CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206968Orig1s000

OTHER ACTION LETTERS

NDA 206968

COMPLETE RESPONSE

InnoPharma Licensing LLC
275 North Field Dr
Bldg H1-3S
Lake Forest, IL 60045

Attention: Arman Nolledo
Manager, Regulatory Affairs

Dear Mr Nolledo:

Please refer to your new drug application (NDA) dated and received May 13, 2014, and your amendments pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Acetaminophen Injection, 10 mg/mL.

We acknowledge receipt of your amendment dated June 30, 2020, which constituted a complete response to our November 9, 2018, action letter.

We also acknowledge receipt of your amendments dated December 7, and 16, 2020, 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.

NONCLINICAL

1. You have not provided adequate validated leachable data to permit a substantive toxicological risk assessment for the proposed container closure system.

   Information needed to resolve deficiency
   Submit a revised toxicological risk assessment based on validated leachable data that characterizes the trends in leachables over the course of the proposed shelf-life. Include later timepoints in your proposed shelf-life to fully inform the trends in leachables, particularly given the observations of novel adducts forming in the drug product solution. The risk assessment should be based on the projected highest level of any leachable over stability. Submit a risk assessment for any compound present over 5 mcg/day taking into consideration the maximum daily dose of your drug product.

2. You have not provided an adequate toxicological risk assessment for the acetaminophen adducts detected as leachables in the drug product. Although your risk assessment is based on in silico and read-across evaluations of the larger fragments of the molecule, there are no data to suggest that this read-across reliably predicts the toxicological potential of the adduct as a whole.

   Information needed to resolve deficiency
   To address this deficiency, either conduct an intravenous toxicology study with the four adducts or provide data to support the conclusion that these adducts are not stable and rapidly convert back to acetaminophen and the presumed (b) (4) degradants from which they are formed.

PRODUCT QUALITY

3. Your PDE-based approach to selecting targeted leachables is concerning because not all leachables above the 5 mcg/day threshold may be observed.

   Information needed to resolve deficiency
   In order to obtain a complete leachables profile for your leachables studies, demonstrate that your validated leachables methods can detect all the extractables above the Analytical Evaluation Threshold (AET) based on an SCT of (b) (4) mcg /day with LODs/LOQs with acceptable S/N.

4. Per your response dated October 23, 2020, your validated method will adopt an AET of (b) (4) mcg /L based on an SCT of (b) (4) mcg/day and a Maximum daily volume (MDV) of (b) (4) L/day without considering a 50% uncertainty factor.

   Information needed to resolve deficiency
   Include a 50% uncertainty factor to the final AET to accommodate variations in response of the compounds with different response factors.

5. In your response dated November 20, 2020, we note that the newly submitted 9-month leachable data were analyzed by the original semi-quantitative methods.

   Information needed to resolve deficiency
   Reanalyze the 9-month and subsequent stability time points, using the fully validated methods that you are developing.

6. The non-volatile leachables at the 9-month point are significantly different from those of the 3-month. Some of 3-month leachables disappeared and some new ones appeared in the 9-month time point.

Information needed to resolve deficiency
This can be indicative of either an issue with the analytical method used or the appearance of secondary leachables. Provide a full leachable profile with data collected on a fresh batch of drug product, at 0, 3, 6, 9, and 12-month time points using well-validated methods.

7. Module P.8.3. states that 6 month accelerated studies under 40° ± 2°C/ NMT 25% RH were provided for 2019 batch stability samples 1907059, 1907060, and 1907061. However, we cannot locate this information.

   Information needed to resolve deficiency
   Provide the complete data for at least three batches of drug product stored under accelerated conditions.

8. Table 2 in the Photostability study report ARL/STDR/0066/19 was not included in the report.

   Information needed to resolve the deficiency
   Provide this information in your resubmission.

PRESCRIBING INFORMATION

9. 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[1] and Pregnancy and Lactation Labeling Final Rule[2] 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.[3]

CARTON AND CONTAINER LABELING

10. Submit draft carton and container labeling revised as follows:

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

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Issue			
1.	The strength (i.e., 1,000 mg) is presented as "1000 mg" (i.e., without a comma).	Numbers greater than 1,000 when presented without a comma may be misinterpreted as hundreds "100".[4]	Present numbers greater than or equal to 1,000 with a comma.
	Container Label		
1.	The location and format of the expiration date and lot number is not specified.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors. Lack of lot number may result in dispensing errors.	Designate an area for inclusion of the expiration date and lot number on the container label. Expiration date is required on all container labels per 21 CFR 201.17, include the expiration date on the label and ensure it is clearly differentiated from other numbers on the label. Additionally, identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters

[4] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2018 NOV 29]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
Overwrap Labeling			
1	The format of the expiration date is not specified.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2	The net quantity (100 mL) statement highlighted by a red box competes for	The net quantity statement should not compete in size or prominence with important information	Reduce the prominence of the net quantity statement.

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	prominence with the product strength.	listed on the label. For more information see draft guidance, Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (April 2013)[5]. As written, the net quantity statement could be misinterpreted as a strength statement (i.e., 100 mg).	
Carton Labeling (Shipper Label)			
1.	As currently presented, the units of temperature measurement (Centigrade and Fahrenheit) following the first numbers in the temperature ranges (e.g., Centigrade symbols (C) following the 20 and the Fahrenheit symbols (F) following the 68) are missing.	The lower temperatures in the ranges may be overlooked.	Add the Centigrade symbol (C) following the 20 and the Fahrenheit symbol (F) following the 68 within the storage statement. For example, "Stored at controlled room temperature 20°C to 25°C (68°F to 77°F)."

[5] When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents

2.	As currently presented, the product strength (i.e., 1,000 mg per 100 mL) is not included on the carton labeling. Only the quantity per milliliter is included (i.e., "10 mg/mL")	The "strength or potency of the dosage form in metric system" is required by 21 CFR 201.57(c)(17)(i).	Add the proposed product strength, "1,000 mg per 100 mL" to the carton labeling. For example, "1,000 mg per 100 mL (10 mg/mL)"
3.	The route of administration is missing.	Missing route of administration statement could pose risk of product administration errors.	Add the route of administration statement without the use of abbreviations to the carton labeling. For consistency, use the same statement that is on the container label, per 21 CFR 201.100(b)(3). For example: "For Intravenous Use Only".
4.	A quantity statement, (b) (4), may be interpreted as one infusion bag per carton.	This quantity statement is misleading and incorrect.	Delete the quantity statement, (b) (4).
5.	The carton labeling does not contain an "Rx Only" statement.	The "Rx Only" statement is required on the drug label and the outside container by Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act.	Consider including an "Rx Only" statement on the carton labeling. We recommend adding the "Rx Only" statement to an area on the carton label that does not interfere with important product identifying information (i.e. product name, product strength).
6.	The carton labeling includes a 2D data matrix barcode, lot number, and expiration date. However, it is not	The DSCSA requires certain prescription drugs to have a human-readable and machine-readable (2D data matrix barcode) product	In September 2018, FDA released the draft guidance, Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers.[6] The Act requires

[6] When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents

	clear if a serial number is included.	identifier on the smallest saleable unit (usually the carton) for tracking and tracing purposes.	manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

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.

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 Kimberly Compton, RPh, RAC, Senior Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

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

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
12/22/2020 10:03:57 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206968

COMPLETE RESPONSE

InnoPharma Licensing LLC
100 Route 206 North
PPK3/0PL/32
Peapack, NJ 07977

Attention: Lakshmi Vemuri
Regulatory Affairs Associate

Dear Ms. Vemuri:

Please refer to your New Drug Application (NDA) dated and received May 13, 2014, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Acetaminophen Injection, 10 mg/mL.

We acknowledge receipt of your amendment dated May 10, 2018, which constituted a complete response to our November 15, 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

1. You have not provided adequate nonclinical data to support the safety of elemental impurities in your drug formulation.

   In accordance with ICH guidance, *Q3D Elemental Impurities*, and FDA guidance for industry, *Elemental Impurities in Drug Products*, submit a risk assessment that includes the elemental impurities, their sources, and the controls and acceptance criteria to address the safety of elemental impurities in your drug product.

   The above guidance documents are available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM371025.pdf and https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM509432.pdf.

FACILITY INSPECTIONS

2. During a recent inspection of the [redacted] (b) (4) 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

Your submission indicates your intention to rely upon the Agency's finding of safety and effectiveness for NDA 022450 OFIRMEV (acetaminophen) injection to support approval of your 505(b)(2) application. However, your 505(b)(2) application does not contain the following:

3. Patent certification
   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 relies upon the Agency's finding of safety and effectiveness for OFIRMEV 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 the listed drug upon which you rely. Specifically, your application does not contain a patent certification or statement with respect to patent 9,987,238 ('238 patent) that is listed in the Orange Book. Submit an appropriate patent certification or statement with respect to the '238 patent.

   Note that if you elect to provide a paragraph IV certification (21 CFR 314.50(i)(1)(i)(A)(4)) with respect to this patent, the certification is to be accompanied by a statement that you will comply with the requirements under 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 which 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 the notice.

4. Written statement from patent owner consenting to approval
   If a 505(b)(2) application is submitted for a drug or method of using a drug claimed by a patent and the applicant has a licensing agreement with the patent owner, the applicant must submit a paragraph IV certification as to that patent and a statement that the applicant has been granted a patent license. If the patent owner consents to approval of the 505(b)(2) application (if otherwise eligible for approval) as of a specific date, the 505(b)(2) application must contain a written statement from the patent owner that it has a licensing agreement with the applicant and that it consents to approval of the 505(b)(2) application as of a specific date. See 21 C.F.R. 314.50(i)(3).

   Notwithstanding the licensing agreement to patents listed in the Orange Book for NDA 022450 referenced in your May 2018 patent certification, you are required to comply with the statutory requirements for sending notice of paragraph IV certification to the NDA holder and each patent owner.

You are required to provide a statement in your 505(b)(2) application certifying that notice of paragraph IV certification for the patent has been provided to the NDA holder and each patent owner identified under 21 CFR 314.52(a) and that the notice met the content requirement under 21 CFR 314.52(c). The name and address of each patent owner (or its representative) can be obtained from the United States Patent and Trademark Office. In addition, you must amend your application to document receipt of notice of paragraph IV certification as described under 21 CFR 314.52(e) by each person required to receive notice.

5. Exclusivity waiver from NDA holder
   Your exclusivity statement certifies: "InnoPharma has received a waiver, effective as of the License Entry Date, for any exclusivity from Mallinckrodt IP, the NDA holder for Ofirmev should any exclusivities exist now or in the future that would prevent final approval of InnoPharma's Acetaminophen Injection 1000mg/10mL product."
   The holder of the NDA waiving its exclusivity with respect to your 505(b)(2) application should submit a statement regarding such waiver. Note that it is possible that, before your application is resubmitted and ready for full approval, another NDA for a single-ingredient acetaminophen drug product may qualify for exclusivity that could affect the approval of your 505(b)(2) application; in such cases, you may submit a statement explaining why such exclusivity does not affect the approval of your application.

PRESCRIBING INFORMATION

6. 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 314.65. 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 FDA guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*, available at, https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.

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 Kimberly Compton, RPh, RAC, Senior Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Joshua Lloyd, MD
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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOSHUA M LLOYD
11/09/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206968

COMPLETE RESPONSE

InnoPharma Licensing LLC
10 Knightsbridge Road
Piscataway NJ 08854

Attention: Christy Meng
Associate Director, Regulatory Affairs

Dear Ms. Meng:

Please refer to your New Drug Application (NDA) dated and received May 13, 2014, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Acetaminophen Injection, 10 mg/mL

We acknowledge receipt of your amendment dated May 17, 2016, which constituted a complete response to our February 27, 2015, action letter.

We also acknowledge receipt of your amendment dated November 3, 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.

NONCLINICAL

1. You have not provided adequate nonclinical safety justification for the drug product formulation. Specifically, the submitted 28-day intravenous rat repeat-dose toxicology study did not establish a NOAEL with respect to local toxicity and the lacked a saline control arm.

   To address this deficiency, conduct a 14-day repeat-dose intravenous rat local tolerance study with the drug product formulation that mimics the proposed clinical dosing regimen, including an additional saline treatment arm and an active comparator arm (the referenced drug product) to support your conclusion that the high incidence rate of thrombosis and inflammation at the local tissue site is a secondary effect of the catheter rather than the drug product solution. Include histological evaluation of the lungs, kidney, liver, and local tissue for all animals in all treatment groups.

PRESCRIBING INFORMATION

2. 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.

FACILITY INSPECTIONS

3. During a recent inspection of the (b) (4) 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

4. 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 relies upon the Agency's finding of safety and effectiveness for NDA 022450 for Ofirmev, 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 the listed drug upon which you rely. After you submitted your 505(b)(2) application, the NDA holder for Ofirmev, timely filed information on U.S. Patent No. 9,399,012 ('012' patent) for listing in the Orange Book. In accordance with section 505(b)(2) of the FDCA and 21 CFR 314.50(i), you must submit an appropriate patent certification or statement with respect to the '012' patent.

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.

ADDITIONAL COMMENTS

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

We remind you of your commitment in your August 8, 2016, submission to conduct long-term stability studies on the first three batches produced (b) (4) and submit those to your NDA.

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 FDA guidance for industry, *Formal Meetings Between FDA and Sponsors or Applicants*, available 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 Kimberly Compton, RPh, Senior Regulatory Project Manager, Regulatory Project Manager, at (301) 796-1191.

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
11/15/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206968

COMPLETE RESPONSE

InnoPharma Licensing LLC
10 Knightsbridge Road
Piscataway NJ 08854

Attention: Christy Meng
Associate Director, Regulatory Affairs

Dear Ms. Meng:

Please refer to your New Drug Application (NDA) dated and received May 13, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Acetaminophen Injection, 10 mg/mL.

We acknowledge receipt of your amendments dated June 27, August 14, October 7 and 31, November 4 and 14, and December 19, 2014, and January 9, and February 5 and 9, 2015.

We also acknowledge receipt of your amendment dated February 13, 2015, 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.

NONCLINICAL

1. You have not provided adequate nonclinical safety justification for the drug product formulation. Specifically, you did not conduct a 28-day repeat-dose toxicology study in an appropriate species to characterize the potential for systemic and local tissue toxicity nor did you conduct an adequate blood compatibility assessment.

   To address this deficiency, conduct a 28-day repeat-dose intravenous toxicology study in a single species with the drug product formulation that includes all standard toxicological endpoints and an assessment of the local tissue toxicity of the drug product. Ideally, the study would mimic the clinical dosing regimen as closely as possible, define a NOAEL, and define the toxicological profile of the drug product formulation. In addition, conduct an in vitro blood compatibility assessment of the drug product to demonstrate that the drug product formulation does not result in red blood cell hemolysis, flocculation of proteins, or aggregation of platelets.

2. You have not provided an adequate characterization of the potential leachables from the container closure system over the course of your stability studies to support your proposed expiration date. In addition, you have not provided an adequate toxicological risk assessment for unidentified leachables, described as multiple "non-volatile organic compounds" that exceed (b) (4) mcg/day or for the levels (b) (4).

   To address these deficiencies provide the following information:

   a. Based on the results of adequate leachable assessment over the course of your stability studies, identify all non-volatile organic compounds and provide a toxicological risk assessment for all of these compounds that exceed the toxicological threshold of concern of (b) (4) mcg/day following administration of the maximum daily dose of acetaminophen via this drug product formulation.

   b. Provide a toxicological risk assessment to justify the safety of the resulting levels (b) (4) following administration of the maximum daily dose with the drug product at the end of expiry.

PRODUCT QUALITY

3. During the formal stability study, data (b) (4), and for all of the unidentified organic leachables noted for Deficiency 2, were not collected.

   To address the deficiencies in the stability studies:

   Provide stability data for all unidentified organic leachables and (b) (4) collected over time as part of the formal stability study.

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. 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 recent inspections of the Hikma Farmacêutica (Portugal), (b) (4) manufacturing facilities for this application, our field investigators conveyed deficiencies to the representatives of the respective facilities. Satisfactory inspection reports for all facilities must be received before this application may be approved.

ADDITIONAL COMMENTS

1. 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.

2. Given the limited leachable assessment of a single batch over the course of up to 18 months stability, since multiple batches are required to be on stability, we recommend that at least three batches be evaluated for leachables through to expiry. We remind you that as more data are generated, a toxicological risk assessment must be provided for any leachable that exceeds 5 mcg/day following administration of the maximum daily dose of acetaminophen via this drug product formulation.

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.

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 Swati Patwardhan, Regulatory Project Manager, at (301) 796-4085.

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(S):
Labeling

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