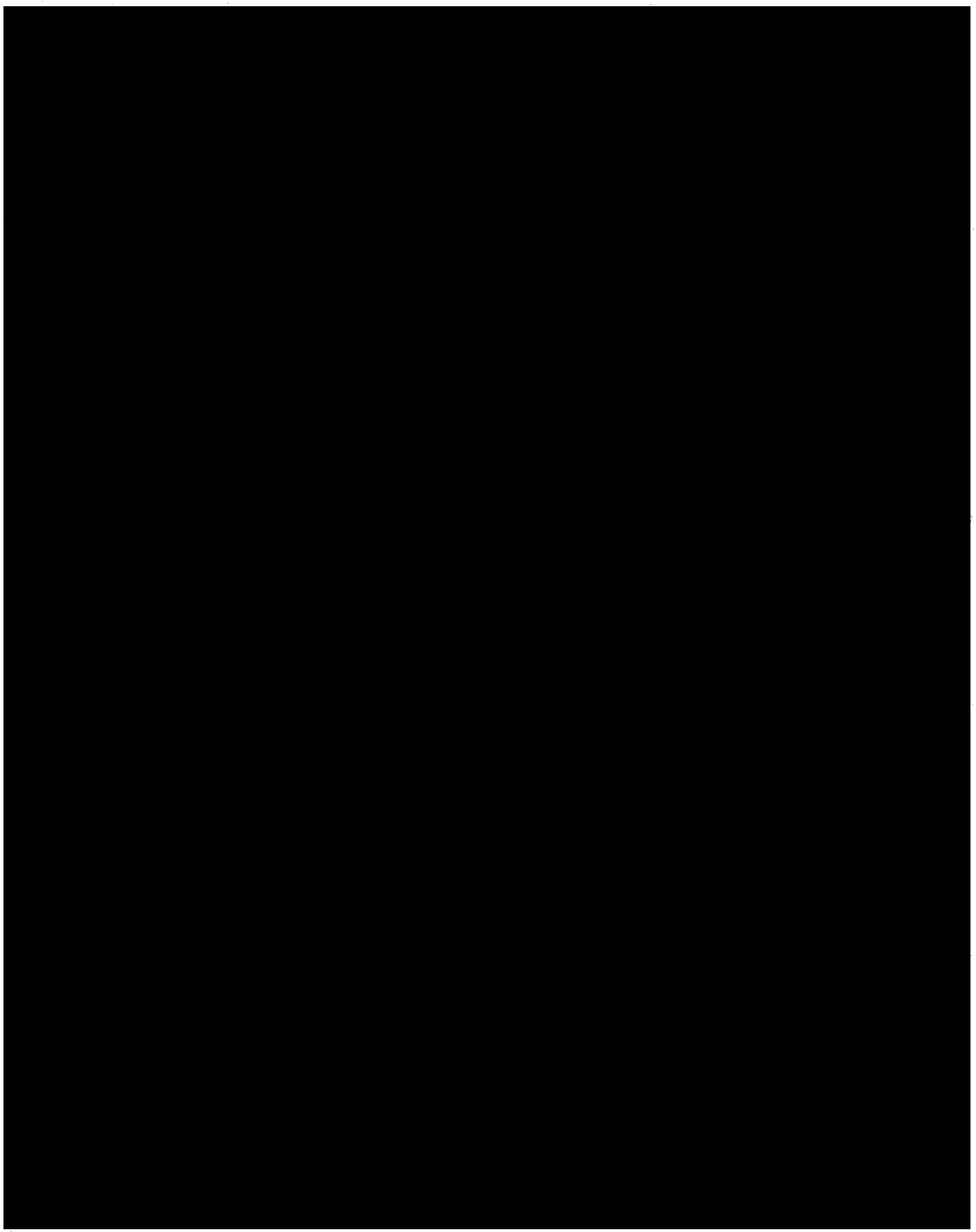


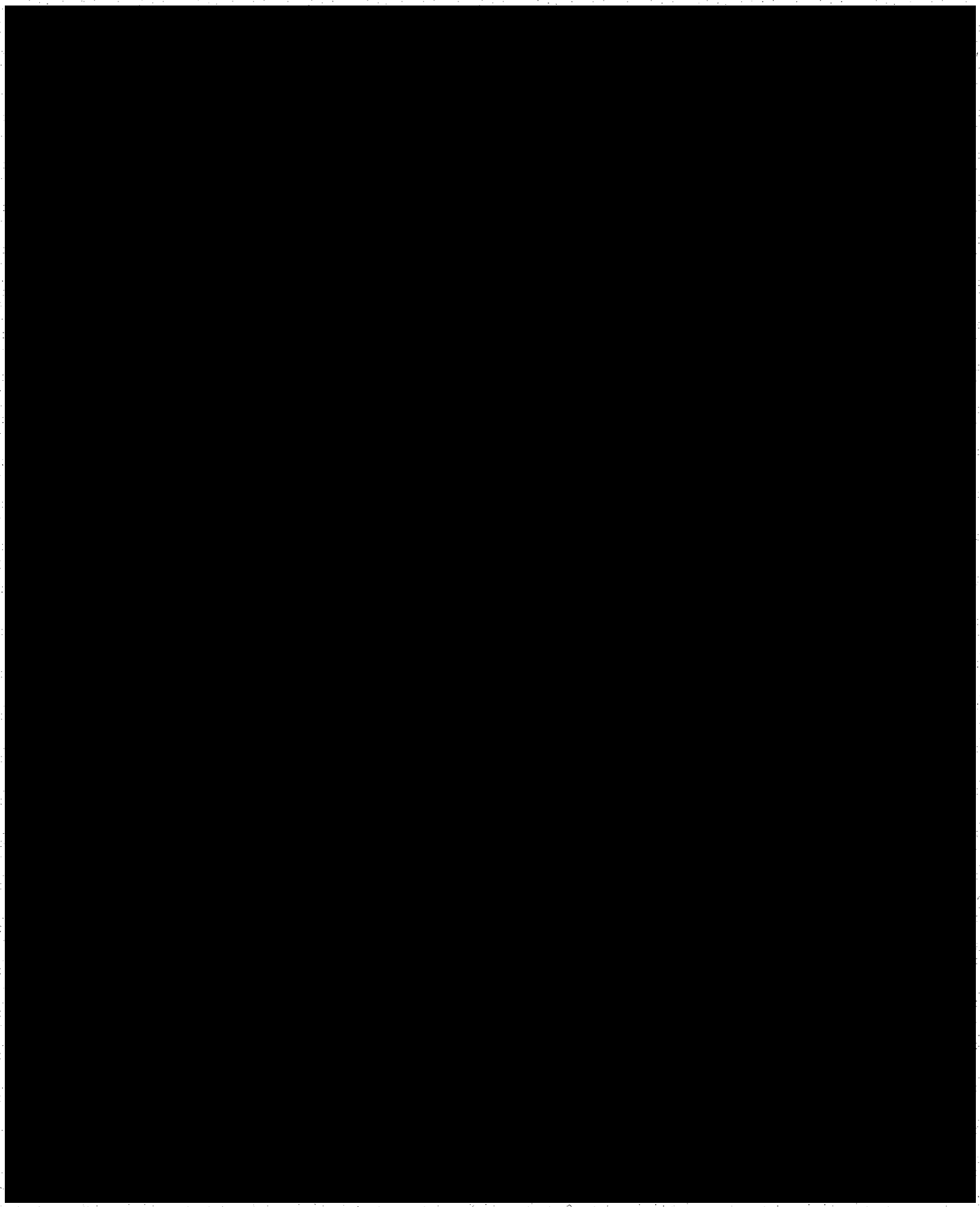


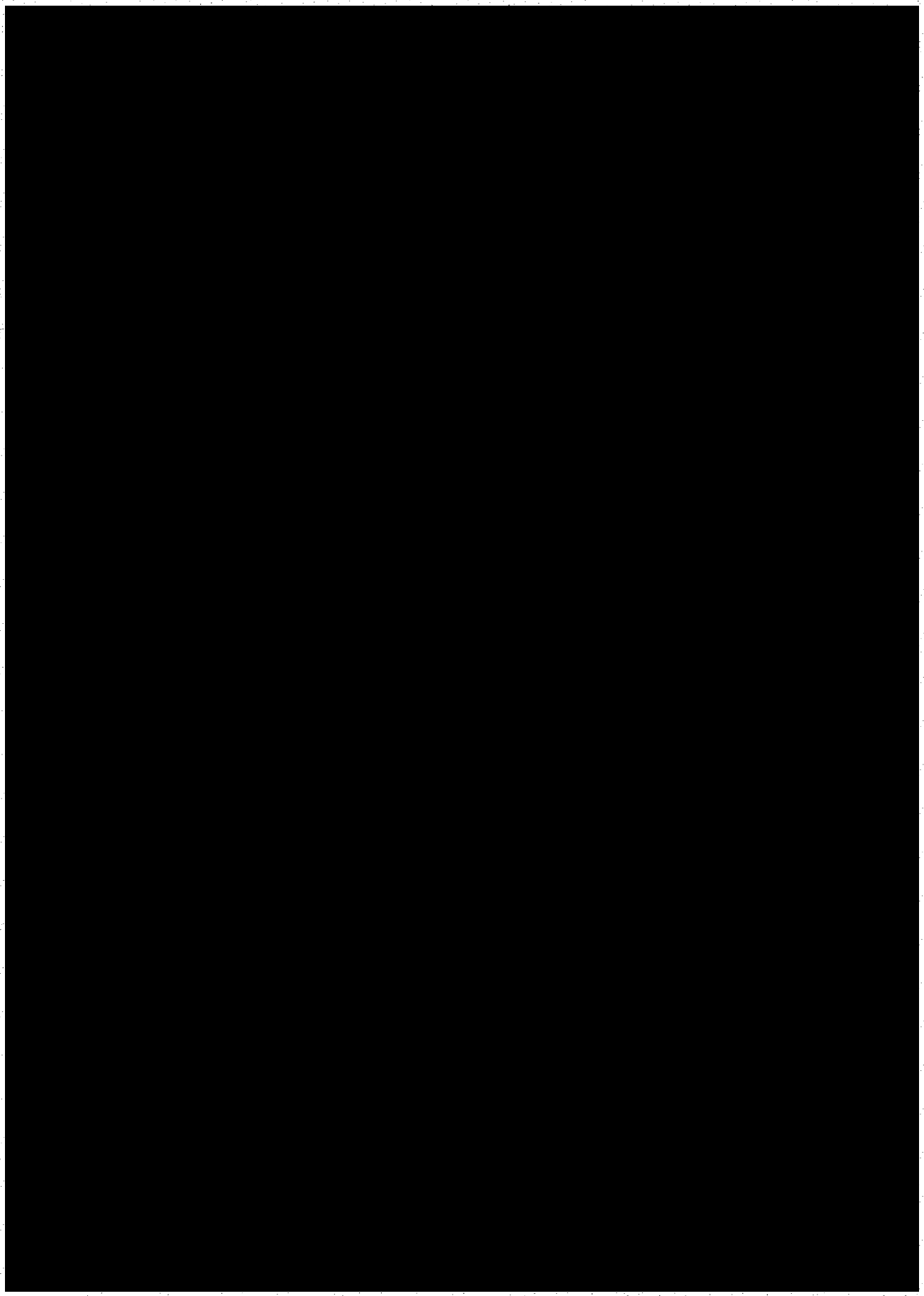


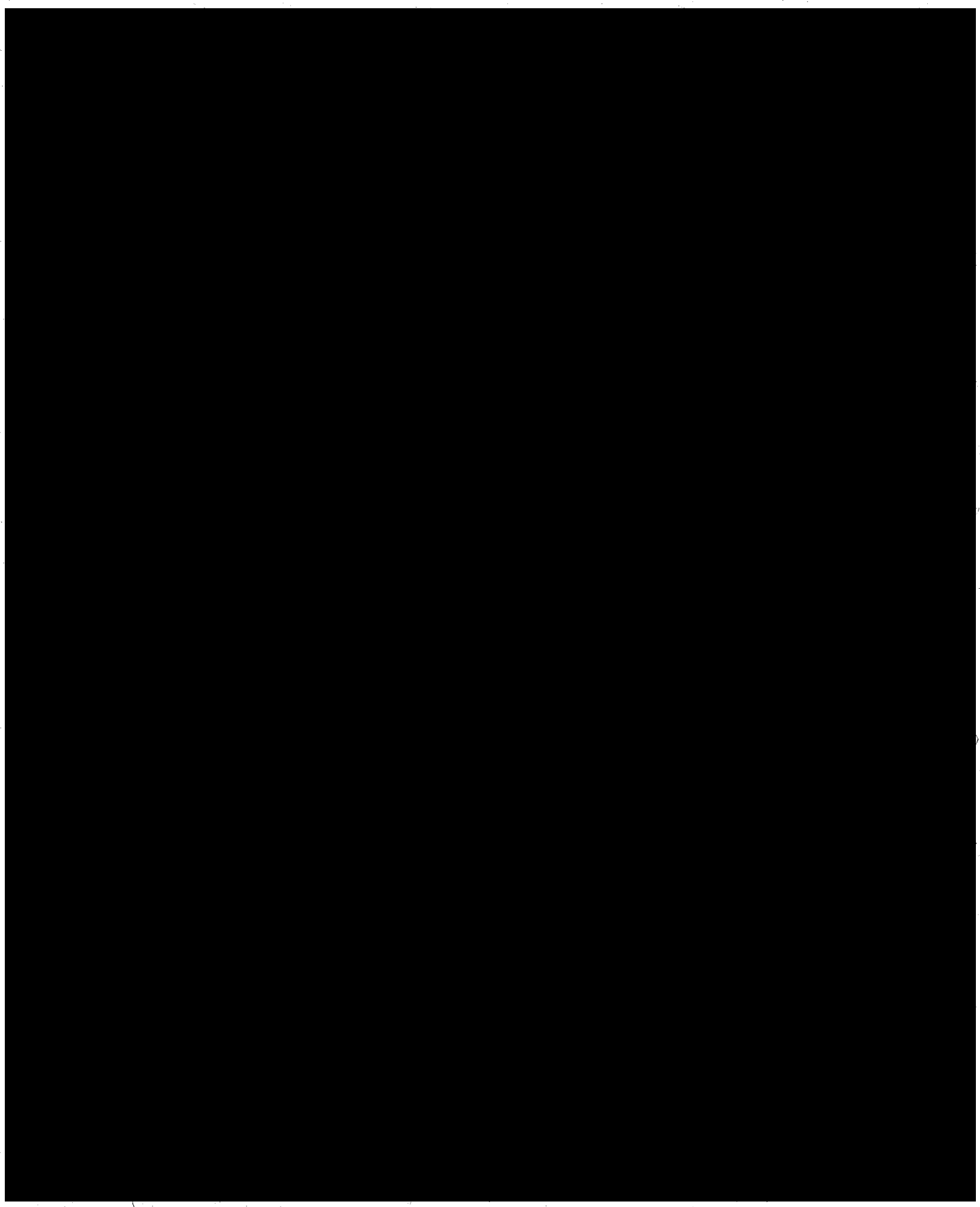


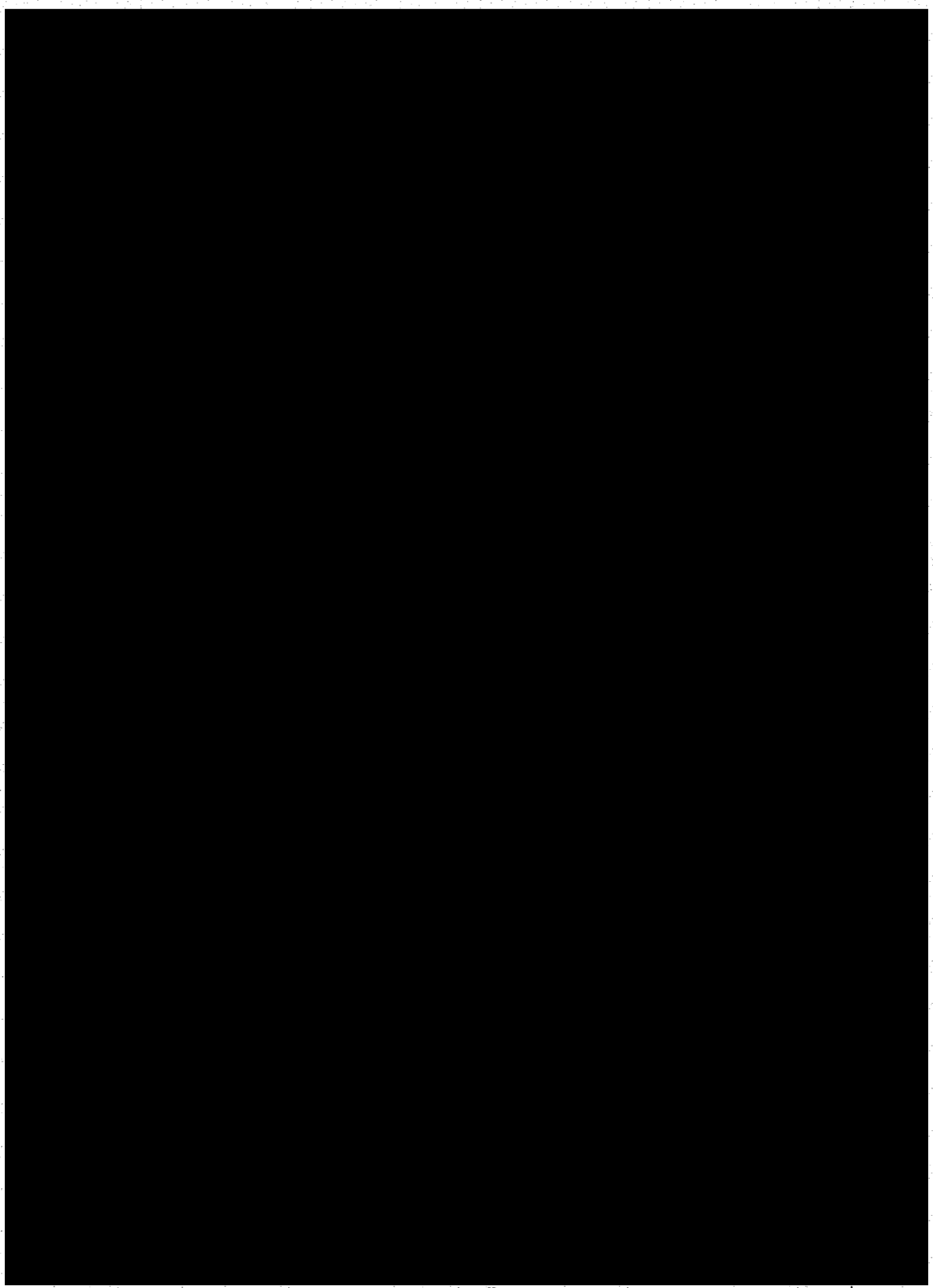


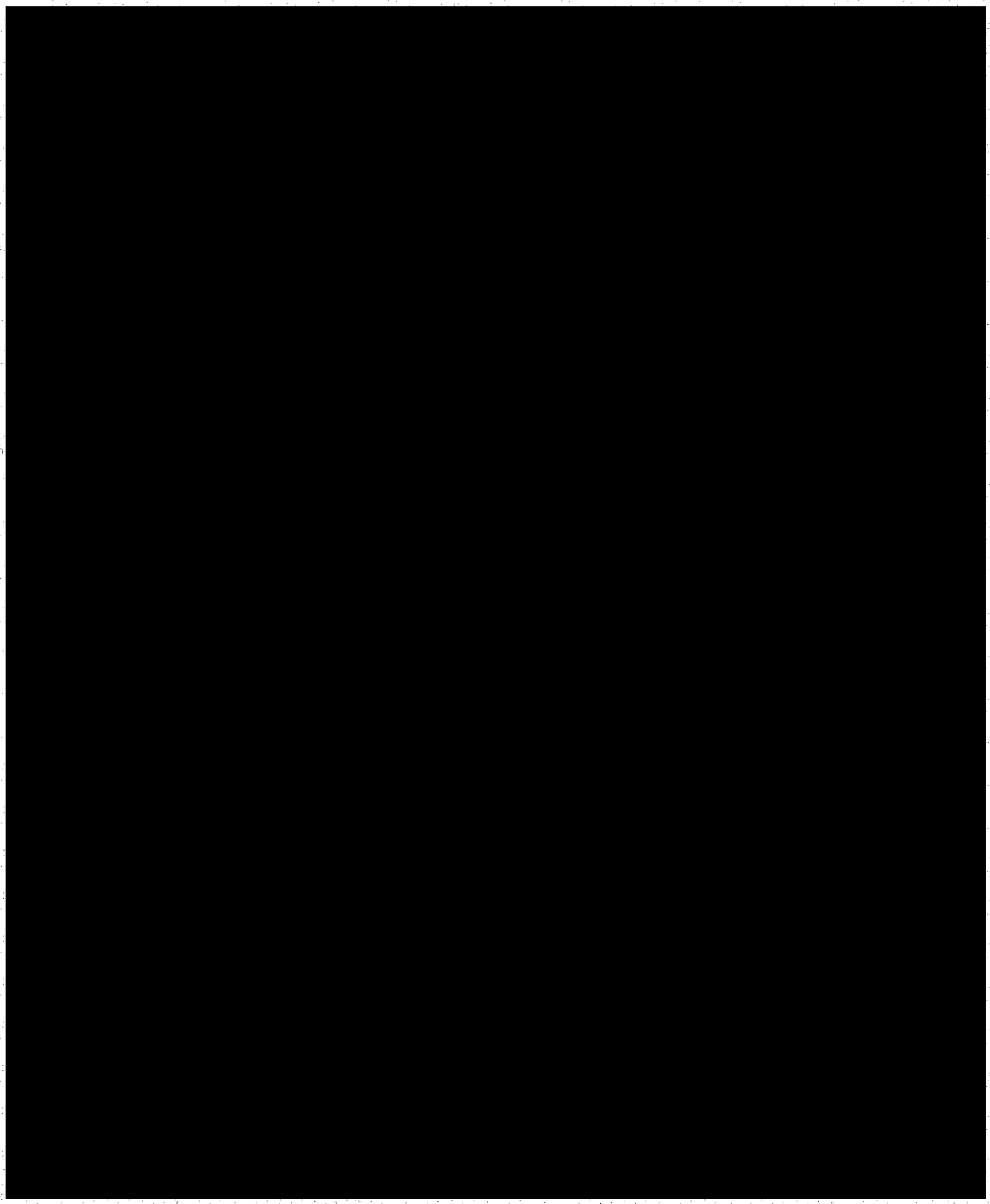


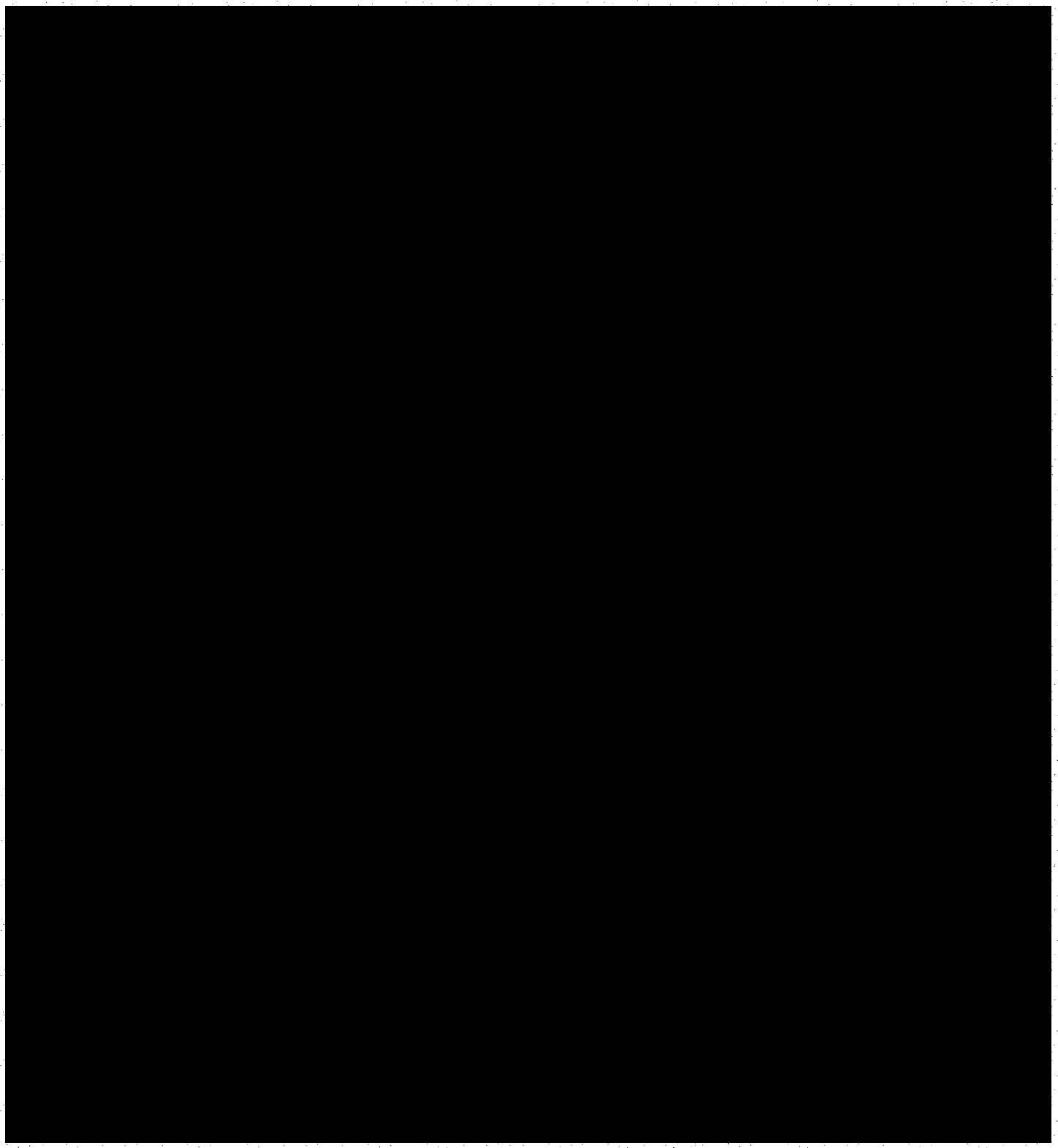


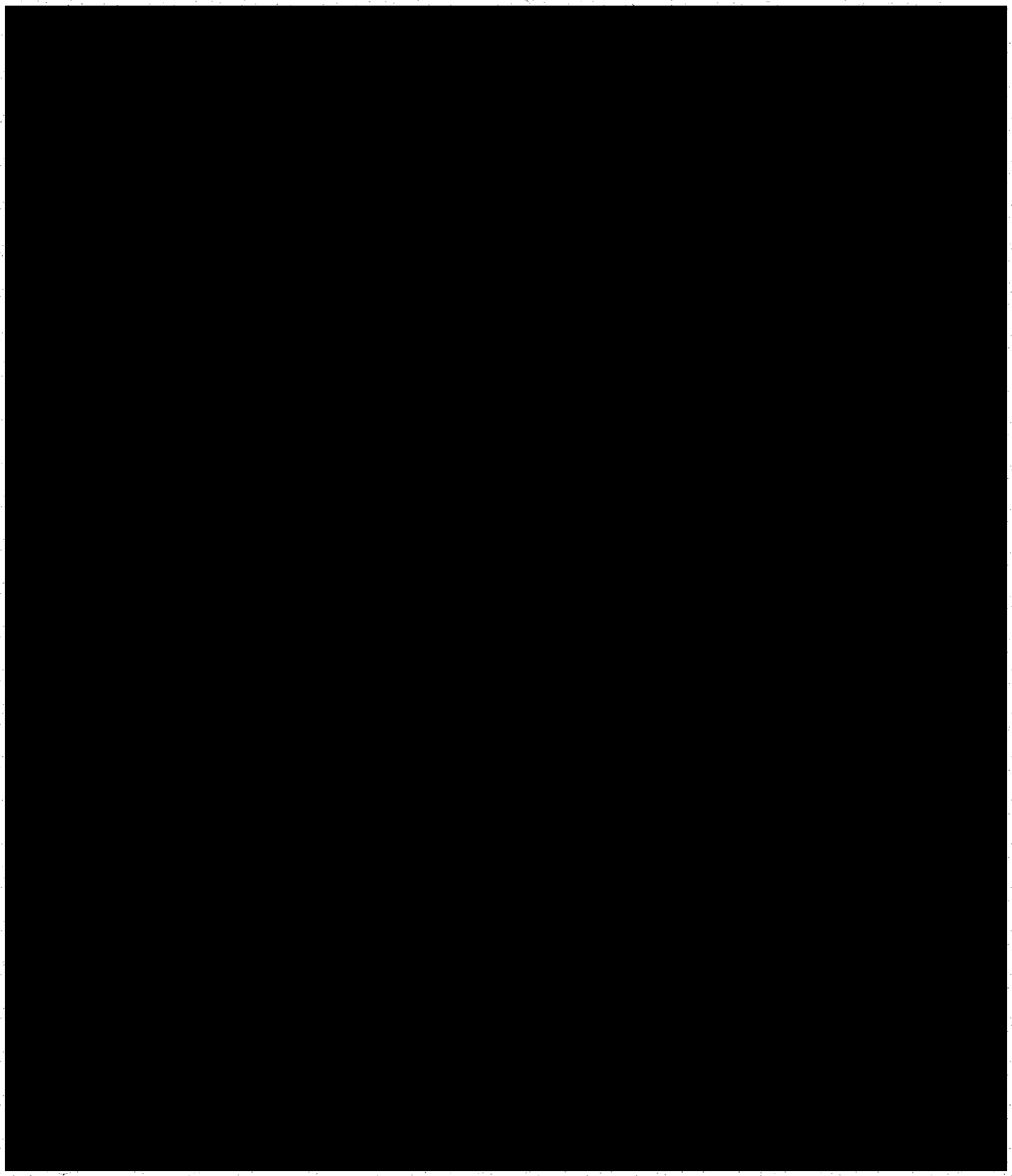


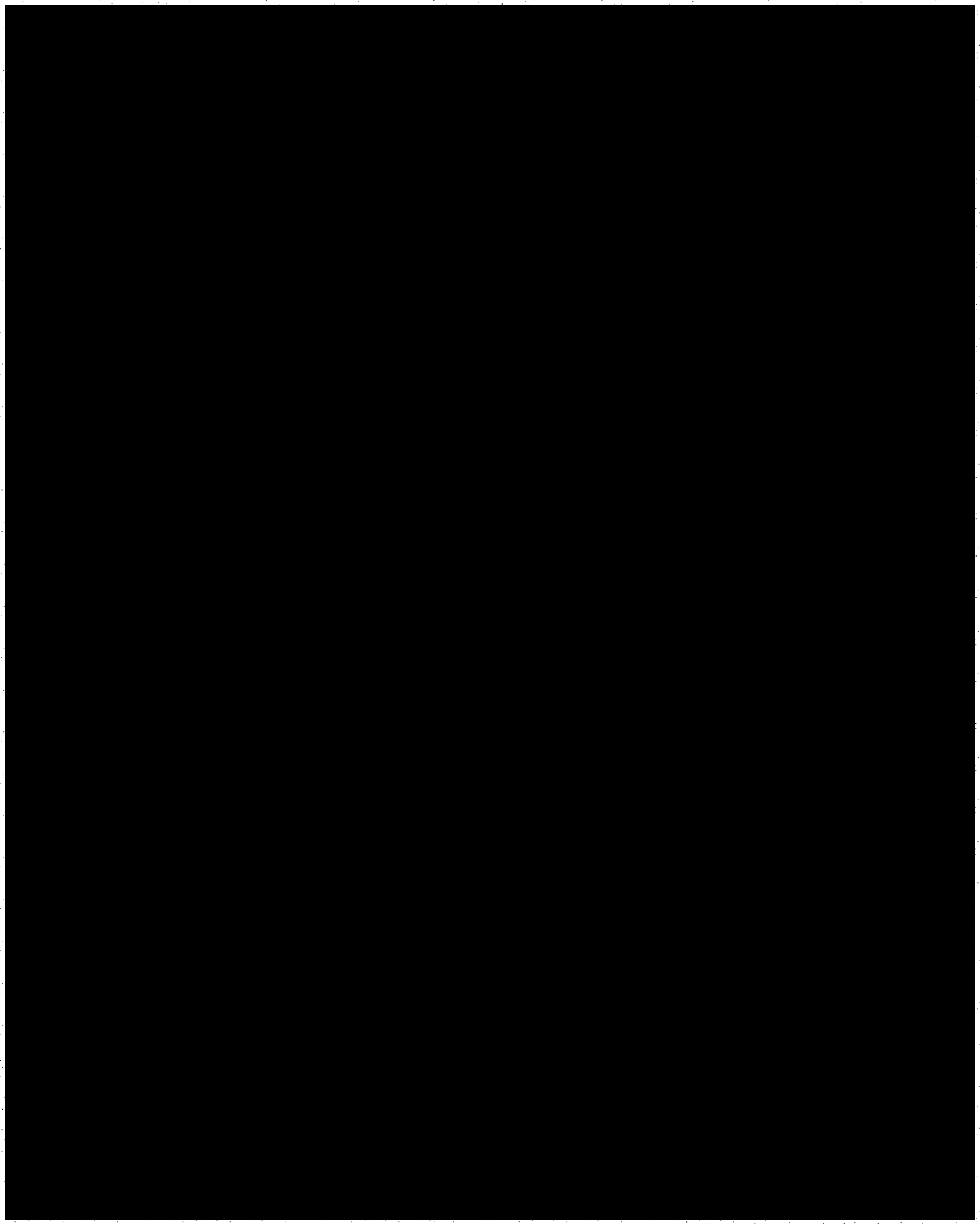


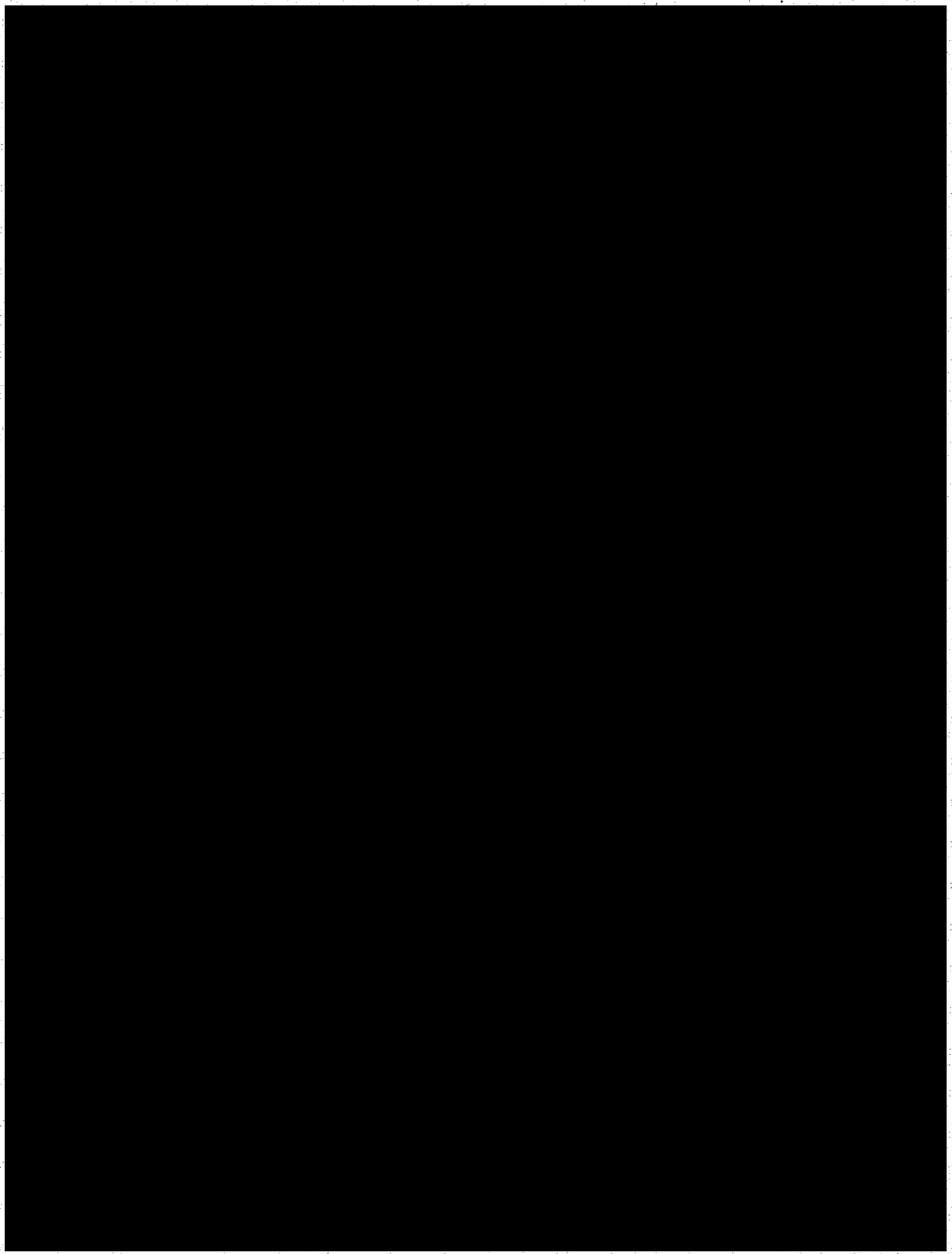


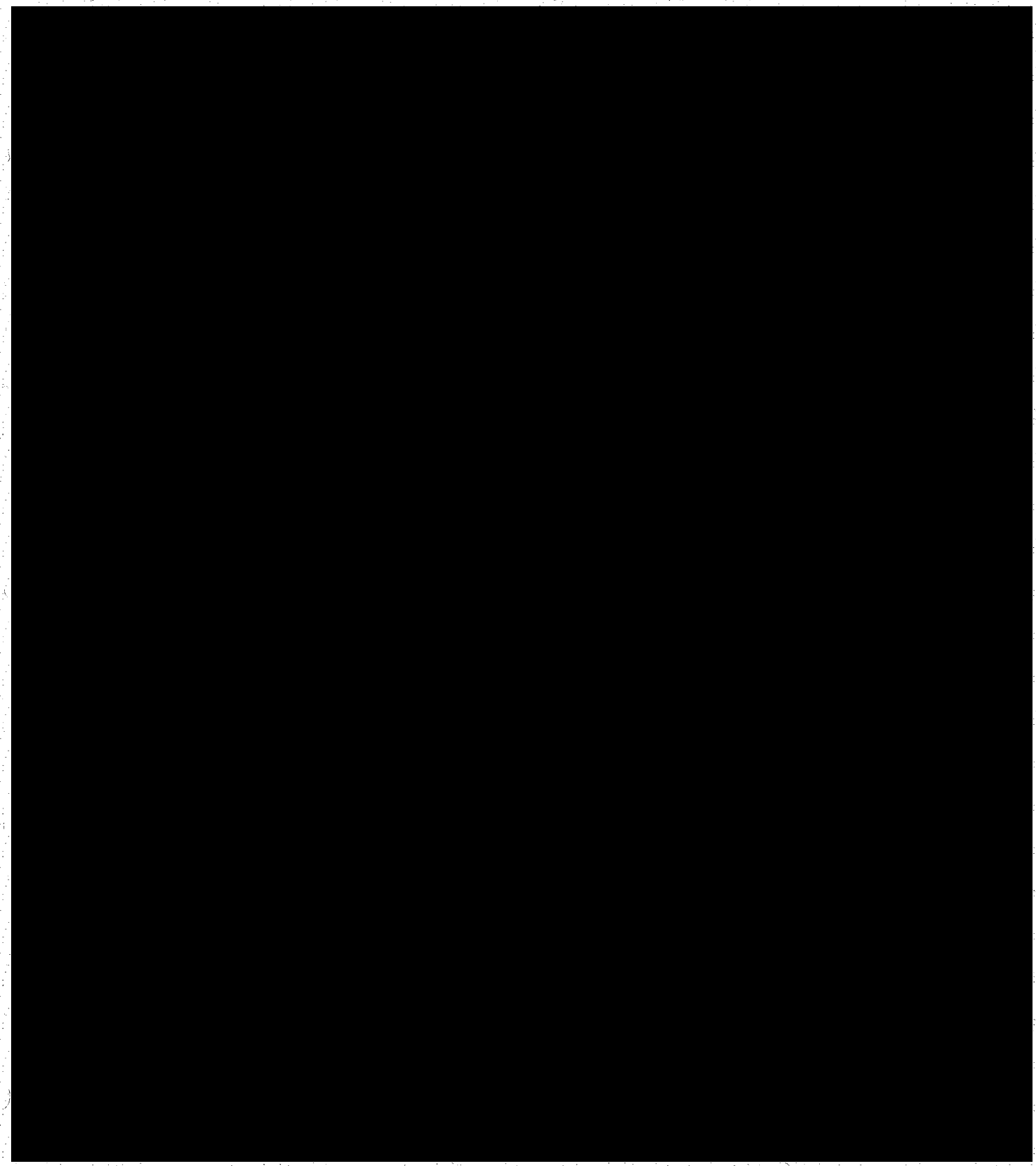


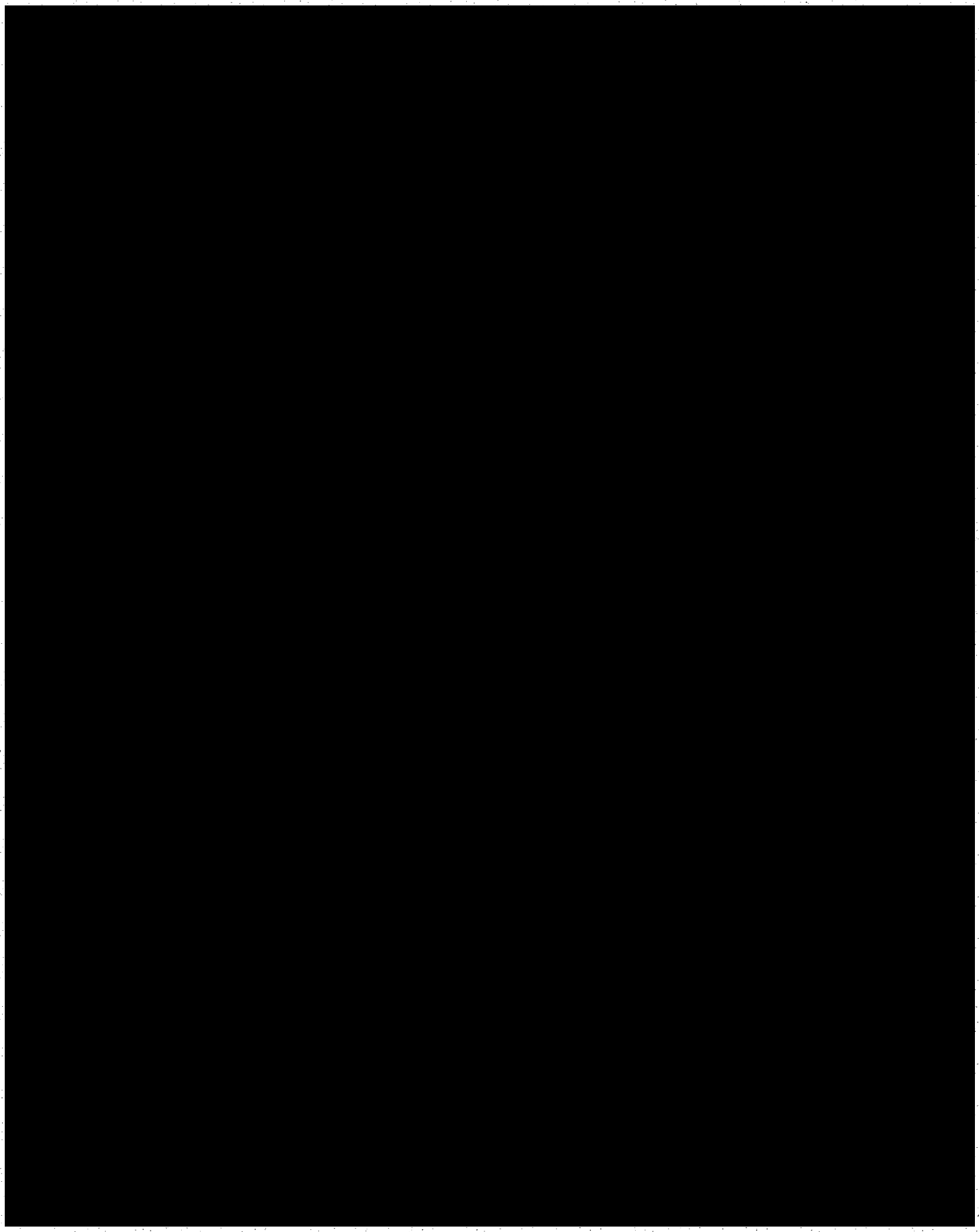


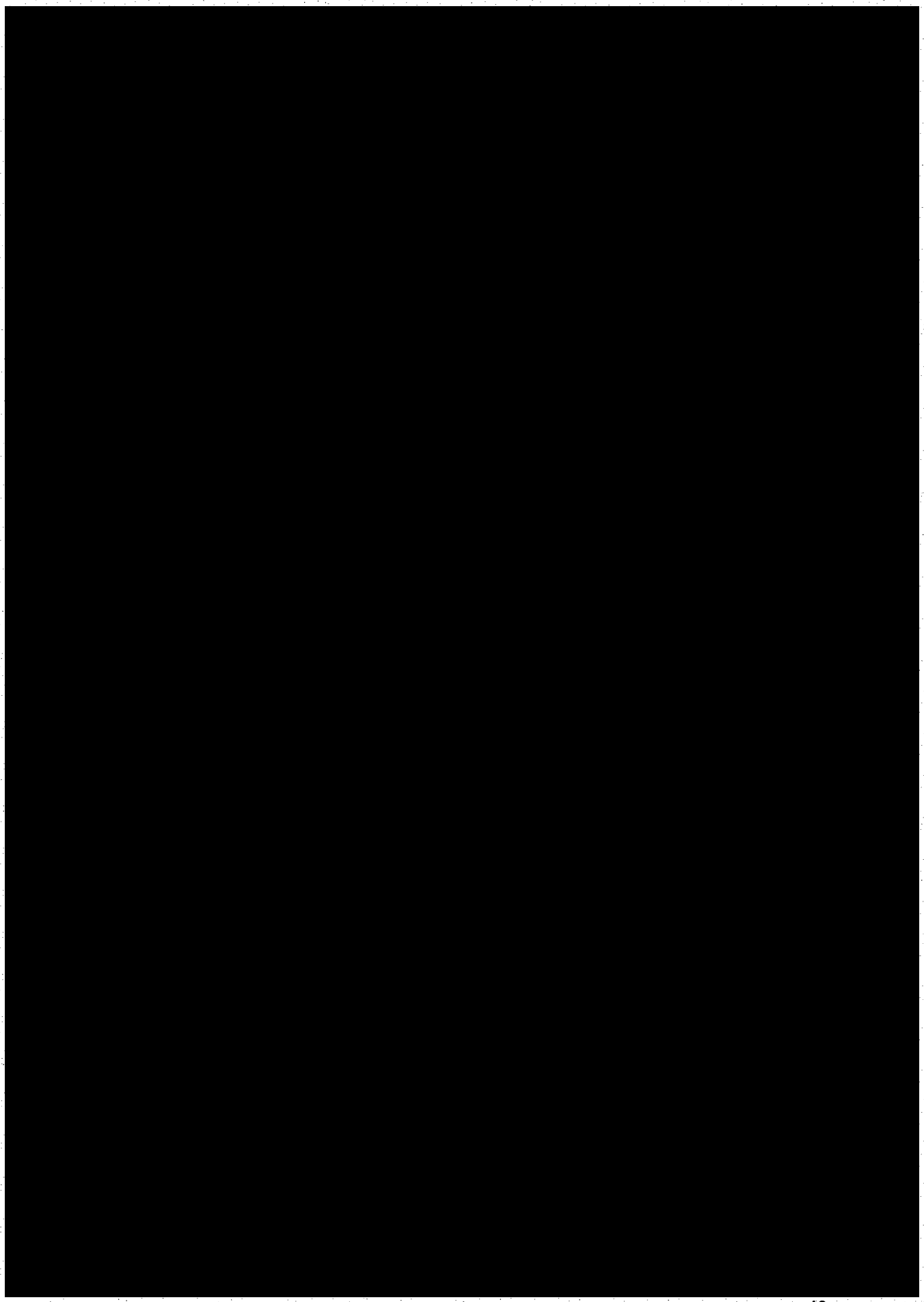


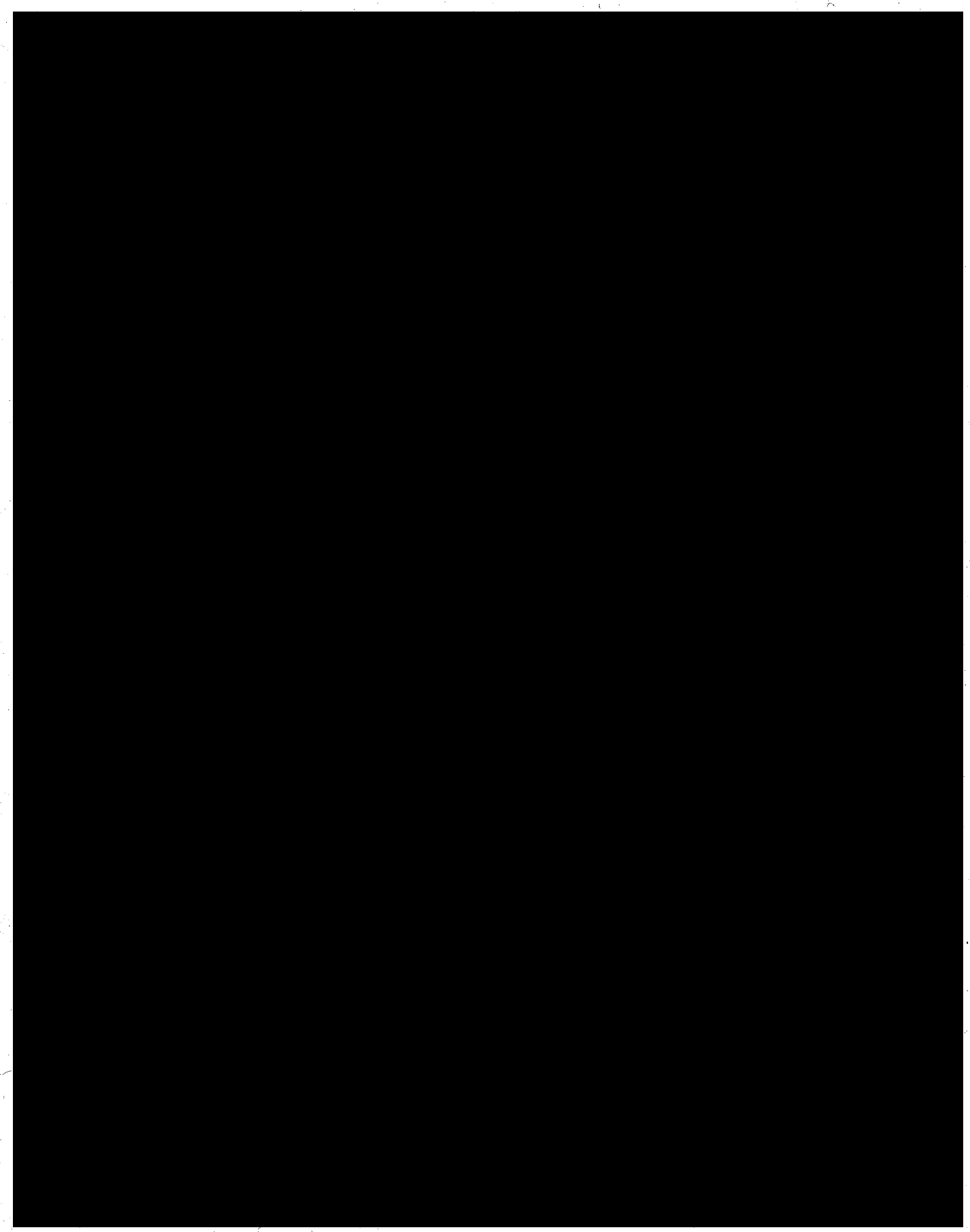


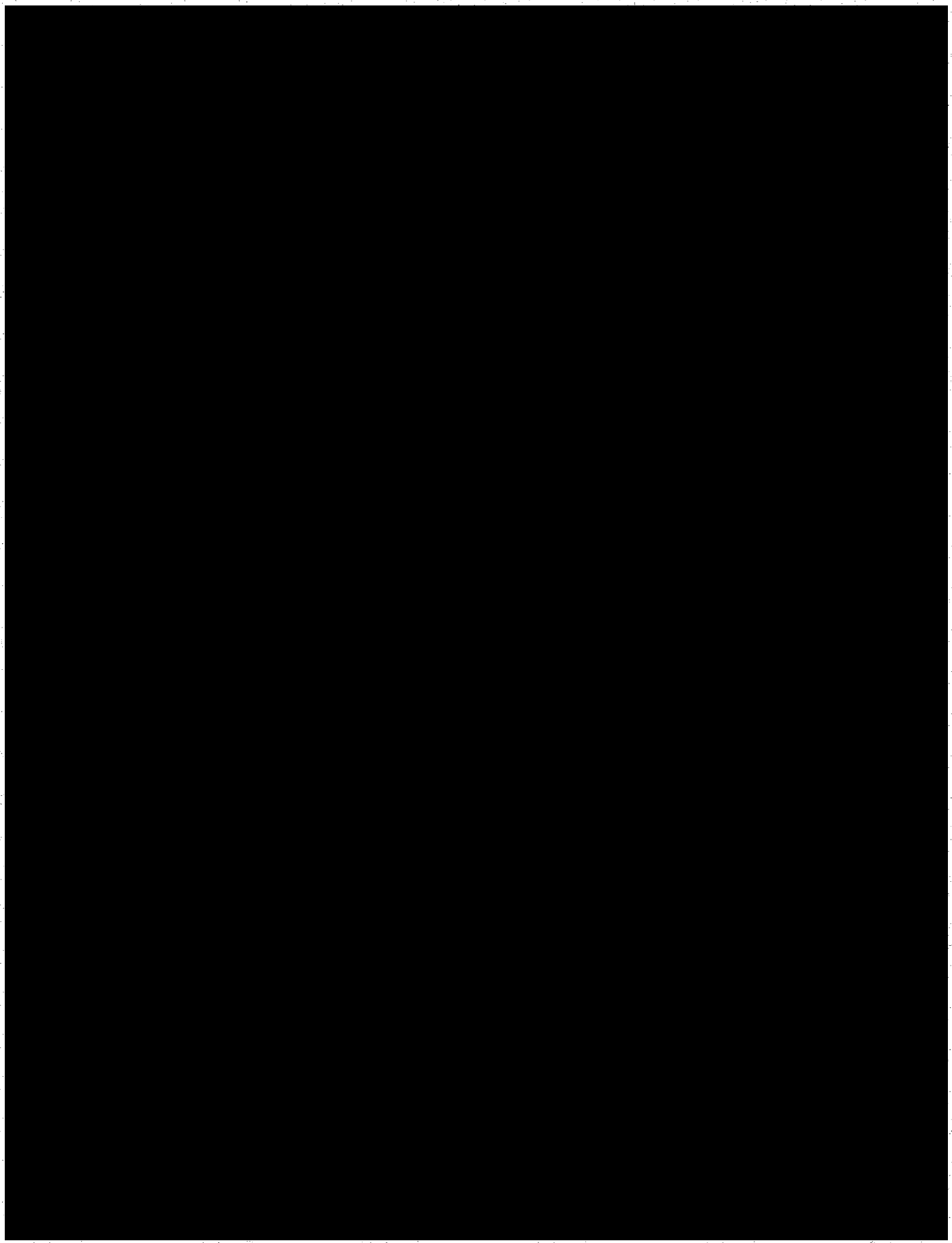


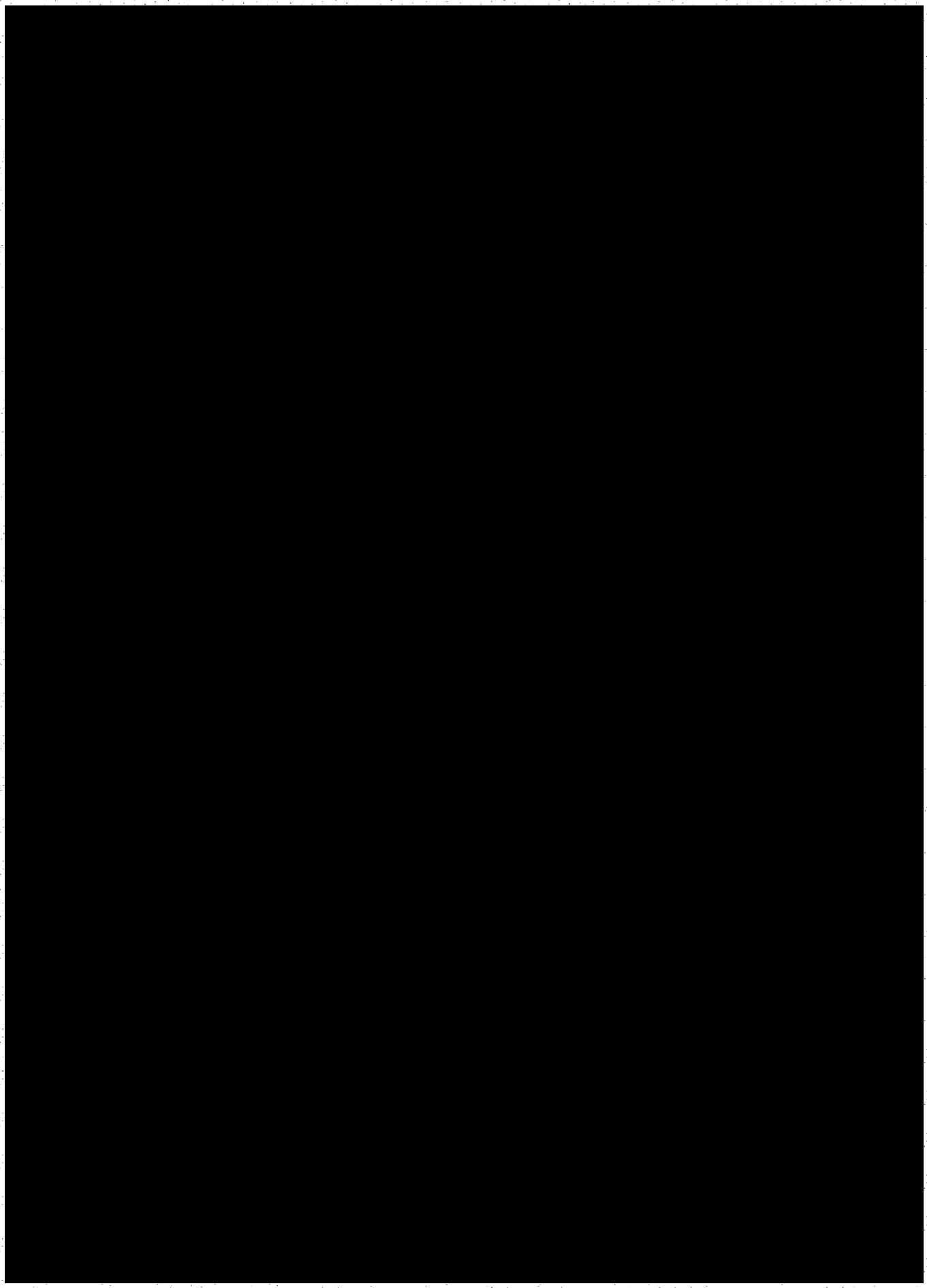


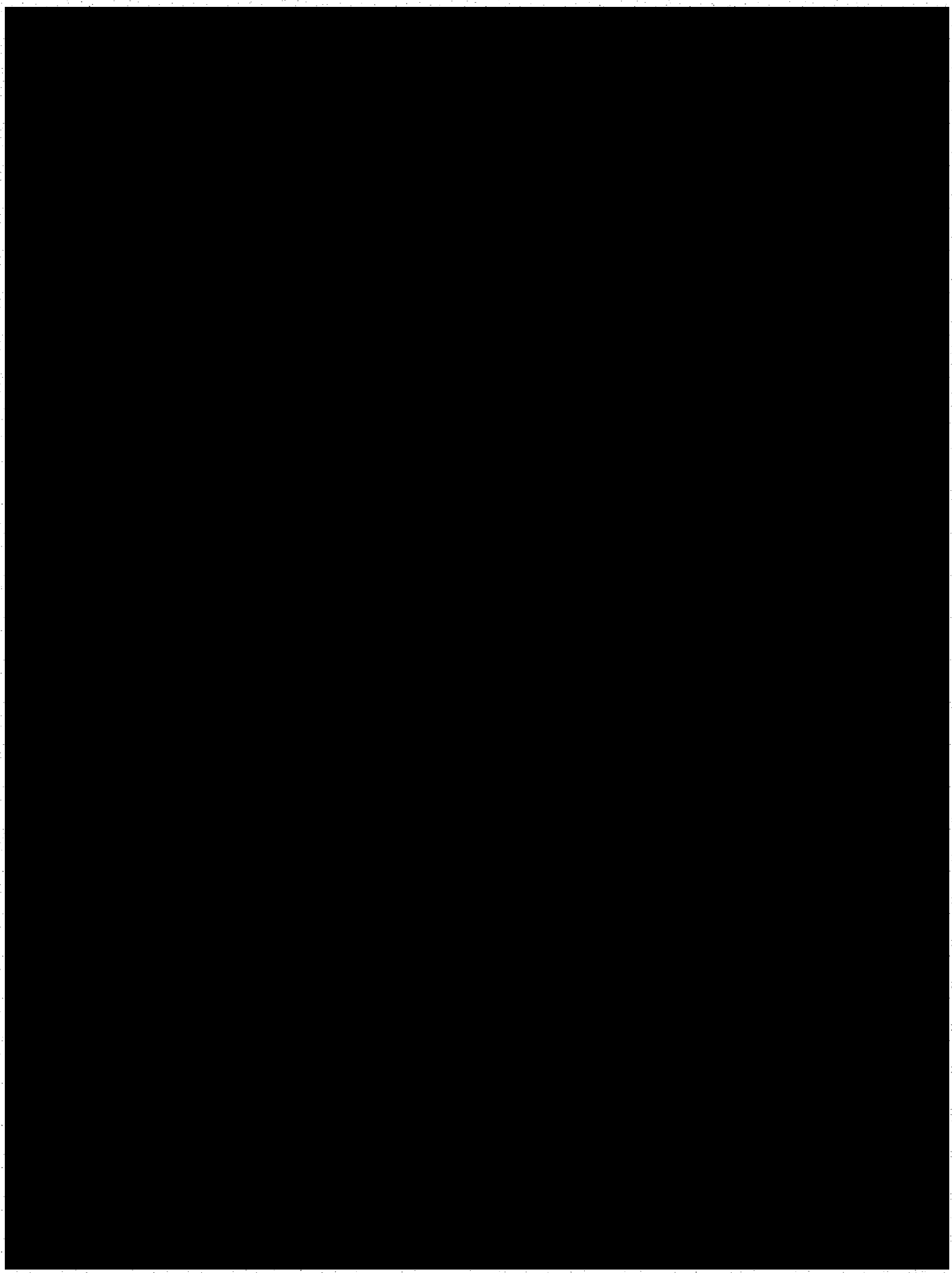


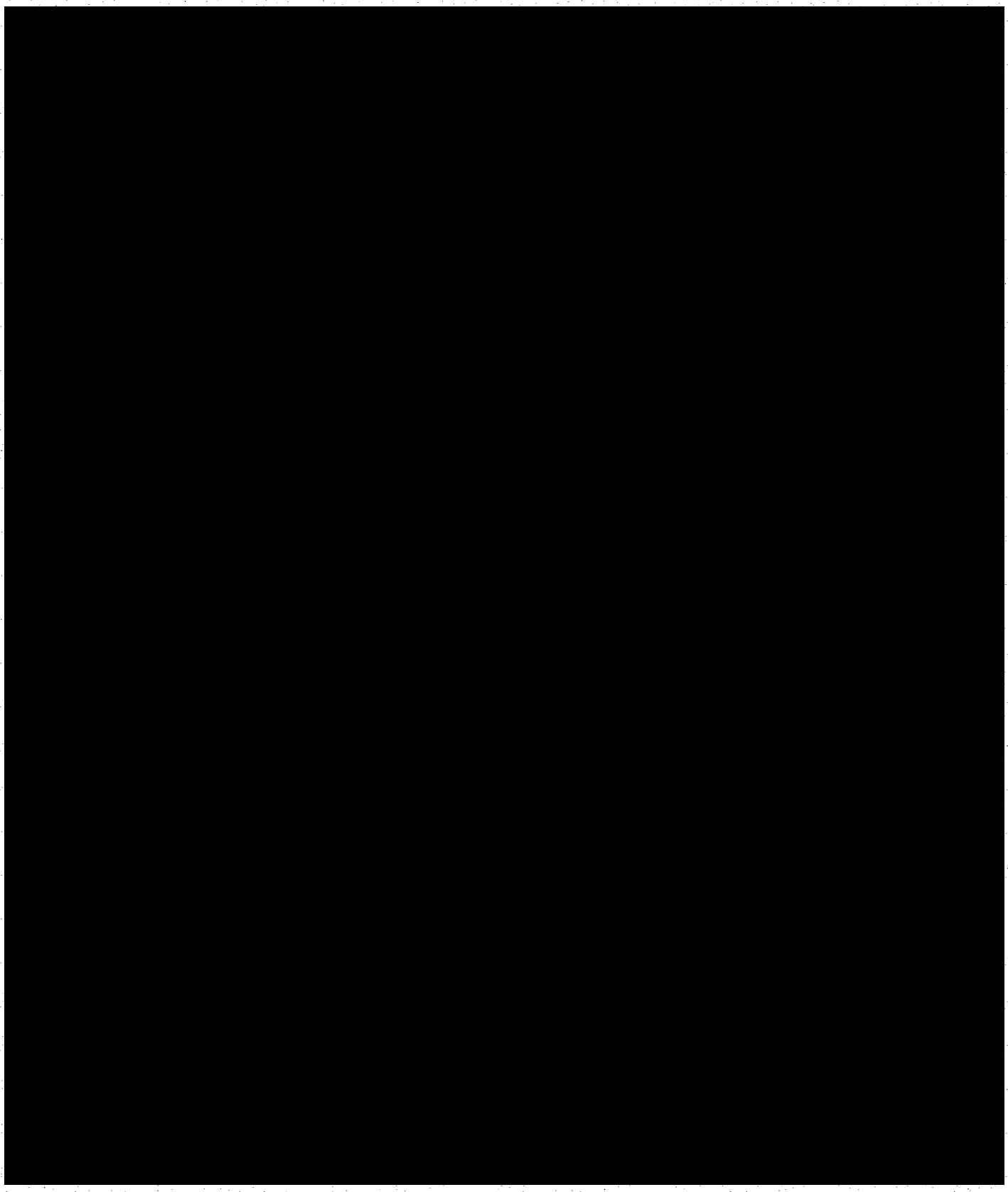












4.2 Individual Study Reviews

**Population PK Analysis Review:**

The population pharmacokinetic (POPPK) analysis of abatacept in JRA/JIA subjects was conducted with data from randomized withdrawal clinical efficacy study # IM101033 conducted in support of the proposed pediatric indication. Study # IM101033 was "A Phase 3, Multi-center, Multi-national, Randomized, Withdrawal Study to Evaluate the Safety and Efficacy of Abatacept in Children and Adolescents with Active Polyarticular Juvenile Rheumatoid Arthritis".

*Pediatric Study # IM101033 Design*

| Study | Study Period | Design | Treatment Doses | Treatment Schedule | Sample Size | PK Sampling Schedule[b,c] |
|---|---|---|---|---|---|---|
| IM101033 (JRA/JIA) | A | Open-label, multi-center, multi-national | • 10mg/kg to subjects <100 kg<br>• 1g to subjects ≥100 kg | IV infusion over 30 minutes on Days A1, A15, A29, and every 28 days thereafter | 186 | • Pre-dose trough (before each dose on Days A15, A29, A57, A85, and A113);<br>• 30 min (end of infusion) sample (on Days A57, A85, and A113)<br>• Week 2–4 (one sample between Days A92 and A110) |
| | B | Randomized, multi-center, multi-national, parallel group | • 10mg/kg to subjects <100 kg<br>• 1g to subjects ≥100 kg<br>**OR**<br>• Placebo | IV infusion over 30 minutes on Days B1 and every 28 days thereafter | 61 for placebo<br>61 for abatacept | • Pre-dose trough (before each dose on Days B29, B57, B85, B113, B141, and B169) |

Study # IM101033 was conducted in three Periods:

Period A: Pediatric JIA/JRA patients were treated with abatacept 10 mg/kg IV infusion in an open-label design for four months. Subjects that met the criteria "American College of Rheumatology (ACR) Pediatric 30 definition of improvement" in Period A were randomized to either abatacept or placebo into the double-blind phase (Period B).

Period B: The primary efficacy endpoint, which was evaluated in the double-blind phase (Period B), was the time to disease flare. The definition of flare was based on the change in the ACR Pediatric core-response variables from the beginning of the double-blind treatment period. Subjects who worsened by 30 percent or more in at least 3 of the 6 core-response variables without improving by 30 percent or more in more than 1 of the 6 core-response variables met the criteria for flare. If Global Assessments were used to define flare, there had to have been a change of at least 2 cm. If the number of active joints and/or joints with limitation of motion was used to define flare, there had to have been a worsening of at least 2 joints.

Period C: Pediatric patients from the following situations received an open-label extension with abatacept therapy (10 mg/kg IV infusion); a) subjects who completed the lead-in phase (Period A) without adequate response were given the option to receive treatment; b) subjects who completed the double-blind phase (Period B) without experiencing flare; c) subjects who discontinued from the double-blind phase (Period B) due to flare.

*Dose and Dosing Regimen*

During Period A, pediatric patients received abatacept 10 mg/kg by IV infusion over 30 minutes (maximum dose of 1000 mg administered to subjects over 100 kg) on Visit Days A1, A15 and A29, and monthly thereafter during the lead-in phase.

During the double-blind phase, Period B, pediatric patients received either of the following treatments every month:
1) Abatacept 10 mg/kg by IV infusion (maximum dose of 1000 mg administered to subjects over 100 kg)
2) Placebo (Dextrose 5% in water [D5W]) or Normal Saline (NS) by IV infusion.

During the open label-extension, Period C, pediatric patients received abatacept 10 mg/kg IV infusion over 30 minutes.

*PK sampling scheme*

Serum samples for abatacept analysis were only collected in the Period A and B at the following times, but no blood samples were collected in period C.

Period A:

• Pre-dose trough (before each dose on Days A15, A29, A57, A85, and A113);

• 30 min (end of infusion) sample (on Days A57, A85, and A113)

• Week 2–4 (one sample between Days A92 and A11

Period B:

• Pre-dose trough (before each dose on Days B29, B57, B85, B113, B141, and B169)

*Immunogenicity analysis sampling*

Blood samples were collected on A57, A113, B85, and B169 indicated as Period Days, for analysis of anti-abatacept and anti-CTLA4 antibodies.

*Data*

All available abatacept serum concentration-time data from the lead in phase (Period A, 1497 samples from 186 subjects) and the double-blind phase (Period B, 590 samples from 122 subjects) of IM101033 were included in the POPPK analysis dataset, whereas the data following early termination and the open label extension phase (Period C) were excluded from the analysis. Abatacept concentration values below the limit of quantification and outliers identified by distributional checks were also excluded from the analysis. In addition, the analysis dataset included time-invariant (baseline demographic and clinical laboratory data) and time-varying covariates (body weight, glomerular filtration rate, creatinine clearance, alanine aminotransferase, and aspartate aminotransferase concentration). Available prior concomitant medication data were also included as time-invariant categorical covariates, by categorizing the medications into 3 categories: methotrexate, non-steroidal anti-inflammatory drugs, and corticosteroids. In addition, disease status data were included as time-varying (number of tender joints and number of swollen joints) and time invariant (baseline disease duration) covariates.

In addition, data that were used to develop the POPPK model for adults with rheumatoid arthritis were also included in this analysis (2148 samples from 388 subjects). Orencia adult population PK study and data analysis is described in Dr. Anil Rajpal's clinical Pharmacology review dated June 17, 2005. There were 2175 blood samples collected from 187 patients in Study IM101033 out of which 1497 samples were collected from 186 patients during Period A, and 590 samples were collected from 122 patients during Period B, and 88 samples were collected from 41 patients who terminated the assigned study treatment during either Period A or B.

| Covariate | Statistic | Summary |
|---|---|---|
| Baseline Age (Years) | Mean (SD) | 12.4 (3) |
| | Median (min,max) | 13.0 (5, 17) |
| Baseline Body Weight (Kg) | Mean (SD) | 41.8 (15.4) |
| | Median (min,max) | 41.7 (14.4, 100) |
| Baseline Height (cm) | Mean (SD) | 145.5 (17.4) |
| | Median (min,max) | 147.8 (101.5, 17 |
| Baseline Body Surface Area (cm2) | Mean (SD) | 1.3 (0.3) |
| | Median (min,max) | 1.3 (0.6, 2.1) |
| Baseline Body Mass Index (Kg/m2) | Mean (SD) | 19.1 (4.2) |
| | Median (min,max) | 18.5 (12, 37) |
| Baseline Lean Body Mass (g) | Mean (SD) | 28892.6 (8804) |
| | Median (min,max) | 29089.2 (11215.4, 51970.6) |
| Gender | | |
| Male | N (%) | 53 (28.5%) |
| Female | N (%) | 133 (71.5%) |
| Race | | |
| White | N (%) | 143 (76.9%) |
| Black/African American | N (%) | 15 (8.1%) |
| Asian | N (%) | 1 (0.5%) |
| Hawaiian/Pacific Islander | N (%) | 1 (0.5%) |
| Others | N (%) | 26 (14.0%) |

## METHODS

Initial development of the POPPK model was conducted with only the JRA/JIA dataset, and subsequent development was conducted with the combined JRA/JIA and adult RA dataset. The adult RA data were included to enhance the robustness of the dataset, and facilitate comparison of PK in JRA/JIA and adult RA subjects. A base model was first developed, followed by the assessment of covariate relationships and the development of the final model.

The base model consists of a structural PK model, an interindividual variability (IIV) model, and a residual error model. Base model development was initiated with a linear 2-compartmental structural model, based on the existing POPPK model for adults with RA. This was followed by assessment of alternative IIV models, residual error models, and the effect of body weight on model parameters. The base model was selected based on a number of criteria including reduction in objective function value, goodness of fit.

In the second stage of POPPK model development, subject-specific covariates were examined to assess whether inclusion of these covariates in the model improved the goodness-of-fit and reduced the IIV in structural parameters or residual errors. Covariate effects were evaluated for statistical significance with the likelihood ratio test, and for clinical relevance (change in a model parameter of more than 20%).

The following time-invariant baseline covariates were tested: body weight, age, gender, race (white vs. non-white), duration of disease, and prior comedication indicators; the following time-varying covariates were tested: hepatic and renal status, disease status, including number of tender and swollen joint counts. Only physiologically reasonable covariate-parameter relationships were considered. The confidence intervals of parameters in the final model were determined by non-parametric bootstrap. Model evaluation was conducted by quantitative predictive performance check of trough serum concentrations. Model-based predictions were used to compare abatacept exposures in the JRA/JIA and adult RA populations. Lastly, the following measures of exposure were evaluated at steady state: Cmin, Cmax, and AUC.

**RESULTS**

The Final Model is a linear 2-compartment model, parameterized in terms of clearance (CL), volume of central compartment (VC), inter-compartmental clearance (Q), and volume of peripheral compartment (VP). The parameter estimates for the Final Model are presented in the table below:

$$CL_{avg} = CL_1 (BWT/BWT_{ref})^{CL_2}$$
$$VC_{avg} = VC_1 (BWT/BWT_{ref})^{VC_2}$$
$$VP_{avg} = VP_1 (BWT/BWT_{ref})^{VP_2}$$

**Pharmacokinetic Parameter Estimates Derived Employing the Final Model**

| Name [Units][a] Fixed Effects | Estimate[b] | Standard Error (RSE%)[c] | 95% Confidence Interval[d] |
|---|---|---|---|
| CL1 [L/h] | 0.0217 | 5.34E-04 (2.46) | 0.0207 - 0.0227 |
| VC1 [L] | 3.07 | 0.0496 (1.62) | 2.97 - 3.17 |
| Qavg [L/h] | 0.0212 | 0.00262 (12.4) | 0.0161 - 0.0263 |
| VP1 [L] | 4.09 | 0.240 (5.87) | 3.62 - 4.56 |
| CL2 | 0.545 | 0.0318 (5.83) | 0.483 - 0.607 |
| VC2 | 0.693 | 0.0336 (4.85) | 0.627 - 0.759 |

| | | | |
|---|---|---|---|
| VP2 | 0.666 | 0.0549 (8.24) | 0.558 - 0.774 |
| **Random Effects** | | | |
| ZCL [-] | 0.0769 (0.277) | 0.00589 (7.66) | 0.0654 - 0.0884 |
| ZVC [-] | 0.0454 (0.213) | 0.00777 (17.1) | 0.0302 - 0.0606 |
| ZVP [-] | 0.164 (0.405) | 0.0337 (20.5) | 0.0979 - 0.230 |
| ZCL:ZVC | 0.0348 (0.589) | 0.00543 (15.6) | 0.0242 - 0.0454 |
| ZVC:ZVP | 0.0423 (0.490) | 0.0101 (23.9) | 0.0225 - 0.0621 |
| **Residual Error** | | | |
| Proportional | 0.252 0.0253 | 0.00879 (3.49) | 0.235 - 0.269 |
| Additive | | 0.0114 (45.1) | 0.00296 - 0.0476 |

[a] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters
[b] Random Effects parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($ZP_i$) and *Covariance (Correlation)* for off-diagonal elements ($ZP_1 : ZP_2$)
[c] RSE% is the relative standard error (Standard Error as a percentage of Estimate)
[d] Confidence intervals of Random Effects parameters are for *Variance* or *Covariance*

**Summary of Models with Covariate Effect of Body Weight Using the JRA/JIA Dataset (Final Model indicated in bold font)**

| Model No | Model Description | MIN | COV | OFV | ΔOFV |
|---|---|---|---|---|---|
| B2001_7C2 | No body weight effect | Successful | Ok | 8040.078 | 0 (REF) |
| B2006_7C2 | TWT on CL, VC, Q, VP | Successful | Ok | 7990.691 | -49.387 |
| **B2104_7C2** | **BWT on CL, VC, VP** | **Successful** | **Ok** | **7914.268** | **-125.** |
| B2108_7C2 | BWT on CL, VC, VP with power term fixed at allometric scaling values (0.75 for CL; and 1 for VC, VP) | Successful | Ok | 7956.021 | -84.057 |

Among the models in above table that employ baseline body weight as the covariate, B2104_7C2 (baseline body weight effect on CL, VC, and VP) has the lowest OFV with successful minimization and covariance step convergence.

As body weight is a significant covariate in the model, and since there was a large overlap of body weight for the JRA/JIA subjects and the adult RA subjects, it was expected that a single population PK model will adequately describe abatacept serum concentration data in JRA/JIA as well as adult RA subjects. Subsequent model development was therefore conducted with the combined JRA/JIA and adult RA dataset.

**Summary of Models with Covariate Effect of Body Weight Using the JRA/JIA and Adult Datasets Combined (Final model Indicated in bold font)**

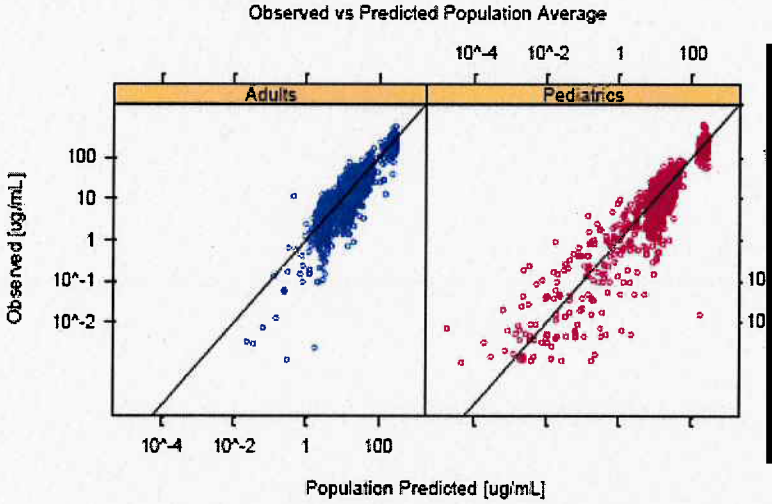
| Model No | Model Description | MIN | COV | OFV | ΔOFV |
|---|---|---|---|---|---|
| F2001_7C2 | No body weight effect | Successful | Ok | 18188.040 | 0 (REF) |
| **F2004_7C2** | **BWT on CL, VC, VP** | **Successful** | **Ok** | **17758.886** | **-429.** |
| F2010_7C2 | BWT on CL, VC, VP with the power term fixed at the allometric | Successful | Ok | 17858.411 | -329.629 |

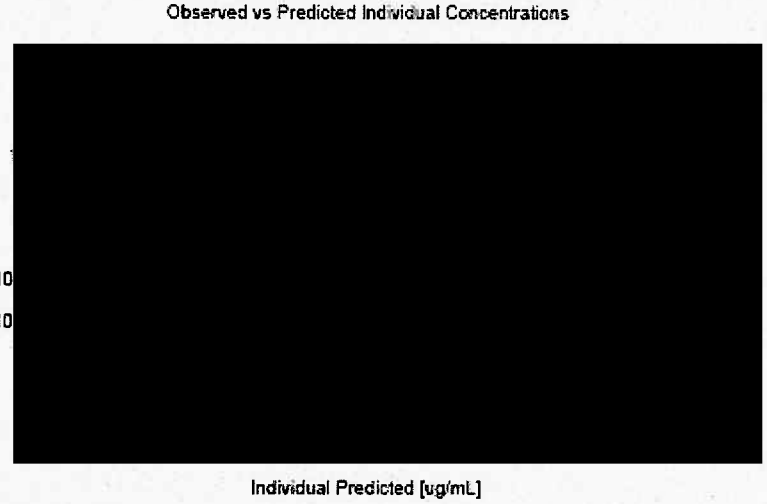
| | | | | | |
|---|---|---|---|---|---|
| | scaling values (0.75 for CL, and 1 for VC, VP) | | | | |
| G2004_7C2 | TWT on CL, VC, VP | Successful | Ok | 17778.349 | -409.691 |

As shown in the table above, all models with successful minimization had a significant decrease in OFV value compared to the reference model (F2001_7C2) with no body weight covariate effect. The model using time-varying body weight (TWT) as covariate had higher OFV values compared to the corresponding model with baseline body weight (BWT). Hence, Model F2004_7C2 was selected as the final model.

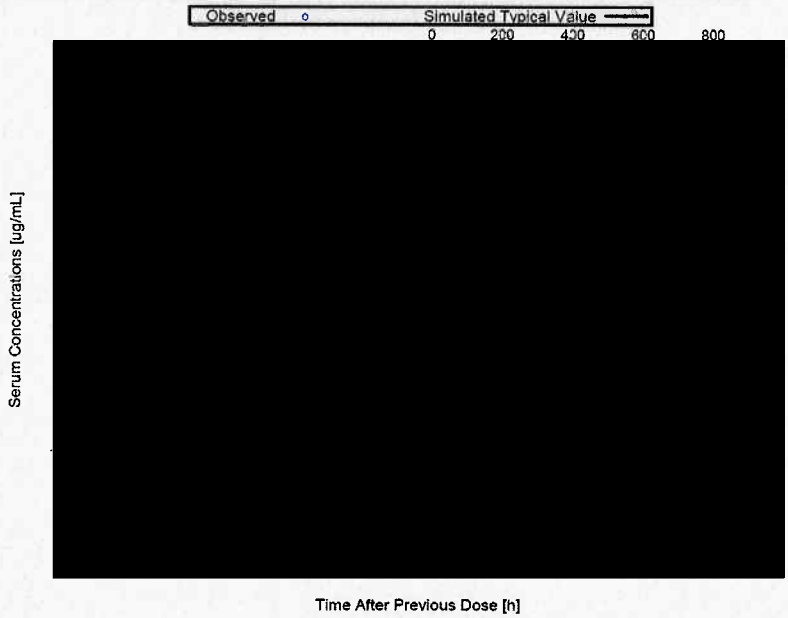
**Goodness of fit plots**

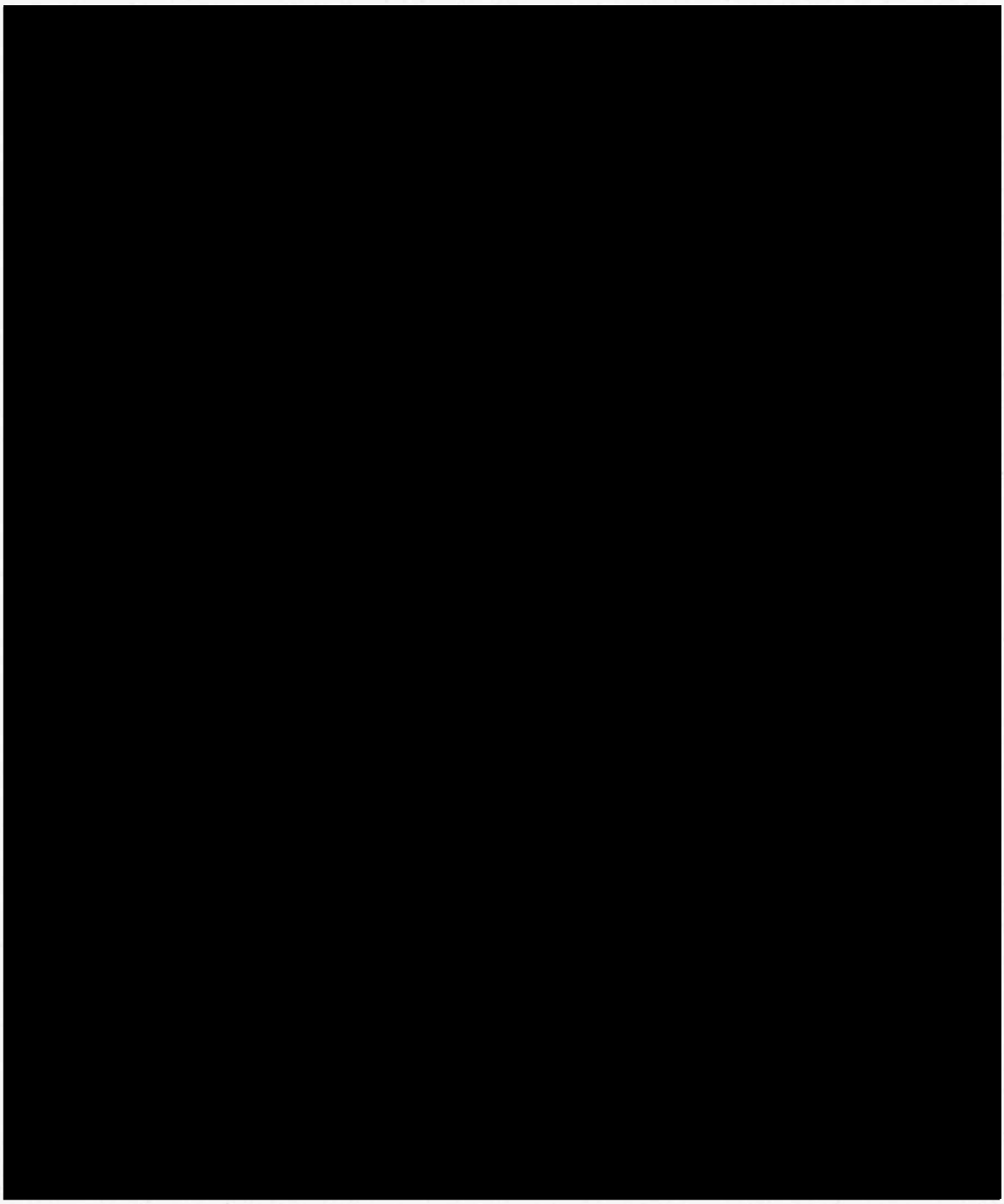
Observed versus Predicted Average Concentrations (Log Scale) (Left-Population; Right – Individual)




Observed Concentrations versus Time After Previous Dose

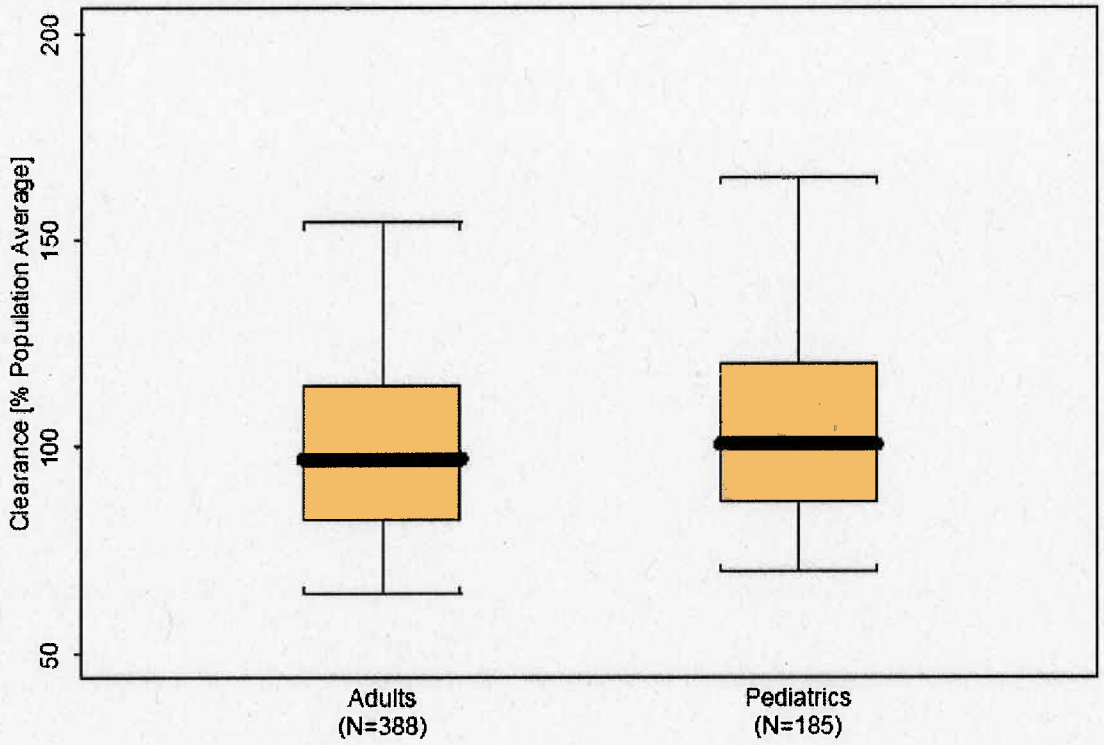




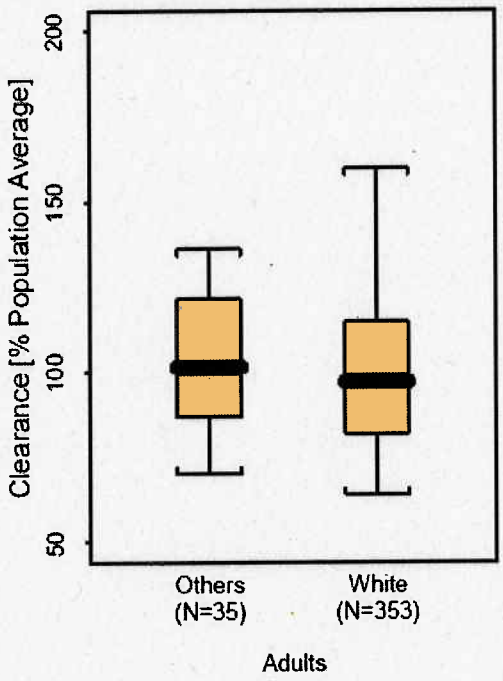
Sample Plots of Observed, Population Predicted and Individual Predicted versus Time after Previous Dose for few subjects.

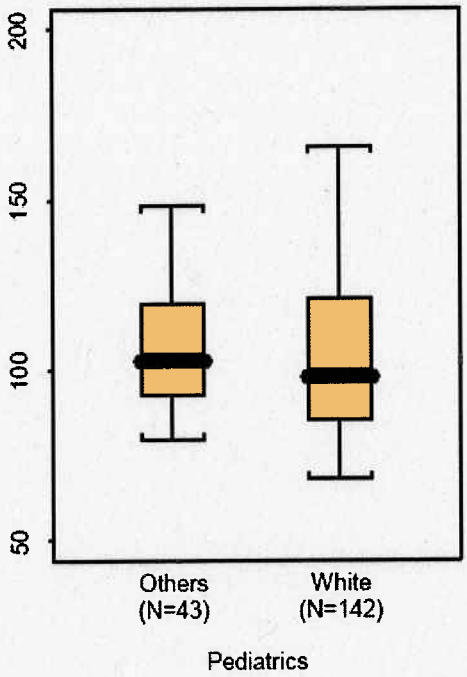
[redacted]

Clearance versus Age Group



Clearance versus Race




Clearance versus Gender