BLA 761367

COMPLETE RESPONSE

CSL Behring LLC
Attention: Loren Kohrs, MS, RAC
Associate Director, Global Regulatory Affairs
1020 First Avenue
P.O. Box 61501
King of Prussia, PA 19406-0901

Dear Loren Kohrs:

Please refer to your biologics license application (BLA) dated October 13, 2023, received October 13, 2023, and your amendments, submitted under section 351(a) of the Public Health Service Act for CSL312 (garadacimab).

We also acknowledge receipt of your amendment dated August 9, 2024, 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.

FACILITY INSPECTIONS

1. Following pre-license inspection of CSL Behring GmbH, Emil-von-Behring-Strasse 76, Marburg, Hesse, Germany (FEI 3003098680), listed in this application, the FDA conveyed the deficiencies to the representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA 483 prior to your complete response to your application. Your complete response should include the date(s) of the facility's response to the FDA Form 483. The assessment of application approvability and the resolution of inspection deficiencies would be evaluated upon receipt of the complete response and may include re-inspection of the facility. Please work with the facility in resolving the related deficiencies.

MICROBIOLOGY

2. The manufacturing process for CSL312 semi-finished product (SFP) is not designed to minimize potential contamination of the sterile drug product. (b) (4)

[redacted] A process performance qualification (PPQ) protocol and the results of the first [redacted] PPQ batch were provided in the amendment received July 12, 2024; however, additional process validation and other supporting data are needed to support the process change. The amendment received August 9, 2024, was submitted late in the review cycle and was not reviewed. In the BLA resubmission, provide complete process validation data for the CSL312 SFP manufacturing process with [redacted] and update Module 3.2.P of the BLA to reflect the new process accordingly. Include [redacted] and sufficient stability data to support consistency, stability and proposed shelf life of the CSL312 SFP manufactured using the new process. In addition, provide a summary of sterilization validation data for [redacted]

PRODUCT QUALITY

3. Based on the information provided in the original BLA submission and the amendments to the BLA received on June 3, and 20, 2024, there is concern that the control for CSL312 drug product manufacturing process is insufficient to ensure consistent product quality. Specifically, a process control of [redacted] was not adequately established. In addition, the proposed process control strategy of [redacted] is inappropriate to ensure consistent and acceptable filling weight/volume of individual syringes during the filling process. In your resubmission, establish an adequate control strategy for [redacted] that is supported by relevant data. In addition, consider the [redacted] process control to ensure accurate monitoring of the filled weight/volume. Additionally, provide a clear description of the actions taken for failure of in-process checks.

4. The process validation data for CSL312 drug product manufacturing are insufficient to demonstrate consistent process performance. Specifically, [redacted]. In addition, the [redacted] data from the PPQ batches are derived from a limited number of samples and insufficient sampling points. This is a concern considering [redacted] during the routine manufacturing process. In your resubmission, provide sufficient [redacted] results for the drug product filling process (refer to the information requests issued on

May 22, and June 11, 2024). Additionally, provide filling capability data that are derived from sufficient samples and multiple sampling points of PPQ batches to demonstrate that the filling process is capable of filling syringes with consistent filling weight/volume.

PRESCRIBING INFORMATION

Submit draft labeling that is responsive to our electronic communication dated October 4, 2024.

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 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.[1]

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

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 Prescription Drug Labeling Resources[2] and Pregnancy and Lactation Labeling Final Rule[3] 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.

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

- Additional resources for the PI, patient labeling, and carton/container labeling.

CARTON AND CONTAINER LABELING

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

PROPRIETARY NAME

Please refer to correspondence dated April 15, 2024, which addresses the proposed proprietary name, Andembry. This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

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 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 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 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 comments/recommendations that are not approvability issues:

Microbiology

1. The plunger movement study described in section 3.2.P.2.5 was not conducted with syringes with the largest air bubble allowed by the process controls; therefore, the study was not performed under worst-case conditions for plunger movement during (b) (4) transport. The amendment received June 11, 2024, noted that a new plunger movement study will be conducted using 15 filled syringes with plunger stopper positions manipulated manually to create a (b) (4) mm air bubble. Provide results from the repeated plunger movement study conducted with syringes with the largest air bubble allowed in the syringe to ensure that sterility of the drug product will be maintained during routine (b) (4) transport under worst-case conditions.

2. (b) (4)

Product Quality

3. We acknowledge that you provided product quality data from relevant studies to support risk assessment of the commercial drug product shipping; however, you did not provide real-time/real-condition drug product shipping validation data in

the BLA submission. In the information request response dated June 3, 2024, you agreed to commit to perform a real-time/real-condition shipping validation study and to submit the data in a future annual report. Submitting the shipping validation data without an approved shipping validation protocol for prospective validation of the actual commercial drug product shipping to a future annual report is inappropriate because product quality cannot be ensured during the actual commercial drug product shipment. Therefore, in your resubmission, we recommend you provide drug product real-time/real-condition shipping validation data.

Device

4. In the information request dated January 29, 2024, the FDA requested device performance testing (either real-time or accelerated aged testing) on a total of 3 batches of the subject prefilled syringe (PFS) with needle safety device (NSD) to include dose accuracy, peak force, injection force, and NSD activation force to demonstrate that the device will perform as intended to the end of its proposed shelf life of 36 months. The FDA also requested testing for a total of 3 batches of the subject autoinjector (AI) to include dose accuracy, injection time, activation force, extended needle length, and lockout force to demonstrate that the device will perform as intended to the end of its proposed shelf-life of 36 months. In the response dated February 5, 2024, we note that two additional drug product batches of CSL312 PFS assembled with NSD and CSL312 PFS assembled with AI will be placed on stability, and this data will be provided in an annual report. In your resubmission, provide the results of the additional stability data rather than in an annual report.

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 product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648 or phuong.ton@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Kathleen Donohue, MD
Deputy Director
Office of Immunology and Inflammation (OII)
Office of New Drugs
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/

KATHLEEN M DONOHUE
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