



Our STN: BL 125845/0

COMPLETE RESPONSE

July 7, 2025

Ultragenyx Pharmaceutical Inc.
Attention: Jad Adaimi
5000 Marina Blvd.
Brisbane, CA 94005

Dear Jad Adaimi:

Please refer to your Biologics License Application (b) (4)
for rebisufligene etisparvovec, (b) (4)
(b) (4)

We have completed our review of all the submissions you have made relating to this BLA with the exception of the information in the amendments submitted (b) (4). After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

Chemistry, Manufacturing, and Controls (CMC)

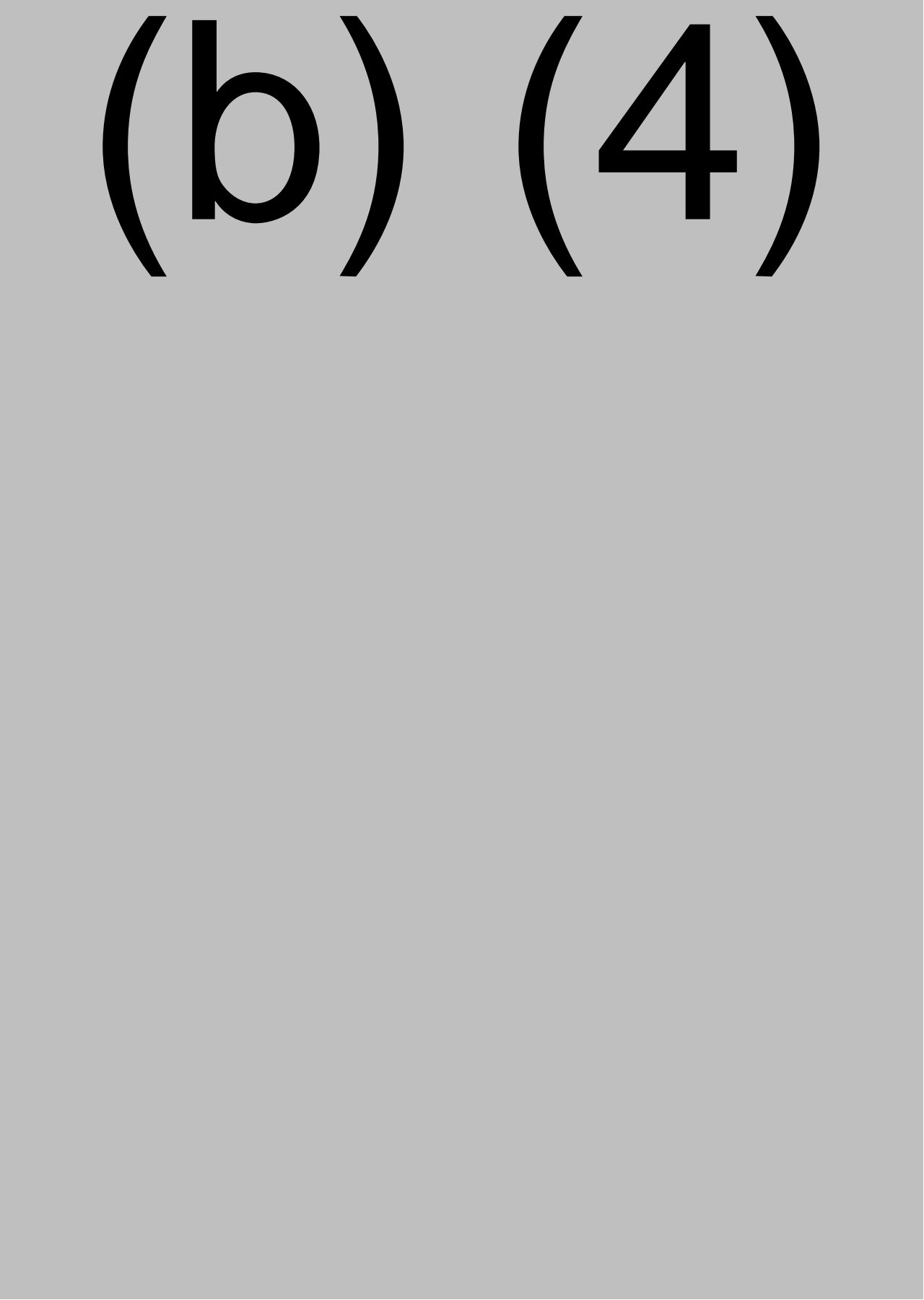
1. CBER conducted a pre-license inspection (PLI) of Ultragenyx Pharmaceutical Inc. in (b) (4), and issued a Form FDA 483, List of Inspectional Observations. CBER has reviewed your responses to the Form FDA 483 received through (b) (4), which do not sufficiently address the deficiencies noted during the inspection. Your corrective actions do not appear to be comprehensive enough to address the systemic issues observed during the inspection. Additionally, your represented corrections may require additional review and verification during a follow-up inspection and therefore remain unresolved. Pursuant to 21 CFR 601.20(a) and (d), at this time, CBER cannot determine that the product and establishment listed in the BLA comply with the standards established in the BLA and the requirements prescribed in FDA regulations, including Current Good Manufacturing Practice requirements.
2. CBER conducted a pre-license inspection (PLI) of Ultragenyx Pharmaceutical Inc. in (b) (4), and issued a Form FDA 483, List of Inspectional Observations. CBER has reviewed your responses to the Form FDA 483 received through (b) (4), which do not sufficiently address the deficiencies noted during the inspection. Your

corrective actions do not appear to be comprehensive enough to address the systemic issues observed during the inspection. Additionally, your represented corrections may require additional review and verification during a subsequent inspection and therefore remain unresolved. Pursuant to 21 CFR 601.20(a) and (d), at this time, CBER cannot determine that the product and establishment listed in the BLA comply with the standards established in the BLA and the requirements prescribed in FDA regulations, including Current Good Manufacturing Practice requirements.

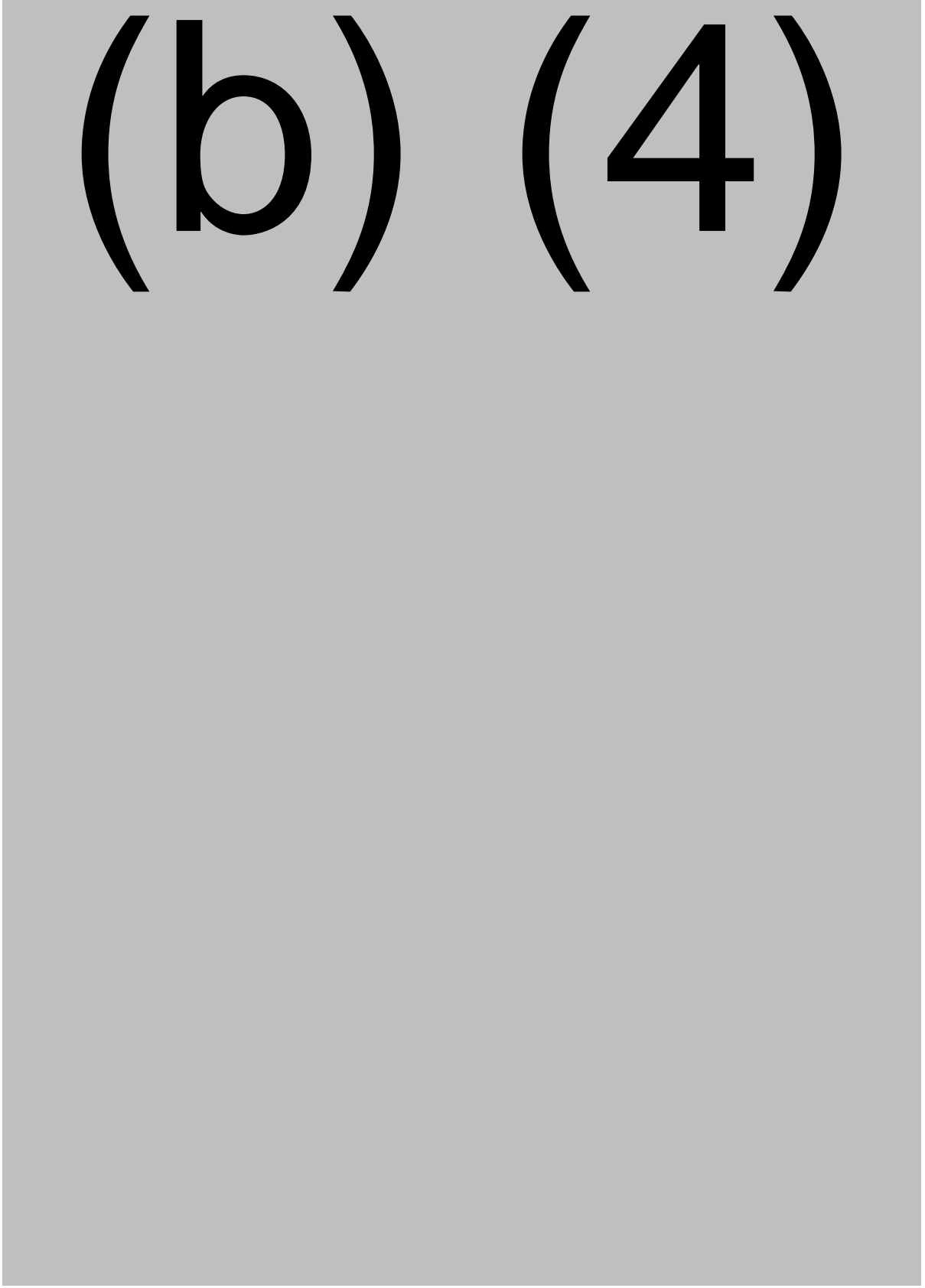
3. CBER conducted a pre-license inspection (PLI) of (b) (4), and issued a Form FDA 483, List of Inspectional Observations. CBER has reviewed your responses to the Form FDA 483 received through (b) (4) which do not sufficiently address the deficiencies noted during the inspection. Your corrective actions do not appear to be comprehensive enough to address the systemic issues observed during the inspection. Additionally, your represented corrections may require additional review and verification during a subsequent inspection and therefore remain unresolved. Pursuant to 21 CFR 601.20(a) and (d), at this time, CBER cannot determine that the product and establishment listed in the BLA comply with the standards established in the BLA and the requirements prescribed in FDA regulations, including Current Good Manufacturing Practice requirements.

(b) (4)

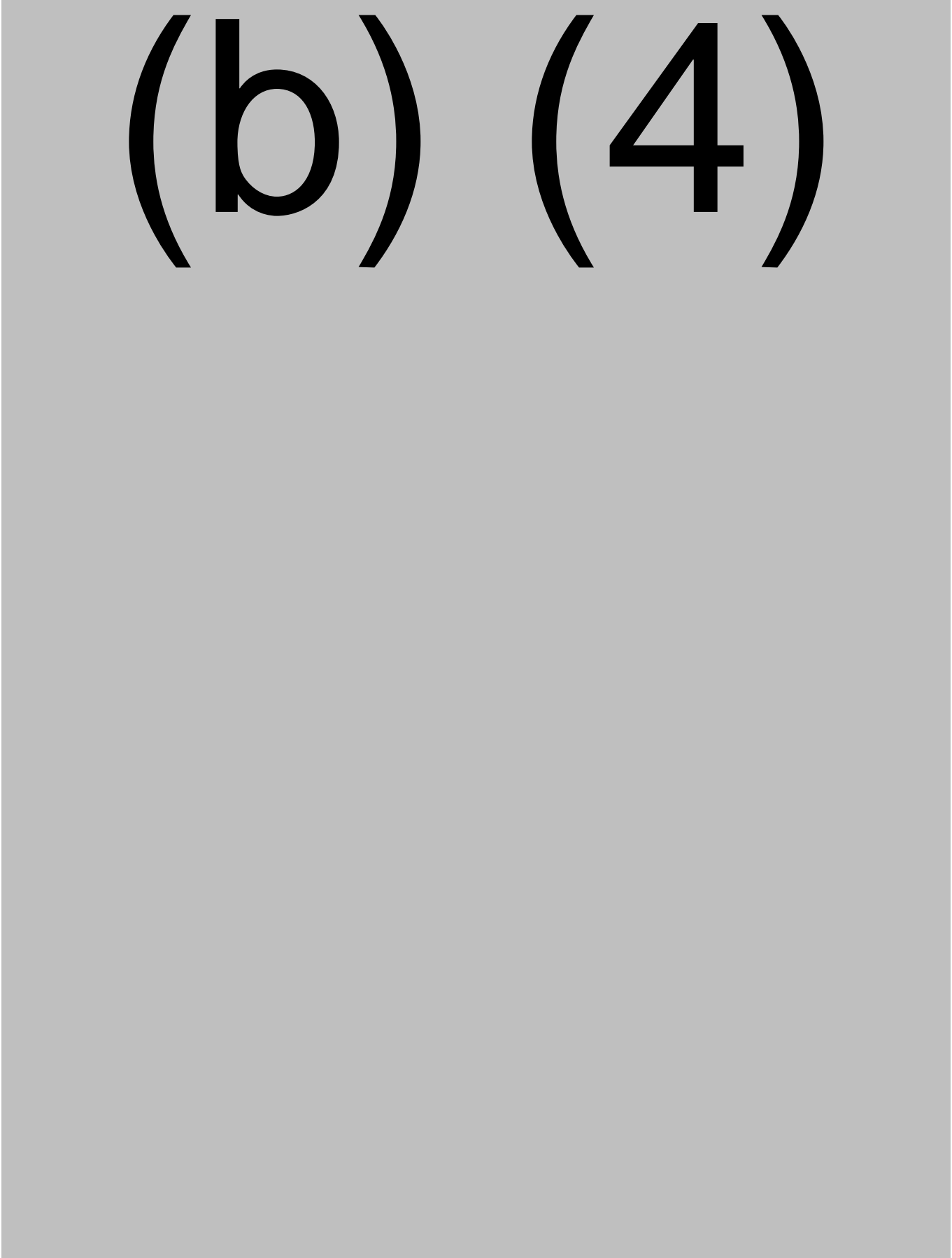
(b) (4)



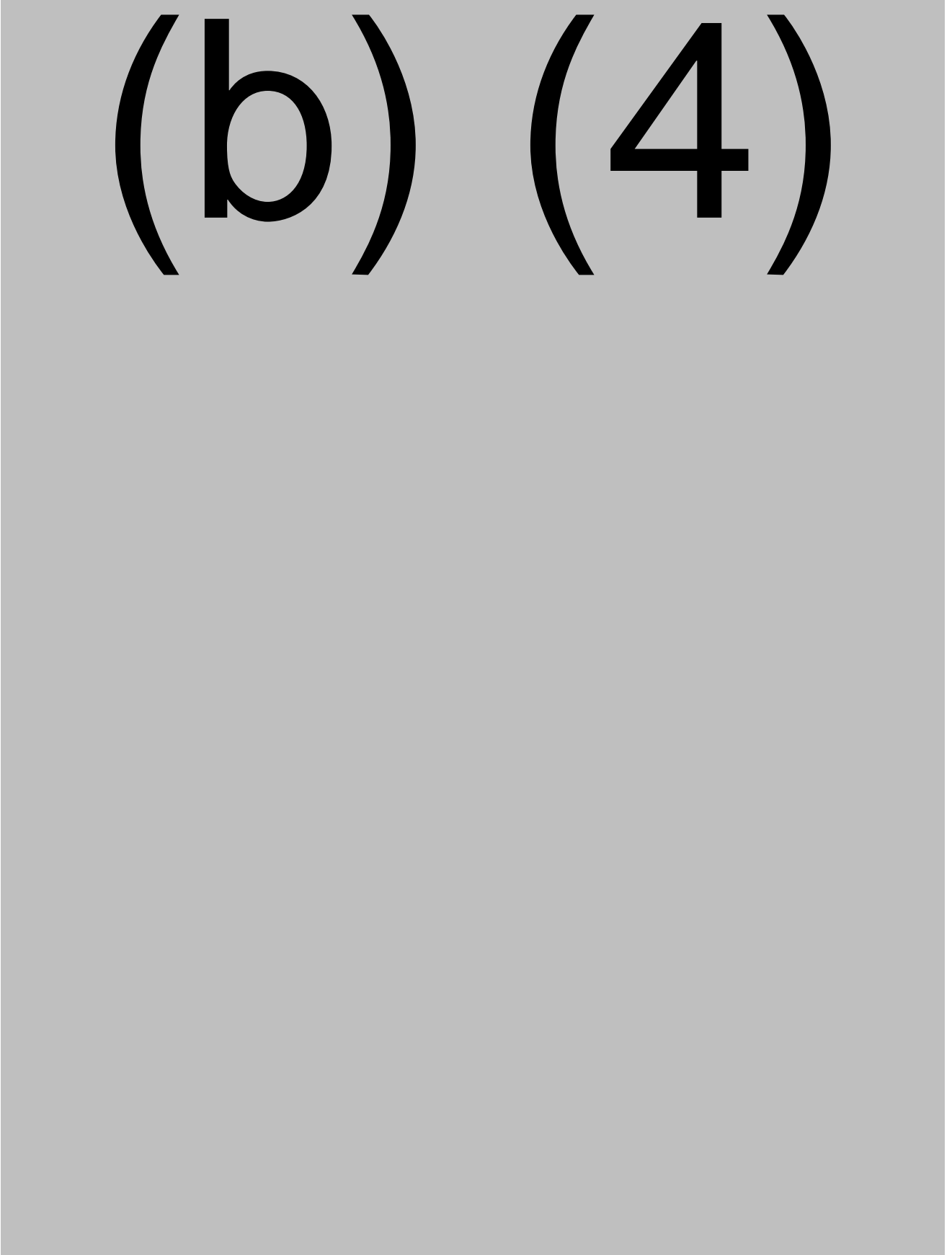
(b) (4)



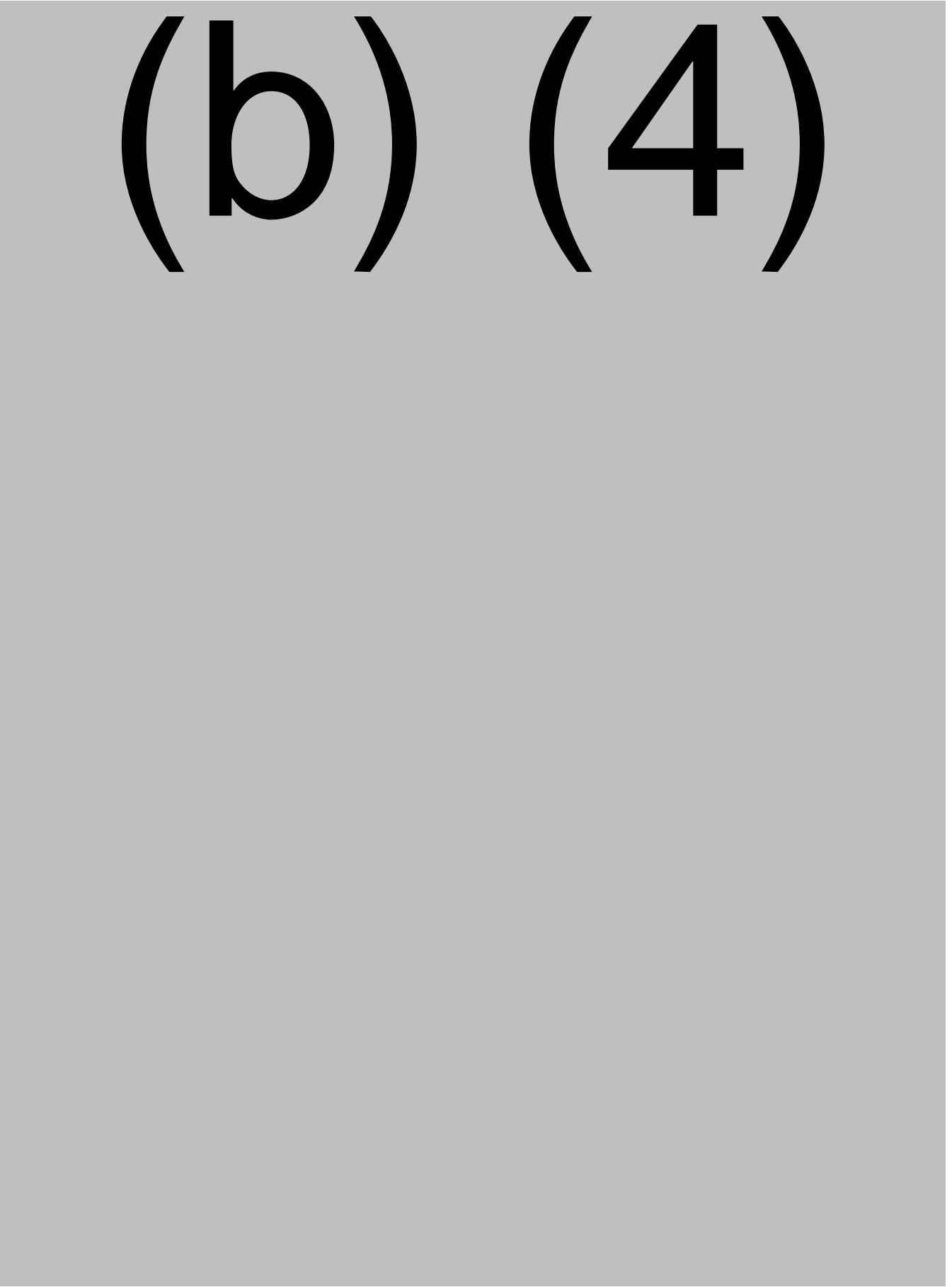
(b) (4)



(b) (4)



(b) (4)



(b) (4)

ADDITIONAL COMMENTS

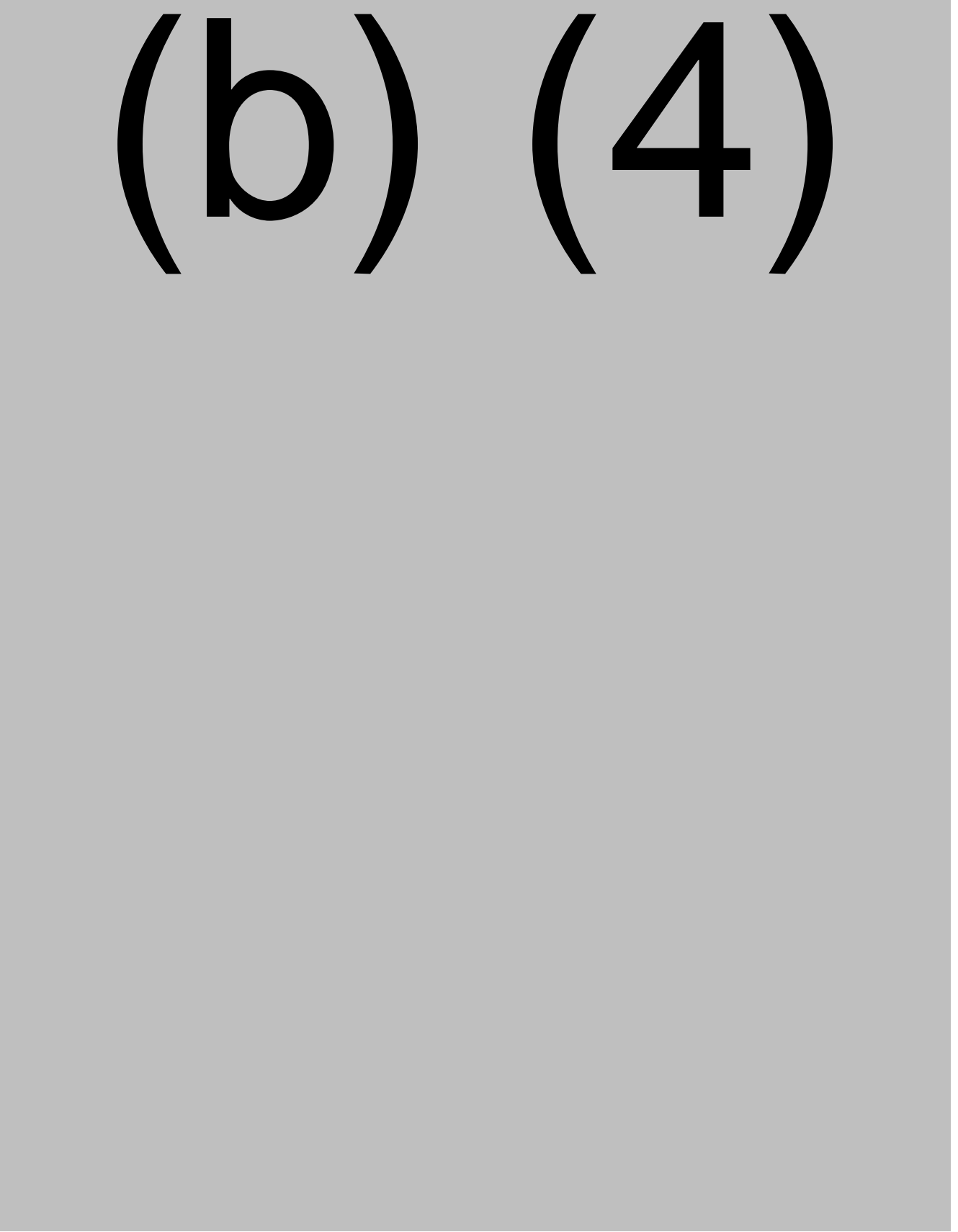
CMC

9. The review of the Lot Release Protocol template will be completed when the issues identified in the complete response letter have been addressed.

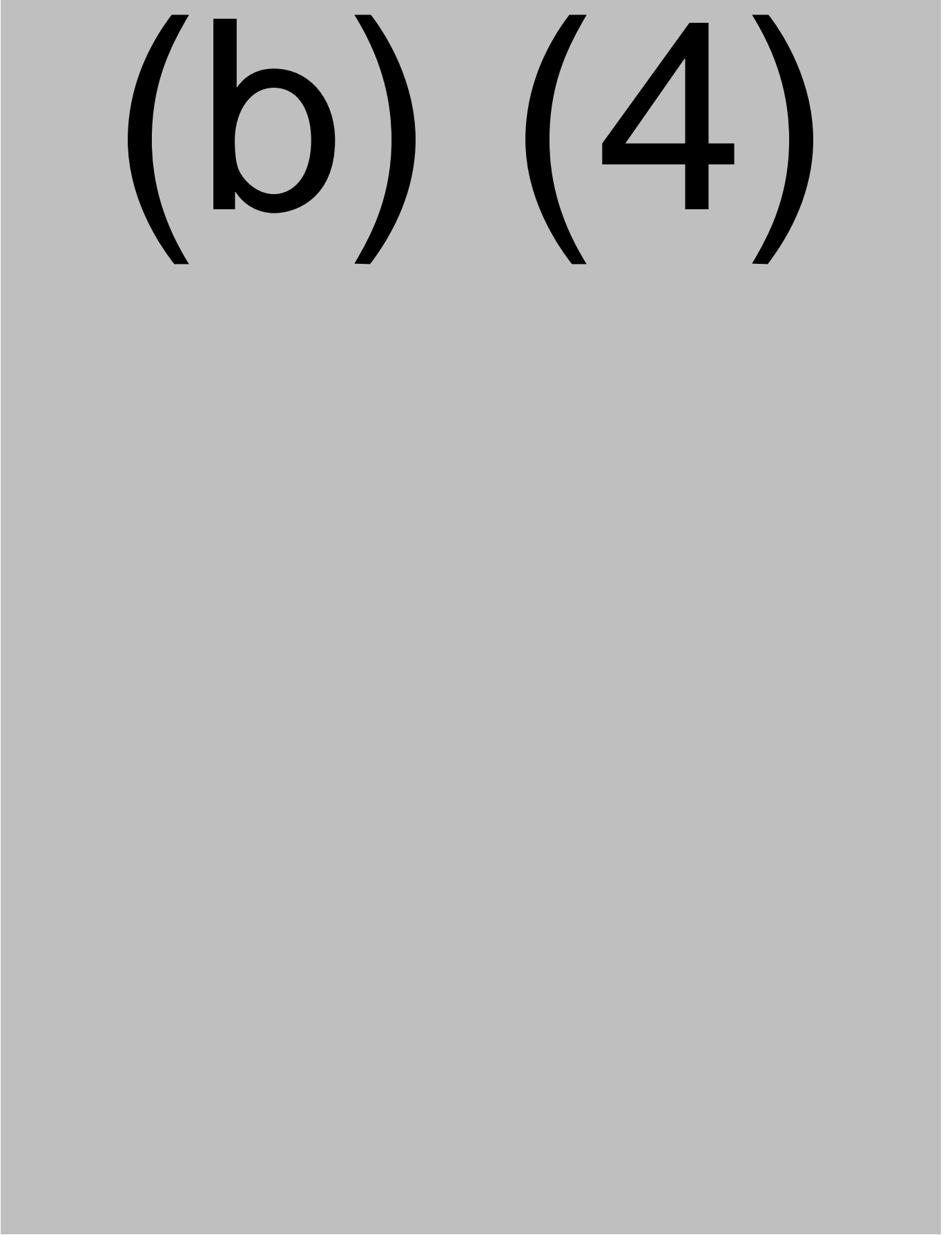
10. Please address the following CMC comments in your BLA resubmission:

(b) (4)

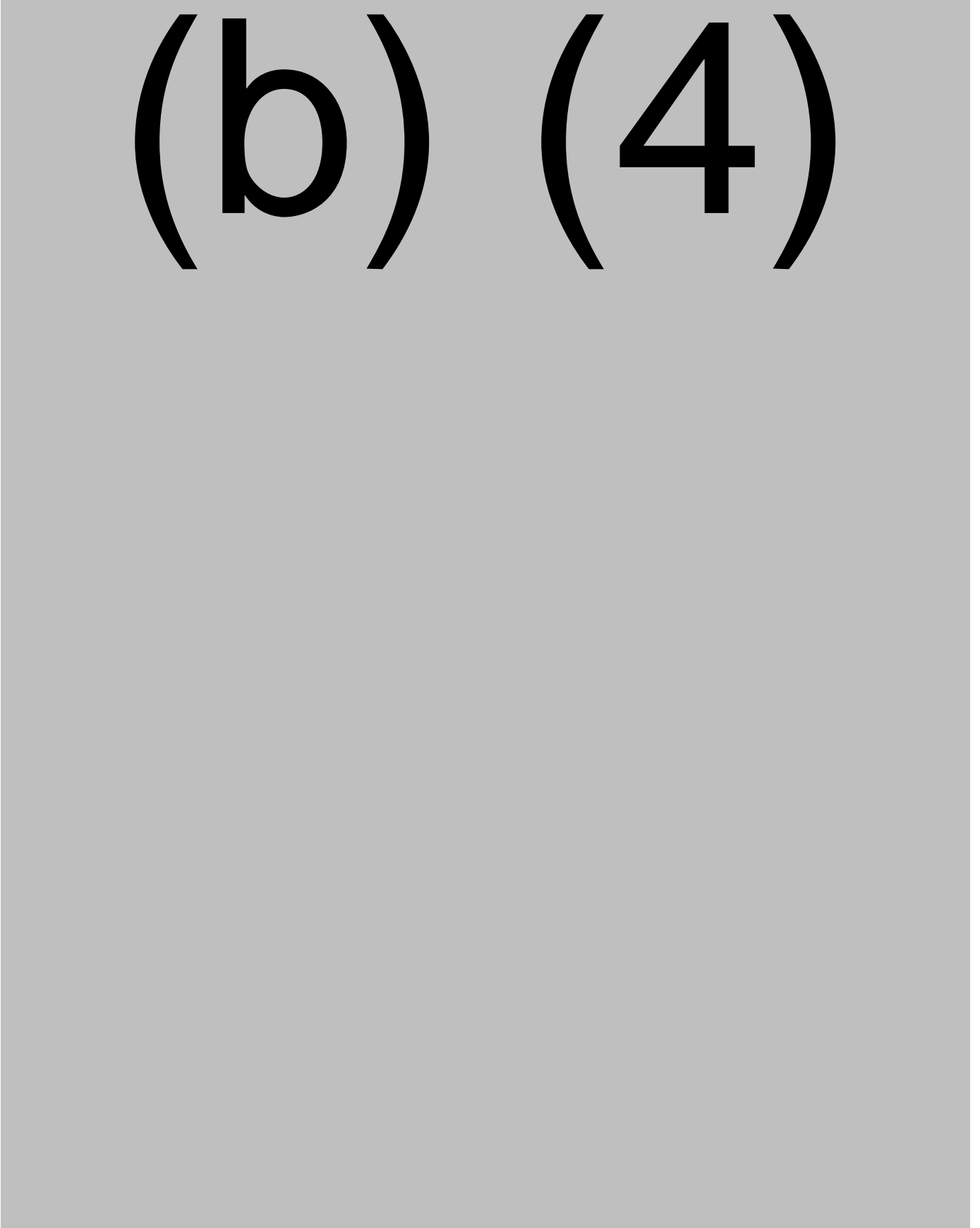
(b) (4)



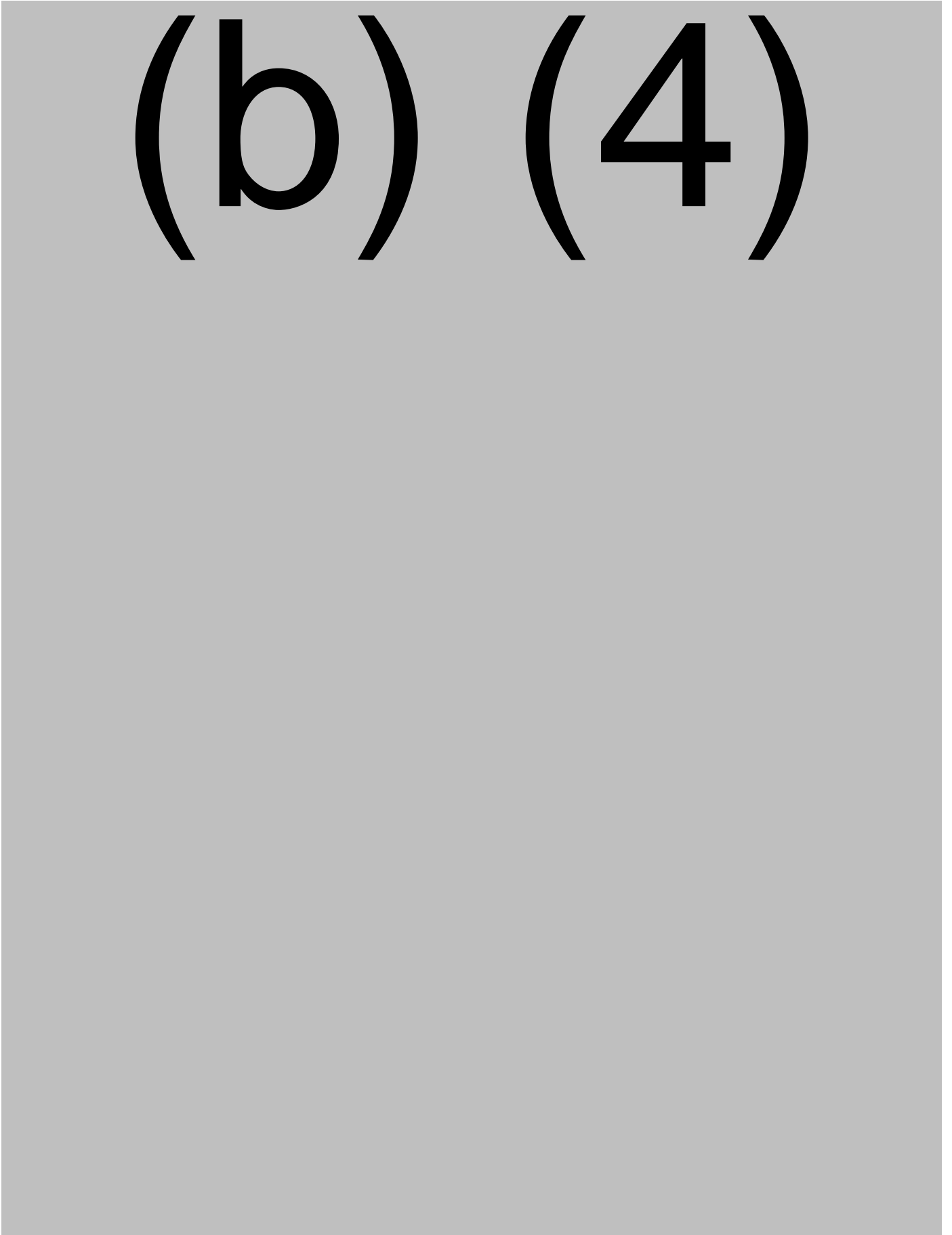
(b) (4)



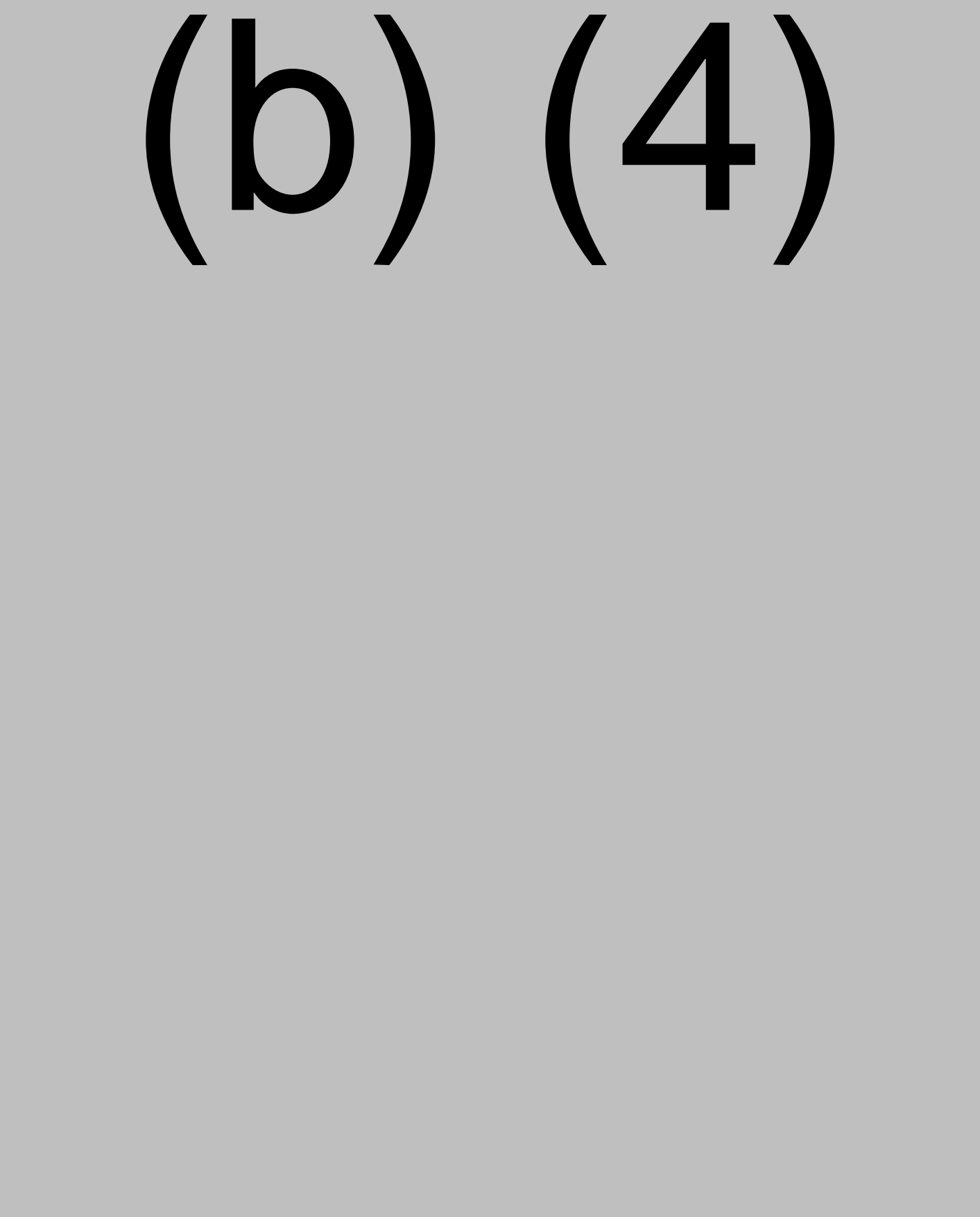
(b) (4)



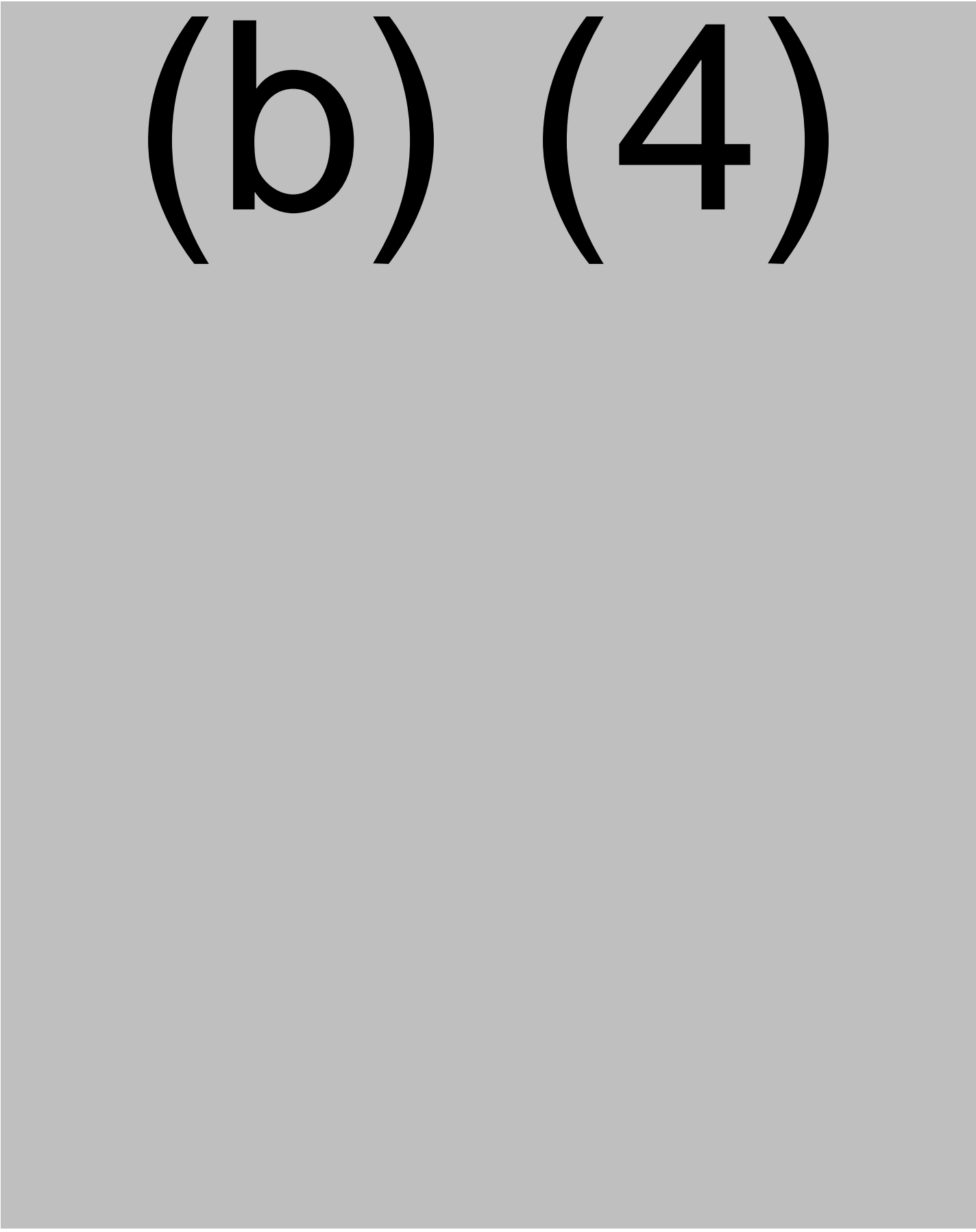
(b) (4)



(b) (4)

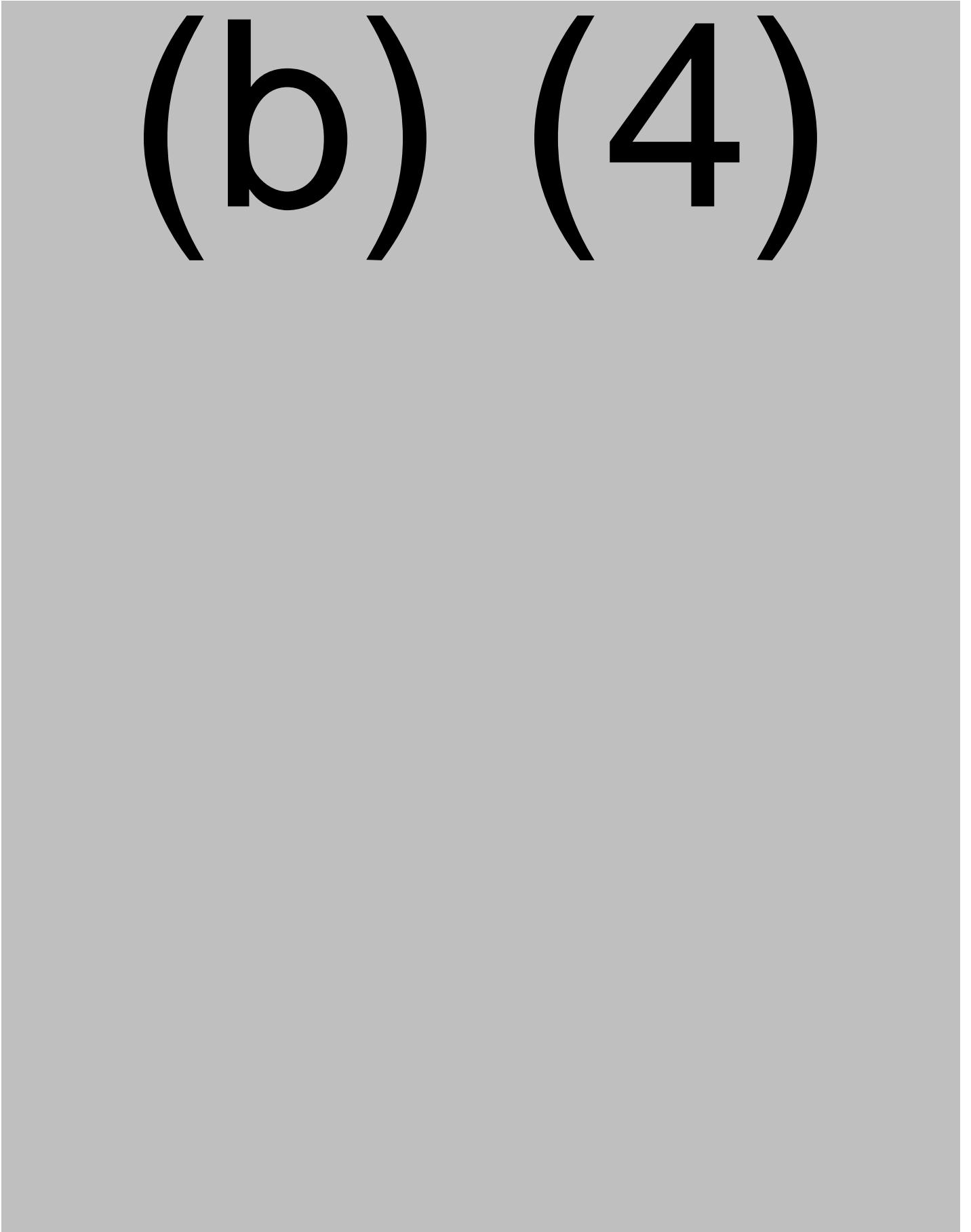


(b) (4)



(b) (4)

(b) (4)



(b) (4)

Clinical

17. We are currently evaluating the clinical data to determine if it adequately supports the proposed indication. With your resubmission, please provide updated safety and efficacy data, including but not limited to Bayley Scales of Infant and Toddler Development-Third Edition (BSITD-III) and Vineland Adaptive Behavioral Scales-Second Edition (VABS-II) raw scores from all cognitive and non-cognitive domains, brain magnetic resonance imaging (MRI) results, and cerebrospinal fluid (CSF) biomarkers (heparan sulfate [HS], ganglioside type 2 [GM2] and ganglioside type 3 [GM3]), from 30 days prior to resubmission for all patients treated across studies with the investigational product.

Regulatory

18. We acknowledge receipt of your proposed labeling and anticipate conducting a detailed labeling review once the above concerns have been fully addressed.

Within one year after the date of this letter, you are required to resubmit or withdraw the application (21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval.

You may request a Type A post-action meeting within 3 months of the date of this letter. Please submit your meeting request as described in the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf>, and CBER's SOPP 8101.1 *Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants* at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm>.

We acknowledge receipt of your amendments received (b) (4)

Please be aware that we have stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response. You may cross reference applicable sections of the amendments dated (b) (4), in your complete response to this letter, and we will review those sections as a part of your complete response.

If you have any questions regarding the above, please contact the (b) (4)

Sincerely,

(b) (4)

Center for Biologics Evaluation and Research