CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761325Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date: February 10, 2025

1. Application/Product Information

BLA number	761325		
Submission Type	Resubmission		
Regulatory Pathway	351(k)		
Associated IND/BLA	IND 136342		
Review Designation	Standard		
Applicant	Sanofi-aventis U.S. LLC		
Indication	To improve glycemic control in adults and pediatric patients with diabetes mellitus		
Rx/OTC dispensed	Rx		
Drug Product Name	SAR341402 (Merilog/Merilog SoloStar)		
	insulin apart-szjj (proposed)		
	RPROT P01308 (INS_HUMAN) INSULIN [SAR341402]		
Drug Product Description	SAR341402 drug product is a sterile, clear, and colorless (b) (4) solution formulated in 1.72 mg metacresol, 1.50 mg phenol, 0.02 mg polysorbate 20, 6.80 mg sodium chloride, 0.04 mg zinc chloride, and Water for Injection, USP, at pH of 7.0-7.8. SAR341402 is proposed biosimilar to U.S.-licensed Novolog, a recombinant rapid-acting human insulin analog homologous to human insulin with the exception of a single substitution of the amino acid proline by aspartic acid at position B28.		
Dosage Form	Liquid		
Strength	100 Units/mL (U-100) in a 10 mL multiple-dose vial and 3 mL single-patient-use prefilled pen		
Route of Administration	Subcutaneous injection		
Primary Container Closure System	Vial and cartridge		
Device Information	Prefilled pen		
Co-packaged Product Information	None		
	Discipline	**Primary**	**Secondary**
	Drug substance	Davinna Ligons	Maria Gutierrez Lugo
	Comparative Analytical Assessment		

OPQ Review Team	Immunogenicity assays		
	Drug product		
	Facility	Reyes Candau-Chacon	Madushini Dharmasena
	Microbiology	Reyes Candau-Chacon	Madushini Dharmasena
	RBPM	Kelly Ballard	
	ATL	Jun Liu/Davinna Ligons	
OPQ Issued Consults	None		

2. Recommendation and Conclusion on Approvability
Recommendation: Approval with Postmarketing Commitment (PMC)

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of BLA 761325 for Merilog/ Merilog SoloStar manufactured by Sanofi-Aventis Deutschland GmbH, Germany (FEI 3003195501). 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 US-licensed NovoLog, notwithstanding minor differences in clinically inactive components. It is recommended that this product be approved for human use under conditions specified in the package insert.

3. CMC Information for Action Letter

a. Manufacturing Location:

- **Drug Substance:** Sanofi-Aventis Deutschland GmbH (FEI 3003195501)
- **Drug Product:** Sanofi-Aventis Deutschland GmbH (FEI 3003195501)

b. Fill size and dosage form:
100 Units/mL (U-100) in a 10 mL multiple-dose vial and 3 mL single-patient-use prefilled pen

c. Dating Period:

- **Drug Product:** 30 months at 2-8°C, protected from light.
- **Drug Substance:** (b) (4) months at (b) (4)
- **For packaged products:** Not packaged
- **Stability Option:** We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug product under 21 CFR 601.12.

d. Exempt from lot release: Merilog/ Merilog SoloStar is exempted from lot release per FR 95-29960.

e. Final Post-Marketing Commitment: 4488-1: To reassess the (b) (4) endotoxin limit of insulin aspart (b) (4) using results of 20 batches and to submit the results to the Agency once the information is available.

4. Basis for Recommendation

a. Summary:

Merilog/Merilog SoloStar, referred to as SAR341402, is a proposed biosimilar to U.S.-licensed NovoLog (insulin aspart). Insulin aspart is a rapid-acting analog of human insulin. SAR341402 is indicated to improve glycemic control in adults and children with diabetes mellitus as is approved for U.S.-licensed Novolog. SAR341402 has the same strength, dosage form, and route of administration as the 100 Units/mL U.S.-licensed Novolog in 10 mL vial and 3 mL prefilled pen. Potency of SAR341402 is controlled using assay insulin aspart (RP-HPLC).

The totality of the comparative analytical evidence supports that SAR341402 is highly similar to U.S.-licensed Novolog, notwithstanding minor differences in clinically inactive components. The Applicant adequately established a three-way scientific bridge between SAR341402, U.S.-licensed Novolog, and E.U.-approved NovoRapid to support the relevance of the data generated from studies using E.U.-approved NovoRapid as the comparator for the assessment of biosimilarity. The strength of the SAR341402 vial and prefilled pen is the same as that of U.S.-licensed NovoLog. Refer to Appendix for detailed summary on the comparative analytical assessment (CAA).

The drug substance (DS) (b) (4) consists of (b) (4) (b) (4) The DP vials are labeled,

packaged, and stored at 2 – 8°C. The DP cartridges are assembled into pens, followed by labeling and packaging, and storage at 2 – 8°C.

Overall, the DS process is under adequate microbial control. Microbial quality is controlled at critical step of the (b) (4) by the use of (b) (4) (b) (4) (b) (4). Adequate controls are in place to maintain microbiological product quality during maximum hold periods and throughout the (b) (4) (b) (4)

(b) (4)

Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for Sanofi-Aventis Deutschland GmbH (FEI 3003195501), proposed for insulin aspart DS manufacture. All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

The overall Merilog/ Merilog SoloStar control strategy incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, and release and stability of the DS and DP. The manufacturing processes and overall control strategies for Merilog/ Merilog SoloStar are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The (b) (4) endotoxin limit of insulin aspart (b) (4) is set at (b) (4) EU/mL, which is consistent with the DP endotoxin release specification, below the (b) (4) EU/mg specification described in the USP monograph, and below the USP safety threshold of (b) (4) EU/Kg. The applicant has committed to reassess this limit once sufficient manufacturing data are available. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. The BLA is

recommended for approval from product quality, facility, and microbiology and sterility assurance constituent perspectives.

b. Subdiscipline Recommendation:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate with PMCs/PMRs**
Immunogenicity Assay	**-**	**Adequate**
Facilities	**-**	**Adequate**
Microbiology	**-**	**Adequate**

c. Environmental Assessment (EA):
Categorical exclusion is claimed by the Applicant and deemed acceptable.

d. Potency Assessment for Labeling:
As an initial matter, we determined that no U.S. standard of potency has been prescribed for SAR341402 (i.e., there is no specific test method described in regulation for SAR341402 that establishes an official standard of potency). We next considered whether potency is a factor for SAR341402 within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if "potency is a factor" and "no U.S. standard of potency has been prescribed." We have determined that potency is not a factor for SAR341402 for purposes of § 610.61(r) because lot variability is not a concern for SAR341402 as SAR341402 manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

b. Drug Substance:

i. Protocols submitted and found adequate:
   1. Column resin lifetime validation protocol
   2. Stability protocol for the current master cell bank (MCB)
   3. Stability protocol for the current working cell bank (WCB)
   4. Qualification and stability protocol for new WCBs
   5. Qualification protocol for new insulin aspart primary reference material
   6. Qualification protocol for new insulin aspart working reference material
   7. Stability protocol for the insulin aspart primary reference material

8. Stability protocol for the insulin aspart working reference material
9. Qualification protocol for new pre-pro insulin aspart primary reference material
10. Qualification protocol for new pre-pro insulin aspart working reference material
11. Stability protocol for the pre-pro insulin aspart primary and working reference material
12. Post-approval stability protocol and stability commitment

ii. Residual risk: None
iii. Future inspection points to consider: None

c. Drug Product:

i. Protocols submitted and found adequate:
   1. Stability protocol for extension of shelf-life to 36 months
   2. Post-approval stability protocol and stability commitment
ii. Residual risk: Refer to PMC comment
iii. Future inspection points to consider: None

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

Appendix. Comparative Analytical Assessment Summary

A. Analytical Assessment Overview and Conclusions

The CAA between SAR341402, U.S.-licensed NovoLog (hereafter referred to as US-NovoLog), and E.U.-approved NovoRapid (hereafter referred to as EU-NovoRapid) compared a total of 27 SAR341402 batches (12 vial and 15 cartridge batches), 31 US-NovoLog batches (16 vial and 15 cartridge batches), and 33 EU-NovoRapid batches (11 vial and 22 cartridge batches).

Although not all 27 SAR341402 DP batches used in the CAA were derived from independent DS batches, only independent DP batches were used in the statistical analyses. Their derivation is as follows:

- 22 DP batches (9 vial and 13 cartridge batches) representative of the commercial process (Processes (b) (4); (b) (4) is the commercial process)
    - 5 DP batches (2 vial and 3 cartridge batches) were PPQ batches, manufactured using DS PPQ batches
    - 3 DP cartridge batches were used in the comparative clinical study
- 4 DP batches (3 vial and 1 cartridge batches) manufactured using a small-scale process representative of the commercial process and DS representative of the comparative clinical (PK/PD) study and commercial DS
- 1 DP cartridge batch manufactured using a small-scale process representative of the commercial process and DS manufactured using a small-scale process representative of the commercial process

The small-scale DS and DP batches were shown to be comparable to the commercial DS and DP batches. The proposed presentations of SAR341402 include a 10 mL vial and a prefilled pen assembled with a 3 mL cartridge. The cartridge is the primary container closure system of the prefilled pen presentation and the assembly process of the prefilled pen was demonstrated to have no impact of the quality attributes of SAR341402. Therefore, it is acceptable to include SAR341402 cartridge batches in the CAA between SAR341402, US-NovoLog, and EU-NovoRapid.

The 31 US-NovoLog batches included 16 vial and 15 cartridge (partially assembled in prefilled pen device) batches with expiry dates from June 2014 to July 2023, which spans the shelf-life of US-NovoLog. The EU-NovoRapid batches included 11 vial and 22 cartridge batches with expiry dates from October 2012 to May 2023, which spans the shelf-life of EU-NovoRapid. One US-NovoLog cartridge batch and 2 EU-NovoRapid cartridge batches were used in the comparative clinical study. The batches were adequate to capture potential batch-to-batch variability in the US-Novolog and EU-NovoRapid products over time.

The CAA was comprised of extensive comparative physiochemical and functional assessment of the quality attributes of SAR341402, US-NovoLog, and EU-NovoRapid. The Applicant used an acceptable risk-based approach for supporting the statistical evaluation of analytical results. The critical quality attributes (CQAs) and attributes linked to CQAs that were tested using quantitative assays were evaluated using quality ranges obtained from US-NovoLog or EU-NovoRapid to account for manufacturing variability and assay variability. In addition, the most sensitive assays for detecting product differences were selected for statistical evaluation using quality ranges. Attributes tested using quantitative assays not amenable to statistical analysis and qualitative assays were evaluated using visual comparisons. The data evaluation methods used were consistent with FDA recommendations during product development. The OBP assessor performed additional independent analyses using the quality range approach for high risk attributes. Results from method validation or qualification studies support the suitability of the methods used in the CAA. The Applicant also provided a comparison of stability under in-use conditions, long-term and accelerated (temperature) conditions, and forced degradation conditions of oxidative stress, hydrolytic (pH) stress, high temperature stress, and light stress (photostability).

Based on the OBP assessment, the SAR341402 and US-NovoLog data supports a demonstration that SAR341402 is highly similar to US-NovoLog, notwithstanding minor differences in clinically inactive components. SAR341402 has the same strength, dosage form, and route of administration as US-NovoLog. The Applicant used a comprehensive array of analytical methods that were suitable to evaluate CQAs of SAR341402 and US-NovoLog to support the demonstration that the products are highly similar. Numbers of batches tested were appropriate to allow for a meaningful evaluation of the results of the comparative analytical studies. While differences were observed in a limited number of attributes, these differences do not preclude a demonstration that SAR341402 is highly similar to US-NovoLog.

In addition, three-way pairwise analytical comparisons of SAR341402, US-NovoLog, and EU-NovoRapid were used to establish the analytical component of the three-way scientific bridge between SAR341402, US-NovoLog, and EU-NovoRapid to support the relevance of the data generated from studies using EU-NovoLog as the comparator for the assessment of biosimilarity. Based on the OBP assessment of the data, the Applicant established the analytical portion of the scientific bridge between SAR341402, US-NovoLog, and EU-NovoRapid, using the same methods and statistical approaches as those to evaluate the similarity between SAR341402 and US-NovoLog. The analytical portion of the scientific bridge was established to support the relevance of the data generated from studies using EU-NovoRapid as the comparator for the assessment of biosimilarity.

B. Results of Comparative Analytical Assessment

The results of these analytical comparisons support a demonstration that SAR341402 is highly similar to US-NovoLog and the establishment of the analytical component of the scientific bridge between SAR341402, US-NovoLog, and EU-NovoRapid and the results are summarized in Table A below.

Table A. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physico-chemical/Functional Characteristics	**Quality Attribute Assessed**	**Supports a Demonstration of Highly Similar**	**Supports the Analytical Component of the Scientific Bridge**
Primary structure	Intact mass (MALDI MS)	Yes	Yes
	Reduced mass (MALDI MS)	Yes	Yes
	Disulfide bonds (MALDI MS peptide map)	Yes	Yes
	N-terminal Edman degradation	Yes	Yes
Secondary structure	FT-IR	Yes	Yes
	Far UV CD	Yes	Yes
Tertiary structure	Near UV CD	Yes	Yes
	NMR spectrometry	Yes	Yes
Higher order structure	DLS	Yes	Yes
	AUC	Yes	Yes
Biological activity	Human insulin receptor binding (cell-based iLITE reporter assay)	Yes	Yes
	Insulin receptor A (IR-A) autophosphorylation (cell-based In-Cell Western assay)	Yes	Yes
	Insulin receptor B (IR-B) autophosphorylation (cell-based In-Cell Western assay)	Yes	Yes
	IR-A binding affinity (cell-based competitive	Yes	Yes

	radioligand binding assay)		
	IR-B binding affinity (cell-based competitive radioligand binding assay)	Yes	Yes
	Binding kinetics to IR-A (SPR)	Yes	Yes
	Binding kinetics to IR-B (SPR)	Yes	Yes
	Stimulation of glucose uptake (cell-based metabolic assay)	Yes	Yes
	Attenuation of G6PC (gluconeogenesis gene) expression (cell-based, qPCR metabolic assay)	Yes	Yes
	Inhibition of lipolysis (cell-based metabolic assay)	Yes	Yes
Mitogenicity	IGF-1 receptor autophosphorylation (cell-based In-Cell Western assay)	Yes	Yes
	Binding kinetics to IGF-1R (SPR)	Yes	Yes
	Stimulation of [14C]-thymidine incorporation (cell-based assay)	Yes	Yes
Content (assay insulin aspart)	RP-HPLC	Yes	Yes
Product-related substances/impurities	(b) (4)	Yes	Yes
		Yes	Yes

	(b) (4)	Yes	Yes
		Yes	Yes
		Yes	Yes
	Any other unspecified, unidentified impurity (RP-HPLC)	Yes	Yes
	Total of other impurities (RP-HPLC)	Yes	Yes
Isoelectric point (pI)	cIEF	Yes	Yes
High molecular weight proteins (HMWP)	SEC	Yes	Yes
Content of zinc	AAS	Yes	Yes
Impurity profile	HPLC-MS	Yes	Yes

C. Analytical Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

The clinical development of SAR341402 included two clinical studies that compared SAR341402 to US-Novolog and EU-NovoRapid:

- Study PDY12695: a single-center (Germany), randomized, double-blind, controlled, single-dose, 3-treatment, 3-period, 6-sequence, crossover euglycemic clamp study in participants with T1DM that compared the PK and PD profiles of SAR341402 with US-NovoLog and EU-NovoRapid when given subcutaneously

- Study EFC15081: a multicenter, randomized, open-label parallel group study in participants with T1DM and T2DM to further demonstrate the efficacy of SAR341402 in comparison to US-NovoLog and EU-NovoRapid and to determine the immunogenicity and safety of SAR341402, US-NovoLog, and EU-NovoRapid when given subcutaneously in combination with Lantus (insulin glargine, 100 U/mL). The study was comprised of a main 6-month period and 6-month safety extension period. Depending on the geographical location of the study sites, US-NovoLog or EU-NovoRapid was provided

To support the relevance of the comparative clinical data (Study EFC15081) generated using EU-NovoRapid as a comparator product for the assessment of biosimilarity, the

Applicant performed three-way, pairwise comparative analytical assessments using a comprehensive array of analytical methods and a three-way pairwise PK similarity study (PDY12695). To support the establishment of the analytical component of the scientific bridge, the Applicant included comparison of SAR341402 to US-NovoLog, SAR341402 to EU-NovoRapid, and US-NovoLog to EU-NovoRapid. The same analytical methods used for supporting a demonstration that SAR341402 is highly similar to US-NovoLog were used for the pairwise comparisons with EU-NovoRapid. The differences observed in the comparative analytical studies do not preclude the establishment of the analytical component of the scientific bridge. See Section D below. The results support the establishment of the analytical component of the scientific bridge.

D. Assessment of Comparative Analytical Study Results

Comparative analytical acceptance criteria were met for all attributes except the following:

(b) (4)

Total of other impurities (RP-HPLC)

Four out of 11 SAR341402 cartridge batches have marginally lower total of other impurities levels (b) (4)%) than the quality range of US-NovoLog cartridge batches (b) (4)%). In general, lower total of other impurities levels suggest comparable or slightly improved purity of SAR341402 relative to US-NovoLog. In addition, levels of total other impurities levels are controlled at SAR341402 drug substance and drug product release and on stability by the RP-HPLC method. The total of other impurities levels are low and the observed difference is not expected to cause detectable difference in biological activity based on the results of the functional assays or impact the safety of SAR341402. Therefore, the observed difference in total of other impurities levels does not preclude a demonstration that SAR341402 is highly similar to US-NovoLog.

Impurity profile (HPLC-MS)

Although all SAR341402 batches (7 vial and 7 cartridge batches) had similar impurity profiles compared to US-NovoLog and EU-NovoRapid batches, small differences in low abundance product-related impurities were observed in the heatmaps and chromatograms between the SAR341402 batches compared to the US-NovoLog and EU-NovoRapid batches. All SAR341402 batches had lower levels of (b) (4) (b) (4) (b) (4) (b) (4) compared to the US-NovoLog and EU-NovoRapid. SAR341402 batches did not have (b) (4) and (b) (4) (b) (4) resulting from the US-NovoLog and EU-NovoRapid yeast expression system, as indicated in the USPI for US-Novolog[1]) and (b) (4) which were detected in US-NovoLog and EU-NovoRapid batches. In addition, SAR341402 batches had (b) (4) (b) (4) (a product-related impurity resulting from the SAR341402 process), which was not detected in US-NovoLog and EU-NovoRapid batches. Some of the small differences could be attributed to the age of the SAR341402, US-NovoLog, and EU-NovoRapid batches. In general, these impurities were low (trace levels) and the observed differences are not expected to cause detectable difference in biological activity based on the results of the functional assays or impact the safety of SAR341402. Therefore, the observed differences in impurity profile do not preclude a demonstration that SAR341402 is highly similar to US-NovoLog or the establishment of the analytical component of the scientific bridge.

[1] For the most recent version of the USPI, check Drugs@FDA FDA-Approved Drugs https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

E. Same Strength

SAR341402 has the same dosage form and route of administration as US-NovoLog. The Applicant is seeking approval of 100 Units/mL SAR341402 in a 10 mL vial and 100 Units/mL SAR341402 in a 3 mL prefilled pen. US-NovoLog is available at these strengths: 100 Units/mL in 10 mL vial and 3 mL prefilled pen. Comparative concentration (Units/mL) was assessed as part of the CAA. The extractable volume and fill weight data were also assessed in the context of manufacturing control. Based on the comparative concentration data and manufacturing data, the 100 Units/mL SAR341402 in 10 mL vial and 3 mL prefilled pen have the same total content of drug substance in units in a container and the same concentration of drug substance in units per unit volume as the corresponding presentations of US-NovoLog. The strength of the SAR341402 vial and prefilled pen is the same as that of US-NovoLog.

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/

DAVINNA L LIGONS
02/10/2025 03:54:01 PM

MARIA T GUTIERREZ LUGO
02/10/2025 04:29:06 PM

Consult MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration

[CDER ICCR# 00871590 – Non-Clinical Consult]

DATE:	May 8, 2023
RECEIVED:	September 20, 2022
TO:	Michael Oyewole, Ph.D., CDER/OND/ORO/DROCHEN
FROM:	Jessica D. Flynn, Ph.D., CDRH/OIR/DCTD/DDDB
THROUGH:	Joshua Balsam, Ph.D., Diabetes Branch Chief, CDRH/OIR/DCTD/DDDB
SUBJECT:	CDER consult request for BLA761325
CDRH ICCR Tracking Number:	ICCR# 00871590 (in Salesforce)
Consult Scope	Sanofi has submitted a Biologics License Application (BLA) for SAR341402, a proposed biosimilar product to NovoLog (100 units/mL, BLA 020986, Novo Nordisk). SAR341402 is proposed to have the same indications (SAR341402 is indicated to improve glycemic control in adults and children with diabetes mellitus), dosage form, route of administration, and dosing regimen as the reference product Novolog. (b) (4) (b) (4) NovoLog, including subcutaneous injection, (b) (4) (b) (4) Please review the associated data regarding use of the product for (b) (4) and provide a recommendation for approval.
Drug Sponsor	Sanofi-aventis U.S. LLC
Drug Name	SAR341402 (insulin aspart)

I. Review Team

The review team for this ICCR is:
Jessica Flynn, PhD; Scientific Reviewer (CDRH/OHT7)
Joshua Balsam, PhD; DDDB Branch Chief (CDRH/OHT7)

II. Background

This memo pertains to the (b) (4) indication initially submitted by the applicant for BLA 761325 for insulin product SAR341402 from Sanofi.

III. Consult Conclusion

(b) (4)

IV. RECOMMENDATION

No final recommendation needed from CDHR/OHT7.

Concurrence History Page

Digital Signature Concurrence Table	
Reviewer Sign-Off	
Branch Chief Sign-Off	
Division Sign-Off	

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/

MICHAEL O OYEWOLE
05/19/2023 05:15:38 PM
Checking in the electronic archive on behalf of Jessica Flynn, Ph.D.

BLA Executive Summary
Assessment Date: September 7, 2023

1. Application/Product Information

BLA number	761325		
Submission Type	Original Submission		
Regulatory Pathway	351(k)		
Associated IND/BLA	IND 136342		
Review Designation	Standard		
Applicant	Sanofi-aventis U.S. LLC		
Indication	To improve glycemic control in adults and pediatric patients with diabetes mellitus		
Rx/OTC dispensed	Rx		
Drug Product Name	SAR341402		
	insulin apart-szjj (proposed)		
	RPROT P01308 (INS_HUMAN) INSULIN [SAR341402]		
Drug Product Description	SAR341402 drug product is a sterile, clear, and colorless (b) (4) solution formulated in 1.72 mg metacresol, 1.50 mg phenol, 0.02 mg polysorbate 20, 6.80 mg sodium chloride, 0.04 mg zinc chloride, and Water for Injection, USP, at pH of 7.0-7.8. SAR341402 is a recombinant rapid-acting human insulin analog homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28.		
Dosage Form	Liquid		
Strength	100 Units/mL (U-100) in a 10 mL multiple-dose vial and 3 mL single-patient-use prefilled pen		
Route of Administration	Subcutaneous injection		
Primary Container Closure System	Vial and cartridge		
Device Information	Prefilled pen		
Co-packaged Product Information	None		
	Discipline	Primary	Secondary
	Drug substance	Davinna Ligons	Massod Rahimi
	Comparative Analytical Assessment		

OPQ Review Team	Immunogenicity assays		
	Drug product	Odile Engel	Nailing Zhang
	Facility	Michael Shanks	Madushini Dharmasena
	Microbiology	Candace Gomez-Broughton	
	RBPM	Kelly Ballard	
	ATL	Massod Rahimi	
OPQ Issued Consults	None		

2. Recommendation and Conclusion on Approvability
Recommendation: Complete Response

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761325 for SAR341402 manufactured by Sanofi-aventis U.S. LLC. The data submitted in this application are not sufficient to support a conclusion that the manufacture of SAR341402 is well-controlled and will lead to a product that is pure and potent. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Sanofi-aventis U.S. LLC to outline the deficiencies noted below and the information and data that will be required to support approval.

3. Complete Response Comments and Additional Comments:

1. 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 IR dated August 31st, 2023, you indicated that rabbit pyrogen test 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 the SAR341402 drug product. Provide an endotoxin test method for SAR341402 drug product release that can reliably detect endotoxin over process-relevant time and temperature.

Additional Comments:

Microbiology

1. You have not clearly identified endotoxin removal steps in the manufacturing process description (3.2.S.2.2).Clearly identify the endotoxin removal steps supported by endotoxin removal 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 (b) (4) studies is incomplete. It is unclear if the (b) (4) (b) (4) used during (b) (4) support the proposed (b) (4) intended for routine manufacturing. Please provide the (b) (4) used during (b) (4) and provide a comparison to routine (b) (4)
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.

Product Quality

8. The reference material system for SAR341402 consists of the secondary reference material (b) (4) To support the product lifecycle, Sanofi 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.

4. Basis for Recommendation

a. Summary:

Merilog/Merilog SoloStar, referred to as SAR341402, is a proposed biosimilar to U.S.-licensed NovoLog. Insulin aspart is a rapid-acting analog of human insulin. SAR341402 is indicated to improve glycemic control in adults and children with diabetes mellitus as is approved for U.S.-licensed Novolog. SAR341402 has the same strength, dosage form, and route of administration as the 100 Units/mL U.S.-licensed Novolog in 10 mL vial and 3 mL prefilled pen. Potency of SAR341402 is controlled using assay insulin aspart (RP-HPLC).

The totality of the comparative analytical evidence supports that SAR341402 is highly similar to U.S.-licensed Novolog, notwithstanding minor differences in clinically inactive components. The Applicant adequately established a three-way scientific bridge between SAR341402, U.S.-licensed Novolog, and E.U.-approved NovoRapid to support the relevance of the data generated from studies using E.U.-approved NovoRapid as the comparator for the assessment of biosimilarity. The strength of the SAR341402 vial and prefilled pen is the same as that of U.S.-licensed NovoLog. Refer to Appendix for detailed summary on the comparative analytical assessment (CAA).

The drug substance (DS) (b) (4) consists of (b) (4) (b) (4) (b) (4) The DP vials are labeled, packaged, and stored at 2 – 8°C. The DP cartridges are assembled into pens, followed by labeling and packaging, and storage at 2 – 8°C.

The overall control strategy incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, and release and stability of the DS and DP. However, the (b) (4) strategy is not adequate. The (b) (4) and overall control strategies for SAR341402 as re not appropriately established to ensure consistency and quality of the final product; therefore, lot variability is a concern. However, the (b) (4) is inadequate because (b) (4) steps were not identified or validated for the DS process and the (b) (4) for DP is not adequately justified. It is unclear whether the level of (b) (4) meets the minimum USP

requirement for insulin products. A fully validated endotoxin release test for DP was not provided.

The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for Sanofi-Aventis Deutschland GmbH (FEI 3003195501), proposed for DS and DP manufacture. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. Based on the assessment of manufacturing site records under the Agency's authority under section 704(a)(4) of the FD&C Act, it was concluded that the Sanofi-Aventis Deutschland GmbH DS and DP manufacturing facility was acceptable to support approval of BLA 761325 and an on-site inspection was not necessary. The BLA is recommended for approval from product quality, facility, and microbiology and sterility assurance constituent perspectives.

Consistent with current expectations for biological products manufactured in cell substrates under a BLA, a two-tiered in-house reference material system should be established. The two-tiered in-house reference material system should be prepared from lot(s) representative of production and clinical materials and be appropriately characterized. This strategy ensures direct control by the manufacturer over the manufacture and qualification and would allow for better control of reference materials over time and prevent drift. The absence of a two-tiered in-house reference standard system is not an approvability issue because there is an in-house working reference material that was adequately qualified for use during release and stability testing.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate with PMCs/PMRs
Drug Product	-	Adequate
Immunogenicity Assay	-	Adequate
Facilities	-	Adequate
Microbiology	-	Inadequate

c. Environmental Assessment (EA):
Categorical exclusion is claimed by the Applicant and deemed acceptable.

d. Potency Assessment for Labeling:
As an initial matter, we determined that no U.S. standard of potency has been prescribed for SAR341402 (i.e., there is no specific test method

described in regulation for SAR341402 that establishes an official standard of potency). We next considered whether potency is a factor for SAR341402 within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if "potency is a factor" and "no U.S. standard of potency has been prescribed." We have determined that potency is not a factor for SAR341402 for purposes of § 610.61(r) because lot variability is not a concern for SAR341402 as SAR341402 manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

b. Drug Substance:

i. Protocols submitted and found adequate but not approved during this cycle due to CR recommendation from OPMA:
   1. Column resin lifetime validation protocol
   2. Stability protocol for the current master cell bank (MCB)
   3. Stability protocol for the current working cell bank (WCB)
   4. Qualification and stability protocol for new WCBs
   5. Stability protocol for the insulin aspart working reference standard
   6. Qualification protocol for new pre-pro insulin aspart primary reference standard
   7. Qualification protocol for new pre-pro insulin aspart working reference standard
   8. Stability protocol for the pre-pro insulin aspart primary and working reference standards
   9. Post-approval stability protocol and stability commitment

ii. Residual risk: The absence of a two-tiered in-house reference standard system is not an approvability issue because there is an in-house working reference material that was adequately qualified for use during release and stability testing

iii. Future inspection points to consider: None

c. Drug Product:

i. Protocols submitted and found adequate but not approved during this cycle due to CR recommendation from OPMA:
   1. Stability protocol for (b) (4)
   2. Post-approval stability protocol and stability commitment

ii. Residual risk: Refer to CR comment

iii. Future inspection points to consider: None

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

Appendix. Comparative Analytical Assessment Summary

A. Analytical Assessment Overview and Conclusions

The CAA between SAR341402, U.S.-licensed NovoLog (hereafter referred to as US-NovoLog), and E.U.-approved NovoRapid (hereafter referred to as EU-NovoRapid) compared a total of 27 SAR341402 batches (12 vial and 15 cartridge batches), 31 US-NovoLog batches (16 vial and 15 cartridge batches), and 33 EU-NovoRapid batches (11 vial and 22 cartridge batches).

Although not all 27 SAR341402 DP batches used in the CAA were derived from independent DS batches, only independent DP batches were used in the statistical analyses. Their derivation is as follows:

- 22 DP batches (9 vi (b) (4) dge batches) representative of the commercial process (Processes is the commercial process)
    - 5 DP batches (2 vial and 3 cartridge batches) were PPQ batches, manufactured using DS PPQ batches
    - 3 DP cartridge batches were used in the comparative clinical study
- 4 DP batches (3 vial and 1 cartridge batches) manufactured using a small-scale process representative of the commercial process and DS representative of the comparative clinical (PK/PD) study and commercial DS
- 1 DP cartridge batch manufactured using a small-scale process representative of the commercial process and DS manufactured using a small-scale process representative of the commercial process

The small-scale DS and DP batches were shown to be comparable to the commercial DS and DP batches. The proposed presentations of SAR341402 include a 10 mL vial and a prefilled pen assembled with a 3 mL cartridge. The cartridge is the primary container closure system of the prefilled pen presentation and the assembly process of the prefilled pen was demonstrated to have no impact of the quality attributes of SAR341402. Therefore, it is acceptable to include SAR341402 cartridge batches in the CAA between SAR341402, US-NovoLog, and EU-NovoRapid.

The 31 US-NovoLog batches included 16 vial and 15 cartridge (partially assembled in prefilled pen device) batches with expiry dates from June 2014 to July 2023, which spans the shelf-life of US-NovoLog. The EU-NovoRapid batches included 11 vial and 22 cartridge batches with expiry dates from October 2012 to May 2023, which spans the shelf-life of EU-NovoRapid. One US-NovoLog cartridge batch and 2 EU-NovoRapid cartridge batches were used in the comparative clinical study. The batches were adequate to capture potential batch-to-batch variability in the US-Novolog and EU-NovoRapid products over time.

The CAA was comprised of extensive comparative physiochemical and functional assessment of the quality attributes of SAR341402, US-NovoLog, and EU-NovoRapid. The Applicant used an acceptable risk-based approach for supporting the statistical evaluation of analytical results. The critical quality attributes (CQAs) and attributes linked to CQAs that were tested using quantitative assays were evaluated using quality ranges obtained from US-NovoLog or EU-NovoRapid to account for manufacturing variability and assay variability. In addition, the most sensitive assays for detecting product differences were selected for statistical evaluation using quality ranges. Attributes tested using quantitative assays not amenable to statistical analysis and qualitative assays were evaluated using visual comparisons. The data evaluation methods used were consistent with FDA recommendations during product development. The OBP assessor performed additional independent analyses using the quality range approach for high risk attributes. Results from method validation or qualification studies support the suitability of the methods used in the CAA. The Applicant also provided a comparison of stability under in-use conditions, long-term and accelerated (temperature) conditions, and forced degradation conditions of oxidative stress, hydrolytic (pH) stress, high temperature stress, and light stress (photostability).

Based on the OBP assessment, the SAR341402 and US-NovoLog data supports a demonstration that SAR341402 is highly similar to US-NovoLog, notwithstanding minor differences in clinically inactive components. SAR341402 has the same strength, dosage form, and route of administration as US-NovoLog. The Applicant used a comprehensive array of analytical methods that were suitable to evaluate CQAs of SAR341402 and US-NovoLog to support the demonstration that the products are highly similar. Numbers of batches tested were appropriate to allow for a meaningful evaluation of the results of the comparative analytical studies. While differences were observed in a limited number of attributes, these differences do not preclude a demonstration that SAR341402 is highly similar to US-NovoLog.

In addition, three-way pairwise analytical comparisons of SAR341402, US-NovoLog, and EU-NovoRapid were used to establish the analytical component of the three-way scientific bridge between SAR341402, US-NovoLog, and EU-NovoRapid to support the relevance of the data generated from studies using EU-NovoLog as the comparator for the assessment of biosimilarity. Based on the OBP assessment of the data, the Applicant established the analytical portion of the scientific bridge between SAR341402, US-NovoLog, and EU-NovoRapid, using the same methods and statistical approaches as those to evaluate the similarity between SAR341402 and US-NovoLog. The analytical portion of the scientific bridge was established to support the relevance of the data generated from studies using EU-NovoRapid as the comparator for the assessment of biosimilarity.

B. Results of Comparative Analytical Assessment

The results of these analytical comparisons support a demonstration that SAR341402 is highly similar to US-NovoLog and the establishment of the analytical component of the scientific bridge between SAR341402, US-NovoLog, and EU-NovoRapid and the results are summarized in Table A below.

Table A. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge
Primary structure	Intact mass (MALDI MS)	Yes	Yes
	Reduced mass (MALDI MS)	Yes	Yes
	Disulfide bonds (MALDI MS peptide map)	Yes	Yes
	N-terminal Edman degradation	Yes	Yes
Secondary structure	FT-IR	Yes	Yes
	Far UV CD	Yes	Yes
Tertiary structure	Near UV CD	Yes	Yes
	NMR spectrometry	Yes	Yes
Higher order structure	DLS	Yes	Yes
	AUC	Yes	Yes
Biological activity	Human insulin receptor binding (cell-based iLITE reporter assay)	Yes	Yes
	Insulin receptor A (IR-A) autophosphorylation (cell-based In-Cell Western assay)	Yes	Yes
	Insulin receptor B (IR-B) autophosphorylation (cell-based In-Cell Western assay)	Yes	Yes
	IR-A binding affinity (cell-based competitive	Yes	Yes

	radioligand binding assay)		
	IR-B binding affinity (cell-based competitive radioligand binding assay)	Yes	Yes
	Binding kinetics to IR-A (SPR)	Yes	Yes
	Binding kinetics to IR-B (SPR)	Yes	Yes
	Stimulation of glucose uptake (cell-based metabolic assay)	Yes	Yes
	Attenuation of G6PC (gluconeogenesis gene) expression (cell-based, qPCR metabolic assay)	Yes	Yes
	Inhibition of lipolysis (cell-based metabolic assay)	Yes	Yes
Mitogenicity	IGF-1 receptor autophosphorylation (cell-based In-Cell Western assay)	Yes	Yes
	Binding kinetics to IGF-1R (SPR)	Yes	Yes
	Stimulation of [14C]-thymidine incorporation (cell-based assay)	Yes	Yes
Content (assay insulin aspart)	RP-HPLC	Yes	Yes
Product-related substances/impurities	(b) (4)	Yes	Yes
		Yes	Yes

	(b) (4)	Yes	Yes
		Yes	Yes
		Yes	Yes
	Any other unspecified, unidentified impurity (RP-HPLC)	Yes	Yes
	Total of other impurities (RP-HPLC)	Yes	Yes
Isoelectric point (pI)	cIEF	Yes	Yes
High molecular weight proteins (HMWP)	SEC	Yes	Yes
Content of zinc	AAS	Yes	Yes
Impurity profile	HPLC-MS	Yes	Yes

C. Analytical Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

The clinical development of SAR341402 included two clinical studies that compared SAR341402 to US-Novolog and EU-NovoRapid:

- Study PDY12695: a single-center (Germany), randomized, double-blind, controlled, single-dose, 3-treatment, 3-period, 6-sequence, crossover euglycemic clamp study in participants with T1DM that compared the PK and PD profiles of SAR341402 with US-NovoLog and EU-NovoRapid when given subcutaneously

- Study EFC15081: a multicenter, randomized, open-label parallel group study in participants with T1DM and T2DM to further demonstrate the efficacy of SAR341402 in comparison to US-NovoLog and EU-NovoRapid and to determine the immunogenicity and safety of SAR341402, US-NovoLog, and EU-NovoRapid when given subcutaneously in combination with Lantus (insulin glargine, 100 U/mL). The study was comprised of a main 6-month period and 6-month safety extension period. Depending on the geographical location of the study sites, US-NovoLog or EU-NovoRapid was provided

To support the relevance of the comparative clinical data (Study EFC15081) generated using EU-NovoRapid as a comparator product for the assessment of biosimilarity, the

Applicant performed three-way, pairwise comparative analytical assessments using a comprehensive array of analytical methods and a three-way pairwise PK similarity study (PDY12695). To support the establishment of the analytical component of the scientific bridge, the Applicant included comparison of SAR341402 to US-NovoLog, SAR341402 to EU-NovoRapid, and US-NovoLog to EU-NovoRapid. The same analytical methods used for supporting a demonstration that SAR341402 is highly similar to US-NovoLog were used for the pairwise comparisons with EU-NovoRapid. The differences observed in the comparative analytical studies do not preclude the establishment of the analytical component of the scientific bridge. See Section D below. The results support the establishment of the analytical component of the scientific bridge.

D. Assessment of Comparative Analytical Study Results

Comparative analytical acceptance criteria were met for all attributes except the following:

(b) (4)

Total of other impurities (RP-HPLC)

Four out of 11 SAR341402 cartridge batches have marginally lower total of other impurities levels (b) (4)%) than the quality range of US-NovoLog cartridge batches ((b) (4)%). In general, lower total of other impurities levels suggest comparable or slightly improved purity of SAR341402 relative to US-NovoLog. In addition, levels of total other impurities levels are controlled at SAR341402 drug substance and drug product release and on stability by the RP-HPLC method. The total of other impurities levels are low and the observed difference is not expected to cause detectable difference in biological activity based on the results of the functional assays or impact the safety of SAR341402. Therefore, the observed difference in total of other impurities levels does not preclude a demonstration that SAR341402 is highly similar to US-NovoLog.

Impurity profile (HPLC-MS)

Although all SAR341402 batches (7 vial and 7 cartridge batches) had similar impurity profiles compared to US-NovoLog and EU-NovoRapid batches, small differences in low abundance product-related impurities were observed in the heatmaps and chromatograms between the SAR341402 batches compared to the US-NovoLog and EU-NovoRapid batches. All SAR341402 batches had lower levels of (b) (4) (b) (4) (b) (4) (b) (4) compared to the US-NovoLog and EU-NovoRapid. SAR341402 batches did not have (b) (4) (b) (4) (b) (4) (b) (4) In addition, SAR341402 batches had (b) (4) (b) (4) (a product-related impurity resulting from the SAR341402 process), which was not detected in US-NovoLog and EU-NovoRapid batches. Some of the small differences could be attributed to the age of the SAR341402, US-NovoLog, and EU-NovoRapid batches. In general, these impurities were low (trace levels) and the observed differences are not expected to cause detectable difference in biological activity based on the results of the functional assays or impact the safety of SAR341402. Therefore, the observed differences in impurity profile do not preclude a demonstration that SAR341402 is highly similar to US-NovoLog or the establishment of the analytical component of the scientific bridge.

[1] For the most recent version of the USPI, check Drugs@FDA FDA-Approved Drugs https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

E. Same Strength

SAR341402 has the same dosage form and route of administration as US-NovoLog. The Applicant is seeking approval of 100 Units/mL SAR341402 in a 10 mL vial and 100 Units/mL SAR341402 in a 3 mL prefilled pen. US-NovoLog is available at these strengths: 100 Units/mL in 10 mL vial and 3 mL prefilled pen. Comparative concentration (Units/mL) was assessed as part of the CAA. The extractable volume and fill weight data were also assessed in the context of manufacturing control. Based on the comparative concentration data and manufacturing data, the 100 Units/mL SAR341402 in 10 mL vial and 3 mL prefilled pen have the same total content of drug substance in units in a container and the same concentration of drug substance in units per unit volume as the corresponding presentations of US-NovoLog. The strength of the SAR341402 vial and prefilled pen is the same as that of US-NovoLog.

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/s/

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