Disclaimer

The following report(s) provides findings from an FDA-initiated query using Sentinel. While Sentinel queries may be undertaken to assess potential medical product safety risks, they may also be initiated for various other reasons. Some examples include determining a rate or count of an identified health outcome of interest, examining medical product use, exploring the feasibility of future, more detailed analyses within Sentinel, and seeking to better understand Sentinel capabilities.

Data obtained through Sentinel are intended to complement other types of evidence such as preclinical studies, clinical trials, postmarket studies, and adverse event reports, all of which are used by FDA to inform regulatory decisions regarding medical product safety. The information contained in this report is provided as part of FDA's commitment to place knowledge acquired from Sentinel in the public domain as soon as possible. Any public health actions taken by FDA regarding products involved in Sentinel queries will continue to be communicated through existing channels.

FDA wants to emphasize that the fact that FDA has initiated a query involving a medical product and is reporting findings related to that query does not mean that FDA is suggesting health care practitioners should change their prescribing practices for the medical product or that patients taking the medical product should stop using it. Patients who have questions about the use of an identified medical product should contact their health care practitioners.

The following report contains a description of the request, request specifications, and results from the modular program run(s).

If you are using a web page screen reader and are unable to access this document, please contact the Sentinel Operations Center for assistance at info@sentinelsystem.org.

Sentinel

Overview for Request: cder_mpl1r_wp235

Request ID: cder_mpl1r_wp235

Request Description: In this report we examined counts and follow-up time for individuals with a diagnosis of gender dysphoria in the Merative™ MarketScan® Research Databases. In addition, we examined counts of individuals using Gonadotropin-Releasing Hormone (GnRH) agonists with or without an inclusion requirement for a diagnosis of gender dysphoria before their GnRH agonist exposure.

Sentinel Routine Querying Module: Cohort Identification and Descriptive Analysis (CIDA) module, version 11.4.0

Data Source: We queried the Merative™ MarketScan® Research Databases on October 5, 2022. The study period included data from October 1, 2015 to June 30, 2021. Please see Appendix A for the list of dates of available data for the Merative™ MarketScan® Research Databases.

Study Design: We adopted a retrospective cohort design and respectively identified individuals with a diagnosis of gender dysphoria, users of GnRH agonists, and users of GnRH agonists with a prior diagnosis of gender dysphoria. Results were stratified by sex and year. This is a Type 2 analysis in the Query Request Package (QRP) documentation.

Index Event of Interest: For the first diagnosis cohort, we defined diagnosis of gender dysphoria as the index event of interest, using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes. Only the first qualifying gender dysphoria diagnosis in any care setting for each individual was included; cohort re-entry was not allowed.

For the two GnRH agonist user cohorts, we defined exposure to GnRH agonists as the index event of interest using Healthcare Common Procedure Coding System (HCPCS) procedure codes and National Drug Codes (NDCs). Only the first qualifying GnRH agonist outpatient pharmacy dispensing or professional administration in any care setting for each individual was included; cohort re-entry was not allowed.

Please see Appendix B for the ICD-10-CM diagnosis codes and the HCPCS procedure codes used to define the index events of interest in this request. Please see Appendix C for a list of generic and brand names of medical products used to define index events of interest in this request.

Cohort Eligibility Criteria: We required members to be enrolled in health plans with medical and drug coverage in the 90 days prior to the date of their index event (index date); a gap in coverage of up to 45 days was allowed and treated as continuous enrollment. For each of the three different cohorts, we constructed an overall cohort requiring all included members to be of age 12-20 years on their index date. In addition, we created two other age-specific cohorts: 12-16 and 17-20 years. In one of the two GnRH agonist user cohorts, we required a gender dysphoria diagnosis in the 90 days prior to and including the index date using ICD-10-CM diagnosis codes. Please see Appendix D for the ICD-10-CM diagnosis codes used to define the inclusion criteria in this request.

Follow-up (At-risk) Time: For the GnRH user cohorts, we created the exposure episodes based on the number of days of product supplied either directly recorded in individual outpatient pharmacy dispensings or pre-assigned to each qualifying HCPCS procedure code. Please see Appendix B for the days supply value assigned to each HCPCS code. We bridged together all exposure episodes by specifying a large allowable exposure gap of 3,000 days. Follow-up began on the index date and continued until the first occurrence of the following: 1) disenrollment; 2) death; 3) the end of the data provided by Merative™ MarketScan® Research Databases; 4) the end of the query period; or 5) exposure episode end.

Observable Time: For all cohorts, observable time began on the index date and continued until the first occurrence of the following: 1) disenrollment; 2) death; 3) the end of the data provided by Merative™ MarketScan® Research Databases; or 4) the end of the query period.

Overview for Request: cder_mpl1r_wp235

Baseline Characteristics: For all cohorts, we assessed the following characteristics on the index date: age, sex, race, Hispanic ethnicity, and year of the index event. For the two GnRH agonist user cohorts, we examined the GnRH agonist code type identified on the index date: a GnRH agonist NDC code in outpatient pharmacy dispensings or of professional administrations, as well as a GnRH agonist HCPCS code of professional administrations.

In addition, we assessed the presence of a gender dysphoria diagnosis code, both including and excluding the ICD-10 CM code Z87.890, in the 90 days prior to and including the index date. Lastly, we examined the presence of at least two gender dysphoria diagnosis codes ever in the patient's enrollment history before, on, and after the index date. Please see Appendix E for a list of generic and brand names of medical products used to define the baseline characteristics in this request. Please see Appendix F for the ICD-10-CM diagnosis codes and the HCPCS procedure codes used to define the baseline characteristics in this request.

Most Frequent Utilization: For all cohorts, we analyzed the most frequently reported ICD-10-CM diagnosis codes in any care setting in the 90 days prior to and including the index date. We reported the top twenty ICD-10-CM codes tallied by patient count.

Please see Appendices G, H and I for the specifications of parameters used in this request.

Limitations: Algorithms to define exposures, outcomes, inclusion and exclusion criteria, and covariates are imperfect; thus, it is possible that there may be misclassification. Therefore, data should be interpreted with this limitation in mind.

Notes: Please contact the Sentinel Operations Center (info@sentinelsystem.org) for questions and to provide comments/suggestions for future enhancements to this document. For more information on Sentinel's routine querying modules, please refer to the documentation (https://dev.sentinelsystem.org/projects/SENTINEL/repos/sentinel-routine-querying-tool-documentation/browse).

Sentinel

Table of Contents

Sentinel

Table of Contents

Sentinel

Glossary of Terms for Analyses Using Cohort Identification and Descriptive Analysis (CIDA) Module*

The following report(s) provides findings from an FDA-initiated query using Sentinel. While Sentinel queries may be undertaken to assess potential medical product safety risks, they may also be initiated for various other reasons. Some examples include determining a rate or count of an identified health outcome of interest, examining medical product use, exploring the feasibility of future, more detailed analyses within Sentinel, and seeking to better understand Sentinel capabilities.

Blackout Period - number of days at the beginning of a treatment episode that events are to be ignored. If an event occurs during the blackout period, the episode is excluded.

Care Setting - type of medical encounter or facility where the exposure, event, or condition code was recorded. Possible care settings include: Inpatient Hospital Stay (IP), Non-Acute Institutional Stay (IS), Emergency Department (ED), Ambulatory Visit (AV), and Other Ambulatory Visit (OA). For laboratory results, possible care settings include: Emergency Department (E), Home (H), Inpatient (I), Outpatient (O), or Unknown or Missing (U). The Care Setting, along with the Principal Diagnosis Indicator (PDX), forms the Care Setting/PDX parameter.

- **Ambulatory Visit (AV)** - includes visits at outpatient clinics, same-day surgeries, urgent care visits, and other same-day ambulatory hospital encounters, but excludes emergency department encounters.
- **Emergency Department (ED)** - includes ED encounters that become inpatient stays (in which case inpatient stays would be a separate encounter). Excludes urgent care visits.
- **Inpatient Hospital Stay (IP)** - includes all inpatient stays, same-day hospital discharges, hospital transfers, and acute hospital care where the discharge is after the admission date.
- **Non-Acute Institutional Stay (IS)** - includes hospice, skilled nursing facility (SNF), rehab center, nursing home, residential, overnight non-hospital dialysis and other non-hospital stays.
- **Other Ambulatory Visit (OA)** - includes other non overnight AV encounters such as hospice visits, home health visits, skilled nursing facility visits, other non-hospital visits, as well as telemedicine, telephone and email consultations.

Charlson/Elixhauser Combined Comorbidity Score - calculated based on comorbidities observed during a requester-defined window around the exposure episode start date (e.g., in the 183 days prior to index).

Code Days - the minimum number of times the diagnosis must be found during the evaluation period in order to fulfill the algorithm to identify the corresponding patient characteristic.

Cohort Definition (drug/exposure) - indicates how the cohort will be defined: 01: Cohort includes only the first valid treatment episode during the query period; 02: Cohort includes all valid treatment episodes during the query period; 03: Cohort includes all valid treatment episodes during the query period until an event occurs.

Computed Start Marketing Date - represents the first observed dispensing date among all valid users within a GROUP (scenario) within each Data Partner site.

Days Supplied - number of days supplied for all dispensings in qualifying treatment episodes.

Eligible Members - number of members eligible for an incident treatment episode (defined by the drug/exposure and event washout periods) with drug and medical coverage during the query period.

Enrollment Gap - number of days allowed between two consecutive enrollment periods without breaking a "continuously enrolled" sequence.

Episodes - treatment episodes; length of episode is determined by days supplied in one dispensing or consecutive dispensings bridged by the episode gap.

Episode Gap - number of days allowed between two (or more) consecutive exposures (dispensings/procedures) to be considered the same treatment episode.

Event Deduplication - specifies how events are counted by the Modular Program (MP) algorithm: 0: Counts all occurrences of a health outcome of interest (HOI) during an exposure episode; 1: de-duplicates occurrences of the same HOI code and code type on the same day; 2: de-duplicates occurrences of the same HOI group on the same day (e.g., de-duplicates at the group level).

Exposure Episode Length - number of days after exposure initiation that is considered "exposed time."

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a treatment episode. Extensions are added after any episode gaps have been bridged.

Lookback Period - number of days wherein a member is required to have evidence of pre-existing condition (diagnosis/procedure/drug dispensing).

Maximum Episode Duration - truncates exposure episodes after a requester-specified number of exposed days. Applied after any gaps are bridged and extension days added to the length of the exposure episode.
Member-Years - sum of all days of enrollment with medical and drug coverage in the query period preceded by an exposure washout period all divided by 365.25.
Minimum Days Supplied - specifies a minimum number of days in length of the days supplied for the episode to be considered.
Minimum Episode Duration - specifies a minimum number of days in length of the episode for it to be considered. Applied after any gaps are bridged and extension days added to the length of the exposure episode.
Monitoring Period - used to define time periods of interest for both sequential analysis and simple cohort characterization requests.
Principal Diagnosis (PDX) - diagnosis or condition established to be chiefly responsible for admission of the patient to the hospital. 'P' = principal diagnosis, 'S' = secondary diagnosis, 'X' = unspecified diagnosis, '.' = blank. Along with the Care Setting values, forms the Caresetting/PDX parameter.
Query Period - period in which the modular program looks for exposures and outcomes of interest.
Switch Evaluation Step Value - value used to differentiate evaluation step. Each switch pattern can support up to 2 evaluation steps (0 = switch pattern evaluation start; 1 = first evaluation; 2 = second evaluation).
Switch Gap Inclusion Indicator - indicator for whether gaps in treatment episodes that are included in a switch episode will be counted as part of the switch episode duration.
Switch Pattern Cohort Inclusion Date - indicates which date to use for inclusion into the switch pattern cohort of interest as well as optionally as the index date of the treatment episode initiating the switch pattern. Valid options are the product approval date, product marketing date, other requester defined date, or computed start marketing date.
Switch Pattern Cohort Inclusion Strategy - indicates how the switch pattern cohort inclusion date will be used: 01: used only as a switch cohort entry date. First treatment episode dispensing date is used as index for computing time to first switch; 02: used as switch cohort entry date and as initial switch step index date for computing time to first switch.
Treatment Episode Truncation Indicator - indicates whether the exposure episode will be truncated at the occurrence of a requester-specified code.
Washout Period (drug/exposure) - number of days a user is required to have no evidence of prior exposure (drug dispensing/procedure) and continuous drug and medical coverage prior to an incident treatment episode.
Washout Period (event/outcome) - number of days a user is required to have no evidence of a prior event (procedure/diagnosis) and continuous drug and medical coverage prior to an incident treatment episode.
Years at Risk - number of days supplied plus any episode gaps and exposure extension periods all divided by 365.25.

*all terms may not be used in this report

Table 1a. Characteristics of Individuals Diagnosed with Gender Dysphoria 12-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Patient Characteristics	Number	
Unique patients	19,332	
Demographic Characteristics	**Mean**	**Standard Deviation**
Mean Age (Years)	16.9	2.4
Age (Years)	**Number**	**Percent**
12-16	9,900	51.2%
17-20	9,432	48.8%
Sex		
Female	13,361	69.1%
Male	5,971	30.9%
Other	0	0.0%
Race[1]		
American Indian or Alaska Native	-	-
Asian	-	-
Black or African American	-	-
Multi-racial	-	-
Native Hawaiian or Other Pacific Islander	-	-
Unknown	19,332	100.0%
White	-	-
Hispanic origin[1]		
Yes	-	-
No	-	-
Unknown	19,332	100.0%
Year		
2015	966	5.0%
2016	2,041	10.6%
2017	2,580	13.3%
2018	3,138	16.2%
2019	3,510	18.2%
2020	4,168	21.6%
2021	2,929	15.2%

[1]Data not available in Merative™ MarketScan® Research Databases.

Table 1b. Characteristics of Users of Gonadotropin-Releasing Hormone (GnRH) Agonists 12-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Patient Characteristics	Number	
Unique patients	1,700	
Demographic Characteristics	**Mean**	**Standard Deviation**
Mean Age (Years)	16.2	2.6
Age (Years)	**Number**	**Percent**
12-16	1,028	60.5%
17-20	672	39.5%
Sex		
Female	1,186	69.8%
Male	514	30.2%
Other	0	0.0%
Race[1]		
American Indian or Alaska Native	.	.
Asian	.	.
Black or African American	.	.
Multi-racial	.	.
Native Hawaiian or Other Pacific Islander	.	.
Unknown	1,700	100.0%
White	.	.
Hispanic origin[1]		
Yes	.	.
No	.	.
Unknown	1,700	100.0%
Year		
2015	65	3.8%
2016	304	17.9%
2017	306	18.0%
2018	278	16.4%
2019	289	17.0%
2020	291	17.1%
2021	167	9.8%
Health Characteristics on the Index Date	**Number**	**Percent**
GnRH agonist use identified via National Drug Codes in outpatient pharmacy dispensings	919	54.1%
GnRH agonist use identified via National Drug Codes in professional administration procedures	0	0.0%
GnRH agonist use identified via Healthcare Common Procedure Coding System (HCPCS) code in professional administration procedures	781	45.9%
Health Characteristics in the 90 days Prior to and Including the Index Date	**Number**	**Percent**
Gender Dysphoria diagnosis	710	41.8%
Gender Dysphoria diagnosis (excluding Z87.890)	708	41.6%
Health Characteristics throughout Enrollment History (before, on, or after the Index Date)	**Number**	**Percent**
Gender Dysphoria diagnosis, 2 or more, on separate days	754	44.4%

[1]Data not available in Merative™ MarketScan® Research Databases.

Table 1c. Characteristics of Users of Gonadotropin-Releasing Hormone (GnRH) Agonists Diagnosed with Gender Dysphoria 12-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Patient Characteristics	Number	
Unique patients	710	
Demographic Characteristics	**Mean**	**Standard Deviation**
Mean Age (Years)	15.0	2.0
Age (Years)	**Number**	**Percent**
12-16	580	81.7%
17-20	130	18.3%
Sex		
Female	381	53.7%
Male	329	46.3%
Other	0	0.0%
Race[1]		
American Indian or Alaska Native	.	.
Asian	.	.
Black or African American	.	.
Multi-racial	.	.
Native Hawaiian or Other Pacific Islander	.	.
Unknown	710	100.0%
White	.	.
Hispanic origin[1]		
Yes	.	.
No	.	.
Unknown	710	100.0%
Year		
2015	15	2.1%
2016	77	10.8%
2017	100	14.1%
2018	107	15.1%
2019	143	20.1%
2020	161	22.7%
2021	107	15.1%
Health Characteristics on the Index Date	**Number**	**Percent**
GnRH agonist use identified via National Drug Codes in outpatient pharmacy dispensings	426	60.0%
GnRH agonist use identified via National Drug Codes in professional administration procedures	0	0.0%
GnRH agonist use identified via Healthcare Common Procedure Coding System (HCPCS) code in professional administration procedures	284	40.0%
Health Characteristics in the 90 days Prior to and Including the Index Date	**Number**	**Percent**
Gender Dysphoria diagnosis	710	100.0%
Gender Dysphoria diagnosis (excluding Z87.890)	708	99.7%
Health Characteristics throughout Enrollment History (before, on, or after the Index Date)	**Number**	**Percent**
Gender Dysphoria diagnosis, 2 or more, on separate days	696	98.0%

[1]Data not available in Merative™ MarketScan® Research Databases.

Table 1d. Characteristics of Individuals Diagnosed with Gender Dysphoria 12-16 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Patient Characteristics	Number	
Unique patients	9,900	
Demographic Characteristics	**Mean**	**Standard Deviation**
Mean Age (Years)	14.8	1.4
Age (Years)	**Number**	**Percent**
12-16	9,900	100.0%
Sex		
Female	7,627	77.0%
Male	2,273	23.0%
Other	0	0.0%
Race[1]		
American Indian or Alaska Native	.	.
Asian	.	.
Black or African American	.	.
Multi-racial	.	.
Native Hawaiian or Other Pacific Islander	.	.
Unknown	9,900	100.0%
White	.	.
Hispanic origin[1]		
Yes	.	.
No	.	.
Unknown	9,900	100.0%
Year		
2015	446	4.5%
2016	996	10.1%
2017	1,249	12.6%
2018	1,579	15.9%
2019	1,733	17.5%
2020	2,216	22.4%
2021	1,681	17.0%

[1]Data not available in Merative™ MarketScan® Research Databases.

Table 1e. Characteristics of Users of Gonadotropin-Releasing Hormone (GnRH) Agonists 12-16 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Patient Characteristics	Number	
Unique patients	1,028	
Demographic Characteristics	**Mean**	**Standard Deviation**
Mean Age (Years)	14.4	1.4
Age (Years)	**Number**	**Percent**
12-16	1,028	100.0%
Sex		
Female	612	59.5%
Male	416	40.5%
Other	0	0.0%
Race[1]		
American Indian or Alaska Native	.	.
Asian	.	.
Black or African American	.	.
Multi-racial	.	.
Native Hawaiian or Other Pacific Islander	.	.
Unknown	1,028	100.0%
White	.	.
Hispanic origin[1]		
Yes	.	.
No	.	.
Unknown	1,028	100.0%
Year		
2015	32	3.1%
2016	154	15.0%
2017	172	16.7%
2018	147	14.3%
2019	195	19.0%
2020	206	20.0%
2021	122	11.9%
Health Characteristics on the Index Date	**Number**	**Percent**
GnRH agonist use identified via National Drug Codes in outpatient pharmacy dispensings	549	53.4%
GnRH agonist use identified via National Drug Codes in professional administration procedures	0	0.0%
GnRH agonist use identified via Healthcare Common Procedure Coding System (HCPCS) code in professional administration procedures	479	46.6%
Health Characteristics in the 90 days Prior to and Including the Index Date	**Number**	**Percent**
Gender Dysphoria diagnosis	580	56.4%
Gender Dysphoria diagnosis (excluding Z87.890)	578	56.2%
Health Characteristics throughout Enrollment History (before, on, or after the Index Date)	**Number**	**Percent**
Gender Dysphoria diagnosis, 2 or more, on separate days	616	59.9%

[1]Data not available in Merative™ MarketScan® Research Databases.

Sentinel

Table 1f. Characteristics of Users of Gonadotropin-Releasing Hormone (GnRH) Agonists Diagnosed with Gender Dysphoria 12-16 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Patient Characteristics	Number	
Unique patients	580	
Demographic Characteristics	**Mean**	**Standard Deviation**
Mean Age (Years)	14.3	1.4
Age (Years)	**Number**	**Percent**
12-16	580	100.0%
Sex		
Female	329	56.7%
Male	251	43.3%
Other	0	0.0%
Race[1]		
American Indian or Alaska Native	.	.
Asian	.	.
Black or African American	.	.
Multi-racial	.	.
Native Hawaiian or Other Pacific Islander	.	.
Unknown	580	100.0%
White	.	.
Hispanic origin[1]		
Yes	.	.
No	.	.
Unknown	580	100.0%
Year		
2015	13	2.2%
2016	63	10.9%
2017	81	14.0%
2018	81	14.0%
2019	118	20.3%
2020	134	23.1%
2021	90	15.5%
Health Characteristics on the Index Date	**Number**	**Percent**
GnRH agonist use identified via National Drug Codes in outpatient pharmacy dispensings	357	61.6%
GnRH agonist use identified via National Drug Codes in professional administration procedures	0	0.0%
GnRH agonist use identified via Healthcare Common Procedure Coding System (HCPCS) code in professional administration procedures	223	38.4%
Health Characteristics in the 90 days Prior to and Including the Index Date	**Number**	**Percent**
Gender Dysphoria diagnosis	580	100.0%
Gender Dysphoria diagnosis (excluding Z87.890)	578	99.7%
Health Characteristics throughout Enrollment History (before, on, or after the Index Date)	**Number**	**Percent**
Gender Dysphoria diagnosis, 2 or more, on separate days	568	97.9%

[1]Data not available in Merative™ MarketScan® Research Databases.

Table 1g. Characteristics of Individuals Diagnosed with Gender Dysphoria 17-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Patient Characteristics	Number	
Unique patients	11,667	
Demographic Characteristics	**Mean**	**Standard Deviation**
Mean Age (Years)	18.7	1.3
Age (Years)	**Number**	**Percent**
17-20	11,667	100.0%
Sex		
Female	7,356	63.0%
Male	4,311	37.0%
Other	0	0.0%
Race[1]		
American Indian or Alaska Native	.	.
Asian	.	.
Black or African American	.	.
Multi-racial	.	.
Native Hawaiian or Other Pacific Islander	.	.
Unknown	11,667	100.0%
White	.	.
Hispanic origin[1]		
Yes	.	.
No	.	.
Unknown	11,667	100.0%
Year		
2015	531	4.6%
2016	1,182	10.1%
2017	1,600	13.7%
2018	1,935	16.6%
2019	2,238	19.2%
2020	2,555	21.9%
2021	1,626	13.9%

[1]Data not available in Merative™ MarketScan® Research Databases.

Table 1h. Characteristics of Users of Gonadotropin-Releasing Hormone (GnRH) Agonists 17-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Patient Characteristics	Number	
Unique patients	672	
Demographic Characteristics	**Mean**	**Standard Deviation**
Mean Age (Years)	19.0	1.2
Age (Years)	**Number**	**Percent**
17-20	672	100.0%
Sex		
Female	574	85.4%
Male	98	14.6%
Other	0	0.0%
Race[1]		
American Indian or Alaska Native	.	.
Asian	.	.
Black or African American	.	.
Multi-racial	.	.
Native Hawaiian or Other Pacific Islander	.	.
Unknown	672	100.0%
White	.	.
Hispanic origin[1]		
Yes	.	.
No	.	.
Unknown	672	100.0%
Year		
2015	33	4.9%
2016	150	22.3%
2017	134	19.9%
2018	131	19.5%
2019	94	14.0%
2020	85	12.6%
2021	45	6.7%
Health Characteristics on the Index Date	**Number**	**Percent**
GnRH agonist use identified via National Drug Codes in outpatient pharmacy dispensings	370	55.1%
GnRH agonist use identified via National Drug Codes in professional administration procedures	0	0.0%
GnRH agonist use identified via Healthcare Common Procedure Coding System (HCPCS) code in professional administration procedures	302	44.9%
Health Characteristics in the 90 days Prior to and Including the Index Date	**Number**	**Percent**
Gender Dysphoria diagnosis	130	19.3%
Gender Dysphoria diagnosis (excluding Z87.890)	130	19.3%
Health Characteristics throughout Enrollment History (before, on, or after the Index Date)	**Number**	**Percent**
Gender Dysphoria diagnosis, 2 or more, on separate days	138	20.5%

[1]Data not available in Merative™ MarketScan® Research Databases.

Table 1i. Characteristics of Users of Gonadotropin-Releasing Hormone (GnRH) Agonists Diagnosed with Gender Dysphoria 17-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Patient Characteristics	Number	
Unique patients	130	N/A
Demographic Characteristics	**Mean**	**Standard Deviation**
Mean Age (Years)	18.1	1.0
Age (Years)	**Number**	**Percent**
17-20	130	100.0%
Sex		
Female	52	40.0%
Male	78	60.0%
Other	0	0.0%
Race[1]		
American Indian or Alaska Native	.	.
Asian	.	.
Black or African American	.	.
Multi-racial	.	.
Native Hawaiian or Other Pacific Islander	.	.
Unknown	130	100.0%
White	.	.
Hispanic origin[1]		
Yes	.	.
No	.	.
Unknown	130	100.0%
Year		
2015	2	1.5%
2016	14	10.8%
2017	19	14.6%
2018	26	20.0%
2019	25	19.2%
2020	27	20.8%
2021	17	13.1%
Health Characteristics on the Index Date	**Number**	**Percent**
GnRH agonist use identified via National Drug Codes in outpatient pharmacy dispensings	69	53.1%
GnRH agonist use identified via National Drug Codes in professional administration procedures	0	0.0%
GnRH agonist use identified via Healthcare Common Procedure Coding System (HCPCS) code in professional administration procedures	61	46.9%
Health Characteristics in the 90 days Prior to and Including the Index Date	**Number**	**Percent**
Gender Dysphoria diagnosis	130	100.0%
Gender Dysphoria diagnosis (excluding Z87.890)	130	100.0%
Health Characteristics throughout Enrollment History (before, on, or after the Index Date)	**Number**	**Percent**
Gender Dysphoria diagnosis, 2 or more, on separate days	128	98.5%

[1]Data not available in Merative™ MarketScan® Research Databases.

Sentinel

Table 2a. Summary of Exposures of Interest Among Individuals 12-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

	Number of Patients	Total Years at Risk[1]	Number of Exposure Episode Defining-Codes (Adjusted for Same-Day Dispensings)	Number of Exposure Episode Defining-Codes (Not Adjusted for Same-Day Dispensings)	Total Days Supply During Exposure Episodes	Mean Days Supply per Episode	Total Observable Years[2]	Total Observable Days[2]
Individuals Diagnosed with Gender Dysphoria								
Individuals Diagnosed with Gender Dysphoria	19,332	28,714.1	N/A	N/A	N/A	N/A	28,714.1	10,487,823
Users of GnRH Agonists[3]								
Users of GnRH Agonists	1,700	1,019.0	5,426	5,427	283,529	166.78	2,918.8	1,066,088
Users of GnRH Agonists Diagnosed with Gender Dysphoria								
Users of GnRH Agonists Diagnosed with Gender Dysphoria	710	585.0	2,497	2,498	166,298	234.22	964.6	352,328

[1]Total Years at Risk calculate the duration of use (or duration of exposure episode), gap days included.

[2]Total Observable Years/Days calculate the amount of time since the index date an individual is in the database.

[3]GnRH: Gonadotropin-Releasing Hormone

Table 2b. Summary of Exposures of Interest Among Individuals 12-16 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

	Number of Patients	Total Years at Risk[1]	Number of Exposure Episode Defining-Codes (Adjusted for Same-Day Dispensings)	Number of Exposure Episode Defining-Codes (Not Adjusted for Same-Day Dispensings)	Total Days Supply During Exposure Episodes	Mean Days Supply per Episode	Total Observable Years[2]	Total Observable Days[2]
Individuals Diagnosed with Gender Dysphoria								
Individuals Diagnosed with Gender Dysphoria	9,900	14,427.4	N/A	N/A	N/A	N/A	14,427.4	5,269,608
Users of GnRH Agonists[3]								
Users of GnRH Agonists	1,028	705.7	3,417	3,418	198,514	193.11	1,640.9	599,341
Users of GnRH Agonists Diagnosed with Gender Dysphoria								
Users of GnRH Agonists Diagnosed with Gender Dysphoria	580	490.3	2,100	2,101	139,326	240.22	779.2	284,596

[1]Total Years at Risk calculate the duration of use (or duration of exposure episode), gap days included.

[2]Total Observable Years/Days calculate the amount of time since the index date an individual is in the database.

[3]GnRH: Gonadotropin-Releasing Hormone

Sentinel

Table 2c. Summary of Exposures of Interest Among Individuals 17-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

	Number of Patients	Total Years at Risk[1]	Number of Exposure Episode Defining-Codes (Adjusted for Same-Day Dispensings)	Number of Exposure Episode Defining-Codes (Not Adjusted for Same-Day Dispensings)	Total Days Supply During Exposure Episodes	Mean Days Supply per Episode	Total Observable Years[2]	Total Observable Days[2]
Individuals Diagnosed with Gender Dysphoria								
Individuals Diagnosed with Gender Dysphoria	11,667	17,291.3	N/A	N/A	N/A	N/A	17,291.3	6,315,646
Users of GnRH Agonists[3]								
Users of GnRH Agonists	672	313.3	2,009	2,009	85,015	126.51	1,277.9	466,747
Users of GnRH Agonists Diagnosed with Gender Dysphoria								
Users of GnRH Agonists Diagnosed with Gender	130	94.7	397	397	26,972	207.48	185.4	67,732

[1]Total Years at Risk calculate the duration of use (or duration of exposure episode), gap days included.

[2]Total Observable Years/Days calculate the amount of time since the index date an individual is in the database.

[3]GnRH: Gonadotropin-Releasing Hormone

Sentinel

Table 3a. Summary of Exposures of Interest Among Individuals 12-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021, by Sex

	Number of Patients	Total Years at Risk[1]	Number of Exposure Episode Defining-Codes (Adjusted for Same-Day	Number of Exposure Episode Defining-Codes (Not Adjusted for Same-Day	Total Days Supply During Exposure Episodes	Mean Days Supply per Episode	Total Observable Years[2]	Total Observable Days[2]
Individuals Diagnosed with Gender Dysphoria								
Female	13,361	19,770.9	N/A	N/A	N/A	N/A	19,770.9	7,221,303
Male	5,971	8,943.2	N/A	N/A	N/A	N/A	8,943.2	3,266,520
Other	0	0.0	N/A	N/A	N/A	N/A	0.0	0
Users of GnRH Agonists[3]								
Female	1,186	649.4	3,823	3,824	179,331	151.21	2,145.2	783,538
Male	514	369.6	1,603	1,603	104,198	202.72	773.6	282,550
Other	0	0.0	0	0	0	NaN	0.0	0
Users of GnRH Agonists Diagnosed with Gender Dysphoria								
Female	381	299.8	1,357	1,358	86,144	226.10	548.1	200,193
Male	329	285.3	1,140	1,140	80,154	243.63	416.5	152,135
Other	0	0.0	0	0	0	NaN	0.0	0

[1]Total Years at Risk calculate the duration of use (or duration of exposure episode), gap days included.

[2]Total Observable Years/Days calculate the amount of time since the index date an individual is in the database.

[3]GnRH: Gonadotropin-Releasing Hormone

Table 3b. Summary of Exposures of Interest Among Individuals 12-16 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021, by Sex

	Number of Patients	Total Years at Risk[1]	Number of Exposure Episode Defining-Codes (Adjusted for Same-Day Dispensings)	Number of Exposure Episode Defining-Codes (Not Adjusted for Same-Day Dispensings)	Total Days Supply During Exposure Episodes	Mean Days Supply per Episode	Total Observable Years[2]	Total Observable Days[2]
Individuals Diagnosed with Gender Dysphoria								
Female	7,627	11,108.3	N/A	N/A	N/A	N/A	11,108.3	4,057,290
Male	2,273	3,319.1	N/A	N/A	N/A	N/A	3,319.1	1,212,318
Other	0	0.0	N/A	N/A	N/A	N/A	0.0	0
Users of GnRH Agonists[3]								
Female	612	400.6	2,071	2,072	112,295	183.49	999.9	365,228
Male	416	305.2	1,346	1,346	86,219	207.26	641.0	234,113
Other	0	0.0	0	0	0	NaN	0.0	0
Users of GnRH Agonists Diagnosed with Gender Dysphoria								
Female	329	263.8	1,185	1,186	75,571	229.70	453.9	165,797
Male	251	226.6	915	915	63,755	254.00	325.3	118,799
Other	0	0.0	0	0	0	NaN	0.0	0

[1]Total Years at Risk calculate the duration of use (or duration of exposure episode), gap days included.

[2]Total Observable Years/Days calculate the amount of time since the index date an individual is in the database.

[3]GnRH: Gonadotropin-Releasing Hormone

Sentinel

Table 3c. Summary of Exposures of Interest Among Individuals 17-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021, by Sex

	Number of Patients	Total Years at Risk[1]	Number of Exposure Episode Defining-Codes (Adjusted for Same-Day Dispensings)	Number of Exposure Episode Defining-Codes (Not Adjusted for Same-Day Dispensings)	Total Days Supply During Exposure Episodes	Mean Days Supply per Episode	Total Observable Years[2]	Total Observable Days[2]
Individuals Diagnosed with Gender Dysphoria								
Female	7,356	10,864.9	N/A	N/A	N/A	N/A	10,864.9	3,968,390
Male	4,311	6,426.4	N/A	N/A	N/A	N/A	6,426.4	2,347,256
Other	0	0.0	N/A	N/A	N/A	N/A	0.0	0
Users of GnRH Agonists[3]								
Female	574	248.8	1,752	1,752	67,036	116.79	1,145.3	418,310
Male	98	64.5	257	257	17,979	183.46	132.6	48,437
Other	0	0.0	0	0	0	NaN	0.0	0
Users of GnRH Agonists Diagnosed with Gender Dysphoria								
Female	52	36.0	172	172	10,573	203.33	94.2	34,396
Male	78	58.7	225	225	16,399	210.24	91.3	33,336
Other	0	0.0	0	0	0	NaN	0.0	0

[1]Total Years at Risk calculate the duration of use (or duration of exposure episode), gap days included.

[2]Total Observable Years/Days calculate the amount of time since the index date an individual is in the database.

[3]GnRH: Gonadotropin-Releasing Hormone

Sentinel

Table 4a. Summary of Exposures of Interest Among Individuals 12-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021, by Sex

	Number of Patients	Total Years at Risk[1]	Number of Exposure Episode Defining-Codes (Adjusted for Same-Day Dispensings)	Number of Exposure Episode Defining-Codes (Not Adjusted for Same-Day Dispensings)	Total Days Supply During Exposure Episodes	Mean Days Supply per Episode	Total Observable Years[2]	Total Observable Days[2]
Individuals Diagnosed with Gender Dysphoria								
2015	966	2,550.4	N/A	N/A	N/A	N/A	2,550.4	931,535
2016	2,041	5,116.6	N/A	N/A	N/A	N/A	5,116.6	1,868,824
2017	2,580	5,860.5	N/A	N/A	N/A	N/A	5,860.5	2,140,540
2018	3,138	5,958.1	N/A	N/A	N/A	N/A	5,958.1	2,176,209
2019	3,510	5,057.1	N/A	N/A	N/A	N/A	5,057.1	1,847,111
2020	4,168	3,490.0	N/A	N/A	N/A	N/A	3,490.0	1,274,708
2021	2,929	681.4	N/A	N/A	N/A	N/A	681.4	248,896
Users of GnRH Agonists[3]								
2015	65	38.5	267	268	11,363	174.82	170.6	62,298
2016	304	207.8	1,140	1,140	56,052	184.38	794.8	290,304
2017	306	202.9	1,054	1,054	54,981	179.68	727.8	265,843
2018	278	192.1	943	943	52,188	187.73	516.3	188,584
2019	289	199.8	982	982	54,971	190.21	423.4	154,642
2020	291	150.0	788	788	44,242	152.03	248.8	90,874
2021	167	28.0	252	252	9,732	58.28	37.1	13,543
Users of GnRH Agonists Diagnosed with Gender Dysphoria								
2015	15	18.2	107	108	4,978	331.87	28.5	10,410
2016	77	96.0	383	383	25,927	336.71	186.3	68,052
2017	100	116.6	475	475	30,245	302.45	227.0	82,921
2018	107	99.5	385	385	28,407	265.49	171.9	62,796
2019	143	133.4	552	552	38,594	269.89	196.7	71,831
2020	161	102.3	445	445	31,431	195.22	131.6	48,049
2021	107	18.9	150	150	6,716	62.77	22.6	8,269

[1]Total Years at Risk calculate the duration of use (or duration of exposure episode), gap days included.

[2]Total Observable Years/Days calculate the amount of time since the index date an individual is in the database.

[3]GnRH: Gonadotropin-Releasing Hormone

Sentinel

Table 4b. Summary of Exposures of Interest Among Individuals 12-16 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021, by Year

	Number of Patients	Total Years at Risk[1]	Number of Exposure Episode Defining-Codes (Adjusted for Same-Day Dispensings)	Number of Exposure Episode Defining-Codes (Not Adjusted for Same-Day Dispensings)	Total Days Supply During Exposure Episodes	Mean Days Supply per Episode	Total Observable Years[2]	Total Observable Days[2]
Individuals Diagnosed with Gender Dysphoria								
2015	446	1,215.4	N/A	N/A	N/A	N/A	1,215.4	443,933
2016	996	2,517.0	N/A	N/A	N/A	N/A	2,517.0	919,316
2017	1,249	2,921.5	N/A	N/A	N/A	N/A	2,921.5	1,067,062
2018	1,579	3,029.3	N/A	N/A	N/A	N/A	3,029.3	1,106,470
2019	1,733	2,521.5	N/A	N/A	N/A	N/A	2,521.5	920,971
2020	2,216	1,829.2	N/A	N/A	N/A	N/A	1,829.2	668,125
2021	1,681	393.5	N/A	N/A	N/A	N/A	393.5	143,731
Users of GnRH Agonists[3]								
2015	32	27.4	173	174	7,860	245.63	87.4	31,928
2016	154	133.2	711	711	37,443	243.14	401.1	146,520
2017	172	141.0	638	638	37,905	220.38	408.2	149,113
2018	147	119.4	508	508	32,721	222.59	258.9	94,545
2019	195	151.3	667	667	41,742	214.06	287.3	104,936
2020	206	113.3	548	548	33,817	164.16	172.5	63,012
2021	122	20.1	172	172	7,026	57.59	25.4	9,287
Users of GnRH Agonists Diagnosed with Gender Dysphoria								
2015	13	18.0	105	106	4,900	376.92	28.3	10,332
2016	63	85.7	350	350	23,365	370.87	152.3	55,636
2017	81	98.8	397	397	25,602	316.07	183.7	67,106
2018	81	74.7	290	290	20,923	258.31	125.3	45,766
2019	118	111.0	458	458	32,541	275.77	162.6	59,395
2020	134	86.2	370	370	26,373	196.81	108.1	39,491
2021	90	15.9	130	130	5,622	62.47	18.8	6,870

[1]Total Years at Risk calculate the duration of use (or duration of exposure episode), gap days included.

[2]Total Observable Years/Days calculate the amount of time since the index date an individual is in the database.

[3]GnRH: Gonadotropin-Releasing Hormone

Sentinel

Table 4c. Summary of Exposures of Interest Among Individuals 17-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021, by Year

	Number of Patients	Total Years at Risk[1]	Number of Exposure Episode Defining-Codes (Adjusted for Same-Day Dispensings)	Number of Exposure Episode Defining-Codes (Not Adjusted for Same-Day Dispensings)	Total Days Supply During Exposure Episodes	Mean Days Supply per Episode	Total Observable Years[2]	Total Observable Days[2]
Individuals Diagnosed with Gender Dysphoria								
2015	531	1,356.0	N/A	N/A	N/A	N/A	1,356.0	495,280
2016	1,182	2,952.3	N/A	N/A	N/A	N/A	2,952.3	1,078,337
2017	1,600	3,550.0	N/A	N/A	N/A	N/A	3,550.0	1,296,654
2018	1,935	3,654.1	N/A	N/A	N/A	N/A	3,654.1	1,334,650
2019	2,238	3,219.4	N/A	N/A	N/A	N/A	3,219.4	1,175,884
2020	2,555	2,178.1	N/A	N/A	N/A	N/A	2,178.1	795,533
2021	1,626	381.4	N/A	N/A	N/A	N/A	381.4	139,308
Users of GnRH Agonists[3]								
2015	33	11.1	94	94	3,503	106.15	83.1	30,370
2016	150	74.6	429	429	18,609	124.06	393.7	143,784
2017	134	61.8	416	416	17,076	127.43	319.6	116,730
2018	131	72.7	435	435	19,467	148.60	257.5	94,039
2019	94	48.5	315	315	13,229	140.73	136.1	49,706
2020	85	36.6	240	240	10,425	122.65	76.3	27,862
2021	45	7.9	80	80	2,706	60.13	11.7	4,256
Users of GnRH Agonists Diagnosed with Gender Dysphoria								
2015	2	0.2	2	2	78	39.00	0.2	78
2016	14	10.2	33	33	2,562	183.00	34.0	12,416
2017	19	17.9	78	78	4,643	244.37	43.3	15,815
2018	26	24.7	95	95	7,484	287.85	46.6	17,030
2019	25	22.5	94	94	6,053	242.12	34.0	12,436
2020	27	16.2	75	75	5,058	187.33	23.4	8,558
2021	17	3.0	20	20	1,094	64.35	3.8	1,399

[1]Total Years at Risk calculate the duration of use (or duration of exposure episode), gap days included.

[2]Total Observable Years/Days calculate the amount of time since the index date an individual is in the database.

[3]GnRH: Gonadotropin-Releasing Hormone

Table 5a. Summary of Time to End of At-Risk Period for Exposures of Interest Among Individuals 12-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021[1]

	Number of Episodes by Episode Length									
		0+ days		Distribution of At-Risk Time in Days, by Episode						
	Total Number of Episodes	Number of Episodes	Percent of Total Episodes	Minimum	Q1	Median	Q3	Maximum	Mean	Standard Deviation
Users of GnRH Agonists[2]										
Users of GnRH Agonists	1,700	1,700	100.0%	1	28	129	312	1,973	218.9	263.1
Users of GnRH Agonists Diagnosed with Gender Dysphoria										
Users of GnRH Agonists Diagnosed with Gender Dysphoria	710	710	100.0%	1	72	232	382	1,936	301.0	305.5

[1]At- Risk Time calculates the duration of use (or duration of exposure episode), gap days included.

[2]GnRH: Gonadotropin-Releasing Hormone

Table 5b. Summary of Time to End of At-Risk Period for Exposures of Interest Among Individuals 12-16 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021[1]

	Number of Episodes by Episode Length									
		0+ days		Distribution of At-Risk Time in Days, by Episode						
	Total Number of Episodes	Number of Episodes	Percent of Total Episodes	Minimum	Q1	Median	Q3	Maximum	Mean	Standard Deviation
Users of GnRH Agonists[2]										
Users of GnRH Agonists	1,028	1,028	100.0%	1	28	160	365	1,936	250.7	288.7
Users of GnRH Agonists Diagnosed with Gender Dysphoria										
Users of GnRH Agonists Diagnosed with Gender	580	580	100.0%	1	77	241	394	1,936	308.8	312.1

[1]At- Risk Time calculates the duration of use (or duration of exposure episode), gap days included.

[2]GnRH: Gonadotropin-Releasing Hormone

Table 5c. Summary of Time to End of At-Risk Period for Exposures of Interest Among Individuals 17-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021[1]

	Number of Episodes by Episode									
		0+ days		Distribution of At-Risk Time in Days, by Episode						
	Total Number of Episodes	Number of Episodes	Percent of Total Episodes	Minimum	Q1	Median	Q3	Maximum	Mean	Standard Deviation
Users of GnRH Agonists[2]										
Users of GnRH Agonists	672	672	100.0%	1	30	114	203	1,973	170.3	209.1
Users of GnRH Agonists Diagnosed with Gender Dysphoria										
Users of GnRH Agonists Diagnosed with Gender Dysphoria	130	130	100.0%	1	61	196	365	1,593	266.1	272.1

[1]At- Risk Time calculates the duration of use (or duration of exposure episode), gap days included.

[2]GnRH: Gonadotropin-Releasing Hormone

Table 6a. Summary of Time to End of Observable Data for Exposures of Interest Among Individuals 12-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021[1]

	Number of Episodes by Observable Time									
		0+ days		Distribution of Observable Time in Days, by Episode						
	Total Number of Episodes	Number of Episodes	Percent of Total Episodes	Minimum	Q1	Median	Q3	Maximum	Mean	Standard Deviation
Individuals Diagnosed with Gender Dysphoria										
Individuals Diagnosed with Gender Dysphoria	19,332	19,332	100.0%	1	161	387	801	2,100	542.5	486.4
Users of GnRH Agonists[2]										
Users of GnRH Agonists	1,700	1,700	100.0%	1	203	464	963	2,099	627.1	529.3
Users of GnRH Agonists Diagnosed with Gender Dysphoria										
Users of GnRH Agonists Diagnosed with Gender	710	710	100.0%	1	141	350	727	2,081	496.2	459.2

[1]Time to end of observable data calculates the amount of time since the index date an individual is in the database. Time to end of observable data is for characterization purposes only. It does not necessarily represent at-risk time, and does not consider episode end, outcome occurrence, blackout period, or delay risk period start.

[2]GnRH: Gonadotropin-Releasing Hormone

Table 6b. Summary of Time to End of Observable Data for Exposures of Interest Among Individuals 12-16 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021[1]

	Number of Episodes by Observable Time									
		0+ days		Distribution of Observable Time in Days, by Episode						
	Total Number of Episodes	Number of Episodes	Percent of Total Episodes	Minimum	Q1	Median	Q3	Maximum	Mean	Standard Deviation
Individuals Diagnosed with Gender Dysphoria										
Individuals Diagnosed with Gender Dysphoria	9,900	9,900	100.0%	1	151	365	794	2,100	532.3	486.2
Users of GnRH Agonists[2]										
Users of GnRH Agonists	1,028	1,028	100.0%	1	183	423	848	2,081	583.0	515.0
Users of GnRH Agonists Diagnosed with Gender Dysphoria										
Users of GnRH Agonists Diagnosed with Gender	580	580	100.0%	1	141	347	720	2,081	490.7	457.2

[1]Time to end of observable data calculates the amount of time since the index date an individual is in the database. Time to end of observable data is for characterization purposes only. It does not necessarily represent at-risk time, and does not consider episode end, outcome occurrence, blackout period, or delay risk period start.

[2]GnRH: Gonadotropin-Releasing Hormone

Table 6c. Summary of Time to End of Observable Data for Exposures of Interest Among Individuals 17-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021[1]

	Number of Episodes by Observable Time									
		0+ days		Distribution of Observable Time in Days, by Episode						
	Total Number of Episodes	Number of Episodes	Percent of Total Episodes	Minimum	Q1	Median	Q3	Maximum	Mean	Standard Deviation
Individuals Diagnosed with Gender Dysphoria										
Individuals Diagnosed with Gender Dysphoria	11,667	11,667	100.0%	1	169	396	787	2,100	541.3	475.9
Users of GnRH Agonists[2]										
Users of GnRH Agonists	672	672	100.0%	1	238	541	1,095	2,099	694.6	543.9
Users of GnRH Agonists Diagnosed with Gender Dysphoria										
Users of GnRH Agonists Diagnosed with Gender Dysphoria	130	130	100.0%	1	150	361	806	1,921	521.0	468.9

[1]Time to end of observable data calculates the amount of time since the index date an individual is in the database. Time to end of observable data is for characterization purposes only. It does not necessarily represent at-risk time, and does not consider episode end, outcome occurrence, blackout period, or delay risk period start.

[2]GnRH: Gonadotropin-Releasing Hormone

Table 7a. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 12-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.0	Transsexualism	Diagnosis	ICD-10-CM	4,871	AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	4,098	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	3,364	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1,645	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM	789	OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	680	OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	421	IPS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	375	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM	341	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	315	OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	260	OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM	232	IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	192	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	177	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	161	IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	142	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	135	IPS
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	111	AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	96	ED
F64.0	Transsexualism	Diagnosis	ICD-10-CM	57	ED
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	52	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	45	IPS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	43	OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	43	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	39	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	37	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	33	IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	31	ED
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	23	ED
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	22	IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	20	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	20	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	19	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS

Table 7a. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 12-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	18	OA
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	18	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	16	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	14	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	13	ED
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	12	IPS
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	12	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	10	IPX
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	9	ISS
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	9	OA
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	9	ED
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	8	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	8	AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	8	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	8	AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	7	OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	7	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	7	IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	6	IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	6	OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	6	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	6	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	5	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV

Table 7a. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 12-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	5	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	5	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	5	ISS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	5	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	5	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	4	ED
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		ED
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	4	AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	4	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM	4	AV
F64	Gender Identity Disorder	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM	4	IPP
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	4	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		ED
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	3	IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		IPX
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	3	IPS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	3	ED
F64.0	Transsexualism	Diagnosis	ICD-10-CM		ED
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	3	AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	3	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	3	OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	3	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	3	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM	3	IPX
F64.0	Transsexualism	Diagnosis	ICD-10-CM	3	ED
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	3	ED
F64.0	Transsexualism	Diagnosis	ICD-10-CM		ED

Table 7a. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 12-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	3	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	3	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	3	IPX
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	3	IPX
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	3	IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	3	IPX
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	3	ISS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	2	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	IPP
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPX
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	IPS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPX
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		ED
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	ED
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	2	AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV

Table 7a. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 12-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	2	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM	2	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		OA
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	2	IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	2	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM	2	ISS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	2	ED
F64.0	Transsexualism	Diagnosis	ICD-10-CM		ED
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM	2	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	2	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	2	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	2	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		ED
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	2	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		OA
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPP
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		IPP
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPX
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		IPX
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	1	IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		IPS

Table 7a. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 12-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	IPX
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPX
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		IPS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPX
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPX
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPX
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPX
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		ISS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		ISS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	ISS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		ISS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	ISS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		ISS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		ED
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		ED
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	AV
F64	Gender Identity Disorder	Diagnosis	ICD-10-CM		AV

Table 7a. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 12-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	OA
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	1	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	1	ED
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	1	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM		AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	1	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	1	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM	1	AV
F64	Gender Identity Disorder	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	AV
F64	Gender Identity Disorder	Diagnosis	ICD-10-CM		AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	AV
F64	Gender Identity Disorder	Diagnosis	ICD-10-CM		OA
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		IPX
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPP
F64.0	Transsexualism	Diagnosis	ICD-10-CM	1	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPX

Table 7a. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 12-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	IPP
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	IPX
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	IPX
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	IPP
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPX
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	IPX
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	IPX
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		ED
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		ED
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		ED
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	ED
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		ED
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		ED
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	IPP
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	ISS

Table 7a. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 12-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		ED
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		OA
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	IPX
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	ISP
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	ED
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		AV

Table 7b. Total Code Counts of Individuals Diagnosed with Gender Dysphoria 12-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts
F64.0	Transsexualism	Diagnosis	ICD-10-CM	7,087
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	6,344
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	4,443
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	2,335
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	577
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	202
F64	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	8

Sentinel

Table 7c. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 12-16 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.0	Transsexualism	Diagnosis	ICD-10-CM	2,271	AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2,046	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1,555	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1,451	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM	343	OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	284	OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	279	IPS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	192	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	163	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM	150	IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	145	IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	123	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	90	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM	69	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	60	ED
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	55	AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	50	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	44	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	34	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	33	IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM	30	ED
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	30	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	28	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	28	ED
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	23	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	23	IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	17	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	16	OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	14	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	14	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	13	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	12	IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	10	ED

Sentinel

Table 7c. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 12-16 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	8	IPX
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	8	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	7	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	6	ISS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	6	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	5	IPS
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	5	OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	5	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	5	ISS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	5	ED
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	4	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	4	ED
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		ED
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	4	IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	4	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	4	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	3	AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	3	OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	3	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM		AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	3	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM	3	IPP
F64.0	Transsexualism	Diagnosis	ICD-10-CM	3	IPX
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	3	IPX
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	3	IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	3	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		ED
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	IPP
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	IPX
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		IPS

Sentinel

Table 7c. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 12-16 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	2	IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		IPS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	2	IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	2	IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPX
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	ED
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		OA
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	2	ED
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	2	OA
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM	2	AV
F64	Gender Identity Disorder	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	2	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	2	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	2	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM	2	ISS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	2	ED
F64.0	Transsexualism	Diagnosis	ICD-10-CM		ED
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM	2	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	2	IPX
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	2	ISS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA

Sentinel

Table 7c. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 12-16 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPX
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPX
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	IPX
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPX
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		IPS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPX
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPX
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	ISS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		ISS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	ED
F64.0	Transsexualism	Diagnosis	ICD-10-CM		ED
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	OA
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	1	AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM	1	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV

Table 7c. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 12-16 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM	1	OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM	1	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	1	IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	AV
F64	Gender Identity Disorder	Diagnosis	ICD-10-CM		AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	AV
F64	Gender Identity Disorder	Diagnosis	ICD-10-CM		OA
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		IPX
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPP
F64.0	Transsexualism	Diagnosis	ICD-10-CM	1	IPX
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	IPP
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	IPX
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM	1	ED
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	ED
F64.0	Transsexualism	Diagnosis	ICD-10-CM		ED
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV

Table 7c. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 12-16 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	IPP
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	IPX
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		ED
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		ED
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		ED
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	ED
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		ED
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		ED
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	IPP
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	IPX
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		ED
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		OA
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	IPX
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	ISP

Table 7d. Total Code Counts of Individuals Diagnosed with Gender Dysphoria 12-16 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts
F64.0	Transsexualism	Diagnosis	ICD-10-CM	3,143
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	3,020
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	2,043
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1,926
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	278
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	69
F64	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	4

Table 7e. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 17-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.0	Transsexualism	Diagnosis	ICD-10-CM	3,322	AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2,440	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	2,140	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM	595	OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	499	OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	368	AV
F64.0		Diagnosis	ICD-10-CM	326	AV
F64.0	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	244	OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	229	AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		OA
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	215	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	165	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	162	IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	105	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM	98	IPS
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	72	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	62	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	48	IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	41	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	40	ED
F64.0	Transsexualism	Diagnosis	ICD-10-CM	34	ED
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	32	OA
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	24	IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	20	IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	18	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	17	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	16	OA
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	14	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV

Table 7e. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 17-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	13	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	13	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	13	ED
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	12	OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	11	ED
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	10	IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	10	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	8	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	8	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	8	AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	7	AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	7	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	7	IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	6	OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	6	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	6	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	6	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	6	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV

Table 7e. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 17-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	5	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	5	OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	5	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	5	ED
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	5	ED
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	4	IPS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	4	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	4	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	3	IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	3	ISS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	3	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	3	AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	3	AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	3	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	3	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	3	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV

Table 7e. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 17-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.0	Transsexualism	Diagnosis	ICD-10-CM	3	AV
F64	Gender Identity Disorder	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	3	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	3	ED
F64.0	Transsexualism	Diagnosis	ICD-10-CM		ED
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	3	IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	3	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	IPX
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	ED
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	ED
F64.0	Transsexualism	Diagnosis	ICD-10-CM		ED
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	2	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	2	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM	2	ED
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV

Table 7e. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 17-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	2	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	2	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	2	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	2	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	2	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	2	IPX
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	2	ISS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	OA
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		OA
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPP
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPP
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPX
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPX
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		IPX
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPX
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPX
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		IPS
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	1	IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPX

Table 7e. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 17-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPX
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	IPX
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	ISS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	ISS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		ISS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		ISS
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	ED
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		ED
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	ED
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		ED
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	1	AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	1	AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	AV
F64	Gender Identity Disorder	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		ED
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		AV

Table 7e. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 17-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	OA
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	1	OA
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	1	IPS
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	1	IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	1	AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM		ED
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	1	AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM		OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	1	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	1	AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	1	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	1	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64	Gender Identity Disorder	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM	1	IPP
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	IPX
F64.0	Transsexualism	Diagnosis	ICD-10-CM		IPS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV

Table 7e. Full Code Distribution of Individuals Diagnosed with Gender Dysphoria 17-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts	Encounter Care Setting
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	OA
F64.0	Transsexualism	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	AV
F64.0	Transsexualism	Diagnosis	ICD-10-CM		OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	IPX
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	IPX
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		IPS
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	IPX
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	IPX
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	ED
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	1	ED
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	AV
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	OA
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM		OA
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	1	AV
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM		ED
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	ISS
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	1	AV
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM		ED

Table 7f. Total Code Counts of Individuals Diagnosed with Gender Dysphoria 17-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Code	Code Description	Code Category	Code Type	Overall Code Counts
F64.0	Transsexualism	Diagnosis	ICD-10-CM	5,004
F64.9	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	3,943
F64.1	Dual Role Transvestism	Diagnosis	ICD-10-CM	2,950
F64.2	Gender Identity Disorder Of Childhood	Diagnosis	ICD-10-CM	541
F64.8	Other Gender Identity Disorders	Diagnosis	ICD-10-CM	354
Z87.890	Personal History Of Sex Reassignment	Diagnosis	ICD-10-CM	146
F64	Gender Identity Disorder Unspecified	Diagnosis	ICD-10-CM	5

Sentinel

Table 8a. Most Frequent Diagnoses among Individuals 12-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Group	Code	Code Category	Code Type	Code Description	Code Count	Patient Count	Rank
Individuals Diagnosed with Gender Dysphoria	F640	Diagnosis	ICD-10	TRANSSEXUALISM	10396	6990	1
Individuals Diagnosed with Gender Dysphoria	F649	Diagnosis	ICD-10	GENDER IDENTITY DISORDER UNS	8403	6326	2
Individuals Diagnosed with Gender Dysphoria	F411	Diagnosis	ICD-10	GENERALIZED ANXIETY DISORDER	17436	4570	3
Individuals Diagnosed with Gender Dysphoria	F641	Diagnosis	ICD-10	DUAL ROLE TRANSVESTISM	6733	4361	4
Individuals Diagnosed with Gender Dysphoria	F329	Diagnosis	ICD-10	MAJ DEPRESS D/O SINGLE EPIS UNS	9274	3824	5
Individuals Diagnosed with Gender Dysphoria	F419	Diagnosis	ICD-10	ANXIETY DISORDER UNSPECIFIED	9145	3767	6
Individuals Diagnosed with Gender Dysphoria	Z23	Diagnosis	ICD-10	ENCOUNTER FOR IMMUNIZATION	3741	3282	7
Individuals Diagnosed with Gender Dysphoria	F642	Diagnosis	ICD-10	GENDER IDENTITY DISORDER CHILDHOOD	3634	2432	8
Individuals Diagnosed with Gender Dysphoria	F331	Diagnosis	ICD-10	MAJ DEPRESS D/O RECURRENT MOD	8074	2293	9
Individuals Diagnosed with Gender Dysphoria	Z00129	Diagnosis	ICD-10	ENC RTN CHLD HLTH EX W/O ABNRM FIND	2497	2269	10
Individuals Diagnosed with Gender Dysphoria	R45851	Diagnosis	ICD-10	SUICIDAL IDEATIONS	4882	1895	11
Individuals Diagnosed with Gender Dysphoria	F332	Diagnosis	ICD-10	MAJ DEPRESS RECURR SEV W/O PSYCH	8458	1822	12
Individuals Diagnosed with Gender Dysphoria	E349	Diagnosis	ICD-10	ENDOCRINE DISORDER UNSPECIFIED	2097	1307	13
Individuals Diagnosed with Gender Dysphoria	Z79899	Diagnosis	ICD-10	OTH LONG TERM CURRENT DRUG THERAPY	1887	1195	14
Individuals Diagnosed with Gender Dysphoria	F4323	Diagnosis	ICD-10	ADJUST D/O MIXED ANX & DEPRESS MOOD	4131	1135	15
Individuals Diagnosed with Gender Dysphoria	F321	Diagnosis	ICD-10	MAJ DEPRESS D/O SINGLE EPIS MOD	3360	1099	16
Individuals Diagnosed with Gender Dysphoria	F900	Diagnosis	ICD-10	ADHD INATTENTIVE TYPE	2803	1035	17
Individuals Diagnosed with Gender Dysphoria	F902	Diagnosis	ICD-10	ADHD COMBINED TYPE	2899	995	18
Individuals Diagnosed with Gender Dysphoria	Z0000	Diagnosis	ICD-10	ENC GEN ADULT EXAM W/O ABNORM FIND	1264	984	19
Individuals Diagnosed with Gender Dysphoria	F4010	Diagnosis	ICD-10	SOCIAL PHOBIA UNSPECIFIED	3029	963	20
Users of GnRH Agonists	F640	Diagnosis	ICD-10	TRANSSEXUALISM	1164	369	1
Users of GnRH Agonists	Z23	Diagnosis	ICD-10	ENCOUNTER FOR IMMUNIZATION	322	279	2
Users of GnRH Agonists	R102	Diagnosis	ICD-10	PELVIC AND PERINEAL PAIN	811	275	3
Users of GnRH Agonists	F649	Diagnosis	ICD-10	GENDER IDENTITY DISORDER UNS	754	271	4
Users of GnRH Agonists	F411	Diagnosis	ICD-10	GENERALIZED ANXIETY DISORDER	1190	266	5
Users of GnRH Agonists	F419	Diagnosis	ICD-10	ANXIETY DISORDER UNSPECIFIED	625	261	6
Users of GnRH Agonists	F642	Diagnosis	ICD-10	GENDER IDENTITY DISORDER CHILDHOOD	713	260	7
Users of GnRH Agonists	N809	Diagnosis	ICD-10	ENDOMETRIOSIS UNSPECIFIED	441	205	8
Users of GnRH Agonists	F329	Diagnosis	ICD-10	MAJ DEPRESS D/O SINGLE EPIS UNS	534	204	9
Users of GnRH Agonists	Z79899	Diagnosis	ICD-10	OTH LONG TERM CURRENT DRUG THERAPY	548	201	10
Users of GnRH Agonists	F641	Diagnosis	ICD-10	DUAL ROLE TRANSVESTISM	703	182	11
Users of GnRH Agonists	N803	Diagnosis	ICD-10	ENDOMETRIOSIS OF PELVIC PERITONEUM	332	181	12
Users of GnRH Agonists	E349	Diagnosis	ICD-10	ENDOCRINE DISORDER UNSPECIFIED	304	160	13

Table 8a. Most Frequent Diagnoses among Individuals 12-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Group	Code	Code Category	Code Type	Code Description	Code Count	Patient Count	Rank
Users of GnRH Agonists	N946	Diagnosis	ICD-10	DYSMENORRHEA UNSPECIFIED	354	157	14
Users of GnRH Agonists	Z00129	Diagnosis	ICD-10	ENC RTN CHLD HLTH EX W/O ABNRM FIND	174	153	15
Users of GnRH Agonists	Z5111	Diagnosis	ICD-10	ENCOUNTER FOR ANTINEOPLASTIC CHEMO	1060	150	16
Users of GnRH Agonists	R109	Diagnosis	ICD-10	UNSPECIFIED ABDOMINAL PAIN	278	135	17
Users of GnRH Agonists	R6252	Diagnosis	ICD-10	SHORT STATURE CHILD	316	114	18
Users of GnRH Agonists	F331	Diagnosis	ICD-10	MAJ DEPRESS D/O RECURRENT MOD	487	109	19
Users of GnRH Agonists	R110	Diagnosis	ICD-10	NAUSEA	206	102	20
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F640	Diagnosis	ICD-10	TRANSSEXUALISM	1164	369	1
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F649	Diagnosis	ICD-10	GENDER IDENTITY DISORDER UNS	754	271	2
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F642	Diagnosis	ICD-10	GENDER IDENTITY DISORDER CHILDHOOD	713	260	3
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F641	Diagnosis	ICD-10	DUAL ROLE TRANSVESTISM	703	182	4
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F411	Diagnosis	ICD-10	GENERALIZED ANXIETY DISORDER	949	179	5
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F419	Diagnosis	ICD-10	ANXIETY DISORDER UNSPECIFIED	357	152	6
Users of GnRH Agonists Diagnosed with Gender Dysphoria	Z23	Diagnosis	ICD-10	ENCOUNTER FOR IMMUNIZATION	153	130	7
Users of GnRH Agonists Diagnosed with Gender Dysphoria	E349	Diagnosis	ICD-10	ENDOCRINE DISORDER UNSPECIFIED	234	128	8
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F329	Diagnosis	ICD-10	MAJ DEPRESS D/O SINGLE EPIS UNS	328	123	9
Users of GnRH Agonists Diagnosed with Gender Dysphoria	Z00129	Diagnosis	ICD-10	ENC RTN CHLD HLTH EX W/O ABNRM FIND	99	91	10
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F331	Diagnosis	ICD-10	MAJ DEPRESS D/O RECURRENT MOD	421	83	11
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F332	Diagnosis	ICD-10	MAJ DEPRESS RECURR SEV W/O PSYCH	315	56	12
Users of GnRH Agonists Diagnosed with Gender Dysphoria	E559	Diagnosis	ICD-10	VITAMIN D DEFICIENCY UNSPECIFIED	65	48	13
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F321	Diagnosis	ICD-10	MAJ DEPRESS D/O SINGLE EPIS MOD	162	47	14
Users of GnRH Agonists Diagnosed with Gender Dysphoria	Z79899	Diagnosis	ICD-10	OTH LONG TERM CURRENT DRUG THERAPY	78	46	15
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F902	Diagnosis	ICD-10	ADHD COMBINED TYPE	156	46	16
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F840	Diagnosis	ICD-10	AUTISTIC DISORDER	301	43	17
Users of GnRH Agonists Diagnosed with Gender Dysphoria	J029	Diagnosis	ICD-10	ACUTE PHARYNGITIS UNSPECIFIED	58	41	18
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F4323	Diagnosis	ICD-10	ADJUST D/O MIXED ANX & DEPRESS MOOD	176	41	19
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F900	Diagnosis	ICD-10	ADHD INATTENTIVE TYPE	175	40	20

Sentinel

Table 8b. Most Frequent Diagnoses among Individuals 12-16 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Group	Code	Code Category	Code Type	Code Description	Code Count	Patient Count	Rank
Individuals Diagnosed with Gender Dysphoria	F640	Diagnosis	ICD-10-CM	TRANSSEXUALISM	4801	3197	1
Individuals Diagnosed with Gender Dysphoria	F649	Diagnosis	ICD-10-CM	GENDER IDENTITY DISORDER UNS	3982	3097	2
Individuals Diagnosed with Gender Dysphoria	F411	Diagnosis	ICD-10-CM	GENERALIZED ANXIETY DISORDER	10923	2642	3
Individuals Diagnosed with Gender Dysphoria	F329	Diagnosis	ICD-10-CM	MAJ DEPRESS D/O SINGLE EPIS UNS	6028	2343	4
Individuals Diagnosed with Gender Dysphoria	F419	Diagnosis	ICD-10-CM	ANXIETY DISORDER UNSPECIFIED	5373	2236	5
Individuals Diagnosed with Gender Dysphoria	F642	Diagnosis	ICD-10-CM	GENDER IDENTITY DISORDER CHILDHOOD	3162	2116	6
Individuals Diagnosed with Gender Dysphoria	F641	Diagnosis	ICD-10-CM	DUAL ROLE TRANSVESTISM	3059	1952	7
Individuals Diagnosed with Gender Dysphoria	Z23	Diagnosis	ICD-10-CM	ENCOUNTER FOR IMMUNIZATION	2164	1934	8
Individuals Diagnosed with Gender Dysphoria	Z00129	Diagnosis	ICD-10-CM	ENC RTN CHLD HLTH EX W/O ABNRM FIND	2061	1886	9
Individuals Diagnosed with Gender Dysphoria	R45851	Diagnosis	ICD-10-CM	SUICIDAL IDEATIONS	3569	1366	10
Individuals Diagnosed with Gender Dysphoria	F331	Diagnosis	ICD-10-CM	MAJ DEPRESS D/O RECURRENT MOD	4444	1228	11
Individuals Diagnosed with Gender Dysphoria	F332	Diagnosis	ICD-10-CM	MAJ DEPRESS RECURR SEV W/O PSYCH	5551	1155	12
Individuals Diagnosed with Gender Dysphoria	F321	Diagnosis	ICD-10-CM	MAJ DEPRESS D/O SINGLE EPIS MOD	2432	757	13
Individuals Diagnosed with Gender Dysphoria	F4323	Diagnosis	ICD-10-CM	ADJUST D/O MIXED ANX & DEPRESS MOOD	2572	686	14
Individuals Diagnosed with Gender Dysphoria	F902	Diagnosis	ICD-10-CM	ADHD COMBINED TYPE	2062	657	15
Individuals Diagnosed with Gender Dysphoria	F900	Diagnosis	ICD-10-CM	ADHD INATTENTIVE TYPE	1678	610	16
Individuals Diagnosed with Gender Dysphoria	F4010	Diagnosis	ICD-10-CM	SOCIAL PHOBIA UNSPECIFIED	2055	610	17
Individuals Diagnosed with Gender Dysphoria	Z00121	Diagnosis	ICD-10-CM	ENC RTN CHLD HLTH EXAM W/ABNRM FIND	621	590	18
Individuals Diagnosed with Gender Dysphoria	F322	Diagnosis	ICD-10-CM	MAJ DEPRESS 1 EPIS SEV W/O PSYCHOT	1851	579	19
Individuals Diagnosed with Gender Dysphoria	Z79899	Diagnosis	ICD-10-CM	OTH LONG TERM CURRENT DRUG THERAPY	883	533	20
Users of GnRH Agonists	F640	Diagnosis	ICD-10-CM	TRANSSEXUALISM	887	292	1
Users of GnRH Agonists	F642	Diagnosis	ICD-10-CM	GENDER IDENTITY DISORDER CHILDHOOD	684	245	2
Users of GnRH Agonists	F649	Diagnosis	ICD-10-CM	GENDER IDENTITY DISORDER UNS	604	214	3
Users of GnRH Agonists	F411	Diagnosis	ICD-10-CM	GENERALIZED ANXIETY DISORDER	947	179	4
Users of GnRH Agonists	Z23	Diagnosis	ICD-10-CM	ENCOUNTER FOR IMMUNIZATION	201	178	5
Users of GnRH Agonists	F419	Diagnosis	ICD-10-CM	ANXIETY DISORDER UNSPECIFIED	380	160	6
Users of GnRH Agonists	F641	Diagnosis	ICD-10-CM	DUAL ROLE TRANSVESTISM	561	139	7
Users of GnRH Agonists	Z00129	Diagnosis	ICD-10-CM	ENC RTN CHLD HLTH EX W/O ABNRM FIND	155	138	8
Users of GnRH Agonists	E349	Diagnosis	ICD-10-CM	ENDOCRINE DISORDER UNSPECIFIED	237	130	9
Users of GnRH Agonists	F329	Diagnosis	ICD-10-CM	MAJ DEPRESS D/O SINGLE EPIS UNS	335	129	10
Users of GnRH Agonists	R6252	Diagnosis	ICD-10-CM	SHORT STATURE CHILD	307	110	11
Users of GnRH Agonists	Z79899	Diagnosis	ICD-10-CM	OTH LONG TERM CURRENT DRUG THERAPY	256	95	12
Users of GnRH Agonists	F331	Diagnosis	ICD-10-CM	MAJ DEPRESS D/O RECURRENT MOD	381	73	13
Users of GnRH Agonists	E300	Diagnosis	ICD-10-CM	DELAYED PUBERTY	193	68	14

Sentinel

Table 8b. Most Frequent Diagnoses among Individuals 12-16 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Group	Code	Code Category	Code Type	Code Description	Code Count	Patient Count	Rank
Users of GnRH Agonists	E559	Diagnosis	ICD-10-CM	VITAMIN D DEFICIENCY UNSPECIFIED	88	64	15
Users of GnRH Agonists	E301	Diagnosis	ICD-10-CM	PRECOCIOUS PUBERTY	139	64	16
Users of GnRH Agonists	Z5111	Diagnosis	ICD-10-CM	ENCOUNTER FOR ANTINEOPLASTIC CHEMO	456	63	17
Users of GnRH Agonists	J029	Diagnosis	ICD-10-CM	ACUTE PHARYNGITIS UNSPECIFIED	93	61	18
Users of GnRH Agonists	F902	Diagnosis	ICD-10-CM	ADHD COMBINED TYPE	167	58	19
Users of GnRH Agonists	F840	Diagnosis	ICD-10-CM	AUTISTIC DISORDER	430	54	20
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F640	Diagnosis	ICD-10-CM	TRANSSEXUALISM	887	292	1
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F642	Diagnosis	ICD-10-CM	GENDER IDENTITY DISORDER CHILDHOOD	684	245	2
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F649	Diagnosis	ICD-10-CM	GENDER IDENTITY DISORDER UNS	604	214	3
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F411	Diagnosis	ICD-10-CM	GENERALIZED ANXIETY DISORDER	864	149	4
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F641	Diagnosis	ICD-10-CM	DUAL ROLE TRANSVESTISM	561	139	5
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F419	Diagnosis	ICD-10-CM	ANXIETY DISORDER UNSPECIFIED	271	118	6
Users of GnRH Agonists Diagnosed with Gender Dysphoria	E349	Diagnosis	ICD-10-CM	ENDOCRINE DISORDER UNSPECIFIED	184	104	7
Users of GnRH Agonists Diagnosed with Gender Dysphoria	Z23	Diagnosis	ICD-10-CM	ENCOUNTER FOR IMMUNIZATION	111	101	8
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F329	Diagnosis	ICD-10-CM	MAJ DEPRESS D/O SINGLE EPIS UNS	256	101	9
Users of GnRH Agonists Diagnosed with Gender Dysphoria	Z00129	Diagnosis	ICD-10-CM	ENC RTN CHLD HLTH EX W/O ABNRM FIND	89	84	10
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F331	Diagnosis	ICD-10-CM	MAJ DEPRESS D/O RECURRENT MOD	362	65	11
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F332	Diagnosis	ICD-10-CM	MAJ DEPRESS RECURR SEV W/O PSYCH	253	46	12
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F321	Diagnosis	ICD-10-CM	MAJ DEPRESS D/O SINGLE EPIS MOD	149	41	13
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F902	Diagnosis	ICD-10-CM	ADHD COMBINED TYPE	143	40	14
Users of GnRH Agonists Diagnosed with Gender Dysphoria	E559	Diagnosis	ICD-10-CM	VITAMIN D DEFICIENCY UNSPECIFIED	50	38	15
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F840	Diagnosis	ICD-10-CM	AUTISTIC DISORDER	272	36	16
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F4323	Diagnosis	ICD-10-CM	ADJUST D/O MIXED ANX & DEPRESS MOOD	159	36	17
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F900	Diagnosis	ICD-10-CM	ADHD INATTENTIVE TYPE	168	35	18
Users of GnRH Agonists Diagnosed with Gender Dysphoria	Z79899	Diagnosis	ICD-10-CM	OTH LONG TERM CURRENT DRUG THERAPY	57	33	19
Users of GnRH Agonists Diagnosed with Gender Dysphoria	J029	Diagnosis	ICD-10-CM	ACUTE PHARYNGITIS UNSPECIFIED	44	33	20

Sentinel

Table 8c. Most Frequent Diagnoses among Individuals 17-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Group	Code	Code Category	Code Type	Code Description	Code Count	Patient Count	Rank
Individuals Diagnosed with Gender Dysphoria	F640	Diagnosis	ICD-10-CM	TRANSSEXUALISM	8509	4937	1
Individuals Diagnosed with Gender Dysphoria	F649	Diagnosis	ICD-10-CM	GENDER IDENTITY DISORDER UNS	6061	3967	2
Individuals Diagnosed with Gender Dysphoria	F641	Diagnosis	ICD-10-CM	DUAL ROLE TRANSVESTISM	5344	2924	3
Individuals Diagnosed with Gender Dysphoria	F411	Diagnosis	ICD-10-CM	GENERALIZED ANXIETY DISORDER	9259	2568	4
Individuals Diagnosed with Gender Dysphoria	F419	Diagnosis	ICD-10-CM	ANXIETY DISORDER UNSPECIFIED	4942	1982	5
Individuals Diagnosed with Gender Dysphoria	F329	Diagnosis	ICD-10-CM	MAJ DEPRESS D/O SINGLE EPIS UNS	4247	1901	6
Individuals Diagnosed with Gender Dysphoria	Z23	Diagnosis	ICD-10-CM	ENCOUNTER FOR IMMUNIZATION	2144	1810	7
Individuals Diagnosed with Gender Dysphoria	F331	Diagnosis	ICD-10-CM	MAJ DEPRESS D/O RECURRENT MOD	4910	1394	8
Individuals Diagnosed with Gender Dysphoria	E349	Diagnosis	ICD-10-CM	ENDOCRINE DISORDER UNSPECIFIED	1805	1105	9
Individuals Diagnosed with Gender Dysphoria	Z0000	Diagnosis	ICD-10-CM	ENC GEN ADULT EXAM W/O ABNORM FIND	1278	993	10
Individuals Diagnosed with Gender Dysphoria	F332	Diagnosis	ICD-10-CM	MAJ DEPRESS RECURR SEV W/O PSYCH	3929	854	11
Individuals Diagnosed with Gender Dysphoria	Z79899	Diagnosis	ICD-10-CM	OTH LONG TERM CURRENT DRUG THERAPY	1234	813	12
Individuals Diagnosed with Gender Dysphoria	R45851	Diagnosis	ICD-10-CM	SUICIDAL IDEATIONS	1666	659	13
Individuals Diagnosed with Gender Dysphoria	Z00129	Diagnosis	ICD-10-CM	ENC RTN CHLD HLTH EX W/O ABNRM FIND	745	654	14
Individuals Diagnosed with Gender Dysphoria	F642	Diagnosis	ICD-10-CM	GENDER IDENTITY DISORDER CHILDHOOD	1208	621	15
Individuals Diagnosed with Gender Dysphoria	F900	Diagnosis	ICD-10-CM	ADHD INATTENTIVE TYPE	1709	588	16
Individuals Diagnosed with Gender Dysphoria	F4323	Diagnosis	ICD-10-CM	ADJUST D/O MIXED ANX & DEPRESS MOOD	2013	559	17
Individuals Diagnosed with Gender Dysphoria	F4010	Diagnosis	ICD-10-CM	SOCIAL PHOBIA UNSPECIFIED	1532	500	18
Individuals Diagnosed with Gender Dysphoria	Z113	Diagnosis	ICD-10-CM	ENC SCREEN INFECTIONS SEXL TRANSMS	751	499	19
Individuals Diagnosed with Gender Dysphoria	F321	Diagnosis	ICD-10-CM	MAJ DEPRESS D/O SINGLE EPIS MOD	1463	494	20
Users of GnRH Agonists	R102	Diagnosis	ICD-10-CM	PELVIC AND PERINEAL PAIN	702	228	1
Users of GnRH Agonists	N809	Diagnosis	ICD-10-CM	ENDOMETRIOSIS UNSPECIFIED	375	175	2
Users of GnRH Agonists	N803	Diagnosis	ICD-10-CM	ENDOMETRIOSIS OF PELVIC PERITONEUM	275	156	3
Users of GnRH Agonists	N946	Diagnosis	ICD-10-CM	DYSMENORRHEA UNSPECIFIED	278	120	4
Users of GnRH Agonists	Z79899	Diagnosis	ICD-10-CM	OTH LONG TERM CURRENT DRUG THERAPY	292	106	5
Users of GnRH Agonists	Z23	Diagnosis	ICD-10-CM	ENCOUNTER FOR IMMUNIZATION	121	101	6
Users of GnRH Agonists	F419	Diagnosis	ICD-10-CM	ANXIETY DISORDER UNSPECIFIED	245	101	7
Users of GnRH Agonists	R109	Diagnosis	ICD-10-CM	UNSPECIFIED ABDOMINAL PAIN	182	89	8
Users of GnRH Agonists	Z5111	Diagnosis	ICD-10-CM	ENCOUNTER FOR ANTINEOPLASTIC CHEMO	604	87	9
Users of GnRH Agonists	F411	Diagnosis	ICD-10-CM	GENERALIZED ANXIETY DISORDER	243	87	10
Users of GnRH Agonists	F640	Diagnosis	ICD-10-CM	TRANSSEXUALISM	277	77	11
Users of GnRH Agonists	F329	Diagnosis	ICD-10-CM	MAJ DEPRESS D/O SINGLE EPIS UNS	199	75	12
Users of GnRH Agonists	Z01818	Diagnosis	ICD-10-CM	ENCOUNTER OTHER PREPROCEDURAL EXAM	91	65	13
Users of GnRH Agonists	R110	Diagnosis	ICD-10-CM	NAUSEA	118	59	14

Sentinel

Table 8c. Most Frequent Diagnoses among Individuals 17-20 Years of Age in the Merative™ MarketScan® Research Databases from October 1, 2015 to June 30, 2021

Group	Code	Code Category	Code Type	Code Description	Code Count	Patient Count	Rank
Users of GnRH Agonists	F649	Diagnosis	ICD-10-CM	GENDER IDENTITY DISORDER UNS	150	57	15
Users of GnRH Agonists	N920	Diagnosis	ICD-10-CM	EXCESS FREQ MENSTRUATION W/REG CYCL	127	56	16
Users of GnRH Agonists	G8929	Diagnosis	ICD-10-CM	OTHER CHRONIC PAIN	106	54	17
Users of GnRH Agonists	Z452	Diagnosis	ICD-10-CM	ENC ADJUSTMENT & MANAGEMENT VAD	140	53	18
Users of GnRH Agonists	R112	Diagnosis	ICD-10-CM	NAUSEA WITH VOMITING UNSPECIFIED	131	52	19
Users of GnRH Agonists	D649	Diagnosis	ICD-10-CM	ANEMIA UNSPECIFIED	144	51	20
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F640	Diagnosis	ICD-10-CM	TRANSSEXUALISM	277	77	1
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F649	Diagnosis	ICD-10-CM	GENDER IDENTITY DISORDER UNS	150	57	2
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F641	Diagnosis	ICD-10-CM	DUAL ROLE TRANSVESTISM	142	43	3
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F419	Diagnosis	ICD-10-CM	ANXIETY DISORDER UNSPECIFIED	86	34	4
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F411	Diagnosis	ICD-10-CM	GENERALIZED ANXIETY DISORDER	85	30	5
Users of GnRH Agonists Diagnosed with Gender Dysphoria	Z23	Diagnosis	ICD-10-CM	ENCOUNTER FOR IMMUNIZATION	42	29	6
Users of GnRH Agonists Diagnosed with Gender Dysphoria	E349	Diagnosis	ICD-10-CM	ENDOCRINE DISORDER UNSPECIFIED	50	24	7
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F329	Diagnosis	ICD-10-CM	MAJ DEPRESS D/O SINGLE EPIS UNS	72	22	8
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F331	Diagnosis	ICD-10-CM	MAJ DEPRESS D/O RECURRENT MOD	59	18	9
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F642	Diagnosis	ICD-10-CM	GENDER IDENTITY DISORDER CHILDHOOD	29	15	10
Users of GnRH Agonists Diagnosed with Gender Dysphoria	Z79899	Diagnosis	ICD-10-CM	OTH LONG TERM CURRENT DRUG THERAPY	21	13	11
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F648	Diagnosis	ICD-10-CM	OTHER GENDER IDENTITY DISORDERS	13	10	12
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F332	Diagnosis	ICD-10-CM	MAJ DEPRESS RECURR SEV W/O PSYCH	62	10	13
Users of GnRH Agonists Diagnosed with Gender Dysphoria	E559	Diagnosis	ICD-10-CM	VITAMIN D DEFICIENCY UNSPECIFIED	15	10	14
Users of GnRH Agonists Diagnosed with Gender Dysphoria	L700	Diagnosis	ICD-10-CM	ACNE VULGARIS	12	9	15
Users of GnRH Agonists Diagnosed with Gender Dysphoria	Z5181	Diagnosis	ICD-10-CM	ENC THERAPEUTC DRUG LEVL MONITORING	12	8	16
Users of GnRH Agonists Diagnosed with Gender Dysphoria	R5383	Diagnosis	ICD-10-CM	OTHER FATIGUE	11	8	17
Users of GnRH Agonists Diagnosed with Gender Dysphoria	J029	Diagnosis	ICD-10-CM	ACUTE PHARYNGITIS UNSPECIFIED	14	8	18
Users of GnRH Agonists Diagnosed with Gender Dysphoria	Z00129	Diagnosis	ICD-10-CM	ENC RTN CHLD HLTH EX W/O ABNRM FIND	10	7	19
Users of GnRH Agonists Diagnosed with Gender Dysphoria	F840	Diagnosis	ICD-10-CM	AUTISTIC DISORDER	29	7	20

Appendix A. Dates of Available Data for Each Data Partner (DP) as of October 5, 2022

Data Partner	DP Start Date	DP End Date[1]
Merative™ MarketScan®	01/01/2010	6/30/2021

[1]End Date represents the earliest of: (1) query end date, or (2) last day of the most recent month for which all of a Data Partner's data tables (enrollment, dispensing, etc.) have at least 80% of the record count relative to the prior month.

Appendix B. List of Healthcare Common Procedure Coding System, Level II (HCPCS) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Codes Used to Define Index Events in this Request

Code	Description	Code Category	Code Type	Assigned Days Supply Value
Gender Dysphoria				
F64	Gender identity disorder	Diagnosis	ICD-10-CM	N/A
F64.0	Transsexualism	Diagnosis	ICD-10-CM	N/A
F64.1	Dual role transvestism	Diagnosis	ICD-10-CM	N/A
F64.2	Gender identity disorder of childhood	Diagnosis	ICD-10-CM	N/A
F64.8	Other gender identity disorders	Diagnosis	ICD-10-CM	N/A
F64.9	Gender identity disorder, unspecified	Diagnosis	ICD-10-CM	N/A
Z87.890	Personal history of sex reassignment	Diagnosis	ICD-10-CM	N/A
Gonadotropin-Releasing Hormone Agonists				
C9016	Injection, triptorelin extended release, 3.75 mg	Procedure	HCPCS	168
C9430	Leuprolide acetate, per 1 mg, brand name	Procedure	HCPCS	28
J1675	Injection, histrelin acetate, 10 mcg	Procedure	HCPCS	28
J1950	Injection, leuprolide acetate (for depot suspension), per 3.75 mg	Procedure	HCPCS	28
J1951	Injection, leuprolide acetate for depot suspension (Fensolvi), 0.25 mg	Procedure	HCPCS	183
J1952	Leuprolide injectable, camcevi, 1 mg	Procedure	HCPCS	183
J3315	Injection, triptorelin pamoate, 3.75 mg	Procedure	HCPCS	28
J3316	Injection, triptorelin, extended-release, 3.75 mg	Procedure	HCPCS	168
J9202	Goserelin acetate implant, per 3.6 mg	Procedure	HCPCS	28
J9217	Leuprolide acetate (for depot suspension), 7.5 mg	Procedure	HCPCS	28
J9218	Leuprolide acetate, per 1 mg	Procedure	HCPCS	28
J9219	Leuprolide acetate implant, 65 mg	Procedure	HCPCS	365
J9225	Histrelin implant (Vantas), 50 mg	Procedure	HCPCS	365
J9226	Histrelin implant (Supprelin LA), 50 mg	Procedure	HCPCS	365
Q2020	Injection, histrelin acetate, 10 mcg	Procedure	HCPCS	28
S0133	Histrelin, implant, 50 mg	Procedure	HCPCS	365

Appendix C. List of Generic and Brand Names of Medical Products Used to Define Index Events in this Request

Generic Name	Brand Name
Gonadotropin-Releasing Hormone Agonists	
goserelin acetate	Zoladex
histrelin acetate	Supprelin LA
histrelin acetate	Vantas
leuprolide acetate	Eligard
leuprolide acetate	Eligard (3 month)
leuprolide acetate	Eligard (4 month)
leuprolide acetate	Eligard (6 month)
leuprolide acetate	Fensolvi
leuprolide acetate	Lupron Depot
leuprolide acetate	Lupron Depot (3 month)
leuprolide acetate	Lupron Depot (4 month)
leuprolide acetate	Lupron Depot (6 Month)
leuprolide acetate	Lupron Depot-Ped
leuprolide acetate	Lupron Depot-Ped (3 month)
leuprolide acetate	leuprolide
leuprolide mesylate	Camcevi (6 month)
nafarelin acetate	Synarel
triptorelin pamoate	Trelstar
triptorelin pamoate	Triptodur

Appendix D. List of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Codes Used to Define Inclusion Criteria in this Request

Code	Description	Code Category	Code Type
	Gender Dysphoria		
F64	Gender identity disorder	Diagnosis	ICD-10-CM
F64.0	Transsexualism	Diagnosis	ICD-10-CM
F64.1	Dual role transvestism	Diagnosis	ICD-10-CM
F64.2	Gender identity disorder of childhood	Diagnosis	ICD-10-CM
F64.8	Other gender identity disorders	Diagnosis	ICD-10-CM
F64.9	Gender identity disorder, unspecified	Diagnosis	ICD-10-CM
Z87.890	Personal history of sex reassignment	Diagnosis	ICD-10-CM

Appendix E. List of Generic and Brand Names of Medical Products Used to Define Covariates in this Request

Generic Name	Brand Name
Gonadotropin-Releasing Hormone Agonists	
goserelin acetate	Zoladex
histrelin acetate	Supprelin LA
histrelin acetate	Vantas
leuprolide acetate	Eligard
leuprolide acetate	Eligard (3 month)
leuprolide acetate	Eligard (4 month)
leuprolide acetate	Eligard (6 month)
leuprolide acetate	Fensolvi
leuprolide acetate	Lupron Depot
leuprolide acetate	Lupron Depot (3 month)
leuprolide acetate	Lupron Depot (4 month)
leuprolide acetate	Lupron Depot (6 Month)
leuprolide acetate	Lupron Depot-Ped
leuprolide acetate	Lupron Depot-Ped (3 month)
leuprolide acetate	leuprolide
leuprolide mesylate	Camcevi (6 month)
nafarelin acetate	Synarel
triptorelin pamoate	Trelstar
triptorelin pamoate	Triptodur

Appendix F. List of Healthcare Common Procedure Coding System, Level II (HCPCS), International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), and National Drug Code (NDC) Codes Used to Define Covariates in this Request

Code	Description	Code Category	Code Type	Assigned Days Supply Value
	Gonadotropin-Releasing Hormone Agonists			
C9016	Injection, triptorelin extended release, 3.75 mg	Procedure	HCPCS	168
C9430	Leuprolide acetate, per 1 mg, brand name	Procedure	HCPCS	28
J1675	Injection, histrelin acetate, 10 mcg	Procedure	HCPCS	28
J1950	Injection, leuprolide acetate (for depot suspension), per 3.75 mg	Procedure	HCPCS	28
J1951	Injection, leuprolide acetate for depot suspension (Fensolvi), 0.25 mg	Procedure	HCPCS	183
J1952	Leuprolide injectable, camcevi, 1 mg	Procedure	HCPCS	183
J3315	Injection, triptorelin pamoate, 3.75 mg	Procedure	HCPCS	28
J3316	Injection, triptorelin, extended-release, 3.75 mg	Procedure	HCPCS	168
J9202	Goserelin acetate implant, per 3.6 mg	Procedure	HCPCS	28
J9217	Leuprolide acetate (for depot suspension), 7.5 mg	Procedure	HCPCS	28
J9218	Leuprolide acetate, per 1 mg	Procedure	HCPCS	28
J9219	Leuprolide acetate implant, 65 mg	Procedure	HCPCS	365
J9225	Histrelin implant (Vantas), 50 mg	Procedure	HCPCS	365
J9226	Histrelin implant (Supprelin LA), 50 mg	Procedure	HCPCS	365
Q2020	Injection, histrelin acetate, 10 mcg	Procedure	HCPCS	28
S0133	Histrelin, implant, 50 mg	Procedure	HCPCS	365
	Gender Dysphoria			
F64	Gender identity disorder	Diagnosis	ICD-10-CM	N/A
F64.0	Transsexualism	Diagnosis	ICD-10-CM	N/A
F64.1	Dual role transvestism	Diagnosis	ICD-10-CM	N/A
F64.2	Gender identity disorder of childhood	Diagnosis	ICD-10-CM	N/A
F64.8	Other gender identity disorders	Diagnosis	ICD-10-CM	N/A
F64.9	Gender identity disorder, unspecified	Diagnosis	ICD-10-CM	N/A
Z87.890	Personal history of sex reassignment	Diagnosis	ICD-10-CM	N/A
	Gender Dysphoria Excluding Z Code			
F64	Gender identity disorder	Diagnosis	ICD-10-CM	N/A
F64.0	Transsexualism	Diagnosis	ICD-10-CM	N/A
F64.1	Dual role transvestism	Diagnosis	ICD-10-CM	N/A
F64.2	Gender identity disorder of childhood	Diagnosis	ICD-10-CM	N/A
F64.8	Other gender identity disorders	Diagnosis	ICD-10-CM	N/A
F64.9	Gender identity disorder, unspecified	Diagnosis	ICD-10-CM	N/A

Appendix G. Specifications Defining Index Events for this Request

This request used the Cohort Identification and Descriptive Analysis (CIDA) module, version 11.4.0, to examine counts and follow-up time for individuals with a diagnosis of gender dysphoria in the Merative™ MarketScan® Research Databases. In addition, we examined counts of individuals using Gonadotropin-Releasing Hormone (GnRH) agonists with or without an inclusion requirement for a diagnosis of gender dysphoria before their GnRH agonist exposure.

Query period: 10/01/2015 - 06/30/2021
Coverage requirement: Medical & Drug Coverage
Pre-index enrollment requirement: 90 days
Post-index requirement: none
Post-episode requirement for Type 2 analyses: none
Enrollment gap: 45
Age groups (years): 12-16, 17-20; 12-16; 17-20
Stratifications: Year, sex
Censor output categorization: Requesting Censor Table
Follow-up time output categorization: Requesting Follow-up Time Table
Most Frequent Utilization: Requesting the Most Frequent Utilization table
Restrictions: None
Envelope macro: On
Distribution of index-defining codes: Yes (Scenario 1)
Never-exposed cohort: No
Freeze data: No

	Exposure						
Scenario	Index Exposure	Cohort definition	Incident exposure washout period	Exclude evidence of days supply if exposure washout includes dispensings	Build Episodes on Point Exposure?	Treatment episode gap	Exposure episode extension
1	Gender Dysphoria	First valid exposure episodes during query period (cohort def: 01)	0	N/A	Yes	N/A	N/A
2	GnRH Agonists	First valid exposure episodes during query period (cohort def: 01)	0	N/A	No	3000 days	0
3	GnRH Agonists	First valid exposure episodes during query period (cohort def: 01)	0	N/A	No	3000 days	0

International Classification of Diseases, Ninth Edition and Tenth Edition (ICD-9 & ICD-10), Healthcare Common Procedure Coding System (HCPCS), and Current Procedural Terminology (CPT) codes are provided by Optum360.
National Drug Codes (NDCs) are checked against First Data Bank's FDB MedKnowledge®.

Appendix G. Specifications Defining Index Events for this Request

This request used the Cohort Identification and Descriptive Analysis (CIDA) module, version 11.4.0, to examine counts and follow-up time for individuals with a diagnosis of gender dysphoria in the Merative™ MarketScan® Research Databases. In addition, we examined counts of individuals using Gonadotropin-Releasing Hormone (GnRH) agonists with or without an inclusion requirement for a diagnosis of gender dysphoria before their GnRH agonist exposure.

	Exposure							
Scenario	Minimum exposure episode duration	Minimum days supplied	Maximum exposure episode duration	Care setting	Principal diagnosis position	Forced supply to attach to dispensings	Create Baseline Table?	Censor treatment episode at evidence of:
1	N/A	N/A	--	Any Care Setting	Any	N/A	Yes	Death; Data Partner end date; Query end date; Disenrollment
2	1	1	no limit	Any Care Setting	N/A	Yes for Procedure=HCPCS and Procedure=NDC (not available in MarketScan), see code-specific assigned values in Appendix B	Yes	Death; Data Partner end date; Query end date; Disenrollment; Episode end
3	1	1	no limit	Any Care Setting	N/A	Yes for Procedure=HCPCS and Procedure=NDC (not available in MarketScan), see code-specific assigned values in Appendix B	Yes	Death; Data Partner end date; Query end date; Disenrollment; Episode end

Appendix G (continued). Specifications Defining Inclusion/Exclusion Criteria for this Request

This request used the Cohort Identification and Descriptive Analysis (CIDA) module, version 11.4.0, to examine counts and follow-up time for individuals with a diagnosis of gender dysphoria in the Merative™ MarketScan® Research Databases. In addition, we examined counts of individuals using Gonadotropin-Releasing Hormone (GnRH) agonists with or without an inclusion requirement for a diagnosis of gender dysphoria before their GnRH agonist exposure.

Inclusion/Exclusion Criteria

Scenario	Inclusion/ Exclusion group	Criteria	Care setting	Principal diagnosis position	Evaluation period start	Evaluation period end	Exclude evidence of days supply if inclusion/ exclusion evaluation period includes dispensings	Number of instances the criteria should be found in evaluation period	Minimum Days Supplied
1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3	Gender dysphoria	Inclusion	Any care setting	Any	-90	0	N/A	1	N/A

International Classification of Diseases, Ninth Edition and Tenth Edition (ICD-9 & ICD-10), Healthcare Common Procedure Coding System (HCPCS), and Current Procedural Terminology (CPT) codes are provided by Optum360.
National Drug Codes (NDCs) are checked against First Data Bank's FDB MedKnowledge®.

Sentinel

Appendix H. Specifications Defining Parameters for Baseline Characteristics in this Request

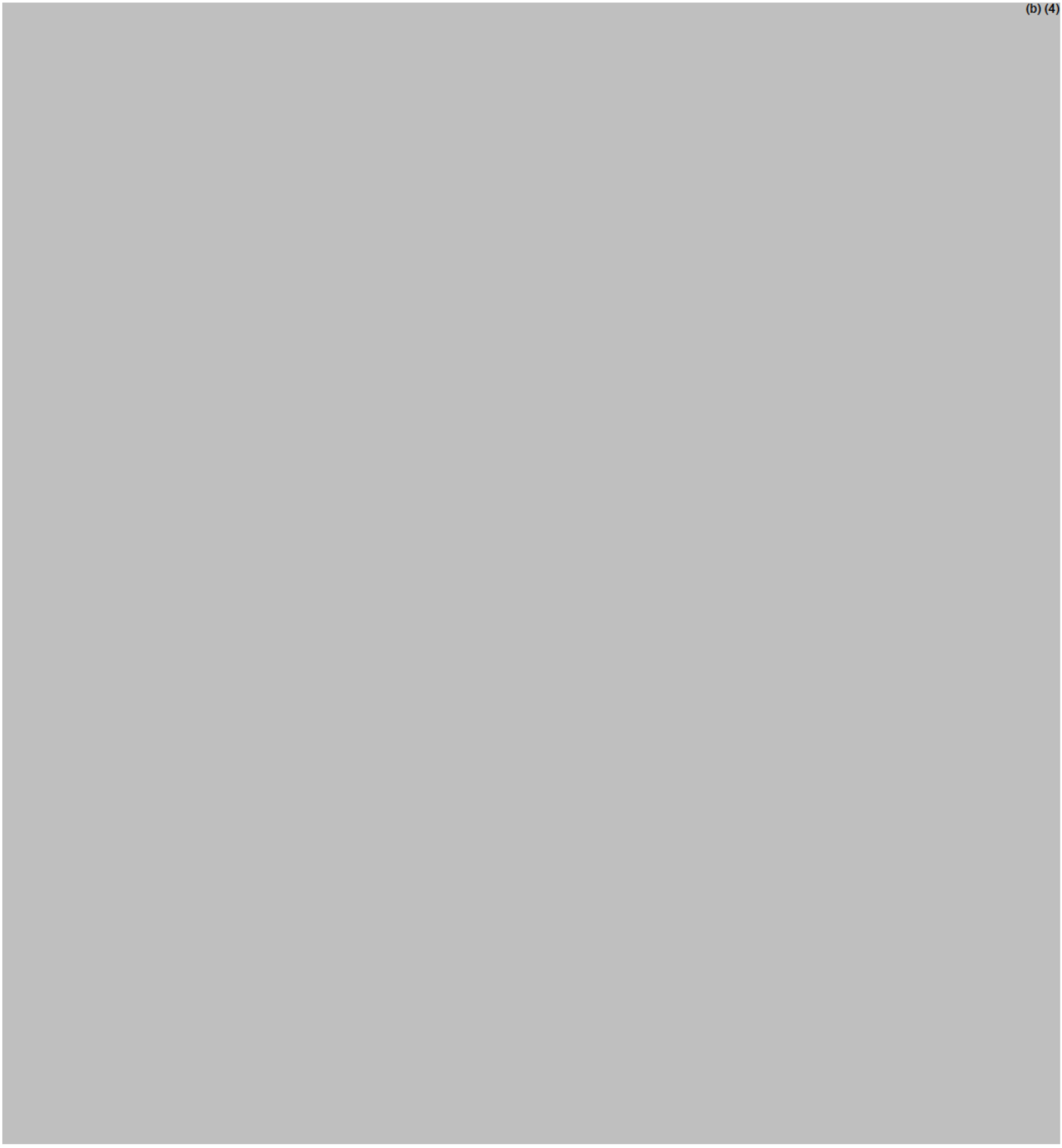
Baseline Characteristics											
Scenario	Covar Num	Covariate	Care setting	Principal diagnosis position	Code Category	Evaluation period start	Evaluation period end	Exclude evidence of days supply if covariate includes dispensings	Number of instances the covariate should be found in evaluation period	Minimum Days Supplied	Forced supply to attach to dispensings
2, 3	1	GnRH agonist use identified via National Drug Codes in outpatient pharmacy dispensings	*Any care setting	*Any	*Drug Code	0	0	*Evaluation period should search for only evidence of a dispensing date	1	1	N/A
2, 3	2	GnRH agonist use identified via National Drug Codes in professional administration procedures	*Any care setting	*Any	*Procedure Code	0	0	N/A	1	N/A	PX=NDC not available in MarketScan
2, 3	3	GnRH agonist use identified via Healthcare Common Procedure Coding System (HCPCS) code in professional administration procedures (Appendix F)	*Any care setting	*Any	*Procedure Code	0	0	N/A	1	N/A	See code-specific assigned values in Appendix F
2, 3	4	Gender Dysphoria	*Any care setting	*Any	*Diagnosis Code	-90	0	N/A	1	N/A	N/A
2, 3	5	Gender Dysphoria	*Any care setting	*Any	*Diagnosis Code	ever	ever	N/A	2	N/A	N/A
2, 3	6	Gender Dysphoria excluding Z87.891	*Any care setting	*Any	*Diagnosis Code	-90	0	N/A	1	N/A	N/A

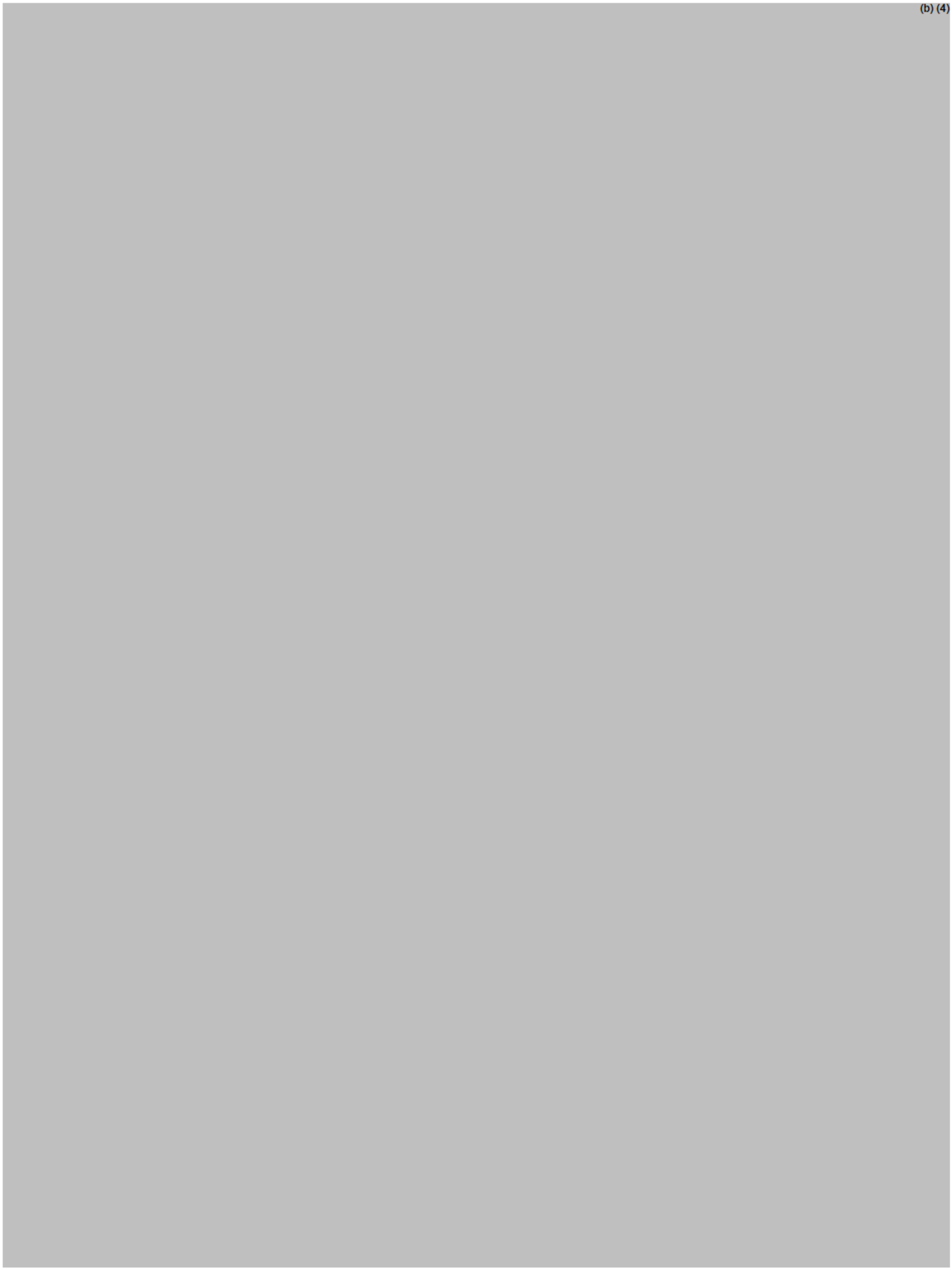
Appendix I. Most Frequent Utilization Specifications Used in this Request

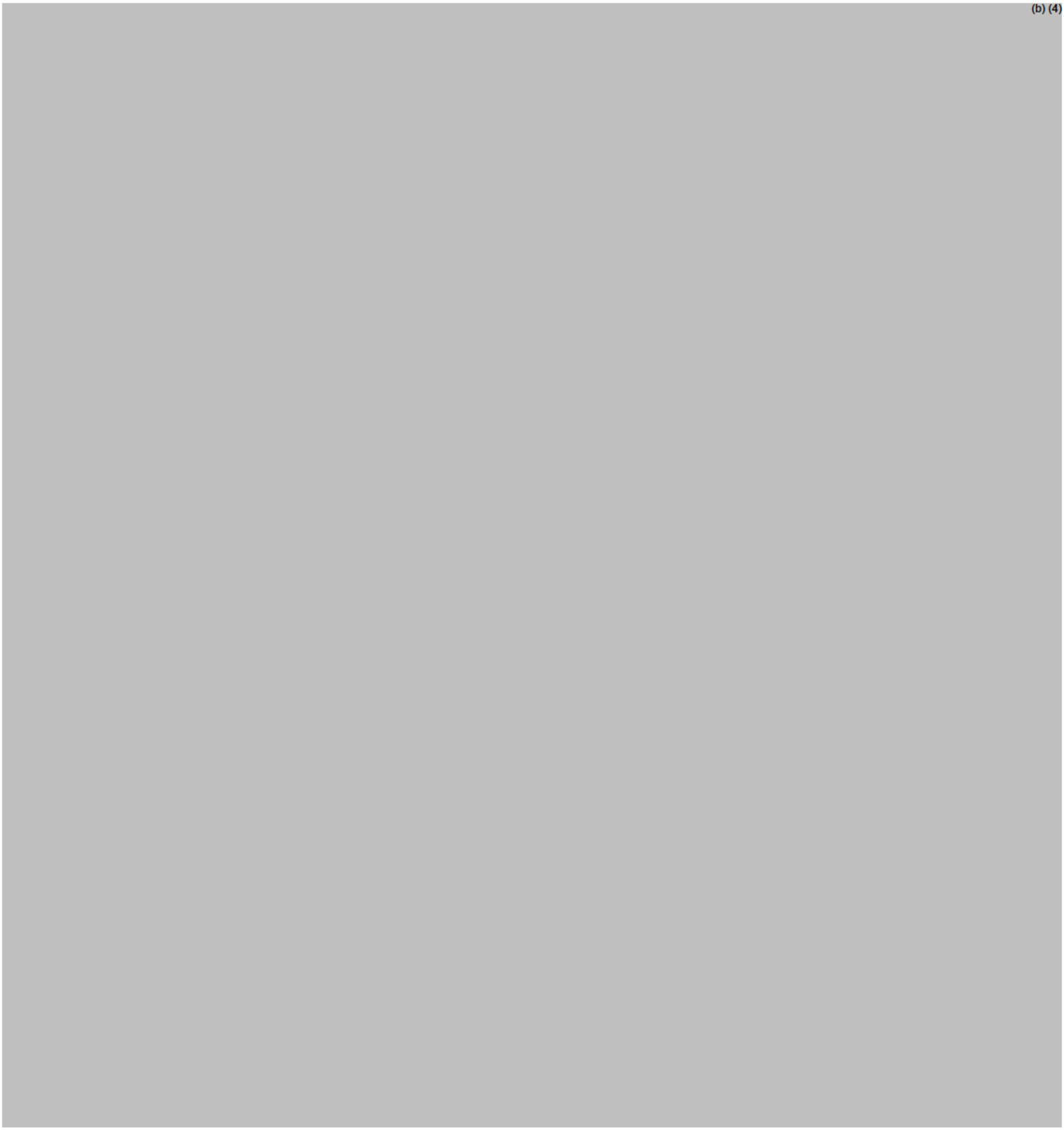
Most Frequent Utilization						
Number of codes to return	**Most Frequent Utilization evaluation period start**	**Most Frequent Utilization evaluation period end**	**Code Category**	**Encounter care setting**	**Principal encounter**	**Counting method**
Top 20	-90	0	*Diagnosis codes	*Any care setting	*Any	*The Most Frequent Utilization output is sorted by patient counts

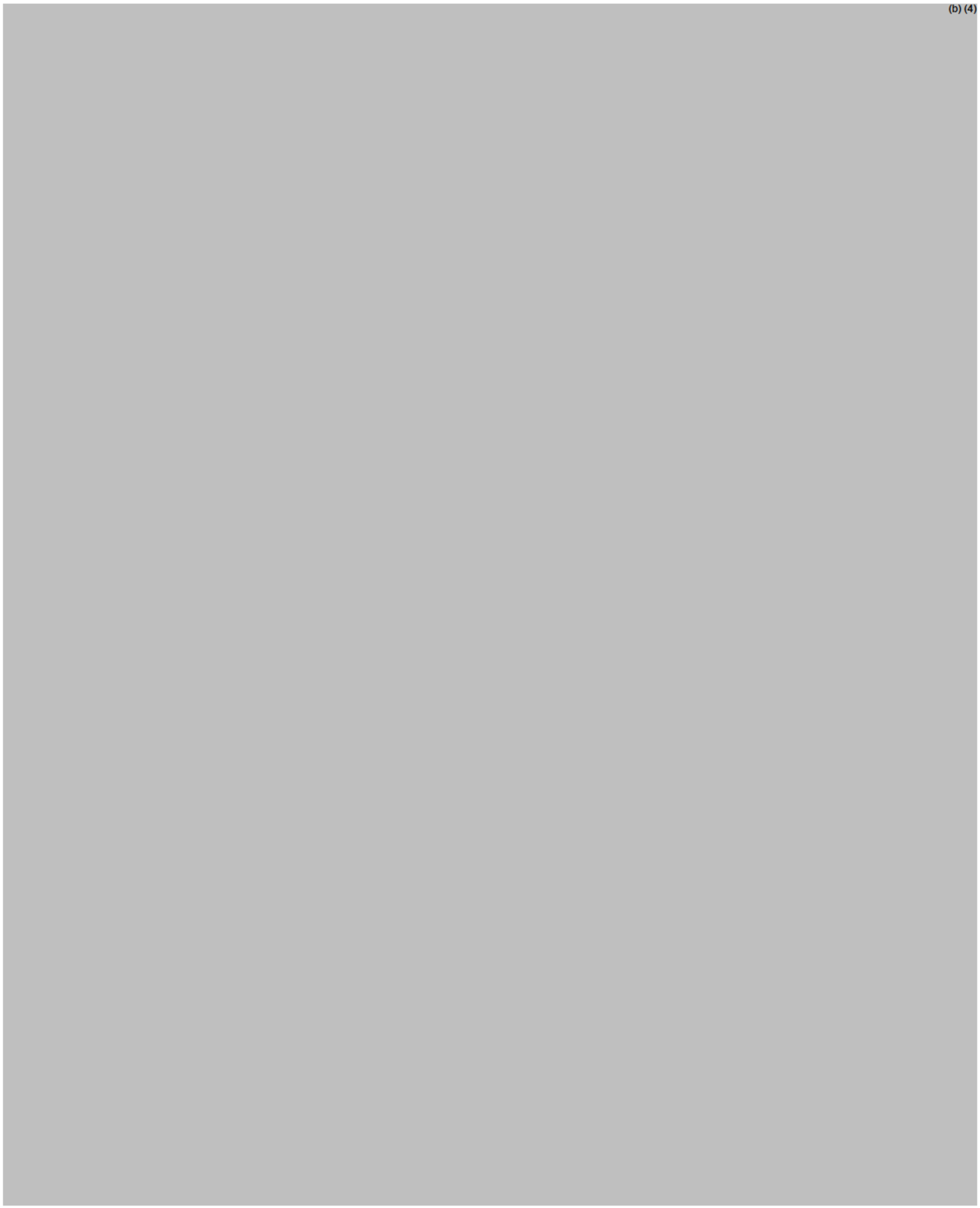
INITIAL INVESTIGATIONAL NEW DRUG APPLICATION

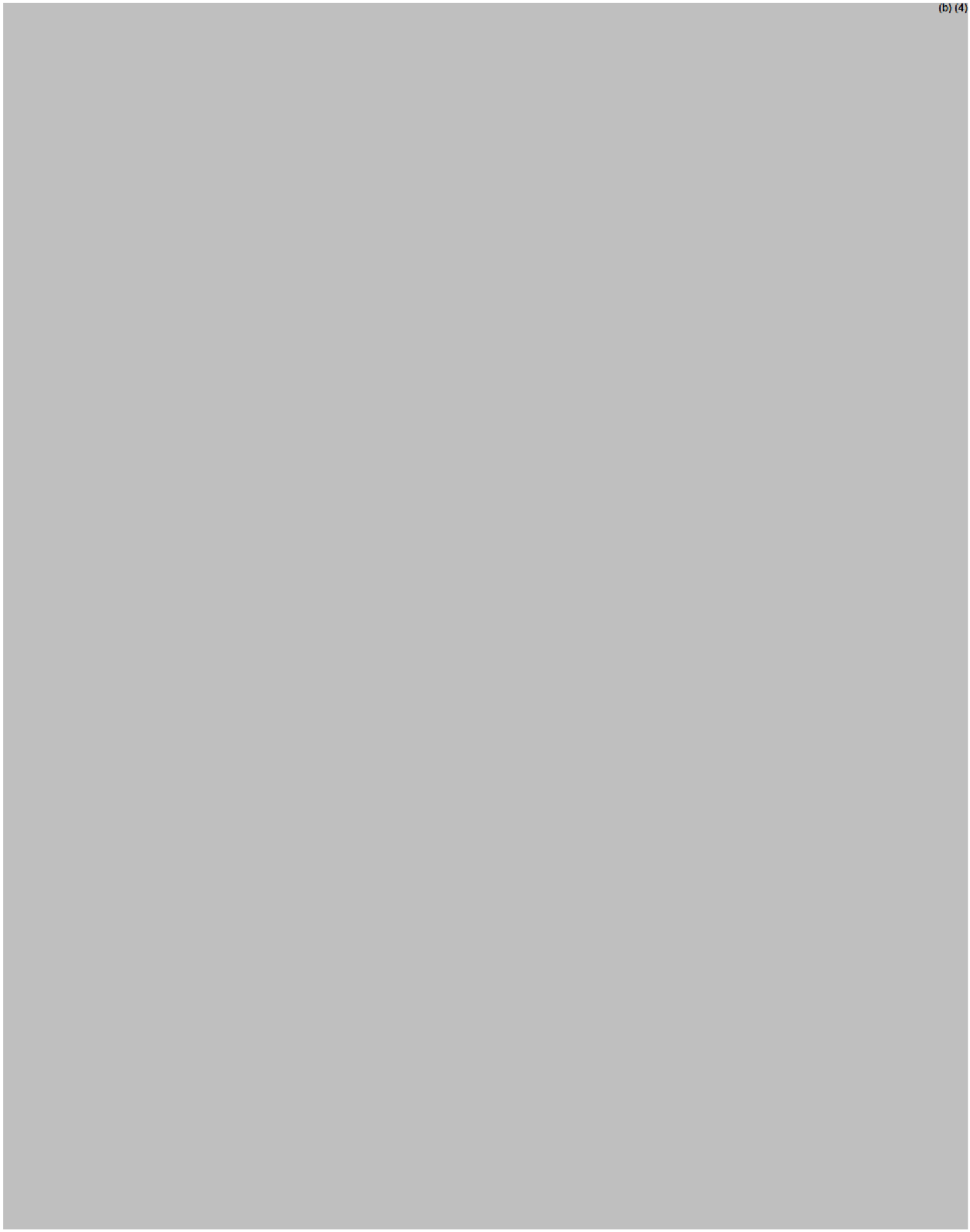
1. FORM FDA 1571

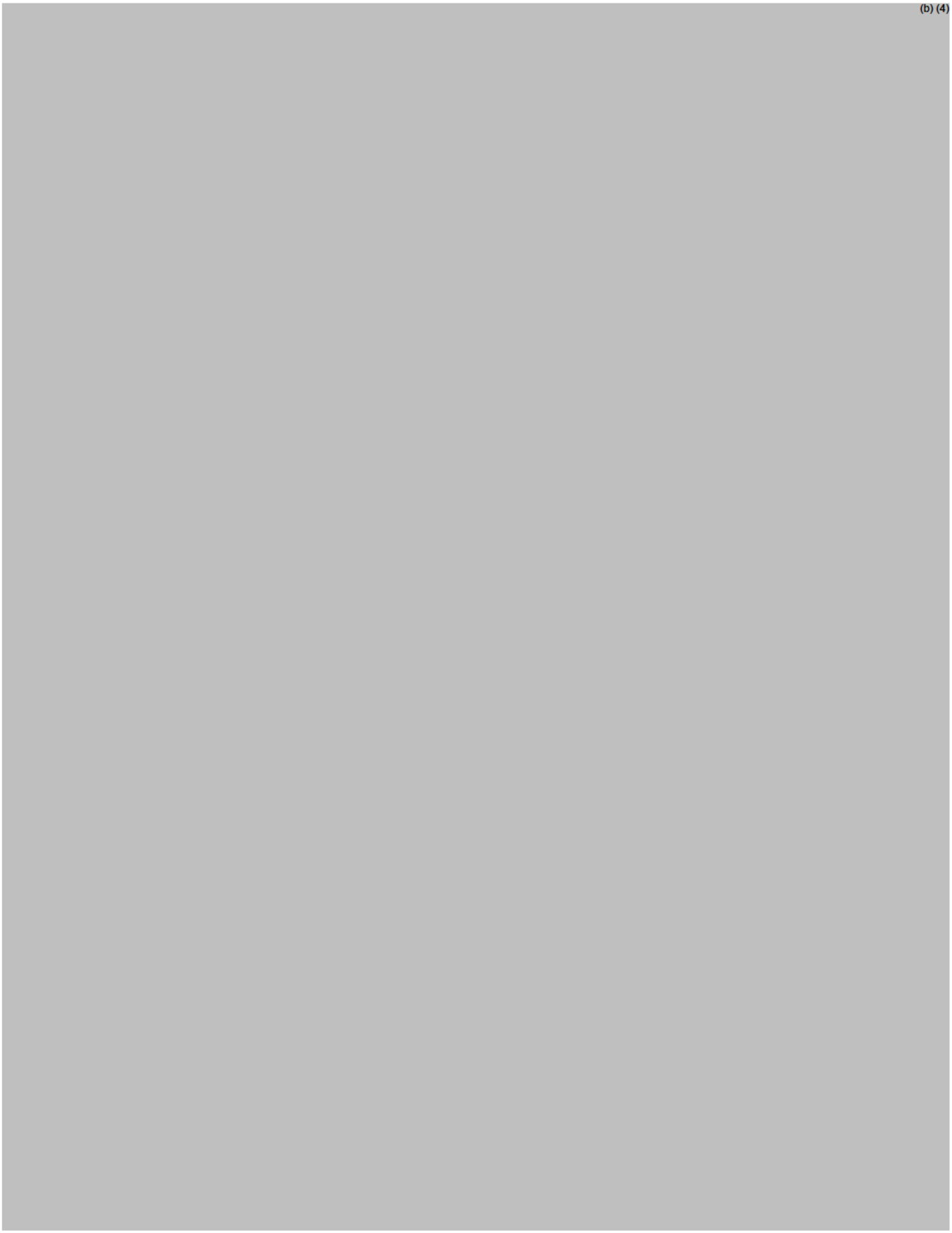


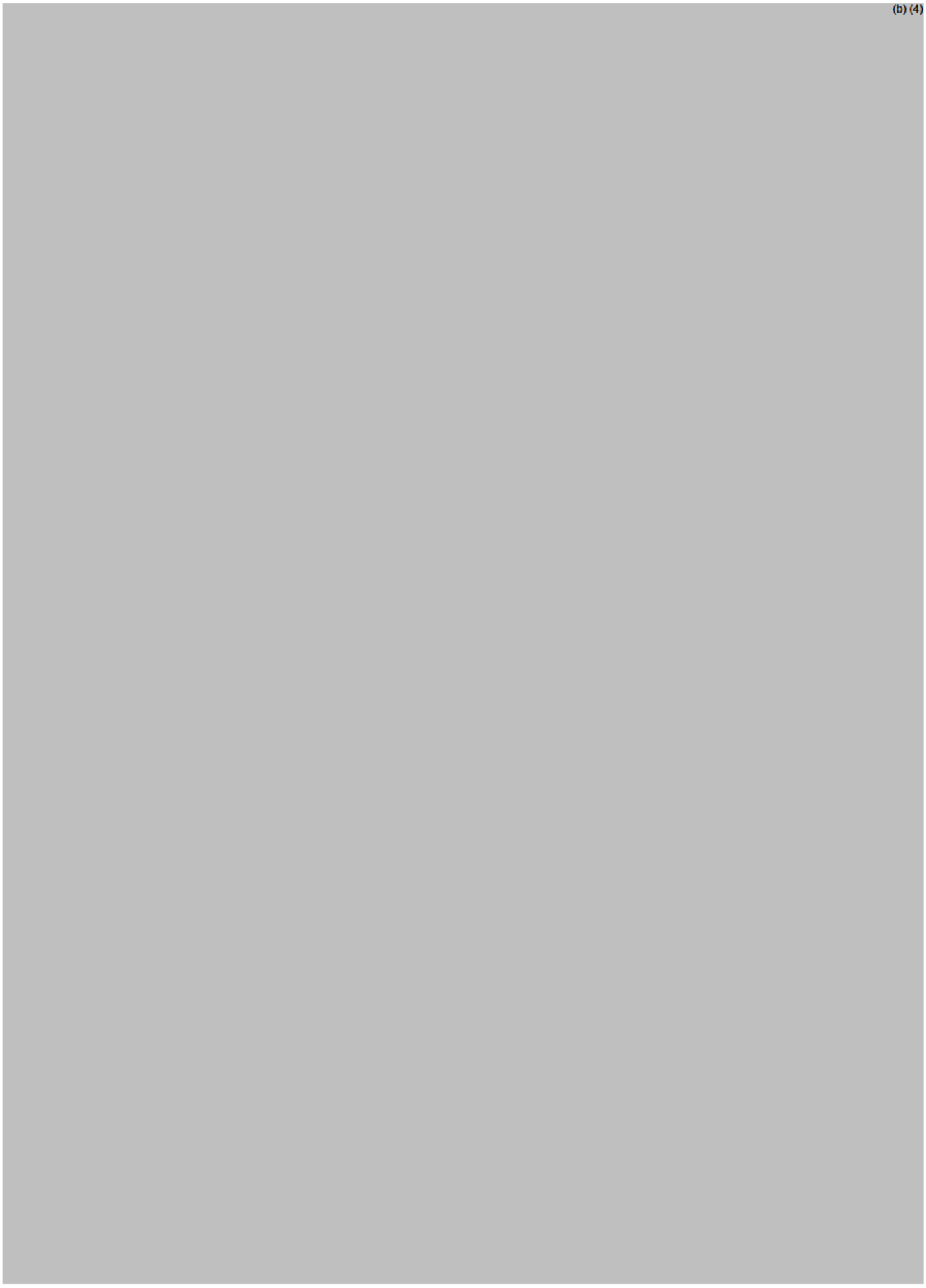

(b) (4)

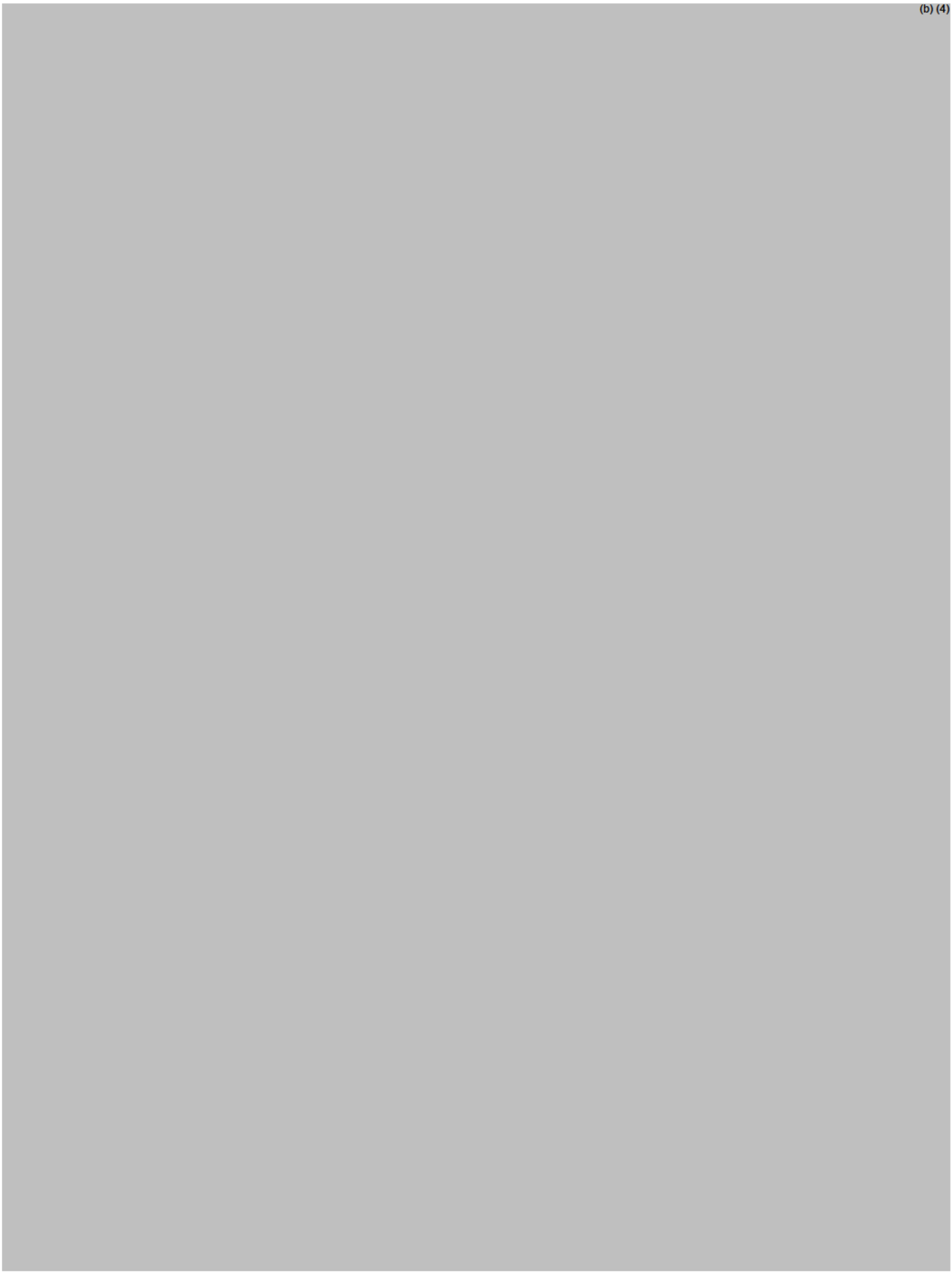

(b) (4)

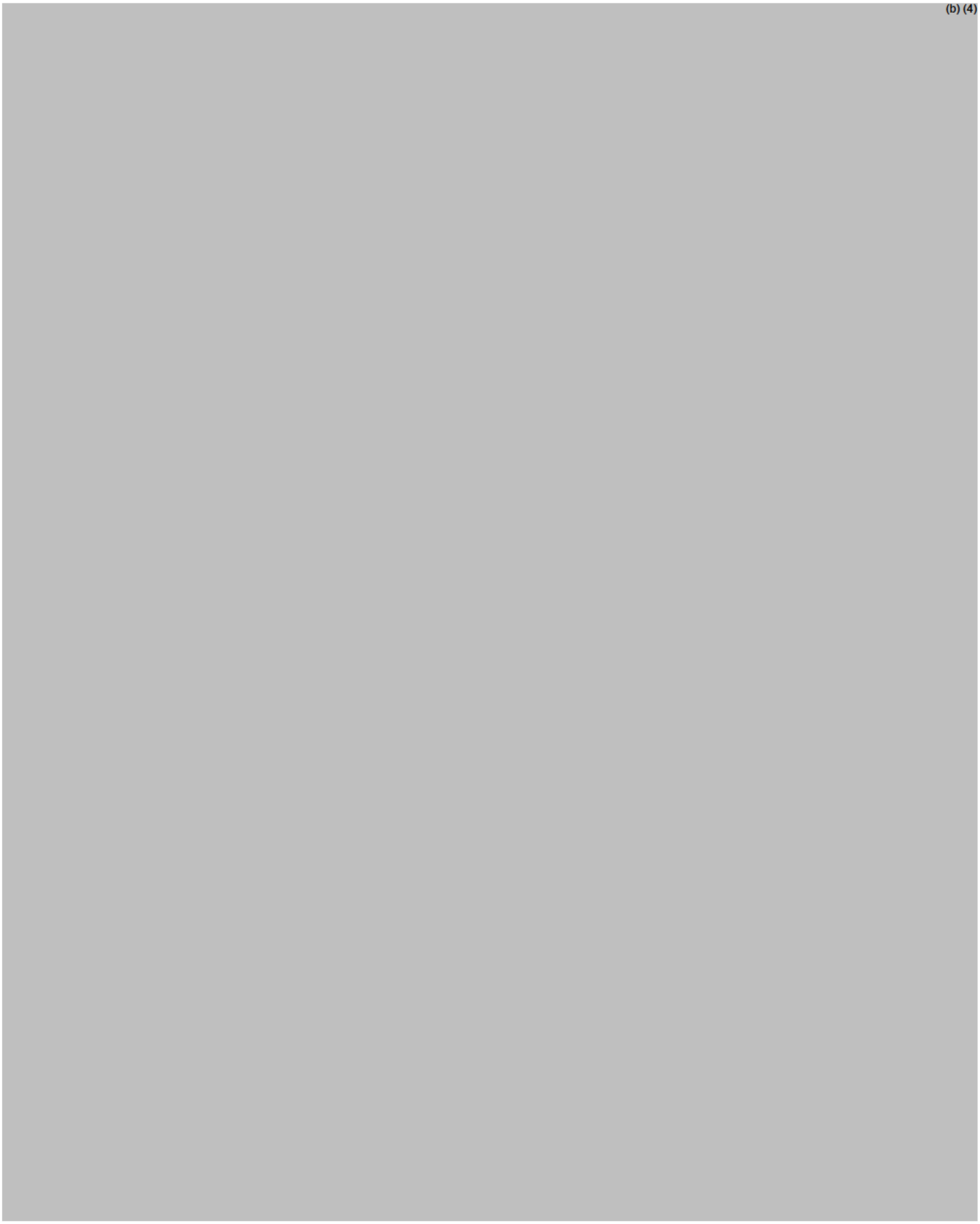


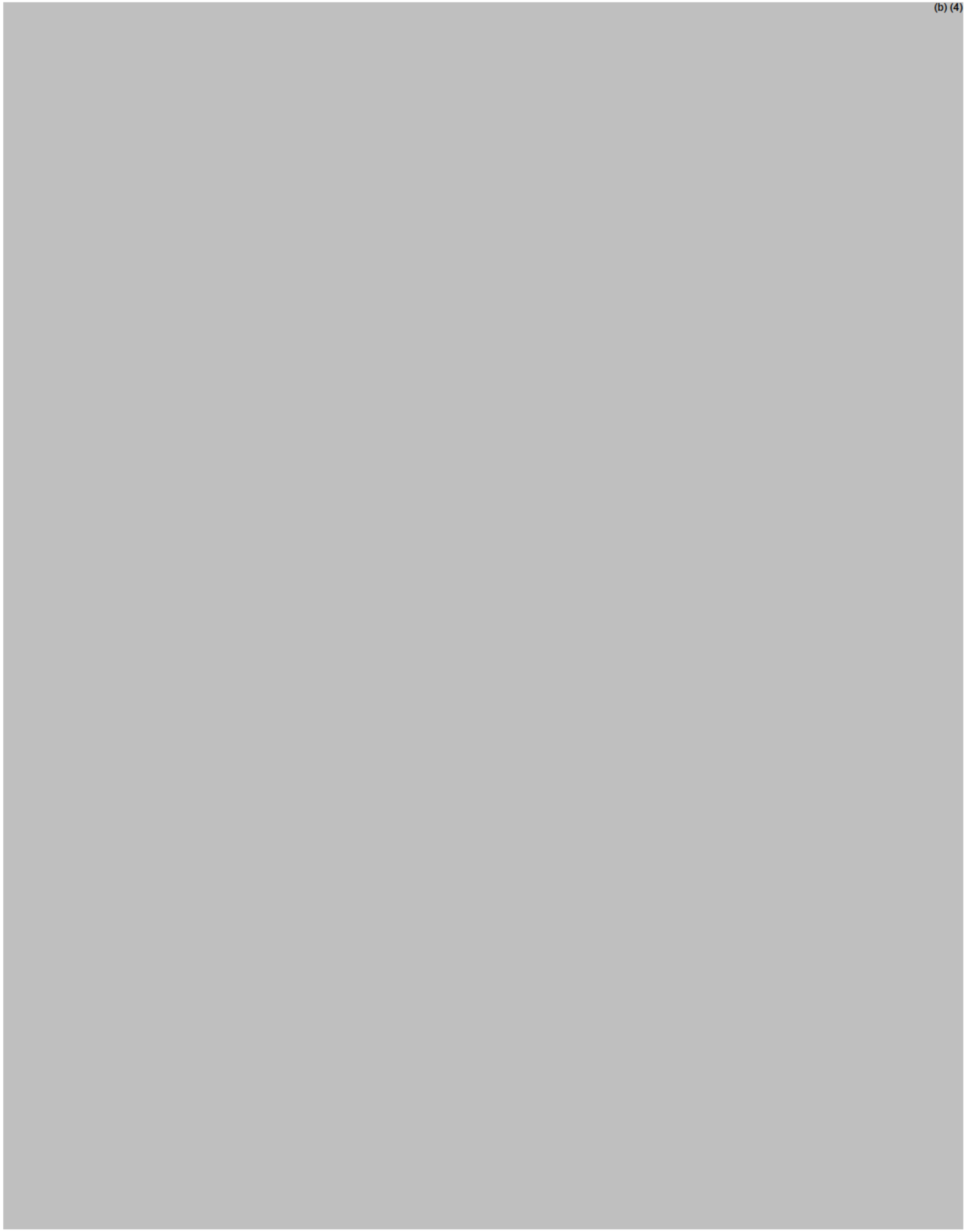


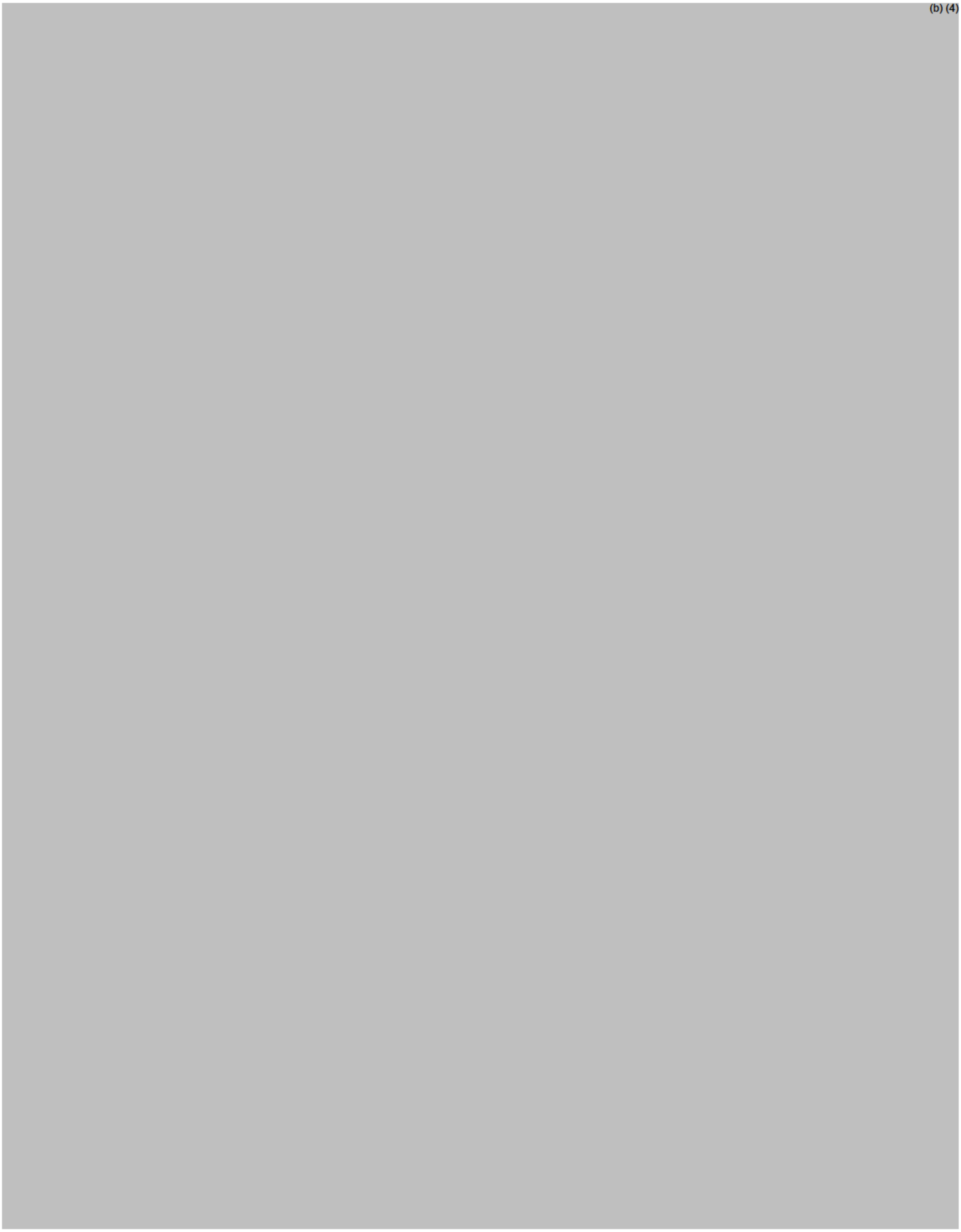


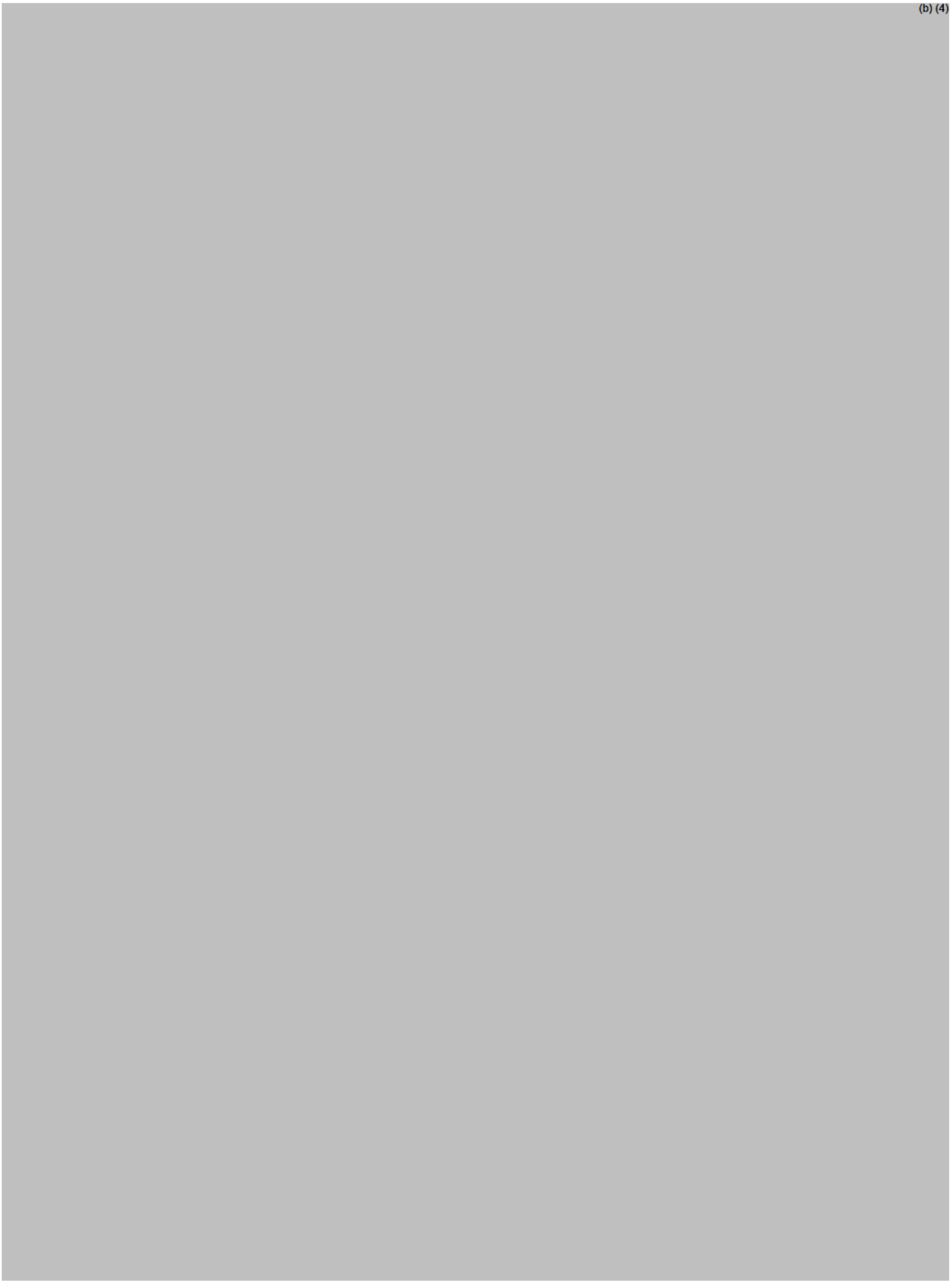


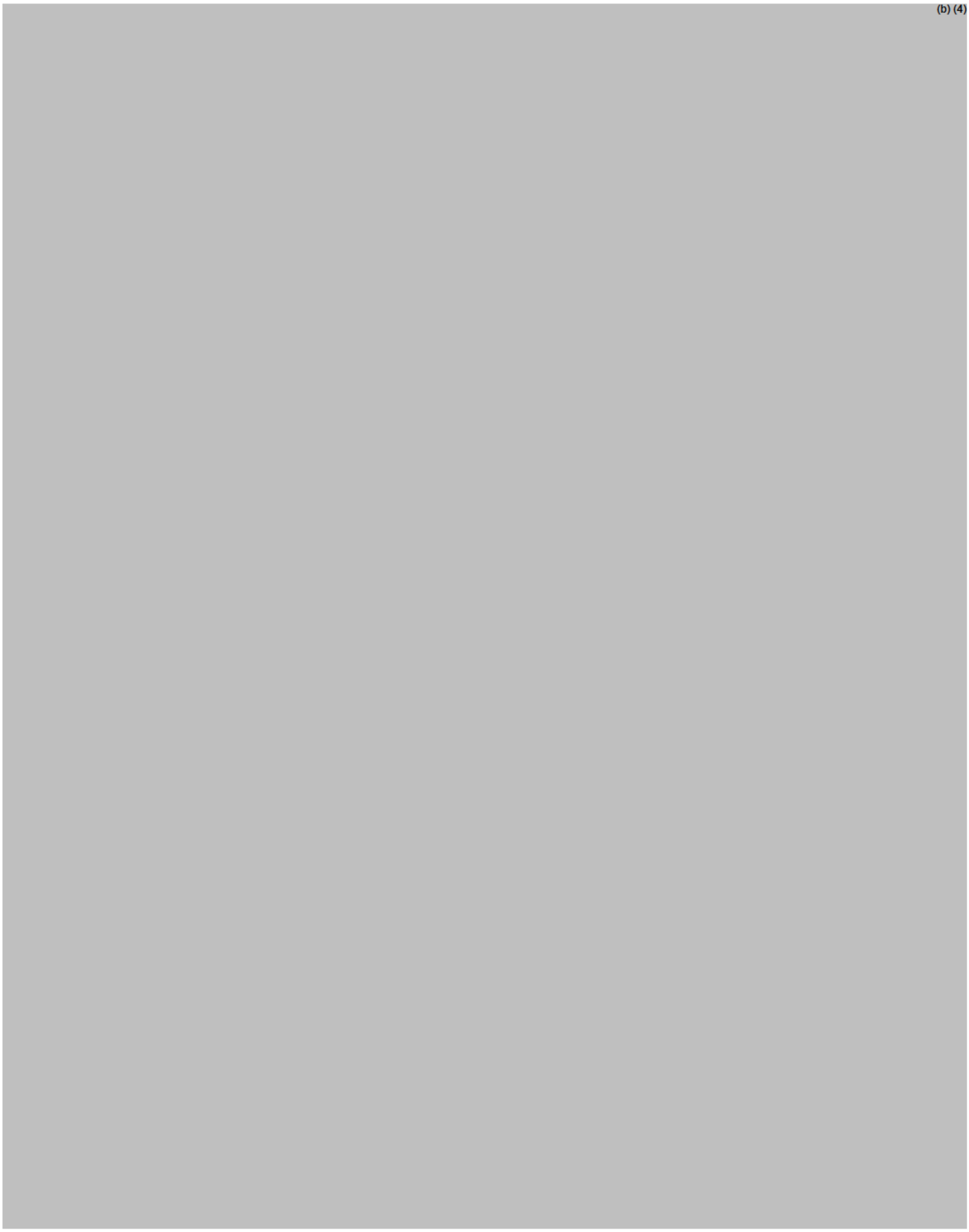




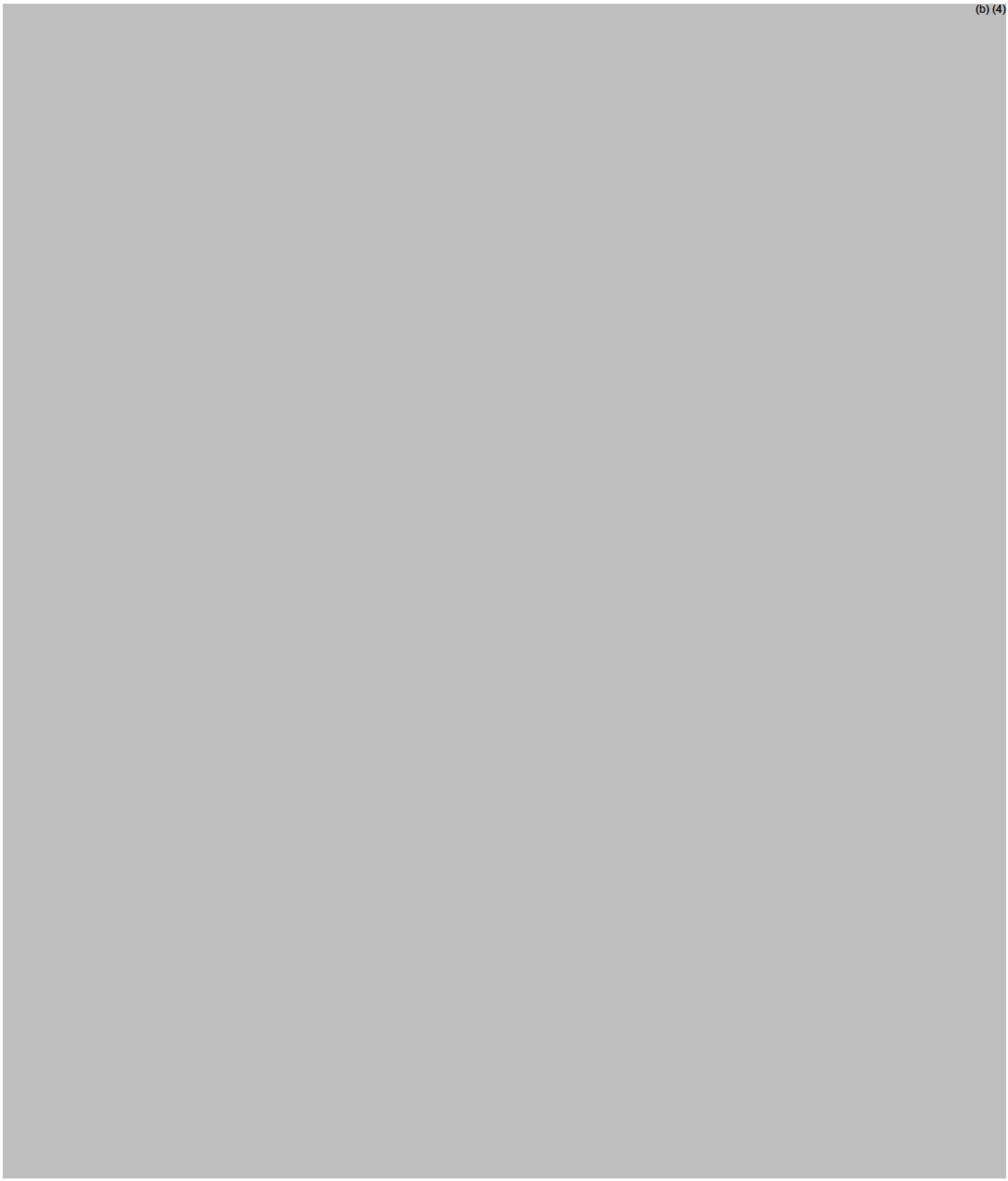


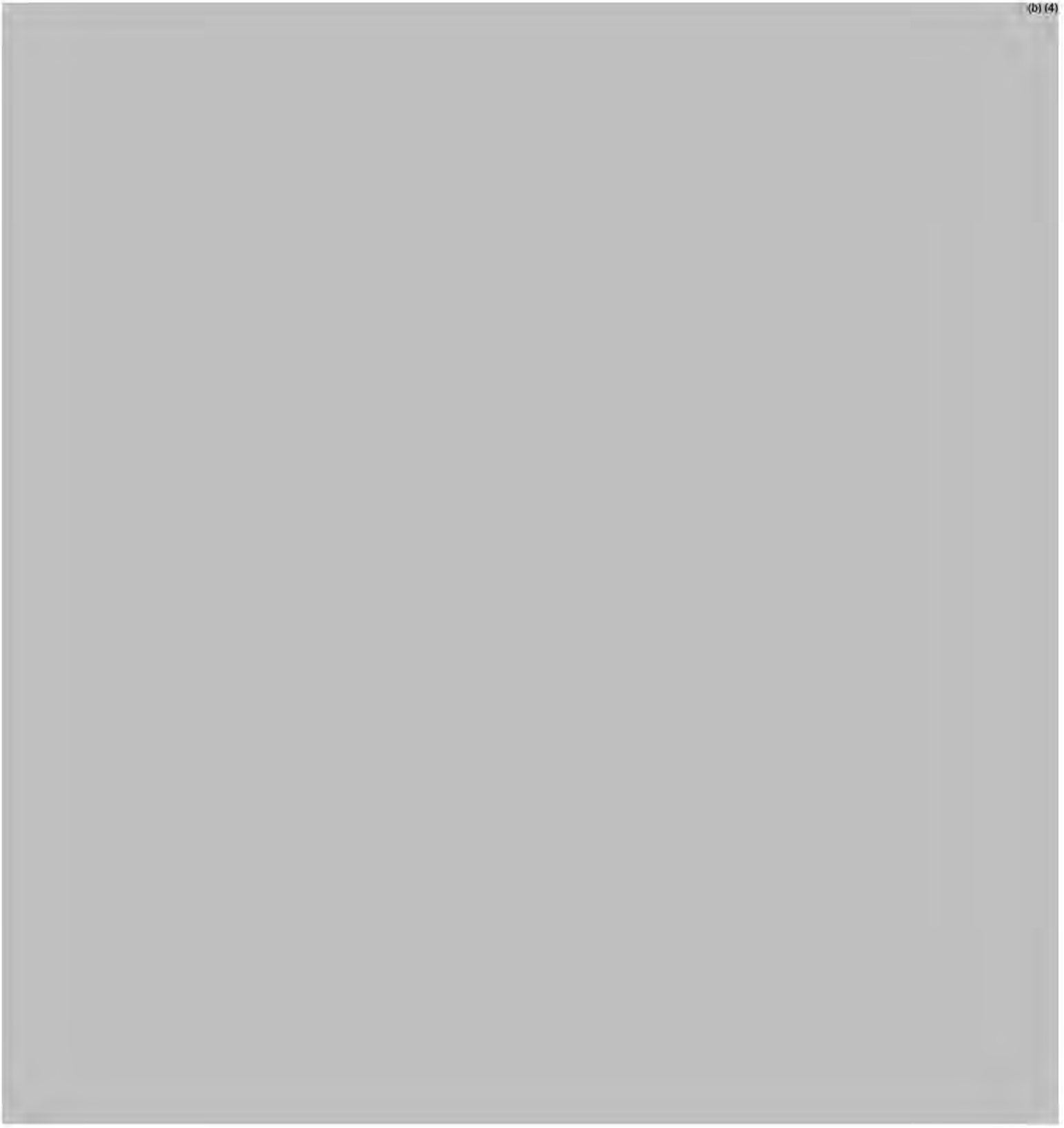






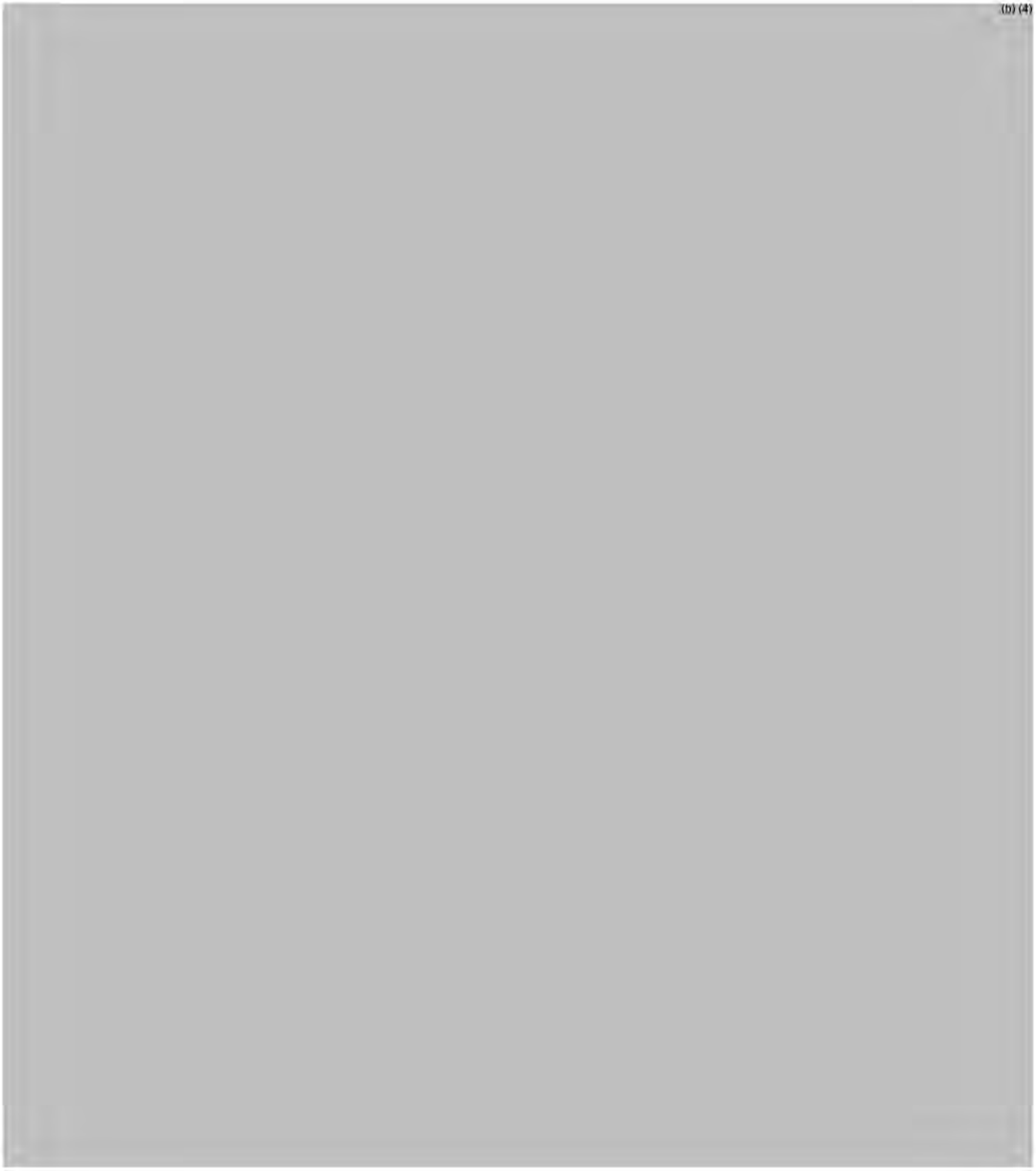
(b) (4)



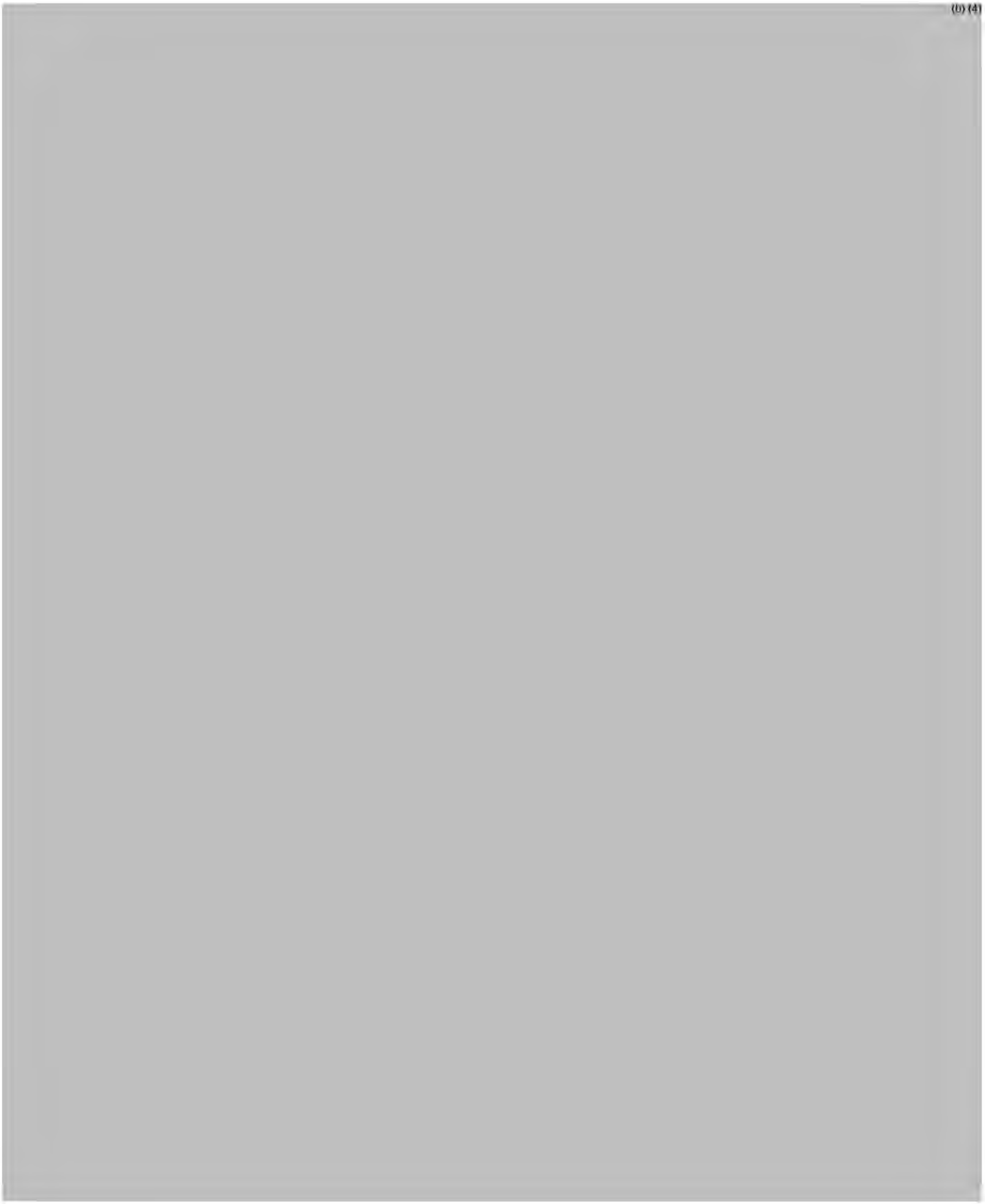


(b) (4)

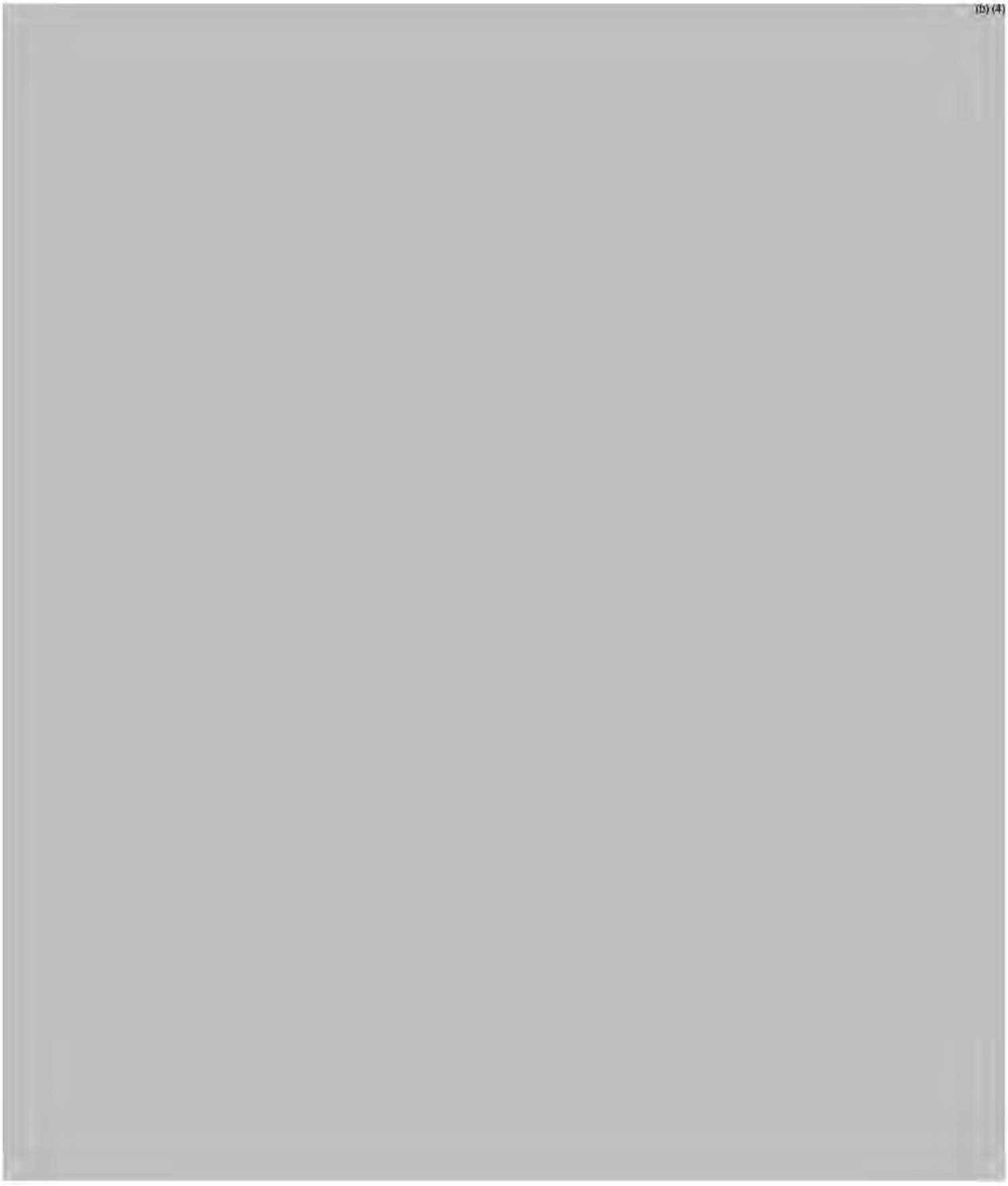
(b) (4)

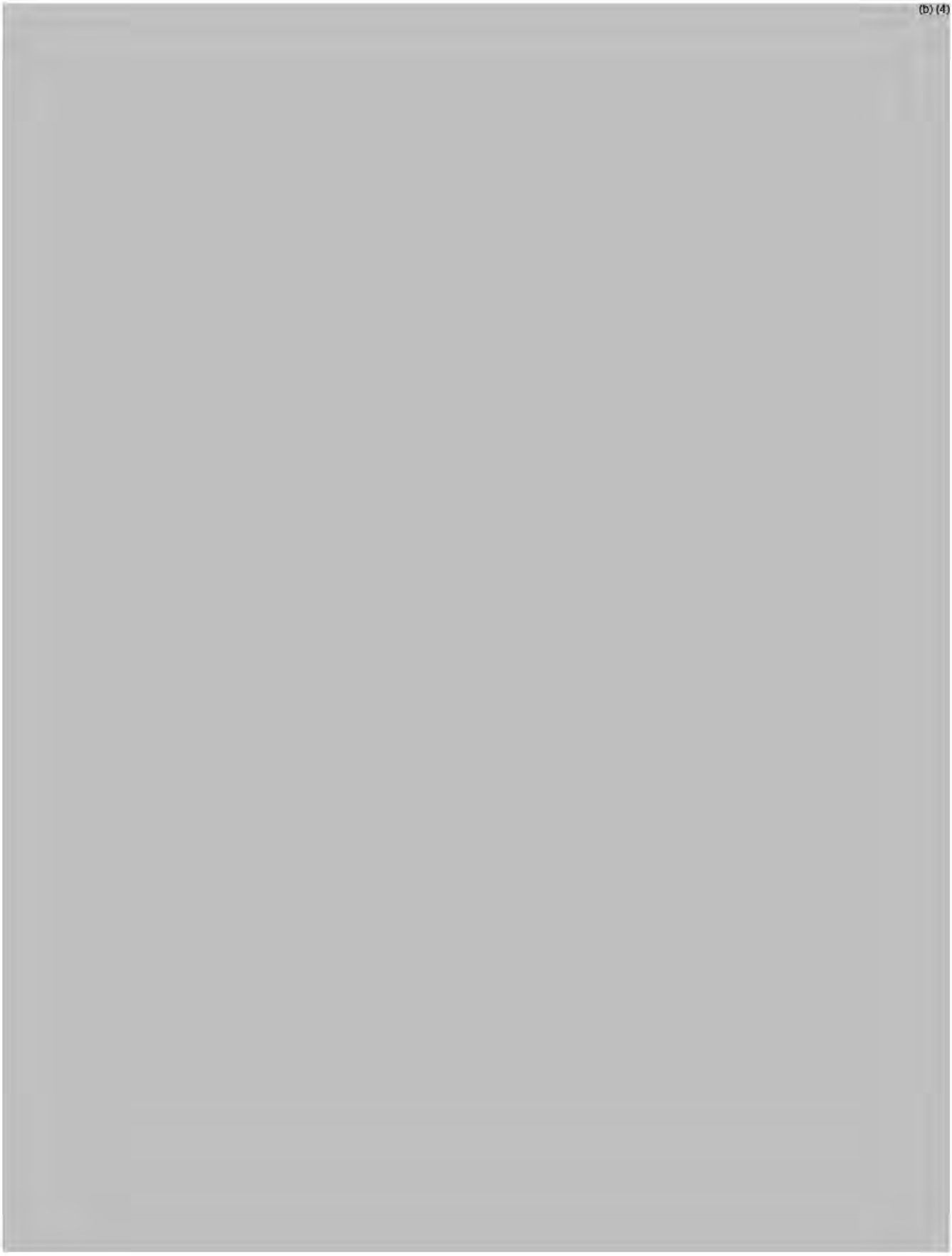


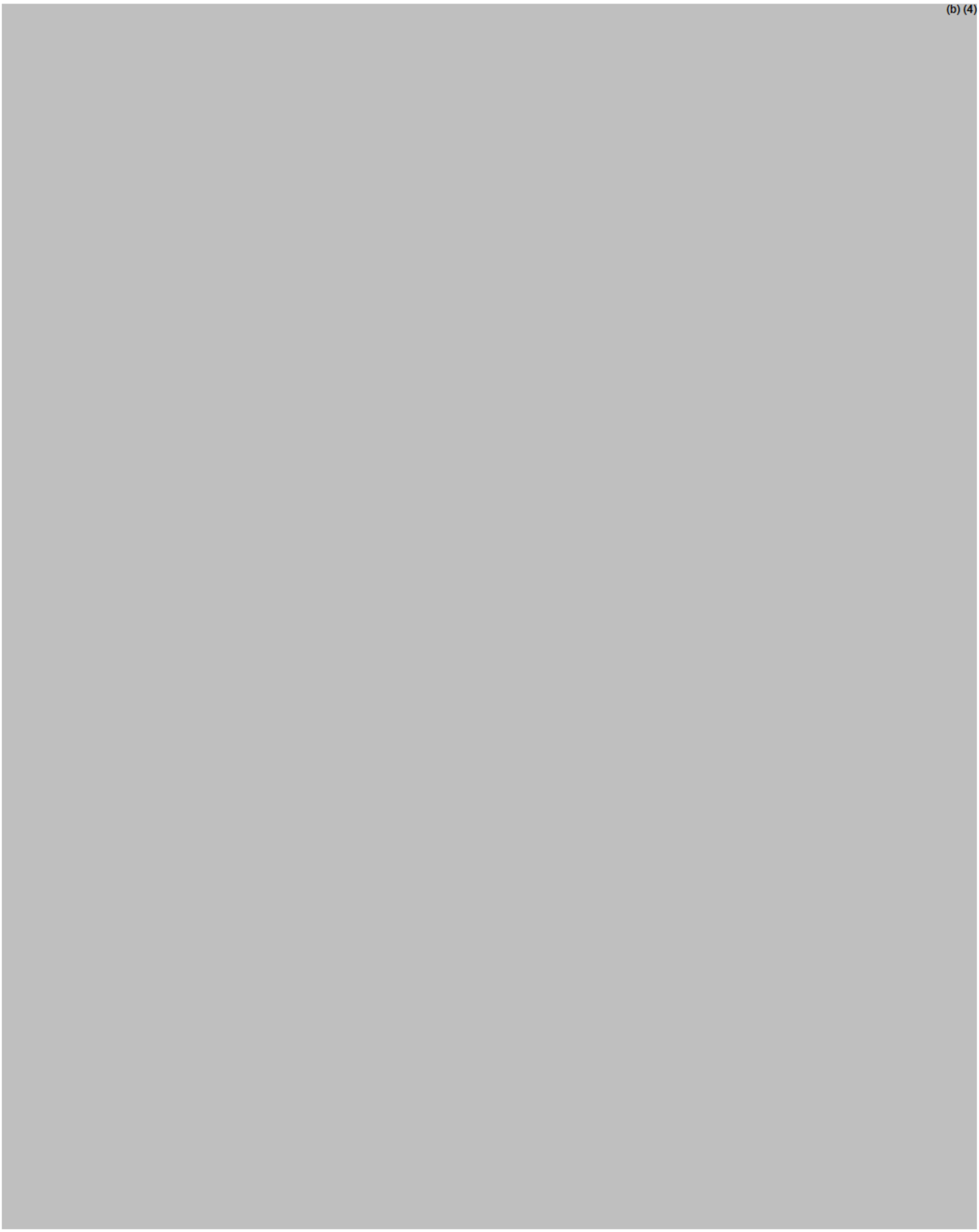
(b) (4)

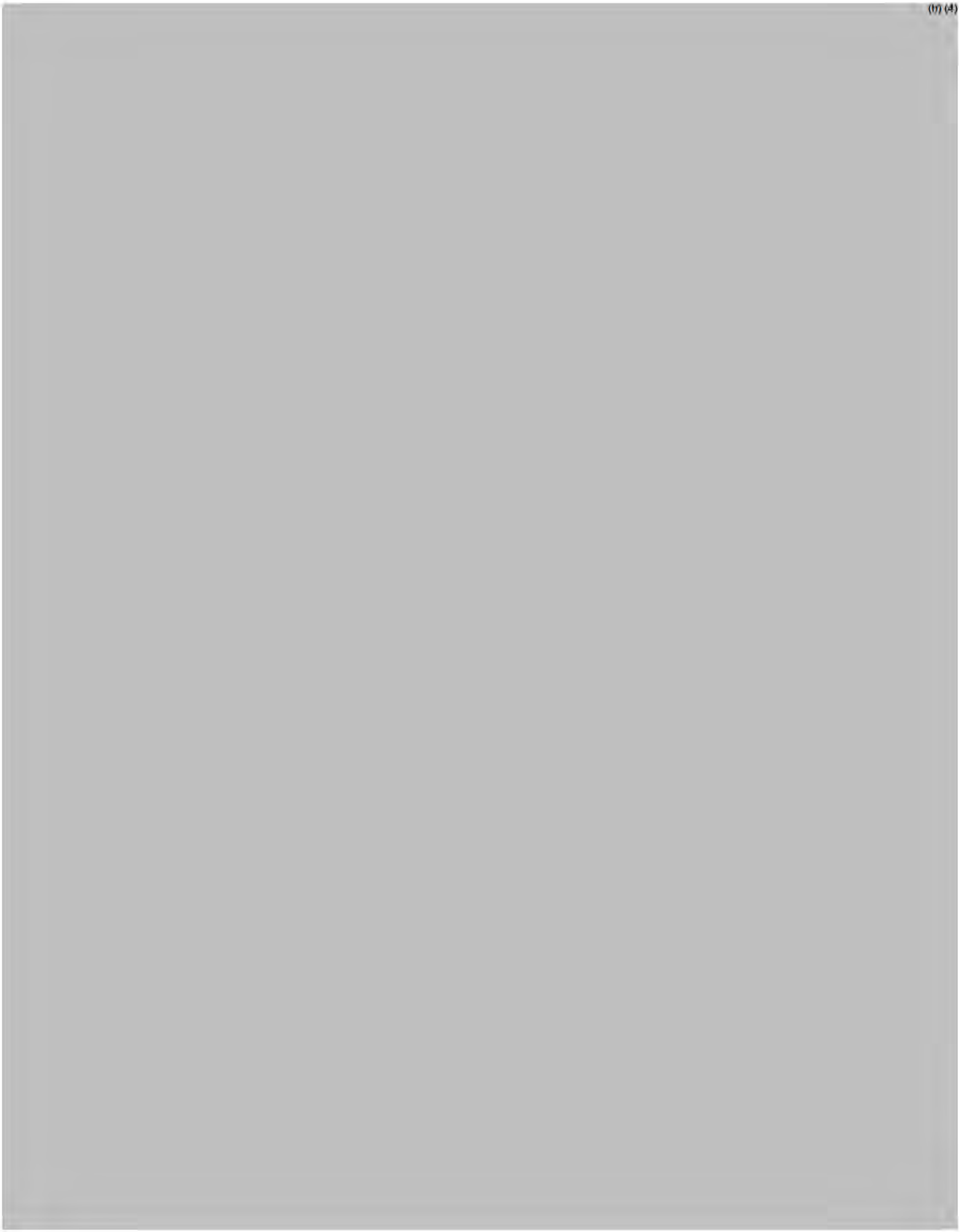


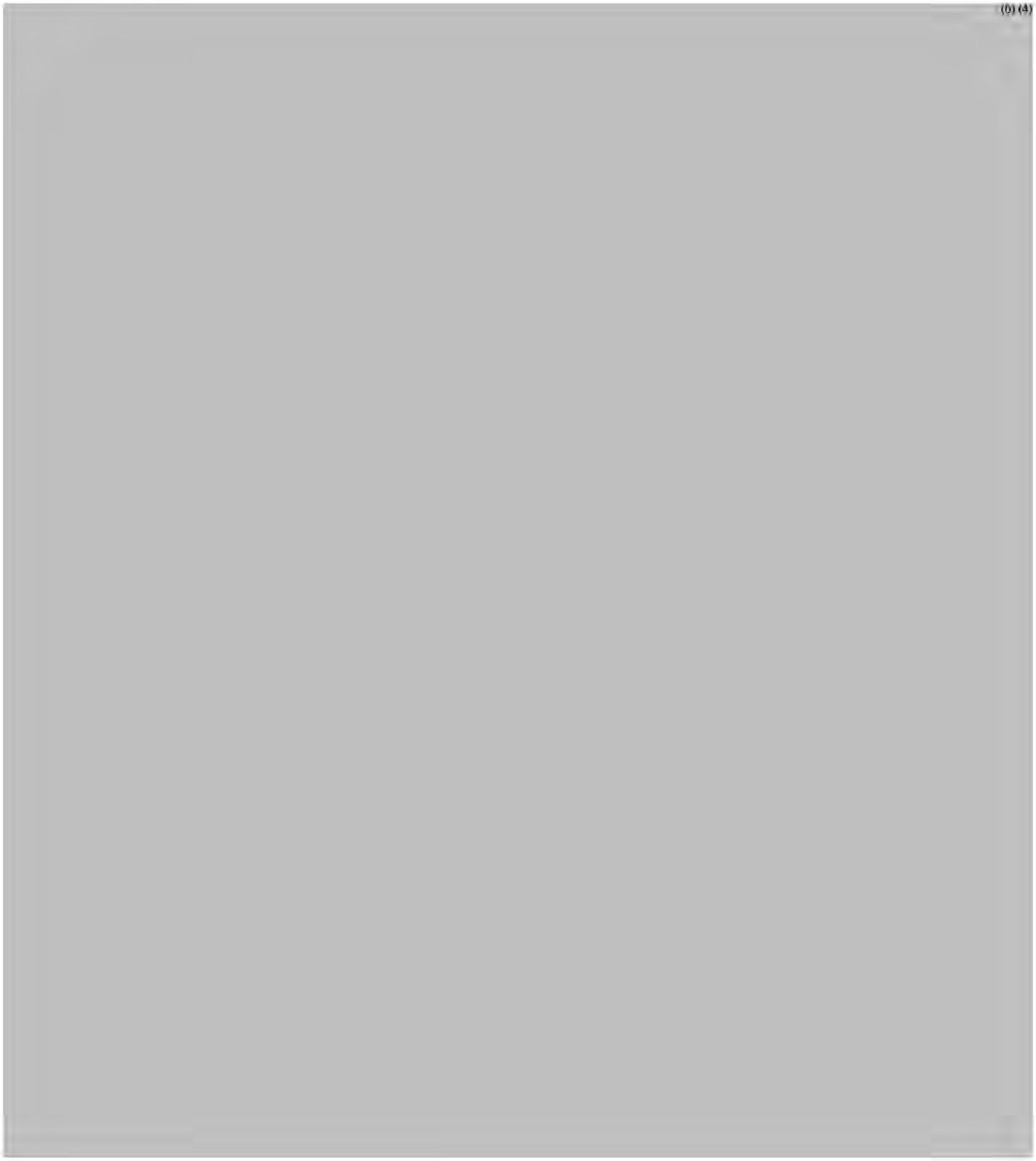
(b) (4)


(b) (4)

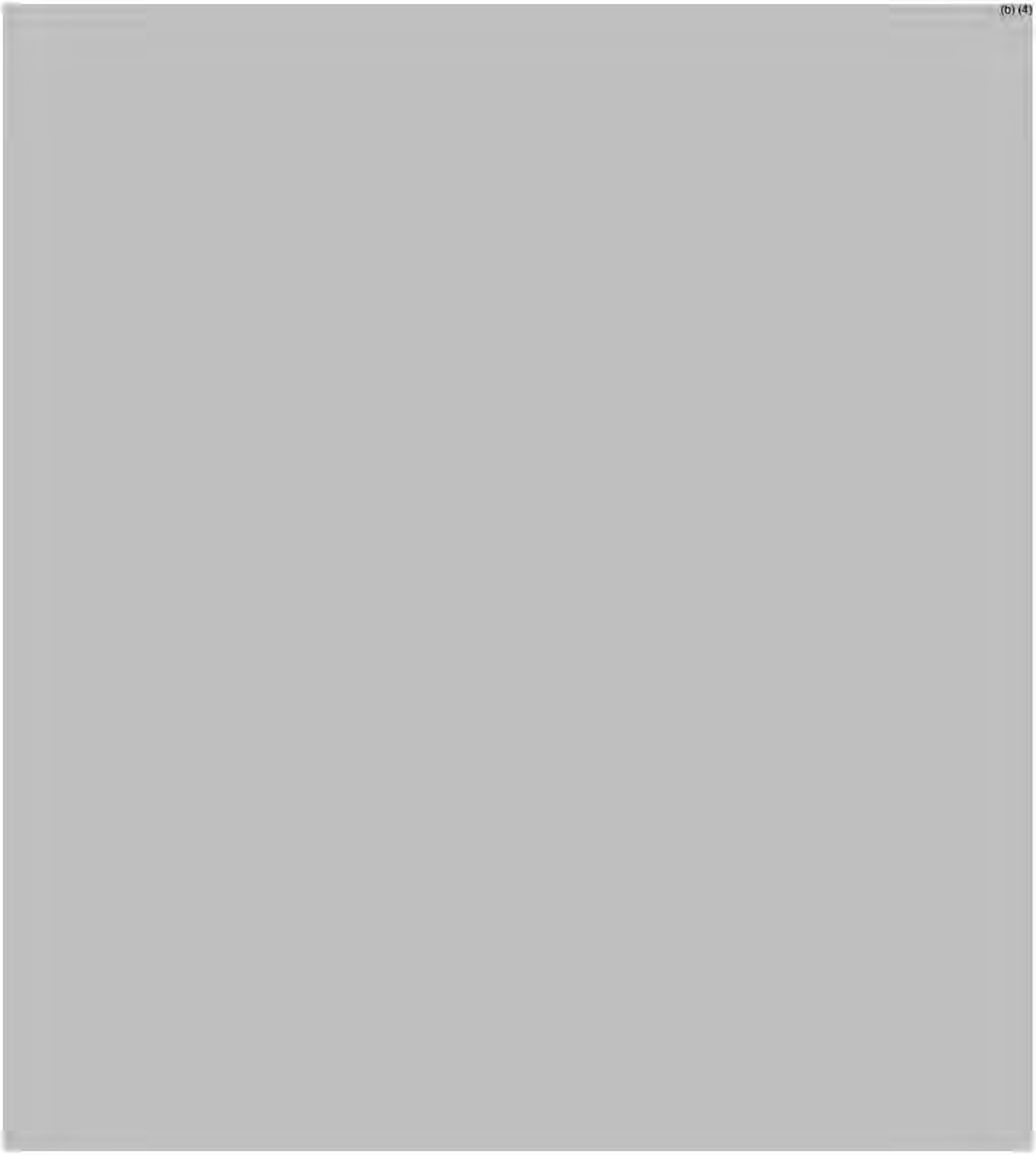

(b) (4)


(b) (4)

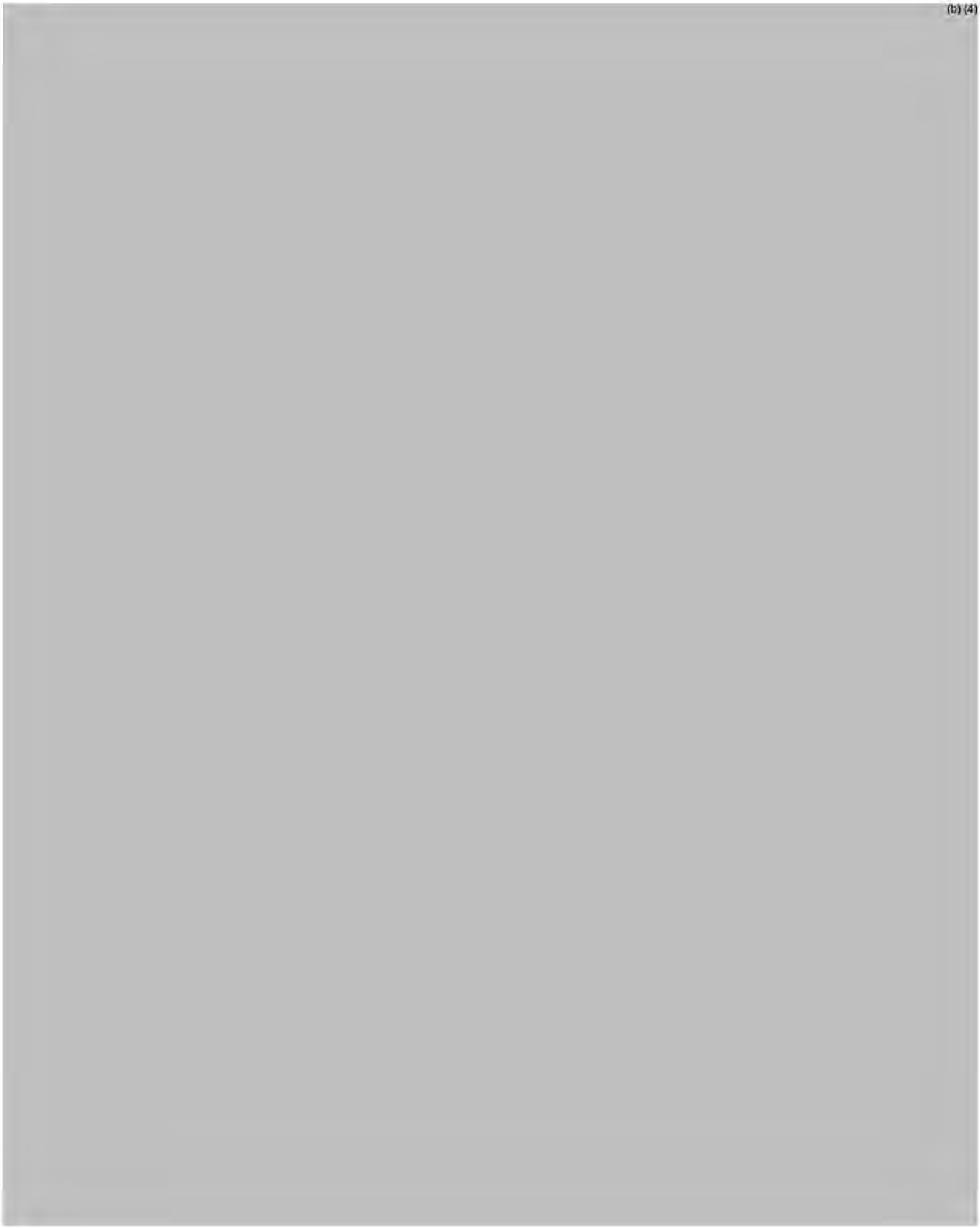

(b) (4)



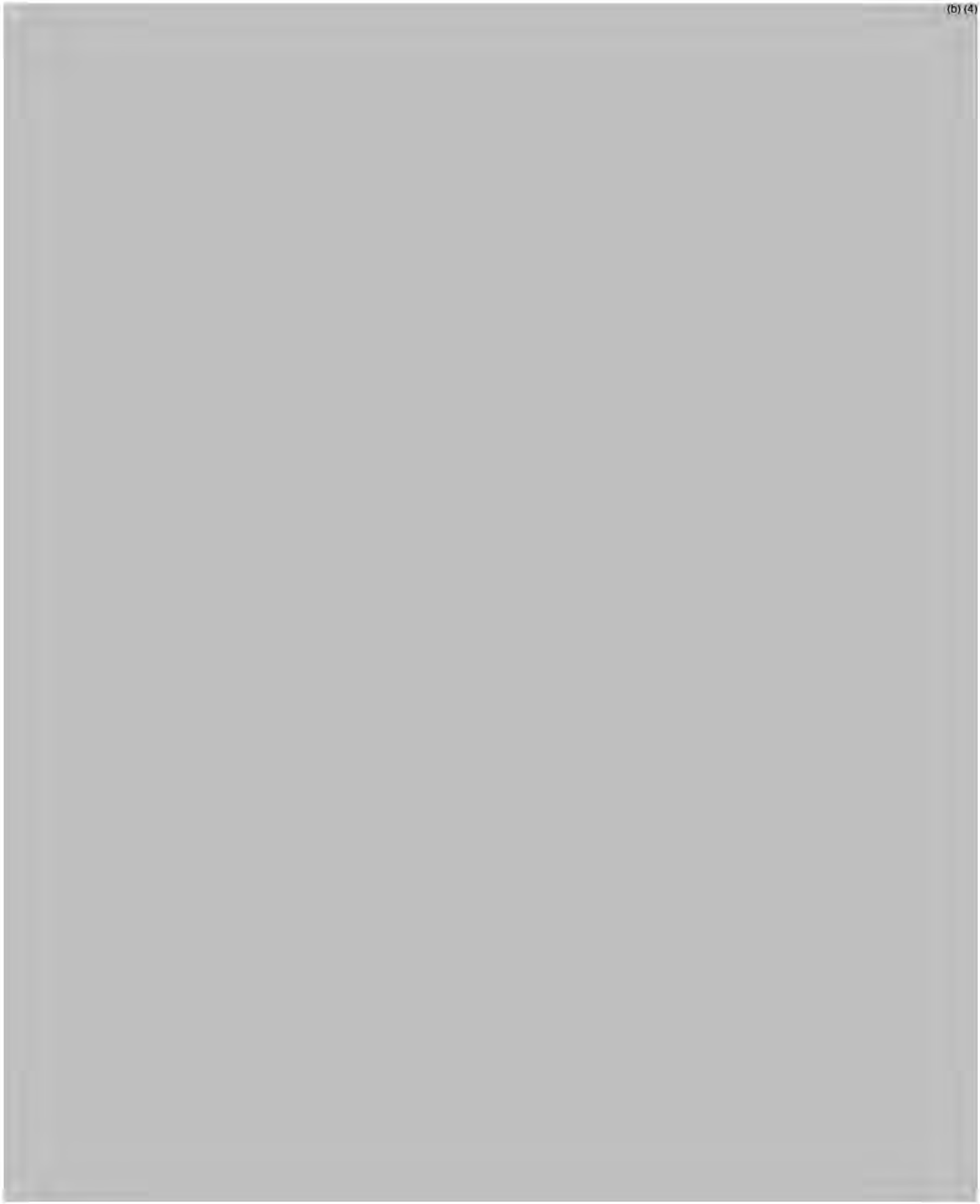
(b) (4)

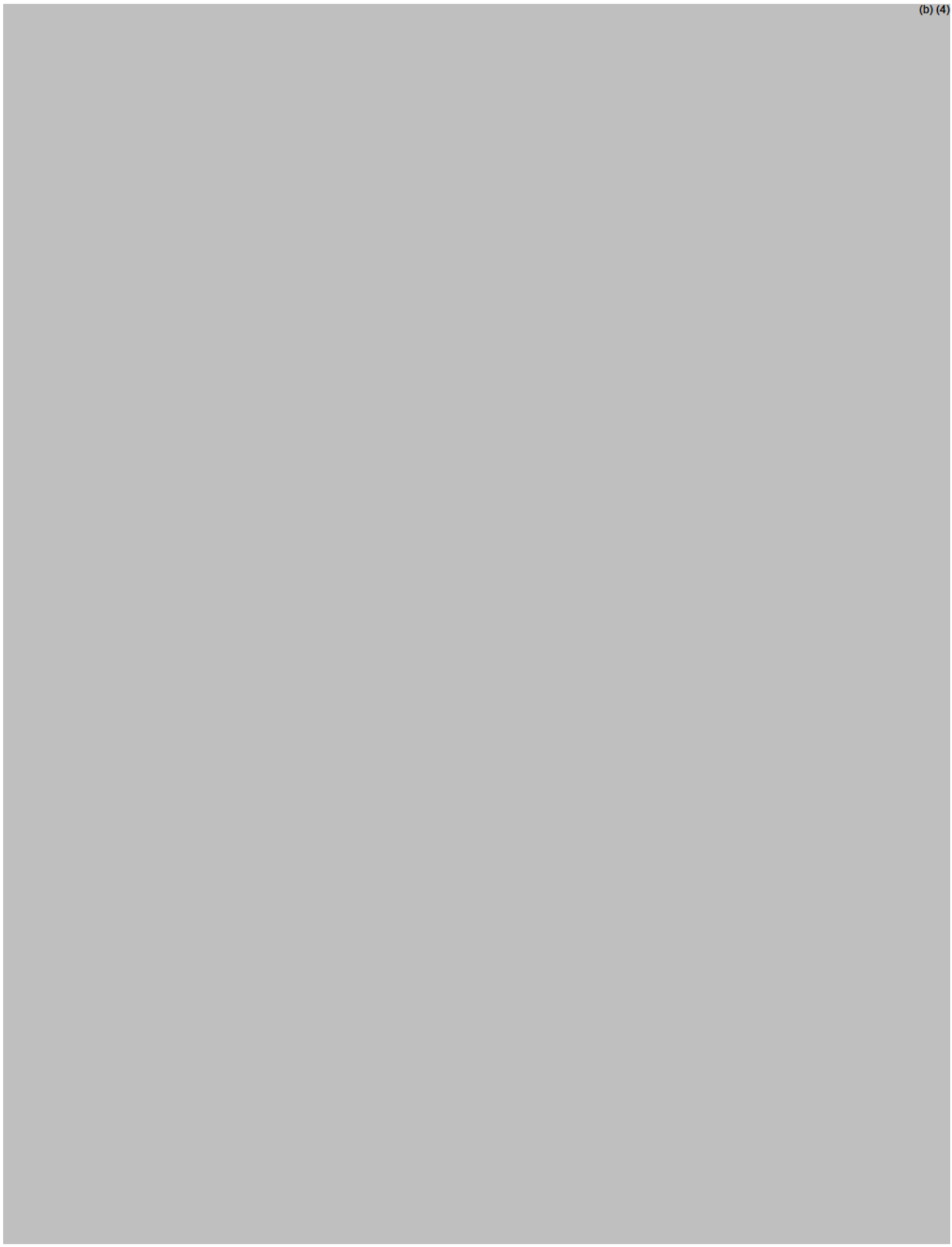


(b) (4)

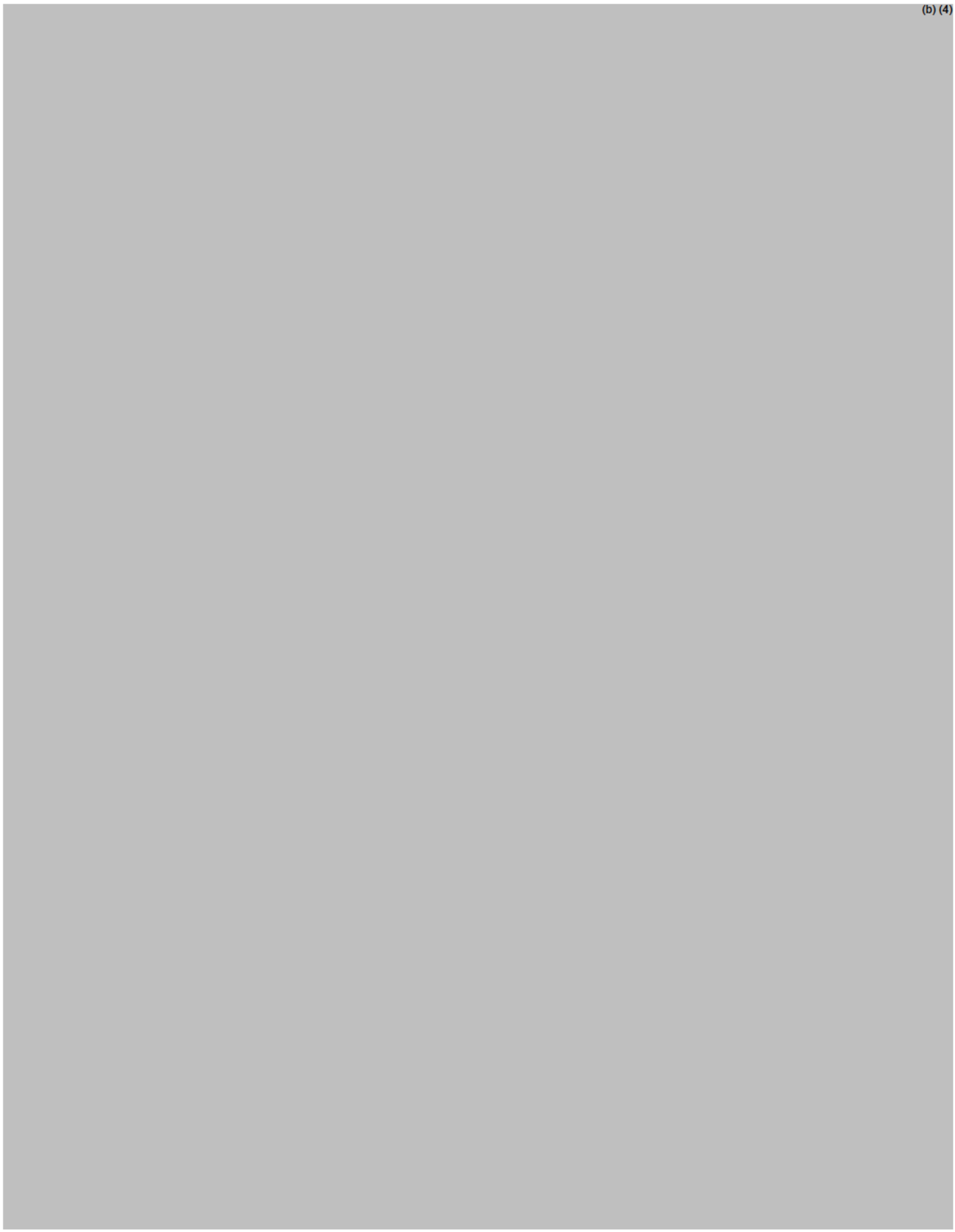


(b) (4)

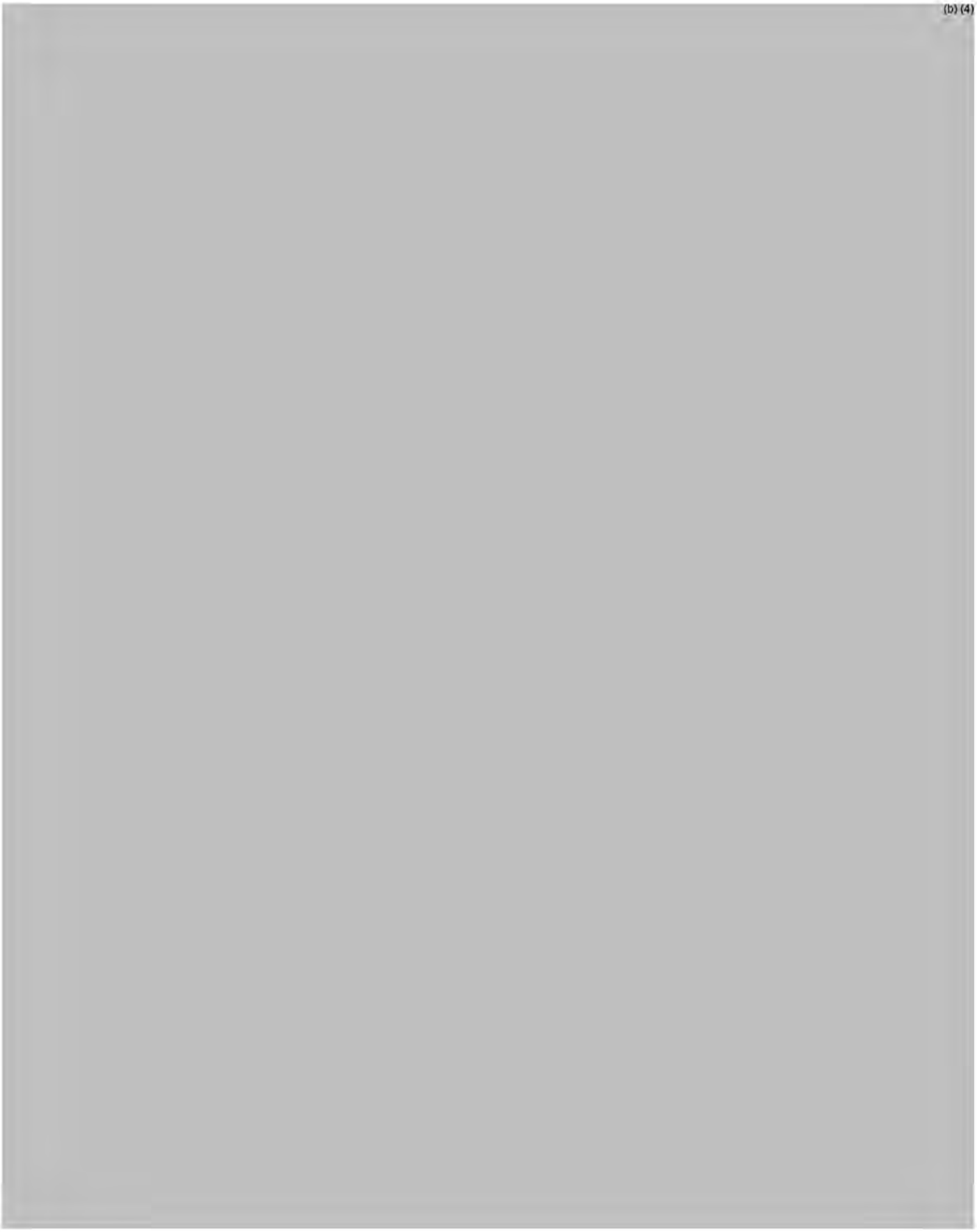

(b) (4)



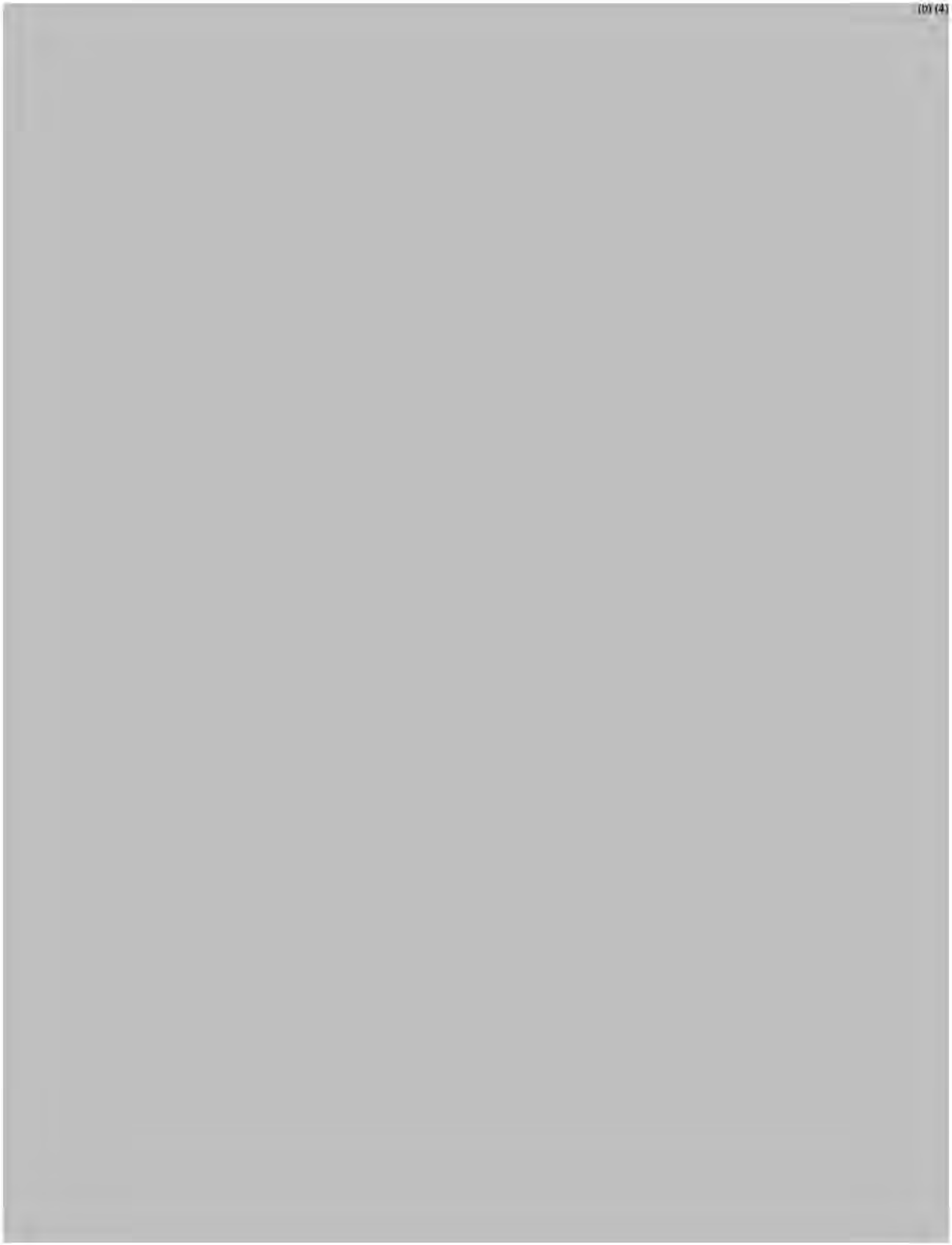
(b) (4)



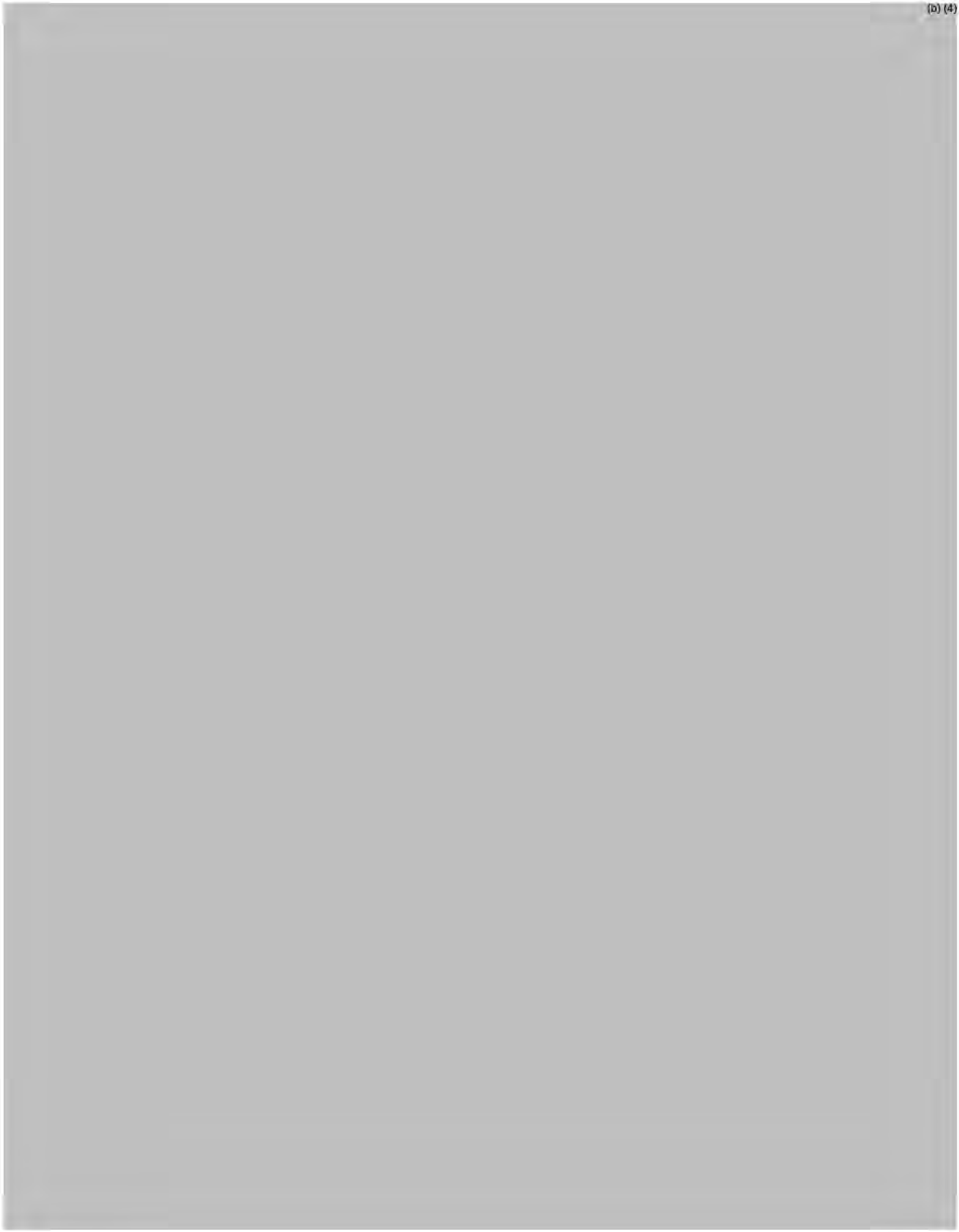
(b) (4)



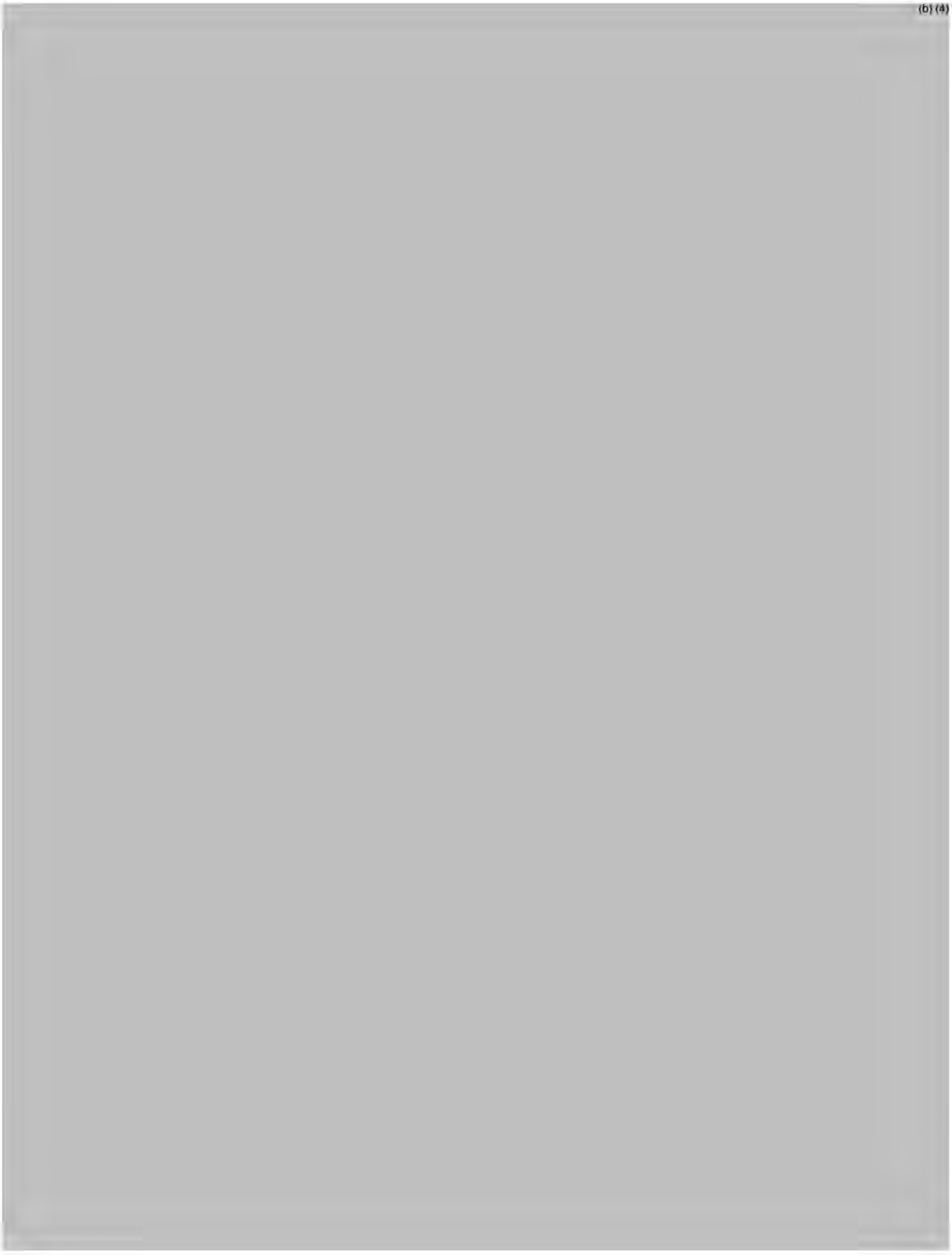
(b) (4)



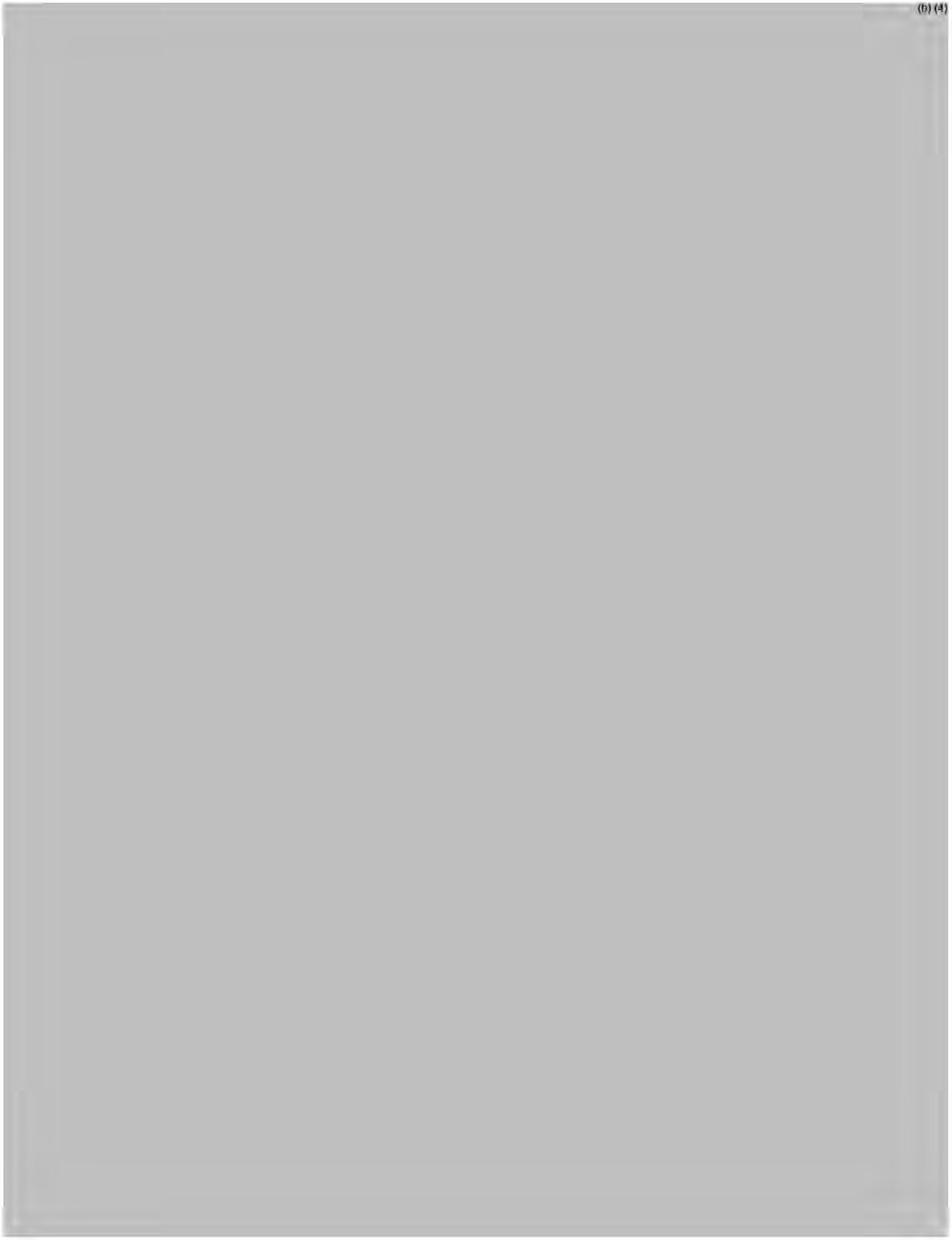
(b) (4)

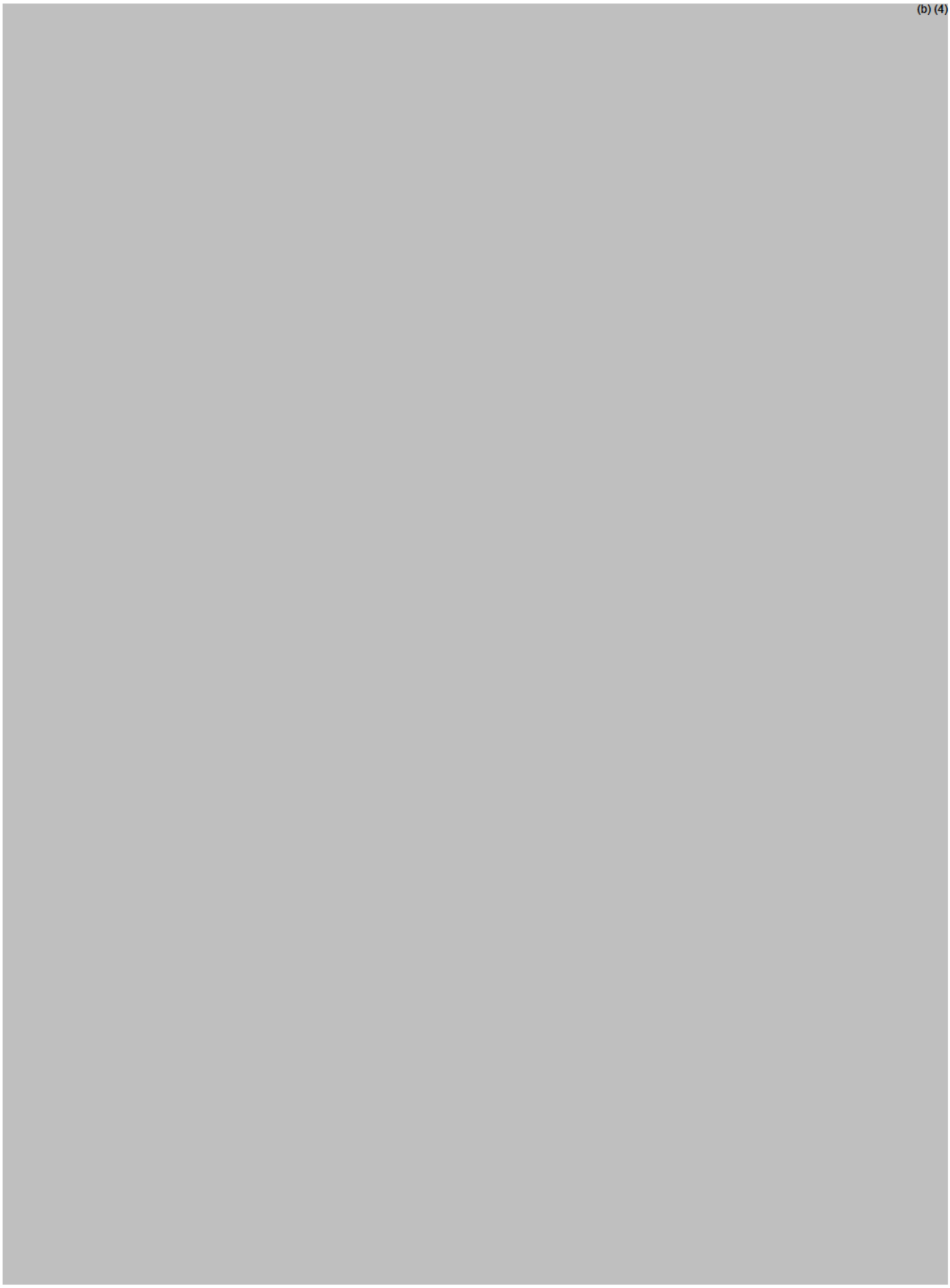


(b) (4)

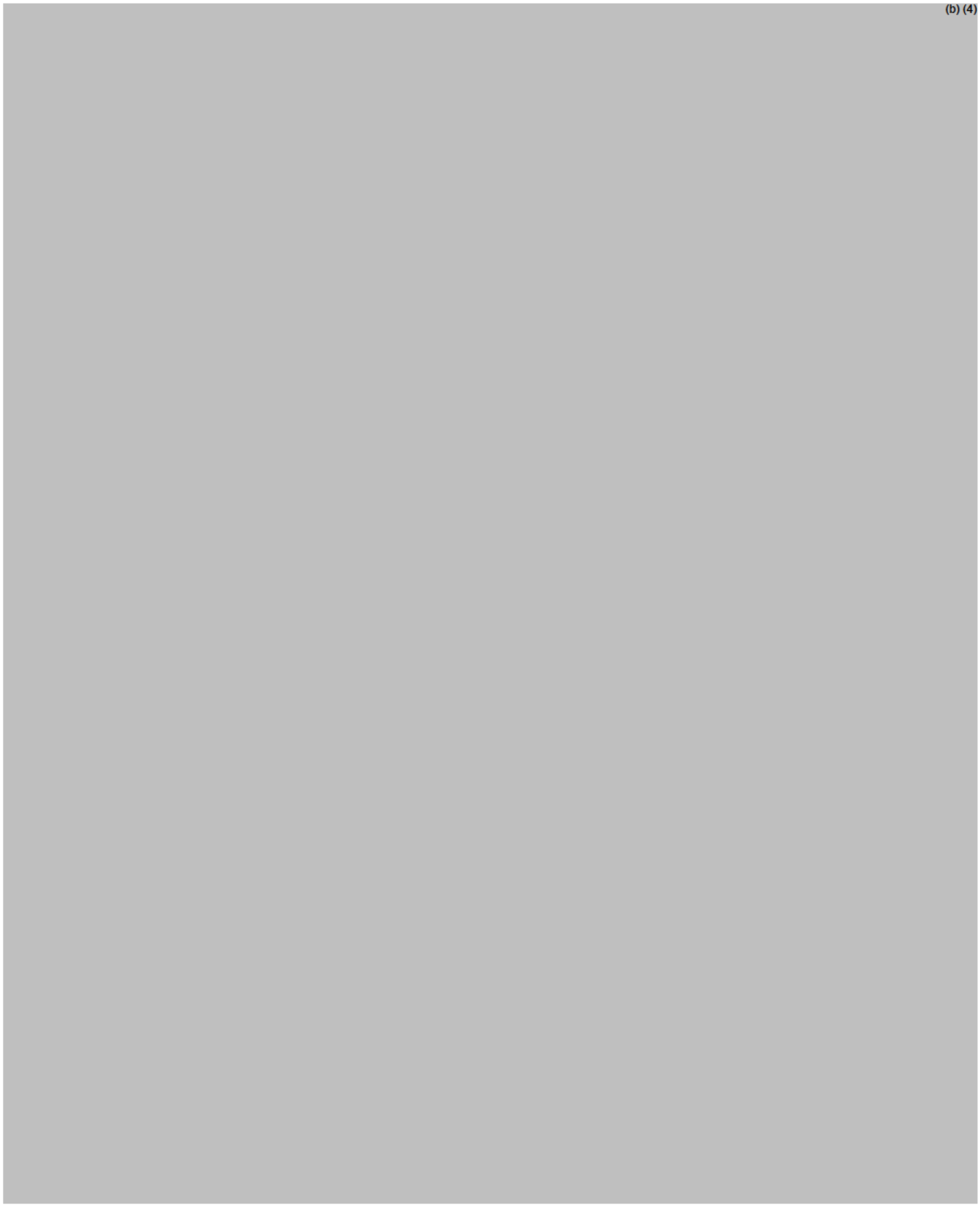


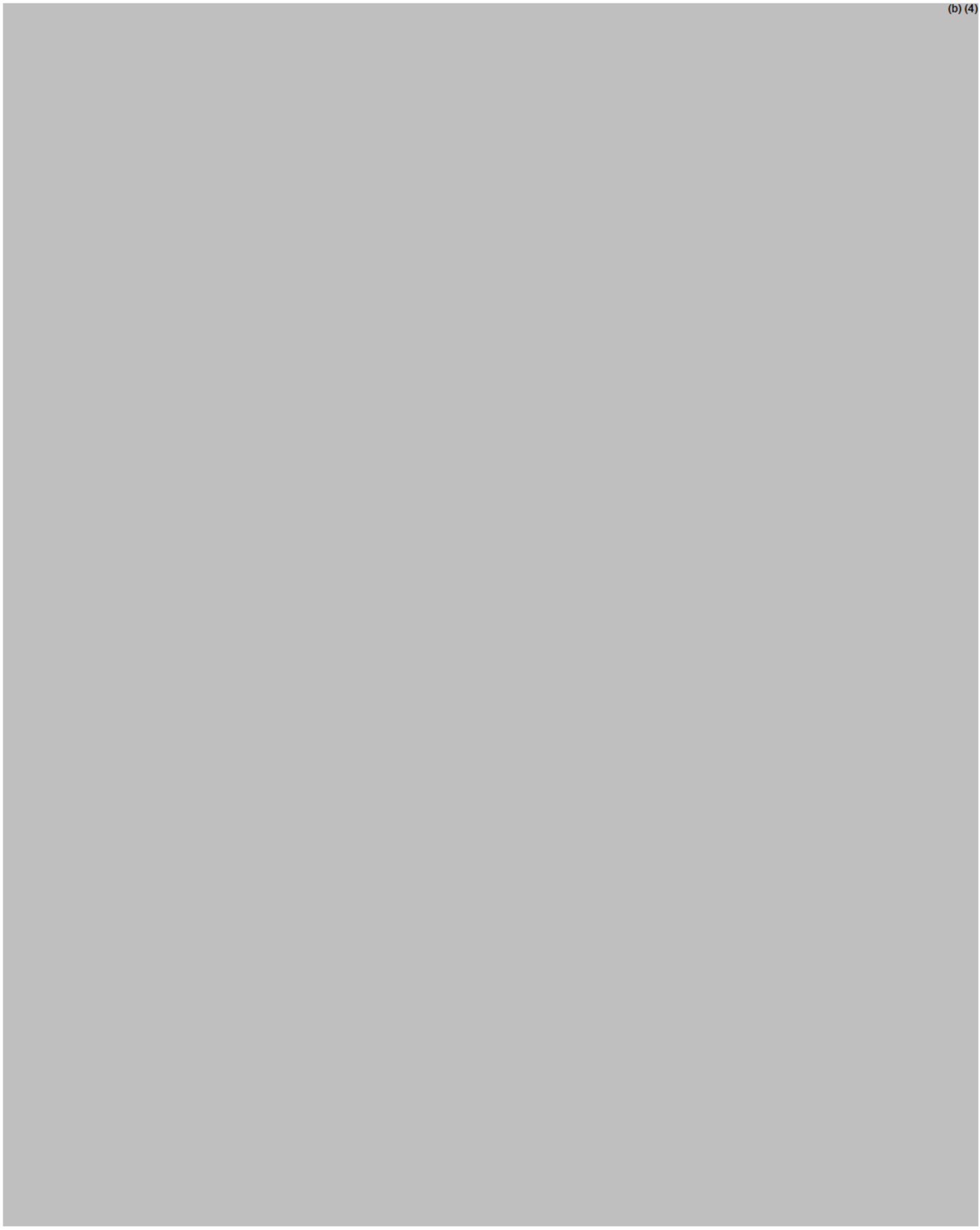
(b) (4)


(b) (4)
(b) (4)

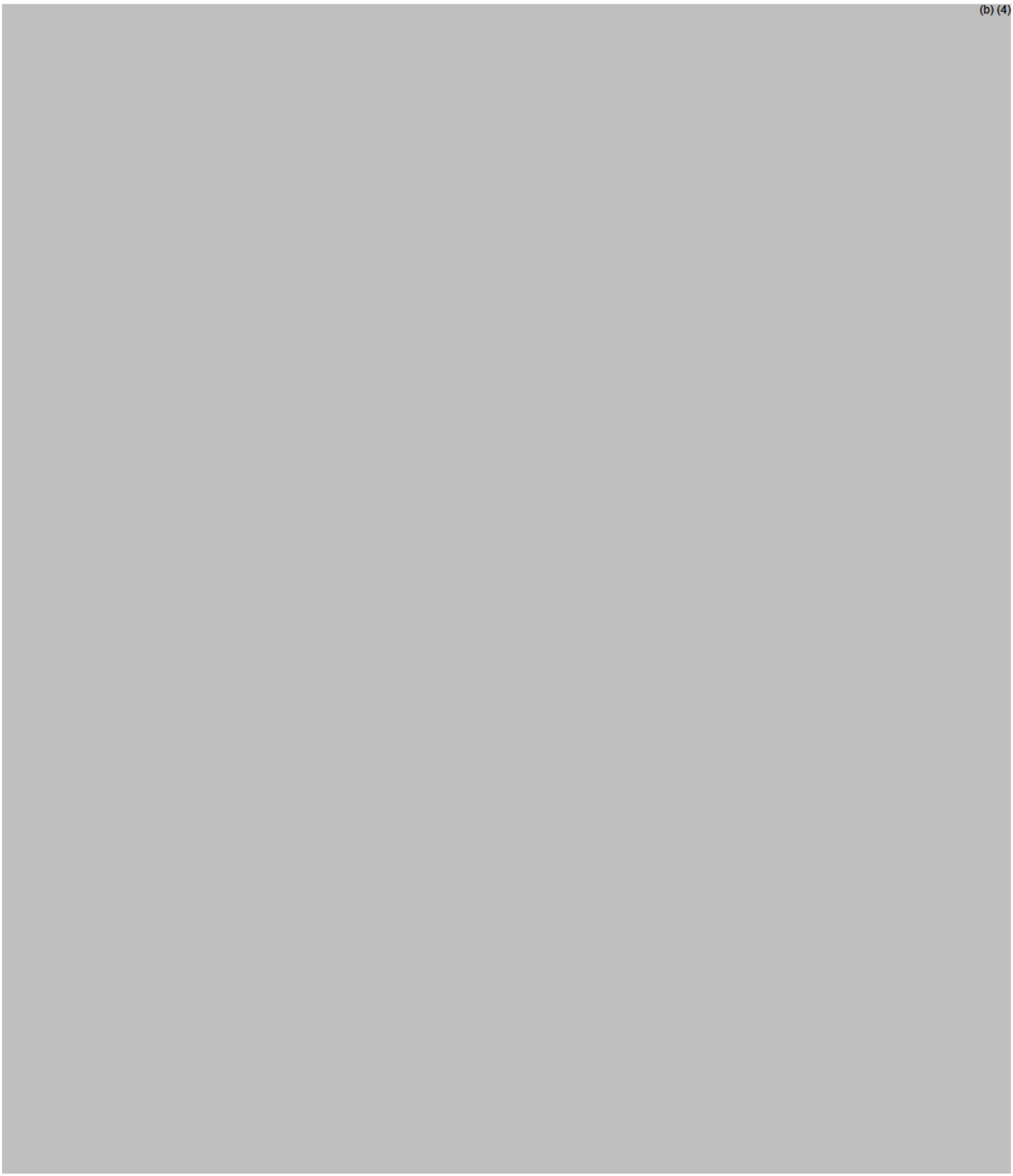


(b) (4)

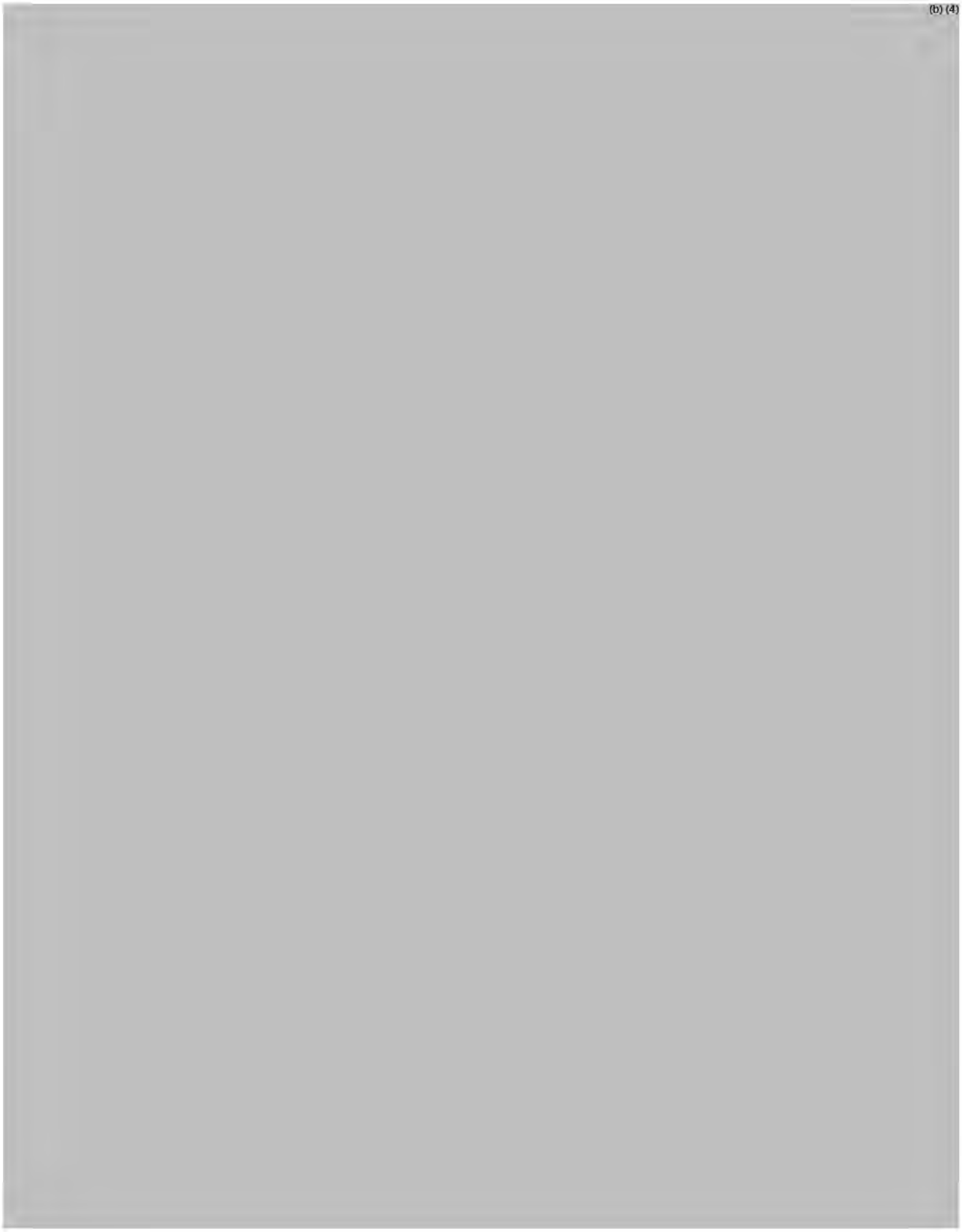

(b) (4)



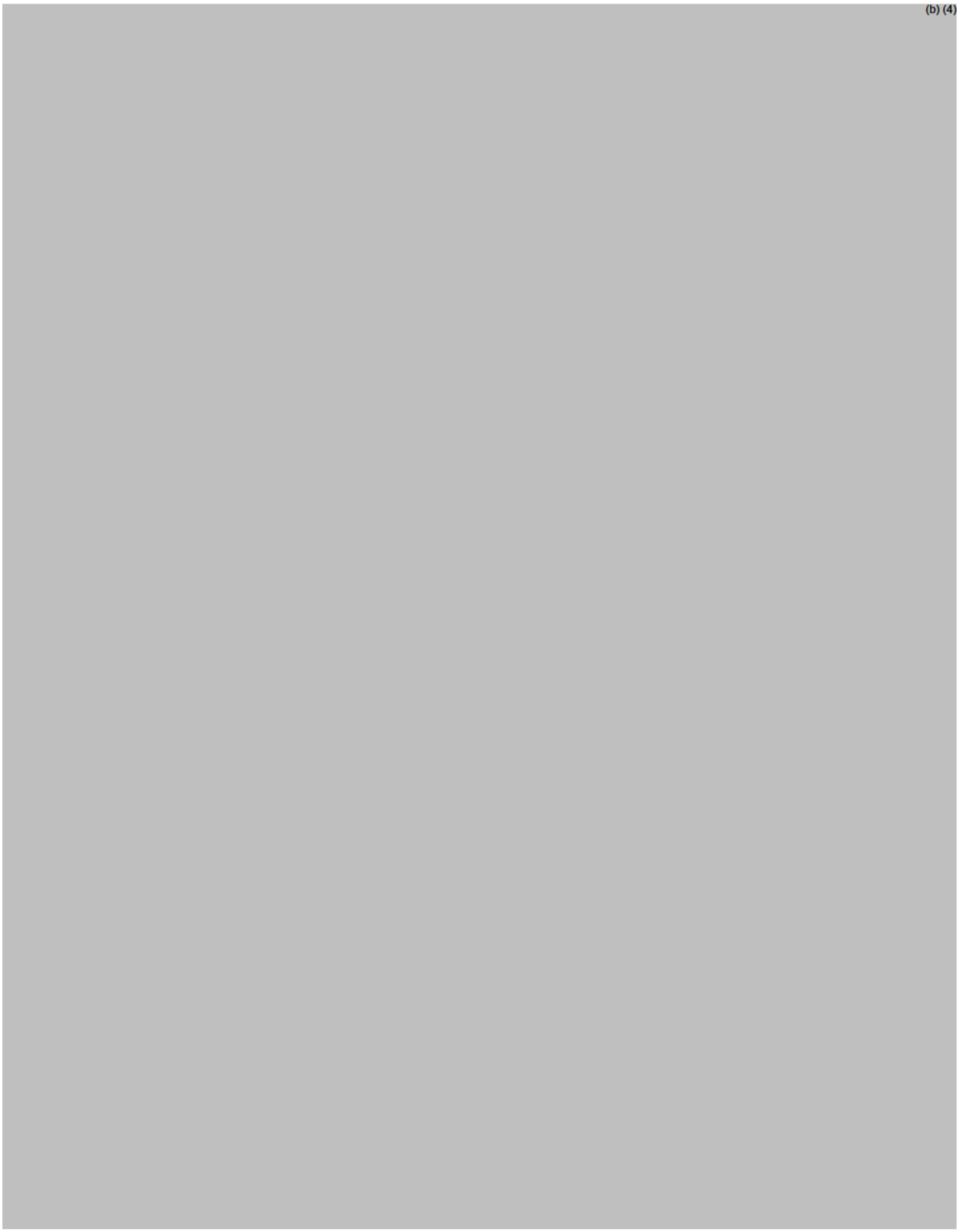
(b) (4)



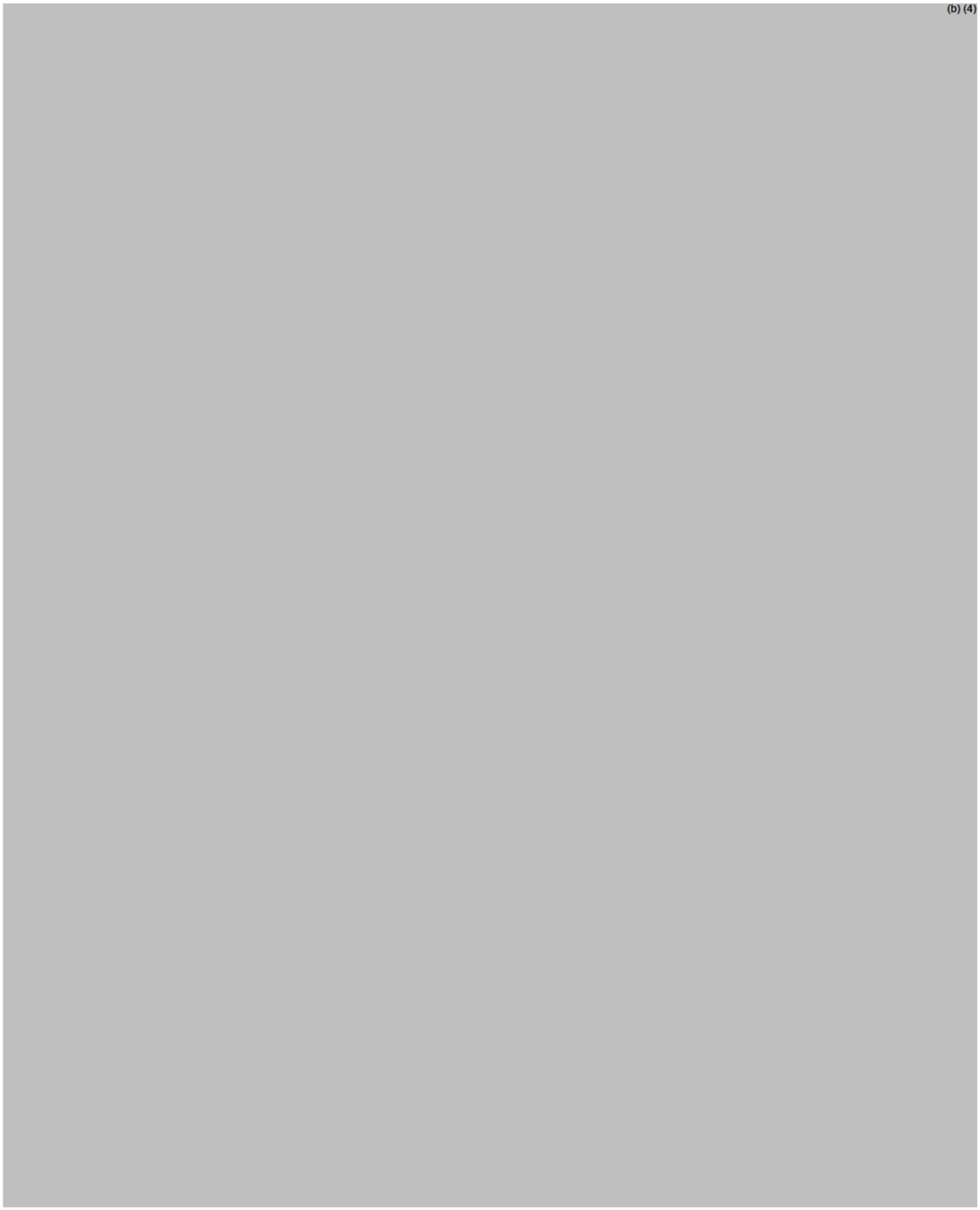
(b) (4)



(b) (4)



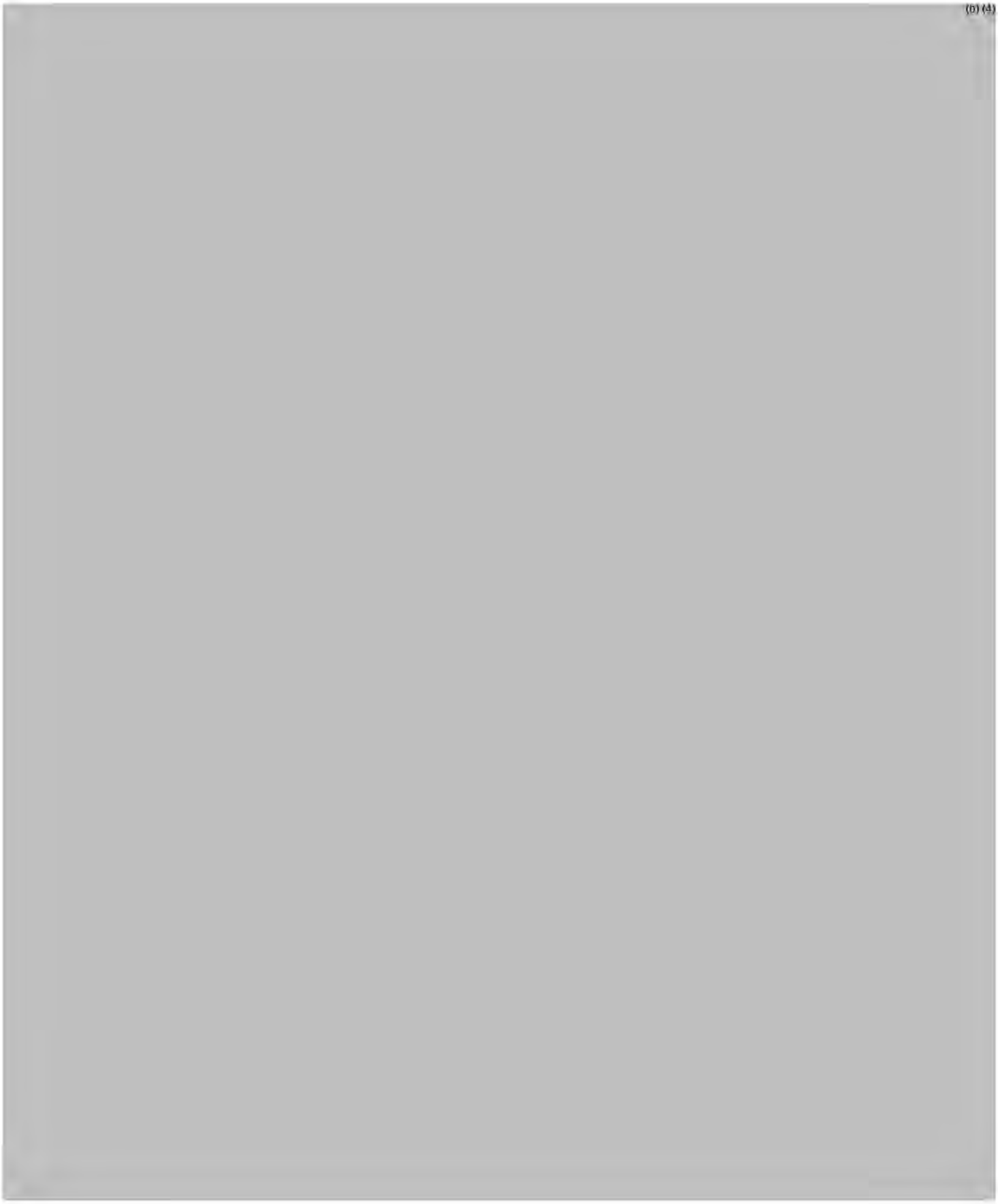
(b) (4)



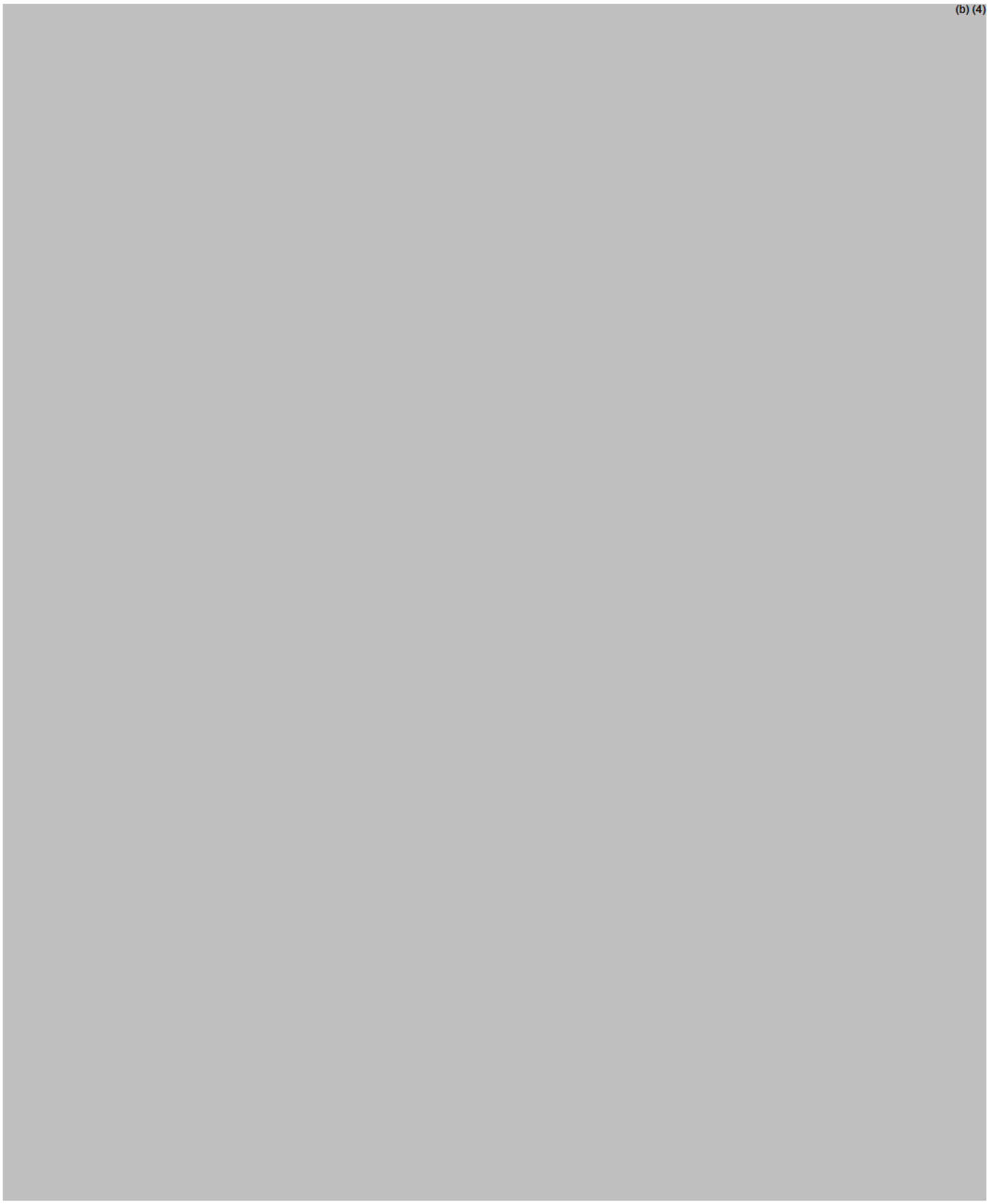
(b) (4)

(b) (4)

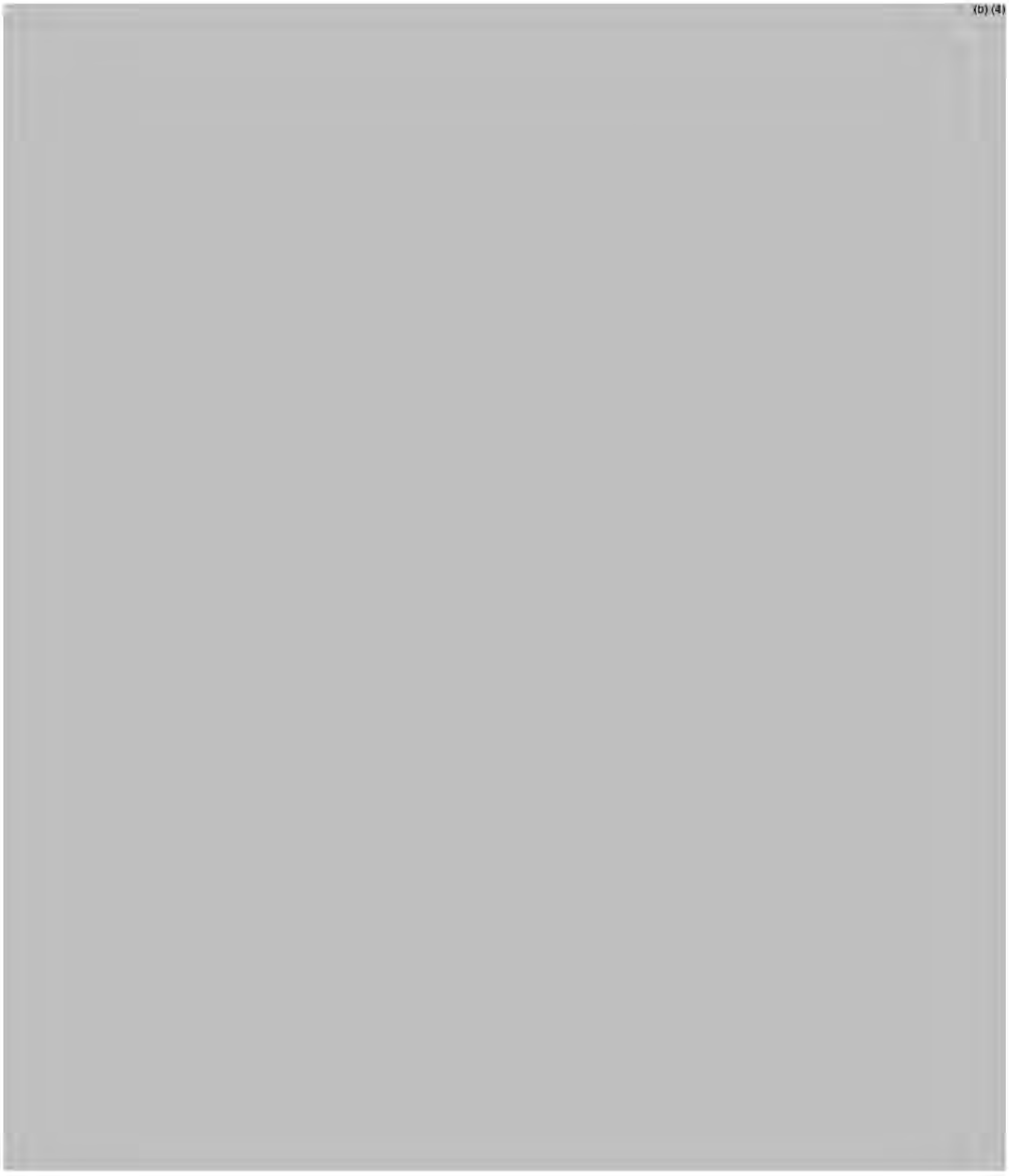

(b) (4)



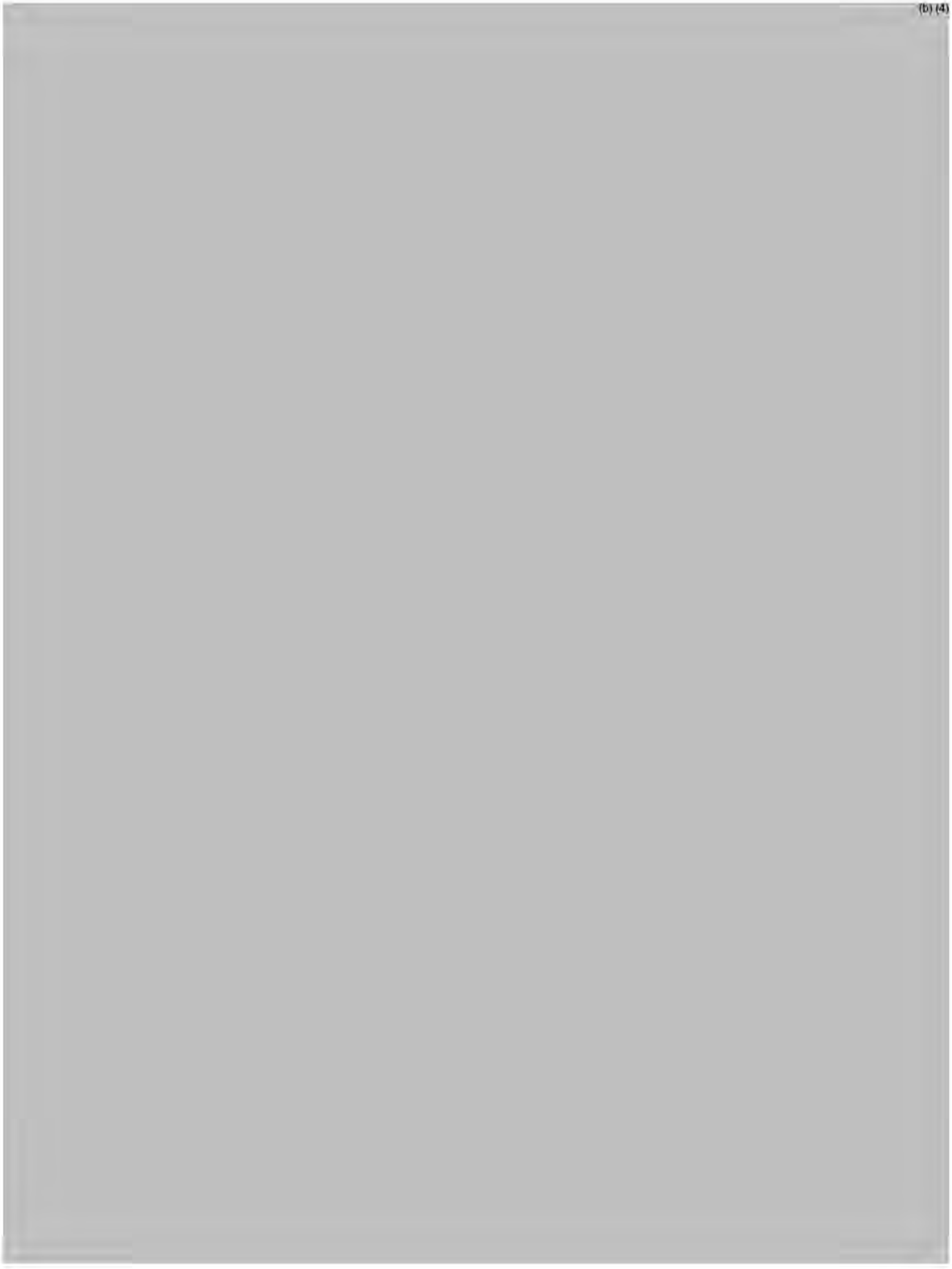
(b) (4)



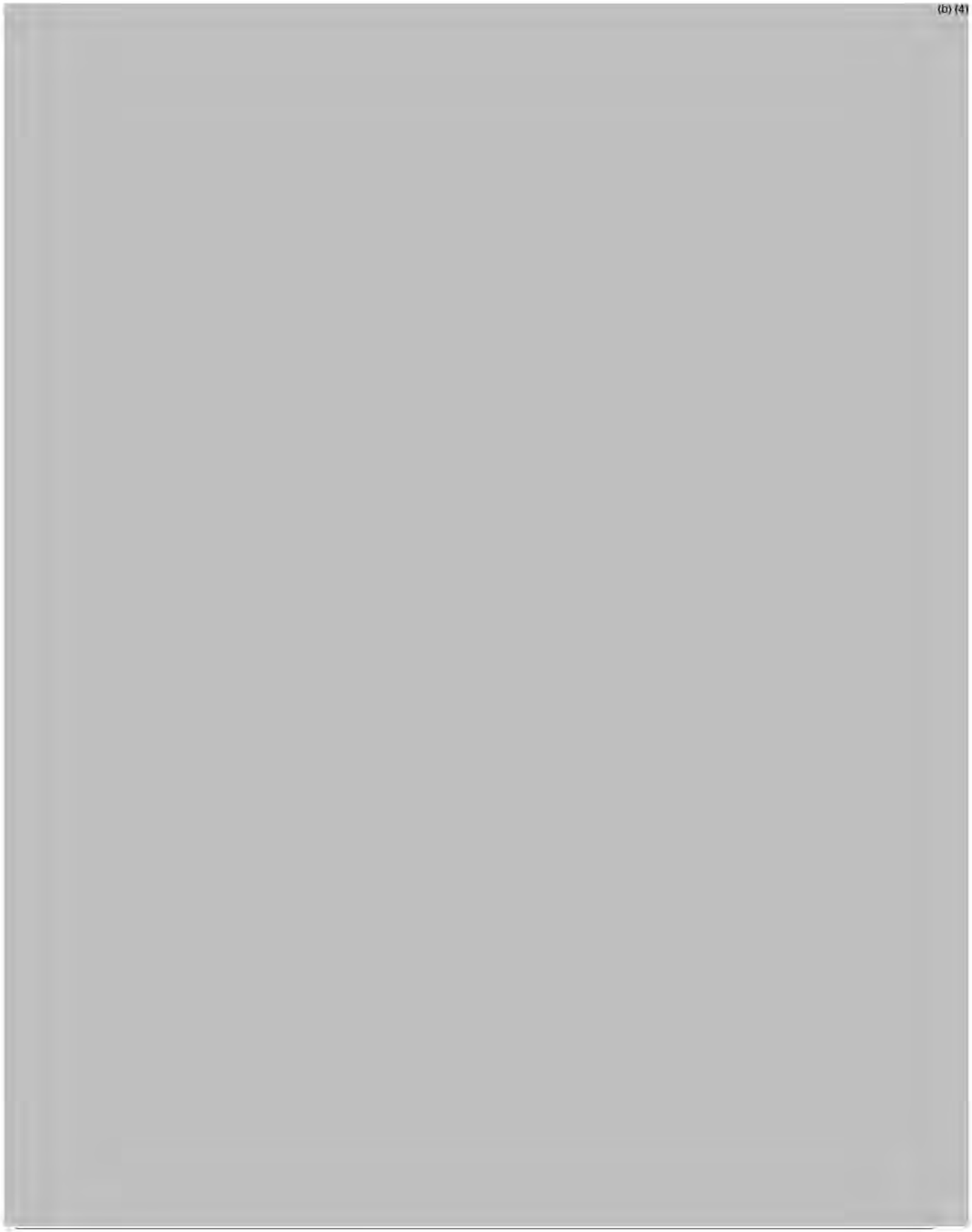
(b) (4)



(b) (4)



(b) (4)



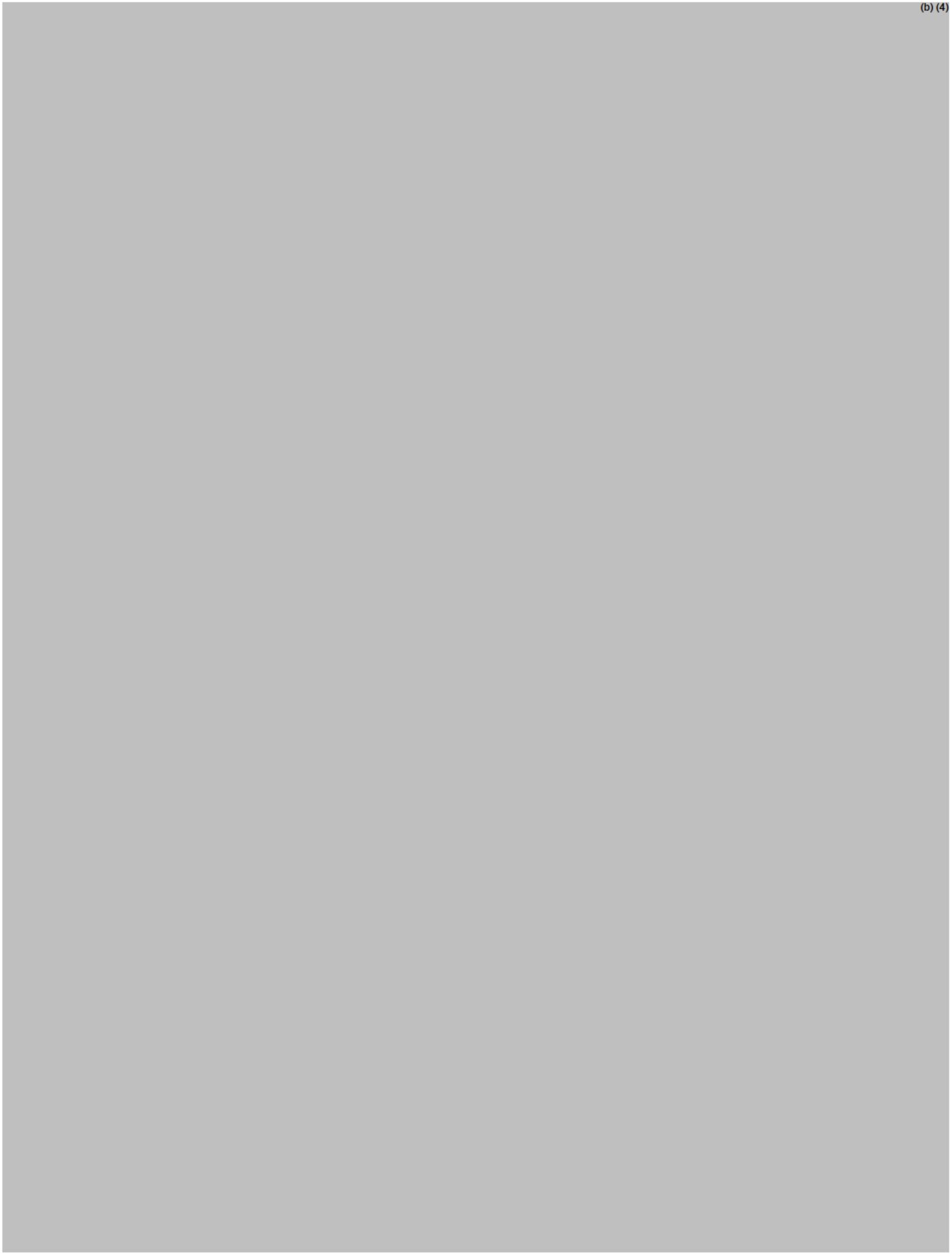
(b) (4)

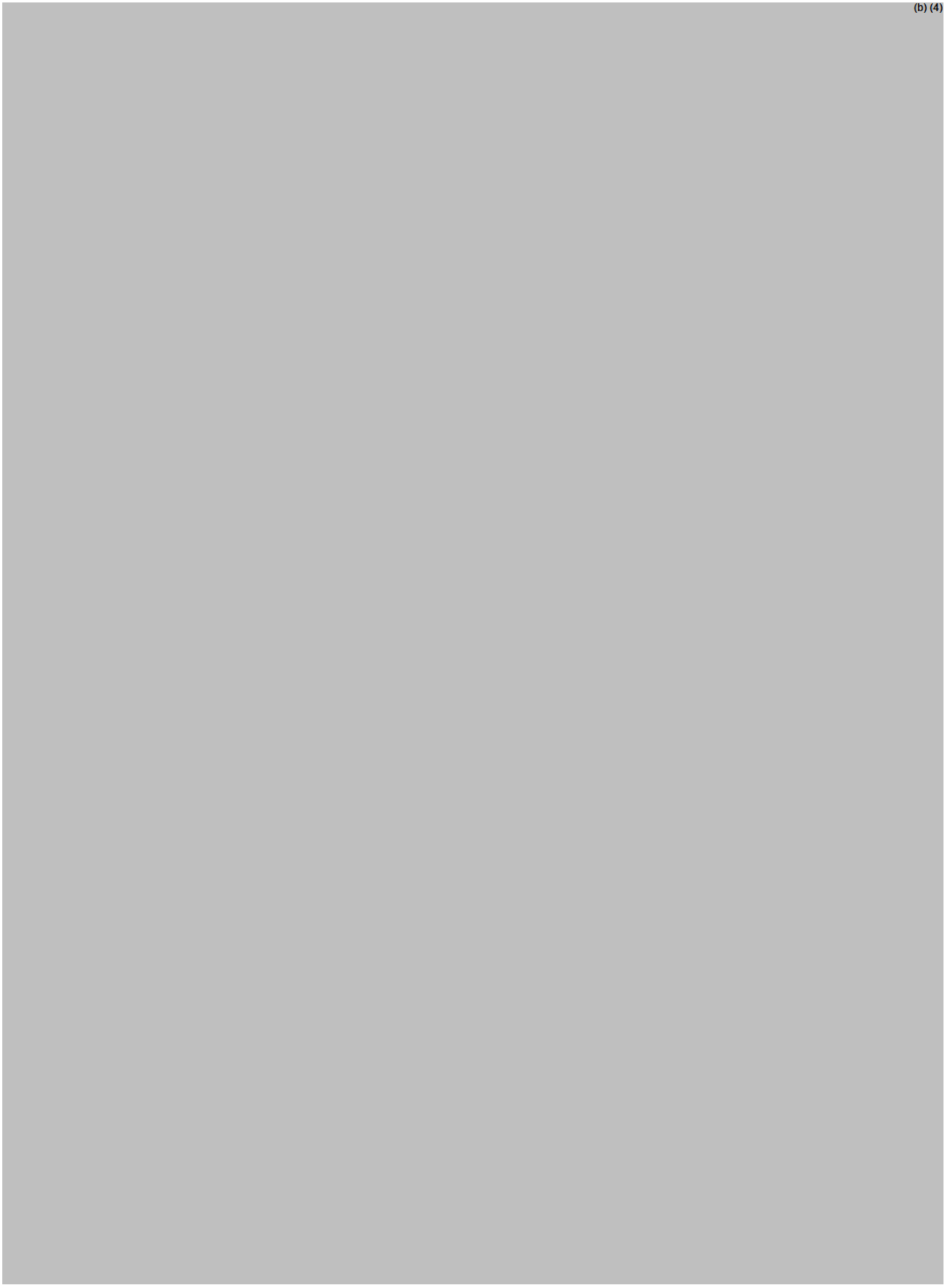
(b) (4)

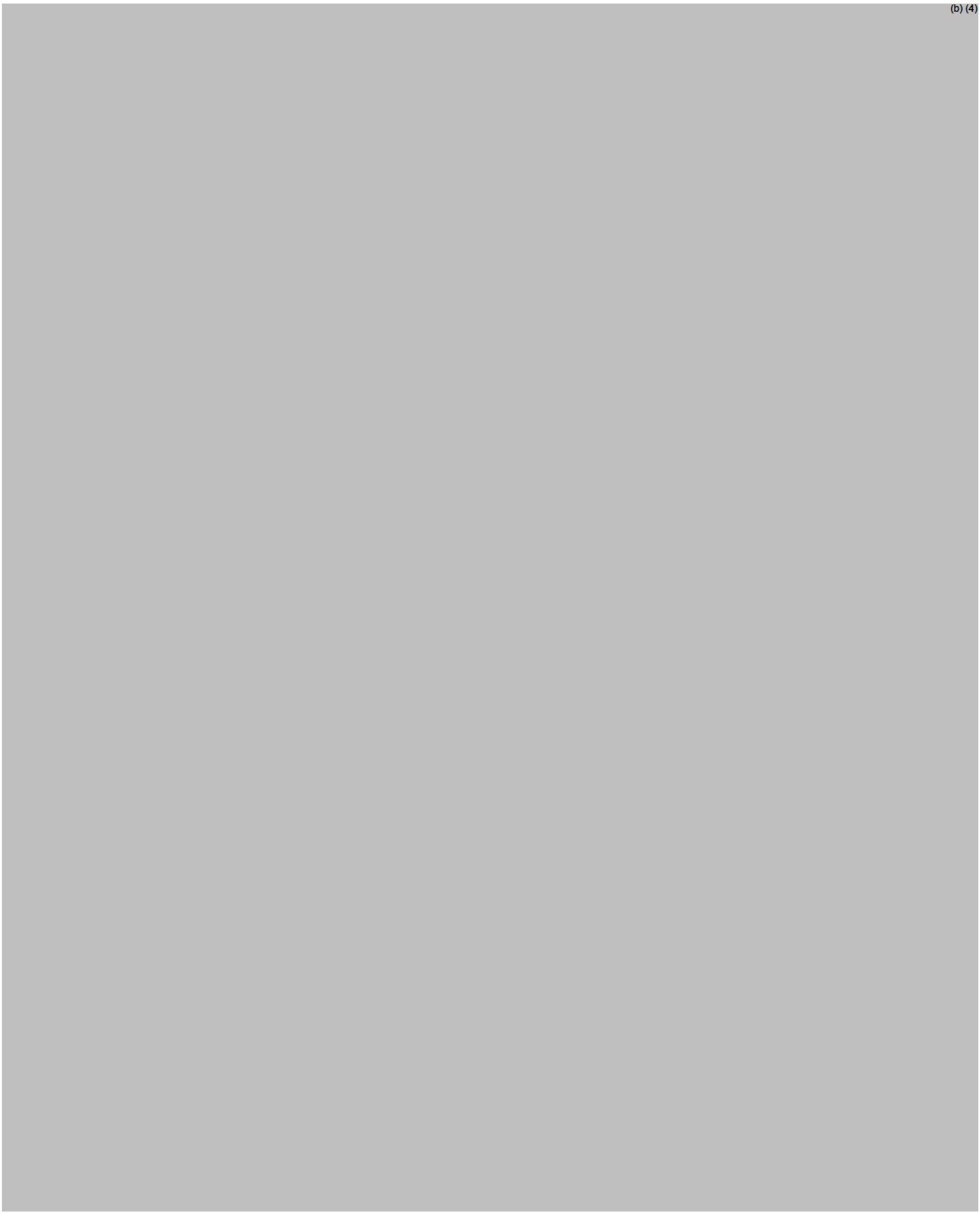
(b) (4)

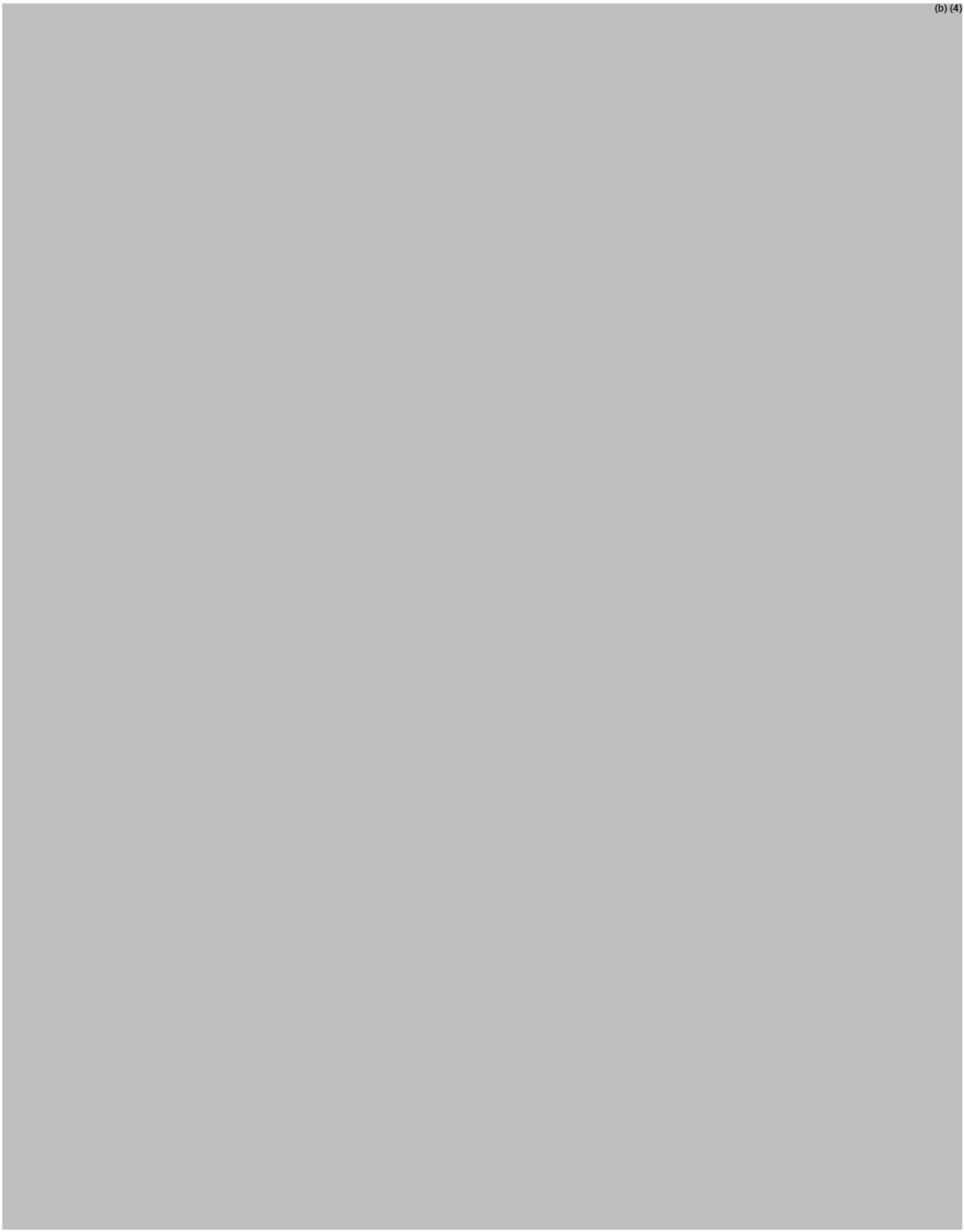
6. PROTOCOL

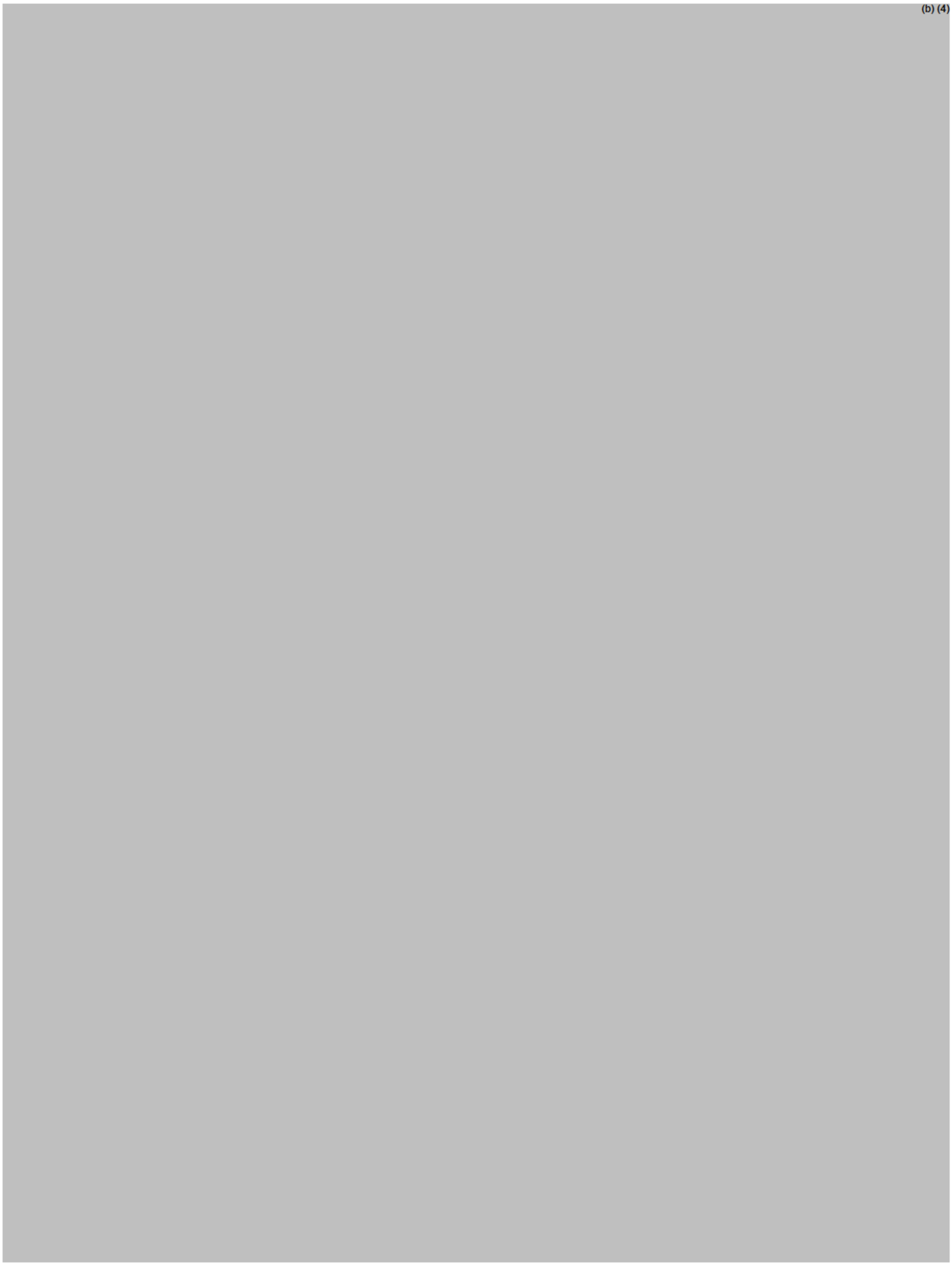
6.1. Study Protocol

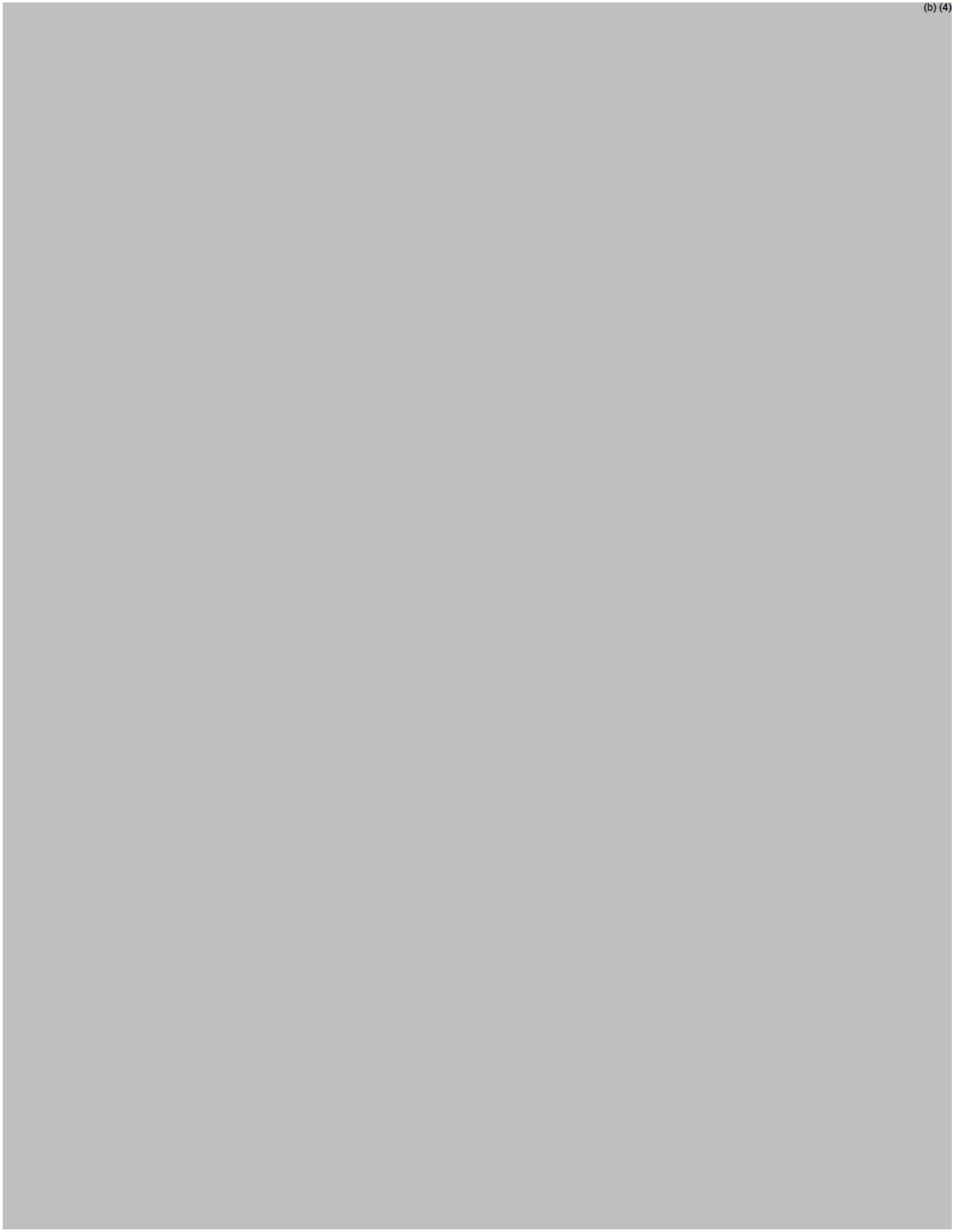

(b) (4)

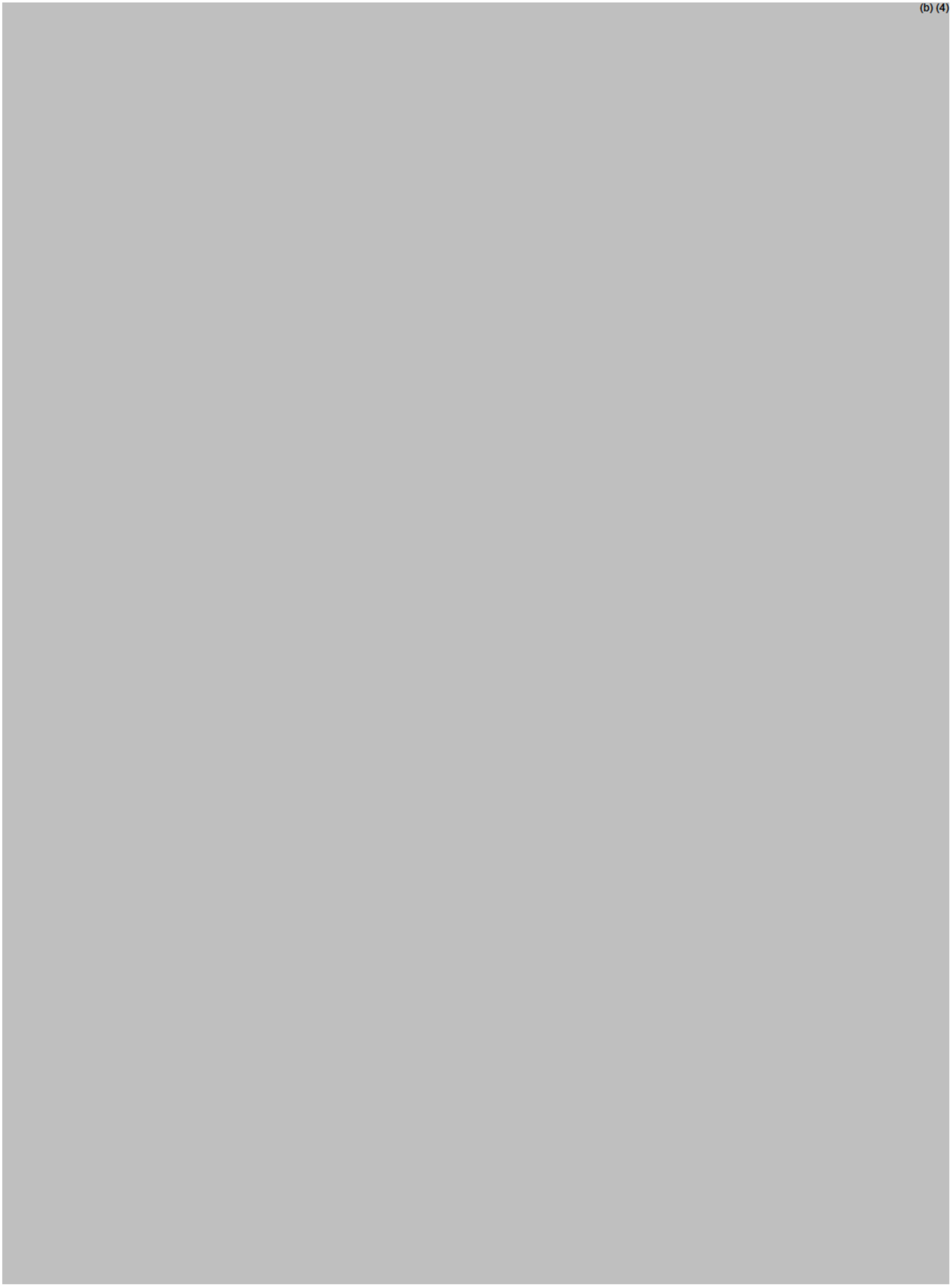

(b) (4)

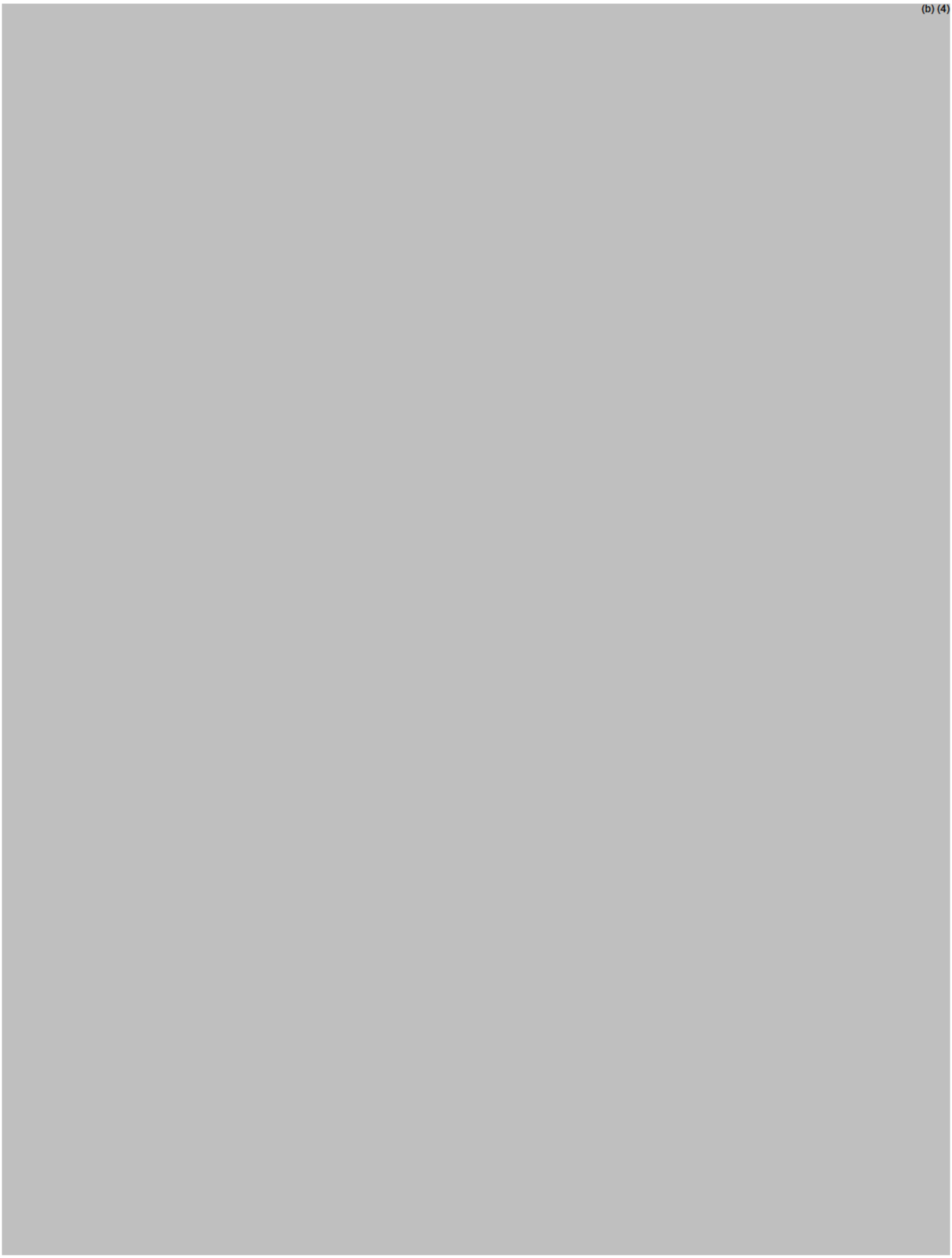

(b) (4)



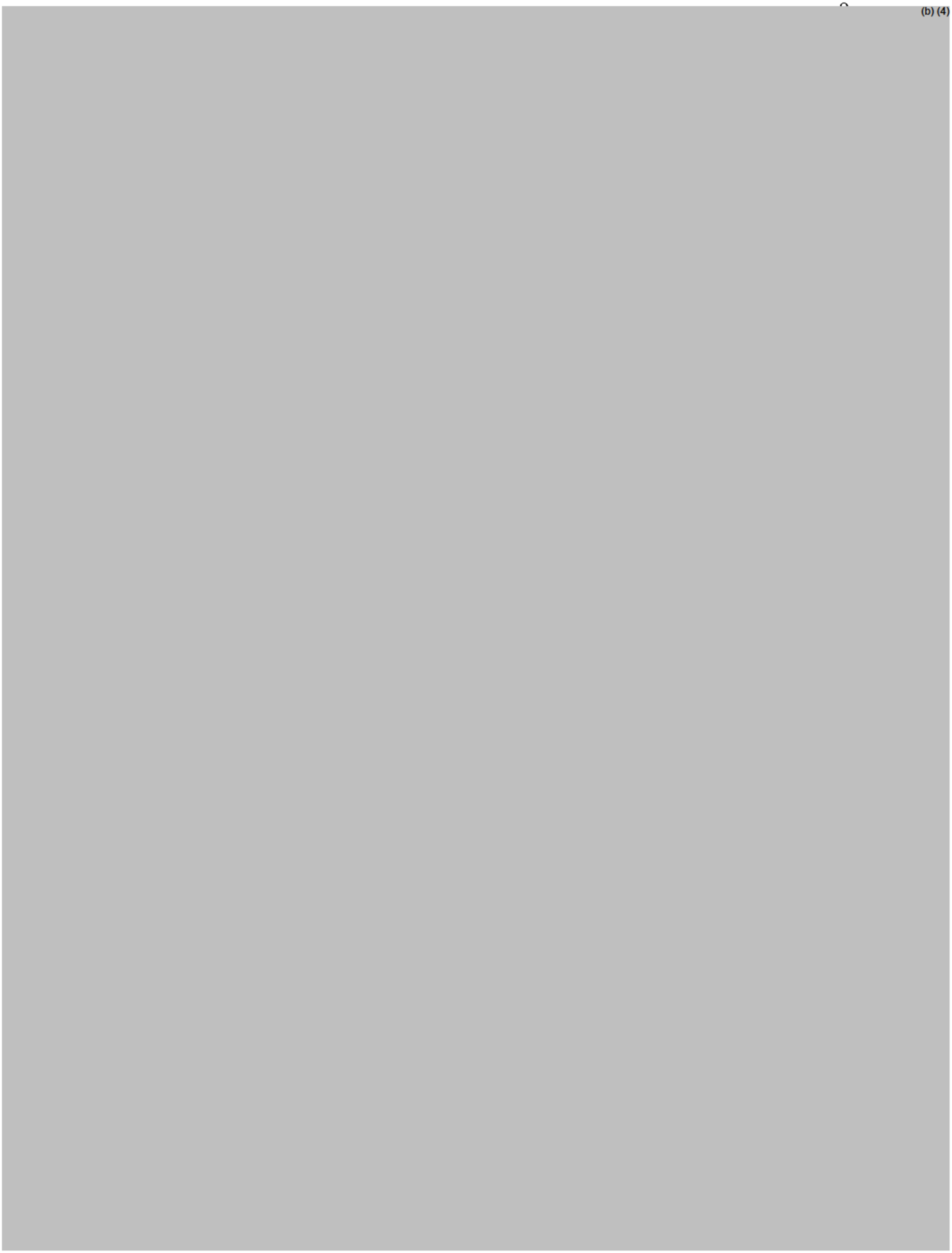

(b) (4)


(b) (4)


(b) (4)

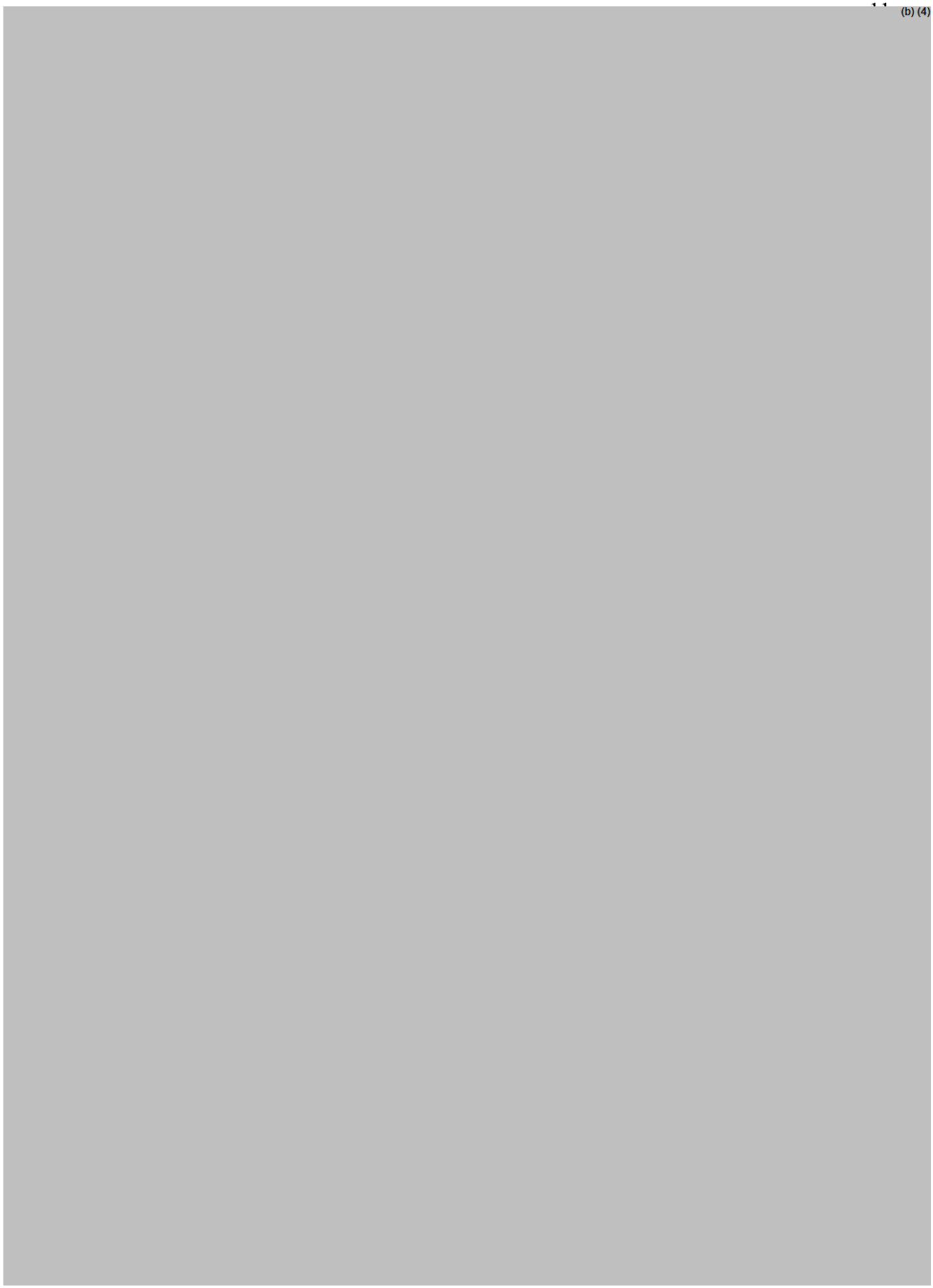

(b) (4)

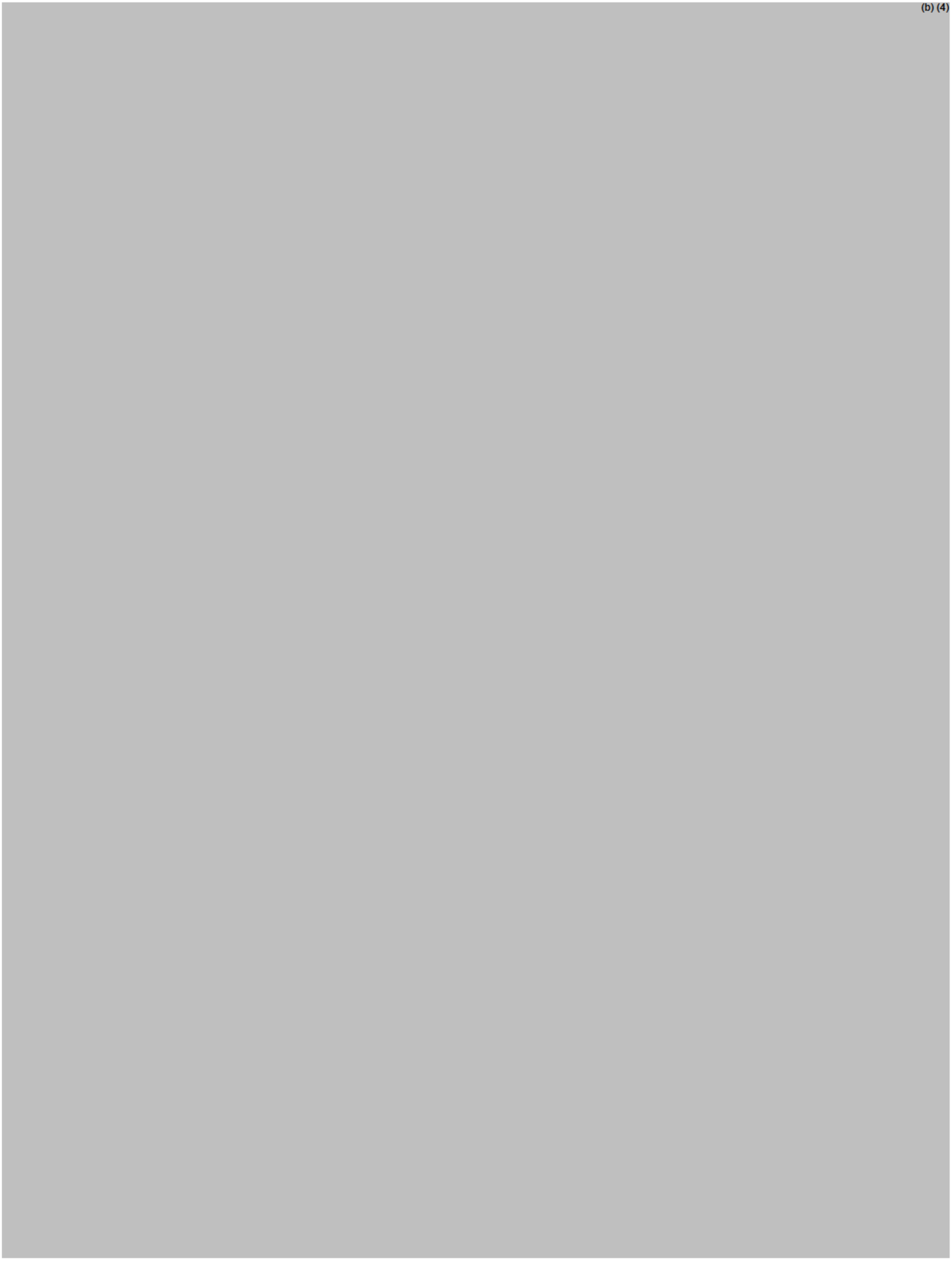
(b) (4)

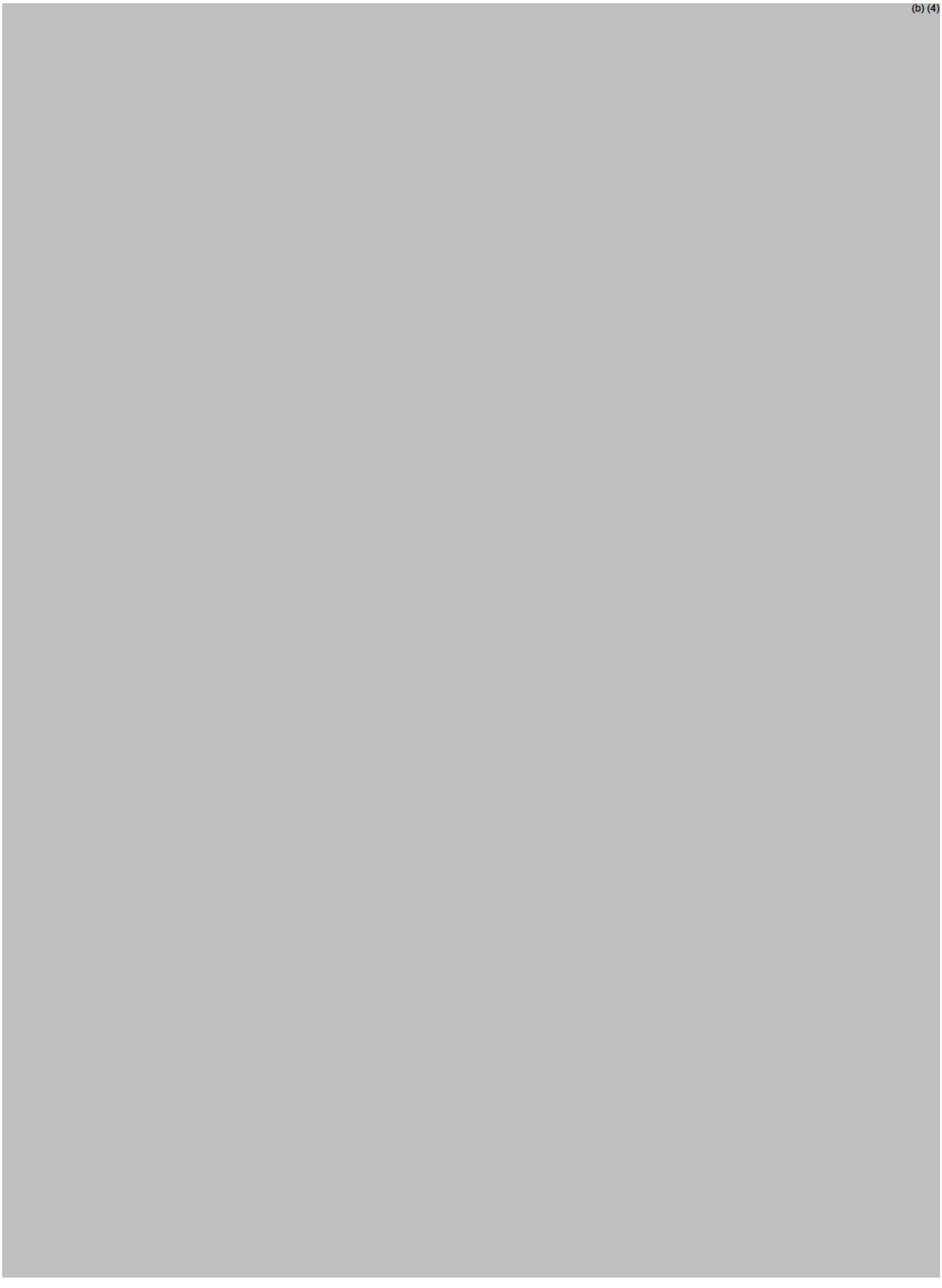


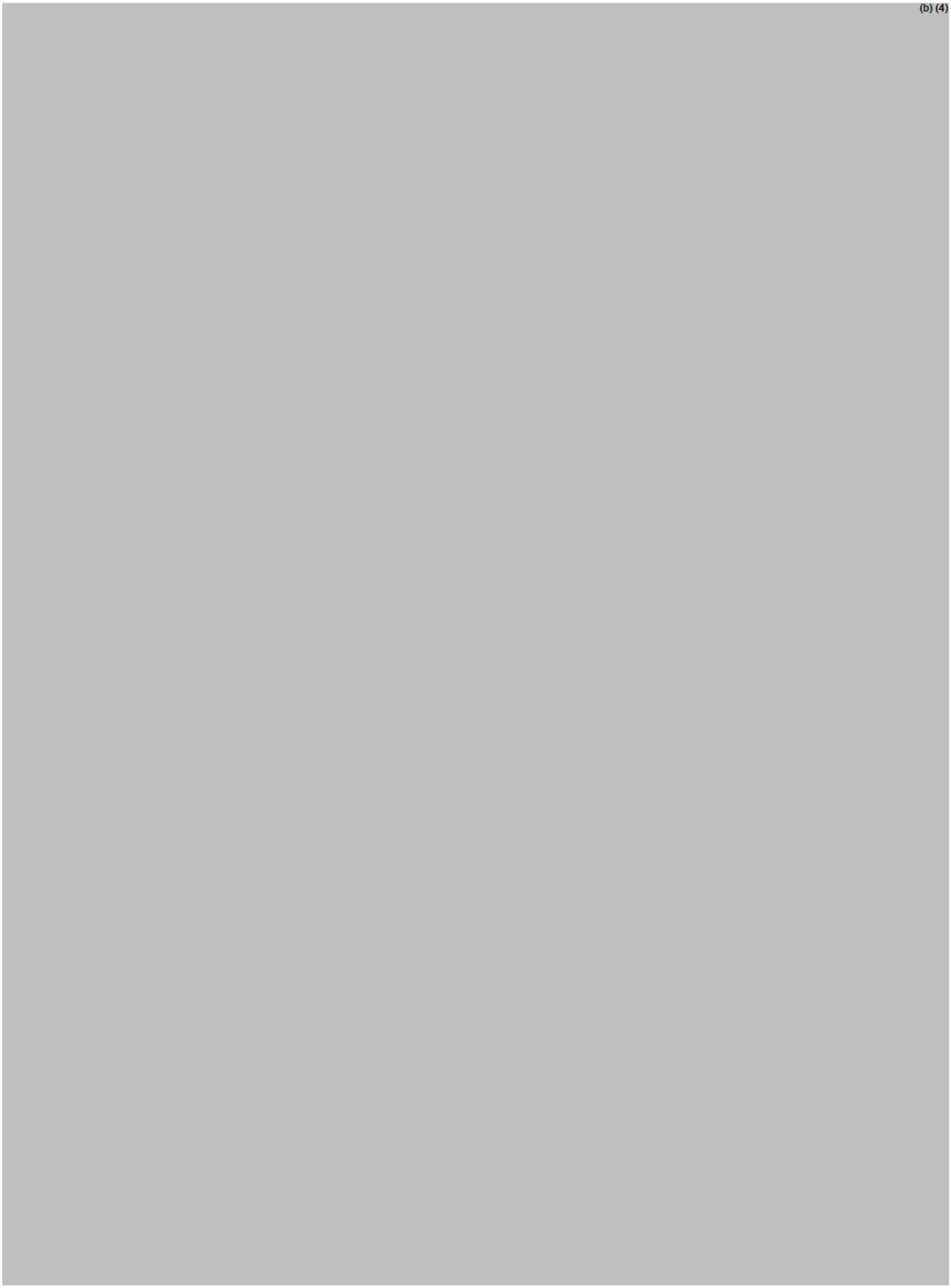

(b) (4)

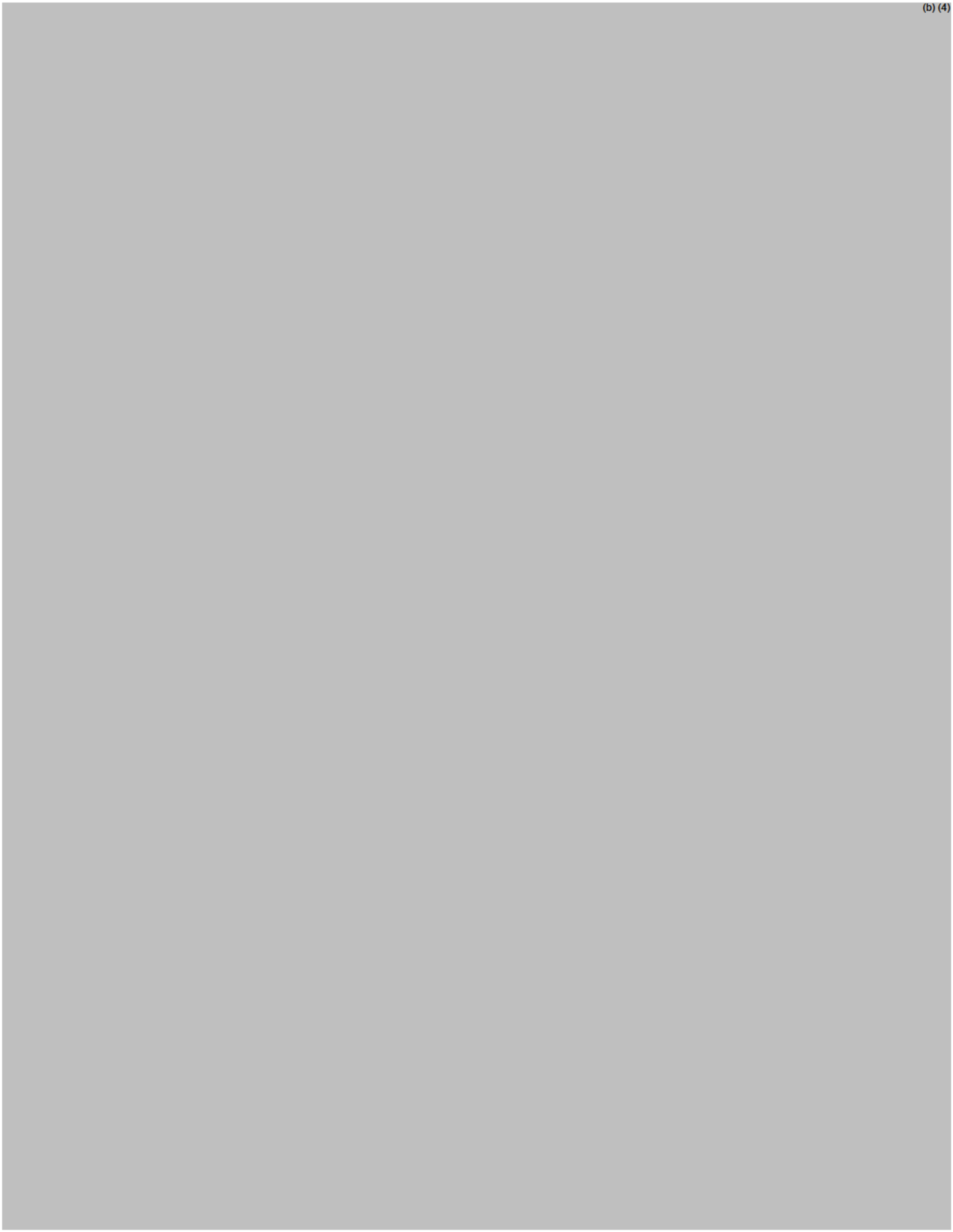

(b) (4)

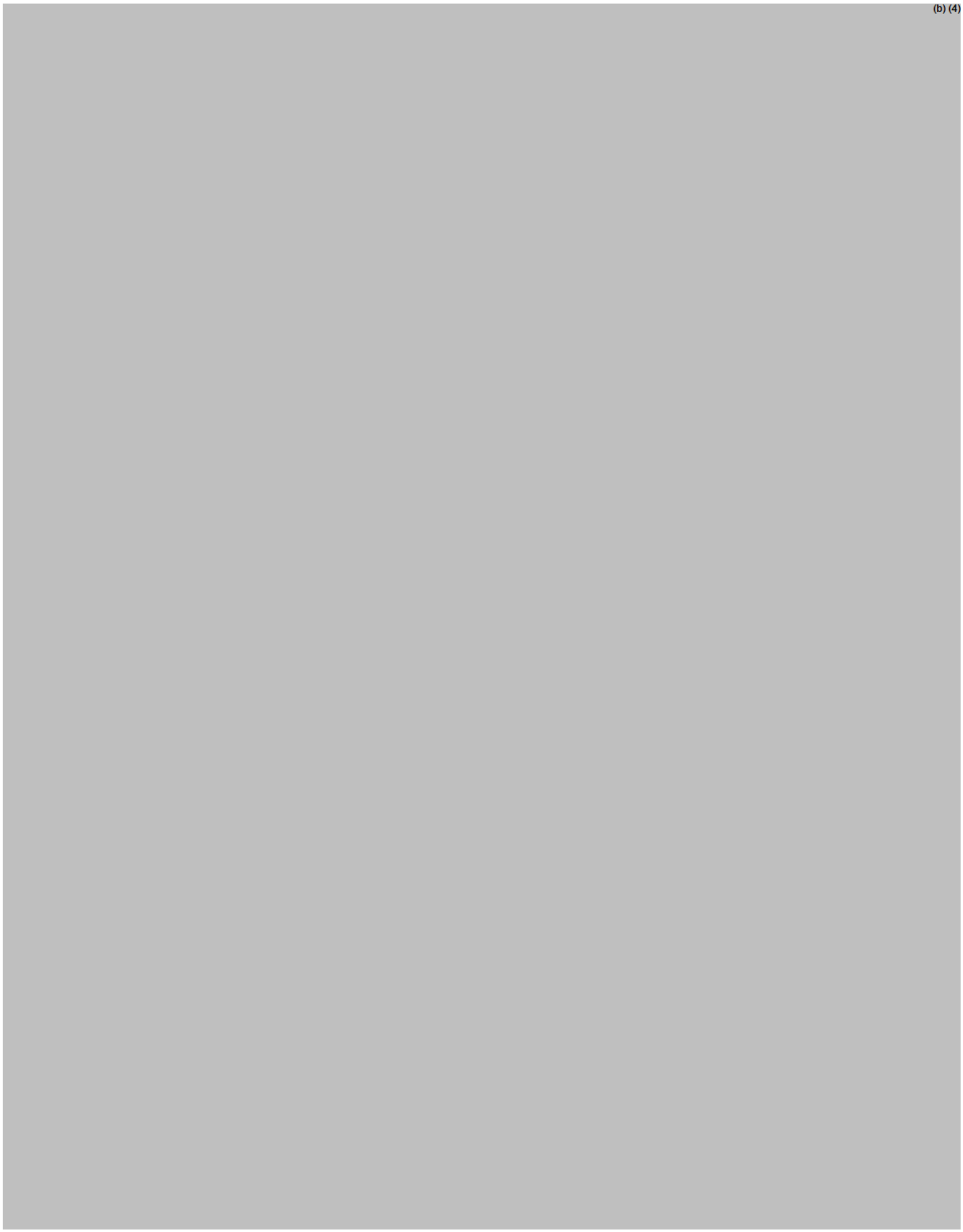


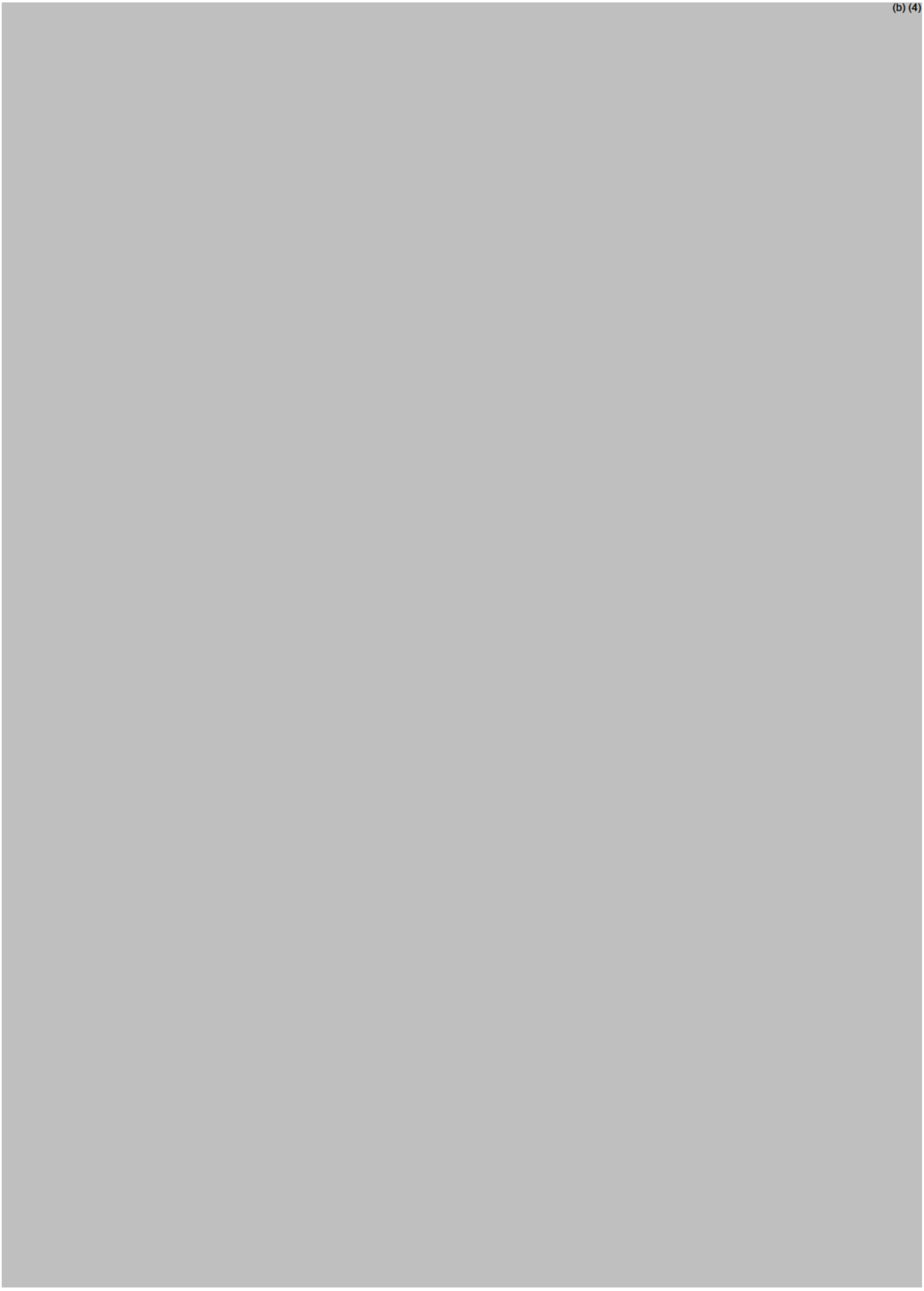


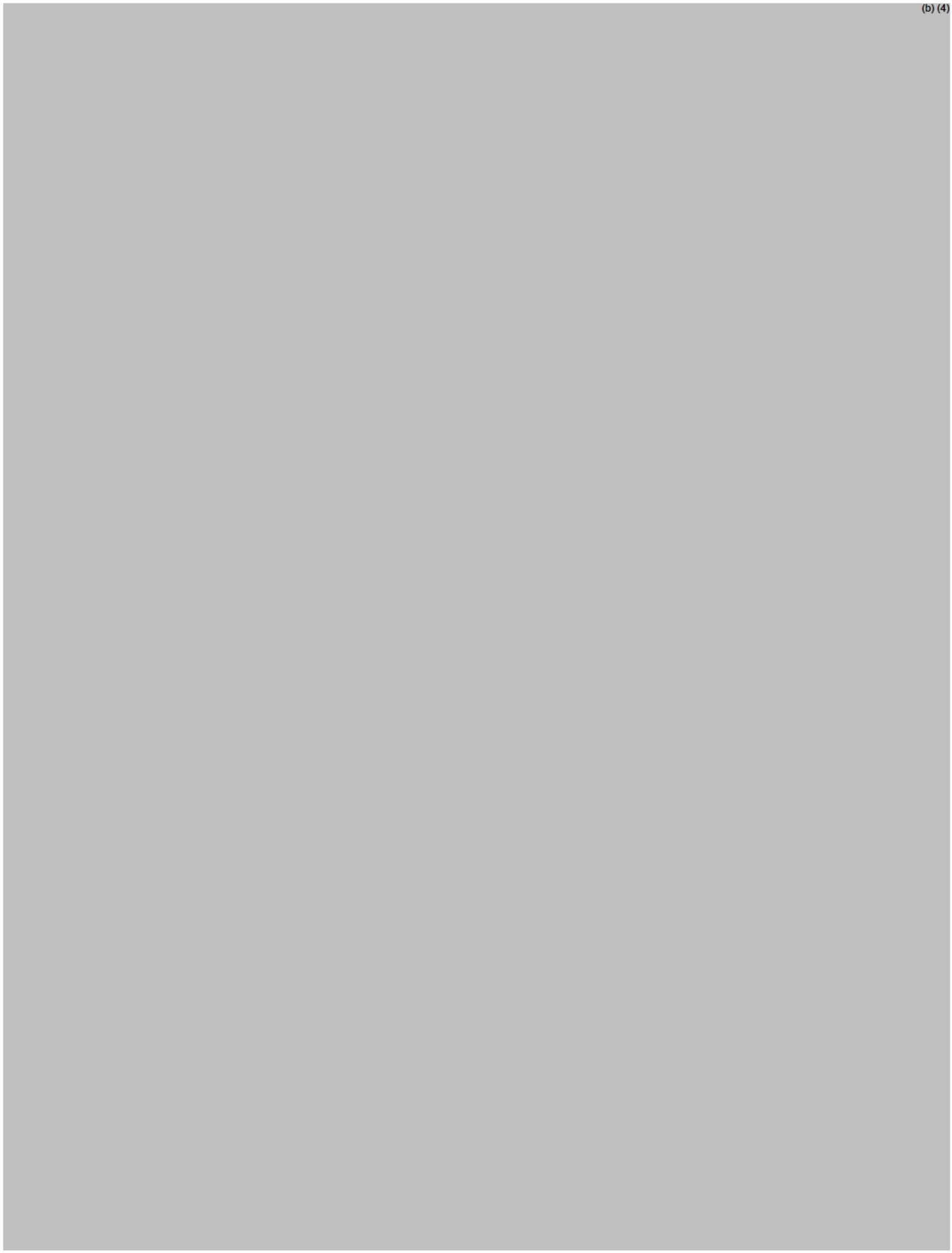

(b) (4)

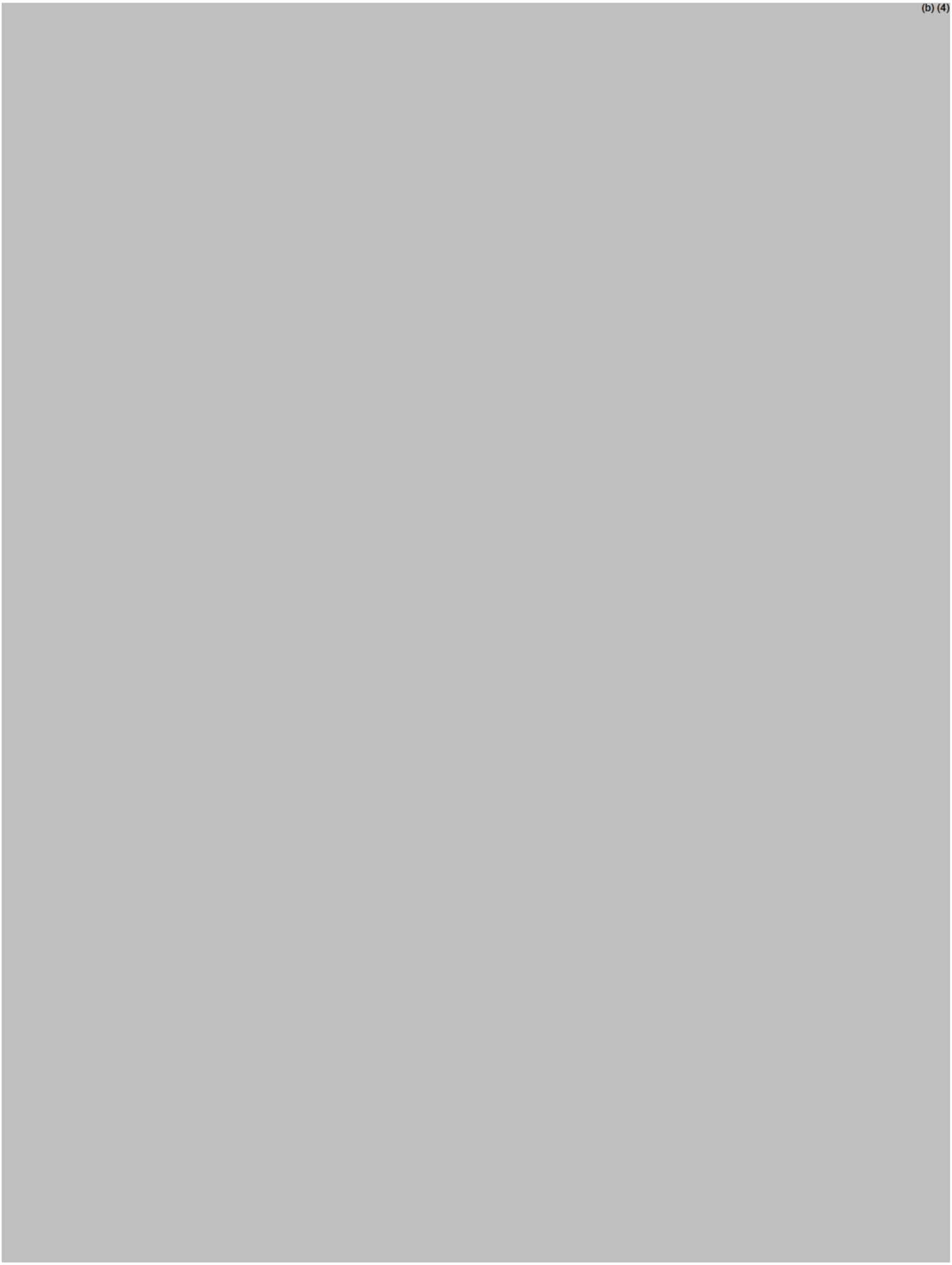

(b) (4)

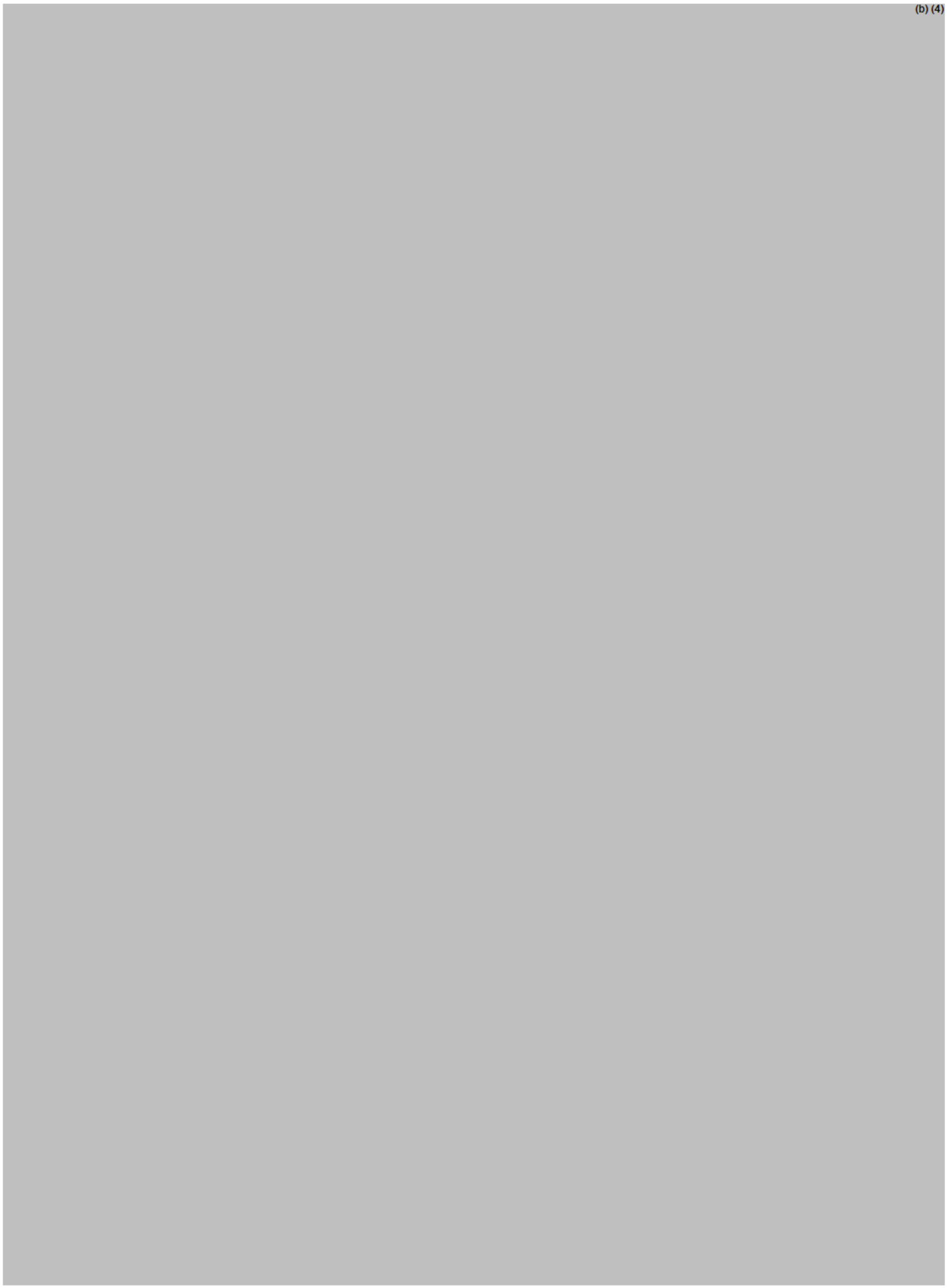

(b) (4)

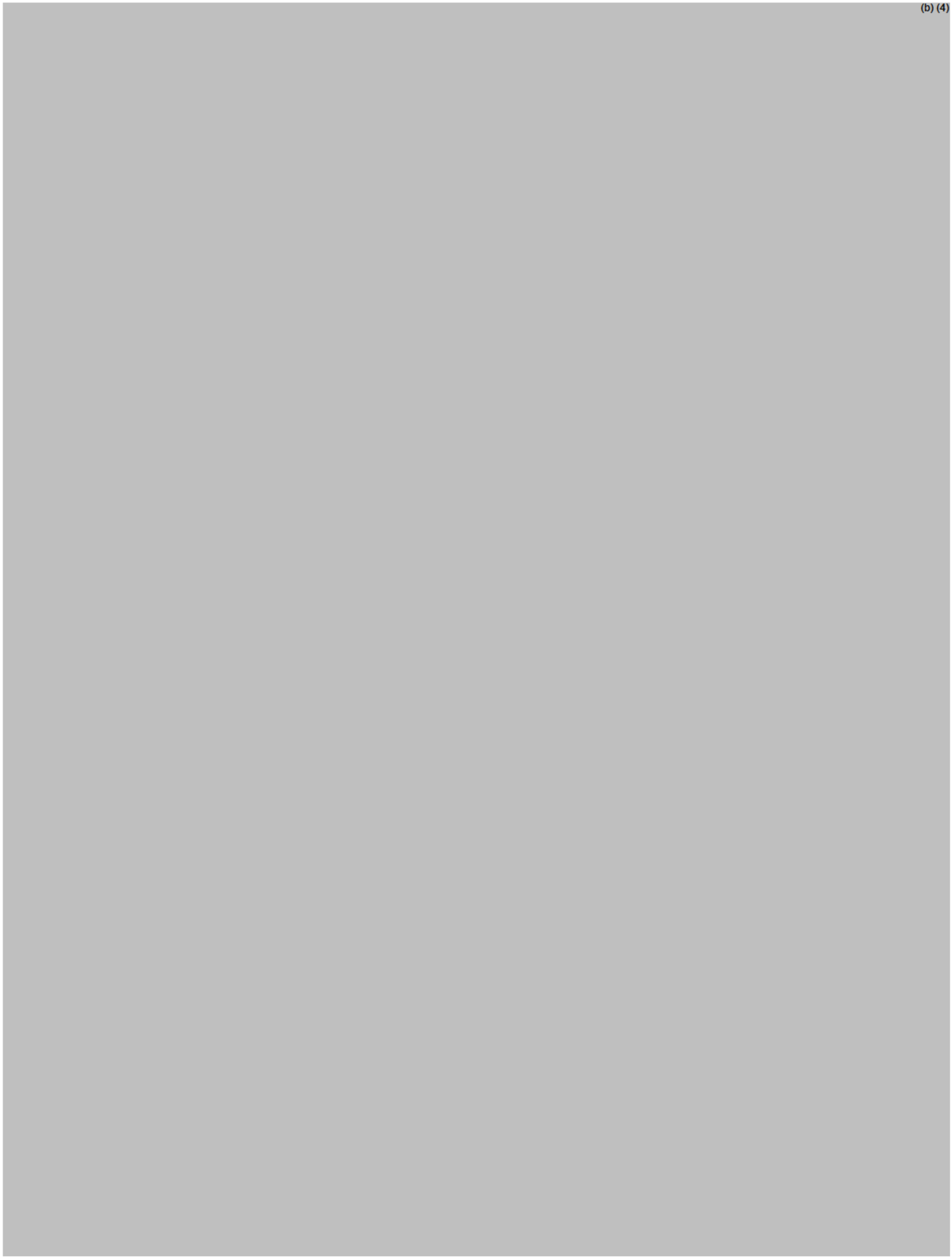

(b) (4)

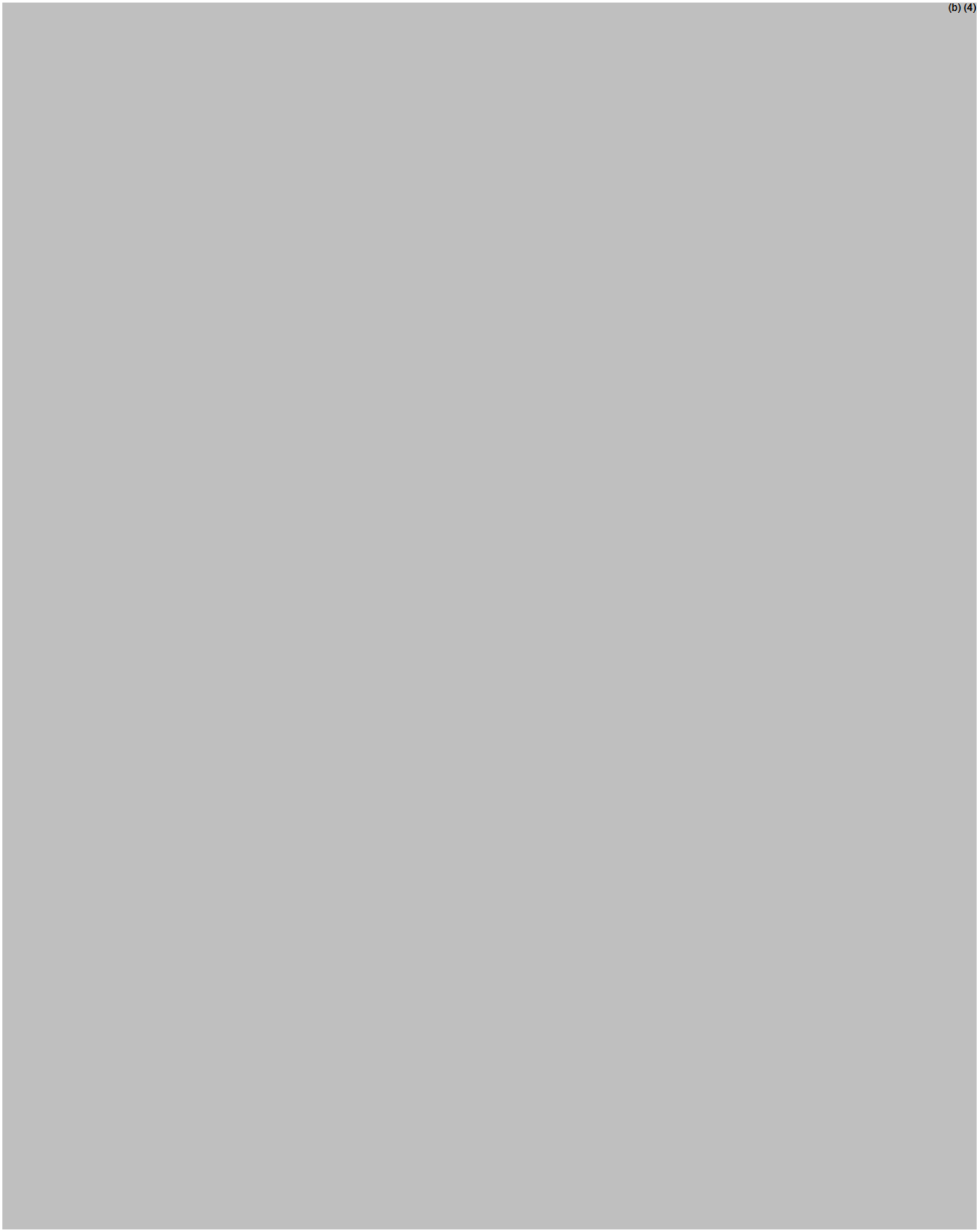

(b) (4)

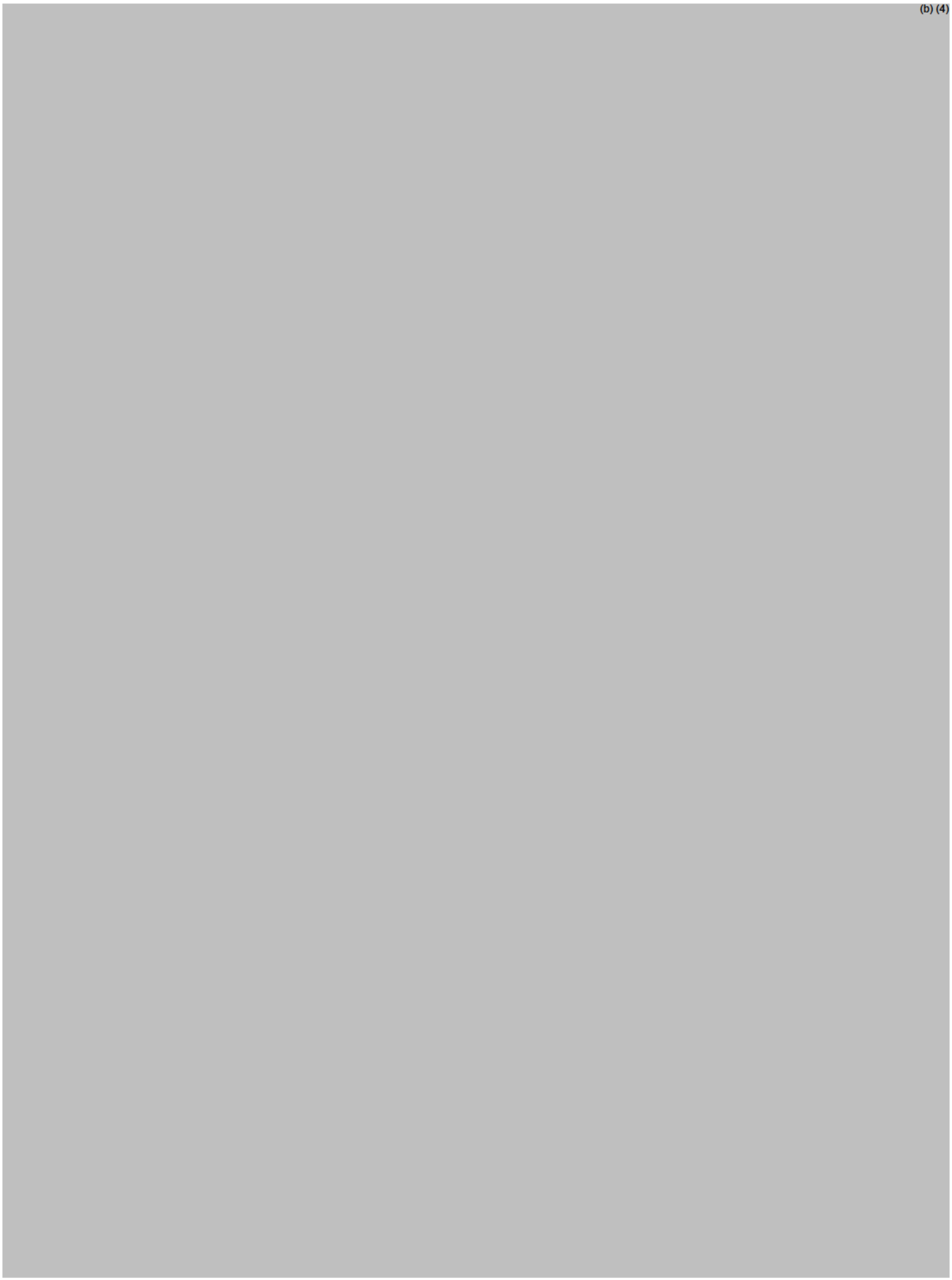

(b) (4)

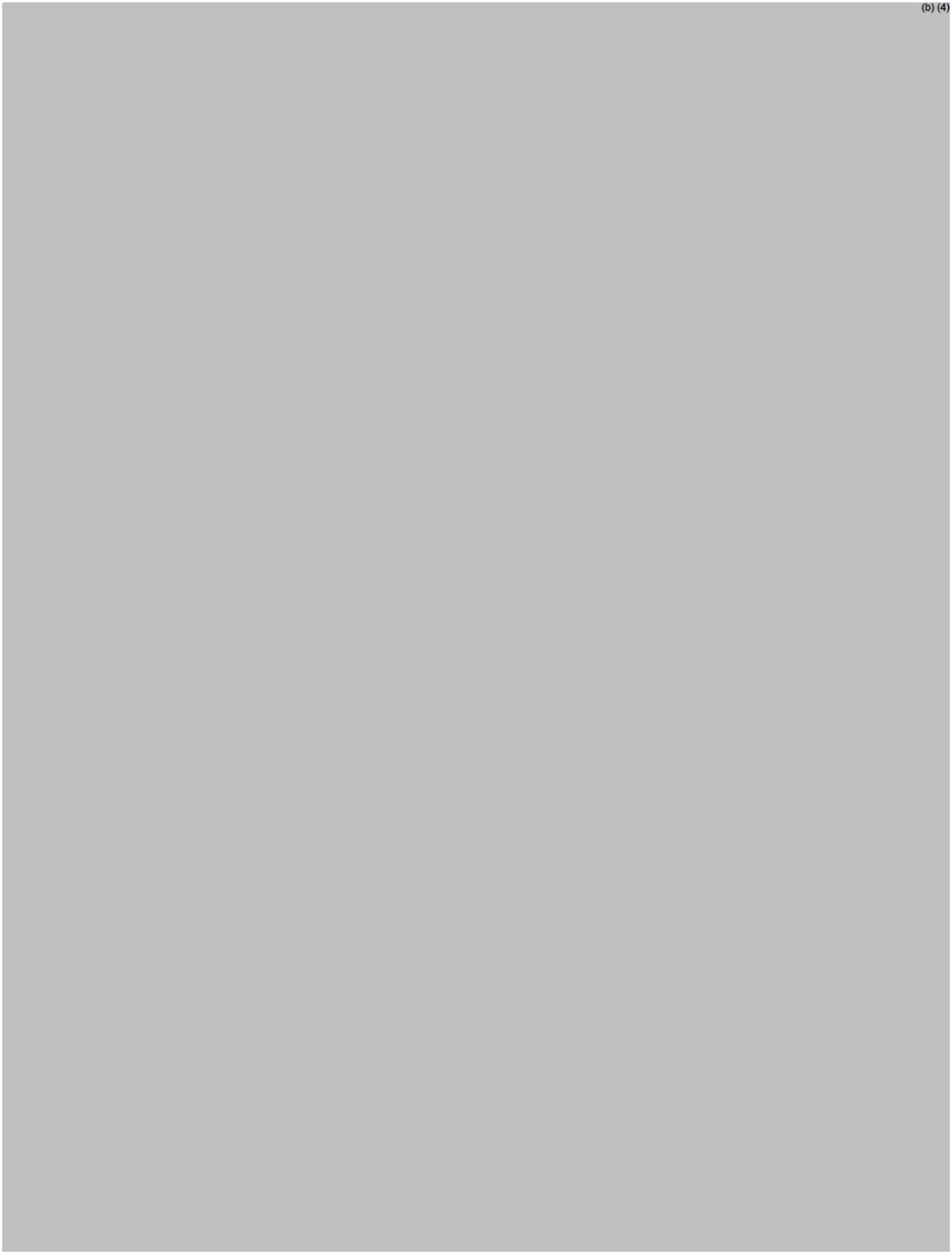


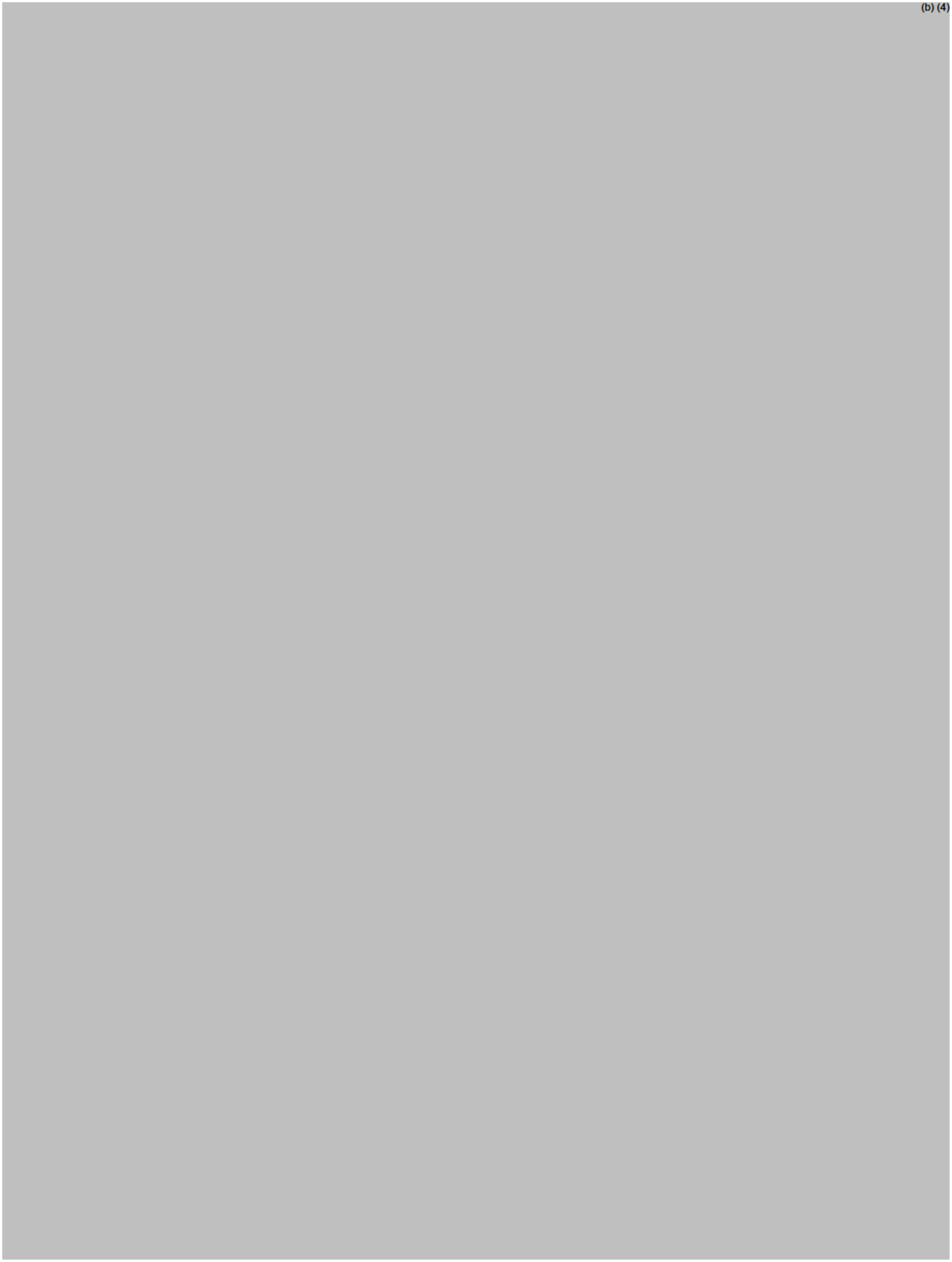

(b) (4)

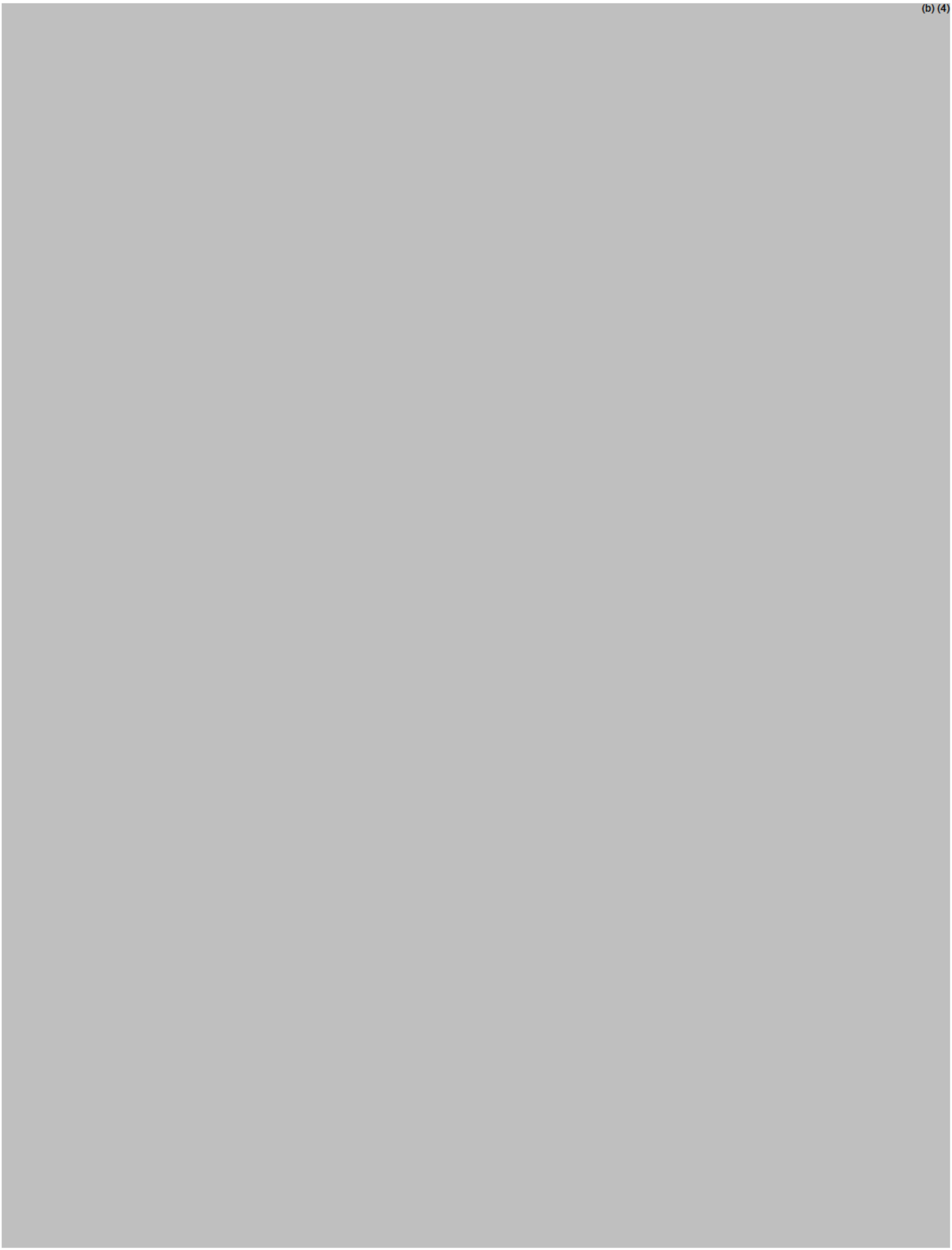

(b) (4)

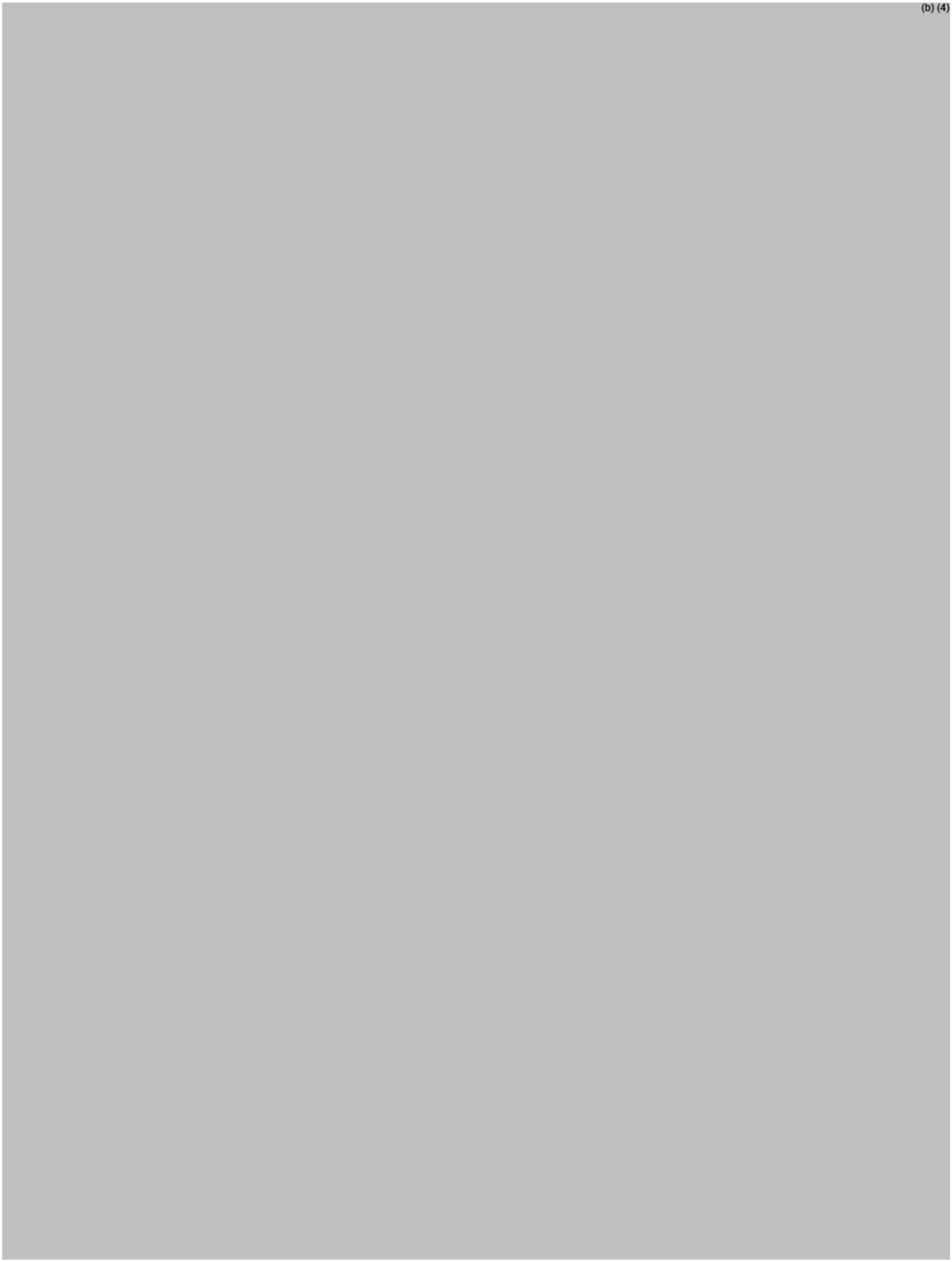

(b) (4)

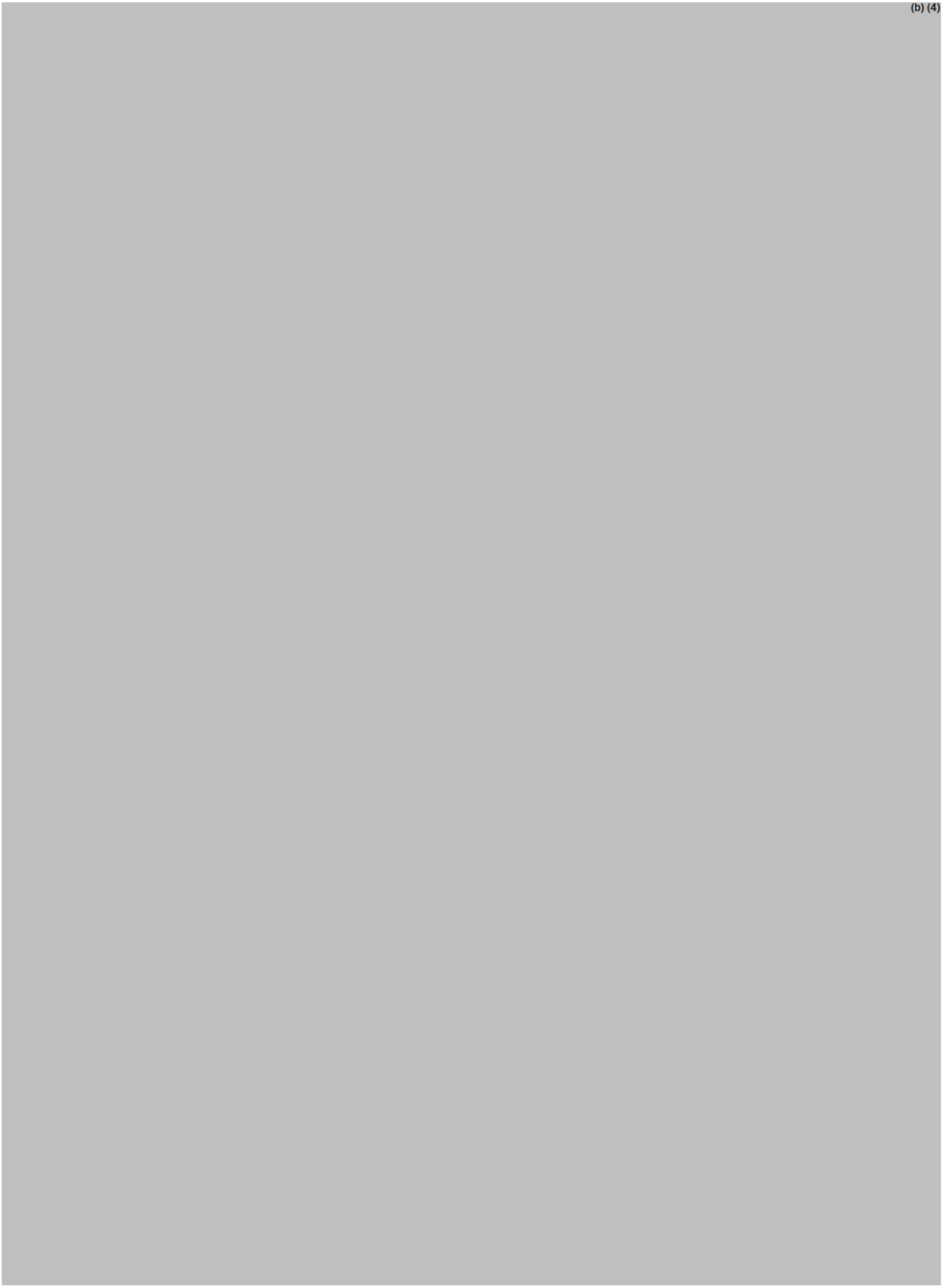

(b) (4)

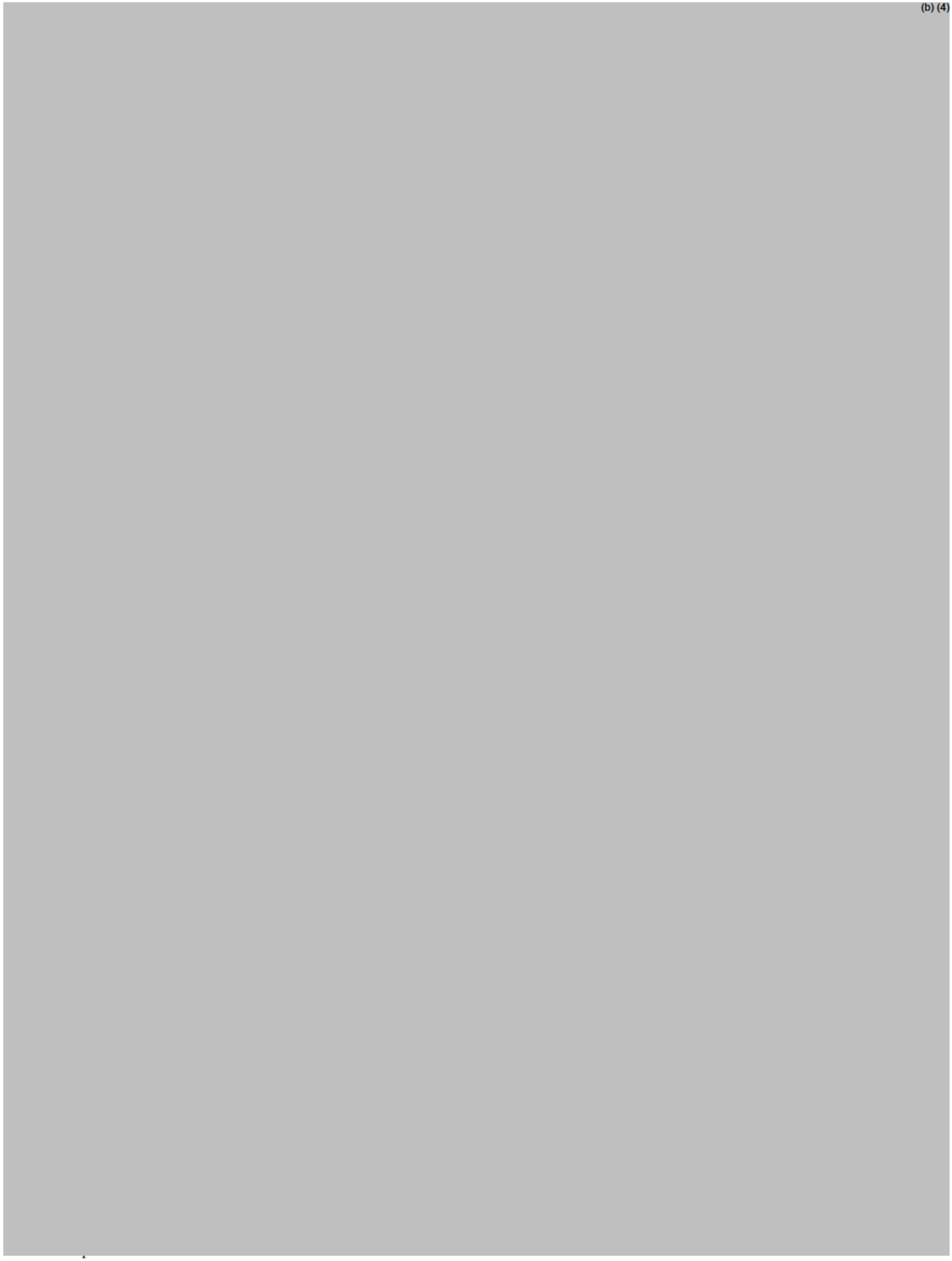

(b) (4)

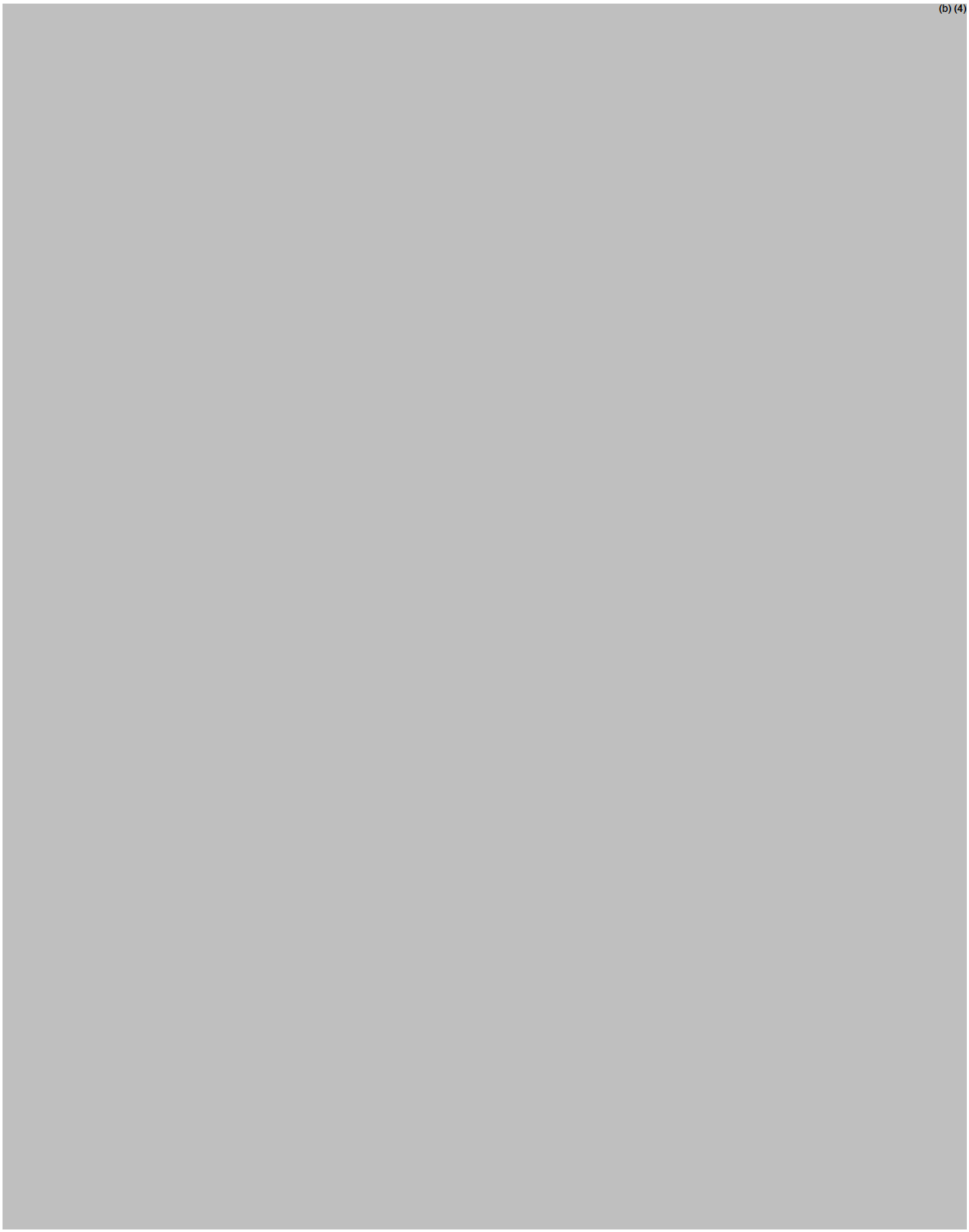

(b) (4)

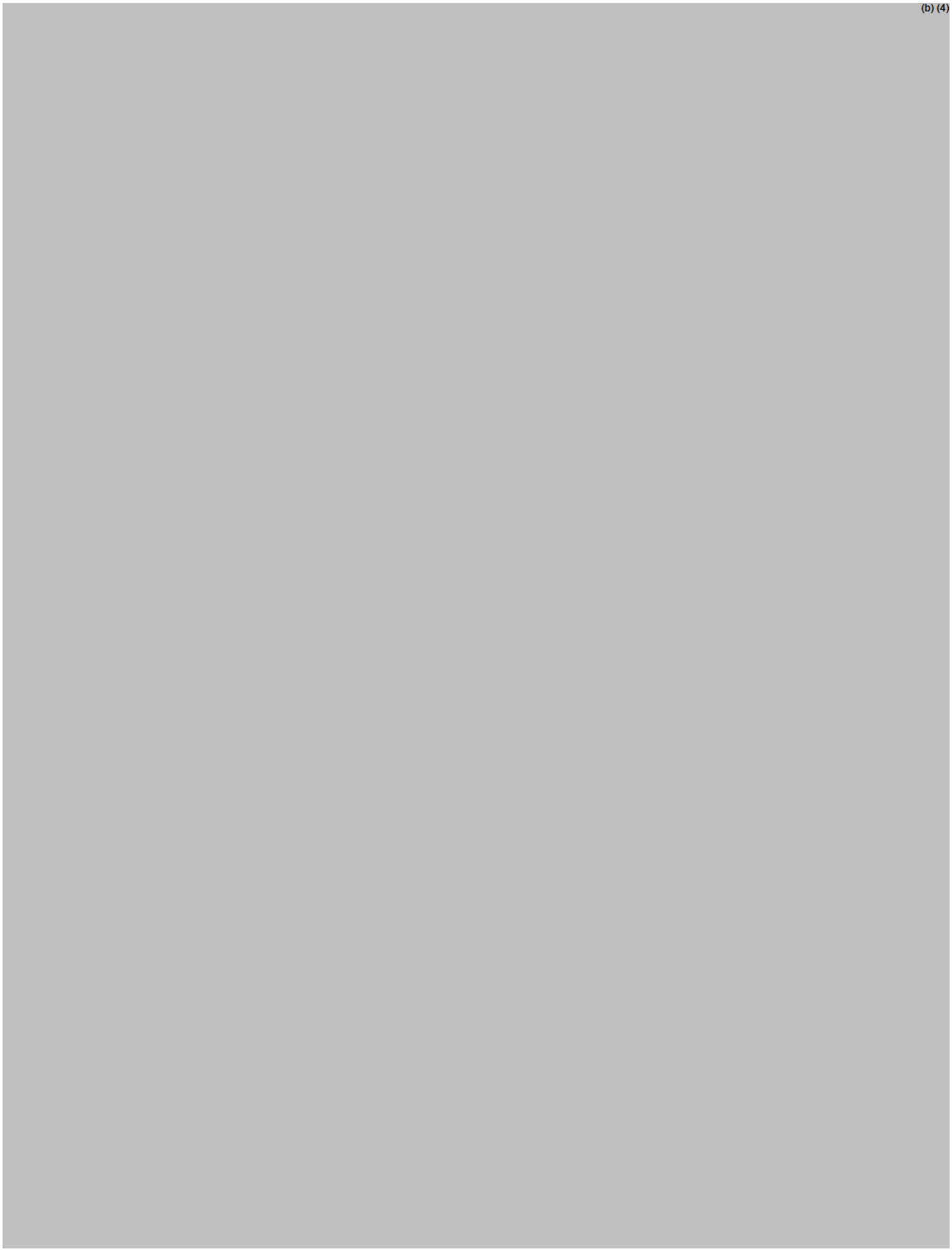

(b) (4)

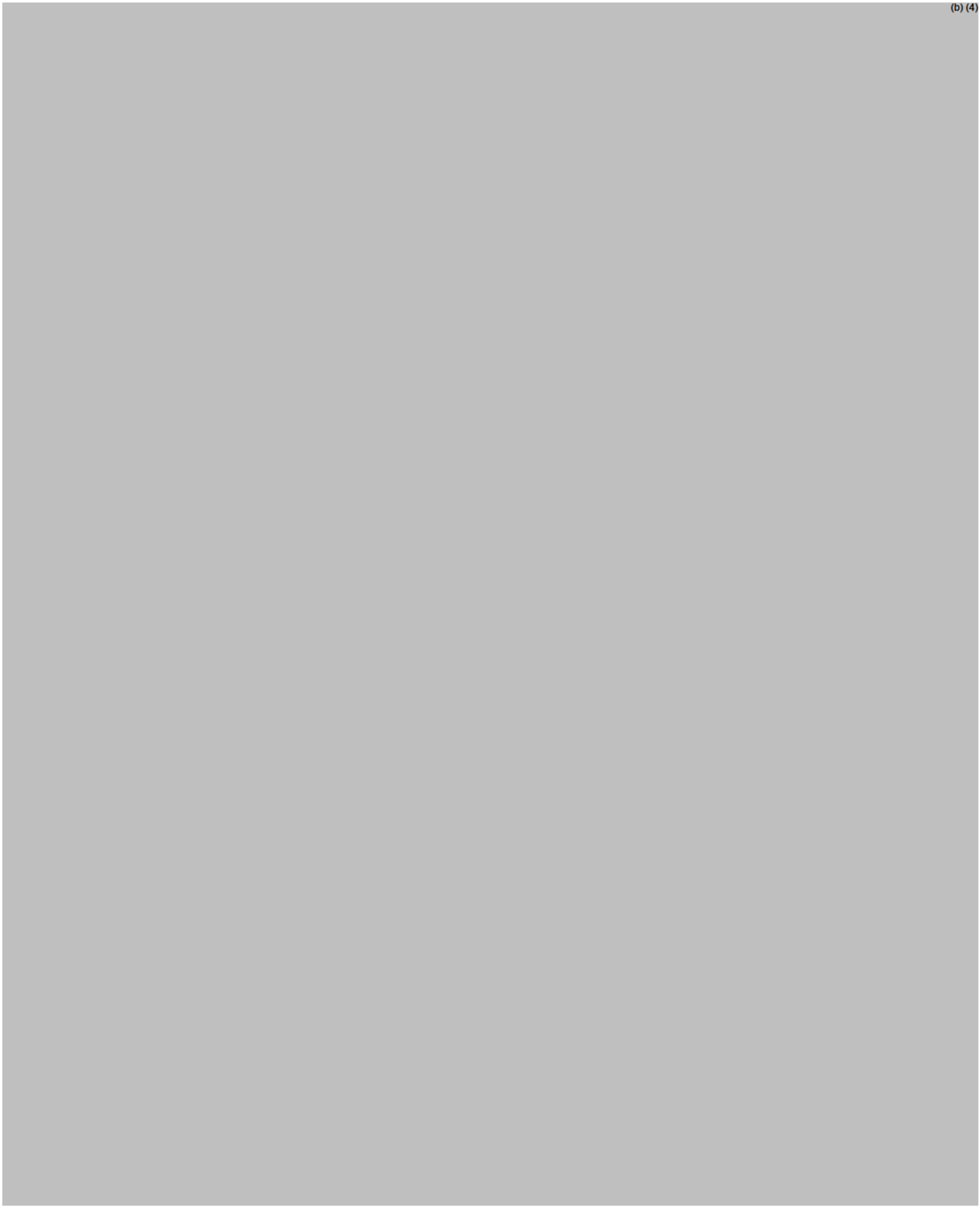


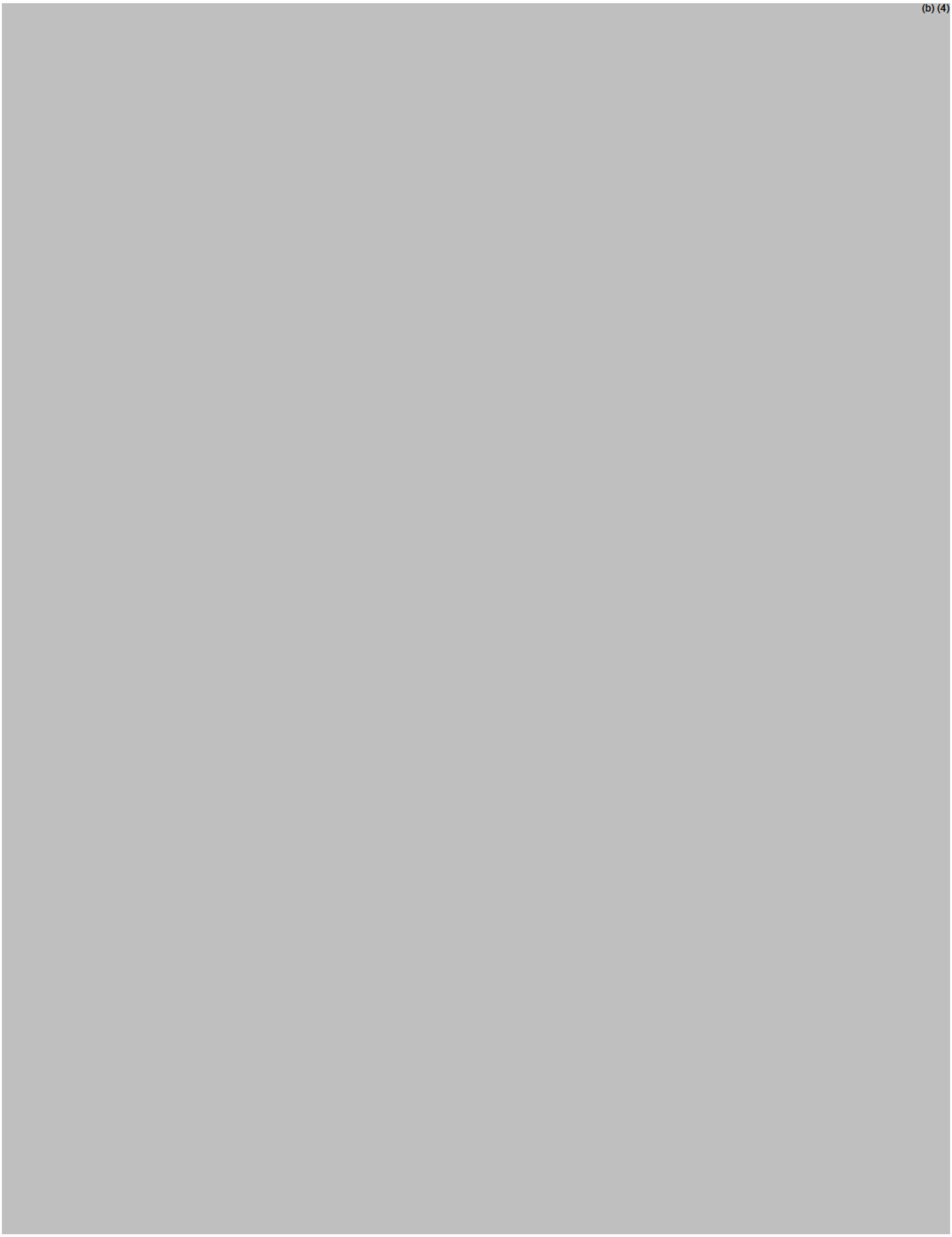

(b) (4)

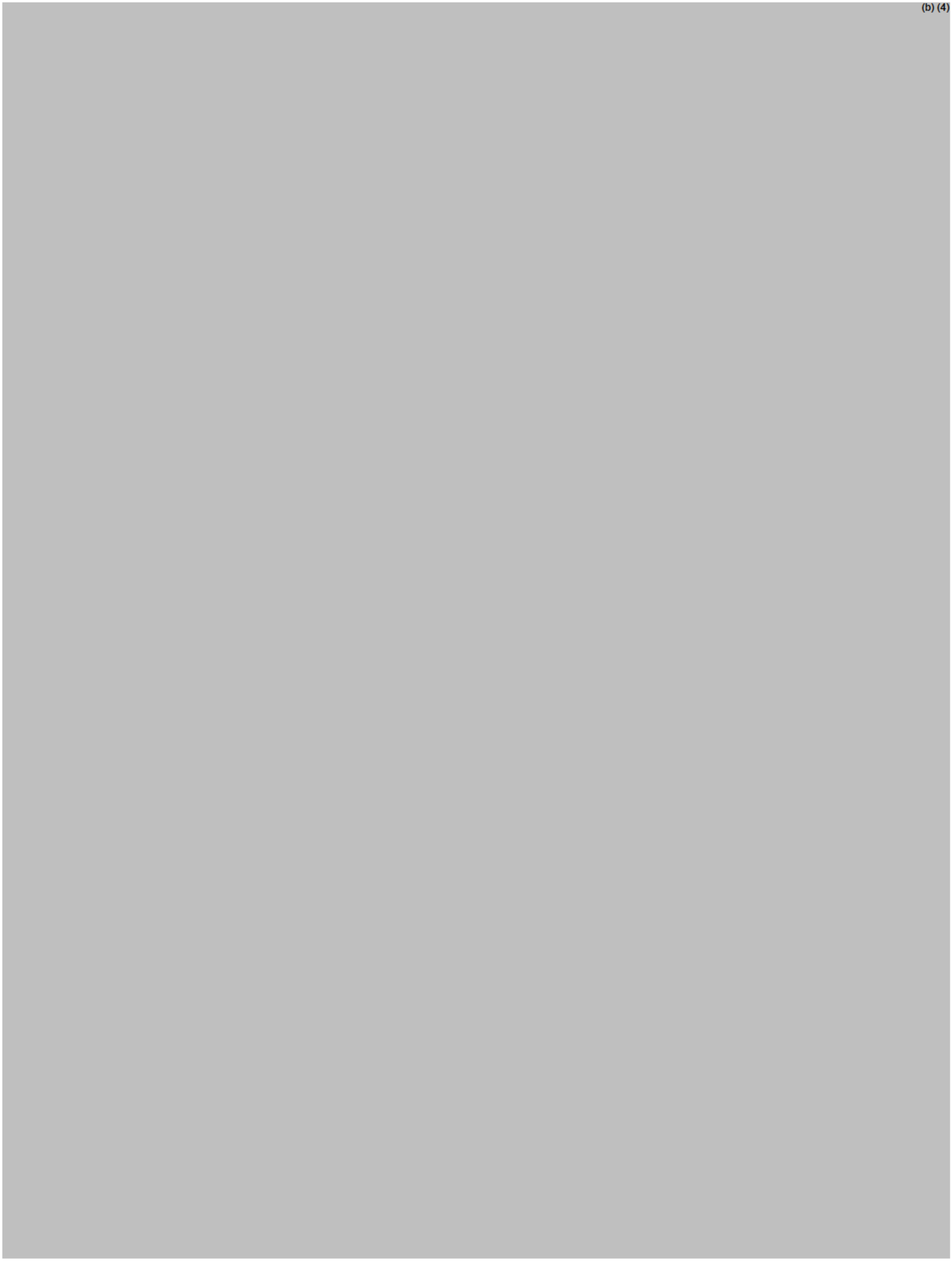

(b) (4)

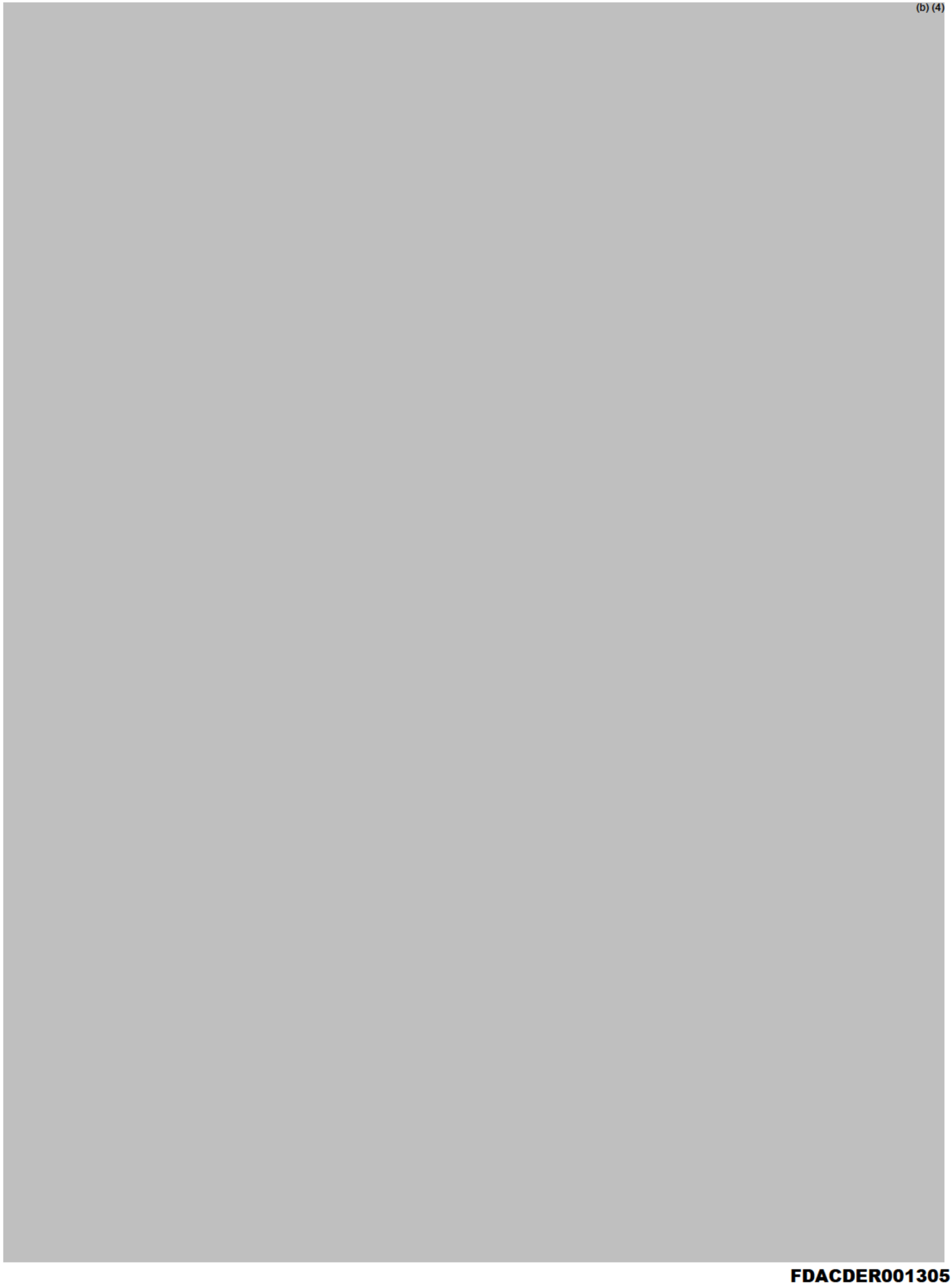

(b) (4)

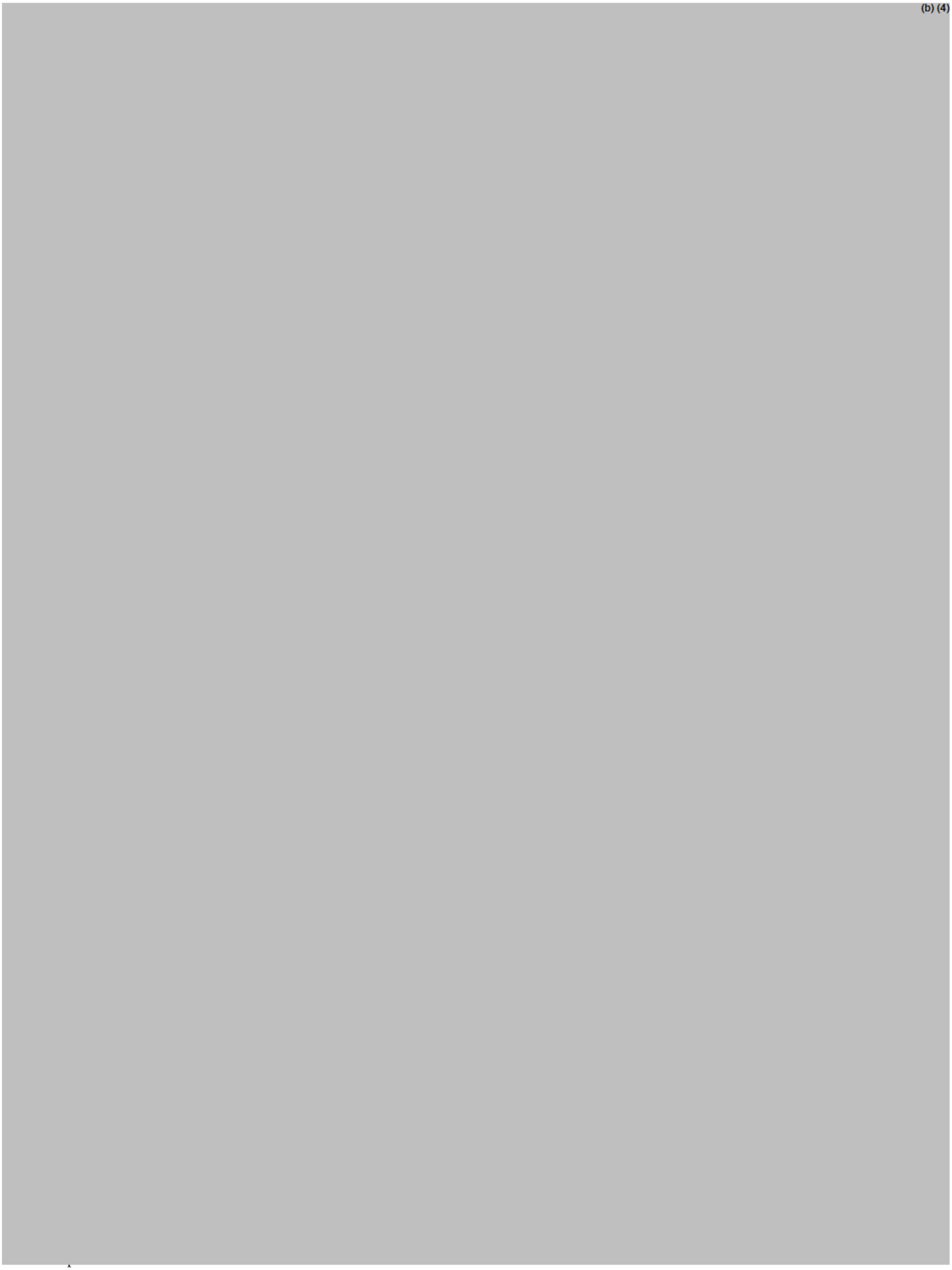

(b) (4)

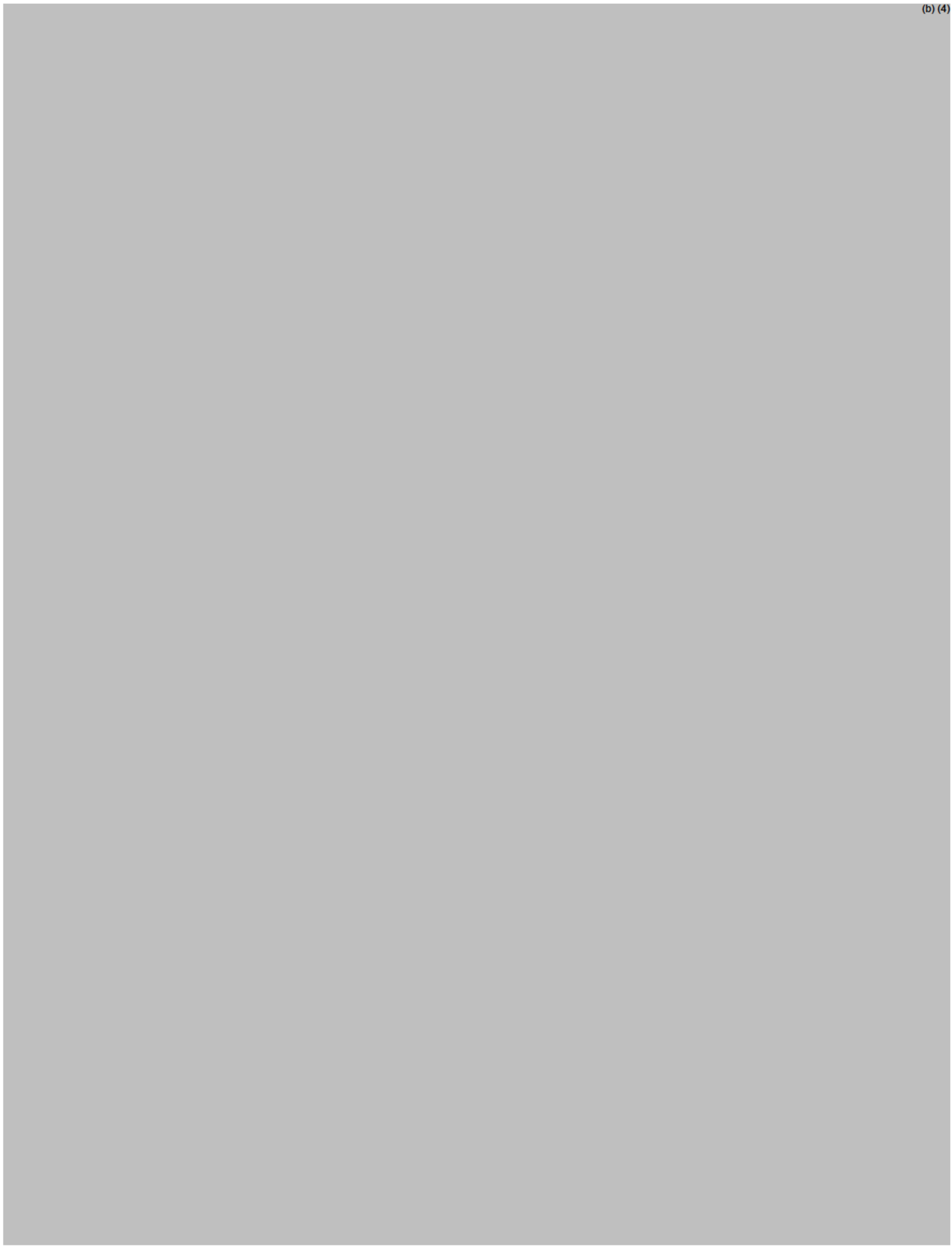

(b) (4)

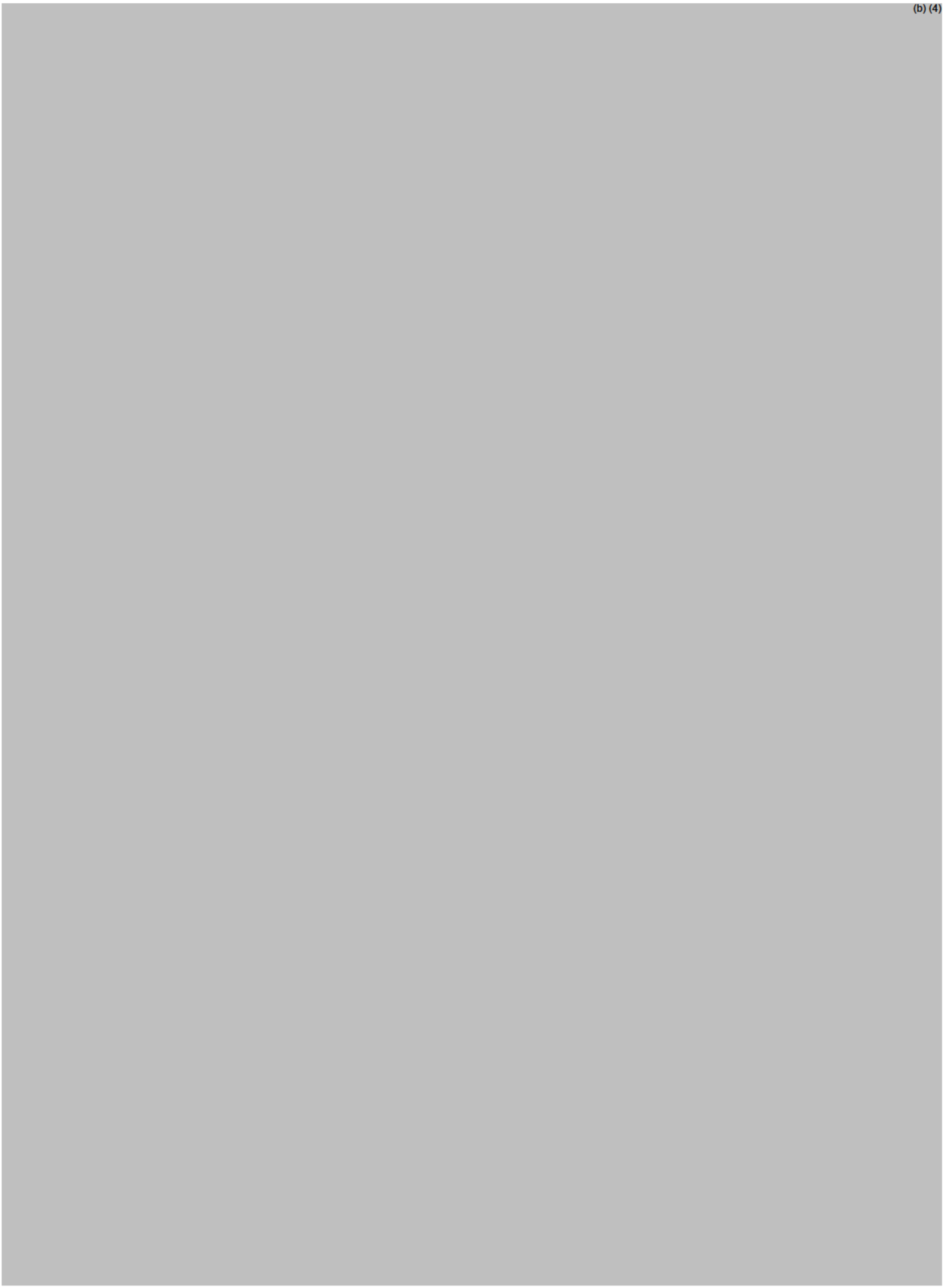


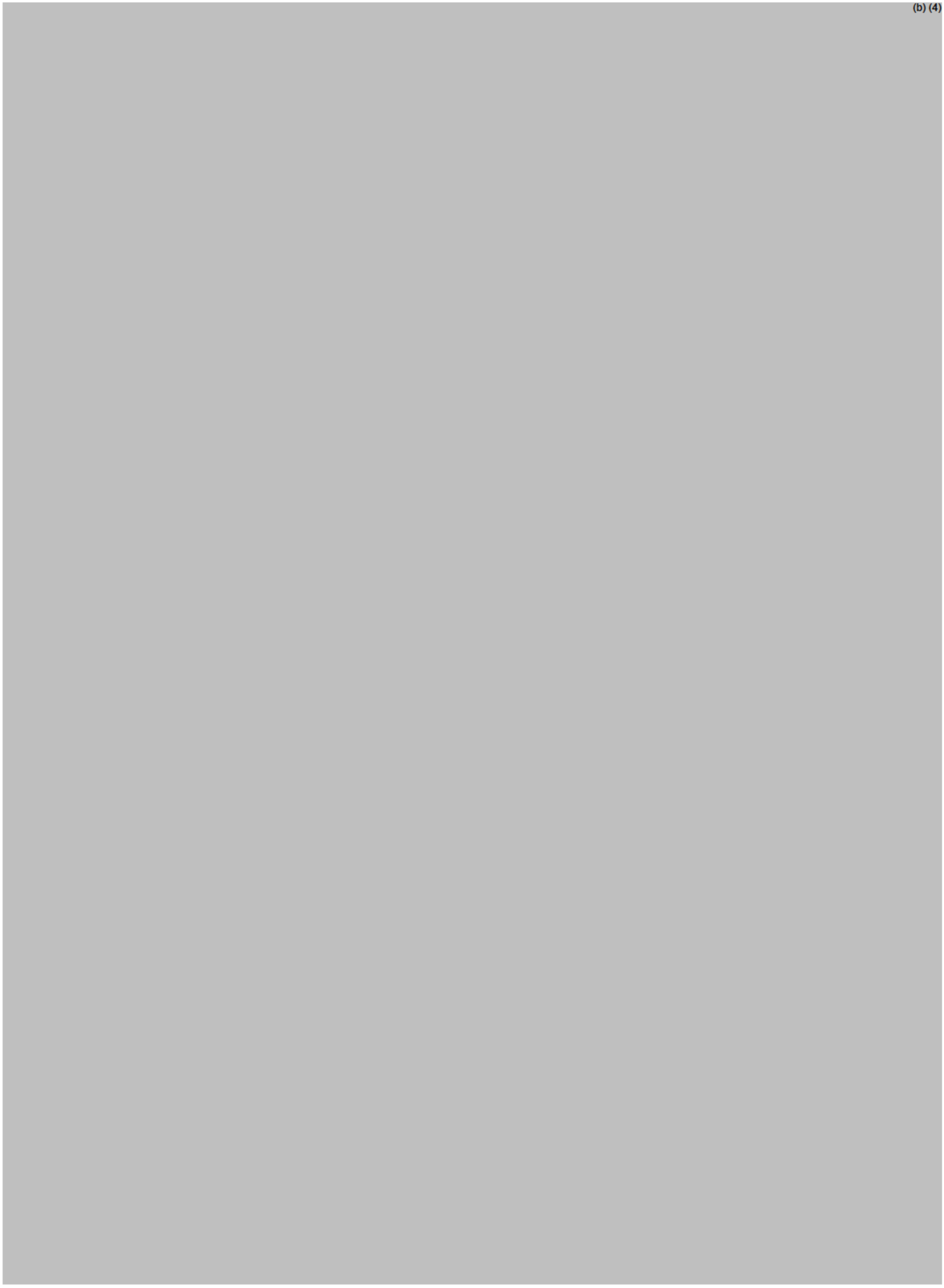


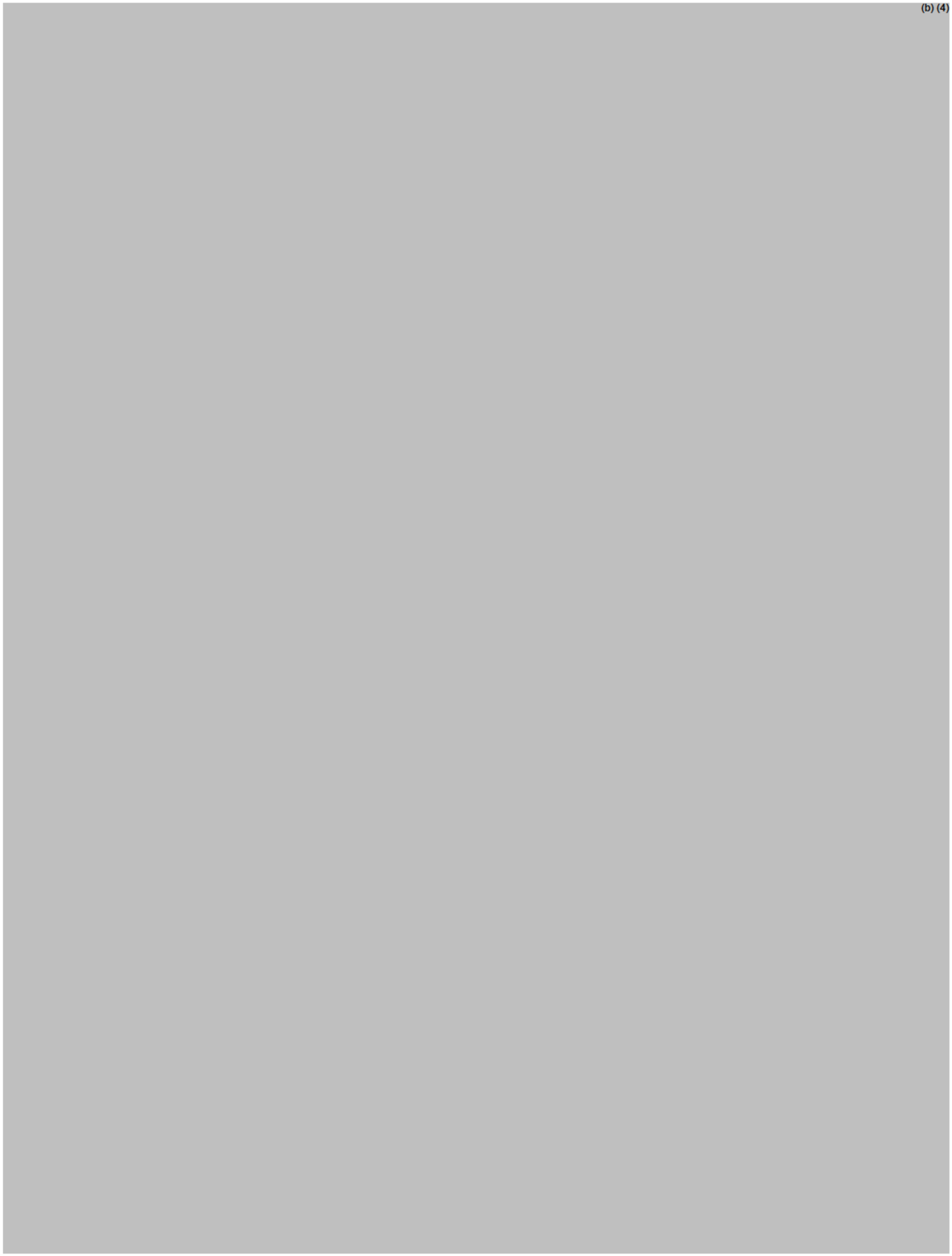


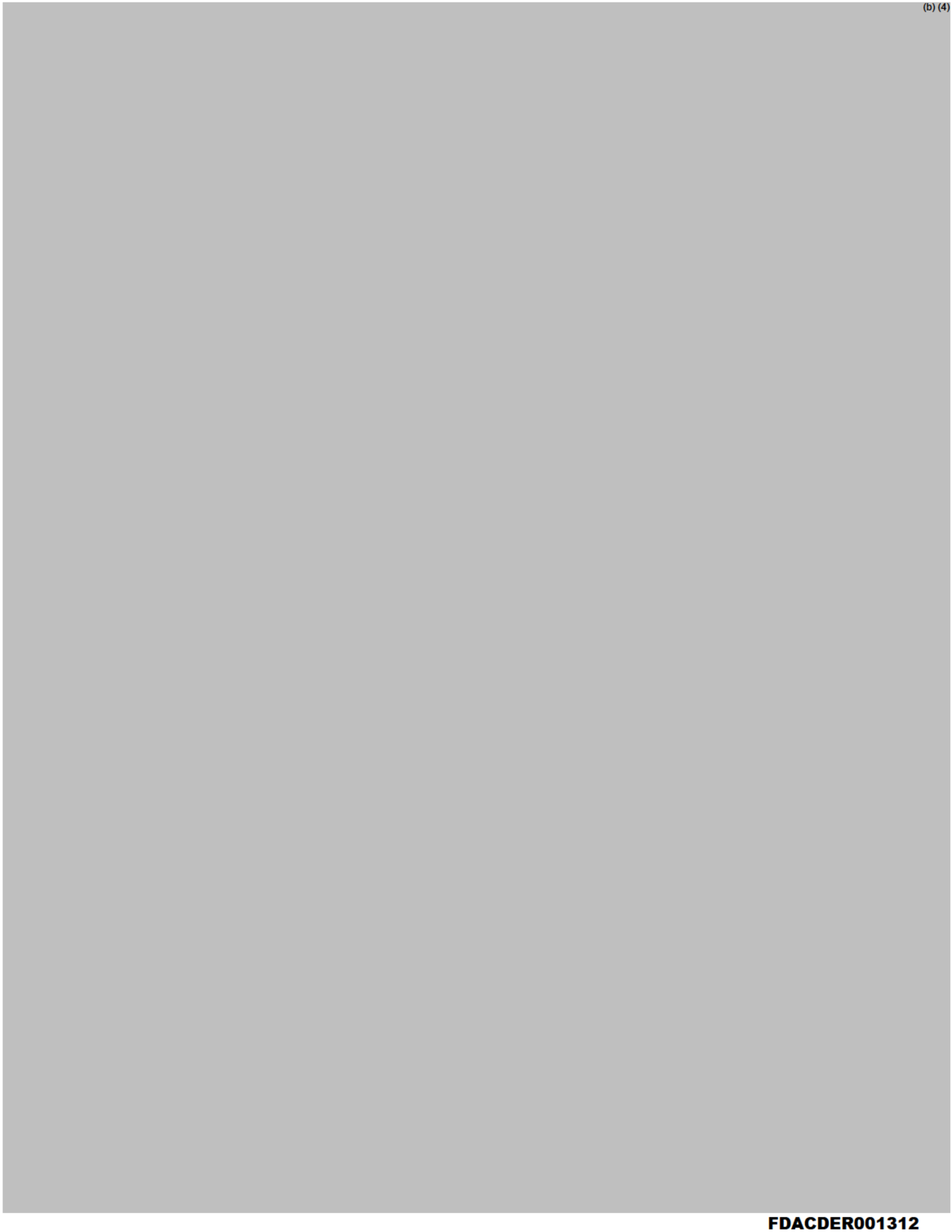

(b) (4)

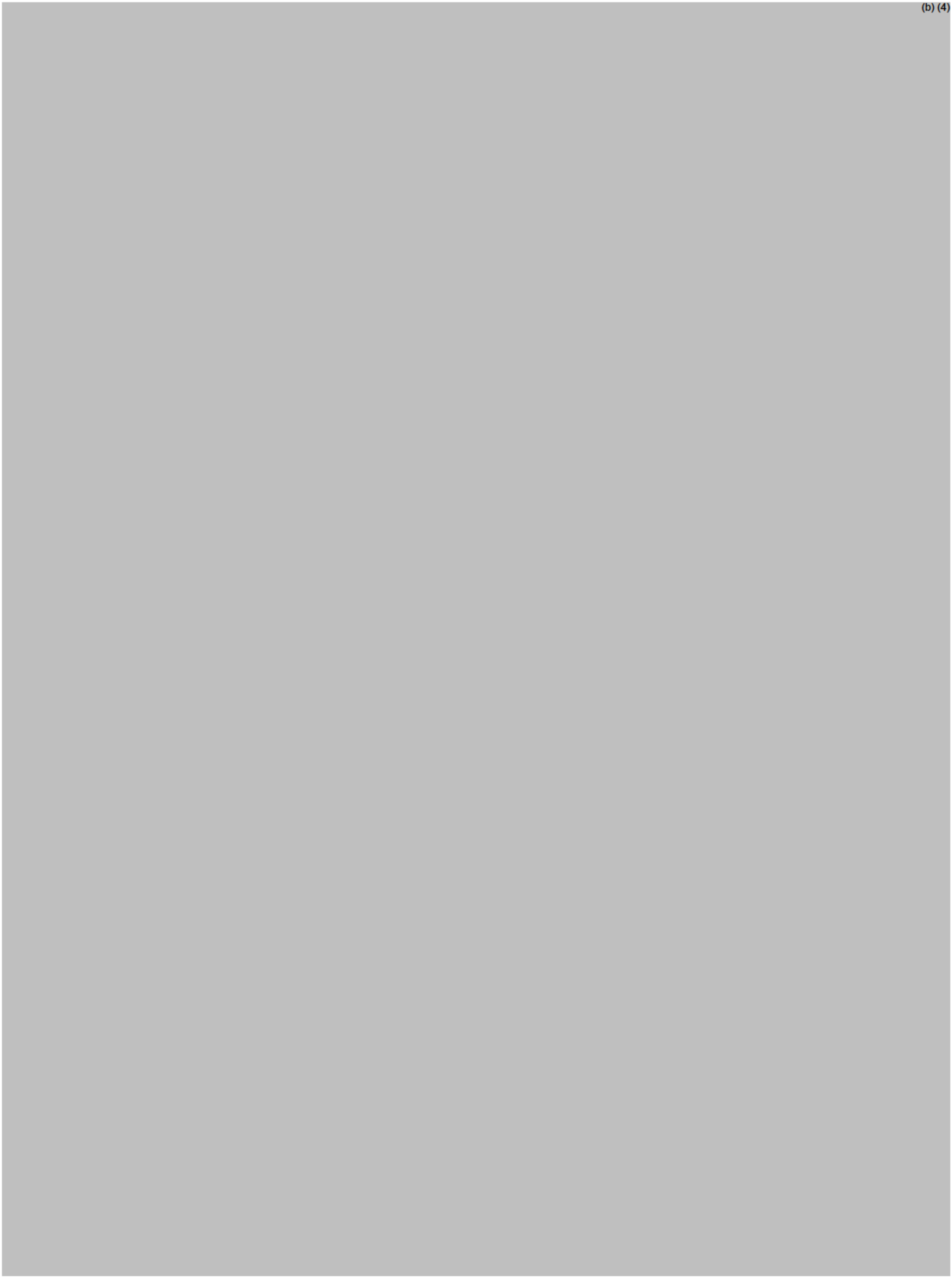

(b) (4)

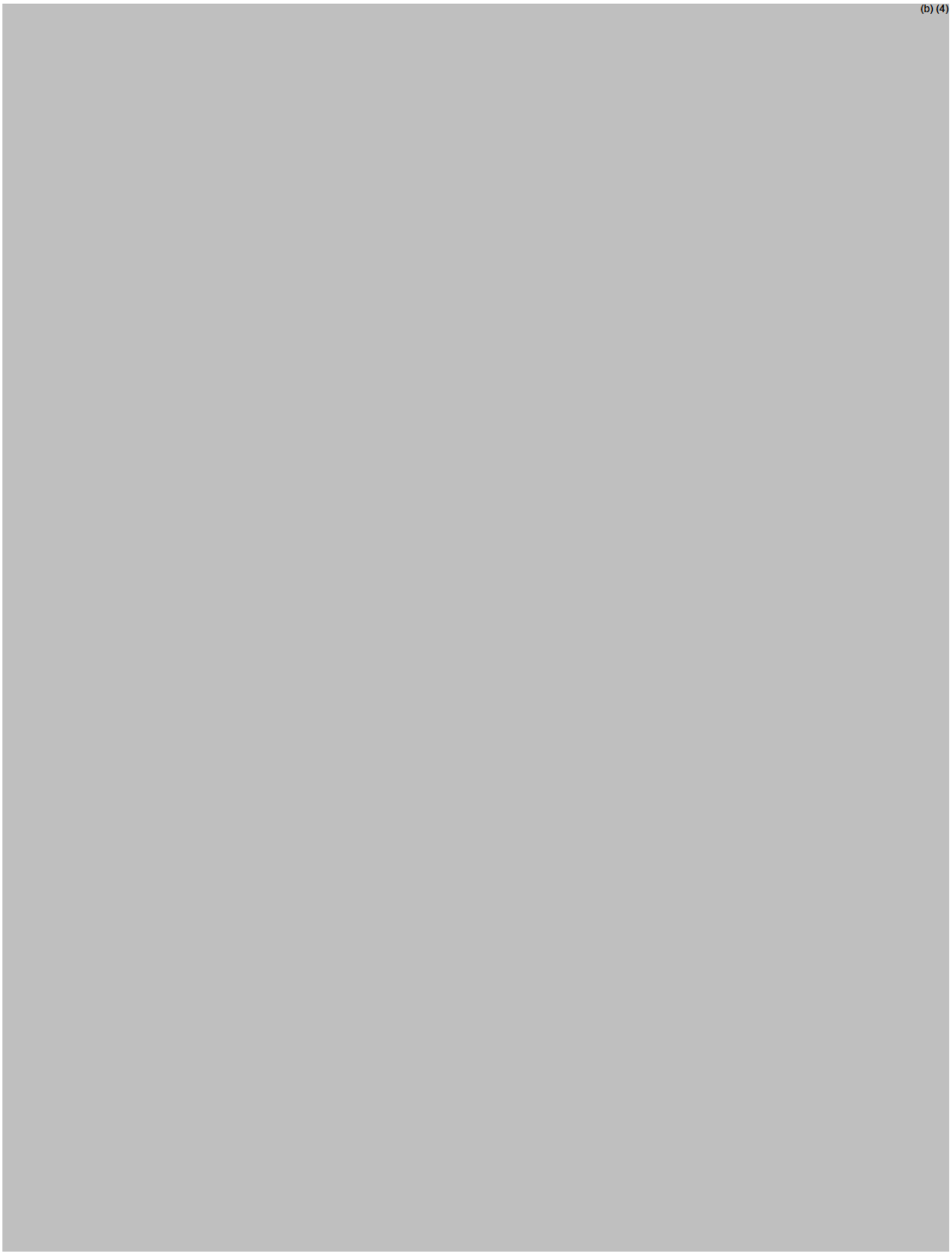


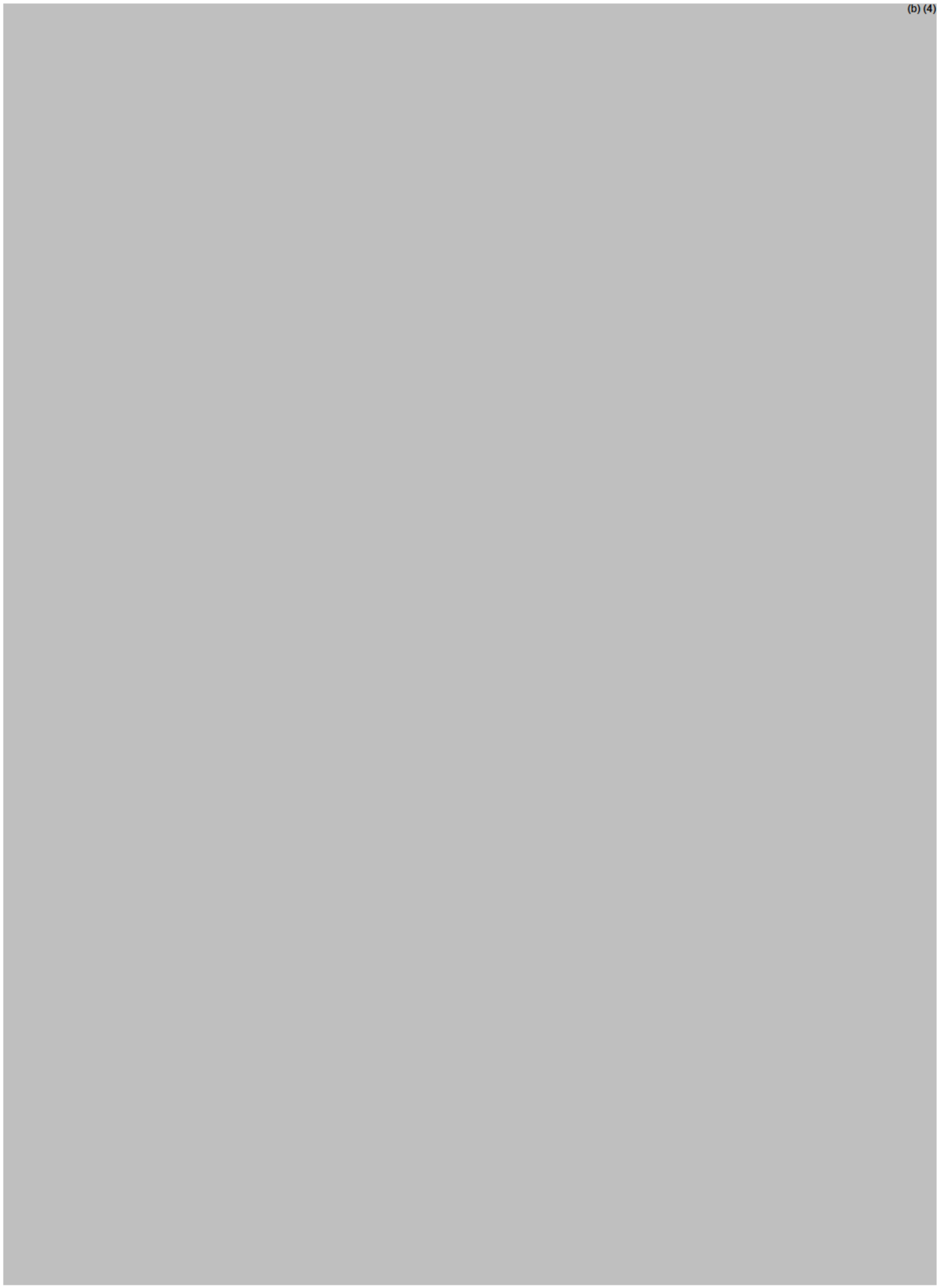

(b) (4)

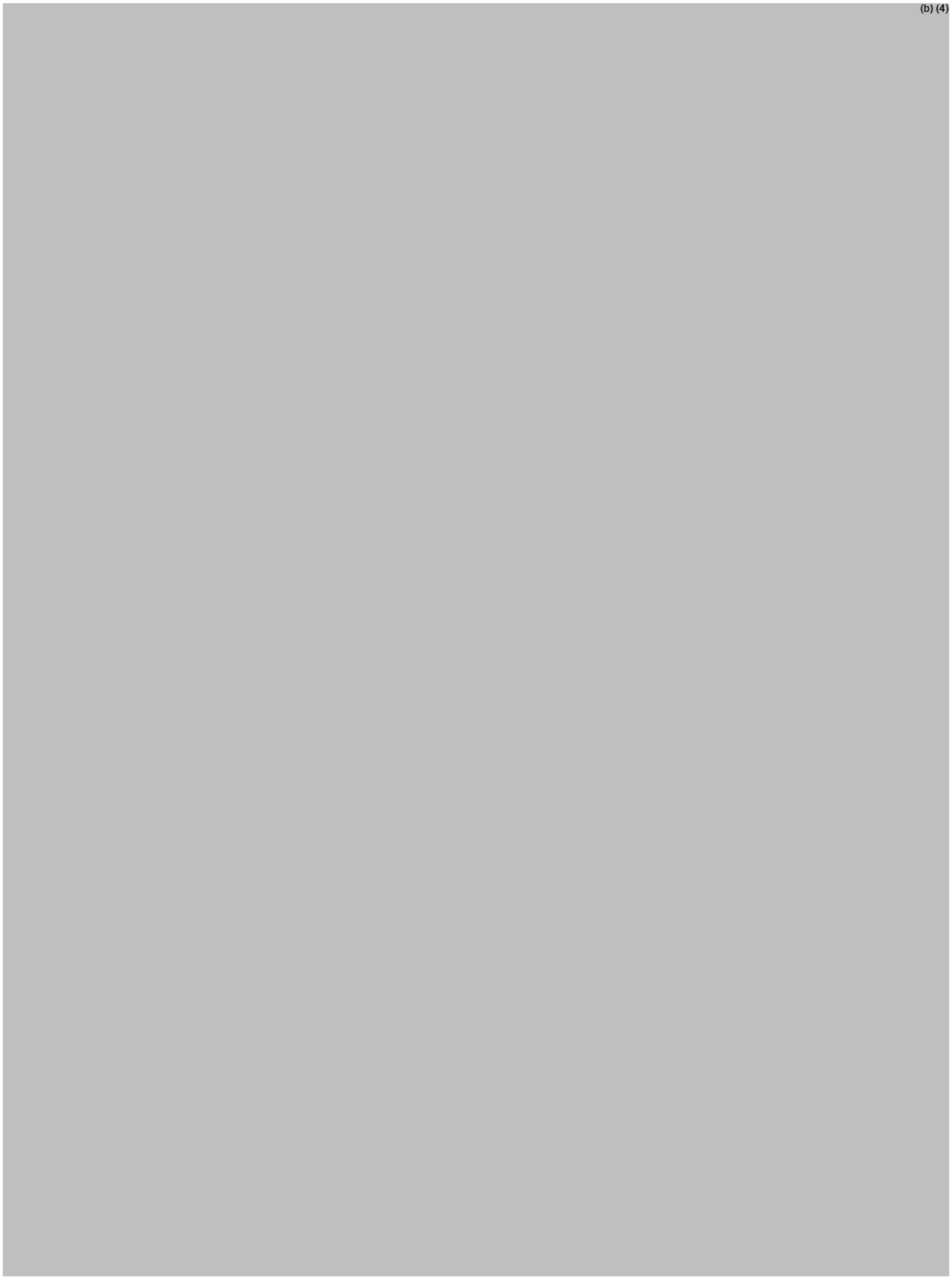

(b) (4)

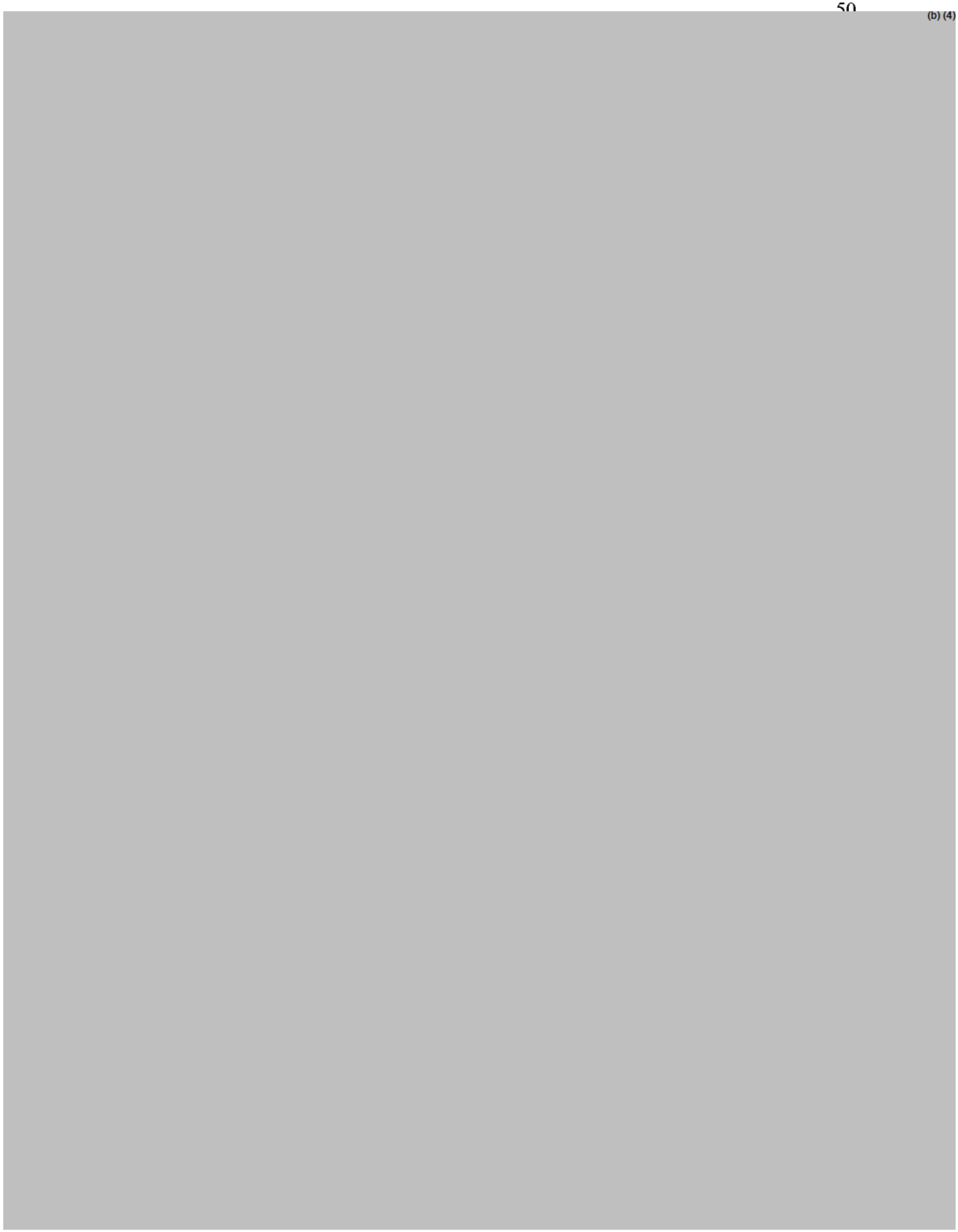





(b) (4)


(b) (4)


(b) (4)

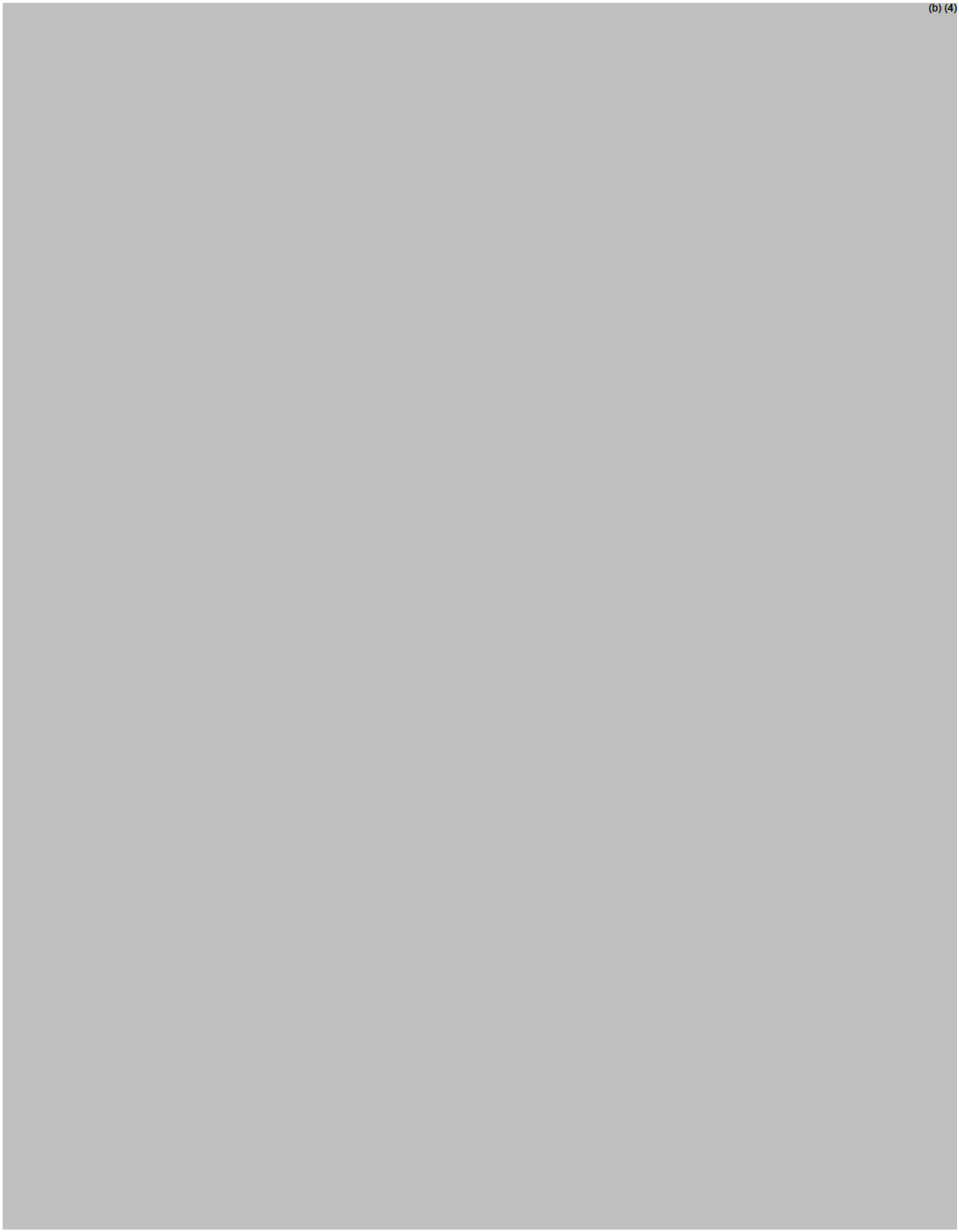

(b) (4)

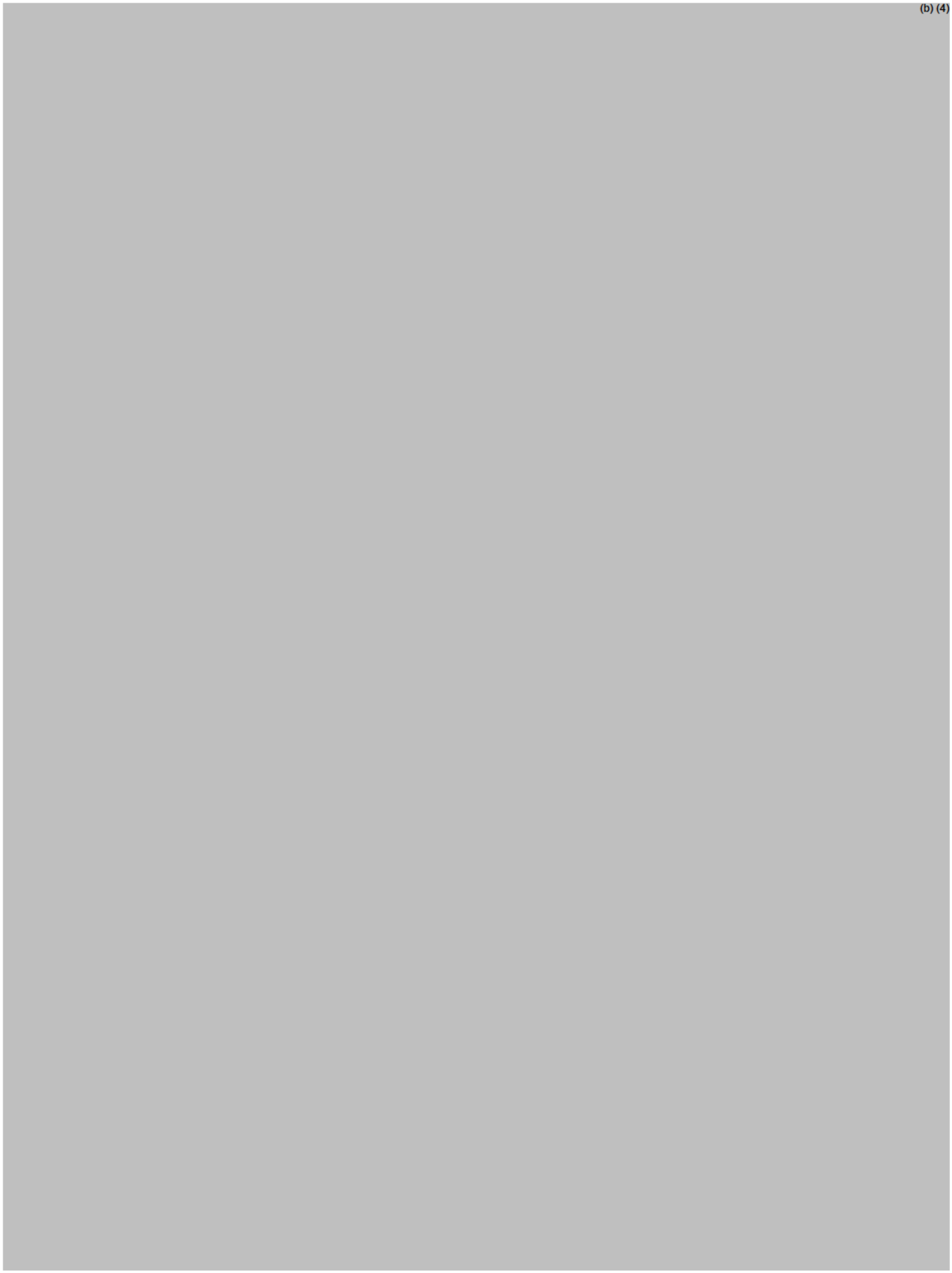

(b) (4)

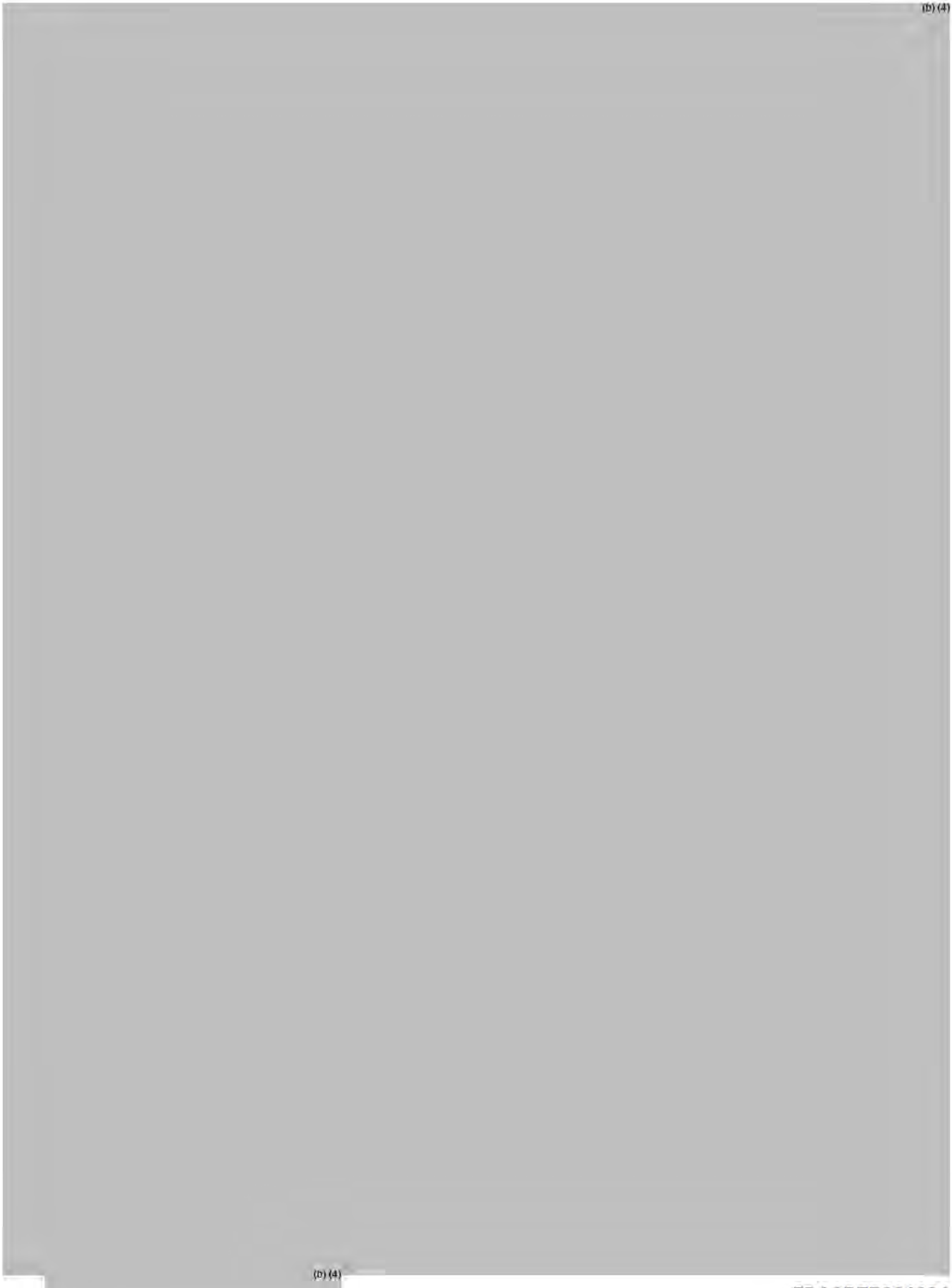

(b) (4)

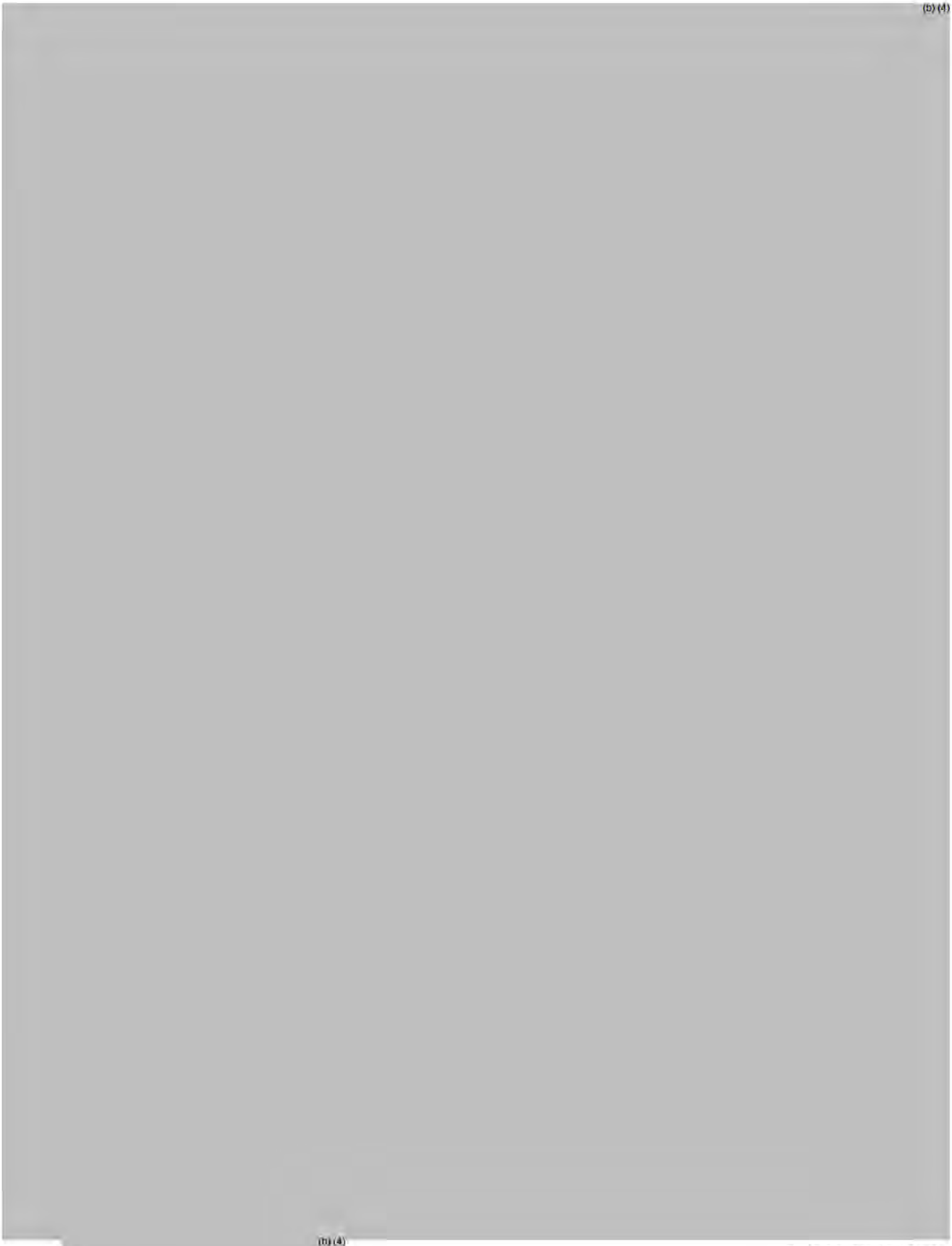
(b) (4)

6.2. Informed Consent



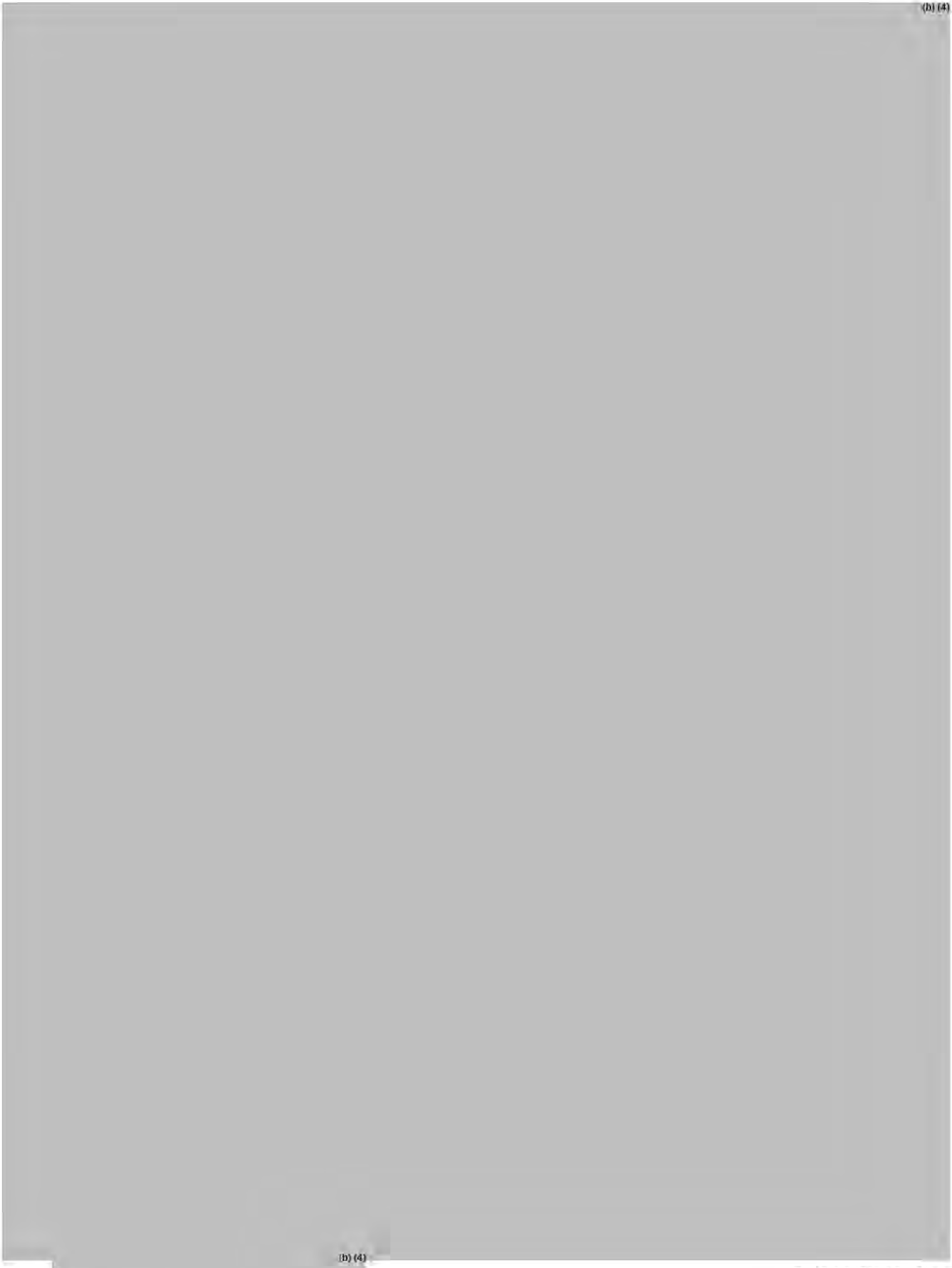

(b) (4)

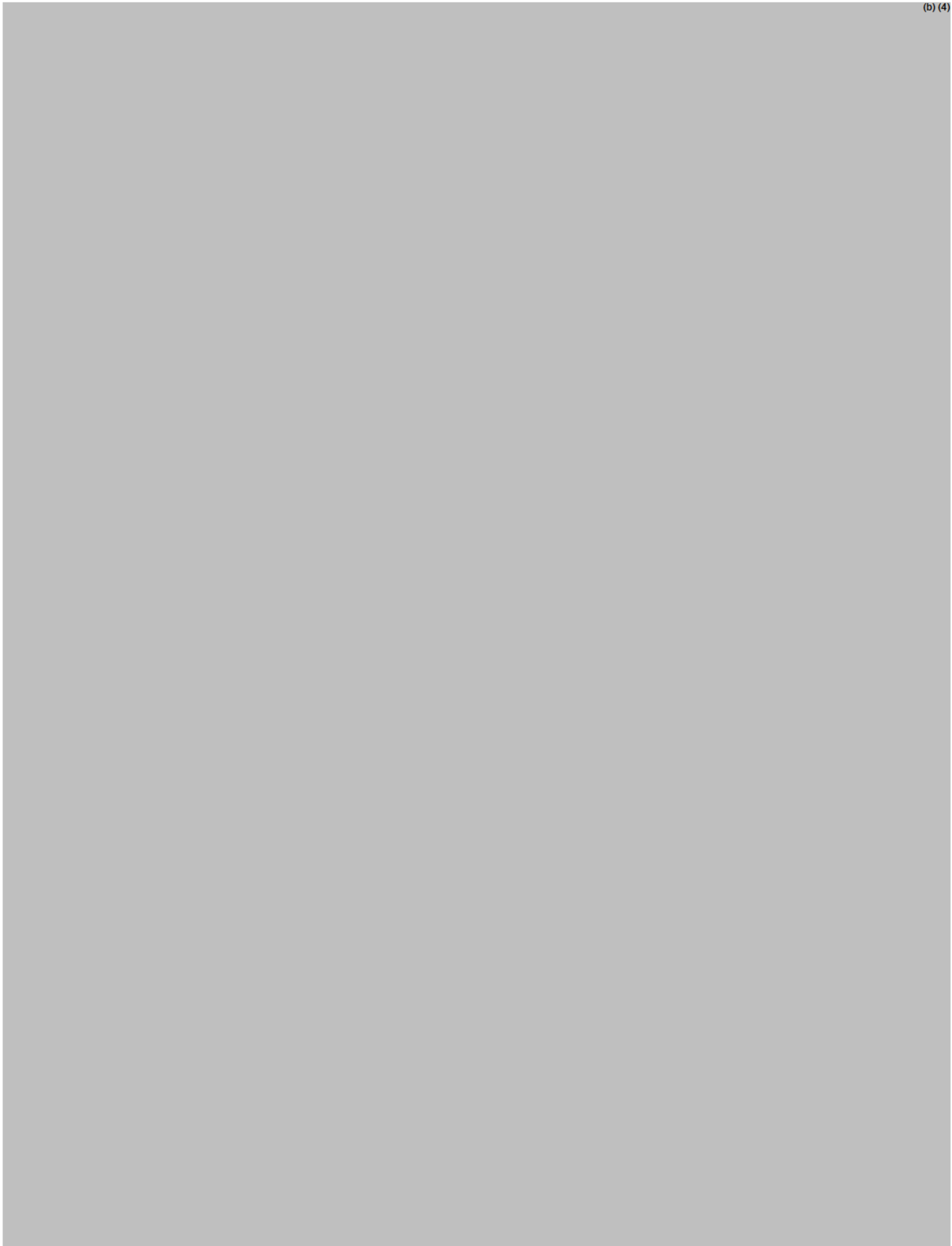

(b) (4)
(b) (4)



(b) (4)

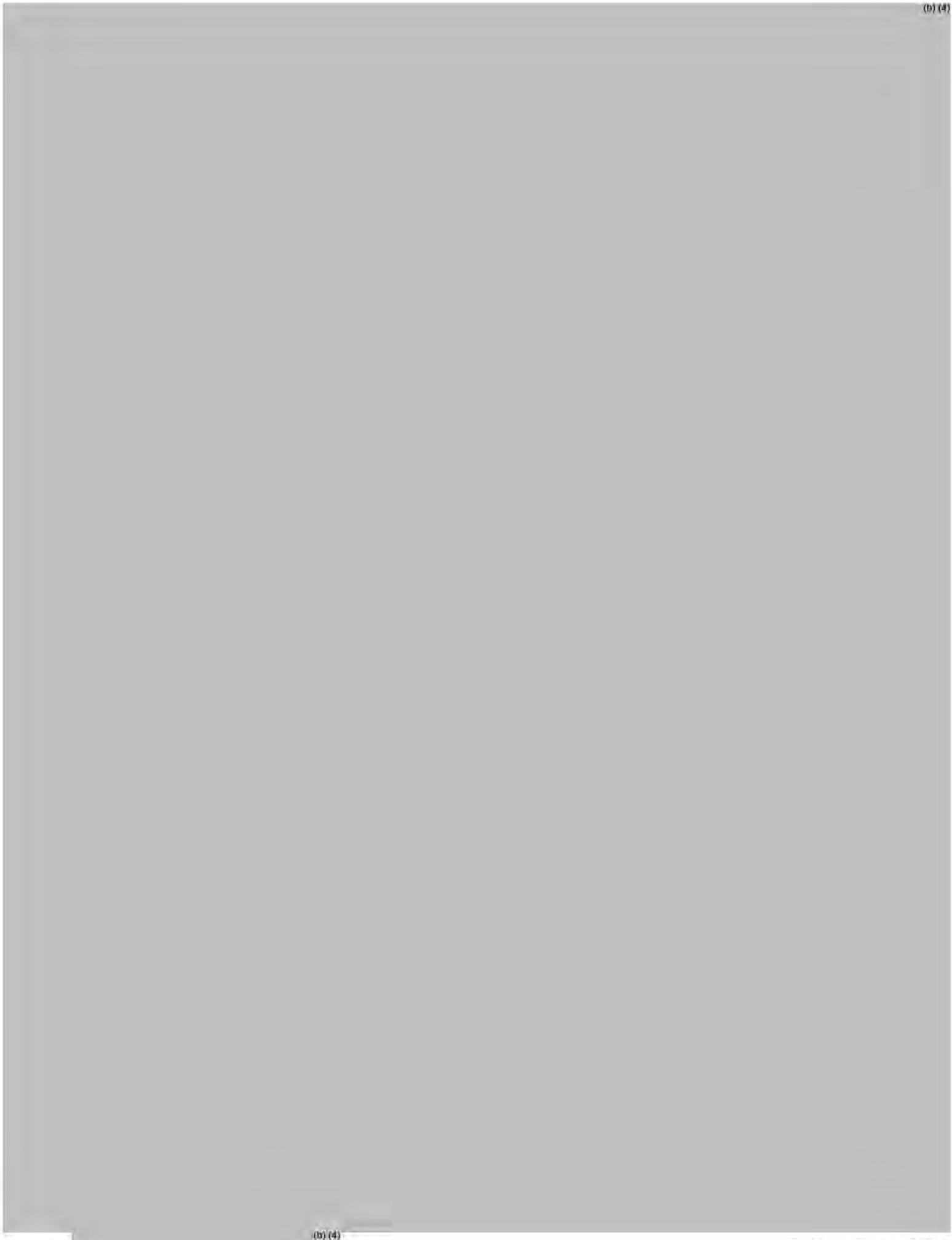
(b) (4)

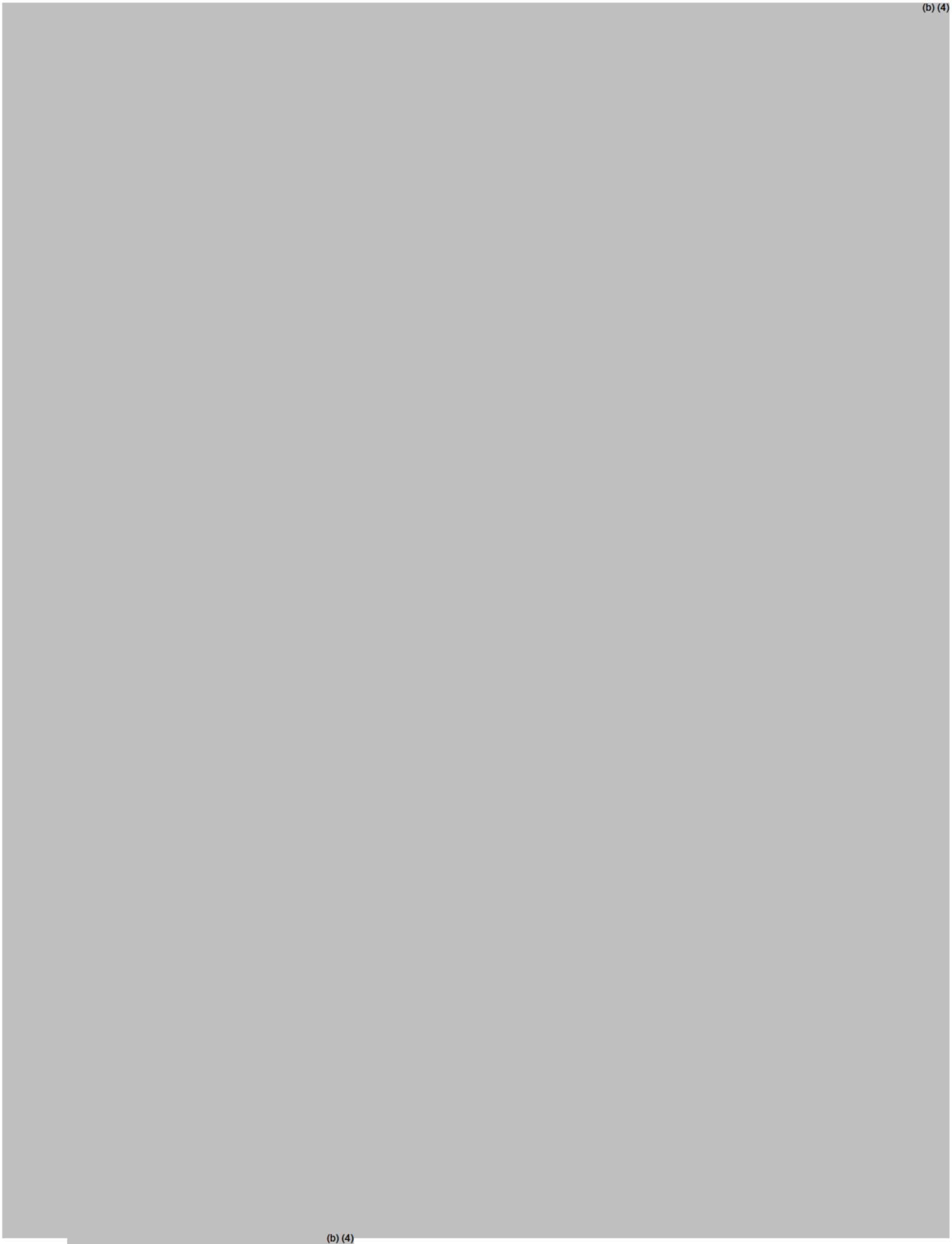

(b) (4)
(b) (4)


(b) (4)
(b) (4)

(b) (4)

(b) (4)


(b) (4)
(b) (4)

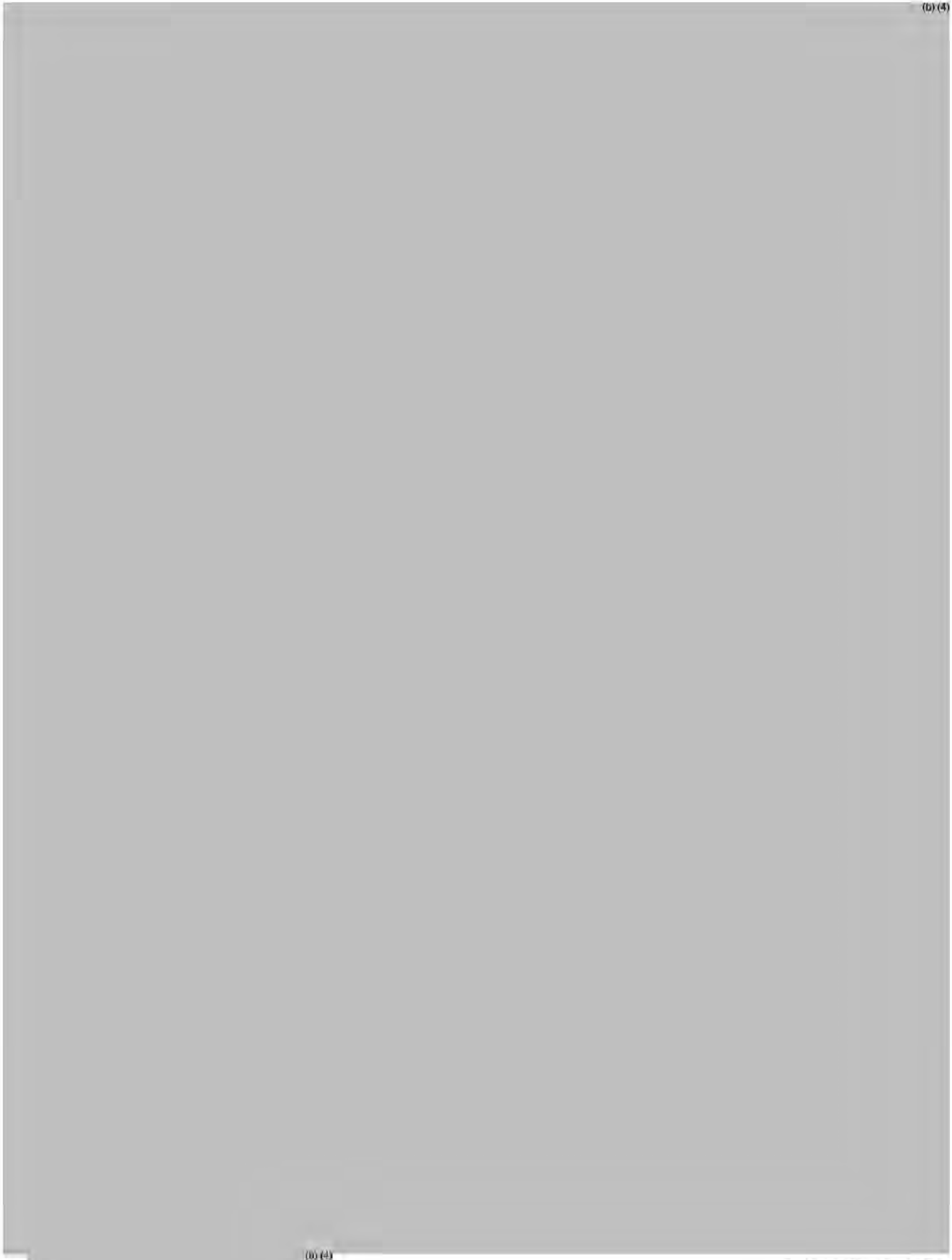

(b) (4)
(b) (4)

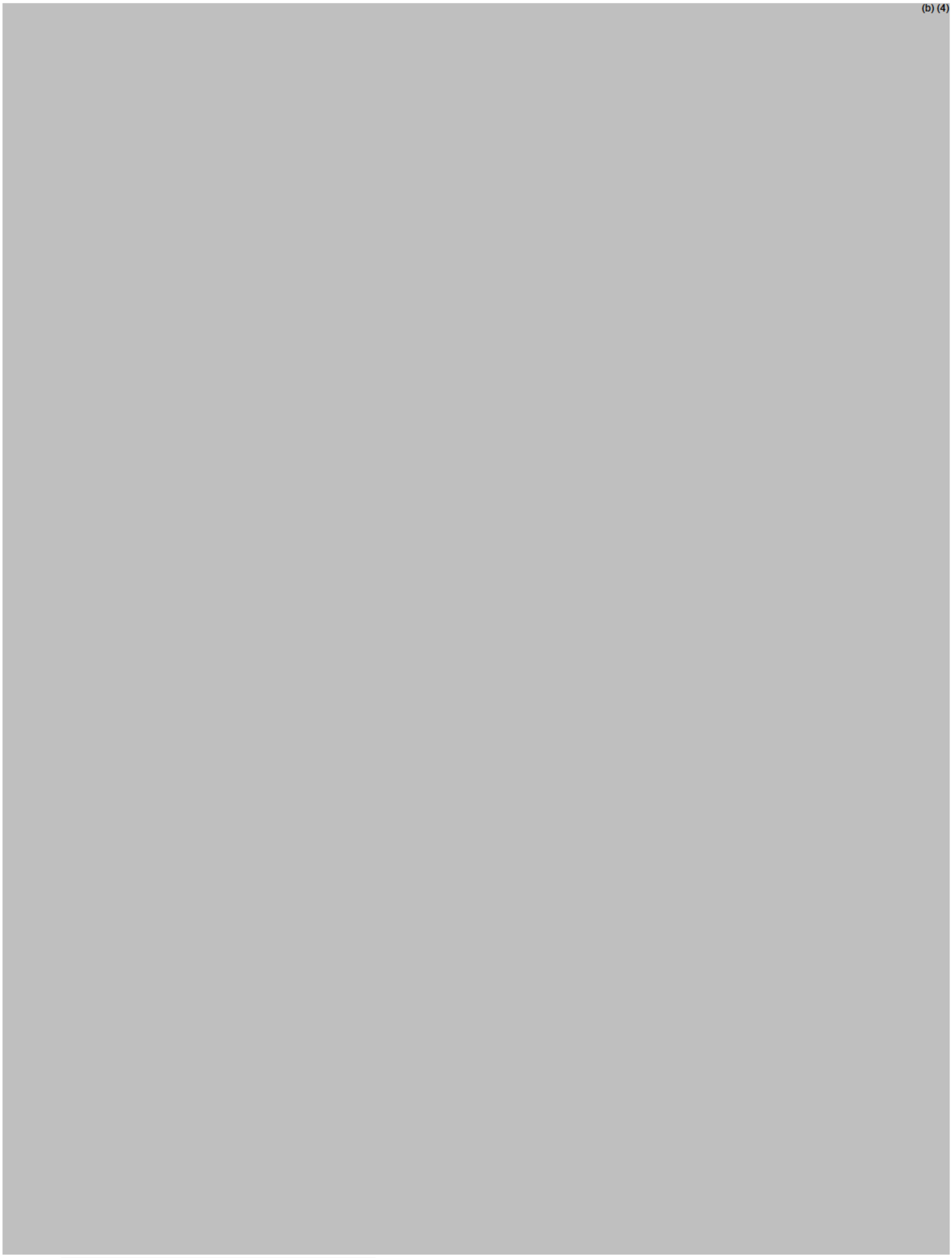
(b) (4)

(b) (4)

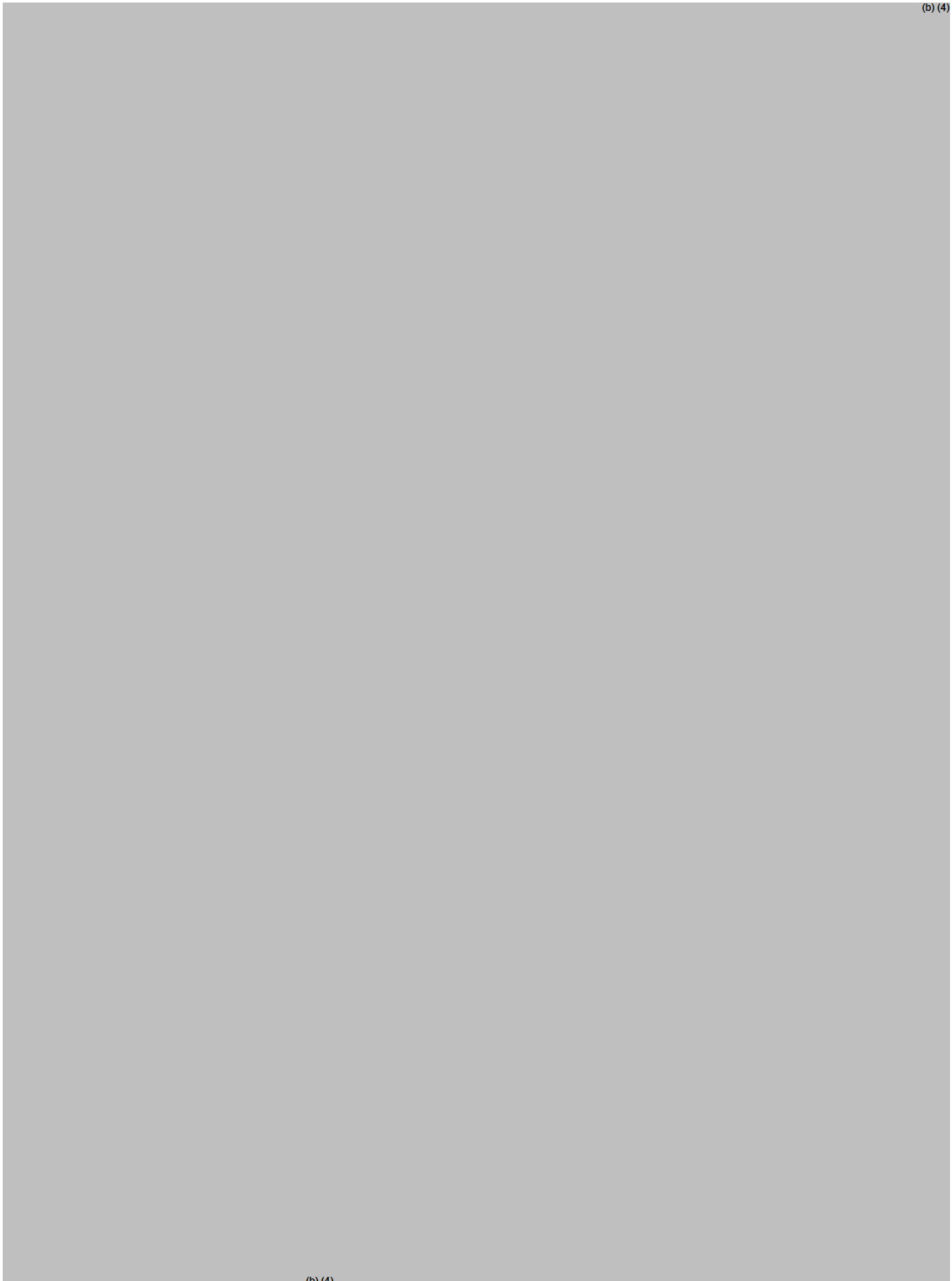
(b) (4)

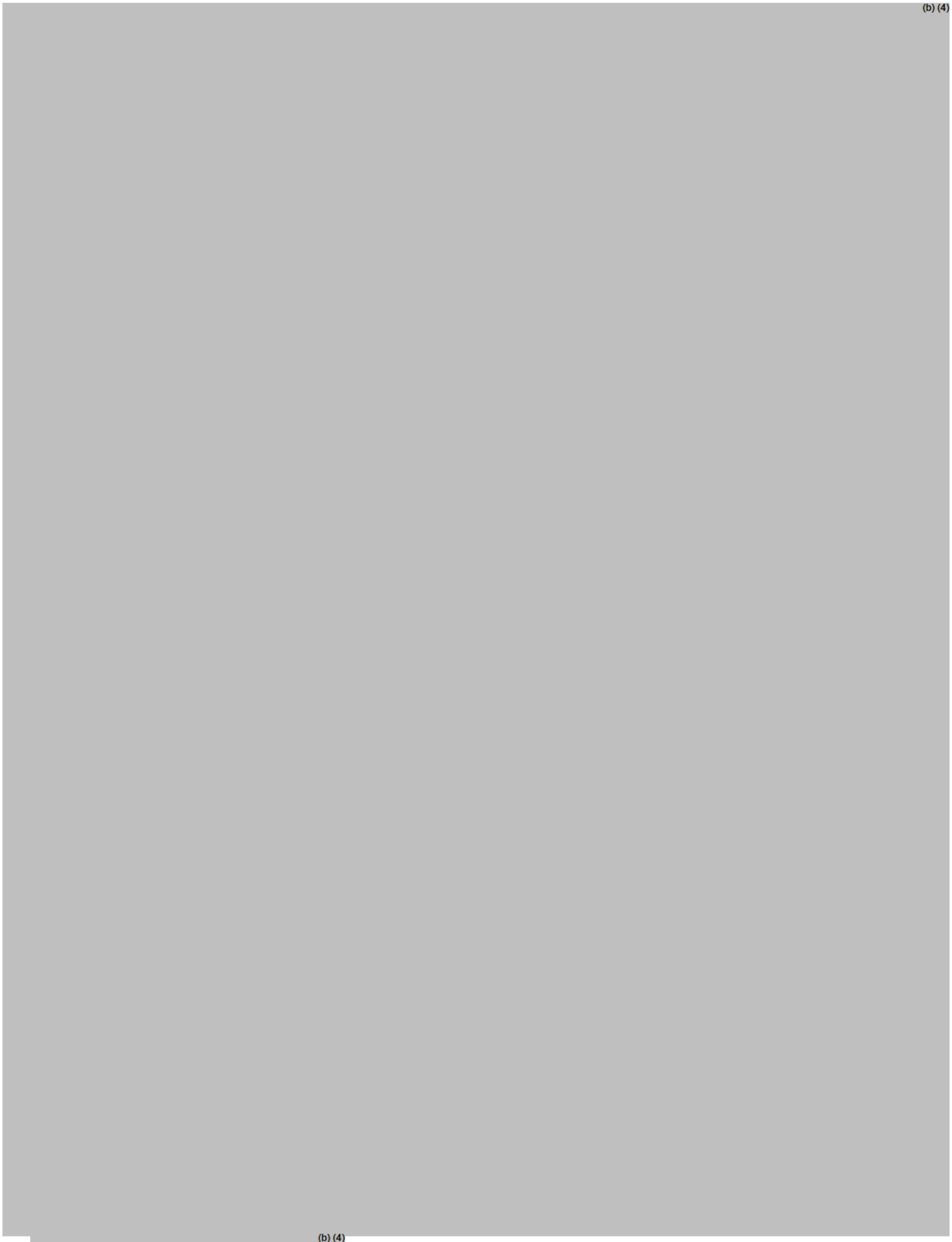
(b) (4)


(b) (4)
(b) (4)


(b) (4)


(b) (4)


(b) (4)
(b) (4)



(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

6.3. Investigator and Facilities Data

Form FDA 1572, Medical License and CV of the principal investigator.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

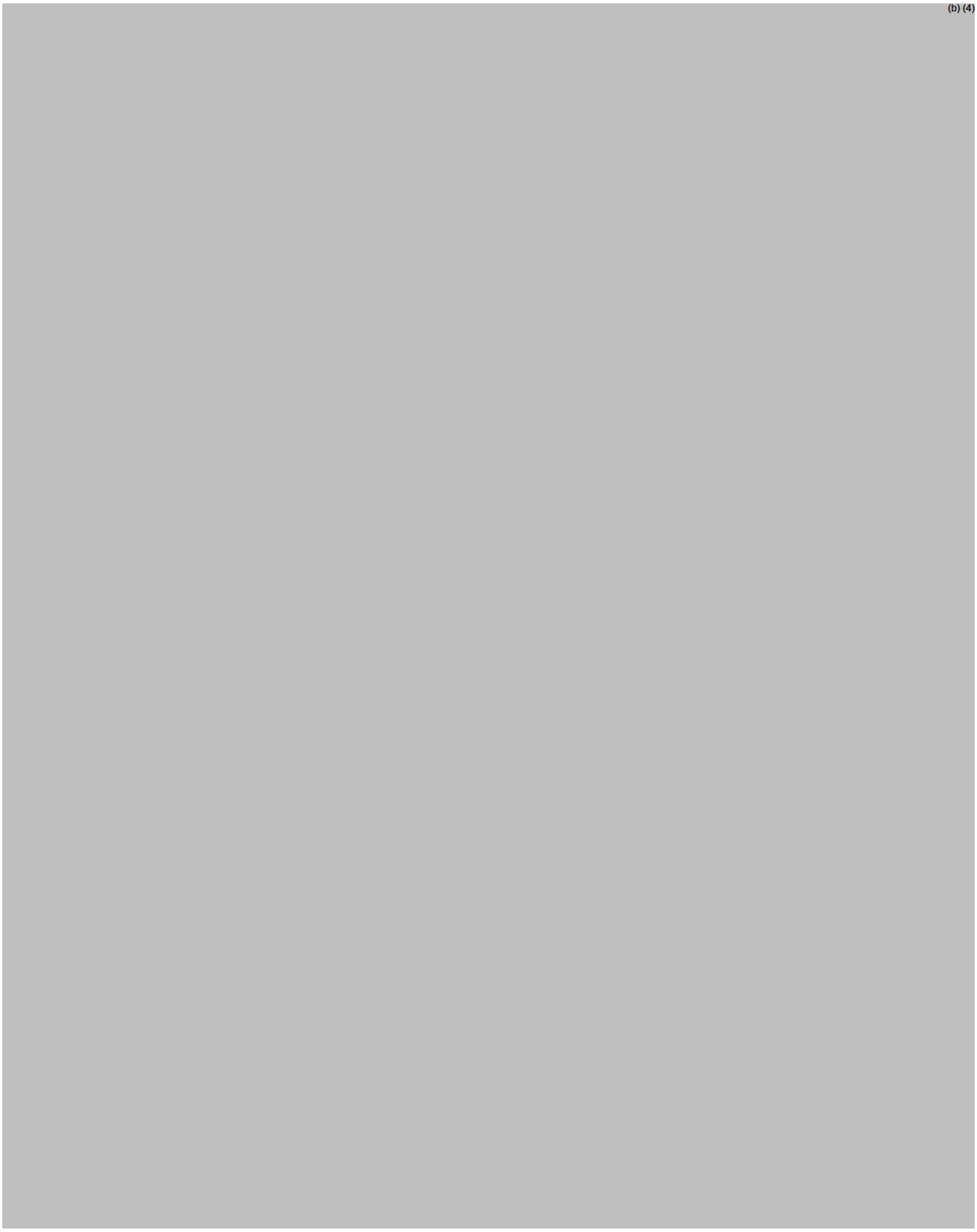
(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014
Expiration Date: March 31, 2022
See OMB Statement on Reverse.

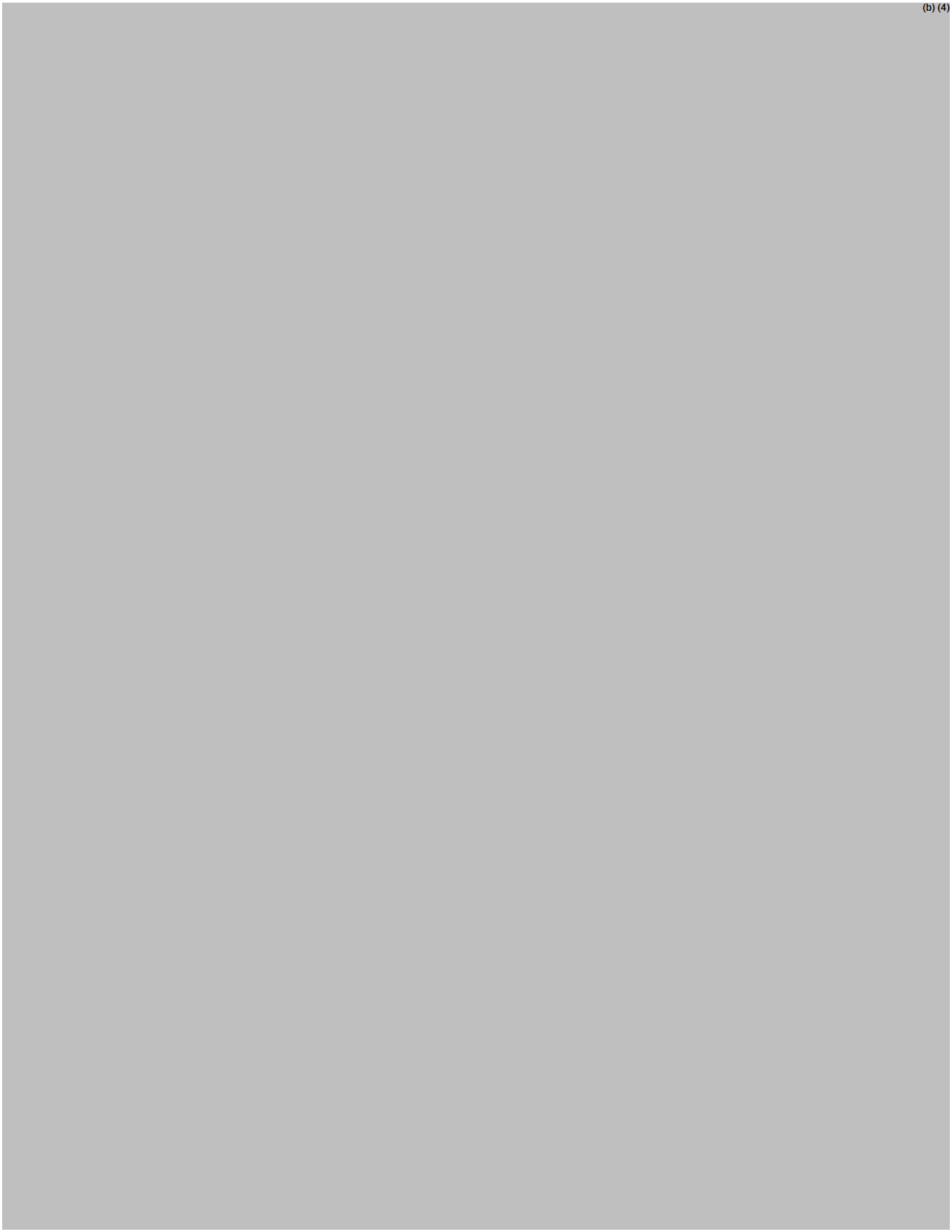
NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

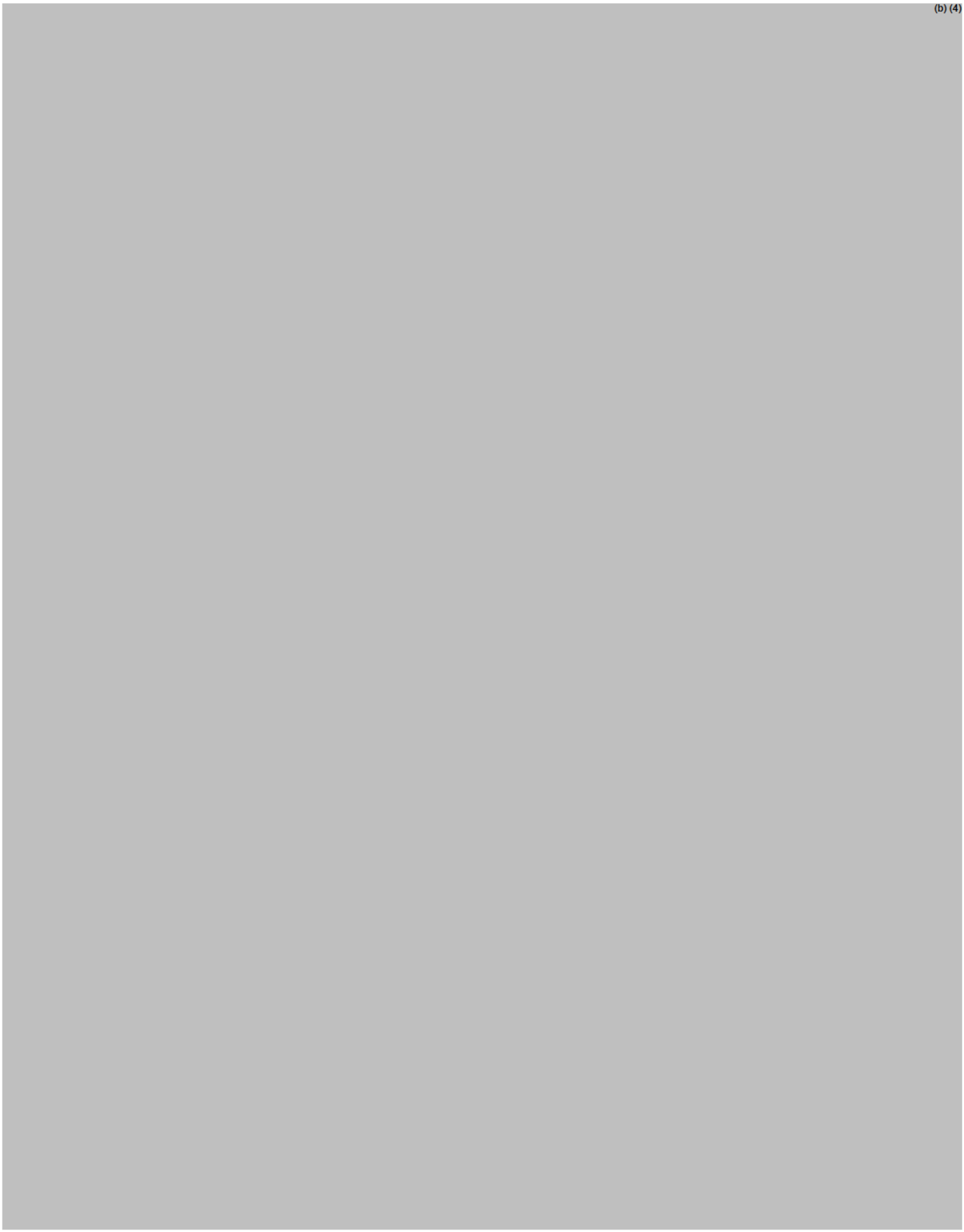
(b) (4)

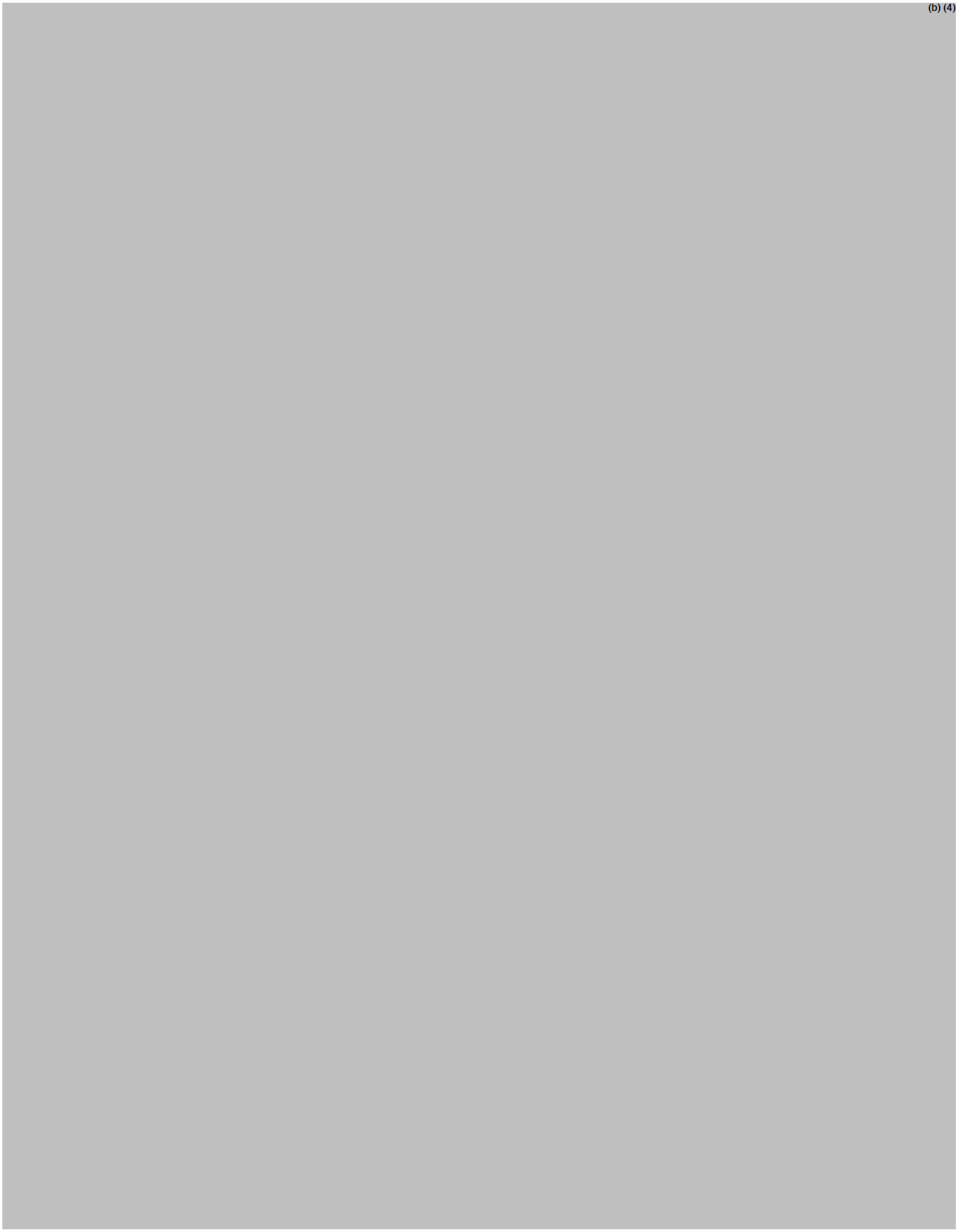
[redacted]

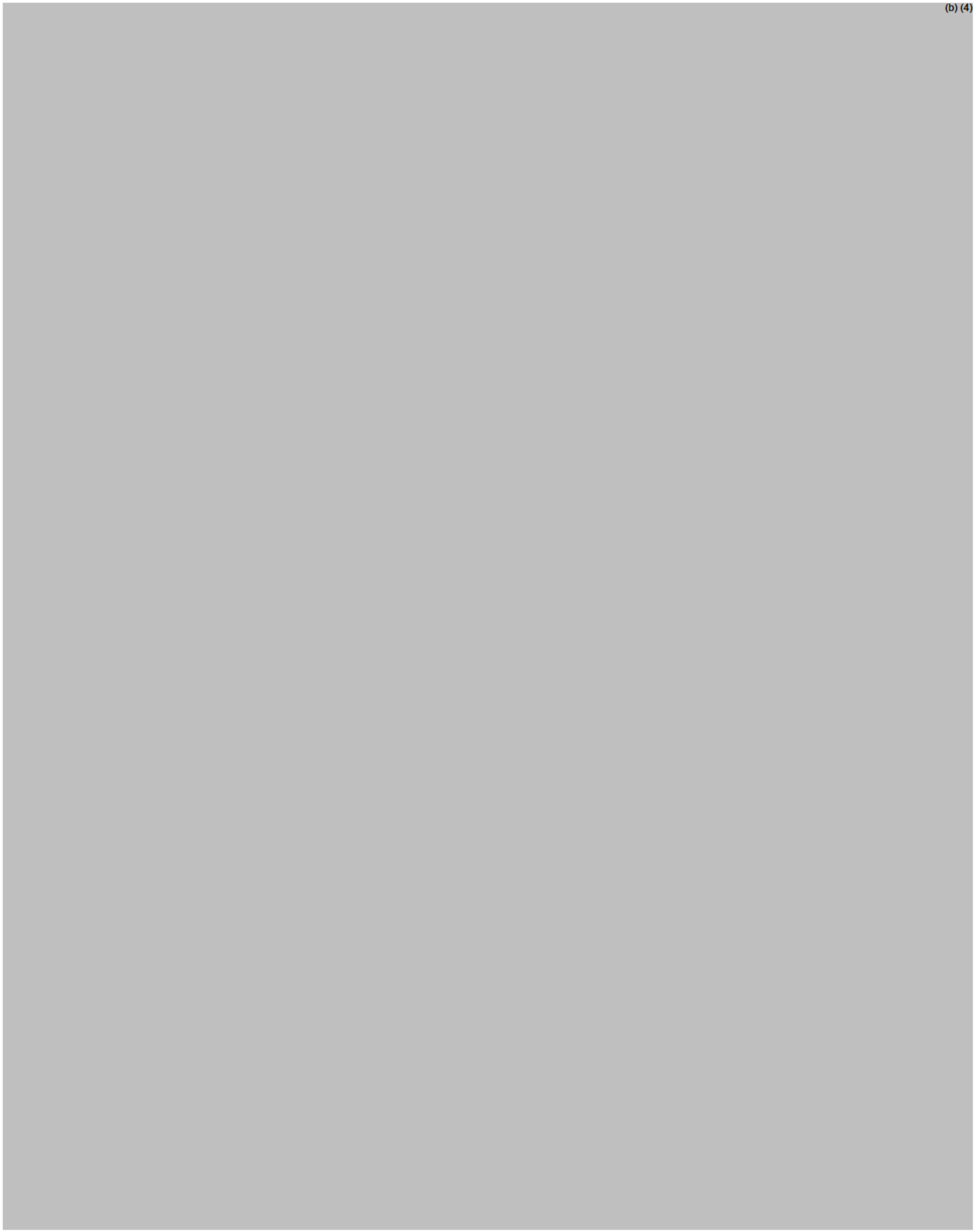


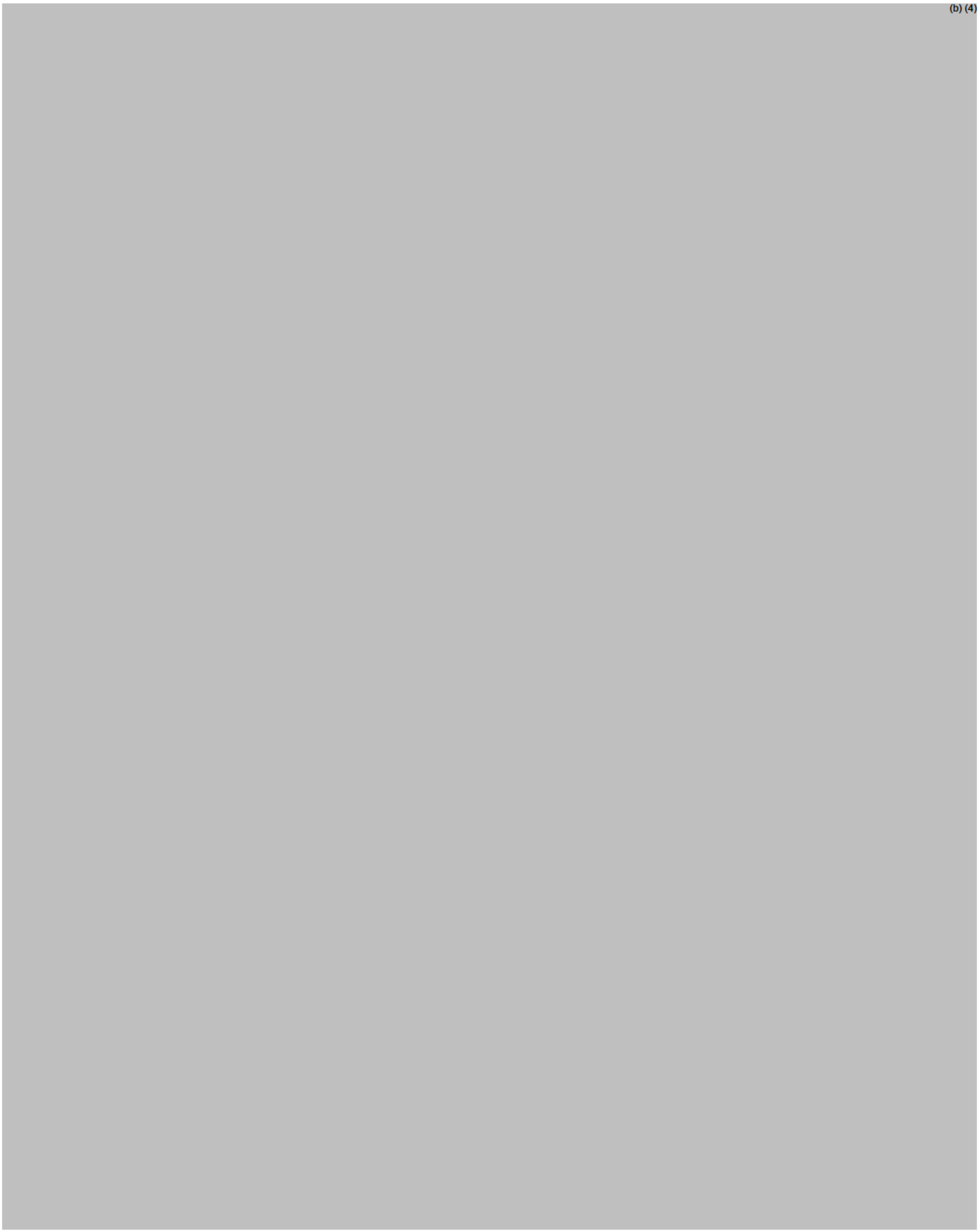

(b) (4)

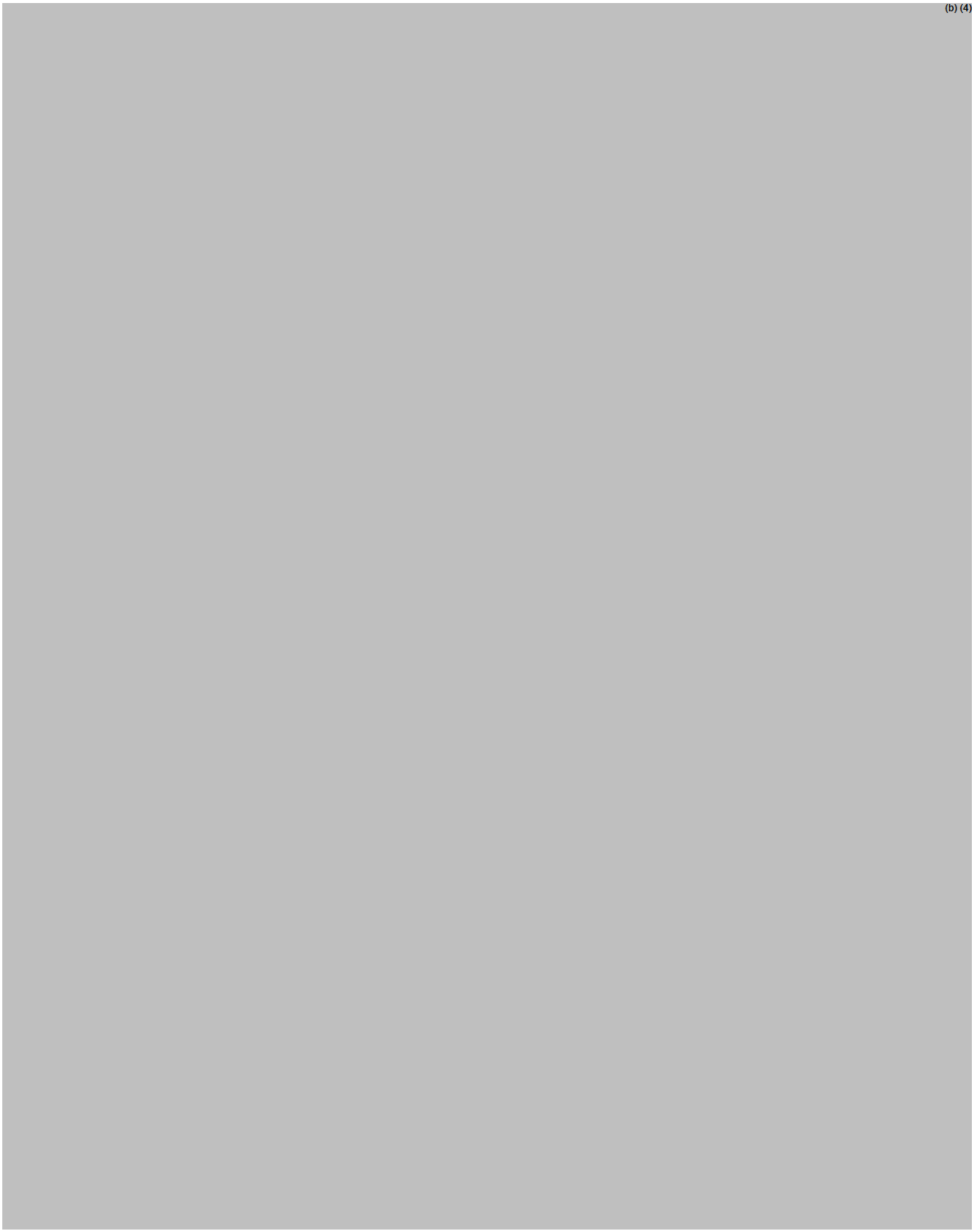


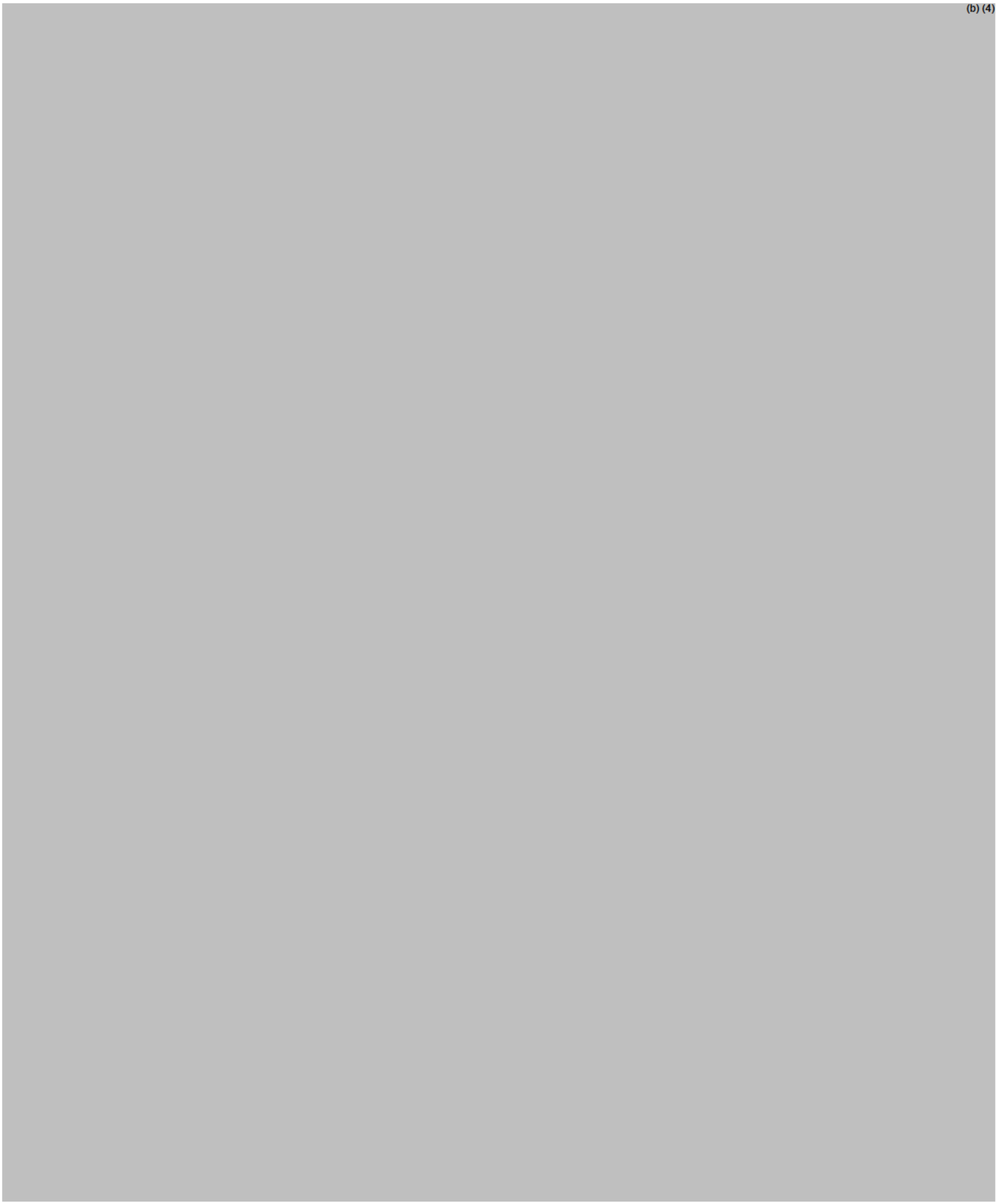













(b) (4)

(b) (4)

7. CHEMISTRY, MANUFACTURING AND CONTROL INFORMATION

(b) (4)

(b) (4)

8. PHARMACOLOGY AND TOXICOLOGY INFORMATION

(b) (4)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Review

Date: November 15, 2021

Reviewer(s): Amy I Chen, PharmD, Safety Evaluator
Division of Pharmacovigilance-I (DPV-I)

David Croteau, MD, Medical Officer
DPV-I

Acting Team Leader: Daniel Woronow, MD, FACC
DPV-I

Division Director: Cindy Kortepeter, PharmD
DPV-I

Product Name(s):

Drug name	Active ingredient	Application	Applicant
Lupron Depot-Ped	Leuprolide acetate	020263	AbbVie Endocrine Inc
Fensolvi	Leuprolide acetate	213150	Tolmar
Synarel	Nafarelin	019886	Pfizer
Supprelin LA	Histrelin	022058	Endo Pharm
Triptodur	Triptorelin	208956	Arbor Pharms LLC

Subject: Idiopathic intracranial hypertension (pseudotumor cerebri)

Application Type/Number: NDA 020263

Submission Number: S-049

Applicant/Sponsor: AbbVie Endocrine Inc.

OSE RCM #: 2021-171

SS ID # 1004605

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The purpose of this Pharmacovigilance Review is for the Division of Pharmacovigilance I (DPV-I) to provide to the Division of General Endocrinology (DGE) an evaluation of idiopathic intracranial hypertension (IIH) [pseudotumor cerebri (PTC)] reported with the use of gonadotropin-releasing hormone (GnRH) agonists that are indicated for the treatment of pediatric patients with central precocious puberty (CPP) from the FDA Adverse Event Reporting System (FAERS) and medical literature. The information and recommendations in this review will assist DGE to determine if IIH (PTC) should be added to labeling for the GnRH agonist class. In addition, this review will assist DGE to determine the approvability of a Prior Approval Supplement (PAS) for Lupron-Depot Ped (NDA 020263, S-049) to update the Warnings and Precautions and Adverse Reactions Postmarketing Experience sections of the United States Prescribing Information (USPI) to include IIH (PTC) in patients treated for CPP.

Based on information identified in this review, DPV concludes there is evidence to support an association between leuprolide acetate and IIH (PTC) including four cases with a temporal relationship with leuprolide therapy, general absence of alternative etiologies for IIH (PTC), and three of these cases with lack of IIH (PTC) recurrence after acetazolamide discontinuation. Evidence from the case series also supports an association between triptorelin and IIH (PTC) based on temporal relationship and general absence of alternative etiologies for IIH (PTC). DPV determined that the cases of IIH (PTC) included in this review were clinically serious with medically important outcomes to warrant the inclusion of IIH (PTC) in the Warnings and Precautions section of the leuprolide acetate and triptorelin label to communicate the risk of IIH (PTC) in pediatric patients diagnosed with CPP. Although we do not have cases for the other two GnRH agonists, nafarelin and histrelin, the biological mechanism is similar for members of the drug class; therefore, DPV does not oppose class labeling for GnRH agonists approved for CPP in the pediatric population.

DPV will continue to monitor the class of GnRH agonists for cases of IIH (PTC), with special attention to drugs with no identifiable cases in our current case series.

Based on this review DPV recommends the following:

- Add information proposed by the Applicant regarding IIH (PTC) to Section 5 of the leuprolide acetate product labeling (for products indicated for CPP):

  WARNINGS AND PRECAUTIONS:

  Pseudotumor cerebri (idiopathic intracranial hypertension)

  Pseudotumor cerebri (idiopathic intracranial hypertension) has been reported in pediatric patients receiving leuprorelin[1] acetate. Monitor patients for signs and symptoms of

[1] Leuprorelin is the generic name of the drug and its International Nonproprietary Name (INN) and British Approved Name (BAN) while leuprolide acetate is its United States Adopted Name (USAN) and established (nonproprietary) name in the United States Pharmacopeia (USP). The current Lupron Depot-Ped® USPI does not use nomenclature for leuprorelin acetate, but rather, leuprolide acetate throughout the label.

pseudotumor cerebri, including headache, papilledema, blurred vision, diplopia, loss of vision, pain behind the eye or pain with eye movement, tinnitus, dizziness, and nausea.

(b) (4)

[redacted]

ADVERSE REACTIONS

Nervous system disorders: pseudotumor cerebri (idiopathic intracranial hypertension)

- Add language to the PATIENT COUNSELING INFORMATION regarding IIH (PTC) such as unusual headaches and visual disturbances.

- Add similar language to the WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS AND PATIENT COUNSELING INFORMATION section of triptorelin product labeling (for products indicated for CPP).

- Although we do not have cases for all the products within the pharmaceutical class of the GnRH agonists, we do not oppose class labeling for GnRH agonists approved for CPP in the pediatric population.

1 INTRODUCTION

The purpose of this Pharmacovigilance Review is for the Division of Pharmacovigilance I (DPV-I) to provide to the Division of General Endocrinology (DGE) an evaluation of idiopathic intracranial hypertension (IIH) [pseudotumor cerebri (PTC)] reported with the use of gonadotropin-releasing hormone (GnRH) agonists that are indicated for the treatment of pediatric patients with central precocious puberty (CPP) [i.e., not for gynecologic or oncologic indications] from the FDA Adverse Event Reporting System (FAERS) and medical literature. The information and recommendations in this review will assist DGE to determine if IIH (PTC) should be added to labeling for the GnRH agonist class. In addition, this review will assist DGE to determine the approvability of a Prior Approval Supplement (PAS) for Lupron-Depot Ped (NDA 020263, S-049) to update the Warnings and Precautions and Adverse Reactions Postmarketing Experience sections of the United States Prescribing Information (USPI) to include IIH (PTC) in patients treated for CPP.

On July 30, 2021 DGE consulted DPV-I to evaluate reports of IIH (PTC) with leuprolide acetate (Lupron-Depot Ped®) to determine if DPV-I agrees with the addition of language proposed by the Applicant in the PAS for Lupron-Depot Ped. DGE also requested DPV assess whether a newly identified safety signal (NISS) should be opened for IIH (PTC) across the class of GnRH agonist products approved for CPP. DPV-I subsequently opened NISS ID #1004605, and moved to the Evaluation Phase after conferring with DGE, which is the basis for this review.

1.1 BACKGROUND

1.1.1 PAS for Leuprolide acetate (NDA 020263, S-049)

On June 18, 2021 AbbVie Endocrinology identified a potential safety signal concerning IIH (PTC) with the use of leuprolide acetate (Lupron-Depot Ped®) in pediatric patients diagnosed with CPP and reported their findings in the AbbVie Leuprolide Clinical Overview.[1] The signal was triggered by a medical literature report describing IIH (PTC) in a 6-year-old female treated with leuprolide for CPP.[2] IIH (PTC) was previously evaluated as a safety signal in December 2016, based on a medical literature report describing a 9-year-old female who developed IIH (PTC) after a dose increase of leuprolide to treat CPP.[3] Given the totality of the data, the previous assessment concluded that there was insufficient information at the time to confirm or rule out a causal association between leuprolide and the occurrence of IIH (PTC). An additional report was identified in the medical literature of a 12-year 5-month-old transgender male, birth assigned female, who developed IIH (PTC) after initiating leuprolide acetate to suppress puberty.[4]

Based on the information in the three literature reports, especially the two reports describing pediatric patients treated with leuprolide for CPP, the Applicant recommended changes to the product labeling for the pediatric CPP population as follows:

Warnings and Precautions:

Pseudotumor cerebri/idiopathic intracranial hypertension

Pseudotumor cerebri (PTC)/idiopathic intracranial hypertension has been reported in pediatric patients receiving leuprorelin acetate. Monitor patients for signs and symptoms of PTC, including headache, papilledema, blurred vision, diplopia, loss of vision, pain behind the eye or pain with eye movement, tinnitus, dizziness, and nausea. (b) (4)

(b) (4)

Adverse Reactions:

Nervous system disorders: pseudotumor cerebri/idiopathic intracranial hypertension

1.1.2 GnRH agonists

GnRH is a decapeptide synthesized in the cell bodies of hypothalamic neurons and secreted by their axon terminals directly into the hypophyseal-portal blood supply.[5] GnRH selectively stimulates gonadotropic cells in the anterior pituitary to release the heterodimeric gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). In turn, LH and FSH stimulate gonadal production of sex steroids and gametogenesis, respectively.[6]

In general, GnRH agonists are derived from native GnRH by substitution of a D-amino acid for the native L-amino acid at position 6 in the decapeptide. GnRH has a short half-life because of the rapid cleavage of the bonds between amino acids at selective positions (5-6, 6-7, 9-10). Substitution at position 6 yields an agonist which is resistant to degradation with an extended half-life and receptor occupancy time.[7] Several unique features mark the physiology of GnRH. First, its secretion is pulsatile in nature and gonadotropic cells require this intermittent form of stimulus-secretion coupling in order to secrete gonadotropins in a physiologic pattern. Second, continuous stimulation of the pituitary either by natural sequence GnRH or by long-acting GnRH agonists desensitizes gonadotropin secretion, resulting in a gonadal suppression that has important clinical applications.[8] A constant intravenous infusion of GnRH or administration of GnRH agonists causes an initial agonistic action, followed by downregulation of receptor concentrations, which desensitizes the pituitary to continued stimulation. Within three to four weeks, a hypogonadotropic hypogonadal state is induced. Initially, the response is due to desensitization and downregulation of the receptors; however, gradual loss of receptors and the uncoupling of the receptor from its effector system occurs over time.[7]

GnRH or its analogs are employed clinically in two different modes. Applications designed to restore fertility in GnRH-deficient men and women must use and intermittently deliver natural-sequence GnRH and hence rely on external delivery devices designed to mimic the physiologic frequency of endogenous GnRH secretion.[9,10] In the second mode of clinical use, a selective and reversible suppression of the pituitary-gonadal axis is sought. This mode of GnRH use (i.e., a biochemical castration) can be achieved by continuous administration of natural sequence GnRH or by the use of long-acting GnRH agonists or antagonists. Single daily injections or depot formulations of GnRH agonists have been introduced in several clinical applications, each of which relies upon complete extinction of gonadotropin secretion with subsequent suppression of gonadal steroids to castrate levels.

CPP, also known as gonadotropin-dependent precocious puberty or true precocious puberty is caused by early maturation of the hypothalamic-pituitary-gonadal axis. It is characterized by sequential maturation of breasts and pubic hair in girls, and of maturation of the testes, penis, and pubic hair in boys. CPP is idiopathic in 80 to 90 percent of cases in girls, whereas intracranial lesions are detected in 40 to 75 percent of boys with CPP.[11]

When warranted, pubertal progression in CPP can be treated by administration of a GnRH agonist. GnRH agonists work by providing continuous stimulation to the pituitary gonadotrophs, instead of physiologic pulsatile stimulation from hypothalamic GnRH. Continuous stimulation leads to desensitization of the gonadotroph cells and suppression of gonadotropins, resulting in decreased sex steroid production,[12] a phenomenon referred to as pituitary-gonadal axis suppression. This treatment can be used for patients with idiopathic or neurogenic CPP[13,14] or for secondary activation of CPP, which may occur in patients who initially present with peripheral precocity. For children with CPP, GnRH agonist administration results in an initial transient stimulation of gonadotropin secretion from the pituitary, followed by a complete, but reversible, suppression of the pituitary-gonadal axis.

1.1.3 IIH (PTC)

IIH is also called PTC, designated herein as IIH. For the purposes of this review, we will use PTC and IIH synonymously, except when quoting an external source. IIH is a disorder defined by clinical criteria that include symptoms and signs isolated to those produced by increased intracranial pressure (ICP) (e.g., headache, papilledema, vision loss), elevated ICP with normal cerebrospinal fluid (CSF) composition, and no other cause of intracranial hypertension evident on neuroimaging or other evaluations. While once called "benign intracranial hypertension" to distinguish it from secondary intracranial hypertension produced by a malignancy, it is not a benign disorder. Many patients suffer from intractable, disabling headaches, and there is a risk of severe, permanent vision loss. Even patients with mild vision loss have an associated reduction in quality of life.[15]

The annual incidence of IIH is 1 to 2 per 100,000 population.[16,17] There is a higher incidence in obese women between the ages of 15 and 44 years (4 to 21 per 100,000).[17,18] IIH is a disorder that primarily affects women of childbearing age who are overweight.[17] In a national prospective population-based cohort study of 185 children with IIH , the national annual incidence (95% CI) of IIH in children aged 1–16 years was 0.71 (0.57 to 0.87) per 100,000 population increasing with age and weight to 4.18 and 10.7 per 100,000 in obese boys and girls aged 12–15 years, respectively.[19] Incidence rates under 7 years were similar in both sexes. From 7 years onwards, the incidence in girls was double that in boys, but only in overweight (including obese) children. In children aged 12–15 years, an estimated 82% of the incidence of IIH was attributable to obesity.[19]

When IIH is associated with factors other than obesity, recent weight gain, and polycystic ovarian syndrome, it is referred as IIH-like syndrome because it is no longer idiopathic. Many case reports and case series describe associations between certain medications and intracranial hypertension. Such medications include vitamin A (hypervitaminosis A) and the vitamin A derivatives isotretinoin and all-trans-retinoic acid, antibiotics (e.g., tetracycline, minocycline,

nalidixic acid, fluoroquinolones, sulfa drugs), hormonal medications (e.g., growth hormone, oral contraceptives, progesterone, danazol), corticosteroid withdrawal (especially among children), and lithium.[20,21,22,23,24,25,26,27,28,29,30,31,32]

Various systemic diseases have been associated with IIH, including systemic lupus erythematosus, underlying malignancies, anemia, Addison's disease, hyperthyroidism and hypothyroidism, and uremia.[33,34,35,36,37,38] Dural venous sinus thrombosis has long been recognized as being associated with intracranial hypertension.[39] Dural sinus occlusion leads to increased venous pressure and higher CSF pressures, with clinical findings of papilledema and headaches. Certain systemic conditions and medications may be associated with IIH via a hypercoagulable state leading to dural sinus thrombosis. These conditions include malignancies, systemic lupus erythematosus, protein C and S deficiencies, antithrombin III deficiency, Factor V Leiden mutations, anticardiolipin antibodies, oral contraceptive use, and pregnancy.[40,41,42,43,44]

Other venous abnormalities that can elevate intracranial venous pressures, including dural arteriovenous fistulae and carotid-cavernous fistulae, have been associated with IIH.[45,46] Iatrogenic disruption of venous drainage, for example, after acoustic neuroma resection, radical neck dissection or catheter-induced subclavian vein thrombosis has also been associated with elevated intracranial venous and CSF pressures.[47,48,49] Venous sinus compression by tumors (e.g., meningiomas) has also been reported.[50]

The pathophysiologic mechanisms of pediatric IIC have not been studied to the same extent as adult IIH. In its most fundamental level, IIC is related to abnormal CSF dynamics, either impaired CSF outflow, or aberrant CSF production, or both. With respect to impaired CSF outflow, increased resistance of CSF flow through arachnoid granulations may contribute to raised ICP. Impaired CSF lymphatic outflow (the "glymphatic pathway"), a CSF drainage pathway recently appreciated in the CNS, may also be contributing. In the pediatric population, IIH is characterized by a multifaceted relationship between age, obesity, pubertal status, and sex, factors which, in truth, may be acting to influence CSF production or outflow. However, many studies have focused on their influence on CSF production. The interaction of these factors may change with age, producing age-dependent phenotypes likely driven by distinct factors with possibly different pathophysiology. For example, adiposity clearly contributes to the presentation of disease in early and late adolescents, who are more frequently obese and female, likely similar to those in adults. Whereas factors other than adiposity likely contribute to the phenotype of young, prepubertal children with IIH, who are less likely to be obese, are equally male and female, and may present without symptoms of headache or visual blurring. Pediatric adiposity has complex pathophysiology and includes potential contributions from alterations in growth hormone and gonadal hormones, factors also known to play a role in IIH-like syndrome.[51,52] Transverse sinus stenoses (TSS) have been found in a large majority of patients with IIH.[53] It is, however, not clear whether they are incidental, secondary to increased ICP, or causal.[54,55]

Headache is the most common symptom of IIH and observed in nearly all patients. IIH headaches are typically generalized, episodic, throbbing, and worse in the morning. They are often aggravated by Valsalva maneuvers (straining or coughing) and may be associated with retro-orbital pain.[56] Neck, shoulder, and arm pain is often involved. In addition, transient visual

symptoms (obscurations, blurring, and scotomata) and diplopia are frequently noted.[57] Pulsatile tinnitus is common and may be the initial complaint.[58]

After recording a complete history, the evaluation should continue with complete neurological and ophthalmological examinations. Papilledema, as a criterion for the condition, is observed for virtually all patients with IIH and is the most important sign. However, there have been numerous case reports of patients with IIH for whom papilledema was not observed, and the absence of papilledema is thus not an exclusionary criterion.[59] Abducens palsy, a false localizing sign thought to be attributable to traction of the sixth cranial nerve resulting from intracranial hypertension is observed in approximately 20% of cases.[60] Facial palsy may also be observed. In cases of suspected IIH, an ophthalmoscopic examination is critical. Papilledema is usually the only objective finding in physical examinations for patients with IIH. The ophthalmoscopic appearance of IIH is usually characterized by bilateral optic nerve head swelling. However, this can be quite subtle and cases of IIH without papilledema have been reported. The magnetic resonance imaging (MRI) findings in IIH are generally reported as unremarkable, but abnormalities may be present in IIH. The abnormalities include a partially empty sella, flattening of the posterior sclera, dilation and tortuosity of the optic nerve sheath, and sometimes gadolinium enhancement of the optic disc.[61] However, the findings are often too subtle and nonspecific to allow the diagnosis of IIH on the basis of MRI scans alone. If the findings on MRI scans do not provide compelling evidence of ICP elevation, then a lumbar puncture, with direct measurement of the lumbar subarachnoid pressure, should be performed in cases of suspected papilledema.

For initial treatment of patients with IIH, the carbonic anhydrase inhibitor acetazolamide is recommended. Carbonic anhydrase inhibitors are believed to reduce the rate of CSF production and have been associated with modestly improved outcomes in patients with IIH.[62] Furosemide is also a diuretic but has little effect on CSF production; it may be used for patients who cannot tolerate acetazolamide. A short course of intravenous glucocorticoids may be helpful for patients with acute visual loss resulting from fulminant papilledema. Serial lumbar punctures or lumbar drainage can be a useful temporizing measure as a prelude to surgery.[55] However, these are not useful for long-term management of IIH in most patients.

Surgical intervention is required as soon as medical treatment fails. The two main surgical procedures in IIH are optic nerve sheath fenestration (ONSF) and cerebrospinal fluid (CSF) shunting procedures. ONSF is usually performed using a medial orbital approach. The optic nerve sheath is identified and a window is cut in the sheath, allowing CSF egress into the orbit. Common complications include diplopia, efferent pupillary dysfunction from ciliary ganglion damage, and vision loss. Vision loss can result from vascular complications, trauma, infections, hemorrhage into the optic nerve sheath, and other operative events.[63] CSF shunting procedures include ventriculoperitoneal shunt (VPS) or lumboperitoneal shunt (LPS). Shunt failure requiring revision is the most common complication of LPS and occurs in approximately half of patients, with a few patients requiring multiple (10 to 38) shunt revisions.[64] In rare cases, shunt failure is accompanied by visual loss that can be rapid and severe.[65] Other complications of shunting include shunt infection, abdominal pain, and over drainage causing low pressure. Rare complications include cerebellar tonsillar herniation, syringomyelia, subdural and subarachnoid hemorrhage, and bowel perforation.

1.2 REGULATORY HISTORY

GnRH agonists are used for a variety of indications including the treatment of infertility and to lower sex hormone levels in the treatment of hormone-sensitive cancers such as prostate cancer and breast cancer, gynecological disorders such as endometriosis and uterine leiomyomas, and the treatment of CPP in pediatric patients. There are five FDA-approved GnRH analogs currently marketed in the U.S for the treatment of CPP in pediatric patients. The first GnRH agonist, nafarelin (Synarel®) was approved by the FDA on February 13, 1990. Table 1 lists the currently available GnRH agonists in the U.S. indicated for the treatment of CPP in pediatric patients.

Table 1. GnRH Agonists Approved by FDA for Treatment of CPP in the U.S.

Active ingredient	**Leuprolide acetate**	**Leuprolide acetate**	**Nafarelin**	**Histrelin**	**Triptorelin pamoate**
Trade name	Lupron-Depot Ped	Fensolvi	Synarel	Supprelin LA	Triptodur
Application NDA	020263	213150	019886	022058	208956
Approval date	4/16/93	5/1/20	2/13/90	5/3/07	6/29/17
Dosage form	IM injection	SQ injection	Nasal spray	SQ implant	IM injection
Dose	7.5 mg, 11.25 mg, 15 mg QMO 11.25 mg, 30 mg Q3MO	45 mg Q6MO	1600-1800 mcg QD	50 mg QYR	22.5 mg Q24 WK

1.3 RELEVANT PRODUCT LABELING

GnRH agonists indicated for the treatment of CPP in pediatric patients are not labeled for IIH.

2 METHODS AND MATERIALS

2.1 CASE DEFINITION AND SELECTION CRITERIA[66]

Case definition of IIH

The case definition of IIH requires the following:

Category I

A reported lumbar puncture opening pressure of ≥250 mm H_2O in adults and ≥280 mm H_2O in children [250 mm if the child is not sedated and not obese][2] AND the following:

A. Papilledema
B. Normal neurological examination except for cranial nerve abnormalities
C. Normal CSF composition[3]
D. Neuroimaging consistent with normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI, with and without gadolinium, for typical patients (female and obese), and MRI,

[2] If criteria A–D are met but the measured CSF pressure is lower than specified here, a diagnosis of IIH is still conceivable but less robust

[3] If CSF values or neurological examination findings are not specifically reported it is appropriate to assume they are unremarkable

with and without gadolinium, and magnetic resonance venography for others; if MRI is unavailable or contraindicated, contrast-enhanced computerized tomography (CT) may be used[3]

OR

Cases lacking papilledema but otherwise fulfilling other criteria above AND with a unilateral or bilateral abducens neuropathy

Category II

Clinical diagnosis including any the following terms:

A. Pseudotumor cerebri
B. Benign intracranial hypertension
C. Idiopathic intracranial hypertension

Selection Criteria

- Inclusion criteria
  - Met the case definition for IIH
  - Reasonable temporal relationship to GnRH agonist exposure
- Exclusion criteria
  - Non-CPP or non-puberty indication[4] (e.g. gynecological or oncological indication)
  - Duplicate report
  - Pediatric patient not reported
  - GnRH agonist use not reported
  - Insufficient information to assess causality

2.2 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2.

Table 2. FAERS Search Strategy*	
Date of search	September 6, 2021
Time period of search	Through September 5, 2021
Search type	FBIS Product Manufacturer Reporting Summary
Product terms	Product active ingredient: leuprolide; leuprolide acetate; leuprolide acetate\lidocaine hydrochloride; leuprolide acetate\norethindrone acetate; nafarelin; nafarelin acetate; histrelin; histrelin acetate; triptorelin; triptorelin acetate; triptorelin pamoate; goserelin; goserelin acetate; elagolix; elagolix sodium; elagolix sodium\estradiol\norethindrone

[4] We included a case, also identified in the Applicant's clinical overview, of a transgender 12-year-old male (birth assigned female) who received leuprolide acetate to suppress puberty.

Table 2. FAERS Search Strategy*	
MedDRA search terms (Version 24.0)	HLT: *Increased intracranial pressure disorders* PT: *Idiopathic intracranial hypertension; CSF pressure increased; Intracranial pressure increased; Papilloedema; Reduction of increased intracranial pressure*
Serious†	Yes
* See Appendix A for a description of the FAERS database. † Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life threatening hospitalizations (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, SOC=System Organ Class, HLGT=High Level Group Term, HLT=High Level Term, PT=Preferred Term	

2.3 DRUG UTILIZATION

Please see Appendix B for a pediatric patient focused drug utilization review of GnRH agonists.[67]

2.4 LITERATURE SEARCH

DPV searched the medical literature with the strategy described in Table 3.

Table 3. Literature Search Strategy	
Date of search	September 5, 2021
Database	PubMed
Search terms	(gonadotropin releasing hormone agonists OR gonadotropin releasing hormone analogs OR gonadorelin derivative OR gonadorelin agonist OR leuprorelin OR leuprolide OR nafarelin OR histrelin OR triptorelin OR goserelin OR elagolix OR "lupron depot ped" OR “Lupron-depot ped” OR fensolvi OR synarel OR “supprelin la” OR triptodur) AND (idiopathic intracranial hypertension OR pseudotumor cerebri OR brain pseudotumor)
Years included in search	All

2.5 APPLICANT'S EVALUATION[1]

AbbVie Endocrinology submitted a clinical overview evaluating IIH, as part of the PAS (NDA 020263, S-049) to update the Warnings and Precautions (Section 5) and Adverse Reactions Postmarketing Experience (Section 6.2) of the USPI for leuprolide acetate (Lupron-Depot Ped®) injection.

3 RESULTS

3.1 FAERS CASE SELECTION

After applying the case selection criteria in Section 2 to both the FAERS and medical literature search results and accounting for duplicate reports, we included six GnRH agonist cases of IIH. (see Figure 2). Appendix B contains a line listing of the FAERS case numbers, FAERS version numbers, and Manufacturer Control numbers for the five GnRH agonist FAERS cases in this case series. The one literature case for GnRH agonist (triptorelin) is cited in the references section.

Figure 2. FAERS Case Selection

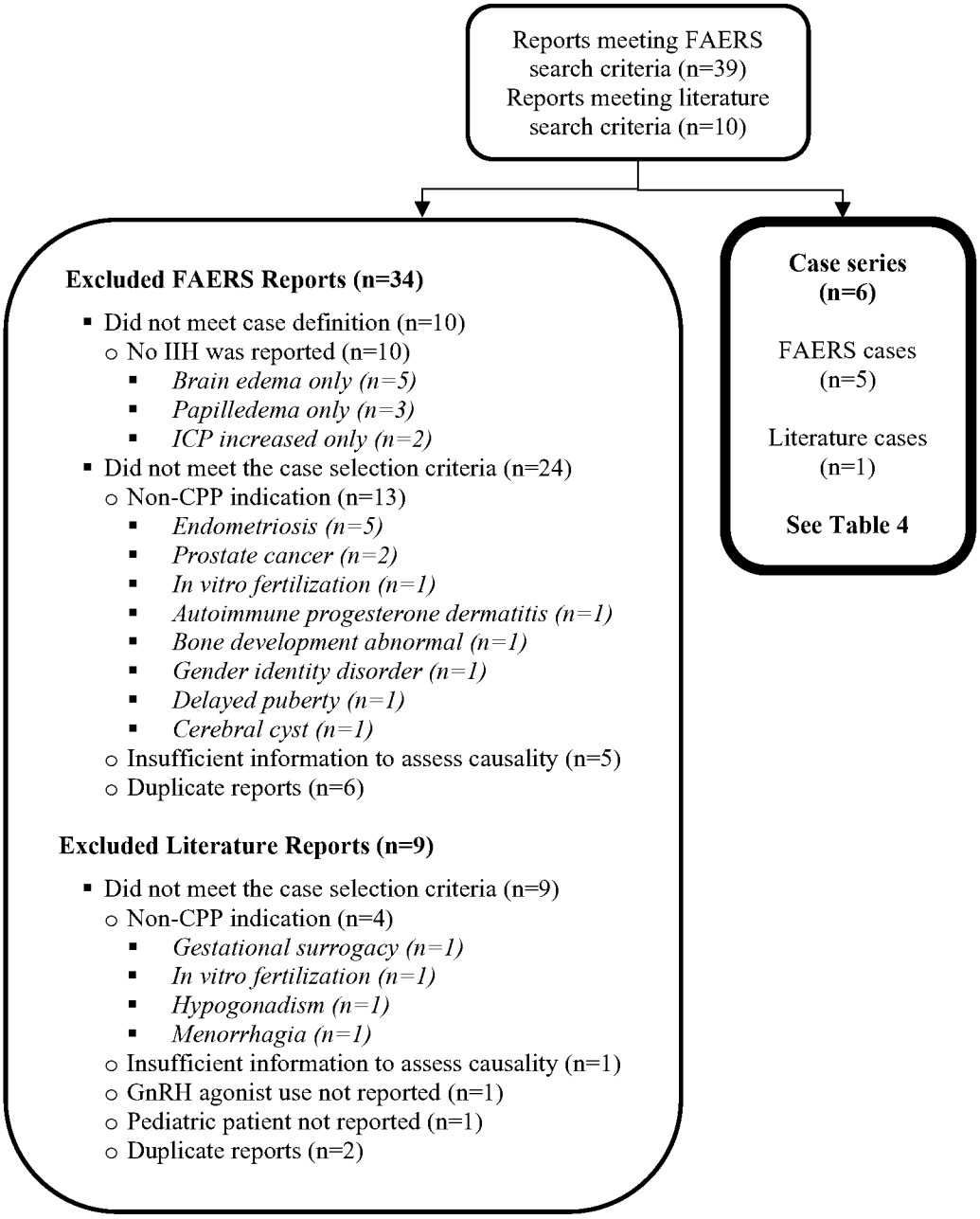


Table 4 summarizes our case series consisting of six FAERS and literature cases of IIH reported with GnRH agonist.

Table 4. Descriptive Characteristics of Cases Reporting IIH in Pediatric Patients with GnRH Agonists in FAERS* and the Published Medical Literature† Received by FDA or Published through September 5, 2021 (n=6)

Characteristic	Leuprolide acetate (n=4)	Triptorelin (n=2)	Total (n=6)
Case source			
FAERS	4	1	5
Literature	0	1	1
Report type			
Expedited	4	1	5
Patient sex			
Female	4	2	6
Male	0	0	0
Age (years)			
Number of cases	4	2	6
Median	10	7	9
Range	6-12	5-9	5-12
Country‡			
Domestic	0	0	0
Foreign	4	2	6
Case Definition Category			
Category I	2	1	3
Category II	2	1	3
Year received by FDA or published			
2000-2010	1	0	1
2011-2020	2	2	4
2021	1	0	1
Serious outcome§			
Other serious	4	1	5
Reporter Type			
Physician	4	1	5
HCP, NOS	0	1	1
Time to onset from the first dose of GnRH agonist (days)‖			
Number of cases	4	2	6
Median	135	62	120
Range	60-240	3-120	3-240
GnRH agonist dose (mg) (non-mutually exclusive)	3.75 (2) 22.5 (1) 11.25 (1) 7.5 (1) 5.6 (1)	3.75 (1)	NA
BMI (kg)			
Number of cases	2	2	4
Median	21	20	20
Range	17-25	18-21	17-25
Reported signs and symptoms (non-mutually exclusive)	Visual disturbances (5) Headache (2) Papilledema (2) Abducens neuropathy(1)	Non-specific findings (4) Headache or vomiting (3) Papilledema (1) Blood pressure increase (1)	Visual disturbances (5) Headache or vomiting (5) Non-specific findings (5) Papilledema (3)

Table 4. Descriptive Characteristics of Cases Reporting IIH in Pediatric Patients with GnRH Agonists in FAERS* and the Published Medical Literature† Received by FDA or Published through September 5, 2021 (n=6)			
Characteristic	**Leuprolide acetate (n=4)**	**Triptorelin (n=2)**	**Total (n=6)**
	Non-specific findings (1)		Abducens neuropathy (1) Blood pressure increase (1)
Lumbar puncture opening pressure (mm H_2O) **Number of cases** **Median** **Range**	 2 380 310-450	 1 460 NA	 3 450 310-460
Treatment or intervention	Acetazolamide (4) Ventriculoperitoneal shunt (1)	Acetazolamide (1)	Acetazolamide (5) Ventriculoperitoneal shunt (1)
Leuprolide discontinued	Yes (2)¶ NR (2)	Yes (1) NR (1)	Yes (3) NR (3)
Patient disposition	Resolved (2) Resolving (1) Not resolved (1)	Resolved (1)	Resolved (3) Resolving (1) Not resolved (1)

* FAERS - includes any case identified in either FAERS alone or in both FAERS and the literature.
† Literature - includes cases only identified in the literature.
‡ Six foreign cases from Brazil (1), Kenya (1), Canada (1), Great Britain (1), Spain (1), Turkey (1).
§ Other serious was the only serious outcome reported. Literature cases are not coded for serious outcomes
‖ Time to onset calculated from the initiation of GnRH agonist to the onset of IIH symptoms or diagnosis, whichever is first.
¶ Case 12789628 reported improvement in conjunction with VPS.
Abbreviations: BMI=body mass index, GnRH=gonadotropin-releasing hormone, HCP= Healthcare professional, NA=not applicable, NOS= not otherwise specified, NR=not reported

REPRESENTATIVE CASES (N=4)

FAERS 12789628 (Brazil, BR-ABBVIE-16P-020- 1734538-002016, September 2016):[3]
A physician reported a 9-year-old female who developed "PTC" four months after receiving leuprolide acetate 3.75 mg once monthly to treat CPP. She presented with axillary odor, accelerated growth velocity and thelarche onset at the age of 7 years, 6 months. On work-up, she showed advancement of bone age (11 years, 6 months, chronological age 9 years), gonadotropins at pubertal levels (FSH 3.3 U/L, LH 2 U/L), and uterine volume of 12.3 ml. The patient's weight was within normal limits [body mass index (BMI) 17.1 kg/m^2, 75^{th} percentile] and no recent weight gain was noted. No medication beyond leuprolide was used before or at the time of the medical visit. In the fourth month of treatment, the dosage of leuprolide acetate was increased to 11.25 mg in once quarterly doses. After four weeks of the first intramuscular (IM) injection of 11.25 mg leuprolide, she presented with moderate holocranial headache. Ten days after the onset of headache, she complained of transient visual obscuration followed by progressive visual loss. Despite the complaints, she received two further doses of 11.25 mg leuprolide as the cause of her headache was still being investigated. After six months, she persisted with holocranial headache and progressive visual loss associated with ocular deviation. Neuro-ophthalmological examination revealed visual acuity of 20/200 in the right eye and 20/40 in the left eye, with relative afferent pupillary defect in the right eye and edema of the optic disc in both eyes. Extrinsic ocular motility examination showed hypofunction of the lateral rectus muscle in both eyes, consistent with bilateral involvement of the abducens nerve. Manual perimetry showed increased blind spot and generalized constriction of the isopters in both eyes. Neurological

examination revealed no significant deficit. CSF analysis showed an opening pressure of 450 mm H_2O. No other alterations were found on CSF examination. MRI of the brain and orbit detected flattening of the posterior sclera and absence of mass or other alteration associated with PTC or optic neuropathy. Magnetic resonance angiography showed no signs of cerebral venous thrombosis. Because of severe visual loss, treatment with acetazolamide was started and leuprolide was discontinued. Headache and transient visual obscuration showed "significant" improvement (day of the lumbar puncture). After one month the CSF pressure was 170 mm H_2O. The acetazolamide was discontinued in less than three months due to metabolic acidosis. After two weeks, headache and transient blurred vision recurred. On that occasion the CSF pressure was 220 mm H_2O. A VPS was performed to control ICP as an alternative to acetazolamide treatment. The follow-up at eighteen months showed CSF pressure of 140 mm H_2O, stabilization of visual acuity and visual field, and resolution of papilledema with persistent optic disc atrophy.

Reviewer's comment: This case fulfills our Category I case definition criteria. The patient presented with symptoms of IIH four months after initiating leuprolide acetate 3.75 mg once monthly to treat CPP. The time to onset from the most recent dose increase of leuprolide acetate to 11.25 mg once quarterly to the onset of the event was four weeks. This case met the Category I case definition of PTC as the patient's lumbar puncture reported an elevated opening pressure of 450 mm H_2O. The patient experienced bilateral papilledema reported as edema of the optic disc in both eyes. Her neurological examination was normal, except for hypofunction of the lateral rectus muscle bilaterally, consistent with bilateral involvement of the sixth cranial nerve (abducens nerve), and this finding is consistent with PTC.[60] Except for flattening of the posterior sclera, a suggestive sign of PTC, no mass or structural lesions were detected on MRI. The onset of PTC temporal to the initiation of leuprolide acetate supports an association between PTC and leuprolide acetate. No alternative etiologies or risk factors for IIH were reported. Although PTC resolved upon discontinuation of leuprolide acetate with acetazolamide, including a reduction in the CSF pressure, the event recurred upon discontinuation of acetazolamide. Pharmacokinetic studies performed following a single leuprolide acetate 11.25 mg or 30 mg for 3-month administration to pediatric patients with CPP showed mean leuprolide plasma concentration remained constant from month 1 to month 3 for both 11.25 and 30 mg doses.[68] It is plausible the acetazolamide was withdrawn before the end of the 11.25 mg leuprolide 3-month effect, thereby causing a recurrence in ICP elevation. The VP shunt, which was placed during this three month interval, exemplifies the seriousness of this case. On 18 month follow-up, the patient continued to do well without recurrence of IIH, which supports a drug-associated etiology, although we acknowledge the contribution of the VPS in improving ICP. Overall, the temporal relationship between the initiation of leuprolide acetate and onset of IIH and the lack of risk factors and alternative etiologies for IIH support a drug-event causal association. Additionally, the Applicant assessed this case as "no alternative etiology."[1]

FAERS 18649727 (Kenya, KE-ABBVIE-20K-089- 3687126-00, December 2020):[2]
A physician reported a 6-year-6 months-old female who developed PTC two months after receiving leuprolide acetate 3.75 mg monthly every 28 days to treat CPP. She was referred to the pediatric endocrinology clinic for breast development and rapid growth for the past six months. There was no significant past medical or family history. On examination her weight was 26.5 kg (75th-90th centile), height 125.5 cm (75th-90th centile), and blood pressure 90/40

mm Hg. Pubertal examination revealed left breast at Tanner 3 and right breast at Tanner 2. Pubic hair was at Tanner 1 and no axillary hair was noted. Investigations revealed bone age at seven years, pelvic ultrasound revealed uterus of 4.2 ml (Tanner 3), right ovarian volume of 3 ml (Tanner 4), and left ovarian volume of 4 ml (Tanner 5). Endometrial thickness of 2 mm was also noted. GnRH stimulation test done with leuprolide acetate revealed LH at 7.78 mIU/ml and FSH at 14.52 mIU/ml. A diagnosis of precocious puberty was made and the patient was started on leuprolide acetate 3.75 mg every 28 days. After two doses of leuprolide acetate 3.75 mg, the patient developed double vision with partial vision loss. There was no history of headache, vomiting, or convulsions. Neurologic and other systemic examination was normal. The patient was referred to an ophthalmologist for a fundoscopy examination. She also had a head tilt to the left with normal extraocular movements. On fundoscopy, there was "severe" bilateral papilledema with blurring of the optic disc margins. The rest of the fundus was normal. Cranial and pituitary MRI did not reveal any space occupying lesion. The patient was not on other medications apart from leuprolide acetate. Because of "severe" papilledema and visual loss leuprolide acetate was discontinued "immediately" and acetazolamide initiated. After six weeks of treatment with acetazolamide, the visual acuity as well as papilledema resolved, and the acetazolamide was then also discontinued, without recurrence of ophthalmologic findings.

Reviewer's comment: This case fulfills our Category II case definition criteria. This patient developed signs of IIH including double vision and partial vision loss two months after starting leuprolide acetate 3.75 mg monthly to treat CPP. The patient's neurologic examination was normal with normal cranial and pituitary MRI. However, a fundoscopy examination showed marked bilateral papilledema with blurred disc margins. Although there was no CSF analysis or pressure measured, papilledema has good sensitivity and specificity for the diagnosis of increased ICP, especially when documented by an ophthalmologist. This, in conjunction with the unremarkable brain MRI, supports the diagnosis of IIH in this patient.[69] This case was characterized by temporal association to the initiation of leuprolide acetate, lack of a clear alternative etiology for IIH, and resolution of IIH after leuprolide discontinuation with medical treatment supporting a causal relationship between IIH and leuprolide acetate. Notably, acetazolamide was discontinued after six weeks of treatment with no recurrence of IIH. Additionally, the Applicant assessed this case as "no alternative etiology."[1]

FAERS 19098245 (Canada, CA-ABBVIE-21K-028-3846355-00, April 2021):[4]
A physician reported a 12 5/12-year-old trans-gender male (birth-assigned female), who developed PTC five months after receiving leuprolide acetate to suppress puberty. The patient started depot leuprolide acetate to suppress puberty at 11 10/12 years of age (early Tanner 2 breast development). He received leuprolide acetate 7.5 mg intramuscularly (IM) for four doses, then 22.5 mg IM every 13 weeks thereafter. Five months after his first injection, a routine eye examination revealed bilateral papilledema and enlarged blind spots, which was confirmed by a pediatric ophthalmologist. He was asymptomatic. There was no marked weight gain in the previous year with a BMI of 24.5 kg/m^2. His blood pressure was 110–123 mm Hg systolic and 71–85 mm Hg diastolic. Neurological examination was normal. Head CT was normal. Cranial MRI showed slight flattening of the optic nerve heads, mild engorgement of optic nerve sheath fluid, and no space-occupying mass. A sedated lumbar puncture revealed elevated opening pressure of 310 mm H2O. CSF analysis, including pathology, was benign. He was managed with acetazolamide. Based on these findings, he was diagnosed with PTC secondary to the

GnRH agonist. Follow-up by the ophthalmologist one month after starting acetazolamide showed significant improvement of the papilledema.

Reviewer's comment: This case fulfills our Category I case definition criteria. This patient received a lumbar puncture with an opening pressure of 310 mm H2O, ophthalmological examination which revealed bilateral papilledema, normal neurological examination, and cranial MRI with no space occupying mass. Although the papilledema improved with the use of acetazolamide, it was unclear if therapy with leuprolide acetate was discontinued. In addition, this report did not provide information regarding the patient's past medical history or concomitant medications.

Literature case (Gul et al., 2016)[70]

A nine-year-old female was admitted because of breast development which had started ten months before. Rapid height growth, adult body odor, and vaginal discharge were reported. The patient had no history of drug use or chronic illness. On physical examination, weight was 34 kg, height 138.3 cm, and blood pressure 100/60 mm Hg. Thelarche Tanner stage 3, pubic hair stage 2, and axillary hair was not detected. Her BMI was normal (17.7 kg/m^2) and she did not have a history of recent weight gain. The patient's bone age was 10.5 years. On pelvic ultrasonography, the length of the uterus (45 mm) and ovarian volumes (2.5 ml and 3.1 ml) were observed in pubertal size. The hypophysis MRI was normal. Gonadotropin levels were within pubertal range (FSH 1.97 mIU/ml, LH 1 mIU/ml). The patient's bone age demonstrated fast progress of one and a half years in six months, and annual follow-up height growth was 7.5 cm. Triptorelin acetate 3.75 mg depot per month was started due to early puberty. The patient had headaches after the fourth dose and her blood pressure was 130/80 mmHg (>99th percentile). Past medical history revealed no history of hypertension and her blood pressure increased after treatment. Multiple measurements showed systolic and diastolic blood pressure in the range of 130-155/85-110 mm Hg. Other system examinations were normal. Complete blood count, renal function tests, and serum electrolyte levels were within normal limits. Echocardiography analysis and renal doppler ultrasound were normal. Plasma renin activity and aldosterone levels were within normal limits. There was no abnormality related to the patient's neurological examination except bilateral papilledema. On cranial MRI, space-occupying mass was not observed and the ventricular system was intact. The orbital section of the MRI revealed bilateral optic nerve enlargement. Lumbar puncture was performed and an elevated initial CSF opening pressure was detected (460 mm H_2O, normal range: 15-25 cm H_2O). Based on the findings, the patient was diagnosed with PTC and triptorelin therapy was discontinued. Except for the GnRH agonist, there were no other risk factors that might lead to PTC such as obesity, renal failure, or other drugs associated with PTC. The patient improved with acetazolamide and the CSF pressure and fundoscopic examinations returned to normal.

Reviewer's comment: This case fulfills our Category I case definition criteria. This patient developed IIH four months after receiving triptorelin acetate 3.75 mg monthly to treat CPP. She experienced symptoms consistent with a diagnosis of IIH including elevated opening pressure of 460 mm H_2O on lumbar puncture and bilateral papilledema on neurological examination. No space occupying mass was observed on MRI; however, the orbital area revealed bilateral optic nerve enlargement, which may be due to enlargement of the perioptic subarachnoid space as previously associated with IIH.[71] *The temporal relationship, and lack of an alternative etiology*

to explain the occurrence of IIH support a causal role of triptorelin with IIH. The patient also developed hypertension during triptorelin therapy, which resolved upon discontinuation, and in ranges not associated with hypertensive encephalopathy. Triptorelin is labeled for hypertension under the Adverse Reactions Postmarketing Experience section of product labeling.[72]

3.2 DRUG UTILIZATION

Please see Appendix B for a pediatric patient focused drug utilization review of GnRH agonists.[67]

3.3 LITERATURE SEARCH

The literature search in Table 3 retrieved ten citations from PubMed, and after de-duplication, a total of eight citations were obtained. Abstracts of these citations were reviewed to identify relevant articles for the development of IIH and GnRH agonists. Three citations reported the use of GnRH agonists for non-CPP indications. One citation did not pertain to the topic of this review. One citation reported GnRH agonist use in pediatric patients with limited information. One citation did not report the use of GnRH agonist and the remaining citation reported GnRH agonist use in an adult. The remaining citation by Gul et al[70] is discussed in Section 3.1.

3.4 APPLICANT'S EVALUATION

AbbVie Endocrinology conducted a signal evaluation for IIH associated with leuprolide acetate. The evaluation included a search of AbbVie's global safety database Adverse Event Global Information System (AEGIS) using the High Level Term (HLT) Intracranial pressure disorders to identify postmarketing cases through January 21, 2021, and the medical literature.

Postmarketing

Of the 44 cases identified in the AbbVie global safety database coded with a Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) from the above HLT, the Applicant noted the following:

- 29 were excluded from further analysis as the cases did not contain follow-up information since the data lock date of the previous assessment.
- Of the 15 remaining cases:
    - 4 cases were newly received after the data lock date of the previous assessment
        - 2 cases contained limited information
        - 1 case was confounded by endoscopic endonasal surgery for olfactory neuroblastoma and concomitant medications (e.g., hormone therapies)
        - 1 case had no alternate etiology [described as the publication that triggered the updated evaluation (Omar et al)][2]
    - 5 cases were assessed as no alternate etiology from the previous assessment
        - 3 cases were confounded by underlying disease e.g., obesity, family history of IIH or concomitant medications (e.g., potential contraceptive use)
        - 1 case reported benign intracranial hypertension in an adult female
        - 1 case had no alternate etiology [described as the publication that triggered the previous evaluation (Germano et al)][3]

- 6 cases reported a pediatric patient or indication of CPP if age was unknown
  - 1 case did not report IIH
  - 4 cases were confounded by underlying disease (e.g., obesity, papilledema, medulloblastoma, hydrocephalus) and malfunction of ventriculoperitoneal shunt
  - 1 case contained limited information

Scientific literature
AbbVie also included the publication by Omar et al[2] (FAERS 18649727) and Gazzaz et al[4] (FAERS 19098245) noted in Section 3.1 of the review.

AbbVie's conclusion
Based on a comprehensive review of the literature and postmarketing cases of IIH in the AbbVie global safety database, the Applicant concluded the evidence is sufficient to support a causal association between IIH and leuprolide acetate. The Applicant recommends a change to the product labeling for the CPP pediatric population treated with leuprolide acetate.

4 DISCUSSION

This review identified six cases in FAERS and the medical literature of IIH associated with the use of GnRH agonists including leuprolide acetate (4) and triptorelin (2). We will provide a separate discussion of IIH with the two GnRH agonists below.

Leuprolide acetate
The evidence from the FAERS cases supports an association between leuprolide acetate and IIH. The median time to onset from the initiation of leuprolide acetate to the onset of IIH was 135 days (range 60 days to 240 days). In one case the time to onset from the most recent dose increase of leuprolide acetate was 28 days. In two of the four cases IIH resolved with discontinuation of leuprolide although we acknowledge a VPS was used in one case. Acetazolamide in all cases was used to treat symptomatic IIH. In one of these cases the recurrence of IIH symptoms was triggered by the discontinuation of acetazolamide after leuprolide withdrawal. The withdrawal occurred within a three-month window when plasma concentrations of leuprolide would be expected to persist in the body, thereby causing a recurrence in symptoms. Eighteen months after discontinuation of leuprolide the symptoms resolved. One case reported resolution of IIH with acetazolamide, however, it was unclear whether leuprolide was discontinued. In the fourth case it was unclear if leuprolide therapy was discontinued. Although acetazolamide is an invalidating intervention affecting the interpretation of dechallenge information, it may be challenging to identify FAERS cases that do not report the use of acetazolamide, as this intervention is normally used to treat patients with IIH symptoms.[62] In the majority of cases, a lumbar puncture was performed where the median opening pressure was 380 mm H_2O (range 310-450 mm H_2O) in two cases. In one of these cases the opening pressure decreased to 140 mm H_2O after discontinuation of leuprolide acetate. In the third case a lumbar puncture was performed revealing "raised intracranial pressure" however no numeric value of the opening pressure was reported. Half of the cases were assessed as having no alternative etiology for the occurrence of IIH. One case did not provide information regarding the patient's past medical history or concomitant medications. In the other case IIH was confounded by underlying cerebellar medulloblastoma and concomitant use of somatropin

(Genotropin) which is labeled for intracranial hypertension in the Warnings and Precautions and Adverse Reactions section of product labeling.[73] The specificity of the case definition utilized in this review allowed us to capture true cases of IIH including three cases that reported elevated CSF opening pressures on lumbar puncture and four cases that were reported by a physician or neurologist.

Triptorelin

Two cases reported the onset of IIH associated with the use of triptorelin to treat CPP. In the first case the time to onset was 120 days from the initiation of triptorelin to onset of the event. An elevated CSF opening pressure of 460 mm H_2O on lumbar puncture was reported in this case. The event resolved upon discontinuation of triptorelin with medical treatment. This patient had no reported risk factors that could explain the occurrence of IIH such as obesity, renal failure, or concomitant medications. The other case reported the onset of "benign intracranial hypertension" in a 5-year-old female three days after the initiation of triptorelin to treat CPP. It was unknown if triptorelin was discontinued and outcome of the event was also unknown. This patient was reported to be overweight with a weight of 30 kg, BMI of 21 (units not provided), and adiposity in the trunk and abdomen.[74] The dose of triptorelin was not reported, however, the authors recommended weight-based dosing, especially in obese children, to avoid clinically relevant adverse drug reactions such as benign intracranial hypertension in pediatric patients.

Drug Utilization

Drug utilization patterns of GnRH agonist use from 2014 – 2016 (Appendix B) showed that the majority of use among pediatric patients (aged 0-17 years) was for leuprolide acetate (Lupron Dept-Ped®) followed by histrelin (Supprelin LA®), and nafarelin (Synarel®).[67] This finding is consistent with the FAERS data which showed that Lupron Depot Ped was the most commonly reported GnRH agonist in our case series reporting pediatric patients with CPP. Lupron Depot-Ped also accounted for the majority of patients aged 6-12 with a prescription and or medical procedure claim, followed by Supprelin LA and Synarel. Note that the drug use review was conducted in 2016 and did not include triptorelin pamoate (Triptodur®), which received FDA approval in 2017.

Case Series Demographics

Notably all the patients in our case series were female. The national annual incidence (95% CI) of IIH in children aged 1–16 years was 0.71 (0.57 to 0.87) per 100,000 population increasing with age and weight to 4.18 and 10.7 per 100,000 in obese boys and girls aged 12–15 years, respectively.[19] There is a strong female predominance of children evaluated for precocious puberty. In a retrospective review of 104 consecutive children referred for evaluation of precocious puberty, 87 percent were female.[75] Whether this represents a true biologic difference or referral bias is not understood. Given the incidence of IIH in patients with CPP is unknown, it is difficult to determine if female patients with CPP are at increased risk of developing IIH with the use of GnRH agonists. Most of the patients in our series were not overweight. Studies examining the differences between prepubertal and postpubertal IIH show that there is a strong female predominance and association with obesity in postpubertal IIH similar to idiopathic IIH in adults. Therefore, the relative lack of obesity in our case series, is consistent with IIH that is generally observed in prepubertal pediatric patients. Also, presenting symptoms of IIH may differ between children and adults. Headache is a less universal finding among younger children

compare with adults. Furthermore, in addition to abducens neuropathy, other cranial nerve deficits may be more common in prepubertal children than in older patients.[76]

Biological Plausibility

Although the etiology of IIH is unknown, increased serum testosterone, and increased CSF testosterone and androstenedione have been observed in women with IIH implicating the role of androgens in disease pathogenesis.[77] GnRH agonists cause a short-term increase of sex steroids that may result in a hypercoagulable state, and it has been hypothesized this may predispose to dural venous sinus thrombosis.[78] Dural venous sinus thrombosis would have led to exclusion of such reports based on our case definition. Furthermore, no such reports were encountered. It has also been hypothesized that GnRH agonists may cause non-obstructive microthrombosis of the dural venous sinuses and consequently impede CSF drainage.[79,80] Such microthrombi may be of insufficient size to be seen on neuroimaging studies.

Considerations for Labeling

The Applicant proposed the addition of IIH (PTC) to the Warnings and Precautions and Adverse Reactions section of the USPI for Lupron Depot-Ped injection. According to the FDA guidance *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling*[81] factors to consider for inclusion in the Warnings and Precautions section of labeling include 1) the frequency of reporting 2) seriousness of the event 3) evidence of a causal association between drug and the adverse event. In general, IIH is a chronic and disabling condition characterized by elevated ICP. If untreated, severe outcomes such as papilledema and residual visual field deficits, including permanent visual loss could occur. It is a clinically significant adverse event because it has implications for prescribing decisions or patient management. Based on 1) serious outcomes associated with IIH in patients receiving leuprolide 2) clinical significance of the adverse event, and 3) evidence to support a causal association between IIH and leuprolide acetate, DPV concurs with the Applicant to add IIH to the Warnings and Precautions and Adverse Reactions section of the leuprolide acetate labeling for products indicated for CPP. DGE requested DPV to assess whether class labeling for the GnRH agonists approved for CPP is warranted. Based on the evidence in FAERS and the medical literature, DPV also recommends the addition of IIH to the Warnings and Precautions and Adverse Reactions section of the triptorelin labeling. Although we do not have cases for the other two GnRH agonists, nafarelin and histrelin, likely due to low usage for CPP in pediatric patients, the biological mechanism is similar for members of the drug class; therefore, DPV does not oppose class labeling for GnRH agonists approved for CPP in the pediatric population.

5 CONCLUSION

DPV concludes there is evidence to support a causal association between leuprolide acetate and IIH in pediatric patients diagnosed with CPP. The evidence also supports a causal association between triptorelin and IIH in pediatric patients diagnosed with CPP. DPV determined that the cases of IIH included in this review were clinically serious with medically important outcomes to warrant the inclusion of IIH in the Warnings and Precautions section of the leuprolide acetate and triptorelin labeling to communicate the risk of IIH in pediatric patients diagnosed with CPP. Although DPV did not identify cases for all members of the GnRH agonists, the biological mechanism is similar for members of the drug class; therefore, DPV does not oppose class labeling for GnRH agonists approved for CPP in the pediatric population.

DPV will continue to monitor the class of GnRH agonists for cases of IIH (PTC), with special attention to drugs with no identifiable cases in our current case series.

6 RECOMMENDATIONS

Based on this review DPV recommends the following

- Add information proposed by the Applicant regarding IIH (PTC) to Section 5 of leuprolide acetate product labeling (for products indicated for CPP):

  WARNINGS AND PRECAUTIONS:

  Pseudotumor cerebri (idiopathic intracranial hypertension)

  Pseudotumor cerebri (idiopathic intracranial hypertension) has been reported in pediatric patients receiving leuprorelin acetate. Monitor patients for signs and symptoms of pseudotumor cerebri, including headache, papilledema, blurred vision, diplopia, loss of vision, pain behind the eye or pain with eye movement, tinnitus, dizziness, and nausea. (b) (4)

  ADVERSE REACTIONS

  Nervous system disorders: pseudotumor cerebri (idiopathic intracranial hypertension)

- Add language to the PATIENT COUNSELING INFORMATION regarding IIH such as unusual headaches and visual disturbances.

- Add similar language to the WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS AND PATIENT COUNSELING INFORMATION section of triptorelin product labeling (for products indicated for CPP).

- Although we do not have cases for all of the products within the pharmaceutical class of the GnRH agonists, we do not oppose class labeling for GnRH agonists approved for CPP in the pediatric population.

7 REFERENCES

1. AbbVie NDA 020263 Leuprolide Clinical Overview. June 18, 2021
2. Omar AA, Nyaga G, Mungai LNW. Pseudotumor cerebri in patient on leuprolide acetate for central precocious puberty. International Journal of Pediatric Endocrinology. 2020;2020(1):22.
3. Germano RAS, Franco RR, Matas S, Moura FC. Pseudotumor Cerebri Associated with Leuprolide Acetate for Central Precocious Puberty-Case Report. Journal of Clinical and Experimental Ophthalmology. 2015;6(3).
4. Gazzaz N, Patel T, Metzger DL. SAT-074 A Rare Endocrine Cause of Pseudotumor Cerebri. Journal of the Endocrine Society. 2020;4(Supplement_1).
5. Conn PM, Crowley WF. Gonadotropin releasing hormone and its analogs. NEJM. 1991;324:93-103.
6. Conn PM, Crowley WF. Gonadotropin-releasing hormone and its analogs. Annu Rev Med. 1994; 45:391-405.
7. Magon N. Gonadotropin releasing hormone agonists: expanding vistas. Indian J Endocrinol Metab 2011 Oct;15(4):261-7
8. Belchetz PE, Plant TM, Nakai Y et al. Hypophysial responses to continuous and intermittent delivery of hypothalamic gonadotropin-releasing hormone. 1978. Science. 202:631-633.
9. Santoro N, Filicori M, Crowley WF. Hypogonadotropic disorders in men and women: diagnosis and therapy with pulsatile GnRH. Endocr 1986;7:11-23.
10. Crowley WF, Filicori M, Spratt DI, Santoro NF. The physiology of gonadotropin-releasing hormone (GnRH) secretion in men and women. In Recent Progress in Hormone Research. 1985;41:473-531.
11. Harrington J, Palmert MR (2020) Treatment of precocious puberty. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com/contents/treatment-of-precocious-puberty?search=treatment%20of%20precocious%20puberty&source=search_result&selectedTitle=1~148&usage_type=default&display_rank=1 Accessed on September 10, 2021
12. Lahlou N, Carel JC, Chaussain JL, Roger M. Pharmacokinetics and pharmacodynamics of GnRH agonists: clinical implications in pediatrics. J Pediatr Endocrinol Metab 2000; 13 Suppl 1:723.
13. Boepple PA, Mansfield MJ, Wierman ME, et al. Use of a potent, long acting agonist of gonadotropin-releasing hormone in the treatment of precocious puberty. Endocr Rev 1986; 7:24.
14. Crowley WF Jr, Comite F, Vale W, et al. Therapeutic use of pituitary desensitization with a long-acting LHRH agonist: a potential new treatment for idiopathic precocious puberty. J Clin Endocrinol Metab 1981; 52:370.
15. Digre KB, Bruce BB, McDermott MP et al. Quality of life in idiopathic intracranial hypertension at diagnosis: IIH Treatment Trial results. Neurology 2015;84:2449
16. Durcan FJ, Corbett JJ, Wall M. The incidence of pseudotumor cerebri. Population studies in Iowa and Louisiana. Arch Neurol 1988; 45:875.
17. Radhakrishnan K, Ahlskog JE, Cross SA, et al. Idiopathic intracranial hypertension (pseudotumor cerebri). Descriptive epidemiology in Rochester, Minn, 1976 to 1990. Arch Neurol 1993; 50:78.
18. Kesler A, Gadoth N. Epidemiology of idiopathic intracranial hypertension in Israel. J Neuroophthalmol 2001; 21:12.
19. Matthew YY, Dean F, Lim MJ, et al. Pseudotumor cerebri syndrome in childhood: incidence, clinical profile and risk factors in a national prospective population-based cohort study. Arch Dis Child. 2017;102(8):715-21.
20. Morrice G: Papilledema and hypervitaminosis A. JAMA 213:1344, 1970 (letter).
21. Roytman M, Frumkin A, Bohn TG: Pseudotumor cerebri caused by isotretinoin. Cutis 42:399–400, 1988.
22. Naderi S, Nukala S, Marruenda F, Kudarvalli P, Koduri PR. Pseudotumour cerebri in acute promyelocytic leukemia: Improvement despite continued ATRA therapy. Ann Hematol 78:333–334, 1999.
23. Chiu AM, Chuenkongkaew WL, Cornblath WT, Trobe JD, Digre KB, Dotan SA, Musson KH, Eggenberger ER: Minocycline treatment and pseudotumor cerebri syndrome. Am J Ophthalmol 126:116–121, 1998.
24. Cohen DN: Intracranial hypertension and papilledema associated with nalidixic acid. Am J Ophthalmol 76:680–682, 1973
25. Getenet JC, Croisile B, Vighetto A, Grochowicki M, Goudable B, Aimard G, Trillet M: Idiopathic intracranial hypertension after ofloxacin treatment. Acta Neurol Scand 87:503–504, 1993.
26. Chien LT: Intracranial hypertension and sulfamethoxazole. N Engl J Med 283:47, 1976 (letter)

27. Rogers AH, Rogers GL, Bremer DL, McGregor ML: Pseudotumor cerebrin children receiving recombinant human growth hormone. Ophthalmology 106:1186–1190, 1999.
28. Walsh FB, Clark DB, Thompson RS, Nicholson DH: Oral contraceptives and neuro-ophthalmologic interest. Arch Ophthalmol 74:628–640, 1965.
29. Sunku AJ, O'Duffy AE, Swanson JW: Benign intracranial hypertension associated with levonorgestrel implants. Ann Neurol 34:299, 1993 (abstr).
30. Hamed LM, Glaser JS, Schatz NJ, Perez TH: Pseudotumor cerebri induced by danazol. Am J Ophthalmol 107:105–110, 1989.
31. Neville BGR, Wilson J: Benign intracranial hypertension following corticosteroid withdrawal in childhood. Br Med J 3:554–556, 1970.
32. Levine SH, Puchalski C: Pseudotumor cerebri associated with lithium therapy in two patients. J Clin Psychiatry 51:251–253, 1990.
33. Carlow TJ, Glaser JS: Pseudotumor cerebri syndrome in systemic lupus erythematosus. JAMA 228:197–200, 1974
34. Wasan H, Mansi JL, Benjamin S, Powles R, Cunningham D: Myeloma and benign intracranial hypertension. BMJ 304:685, 1992.
35. Capriles LF: Intracranial hypertension and iron-deficiency anemia. Arch Neurol 9:147–153, 1963.
36. Condulis N, Germain G, Charest N, Levy S, Carpenter TO: Pseudotumor cerebri: A presenting manifestation of Addison's disease. Clin Pediatr 36:711–713, 1997.
37. Campos SP, Olitsky S: Idiopathic intracranial hypertension after l-thyroxine therapy for acquired primary hypothyroidism. Clin Pediatr 34:334–337, 1995.
38. Chang D, Nagamoto G, Smith WE: Benign intracranial hypertension and chronic renal failure. Cleve Clin J Med 59:419–422, 1992
39. Couban S, Maxner CE: Cerebral venous sinus thrombosis presenting as idiopathic intracranial hypertension. Can Med Assoc J 145:657–659, 1991.
40. Pasquale LR, Moster ML, Schmaier A: Dural sinus thrombosis with abnormalities of protein S and fibrinogen. Arch Ophthalmol 108:644, 1990.
41. Ludemann P, Nabavi DG, Junker R, Wolff E, Papke K, Buchner H, Assmann G, Ringelstein EB: Factor V Leiden mutation is a risk factor for cerebral venous thrombosis: A case control study of 55 patients. Stroke 29:2507–2510, 1998.
42. Leker RR, Steiner I: Anticardiolipin antibodies are frequently present in patients with idiopathic intracranial hypertension. Arch Neurol 55:817–820, 1998.
43. Walsh FB, Clark DB, Thompson RS, Nicholson DH: Oral contraceptive and neuro-ophthalmologic interest. Arch Ophthalmol 74:628–640, 1965.
44. Cantu C, Barinagarrementeria F: Cerebral venous thrombosis associated with pregnancy and puerperium: Review of 67 cases. Stroke 24:1880–1884, 1993.
45. Cognard C, Casasco A, Toevi M, Houdart E, Chiras J, Merland JJ: Dural arteriovenous fistulas as a cause of intracranial hypertension due to impairment of cranial venous outflow. J Neurol Neurosurg Psychiatry 65:308–316, 1998.
46. Halbach VV, Hieshima GB, Higashida RT, Reicher M: Carotid cavernous fistulae: Indications for urgent treatment. AJR Am J Roentgenol 149:587–593, 1987.
47. Vijayan N: Postoperative headache in acoustic neuroma. Headache 35:98– 100, 1995.
48. Kiers L, King JO: Increased intracranial pressure following bilateral neck dissection and radiotherapy. Aust N Z J Surg 61:459–461, 1991.
49. Birdwell BG, Yeager R, Whitsett TL: Pseudotumor cerebri: A complication of catheter-induced subclavian vein thrombosis. Arch Intern Med 154: 808–811, 1994.
50. Marr WG, Chambers JW: Occlusion of the cerebral dural sinuses by tumor simulating pseudotumor cerebri. Am J Ophthalmol 61:45–49, 1966.
51. Rangwala LM, Liu GT. Pediatric idiopathic intracranial hypertension. Surv Ophthalmol. 2007 Nov-Dec;52(6):597-617. doi: 10.1016/j.survophthal.2007.08.018. PMID: 18029269.
52. Sheldon CA, Paley GL, Beres SJ, McCormack SE, Liu GT. Pediatric Pseudotumor Cerebri Syndrome: Diagnosis, Classification, and Underlying Pathophysiology. Semin Pediatr Neurol. 2017;24(2):110-115. doi:10.1016/j.spen.2017.04.002
53. Morris PP, Black DF, Port J, Campeau N. American Journal of Neuroradiolog, March 2017,38 (3) 471-477

54. Bateman GA, Stevens SA, Stimpson J. A mathematical model of idiopathic intracranial hypertension incorporating increased arterial inflow and variable venous outflow collapsibility. J Neurosurg. 2009; 110:446–456.
55. Ahmed R, Friedman DI, Halmagyi GM. Stenting of the transverse sinuses in idiopathic intracranial hypertension. J Neuroophthalmol. 2011; 31:374–380.
56. Wall M: The headache profile of idiopathic intracranial hypertension. Cephalalgia 10:331–335, 1990.
57. Giuseffi V, Wall M, Siegel PZ, Rojas PB: Symptoms and disease associations in idiopathic intracranial hypertension (pseudotumor cerebri): A case-control study. Neurology 41:239–244, 1991.
58. Biousse V, Newman NJ, Lessell S: Audible pulsatile tinnitus in idiopathic intracranial hypertension. Neurology 50:1185–1186, 1998
59. Krishna R, Kosmorsky GS, Wright KW: Pseudotumor cerebri sine papilledema with unilateral sixth nerve palsy. J Neuroophthalmol 18:53–55, 1998
60. Johnston I, Patterson A: Benign intracranial hypertension: Part II—CSF pressure and circulation. Brain 97:301–312, 1974.
61. Brodsky MC, Vaphiades M: Magnetic resonance imaging in pseudotumor cerebri. Ophthalmology 105:1686–1693, 1998.
62. NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee, Wall M, McDermott MP, et al. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial. JAMA 2014; 311:1641.
63. Kelman SE, Heaps R, Wolf A, Elman MJ. Optic nerve decompression surgery improves visual function in patients with pseudotumor cerebri. Neurosurgery 1992; 30:391.
64. Burgett RA, Purvin VA, Kawasaki A. Lumboperitoneal shunting for pseudotumor cerebri. Neurology 1997; 49:734.
65. Liu GT, Volpe NJ, Schatz NJ, et al. Severe sudden visual loss caused by pseudotumor cerebri and lumboperitoneal shunt failure. Am J Ophthalmol 1996; 122:129.
66. Croteau D, Weintraub J. OSE case definition idiopathic intracranial hypertension (pseudotumor cerebri). January 2017
67. Sadiq N. OSE Drug Utilization Review GnRH agonist utilization in pediatric patients. December 7, 2016.
68. Lupron Depot-Ped (leuprolide acetate) [product label]. North Chicago, IL: AbbVie Inc; Revised March 2021. Accessed Daily Med October 27, 2020
69. Funnell JP, Craven CL, D'Antona L, Thompson SD, Chari A, Thorne L, Watkins LD, Toma AK. Intracranial pressure in patients with papilloedema. Acta Neurol Scand. 2018 Aug;138(2):137-142. doi: 10.1111/ane.12922. Epub 2018 Mar 12. PMID: 29532475.
70. Gul U, Bayram AK, Kendirci M, et al. Pseudotumor cerebri presentation in a child under the gonadotropin-releasing hormone agonist treatment. J Clin Res Pediatr Endocrinol 2016; 8(3):365-376.
71. Degnan AJ, Levy LM. Narrowing of Meckel's cave and cavernous sinus and enlargement of the optic nerve sheath in Pseudotumor Cerebri. J Comput Assist Tomogr 2011; 35:308.
72. Triptodur (triptorelin) [product label]. Atlanta, GA: Arbor Pharmaceuticals; Revised July 2021. Accessed Daily Med October 25, 2021.
73. Genotropin (somatropin) [product label]. NY, NY: Pharmacia and Upjohn Co; Revised April 2020. Accessed Daily Med October 25, 2021
74. Rodriguez Jimenez CM, Fernandez del Campo CB, Qintana EF, Sanchez-Colomer MG, del Mar Garcia M. Suspicion of benign intracranial hypertension in girl treated with triptorelin. Basic Clin Pharmacol Toxicol 2014;115 Suppl 3:35
75. Kaplowitz P. Clinical characteristics of 104 children referred for evaluation of precocious puberty. J Clin Endocrinol Metab. 2004 Aug;89(8):3644-50.
76. Lee AG, Wall M (2021) Idiopathic Intracranial Hypertension (Pseudotumor Cerebri) Clinical Features and Diagnosis. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com/contents/idiopathic-intracranial-hypertension-pseudotumor-cerebri-clinical-features-and-diagnosis?search=idiopathic%20intracranial%20hypertension&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed November 11, 2021.
77. O'Reilly MW, Westgate CSJ, Hornby C, et al. A unique androgen excess signature in idiopathic intracranial hypertension is linked to cerebrospinal fluid dynamics. JCI Insight. 2019;4(6).
78. Bhatt UK, Haq I, Avadhanam VS, Bibby K. A 43-year-old woman on triptorelin presenting with pseudotumor cerebri: a case report. J Med Case Rep 2012;6:122.

79. Glueck CJ, Iyengar S, Goldenberg N, et al. Idiopathic intracranial hypertension: associations with coagulation disorders and polycystic-ovary syndrome. J Lab Clin Med 2003; 142:35.
80. Ooi LY, Walker BR, Bodkin PA, Whittle IR. Idiopathic intracranial hypertension: can studies of obesity provide the key to understanding pathogenesis? Br J Neurosurg 2008; 22:187.
81. Guidance for Industry Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products Content and Format. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) October 2011.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.2 APPENDIX B. GNRH AGONISTS DRUG UTILIZATION REVIEW IN PEDIATRIC PATIENTS

GnRH agonist DUR review.pdf

Attached below is a Summary Table from the Drug Utilization Review on GnRH agonist utilization in pediatric patients as of July 2016, and the complete Review is attached above.

Number of pediatric patients with prescription and/or procedure claims* for Lupron Depot-PED, Supprelin LA and Synarel from study a sample, stratified by patient age (0-17 years)***, August 2014 through July 2016, annually**

	Year 1 (August 2014-July 2015)		Year 2 (August 2015-July 2016)	
	Patients (N)	Share (%)	Patients (N)	Share (%)
Total GnRH agonist	(b) (4)			
Lupron Depot-PED				
0-5 year				
6-12 year				
13-17 year				
Supprelin LA				
0-5|year				
6-12 year				
13-17 year				
Synarel				
0-5 year				
6-12 year				
13-17 year				

* Claims are from U.S.Commercial, medicare Part D, Cash, and Medicaid plans

**Claims data from sample of 80 pharmacies & 6,366 clinics, hospitals and physician offices

*** Age is at first claim during examined time period. Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-17 years include patients less than 18 years of age (17 years and 11 months).

Source: Symphony Health Solutions' Integrated Dataverse (IDV)™ . August 2014-July 2016. Extracted October 2016. File: 2016-2369-CPA-GnRH Agonist stratified by products (brand names) and age. 11.03.2016

8.3 APPENDIX C. FAERS LINE LISTING OF IIH IN PEDIATRIC PATIENTS WITH CPP CASE SERIES

Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
11/18/2015	11749523	1	ES-WATSON-2015-19356	Expedited (15-DAY)	5	Female	Spain	OT
09/28/2016	12789628	1	BR-ABBVIE-16P-020-1734538-00	Expedited (15-DAY)	9	Female	Brazil	OT
12/22/2020	18649727	1	KE-TOLMAR, INC.-20KE024472	Expedited (15-DAY)	6	Female	Kenya	OT
04/06/2021	19098245	2	CA-ABBVIE-21K-028-3846355-00	Expedited (15-DAY)	12	Female	Canada	OT
11/22/2002	3870025	1	THQ2002A01439	Expedited (15-DAY)	10	Female	Great Britain	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case can have more than one serious outcome.
Abbreviations: OT=other medically significant

8.4 APPENDIX D. CASE CHARACTERISTICS OF IIH IN PEDIATRIC PATIENTS WITH CPP REPORTED WITH GNRH AGONIST USE (N=6)

FAERS Case # Literature report	Age (years)	Sex	Time to onset (days)	PT	Clinical signs and symptoms	Other diagnostic criteria	Country	Opening pressure (mm H_2O)	BMI (kg/m^2)	DC	Comments
LEUPROLIDE CASES (N=4)											
12789628	9	F	120	Idiopathic intracranial hypertension	Bilateral papilledema, abducens neuropathy, progressive visual loss, headache	Lumbar puncture, MRI unremarkable brain structures	Brazil	450	17	yes	Resolved with acetazolamide. and VPS
18649727	6	F	60	Idiopathic intracranial hypertension	Bilateral papilledema, visual loss	Fundoscopy MRI unremarkable brain structures	Kenya	NA	NR	yes	Acetazolamide DC after 6 weeks. No IIH recurrence
19098245	12	F*	150	Idiopathic intracranial hypertension	Bilateral papilledema	Lumbar puncture, MRI unremarkable brain structures	Canada	310	25	NR	Discontinuation status unknown. IIH resolved
3870025	10	F	240	Idiopathic intracranial hypertension	Headache	Lumbar puncture	Great Britain	"raised ICP"	NR	unclear	Medulloblastoma and concomitant somatropin. Discontinuation status unknown IIH not resolved
TRIPTORELIN CASES (N=2)											
11749523	5	F	3	Idiopathic intracranial hypertension	Headache, vomiting	MRI unremarkable brain structures	Spain	NA	21	NR	Overweight Discontinuation status unknown. IIH outcome unknown
Gul et al	9	F	120	Idiopathic intracranial hypertension	Bilateral papilledema, hypertension	Lumbar puncture, MRI unremarkable brain structures	Turkey	460	18	yes	Resolved with acetazolamide

*Transgender male, birth assigned female
Abbreviations: BMI=body mass index, DC=discontinued, F=female, ICP=intracranial pressure, IIH=idiopathic intracranial hypertension, MRI=magnetic resonance imaging, NA=not applicable, NR=not reported, PT=preferred term, VPS=ventriculoperitoneal shunt

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AMY I CHEN
11/15/2021 09:16:47 AM

DAVID J CROTEAU
11/15/2021 09:29:19 AM

DANIEL I WORONOW
11/16/2021 12:30:20 PM

CINDY M KORTEPETER
11/16/2021 12:35:35 PM

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUPRON DEPOT-PED safely and effectively. See full prescribing information for LUPRON DEPOT-PED.

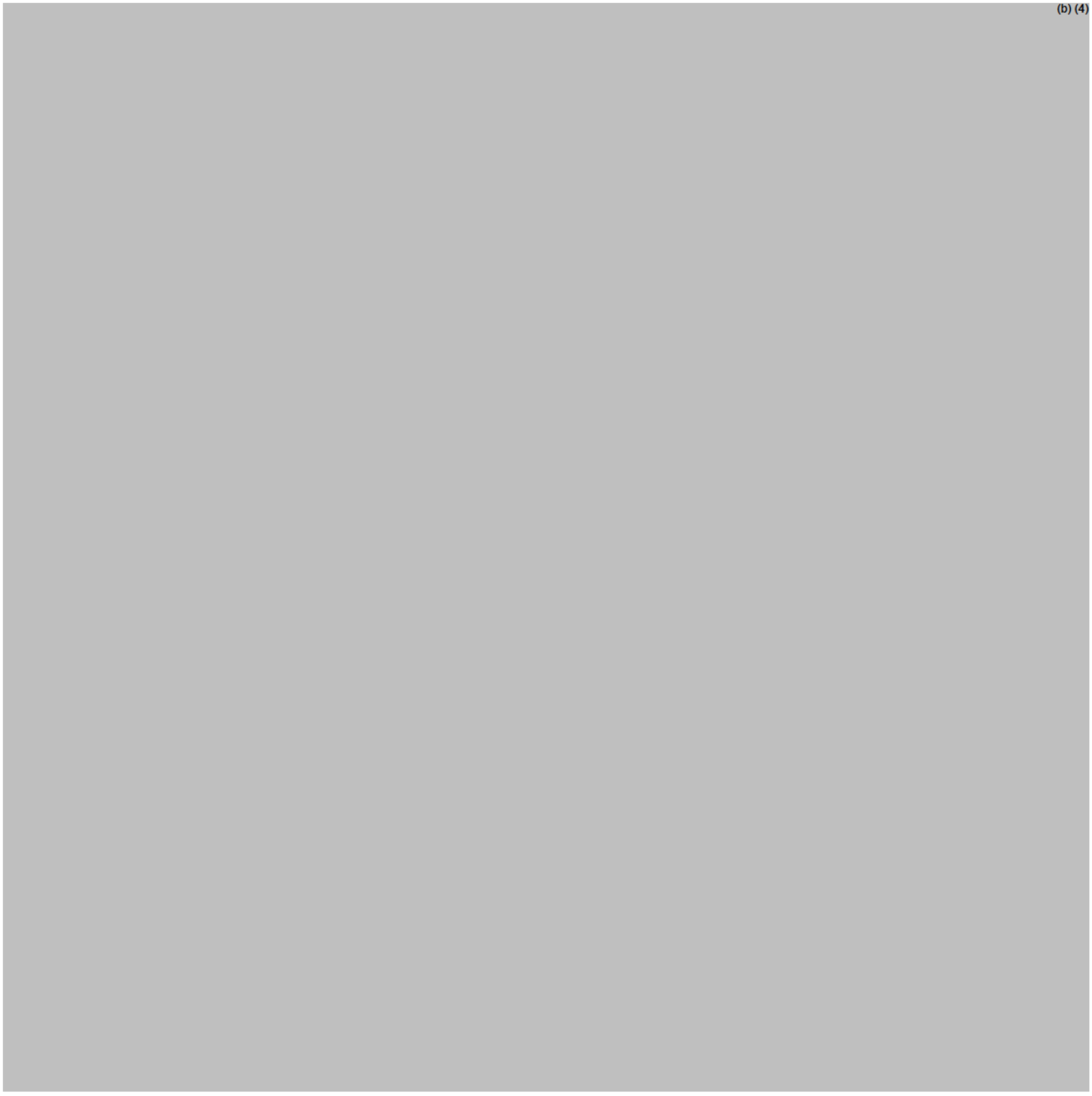
LUPRON DEPOT-PED (leuprolide acetate for depot suspension), for intramuscular use
Initial U.S. Approval: 1985

(b) (4)

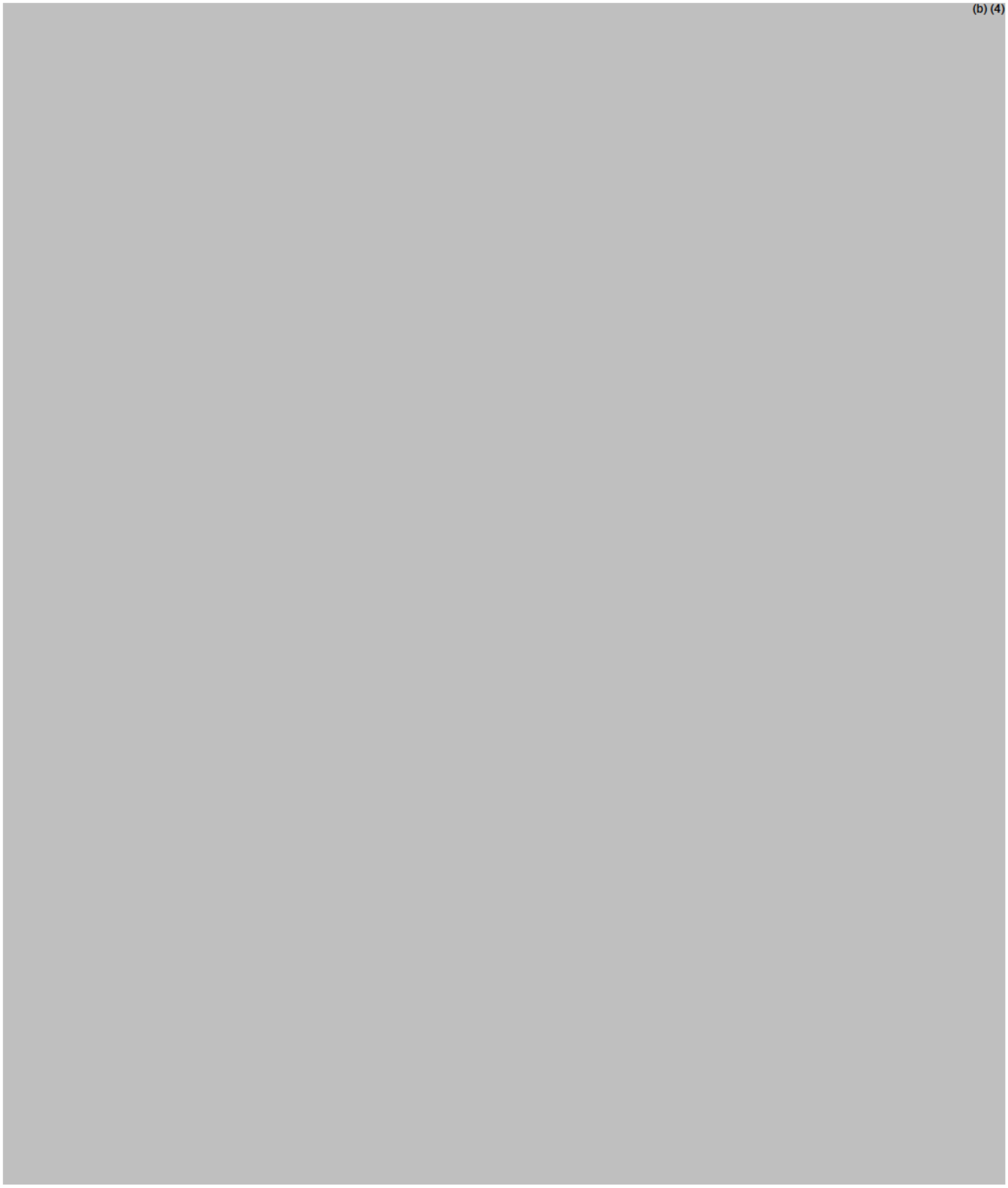
(b) (4)

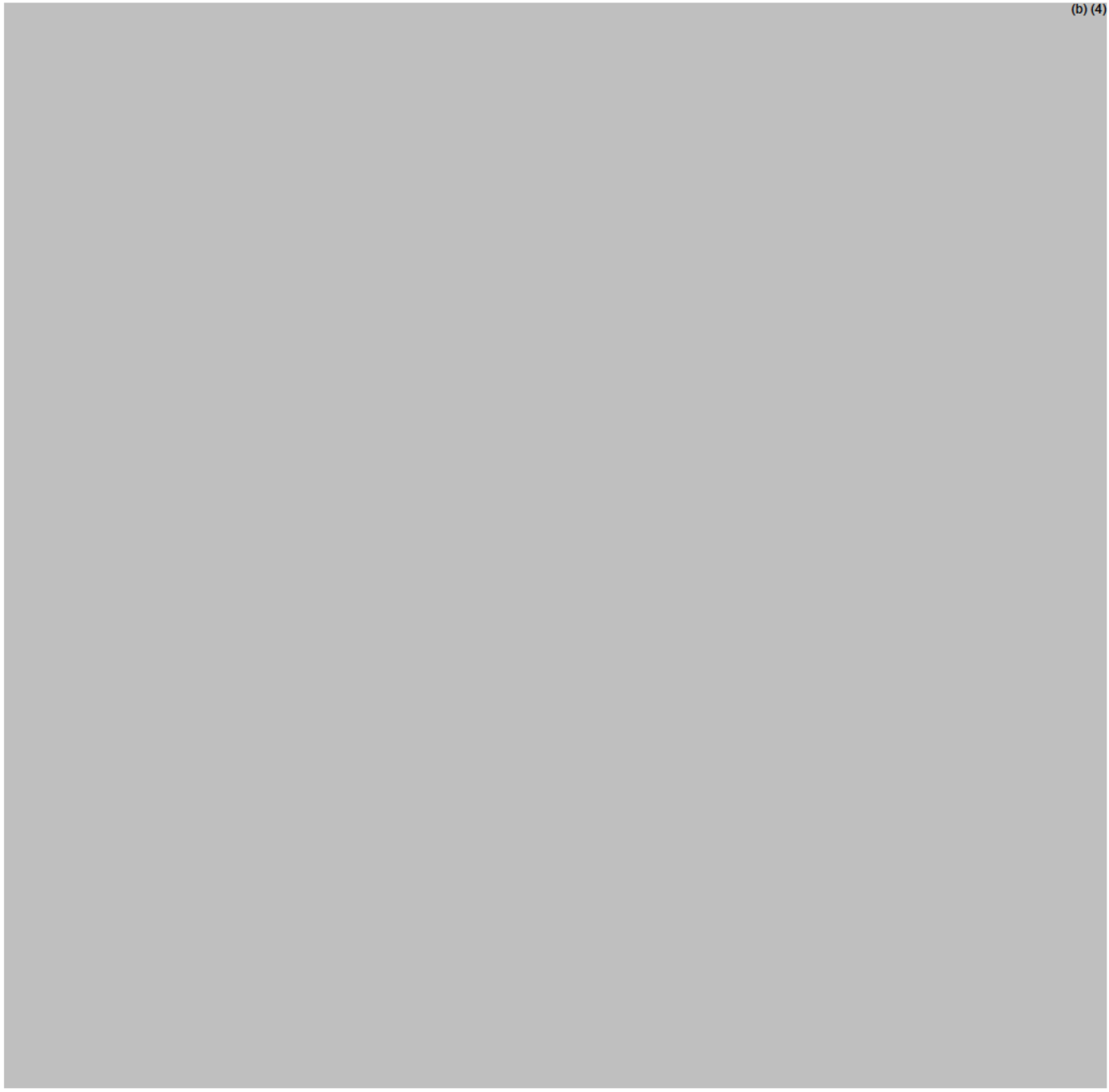
Revised: XX/2021

FULL PRESCRIBING INFORMATION: CONTENTS| HYPERLINK "" \l "section_TOCFootnote" \o "Footnote Content"]

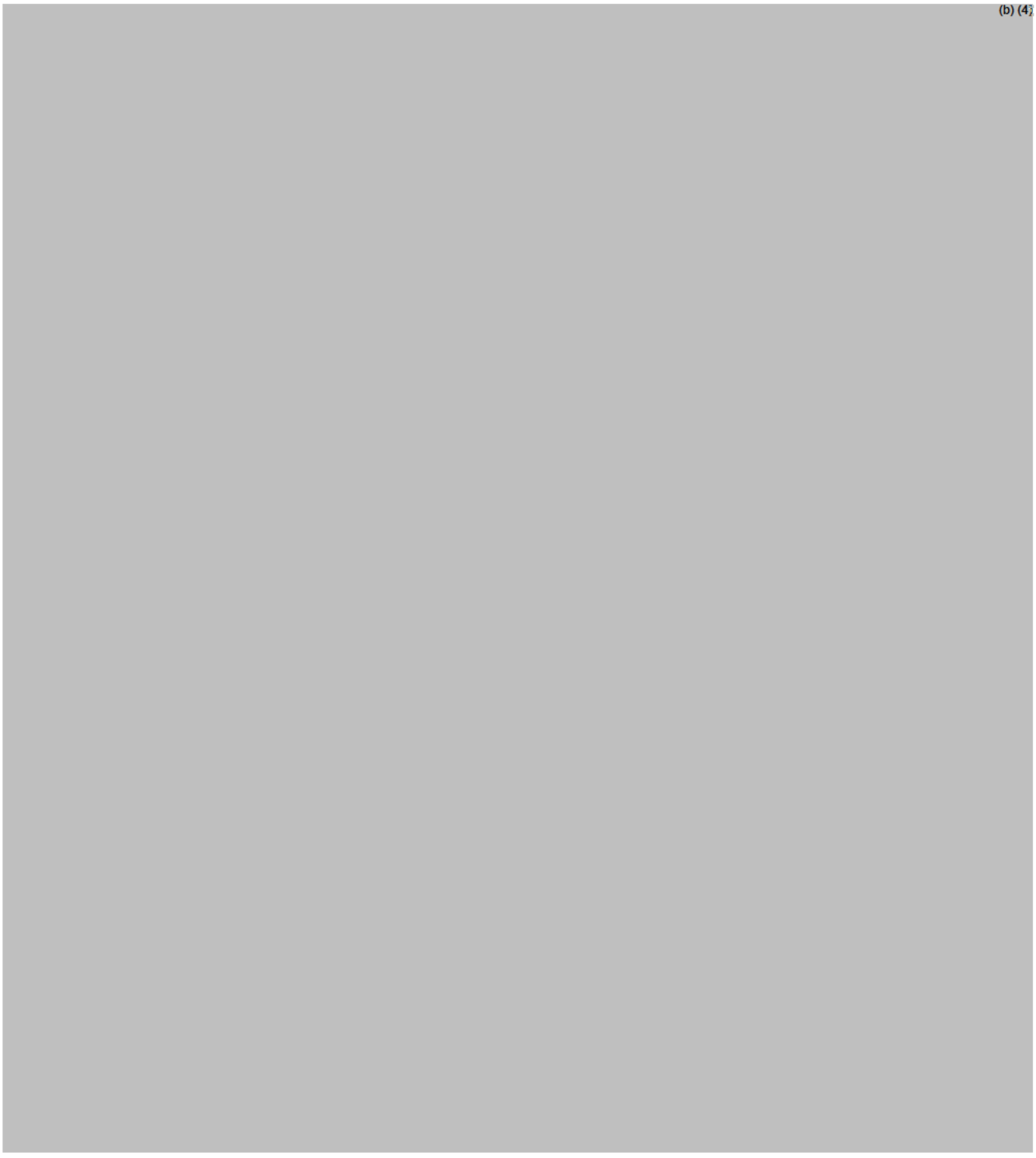

(b) (4)

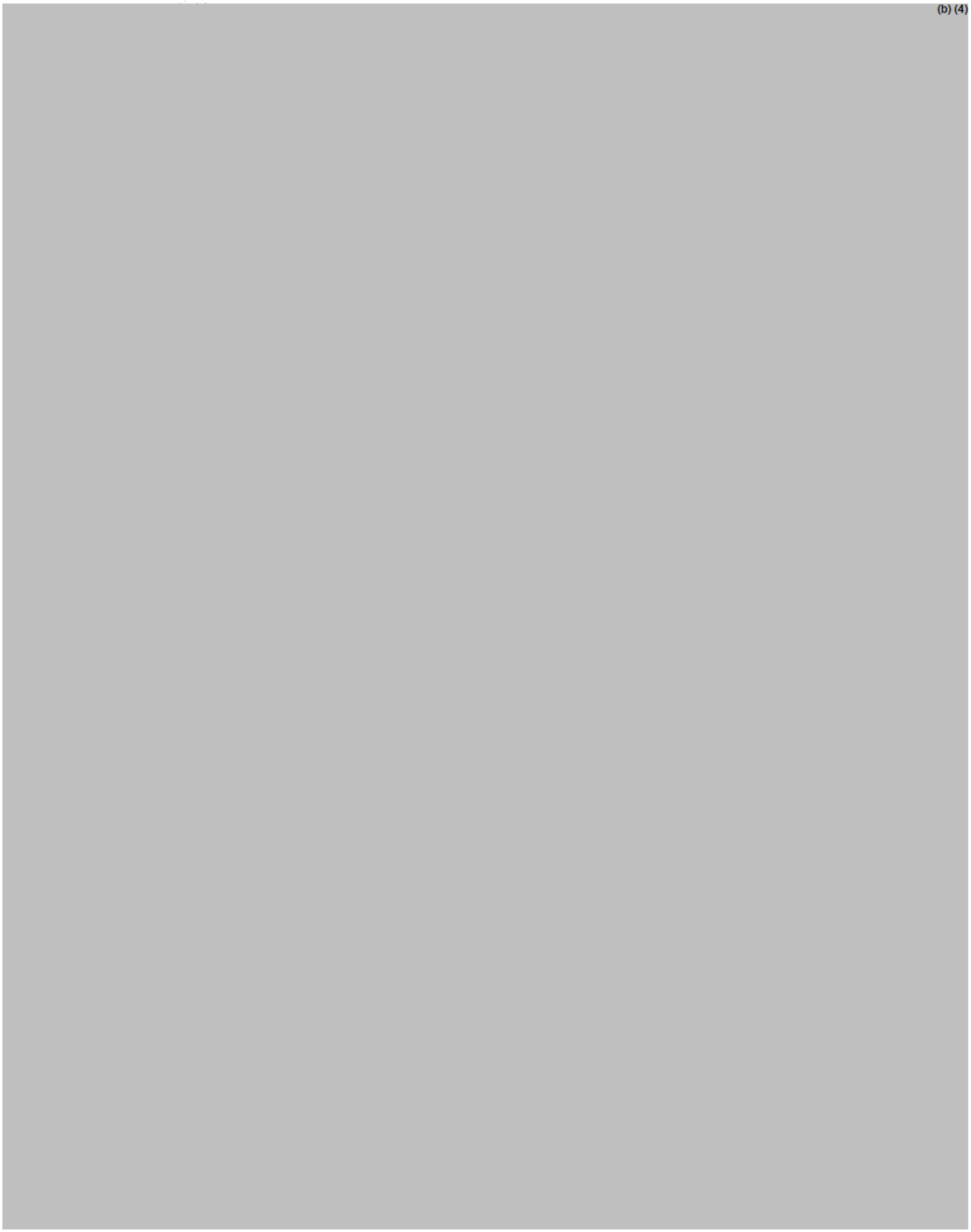
FULL PRESCRIBING INFORMATION



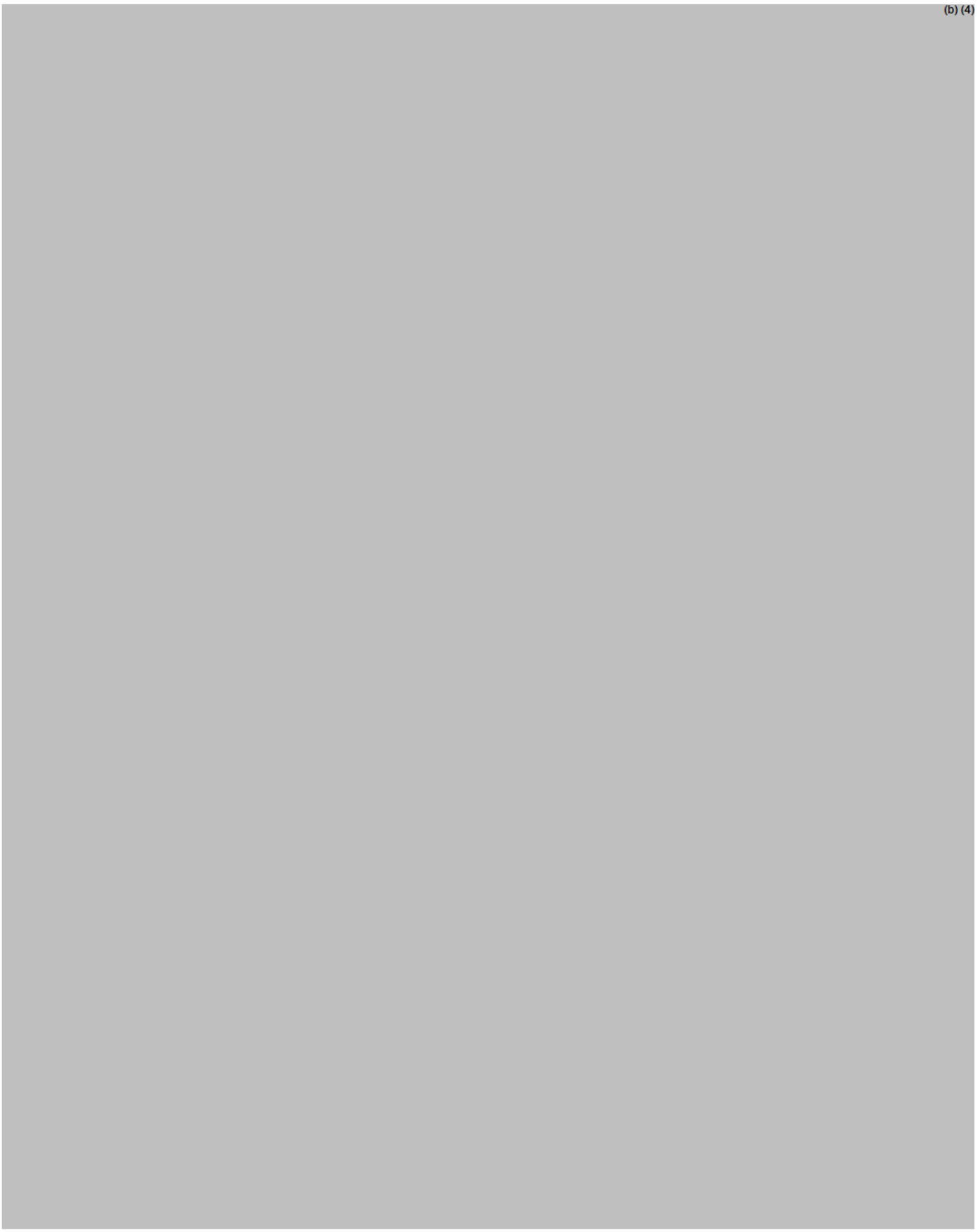

(b) (4)

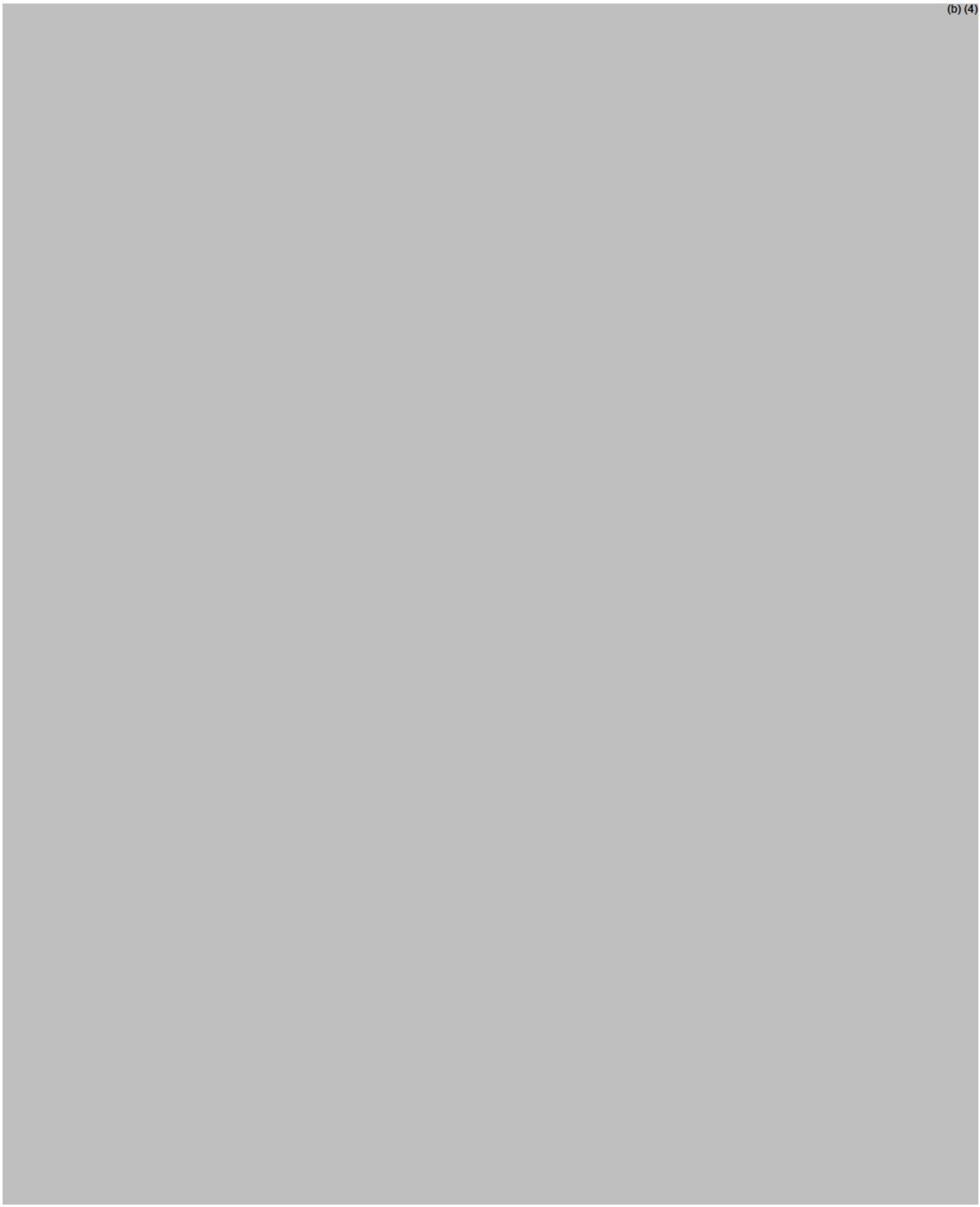

(b) (4)

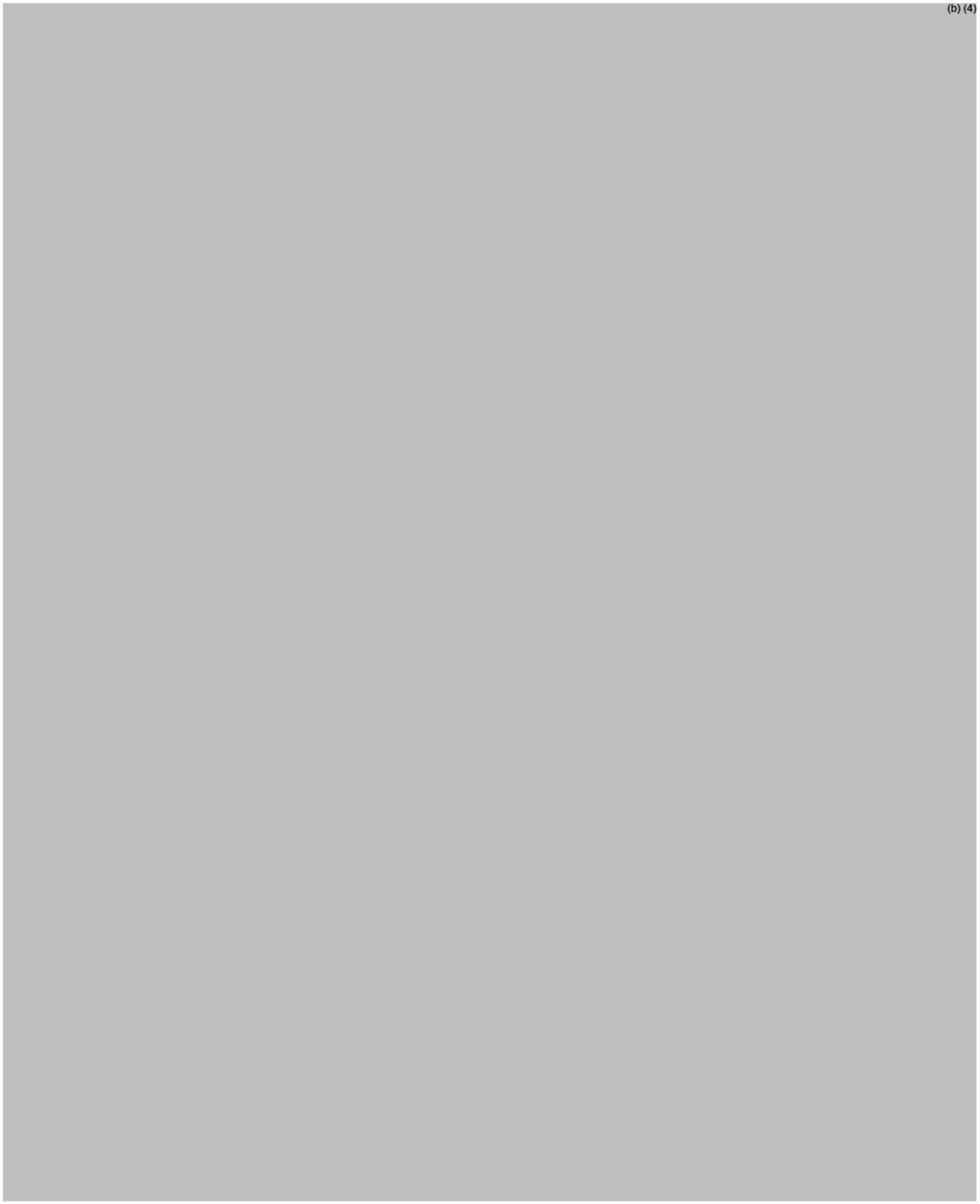

(b) (4)

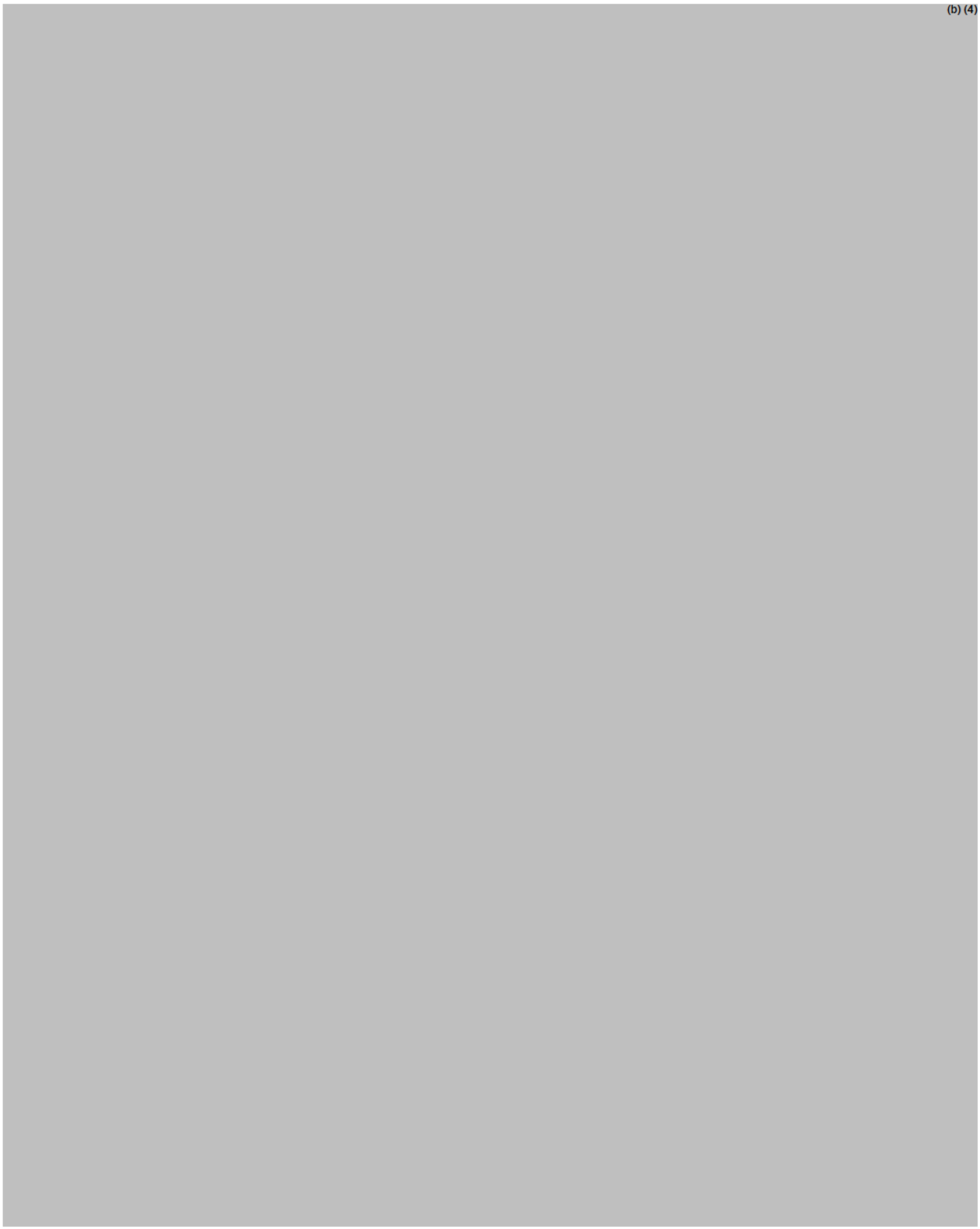

(b) (4)

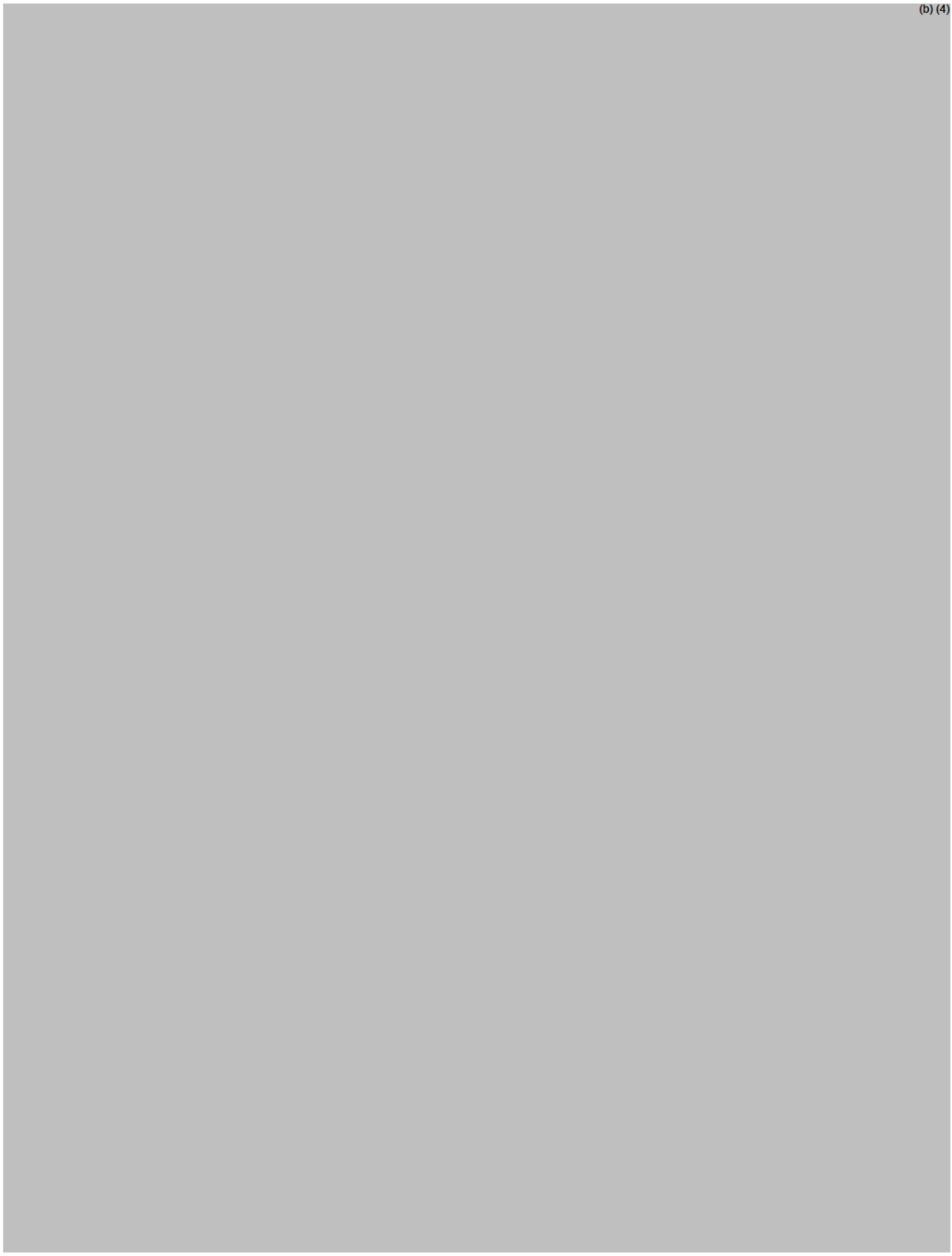
(b) (4)

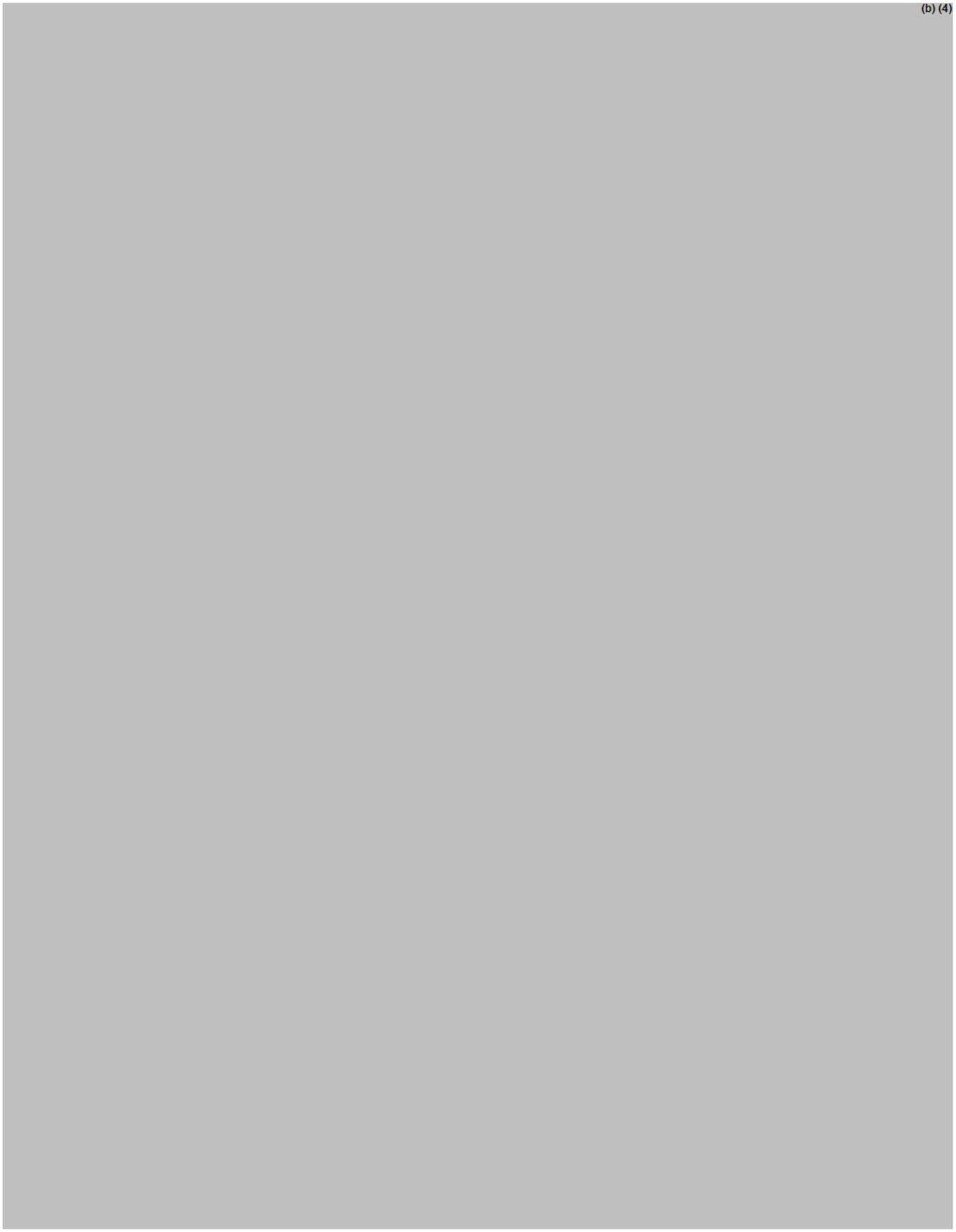


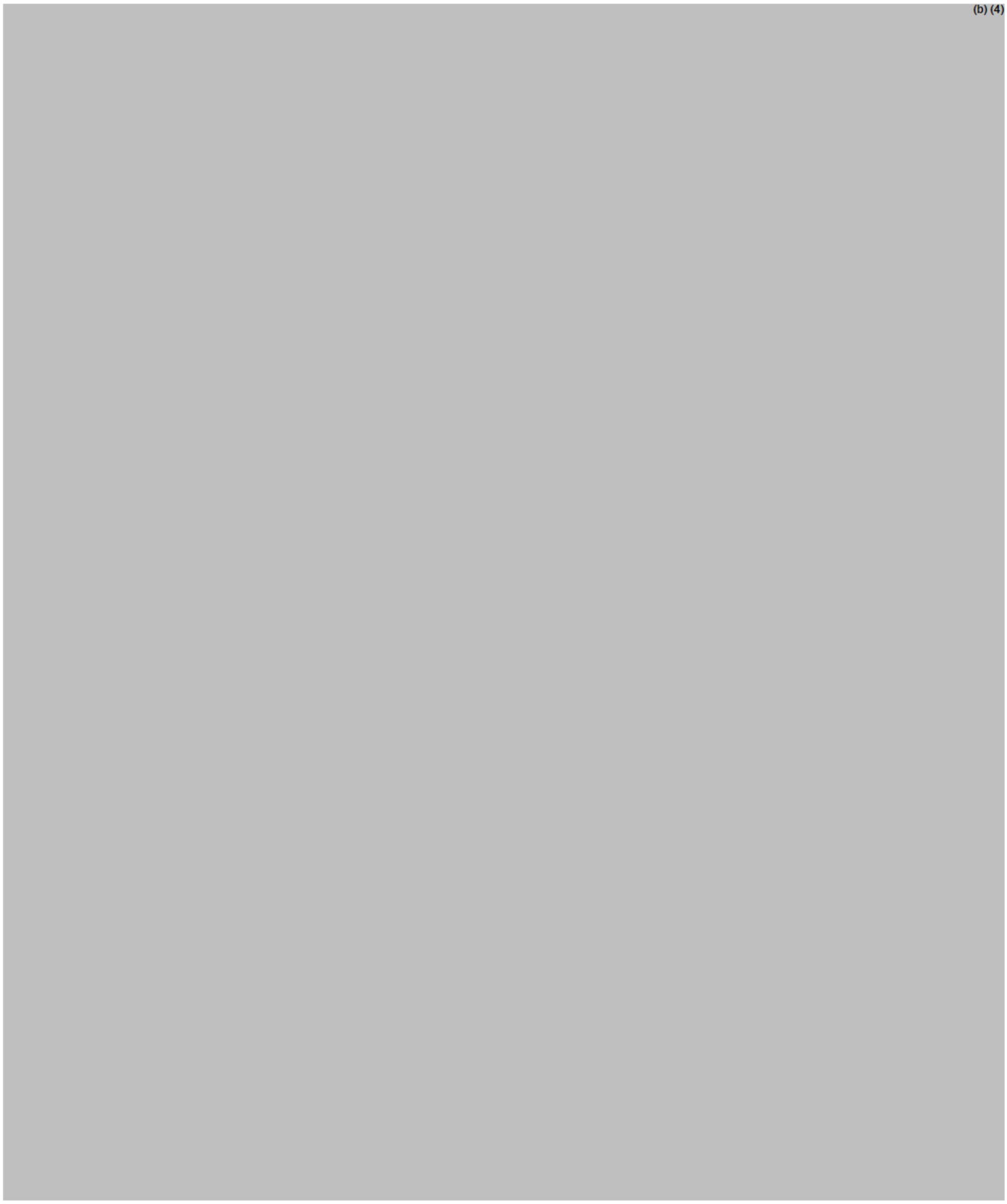

(b) (4)

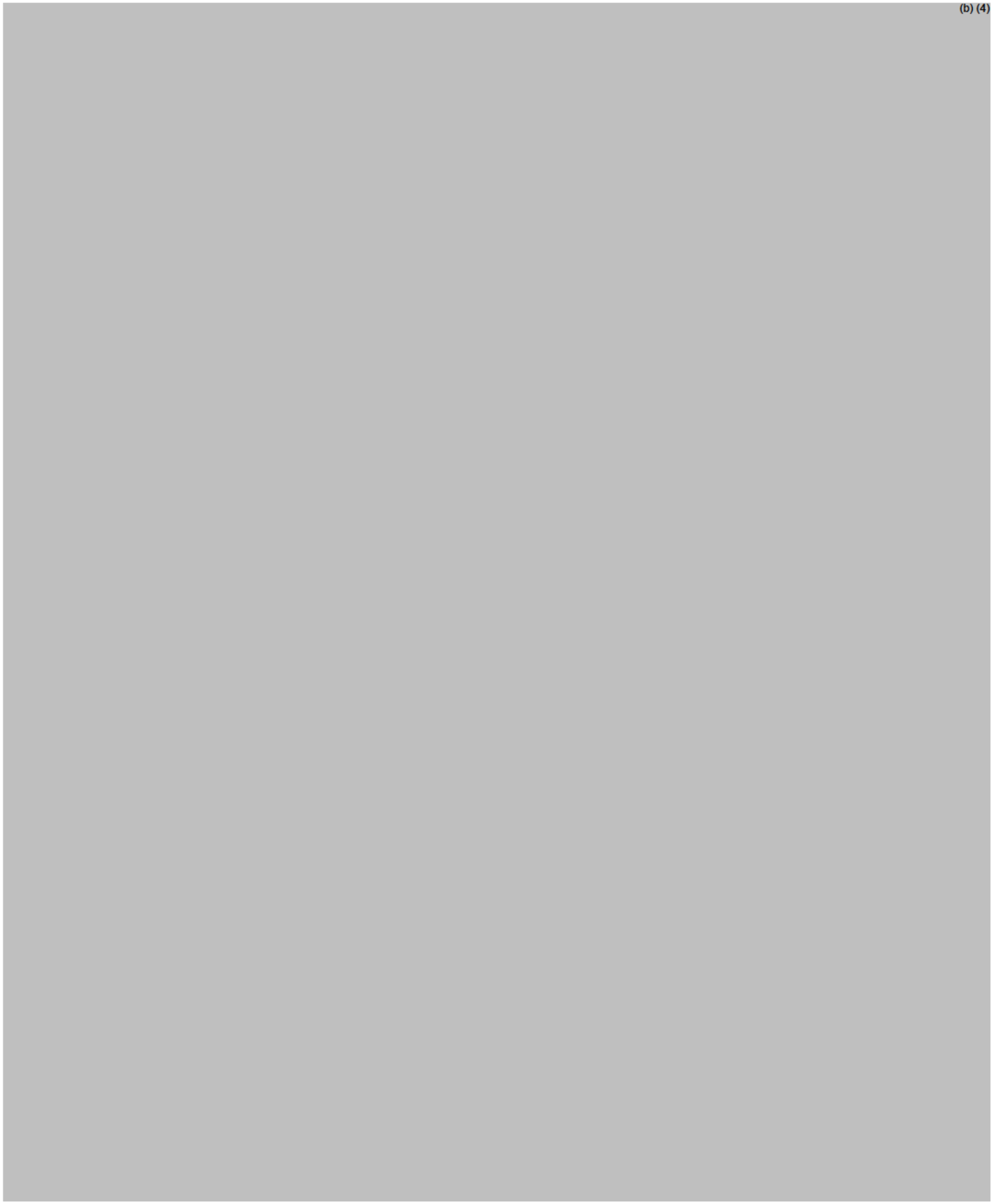

(b) (4)

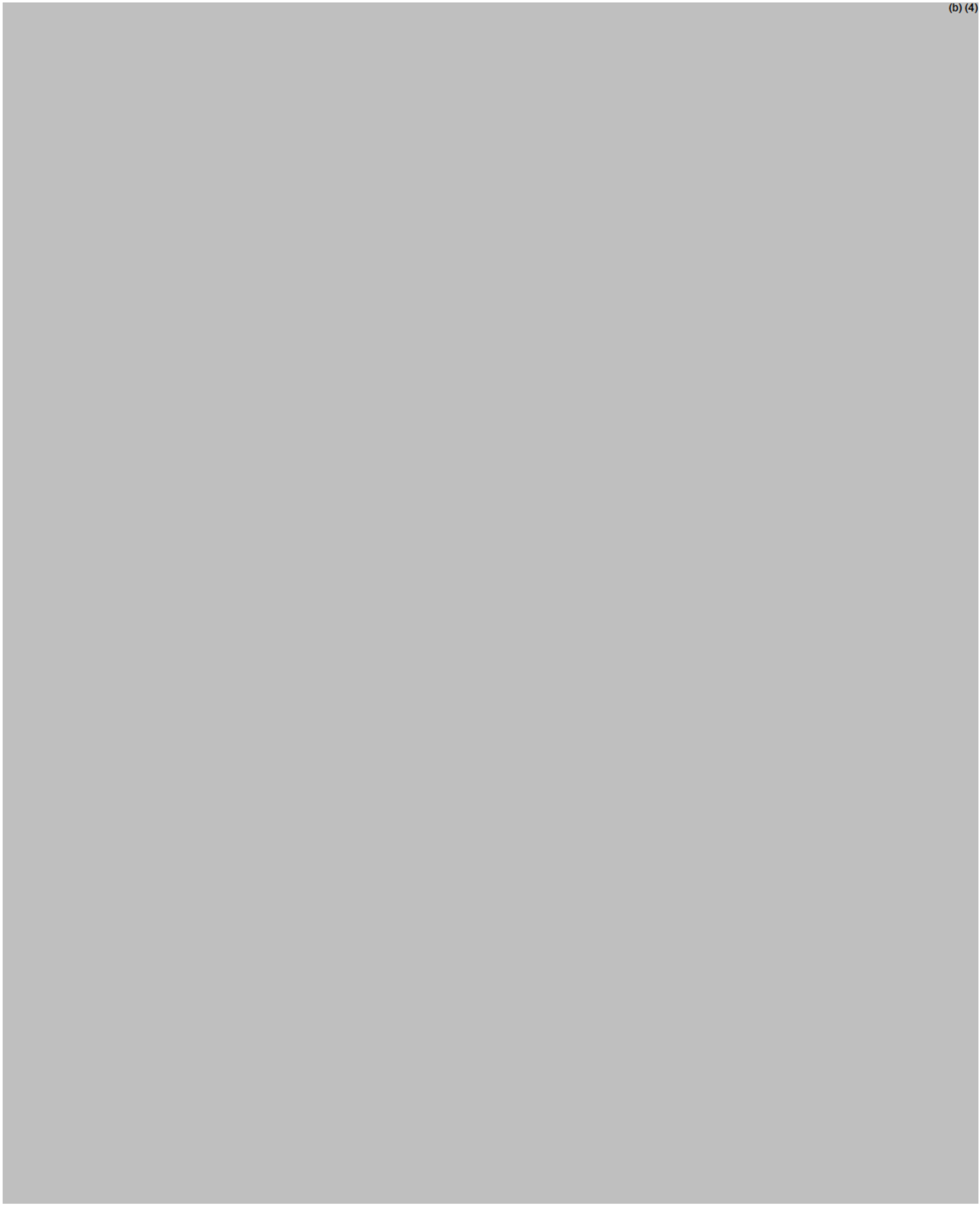

(b) (4)

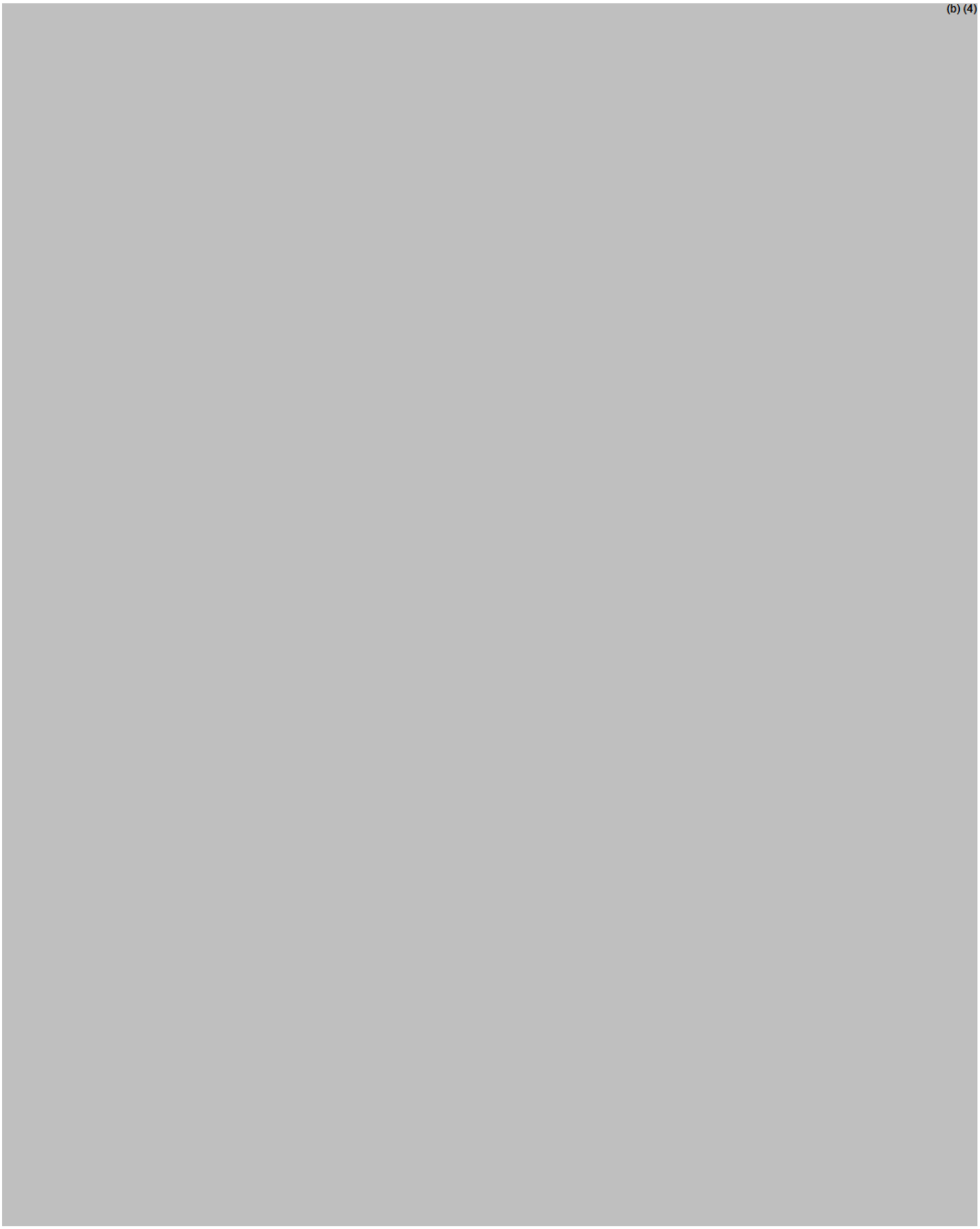

(b) (4)

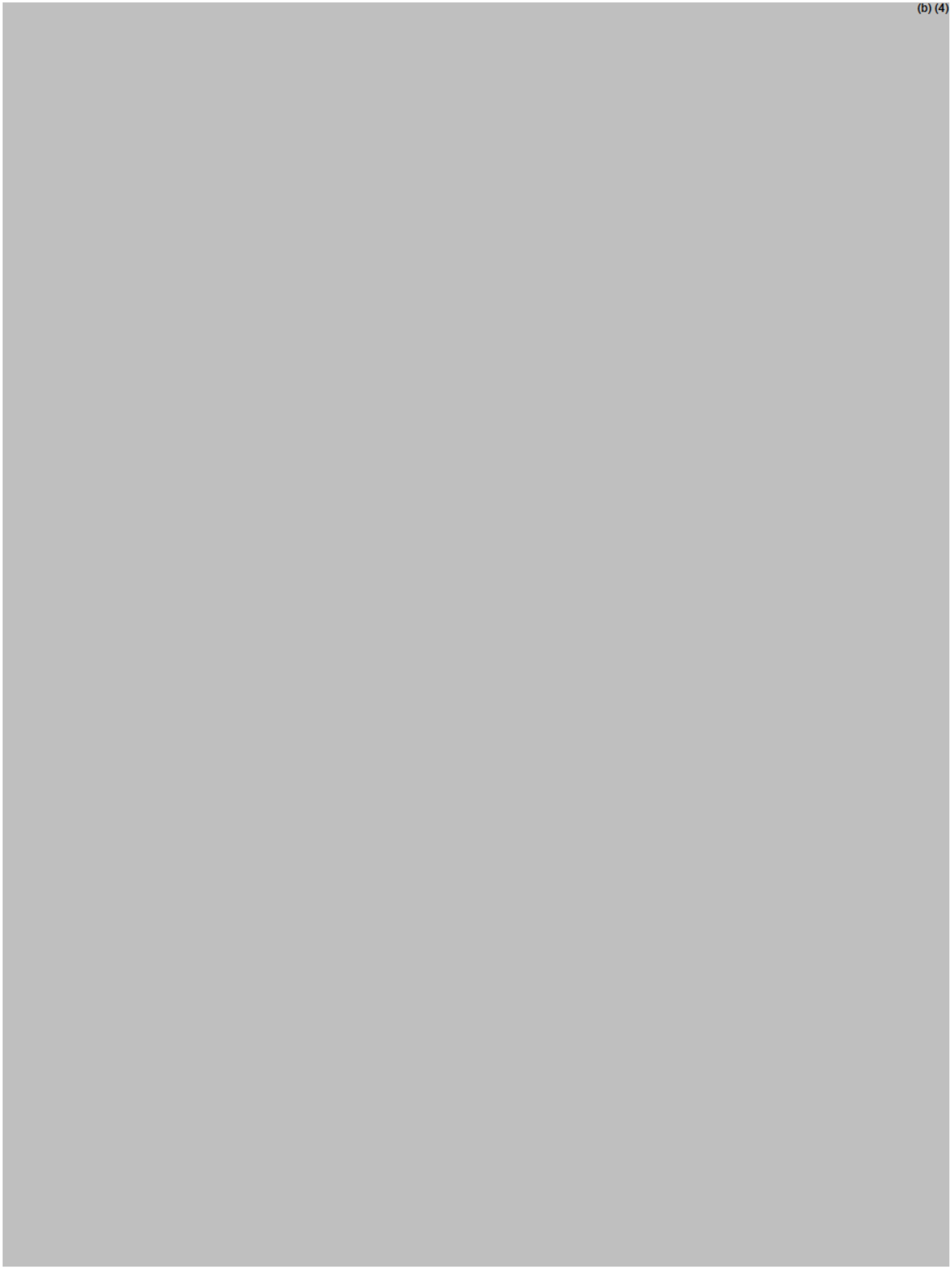

(b) (4)

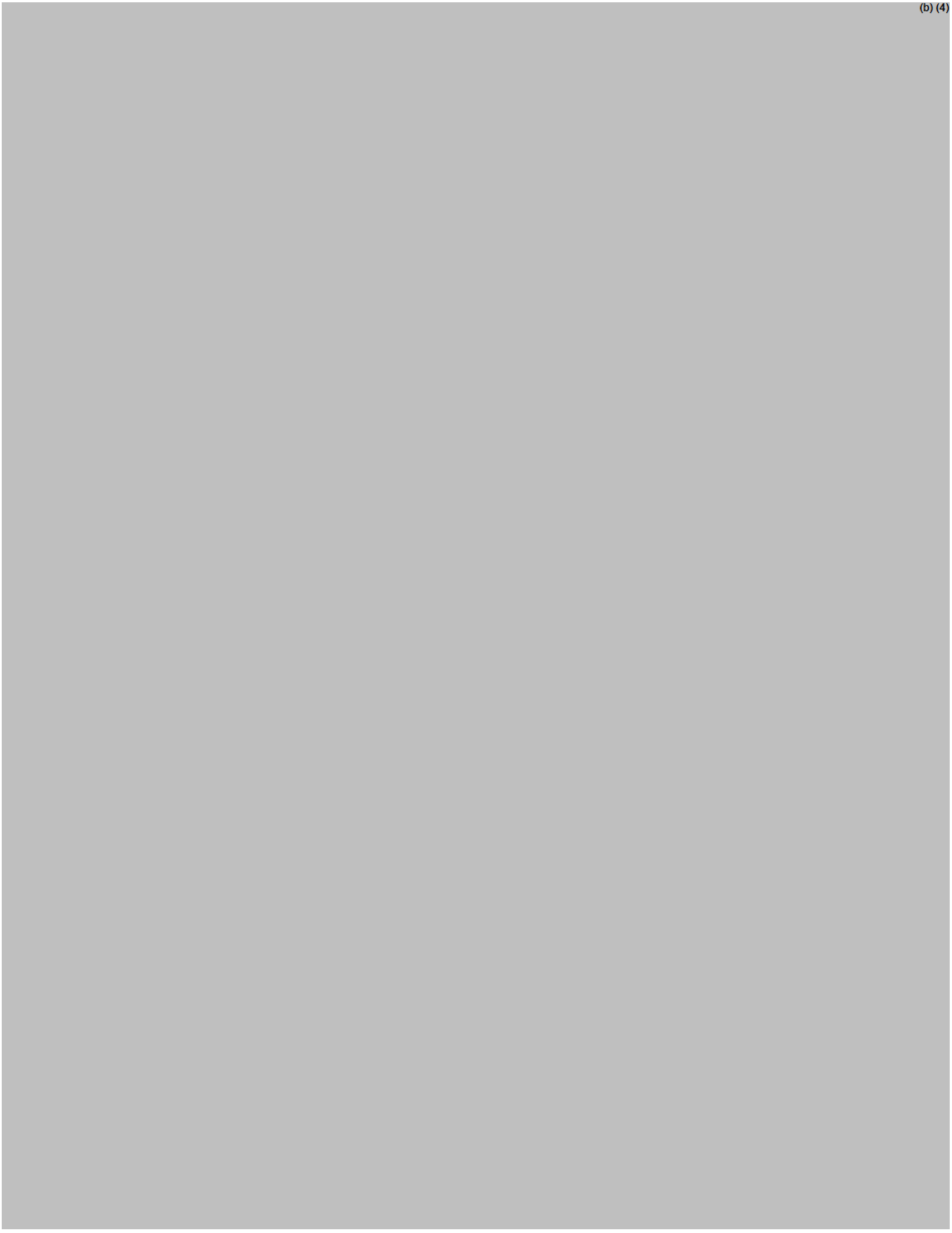

(b) (4)


(b) (4)


(b) (4)

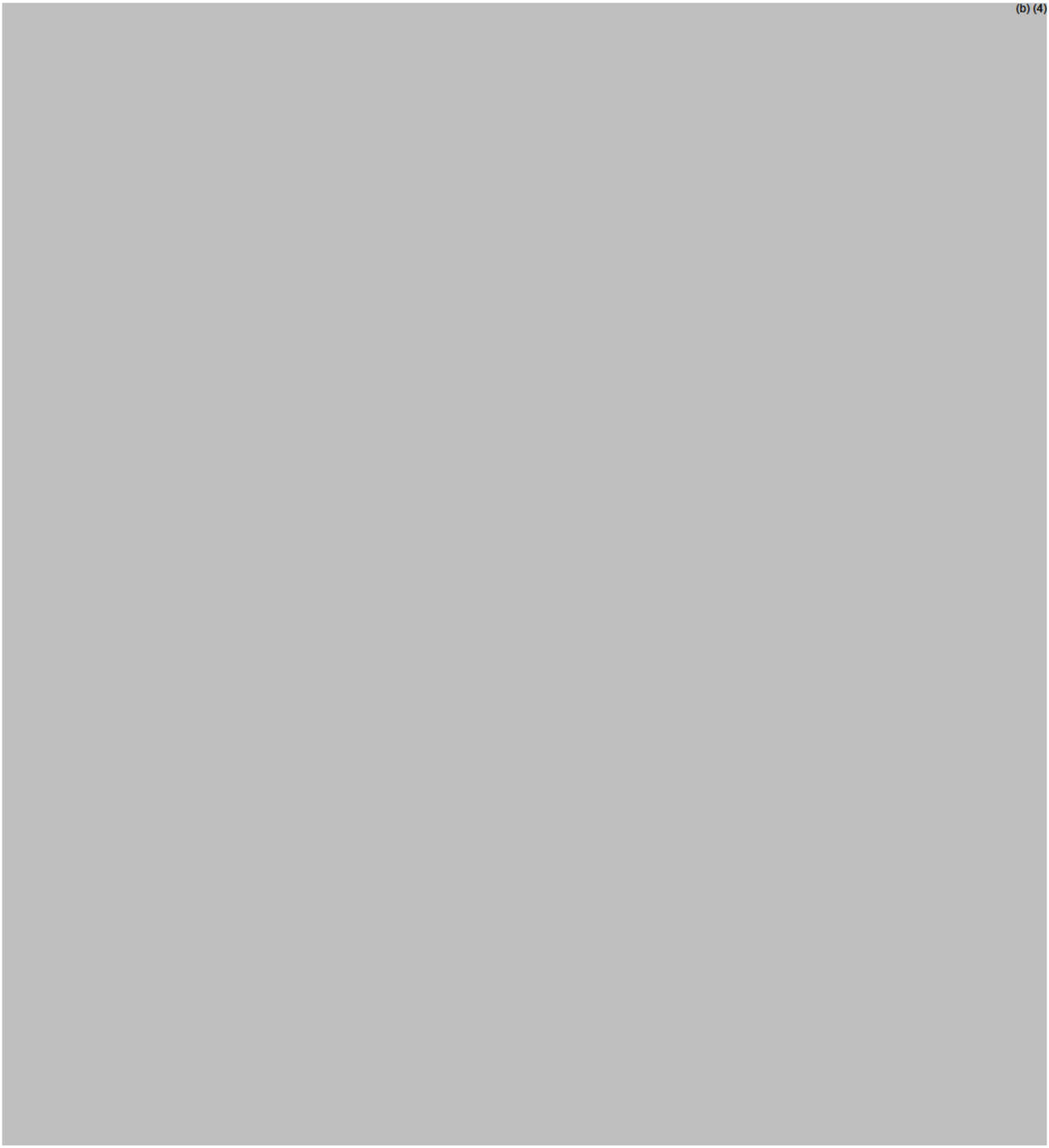

(b) (4)

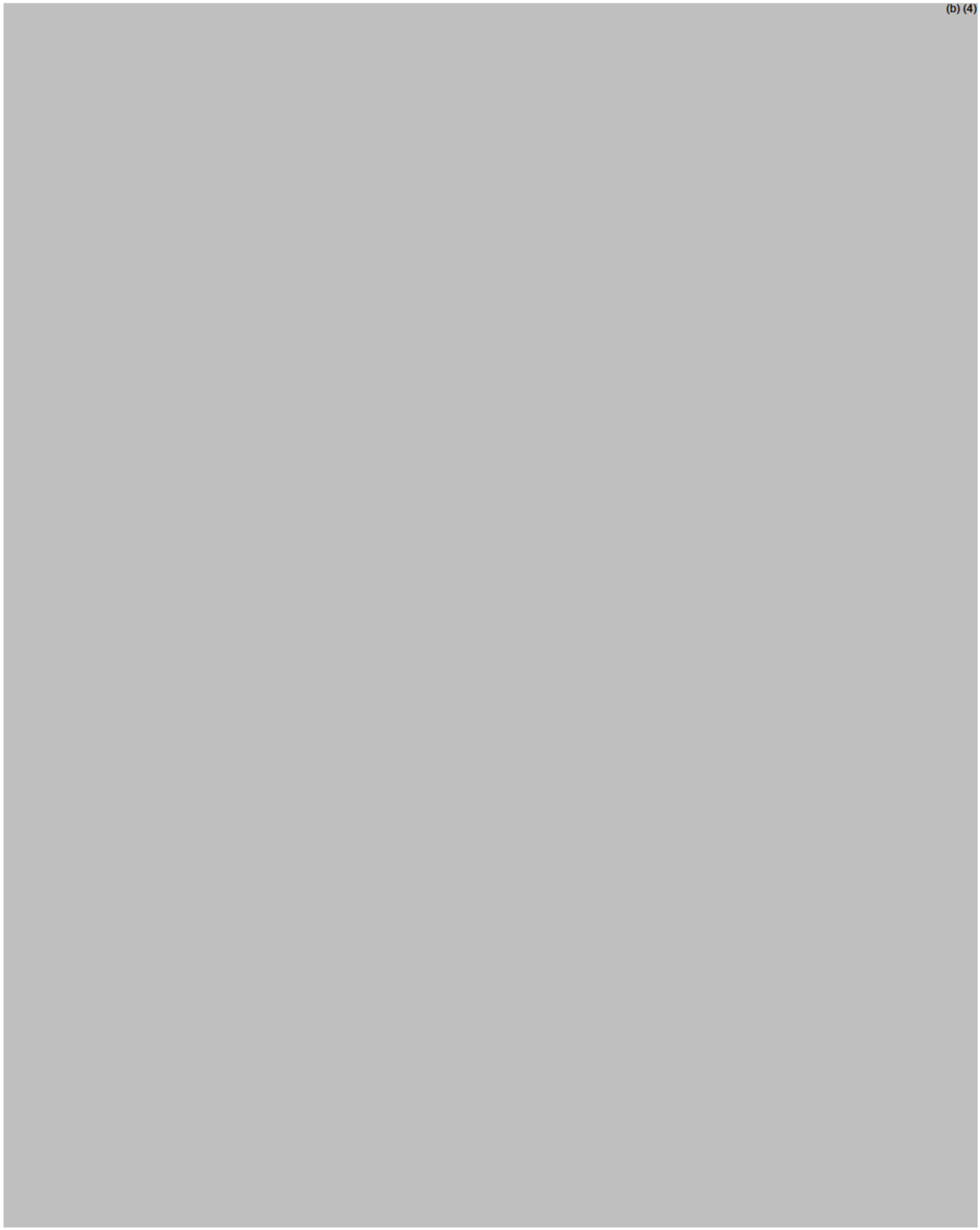

(b) (4)

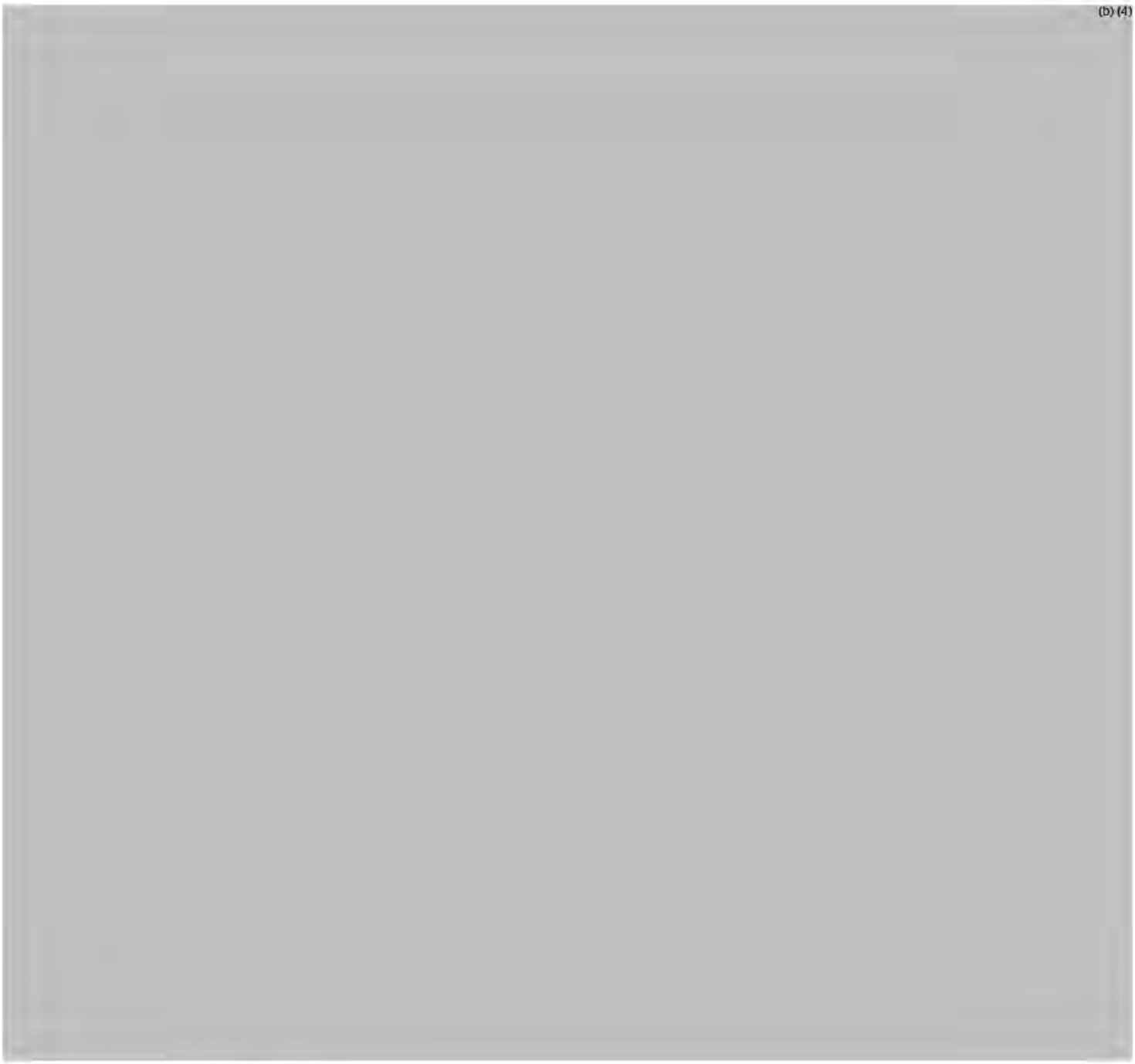

(b) (4)


(b) (4)

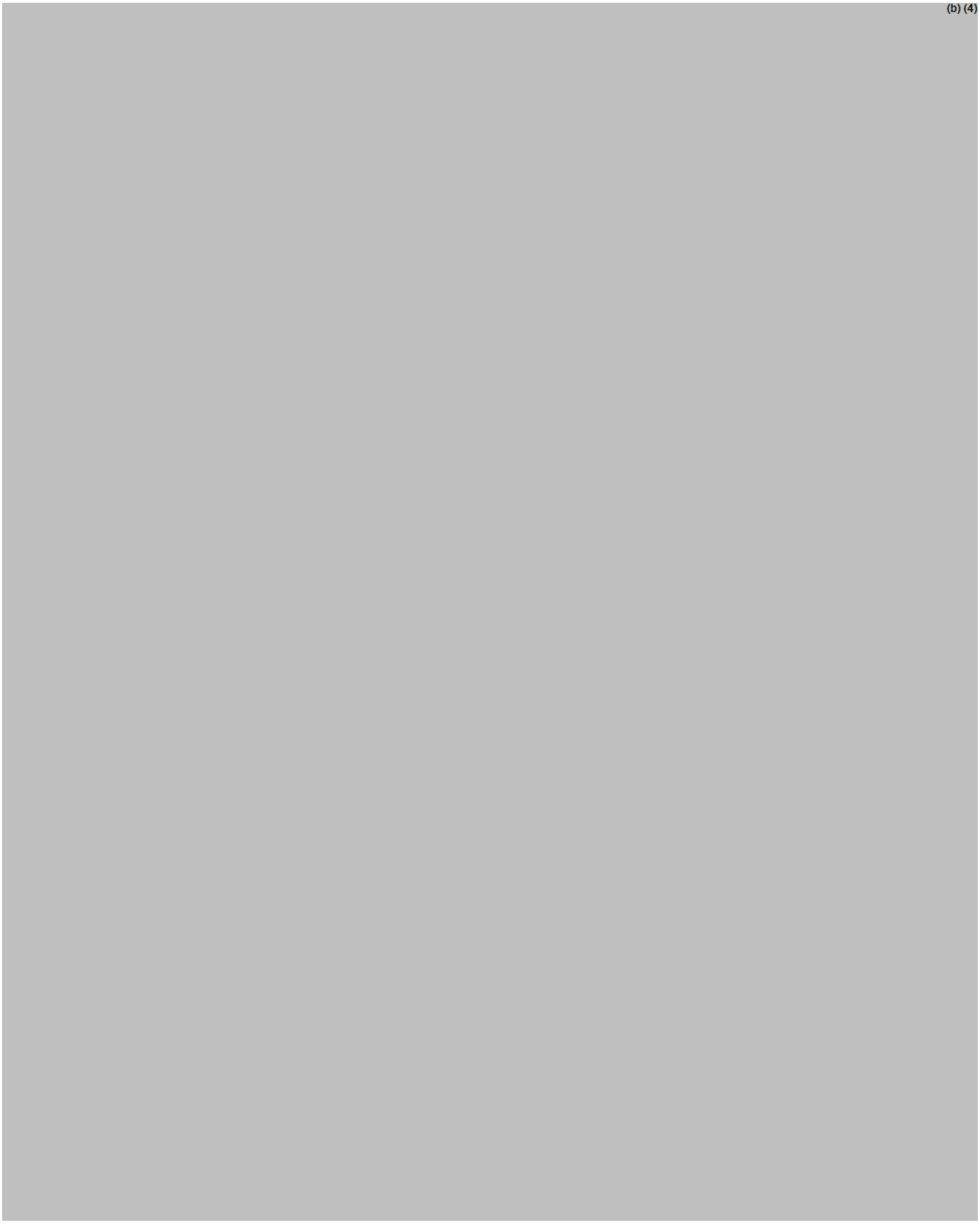

(b) (4)

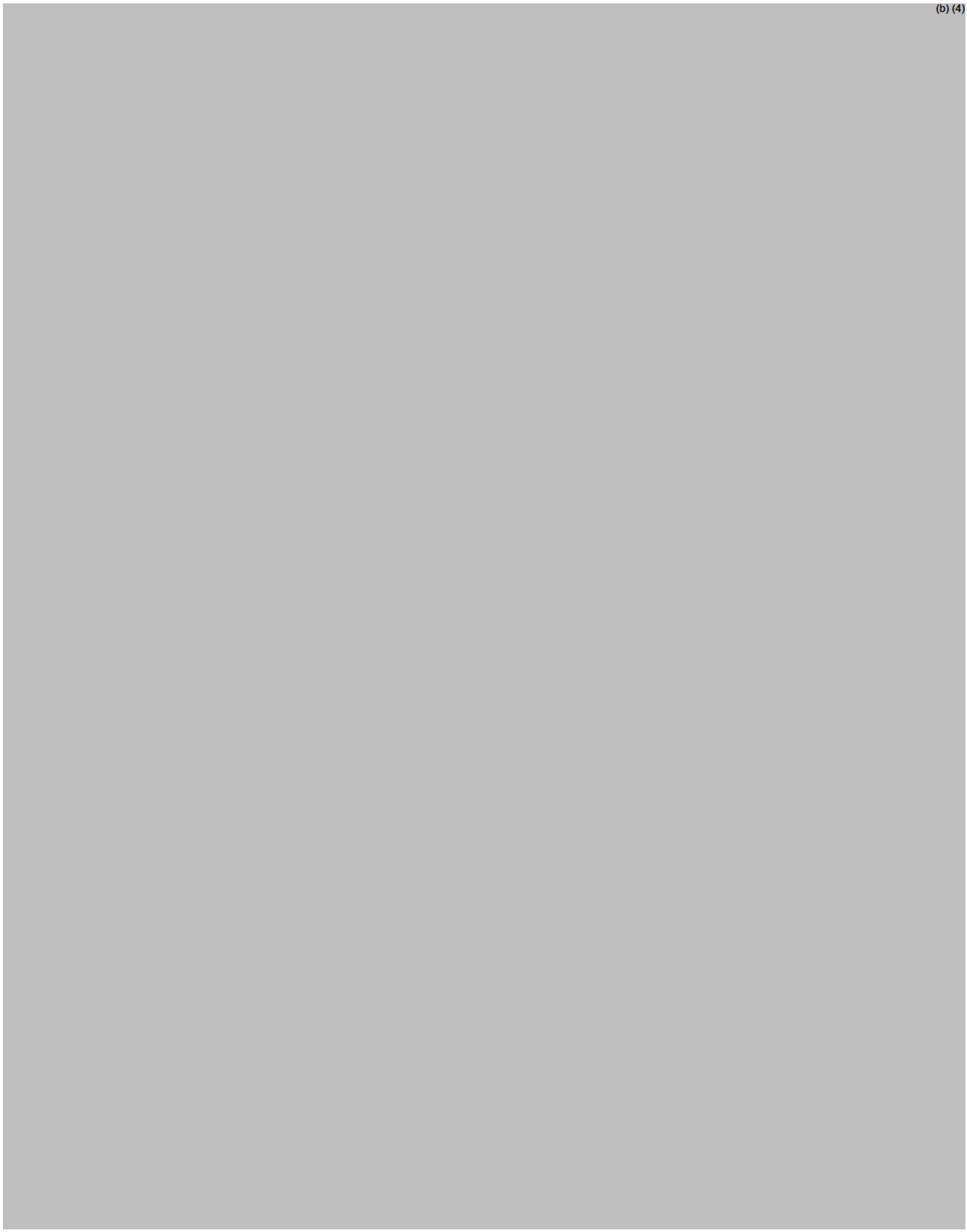

(b) (4)


(b) (4)



XXXXXXXX Month, 2021


(b) (4)


(b) (4)

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: Month, 2021

XXXXXXXX

Synarel®

(nafarelin acetate)
nasal solution

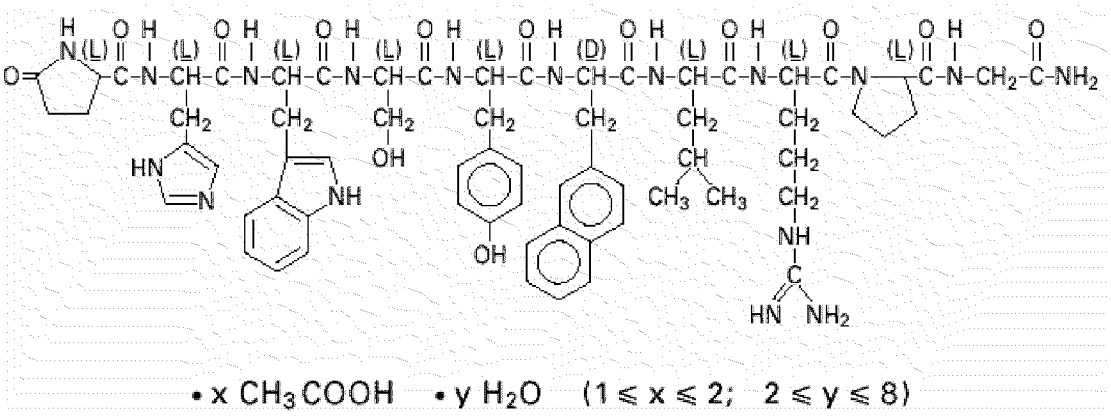
CENTRAL PRECOCIOUS PUBERTY
(FOR ENDOMETRIOSIS, SEE REVERSE SIDE)

PHYSICIAN LABELING

DESCRIPTION

SYNAREL (nafarelin acetate) Nasal Solution is intended for administration as a spray to the nasal mucosa. Nafarelin acetate, the active component of SYNAREL Nasal Solution, is a decapeptide with the chemical name: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-3-(2-naphthyl)-D-alanyl-L-leucyl-L-arginyl-L-prolyl-glycinamide acetate. Nafarelin acetate is a synthetic analog of the naturally occurring gonadotropin-releasing hormone (GnRH).

Nafarelin acetate has the following chemical structure:



SYNAREL Nasal Solution contains nafarelin acetate (2 mg/mL, content expressed as nafarelin base) in a solution of benzalkonium chloride, glacial acetic acid, sodium hydroxide or hydrochloric acid (to adjust pH), sorbitol, and purified water.

After priming the pump unit for SYNAREL, each actuation of the unit delivers approximately 100 µL of the spray containing approximately 200 µg nafarelin base. The contents of one spray bottle are intended to deliver at least 60 sprays.

CLINICAL PHARMACOLOGY

Nafarelin acetate is a potent agonistic analog of gonadotropin-releasing hormone (GnRH). At the onset of administration, nafarelin stimulates the release of the pituitary gonadotropins, LH and FSH, resulting in a temporary increase of gonadal steroidogenesis. Repeated dosing abolishes the stimulatory effect on the pituitary gland.

Twice daily administration leads to decreased secretion of gonadal steroids by about 4 weeks; consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent.

In **children,** nafarelin acetate was rapidly absorbed into the systemic circulation after intranasal administration. Maximum serum concentrations (measured by RIA) were achieved between 10 and 45 minutes. Following a single dose of 400 µg base, the observed peak concentration was 2.2 ng/mL, whereas following a single dose of 600 µg base, the observed peak concentration was 6.6 ng/mL. The average serum half-life of nafarelin following intranasal administration of a 400 µg dose was approximately 2.5 hours. It is not known and cannot be predicted what the pharmacokinetics of nafarelin will be in children given a dose above 600 µg.

In **adult women,** nafarelin acetate was rapidly absorbed into the systemic circulation after intranasal administration. Maximum serum concentrations (measured by RIA) were achieved between 10 and 40 minutes. Following a single dose of 200 µg base, the observed average peak concentration was 0.6 ng/mL (range 0.2 to 1.4 ng/mL), whereas following a single dose of 400 µg base, the observed average peak concentration was 1.8 ng/mL (range 0.5 to 5.3 ng/mL). Bioavailability from a 400 µg dose averaged 2.8% (range 1.2 to 5.6%). The average serum half-life of nafarelin following intranasal administration was approximately 3 hours. About 80% of nafarelin acetate was bound to plasma proteins at 4°C. Twice daily intranasal administration of 200 or 400 µg of SYNAREL in 18 healthy women for 22 days did not lead to significant accumulation of the drug. Based on the mean C_{min} levels on Days 15 and 22, there appeared to be dose proportionality across the two dose levels.

After subcutaneous administration of ^{14}C-nafarelin acetate to men, 44–55% of the dose was recovered in urine and 18.5–44.2% was recovered in feces. Approximately 3% of the administered dose appeared as unchanged nafarelin in urine. The ^{14}C serum half-life of the metabolites was about 85.5 hours. Six metabolites of nafarelin have been identified of which the major metabolite is Tyr-D(2)-Nal-Leu-Arg-Pro-Gly-NH_2(5-10). The activity of the metabolites, the metabolism of nafarelin by nasal mucosa, and the pharmacokinetics of the drug in hepatically- and renally-impaired patients have not been determined.

There appeared to be no significant effect of rhinitis, i.e., nasal congestion, on the systemic bioavailability of SYNAREL; however, if the use of a nasal decongestant for rhinitis is necessary during treatment with SYNAREL, the decongestant should not be used until at least 2 hours following dosing with SYNAREL.

When used regularly in girls and boys with **central precocious puberty (CPP)** at the recommended dose, SYNAREL suppresses LH and sex steroid hormone levels to prepubertal levels, affects a corresponding arrest of secondary sexual development, and slows linear growth and skeletal maturation. In some cases, initial estrogen withdrawal bleeding may occur, generally within 6 weeks after initiation of therapy. Thereafter, menstruation should cease.

In clinical studies the peak response of LH to GnRH stimulation was reduced from a pubertal response to a prepubertal response (< 15 mlU/mL) within one month of treatment.

Linear growth velocity, which is commonly pubertal in children with CPP, is reduced in most children within the first year of treatment to values of 5 to 6 cm/year or less. Children with CPP are frequently taller than their chronological age peers; height for chronological age approaches normal in most children during the second or third year of treatment with SYNAREL. Skeletal maturation rate (bone age velocity—change in bone age divided by change in chronological age) is usually abnormal (greater than 1) in children with CPP; in most children, bone age velocity approaches normal (1) during the first year of treatment. This results in a narrowing of the gap between bone age and chronological age, usually by the second or third year of treatment. The mean predicted adult height increases.

In clinical trials, breast development was arrested or regressed in 82% of girls, and genital development was arrested or regressed in 100% of boys. Because pubic hair growth is largely controlled by adrenal androgens, which are unaffected by nafarelin, pubic hair development was arrested or regressed only in 54% of girls and boys.

Reversal of the suppressive effects of SYNAREL has been demonstrated to occur in all children with CPP for whom one-year post-treatment follow-up is available (n=69). This demonstration consisted of the appearance or return of menses, the return of pubertal gonadotropin and gonadal sex steroid levels, and/or the advancement of secondary sexual development. Semen analysis was normal in the two ejaculated specimens obtained thus far from boys who have been taken off therapy to resume puberty. Fertility has not been documented by pregnancies and the effect of long-term use of the drug on fertility is not known.

INDICATIONS AND USAGE FOR CENTRAL PRECOCIOUS PUBERTY

(For Endometriosis, *See Reverse Side*)

SYNAREL is indicated for treatment of **central precocious puberty (CPP)** (gonadotropin-dependent precocious puberty) in children of both sexes.

The diagnosis of **central precocious puberty (CPP)** is suspected when premature development of secondary sexual characteristics occurs at or before the age of 8 years in girls and 9 years in boys, and is accompanied by significant advancement of bone age and/or a poor adult height prediction. The diagnosis should be confirmed by pubertal gonadal sex steroid levels and a pubertal LH response to stimulation by native GnRH. Pelvic ultrasound assessment in girls usually reveals enlarged uterus and ovaries, the latter often with multiple cystic formations. Magnetic resonance imaging or CT-scanning of the brain is recommended to detect hypothalamic or pituitary tumors, or anatomical changes associated with increased intracranial pressure. Other causes of sexual precocity, such as congenital adrenal hyperplasia, testotoxicosis, testicular tumors and/or other

autonomous feminizing or masculinizing disorders must be excluded by proper clinical hormonal and diagnostic imaging examinations.

CONTRAINDICATIONS

1. Hypersensitivity to GnRH, GnRH agonist analogs or any of the excipients in SYNAREL;
2. Undiagnosed abnormal vaginal bleeding;
3. Use in pregnancy or in women who may become pregnant while receiving the drug. SYNAREL may cause fetal harm when administered to a pregnant woman. Major fetal abnormalities were observed in rats, but not in mice or rabbits after administration of SYNAREL during the period of organogenesis. There was a dose-related increase in fetal mortality and a decrease in fetal weight in rats *[see **Pregnancy**]*. The effects on rat fetal mortality are expected consequences of the alterations in hormonal levels brought about by the drug. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus;
4. Use in women who are breast-feeding *[see **Nursing Mothers**]*.

WARNINGS

The diagnosis of central precocious puberty (CPP) must be established before treatment is initiated. Regular monitoring of CPP patients is needed to assess both patient response as well as compliance. This is particularly important during the first 6 to 8 weeks of treatment to assure that suppression of pituitary-gonadal function is rapid. Testing may include LH response to GnRH stimulation and circulating gonadal sex steroid levels. Assessment of growth velocity and bone age velocity should begin within 3 to 6 months of treatment initiation.

Some patients may not show suppression of the pituitary-gonadal axis by clinical and/or biochemical parameters. This may be due to lack of compliance with the recommended treatment regimen and may be rectified by recommending that the dosing be done by caregivers. If compliance problems are excluded, the possibility of gonadotropin independent sexual precocity should be reconsidered and appropriate examinations should be conducted. If compliance problems are excluded and if gonadotropin independent sexual precocity is not present, the dose of SYNAREL may be increased to 1800 μg/day administered as 600 μg tid.

Psychiatric events have been reported in patients taking GnRH agonists. Postmarketing reports with this class of drugs includes symptoms of emotional lability, such as crying, irritability, impatience, anger, and aggression. Monitor for development or worsening of psychiatric symptoms during treatment with SYNAREL.

Post-marketing reports of convulsions have been observed in patients receiving GnRH agonists. These have included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above.

PRECAUTIONS

General

As with other drugs that stimulate the release of gonadotropins or that induce ovulation, in adult women with endometriosis ovarian cysts have been reported to occur in the first two months of therapy with SYNAREL. Many, but not all, of these events occurred in women with polycystic ovarian disease. These cystic enlargements may resolve spontaneously, generally by about four to six weeks of therapy, but in some cases may require discontinuation of drug and/or surgical intervention. The relevance, if any, of such events in children is unknown.

Information for Patients, Patients' Parents or Guardians

An information pamphlet for patients is included with the product. Patients and their caregivers should be aware of the following information:

1. Reversibility of the suppressive effects of nafarelin has been demonstrated by the appearance or return of menses, by the return of pubertal gonadotropin and gonadal sex steroid levels, and/or by advancement of secondary sexual development. Semen analysis was normal in the two ejaculated specimens obtained thus far from boys who have been taken off therapy to resume puberty. Fertility has not been documented by pregnancies and the effect of long-term use of the drug on fertility is not known.

2. Patients and their caregivers should be adequately counseled to assure full compliance; irregular or incomplete daily doses may result in stimulation of the pituitary-gonadal axis.

3. Inform parents that reports of convulsions have been observed in patients receiving GnRH agonists. Patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions may be at increased risk *[see **Warnings**]*.

4. Inform caregivers that reports of convulsions have been observed in patients receiving GnRH agonists. Patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions may be at increased risk *[see **Warnings**]*.

5. During the first month of treatment with SYNAREL, some signs of puberty, e.g., vaginal bleeding or breast enlargement, may occur. This is the expected initial effect of the drug. Such changes should resolve soon after the first month. lf such resolution does not occur within the first two months of treatment, this may be due to lack of compliance or the presence of gonadotropin independent sexual precocity. If both possibilities are definitively excluded, the dose of SYNAREL may be increased to 1800 μg/day administered as 600 μg tid.

6. Patients with intercurrent rhinitis should consult their physician for the use of a topical nasal decongestant. If the use of a topical nasal decongestant is required during treatment with SYNAREL, the decongestant should not be used until at least 2 hours following dosing with SYNAREL.

Sneezing during or immediately after dosing with SYNAREL should be avoided, if possible, since this may impair drug absorption.

Drug Interactions
No pharmacokinetic-based drug-drug interaction studies have been conducted with SYNAREL. However, because nafarelin acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes, and the drug is only about 80% bound to plasma proteins at 4°C, drug interactions would not be expected to occur.

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenicity studies of nafarelin were conducted in rats (24 months) at doses up to 100 µg/kg/day and mice (18 months) at doses up to 500 µg/kg/day using intramuscular doses (up to 110 times and 560 times the maximum recommended human intranasal dose, respectively). These multiples of the human dose are based on the relative bioavailability of the drug by the two routes of administration. As seen with other GnRH agonists, nafarelin acetate given to laboratory rodents at high doses for prolonged periods induced proliferative responses (hyperplasia and/or neoplasia) of endocrine organs. At 24 months, there was an increase in the incidence of pituitary tumors (adenoma/carcinoma) in high-dose female rats and a dose-related increase in male rats. There was an increase in pancreatic islet cell adenomas in both sexes, and in benign testicular and ovarian tumors in the treated groups. There was a dose-related increase in benign adrenal medullary tumors in treated female rats. In mice, there was a dose-related increase in Harderian gland tumors in males and an increase in pituitary adenomas in high-dose females. No metastases of these tumors were observed. It is known that tumorigenicity in rodents is particularly sensitive to hormonal stimulation.

Mutagenicity studies were performed with nafarelin acetate using bacterial, yeast, and mammalian systems. These studies provided no evidence of mutagenic potential.

Reproduction studies in male and female rats have shown full reversibility of fertility suppression when drug treatment was discontinued after continuous administration for up to 6 months. The effect of treatment of prepubertal rats on the subsequent reproductive performance of mature animals has not been investigated.

Pregnancy
Teratogenic Effects
See ***Contraindications***. Intramuscular SYNAREL was administered to rats during the period of organogenesis at 0.4, 1.6, and 6.4 µg/kg/day (about 0.5, 2, and 7 times the maximum recommended human intranasal dose based on the relative bioavailability by the two routes of administration). An increase in major fetal abnormalities was observed in 4/80 fetuses at the highest dose. A similar, repeat study at the same doses in rats and studies in mice and rabbits at doses up to 600 µg/kg/day and 0.18 µg/kg/day, respectively, failed to demonstrate an increase in fetal abnormalities after administration during the period of organogenesis. In rats and rabbits, there was a dose-related increase in fetal mortality and a decrease in fetal weight with the highest dose.

Nursing Mothers
It is not known whether SYNAREL is excreted in human milk. Because many drugs are excreted in human milk, and because the effects of SYNAREL on lactation and/or the breastfed child have not been determined, SYNAREL should not be used by nursing mothers.

ADVERSE REACTIONS

In clinical trials of 155 pediatric patients, 2.6% reported symptoms suggestive of drug sensitivity, such as shortness of breath, chest pain, urticaria, rash, and pruritus.

In these 155 patients treated for an average of 41 months and as long as 80 months (6.7 years), adverse events most frequently reported (>3% of patients) consisted largely of episodes occurring during the first 6 weeks of treatment as a result of the transient stimulatory action of nafarelin upon the pituitary-gonadal axis:

acne (10%)
transient breast enlargement (8%)
vaginal bleeding (8%)
emotional lability (6%) *[see **Warnings**]*
transient increase in pubic hair (5%)
body odor (4%)
seborrhea (3%)

Hot flashes, common in adult women treated for endometriosis, occurred in only 3% of treated children and were transient. Other adverse events thought to be drug-related, and occurring in >3% of patients were rhinitis (5%) and white or brownish vaginal discharge (3%). Approximately 3% of patients withdrew from clinical trials due to adverse events.

In one male patient with concomitant congenital adrenal hyperplasia, and who had discontinued treatment 8 months previously to resume puberty, adrenal rest tumors were found in the left testis. Relationship to SYNAREL is unlikely.

Regular examinations of the pituitary gland by magnetic resonance imaging (MRI) or computer assisted tomography (CT) of children during long-term nafarelin therapy as well as during the post-treatment period has occasionally revealed changes in the shape and size of the pituitary gland. These changes include asymmetry and enlargement of the pituitary gland, and a pituitary microadenoma has been suspected in a few children. The relationship of these findings to SYNAREL is not known.

Post-Marketing
Pituitary apoplexy: During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed, with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes,

ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

Psychiatric adverse events: Emotional lability, such as crying, irritability, impatience, anger, and aggression has been observed with GnRH agonists *[see **Warnings**]*; Depression, including rare reports of suicidal ideation and attempt, has been reported for GnRH agonists in children treated for central precocious puberty. Many, but not all, of these patients had a history of psychiatric illness or other comorbidities with an increased risk of depression.

Central/peripheral nervous adverse events: Convulsion.

OVERDOSAGE

In experimental animals, a single subcutaneous administration of up to 60 times the recommended human dose (on a µg/kg basis, not adjusted for bioavailability) had no adverse effects. At present, there is no clinical evidence of adverse effects following overdosage of GnRH analogs.

Based on studies in monkeys, SYNAREL is not absorbed after oral administration.

DOSAGE AND ADMINISTRATION

For the treatment of central precocious puberty (CPP), the recommended daily dose of SYNAREL is 1600 µg. The dose can be increased to 1800 µg daily if adequate suppression cannot be achieved at 1600 µg/day.

The 1600 µg dose is achieved by two sprays (400 µg) into each nostril in the morning (4 sprays) and two sprays into each nostril in the evening (4 sprays), a total of 8 sprays per day. The 1800 µg dose is achieved by 3 sprays (600 µg) into alternating nostrils three times a day, a total of 9 sprays per day. The patient's head should be tilted back slightly, and 30 seconds should elapse between sprays.

If the prescribed therapy has been well tolerated by the patient, treatment of CPP with SYNAREL should continue until resumption of puberty is desired.

There appeared to be no significant effect of rhinitis, i.e., nasal congestion, on the systemic bioavailability of SYNAREL; however, if the use of a nasal decongestant for rhinitis is necessary during treatment with SYNAREL, the decongestant should not be used until at least 2 hours following dosing with SYNAREL.

Sneezing during or immediately after dosing with SYNAREL should be avoided, if possible, since this may impair drug absorption.

At 1600 µg/day, a bottle of SYNAREL provides about a 7-day supply (about 56 sprays). If the daily dose is increased, increase the supply to the patient to ensure uninterrupted treatment for the duration of therapy.

HOW SUPPLIED

Each 0.5 ounce bottle (NDC 0025-0166-08) contains 8 mL SYNAREL (nafarelin acetate) Nasal Solution 2 mg/mL (as nafarelin base), and is supplied with a metered spray pump that delivers 200 µg of nafarelin per spray. A dust cover and a leaflet of patient instructions are also included.

Store upright at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from light.

Distributed by

Pfizer Labs

Division of Pfizer Inc, NY, NY 10017

LAB-1048-3.0
Revised: December 2020

Synarel®

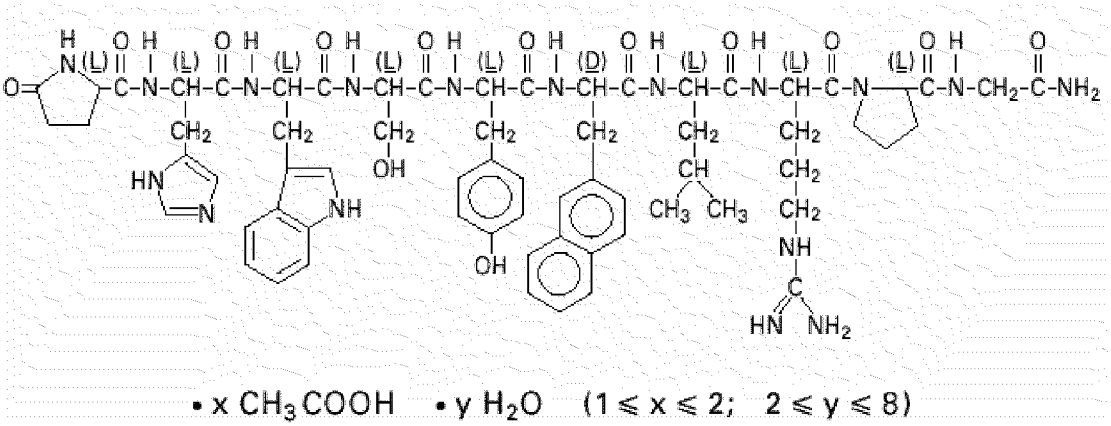
(nafarelin acetate)
nasal solution

ENDOMETRIOSIS
(FOR CENTRAL PRECOCIOUS PUBERTY, SEE REVERSE SIDE)

PHYSICIAN LABELING

DESCRIPTION

SYNAREL (nafarelin acetate) Nasal Solution is intended for administration as a spray to the nasal mucosa. Nafarelin acetate, the active component of SYNAREL Nasal Solution, is a decapeptide with the chemical name: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-3-(2-naphthyl)-D-alanyl-L-leucyl-L-arginyl-L-prolyl-glycinamide acetate. Nafarelin acetate is a synthetic analog of the naturally occurring gonadotropin-releasing hormone (GnRH).
Nafarelin acetate has the following chemical structure:



SYNAREL Nasal Solution contains nafarelin acetate (2 mg/mL, content expressed as nafarelin base) in a solution of benzalkonium chloride, glacial acetic acid, sodium hydroxide or hydrochloric acid (to adjust pH), sorbitol, and purified water.

After priming the pump unit for SYNAREL, each actuation of the unit delivers approximately 100 µL of the spray containing approximately 200 µg nafarelin base. The contents of one spray bottle are intended to deliver at least 60 sprays.

CLINICAL PHARMACOLOGY

Nafarelin acetate is a potent agonistic analog of gonadotropin-releasing hormone (GnRH). At the onset of administration, nafarelin stimulates the release of the pituitary gonadotropins, LH and FSH, resulting in a temporary increase of ovarian steroidogenesis. Repeated dosing abolishes the stimulatory effect on the pituitary gland. Twice daily

administration leads to decreased secretion of gonadal steroids by about 4 weeks; consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent.

Nafarelin acetate is rapidly absorbed into the systemic circulation after intranasal administration. Maximum serum concentrations (measured by RIA) were achieved between 10 and 40 minutes. Following a single dose of 200 µg base, the observed average peak concentration was 0.6 ng/mL (range 0.2 to 1.4 ng/mL), whereas following a single dose of 400 µg base, the observed average peak concentration was 1.8 ng/mL (range 0.5 to 5.3 ng/mL). Bioavailability from a 400 µg dose averaged 2.8% (range 1.2 to 5.6%). The average serum half-life of nafarelin following intranasal administration is approximately 3 hours. About 80% of nafarelin acetate is bound to plasma proteins at 4°C. Twice daily intranasal administration of 200 or 400 µg of SYNAREL in 18 healthy women for 22 days did not lead to significant accumulation of the drug. Based on the mean C_{min} levels on Days 15 and 22, there appeared to be dose proportionality across the two dose levels.

After subcutaneous administration of ^{14}C-nafarelin acetate to men, 44–55% of the dose was recovered in urine and 18.5–44.2% was recovered in feces. Approximately 3% of the administered dose appeared as unchanged nafarelin in urine. The ^{14}C serum half-life of the metabolites was about 85.5 hours. Six metabolites of nafarelin have been identified of which the major metabolite is Tyr-D(2)-Nal-Leu-Arg-Pro-Gly-NH_2(5-10). The activity of the metabolites, the metabolism of nafarelin by nasal mucosa, and the pharmacokinetics of the drug in hepatically- and renally-impaired patients have not been determined.

There appeared to be no significant effect of rhinitis, i.e., nasal congestion, on the systemic bioavailability of SYNAREL; however, if the use of a nasal decongestant for rhinitis is necessary during treatment with SYNAREL, the decongestant should not be used until at least 2 hours following dosing of SYNAREL.

In controlled clinical studies, SYNAREL at doses of 400 and 800 µg/day for 6 months was shown to be comparable to danazol, 800 mg/day, in relieving the clinical symptoms of endometriosis (pelvic pain, dysmenorrhea, and dyspareunia) and in reducing the size of endometrial implants as determined by laparoscopy. The clinical significance of a decrease in endometriotic lesions is not known at this time and, in addition, laparoscopic staging of endometriosis does not necessarily correlate with severity of symptoms.

In a single controlled clinical trial, intranasal SYNAREL (nafarelin acetate) at a dose of 400 µg per day was shown to be clinically comparable to intramuscular leuprolide depot, 3.75 mg monthly, for the treatment of the symptoms (dysmenorrhea, dyspareunia and pelvic pain) associated with endometriosis.

SYNAREL 400 µg daily induced amenorrhea in approximately 65%, 80%, and 90% of the patients after 60, 90, and 120 days, respectively. In the first, second, and third post-treatment months, normal menstrual cycles resumed in 4%, 82%, and 100%, respectively, of those patients who did not become pregnant.

At the end of treatment, 60% of patients who received SYNAREL, 400 µg/day, were symptom free, 32% had mild symptoms, 7% had moderate symptoms, and 1% had severe symptoms. Of the 60% of patients who had complete relief of symptoms at the end of treatment, 17% had moderate symptoms 6 months after treatment was discontinued, 33% had mild symptoms, 50% remained symptom free, and no patient had severe symptoms.

During the first two months use of SYNAREL, some women experience vaginal bleeding of variable duration and intensity. In all likelihood, this bleeding represents estrogen withdrawal bleeding and is expected to stop spontaneously. If vaginal bleeding continues, the possibility of lack of compliance with the dosing regimen should be considered. If the patient is complying carefully with the regimen, an increase in dose to 400 µg twice a day should be considered.

There is no evidence that pregnancy rates are enhanced or adversely affected by the use of SYNAREL.

INDICATIONS AND USAGE FOR ENDOMETRIOSIS

(For Central Precocious Puberty, See *Reverse Side*)

SYNAREL is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. Experience with SYNAREL for the management of endometriosis has been limited to women 18 years of age and older treated for 6 months.

CONTRAINDICATIONS

1. Hypersensitivity to GnRH, GnRH agonist analogs or any of the excipients in SYNAREL;
2. Undiagnosed abnormal vaginal bleeding;
3. Use in pregnancy or in women who may become pregnant while receiving the drug. SYNAREL may cause fetal harm when administered to a pregnant woman. Major fetal abnormalities were observed in rats, but not in mice or rabbits after administration of SYNAREL during the period of organogenesis. There was a dose-related increase in fetal mortality and a decrease in fetal weight in rats *[see **Pregnancy**]*. The effects on rat fetal mortality are expected consequences of the alterations in hormonal levels brought about by the drug. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus;
4. Use in women who are breast-feeding *[see **Nursing Mothers**]*.

WARNINGS

Safe use of nafarelin acetate in pregnancy has not been established clinically. Before starting treatment with SYNAREL, pregnancy must be excluded.

When used regularly at the recommended dose, SYNAREL usually inhibits ovulation and stops menstruation. Contraception is not insured, however, by taking SYNAREL, particularly if patients miss successive doses. Therefore, patients should use nonhormonal methods of contraception. Patients should be advised to see their physician if they believe they may be pregnant. If a patient becomes pregnant during treatment, the drug must be discontinued and the patient must be apprised of the potential risk to the fetus.

PRECAUTIONS

General

As with other drugs that stimulate the release of gonadotropins or that induce ovulation, ovarian cysts have been reported to occur in the first two months of therapy with SYNAREL. Many, but not all, of these events occurred in patients with polycystic ovarian disease. These cystic enlargements may resolve spontaneously, generally by about four to six weeks of therapy, but in some cases may require discontinuation of drug and/or surgical intervention.

Information for Patients

An information pamphlet for patients is included with the product. Patients should be aware of the following information:

1. Since menstruation should stop with effective doses of SYNAREL, the patient should notify her physician if regular menstruation persists. The cause of vaginal spotting, bleeding or menstruation could be noncompliance with the treatment regimen, or it could be that a higher dose of the drug is required to achieve amenorrhea. The patient should be questioned regarding her compliance. If she is careful and compliant, and menstruation persists to the second month, consideration should be given to doubling the dose of SYNAREL. If the patient has missed several doses, she should be counseled on the importance of taking SYNAREL regularly as prescribed.

2. Patients should not use SYNAREL if they are pregnant, breastfeeding, have undiagnosed abnormal vaginal bleeding, or are allergic to any of the ingredients in SYNAREL.

3. Safe use of the drug in pregnancy has not been established clinically. Therefore, a nonhormonal method of contraception should be used during treatment. Patients should be advised that if they miss successive doses of SYNAREL, breakthrough bleeding or ovulation may occur with the potential for conception. If a patient becomes pregnant during treatment, she should discontinue treatment and consult her physician.

4. Those adverse events occurring most frequently in clinical studies with SYNAREL are associated with hypoestrogenism; the most frequently reported are hot flashes, headaches, emotional lability, decreased libido, vaginal dryness, acne, myalgia, and reduction in breast size. Estrogen levels returned to normal after treatment was discontinued. Nasal irritation occurred in about 10% of all patients who used intranasal nafarelin.

5. The induced hypoestrogenic state results in a small loss in bone density over the course of treatment, some of which may not be reversible. During one six-month treatment period, this bone loss should not be important. In patients with major risk factors for decreased bone mineral content such as chronic alcohol and/or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, therapy with SYNAREL may pose an additional risk. In these patients the risks and benefits must be weighed carefully before therapy with SYNAREL is instituted. Repeated courses of treatment with gonadotropin-releasing

hormone analogs are not advisable in patients with major risk factors for loss of bone mineral content.

6. Patients with intercurrent rhinitis should consult their physician for the use of a topical nasal decongestant. If the use of a topical nasal decongestant is required during treatment with SYNAREL, the decongestant should not be used until at least 2 hours following dosing with SYNAREL.

Sneezing during or immediately after dosing with SYNAREL should be avoided, if possible, since this may impair drug absorption.

7. Retreatment cannot be recommended since safety data beyond 6 months are not available.

Drug Interactions
No pharmacokinetic-based drug-drug interaction studies have been conducted with SYNAREL. However, because nafarelin acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes, and the drug is only about 80% bound to plasma proteins at 4°C, drug interactions would not be expected to occur.

Drug/Laboratory Test Interactions
Administration of SYNAREL in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within 4 to 8 weeks after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and up to 4 to 8 weeks after discontinuation of therapy with SYNAREL may be misleading.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies of nafarelin were conducted in rats (24 months) at doses up to 100 µg/kg/day and mice (18 months) at doses up to 500 µg/kg/day using intramuscular doses (up to 110 times and 560 times the maximum recommended human intranasal dose, respectively). These multiples of the human dose are based on the relative bioavailability of the drug by the two routes of administration. As seen with other GnRH agonists, nafarelin acetate given to laboratory rodents at high doses for prolonged periods induced proliferative responses (hyperplasia and/or neoplasia) of endocrine organs. At 24 months, there was an increase in the incidence of pituitary tumors (adenoma/carcinoma) in high-dose female rats and a dose-related increase in male rats. There was an increase in pancreatic islet cell adenomas in both sexes, and in benign testicular and ovarian tumors in the treated groups. There was a dose-related increase in benign adrenal medullary tumors in treated female rats. In mice, there was a dose-related increase in Harderian gland tumors in males and an increase in pituitary adenomas in high-dose females. No metastases of these tumors were observed. It is known that tumorigenicity in rodents is particularly sensitive to hormonal stimulation.

Mutagenicity studies were performed with nafarelin acetate using bacterial, yeast, and mammalian systems. These studies provided no evidence of mutagenic potential.

Reproduction studies in male and female rats have shown full reversibility of fertility suppression when drug treatment was discontinued after continuous administration for up to 6 months. The effect of treatment of prepubertal rats on the subsequent reproductive performance of mature animals has not been investigated.

Pregnancy

Teratogenic Effects

See ***Contraindications***. Intramuscular SYNAREL was administered to rats during the period of organogenesis at 0.4, 1.6, and 6.4 µg/kg/day (about 0.5, 2, and 7 times the maximum recommended human intranasal dose based on the relative bioavailability by the two routes of administration). An increase in major fetal abnormalities was observed in 4/80 fetuses at the highest dose. A similar, repeat study at the same doses in rats and studies in mice and rabbits at doses up to 600 µg/kg/day and 0.18 µg/kg/day, respectively, failed to demonstrate an increase in fetal abnormalities after administration during the period of organogenesis. In rats and rabbits, there was a dose-related increase in fetal mortality and a decrease in fetal weight with the highest dose.

Nursing Mothers

It is not known whether SYNAREL is excreted in human milk. Because many drugs are excreted in human milk, and because the effects of SYNAREL on lactation and/or the breastfed child have not been determined, SYNAREL should not be used by nursing mothers.

Pediatric Use

Safety and effectiveness of SYNAREL for endometriosis in patients younger than 18 years have not been established.

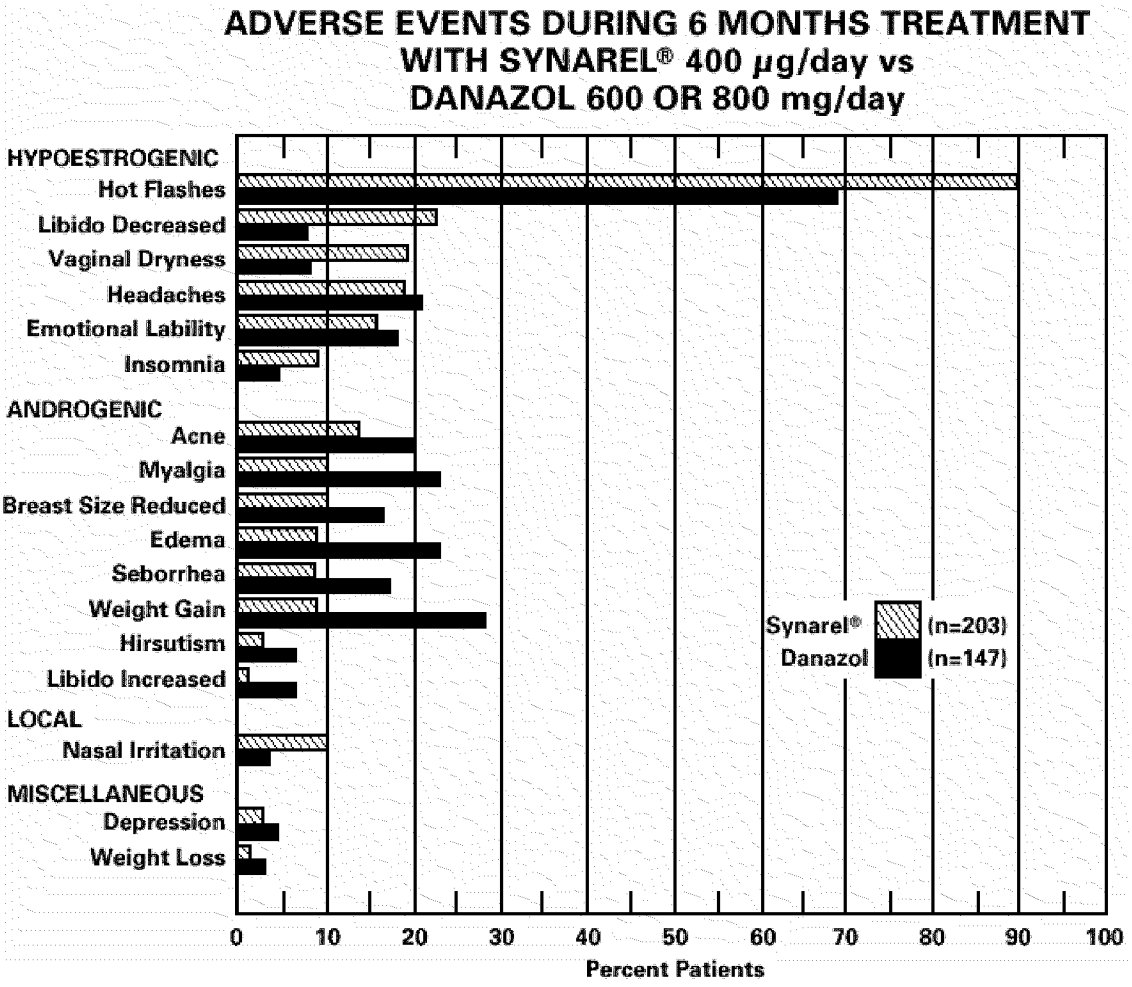
ADVERSE REACTIONS

Clinical Studies

In formal clinical trials of 1509 healthy adult patients, symptoms suggestive of drug sensitivity, such as shortness of breath, chest pain, urticaria, rash and pruritus occurred in 3 patients (approximately 0.2%).

As would be expected with a drug which lowers serum estradiol levels, the most frequently reported adverse reactions were those related to hypoestrogenism.

In controlled studies comparing SYNAREL (400 µg/day) and danazol (600 or 800 mg/day), adverse reactions most frequently reported and thought to be drug-related are shown in the figure below:



In addition, less than 1% of patients experienced paresthesia, palpitations, chloasma, maculopapular rash, eye pain, asthenia, lactation, breast engorgement, and arthralgia.

Changes in Bone Density

After six months of treatment with SYNAREL, vertebral trabecular bone density and total vertebral bone mass, measured by quantitative computed tomography (QCT), decreased by an average of 8.7% and 4.3%, respectively, compared to pretreatment levels. There was partial recovery of bone density in the post-treatment period; the average trabecular bone density and total bone mass were 4.9% and 3.3% less than the pretreatment levels, respectively. Total vertebral bone mass, measured by dual photon absorptiometry (DPA), decreased by a mean of 5.9% at the end of treatment.

After six months treatment with SYNAREL, bone mass as measured by dual x-ray bone densitometry (DEXA), decreased 3.2%. Mean total vertebral mass, re-examined by DEXA six months after completion of treatment, was 1.4% below pretreatment. There was little, if any, decrease in the mineral content in compact bone of the distal radius and second metacarpal. Use of SYNAREL for longer than the recommended six months or in the presence of other known risk factors for decreased bone mineral content may cause additional bone loss.

Changes in Laboratory Values During Treatment

Plasma enzymes. During clinical trials with SYNAREL, regular laboratory monitoring revealed that SGOT and SGPT levels were more than twice the upper limit of normal in only one patient each. There was no other clinical or laboratory evidence of abnormal liver function and levels returned to normal in both patients after treatment was stopped.

Lipids. At enrollment, 9% of the patients in the group taking SYNAREL 400 μg/day and 2% of the patients in the danazol group had total cholesterol values above 250 mg/dL. These patients also had cholesterol values above 250 mg/dL at the end of treatment.

Of those patients whose pretreatment cholesterol values were below 250 mg/dL, 6% in the group treated with SYNAREL and 18% in the danazol group, had post-treatment values above 250 mg/dL.

The mean (± SEM) pretreatment values for total cholesterol from all patients were 191.8 (4.3) mg/dL in the group treated with SYNAREL and 193.1 (4.6) mg/dL in the danazol group. At the end of treatment, the mean values for total cholesterol from all patients were 204.5 (4.8) mg/dL in the group treated with SYNAREL and 207.7 (5.1) mg/dL in the danazol group. These increases from the pretreatment values were statistically significant ($p<0.05$) in both groups.

Triglycerides were increased above the upper limit of 150 mg/dL in 12% of the patients who received SYNAREL and in 7% of the patients who received danazol.

At the end of treatment, no patients receiving SYNAREL had abnormally low HDL cholesterol fractions (less than 30 mg/dL) compared with 43% of patients receiving danazol. None of the patients receiving SYNAREL had abnormally high LDL cholesterol fractions (greater than 190 mg/dL) compared with 15% of those receiving danazol. There was no increase in the LDL/HDL ratio in patients receiving SYNAREL, but there was approximately a 2-fold increase in the LDL/HDL ratio in patients receiving danazol.

Other changes. In comparative studies, the following changes were seen in approximately 10% to 15% of patients. Treatment with SYNAREL was associated with elevations of plasma phosphorus and eosinophil counts, and decreases in serum calcium and WBC counts. Danazol therapy was associated with an increase of hematocrit and WBC.

Post-Marketing

Pituitary apoplexy: During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed, with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

Cardiovascular adverse events: Cases of serious venous and arterial thromboembolism have been reported, including deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, and transient ischemic attack. Although a temporal relationship was reported in some cases, most cases were confounded by risk factors or concomitant medication use. It is unknown if there is a causal association between the use of GnRH analogs and these events.

Central/peripheral nervous adverse events: Convulsion.
Hepatic adverse events: Rarely reported serious liver injury.
Reproductive system adverse events: Cases of ovarian hyperstimulation syndrome have been reported with Synarel monotherapy when used for Assisted Reproductive Technology which is not an approved indication.

OVERDOSAGE

In experimental animals, a single subcutaneous administration of up to 60 times the recommended human dose (on a µg/kg basis, not adjusted for bioavailability) had no adverse effects. At present, there is no clinical evidence of adverse effects following overdosage of GnRH analogs.

Based on studies in monkeys, SYNAREL is not absorbed after oral administration.

DOSAGE AND ADMINISTRATION

For the management of endometriosis, the recommended daily dose of SYNAREL is 400 µg. This is achieved by one spray (200 µg) into one nostril in the morning and one spray into the other nostril in the evening. Treatment should be started between days 2 and 4 of the menstrual cycle.

In an occasional patient, the 400 µg daily dose may not produce amenorrhea. For these patients with persistent regular menstruation after 2 months of treatment, the dose of SYNAREL may be increased to 800 µg daily. The 800 µg dose is administered as one spray into each nostril in the morning (a total of two sprays) and again in the evening.

The recommended duration of administration is six months. Retreatment cannot be recommended since safety data for retreatment are not available. If the symptoms of endometriosis recur after a course of therapy, and further treatment with SYNAREL is contemplated, it is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits.

There appeared to be no significant effect of rhinitis, i.e., nasal congestion, on the systemic bioavailability of SYNAREL; however, if the use of a nasal decongestant for rhinitis is necessary during treatment with SYNAREL, the decongestant should not be used until at least 2 hours following dosing with SYNAREL.

Sneezing during or immediately after dosing with SYNAREL should be avoided, if possible, since this may impair drug absorption.

At 400 µg/day, a bottle of SYNAREL provides a 30-day (about 60 sprays) supply. If the daily dose is increased, increase the supply to the patient to ensure uninterrupted treatment for the recommended duration of therapy.

HOW SUPPLIED

Each 0.5 ounce bottle (NDC 0025-0166-08) contains 8 mL SYNAREL (nafarelin acetate) Nasal Solution 2 mg/mL (as nafarelin base), and is supplied with a metered spray pump that delivers 200 µg of nafarelin per spray. A dust cover and a leaflet of patient instructions are also included.

Store upright at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from light.

Distributed by

Pfizer Labs

Division of Pfizer Inc, NY, NY 10017

LAB-0173-11.0
Revised: December 2020

SYNAREL
nafarelin acetate
Nasal Spray

Patient Instructions for Use

Introduction

Your doctor has prescribed SYNAREL Nasal Solution to treat your symptoms of endometriosis. This pamphlet has two purposes:

1.) to review information your doctor has given you about SYNAREL; and
2.) to give you information about how to use SYNAREL properly.

Please read this pamphlet carefully. If you still have questions after reading it or if you have questions at any time during your treatment with SYNAREL, be sure to check with your doctor.

SYNAREL is used to relieve the symptoms of endometriosis. The lining of the uterus is called the endometrium, and part of it is shed during menses. In endometriosis, endometrial tissue is also found outside the uterus and, like normal endometrial tissue, can bleed during a menstrual cycle. It is, in part, this monthly activity that causes you to have symptoms during your cycle. Most often, this out-of-place endometrial tissue is found around the uterus, ovaries, the intestine or other organs in the pelvis. Although some women with endometriosis have no symptoms, many have problems such as severe menstrual cramps, pain during sexual intercourse, low back pain, and painful bowel movements.

Endometrial tissue is affected by the body's hormones, especially estrogen, which is made by the ovaries. When estrogen levels are low, endometrial tissue shrinks (perhaps even disappears), and symptoms of endometriosis ease. SYNAREL temporarily reduces estrogen in the body and temporarily relieves the symptoms of endometriosis.

Important Information about SYNAREL

1. You should **not** use SYNAREL if
    - you are pregnant.
    - you are breast feeding.
    - you have abnormal vaginal bleeding that has not been checked into by your doctor.
    - you are allergic to any of the ingredients of SYNAREL (nafarelin acetate, benzalkonium chloride, acetic acid, sodium hydroxide, hydrochloric acid, sorbitol, purified water).
2. SYNAREL is a prescription medicine that should be used according to your doctor's directions. SYNAREL comes as a special nasal spray that gives a measured amount of medicine. To be effective, SYNAREL must be used every day, twice a day, for the whole treatment period.

3. It is important to use a non-hormonal method of contraception (such as diaphragm with contraceptive jelly, IUD, condoms) while taking SYNAREL. You should not use birth control pills while taking SYNAREL.
4. If you miss 1 or more doses of SYNAREL, vaginal bleeding (often called breakthrough bleeding) may occur. If you miss successive doses of SYNAREL and have not been using contraception as described above, release of an egg from the ovary (ovulation) may occur, with the possibility of pregnancy. Under these circumstances you must see your physician to make sure you are not pregnant. If you should become pregnant while using SYNAREL, you must discuss the possible risks to the fetus and the choices available to you with your physician.
5. Because SYNAREL works by temporarily reducing the body's production of estrogen, a female hormone produced by the ovary, you may have some of the same changes that normally occur at the time of menopause, when the body's production of estrogen naturally decreases. For the first two months after you start using SYNAREL, you may experience some irregular vaginal spotting or bleeding. The duration and intensity of this bleeding may vary; it may be similar to your usual menstruation, or it may be lighter or heavier. The duration may also vary from brief to prolonged. In any case, you can expect this bleeding to stop by itself. After the first two months of treatment with SYNAREL, you can expect a decrease in menstrual flow, and your periods may stop altogether. However, if you miss one or more doses of SYNAREL, you may continue to experience vaginal bleeding. If you continue to experience normal menstrual cycles after two months use of SYNAREL, you should see your doctor about the continued periods. Other changes due to decreased estrogen include hot flashes, vaginal dryness, headaches, mood changes, and decreased interest in sex. Most of these changes are caused by low estrogen levels and may occur during treatment with SYNAREL. Some patients may also experience acne, muscle pain, reduced breast size, and irritation of the tissues inside the nose. These symptoms should disappear after you stop taking the drug.
6. When you take SYNAREL, your estrogen levels will be low. Low estrogen levels can result in a small loss of mineral from bone, some of which may not be reversible. During one six-month treatment period, this small loss of mineral from bone should not be important. There are certain conditions that may increase the possibility of the thinning of your bones when you take a drug such as SYNAREL. They are:
    - excessive use of alcohol;
    - smoking;
    - family history of osteoporosis (thinning of the bones with fractures);
    - taking other medications that can cause thinning of the bones.

    You should discuss the possibility of osteoporosis or thinning of the bones with your physician before starting SYNAREL. You should also be aware that repeat treatments are not recommended since they may

put you at greater risk of bone thinning, particularly if you have the above conditions.

7. During studies, menstruation usually resumed within 2 to 3 months of stopping treatment with SYNAREL. At the end of treatment 60% of patients treated with SYNAREL were symptom free, 32% had mild symptoms, 7% had moderate symptoms and 1% had severe symptoms.
   Of the 60% of patients who had complete relief of symptoms at the end of treatment, 17% had moderate symptoms at the end of the six month post-treatment period; 33% had mild symptoms; 50% were symptom free; no patient had severe symptoms.
8. Retreatment cannot be recommended since the safety of such retreatment is not known.
9. It is all right to use a nasal decongestant spray while you are being treated with SYNAREL if you follow these simple rules. Use SYNAREL first. Wait at least 2 hours after using SYNAREL before you use the decongestant spray.
10. You should avoid sneezing during or immediately after using SYNAREL, if possible, since sneezing may impair drug absorption.

Proper use of SYNAREL for Treatment of Endometriosis

1. When you start to use SYNAREL, the first dose should be taken between the second and fourth day after the beginning of your menstrual bleeding. You should continue taking SYNAREL every day as prescribed.
   Do not miss a single dose.
2. Unless your doctor has given you special instructions, follow the steps for using SYNAREL **twice each day**, about 12 hours between doses:
   - once in the morning in one nostril (for example, 7 a.m.)
   - once in the evening in the other nostril (for example, 7 p.m.)

   The length of treatment is usually about 6 months, unless your doctor has given you special instructions.
3. Because it is so important that you do not miss a single dose of SYNAREL, here are some suggestions to help you remember:
   - Keep your SYNAREL in a place where you will be reminded to use it each morning and each evening — next to your toothbrush is one possibility.
   - Keep track of each dose on a calendar.
   - Make a note on your calendar on the day you start a new bottle of SYNAREL. You can also mark the date you started right on the bottle. Be sure to refill your prescription before the 30 days are up so you will have a new bottle on hand.
4. A bottle of SYNAREL should not be used for longer than 30 days (60 sprays). Each bottle contains sufficient quantity of nasal solution for initial priming of the pump and 30 days (60 sprays) of treatment. At the end of 30 days, a small amount of liquid will be left in the bottle. **Do not try to use up that leftover amount** because you might get

too low a dose, which could interfere with the effectiveness of your treatment. Dispose of the bottle and do not reuse.

5. If your doctor increases your daily dose of SYNAREL, then your bottle will not last the standard 30 days. Please discuss this with your doctor to be sure that you have an adequate supply for uninterrupted treatment with SYNAREL to complete the recommended treatment period.

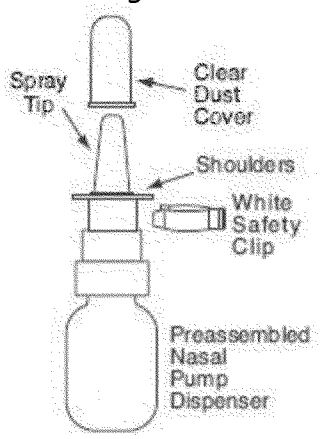
Preparation of the SYNAREL Nasal Spray unit
For use in your nose only.

Before you use SYNAREL nasal spray for the first time, you will need to prime it. This will ensure that you get the right dose of medicine each time you use it.

Important Tips about using SYNAREL

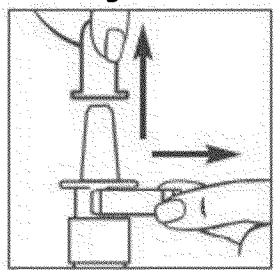
- Your pump should produce a fine mist, which can only happen by a quick and firm pumping action. It is normal to see some larger droplets of liquid within the fine mist. However, if SYNAREL comes out of the pump as a thin stream of liquid instead of a fine mist, SYNAREL may not work as well, and you should talk to your pharmacist.
- Be sure to clean the Spray Tip **before and after every use**. (See Step 4). Failure to do this may result in a clogged tip that may cause you not to get the right amount of medicine that is prescribed for you.
- The pump is made to deliver only a set amount of medicine, no matter how hard you pump it.
- **Do Not try to make the tiny hole in the spray tip larger**. If the hole is made larger the pump will deliver a wrong dose of SYNAREL.

Figure A



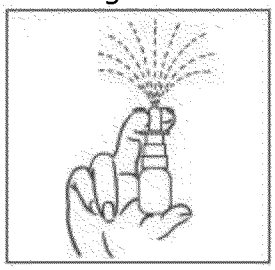
To Prime the Pump:

Figure B



1. Remove and save the white safety clip and the clear plastic dust cover from the spray bottle (See Figure B).

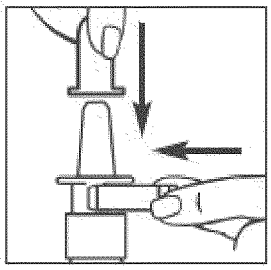
Figure C



2. Hold the bottle in an upright position away from you. Put two fingers on the "shoulders" of the spray bottle and put your thumb on the bottom of the bottle. Apply pressure **evenly** to the "shoulders" and push down **quickly and firmly** 7 to 10 times, until you see a fine spray. Usually you will see the spray after about 7 pumps. (See Figure C).

3. The pump is now primed**. Priming only needs to be done 1 time, when you start using a <u>new</u> bottle of SYNAREL**. You will waste your medicine if you prime the pump every time you use it and may not have enough medicine for 30 days of treatment.

Figure D

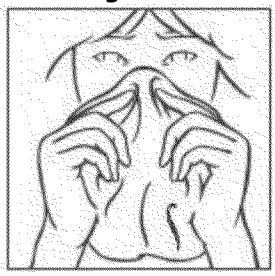


4. **Clean the Spray Tip after Priming:**
   - Hold the bottle in a horizontal position. Rinse the spray tip with **warm** water while wiping the tip with your finger or soft cloth for 15 seconds.
   - Wipe the spray tip with a soft cloth or tissue to dry.
   - Replace the white safety clip and the clear plastic dust cover on the spray bottle (See Figure D).
   - **Do Not** try to clean the spray tip using a pointed object. **Do Not** take apart the pump.

[SHAPE * MERGEFORMAT]

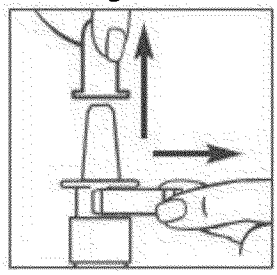
How to use the SYNAREL Nasal Spray unit for the treatment of Endometriosis

Figure E



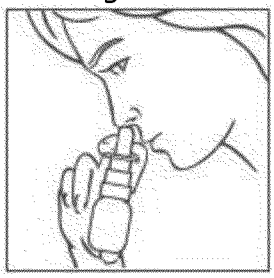
5. Gently blow your nose to clear both nostrils before you use SYNAREL nasal spray (See Figure E).

Figure F



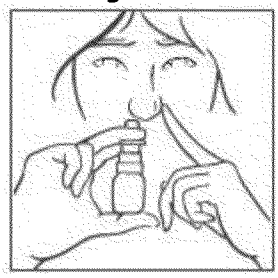
6. **Clean the Spray Tip.** Remove and save the white safety clip and the clear plastic dust cover from the spray bottle (See Figure F).
   - Hold the bottle in a horizontal position. Rinse the spray tip with **warm** water while wiping the tip with your finger or soft cloth for 15 seconds.
   - Wipe the spray tip with a soft cloth or tissue to dry.
   - **Do Not** try to clean the spray tip using a pointed object.
   - **Do Not** try to take apart the pump.

Figure G



7. Bend your head forward and put the spray tip into one nostril. The tip should **not** reach too far into your nose. Aim the spray tip toward the **back and outer side** of your nose (See Figure G).

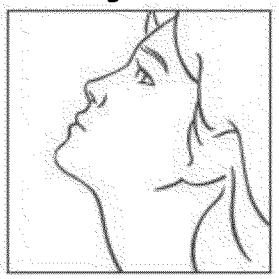
Figure H



8. Close the other nostril with your finger (See Figure H).

9. Apply pressure **evenly** to the "shoulders" and push down **quickly and firmly.** Pump the sprayer 1 time, at the same time as you sniff in gently. If the sprayer fails to deliver the dose clean the spray tip (See Step 6 **Clean the Spray Tip**).

Figure I



10. Remove the spray tip from your nose and tilt your head backwards for a few seconds. This lets the SYNAREL spray spread over the back of your nose (See Figure I).

    Do not spray in your other nostril unless your doctor has instructed you to do so.

Figure J
[SHAPE * MERGEFORMAT]

11. Clean the Spray Tip after use (See Step 4).

It is important that you clean the spray tip before and after every use. Failure to do this may result in a clogged tip that may cause you to get the wrong dose of medicine.

Important Reminder: Treatment with SYNAREL must be uninterrupted with no missed doses to be effective.

Make sure you use SYNAREL exactly as your doctor tells you. Make sure to note the date you start each bottle so you do not run out of medicine and miss doses.

Keep out of the reach of children and use carefully as directed.

Storage Instructions:

- Store SYNAREL at 59°F to 86°F (15°C to 30°C).
- Store the SYNAREL bottle upright.
- Keep SYNAREL out of the light.
- Do not freeze SYNAREL.

This product's label may have been updated. For current full prescribing information, please visit [HYPERLINK "http://www.pfizer.com"].

Distributed by

Pfizer Labs

Division of Pfizer Inc, NY, NY 10017

LAB-0278-7.0
Revised: December 2020

MEDICATION GUIDE
SYNAREL (sin-na-rell)
(nafarelin acetate) nasal solution

What is the most important information I should know about SYNAREL?

- Some people taking GnRH agonists like SYNAREL have had new or worsened mental (psychiatric) problems. Mental (psychiatric) problems may include emotional symptoms such as:
  - crying
  - irritability
  - restlessness (impatience)
  - anger
  - acting aggressive

Call your child's doctor right away if your child has any new or worsening mental symptoms or problems while taking SYNAREL

- Some people taking GnRH agonists like SYNAREL have had seizures. The risk of seizures may be higher in people who:
  - have a history of seizures.
  - have a history of epilepsy.
  - have a history of brain or brain vessel (cerebrovascular) problems or tumors.
  - are taking a medicine that has been connected to seizures such as taking bupropion or selective serotonin reuptake inhibitors (SSRIs).

Seizures have also happened in people who have not had any of these problems.

Call your child's doctor right away if your child has a seizure while taking SYNAREL.

What is SYNAREL?

SYNAREL is a gonadotropin releasing hormone (GnRH) medicine used for the treatment of children with central precocious puberty (CPP).

Do not give SYNAREL if your child:

- is allergic to gonadotropin releasing hormone (GnRH), GnRH agonist medicines, or any of the ingredients in SYNAREL. See the end of this Medication Guide for a complete list of ingredients in SYNAREL.
- has unusual vaginal bleeding that has not been checked by her doctor.
- is pregnant or may become pregnant. SYNAREL can cause birth defects or loss of the baby. If your child becomes pregnant call your doctor.
- is breastfeeding or plans to breastfeed. It is not known if SYNAREL passes into breast milk. You and your child's doctor should decide if your child will take SYNAREL or breastfeed. **Do not breastfeed while taking SYNAREL.**

Before your child takes SYNAREL, tell your doctor about all of your child's medical conditions, including if they:

- have a history of mental (psychiatric) problems.
- have or have had a history of seizures.
- have a history of epilepsy.
- have a history of brain or brain vessel (cerebrovascular) problems or tumors
- are taking a medicine that has been connected to seizures such as bupropion or selective serotonin reuptake inhibitors (SSRIs).

Tell your doctor about all the medicines your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should your child take SYNAREL?

- Your child's doctor should do tests to make sure your child has CPP before treating your child with SYNAREL.
- Keep all scheduled visits to the doctor. If scheduled doses are missed, your child may start having signs of puberty again. The doctor will do regular exams and blood tests to check for

signs of puberty.

- Take SYNAREL exactly as your doctor tells you to take it. See detailed **"Instructions for Use"** at the end of this Medication Guide for information about the right way to use SYNAREL.
- Your child's doctor will tell you how much SYNAREL your child is to take and when to take it. If your doctor increases your child's daily dose of SYNAREL, 1 bottle will not last the standard 7 days. Talk with your child's doctor to make sure your child has enough SYNAREL to take their prescribed dose every day.

What should your child avoid while taking SYNAREL?

- Your child should avoid sneezing while taking SYNAREL or right after using it, if possible. This could reduce the amount of medicine your child's body absorbs.
- If your child needs to use a nasal decongestant spray while being treated with SYNAREL, they should not use the decongestant spray for at least 2 hours after taking the dose of SYNAREL.

What are the possible side effects of SYNAREL?

SYNAREL may cause serious side effects, including:

- See **"What is the most important information I should know about SYNAREL"**
- in the first month of treatment, SYNAREL can cause an increase in some hormones. During this time you may notice more signs of puberty in your child, including vaginal bleeding and breast enlargement in girls. Within 1 month of treatment, you should see signs in your child that puberty is stopping.

The side effects of SYNAREL include:

- allergic reactions such as shortness of breath, chest pain, hives, rash, and itching
- acne
- temporary increase in pubic hair
- body odor
- flaky, scaly skin
- hot flashes
- stuffy or runny nose (rhinitis)
- white or brown vaginal discharge

These are not all of the possible side effects of SYNAREL. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General Information about the safe and effective use of SYNAREL.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SYNAREL for a condition for which it is not prescribed. Do not give SYNAREL to other people, even if they have the same symptoms that you have. It may harm them.
You can ask your doctor or pharmacist for information about SYNAREL that is written for health professionals.

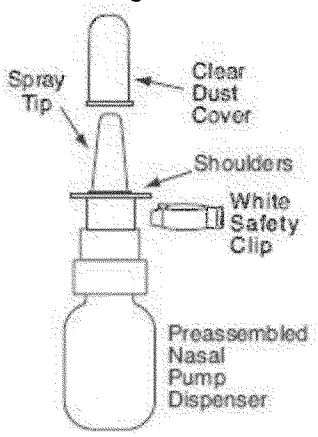
What are the ingredients in SYNAREL?

Active ingredient: nafarelin acetate
Inactive ingredients: benzalkonium chloride, glacial acetic acid, sodium hydroxide or hydrochloric acid (to adjust pH), sorbitol, and purified water

Instructions for Use
SYNAREL(sin-na-rell)
(nafarelin acetate)
nasal solution

For use in the nose only.

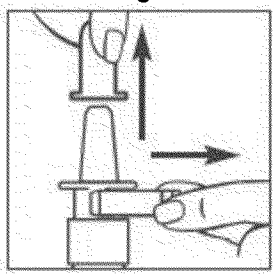
Figure A



Before you use SYNAREL nasal spray for the first time, you will need to prime it. This will make sure that you get the right dose of medicine each time you use it. Priming only needs to be done 1 time, when you start using a **new** bottle of SYNAREL.

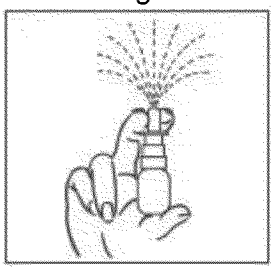
To Prime the Pump:

Figure B



1. Remove and save the white safety clip and the clear plastic dust cover from the spray bottle (See Figure B).

Figure C



2. Hold the bottle in an upright position away from you. Put 2 fingers on the “shoulders” of the spray bottle and put your thumb on the bottom of the bottle. Apply pressure **evenly** to the “shoulders” and push down **quickly and firmly** 7 to 10 times, until you see a fine mist spray. Usually you will see the spray after about 7 pumps. (See Figure C). The pump is now primed.

   It is normal to see some larger droplets of liquid within the fine mist. However, if SYNAREL comes out of the pump as a thin stream of liquid instead of a fine mist, SYNAREL may not work as well, and you should talk to your pharmacist.

Figure D

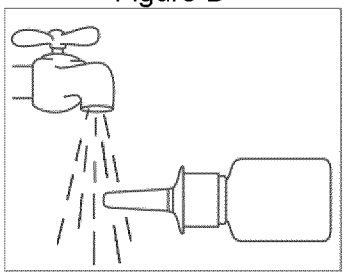
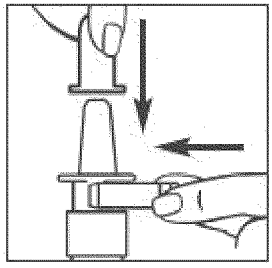


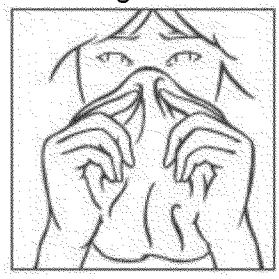
Figure E



3. **Clean the Spray Tip after Priming:**
   - Hold the bottle in sideways (horizontal) position (see Figure D).
     Rinse the “spray tip" with **warm** water while wiping the tip with your finger or soft cloth for 15 seconds.
   - Wipe the spray tip with a soft cloth or tissue to dry.
   - Replace the white safety clip and the clear plastic dust cover on the spray bottle. (See Figure E).
   - **Do not** try to clean the spray tip using a pointed object.
   - **Do not** take apart the pump.

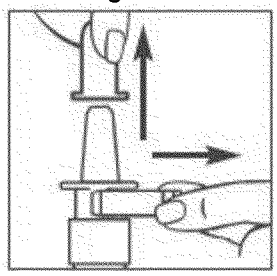
How to use the SYNAREL Nasal Spray for the treatment of Central Precocious Puberty

Figure F



4. Have your child blow their nose to clear both nostrils before using SYNAREL nasal spray (see Figure F). If the child is too young to blow their nose, you may need to clear the child's nostrils with a bulb syringe.

Figure G

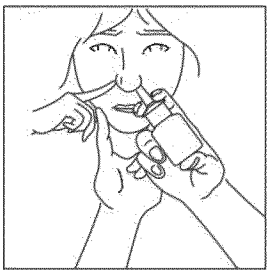


5. **Clean the Spray Tip each time before and after using SYNAREL.**
   - Remove and save the white safety clip and the clear plastic dust cover from the spray bottle (See Figure G).
   - Hold the bottle in sideways (horizontal) position. Rinse the spray tip with **warm** water while wiping the tip with your finger or soft cloth for 15 seconds.
   - Wipe the spray tip with a soft cloth or tissue to dry.
   - **Do not** try to clean the spray tip using a pointed object.
   - **Do not** try to take apart the pump.

Figure H

6. The child's head should be bent back a little and the spray tip put into one nostril. The tip should **not** reach too far into the nose. Aim the spray tip toward the **back and outer side** of the nose (See Figure H).

Figure I



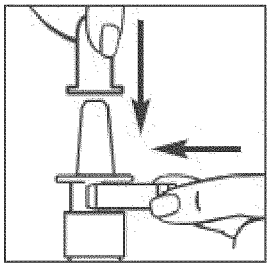
7. Close the other nostril with a finger (See Figure I).

Put pressure **evenly** to the "shoulders" and push down **quickly and firmly.** Pump the sprayer 1 time, at the same time as the child sniffs in gently. Wait about 30 seconds and put one more spray in the same nostril. Repeat this process in the other nostril, for a total of four sprays. If the sprayer fails to deliver the dose, clean the spray tip (See Step 5 **Clean the Spray Tip each time before and after using SYNAREL**).

Figure J

8. Remove the spray tip from the child's nose after all sprays are completed. Keep the child's head tilted back for a few seconds. This lets the SYNAREL spray spread over the back of the nose (See Figure J).

Figure K



9. Clean the Spray Tip after use (See Step 5. Put on the white safety clip and the clear plastic dust cover (see Figure K).

It is important that you clean the spray tip before and after every use. Not doing this may result in a clogged tip that may cause you to get the wrong dose of medicine.

How should I store SYNAREL?

- Store SYNAREL at room temperature between 59°F to 86°F (15°C to 30°C).
- Store the SYNAREL bottle upright.
- Keep SYNAREL out of the light.

Keep SYNAREL and all medicines out of the reach of children.

For more information call 1-800-438-1985.

This Medication Guide and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Manufactured for: Pfizer Inc., 235 East 42nd Street, New York, NY, 10017

Distributed by

Pfizer Labs

Division of Pfizer Inc, NY, NY 10017

LAB-1049-2.0
Revised: December 2020

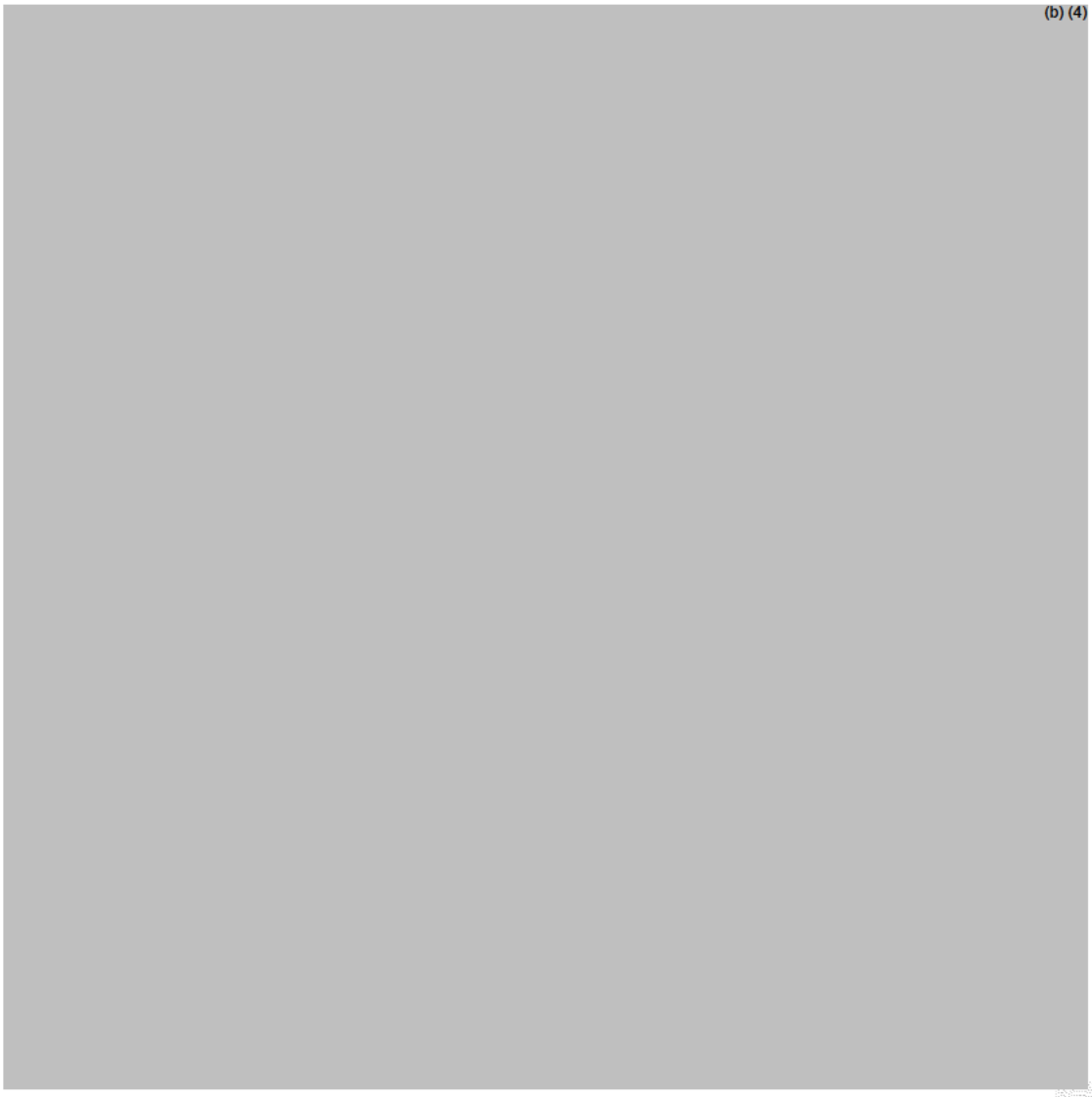
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUPRON DEPOT-PED safely and effectively. See full prescribing information for LUPRON DEPOT-PED.

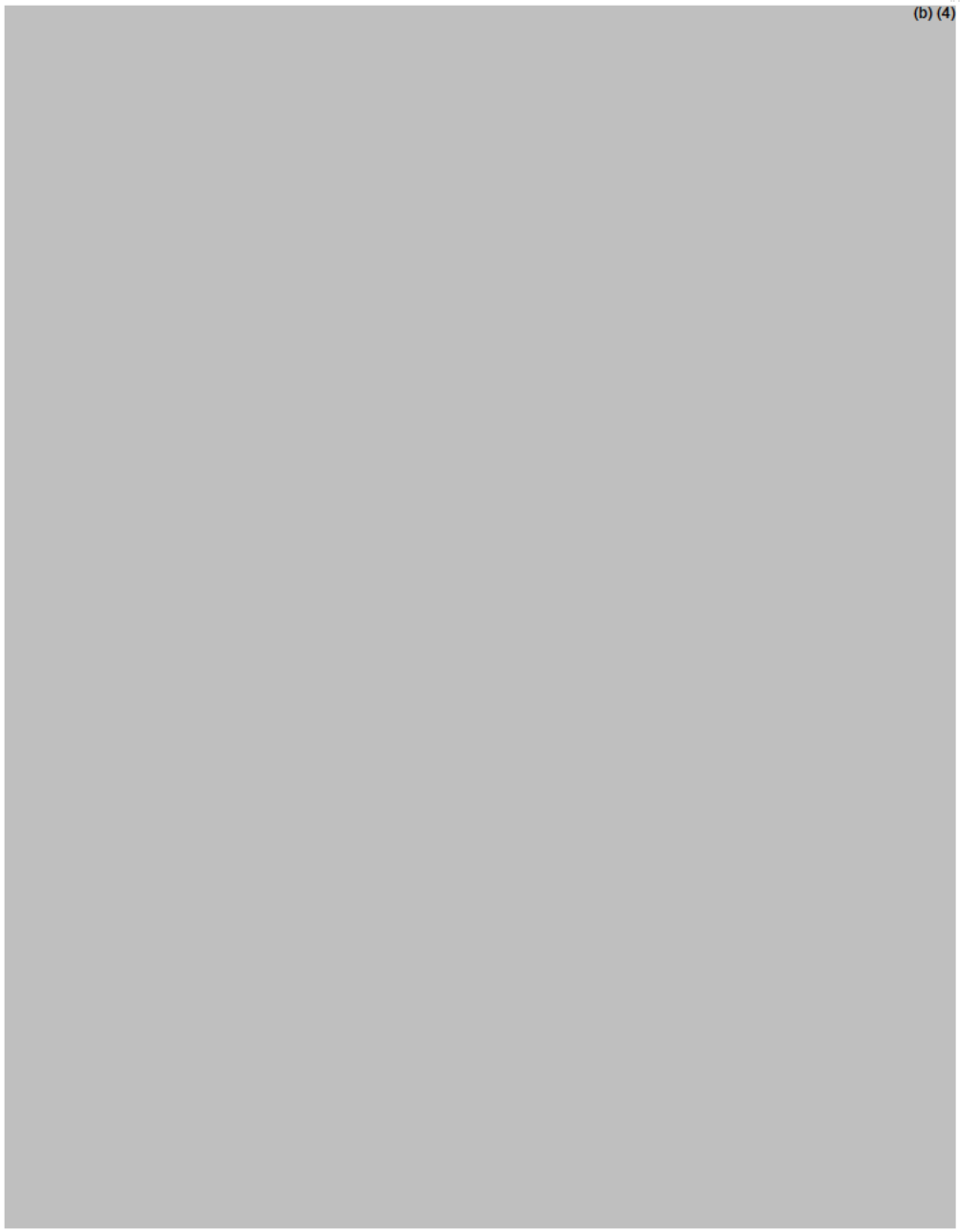
LUPRON DEPOT-PED (leuprolide acetate for depot suspension), for intramuscular use
Initial U.S. Approval: 1985

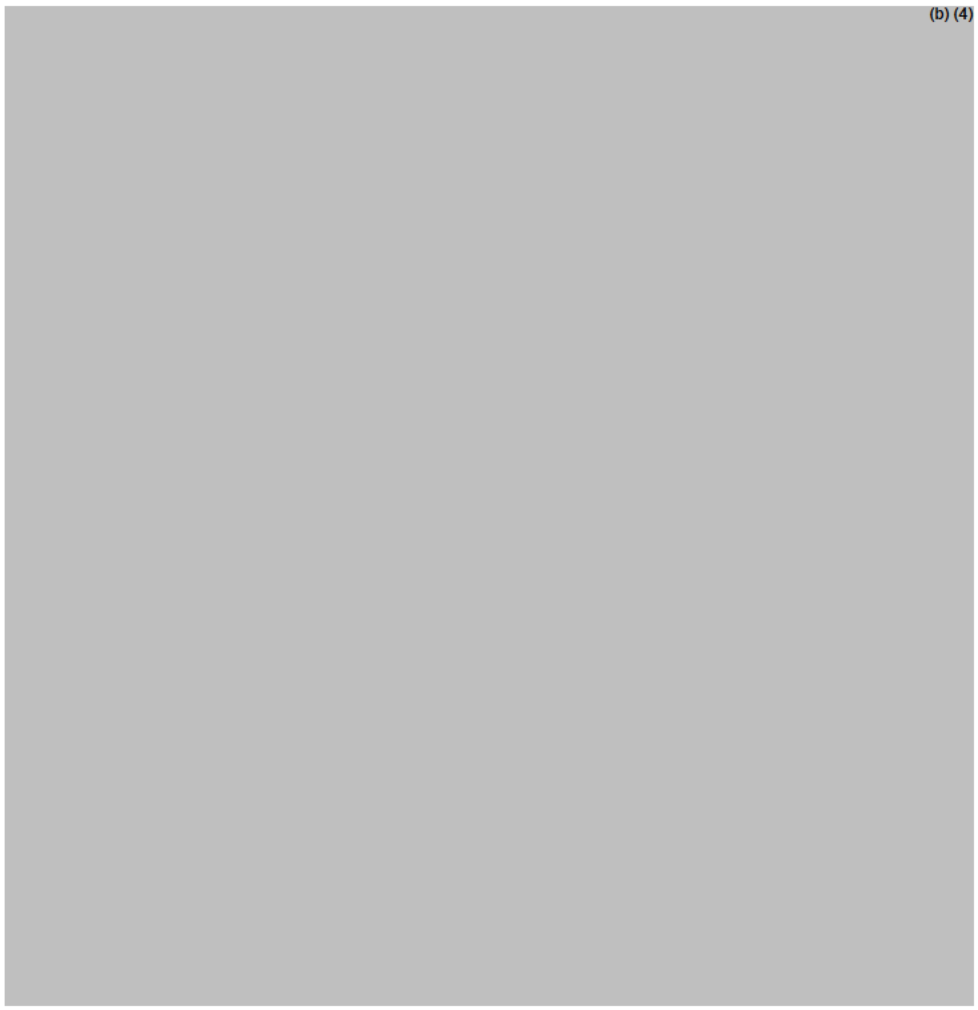
(b) (4)

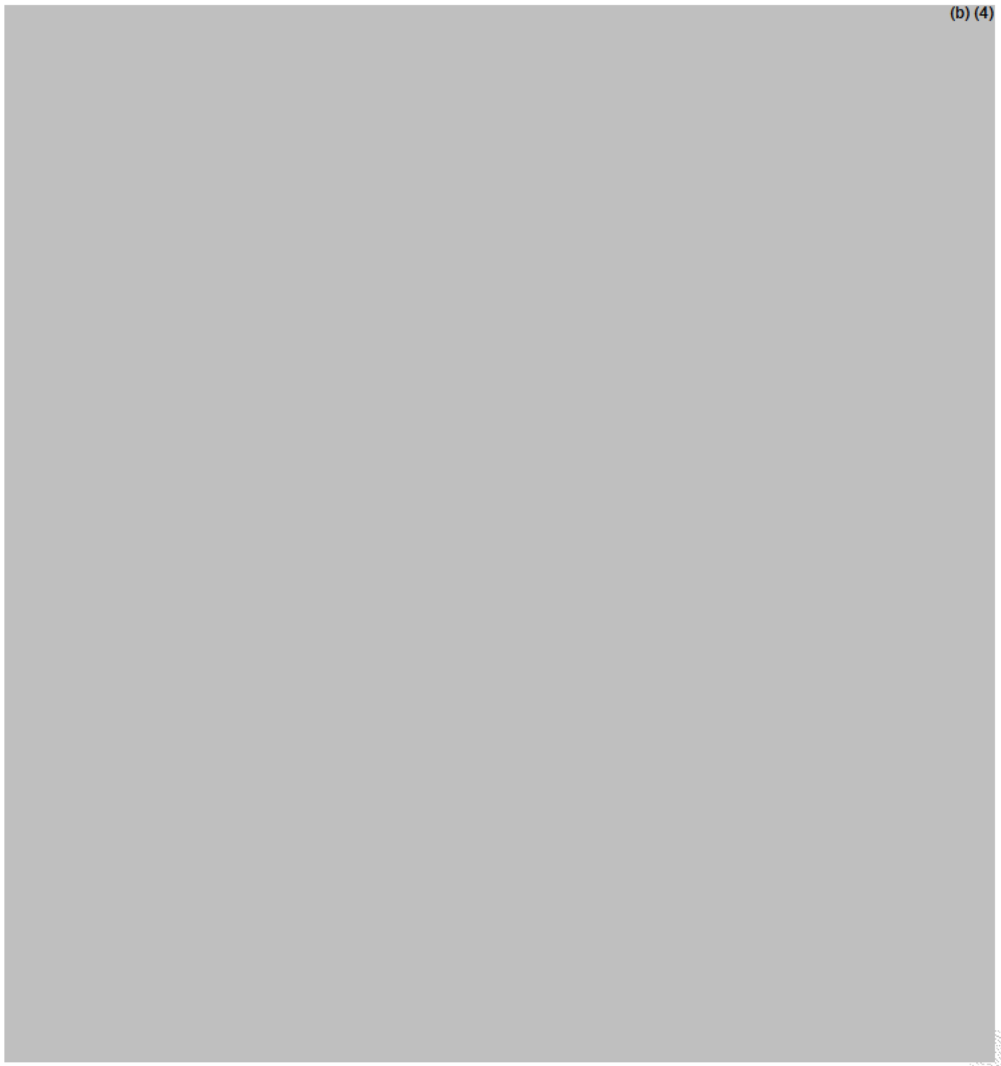
(b) (4)

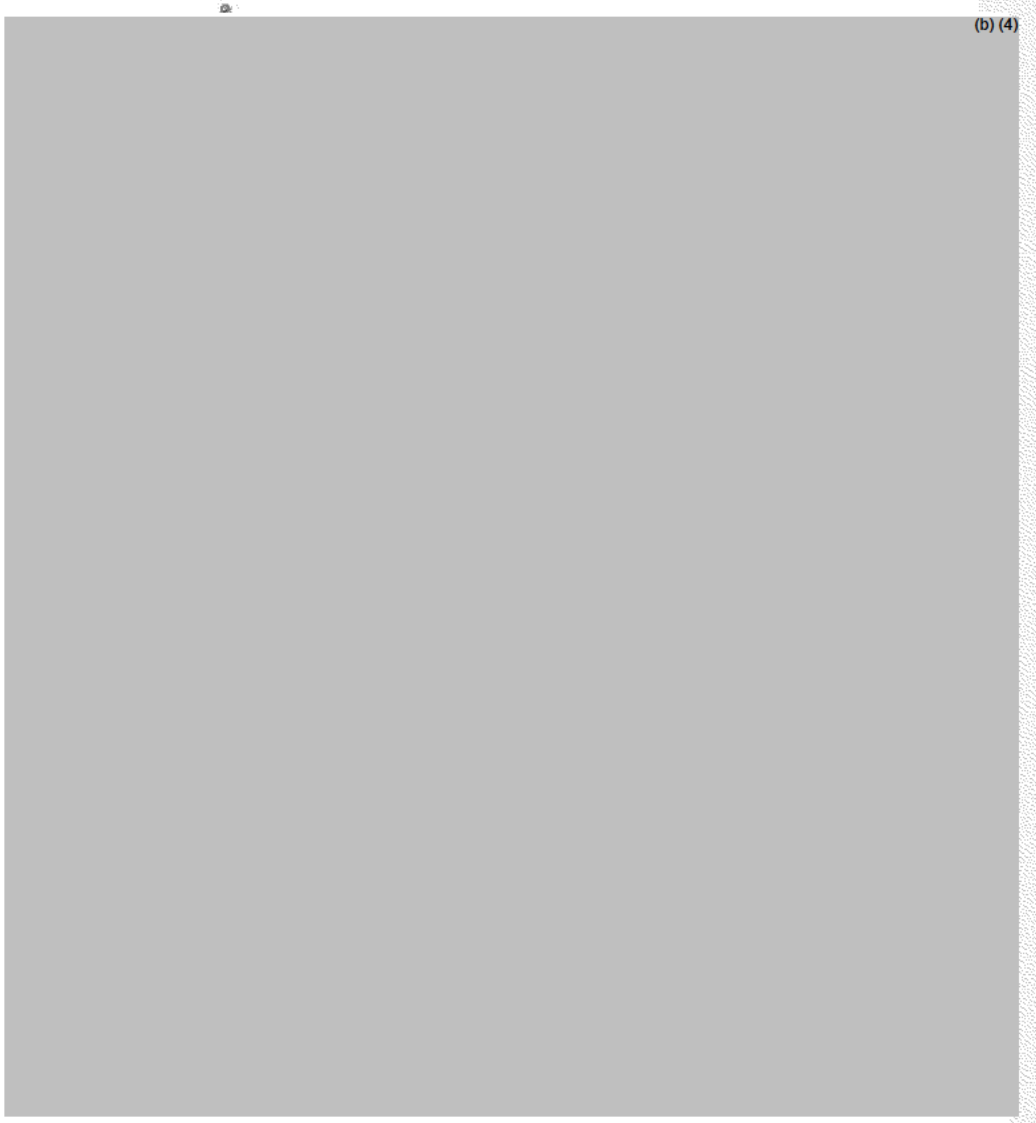
FULL PRESCRIBING INFORMATION: CONTENTS| HYPERLINK "" \l "section_TOCFootnote" \o "Footnote Content"]

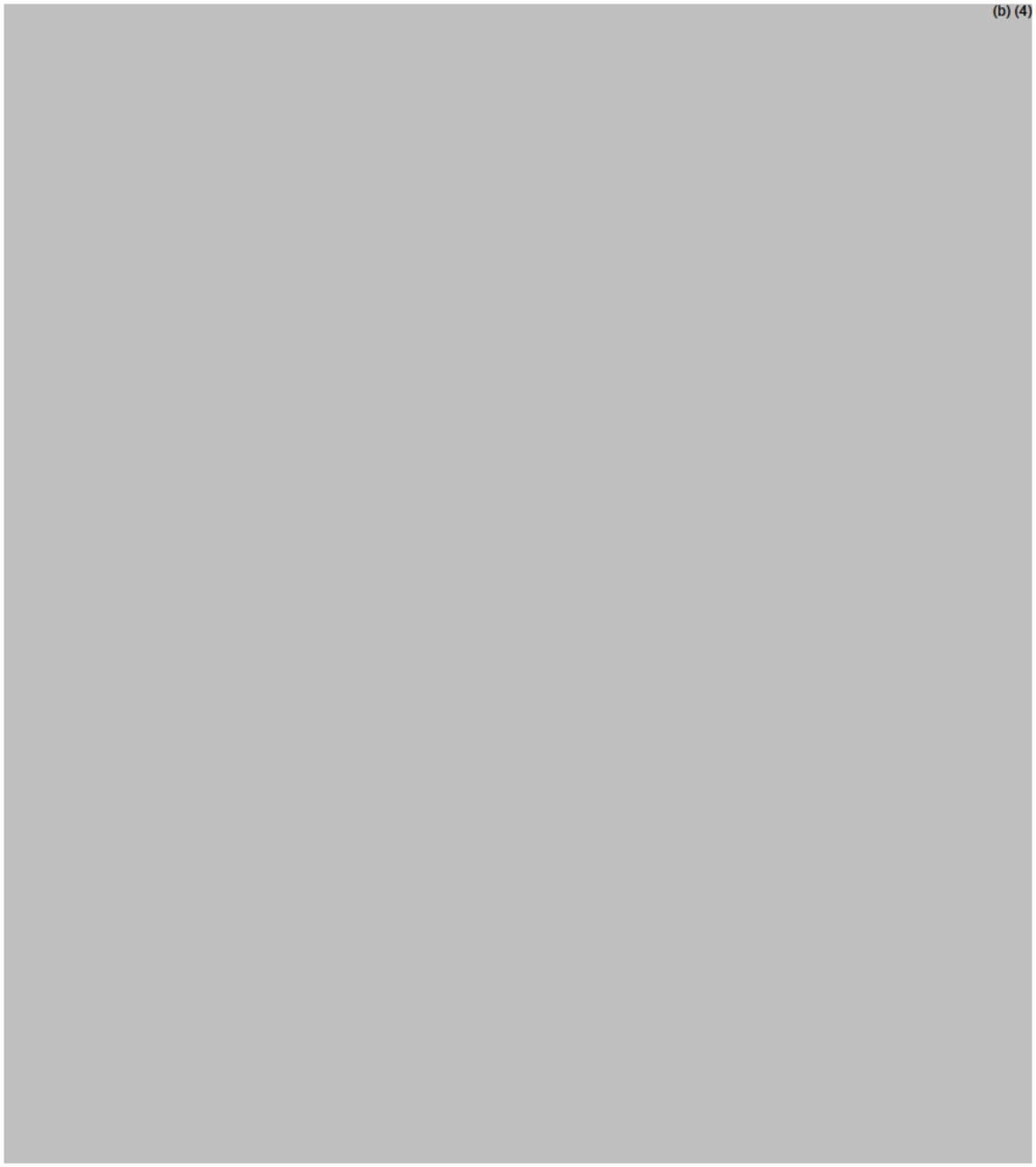

(b) (4)


(b) (4)

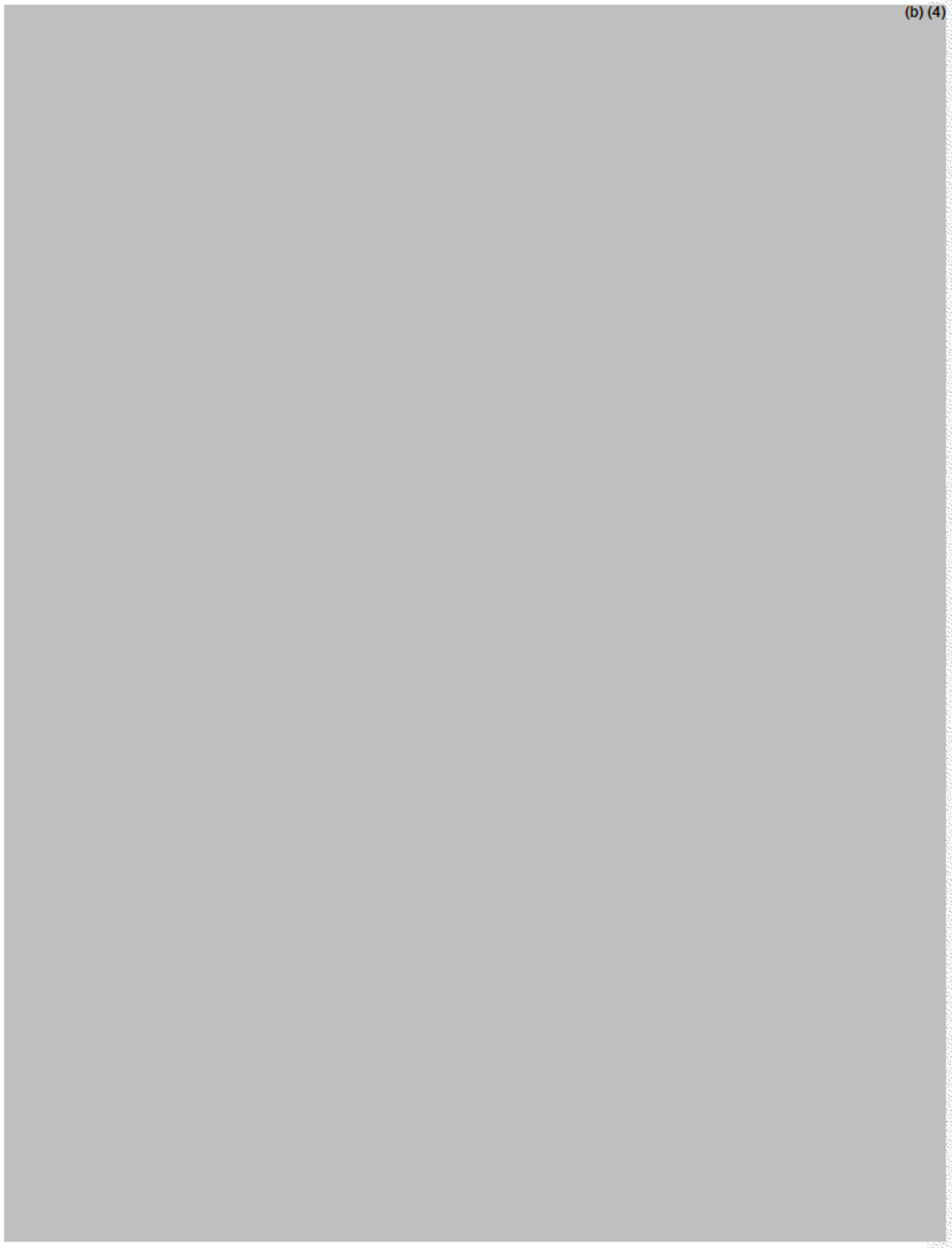

(b) (4)

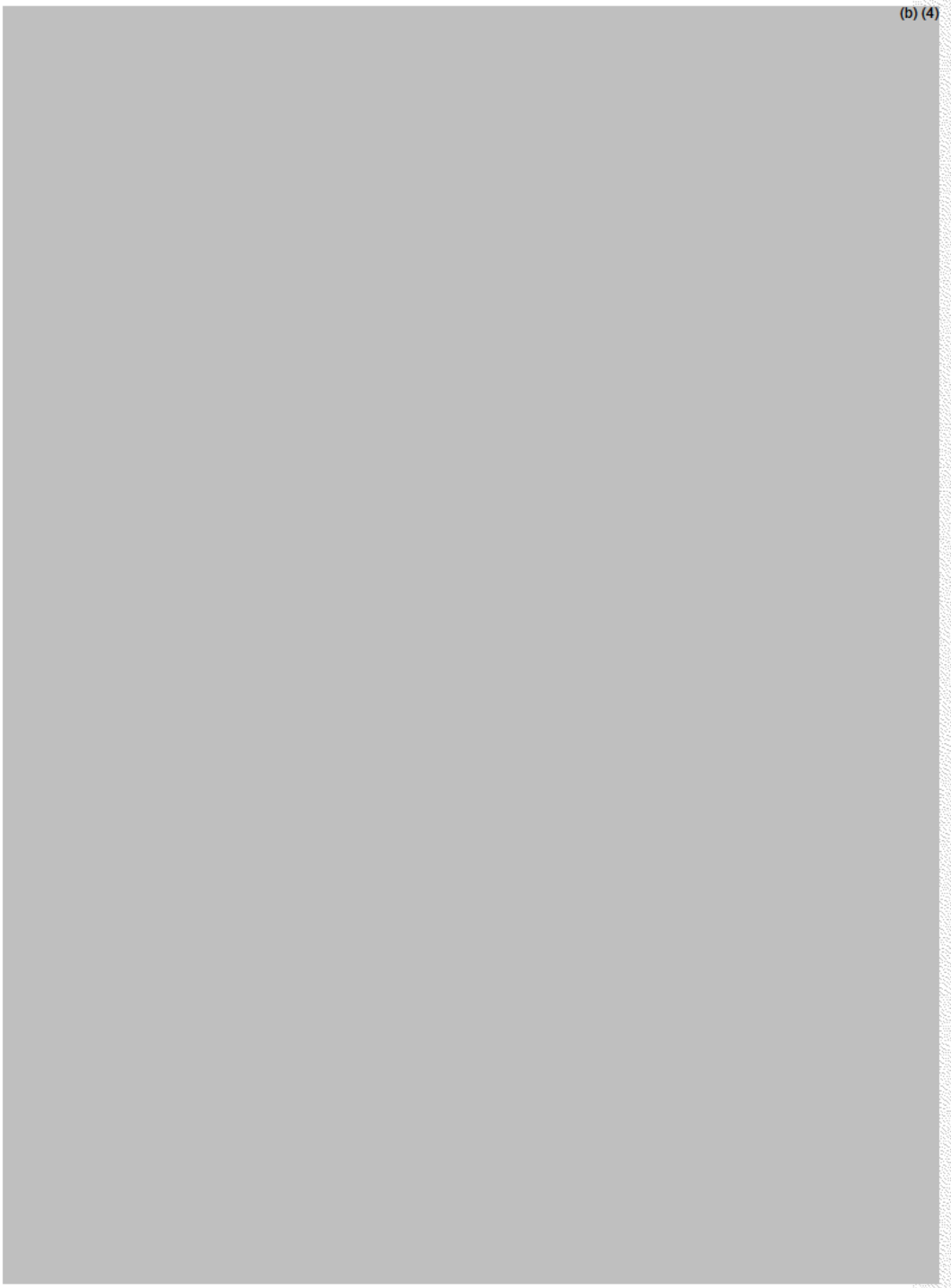

(b) (4)

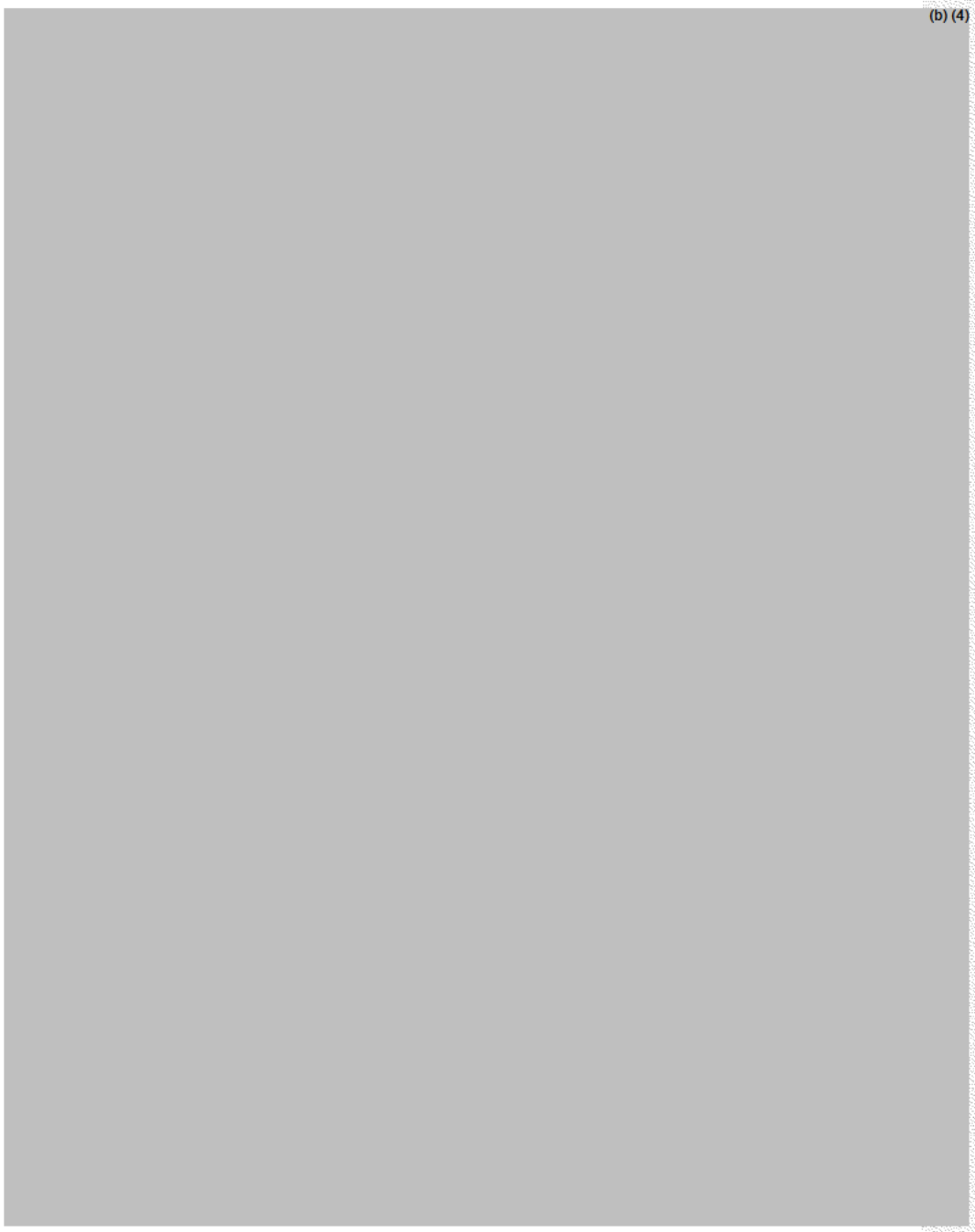

(b) (4)

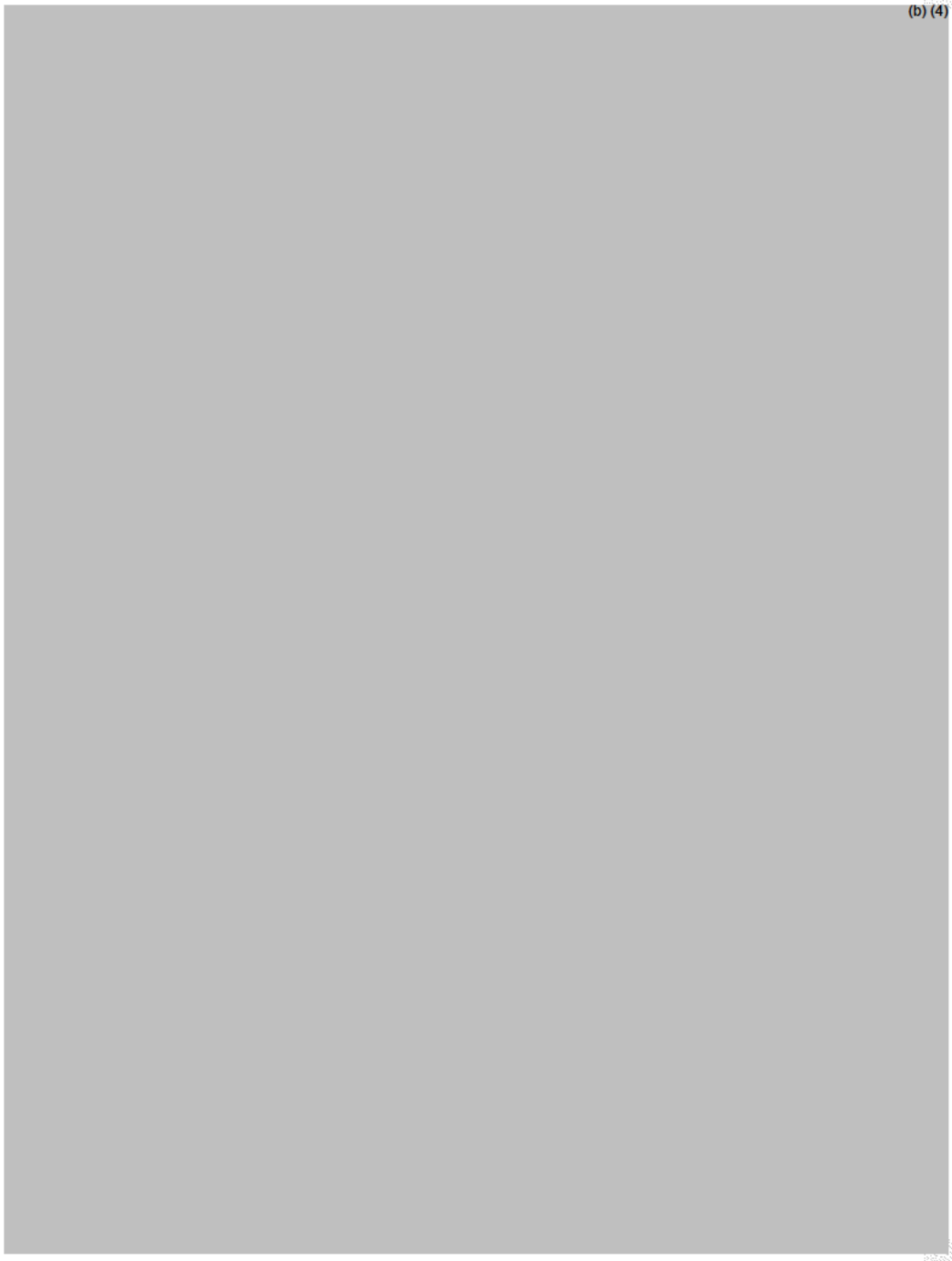

(b) (4)

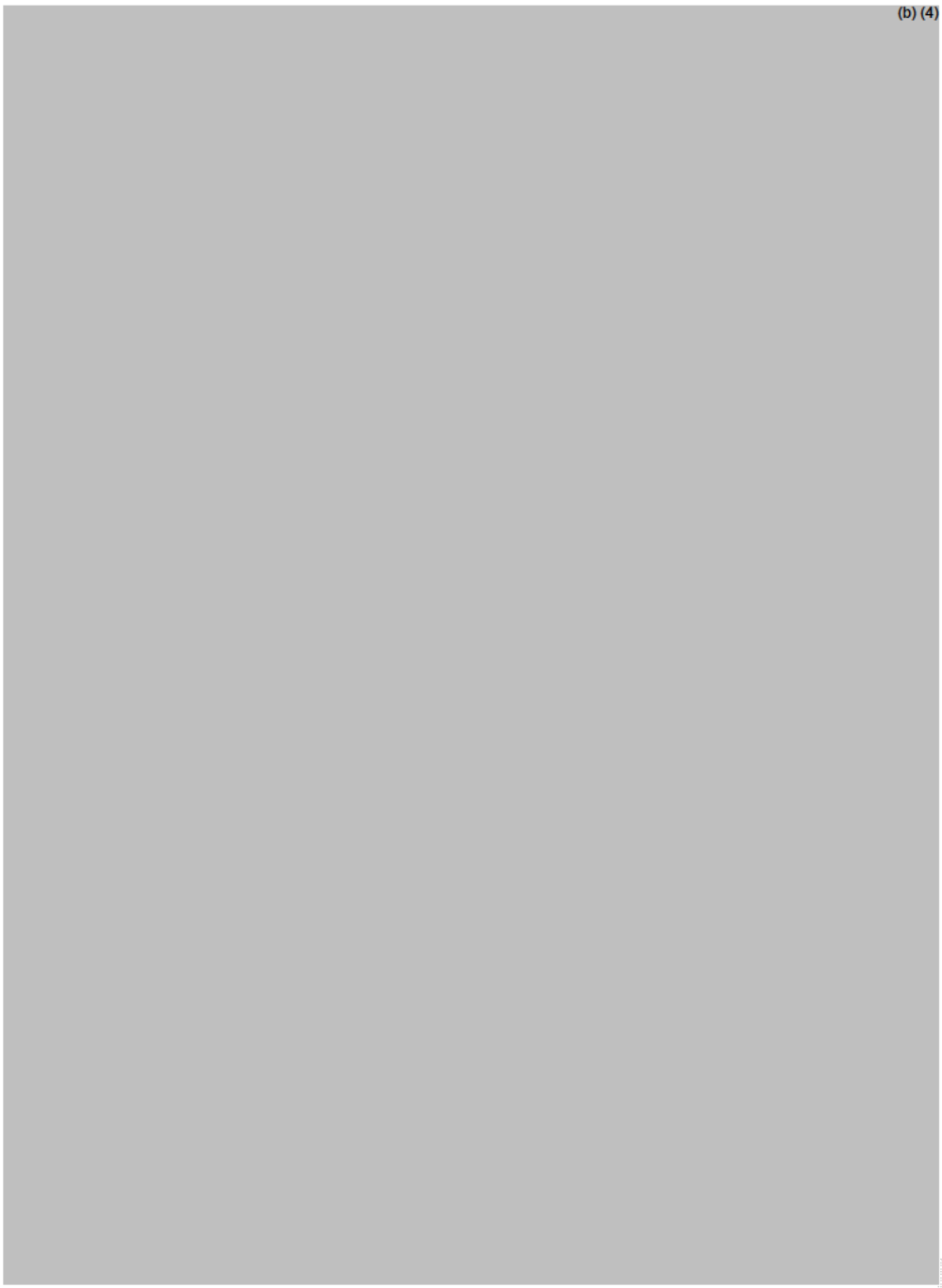

(b) (4)

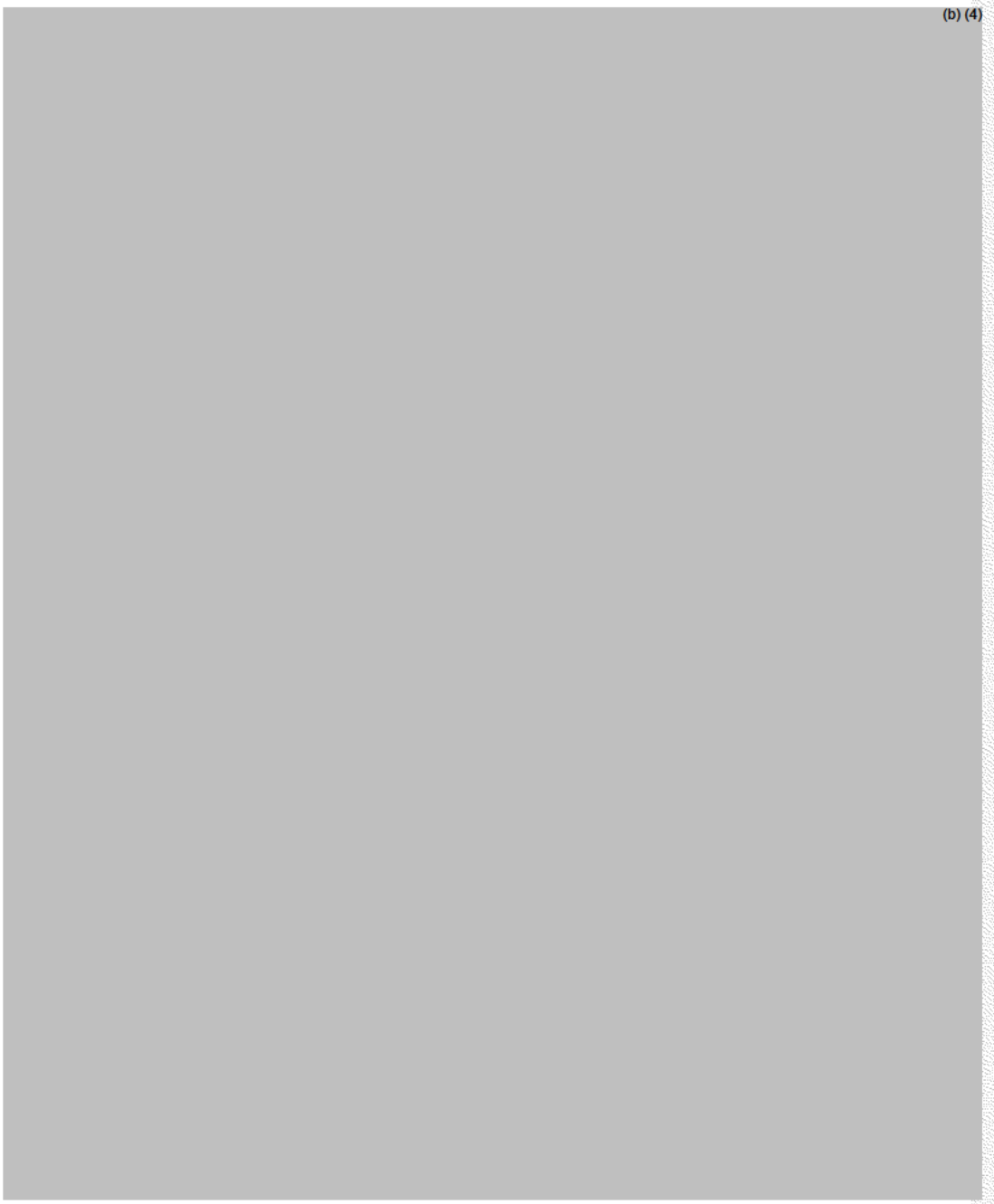

(b) (4)

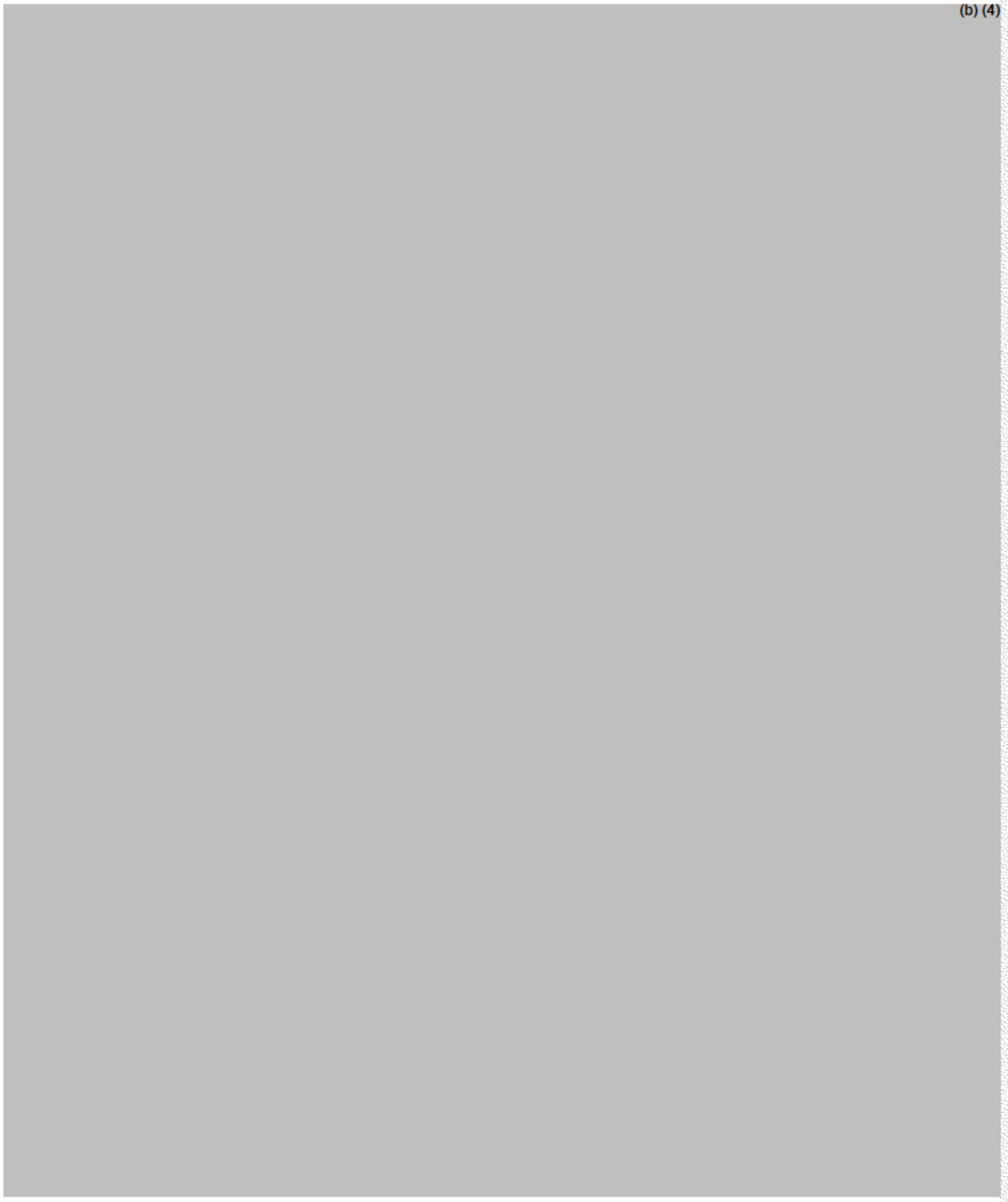

(b) (4)

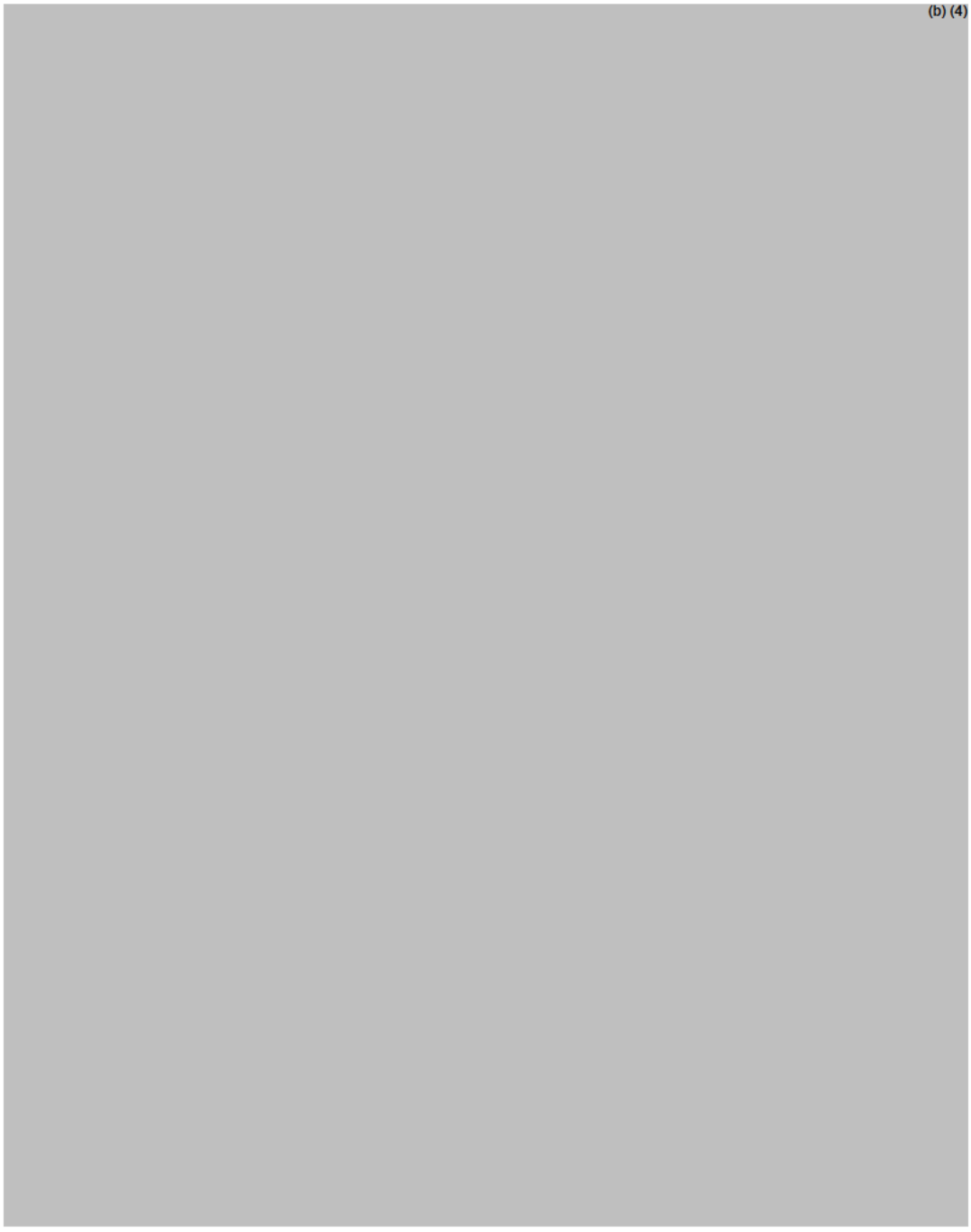

(b) (4)

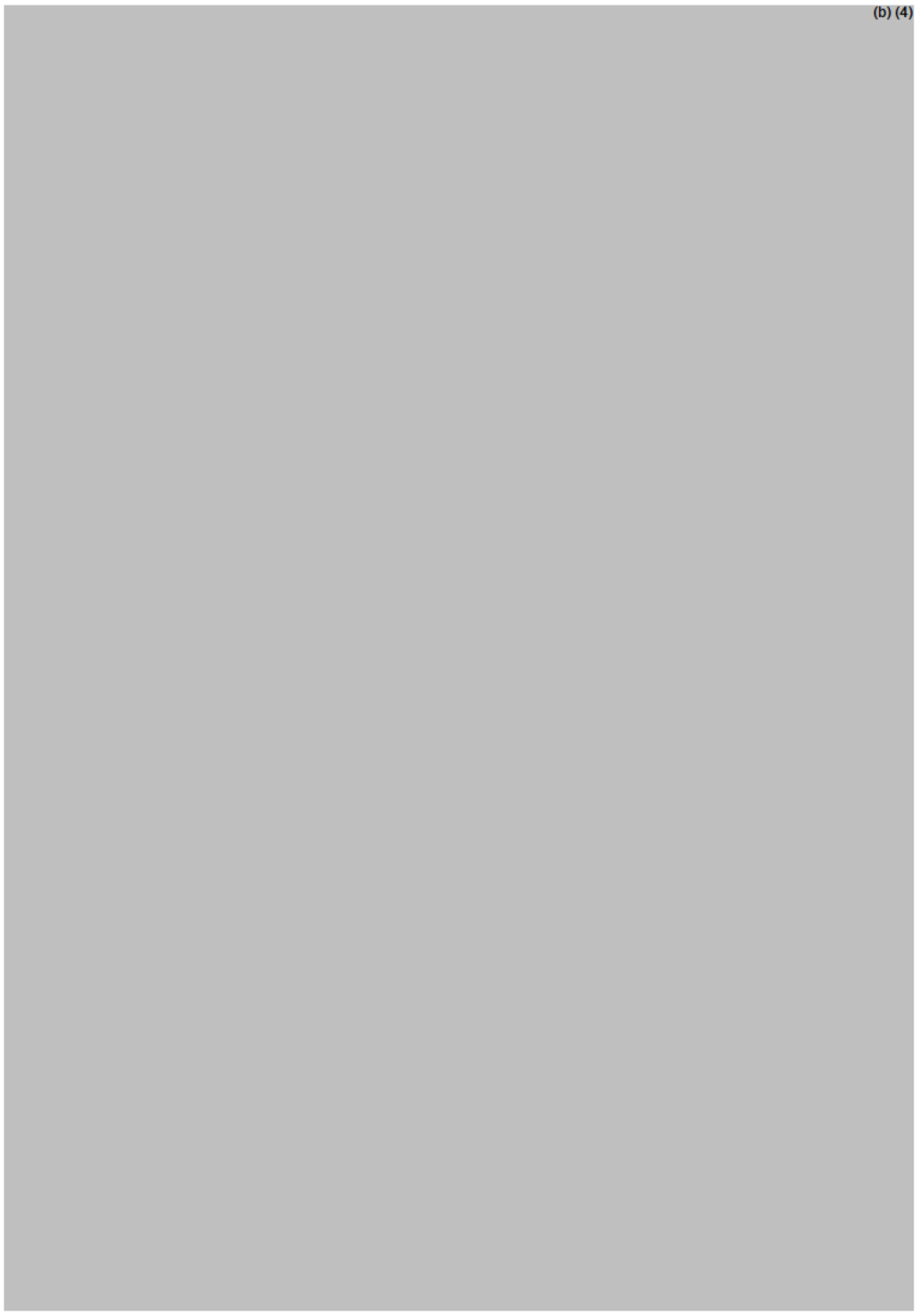

(b) (4)

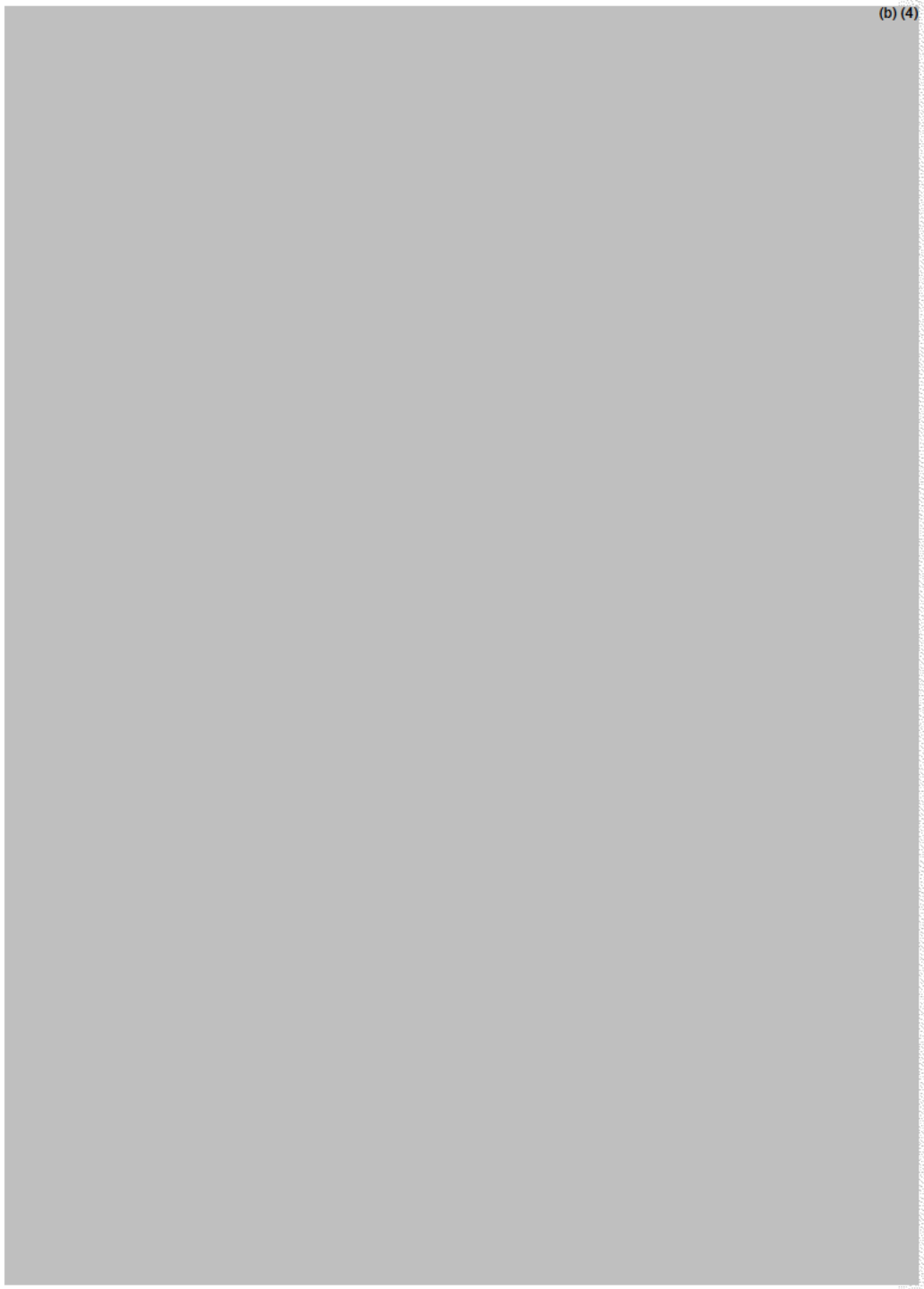

(b) (4)

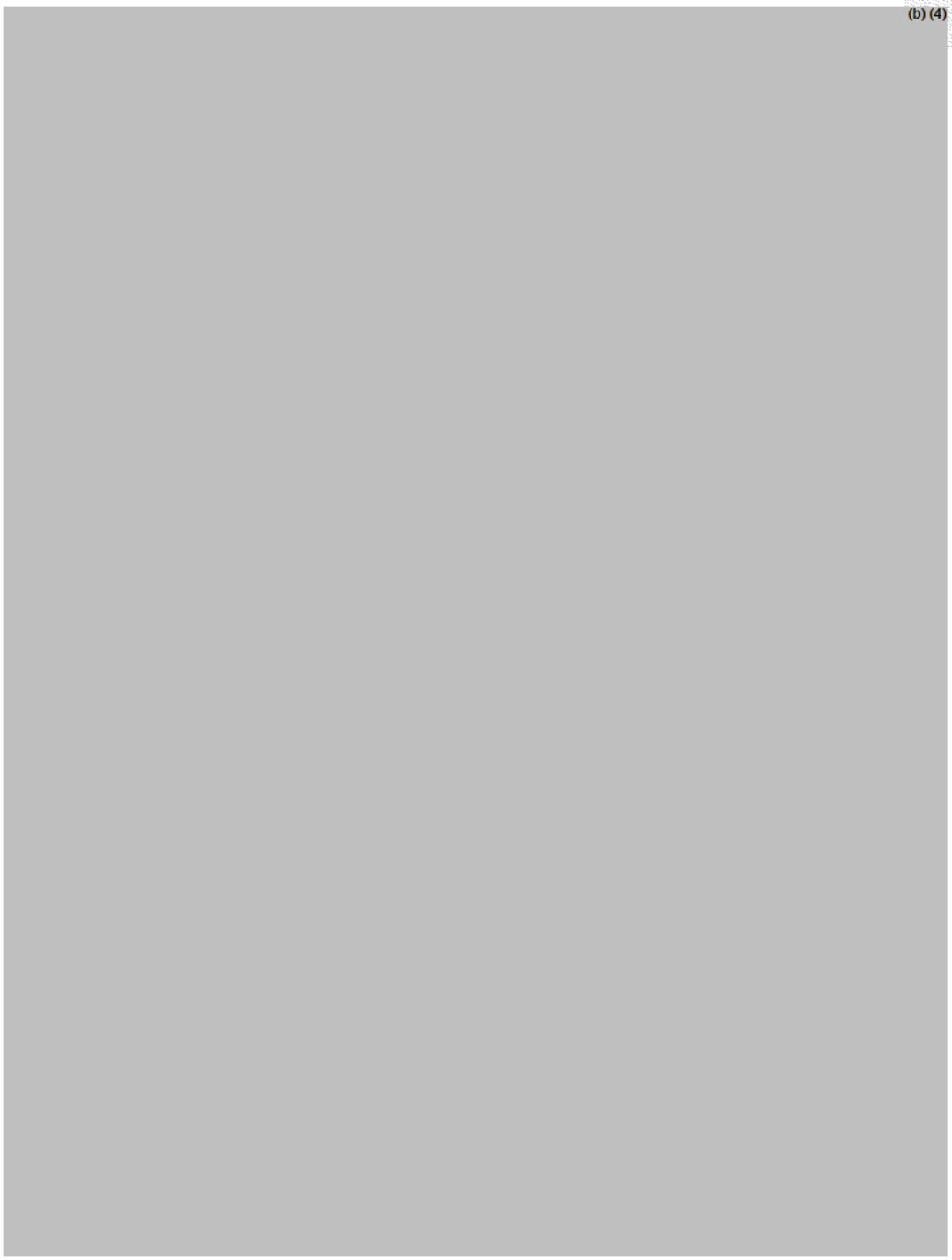

(b) (4)


(b) (4)


(b) (4)

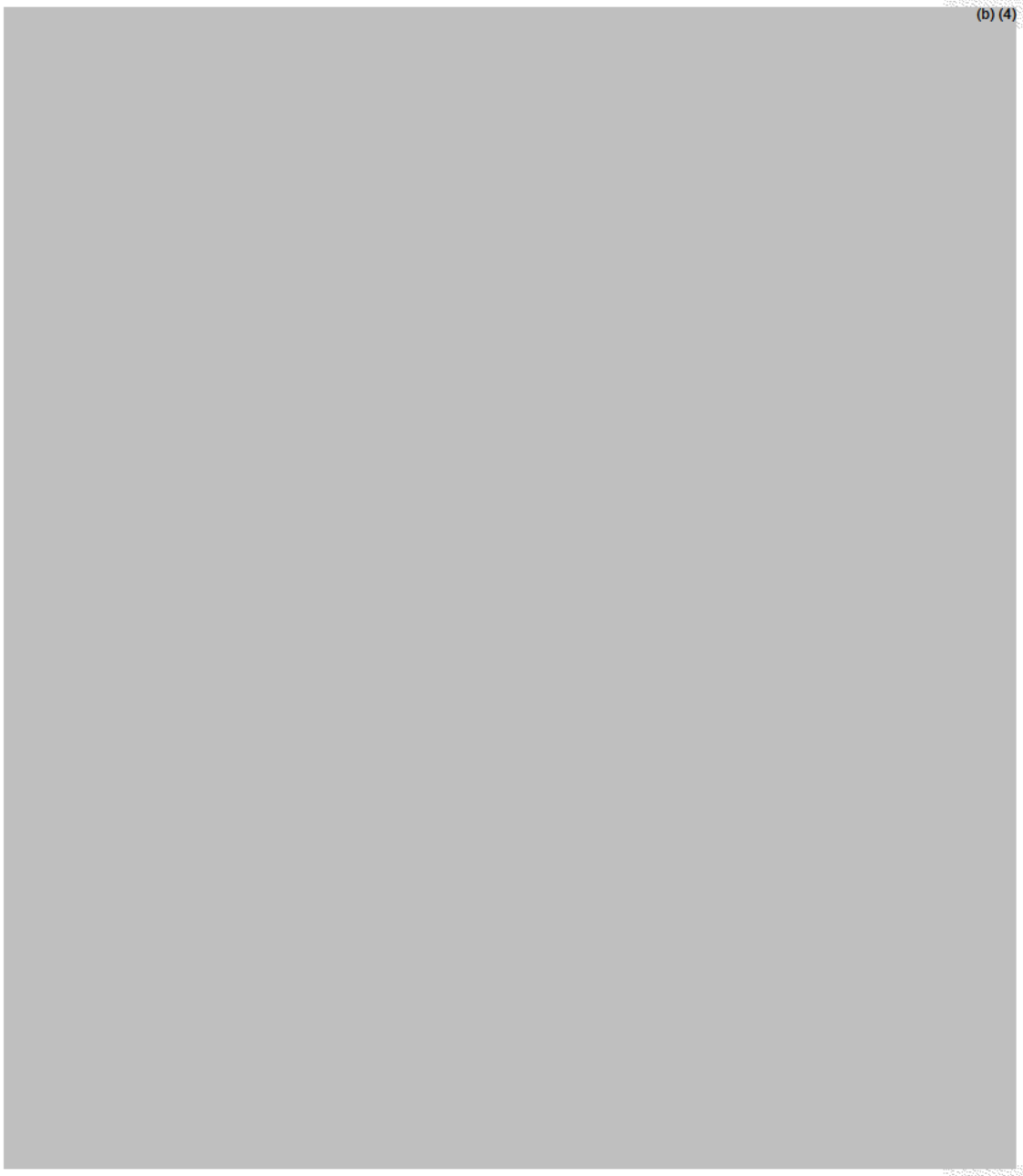

(b) (4)

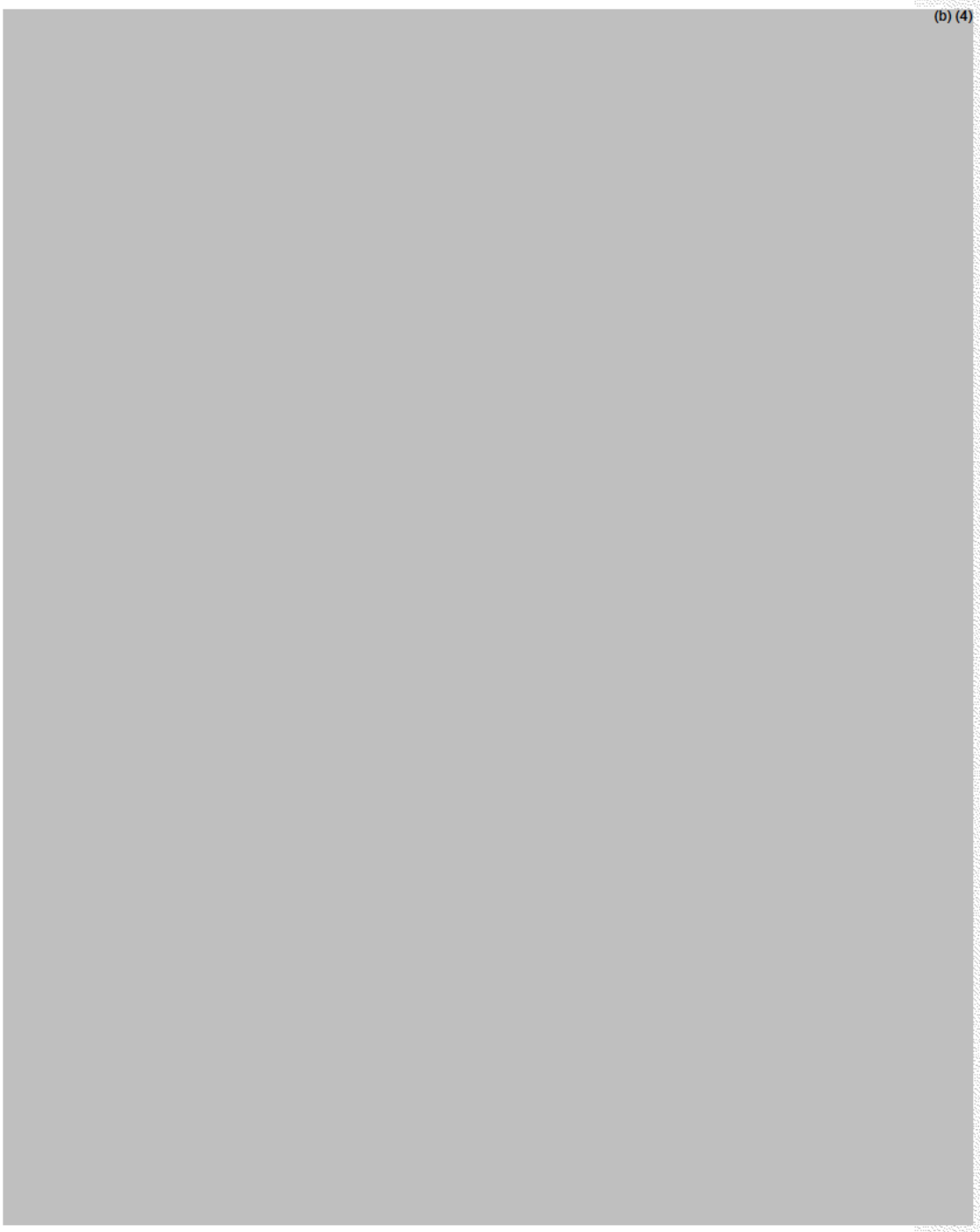

(b) (4)

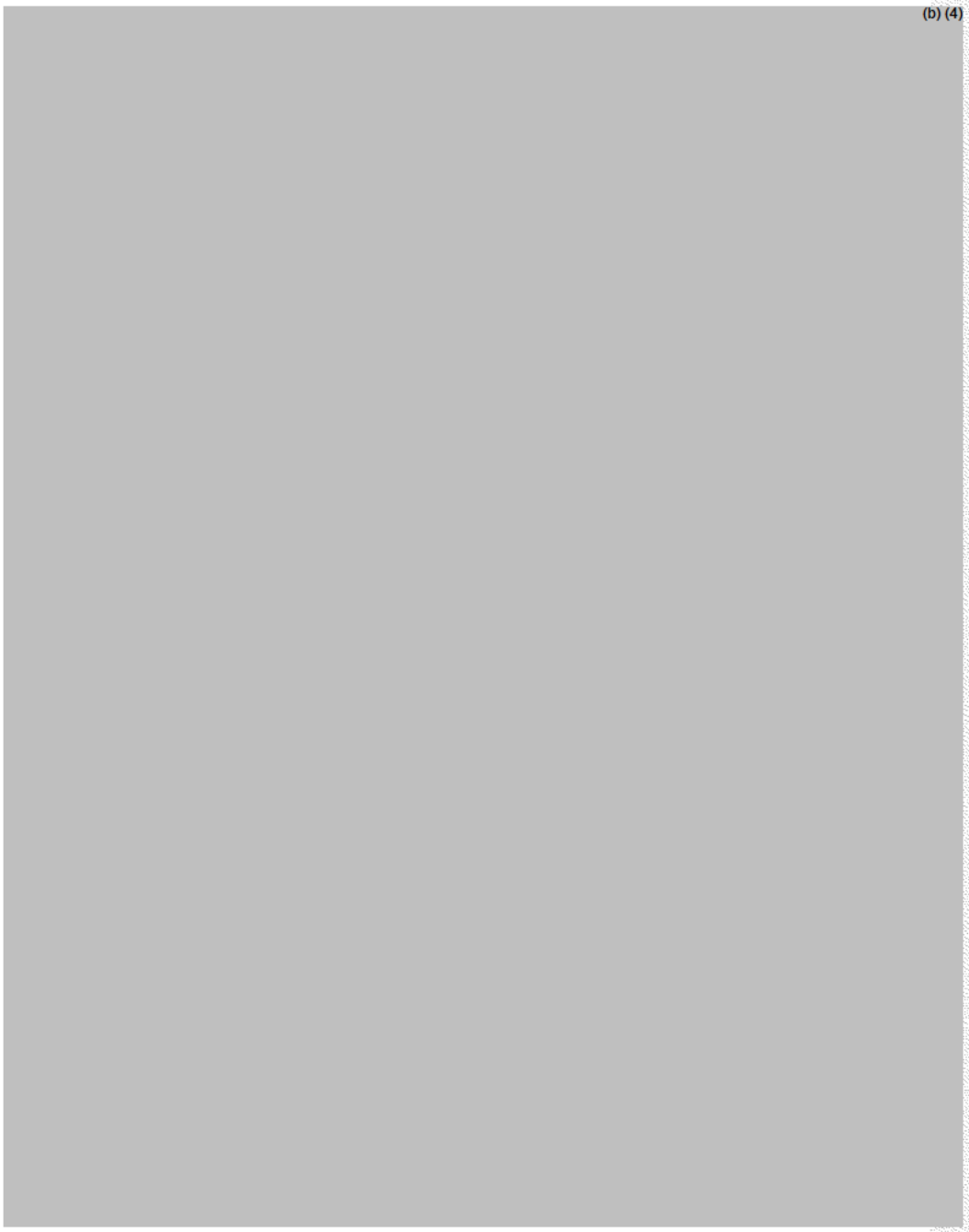

(b) (4)

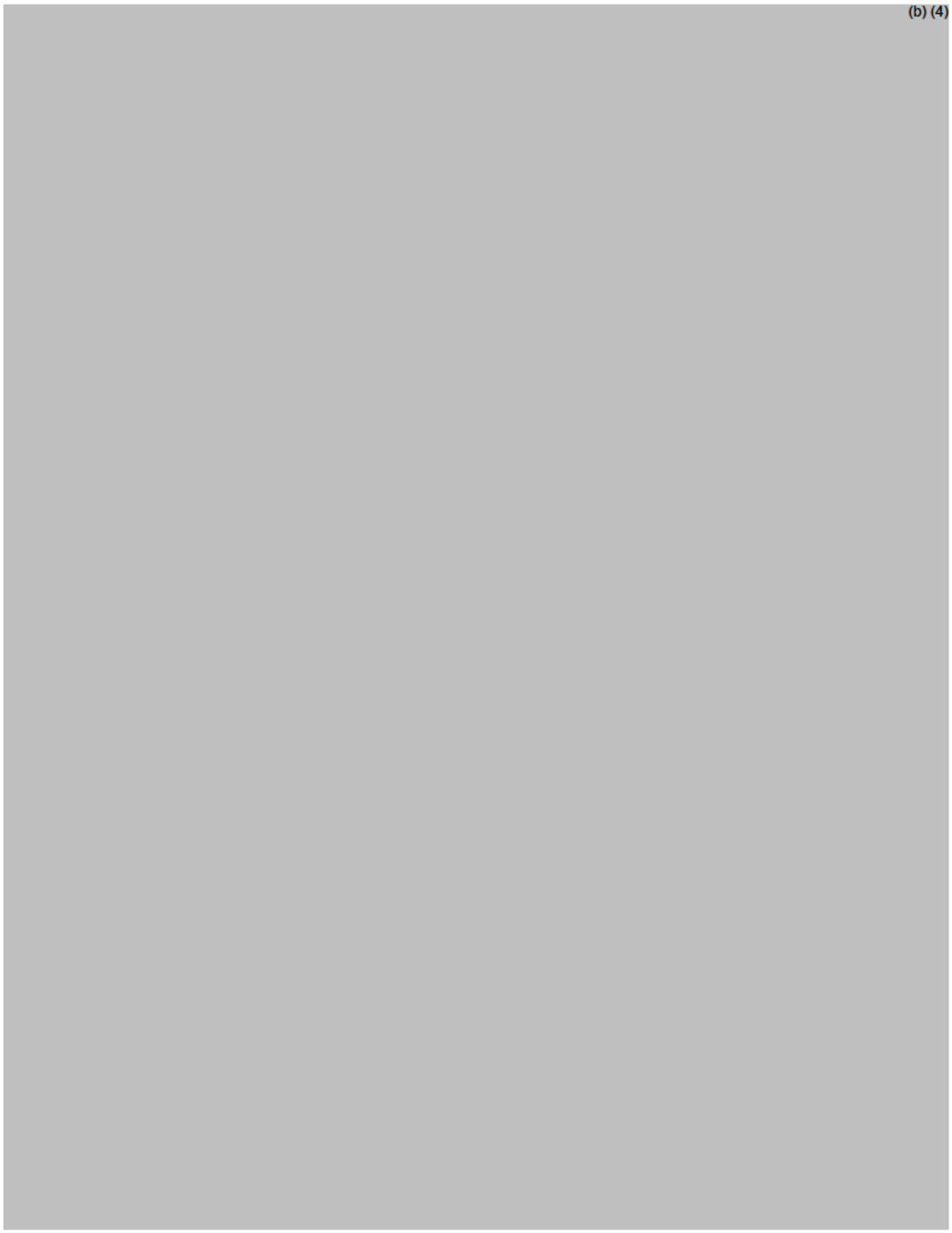

(b) (4)

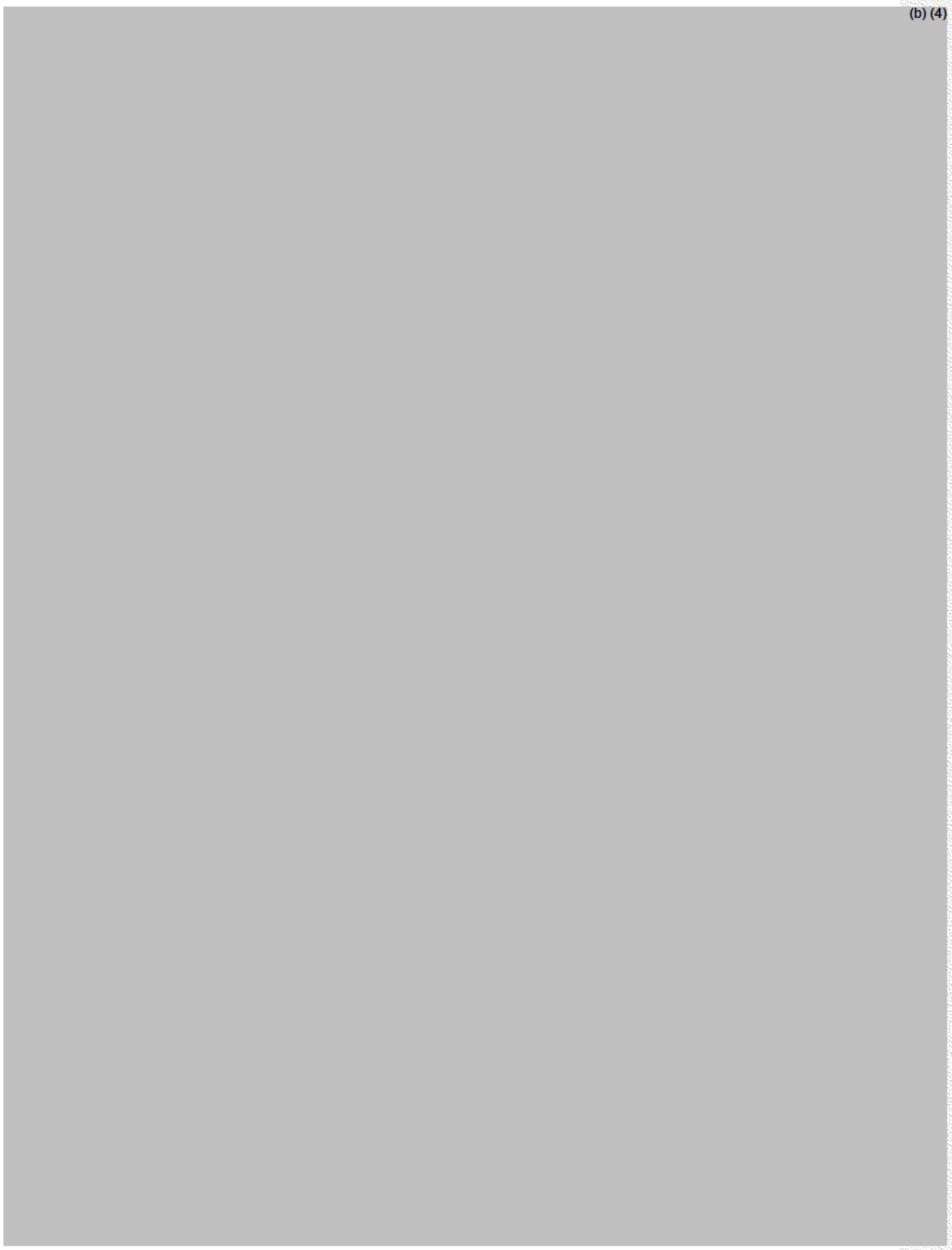

(b) (4)


(b) (4)


(b) (4)


(b) (4)


(b) (4)


(b) (4)


(b) (4)

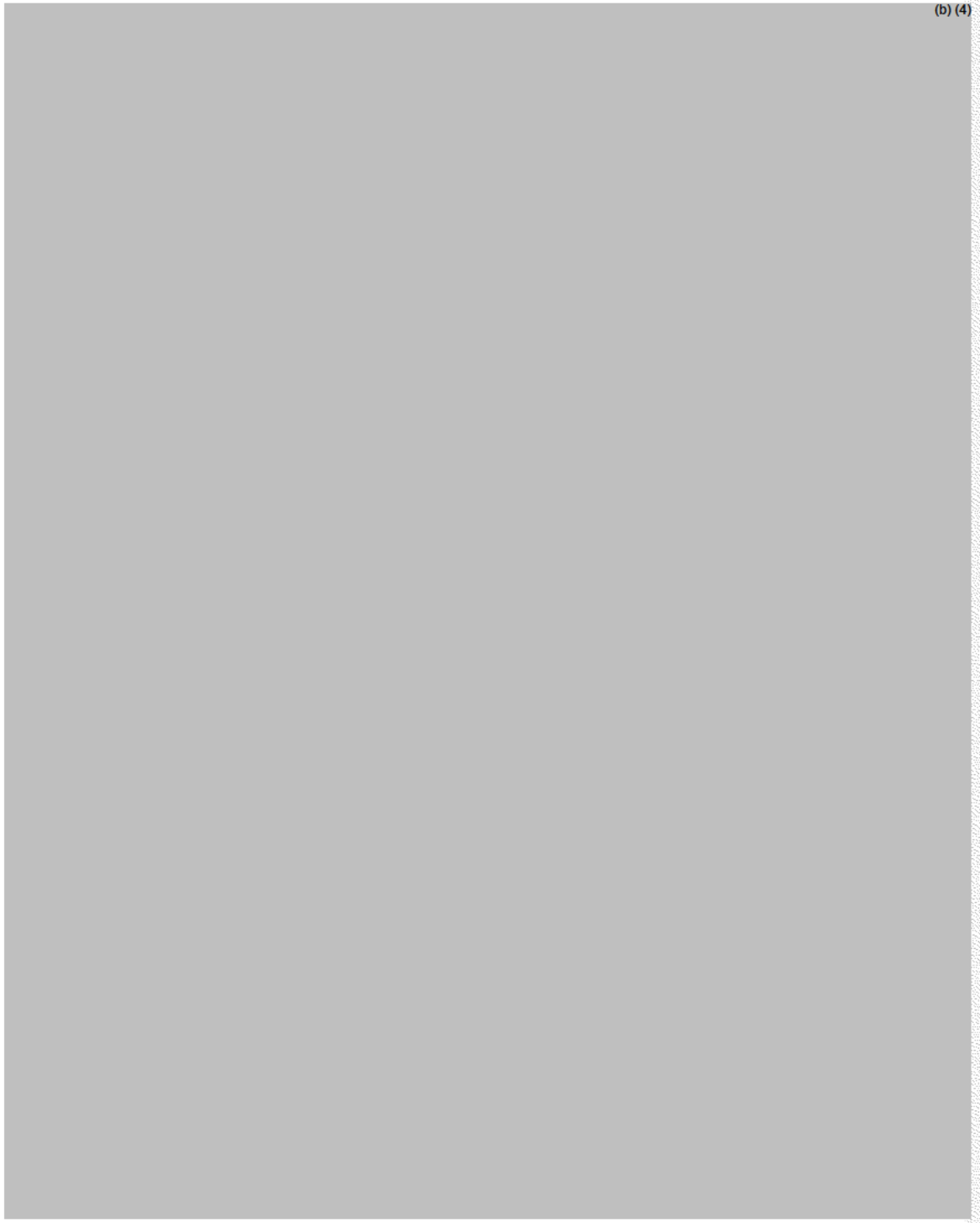
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SUPPRELIN® LA safely and effectively. See full prescribing information for SUPPRELIN LA.

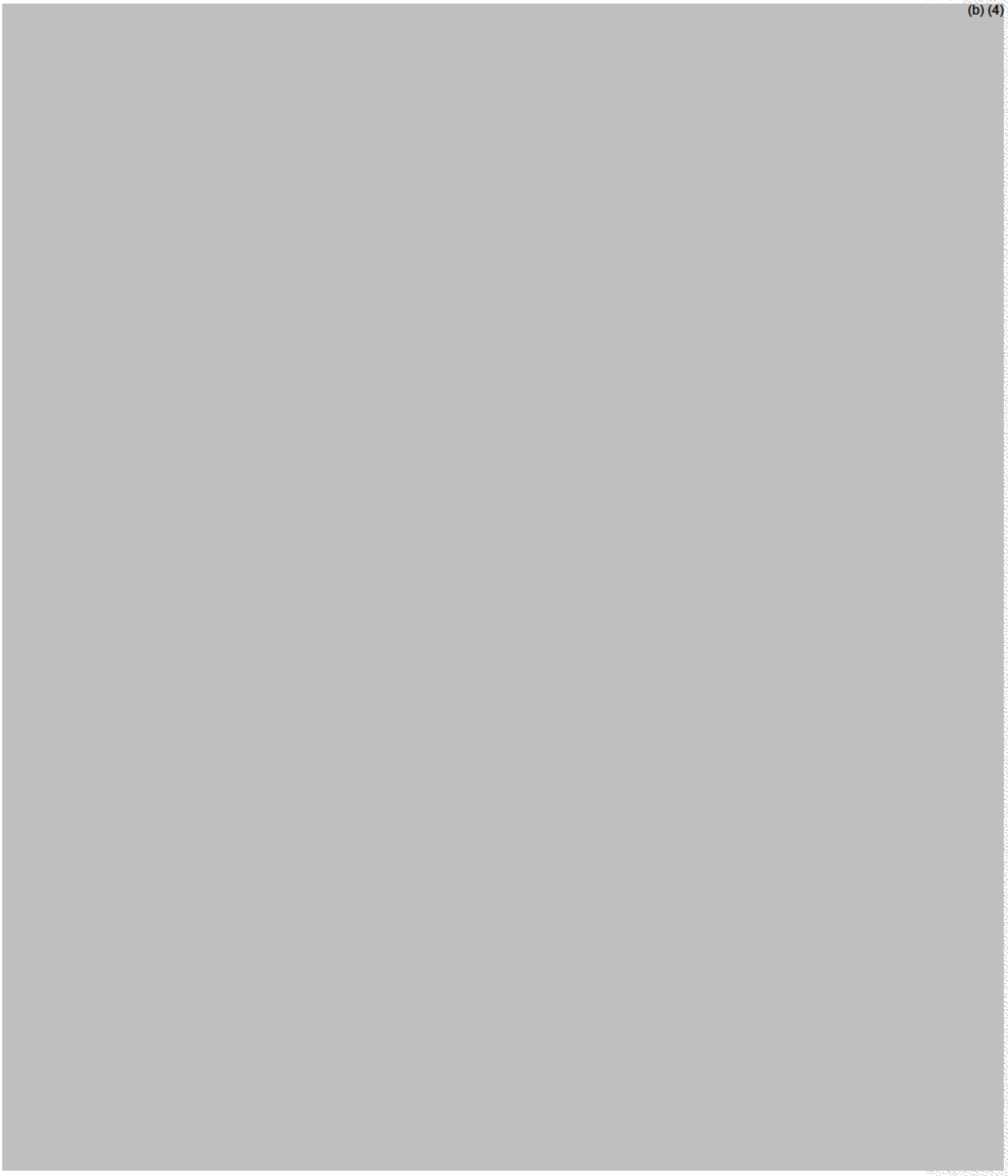
(b) (4)

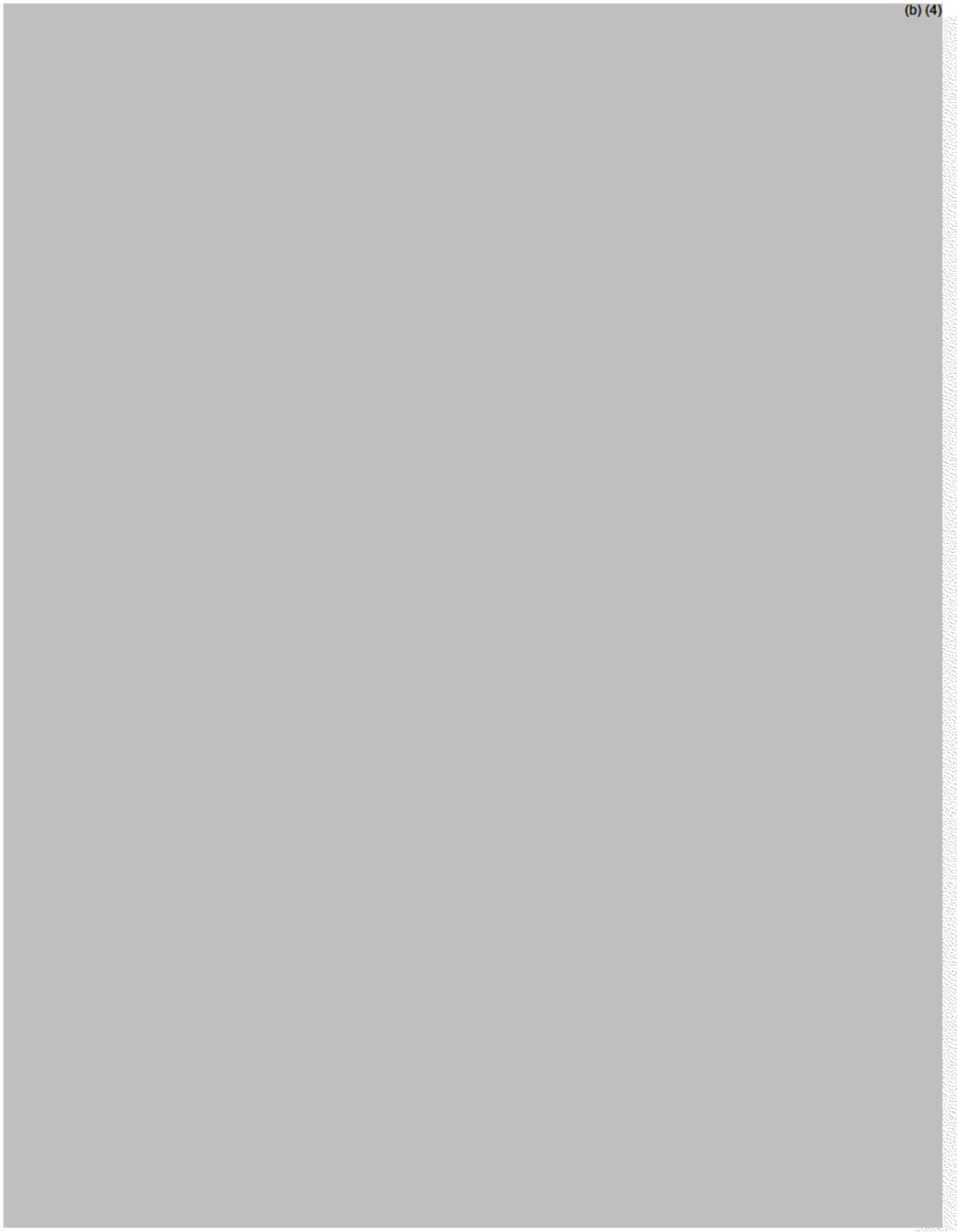
(b) (4)

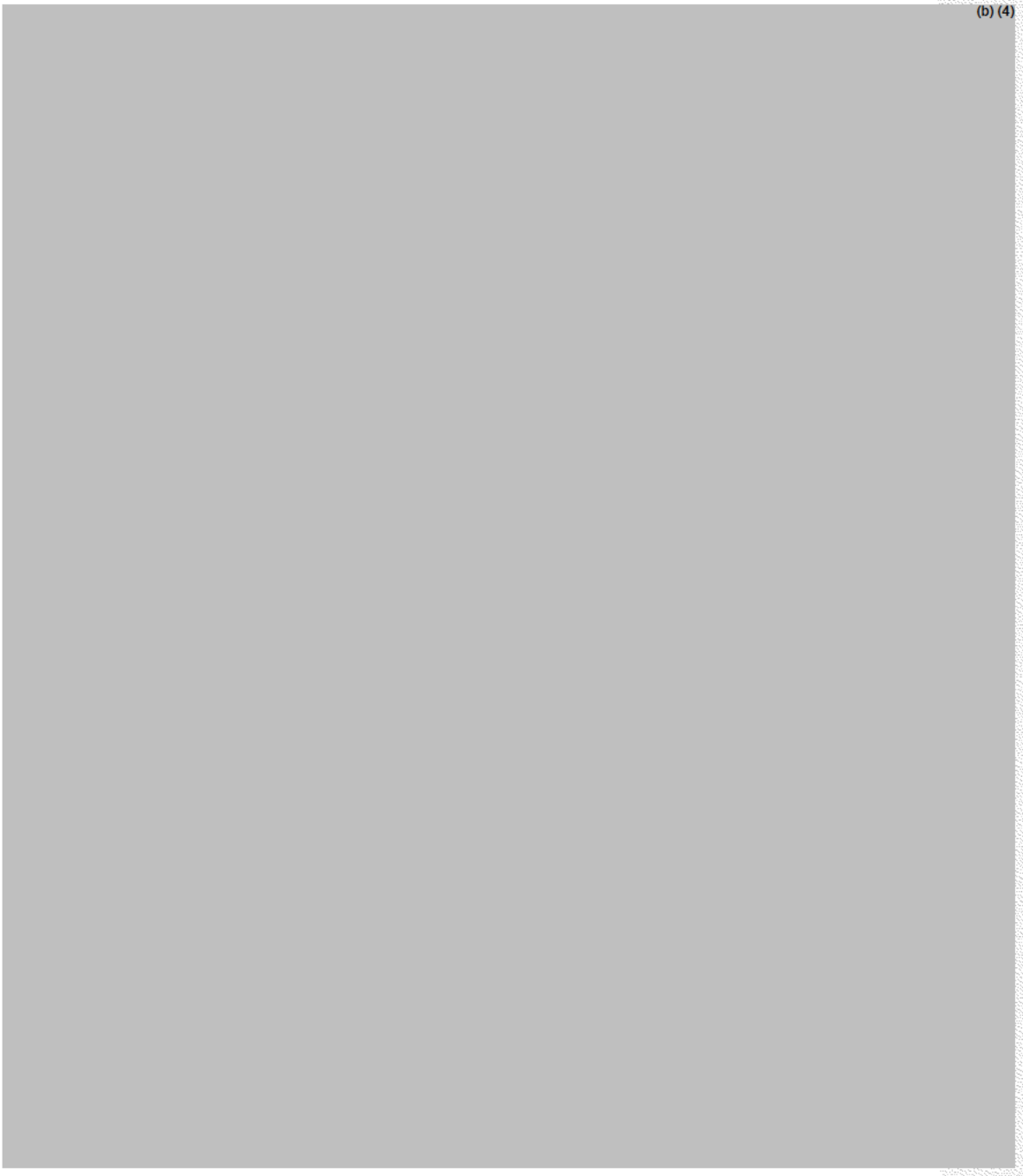
[TOC \o "2-2" \n \h \z \t "Heading 1,1"]

* Sections or subsections omitted from the full prescribing information are not listed


(b) (4)



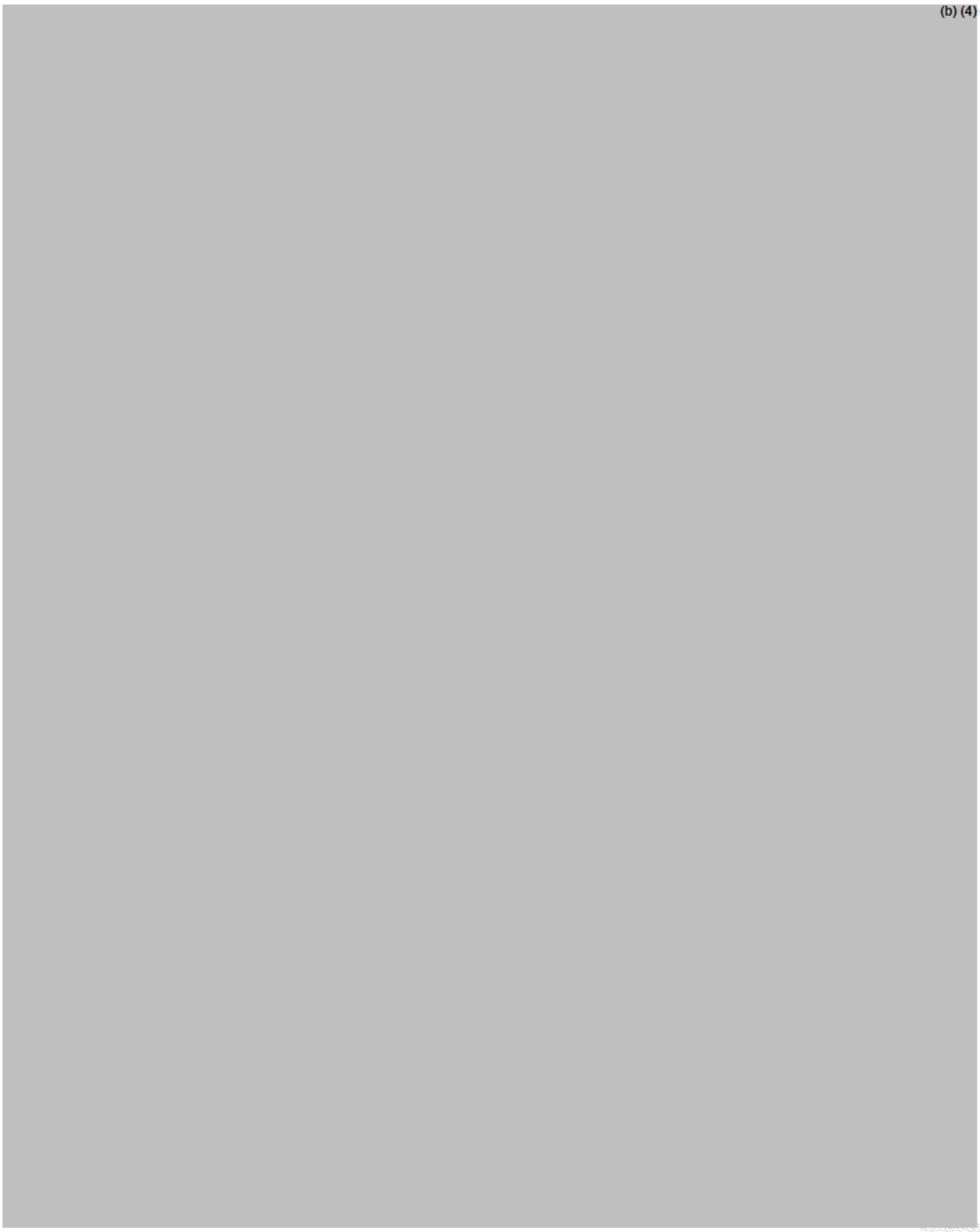

(b) (4)


(b) (4)

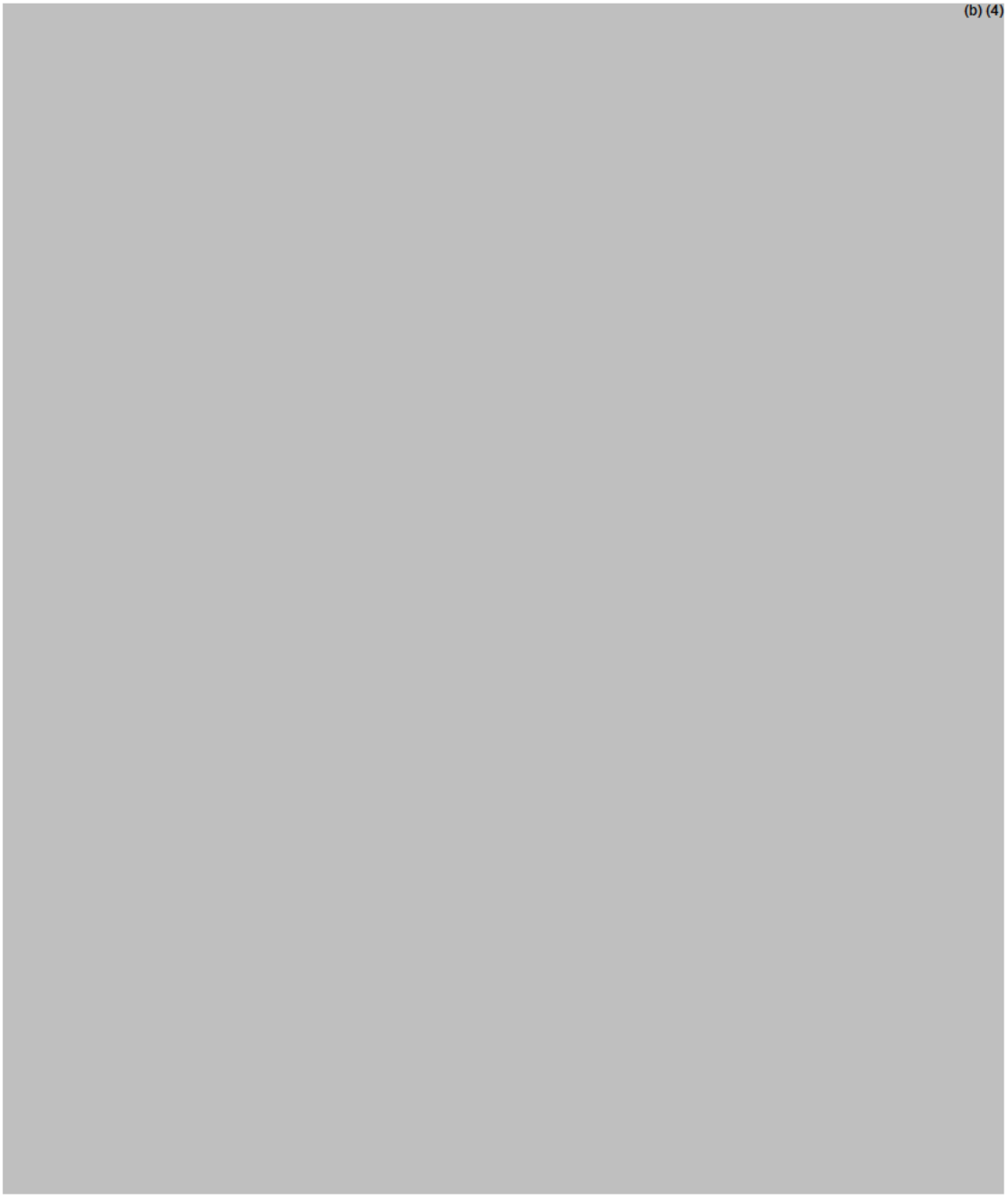
(b) (4)

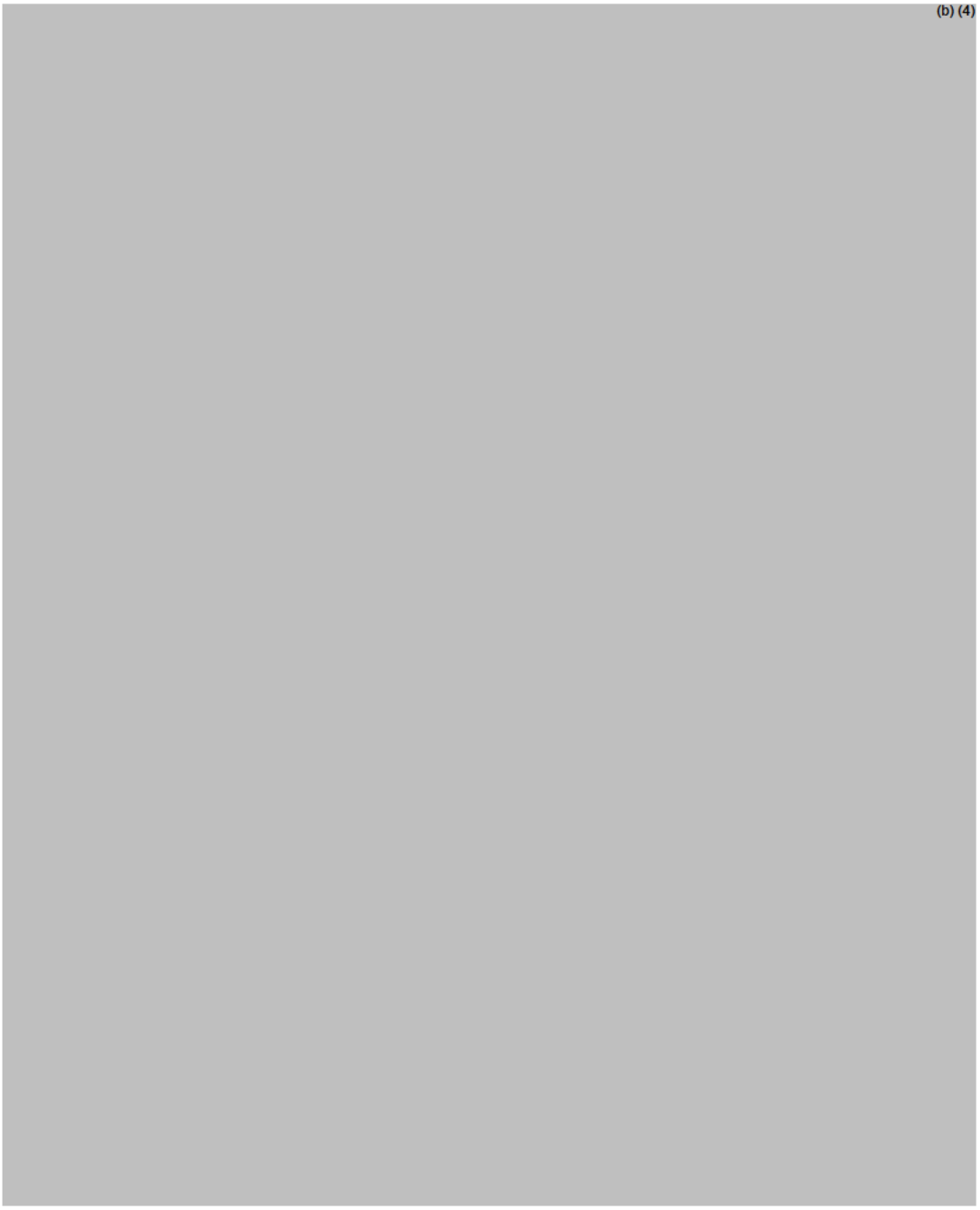
[PAGE * MERGEFORMAT]

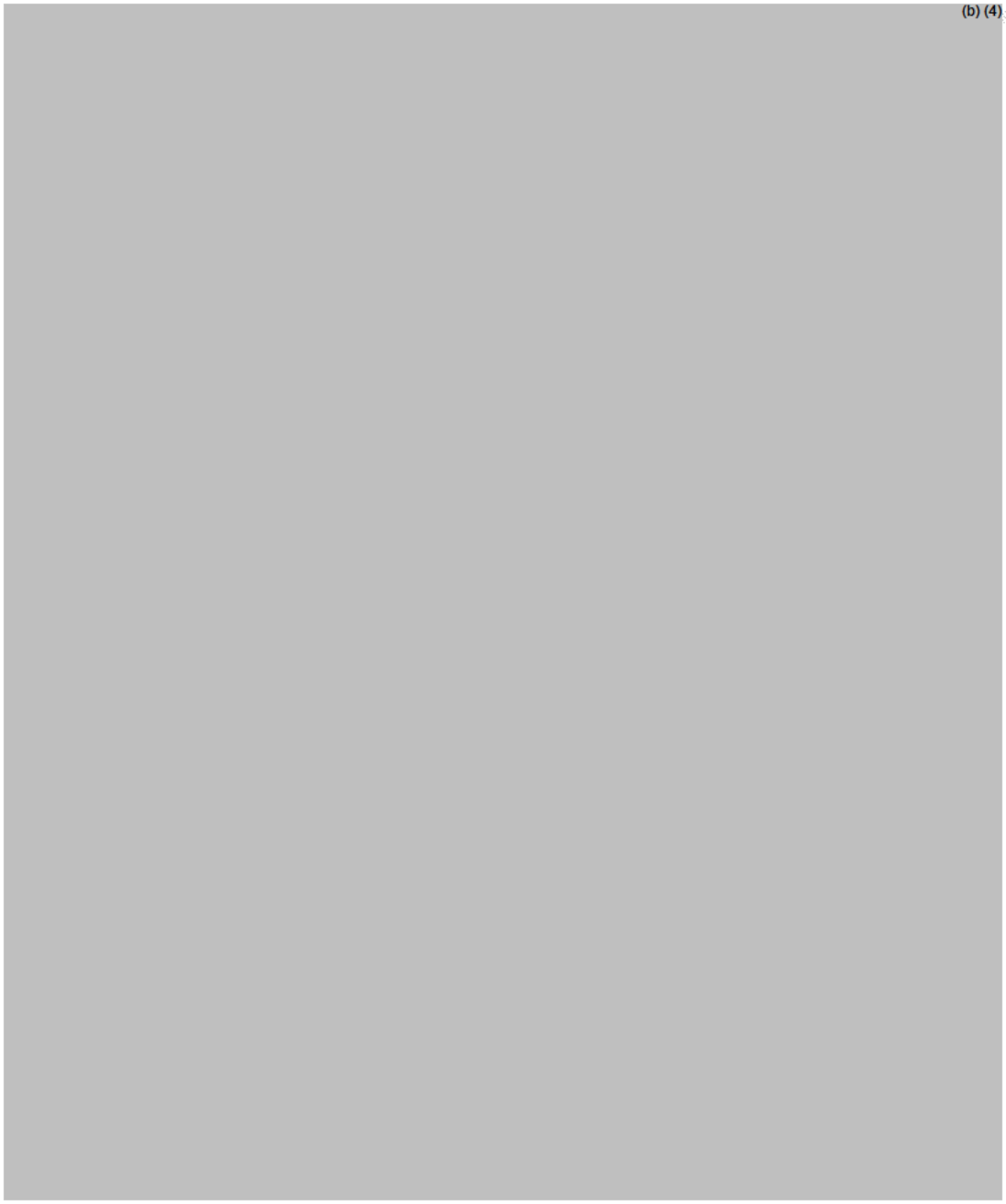
(b) (4)

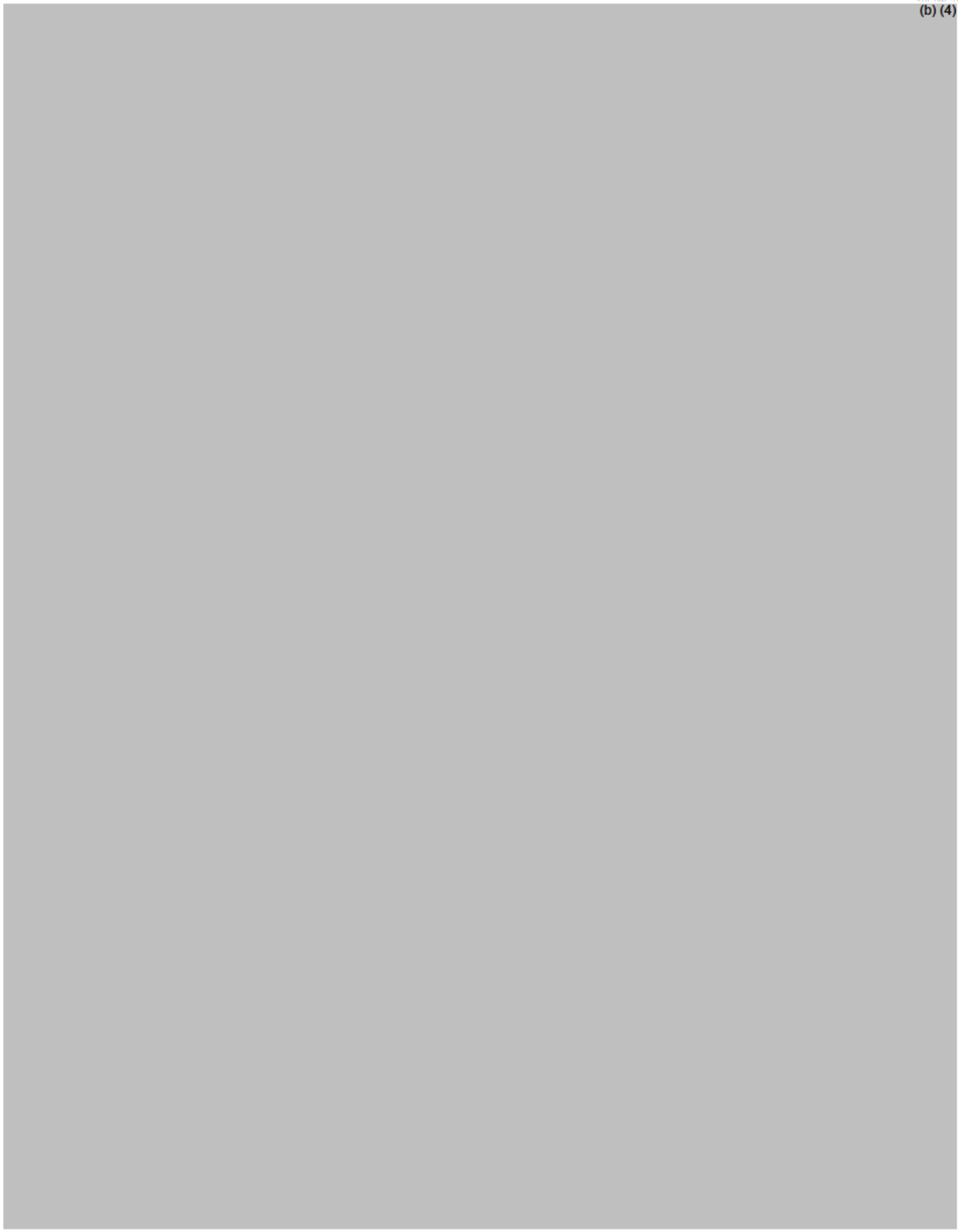


[PAGE * MERGEFORMAT]

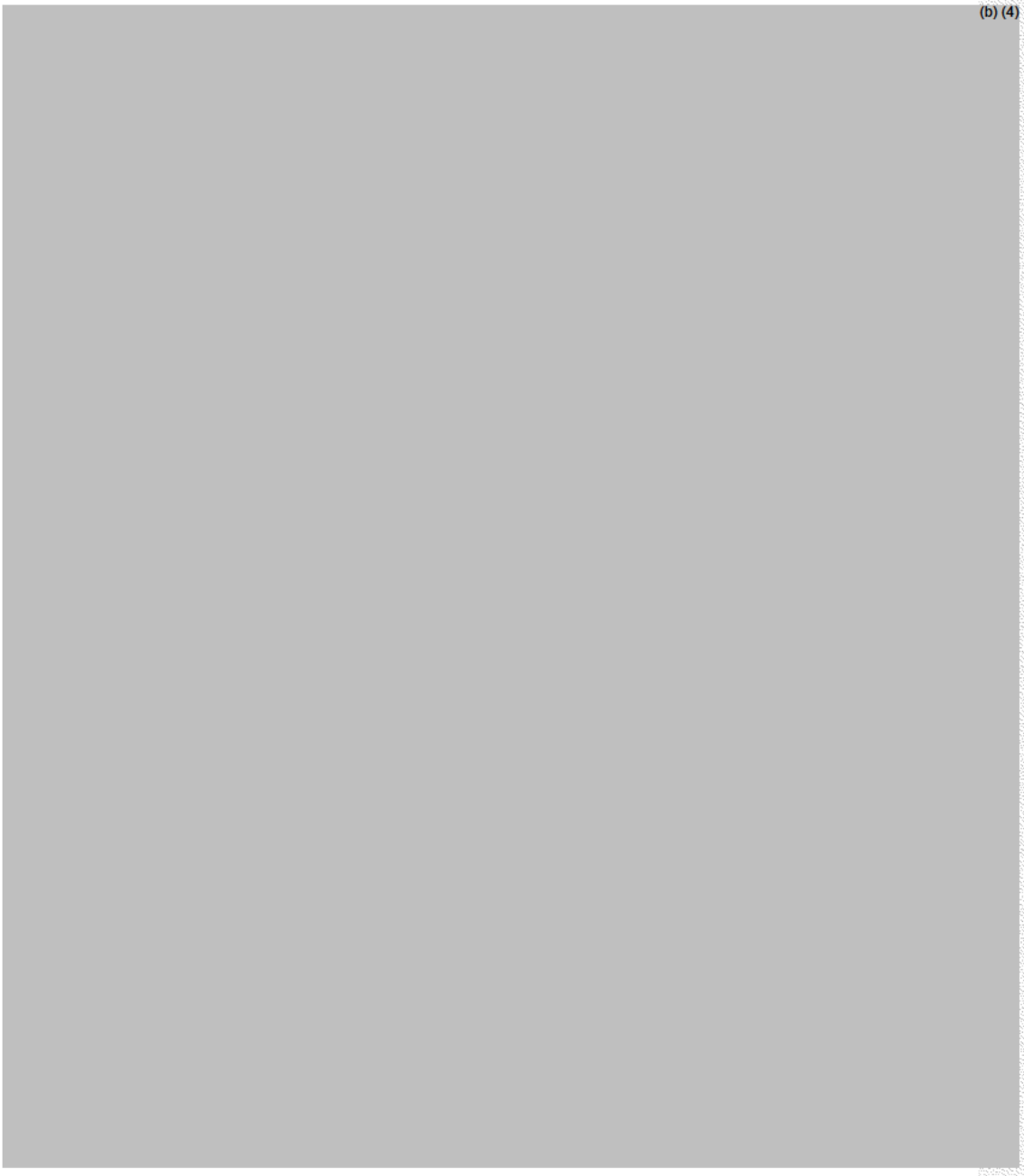



(b) (4)


(b) (4)


(b) (4)

(b) (4)

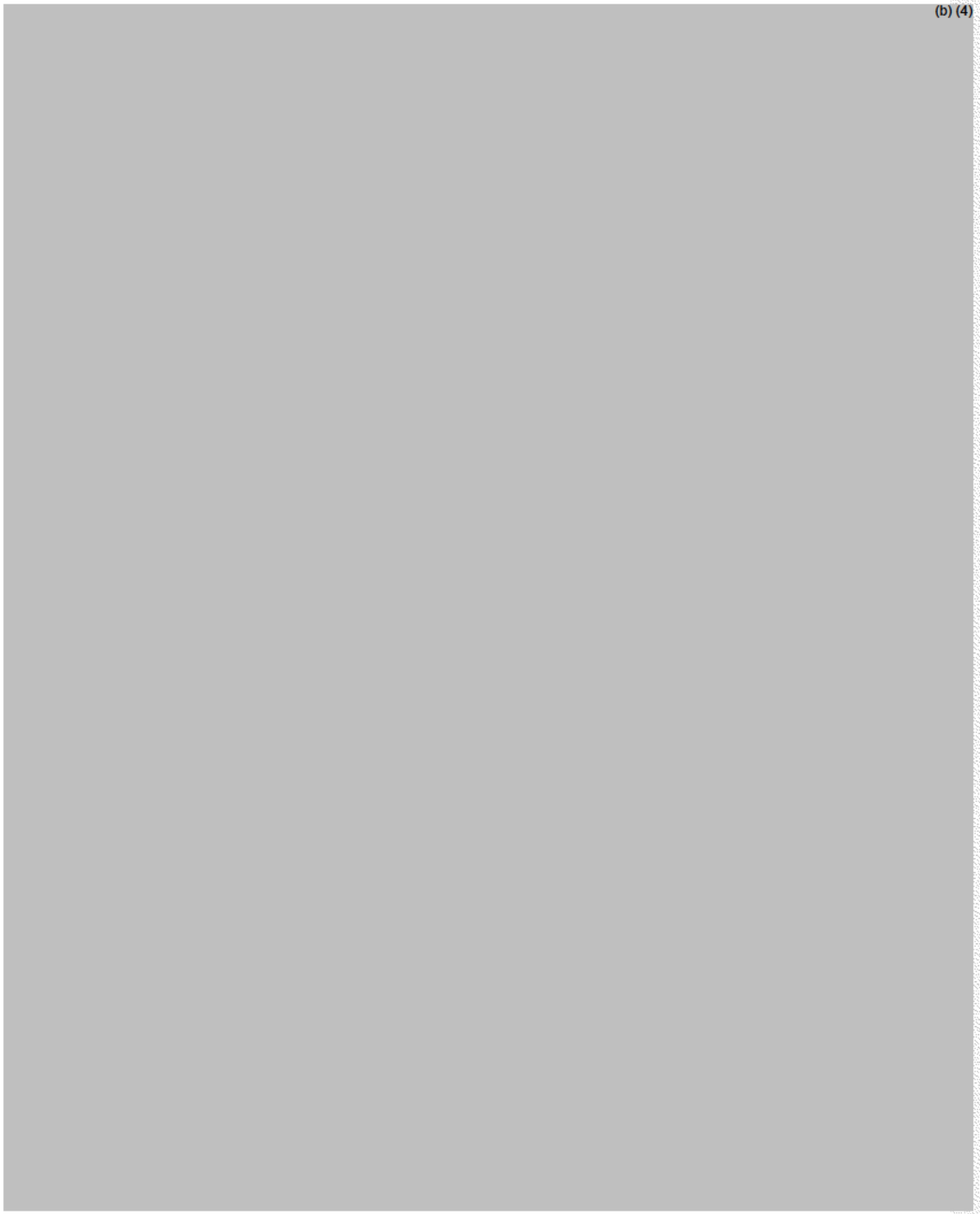


[PAGE * MERGEFORMAT]

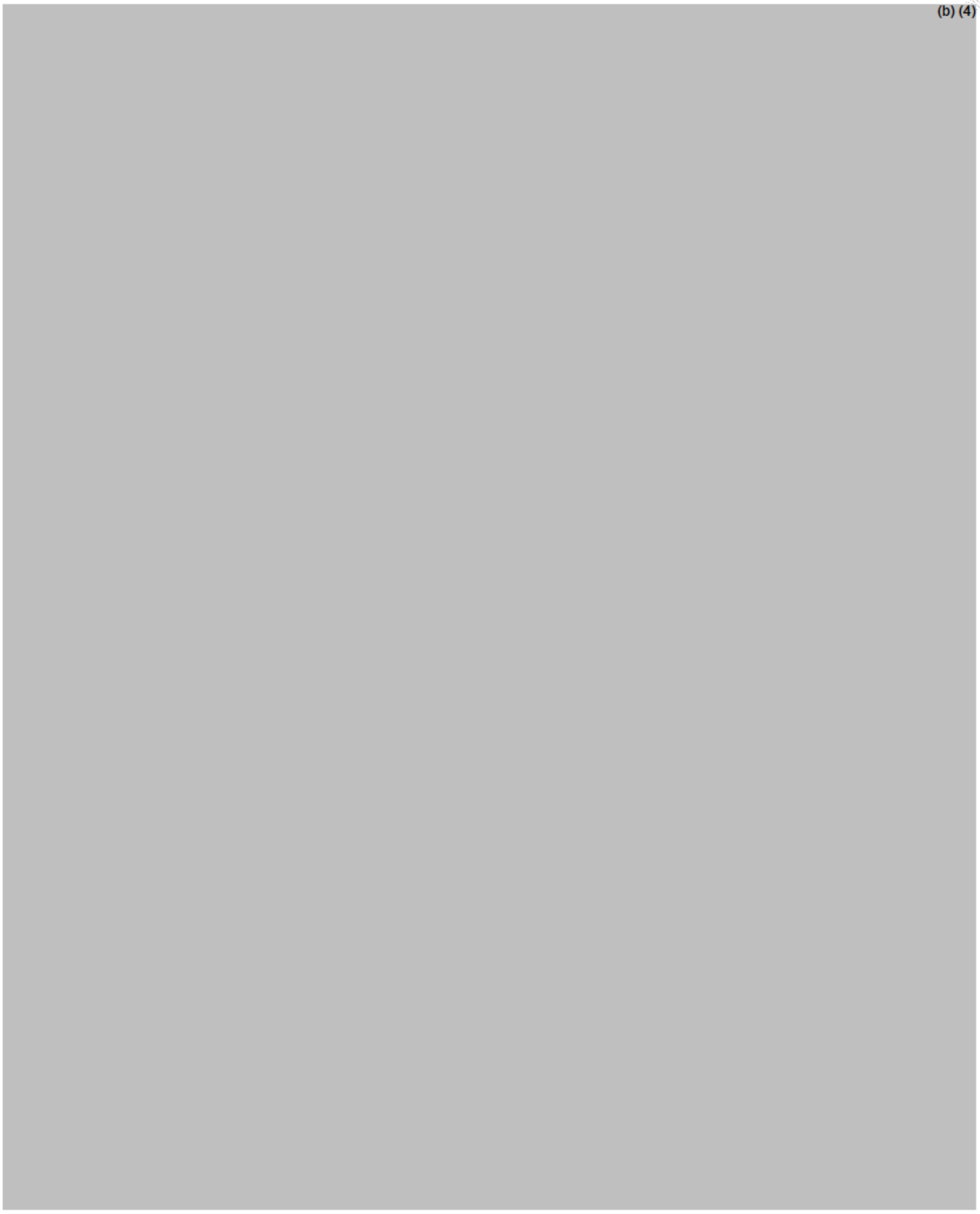
(b) (4)

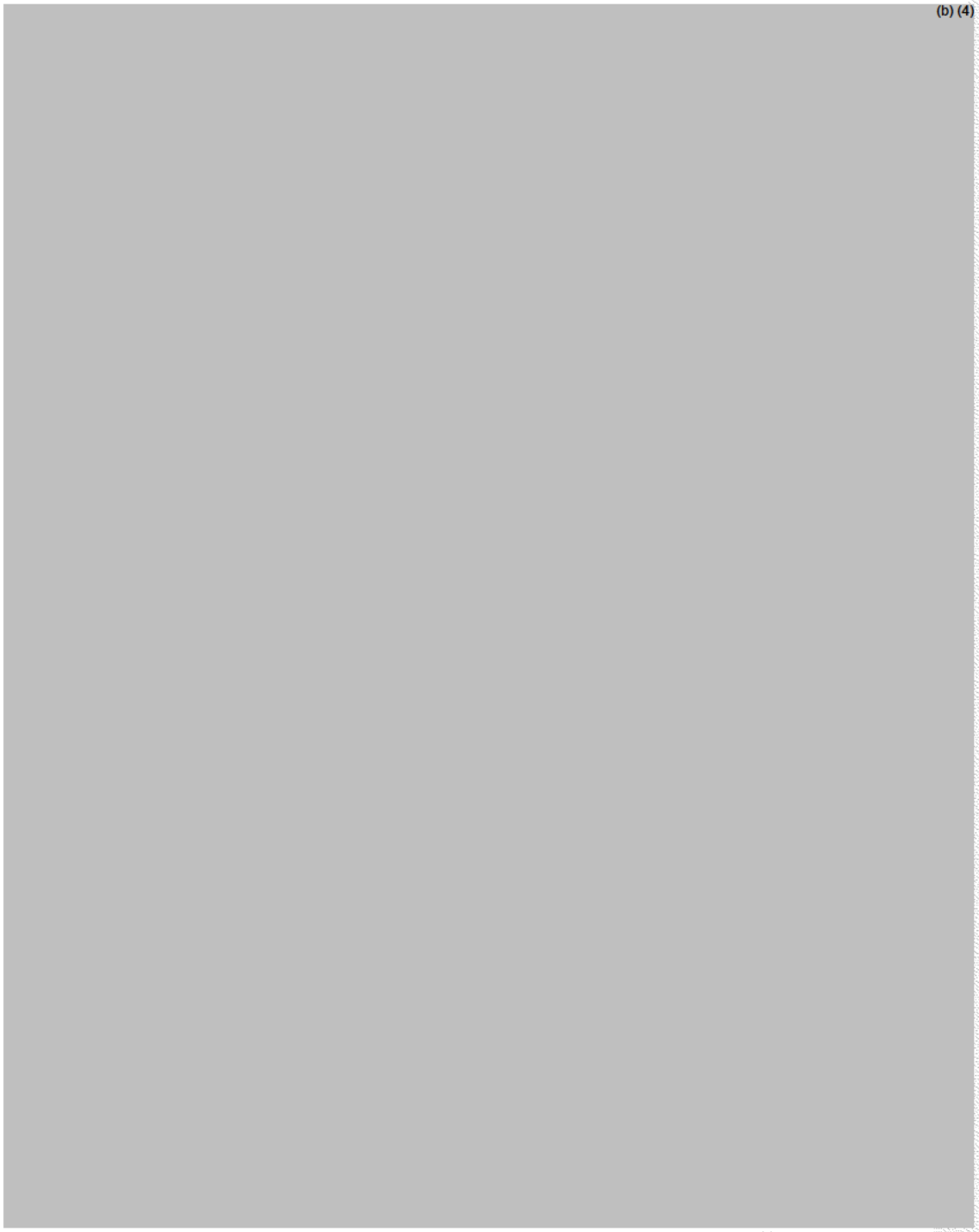
[PAGE * MERGEFORMAT]

(b) (4)

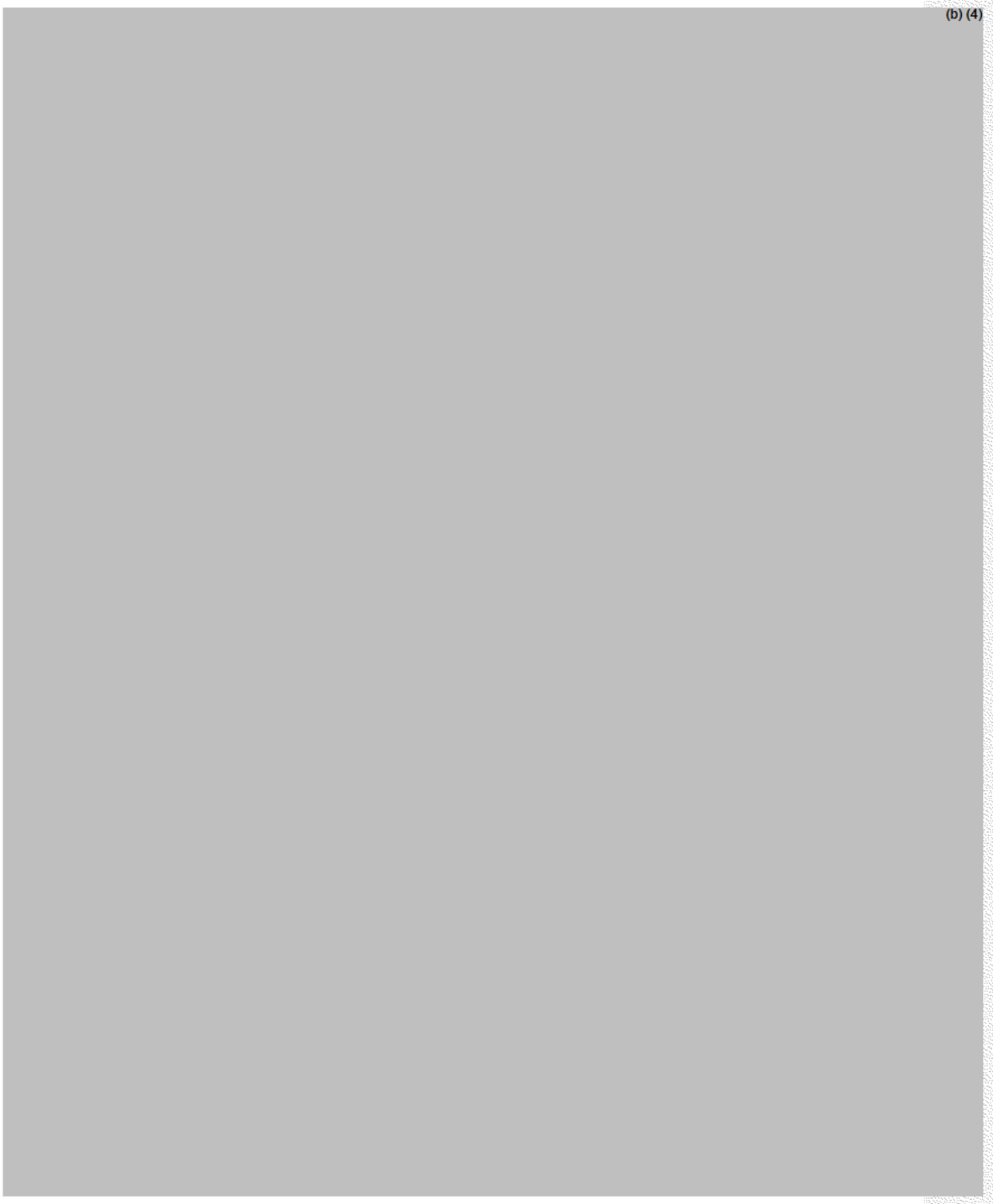


[PAGE * MERGEFORMAT]


(b) (4)


(b) (4)


(b) (4)


(b) (4)

(b) (4)

Revised: 11/2019

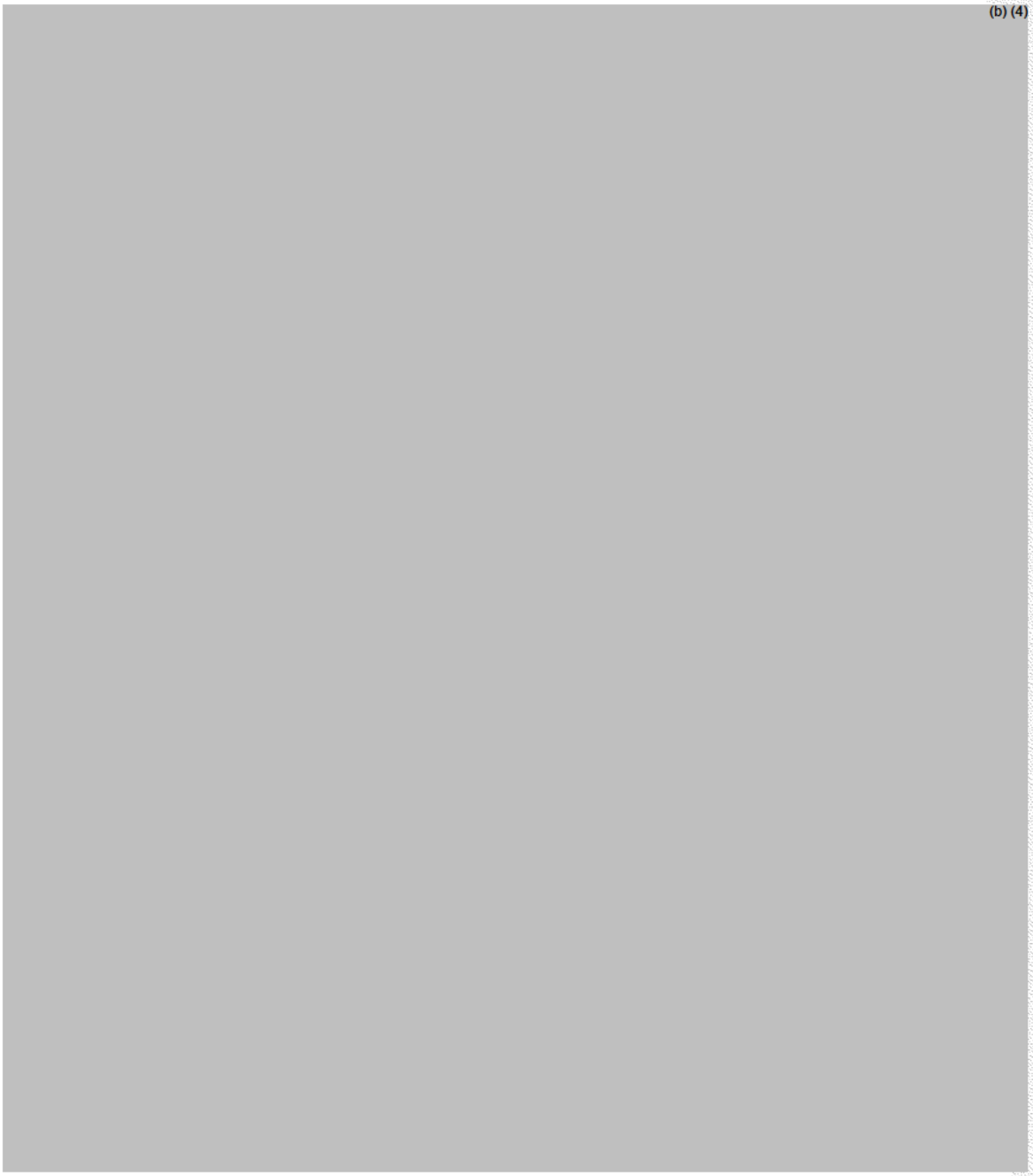
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRIPTODUR safely and effectively. See full prescribing information for TRIPTODUR.

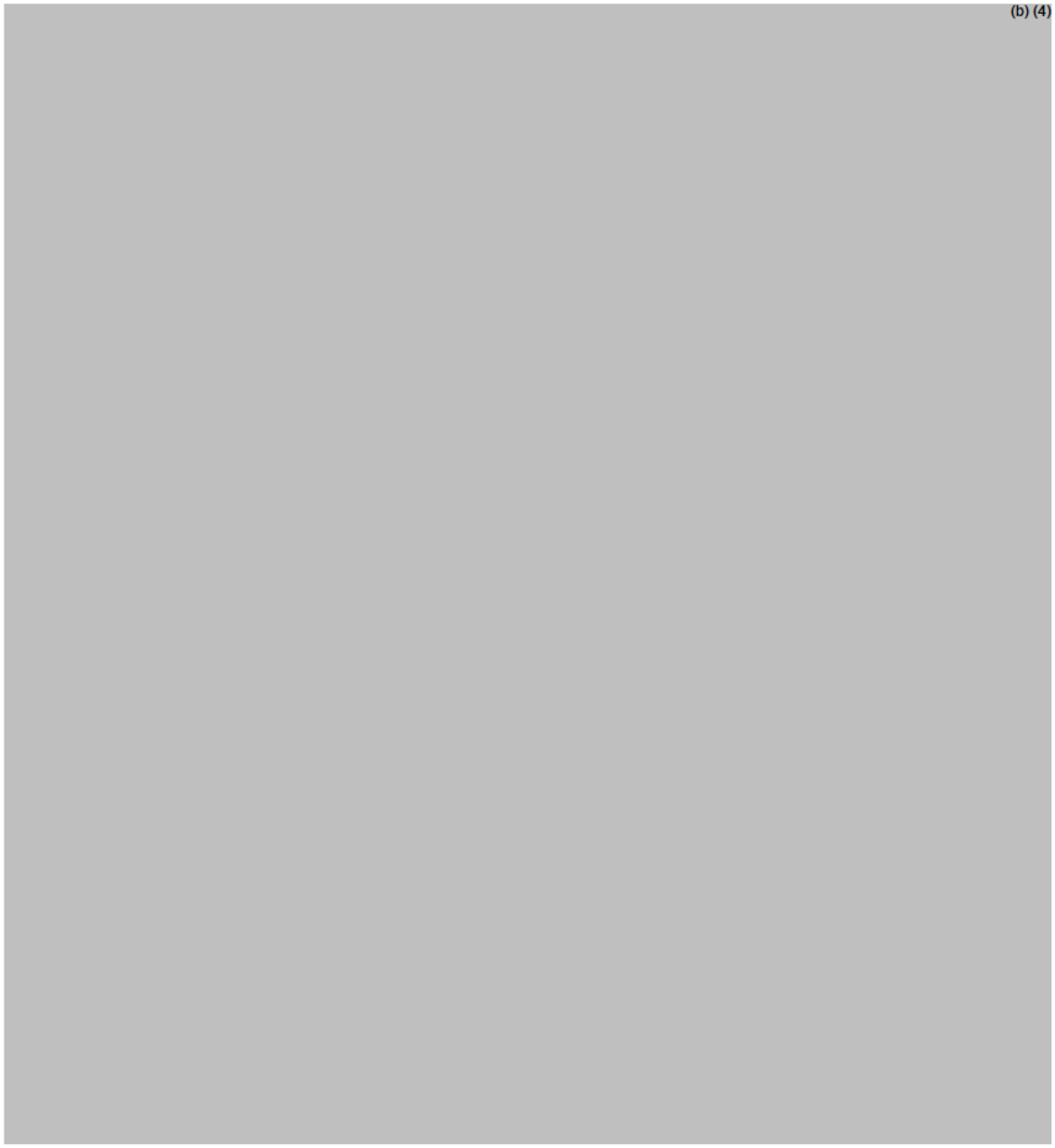
TRIPTODUR (triptorelin) for extended-release injectable suspension, for intramuscular use
Initial U.S. Approval: 2000

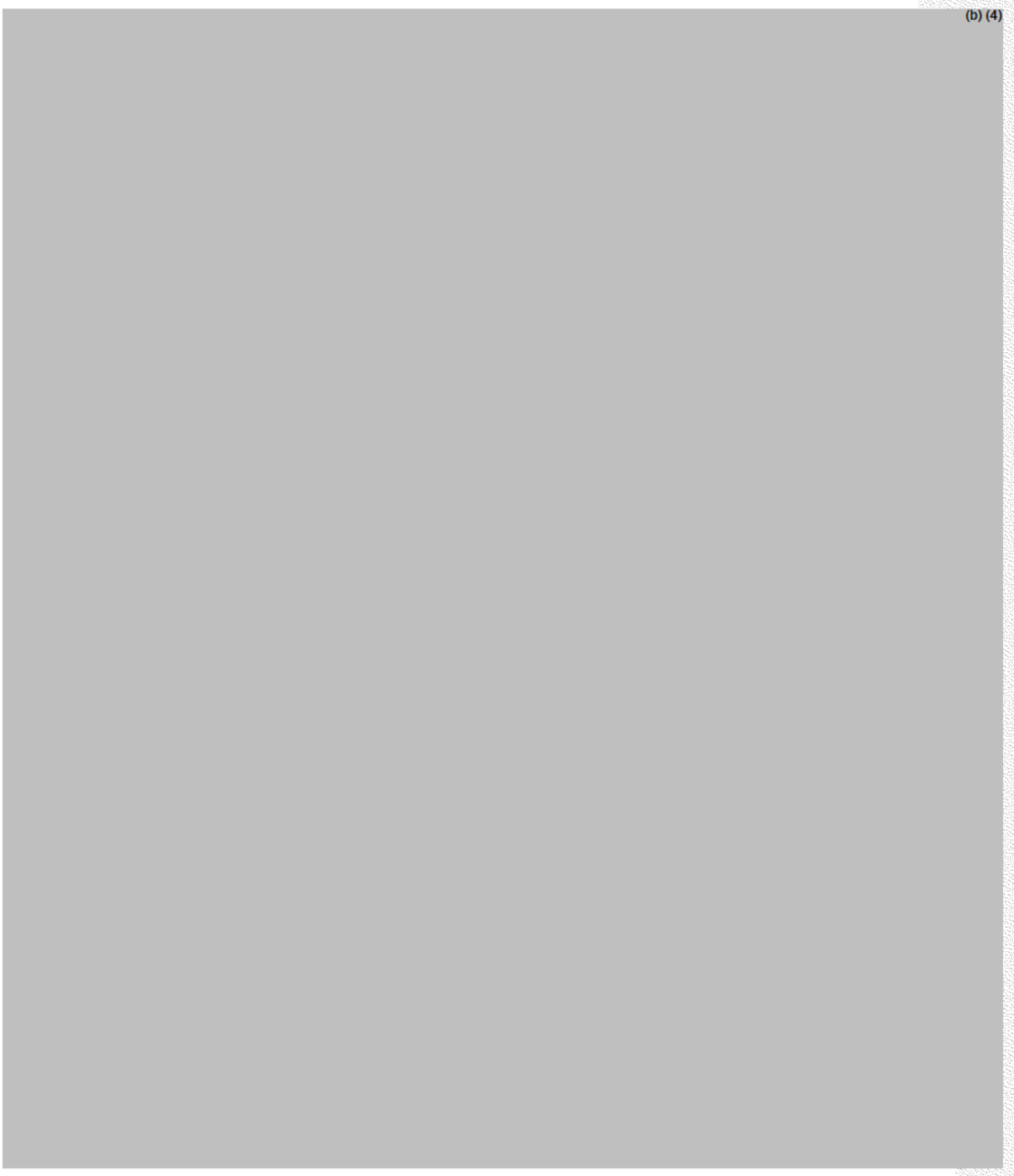
(b) (4)

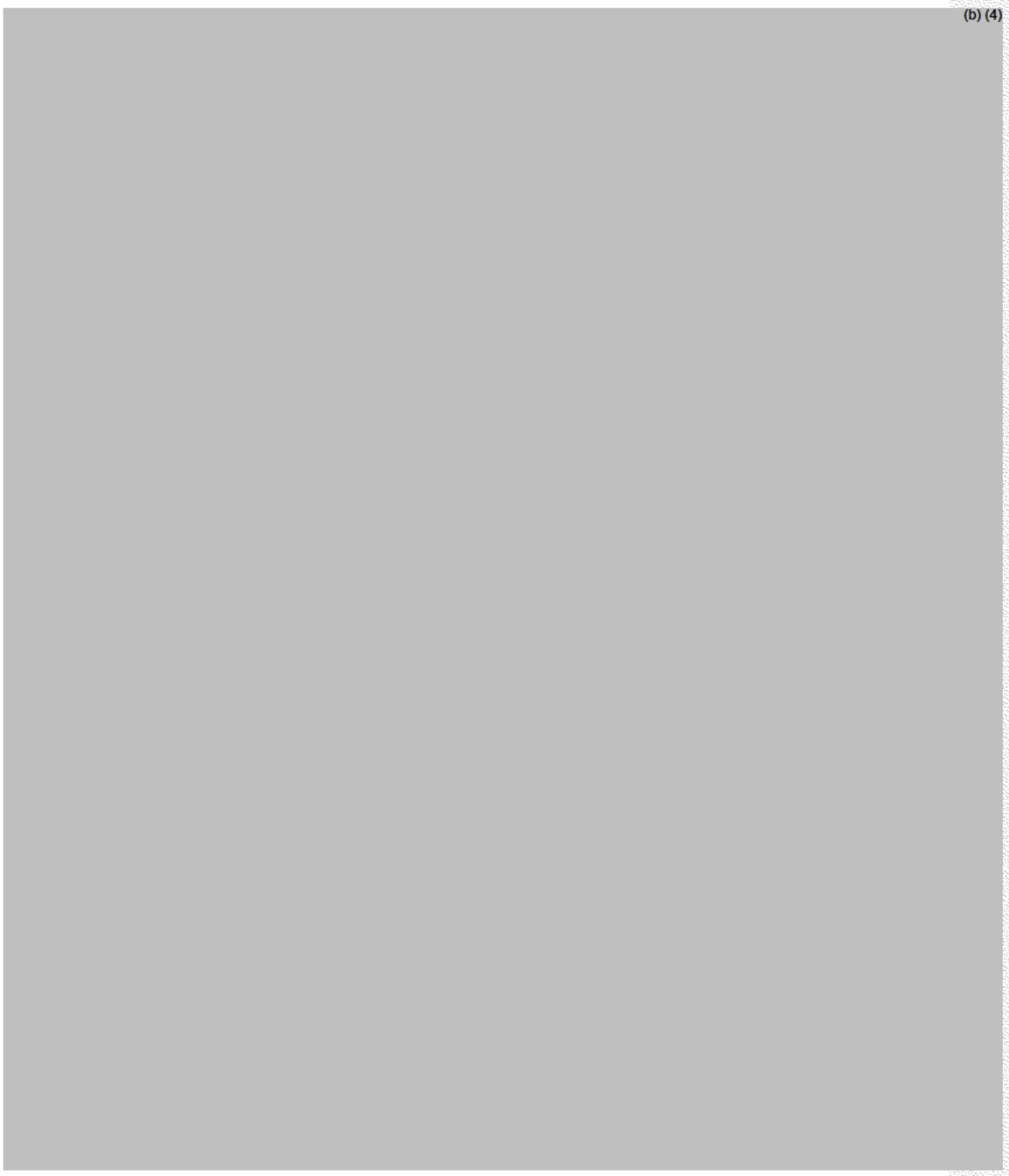
(b) (4)

[PAGE * MERGEFORMAT]

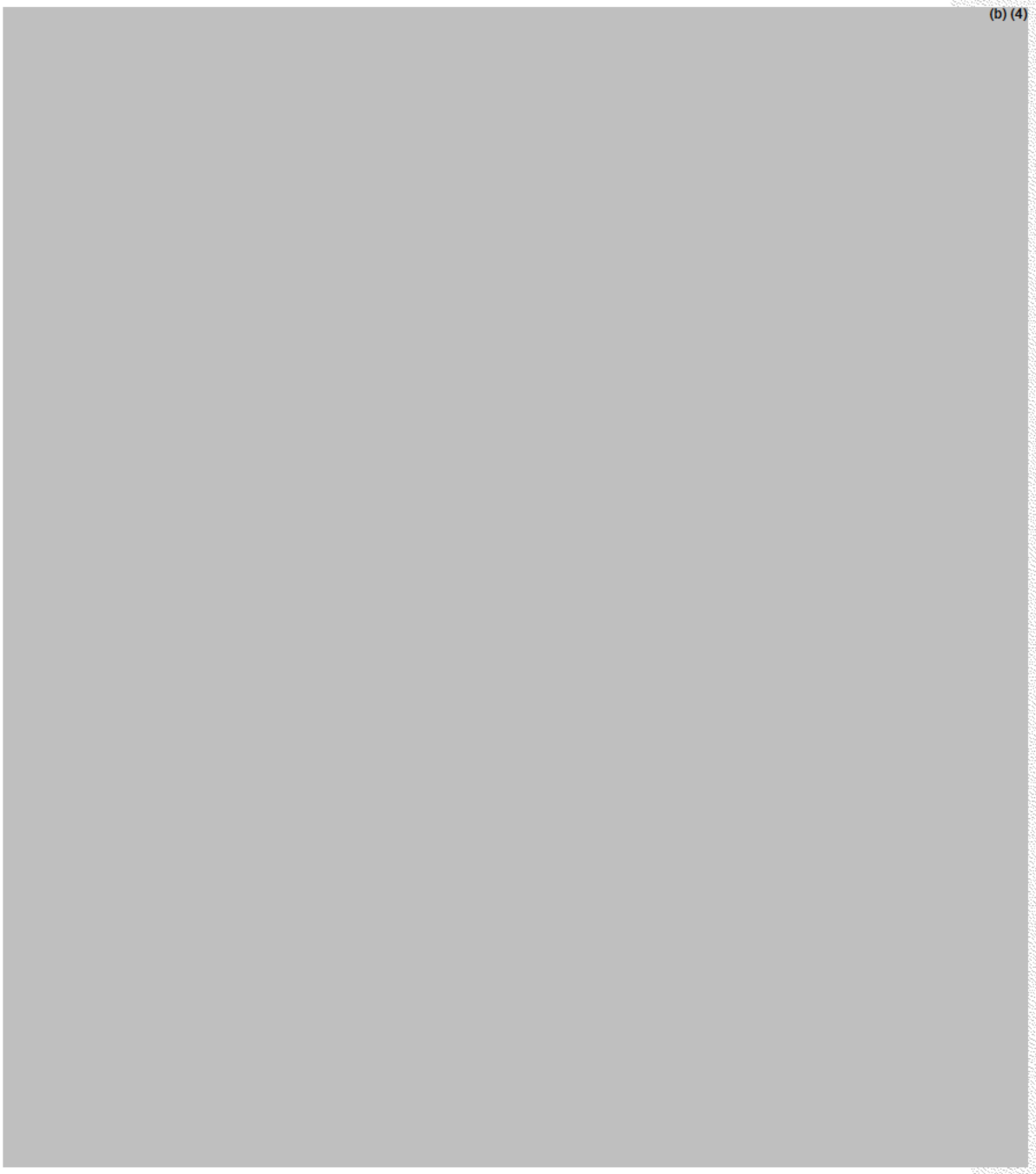

(b) (4)

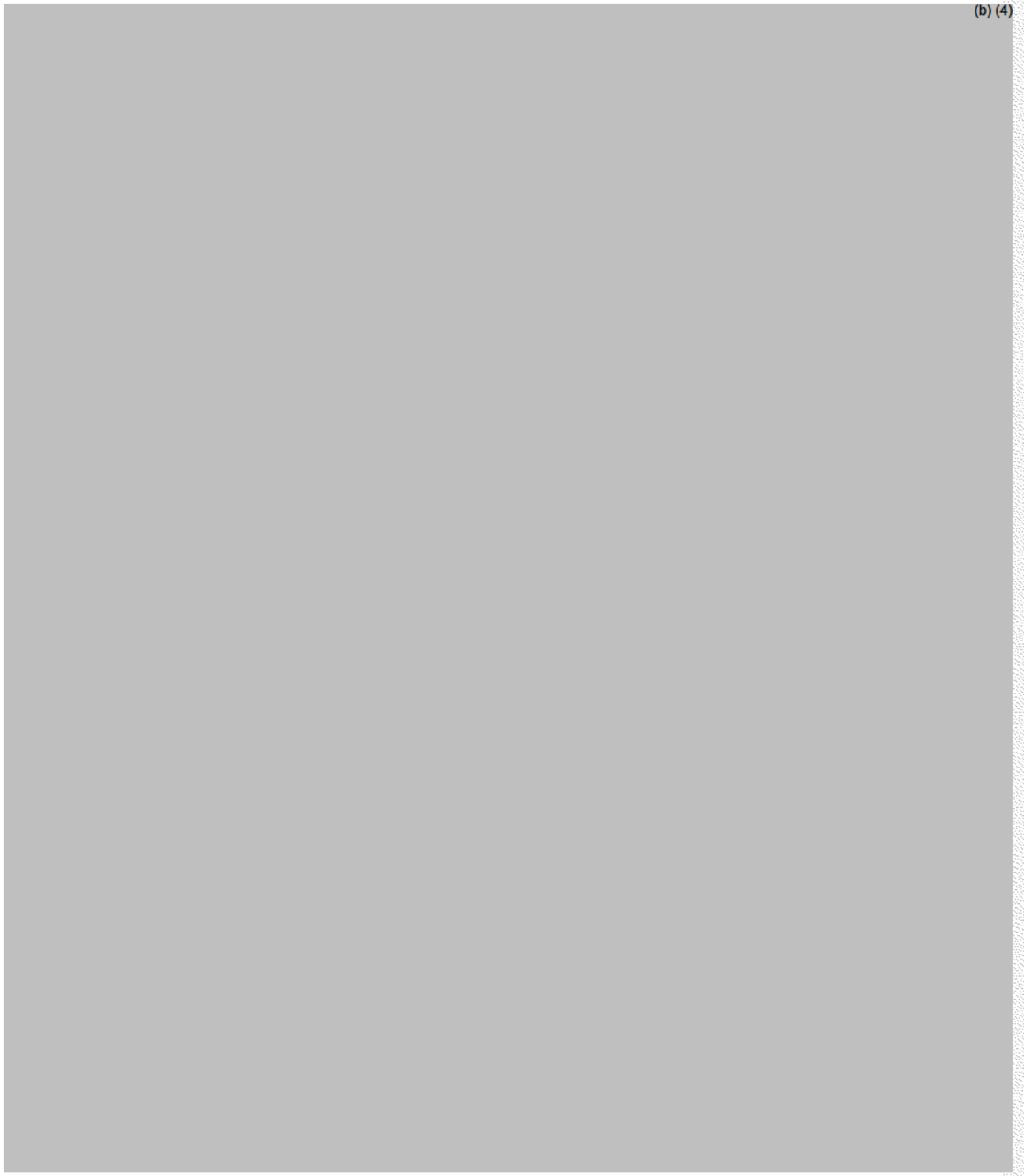

(b) (4)

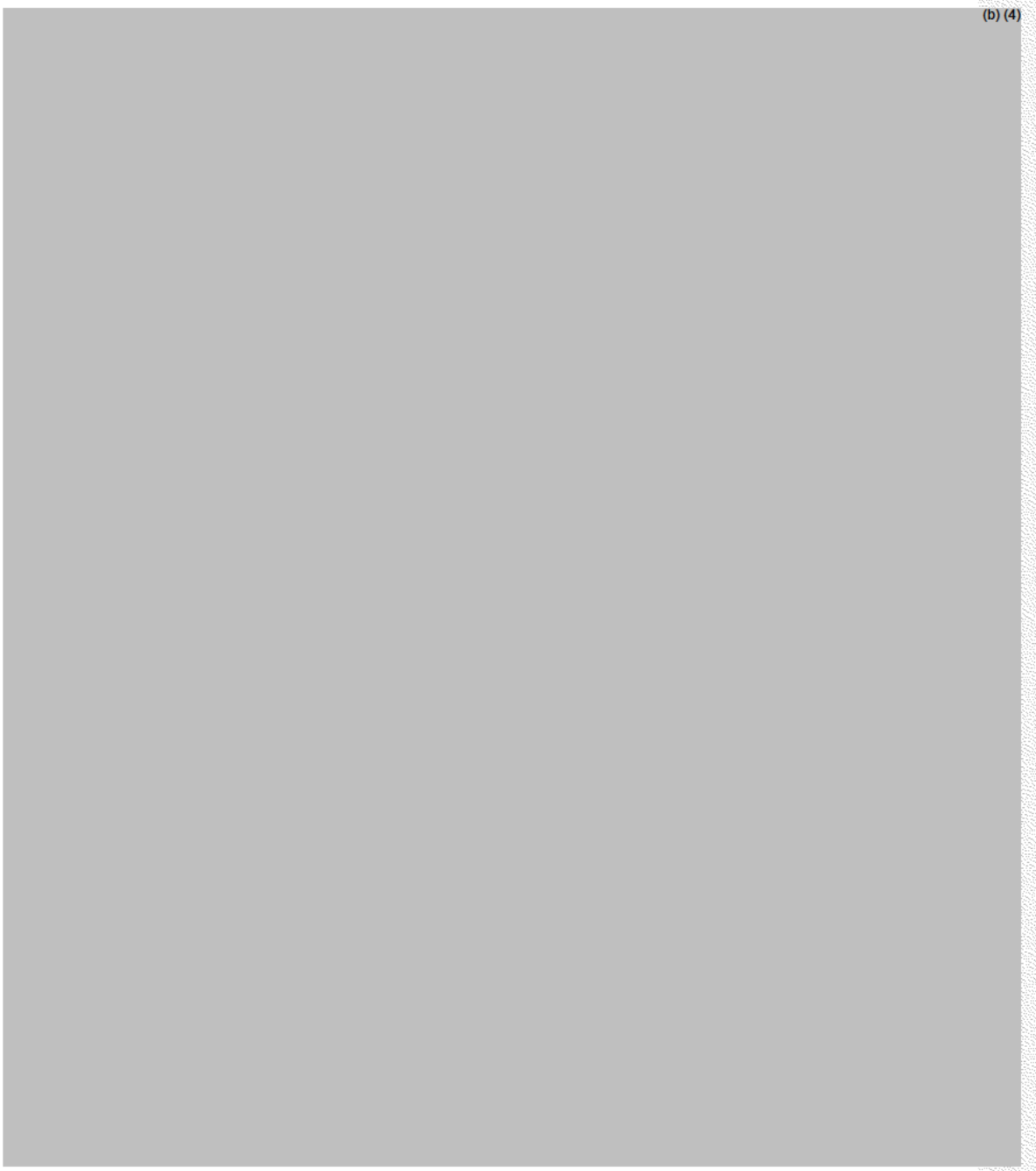

(b) (4)

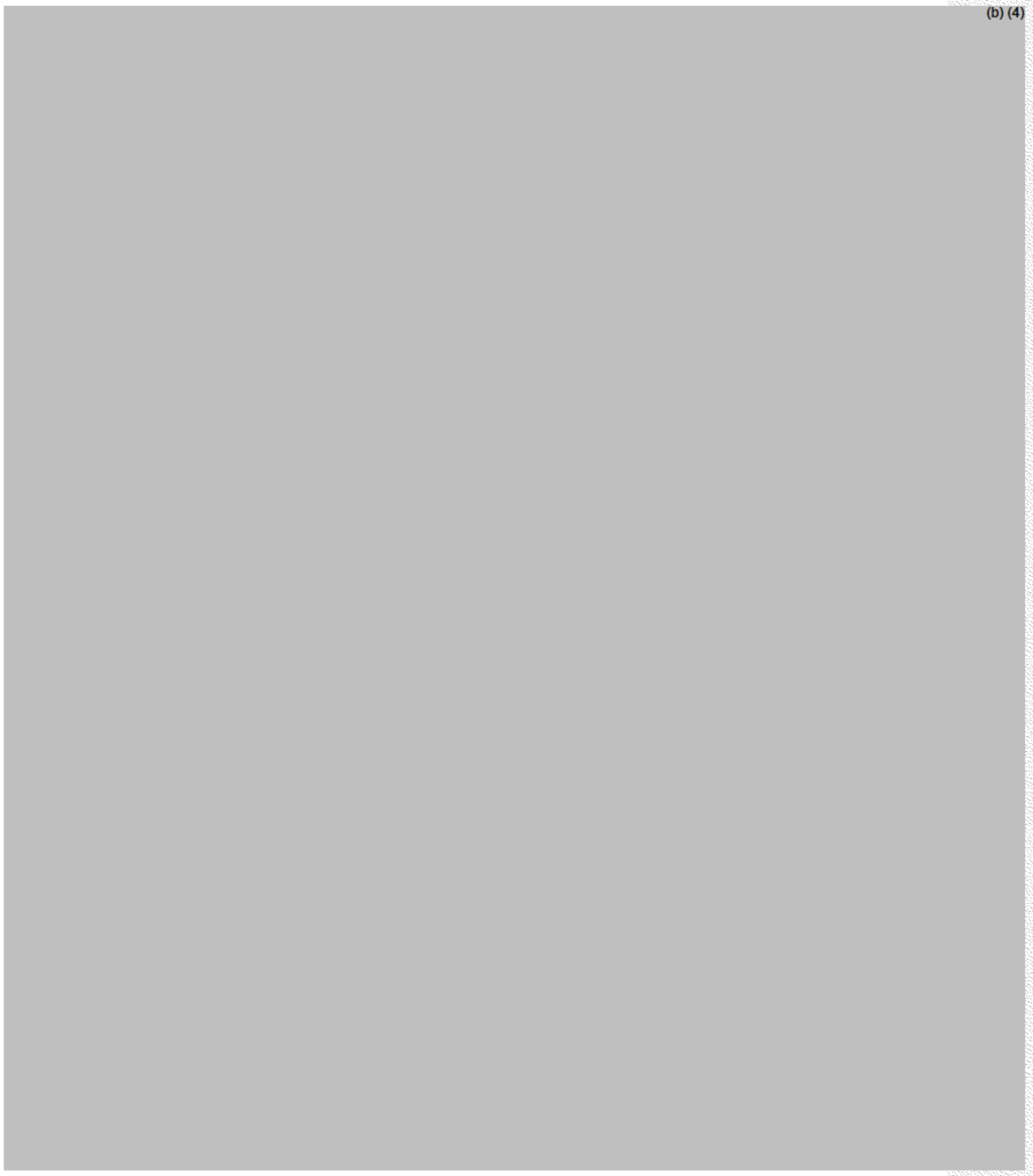


[PAGE * MERGEFORMAT]


(b) (4)


(b) (4)


(b) (4)



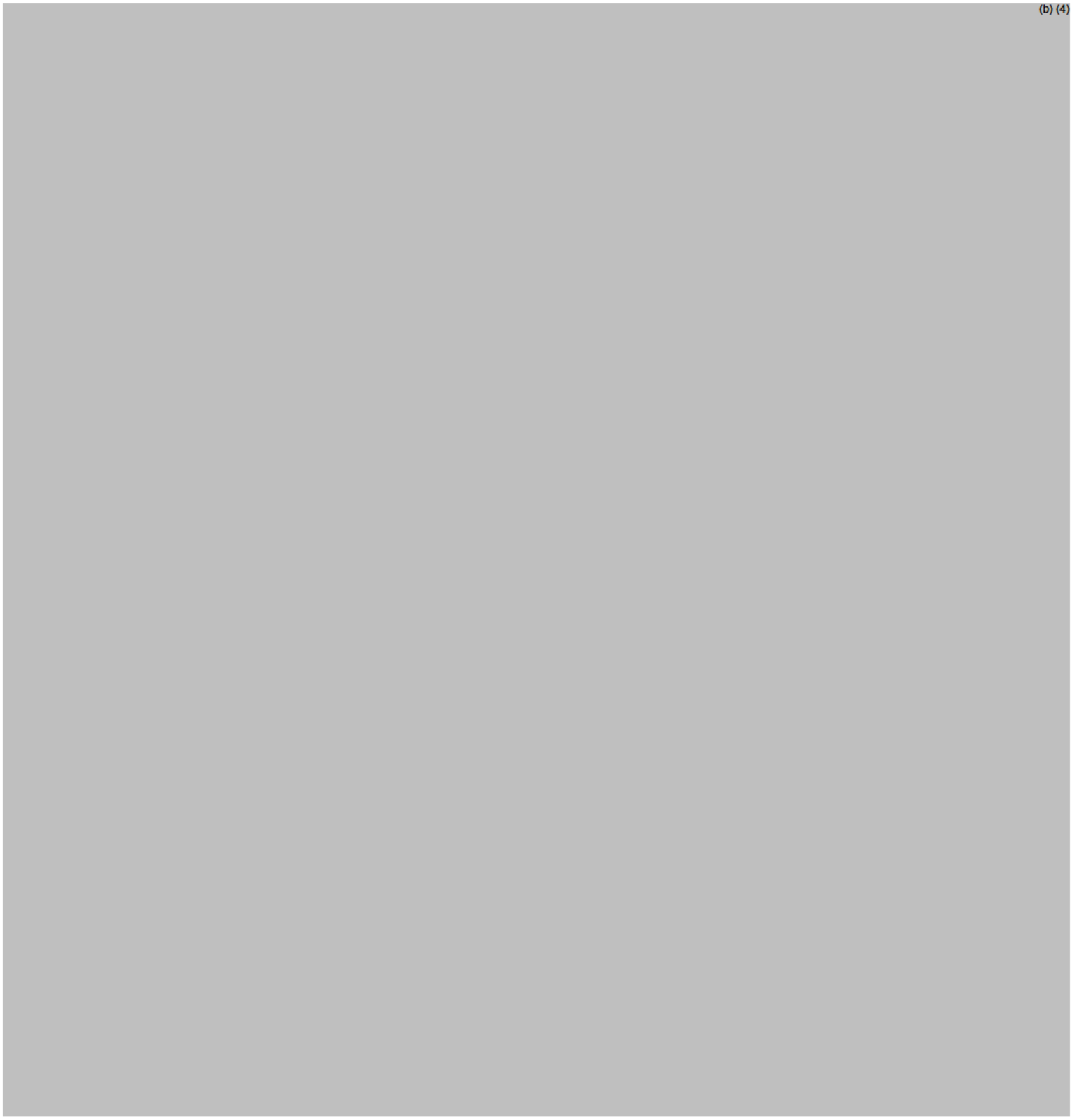

(b) (4)

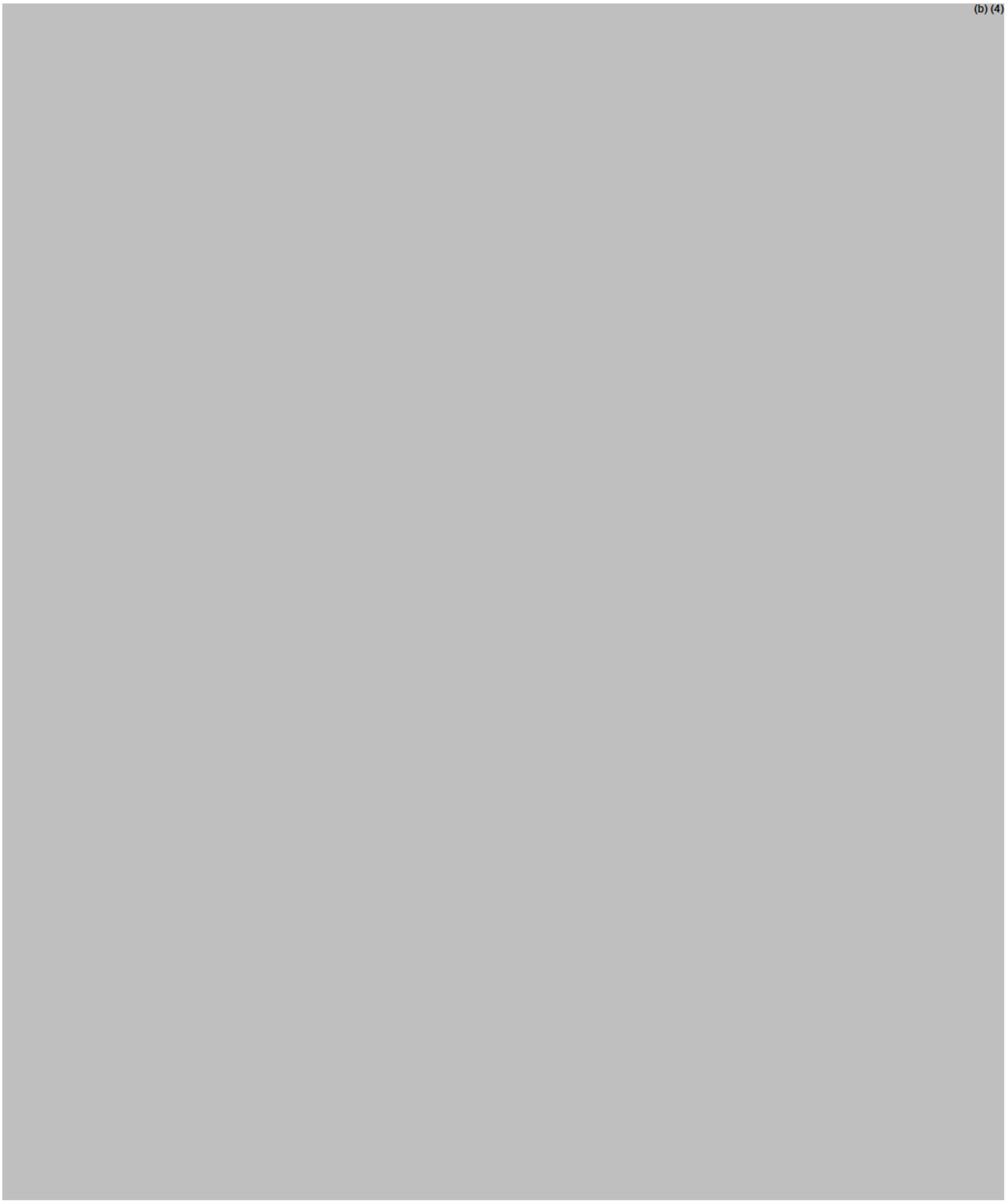
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FENSOLVI® safely and effectively. See full prescribing information for FENSOLVI.

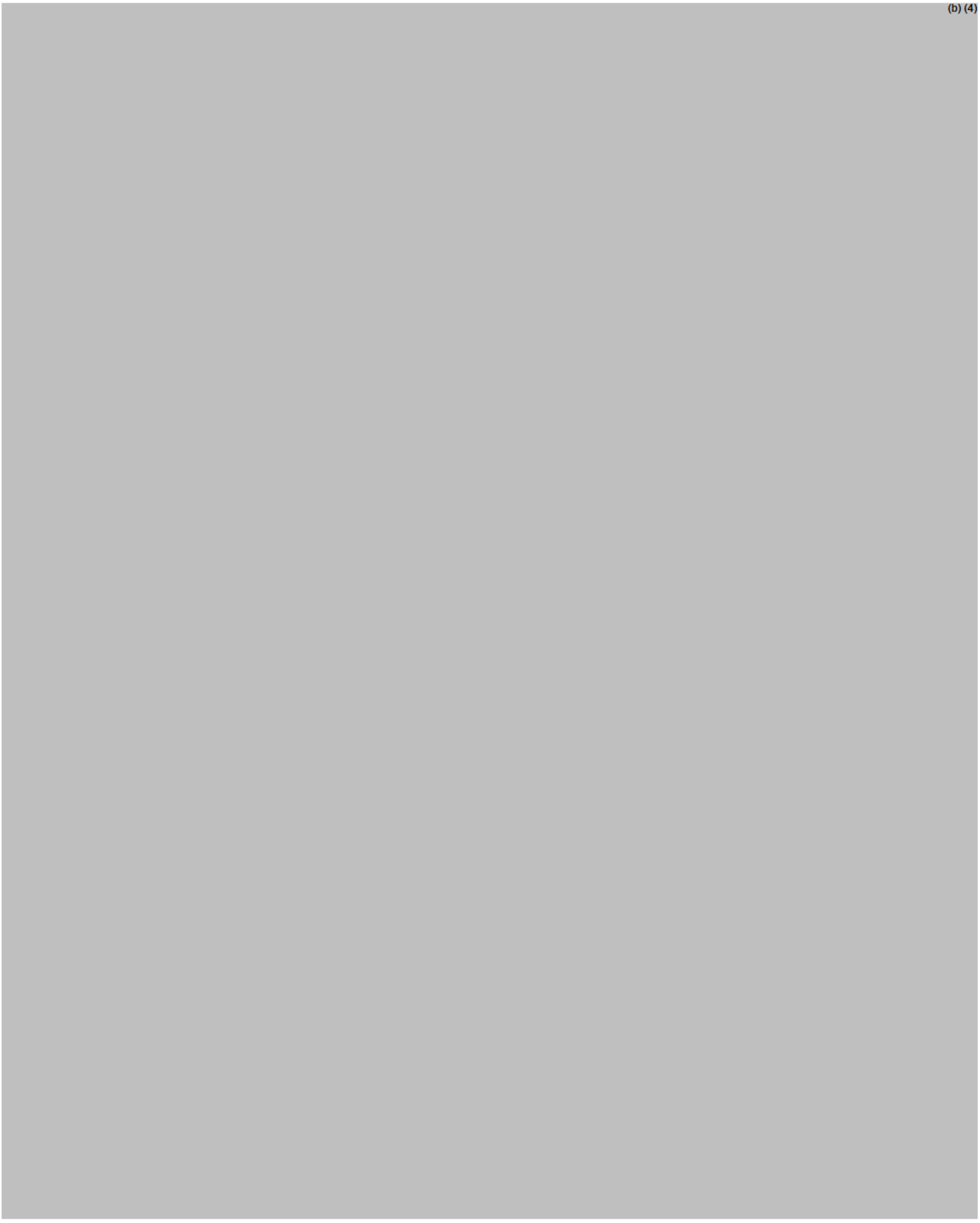
FENSOLVI (leuprolide acetate) for injectable suspension, for subcutaneous use
Initial U.S. Approval: 1985

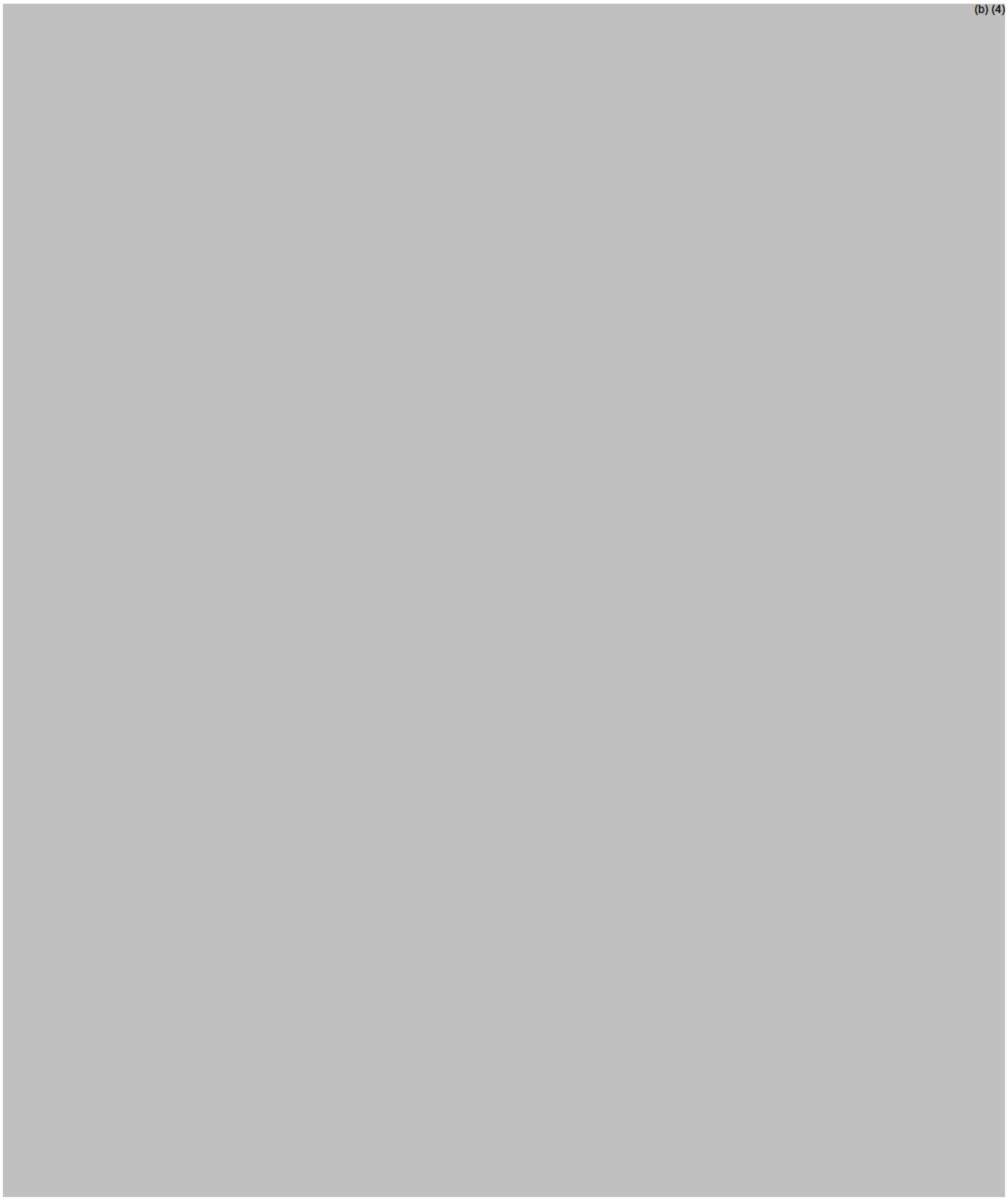
(b) (4)

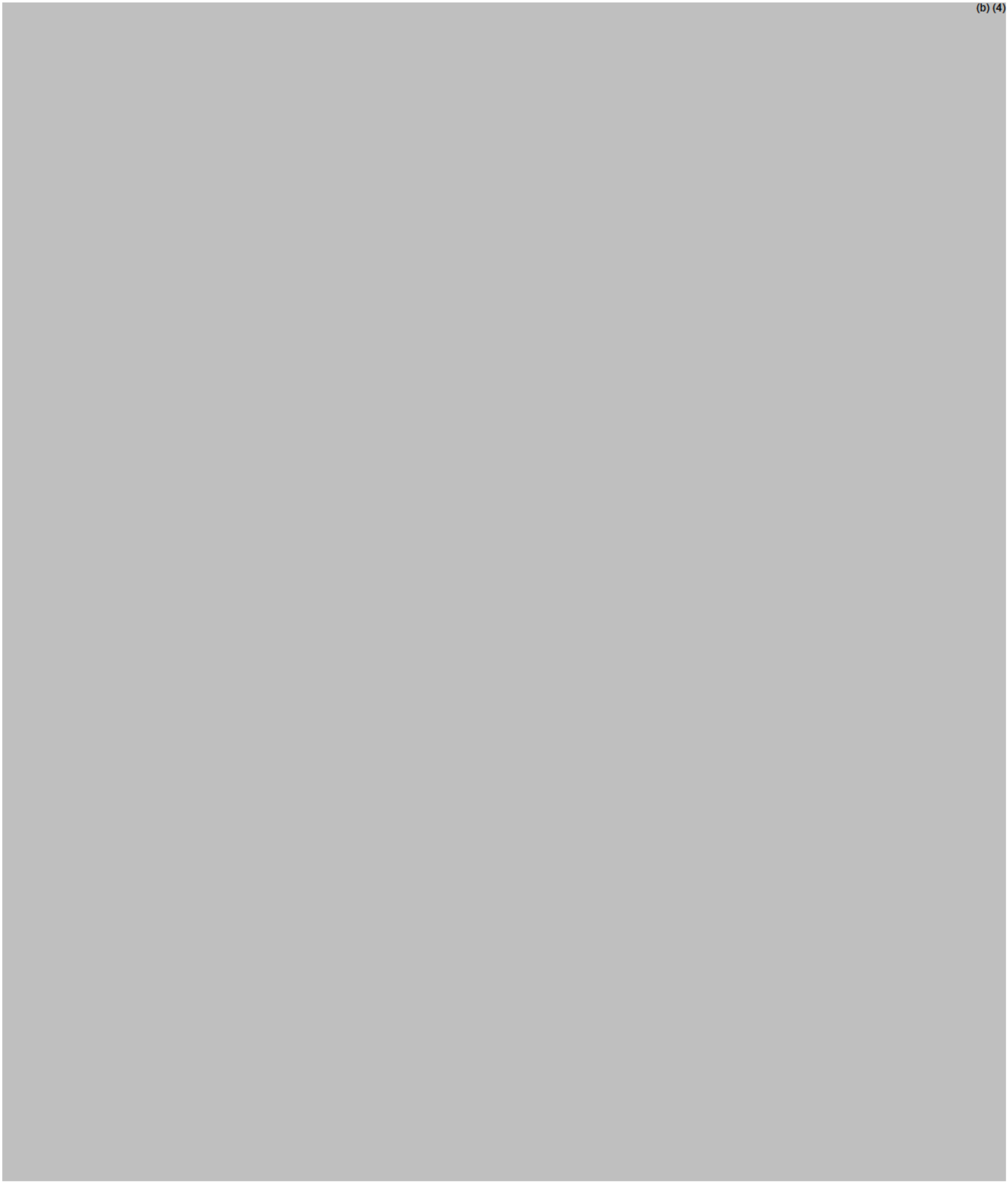
(b) (4)


(b) (4)

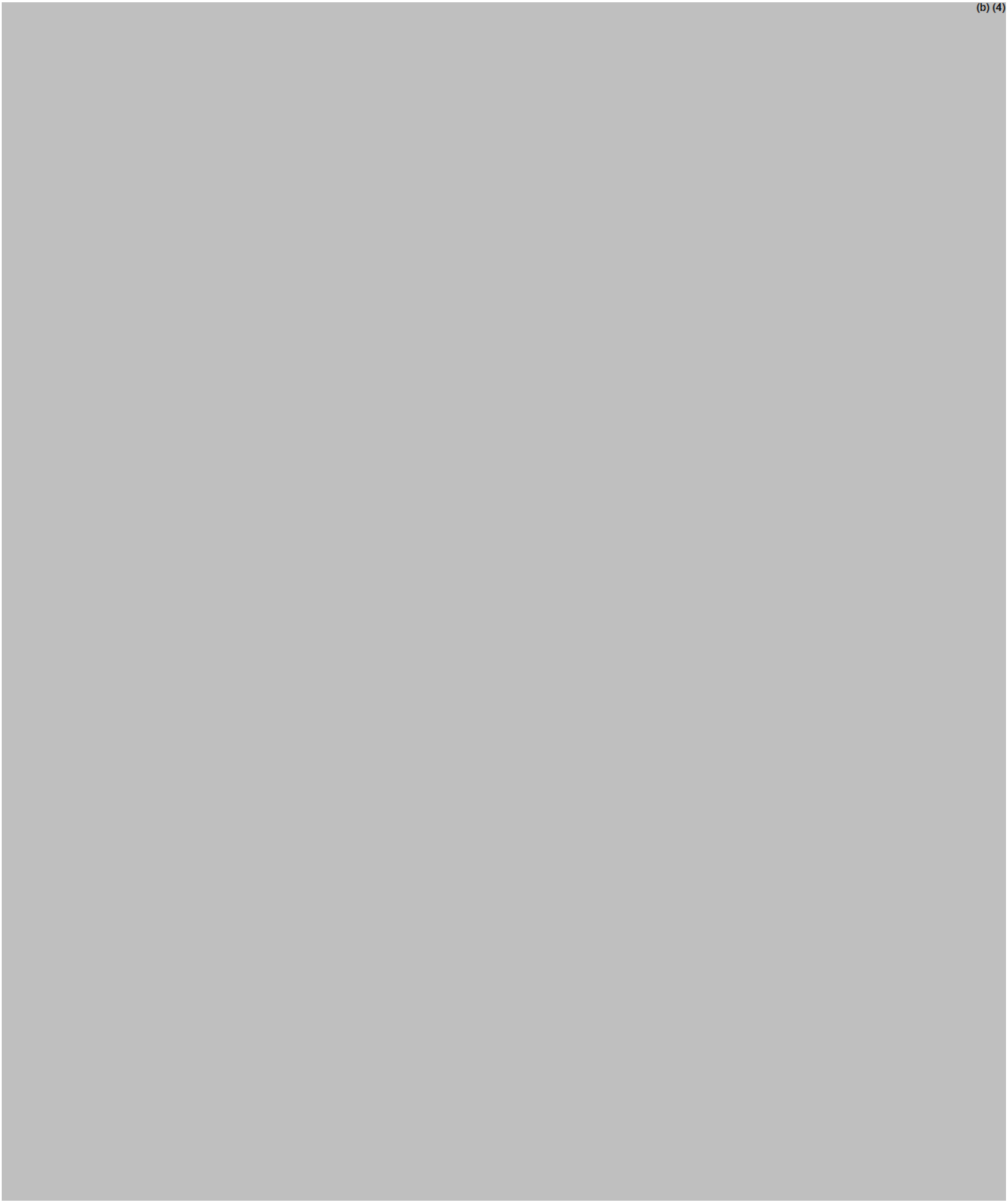

(b) (4)

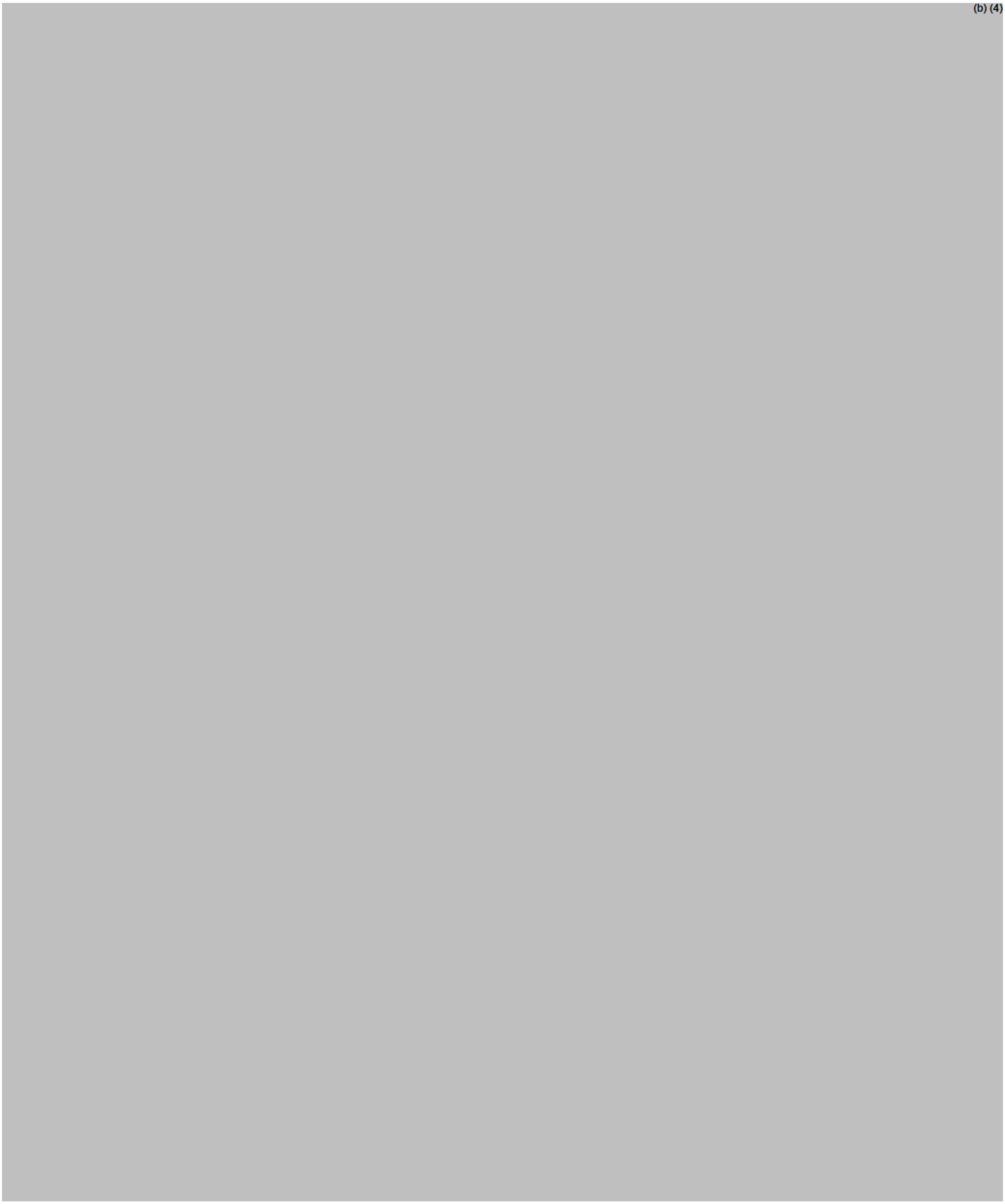

(b) (4)

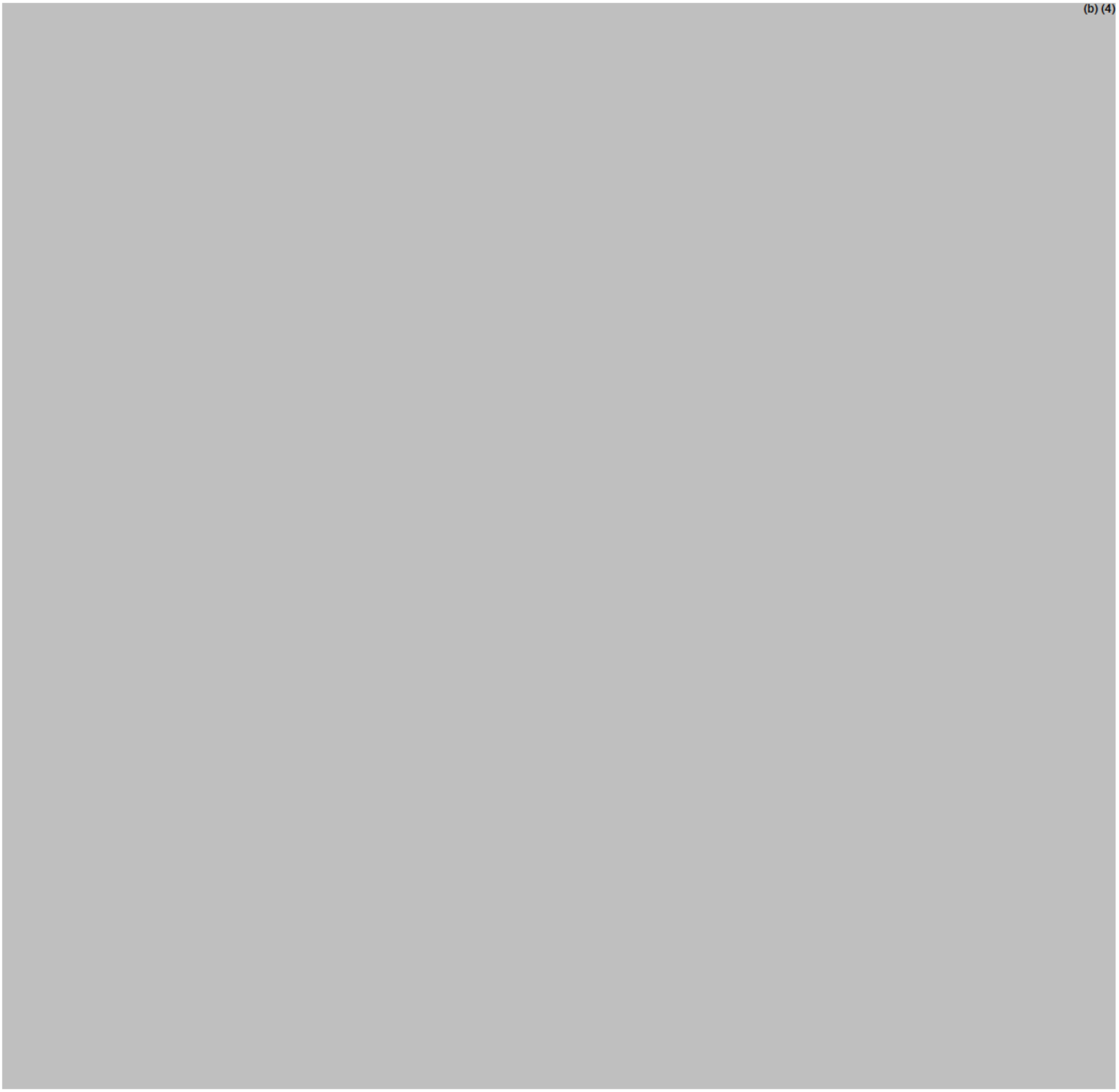

(b) (4)

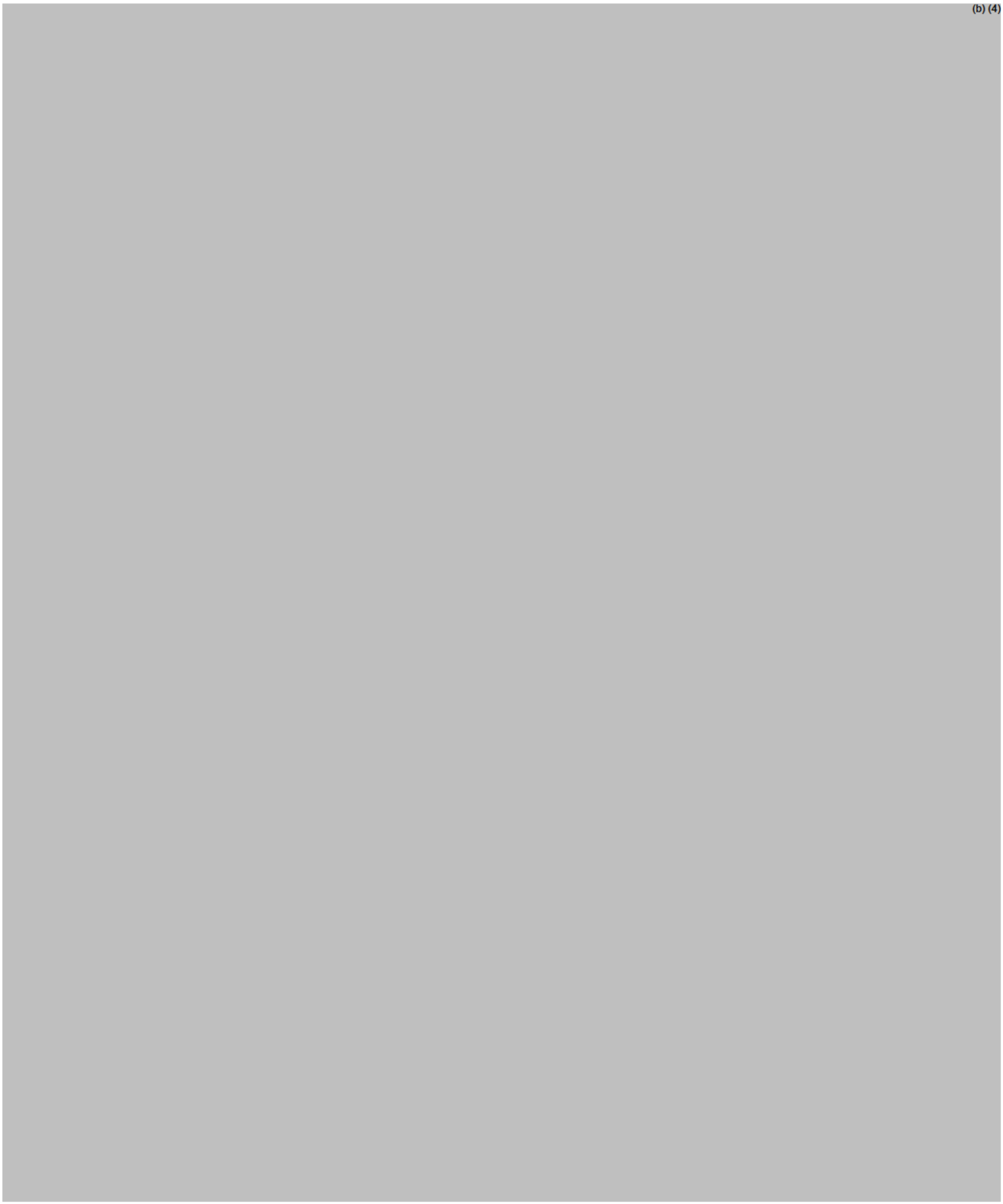

(b) (4)

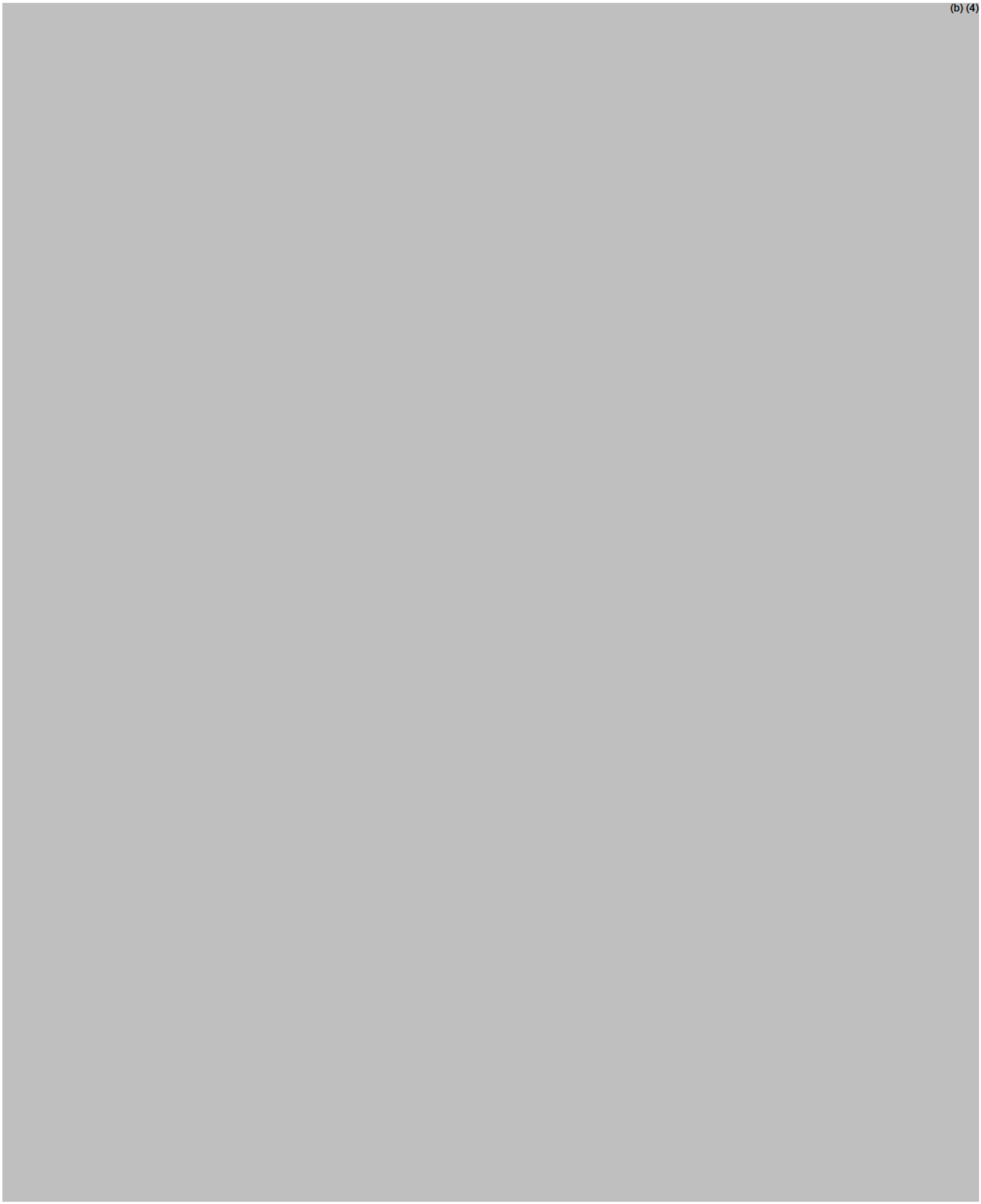
(b) (4)

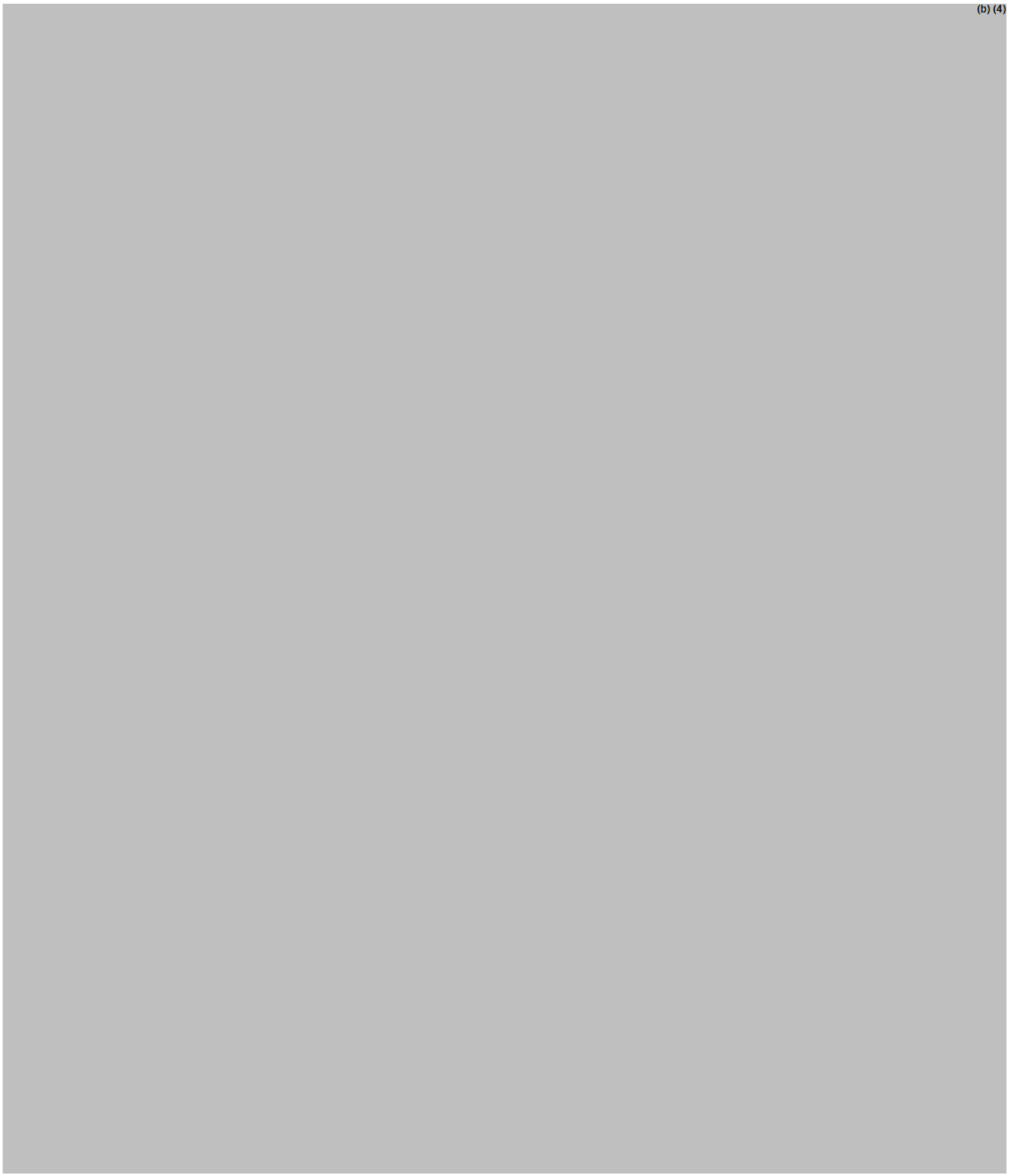

(b) (4)

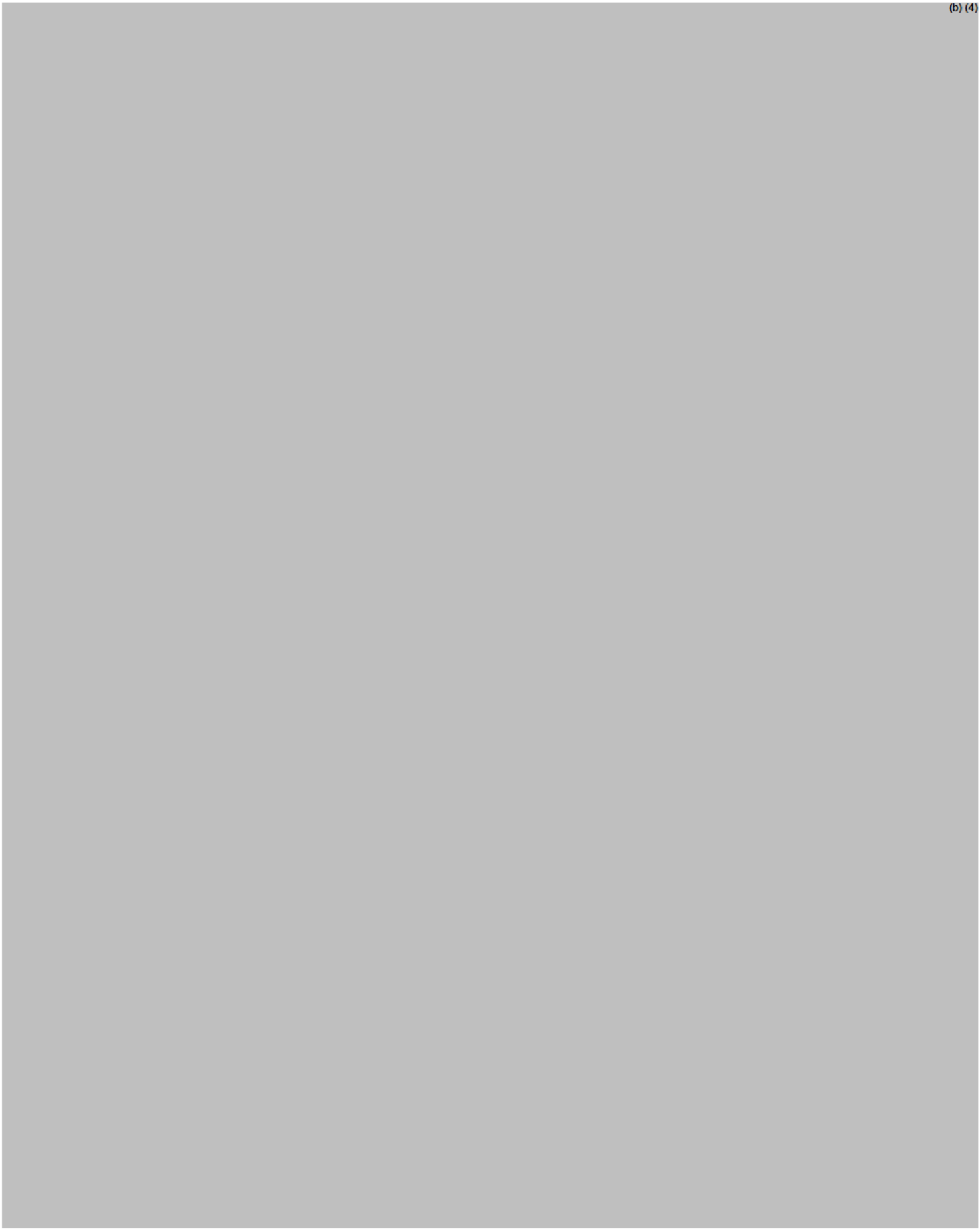

(b) (4)

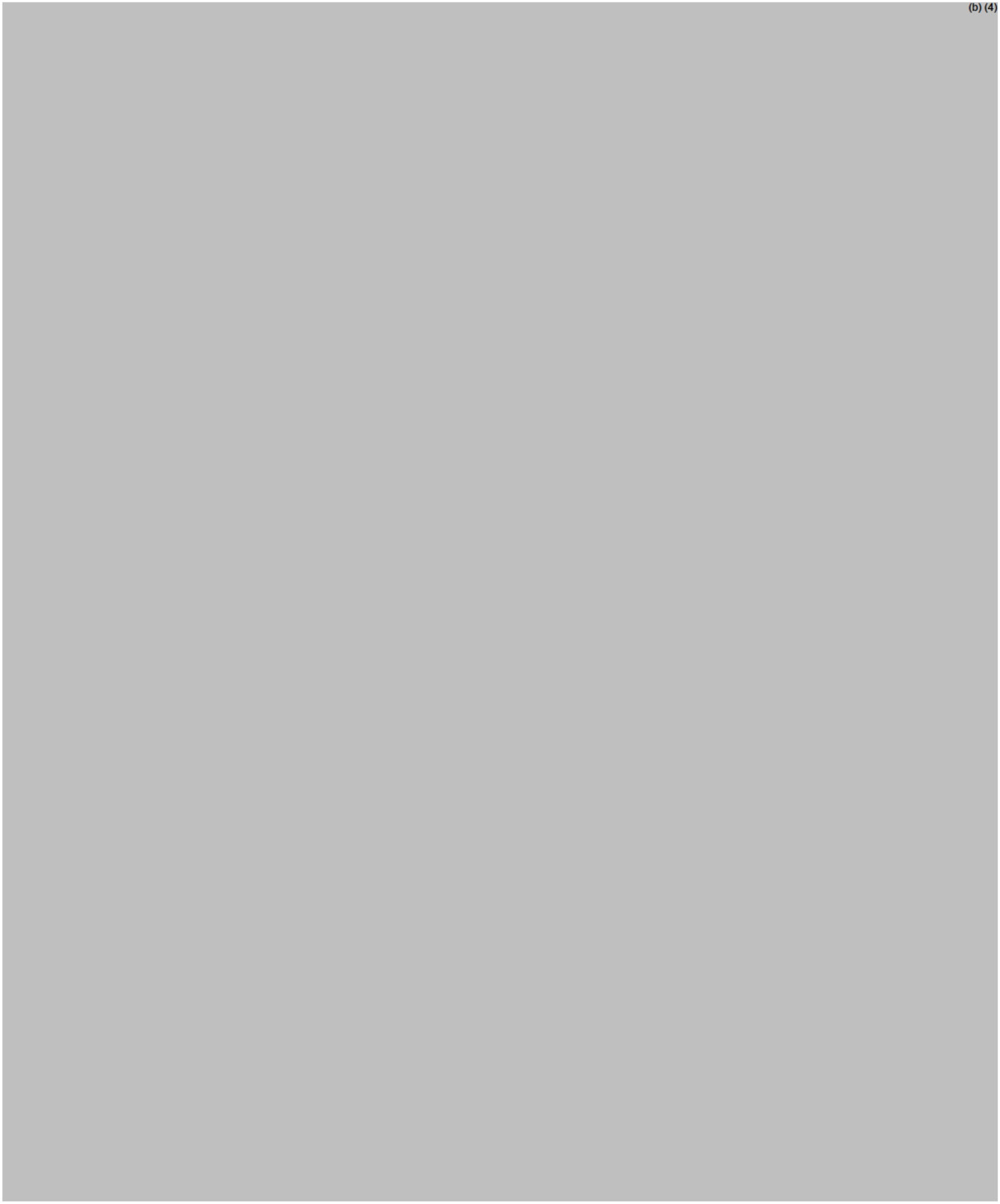

(b) (4)


(b) (4)


(b) (4)


(b) (4)


(b) (4)

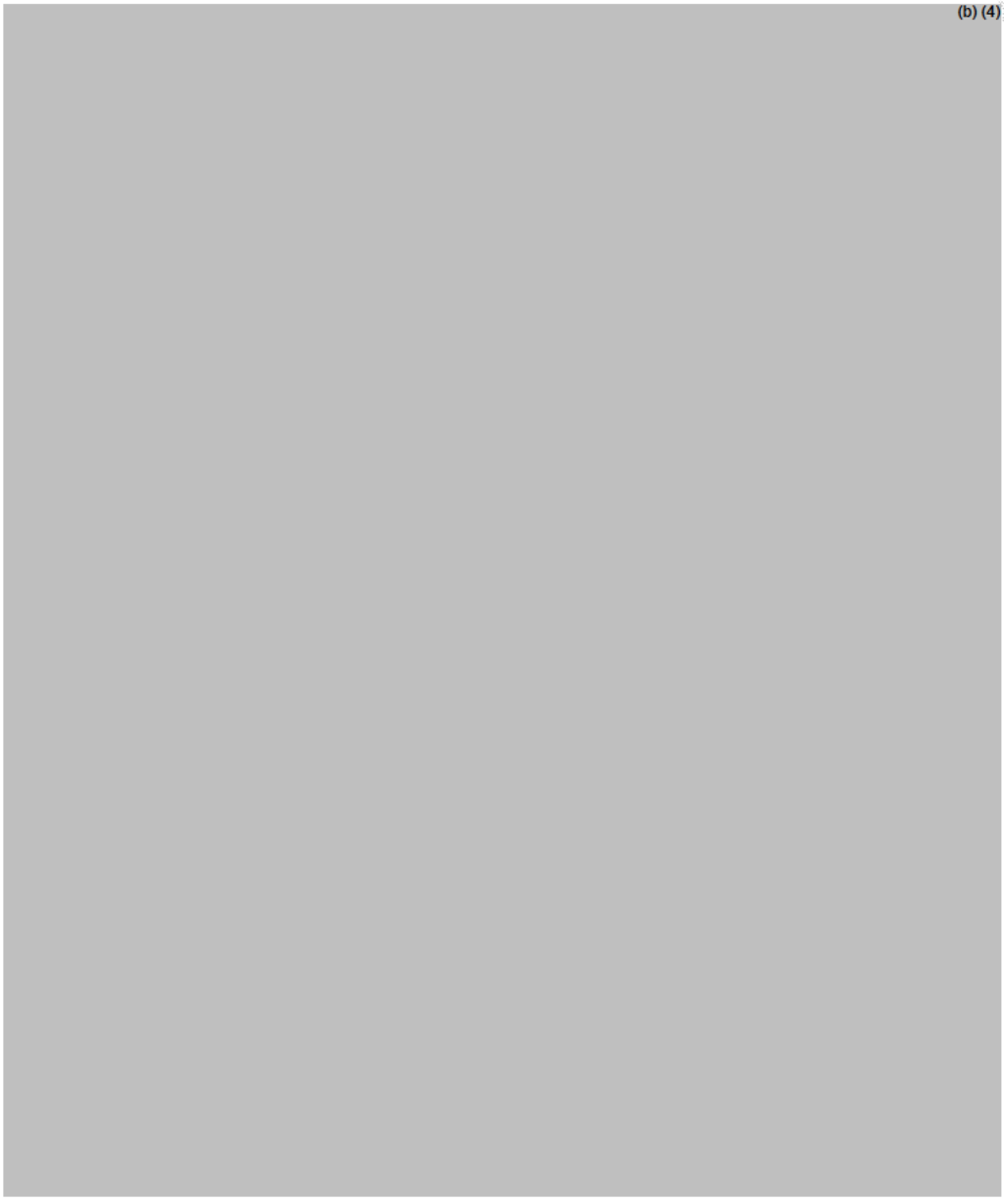

(b) (4)

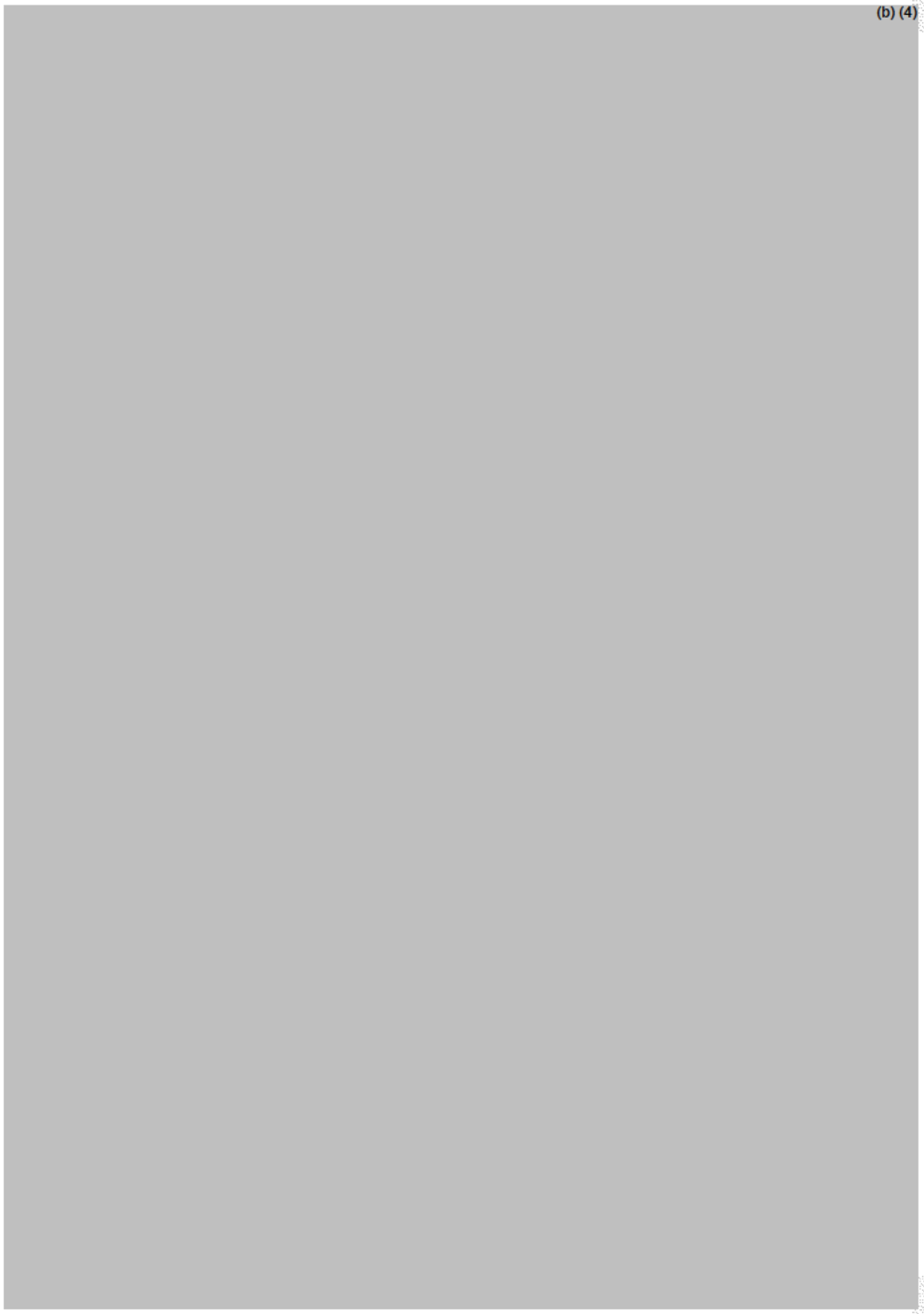
(b) (4)

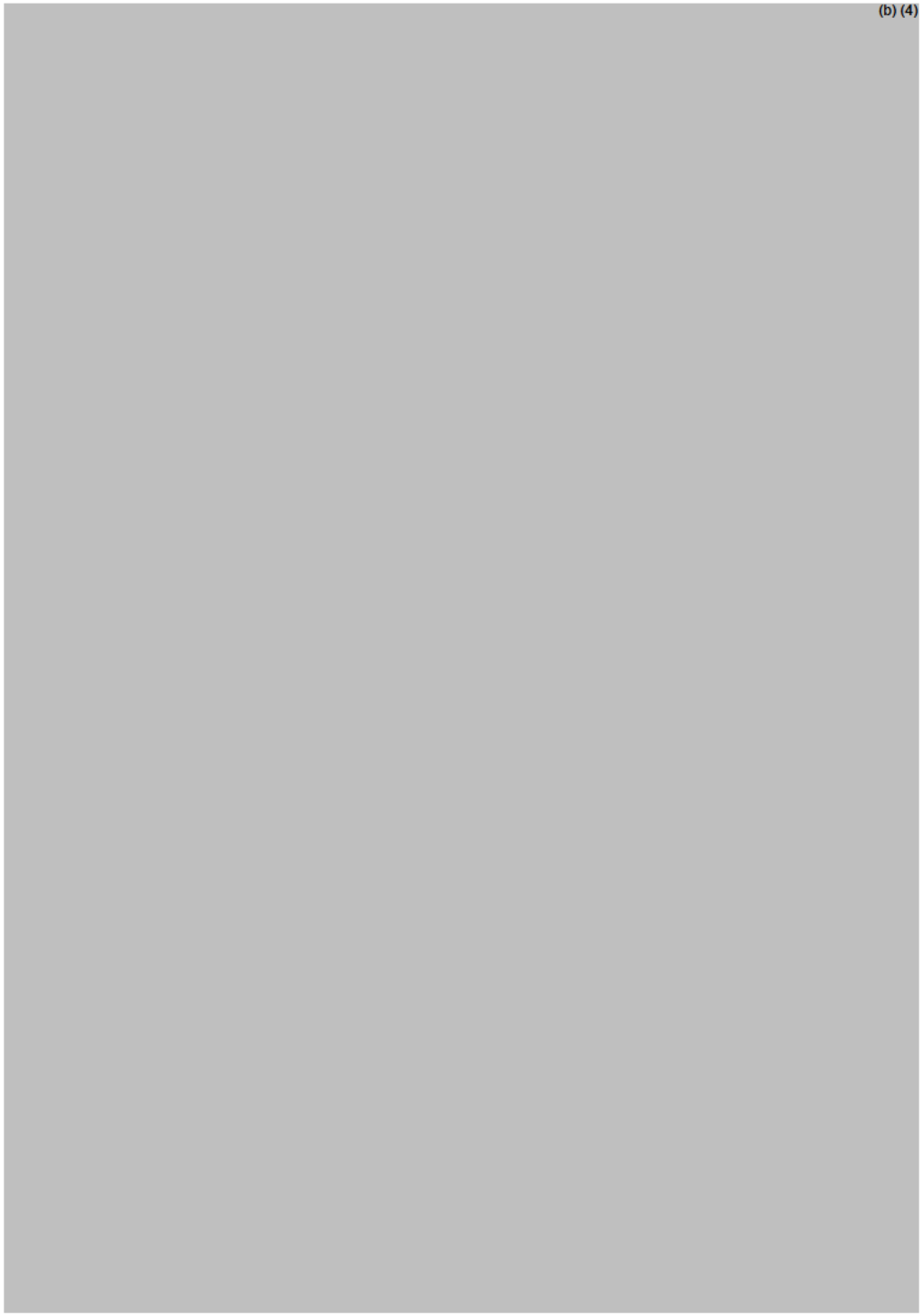
APPEARS THIS WAY ON ORIGINAL

Synarel®
(nafarelin acetate)
nasal solution

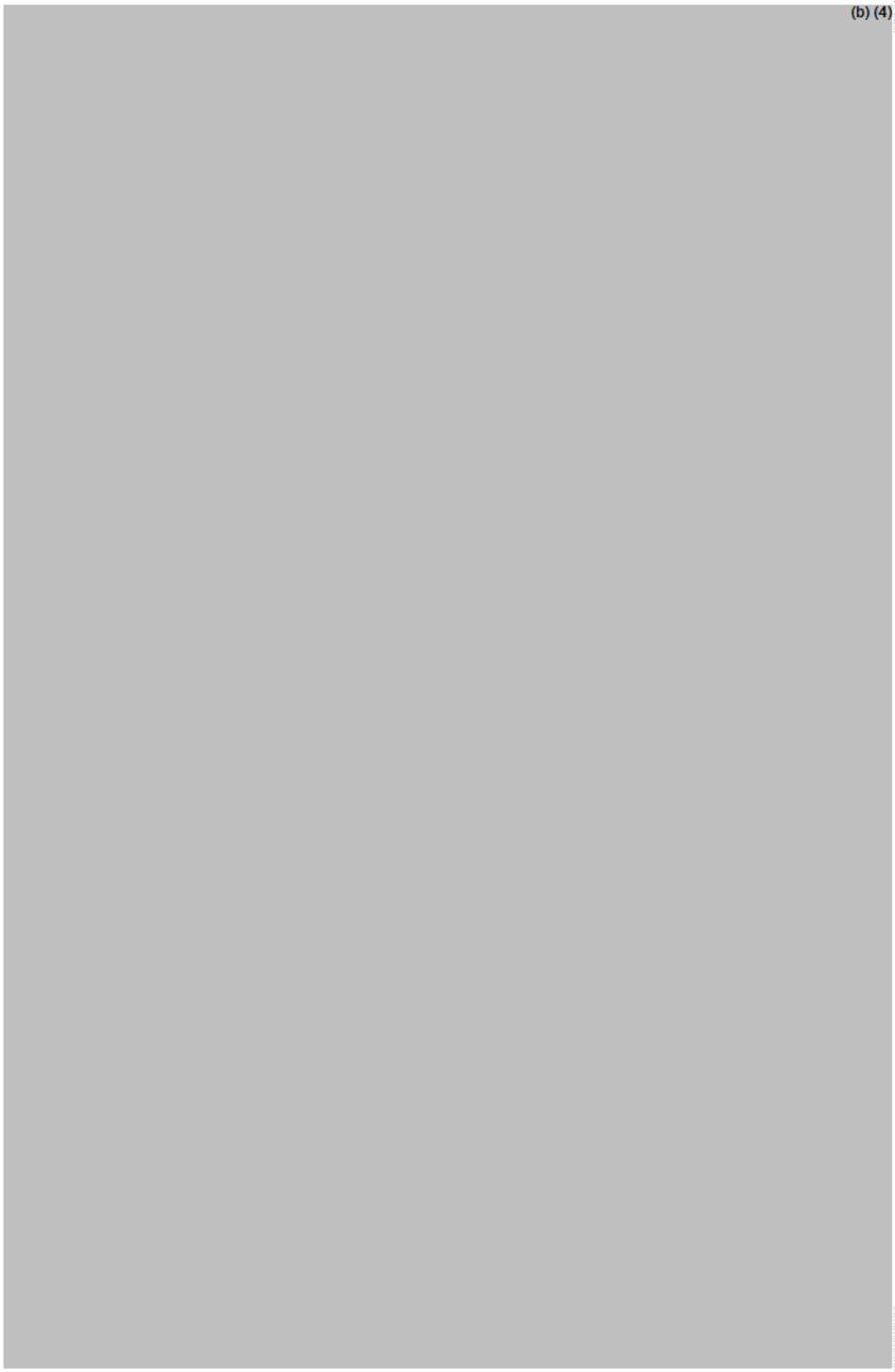
(b) (4)




(b) (4)


(b) (4)

(b) (4)

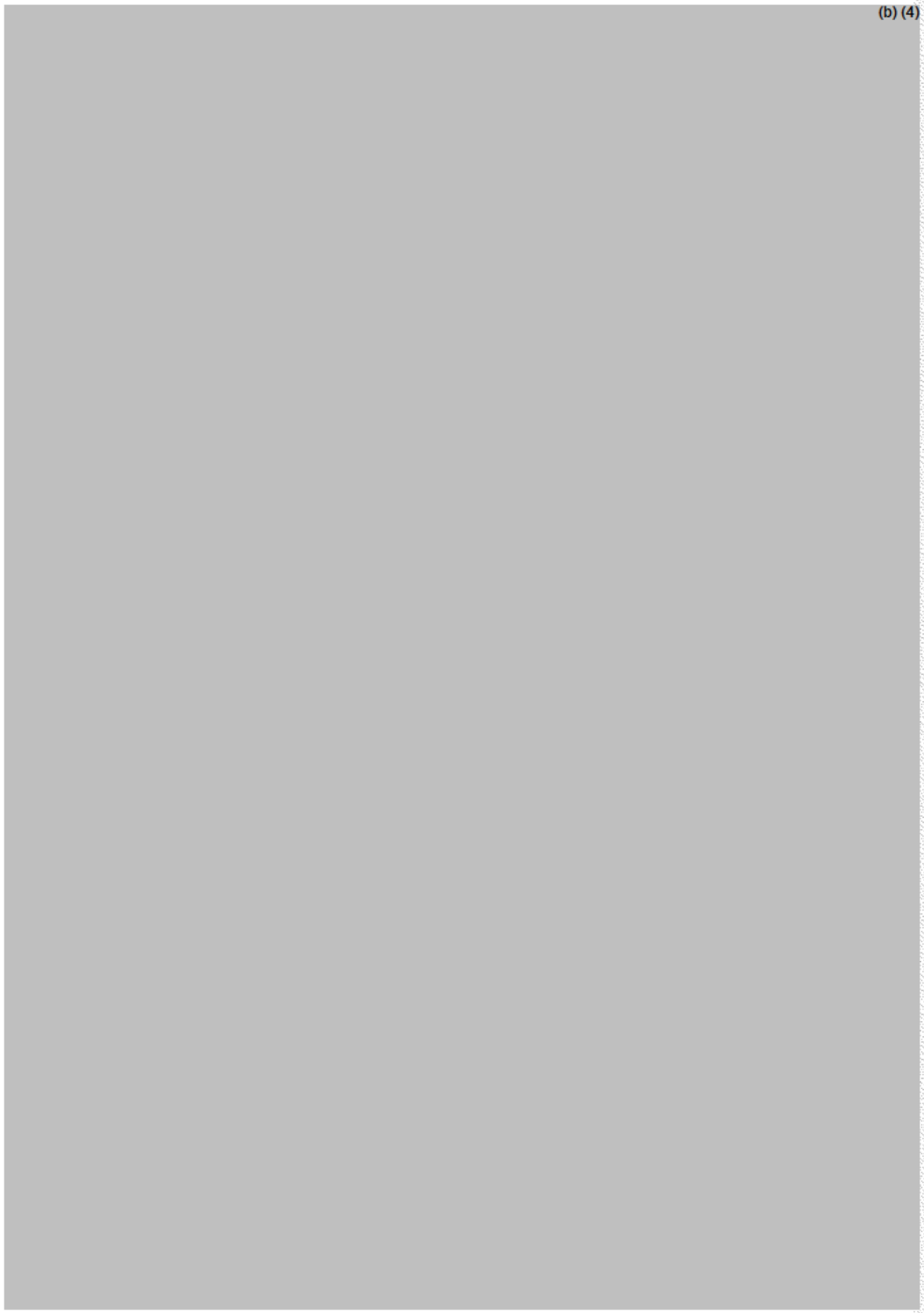


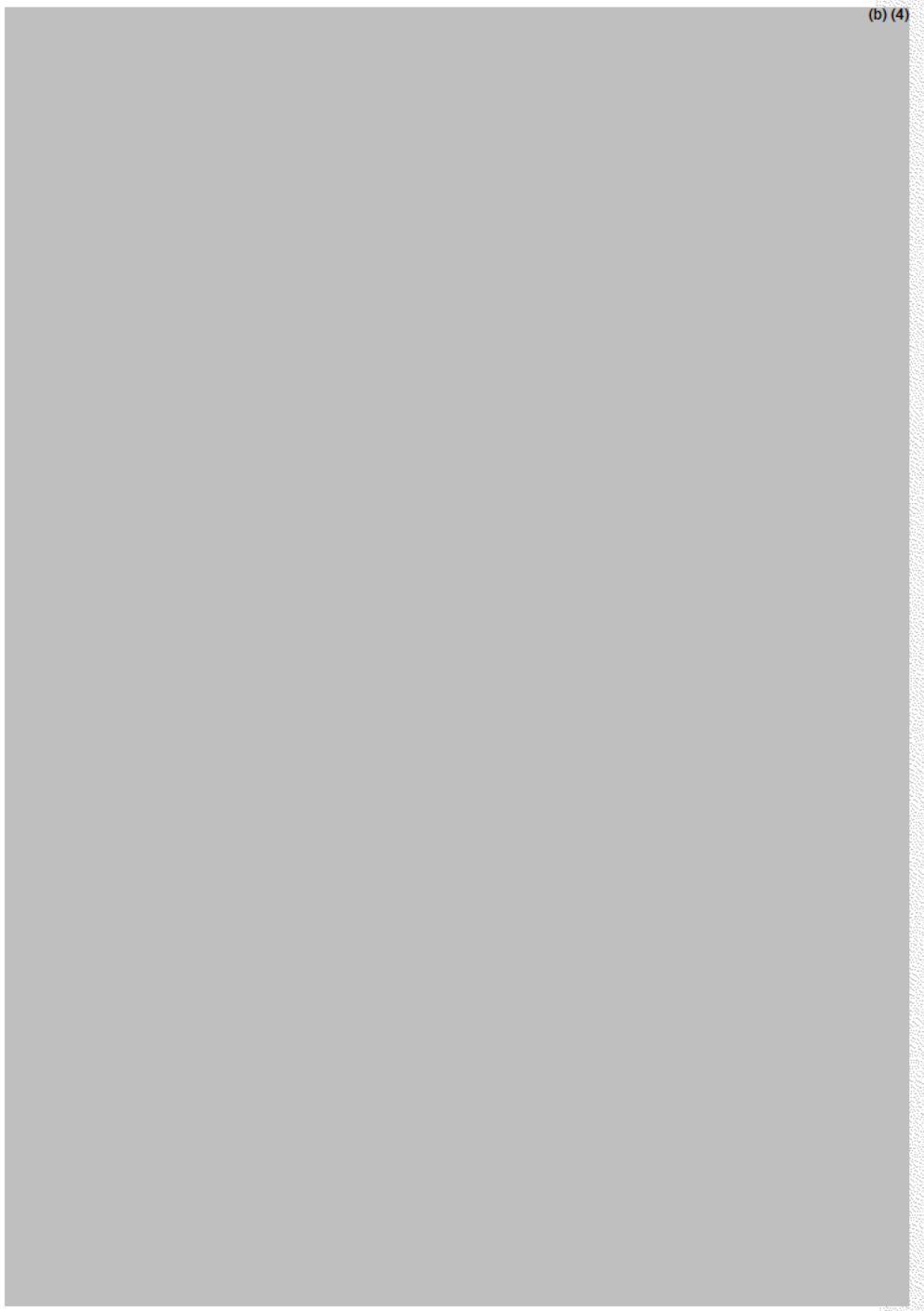
(b) (4)

[redacted]

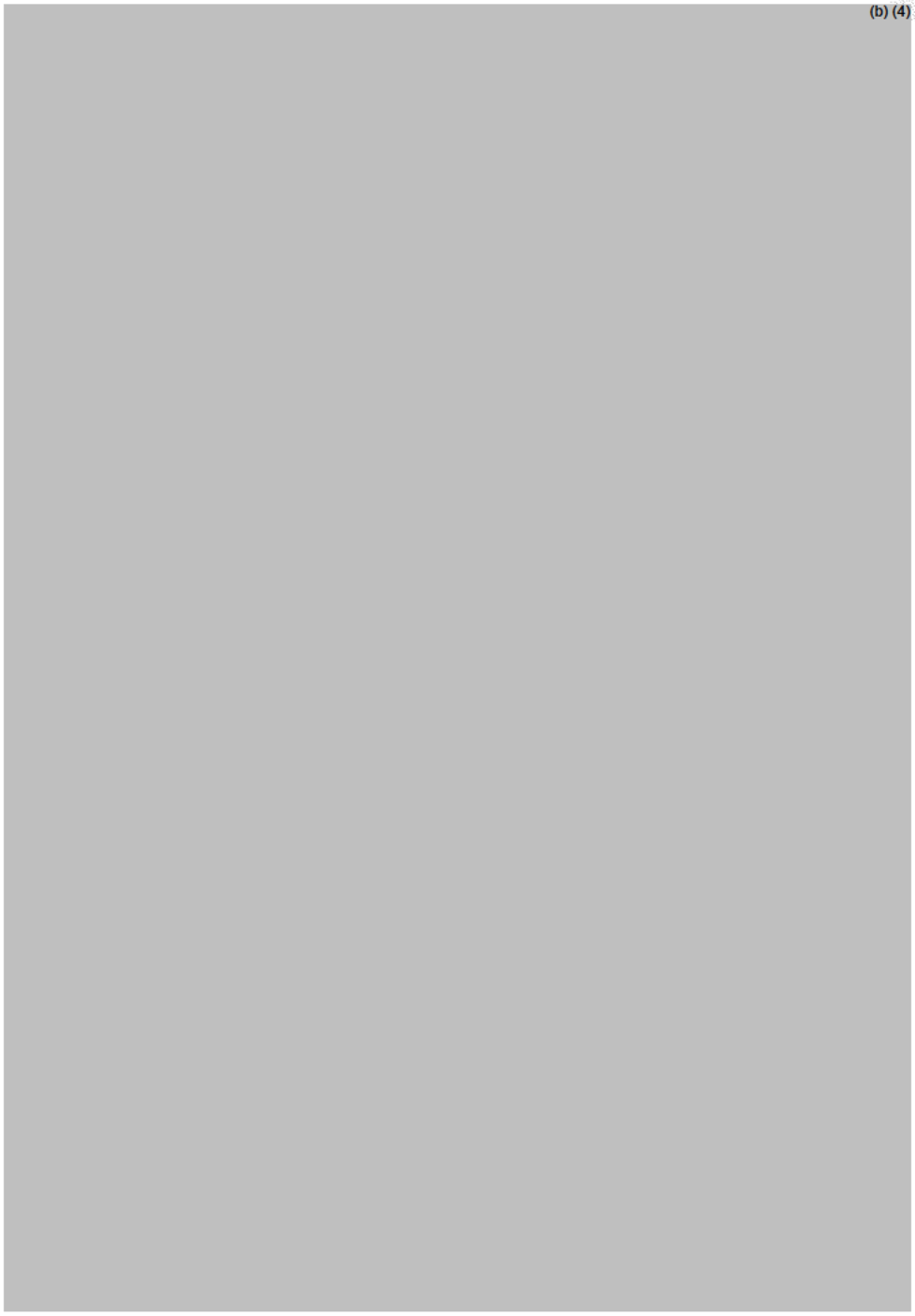
Commented [VS1]: This was removed as it's a duplicate

(b) (4)




(b) (4)

(b) (4)




(b) (4)

Synarel®

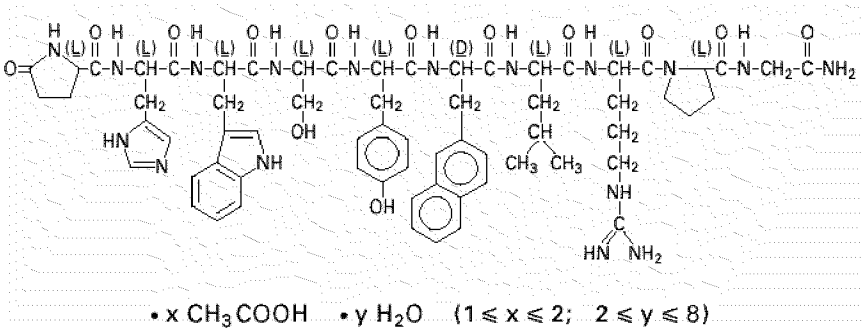
(nafarelin acetate)
nasal solution

ENDOMETRIOSIS
(FOR CENTRAL PRECOCIOUS PUBERTY, SEE REVERSE SIDE)

PHYSICIAN LABELING

DESCRIPTION

SYNAREL (nafarelin acetate) Nasal Solution is intended for administration as a spray to the nasal mucosa. Nafarelin acetate, the active component of SYNAREL Nasal Solution, is a decapeptide with the chemical name: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-3-(2-naphthyl)-D-alanyl-L-leucyl-L-arginyl-L-prolyl-glycinamide acetate. Nafarelin acetate is a synthetic analog of the naturally occurring gonadotropin-releasing hormone (GnRH).
Nafarelin acetate has the following chemical structure:



SYNAREL Nasal Solution contains nafarelin acetate (2 mg/mL, content expressed as nafarelin base) in a solution of benzalkonium chloride, glacial acetic acid, sodium hydroxide or hydrochloric acid (to adjust pH), sorbitol, and purified water.

After priming the pump unit for SYNAREL, each actuation of the unit delivers approximately 100 µL of the spray containing approximately 200 µg nafarelin base. The contents of one spray bottle are intended to deliver at least 60 sprays.

CLINICAL PHARMACOLOGY

Nafarelin acetate is a potent agonistic analog of gonadotropin-releasing hormone (GnRH). At the onset of administration, nafarelin stimulates the release of the pituitary gonadotropins, LH and FSH, resulting in a temporary increase of ovarian steroidogenesis. Repeated dosing abolishes the stimulatory effect on the pituitary gland. Twice daily

administration leads to decreased secretion of gonadal steroids by about 4 weeks; consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent.

Nafarelin acetate is rapidly absorbed into the systemic circulation after intranasal administration. Maximum serum concentrations (measured by RIA) were achieved between 10 and 40 minutes. Following a single dose of 200 µg base, the observed average peak concentration was 0.6 ng/mL (range 0.2 to 1.4 ng/mL), whereas following a single dose of 400 µg base, the observed average peak concentration was 1.8 ng/mL (range 0.5 to 5.3 ng/mL). Bioavailability from a 400 µg dose averaged 2.8% (range 1.2 to 5.6%). The average serum half-life of nafarelin following intranasal administration is approximately 3 hours. About 80% of nafarelin acetate is bound to plasma proteins at 4°C. Twice daily intranasal administration of 200 or 400 µg of SYNAREL in 18 healthy women for 22 days did not lead to significant accumulation of the drug. Based on the mean C_{min} levels on Days 15 and 22, there appeared to be dose proportionality across the two dose levels.

After subcutaneous administration of ^{14}C-nafarelin acetate to men, 44–55% of the dose was recovered in urine and 18.5–44.2% was recovered in feces. Approximately 3% of the administered dose appeared as unchanged nafarelin in urine. The ^{14}C serum half-life of the metabolites was about 85.5 hours. Six metabolites of nafarelin have been identified of which the major metabolite is Tyr-D(2)-Nal-Leu-Arg-Pro-Gly-NH_2(5-10). The activity of the metabolites, the metabolism of nafarelin by nasal mucosa, and the pharmacokinetics of the drug in hepatically- and renally-impaired patients have not been determined.

There appeared to be no significant effect of rhinitis, i.e., nasal congestion, on the systemic bioavailability of SYNAREL; however, if the use of a nasal decongestant for rhinitis is necessary during treatment with SYNAREL, the decongestant should not be used until at least 2 hours following dosing of SYNAREL.

In controlled clinical studies, SYNAREL at doses of 400 and 800 µg/day for 6 months was shown to be comparable to danazol, 800 mg/day, in relieving the clinical symptoms of endometriosis (pelvic pain, dysmenorrhea, and dyspareunia) and in reducing the size of endometrial implants as determined by laparoscopy. The clinical significance of a decrease in endometriotic lesions is not known at this time and, in addition, laparoscopic staging of endometriosis does not necessarily correlate with severity of symptoms.

In a single controlled clinical trial, intranasal SYNAREL (nafarelin acetate) at a dose of 400 µg per day was shown to be clinically comparable to intramuscular leuprolide depot, 3.75 mg monthly, for the treatment of the symptoms (dysmenorrhea, dyspareunia and pelvic pain) associated with endometriosis.

SYNAREL 400 µg daily induced amenorrhea in approximately 65%, 80%, and 90% of the patients after 60, 90, and 120 days, respectively. In the first, second, and third post-treatment months, normal menstrual cycles resumed in 4%, 82%, and 100%, respectively, of those patients who did not become pregnant.

At the end of treatment, 60% of patients who received SYNAREL, 400 µg/day, were symptom free, 32% had mild symptoms, 7% had moderate symptoms, and 1% had severe symptoms. Of the 60% of patients who had complete relief of symptoms at the end of treatment, 17% had moderate symptoms 6 months after treatment was discontinued, 33% had mild symptoms, 50% remained symptom free, and no patient had severe symptoms.

During the first two months use of SYNAREL, some women experience vaginal bleeding of variable duration and intensity. In all likelihood, this bleeding represents estrogen withdrawal bleeding and is expected to stop spontaneously. If vaginal bleeding continues, the possibility of lack of compliance with the dosing regimen should be considered. If the patient is complying carefully with the regimen, an increase in dose to 400 µg twice a day should be considered.

There is no evidence that pregnancy rates are enhanced or adversely affected by the use of SYNAREL.

INDICATIONS AND USAGE FOR ENDOMETRIOSIS

(For Central Precocious Puberty, See *Reverse Side*)

SYNAREL is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. Experience with SYNAREL for the management of endometriosis has been limited to women 18 years of age and older treated for 6 months.

CONTRAINDICATIONS

1. Hypersensitivity to GnRH, GnRH agonist analogs or any of the excipients in SYNAREL;
2. Undiagnosed abnormal vaginal bleeding;
3. Use in pregnancy or in women who may become pregnant while receiving the drug. SYNAREL may cause fetal harm when administered to a pregnant woman. Major fetal abnormalities were observed in rats, but not in mice or rabbits after administration of SYNAREL during the period of organogenesis. There was a dose-related increase in fetal mortality and a decrease in fetal weight in rats *[see **Pregnancy**]*. The effects on rat fetal mortality are expected consequences of the alterations in hormonal levels brought about by the drug. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus;
4. Use in women who are breast-feeding *[see **Nursing Mothers**]*.

WARNINGS

Safe use of nafarelin acetate in pregnancy has not been established clinically. Before starting treatment with SYNAREL, pregnancy must be excluded.

When used regularly at the recommended dose, SYNAREL usually inhibits ovulation and stops menstruation. Contraception is not insured, however, by taking SYNAREL, particularly if patients miss successive doses. Therefore, patients should use nonhormonal methods of contraception. Patients should be advised to see their physician if they believe they may be pregnant. If a patient becomes pregnant during treatment, the drug must be discontinued and the patient must be apprised of the potential risk to the fetus.

PRECAUTIONS

General

As with other drugs that stimulate the release of gonadotropins or that induce ovulation, ovarian cysts have been reported to occur in the first two months of therapy with SYNAREL. Many, but not all, of these events occurred in patients with polycystic ovarian disease. These cystic enlargements may resolve spontaneously, generally by about four to six weeks of therapy, but in some cases may require discontinuation of drug and/or surgical intervention.

Information for Patients

An information pamphlet for patients is included with the product. Patients should be aware of the following information:

1. Since menstruation should stop with effective doses of SYNAREL, the patient should notify her physician if regular menstruation persists. The cause of vaginal spotting, bleeding or menstruation could be noncompliance with the treatment regimen, or it could be that a higher dose of the drug is required to achieve amenorrhea. The patient should be questioned regarding her compliance. If she is careful and compliant, and menstruation persists to the second month, consideration should be given to doubling the dose of SYNAREL. If the patient has missed several doses, she should be counseled on the importance of taking SYNAREL regularly as prescribed.

2. Patients should not use SYNAREL if they are pregnant, breastfeeding, have undiagnosed abnormal vaginal bleeding, or are allergic to any of the ingredients in SYNAREL.

3. Safe use of the drug in pregnancy has not been established clinically. Therefore, a nonhormonal method of contraception should be used during treatment. Patients should be advised that if they miss successive doses of SYNAREL, breakthrough bleeding or ovulation may occur with the potential for conception. If a patient becomes pregnant during treatment, she should discontinue treatment and consult her physician.

4. Those adverse events occurring most frequently in clinical studies with SYNAREL are associated with hypoestrogenism; the most frequently reported are hot flashes, headaches, emotional lability, decreased libido, vaginal dryness, acne, myalgia, and reduction in breast size. Estrogen levels returned to normal after treatment was discontinued. Nasal irritation occurred in about 10% of all patients who used intranasal nafarelin.

5. The induced hypoestrogenic state results in a small loss in bone density over the course of treatment, some of which may not be reversible. During one six-month treatment period, this bone loss should not be important. In patients with major risk factors for decreased bone mineral content such as chronic alcohol and/or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, therapy with SYNAREL may pose an additional risk. In these patients the risks and benefits must be weighed carefully before therapy with SYNAREL is instituted. Repeated courses of treatment with gonadotropin-releasing

hormone analogs are not advisable in patients with major risk factors for loss of bone mineral content.

6. Patients with intercurrent rhinitis should consult their physician for the use of a topical nasal decongestant. If the use of a topical nasal decongestant is required during treatment with SYNAREL, the decongestant should not be used until at least 2 hours following dosing with SYNAREL.

Sneezing during or immediately after dosing with SYNAREL should be avoided, if possible, since this may impair drug absorption.

7. Retreatment cannot be recommended since safety data beyond 6 months are not available.

Drug Interactions
No pharmacokinetic-based drug-drug interaction studies have been conducted with SYNAREL. However, because nafarelin acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes, and the drug is only about 80% bound to plasma proteins at 4°C, drug interactions would not be expected to occur.

Drug/Laboratory Test Interactions
Administration of SYNAREL in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within 4 to 8 weeks after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and up to 4 to 8 weeks after discontinuation of therapy with SYNAREL may be misleading.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies of nafarelin were conducted in rats (24 months) at doses up to 100 µg/kg/day and mice (18 months) at doses up to 500 µg/kg/day using intramuscular doses (up to 110 times and 560 times the maximum recommended human intranasal dose, respectively). These multiples of the human dose are based on the relative bioavailability of the drug by the two routes of administration. As seen with other GnRH agonists, nafarelin acetate given to laboratory rodents at high doses for prolonged periods induced proliferative responses (hyperplasia and/or neoplasia) of endocrine organs. At 24 months, there was an increase in the incidence of pituitary tumors (adenoma/carcinoma) in high-dose female rats and a dose-related increase in male rats. There was an increase in pancreatic islet cell adenomas in both sexes, and in benign testicular and ovarian tumors in the treated groups. There was a dose-related increase in benign adrenal medullary tumors in treated female rats. In mice, there was a dose-related increase in Harderian gland tumors in males and an increase in pituitary adenomas in high-dose females. No metastases of these tumors were observed. It is known that tumorigenicity in rodents is particularly sensitive to hormonal stimulation.

Mutagenicity studies were performed with nafarelin acetate using bacterial, yeast, and mammalian systems. These studies provided no evidence of mutagenic potential.

Reproduction studies in male and female rats have shown full reversibility of fertility suppression when drug treatment was discontinued after continuous administration for up to 6 months. The effect of treatment of prepubertal rats on the subsequent reproductive performance of mature animals has not been investigated.

Pregnancy

Teratogenic Effects

See ***Contraindications***. Intramuscular SYNAREL was administered to rats during the period of organogenesis at 0.4, 1.6, and 6.4 µg/kg/day (about 0.5, 2, and 7 times the maximum recommended human intranasal dose based on the relative bioavailability by the two routes of administration). An increase in major fetal abnormalities was observed in 4/80 fetuses at the highest dose. A similar, repeat study at the same doses in rats and studies in mice and rabbits at doses up to 600 µg/kg/day and 0.18 µg/kg/day, respectively, failed to demonstrate an increase in fetal abnormalities after administration during the period of organogenesis. In rats and rabbits, there was a dose-related increase in fetal mortality and a decrease in fetal weight with the highest dose.

Nursing Mothers

It is not known whether SYNAREL is excreted in human milk. Because many drugs are excreted in human milk, and because the effects of SYNAREL on lactation and/or the breastfed child have not been determined, SYNAREL should not be used by nursing mothers.

Pediatric Use

Safety and effectiveness of SYNAREL for endometriosis in patients younger than 18 years have not been established.

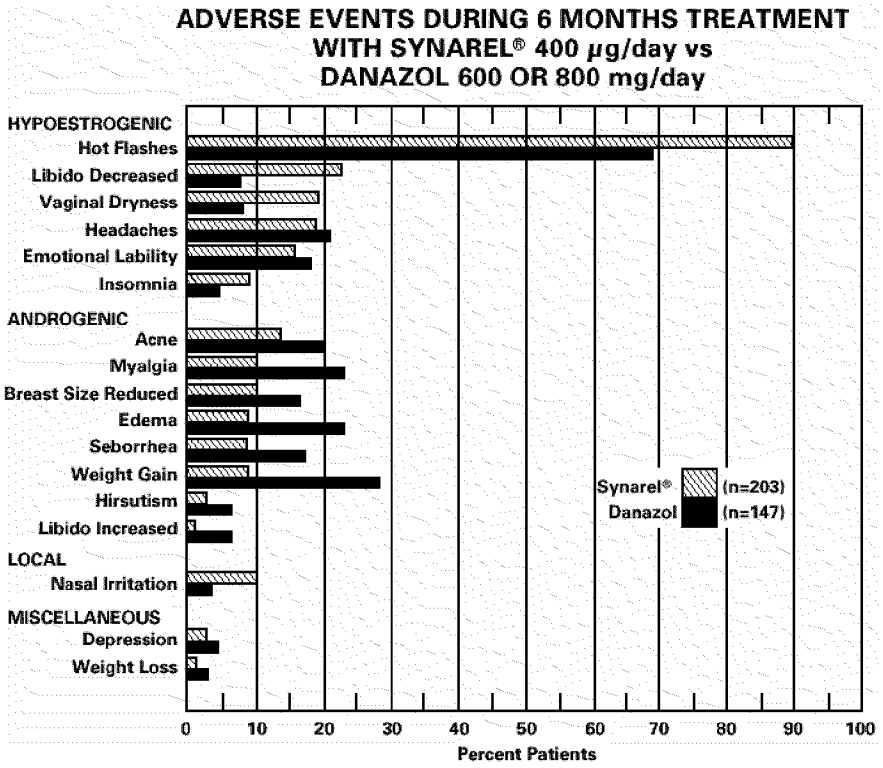
ADVERSE REACTIONS

Clinical Studies

In formal clinical trials of 1509 healthy adult patients, symptoms suggestive of drug sensitivity, such as shortness of breath, chest pain, urticaria, rash and pruritus occurred in 3 patients (approximately 0.2%).

As would be expected with a drug which lowers serum estradiol levels, the most frequently reported adverse reactions were those related to hypoestrogenism.

In controlled studies comparing SYNAREL (400 µg/day) and danazol (600 or 800 mg/day), adverse reactions most frequently reported and thought to be drug-related are shown in the figure below:



In addition, less than 1% of patients experienced paresthesia, palpitations, chloasma, maculopapular rash, eye pain, asthenia, lactation, breast engorgement, and arthralgia.

Changes in Bone Density

After six months of treatment with SYNAREL, vertebral trabecular bone density and total vertebral bone mass, measured by quantitative computed tomography (QCT), decreased by an average of 8.7% and 4.3%, respectively, compared to pretreatment levels. There was partial recovery of bone density in the post-treatment period; the average trabecular bone density and total bone mass were 4.9% and 3.3% less than the pretreatment levels, respectively. Total vertebral bone mass, measured by dual photon absorptiometry (DPA), decreased by a mean of 5.9% at the end of treatment.

After six months treatment with SYNAREL, bone mass as measured by dual x-ray bone densitometry (DEXA), decreased 3.2%. Mean total vertebral mass, re-examined by DEXA six months after completion of treatment, was 1.4% below pretreatment. There was little, if any, decrease in the mineral content in compact bone of the distal radius and second metacarpal. Use of SYNAREL for longer than the recommended six months or in the presence of other known risk factors for decreased bone mineral content may cause additional bone loss.

Changes in Laboratory Values During Treatment

Plasma enzymes. During clinical trials with SYNAREL, regular laboratory monitoring revealed that SGOT and SGPT levels were more than twice the upper limit of normal in only one patient each. There was no other clinical or laboratory evidence of abnormal liver function and levels returned to normal in both patients after treatment was stopped.

Lipids. At enrollment, 9% of the patients in the group taking SYNAREL 400 µg/day and 2% of the patients in the danazol group had total cholesterol values above 250 mg/dL. These patients also had cholesterol values above 250 mg/dL at the end of treatment.

Of those patients whose pretreatment cholesterol values were below 250 mg/dL, 6% in the group treated with SYNAREL and 18% in the danazol group, had post-treatment values above 250 mg/dL.

The mean (± SEM) pretreatment values for total cholesterol from all patients were 191.8 (4.3) mg/dL in the group treated with SYNAREL and 193.1 (4.6) mg/dL in the danazol group. At the end of treatment, the mean values for total cholesterol from all patients were 204.5 (4.8) mg/dL in the group treated with SYNAREL and 207.7 (5.1) mg/dL in the danazol group. These increases from the pretreatment values were statistically significant ($p<0.05$) in both groups.

Triglycerides were increased above the upper limit of 150 mg/dL in 12% of the patients who received SYNAREL and in 7% of the patients who received danazol.

At the end of treatment, no patients receiving SYNAREL had abnormally low HDL cholesterol fractions (less than 30 mg/dL) compared with 43% of patients receiving danazol. None of the patients receiving SYNAREL had abnormally high LDL cholesterol fractions (greater than 190 mg/dL) compared with 15% of those receiving danazol. There was no increase in the LDL/HDL ratio in patients receiving SYNAREL, but there was approximately a 2-fold increase in the LDL/HDL ratio in patients receiving danazol.

Other changes. In comparative studies, the following changes were seen in approximately 10% to 15% of patients. Treatment with SYNAREL was associated with elevations of plasma phosphorus and eosinophil counts, and decreases in serum calcium and WBC counts. Danazol therapy was associated with an increase of hematocrit and WBC.

Post-Marketing

Pituitary apoplexy: During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed, with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

Cardiovascular adverse events: Cases of serious venous and arterial thromboembolism have been reported, including deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, and transient ischemic attack. Although a temporal relationship was reported in some cases, most cases were confounded by risk factors or concomitant medication use. It is unknown if there is a causal association between the use of GnRH analogs and these events.

Central/peripheral nervous adverse events: Convulsion.
Hepatic adverse events: Rarely reported serious liver injury.
Reproductive system adverse events: Cases of ovarian hyperstimulation syndrome have been reported with Synarel monotherapy when used for Assisted Reproductive Technology which is not an approved indication.

OVERDOSAGE

In experimental animals, a single subcutaneous administration of up to 60 times the recommended human dose (on a µg/kg basis, not adjusted for bioavailability) had no adverse effects. At present, there is no clinical evidence of adverse effects following overdosage of GnRH analogs.

Based on studies in monkeys, SYNAREL is not absorbed after oral administration.

DOSAGE AND ADMINISTRATION

For the management of endometriosis, the recommended daily dose of SYNAREL is 400 µg. This is achieved by one spray (200 µg) into one nostril in the morning and one spray into the other nostril in the evening. Treatment should be started between days 2 and 4 of the menstrual cycle.

In an occasional patient, the 400 µg daily dose may not produce amenorrhea. For these patients with persistent regular menstruation after 2 months of treatment, the dose of SYNAREL may be increased to 800 µg daily. The 800 µg dose is administered as one spray into each nostril in the morning (a total of two sprays) and again in the evening.

The recommended duration of administration is six months. Retreatment cannot be recommended since safety data for retreatment are not available. If the symptoms of endometriosis recur after a course of therapy, and further treatment with SYNAREL is contemplated, it is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits.

There appeared to be no significant effect of rhinitis, i.e., nasal congestion, on the systemic bioavailability of SYNAREL; however, if the use of a nasal decongestant for rhinitis is necessary during treatment with SYNAREL, the decongestant should not be used until at least 2 hours following dosing with SYNAREL.

Sneezing during or immediately after dosing with SYNAREL should be avoided, if possible, since this may impair drug absorption.

At 400 µg/day, a bottle of SYNAREL provides a 30-day (about 60 sprays) supply. If the daily dose is increased, increase the supply to the patient to ensure uninterrupted treatment for the recommended duration of therapy.

HOW SUPPLIED

Each 0.5 ounce bottle (NDC 0025-0166-08) contains 8 mL SYNAREL (nafarelin acetate) Nasal Solution 2 mg/mL (as nafarelin base), and is supplied with a metered spray pump that delivers 200 µg of nafarelin per spray. A dust cover and a leaflet of patient instructions are also included.

Store upright at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from light.

Distributed by

Pfizer Labs

Division of Pfizer Inc, NY, NY 10017

LAB-0173-11.0
Revised: December 2020

SYNAREL
nafarelin acetate
Nasal Spray

Patient Instructions for Use

Introduction

Your doctor has prescribed SYNAREL Nasal Solution to treat your symptoms of endometriosis. This pamphlet has two purposes:

1.) to review information your doctor has given you about SYNAREL; and
2.) to give you information about how to use SYNAREL properly.

Please read this pamphlet carefully. If you still have questions after reading it or if you have questions at any time during your treatment with SYNAREL, be sure to check with your doctor.

SYNAREL is used to relieve the symptoms of endometriosis. The lining of the uterus is called the endometrium, and part of it is shed during menses. In endometriosis, endometrial tissue is also found outside the uterus and, like normal endometrial tissue, can bleed during a menstrual cycle. It is, in part, this monthly activity that causes you to have symptoms during your cycle. Most often, this out-of-place endometrial tissue is found around the uterus, ovaries, the intestine or other organs in the pelvis. Although some women with endometriosis have no symptoms, many have problems such as severe menstrual cramps, pain during sexual intercourse, low back pain, and painful bowel movements.

Endometrial tissue is affected by the body's hormones, especially estrogen, which is made by the ovaries. When estrogen levels are low, endometrial tissue shrinks (perhaps even disappears), and symptoms of endometriosis ease. SYNAREL temporarily reduces estrogen in the body and temporarily relieves the symptoms of endometriosis.

Important Information about SYNAREL

1. You should **not** use SYNAREL if
    - you are pregnant.
    - you are breast feeding.
    - you have abnormal vaginal bleeding that has not been checked into by your doctor.
    - you are allergic to any of the ingredients of SYNAREL (nafarelin acetate, benzalkonium chloride, acetic acid, sodium hydroxide, hydrochloric acid, sorbitol, purified water).
2. SYNAREL is a prescription medicine that should be used according to your doctor's directions. SYNAREL comes as a special nasal spray that gives a measured amount of medicine. To be effective, SYNAREL must be used every day, twice a day, for the whole treatment period.

3. It is important to use a non-hormonal method of contraception (such as diaphragm with contraceptive jelly, IUD, condoms) while taking SYNAREL. You should not use birth control pills while taking SYNAREL.
4. If you miss 1 or more doses of SYNAREL, vaginal bleeding (often called breakthrough bleeding) may occur. If you miss successive doses of SYNAREL and have not been using contraception as described above, release of an egg from the ovary (ovulation) may occur, with the possibility of pregnancy. Under these circumstances you must see your physician to make sure you are not pregnant. If you should become pregnant while using SYNAREL, you must discuss the possible risks to the fetus and the choices available to you with your physician.
5. Because SYNAREL works by temporarily reducing the body's production of estrogen, a female hormone produced by the ovary, you may have some of the same changes that normally occur at the time of menopause, when the body's production of estrogen naturally decreases. For the first two months after you start using SYNAREL, you may experience some irregular vaginal spotting or bleeding. The duration and intensity of this bleeding may vary; it may be similar to your usual menstruation, or it may be lighter or heavier. The duration may also vary from brief to prolonged. In any case, you can expect this bleeding to stop by itself. After the first two months of treatment with SYNAREL, you can expect a decrease in menstrual flow, and your periods may stop altogether. However, if you miss one or more doses of SYNAREL, you may continue to experience vaginal bleeding. If you continue to experience normal menstrual cycles after two months use of SYNAREL, you should see your doctor about the continued periods. Other changes due to decreased estrogen include hot flashes, vaginal dryness, headaches, mood changes, and decreased interest in sex. Most of these changes are caused by low estrogen levels and may occur during treatment with SYNAREL. Some patients may also experience acne, muscle pain, reduced breast size, and irritation of the tissues inside the nose. These symptoms should disappear after you stop taking the drug.
6. When you take SYNAREL, your estrogen levels will be low. Low estrogen levels can result in a small loss of mineral from bone, some of which may not be reversible. During one six-month treatment period, this small loss of mineral from bone should not be important. There are certain conditions that may increase the possibility of the thinning of your bones when you take a drug such as SYNAREL. They are:
    - excessive use of alcohol;
    - smoking;
    - family history of osteoporosis (thinning of the bones with fractures);
    - taking other medications that can cause thinning of the bones.

    You should discuss the possibility of osteoporosis or thinning of the bones with your physician before starting SYNAREL. You should also be aware that repeat treatments are not recommended since they may

put you at greater risk of bone thinning, particularly if you have the above conditions.

7. During studies, menstruation usually resumed within 2 to 3 months of stopping treatment with SYNAREL. At the end of treatment 60% of patients treated with SYNAREL were symptom free, 32% had mild symptoms, 7% had moderate symptoms and 1% had severe symptoms.
   Of the 60% of patients who had complete relief of symptoms at the end of treatment, 17% had moderate symptoms at the end of the six month post-treatment period; 33% had mild symptoms; 50% were symptom free; no patient had severe symptoms.
8. Retreatment cannot be recommended since the safety of such retreatment is not known.
9. It is all right to use a nasal decongestant spray while you are being treated with SYNAREL if you follow these simple rules. Use SYNAREL first. Wait at least 2 hours after using SYNAREL before you use the decongestant spray.
10. You should avoid sneezing during or immediately after using SYNAREL, if possible, since sneezing may impair drug absorption.

Proper use of SYNAREL for Treatment of Endometriosis

1. When you start to use SYNAREL, the first dose should be taken between the second and fourth day after the beginning of your menstrual bleeding. You should continue taking SYNAREL every day as prescribed.
   Do not miss a single dose.
2. Unless your doctor has given you special instructions, follow the steps for using SYNAREL **twice each day**, about 12 hours between doses:
   - once in the morning in one nostril (for example, 7 a.m.)
   - once in the evening in the other nostril (for example, 7 p.m.)

   The length of treatment is usually about 6 months, unless your doctor has given you special instructions.
3. Because it is so important that you do not miss a single dose of SYNAREL, here are some suggestions to help you remember:
   - Keep your SYNAREL in a place where you will be reminded to use it each morning and each evening — next to your toothbrush is one possibility.
   - Keep track of each dose on a calendar.
   - Make a note on your calendar on the day you start a new bottle of SYNAREL. You can also mark the date you started right on the bottle. Be sure to refill your prescription before the 30 days are up so you will have a new bottle on hand.
4. A bottle of SYNAREL should not be used for longer than 30 days (60 sprays). Each bottle contains sufficient quantity of nasal solution for initial priming of the pump and 30 days (60 sprays) of treatment. At the end of 30 days, a small amount of liquid will be left in the bottle. **Do not try to use up that leftover amount** because you might get

too low a dose, which could interfere with the effectiveness of your treatment. Dispose of the bottle and do not reuse.

5. If your doctor increases your daily dose of SYNAREL, then your bottle will not last the standard 30 days. Please discuss this with your doctor to be sure that you have an adequate supply for uninterrupted treatment with SYNAREL to complete the recommended treatment period.

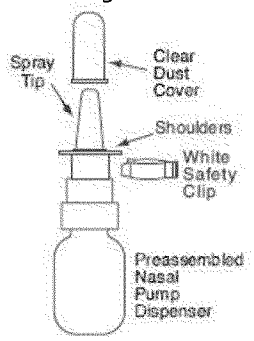
Preparation of the SYNAREL Nasal Spray unit
For use in your nose only.

Before you use SYNAREL nasal spray for the first time, you will need to prime it. This will ensure that you get the right dose of medicine each time you use it.

Important Tips about using SYNAREL

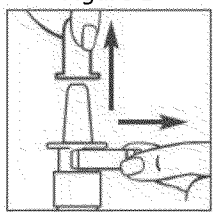
- Your pump should produce a fine mist, which can only happen by a quick and firm pumping action. It is normal to see some larger droplets of liquid within the fine mist. However, if SYNAREL comes out of the pump as a thin stream of liquid instead of a fine mist, SYNAREL may not work as well, and you should talk to your pharmacist.
- Be sure to clean the Spray Tip **before and after every use**. (See Step 4). Failure to do this may result in a clogged tip that may cause you not to get the right amount of medicine that is prescribed for you.
- The pump is made to deliver only a set amount of medicine, no matter how hard you pump it.
- **Do Not try to make the tiny hole in the spray tip larger**. If the hole is made larger the pump will deliver a wrong dose of SYNAREL.

Figure A



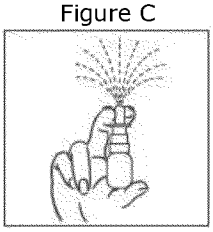
To Prime the Pump:

Figure B



1. Remove and save the white safety clip and the clear plastic dust cover from the spray bottle (See Figure B).

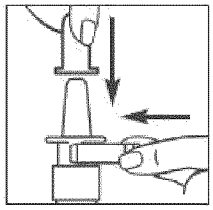
Figure C



2. Hold the bottle in an upright position away from you. Put two fingers on the "shoulders" of the spray bottle and put your thumb on the bottom of the bottle. Apply pressure **evenly** to the "shoulders" and push down **quickly and firmly** 7 to 10 times, until you see a fine spray. Usually you will see the spray after about 7 pumps. (See Figure C).

3. The pump is now primed**. Priming only needs to be done 1 time, when you start using a <u>new</u> bottle of SYNAREL**. You will waste your medicine if you prime the pump every time you use it and may not have enough medicine for 30 days of treatment.

Figure D

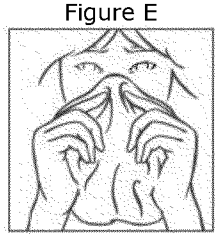


4. **Clean the Spray Tip after Priming:**
   - Hold the bottle in a horizontal position. Rinse the spray tip with **warm** water while wiping the tip with your finger or soft cloth for 15 seconds.
   - Wipe the spray tip with a soft cloth or tissue to dry.
   - Replace the white safety clip and the clear plastic dust cover on the spray bottle (See Figure D).
   - **Do Not** try to clean the spray tip using a pointed object. **Do Not** take apart the pump.

[SHAPE * MERGEFORMAT]

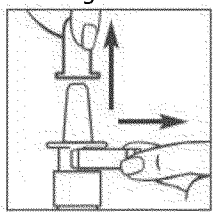
How to use the SYNAREL Nasal Spray unit for the treatment of Endometriosis

Figure E



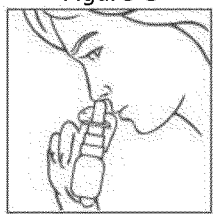
5. Gently blow your nose to clear both nostrils before you use SYNAREL nasal spray (See Figure E).

Figure F



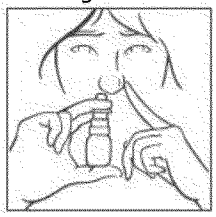
6. **Clean the Spray Tip.** Remove and save the white safety clip and the clear plastic dust cover from the spray bottle (See Figure F).
   - Hold the bottle in a horizontal position. Rinse the spray tip with **warm** water while wiping the tip with your finger or soft cloth for 15 seconds.
   - Wipe the spray tip with a soft cloth or tissue to dry.
   - **Do Not** try to clean the spray tip using a pointed object.
   - **Do Not** try to take apart the pump.

Figure G



7. Bend your head forward and put the spray tip into one nostril. The tip should **not** reach too far into your nose. Aim the spray tip toward the **back and outer side** of your nose (See Figure G).

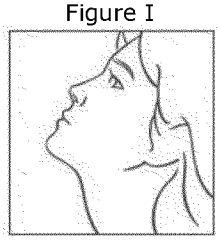
Figure H



8. Close the other nostril with your finger (See Figure H).

9. Apply pressure **evenly** to the "shoulders" and push down **quickly and firmly.** Pump the sprayer 1 time, at the same time as you sniff in gently. If the sprayer fails to deliver the dose clean the spray tip (See Step 6 **Clean the Spray Tip**).

Figure I



10. Remove the spray tip from your nose and tilt your head backwards for a few seconds. This lets the SYNAREL spray spread over the back of your nose (See Figure I).

    Do not spray in your other nostril unless your doctor has instructed you to do so.

Figure J
[SHAPE * MERGEFORMAT]

11. Clean the Spray Tip after use (See Step 4).

It is important that you clean the spray tip before and after every use. Failure to do this may result in a clogged tip that may cause you to get the wrong dose of medicine.

Important Reminder: Treatment with SYNAREL must be uninterrupted with no missed doses to be effective.

Make sure you use SYNAREL exactly as your doctor tells you. Make sure to note the date you start each bottle so you do not run out of medicine and miss doses.

Keep out of the reach of children and use carefully as directed.

Storage Instructions:

- Store SYNAREL at 59°F to 86°F (15°C to 30°C).
- Store the SYNAREL bottle upright.
- Keep SYNAREL out of the light.
- Do not freeze SYNAREL.

This product's label may have been updated. For current full prescribing information, please visit [HYPERLINK "http://www.pfizer.com"].

Distributed by

Pfizer Labs

Division of Pfizer Inc, NY, NY 10017

LAB-0278-7.0
Revised: December 2020

MEDICATION GUIDE
SYNAREL (sin-na-rell)
(nafarelin acetate) nasal solution

What is the most important information I should know about SYNAREL?

- Some people taking GnRH agonists like SYNAREL have had new or worsened mental (psychiatric) problems. Mental (psychiatric) problems may include emotional symptoms such as:
  - crying
  - irritability
  - restlessness (impatience)
  - anger
  - acting aggressive

Call your child's doctor right away if your child has any new or worsening mental symptoms or problems while taking SYNAREL

- Some people taking GnRH agonists like SYNAREL have had seizures. The risk of seizures may be higher in people who:
  - have a history of seizures.
  - have a history of epilepsy.
  - have a history of brain or brain vessel (cerebrovascular) problems or tumors.
  - are taking a medicine that has been connected to seizures such as taking bupropion or selective serotonin reuptake inhibitors (SSRIs).

Seizures have also happened in people who have not had any of these problems.

Call your child's doctor right away if your child has a seizure while taking SYNAREL.

What is SYNAREL?

SYNAREL is a gonadotropin releasing hormone (GnRH) medicine used for the treatment of children with central precocious puberty (CPP).

Do not give SYNAREL if your child:

- is allergic to gonadotropin releasing hormone (GnRH), GnRH agonist medicines, or any of the ingredients in SYNAREL. See the end of this Medication Guide for a complete list of ingredients in SYNAREL.
- has unusual vaginal bleeding that has not been checked by her doctor.
- is pregnant or may become pregnant. SYNAREL can cause birth defects or loss of the baby. If your child becomes pregnant call your doctor.
- is breastfeeding or plans to breastfeed. It is not known if SYNAREL passes into breast milk. You and your child's doctor should decide if your child will take SYNAREL or breastfeed. **Do not breastfeed while taking SYNAREL.**

Before your child takes SYNAREL, tell your doctor about all of your child's medical conditions, including if they:

- have a history of mental (psychiatric) problems.
- have or have had a history of seizures.
- have a history of epilepsy.
- have a history of brain or brain vessel (cerebrovascular) problems or tumors
- are taking a medicine that has been connected to seizures such as bupropion or selective serotonin reuptake inhibitors (SSRIs).

Tell your doctor about all the medicines your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should your child take SYNAREL?

- Your child's doctor should do tests to make sure your child has CPP before treating your child with SYNAREL.
- Keep all scheduled visits to the doctor. If scheduled doses are missed, your child may start having signs of puberty again. The doctor will do regular exams and blood tests to check for

signs of puberty.

- Take SYNAREL exactly as your doctor tells you to take it. See detailed **"Instructions for Use"** at the end of this Medication Guide for information about the right way to use SYNAREL.
- Your child's doctor will tell you how much SYNAREL your child is to take and when to take it. If your doctor increases your child's daily dose of SYNAREL, 1 bottle will not last the standard 7 days. Talk with your child's doctor to make sure your child has enough SYNAREL to take their prescribed dose every day.

What should your child avoid while taking SYNAREL?

- Your child should avoid sneezing while taking SYNAREL or right after using it, if possible. This could reduce the amount of medicine your child's body absorbs.
- If your child needs to use a nasal decongestant spray while being treated with SYNAREL, they should not use the decongestant spray for at least 2 hours after taking the dose of SYNAREL.

What are the possible side effects of SYNAREL?

SYNAREL may cause serious side effects, including:

- See **"What is the most important information I should know about SYNAREL"**
- in the first month of treatment, SYNAREL can cause an increase in some hormones. During this time you may notice more signs of puberty in your child, including vaginal bleeding and breast enlargement in girls. Within 1 month of treatment, you should see signs in your child that puberty is stopping.

The side effects of SYNAREL include:

- allergic reactions such as shortness of breath, chest pain, hives, rash, and itching
- acne
- temporary increase in pubic hair
- body odor
- flaky, scaly skin
- hot flashes
- stuffy or runny nose (rhinitis)
- white or brown vaginal discharge

These are not all of the possible side effects of SYNAREL. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General Information about the safe and effective use of SYNAREL.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SYNAREL for a condition for which it is not prescribed. Do not give SYNAREL to other people, even if they have the same symptoms that you have. It may harm them.
You can ask your doctor or pharmacist for information about SYNAREL that is written for health professionals.

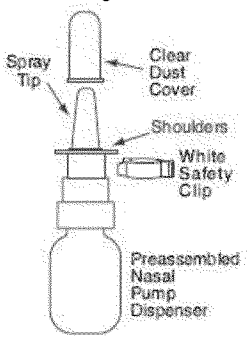
What are the ingredients in SYNAREL?

Active ingredient: nafarelin acetate
Inactive ingredients: benzalkonium chloride, glacial acetic acid, sodium hydroxide or hydrochloric acid (to adjust pH), sorbitol, and purified water

Instructions for Use
SYNAREL(sin-na-rel)
(nafarelin acetate)
nasal solution

For use in the nose only.

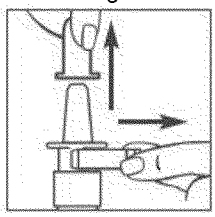
Figure A



Before you use SYNAREL nasal spray for the first time, you will need to prime it. This will make sure that you get the right dose of medicine each time you use it. Priming only needs to be done 1 time, when you start using a **new** bottle of SYNAREL.

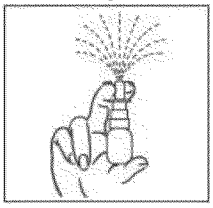
To Prime the Pump:

Figure B



1. Remove and save the white safety clip and the clear plastic dust cover from the spray bottle (See Figure B).

Figure C



2. Hold the bottle in an upright position away from you. Put 2 fingers on the "shoulders" of the spray bottle and put your thumb on the bottom of the bottle. Apply pressure **evenly** to the "shoulders" and push down **quickly and firmly** 7 to 10 times, until you see a fine mist spray. Usually you will see the spray after about 7 pumps. (See Figure C). The pump is now primed.

   It is normal to see some larger droplets of liquid within the fine mist. However, if SYNAREL comes out of the pump as a thin stream of liquid instead of a fine mist, SYNAREL may not work as well, and you should talk to your pharmacist.

Figure D

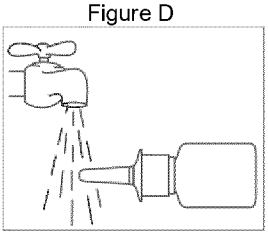
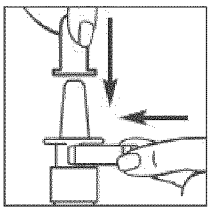


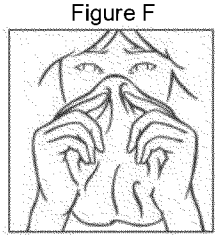
Figure E



3. **Clean the Spray Tip after Priming:**
   - Hold the bottle in sideways (horizontal) position (see Figure D).
     Rinse the "spray tip" with **warm** water while wiping the tip with your finger or soft cloth for 15 seconds.
   - Wipe the spray tip with a soft cloth or tissue to dry.
   - Replace the white safety clip and the clear plastic dust cover on the spray bottle. (See Figure E).
   - **Do not** try to clean the spray tip using a pointed object.
   - **Do not** take apart the pump.

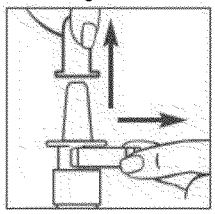
How to use the SYNAREL Nasal Spray for the treatment of Central Precocious Puberty

Figure F



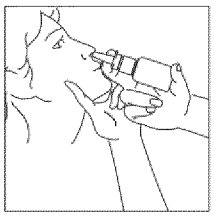
4. Have your child blow their nose to clear both nostrils before using SYNAREL nasal spray (see Figure F). If the child is too young to blow their nose, you may need to clear the child's nostrils with a bulb syringe.

Figure G



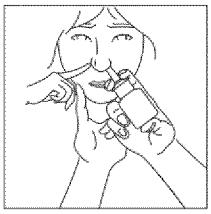
5. **Clean the Spray Tip each time before and after using SYNAREL.**
   - Remove and save the white safety clip and the clear plastic dust cover from the spray bottle (See Figure G).
   - Hold the bottle in sideways (horizontal) position. Rinse the spray tip with **warm** water while wiping the tip with your finger or soft cloth for 15 seconds.
   - Wipe the spray tip with a soft cloth or tissue to dry.
   - **Do not** try to clean the spray tip using a pointed object.
   - **Do not** try to take apart the pump.

Figure H



6. The child's head should be bent back a little and the spray tip put into one nostril. The tip should **not** reach too far into the nose. Aim the spray tip toward the **back and outer side** of the nose (See Figure H).

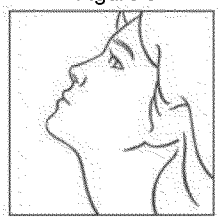
Figure I



7. Close the other nostril with a finger (See Figure I).

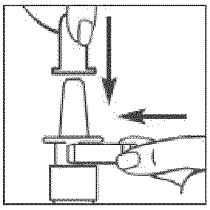
Put pressure **evenly** to the "shoulders" and push down **quickly and firmly.** Pump the sprayer 1 time, at the same time as the child sniffs in gently. Wait about 30 seconds and put one more spray in the same nostril. Repeat this process in the other nostril, for a total of four sprays. If the sprayer fails to deliver the dose, clean the spray tip (See Step 5 **Clean the Spray Tip each time before and after using SYNAREL**).

Figure J



8. Remove the spray tip from the child's nose after all sprays are completed. Keep the child's head tilted back for a few seconds. This lets the SYNAREL spray spread over the back of the nose (See Figure J).

Figure K



9. Clean the Spray Tip after use (See Step 5. Put on the white safety clip and the clear plastic dust cover (see Figure K).

It is important that you clean the spray tip before and after every use. Not doing this may result in a clogged tip that may cause you to get the wrong dose of medicine.

How should I store SYNAREL?

- Store SYNAREL at room temperature between 59°F to 86°F (15°C to 30°C).
- Store the SYNAREL bottle upright.
- Keep SYNAREL out of the light.

Keep SYNAREL and all medicines out of the reach of children.

For more information call 1-800-438-1985.

This Medication Guide and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Manufactured for: Pfizer Inc., 235 East 42nd Street, New York, NY, 10017

Distributed by

Pfizer Labs

Division of Pfizer Inc, NY, NY 10017

LAB-1049-2.0
Revised: December 2020

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 26, 2022

To: Shannon Sullivan, M.D., Team Leader
Division of General Endocrinology (DGE)

Jennifer Johnson, Project Manager, (DGE)

Monika Houstoun, Associate Director for Labeling, (DGE)

From: Charuni Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for

NDA 020263	Lupron Depot-Ped (leuprolide acetate for depot suspension), for intramuscular use
NDA 022058	Supprelin LA (histrelin acetate) subcutaneous implant
NDA 208956	Triptodur (triptorelin) for extended-release injectable suspension
NDA 213150	Fensolvi (leuprolide acetate) for injectable suspension

---

In response to DGE's consult request dated January 17, 2022, OPDP has completed a focused review on the attached document for proposed labeling that provides for a Safety Labeling Change regarding idiopathic intracranial hypertension (IIH)/pseudotumor cerebri (PTC) in products indicated for precocious puberty.

OPDP's comments on the proposed labeling are based on the draft materials sent by DGE on January 19, 2022 and are provided below. We have no comments on the proposed labeling at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed patient labeling will be sent under separate cover.

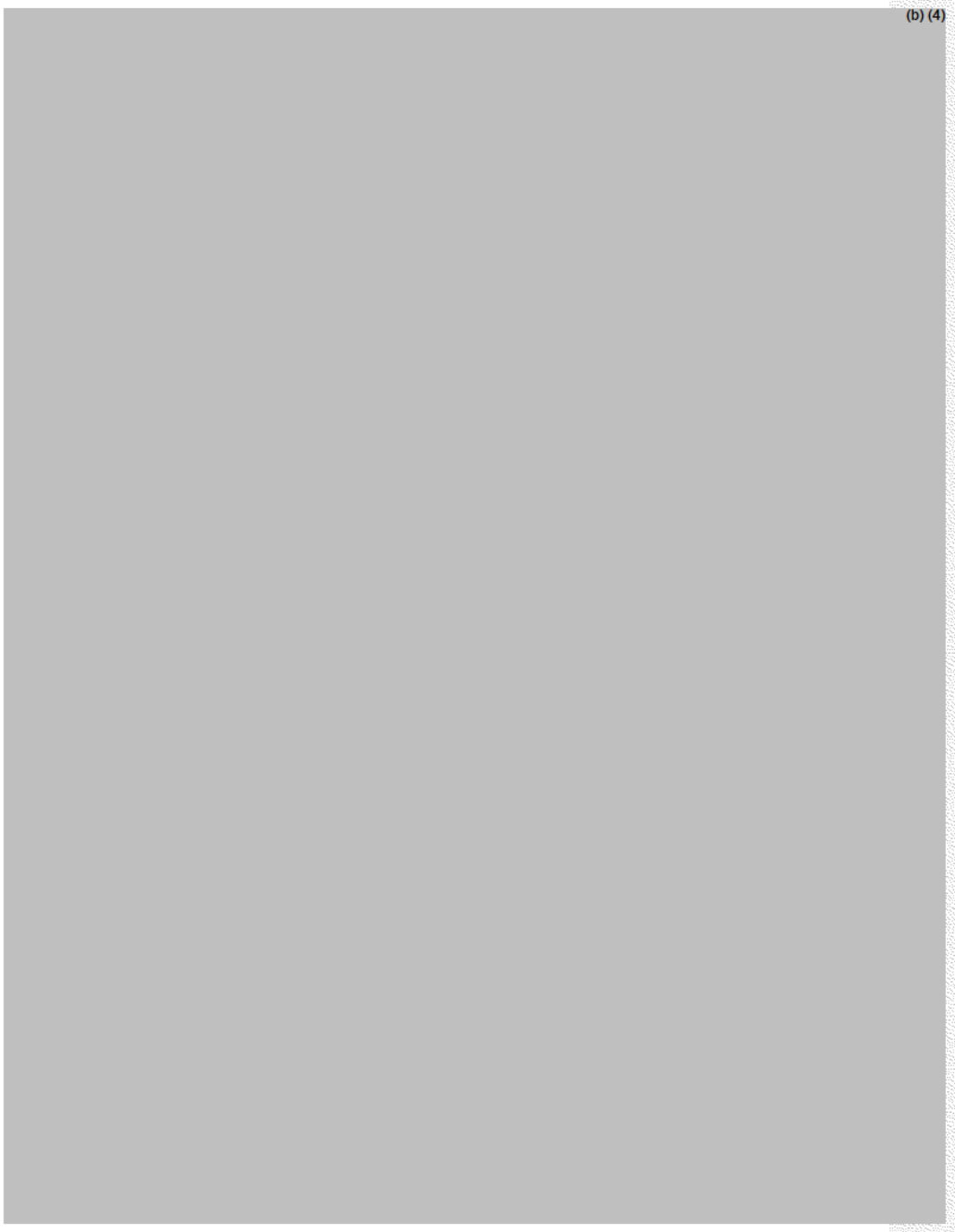
Thank you for your consult. If you have any questions, please contact Charuni Shah at (240) 402-4997 or charuni.shah@fda.hhs.gov.

(b) (4)

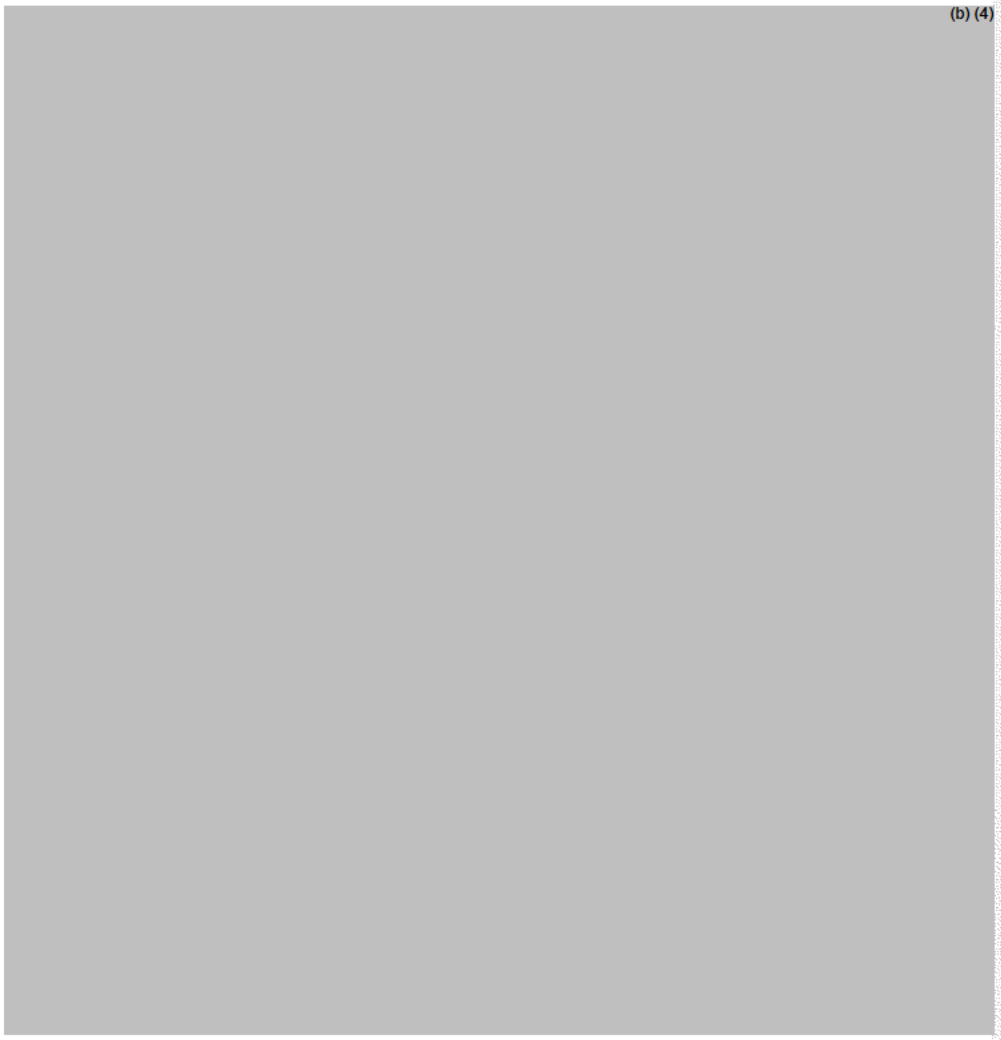
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUPRON DEPOT-PED safely and effectively. See full prescribing information for LUPRON DEPOT-PED.

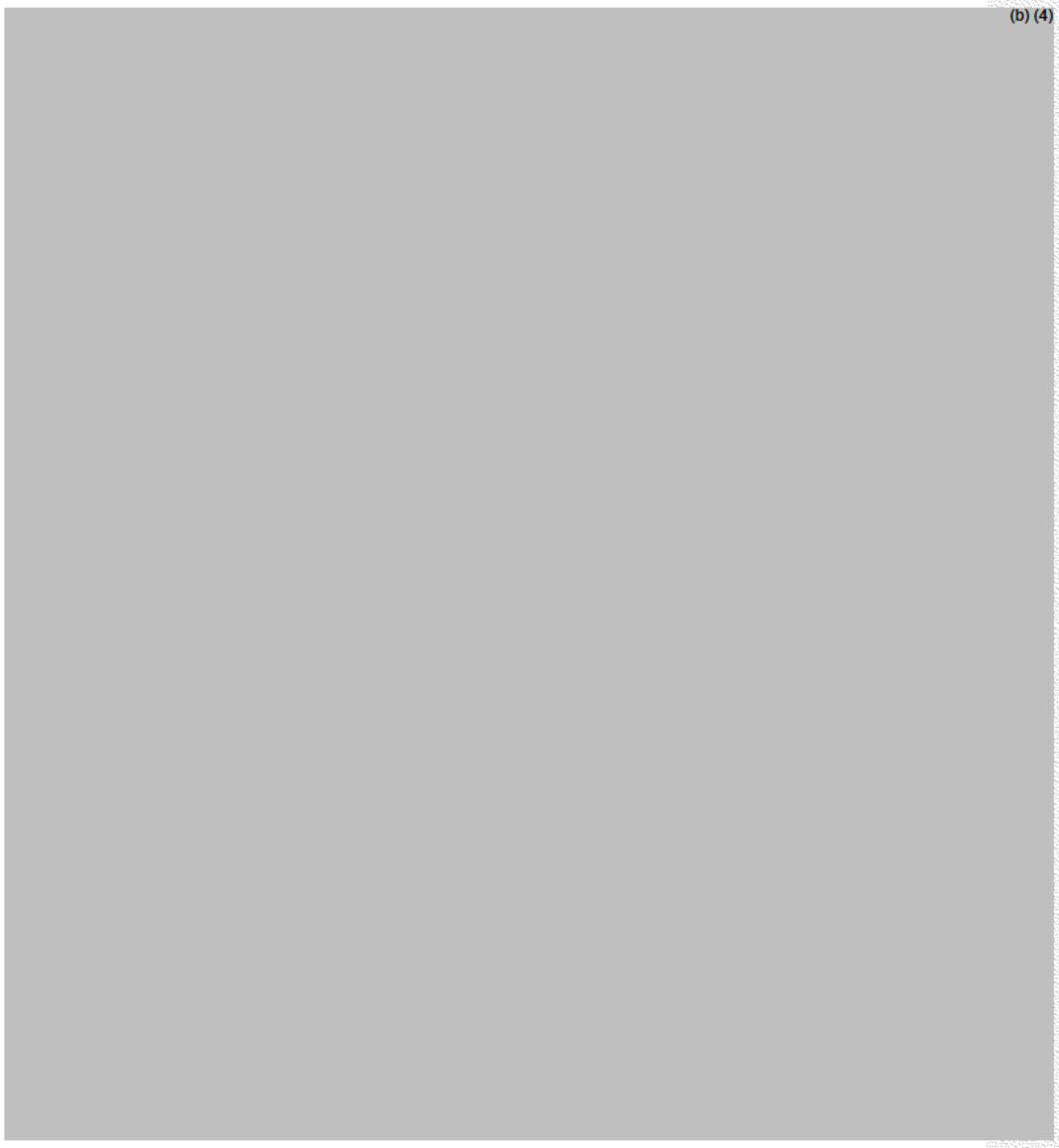
LUPRON DEPOT-PED (leuprolide acetate for depot suspension), for intramuscular use
Initial U.S. Approval: 1985

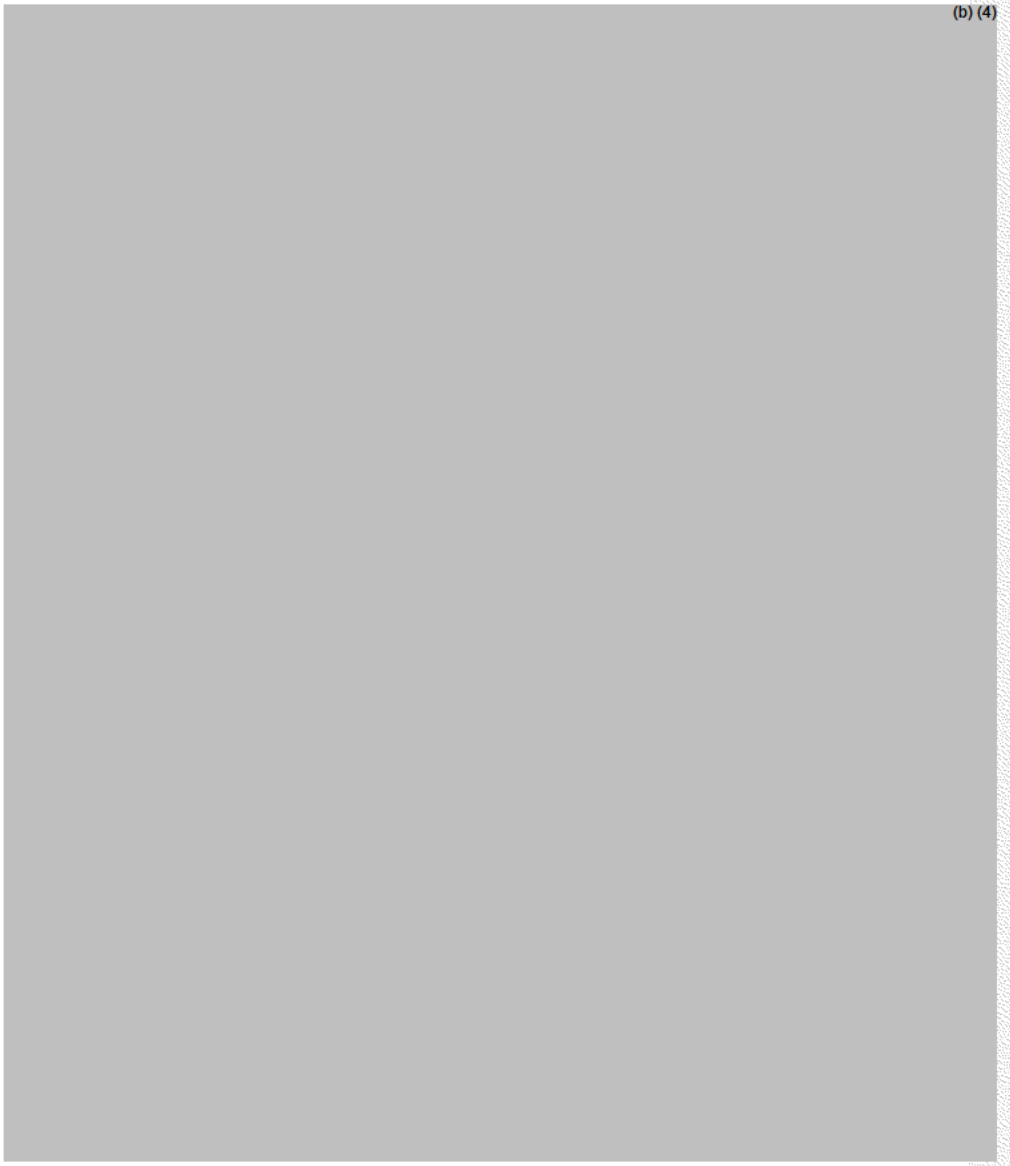
(b) (4

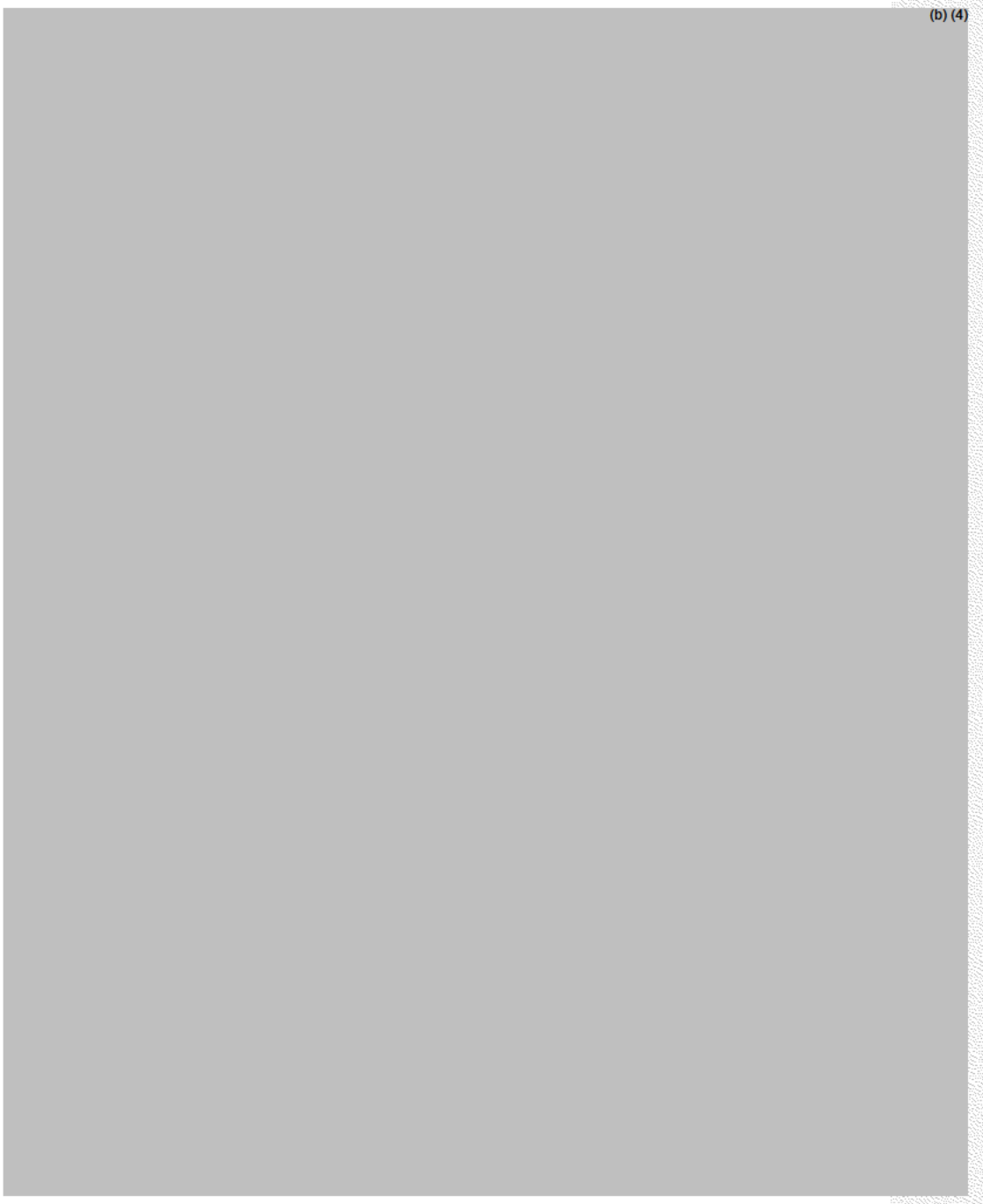

(b) (4)

(b) (4)



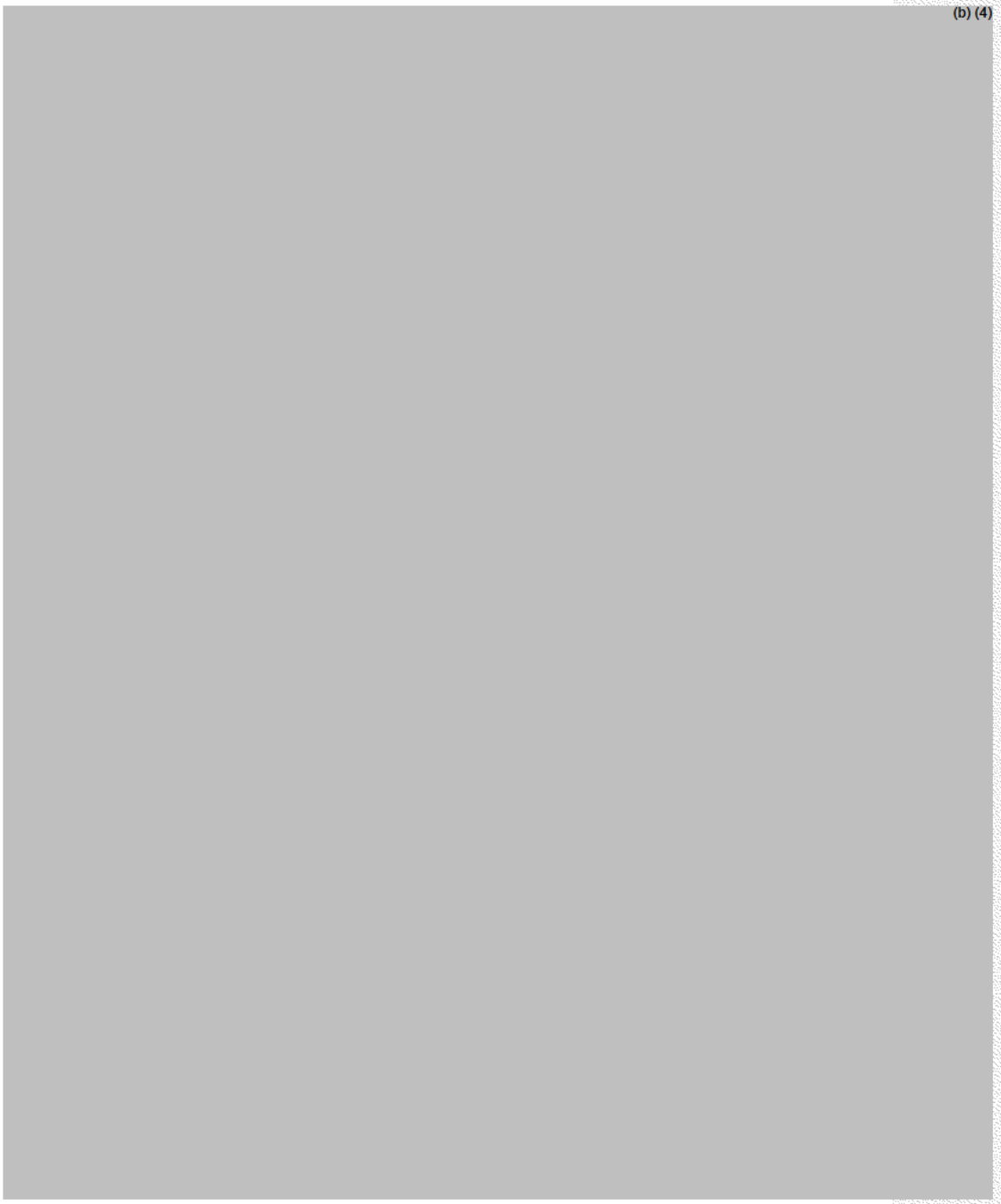

(b) (4)


(b) (4)

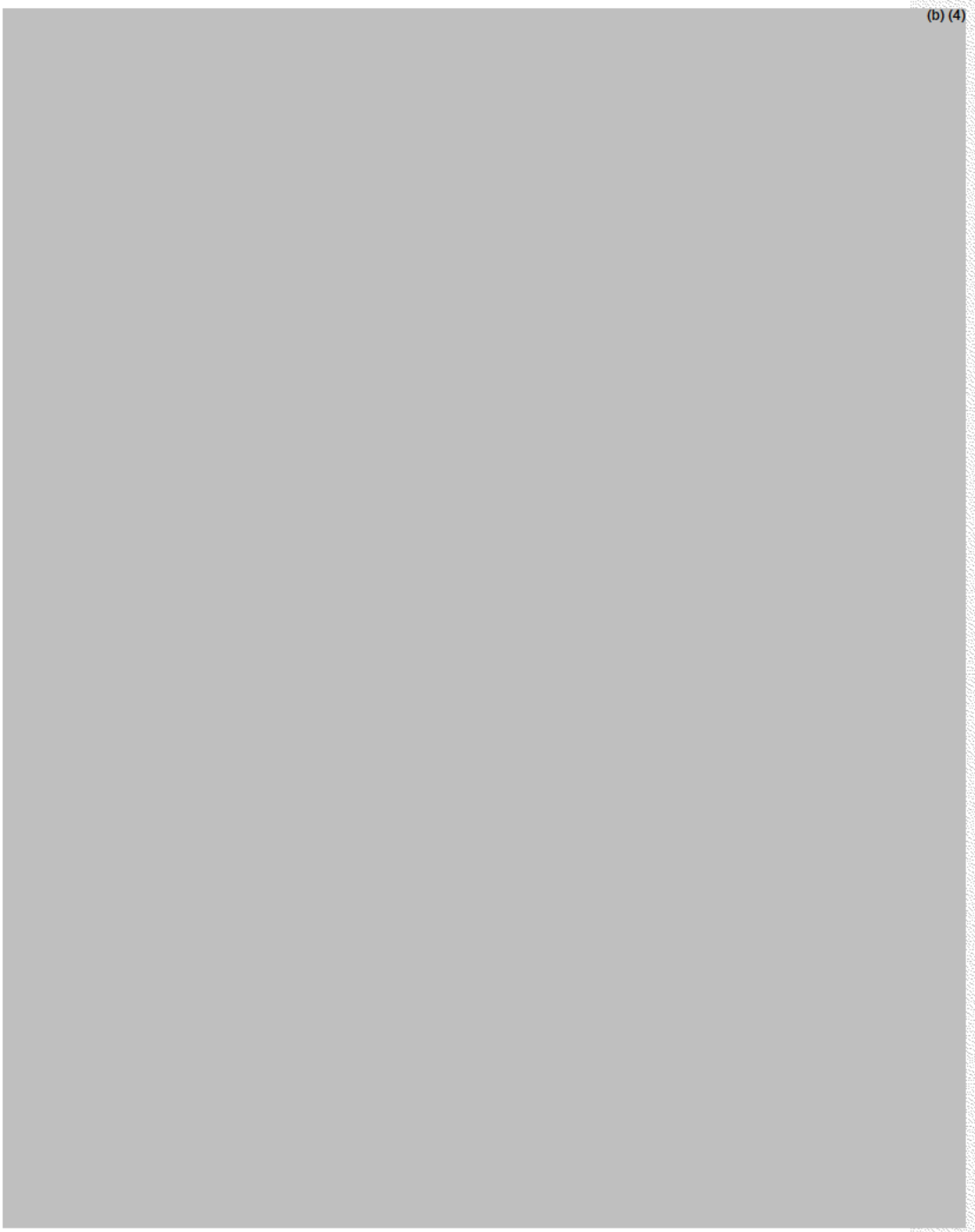

(b) (4)


(b) (4)

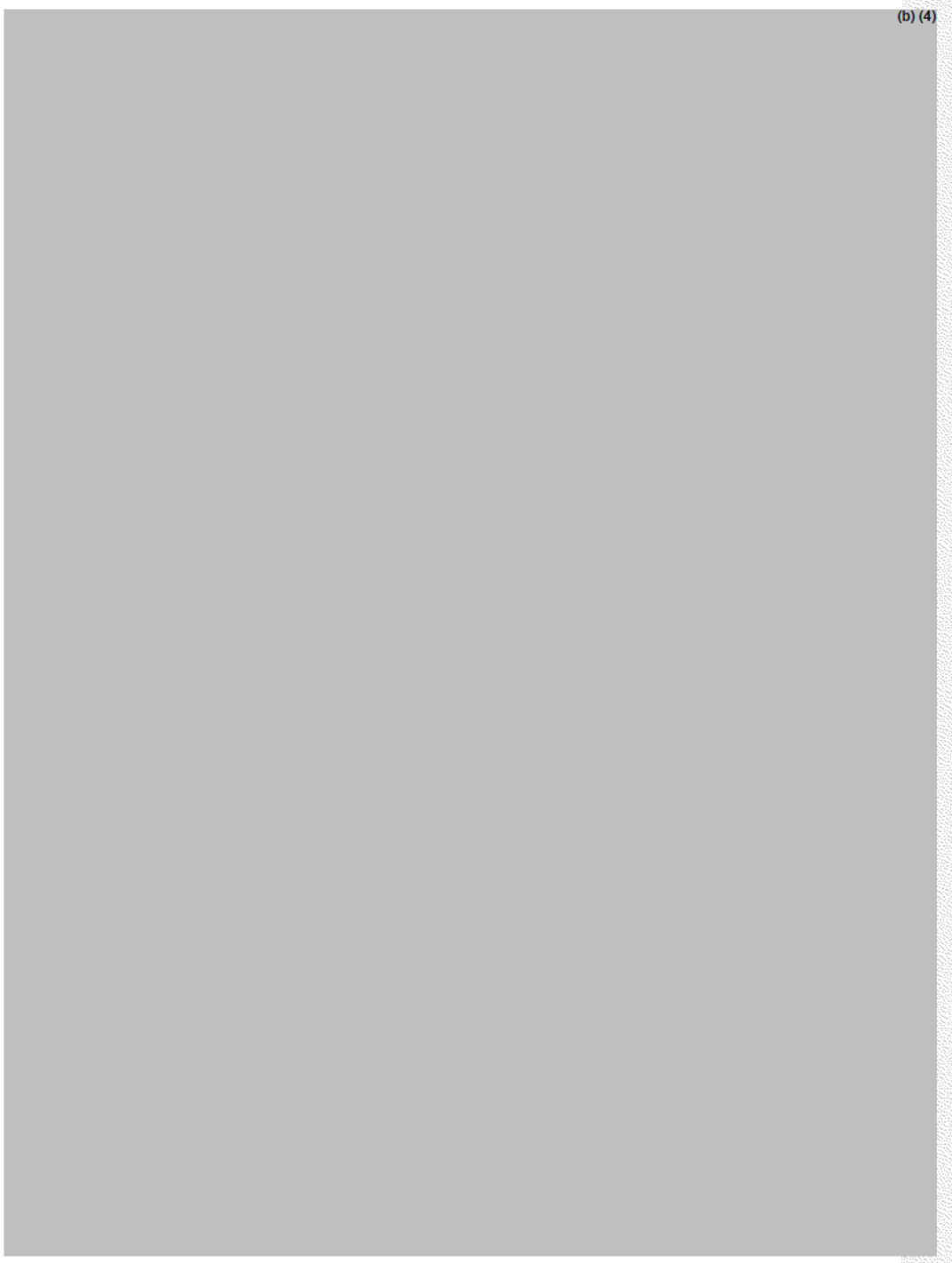
(b) (4)



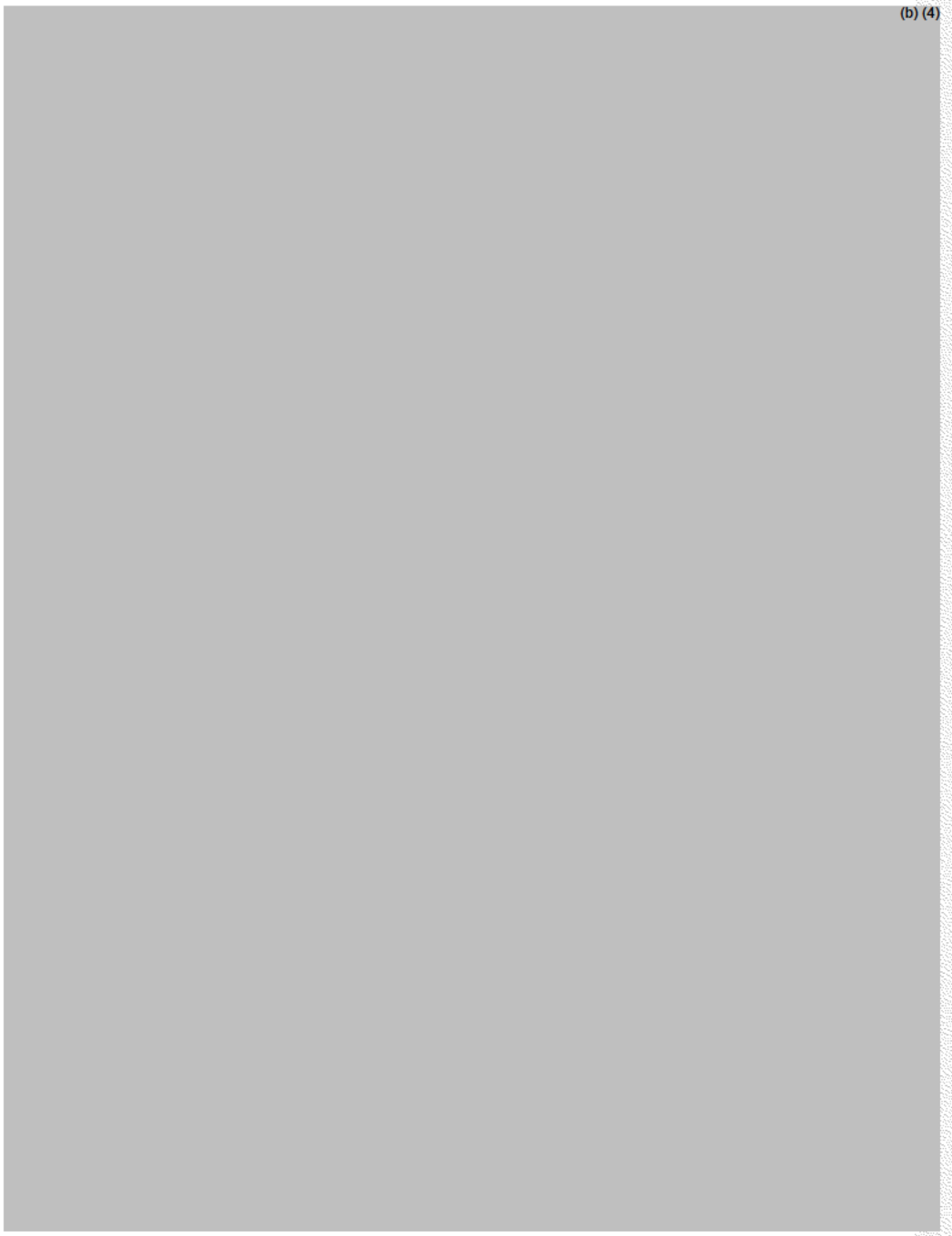
(b) (4)

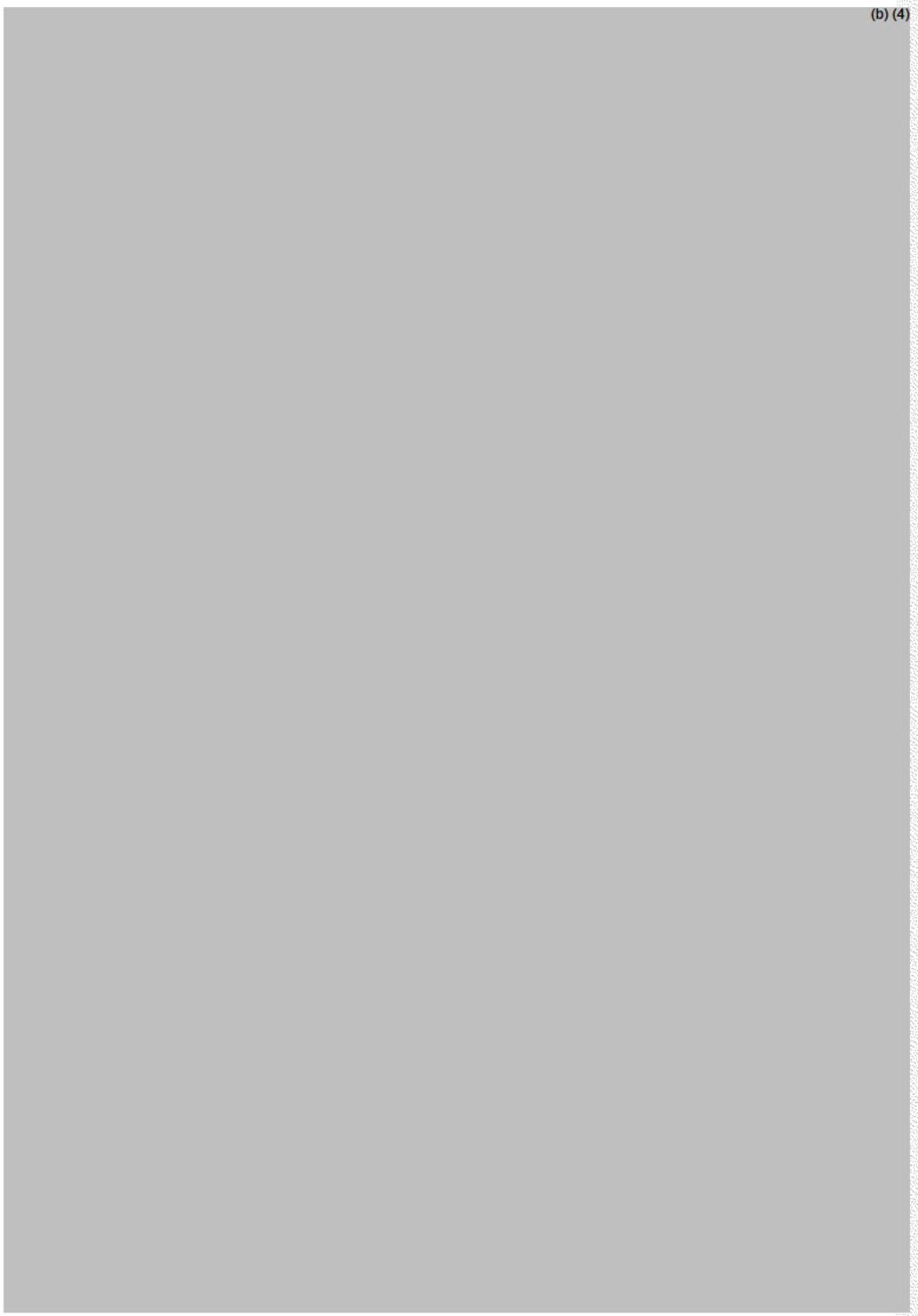


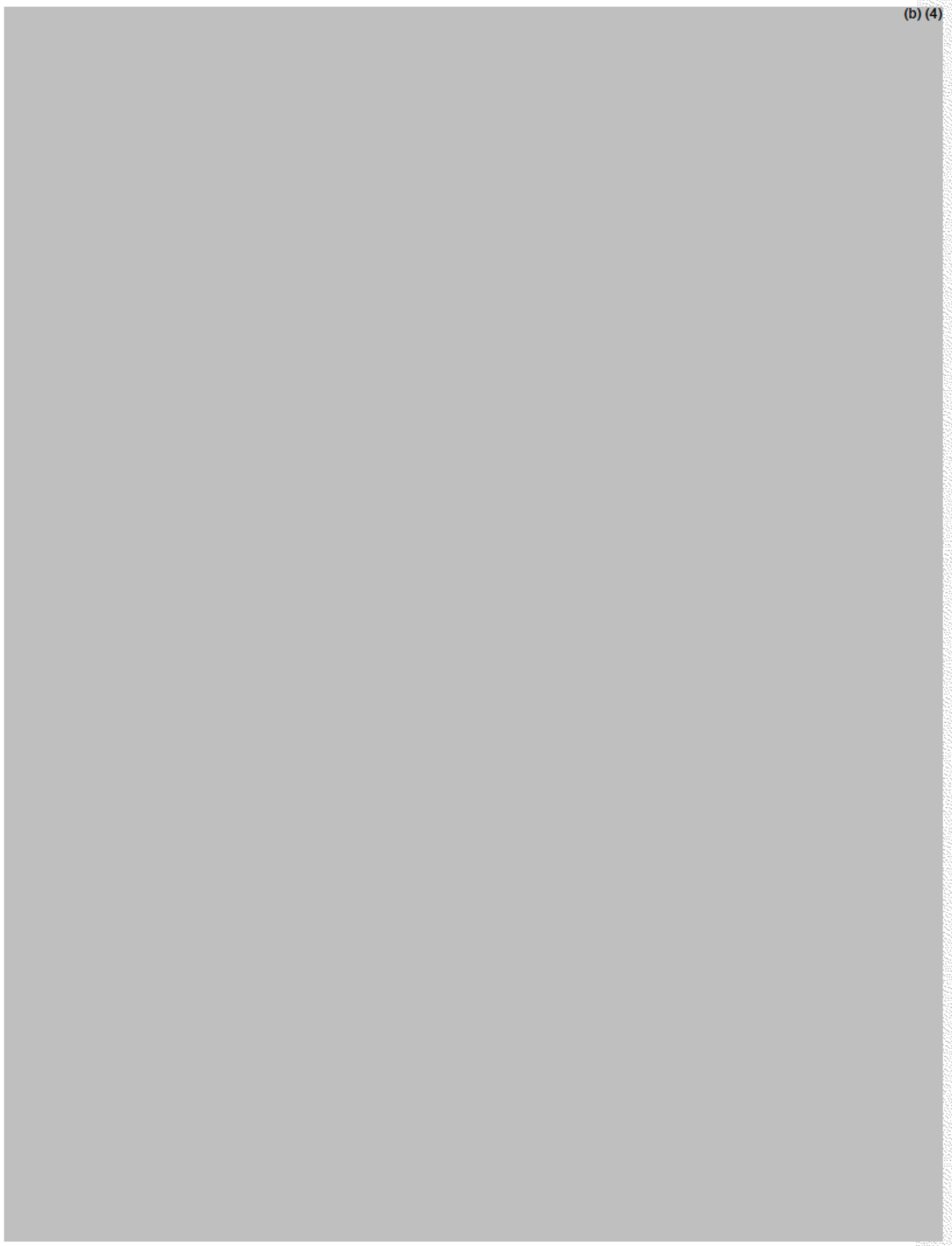
(b) (4)

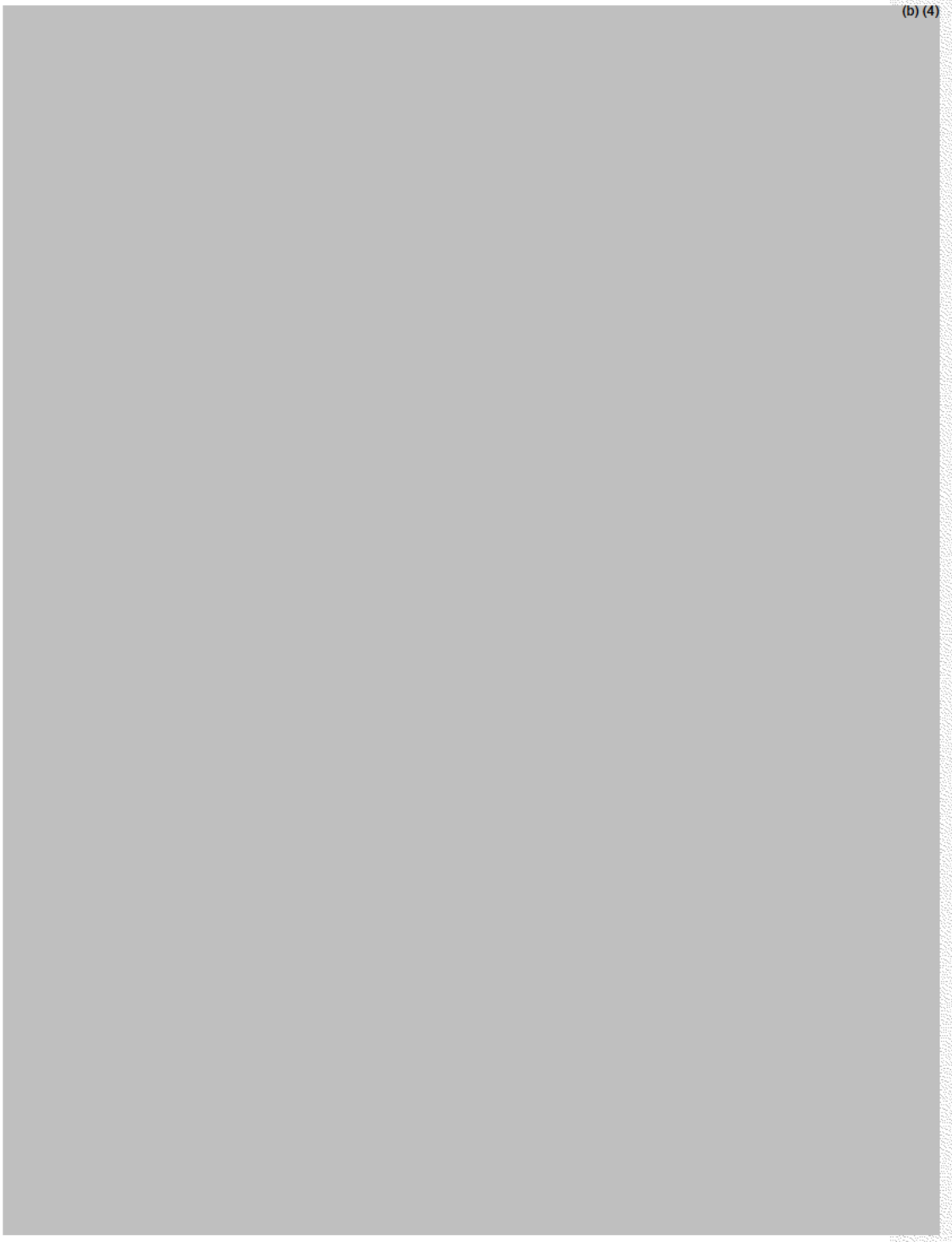


(b) (4)

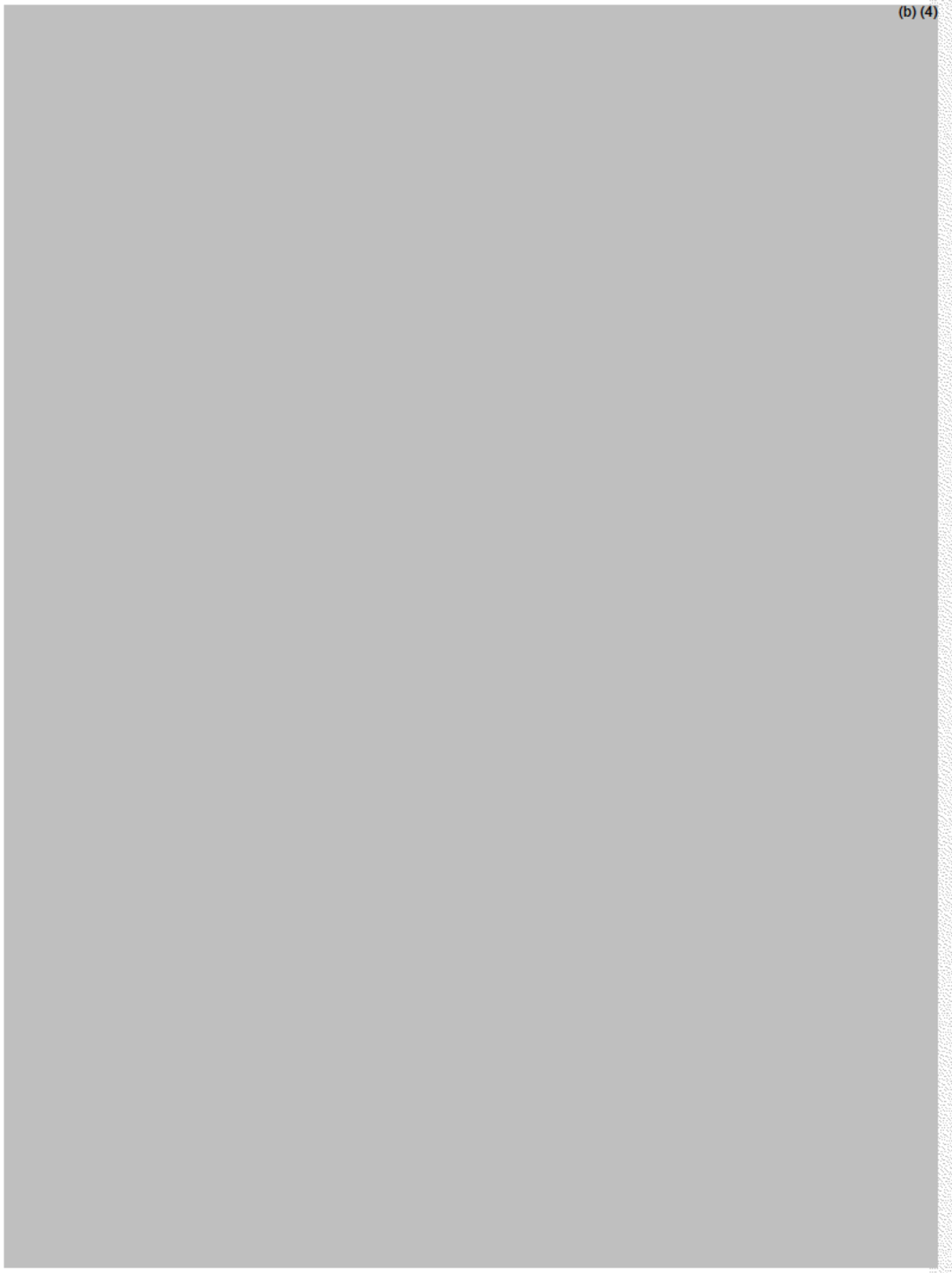


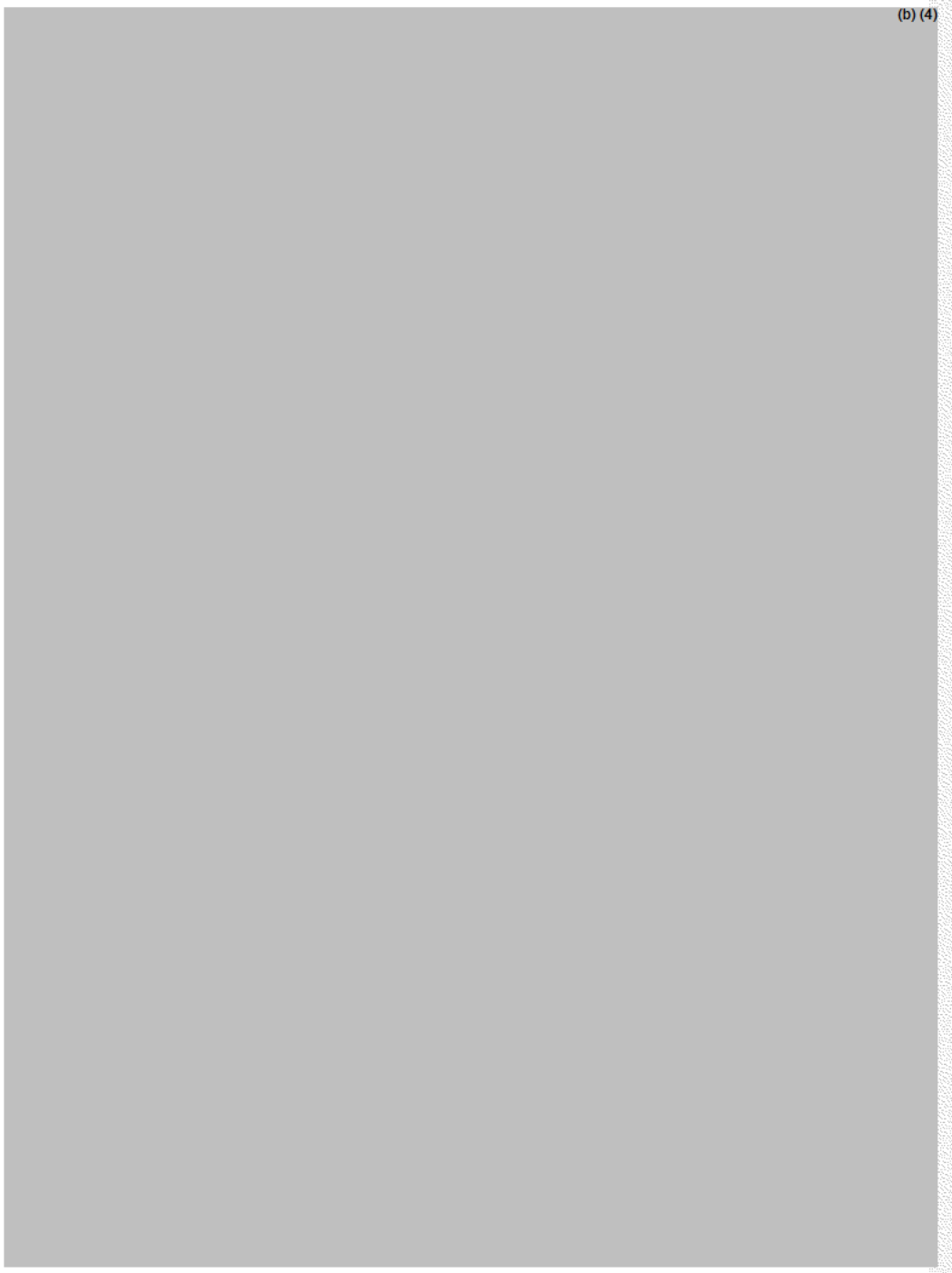

(b) (4)


(b) (4)

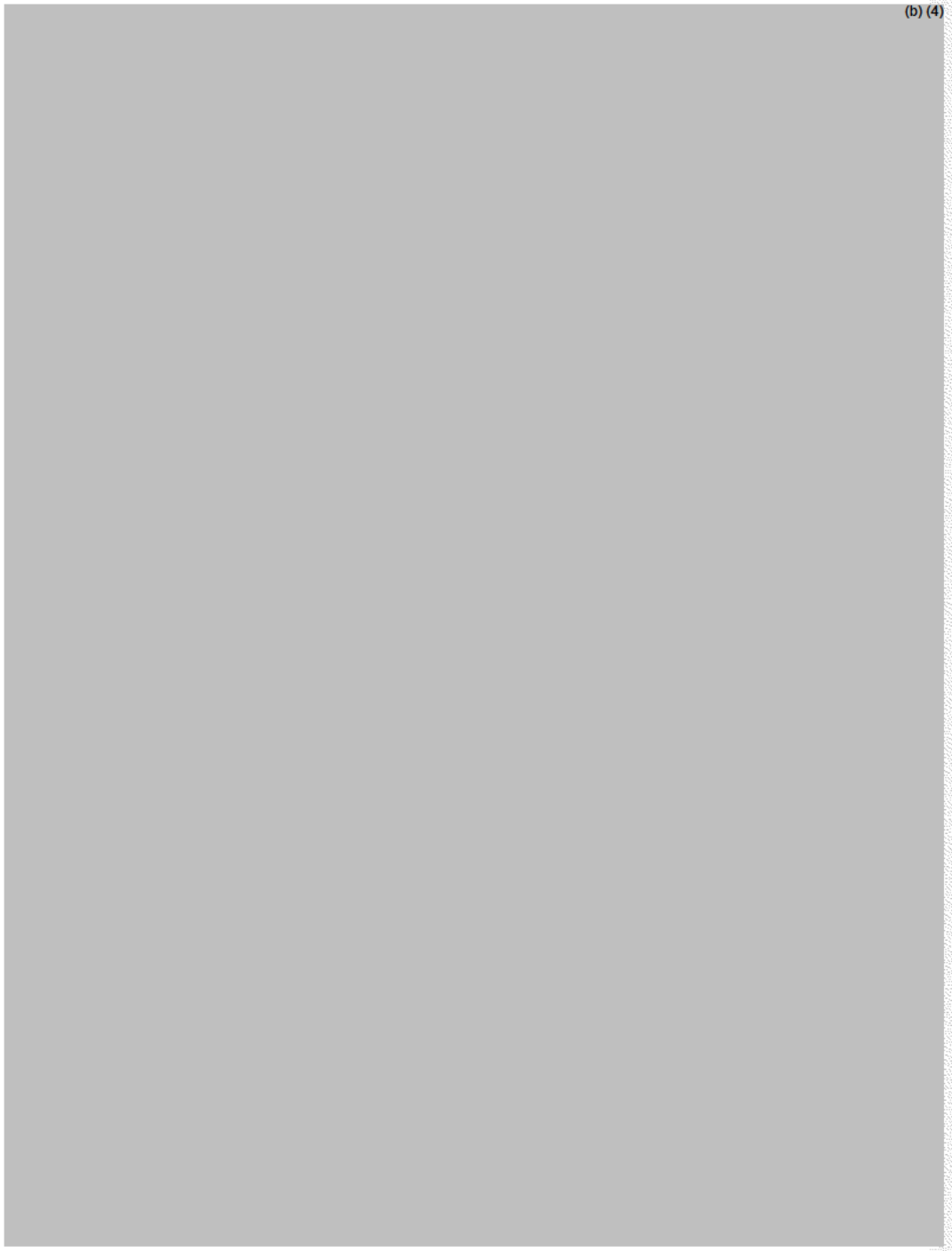

(b) (4)

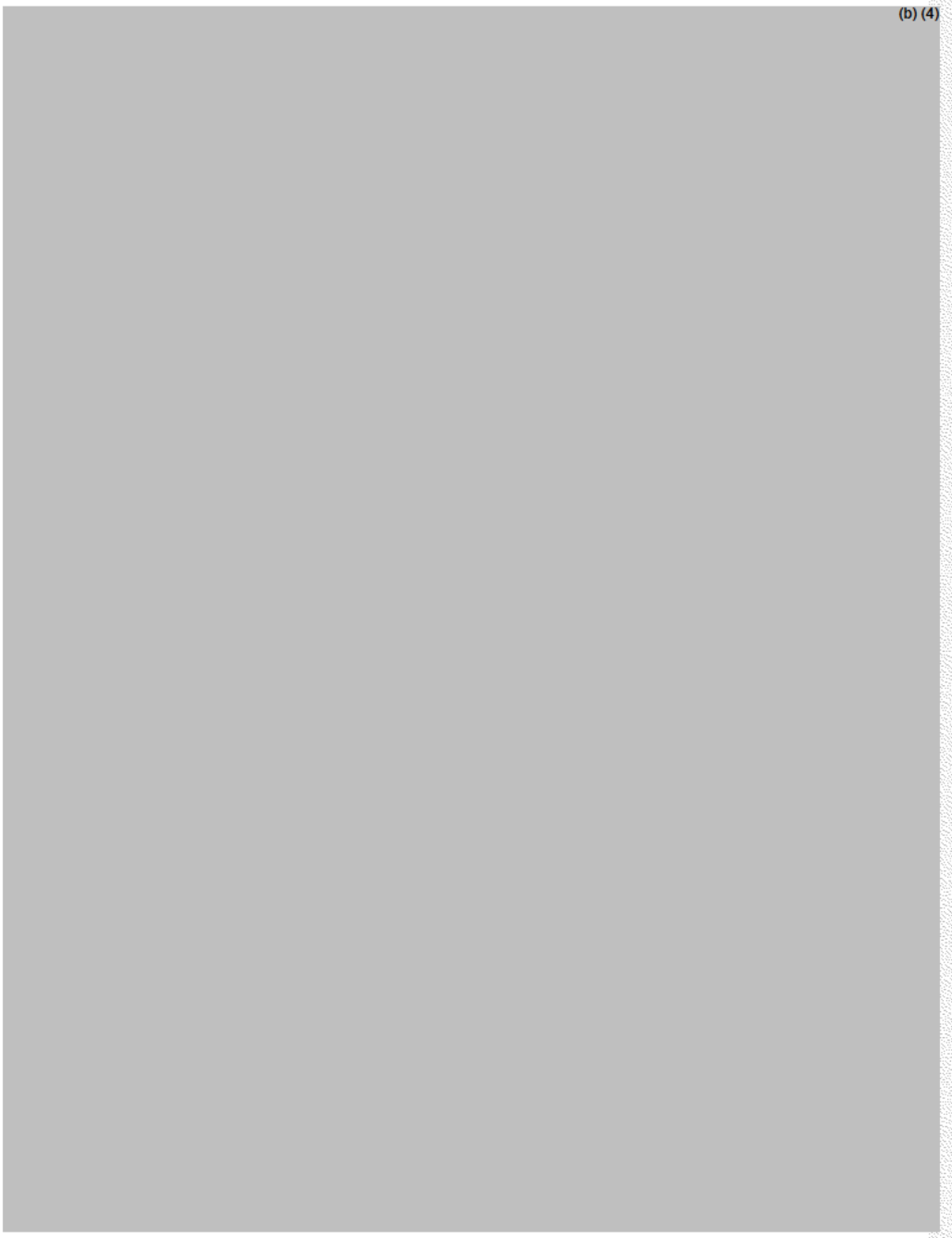
(b) (4)




(b) (4)

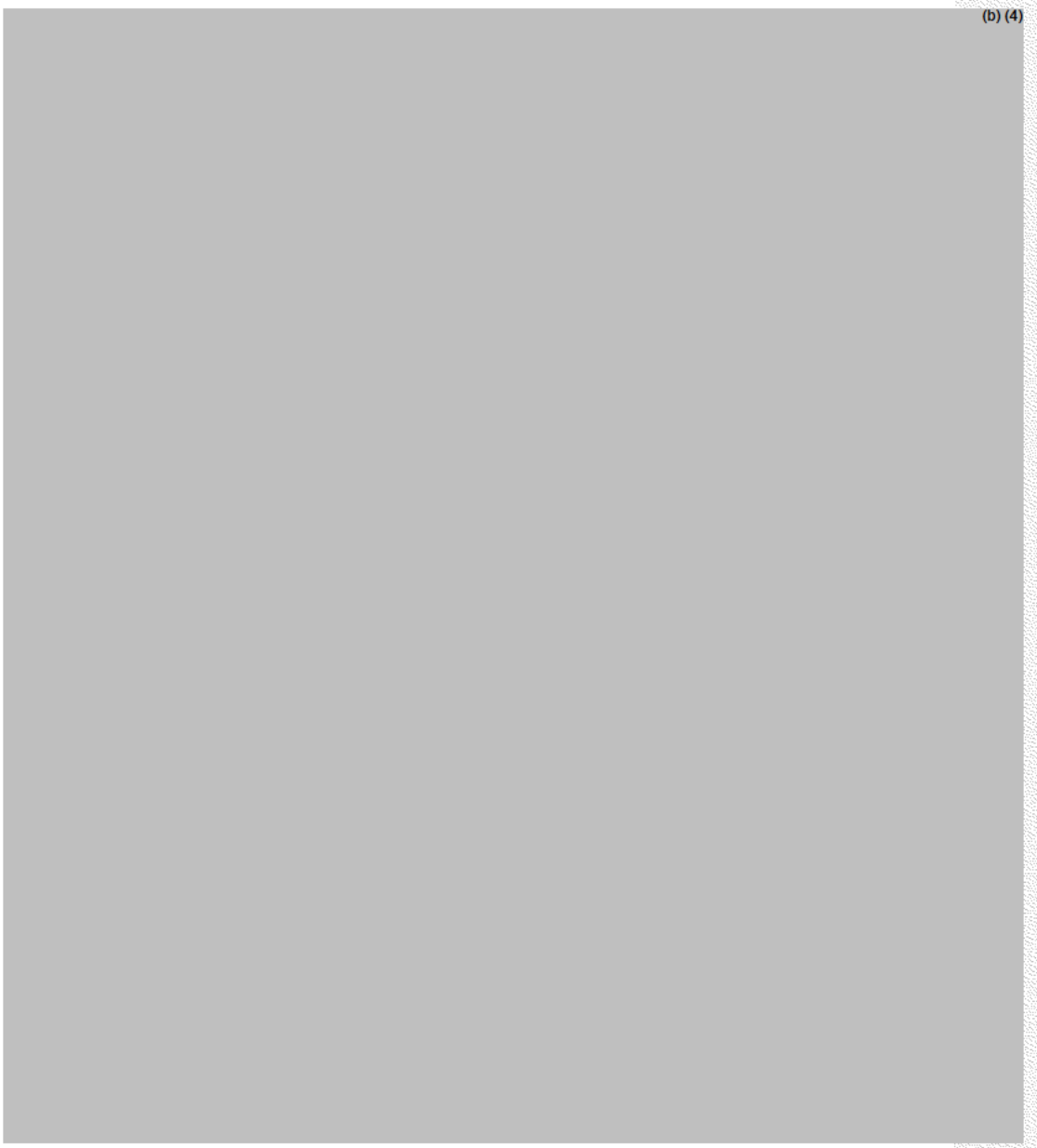
(b) (4)




(b) (4)

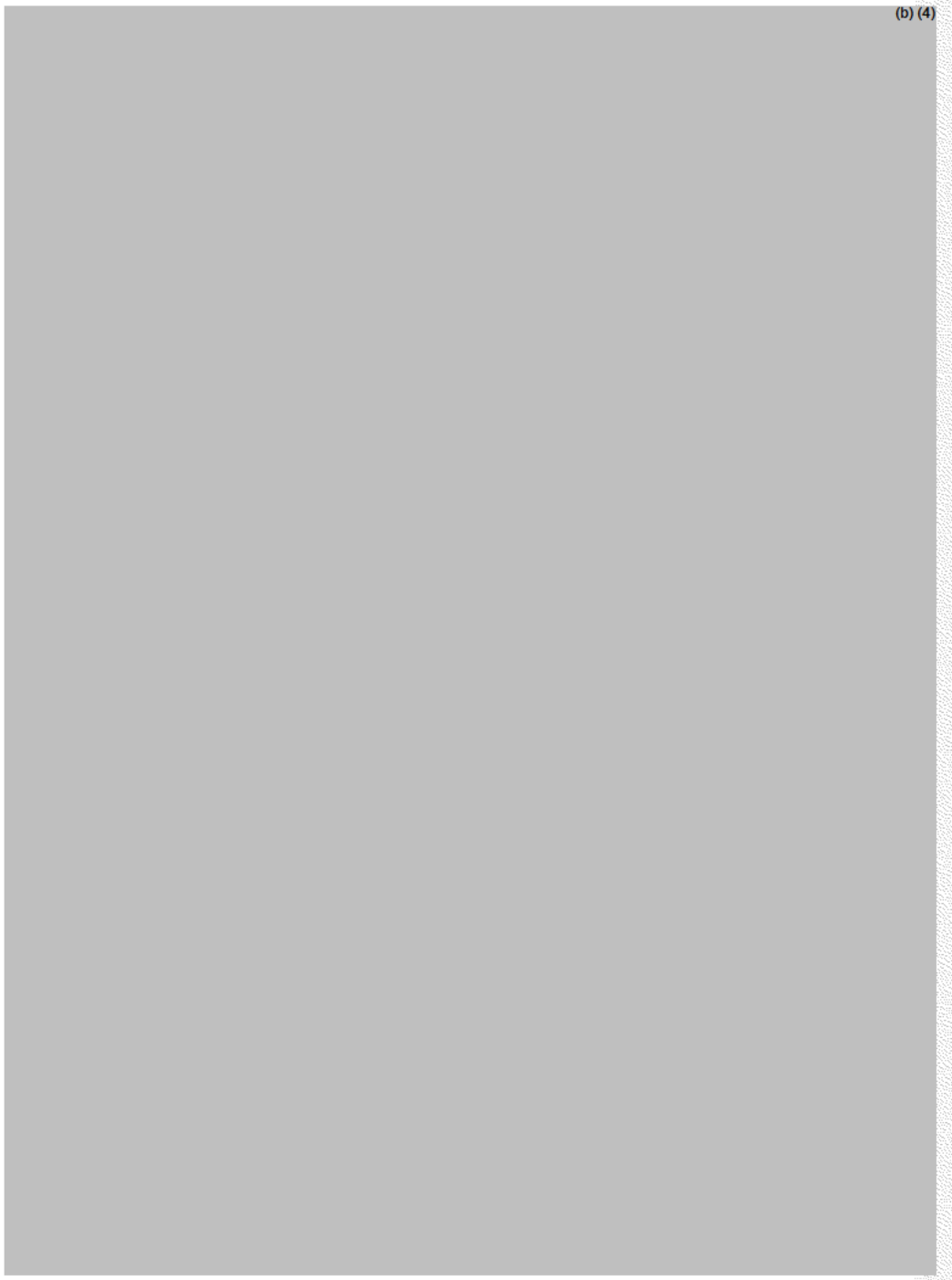
(b) (4)

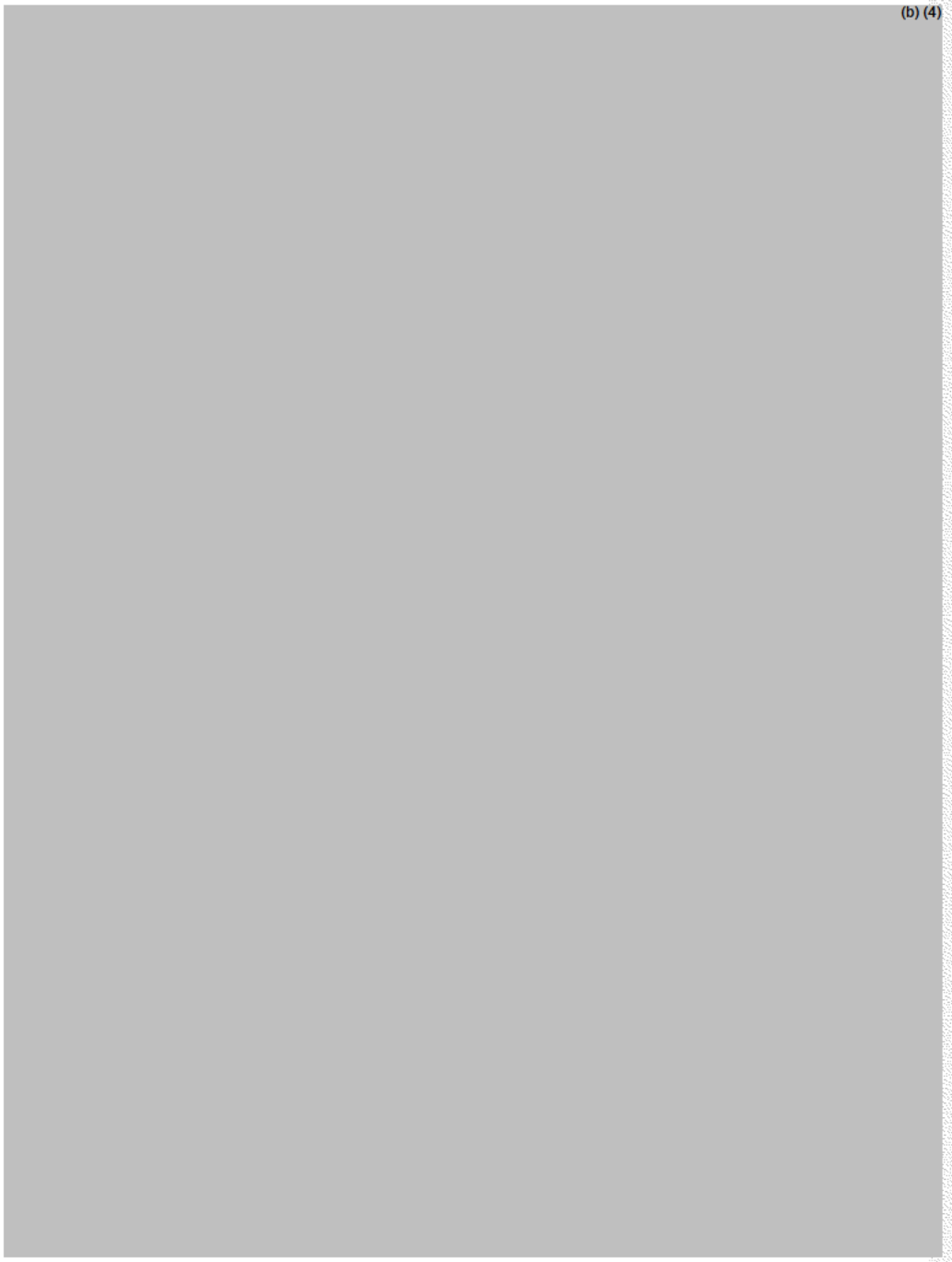

(b) (4)

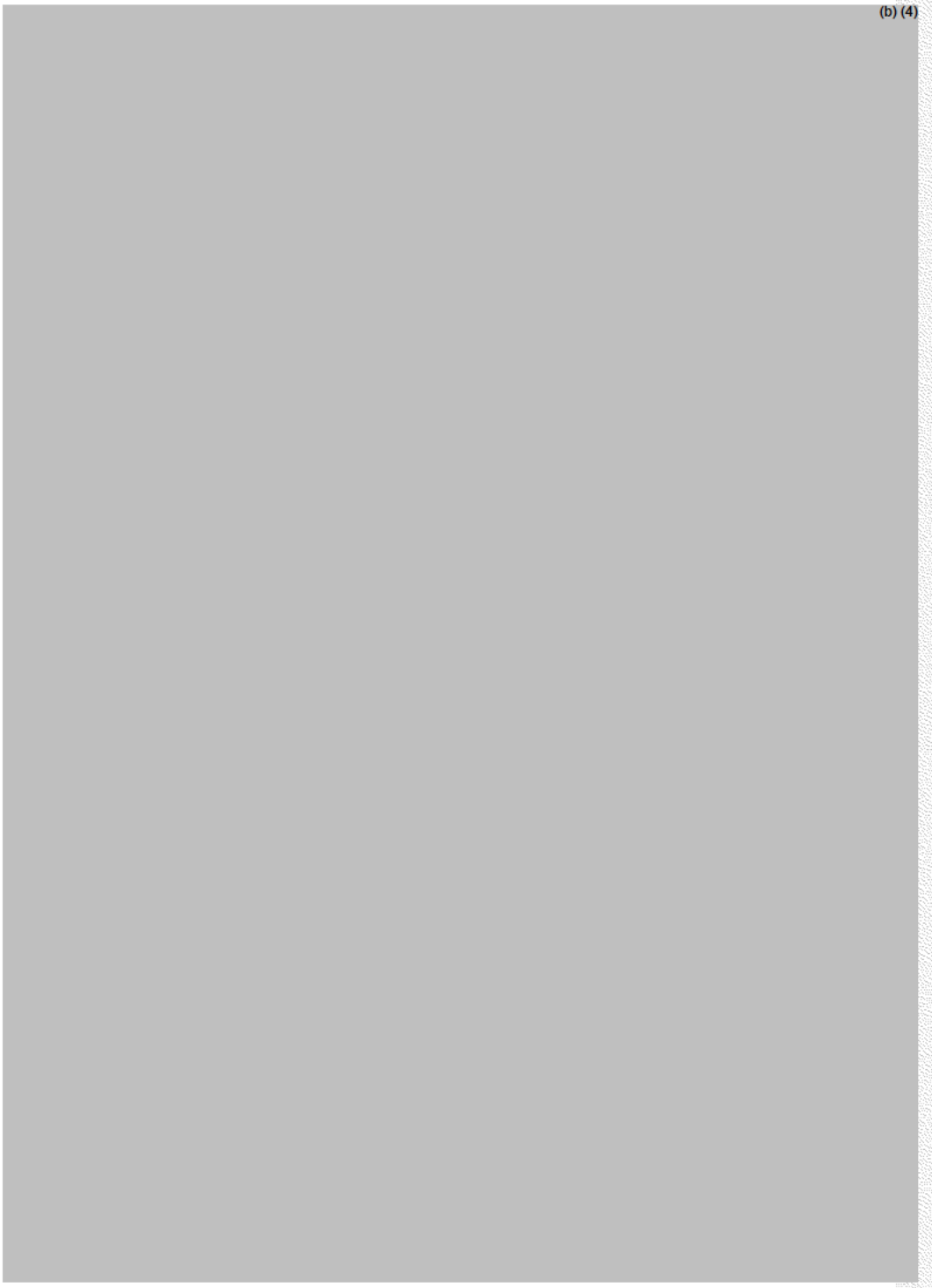

(b) (4)

(b) (4)

(b) (4)




(b) (4)


(b) (4)


(b) (4)

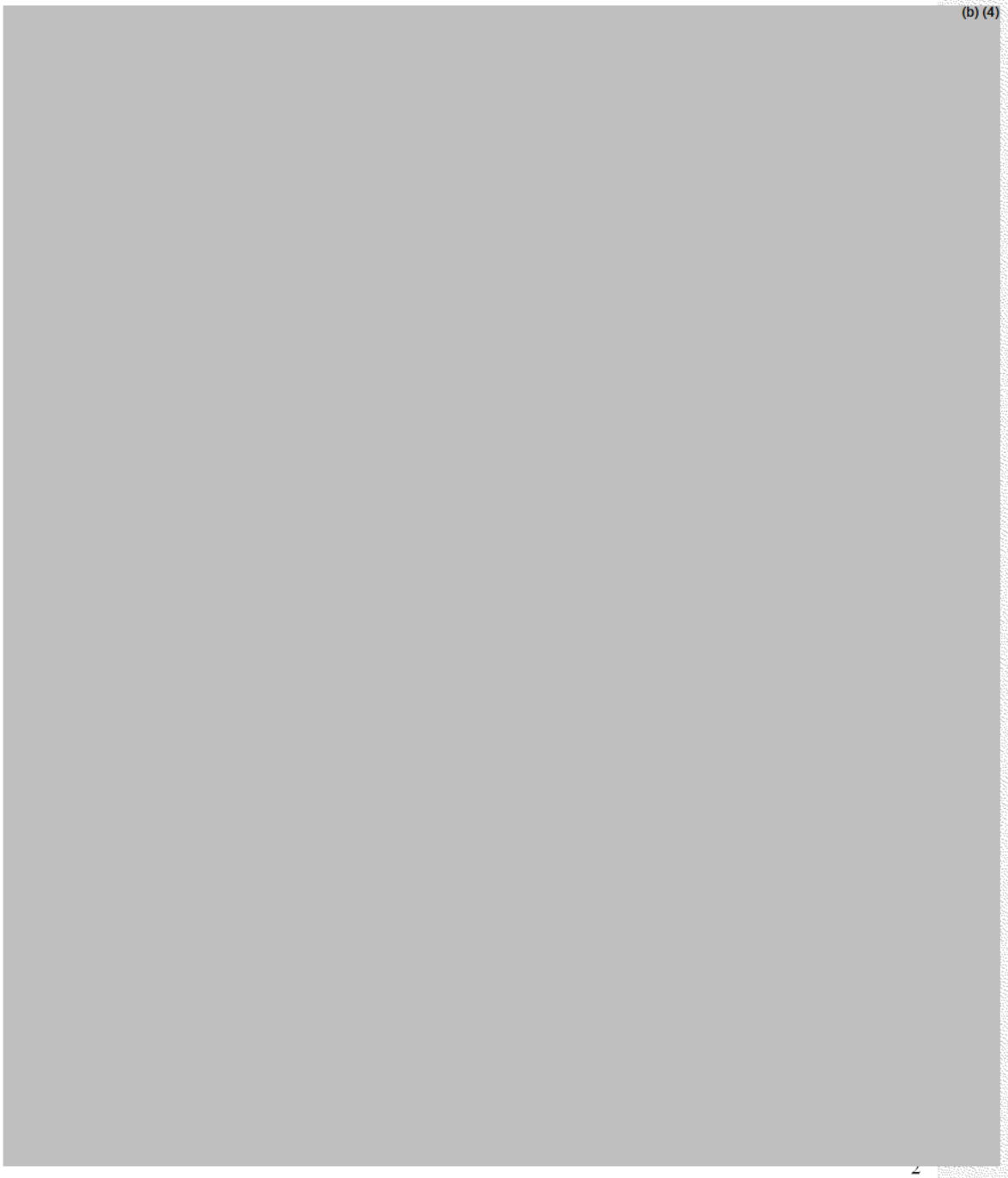
(b) (4)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRIPTODUR safely and effectively. See full prescribing information for TRIPTODUR.

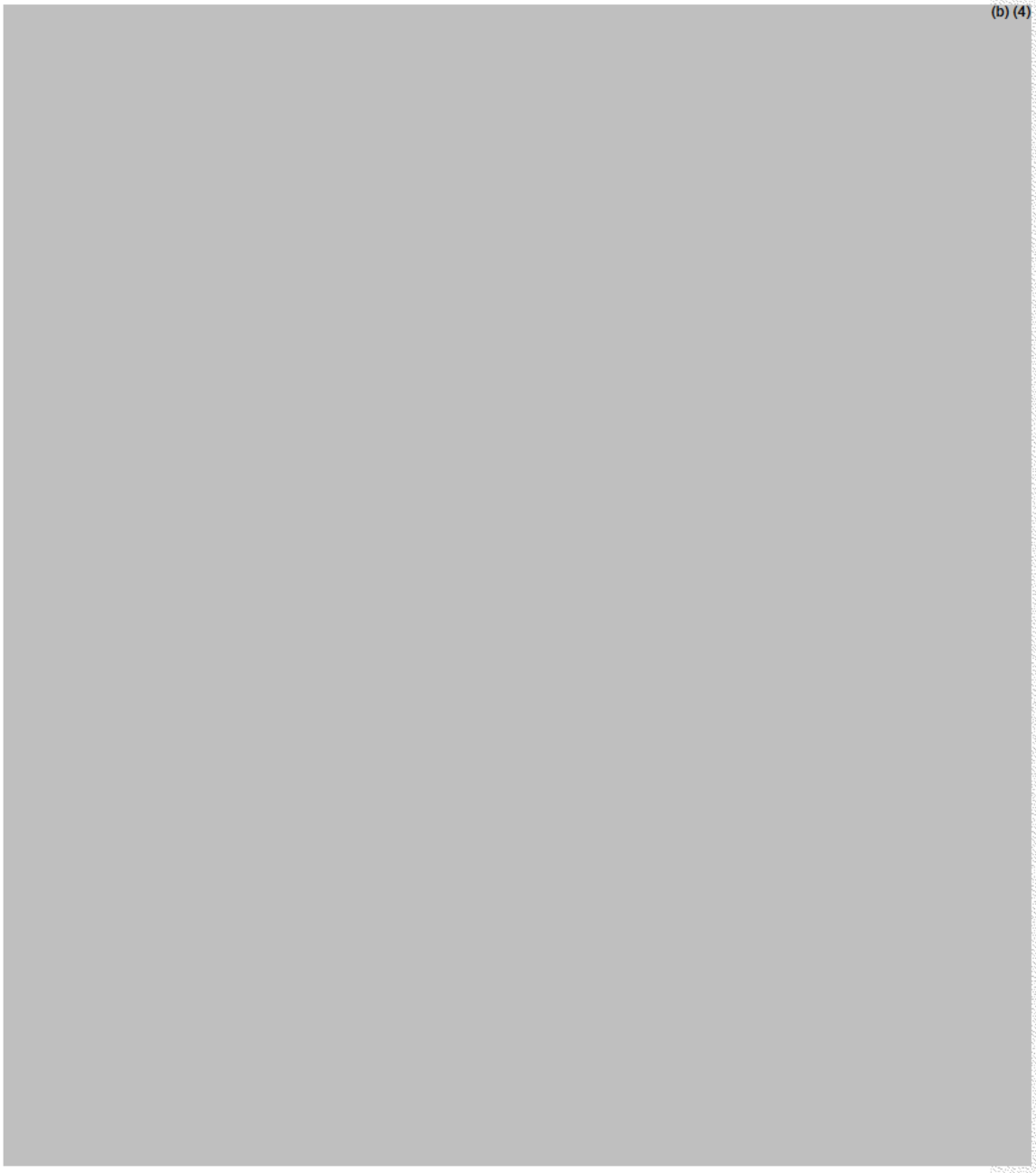
TRIPTODUR (triptorelin) for extended-release injectable suspension, for intramuscular use
Initial U.S. Approval: 2000

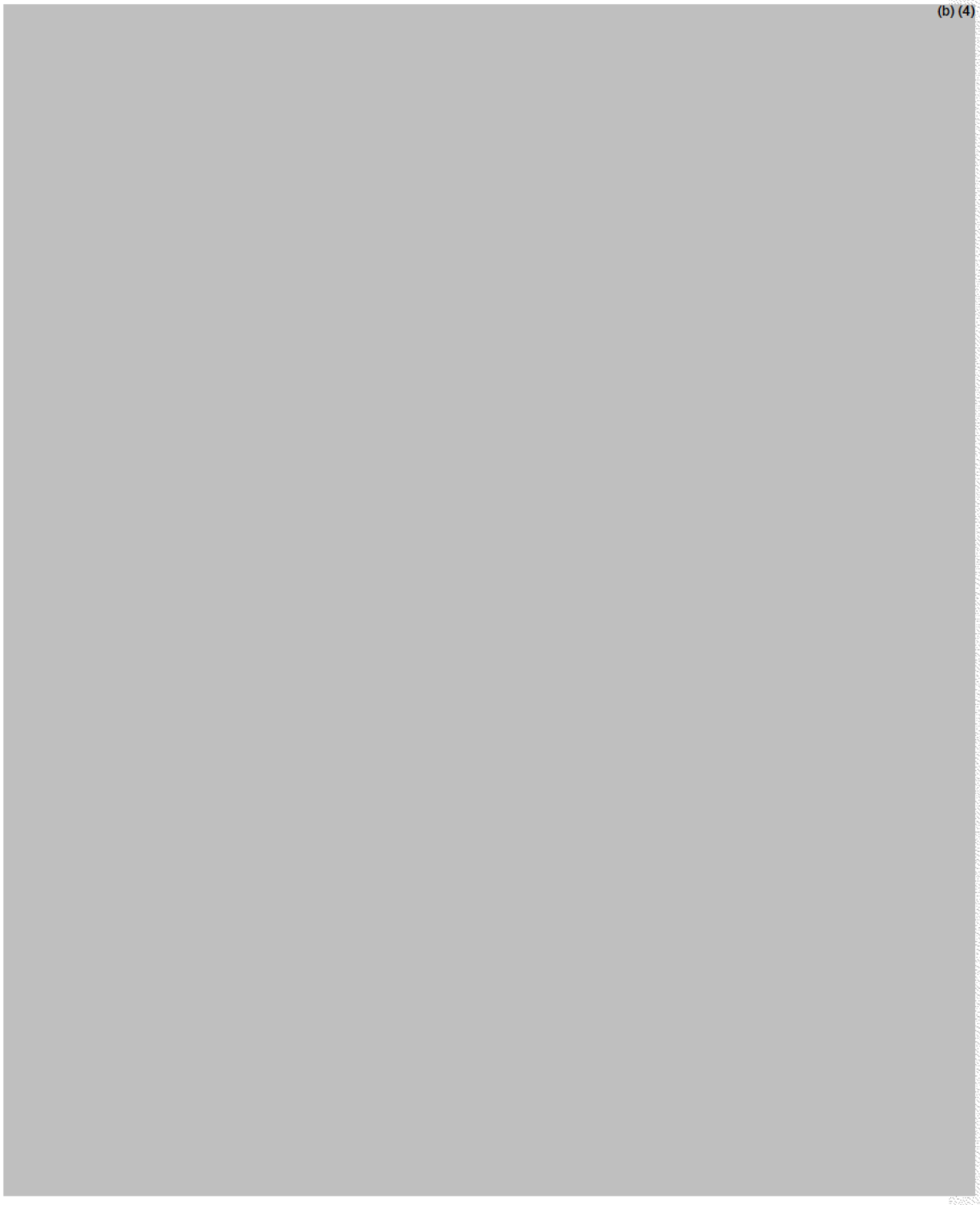
(b) (4)

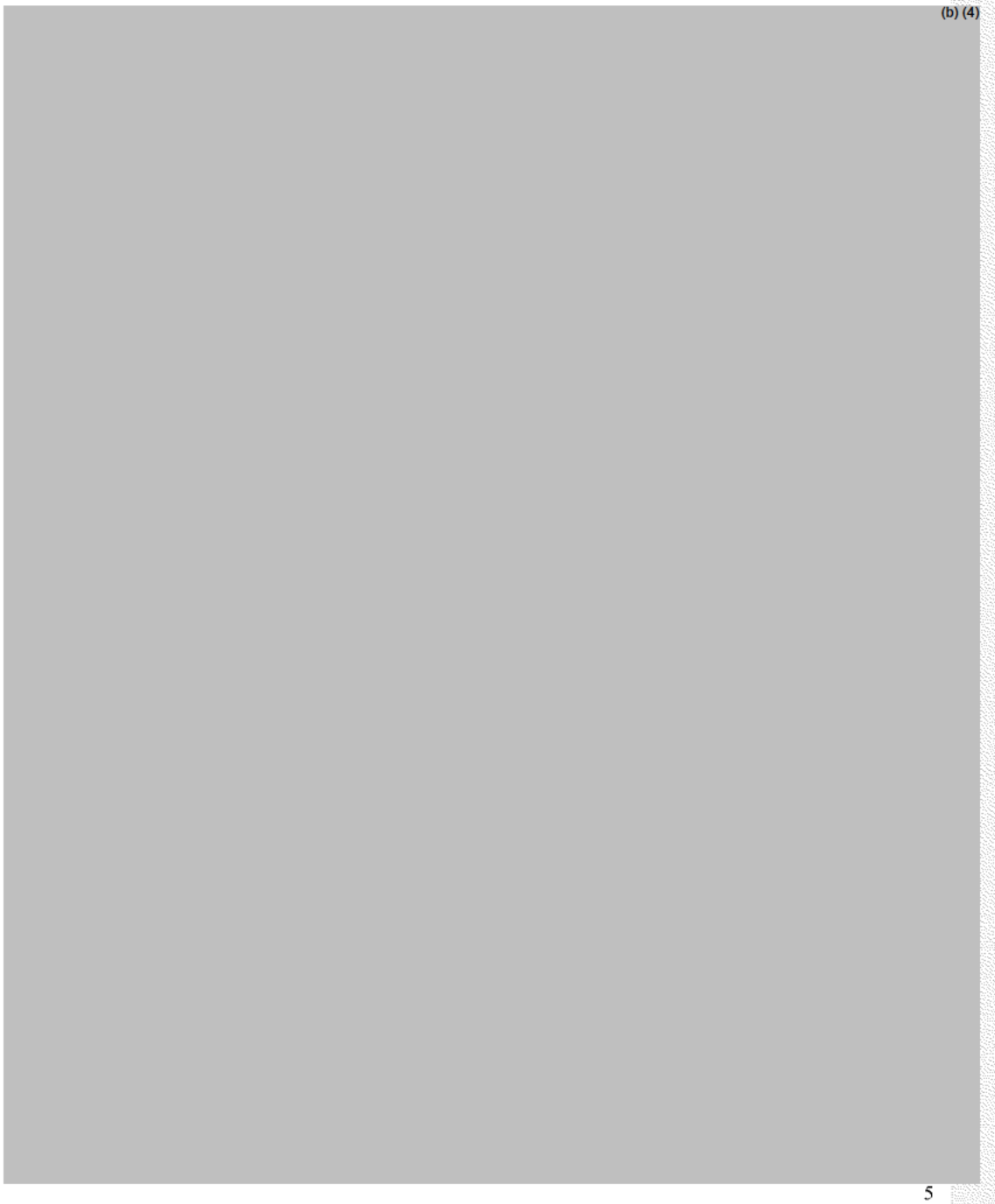
(b) (4)



(b) (4)

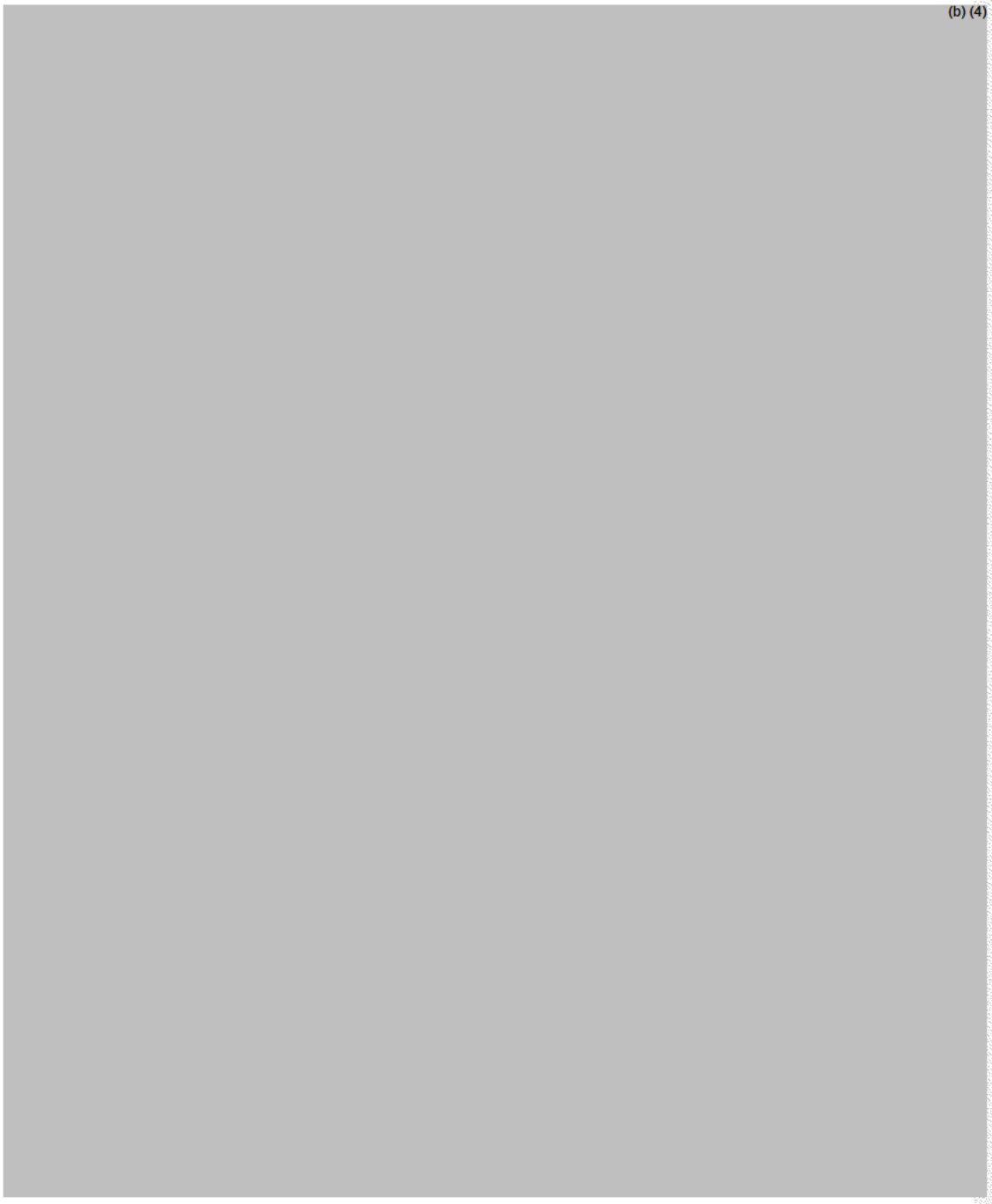




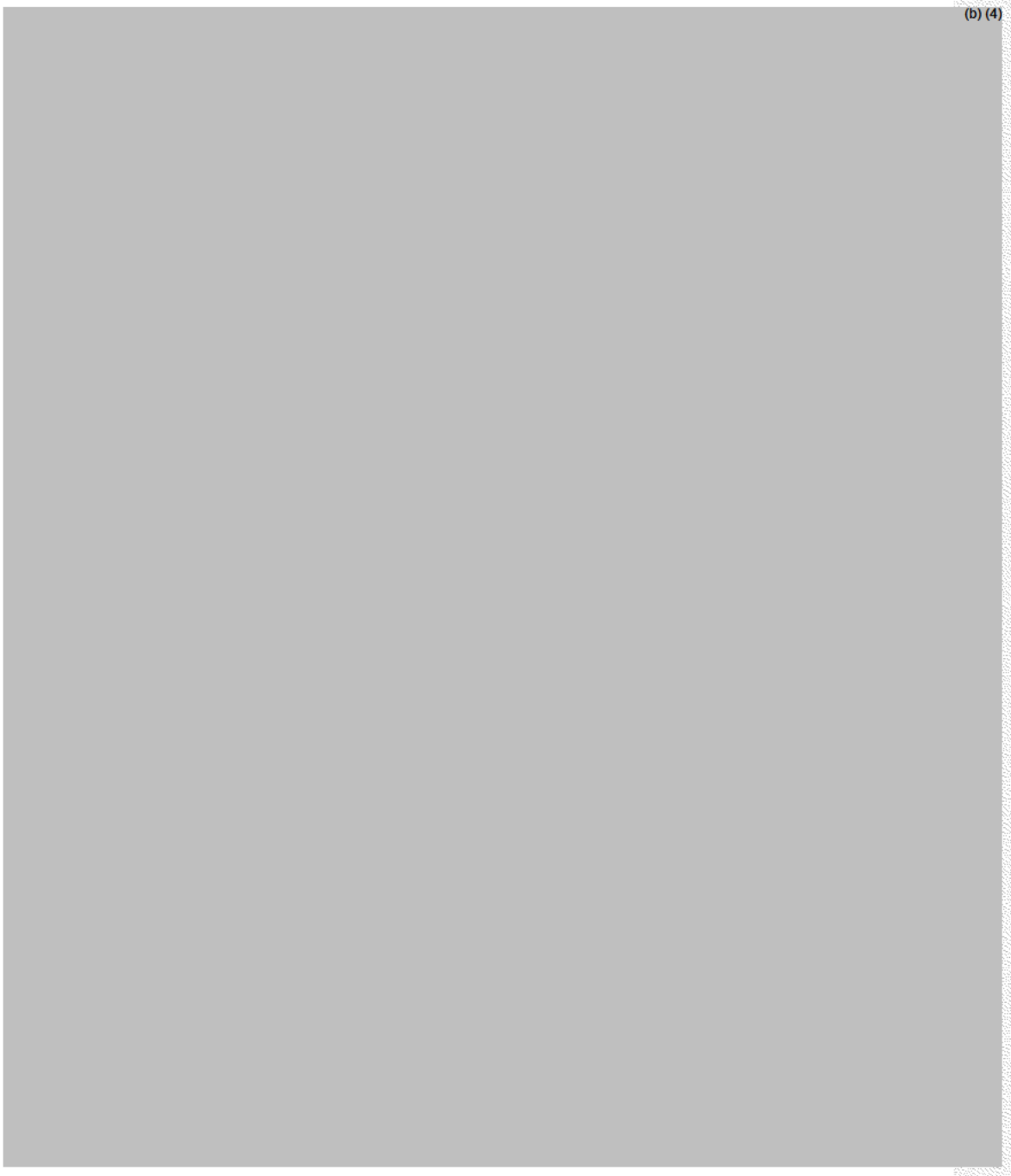


(b) (4)

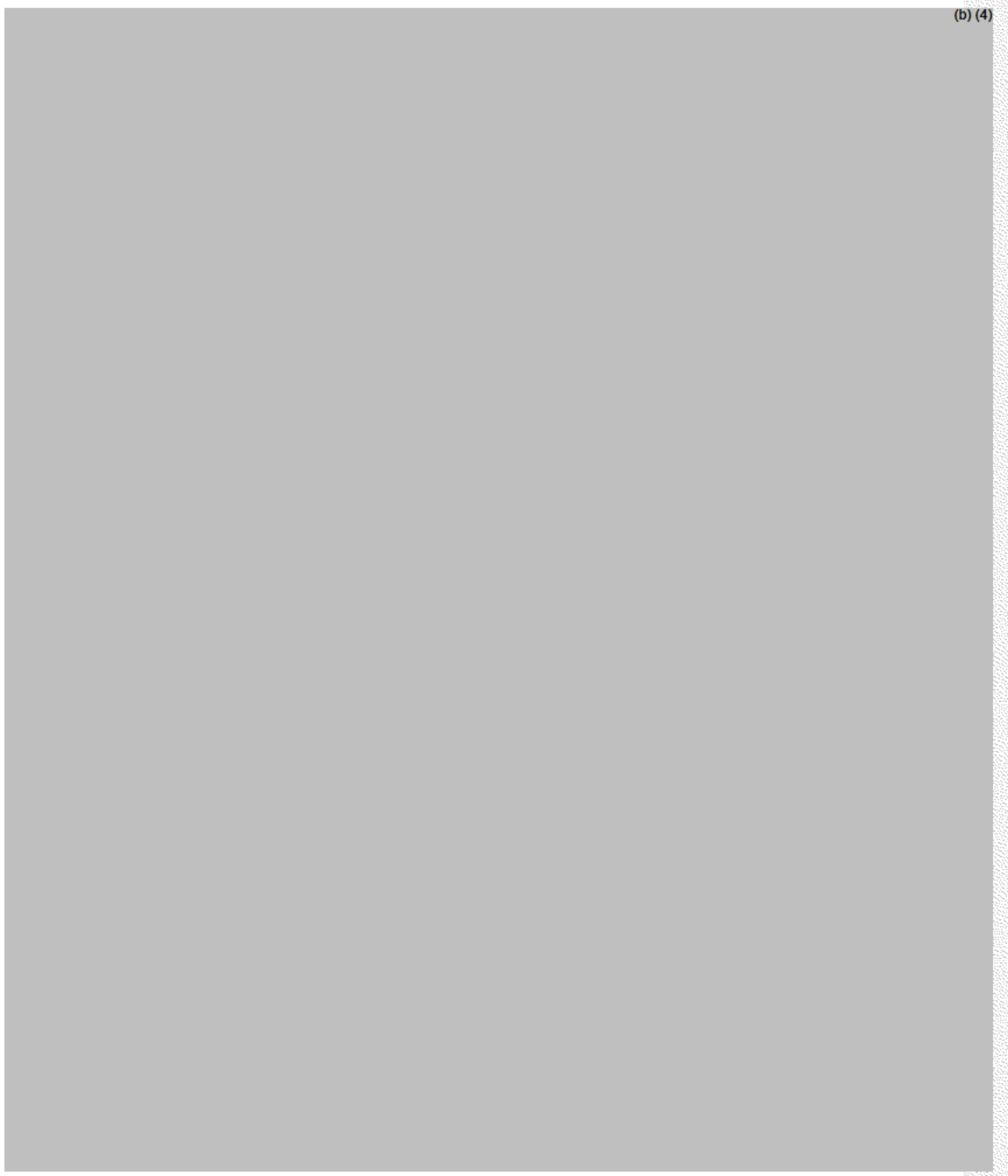
(b) (4)



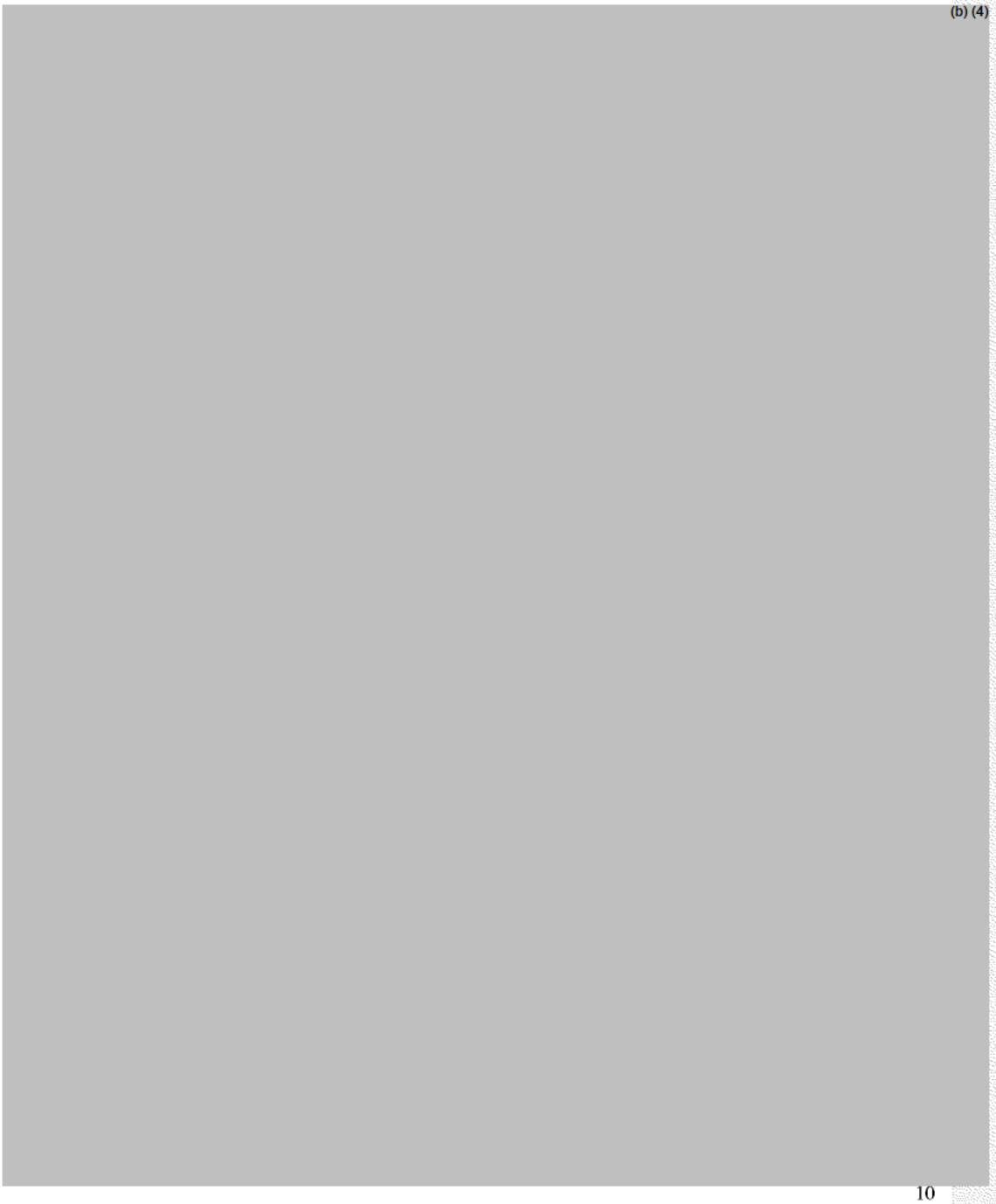
(b) (4)



(b) (4)



(b) (4)



(b) (4)

HIGHLIGHTS OF PRESCRIBING INFORMATION

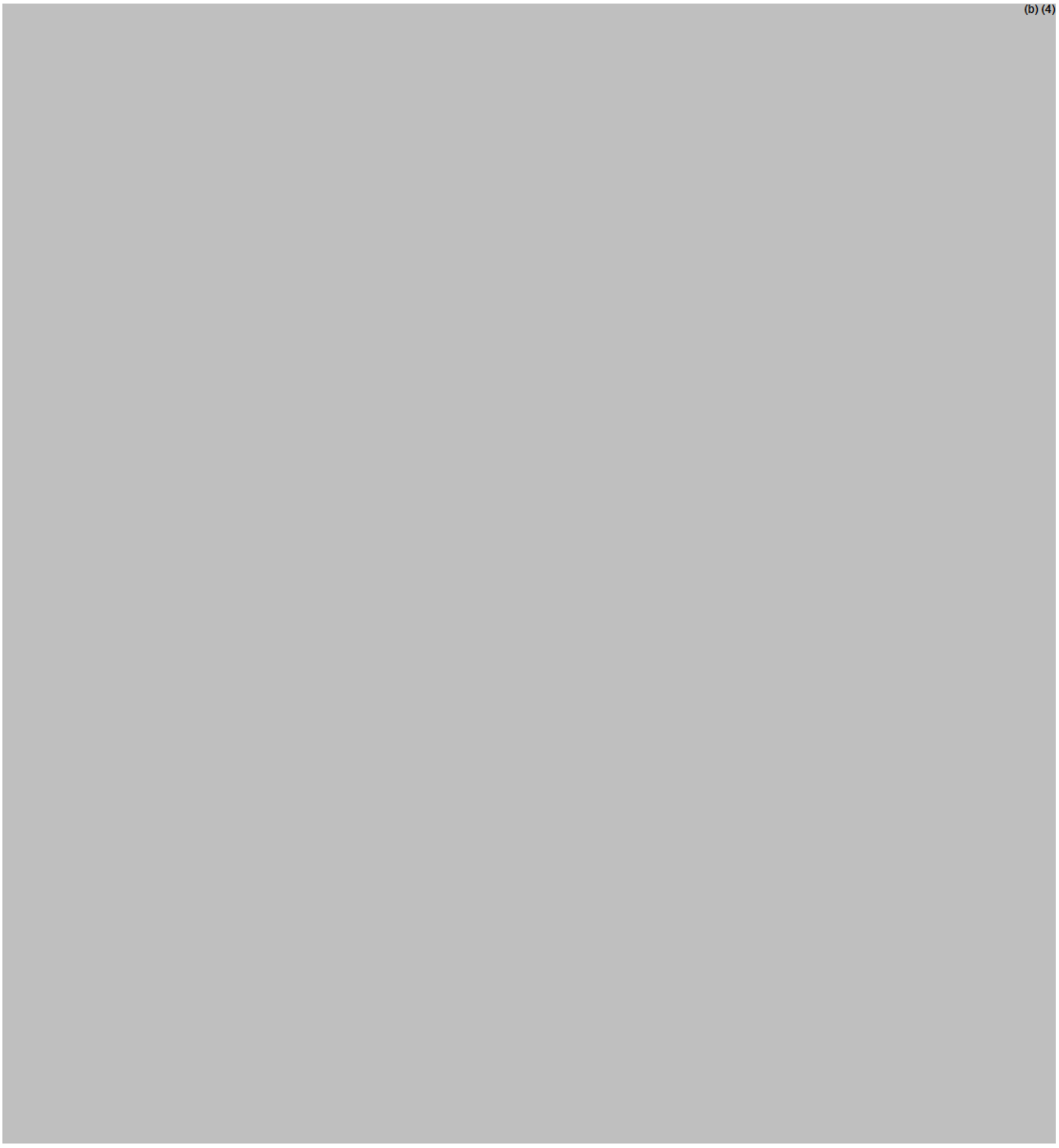
These highlights do not include all the information needed to use FENSOLVI® safely and effectively. See full prescribing information for FENSOLVI.

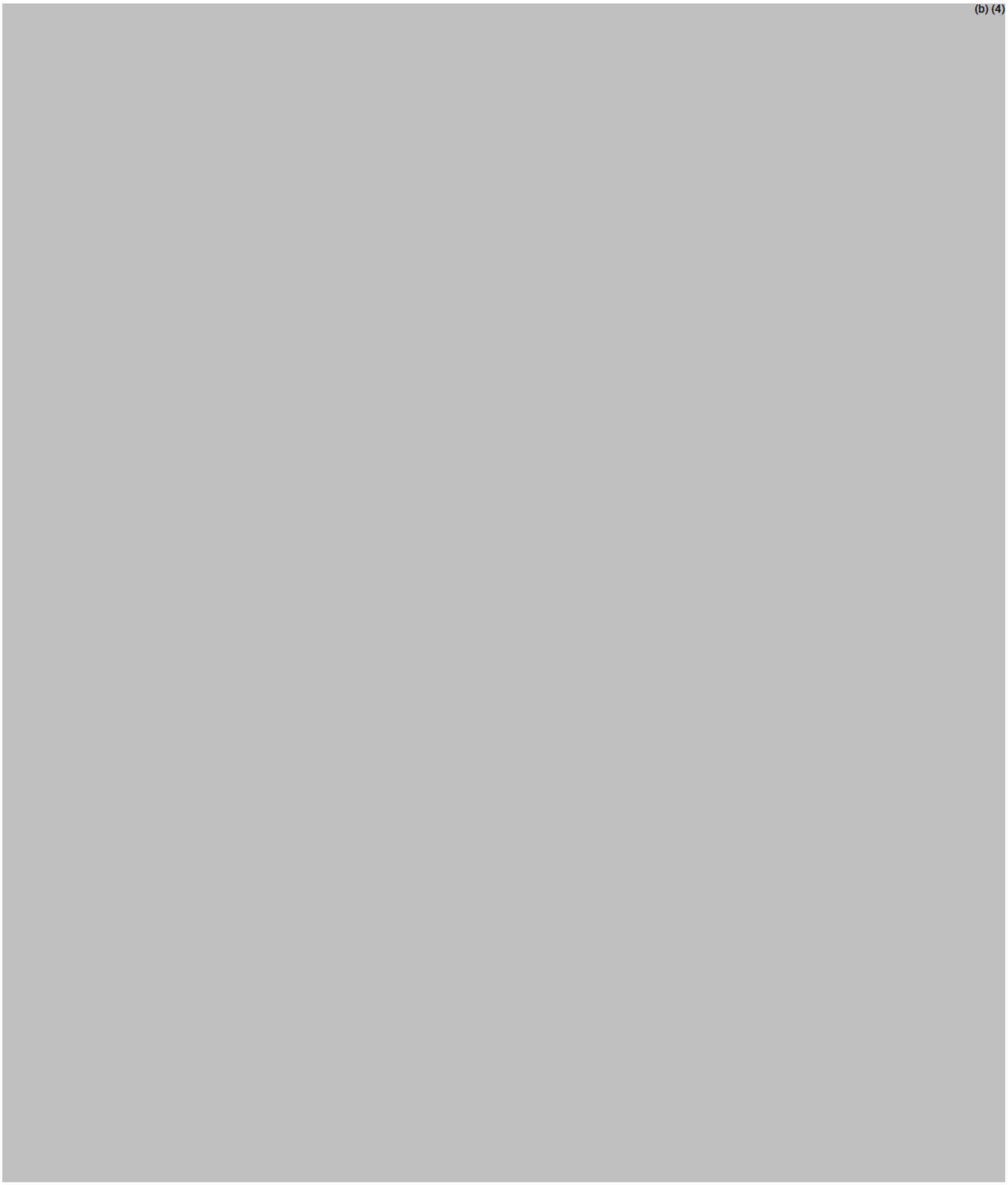
FENSOLVI (leuprolide acetate) for injectable suspension, for subcutaneous use

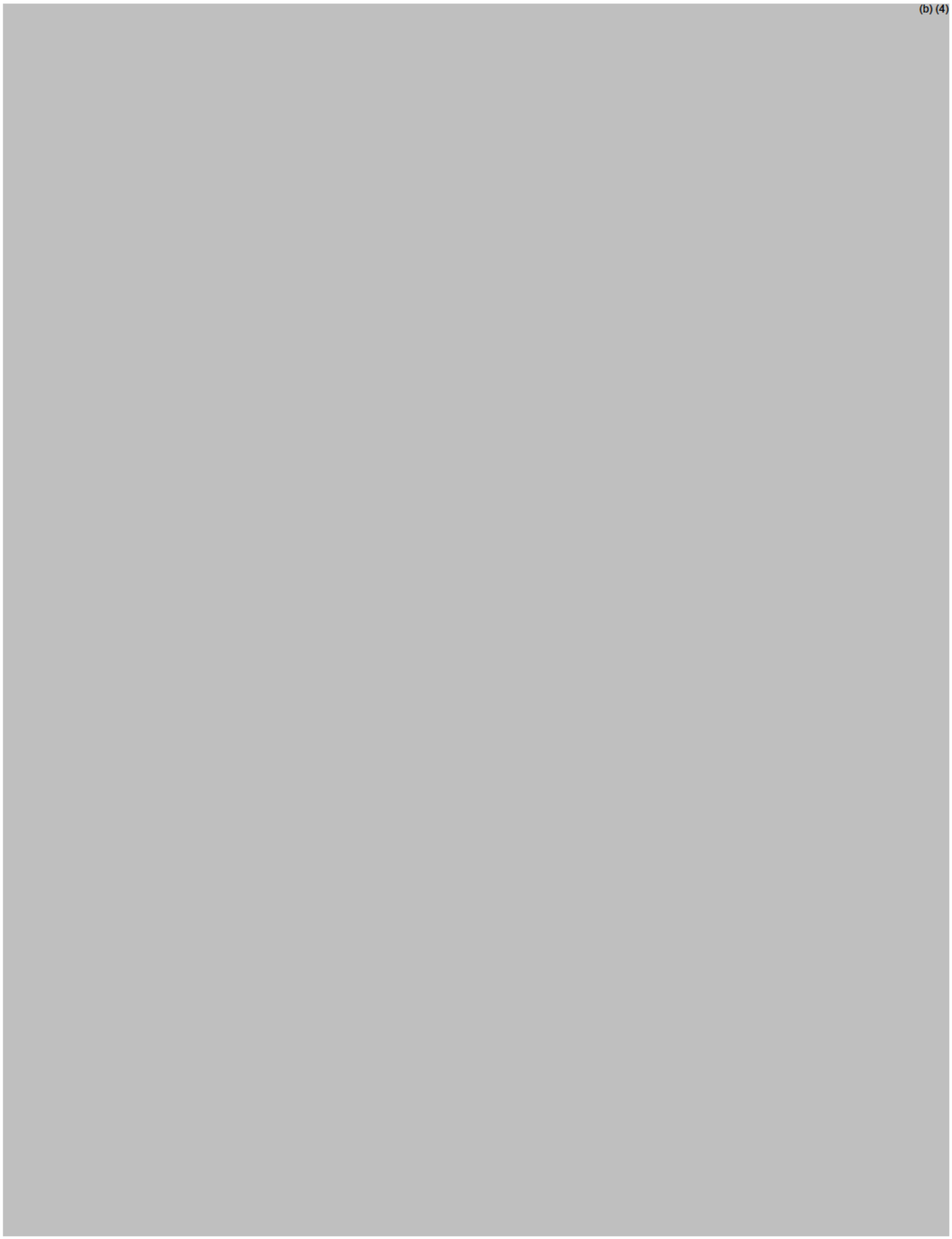
Initial U.S. Approval: 1985

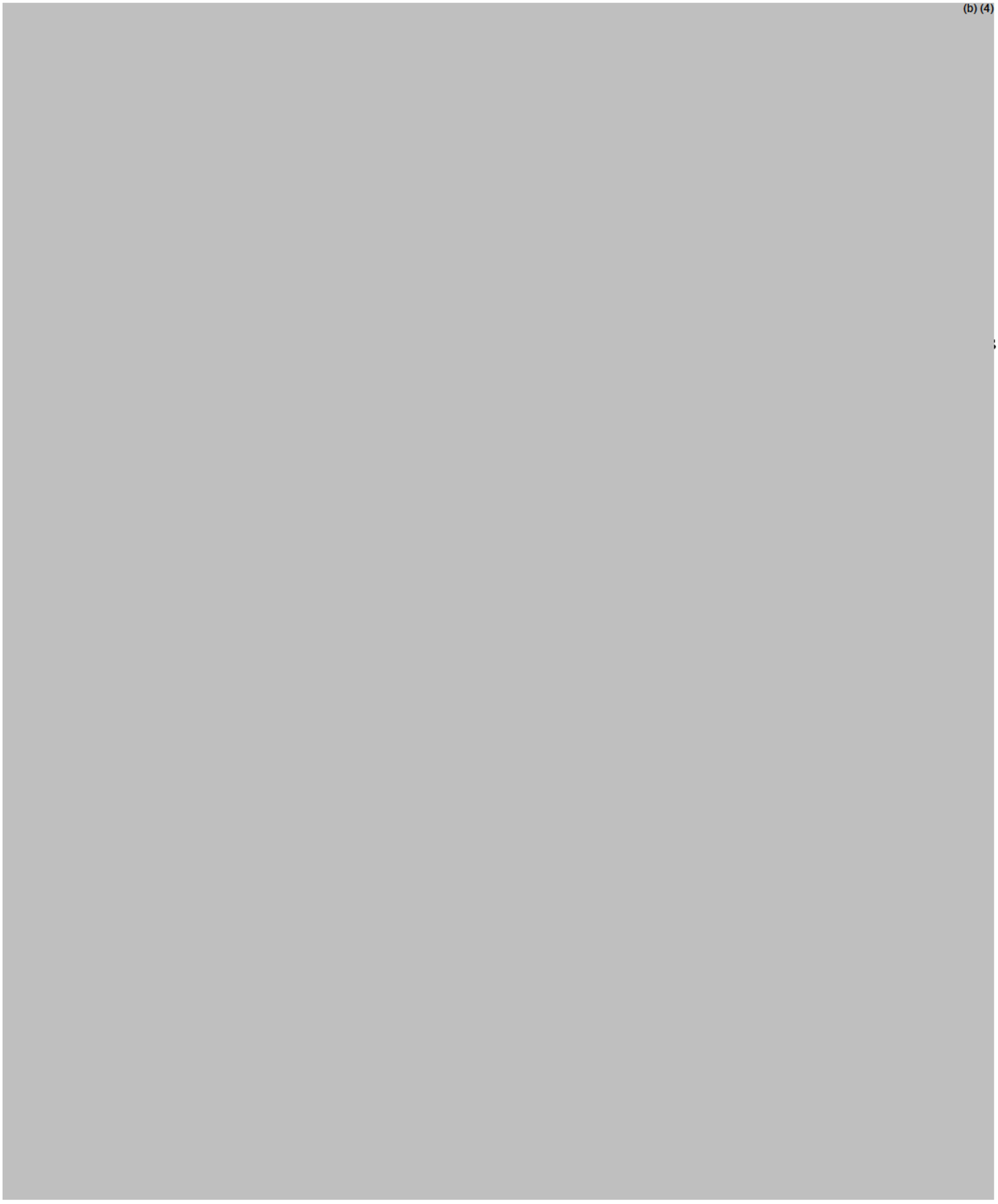
(b) (4)

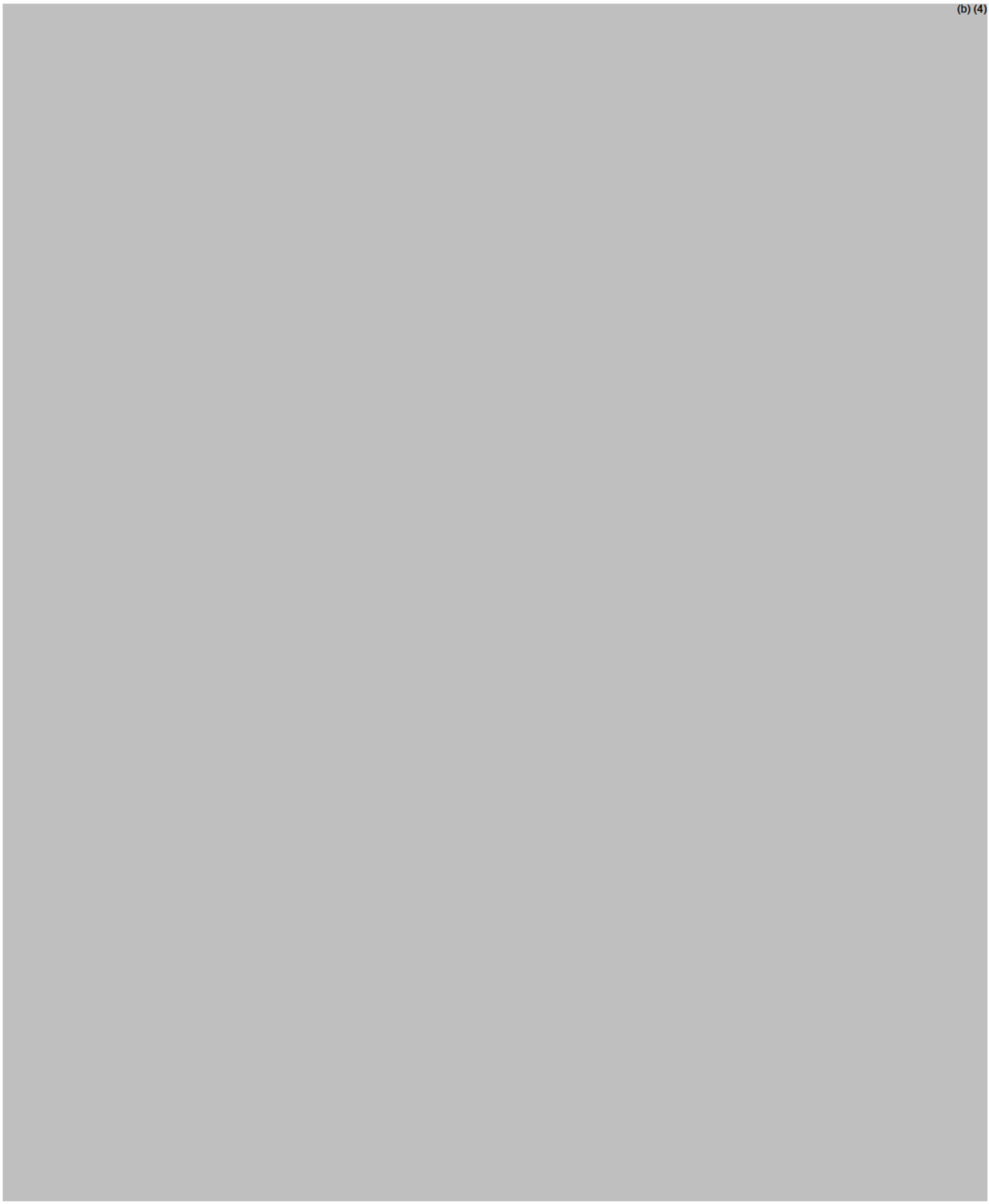
(b) (4)


(b) (4)


(b) (4)


(b) (4)

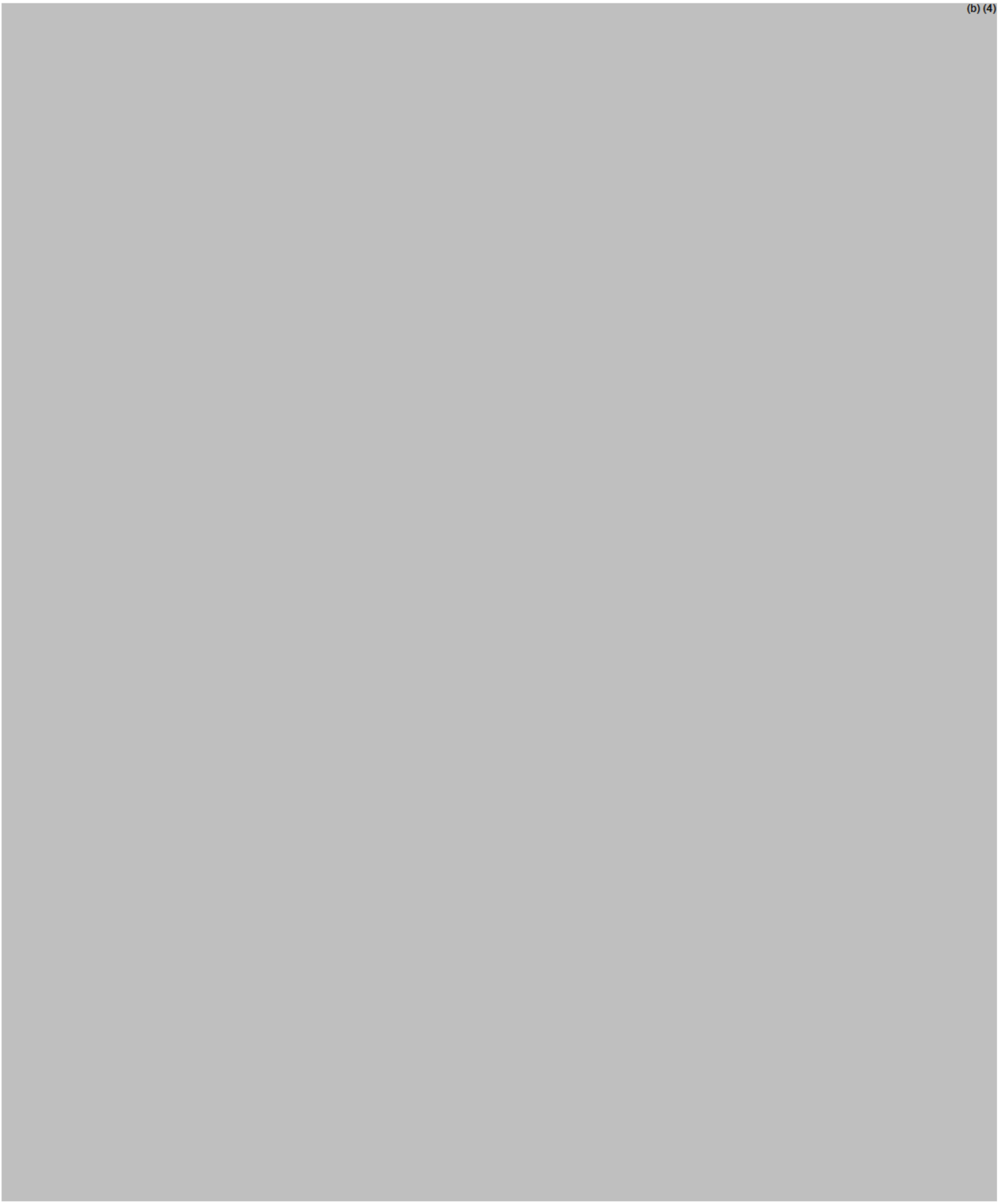

(b) (4)

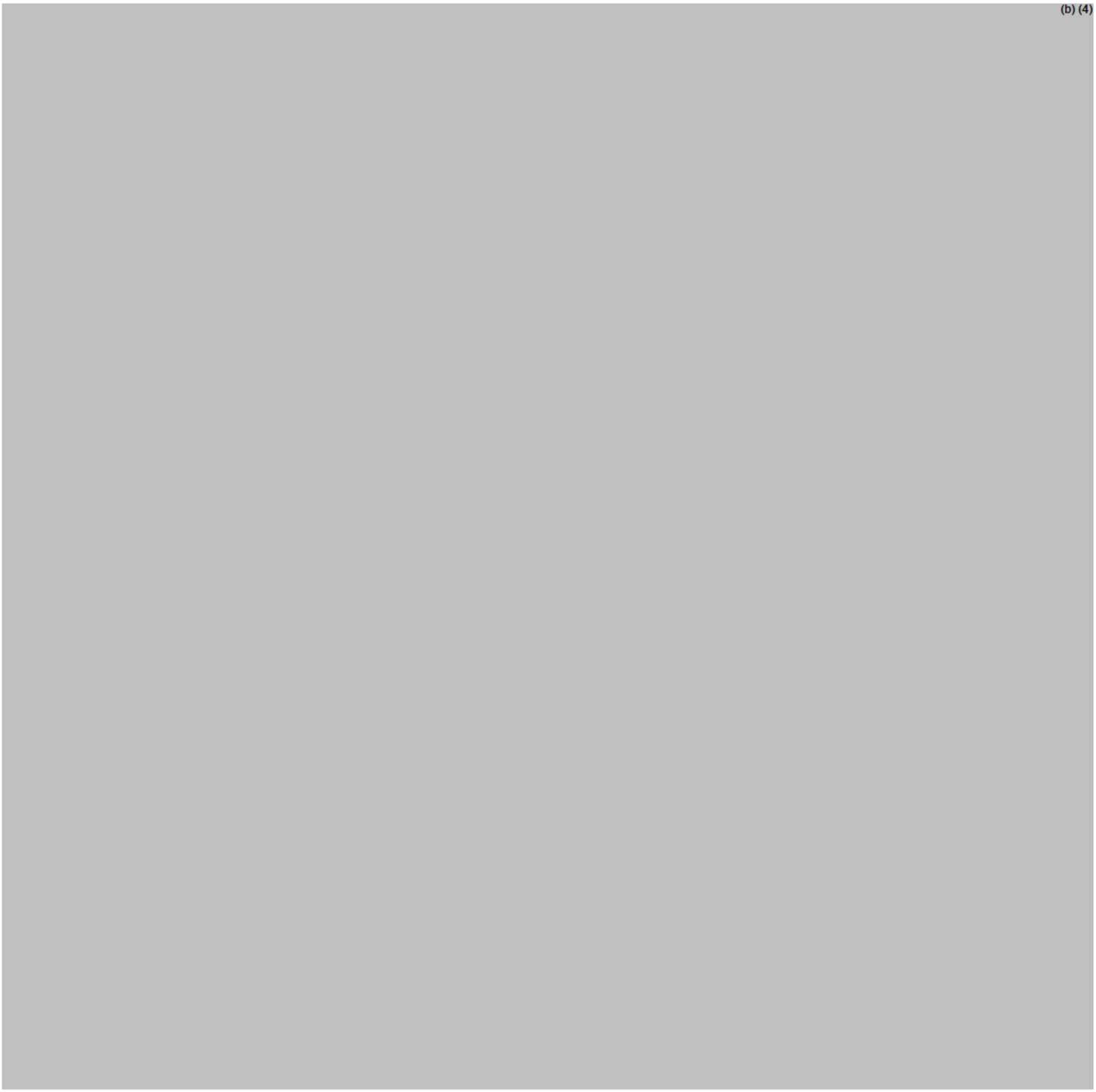

(b) (4)

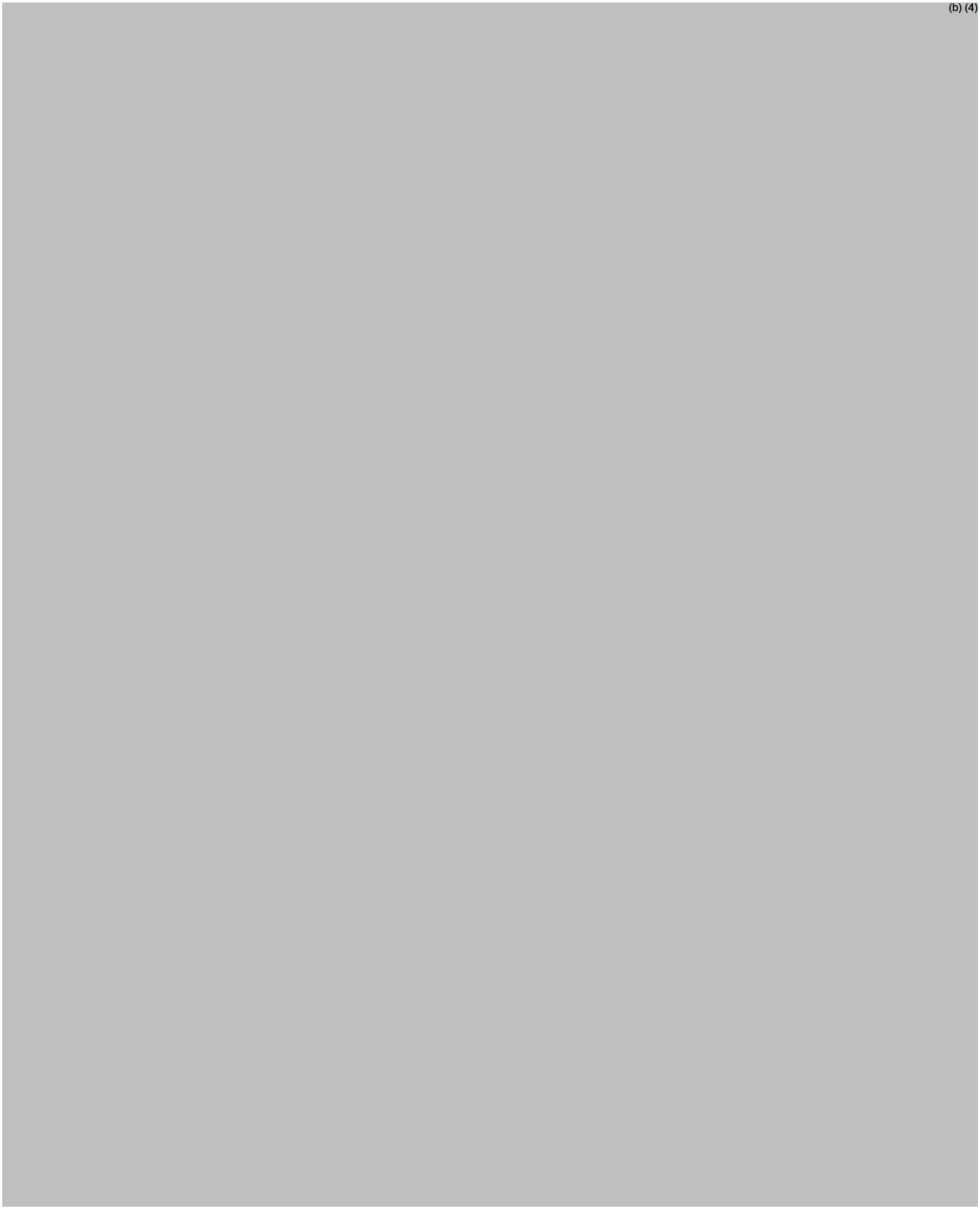
(b) (4)

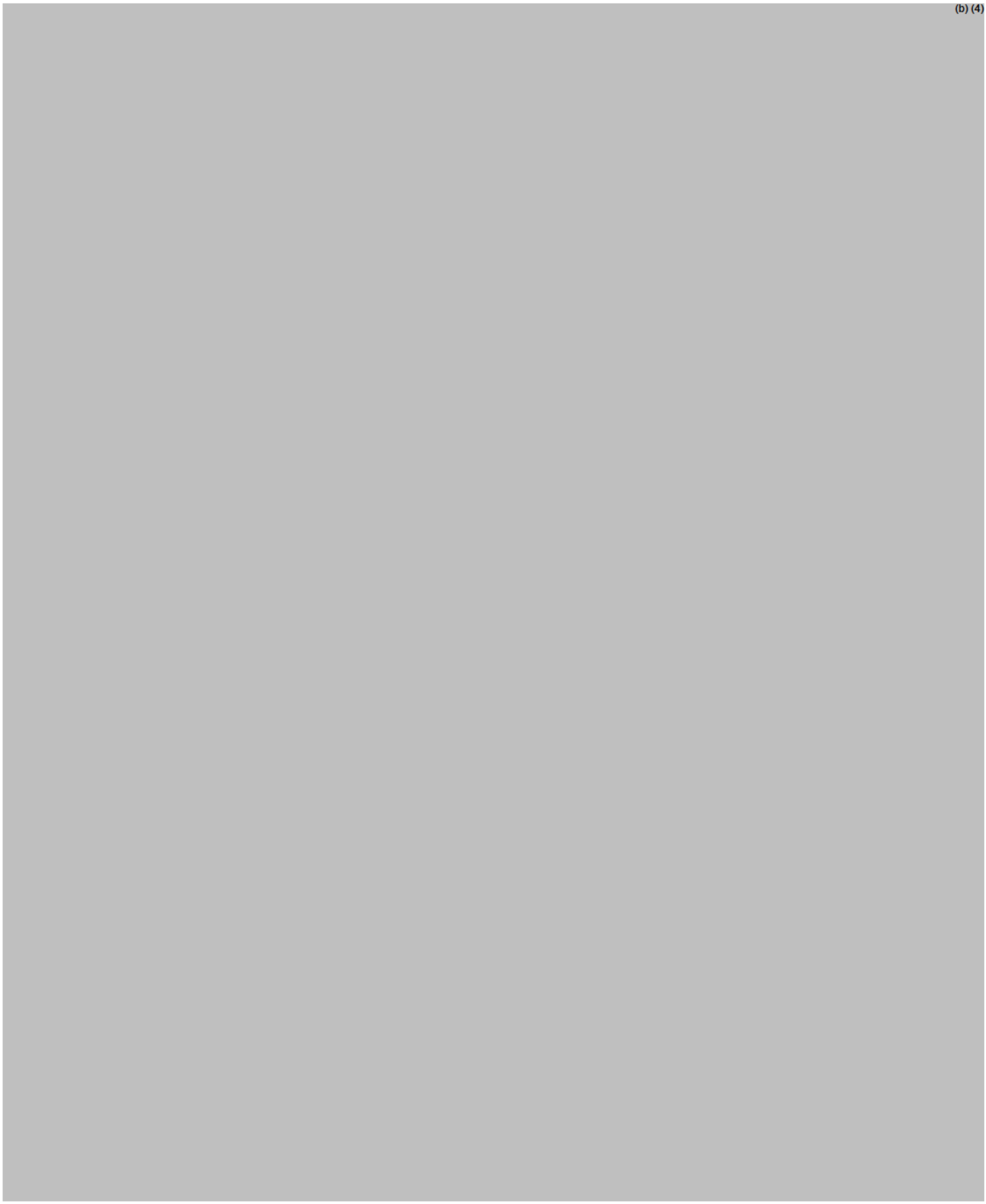

(b) (4)

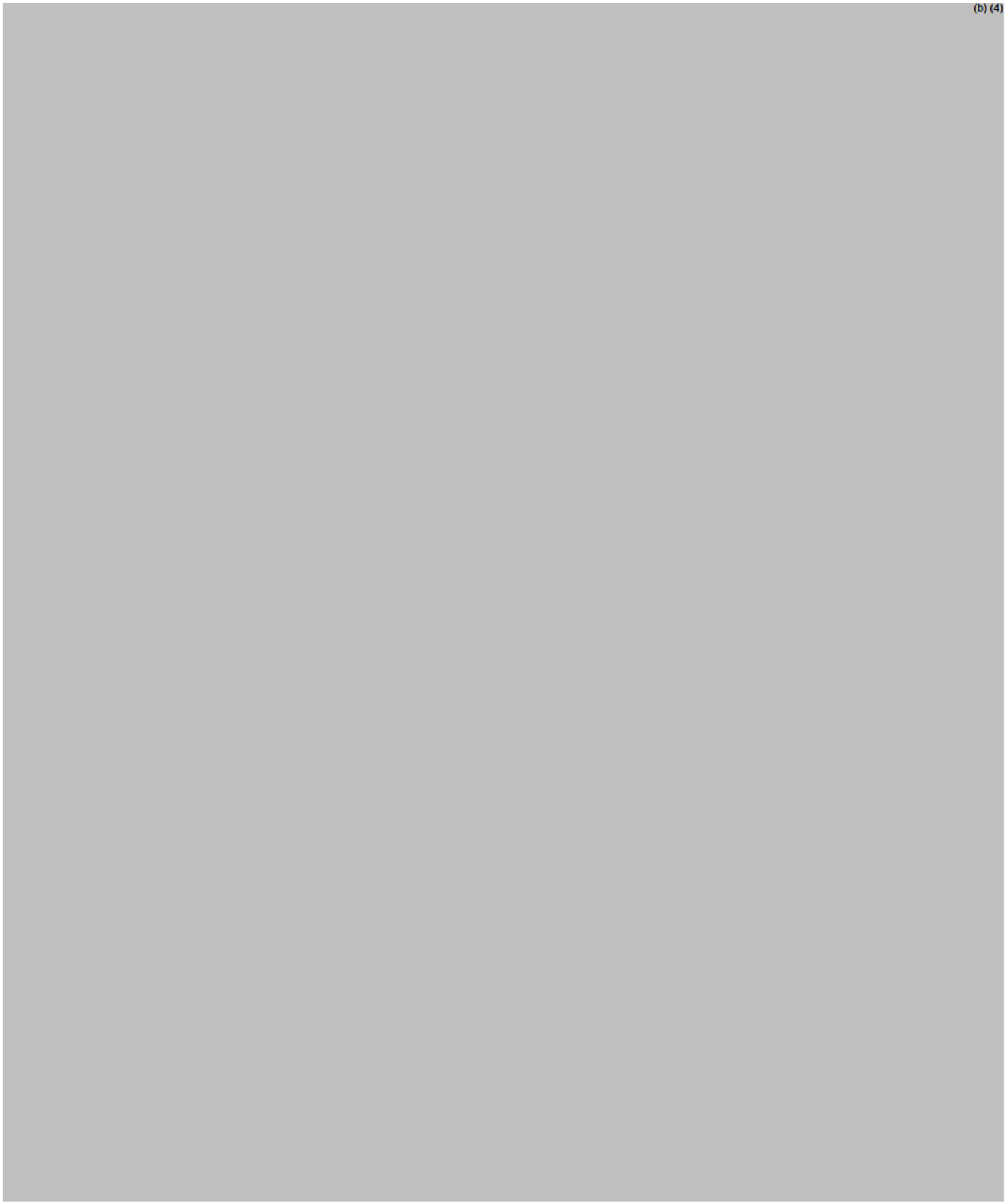
(b) (4)


(b) (4)

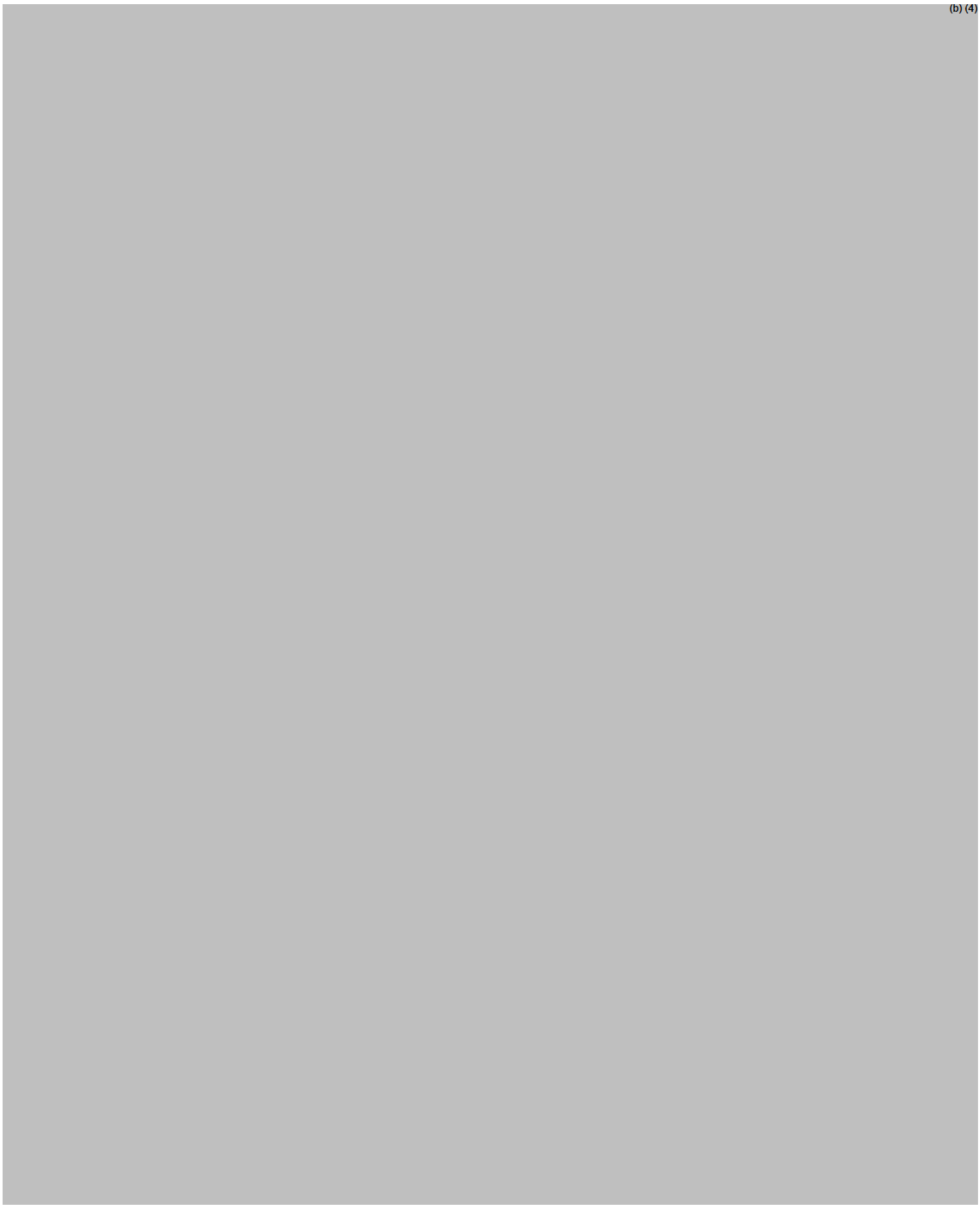

(b) (4)


(b) (4)


(b) (4)


(b) (4)

(b) (4)


(b) (4)

(b) (4)

APPEARS THIS WAY ON ORIGINAL

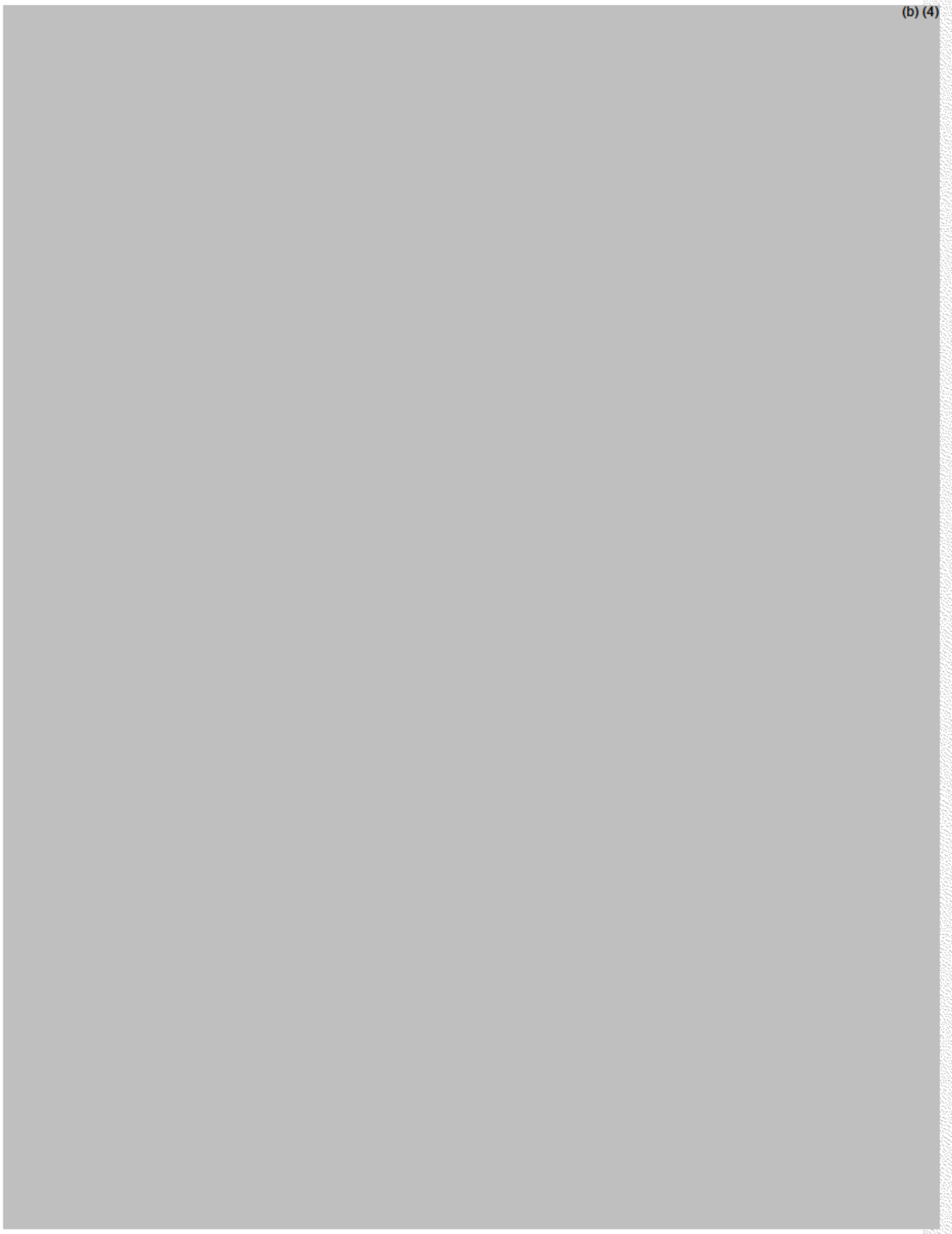
(b) (4)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SUPPRELIN® LA safely and effectively. See full prescribing information for SUPPRELIN LA.

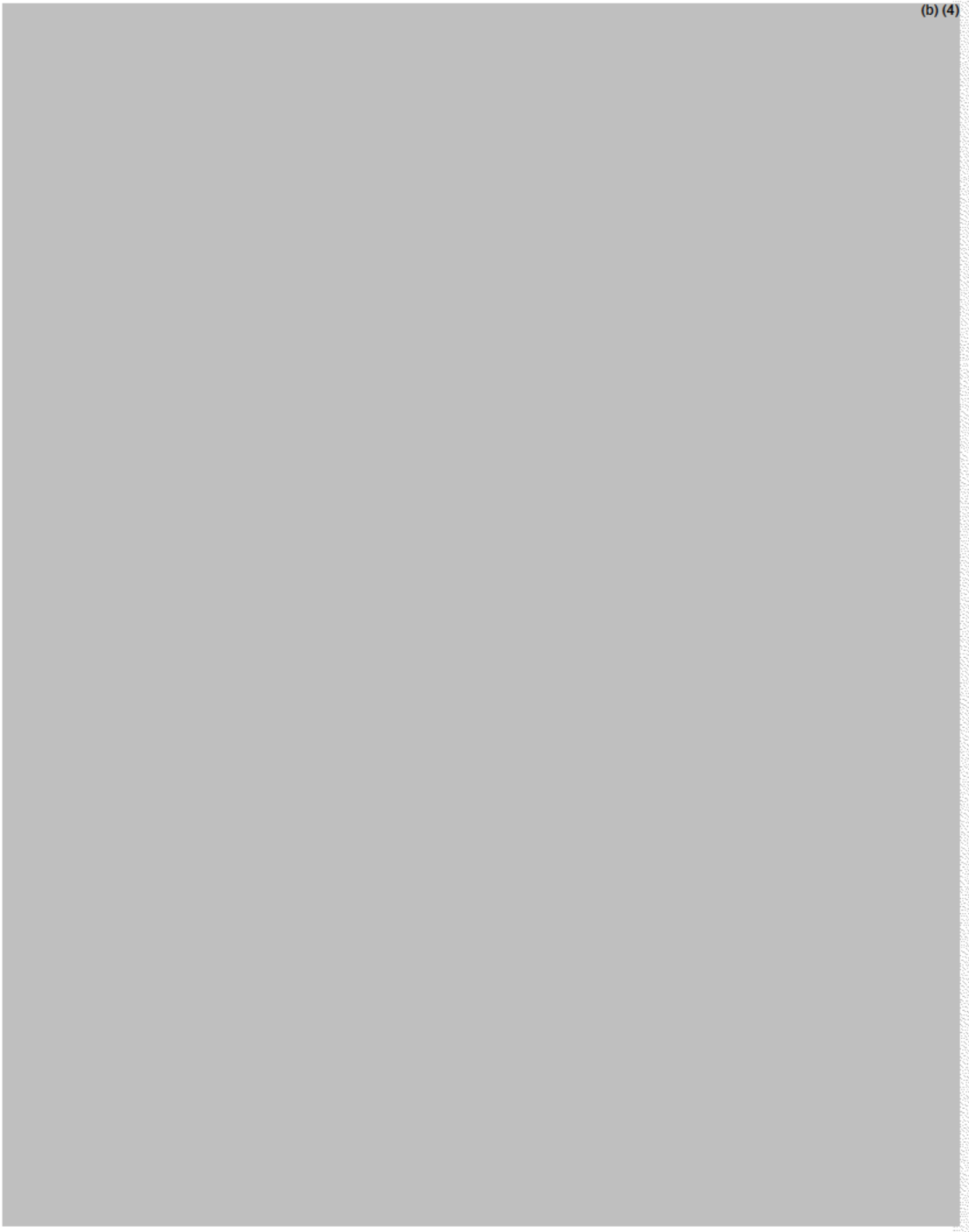
SUPPRELIN LA (histrelin acetate) subcutaneous implant
Initial U.S. Approval: 1991

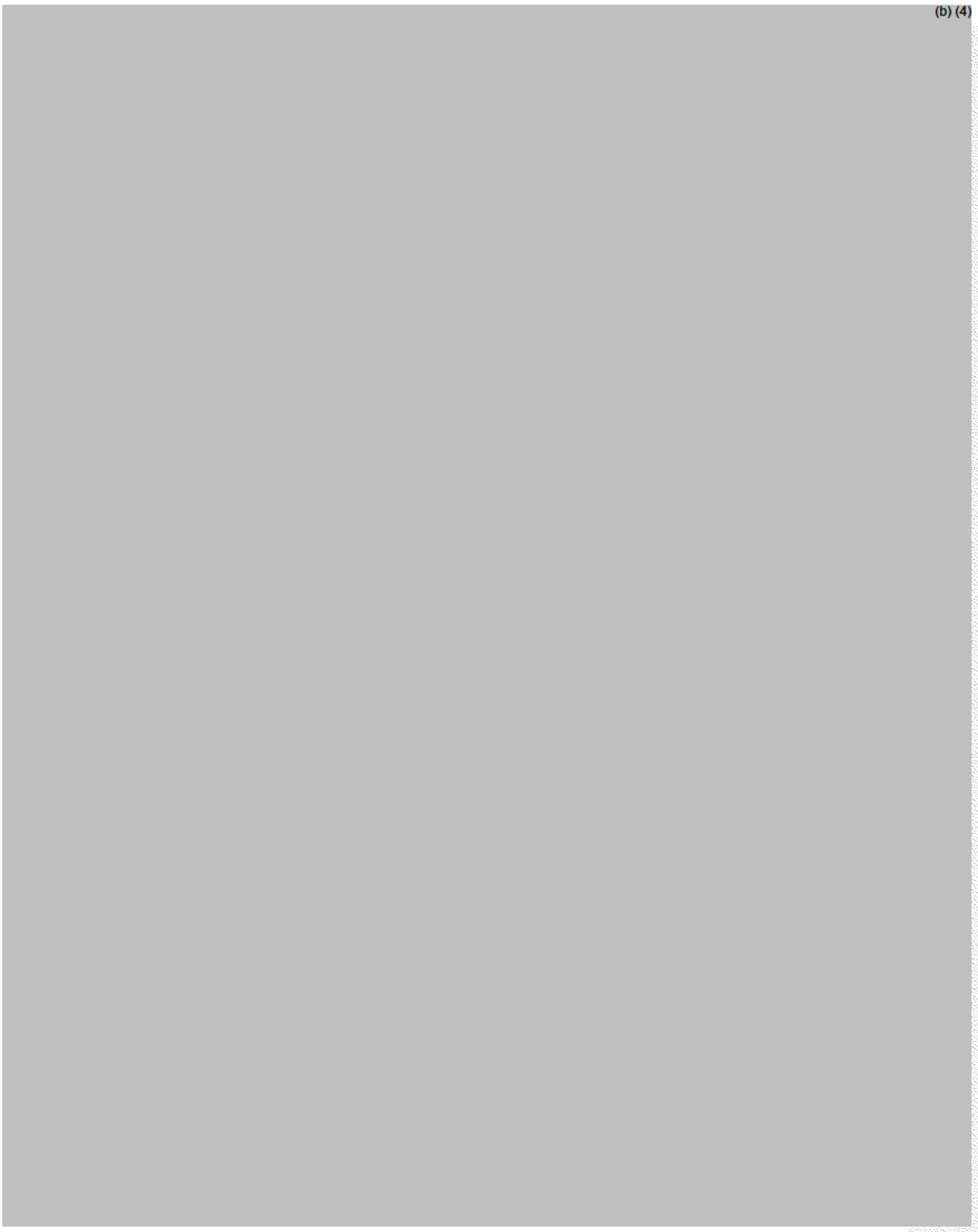
(b) (4)

(b) (4)

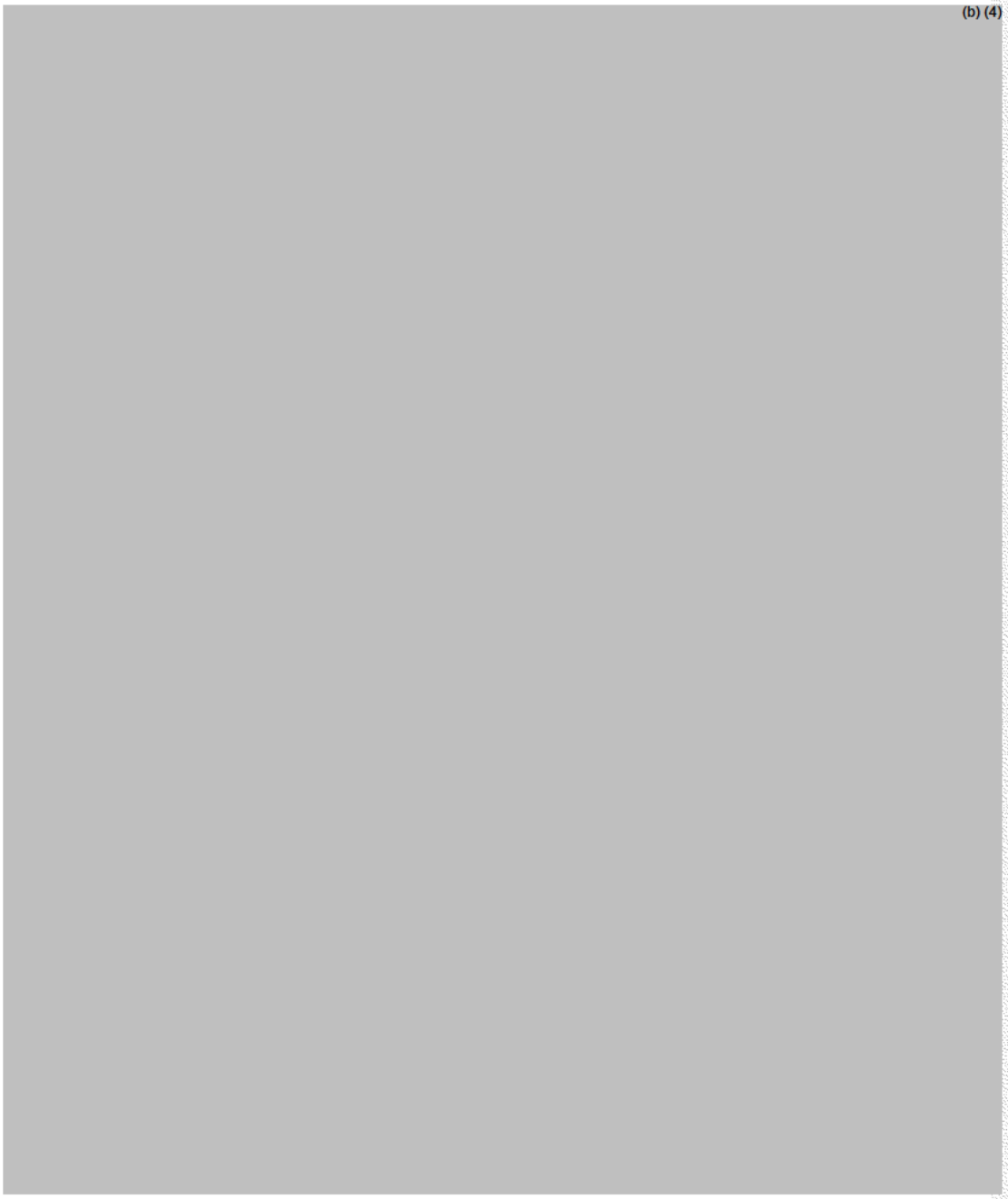

(b) (4)

(b) (4)



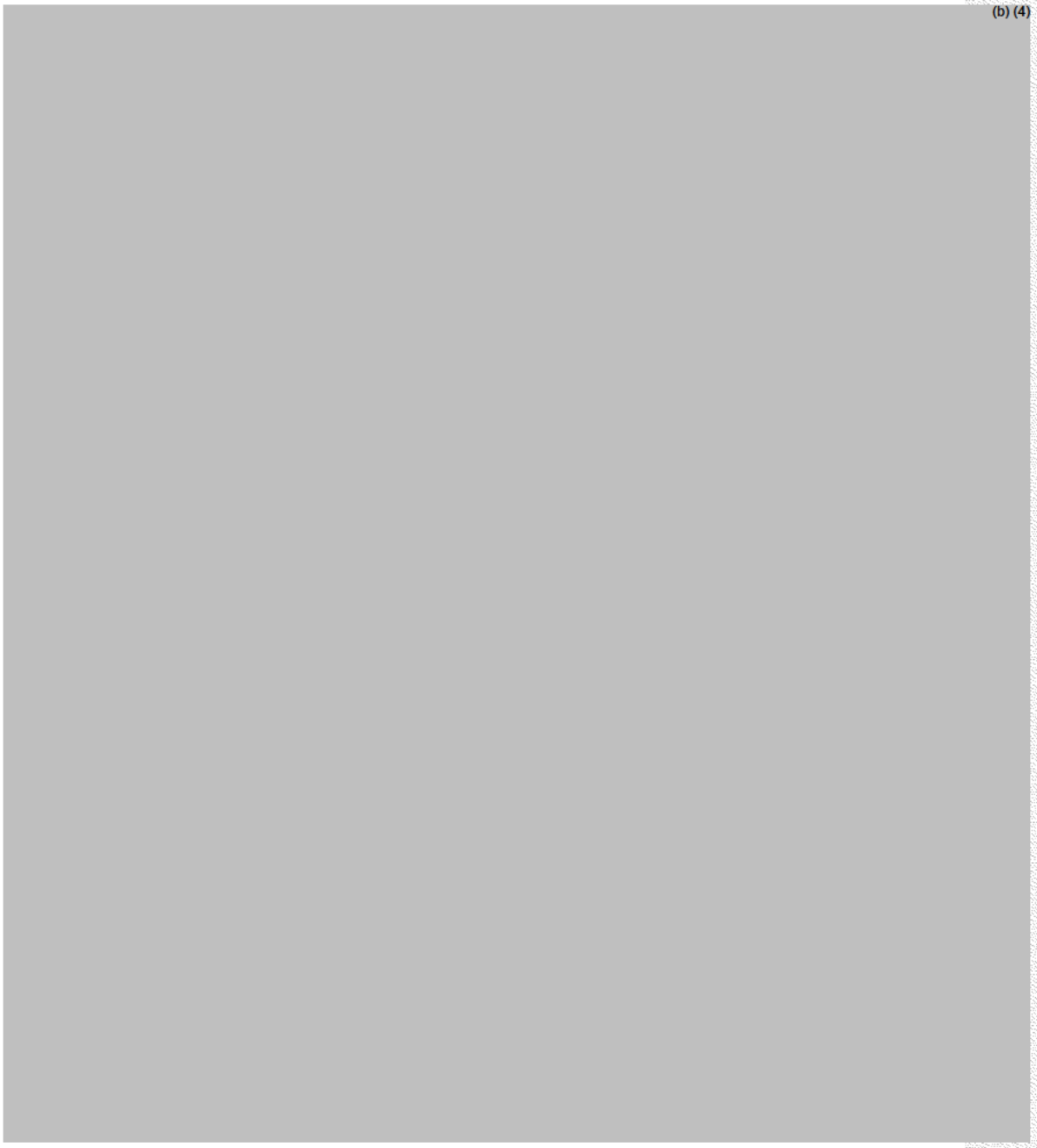


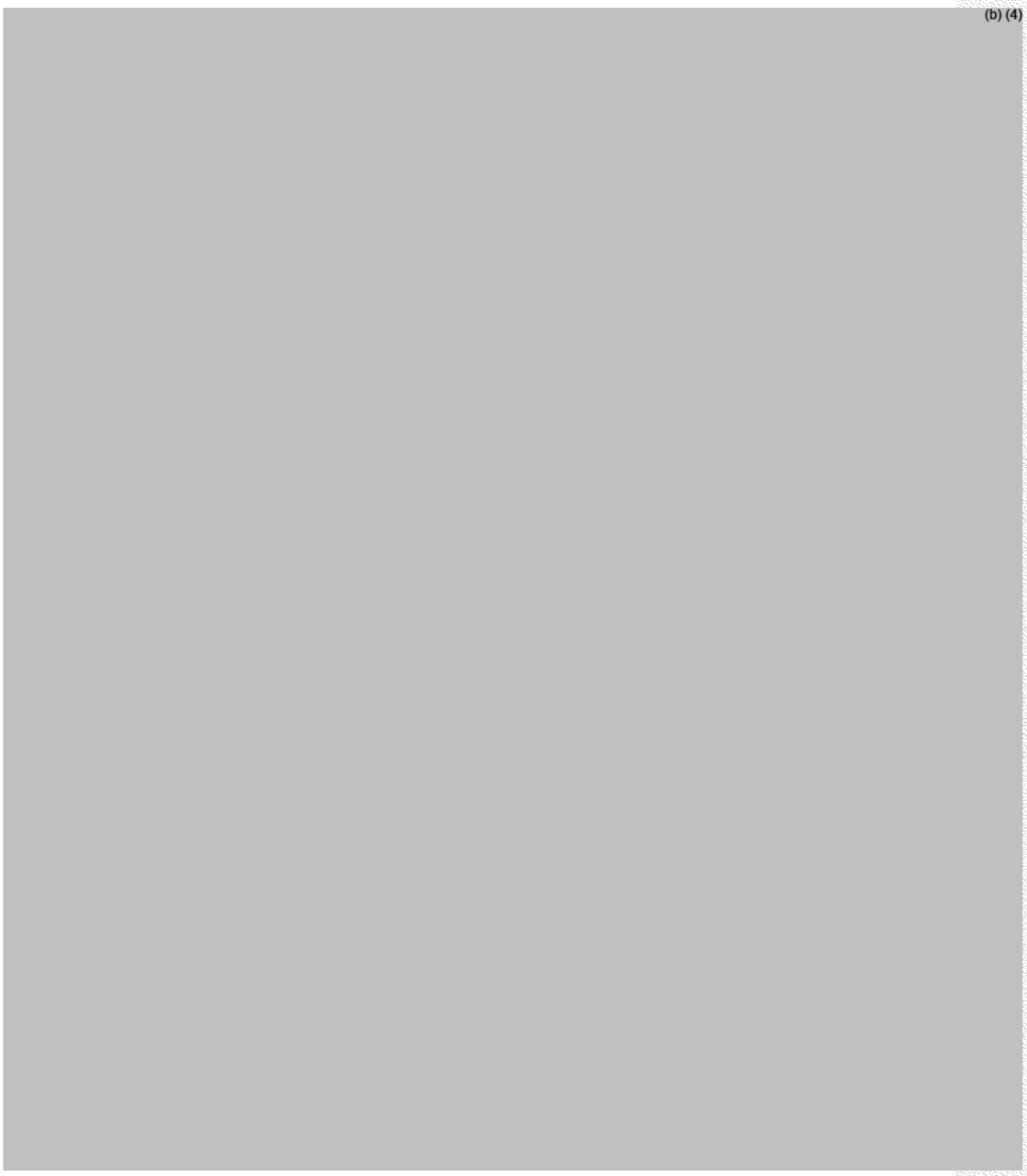
(b) (4)

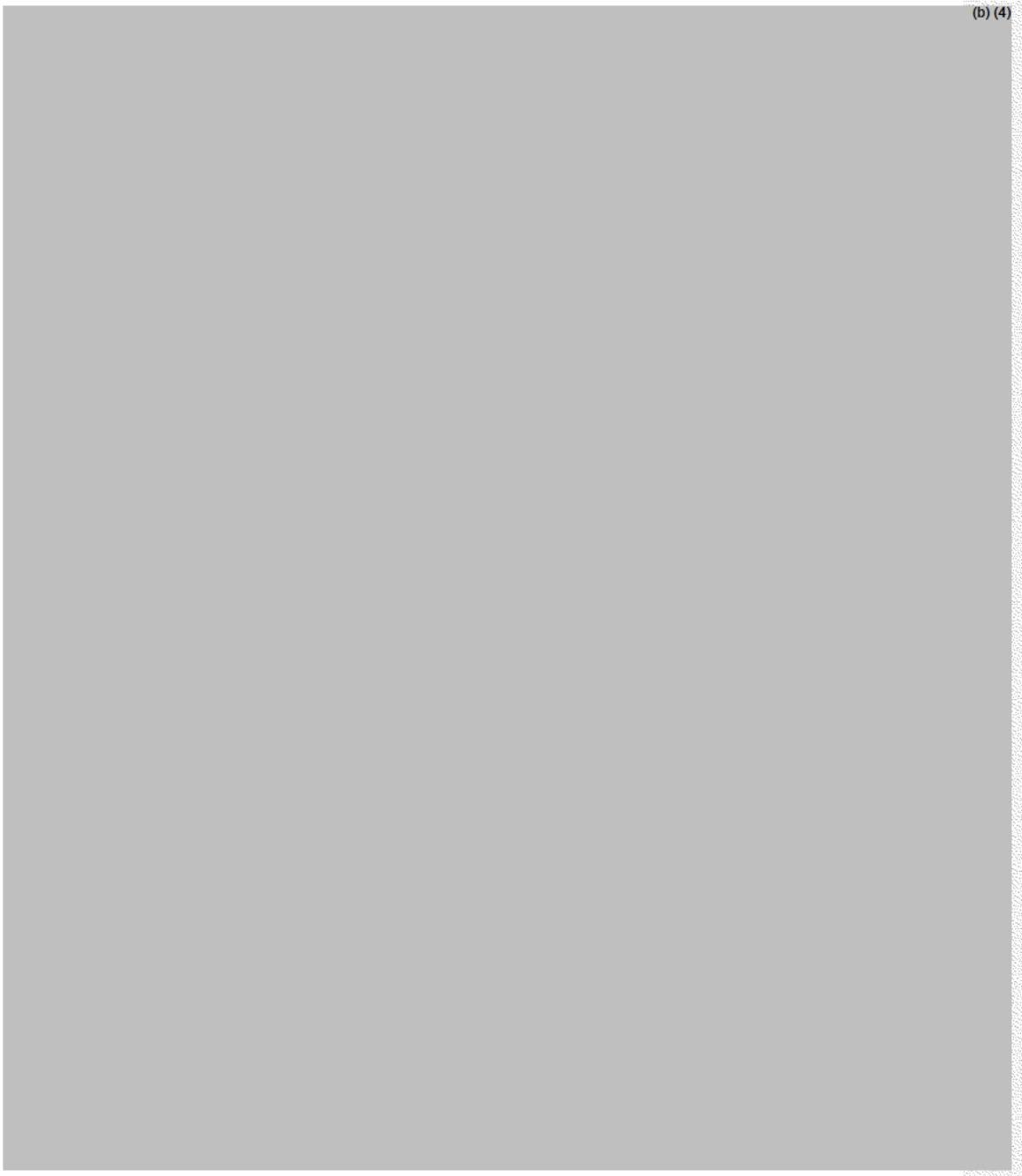


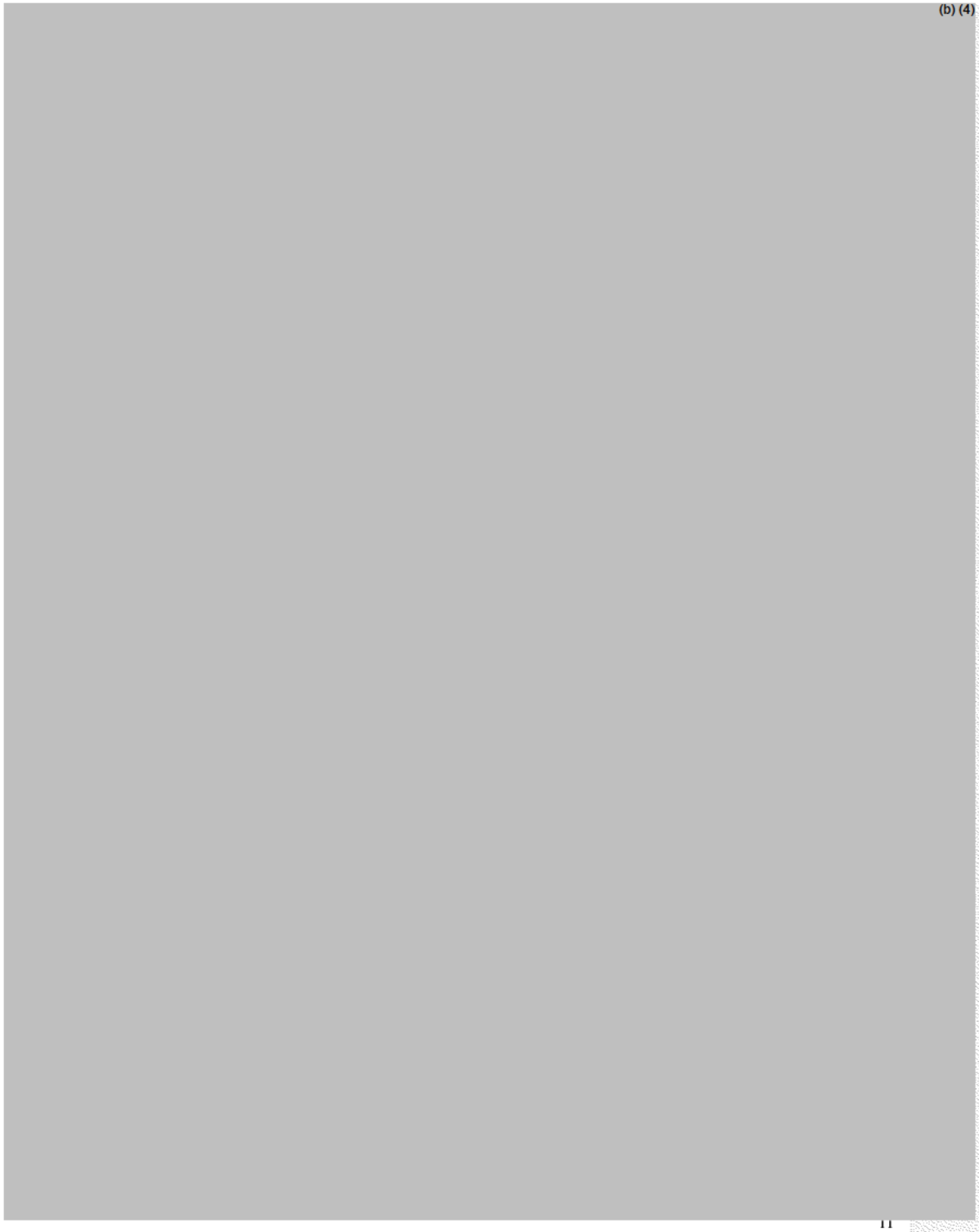
(b) (4)

(b) (4)





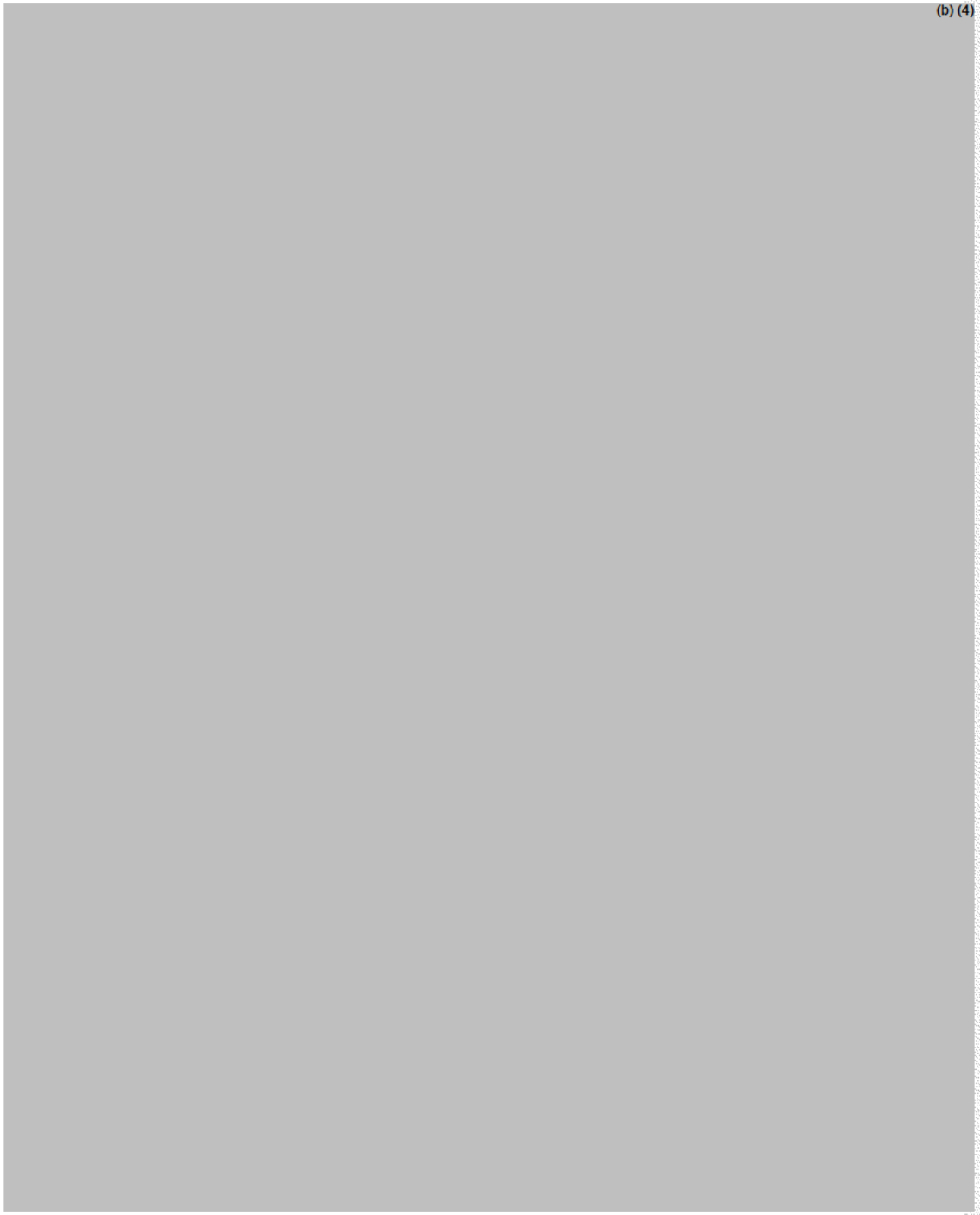


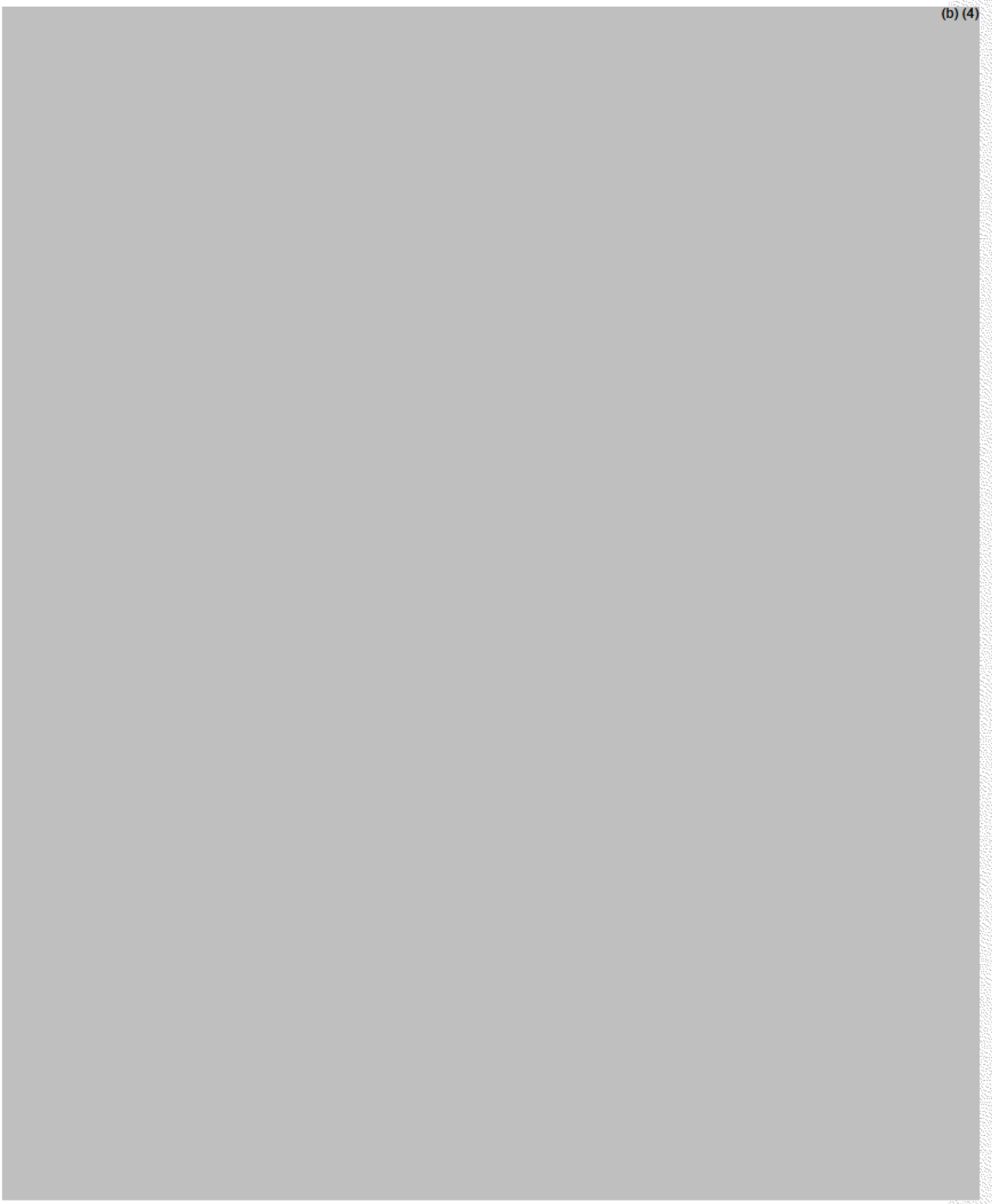


(b) (4)

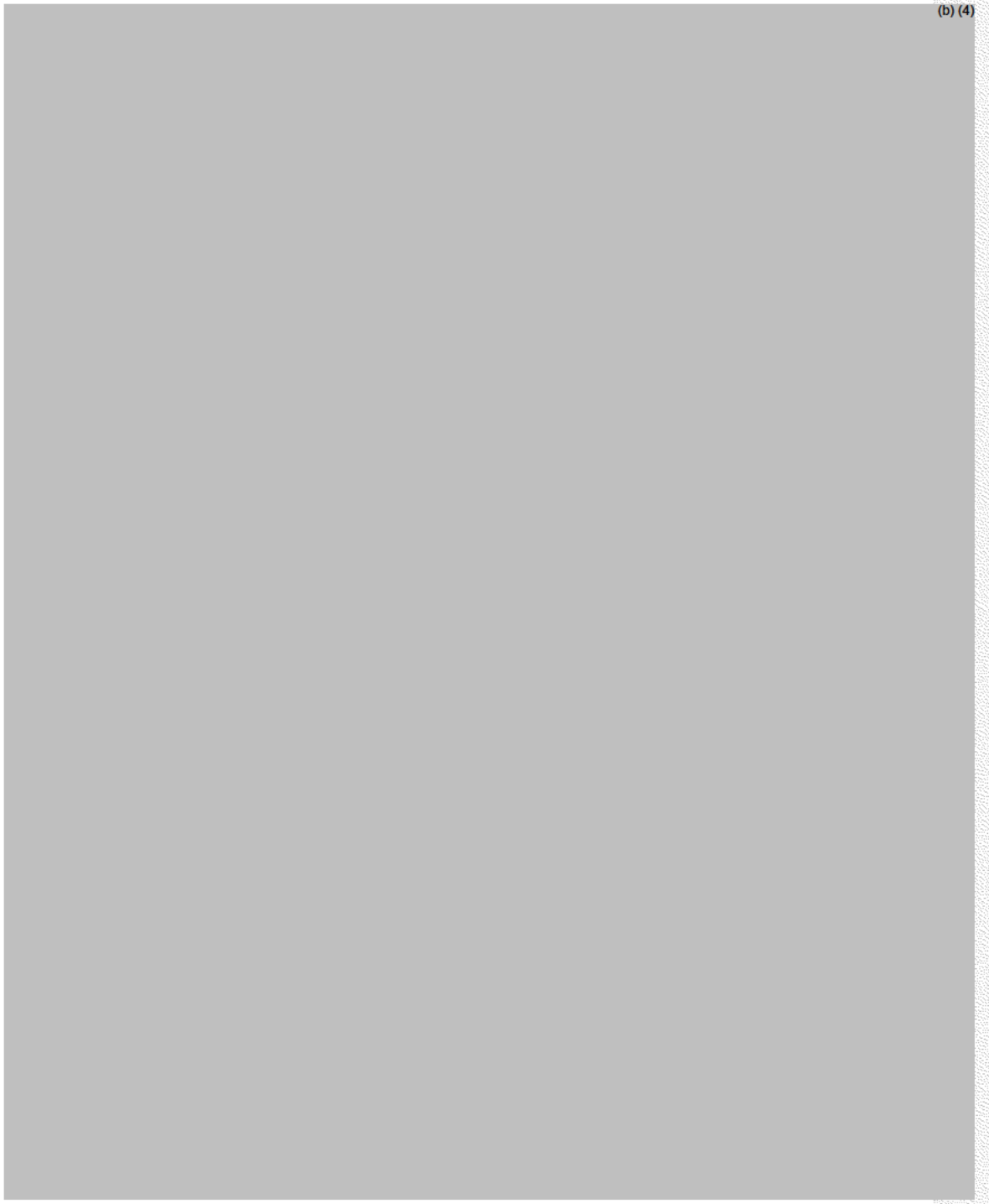
(b) (4)

(b) (4)

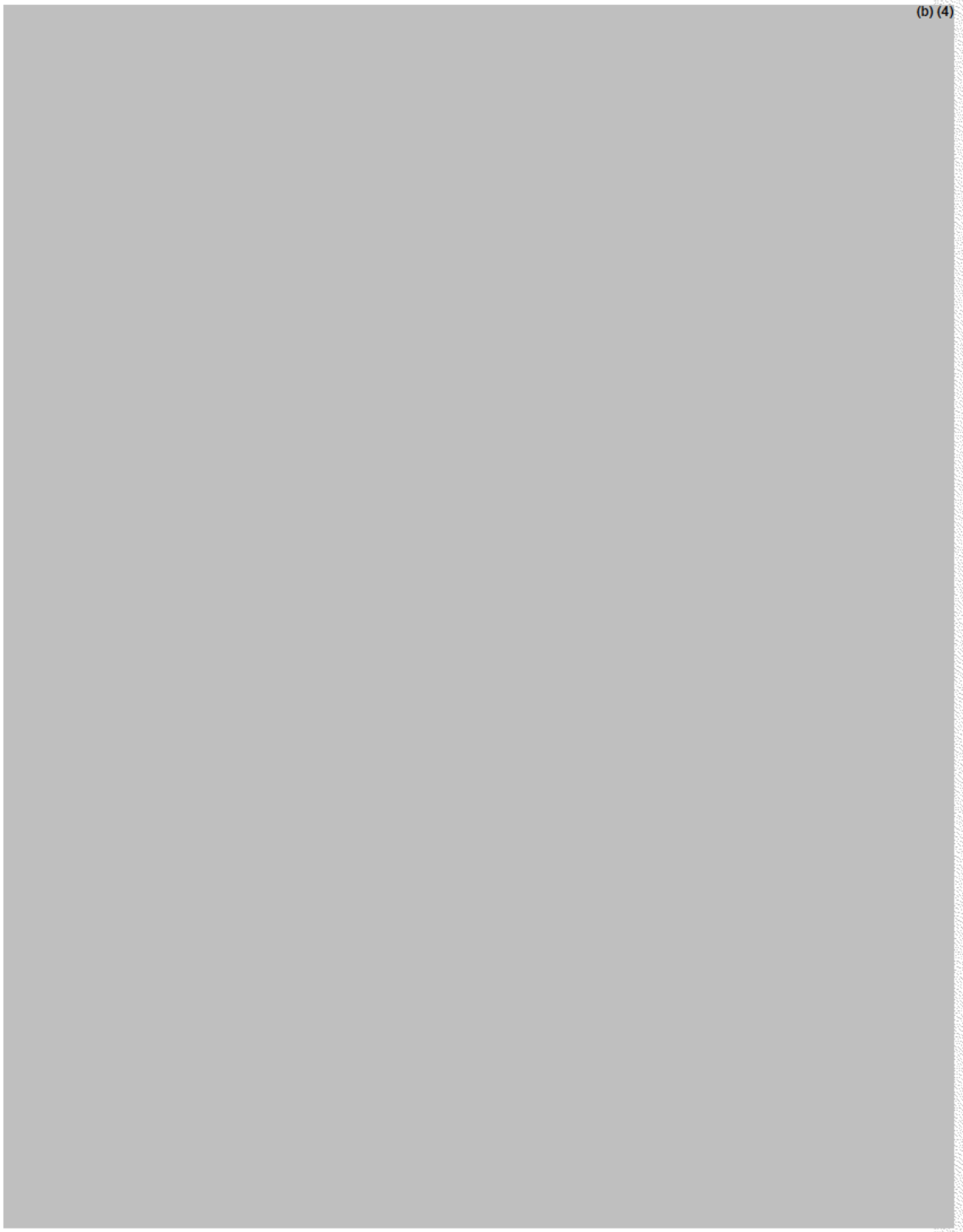




(b) (4)



(b) (4)



(b) (4)

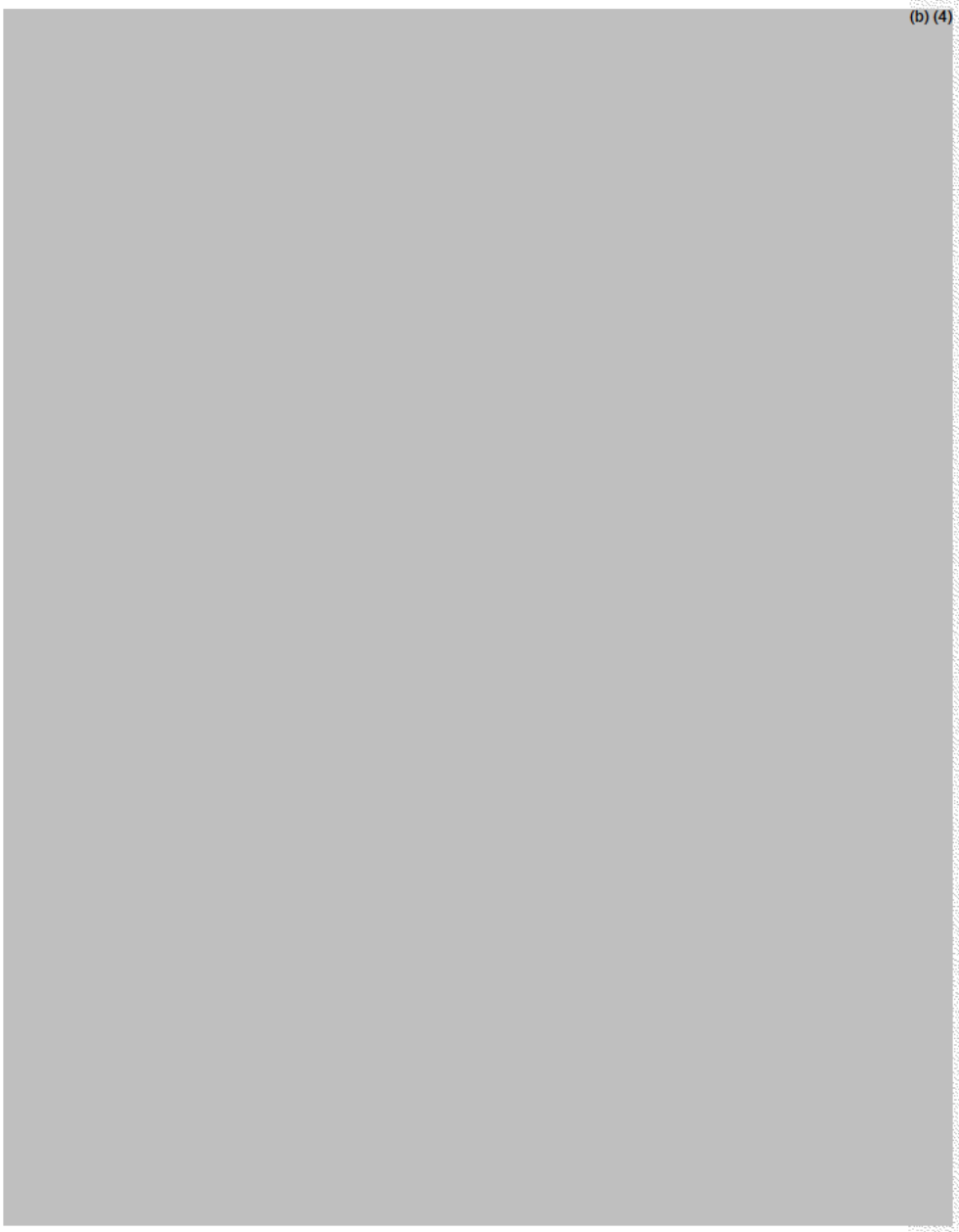
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

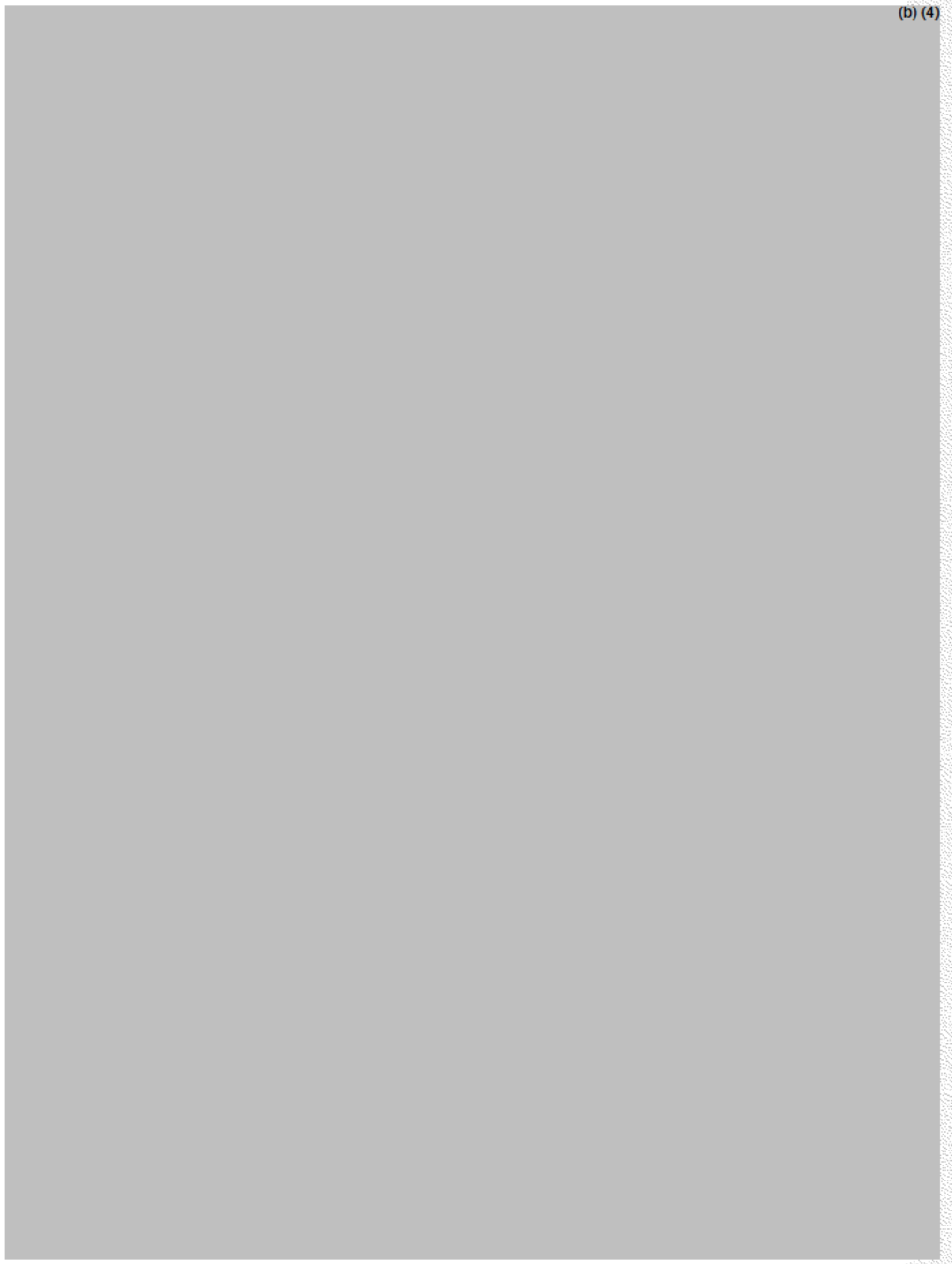
/s/

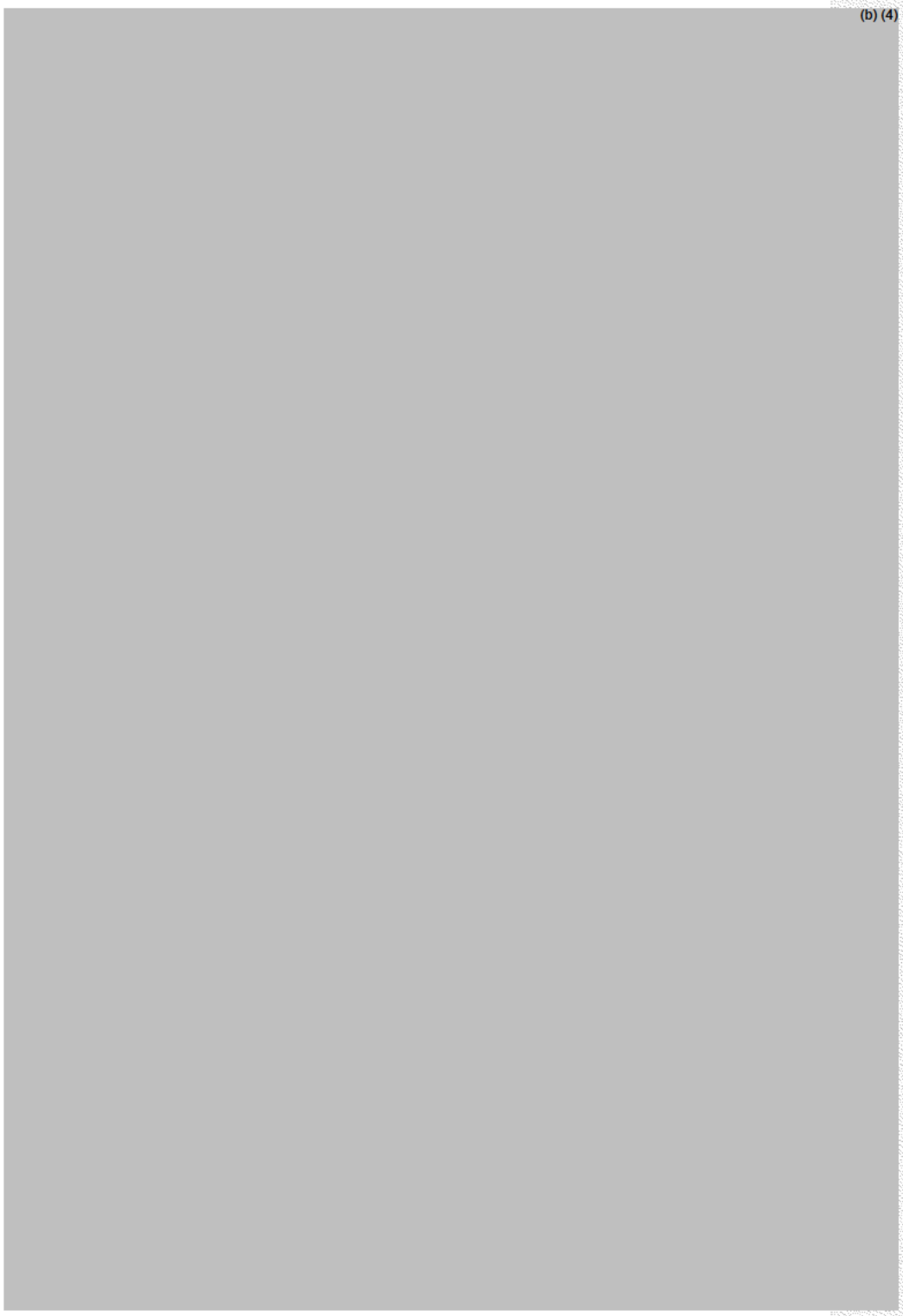
CHARUNI P SHAH
01/26/2022 08:56:35 AM

Synarel®
(nafarelin acetate)
nasal solution

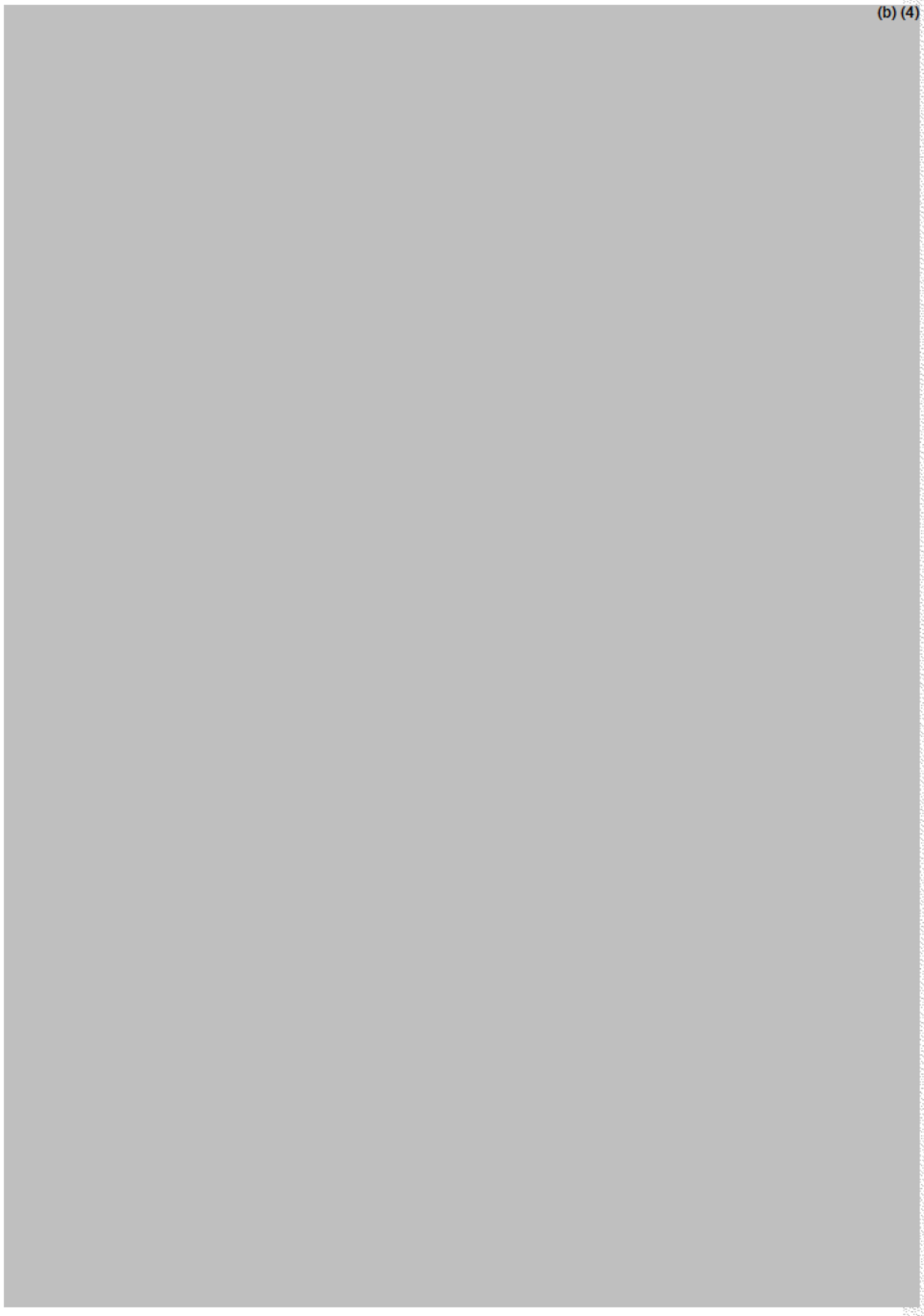
(b) (4)




(b) (4)


(b) (4)

(b) (4)

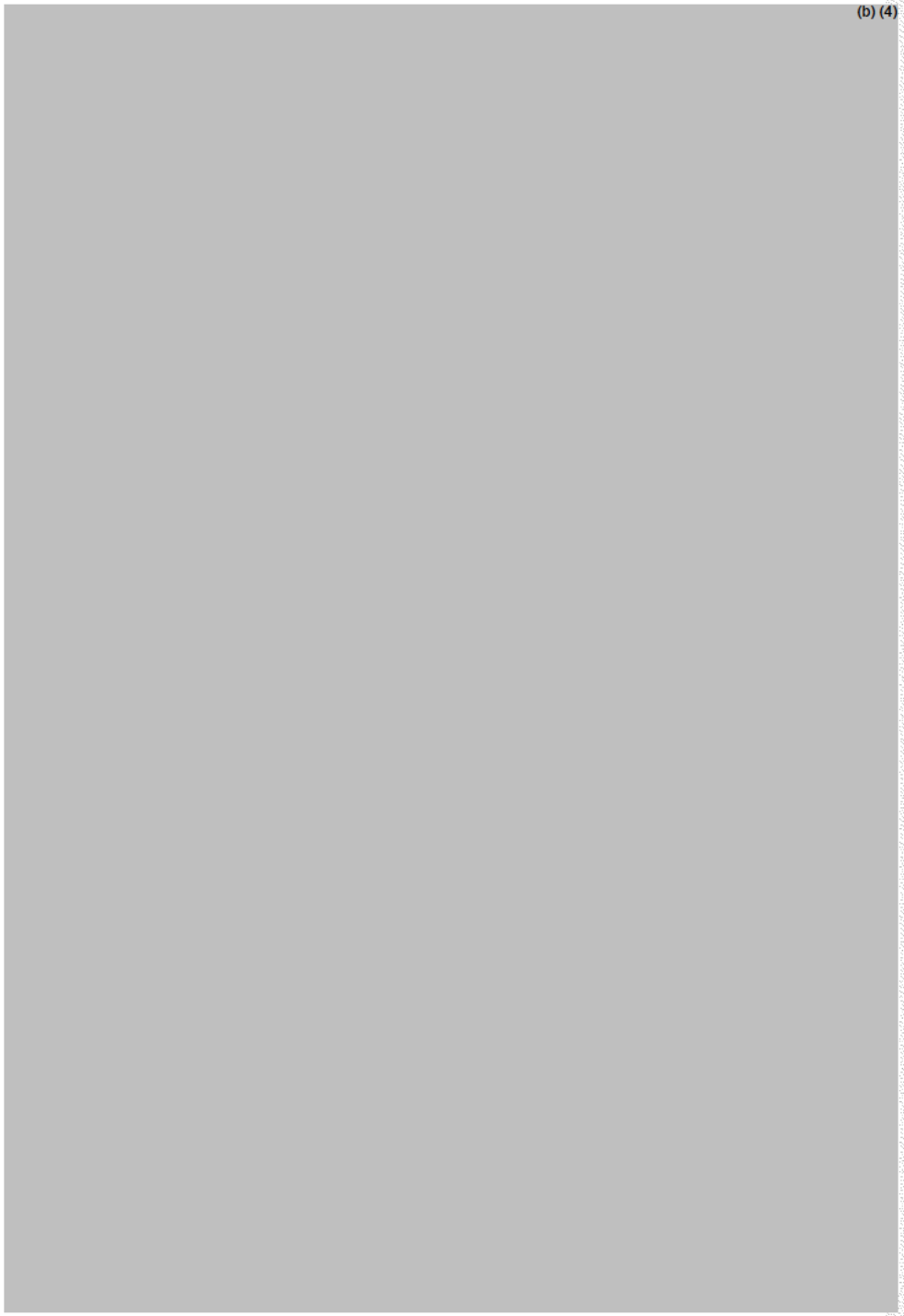


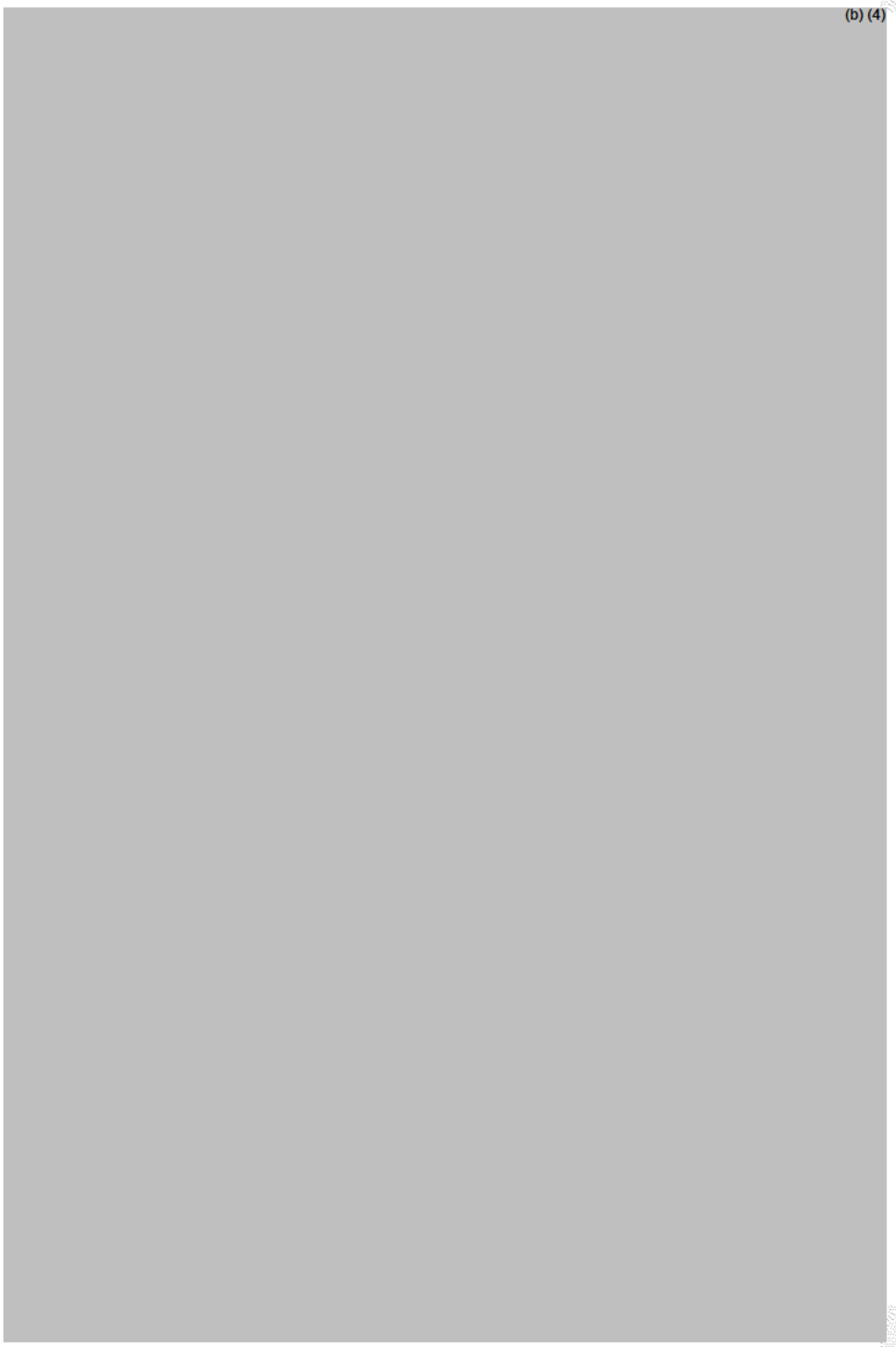
(b) (4)

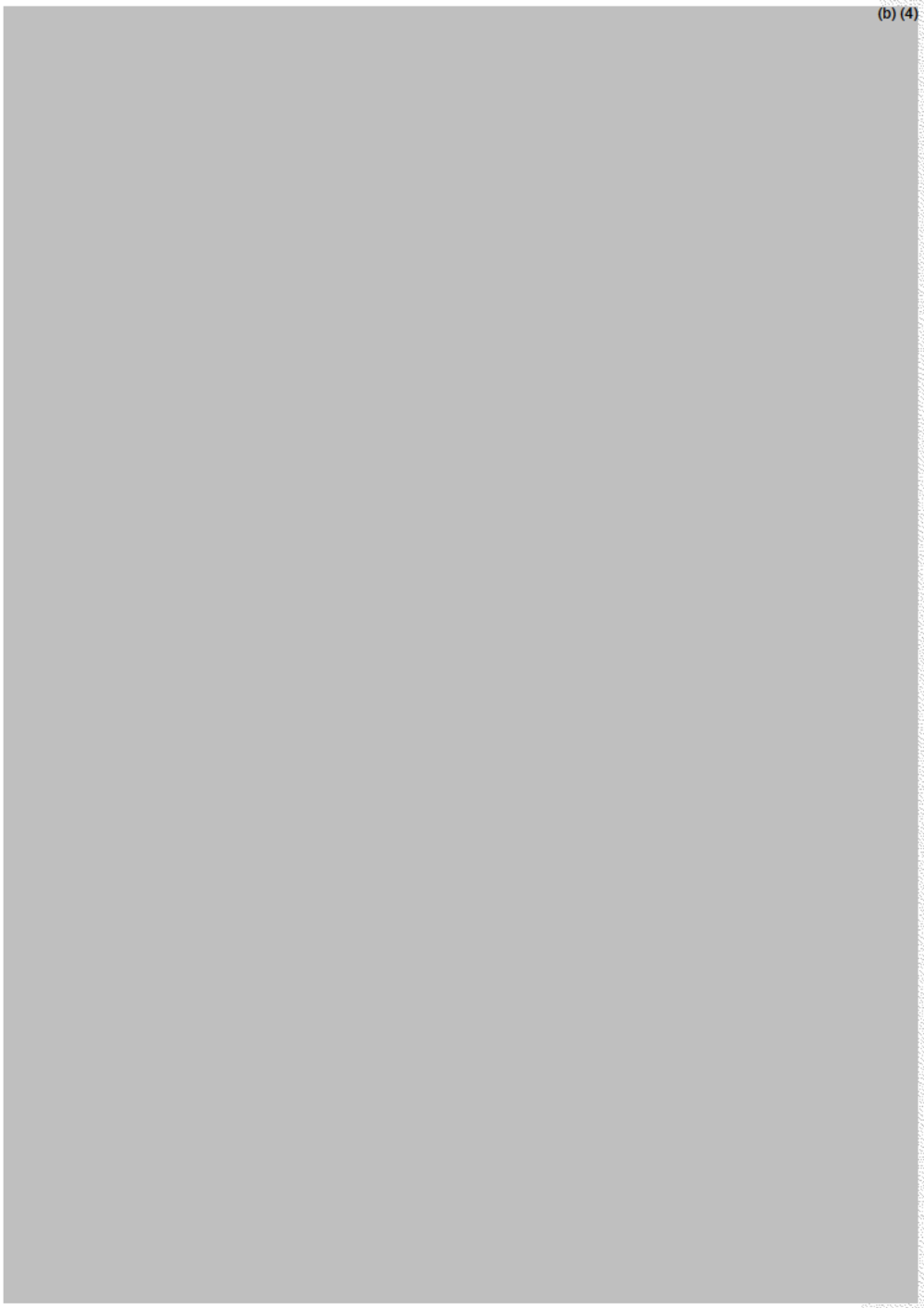
[redacted]

Commented [VS1]: This was removed as it's a duplicate

(b) (4)




(b) (4)


(b) (4)


(b) (4)

Synarel®

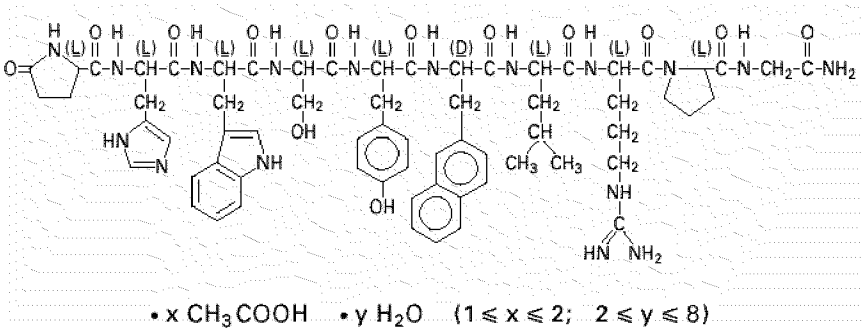
(nafarelin acetate)
nasal solution

ENDOMETRIOSIS
(FOR CENTRAL PRECOCIOUS PUBERTY, SEE REVERSE SIDE)

PHYSICIAN LABELING

DESCRIPTION

SYNAREL (nafarelin acetate) Nasal Solution is intended for administration as a spray to the nasal mucosa. Nafarelin acetate, the active component of SYNAREL Nasal Solution, is a decapeptide with the chemical name: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-3-(2-naphthyl)-D-alanyl-L-leucyl-L-arginyl-L-prolyl-glycinamide acetate. Nafarelin acetate is a synthetic analog of the naturally occurring gonadotropin-releasing hormone (GnRH).
Nafarelin acetate has the following chemical structure:



SYNAREL Nasal Solution contains nafarelin acetate (2 mg/mL, content expressed as nafarelin base) in a solution of benzalkonium chloride, glacial acetic acid, sodium hydroxide or hydrochloric acid (to adjust pH), sorbitol, and purified water.

After priming the pump unit for SYNAREL, each actuation of the unit delivers approximately 100 µL of the spray containing approximately 200 µg nafarelin base. The contents of one spray bottle are intended to deliver at least 60 sprays.

CLINICAL PHARMACOLOGY

Nafarelin acetate is a potent agonistic analog of gonadotropin-releasing hormone (GnRH). At the onset of administration, nafarelin stimulates the release of the pituitary gonadotropins, LH and FSH, resulting in a temporary increase of ovarian steroidogenesis. Repeated dosing abolishes the stimulatory effect on the pituitary gland. Twice daily

administration leads to decreased secretion of gonadal steroids by about 4 weeks; consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent.

Nafarelin acetate is rapidly absorbed into the systemic circulation after intranasal administration. Maximum serum concentrations (measured by RIA) were achieved between 10 and 40 minutes. Following a single dose of 200 µg base, the observed average peak concentration was 0.6 ng/mL (range 0.2 to 1.4 ng/mL), whereas following a single dose of 400 µg base, the observed average peak concentration was 1.8 ng/mL (range 0.5 to 5.3 ng/mL). Bioavailability from a 400 µg dose averaged 2.8% (range 1.2 to 5.6%). The average serum half-life of nafarelin following intranasal administration is approximately 3 hours. About 80% of nafarelin acetate is bound to plasma proteins at 4°C. Twice daily intranasal administration of 200 or 400 µg of SYNAREL in 18 healthy women for 22 days did not lead to significant accumulation of the drug. Based on the mean C_{min} levels on Days 15 and 22, there appeared to be dose proportionality across the two dose levels.

After subcutaneous administration of ^{14}C-nafarelin acetate to men, 44–55% of the dose was recovered in urine and 18.5–44.2% was recovered in feces. Approximately 3% of the administered dose appeared as unchanged nafarelin in urine. The ^{14}C serum half-life of the metabolites was about 85.5 hours. Six metabolites of nafarelin have been identified of which the major metabolite is Tyr-D(2)-Nal-Leu-Arg-Pro-Gly-NH_2(5-10). The activity of the metabolites, the metabolism of nafarelin by nasal mucosa, and the pharmacokinetics of the drug in hepatically- and renally-impaired patients have not been determined.

There appeared to be no significant effect of rhinitis, i.e., nasal congestion, on the systemic bioavailability of SYNAREL; however, if the use of a nasal decongestant for rhinitis is necessary during treatment with SYNAREL, the decongestant should not be used until at least 2 hours following dosing of SYNAREL.

In controlled clinical studies, SYNAREL at doses of 400 and 800 µg/day for 6 months was shown to be comparable to danazol, 800 mg/day, in relieving the clinical symptoms of endometriosis (pelvic pain, dysmenorrhea, and dyspareunia) and in reducing the size of endometrial implants as determined by laparoscopy. The clinical significance of a decrease in endometriotic lesions is not known at this time and, in addition, laparoscopic staging of endometriosis does not necessarily correlate with severity of symptoms.

In a single controlled clinical trial, intranasal SYNAREL (nafarelin acetate) at a dose of 400 µg per day was shown to be clinically comparable to intramuscular leuprolide depot, 3.75 mg monthly, for the treatment of the symptoms (dysmenorrhea, dyspareunia and pelvic pain) associated with endometriosis.

SYNAREL 400 µg daily induced amenorrhea in approximately 65%, 80%, and 90% of the patients after 60, 90, and 120 days, respectively. In the first, second, and third post-treatment months, normal menstrual cycles resumed in 4%, 82%, and 100%, respectively, of those patients who did not become pregnant.

At the end of treatment, 60% of patients who received SYNAREL, 400 µg/day, were symptom free, 32% had mild symptoms, 7% had moderate symptoms, and 1% had severe symptoms. Of the 60% of patients who had complete relief of symptoms at the end of treatment, 17% had moderate symptoms 6 months after treatment was discontinued, 33% had mild symptoms, 50% remained symptom free, and no patient had severe symptoms.

During the first two months use of SYNAREL, some women experience vaginal bleeding of variable duration and intensity. In all likelihood, this bleeding represents estrogen withdrawal bleeding and is expected to stop spontaneously. If vaginal bleeding continues, the possibility of lack of compliance with the dosing regimen should be considered. If the patient is complying carefully with the regimen, an increase in dose to 400 µg twice a day should be considered.

There is no evidence that pregnancy rates are enhanced or adversely affected by the use of SYNAREL.

INDICATIONS AND USAGE FOR ENDOMETRIOSIS

(For Central Precocious Puberty, See *Reverse Side*)

SYNAREL is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. Experience with SYNAREL for the management of endometriosis has been limited to women 18 years of age and older treated for 6 months.

CONTRAINDICATIONS

1. Hypersensitivity to GnRH, GnRH agonist analogs or any of the excipients in SYNAREL;
2. Undiagnosed abnormal vaginal bleeding;
3. Use in pregnancy or in women who may become pregnant while receiving the drug. SYNAREL may cause fetal harm when administered to a pregnant woman. Major fetal abnormalities were observed in rats, but not in mice or rabbits after administration of SYNAREL during the period of organogenesis. There was a dose-related increase in fetal mortality and a decrease in fetal weight in rats *[see **Pregnancy**]*. The effects on rat fetal mortality are expected consequences of the alterations in hormonal levels brought about by the drug. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus;
4. Use in women who are breast-feeding *[see **Nursing Mothers**]*.

WARNINGS

Safe use of nafarelin acetate in pregnancy has not been established clinically. Before starting treatment with SYNAREL, pregnancy must be excluded.

When used regularly at the recommended dose, SYNAREL usually inhibits ovulation and stops menstruation. Contraception is not insured, however, by taking SYNAREL, particularly if patients miss successive doses. Therefore, patients should use nonhormonal methods of contraception. Patients should be advised to see their physician if they believe they may be pregnant. If a patient becomes pregnant during treatment, the drug must be discontinued and the patient must be apprised of the potential risk to the fetus.

PRECAUTIONS

General

As with other drugs that stimulate the release of gonadotropins or that induce ovulation, ovarian cysts have been reported to occur in the first two months of therapy with SYNAREL. Many, but not all, of these events occurred in patients with polycystic ovarian disease. These cystic enlargements may resolve spontaneously, generally by about four to six weeks of therapy, but in some cases may require discontinuation of drug and/or surgical intervention.

Information for Patients

An information pamphlet for patients is included with the product. Patients should be aware of the following information:

1. Since menstruation should stop with effective doses of SYNAREL, the patient should notify her physician if regular menstruation persists. The cause of vaginal spotting, bleeding or menstruation could be noncompliance with the treatment regimen, or it could be that a higher dose of the drug is required to achieve amenorrhea. The patient should be questioned regarding her compliance. If she is careful and compliant, and menstruation persists to the second month, consideration should be given to doubling the dose of SYNAREL. If the patient has missed several doses, she should be counseled on the importance of taking SYNAREL regularly as prescribed.

2. Patients should not use SYNAREL if they are pregnant, breastfeeding, have undiagnosed abnormal vaginal bleeding, or are allergic to any of the ingredients in SYNAREL.

3. Safe use of the drug in pregnancy has not been established clinically. Therefore, a nonhormonal method of contraception should be used during treatment. Patients should be advised that if they miss successive doses of SYNAREL, breakthrough bleeding or ovulation may occur with the potential for conception. If a patient becomes pregnant during treatment, she should discontinue treatment and consult her physician.

4. Those adverse events occurring most frequently in clinical studies with SYNAREL are associated with hypoestrogenism; the most frequently reported are hot flashes, headaches, emotional lability, decreased libido, vaginal dryness, acne, myalgia, and reduction in breast size. Estrogen levels returned to normal after treatment was discontinued. Nasal irritation occurred in about 10% of all patients who used intranasal nafarelin.

5. The induced hypoestrogenic state results in a small loss in bone density over the course of treatment, some of which may not be reversible. During one six-month treatment period, this bone loss should not be important. In patients with major risk factors for decreased bone mineral content such as chronic alcohol and/or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, therapy with SYNAREL may pose an additional risk. In these patients the risks and benefits must be weighed carefully before therapy with SYNAREL is instituted. Repeated courses of treatment with gonadotropin-releasing

hormone analogs are not advisable in patients with major risk factors for loss of bone mineral content.

6. Patients with intercurrent rhinitis should consult their physician for the use of a topical nasal decongestant. If the use of a topical nasal decongestant is required during treatment with SYNAREL, the decongestant should not be used until at least 2 hours following dosing with SYNAREL.

Sneezing during or immediately after dosing with SYNAREL should be avoided, if possible, since this may impair drug absorption.

7. Retreatment cannot be recommended since safety data beyond 6 months are not available.

Drug Interactions
No pharmacokinetic-based drug-drug interaction studies have been conducted with SYNAREL. However, because nafarelin acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes, and the drug is only about 80% bound to plasma proteins at 4°C, drug interactions would not be expected to occur.

Drug/Laboratory Test Interactions
Administration of SYNAREL in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within 4 to 8 weeks after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and up to 4 to 8 weeks after discontinuation of therapy with SYNAREL may be misleading.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies of nafarelin were conducted in rats (24 months) at doses up to 100 µg/kg/day and mice (18 months) at doses up to 500 µg/kg/day using intramuscular doses (up to 110 times and 560 times the maximum recommended human intranasal dose, respectively). These multiples of the human dose are based on the relative bioavailability of the drug by the two routes of administration. As seen with other GnRH agonists, nafarelin acetate given to laboratory rodents at high doses for prolonged periods induced proliferative responses (hyperplasia and/or neoplasia) of endocrine organs. At 24 months, there was an increase in the incidence of pituitary tumors (adenoma/carcinoma) in high-dose female rats and a dose-related increase in male rats. There was an increase in pancreatic islet cell adenomas in both sexes, and in benign testicular and ovarian tumors in the treated groups. There was a dose-related increase in benign adrenal medullary tumors in treated female rats. In mice, there was a dose-related increase in Harderian gland tumors in males and an increase in pituitary adenomas in high-dose females. No metastases of these tumors were observed. It is known that tumorigenicity in rodents is particularly sensitive to hormonal stimulation.

Mutagenicity studies were performed with nafarelin acetate using bacterial, yeast, and mammalian systems. These studies provided no evidence of mutagenic potential.

Reproduction studies in male and female rats have shown full reversibility of fertility suppression when drug treatment was discontinued after continuous administration for up to 6 months. The effect of treatment of prepubertal rats on the subsequent reproductive performance of mature animals has not been investigated.

Pregnancy

Teratogenic Effects

See ***Contraindications***. Intramuscular SYNAREL was administered to rats during the period of organogenesis at 0.4, 1.6, and 6.4 µg/kg/day (about 0.5, 2, and 7 times the maximum recommended human intranasal dose based on the relative bioavailability by the two routes of administration). An increase in major fetal abnormalities was observed in 4/80 fetuses at the highest dose. A similar, repeat study at the same doses in rats and studies in mice and rabbits at doses up to 600 µg/kg/day and 0.18 µg/kg/day, respectively, failed to demonstrate an increase in fetal abnormalities after administration during the period of organogenesis. In rats and rabbits, there was a dose-related increase in fetal mortality and a decrease in fetal weight with the highest dose.

Nursing Mothers

It is not known whether SYNAREL is excreted in human milk. Because many drugs are excreted in human milk, and because the effects of SYNAREL on lactation and/or the breastfed child have not been determined, SYNAREL should not be used by nursing mothers.

Pediatric Use

Safety and effectiveness of SYNAREL for endometriosis in patients younger than 18 years have not been established.

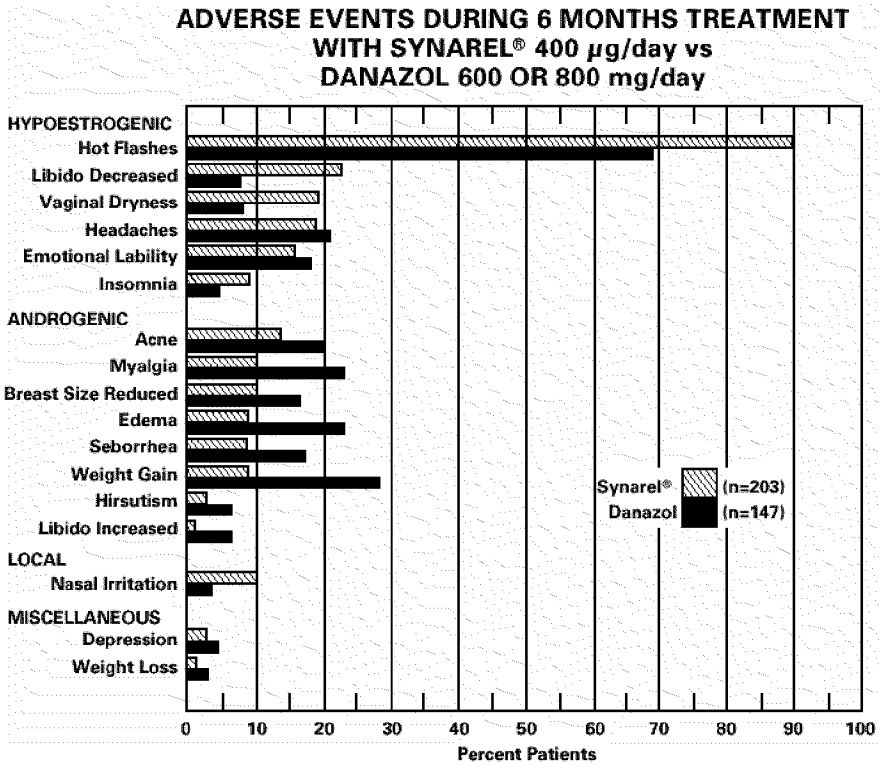
ADVERSE REACTIONS

Clinical Studies

In formal clinical trials of 1509 healthy adult patients, symptoms suggestive of drug sensitivity, such as shortness of breath, chest pain, urticaria, rash and pruritus occurred in 3 patients (approximately 0.2%).

As would be expected with a drug which lowers serum estradiol levels, the most frequently reported adverse reactions were those related to hypoestrogenism.

In controlled studies comparing SYNAREL (400 µg/day) and danazol (600 or 800 mg/day), adverse reactions most frequently reported and thought to be drug-related are shown in the figure below:



In addition, less than 1% of patients experienced paresthesia, palpitations, chloasma, maculopapular rash, eye pain, asthenia, lactation, breast engorgement, and arthralgia.

Changes in Bone Density

After six months of treatment with SYNAREL, vertebral trabecular bone density and total vertebral bone mass, measured by quantitative computed tomography (QCT), decreased by an average of 8.7% and 4.3%, respectively, compared to pretreatment levels. There was partial recovery of bone density in the post-treatment period; the average trabecular bone density and total bone mass were 4.9% and 3.3% less than the pretreatment levels, respectively. Total vertebral bone mass, measured by dual photon absorptiometry (DPA), decreased by a mean of 5.9% at the end of treatment.

After six months treatment with SYNAREL, bone mass as measured by dual x-ray bone densitometry (DEXA), decreased 3.2%. Mean total vertebral mass, re-examined by DEXA six months after completion of treatment, was 1.4% below pretreatment. There was little, if any, decrease in the mineral content in compact bone of the distal radius and second metacarpal. Use of SYNAREL for longer than the recommended six months or in the presence of other known risk factors for decreased bone mineral content may cause additional bone loss.

Changes in Laboratory Values During Treatment

Plasma enzymes. During clinical trials with SYNAREL, regular laboratory monitoring revealed that SGOT and SGPT levels were more than twice the upper limit of normal in only one patient each. There was no other clinical or laboratory evidence of abnormal liver function and levels returned to normal in both patients after treatment was stopped.

Lipids. At enrollment, 9% of the patients in the group taking SYNAREL 400 μg/day and 2% of the patients in the danazol group had total cholesterol values above 250 mg/dL. These patients also had cholesterol values above 250 mg/dL at the end of treatment.

Of those patients whose pretreatment cholesterol values were below 250 mg/dL, 6% in the group treated with SYNAREL and 18% in the danazol group, had post-treatment values above 250 mg/dL.

The mean (± SEM) pretreatment values for total cholesterol from all patients were 191.8 (4.3) mg/dL in the group treated with SYNAREL and 193.1 (4.6) mg/dL in the danazol group. At the end of treatment, the mean values for total cholesterol from all patients were 204.5 (4.8) mg/dL in the group treated with SYNAREL and 207.7 (5.1) mg/dL in the danazol group. These increases from the pretreatment values were statistically significant ($p<0.05$) in both groups.

Triglycerides were increased above the upper limit of 150 mg/dL in 12% of the patients who received SYNAREL and in 7% of the patients who received danazol.

At the end of treatment, no patients receiving SYNAREL had abnormally low HDL cholesterol fractions (less than 30 mg/dL) compared with 43% of patients receiving danazol. None of the patients receiving SYNAREL had abnormally high LDL cholesterol fractions (greater than 190 mg/dL) compared with 15% of those receiving danazol. There was no increase in the LDL/HDL ratio in patients receiving SYNAREL, but there was approximately a 2-fold increase in the LDL/HDL ratio in patients receiving danazol.

Other changes. In comparative studies, the following changes were seen in approximately 10% to 15% of patients. Treatment with SYNAREL was associated with elevations of plasma phosphorus and eosinophil counts, and decreases in serum calcium and WBC counts. Danazol therapy was associated with an increase of hematocrit and WBC.

Post-Marketing

Pituitary apoplexy: During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed, with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

Cardiovascular adverse events: Cases of serious venous and arterial thromboembolism have been reported, including deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, and transient ischemic attack. Although a temporal relationship was reported in some cases, most cases were confounded by risk factors or concomitant medication use. It is unknown if there is a causal association between the use of GnRH analogs and these events.

Central/peripheral nervous adverse events: Convulsion.
Hepatic adverse events: Rarely reported serious liver injury.
Reproductive system adverse events: Cases of ovarian hyperstimulation syndrome have been reported with Synarel monotherapy when used for Assisted Reproductive Technology which is not an approved indication.

OVERDOSAGE

In experimental animals, a single subcutaneous administration of up to 60 times the recommended human dose (on a µg/kg basis, not adjusted for bioavailability) had no adverse effects. At present, there is no clinical evidence of adverse effects following overdosage of GnRH analogs.

Based on studies in monkeys, SYNAREL is not absorbed after oral administration.

DOSAGE AND ADMINISTRATION

For the management of endometriosis, the recommended daily dose of SYNAREL is 400 µg. This is achieved by one spray (200 µg) into one nostril in the morning and one spray into the other nostril in the evening. Treatment should be started between days 2 and 4 of the menstrual cycle.

In an occasional patient, the 400 µg daily dose may not produce amenorrhea. For these patients with persistent regular menstruation after 2 months of treatment, the dose of SYNAREL may be increased to 800 µg daily. The 800 µg dose is administered as one spray into each nostril in the morning (a total of two sprays) and again in the evening.

The recommended duration of administration is six months. Retreatment cannot be recommended since safety data for retreatment are not available. If the symptoms of endometriosis recur after a course of therapy, and further treatment with SYNAREL is contemplated, it is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits.

There appeared to be no significant effect of rhinitis, i.e., nasal congestion, on the systemic bioavailability of SYNAREL; however, if the use of a nasal decongestant for rhinitis is necessary during treatment with SYNAREL, the decongestant should not be used until at least 2 hours following dosing with SYNAREL.

Sneezing during or immediately after dosing with SYNAREL should be avoided, if possible, since this may impair drug absorption.

At 400 µg/day, a bottle of SYNAREL provides a 30-day (about 60 sprays) supply. If the daily dose is increased, increase the supply to the patient to ensure uninterrupted treatment for the recommended duration of therapy.

HOW SUPPLIED

Each 0.5 ounce bottle (NDC 0025-0166-08) contains 8 mL SYNAREL (nafarelin acetate) Nasal Solution 2 mg/mL (as nafarelin base), and is supplied with a metered spray pump that delivers 200 µg of nafarelin per spray. A dust cover and a leaflet of patient instructions are also included.

Store upright at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from light.

Distributed by

Pfizer Labs

Division of Pfizer Inc, NY, NY 10017

LAB-0173-11.0
Revised: December 2020

SYNAREL
nafarelin acetate
Nasal Spray

Patient Instructions for Use

Introduction

Your doctor has prescribed SYNAREL Nasal Solution to treat your symptoms of endometriosis. This pamphlet has two purposes:

1.) to review information your doctor has given you about SYNAREL; and
2.) to give you information about how to use SYNAREL properly.

Please read this pamphlet carefully. If you still have questions after reading it or if you have questions at any time during your treatment with SYNAREL, be sure to check with your doctor.

SYNAREL is used to relieve the symptoms of endometriosis. The lining of the uterus is called the endometrium, and part of it is shed during menses. In endometriosis, endometrial tissue is also found outside the uterus and, like normal endometrial tissue, can bleed during a menstrual cycle. It is, in part, this monthly activity that causes you to have symptoms during your cycle. Most often, this out-of-place endometrial tissue is found around the uterus, ovaries, the intestine or other organs in the pelvis. Although some women with endometriosis have no symptoms, many have problems such as severe menstrual cramps, pain during sexual intercourse, low back pain, and painful bowel movements.

Endometrial tissue is affected by the body's hormones, especially estrogen, which is made by the ovaries. When estrogen levels are low, endometrial tissue shrinks (perhaps even disappears), and symptoms of endometriosis ease. SYNAREL temporarily reduces estrogen in the body and temporarily relieves the symptoms of endometriosis.

Important Information about SYNAREL

1. You should **not** use SYNAREL if
    - you are pregnant.
    - you are breast feeding.
    - you have abnormal vaginal bleeding that has not been checked into by your doctor.
    - you are allergic to any of the ingredients of SYNAREL (nafarelin acetate, benzalkonium chloride, acetic acid, sodium hydroxide, hydrochloric acid, sorbitol, purified water).
2. SYNAREL is a prescription medicine that should be used according to your doctor's directions. SYNAREL comes as a special nasal spray that gives a measured amount of medicine. To be effective, SYNAREL must be used every day, twice a day, for the whole treatment period.

3. It is important to use a non-hormonal method of contraception (such as diaphragm with contraceptive jelly, IUD, condoms) while taking SYNAREL. You should not use birth control pills while taking SYNAREL.
4. If you miss 1 or more doses of SYNAREL, vaginal bleeding (often called breakthrough bleeding) may occur. If you miss successive doses of SYNAREL and have not been using contraception as described above, release of an egg from the ovary (ovulation) may occur, with the possibility of pregnancy. Under these circumstances you must see your physician to make sure you are not pregnant. If you should become pregnant while using SYNAREL, you must discuss the possible risks to the fetus and the choices available to you with your physician.
5. Because SYNAREL works by temporarily reducing the body's production of estrogen, a female hormone produced by the ovary, you may have some of the same changes that normally occur at the time of menopause, when the body's production of estrogen naturally decreases. For the first two months after you start using SYNAREL, you may experience some irregular vaginal spotting or bleeding. The duration and intensity of this bleeding may vary; it may be similar to your usual menstruation, or it may be lighter or heavier. The duration may also vary from brief to prolonged. In any case, you can expect this bleeding to stop by itself. After the first two months of treatment with SYNAREL, you can expect a decrease in menstrual flow, and your periods may stop altogether. However, if you miss one or more doses of SYNAREL, you may continue to experience vaginal bleeding. If you continue to experience normal menstrual cycles after two months use of SYNAREL, you should see your doctor about the continued periods. Other changes due to decreased estrogen include hot flashes, vaginal dryness, headaches, mood changes, and decreased interest in sex. Most of these changes are caused by low estrogen levels and may occur during treatment with SYNAREL. Some patients may also experience acne, muscle pain, reduced breast size, and irritation of the tissues inside the nose. These symptoms should disappear after you stop taking the drug.
6. When you take SYNAREL, your estrogen levels will be low. Low estrogen levels can result in a small loss of mineral from bone, some of which may not be reversible. During one six-month treatment period, this small loss of mineral from bone should not be important. There are certain conditions that may increase the possibility of the thinning of your bones when you take a drug such as SYNAREL. They are:
    - excessive use of alcohol;
    - smoking;
    - family history of osteoporosis (thinning of the bones with fractures);
    - taking other medications that can cause thinning of the bones.

    You should discuss the possibility of osteoporosis or thinning of the bones with your physician before starting SYNAREL. You should also be aware that repeat treatments are not recommended since they may

put you at greater risk of bone thinning, particularly if you have the above conditions.

7. During studies, menstruation usually resumed within 2 to 3 months of stopping treatment with SYNAREL. At the end of treatment 60% of patients treated with SYNAREL were symptom free, 32% had mild symptoms, 7% had moderate symptoms and 1% had severe symptoms.
   Of the 60% of patients who had complete relief of symptoms at the end of treatment, 17% had moderate symptoms at the end of the six month post-treatment period; 33% had mild symptoms; 50% were symptom free; no patient had severe symptoms.
8. Retreatment cannot be recommended since the safety of such retreatment is not known.
9. It is all right to use a nasal decongestant spray while you are being treated with SYNAREL if you follow these simple rules. Use SYNAREL first. Wait at least 2 hours after using SYNAREL before you use the decongestant spray.
10. You should avoid sneezing during or immediately after using SYNAREL, if possible, since sneezing may impair drug absorption.

Proper use of SYNAREL for Treatment of Endometriosis

1. When you start to use SYNAREL, the first dose should be taken between the second and fourth day after the beginning of your menstrual bleeding. You should continue taking SYNAREL every day as prescribed.
   Do not miss a single dose.
2. Unless your doctor has given you special instructions, follow the steps for using SYNAREL **twice each day**, about 12 hours between doses:
   - once in the morning in one nostril (for example, 7 a.m.)
   - once in the evening in the other nostril (for example, 7 p.m.)

   The length of treatment is usually about 6 months, unless your doctor has given you special instructions.
3. Because it is so important that you do not miss a single dose of SYNAREL, here are some suggestions to help you remember:
   - Keep your SYNAREL in a place where you will be reminded to use it each morning and each evening — next to your toothbrush is one possibility.
   - Keep track of each dose on a calendar.
   - Make a note on your calendar on the day you start a new bottle of SYNAREL. You can also mark the date you started right on the bottle. Be sure to refill your prescription before the 30 days are up so you will have a new bottle on hand.
4. A bottle of SYNAREL should not be used for longer than 30 days (60 sprays). Each bottle contains sufficient quantity of nasal solution for initial priming of the pump and 30 days (60 sprays) of treatment. At the end of 30 days, a small amount of liquid will be left in the bottle. **Do not try to use up that leftover amount** because you might get

too low a dose, which could interfere with the effectiveness of your treatment. Dispose of the bottle and do not reuse.

5. If your doctor increases your daily dose of SYNAREL, then your bottle will not last the standard 30 days. Please discuss this with your doctor to be sure that you have an adequate supply for uninterrupted treatment with SYNAREL to complete the recommended treatment period.

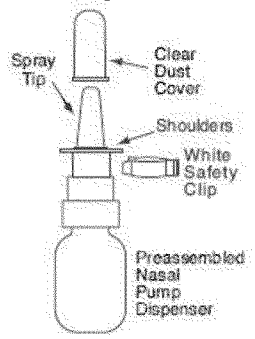
Preparation of the SYNAREL Nasal Spray unit
For use in your nose only.

Before you use SYNAREL nasal spray for the first time, you will need to prime it. This will ensure that you get the right dose of medicine each time you use it.

Important Tips about using SYNAREL

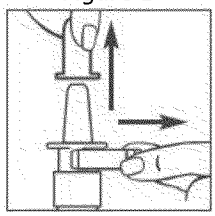
- Your pump should produce a fine mist, which can only happen by a quick and firm pumping action. It is normal to see some larger droplets of liquid within the fine mist. However, if SYNAREL comes out of the pump as a thin stream of liquid instead of a fine mist, SYNAREL may not work as well, and you should talk to your pharmacist.
- Be sure to clean the Spray Tip **before and after every use**. (See Step 4). Failure to do this may result in a clogged tip that may cause you not to get the right amount of medicine that is prescribed for you.
- The pump is made to deliver only a set amount of medicine, no matter how hard you pump it.
- **Do Not try to make the tiny hole in the spray tip larger**. If the hole is made larger the pump will deliver a wrong dose of SYNAREL.

Figure A



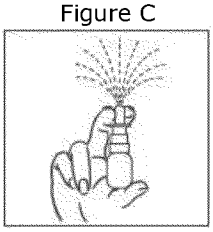
To Prime the Pump:

Figure B



1. Remove and save the white safety clip and the clear plastic dust cover from the spray bottle (See Figure B).

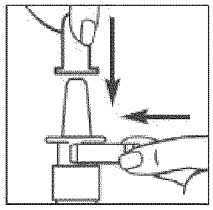
Figure C



2. Hold the bottle in an upright position away from you. Put two fingers on the "shoulders" of the spray bottle and put your thumb on the bottom of the bottle. Apply pressure **evenly** to the "shoulders" and push down **quickly and firmly** 7 to 10 times, until you see a fine spray. Usually you will see the spray after about 7 pumps. (See Figure C).

3. The pump is now primed**. Priming only needs to be done 1 time, when you start using a <u>new</u> bottle of SYNAREL**. You will waste your medicine if you prime the pump every time you use it and may not have enough medicine for 30 days of treatment.

Figure D

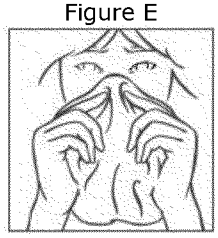


4. **Clean the Spray Tip after Priming:**
   - Hold the bottle in a horizontal position. Rinse the spray tip with **warm** water while wiping the tip with your finger or soft cloth for 15 seconds.
   - Wipe the spray tip with a soft cloth or tissue to dry.
   - Replace the white safety clip and the clear plastic dust cover on the spray bottle (See Figure D).
   - **Do Not** try to clean the spray tip using a pointed object. **Do Not** take apart the pump.

[SHAPE * MERGEFORMAT]

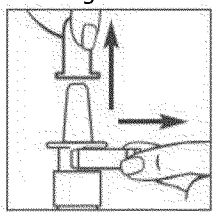
How to use the SYNAREL Nasal Spray unit for the treatment of Endometriosis

Figure E



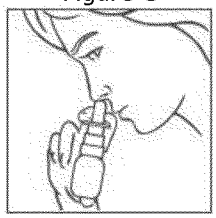
5. Gently blow your nose to clear both nostrils before you use SYNAREL nasal spray (See Figure E).

Figure F



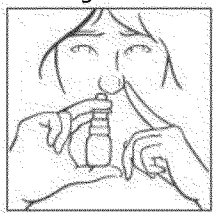
6. **Clean the Spray Tip.** Remove and save the white safety clip and the clear plastic dust cover from the spray bottle (See Figure F).
   - Hold the bottle in a horizontal position. Rinse the spray tip with **warm** water while wiping the tip with your finger or soft cloth for 15 seconds.
   - Wipe the spray tip with a soft cloth or tissue to dry.
   - **Do Not** try to clean the spray tip using a pointed object.
   - **Do Not** try to take apart the pump.

Figure G



7. Bend your head forward and put the spray tip into one nostril. The tip should **not** reach too far into your nose. Aim the spray tip toward the **back and outer side** of your nose (See Figure G).

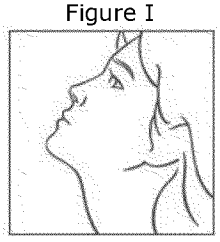
Figure H



8. Close the other nostril with your finger (See Figure H).

9. Apply pressure **evenly** to the "shoulders" and push down **quickly and firmly.** Pump the sprayer 1 time, at the same time as you sniff in gently. If the sprayer fails to deliver the dose clean the spray tip (See Step 6 **Clean the Spray Tip**).

Figure I



10. Remove the spray tip from your nose and tilt your head backwards for a few seconds. This lets the SYNAREL spray spread over the back of your nose (See Figure I).

    Do not spray in your other nostril unless your doctor has instructed you to do so.

Figure J
[SHAPE * MERGEFORMAT]

11. Clean the Spray Tip after use (See Step 4).

It is important that you clean the spray tip before and after every use. Failure to do this may result in a clogged tip that may cause you to get the wrong dose of medicine.

Important Reminder: Treatment with SYNAREL must be uninterrupted with no missed doses to be effective.

Make sure you use SYNAREL exactly as your doctor tells you. Make sure to note the date you start each bottle so you do not run out of medicine and miss doses.

Keep out of the reach of children and use carefully as directed.

Storage Instructions:

- Store SYNAREL at 59°F to 86°F (15°C to 30°C).
- Store the SYNAREL bottle upright.
- Keep SYNAREL out of the light.
- Do not freeze SYNAREL.

This product's label may have been updated. For current full prescribing information, please visit [HYPERLINK "http://www.pfizer.com"].

Distributed by

Pfizer Labs

Division of Pfizer Inc, NY, NY 10017

LAB-0278-7.0
Revised: December 2020

MEDICATION GUIDE
SYNAREL (sin-na-rell)
(nafarelin acetate) nasal solution

What is the most important information I should know about SYNAREL?

- Some people taking GnRH agonists like SYNAREL have had new or worsened mental (psychiatric) problems. Mental (psychiatric) problems may include emotional symptoms such as:
  - crying
  - irritability
  - restlessness (impatience)
  - anger
  - acting aggressive

Call your child's doctor right away if your child has any new or worsening mental symptoms or problems while taking SYNAREL

- Some people taking GnRH agonists like SYNAREL have had seizures. The risk of seizures may be higher in people who:
  - have a history of seizures.
  - have a history of epilepsy.
  - have a history of brain or brain vessel (cerebrovascular) problems or tumors.
  - are taking a medicine that has been connected to seizures such as taking bupropion or selective serotonin reuptake inhibitors (SSRIs).

Seizures have also happened in people who have not had any of these problems.

Call your child's doctor right away if your child has a seizure while taking SYNAREL.

What is SYNAREL?

SYNAREL is a gonadotropin releasing hormone (GnRH) medicine used for the treatment of children with central precocious puberty (CPP).

Do not give SYNAREL if your child:

- is allergic to gonadotropin releasing hormone (GnRH), GnRH agonist medicines, or any of the ingredients in SYNAREL. See the end of this Medication Guide for a complete list of ingredients in SYNAREL.
- has unusual vaginal bleeding that has not been checked by her doctor.
- is pregnant or may become pregnant. SYNAREL can cause birth defects or loss of the baby. If your child becomes pregnant call your doctor.
- is breastfeeding or plans to breastfeed. It is not known if SYNAREL passes into breast milk. You and your child's doctor should decide if your child will take SYNAREL or breastfeed. **Do not breastfeed while taking SYNAREL.**

Before your child takes SYNAREL, tell your doctor about all of your child's medical conditions, including if they:

- have a history of mental (psychiatric) problems.
- have or have had a history of seizures.
- have a history of epilepsy.
- have a history of brain or brain vessel (cerebrovascular) problems or tumors
- are taking a medicine that has been connected to seizures such as bupropion or selective serotonin reuptake inhibitors (SSRIs).

Tell your doctor about all the medicines your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should your child take SYNAREL?

- Your child's doctor should do tests to make sure your child has CPP before treating your child with SYNAREL.
- Keep all scheduled visits to the doctor. If scheduled doses are missed, your child may start having signs of puberty again. The doctor will do regular exams and blood tests to check for

signs of puberty.

- Take SYNAREL exactly as your doctor tells you to take it. See detailed **"Instructions for Use"** at the end of this Medication Guide for information about the right way to use SYNAREL.
- Your child's doctor will tell you how much SYNAREL your child is to take and when to take it. If your doctor increases your child's daily dose of SYNAREL, 1 bottle will not last the standard 7 days. Talk with your child's doctor to make sure your child has enough SYNAREL to take their prescribed dose every day.

What should your child avoid while taking SYNAREL?

- Your child should avoid sneezing while taking SYNAREL or right after using it, if possible. This could reduce the amount of medicine your child's body absorbs.
- If your child needs to use a nasal decongestant spray while being treated with SYNAREL, they should not use the decongestant spray for at least 2 hours after taking the dose of SYNAREL.

What are the possible side effects of SYNAREL?

SYNAREL may cause serious side effects, including:

- See **"What is the most important information I should know about SYNAREL"**
- in the first month of treatment, SYNAREL can cause an increase in some hormones. During this time you may notice more signs of puberty in your child, including vaginal bleeding and breast enlargement in girls. Within 1 month of treatment, you should see signs in your child that puberty is stopping.

The side effects of SYNAREL include:

- allergic reactions such as shortness of breath, chest pain, hives, rash, and itching
- acne
- temporary increase in pubic hair
- body odor
- flaky, scaly skin
- hot flashes
- stuffy or runny nose (rhinitis)
- white or brown vaginal discharge

These are not all of the possible side effects of SYNAREL. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General Information about the safe and effective use of SYNAREL.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SYNAREL for a condition for which it is not prescribed. Do not give SYNAREL to other people, even if they have the same symptoms that you have. It may harm them.
You can ask your doctor or pharmacist for information about SYNAREL that is written for health professionals.

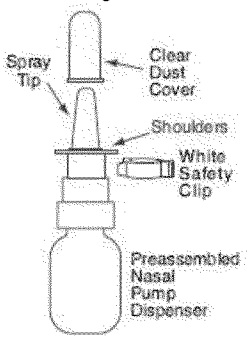
What are the ingredients in SYNAREL?

Active ingredient: nafarelin acetate
Inactive ingredients: benzalkonium chloride, glacial acetic acid, sodium hydroxide or hydrochloric acid (to adjust pH), sorbitol, and purified water

Instructions for Use
SYNAREL(sin-na-rel)
(nafarelin acetate)
nasal solution

For use in the nose only.

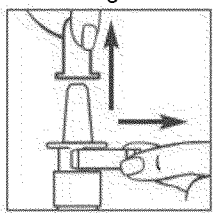
Figure A



Before you use SYNAREL nasal spray for the first time, you will need to prime it. This will make sure that you get the right dose of medicine each time you use it. Priming only needs to be done 1 time, when you start using a **new** bottle of SYNAREL.

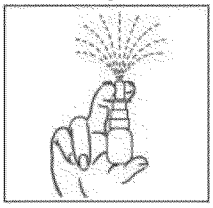
To Prime the Pump:

Figure B



1. Remove and save the white safety clip and the clear plastic dust cover from the spray bottle (See Figure B).

Figure C



2. Hold the bottle in an upright position away from you. Put 2 fingers on the "shoulders" of the spray bottle and put your thumb on the bottom of the bottle. Apply pressure **evenly** to the "shoulders" and push down **quickly and firmly** 7 to 10 times, until you see a fine mist spray. Usually you will see the spray after about 7 pumps. (See Figure C). The pump is now primed.

   It is normal to see some larger droplets of liquid within the fine mist. However, if SYNAREL comes out of the pump as a thin stream of liquid instead of a fine mist, SYNAREL may not work as well, and you should talk to your pharmacist.

Figure D

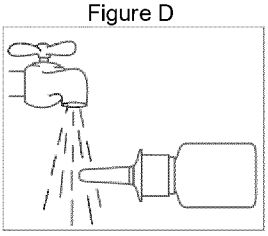
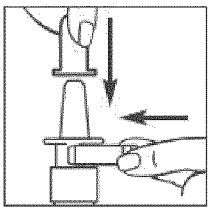


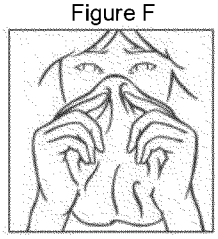
Figure E



3. **Clean the Spray Tip after Priming:**
   - Hold the bottle in sideways (horizontal) position (see Figure D).
     Rinse the "spray tip" with **warm** water while wiping the tip with your finger or soft cloth for 15 seconds.
   - Wipe the spray tip with a soft cloth or tissue to dry.
   - Replace the white safety clip and the clear plastic dust cover on the spray bottle. (See Figure E).
   - **Do not** try to clean the spray tip using a pointed object.
   - **Do not** take apart the pump.

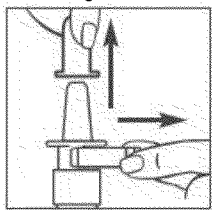
How to use the SYNAREL Nasal Spray for the treatment of Central Precocious Puberty

Figure F



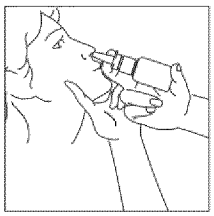
4. Have your child blow their nose to clear both nostrils before using SYNAREL nasal spray (see Figure F). If the child is too young to blow their nose, you may need to clear the child's nostrils with a bulb syringe.

Figure G



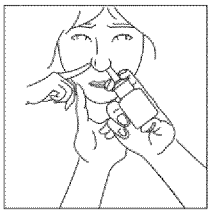
5. **Clean the Spray Tip each time before and after using SYNAREL.**
   - Remove and save the white safety clip and the clear plastic dust cover from the spray bottle (See Figure G).
   - Hold the bottle in sideways (horizontal) position. Rinse the spray tip with **warm** water while wiping the tip with your finger or soft cloth for 15 seconds.
   - Wipe the spray tip with a soft cloth or tissue to dry.
   - **Do not** try to clean the spray tip using a pointed object.
   - **Do not** try to take apart the pump.

Figure H



6. The child's head should be bent back a little and the spray tip put into one nostril. The tip should **not** reach too far into the nose. Aim the spray tip toward the **back and outer side** of the nose (See Figure H).

Figure I



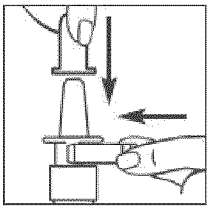
7. Close the other nostril with a finger (See Figure I).

Put pressure **evenly** to the "shoulders" and push down **quickly and firmly.** Pump the sprayer 1 time, at the same time as the child sniffs in gently. Wait about 30 seconds and put one more spray in the same nostril. Repeat this process in the other nostril, for a total of four sprays. If the sprayer fails to deliver the dose, clean the spray tip (See Step 5 **Clean the Spray Tip each time before and after using SYNAREL**).

Figure J

8. Remove the spray tip from the child's nose after all sprays are completed. Keep the child's head tilted back for a few seconds. This lets the SYNAREL spray spread over the back of the nose (See Figure J).

Figure K



9. Clean the Spray Tip after use (See Step 5. Put on the white safety clip and the clear plastic dust cover (see Figure K).

It is important that you clean the spray tip before and after every use. Not doing this may result in a clogged tip that may cause you to get the wrong dose of medicine.

How should I store SYNAREL?

- Store SYNAREL at room temperature between 59°F to 86°F (15°C to 30°C).
- Store the SYNAREL bottle upright.
- Keep SYNAREL out of the light.

Keep SYNAREL and all medicines out of the reach of children.

For more information call 1-800-438-1985.

This Medication Guide and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Manufactured for: Pfizer Inc., 235 East 42nd Street, New York, NY, 10017

Distributed by

Pfizer Labs

Division of Pfizer Inc, NY, NY 10017

LAB-1049-2.0
Revised: December 2020

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUPRON DEPOT-PED safely and effectively. See full prescribing information for LUPRON DEPOT-PED.

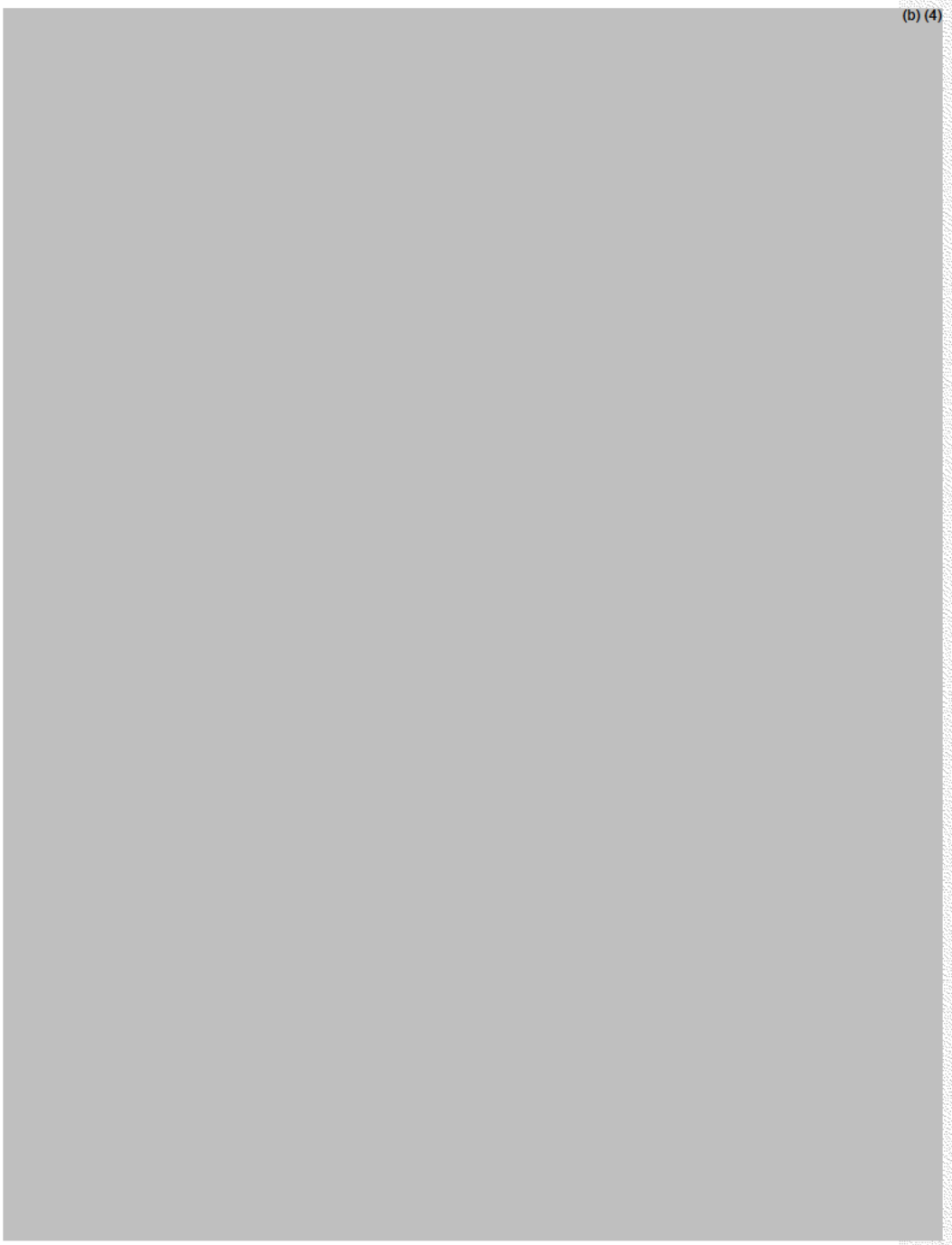
LUPRON DEPOT-PED (leuprolide acetate for depot suspension), for intramuscular use
Initial U.S. Approval: 1985

(b) (4)

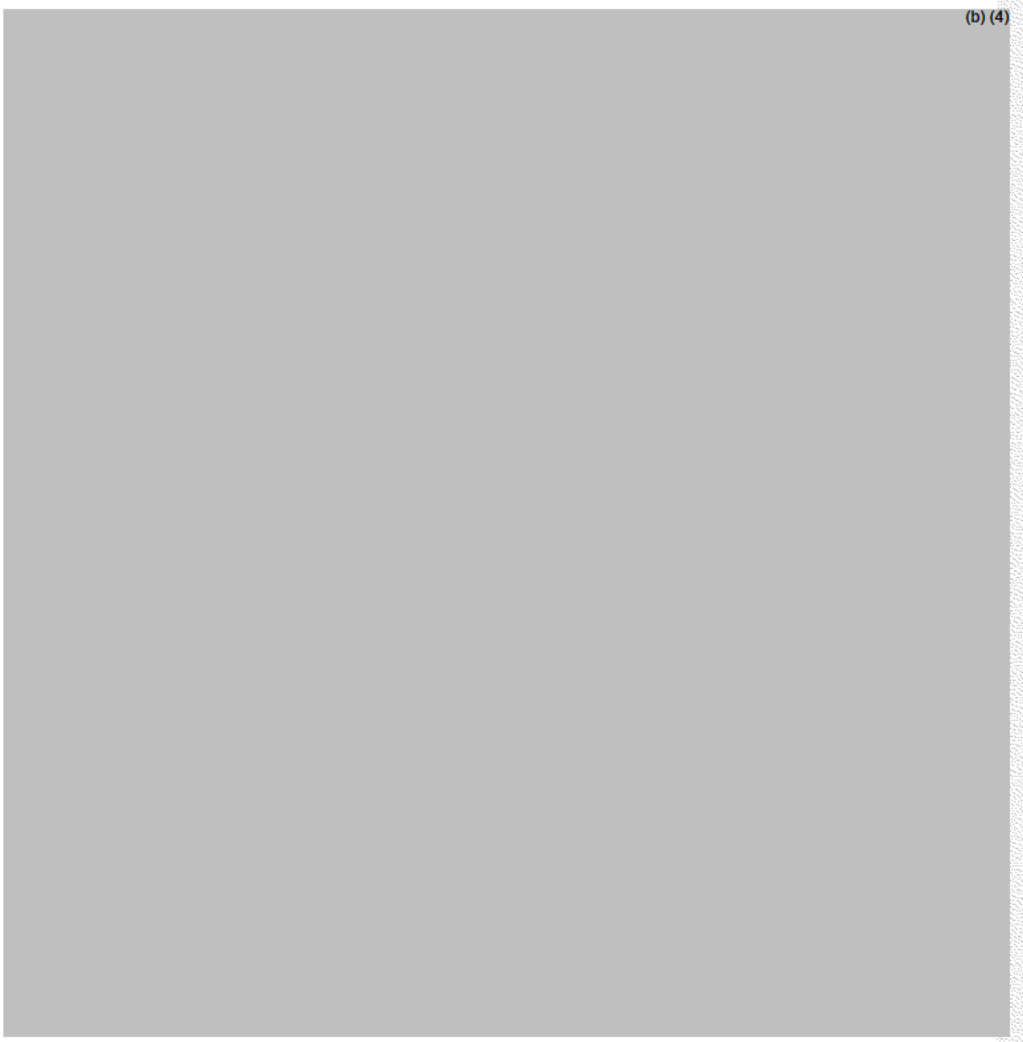
(b) (4)

FULL PRESCRIBING INFORMATION: CONTENTS| HYPERLINK "" \l "section_TOCFootnote" \o "Footnote Content"]

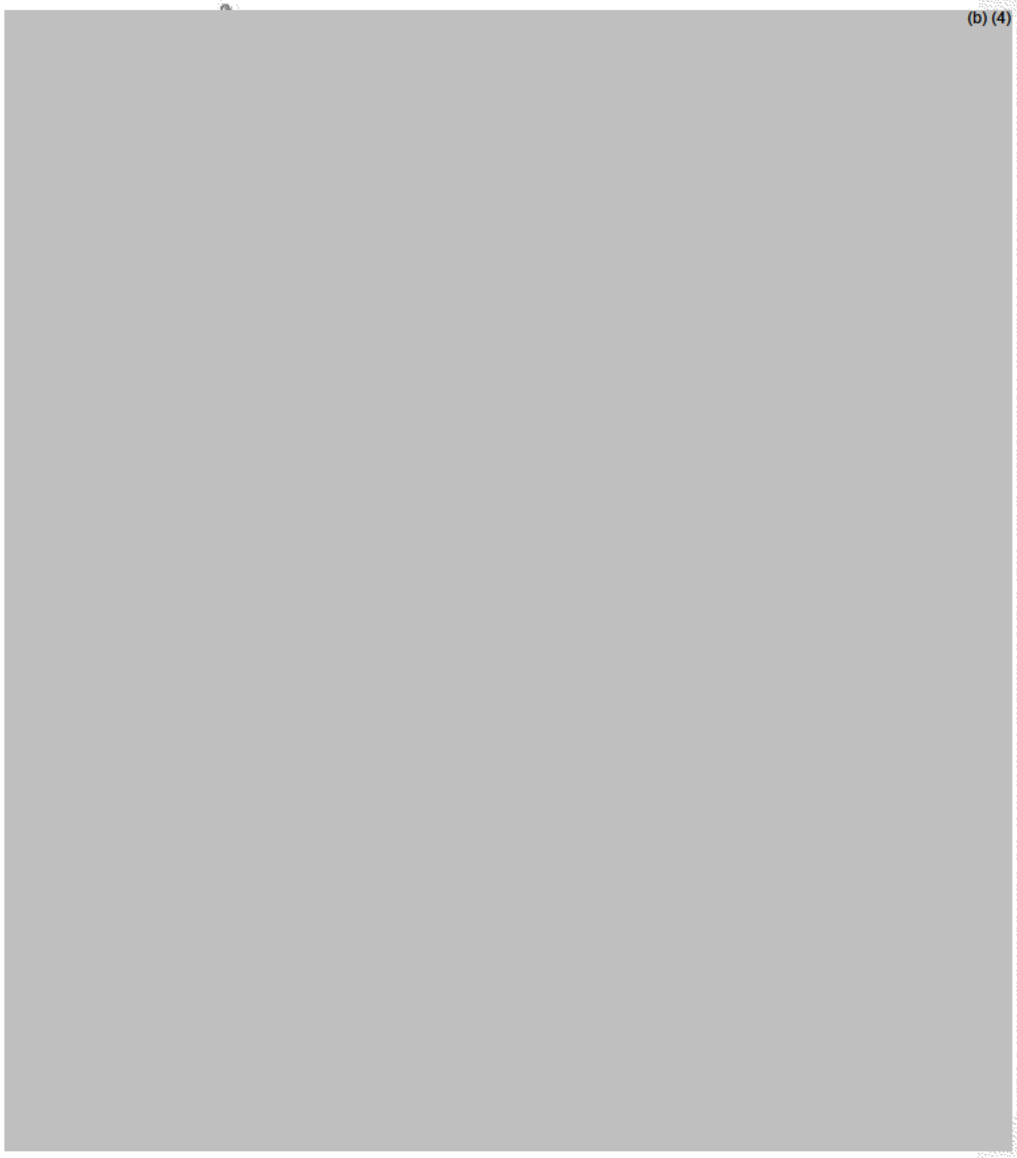
(b) (4)

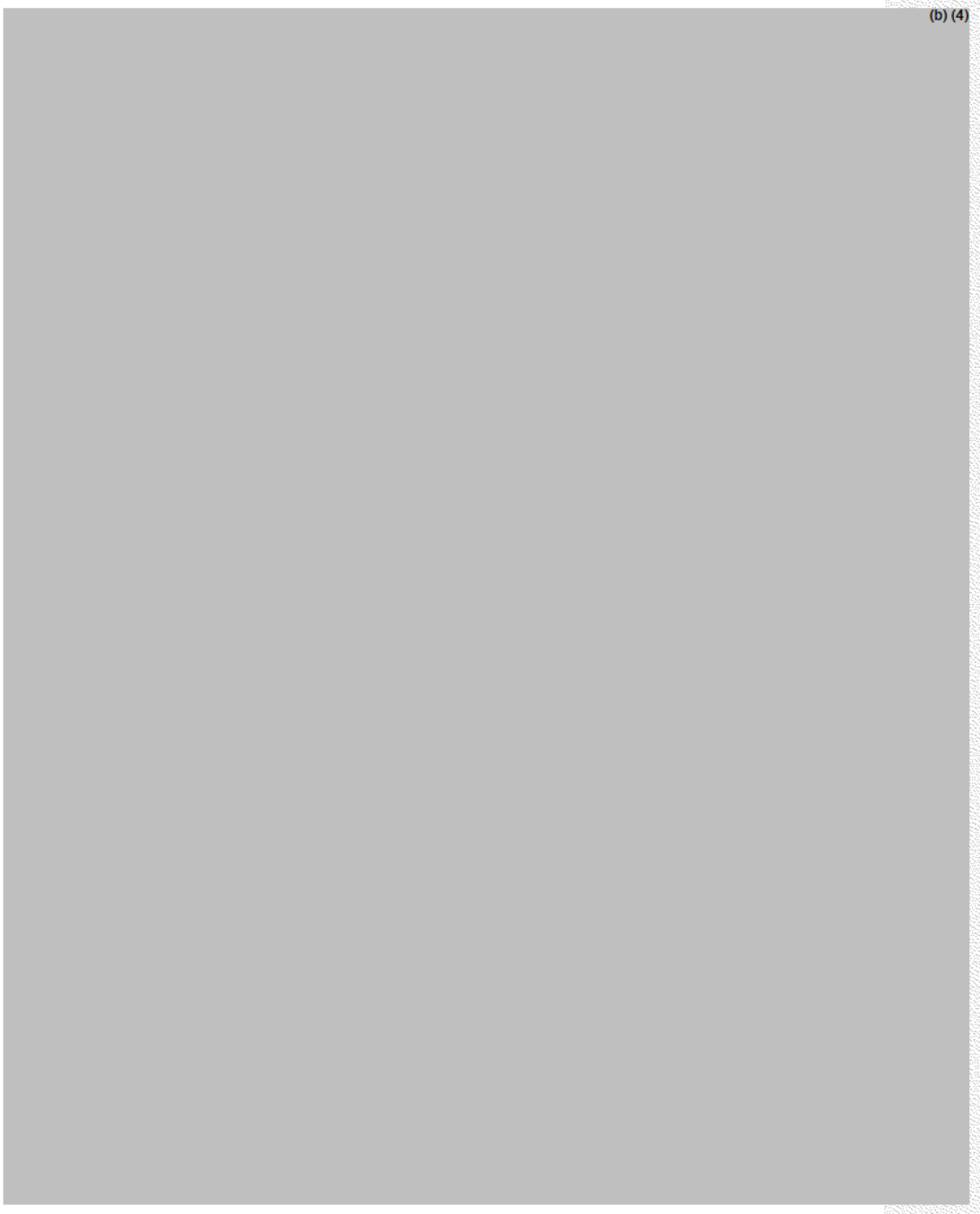

(b) (4)

(b) (4)



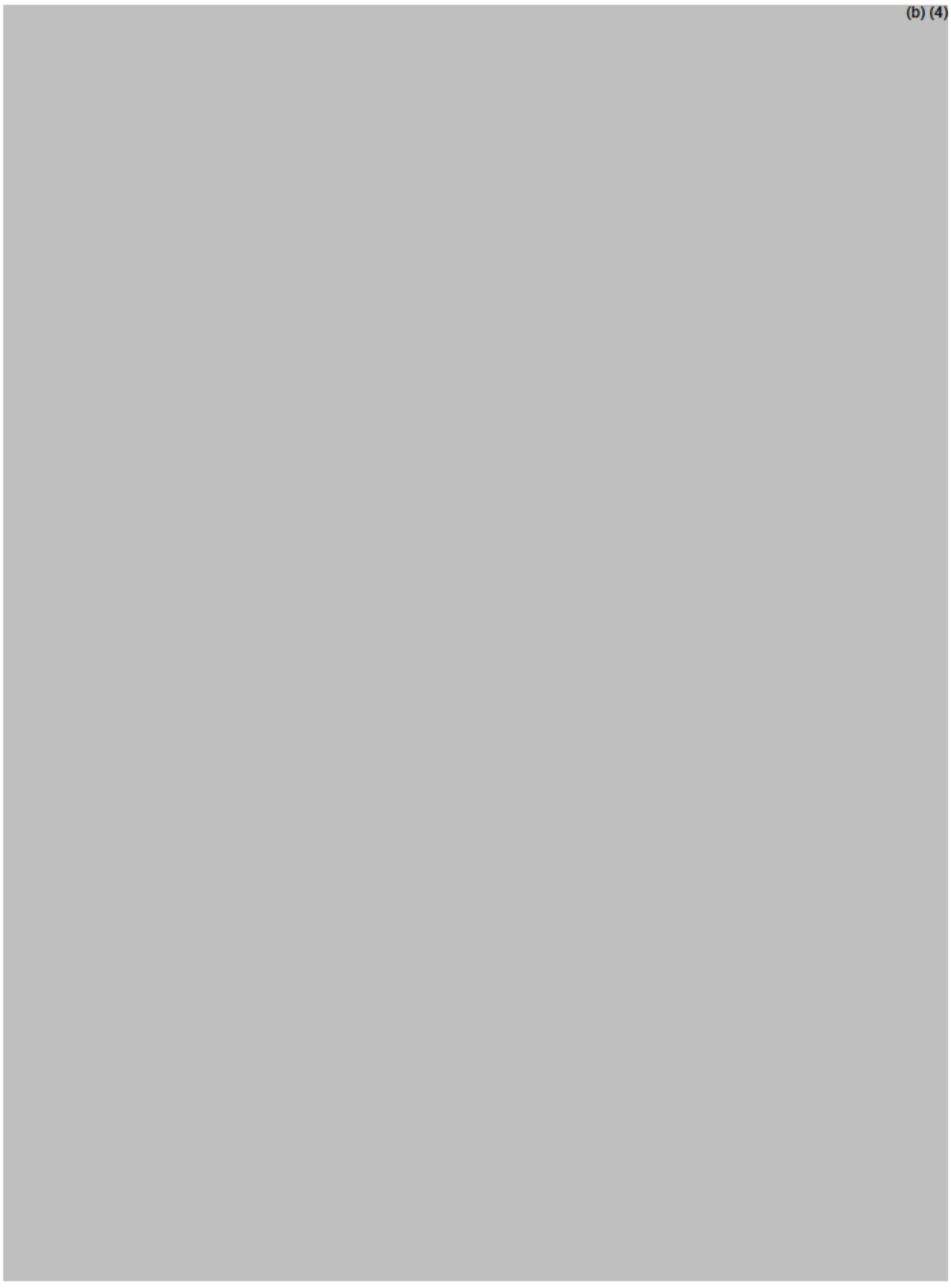

(b) (4)

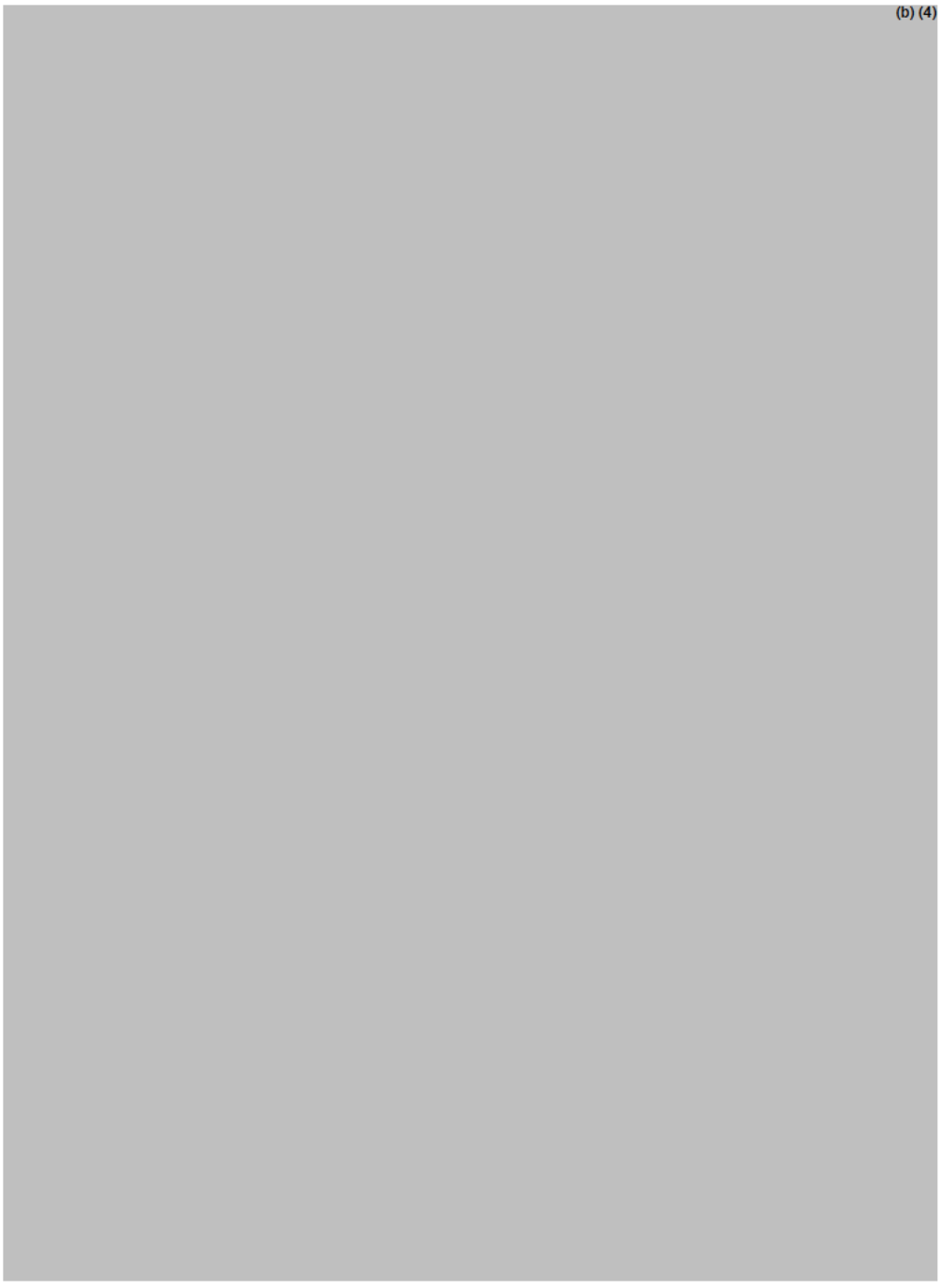

(b) (4)


(b) (4)

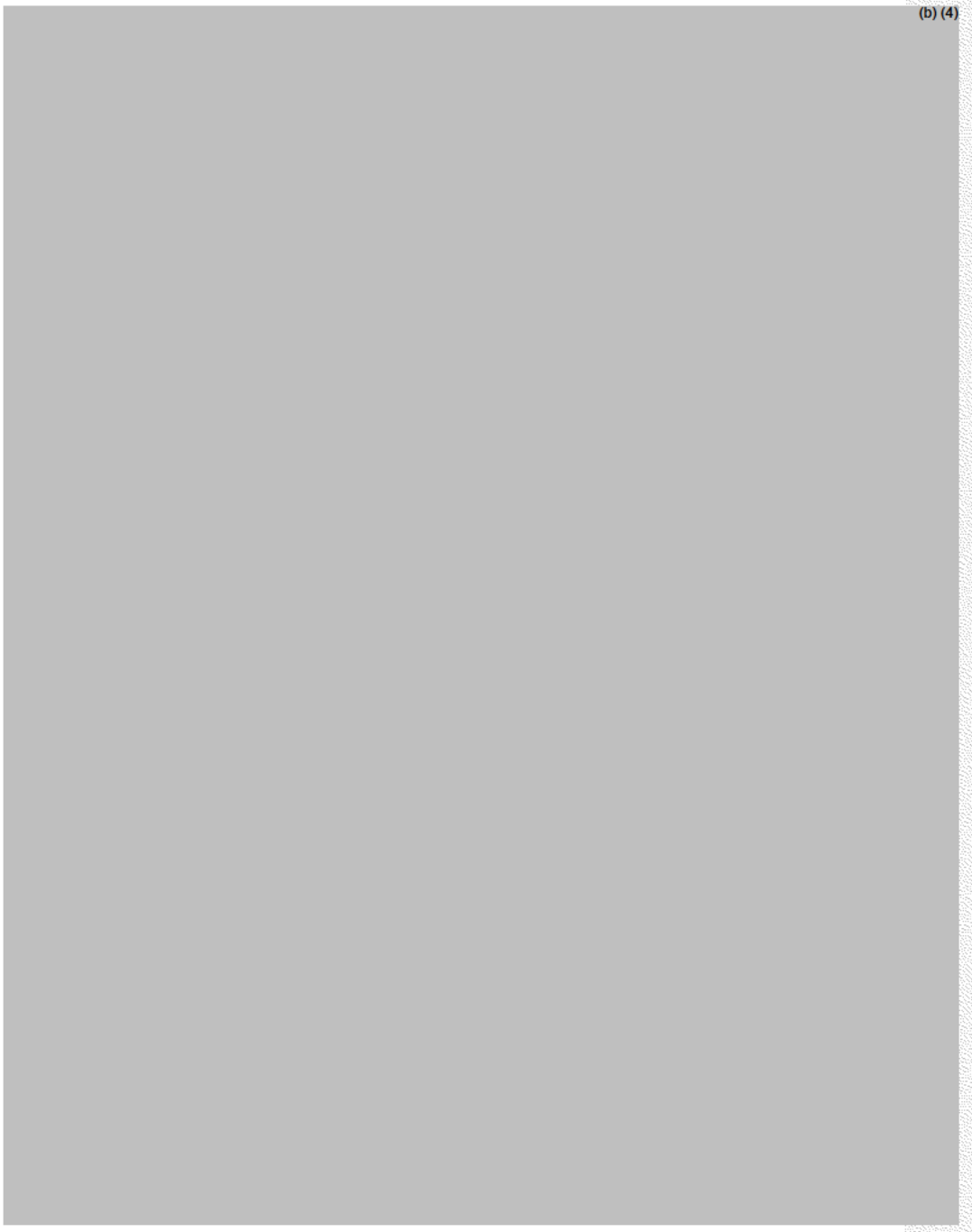

(b) (4)

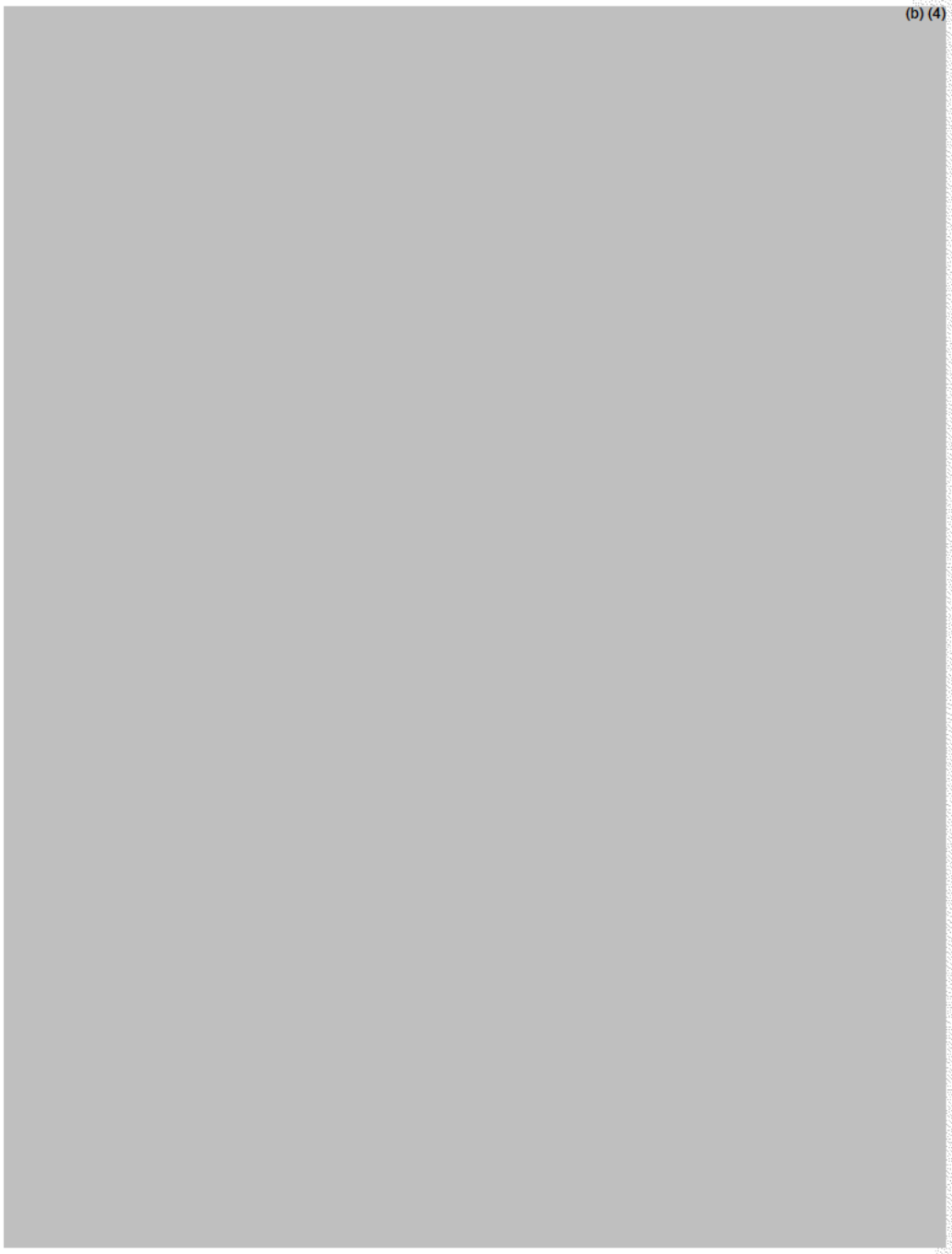
(b) (4)

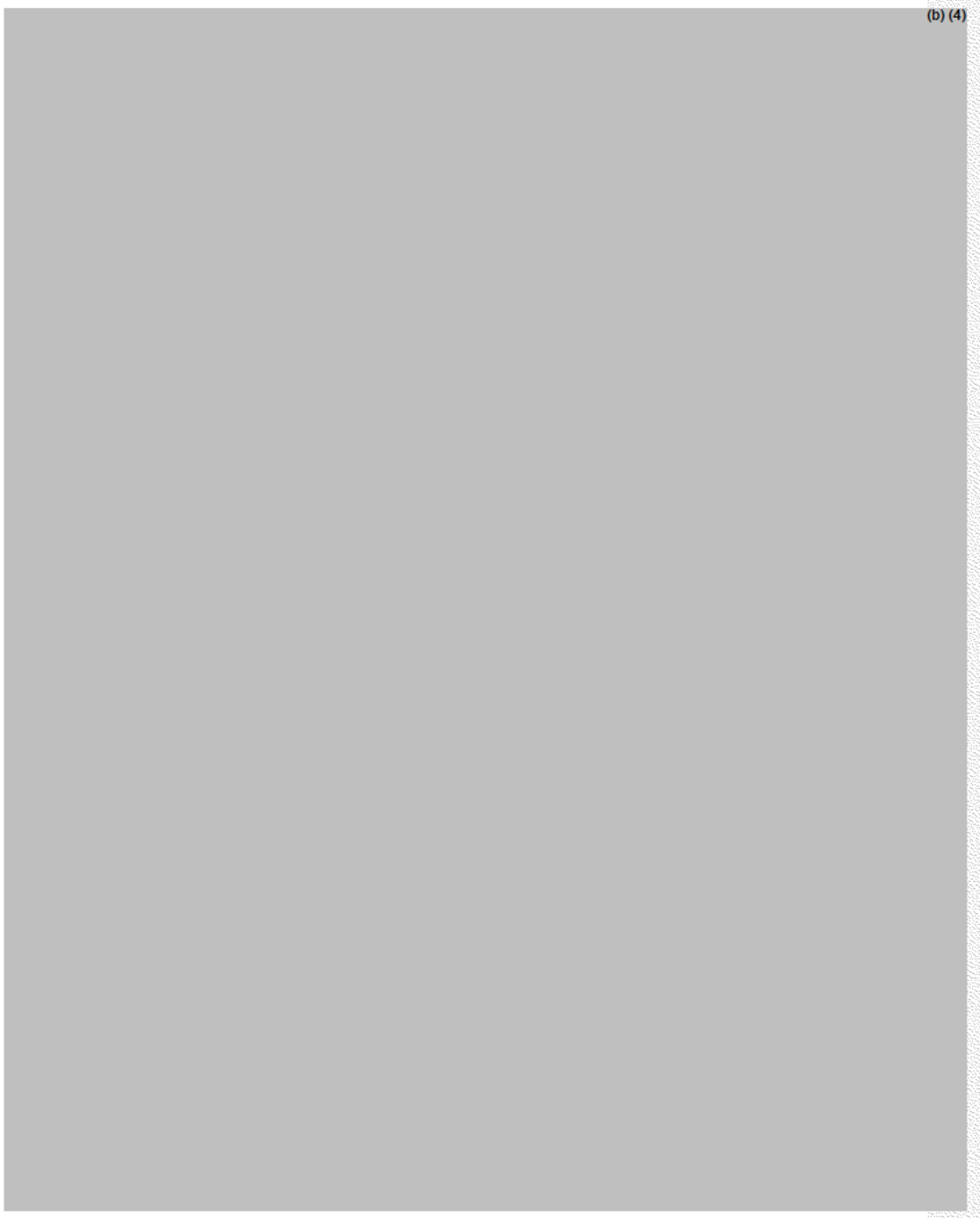


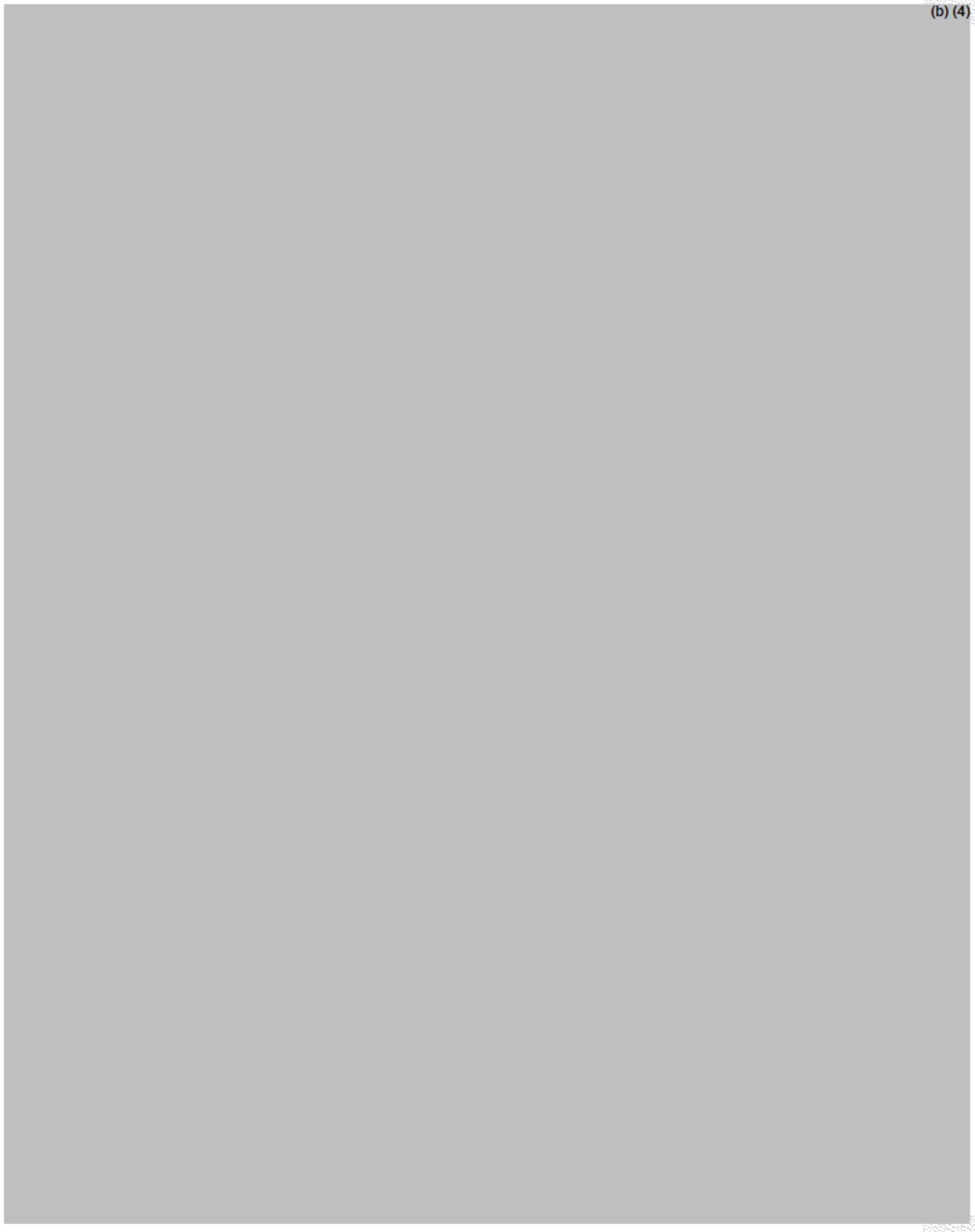

(b) (4)

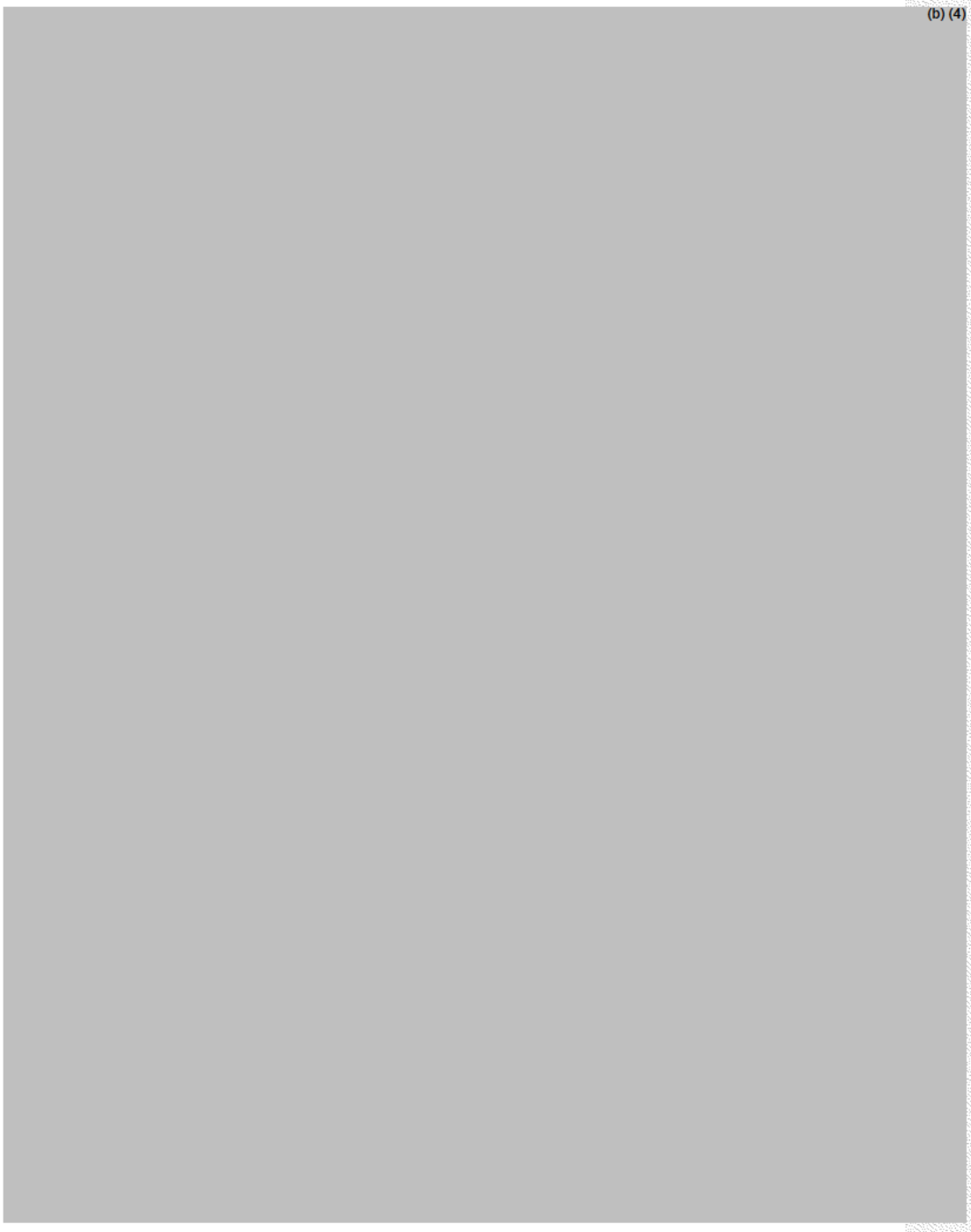
(b) (4)

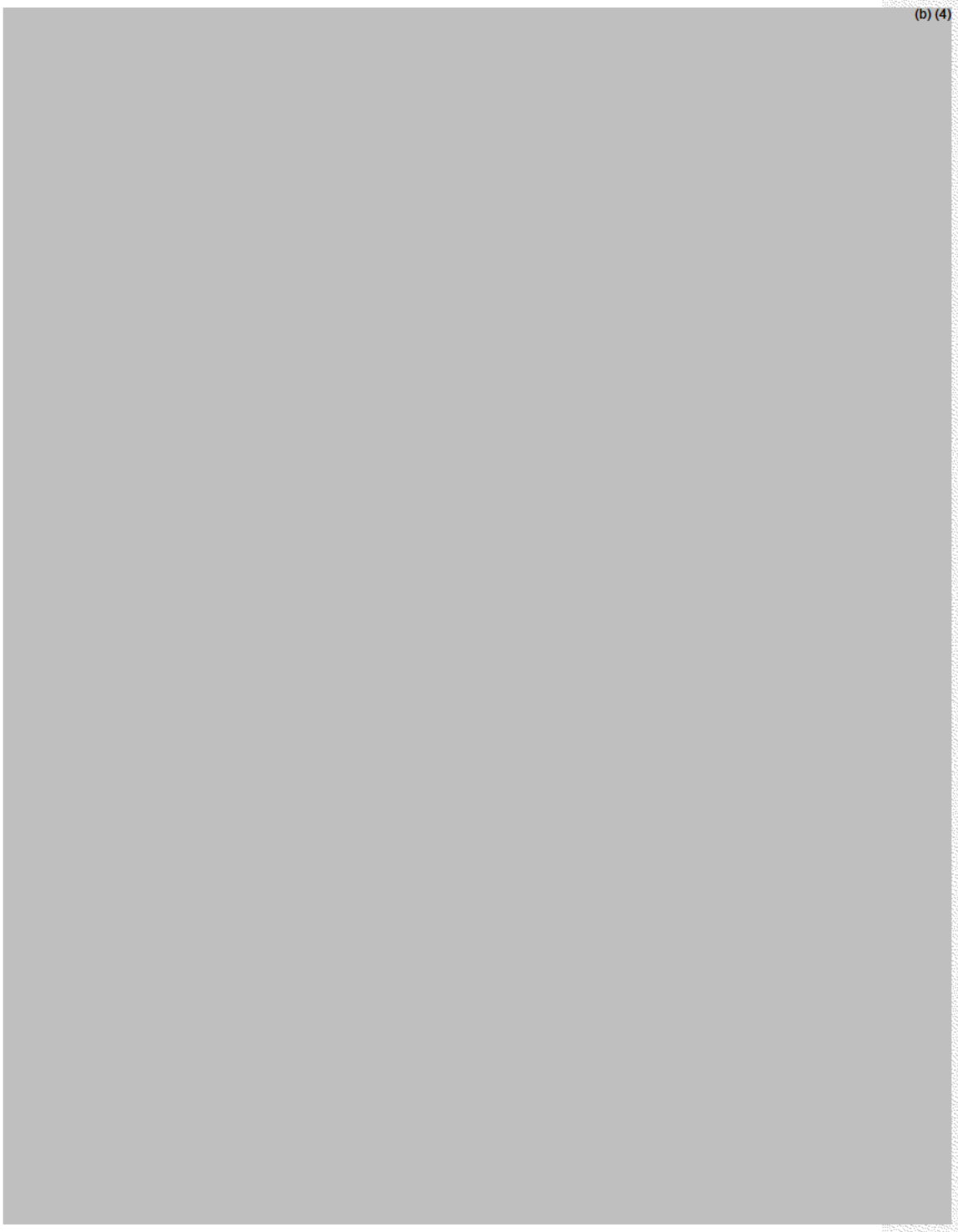


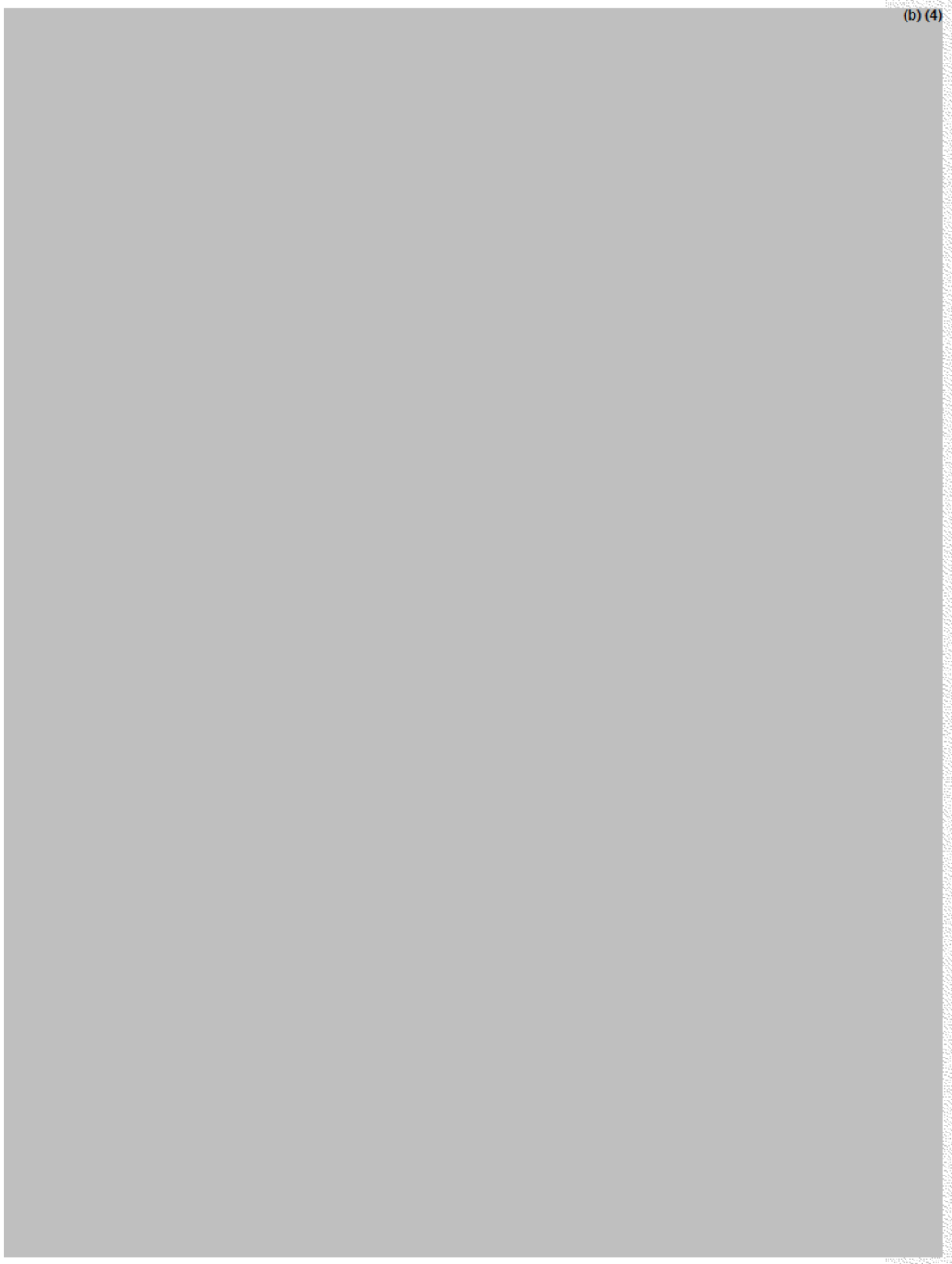

(b) (4)


(b) (4)

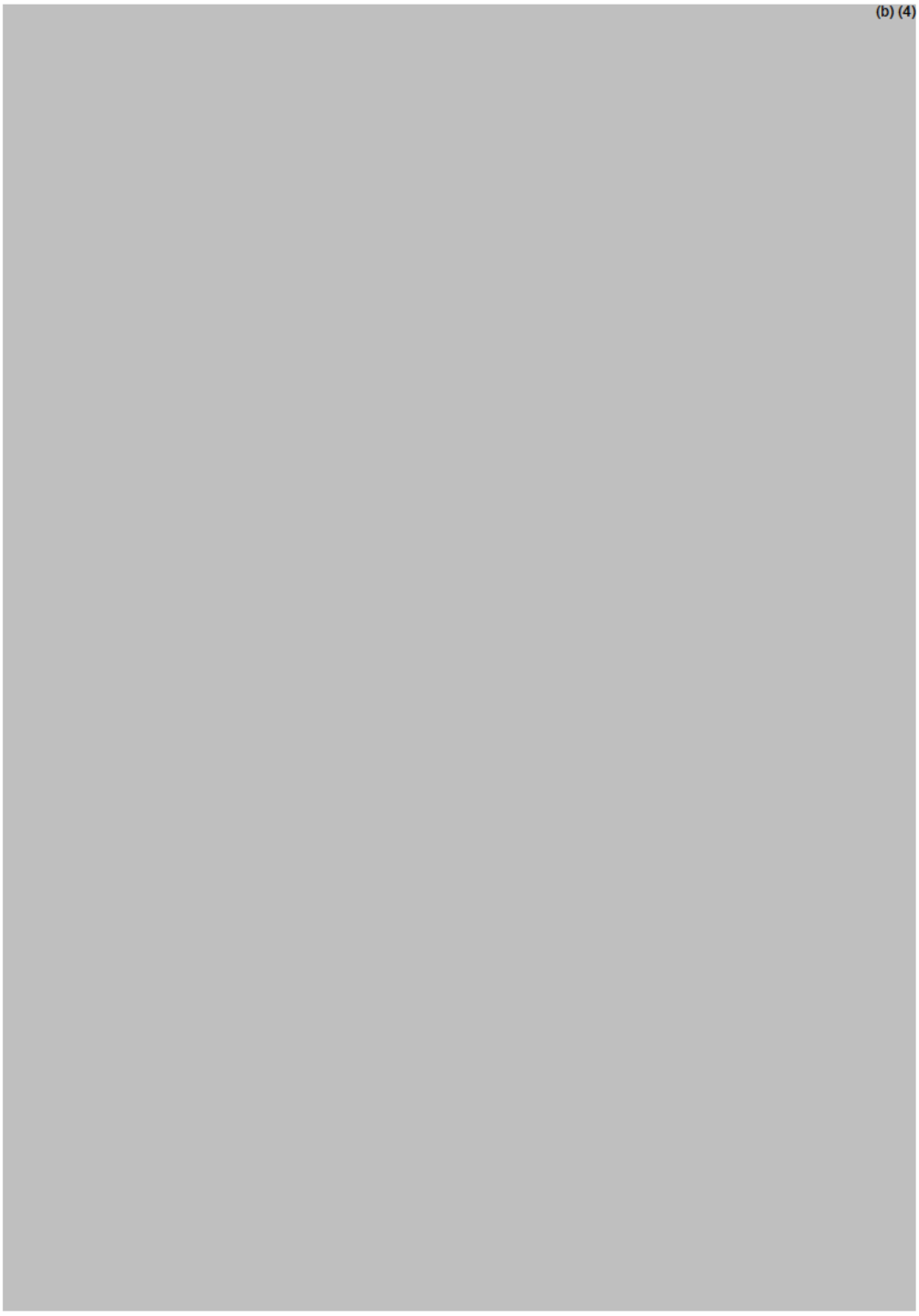

(b) (4)

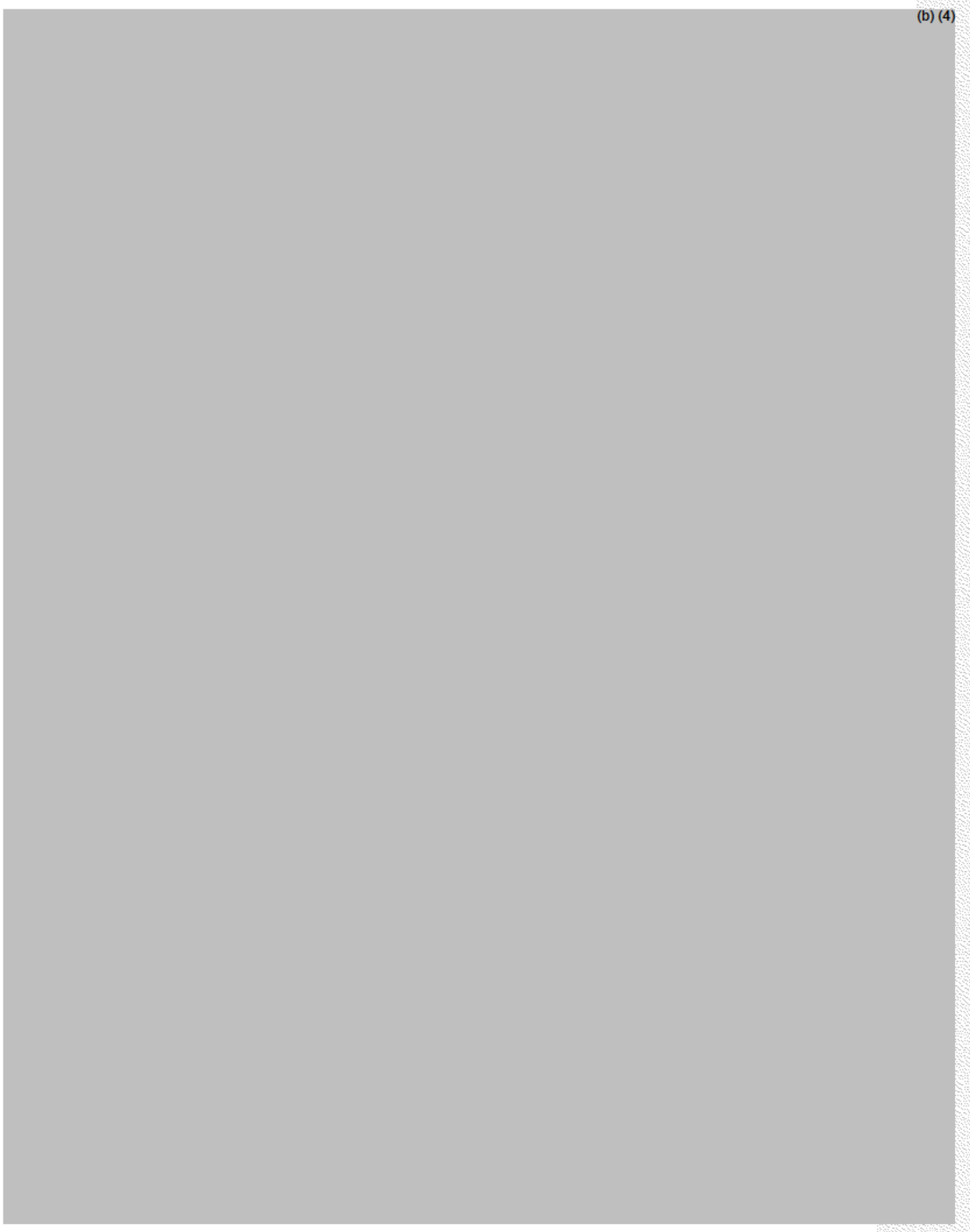

(b) (4)


(b) (4)


(b) (4)

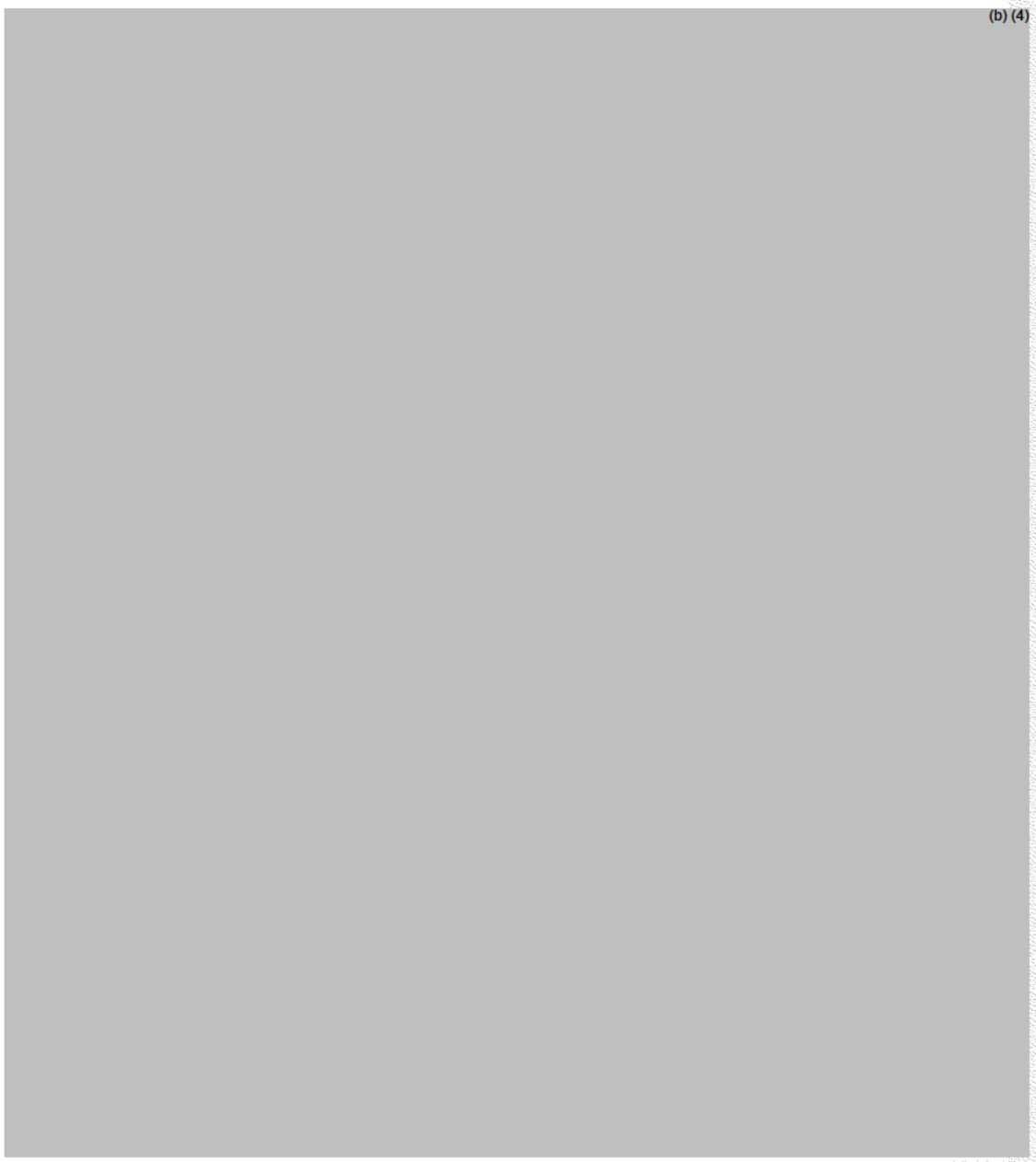
(b) (4)

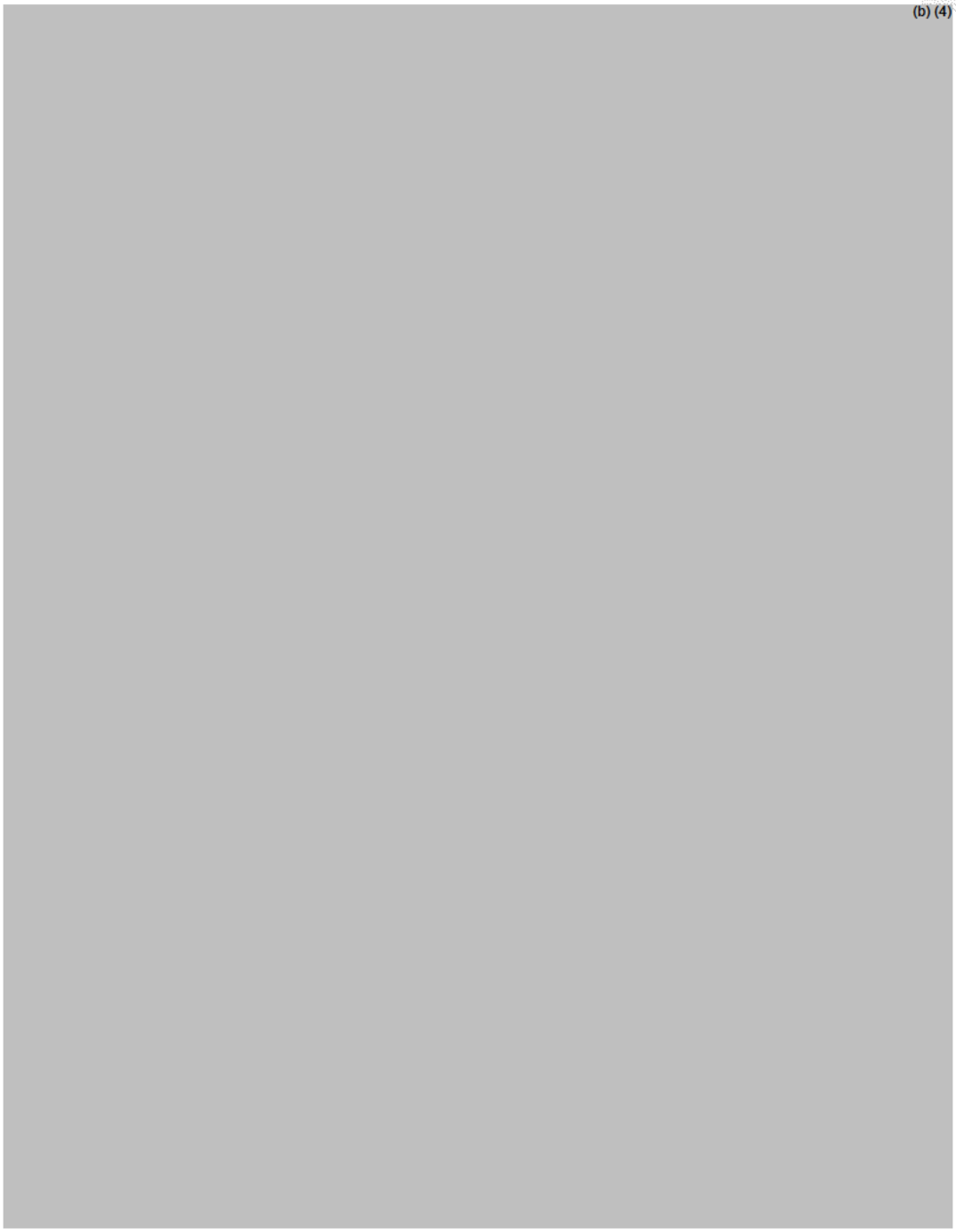



(b) (4)

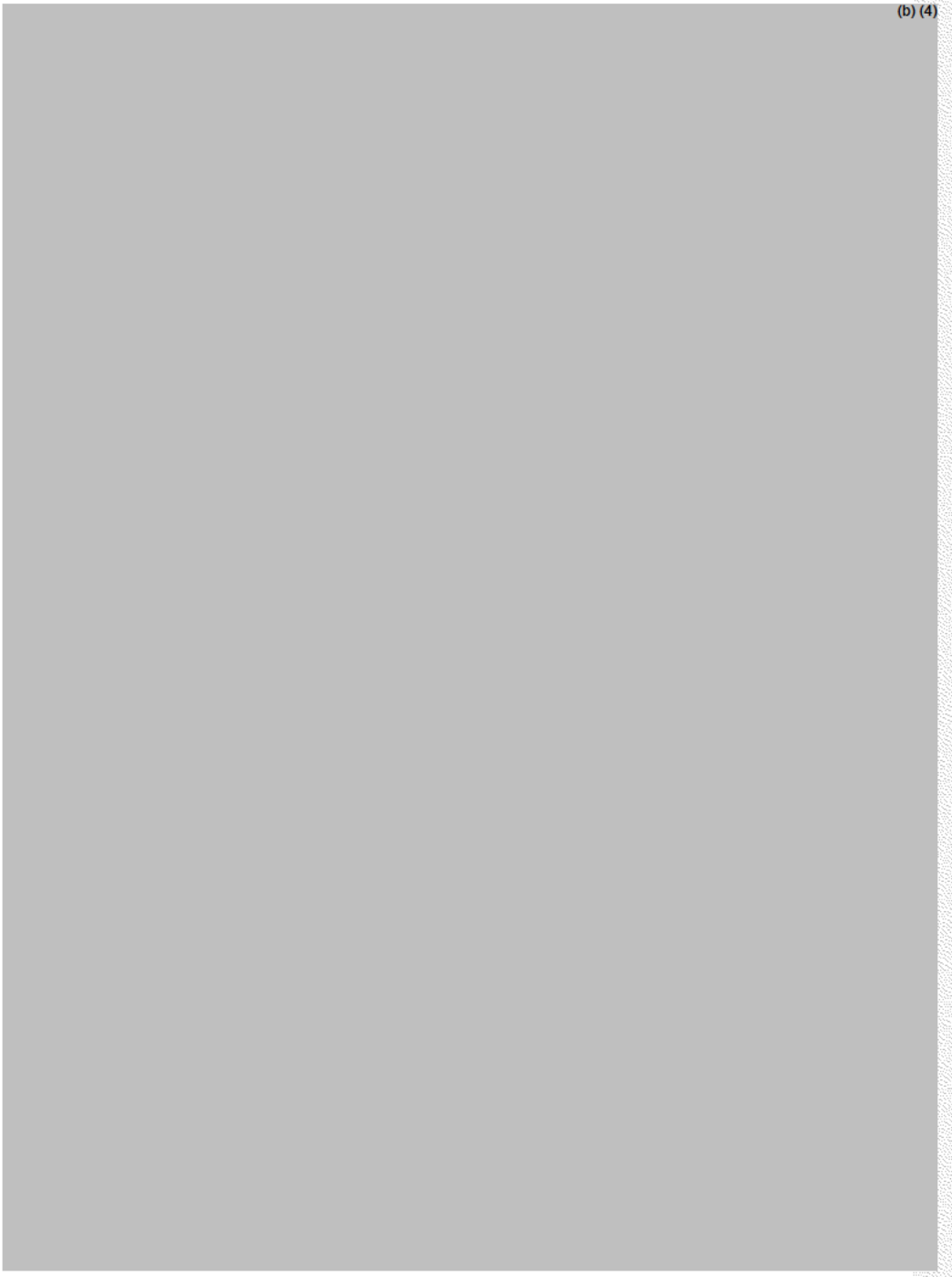

(b) (4)

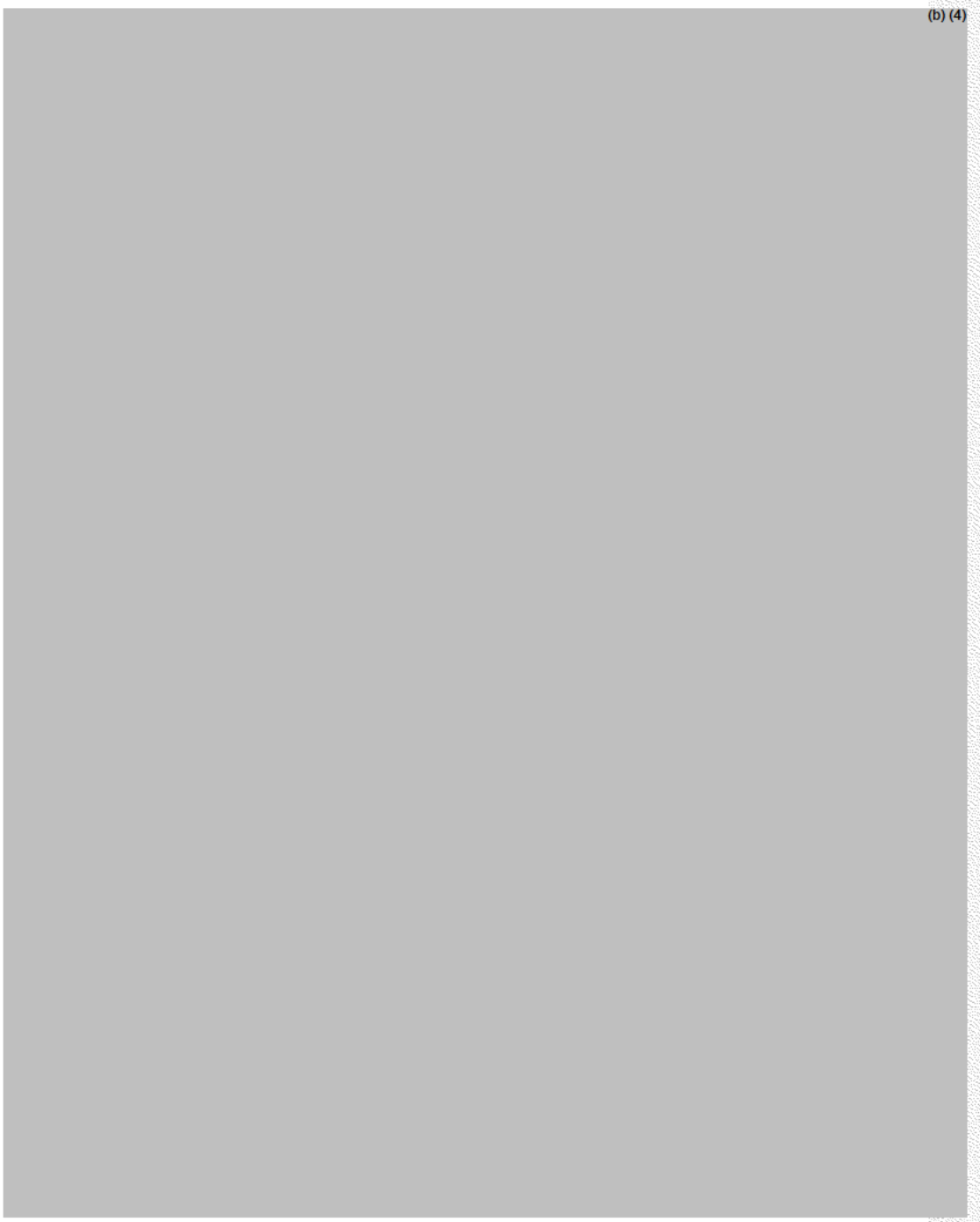

(b) (4)

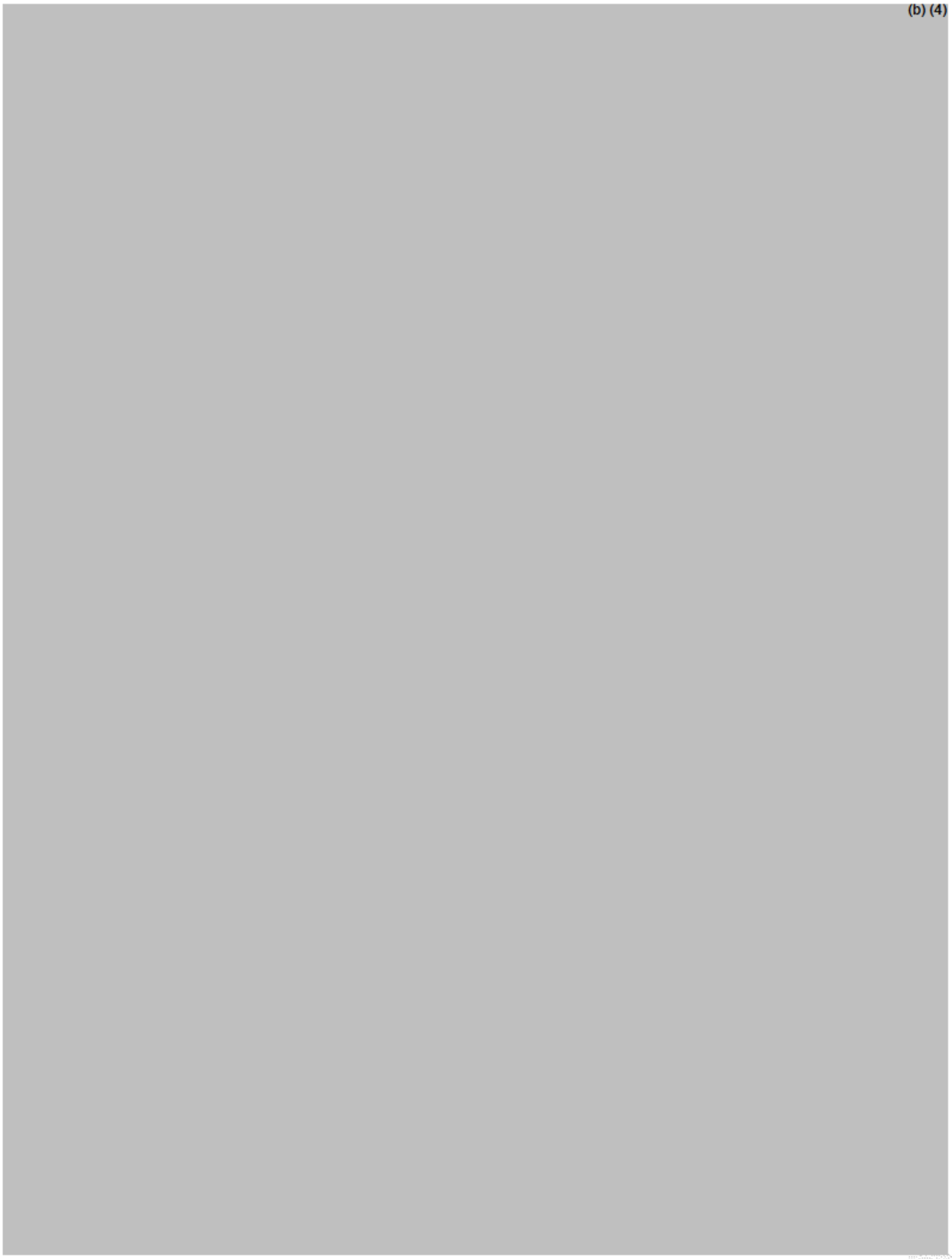

(b) (4)


(b) (4)

(b) (4)




(b) (4)


(b) (4)


(b) (4)

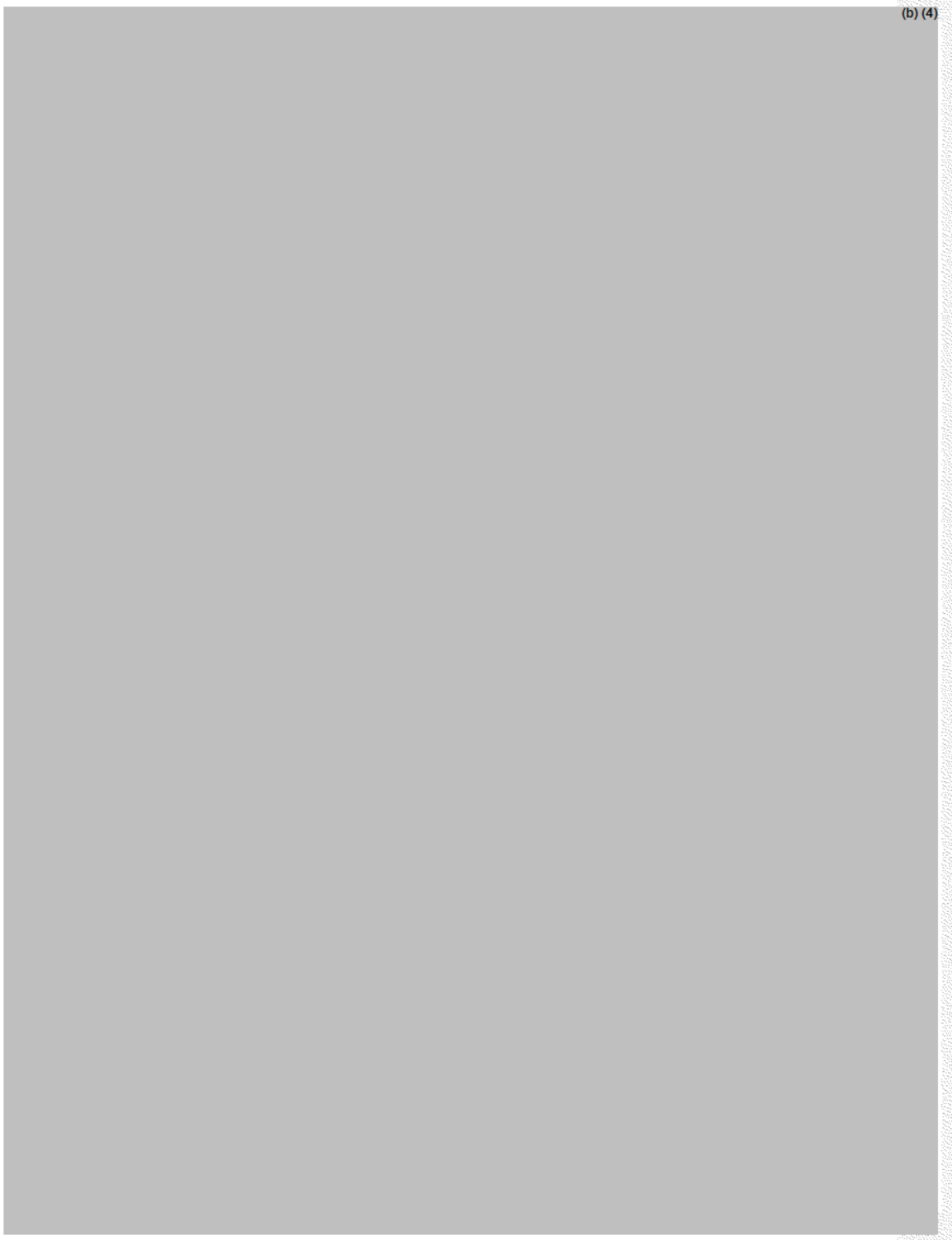
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SUPPRELIN® LA safely and effectively. See full prescribing information for SUPPRELIN LA.

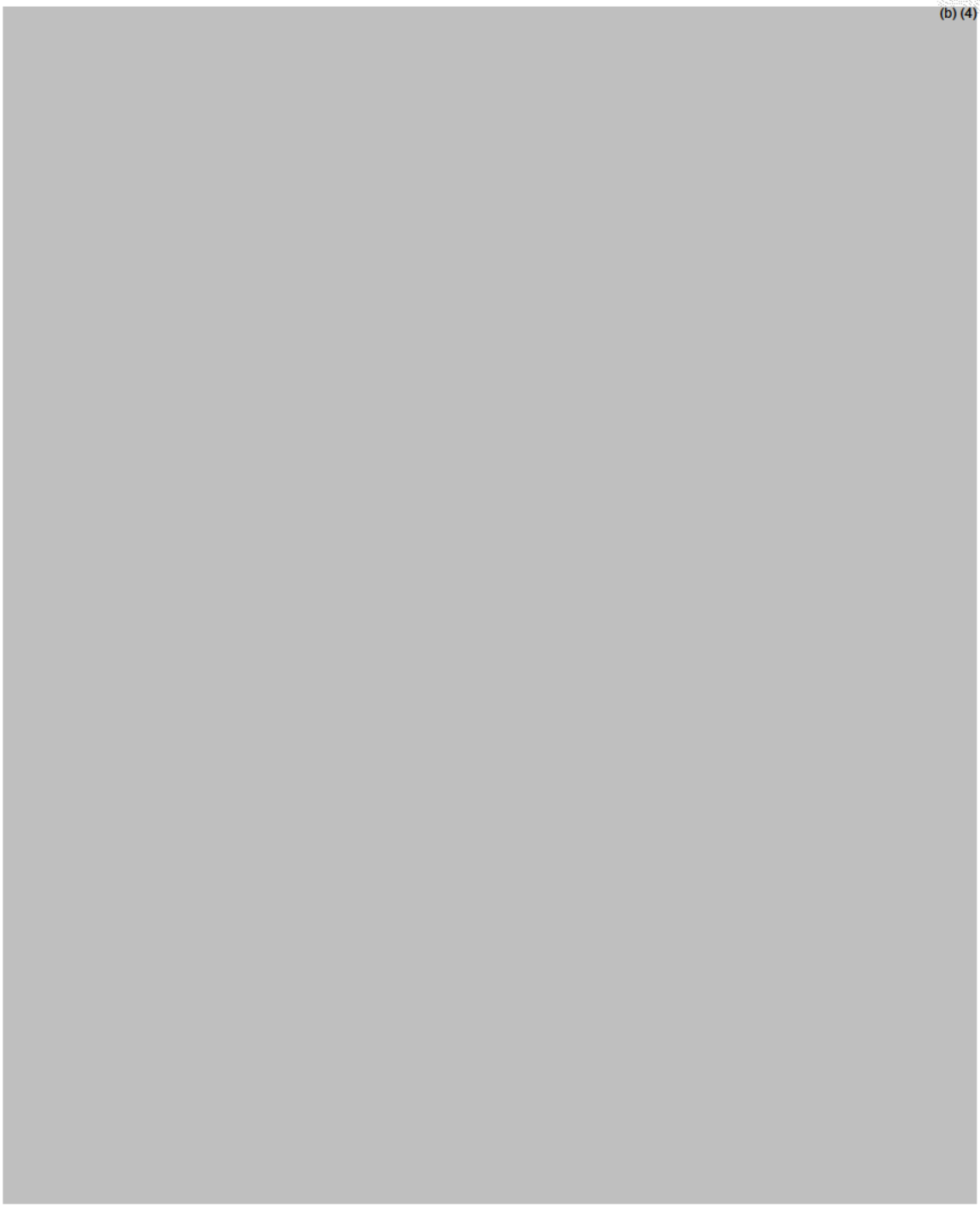
(b) (4)

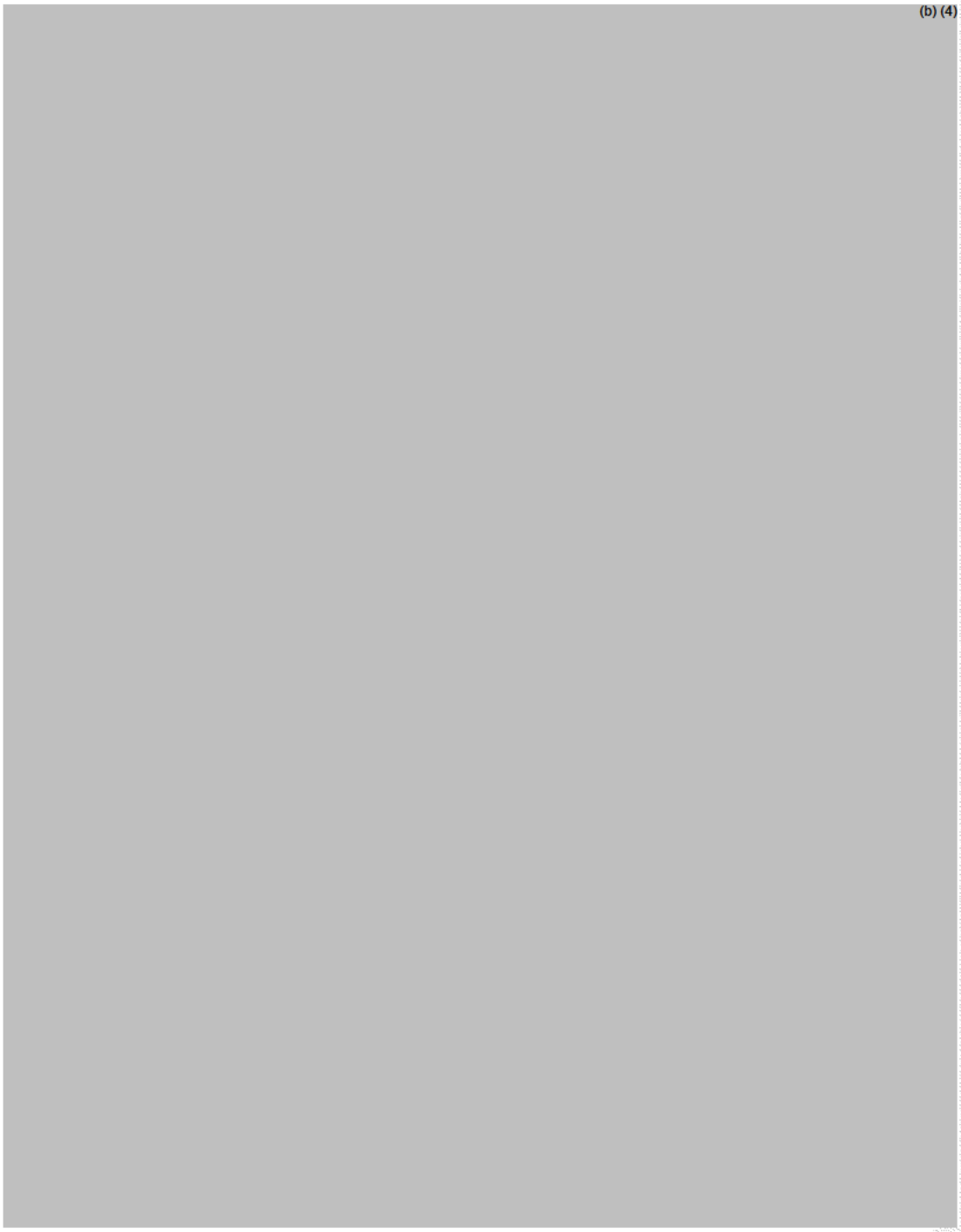
(b) (4)

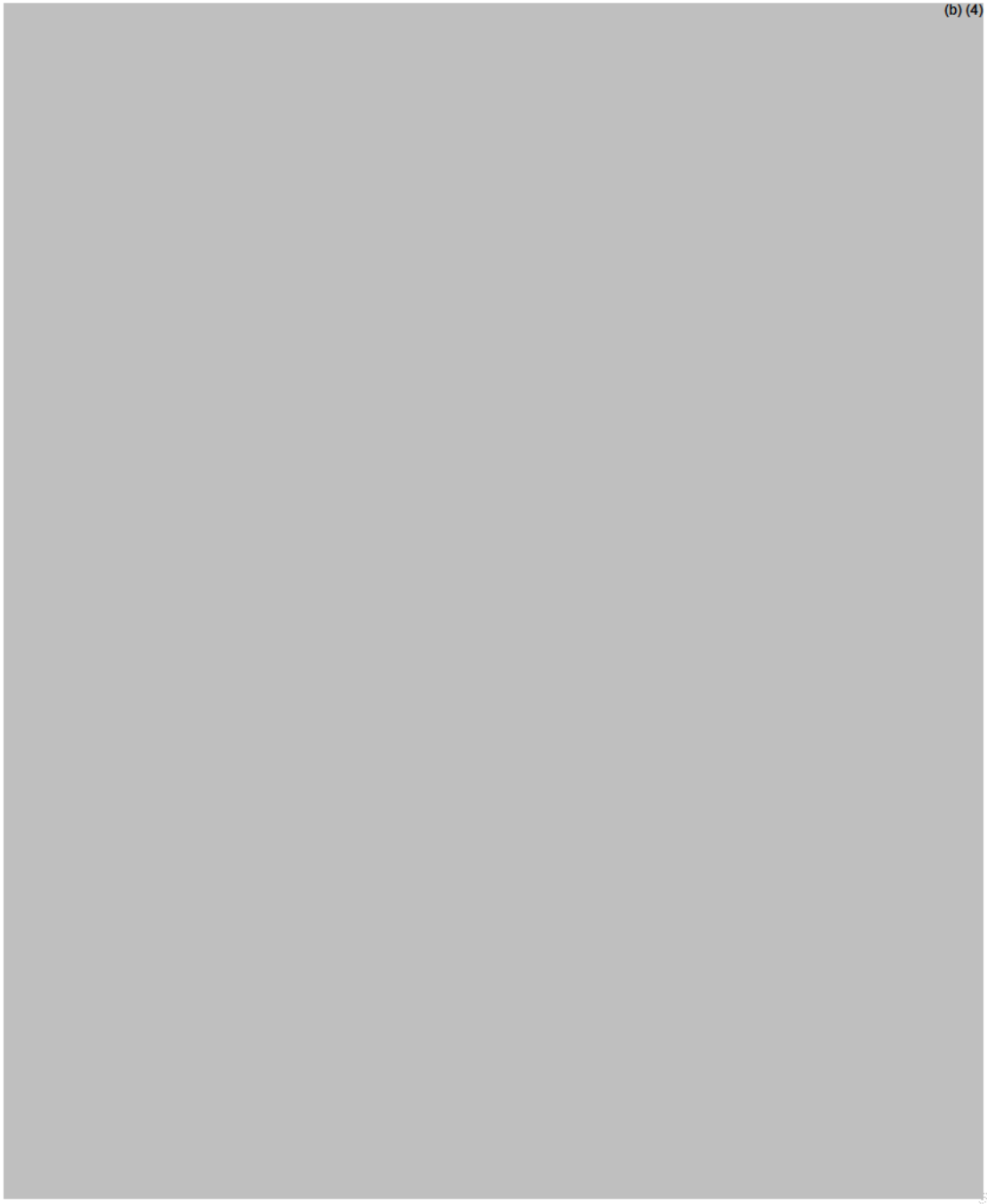
[TOC \o "2-2" \n \h \z \t "Heading 1,1"]

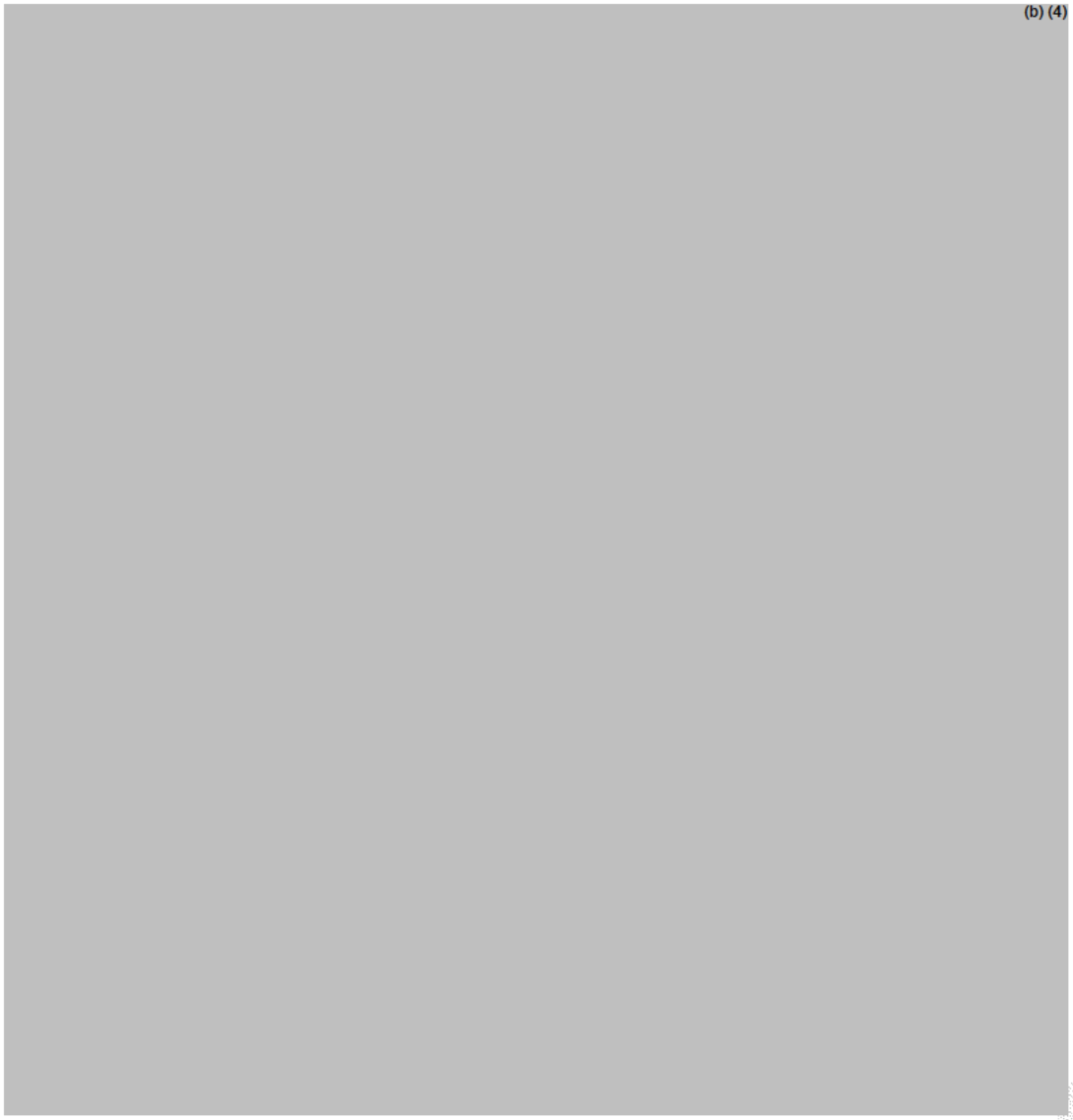
* Sections or subsections omitted from the full prescribing information are not listed

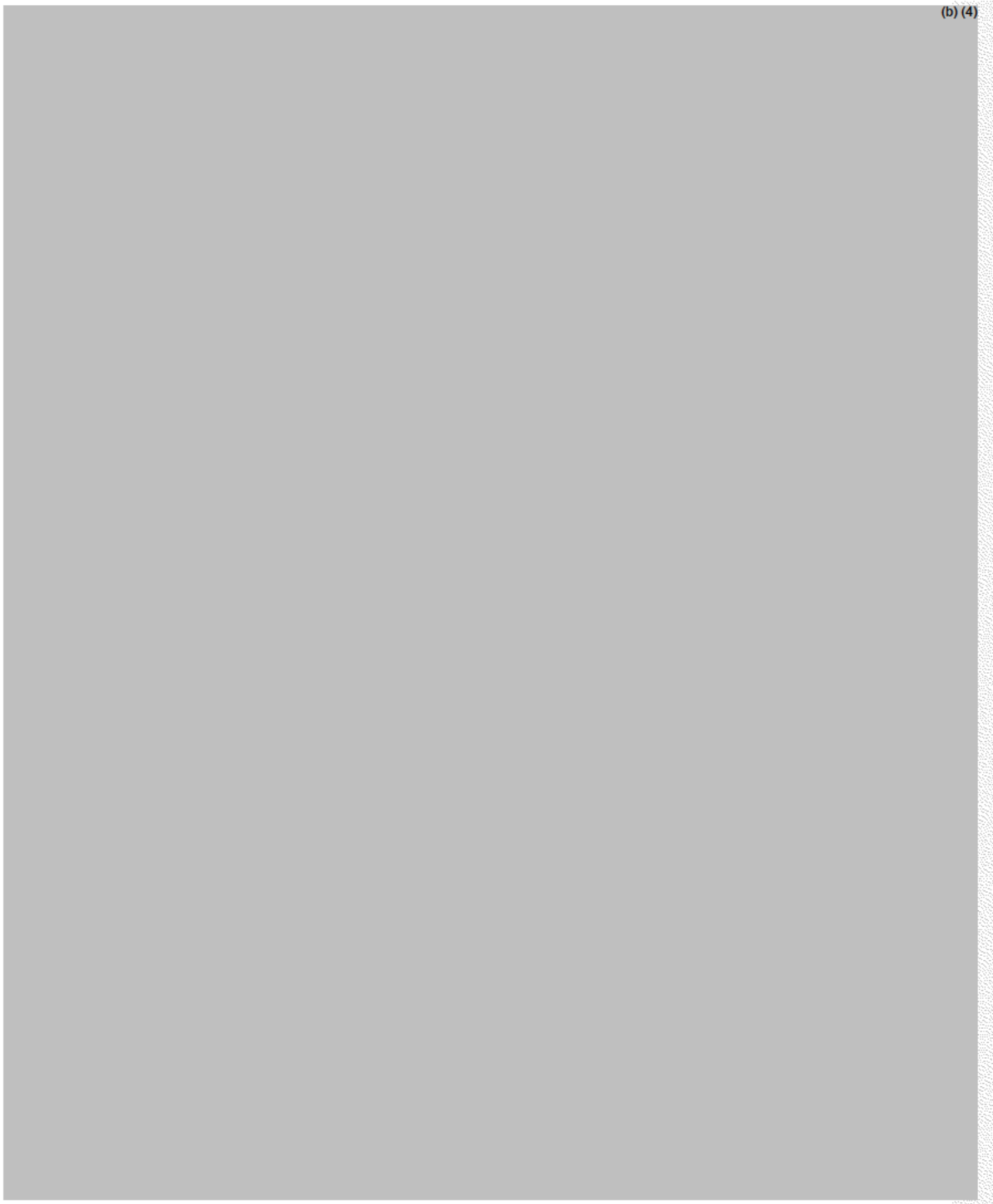

(b) (4)

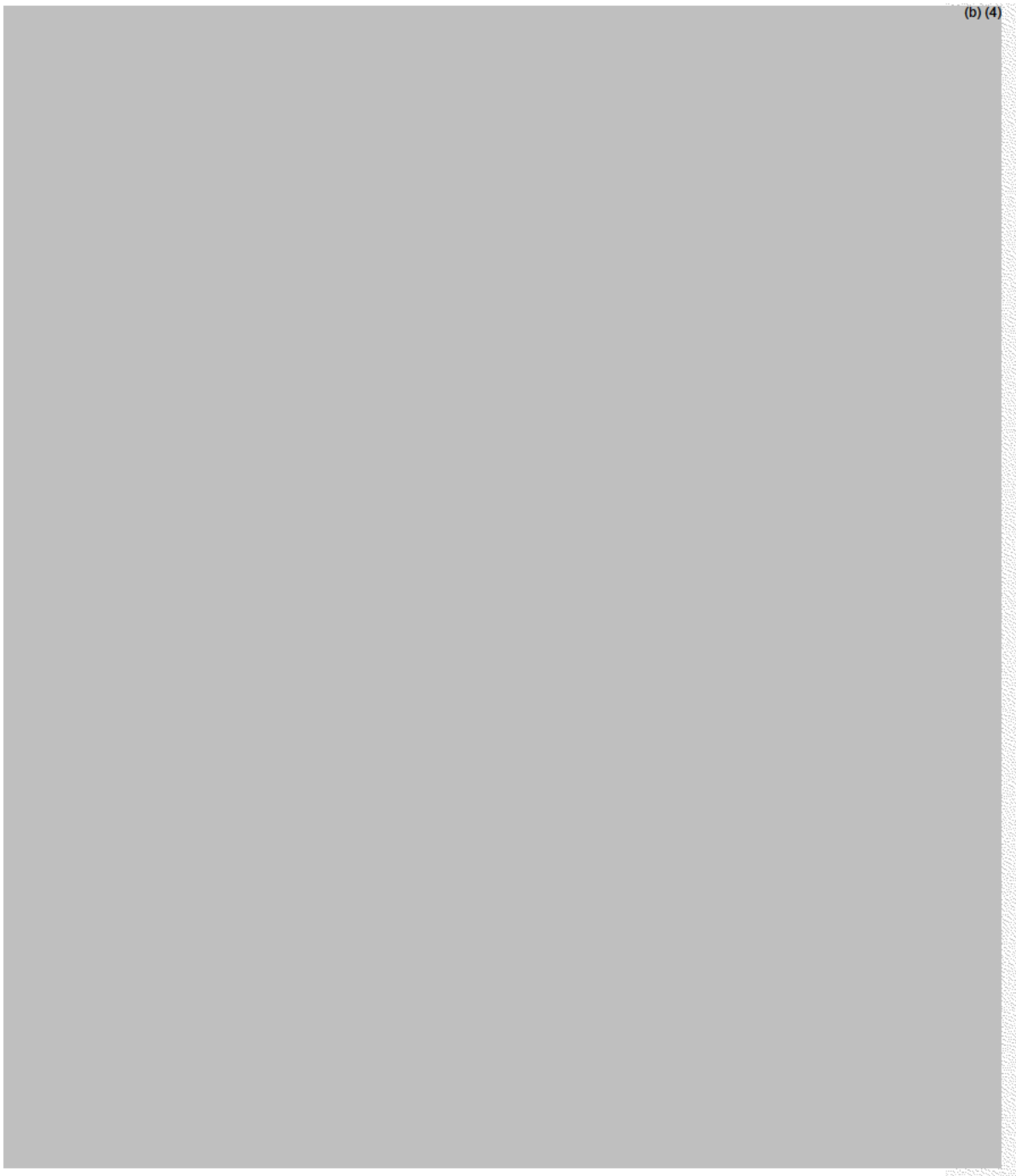

(b) (4)

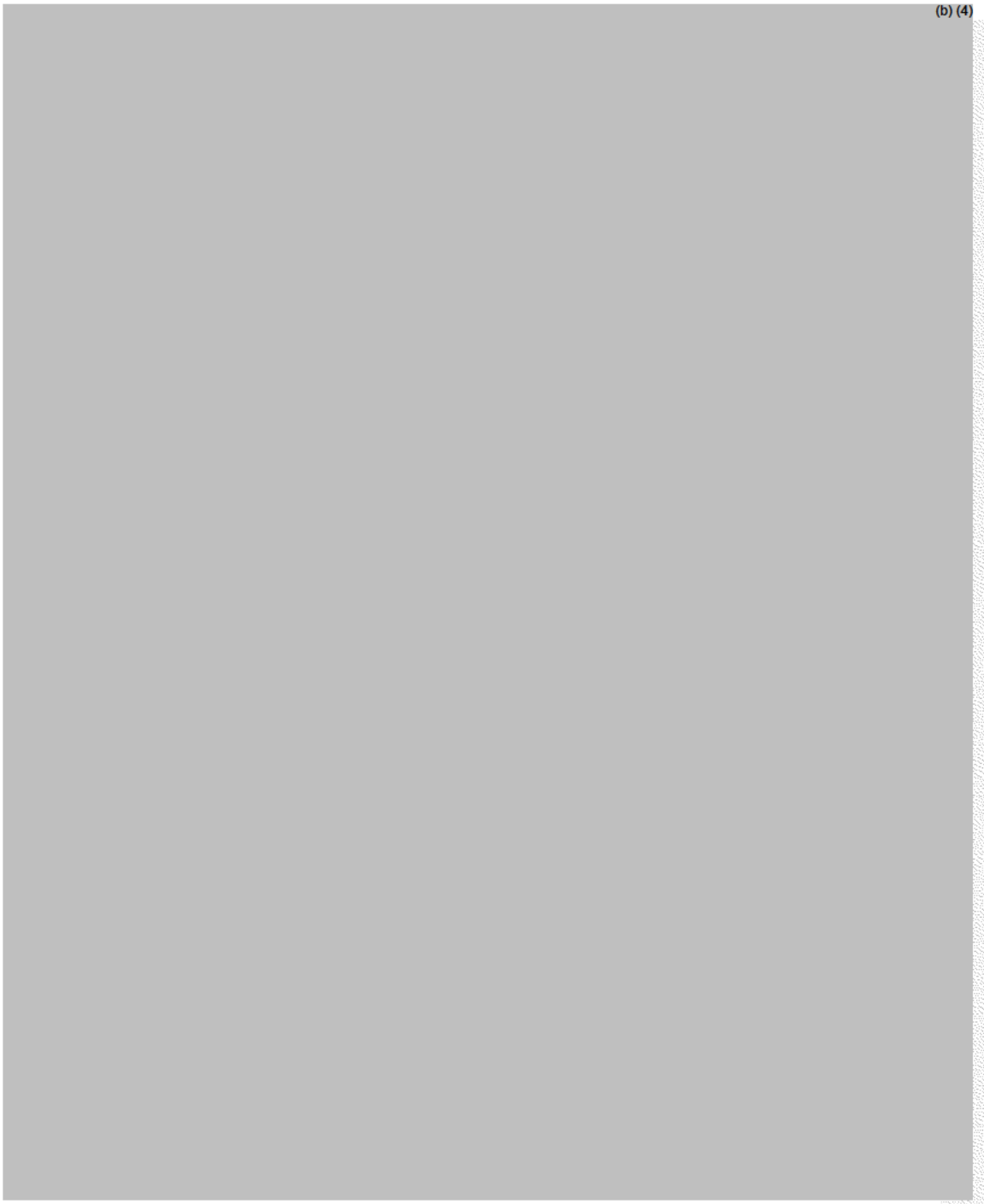

(b) (4)

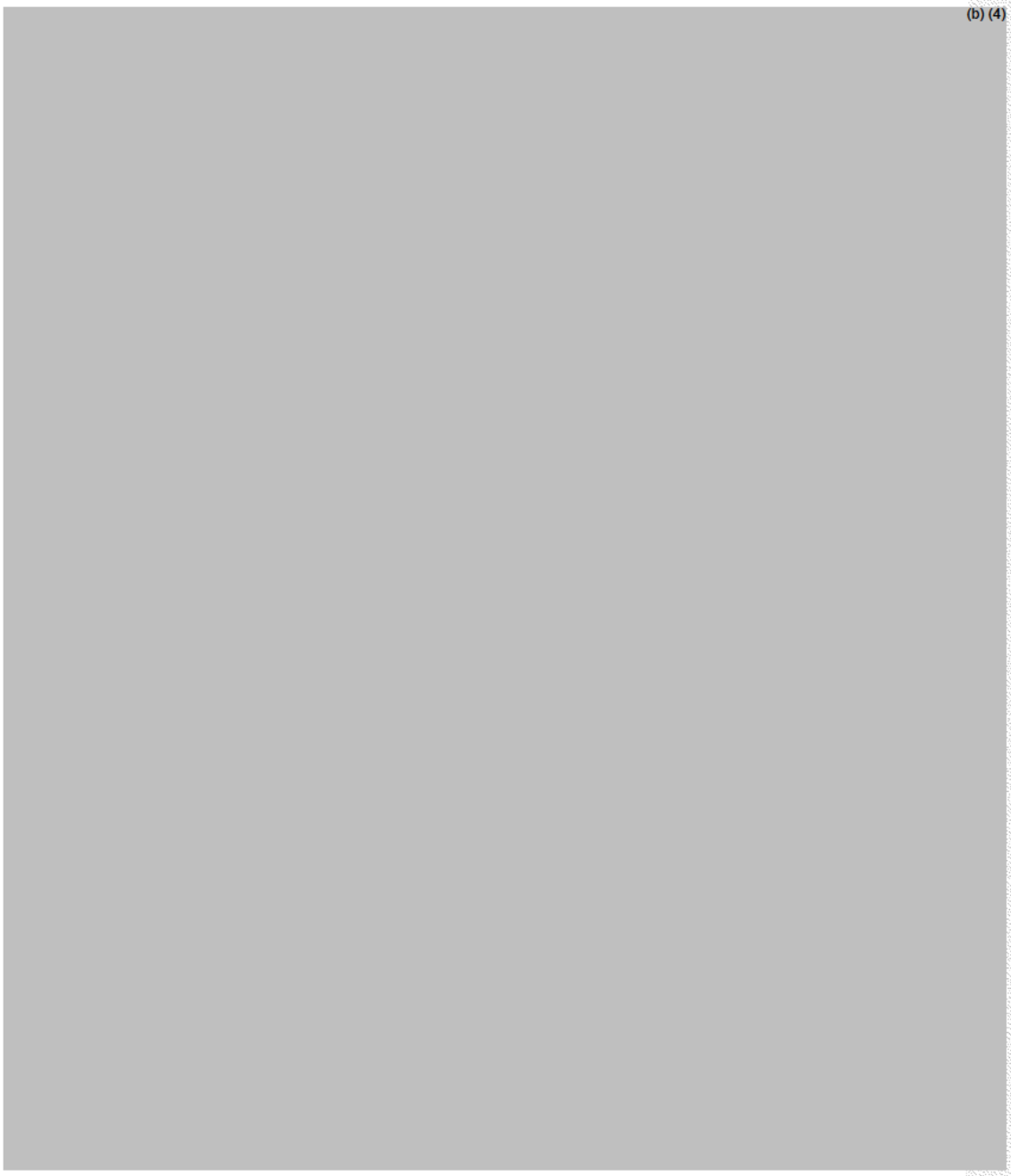

(b) (4)

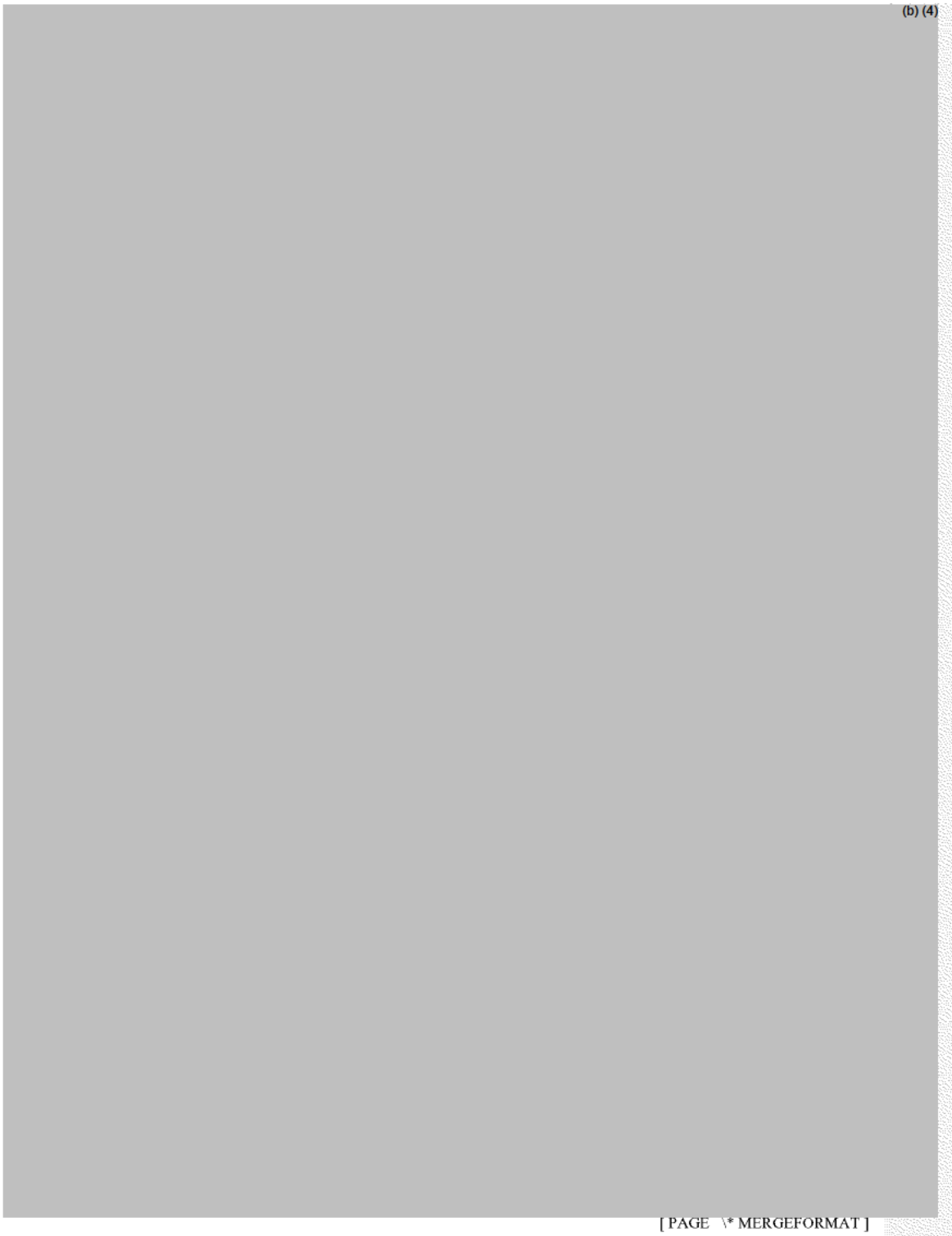

(b) (4)


(b) (4)

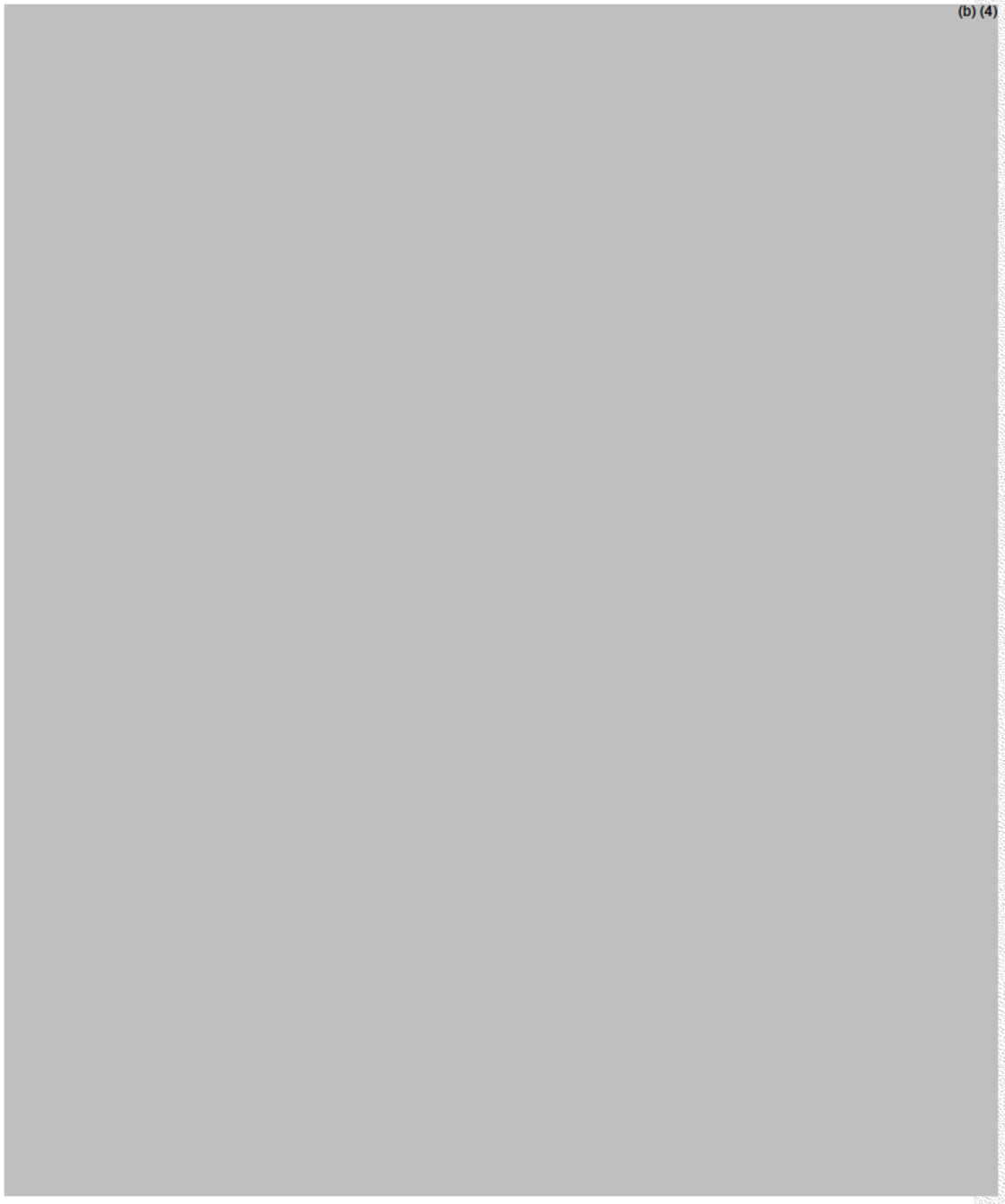

(b) (4)


(b) (4)


(b) (4)


(b) (4)

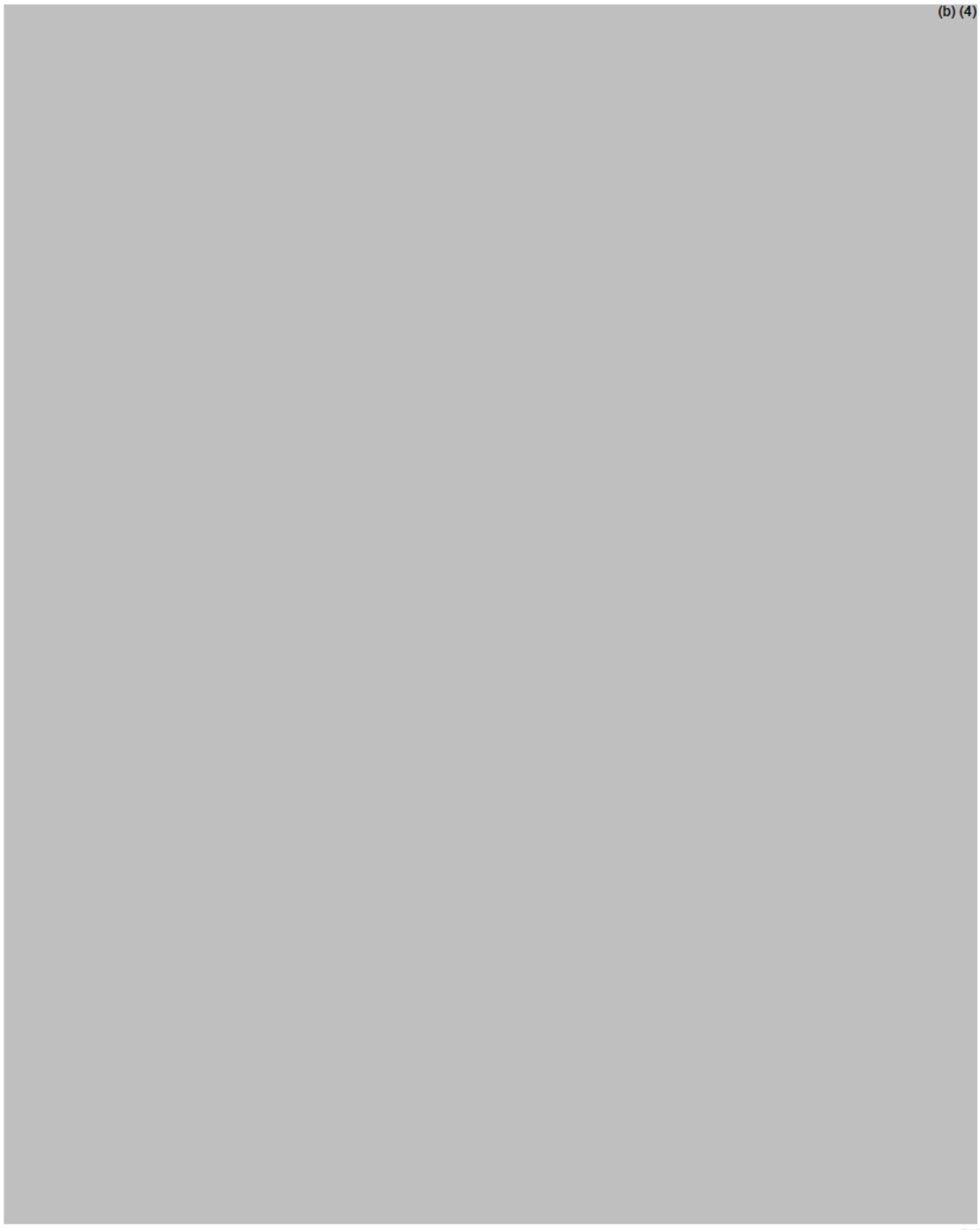
(b) (4)



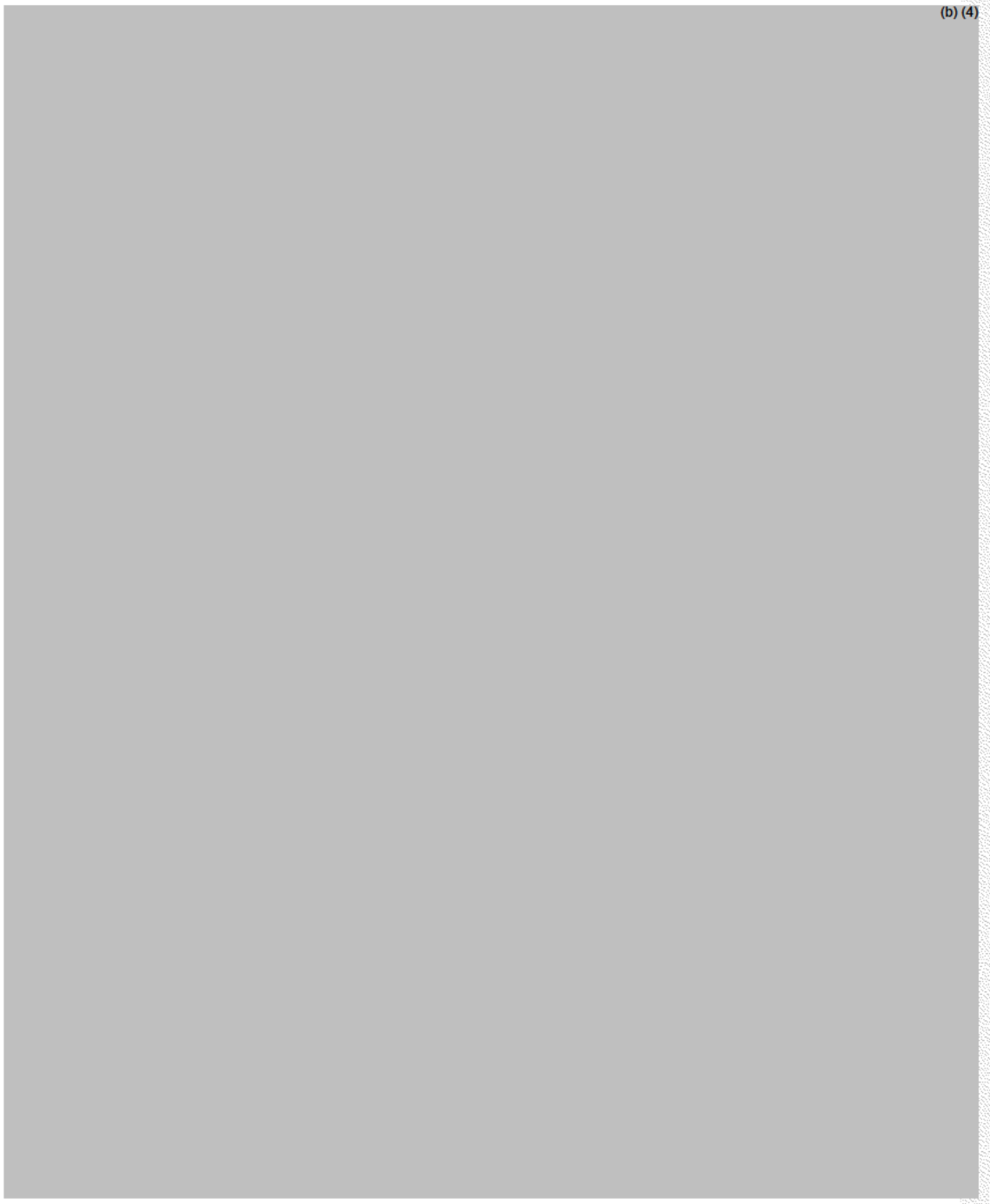
[PAGE * MERGEFORMAT]

(b) (4)

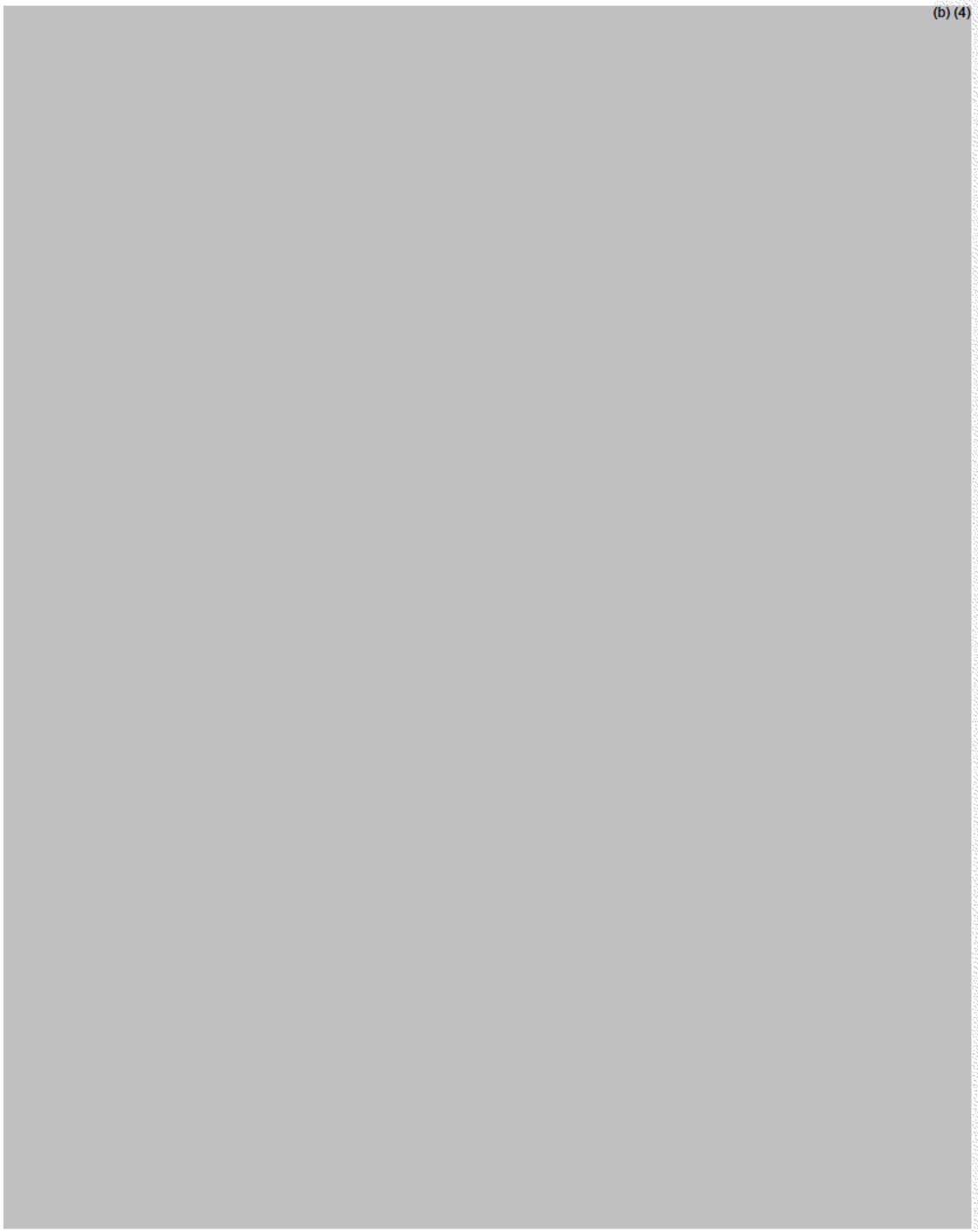
[PAGE * MERGEFORMAT]



[PAGE * MERGEFORMAT]


(b) (4)

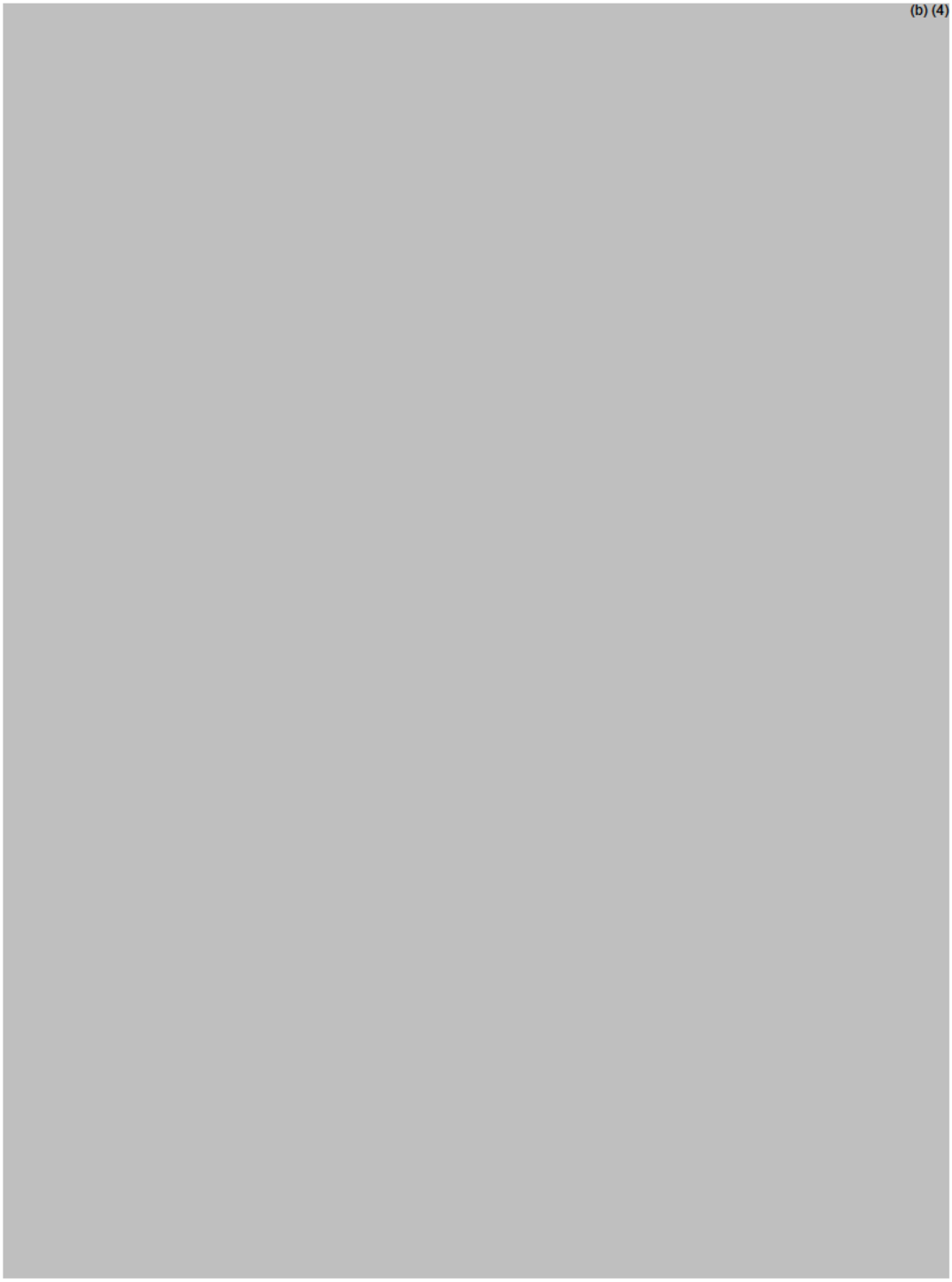
(b) (4)



[PAGE * MERGEFORMAT]

(b) (4)

[PAGE * MERGEFORMAT]


(b) (4)

(b) (4)

[PAGE * MERGEFORMAT]

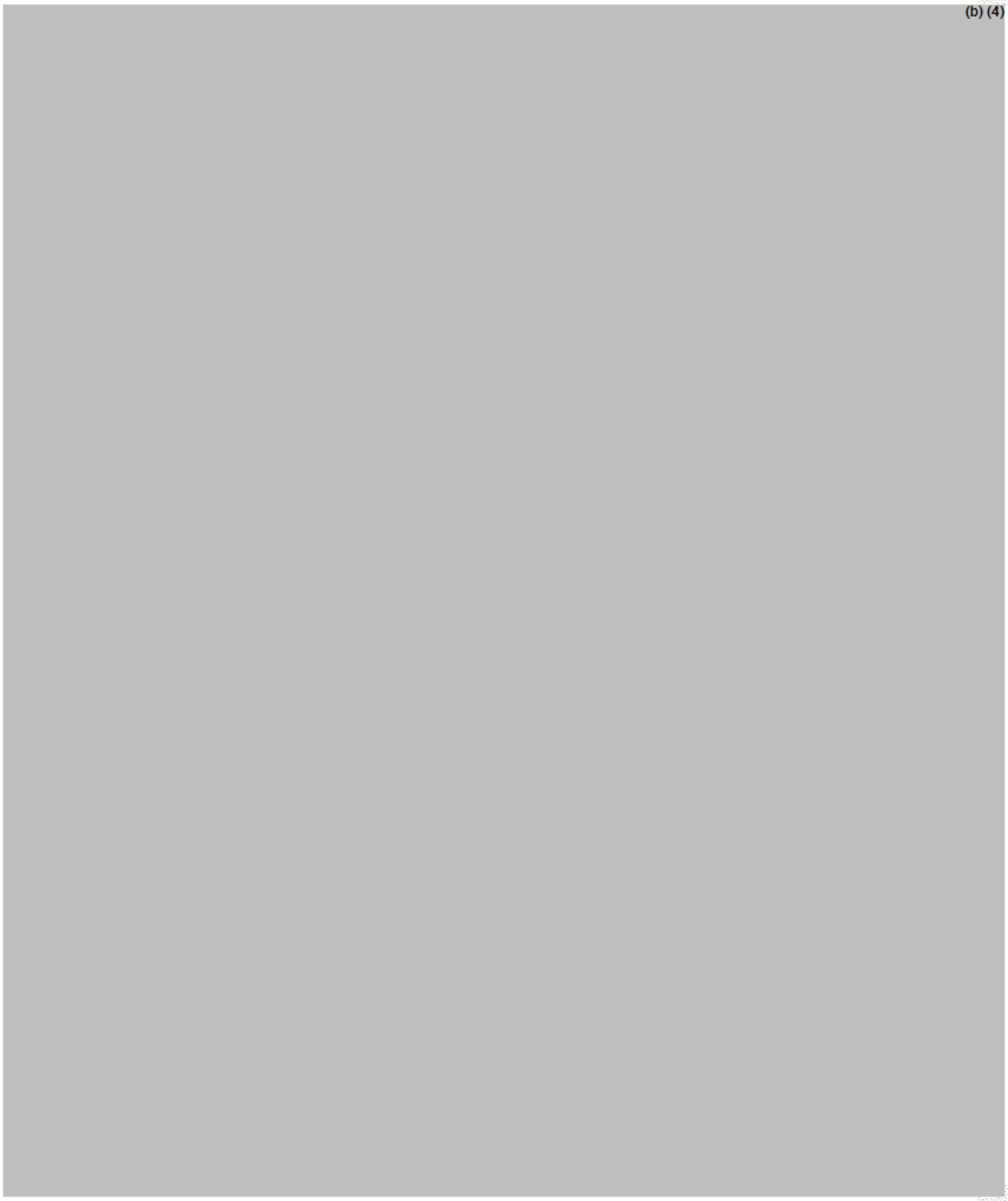
(b) (4)

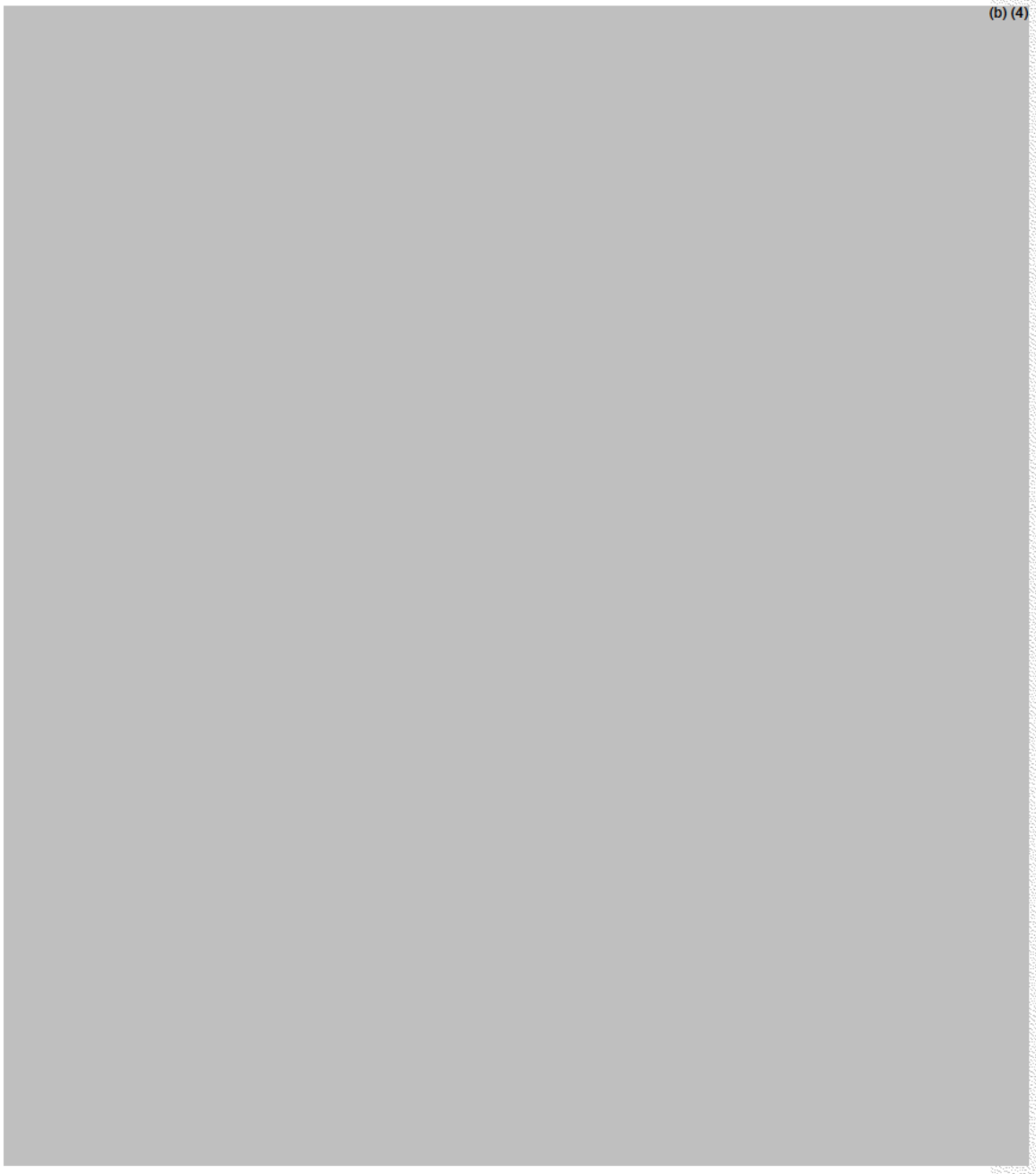
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRIPTODUR safely and effectively. See full prescribing information for TRIPTODUR.

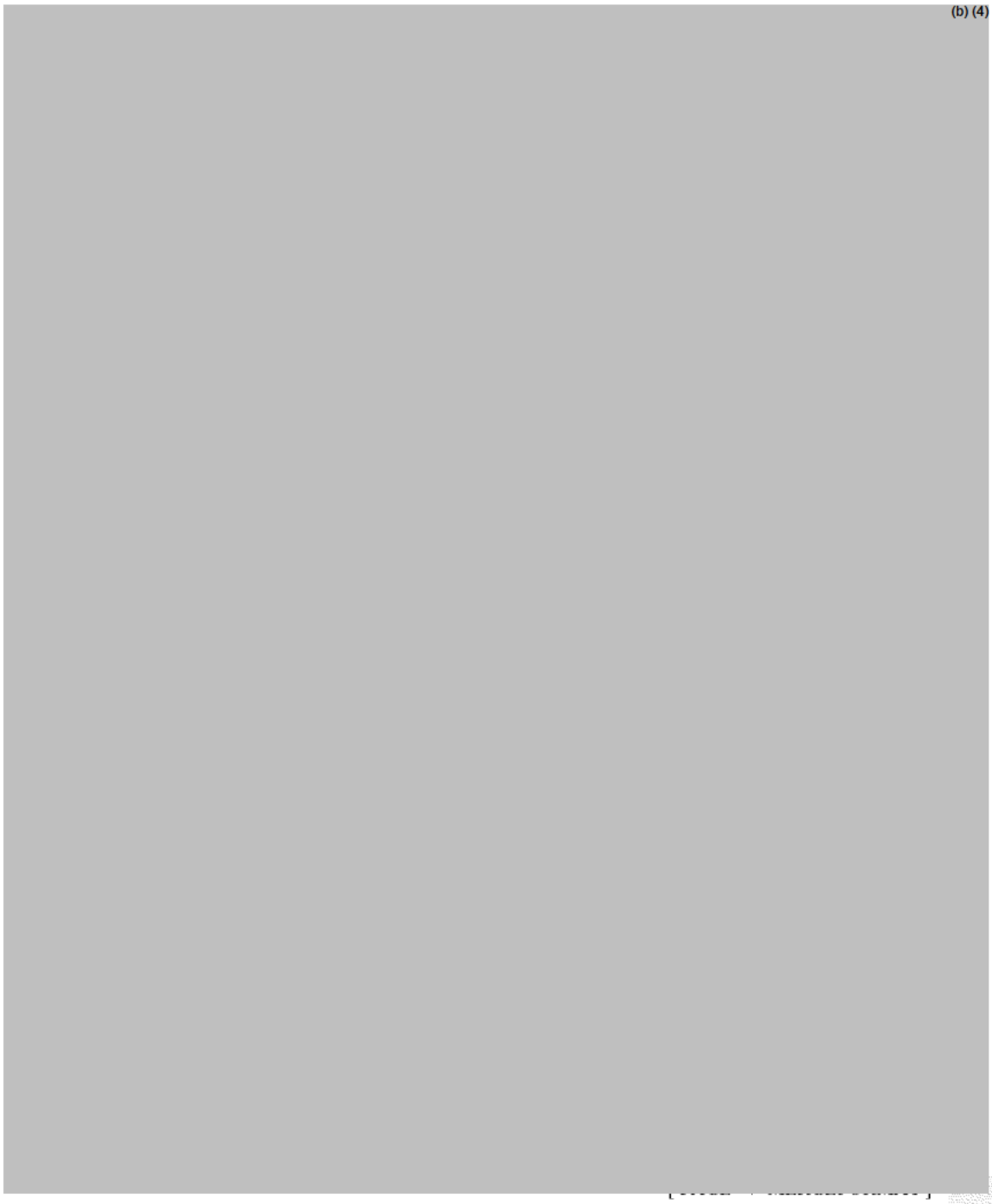
TRIPTODUR (triptorelin) for extended-release injectable suspension, for intramuscular use
Initial U.S. Approval: 2000

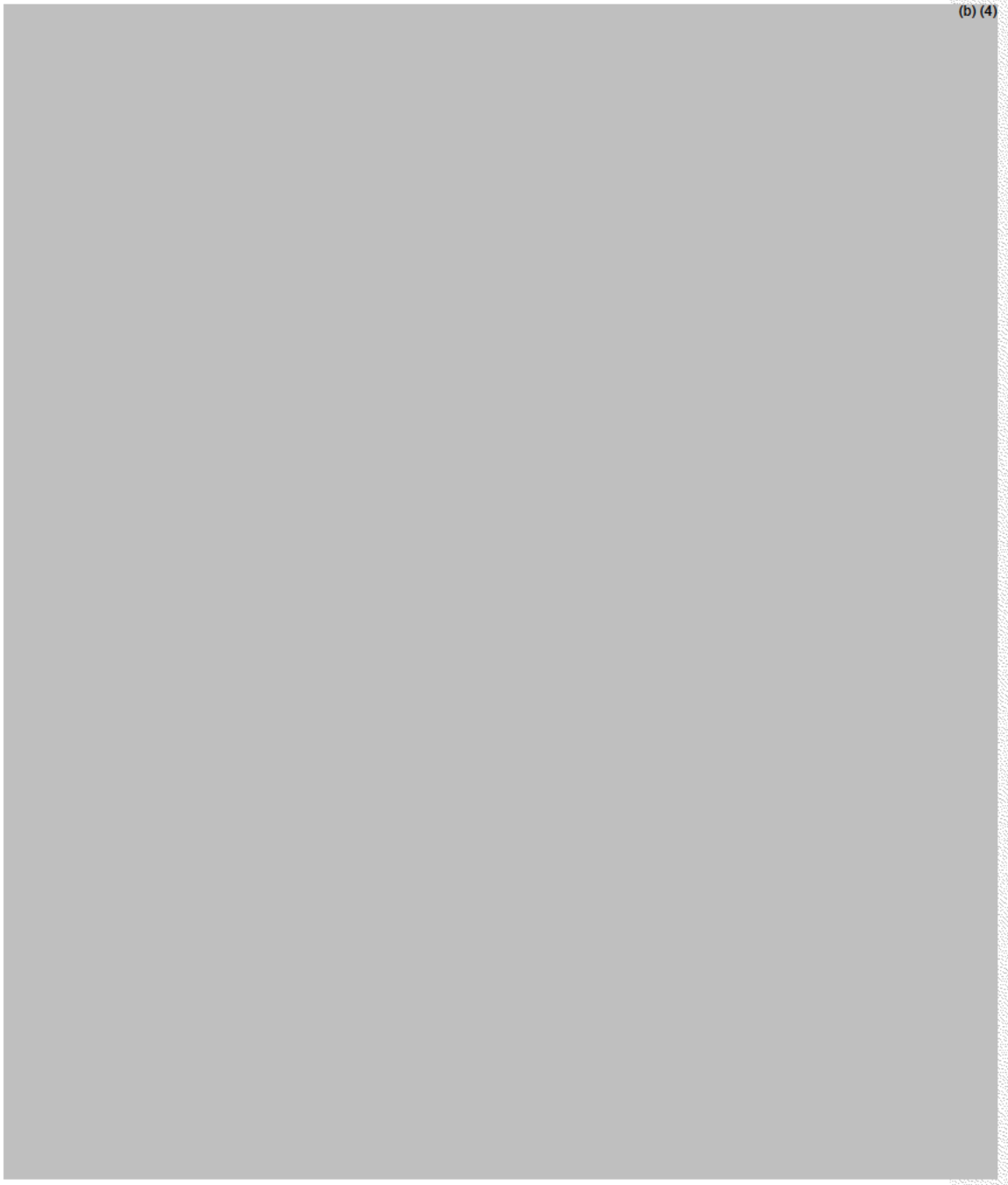
(b) (4)

(b) (4)


(b) (4)

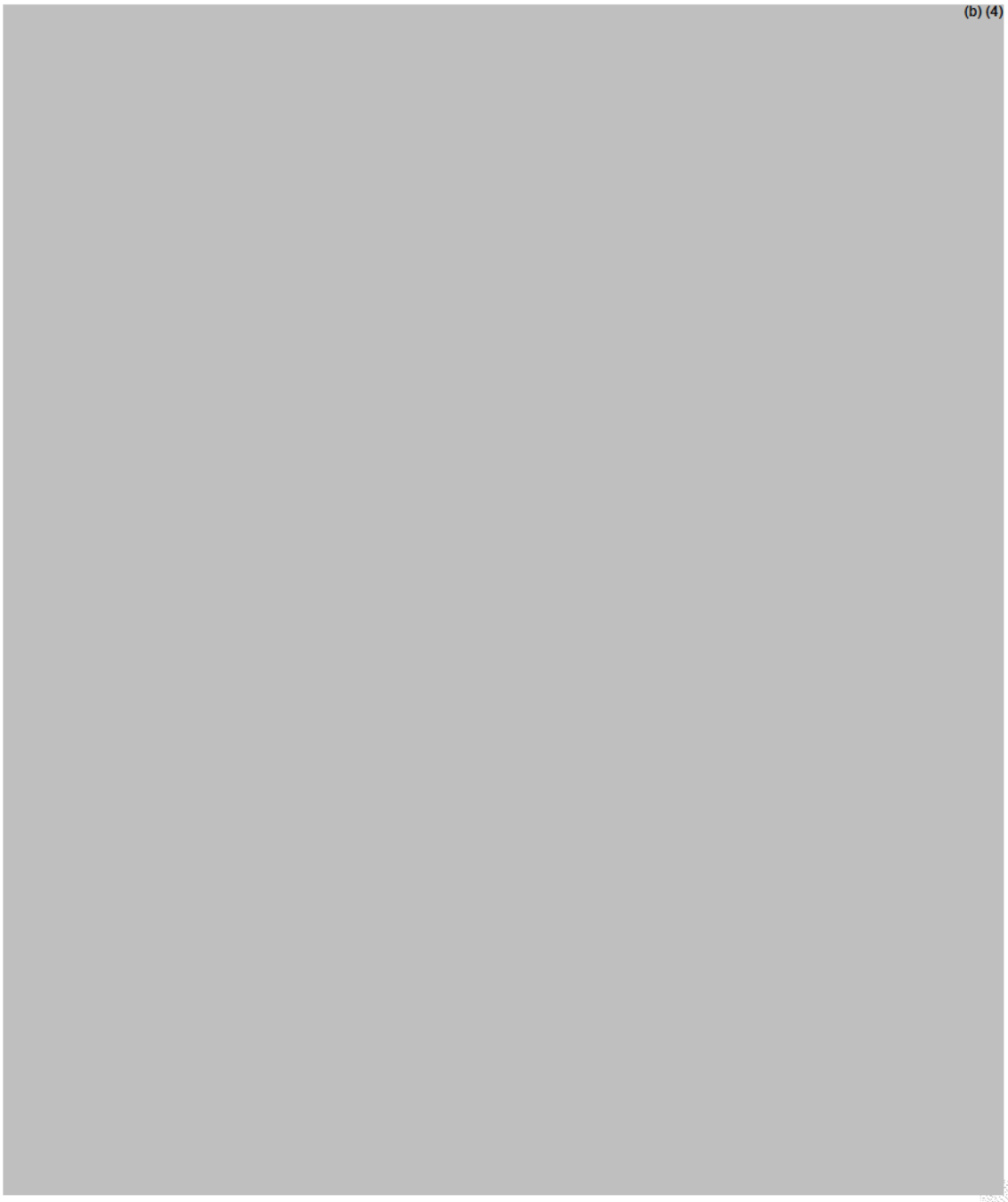

(b) (4)

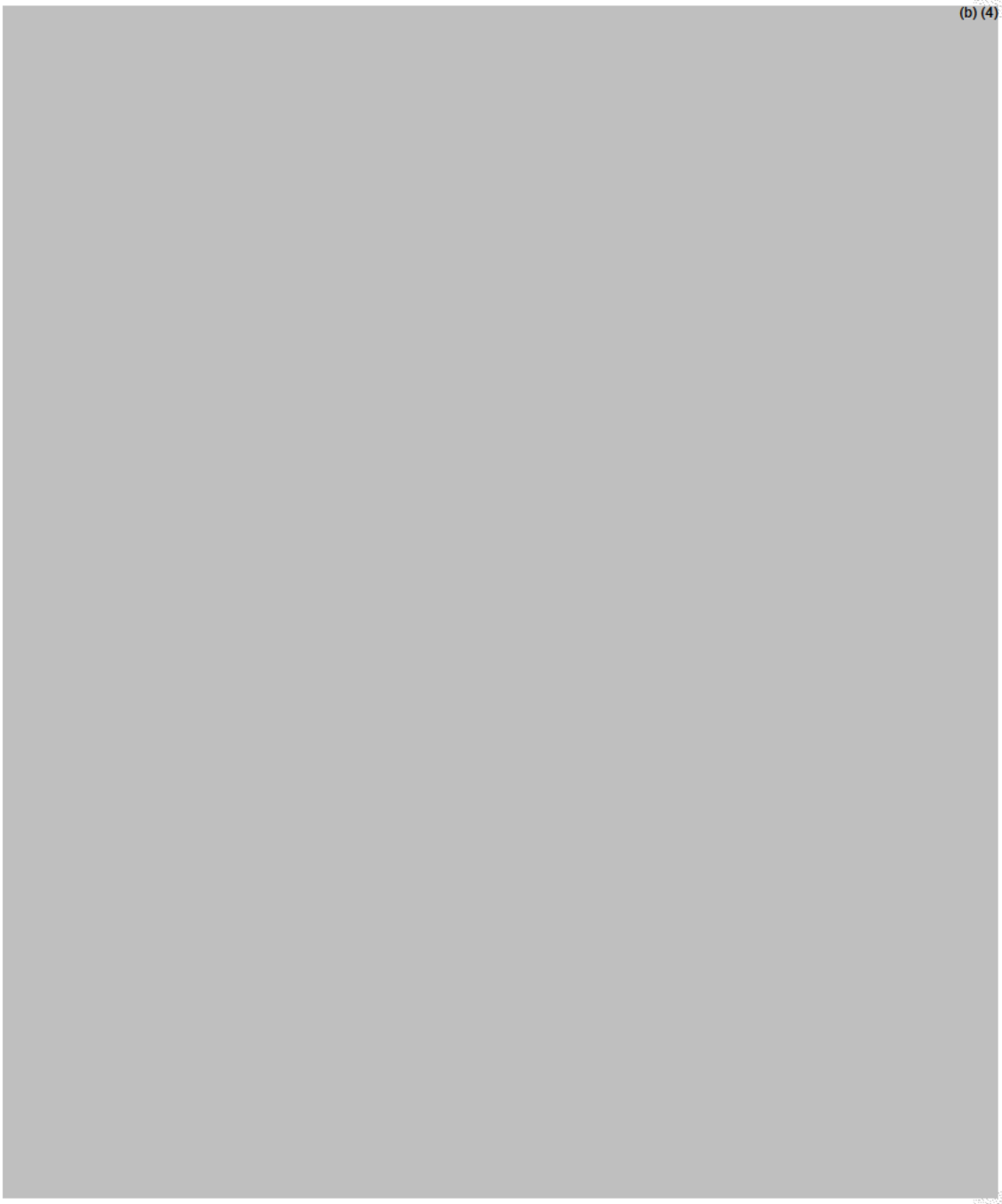

(b) (4)



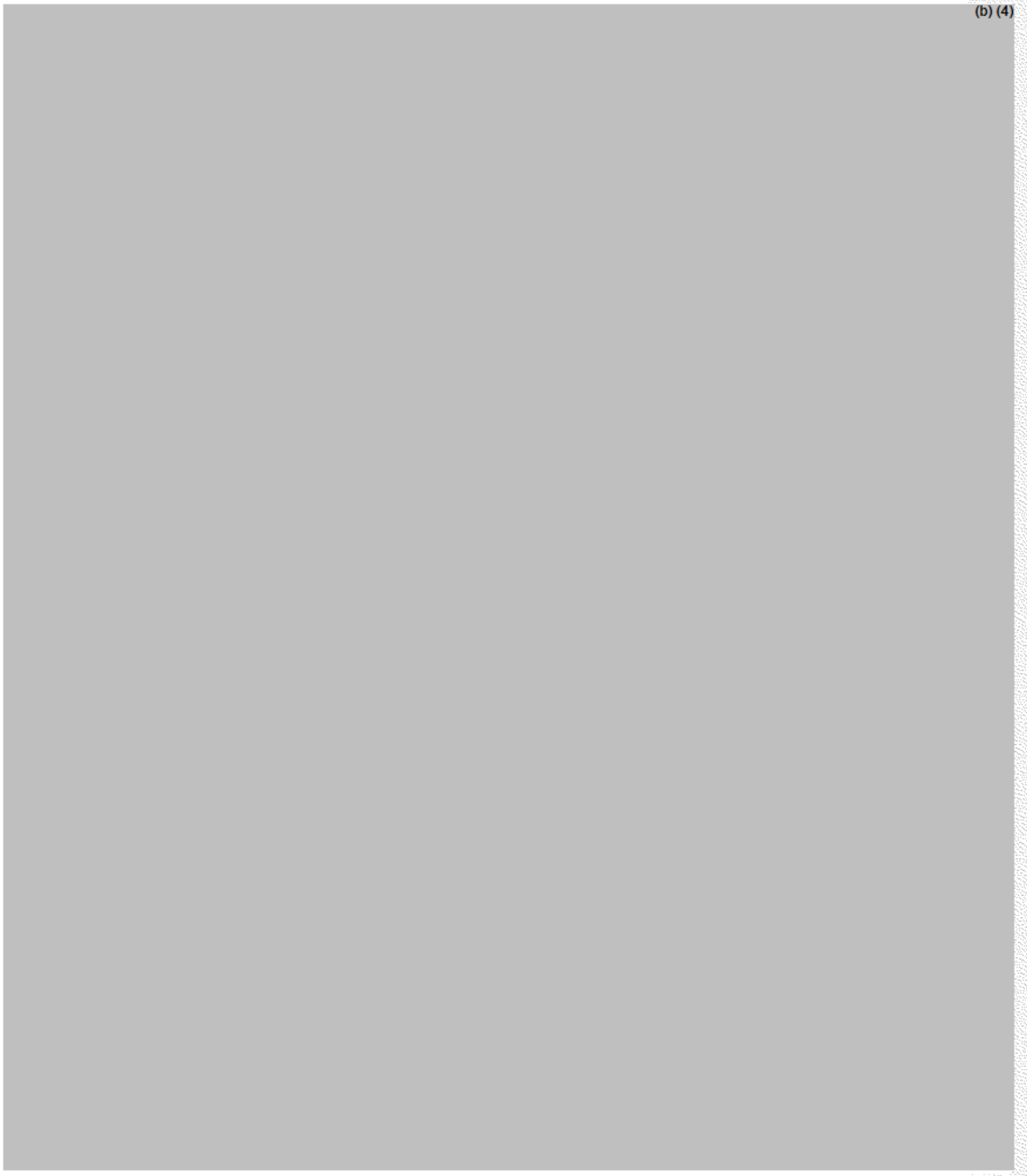
(b) (4)

[PAGE * MERGEFORMAT]

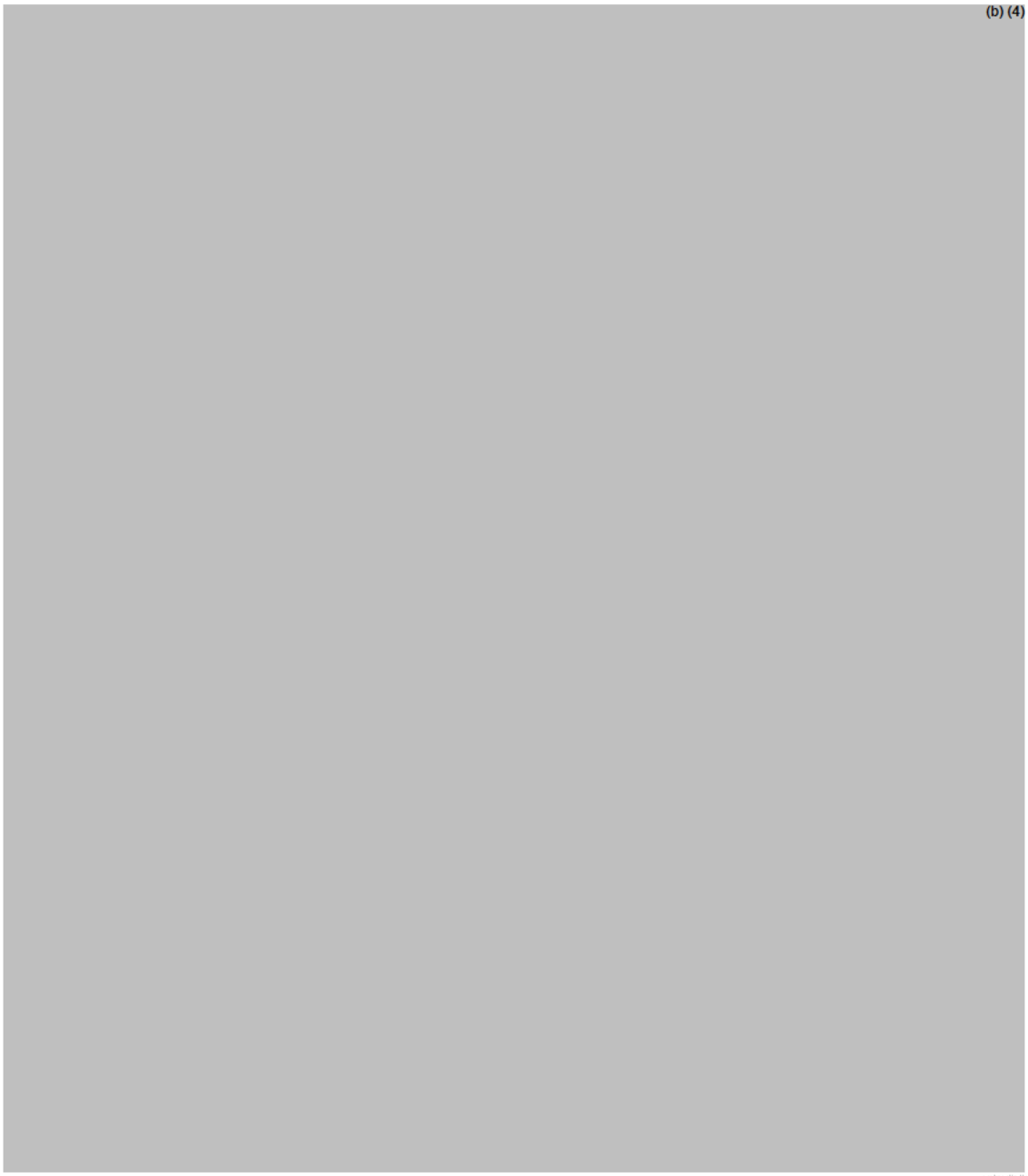

(b) (4)


(b) (4)

(b) (4)



[PAGE * MERGEFORMAT]


(b) (4)

(b) (4)

[PAGE * MERGEFORMAT]

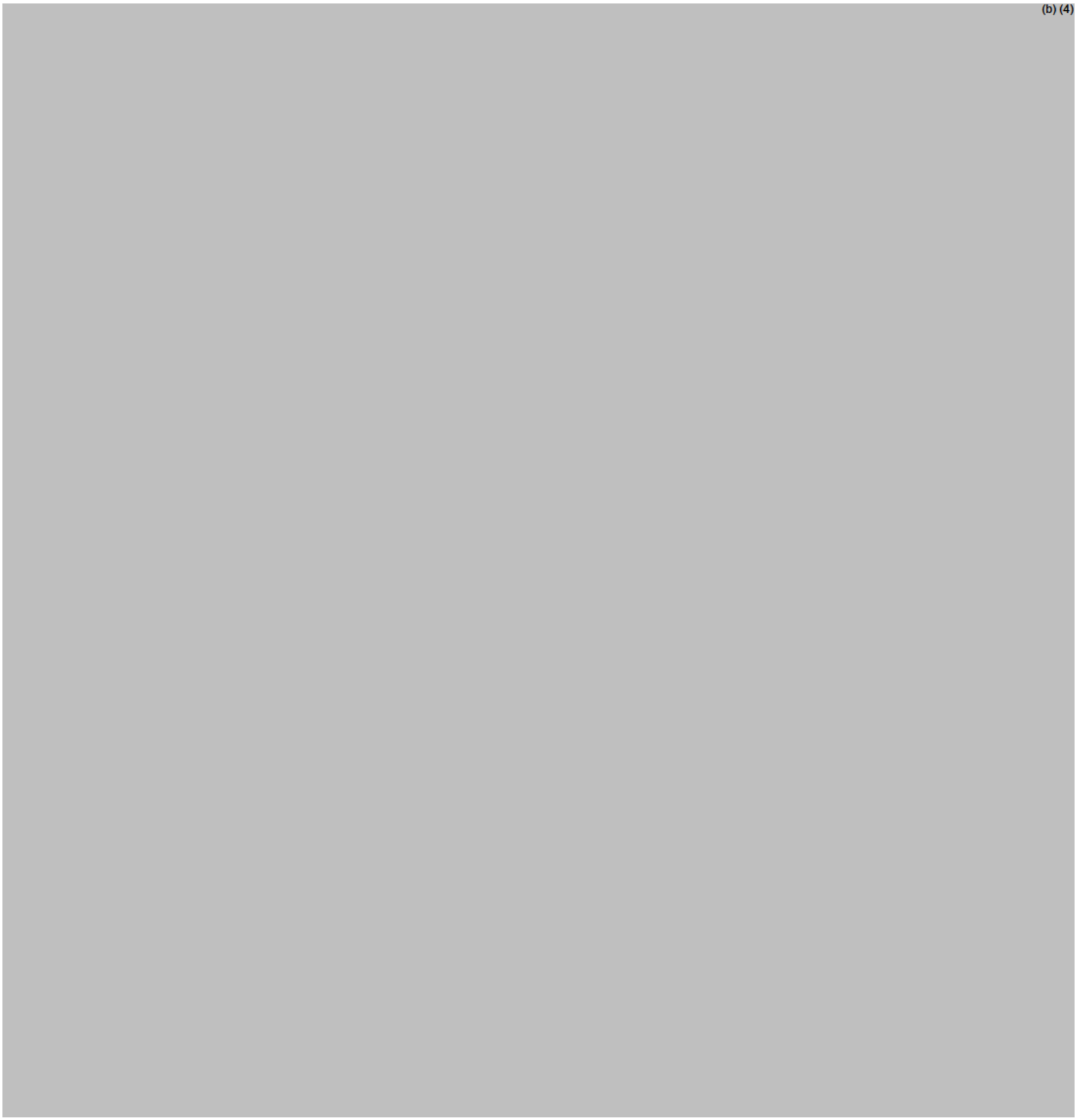
HIGHLIGHTS OF PRESCRIBING INFORMATION

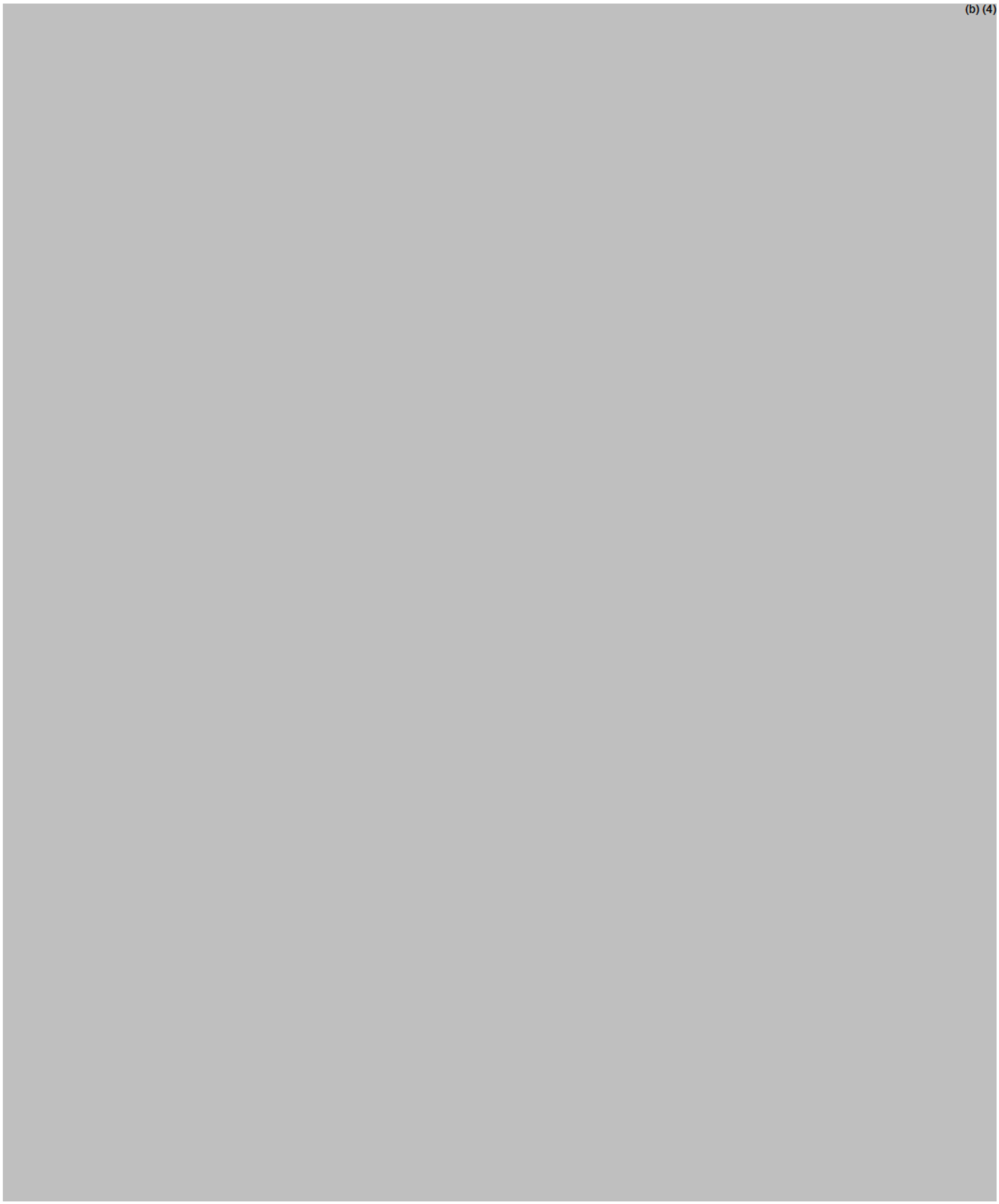
These highlights do not include all the information needed to use FENSOLVI® safely and effectively. See full prescribing information for FENSOLVI.

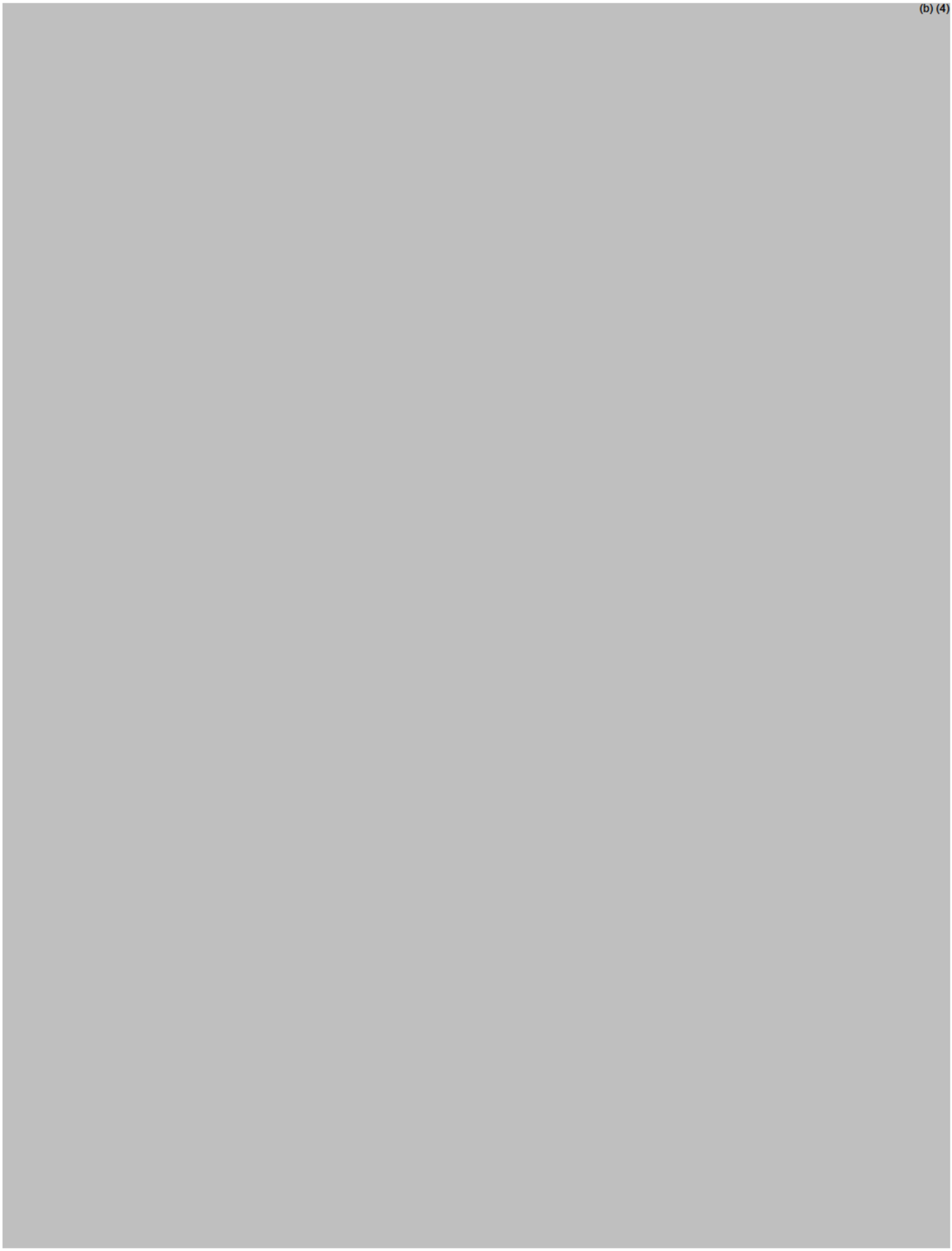
FENSOLVI (leuprolide acetate) for injectable suspension, for subcutaneous use
Initial U.S. Approval: 1985

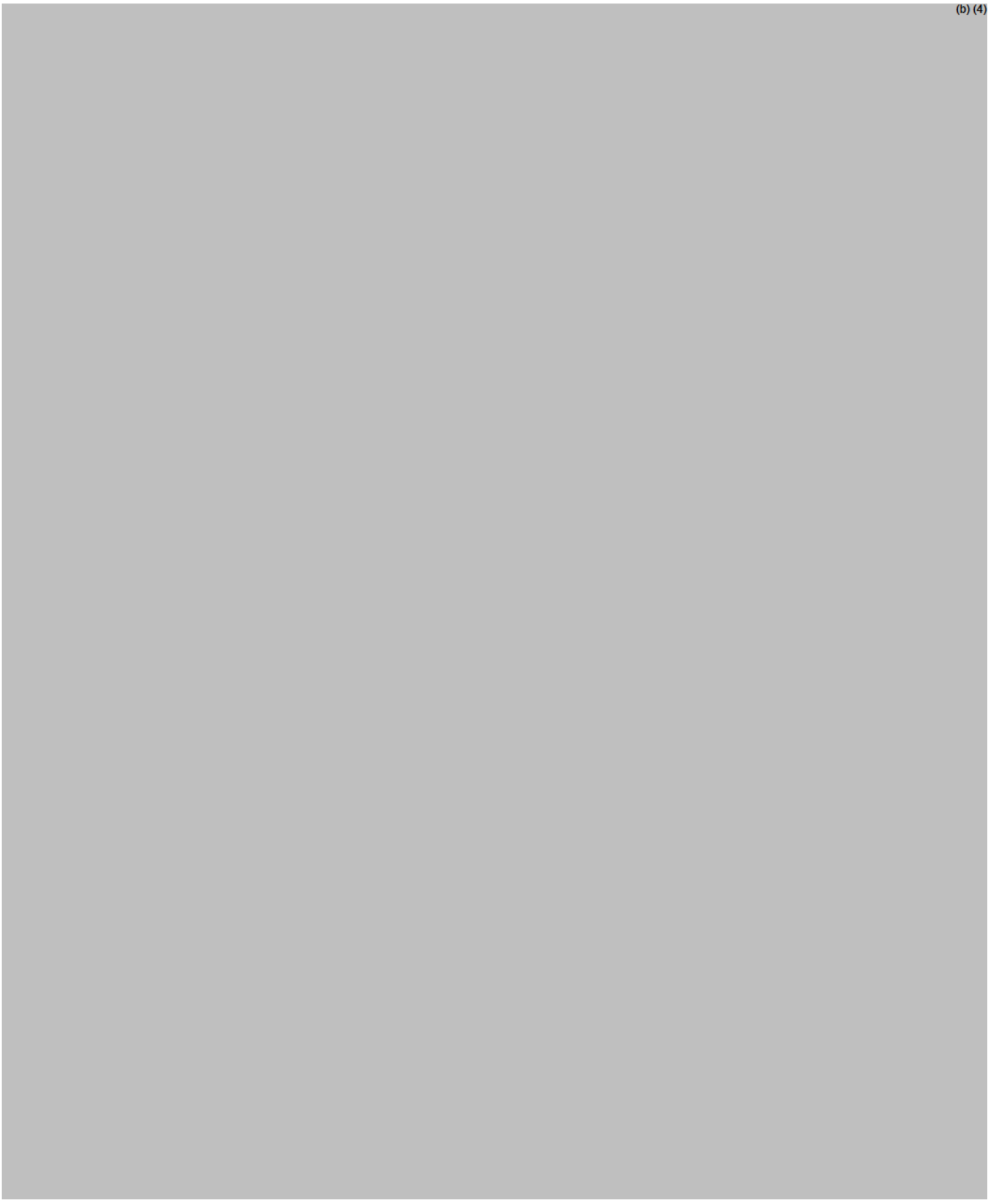
(b) (4)

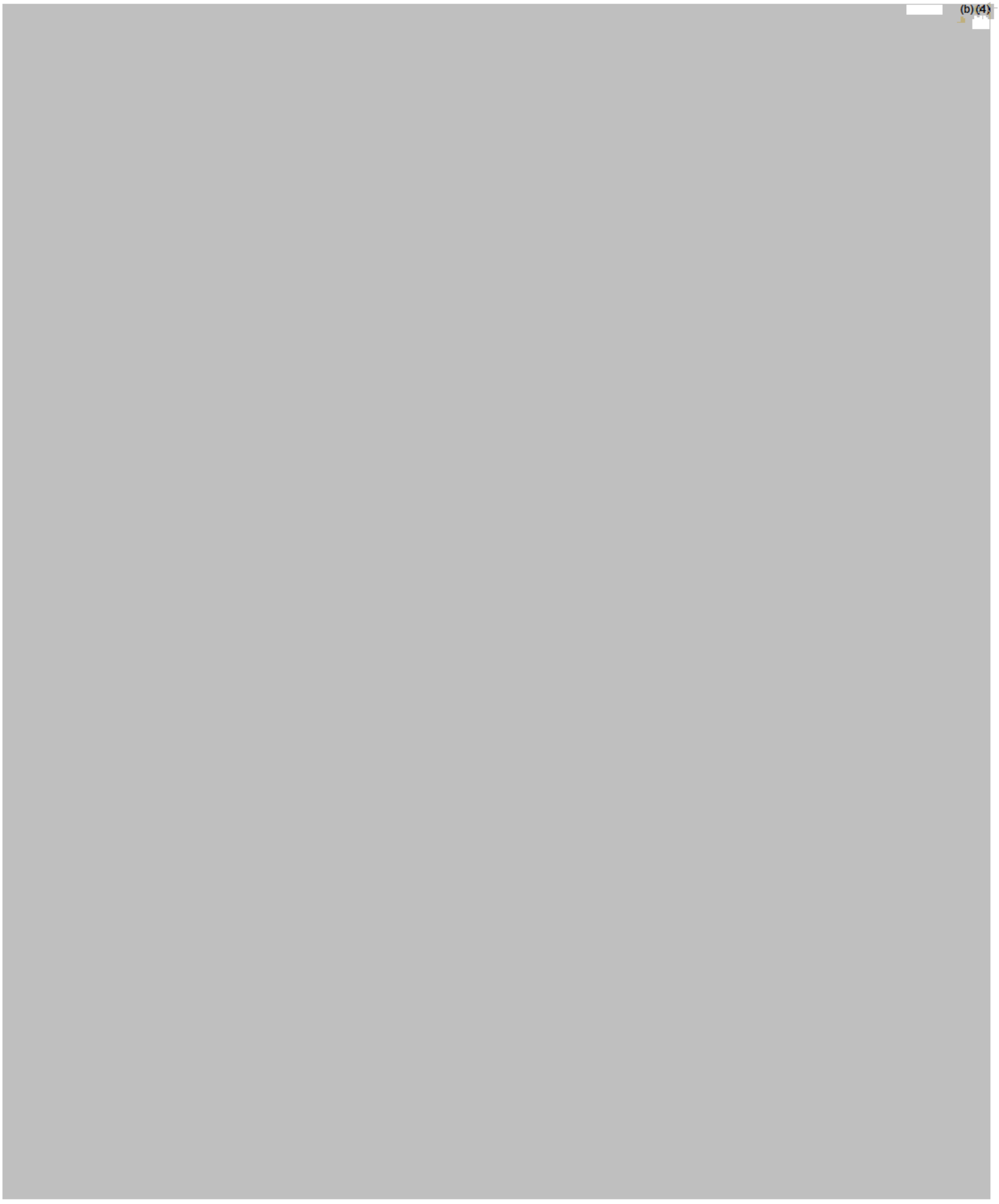
(b) (4)

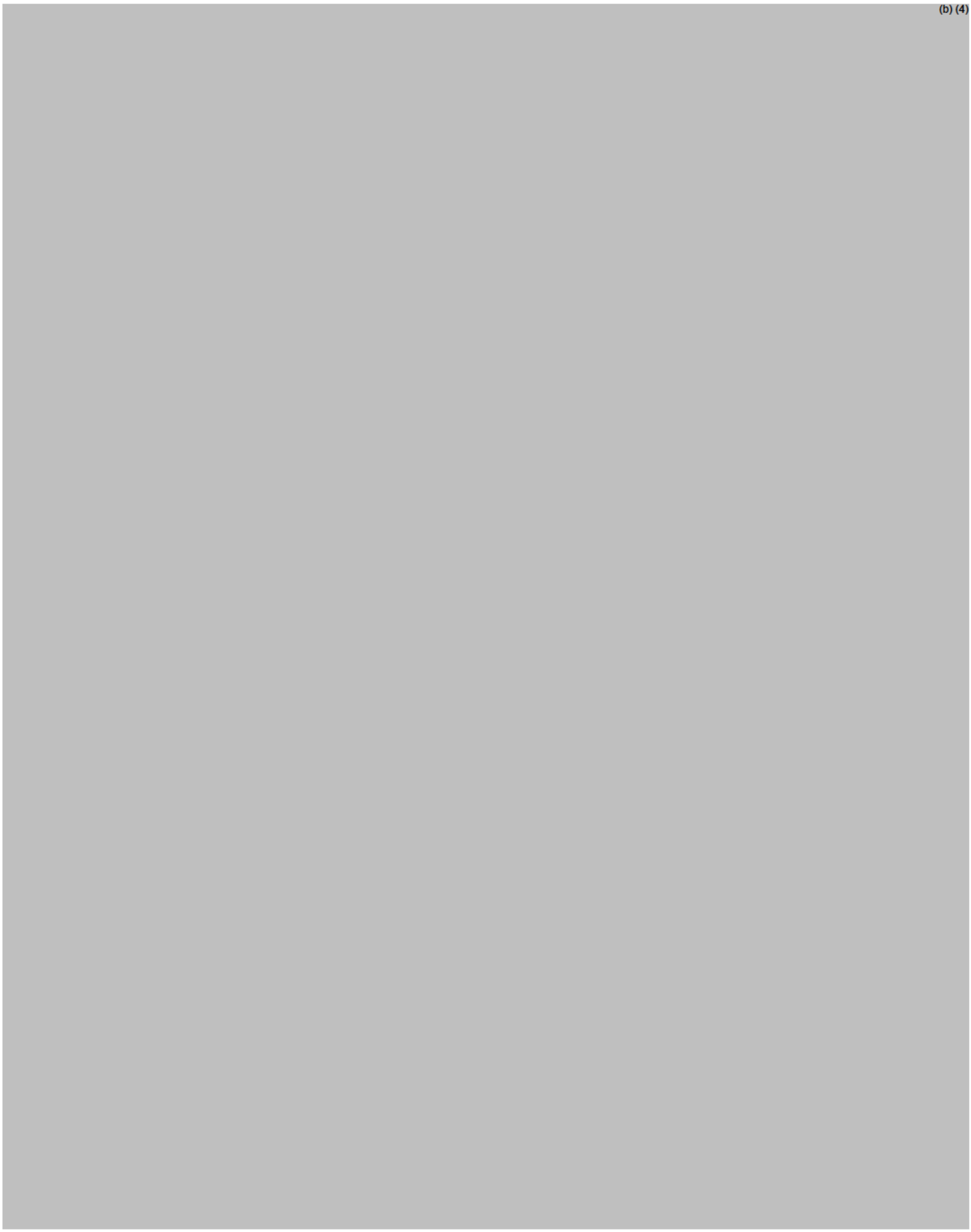

(b) (4)


(b) (4)

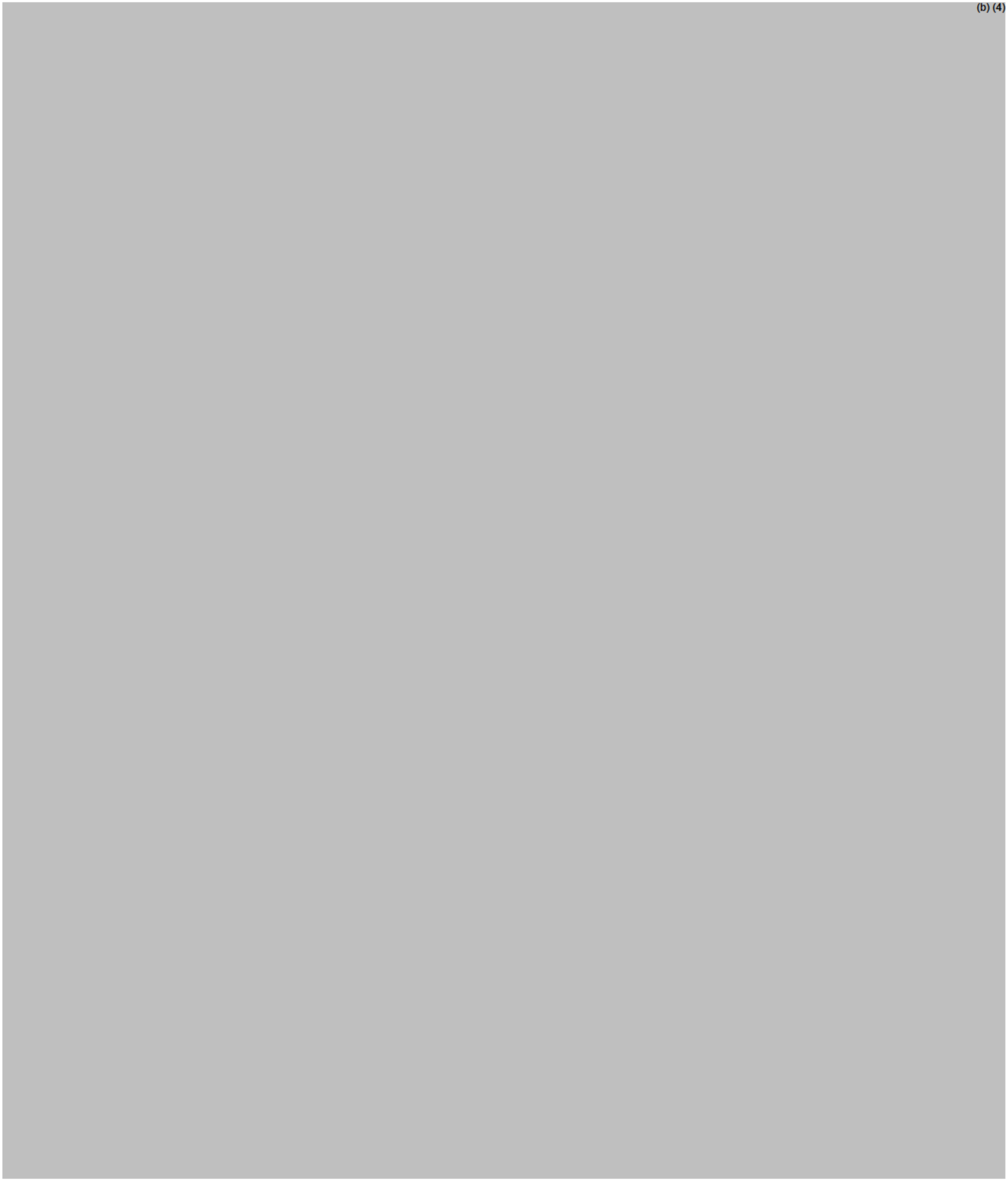

(b) (4)

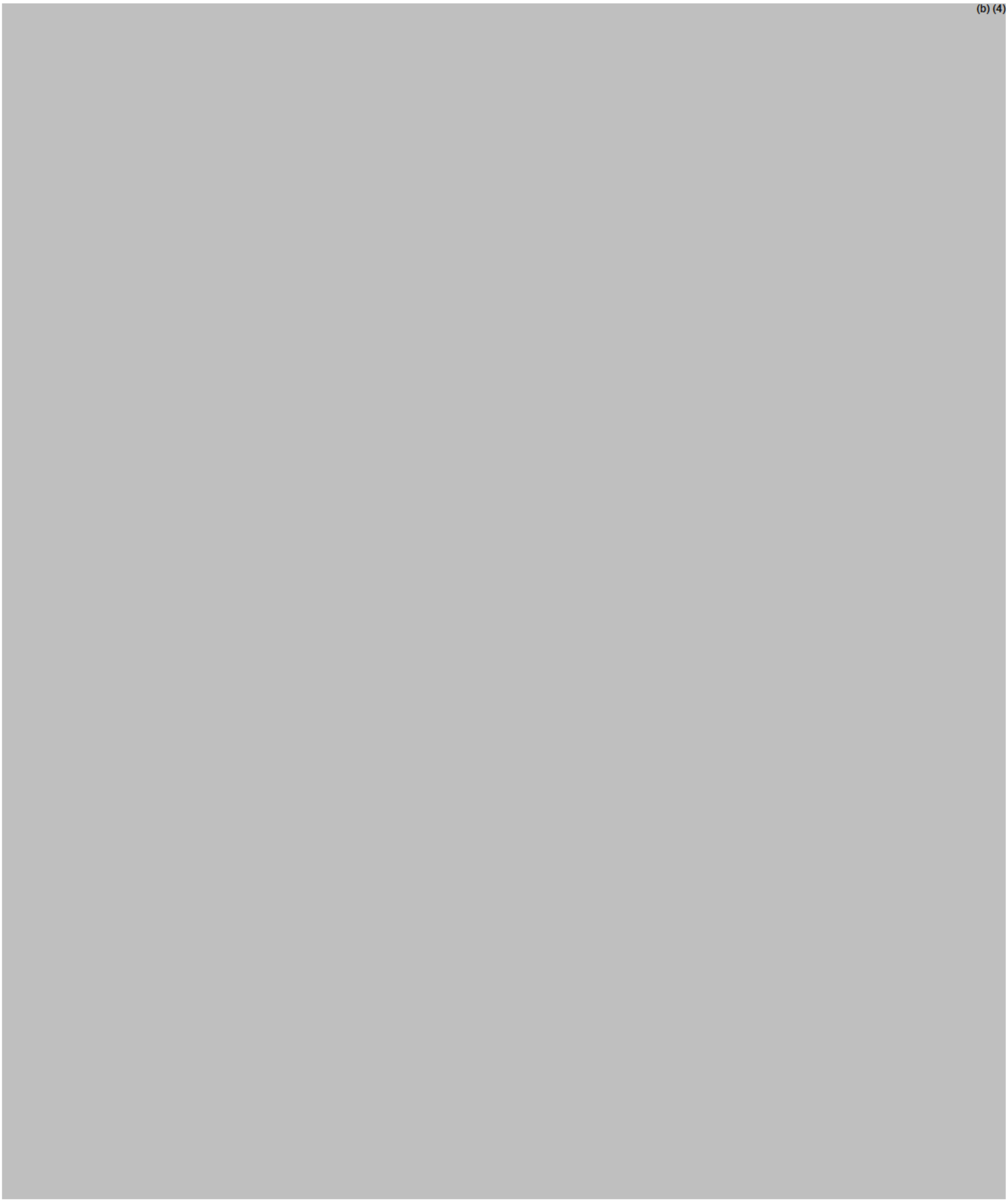

(b) (4)

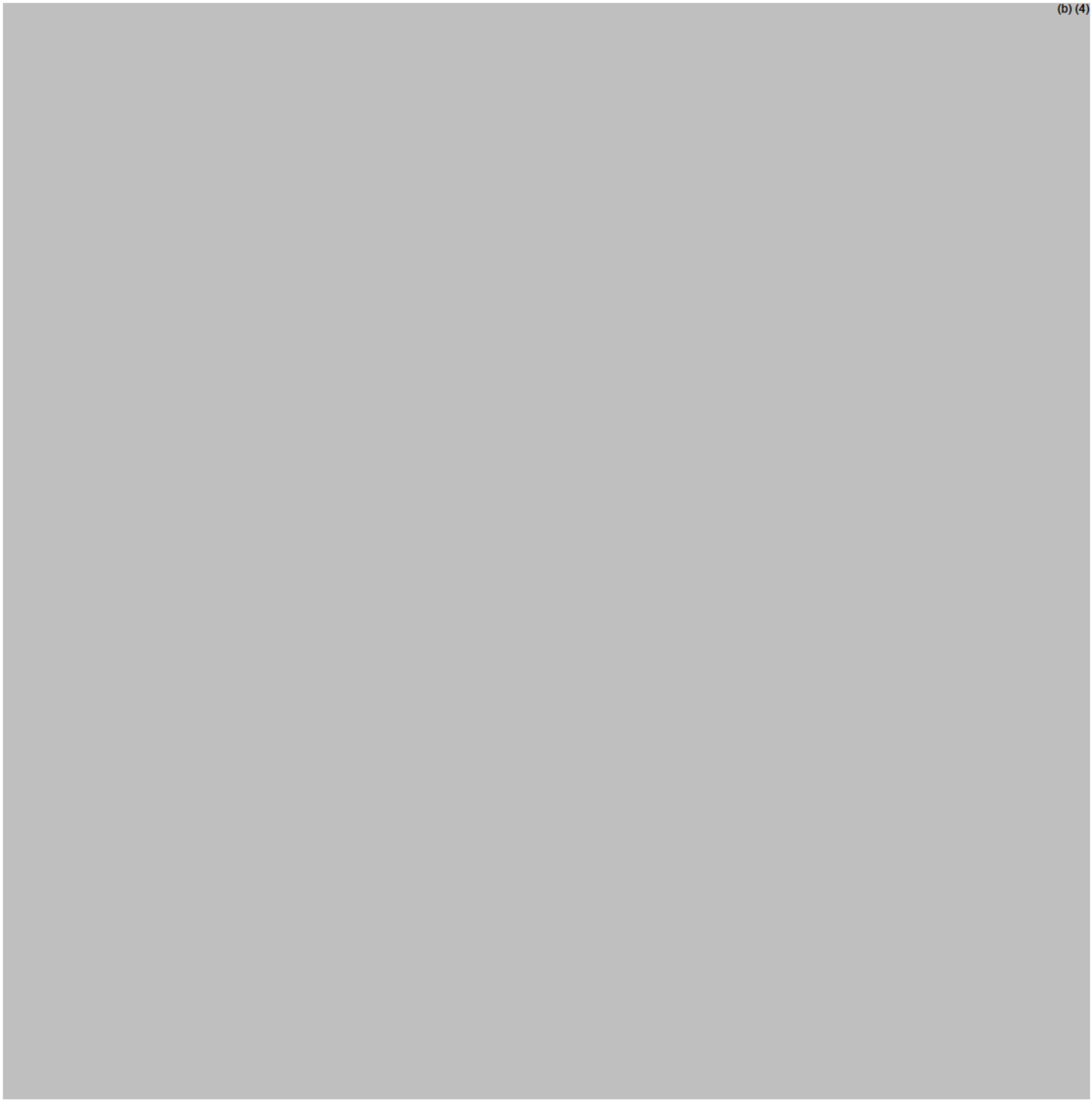

(b) (4)

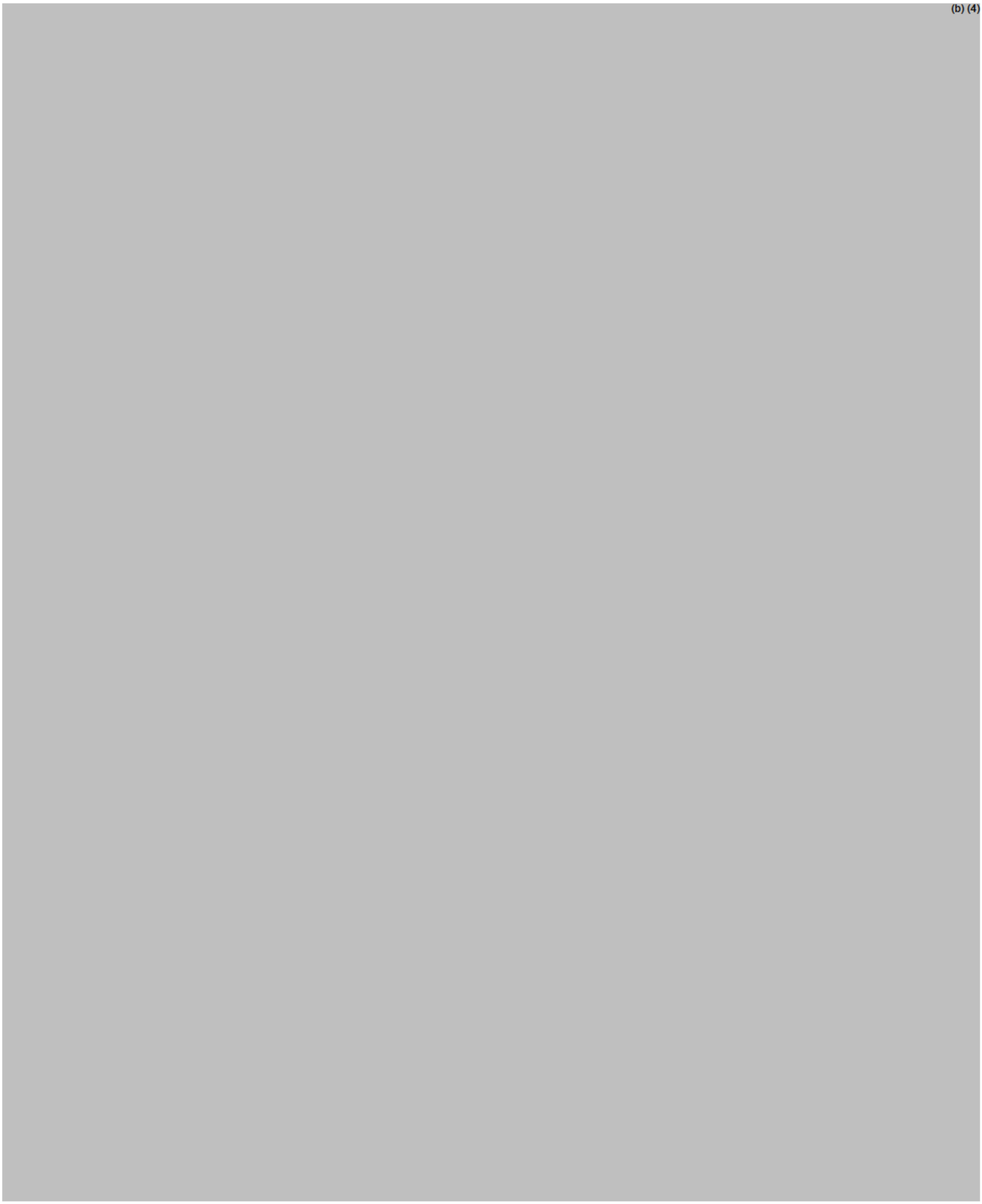

(b) (4)

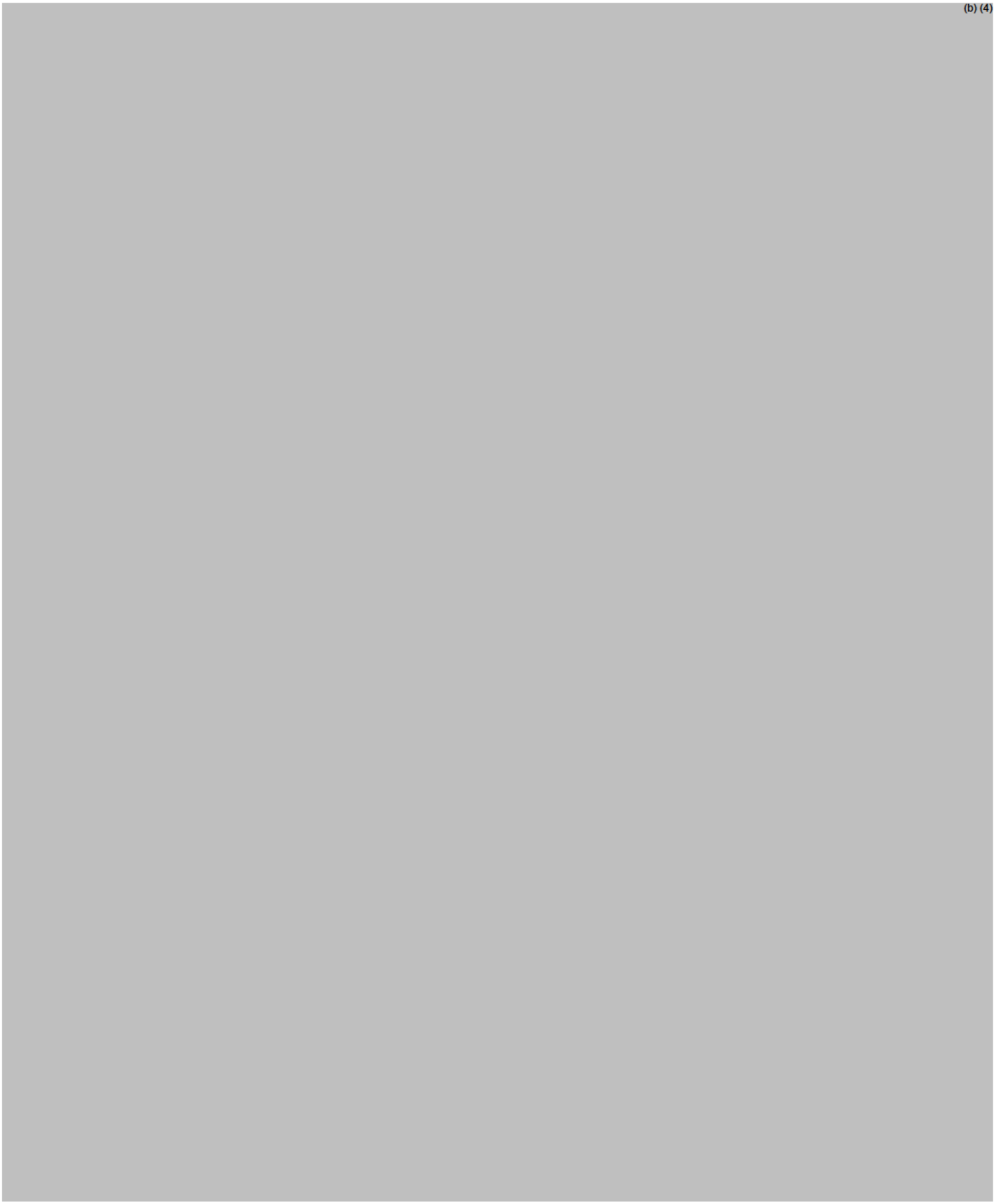

(b) (4)

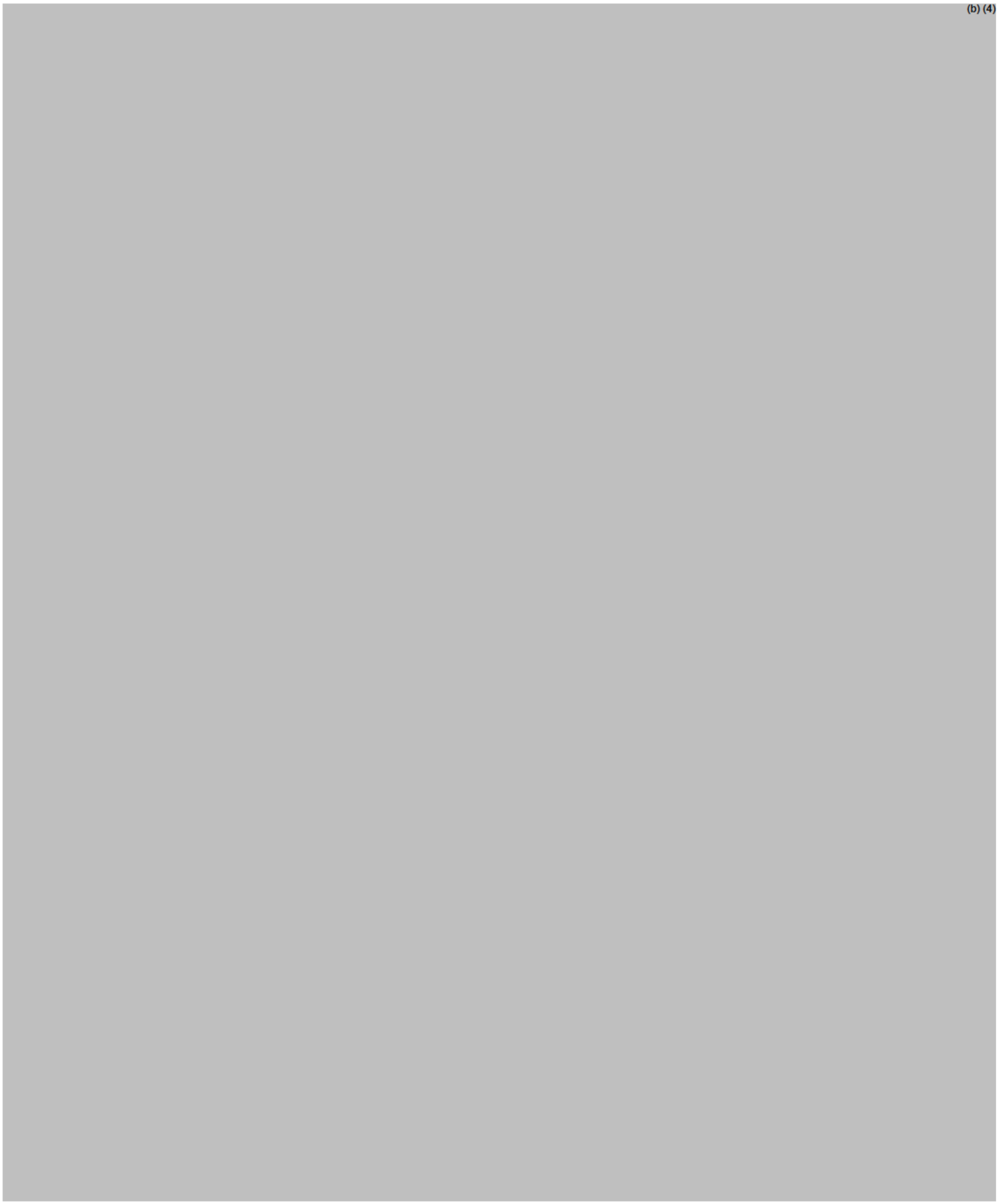


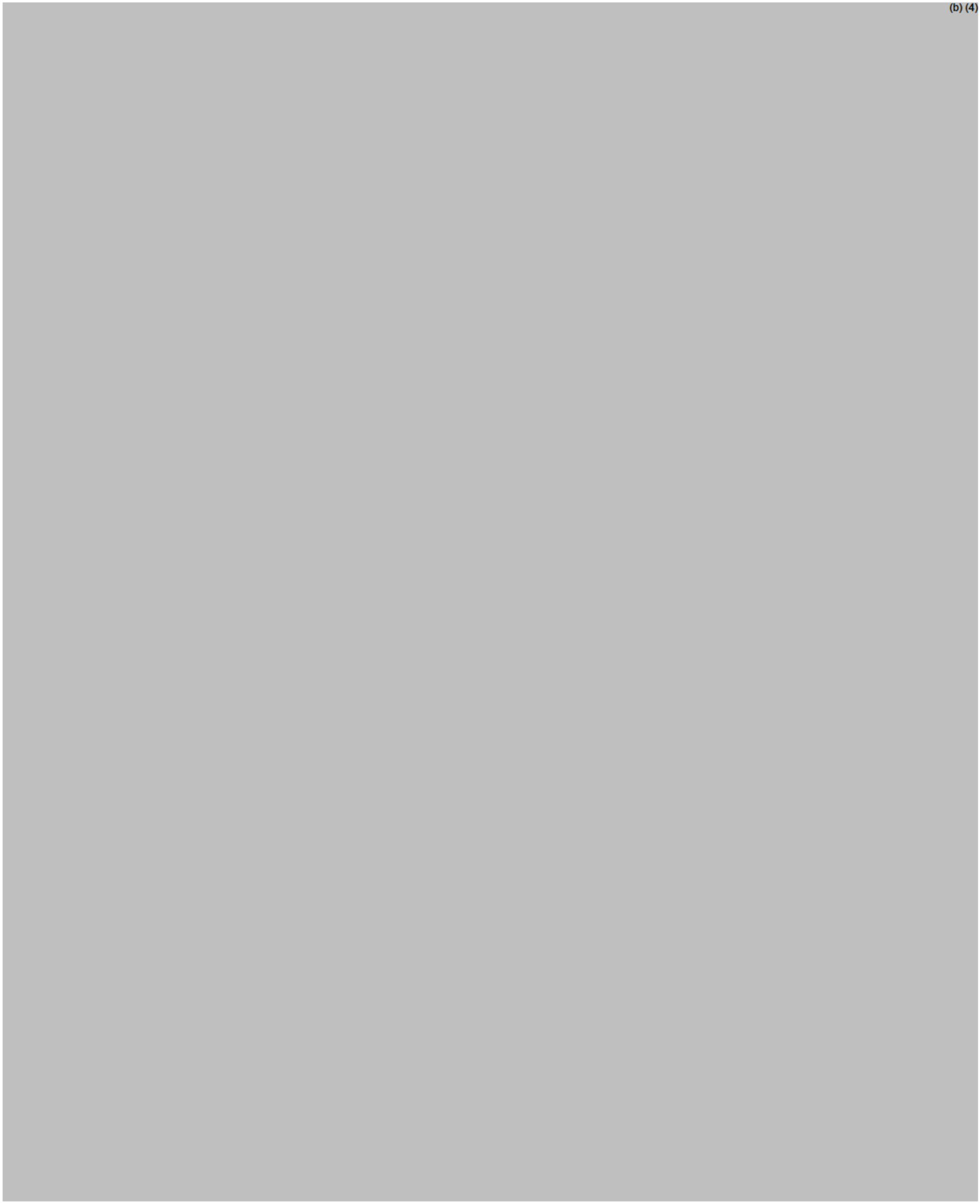

(b) (4)

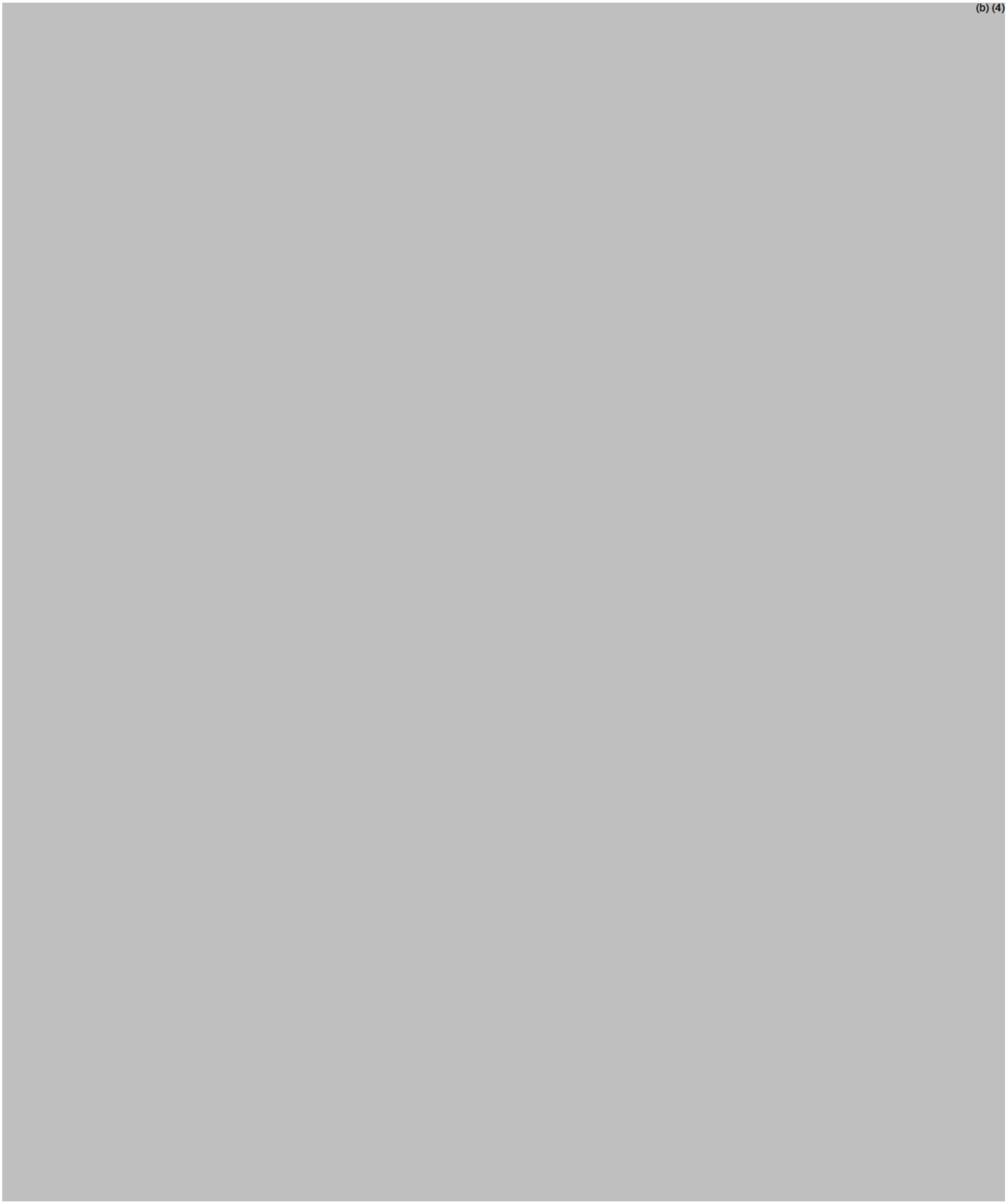

(b) (4)


(b) (4)


(b) (4)


(b) (4)


(b) (4)


(b) (4)

(b) (4)

APPEARS THIS WAY ON ORIGINAL