OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-214	Submission Date(s): 9/4/07
Brand Name	Arimidex®
Generic Name	Anastrozole
Reviewer	Jayabharathi Vaidyanathan, Ph.D.
PM Reviewer	Manoj Khurana, Ph.D.
PM Secondary Review	Raj Madabushi, Ph.D.
Team Leader	Sally Choe, Ph.D.
OCP Division	Clinical Pharmacology -2
OND division	Metabolic and Endocrine Products
Sponsor	AstraZeneca
Submission Type; Code	SE5 (Pediatric Exclusivity); Priority
Formulation; Strength(s)	1 mg tablets for oral administration
Indication	Treatment of pubertal gynecomastia in boys and treatment of precocious puberty in girls with McCune-Albright Syndrome (MAS)

1. Executive Summary

Anastrozole (Arimidex™) is a potent and selective nonsteroidal aromatase inhibitor. Arimidex (1 mg oral tablet) is approved for the treatment of advanced breast cancer in postmenopausal women whose tumors have recurred following treatment with tamoxifen as well as an adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer. The purpose of this application is to provide data (b) (4) anastrozole in other diseases that result from increased estrogen production for example, the treatment of pubertal gynecomastia in boys and treatment of precocious puberty in girls with McCune-Albright Syndrome (MAS). This application contains data examining the safety and efficacy of anastrozole in these pediatric populations in response to the Written Request from the FDA to obtain 6-month exclusivity for Arimidex tablets. Pediatric exclusivity was granted on 12/21/07.

No indication is being sought in this application. The sponsor proposes that appropriate sections of the Arimidex label should be updated to include data from the studies submitted.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 (OCP/DCP-2) has reviewed NDA 22-214 submitted on 9/4/07 (b) (4)

1.2 PHASE IV COMMITMENTS

Not applicable.

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

This application contains 2 studies (Study 0001 & Study 0046) that were conducted to investigate the PK of anastrozole in pediatric patients.

Anastrozole following multiple oral administrations (1 mg daily) was rapidly absorbed (median Tmax 1 hr). Concentrations then rapidly decreased over 1.5 - 4 hour followed by a gradual decline through the sampling period. The mean elimination half-life was 46.8 h. The clearance was 1.54 L/h and the drug was widely distributed (Vz/F = 98.4 L). Population pharmacokinetic modeling of data obtained from study 0046 and study 001 indicated that there was no effect of gender or age on the clearance of anastrozole in pediatric patients.

The PK of anastrozole in pediatric patients was similar to what has been observed in adult postmenopausal breast cancer patients.

2. QBR

2.1 GENERAL ATTRIBUTES

What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and Biopharmaceutics of the drug?

The written request from the FDA dated 9 May 2001 (and subsequently amended) required the sponsor to conduct 4 studies to obtain 6-month pediatric exclusivity for Arimidex 1 mg tablets. The current application provides data from these studies.

- A double-blind, placebo-controlled study to assess the safety and efficacy of anastrozole versus placebo for the treatment of gynecomastia in pubertal boys (Study 1033US/0006; referred to hereafter as Study 0006 [FDA Written Request reference "*Study 1*"]), which was conducted in 24 centers in the USA and included 80 treated patients

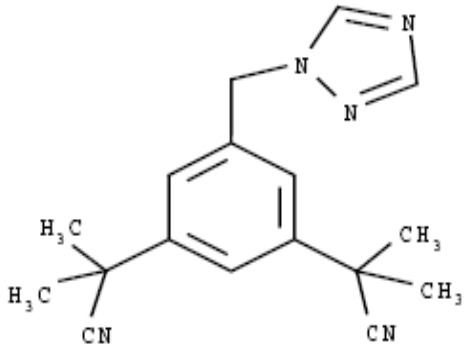
- An open-label pharmacokinetic (PK) and pharmacodynamic (PD) study of anastrozole used to treat pubertal boys with gynecomastia of recent onset (Study D5394C00001; referred to hereafter as Study 0001 [FDA Written Request reference "*Study 3*"]), which enrolled patients from 2 centers in the USA and included 38 treated patients

- An open-label study evaluating the safety and efficacy of anastrozole in the treatment of precocious puberty in girls with McCune-Albright Syndrome (MAS) (Study 1033IL/0046 [D5394C00046]; referred to hereafter as Study 0046 [FDA Written Request reference "*Study 2*" and "*Study 4*"]), which was conducted in 14 centers in 7 countries worldwide and included 28 treated patients

- A population PK study (D5394000000) (FDA Written Request reference "*Study 4*") in girls enrolled in Study 0046 (hereafter referred to specifically as the "Study 0046 [Population PK report]", as distinct from "Study 0046" that is used to denote the Clinical Study Report [CSR]).

The human pharmacokinetics and bioavailability (HPB) section of the Arimidex NDA 20-541, submitted to the Agency contained the full array of HPB studies. This application contains 2 studies (Study 0001 & Study 0046) that were conducted to investigate the PK of anastrozole in pediatric patients.

What is the chemical structure of Arimidex?



What is the mechanism of action and therapeutic indication?

Anastrozole is a potent and selective nonsteroidal aromatase inhibitor. Aromatase inhibitors are a class of compounds that act systemically to inhibit estrogen synthesis in tissues thereby reducing estrogen production. These compounds prevent synthesis by inhibiting the enzyme aromatase, which catalyzes the conversion of the adrenal androgens, androstenedione and testosterone to the estrogens, estrone and estradiol respectively.

No indication is being sought in this application.

What are the proposed dosage and route of administration?

1 mg tablets for oral administered once daily.

2.2 GENERAL CLINICAL PHARMACOLOGY

What is known about the general pharmacology of anastrozole?

Refer to original NDA 20-541 for Arimidex.

What is the primary measurement of efficacy?

Male pediatric populations with gynecomastia: The primary objective was to determine whether anastrozole was more effective than placebo as assessed by changes in breast tissue size and symptoms. The primary efficacy endpoint was a response defined as a ≥ 50% reduction between Day 1 (Visit 1) and after 6 months of study treatment (end of study) in the calculated volume of gynecomastia of both breasts combined as measured by ultrasound. Secondary efficacy endpoint included: actual percent change in breast volume of gynecomastia from Visit 1 to after 6 months, pain response in symptomatic patients, change in hormone levels (sex steroids and gonadotropins) and change in height.

Female pediatric populations with McCune-Albright syndrome: The primary efficacy variables included change in frequency of annualized episodes of vaginal bleeding on treatment compared to baseline; proportion of patients with baseline vaginal bleeding who experienced > 50% reduction in the number of vaginal bleeding episodes on treatment; proportion of patients with baseline vaginal bleeding who experienced cessation of vaginal bleeding episodes over a 6-month period; change in growth velocity as compared to baseline. Secondary variables included change in Tanner stage (measure of pubertal progression), change in mean ovarian and uterine volumes by ultrasound.

What is the pharmacodynamic response to anastrozole?

Study 0001: Changes in concentrations of hormone levels at baseline and month 6 were measured. The hormones included testosterone, estradiol, FSH, LH, and SHBG. After 6 months of treatment with anastrozole, testosterone, FSH, and LH increased while the estradiol and sex hormone binding globulin (SHBG) decreased. The sponsor also measured the testosterone/estradiol ratio which increased. This change reflects the known pharmacological effects of anastrozole.

Table 1: Hormone levels and change from baseline in boys with gynecomastia

	Anastrozole 1 mg (N=25)			
	n	Mean (SD)	95% CI	Range
Testosterone (nmol/L)				
Baseline	25	5.55 (5.14)	3.43, 7.67	0.76 to 16.02
Month 6	25	13.29 (7.40)	10.24, 16.35	1.38 to 24.70
Change from baseline to Month 6	25	7.74 (4.92)	5.71, 9.77	-0.45 to 17.27
Percent change, baseline to Month 6	25	285.90 (251.74)	181.99, 389.82	-4.00 to 847.40
Estradiol (sensitive assay) (pmol/L)				
Baseline	24	16.81 (15.39)	10.31, 23.31	9.18 to 72.30
Month 6	24	11.17 (4.25)	9.37, 12.96	9.18 to 23.86
Change from baseline to Month 6	23	-5.89 (14.30)	-12.07, 0.30	-63.12 to 5.87
Percent change, baseline to Month 6	23	-13.17 (29.47)	-25.91, -0.43	-87.30 to 48.50
Testosterone/estradiol ratio				
Baseline	24	377.79 (323.82)	241.05, 514.53	50.20 to 1266.90
Month 6	24	1227.84 (720.94)	923.41, 1532.27	150.30 to 2690.60
Change from baseline to Month 6	23	932.43 (599.59)	673.15, 1191.71	-329.20 to 1881.20
Percent change, baseline to Month 6	23	465.69 (644.50)	186.99, 744.39	-35.30 to 3241.80
FSH (IU/L)				
Baseline	25	1.98 (1.09)	1.53, 2.43	0.60 to 4.50
Month 6	25	3.85 (2.04)	3.01, 4.69	1.40 to 10.50
Change from baseline to Month 6	25	1.87 (1.65)	1.19, 2.55	-0.40 to 7.10
Percent change, baseline to Month 6	25	125.80 (114.24)	78.65, 172.96	-12.50 to 400.00
LH (IU/L)				
Baseline	25	1.55 (1.42)	0.96, 2.14	0.10 to 4.50
Month 6	25	3.56 (2.06)	2.71, 4.41	0.70 to 7.80
Change from baseline to Month 6	25	2.01 (1.61)	1.34, 2.67	-0.90 to 5.70
Percent change, baseline to Month 6	25	536.63 (890.40)	169.09, 904.17	-28.10 to 4000.00
SHBG (nmol/L)				
Baseline	25	21.64 (7.31)	18.62, 24.66	5.00 to 34.00
Month 6	25	18.08 (7.29)	15.07, 21.09	7.00 to 34.00
Change from baseline to Month 6	25	-3.56 (6.67)	-6.31, -0.81	-15.00 to 18.00
Percent change, baseline to Month 6	25	-11.87 (34.65)	-26.18, 2.43	-60.00 to 112.50

CI Confidence interval; FSH Follicle-stimulating hormone; LH Luteinizing hormone; SD Standard deviation; SHBG Sex-hormone binding globulin.

Are the active moieties in the plasma appropriately identified and measured?

Yes.

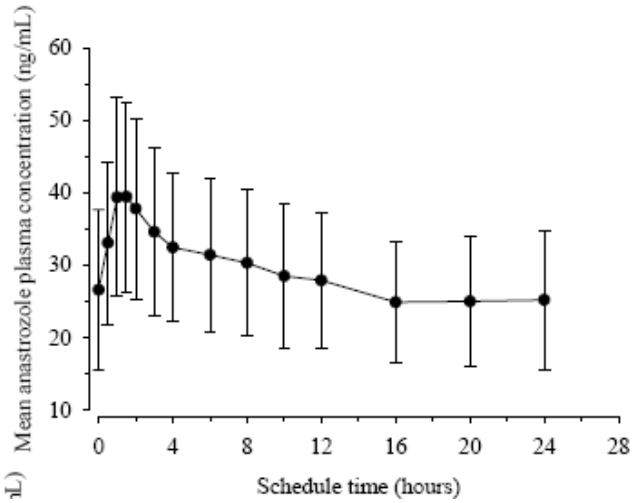
2.3 INTRINSIC FACTORS

What are the pharmacokinetics characteristics of anastrozole in pediatric patients?

Study 0001: The PK study was a multicenter, single arm open label study in boys with pubertal gynecomastia of recent onset in which anastrozole 1 mg was administered daily for 6 months. The primary and secondary endpoints were evaluated after the last patient completed 6 months of treatment. PK samples were collected on Visit 3 [Visit 3 occurred at least 14 days after Visit 2 (first dose). Patients had to have 7 consecutive days of study drug immediately prior to their PK assessments. The dose of study drug at Visit 3 was taken under fasting conditions and the patients had to fast 2 h post Visit 3 dose.] Blood samples were collected as follows: 30 min pre-dose, 0.5 h, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 h post dose.

Anastrozole following multiple oral administrations was rapidly absorbed (median Tmax 1 hr). Concentrations then rapidly decreased over 1.5 - 4 hour followed by a gradual decline through the sampling period (Figure 1). The elimination half-life was approximately 2 days. PK sampling was done only through 24 hours. However, based on the similarity of mean $C_{ss,min}$ in boys (21.5 ng/mL; 6.05-47.2 ng/mL) and postmenopausal women (25.7 ng/mL; Clin Pharm Review of NDA 20-541/S-006) observed after multiple doses of 1 mg anastrozole, this estimation of half-life seems to be reasonable. The clearance appeared to be slow (1.54 L/h) and the drug was widely distributed (Table 2). (Note: Measurable plasma concentrations were observed at pre-dose time point for all patients. Individual concentration-time profiles among patients were similar).

Figure 1: Anastrozole mean plasma concentration versus time after multiple oral administration of anastrozole 1 mg once daily



PK parameters were derived using WinNonlin (non-compartmental methods). Summary statistics for steady state PK parameter estimates (Visit 3) for anastrozole following multiple oral administration of anastrozole 1 mg is shown below. The estimated PK parameters showed an inter-individual variability of 34% - 44%.

Table 2: Summary statistics of anastrozole PK parameters

Parameter	Statistic					
	N	Geometric mean	CV%	Median	Minimum	Maximum
$C_{ss,max}$ (ng/ml)	36	39.3	34.3	41.4	17.2	75.6
t_{max} (hr)	36	-	-	1.00	0.50	3.00
$C_{ss,min}$ (ng/ml)	36	21.5	44.1	22.1	6.05	47.2
$AUC_{ss\ (0\text{-}tau)}$ (ng.hr/ml)	36	648	37.0	682	221	1300
CL/F (L/hr)	36	1.54	37.0	1.47	0.771	4.53
V_z/F (L)	36	98.4	42.6	100	50.7	330

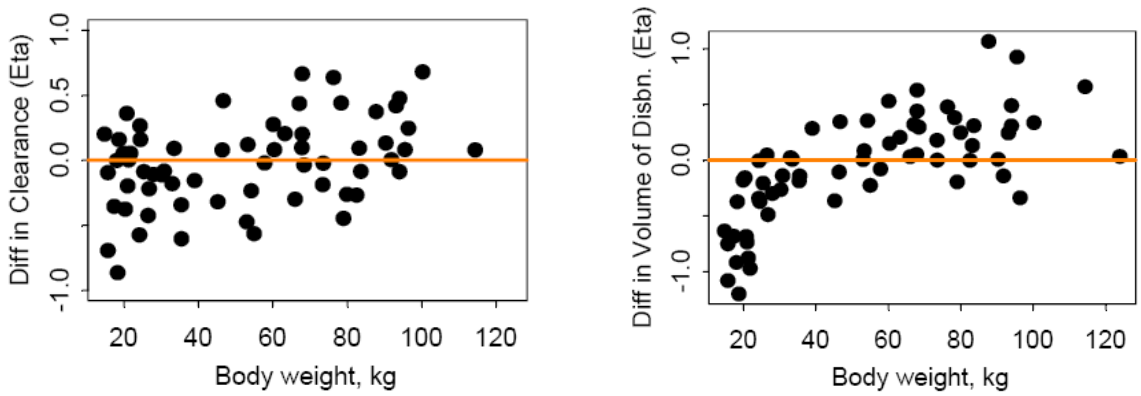
Comments: The PK parameters obtained by the sponsor using non-compartmental analysis seems appropriate. The sponsor also analyzed the effect of age and body weight using ANOVA. The effect of these covariates is better addressed using the population analysis (see below).

Population PK analysis:

The population PK analysis was conducted using the data collected in two open-label, exploratory Phase 2 studies, a safety and efficacy study of anastrozole in 28 girls with precocious puberty with MAS aged ≤10 yr (Study 1033IL/0046) and a pharmacokinetic and pharmacodynamic study in 36 pubertal boys aged ≥11 to ≤18 yr with gynecomastia (Study D5394C00001). Each girl in study 0046 received anastrozole 1 mg once daily (od) for up to 12 months. Two blood samples were collected during Month 1 (Visit 2); the first sample was collected between 0 and 2 h after the first anastrozole dose, the second sample was collected between 3 and 24 h after the first anastrozole dose. Two additional blood samples were collected randomly at anytime after 3 months (Visits 3 or 4) on anastrozole therapy. Boys in Study 0001 received oral anastrozole 1 mg od for 14 consecutive days; blood samples were collected on day 14 at predose (0 h) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 h after dosing. The analysis was conducted to characterize PK of anastrozole and to evaluate the impact of covariates such as age, body weight (WT), and others on anastrozole PK was also evaluated.

Based on the results of the population PK analysis, the anastrozole apparent clearance and volume of distribution were found to be 1.4 L/hr and 51.4 L, respectively. Only body weight was found to be a significant predictor of the apparent oral clearance and volume of distribution of anastrozole, as shown in Figure 2.

Figure 2: Body weight is a significant predictor of anastrozole apparent clearance and volume of distribution (Note: From Base Model)



Upon accounting for the effect of body weight, 4% intersubject variability in clearance, 27% intersubject variability in volume of distribution could be described in the data.

Are there any gender based differences in the PK of anastrozole in pediatric patients?

In sponsor's population PK analysis, it was concluded that clearance in girls was different from boys. Hence, the effect of gender on the PK of anastrozole was explored. The reviewer noted that the body weight in boys (Study D5394C00001) and girls (Study 1033IL/0046) were significantly different as shown in Figure 3. Therefore, what appears as a gender effect could be an artifact of the inherent differences in body weights between boys and girls. Upon accounting for the effect of body weight on the oral clearance and volume of distribution, the effect of gender disappears, as shown in Figure 4.

Figure 3: Body weight is different between boys (Males) and girls (Females)

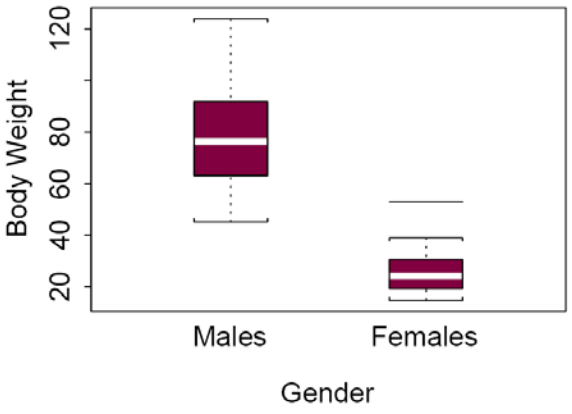
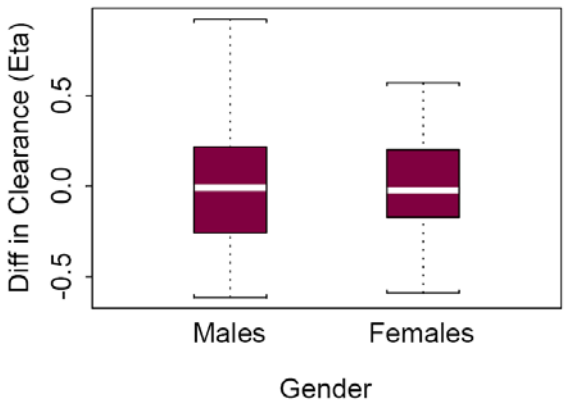


Figure 4: Body weight accounts for the difference in clearance between boys (Males) and girls (Females)



What is the influence of age on PK of anastrozole in pediatric patients?

Age and body weight were correlated in the population evaluated in the current analysis (Figure 5). Upon accounting for the effect of body weight on the oral clearance and volume of distribution, there is no effect of age evident on these PK parameters of anastrozole, as shown in Figure 6.

Figure 5: Age and body weight are correlated

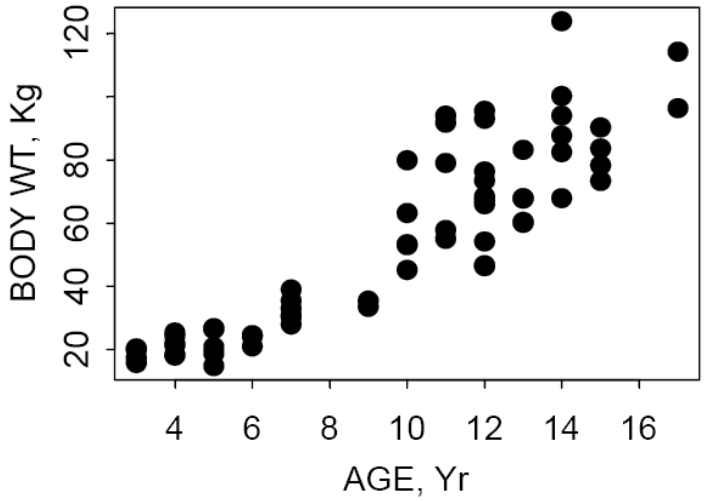
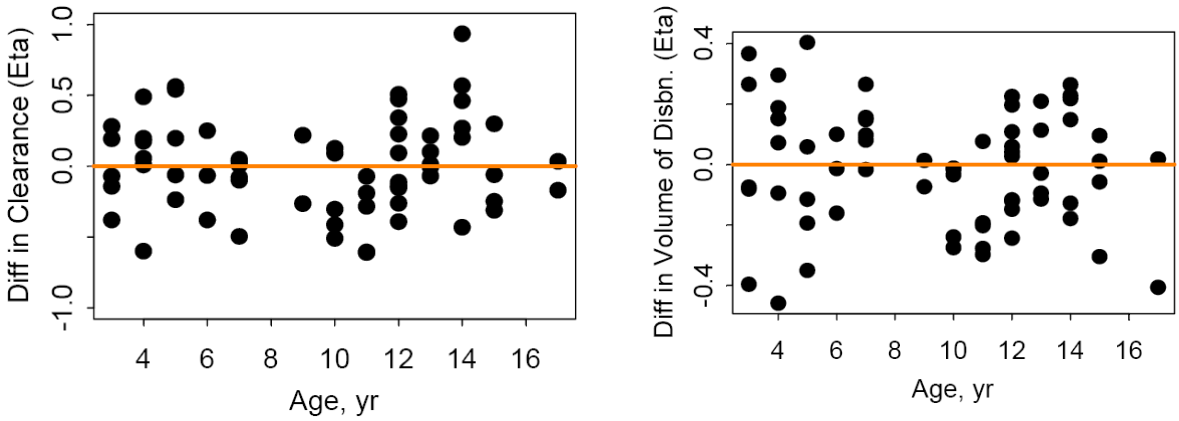


Figure 6. No effect of age on body weight adjusted PK parameters of anastrozole.



How do the PK characteristics of anastrozole in boys with pubertal gynecomastia and girls with MAS compare to those in postmenopausal women?

The PK of anastrozole in pediatric patients (Table 2) was similar to that seen in adults.

Package insert of anastrozole states that in adults **t**he PK of anastrozole is linear over the dose range of 1 to 20 mg. Mean plasma terminal elimination half-life was approximately 50 h approaching the steady-state at about 7 days of once daily dosing. No age related

effects on PK were seen over 50-80 years range. In postmenopausal women/healthy subjects Cmax occurred within 2 h post-dose.

2.4 EXTRINSIC FACTORS

Not applicable.

2.5 GENERAL BIOPHARMACEUTICS

Not applicable.

2.6 ANALYTICAL SECTION

Study 0001: Samples were analyzed using a validated HPLC with tandem MS method. The LOQ for anastrozole is 0.1 ng/mL. There was no evidence of any interference from other compounds with the quantification of anastrozole or the internal standard as seen from the chromatograms.

Accuracy (%bias) and precision (%CV) of spiked plasma calibration standards for anastrozole (ng/mL):

	0.100 ng/mL	0.250 ng/mL	1.00 ng/mL	2.50 ng/mL	10.0 ng/mL	25.0 ng/mL	50.0 ng/mL	60.0 ng/mL
Mean	0.0977	0.263	1.01	2.51	9.58	24.9	50.0	60.1
S.D.	0.00558	0.0135	0.0348	0.0737	0.259	0.972	1.90	1.81
%CV	5.7	5.1	3.4	2.9	2.7	3.9	3.8	3.0
%Bias	-2.3	5.2	1.0	0.4	-4.2	-0.4	0.0	0.2
n	22	23	23	23	23	24	24	24

Accuracy (%bias) and precision (%CV) of quality control samples for anastrozole (ng/mL):

	QC A 0.300 ng/mL	QC B 5.00 ng/mL	QC B 8.00 ng/mL	QC C 48.0 ng/mL	QC D 48.0 ng/mL
Mean	0.301	5.19	7.56	48.3	46.2
S.D.	0.0200	0.170	0.117	2.02	2.55
%CV	6.6	3.3	1.5	4.2	5.5
%Theoretical	100.3	103.8	94.5	100.6	96.3
%Bias	0.3	3.8	-5.5	0.6	-3.8
n	24	14	10	24	6

Study 0046: The bioanalytical portion of this study was conducted in three parts by (b) (4) facility. One of the three parts was during 15 Jan, 2004 – 21 Jan, 2004 which is in the period where the Agency identified significant problems with studies conducted by (b) (4). In Dec 2007, the sponsor contracted (b) (4) to conduct an independent review of the work performed at (b) (4)

to assure the study conducted satisfied the regulatory expectations. The review did not find any issues affecting the acceptability of the data (Refer to the memo in DFS regarding the review of the full audit report).

3. Detailed Labeling Recommendations

(b) (4)

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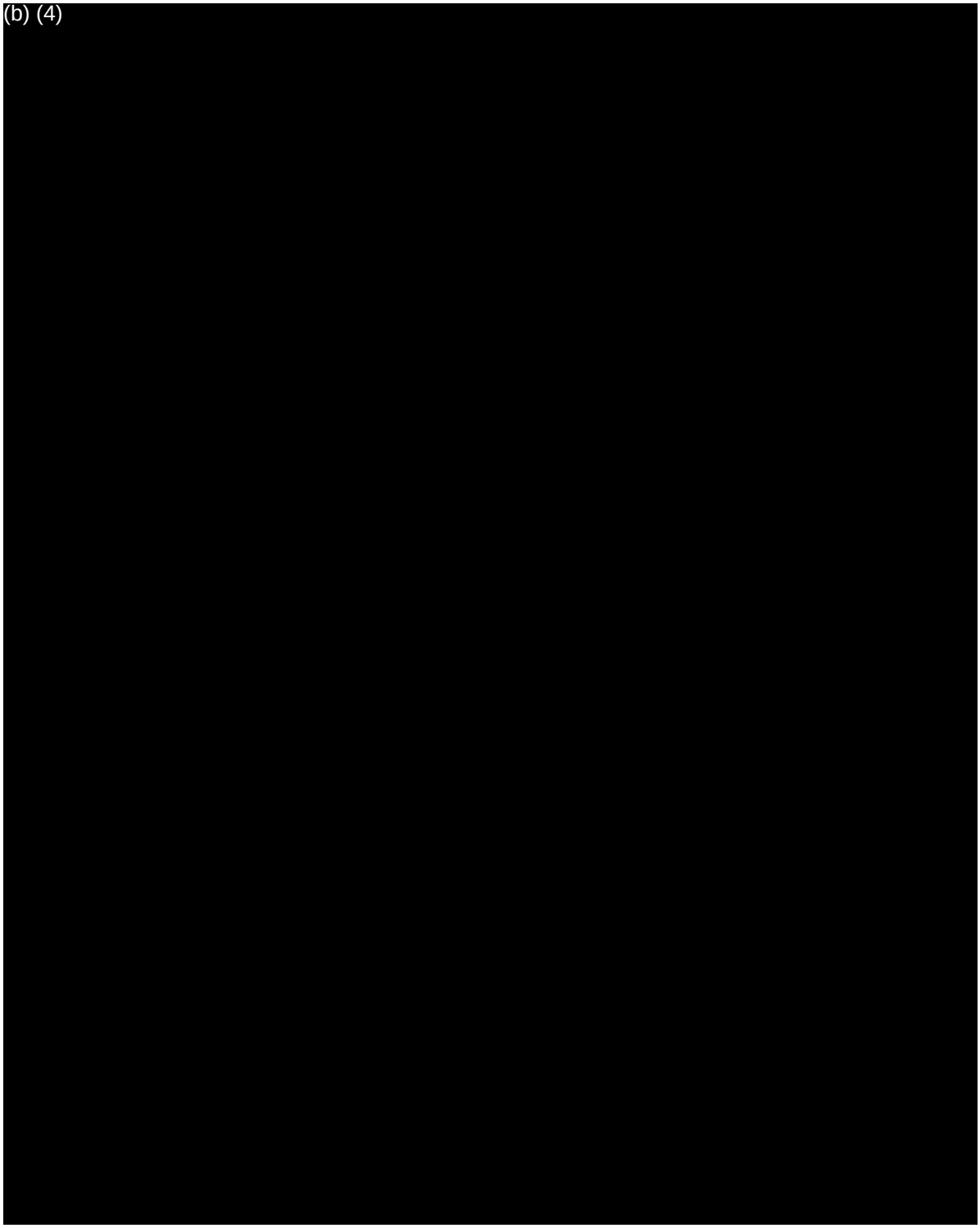
4. Appendix

4.1 PROPOSED LABELING

(b) (4)



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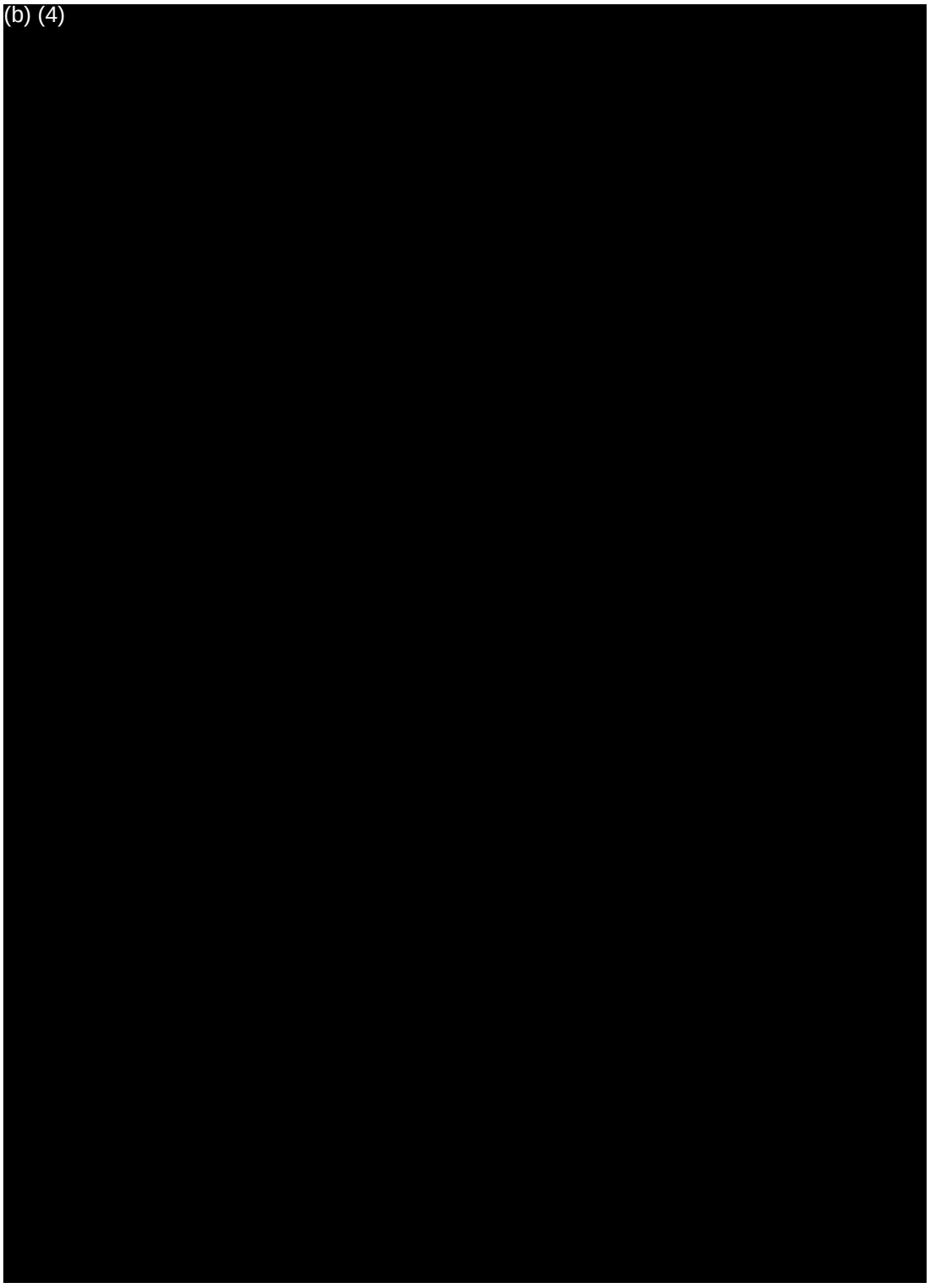

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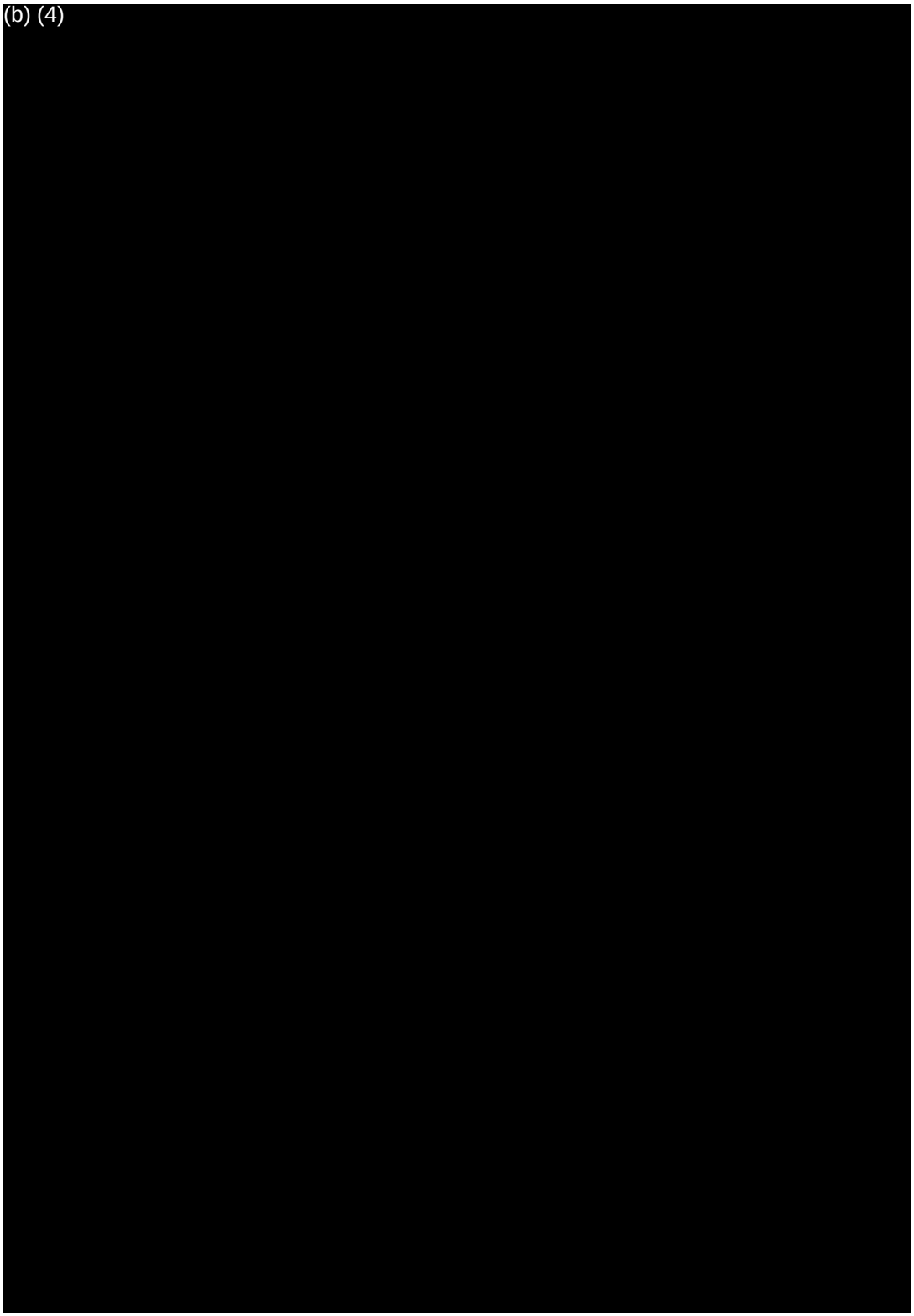

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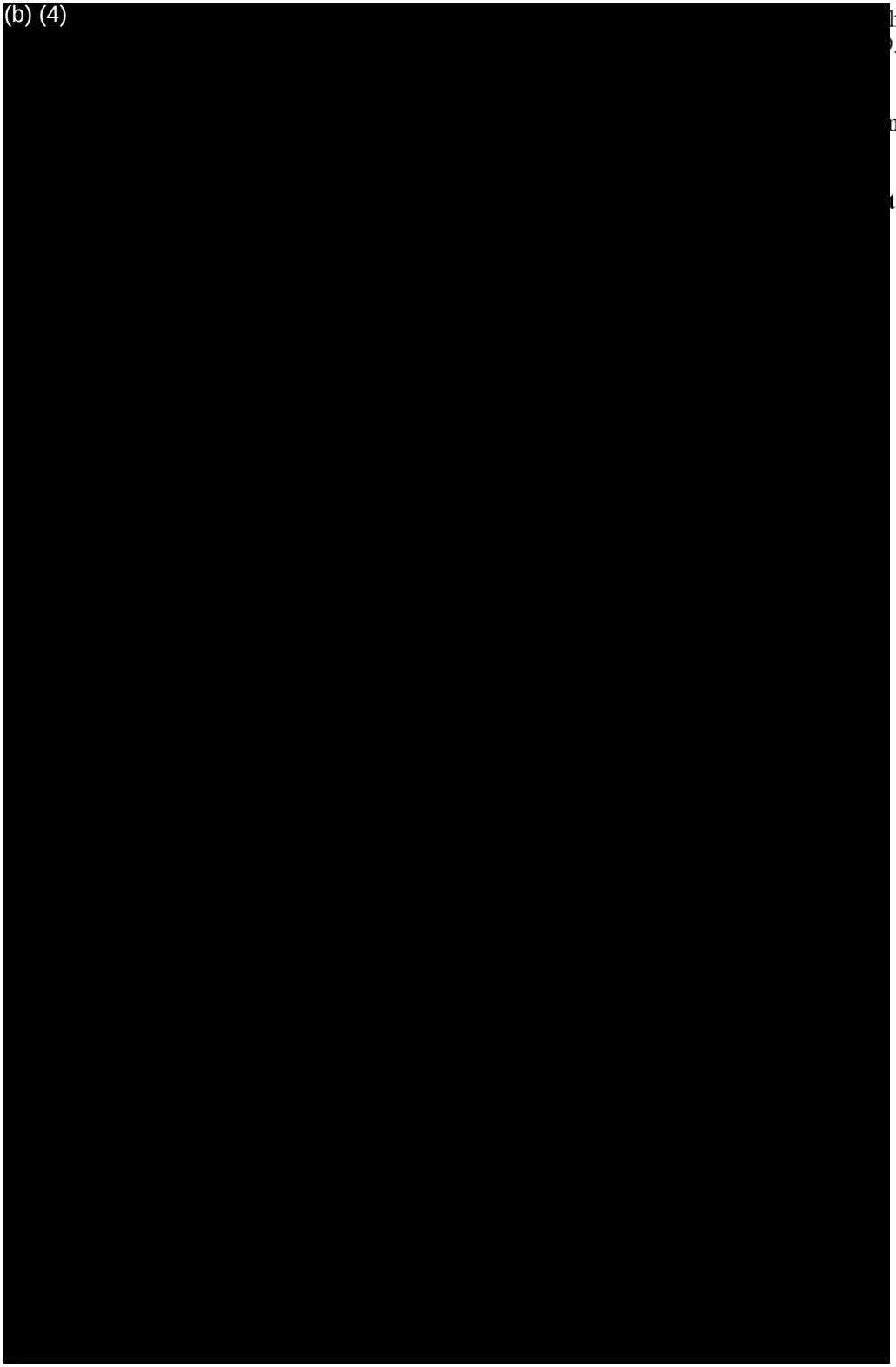

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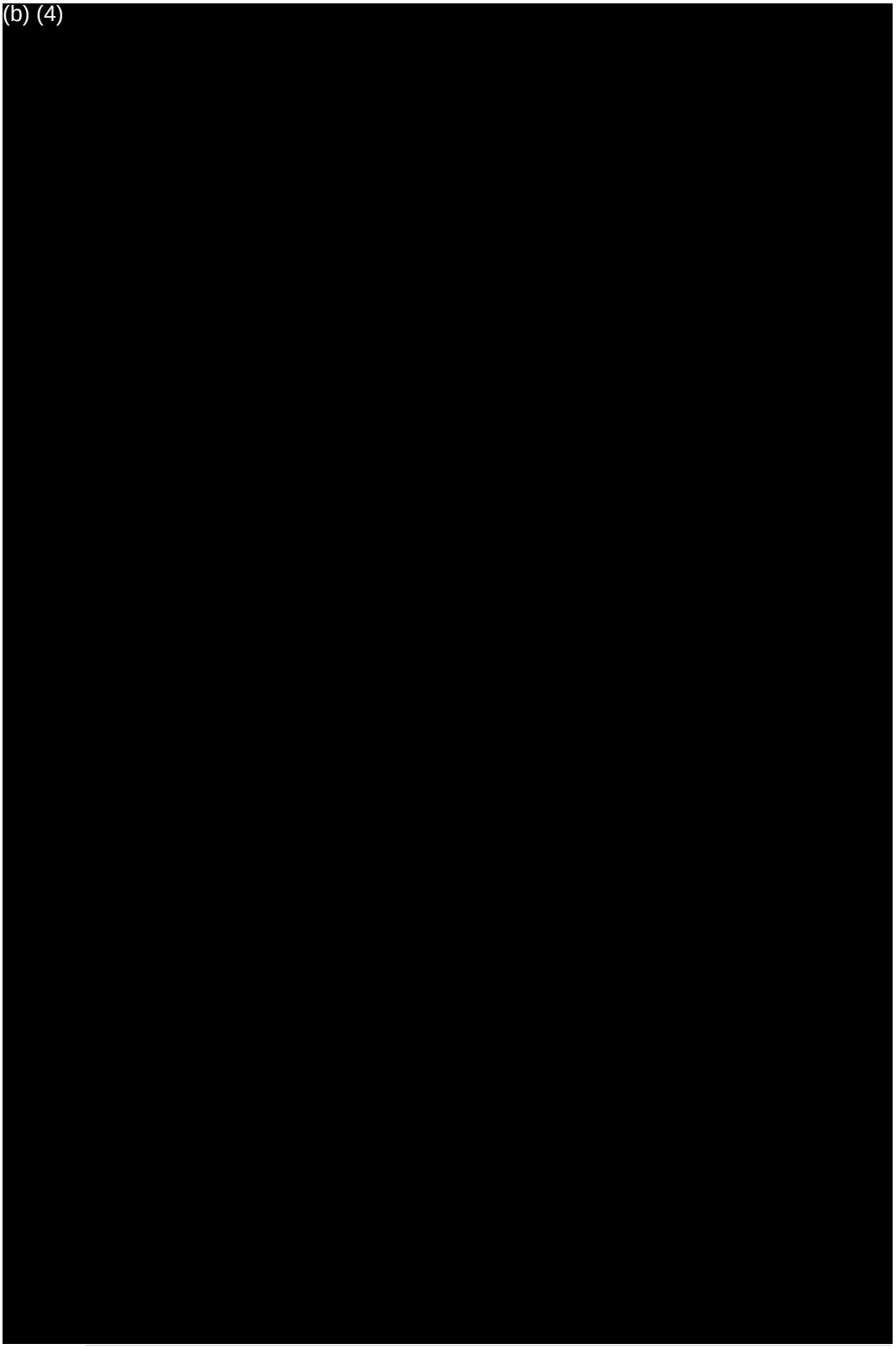

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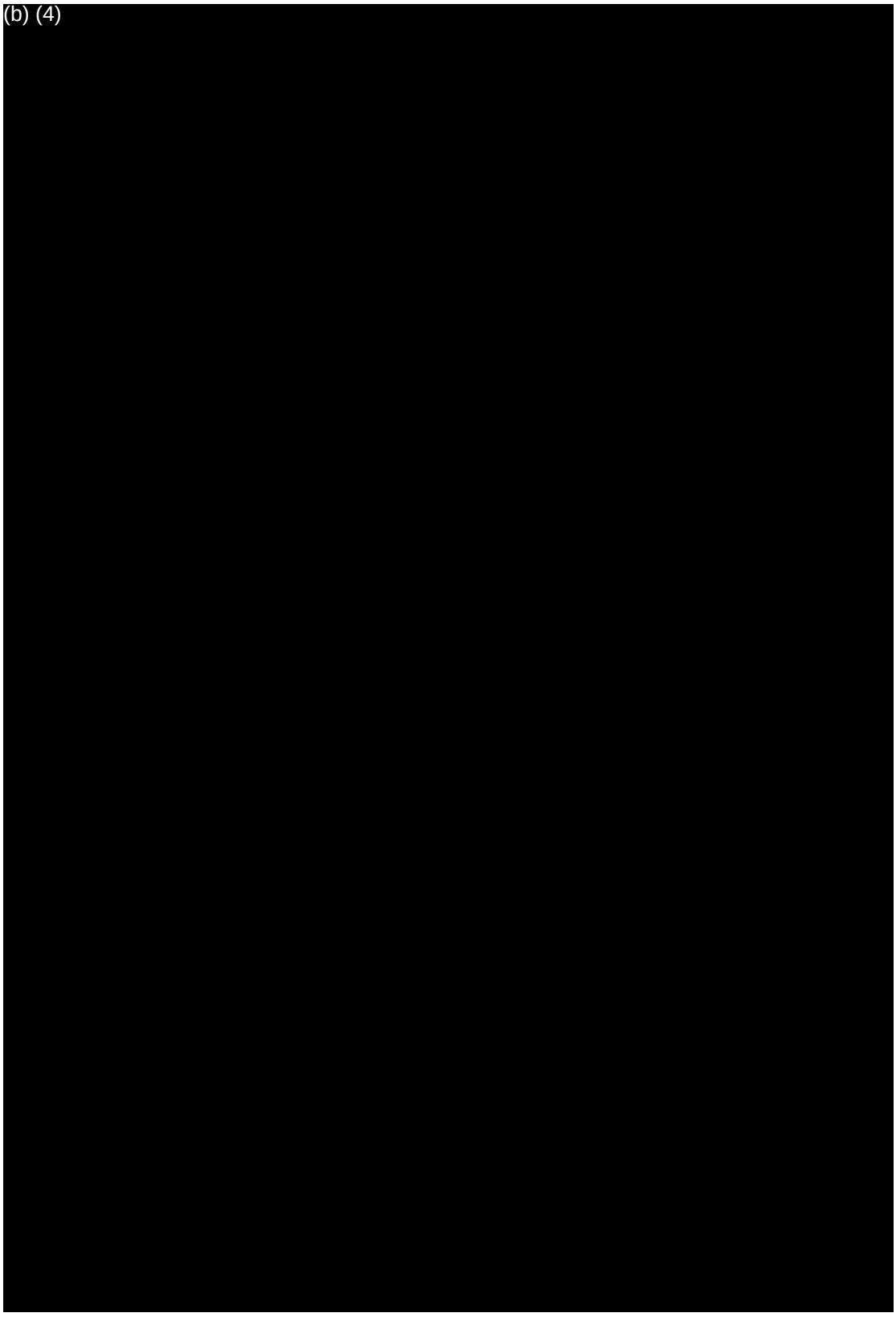

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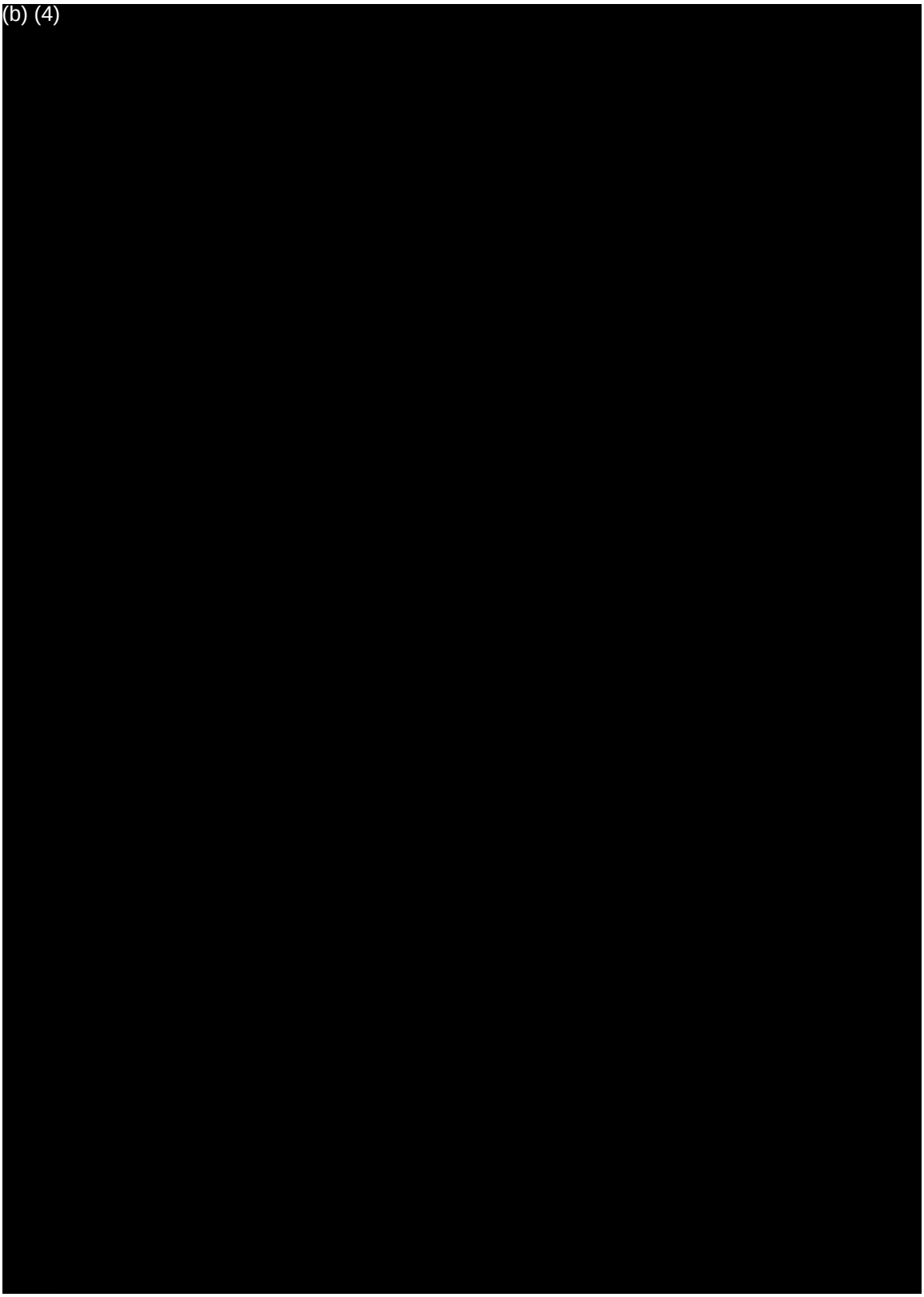

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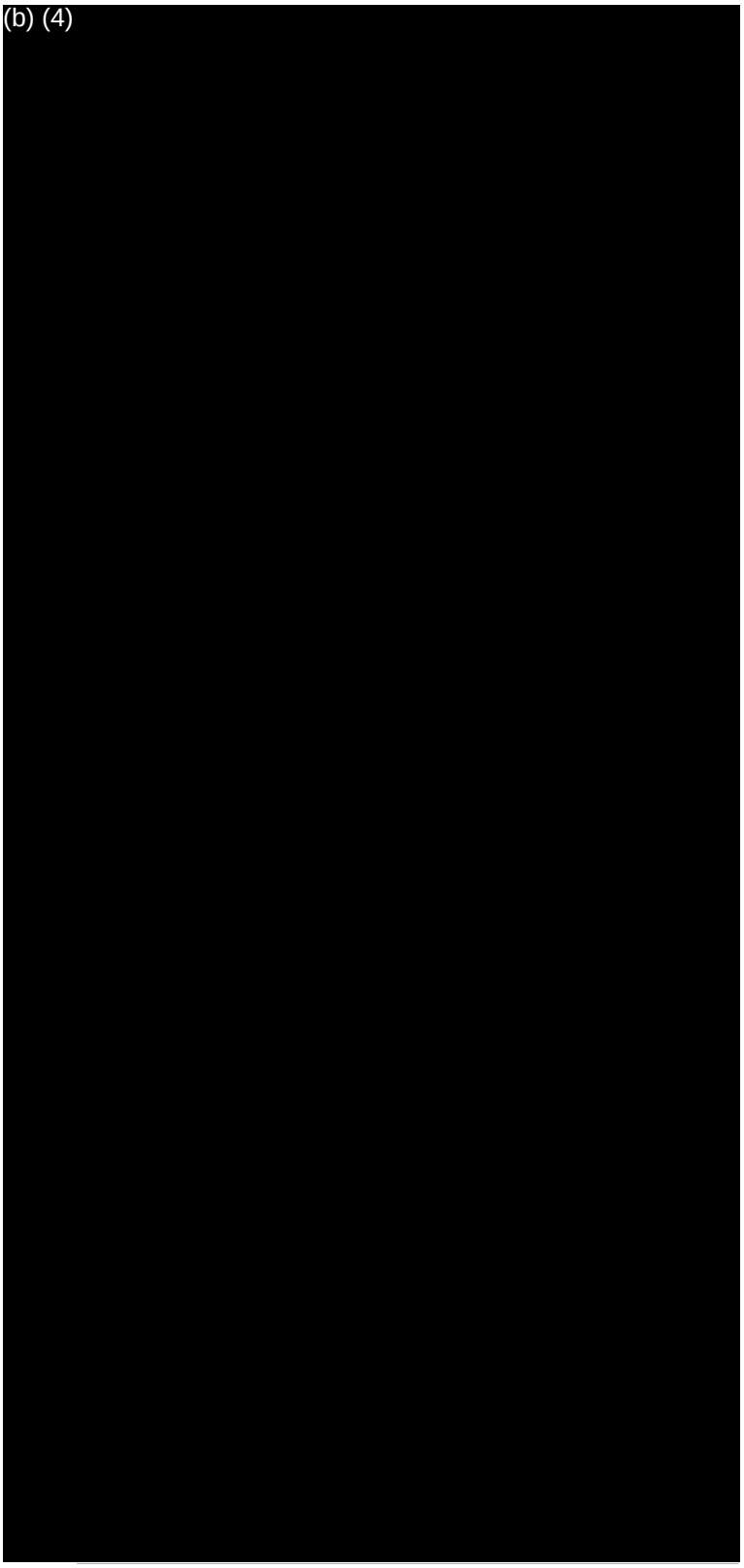

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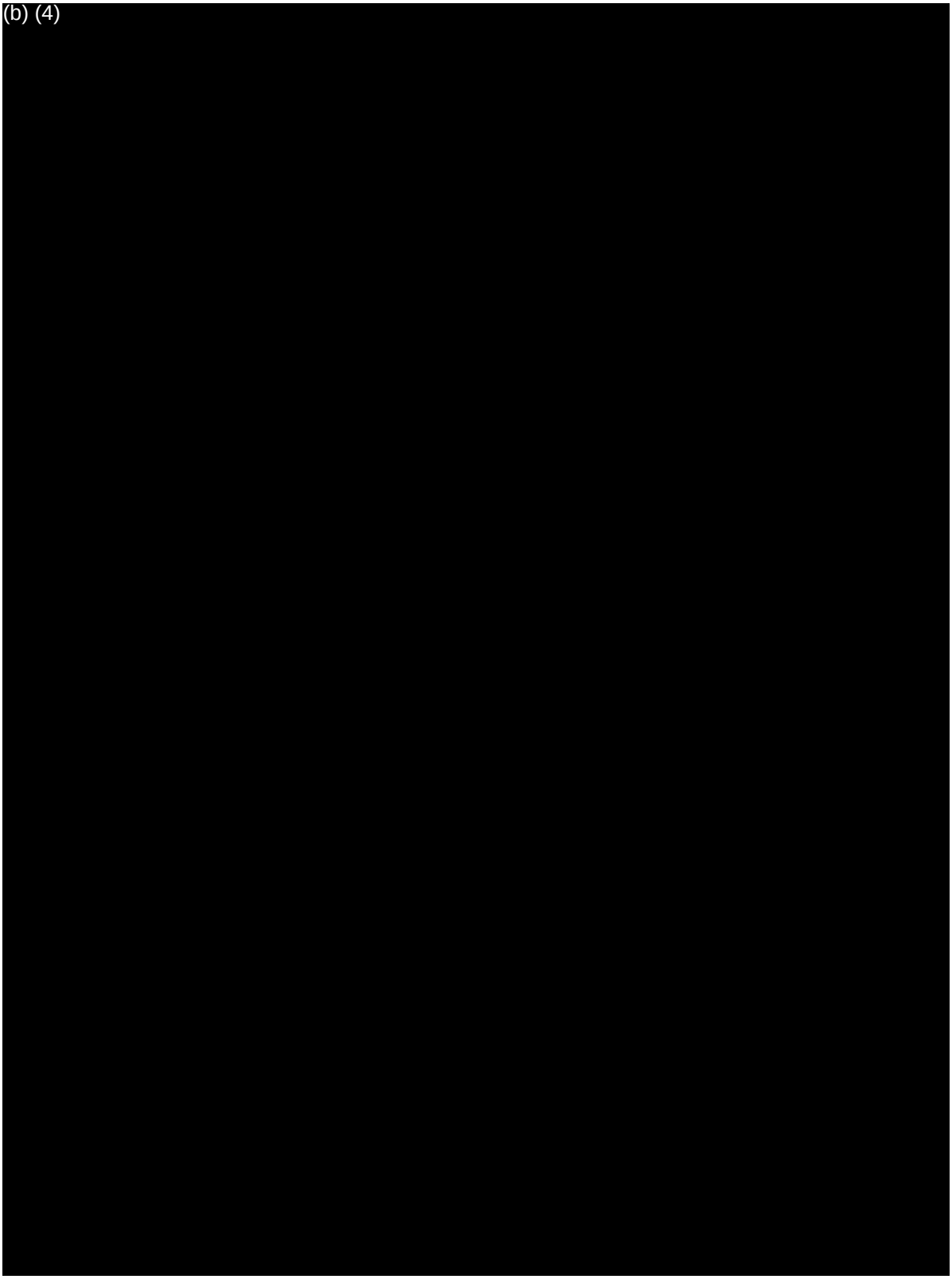

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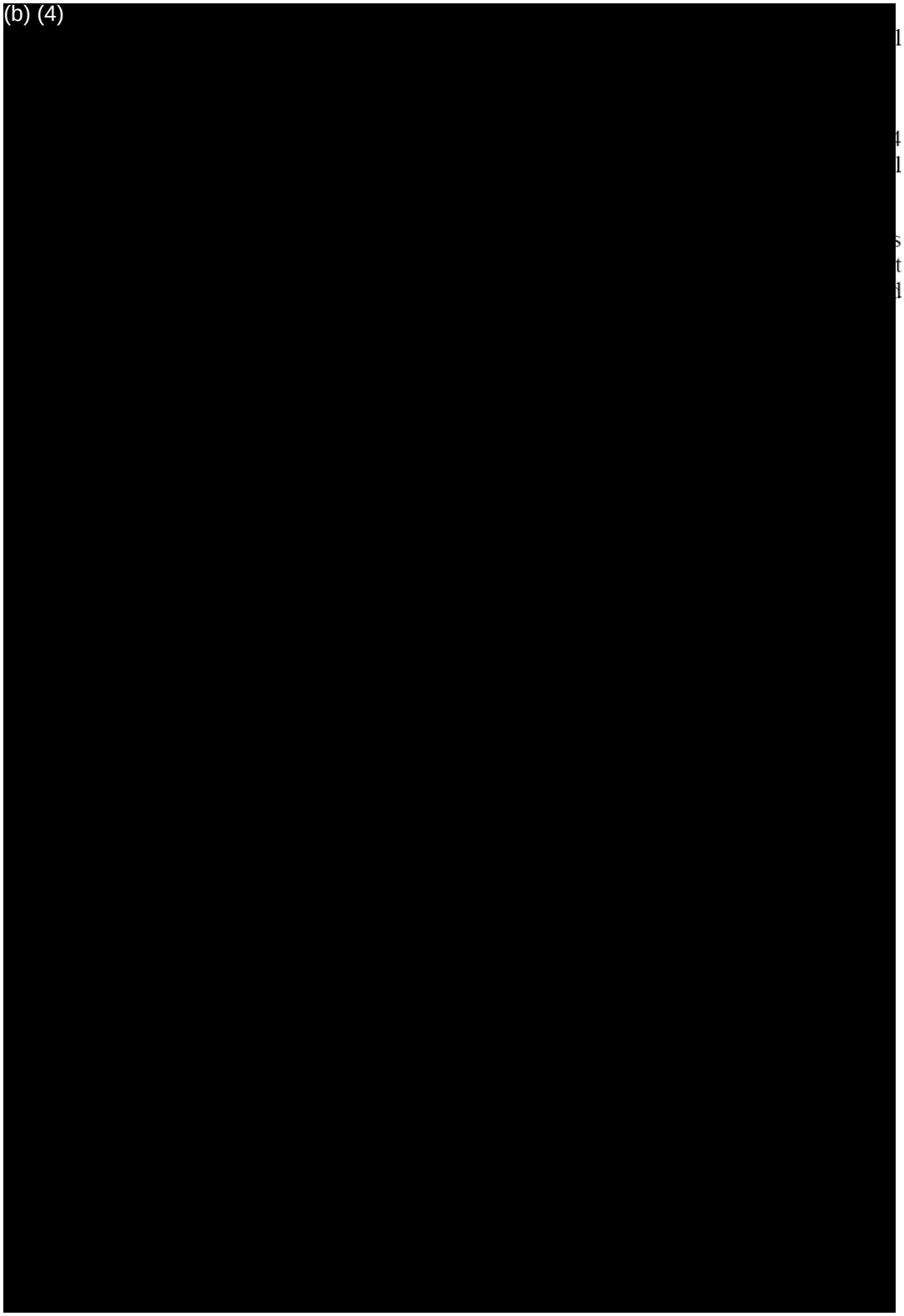

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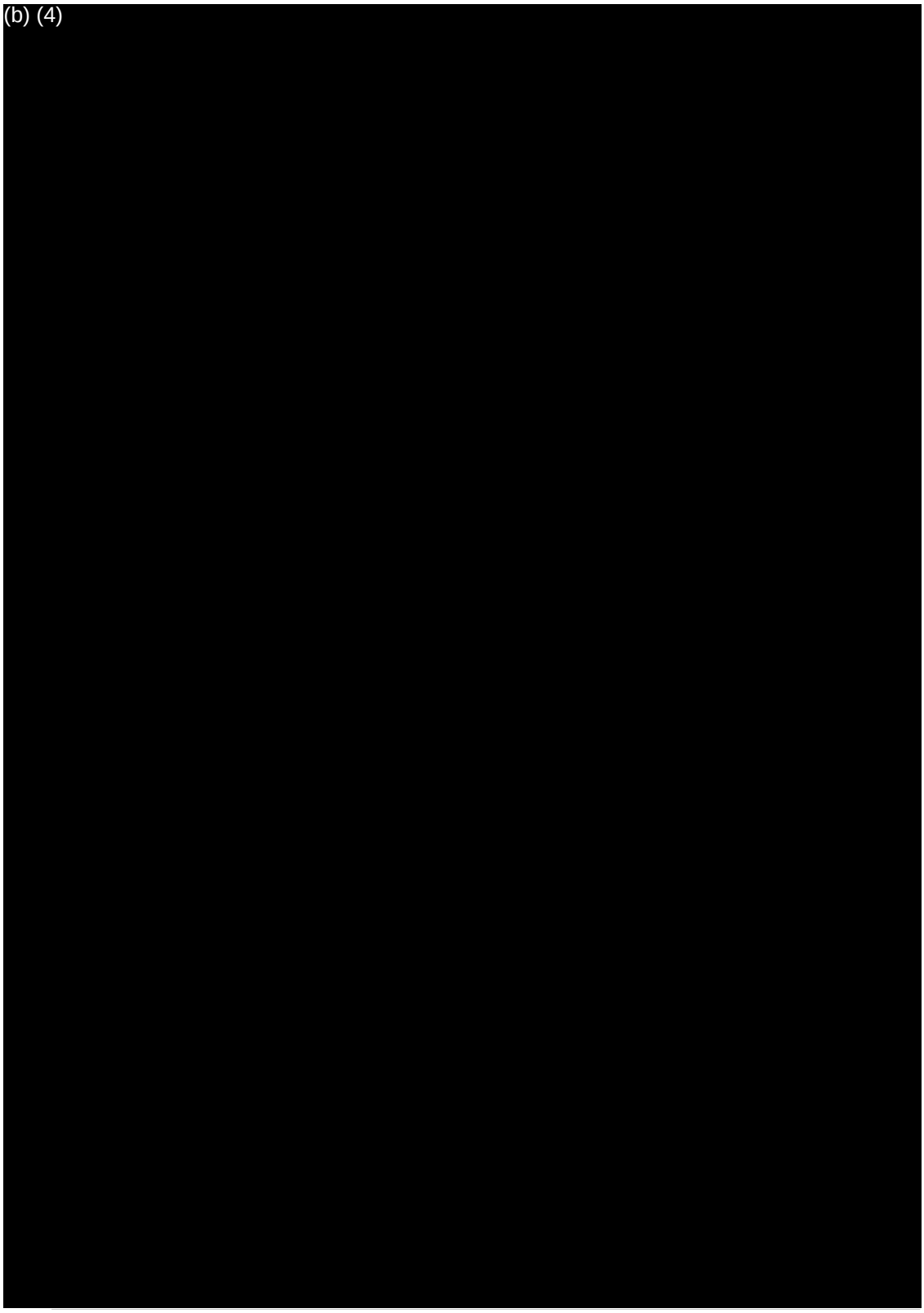

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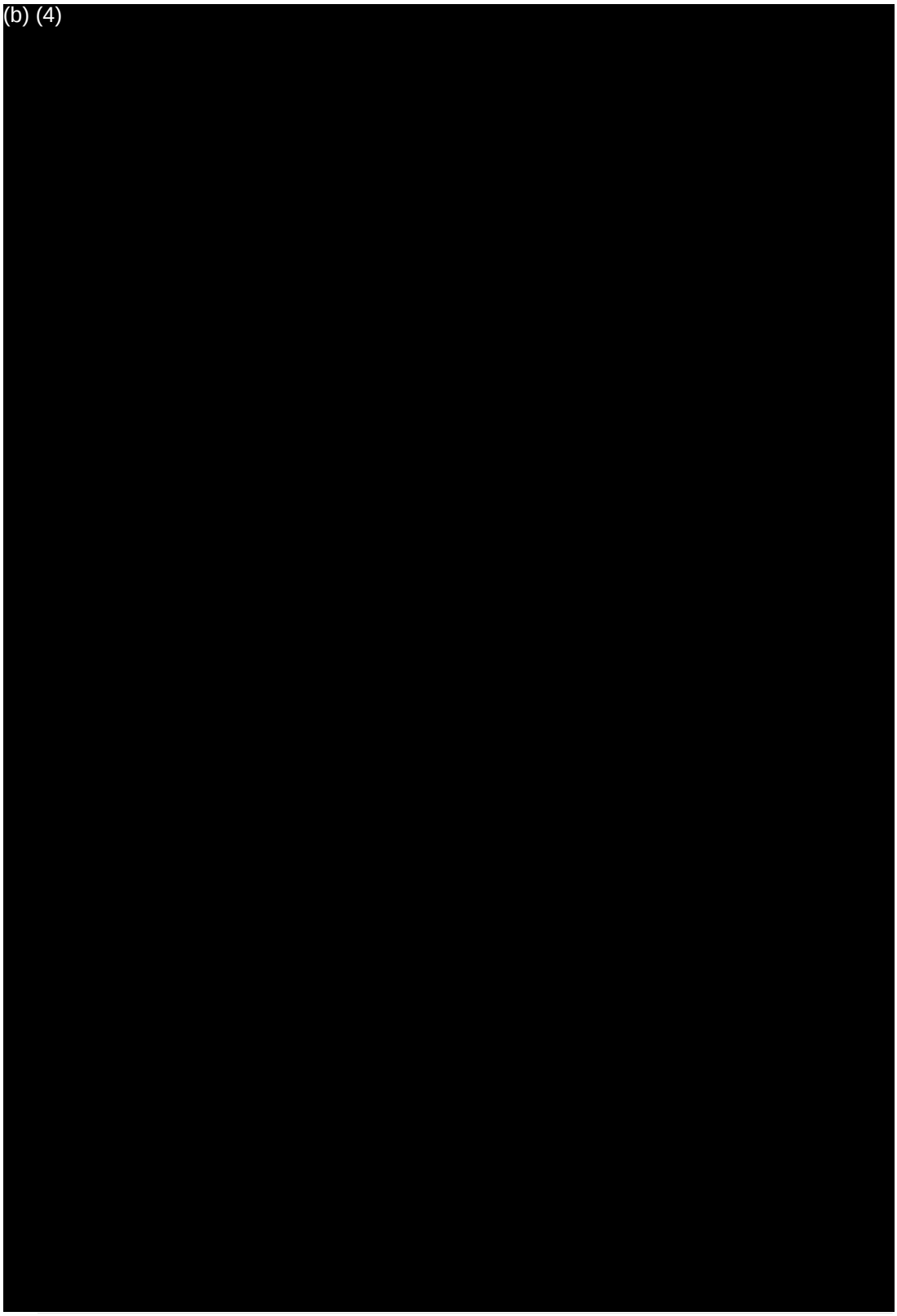

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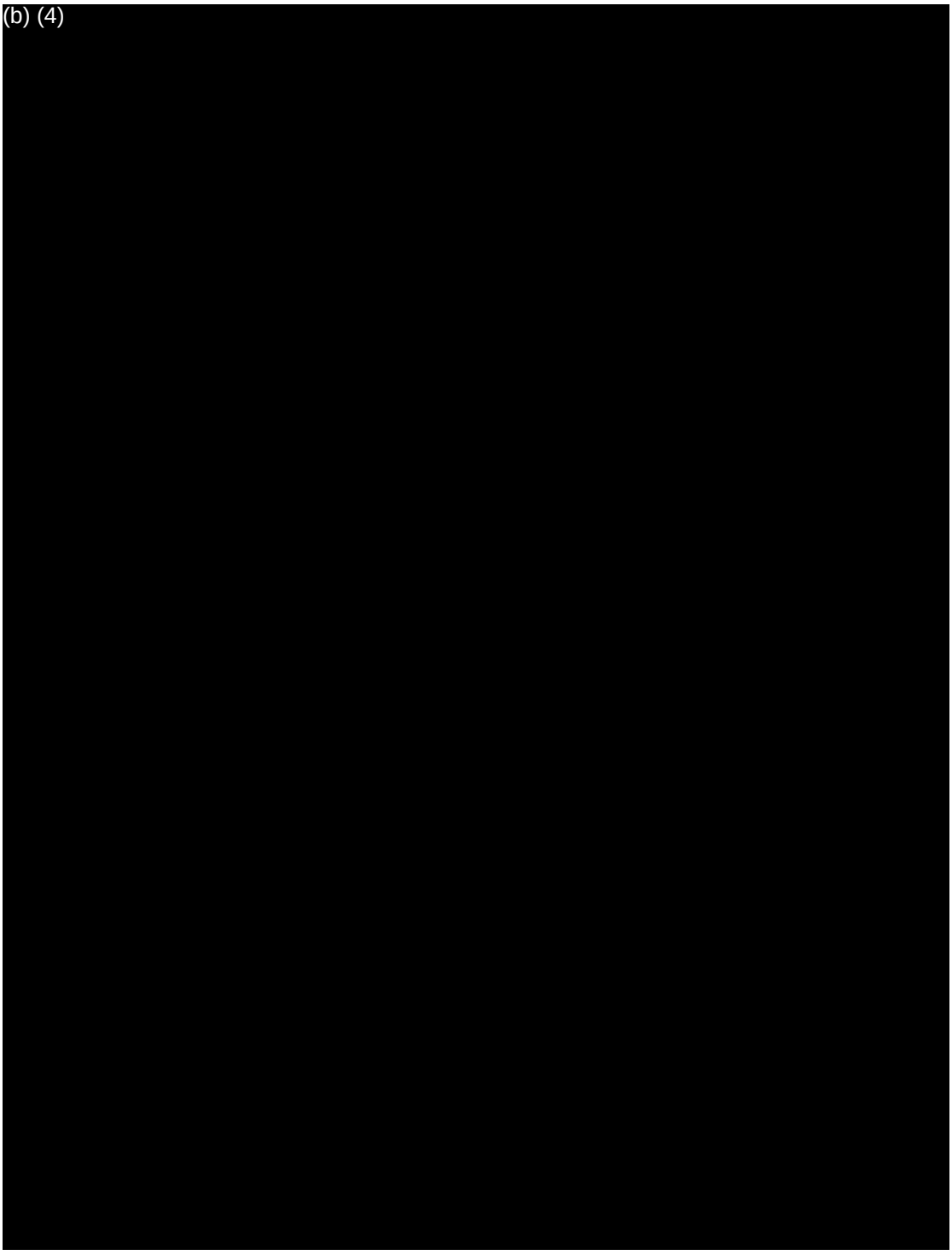

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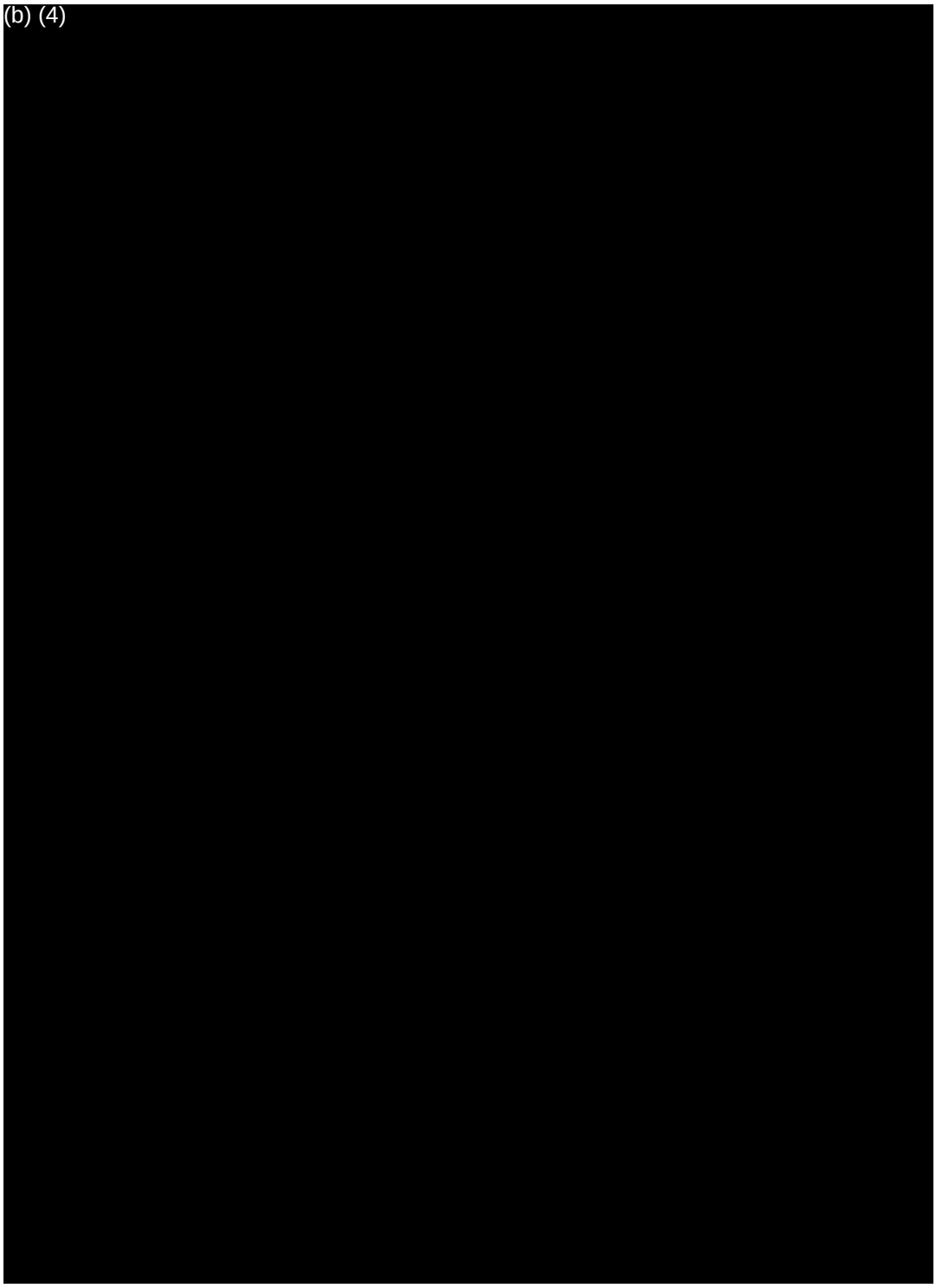

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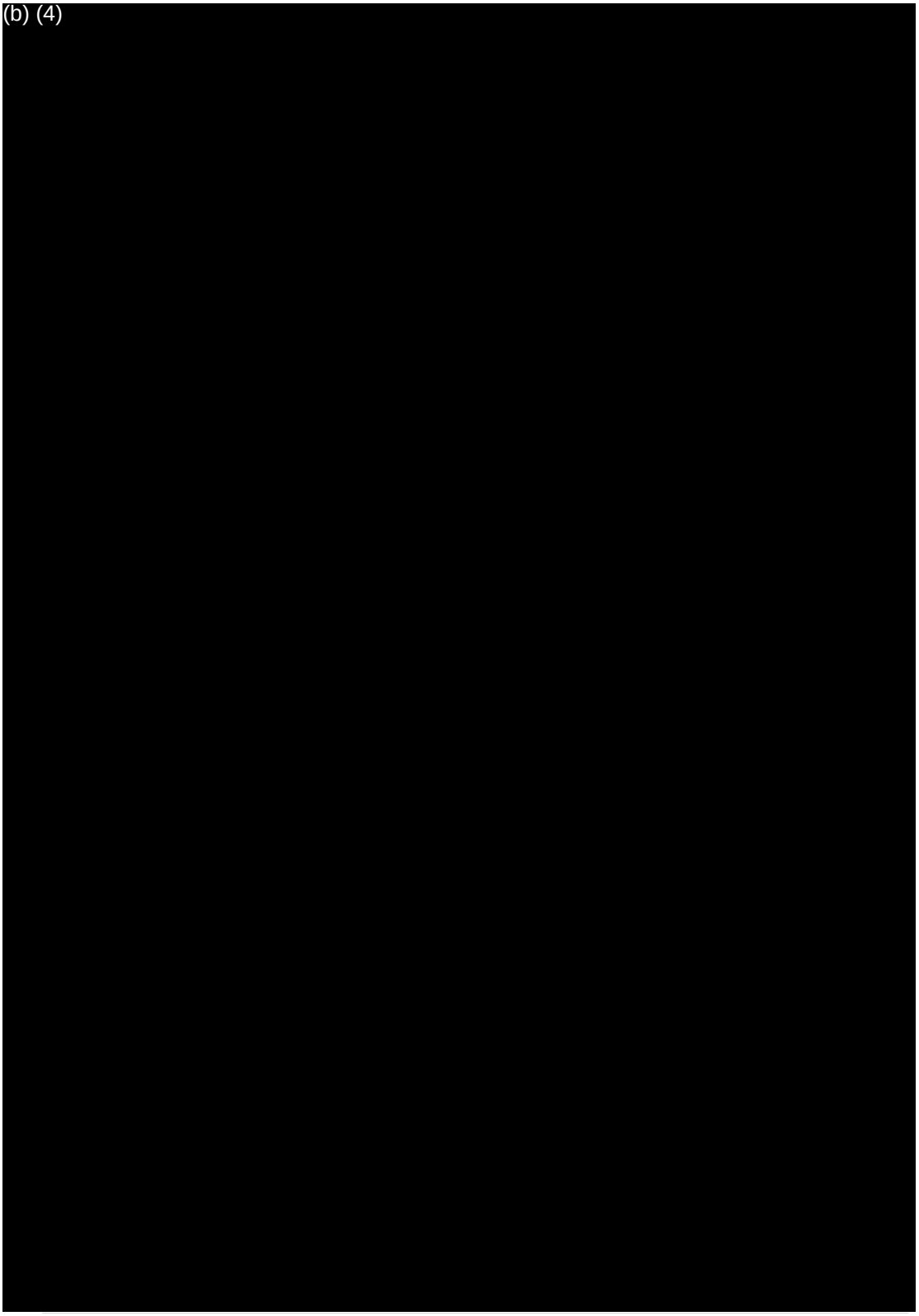

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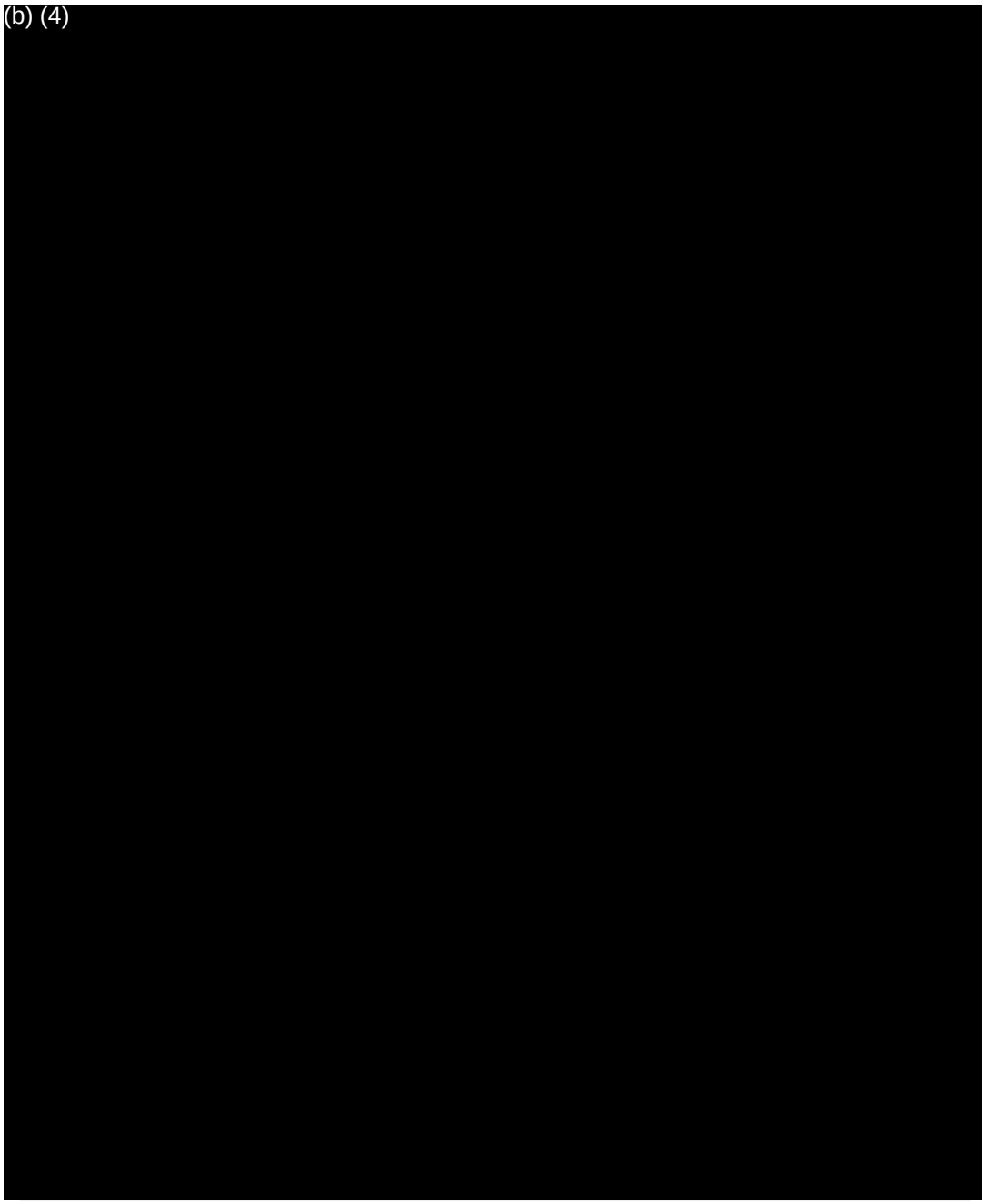

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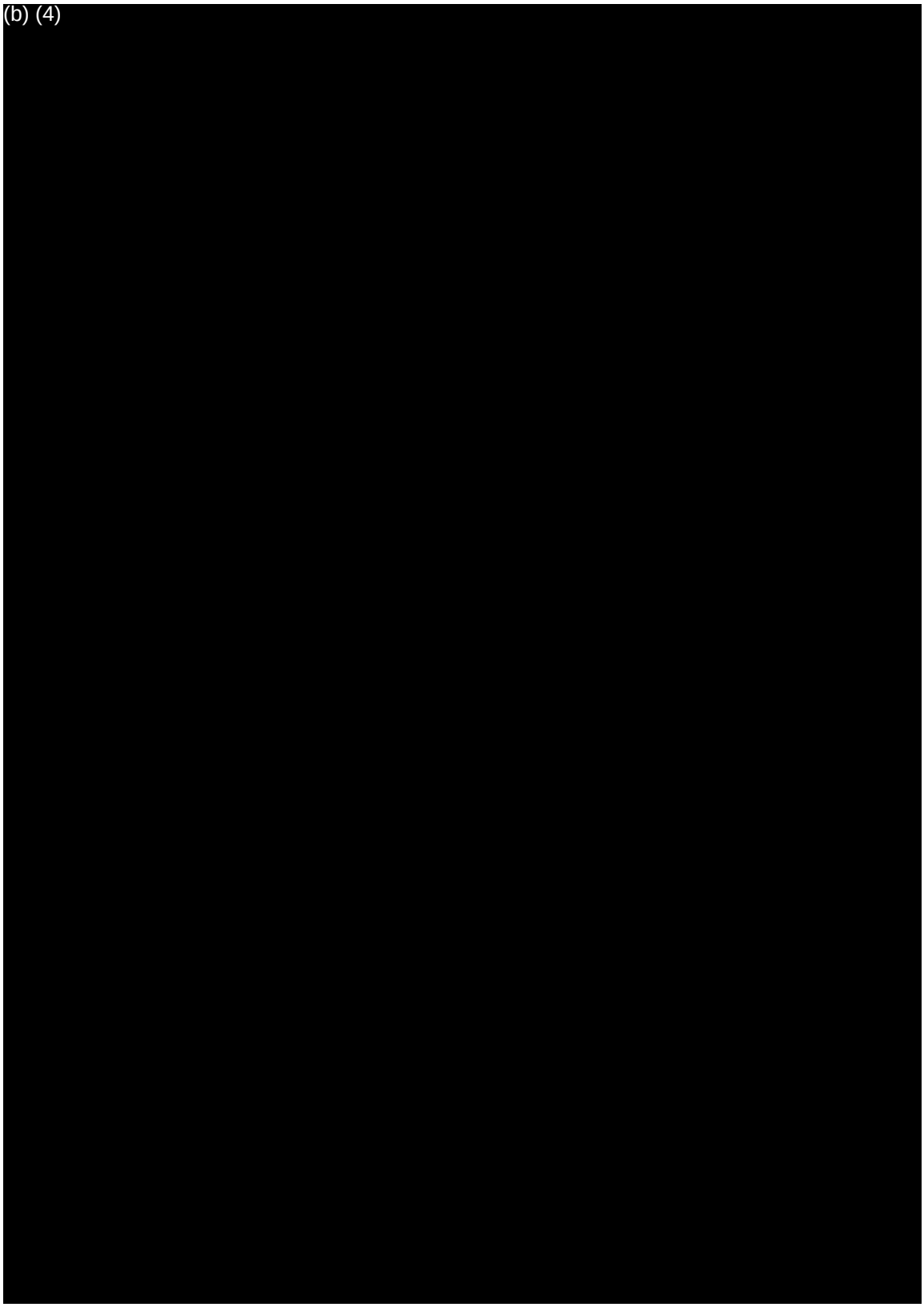

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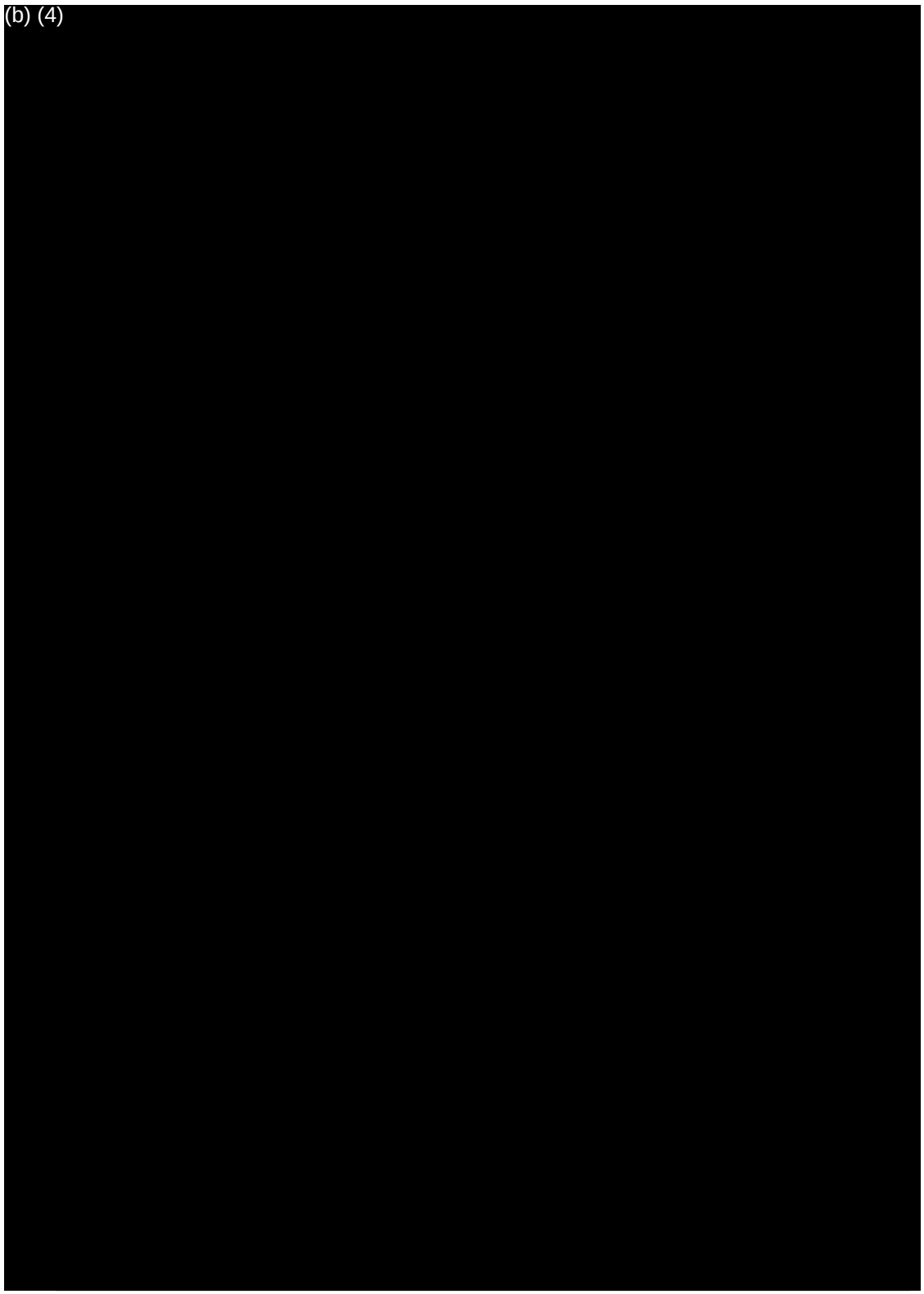

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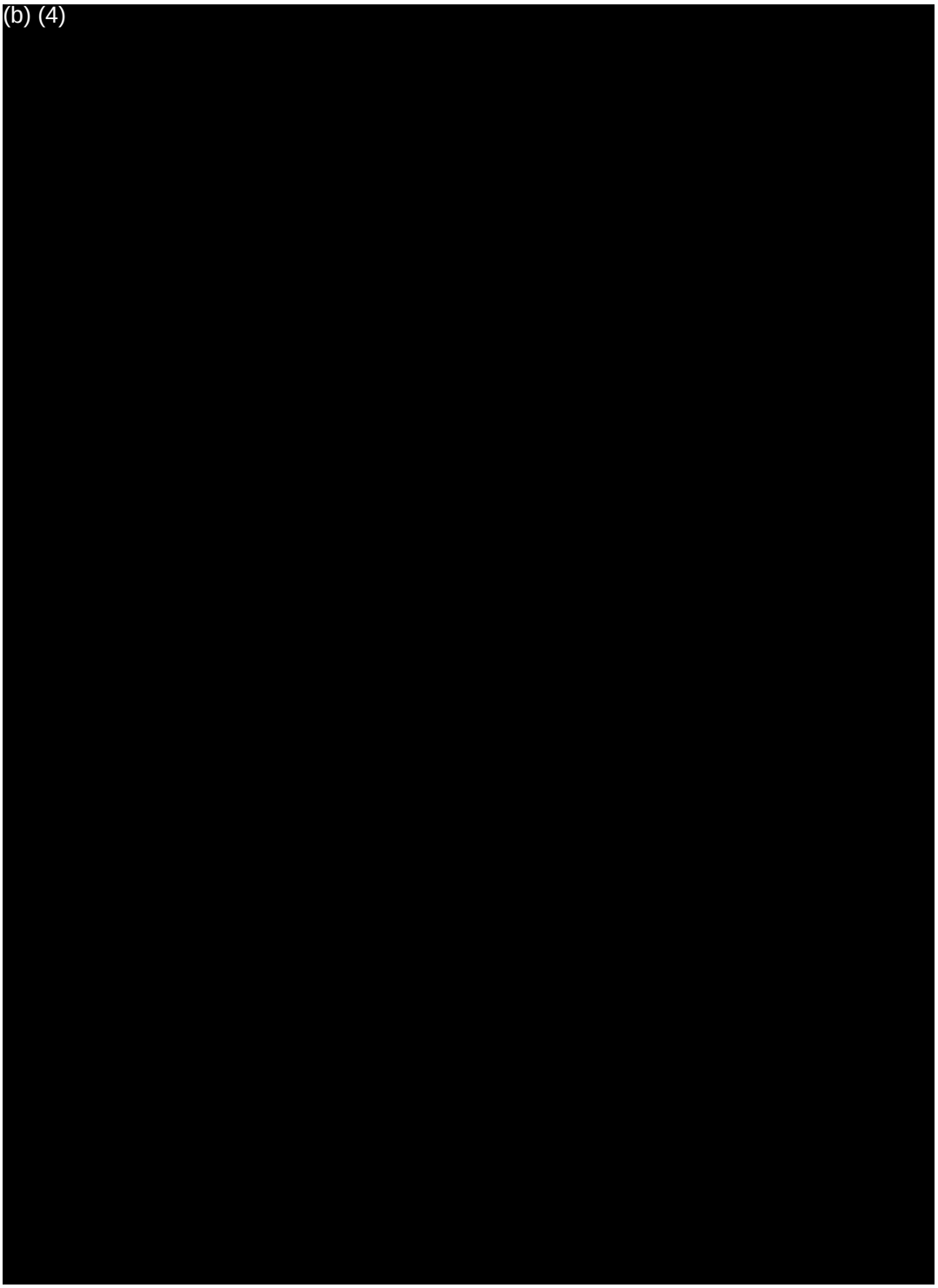

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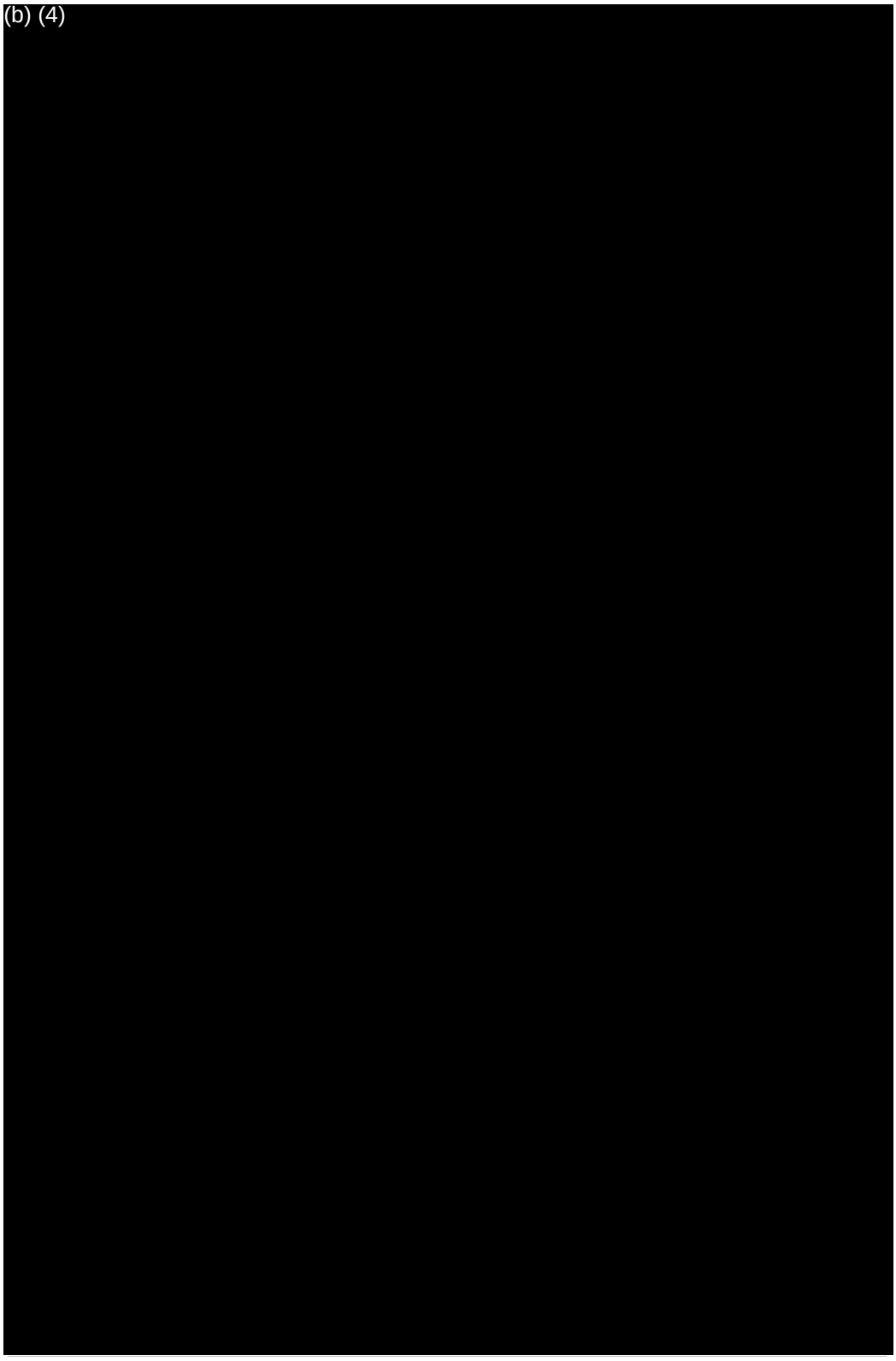

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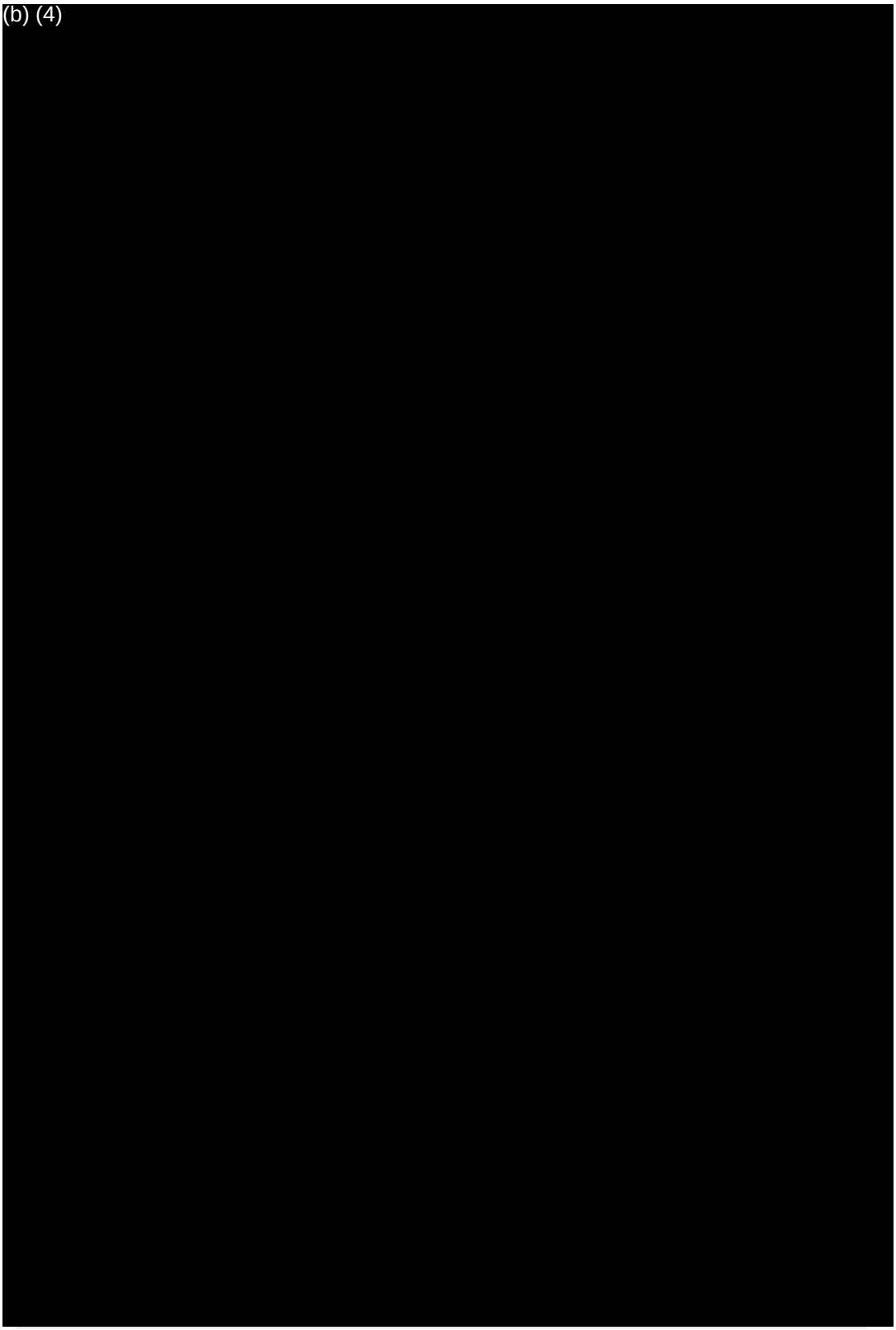

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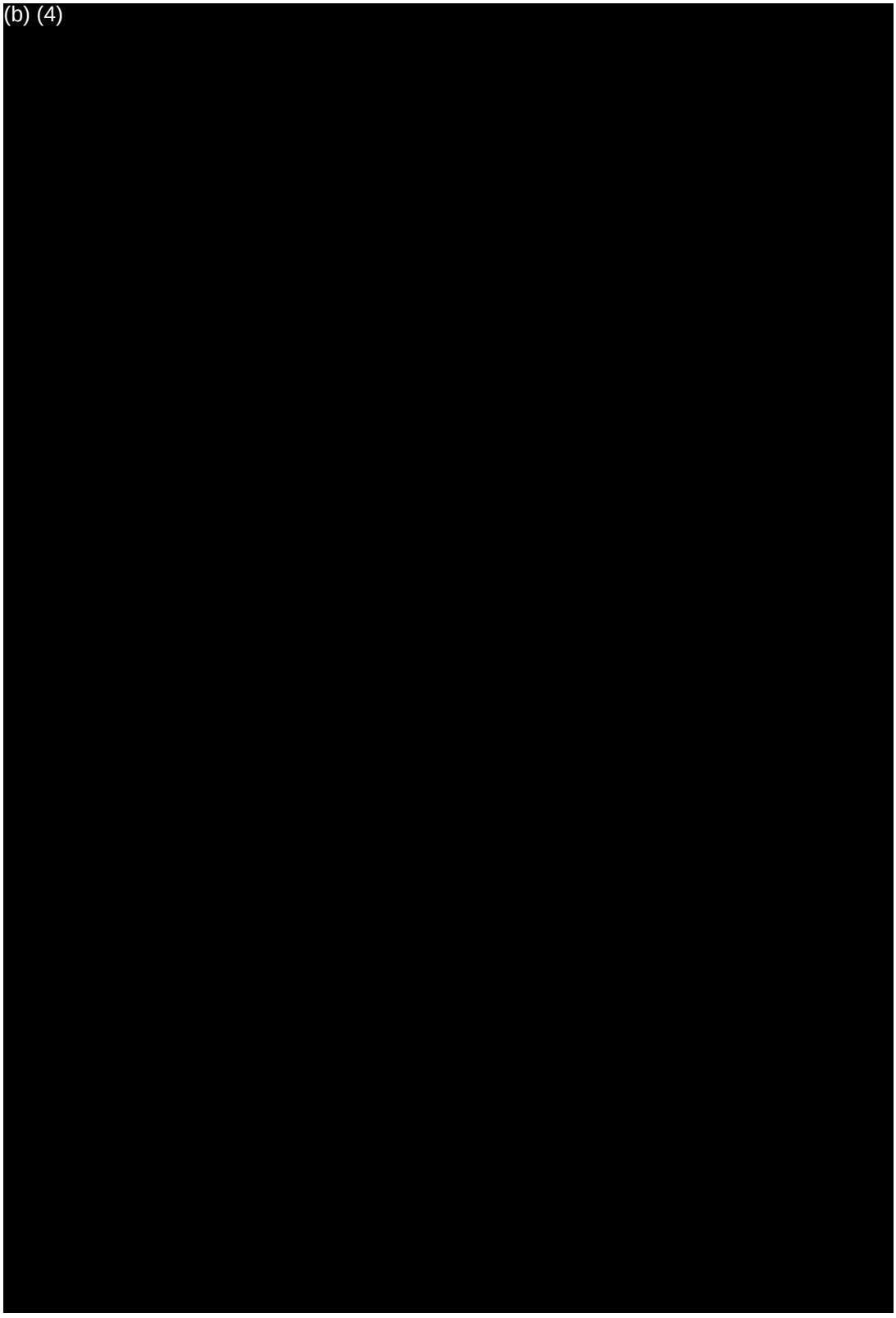

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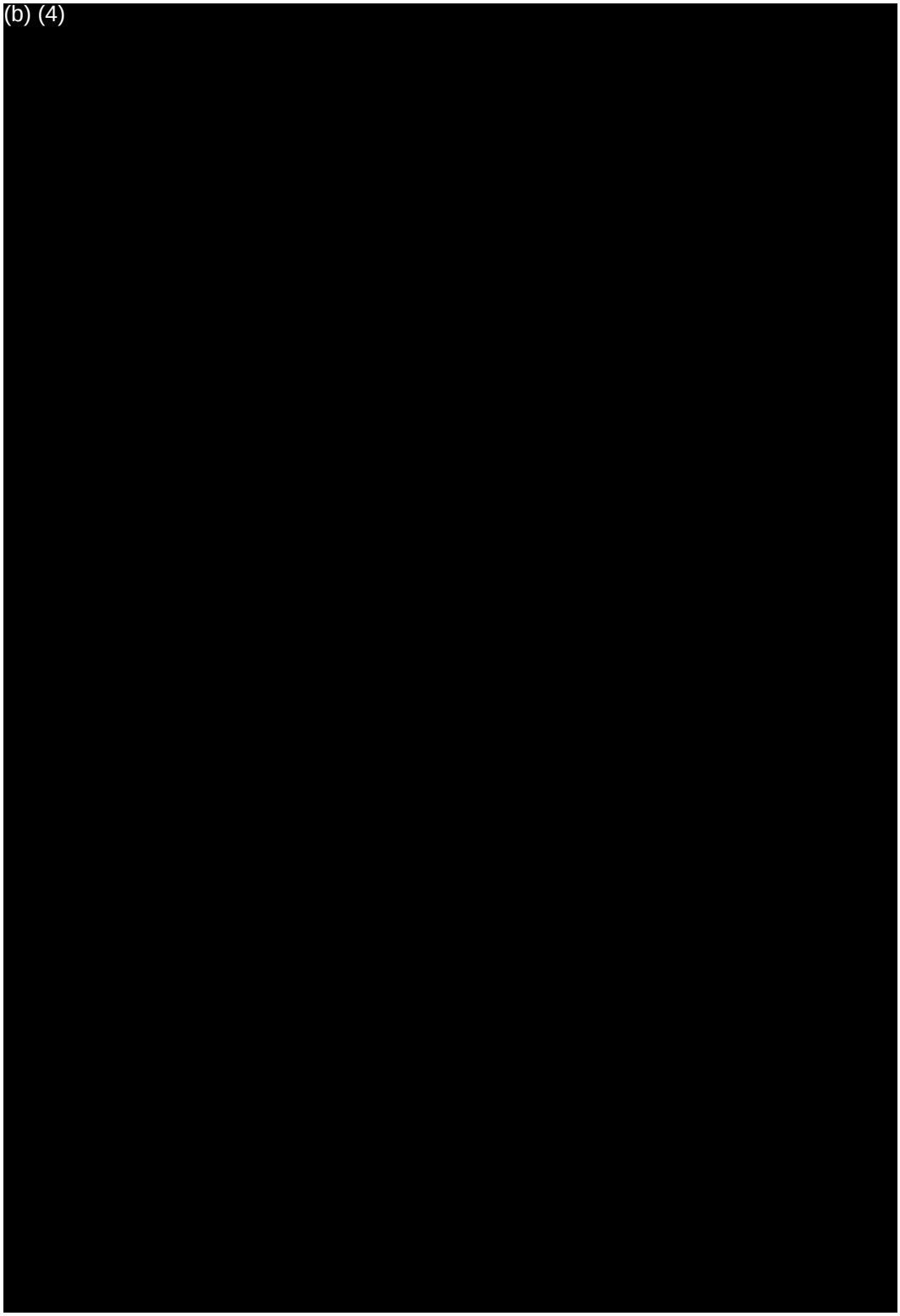

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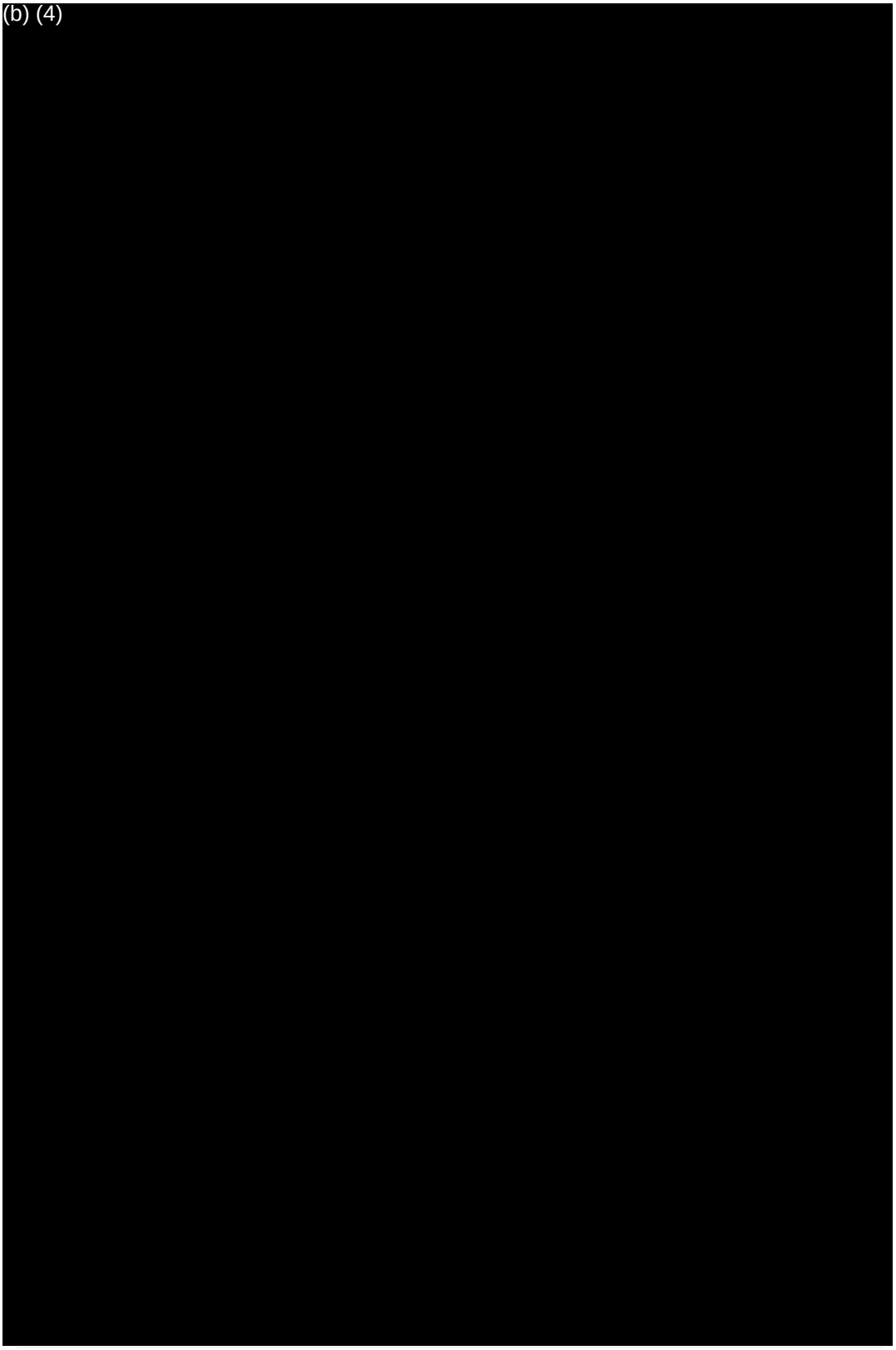

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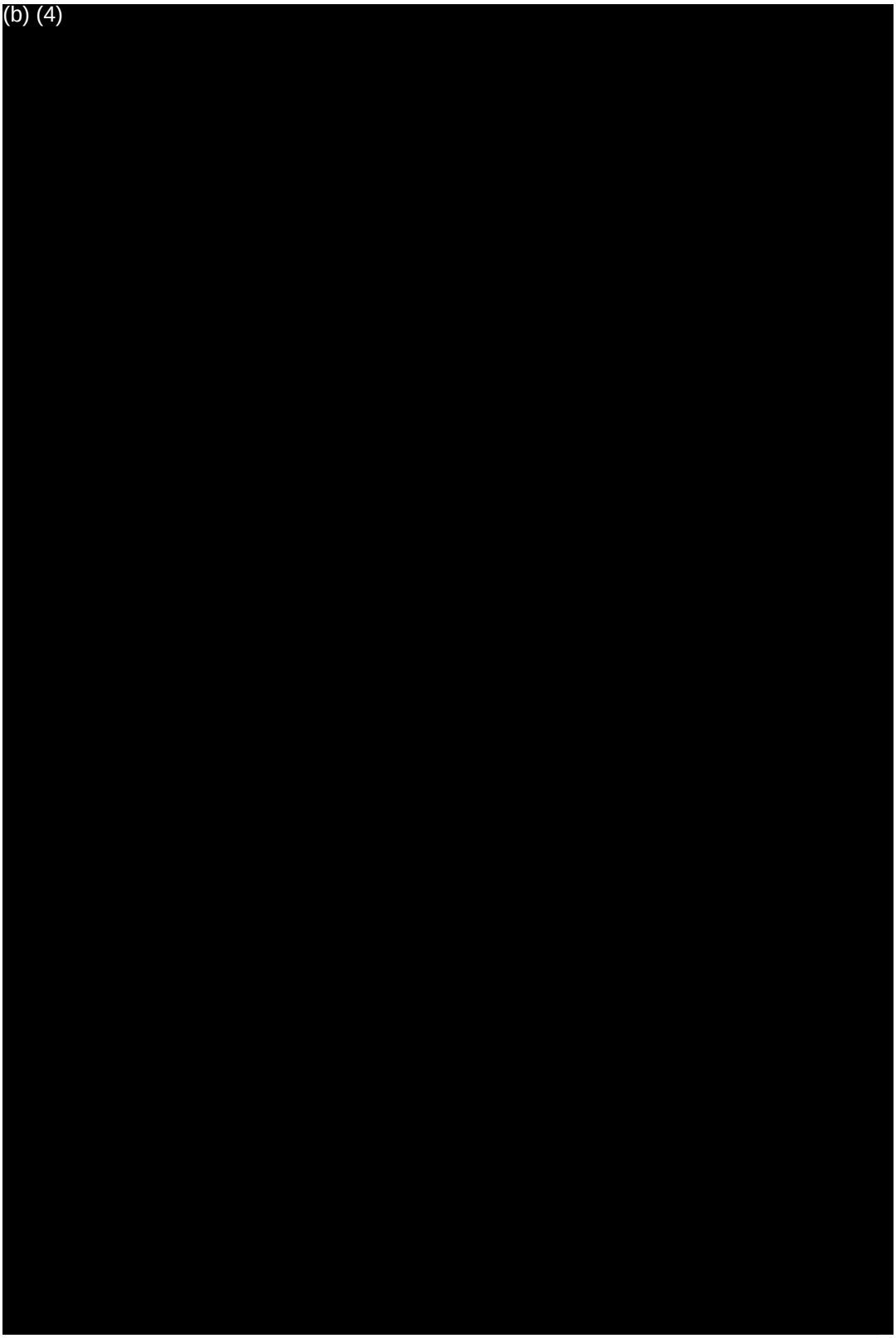

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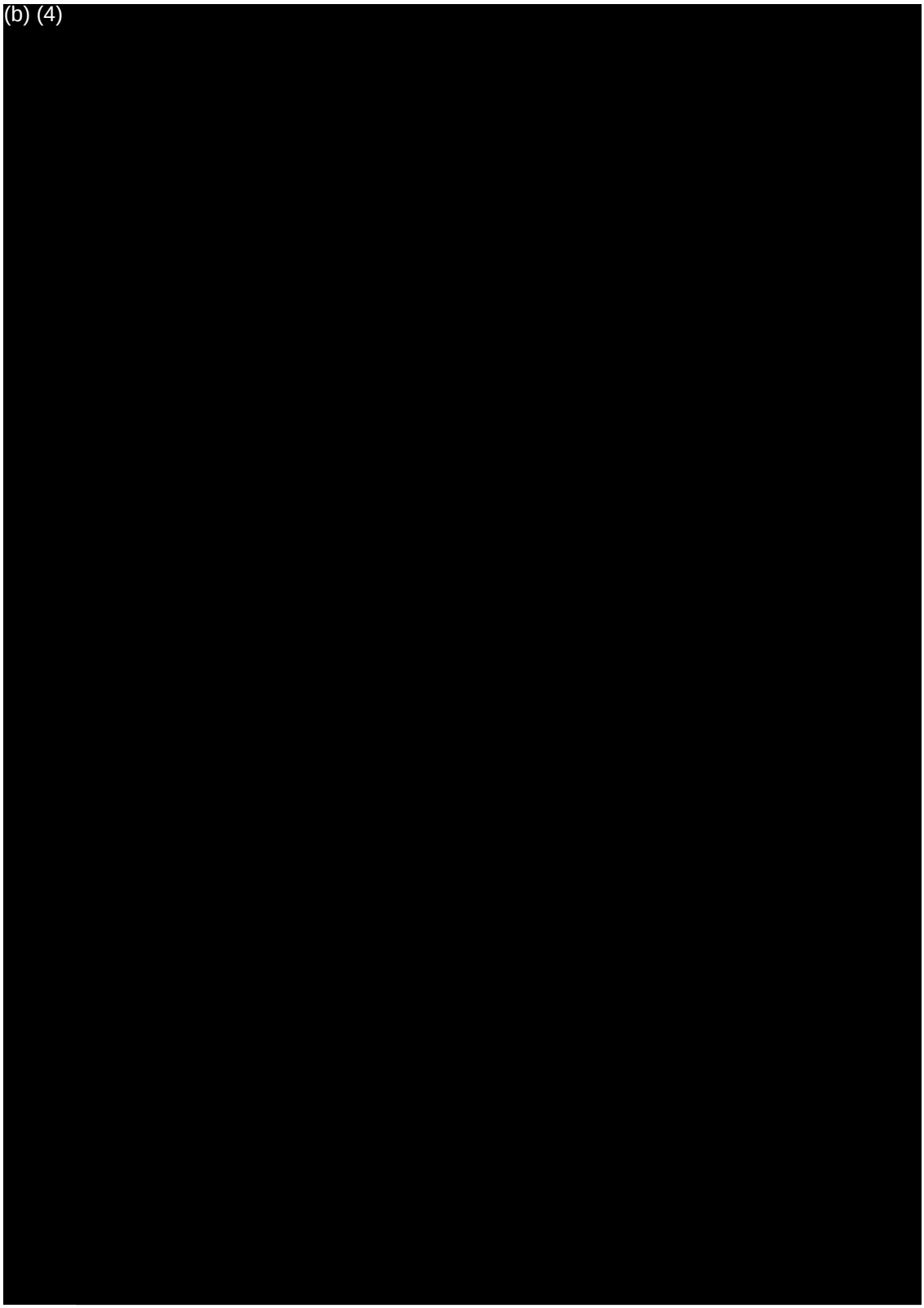

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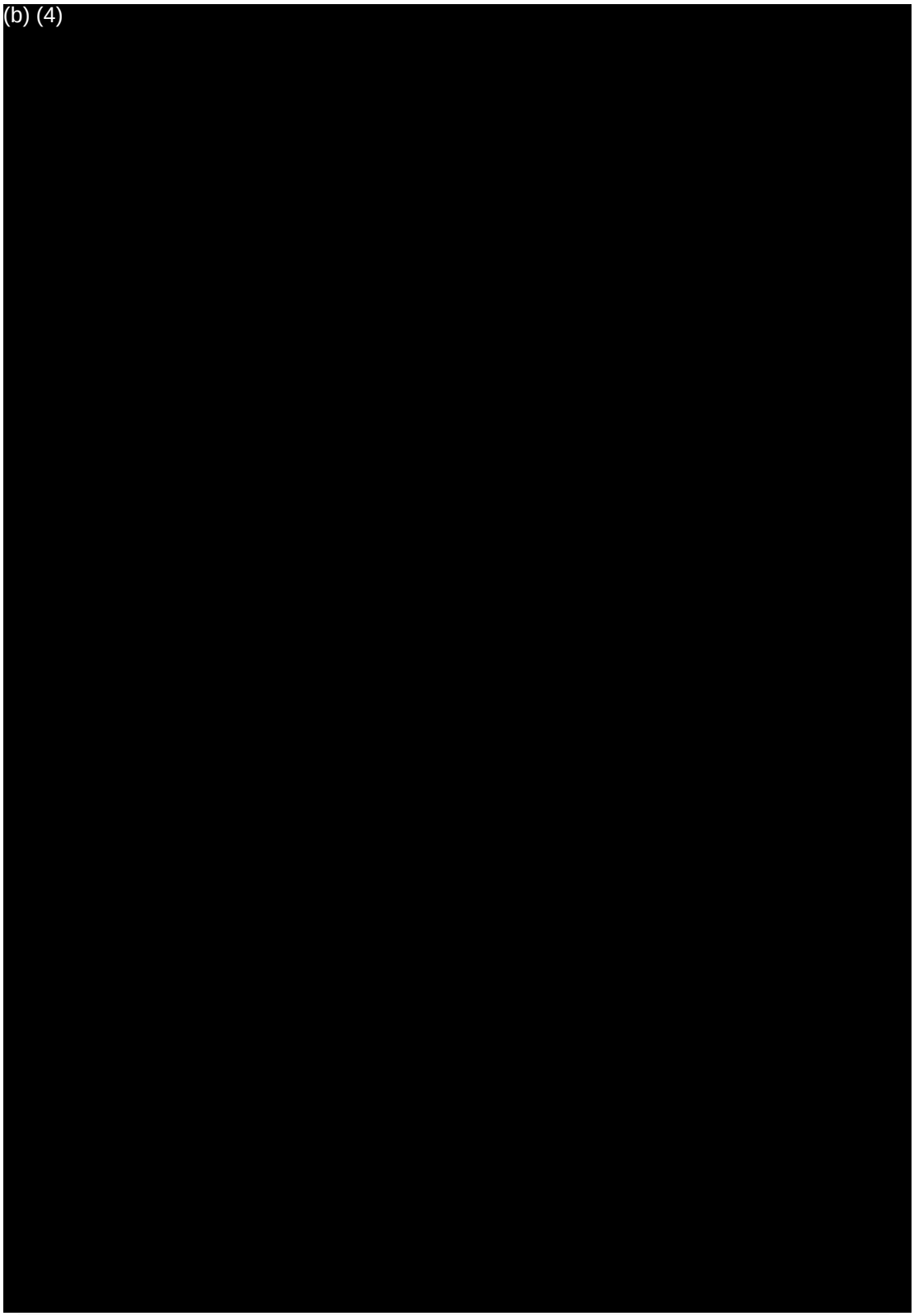

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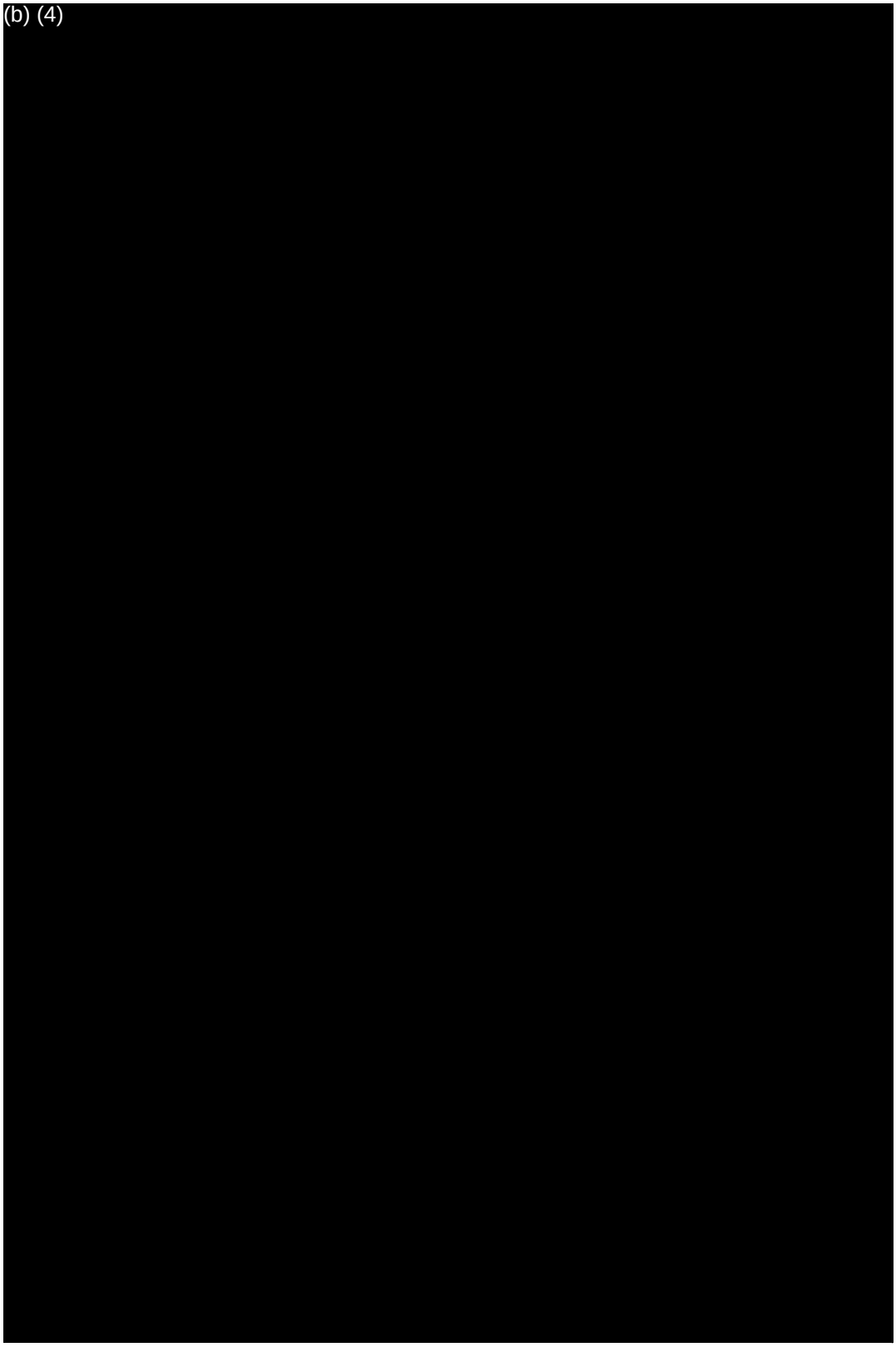

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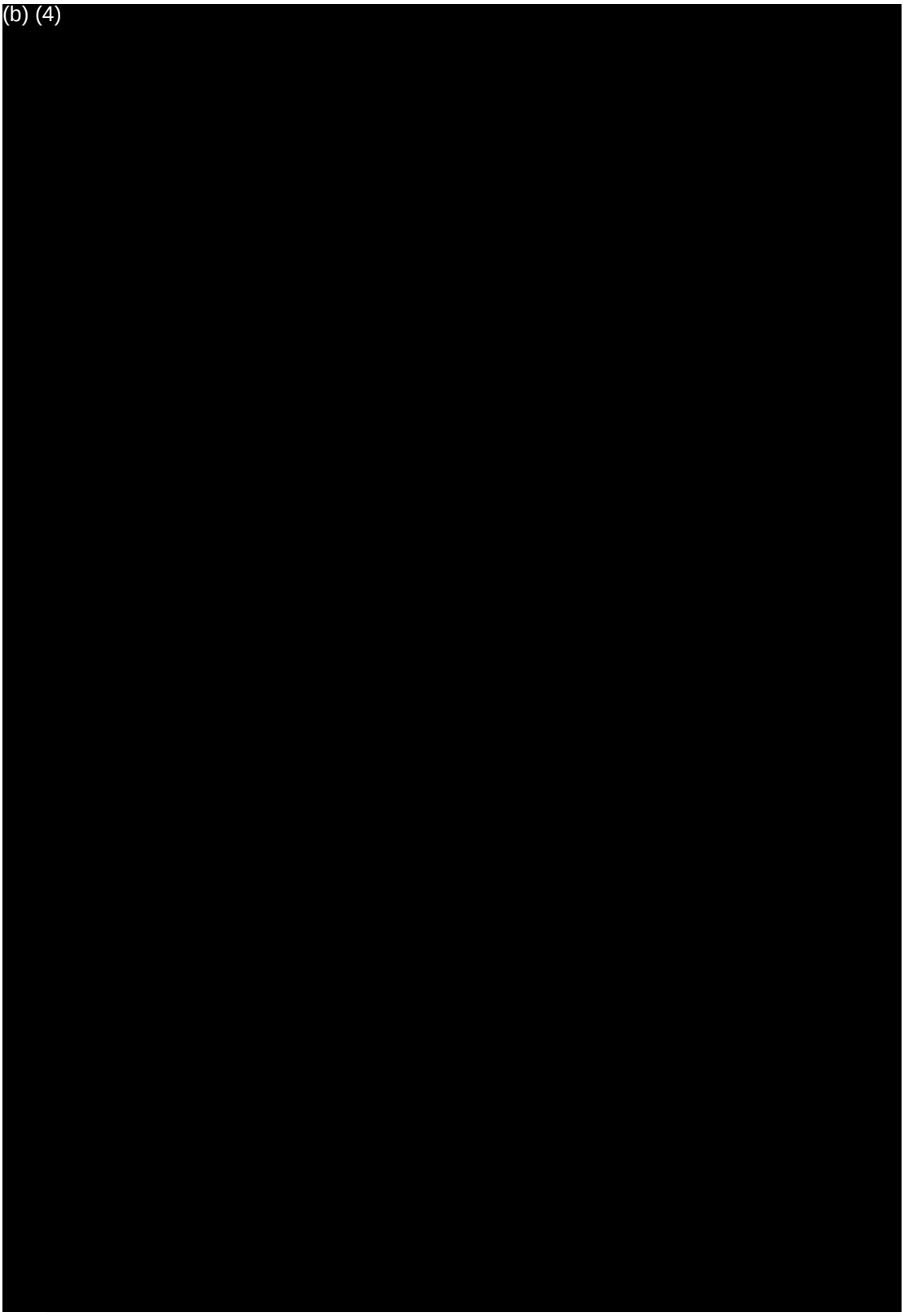

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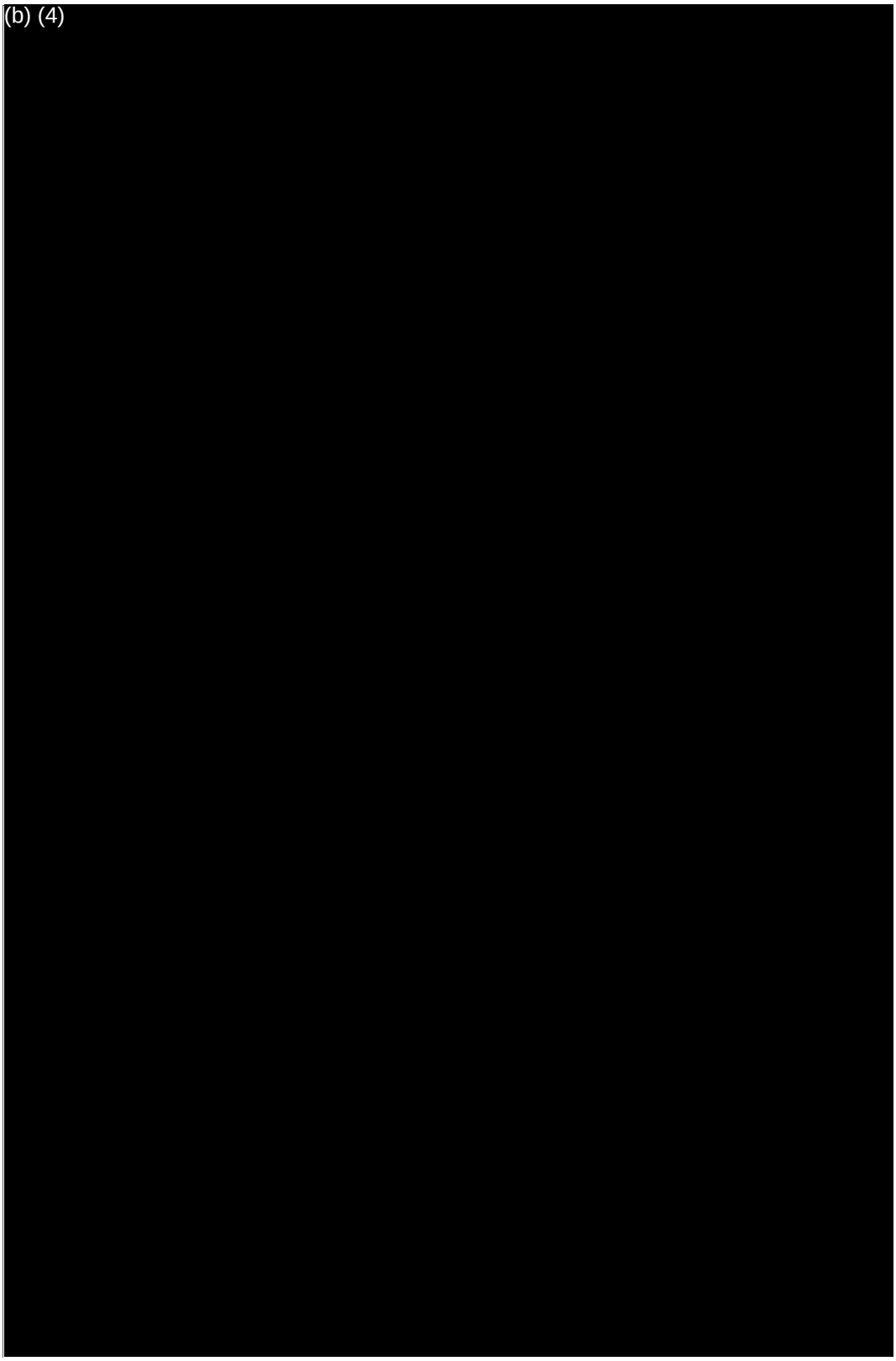

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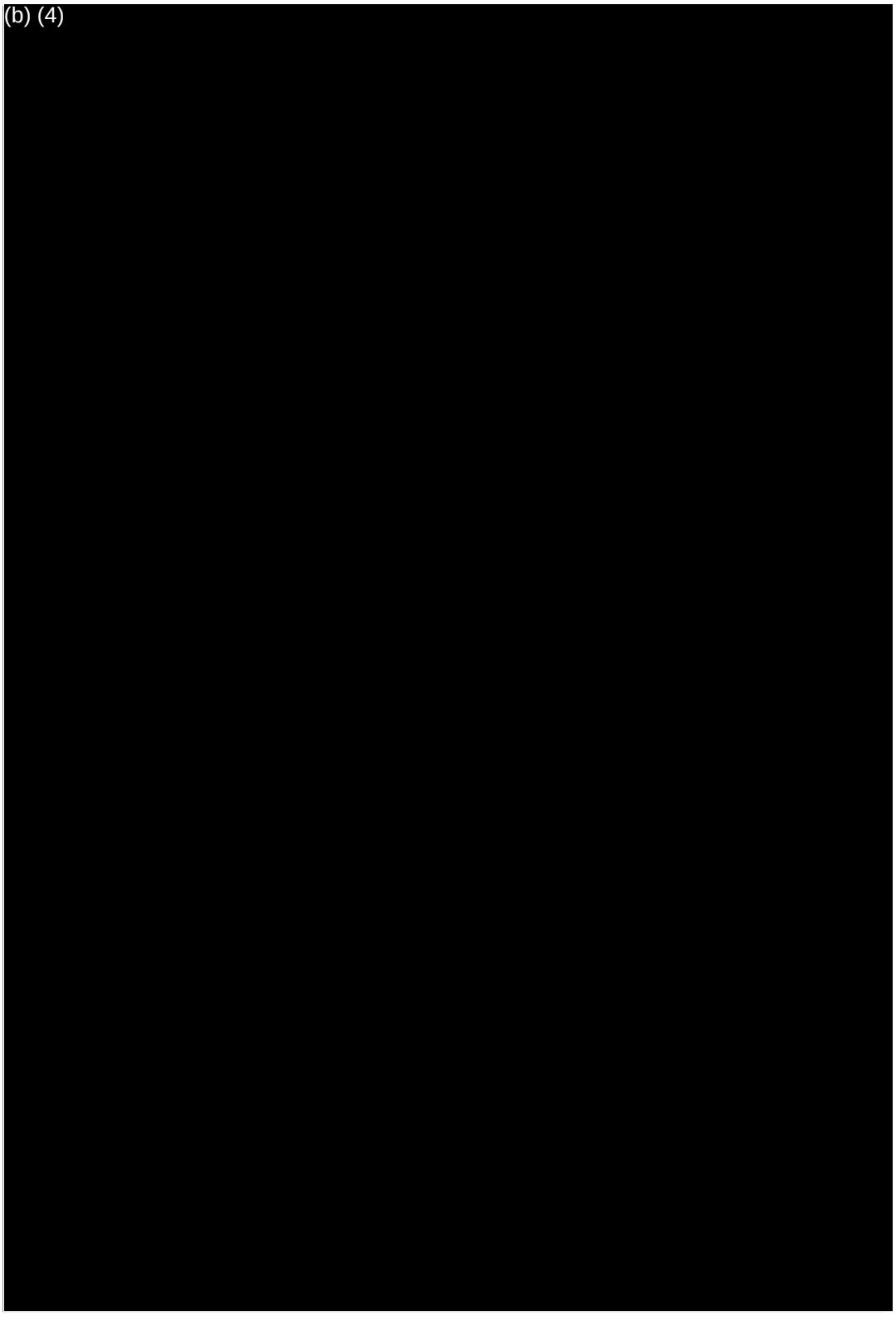

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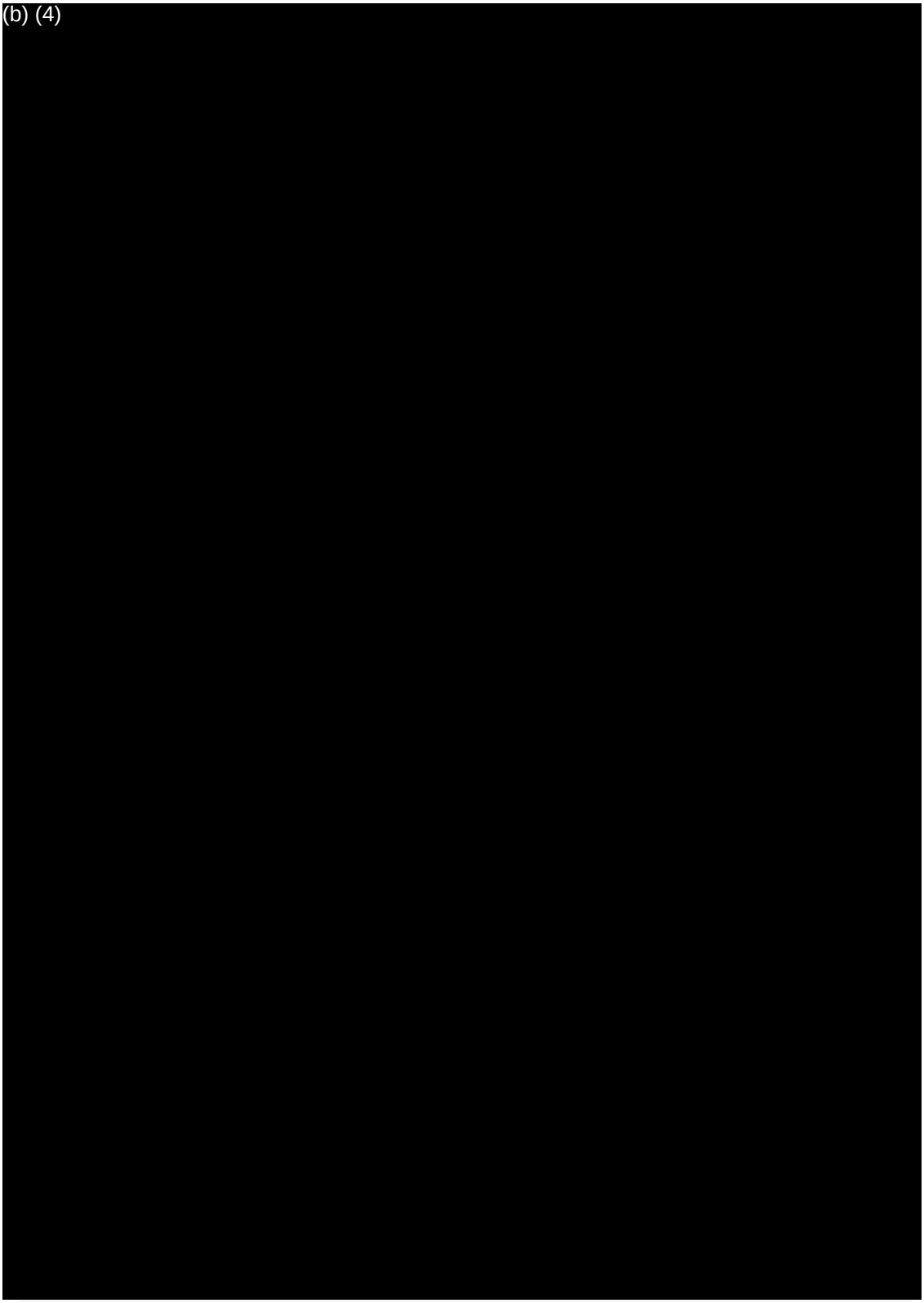

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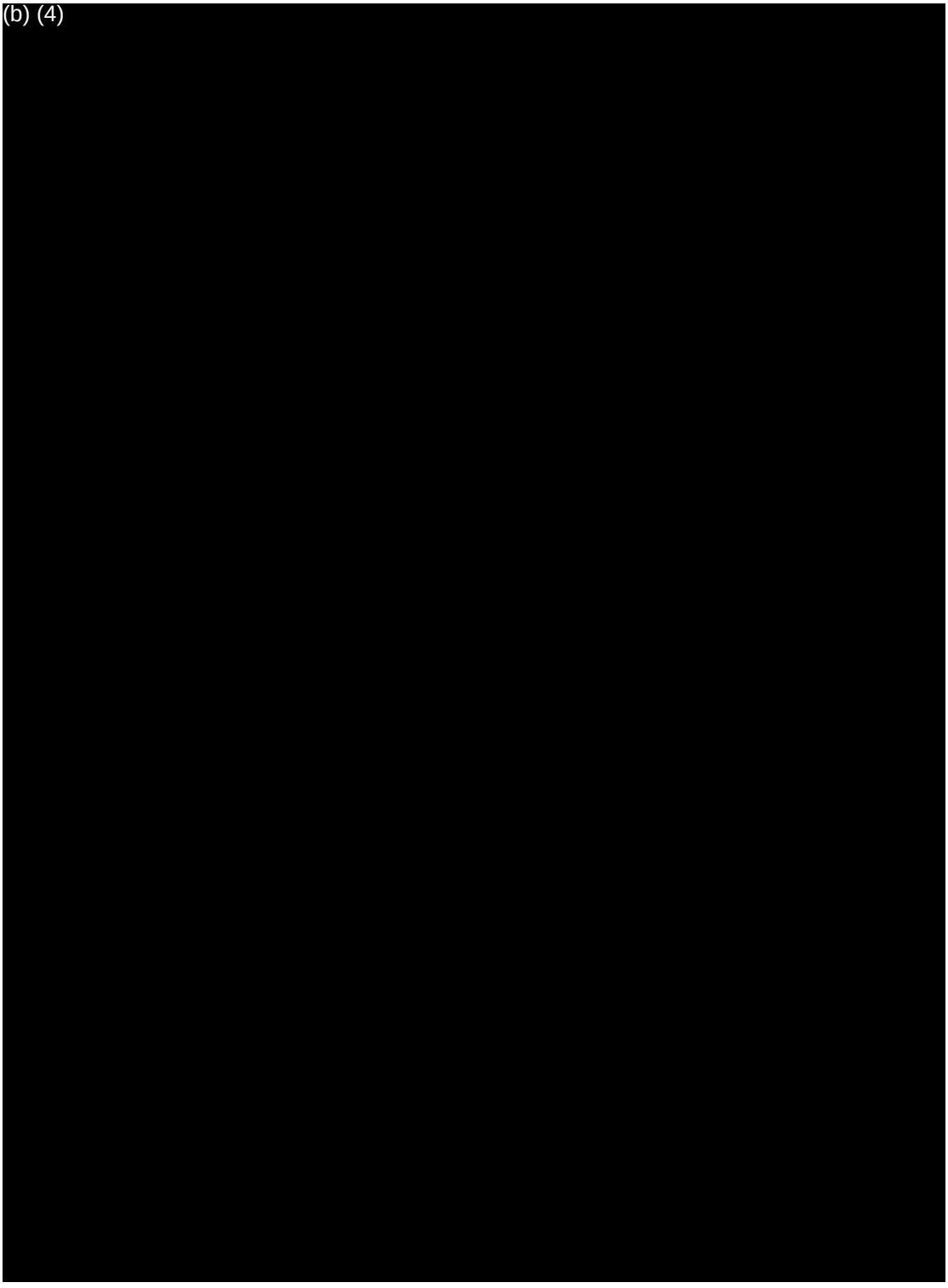


4.2 PHARMACOMETRIC REVIEW

Office of Clinical Pharmacology and Biopharmaceutics Pharmacometrics Review

NDA	22-214
Submission Date(s)	09/05/2007
Drug Name	Arimidex
Dosage Form	Tablet
Dosage Regimen	1 mg OD
Pharmacometrics Reviewer	Manoj Khurana, Ph.D.
Secondary Pharmacometrics Reviewer	Rajanikanth, Madabushi, Ph.D.
Clinical Pharmacology Reviewer	Jaya Vaidyanathan, Ph.D.
Clinical Pharmacology Team Leader	Sally Choe, Ph.D.
Sponsor	Astrazeneca
Submission Type	SE5 (Pediatric Exclusivity); Priority
Proposed indication	Pubertal Gynecomastia in Boys McCune-Albright Syndrome in Girls

Executive Summary

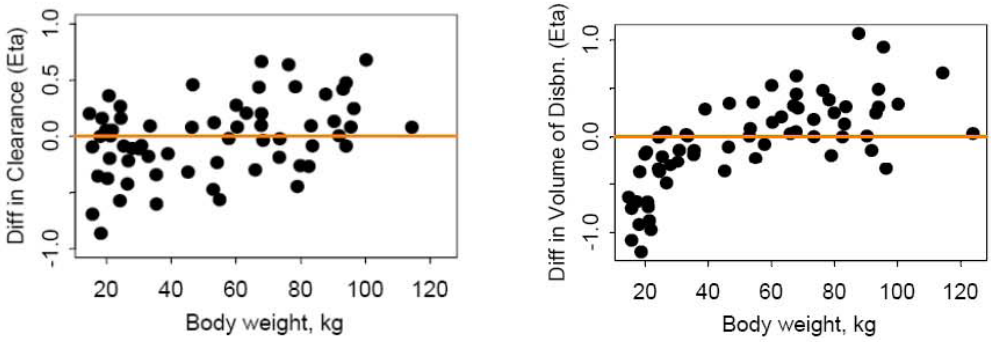
The aim of the document is to review the sponsor's population pharmacokinetic (PK) analysis, [redacted]

The key questions and findings of the present submission are:

1. What are the pharmacokinetic characteristics of anastrozole in pediatric population?

Based on the results of the population PK analysis, the anastrozole apparent clearance and volume of distribution were found to be 1.4 L/hr and 51.4 L, respectively. Only body weight was found to be a significant predictor of the apparent oral clearance and volume of distribution of anastrozole, as shown in Figure A.

Figure A: Body weight is a significant predictor of anastrozole apparent clearance and volume of distribution (Note: From Base Model)



Upon accounting for the effect of body weight, 4% intersubject variability in clearance, 27% intersubject variability in volume of distribution could be described in the data.

2. Are there any gender based differences in the PK of anastrozole?

In sponsor's analysis, it was concluded that clearance in girls was different from boys. Hence the effect of gender on the PK of anastrozole was explored. The reviewer noted that the body weight in boys (Study D5394C00001) and girls (Study 1033IL/0046) were significantly different as shown in Figure B. Therefore, what appears as a gender effect could be an artifact of the inherent differences in body weights between boys and girls. Upon accounting for the effect of body weight on the oral clearance and volume of distribution, the effect of gender disappears, as shown in Figure C.

Figure B: Body weight is different between boys (Males) and girls (Females)

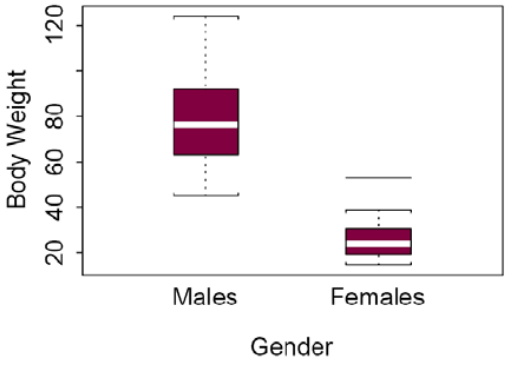
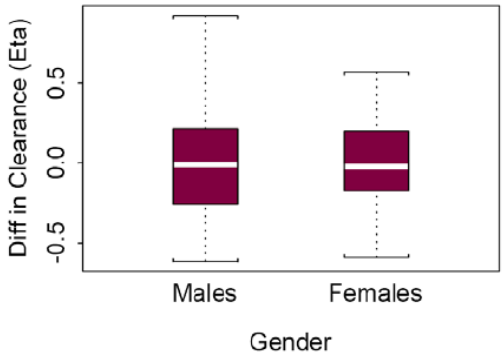


Figure C: Body weight accounts for the difference in clearance between boys (Males) and girls (Females)



3. What is the influence of age on PK of anastrozole in pediatric patients?

Age and body weight were correlated in the population evaluated in the current analysis (Figure D). Upon accounting for the effect of body weight on the oral clearance and volume of distribution, there is no effect of age evident on these PK parameters of anastrozole, as shown in Figure E.

Figure D: Age and body weight are correlated

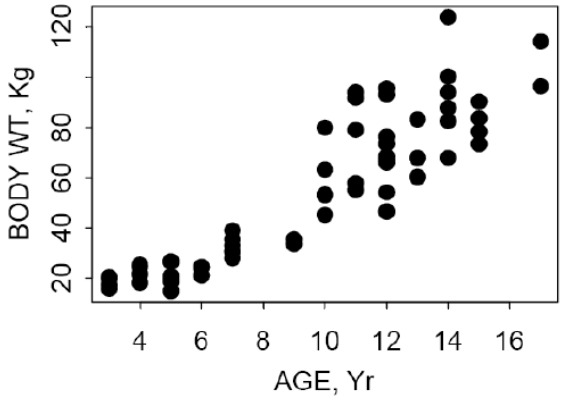
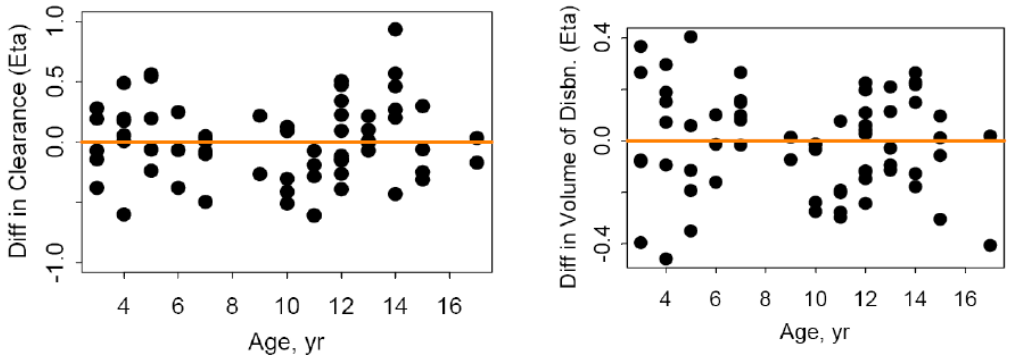


Figure E. No effect of age on body weight adjusted PK parameters of anastrozole.



Recommendations

(b) (4)

Introduction

Anastrozole (ARIMIDEX®) is a potent and selective nonsteroidal third generation aromatase inhibitor. Aromatase inhibitors are a class of compounds that systemically inhibit estrogen synthesis in tissues by inhibiting the enzyme aromatase, which catalyses the conversion of the adrenal androgens, androstenedione, and testosterone to the respective estrogen, estrone, and estradiol. Inhibition of aromatase activity is primarily attributed to anastrozole, the parent drug. The approved (NDA 20-541) indication is the treatment of advanced breast cancer in post-menopausal women.

(b) (4) anastrozole in other diseases that manifest symptoms resulting from increased estrogen production, the treatment of pubertal gynecomastia in boys, and in the treatment of precocious puberty in girls with McCune-Albright Syndrome (MAS) was evaluated in the studies under the current submission (NDA 22-214). The purpose of this application was to provide data from studies designed to examine the safety, efficacy and PK of anastrozole in these pediatric populations, in response to the Written Request from the Food and Drug Administration (FDA), dated 9 May 2001, reissued 2 July 2002, amended 19 November 2002, 19 December 2003, 7 May 2004, and 8 April 2005, to obtain 6-month pediatric exclusivity for ARIMIDEX 1 mg tablets.

The PK of anastrozole (1 mg administered orally once-daily) in children was evaluated concurrently in 2 open-label, exploratory Phase II studies. AstraZeneca conducted a safety and efficacy study of anastrozole in 28 girls with precocious puberty with MAS aged ≤10 y (Study 1033IL/0046) and a pharmacokinetic and pharmacodynamic study in 36 pubertal boys aged ≥11 to ≤18 y with gynecomastia (Study D5394C00001).

The safety and efficacy of anastrozole was evaluated in three studies; Study 1033US/0006, Study D5394C00001 and1033IL/0046, although the efficacy evaluation was a secondary objective in Study D5394C00001.

The primary objective of Study 0006 was to determine whether anastrozole was more effective than placebo in the treatment of gynecomastia in pubertal boys as assessed by changes in breast tissue size and symptoms. For the primary efficacy endpoint, a response was defined as a ≥50% reduction between Day 1 (Visit 1) and after 6 months of study treatment (end of study) in the calculated volume of gynecomastia of both breasts combined, as measured by ultrasound. The response rate was defined as the proportion of patients achieving a response after 6 months of study treatment. The response rates for a total breast volume decrease ≥50% were 38.5% (15/39) and 31.4% (11/35) for anastrozole and placebo, respectively (odds ratio = 1.513, 95% CI 0.496 to 4.844, p=0.4687). One patient in the anastrozole group had complete regression of gynecomastia after 6 months of therapy. The testosterone/estradiol ratio after 6 months was 171 ± 143 (mean ± standard deviation [SD]) in the anastrozole group compared with 35 ± 114 in the placebo group which reflected the pharmacodynamic activity of anastrozole. There were no treatment group differences in the changes of absolute values of breast volumes, or of height, weight, or body mass index [BMI]. Breast pain was resolved in 90.9% (10/11) in the anastrozole group and 100% (9/9) in the placebo group. (b) (4) There were no safety or tolerability concerns arising from this study.

In Study D5394C00001 in boys, the response rate for a breast volume decrease ≥50% after 6 months' treatment was 55.6% (20/36) and no patients experienced complete regression. The mean breast volume was reduced by 126.6 ml (44.8%) and breast pain was resolved in 4 of the 5 patients who were symptomatic at baseline. During the 6-month study period, mean height increased by 3.4 cm (z-score 0.02).

Primary efficacy variables for Study 0046 in girls with MAS were: change in frequency of annualized episodes of vaginal bleeding on treatment compared to baseline, proportion of patients with baseline vaginal bleeding who experienced >50% reduction in the number of vaginal bleeding episodes on treatment, proportion of patients with baseline vaginal bleeding who experienced cessation of vaginal bleeding episodes over a 6-month study period and over the whole 12-month study, change in bone age advancement on treatment compared to change during baseline, change in growth velocity on treatment compared to change during baseline. Analysis of the efficacy data indicated that:

- There was a slight increase in the frequency of bleeding days during treatment compared to baseline (median increase of 1.9 days) (b) (4) [redacted]
- Seven (28%) of the 25 patients with baseline vaginal bleeding experienced a ≥50% reduction in the frequency of vaginal bleeding days on treatment
- Ten (40%) of the 25 patients with baseline vaginal bleeding experienced a cessation in vaginal bleeding on treatment over a 6-month (ie, ≥180 days) study period. Three (12%) of those 10 patients experienced a cessation in vaginal bleeding on treatment over the whole 12-month study period (ie, from Day 1 to Day 360)
- The mean (and median) rate of increase in bone age decreased from the 6-month pre-baseline period over the 12-month on treatment period, with a slightly greater decrease in rate over the second 6 months of treatment. The change in rate of increase was not statistically significant for pre-treatment to during treatment, pre-treatment to the first 6 months of treatment, or for pre-treatment to the second 6 months of treatment
- Growth rate (in cm/year) was significantly reduced ($p<0.05$) from pre-treatment to during treatment (Month 0 to Month 12) (median change –2.1 cm/year; p=0.0356), and from pre-treatment to the second 6 months of treatment (median change -2.2 cm/year; p=0.0186). Growth rate (in Z-score) changes (b) (4) [redacted] showed a trend in reduction consistent with the growth rate in cm/year.

Sponsor's analysis

In the current submission, the sponsor submitted one report that summarizes the population pharmacokinetic analysis of anastrozole.

Objective of the analysis

The overall purpose of the population pharmacokinetic analysis was to characterize the PK of anastrozole in girls ≤10 y with MAS.

The specific objectives of the population analysis were:

- to identify the structural model of anastrozole for characterizing the pharmacokinetic properties of anastrozole in these girls
- to estimate the population pharmacokinetic parameters for anastrozole, including typical values and random sources (inter-individual and residual) of variability
- to evaluate the impact of covariates such as age, body weight (WT), and others on anastrozole PK
- to generate post-hoc Bayesian estimates of individual pharmacokinetic parameters for all patients included in the analysis.

Methods

Study Design and Data

Data from 2 clinical studies were used for the population pharmacokinetic database. The details of the studies with the sampling strategies are shown in Table 1 below:

Table 1 Studies included in the population pharmacokinetics analysis

Study No	Study phase	Number and description of patients	Formulation and anastrozole dosage (number of patients)	Plasma sampling schedules
1033IL/0046	II	28 girls with McCune-Albright Syndrome	Tablets 1 mg as single daily dose for 12 m (28)	Four samples were taken, 2 at single dose and 2 at steady state. Within 2 h after the first administration, from 3 to 24 h after the first administration and before the second administration, and at two times at least 2 wk after the first administration (at steady state) (if the 2 blood draws at steady state were taken at the same visit, they were to be separated by at least 3 h)
D5394C00001	II	36 pubertal boys with gynecomastia	Tablets 1 mg as single daily dose for 6 m (36)	Fourteen samples were taken at steady state. Within 30 min before administration and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours post dose after the Week 2 visit (≥14 d)

Data derived from individual study reports.

Data Quality Control and Editing:

Quantifiable anastrozole plasma concentrations after oral administration of anastrozole were included in the analysis. Data sets were prepared with SAS from each study according to the format required by the non-linear mixed effect modeling (NONMEM) program. SAS command files, logs, and listings pertaining to data file conversion and merging were reviewed by an independent analyst.

A total of 615 anastrozole plasma concentration data from 64 patients were available for the population pharmacokinetic analysis. Twenty-eight (28) patients from Study 0046 contributed 111 plasma concentration data and 36 patients from Study 0001 contributed 504 plasma concentration data. A total of 21 records were removed from the data set prior to any analysis. Reasons for the removal of plasma concentration observations included: concentration below the limit of quantification (BLQ, 19), non-reported samples (2), and one sample was excluded during the analysis as pharmacokinetic outlier (1) based on NONMEM weighted residual |WRES| >4.

Analysis Methods

The overview of analysis methodology is summarized in Fig. 1 below. The population pharmacokinetic approach was used to analyze anastrozole plasma concentrations using the NONMEM software, Version V1.1. Exploratory data analysis was undertaken to examine the basic structure of the concentration-time profile and to identify any outliers. Various structural models were evaluated on the basis of the reasonability and precision of parameter estimates, the residual variability, the change in objective function value (OFV) ($p<0.01$), and the goodness-of-fit.

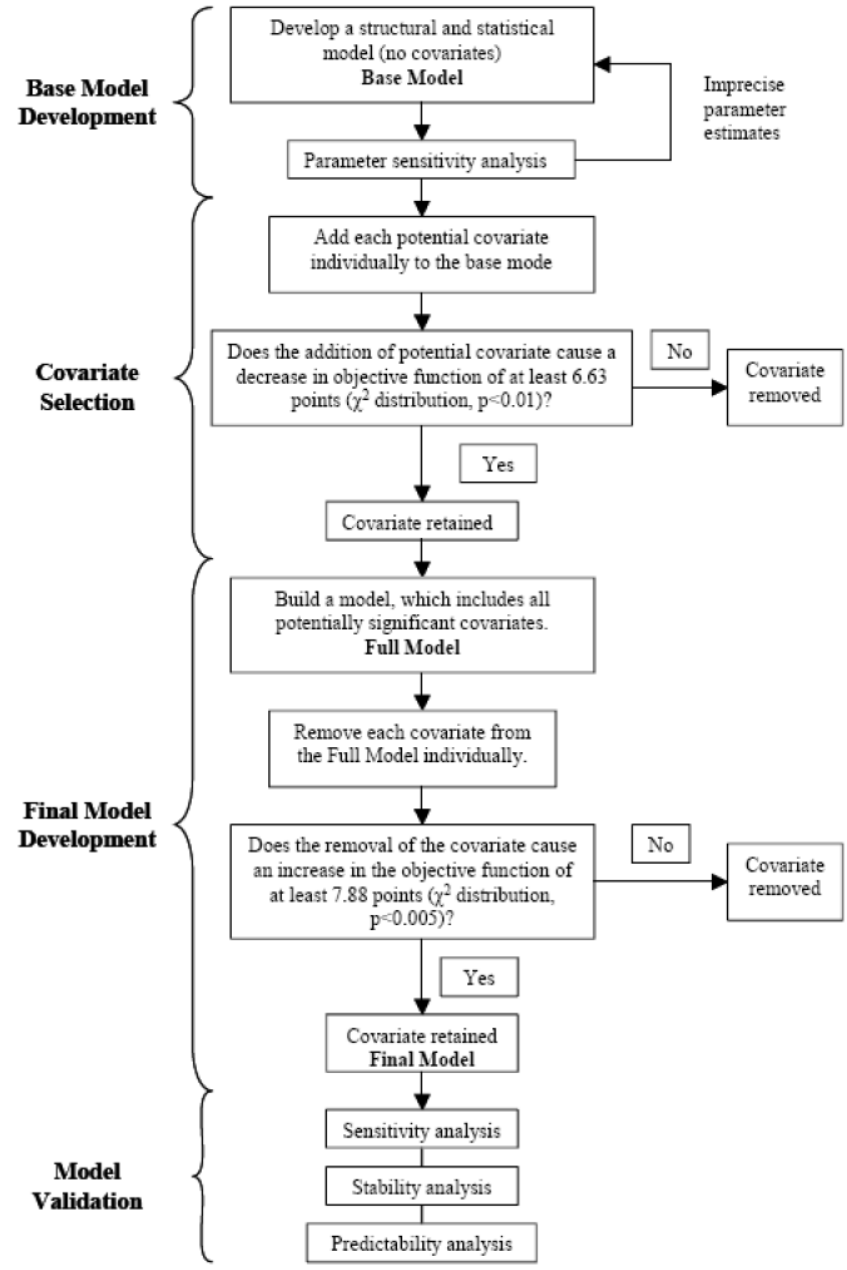
Once the appropriate base model was selected, univariate selection of covariates was performed on the pharmacokinetic parameters by adding the covariates sequentially ($p<0.01$). Covariates

tested were age, race, sex, WT, body mass index (BMI), BSA, and lean body mass (LBM). Stepwise backward elimination of covariates was performed on the full multivariable model by deleting each covariate-parameter relationship, one at a time ($p<0.005$).

The covariate model resulting from the backward elimination process was evaluated for stability, sensitivity, and predictability. The final model was then used to calculate individual Bayesian estimates of pharmacokinetic parameters for each patient using the posterior condition estimation (POSTHOC) technique with first-order conditional estimation (FOCE) method.

The pharmacokinetic parameter endpoints were apparent oral clearance (CL/F), apparent volume of distribution at steady state (Vss/F), maximum anastrozole plasma concentration (Cmax), area under the anastrozole plasma concentration-time curve over the dosing interval (AUC), and terminal elimination half-life ($t_{1/2}$).

Figure 1 **Overview of modeling steps**



Pharmacokinetics

Structural Model

Various structural models were evaluated, for example, a one-compartment model with bolus input, a one-compartment model with first-order absorption, a 2-compartment model with first-order absorption and a 3-compartment model with first order absorption. All the models were parameterized in terms of clearance (CL, Q) and the volume of distribution (V, VSS).

Covariate Model

Covariates were added to the base model sequentially and tested by NONMEM to determine if they were indeed statistically significant. A p-value of 0.01 was used as the criteria for statistical significance.

Categorical covariates were entered into the model using dummy variables (0 or 1) using a fractional change model. For the linear model with a dichotomous covariate:

$$P_j = \theta_0 \cdot (1 + \theta_1 \cdot X_1)$$

Where, $1 + \theta_1$ is the fractional multiplier for X_1. Thus when $X_1=1$, $P_j=\theta_0 \cdot (1 + \theta_1)$. When $X_1=0$, $P_j=\theta_0$.

Continuous covariates (WT, BSA, AGE, and LBM) were entered into the model in a median-centered manner:

$$P_j = \theta_0 + \theta_1 \cdot [X_1 - M(X_1)]$$

Where, P_j is the jth parameter, θ_0 is the intercept, θ_1 is the slope relating the covariate, X_1, to the pharmacokinetic parameter, and $M(X_1)$ is the median of X_1.

Missing continuous covariate was imputed with the median population value. Missing RACE was assigned a value of 4 (Other).

Random Variance Models

Random effects (inter-individual variability on the pharmacokinetic parameters) assumed a log-normal distribution $P_j=\theta_j * \exp(\eta_j)$. The residual error models, e.g. proportional error, additive error or combined proportional and additive error were evaluated.

Model Selection

Initial Model Selection

Model selection was based on (a) the criteria of a significant reduction in the OFV based on the likelihood ratio test (LRT) if the models being compared were nested or Akaike Information Criteria (AIC) if the models being compared were not nested, (b) goodness-of-fit plots evaluation and (c) % CV of parameter estimates < 50.

Final Model Selection

Various model qualification methods such as sensitivity analysis, stability analysis and predictability analysis were employed.

Software

Creation of data sets was done with SAS for Windows, version 8.2 (SAS Institute, Cary, NC). The population PK of anastrozole was analyzed by NONMEM (Version V1.1, GloboMax LLC, Hanover, MD). NONMEM was accessed through the GloboMax PDxPop® User Interface Application, Version 2.0 (Build a). NONMEM was run on an IBM Thinkpad laptop computer T40, equipped with a Compaq Visual Fortran compiler and Active Perl, Version 5.6. Figures were prepared with S-Plus Version 6 (Mathsoft, Seattle, WA), Microsoft Excel 2000, and/or SigmaPlot Version 8 (SPSS, Chicago, IL).

Results (Sponsor's Analysis)

Model and Model Selection:

Base Model

Model description

The base model was a 2-compartment model with first-order absorption and linear clearance. This model was parameterized in terms of clearance (CL), the volume of distribution of the central (V), steady state volume of distribution (VSS), inter-compartmental clearance (Q) and first-order absorption rate constant (ka). The residual error model was a constant coefficient of variation (CCV) model. Inter-individual variability was described for CL, V, VSS and Q. The first order conditional estimation (FOCE) method with Interaction was employed in NONMEM.

Parameter estimation results

The parameter estimates from the base pharmacokinetic model are shown in table below.

Table 2: Anastrozole base population pharmacokinetic model (First order conditional estimation method)

Model Parameters	Parameter	Estimate	Standard Error	RSE, %
Objective Function Value	OFV	2679.367	NA	NA
Apparent oral clearance, CL/F (L/h)	θ (1)	1.47	0.0898	6.11
Apparent volume of distribution, V/F (L)	θ (2)	40.8	5.49	13.5
Apparent inter-compartmental clearance, Q/F (L/h)	θ (3)	1.74	0.574	33.0
Apparent steady state volume of distribution, V_{ss}/F (L)	θ (4)	142	17.1	12.0
Absorption rate constant, ka (1/h)	θ (5)	2.37	0.437	18.4
Inter-individual variability, CL/F	η (1)	0.145 CV = 38.1%	0.0321	22.1
Inter-individual variability, V/F	η (2)	0.376 CV = 61.3%	0.0960	25.5
Residual variability	ε (1)	0.0188 CV = 13.7%	0.00288	15.3

Goodness of fit

Goodness of fit plots from the base model are presented in Figure 2 below:

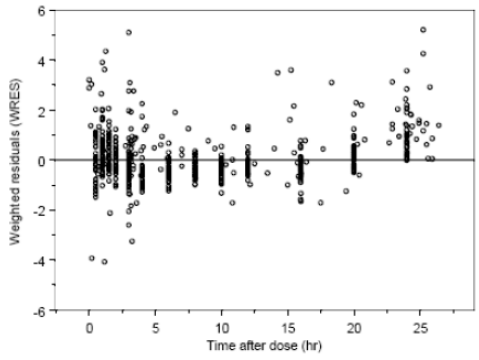
Figure 2: Goodness of fit plots from the base model.

Panel A: IPRE versus observed concentration Panel B: PRED versus observed concentration

(b) (4)

The solid line is the line of unity; the dotted line is obtained from linear regression.

Panel C: WRES versus time after dose Panel D: WRES versus PRED



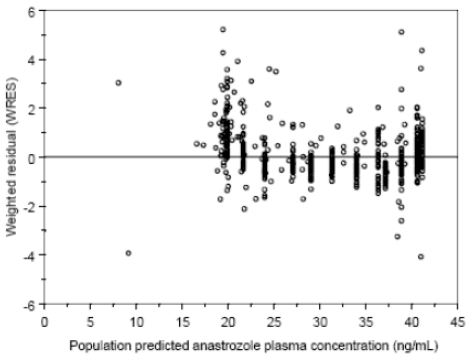
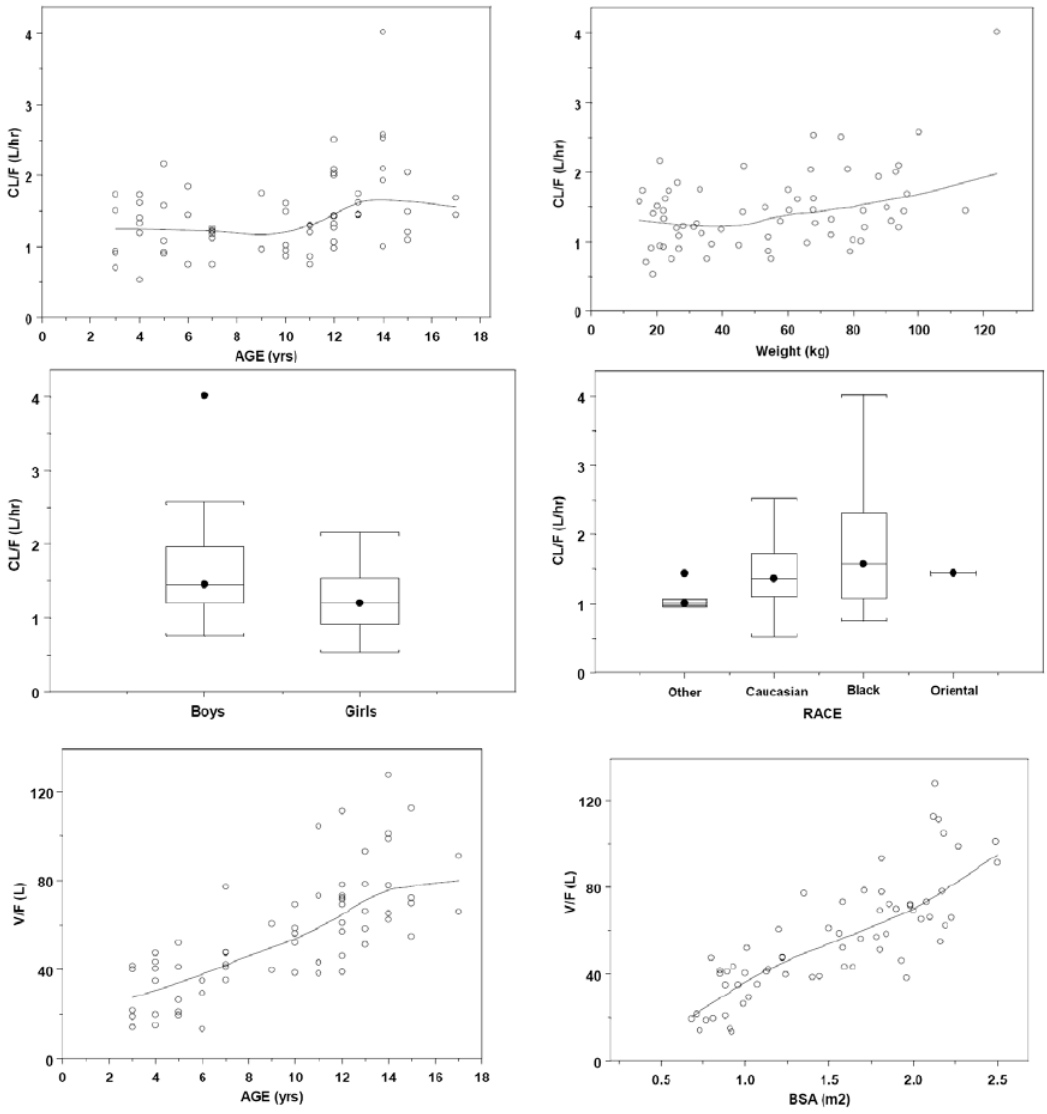


Figure 3: Individual Bayesian estimates of anastrozole apparent oral clearance (CL/F) and apparent central volume of distribution (V/F) versus covariates (base model)



Model Selection

The outcome of initial evaluations indicated that the 2-compartment PO models generally performed better than the 1- or 3-compartment models, which was further confirmed by visual inspection of concentration-time plots. Following evaluation of all the models, a 2-compartment model with first order absorption, with inter-individual variability (IIV) on CL/F and V/F was selected as the best structural model based on the accuracy and reasonability of parameter estimates and goodness-of-fit plots.

Further, this model was modified to examine the impact of using both additive and proportional error terms to model residual variability and was also modified to use an additive residual error model. Although the objective function values (OFVs) for the combined additive and proportional error model (APEM) and additive error model (AEM) were lower than for proportional error model (PEM), PEM was chosen as the best base structural model because of superior parameter estimates, precision of parameter estimates, IIV, residual error, and goodness-of-fit plots.

A total of 7 data points were associated with absolute weighted residuals (WRES) greater than 4 upon fitting this model to the initial data set (ARIMIDEXDATA100.xpt). These data points did not appear to be discordant from the rest of the data with the exception of 1 data point, which had a WRES of 9.76. This datum was consequently identified as pharmacokinetic outlier and excluded from the dataset. Models with proportional, proportional plus additive and additive error were re-evaluated against the final NONMEM dataset (ARIMIDEXDATA101.xpt). Although the OFVs for the APEM and AEM were lower than for PEM, PEM was chosen as the best base structural model because of superior parameter estimates, precision of parameter estimates, IIV, residual error, and goodness-of-fit plots. Weighted residuals were not re-evaluated to further identify pharmacokinetic outliers.

Final Model

Model description

The full multivariable model obtained from forward selection contained a relationship between CL/F and SEX and a relationship between V/F and BSA. The full covariate model obtained after the forward addition of these covariates was significantly degraded by the removal of any covariate terms in the full model; the removal of either SEX on CL/F or BSA on V/F increased the OFV by at least 7.879 points ($p \leq 0.005$). Therefore, this model was considered as the final fully parameterized population pharmacokinetic model.

The final population pharmacokinetic model for anastrozole was a 2-compartment oral model with first-order absorption and elimination, exponential IIV terms for CL/F and V/F, and a proportional residual error term. SEX was found to affect anastrozole CL/F and BSA to affect anastrozole V/F. Comparison of the estimated population pharmacokinetic parameters between the base and final models indicated similar estimates and CIs for the pharmacokinetic parameters. In both, the model parameters were well estimated with the 95% CIs of parameter estimates not including the value zero (0), and the precision of parameter estimates, the relative standard error (RSE), well below 50%. In comparison to the base model, the CV of inter-individual variability of CL/F decreased from 38.1% to 37.8%, and that of V/F decreased from 61.3% to 28.9% in the final model. However, residual variability remained unchanged at 13.7%.

Parameter estimation results

Table 6: Parameter estimates from base and final model

Model Parameters	Parameter	Estimate	SE	RSE, %	95% CI
Base Model (Model 2CPO206)					
Objective Function Value	OFV	2679.367	NA	NA	NA
Apparent oral clearance, CL/F (L/h)	θ (1)	1.47	0.0898	6.11	1.29 to 1.65
Apparent volume of distribution, V/F (L)	θ (2)	40.8	5.49	13.5	30.0 to 51.6
Apparent inter-compartmental clearance, Q/F (L/h)	θ (3)	1.74	0.574	33.0	0.615 to 2.87
Apparent steady state volume of distribution, V_{ss}/F (L)	θ (4)	142	17.1	12.0	108 to 176
Absorption rate constant, ka (1/h)	θ (5)	2.37	0.437	18.4	1.51 to 3.23
Inter-individual variability, CL/F	η(1)	0.145 CV = 38.1%	0.0321	22.1	0.0821 to 0.208
Inter-individual variability, V/F	η(2)	0.376 CV = 61.3%	0.0960	25.5	0.188 to 0.564
Residual variability	ε(1)	0.0188 CV = 13.7%	0.00288	15.3	0.0132 to 0.0244
Final Model (Model COVMOD207)					
Objective Function Value	OFV	2412.647	NA	NA	NA
Apparent oral clearance, CL/F (L/h) CL/F = θ (1)*(1+θ (7)*SEX)	θ (1) θ (7)	1.83 -0.466	0.163 0.0554	8.91 14.0	1.51 to 2.15 –0.594 to –0.338
Apparent volume of distribution, V/F (L) V/F= θ (2)+θ (6)*(BSA–1.58)	θ (2) θ (6)	58.9 52.3	3.20 4.22	5.43 8.07	52.6 to 65.2 44.0 to 60.6
Apparent inter-compartmental clearance, Q/F (L/h)	θ (3)	2.72	0.321	11.8	2.09 to 3.35
Apparent steady state volume of distribution, V_{ss}/F (L)	θ (4)	194	25.8	13.3	143 to 245
Absorption rate constant, ka (1/h)	θ (5)	2.80	0.334	11.9	2.15 to 3.45
Inter-individual variability, CL/F	η(1)	0.143 CV = 37.8%	0.0336	23.5	0.0771 to 0.209
Inter-individual variability, V/F	η(2)	0.0838 CV = 28.9%	0.0232	27.7	0.0383 to 0.129
Residual variability	ε(1)	0.0187 CV = 13.7%	0.00295	15.8	0.0129 to 0.0245

Data source: Appendix R.
Coefficient of variation (CV) was calculated as $(\text{Variance})^{1/2} * 100$ for both random and residual error.
Relative standard error was calculated as Standard Error * 100 / Estimate.
Data were modelled using a 2-compartment model using first-order conditional estimation method. Clearance and volume were modelled with exponential inter-individual variability. Residual error was proportional. The covariate SEX was assigned the value of 1 for girls and 0 for boys.
NA No: applicable; RSE Relative standard error, SE Standard error of the estimate.

Goodness of fit

Diagnostic plots for the final pharmacokinetic model for anastrozole (2-compartment PO model, IIV on CL/F and V/F, PEM) are presented in Figure 4 below.

Figure 4: Goodness of fit plots from the final model

Panel A: IPRE versus observed concentration Panel B: PRED versus observed concentrat

(b) (4)

The solid line is the line of unity; the dotted line is obtained from linear regression.

Panel C: WRES versus time after dose Panel D: WRES versus PRED

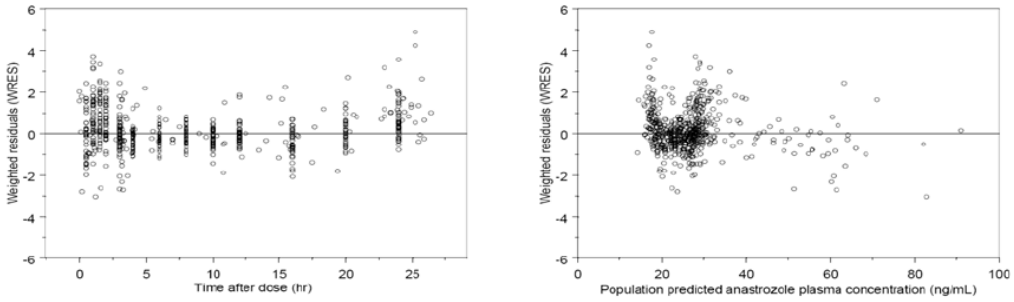


Table 7: Effect of sex on anastrozole apparent oral clearance

SEX	Population estimate of CL/F (L/h) CL/F = θ (1)*(1+θ (7)*SEX)
Girls	0.977
Boys	1.83

Table 8: Effect of body surface area on anastrozole apparent central volume of distribution

Statistics	Body surface area (m^2)	Population estimate of V/F (L) V/F = θ (2) + θ (6)*(BSA–1.58)
Population minimum	0.680	11.8
Population 25th percentile	0.980	27.4
Population median	1.58	58.9
Population 75th percentile	1.98	79.8
Population maximum	2.50	107

Model Qualification

The final population pharmacokinetic model was considered very stable (based on condition number=108) and insensitive to small changes in anastrozole plasma concentrations and sample collection times. However, variation of BSA by 10% resulted in minimal changes in VSS/F of –17.5%, on V/F of –42.6%, and IIV on V/F of 27.7%; misclassification of the sex in 10% of patients resulted in minimal changes in the effect of sex on CL/F of –31.3% and IIV on V/F of 14.8% relative to the final model. This variability does not impact the stability of the model. The predictability of the final model was adequate and unbiased. However, based on the 95% CI of the standard deviation of the mean-squared prediction error (SMPE) obtained by a bootstrap re-sampling technique with 10,000 iterations, the model did not adequately describe the variability in the concentrations. The observed evaluable anastrozole plasma concentrations ranged from 4.2 to 100.0 ng/mL and the predicted concentrations ranged from 14.2 to 91.5 ng/mL, indicating that the final model slightly over and under predicted low and high concentrations, respectively. However, based on the final model there was high concordance between individual-predicted and observed estimates of anastrozole plasma concentrations (R^2=0.91).

Conclusions (Sponsor's)

- A 2-compartment model with first-order absorption and elimination adequately describes the population PK of anastrozole after multiple oral administrations of ARIMIDEX 1 mg in girls with MAS. Inter-individual variability was 37.8% for CL/F and 28.9% for V/F. Residual variability was 13.7%.
- Sex affects CL/F of anastrozole, and BSA affects V/F. Apparent clearance and V/F decreased 30% and 40%, respectively in girls relative to boys.
- Apparent oral clearance and Vss/F of anastrozole in girls <10 y with MAS were 1.14 L/h (range: 0.56 to 1.64 L/h) and 194 L, respectively. At steady state, estimated Cmax was 63.1 ng/mL (range: 35.8 to 108 ng/mL) and AUC was 941 ngh/mL (range: 608 to 1770 ngh/mL). Mean t1/2 in girls was 19.8 h (range: 6.92 to 43.0 h).
- The exposure of anastrozole was higher in girls than boys. The maximum anastrozole plasma concentration and AUC were 70% and 34% higher, respectively, in girls than boys.

Reviewer's Comments

Following are the specific comments/observation of the reviewer:

- Sponsor conducted a systematic and well documented population analysis.
- A 2-compartment model with first order elimination adequately describes the population PK of anastrozole after multiple oral administration of 1 mg ARIMIDEX both in girls with MAS and boys with pubertal gynecomastia.
- Sponsor's conclusion of the gender differences in anastrozole clearance is incorrect. The conclusions of the sponsor's analysis, with regards to the effect of gender on clearance and body surface area (BSA) on volume of distribution, were based on statistical improvement in the analysis. The analysis approach does not take into account the distinct difference in the body weight ranges between the population of boys and girls included in the study. The true gender difference can only be assessed if the weight ranges in the two groups are similar. Further the BSA is a body weight derived parameter.
- The sponsor was issued a letter by the agency identifying the issues with the anastrozole concentration data from study 0046, for which the bioanalytical portion of was conducted by (b) (4) facility. In response to the letter, the sponsor submitted the audit report from (b) (4), an independent third party expert, on the bioanalytical work performed by (b) to assure that the study conducted satisfied the regulatory expectations. The review did not find any issues with the acceptability of the data.

Reviewer's Analysis

Pharmacokinetics

Reviewer's population PK analysis was performed using the data set provided by the sponsor. NONMEM Version V1.1 was run on an IBM Thinkpad laptop computer T60, equipped with a Compaq Visual Fortran compiler. The base model of the sponsor (2 compartment model with first order absorption and first order elimination with IIV on CL and V) was modified to include η-ε interaction term since a proportional error model was used with FOCE. Also VSS was parameterized as VSS = V + θ_j to allow it to be always higher than V.

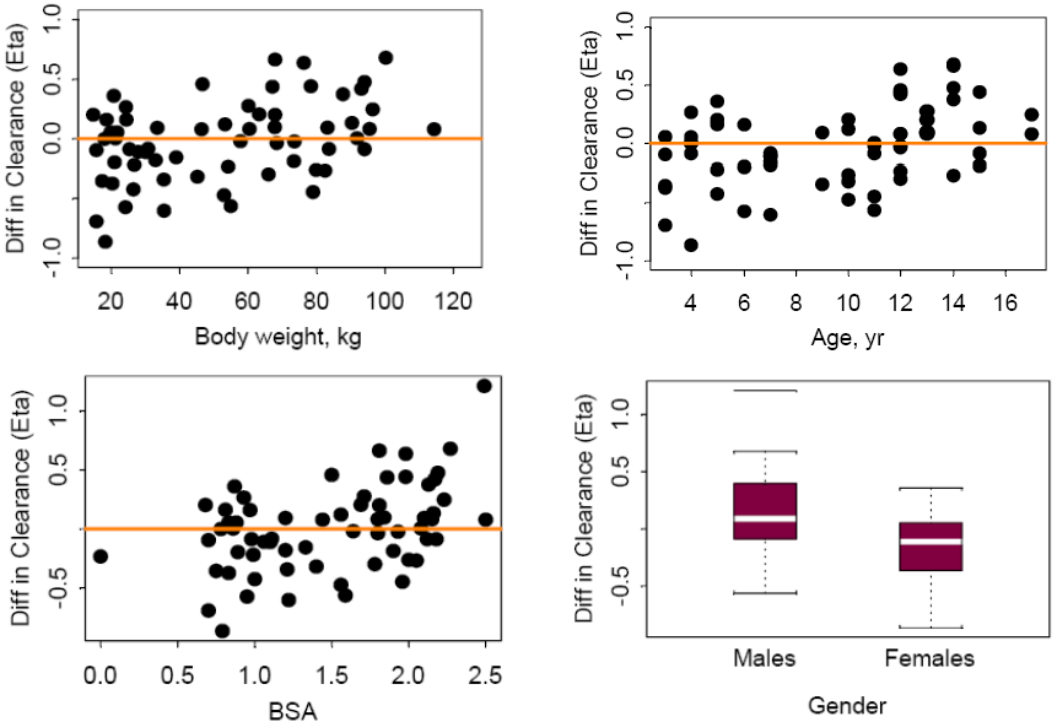
Graphical analysis of the output of the base model (Eta-covariate plots) revealed that body weight, body surface area, gender and age are likely predictors of the between-subject variability in the apparent oral clearance and volume of distribution of anastrozole as shown in **Figure 5**.

It was also seen that bodyweight is correlated with body surface area, age and gender. Hence body weight was the first covariate tested to explain the variability in clearance and volume of distribution of anastrozole as shown in **Figure 6**.

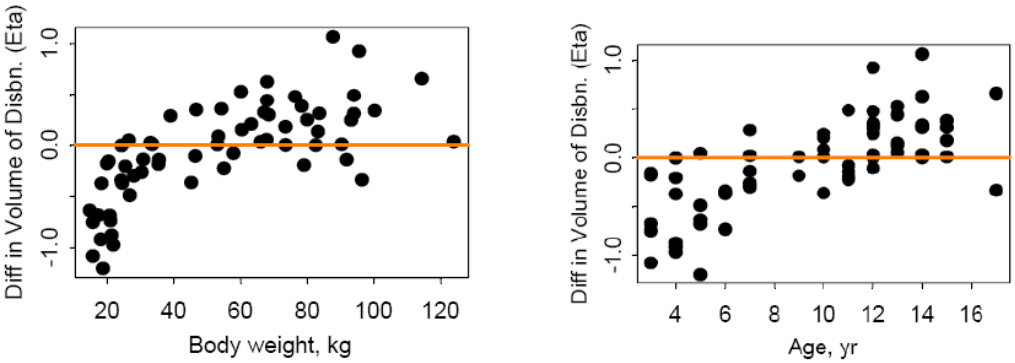
When clearance, volume of distribution and inter-compartmental clearance were adjusted for body weight (as a covariate), no relationship of Gender, BSA, AGE was evident on inter-individual variability (represented by Eta's in the model) in any of the PK parameters of anastrozole as shown in **Figure 7** below.

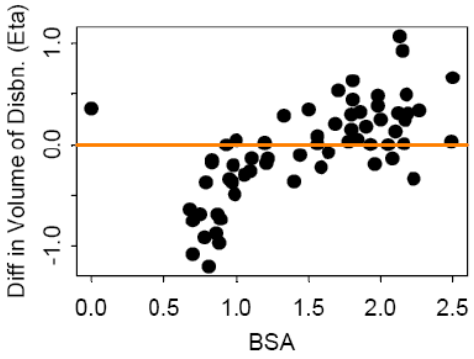
Figure 5: Body weight, body surface area, gender and age are likely predictors of the between-subject variability in the apparent oral clearance and volume of distribution of anastrozole (From base model)

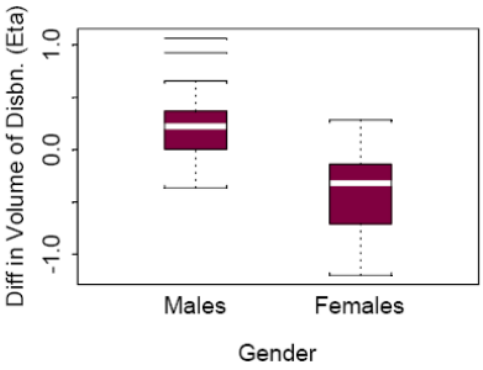
(a) Apparent oral clearance



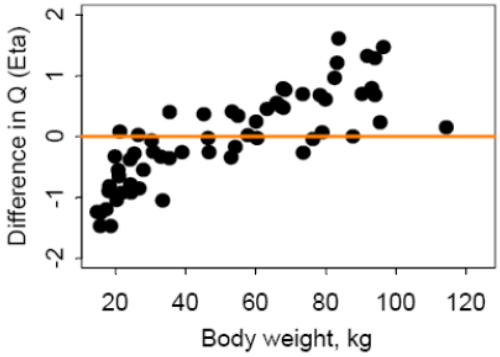
(b) Apparent volume of distribution

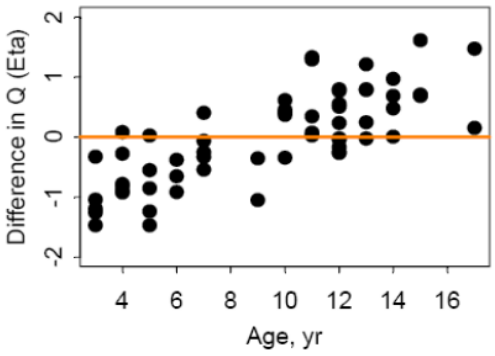


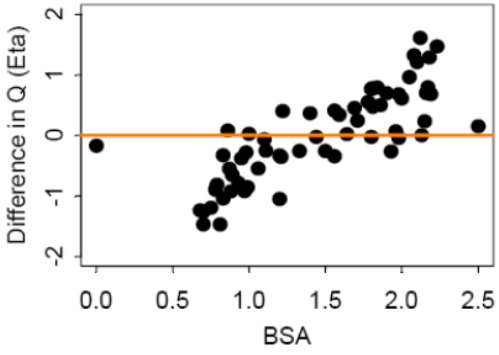




(c) Inter-compartment clearance







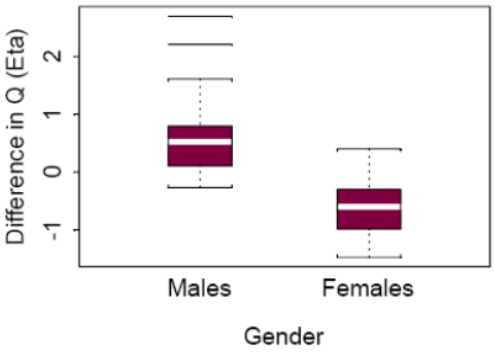


Figure 6: Bodyweight is correlated with age, gender and body surface area

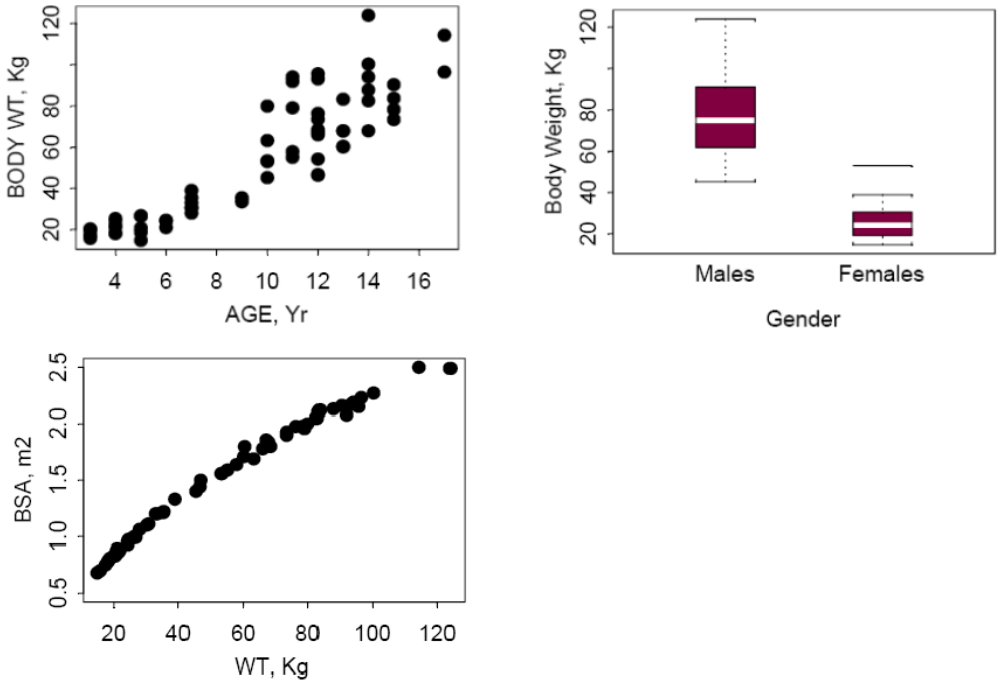
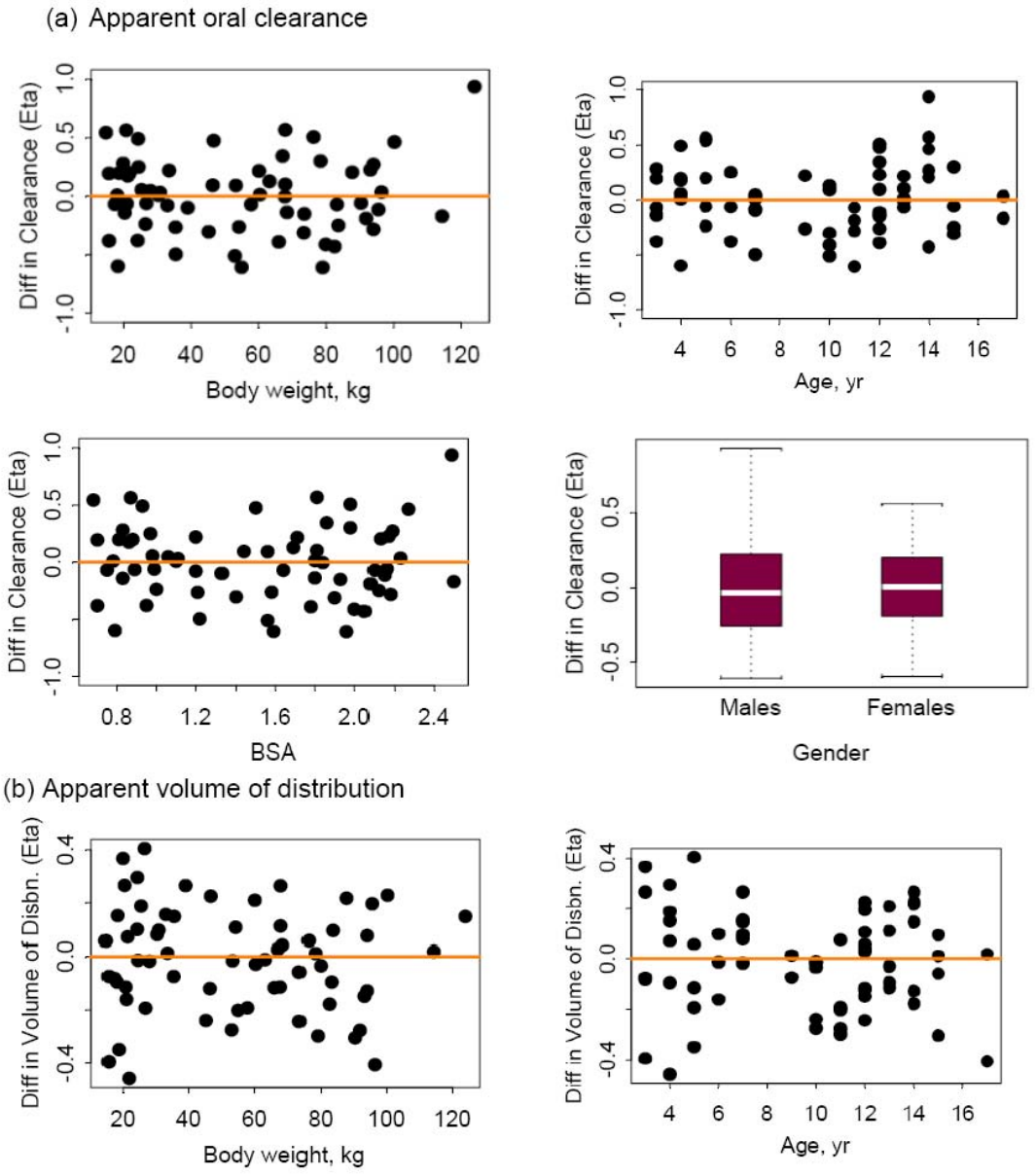
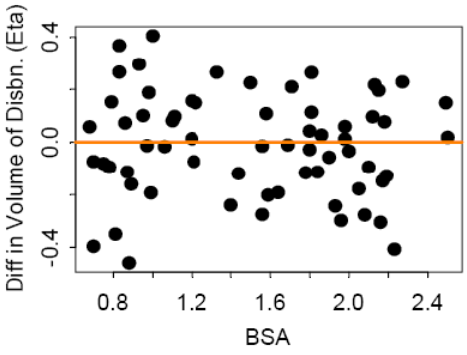
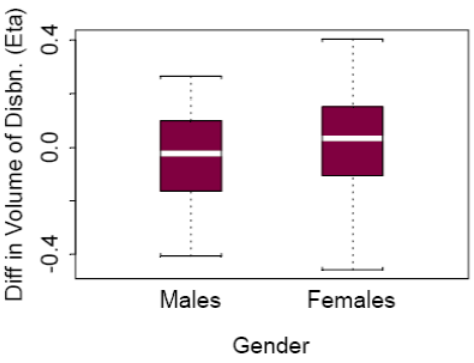


Figure 7: Body weight explains between subject variability of anastrozole apparent clearance and volume of distribution (From final model)







Pharmacodynamics

The graphical evaluation of the data revealed no clear relationship between serum estradiol changes from baseline and changes in total breast volume (in boys with pubertal gynecomastia), or to changes in vaginal bleeding frequency (in girls with MAS). The data was therefore considered insufficient to conduct a meaningful exposure-response analysis and was not pursued further.

Conclusions (Reviewer's)

- The anastrozole apparent clearance and volume of distribution were found to be 1.4 L/hr and 50.5 L, respectively. Body weight accounted for 4% intersubject variability in clearance and 29% intersubject variability in volume of distribution.
- In sponsor's analysis, it was concluded that clearance in girls was different from boys. Hence the effect of gender on the PK of anastrozole was explored. The reviewer noted that the body weight in boys (Study D5394C00001) and girls (Study 1033IL/0046) were significantly different. Therefore, what appears as a gender effect could be an artifact of the inherent differences in body weights between boys and girls. Upon accounting for the effect of body weight on the oral clearance and volume of distribution, the effect of gender disappears.
- Body weight was also correlated with age and BSA in the population evaluated in the current analysis. Upon accounting for the effect of body weight on the oral clearance and volume of distribution, there is no effect of either age or BSA on the PK parameters of anastrozole.

Appendix

Reviewer's Base Model:

2-Compartment Model with first-order absorption CL, V, Q, VSS Parametrization

Differences from Sponsor's base model

- FOCE with (η-ε) Interaction
- Code for VSSj = Vj + θj
- IIV on Q and Ka

Control Stream File:

(b) (4)

(b) (4)

Table 12. Summary of Population PK parameters from the base model

Model Parameters	Parameter	Estimate	%RSE
Objective function value	OFV	2447.754	NA
Apparent oral clearance (CL/F), (L/h)	$\theta 1$	1.35	4.7
Apparent volume of distribution (V/F), (L)	$\theta 2$	43.7	6.1
Apparent inter-compartment clearance (Q/F), (L/h)	$\theta 3$	4.49	17.7
Apparent steady-state volume of distribution (Vss/F), (L)	$\theta 4$	219	11.0
Absorption rate constant (Ka), (1/h)	$\theta 5$	1.87	14.2
Inter-individual variability, CL/F	η_1	0.14 CV=37%	21.5
Inter-individual variability, V/F	η_2	0.29 CV=54%	21.8
Inter-individual variability, Q/F	η_3	1.28 CV=114%	28.3
Inter-individual variability, Ka	η_4	0.41 CV=64%	37.8
Residual Variability	ε	0.01 CV=10%	16.6

Reviewer's Final Model:

2-Compartment Model with first-order absorption CL, V, Q, VSS Parametrization

Differences from Sponsor's final model

- FOCE with (η-ε) Interaction
- Code for VSSj = Vj + θj
- IIV on Q
- WT as allometric covariate on CL, V and Q

Control Stream File:

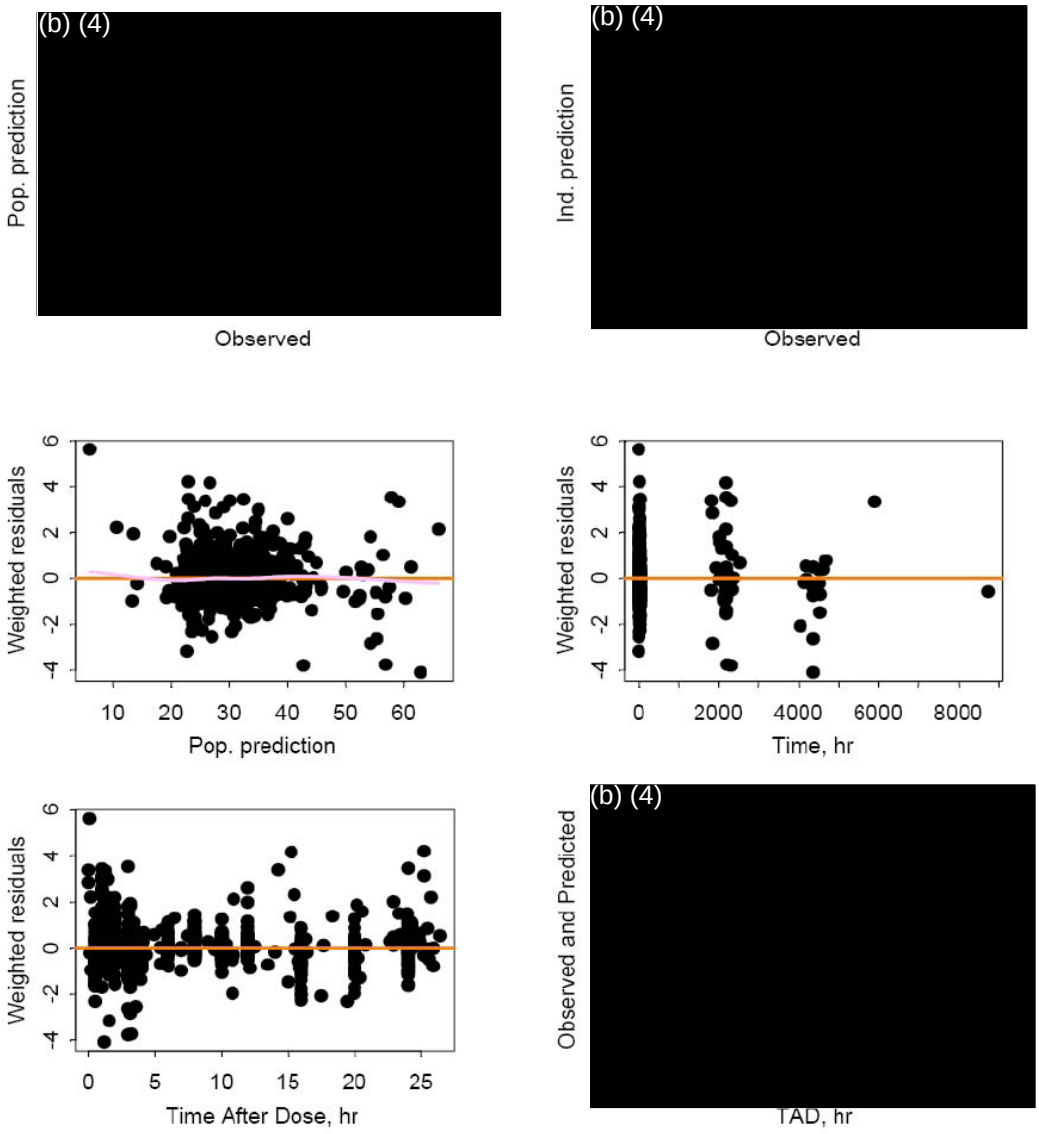
(b) (4)

(b) (4)

Table 12. Summary of Population PK parameters from the final model

Model Parameters	Parameter	Estimate	%RSE
Objective function value	OFV	2298.69 (ΔOFV=149.1)	NA
Apparent oral clearance (CL/F), (L/h)	θ_1	1.4	4.4
Apparent volume of distribution (V/F), (L)	θ_2	50.5	7.6
Apparent inter-compartment clearance (Q/F), (L/h)	θ_3	6.55	20.2
Apparent steady-state volume of distribution (Vss/F), (L)	θ_4	267	46.1
Absorption rate constant (Ka), (1/h)	θ_5	2.06	27.0
Allometric Exponent, CL/F	θ_6	0.298	29.4
Allometric Exponent, V/F	θ_7	0.64	21.6
Allometric Exponent, Q/F	θ_8	1.55	38.6
Inter-individual variability, CL/F	η_1	0.11 CV=33%	17.7
Inter-individual variability, V/F	η_2	0.06 CV=25%	21.8
Inter-individual variability, Ka	η_3	0.57 CV=75%	28.3
Residual Variability	ε	0.01 CV=10%	16.0

Figure 8: Diagnostic plots from the final model (Reviewer's Analysis)



4.3 OCP FILING MEMO

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	22-214/000	Brand Name	Arimidex (Anastrazole)
OCP Division (I, II, III, IV, V)	DCP II	Generic Name	-
Medical Division	DMEP	Drug Class	
OCP Reviewer	Manoj Khurana, Ph.D.	Indication(s)	Treatment of pubertal gynecomastia in boys, and The treatment of precocious puberty in girls with McCune-Albright Syndrome (MAS)
OCP Pharmacometrics Reviewer		Dosage Form	Tablet
OCPB Team Leader	Sally Choe, Ph.D. (Acting)	Dosing Regimen	
Date of Submission	September 4, 2007	Route of Administration	Oral
Estimated Due Date of OCP Review	February 05, 2008	Sponsor	AstraZeneca
PDUFA Due Date	March 05, 2008	Priority Classification	High
Division Due Date			

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
PD:				
Phase 2:	**X**	2	2	**Study 0006:** A randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of anastrozole (ZD1033, ARIMIDEXTM) versus placebo for the treatment of gynecomastia in pubertal boys **Study 0046:** An Open-label Study Evaluating the Safety and Efficacy of Anastrozole (ARIMIDEX™) in the Treatment of Precocious Puberty in Girls with McCune-Albright Syndrome (MAS)
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	**X**	1	1	(Study 0001) An open-label pharmacokinetic and pharmacodynamic study of anastrozole (ARIMIDEX™) used to treat pubertal boys with gynecomastia of recent onset
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**X**	1	1	Population pharmacokinetics for anastrozole (ARIMIDEX) in pediatric girls with McCune-Albright Syndrome (MAS) (Study 0046) and PK data from Study 0001 included in the Population PK analysis
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution: (IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**4**		

Filability

	"X" if yes	Comments
Application filable?	**X**	**Comments to the Sponsor:** For Study 0046 titled, "An Open-label Study Evaluating the Safety and Efficacy of Anastrozole (ARIMIDEX™) in the Treatment of Precocious Puberty in Girls with McCune-Albright Syndrome (MAS)", the pharmacokinetic sample analysis was conducted in three parts by (b) (4) (b) (4) (b) (4) on following dates: *Part* / *Start Analysis* / *End Analysis* 1 / 15-Jan-2004 / 21-Jan-2004 2 / 14-Jan-2005 / 27-Jan-2005 3 / 08-Nov-2005 / 11-Nov-2005 The analysis date for Part 1 falls under the period (January 2000 to December 2004) for which Agency issued the letter (Feb 1, 2007) to Sponsors regarding the significant concerns about the validity of the bioanalytical studies conducted by (b) (4) (b) (4) Therefore, the Agency requests the sponsor to address this concern by conducting one of the following, in order of preference: • Repeat the study (0046). • Re-assay the samples for anastrazole at a different bioanalytical facility. For this option, the integrity of the original samples must be demonstrated for the frozen storage period. • Commission a scientific audit by a qualified independent expert, who is knowledgeable in the area of clinical pharmacology studies and bioanalytical data, and selected by the sponsor's company rather than by (b) , to verify the results obtained by (b)

Submission in Brief:
See the details below.

Reviewer's Comments: For Study 0046, the sample analysis was conducted by (b) (4) (b) (4) Study: AA15048-CJY) on following dates:

Part	*Start analysis*	*End analysis*
1	15-Jan-2004	21-Jan-2004
2	14-Jan-2005	27-Jan-2005
3	08-Nov-2005	11-Nov-2005

Around 60% of the samples were received and analyzed during Part 1 of the analysis as per the following information from the bioanalytical report for Study 0046:

Part	*Date of Shipment*	*USA/EURO*	*Receipt Date at* (b) (4)	*Number of Samples Received and analyzed*
1	06-Oct-2003	USA	07-Oct-2003	8
1	06-Oct-2003	EURO	08-Oct-2003	56
1	02-Dec-2003	USA	03-Dec-2003	5
2	08-Nov-2004	USA	09-Nov-2004	7
2	09-Nov-2004	EURO	11-Nov-2004	18
3	06-Sep-2005	EURO	08-Sep-2005	17
			Total	111

The validity of data from Part 1 analysis is under question as the analysis date for this part fall under the period (January 2000 to December 2004) (b) (4) (b) (4) regarding the deficiencies identified by the Agency with the (b) audit on the analysis conducted during this period.
However, for Study 0001, the sample analysis was conducted by (b) (4) (b) (4) Project No. AA25112-ADU) between 09 Jan 2006 and 13 Jul 2006.

Clinical Pharmacology Review will focus on study results from Study 0001, 0006, 0046, population PK analysis result, (b) (4) once the sponsor addresses the issue with their data. Subsequently, a pharmacometric review consult will be placed with the PM division for the population PK analysis.

Submission in Brief:

The sponsor, AstraZeneca Pharmaceuticals LP (AstraZeneca), submitted this NDA that provides safety, efficacy and pharmacokinetic information on the use of ARIMIDEX (anastrozole) in male pubertal patients with gynecomastia and female pediatric patients with McCune-Albright syndrome with progressive precocious puberty. This NDA is filed [redacted]. Sponsor made the reference to the FDA Pediatric Written Request dated May 9, 2001, revised on July 2, 2002, and as amended November 19, 2002 (amendment #1), December 19, 2003 (amendment #2), May 7, 2004 (amendment not numbered), April 8, 2005 (amendment #4), which requested the submission of information on the safety, efficacy, and pharmacokinetics of ARIMIDEX® (anastrozole) in pubertal boys in the treatment of gynecomastia and in pediatric patients with McCune-Albright Syndrome.

The application contains two studies that were conducted to investigate the PK of anastrozole in pediatric patients:

- Study D5394C00001; also referred to as Study 0001 in the submission (FDA Written Request reference "Study 3")
- A population PK study (FDA Written Request reference "Study 4") in girls enrolled in Study 1033IL/0046 - D5394C00046 (also referred to specifically as the "Study 0046 [Population PK report]")

Sponsor also conducted safety and efficacy study of anastrazole for the treatment of gynecomastia in pubertal boys and female pediatric patients with McCune-Albright syndrome with progressive precocious puberty, reported under Study 0006 and Study 0046, respectively.

The results from Study No. 0001, Study 0006 and Study No. 0046 are described in Attachment 1.

ATTACHMENT 1

Study No. 0001:

Title: An open-label pharmacokinetic and pharmacodynamic study of anastrozole (ARIMIDEX™) used to treat pubertal boys with gynecomastia of recent onset

Trial and Analytical Sites:
Coordinating investigator: (b) (4), (b) (4), United States of America (USA).

Study centre(s): Patients were enrolled from 2 centers in the USA.

Study dates: First patient enrolled 16 June 2005, Last patient completed 7 November 2006

Analytical Site for this study was (b) (4) (b) (4)
Date(s) of sample receipt: 15-Dec 2005 to 10-May 2006
Date bioanalysis started: 09 Jan 2006
Date bioanalysis completed: 13 Jul 2006

Investigational product:
Anastrozole (ZD1033, ARIMIDEX™) 1 mg tablet, orally once daily. The formulation number was F11292 and batch numbers were 2000077658, 2000083628, 2000085466 and 2000088657.

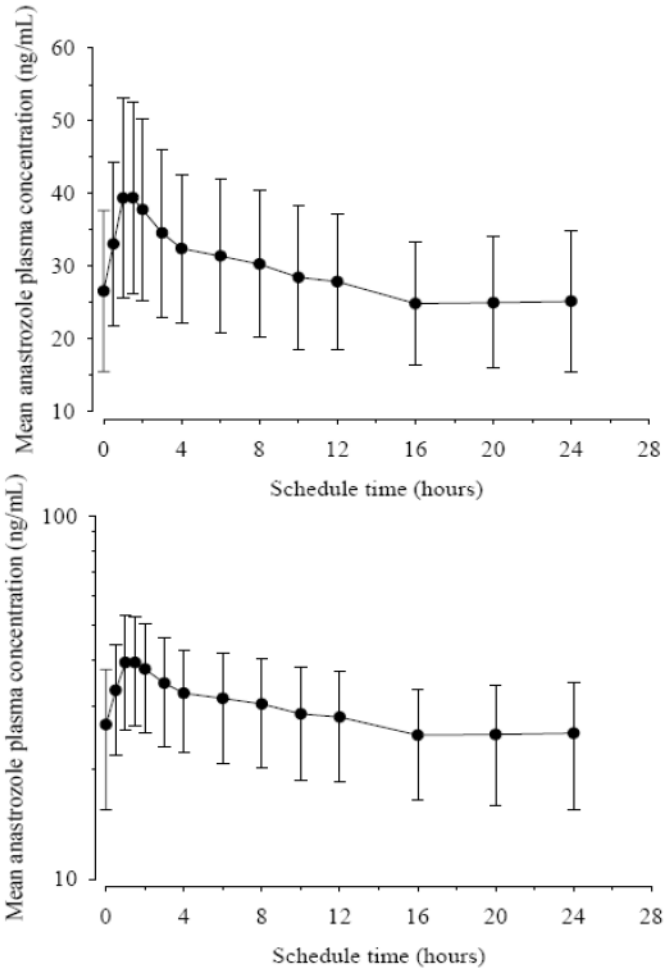
Primary Objective:
The primary objective of this study was to assess anastrozole PK in boys aged 11 to 18 years (after his 10th and prior to his 19th birthday) with pubertal gynecomastia of less than 2 months' duration.

Study Design:
Study 0001 was a multi-centre, single-arm, open-label PK, phase II study in which boys with pubertal gynecomastia of a recent onset were given anastrozole 1 mg daily for 6 months. The key inclusion criteria for this study were: male aged between 11 and 18 years (after his10th and prior to his 19th birthday); gynecomastia, one breast measuring $\geq$ 2 cm in diameter (by ultrasound or caliper measurement) that had not decreased during the prior 3-month period by clinical history and had been present for less than 12 months; normal renal, liver, and thyroid function; no evidence of hormone-producing tumor; no evidence of hypogonadism or androgen resistance; provision of informed consent of parent/legal guardian and patient consent. The study was designed to have 24 boys complete the study. Commercial ARIMIDEX (anastrozole 1 mg oral tablet) was used in the study and patients were dosed daily for a treatment period of 6 months. Blood samples were drawn for PK analysis over a 24-hour period at steady state (Visit 3, $\geq$ 14 days after commencing dosing). The following PK parameters were used to meet the PK primary objective: maximum anastrozole plasma drug concentration (Css,max), minimum anastrozole plasma concentration (Css,min), time to reach the maximum anastrozole concentration (tmax), area under plasma concentration-time curve at the steady-state (AUCss), apparent oral clearance (CL/F), and apparent volume of distribution during terminal phase (Vz/F).

Study Results:

Pharmacokinetics:

Figure 1 **Anastrozole plasma concentration[1] versus time after multiple oral administration of anastrozole 1 mg once daily (Study 0001: PK population)**



[1] (Arithmetic mean [± standard deviation] shown. Upper figure linear; lower figure semi-logarithmic)

Table 2 Summary statistics for steady state PK parameters estimates (Study 0001: PK population)

Parameter[a, b]	Statistic					
	N	Geometric mean	CV%	Median	Minimum	Maximum
$C_{ss,max}$ (ng/mL)	36	39.3	34.3	41.4	17.2	75.6
t_{max} (h)	36	-	-	1.00	0.50	3.00
$C_{ss,min}$ (ng/mL)	36	21.5	44.1	22.1	6.05	47.2
AUC_{ss} (ng.h/mL)	36	648	37.0	682	221	1300
CL/F (L/h)	36	1.54	37.0	1.47	0.771	4.53
V_z/F (L)	36	98.4	42.6	100	50.7	330

[a] For all PK analyses, pre-dose sample times were assigned a value of '0-hour'.
[b] The PK parameters for Study 0001 were conducted using non-compartmental analysis method
AUC_{ss}, area under the curve at steady state; CL/F, apparent oral clearance; $C_{ss,max}$, maximum anastrozole plasma concentration; $C_{ss,min}$, minimum anastrozole plasma concentration; CV, coefficient of variation (geometric CV presented); t_{max}, time to reach the maximum anastrozole concentration; V_z/F, apparent volume of distribution during terminal phase.
Data derived from Table 23 Study 0001 CSR.

Table 3 Effects of baseline covariates on PK parameters

Statistic	Parameter	
	Apparent oral clearance (CL/F)	Apparent volume of distribution (V_z/F)
R^2	0.18	0.18
P-value[a] for age	0.26	0.93
P-value[a] for weight	0.15	0.03

[a] Statistically significant at p-values ≤0.05
R^2, coefficient of determination
Data derived from Table 24 in the Study 0001 CSR.

Pharmacodynamics:

Table 25 Hormone levels and change from baseline (PD population)

		Anastrozole 1 mg (N=25)		
	n	Mean (SD)	95% CI	Range
Testosterone (nmol/L)				
Baseline	25	5.55 (5.14)	3.43, 7.67	0.76 to 16.02
Month 6	25	13.29 (7.40)	10.24, 16.35	1.38 to 24.70
Change from baseline to Month 6	25	7.74 (4.92)	5.71, 9.77	-0.45 to 17.27
Percent change, baseline to Month 6	25	285.90 (251.74)	181.99, 389.82	-4.00 to 847.40
Estradiol (sensitive assay) (pmol/L)				
Baseline	24	16.81 (15.39)	10.31, 23.31	9.18 to 72.30
Month 6	24	11.17 (4.25)	9.37, 12.96	9.18 to 23.86
Change from baseline to Month 6	23	-5.89 (14.30)	-12.07, 0.30	-63.12 to 5.87
Percent change, baseline to Month 6	23	-13.17 (29.47)	-25.91, -0.43	-87.30 to 48.50
Testosterone/estradiol ratio				
Baseline	24	377.79 (323.82)	241.05, 514.53	50.20 to 1266.90
Month 6	24	1227.84 (720.94)	923.41, 1532.27	150.30 to 2690.60
Change from baseline to Month 6	23	932.43 (599.59)	673.15, 1191.71	-329.20 to 1881.20
Percent change, baseline to Month 6	23	465.69 (644.50)	186.99, 744.39	-35.30 to 3241.80
FSH (IU/L)				
Baseline	25	1.98 (1.09)	1.53, 2.43	0.60 to 4.50
Month 6	25	3.85 (2.04)	3.01, 4.69	1.40 to 10.50
Change from baseline to Month 6	25	1.87 (1.65)	1.19, 2.55	-0.40 to 7.10
Percent change, baseline to Month 6	25	125.80 (114.24)	78.65, 172.96	-12.50 to 400.00
LH (IU/L)				
Baseline	25	1.55 (1.42)	0.96, 2.14	0.10 to 4.50
Month 6	25	3.56 (2.06)	2.71, 4.41	0.70 to 7.80
Change from baseline to Month 6	25	2.01 (1.61)	1.34, 2.67	-0.90 to 5.70
Percent change, baseline to Month 6	25	536.63 (890.40)	169.09, 904.17	-28.10 to 4000.00
SHBG (nmol/L)				
Baseline	25	21.64 (7.31)	18.62, 24.66	5.00 to 34.00
Month 6	25	18.08 (7.29)	15.07, 21.09	7.00 to 34.00
Change from baseline to Month 6	25	-3.56 (6.67)	-6.31, -0.81	-15.00 to 18.00
Percent change, baseline to Month 6	25	-11.87 (34.65)	-26.18, 2.43	-60.00 to 112.50

CI Confidence interval; FSH Follicle-stimulating hormone; LH Luteinizing hormone; SD Standard deviation; SHBG Sex-hormone binding globulin.
Data derived from Table 11.2.4.1.1, Section 11.2. Confidence intervals are presented in Appendix 12.1.9.

Study No. 0046:

Title: An Open-label Study Evaluating the Safety and Efficacy of Anastrozole (ARIMIDEX™) in the Treatment of Precocious Puberty in Girls with McCune-Albright Syndrome (MAS)

Trial and Analytical Sites:
Patients were enrolled from 14 centers in 7 countries: France (3) Germany (3), Italy (1), Russia (1), Spain (1), United Kingdom (1) and United States (5).

Study dates: First patient enrolled 23 October 2002, Last patient completed 6 February 2006

Analytical Site for this study was [redacted]. Sample analysis dates are as follows:

Part	*Start analysis*	*End analysis*
1	15-Jan-2004	21-Jan-2004
2	14-Jan-2005	27-Jan-2005
3	08-Nov-2005	11-Nov-2005

Study Design:

This was an international, multi-center, open-label, exploratory study to examine potential clinical efficacy, tolerability and safety of a 1 mg daily dose of anastrozole, given to girls with MAS, over a treatment period of 12 months.

Investigational Products:

Anastrozole (ZD1033, ARIMIDEX™) 1 mg tablet, orally once-daily. The formulation numbers and batch numbers are shown in Table S1.

Table S1 Details of investigational product and any other study treatments

Investigational product or other treatment	Dosage form and strength	Manufacturer	Formulation number	Batch number
Anastrozole	1 mg oral tablet	AstraZeneca	F011292	12865H03, 22683I04, 82954C01, 82955K01, 90695F02, 93033A02, 93034I02, 93037K02
			MP001624	2000037400, 2000047082, 2000049687, 2000066148, 2000076213, 2000082747, 2000087319
			MP001625	2000059927, 2000067877, 2000076362, 2000086766

Objectives
The primary objective of this study was to evaluate the safety and efficacy of anastrozole (daily 1 mg dose) for the treatment of McCune-Albright Syndrome (MAS) in girls up to the age of 10 years, receiving treatment for 1 year. The tolerability and safety of study treatment was assessed by assessment of adverse events, withdrawals and laboratory data. The efficacy of study treatment was assessed based on the change from baseline measurements relating to vaginal bleeding, bone age, and growth velocity.

Secondary objectives included assessments of pubertal progression through Tanner Staging and mean ovarian and uterine volume as assessed by ultrasound, bone growth by assessment of predicted adult height for children aged over 6 years and pharmacokinetic assessment.

Study Results:

Efficacy and pharmacokinetic results

- There was a slight increase in the frequency of bleeding days during treatment compared to baseline (median increase of 1.9 days) (b) (4) (b) (4)
- Seven (28%) of the 25 patients with baseline vaginal bleeding experienced a ≥50% reduction in the frequency of vaginal bleeding days on treatment
- Ten (40%) of the 25 patients with baseline vaginal bleeding experienced a cessation in vaginal bleeding on treatment over a 6-month (ie, ≥180 days) study period. Three (12%) of those 10 patients experienced a cessation in vaginal bleeding on treatment over the whole 12-month study period (ie, from Day 1 to Day 360)
- The mean (and median) rate of increase in bone age decreased from the 6-month pre-baseline period over the 12-month on treatment period, with a slightly greater decrease in rate over the second 6 months of treatment. The change in rate of increase (b) (4) for pre-treatment to during treatment, pre-treatment to the first 6 months of treatment, or for pre-treatment to the second 6 months of treatment
- Growth rate (in cm/year) was (b) (4) reduced ($p<0.05$) from pre-treatment to during treatment (Month 0 to Month 12) (median change –2.1 cm/year; $p=0.0356$), and from pre-treatment to the second 6 months of treatment (median change -2.2 cm/year; $p=0.0186$). Growth rate (in Z-score) changes (b) (4) (b) (4) showed a trend in reduction consistent with the growth rate in cm/year
- There was (b) (4) in breast or pubic Tanner staging from pre-treatment to end of treatment
- There (b) (4) in mean ovarian volume or mean uterine volume compared to screening, although marked variations in recordings were observed
- (b) (4) mean predicted adult height compared to screening. An increase of 0.9 cm in mean predicted adult height was observed following 12 months of study treatment, which corresponds to a 0.6 percent change
- Serum estradiol and serum estrone levels appeared to decrease over the first
- 6 months and then increase slightly during the second 6-month interval, while little to no change in dehydroepiandrosterone (DHEA) sulfate and testosterone was observed. Although follicle-stimulating hormone (FSH) is not as strong a marker as luteinizing hormone (LH) for central puberty, there was no obvious reason for their changes over time
- A detailed presentation of the population PK analysis of anastrozole in the pediatric MAS population was provided in an accompanying stand-alone

population PK report entitled: Population pharmacokinetic analysis of anastrozole in pediatric girls with McCune-Albright syndrome and pubertal boys with gynecomastia

- The results based on the protocol-valid population from the primary analysis population.

Results of Population PK analysis:

Table 4 Summary of typical anastrozole population pharmacokinetic parameters of the final model (first-order conditional estimate)

Model parameters	Estimate (standard error)	95% confidence interval
Apparent oral clearance, CL/F (L/h)	1.83 (0.163)	1.51 to 2.15
Volume of distribution, V/F (L)	58.9 (3.20)	52.6 to 65.2
Inter-compartmental clearance, Q/F (L/h)	2.72 (0.321)	2.09 to 3.35
Steady-state volume of distribution, V_{ss}/F (L)	194 (25.8)	143 to 245
Absorption rate constant, ka (1/h)	2.80 (0.334)	2.15 to 3.45
Effect of body surface area on V/F V/F = θ (2) + θ (6)*(BSA–1.58)	52.3 (4.22)	44.0 to 60.6
Effect of sex on CL/F CL/F = θ (1)*(1+θ (7)*SEX)	–0.466 (0.0654)	–0.594 to –0.338
Inter-individual variability, CL/F	0.143 (0.0336) CV = 37.8%	0.0771 to 0.209
Inter-individual variability, V/F	0.0838 (0.0232) CV = 28.9%	0.0383 to 0.129
Residual variability	0.0187 (0.00295) CV = 13.7%	0.0129 to 0.0245

CV Coefficient of variation

Data derived from Table S1 of the Study 0046 population PK report.

Table 5 Bayesian estimates of individual model-predicted pharmacokinetic parameters (Final model)

Parameters	Girls			Boys
	3 to 6 y N=19	7 to 10 y N=9	All Girls N=28	All Boys N=36
CL/F (L/h)				
Mean (SD)	1.16 (0.327)	1.12 (0.253)	1.14 (0.301)	1.62 (0.660)
Median	1.16	1.17	1.17	1.46
Range	0.565 to 1.64	0.746 to 1.62	0.565 to 1.64	0.753 to 4.24
CL/F/kg (L/h/kg)				
Mean (SD)	0.0566 (0.0189)	0.0330 (0.0103)	0.0490 (0.0199)	0.0218 (0.00810)
Median	0.0540	0.0331	0.0463	0.0214
Range	0.0307 to 0.0964	0.0162 to 0.0484	0.0162 to 0.0964	0.0108 to 0.0453
V/F (L)				
Mean (SD)	23.8 (7.84)	44.0 (9.65)	30.3 (12.7)	75.1 (23.9)
Median	23.5	43.3	28.4	72.3
Range	12.4 to 40.2	30.1 to 57.3	12.4 to 57.3	38.3 to 131
V_{ss}/F (L)				
Mean (SD)	194 (–)*	194 (–)*	194 (–)*	194 (–)*
C_{max} (ng/mL)				
Mean (SD)	68.2 (17.0)	52.3 (9.23)	63.1 (16.6)	37.2 (11.5)
Median	65.7	51.1	59.6	36.9
Range	43.3 to 108	35.8 to 67.6	35.8 to 108	14.5 to 67.6

Table 5 Bayesian estimates of individual model-predicted pharmacokinetic parameters (Final model)

Parameters	Girls			Boys
	3 to 6 y N=19	7 to 10 y N=9	All Girls N=28	All Boys N=36
AUC_{ss} (ng·h/mL)				
Mean (SD)	943 (312)	938 (215)	941 (280)	701 (237)
Median	859	857	858	686
Range	608 to 1770	617 to 1340	608 to 1770	236 to 1330
$t_{1/2}$ (h)				
Mean (SD)	15.7 (8.57)	28.5 (9.02)	19.8 (10.5)	34.6 (11.9)
Median	12.4	26.8	16.8	29.7
Range	6.92 to 39.8	17.7 to 43.0	6.92 to 43.0	19.3 to 62.3
Q/F (L/h)				
Mean (SD)	2.72 (–)*	2.72 (–)*	2.72 (–)*	2.72 (–)*
ka (L/h)				
Mean (SD)	2.80 (–)*	2.80 (–)*	2.80 (–)*	2.80 (–)*

* Steady state total apparent volume of distribution, inter-compartmental clearance, and absorption rate constant were modelled as constant across subject (ie, without random inter-individual error term); therefore, all subjects had a similar estimate for V_{ss}/F, Q/F, and ka.

AUC_{ss} Area under the plasma concentration-time curve at steady state; CL/F Apparent oral clearance; C_{max} Maximum anastrozole plasma concentration; ka Absorption rate constant; SD Standard deviation of the estimate; $t_{1/2}$ Terminal elimination half life; V/F volume of central compartment; V_{ss}/F Apparent volume of distribution at steady state; Q/F Apparent inter-compartment clearance.

Data derived from Table 18 of the Study 0046 population PK report.

Study 0006:

Title: A randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of anastrozole (ZD1033, ARIMIDEXTM) versus placebo for the treatment of gynecomastia in pubertal boys (1033US/0006)

Trial and Analytical Sites:
Study center(s)
This study was conducted in 24 centers in the USA.
International Co-ordinating investigator for this study was:
Edward Reiter, MD
Chairman, Department of Pediatrics, Baystate Medical Center-Children's Hospital
759 Chestnut Street, Springfield, MA 01199

Study Design:

Study 0006 was a randomized, double-blind, placebo-controlled, multicenter study in which 80 boys (aged 11 to 18 years inclusive) received either anastrozole 1 mg or placebo daily for up to 6 months for the treatment of pubertal gynecomastia. The primary response variable was a ≥50% reduction in the calculated volume of gynecomastia of both breasts as measured by ultrasound. Secondary variables were; complete regression of gynecomastia, actual and percent change in calculated volume, pain response, emotional/psychological effects, change in hormone levels and height. Safety and tolerability were assessed by adverse event (AE) reporting, withdrawals and laboratory data.

Investigational Products:
AstraZeneca ZD1033 (Anastrozole, ARIMIDEX®), 1 mg orally, daily, and placebo for ARIMIDEX. Formulation number for anastrozole (1 mg) was F11292 (ADM3833097; US Analytical #: N83014A); and for the placebo for anastrozole, F11314 (Manufacturing #9026A; US Analytical #: N83091A).

Objectives: The primary objective was to determine whether anastrozole was more effective than placebo in the treatment of gynecomastia in pubertal boys as assessed by changes in breast tissue size and symptoms. Secondary objectives were to assess the safety and tolerability of anastrozole.

Study Results:
Efficacy: The response rates for a total breast volume decrease ≥50% were 38.5% (15/39) and 31.4% (11/35) for anastrozole and placebo, respectively (odds ratio = 1.513, 95% CI 0.496 to 4.844, p=0.4687). One patient in the anastrozole group had complete regression of gynecomastia after 6 months of therapy. The testosterone/estradiol ratio after 6 months was 171 ± 143 (mean ± standard deviation [SD]) in the anastrozole group compared with 35 ± 114 in the placebo group which reflected the pharmacodynamic activity of anastrozole. There were no treatment group differences in the changes of absolute values of breast volumes, or of height, weight, or body mass index [BMI]. Breast pain was resolved in 90.9% (10/11) in the anastrozole group and 100% (9/9) in the

placebo group. There were no treatment group differences in the Behavioral Assessment System or Focused Gynecomastia Questionnaire scores.

Safety: Mean exposures to anastrozole and placebo in this study were 182.0 and 183.5 days, respectively. Anastrozole was well tolerated. AEs were reported by 77% and 65% of patients in the anastrozole and placebo groups, respectively. Over 99% of events were reported as mild or moderate and with the exception of rash (9.0% [4/43] for anastrozole vs 0 for placebo), specific AEs were reported by similar proportions in the 2 treatment groups. The most common AEs for both groups were childhood illnesses and conditions deemed typical for a pediatric population (eg, headache, pharyngitis, rhinitis, acne, sinusitis, accidental injury, pain and rash). There were no deaths or serious AEs in this study. One patient in the anastrozole group withdrew due to an AE (increased testicular volume) that was considered by the investigator to be possibly related to treatment.

Conclusions: (b) (4) [redacted]. There were no safety or tolerability concerns arising from this study.

4.4 PEDIATRIC WRITTEN REQUEST

Annotated Written Request for Arimidex® (anastrozole) tablets

Text From April 8, 2005 Written Request (Amendment #4)

Please refer to your October 28, 2004 correspondence to IND 62,138 requesting changes to FDA's December 19, 2003 Written Request Amendment #2 (as amended by the unnumbered amendment dated May 7, 2004) for pediatric studies for ARIMIDEX (anastrozole) tablets.

We reviewed your proposed changes and are amending the Written Request. For convenience, the full text to the Written Request, as amended, follows, with highlighted (**Bold**) text denoting changes. This Written Request supersedes the Written Request dated May 9, 2001, as revised July 2, 2002, and as amended November 19, 2002 (amendment #1), December 19, 2003 (amendment #2), and May 7, 2004 (amendment not numbered).

Types of studies:

Study 1. [1]A six-month, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of anastrozole in pediatric patients with moderate-to-severe pubertal gynecomastia.

1. Refer to Module 1.9.6, 20 November 2006 page 3 - Refer to NDA 20-541 and IND 62,138, Serial No. 30, 20 August 2003, for Clinical Study Report (CSR) for Trial 1033US/0006 entitled "A Randomized, Double-blind, Placebo-controlled Trial to Assess the Safety and Efficacy of Anastrozole (ZD1033, ARIMIDEX™) versus Placebo for the Treatment of Gynecomastia in Pubertal Boys".

Study 2.	[2]A one-year, open-label, multicenter study to assess the efficacy and safety of anastrozole in pediatric patients with McCune Albright Syndrome (MAS).	2. Refer to Module 5.3.5.2, the CSR for Trial 1033IL/0046 (D5394C000046) entitled "An Open-label Study Evaluating the Safety and Efficacy of Anastrozole (ARIMIDEX™) in the Treatment of Precocious Puberty in girls with McCune-Albright Syndrome".
Study 3.	[3]A pharmacokinetic (PK) study of anastrozole in male pediatric patients with pubertal gynecomastia.	3. Refer to Module 5.3.3.2, the CSR for Trial D5394C00001 entitled "An open-label pharmacokinetic and pharmacodynamic study of anastrozole (ARIMIDEX™) used to treat pubertal boys with gynecomastia of recent onset".
Study 4.	[4]A PK study in pediatric patients enrolled in Study 2.	4. Refer to Module 5.3.3.5, the CSR for Trial D5394000000 entitled "Population pharmacokinetic report for anastrozole (ARIMIDEX®) in pediatric girls with McCune-Albright syndrome".
Objectives/rationale *(indications to be studied):*		5. Refer to Module 1.9.6, 20 November 2006, page 3 – Also Refer to NDA 20-541 and IND 62,138, Serial No. 30, 20 August 2003, for CSR 1033US/0006, Section 4 – Objectives, Section 7 – Efficacy Results and Section 8 – Safety Results.
[5]Study 1. To assess the safety and efficacy of anastrozole in reversing breast development in boys with severe pubertal gynecomastia.		
[6]Study 2. To assess the safety and effectiveness of anastrozole in slowing the progression of puberty in girls with gonadotropin-independent precocious puberty due to MAS.		6. Refer to Module 5.3.5.2 for CSR 1033IL/0046, Section 4.1 – Primary Objectives and Section 7 - Efficacy and Pharmacokinetic Results.

[7]Study 3. Primary: to assess anastrozole PK in boys with pubertal gynecomastia and Secondary: to explore the effectiveness of anastrozole in reversing breast development in boys with moderate-to-severe pubertal gynecomastia of shorter duration than that evaluated in Study 1.

7. Refer to Module 5.3.3.2, CSR D5394C00001, Section 4 Study Objectives.

[8]Study 4. To assess anastrozole PK in patients with MAS.

8. Refer to Module 5.3.3.5, CSR D5394000000, Section 2.

Study design:

[9]Study 1. A double-blind, randomized, placebo-controlled safety and efficacy study in which boys with gynecomastia will receive anastrozole or placebo for up to six months.

[10]Study 2. An open-label safety and efficacy study in which girls with MAS will receive anastrozole for one year. A six-month observational period prior to study treatment will be included.

[11]Study 3. A 6-month open-label PK and clinical study in boys with pubertal gynecomastia. Serial blood samples must be collected over a 24-hour dosing interval at steady state to assess anastrozole PK.

[12, 13]Study 4. A population pharmacokinetic study in girls enrolled in Study 2; a sparse sampling strategy will be acceptable. For each patient, approximately two blood samples will be collected after initial dose. The first blood sample will be drawn between the initial dose and 2 hours post-dose (0-2 hr after first dose). The second blood sample will be drawn at any time between 3 hours post the initial dose and before the second dose (i.e., 24 hours). The patient will continue to take anastrozole once every 24 hours after the initial dose. The following

9. Refer to Module 1.9.6, 20 November 2006, page 3. Also Refer to NDA 20-541 and IND 62,138, Serial No. 30, 20 August 2003, for CSR 1033US/0006, Section 5.1 - Overall study design and flow chart.

10. Refer to Module 5.3.5.2, CSR 1033IL/0046 (D5394C00046), Section 5.1 – Overall study design and flow chart.

11. Refer to Module 5.3.3.2, CSR D5394C0001, Section 5.1 – Overall study design and flow chart; Section 5.2 – Rationale for study design, doses and control groups.

12. Refer to Module 5.3.5.2 CSR 1033IL/0046 (D5394C00046), Section 5.1 – Overall study design; and Section 5.5.6.2 – Collection of biological samples.

13. Refer to Module 5.3.3.5, CSR D5394000000, Section 3.1 Overall Study Design

should be recorded: time of daily administration, time of blood collection, and time of last dose with respect to collection of each blood sample. Two additional blood samples will be drawn after two weeks of drug treatment for steady-state monitoring. A fixed sampling time should be avoided.

Alternatively, a single-dose population pharmacokinetic study can be conducted in girls enrolled in Study 2. If this is the case, five sparse blood samples each will be needed from approximately 80% of the patients enrolled in Study 2. The first sample will be drawn 0 – 2 hours post initial dose. The second, third, fourth, and fifth blood samples will be drawn 3 – 6 hours, 24 – 30 hours, 45 – 48 hours, and 72 – 96 hours post the initial dose, respectively. A fixed time sampling should be avoided. After the pharmacokinetic sampling is complete, the girls will receive anastrozole once every 24 hours for the duration of Study 2.

Not Applicable

Age groups in which studies should be performed:

Study 1. [14]Boys ≥ 11 years and ≤ 18 years of age will be enrolled.

Study 2. [15]Girls ≤ 10 years of age will be enrolled.

Study 3. [16]Boys ≥ 11 years and ≤ 18 years of age with pubertal gynecomastia.

Study 4. [17]Girls ≤ **10 years** of age will be enrolled.

14. Refer to Module 1.9.6, 20 November 2006, page 3 and Refer to NDA 20-541 and IND 62,138, Serial No. 30, 20 August 2003, for CSR 1033US/0006, Section 5.3.1 – Inclusion Criteria.

15. Refer to Module 5.3.5.2 CSR 1033IL/0046 (D5394C00046), Section 5.3.1 – Inclusion Criteria.

16. Refer to Module 5.3.3.2, CSR D5394C00001, Section 5.3.1 – Inclusion criteria.

17. Refer to Module 5.3.5.2, CSR 1033IL/0046, Section 5.3.1 – Inclusion Criteria.

Number of patients to be studied:

Study 1. [18]At least 60 boys will be treated for six months.

Study 2. [19]At least 20 girls will be treated for one year.

Study 3. [20]24 boys who complete the study, **with an age distribution of subjects approximately consistent with the age distribution of pubertal gynecomastia within the age group specified above.**

Study 4. [21]All patients treated in Study 2, if possible, should be enrolled in the population PK study or at least 80% of the patients in Study 2 if you opt for the single-dose population PK study.

Entry criteria:

Study 1. [22]Boys with pubertal gynecomastia with breast diameter ≥ 3 cm that has not decreased in diameter by ≥ 0.5 cm during threes months of clinical observation.

Study 2. [23]Girls with classical or atypical MAS and progressive precocious puberty manifested by signs of pubertal development, **vaginal bleeding**, and/or significantly advanced bone age **(bone age at least 12 months beyond chronological age at the time of screening.)**

18. Refer to Module 1.9.6, 20 November 2006, page 3 and Refer to NDA 20-541 and IND 62,138, Serial No. 30, 20 August 2003, for CSR 1033US/0006, Section 5.2 – Discussion of study design, doses and control groups; Section 5.3 – Selection of study population.

19. Refer to Module 5.3.5.2 CSR 1033IL/0046 (D5394C00046), Section 5.1 – Overall study design and flow chart.

20. Refer to Module 5.3.3.2, CSR D5394C00001, Section 5.1 – Overall study design and flow chart; Section 5.7.5 – Determination of sample size.

21. Refer to Module 5.3.5.2, CSR 1033IL/0046 (D5394C00046), Section 5.1 – Overall study design and flow chart.

22. Refer to Module 1.9.6, 20 November 2006, page 3 and Refer to NDA 20-541 and IND 62,138, Serial No. 30, 20 August 2003, CSR 1033US/0006, Section 5.3.1 – Inclusion Criteria.

23. Refer to Module 5.3.5.2 CSR 1033IL/0046 (D5394C00046), Section 5.3.1 - Inclusion Criteria.

Study 3. [24]Boys with pubertal gynecomastia with a breast measurement of at least 2 cm in diameter that has not decreased in diameter during 3 months of clinical observation.

Study 4. [25]Patients enrolled in Study 2.

Study endpoints:

[26]Study 1:

[27]Primary:
A ≥50% reduction between visit 1 and end of study in the calculated breast volume (combined) based on ultrasound.

Additional endpoints:

a) [28]Proportion of patients with ≥50% reduction in breast volume by end of study

b) [29]Actual percent change in breast volume

c) [30]Change in breast pain in symptomatic patients

d) [31]Changes in sex steroid and gonadotropin levels

e) [32]Changes in height

f) [33]Tolerability and safety

24. Refer to Module 5.3.3.2 CSR D5394C00001, Section 5.3.1 – Inclusion criteria.

25. Refer to Module 5.3.5.2 CSR 1033IL/0046, Section 5.3.1 – Inclusion Criteria.

26. Refer to Module 1.9.6, 20 November 2006, page 3 and Refer to NDA 20-541 and IND 62,138, Serial No. 30, 20 August 2003, CSR 1033US/0006

27. CSR 1033US/0006, Section 7.2.1 Primary variable - Response rate.

28. CSR 1033US/0006, Section 7.2.2.1 Proportion of patients who had complete regression of gynecomastia.

29. CSR 1033US/0006, Section 7.2.2.2 Actual change and percent change in calculated volume of gynecomastia while on trial therapy.

30. CSR 1033US/0006, Section 7.2.2.3 – Change in pain response in symptomatic patients.

31. CSR 1033US/0006, Section 7.2.2.4 – Change in hormone levels.

32. CSR 1033US/0006, Section 7.2.2.5 – Change in height, weight, and BMI.

Study 2:

a) [34]Changes in frequency of annualized episodes of vaginal bleeding on treatment compared to baseline (collection of data on the duration of vaginal bleeding is, whenever possible, strongly recommended).

b) [35]Proportion of patients with baseline vaginal bleeding who experienced ≥50% reduction in the number of vaginal bleeding episodes on treatment.

c) [36]Proportion of patients with baseline bleeding who experienced cessation of vaginal bleeding episodes over a 6-month trial period and over the whole 12-month trial.

d) [37]Change in bone age advancement on treatment compared to change during baseline (provide data for both the 6-month and the 12-month time points).

e) [38]Change in growth velocity on treatment compared to change during baseline (provide data for both the 6-month and the 12-month time points).

Additional assessments:
[39]a) Change in Tanner stage (breast and pubic hair) at 12 months relative to baseline

34. Refer to Module 5.3.5.2 CSR 1033IL/0046 (D5394C00046), Section 5.5.3.1 Summary of Efficacy Objective and Variable and Section 7.2.2.2 – Change in frequency of annualized episodes of vaginal bleeding on treatment compared to baseline.

35. Refer to Module 5.3.5.2 CSR 1033IL/0046, Section 7.2.2.3 – Proportion of patients with baseline vaginal bleeding who experienced ≥50% reduction in the number of vaginal bleeding episodes on treatment.

36. Refer to Module 5.3.5.2 CSR 1033IL/0046, Section 7.2.2.4 – Proportion of patients with baseline vaginal bleeding who experienced cessation of vaginal bleeding episodes over a 6-month study period and over the whole 12-month study.

37. Refer to Module 5.3.5.2 CSR 1033IL/0046, Section 7.2.2.5 – Change in bone age advancement on treatment compared to change during baseline.

38. Refer to Module 5.3.5.2 CSR 1033IL/0046, Section 7.2.2.6 – Change in growth velocity on treatment compared to change during baseline.

39. Refer to Module 5.3.5.2 CSR 1033IL/0046, Section 7.2.3.1 – Change in Tanner stage (measure of pubertal progression).

[40]b) Change in uterine volume at 6 months and 12 months of the trial relative to baseline uterine volume
[40]c) Change in ovarian volume at 6 months and 12 months of the trial relative to baseline ovarian volume (categorization of the number and size of the ovarian cysts should be attempted)

[41]d) Predicted adult height at 12 months of the trial relative to baseline

[42]e) Tolerability and safety data

Study 3.

[43]Primary:

PK endpoints such as $C_{ss,max}$, $C_{ss,min}$, t_{max}, AUC_{ss}, CL/F, and V_z/F will be determined.

[44]Secondary:

a) proportion of patients with ≥50% reduction in breast volume by end of study
b) actual percent change in breast volume
c) change in breast pain in symptomatic patients
d) tolerability and safety

[45]Studies 3 and 4

The effects of demographic covariates (e.g., age, body weight, sex) on anastrozole PK in these populations should be analyzed.

40. Refer to Module 5.3.5.2 CSR 1033IL/0046 (D5394C00046), Section 7.2.3.2 – Change in mean ovarian and uterine volumes by ultrasound, including the number of ovarian cysts and size of the largest cyst.

41. Refer to Module 5.3.5.2 CSR 1033IL/0046, Section 7.2.3.3 – Predicted adult height for children over 6 years of age.

42. Refer to Module 5.3.5.2 CSR 1033IL/0046, Section 8 – Safety Results.

43. Refer to Module 5.3.3.2 CSR D5394C00001, Section 4.1 – Primary objectives; Section 5.5.1 – Primary variable; Section 7.5 – Pharmacokinetic results

44. Refer to Module 5.3.3.2 CSR D5394C00001, Section 4.2 – Secondary Objectives; Section 5.5.3.1 Summary of efficacy objective and variables Table 5 – Efficacy objectives and outcome variables relating to each objective - Secondary outcome variables; Section 7.2 Efficacy Results; Section 8 Safety Results

45. Refer to Module 5.3.3.2 Study 3 CSR D5394C00001, Section 5.7.4 – Methods of statistical analysis; Section 7.5.2 Pharmacokinetic parameters ; Refer to Module 5.3.5.5 Study 4: CSR D5394000000, Section 2 Objectives, hypotheses, and assumptions; Section 3.4.5 Evaluation of potential covariates and final model selection, Section 4.3.3. Evaluation of covariates and final model selection.

[46]Study 4.

PK endpoints such as AUC, C_{max}, $T_{1/2}$, CL/F, and V_{ss}/F will be determined.

Drug information:

[47]*dosage form:*	tablet
[48]*route of administration:*	oral
regimen:	dose up to 1mg/day (Studies 1 and 3); dose up to 10 mg/day (Studies 2 and 4);
[49]*formulation:*	marketed tablet

46. Refer to Module 5.3.3.2 CSR D5394000000, Section 4.3.3 Evaluation of Covariates and final model selection; Section 4.3.4 Bayesian estimates of individual anastrozole PK parameters; Section 4.3.5 Model validation

47. Study 1: Refer to Module 1.9.6, 20 November 2006, page 3 and Refer to NDA 20-541 and IND 62,138, Serial No. 30, 20 August 2003, CSR 1033US/0006 Section 5.4.2 – Investigational products; Study 2 and 4: CSR 1033IL/0046, Section 5.4.1 – Investigational products; Study 3: CSR D5394C00001, Section 5.4.1 – Investigational products.

48. Study 1:Refer to Module 1.9.6, 20 November 2006, page 3 and Refer to NDA 20-541 and IND 62,138, Serial No. 30, 20 August 2003, CSR 1033US/0006, Section 5.4.1 – Doses and treatment regimens; Study 3: Refer to Module 5.3.3.2 CSR D5394C00001, Section 5.2 Rationale for study design, dosage and control group; Study 2 and 4: Module 5.3.5.2 CSR 1033IL/0046, Section 5.2 Rationale for study design, dosage and control group

49. Study 1: Refer to Module 1.9.6, 20 November 2006, page 3 and Refer to NDA 20-541 and IND 62,138, Serial No. 30, 20 August 2003, CSR 1033US/0006 , Section 5.4.2 – Investigational products; Study 2 and 4: CSR 1033IL/0046, Section 5.4.1 – Investigational products; Refer to Module 5.3.3.2 – Study 3: CSR D5394C00001, Section 5.4.1 – Investigational products

[50]**Use an age-appropriate formulation in the studies described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.**

50. Refer to Module 1.9.6 15 September 2006 (FDA correspondence) Confirmation received from FDA that the marketed tablet is appropriate for use in trials.

Development of a commercially marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.
If you cannot develop a commercially marketable, age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed, step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the

approved drug to the age-appropriate formulation may be conducted in adults.

Drug-specific safety concerns:

[51]Diarrhea, nausea, vomiting, liver abnormalities.

Statistical information, including power of safety and statistical assessments:

[52]Study 1 The proportions of patients achieving the primary endpoint in each treatment group will be compared using the appropriate statistical methods. At least one analysis of the primary endpoint will make use of the intent-to-treat (ITT) population consisting of all randomized subjects with an observation at visit 1 and at least one observation after randomization. Additional endpoints as well as safety will be analyzed descriptively.

[53]Study 2 Paired t tests will be used to compare the mean growth rate, mean bone age advancement, and mean frequency and duration of vaginal bleeding episodes during baseline period to the mean rates during treatment. A 95% confidence interval should also be constructed for the mean difference between treatment and baseline. Appropriate nonparametric methods will be used if assumptions for t test are not satisfied. Correlations between growth rate changes and bone age changes should be performed.

Descriptive statistics should be presented for all study endpoints. Descriptive statistics for continuous variables should include sample

51. Refer to Module 1.9.6 20 November 2006, page 3, NDA 20-541 and IND 62,138, Serial No. 30, 20 August 2003; Study 1: CSR 1033US/0006, Section 8 – SAFETY RESULTS Study 2: CSR 1033IL/0046 (D5394C00046), Section 8 – SAFETY RESULTS; Refer to Module 5.3.3.2 – Study 3: CSR D5394C00001, Section 8 SAFETY RESULTS.

52. Refer to Module 1.9.6 20 November 2006, page 3 NDA 20-541 and IND 62,138, Serial No. 30, 20 August 2003; Study 1: CSR 1033US/0006 Section 5.7 – Statistical methods and determination of sample size; Section 12.1.9 - Documentation of statistical methods and supporting statistical analysis.

53. Refer to Module 5.3.5.2 CSR 1033IL/0046 (D5394 C00046), Section 5.7 – Statistical methods and determination of sample size; Section 12.1.9 - Documentation of statistical methods and supporting statistical analysis.

size, mean, median, range, as well as individual changes. You should conduct two sets of analyses: (1) all patients exposed to treatment and (2) a protocol-valid analysis.

Study 3

Primary:

[54]Descriptive statistics will be reported for the PK parameters and the effect of covariates on CL/F; $\mathbf{V_z/F}$ will be studied using the appropriate statistical methods.

54. Refer to Module 5.3.3.2, Study 3: CSR D5394C00001, Section 5.7.4 – Methods of Statistical Analysis; Section 12.1.9 - Documentation of statistical methods and supporting statistical analysis.

Secondary:

[55]Descriptive analyses for both efficacy and safety endpoints.

55. Refer to Module 5.3.3.2, Study 3: CSR D5394C00001, Section 5.7.4 – Methods of Statistical Analysis; Section 12.1.9 - Documentation of statistical methods and supporting statistical analysis.

Study 4

[56]Descriptive statistics will be reported for the PK parameters and the effect of covariates on CL/F; $\mathbf{V_{ss}/F}$ will be studied using the appropriate statistical methods.

56. Refer to Module 5.3.3.5, CSR D5394000000 - Population pharmacokinetic report for anastrozole in pediatric girls with McCune-Albright Syndrome. Section 3.4.6 Calculated individual PK parameters; Section 3.4.7.3 Model Predictability; Appendix B - Data Analysis Plan

Labeling that may result from the studies:

[57]Appropriate sections of the label may be changed to incorporate the findings of the studies.

57. Refer to Module 1.14.1.2 – Annotated Draft Labeling and Module 1.14.1.3 Draft Labeling (non-annotated).

Format of reports to be submitted:

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.

[58]In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies **should** be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific islander or White. For ethnicity one of the following designations **should** be used: Hispanic/Latino or Not Hispanic/Latino.

[59]Although not required to obtain pediatric exclusivity, we request that you make a commitment to monitor annually the participants in Study 2 until age 12 or until discontinuation of drug and that you submit information in your annual reports. The patients should be monitored with respect to the Study 2 endpoints and the drug safety parameters.

Timeframe for submitting reports of the studies:

[60]Reports of the studies that meet the terms of this Written Request must be submitted to the Agency on or before **October 31, 2007**, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act. **Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.**

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

58. Study 1: Refer to Module 1.9.6, 20 November 2006, page 3. Refer to NDA 20-541 and IND 62,138, Serial No. 30, 20 August 2003; CSR 1033US/0006, Section 6.5 – Demographic and other patient characteristics; Study 2 and 4: Refer to Module 5.3.5.2 CSR 1033IL/0046 (D5394C00046), Section 6.5 – Demographic and other patient characteristics; Study 3: Refer to Module 5.3.3.2, CSR D5394C00001, Section 6.5 – Demographic and other patient characteristics.

59. AZ began monitoring and reporting the information in the May 5, 2004 Annual Report for IND 62,138 (Serial No. 0034). Subsequent reports have been submitted April 13, 2005 (Serial No. 0040); April 24, 2006 (Serial No. 0046); and April 13, 2007 (Serial No. 0056)

60. Study 1(CSR 1033US/0006) submitted to IND 62,138 on 20 August 2003 as an Information Amendment – Clinical, Serial Number 030 and in electronic format for archiving to NDA 20-541. Studies 2 (Refer to Module 5.3.5.2 CSR 1033IL/0046 (D5394C00046)), 3 (Refer to Module 5.3.3.2, CSR D5394C00001), and 4 (Refer to Module 5.3.3.5, CSR D5394C00000) contained in NDA 22-214.

Submit reports of the studies as a **new drug application (NDA)** with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. [61]In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

61. NDA 22-214 was provided via FDA's Electronic Submissions Gateway

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e., approval, not approvable); or
4. the exclusivity determination (i.e., granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, submit a proposed changes and the reasons for the proposed changes to **IND 62,138**. Clearly mark submissions of proposed changes to this request

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/s/

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