CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761325Orig1s000

OTHER ACTION LETTERS

BLA 761325

COMPLETE RESPONSE

Sanofi-aventis U.S. LLC
Attention: Selina Feng, MBS., RAC
Regulatory Strategist, Global Regulatory Affairs
55 Corporate Drive
Mail Stop: 55C-300
Bridgewater, New Jersey 08807-5925

Dear Selina Feng:

Please refer to your biologics license application (BLA) dated and received September 8, 2022, and your amendments, submitted under section 351(k) of the Public Health Service Act for SAR341402.

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

The data provided are inadequate to demonstrate that the Rabbit Pyrogen Test (RPT) is suitable to detect endotoxin in SAR341402 drug product as a release test. In response to the information request dated August 31, 2023, you indicated that RPT according to USP <151> is applied for Drug Product release testing to demonstrate the absence of endotoxins and other pyrogens. To circumvent the physiological responses in rabbits to the insulin, a glucose solution is injected in parallel to the application of the test solution. However, the data submitted to the BLA did not adequately demonstrate that insulin's mechanism of action does not result in physiological responses and temperature changes in the rabbits that are unrelated to endotoxin. Additionally, the data provided did not include endotoxin spiking studies to demonstrate that the RPT can adequately detect endotoxin present in SAR341402 drug product. Provide an endotoxin test method for SAR341402 drug product release that can reliably detect endotoxin over process-relevant time and temperature.

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. In addition, we encourage you to review the FDA guidance for industry *Labeling for Biosimilar Products*.

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.

PROPRIETARY NAME

Please refer to correspondence dated, August 28, 2023, which addresses the proposed proprietary name, Merilog. 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.

FACILITY INSPECTIONS

A review of requested manufacturing site records under Section 704(a)(4) was conducted for the drug substance and drug product manufacturing facility, Sanofi-Aventis Deutschland GmbH (FEI: 3003195501) located in Frankfurt am Main, Germany. Per 704(a)(4), these requested records may be used in advance of or in lieu of inspection. Based on the records review, a waiver for the pre-license inspection of BLA 761325 SAR341402 drug substance and drug product manufacturing at Sanofi-Aventis Deutschland GmbH has been determined.

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 of the product under consideration regardless of indication, dosage form, or dose level.

---

[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

(1) Describe in detail any significant changes or findings in the safety profile and their relevance, if any, to whether there may be clinically meaningful differences between the proposed biosimilar product and the U.S.-licensed reference product.

(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 clinical studies for the proposed indication using the same format as the original BLA submission.
- Present tabulations of the new safety data combined with the original BLA data.
- Include tables that compare frequencies of adverse events in the original BLA with the retabulated frequencies described in the bullet above.

(3) Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each subject who died during a clinical study or who did not complete a study 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 BLA data.

(6) Provide updated exposure information for the clinical studies (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this product, including adverse events known to be associated with the use of the product and immunogenicity. Include an updated estimate of use for this 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:

1. You have not clearly identified (b) (4) in the manufacturing

process description (3.2.S.2.2). Clearly identify the [redacted] supported by [redacted] validation data obtained during manufacture of the process performance qualification lots (PPQ).

2. The microbial contamination test (IPC 3.3) was not adequately validated. Submit method validation studies using samples from three batches of SAR341402.

3. Descriptions of the microbial contamination and bacterial endotoxin tests for drug substance release were not adequately described. Provide brief descriptions of each method.

4. The description of the [redacted] studies is incomplete. It is unclear if the [redacted] used during [redacted] support the proposed [redacted] intended for routine manufacturing. Provide the [redacted] used during [redacted] and provide a comparison to routine [redacted]

5. Container closure integrity test data supporting the proposed crimping pressure used for cartridges and vials was not provided. Submit these data to support the proposed crimping pressure ranges for both cartridges and vials.

6. The container closure integrity test used for stability testing lacks sensitivity. Develop a method that can detect breaches of ≤ 20µm.

7. You state that the execution of the LAL test for endotoxin according to USP <85> is not possible due to a Low Endotoxin Recovery (LER) effect. However, the LER study data was not submitted to the BLA. Submit the LER study data.

8. The reference material system for SAR341402 consists of the secondary reference material [redacted] To support the product lifecycle, you should develop and implement a two-tiered in-house reference material system consisting of primary and secondary reference materials generated with in-house material(s). The reference material system should be prepared from lot(s) representative of production and clinical materials and be demonstrated to be fit for intended use. For example, as a reference material for content, potency, and specific activity testing. The qualification of the reference materials should include release and characterization testing, as appropriate, with justified acceptance criteria and number of replicates and ampoules assessed for each attribute.

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 Biosimilar Biological Product Sponsors or Applicants*.

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 Michael Oyewole, Regulatory Project Manager, at (301) 796-3897.

Sincerely,

{See appended electronic signature page}

Patrick Archdeacon, M.D.
Deputy Director
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology
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/

PATRICK ARCHDEACON
09/08/2023 04:30:05 PM