Cross-Discipline Team Leader Review and Summary Memo

Date	See digital signature
From	Patrick Archdeacon, MD (Signatory) Deputy Director DDLO
BLA #	BLA 761325
Applicant	Sanofi-aventis U.S. LLC
Date of Submission Receipt	August 16, 2024
PDUFA Goal Date	February 16, 2025
Established or Proper Name	Insulin aspart-szjj
(Proposed) Trade name	Merilog and Merilog SoloStar
Dosage forms / Strength	100 units/mL
Applicant Proposed Indication(s)/Population(s) Recommended Action	To improve glycemic control in adults and pediatric patients with diabetes mellitus
Recommendation on Regulatory Action	Approval as biosimilar to U.S.-licensed NovoLog (insulin aspart)

This memo summarizes the following reviews:

Material Reviewed/Consulted		
Office of Pharmaceutical Quality (OPQ) Integrated Quality Review	February 10, 2025	Davinna Ligons, Maria Gutierrez Lugo
Product Quality Facility Assessment	February 7, 2025	Madushini Dharmasena, Kamal Tiwari
Product Quality Microbiology Assessment	January 23, 2025	Reyes Candau-Chacon, Madushini Dharmasena
Biosimilar Multidisciplinary Evaluation and Review for original NDA submission	September 8, 2023	Patrick Archdeacon, Melinda Wilson, Dolly Misra, Edwin Chow, Mohamad Kronfol, Federica Basso, Elena Braithwaite
Division of Medication Error Prevention and Analysis 1 (DMEPA) – Labeling Review	November 29, 2024	Vraj Patel, Damon Birkemeier
Division of Medication Error Prevention and Analysis 1 (DMEPA) – Proprietary Name Review	October 25, 2024	Vraj Patel, Idalia Rychlik
Patient Labeling Team and Office of Prescription Drug Promotion (OPDP)	January 24, 2025 and January 29, 2025	Nyedra Booker, Tierra Butler, LaShawn Griffiths

1. Executive Summary

Sanofi-aventis U.S. LLC (hereafter referred to as "the Applicant") resubmitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for SAR341402 as a proposed biosimilar to U.S.-licensed NovoLog (insulin aspart, BLA 020986) on August 16, 2024. SAR341302 (proposed non-proprietary name insulin aspart-szjj; proposed proprietary name Merilog and Merilog SoloStar) is a rapid acting insulin analog. The sequence of SAR341402 and U.S.-licensed NovoLog (U.S.- NovoLog) is homologous with human insulin with

the exception of a single substitution of the amino acid proline by aspartic acid in position B28. SAR341402 is produced by recombinant DNA technology using a non-pathogenic laboratory strain of *Escherichia coli* as the production organism. SAR341402 is supplied at 100 units/ml (U-100) in a 3 mL single-patient use pre-filled pen for subcutaneous (SC) injection using the SoloStar pen-injector platform. SAR341402 is also supplied at U-100 in a 10 mL multiple-dose vial for SC injection.

The Applicant is seeking licensure of SAR341402 for the following indication for which U.S.-NovoLog has been previously approved:

- To improve glycemic control in adults and pediatric patients with diabetes mellitus.

In considering the totality of the evidence submitted in the application, including the evidence provided by the Applicant in the resubmission, the information demonstrates that SAR341402 is biosimilar to U.S.-NovoLog for the proposed indication.

2. Background

The Applicant originally submitted BLA 761325 on September 8, 2022. The review of the original submission noted that SAR341402 is proposed as follows:

Route of Administration: subcutaneous injection (pen and vial)
Dosage Form: injection
Strength: 300 units per 3 mL single-patient use pre-filled pen and 1000 units per 10 mL multiple-dose vial; concentration 100 units/mL (U-100)

Each strength of SAR341402 in the prefilled-pen and the vial is the same as that of U.S.-NovoLog. SAR341402 has the same dosage form as that of U.S.-NovoLog. SAR341402 and U.S.-NovoLog both have a subcutaneous route of administration. U.S.-NovoLog has an intravenous route of administration, which the Applicant is not seeking for SAR341402 in this submission. The Applicant is not seeking licensure for all the condition(s) of use that have been previously approved for U.S.-NovoLog: in addition to not seeking an intravenous route of administration, the application is not seeking labeling for continuous subcutaneous infusion (i.e., use with an insulin pump). However, the dosage form and route of administration and the condition(s) of use for which the Applicant is seeking licensure for SAR341402 have previously been approved for U.S.-NovoLog.

During the original review of BLA 761325, FDA concluded that the data submitted by the Applicant demonstrate that SAR341402 is highly similar to U.S.-NovoLog, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between SAR341402 and U.S.-NovoLog in terms of the safety, purity, and potency of the product. FDA also concluded that the information submitted by the Applicant, including justification for extrapolation of data and information, demonstrates that SAR341402 is biosimilar to U.S.-NovoLog for each of the following indications for which U.S.-NovoLog has been previously approved and for which the Applicant is seeking licensure of SAR341402: to improve glycemic control in adults and pediatric patients with diabetes mellitus.

It is noteworthy that U.S.-NovoLog has an additional condition of use (administration by continuous subcutaneous insulin infusion (CSII)) and an additional intravenous (IV) route of administration, neither of which is sought by the Applicant for SAR341402 in this resubmission. The Agency communicated to the Applicant that differences between the formulations of SAR341402 and (b) (4)

(b) (4)

The original submission of BLA 761325 received a Complete Response on September 8, 2023. The deficiency that precluded approval of the application was the inadequacy of the proposed endotoxin test method for SAR341402 drug product release that can reliably detect endotoxin over process-relevant time and temperature. During the review of the original submission, all proposed manufacturing and testing facilities were deemed acceptable based on their acceptable CGMP compliance status and historically recent relevant inspectional coverage, without an on-site inspection. After the September 8, 2023, Complete Response, an audit of the facility that manufactures SAR341402 (b) (4) conducted for an unrelated application identified facility deficiencies. For that reason, OPQ determined that a prelicense inspection of the manufacturing facility would be required as part of the review of the resubmission of BLA 761325, in addition to the review of the new data supporting the adequacy of the proposed endotoxin test method for SAR341402 drug product release.

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) recommends approval of BLA 761325 for Merilog/Merilog SoloStar manufactured by Sanofi-Aventis Deutschland GmbH, Germany (FEI 30013195501). OPQ concluded that the data submitted in this application are adequate to support the conclusion that the manufacture of Merilog/Merilog SoloStar is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that Merilog/Merilog SoloStar is highly similar to U.S.-licensed NovoLog, notwithstanding minor differences in clinically inactive components. OPQ recommends that the product be approved for human use under conditions specified in the package insert. I concur with the recommendation from OPQ. See brief summaries below regarding 1) the prelicense inspection required as part of the review of the resubmission and 2) the review of the new data supporting the adequacy of the endotoxin test method for SAR 341402 drug product release. See the OPQ reviews for additional details.

Manufacturing Facility Assessment

On the first cycle, all proposed manufacturing and testing facilities were deemed acceptable based on their acceptable CGMP compliance status and previous history. However, OPQ determined that a prelicense inspection of the Sanofi-Aventis Deutschland GmbH manufacturing facility (FEI 3003195501) would be required as part of the review of the resubmission of BLA 761325 as a consequence of findings from a facilities inspection conducted for (b) (4) The other manufacturing and testing facilities were still deemed acceptable based on previous history. The inspection for Sanofi-Aventis Deutschland GmbH manufacturing facility (FEI 3003195501) for the current submission covered the insulin aspart Drug Substance manufactured in (b) (4) and insulin aspart and Soliqua DP manufactured (b) (4) (b) (4) in building (b) (4) The on-site inspection at Sanofi-Aventis Deutschland GmbH was conducted from January 8 to January 16, 2025. A 4 -item Form FDA 483 was issued to the firm on January 16, 2025 for the following observations:

(b) (4)

The initial field recommendation is withhold. Responses to 483 were reviewed as part of the compliance review and satisfactory responses were provided. The final recommendation is approval.

Microbiology Assessment

Dr. Reyes Candau-Chacon and Dr. Madushini Dharmasena reviewed the resubmission from the product quality perspective and sterility perspective and recommend Approval with the following post-marketing commitment: "To reassess the endotoxic limit of insulin aspart using results of 20 batches and to submit the results to the Agency once the information is available. The final report or an update will be submitted to the Agency by February 2026." See below for a summary of high level findings from the Product Quality Microbiology review; see also the Product Quality Microbiology review for full details. I concur with the recommendations from the perspective of microbiology.

Dr. Candau-Chacon and Dr. Dharmasena concluded that is controlled by the use of Adequate controls are in place to maintain product quality during With regard to the endotoxin test method (i.e., with regard to the deficiency which precluded approval on the first submission cycle), Dr. Candau-Chacon and Dr. Dharmasena concluded that after modifications to the endotoxin test method, the method was successfully validated and adopted as a and as a The Dr. Candau-Chacon and Dr. Dharmasena concluded that the submitted information addressed the microbiology deficiency that was the basis of the September 8, 2023, Complete Response.

4. Labeling

Review of proposed labeling for SAR341402 was conducted by the Division of Medication Error Prevention and Analysis 1 (DMEPA1), the Office of Prescription Drug Promotion (OPDP), and the patient labeling team in the Division of Medical Policy Programs (DMPP).

DMEPA1 reviewed the revised container labels and carton labeling. They concluded that the Applicant had implemented all previous recommendations.

OPDP reviewed the proposed Prescribing Information (PI), Patient Package Insert/Instructions for Use (PPI/IFU), and carton and container labeling and provided recommendations to finalize labeling. OPDP and DMPP also provided a combined review of the PPI/IFU and concluded that the PPI and IFU were acceptable with recommended changes.

The final agreed upon labeling removed all language related to

(b) (4)

(b) (4)

5. Recommendation

Approval of SAR341402 as a biosimilar to U.S.licensed NovoLog (insulin aspart).

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
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