CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209511Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209511

COMPLETE RESPONSE

Innocoll Pharmaceuticals
c/o The Weinberg Group
3803 West Chester Pike
Newtown Square, PA 19073

Attention: Daniel S. Solorio
Vice President Regulatory Program Management

Dear Mr. Solorio:

Please refer to your New Drug Application (NDA) dated and received October 31, 2016, our Refuse to File letter dated December 23, 2016, your resubmission dated February 2, 2018, and your amendments, submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for bupivacaine hydrochloride collagen-matrix implants, 100 mg per implant.

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 an adequate characterization of the systemic safety of bupivacaine exposures via your drug product formulation. Specifically, based on the existing human pharmacokinetic data, your product results in an $AUC_{(0\text{-last})}$ that is twice that of the referenced product. Your existing toxicology data in the rat model do not test exposures that provide coverage for the human exposures via your product.

   To address this deficiency:
   Conduct adequate toxicology studies in two species that provide adequate coverage for the proposed human exposures via your drug product (AUC and C_{max}) or provide clinical data to support the safety of the proposed exposure.

2. You have not provided a valid in vivo micronucleus assay for bupivacaine. Specifically, the high dose selected for the assay did not result in frank toxicity.

   To address this deficiency:
   Repeat the in vivo micronucleus assay for bupivacaine testing doses that result in frank toxicity in accordance with the ICH guidance document: *S2(R1) Genotoxicity Testing*

and Data Interpretation for Pharmaceuticals Intended for Human Use, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074931.pdf.

3. You have not provided an adequate extractables/leachables evaluation to support the safety of your proposed container closure system. Specifically, although your extraction study submitted September 20, 2018, was capable of detecting compounds at the requested safety concern threshold of (b) (4) mcg/day, you did not identify many of the compounds detected above this safety threshold. Further, you did not provide adequate leachables data from multiple batches at release with compounds identified in the extraction study targeted using validated methods.

   To address this deficiency:
   Identify the compounds detected in the extraction studies completed to date and evaluate the drug product stability batches for the presence of any extractable detected at (b) (4) mcg/day or higher. Provide a toxicological risk assessment for any leachable compound present in the drug product at (b) (4) mcg/day or greater.

4. You have not provided adequate justification for the proposed specification for (b) (4) (b) (4) in the drug product formulation.

   To address this deficiency:
   Either reduce the specification for (b) (4) to NMT (b) (4) mcg/day or provide an adequate toxicological risk assessment for this compound to justify the proposed specification in accordance with the ICH guidance document: *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf.

PRODUCT QUALITY

5. The leachables assessment you have provided is incomplete. An analytical method for the detection of leachables has not been provided, and therefore, a correlation between the extractables and leachables cannot be made. Leachables testing should be performed on (b) (4) manufactured product (b) (4) (b) (4)

   To address this deficiency:

   a. From the robust extractables profiles of both primary and secondary packaging, identify and determine the target leachables.

   b. Develop methods which can detect these leachables in the drug product.

   c. Test 3 batches of drug product at multiple time-points on stability with emphasis on (b) (4) manufactured product that includes ink labeling on individual blisters as planned for commercial product.

We also refer you to USP <1663> and <1664> for additional information.

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

PROPRIETARY NAME

7. Please refer to our correspondence dated May 3, 2018, which addresses the proposed proprietary name, XARACOLL. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the product 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 product. Include an updated estimate of use for product marketed in other countries.

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

ADDITIONAL COMMENTS

We have the following additional comments for your consideration:

1. The indication you have proposed, *"for placement into the surgical site to produce postsurgical analgesia following* (b) (4) is not supported by the clinical data you have presented in the NDA submission. You were notified of our concerns regarding the proposed broad indication in several written correspondences, including the End-of-Phase 2 Meeting Minutes dated January 12, 2012; Refuse to File Letter dated December 23, 2016; and most recently in the Filing Communication dated April 17, 2018. The final determination of the indication for your drug product will be made at the time of approval, however, it is likely to include only the surgical population in which the drug product was tested and demonstrated to be safe and effective.

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

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," December 2017 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 Allison Meyer, Regulatory Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, 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/

RIGOBERTO A ROCA
11/30/2018