

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212854Orig1s000

OTHER ACTION LETTERS



NDA 212854

COMPLETE RESPONSE

Adamis Pharmaceuticals Corporation
c/o Target Health LLC
261 Madison Avenue, 24th flr.
New York, NY 10016

Attention: Adam Harris, MM, RAC
Director, Regulatory Affairs

Dear Mr. Harris:

Please refer to your new drug application (NDA) dated and received December 31, 2018, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Naloxone HCl Injection, 5 mg/0.5 mL.

We acknowledge receipt of your amendment dated May 15, 2020, which constituted a complete response to our November 22, 2019, action 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.

CLINICAL

1. You have not provided adequate data to support the safe use of the proposed product ZIMHI (Naloxone HCl Injection, 5 mg/0.5 mL) pre-filled syringe for the emergency treatment of opioid overdose in community settings. The product as currently designed raises safety concerns for intended users. Specifically, you haven't provided data to demonstrate that intended users are able to deploy needle safety guard without difficulties with the current user interface in the intended use environments. Failure to deploy the needle safety guard will result in risk of needlestick injury after the injection. Additionally, patients who will be prescribed may have familiarity with your product. However, the intended users could include laypersons, who may administer this to patients. Your product, if approved, is anticipated to be widely used in community settings by laypersons who are not familiar with the use of the product at all. There is possibility that your product will be used on patients with an increased rate of bloodborne pathogens disease than the general public¹. Potential risks of transmission of bloodborne pathogens from opioid-

¹ <https://www.cdc.gov/pwid/index.html>

overdose patients to the intended users are high for your product. Your current user interface is not adequate to mitigate potential risks of needlestick injury and prevent risks of transmission of bloodborne pathogens from opioid-overdose patients to the intended users.

To address this deficiency

Modify your device to include an automatically deploying needle safety element to decrease the risk of needlestick injury (to avoid transmission of bloodborne pathogens).

Submit your updated comprehensive use-related risk analysis (URRA) taking into consideration the changes to the user interface. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures.

Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.

Based on this risk analysis, you will need to submit the results of a human factors (HF) validation study conducted under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use of the product.

We recommend you submit your HF validation study protocol for feedback from the Agency before commencing your study. Note that we will need 60 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly. Note that submission of a protocol for review is not a requirement. If you decide not to submit a protocol, this approach carries some risk to you because prospective Agency review is not possible, but this is a decision for your company.

Please refer to our draft guidance titled Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications² for the content of a human factors validation study protocol submission.

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

The requested information should be submitted to the IND. Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in the following guidance documents³:

Applying Human Factors and Usability Engineering to Medical Devices

Guidance on Safety Considerations for Product Design to Minimize Medication Errors

Note that we recently published three draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling⁴:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development

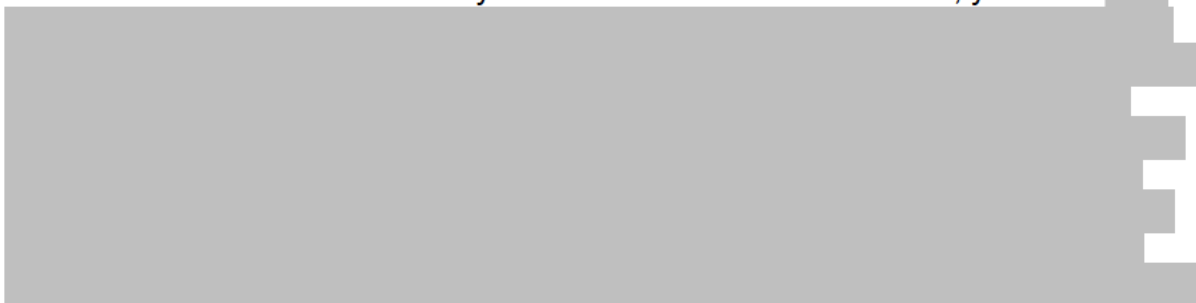
Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications

DEVICE

2. In response to our October 2, 2020, request for a fault tree analysis which provides pointers between Panels A-E to demonstrate your device's overall reliability of successful activation/dose delivery at 99.999% and 95% confidence, you state

(b) (4)



Your Fault Tree Analysis (Panels A-E) should consider all applicable basic failure modes of your device, grouped in a fashion to consider the

³ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁴ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

logical relation (i.e., and/or) so that your device's overall reliability calculation is accurate and complete.

To address this deficiency:

Revise your Fault Tree Analysis to consider all the basic design and manufacturing failure modes.

3. In your revision to Panel A from SN0053 (August 17, 2020) and Panel E from SN0055 (September 10, 2020) you make consistent logical and scientific arguments which are unsubstantiated by your evidence or do not clearly support your claims. Without this information, you cannot support your overall claim of successful activation/dose delivery at 99.999% reliability and 95% confidence or 99.99% reliability and 95% confidence. This is not intended to be an exhaustive list due to the consistent errors identified.

To address this deficiency:

Revise your fault tree analysis and address the following:

a.



- ii. You provide no explanation on how you link Cpk to failure rate.

Therefore, your claimed failure rate of (b) (4) is unsubstantiated by this evidence. This is similarly noted for items in SN0055. Provide a clear explanation linking of Cpk or other data sources (e.g., Monte Carlo Simulations, qualifications of go-no/go gauges) to your basic failure rates for items which you rely on statistical data.

- b. In SN0055, Table 1 of 1.11.1, for the basic failure mode "*unable to actuate due to part defects*," you point to 3.2.P.7.8.1.2.4 Tables 18 and 20-23 and state the assessed failure rate is (b) (4) with "*Reliability analysis of each manufactured part was found to be 99.999999%.*" However:

i.

(b) (4)
There are three items connected to this basic failure event with an 'OR' gate (b) (4)

Therefore, this

appears to be combining data from several sources without explaining how you relate these to your stated failure rate. Provide an analysis that uses a single failure rate for each failure mode and clearly link these data with logical connectors (i.e., AND, OR) to arrive at failure rate.

- ii. The critical dimension data in the referenced tables refers to several Cpk values, including (b) (4). You do not clearly relate these Cpk values to your stated failure rate of (b) (4). Provide the assessment described in 2.a: a linking of Cpk(s) to a failure rate.
 - iii. Under Table 23 you state, *“Due to the high process capability for the manufacture of these parts, with a Cpk of (b) (4) (b) (4) the critical the failure probability of this basic failure mode was considered negligible but will be set at the (b) (4) for the purpose of the fault tree analysis quantification.”* Therefore, it is unclear why you do not use the lowest identified Cpk in your analysis or considering all the parts’ failure rates. Provide failure rate data for the basic events in your analysis.
 - iv. You appear to use Cpk data in Table 18, 22, and 23 to arrive at a failure rate. You do not provide evidence that the data is normal. Cpk analyses are predicated on a normal data set. Provide a normality test to demonstrate your analysis is valid.
 - v. You appear to use Cpk data in Table 20 and 21 to arrive at a failure rate. You failed your normality test. Therefore, your Cpk analysis, as presented, is invalid. Provide an assessment of your non-normal data to determine why your data is non-normal and provide a statistical analysis which is valid for your data set.
- c. You provide a failure rate based on your pFMEA for several items and justify these based on validated assembly figures and work instructions. You do not provide process validation references demonstrating your assembly line has been determined to be adequate. Therefore, your determined failure rates are unsubstantiated. Provide evidence that your assembly process and equipment are validated and can adequately identify parts as passing or failing. Ensure the evidence clearly supports your proposed failures rates.
 - d. In response to comment b in SN0055, you provide a statistical tolerance analysis. However, you do not provide the source of these data, the areas of your Fault Tree Analysis these data are supporting, or a normality assessment of these data. We are unable to determine if your statistical

tolerance analysis is valid without knowing the source of the data, how you collected it, how you are using it to support your claims, and that your analysis techniques are valid. Provide a reference to the original location of these data, explain where these data are being used in your Fault Tree Analysis, and provide a normality test of these to determine the presented analysis is valid.

Also consider the Complete Response Deficiency 4 regarding your needle safety device as you revise your Fault Tree Analysis and consider that any changes to your device design should be considered as you address this comment.

4. You provide SN0057 (October 7, 2020), in response to our September 23, 2020, Information Request, Issue 1, which contains Table 1 and a discussion of how you meet the recommendations in *"Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features"* (<https://www.fda.gov/media/71142/download>) from August 2005. However, the evidence you reference to support your claimed device malfunction mitigations in 3.2.P.2.4.4.2.4, 3.2.P.2.4.4.2.6, 3.2.P.2.4.4.2.7, 3.2.P.2.4.4.2.8 contain consistent scientific flaws:
 - a. You do not detail your test methods or explain why the methods chosen are adequate in demonstrating your requirements are verified
 - b. You do not state the number of samples used to verify each requirement
 - c. You do not justify your sample size based on the risks present in your system
 - d. You do not present a complete analysis of your data: You lack both a discussion of your approach (e.g., variable or attribute) and statistical analysis demonstrating adequacy of the data (e.g., data normality for variable data)
 - e. Your samples are not representative of your use case. For example, in Section 3.2.P.2.4.4.2.6 you state:
 - i. *"Units were held at 55°C for the 5.5 weeks period to simulate a 12-month shelf and use life."* We understand your device has a shelf-life of 18 months. Therefore, your data do not demonstrate your device functions at expiry.
 - ii. *"All samples subject to accelerated life testing were fabricated from alpha build components..."* However, you present no discussion comparing the components from alpha builds to the to-be-marketed device or state there are no functional/design changes between

these components and your to-be-marketed device. Therefore, the device used is not understood to be representative of your to-be-marketed device.

- f. While you state, "...after storage at 55 °C for simulated aging to 18 months, 576 devices were evaluated for needle guard function... The result was recorded as a Pass/Fail. The acceptance criteria was: (b) (4) failures are required to demonstrate a (b) (4) % confidence that the true failure rate is no higher than (b) (4) % and a (b) (4) % confidence that the true failure rate is no higher than (b) (4) %..." under Simulated Clinical Use Testing.
- i. Your referenced data in Section 3.2.P.2.4.4.2.6, which refers to devices aged only to 12 months, contradicts this statement.
- ii. You provide no other data location to support this statement.

To address this deficiency:

You should demonstrate that your device functions safely at worst-case, reasonably conceivable conditions (i.e., sterile device, at expiry, following shipping challenge), with testing to verify your requirements are adequately met. We recommend you review the following guidance documents as you address this deficiency and consider the recommendations contained within:

- *Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submission*, available at <https://www.fda.gov/media/113230/download>
- *Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices*, available at <https://www.fda.gov/media/71983/download>

Provide data verifying and validating that your needle safety function effectively protects against accidental needle sticks per FDA Guidance Document "*Medical Devices with Sharps Injury Prevention Features*, available at <https://www.fda.gov/files/medical%20devices/published/Medical-Devices-with-Sharps-Injury-Prevention-Features---Guidance-for-Industry-and-FDA-Staff-%28PDF%29.pdf> .

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information⁵ and Pregnancy and Lactation Labeling Final Rule⁶ websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.⁷

CARTON AND CONTAINER LABELING

We reserve comment on the proposed packaging labels until the application is otherwise adequate

PROPRIETARY NAME

Please refer to correspondence dated, October 7, 2020, which addresses the proposed proprietary name, Zimhi. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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:

⁵ <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

⁶ <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>

⁷ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

- 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 patient 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.

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

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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

If you have any questions, call Swati Patwardhan, Regulatory Project Manager, at (301)796-4085.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Director
Division of Anesthesiology, Addiction Medicine
and Pain Medicine
Office of Neuroscience
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/

RIGOBERTO A ROCA
11/13/2020 05:08:53 PM



NDA 212854

COMPLETE RESPONSE

Adamis Pharmaceuticals Corporation
c/o Target Health Inc.
261 Madison Avenue, 24th floor
New York, NY 10016

Attention: Adam Harris, MM, RAC
Associate Director, Regulatory Affairs

Dear Mr. Harris:

Please refer to your new drug application (NDA) dated and received December 31, 2018, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Naloxone hydrochloride injection, 5 mg/0.5 mL.

We also acknowledge receipt of your amendments dated September 27 and October 25, 2019, which were 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.

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

1. There is no correlation established between the extractable and leachable studies. The extractables studies failed to detect any extractables and specifically failed to detect the leachables observed in the leachable study.

To address this deficiency:

Perform a more vigorous extractables studies that can establish a good correlation with the leachable assessments. Use USP <1663> and <1664> as guides in conducting these studies.

2. We note inconsistency in the leachable data during stability testing. Additional data are required to justify these results:

To address this deficiency:

- a. Provide the lapsed time between the sample's withdrawal and date of reanalysis of the 6-month time point.
 - b. Justify the use of (b) (4) for the 6-month sample time point, analyzed at (b) (4) and not for the original data presented at other time points.
 - c. Explain why the (b) (4) related leachants have not been observed in the (b) (4) and have not been removed after (b) (4).
 - d. Provide the background peaks from the (b) (4) (b) (4) to confirm that the extra peaks are from the (b) (4).
 - e. Unambiguously establish the structures of the leachables at RRT (b) (4) and (b) (4) by comparison with reference standards if available, or spectroscopic techniques such as Mass spectra, UV, IR and NMR.
 - f. Repeat the leachable study at each time point of the stability study, using validated analytical methods. Run blanks to establish background. Provide all data in your resubmission.
3. The photo-degradants at RRT (b) (4) have not been identified.

To address this deficiency:

Unequivocally establish the structures of the photo-degradants at RRT (b) (4) by comparison with reference standards if available, or spectroscopic techniques such as Mass spectra, UV, IR and NMR.

4. Particulate matter is a critical attribute for injectables. We note an inconsistency in the data provided at the 6-month time point for particulate matter testing under the long-term condition for Batch 1838-022. These out of trend results may mean variation in the analytical methods used for determination of particulate matter.

To address this deficiency:

Re-evaluate the analytical method and revalidate if required.

5. As the naloxone product may be widely available in the community, it could be stored in other than controlled conditions (such as a vehicle in the summer or winter). Sufficient data to support these storage conditions were not provided.

To address this deficiency:

Provide additional accelerated stability data to demonstrate lack of degradation, color change, or particulate formations. Similarly test the product when frozen and thawed. Report any particulate formation, color change, degradation and time required to thaw.

DEVICES

6. We previously requested reliability testing and analysis to demonstrate that the reliability for drug delivery using a single device is 99.99% or greater. The provided results demonstrate that the reliability of a single device is 99.96%. Your analysis uses the availability of two devices to achieve 99.99%; however, this does not adequately mitigate the risk of a patient failing to receive the complete dose because they may need both doses. The expectation is that the reliability of an individual product dose delivery is not less than 99.99%.

To address this deficiency:

Implement appropriate modifications to the device control strategy and provide additional data demonstrating that the product has a reliability of at least 99.99% for a single device.

NONCLINICAL

7. You have not provided appropriate extractable/ leachables data to permit a substantive nonclinical toxicological risk assessment for the proposed container closure system.

To address this deficiency:

Submit a revised toxicological risk assessment based on adequate extractable leachable data. To inform the risk assessment, conduct adequate extractable leachable studies to support the safety of your proposed container closure system, taking into consideration the following:

- a. Results of the extraction studies should establish an acceptable extractable leachables correlation that will assure adequate monitoring of the drug product stability samples for all potential leachables from the container closure system.
- b. Provide a justification for the compounds targeted in the leachable study based on the extraction data. In general, all extractables exceeding 5 mcg/day should be targeted in the leachable study.

- c. Based on the results of the leachable studies, identify all compounds in the drug product present at levels equal to or greater than 5 mcg/day taking into consideration the maximum daily dose of your drug product and submit a toxicological risk assessment for every leachable present in the drug product at or above the 5 mcg/day qualification threshold. The risk assessment must be based on the highest level of the leachable over the course of the proposed shelf-life.
- d. Toxicology data from published literature or from the public domain that are used to support leachable qualifications must meet regulatory standards with adequate details to permit substantive independent review. Referencing databases, such as ECHA, with limited details regarding toxicity information is not acceptable. QSAR analysis and identification of a NOAEL (no observed adverse effect level) for structurally similar compounds to qualify leachables that have limited toxicity information is not acceptable unless it is accompanied with adequate justification via scientific data or literature that allows for such a bridge or extrapolation. These databases can be used to identify the pivotal studies used to support your toxicological risk assessment; however, the pivotal studies should be submitted with the NDA to permit independent review. Revise your toxicological risk assessment to employ permission daily exposure levels accordingly as per ICH Q3C(R5) principles. Submit copies of toxicology risk assessment reports and cited literature.

CLINICAL PHARMACOLOGY

8. Although you submitted relative bioavailability Study APC 6000-03, this information was submitted too late in the review cycle to allow for a substantive review. Therefore, we have not determined whether you have established an acceptable scientific bridge between your proposed drug product and the referenced Narcan product to demonstrate that such reliance is scientifically justified. We are withholding any comments on the relative bioavailability study until after you submit a response to this Complete Response letter.

PRESCRIBING INFORMATION

9. During our review of your submitted labeling, we identified the following labeling issue that should be addressed in your resubmission:

Your annotated labeling submitted December 31, 2018, included the following

(b) (4)

(b) (4)

The acceptability of the labeling will be a review issue.

We reserve remaining comments on the proposed labeling until the application is otherwise adequate.

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. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at FDA.gov.¹

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

CARTON AND CONTAINER LABELING

10. We acknowledge receipt of the revised draft carton and container labeling on September 30, 2019. We reserve our comments on the acceptability of the packaging labels for the next review cycle.

PROPRIETARY NAME

11. Please refer to correspondence dated, March 28, 2019, which addresses the proposed proprietary name, Zimhi. This name was found acceptable pending approval of the application in the current review cycle. Resubmit the proposed proprietary name when you respond to the application deficiencies.

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.

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

- (2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - a. Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
 - b. Present tabulations of the new safety data combined with the original application data.
 - c. Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
 - d. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
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- (4) Provide case report forms and narrative summaries for each patient 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.
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OTHER

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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. Note that resubmission goals will not apply to any resubmission of this application.

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

If you have any questions, call Swati Patwardhan, Regulatory Project Manager, at 301-796-4085.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesia, Addiction, and
Pain Medicine
Office of Neuroscience
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/

SHARON H HERTZ
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