CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206610Orig1s000

OTHER ACTION LETTERS

NDA 206610

COMPLETE RESPONSE

Mylan Laboratories Limited
c/o Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
Morgantown, WV 26505

Attention: Shane Shupe
Director, Regulatory Affairs

Dear Mr. Shupe:

Please refer to your new drug application (NDA) dated May 5, 2014, received May 5, 2014, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Acetaminophen (b) (4) for Injection, 1 g/vial.

We acknowledge receipt of your amendment dated December 6, 2018, which constituted a complete response to our December 6, 2017, 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.

FACILITY INSPECTIONS

1. During a recent inspection of the Mylan Laboratories Limited [Specialty Formulation Facility] manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

REGULATORY

2. We refer to the outstanding deficiencies communicated to you in our May 14, 2019, information request:

   a. Provide updated letters from Mallinckrodt that clearly indicate a specific date upon which your application can be approved.

   b. Provide appropriate patent certification, recertification or statement to U.S. patent 9,399,012 which is listed in the Orange Book with new use codes since your

January 24, 2017, paragraph IV certification for NDA 022450 for Ofirmev (acetaminophen).

c. Provide an appropriate patent certification or recertification for the new condition of use (new dosing instructions for neonates and infants) proposed in your draft labeling.

PRESCRIBING INFORMATION

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 PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] 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.

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.

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[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.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:

- 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 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 Christopher Hilfiger, Regulatory Project Manager, at (301) 796-4131.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Division 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHARON H HERTZ
06/06/2019 04:13:20 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206610

COMPLETE RESPONSE

Mylan Laboratories Limited
c/o Mylan Pharmaceuticals Inc.
81 Chestnut Ridge Road
Morgantown, WV 26505

Attention: Anil Sachdeva
Senior Director - Regulatory Affairs

Dear Mr. Sachdeva:

Please refer to your New Drug Application (NDA) dated May 3, 2014, received May 5, 2014, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Acetaminophen (b) (4) for Injection, 1 g/vial.

We acknowledge receipt of your submission dated June 7, 2017, which constituted a complete response to our February 1, 2017, 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.

NONCLINICAL

You have not provided an adequate assessment of the presence of possible extractable and leachable compounds from the (b) (4) in the final drug product formulation. An adequate safety justification was not provided for several leachable/extractable compounds that includes (b) (4) because the referenced studies cannot be independently evaluated. Further, adequate safety justification was not provided for the presumed drug product-related impurities (b) (4) as QSAR evaluations for general toxicity are not acceptable.

Information needed to address these deficiencies:

Conduct a 14-day repeat-dose intravenous toxicology study testing an (b) (4)

(b) (4) Include a dosing regimen that mimics the clinical dosing regimen. The study design must define a NOAEL for the levels of each of these compounds. Calculate the safety margin for human exposure for these NOAELs based on body surface area (mg/m^2). The study report must also include quantitative analysis of the above compounds with an identification of the (b) (4) compound in the solutions administered to the animals to ensure that the safety of the compounds leached from the (b) (4) have been adequately qualified for safety in the study.

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

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 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. 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 FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.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 Christopher Hilfiger, Regulatory Project Manager, at (301) 796-4131.

Sincerely,

{See appended electronic signature page}

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

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/s/

ELLEN W FIELDS
12/06/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206610

COMPLETE RESPONSE

Mylan Laboratories Limited
c/o Mylan Pharmaceuticals Inc.
81 Chestnut Ridge Road
Morgantown, WV 26505

Attention: Anil Sachdeva
Senior Director - Regulatory Affairs

Dear Mr. Sachdeva:

Please refer to your New Drug Application (NDA) dated May 3, 2014, received May 5, 2014, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Acetaminophen (b) (4) for Injection, 1 g/vial.

We acknowledge receipt of your amendment dated August 4, 2016, which constituted a complete response to our March 10, 2016, 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.

NONCLINICAL

You have not provided an adequate assessment of the presence of possible extractables from the (b) (4) in the final drug product formulation. We are unable to complete our review of the data submitted to date without responses to the following information request:

1. Your limit of detection (LOD) and limit of quantitation (LOQ) from your extractable study report and leachable study report are not consistent. Specifically, you appear to be able to detect lower levels of compounds in your extraction study than you were able to detect in the leachable study.

2. Based on the data provided, there is not an adequate extractables/leachables correlation. Specifically, based on your assessment (b) (4) however, your extraction study results only predic (b) ( ) mcg/day. This suggests that either the extraction conditions were not adequate or (b) (4)

3. There are still two unknowns listed in your extraction study and four unknowns in the leachable study that exceed the qualification threshold of (b) (4) mcg/day.

Information needed to address these deficiencies:

1. Explain the apparent discrepancy in the LOD and LOQ in your extraction studies and leachable studies and provide the basis for these limits in both the extractable study and the leachable study in light of the Analytic Evaluation Threshold (AET). For a (b) (4) mL total daily dose, we calculate an AET of (b) (4) ppm will be necessary to be able to detect a compound that would result in exposure of (b) (4) mcg/day or greater. If you believe that this AET is not feasible, justify your analytical capability. If your assay cannot meet our calculated AET, the toxicological risk assessment will be based on the limit of quantitation (LOQ). Revise your toxicological risk assessment accordingly.

2. Provide an analysis of the extractables/leachables correlation and justify the conditions of your assays. In the absence of an adequate justification for your extractable leachable study conditions, it is not clear if the extractable/leachable data accurate reflect the levels of potential (b) (4) contaminants in the final drug product.

3. In order to complete a toxicological risk assessment, identify all unknowns greater than (b) (4) mcg/day from both the extractable and leachable studies and update the toxicological ri assessment accordingly.

Alternatively, analyze the final lyophilized drug product to determine if the compounds identified in the extraction study of the (b) (4) are present in the final product using an analytical method able to detect (b) (4) cg/day.

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

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 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. 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 FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.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 Christopher Hilfiger, Regulatory Project Manager, at (301) 796-4131.

Sincerely,

{See appended electronic signature page}

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

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/s/

ELLEN W FIELDS
02/01/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206610

COMPLETE RESPONSE

Mylan Laboratories Limited
c/o Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
Morgantown, WV 26505

Attention: Anil Sachdeva
Senior Director - Regulatory Affairs

Dear Mr. Sachdeva:

Please refer to your New Drug Application (NDA) dated May 3, 2014, received May 5, 2014, and your amendments, submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Acetaminophen (b) (4) for Injection, 1 g/vial.

We acknowledge receipt of your amendment dated September 10, 2015, which constituted a complete response to our February 27, 2015, 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.

NONCLINICAL

You have not provided an adequate assessment of the presence of possible extractables from the (b) (4) in the final drug product formulation. Based on your extraction study, as much as approximately (b) (4) (b) (4) mcg/day) of unknown material could be present (b) (4) This exceeds the threshold of toxicological concern of (b) (4) mcg/day and, therefore, requires adequate safety justification based on a toxicological risk assessment for the identified materials.

To address this deficiency, provide the following information:

1. Finalize and submit the study report for the ongoing scientific study designed to analyze the final drug product for the presence of potential leachables from (b) (4)

2. Definitively identify the unknown extractables (b) (4)) and determine if they are present in the final drug product formulation.

3. Quantitate and characterize any unidentified foreign material from the (b) (4) that is present in the final drug product. The study must be conducted on the final drug product at release.

4. Submit a revised toxicological risk assessment for every leachable that is above the Toxicological Threshold of Concern of (b) (4) mcg/day. We remind you that GRAS designations are not applicable to intravenous drug products.

5. Include copies of all relevant literature cited as part of your toxicological justification. Any publication that is not in English must be translated.

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

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.

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 Christopher Hilfiger, Regulatory Project Manager, at (301) 796-4131.

Sincerely,

{See appended electronic signature page}

Ellen Fields, MD
Deputy Division 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
03/10/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206610

COMPLETE RESPONSE

Mylan Pharmaceuticals, Inc.
781 Chestnut Ridge Road
Morgantown, WV 26505

Attention: Anil Sachdeva
Senior Director of Regulatory Affairs

Dear Mr. Sachdeva:

Please refer to your New Drug Application (NDA) dated May 2, 2014, received May 5, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for acetaminophen (b) (4) for injection, 1 g/vial.

We acknowledge receipt of your amendments dated July 18 and 25, August 7, November 12, and December 9, 2014, and January 8, 16, 20, and 21, and February 20, 2015.

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.

NONCLINICAL

1. The drug substance impurity (b) (4) is reported to be clastogenic and therefore your proposed drug substance specification of NMT (b) (4) % is unacceptable.

   To address this deficiency, update the drug substance specification for (b) (4) We recommend that you contact your DMF holder to determine an appropriate specification.

2. The drug substance impurity (b) (4) is predicted to be mutagenic via QSAR analysis and therefore, the proposed specification of NMT (b) (4) % is unacceptable.

   To address this deficiency, either update your drug substance specification for (b) (4) to NMT (b) (4) mcg/day (NMT (b) (4) %) or conduct an adequate Ames assay to demonstrate that the compound is not mutagenic.

3. You have not provided an adequate characterization of potential leachables from the (b) (4) Based on your extraction study, as much as approximately (b) (4) ((b) (4) mcg/day) of unknown material could be presen (b) (4) This exceeds the threshold of toxicological concern of (b) (4) cg/day and, therefore, requires

adequate safety justification based on a toxicological risk assessment for the identified materials.

To address this deficiency, identify the extractables from the [redacted] study and determine if they are present in the drug product formulation. Quantitate and characterize any unidentified foreign material from the [redacted] that is present in the drug product. Submit an adequate toxicological risk assessment for any leachable that is above the Toxicological Threshold of Concern of [redacted] mcg/day.

PRESCRIBING INFORMATION

4. 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* website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

   If you revise labeling, use the SRPI checklist to ensure that the PI 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.

   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. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

   - The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
   - 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 42 important format items from labeling regulations and guidances.

   Submit draft labeling that addresses our proposed revisions in the attached labeling.

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

   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.

FACILITY INSPECTIONS

During a recent inspection of the Agila Specialties Private Limited (FEI: 3007648351) manufacturing facility and Agila Specialties Private Limited Control Testing Laboratory (FEI: 3003813519) for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory inspection reports for all facilities must be received before this application 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 COMMENT

The listed drug upon which your application relies is subject to a period of patent protection and therefore final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until the period has expired.

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.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference 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 the 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 Christopher Hilfiger, Regulatory Project Manager, at (301) 796-4131.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Acting Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Labeling

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

SHARON H HERTZ
02/27/2015