CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215212Orig1s000

OTHER ACTION LETTERS

NDA 215212

COMPLETE RESPONSE

HQ Specialty Pharma Corporation
Attention: Stephanie Boffa
Vice President Regulatory Affairs
120 Route 17 North, Suite 130
Paramus, NJ 07652

Dear Ms. Boffa:

Please refer to your new drug application (NDA) dated November 16, 2020, received November 16, 2020, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Meropenem for Injection (b) (4) 2 g/vial.

We also refer to your amendments dated January 5 and 15, February 1 and 16, March 31, April 9 and 30, and July 12 and 13, 2021.

We have completed our review of this application 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. We acknowledge your plan to initiate your "*14-Day Repeat Dose Toxicity Study via Intravenous Injection in Beagle Dogs with a 14-Day Recovery Period*" to qualify the identified leachables September 21, 2021 with submission of draft and final study reports in December 2021. Because any preliminary findings from the study will not be available until after the PDUFA goal date of September 16, 2021, we can only rely on the information provided in your submitted "Risk assessment of leachables from 'Meropenem for Injection' 2g: drug product (b) (4)) in a primary closure system consisting of a glass vial closed with a rubber stopper (b) (4)). As previously communicated, the risk assessment does not adequately qualify the safety of the identified (b) (4) leachables detected with your drug product for the following reasons:
    a) You propose using the Cramer decision tree to derive an acceptable intake of (b) (4) for the identified (b) (4) leachables. However, the FDA recommends 5 mcg/day as the qualification threshold for non-genotoxic leachables.
    b) You applied a modified Haber's rule on the Product Quality Research Institute's (PQRI) qualification threshold of 50 mcg/day for leachables

detected in parenteral drug products to calculate acceptable intakes of [redacted] leachables. This approach is not adequate because application of Haber's rule has not been considered for regulatory decisions on the qualification of leachables (or impurities) for safety.

c) You rely on (Q)SAR analysis to qualify the identified leachables for safety. Other than for mutagenicity, (Q)SAR assessments for general toxicity endpoints (i.e., nephrotoxicity), while informative, are not adequate to support safety of the identified leachables.

Information needed to resolve the deficiency

Given the absence of sufficient toxicity information for the identified leachables, we recommend that you proceed with the planned "*14-Day Repeat Dose Toxicity Study via Intravenous Injection in Beagle Dogs with a 14-Day Recovery*" using the cefazolin drug product to qualify the [redacted] leachables. Plan to submit the final, complete study report for this nonclinical qualification study for the identified leachables in a future NDA resubmission.

PRODUCT QUALITY

2. We acknowledge information provided in the amendment dated April 30, 2021, SDN 011, and the proposal to apply a [redacted] overfill for the drug product vials. However, the proposed overfill amount exceeds the recommendations of the USP General Chapter <1151>.

Information needed to resolve the deficiency

Conduct and provide results of a study to justify the proposed overfill and to demonstrate that the labeled drug amount can be consistently withdrawn from the vial according to the labeling reconstitution instructions. Adjust and justify any changes to the [redacted] range and/or the labelling reconstitution instructions based on the results of these studies.

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 Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

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

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

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.

[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

- 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 dropouts 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 comments/recommendations that are not approvability issues:

CLINICAL

1. Clarify whether (b) (4) is still proposed and, if so, provide safety information to support (b) (4) Provide a revised Meropenem for Injection prescribing information (PI) with tracked changes, including but not limited to changes made in the Dosage and Administration section.

2. Clarify why you are not including the other indications listed in the labeling of the listed drug (b) (4) (b) (4)

CLINICAL MICROBIOLOGY

The first and second lists of organisms in subsection 12.4 of the PI should list only those organisms that are relevant to the indication(s) stated in the same PI.

OTHER

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

www.fda.gov

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*.
If you have any questions, call Eva Zuffova, Regulatory Project Manager, at 301-796-0697.

Sincerely,

{See appended electronic signature page}

Dmitri Iarikov, MD, PhD
Deputy Director
Division of Anti-Infectives
Office of Infectious Diseases
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/

DMITRI IARIKOV
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