CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761325Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 24, 2025
To:	Michael Oyewole, PharmD Regulatory Project Manager **Division of Diabetes, Lipid Disorders, and Obesity (DDLO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Tierra Butler, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (nonproprietary name):	MERILOG (insulin aspart-szjj)[1]
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761325
Applicant:	sanofi-aventis U.S. LLC

[1] MERILOG has been developed as a proposed biosimilar to NOVOLOG (insulin aspart), BLA 020986. The proposed nonproprietary name "insulin aspart-szjj" was found to be conditionally acceptable for this BLA on May 10, 2023. The proposed proprietary name Merilog was found to be conditionally acceptable for this BLA on October 25, 2024.

1 INTRODUCTION

On August 16, 2024, sanofi-aventis U.S. LLC, submitted for the Agency's review a *Resubmission to a Complete Response (CR) Letter* to the initial 351(k) Biologics License Application (BLA) 761325 for MERILOG (insulin aspart-szjj) injection, for subcutaneous use. MERILOG (insulin aspart-szjj) is a proposed biosimilar to NOVOLOG (insulin aspart). The proposed indication for MERILOG (insulin aspart-szjj) is to improve glycemic control in adults and pediatric patients with diabetes mellitus.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) on September 13, 2024 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for MERILOG (insulin aspart-szjj) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft MERILOG (insulin aspart-szjj) injection, for subcutaneous use PPI and IFU received on August 16, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 16, 2025.
- Draft MERILOG (insulin aspart-szjj) injection, for subcutaneous use Prescribing Information (PI) received on April 16, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 16, 2025.
- Approved NOVOLOG (insulin aspart) comparator labeling dated February 28, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted PPI and IFU documents using the Arial font, size 10 and 11 respectively.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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LASHAWN M GRIFFITHS
01/24/2025 09:16:12 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 28, 2025

To: Michael Oyewole, Regulatory Project Manager, Division of Cardiology, Hematology, Endocrinology, and Nephrology (CHEN)

Dolly Misra, Clinical Reviewer, Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Melinda Wilson, Associate Director for Labeling, DDLO

From: Tierra Butler, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sapna Shah, Team Leader, OPDP

Subject: OPDP Labeling Comments for Merilog (insulin aspart-szjj) injection, for subcutaneous use

BLA: 761325

Background:
In response to DDLO's consult request dated September 13, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI) /Instructions for Use (IFU), and carton and container labeling for the original BLA submission for Merilog (insulin aspart-szjj) injection, for subcutaneous use.

PI/PPI/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on January 16, 2025, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI/IFU, and comments were sent under separate cover on January 24, 2025.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on January 16, 2025 and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Tierra Butler at (301) 796-1368 or tierra.butler@fda.hhs.gov.

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 29, 2024
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	BLA 761325
Product Name, Dosage Form, and Strength:	Merilog (insulin aspart-szjj) injection, 100 units/mL Merilog SoloStar (insulin aspart-szjj) injection, 100 units/mL
Applicant Name:	Sanofi-aventis U.S. LLC (Sanofi)
FDA Received Date:	August 16, 2024
TTT ID #:	2022-1245-2
DMEPA 1 Safety Evaluator:	Vraj Patel, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT

1 PURPOSE OF MEMORANDUM

Sanofi-aventis U.S. LLC re-submitted revised container labels and carton labeling received on August 16, 2024 for Merilog and Merilog SoloStar. The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the revised container labels and carton labeling for Merilog (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 REGULATORY HISTORY

Sanofi previously submitted their application for BLA 761325 on September 08, 2022.[b]
However, Sanofi received a Complete Response due to product quality issues on September 08, 2023.[c]
Thus, Sanofi-aventis U.S. LLC submitted a Class 2 Resubmission on August 16, 2024.[d]

3 CONCLUSION

Sanofi-aventis U.S. LLC implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Conrad, A. Label and Labeling Review for Merilog (BLA 761325). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 Sep 08. TTT ID: 2022-1245-1.

[b] Original BLA for insulin aspart-szjj BLA 761325. Bridgewater (NJ): Sanofi-aventis U.S. LLC; 2022 Sep 08. Available from: \\CDSESUB1\EVSPROD\bla761325\0001\m1\us\cover.pdf.

[c] Oyewole, M. Complete response for insulin aspart-szjj BLA 761325. Silver Spring (MD): FDA, CDER, OND, DDLO (US); 2023 Sep 08.

[d] Resubmission to a Complete Response Letter Merilog BLA 761325. Bridgewater (NJ): Sanofi-aventis U.S. LLC; 2024 Aug 16. Available from: \\CDSESUB1\EVSPROD\bla761325\0049\m1\us\cover.pdf.

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 22, 2023

TO: Rigoberto A. Roca, M.D.
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Office of Neuroscience (ON)
Office of New Drugs (OND)

Partha Roy, Ph.D.
Director
Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)

Teresa Buracchio, M.D.
Deputy Director
Division of Neurology (DN-I)
Office of Neuroscience (ON)
Office of New Drugs (OND)

John Sharrets, M.D.
Director
Division of Diabetes, Lipid Disorders and Obesity (DDLO)
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
Office of New Drugs (OND)

FROM: Monica Javidnia, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun Julia Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: (b) (4) (b) (4)

1. RRA Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote re ssessm f ic ion of Studies NON-RESPONSIVE (NDA NON-RESPONSIVE , NON-RESPONSIVE , NON-RESPONSIVE and

NON-RESPONSIVE (ANDA NON-RESPONSIVE, NON-RESPONSIVE, NON-RESPONSIVE (NDA NON-RESPONSIVE NON-RESPONSIVE NON-RESPONSIVE), and PDY12695 (BLA 761325, SAR341402) conducted at (b) (4) (b) (4)

I did not observe any objectionable conditions during the RRA. Therefore, I conclude that data from the audited studies are reliable.

2. Reviewed Studies

(b) (4)

Study PDY12695 (BLA 761325)
Analysis of SAR341402 in Human EDTA K2 Plasma Samples from Study PDY12695
Sample Analysis Period: (b) (4)

3. Scope of RRA

OSIS scientist Monica Javidnia, Ph.D. revi ytical portion of the above studies conducted at (b) (4) (b) (4) from (b) (4) (b) (4)

The RRA included an examination of records and processes for method validation, and study sample analysis. The RRA also included interviews with the firm's management and staff and a facility tour. Additionally, the RRA included a review of study-related SOPs, study-related correspondence, sample receipt, raw study data, audit trails, chromatograms, sample processing forms, select training records for study staff, calibration and maintenance records, and interviews with staff about IT, data security, and archiving processes.

4. RRA Observations

At the conclusion of the RRA, I did not observe any objectionable conditions. No items were discussed with firm's management during the RRA close-out meeting.

4.1 Note to DDLO/OCHEN/OND

During review of sample analysis data for Study PDY12695 (BLA 761325), I identified a discrepancy in the file named 'PC.xpt' in the submission data, with 36 samples having reportable concentration values >LLOQ in the 'PCORRES' column but reported as <LLOQ in the 'PCSTRESC' column. I confirmed the 'PCORRES' column data accuracy through source data from the analytical firm. In addition, the bioanalytical report lists the same values in the 'PCORRES' column. On 01/12/2023, I notified the review division about this discrepancy. The email communication is included as **Attachment 1**. I recommend the review division contact the sponsor to determine the reason for the sample values being reported as <LLOQ.

Draft: MJ 02/17/2023; 02/22/2023
Edit: HAI 02/21/2023; MO 02/21/2023; JC 02/22/2023

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE_Program/ANALYTICAL/(b) (4), (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)/(b) (4)

http://ecmsweb.f ctId/0b0026f883b89cf3
OSIS File #: BE (b) (4)

ATTACHMENTS

Attachment 1: Email communication to review division.

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/s/

MONICA JAVIDNIA
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SEONGEUN CHO
02/22/2023 04:27:31 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 21, 2023
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	BLA 761325
Product Name, Dosage Form, and Strength:	(b) (4)(insulin aspart-xxxx)[b] injection, 100 units/mL (b) (4)SoloStar (insulin aspart-xxxx) injection, 100 units/mL
Product Type:	Single Ingredient Product, Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Sanofi-aventis U.S. LLC (Sanofi)
FDA Received Date:	September 8, 2022; November 1, 2022; April 17, 2023
TTT ID #:	2022-1245
DMEPA 1 Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

[a] The proposed proprietary names, (b) (4) and (b) (4)SoloStar, were submitted to DMEPA for review (PNR ID# 2022-1044724757). Of note, Sanofi also refers to (b) (4) as SAR341402 throughout their submission.

[b] The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder "insulin aspart-xxxx" is used throughout this review to refer to the nonproprietary name for this product.

1 REASON FOR REVIEW

As part of the approval process for [redacted](b) (4)(insulin aspart-xxxx) injection, the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the proposed [redacted](b) (4)prescribing information (PI), Instructions for Use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters*	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	C

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the prescribing information (PI), Instructions for Use (IFU), container labels, and carton labeling for [redacted](b) (4)to identify areas of vulnerability that may lead to medication errors and other areas of improvement. We determined that the proposed PI is acceptable. However, we identified some areas of concern for the proposed IFU and the proposed carton and container labels and we provide our recommendations below in Section 4.1 for the Division and Section 4.2 for Sanofi.

4 CONCLUSION & RECOMMENDATIONS

The proposed labels and labeling for [redacted](b) (4)are not acceptable from a medication error perspective and we have provided recommendations to improve clarity below in Sections 4.1 and 4.2.

Note that additional label and labeling comments may be forthcoming when we have completed our evaluation of your human factors differentiation study results.

4.1 RECOMMENDATIONS FOR DIVISION OF DIABETES, LIPID DISORDERS, AND OBESITY (DDLO)

A. Instructions for Use

1. We note that the nonproprietary name will require a four-letter suffix; however, the proposed IFU and PPI lack a placeholder (i.e., insulin aspart-xxxx) in the document heading. We recommend adding the nonproprietary name placeholder, which will be replaced with a conditionally approved suffix once determined.
2. The statement "100 Units/mL" appears in the document headings for the IFU and PPI. We note that use of an uppercase "U" for units could be mistaken as an additional zero, per the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations. Therefore, we recommend revising this statement to read "100 units/mL" to minimize the risk for confusion.
3. For the SoloStar IFU, we note that the sites of administration listed and labeled on the image in the "Places to Inject" section are not consistent with the prescribing information because "buttocks" is omitted. However, we note that the image for the vial IFU identifies each approved administration site and includes corresponding images. Thus, we recommend adding "buttocks" as an administration site to align with the information in the vial IFU and prescribing information. In addition, we recommend adding a corresponding image with this site identified.
4. We note the following recommendation in the "Throwing your pen away" section of the SoloStar IFU: (b) (4) SoloStar (b) (4) (b) (4) (b) (4) SoloStar (b) (4) Typically, disposable pens can be thrown away in the trash if the needle is removed; therefore, we recommend revising this bullet to read as follows for consistency with the approved labeling of other prefilled insulin pens unless the sponsor can provide a rationale for retaining the proposed language:
    - "The used (b) (4) SoloStar pen may be thrown away in your household trash after you have removed the needle.
    - Put your used needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles in your household trash."

4.2 RECOMMENDATIONS FOR SANOFI-AVENTIS U.S. LLC

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container labels & Carton Labeling)

1. We note that the nonproprietary name will require a four-letter suffix; however, your proposed labels and labeling lack a placeholder (i.e., insulin aspart-xxxx). We request that you add a nonproprietary name placeholder to the proposed

labels and labeling, which must be replaced with a conditionally approved suffix once determined.

2. We note that you intend to use the "DD.MM.YYYY" format for this product's expiration date on the multiple dose vial. FDA recommends that the human-readable expiration date on the drug package label appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. In addition, FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date. Please clarify the format that you intend to use.

3. Consider revising the strength/concentration "100 units/mL (U-100)" presentation on the principal display panel to appear using the same font size and bold font ("100 units/mL (U-100)") for improved readability.

4. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.

   The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.

5. As currently presented, lot number is in close proximity to the expiration date. Numbers or codes located near the expiration date may be mistaken as the expiration date. We recommend you ensure that there are no other numbers located in close proximity to the expiration date.

6. Note that additional label and labeling comments may be forthcoming when we have completed our evaluation of your human factors differentiation study results.

B. Vial Container Label

1. We recommend revising the route of administration statement to read "For subcutaneous injection (b) (4) and move the statement (b) (4) to the PDP of the

carton. We note that this statement is not required on the container label and appears to clutter the label.

C. Vial Carton Labeling

1. We recommend adding the statement "use only with a U-100 syringe" to the principal display panel.
2. Consider revising the route of administration statement to list the subcutaneous route first (i.e., "for subcutaneous (b) (4) use") for clarity regarding the primary route of administration for this product. In addition, revise the route of administration statement to read "For subcutaneous injection (b) (4) (b) (4)
3. In addition to moving the statement (b) (4) (b) (4) to the PDP of the carton as noted above, we recommend removing the bold font from this statement to ensure that it does not appear more prominent than the primary route of administration information on the label (i.e., "for subcutaneous (b) (4).

D. Pen Carton Labeling

1. Add the required statement "Dispense in this sealed carton" to the PDP.
2. Consider removing the (b) (4) font used for the following statements on the side panel: "If the carton seal is broken before use, contact pharmacist.", "Warning: Any changes of insulin doses should be made cautiously and only under medical supervision." and "IMPORTANT: SEE WARNINGS ON ACCOMPANYING INSERT.".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for [redacted] (b) (4) received on April 17, 2023 from Sanofi-aventis U.S. LLC, and the listed drug (LD).

Table 2. Relevant Product Information for [redacted] (b) (4) and the Listed Drug		
Product Name	[redacted] (b) (4)	**Novolog[c]**
Initial Approval Date	N/A	06/07/2000
Proper Name	insulin aspart-xxxx	Insulin aspart
Indication	to improve glycemic control in adults and pediatric patients with diabetes mellitus	
Route of Administration	Subcutaneous, intravenous	
Dosage Form	injection	
Strength	100 units/mL	
Dose and Frequency	• Inject individualized dose subcutaneously within 5-10 minutes before a meal • [redacted] (b) (4)	• Inject individualized dose subcutaneously within 5-10 minutes before a meal • Administer by continuous subcutaneous infusion using an insulin pump • Dilute to concentrations from 0.05 unit/mL to 1 unit/mL for intravenous infusion
How Supplied	• 10 mL multiple-dose vial • 3 mL single-patient-use SoloStar prefilled pen	• 10 mL multiple-dose vial • 3 mL single-patient-use PenFill® cartridges • 3 mL single-patient-use FlexPen® • 3 mL single-patient-use FlexTouch®
Storage	• Unopened: room temperature (up to 30°C [86°F]) for up to 28 days • Unopened: refrigerate (2°C - 8°C [36°F - 46°F]) until expiration date	

[c] Novolog [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2023 Jan 26. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020986Orig1s095lbl.pdf.

	• Opened vial: refrigerated or at room temperature (up to 30°C [86°F]) for up to 28 days • Opened cartridges and pen: room temperature (up to 30°C [86°F]) for up to 28 days (do not refrigerate)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 26, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, "NDA 761325" and "IND 136342". Our search identified 2 previous reviews[d] and we considered our previous recommendations to see if they are applicable for this current review.

[d] Birkemeier, D. Use-Related Risk Analysis and Comparative Analyses Review for SAR341402 (IND 136342). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Oct 14. RCM No.: 2022-568.

Ogbonna, C. Human Factors Validation Study Protocol Review for SAR341402 (IND 133678). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Jan 30. RCM No.: 2017-2386.

APPENDIX C. LABELS AND LABELING

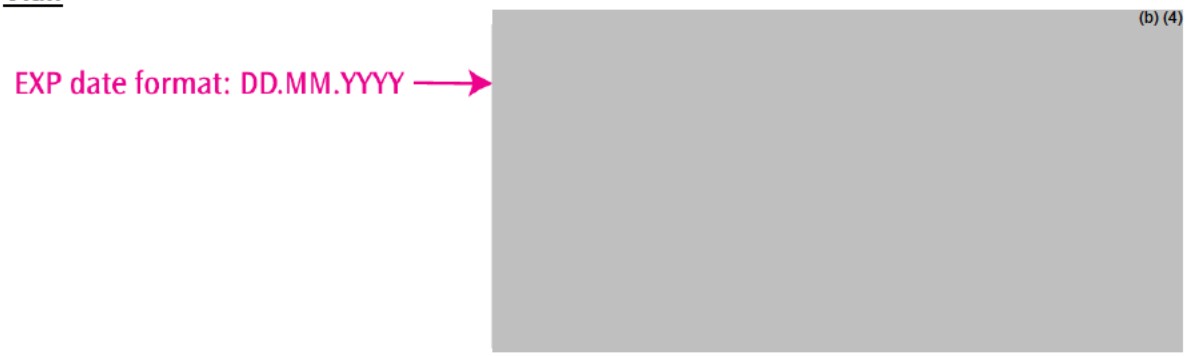
C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following (b) (4) labels and labeling submitted by Sanofi-aventis U.S. LLC.

- Container labels received on September 8, 2022
- Carton labeling received on September 8, 2022
- Prescribing Information, Instructions for Use (IFUs), and Patient Package Insert (PPI) received on April 17, 2023
    - \\CDSESUB1\EVSPROD\bla761325\0021\m1\us\proposedpi.doc

C.2 Label and Labeling Images

Vial:



[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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HUMAN FACTORS DIFFERENTATION STUDY REPORT REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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Date of This Review:	June 22, 2023
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	BLA 761325
Product Type:	Combination Product (Drug-Device)
Product, Name, Dosage Form and Strength:	SAR341402[a] (insulin aspart-szjj)[b] injection, 300 units/3 mL (100 units per mL)
Device Constituent:	Prefilled Pen
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Sanofi-aventis U.S. LLC
FDA Received Date:	September 8, 2022, January 24, 2023, May 22, 2023, June 12, 2023
OSE TTT #:	2022-1244
DMEPA 1 Safety Evaluator:	Neha Kumar, PharmD
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Deputy Director:	Jason Flint, MBA, PMP

[a] SAR341402 is a proposed biosimilar to US-licensed NovoLog FlexPen. At the time this review was written, a proprietary name for this proposed product was not approved. Therefore, the proprietary name placeholder, SAR341402, is used throughout the review.

[b] The proposed nonproprietary name, insulin aspart-szjj, was conditionally accepted on May 10, 2023.

1 REASON FOR REVIEW

This review evaluates the human factors (HF) differentiation study report submitted under biological license application (BLA) 761325 for SAR341402 (insulin aspart-szjj) prefilled pen, 300 units/3 mL (100 units per mL).

1.1 PRODUCT INFORMATION

Table 1 presents relevant product information for SAR341402 received on April 17, 2023 from Sanofi-aventis U.S. LLC, and Novolog.

Table 1. Relevant Product Information for SAR341402 and NovoLog

Product Name	SAR341402	NovoLog[c]
Initial Approval Date	N/A	June 7, 2000
Nonproprietary name	Insulin aspart-szjj	Insulin aspart
Indication	Improve glycemic control in adults and children with diabetes mellitus	
Route of Administration	• Subcutaneous (injection) • (b) (4)	• Subcutaneous (injection and continuous infusion) • Intravenous
Dosage Form	Injection	
Strength	100 units/mL	
Dose and Frequency	• Individualize the dosage of SAR341402 based on the route of administration, the patient's metabolic needs, blood glucose monitoring results and glycemic control goal. • Dosage adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake),	• Individualize the dosage of Novolog based on the route of administration, the patient's metabolic needs, blood glucose monitoring results and glycemic control goal. • Dosage adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake),

[c] Novolog [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2023 FEB 28. [cited 2023 MAR 9]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020986s096lbl.pdf

	changes in renal or hepatic function or during acute illness [see Prescribing Information Warnings and Precautions (5.2, 5.3) and Use in Specific Populations (8.6, 8.7)]. • When switching from another insulin to SAR341402, a different dosage of SAR341402 may be needed [see Prescribing Information Warnings and Precautions (5.2)]. • (b) (4) • During changes to a patient's insulin regimen, increase the frequency of blood glucose monitoring [see Prescribing Information Warnings and Precautions (5.2)]. • For subcutaneous injection, inject SAR341402 subcutaneously within 5-10 minutes before a meal into the abdominal area, thigh, buttocks or upper arm.	changes in renal or hepatic function or during acute illness [see Prescribing Information Warnings and Precautions (5.2, 5.3) and Use in Specific Populations (8.6, 8.7)]. • When switching from another insulin to Novolog, a different dosage of Novolog may be needed [see Prescribing Information Warnings and Precautions (5.2)] • During changes to a patient's insulin regimen, increase the frequency of blood glucose monitoring [see Prescribing Information Warnings and Precautions (5.2)]. • For subcutaneous injection, inject Novolog subcutaneously within 5-10 minutes before a meal into the abdominal area, thigh, buttocks or upper arm.
How Supplied	• 1,000 units/10 mL multiple-dose vial • 300 units/3 mL (100 units/mL) single patient use, multiple dose prefilled pen	• NovoLog: 1,000 units/10 mL multiple-dose vial • PenFill prefilled cartridge: 300 units/3 mL single-patient, multiple dose cartridge for PenFill cartridge compatible insulin delivery device • NovoLog FlexPen: 300 units/3 mL single patient use, multiple dose prefilled pen • Novolog Flextouch: 300 units/3 mL single patient, multiple use prefilled pen
Storage	Unused insulin aspart should be stored in a refrigerator between 2°C and 8°C (36°F to 46°F). Do not freeze.	Unused insulin aspart should be stored in a refrigerator between 2°C and 8°C (36°F to 46°F). Do not freeze.

SAR341402 Presentation	Not in-use (unopened) Room Temperature (up to 30°C [86°F])	Not in-use (unopened) Refrigerated (2°C to 8°C [36°F to 46°F])	In-use (opened) Room Temperature (up to 30°C [86°F])
10 mL multiple-dose vial	28 days	Until expiration date	28 days (refrigerated /room temperature)
3 mL single-patient use SoloStar prefilled pen	28 days	Until expiration date	28 days (do not refrigerate)

(b) (4)

NovoLog Presentation	Not in-use (unopened) Room Temperature (up to 30°C [86°F])	Not in-use (unopened) Refrigerated (2°C to 8°C [36°F to 46°F])	In-use (opened) Room Temperature (up to 30°C [86°F])
10 mL multiple-dose vial	28 days	Until expiration date	28 days* (refrigerated/ room temperature)
3 mL single-patient use PenFill cartridges	28 days	Until expiration date	28 days (do not refrigerate)
3 mL single-patient use NovoLog FlexPen	28 days	Until expiration date	28 days (do not refrigerate)
3 mL single-patient use NovoLog FlexTouch	28 days	Until expiration date	28 days (do not refrigerate)

*For insulin pump use, the total in-use time is 19 days, including 7 days pump in-use time.

Storage in External Insulin Pump: Change the NovoLog in the pump reservoir at least every 7 days or according to the pump user manual, whichever is shorter, or after exposure to temperatures that exceed 37°C (98.6°F).

Storage of Diluted NovoLog: NovoLog diluted with insulin diluting medium for NovoLog to a concentration equivalent to U-10 or equivalent to U-50 prepared as indicated under Prescribing Information Dosage and

		Administration (2.2) may remain in patient use at temperatures up to 30°C (86°F) for 28 days. Storage of NovoLog in Intravenous Infusion Fluids: Infusion bags prepared as indicated under Prescribing Dosage and Administration (2.2) are stable at room temperature for 24 hours.
Intended Users	Healthcare providers, patients, caregivers	
Intended Use Environment	Hospital setting, clinic, physician's office, home setting	

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HF DEVELOPMENT PROGRAM

- On August 4, 2017, the Applicant submitted a Biosimilar Biological Product Development (BPD) Type 2 meeting request and background materials under IND 136342 for SAR341402. In the meeting background, the Applicant indicated that they intend to conduct an HF validation study. However, based on previous discussions, the Agency agreed that an HF validation study was not needed. Therefore, the Agency sent an information request (IR) to the Applicant to clarify whether they intended to conduct an HF validation study or a differentiation study, as previously agreed.[d] In the IR response dated September 11, 2017, the Applicant responded that they would conduct an HF validation study only to evaluate the differentiability of the SAR341402 SoloStar device and its packaging.[e]

- On November 17, 2017, the Applicant submitted their HF differentiation study protocol under IND 133678 for SAR341402 (insulin aspart-szjj) injection, 300 units/3 mL (100 units per mL). We reviewed the protocol and provided recommendations.[f]

- On October 24, 2018, the Applicant requested a Biosimilar BPD Type 2 meeting under 136342 and asked the following question, (b) (4) (b) (4) (b) (4) ? In the Agency's final written response dated January 1, 2019, we provided the following response to the aforementioned question:
  "*To support a demonstration of biosimilarity for your proposed product with Novolog, we refer you to the communication dated September 11, 2017, where you agreed to conduct a differentiation study.*
  (b) (4)

[d] White, M. FDA Communication: PIND136342, SAR341402: Information Request. Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2017 SEP 6. IND 136342. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80459c90

[e] Response to Agency Information Request Regarding BPD Type 2 Meeting for SAR341402 (IND 136342). Bridgewater (NJ): Sanofi US Services Inc; 2017 SEP11. Available from: \\CDSESUB1\EVSPROD\ind136342\0002\m1\us\quality-response-to-06-sep-2017-request.pdf

[f] Ogbonna, C. SAR341402 (insulin aspart) Human Factors Protocol Review (IND 133469). FDA, CDER, OSE, DMEPA (US); 2018 JAN 30. RCM No.: 2017-2386.

(b) (4)

- On March 18, 2022, the Applicant submitted their use-related risk analysis (URRA) and comparative analyses under IND 136342 for SAR341402 (insulin aspart-szjj) injection, 300 units/3 mL (100 units per mL) as a proposed (b) (4) to US-licensed Novolog Flexpen, BLA 020986 (hereafter called Novolog Flexpen). We reviewed the URRA and comparative analyses and determined that the Applicant does not need to submit the results of a comparative use human factors (CUHF) study to support their 351(k)(4) application seeking licensure as (b) (4) biosimilar to NovoLog FlexPen.[h]
- On September 8, 2022, the Applicant submitted a Biologics License Application, BLA 761325, for SAR341402 (insulin aspart-szjj) injection, 300 units/3 mL (100 units per mL) as a proposed biosimilar to Novolog Flexpen. This submission included the HF differentiation study results report including adult patient, nurse, and pharmacist participants. On January 18, 2023, we issued an IR requesting HF differentiation study data for pediatric patients (10-17 years) with type 1 or type 2 diabetes.[i] On May 22, 2023, the Applicant submitted the HF differentiation study results with pediatric patients. The September 8, 2022 and May 22, 2023 HF differentiation study results are the topic of this review.

[g] White M. Final written response for SAR341402. Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2019 JAN 1. IND 136342.

[h] Birkemeier, D. SAR341402 (insulin aspart) URRA and Comparative Analyses Review (IND 136342). FDA, CDER, OSE, DMEPA 1 (US); 2022 OCT 14. RCM No.: 2022-568.

[i] Thomas, T. Information request for insulin aspart BLA 761325. Silver Spring (MD): FDA, CDER, OSE, PMS (US); 2023 JAN 18. BLA 761325. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806aae30

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review.

Table 2. Materials Considered For This Review	
Material Reviewed	**Appendix or Section (for Methods and Results)**
Product Information/Prescribing Information	Section 1.1
Background Information Previous DMEPA HF Reviews	B
Human Factors Differentiation Study Results Report	C
Information Requests Issued During the Review	D
Label and Labeling	E

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors observed, and our analysis to determine if the results indicate that the user interface has been appropriately designed to support the safe and effective use of the proposed product.

2.1 SUMMARY OF STUDY DESIGN

Table 3 presents a summary of the HF differentiation study design. See Appendix B for more details on the study design.

Table 3. Study Methodology for Human Factors (HF) Differentiation Study	
Study Design Elements	**Details submitted by Applicant**
Participants	• 15 pen-naïve adult type 1 or type 2 diabetes patients • 16 pen-experienced adult type 1 or type 2 diabetes patients • 8 pen-naïve pediatric (10 – 17 years old) type 1 or type 2 diabetes patients • 9 pen-experienced pediatric (10 – 17 years old) type 1 or type 2 diabetes patients • 15 nurses currently treating patients with diabetes • 15 pharmacists currently dispensing insulin products
Training	No training was provided to the participants
Test Environment & Materials	• The setting for the HF differentiation study for the patient participants resembled a home environment with regard to

	furnishings (e.g., couch, table) and lighting level (i.e., approximately 50 lux). • The setting for the HF differentiation study for the nurses and pharmacists resembled a clinical environment with regard to room furnishings (e.g., desk or table) and lighting level (i.e., approximately 500 lux). • Single pens with the proposed name, (b) (4) Solostar, were placed in drawers • Pen cartons with the proposed name, (b) (4) Solostar, were placed in the refrigerator • Comparator products (carton and pens) use in the HF differentiation study: o Novolog Flexpen o Novolog Mix 70/30 Flexpen o Levemir Flexpen o Humalog Kwikpen o Humalog Mix 75/25 Kwikpen o Humalog Mix 50/50 Kwikpen o Lantus SoloStar o Apidra SoloStar o Toujeo SoloStar o Admelog SoloStar o Humalog Kwikpen U-200 o Humalog Junior Kwikpen o Insulin aspart Mix 30/70 o Soliqua 100/33 (SoloStar)
Sequence of Study	Patients and nurses were: 1. shown the insulin aspart pen injector carton and pen labeled with the name (b) (4). 2. asked to identify the correct carton from a set of cartons, including comparator cartons, in a refrigerator. 3. asked if they had any difficulties finding the correct carton and why they chose the carton they did. 4. asked to identify the correct pen from a set of pens, including comparator pens, in a drawer. 5. asked if they had any difficulties finding the correct pen and why they chose the pen they did. Pharmacists were: 1. given a written prescription for (b) (4) (insulin aspart) pen injector 2. asked to identify the correct carton from a set of cartons, including comparator cartons, in the refrigerator.

	3. asked if they had any difficulties finding the correct carton and why they chose the carton they did.

2.2 RESULTS AND ANALYSIS

We have carefully reviewed each observed event, the Applicant's URRA, the participants' subjective feedback, and the Applicant's RCA and comments.

The HF differentiation study showed one use error with a pharmacist participant for the "select the correct carton" task:

There was one use error observed for this task (one pharmacist selected Novolog Flexpen (insulin aspart). The root cause analysis (RCA) indicated this error was due to the participant's concentration on the type of insulin and their familiarity with the currently marketed product, Novolog Flexpen (insulin aspart). Additionally, the orange color and the "*Log*" part of the name supported the participant's decision.

Insulin aspart-szjj and Novolog Flexpen (insulin aspart) contain the same concentration of insulin aspart. Therefore, the Applicant stated that the risk associated with a mix-up between insulin aspart-szjj and Novolog Flexpen (insulin aspart) is low if a patient has both at home and accidentally injects themselves with the incorrect product. The Applicant did not provide any mitigations strategies to address this error. Based on our review of the user interface, subjective feedback, and root cause analysis, we did not identify any additional risk controls to address this use error and have no recommendations at this time.

3 LABELS AND LABELING

The DMEPA 1 primary review team evaluated product specific label and labeling under a separate cover and label and labeling comments have been sent to the Applicant based on the outcome of that review.[j]

4 CONCLUSION

The results of the HF differentiation study demonstrated one use error with a critical task. However, based on our review of the available participant's subjective feedback and the Applicant's root cause analysis from the HF differentiation study we did not identify any risk controls to address the use error. We find that the risks have been mitigated to an acceptable level and no further changes to the user interface are likely to further mitigate these risks. As such, we have no recommendations for this BLA.

[j] Conrad, A. Label and Labeling Review for (b) (4) (insulin aspart-szjj). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2023 APR 21. OSE RCM No.: 2022-1245.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX B. PREVIOUS REVIEWS

B.1.1 Methods

On March 5, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, “136342”, “133678”, “761325” and “insulin aspart”.

B.1.2 Results

Our search identified two previous reviews[fh] and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX C. HUMAN FACTORS DIFFERENTIATION STUDY RESULTS REPORT

The human factors differentiation results report with adult patient, nurse, and pharmacist participants can be accessed in EDR via: \\CDSESUB1\EVSPROD\bla761325\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetes-mellitus\5354-other-stud-rep\human-factor\hfe-summary-report-insulin-aspart.pdf

The human factors differentiation results report with 10-17 year old participants can be accessed in EDR via: \\CDSESUB1\EVSPROD\bla761325\0028\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetes-mellitus\5354-other-stud-rep\human-factor\pen-injector-1000u-ml-supp-hfe.pdf

APPENDIX D. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On January 18, 2023, we issued an information request stating that in order to evaluate if the Applicant’s proposed product can be adequately differentiated from other injectable diabetes medications, the Applicant should conduct a human factors differentiation study with 15 children ages 10-17 years old with diabetes mellitus. We also asked the Applicant to provide their planned timeline for completion of the human factors differentiation study.

On January 24, 2023 and May 22, 2023, the Applicant provided an acceptable response that can be accessible in EDR via:
\\CDSESUB1\EVSPROD\bla761325\0011\m1\us\clinical-response-18jan2023pdf.pdf
\\CDSESUB1\EVSPROD\bla761325\0028\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetes-mellitus\5354-other-stud-rep\human-factor\pen-injector-1000u-ml-supp-hfe.pdf

On May 30, 2023, we issued an information requesting clarification on if any parents or guardians interacted with the patient participants in the human factors differentiation study, and if so, to include all subjective feedback and root cause analyses regarding these interactions. We also asked the Applicant to provide the age of each participant included in the human factors differentiation study.

On June 12, 2023, the Applicant provided an acceptable response that can be accessible in EDR via: \\CDSESUB1\EVSPROD\bla761325\0031\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetes-mellitus\5354-other-stud-rep\human-factor\hf-response-30may2023.pdf

APPENDIX E. LABEL AND LABELING

Label and labeling for SAR341402 (insulin aspart-szjj) 300 units/3 mL (100 units/mL) submitted by Sanofi-aventis U.S. LLC on May 22, 2023:

Carton labeling

(b) (4)

[redacted]

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 10, 2023

TO: John M. Sharretts, MD
Director
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology

FROM: Kara A. Scheibner, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Kimberly A. Benson, Ph.D.
Deputy Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Routine inspection of PROFIL Institut für Stoffwechselforschung GmbH, Neuss, Germany

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portions of study PDY12695 (BLA 761325) conducted at PROFIL Institut für Stoffwechselforschung GmbH, Neuss, Germany.

Form FDA 483 was not issued at the inspection close-out, but two inspectional findings were discussed with the firm.

I reviewed the inspectional findings, the EIR, and exhibits collected during the inspection, and although objectionable conditions were observed, I conclude that they likely will not impact data reliability. Thus, the data from study PDY12695 are reliable.

Please note, there were minor discrepancies identified between premature end of euglycemic clamp times in the source records collected on site and the reported data listings in section 16.2.6.4.4 of the submission for six subjects (see section 3 for details). I defer to the review division to determine whether these discrepancies affect critical PK or PD parameters.

2. Inspected Study:

BLA 761325

Study Number: PDY12695
Study Title: "A randomized, double-blind, controlled, single-dose, 3-treatment, 3-period, 6-sequence crossover study to compare exposure and activity of SAR341402 to NovoRapid® and NovoLog® using the euglycemic clamp technique, in subjects with type 1 diabetes mellitus"
Dates of conduct: 11/14/2012 – 12/28/2012

Clinical site: PROFIL Institut für Stoffwechselforschung GmbH
Hellersbergstrasse 9
Neuss, North Rhine-Westphalia, 41460, Germany

3. Inspectional Findings

ORA investigator Alanna Mussawwir-Bias inspected PROFIL Institute für Stoffwechselforschung GmbH, Neuss, Germany (PROFIL) from March 20-24, 2023.

The previous OSIS inspection of PROFIL was conducted in January 2018. At the conclusion of the inspection, Form FDA 483 was not issued. The recommendation was NAI.

The current inspection included an audit of the following:

- Study protocols
- Subject selection criteria
- The informed consent process
- Test article dosing and accountability
- Reserve samples
- Adverse event reporting
- Clinical laboratory testing
- Euglycemic clamp device cleaning, maintenance, and calibration
- Source data for selected study subjects, including glucose infusion rates and premature end of clamp times

At the conclusion of the inspection, investigator Mussawwir-Bias did not issue Form FDA 483 to the clinical site. However, she discussed two inspectional findings with the firm at the close-out meeting.

The findings, and my evaluation, are presented below.

3.1 Finding 1: Routine cleaning, maintenance, and calibration of euglycemic clamp devices were not accurately documented consistently.

OSIS Evaluation: Based on the information collected during the inspection and the EIR, I cannot confirm that this finding is true-in-fact. I can confirm the following information:

- Biostator device 18.24 was used for subject (b) (6) from (b) (6) (**Attachment 01**)
- (b) (6) as used for subject (b) (6) from (b) (6) (**Attachment 01**)
- On (b) (6) and (b) (6) the following procedures were not completed for Biostator device 18.24: disinfection of the bed, disinfection of the hotbox, and disinfection of the Biostator (**Attachment 02**)

An English translation of the Continuous Biostator Control SOP Form P06.F69 was provided (**Attachment 03**). However, the exhibit provided for SOP P06.A22 was in German (**Attachment 03**). Thus, I was able to determine which maintenance steps were skipped on certain dates, but I cannot determine whether the firm followed their SOP and which maintenance steps were required. Furthermore, the ORA investigator did not provide evidence to demonstrate that inconsistencies in maintenance procedures affected study data.

3.2 Finding 2: Premature End of Clamp subject data listings for clamp stop times were inconsistent with the source data for six subjects.

OSIS Evaluation: This finding is true-in-fact. Exhibits collected during the inspection from subjects (b) (6) (b) (6) and (b) (6) (**Attachment 04**) were inconsistent with data listings in section 16.2.6.4.4 of the submission. The discrepancies are summarized in the table below.

Subject Number	Source Data Date	Source Data Time	16.2.6.4.4 Listing Date	16.2.6.4.4 Listing Time
(b) (6)		12:13:00 AM	(b) (6)	12:10:00 AM
		12:02:00 AM		12:01:00 AM
		1:17:00 AM		1:03:00 AM
		10:12:00 PM		10:11:00 PM
		11:07:00 PM		11:06:00 PM
		11:27:00 PM		11:28:00 PM
		9:32:00 PM		9:34:00 PM
		9:42:00 PM		9:40:00 PM
		10:13:00 PM		10:17:00 PM
		8:32:00 PM		8:33:00 PM

End of clamp times were verified between multiple data sources collected from the site including paper case report forms (CRFs), Biostator print-outs, and electronic CRFs.

During the inspection, the CEO of PROFIL's non-clinical administration group stated that raw source data was provided directly to the sponsor in January 2013 (**Attachment 05**). He believed that the sponsor may have submitted a calculated/ mathematical endpoint, however, this was not confirmed during the inspection.

Section 8.7.2.2.2.5 of the clinical report states that a listing of subjects with premature end of clamp was provided (section 16.2.6.4.4), including the post-dose times when the clamp ended. Section 10 notes that the clamp was stopped prematurely in subjects within each treatment group. Neither section included a discussion of calculations used to mathematically determine the end of clamp times.

Based on the information collected during the inspection, we can confirm that there were discrepancies between source records and submitted data. However, we cannot determine why the original source data was not reported by the sponsor, or whether these discrepancies affect PK or PD data. Thus, we recommend that the review division determine whether the discrepancies have an impact on the final PK and PD data sets.

Kara A. Scheibner, Ph.D.
Pharmacologist

Draft: KAS 07/07/2023
Edit: MFS 07/07/2023; KAB 07/10/2023

OSIS File #: BE9751

eNSpect Assignment ID: 215470
eNSpect OpID: 243215

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KIMBERLY A BENSON
07/10/2023 02:29:57 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 31, 2023

To: Michael Oyewole, PharmD, Regulatory Project Manager, of Diabetes, Lipid Disorders, and Obesity (DDLO)

Dolly Misra, MD, Clinical Reviewer, DDLO

Melinda Wilson, PharmD, MPH, Associate Director for Labeling, DDLO

From: Tierra Butler, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for (b) (4) (insulin aspart-szjj) injection, for subcutaneous use

BLA: 761325

Background:

In response to DDLO's consult request dated September 20, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI)/Instructions for Use (IFU), and carton and container labeling for the original BLA submission for Truvelog (insulin aspart-szjj) injection, for subcutaneous use.

PI/PPI/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on July 20, 2023, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI/IFU, and comments will be sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on July 25, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Tierra Butler at 301-796-1368 or tierra.butler@fda.hhs.gov.

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TIERRA N BUTLER
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 14, 2023
To:	Michael Oyewole, PharmD Regulatory Project Manager **Division of Diabetes, Lipid Disorders, and Obesity (DDLO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Tierra Butler, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (nonproprietary name):	SAR341402 (insulin aspart-szjj)[1]
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761325
Applicant:	sanofi-aventis U.S. LLC

[1] SAR341402 has been developed as a proposed biosimilar to NOVOLOG (insulin aspart), BLA 020986. The nonproprietary name "insulin aspart-szjj" was found to be conditionally acceptable for this BLA on May 10, 2023. The proposed proprietary name (b) (4) was found to be unacceptable on April 24, 2023.

1 INTRODUCTION

On September 8, 2022, sanofi-aventis U.S. LLC, submitted for the Agency's review a 351(k) Biologics License Application (BLA) 761325 for SAR341402 (insulin aspart-szjj) injection, for subcutaneous use. SAR341402 (insulin aspart-szjj) is a proposed biosimilar to NOVOLOG (insulin aspart). The proposed indication for SAR341402 (insulin aspart-szjj) is to improve glycemic control in adults and pediatric patients with diabetes mellitus.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) on September 20, 2022 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for SAR341402 (insulin aspart-szjj) injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on April 21, 2023.

2 MATERIAL REVIEWED

- Draft SAR341402 (insulin aspart-szjj) injection, for subcutaneous use PPI and IFU received on September 8, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 21, 2023.
- Draft SAR341402 (insulin aspart-szjj) injection, for subcutaneous use Prescribing Information (PI) received on September 8, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 21, 2023.
- Approved NOVOLOG (insulin aspart) comparator labeling dated February 28, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 8, 2023
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	BLA 761325
Product Name, Dosage Form, and Strength:	Merilog[a] (insulin aspart- szjj) injection, 100 units/mL Merilog[a] SoloStar (insulin aspart- szjj) injection, 100 units/mL
Applicant/Sponsor Name:	Sanofi-aventis U.S. LLC (Sanofi)
TTT ID #:	2022-1245-1
DMEPA 1 Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling for Merilog on September 7, 2023. The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the revised container labels and carton labeling for Merilog (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b] In addition, we note that Sanofi submitted new mockups of Merilog SoloStar professional sample labels and labeling for review.

In response to our comments regarding the differing expiration date formats for the vial and SoloStar labels, Sanofi noted that their current format for the human-readable expiration date on the Merilog vial label and carton labeling is "DD.MM.YYYY" while the expiration format used for their Merilog SoloStar label and carton labeling is "YYYY-MM-DD". However, they

[a] Vee, S. Proprietary Name Review for Merilog and Merilog SoloStar (BLA 761325). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 Aug 16. PNR ID No.: 2023-1044725162 and 2023-1044725166.

[b] Conrad, A. Label and Labeling Review for (b) (4) (BLA 761325). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 Apr 21. TTT ID No.: 2022-1245.

subsequently provided mockups revising the vial label and carton expiration date format "DD.MM.YYYY" to "YYYY-MM-DD" for consistency with their other Merilog labels and labeling.

2 CONCLUSION

We reviewed the resubmitted labels and labeling for Merilog and Merilog SoloStar to determine if they are acceptable from a medication error perspective and we determined that the labels and labeling are acceptable. We have no additional recommendations at this time.

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