CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761240Orig1s000

OTHER ACTION LETTERS

BLA 761240

COMPLETE RESPONSE

Coherus BioSciences, Inc.
c/o DataRevive USA LLC
Attention: Herbert W. Hutman, M.D.
President
30 West Gude Drive, Suite 280
Rockville, Maryland 20850

Dear Dr. Hutman:

Please refer to your biologics license application (BLA) dated August 31, 2021, received August 31, 2021, and your amendments, submitted under section 351(a) of the Public Health Service Act for (b) (4) (toripalimab-tpzi) injection.

We also acknowledge receipt of your amendments dated April 25, and April 28, 2022. 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.

PRODUCT QUALITY

1. We have determined that manufacturing control strategy for toripalimab manufacturing at (b) (4) does not align with current industry standards and ICH Q5A guidelines. Specifically, no adventitious virus testing is performed for unprocessed bulks (UPBs) in the manufacturing process to produce toripalimab and other product(s) for non-US market. Those processes share common equipment and/or materials with toripalimab manufacturing for the US market. ICH guideline Q5A Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin recommends that "Appropriate testing for viruses should be performed at the unprocessed bulk level [...]" and "the safety of these products [biotechnology products derived from cell lines] with regard to viral contamination can be reasonably assured only by the application of a virus testing program and assessment of virus removal and inactivation achieved by the manufacturing process […]" through "testing the product at appropriate steps of production for absence of contaminating infectious viruses," as well as requires "manufacturers develop programs for the

ongoing assessment of adventitious viruses in production batches." The lack of an adventitious virus testing program for non-US manufacturing processes poses a risk of adventitious virus cross-contamination of toripalimab batches for the US market manufactured using the same equipment and materials, as well as risk of manufacturing facility disruptions that could risk patient supply.

To address the deficiency, provide the following information on control strategy and measures implemented to assure that all toripalimab batches are produced per current industry standards and aligned with ICH Q5A guidelines:

a. You committed to implement virus testing for UPB for every batch of all products which share equipment or materials or any other product-contacting surface with toripalimab intended for the US market. Submit change control report(s) demonstrating implementation of the virus testing for UPB for all products manufactured on the same equipment as toripalimab drug substance.

b. The materials and equipment used downstream of the UPB testing point carry risk of being contaminated by unknown adventitious virus from previously untested production batches. To mitigate this risk, implement the following and submit applicable documentation demonstrating implementation:

   i. Replace the multi-use materials in manufacturing that harbor the greatest risk of contamination, such as (b) (4) with new materials. Submit qualification and implementation reports of these multi-use materials.

   ii. Sterilize shared product-contact equipment that is amenable to sterilization using methods sufficient for removal or inactivation of viruses. Submit reports of the sterilization activities that assure a virus-free process, including documentation of the method(s) used and scientific justification for their suitability for removing or inactivating virus.

c. Due to the risk of potential contamination of toripalimab batches produced prior to the implementation of adequate viral safety measures, toripalimab batches manufactured prior to implementation of these measures should not be distributed for human use in the US. To fulfill 21 CFR 601.20(b) requirements, confirm that toripalimab drug product produced from drug substance manufactured after implementation of the corrective measurements described in items a and b will be available within the review timeline of the re-submitted application.

d. Submit a comprehensive rationale on how the revised BLA control strategy aligns with current industry standards and ICH Q5A guidelines.

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 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 601.14(b)] 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.

MEDICATION GUIDE

Add the following bolded statement or appropriate alternative to the carton and container labeling per 21 CFR 208.24(d): "**ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide**."

PROPRIETARY NAME

Please refer to correspondence dated, October 6, 2021, which addresses the proposed proprietary name, (b) (4) 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.

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

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. 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 subject 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. We acknowledge receipt of your submission on February 11, 2022, of a draft protocol synopsis for a proposed clinical trial intended to characterize the efficacy and safety of toripalimab in combination with cisplatin and gemcitabine for the treatment of patients with nasopharyngeal carcinoma in a study population whose demographic and disease characteristics are representative of the U.S. patient population. We recommend you request a meeting or teleconference with us to discuss your proposal. Submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

2. If you chose to resubmit the application, provide revised ADLB datasets conforming to data specifications found at https://www.fda.gov/media/133252/download, for the pooled safety sample of patients treated with toripalimab at 3 mg/kg every 2 weeks (N=851) and a separate dataset for the POLARIS-02/Cohort 3 trial (N=190).

3. Clinical site inspections were not performed during this review cycle due to the ongoing travel restrictions related to the COVID-19 pandemic in China. These inspections are required before this application can be approved.

Clinical Pharmacology

4. For the post-platinum treatment as monotherapy indication, you proposed both a weight-based dose of 3 mg/kg every two weeks (Q2W) (b) (4) [redacted]

Product Quality

5. Develop and validate an assay to evaluate the neutralizing capacity of an ADA detected in the patient samples. The assay should be capable of sensitively detect neutralizing anti-drug antibodies (ADAs) in the presence of toripalimab levels that are expected to be present in serum at the time of patient sampling.

Submit the neutralizing ADA assay validation report and assay standard operating procedure.

6. In response to information request (IR) comment #22 received on March 14, 2022, you confirmed that ADA titer assay was not validated. Perform validation of titer measurement of the ADA assay used for clinical studies CT-5 and CT-15 and submit the validation report.

7. The information provided in the original BLA submission and in your response to IR comment #2a received on March 23, 2022, indicate that process characterization of (b) (4) was performed within a narrow range (b) (4) Update sections 3.2.S.2.2 and 3.2.S.2.4 with the elevated criticality categorization and the action/acceptance range for (b) (4)

8. The BLA does not contain sufficient details of extractables and leachables of drug product (DP) manufacturing process. Provide extractables and leachables assessment of DP manufacturing process specifying the risks for product-contacting materials, identified extractables and leachables, risks regarding patient safety, etc.

9. Submit data from the winter and summer shipping qualification studies for the shipping lane from (b) (4) or the finished DP.

10. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response. An inspection of the (b) (4) facility is required before this application can be approved. FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel, we were unable to complete an inspection during the current review cycle for your application. You may respond to deficiencies in this Complete Response Letter while the travel restrictions remain in effect. However, even if these deficiencies are addressed, the application cannot be approved until the required FDA inspection is conducted and any findings are assessed with regard to your application. We will continue to monitor the public health situation as well as travel restrictions.

    Please see the FDA's "An Update to the Resiliency Roadmap for FDA Inspectional Oversight" for more information on FDA's plan to resume inspections (https://www.fda.gov/media/154293/download). Also see the FDA guidances related to COVID 19. These guidances can be found at

https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders.

11. Because approval of your application requires an inspection that cannot be conducted in a timely manner due to COVID-19 travel restrictions, the FDA has made an initial determination that the amendment to your application in response to this complete response letter will be received as a Class 2 review timeline as described in the 2020 Guidance for Industry Review Timelines for Applicant Reponses to Complete Response Letters When a Facility Assessment Is Needed During the COVID-19 Public Health Emergency.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b). 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 601.3(c). 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, contact Emily Pak, Pharm.D., Regulatory Health Project Manager at Emily.Pak@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Deputy Office Director (Acting)
Office of Oncologic 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/

JULIA A BEAVER
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