CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207962Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207962

COMPLETE RESPONSE

Scilex Pharmaceuticals, Inc.
c/o Clinipace Worldwide
4840 Pearl East Circle
Suite #201E
Boulder, CO 80301

Attention: Kip Vought
Vice President, Regulatory and Strategic Development

Dear Mr. Vought:

Please refer to your New Drug Application (NDA) dated July 10, 2015, received July 10, 2015, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for ZTlido (lidocaine patch 1.8%).

We also acknowledge receipt of your amendment dated March 18 and 24, and April 11, 14 and 15, 2016, which 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.

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.

REGULATORY

1. Under 21 CFR 314.54(a)(1)(vi), a 505(b)(2) application must contain a patent certification or statement with respect to any relevant patents that claim the listed drug or that claim any other drugs on which the investigations relied on for approval of the application were conducted, or that claim a use for the listed or other drug. Your 505(b)(2) application includes a reference to (b) (4) in the annotated labeling, but does not contain a patent certification or statement with respect to each patent listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) for (b) (4) Specifically, your application does not contain a patent certification or statement with respect to patents (b) (4) which are listed in the Orange Book for (b) (4)

   To address this deficiency, either remove references to (b) (4)), or submit appropriate patent certification or statements with respect to each of these patents. Note that if you elect to provide a paragraph IV certification (21 CFR 314.50(i)(1)(i)(A)(4))

with respect to a patent, the certification must be accompanied by a statement that you will comply with the requirements described at 21 CFR 314.52(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the drug product that is claimed by the patent or a use of which is claimed by the patent, and with the requirements under 21 CFR 314.52(c) with respect to the content of such notice.

Additionally, if you intend to rely for approval on FDA's finding of safety and/or effectiveness for [redacted] (b) (4), you must establish that such reliance is scientifically appropriate, and establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and [redacted] (b) (4)

2. Your application also relies for approval on studies described in published literature. You must establish that reliance on the studies described in the published literature is scientifically appropriate. Provide the scientific justification for each literature reference that is essential to the approval of your 505(b)(2) application. Include a copy of all referenced published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

CLINICAL

3. The 74-day letter dated September 22, 2015, included the following comment about the adhesion data provided in your application:

   "You have submitted only a one-time adhesion evaluation after 48 hours for subjects in Cohort 1 of your dermal sensitization and cumulative irritation study, SCI-LIDO-DERM-001. As discussed during the pre-NDA meeting, your proposed product and the listed drug, Lidoderm, are intended for a maximum use of 12-hours in a 24-hour period. Therefore, an assessment of whether adhesion is adequate for the product when used as directed in the proposed labeling cannot be made, and the results from the 48-hour assessment are inadequate to support approval based on current patch adhesion expectations (90% adhesion in 90% of subjects)."

   To address this deficieincey, either submit adhesion data after 12 hours of use from Study SCI-LIDO-DERM-001, or conduct a new study to evaluate adhesion using the duration and method of administration for ZTlido that will be proposed for labeling and that administers Lidodoerm according to its package insert. Also, as Lidoderm is intended for 12-hour use, the data from 48 hours cannot be used to support any comparative claim about superior adhesion with your product.

   Additional data from Study SCI-LIDO-ADH-001 submitted during the review cycle were not reviewed. You may reference the submission as part of your response to the deficiencies cited in this letter.

CLINICAL PHARMACOLOGY

4. The comparative bioavailability study, SCI-LIDO-PK-001, intended to bridge to the Agency's previous findings of efficacy and safety for Lidoderm patch 5%, cannot be used to establish bioequivalence because surgical tape was used to secure the Lidoderm 5% patches, and adequate evidence was not provided to justify that the use of tape would not affect lidocaine absorption from Lidoderm patch 5%.

   To address this deficiency, conduct a new adequately-designed comparative bioavailability study to demonstrate equivalent systemic exposure to Lidoderm patch 5%. The list drug product, Lidoderm patch 5%, must be used according to the approved package insert (e.g., without use of an overlay or tape).

   Additional data from Study SCI-LIDO-HEX-001 submitted during the review cycle were not reviewed. You may reference the submission as part of your response to the deficiencies cited in this letter.

NONCLINICAL

5. Your proposed specification for the drug product degradant 2,6-xylidine, which is a known rat carcinogen, exceeds the acceptable daily intake level of 10 mcg per day per the ICH guidance for industry: *M7 Assessment And Control of DNA Reactive (Mutagenic) Impurities In Pharmaceuticals To Limit Potential Carcinogenic Risk*. The data submitted to justify that the proposed specification of NMT (b) (4)% would limit the impurity level in your product to be within levels observed in the listed drug does not take into consideration the level of impurity that will be released from the patch and to which the patient will be exposed. Ztlido was designed to achieve systemic exposure to lidocaine comparable to the listed drug, despite containing nearly 19-fold less lidocaine per patch, indicating that a much higher proportion of lidocaine and its associated impurities/degradants will be released from your product, relative to the amount released from the listed drug. Therefore, your justification is unacceptable.

   To address this deficiency, either reduce the specification of the drug product degradant 2,6-xylidine to NMT 10 mcg per day or provide data to demonstrate that the level released from ZTlido under conditions of use is within the level released from the listed drug.

6. Your proposed specifications for Impurities (b) (4) and (b) (4) exceed the qualification threshold of 0.2% or 3 mg total daily intake, whichever is lower, per the ICH guidance for industry: *Q3B(R2) Impurities in New Drug Products*. The toxicological risk assessment submitted to support the proposed specifications based on a permissible daily exposure approach as outlined in the ICH guidance for industry: *Q3C Impurities: Residual Solvents*, is unacceptable as adequate qualification of drug product degradants must be performed in accordance with ICH Q3B(R2).

   To address this deficiency, either reduce the proposed specifications for Impurities (b) (4) and (b) (4) to NMT 0.2% or 3 mg TDI, whichever is lower, or adequately qualify the safety

of the impurities in accordance with the ICH Q3B(R2) guidance. The following studies are required to provide adequate qualification:

a. A minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

b. A repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 90 days should be completed.

   Refer to Guidance for industry: *Q3B (R2) Impurities in New Drug Products* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf

   and

   Guidance for industry: *Q3C Impurities: Residual Solvents* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073394.pdf

c. Alternatively, you may be able to justify the safety of these drug product degradants via comparative analytical studies that demonstrate that the levels of the degradant in your drug product are equal to or below the levels found in and released from the referenced drug product. As noted in Deficiency 1 above, you must determine the level that is released from the patches. If you elect to pursue this approach, refer to the FDA guidance for industry: *ANDAs: Impurities in Drug Products*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072861.pdf.

7. There is inadequate information to justify the systemic safety of dipropylene glycol, isostearic acid, SIS block copolymer, and terpene resin based on the intended clinical use of your product. Specifically it is not clear how the currently accepted uses of these excipients in FDA-approved products compare to the exposure that would occur with use of ZTlido when used at the maximum recommended daily dose.

   To address this deficiency, submit a toxicological risk assessment that supports the systemic safety of dipropylene glycol, isostearic acid, SIS block copolymer, and terpene resin based on the maximum recommended daily dose of your product. Such a justification can include data to show that these compounds are not released from the patch via a leachables study, do not get absorbed into the systemic circulation when the patches are used at the maximum daily dose, or include a discussion of the molecular weight of the excipient to justify the lack of systemic exposure. The risk assessment should address the general chronic toxicity, genetic toxicity, reproductive and developmental toxicity, and carcinogenic potential of the material. However, we acknowledge that we previously stated we would allow chronic toxicology and

carcinogenicity evaluations to be submitted as post-marketing requirements due to the unique situation of the change in duration of the indication for this drug product development program. Therefore, to support approval of the product, provide adequate safety justification supporting at least 3 months of treatment along with the an assessment of the reproductive and developmental effects of these excipients. If there is inadequate nonclinical information to support chronic use of your product, it may be possible to defer completion of definitive studies to the post-marketing period.

8. There is inadequate information regarding polyisobutylene in the drug product formulation in to permit a complete safety evaluation of this excipient or to permit extrapolation of safety via comparison to its use in an FDA-approved drug product formulation. Specifically, it is not clear how the molecular weight range of the low and high molecular weight polyisobutylenes used in ZTlido compare to the materials listed in the FDA Inactive Ingredient Database.

   To address this deficiency, submit the specific molecular weight range for the low and high molecular weight polyisobutylene materials in ZTlido and submit a toxicological risk assessment that includes a discussion of what, if any, of the materials can be absorbed by the body.

9. An adequate leachables evaluation was not submitted to the NDA with sufficient time for review during this review cycle.

   To address this deficiency, submit or refer to previously submitted information on potential leachables and extractables from the drug product formulation that includes a toxicological risk assessment for the leachables detected from the drug product when the product is used up to the maximum daily dose. In the evaluation of extractables and leachables from your drug product, include specific assessments for residual monomers, (b) (4), etc. Use the results of the extraction studies to assure that you are adequately monitoring the drug product stability samples for potential leachables. For the leachables study, evaluate at least three batches of your drug product over the course of stability studies, and base the final safety assessment on the levels of leachables identified and the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these leachables may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, refer to the FDA guidance for industry: *Container Closure Systems for Packaging Human Drugs and Biologics*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf and the FDA guidance for industry: *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and*

Controls Documentation, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070575.pdf. Submit a toxicological risk assessment for any leachable that exceeds 5 mcg/day. From a genetic toxicology perspective, any leachable that contains a structural alert for mutagenicity must not exceed 10 mcg/day total daily exposure for this indication, or be adequately qualified for safety. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified.

PRODUCT QUALITY

Drug Product

10. DMF (b) (4), which was referenced for the (b) (4), was found inadequate to support this NDA.

    To address the DMF deficiencies, a letter was sent to the holder of DMF (b) (4).

11. DMF (b) (4), which was referenced for the (b) (4), was found inadequate to support this NDA. This DMF describes multiple products. Provide the product name which this NDA is referencing for the container closure system.

    To address the DMF deficiencies, a letter was sent to the holder of DMF (b) (4).

12. In conjunction with the new comparative bioavailability study discussed in the Clinical Pharmacology section above, provide residual drug data for your product and the comparator at the completion of the delivery period. Determine residual drug data based on analysis of used drug product and not a theoretical calculation. Assess and account for the amount of drug left on the skin surface and any drug that may have been transferred to packaging or other components during storage or use in an attempt to perform a mass balance. Your control should include an analysis of a sufficient number of unused products from the same lot as those used in the trial to provide an estimate of drug load and not simply an expression of label claim.

13. (b) (4)

14.

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(b) (4)

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Biopharmaceutics

39. The complete in vitro drug release stability data (individual, mean, standard deviation, and profiles) for at least 12 units of the registration lots were not submitted.

    To address this deficiency, provide the complete in vitro drug release stability data (individual, mean, standard deviation, and profiles) for at least 12 units of the registration lots.

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 Information* and *Pregnancy and Lactation Labeling Final Rule* 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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

PROPRIETARY NAME

Please refer to correspondence dated, July 10, 2015, which addresses the proposed proprietary name, ZTlido (lidocaine patch 1.8). 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.

FACILITY INSPECTIONS

During recent inspections of (b) (4) and **Oishi Koseido Co. Ltd. (FEI 3010166685)** manufacturing facilities for this NDA, our field investigators conveyed deficiencies to the representative of the facilities. Satisfactory resolution of these deficiencies is required before this NDA may be approved.

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 the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA 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 NDA 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 additional comments and requests:

Clinical

Based on the results of SCI-LIDO-DERM-001, ZTlido has shown the potential to cause more severe skin irritation than Lidoderm. ZTlido was associated with a higher proportion of subjects with an irritation score of 3 or above (8% versus 0%), and approximately 26% of subjects had a cumulative score greater than or equal to 2 with ZTlido versus 1.8% with Lidoderm. Also, there were three significant dermatologic events during that study that were attributed to ZTlido and that were characterized as severe or that resulted in discontinuation. Very brief narratives were provided for each of these three cases and the case report form was provided for one. However, detailed information for the cases was lacking.

Provide a risk-benefit analysis addressing the potential benefits of ZTlido that would offset concerns about the dermal safety profile. Also, include a better characterization of the three events described above, detailing the history of the dermal lesions, any interventions used to treat the lesions, and the eventual outcome for each of the three subjects.

Product Quality

1. The submission does not include adequate (b) (4) testing results of lidocaine in the adhesive (b) (4).

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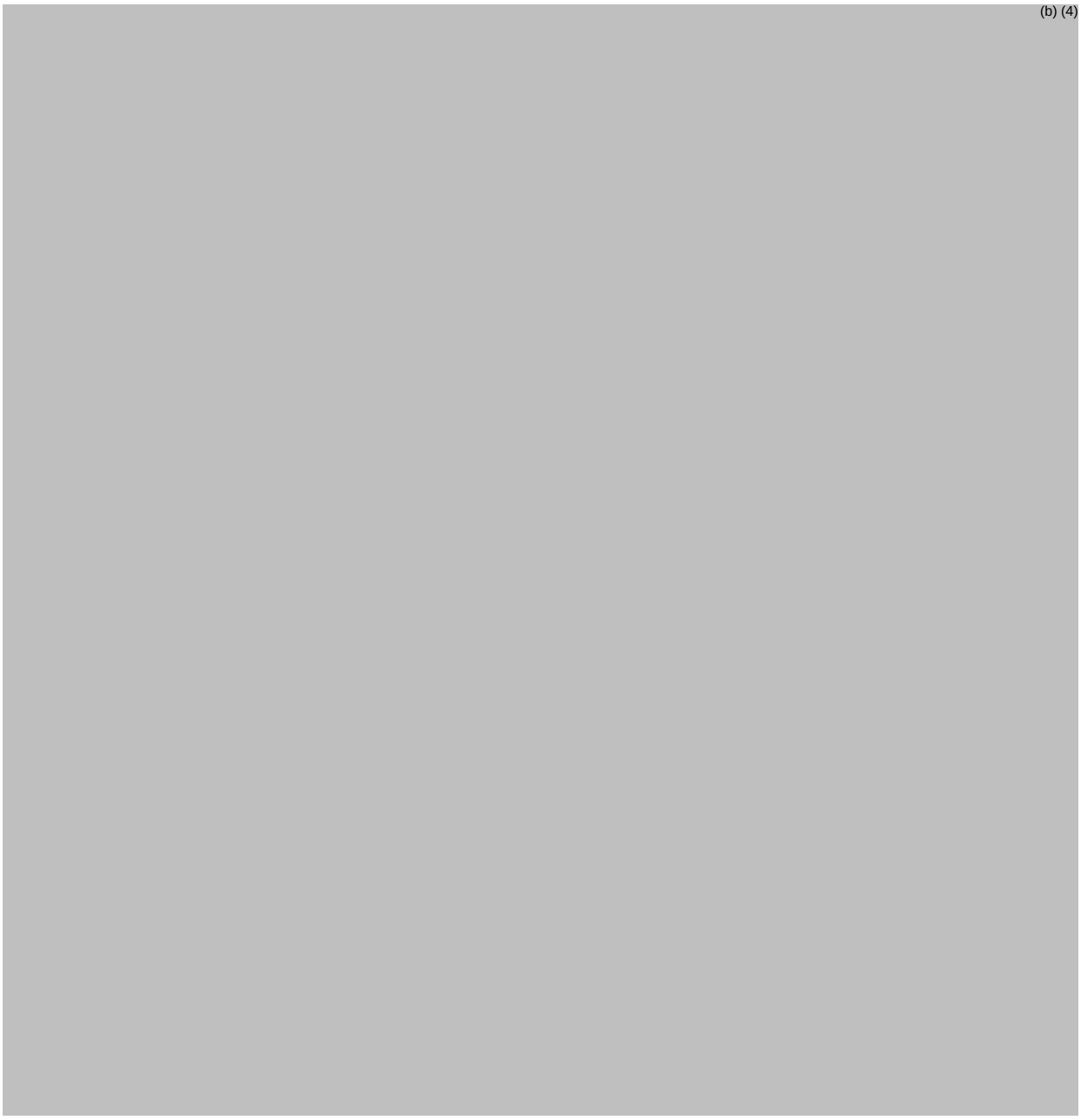

7. Add Impurity A, Impurity (b) (4), and (b) (4) to the drug product specifications. Update and validate the analytical method for degradation products for the measurement of these impurities.

8. The leachable and extractables data submitted March 24, 2016, were not reviewed, therefore, we cannot comment on the adequacy of the data.

9. The shelf-life of this product will be determined at the time of the approval, when all the deficiencies identified for this product are resolved.

10. The Environmental Assessment reference included in your submission is for the INDs Providean applicable CFR reference for the NDA, and include required information for the Environmental Assessment.

Nonclinical

We remind you that as per our pre-NDA comments, chronic toxicology studies and carcinogenicity studies will be required for any new excipients that have not been adequately qualified per the FDA guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf. Based on our review of your submission to date, the following studies will be required to be completed as post-marketing requirements unless justified otherwise:

1. A 6-month repeat-dose toxicology study in the rodent that evaluates the systemic safety of terpene, SIS block copolymer, isostearic acid, polyisobutylene, and dipropylene glycol, unless adequately justified otherwise. Such a justification can include data to show that these compounds are not released from the patch via a leachables study or do not get absorbed into the systemic circulation when the patches are used at the maximum daily dose. This justification could also include a discussion of the molecular weight to justify the lack of systemic exposure and reference to the leachable studies. The 6-month study can be completed via a parenteral route of administration in order to assure systemic delivery of these excipients.

2. A 9-month repeat-dose dermal toxicology study in the minipig testing the final to-be-marketed drug product formulation.

3. A carcinogenicity assessment in a single rodent species via the dermal route testing isostearic acid, SIS block copolymer, terpene, and polyisobutylene, unless adequately justified otherwise.

4. A carcinogenicity assessment in a second rodent species via a systemic route testing isostearic acid, SIS block copolymer, terpene, polyisobutylene, and dipropylene glycol, unless adequately justified otherwise.

We encourage you to initiate these studies as soon as possible and submit them as soon as final study reports are completed. If these studies are not completed by the time of your planned complete response to the deficiencies noted above, they will be required to be completed as post-marketing requirements.

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. 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 FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

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 Allison Meyer, Regulatory Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Ellen Fields, MD, MPH
Deputy Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLEN W FIELDS
05/10/2016