16.1.1 Protocol and Protocol Amendments

Protocol Version	Protocol Date
Protocol Version 07	14 Aug 2014
Protocol Version 06	21 May 2014
Protocol Version 05	03 Feb 2014
Protocol Version 04	16 May 2013
Protocol Version 03	26 Feb 2013
Protocol Version 02	04 Oct 2012
Protocol Version 01	20 Apr 2012
Protocol Version 00	27 Jan 2012

SAREPTA THERAPEUTICS

CLINICAL STUDY PROTOCOL

DRUG:	Eteplirsen Injection
PROTOCOL NUMBER:	4658-us-202
PROTOCOL TITLE:	Open-Label, Multiple-Dose, Efficacy, Safety, and Tolerability Study of Eteplirsen in Subjects with Duchenne Muscular Dystrophy who Participated in Study 4658-us-201
IND NUMBER:	077,429
SPONSOR:	Sarepta Therapeutics, Inc. 215 First Street Cambridge, MA 02142 USA Phone: (617) 274-4000
CURRENT VERSION (DATE):	07 (14 Aug 2014)
PRIOR VERSIONS (DATES):	06 (21 May 2014) 05 (03 February 2014) 04 (16 May 2013) 03 (26 February 2013) 02 (04 October 2012) 01 (20 April 2012) 00 (27 January 2012)

(b) (4) [redacted]

SIGNATURE PAGE FOR SPONSOR'S REPRESENTATIVE

Protocol Title:	Open-Label, Multiple-Dose, Efficacy, Safety, and Tolerability Study of Eteplirsen in Subjects with Duchenne Muscular Dystrophy who Participated in Study 4658-us-201
Study No:	4658-us-202
Current Version (Date):	07 (14 Aug 2014)
Prior Versions (Dates):	06 (21 May 2014)- not implemented 05 (03 February 2014) 04 (16 May 2013) 03 (26 February 2013) 02 (04 October 2012) 01 (20 April 2012) 00 (27 January 2012)

This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the Sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of GCP as described in 21 CFR parts 50, 54, 56 and 312 and according to applicable local requirements.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Edward M. Kaye MD

14 Aug 2014

Edward M. Kaye, MD
Chief Medical Officer and Senior Vice President, Clinical Development
Sarepta Therapeutics Inc.
215 First Street
Cambridge, MA 02142 USA

Date

STUDY SYNOPSIS

NAME OF COMPANY	NAME OF FINISHED PRODUCT
Sarepta Therapeutics Inc. 215 First Street Cambridge, MA 02142 USA Phone: (617) 274-4000	Eteplirsen Injection **NAME OF ACTIVE INGREDIENT** Eteplirsen

TITLE:

Open-Label, Multiple-Dose, Efficacy, Safety, and Tolerability Study of Eteplirsen in Subjects with Duchenne Muscular Dystrophy who Participated in Study 4658-us-201

PROTOCOL NO.:

4658-us-202

INVESTIGATOR STUDY SITES:

This study will be conducted at approximately 12 study sites located in the United States.

OBJECTIVES:

The primary objective of this study is to assess the ongoing efficacy, safety, and tolerability of an additional 212 weeks of treatment with eteplirsen injection in Duchenne muscular dystrophy (DMD) subjects who have successfully completed the 28-week eteplirsen study: Study 4658-us-201. This study will also evaluate the correlation between biomarkers for DMD and the clinical status of participating DMD subjects.

METHODOLOGY:

This is an open-label, multiple-dose extension study to assess the ongoing efficacy, safety, and tolerability of weekly intravenous (IV) infusions of eteplirsen in DMD subjects who have successfully completed Study 4658-us-201.

Subjects will have the opportunity to enroll in this study during the last visit of Study 4658-us-201 (Week 28). Eligible subjects will receive once weekly IV infusions of eteplirsen (50 or 30 mg/kg) for an additional 212 weeks. Subjects will receive the same dose of eteplirsen they received in Study 4658-us-201.

Safety, efficacy, pharmacokinetic (PK), and biomarker assessments will be performed at scheduled visits; adverse events (AEs) and concomitant medications and therapies will be continuously monitored.

If review of data from this open-label study suggests that continued treatment with eteplirsen is warranted, this study may be extended by protocol amendment or subjects who successfully complete this study may have the opportunity to participate in a separate follow-on, open-label eteplirsen study.

NUMBER OF SUBJECTS:

Twelve (12) subjects participated in Study 4658-us-201 and may be eligible to participate in this study.

INCLUSION/EXCLUSION CRITERIA:

Inclusion Criteria:

A subject must meet all of the following criteria to be eligible for this study.

1. The subject and/or their parent/legal guardian are willing and able to provide signed informed consent.
2. The subject has successfully completed 28 weeks of treatment in Study 4658-us-201.
3. The subject has a parent(s) or legal guardian(s) who is able to understand and comply with all of the study

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procedure requirements.

Exclusion Criteria:

A subject who meets any of the following criteria will be excluded from this study.

1. The subject has a prior or ongoing medical condition that, in the Investigator's opinion, could adversely affect the safety of the subject or make it unlikely that the course of treatment or follow-up would be completed or impair the assessment of study results.

DOSE/ROUTE/REGIMEN (TEST ARTICLE):

The dose of eteplirsen will be calculated based on the most recent subject weight obtained at the site prior to the current visit. Please refer to the study-specific pharmacy manual for information on preparation and administration of eteplirsen.

Subjects will receive the same dose of eteplirsen they received during Study 4658-us-201 (see table below).

Group	Treatment/Dose in Study 4658-us-201	Dose of Eteplirsen Injection For Study 4658-us-202
1	50 mg/kg eteplirsen for 28 weeks	50 mg/kg eteplirsen
2	30 mg/kg eteplirsen for 28 weeks	30 mg/kg eteplirsen
3a	Placebo for 24 weeks followed by 50 mg/kg eteplirsen for 4 weeks	50 mg/kg eteplirsen
3b	Placebo for 24 weeks followed by 30 mg/kg eteplirsen for 4 weeks	30 mg/kg eteplirsen

(b) (4) [redacted]

REFERENCE TREATMENT:

Not applicable.

CRITERIA FOR EVALUATION:

Efficacy:

The primary biological efficacy endpoint will be the change from baseline at Week 20 in the percent of dystrophin positive fibers (type = anti-dystrophin antibody MANDYS106) in muscle biopsy tissue as measured by immunohistochemistry (IHC).

The primary functional efficacy endpoint will be the change from baseline to end-of-study on the 6-Minute Walk Test (6MWT).

Additional exploratory and supportive efficacy endpoints will evaluate changes from baseline in:

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- Dystrophin intensity per fiber in muscle biopsy tissue as determined by IHC
- CD3, CD4, and CD8 lymphocyte count in muscle biopsy tissue
- Total dystrophin protein in muscle biopsy tissue as determined by Western blot analysis
- Exon skipping in muscle biopsy tissue as assessed by reverse transcriptase polymerase chain reaction (RT-PCR)
- Timed 4-Step Test results
- North Star Ambulatory Assessment (NSAA) results
- Maximum voluntary isometric contraction test (MVICT) results
- 9-Hole Peg Test results
- Pediatric Quality of Life Inventory™ (PedsQL) results, including the neuromuscular module (NMM)
- Pulmonary function test results including forced vital capacity (FVC), percent predicted FVC, forced expiratory volume in 1 second (FEV_1), FEV_1%, FEV_1/FVC ratio, maximum inspiratory pressure (MIP), and maximum expiratory pressure (MEP)

Safety:

The safety and tolerability of eteplirsen will be assessed through a review and evaluation of:

- The frequency and severity of AEs, serious adverse events (SAEs), and discontinuations due to AEs
- Laboratory testing including hematology, coagulation, and serum chemistry and urinalysis (e.g., urinary KIM-1, serum cystatin C and anti-dystrophin antibody formation)
- T-cell response to the newly produced dystrophin peptide fragments using enzyme-linked immunosorbent spot (ELISPOT) assay
- Cardiac function including electrocardiogram (ECG) and echocardiogram (ECHO)
- Vital signs
- Physical examinations

Pharmacokinetics:

The PK of eteplirsen will be determined from blood samples.

(b) (4) [redacted]

STATISTICAL METHODS:

All data will be presented in subject data listings. The safety population will include all subjects randomized into study 4658-us-201 who receive any amount of study drug. For the purpose of any efficacy analysis, the safety population will also be referred to as the intent-to-treat (ITT) population. A modified intent-to-treat (mITT) population will be similar to the ITT but will exclude 2 subjects who showed rapid disease progression during the first few weeks of study 4658-us-201.

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The analysis of the primary biological endpoint will be based on a restricted maximum likelihood (REML)-based mixed model with treatment as fixed effect, subject nested within treatment as random effect, with the baseline value and time since DMD diagnosis as covariates.

The analysis of the primary functional endpoint will be based on a REML-based mixed model repeated measures (MMRM) with treatment (placebo to eteplirsen, 30.0 mg/kg eteplirsen, 50.0 mg/kg eteplirsen), time, and treatment-by-time interaction terms as fixed effect, subject nested within treatment as random effect, with the baseline value and time since DMD diagnosis as covariates.

All other efficacy and safety endpoints will be summarized using inferential and descriptive statistics as appropriate. Further details of the statistical analysis will be provided in the statistical analysis plan (SAP).

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Term	Definition
2D	2 dimensional
6-MWT	6-Minute Walk Test
ACE	angiotensin-converting enzyme
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under plasma concentration-time curve
BMD	Becker muscular dystrophy
BUN	blood urea nitrogen
C	Celsius
CFR	Code of Federal Regulations
CK	creatine kinase
C_{max}	maximum observed concentration
CRF	case report form
CRP	C-reactive protein
CS	clinically significant
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic case report form
EDB	extensor digitorum brevis
eDCRs	electronic data clarification requests
EF	ejection fraction
ELISPOT	enzyme-linked immunosorbent spot
FDA	US Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FEV_1%	forced expiratory volume in 1 second percent
FS	fractional shortening
FVC	forced vital capacity
GCP	Good Clinical Practices

GGT	gamma-glutamyl transferase
GMP	Good Manufacturing Practice
hDMD	human Duchenne muscular dystrophy mouse model
HEENT	head, ears, eyes, nose, throat
IAP	Interim Analysis Plan
ICH	International Conference on Harmonization
IHC	immunohistochemistry
IM	intramuscular, intramuscularly
IND	Investigational New Drug application
INR	international normalized ratio
IRB	institutional review board
ITT	Intent to Treat population
IV	intravenous, intravenously
KIM-1	Kidney injury molecule -1
LDH	lactate dehydrogenase
MedDRA®	Medical Dictionary for Regulatory Activities®
MEP	maximum expiratory pressure
MIP	maximum inspiratory pressure
MMP-9	matrix metalloproteinase-9
miRNA	micro ribonucleic acid sequence
MMRM	mixed model repeated measures
mRNA	messenger ribonucleic acid
MVICT	maximum voluntary isometric contraction test
NCS	non-clinically significant
N/n	number
NMM	Neuromuscular module (of PedsQL)
NSAA	North Star Ambulatory Assessment
PedsQL	Pediatric Quality of Life Inventory™
PFTs	pulmonary function tests
PHI	protected health information
PK	pharmacokinetic
PMO	phosphorodiamidate morpholino oligomer
PT	prothrombin time
QMA	Quantitative Movement Assessment
RBC	red blood cells

REML	restricted maximum likelihood
RNA	ribonucleic acid
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOM	Study Operations Manual
SP(POW)	spatial power
TEAE	treatment-emergent adverse event
TIMP-1	tissue inhibitor of metalloproteinase
US/USA	United States
WBC	white blood cell

1 INTRODUCTION AND RATIONALE

Purpose of Study

The purpose of this study is to evaluate the ongoing safety, tolerability, and efficacy of once weekly intravenous (IV) infusions of eteplirsen (AVI-4658) in Duchenne muscular dystrophy (DMD) subjects who successfully completed Study 4658-us-201, a phase 2, randomized, double-blind, placebo-controlled, multiple-dose, 28-week study of eteplirsen.

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a degenerative disease with an X-linked recessive inheritance caused by mutations in the dystrophin gene. The mutations that cause DMD disrupt the messenger ribonucleic acid (mRNA) reading frame and prohibit production of dystrophin, a critically important part of the protein complex that connects the cytoskeleton of a muscle fiber to the extracellular matrix. In the absence of dystrophin, the stress of muscle contraction causes progressive muscle damage.

The clinical effect of this disrupted dystrophin reading frame is dramatic and lethal; affected individuals develop severe muscle wasting and weakness, and experience a T-cell mediated inflammatory response in the damaged muscle tissue (Arahata 1984). DMD is often first diagnosed between the ages of 3 to 5 years, when toddlers develop a waddling gait, and patients often stop walking by 10 years of age (Emery 2002). While pulmonary and cardiac function are generally normal during childhood, cardiac and diaphragmatic muscles become progressively weaker during adolescence, and patients often die from respiratory or cardiac failure in their early 20s (Brooke 1989, Eagle 2002). Currently, only palliative treatments exist for DMD. These include corticosteroids, which may prolong ambulation and reduce the incidence of severe scoliosis, and artificial ventilation, which may increase life span.

EteplirsenInjection

Sarepta Therapeutics Inc. is developing eteplirsen for the treatment of DMD. Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO), which is a class of synthetic molecules based on a fundamental redesign of the natural nucleic acid structure. PMOs bind to complementary sequences of ribonucleic acid (RNA) by standard nucleic acid base-pairing, but are different from RNA and deoxyribonucleic acid (DNA) in that their nucleic acid bases are bound to 6-member, synthetic morpholino rings instead of ribose (as in RNA) or deoxyribose (as in DNA) rings, and are linked through neutral phosphorodiamidate moieties instead of negatively charged phosphodiesters.

Eteplirsen is designed to target the pre-mRNA transcripts of the dystrophin gene, so that exon 51 is excluded, or skipped, from the mature, spliced mRNA. In doing so, eteplirsen should restore the reading frame for patients with certain deletions in exons 45-50, 47-50, 48-50, 50, 52, or 52-63 of this gene, and enable the production of an internally truncated, yet functional dystrophin protein, similar to that observed in Becker Muscular Dystrophy (BMD). BMD is an allelic form of muscular dystrophy characterized by mutations that result in the production of an internally

truncated, but still active dystrophin protein (Bushby 1993a, Heald 1994, Muntoni 2003). Accordingly, unless affected by severe cardiomyopathy, most BMD patients remain ambulatory and have a near-normal life expectancy (Bushby 1993b).

If ongoing treatment with eteplirsen results in the sustained production of functional dystrophin protein, it is hypothesized that eteplirsen will improve the quality of life and prognosis for DMD patients, essentially switching their clinical symptoms and prognosis to be more similar to patients with BMD. This hypothesis is supported by results of nonclinical studies in primary muscle cells of DMD patients and in the human DMD (*hDMD*) mouse model showing that eteplirsen induces skipping of exon 51 and results in the production of internally truncated, functional dystrophin protein (Arechavala-Gomeza 2007). Further support for the potential efficacy of eteplirsen is derived from nonclinical and clinical studies of other PMOs (as discussed in the Investigator's Brochure), and results of the eteplirsen clinical studies completed to date (see below).

Clinical Experience with Eteplirsen

Two phase 1, open-label clinical studies of eteplirsen provide initial support for the safety and potential efficacy of eteplirsen in the treatment of DMD. In the phase 1/2 study, AVI-4658-33, 7 nonambulatory DMD boys aged 10 to 17 years received a single intramuscular (IM) dose of eteplirsen 0.09 mg (n=2) or 0.9 mg (n=5) in the extensor digitorum brevis (EDB) muscle of one foot and a single IM dose of placebo in the opposite foot. The 5 subjects who received the 0.9 mg dose showed evidence of exon skipping, increased dystrophin expression, and an increase in the number of dystrophin-positive fibers in the eteplirsen-treated foot, but not the placebo-treated foot. In the phase 1b/2 study, AVI-4658-28, 19 DMD boys aged 6 to 13 years received up to 12 weekly intravenous (IV) infusions of eteplirsen at doses of 0.5, 1.0, 2.0, 4.0, 10.0, or 20.0 mg/kg. Two weeks after the last dose of eteplirsen, 7 of the 17 subjects with post-treatment muscle biopsies showed increases in dystrophin on at least 2 of the 3 methods used to assess dystrophin expression, which included: the number of dystrophin-positive fibers as assessed by immunohistochemistry (IHC), the amount of dystrophin protein as assessed by semi-quantitative IHC, and the amount of dystrophin protein as assessed by Western blotting. These increases appeared dose-related at doses ≥2.0 mg/kg. (b) (4) This finding is particularly meaningful since the infiltration of immune cells into the muscle of DMD patients produces chronic inflammation, necrosis, and severe muscle degeneration and markedly exacerbates disease progression in these patients (Spencer 2001). Eteplirsen was well tolerated in both studies; most adverse events (AEs) were assessed as mild to moderate in intensity and related to the biopsy procedures (e.g., mild edema over the EDB biopsy site, pain post-biopsy) and/or the underlying disease (e.g., worsening of pre-study cardiomyopathy or myoglobinuria) as opposed to eteplirsen itself. Moreover, no clinically significant effects of eteplirsen on laboratory tests, vital signs, physical examinations, or electrocardiograms (ECGs) were observed.

In light of these positive findings, the double-blind, placebo-controlled Phase 2 study, 4658-us-201, was initiated in August 2011. This study randomized 12 subjects aged 7 to 13 years

to receive once weekly infusions of eteplirsen or placebo as follows: Group 1 received 50 mg/kg eteplirsen for 28 weeks (n=4); Group 2 received 30 mg/kg eteplirsen for 28 weeks (n=4); Group 3a received placebo for 24 weeks followed by 50 mg/kg eteplirsen for 4 weeks (n=2); and Group 3b received placebo for 24 weeks followed by 30 mg/kg eteplirsen for 4 weeks (n=2). Study 4658-us-201 was completed in March 2012 and subjects who successfully completed that study were given the opportunity to enroll in the present open-label, extension study.

1.1 Summary of Potential Risks

Based on analysis of the Phase 1 study data, there are no identified risks associated with eteplirsen. For a discussion of the potential and theoretical safety concerns related to eteplirsen and for further details concerning warnings, precautions, and contraindications, the Investigator should refer to the appropriate section of the Investigator's Brochure.

In order to evaluate the effects of eteplirsen on dystrophin expression, subjects will undergo a muscle biopsy during this study. While the biopsies do entail surgical risk, muscle biopsy is the only reliable way to obtain the tissue needed to assess the de novo production of dystrophin. To minimize subject discomfort and optimize subject safety, subjects will only be required to undergo 1 biopsy during this 212-week extension study, and a physician experienced in performing this procedure will perform all biopsies at the central study site. An additional optional biopsy may be performed after Week 140 functional assessment visit for patients who consent to this procedure. The purpose of the Week 140 biopsy is to gain additional data on eteplirsen-induced novel dystrophin expression as well as other biomarkers after more than 2 years of eteplirsen treatment.

In addition, a fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating adverse reactions of all types should be immediately available at each study site.

It should be noted that the subjects who participate in this study will receive standard of care in addition to eteplirsen, therefore, no obvious compromise to their ongoing DMD treatment will occur.

1.2 Summary of Potential Benefits

Phase 1 clinical study results support the safety and tolerability of up to 12 weekly infusions of eteplirsen in subjects with DMD and demonstrate eteplirsen's ability to induce exon skipping and produce internally truncated, but functional dystrophin protein and a corresponding reduction in inflammatory infiltrates in these subjects. While clear clinical benefits of eteplirsen have not yet been demonstrated, this is most likely a function of the chronic and progressive nature of the underlying disease and the brevity of exposure to eteplirsen in prior studies. It is believed that with longer exposure, e.g., up to 28 weeks in the 4658-us-201 study and up to approximately 4.6 years (240 weeks) for subjects who received eteplirsen from the start of that study and continue on eteplirsen in this study (i.e., subjects in Groups 1 and 2), eteplirsen will produce more consistent and substantial increases in dystrophin and result in measurable clinical benefit.

2 STUDY OBJECTIVES

The primary objective of this study is to assess the ongoing efficacy, safety, and tolerability of an additional 212 weeks of treatment with eteplirsen (AVI-4658) in DMD subjects who have successfully completed the 28-week eteplirsen study: Study 4658-us-201. This study will also evaluate the correlation between biomarkers for DMD and the clinical status of participating DMD subjects.

3 INVESTIGATIONAL PLAN

This is a continuing, open-label, multiple-dose study to assess the ongoing efficacy, safety, and tolerability of weekly IV infusions of eteplirsen (50 or 30 mg/kg) in DMD subjects who have successfully completed Study 4658-us-201. Subjects will have the opportunity to enroll in this study during the last visit of Study 4658-us-201 (Week 28).

Eligible subjects will receive once weekly eteplirsen (50 or 30 mg/kg) for 212 weeks Subjects will receive the same dose of eteplirsen they received in Study 4658-us-201.

Safety, efficacy, pharmacokinetic (PK), and biomarker assessments will be performed at scheduled visits. All subjects will undergo muscle biopsies for analysis of exon skipping, dystrophin expression, and inflammatory markers at Week 20 (b) (4)
(b) (4)

All infusions and assessments will be performed at the central study site until a suitable satellite site closer to the subject is identified and initiated. Once a subject begins receiving weekly infusions at satellite sites, all subsequent infusions will be administered at the subject's satellite site unless otherwise indicated and approved by the Medical Monitor. Collection of AEs, concomitant medications, vital signs and weight, and blood for safety laboratory, biomarker, and PK analyses will also be performed at the satellite sites; all other assessments will be performed at the central site throughout the study unless otherwise indicated and approved by the Medical Monitor.

If review of data from this open-label study suggests that continued treatment with eteplirsen is warranted, this study may be extended by protocol amendment or subjects who successfully complete this study may have the opportunity to participate in a separate follow-on, open-label eteplirsen study.

3.1 Endpoints

3.1.1 Efficacy Endpoints

3.1.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be the change from baseline in the percent of dystrophin positive fibers in muscle biopsy tissue as measured by immunohistochemistry (IHC).

3.1.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will be the change from baseline in:

- CD3, CD4, and CD8 lymphocyte count in muscle biopsy tissue
- 6-Minute Walk Test (6-MWT) results

3.1.1.3 Additional Efficacy Endpoints

Additional efficacy endpoints will evaluate changes from baseline in:

- Dystrophin intensity per fiber in muscle biopsy tissue as determined by IHC
- Total dystrophin protein in muscle biopsy tissue as determined by Western blot analysis
- Exon skipping in muscle biopsy tissue as assessed by reverse transcriptase polymerase chain reaction (RT-PCR)
- Intermediate time points results in the 6-MWT (2, 3, and 4 minutes)
- Timed 4-Step Test results
- North Star Ambulatory Assessment (NSAA) results
- Maximum voluntary isometric contraction test (MVICT) results
- 9-Hole Peg Test results
- Pediatric Quality of Life InventoryTM (PedsQL) results, including the neuromuscular module (NMM)
- Pulmonary function test results including forced vital capacity (FVC), percent predicted FVC, forced expiratory volume in 1 second (FEV_1), FEV_1%, FEV_1/FVC ratio, maximum inspiratory pressure (MIP), and maximum expiratory pressure (MEP)

3.1.2 Safety Endpoints

The safety and tolerability of eteplirsen will be assessed through a review and evaluation of:

- The frequency and severity of AEs, serious AEs (SAEs), and discontinuations due to AEs
- Laboratory testing including hematology, coagulation, and serum chemistry and urinalysis (e.g., urinary KIM-1, and serum cystatin C, and anti-dystrophin antibody formation)
- T-cell response to the newly produced dystrophin peptide fragments using enzyme-linked immunosorbent spot (ELISPOT) assay

- Cardiac function including ECG and echocardiogram (ECHO)
- Vital signs
- Physical examinations

3.1.3 Pharmacokinetic Endpoints

The PK of eteplirsen will be determined from blood samples at time points specified in (b) (4) [redacted]

(b) (4) [redacted]

3.2 Study Design

This is an open-label, multiple-dose extension study to assess the ongoing efficacy, safety, and tolerability of weekly IV eteplirsen (50 or 30 mg/kg) in DMD subjects who have successfully completed Study 4658-us-201.

3.2.1 Completion of a Subject's Participation in the Study and Overall Study Completion

3.2.1.1 Completion of a Subject's Participation in the Study

The length of a subject's participation will be from the time the informed consent form is signed until completion of the Week 212 assessments. A subject will be considered "completed" when the subject receives the Week 212 infusion and completes the Week 212 assessments.

3.2.1.1.1 Premature Subject Discontinuation from the Study

Subjects are free to withdraw consent and/or discontinue participation in the study at any time, without prejudice to further treatment. A subject's participation in the study may also be discontinued at any time at the discretion of the Investigator or Sponsor.

The reasons indicated in Section 5.3.3 for withdrawing a subject from treatment may also be justifiable reasons for the Investigator or Sponsor to remove a subject from the study. Subjects may be discontinued from the study if the study is terminated by the Sponsor (see Section 11.5).

(b) (4) [redacted] Post-study SAEs will be reported according to Section 7.4. A subject will be considered prematurely withdrawn if they are withdrawn before receiving the Week 212 infusion of eteplirsen. A subject will be considered discontinued due to an AE if the AE (whether or not related to eteplirsen) causes the subject to withdraw their consent from further participation.

At the end of the subject's participation in the study, the Investigator will document the reason(s) for study discontinuation on the appropriate screen/form of the electronic case report form (eCRF). Subjects who are withdrawn from the study will not be replaced.

3.2.1.2 Overall Study Completion

The study will be considered to be complete when the last subject has completed their Week 212 or early termination assessments.

3.3 Discussion of Study Design

This open-label extension study will allow subjects who received once weekly infusions of eteplirsen at doses of 50 or 30 mg/kg in Study 4658-us-201 to continue treatment with this potentially disease modifying therapy for an additional 212 weeks and yield approximately 4.6 years of safety data for these subjects.

We believe that eteplirsen's safety profile along with the evidence of exon skipping and dystrophin expression observed in preclinical and clinical studies to date support the continued examination of eteplirsen for longer periods of time. As previously noted, eteplirsen was well tolerated when administered as a 60-minute IV infusion to DMD subjects at doses of 0.5 mg/kg to 20.0 mg/kg for 12 consecutive weeks in Study AVI-4658-28, and dose-dependent increases in dystrophin production and decreases in lymphocyte infiltration were observed in muscle. Although no clear effect of eteplirsen on motor function was observed in that study, given that DMD is a chronic and degenerative disease and that eteplirsen must induce de novo dystrophin in these subjects, it is highly likely that changes in ambulation, muscle function, and strength will require longer periods of exposure.

No patient has withdrawn from Study 4658-us-202 due to an adverse event (AE). Through 120 weeks, eteplirsen has continued to be well tolerated, and there have been no reported clinically significant treatment-related adverse events and no treatment-related serious adverse events. In addition, there have been no treatment-related hospitalizations or discontinuations.

(b) (4) [redacted]

Refer to the Investigator's Brochure for further details on the nonclinical and additional clinical data for eteplirsen.

The safety measures used in this study are standard and reflect appropriate monitoring of pediatric subjects receiving an investigational drug. Although renal function was unaltered even

at maximum feasible doses in preclinical studies, nontoxic accumulation of basophilic material in the kidneys has been observed in primates and in mice (please refer to the Investigator's Brochure), hence renal function will also be assessed by KIM-1 measurements in this study.

With respect to efficacy, dystrophin production, exon skipping, and (b) (4) (b) (4) will be evaluated in biopsied muscle tissue using IHC, Western blot analysis, and RT-PCR. While muscle biopsies do entail some degree of surgical risk, muscle biopsy is generally considered the most reliable way to obtain the tissue needed to assess the de novo production of dystrophin. The potential effects of eteplirsen on motor function, muscle strength, respiratory function, and self-reported qualify of life will be assessed using widely used and well-validated measures of these constructs including the 6-MWT, standard spirometry, and the PedsQL. Finally, eteplirsen's effect on disease progression will be examined indirectly using biomarkers known to reflect muscle involvement in DMD subjects including changes in miRNAs (Cacchiarelli 2011) and MMP-9 and TIMP levels (Nadarajah 2011).

4 SUBJECT POPULATION AND SELECTION

4.1 Inclusion Criteria

A subject must meet all of the following criteria to be eligible for this study.

1. The subject and/or their parent/legal guardian are willing and able to provide signed informed consent.
2. The subject has successfully completed 28 weeks of treatment in Study 4658-us-201.
3. The subject has a parent(s) or legal guardian(s) who is able to understand and comply with all of the study procedure requirements.

4.2 Exclusion Criteria

A subject who meets any of the following criteria will be excluded from this study.

1. The subject has a prior or ongoing medical condition that, in the Investigator's opinion, could adversely affect the safety of the subject or make it unlikely that the course of treatment or follow-up would be completed or impair the assessment of study results.

5 TREATMENTS

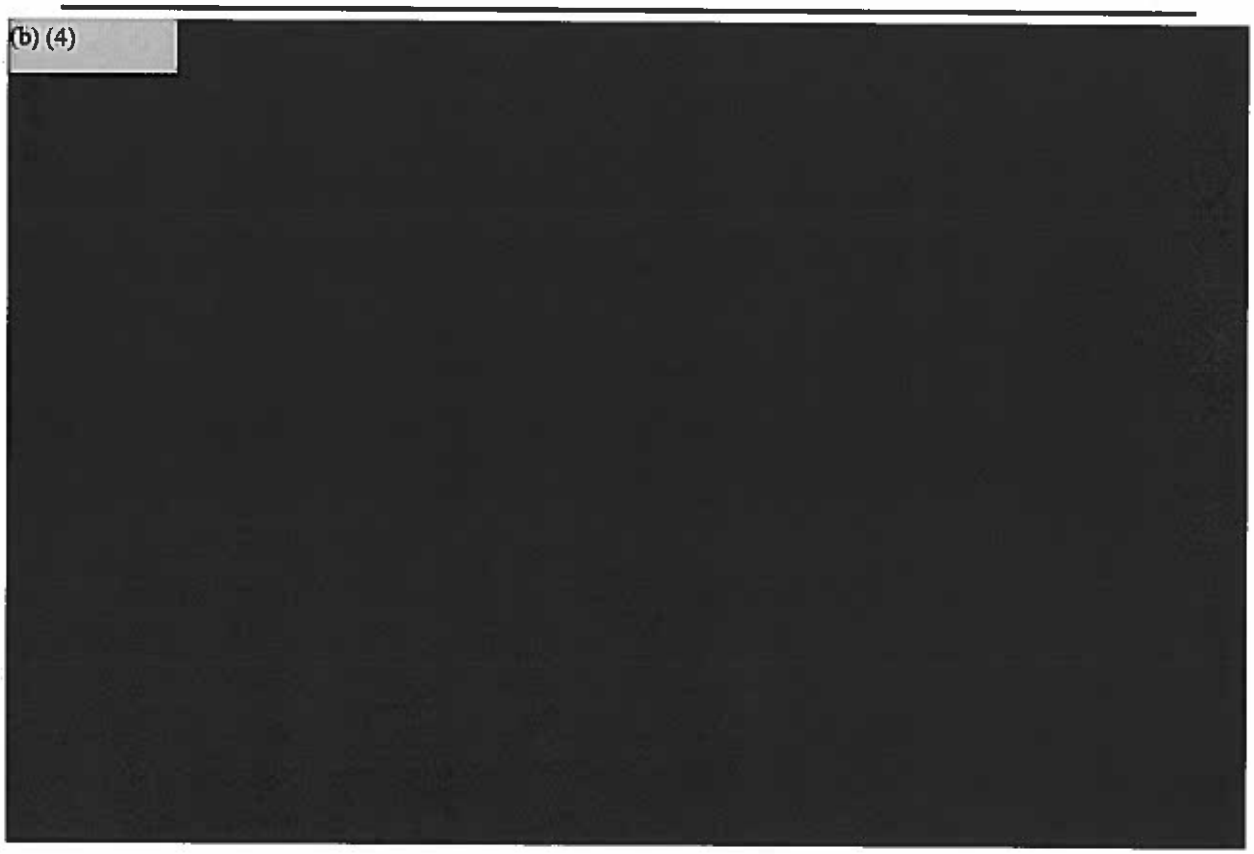
5.1 Treatments Administered

Eligible subjects will receive once weekly eteplirsen (50 or 30 mg/kg) for 212 weeks; subjects will receive the same dose of eteplirsen they received during Study 4658-us-201 (see Table 5-1 below).

Table 5-1: Eteplirsen Dosing

Group	Treatment/Dose in Study 4658-us-201	Dose of Eteplirsen For Study 4658-us-202
1	50 mg/kg eteplirsen for 28 weeks	50 mg/kg eteplirsen
2	30 mg/kg eteplirsen for 28 weeks	30 mg/kg eteplirsen
3a	Placebo for 24 weeks followed by 50 mg/kg eteplirsen for 4 weeks	50 mg/kg eteplirsen
3b	Placebo for 24 weeks followed by 30 mg/kg eteplirsen for 4 weeks	30 mg/kg eteplirsen

(b) (4)



5.2 Investigational Product(s)

Eteplirsen Injection .

5.2.1 Packaging and Labeling

Please refer to the study-specific pharmacy manual for information on packaging and labeling.

The label text for the investigational product will comply with Good Manufacturing Practice (GMP) and other applicable regulatory requirements and will minimally include the protocol number, contents of the vial, the appropriate cautionary statements per 21 CFR 312.6, lot number (or alternative code), storage conditions, and the name of the Sponsor.

5.2.2 Storage

Eteplirsen will be shipped with cold packs. Vials of study drug must be stored at a consistent temperature from 2 °C to 8 °C in a secured, limited-access area with temperature recording, controls and monitoring. Please refer to the study-specific pharmacy manual for further information on storage.

5.2.3 Preparation and Administration of the Investigational Product

The dose of eteplirsen will be calculated based on the most recent subject weight obtained at the site prior to the current visit. Please refer to the study-specific pharmacy manual for information on preparation and administration of eteplirsen.

(b) (4) [redacted]

An implanted venous access port may be inserted for eteplirsen administration at the discretion of the Investigator. If study drug is administered into an existing IV line, the line should be flushed with normal saline before and after administration of study drug. After study drug administration and the saline flush, the port may be flushed with heparin to heplock the port prior to de-access.

No other medication may be administered concomitantly during the study drug infusion.

(b) (4) [redacted]

For in-home dosing, additional instructions will be provided in a separate manual to the visiting nurse.

5.3 Dosing Considerations

5.3.1 Dose Selection Rationale

The doses of eteplirsen used in Study 4658-us-201 (50.0 mg/kg and 30.0 mg/kg) were expected to be well tolerated based on preclinical data in non-human primates and mice (*mdx* and wild

type) showing that the maximum feasible doses (320 mg/kg and 960 mg/kg, respectively) were well tolerated when administered once weekly for 12 weeks. The highest dose tested in the clinical study AVI-4658-28 (20 mg/kg) was also well tolerated over 12 weekly infusions and was associated with increased dystrophin production. Of note, the subject with the greatest increase in dystrophin production in that study had approximately 50% greater maximum observed concentration (C_{max}) and area under plasma concentration-time curve (AUC) of eteplirsen than the other subjects receiving this dose, suggesting that doses higher than the 20 mg/kg tested in study AVI-4658-28 might lead to larger and more consistent responses in dystrophin expression.

This extension study will allow subjects to continue receiving the same dose of eteplirsen they received in Study 4658-us-201. The continued administration of eteplirsen will allow for the collection of long-term safety data and may increase the likelihood of observing positive results on the clinical assessments being used (e.g., the 6MWT).

5.3.2 Dose Modification, Reduction, or Delay

(b) (4) [redacted]

If review of data from this open-label study suggests that continued treatment with eteplirsen is warranted, this study may be extended by protocol amendment or subjects who successfully complete this study may have the opportunity to participate in a separate follow-on, open-label eteplirsen study.

5.3.3 Treatment Discontinuation

A subject's study treatment may be discontinued at any time at the subject's request or at the discretion of the Investigator or Sponsor. The following may be justifiable reasons for the Investigator or Sponsor to discontinue a subject from treatment:

- The subject was erroneously included in the study (i.e., was found to not have met the eligibility criteria).
- The subject experiences an intolerable or unacceptable AE.
- The subject is unable to comply with the requirements of the protocol.
- The subject participates in another investigational study without the prior written authorization of the Sponsor.

(b) (4) [redacted]

The Investigator will document the reason(s) for treatment discontinuation on the eCRF.

5.4 Prior and Concomitant Medications and Therapeutic Procedures

The following therapies may be used before enrollment and throughout the study; however, attempts should be made to keep the dosage constant throughout the treatment period:

- Oral corticosteroids including, but not limited to prednisolone, prednisone, and deflazacort
- Oral angiotensin-converting enzyme (ACE) inhibitors, including but not limited to perindopril and lisinopril
- Oral β-blockers including but not limited to carvedilol and atenolol
- Angiotensin-receptor blockers, including but not limited to losartan, irbesartan, valsartan, and candesartan
- Oral laxatives, including but not limited to lactulose, Senokot, and Movicol
- Vitamin D and calcium supplements
- Over-the-counter herbal preparations, including herbal supplements, vitamins, minerals, and homeopathic preparations, provided the subject had been on stable doses for 24 weeks before enrollment in this study

Other concomitant medications (e.g., bisphosphonates or other non-RNA antisense medications) may also be taken, but every attempt should be made to keep the dosage constant throughout the study period (i.e., through Week 212).

While there are no restrictions or prescriptions for physical and respiratory therapy during this study, sites are encouraged to maintain the same general level of support throughout the study.

The following therapies are not permitted during the conduct of this study:

- Intranasal and/or inhaled and topical steroids for a condition other than DMD
- Investigational agents for the treatment of DMD
- Any medication with the potential to affect muscle mass, strength, and/or function, such as, but not limited to, growth hormone
- Immunosuppressants (other than oral or systemic corticosteroids)
- Aminoglycoside antibiotic (unless discussed and agreed with the Investigator and Medical Monitor)

5.5 Method of Assigning Subjects to Treatment

Subjects will receive the same dose of eteplirsen they received in Study 4658-us-201.

5.6 Blinding and Randomization

Not applicable.

5.7 Treatment Compliance

Treatment compliance will be assessed via compliance with scheduled weekly infusions and documented on appropriate screens/forms of the eCRF.

6 EFFICACY AND SAFETY ASSESSMENTS

6.1 Study Schedule of Events

Schedules outlining the study assessments and times of assessments are shown in (b) (4) (b) (4) Written informed consent (and assent as applicable) to participate in this study must be obtained from the parent/legal guardian(s) and subject (as applicable) at Week 28 of Study 4658-us-201.

All infusions and assessments will be performed at the central study site until a suitable satellite site closer to the subject is identified and initiated. Once a subject begins receiving weekly infusions at satellite sites, all subsequent infusions will be administered at the subject's satellite site unless otherwise indicated and approved by the Medical Monitor. Collection of AEs, concomitant medications, vital signs and weight, and blood for PK will also be performed at the satellite sites; all other assessments will be performed at the central site throughout the study unless otherwise indicated and approved by the Medical Monitor.

For visits where safety assessments are not being collected, optional in-home study treatment administration by a visiting nurse may be available after Week 124.

Unless otherwise noted, assessments should be performed in the order in which they occur in the schedule of study events.

6.2 Demographic and Screening Assessments

Informed consent (and assent as applicable) will be obtained and the subject's eligibility for the study will be determined by the Investigator according to the Inclusion and Exclusion Criteria in Section 4 at Week 28 of Study 4658-us-201. Demographic data will be based on information collected during the baseline and screening assessments of Study 4658-us-201.

6.3 Efficacy Assessments

Efficacy will be assessed by evaluating: dystrophin production in muscle biopsy tissue using IHC and Western blot analysis; exon skipping in muscle biopsy tissue using RT-PCR, lymphocyte infiltration in muscle biopsy tissue using IHC, (b) (4) (b) (4) using the 6-MWT, (b) (4), the NSAA, (b) (4) (b) (4) Additionally, respiratory function will be assessed via standard pulmonary function testing, and subject quality of life will evaluated using the PedsQL.

The efficacy assessments performed during this study are briefly summarized below in Section 6.3.1 through Section 6.3.4. Detailed instructions for performing these assessments are provided in the Study Operations Manual (SOM).

(b) (4)

6.3.2 Muscle/Motor Function and Strength

For the following assessments, every effort will be made for the same evaluator to make the same assessment on each subject throughout the study and for the assessments to be made at the same approximate time of day (which will be noted). Muscle/motor function and strength assessments will be performed at the central site.

(b) (4)

(b) (4)

6.3.2.3 North Star Ambulatory Assessment (NSAA)

The North Star Ambulatory Assessment (NSAA) will be performed at the central site at the time points specified in (b) (4) The NSAA is a clinician-administered scale that rates subject performance on various functional activities (Mazzone 2010). During this assessment, subjects will be asked to perform 17 different functional activities, including a 10 m walk/run, rising from a sit to stand, standing on 1 leg, climbing stairs, descending stairs, rising from lying to sitting, rising from the floor, lifting the head, standing on heels, and jumping. Subjects will be graded as follows: 2 = normal, no obvious modification of activity; 1 = modified method but achieves goal independent of physical assistance from another; and 0 = unable to achieve goal independently. (b) (4)

(b) (4)

(b) (4)

[redacted]

[redacted]

6.3.3 *Pulmonary Function Tests*

Pulmonary function testing will be performed at the central site at the time points specified in (b) (4) [redacted] using standard spirometry procedures. The following will.

be recorded: FVC, percent predicted FVC, FEV_1, FEV_1%, FEV_1/FVC ratio, MIP and MEP.
(b) (4) [redacted]

6.3.4 *Muscle biopsy*

Muscle biopsies will be performed at the central site at Week 20 and, for patients who consent to an additional biopsy at the Week 140 visit (b) (4) [redacted] Tissue obtained from a previously unbiopsied muscle such as the belly of the deltoid (or from the belly of an alternative upper arm muscle or quadriceps muscle in leg) will be used to evaluate the number of dystrophin-positive fibers (using IHC), the total amount of dystrophin protein (using semi-quantitative IHC and Western blot analysis), exon skipping using RT-PCR or quantitative RT-PCR (qRT-PCR), and lymphocyte infiltration using IHC. Any unused sample will be stored and may be used for future DMD biomarker and PMO research.

6.4 Safety Assessments

Safety will be assessed for all enrolled subjects from the time the informed consent is signed through Week 212. Safety parameters will include physical examinations, vital signs, clinical laboratory testing (hematology, chemistry, and urinalysis), the use of concomitant medications and collection of AEs, as described in Section 7.

6.4.1 *Electrocardiogram*

A 12-lead ECG will be obtained at the time points specified in (b) (4) [redacted] (b) (4) at the central site. ECGs will be performed only after the subject is positioned supine, resting, and quiet for a minimum of 15 minutes. The ECG will be manually reviewed and interpreted by medically qualified personnel. The Investigator will review the results of the ECG report and designate the findings as normal, abnormal (NCS or CS). ECGs collected during 2-day functional assessment visits may be collected on either Day1 or Day2.

6.4.2 *Echocardiogram*

A standard 2-dimensional (2D) ECHO will be obtained at the time points specified in (b) (4) [redacted] at the central site. The ECHO will be reviewed and interpreted by medically qualified personnel. Ejection fraction (EF) and fractional shortening (FS) will be noted. The Investigator will review the results of the ECHO report and designate the findings as normal, abnormal (CS or NCS). ECHOs collected during 2-day functional assessment visits may be collected on either Day1 or Day2.

6.4.3 *Concomitant Medications and Therapies*

Review of all concomitant medications, changes in dosage of concomitant medications, and concomitant therapies will be assessed at each visit from the time the subject signed informed consent.

6.4.4 *Vital Signs, Weight and Height*

Vital signs (oral temperature, pulse rate, respiratory rate, and blood pressure) and weight will be measured at the time points specified in (b) (4) [redacted] Vital signs will be measured prior to infusion and approximately 5 and 30 minutes after infusion. Clinically significant changes will be documented in the subject source records and eCRF as an AE. All assessments will be performed after subjects have remained seated for 5 minutes. Temperature should be recorded in degrees Celsius (° C), weight should be recorded in kg, and pulse rate and respiratory rate should be measured over 1 minute.

Vital signs and body weight will be collected at the central study site until a suitable satellite site closer to the subject is identified and initiated. Once a subject begins receiving weekly infusions at satellite sites, vital signs and body weight will be performed at the satellite site unless otherwise indicated and approved by the Sponsor. On occasions when a subject is scheduled to visit their satellite site and the central site within the same week, vital signs should be recorded at both sites.

Height will be measured at the time points specified in (b) (4) [redacted] at the central site. Height should be measured with shoes off and recorded in centimeters. If standing height cannot be obtained, height should be calculated using the following equation (Gauld 2004):

Height (cm) = 4.605U + 1.308A + 28.003,

Where U is length of the ulna measured using an anthropometer or callipers, and A is patient's age in years.

6.4.5 *Physical Examination*

Physical examinations, full and brief, will be conducted at the time points specified in (b) (4) [redacted] Physical examinations will be performed by the Investigator, an MD Sub-Investigator, or a Nurse Practitioner (if licensed in the state to perform physical examinations). Full physical examinations will be performed at the central site throughout the study and will include examination of general appearance, head, eyes, ears, nose, and throat (HEENT), heart, lungs, chest, abdomen, skin, lymph nodes, musculoskeletal, and neurological systems. Brief physical examinations will be performed on a weekly basis and will include examination of general appearance, HEENT, heart, lungs, chest, abdomen, and skin. Brief physical examinations will be performed at the central study site until a suitable satellite site closer to the subject is identified and initiated. Once a subject begins receiving weekly infusions at satellite sites, brief physical examinations will be performed at the satellite site unless otherwise indicated and approved by the Sponsor. Clinically significant changes will be documented in the eCRF as an AE.

(b) (4) [redacted]

6.4.7 *Clinical Laboratory Tests*

The following routine clinical laboratory tests will be collected at the time points specified in (b) (4) and analyzed by an accredited central laboratory selected by the Sponsor:

Hematology:	Red blood cells (RBCs), total white blood cells (WBCs), hemoglobin, hematocrit, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, and abnormal cells
Coagulation Screen:	Prothrombin time (PT), International Normalized Ratio (INR), and activated partial thromboplastin time (aPTT)
Chemistry:	Sodium, chloride, potassium, calcium, glucose, creatinine, blood urea nitrogen (BUN), albumin, uric acid, total bilirubin, alkaline phosphatase, amylase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), lactase dehydrogenase (LDH), C-reactive protein (CRP), creatine kinase (CK), and serum cystatin C.
Urinalysis:	pH, specific gravity, protein, glucose, ketones, cytology, hemoglobin, and KIM-1.

Any value outside of the current reference ranges for the laboratory performing the test will be flagged on the laboratory results. The Investigator will score all abnormal assessment results as either clinically significant (CS), or not clinically significant (NCS). Clinical significance is defined as any variation in assessment results that has medical relevance resulting in an alteration in medical care. If clinically significant deterioration from baseline levels is noted, the changes will be documented in the eCRF as an AE. The Investigator will continue to monitor the subject with additional assessments until:

- Values have reached normal range and/or baseline levels; or
- In the judgment of the Investigator together with the Sponsor's Medical Monitor, abnormal values are not related to the administration of test article or other protocol-specific procedures, and additional assessments are not medically indicated.

6.5 Pharmacokinetic Endpoints

Blood samples for PK analysis will be collected at the time points specified in (b) (4)
(b) (4)

(b) (4)

(b) (4)

7 ADVERSE EVENT REPORTING

At each study visit, subjects will be evaluated for new AEs and the status of existing AEs. The Investigator may elicit symptoms using an open-ended question, followed by appropriate questions that clarify the subject's verbatim description of AEs or change in concomitant medications. All AEs from the time that subjects provide written informed consent through Week 212 will be recorded in the subjects' source documentation and then in the eCRF.

(b) (4)

[redacted]

7.1 Definitions

7.1.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject, which does not necessarily have a causal relationship with the investigational product (active or placebo drug, biologic, or device). An AE can, therefore, be any unfavorable and unintended symptom, sign, disease or condition, or test abnormality whether or not considered related to the investigational product.

Adverse events include:

- Symptoms described by the subject or signs observed by the Investigator or medical staff.
- Test abnormalities (laboratory tests, ECG, X-rays, etc.) that result in an alteration in medical care (diagnostic or therapeutic).

Abnormalities present at baseline are considered AEs only if they reoccur after resolution or they worsen during the study.

7.1.2 Definition of a Serious Adverse Event

An SAE is any AE that results in any of the following:

Death: The subject died as the result of the event.

Life-threatening event: Any AE that places the subject, in the view of the Investigator or Sponsor, at immediate risk of death from the AE as it occurred, i.e., does not include an AE that had it occurred in a more severe form, might have caused death.

Required or prolonged inpatient hospitalization: The AE resulted in an initial inpatient hospitalization or prolonged an existing hospitalization of the patient. If a patient is hospitalized as part of the clinical use of the product, a period of normal hospitalization will be outlined in the protocol or by the judgment of the Investigator. Hospitalizations longer than this period will be prolonged hospitalizations.

Persistent or significant disability/incapacity: An AE that results in a substantial disruption of a person's ability to conduct normal life functions.

Congenital anomaly/birth defect: A congenital anomaly/birth defect that occurs in the offspring of a subject exposed to the investigational product.

Important medical events: An AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

7.2 Evaluation of Adverse Events/Serious Adverse Events

7.2.1 Relationship to Study Treatment

Assessment of the association between the AE and study exposure is important for regulatory reporting. For each AE/SAE the Investigator determines whether there is a reasonable possibility that the AE may have been caused by the study treatment according to the categories below:

Unrelated: The event is *clearly not related* to the investigational agent.

Possibly/probably related: The event *could be related/is likely to be related* to the investigational agent.

Definitely related: The event is *clearly related* to the investigational agent.

In judging relationship to investigational product, it is expected that the temporal sequence of onset of the event during or after administration of investigational product and the existence of other potential causes will be taken into account. AEs that the Investigator considers to be possibly, probably, or definitely related to the study drug will be considered to constitute drug-related AEs.

A relationship to the investigational product must be given for each AE/SAE recorded, even if there is only limited information at the time. The Investigator may change his/her opinion of causality in light of follow-up information, amending the AE/SAE report accordingly.

7.2.2 Severity Grading of Adverse Event Scoring

Note that severity is not the same as "seriousness," which is defined in Section 7.1.2, and which serves as a guide for defining regulatory reporting obligations.

7.2.2.1 Severity Grading

The Investigator will assess the severity of all AEs/SAEs as Mild, Moderate, or Severe, based on the following definitions.

Mild: The event does not interfere with the subject's usual activities.

Moderate: The event interferes with the subject's usual activities.

Severe: The event prevents the subject from undertaking their usual activities and requires therapeutic intervention or cessation of the study drug.

7.2.3 Outcome

Outcome describes the status of the AE. The Investigator will provide information regarding the subject outcome of each AE.

7.2.4 Action Taken Regarding the Investigational Product

The Investigator will provide information regarding the action taken with respect to the investigational product in response to the AE.

7.3 Timeframe for Collection of Adverse Events/Serious Adverse Events

7.3.1 Adverse Events Occurring Prior to Study Treatment

Adverse events will be collected from the time informed consent to participate in this study is obtained.

7.3.2 Adverse Events Occurring After Study Treatment

Adverse events and Serious AEs will be collected from the time of the subject's first receipt of eteplirsen at Week 1 of this extension study until Week 212 or early termination.

7.3.3 Adverse Events Occurring Following Subject Discontinuation of Treatment

(b) (4) [redacted] See Section 7.3.4 for reporting requirements after the subject completes the study.

7.3.4 Adverse Events Occurring Following Subject Completion of the Study

If, at any time after the subject has completed participation in the study (as defined in Section 3.2.1.1), the Investigator or study staff becomes aware of an SAE that the Investigator believes is possibly/probably or definitely related to the investigational product (see Section 7.2.1), then the event and any known details should be reported promptly to the Sponsor. Follow the reporting instructions in Section 7.5.

7.4 Recording of Adverse Events/Serious Adverse Events

All AEs/SAEs experienced by the subject will be recorded in the subject's source documentation and then in the eCRF. Information including a concise description of the event; date and time of event onset and resolution; determination of seriousness, severity, corrective treatment, outcome, and relationship to investigational product; and action taken regarding the investigational product will be recorded. Resolution occurs when the subject has returned to his/her baseline state of health or further improvement or worsening of the event is not expected.

Abnormalities in vital signs, laboratory results, and other safety assessments noted in Section 6.4 will be recorded as an AE if they meet the definition of an AE (see Section 7.1.1). When possible, a diagnosis should be recorded as an AE, rather than symptoms or isolated laboratory abnormalities related to that diagnosis. A medical or surgical procedure is not an AE; rather the condition leading to the procedure should be recorded as the AE. If the condition is not known, the procedure must be reported as an AE instead. Similarly, death is not an AE, but is rather the outcome of the AE(s) that resulted in death. If the AE(s) leading to death are not known, then death must be reported as an AE.

All SAEs experienced by the subject will be recorded on an SAE Report Form and reported to the Sponsor according to Section 7.5.

7.5 Reporting of Serious Adverse Events

The necessity and time requirements for reporting of SAEs to the Sponsor or its designee and/or regulatory agencies are as follows:

- All SAEs must be reported to the Sponsor/designee within 1 calendar day of the Investigator's first knowledge of the event by fax or e-mail regardless of relationship to study procedures or treatment. The Investigator is requested to supply detailed information regarding the event at the time of the initial report.

- A completed Clinical Study SAE Report Form containing a detailed written description of the event along with additional supporting documents (e.g., discharge letters, autopsy reports, and other documents) will be faxed to the Sponsor within 2 calendar days of the Investigator's first knowledge of the event. (If faxed within 1 calendar day of the Investigator's first knowledge, this form may serve as the initial notification.)

- Follow-up information, which may include copies of relevant subject records and other documents not available at the time the initial SAE Report Form was completed, must be sent to the Sponsor as soon as available. Follow-up SAE reports may describe the evolution of the reported events and any new assessment of their outcome and/or relationship to treatment. Full supporting documentation should be solicited by the investigative site even if the SAE occurred at another institution. Such documentation may include copies of relevant subject/hospital records, and pathology or autopsy reports.

- Investigators will receive copies of expedited safety reports that the Sponsor sends to regulatory agencies. The Investigator is responsible for fulfilling local reporting

requirements to their IRB. Investigators will report events to their IRB in accordance with applicable standard operating procedures and/or local reporting requirements. Investigators must forward copies of the IRB notification to the Sponsor.

7.5.1 Follow Up of Adverse Events/Serious Adverse Events

All AEs/SAEs documented at a previous visit/contact that are designated as not recovered/ not resolved or recovering/resolving will be reviewed by the Investigator at subsequent visits/ contacts.

The Investigator will provide follow-up information for any SAE to the Sponsor as soon as it is available. The Sponsor or regulatory authorities may request additional information regarding an SAE.

All AEs will be followed until the resolution of AE, completion of the subject's participation, or study termination, whichever occurs first. Serious AEs will be followed until resolution, the condition stabilizes, or the Investigator and Sponsor agree that follow up is no longer necessary. Rules for AE/SAE follow up apply to all subjects, including those withdrawn prematurely to the extent allowed by the subject's consent. The Investigator will ensure that follow up includes further investigations consistent with appropriate medical management and subject consent to elucidate the nature and/or causality of the AE/SAE.

7.6 Pregnancy Reporting

This section does not apply in this clinical study because participants are male children.

8 DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

8.1 Recording of Data

The Investigator or personnel designated by the Investigator will perform primary data collection based on source-document hospital or clinic records or other source documentation. All required study information must be recorded on the appropriate eCRF screens/forms. The eCRFs are considered complete when all data fields are completed. The study monitor will conduct 100% source data verification to ensure maximum data integrity before review and approval of each subject's eCRF. In addition, as the person ultimately responsible for the accuracy of all CRF data, the Investigator will provide electronic endorsement that the data on the eCRFs are accurate and complete.

8.2 Data Quality Assurance

The eCRFs will be reviewed by a clinical monitor from the Sponsor or a representative of the Sponsor against the source notes for identification and clarification of any discrepancies. Automated quality assurance programs will be in place to identify discrepancies, such as missing data, selected protocol violations, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be documented on electronic data clarification requests (eDCRs) and forwarded to the Investigator or study coordinator for resolution. All changes to the eCRFs will be tracked to provide an audit trail.

The Investigator must make study data accessible to the study monitor, to other authorized representatives of the Sponsor, and to the appropriate regulatory authority inspectors upon request.

8.3 Data Management

The Sponsor in close collaboration with any designee will be responsible for:

- database creation and validation
- eCRF review and data validation
- query resolution
- data analysis and reporting

9 STATISTICAL METHODS AND PLANNED ANALYSES

9.1 General Considerations

Prior to finalizing and locking the database, all decisions concerning the inclusion or exclusion of data from the analysis for each subject will be determined and documented by appropriate clinical and statistical personnel. The Sponsor's representative or designee will perform the statistical analysis of the data derived from this study. The analysis will be performed using the SAS® statistical software system as appropriate.

All data collected in this study will be documented using summary tables and subject data listings. Summary statistics for continuous variables will minimally include n, mean, standard deviation (SD), minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. Graphical displays will be provided as appropriate.

Endpoints will be assessed primarily using simple descriptive statistics and/or inferential statistics. Where appropriate, changes from baseline will be analyzed. For subjects who received eteplirsen for 28 weeks in Study 4658-us-201, changes will generally be measured relative to baseline assessments performed during that study. For subjects who received placebo for 24 weeks followed by eteplirsen for 4 weeks in Study 4658-us-201, baseline of Study 4658-us-201 and the Week 24 assessments for that study will constitute baselines for this study (see Table 9-1). Further details regarding the data analyses will be provided in the SAP.

Table 9-1: Baseline Assessments for 4658-us-202

Group	Treatment/Dose in 4658-us-201	Dose of Eteplirsen in 4658-us-202	Baseline for 4658-us-202[a]
1	50 mg/kg eteplirsen for 28 weeks	50 mg/kg eteplirsen	Baseline of 4658-us-201
2	30 mg/kg eteplirsen for 28 weeks	30 mg/kg eteplirsen	Baseline of 4658-us-201
3a	Placebo for 24 weeks followed by 50 mg/kg eteplirsen for 4 weeks	50 mg/kg eteplirsen	Baseline and Week 24 of 4658-us-201[b]
3b	Placebo for 24 weeks followed by 30 mg/kg eteplirsen for 4 weeks	30 mg/kg eteplirsen	Baseline and Week 24 of 4658-us-201

[a] Further details regarding analysis of changes from baseline will be provided in the SAP.
[b] Muscle biopsy results from Week 12 of Study 4658-us-201 will serve as baseline for this group of subjects as this constitutes the most recent biopsy prior to initiation of treatment with eteplirsen.

A statistical analysis plan (SAP) will be created and approved prior to the review of any data from this study. This document will provide a more technical and detailed description of the proposed data analysis methods and procedures.

9.2 Determination of Sample Size

This open-label extension study will be open to all subjects who successfully complete Study 4658-us-201, in which 12 subjects received eteplirsen or placebo. It is anticipated that this study

will provide additional safety and efficacy information in up to 12 subjects treated with eteplirsen (up to 6 subjects per dose group).

9.3 Analysis Populations

Subjects will be analyzed according to the actual dose of eteplirsen they received. Three analysis populations will be considered:

9.3.1 Safety Population

The safety population will consist of all subjects who are enrolled in the study and receive at least 1 dose of eteplirsen in this study. .

9.3.2 Intent-to-Treat Population (ITT)

The ITT population will include all subjects randomized into study 4658-us-201. This population is similar to the safety population and will be used for all efficacy analyses.

9.3.3 Modified Intent-to-Treat Population (ITT)

The mITT will be similar to the ITT but will exclude 2 subjects who showed rapid disease progression during the first few weeks of study 4658-us-201.

9.4 Demographics and Baseline Characteristics

Subject demographic data (e.g., age, sex, race, and ethnicity) and baseline characteristics (e.g., body weight, height, body mass index) will be summarized by dose group.

9.5 Subject Accountability

The number and percentage of subjects completing or prematurely discontinuing the study will be summarized by dose group. Reasons for premature discontinuation will be summarized.

9.6 Study Treatment Usage and Compliance

The total number of infusions administered as well as the cumulative exposure to eteplirsen will be summarized by dose group.

9.7 Efficacy Analyses

9.7.1 Primary Efficacy Analysis

The primary biological efficacy endpoint is the change from baseline at week 48 (week 20 of this study) in the percent of dystrophin positive fibers in muscle biopsy tissue (type = anti-dystrophin antibody MANDYS106) as measured by IHC. Baseline values will be the values of the first biopsy performed in Study 4658-us-201. Actual values and change from baseline values will be summarized by time point and dose group.

The analysis will be based on a restricted maximum likelihood (REML)-based mixed model with treatment (Placebo to 30 mg/kg for 24 weeks, Placebo to 50 mg/kg for 24 weeks, 30.0 mg/kg for 48 weeks, 50.0 mg/kg for 48 weeks – all durations are based on the combined 4658-us-201 and 4658-us-202 studies) as fixed effect, subject nested within treatment as random effect, with the baseline value and time since DMD diagnosis as covariates. A first-order autoregressive (AR1) covariance structured matrix will be used. Pairwise treatment comparison using the least square difference will be made between each of the 4 treatment groups. The same mixed model will be repeated using Eteplirsen for 24 weeks and Eteplirsen for 48 weeks as the fixed treatment effect.

If there is strong evidence suggesting that the change from baseline in the MANDYS106 data deviate from normal distribution, then ANCOVA for ranked data as described by Stokes (2000) will be utilized.

Additionally, for each of the four treatment groups, for the "Eteplirsen for 48 weeks" (N=8), and for "Eteplirsen for 24 weeks" (N=4), a paired t-test will be used to compare the on treatment value of MANDYS106 with the baseline value.

The analysis of changes from baseline to end-of-study in the 6MWT will be based on a REML-based mixed model repeated measures (MMRM) with treatment (placebo to eteplirsen, 30.0 mg/kg, 50.0 mg/kg), time, and treatment-by-time interaction terms as fixed effect, subject nested within treatment as random effect, with the baseline value and time since DMD diagnosis as covariates. A spatial power SP (POW) covariance structured matrix will be used to adjust for the unequal intervals in the repeated measurements. The treatment comparison will be made between the treatment groups at end-of-study and at each of the other post-baseline visits.

This procedure does not imply to replace missing data, as the mixed model would use all available on-treatment assessments. In this analysis in which the MMRM is fitted to all post-baseline data, subjects in the ITT and mITT populations who do not have complete data will still contribute to the estimates at Week 48, but will have less weight in the analysis than those subjects with complete data. Estimates for changes from baseline at each time-point in each treatment group and for treatment difference will be provided with 95% confidence intervals and p-values using the least significant difference contrasts from the model.

If there is strong evidence suggesting that the 6MWT results deviate from normal distribution, then ANCOVA for ranked data (ranked at every visit for the subjects included in the analysis) as described by Stokes (2000) will be utilized.

9.7.2 Additional Exploratory and Supportive Efficacy Analyses

Additional efficacy endpoints will evaluate changes from baseline in:

- Dystrophin intensity per fiber in muscle biopsy tissue as determined by IHC
- CD3, CD4, and CD8 lymphocyte count in muscle biopsy tissue
- Total dystrophin protein in muscle biopsy tissue as determined by Western blot analysis

- Exon skipping in muscle biopsy tissue as assessed by RT-PCR
- Timed 4-Step Test results
- NSAA results
- MVICT results
- 9-Hole Peg Test results
- PedsQL results, including the NMM
- Pulmonary function test results including FVC, percent predicted FVC, FEV_1, FEV_1%, FEV_1/FVC ratio, MIP, and MEP

Baseline values will be determined as described in Table 9-1. Actual values and change from baseline values will be summarized by time point and dose group.

9.8 Safety Analyses

Safety data will be summarized for the safety set and will be descriptive in nature. All data reported will be presented in subject data listings.

9.8.1 Physical Examination and Vital Signs

Vital signs, weight, and height will be presented by dose group and time point, summarizing the actual values and change from baseline to each post-baseline time point for each parameter using descriptive statistics. Results from physical examinations will be presented in subject data listings.

9.8.2 Clinical Laboratory Tests

The actual value and change from baseline to each on-study evaluation will be summarized by dose group for each continuous clinical laboratory parameter.

9.8.3 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). An AE will be considered treatment emergent if it begins on or after dosing with study drug in this study and up until (b) (4) after the last administration of study drug within this study. The incidence of treatment emergent AEs (TEAEs) will be tabulated and presented by system organ class and preferred term for each dose group. The number and percentage of subjects who experience at least one of the following: TEAEs, treatment-related TEAEs, SAEs, treatment-related SAEs, or TEAEs that lead to study drug discontinuation, will be summarized by dose group and severity (if appropriate). If a subject experiences multiple episodes of the same event, the subject will only be counted once for that particular event, and the event with the maximum severity or strongest relationship to study drug will be used. Treatment-related TEAEs

will be defined as those that the Investigator considers possibly, probably, or definitely related to the study drug. In the event data on the relationship of a TEAE to the study drug is missing (i.e., the relationship was not recorded on the eCRF), the event will be considered treatment-related.

All AEs, regardless of treatment emergence, will be presented in a subject data listing.

9.8.4 Concomitant Medications

All prior and concomitant medications will be coded using the World Health Organization Drug Dictionary. These data will be presented in a subject data listing.

9.8.5 Twelve-Lead Electrocardiograms

The actual value and change from baseline to each on-study evaluation will be summarized by dose group.

9.8.6 Echocardiograms

The actual value and change from baseline to each on-study evaluation will be summarized by dose group for each ECHO for EF and FS.

9.8.7 PK Analysis

The plasma concentrations values will be listed.

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[redacted]

9.10 Other Statistical Issues

Additional analyses may be conducted. Any such analyses will be detailed in the SAP.

9.10.1 Significance Levels

No formal statistical testing is planned for this study.

9.10.2 Missing or Invalid Data

In general, no substitutions will be made to accommodate missing data points. Data analyses and summaries will be based upon observed data. Data recorded on the eCRFs will be included in the subject data listings.

10 SPECIAL REQUIREMENTS AND PROCEDURES

10.1 Compliance with Ethical and Regulatory Guidelines

This study was designed and will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and in conformance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) E6 guidance documents. The study will comply with the requirements that are enunciated in the US Code of Federal Regulations (CFR) related to the protection of human subjects (21 CFR Part 50), IRBs (21 CFR Part 56) and investigational new drug applications (INDs) (21 CFR Part 312), electronic records and electronic signatures (21 CFR 11) and financial disclosure (21 CFR 54).

10.2 Institutional and Ethics Review

This study will be conducted in full compliance with the IRB regulations in 21 CFR 56. Before enrollment of subjects into the study, the protocol and informed assent (for subjects) and informed consent (for parents/legal guardians) documents will be reviewed and approved by an IRB that is in compliance with 21 CFR 56. Amendments to the protocol will be subjected to the same IRB review requirements as the original protocol. The Investigator will promptly notify the IRB and Sponsor of any serious or unexpected AEs or of any other information that might affect the safe use of the study drug during the study. A letter documenting the IRB approvals must be sent to the Sponsor before initiation of the study or before an amendment is instituted. All correspondence with the IRB should be retained in the study files.

10.3 Informed Consent/Assent and Authorization for Use and Disclosure of Protected Health Information

Written informed consent from each subject's parent(s) or legal guardian(s), written assent from each subject for whom it is applicable, and written authorization of use and disclosure of protected health information (PHI) from each subject's parent(s) or legal guardian(s) must be obtained before any study-specific screening or baseline period evaluations are performed. One copy of the signed informed consent/assent documents and the signed authorization for use and disclosure of PHI will be given to the subject; the Investigator will retain the original copies of these documents.

The informed consent/assent documents and authorization for use and disclosure of PHI, which are prepared by the Investigator or the site, must be reviewed and approved by the Sponsor and the IRB before initiation of the study. The informed consent document must contain the basic required elements of consent and additional elements, as applicable, as specified in 21 CFR 50.25. The authorization for use and disclosure of PHI must contain the elements required by 45 CFR 164.508(b) in the US for valid authorizations.

10.4 Confidentiality

10.4.1 Data

All information regarding the nature of the proposed investigation that is provided to the Investigator by the Sponsor, the Sponsor's designee, or the study monitor, with the exception of information that is required by law or regulations to be disclosed to the IRB, the subject's parent(s) or legal guardian(s) or the appropriate regulatory authority, must be kept in confidence by the Investigator in accordance with current Health Insurance Portability and Accountability Act standards.

10.4.2 Subject Anonymity

The anonymity of participating subjects will be maintained to the extent required by applicable laws and in accordance with current Health Insurance Portability and Accountability Act standards. Subjects will be identified by their initials and an assigned subject identification number on the eCRFs and other documents that are reviewed by the study monitor. The Investigator must maintain all documents related to the study that identify the subject (e.g., the signed informed consent document) in strict confidence, except to the extent necessary to allow auditing by the appropriate regulatory authorities, the IRB, the study monitor, or the Sponsor or its representatives.

10.5 Changes to the Conduct of the Study or Protocol

Substantive changes to the protocol include changes that affect the safety of subjects or changes that alter the scope of the investigation, the scientific quality of the study, the experimental design, doses, assessment variables, the number of subjects to be treated, or the subject selection criteria. Such changes must be documented as a protocol amendment by the Sponsor and must only be implemented upon joint approval of the Sponsor, Investigator, and IRB.

A protocol amendment must receive IRB approval before implementation. In parallel with the IRB-approval process, the protocol amendment will be submitted to the US FDA as an amendment to the IND application. If a protocol amendment requires changes in the informed consent and assent documents, the revised documents must be reviewed and approved by the Sponsor before review and approval by the IRB.

Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular subject and that are deemed by the Investigator as crucial for the safety and well-being of that subject may be instituted for that subject only. The Investigator will contact the medical monitor as soon as possible regarding such a departure. These departures do not require preapproval by the IRB; however, the IRB and medical monitor must be notified in writing as soon as possible in accordance with the IRB policies after the departure has been made. In addition, the Investigator will document the reasons for the protocol deviation and the ensuing events in the subject's eCRF. Documentation of IRB approval of any amendments must be returned to the Sponsor or designee.

11 STUDY DOCUMENTATION AND ADMINISTRATIVE DATA

11.1 Case Report Forms

An eCRF is required and must be completed for each subject, with all required study data accurately recorded such that the information matches the data contained in medical records (e.g., physician's notes, clinic charts, and other study-specific source documents). The Investigator or designee (e.g., study coordinator) will be trained in the use of the study-specific eCRFs and will enter the data for each subject directly onto the eCRFs.

Source documents will be filled out legibly and completely in ink. Unless explicitly directed, blank data fields are not acceptable. Any erroneous entries made on the source documents will be crossed out with a single line, initialed and dated, and the correct entry, if appropriate, will be recorded. Copies of source documents will be provided to the Sponsor or designee as appropriate, while original source documents will be maintained in the Investigator's site file. Illegible or incomplete entries or entries needing additional explanation will be returned or queried to the Investigator for clarification.

Data will be entered by the site onto the eCRFs. Unless explicitly directed, blank data fields are not acceptable. Any erroneous entries made on the eCRFs should be corrected. Changes made to the data after initial entry into the eCRF will be captured via an electronic audit trail, and should include the reason for change. Incomplete entries or entries needing additional explanation will be highlighted or queried to the Investigator for clarification.

The eCRFs will be reviewed and source verified by the study monitor (e.g., clinical research associate) during periodic site visits. During the data collection process, automated quality assurance programs will be in place to identify discrepancies, such as missing data, selected protocol violations, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be documented on eDCRs and forwarded to the Investigator or study coordinator for resolution. The Investigator or study coordinator will be responsible for providing resolutions to the data queries and for correcting the eCRFs, as appropriate. All changes to the eCRFs will be tracked to provide an audit trail. The Investigator has the final responsibility for the accuracy of all clinical data that are entered on the eCRFs and will be required to provide written endorsement that the data are accurate and complete.

11.2 Study Files

Documentation concerning Investigator data (e.g., a signed Form FDA 1572, Curriculum vitae, and completed and signed Financial Disclosure Form), IRB data (including documentation of IRB approval and compliance), and clinical laboratory information, as well as the signed protocol page and a blank copy of the IRB-approved informed consent and assent documents and authorization, are among the critical documents required before study site initiation visit is to occur. Copies of these documents, as well as supplemental information, such as the Investigator's Brochure, responsibilities and obligations of Investigators and Sponsor, and the Clinical Study Operations Manual, final protocol, and a detailed description of the Sponsor and Investigator responsibilities must be kept on-site in a special study file. This file also will contain copies of

blank CRFs (i.e., copies of blank data entry screens), the Statement of Investigator Forms (Form FDA 1572 in the US), curricula vitae and financial disclosure forms for the Investigator and Sub-Investigators, subject accountability records, drug accountability (receipt/dispensing) records, Sponsor/Investigator correspondence, IRB correspondence, changes to the protocol, information on monitoring activities, biological sample records, and SAE and safety reports.

11.3 Study Monitoring and Data Quality Control and Quality Assurance

Study monitor who have been selected and prequalified by the Sponsor for their experience, education and training, in accordance with the Sponsor's requirements and after having documentation of training in the applicable regulations, ICH guidelines and GCP and study specific procedures and protocol, will ensure that the study is conducted and documented properly by carrying out the relevant activities, as outlined in GCPs (ICH E6, Section 5.18.4). The progress of the study will be monitored through:

- Periodic on-site visits
- Frequent telephone communications between the site (Investigator and study coordinator) and the study monitor(s), medical monitor and Sarepta Therapeutics Inc.
- Review of eCRFs, source documentation and clinical records
- Following the approved monitoring plan

Sponsor representatives may accompany the study monitor to the site during scheduled visits.

The Investigator or personnel designated by the Investigator will perform primary data collection based on source-document hospital or clinic records or other source documentation. All required study information must be recorded on the appropriate eCRF pages. The eCRFs are considered complete when all data fields are completed. The study monitor will conduct 100% source data verification to ensure maximum data integrity before review and approval of the each subject's eCRFs. In addition, as the person ultimately responsible for the accuracy of all eCRF data, the Investigator will provide electronic endorsement that the data on the eCRFs are accurate and complete. Automated quality assurance programs will be in place to identify discrepancies, such as missing data, selected protocol violations, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be documented on eDCRs and forwarded to the Investigator or study coordinator for resolution. All changes to the eCRFs will be tracked to provide an audit trail.

Audits may be carried out by the Sponsor's representatives, and inspections may be performed by regulatory authorities or IRBs before, during, or after the study. The Investigator will allow and assist the Sponsor's representatives and any regulatory agency to have direct access to all study records, eCRFs, subject medical records and other source documentation, investigational product dispensing records and investigational product storage area, study facilities, and any other documents considered source documentation. Audit certificate(s) will be provided.

The Investigator must make study data accessible to the study monitor, to other authorized representatives of the Sponsor, and to the appropriate regulatory authority inspectors such as the FDA.

11.4 Retention of Study Documents

At study completion, all eCRFs data will be loaded onto a write-protected disc. This disc will be presented to the Investigator. The supporting documentation and administrative records all must be retained by the Investigator for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

In compliance with ICH E6, essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. No study documents will be destroyed or moved to a new location without prior written approval from the Sponsor. If the Investigator relocates, retires, or withdraws from the clinical study for any reason, all records that are required to be maintained for the study should be transferred to an agreed-upon designee.

Subject records or other source data must be kept for the maximum period of time mandated by the hospital, institution, or private practice, but not less than 15 years.

If off-site archiving is used, all records should be retrieved and made available for review at the time of an audit or regulatory authority inspection.

11.5 Termination of Study or Study Site

If the Sponsor, the Investigator, the medical monitor, the study monitor, IRB, or appropriate regulatory officials discover conditions arising during the study that indicate the study should be halted or that the study center should be terminated, appropriate action may be taken after consultation among the Sponsor, the Investigator, IRB and the medical monitor.

Conditions that may warrant termination of the study or an individual site include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study
- A decision by the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- Failure of the Investigator to enroll subjects into the study at an acceptable rate

- Failure of the Investigator to comply with pertinent regulations of IRB or appropriate regulatory authorities such as the statement of the Investigator (Form FDA 1572), 21 CFR 11, 50, 54 and 312.
- Submission of knowingly false information from the research facility to the Sponsor, the study monitor, IRB or regulatory authority
- Insufficient adherence to protocol requirements consistent with 21 CFR 312.56B, compliance with the signed agreement (Form FDA 1572), the general investigational plan (protocol), and requirements of 21 CFR 312.

Study termination and follow-up will be performed in compliance with the conditions set forth in ICH E6 on GCP (Sections 4.12, ICH E6 4.13, ICH E6 5.20, and ICH E6 5.21) as well as 21 CFR 312.56b, which requires a Sponsor to ensure an Investigator's compliance with the signed agreement (Form FDA-1572), the general investigational plan (protocol), or the requirements of 21 CFR 312 or other applicable parts and to promptly either secure compliance or discontinue shipments of the investigational new drug to the Investigator and end the Investigator's participation in the investigation.

11.6 General Information

The Investigator should refer to the associated most current and up to date Investigator's Brochure, the Clinical Study Operations Manual, the information that is provided during the study initiation visit, the information that is provided by the study monitor during routine monitoring visits, and the appendices of this protocol for further information on this investigational new product or details of the procedures that are to be followed during this study.

11.7 Dissemination of Study Results

The information that is developed during the conduct of this clinical study is considered to be strictly confidential. This information may be disclosed only as deemed necessary by Sarepta Therapeutics Inc. However, at the conclusion of this clinical study, a clinical study report will be prepared. In addition a manuscript will be prepared for publication in a reputable scientific journal under the direction of the Investigator and Sarepta Therapeutics Inc. The sponsor, Sarepta Therapeutics Inc., and the Investigator intend to publish and communicate the clinical study results, irrespective of positive or negative findings. Data generated for this study will be exclusively owned by Sarepta Therapeutics Inc., as detailed in the Clinical Trial Agreement. The study will be registered on ClinicalTrials.gov once appropriate approval has been received and before the first subject is enrolled.

11.8 Investigational Product Control

11.8.1 Receipt of Investigational Product

A proof of receipt, which details the quantity and description of the investigational product, will accompany the shipment from the Sponsor to the Investigator. This receipt must be signed, dated, and sent to the Sponsor or Sponsor designee within 48 hours after receipt, while retaining

the original within the site pharmacy files. The Investigator must ensure that the investigational product is maintained in a controlled location, with limited access, and under appropriate storage conditions.

11.8.2 Disposition of Unused Investigational Product

All unused investigational products must be maintained under adequate storage conditions in a limited-access area. If any unused material is remaining upon completion of the study, the material will be returned to the Sponsor or destroyed only after the following has been completed:

- Accountability has been performed by a representative of the Sponsor.
- An Investigational Product Returns and Destruction Form has been completed by the pharmacist or designee and a copy provided to the Sponsor

11.8.3 Product Handling and Complaints Reporting

If there are any issues during the course of the study related to the quality of the investigational product, the Investigator, clinical site pharmacist or pharmacy designee should contact the Sponsor.

12 REFERENCES

Arahata K, Engel AG. Monoclonal antibody analysis of mononuclear cells in myopathies. I: Quantitation of subsets according to diagnosis and sites of accumulation and demonstration and counts of muscle fibers invaded by T cells. Ann Neurol. 1984; 16(2):193-208.

Arechavala-Gomeza V, Graham IR, Popplewell LJ, Adams AM, Aartsma-Rus A, Kinali M. Comparative Analysis of antisense oligonucleotide sequences for targeted skipping of exon 51 during dystrophin pre-mRNA splicing in human muscle. Hum Gene Ther. 2007;18:798-810.

Brooke MH, Fenichel GM, Griggs RC, et al. Duchenne muscular dystrophy: patterns of clinical progression and effects of supportive therapy. Neurology. 1989 Apr;39(4):475-81.

Bushby KM, Gardner-Medwin D, Nicholson LV, et al. The clinical, genetic and dystrophin characteristics of Becker muscular dystrophy. II. Correlation of phenotype with genetic and protein abnormalities. J Neurol. 1993a;240(2):105-12.

Bushby KM, Gardner-Medwin D. The clinical, genetic and dystrophin characteristics of Becker muscular dystrophy. I. Natural history. J Neurol. 1993b;240(2):98-104.

Cacchiarelli D, Legnini I, Martone J, Cazzella V, D'Amico A, Bertini E, Bozzoni. miRNAs as serum biomarkers for Duchenne muscular dystrophy. EMBO Mol Med. 2011;3(5):258–265.

Davis SE, Hynan LS, Limbers CA, et al. The PedsQL in pediatric patients with Duchenne muscular dystrophy: feasibility, reliability, and validity of the Pediatric Quality of Life Inventory Neuromuscular Module and Generic Core Scales. J Clin Neuromuscul Dis. 2010 Mar;11(3):97-109.

Eagle M, Baudouin SV, Chandler C, Giddings DR, Bullock R, Bushby K. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. Neuromuscul Disord. 2002;12(10):926-9.

Emery AE. The muscular dystrophies. Lancet. 2002;359(9307):687-95.

Gauld LM, Kappers J, Carlin JB, Robertson CF. Height prediction from ulna length. Dev Med Child Neurol. 2004;46:475-480.

Heald A, Anderson LV, Bushby KM, Shaw PJ. Becker muscular dystrophy with onset after 60 years. Neurology. 1994;44(12):2388-90.

Mazzone E, Martinelli D, Berardinelli A, et al. North Star Ambulatory Assessment, 6-minute walk test and timed items in ambulant boys with Duchenne muscular dystrophy. Neuromuscul Disord. 2010 Nov;20(11):712-6. Epub 2010 Jul 14.

Muntoni F, Torelli S, Ferlini A. Dystrophin and mutations: one gene, several proteins, multiple phenotypes. Lancet Neurol. 2003; 2(12):731-40.

Nadarajah VD, van Putten M, Chaouch A, Garrood P, Straub V, Lochmüller H, Ginjaar HB, Aartsma-Rus AM, van Ommen GJ, den Dunnen JT, 't Hoen PA. Serum matrix metalloproteinase-9 (MMP-9) as a biomarker for monitoring disease progression in Duchenne muscular dystrophy (DMD). Neuromuscul Disord. 2011 Aug;21(8):569-78

Spencer MJ, Tidball JG. Do immune cells promote the pathology of dystrophin-deficient myopathies? Neuromuscul Disord. 2001 Sep;11(6-7):556-564.

Stokes ME, Davis CS, and Koch GG. Categorical data analysis using SAS® system, 2nd Edition. SAS Publishing. 2000.

Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care. 2001 Aug;39(8):800-12.

Visser J, Mans E, de Visser M, et al. Comparison of maximal voluntary isometric contraction and hand-held dynamometry in measuring muscle strength of patients with progressive lower motor neuron syndrome. Neuromuscul Disord. 2003 Nov;13(9):744-750.

13 APPENDICES

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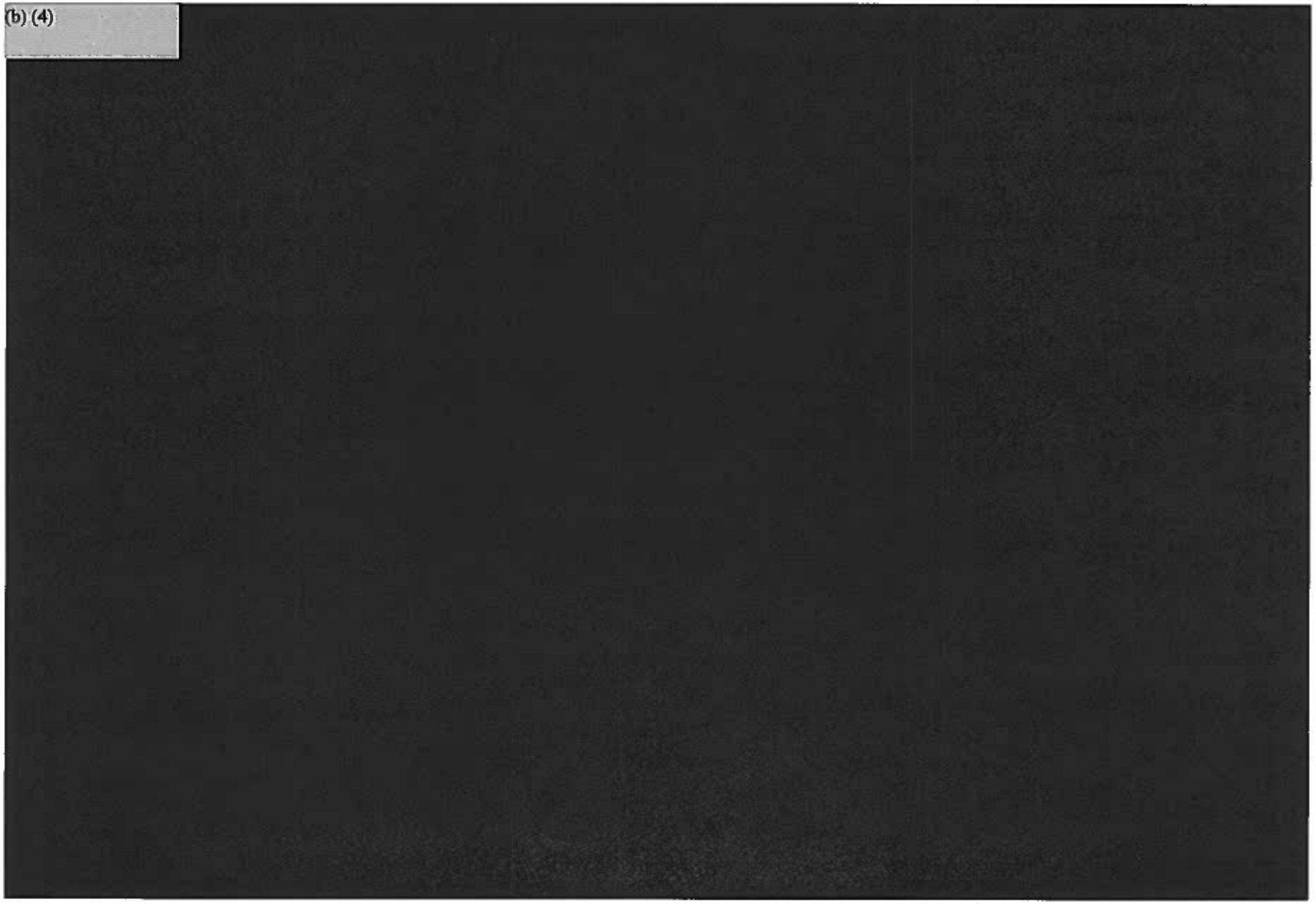

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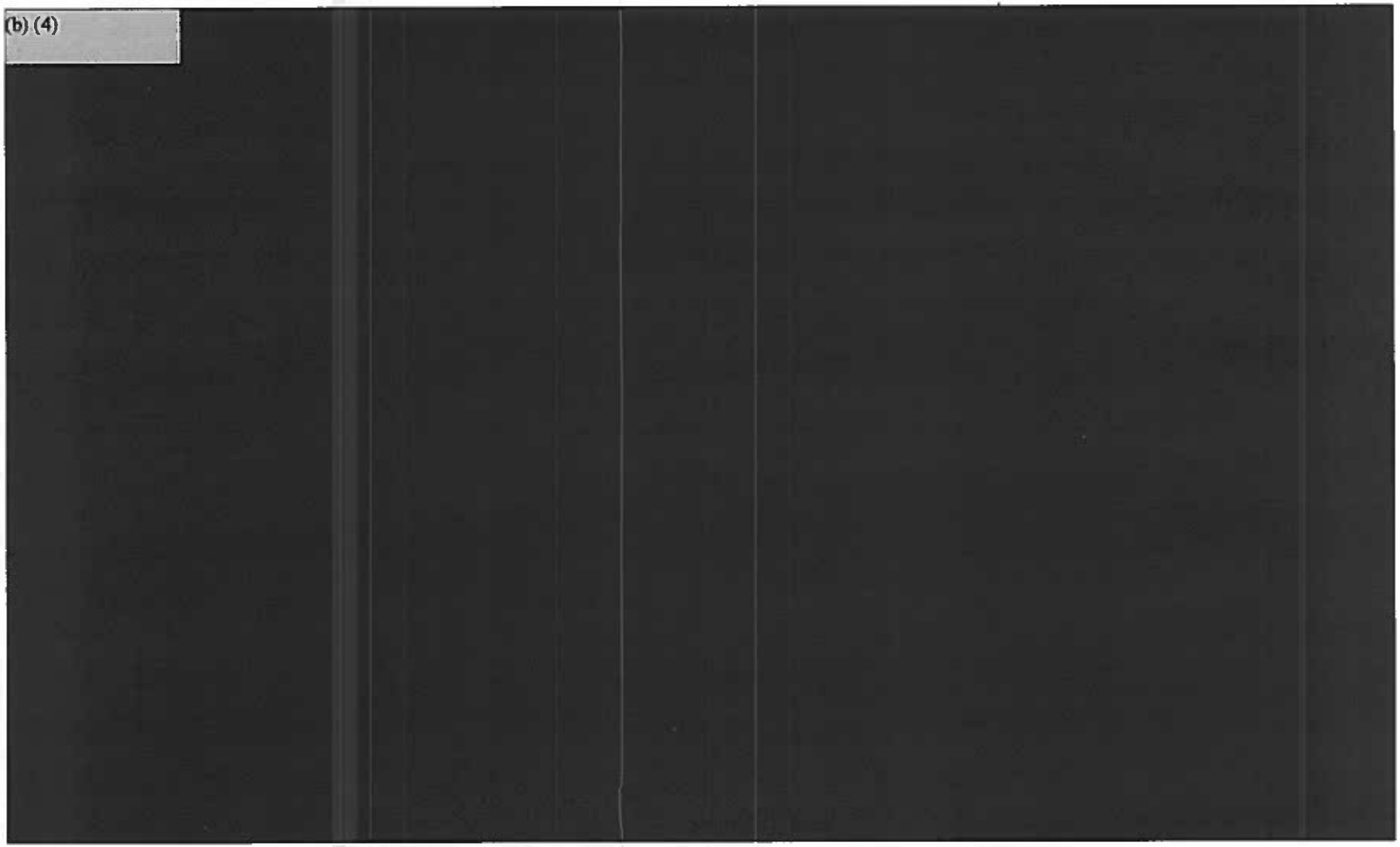

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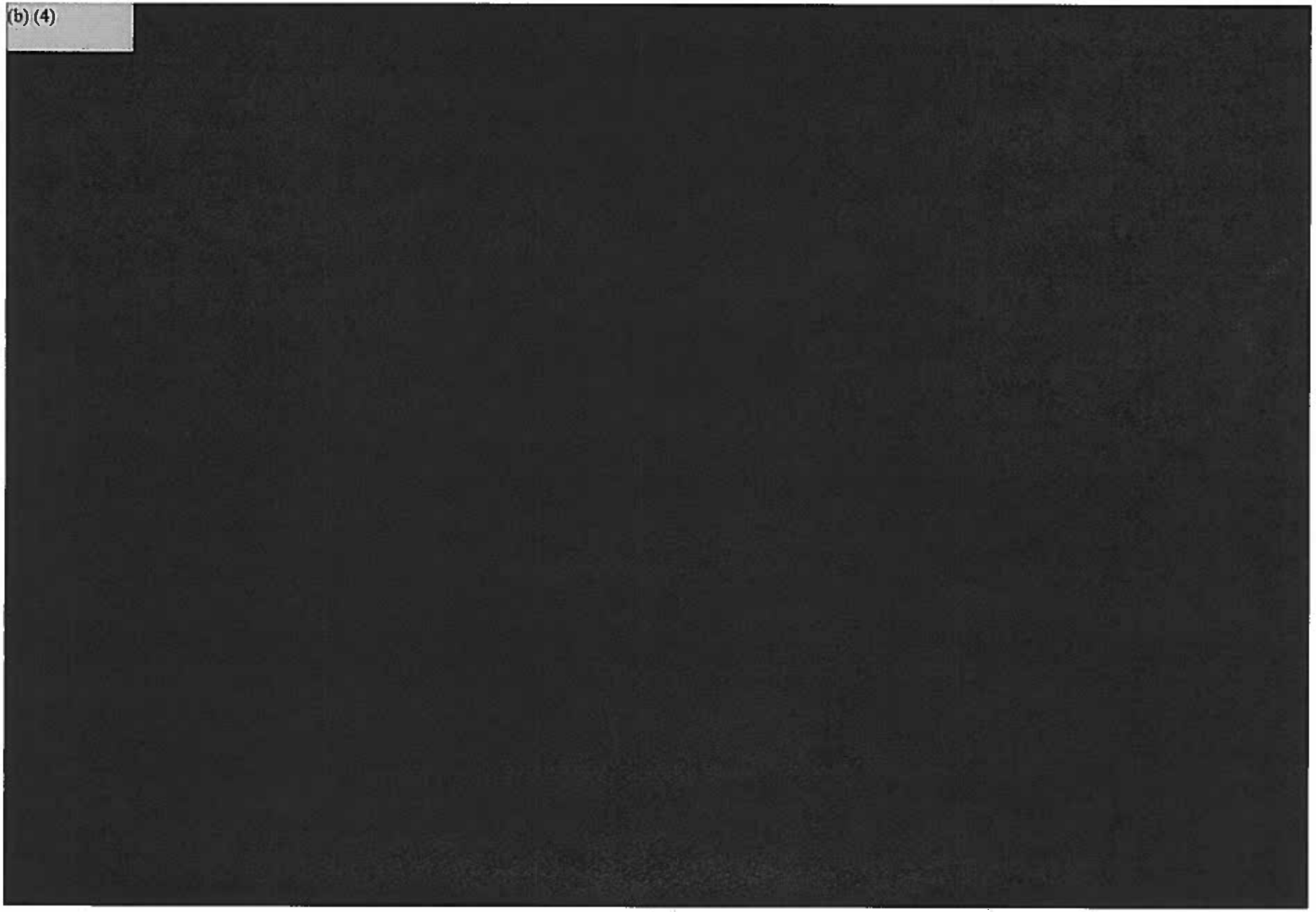

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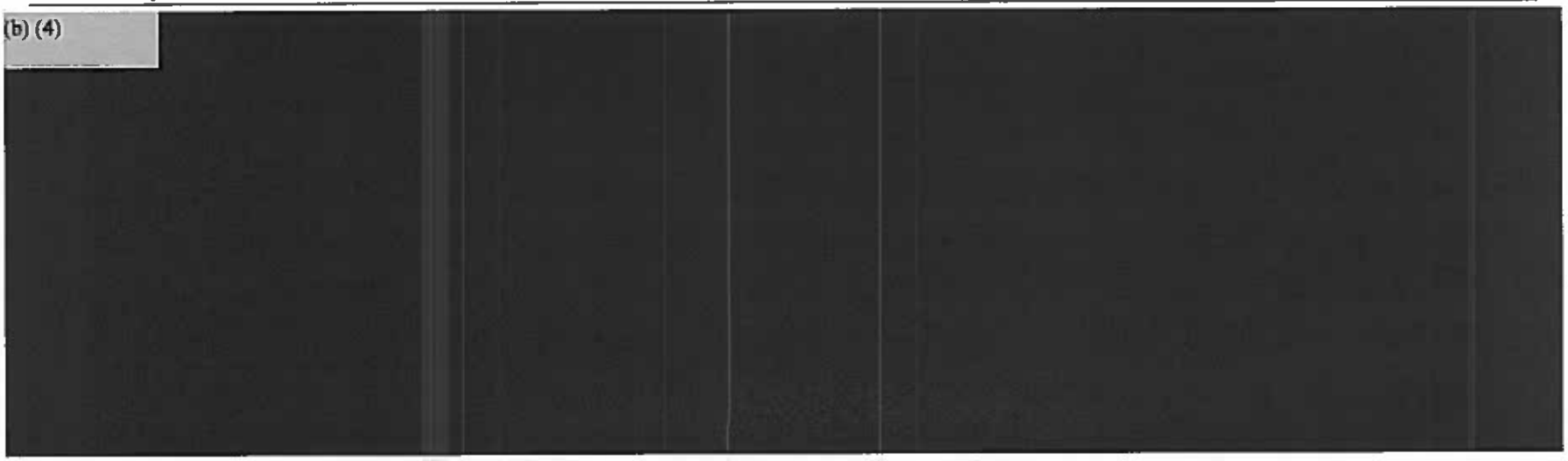

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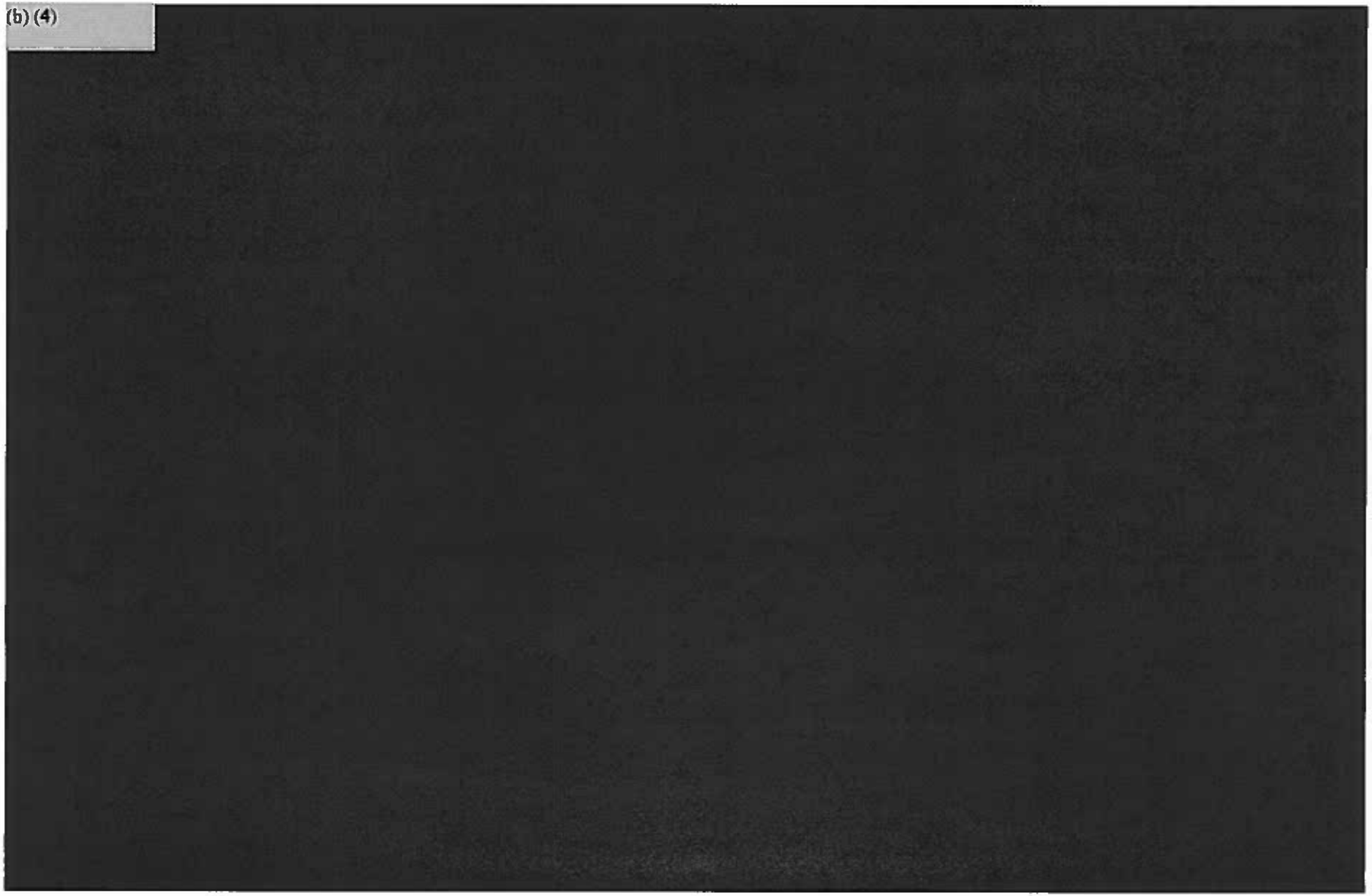

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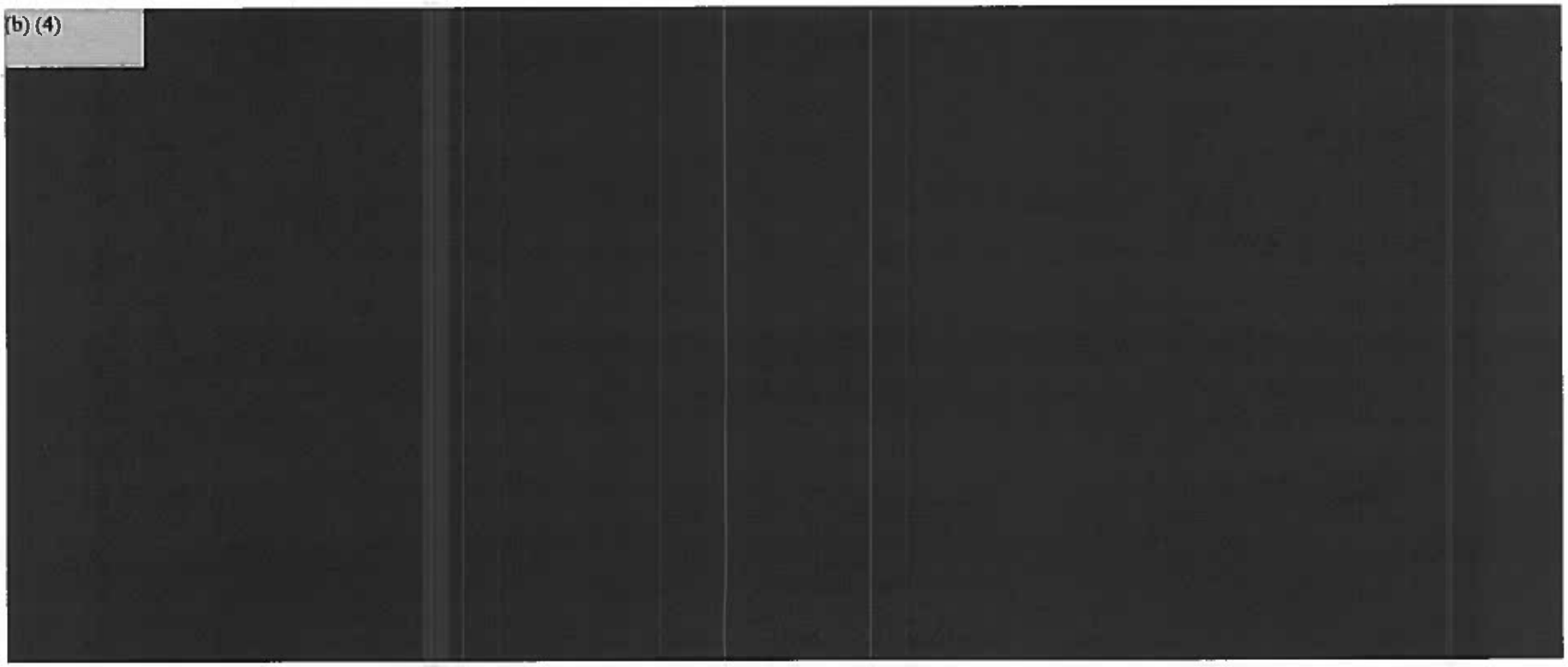

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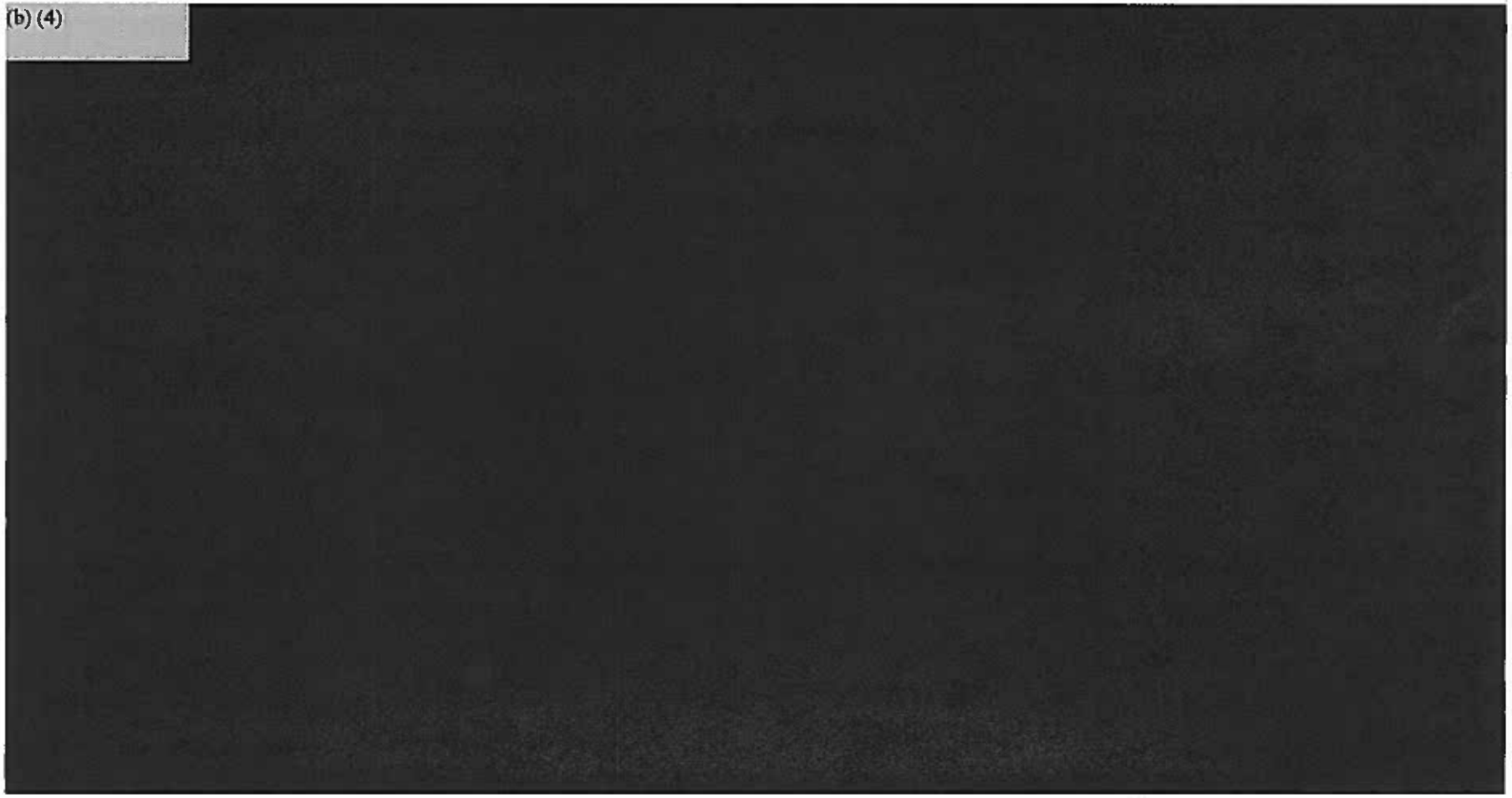

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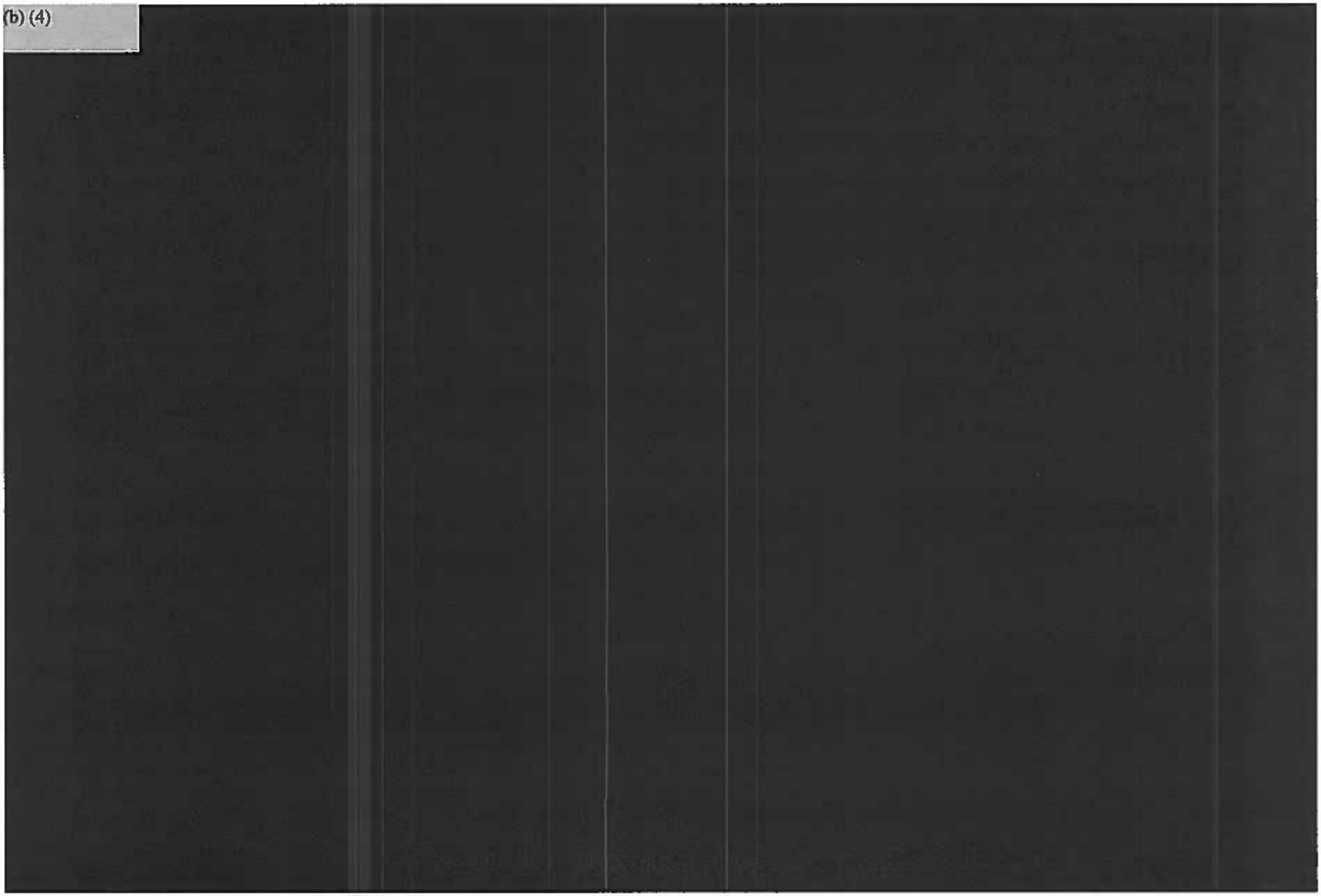

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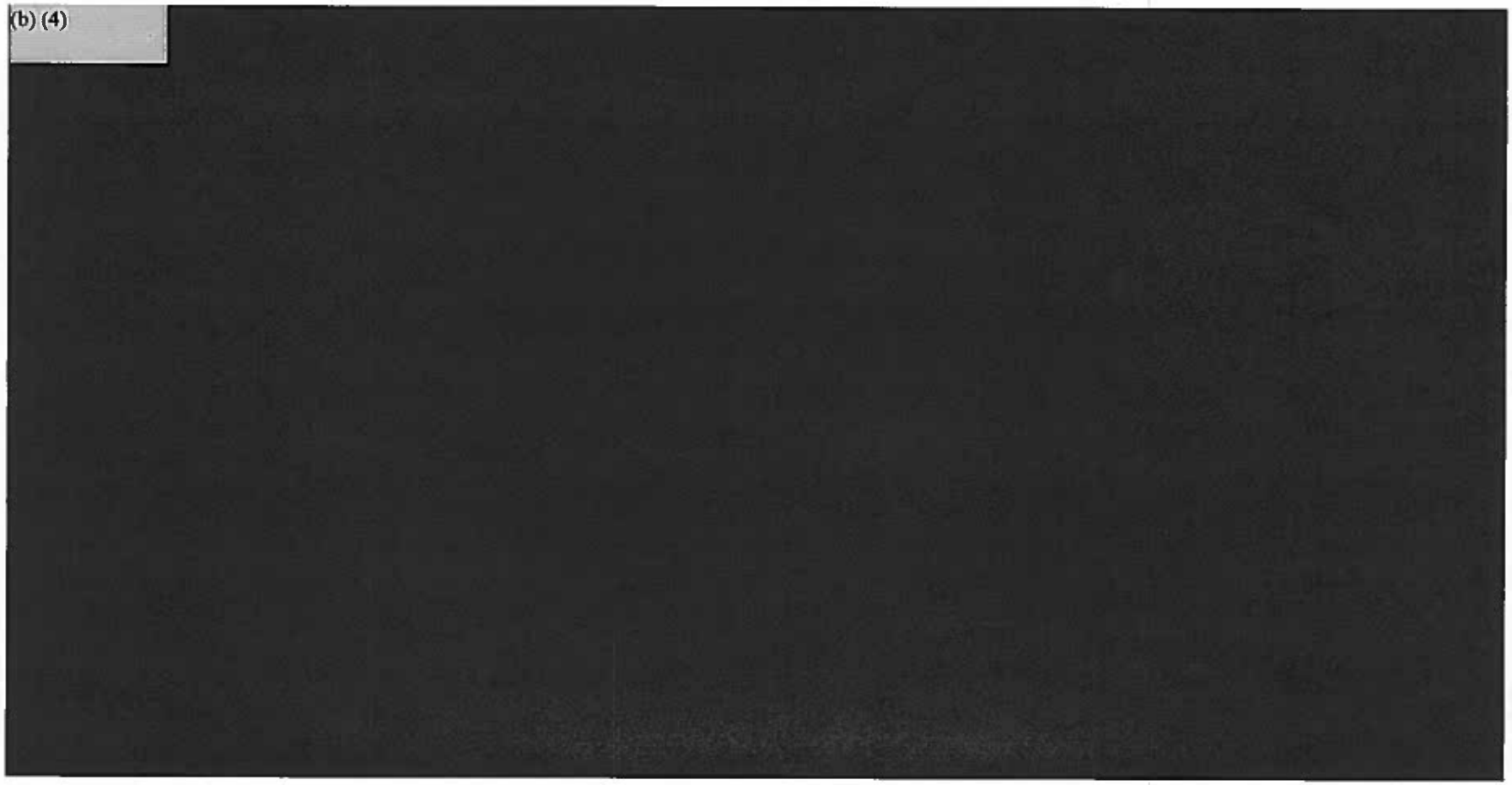

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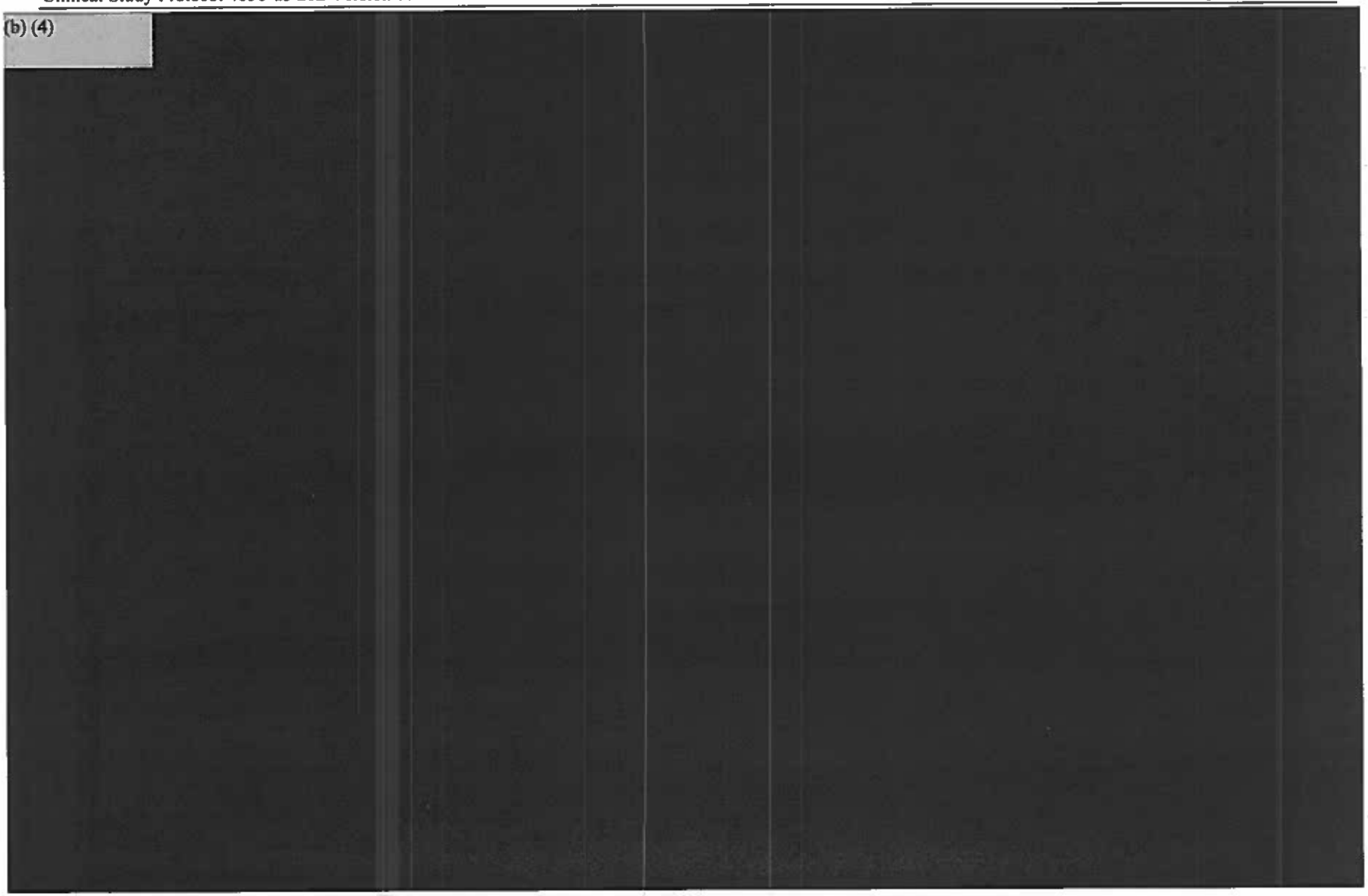

13.2 Appendix II: CONFIDENTIALITY AND INVESTIGATOR STATEMENT

I have received and read the Investigator's Brochure for eteplirsen. I have read Protocol 4658-us-202-07, "Open-Label, Multiple-Dose, Efficacy, Safety, and Tolerability Study of Eteplirsen Injection in Subjects with Duchenne Muscular Dystrophy who Participated in Study 4658 us 201" and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

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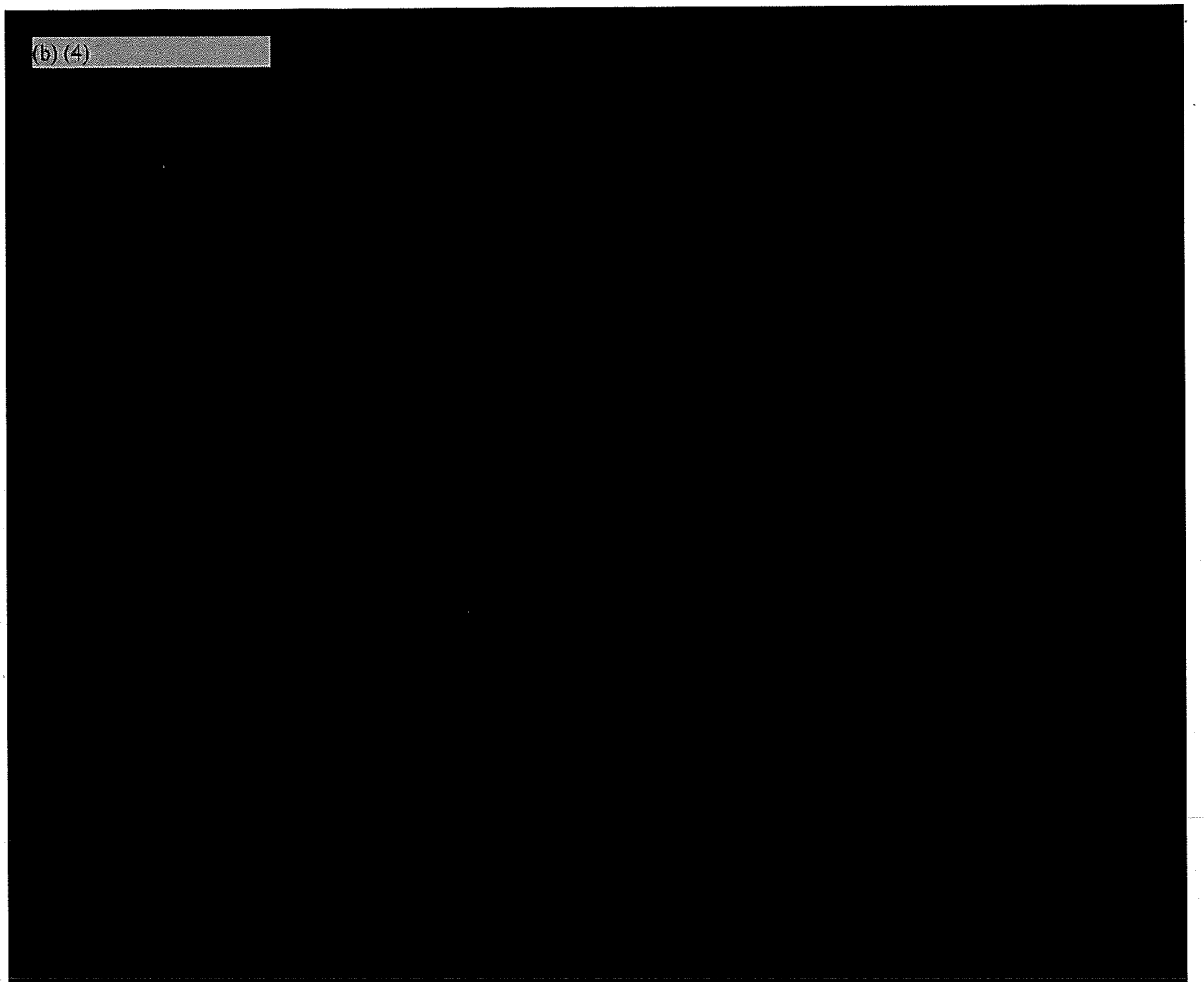

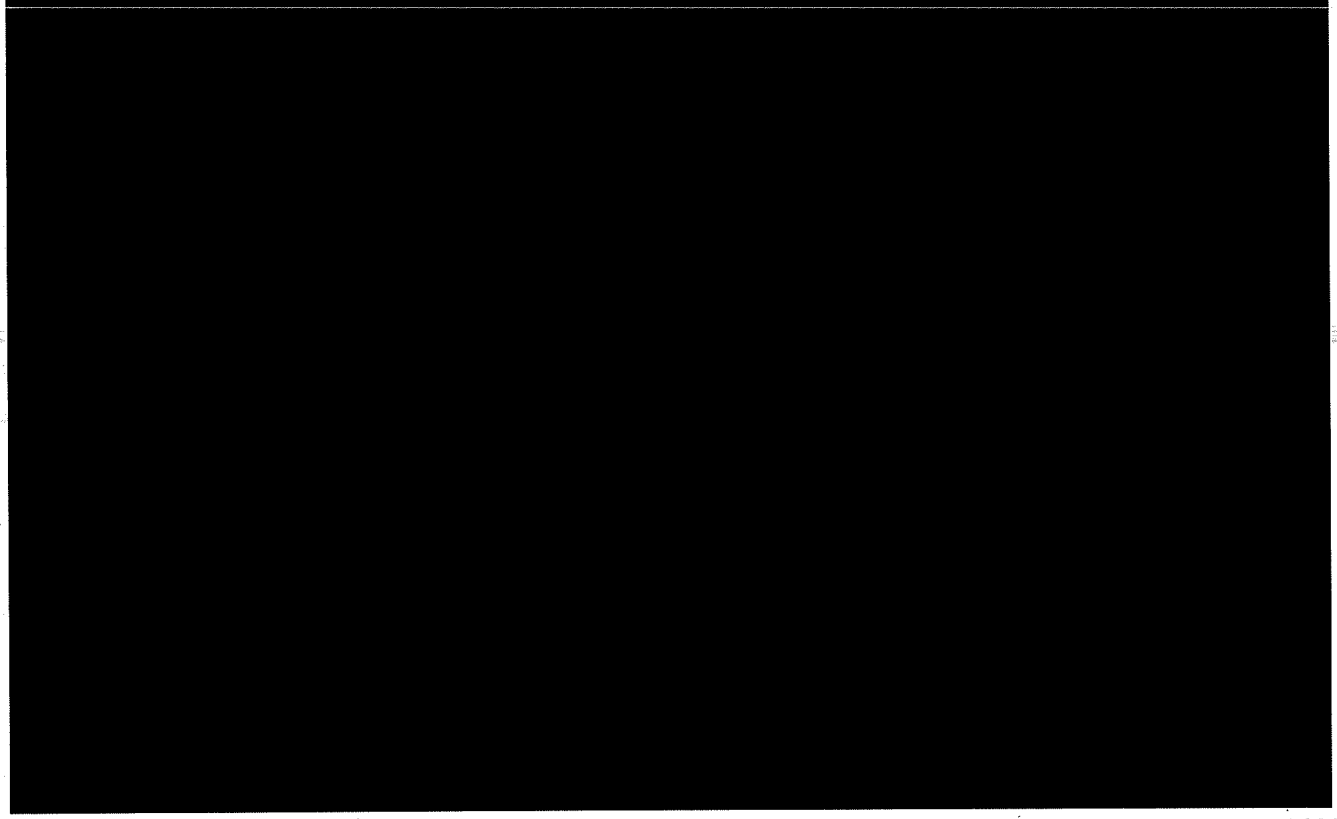

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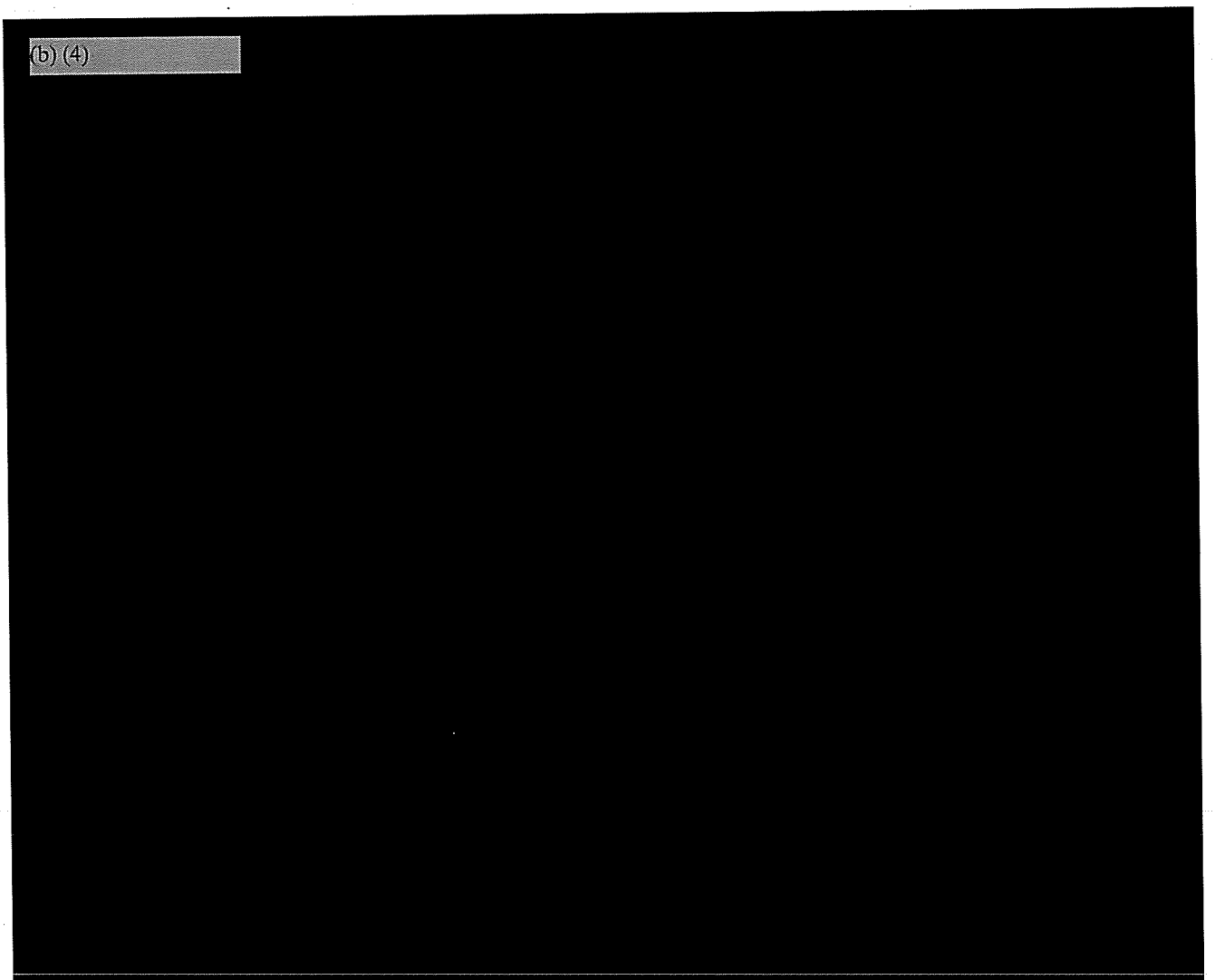

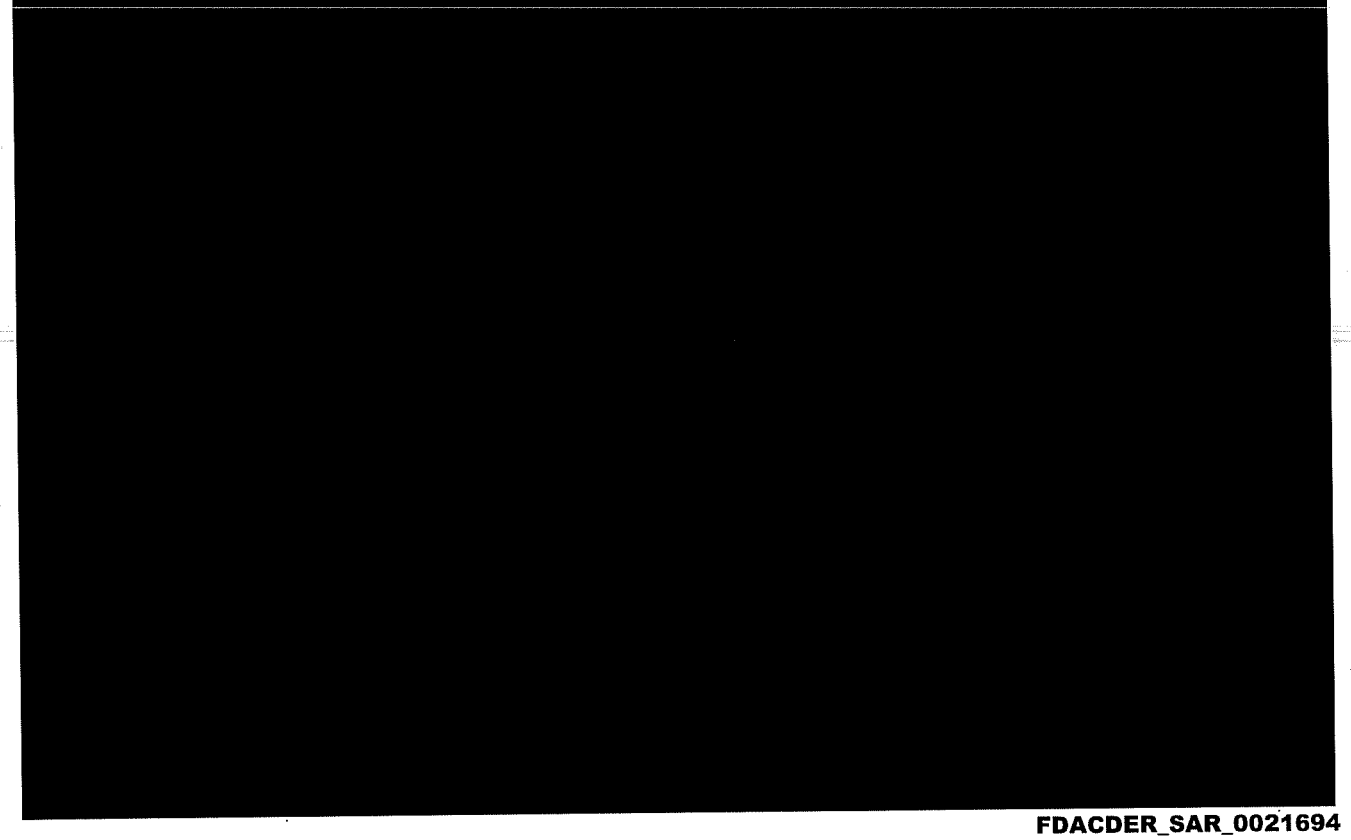

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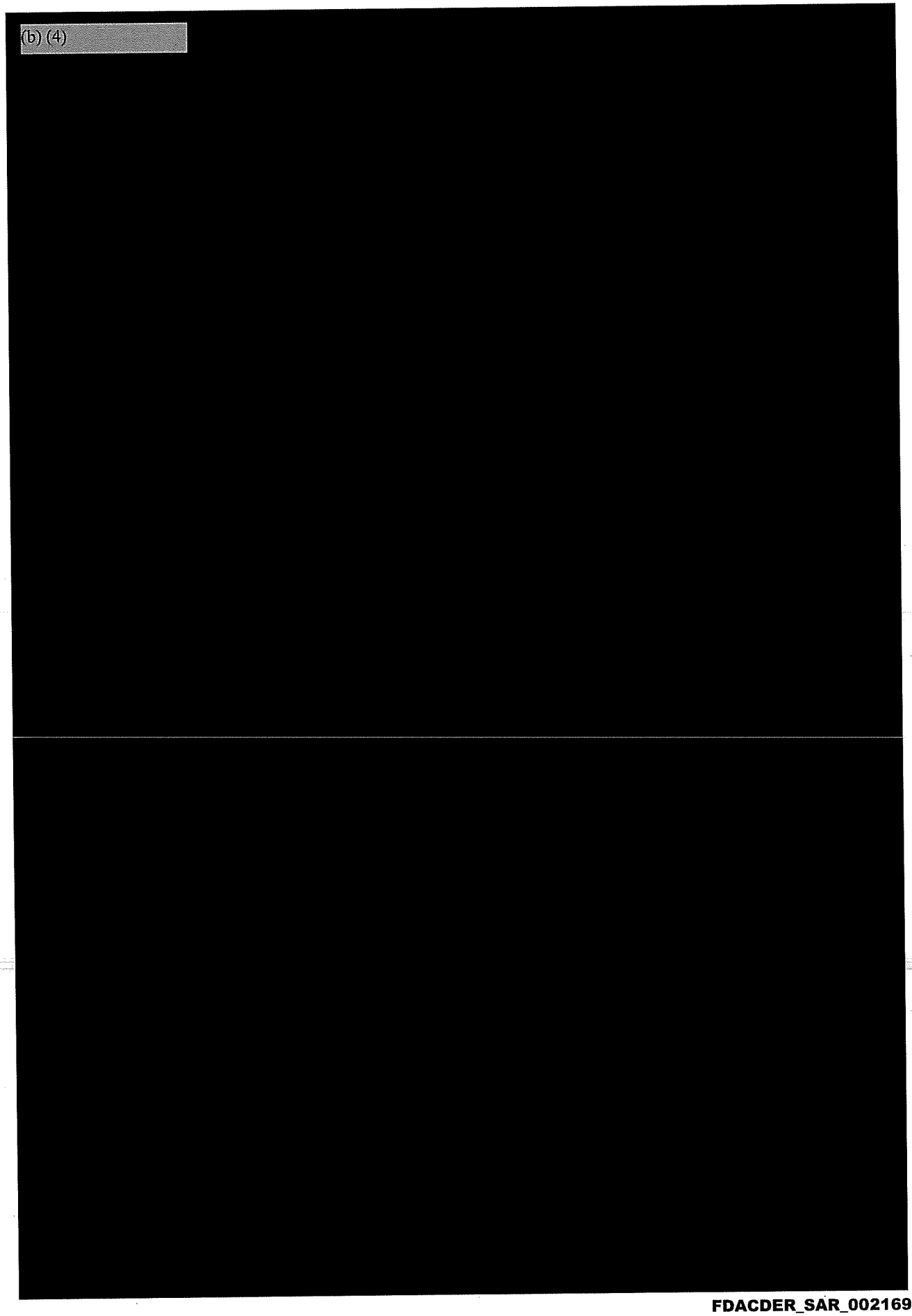

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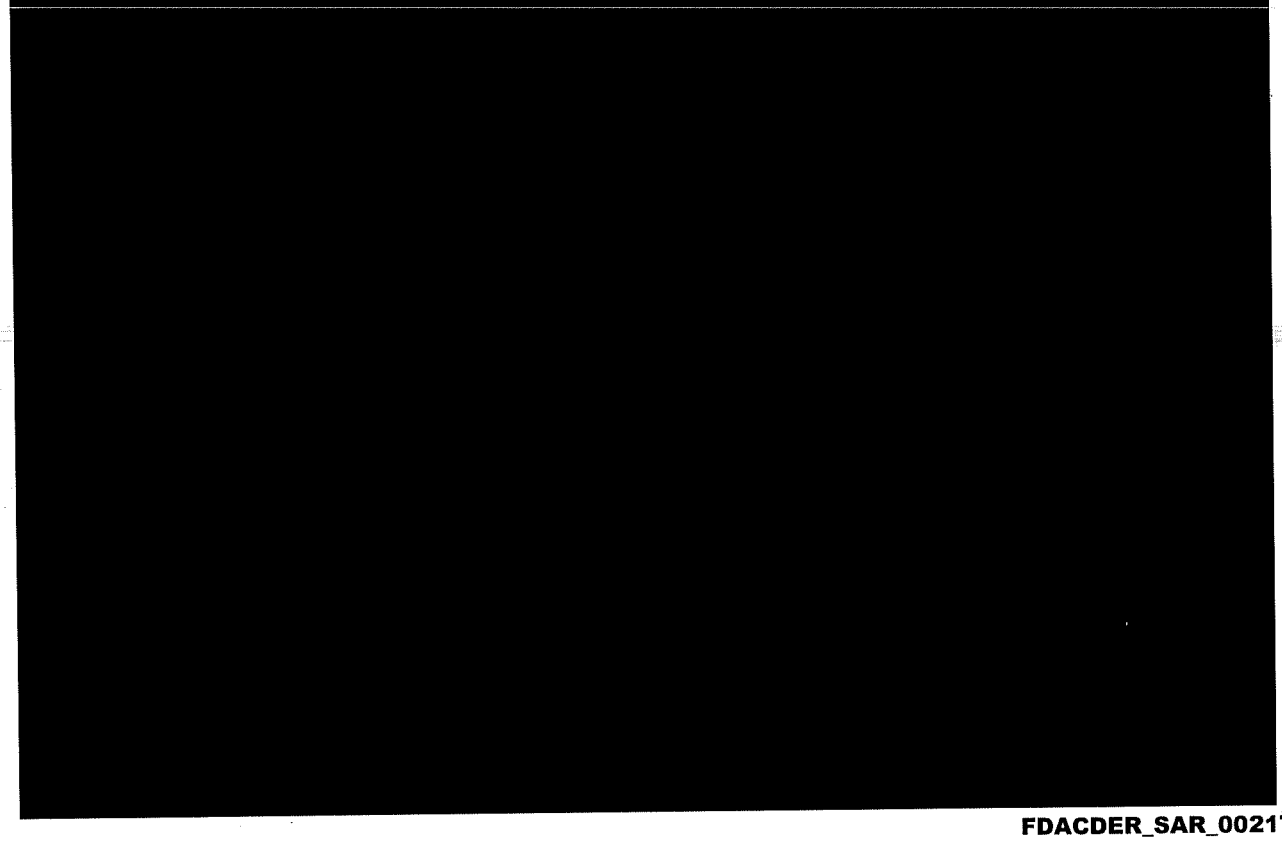

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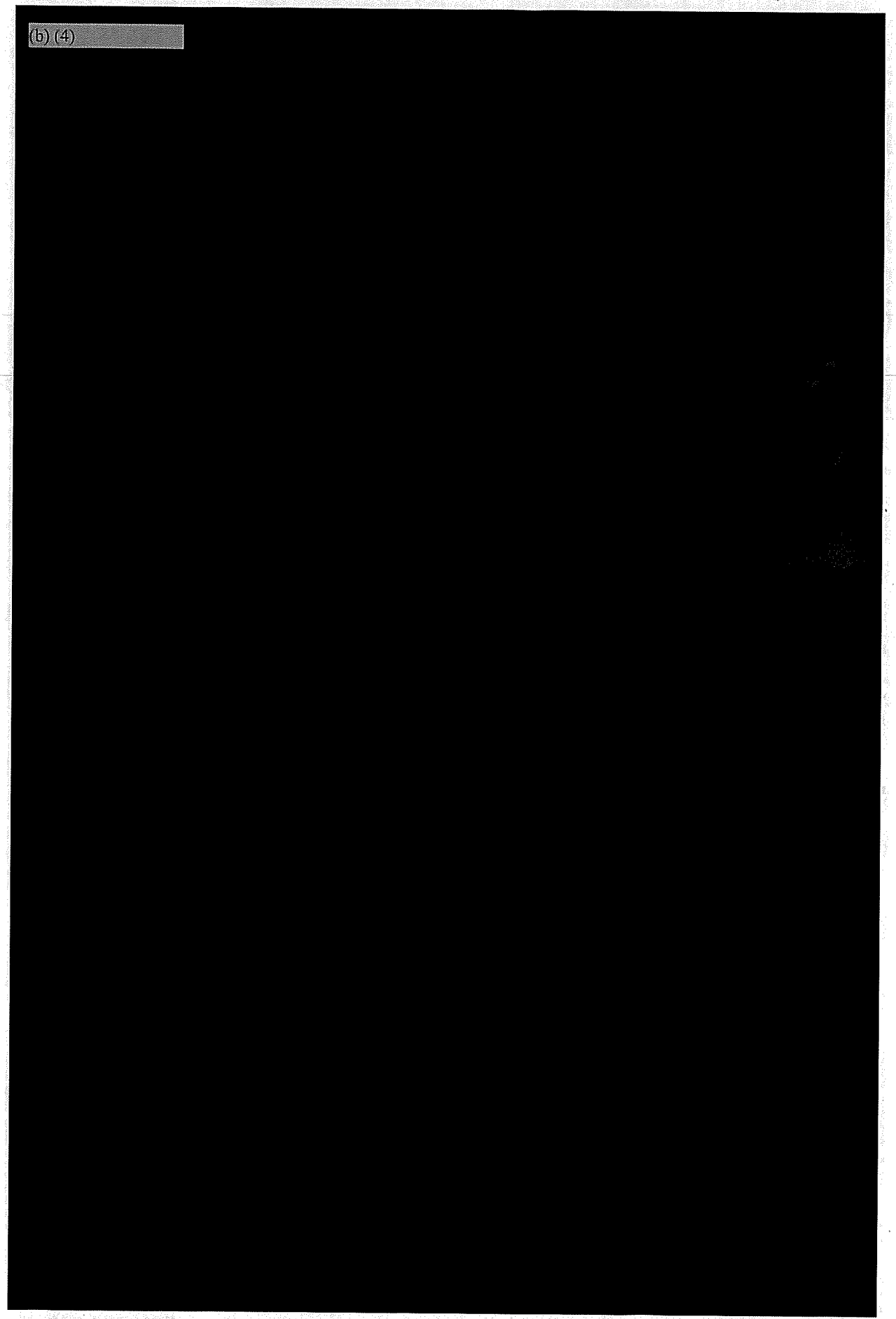

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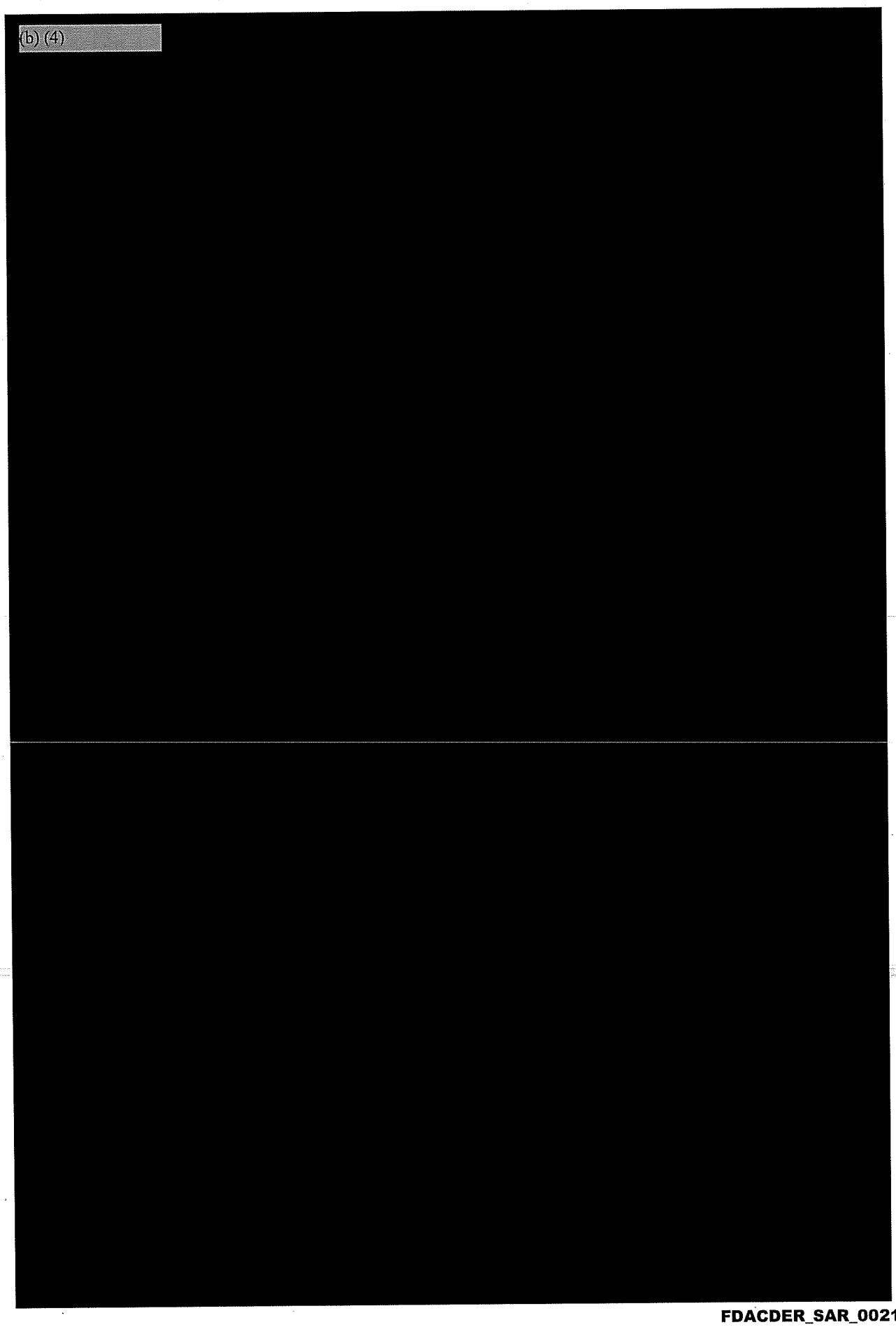

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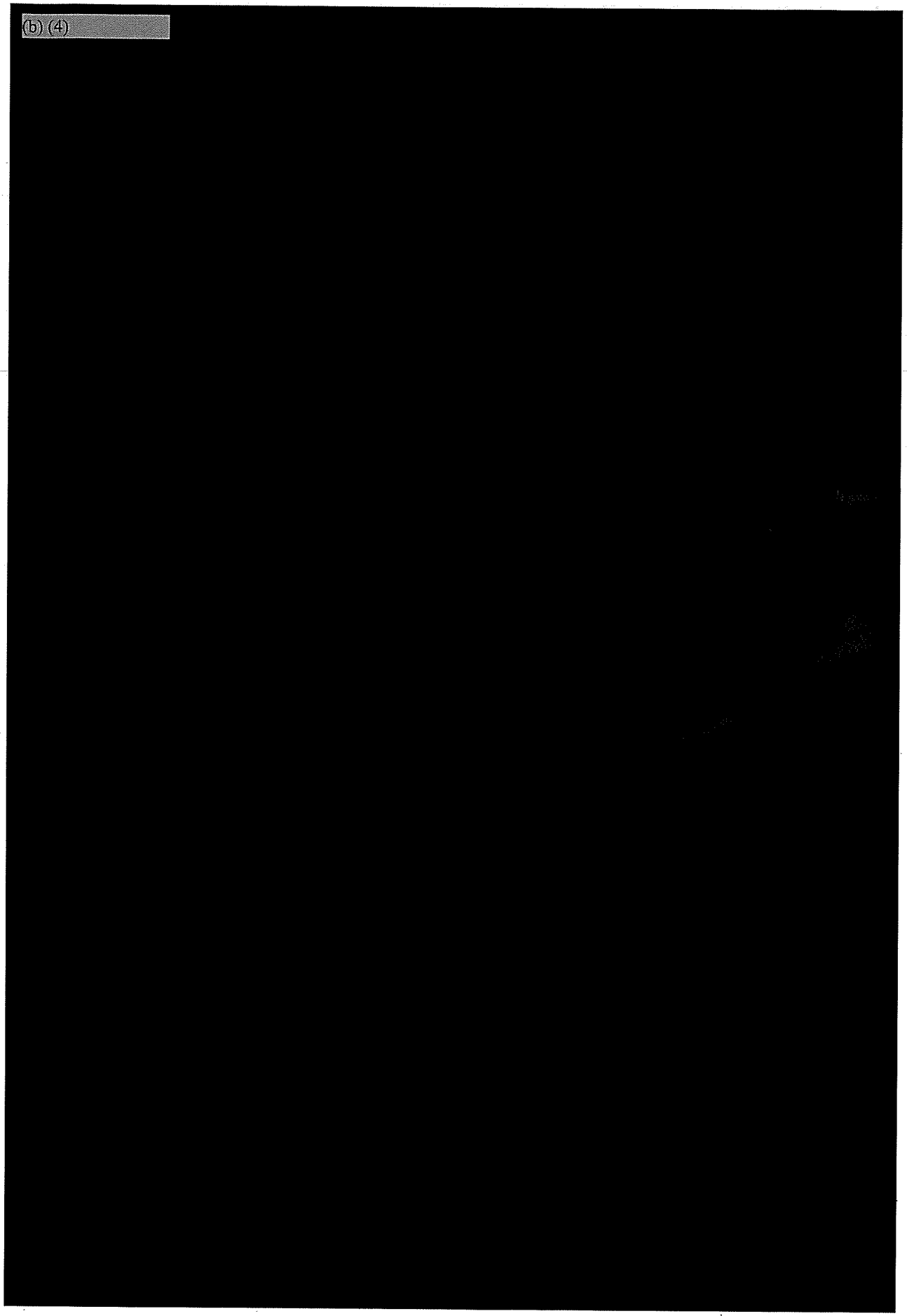

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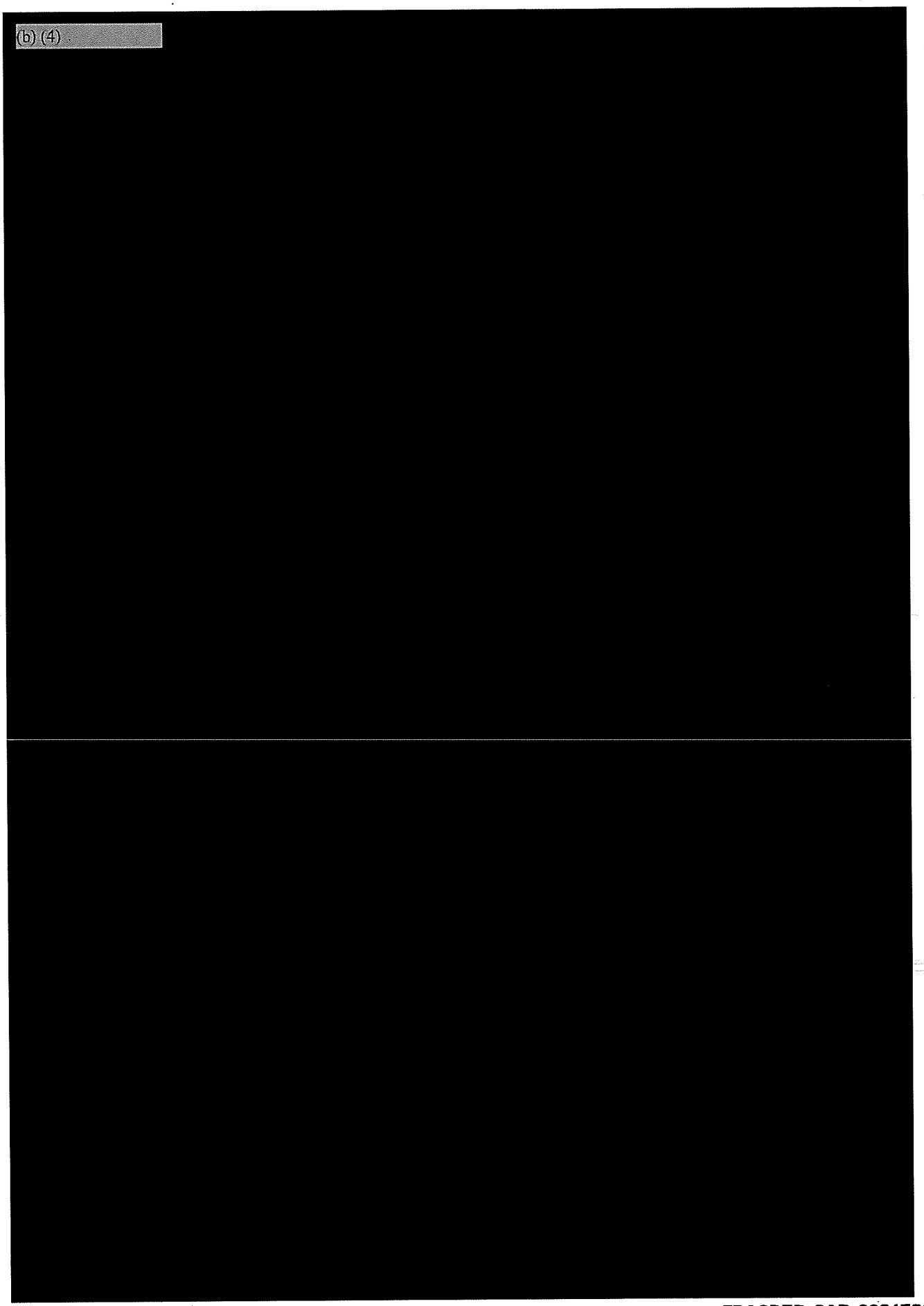

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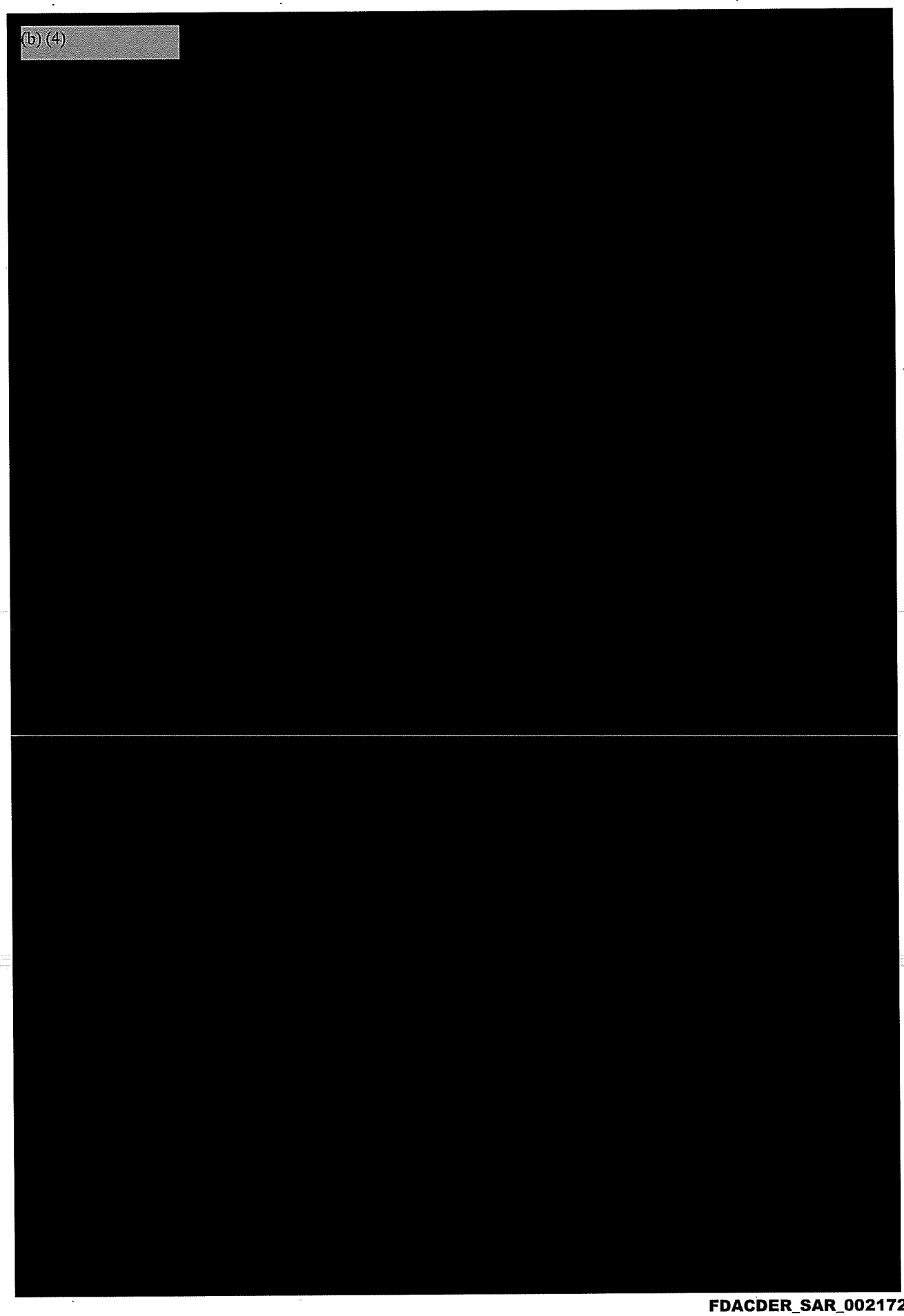

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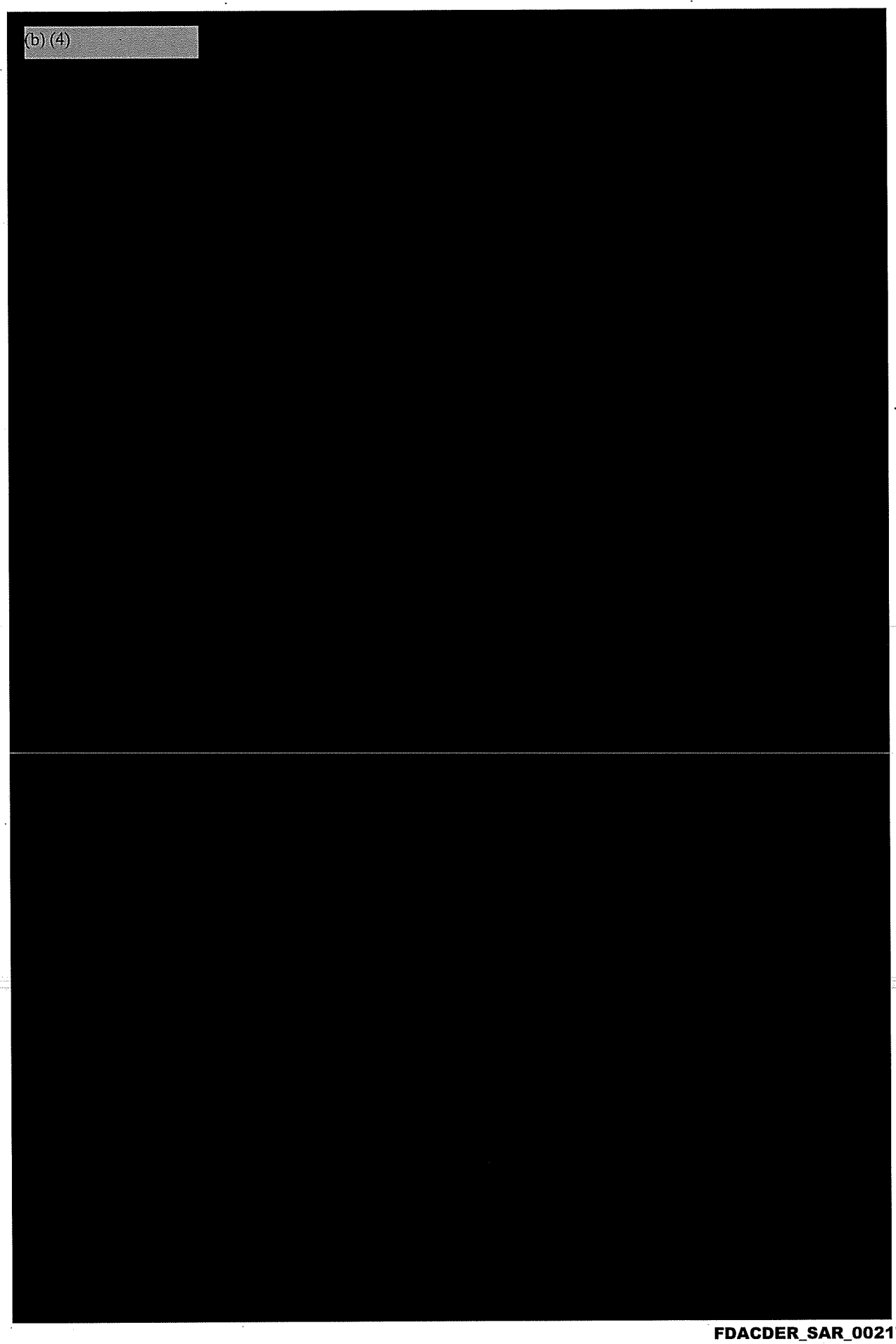

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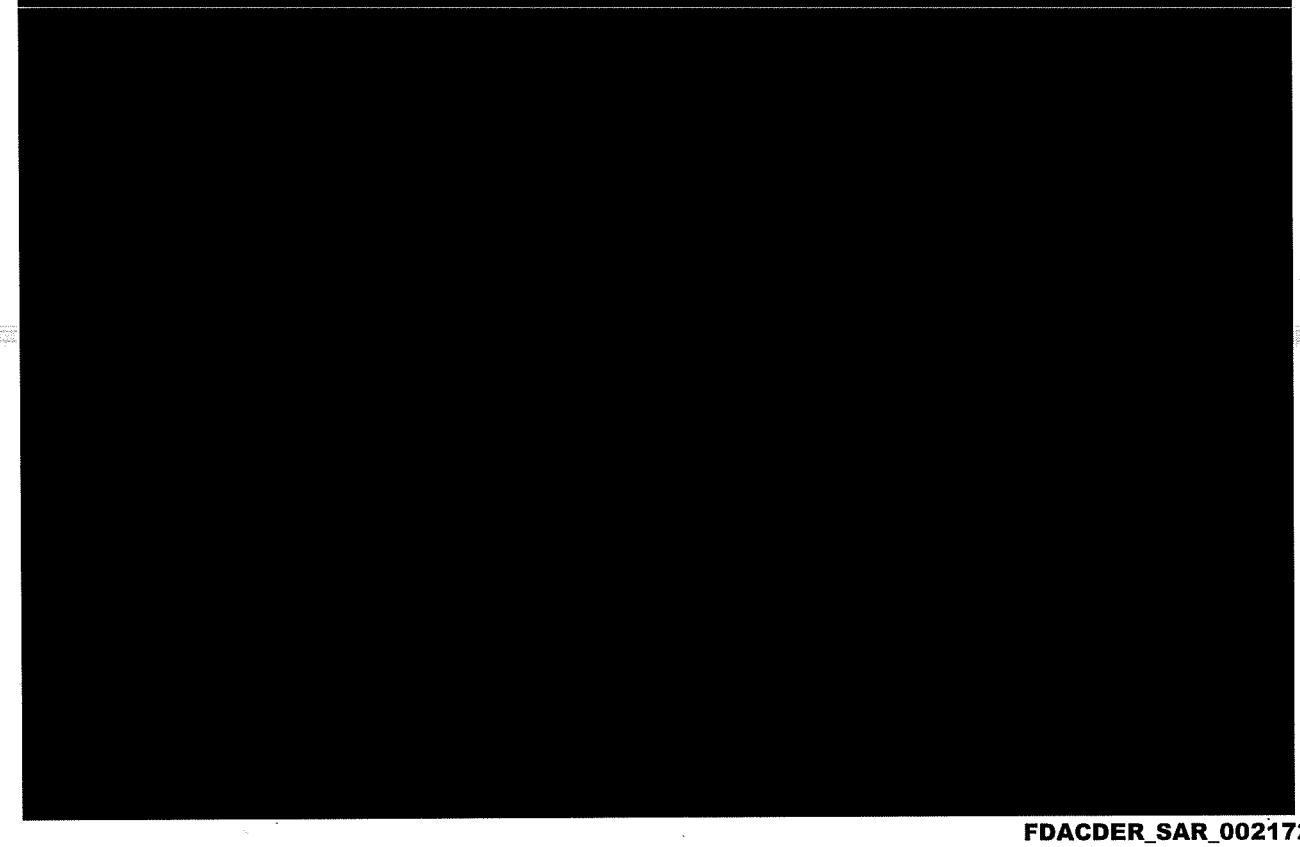

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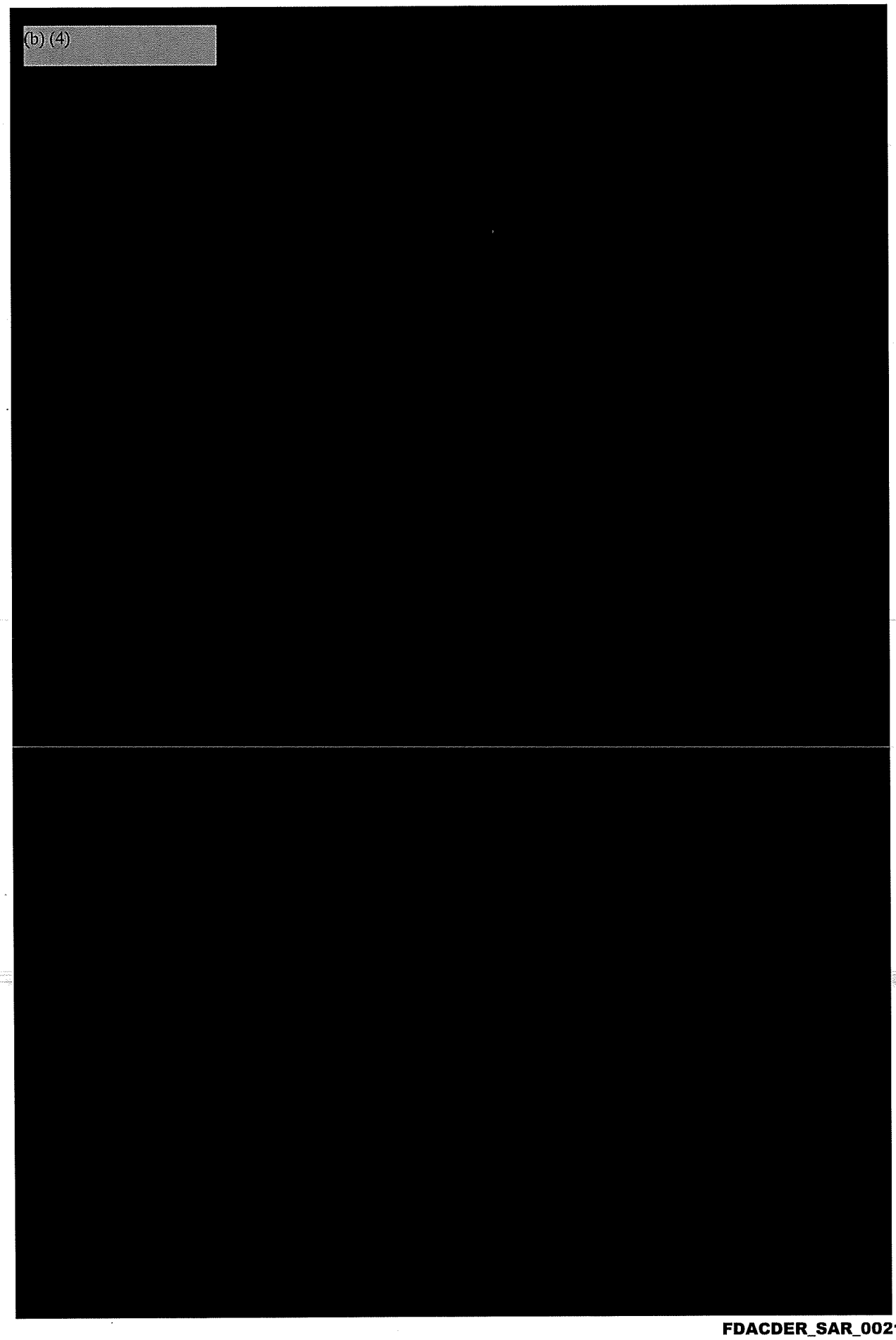

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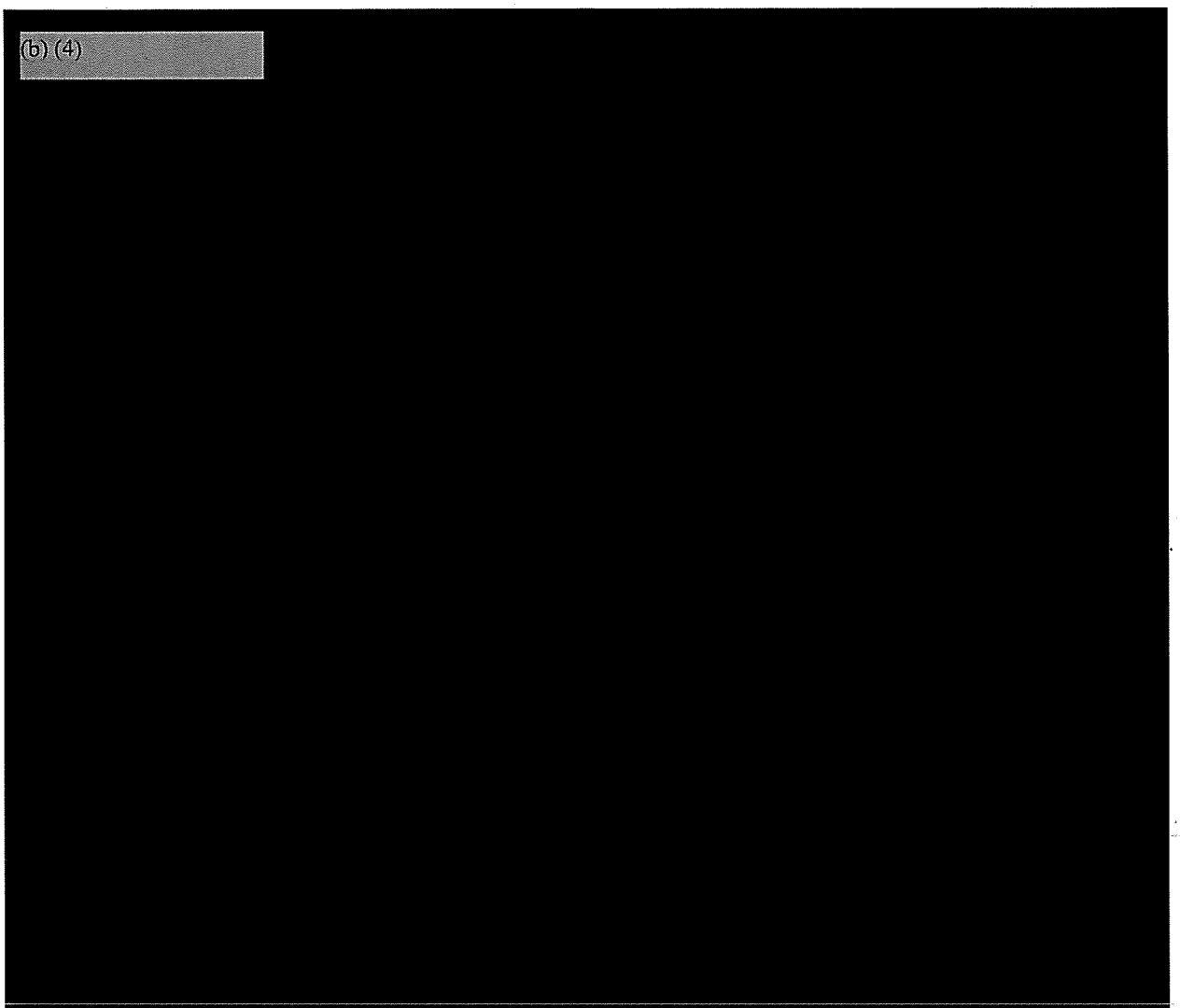

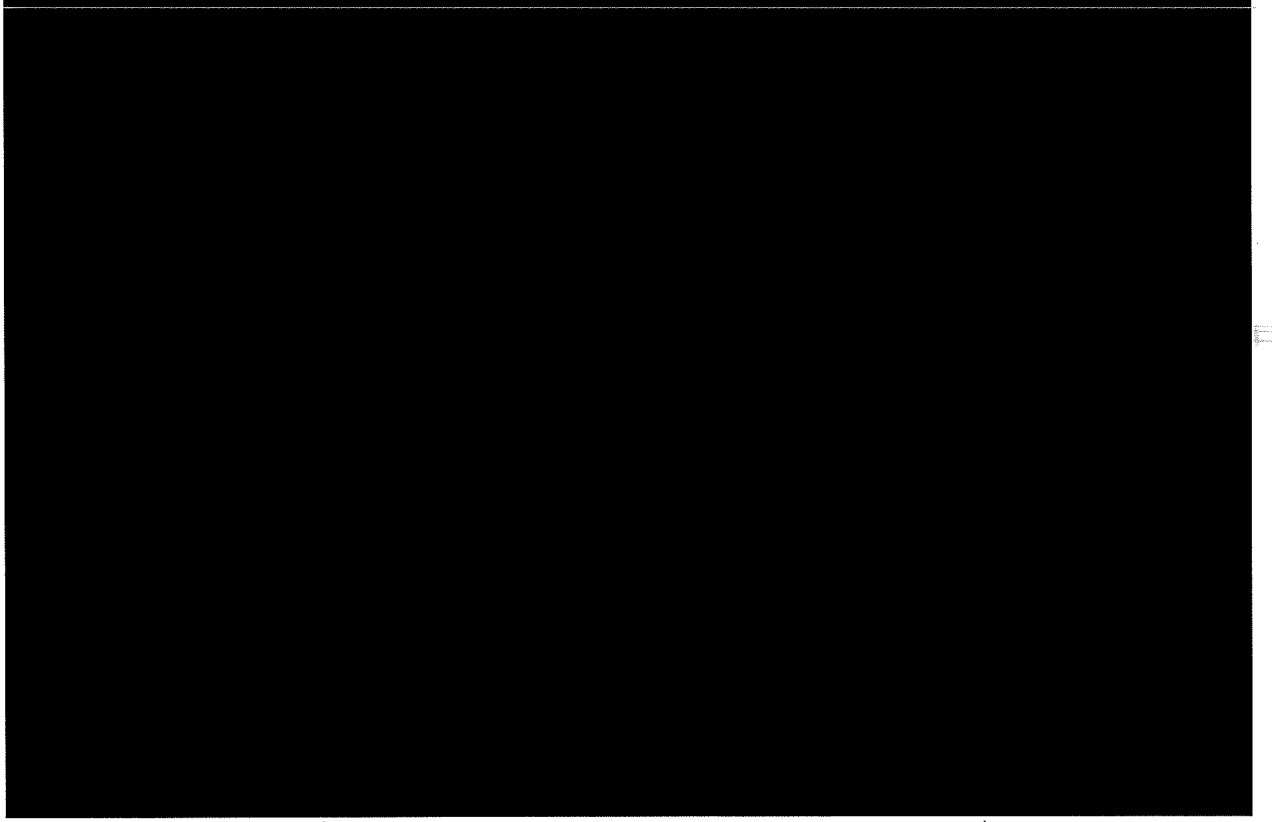

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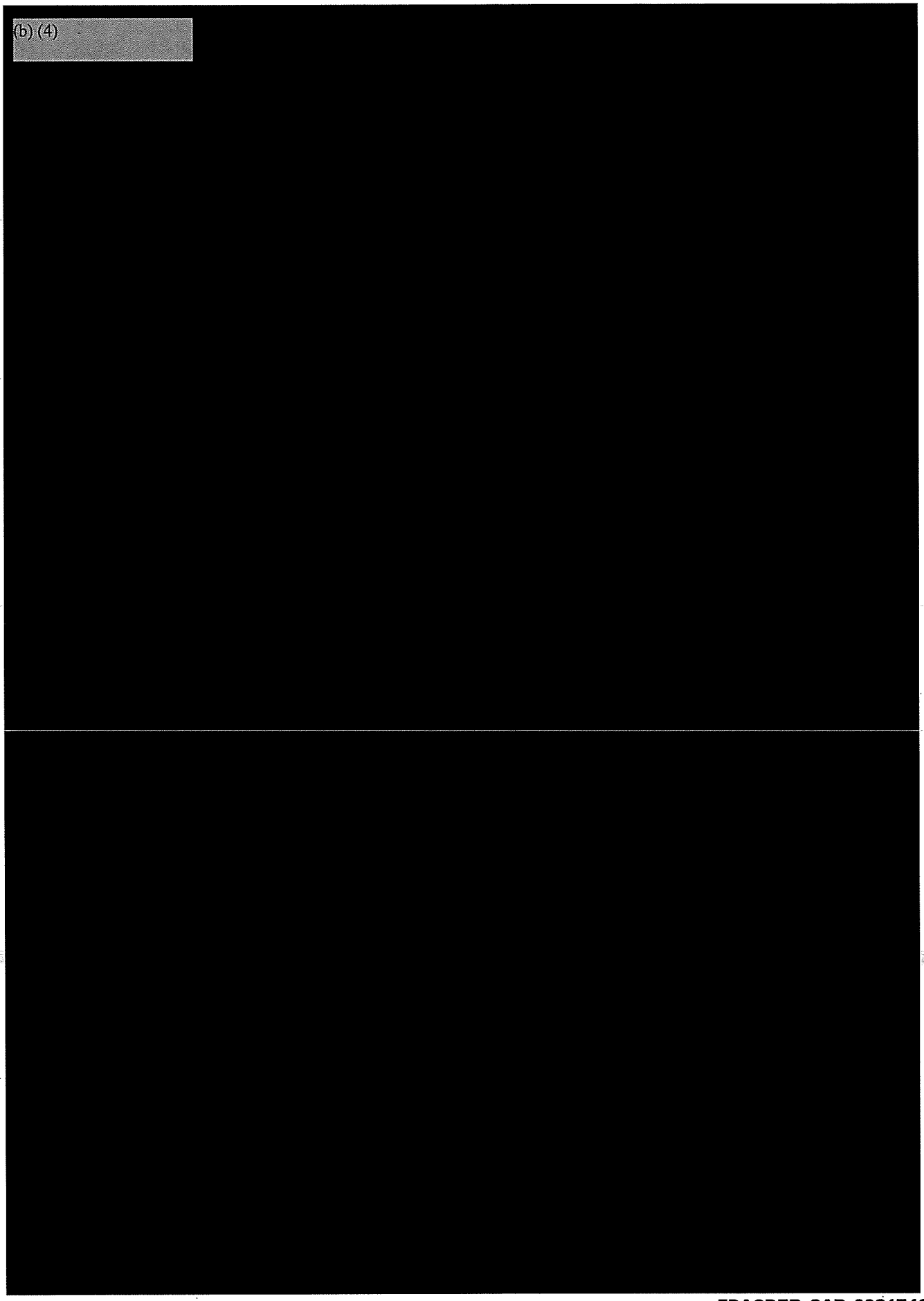

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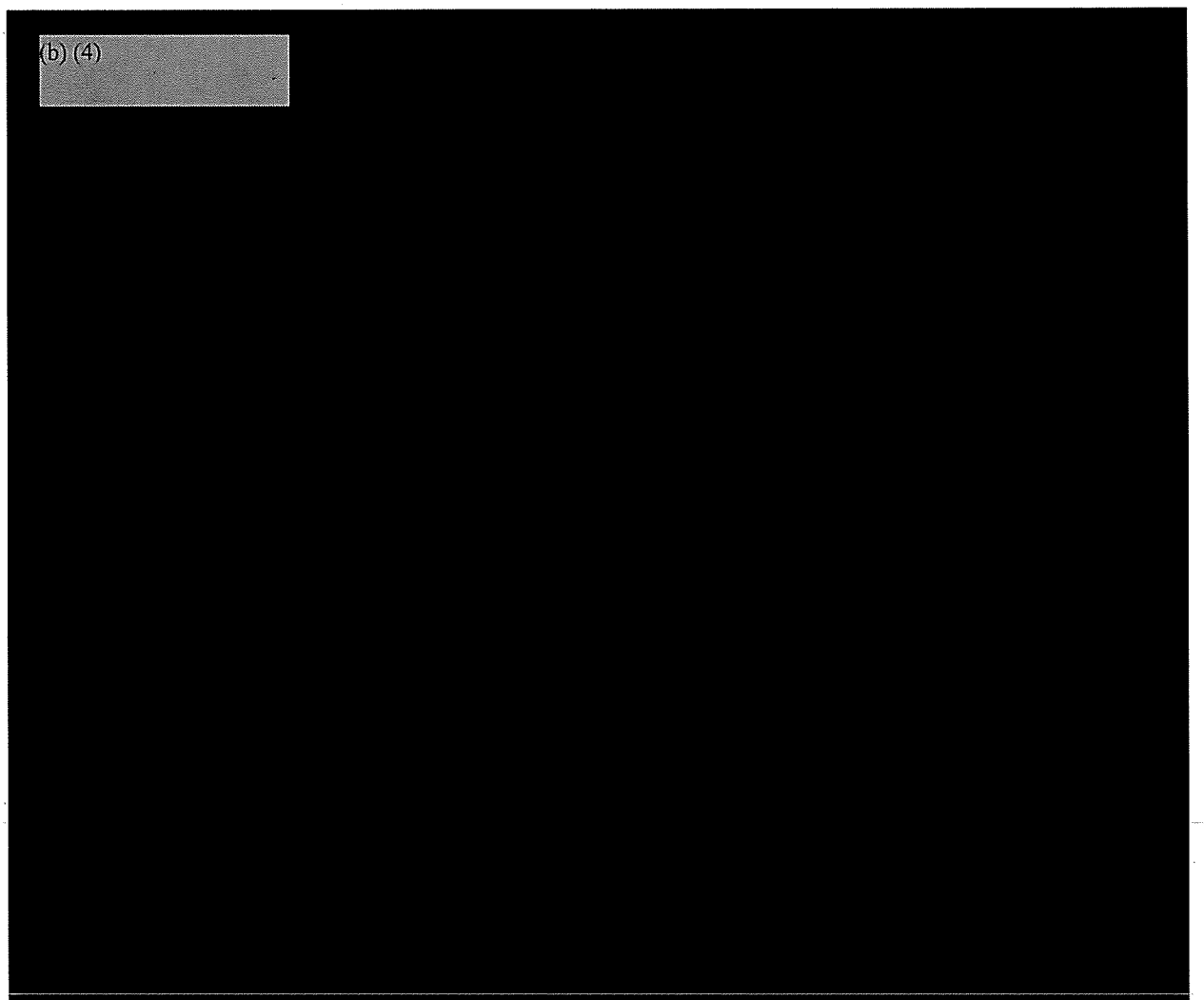

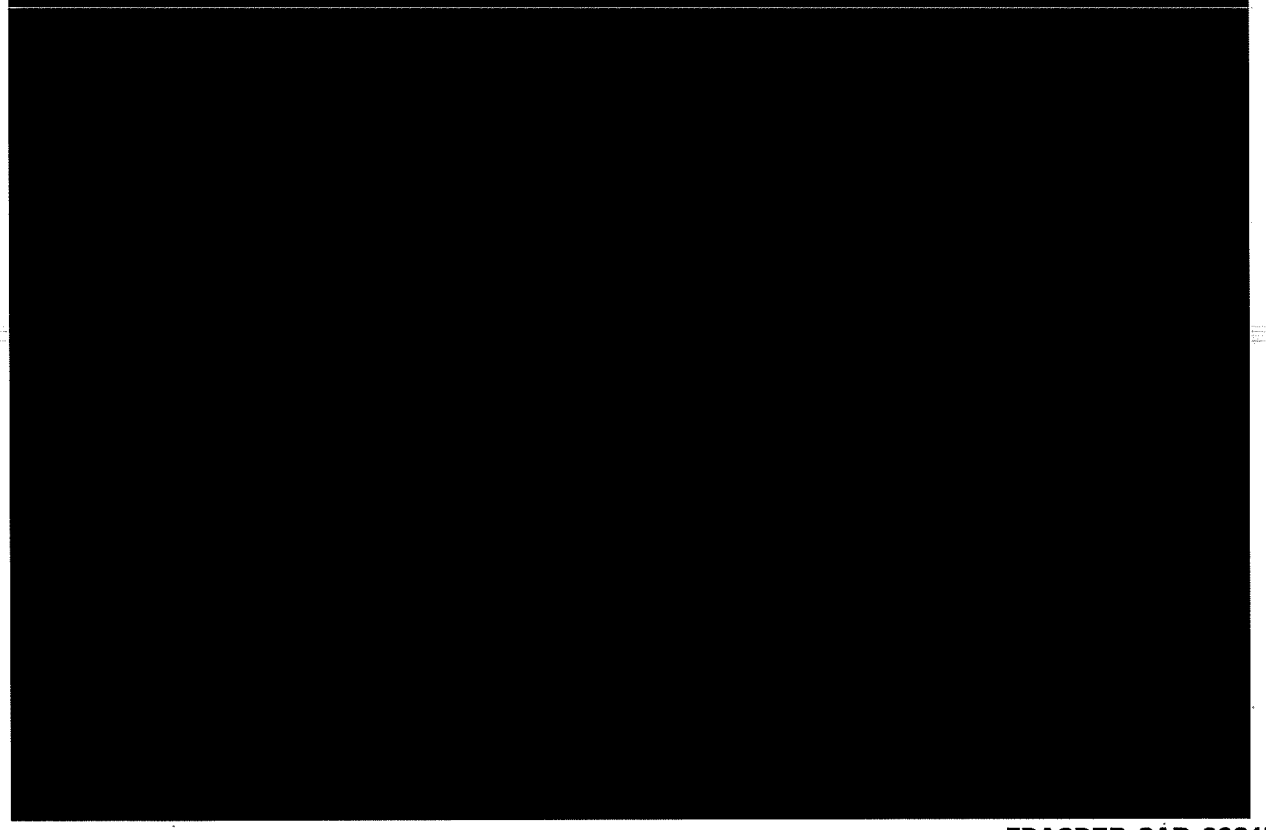

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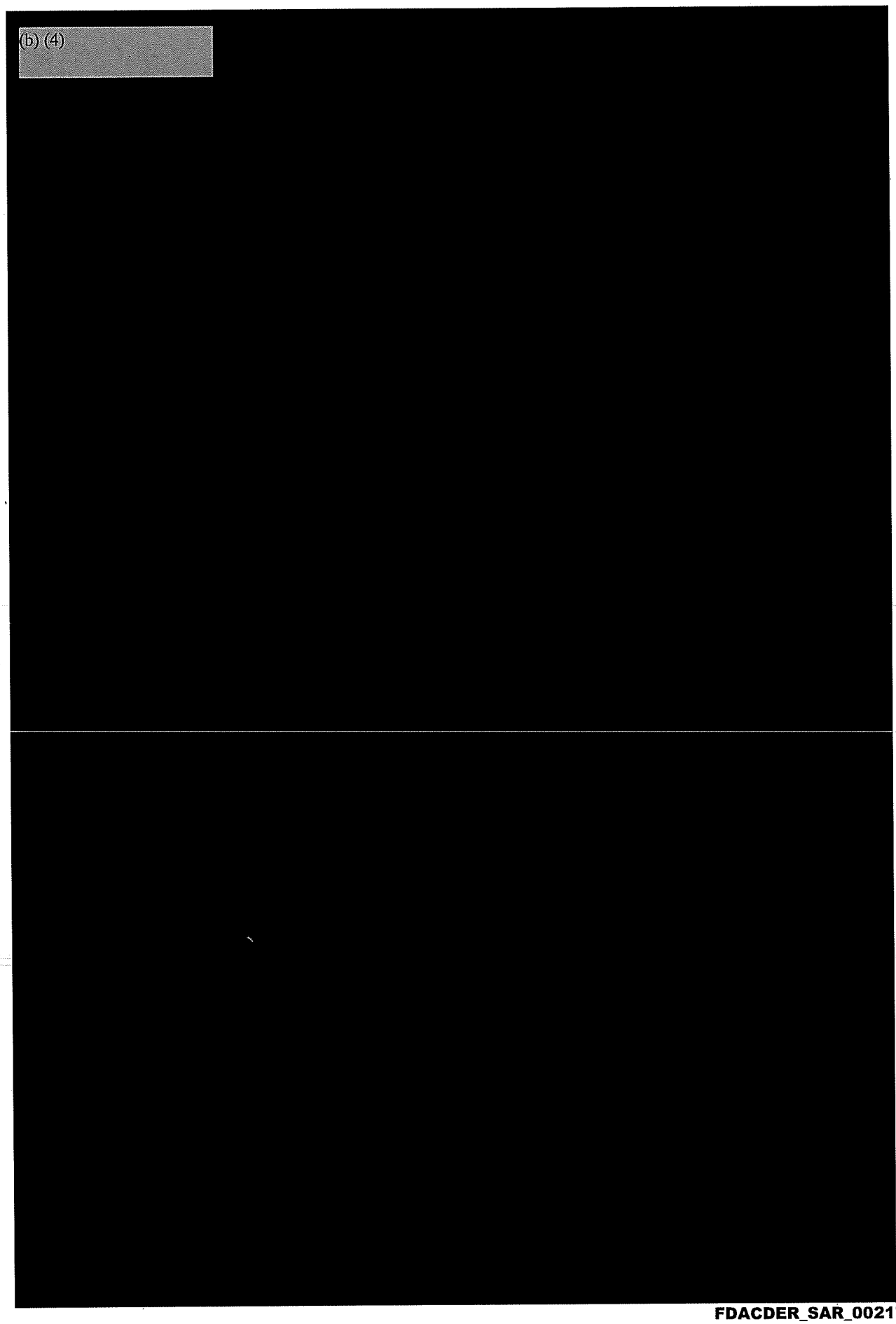

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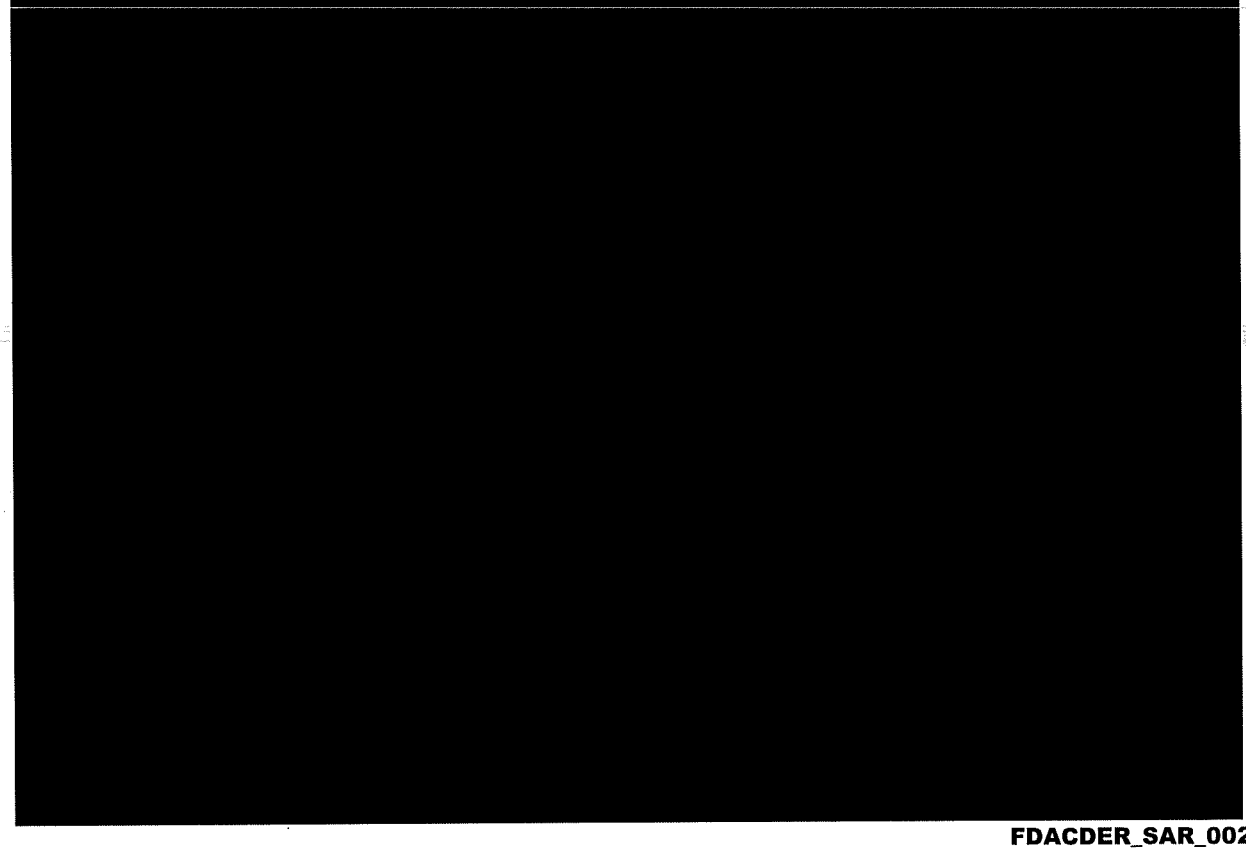

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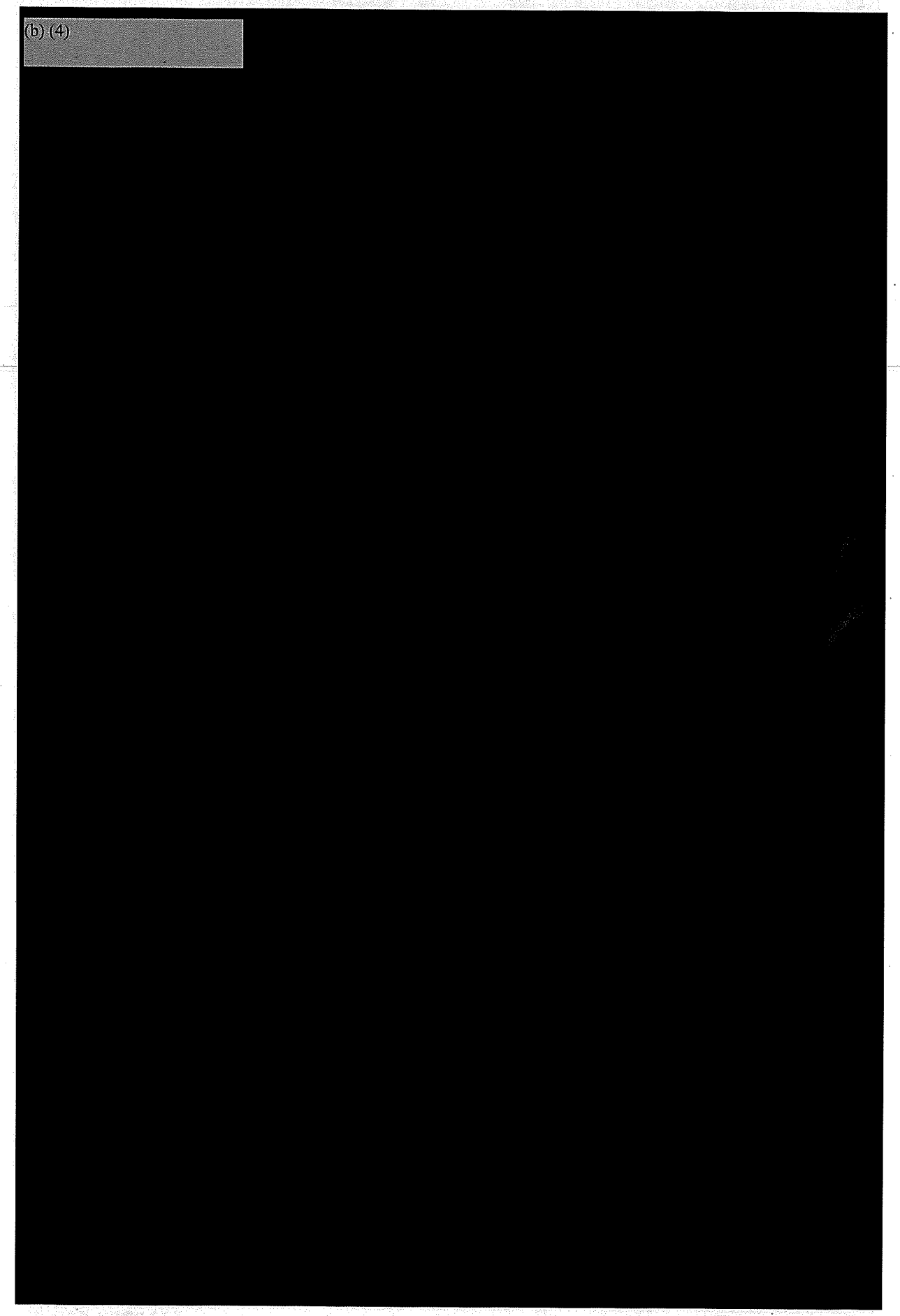

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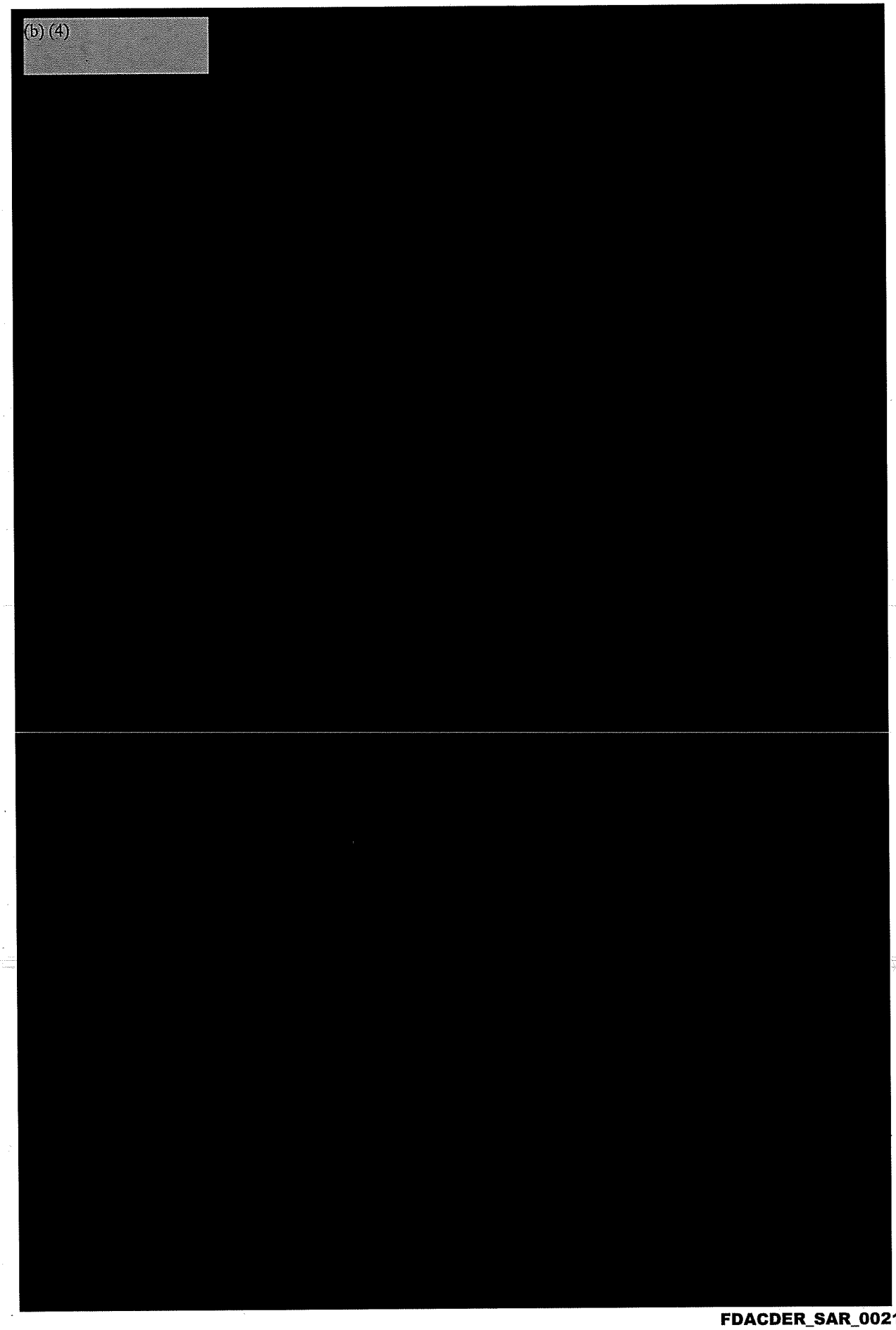

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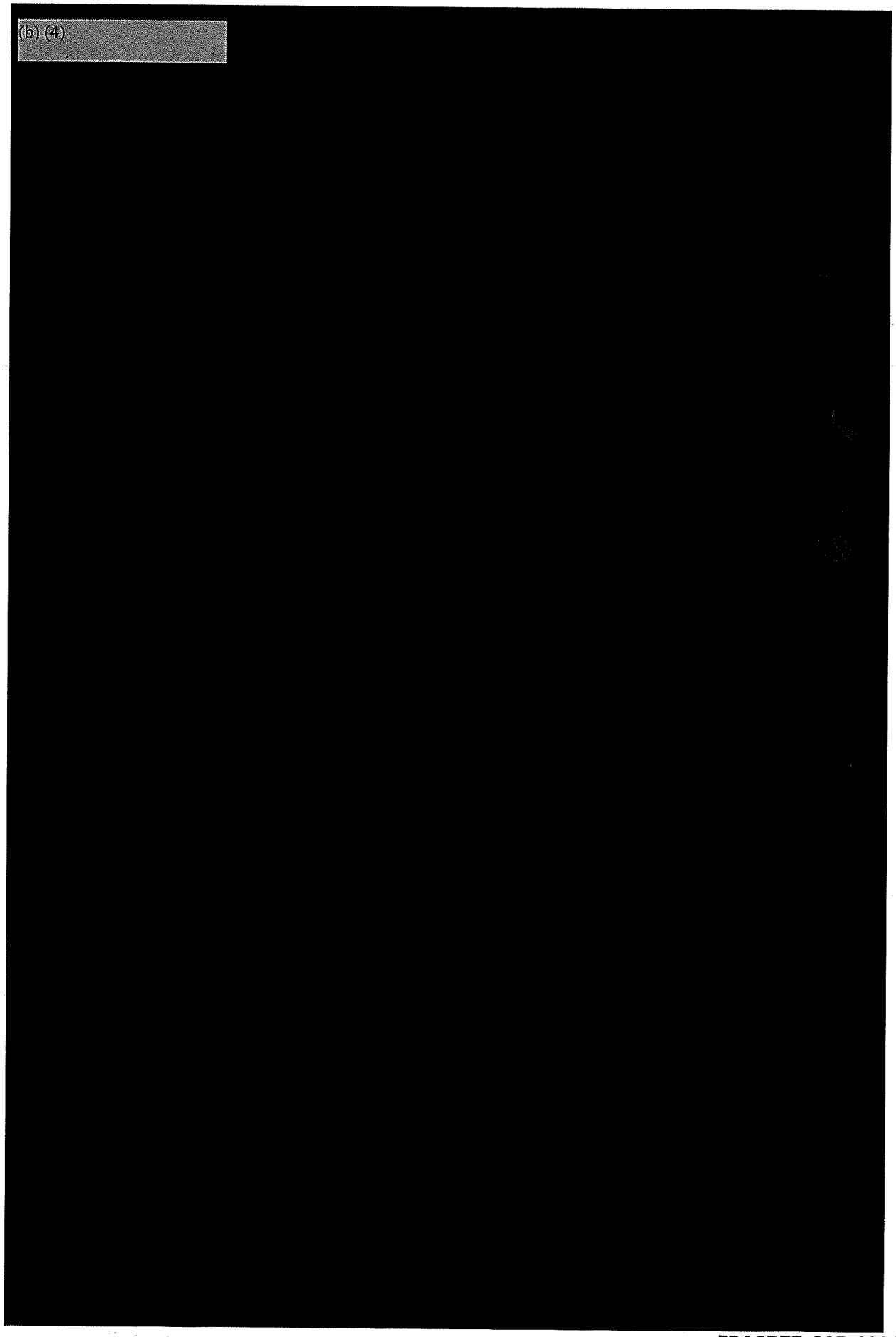

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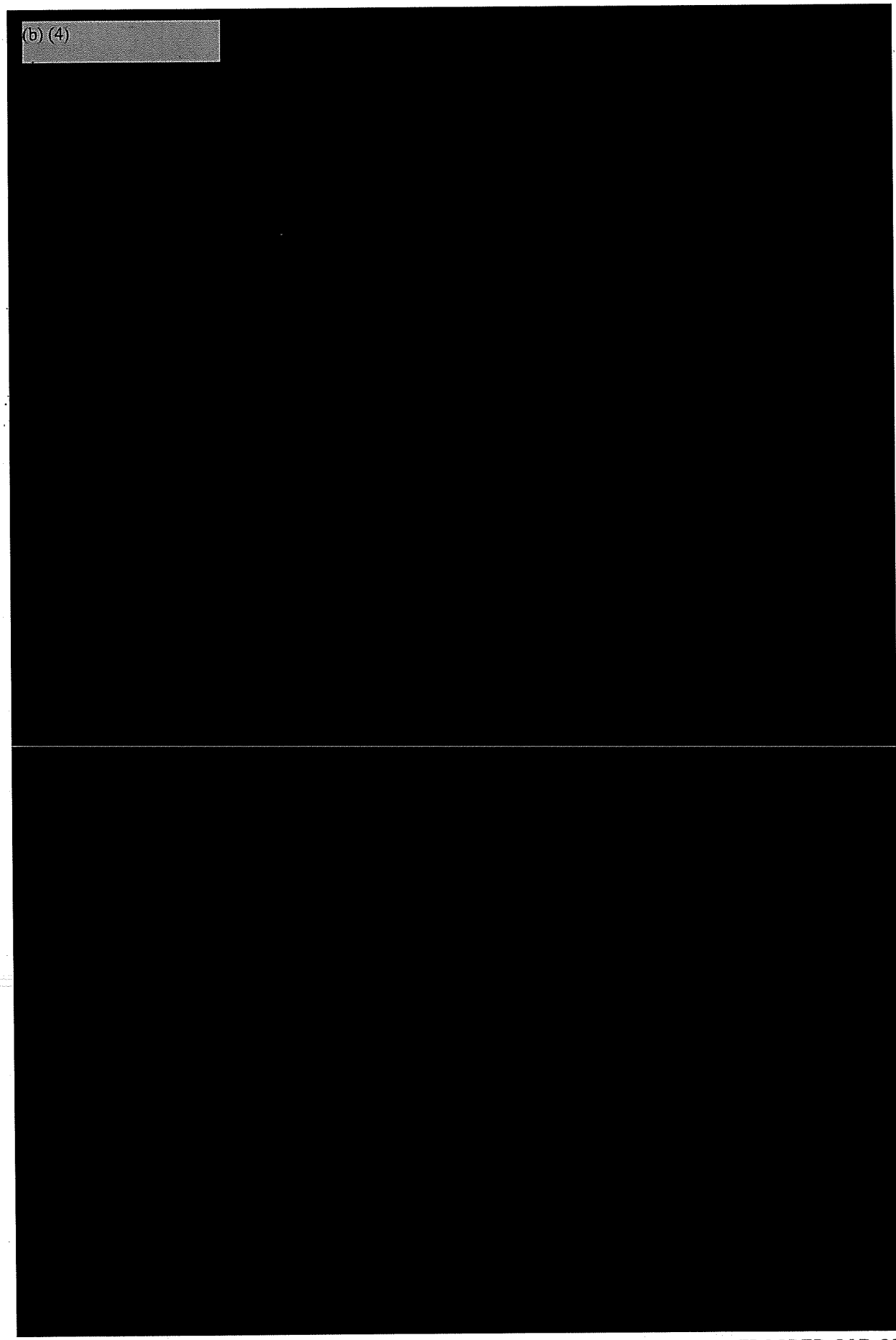

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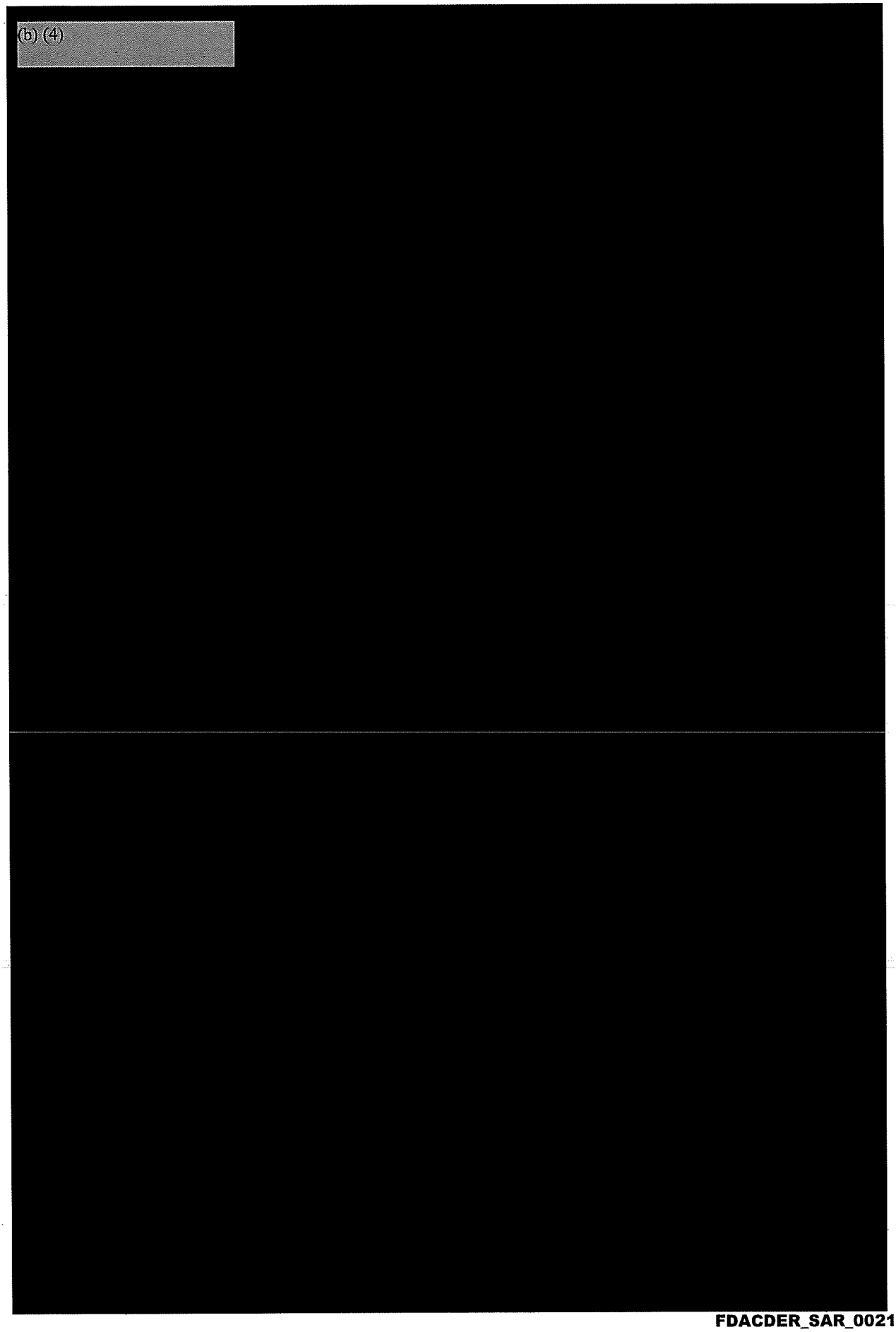

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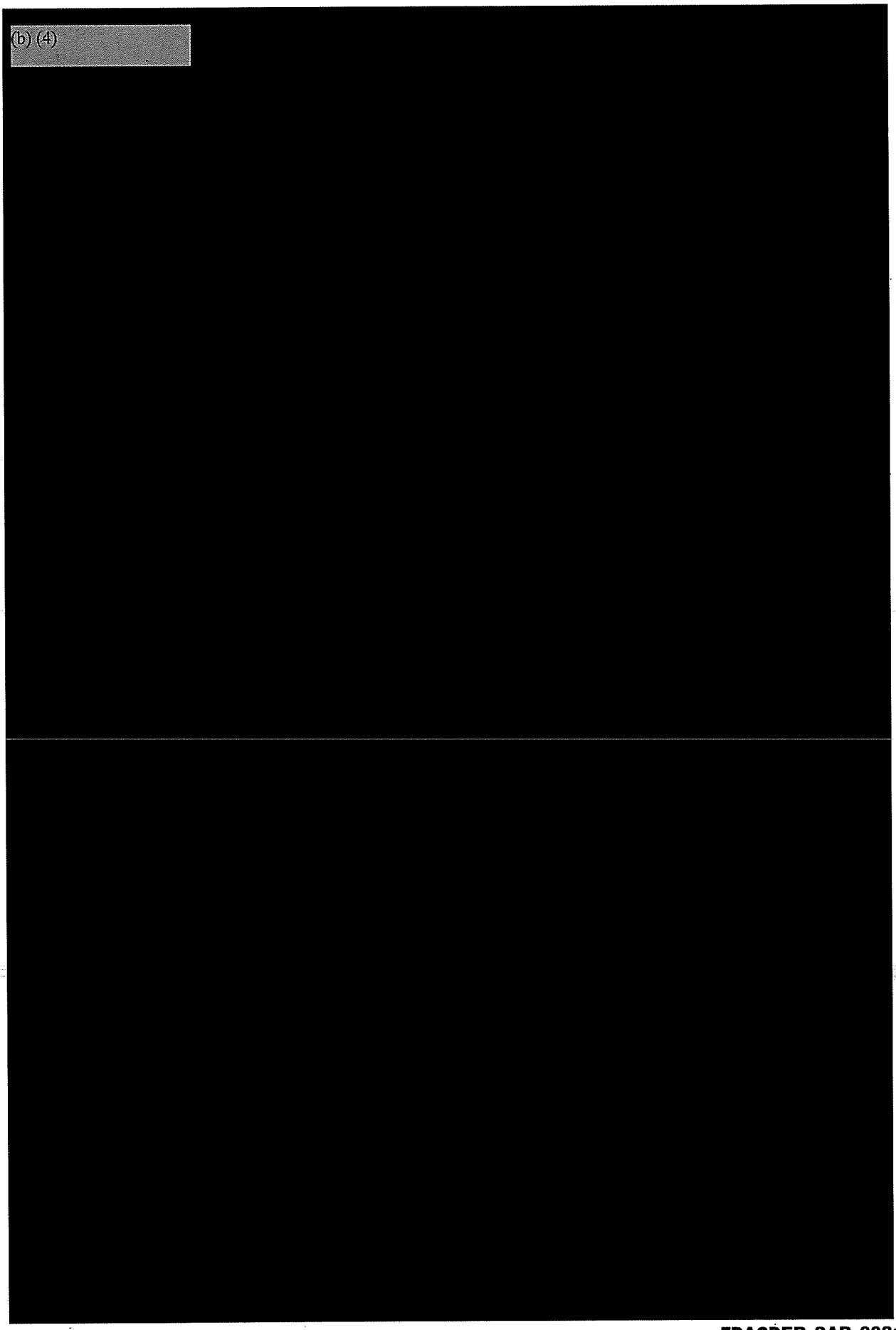

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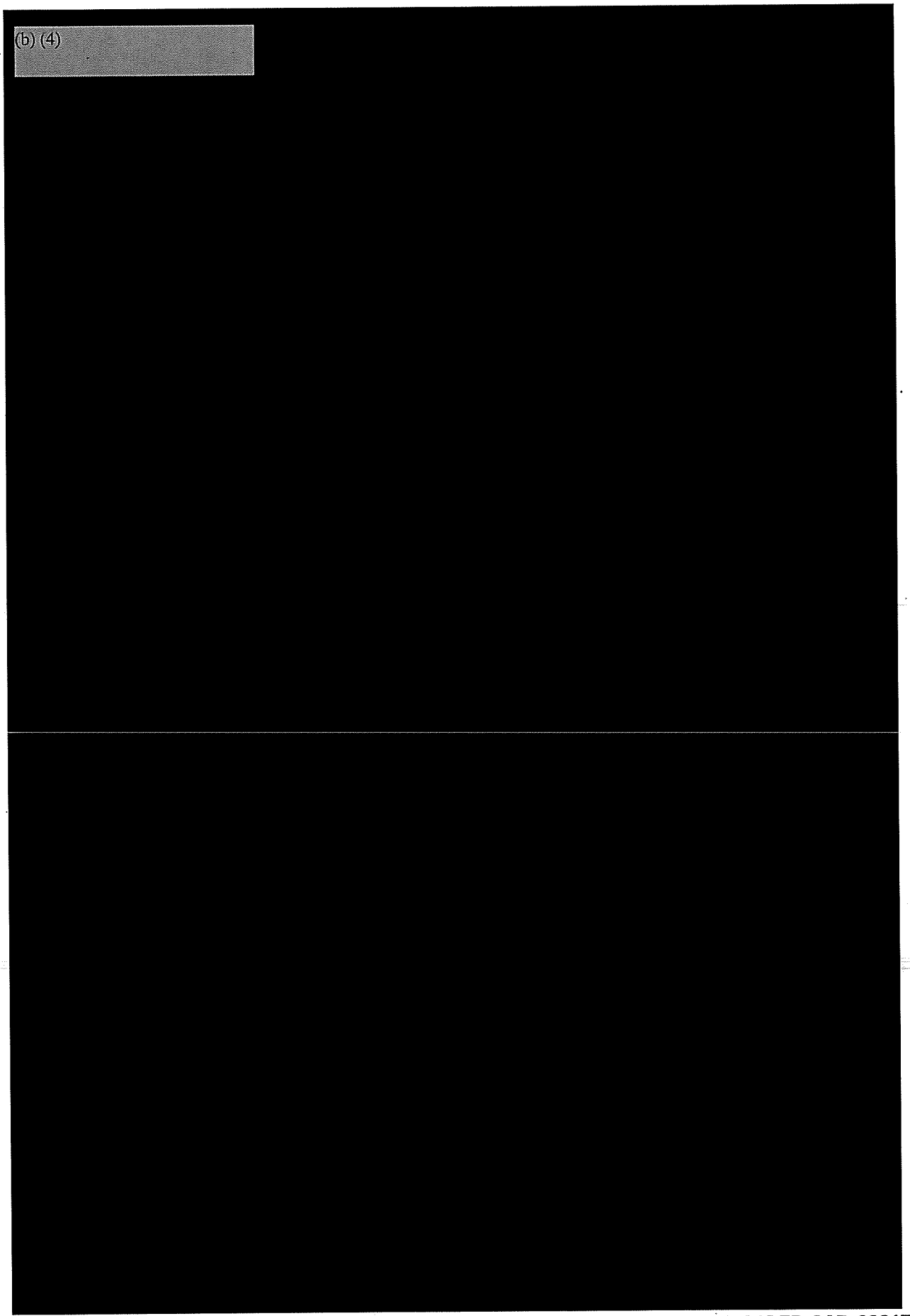

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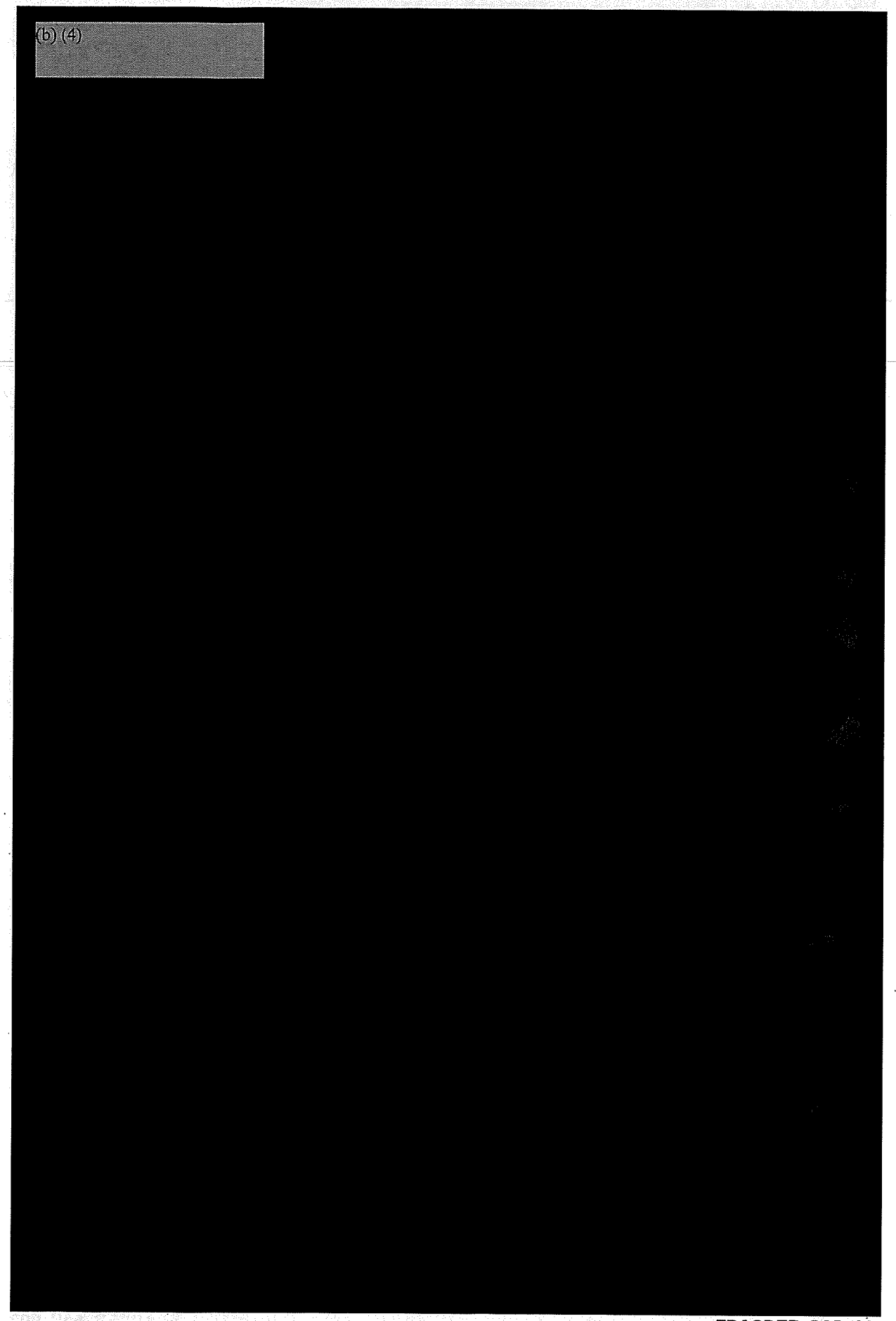

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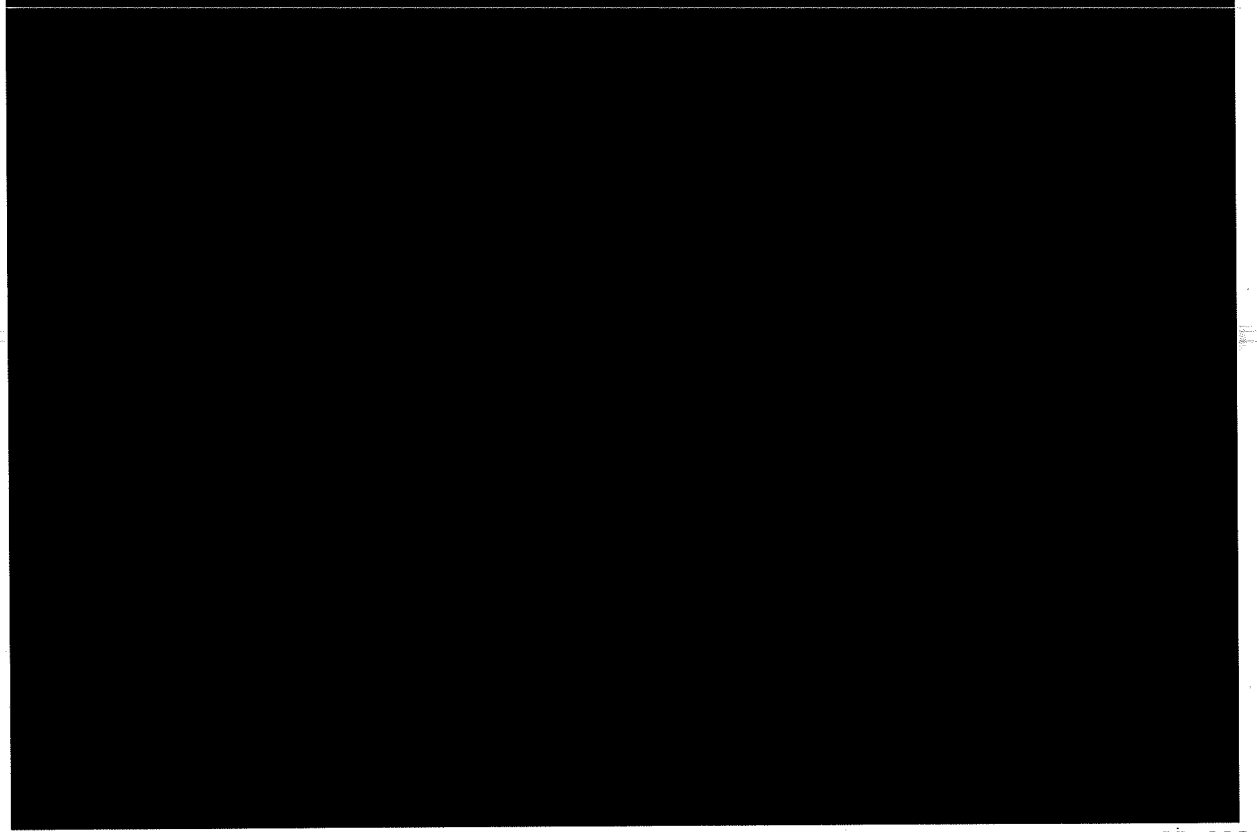

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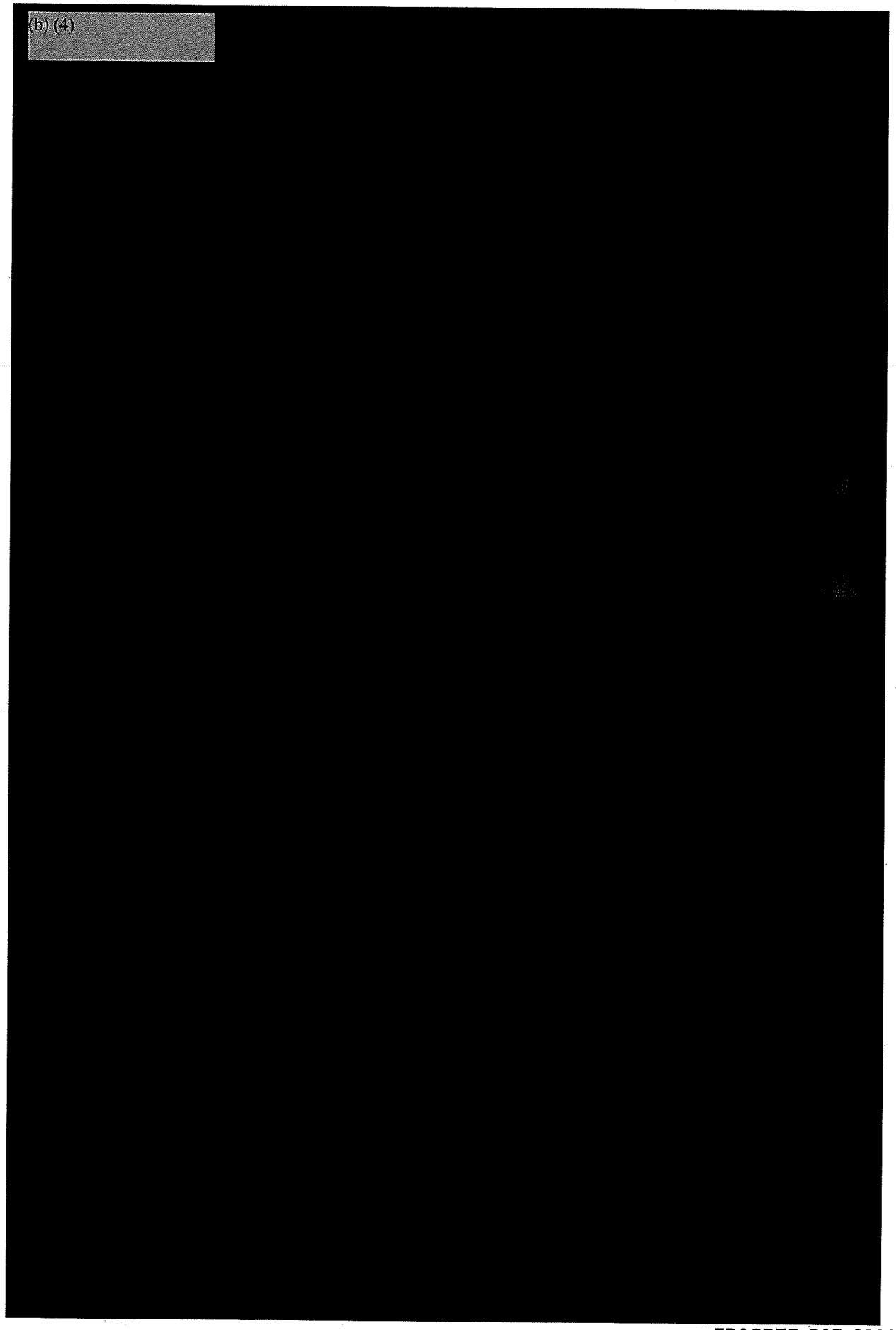

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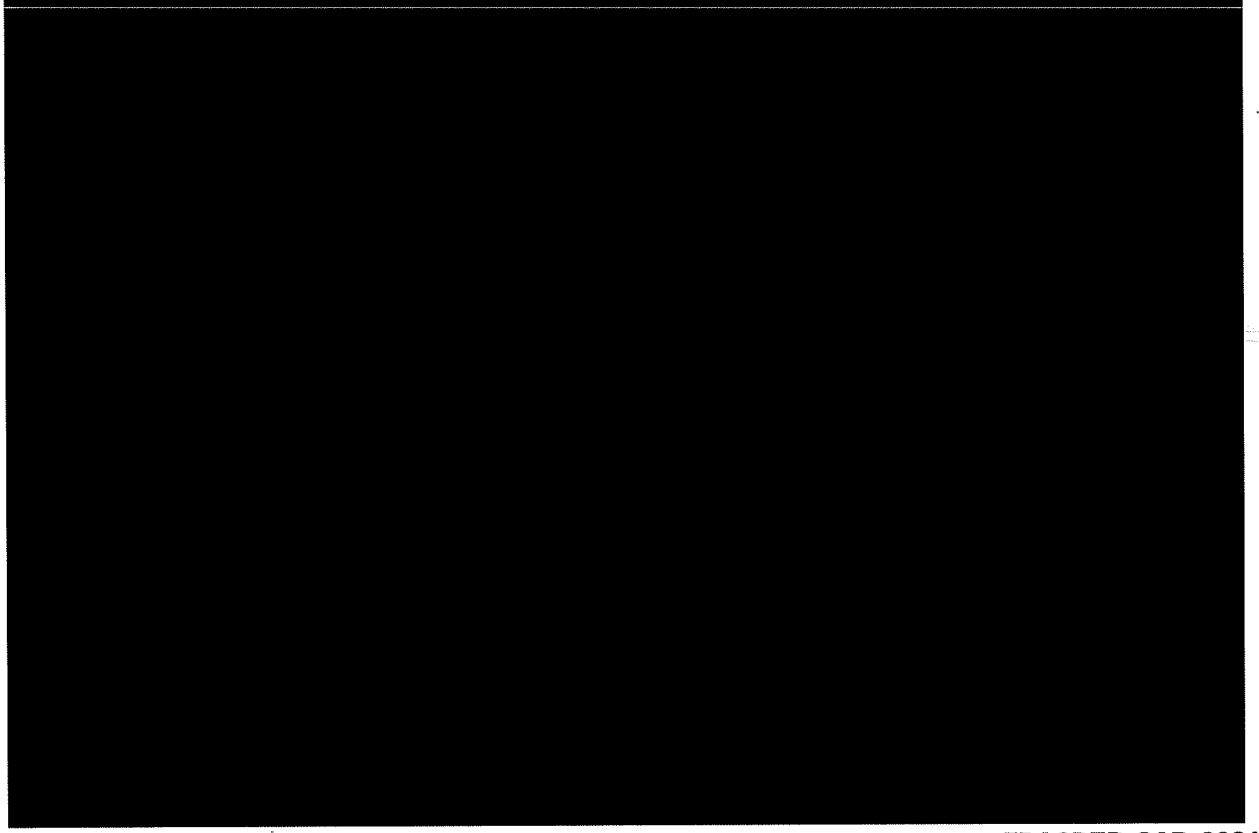

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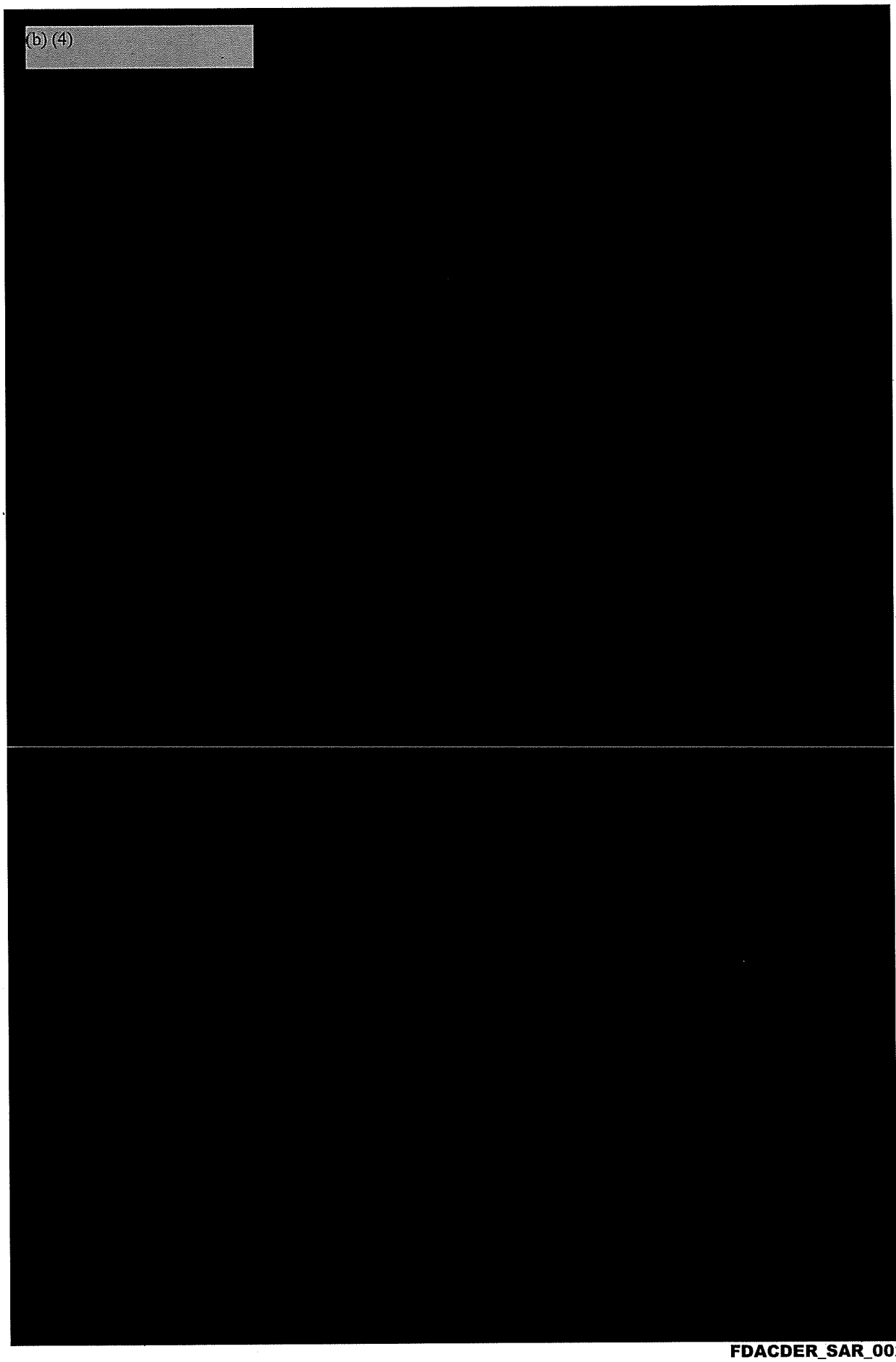

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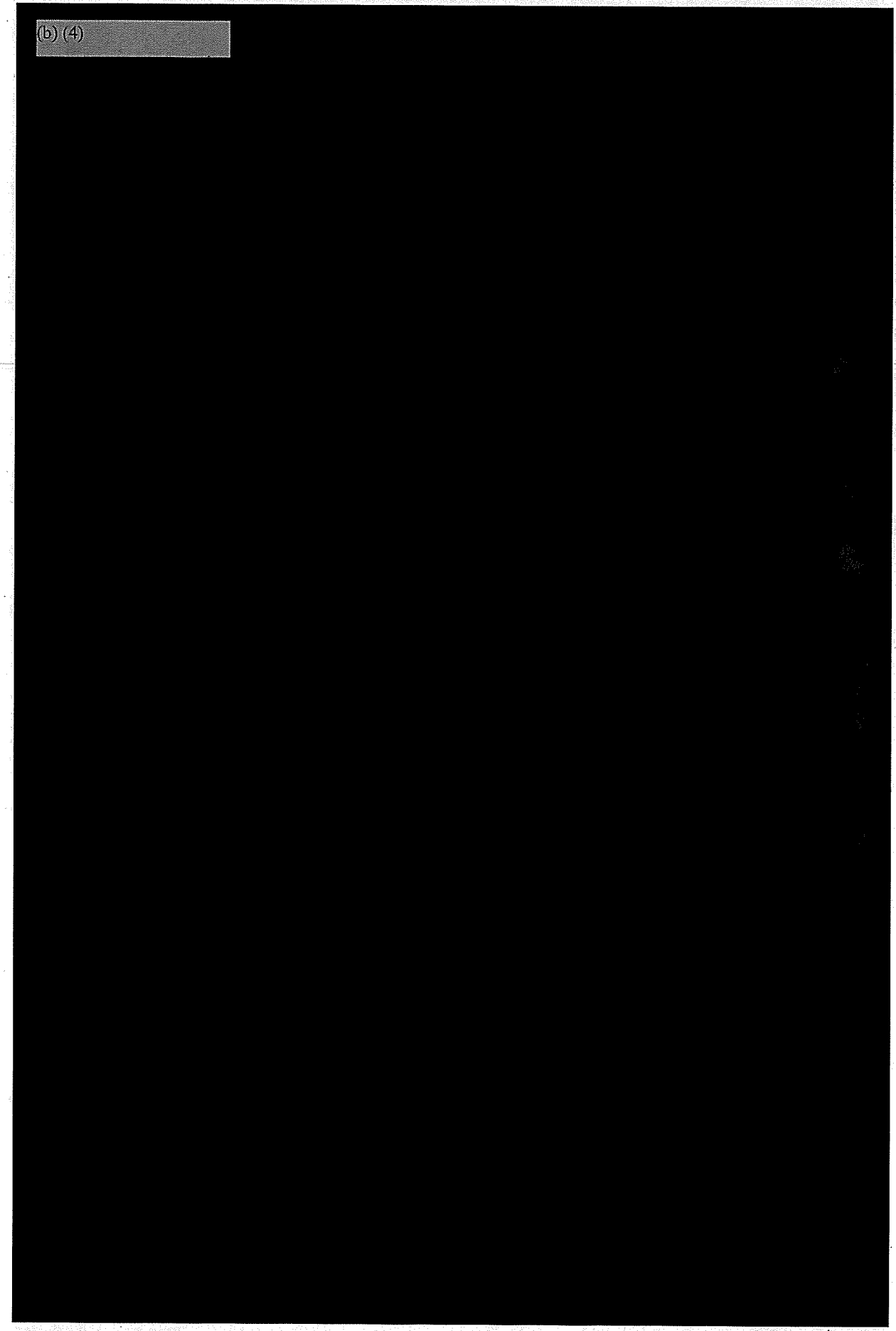

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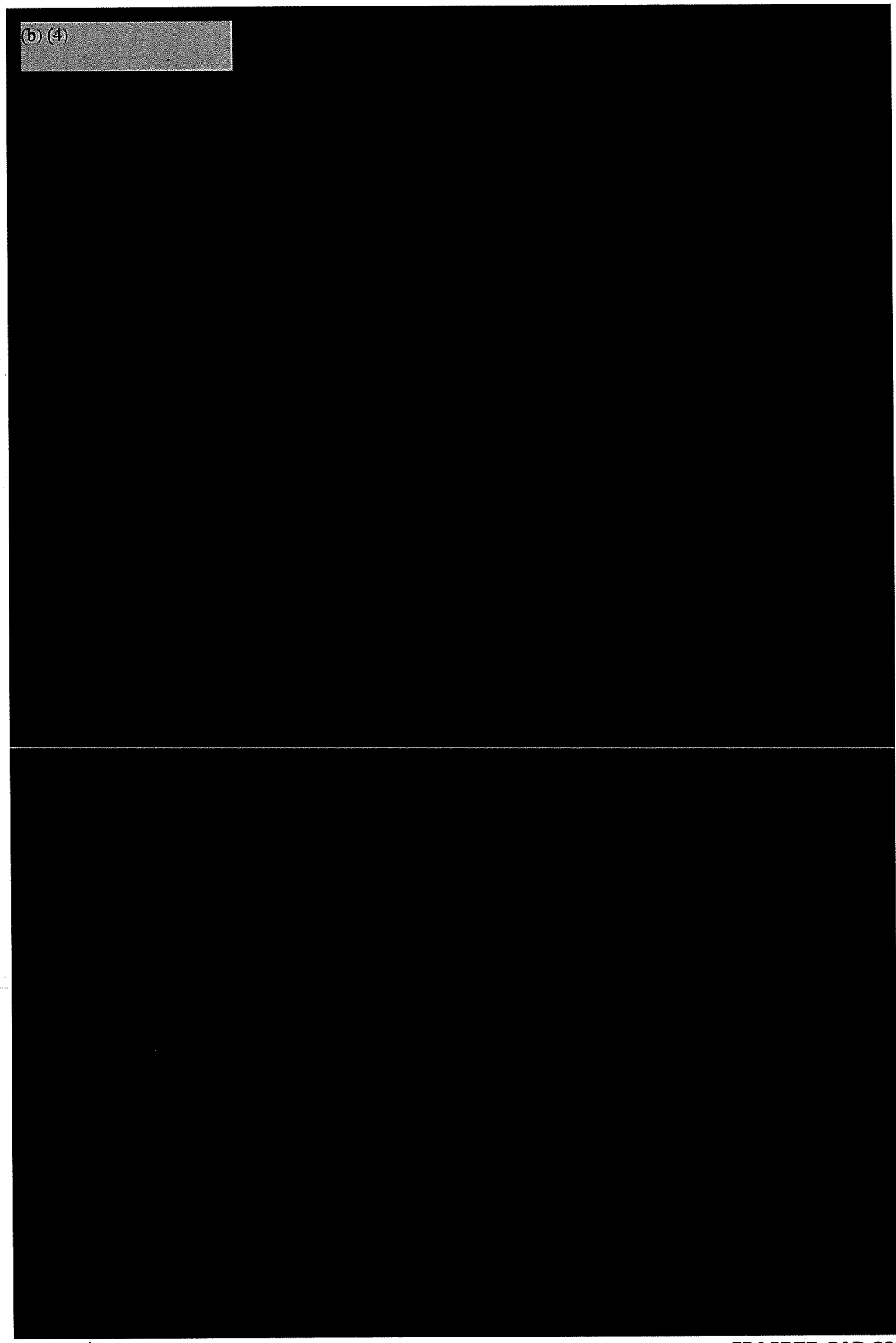

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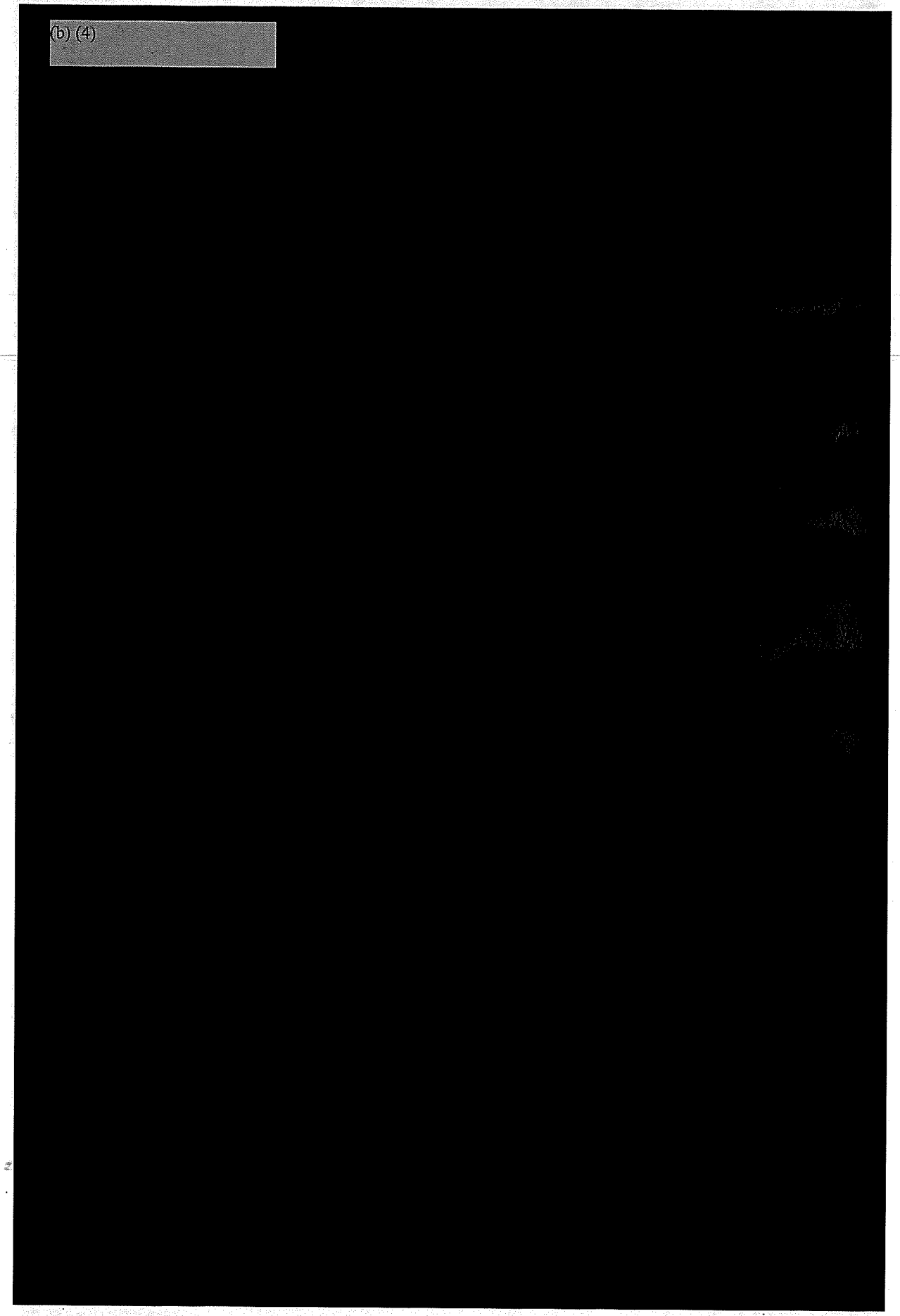

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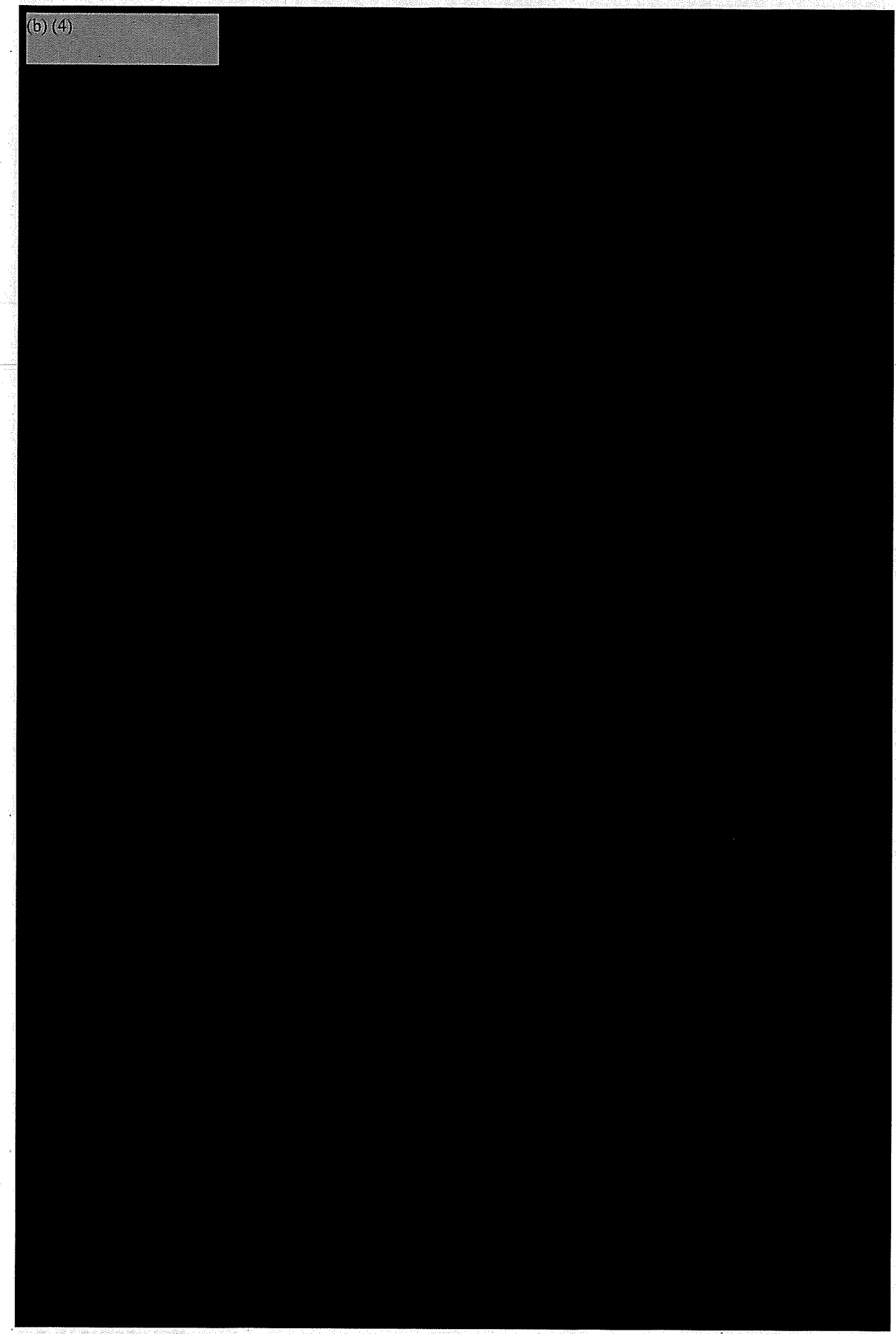

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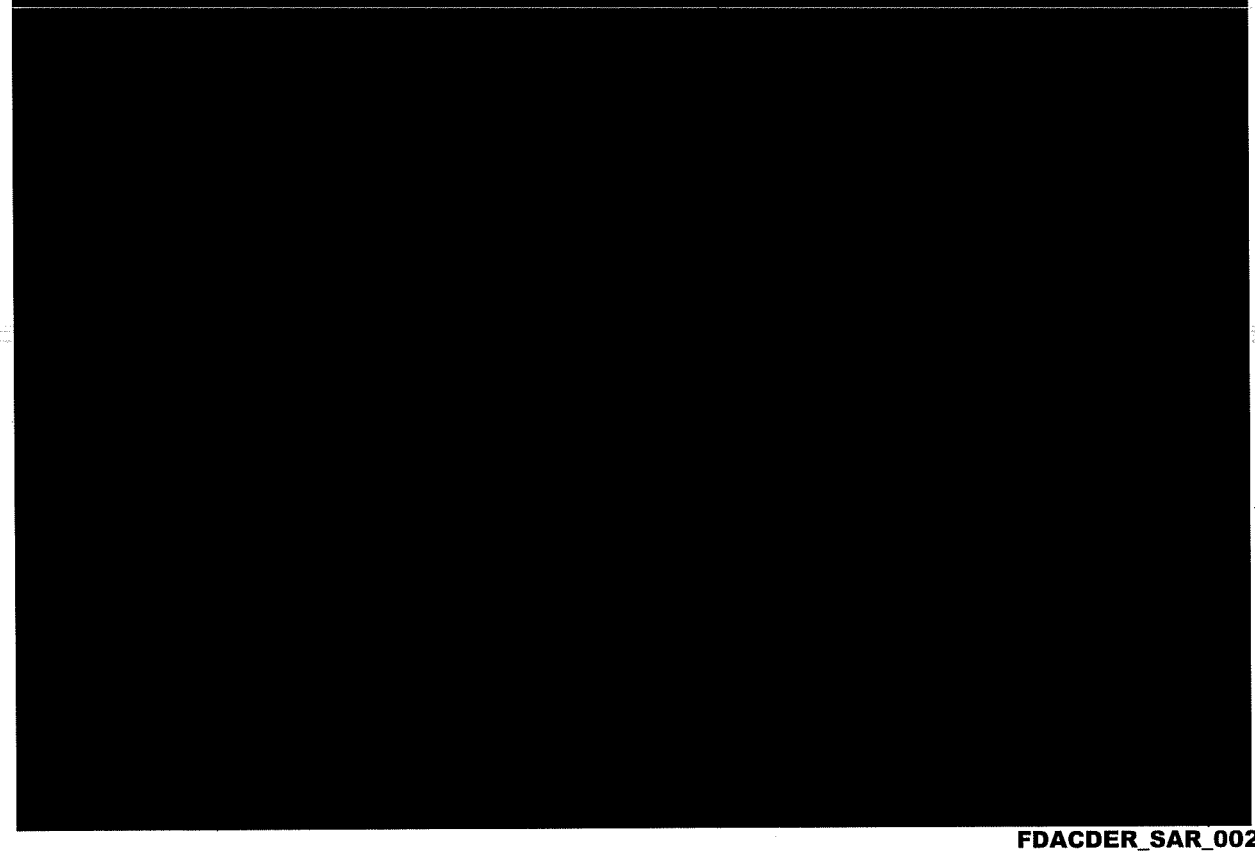

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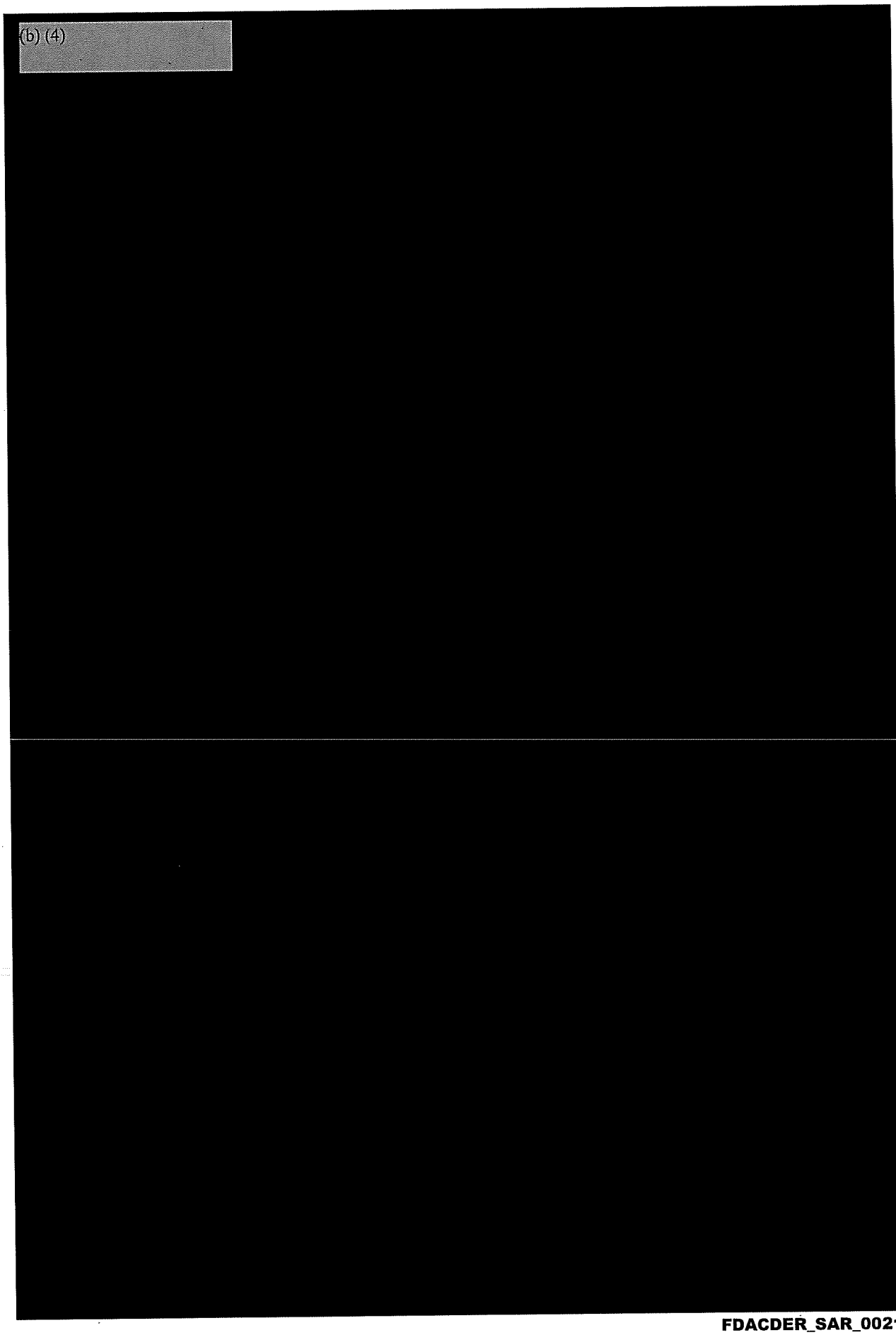

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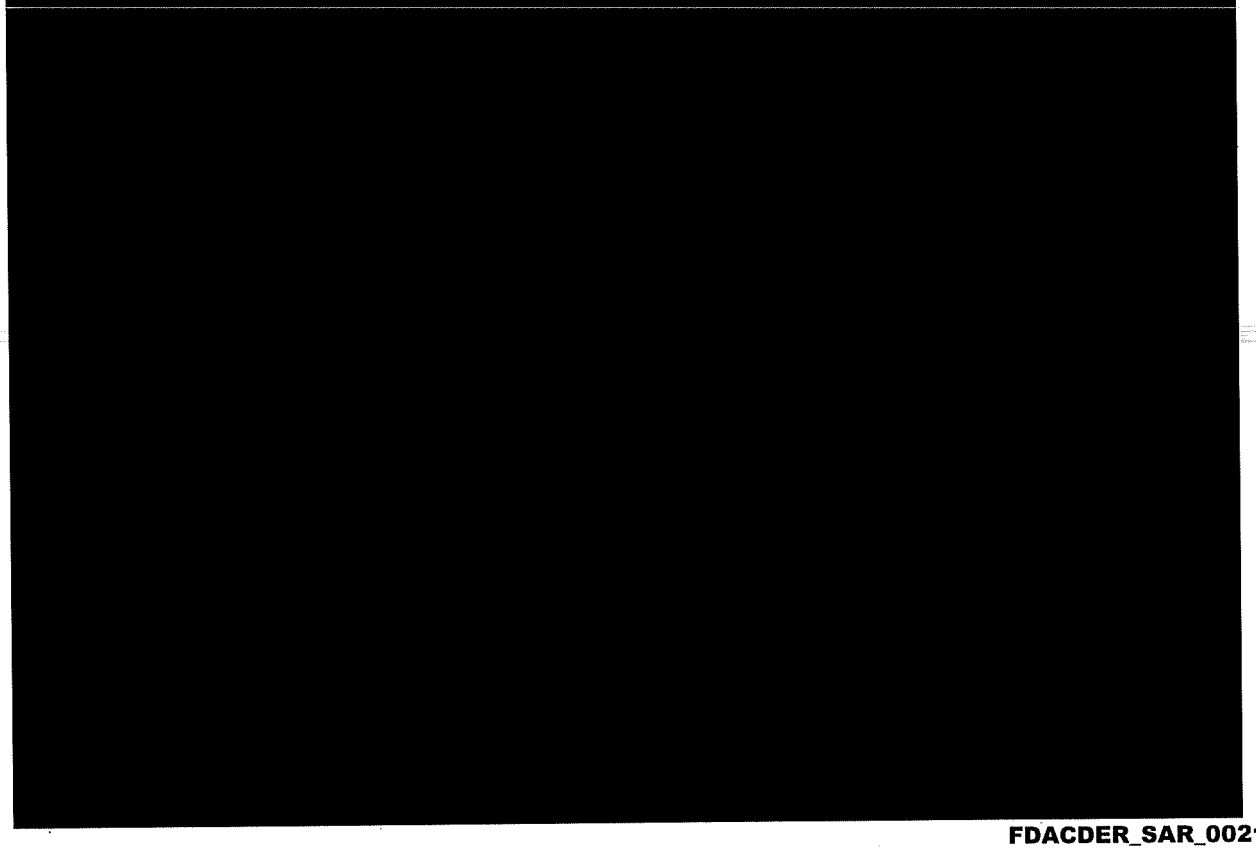

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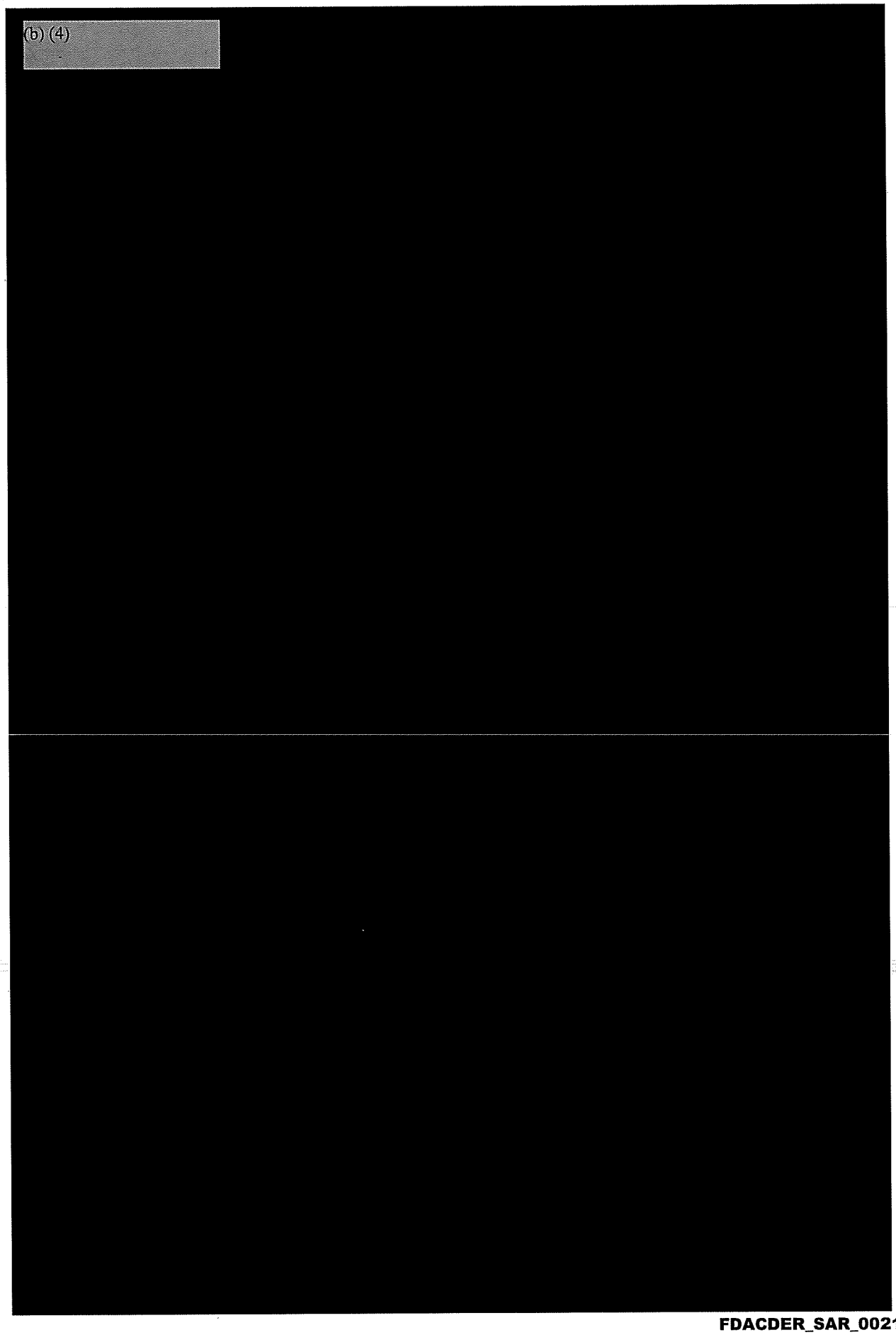

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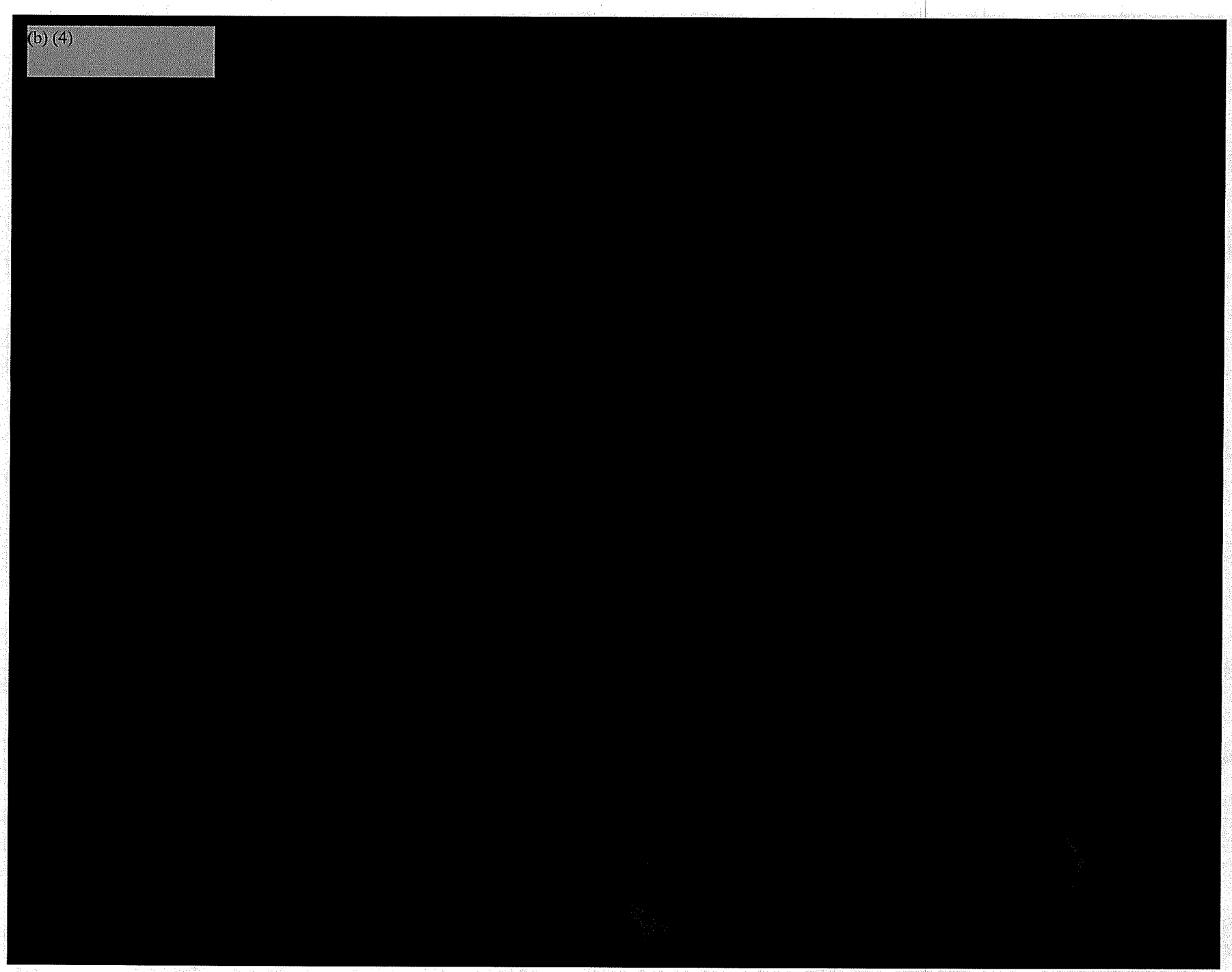

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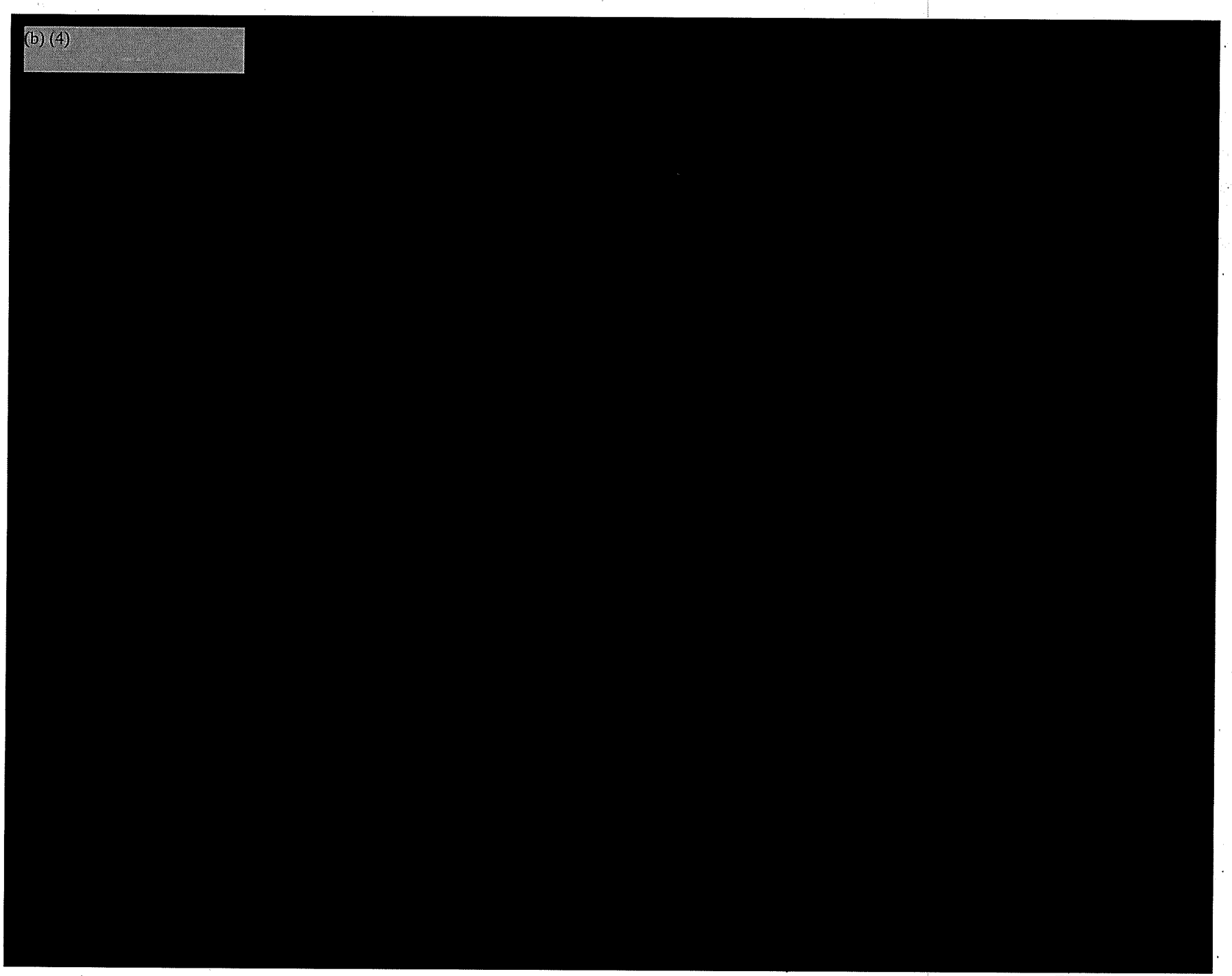

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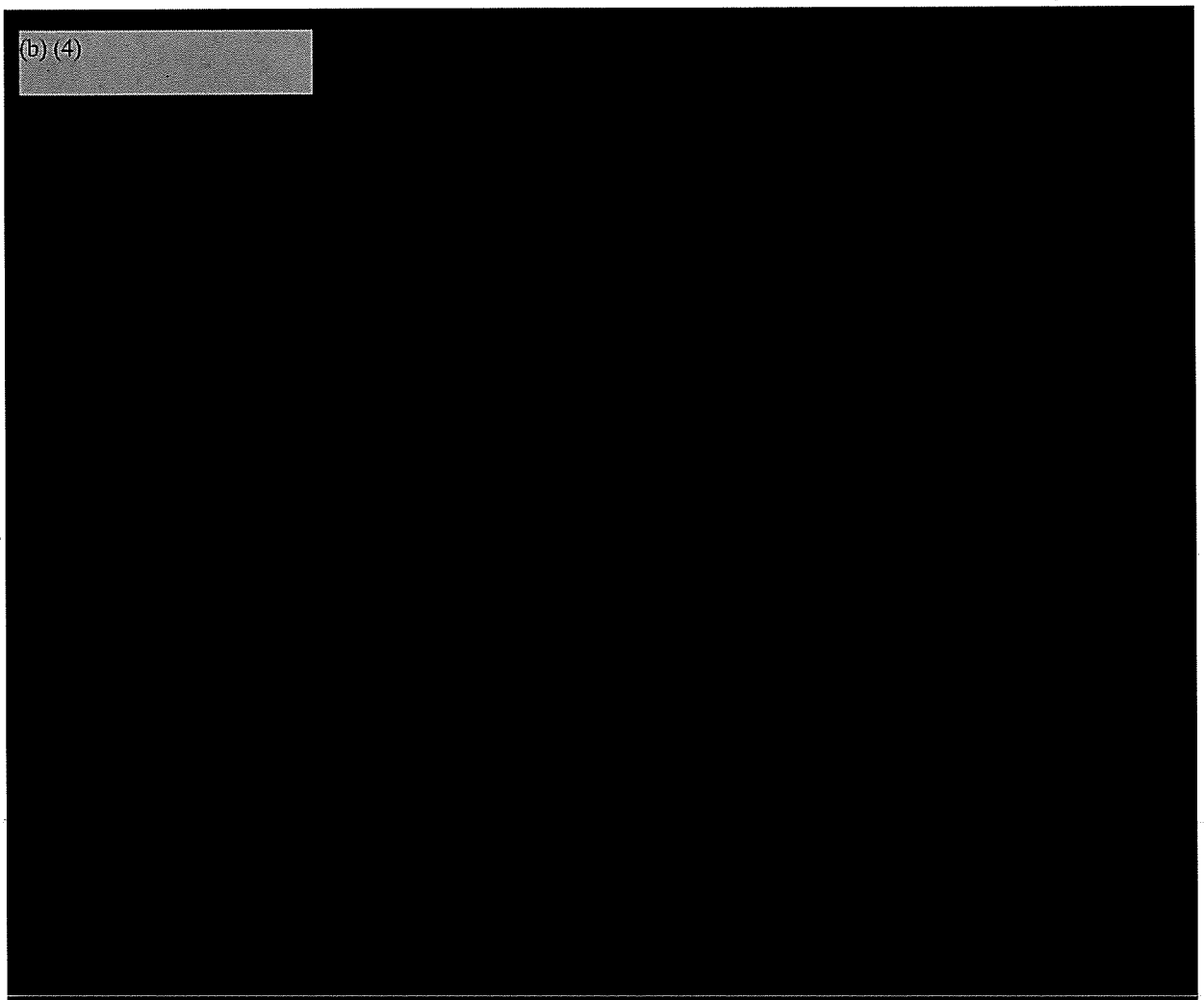

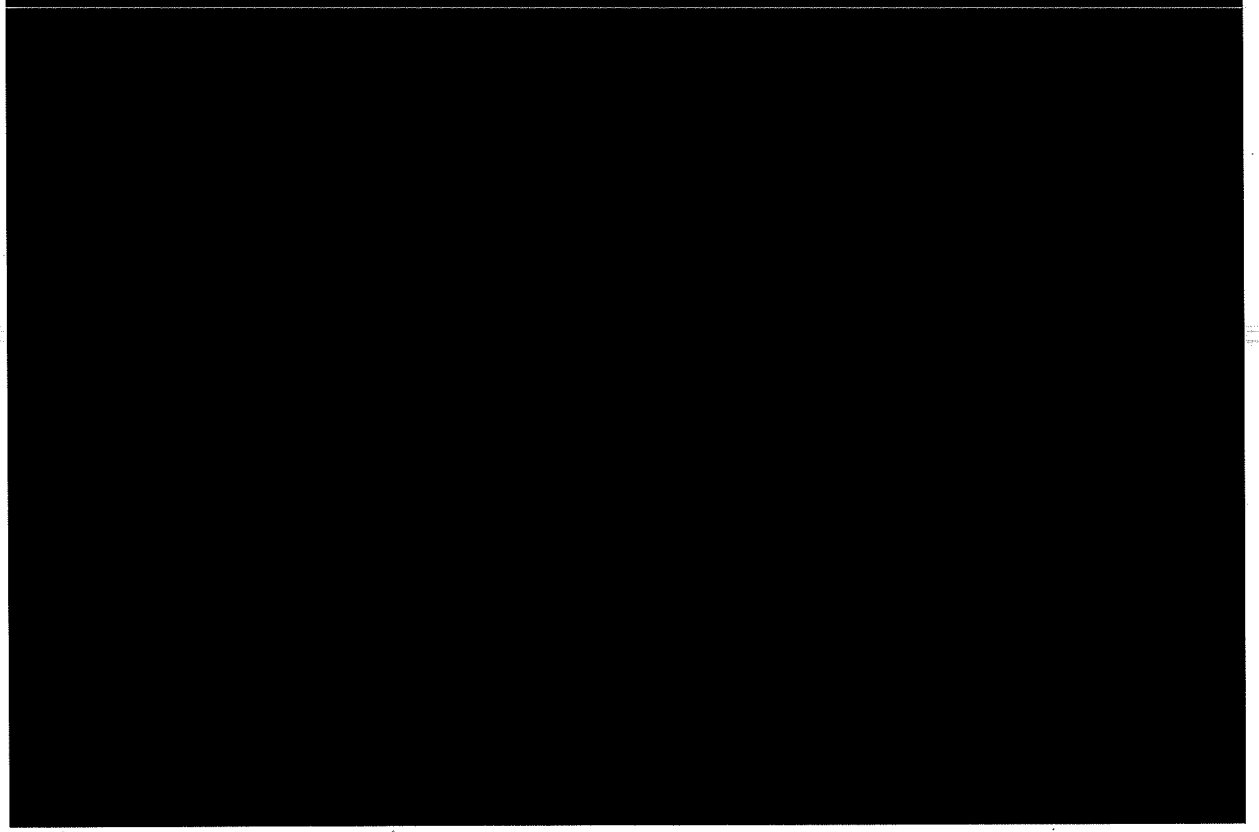

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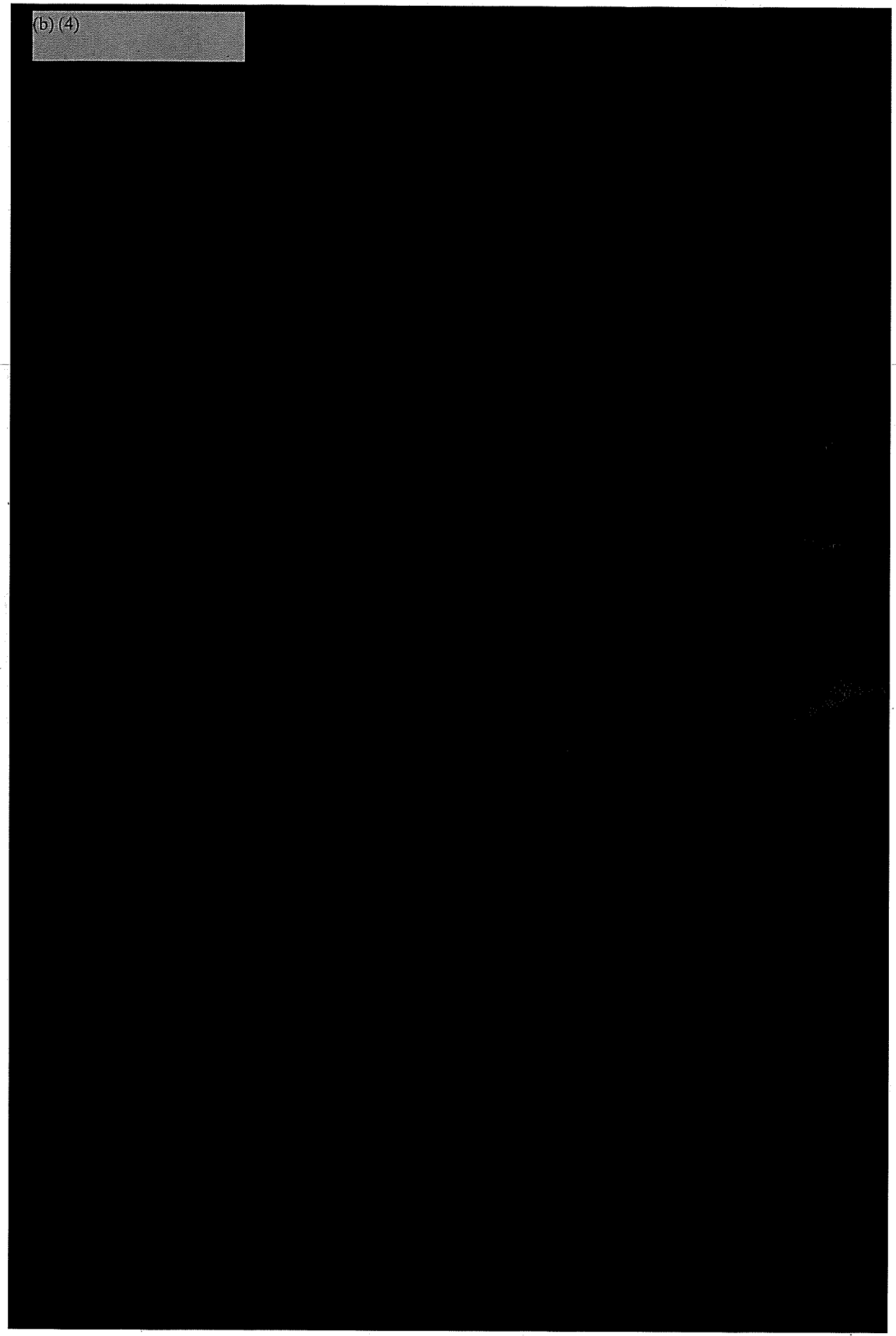

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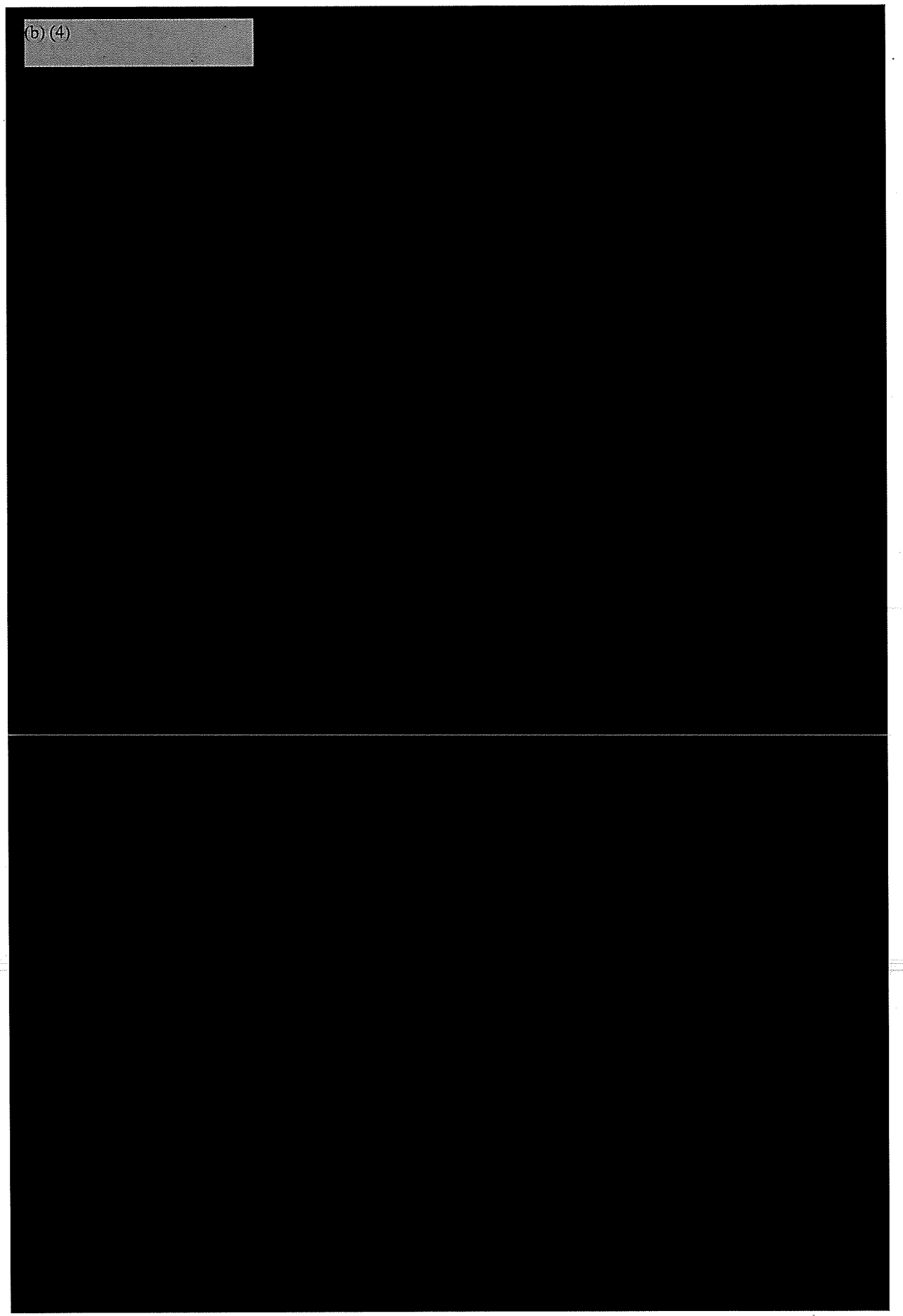

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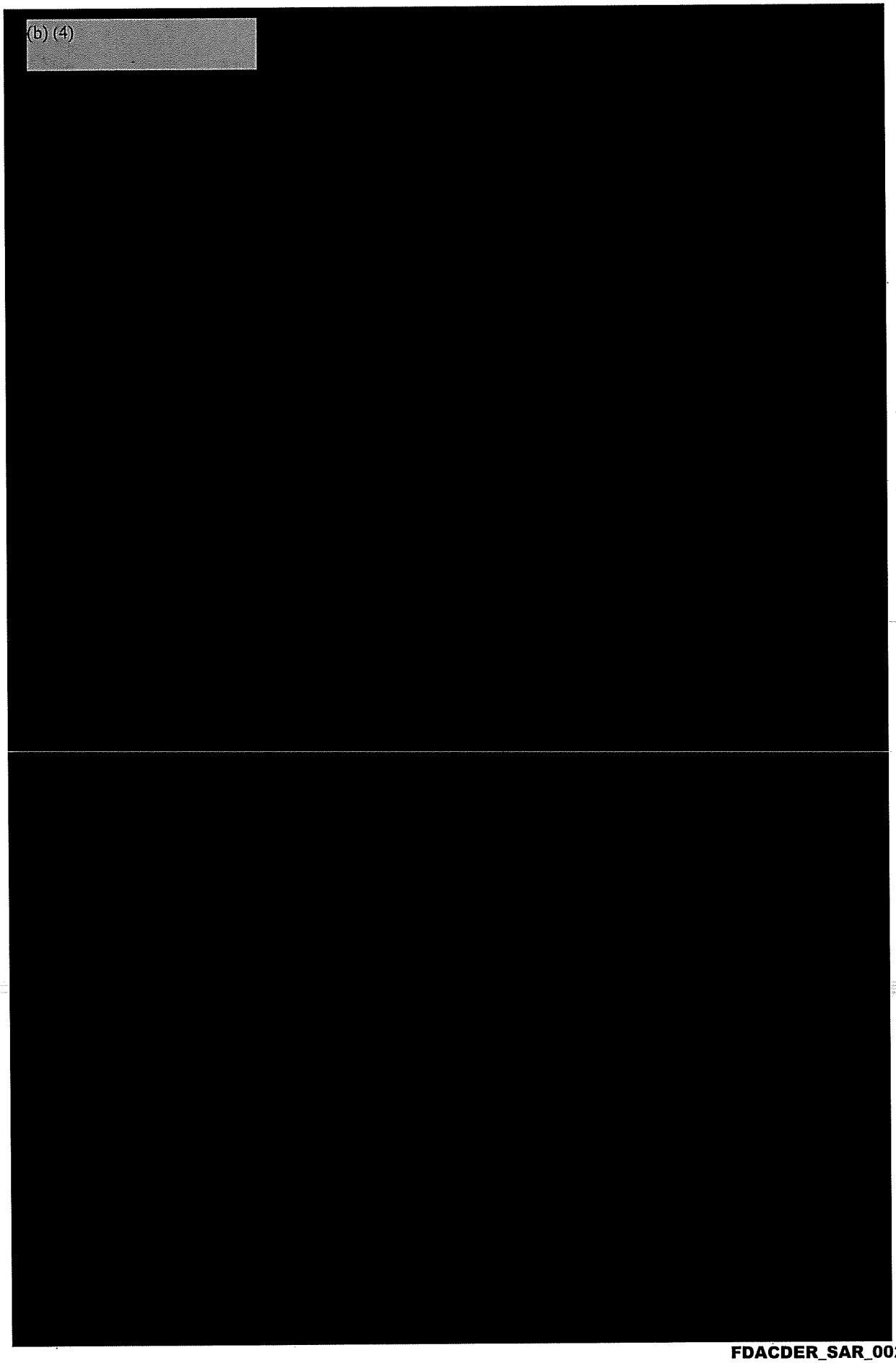

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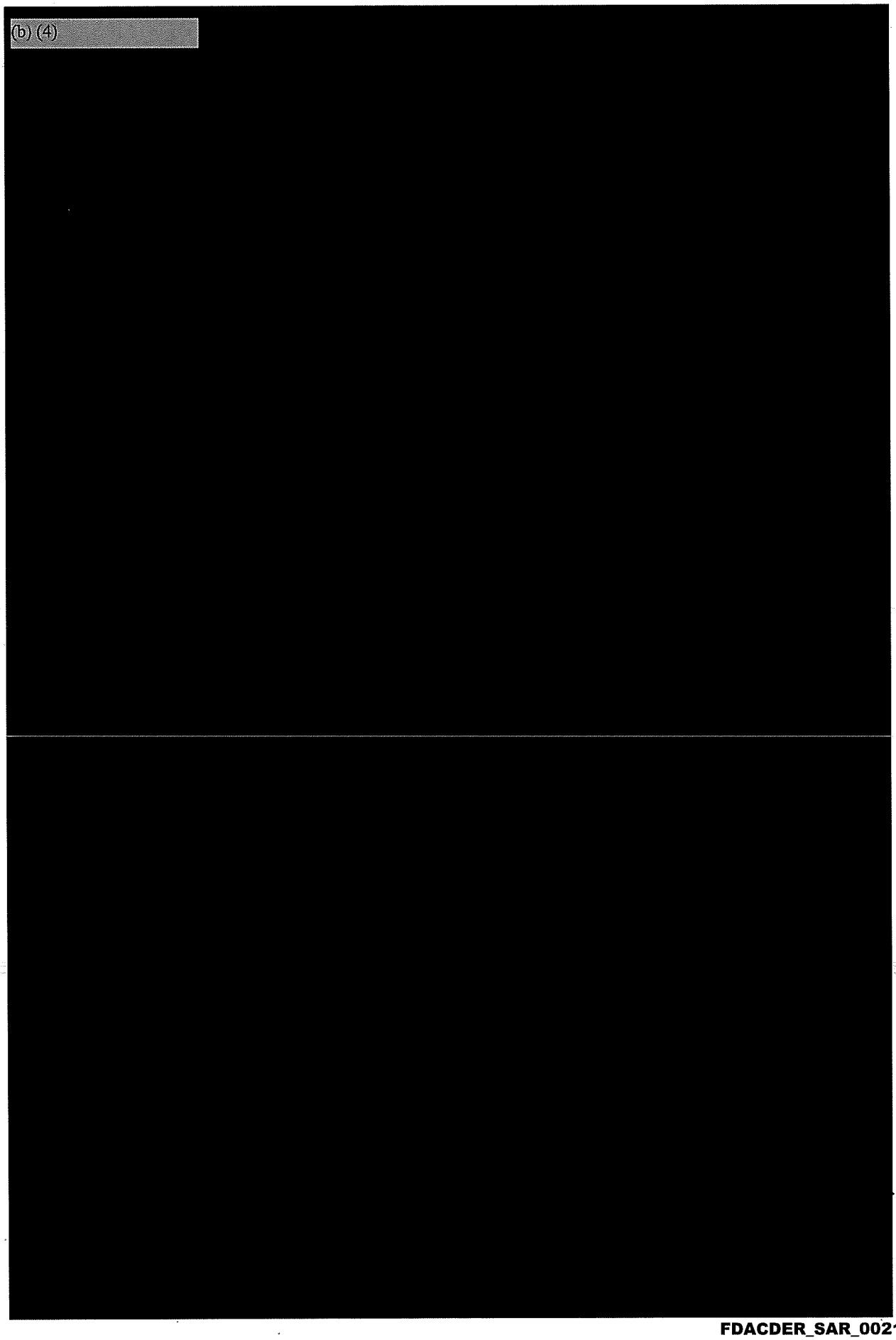

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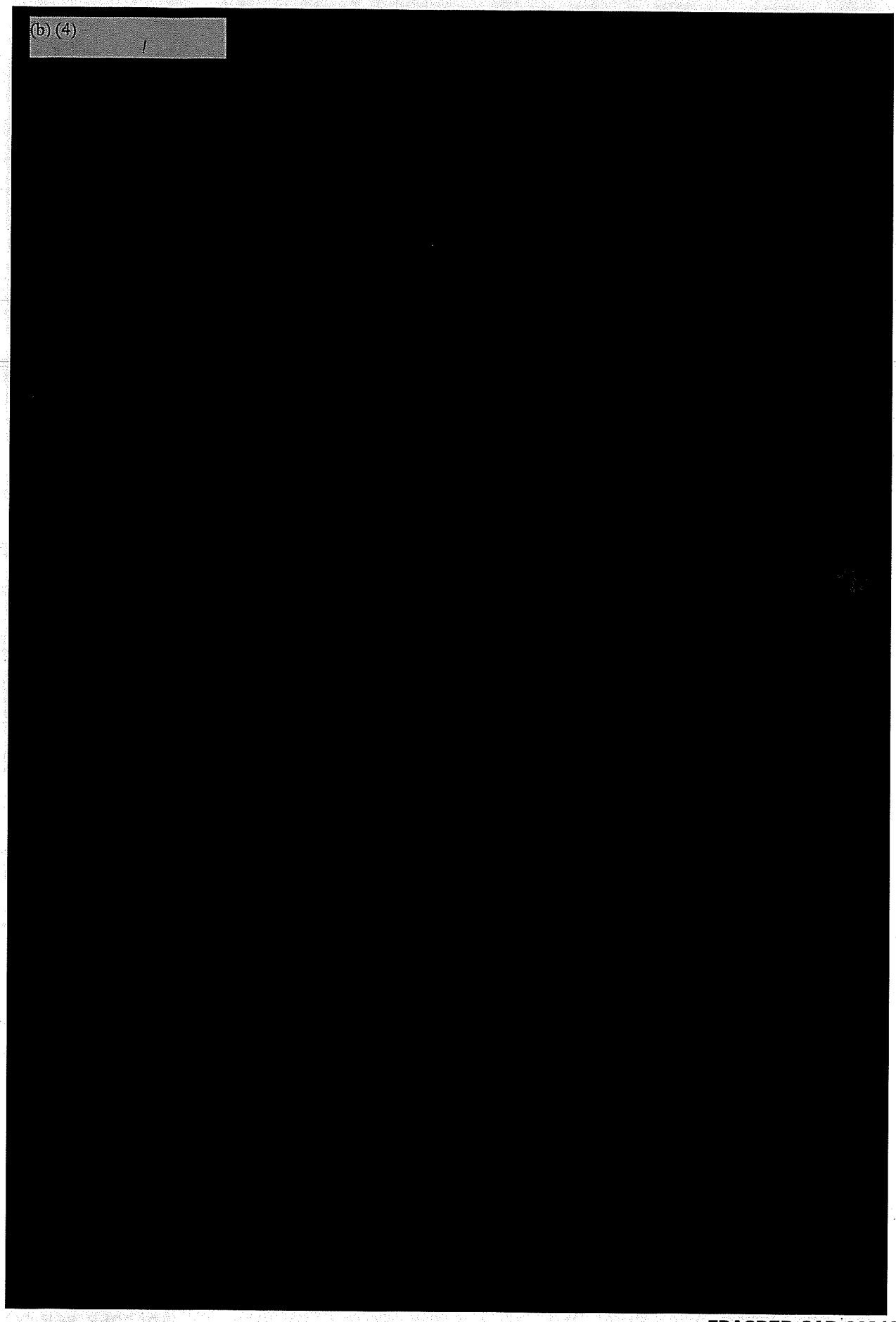

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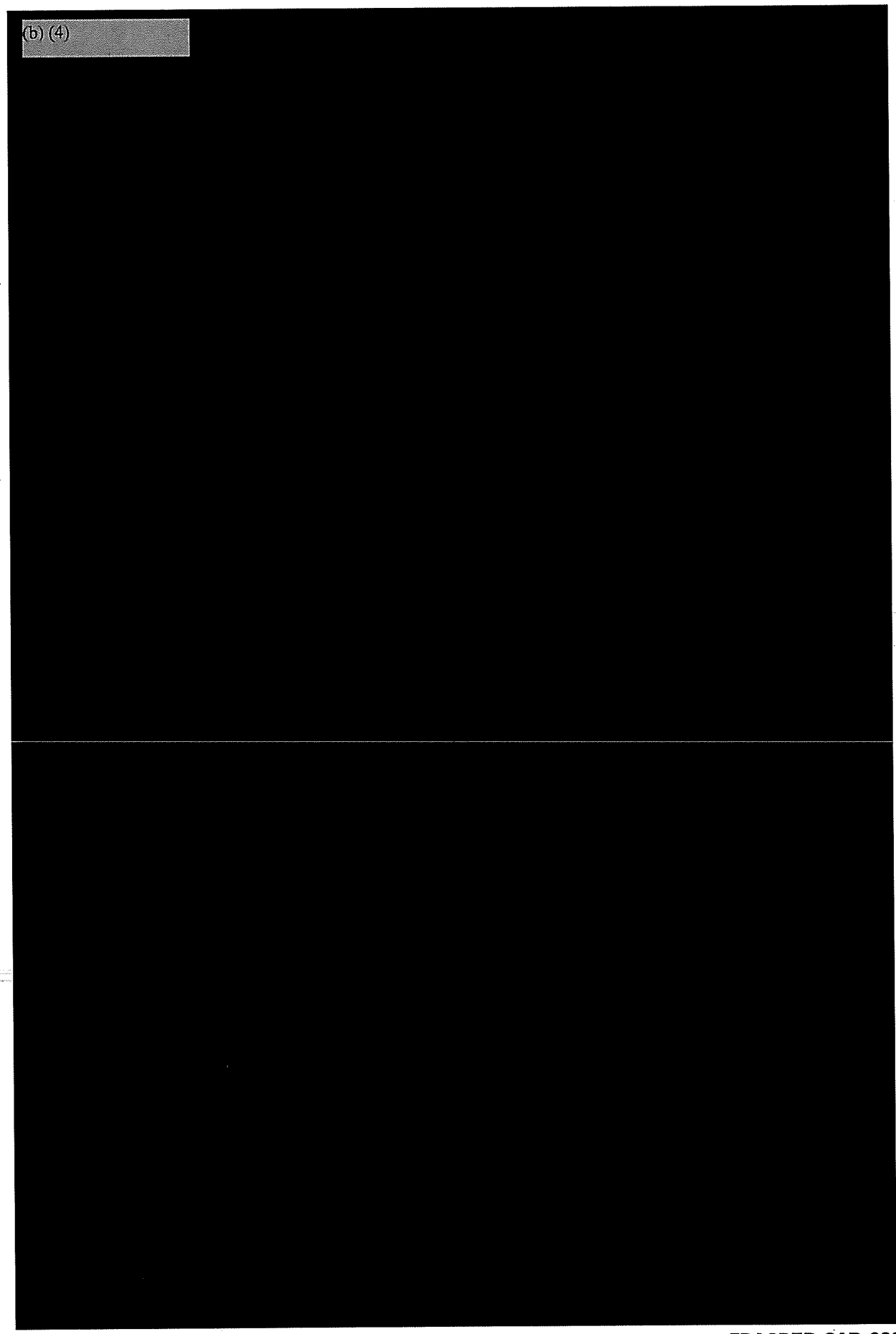

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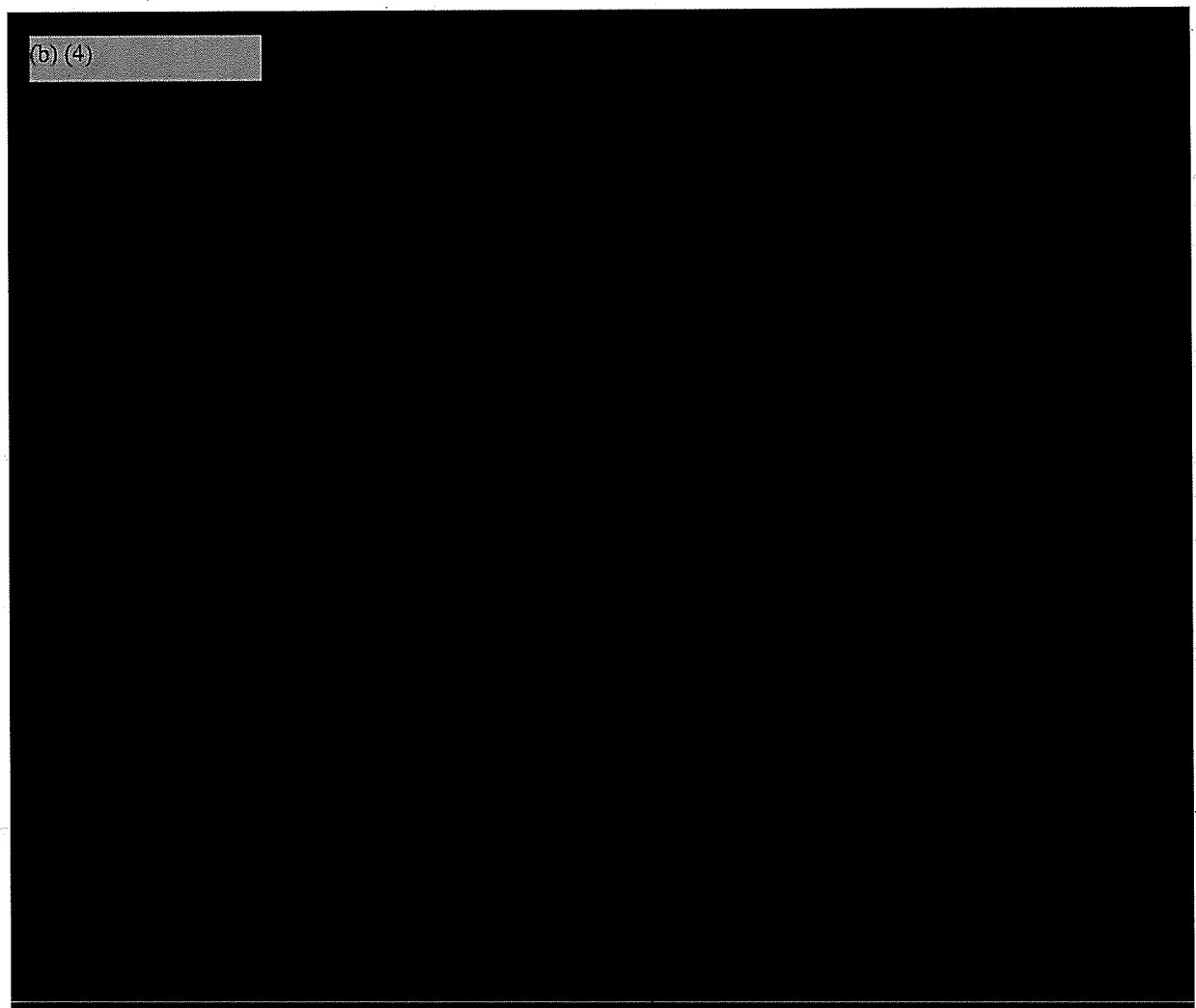

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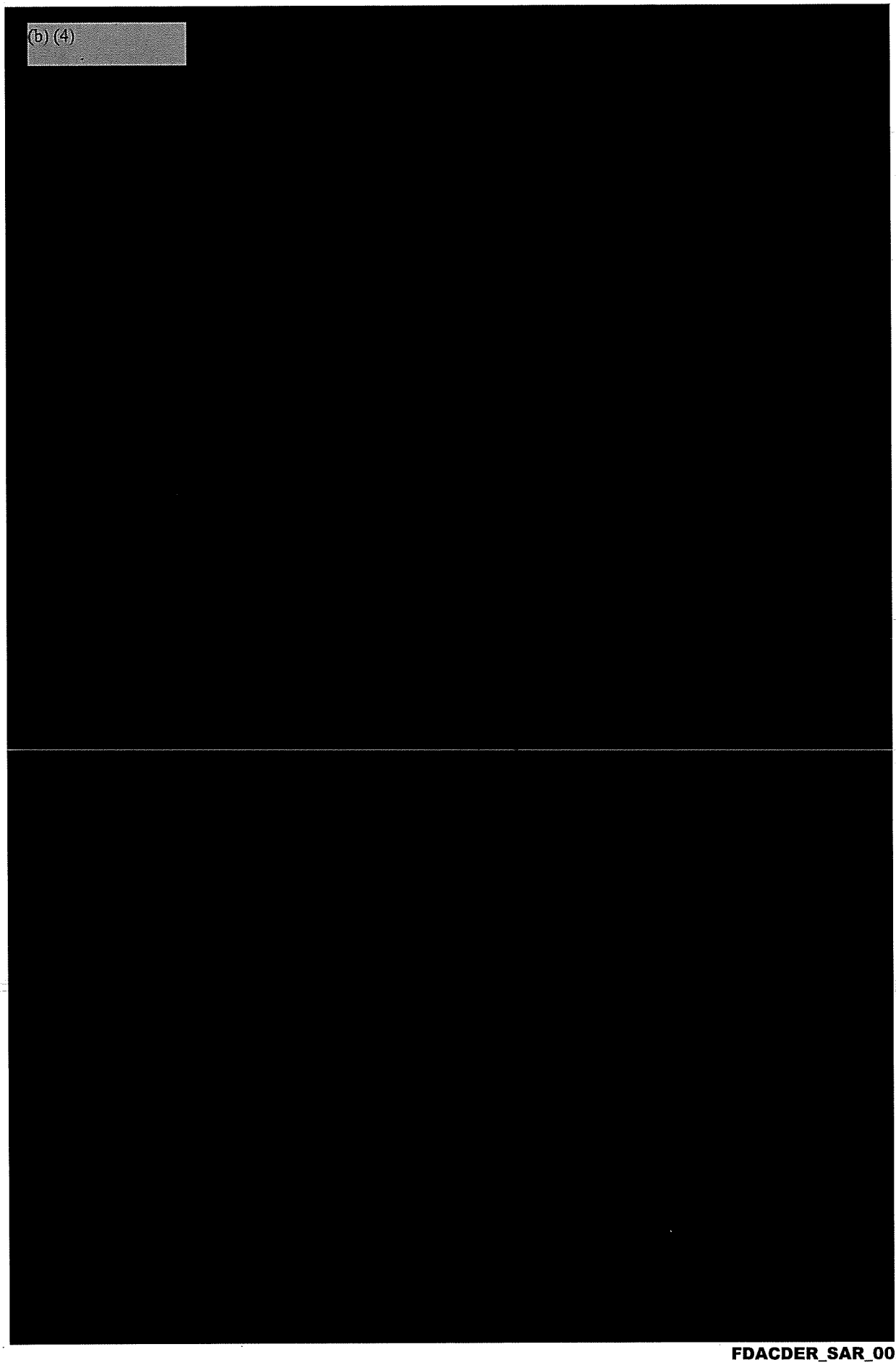

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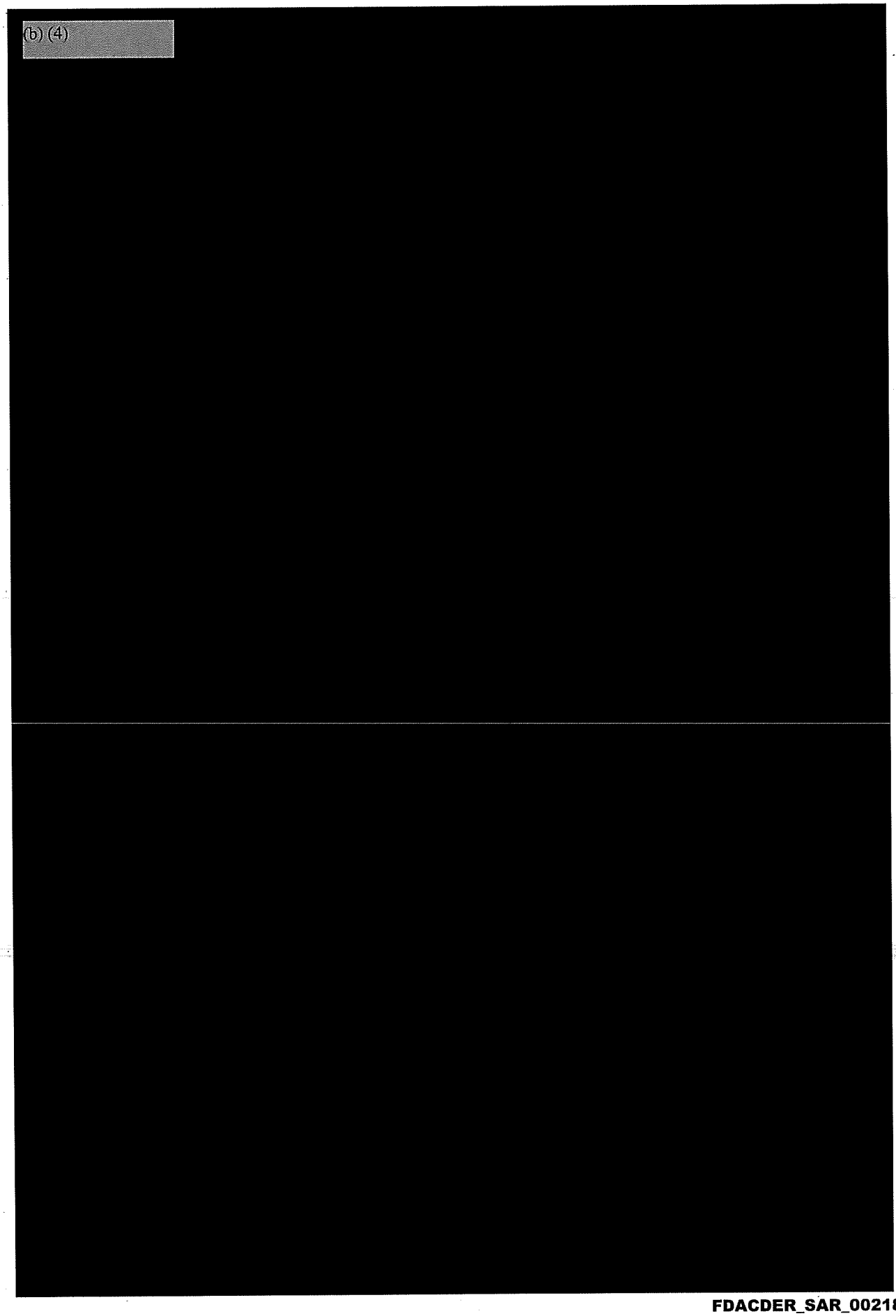

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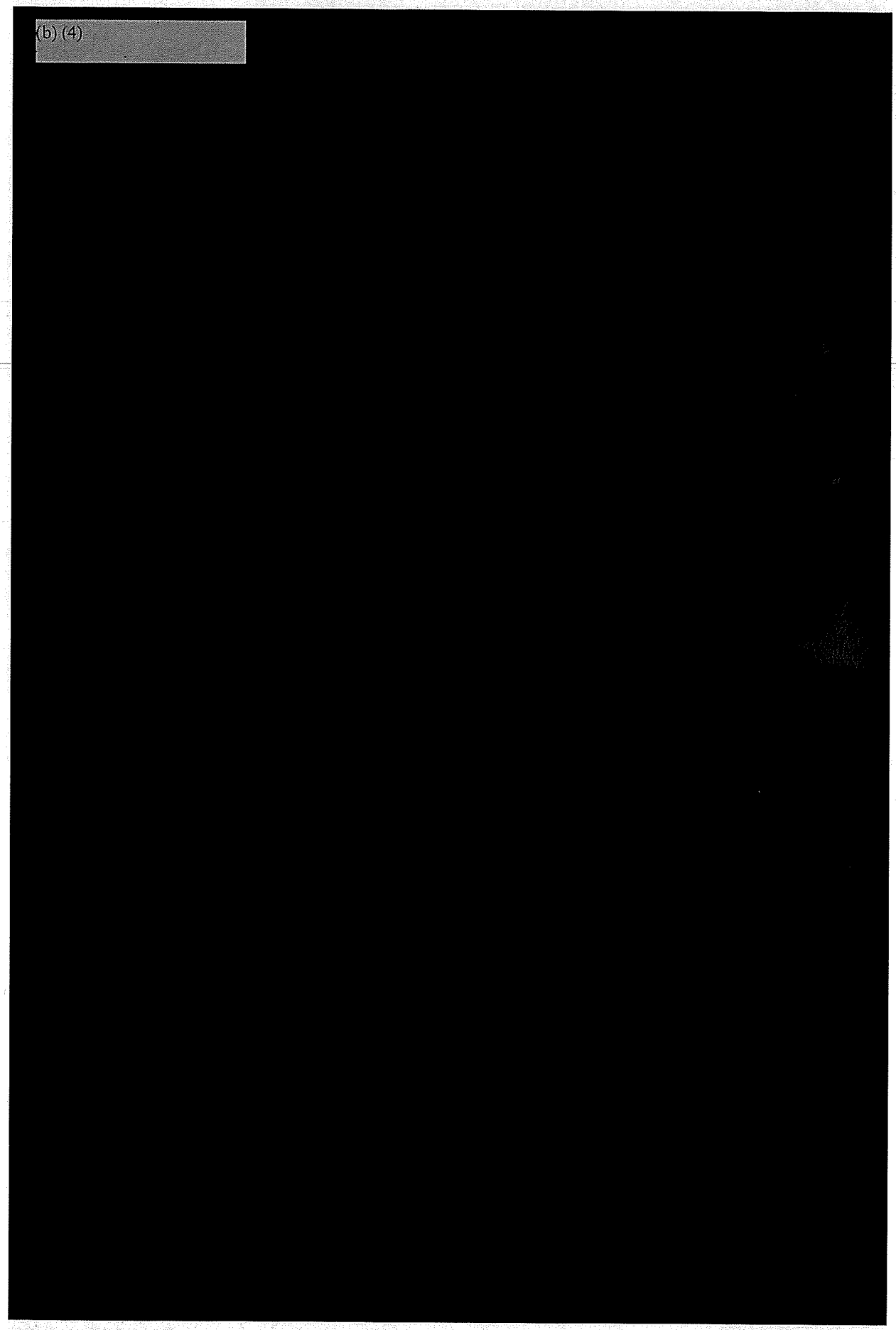

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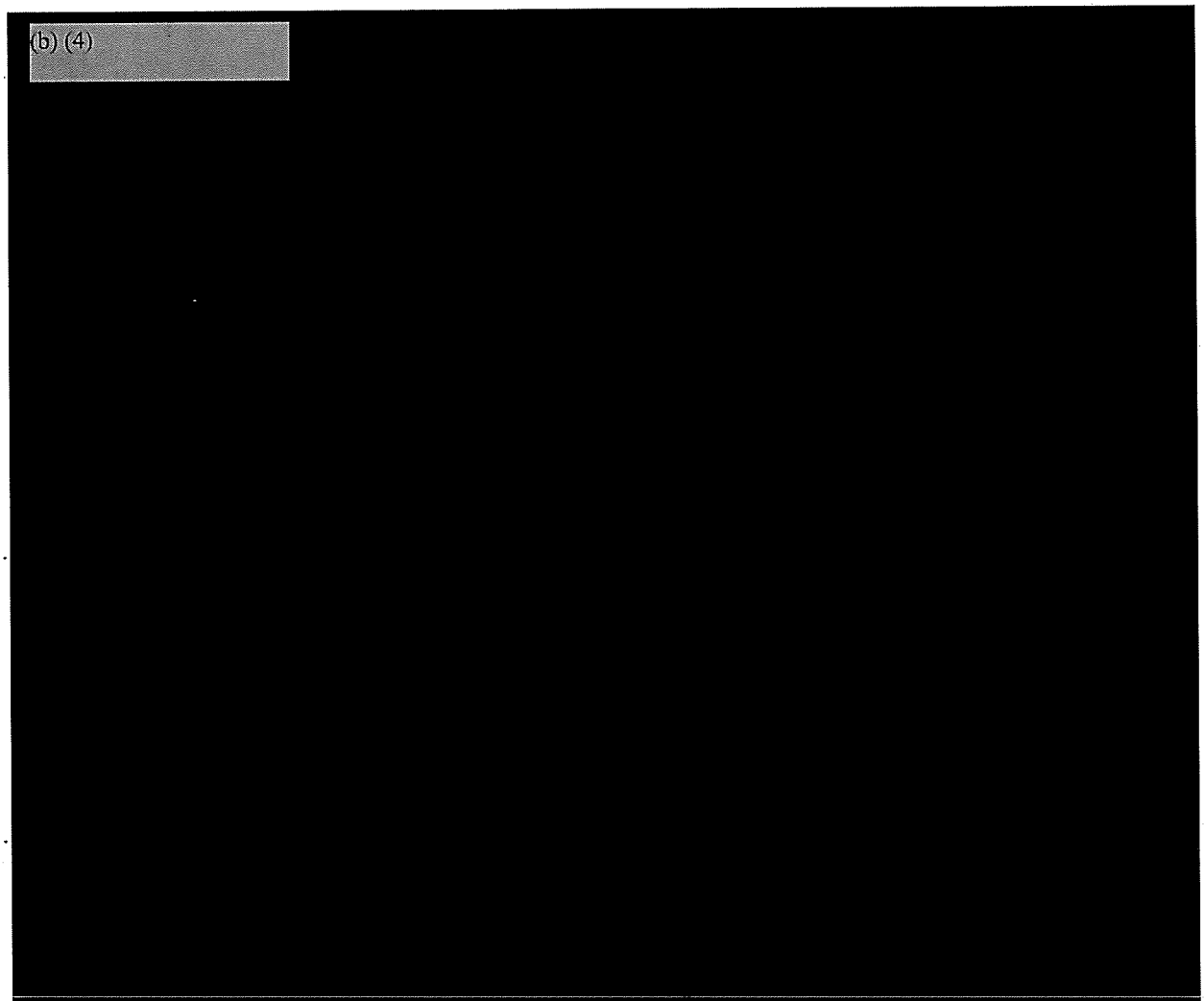

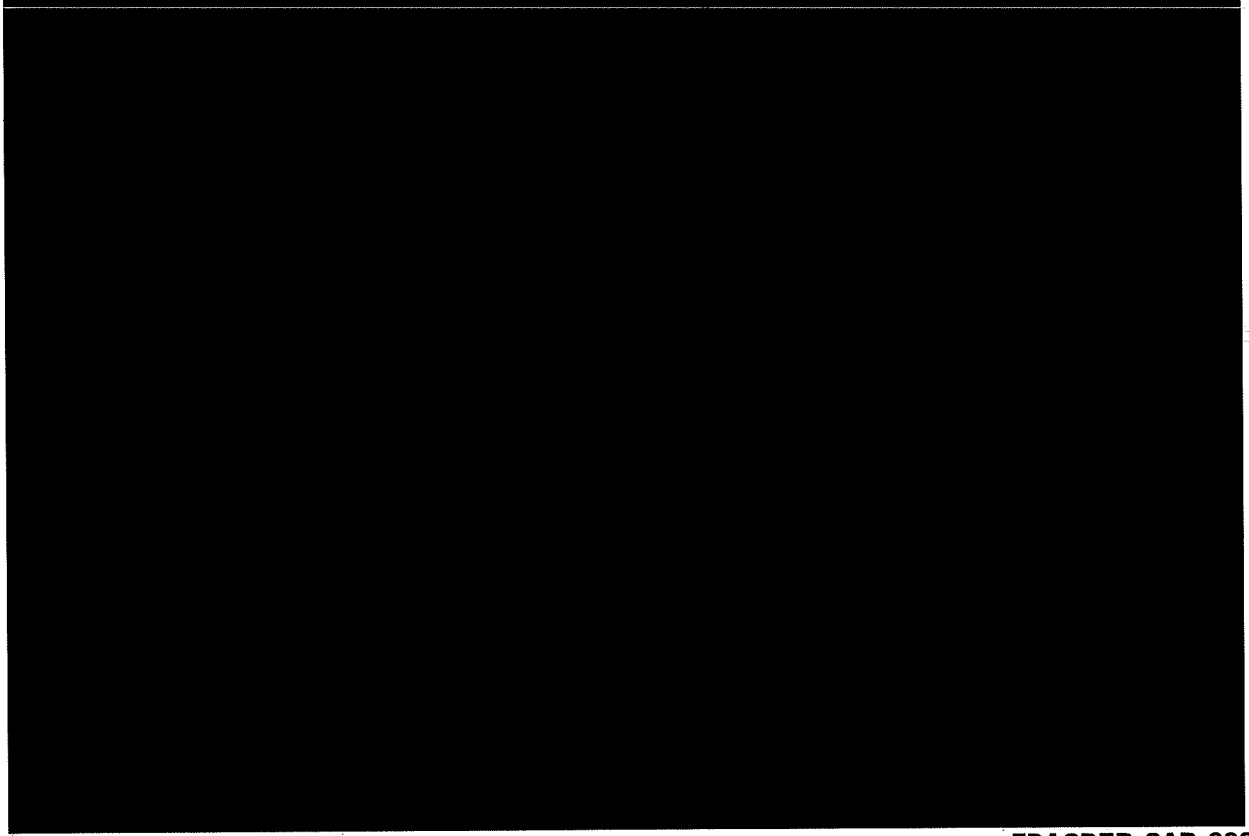

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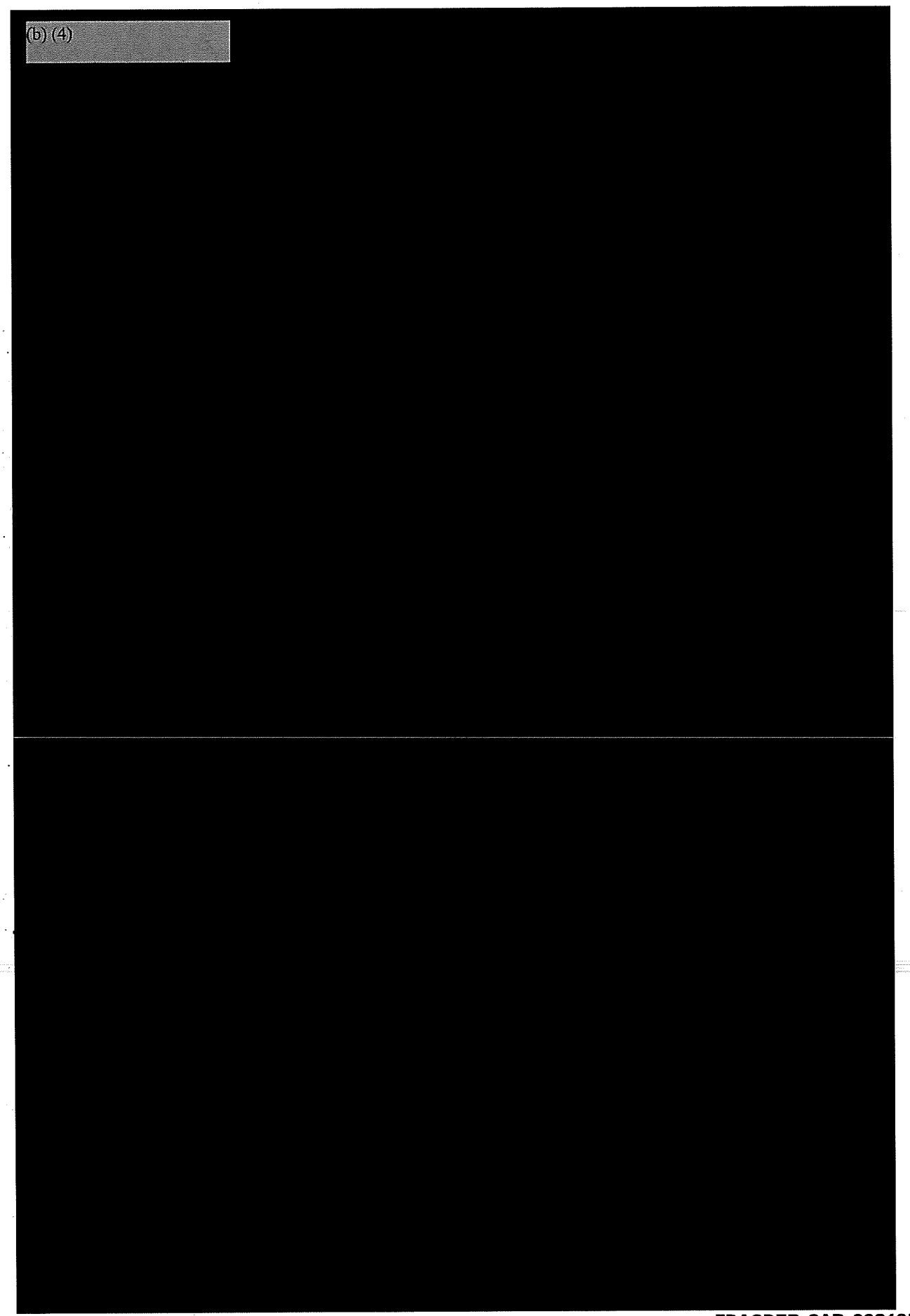

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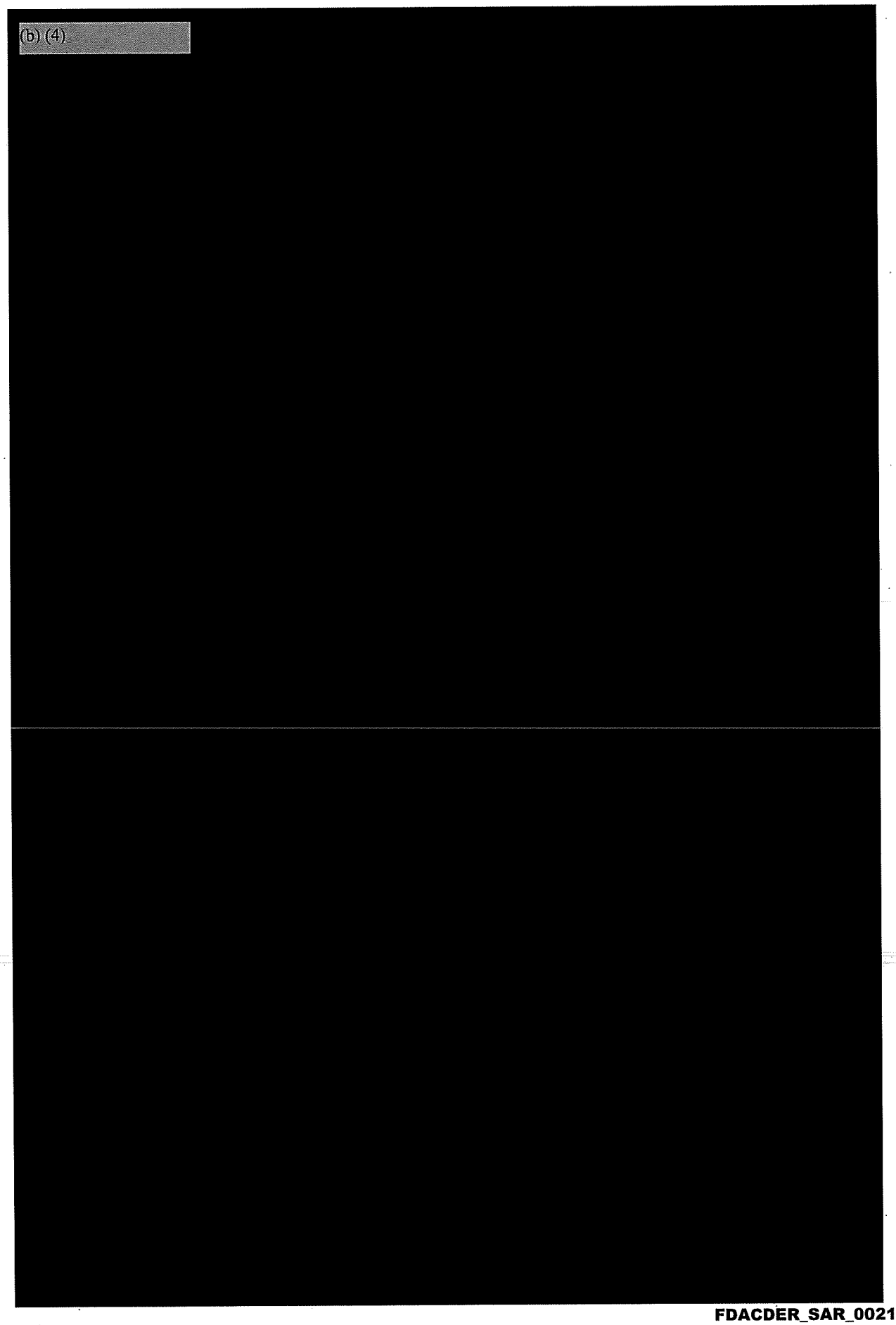

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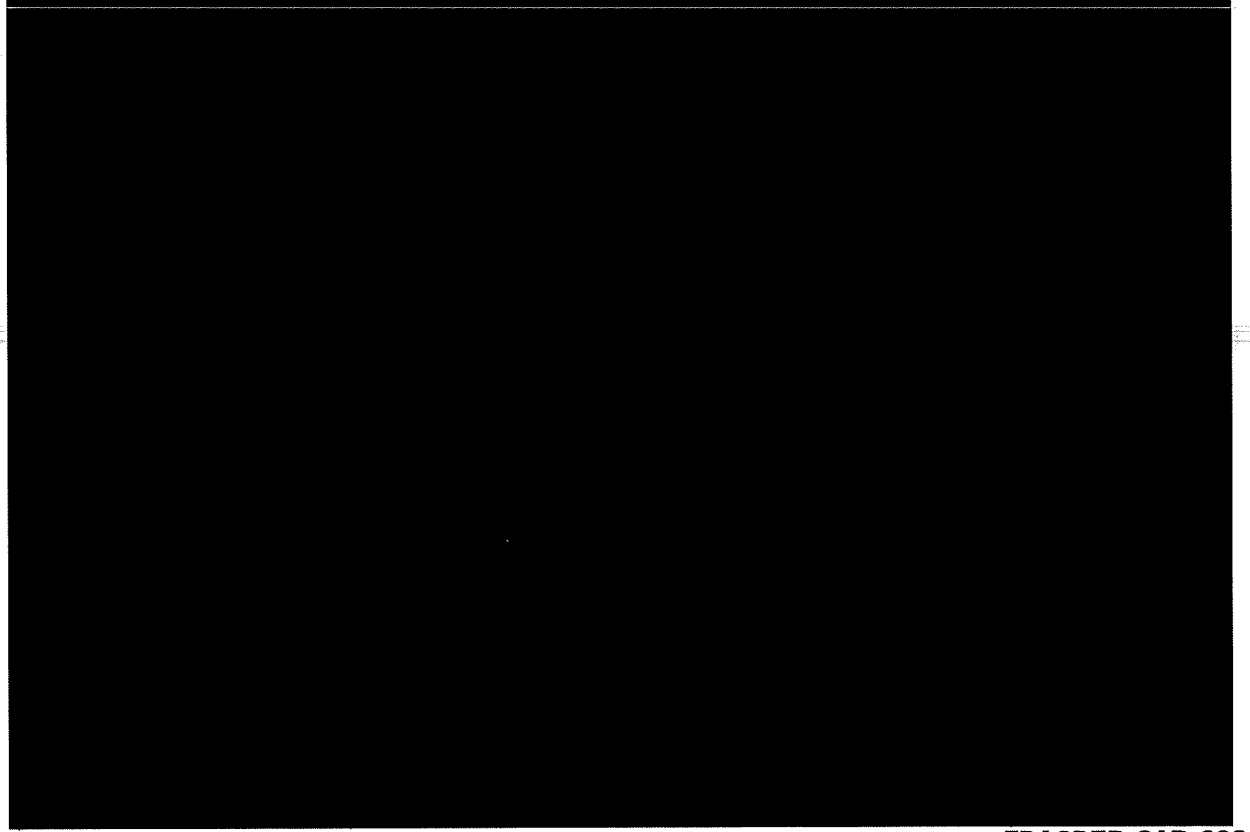

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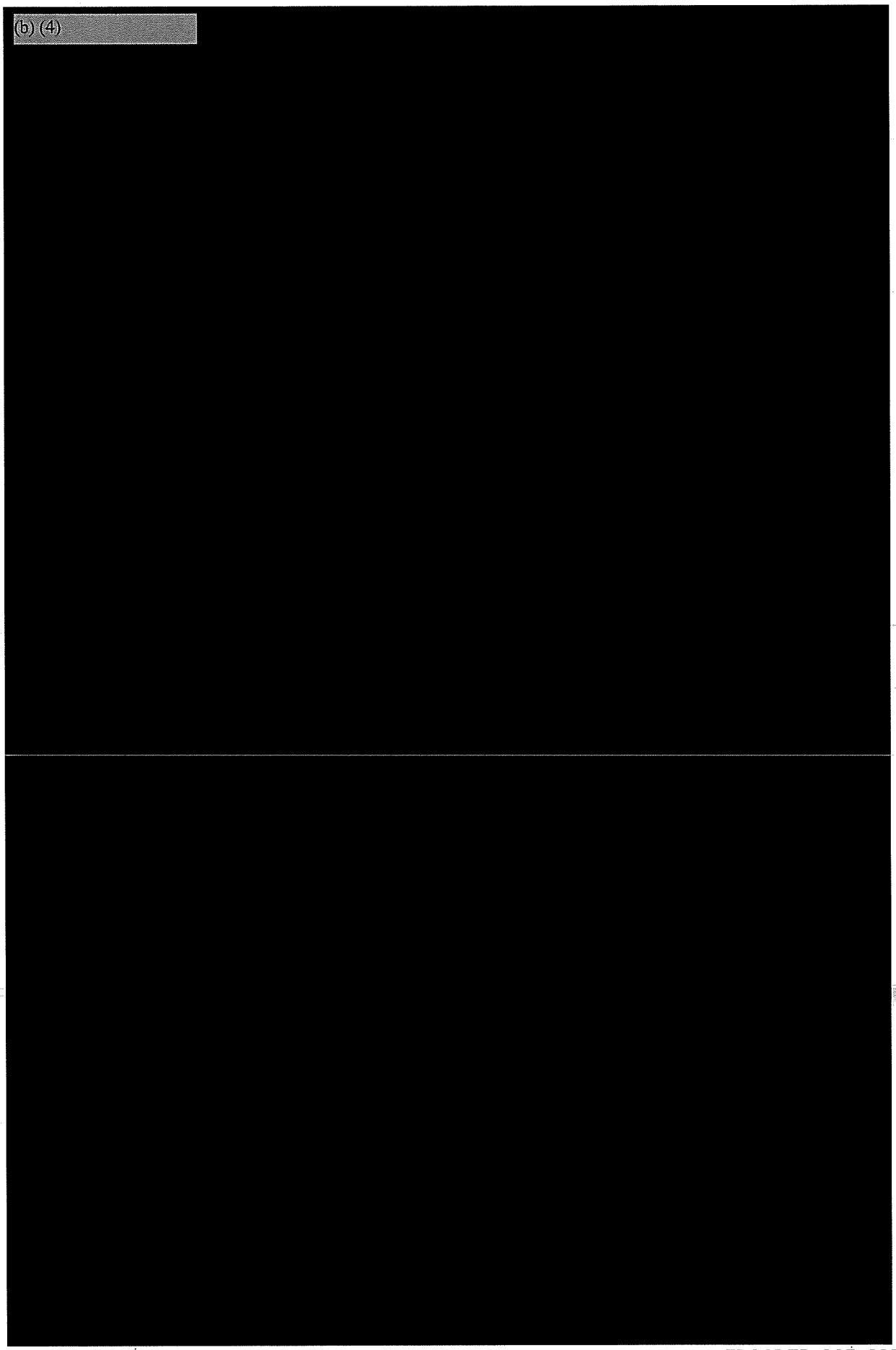

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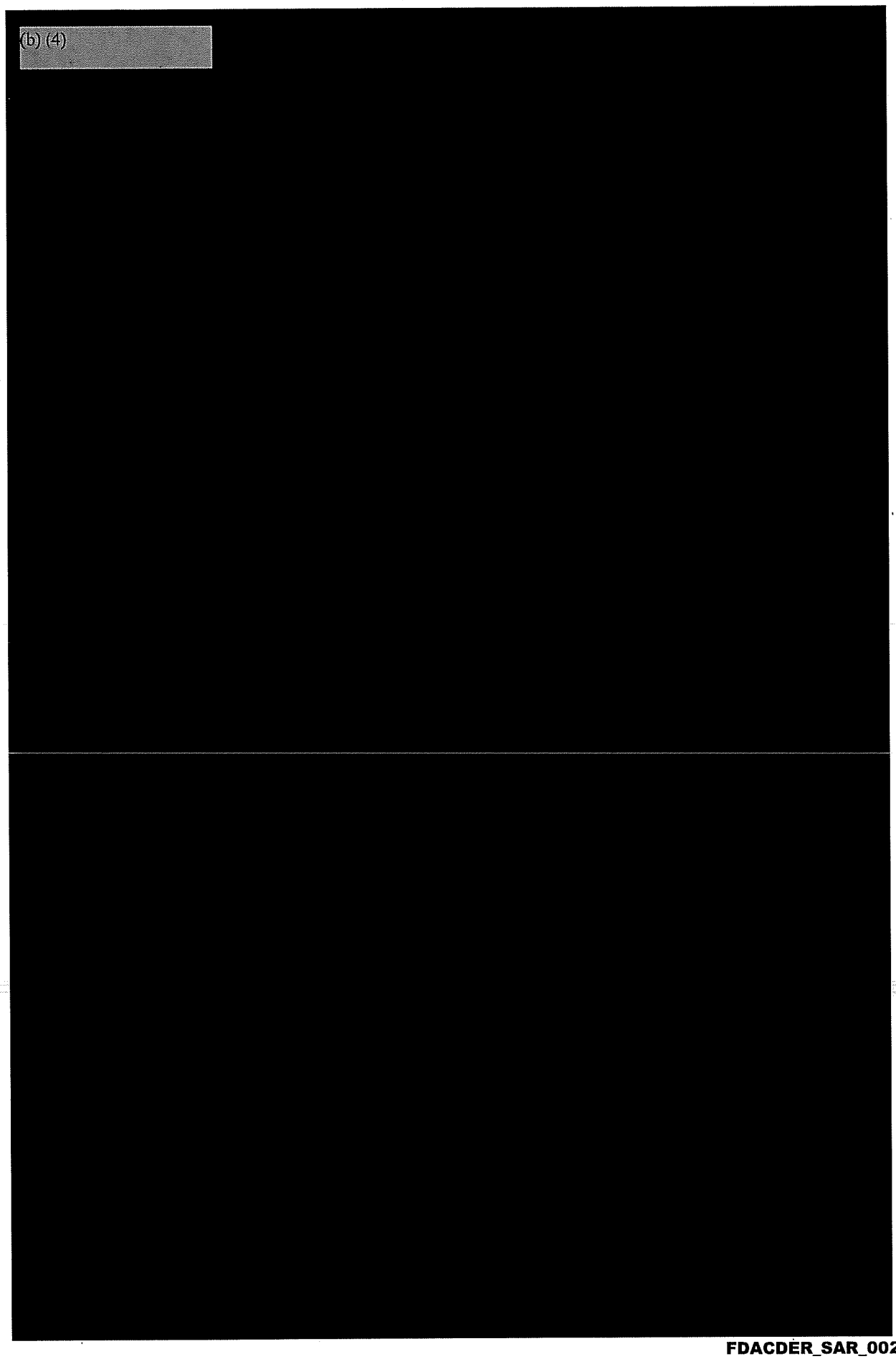

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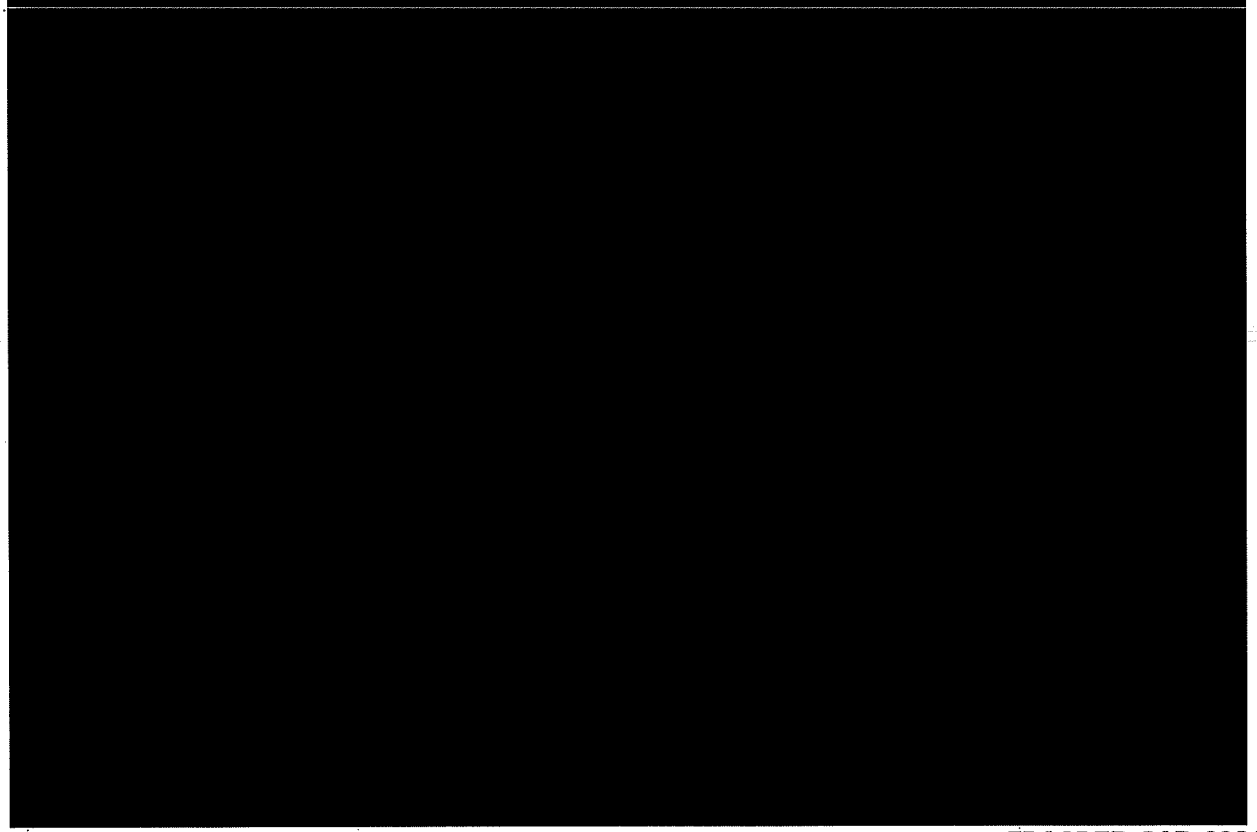

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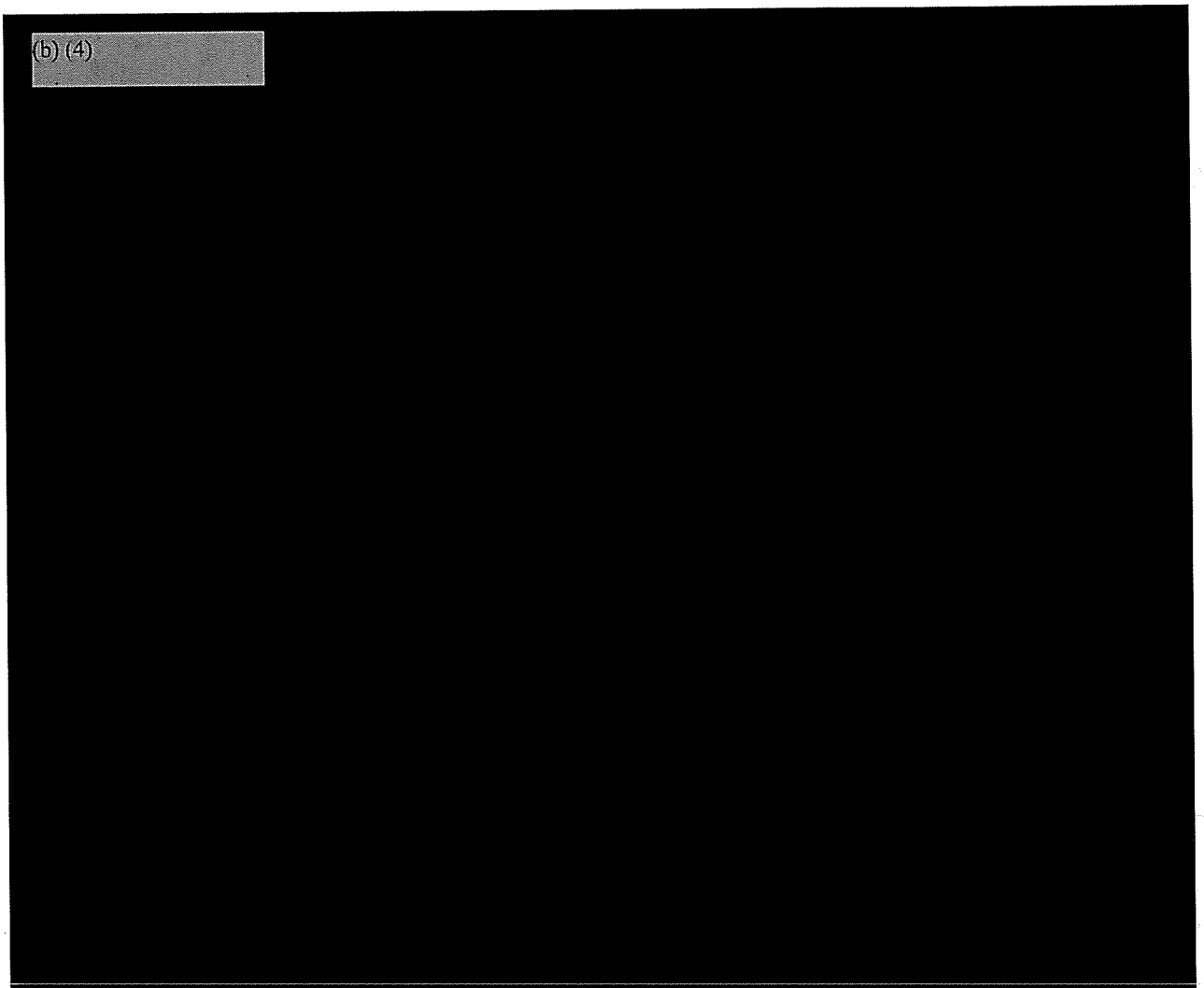

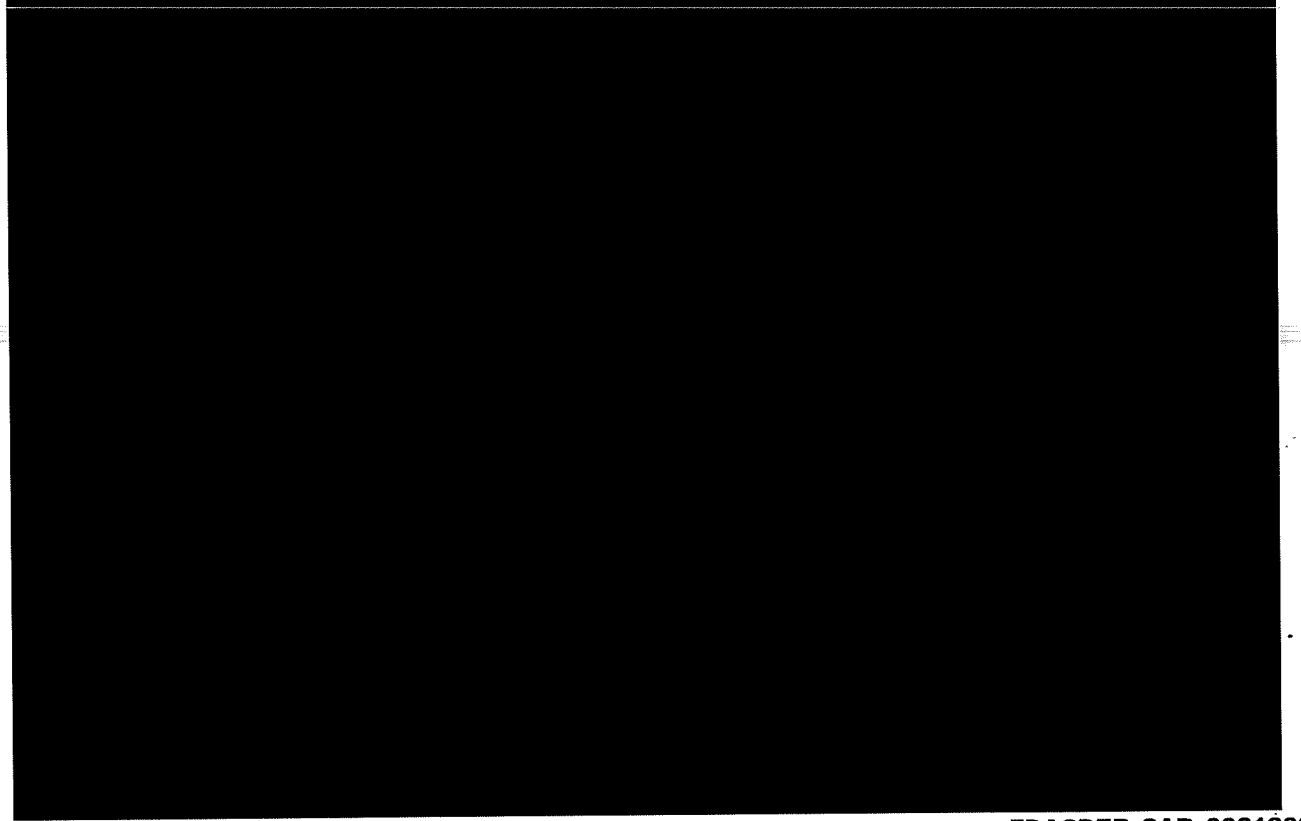

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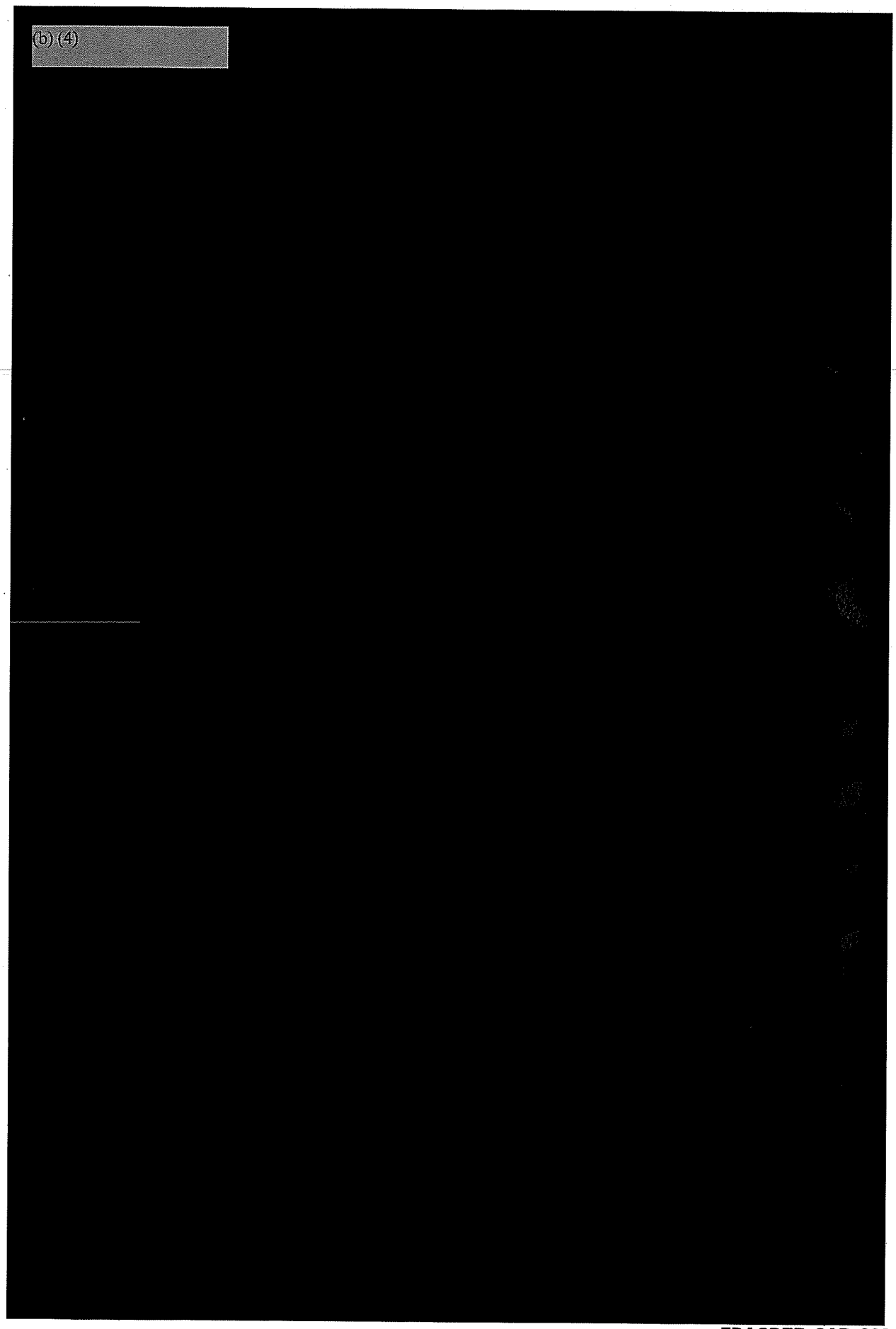

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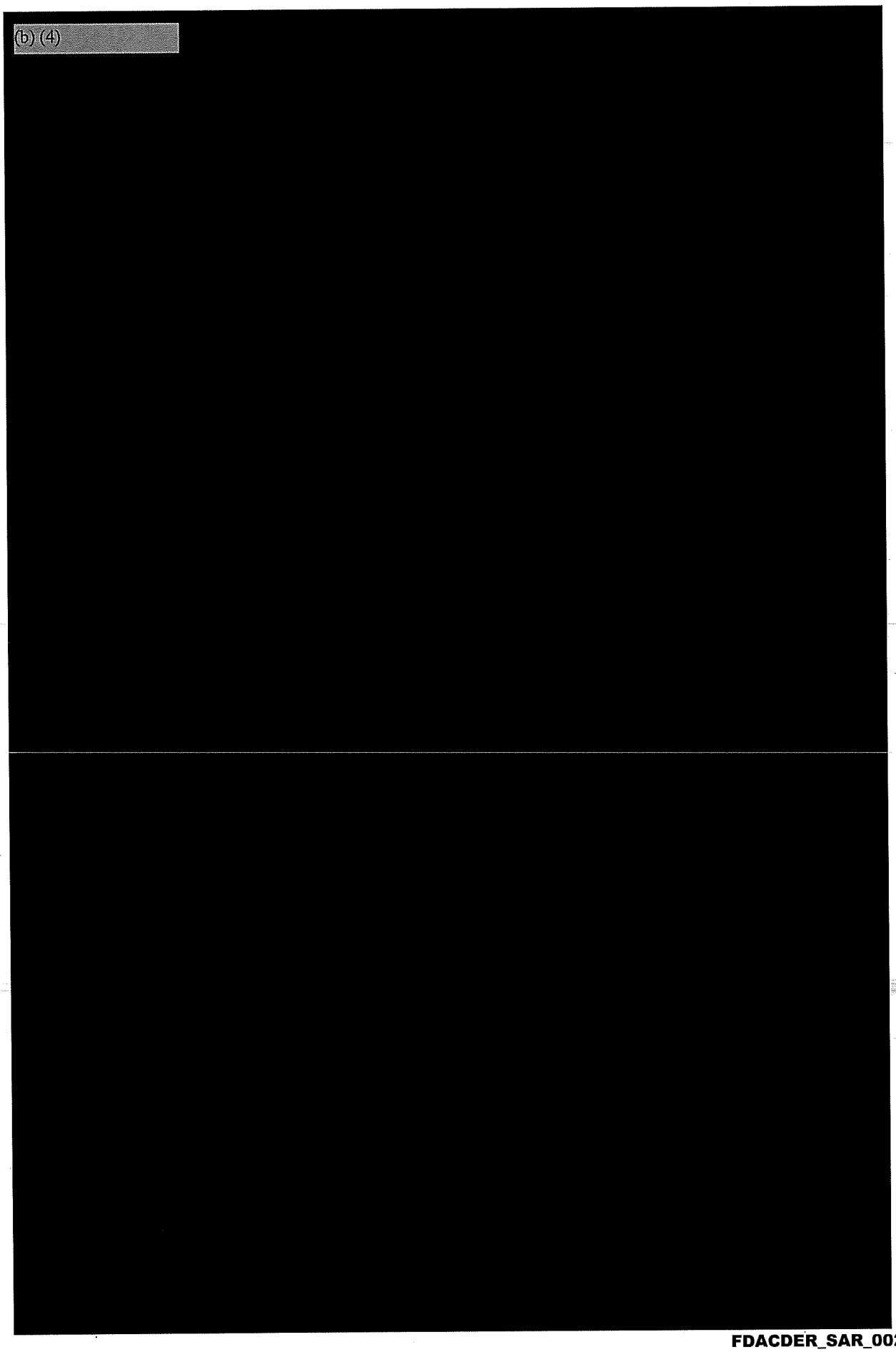

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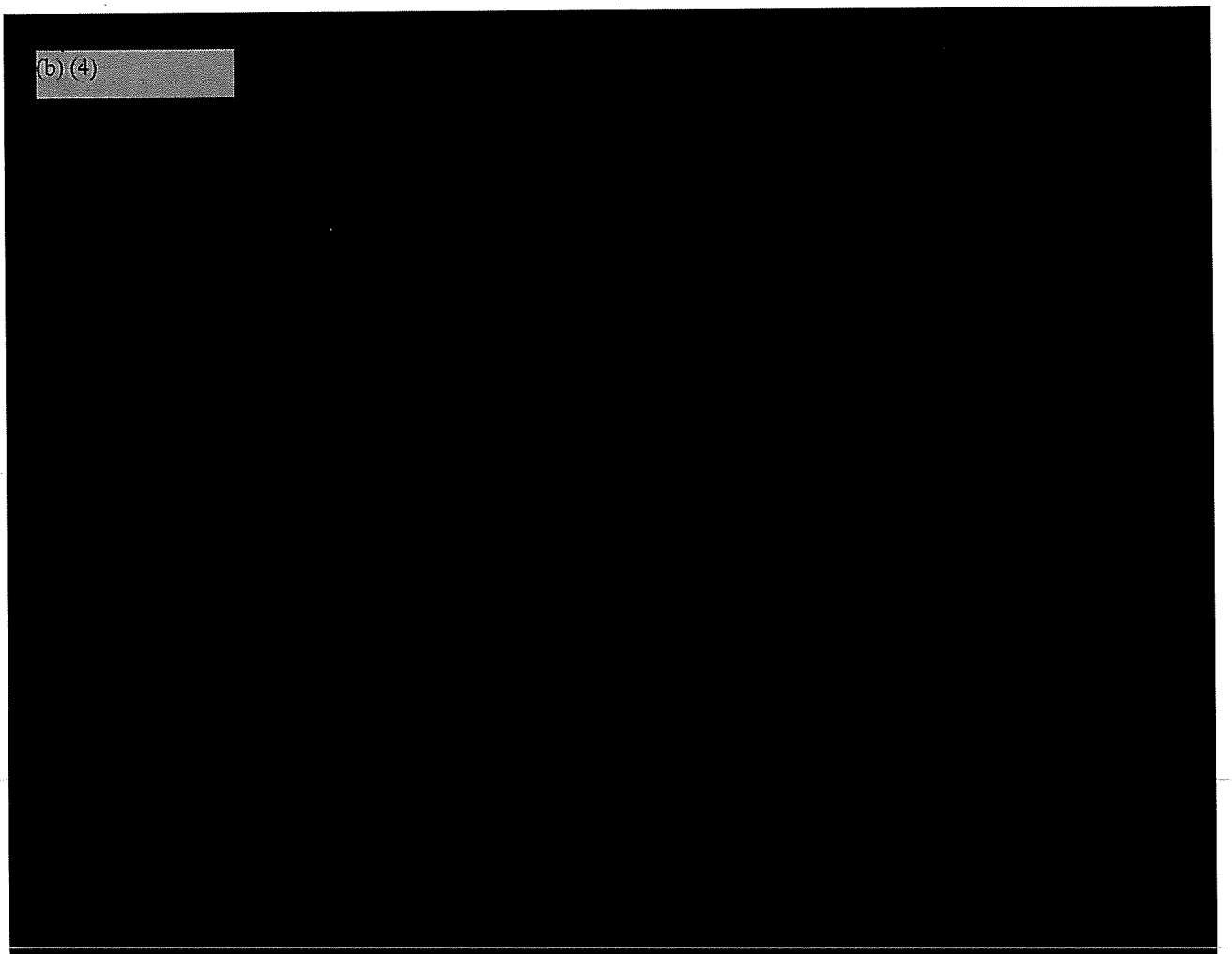

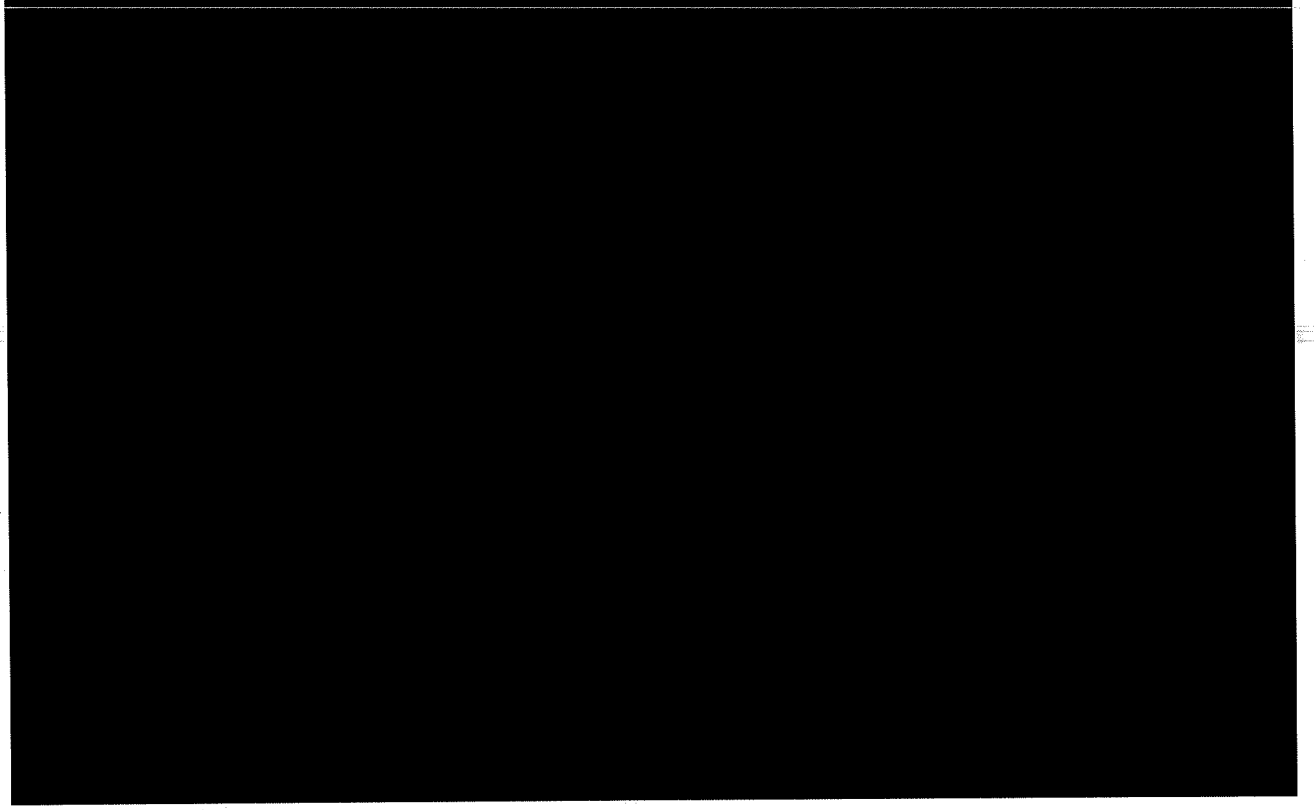

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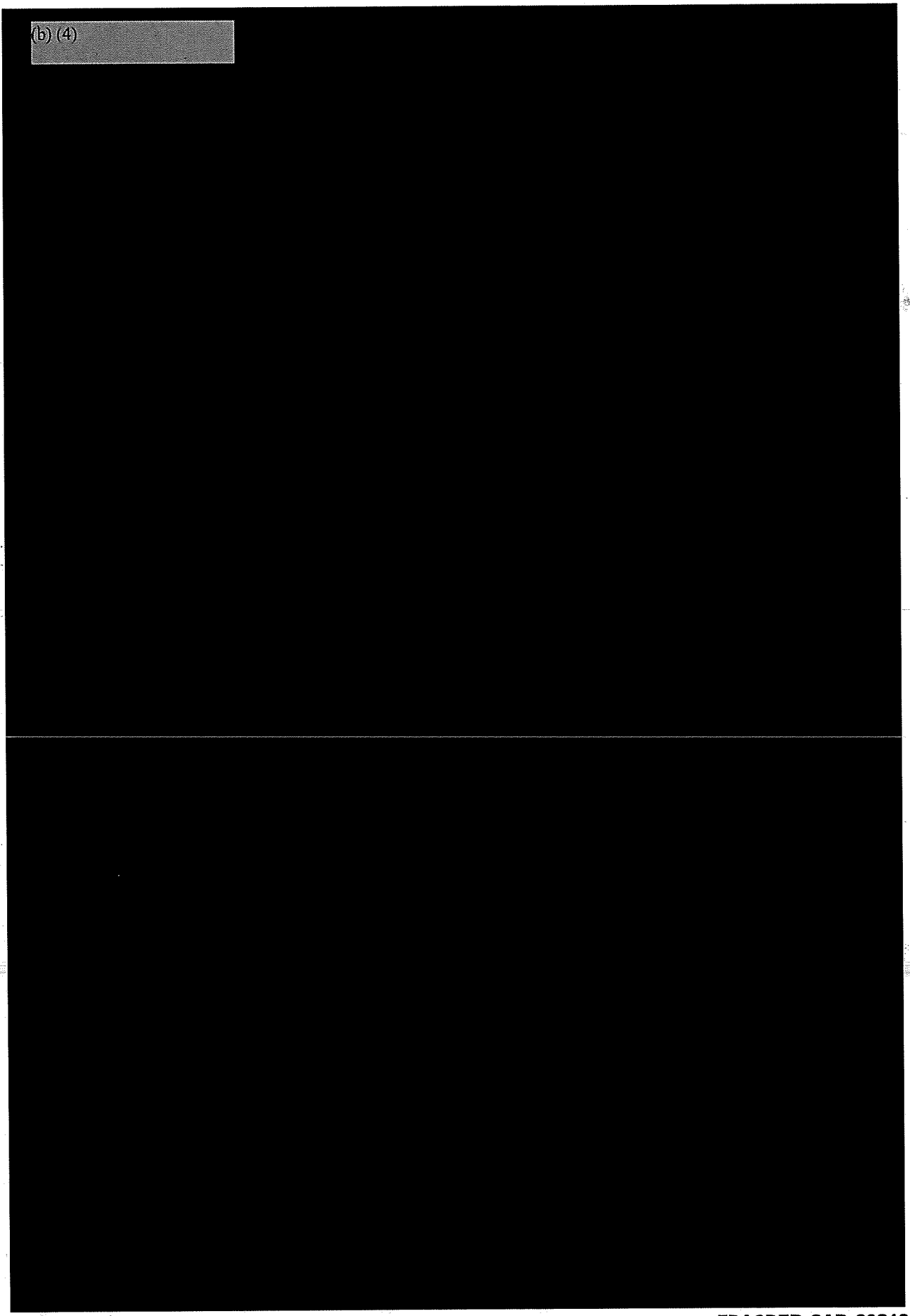

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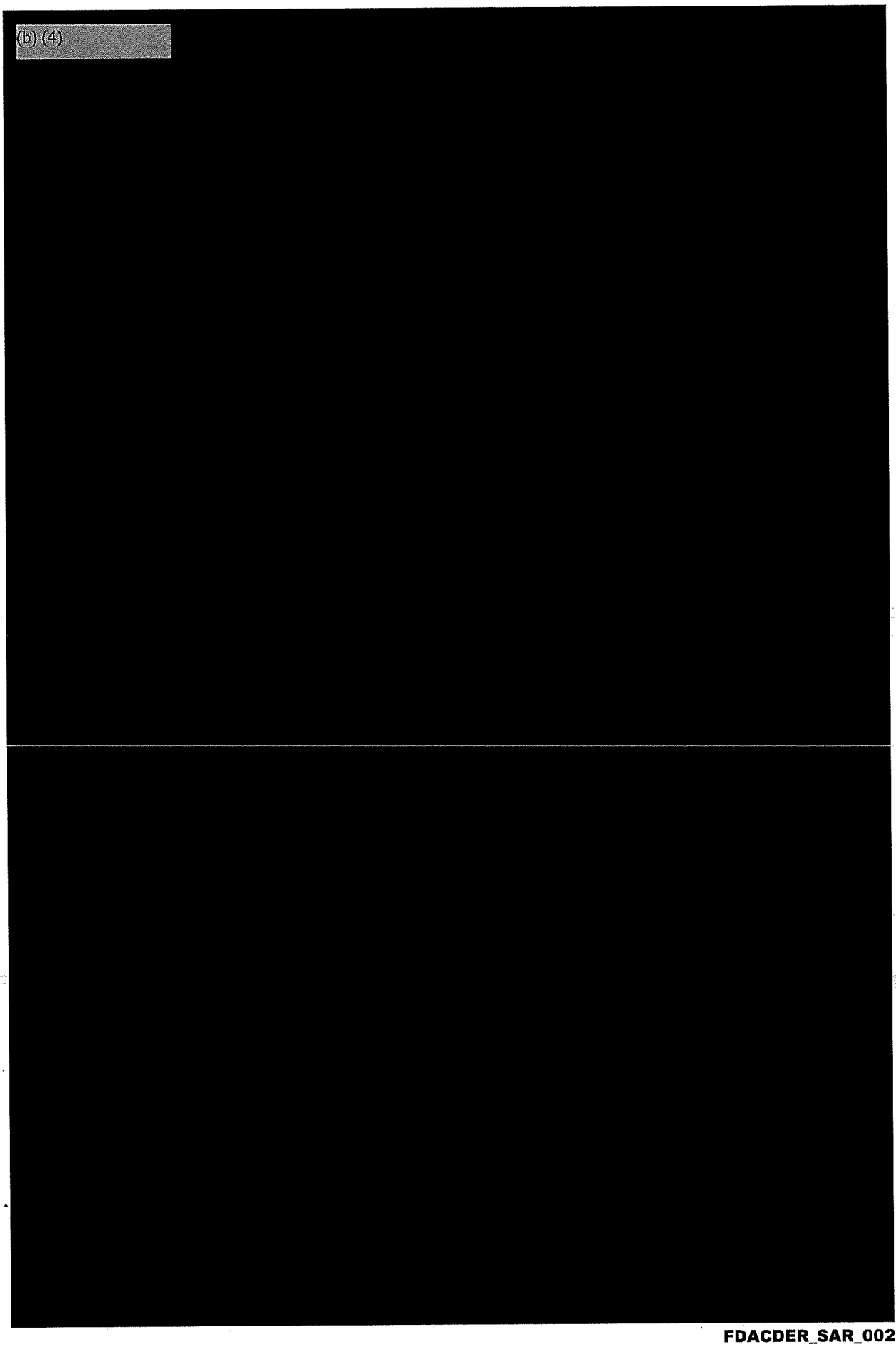

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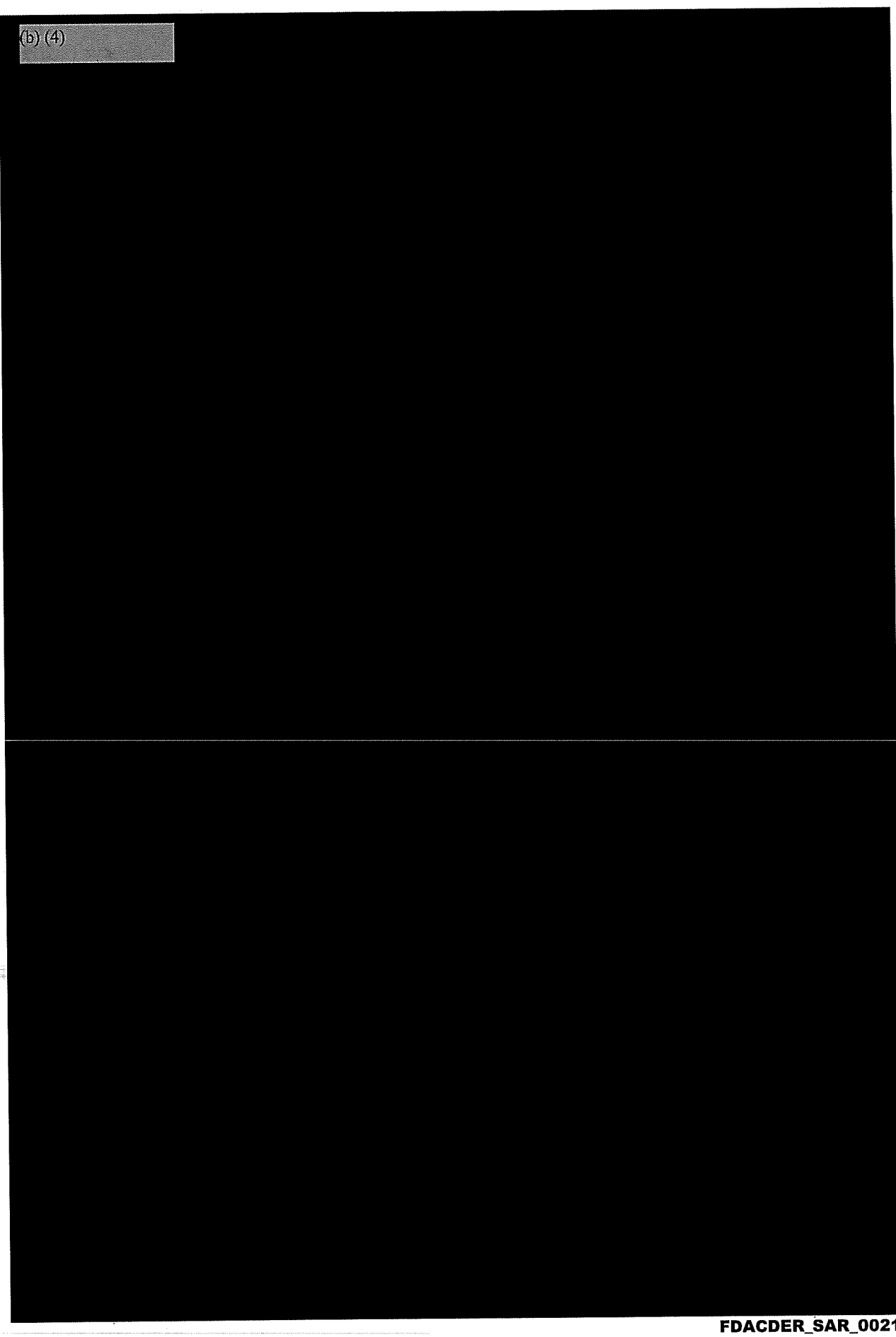

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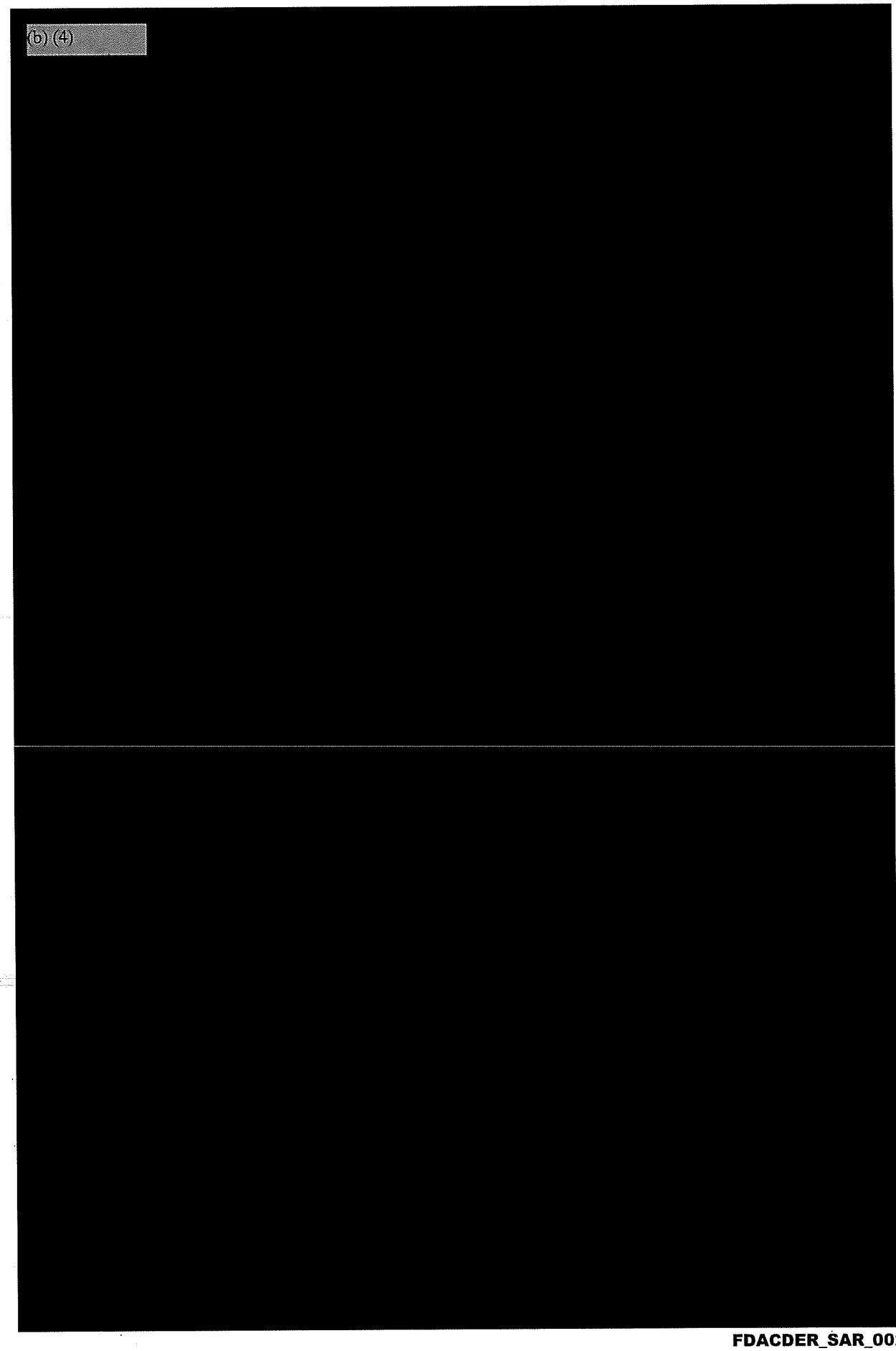

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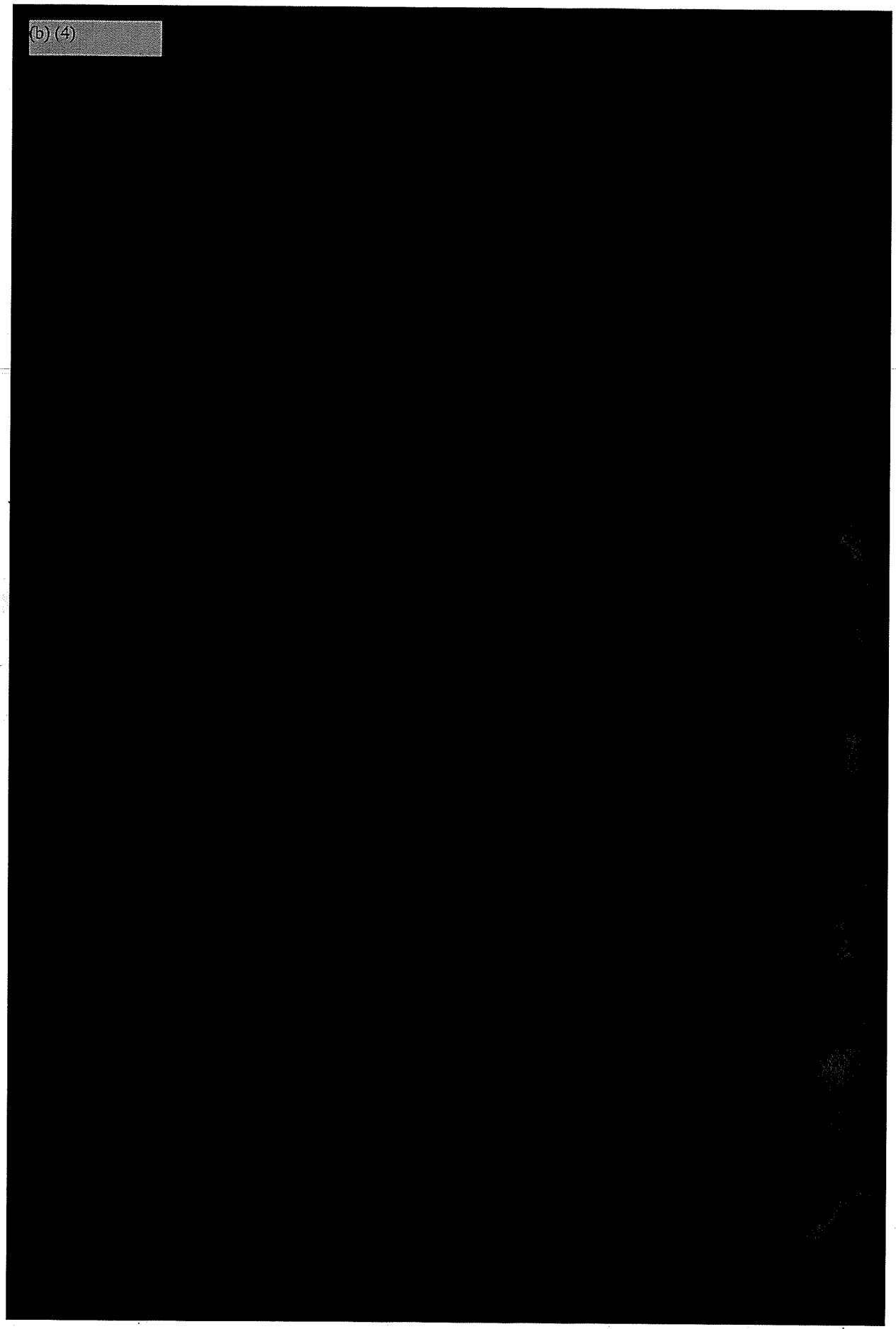

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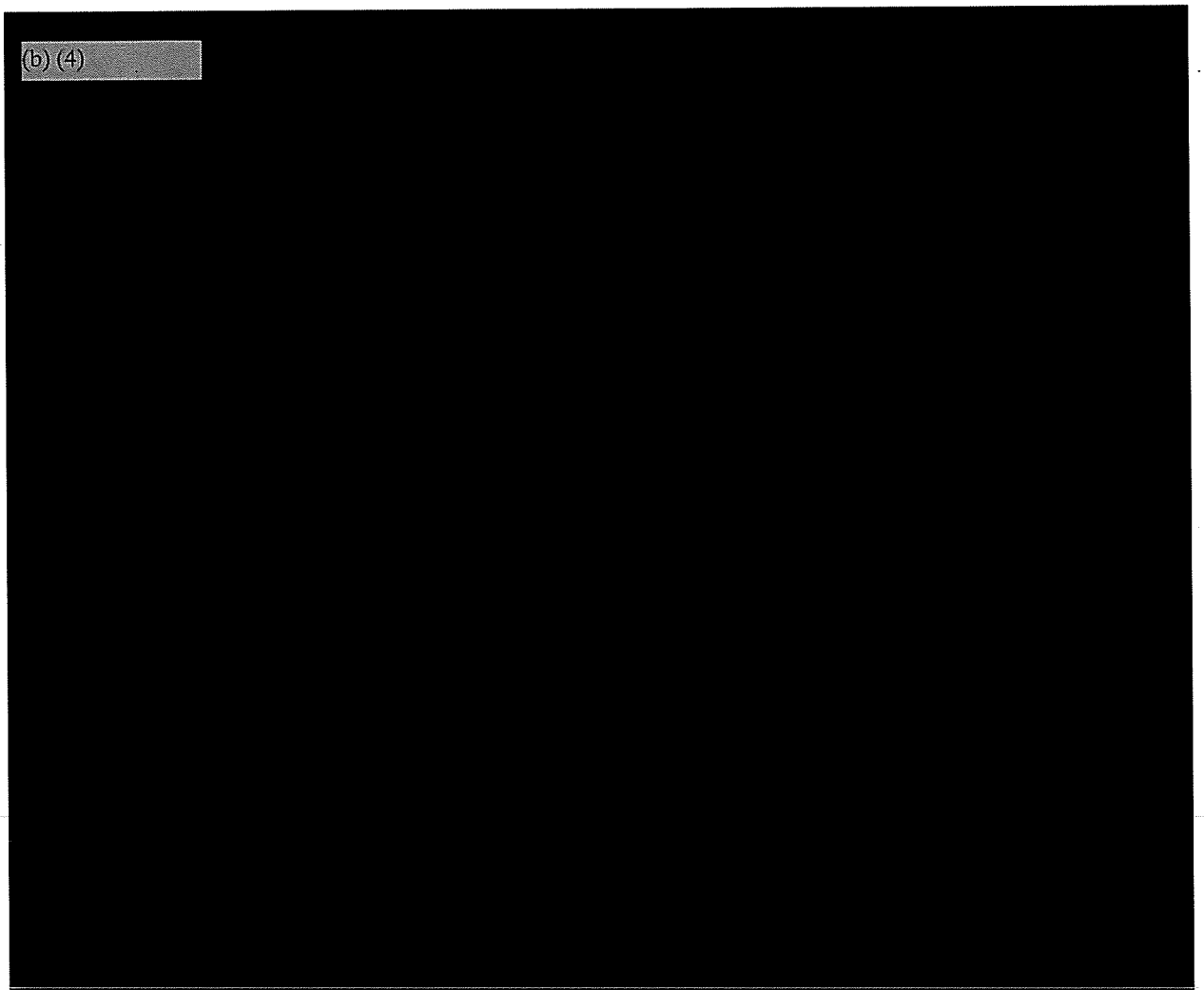

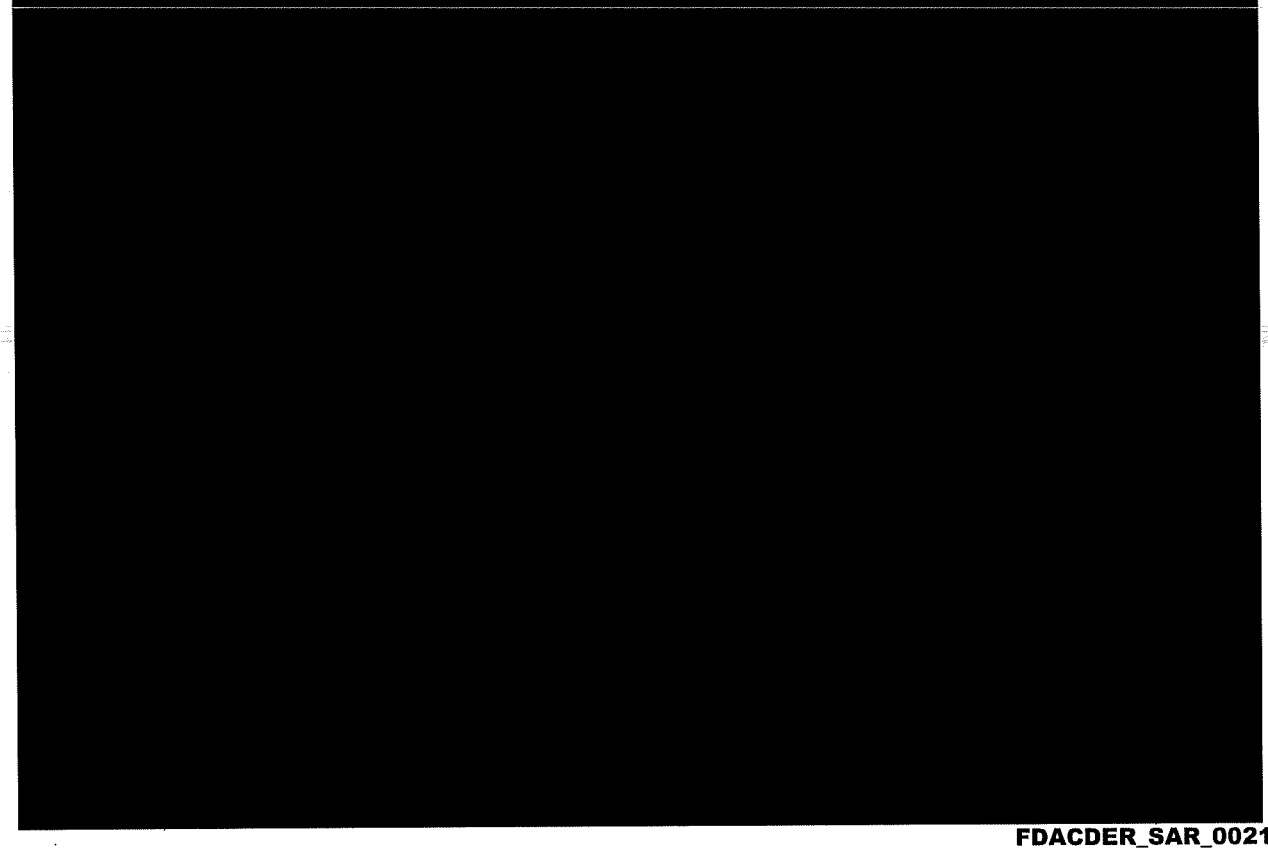

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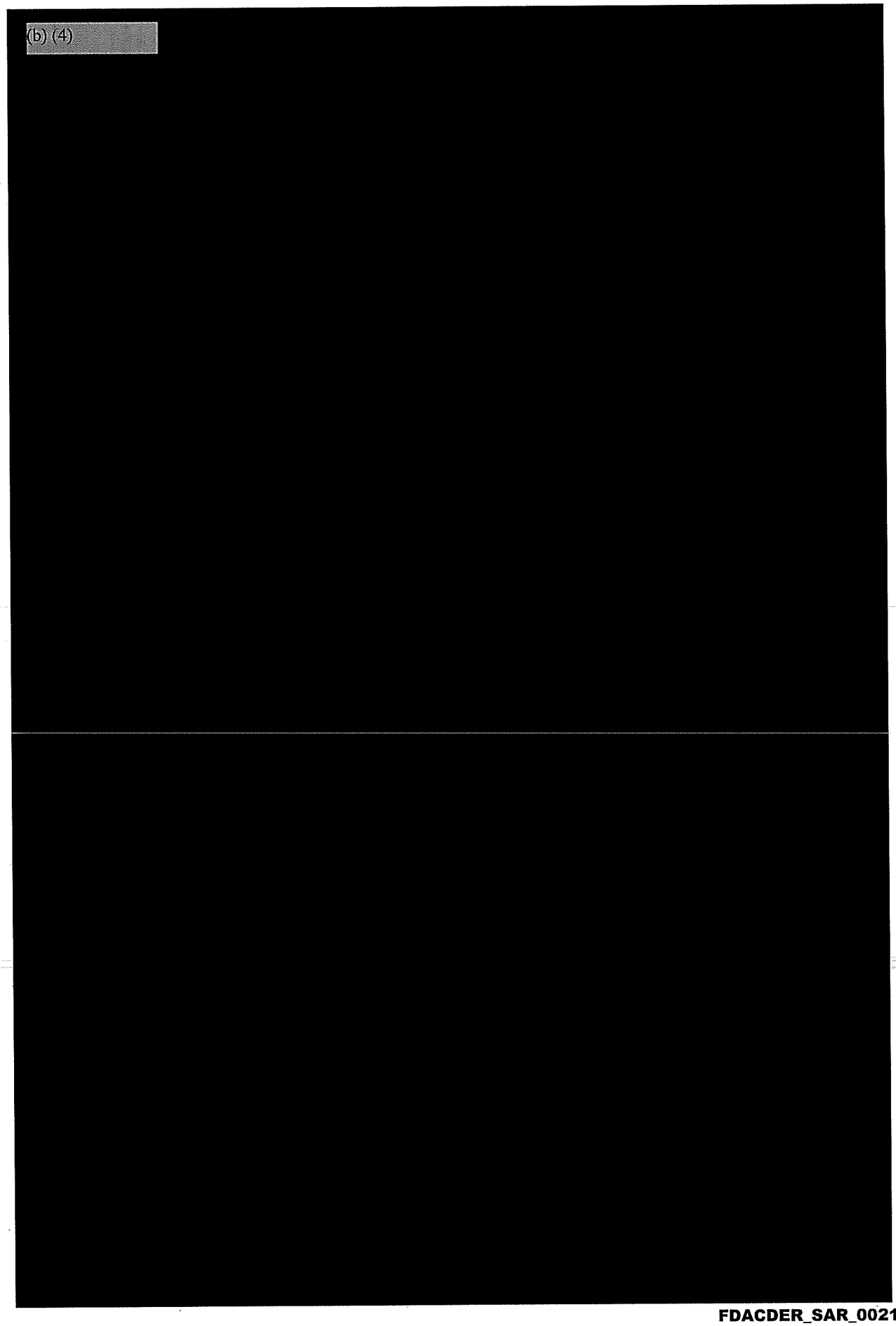

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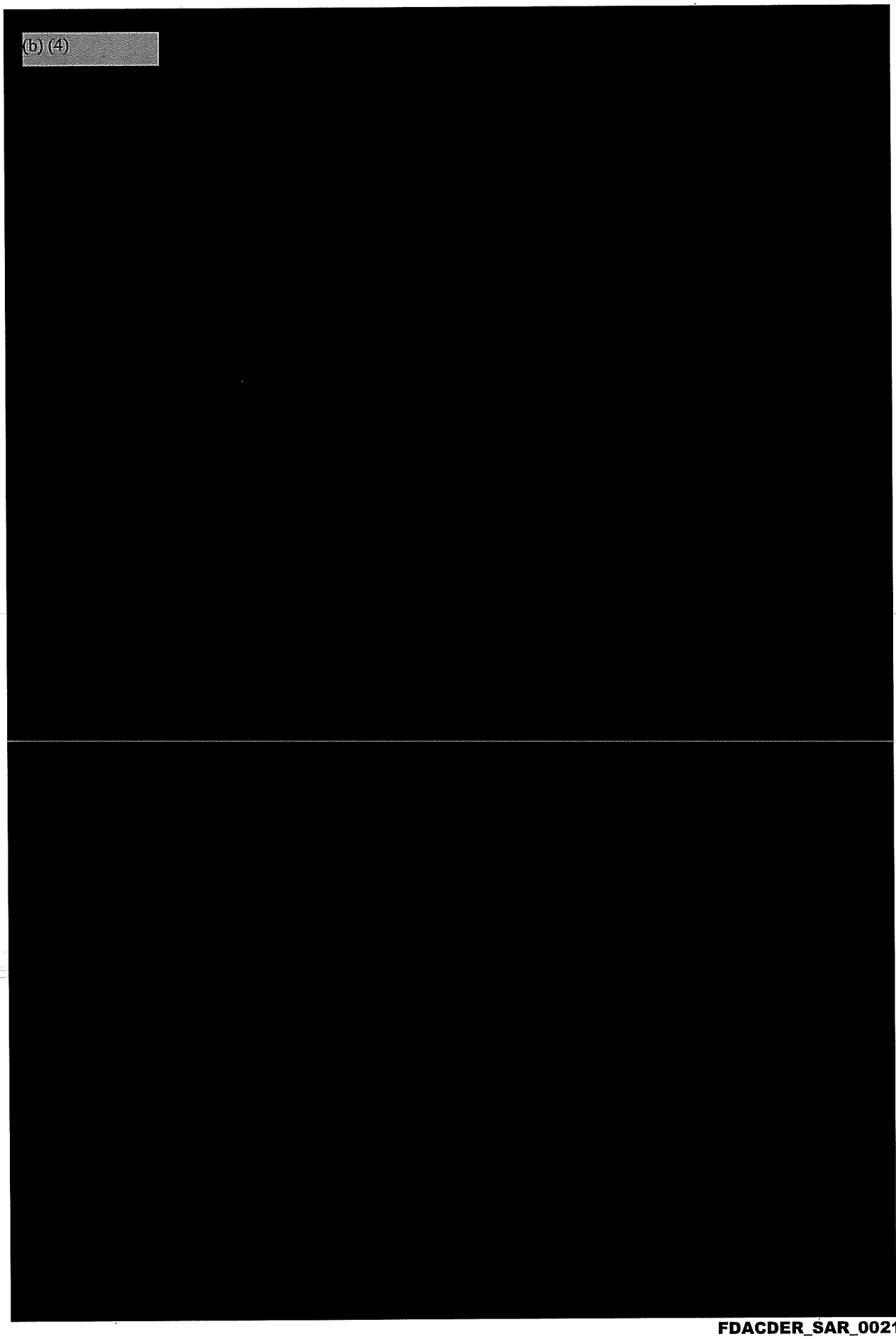

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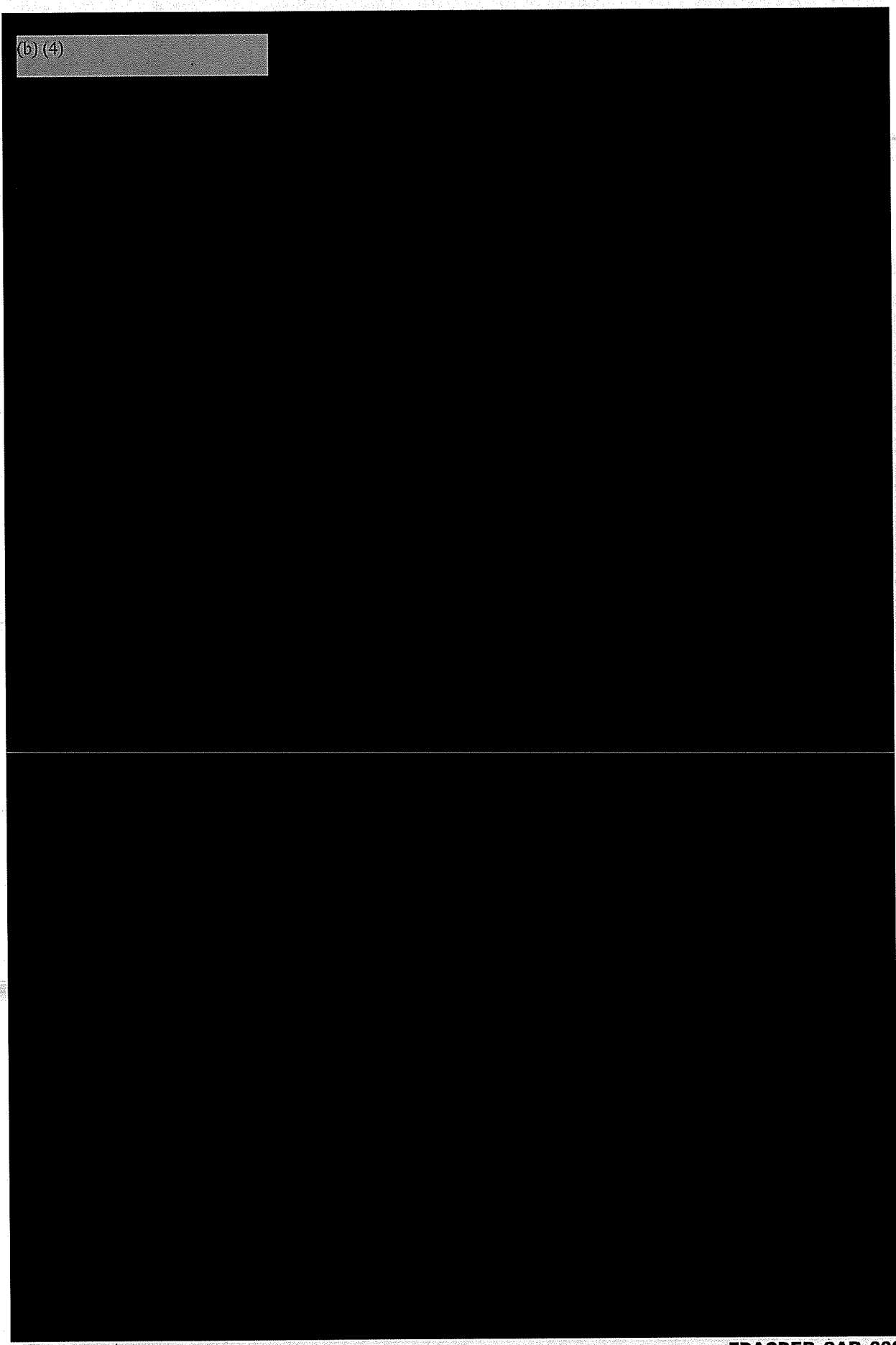

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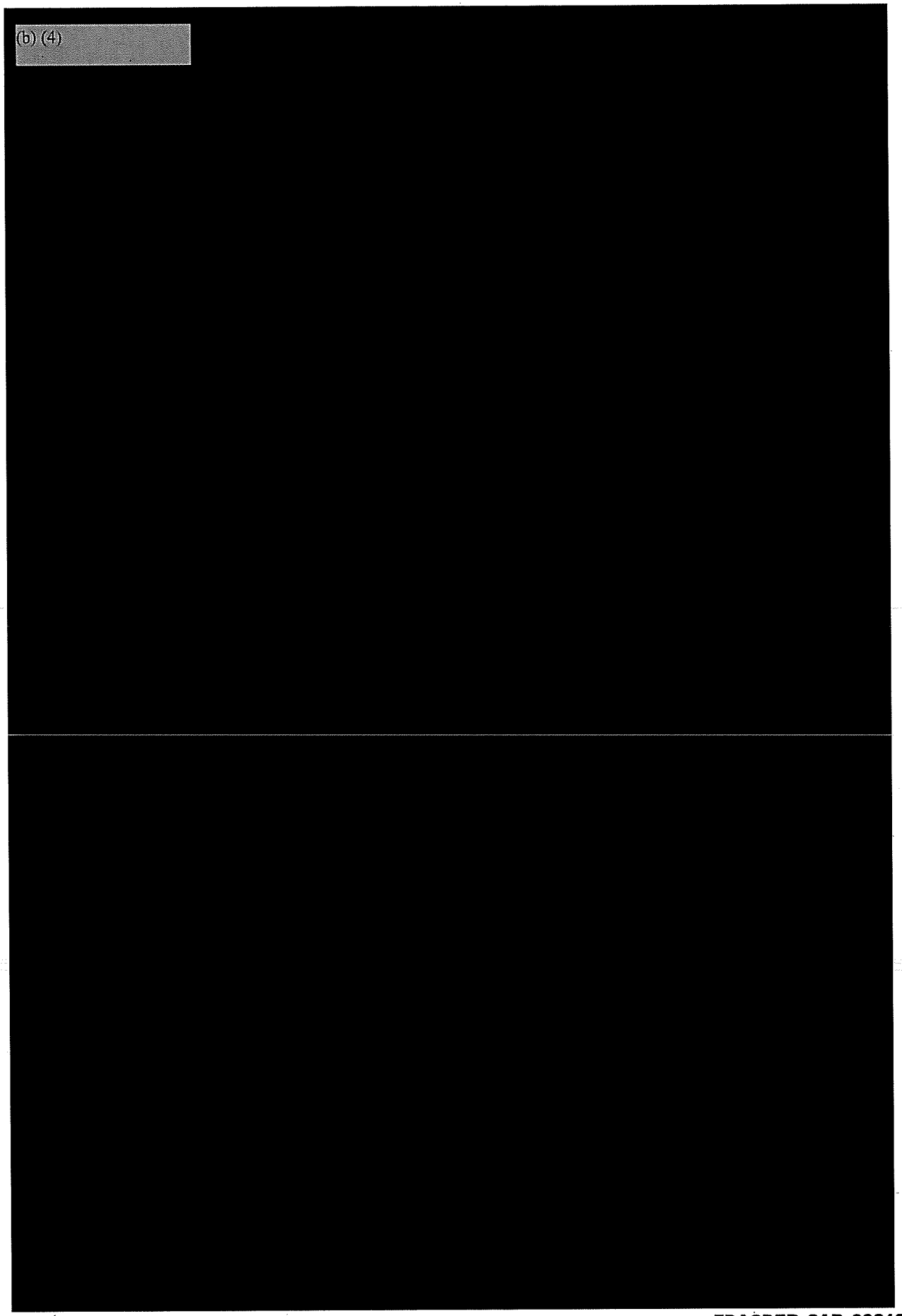

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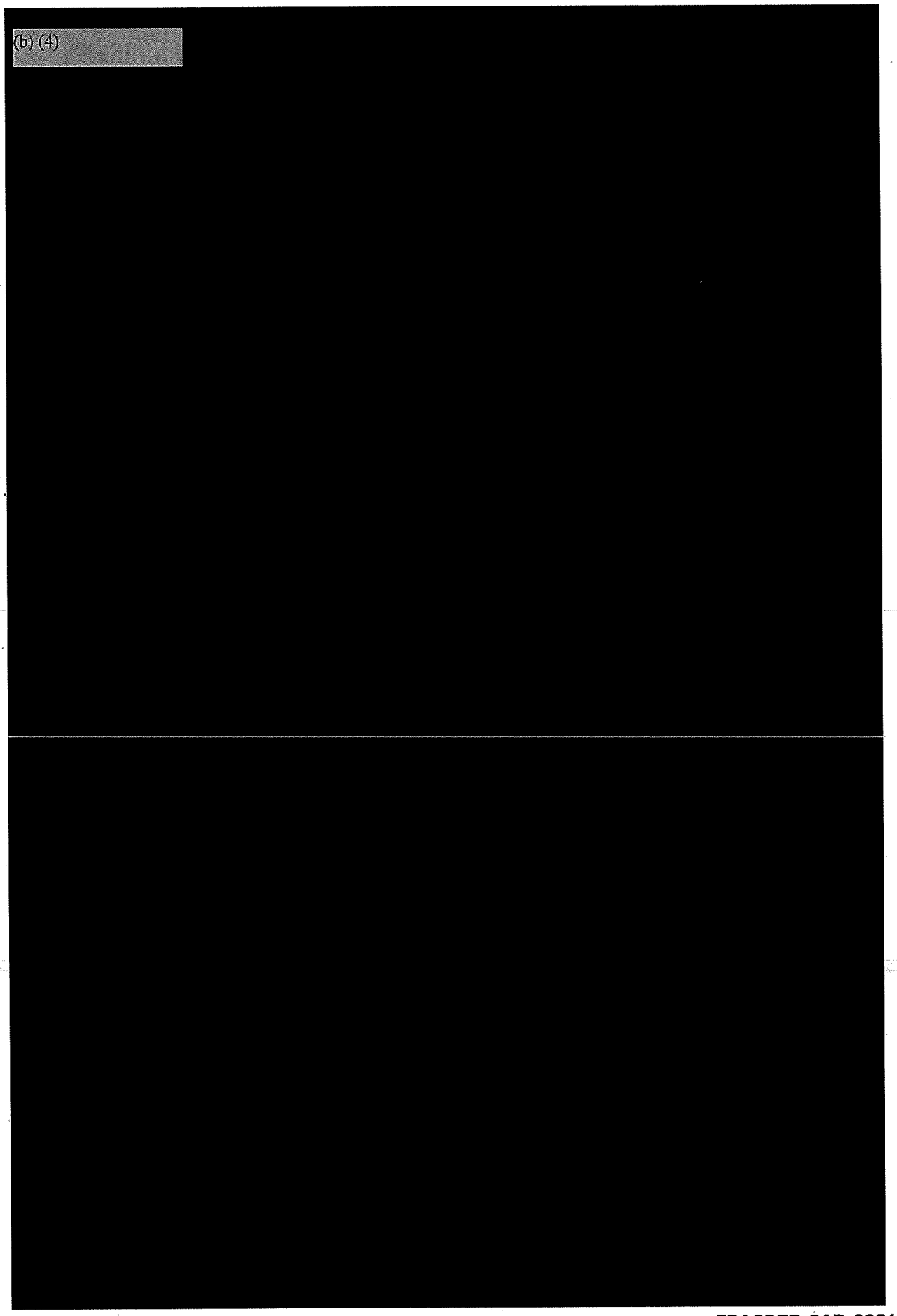

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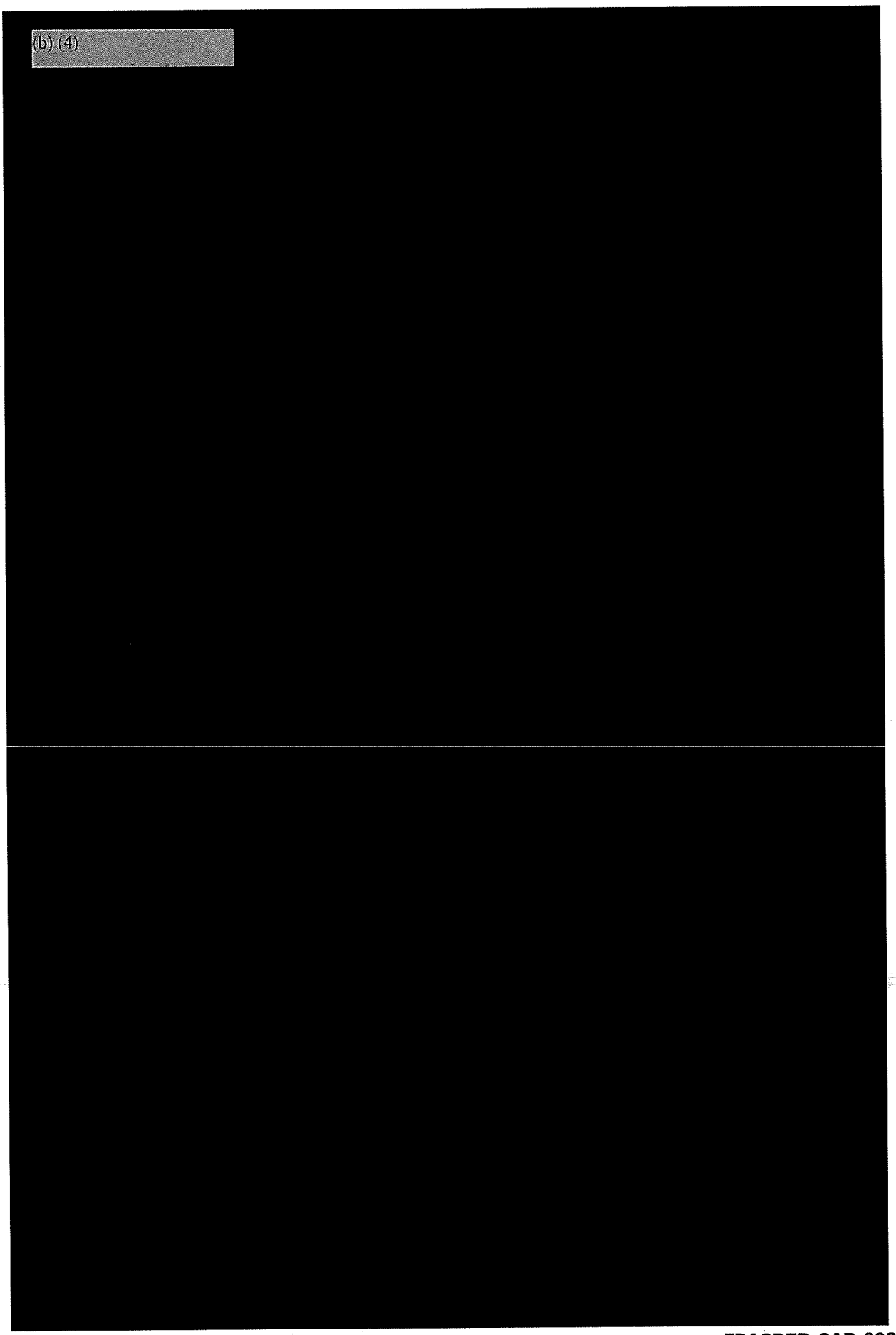

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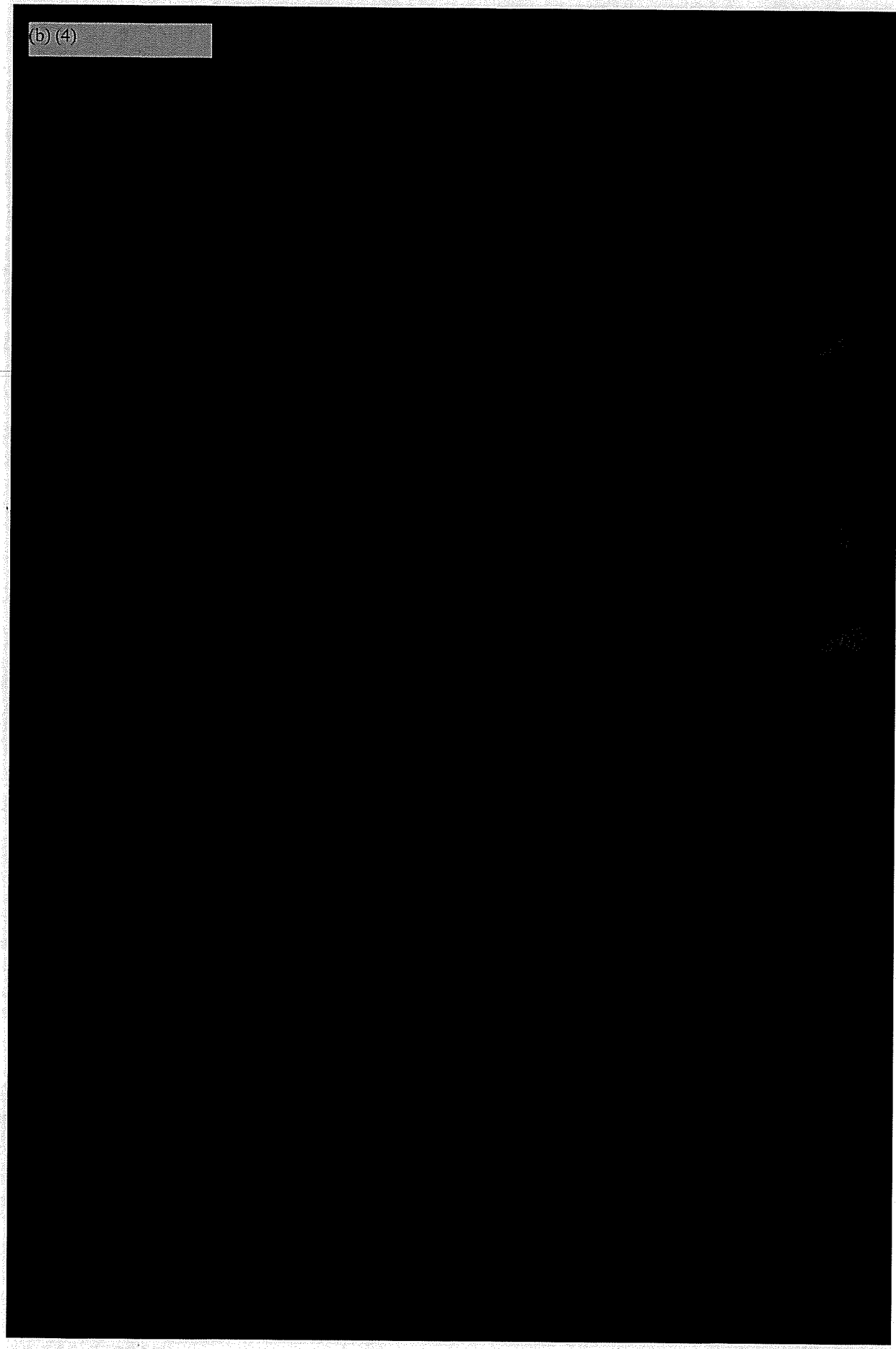

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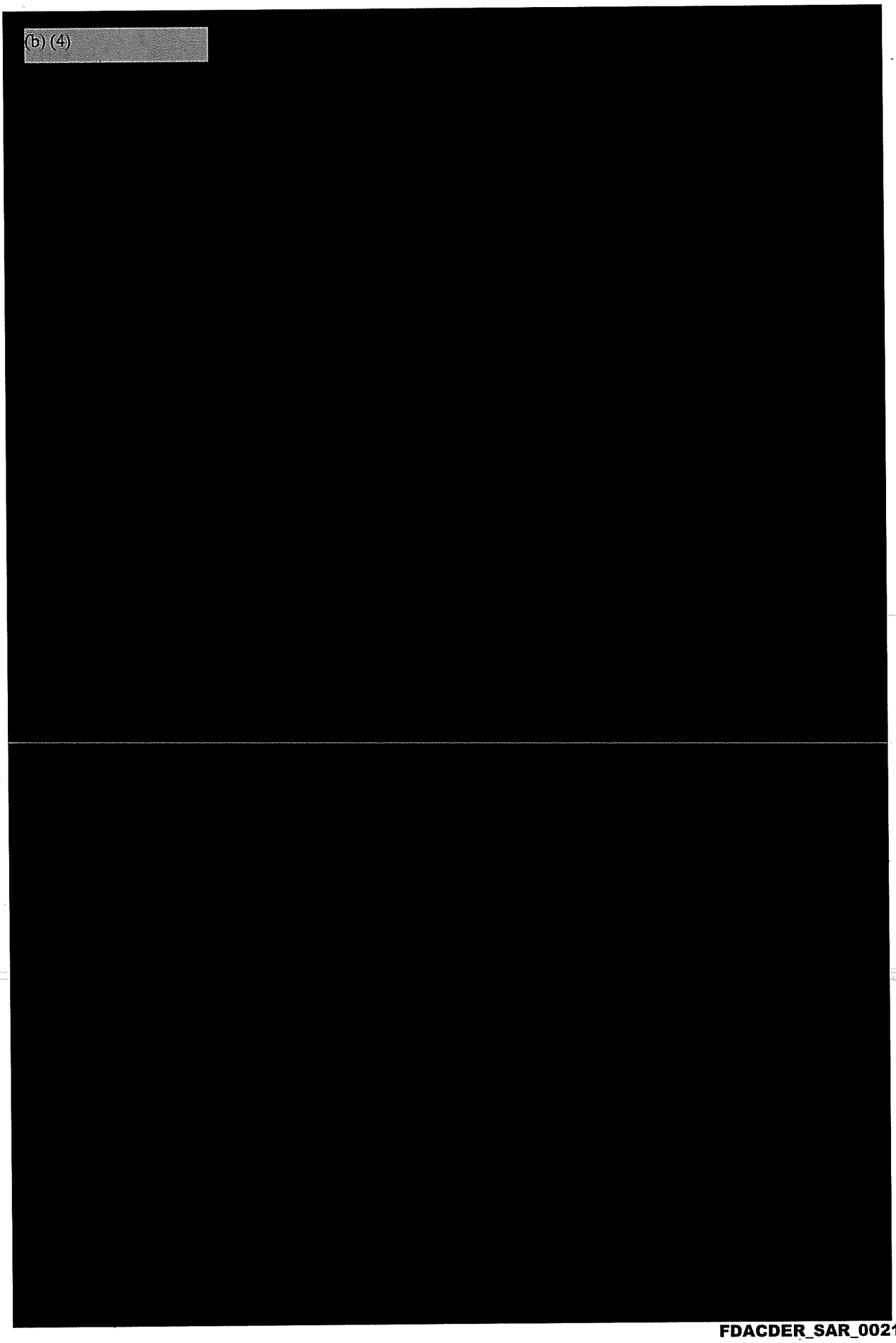

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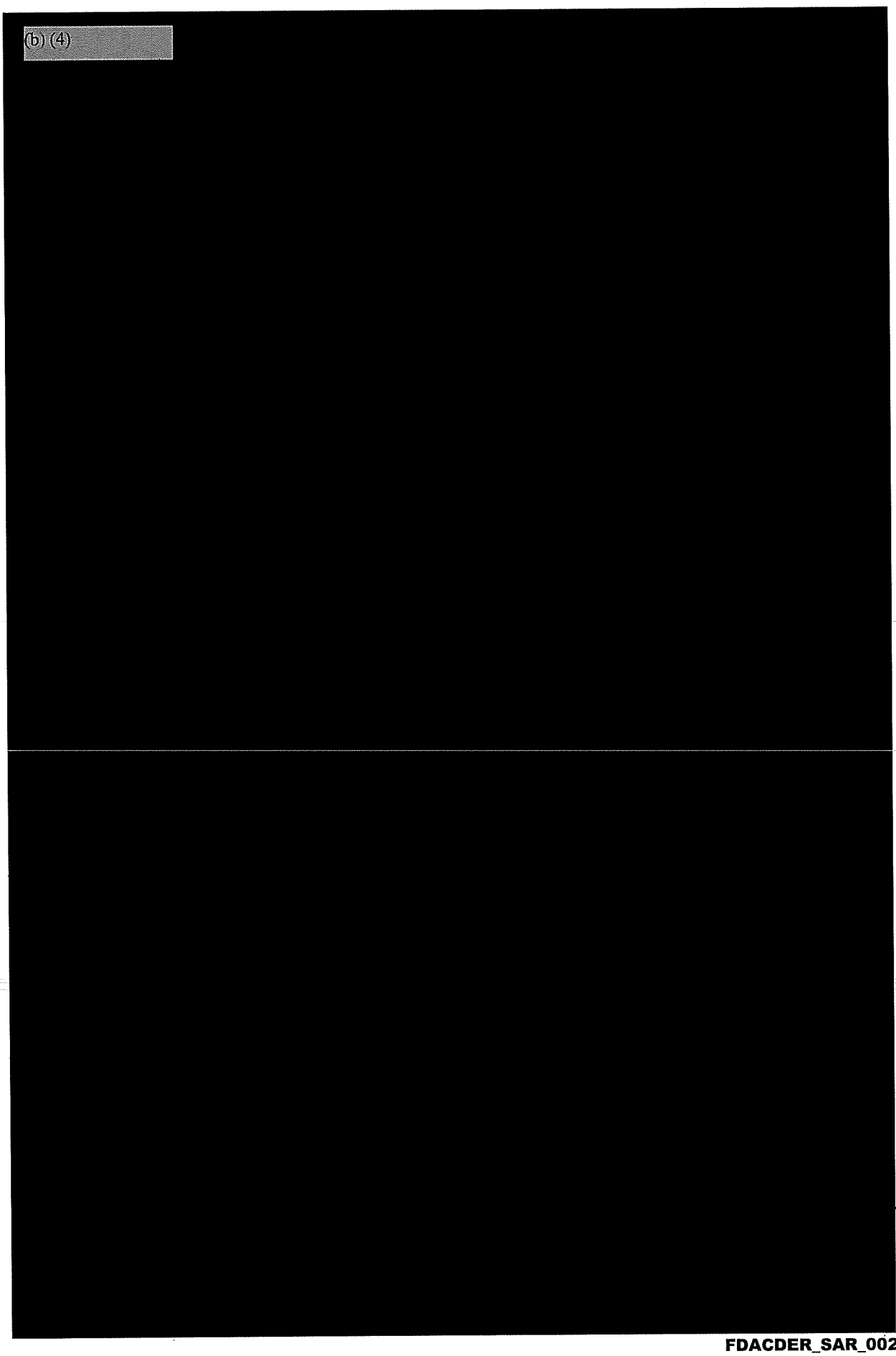

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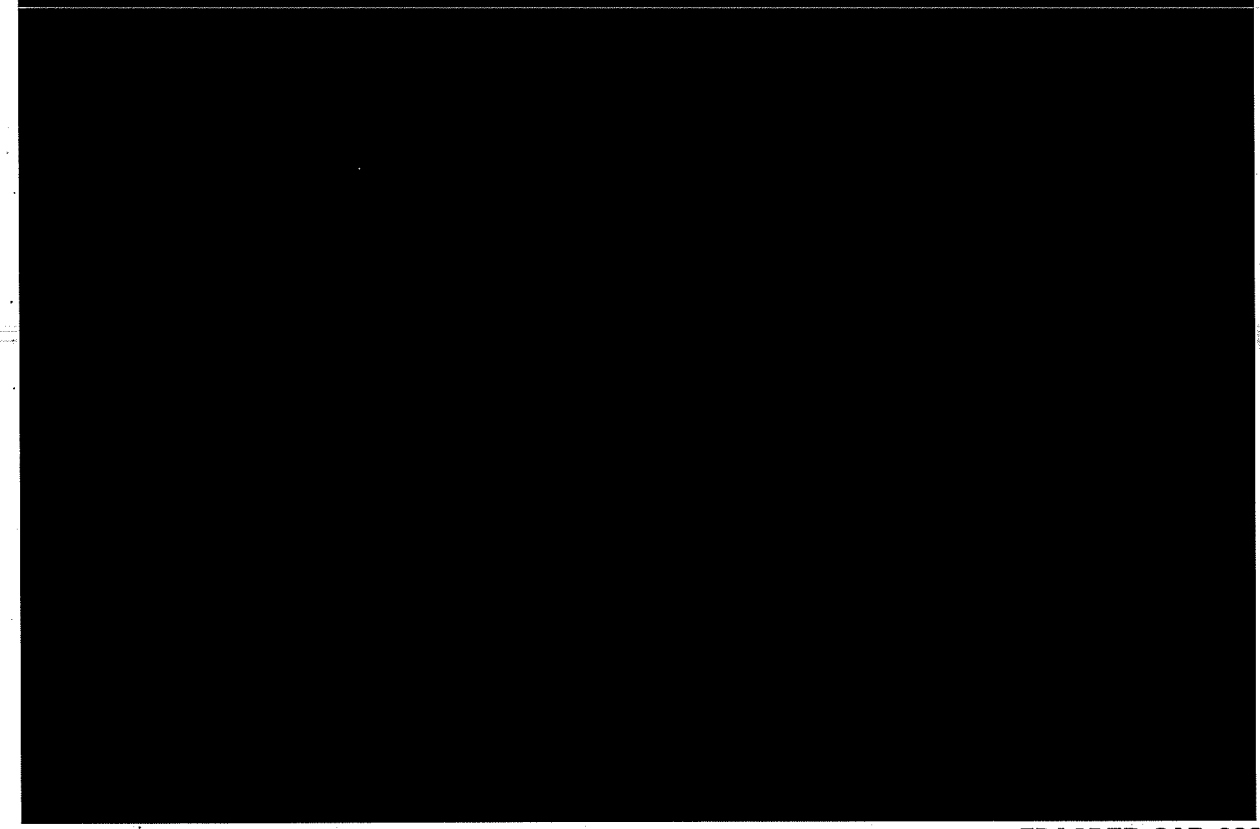

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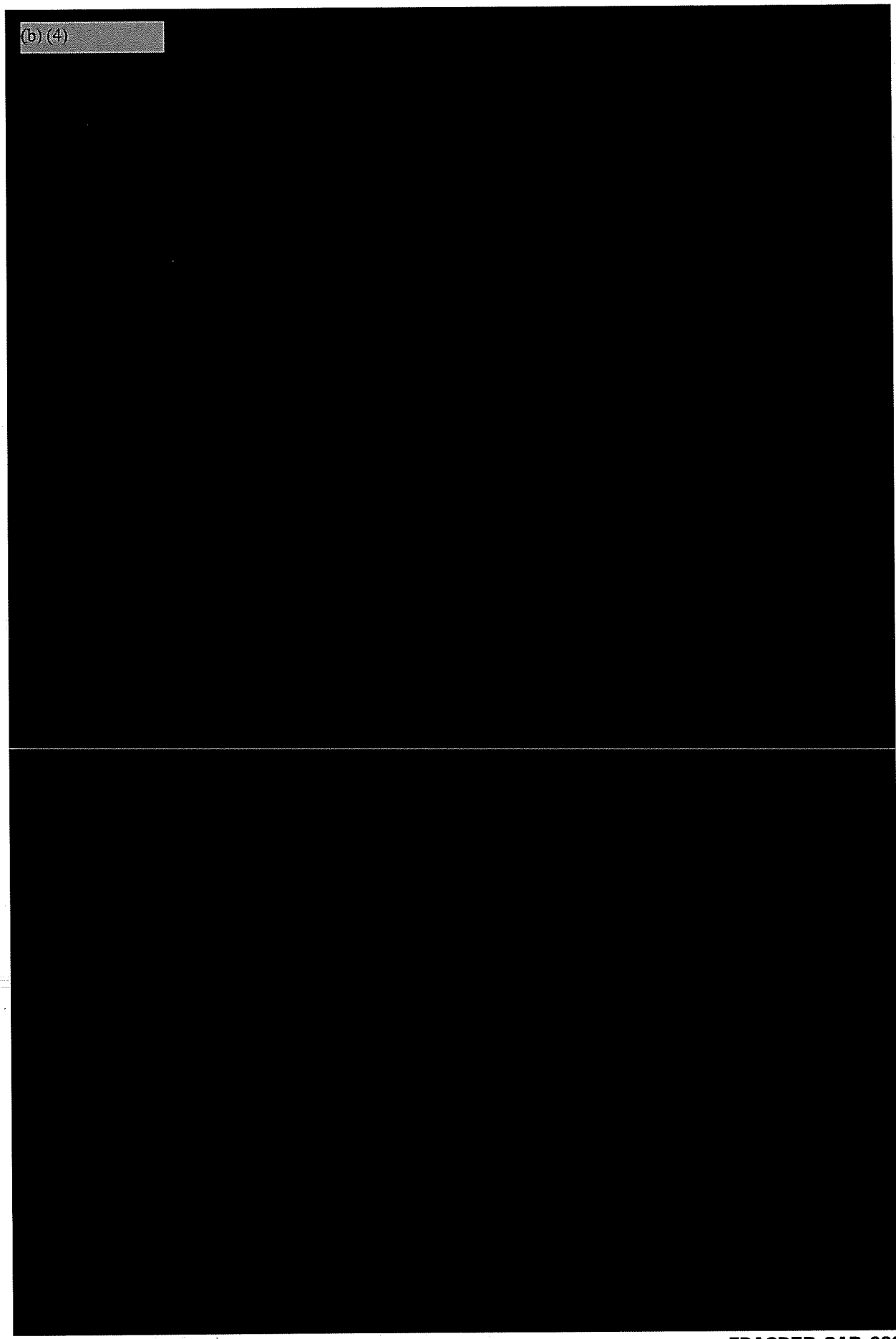

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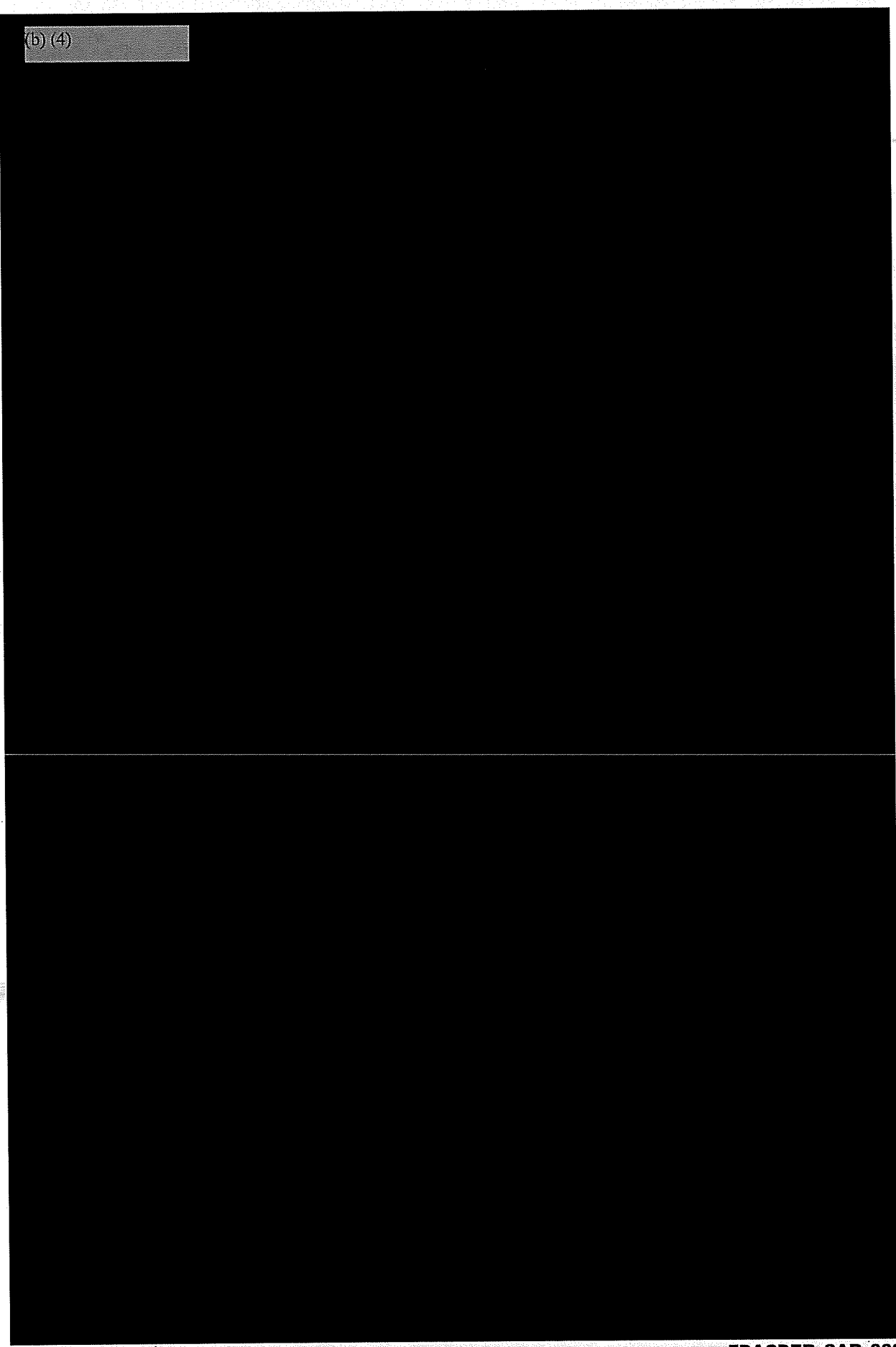

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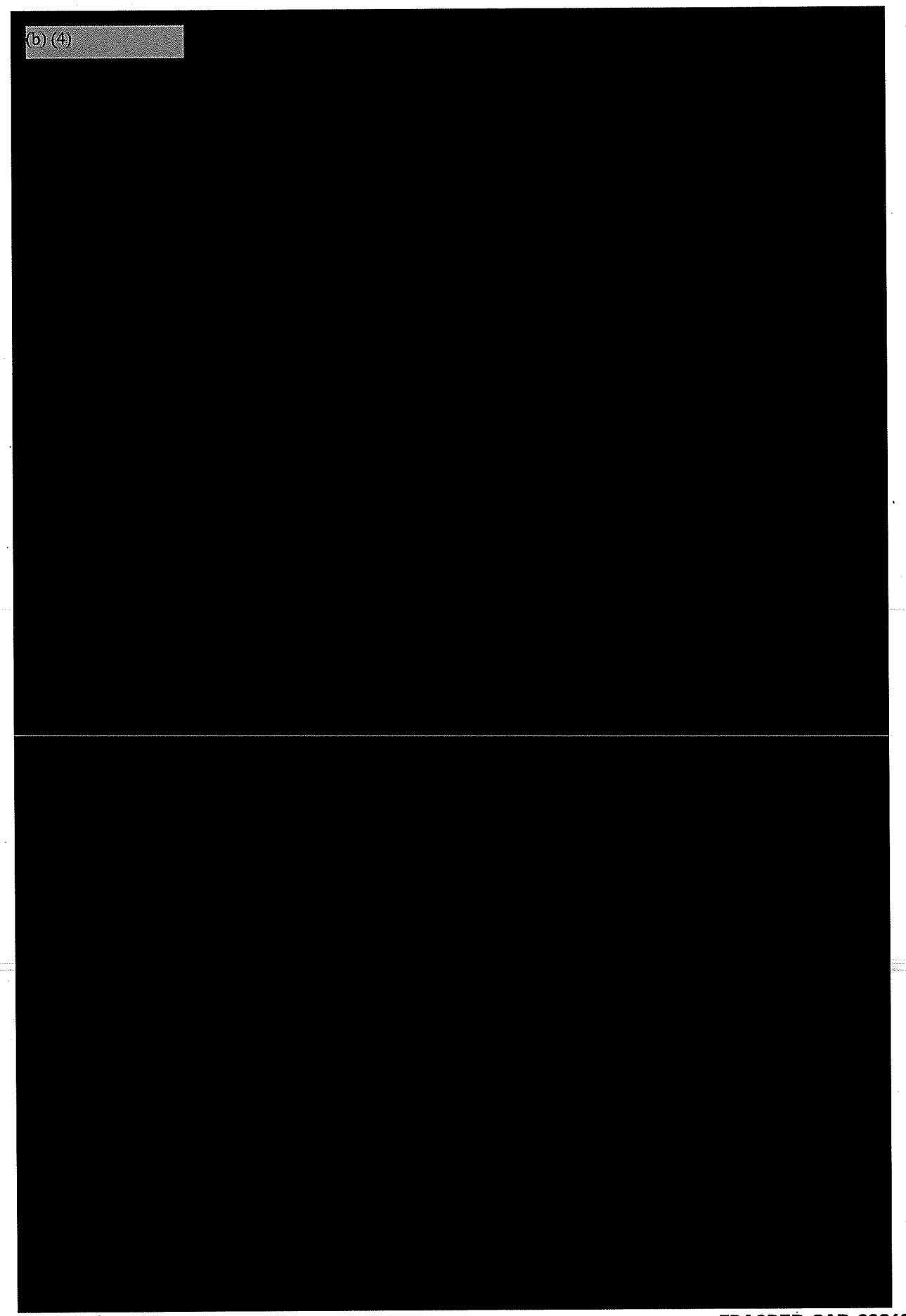

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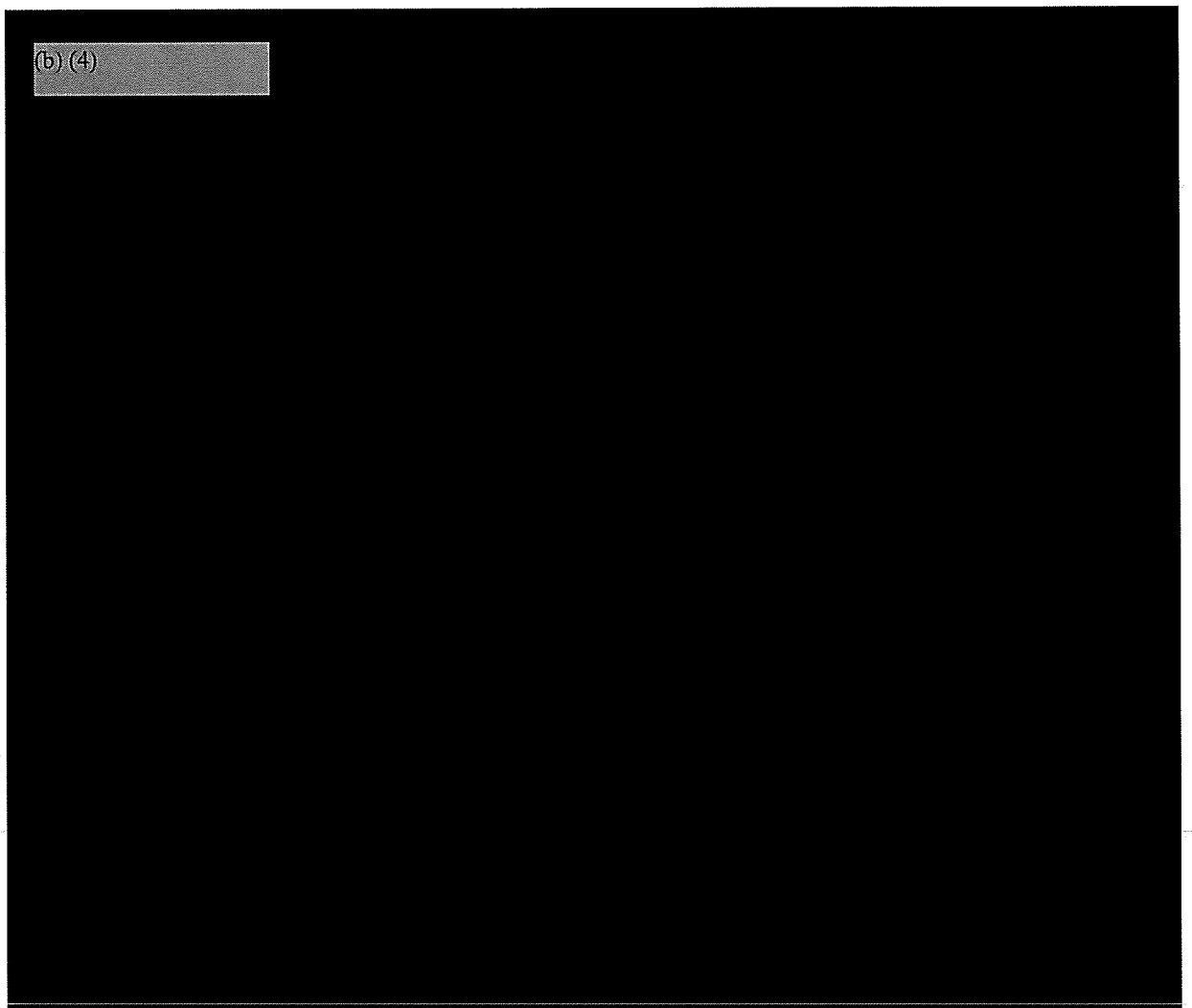

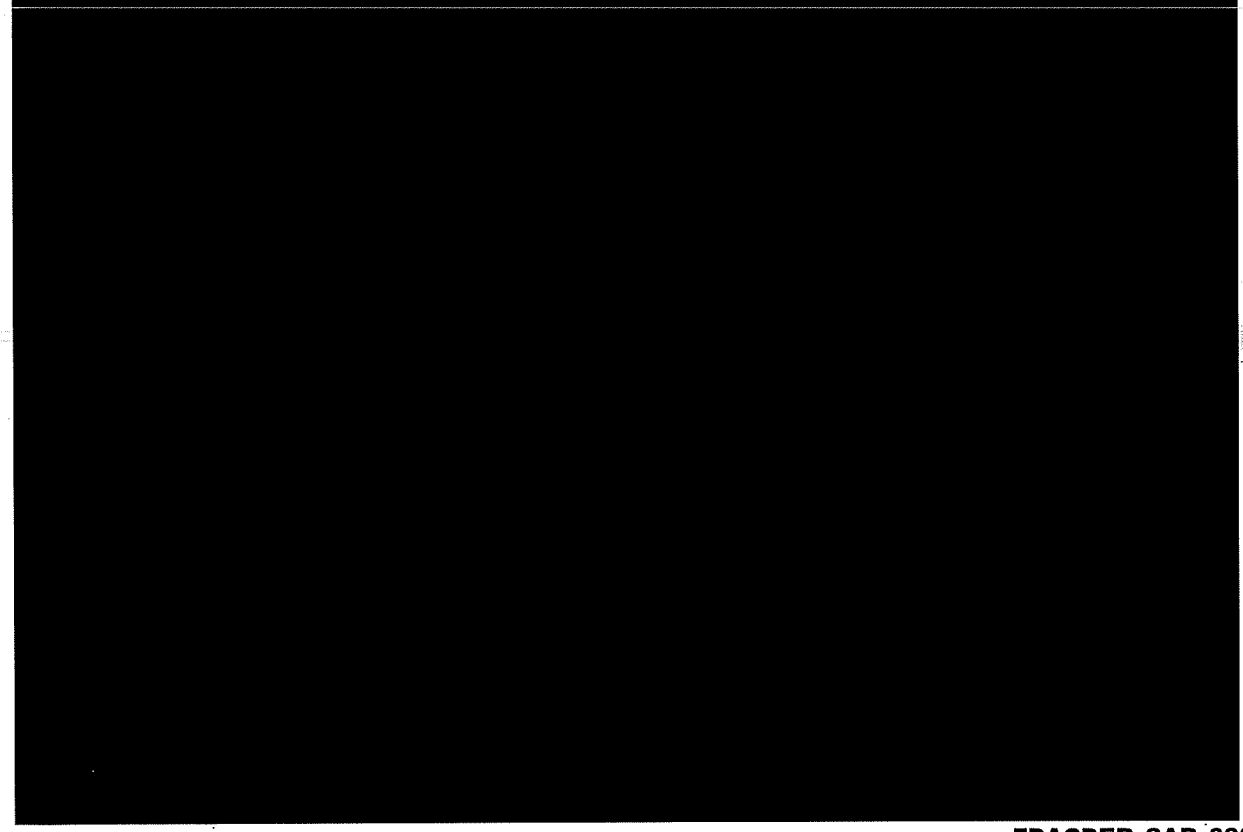

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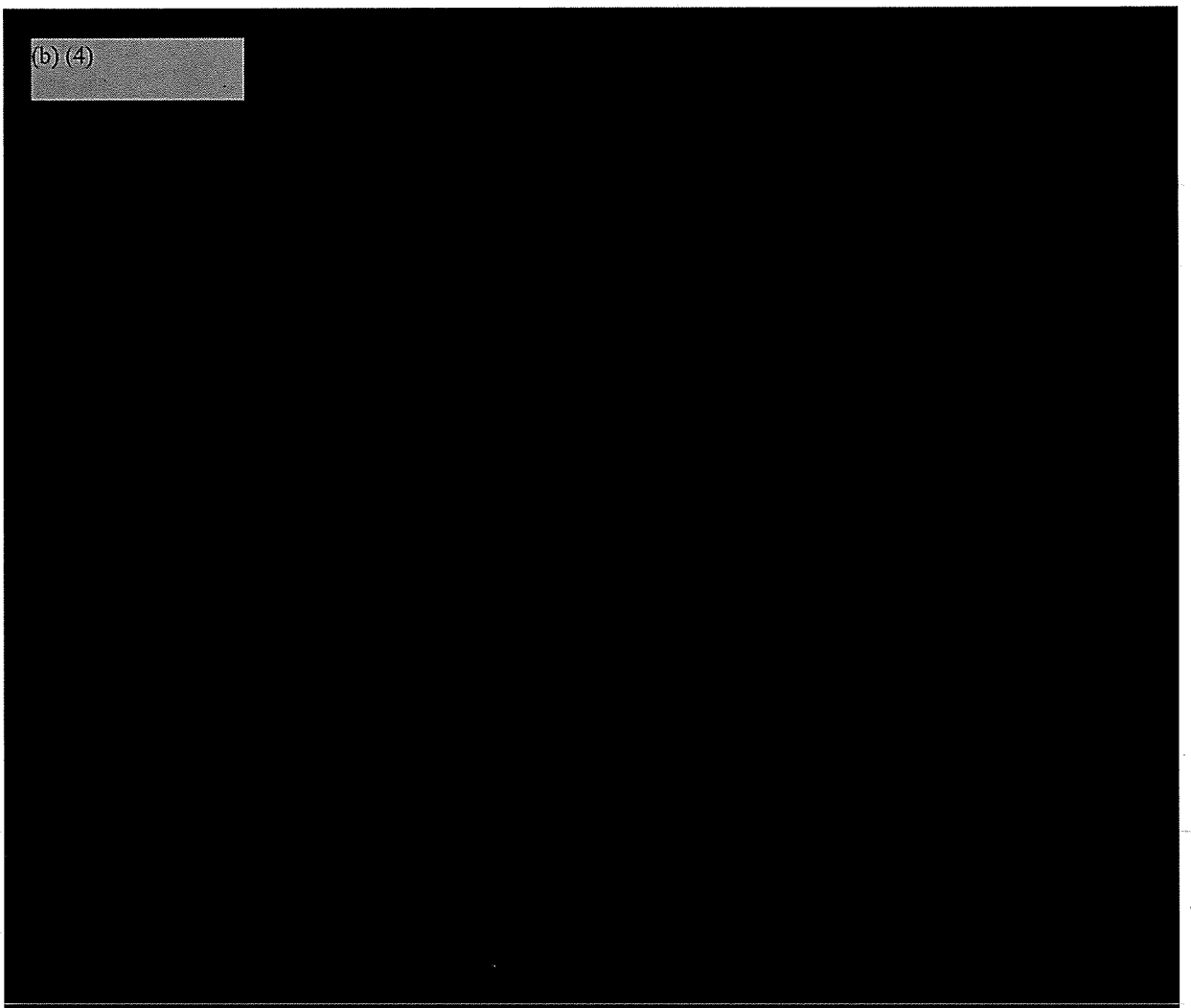

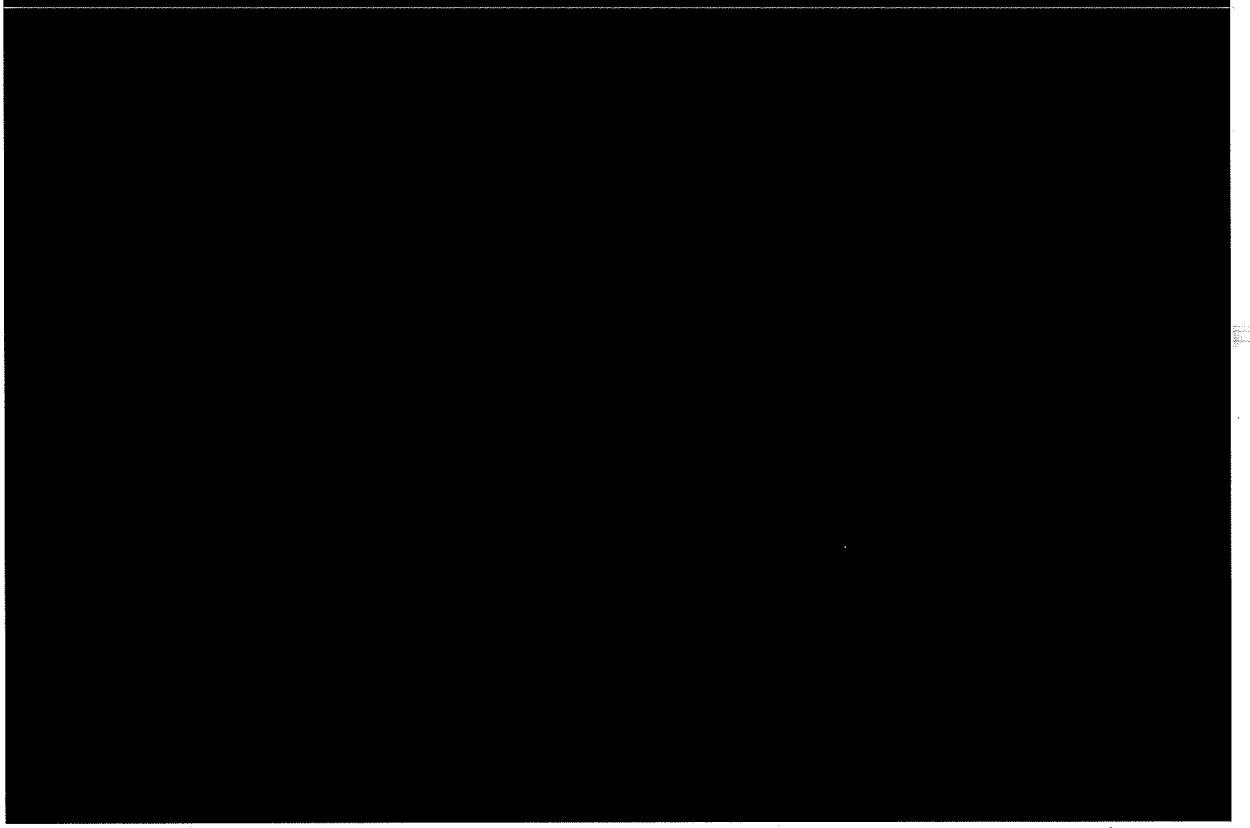

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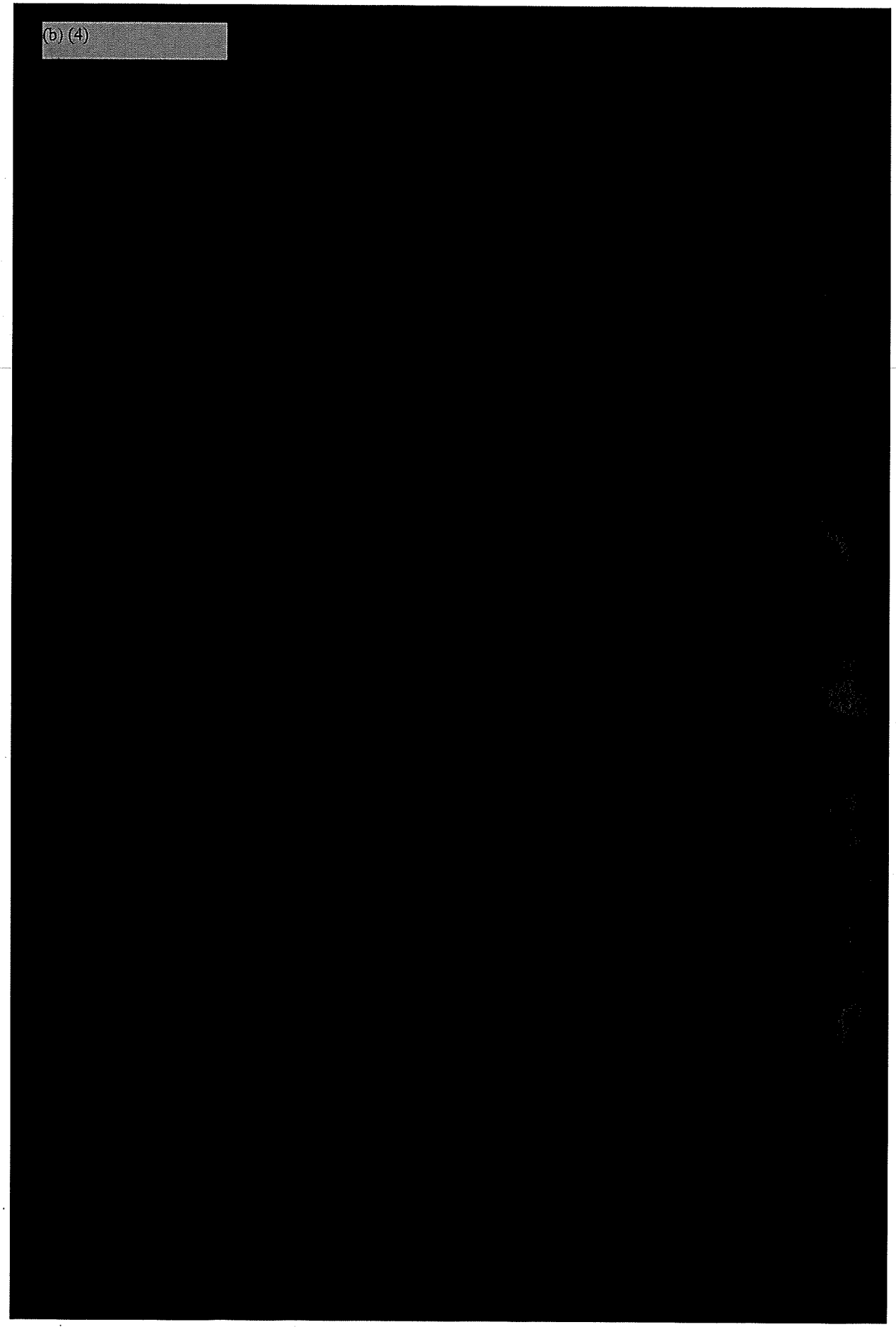

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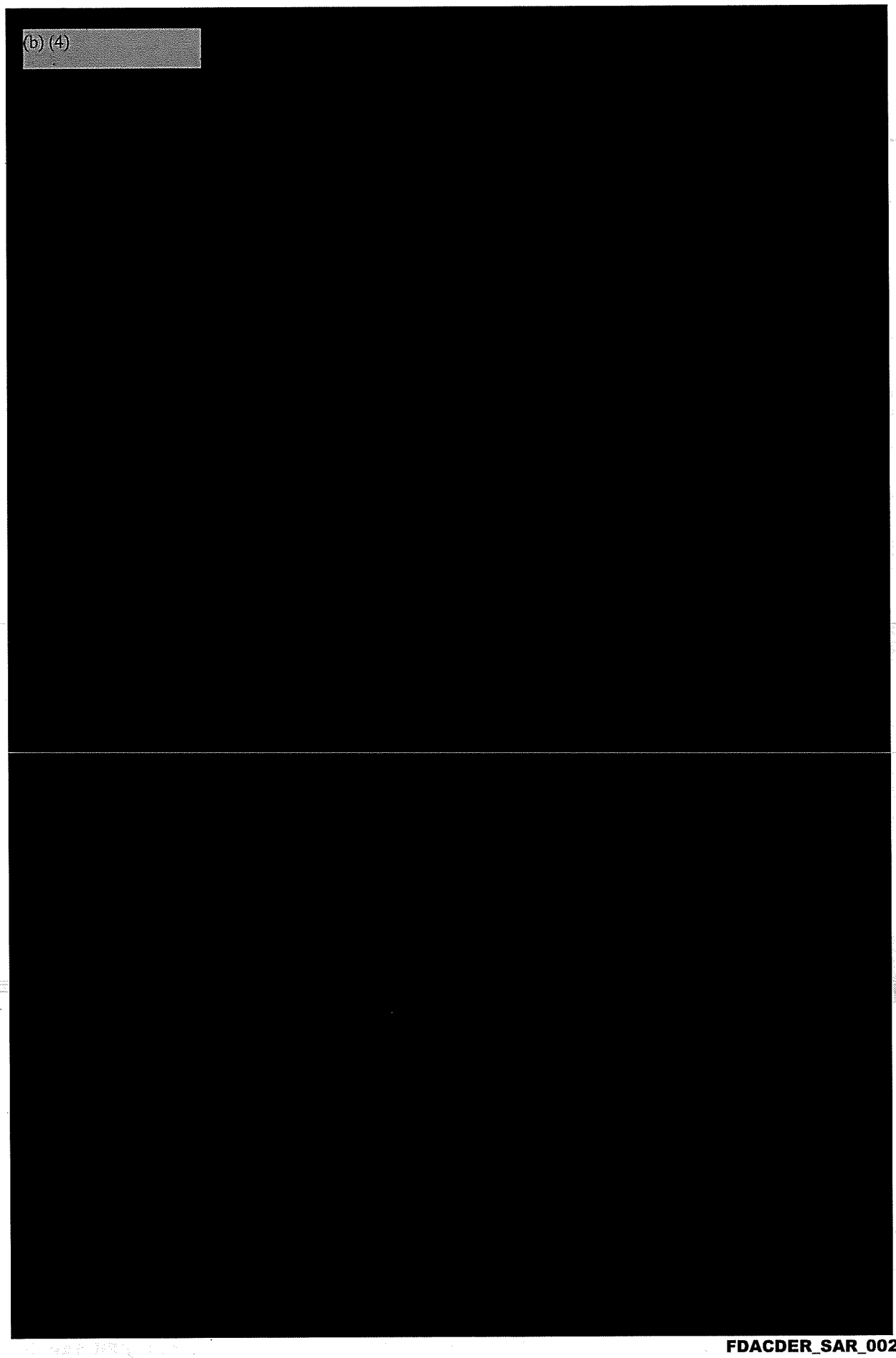

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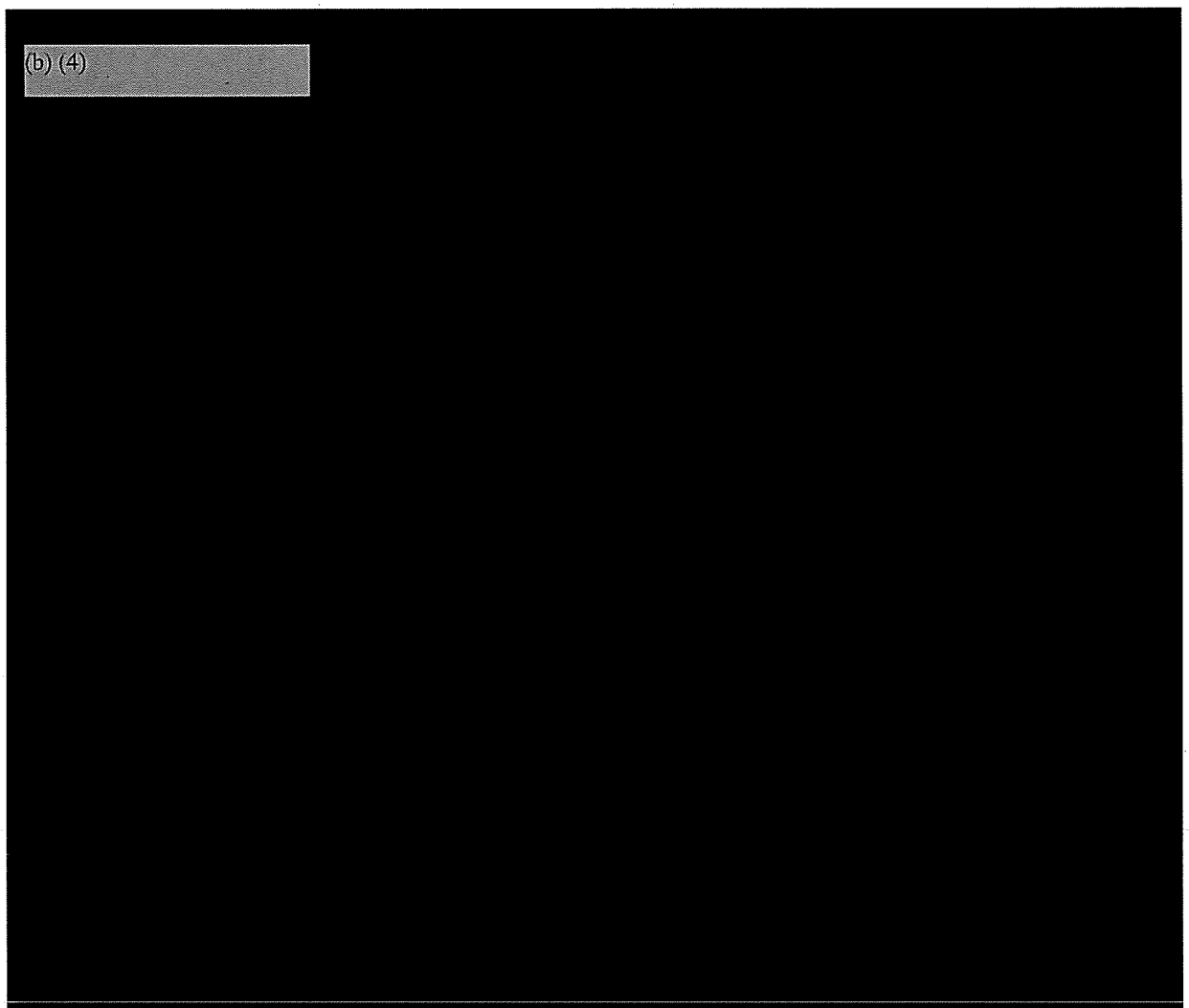

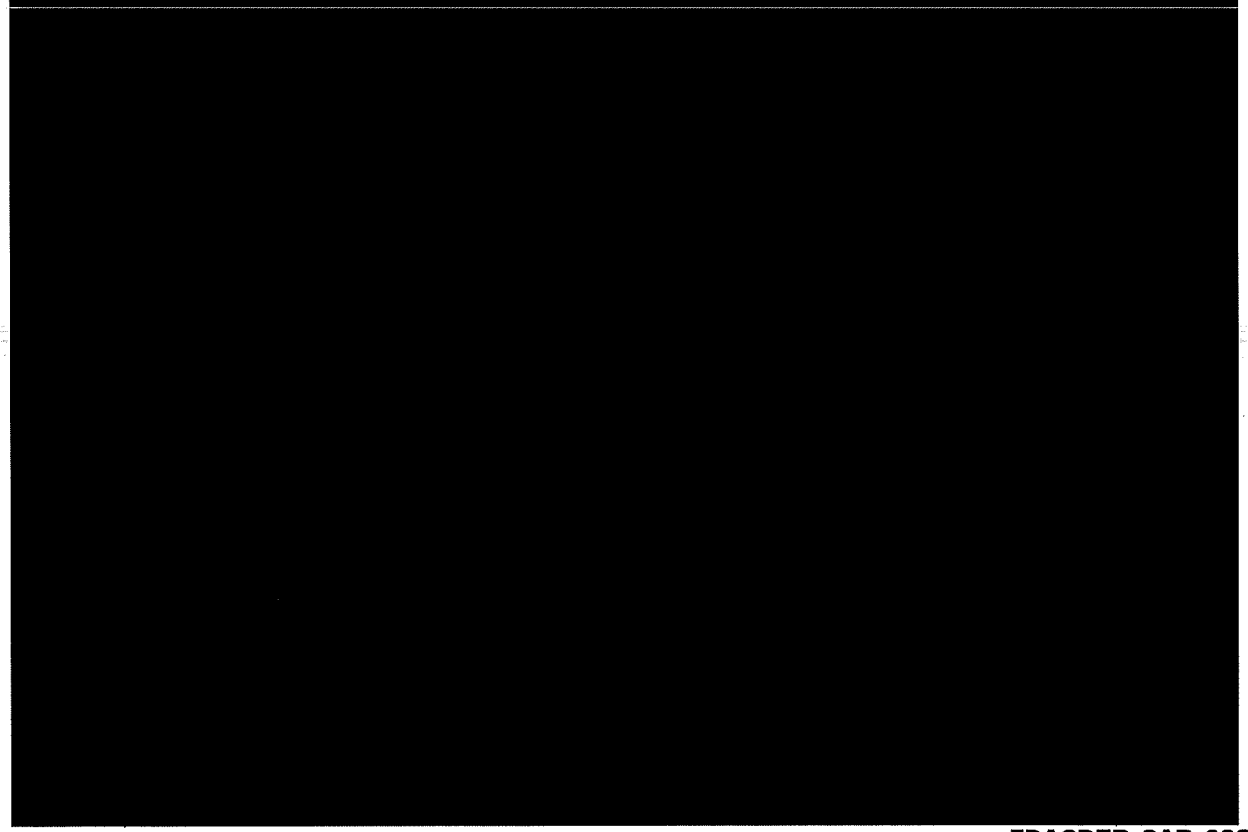

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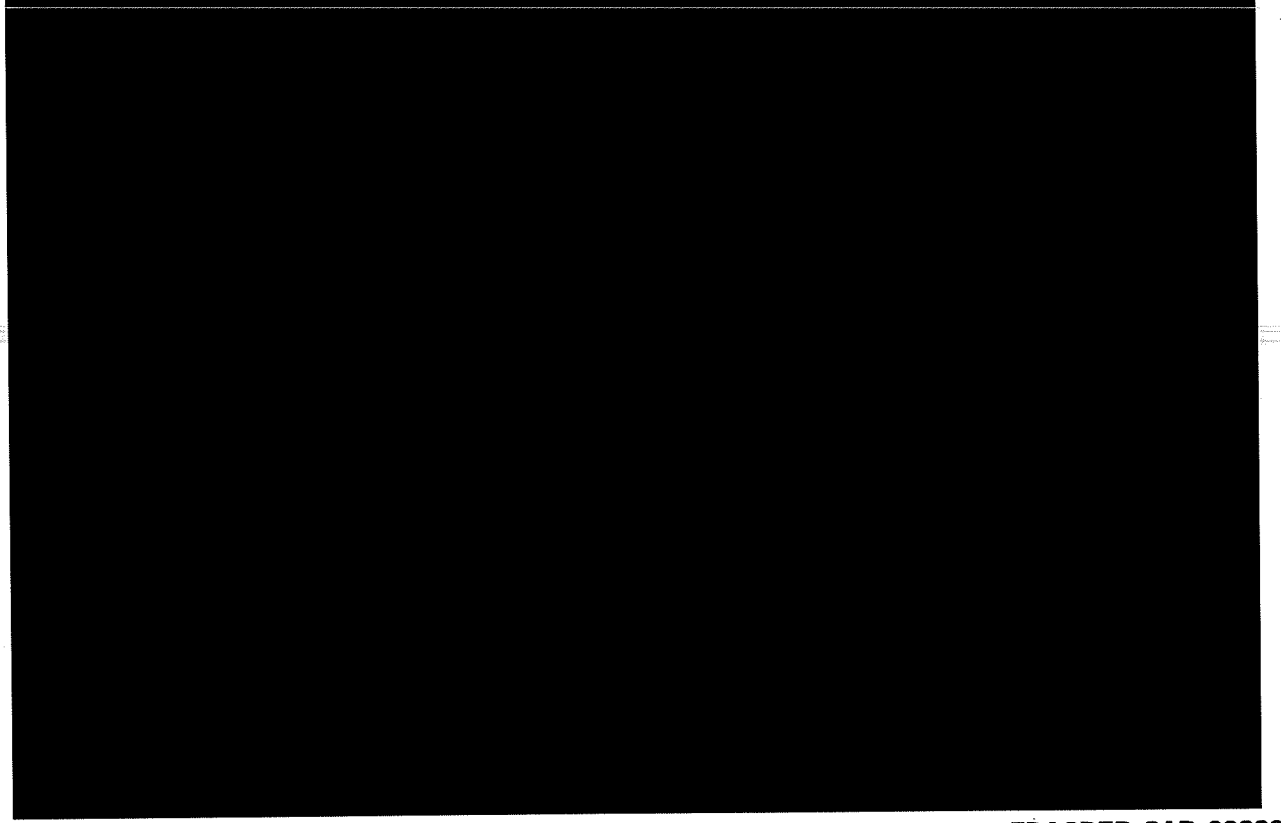

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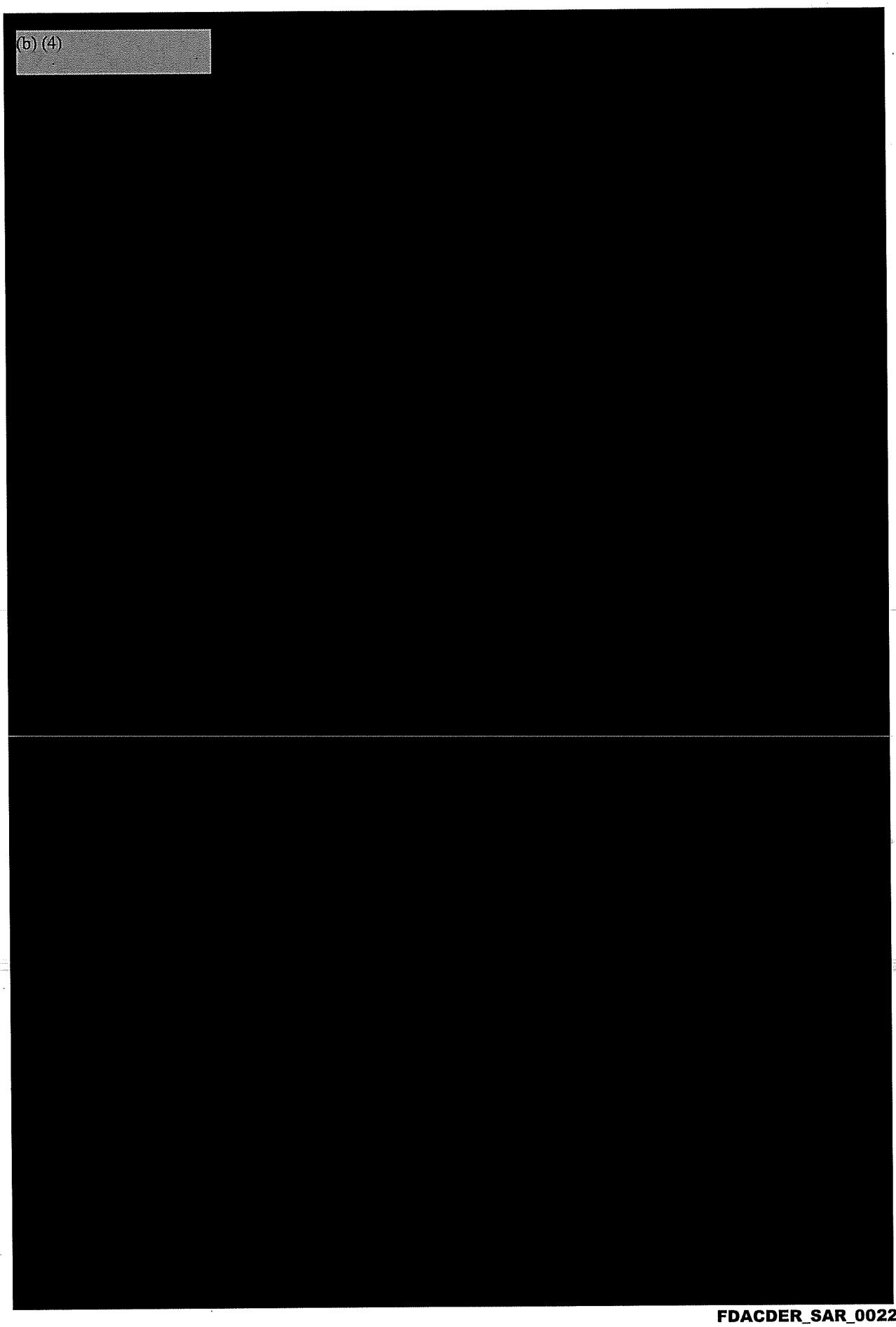

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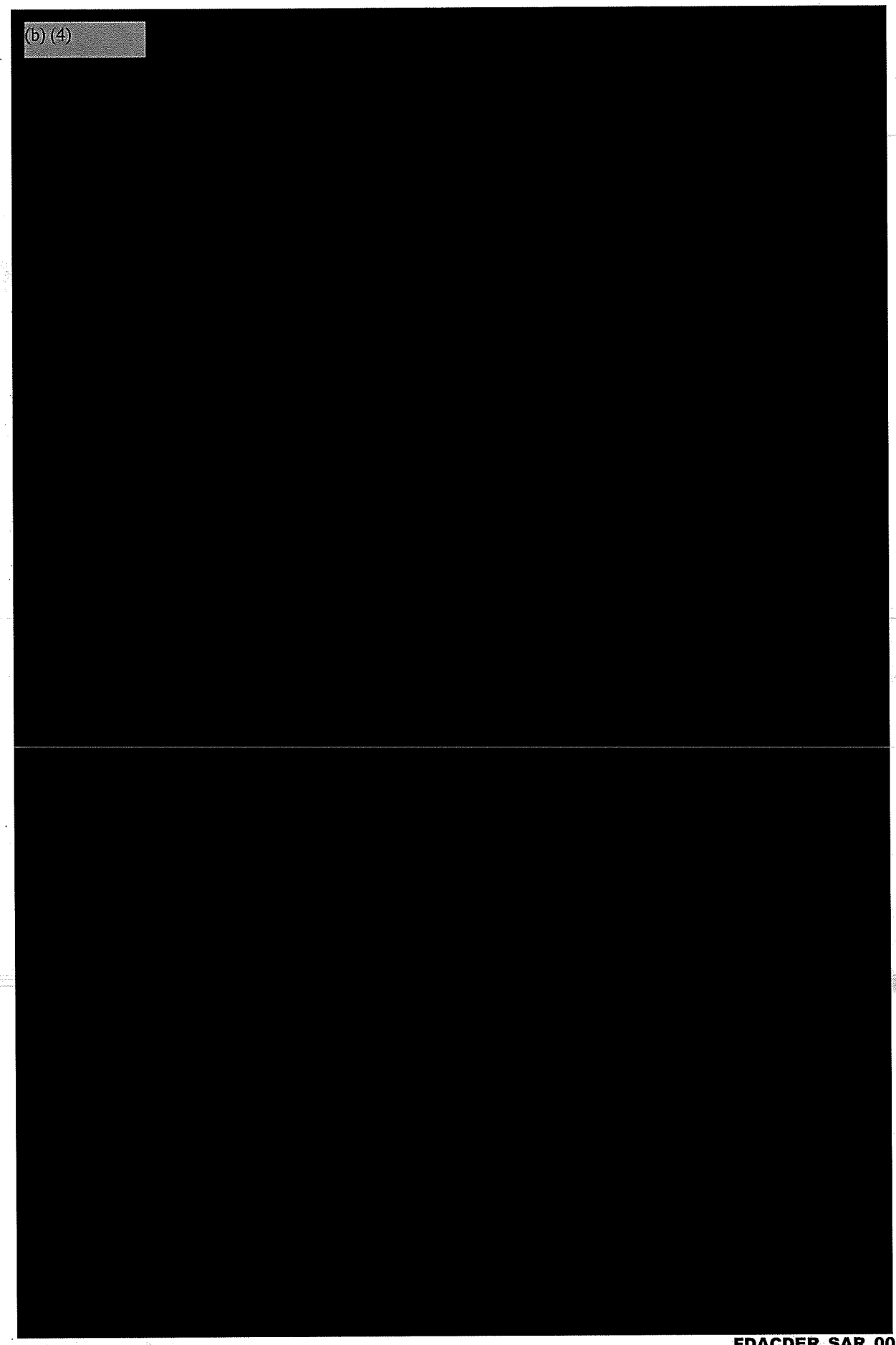

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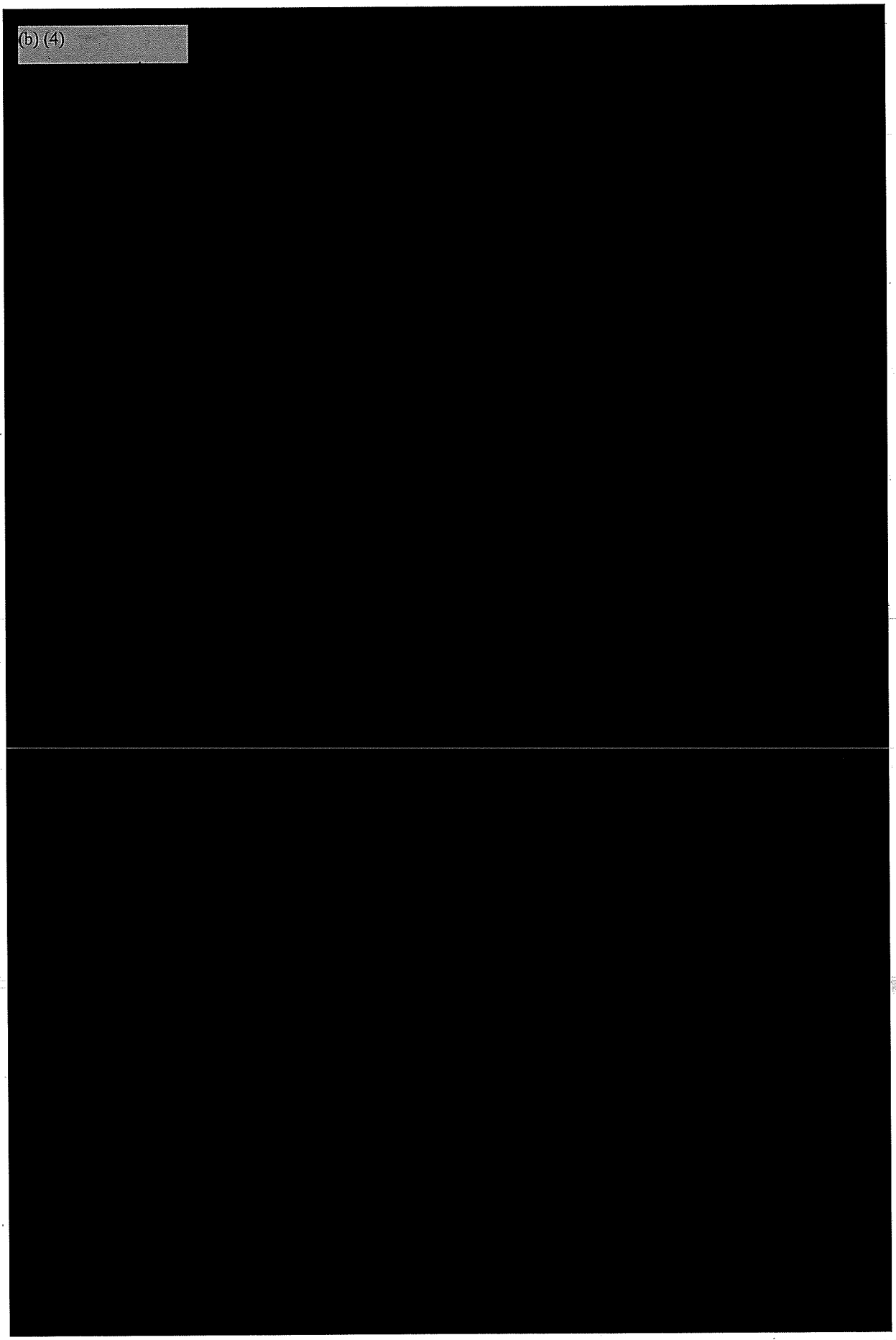

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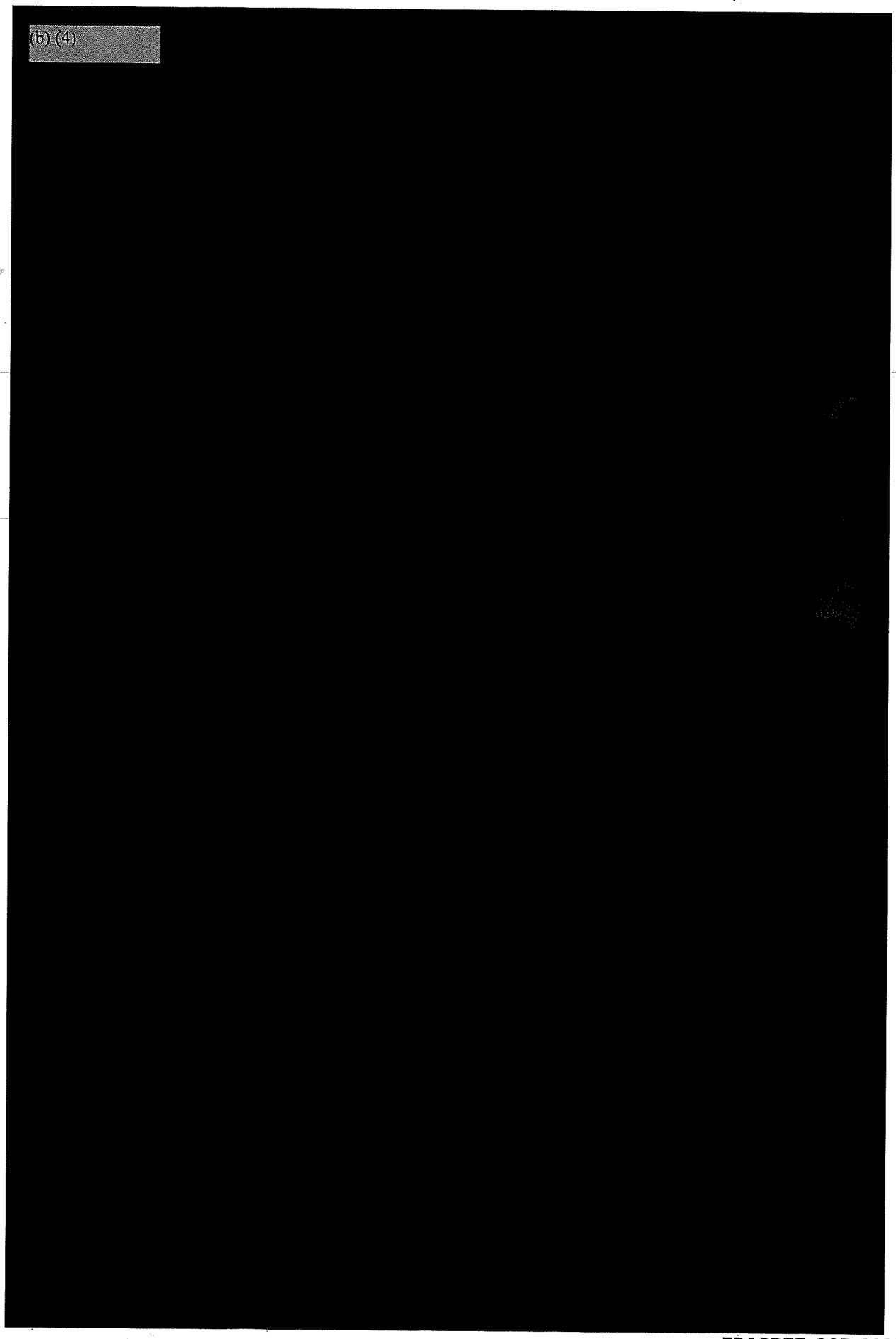

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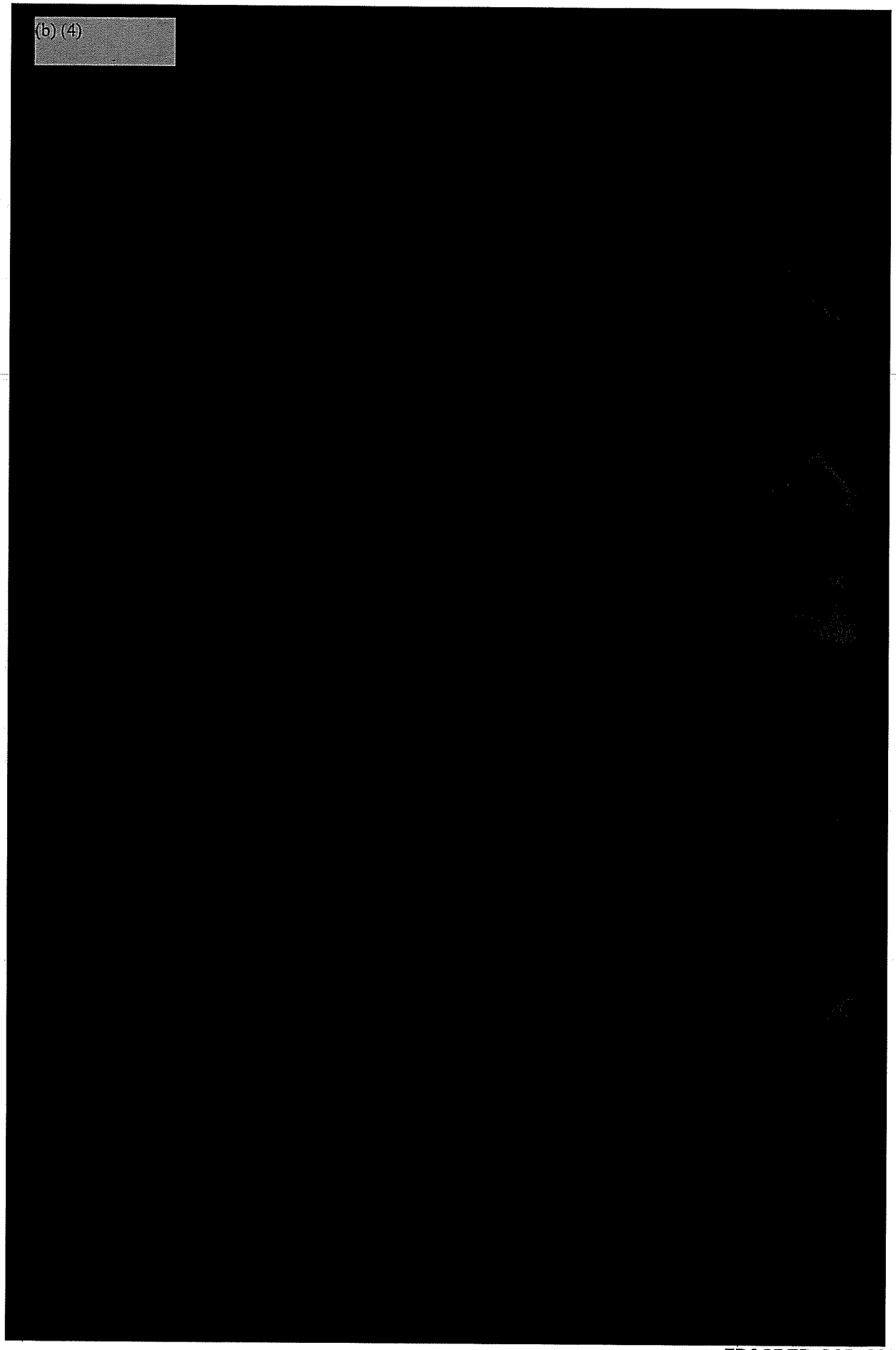

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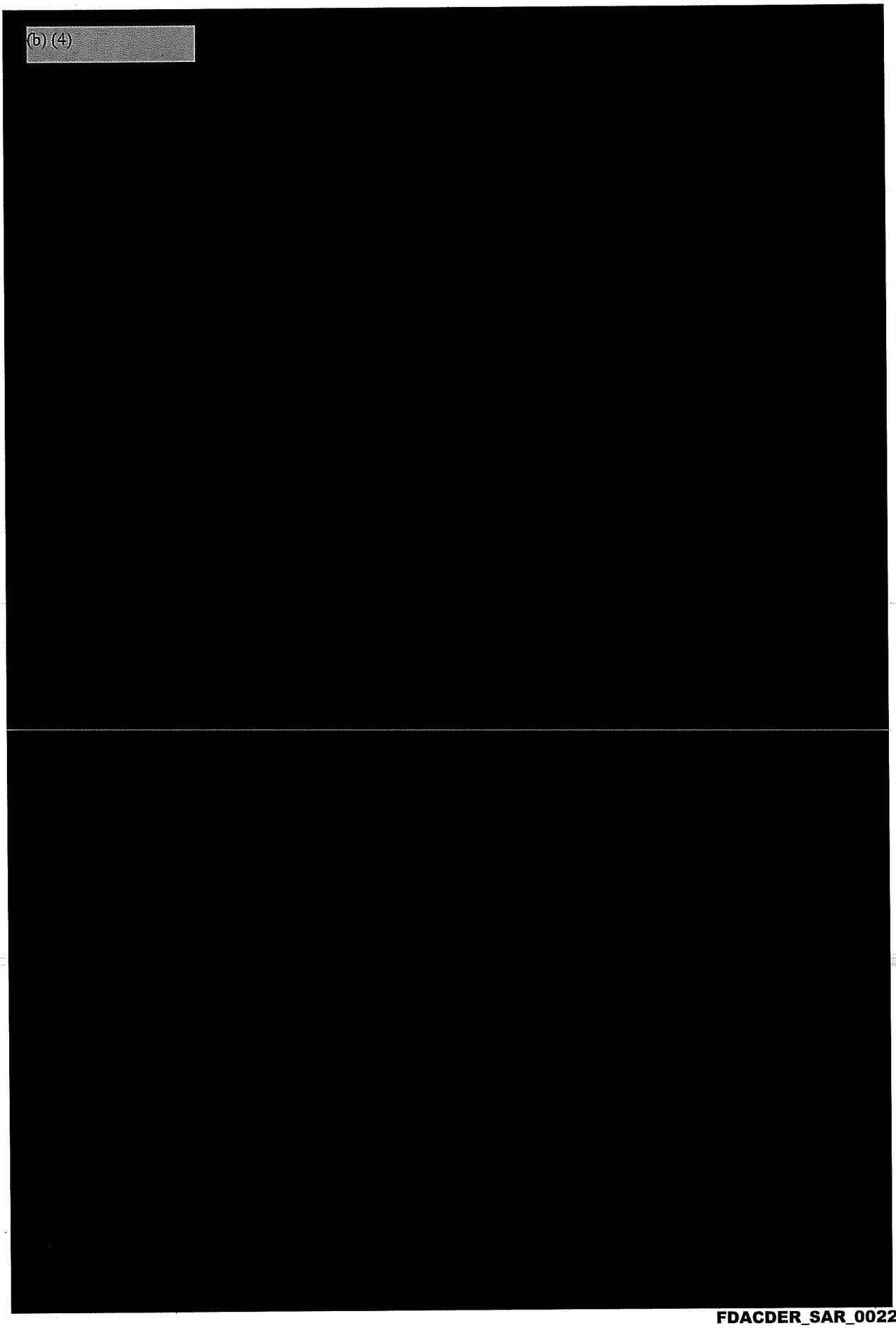

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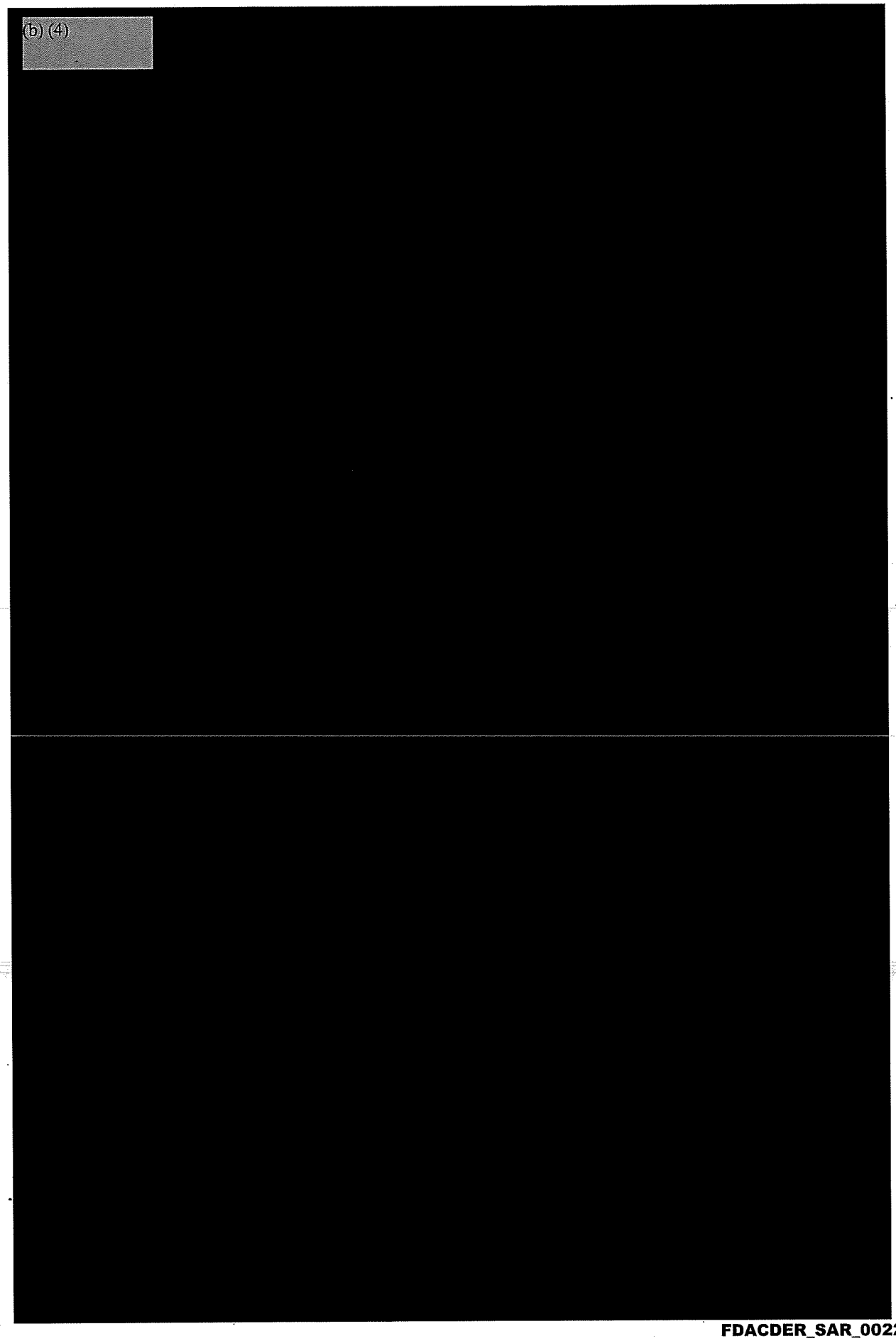

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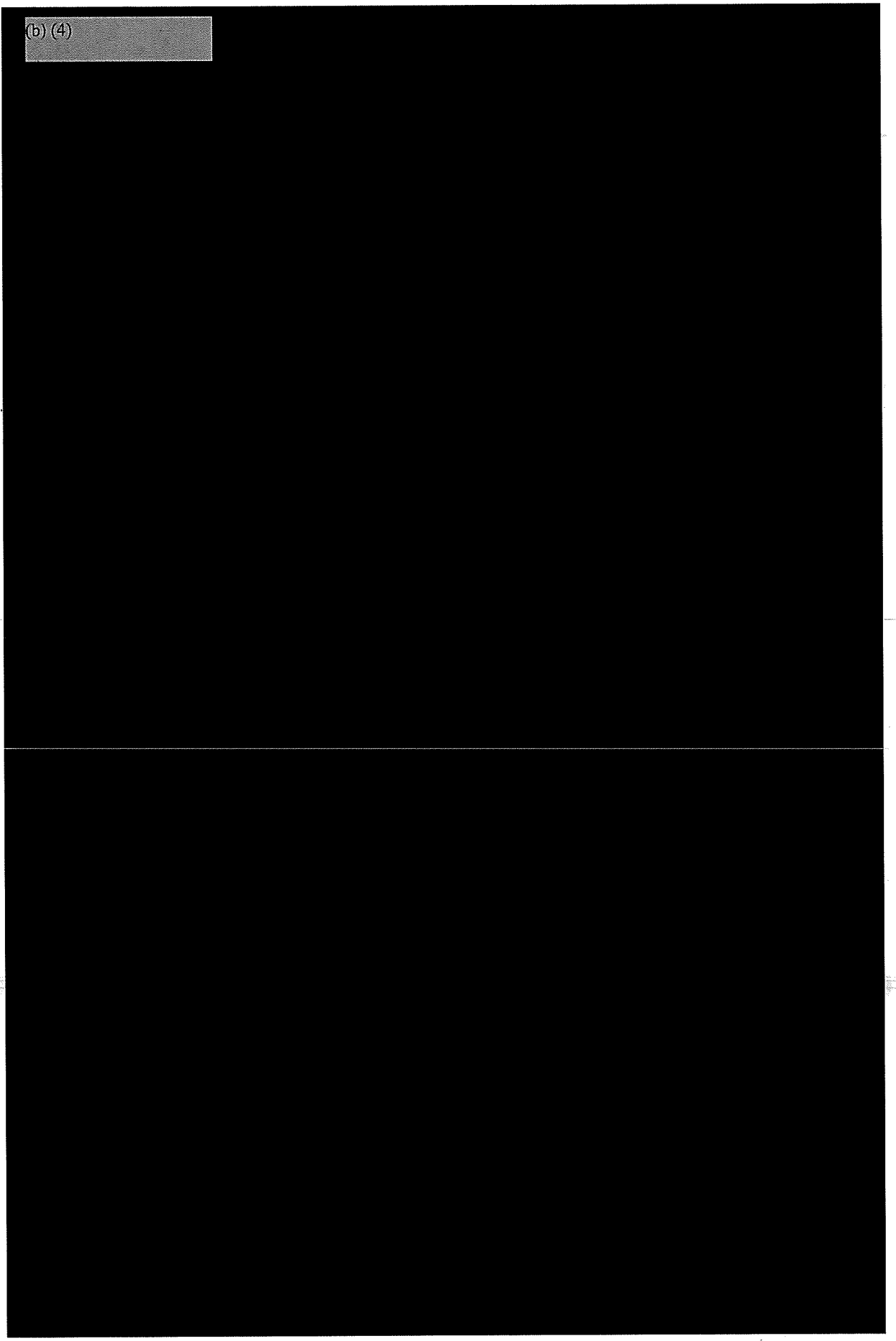

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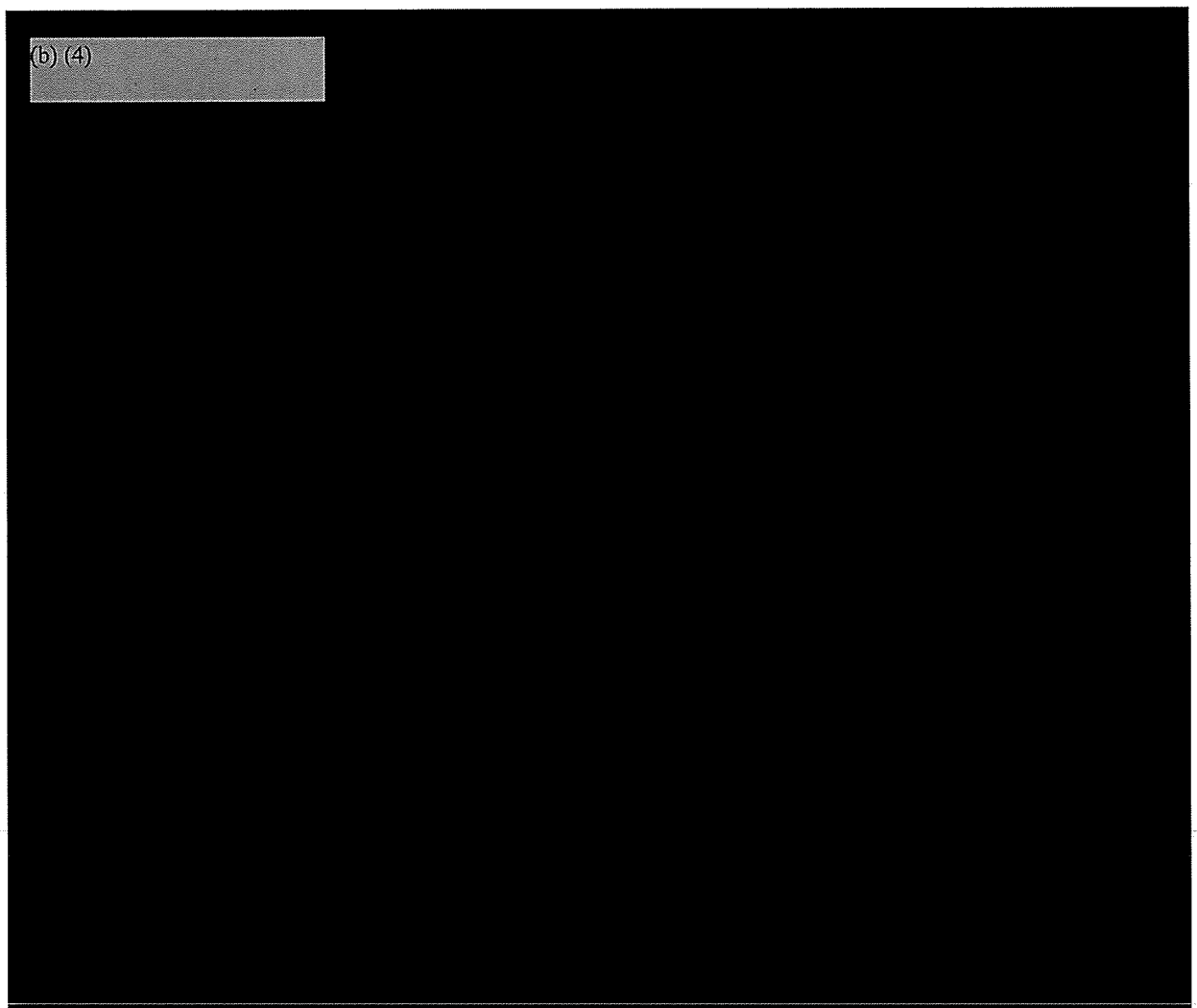

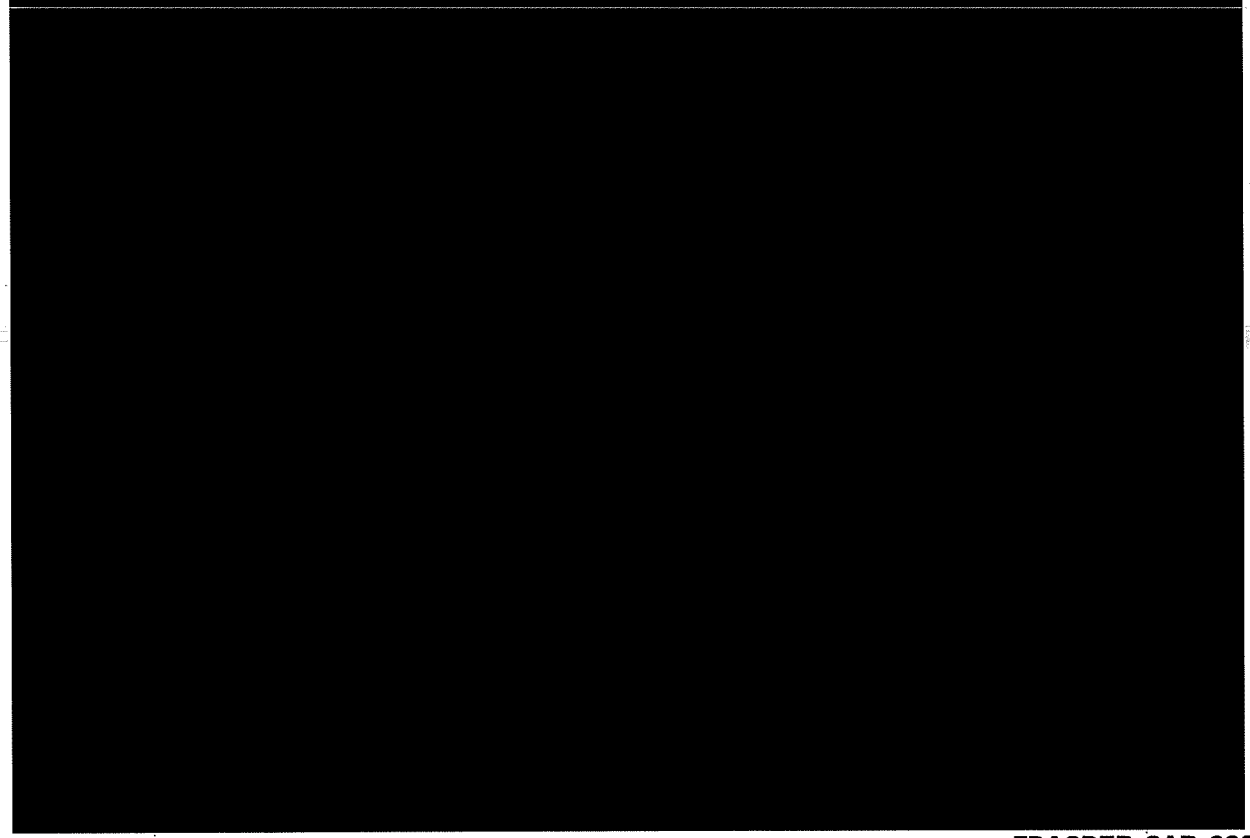

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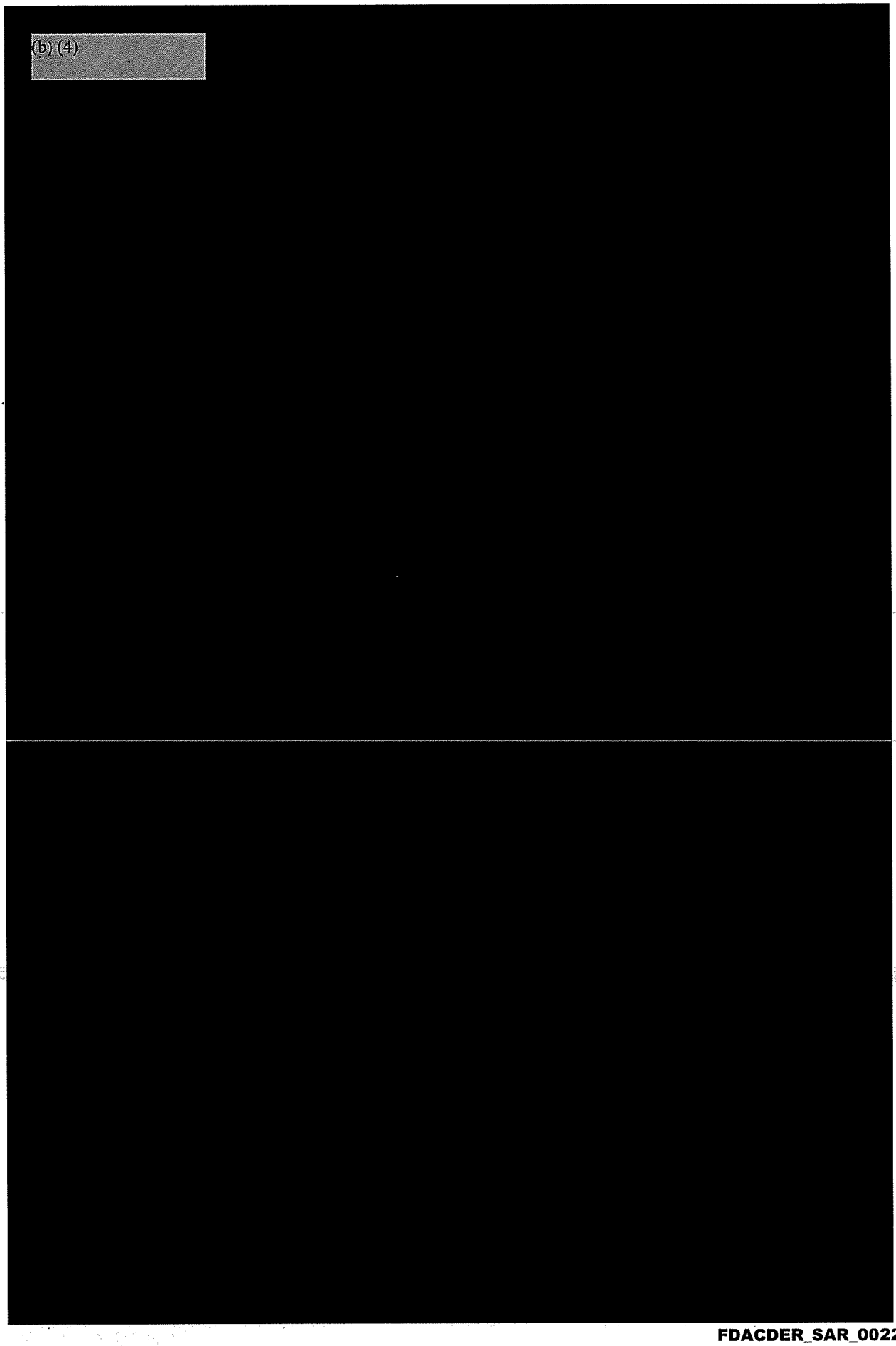

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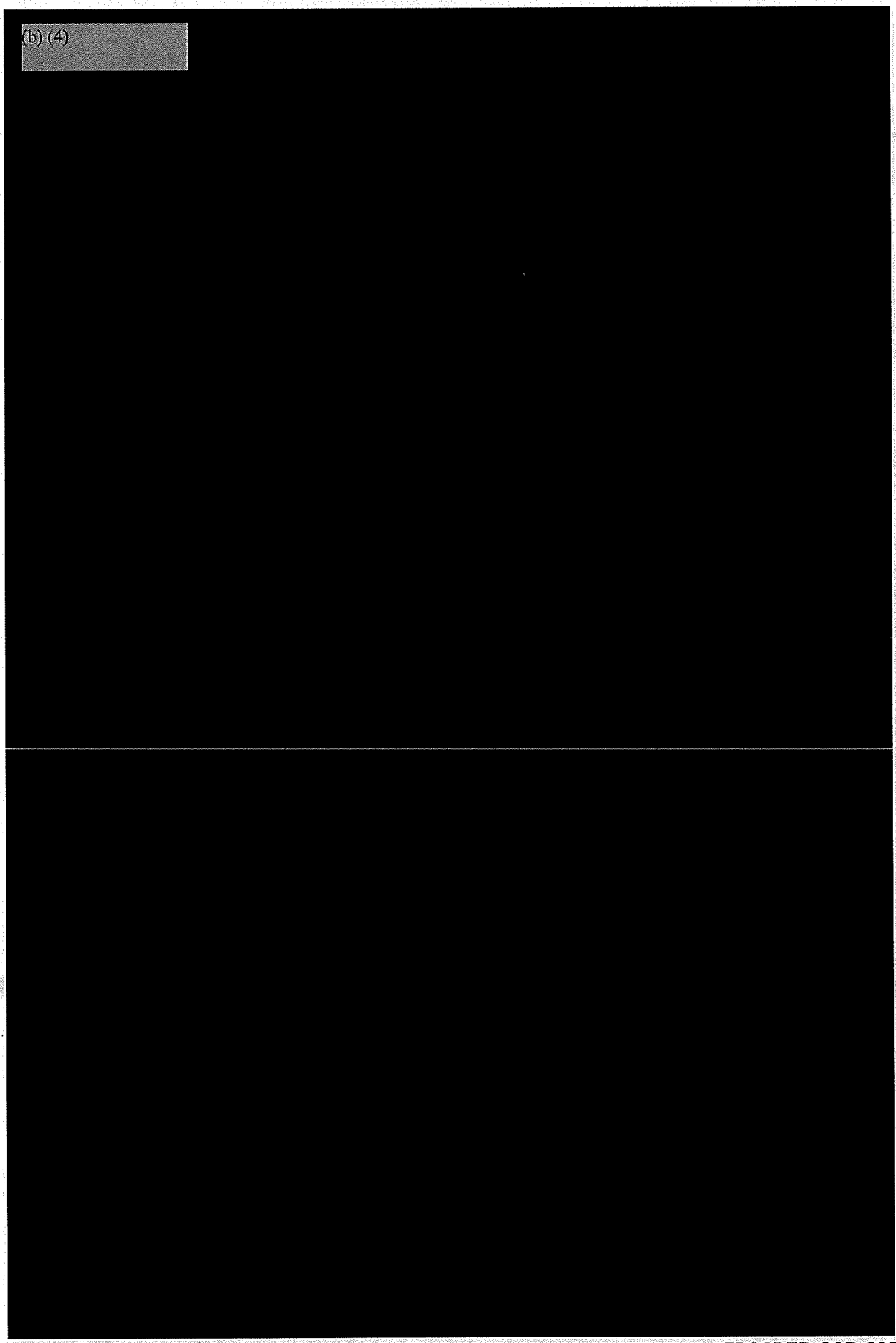

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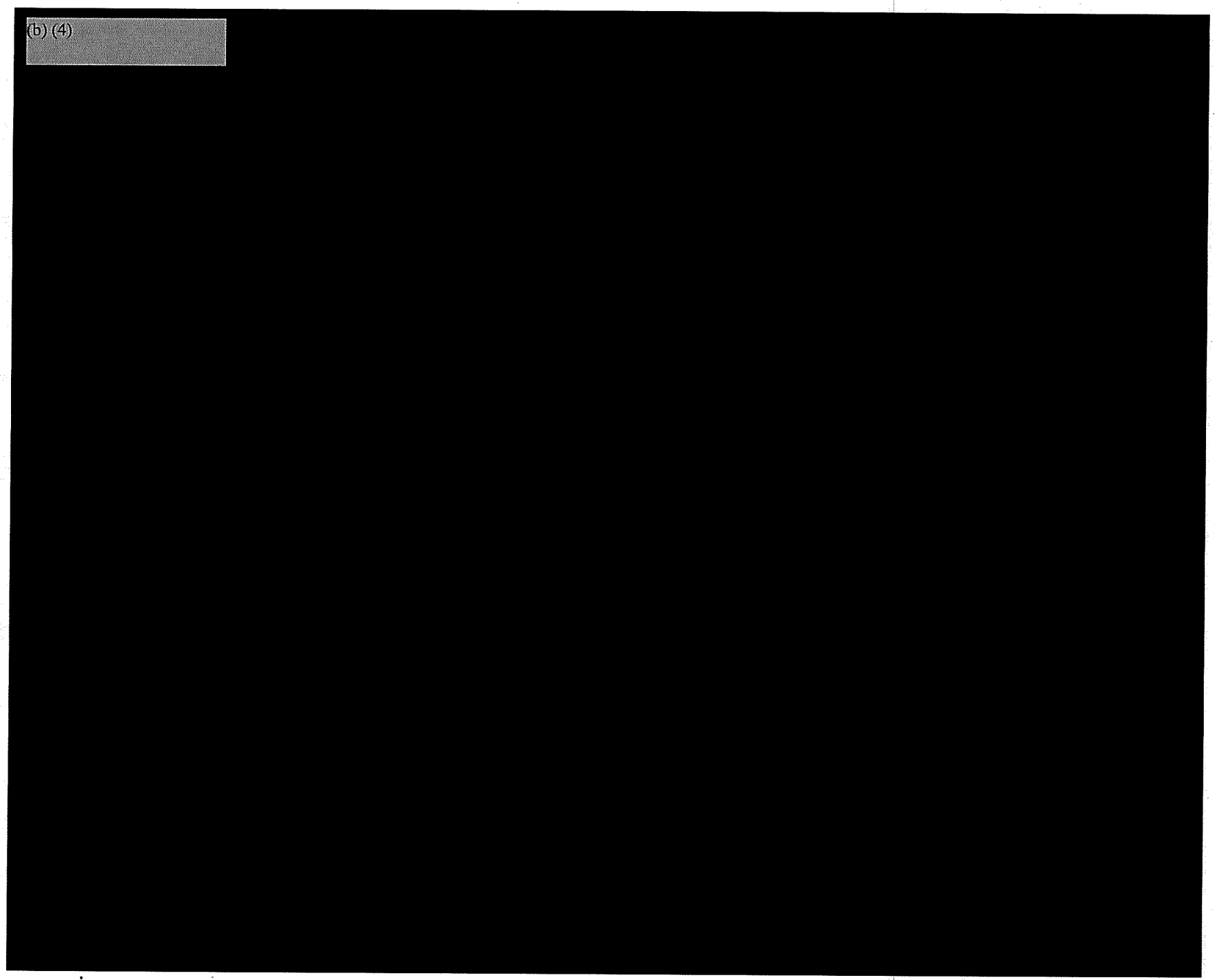

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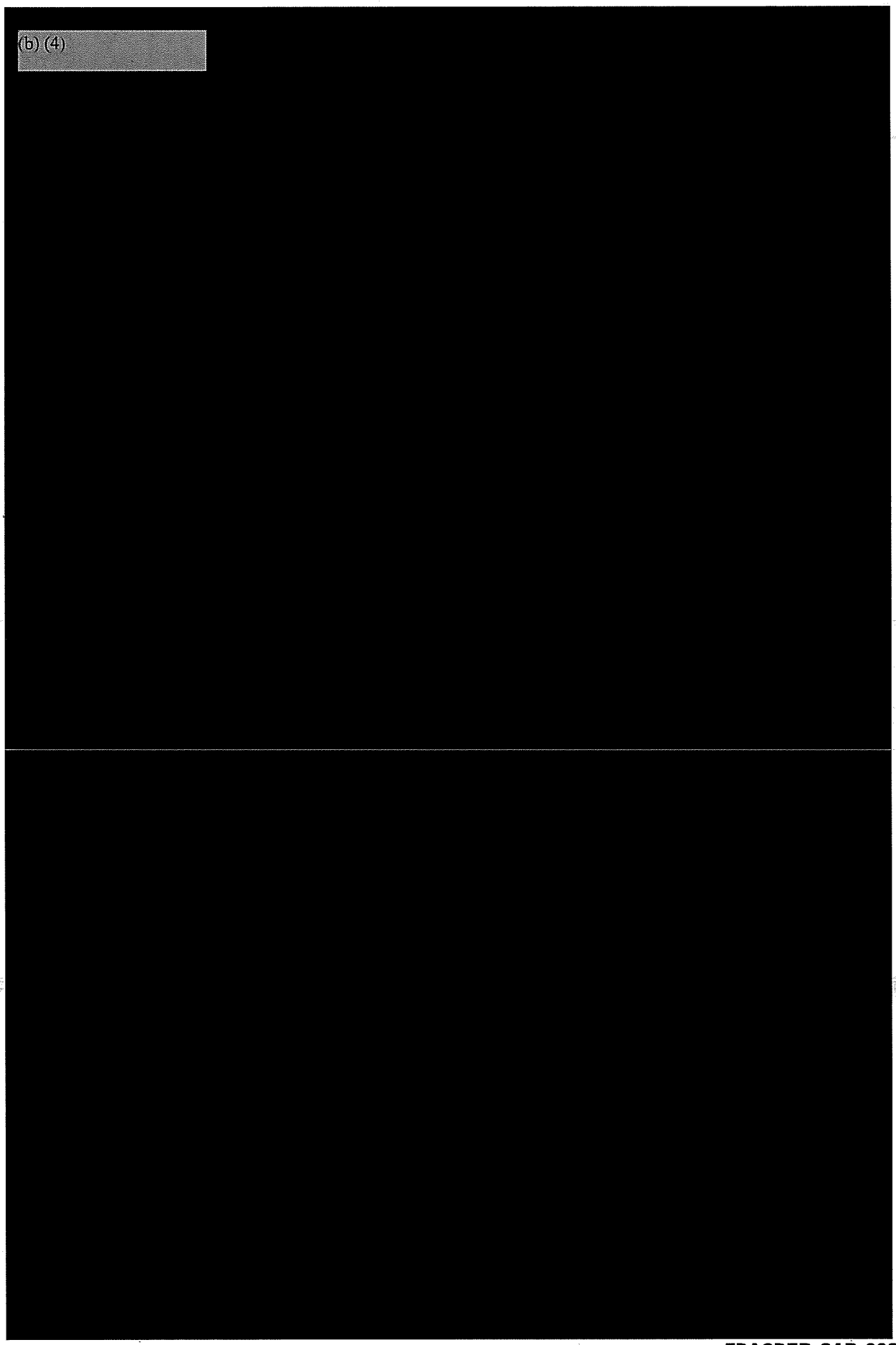

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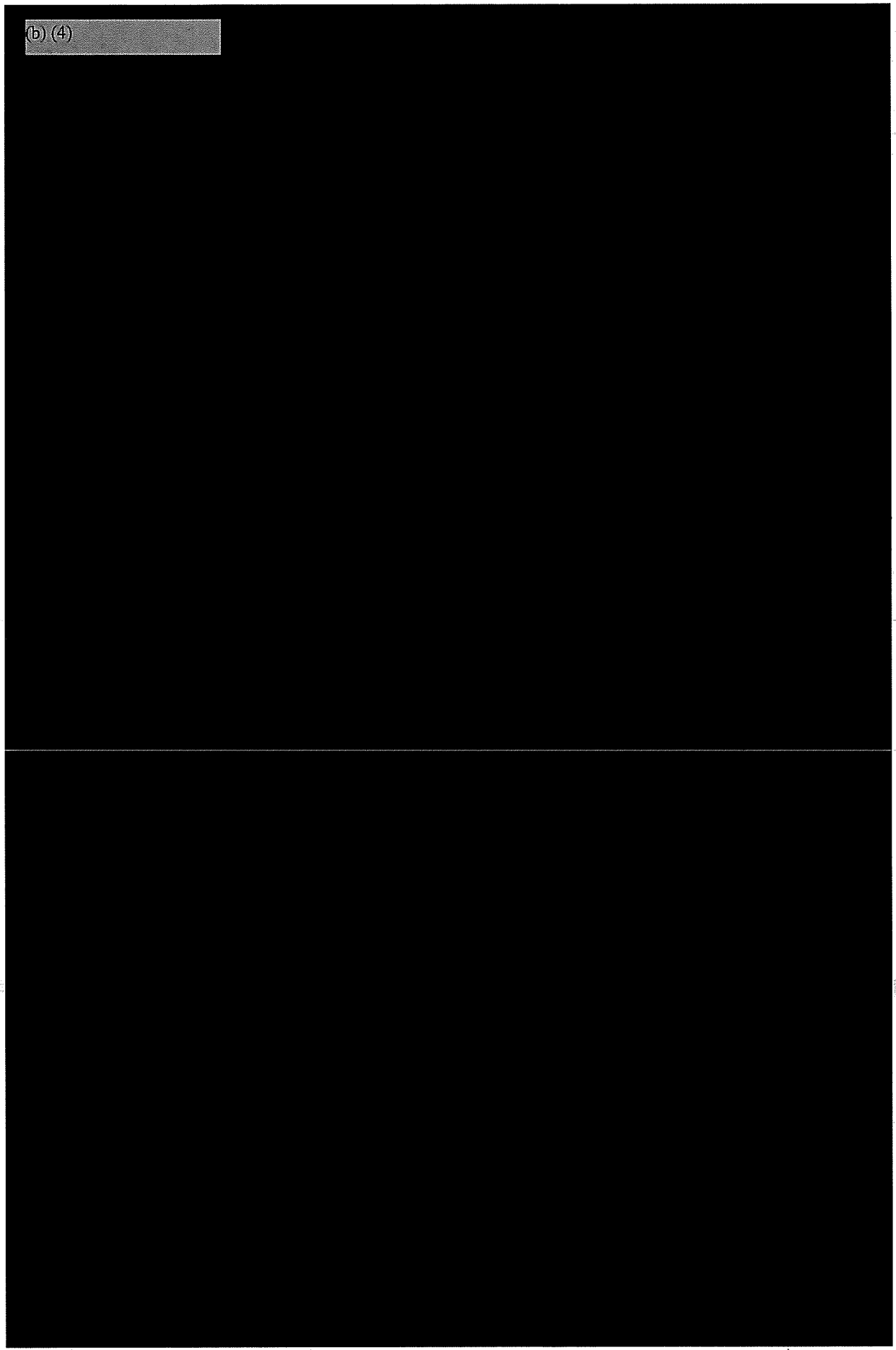

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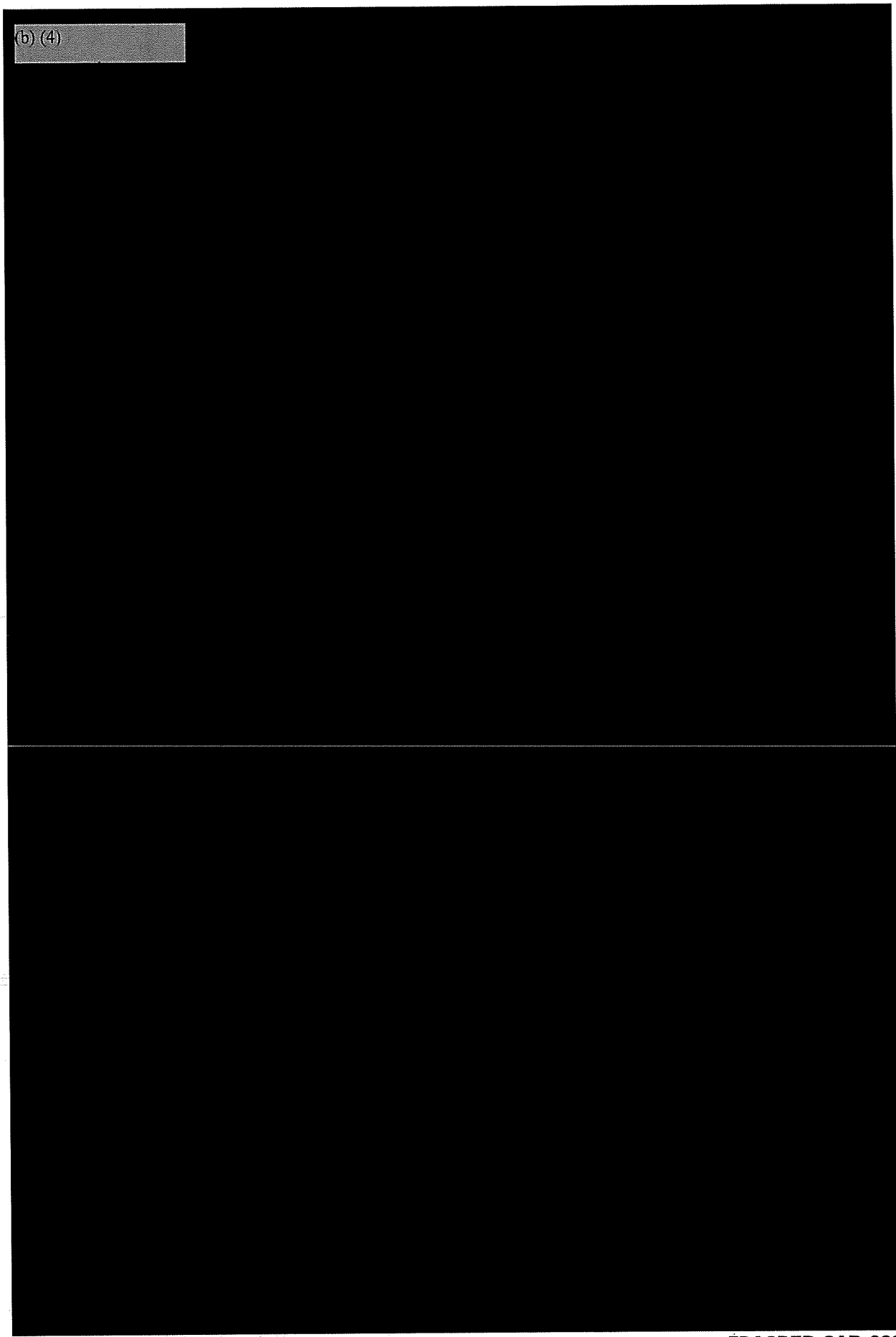

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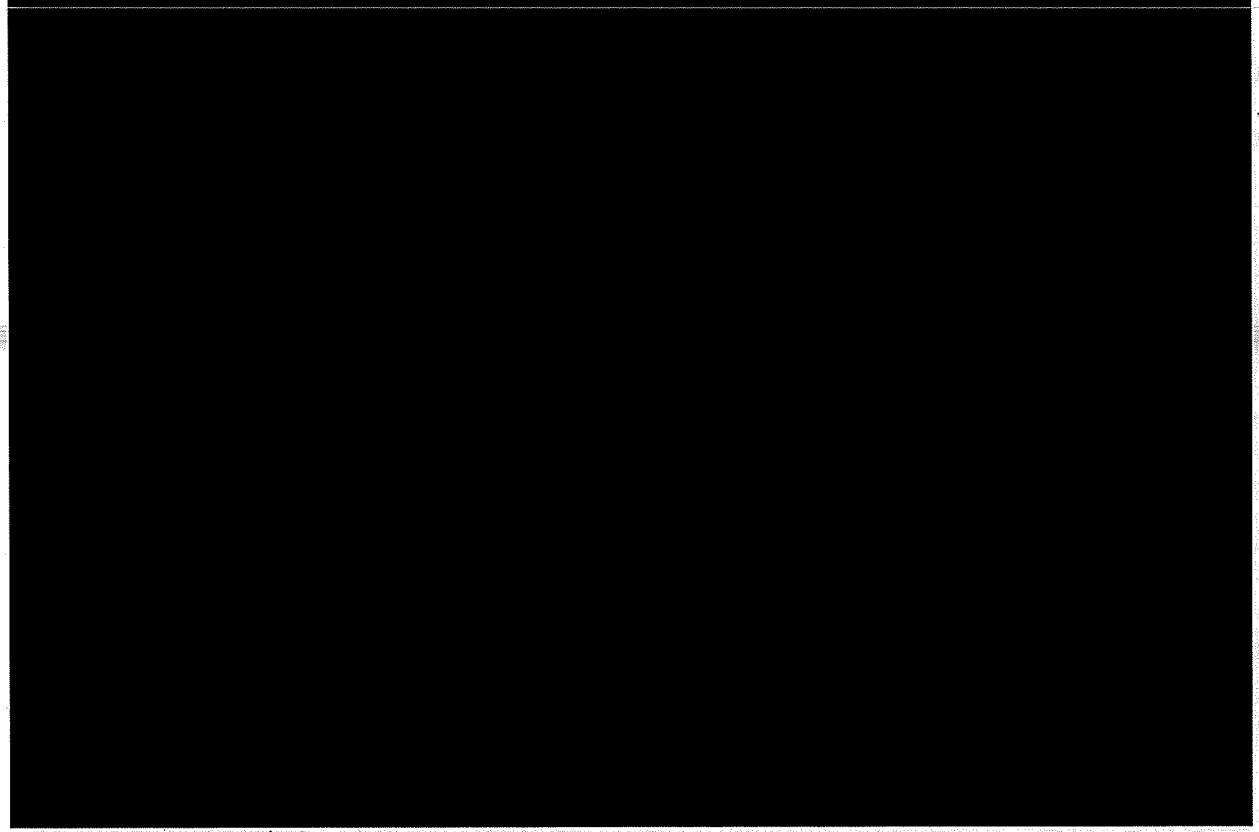

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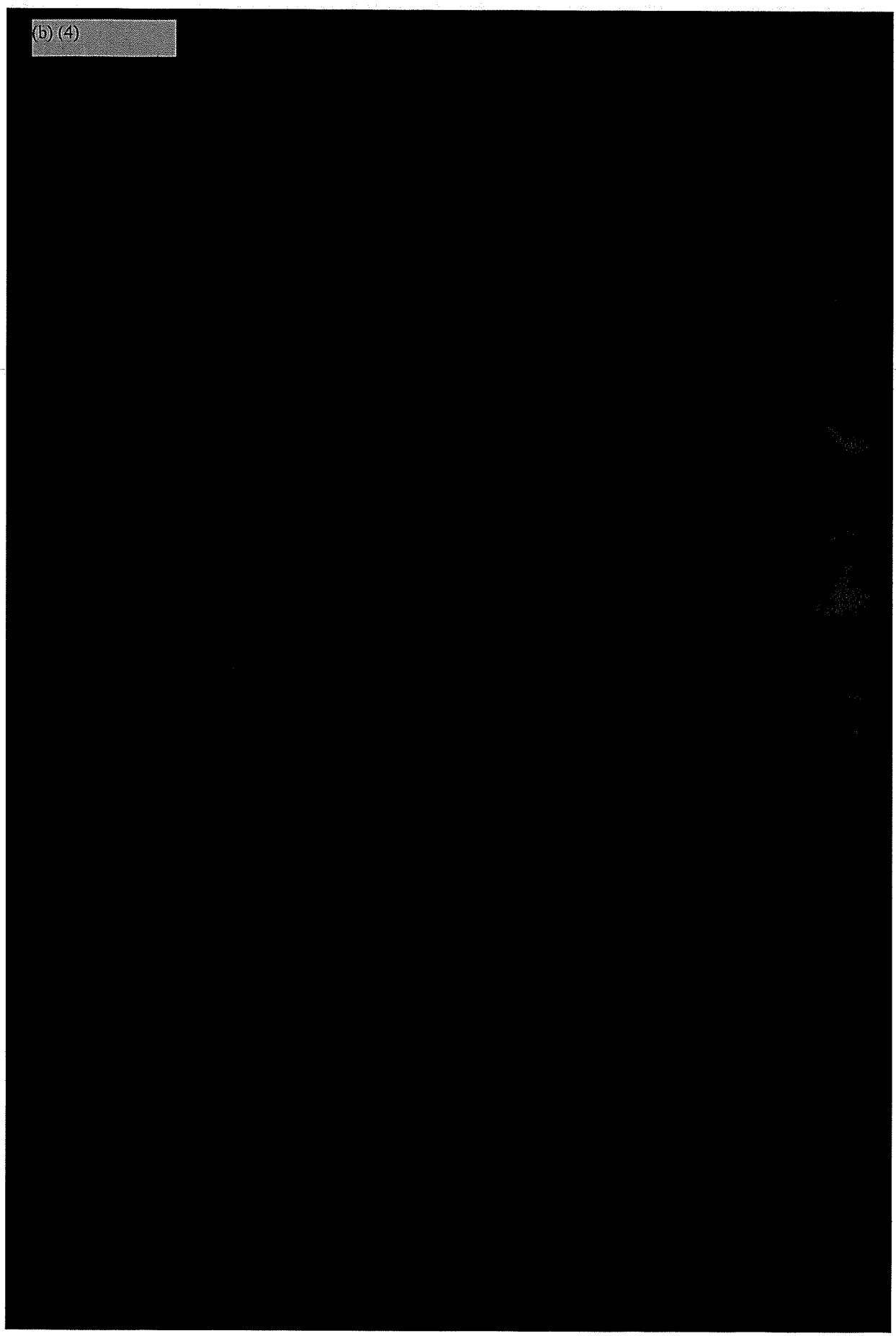

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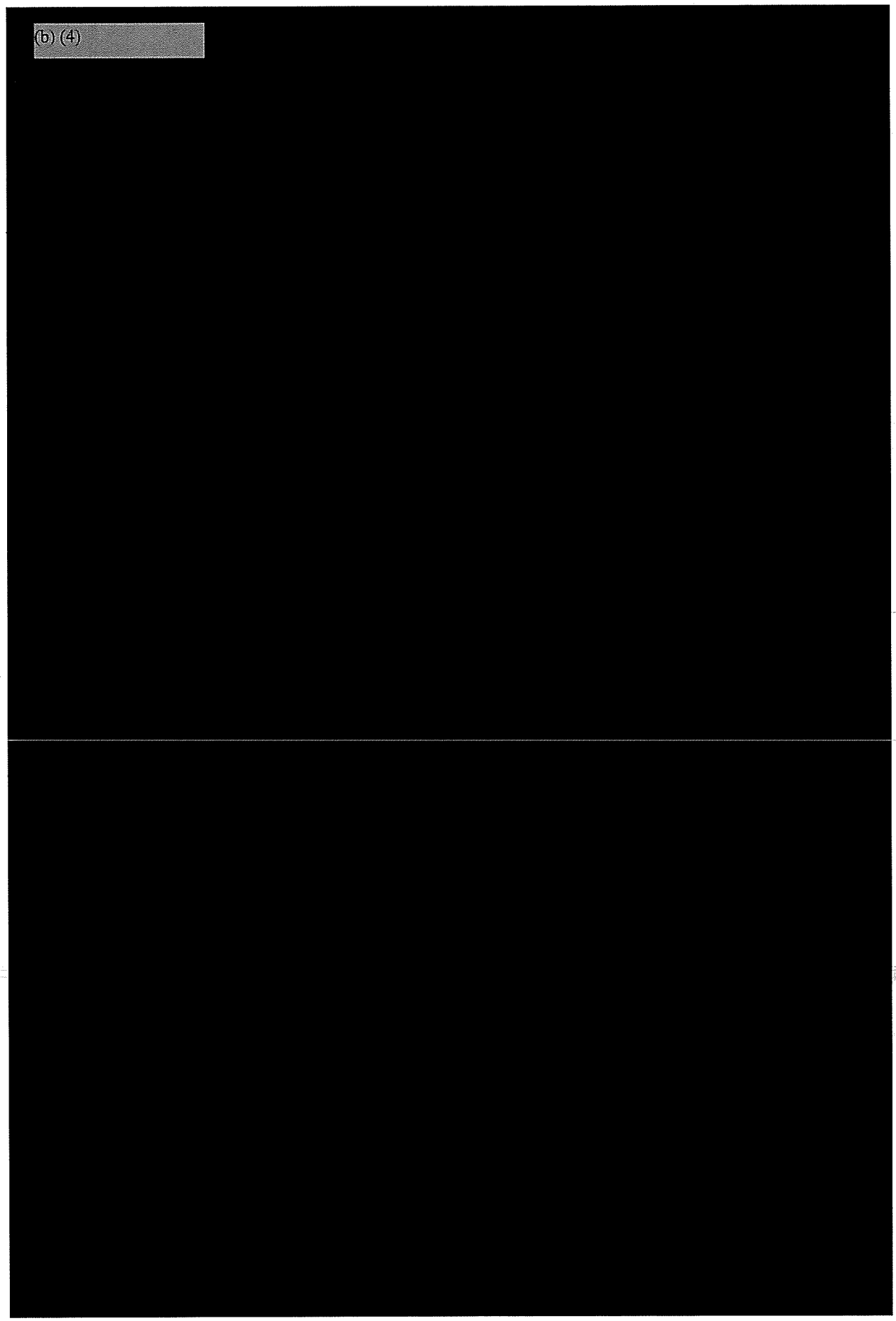

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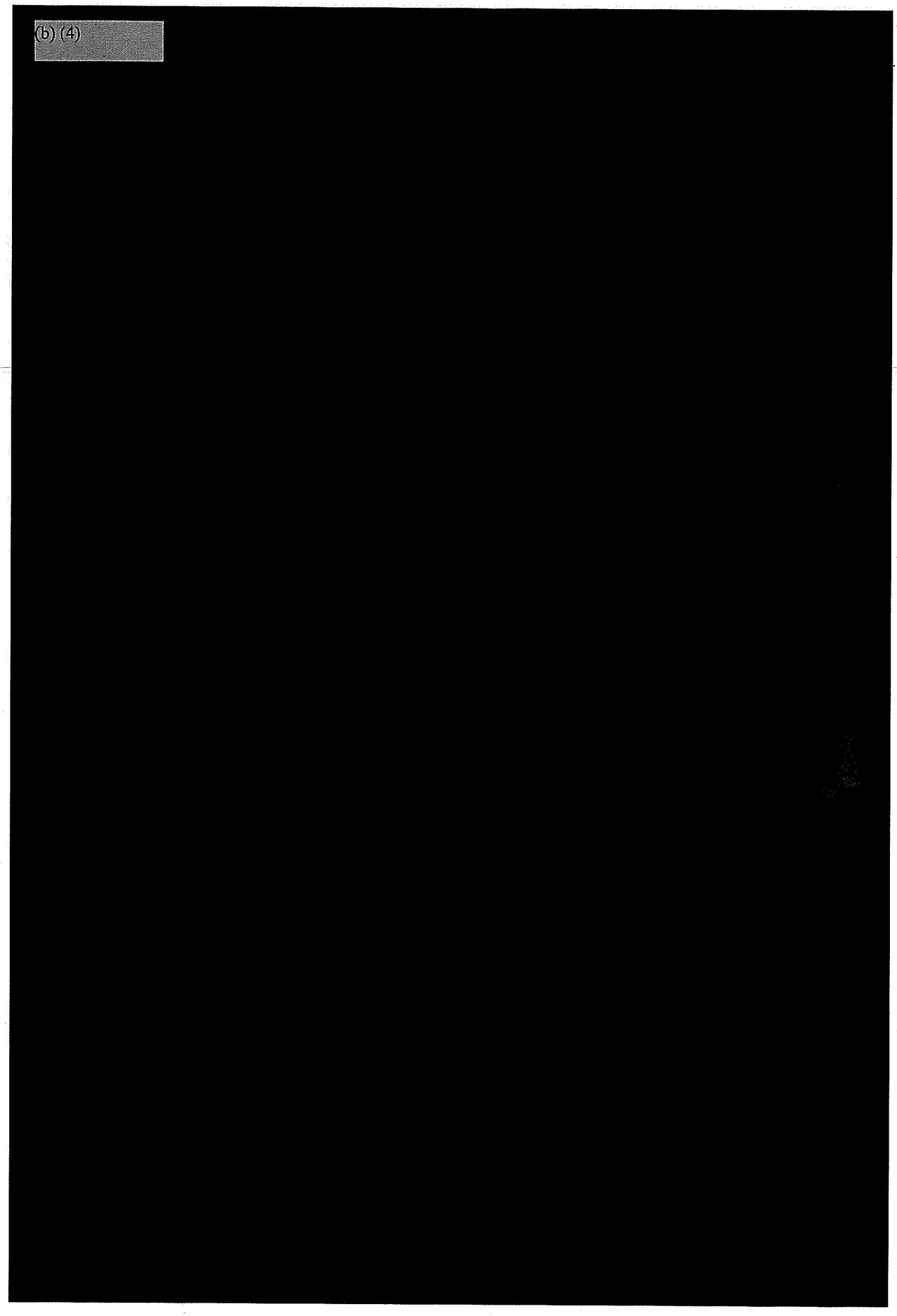

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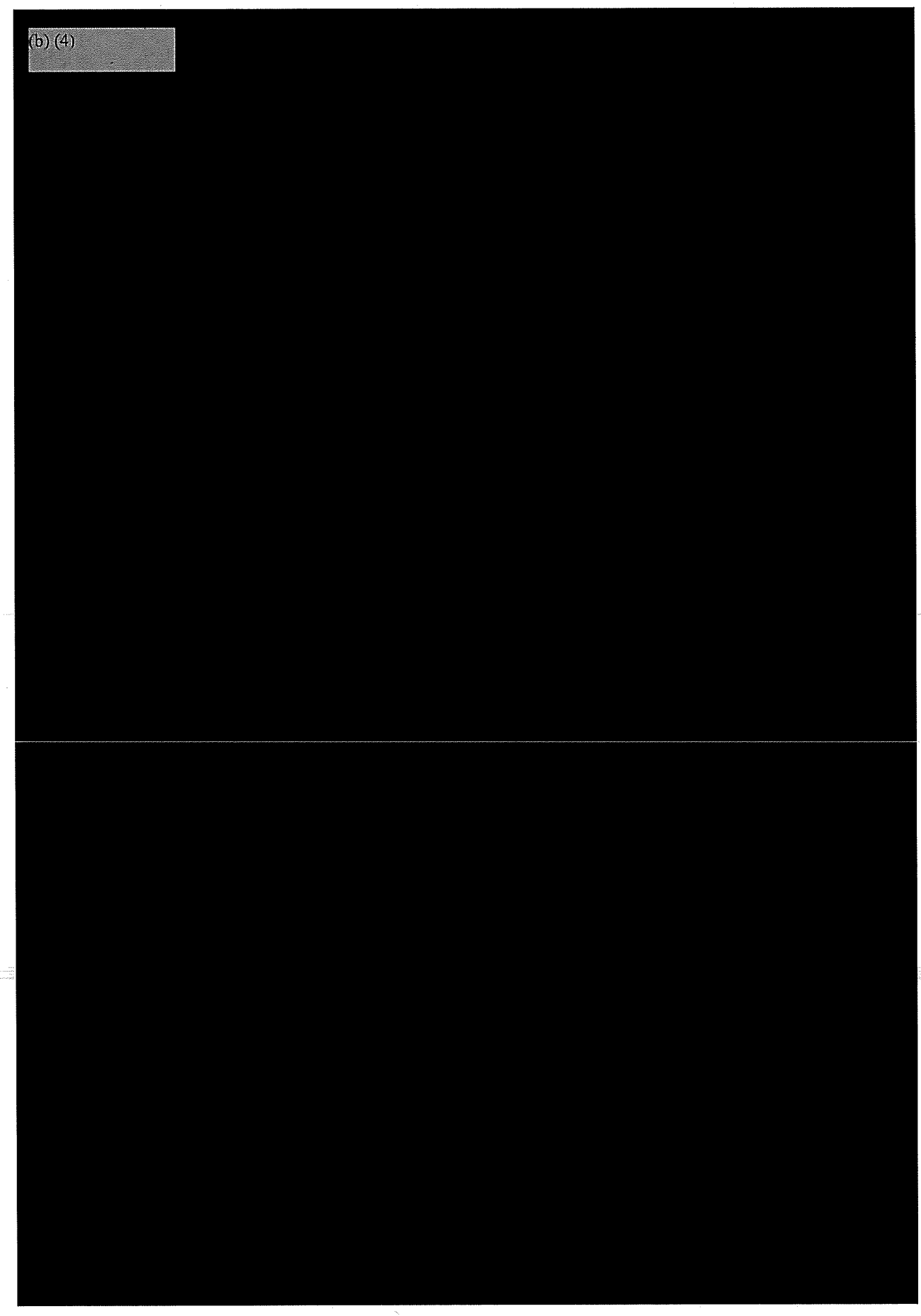

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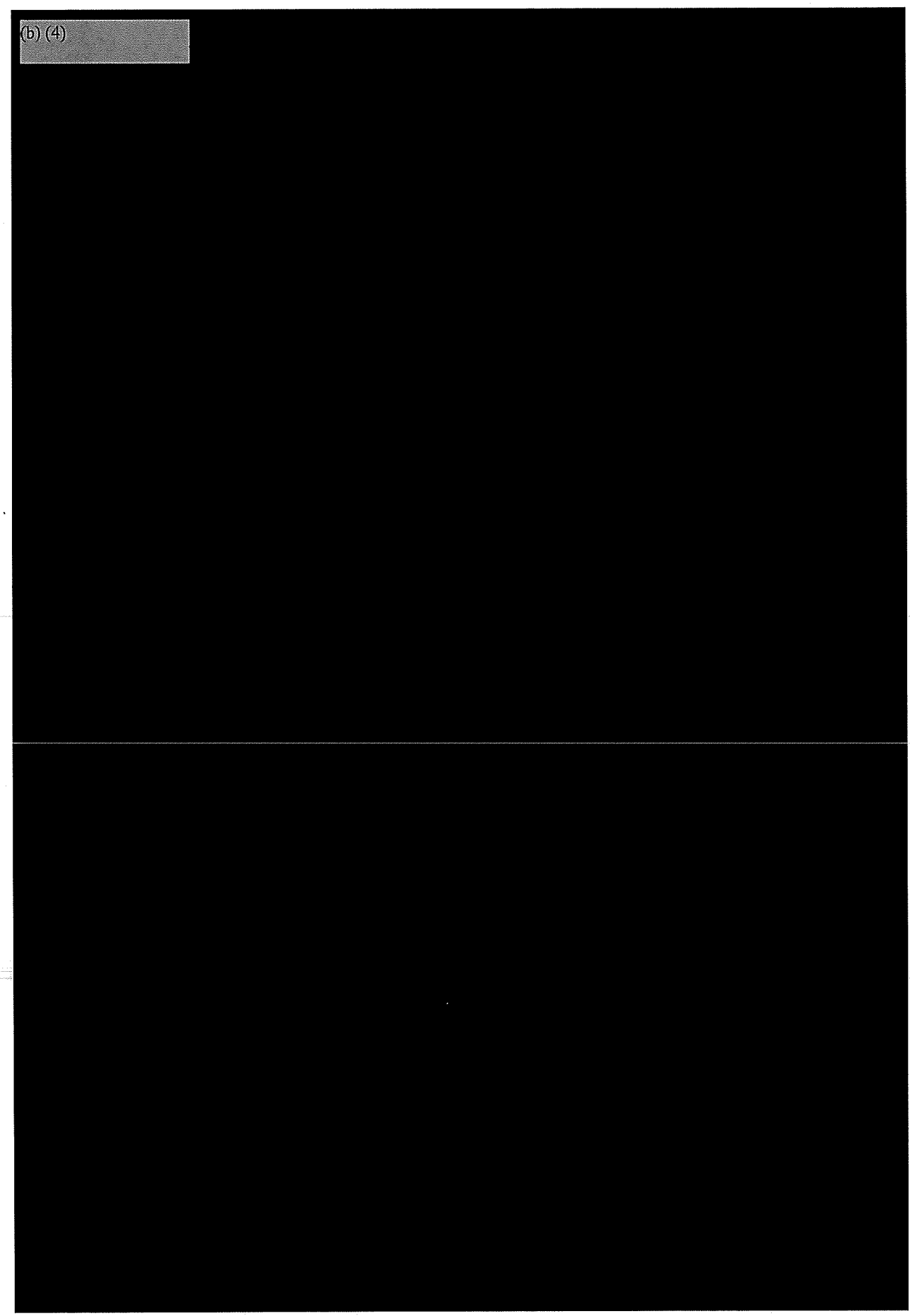

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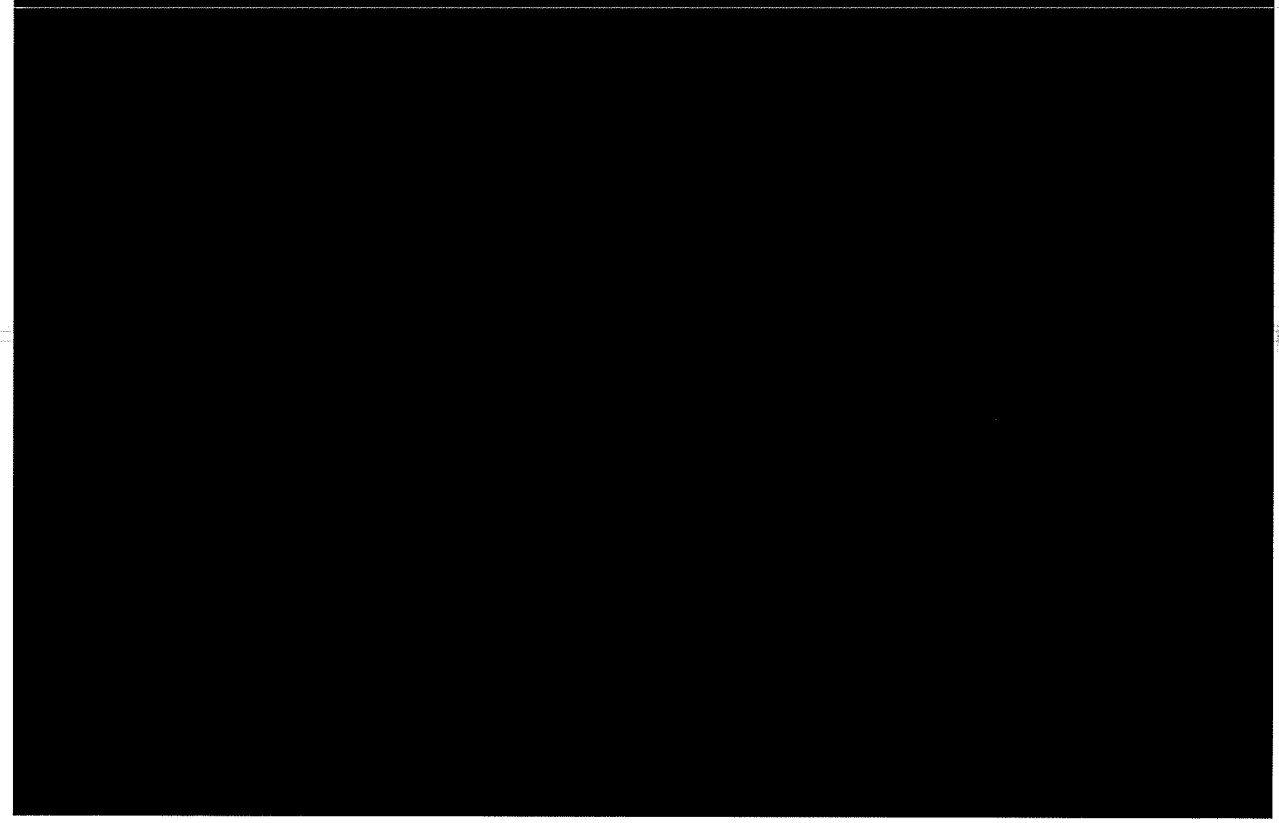

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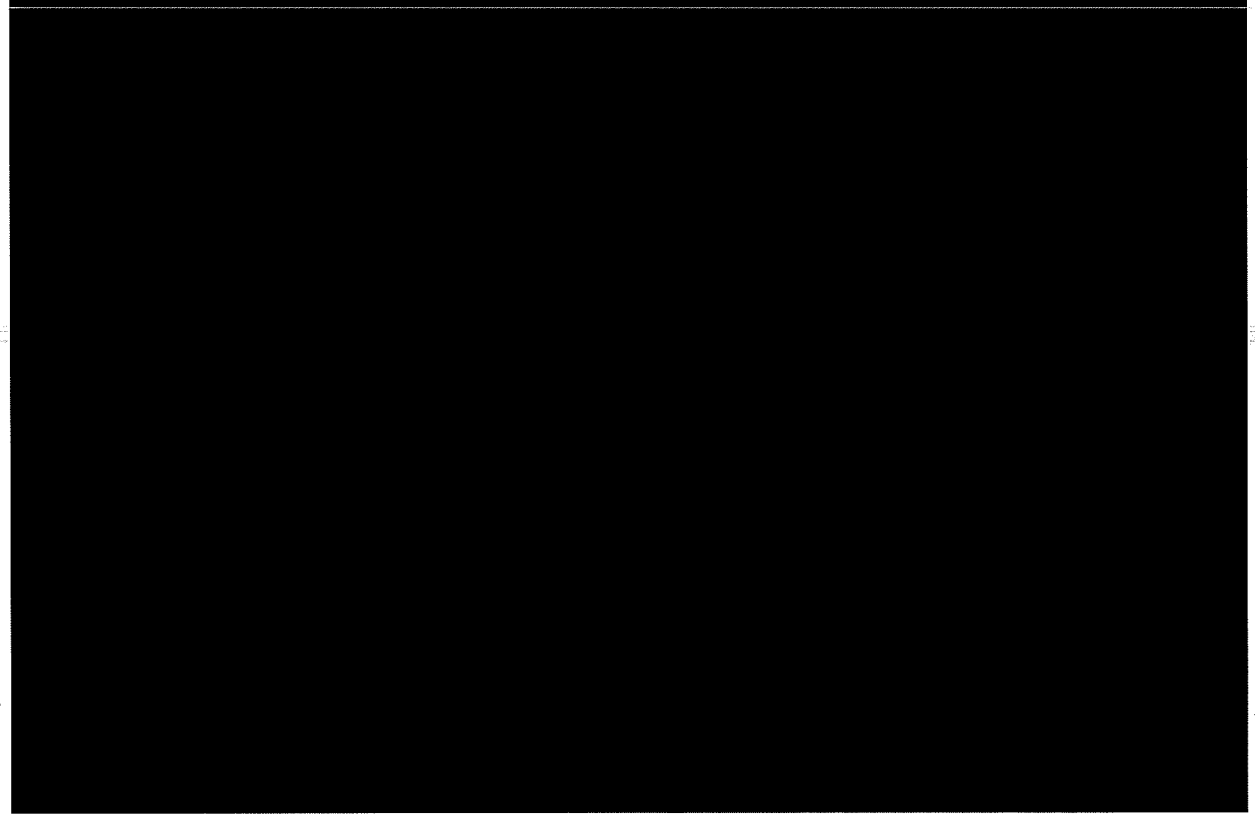

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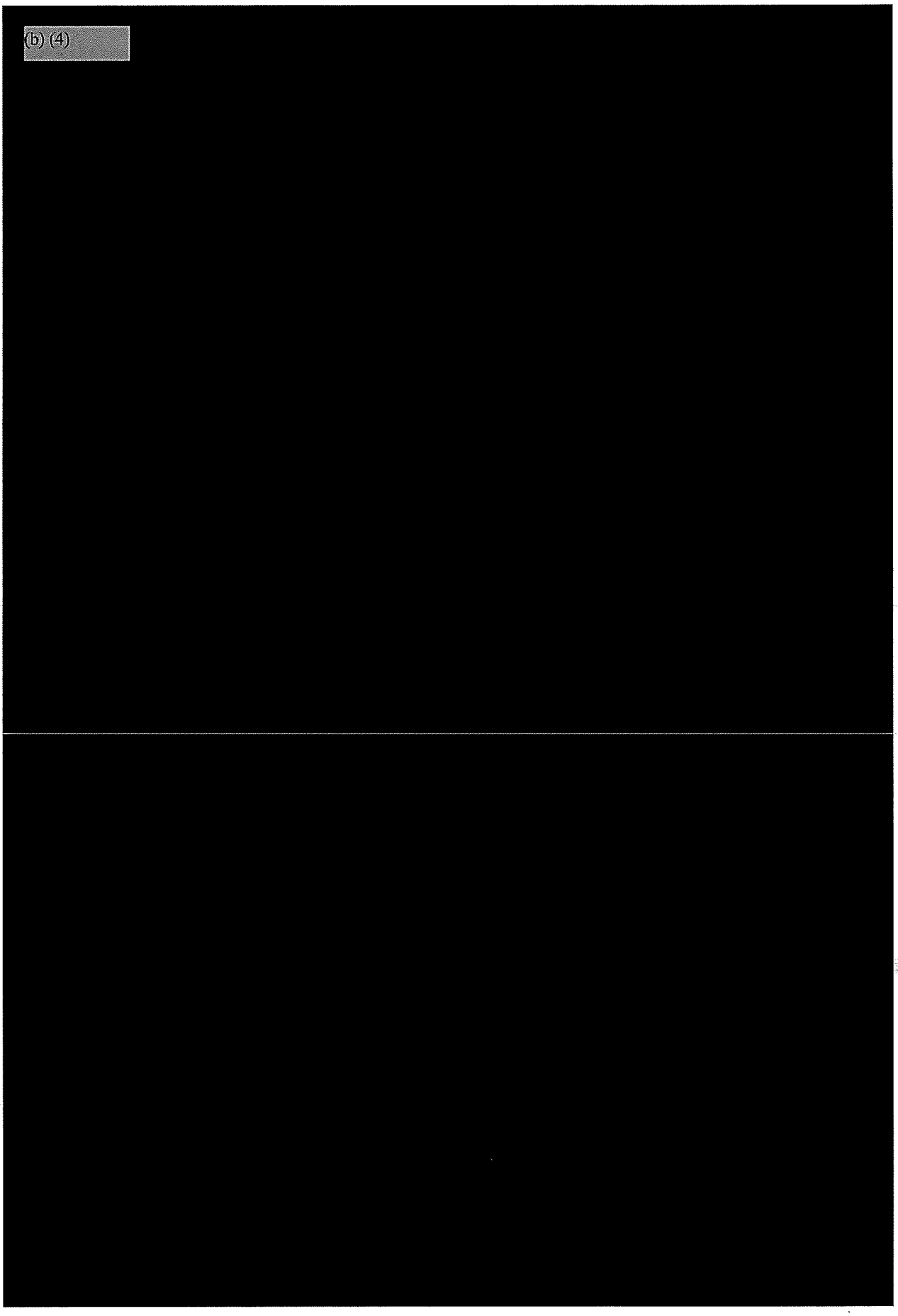

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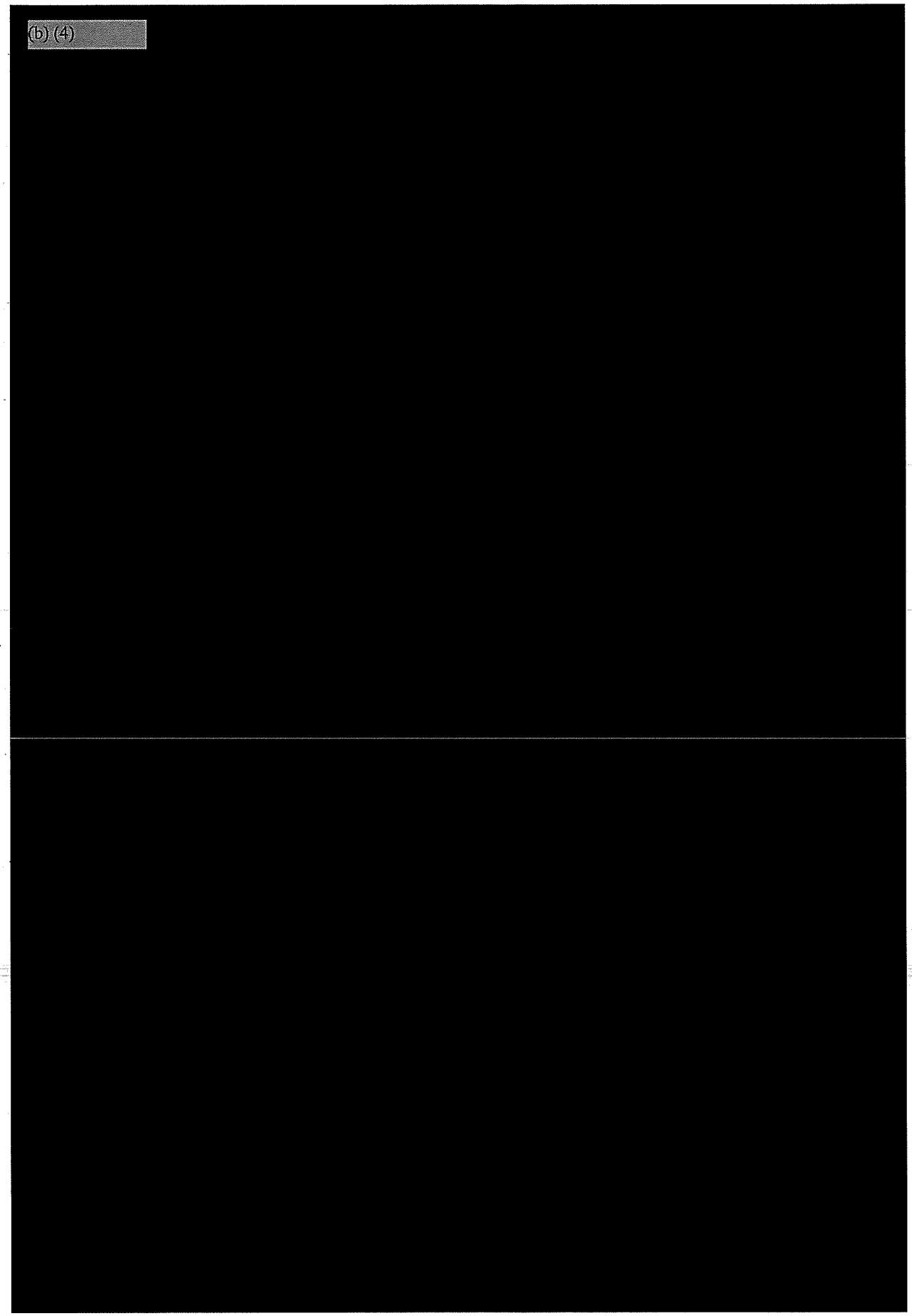

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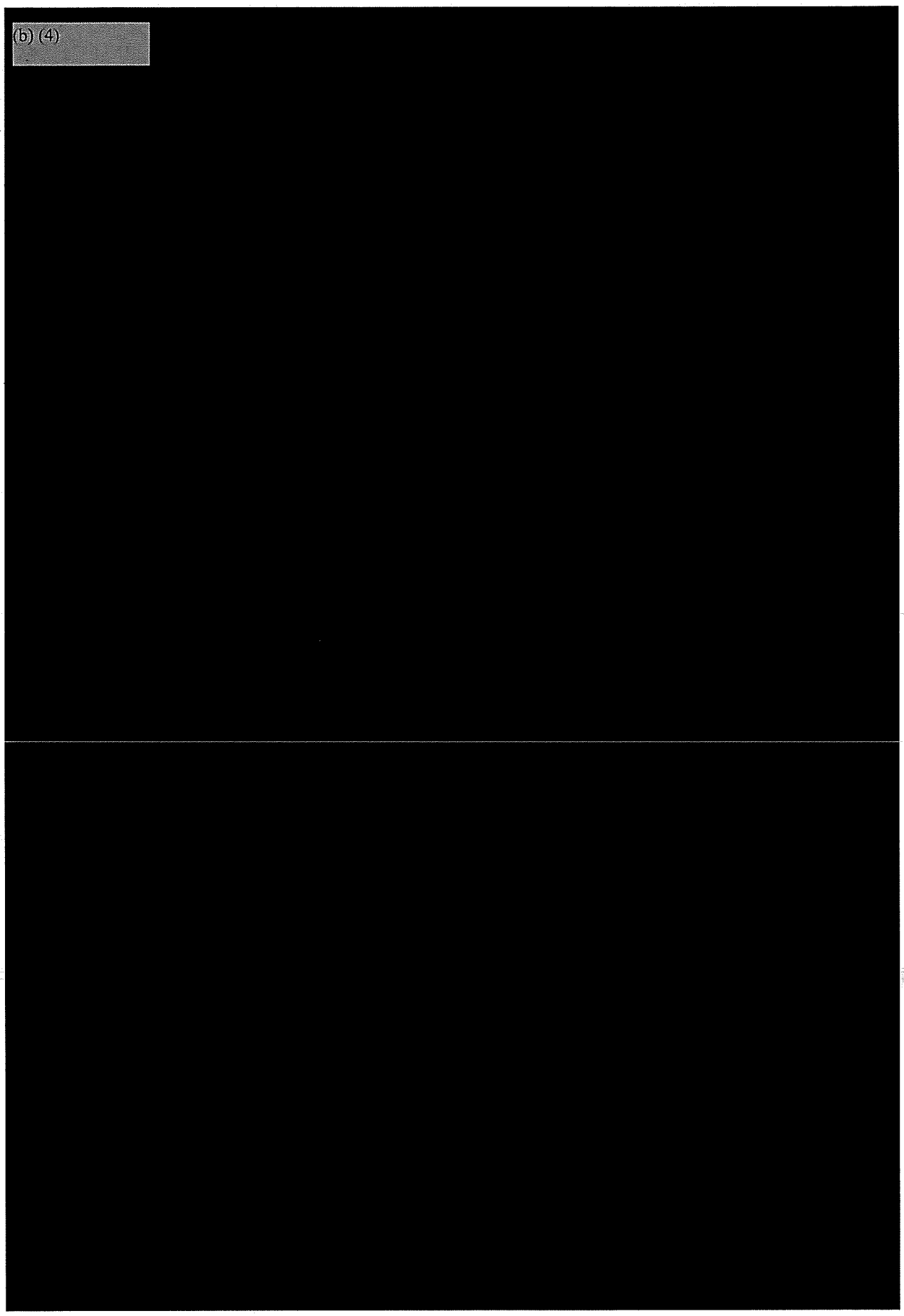

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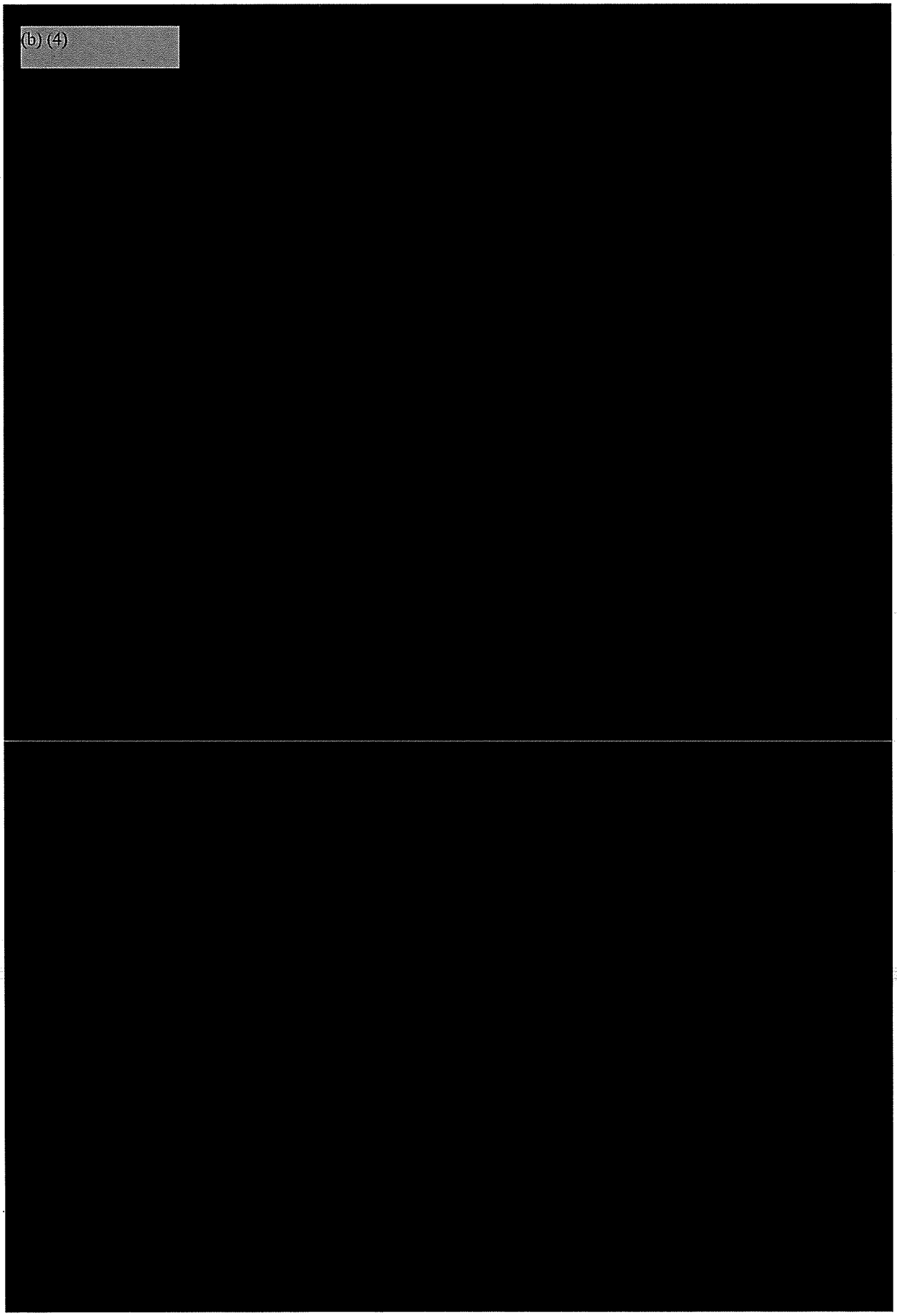

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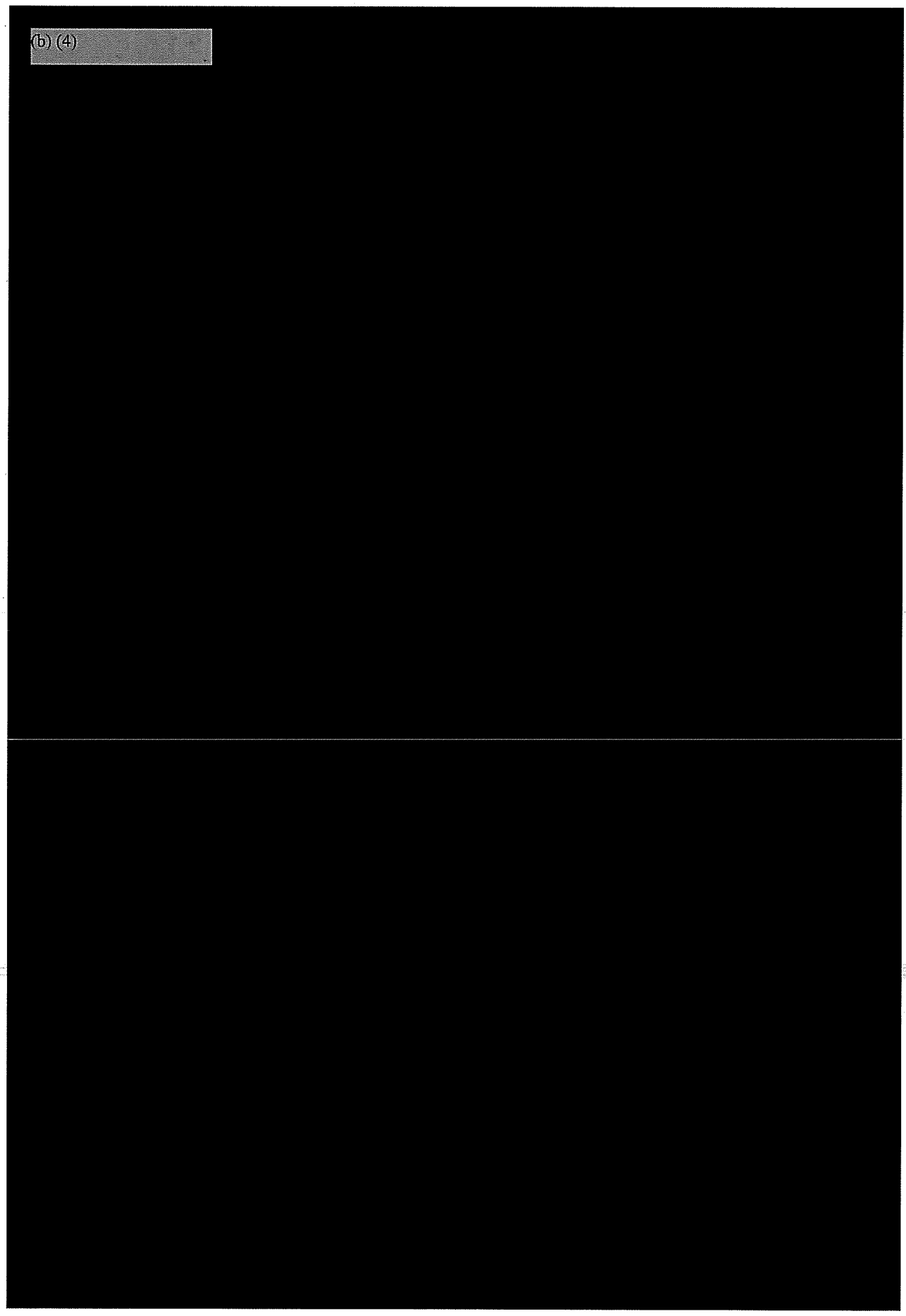

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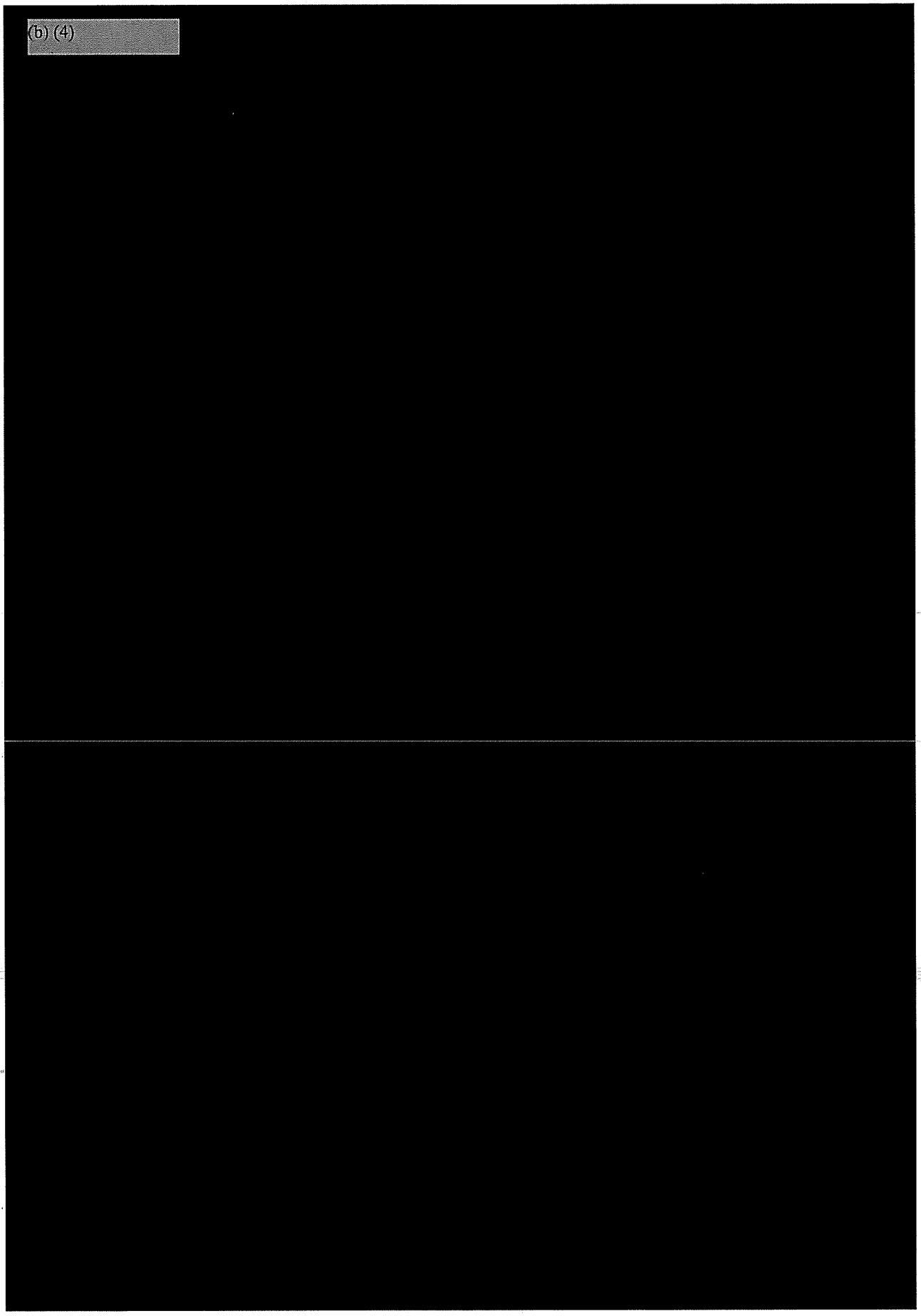

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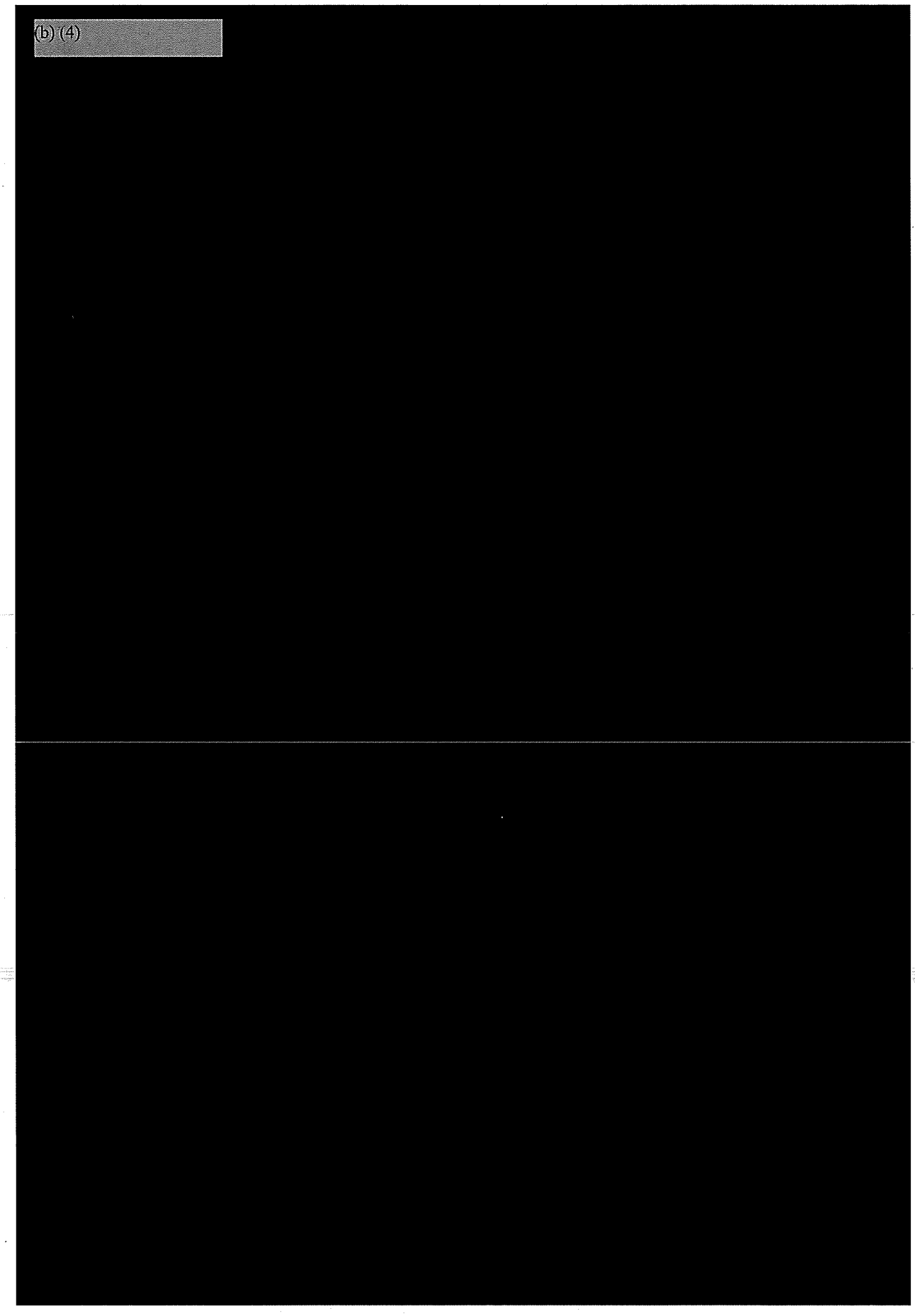

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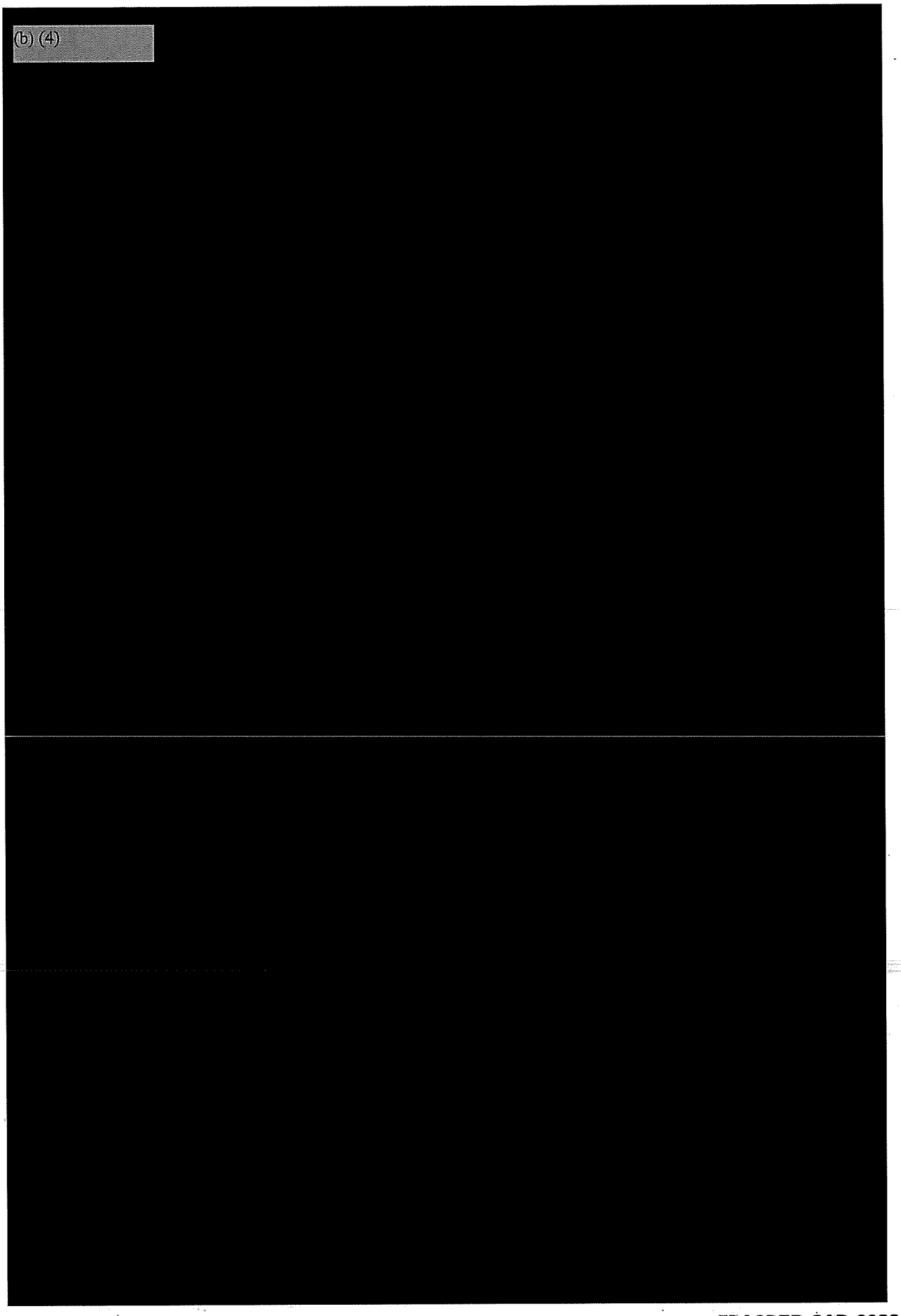

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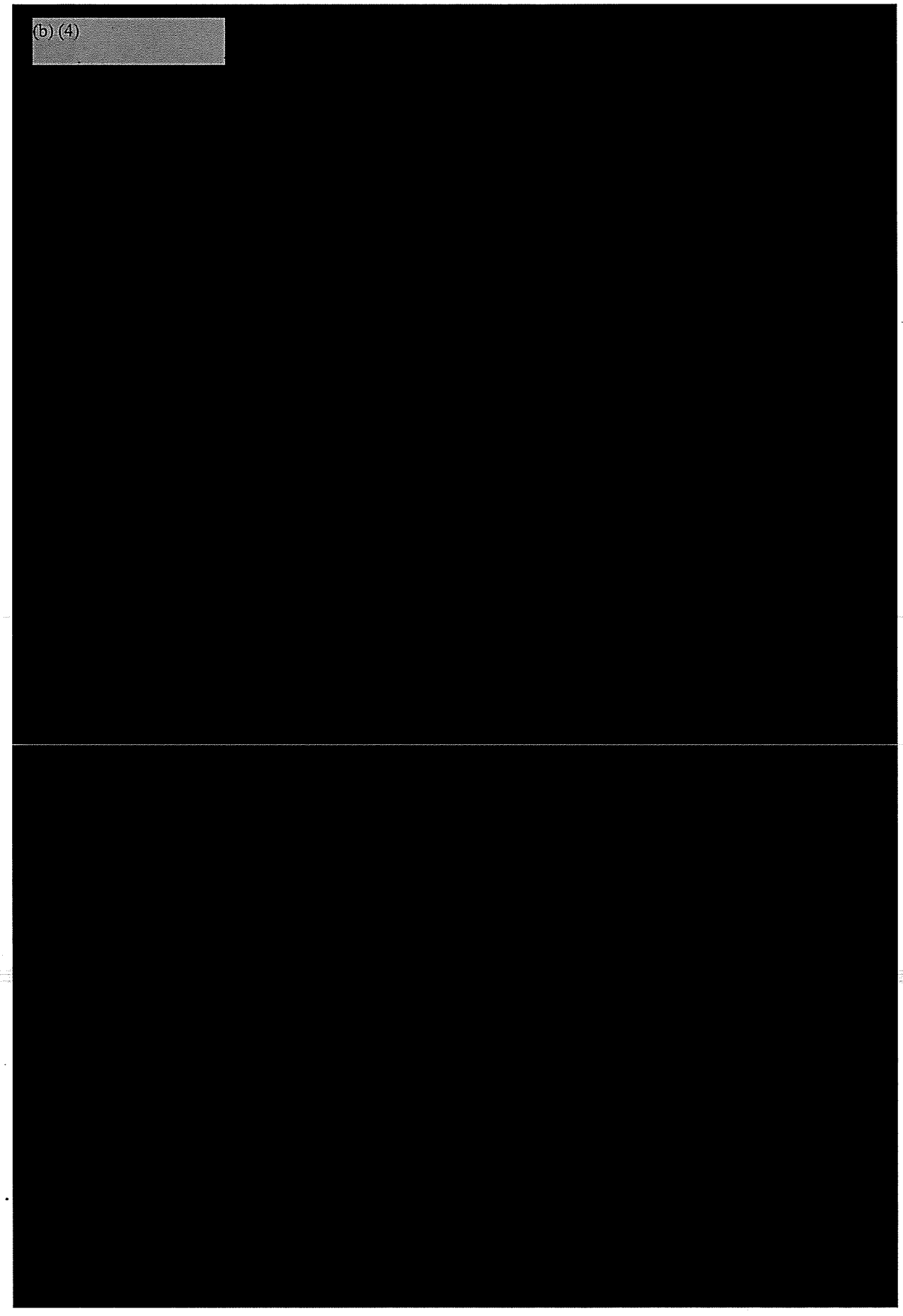

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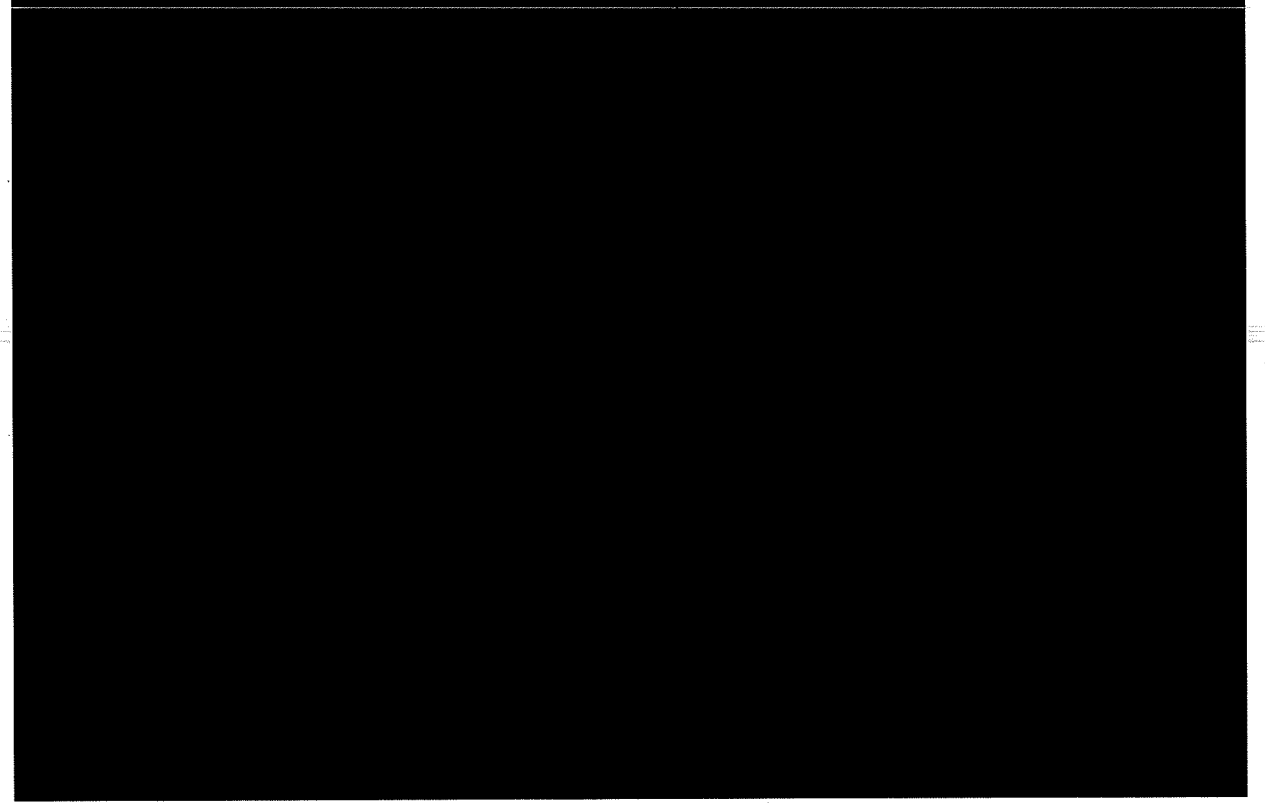

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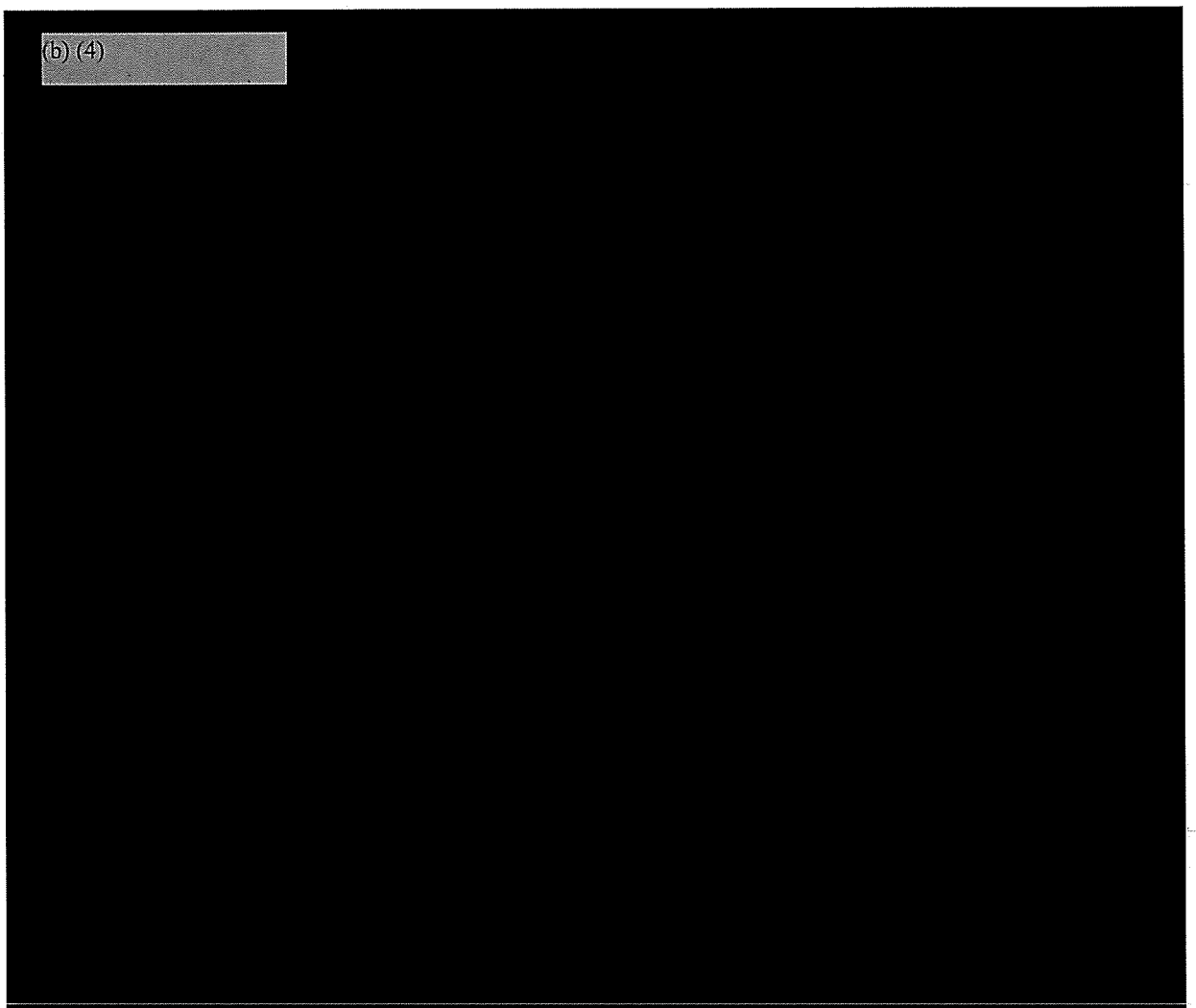

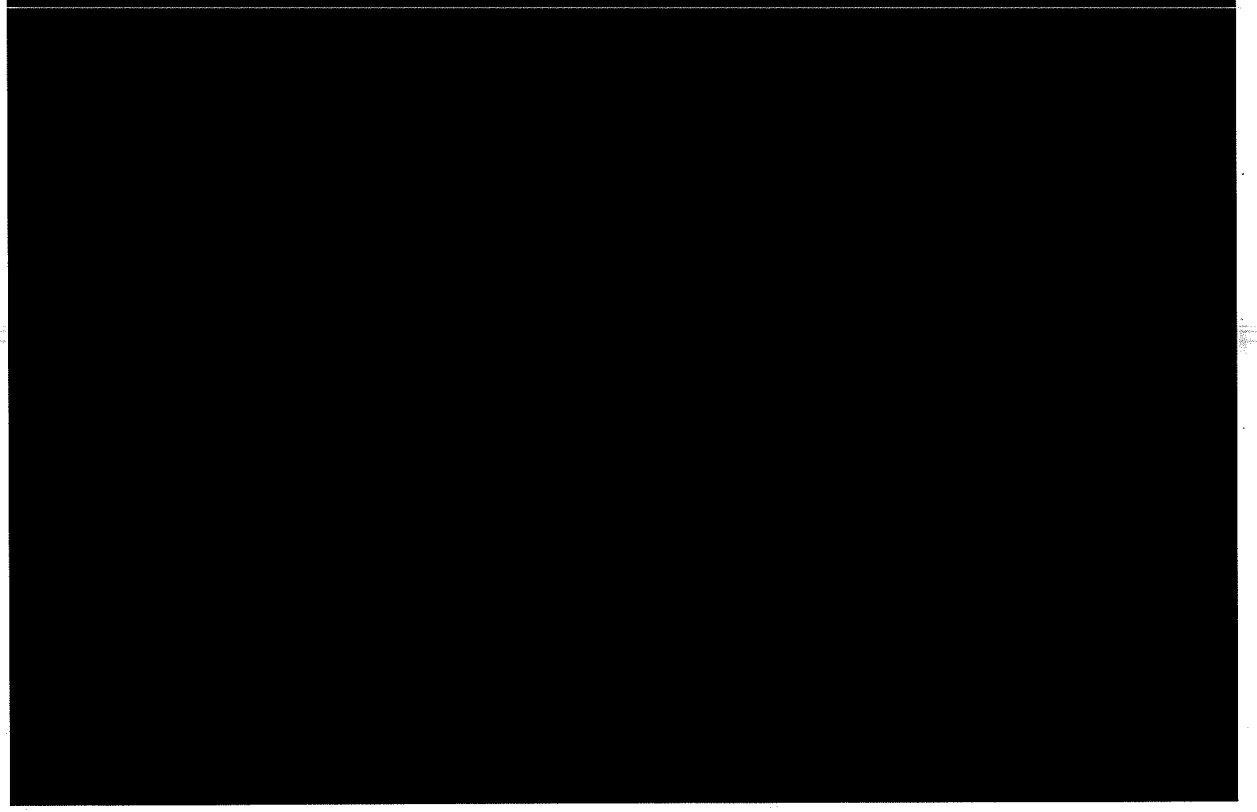

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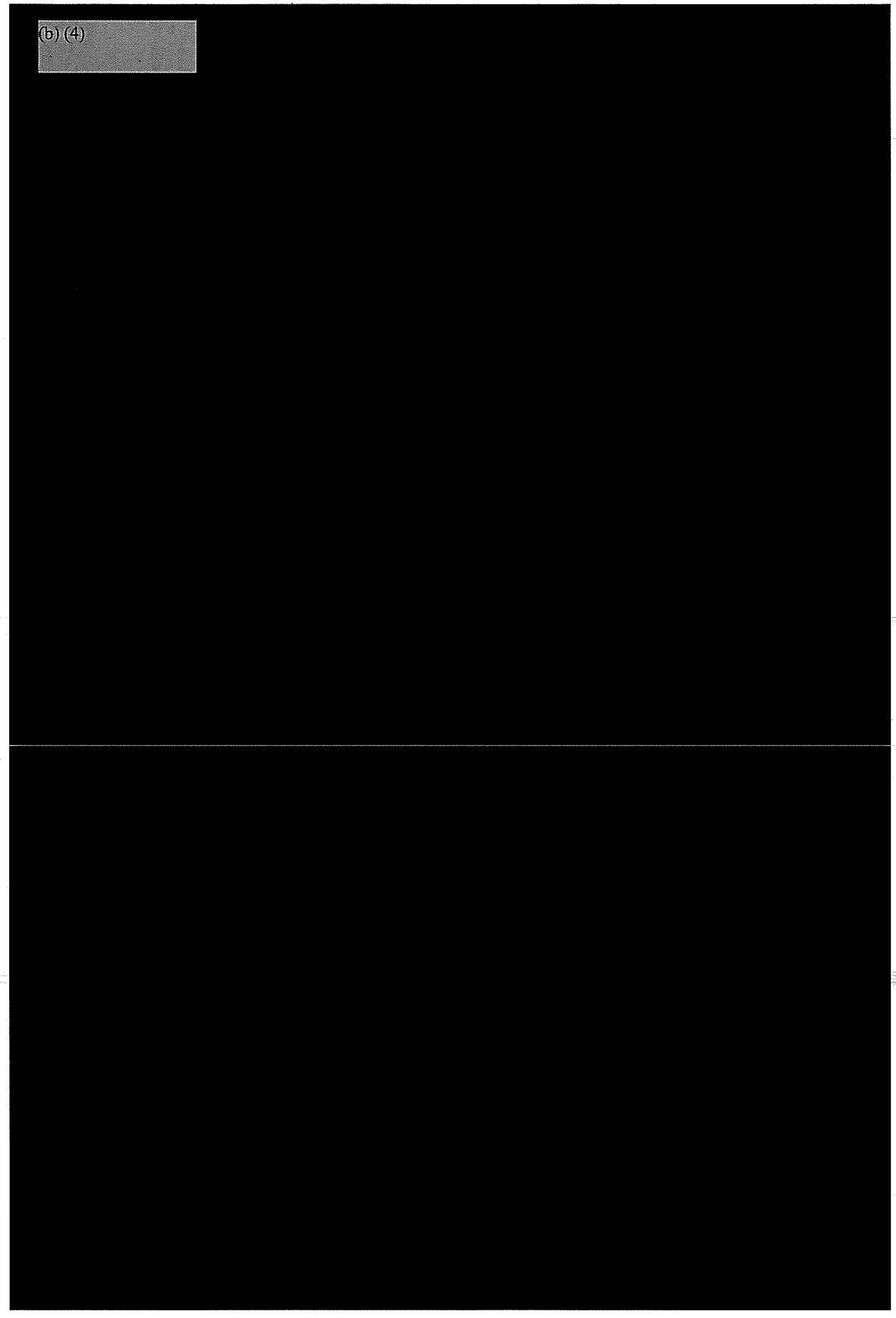

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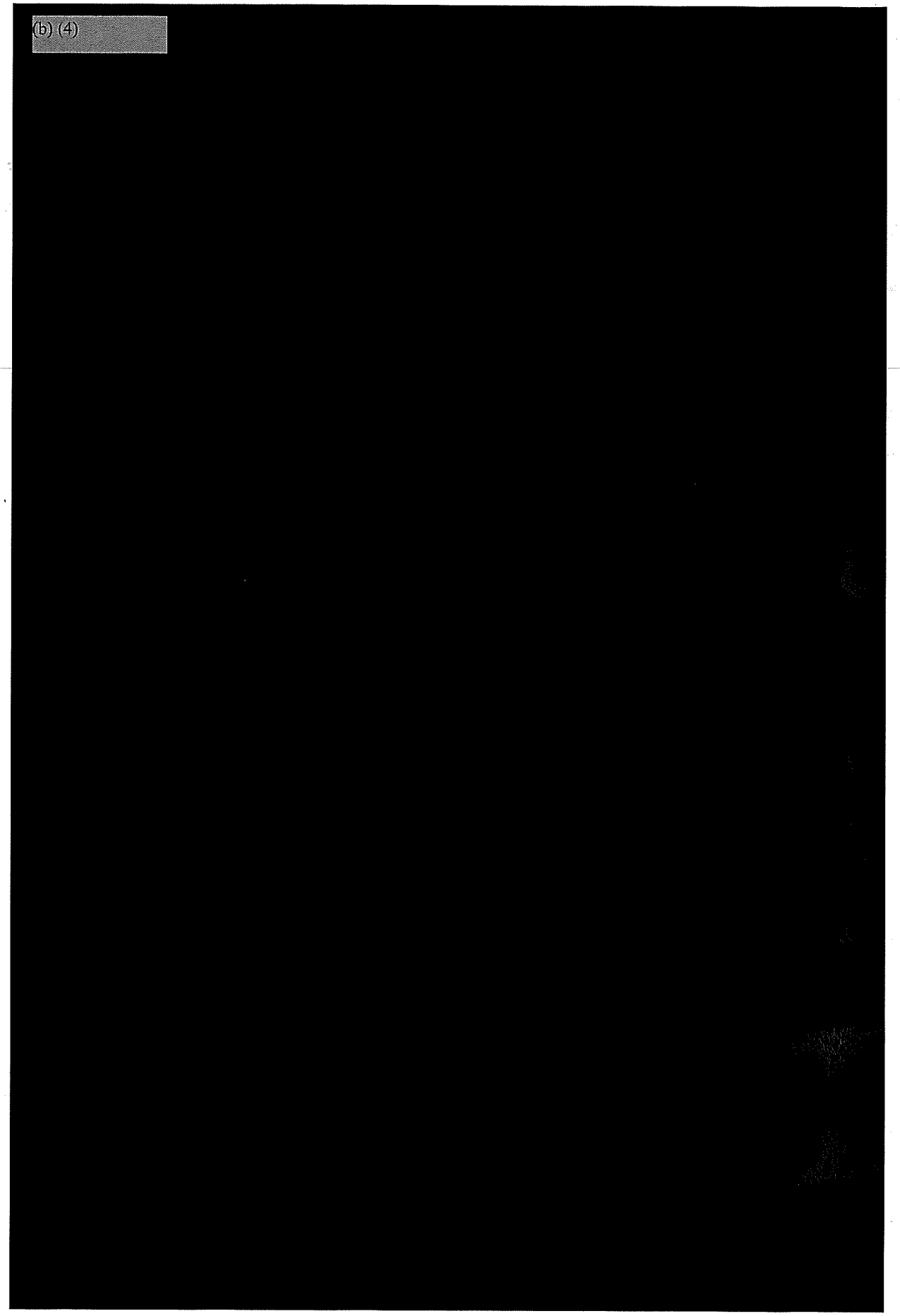

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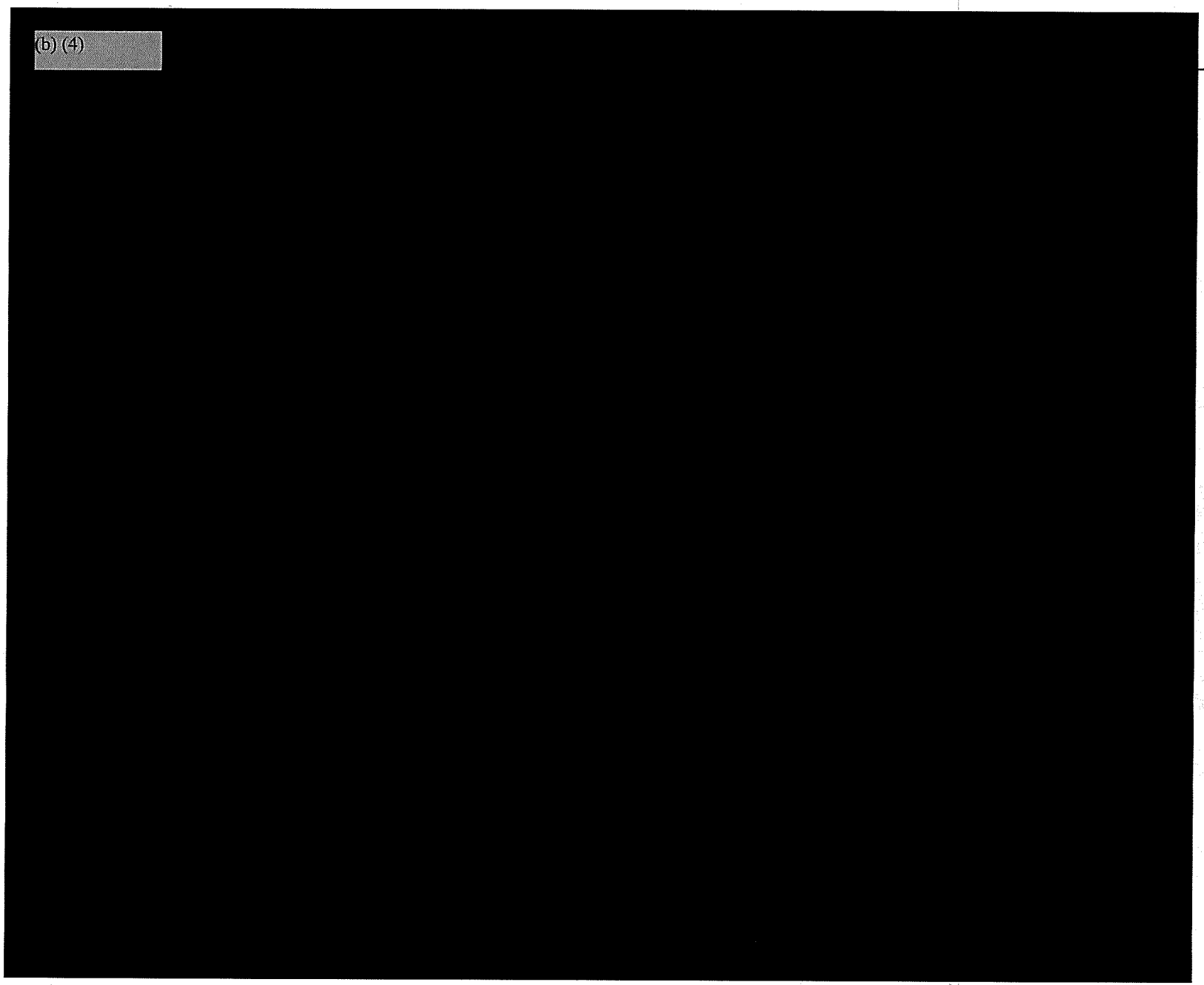
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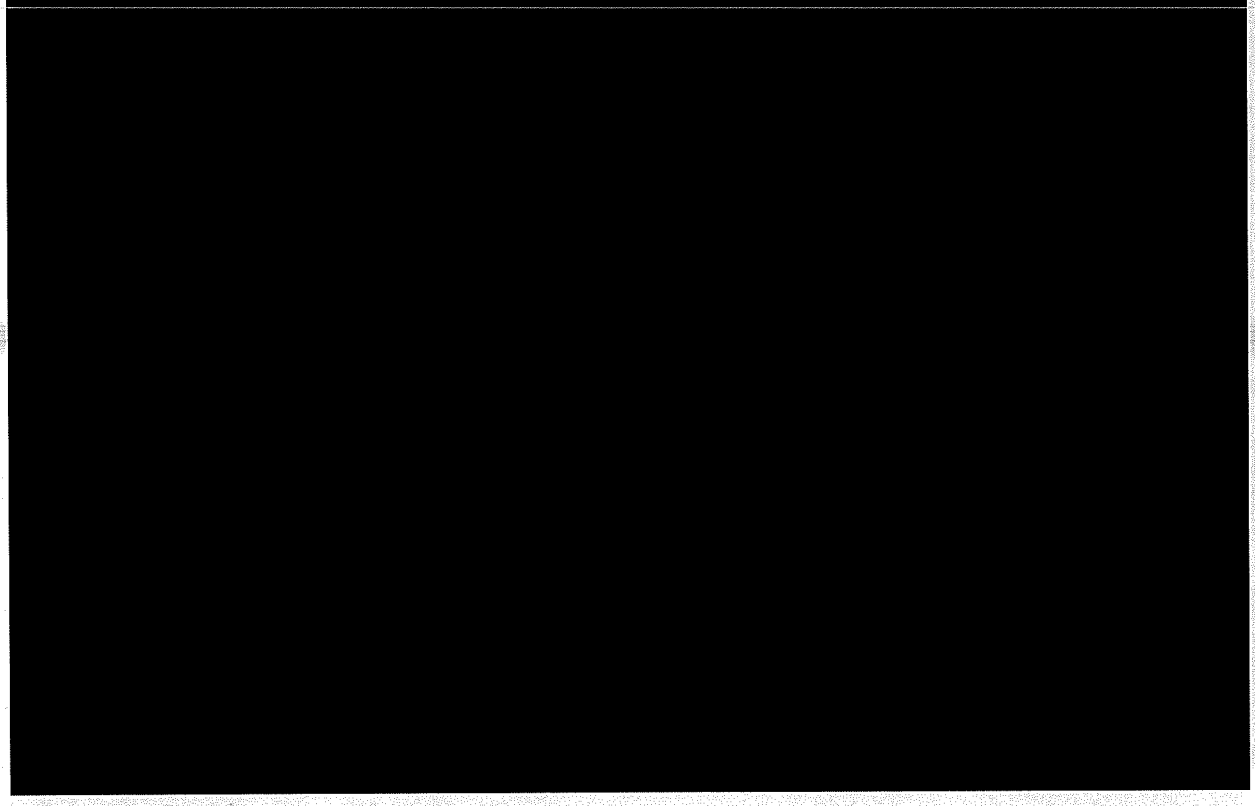

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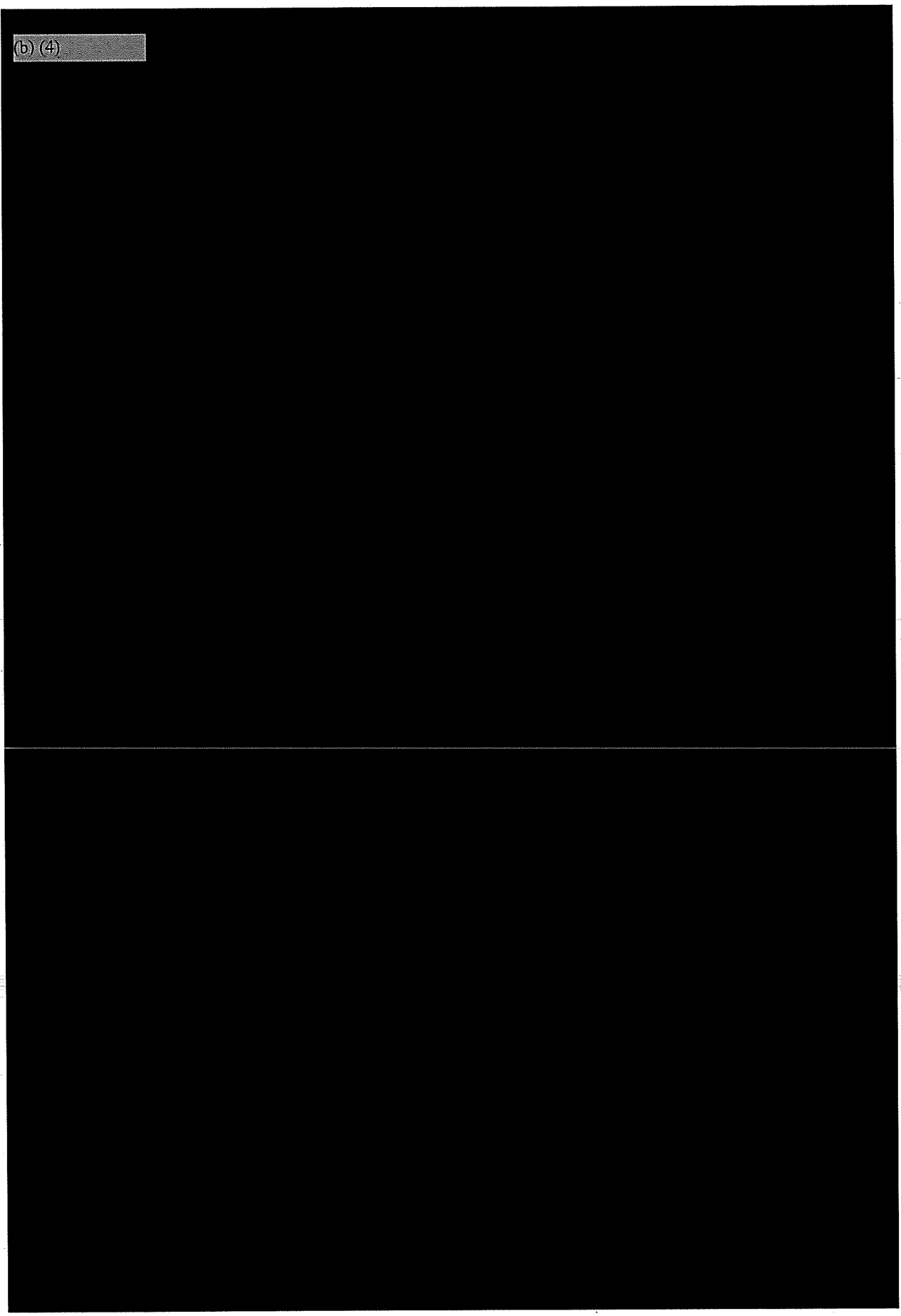

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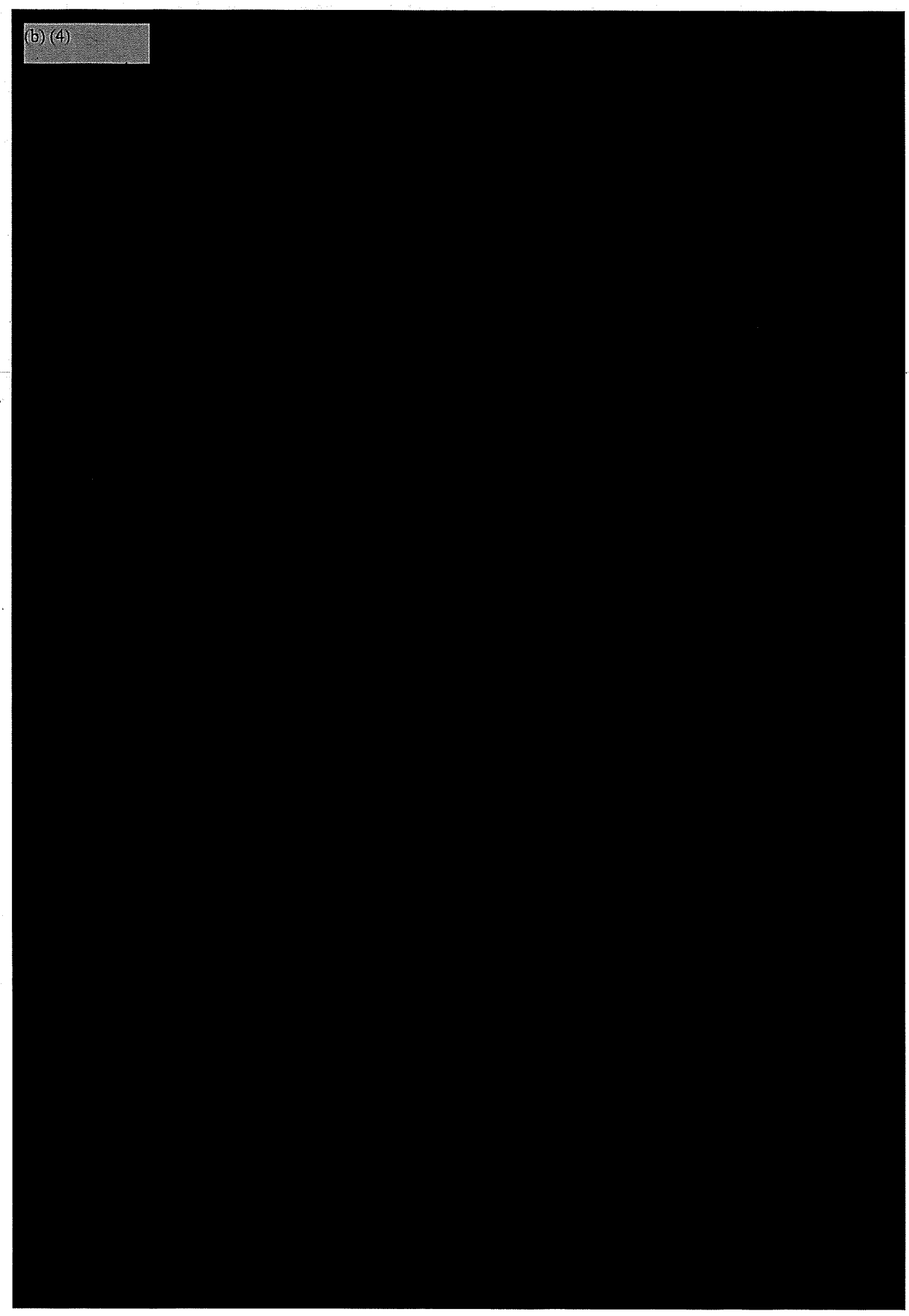

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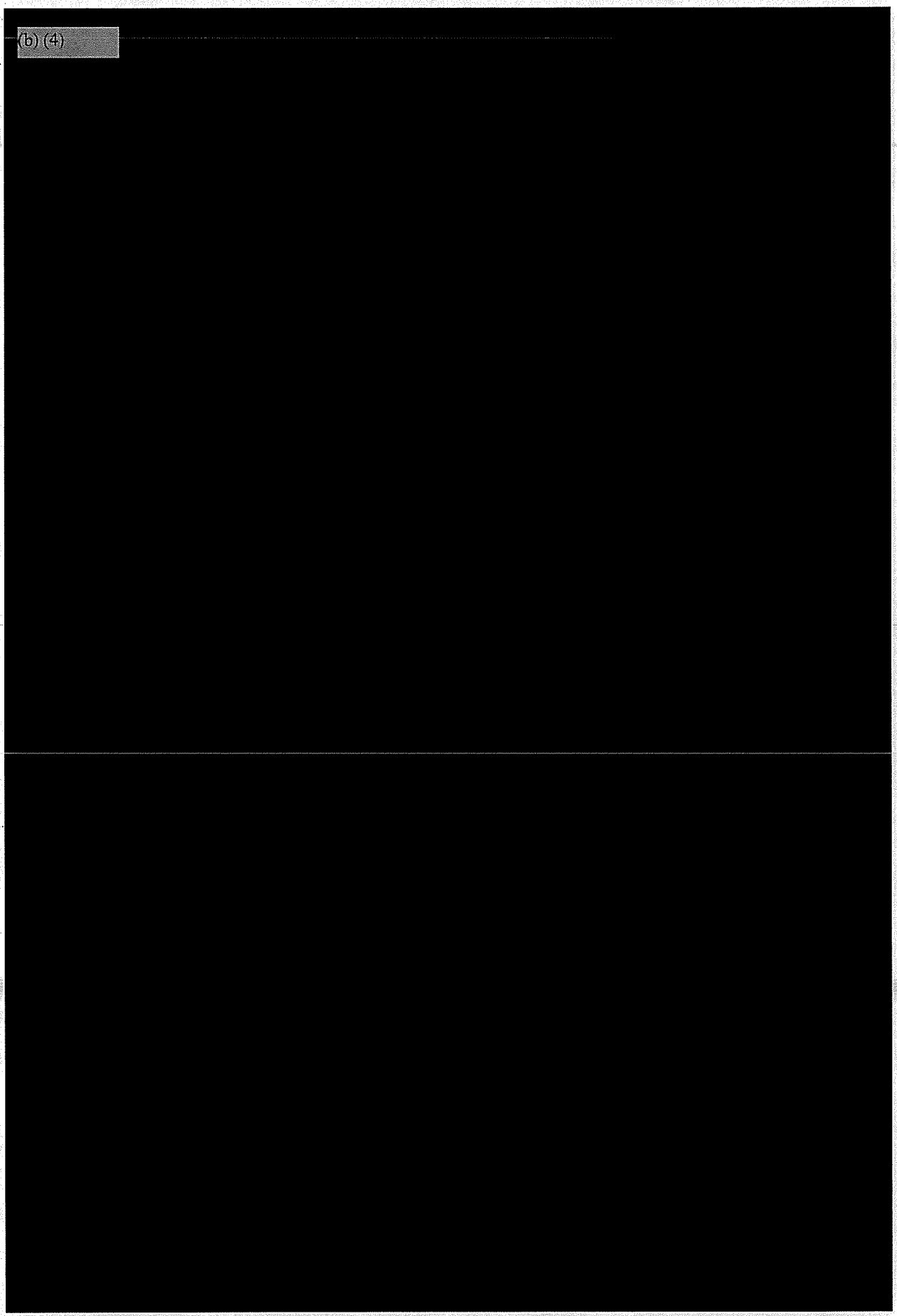

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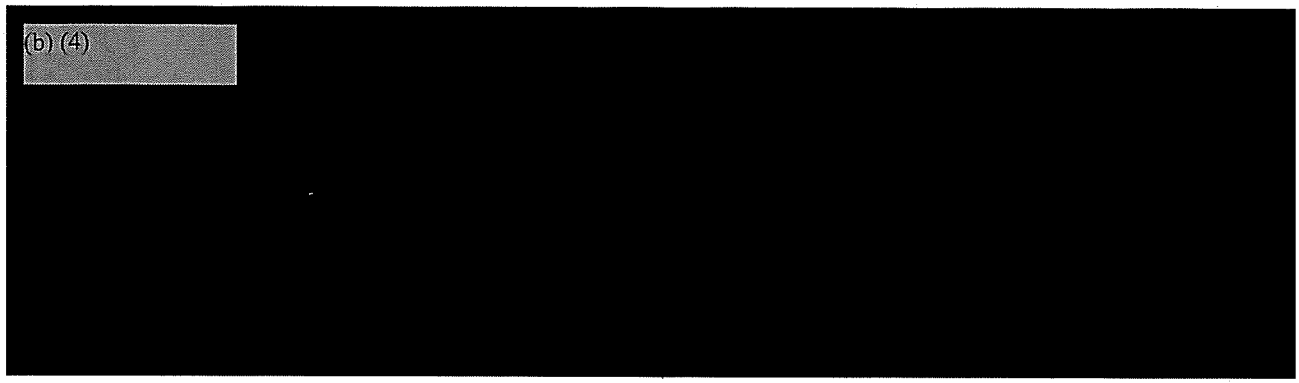
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