U.S. FOOD & DRUG ADMINISTRATION

NDA 220184

**COMPLETE RESPONSE**

MedicaSafe, Inc.
131 Varick Street, #901
New York, NY 10013

Attention: Malcolm Dell
VP of Product and Operations

Dear Malcolm Dell:

Please refer to your new drug application (NDA) (b) (4) for buprenorphine and naloxone sublingual tablets dispensing system.

We also acknowledge receipt of your amendments dated (b) (4), which were not reviewed for this action. You may incorporate applicable sections of the amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

## PRODUCT QUALITY

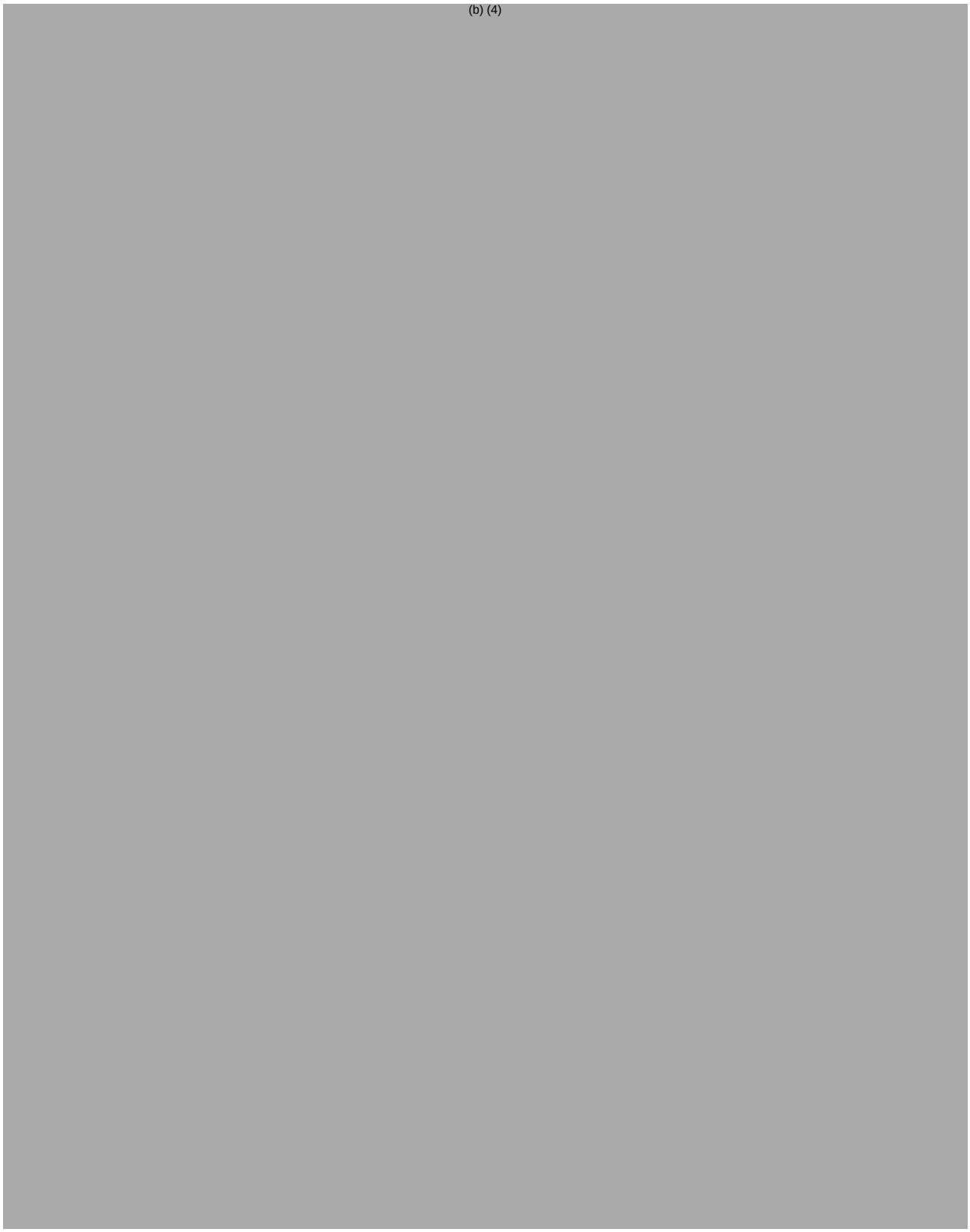
### DRUG PRODUCT

(b) (4)

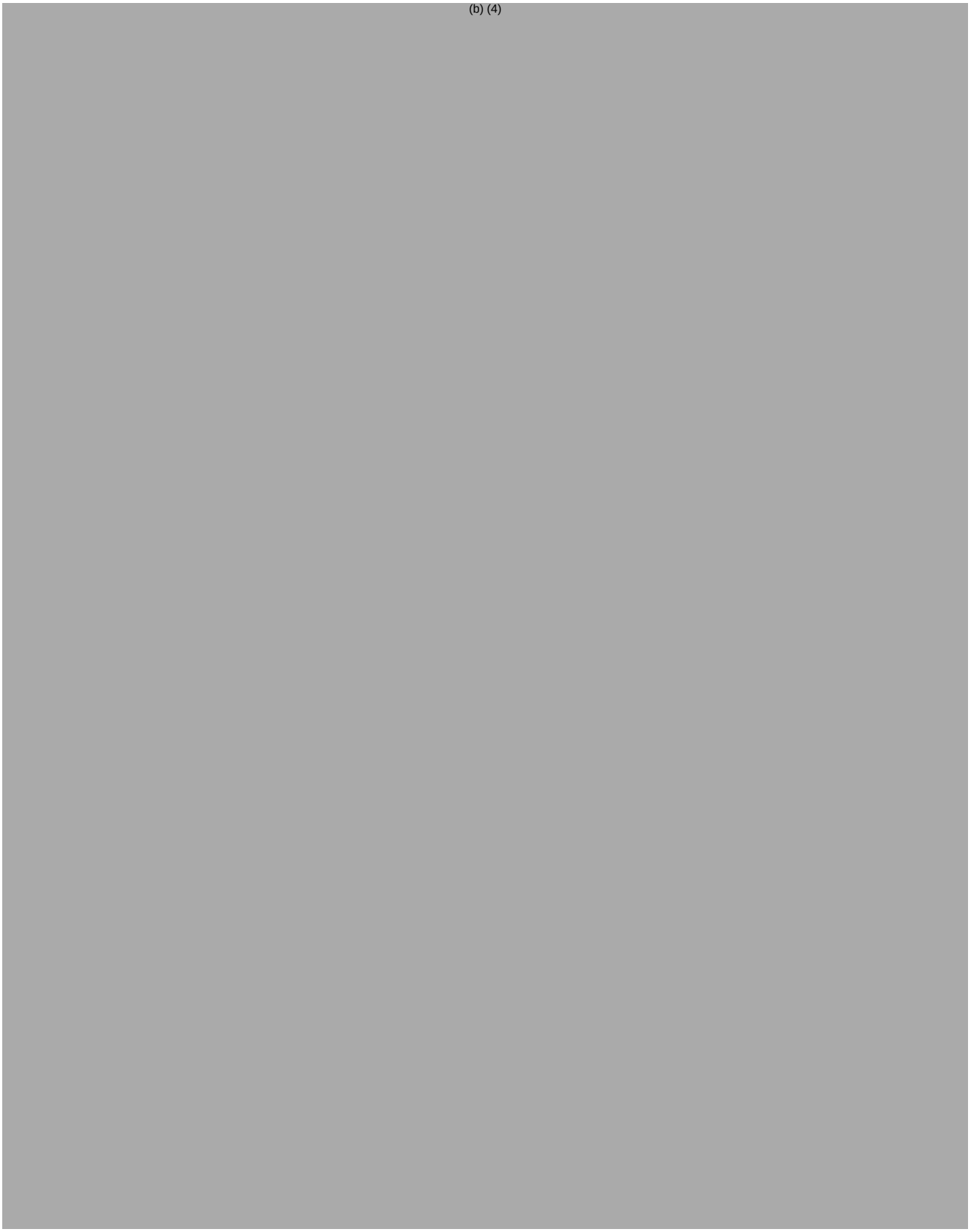
(b) (4)

(b) (4)

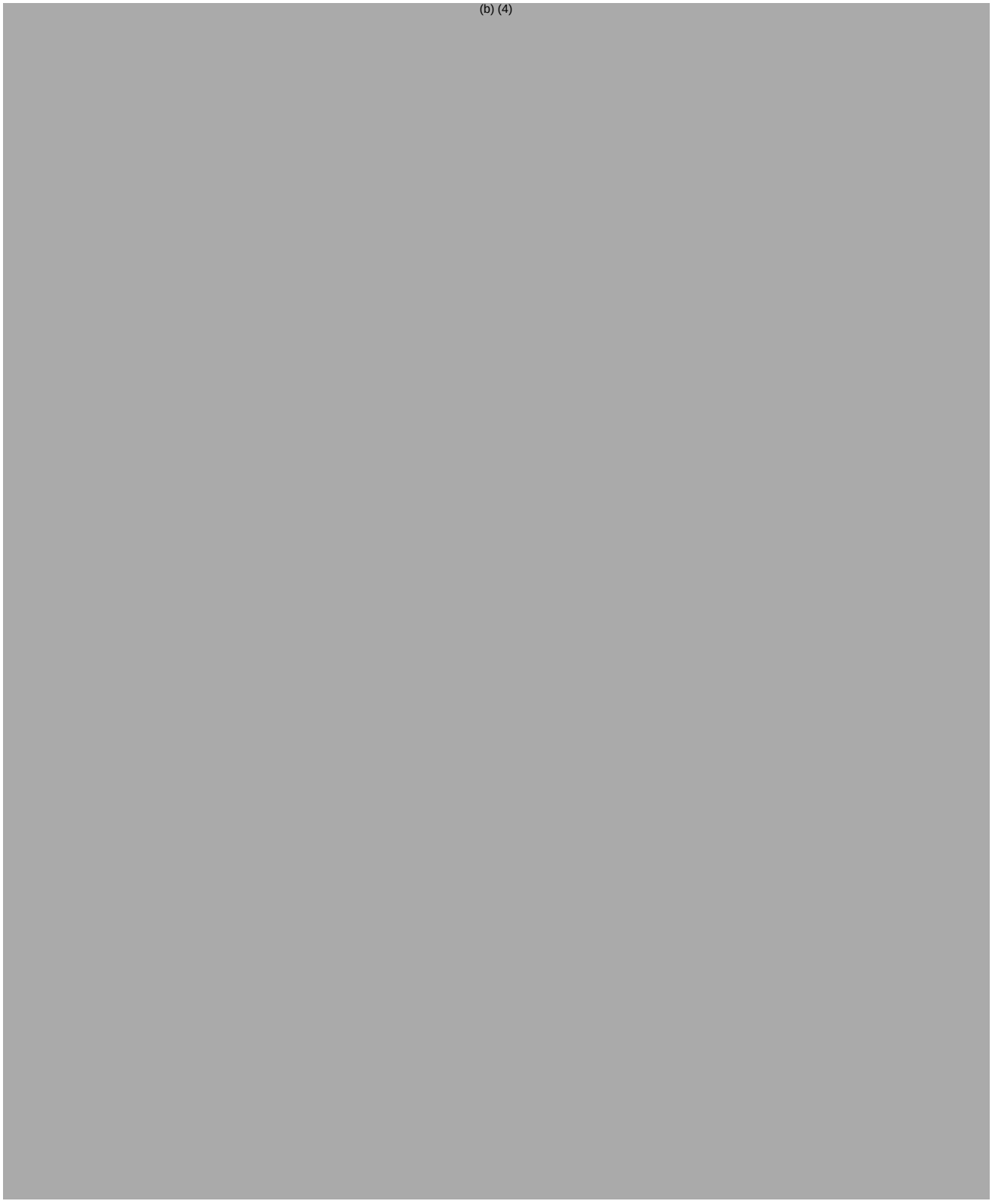
(b) (4)



(b) (4)

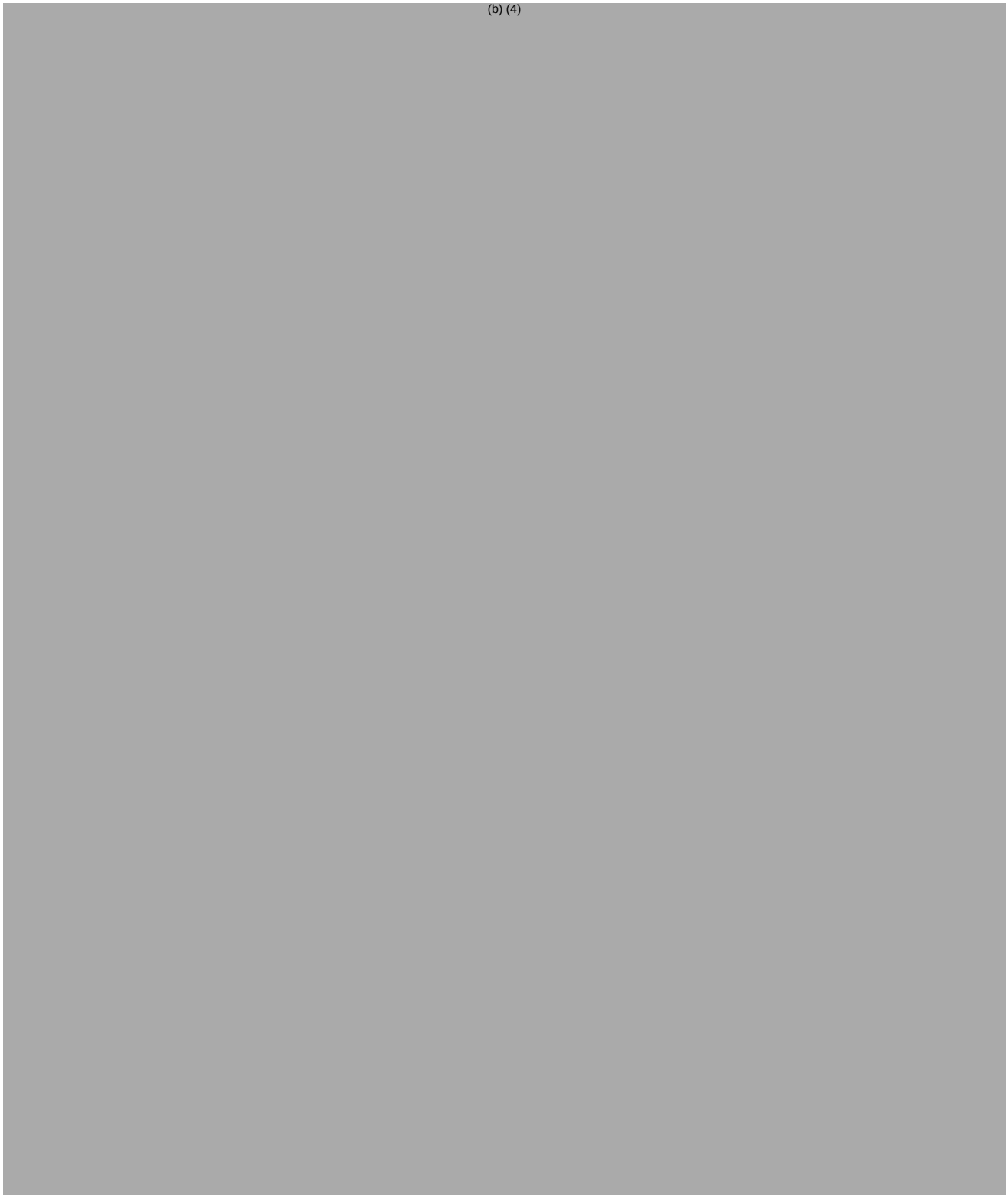


(b) (4)

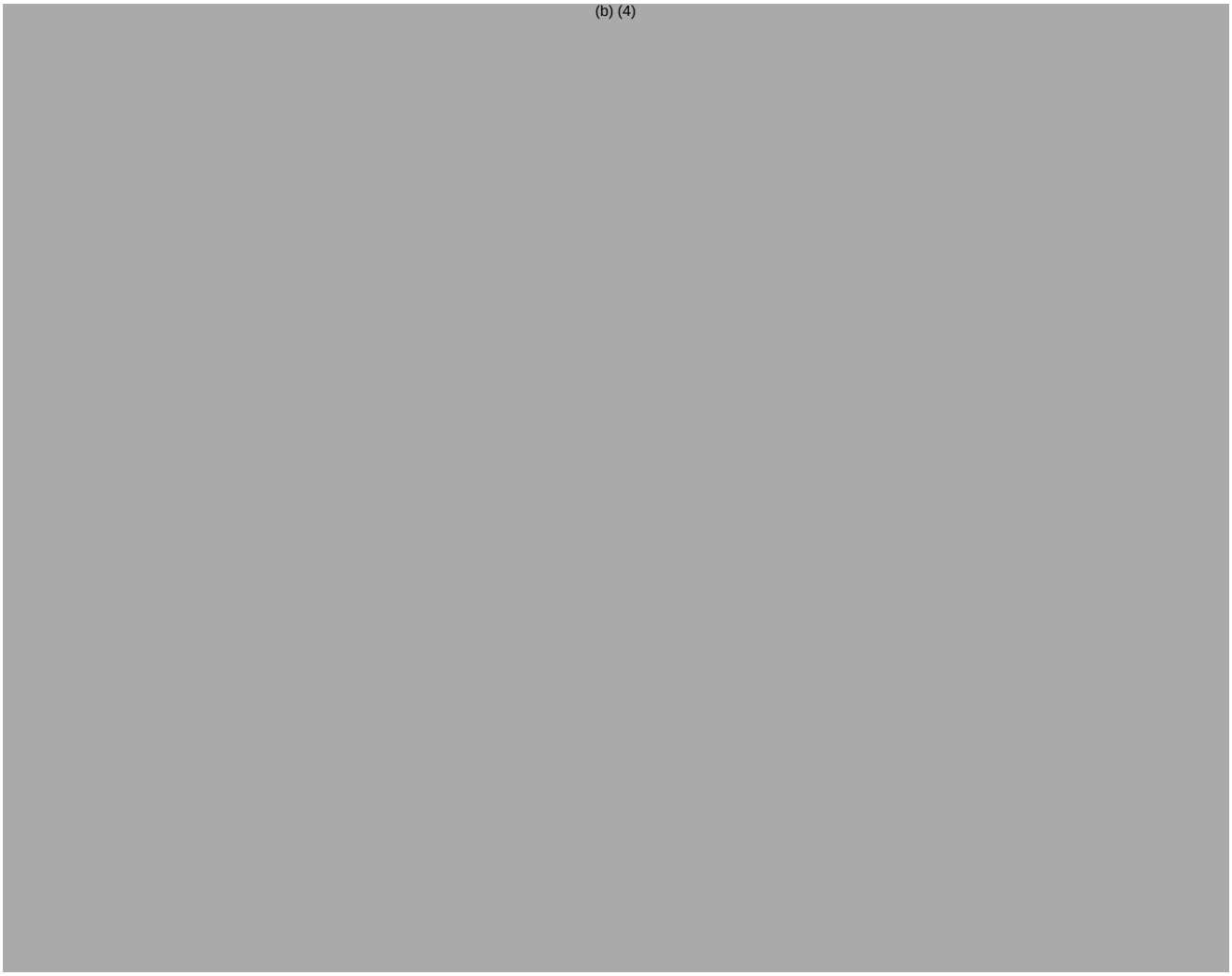


## PROCESS

(b) (4)



(b) (4)

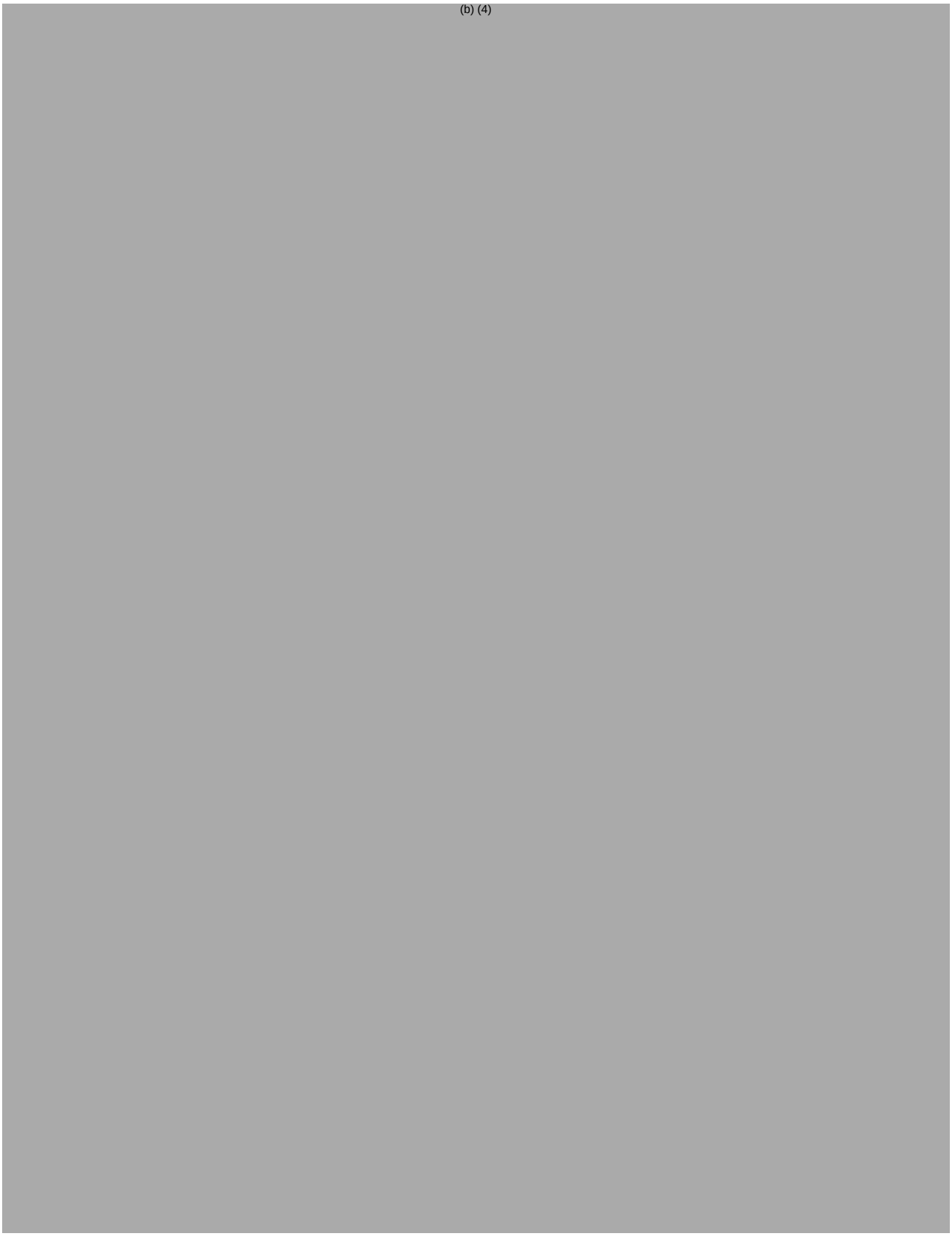


## CENTER FOR DEVICES AND RADIOLOGIC HEALTH (CDRH)

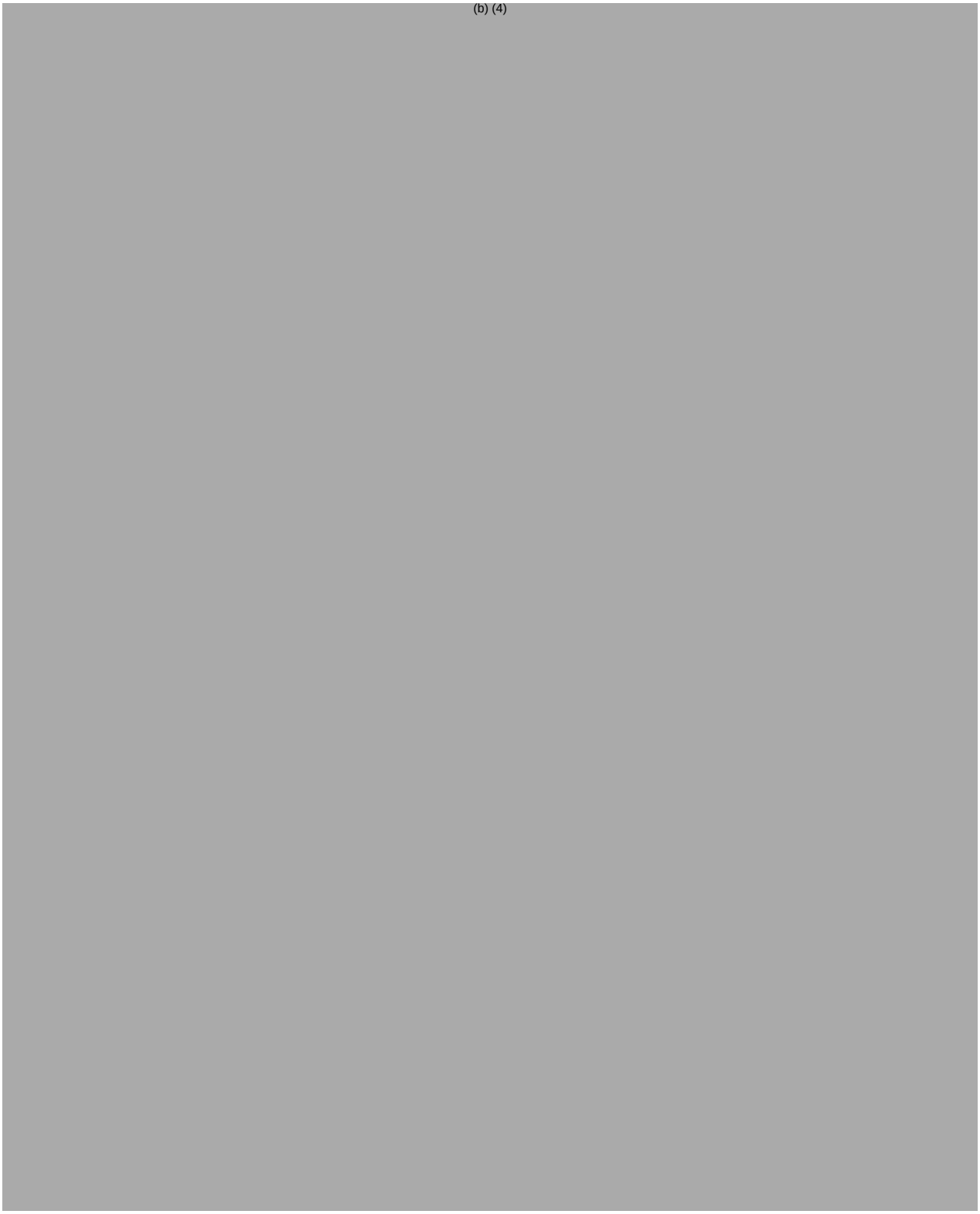
## PERFORMANCE TESTING

(b) (4)

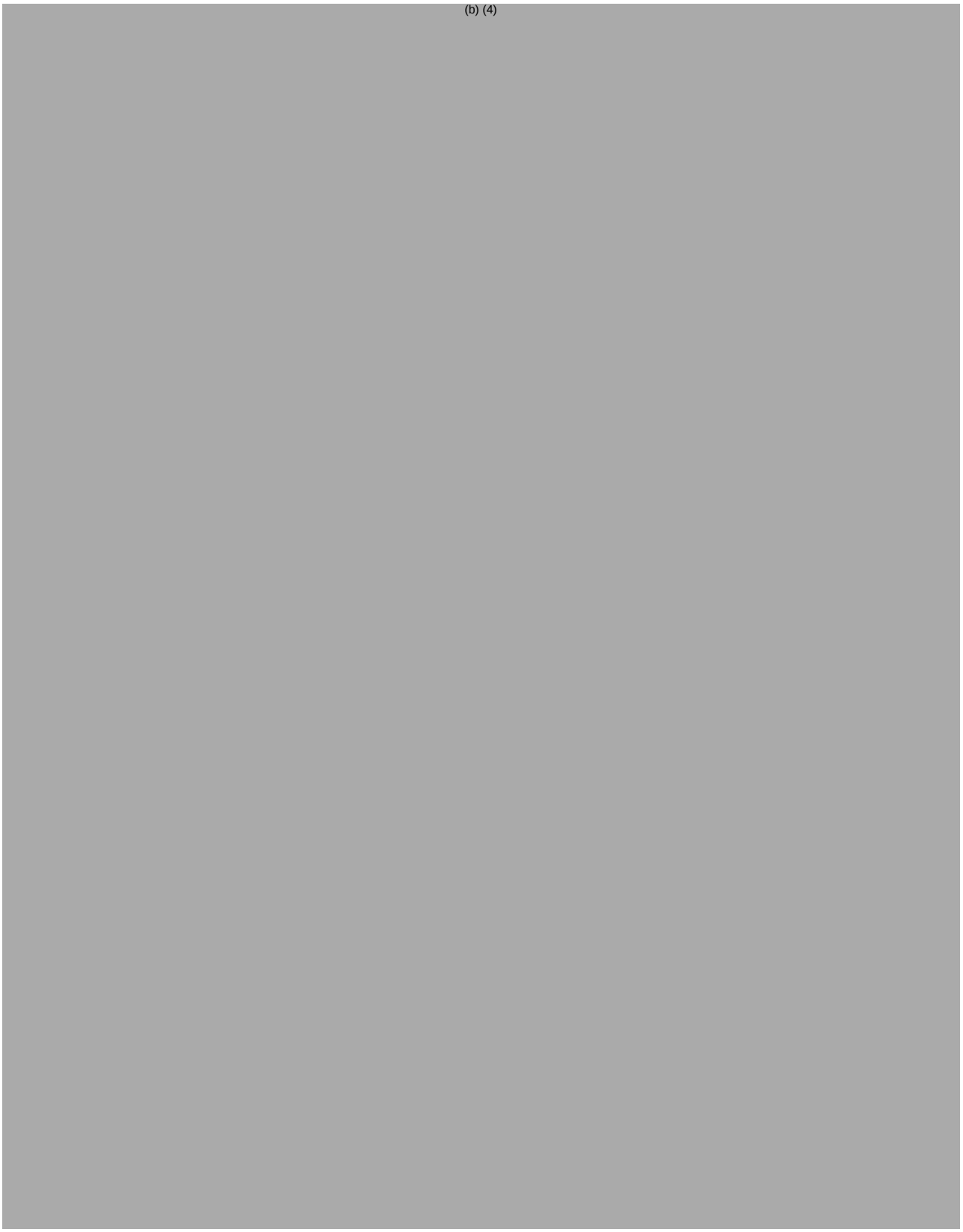
(b) (4)



(b) (4)

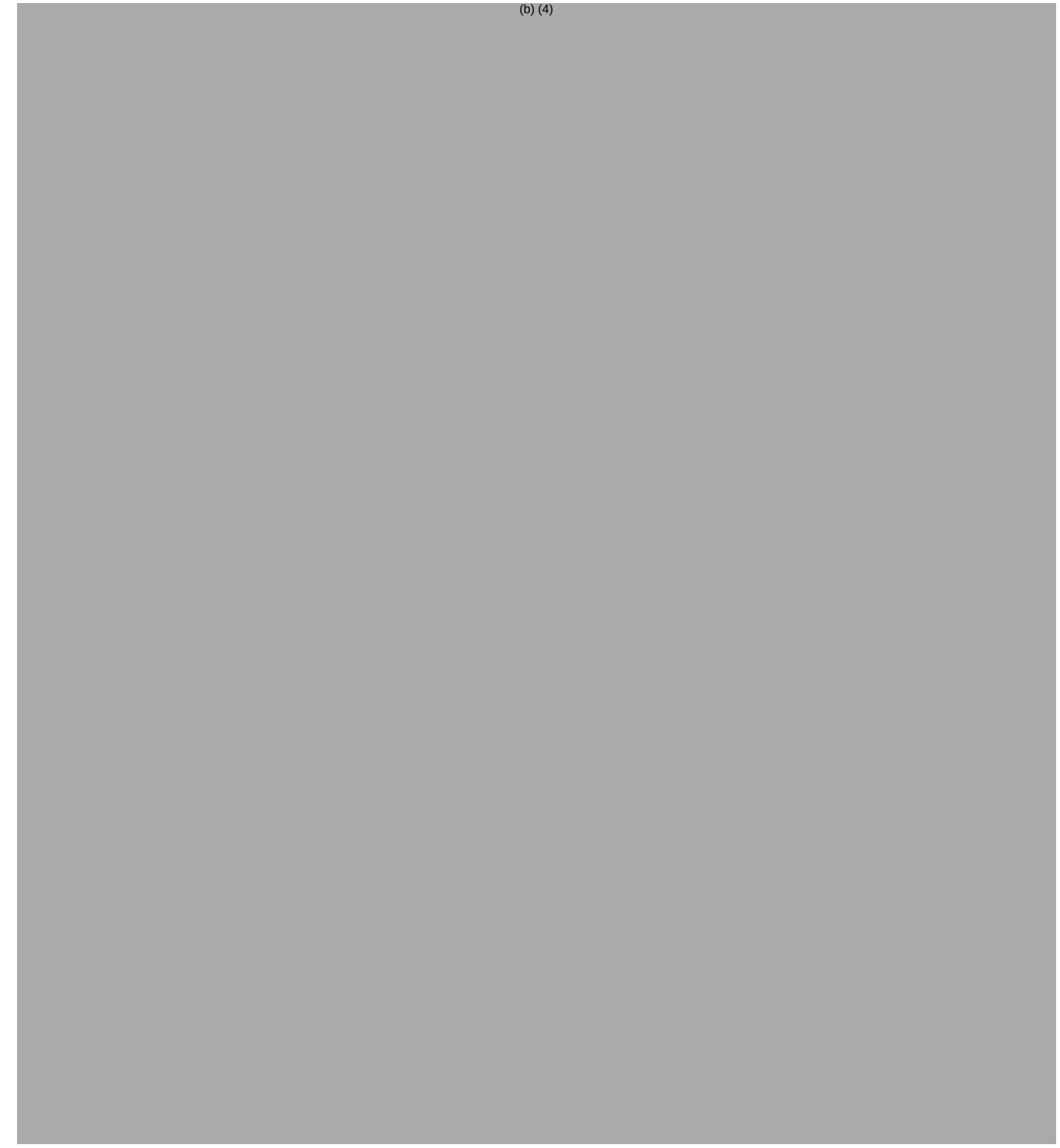


(b) (4)

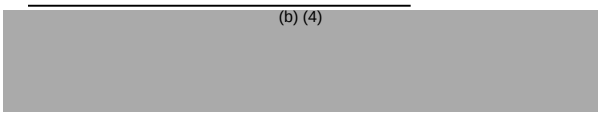


## SOFTWARE

(b) (4)



(b) (4)



(b) (4)

(b) (4)

(b) (4)

## ELECTRICAL SAFETY

(b) (4)

(b) (4)

(b) (4)

## ELECTROMAGNETIC COMPATIBILITY (EMC)

(b) (4)

(b) (4)

(b) (4)

## PRESCRIBING INFORMATION

We acknowledge receipt of your (b) (4), amendment containing draft labeling, in response to our proposed revisions dated (b) (4). This amendment was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition,

submit updated content of labeling 21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at FDA.gov.[11]

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[12] and Pregnancy and Lactation Labeling Final Rule[13] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading
- Additional resources for the PI, patient labeling, and carton/container labeling

**CARTON AND CONTAINER LABELING**

Based on our review of your Human Factors (HF) Validation Study, we have the following recommendation:

The cartridge container label does not include information on how to orient the cartridge to insert into the (b) (4) dispensing device. The HF validation study results identified subjective feedback that indicated a participant did not understand the proper orientation of the cartridge and they attempted to insert the cartridge into the (b) (4)

[11] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[12] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[13] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

dispensing device backwards. Based on the use-related risk analysis (URRA), if the user uses an improper technique while interacting with the product ((b) (4), cartridge), there is risk of opioid withdrawal symptoms. As such, we recommend you include information on the cartridge label regarding which orientation to insert the cartridge into the (b) (4) dispensing device.

Additionally, we acknowledge receipt of your (b) (4), amendment containing draft carton and container labeling, in response to our proposed revisions dated (b) (4). This amendment was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

## MEDICATION GUIDE

Add the following bolded statement or appropriate alternative to the carton and container labeling per 21 CFR 208.24(d): "**ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide**."

## RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for (b) (4) to ensure that the benefits of the drug outweigh the risks of accidental overdose, misuse, and abuse. Your application cannot be approved without a REMS; therefore, you must include your proposed REMS as part of your response to the deficiencies cited in this letter.

Your proposed REMS must include the following:

**Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that (b) (4) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of (b) (4). FDA has determined that (b) (4) is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use or continue to use (b) (4), and that the drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness. Under section 505-1 of the FDCA, FDA has also determined that a Medication Guide is

necessary to ensure the benefits of the drug outweigh the risks accidental overdose, misuse, and abuse.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed (b) (4).

In addition, under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels for all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend one of the following two statements, depending upon whether the Medication Guide accompanies the product or is enclosed in the carton:

- “Dispense the enclosed Medication Guide to each patient.”
- “Dispense the accompanying Medication Guide to each patient.”

**Elements to Assure Safe Use:** Pursuant to 505-1(f)(1), we have also determined that elements to assure safe use are necessary to mitigate the serious risks of accidental overdose, misuse, and abuse listed in the labeling of the drug. In addition, we have determined that a Medication Guide and a communication plan are not sufficient to mitigate these serious risks.

Your REMS must include elements to mitigate these risks, including at least the following:

- The drug is dispensed to patients with evidence or other documentation of safe-use conditions
- Each patient using the drug is subject to certain monitoring

**Implementation System:** The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require the drug be dispensed to patients with documentation of safe use conditions. The implementation system must include mechanism(s) to provide access to REMS materials such as a website or call center, maintenance of records, and plans for monitoring for and addressing noncompliance.

**Timetable for Submission of Assessments:** The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 12 months from (b) (4), and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. For example, the

reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a REMS (REMS document and REMS materials) and a REMS supporting document. Additionally, all relevant proposed REMS materials including educational and communication materials should be appended to the proposed REMS. The REMS supporting document should expand on information in the REMS document, and provide additional information about the REMS, such as the rationale for and supporting information about the design, implementation, and plan for REMS assessment. A REMS document template and instructions for use can be found in the draft guidance for industry *Format and Content of a REMS Document*.[14]

Once FDA finds the content acceptable and determines that the application can be approved, we will include the REMS document and REMS materials as an attachment to the approval letter. The REMS, once approved, will create enforceable obligations.

For administrative purposes, designate the proposed REMS submission as "**PROPOSED REMS for NDA 220184**." and all subsequent submissions related to the proposed REMS as "**PROPOSED REMS for NDA 220184 -AMENDMENT**."

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms or website screenshots, are available only in PDF format, they may be submitted as such, but Word format is preferred.

## PROPRIETARY NAME

Please refer to our correspondence dated, (b) (4), which addresses the proposed proprietary name, (b) (4). This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

[14] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

## SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

## ADDITIONAL COMMENTS

We have the following comment that is not an approvability issue:

1. You have provided the Instructions for use for your (b) (4) device, however there is no information included on the version of software the instructions are relevant to. This information is important to ensure that the device works as intended, and that the user is adequately able to follow the instructions for use. Therefore, update your labeling to include the Software Version.

## OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110 . 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 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. 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 what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, email (b) (4) .

Sincerely,

*{See appended electronic signature page}*

(b) (4)

Center for Drug Evaluation and Research

---

**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/

---

(b) (4)

12/22/2025 05:01:34 PM