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(b) (4)

## REGARDING THE MANUFACTURING OF DRUG SUBSTANCE (DS)

### QUERY 1

The (b) (4) (b) (4) was listed as one of the process parameters under IND/EUA. In your BLA 125742 submission, this process parameter was removed as shown in Table 3.2.S.2.2-3 (b) (4) Parameters. Please specify the acceptable (b) (4) range of the (b) (4) (b) (4) (b) (4)

### RESPONSE 1

The (b) (4) and was initially evaluated at (b) (4) based on BioNTech platform knowledge. As stated in 3.2.S.2.6 Process Development and Characterization section, the lower range of (b) (4)

(b) (4)

**Literature References**

None

**SUPPORTING DOCUMENTATION**

**New or Replaced Supporting Documentation**

3.2.S.2.2 Manufacturing Process [Andover] **Replaced**

**Previously submitted supporting documentation**

3.2.S.2.5 Manufacturing Process [Andover-(b) (4)

3.2.S.2.5 Manufacturing Process [Andover-(b) (4) ]

3.2.S.2.6 Risk Assessment of Process Related Impurities

**QUERY 2**

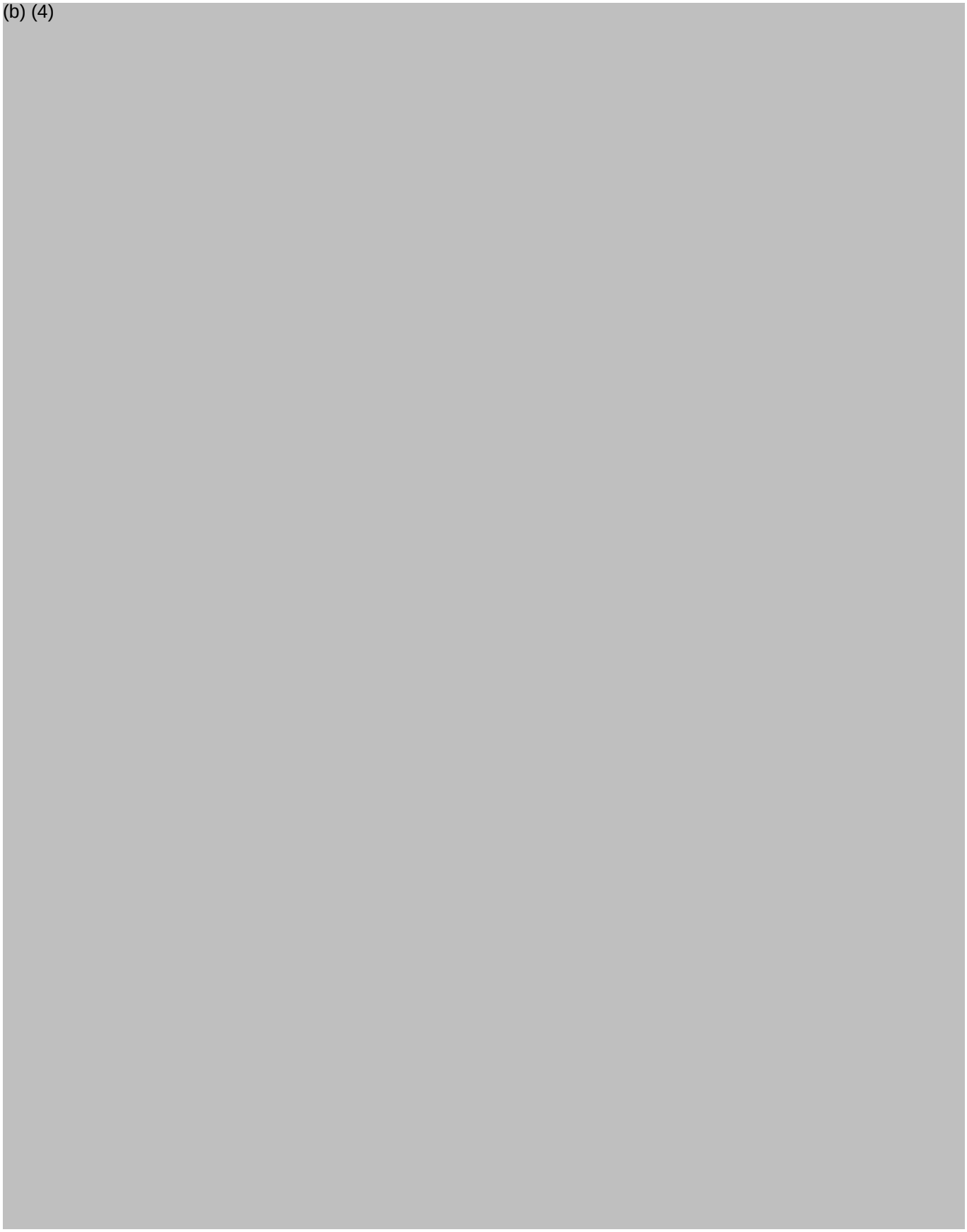
In Section 3.2.S.2.5, you stated that the (b) (4) for UFDF (b) (4) at commercial scale is (b) (4) . Please provide the performance test results for the commercial-scale (b) (4) , including the (b) (4) data and evaluation of the (b) (4) performance during (b) (4) .

**RESPONSE 2**

The (b) (4) is evaluated based on (b) (4) parameters evaluated for (b) (4) as stated in **Section 3.2.S.2.5 Process Validation and/or Evaluation - Additional Process Evaluation [Andover]** are listed below in Table 2.

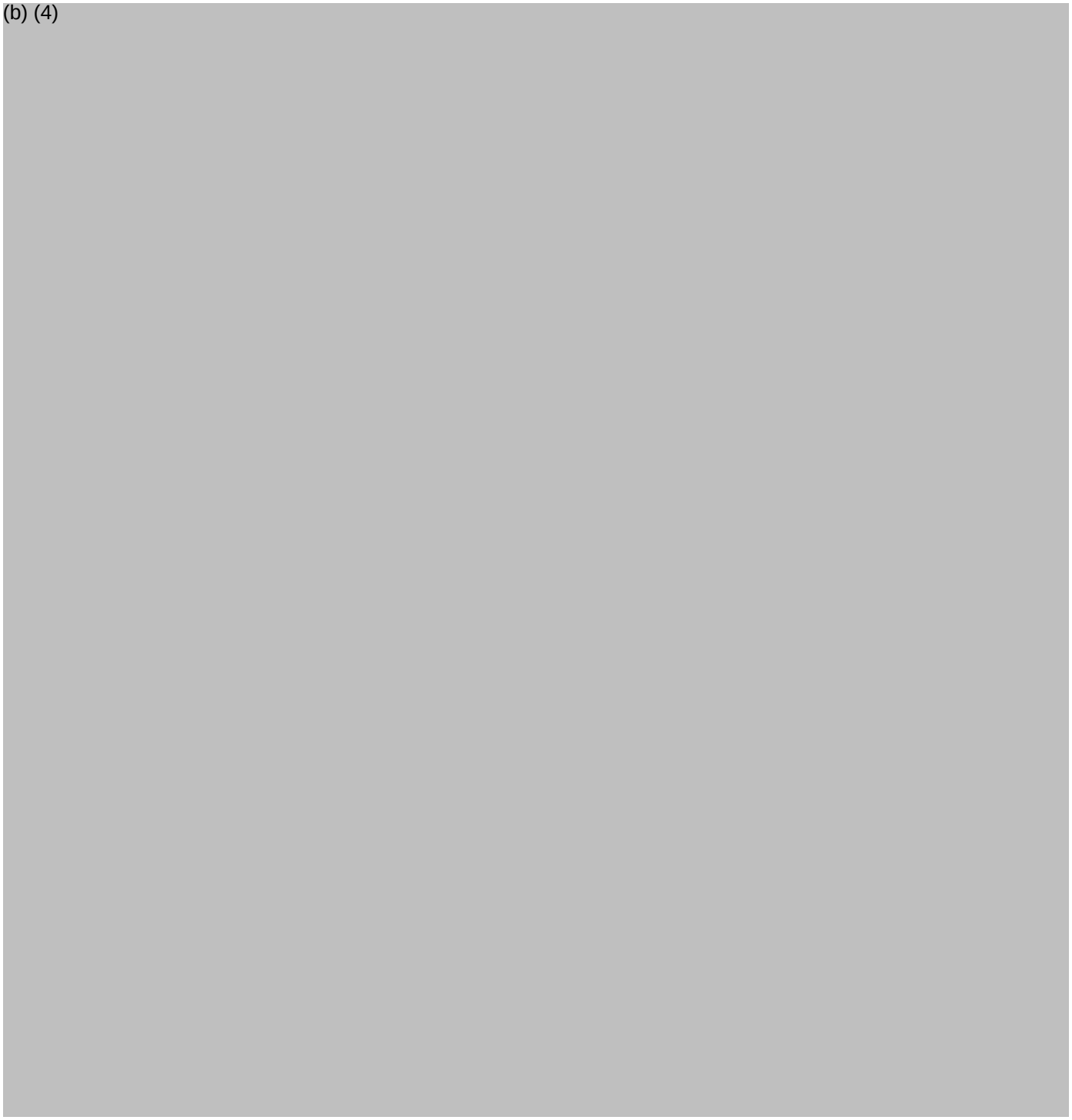
(b) (4)

(b) (4)



(b) (4)

(b) (4)



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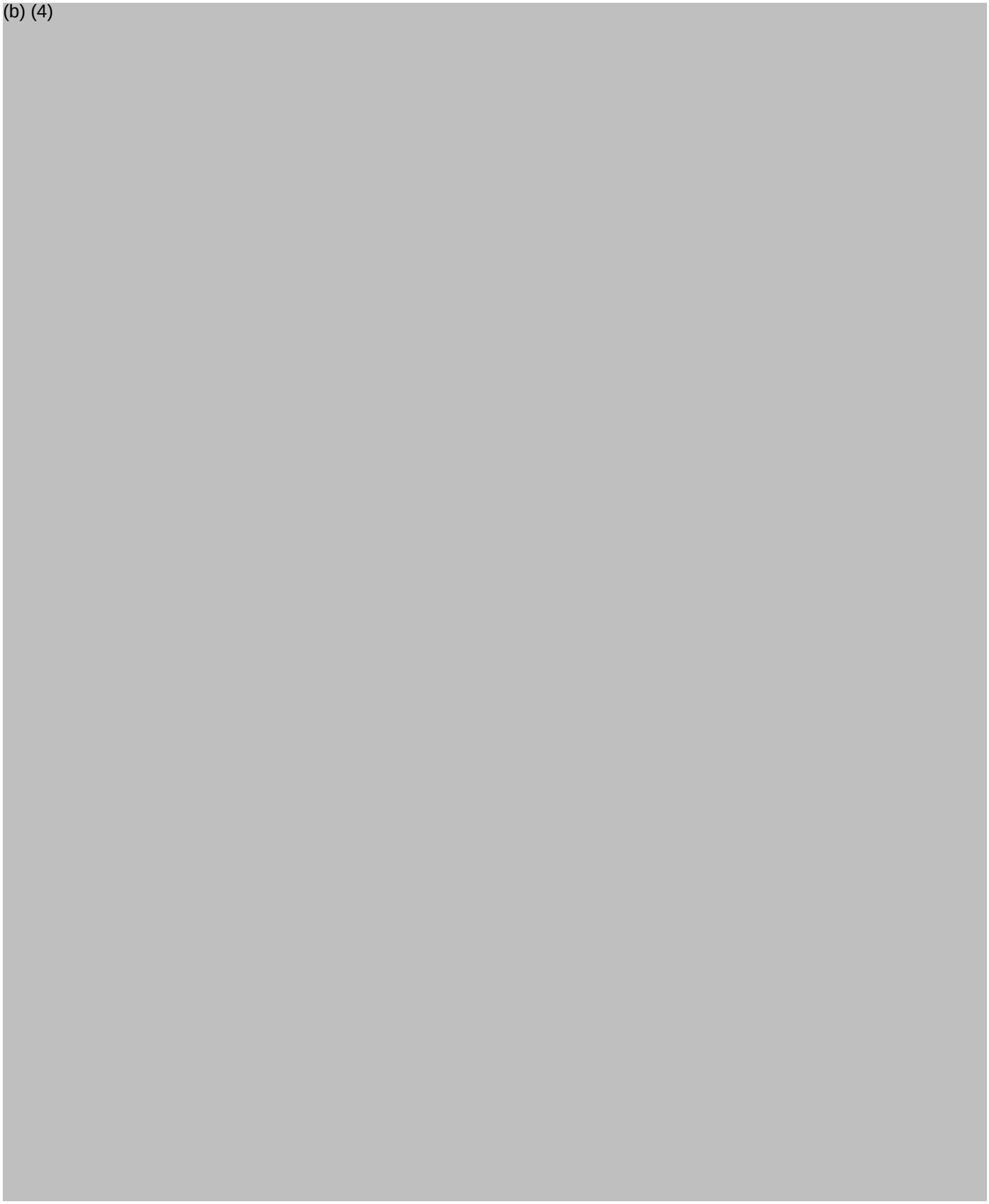
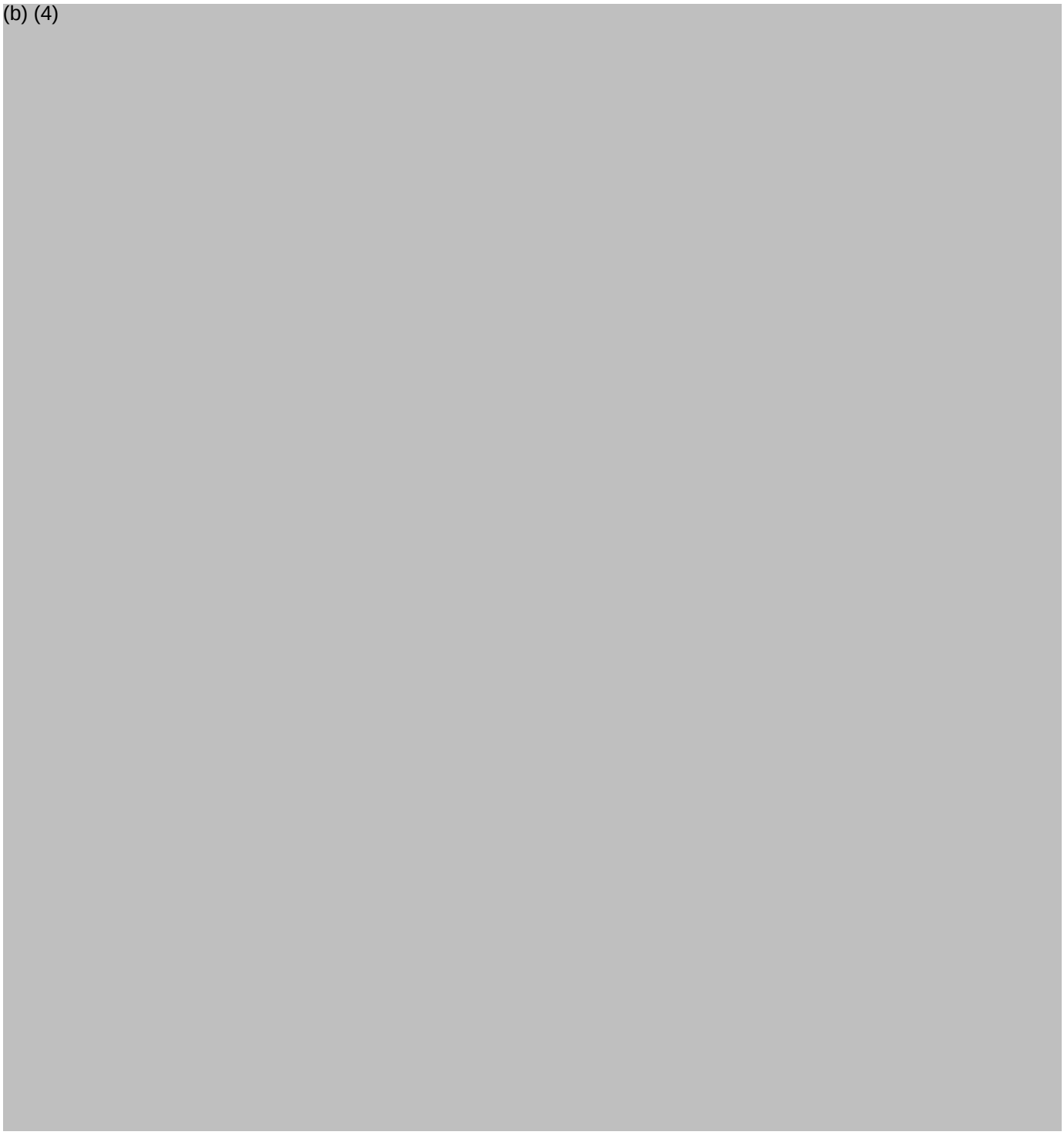
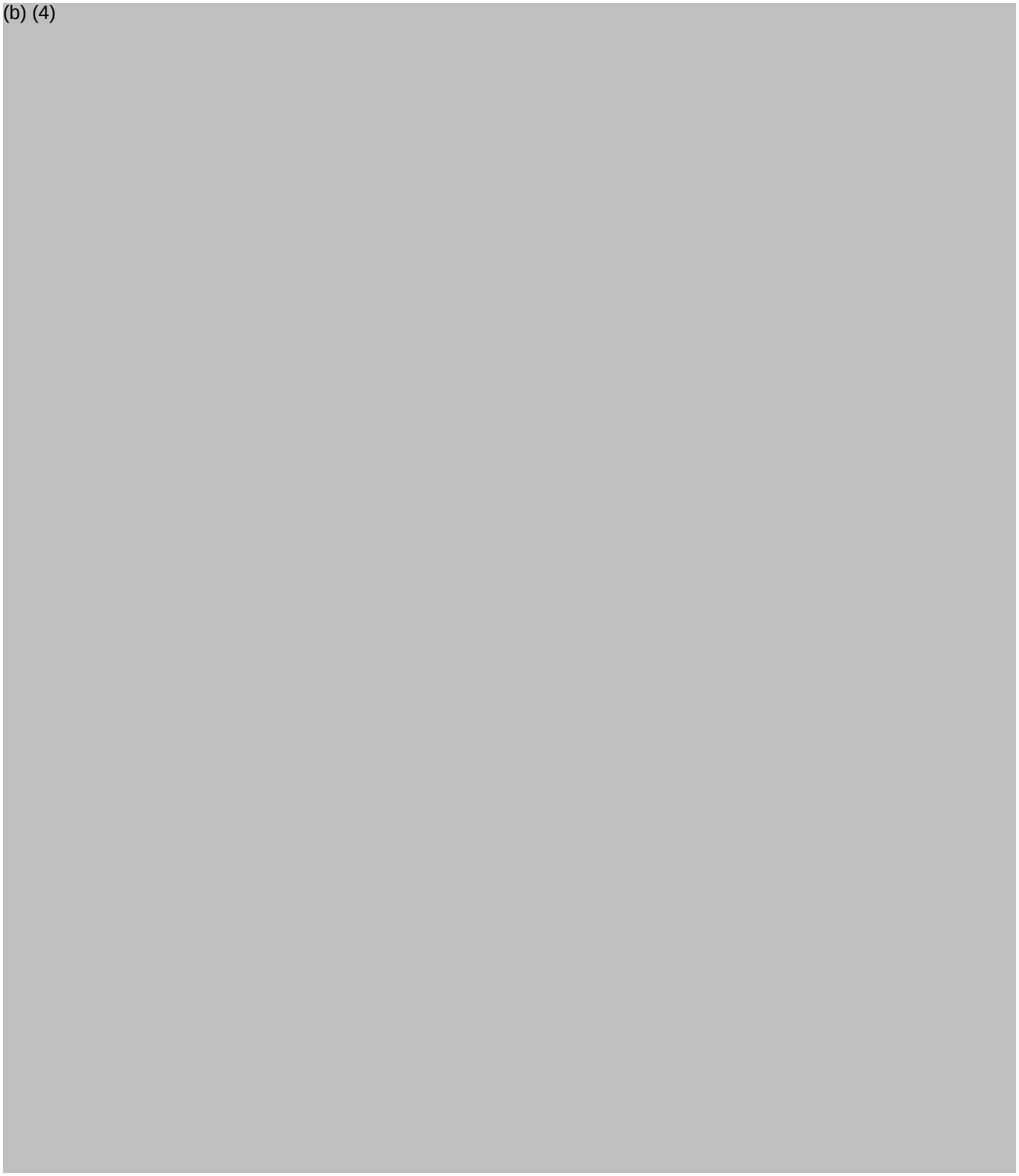


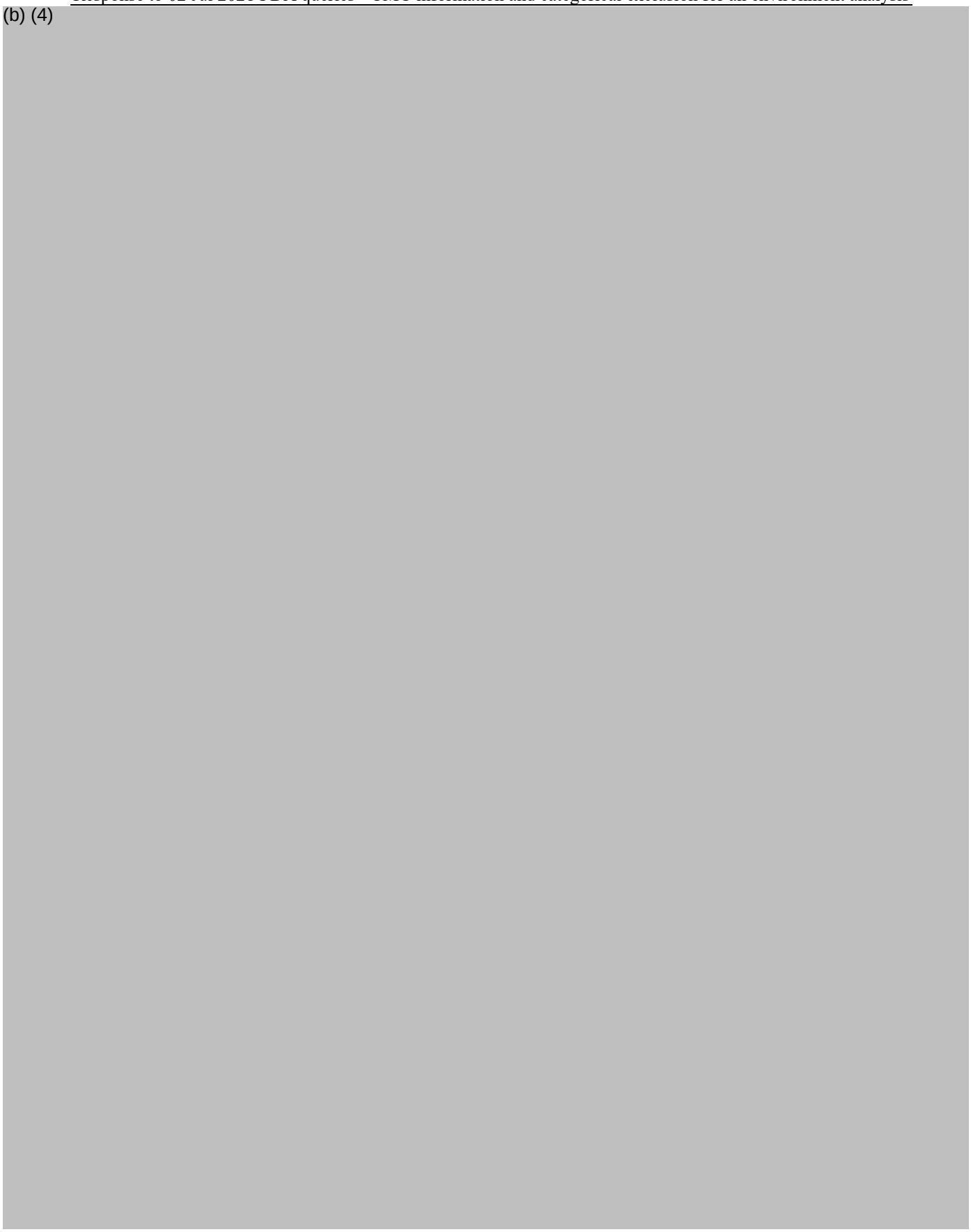
(b) (4)



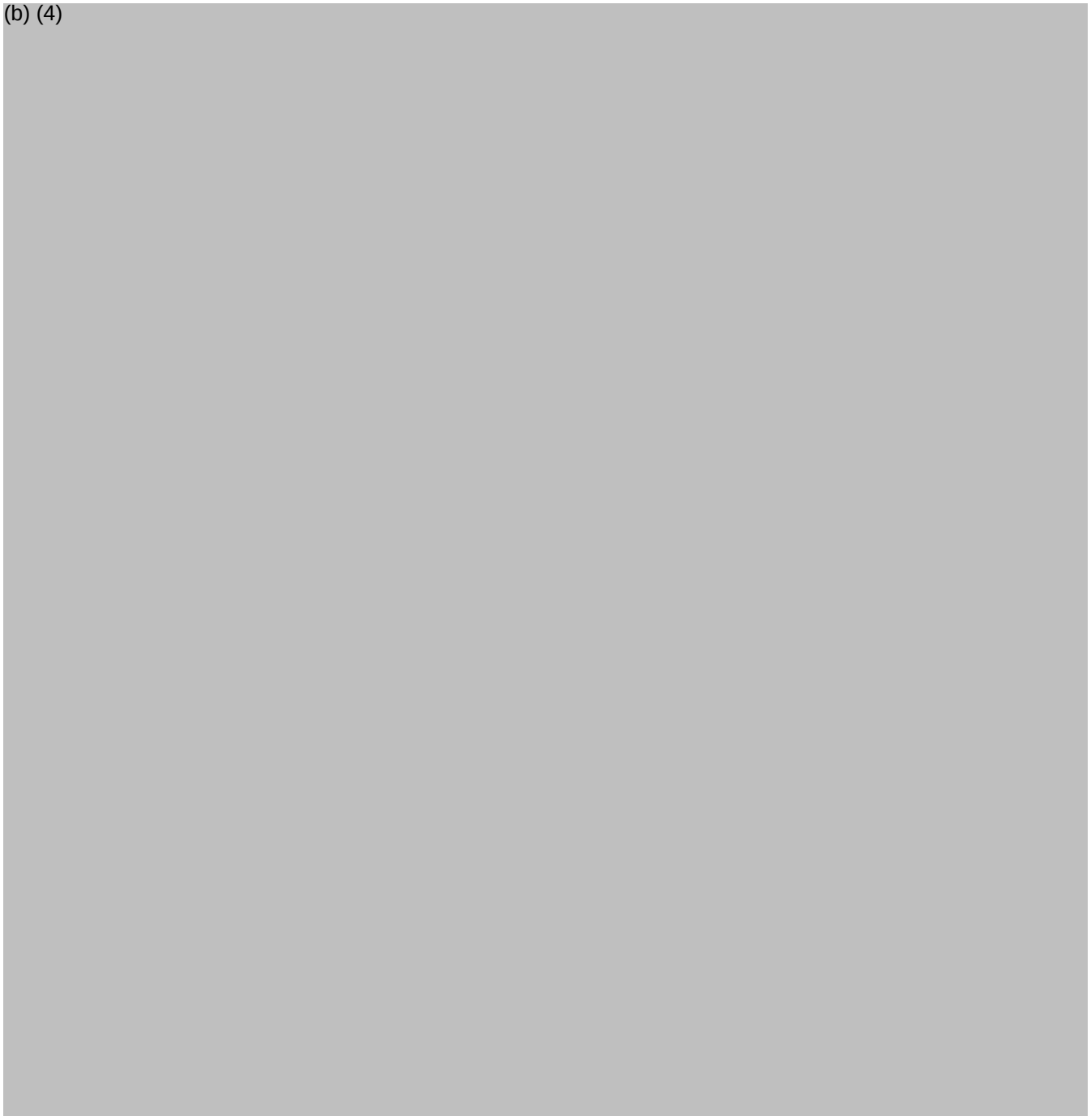
(b) (4)



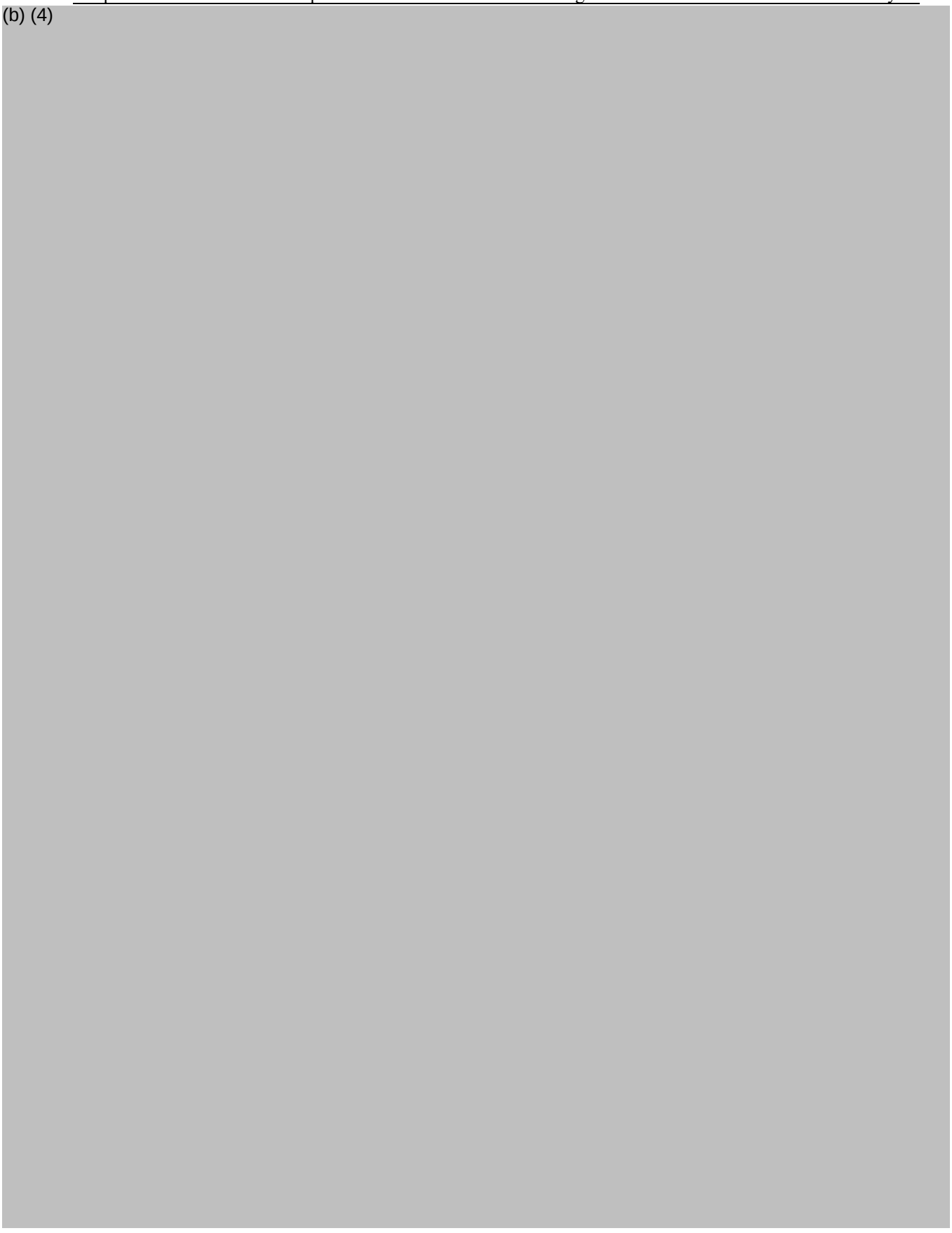
(b) (4)



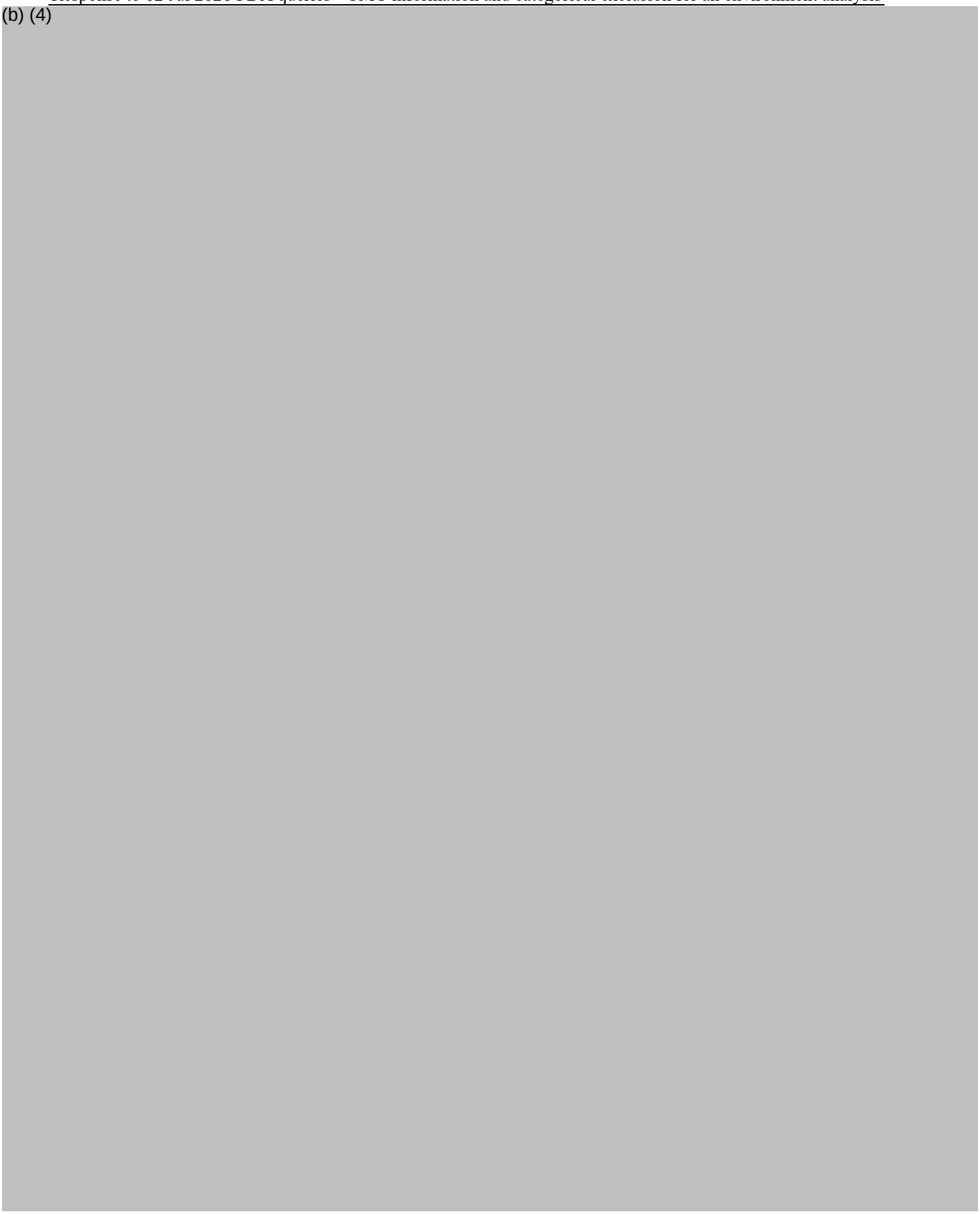
(b) (4)



(b) (4)

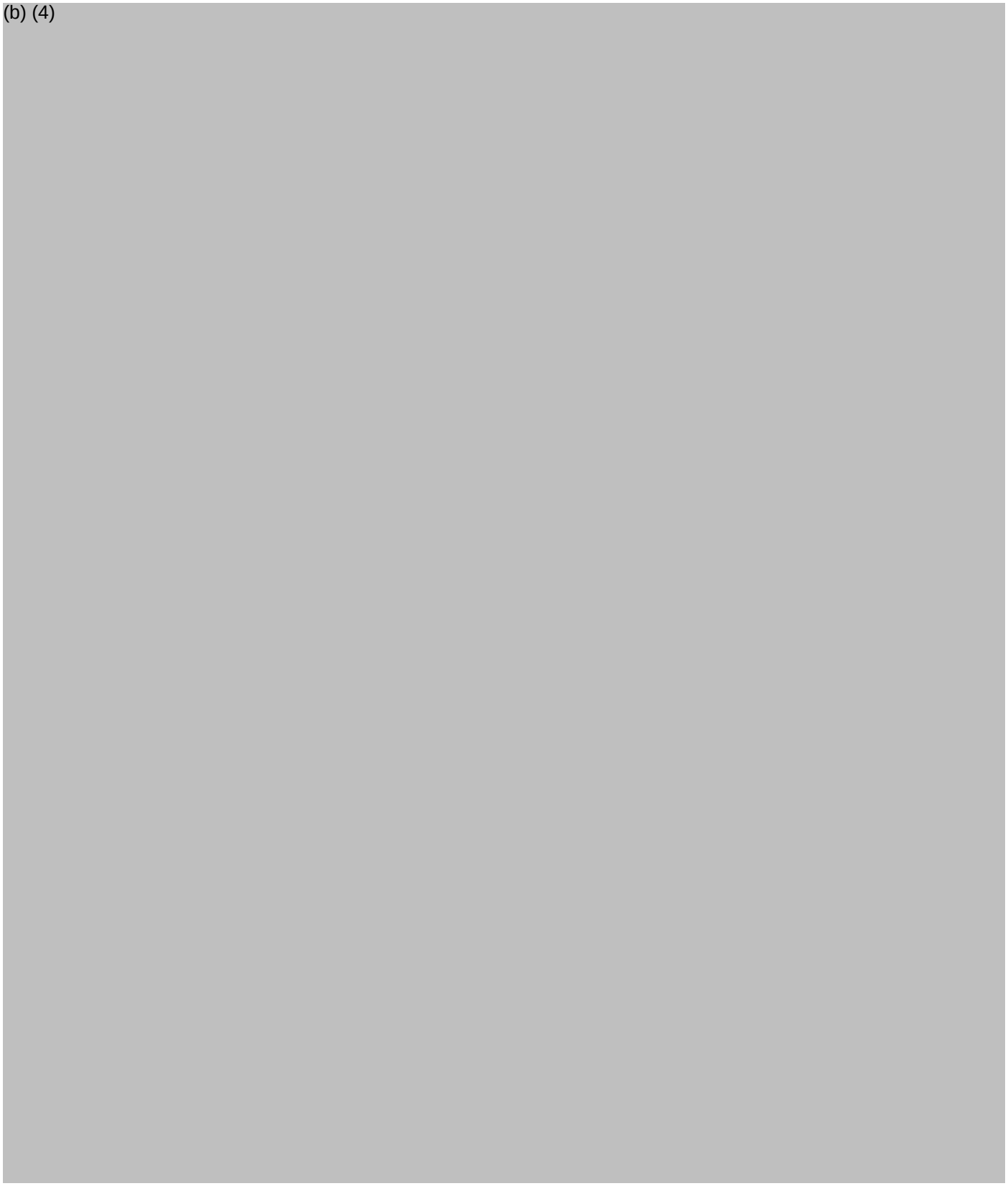


(b) (4)



(b) (4)

(b) (4)



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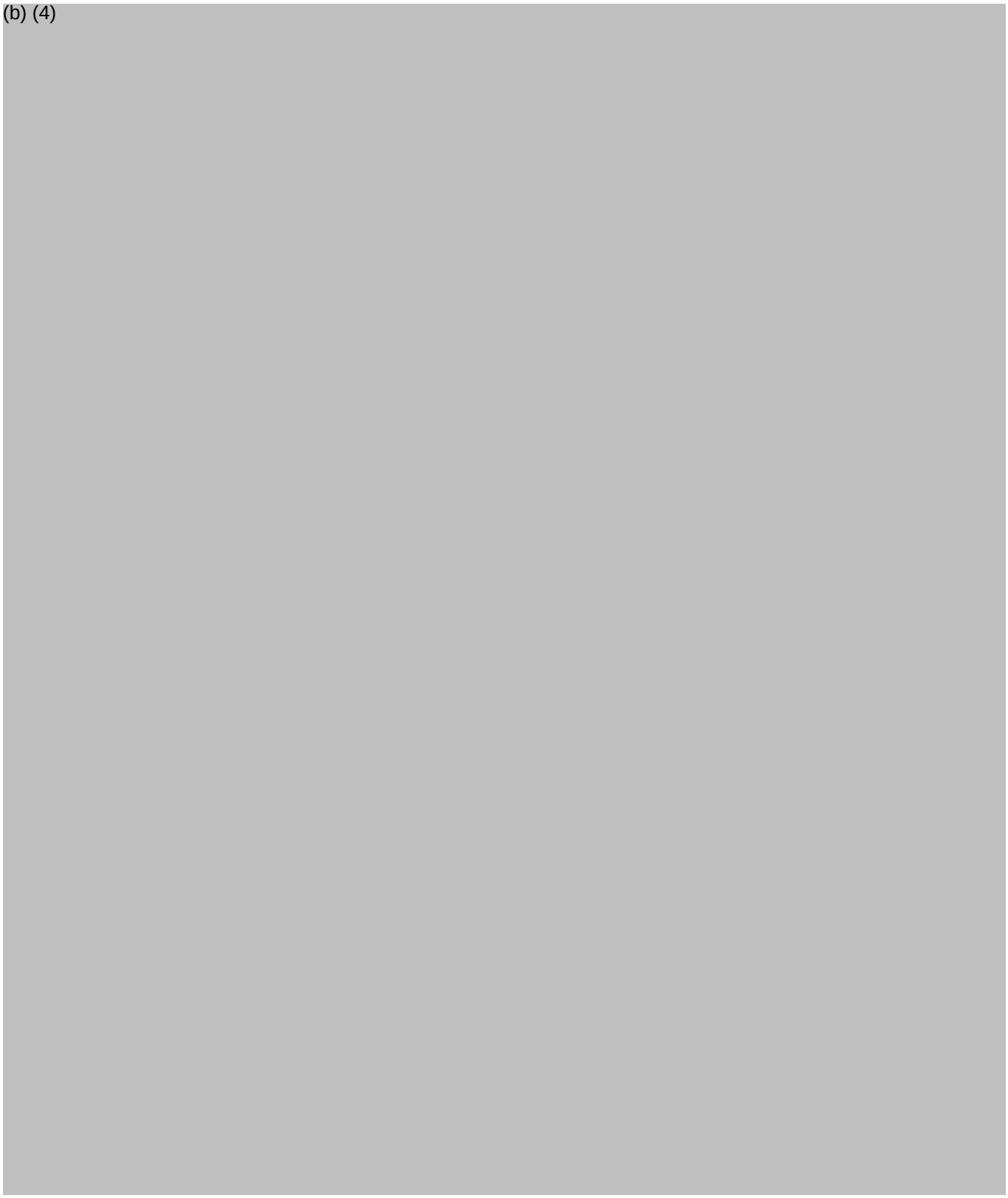
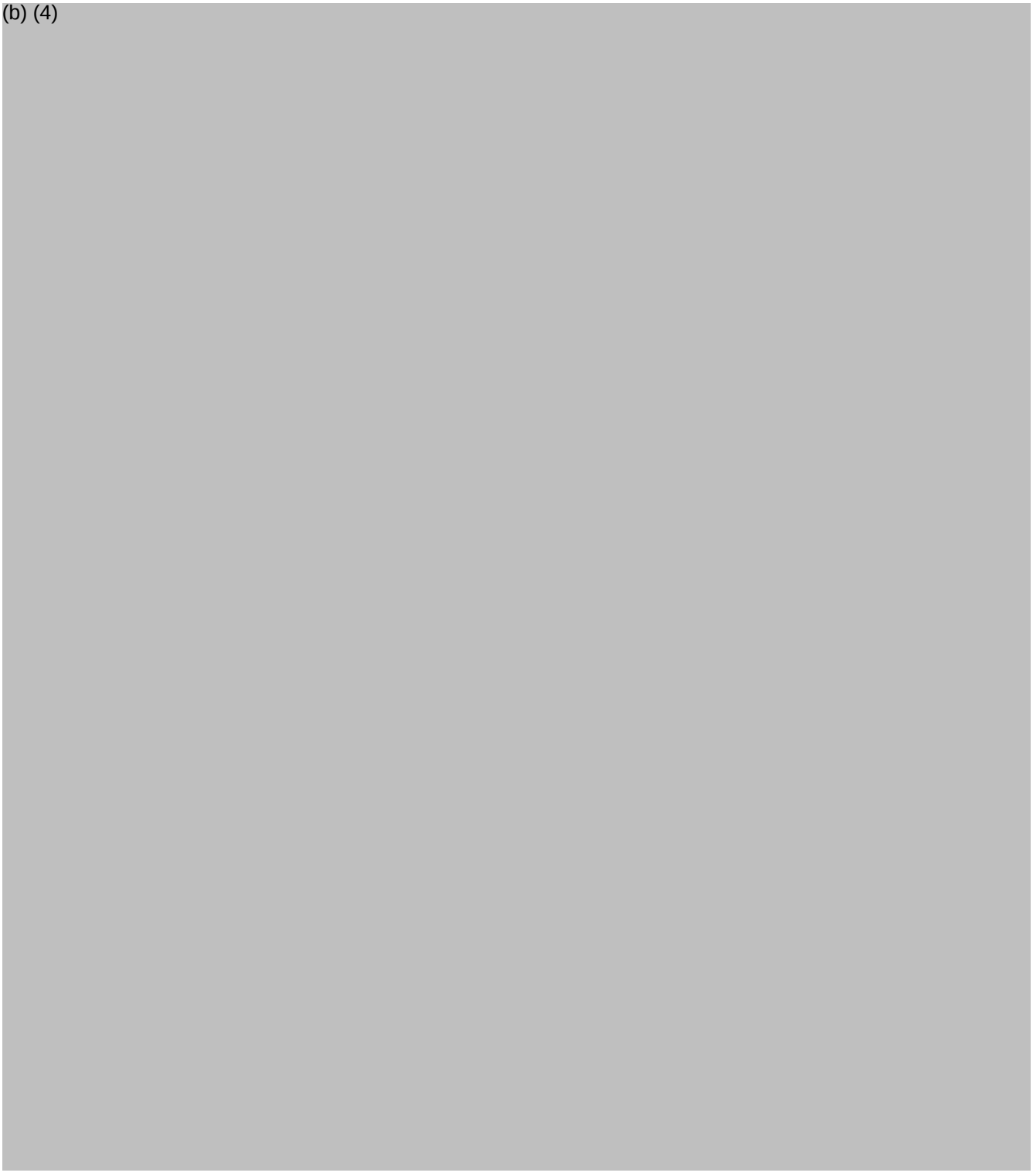
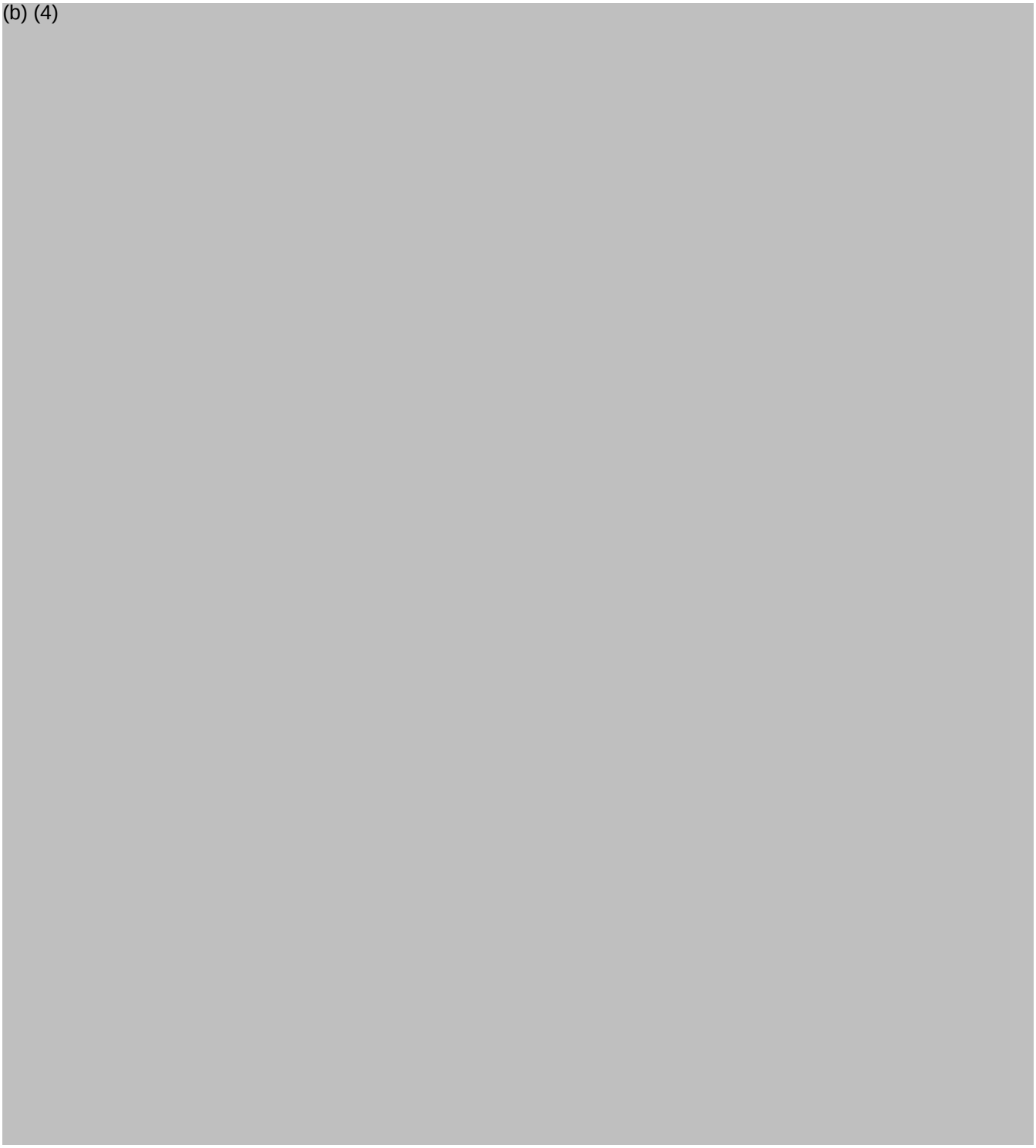


(b) (4)



(b) (4)



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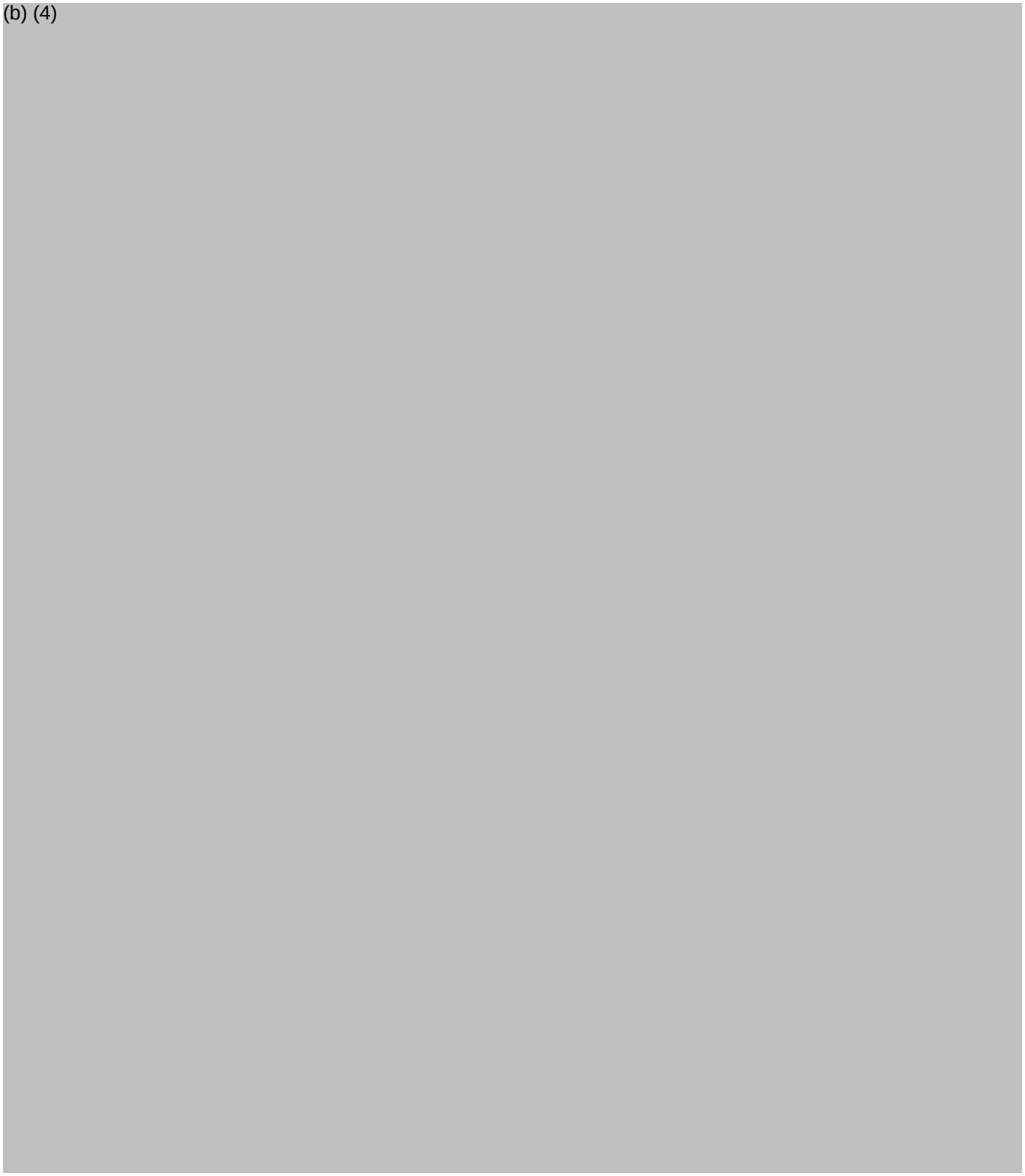




**Conclusion:**

Based on the acceptable criteria, the (b) (4) is acceptable (b) (4) with the exception of the residual DNA template result for batch (b) (4) which is being

investigated for root cause, all other results that exceeded (b) (4) monitoring limits have been determined to be unrelated to (b) (4).

**Literature References**

None

**SUPPORTING DOCUMENTATION**

**New or Replaced Supporting Documentation**

None

**Previously submitted supporting documentation**

None

## QUERY 3

In Figure 3.2.S.2.2-1 RNA Manufacturing Process, step yield is designated as a process performance attribute throughout the manufacturing process. Please specify the acceptable range/control limit at each manufacturing step (i.e., (b) (4) (b) (4) ) to ensure appropriate monitoring and controls during the manufacture of DS.

## RESPONSE 3

(b) (4)

### Literature References

None

### SUPPORTING DOCUMENTATION

### New or Replaced Supporting Documentation

None

### Previously submitted supporting documentation

None

## QUERY 4

Regarding the action limits for bioburden and endotoxin testing listed in document 3.2.S.2.2 Manufacturing Process Andover, it appears that there are multiple typographical errors ("≤" instead of ">") in Table 3.2.S.2.2-4 In-Process Tests (Monitoring) for (b) (4) Control and in Table 3.2.S.2.2-7 In-Process Tests (Monitoring) for (b) (4) Control. Please confirm and correct the errors.

## RESPONSE 4

The Bioburden and Endotoxin limits listed in Table 3.2.S.2.2-4 and 3.2.S.2.2-7 are designated as Action limits that would require an action when the limits are exceeded. In Pfizer's quality system, a test result greater than the action limit requires an investigation and therefore the symbols are accurate as depicted.

(b) (4)

**Literature References**

None

**SUPPORTING DOCUMENTATION**

**New or Replaced Supporting Documentation**

None

**Previously submitted supporting documentation**

None

## REGARDING THE FILL AND FINISH MANUFACTURING PROCESS

## QUERY 5

Please update the documents 3.2.P.3.3 Description of Manufacturing Process and Process Controls – LNP Production and Bulk Drug Product Formulation [Puurs] to include a brief description for the primary areas and equipment involved in BNT162b2 LNP production and bulk DP formulation.

## RESPONSE 5

An updated Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls – LNP Production and Bulk Drug Product Formulation [Puurs] is provided to include the primary areas and their classifications.

### Literature References

None

### SUPPORTING DOCUMENTATION

### New or Replaced Supporting Documentation

3.2.P.3.3 Description of Manufacturing Process and Process Controls – LNP Production and Bulk Drug Product Formulation [Puurs], replaced

### Previously submitted supporting documentation

None

## QUERY 6

You stated that (b) (4) (b) (4) Please provide relevant supportive data (e.g., stability of the (b) (4) ) to demonstrate that this (b) (4) step has no significant impact on the quality of the (b) (4) .

## RESPONSE 6

As described in previously provided Section 3.2.P.2.3 Process Development and Characterization, subsection 3.2.P.2.3.3.2 Characterization of (b) (4) (b) (4) (b) (4) Operations, a study was performed with BNT162b2 (b) (4) using batch (b) (4) .

(b) (4)

### Literature References

None

### SUPPORTING DOCUMENTATION

### New or Replaced Supporting Documentation

None

### Previously submitted supporting documentation

(b) (4)

Section 3.2.P.2.3 Process Development and Characterization

## QUERY 7

You stated that (b) (4) (b) (4) between lots. (b) (4)

### Literature References

None

### SUPPORTING DOCUMENTATION

### New or Replaced Supporting Documentation

Section 3.2.P.3.5 Process Validation and/or Evaluation – (b) (4) (b) (4) [Puurs], new

Section 3.2.P.3.5 Process Validation and/or Evaluation – (b) (4) (b) (4) [Kalamazoo], new

### Previously submitted supporting documentation

None

## QUERY 8

Please clarify whether the (b) (4) (b) (4) steps) at Pfizer Kalamazoo submitted to IND/EUA will also be implemented under the BLA. Please update the relevant documents if you intend to include (b) (4) for the manufacture of the DP at Pfizer Kalamazoo.

## RESPONSE 8

Pfizer Kalamazoo intends to implement (b) (4) under the BLA. The (b) (4) will be submitted to the BLA as a post-approval change.

### Literature References

None

### SUPPORTING DOCUMENTATION

### New or Replaced Supporting Documentation

None

### Previously submitted supporting documentation

None

## QUERY 9

Regarding the process control/parameters, please address the following at each manufacturing site (Puurs and Kalamazoo):

Please specify the (b) (4) for DS (b) (4)
Please specify the (b) (4) .

## RESPONSE 9

**Puurs**

(b) (4)

**Kalamazoo**

(b) (4)

**Literature References**

None

**SUPPORTING DOCUMENTATION**

**New or Replaced Supporting Documentation**

Section 3.2.P.3.3 LNP Production and Bulk Drug Product Formulation [Puurs], replaced

**Previously submitted supporting documentation**

None

## QUERY 10

Please update the documents 3.2.P.3.3 Description of Manufacturing Process and Process Controls – Fill and Finish [Puurs] to include a brief description for the primary areas and equipment involved in BNT162b2 DP fill and finish operations.

## RESPONSE 10

An updated Section 3.2.P.3.3 Fill and Finish [Puurs] is provided to include the primary areas and their classifications. Additionally, Table 3.2.P.3.3-6 Process Parameters for Capping is updated to correct inverted values between the (b) (4) (typographical error).

### Literature References

None

### SUPPORTING DOCUMENTATION

### New or Replaced Supporting Documentation

Section 3.2.P.3.3 Fill and Finish [Puurs], replaced

### Previously submitted supporting documentation

None

## QUERY 11

Please update the Table 3.2.P.3.3-8 Process Parameters for Storage Shipping to define the maximum allowable numbers of (b) (4) (b) (4) EUA 27034 in amendment 176 on May 17, 2021.

## RESPONSE 11

Footnote d (in Table 3.2.P.3.3-8 Process Parameters for Storage and Shipping and Table 3.2.P.3.4-2 Time Out of Storage Condition for BNT162b2 Drug Product) has been updated to include a maximum of (b) (4) A representative table, as updated in the relevant sections for both Puurs and Kalamazoo, is shown below.

(b) (4)

**Literature References**

None

**SUPPORTING DOCUMENTATION**

**New or Replaced Supporting Documentation**

Section 3.2.P.3.3 Fill and Finish [Puurs], replaced

Section 3.2.P.3.3 Fill and Finish [Kalamazoo], replaced

Section 3.2.P.3.4 Process Step Hold Times – Fill and Finish [Puurs], replaced

Section 3.2.P.3.4 Process Step Hold Times – Fill and Finish [Kalamazoo], replaced

**Previously submitted supporting documentation**

None

## REGARDING THE ANALYTICAL PROCEDURES

## QUERY 12

Please identify all the test sites that will be used for the release and stability testing of the BNT162b2 DS and DP under the BLA submission and include listings for analytical procedures performed at each site. Please note that site-specific validation studies for analytical procedures or the demonstration of comparable assay performance of the receiving site to the transfer site that completed the validation are required for BLA submission.

## RESPONSE 12

All test sites used for release and stability testing of the BNT162b2 DS and DP under BLA submission are included in Section 3.2.S.2.1 Manufacturer(s) and Section 3.2.P.3.1 Manufacturer(s).

Section 3.2.R Standard Operating Procedures, Method Validation and Transfer Reports includes listings for analytical procedures performed at each site and has been updated to include additional DS and DP testing sites filed to the EUA on June 30, 2021 and to be filed to the EUA by July 30, 2021. (b) (4) Due to these additions, analytical procedures are updated with minor edits and included (see Supporting Documentation below).

The appropriate supportive documentation (analytical procedures and validation/transfer) for each testing site which is referenced in Section 3.2.R Standard Operating Procedures, Method Validation and Transfer Reports is also available within the 3.2.R section.

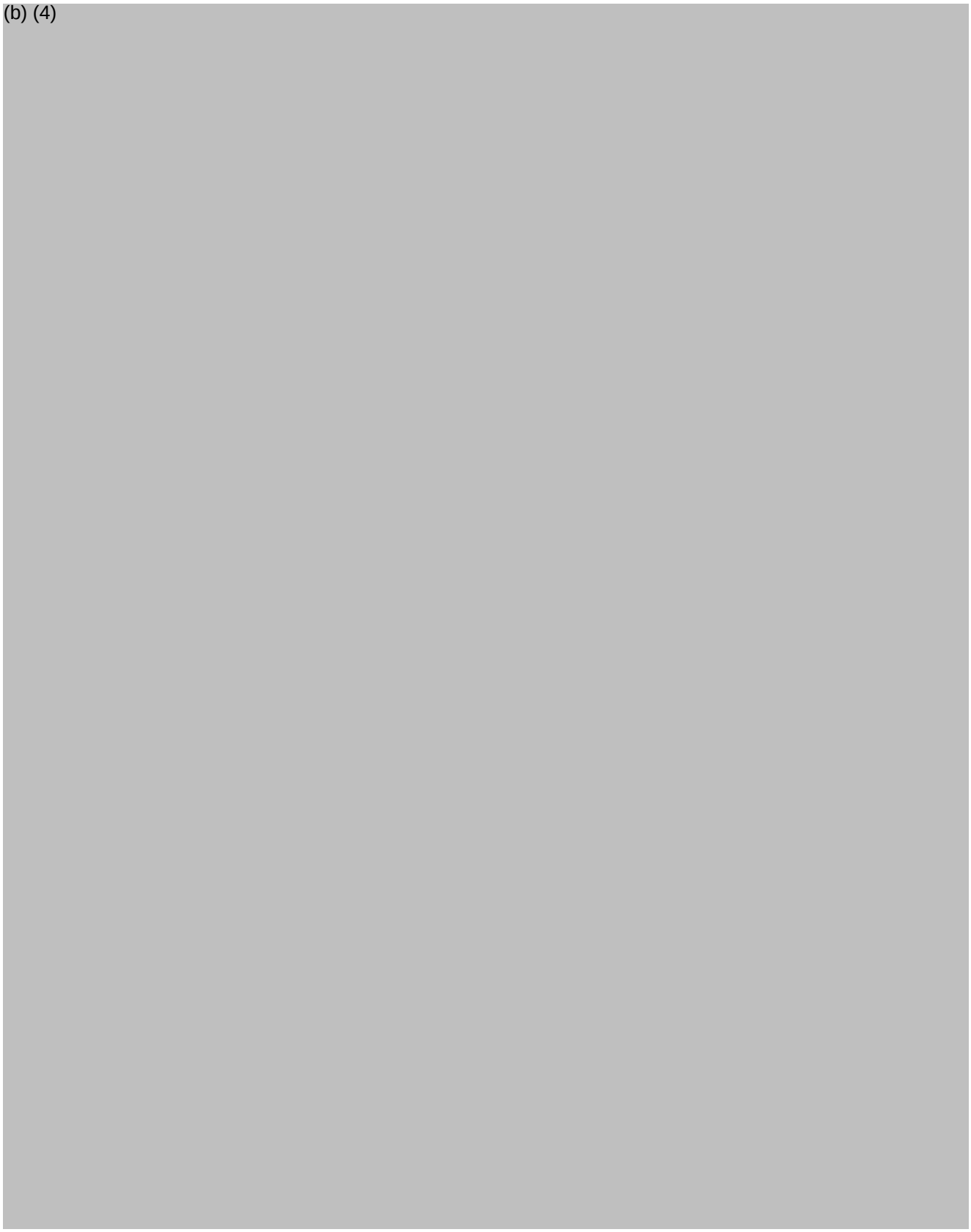
**Literature References**

None

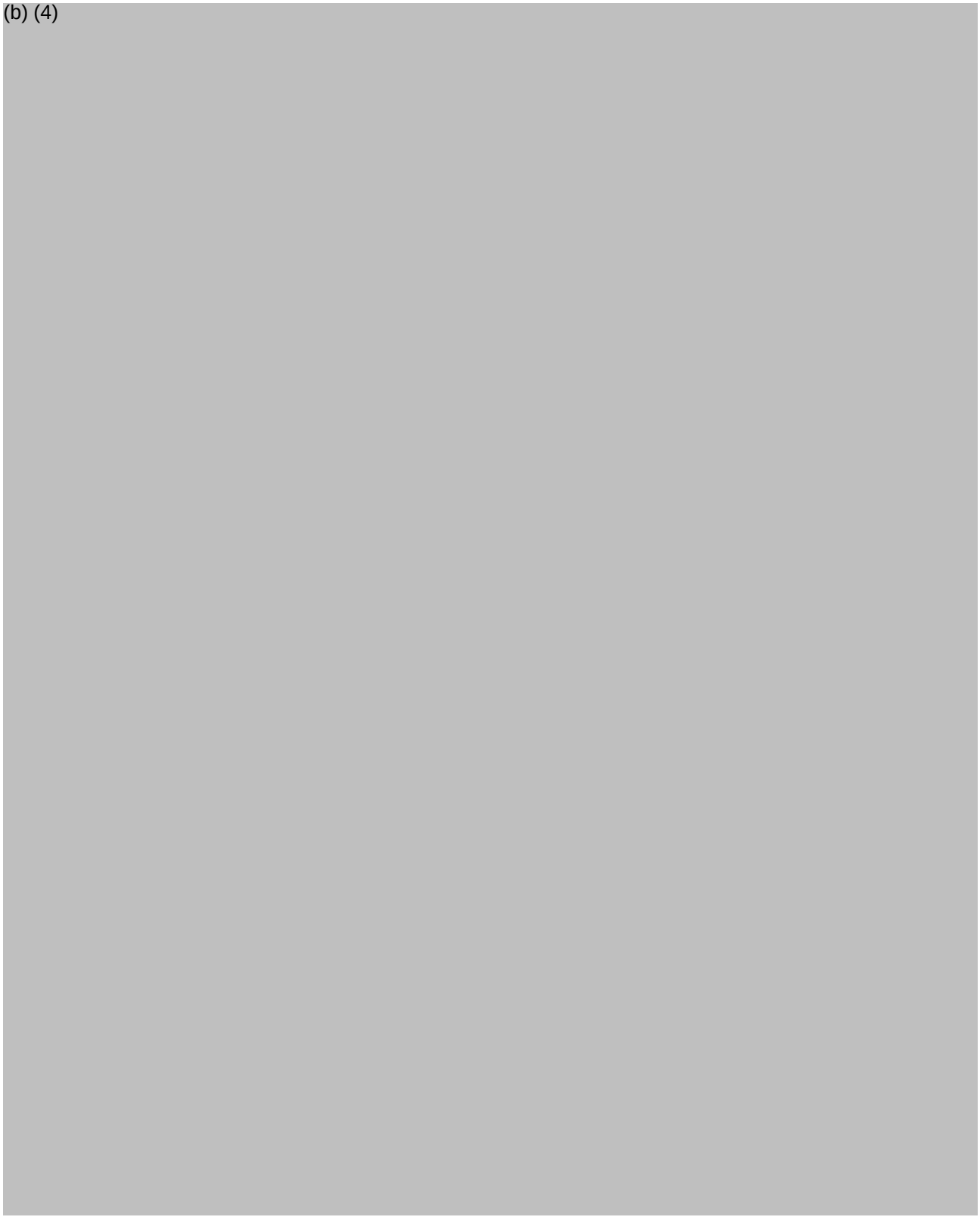
**SUPPORTING DOCUMENTATION**

**New or Replaced Supporting Documentation**

(b) (4)



(b) (4)



## REGARDING THE REFERENCE STANDARDS USED IN THE ANALYTICAL ASSAYS

### QUERY 13

We acknowledge that qualifications of the analytical assays were originally conducted to support vaccine distribution under the EUA. However, validation of the analytical release assays for DS and DP is required for the BLA submission and pre-established acceptance criteria should be based on your previous qualification studies. Please provide the full validation reports for the following analytical procedures:

a. Quantification of Poly(A) tail in BNT162b2 DS by ddPCR

b. Quantification of residual DNA template content in BNT162b2 DS by qPCR

c. Quantification of total RNA concentration and the relative percentage of encapsulated RNA in BNT162b2 DP by (b) (4) fluorescence assay

d. Determination of the in-vitro expression of the BNT162b2 DP by cell-based flow cytometry

### RESPONSE 13

The following sections are updated with validation and/or transfer data supporting multiple testing sites:

- 3.2.S.4.3 Validation of Analytical Procedure – qPCR
- 3.2.S.4.3 Validation of Analytical Procedure – ddPCR
- 3.2.P.5.3 Validation of Analytical Procedure – Fluorescence
- 3.2.P.5.3 Validation of Analytical Procedure – Cell-based Flow Cytometry

In addition, the 3.2.R Standard Operating Procedures, Method Validation and Transfer Reports is updated with all references to supporting documentation (Method SOP's and full validation and/or transfer reports for each site). The 3.2.S.4.2 Analytical Procedures – qPCR and 3.2.P.5.2 Analytical Procedures – Fluorescence is also updated to outline method changes addressed in the EUA submitted on 30 June 2021 and to be filed to the EUA by 30 July 2021 respectively.

**Literature References**

None

## SUPPORTING DOCUMENTATION

### New or Replaced Supporting Documentation

- 3.2.S.4.3 Validation of Analytical Procedure – qPCR- Replaced
- 3.2.S.4.3 Validation of Analytical Procedure – ddPCR - Replaced
- 3.2.P.5.3 Validation of Analytical Procedure – Fluorescence - Replaced
- 3.2.P.5.3 Validation of Analytical Procedure – Cell-based Flow Cytometry - Replaced
- 3.2.R Standard Operating Procedures, Method Validation and Transfer Reports - Replaced
- 3.2.S.4.2 Analytical Procedures – qPCR - Replaced
- 3.2.P.5.2 Analytical Procedures – Fluorescence - Replaced

### Previously submitted supporting documentation

None

## QUERY 14

Please confirm that the BNT162b2 DS assay control used in multiple DS analytical procedures (i.e., CGE for RNA integrity, RP-HPLC for 5'-cap, ddPCR for poly(A) tail, and immunoblot for dsRNA) is the same one ((b) (4) ) as described in Section 3.2.S.5 Reference Standards or Materials.

## RESPONSE 14

The drug substance (DS) analytical procedures do not require the use of DS reference material (b) (4) ). Any DS batch that meets the release criteria (3.2.S.4.1 Specification) at the time of manufacture is suitable as a control. DS material will be used as an internal control representative of the sample tested.

### Literature References

None

### SUPPORTING DOCUMENTATION

### New or Replaced Supporting Documentation

None

### Previously submitted supporting documentation

None

## QUERY 15

Please update the document 3.2.P.6 Reference Standards and Materials to describe the BNT162b2 DP assay control(s) used in multiple DP analytical procedures (e.g., CGE for RNA integrity, in vitro expression potency assay, fluorescence assay for RNA content and RNA encapsulation, and DLS for LNP size and polydispersity), including the DP lot number, the lot-release testing results, the qualification data to support its intended use as a reference standard, and any available stability data.

## RESPONSE 15

The DP assay controls used within multiple DP analytical procedures (CGE for RNA integrity, in vitro expression potency assay, fluorescence assay for RNA content and RNA encapsulation, and DLS for LNP size and polydispersity) are not considered reference standards since the final sample results do not rely on quantitation of this material in the method. They are used as an internal control representative of the sample tested. Any DP batch that meets the release criteria (3.2.P.5.1 Specification) at the time of manufacture is suitable as a control.

**Literature References**

None

**SUPPORTING DOCUMENTATION**

**New or Replaced Supporting Documentation**

None

**Previously submitted supporting documentation**

None

## REGARDING THE CLINICAL ASSAYS

### QUERY 16

Please submit the SOP VR-TM-10295 for the Cepheid Xpert Xpress SARS-CoV-2 RT-PCR assay.

### RESPONSE 16

SOP VR-TM-10295 for the Cepheid Xpert Xpress SARS-CoV-2 RT-PCR is attached.

**Literature References**

None

**SUPPORTING DOCUMENTATION**

**New or Replaced Supporting Documentation**

VR-TM-10295

**Previously submitted supporting documentation**

None

## QUERY 17

Please provide the method validation report(s) for the Single-plex Direct Luminex assay (dLIA) for quantification of IgG antibodies to SARS-CoV-2 S1 and RBD proteins in human serum.

## RESPONSE 17

VR-MVR-10077, the method validation report for the Single-plex Direct Luminex assay (dLIA) for quantification of IgG antibodies to SARS-CoV-2 S1 and RBD proteins in human serum is attached.

**Literature References**

None

**SUPPORTING DOCUMENTATION**

**New or Replaced Supporting Documentation**

VR-MVR-10077

**Previously submitted supporting documentation**

None

## REGARDING THE CATEGORICAL EXCLUSION FOR AN ENVIRONMENT ANALYSIS

### QUERY 18

Please provide background information for the lipids in the LNP to support the claim that each of the lipids is naturally occurring and does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

### RESPONSE 18

As per the FDA July 1998 Guidance for Industry, submissions to CDER or CBER that ordinarily are excluded categorically under the regulations include actions on the use of an active moiety or drug substance. The pharmacologically active moiety or drug substance in COMIRNATY is messenger RNA (mRNA), which is recognized as naturally occurring. Therapeutic use of COMIRNATY will not significantly alter the concentration or distribution of mRNA, its metabolites, or degradation products in the environment.

COMIRNATY contains four pharmacologically inactive lipid excipients, each with a functional or structural purpose in the lipid nanoparticle (LNP) component of the drug product, as summarized in Table 15:

**Table 15. Lipid Components of COMIRNATY Lipid Nanoparticles**

| Lipid | Description | Chemical Name | Amount per dose (mg) |
|---|---|---|---|
| ALC-0315 | Novel cationic lipid | ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) | (b) (4) |
| ALC-0159 | Novel PEGylated lipid | 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide | |
| DSPC | Phospholipid | 1,2-Distearoyl-sn-glycero-3-phosphocholine | |
| Cholesterol | Sterol lipid | Cholesterol | |

The phospholipid (DSPC) and the sterol lipid (cholesterol) are both recognized as naturally occurring membrane lipids. Therapeutic use of COMIRNATY will not alter significantly the concentration or distribution of these lipids, their metabolites, or degradation products in the environment.

ALC-0315 and ALC-0159 are novel lipids and therefore not recognized as naturally occurring. However, the presence of these lipids in the drug product is not expected to have an impact on the environment, as the very conservatively estimated concentrations of each lipid at the point of entry into the aquatic environment will be significantly below 1 part per billion, as presented below.

(b) (4)

(b) (4)

(b) (4)

## Literature References

US Food and Drug Administration. Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications. Rockville, MD: Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research; July 1998.

The United States Census Bureau. U.S. and World Population Clock. Available from: https://www.census.gov/popclock. Accessed: 06 July 2021.

## SUPPORTING DOCUMENTATION

### New or Replaced Supporting Documentation

None

### Previously submitted supporting documentation

None