CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209196Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval
(Including the Facility Review/Manufacturing Inspection Recommendation)

NDA 209196
Review 1
Review Date: 7/25/17

Drug Name/Dosage Form	Insulin lispro injection/Solution for injection
Trade Name	Admelog and Admelog Solostar
Strength	100 units/mL
Route of Administration	Subcutaneous injection
Rx/OTC Dispensed	Rx
Applicant	Sanofi
Indication	Glycemic control in adults and children with diabetes

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original and Amendments	*11/01/16, 1/10/17, 3/06/17, 4/03/17, 5/09/17, 6/02/17, 6/16/17, and 7/14/17*	*Quality (Module 3.2. and 1.1)*

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Xavier Ysern/Donna Christner	Division of New Drug API/ONDP
Drug Product	Muthukumar Ramaswamy/Danae Christodoulou	New Drug Products II/ONDP
Process	Khalid Khan/ Yong Hu	Process Assessment/OPF
Microbiology	Z. Cusumano (initial) / Jessica Chiaruttini/John Metcalfe	Microbiology Assessment/OPF
Facility (OPF)	Krishna Ghosh/Juandria Williams	Division of Inspectional Assessment/OPF
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management/OPRO
Application Technical Lead	Muthukumar Ramaswamy	New Drug Products II/ONDP
Facility (CDRH)	Crystal Lewis	CDRH Compliance
ORA Lead	N/A	N/A
Environmental Analysis (EA)	Muthukumar Ramaswamy	New Drug Products II/ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Sufficient information provided in NDA		LOA 1124/16
	Type III					LOA 1/13/16
	Type III					LOA 3/02/16
	Type III					LOA 1/14/16
	Type III					LOA 1/13/16 and 1/12/16
	Type III					LOA 1/12/16
	Type III					2/22/16 and 1/14/16
	Type V			Adequate. Refer to microbiology review		LOA 2/22/16
	Type V					LOA 1/14/16

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	120511	Insulin lispro

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharmacology/Toxicology	Complete	Acceptable. See review in DARRTS 7/20/17 (Impurities and leachables)	3/07/17 and 3/23/17	Dr. Daniel Minck
CDRH- Compliance	Complete	Acceptable, See review in DARRTS 7/18/17	7/13/17	Crystal Lewis

Executive Summary

I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (including the manufacturing inspection recommendation) is approval. CMC Labeling comments (related to CMC micro and drug product) will be finalized during multi-disciplinary review managed by OND.

The following should be included in the Approval Letter:
1. Based on available stability data and the regulatory drug substance specification, (b) (4) (b) (4)

2. Based on all available data and the regulatory drug product specification, the long-term shelf life is 36 months (b) (4) ***and the in-use shelf life is 28 days at*** (b) (4) ***30°C after initial use for the combination product.***
3. The analytical strategy for a biosimilar product was considered as secondary supporting information in our review of the NDA.

II. Summary of Quality Assessments

This NDA is a 505(b)(2) Type 5 application for recombinant insulin lispro. The applicant relies on safety and efficacy information in the labeling of the referenced drug Humalog (Insulin lispro injection). Humalog was approved under NDA 020563. The proposed product is a clear, colorless solution filled in 10mL vial or in 3mL cartridge preassembled in a pen injector for subcutaneous or intravenous injection or for continuous subcutaneous infusion using an insulin pump. The drug product has the same composition and strength as the referenced approved drug. Sanofi assigned code for insulin lispro is SAR342434.

The applicant provided an analytical comparison between the proposed product (SAR342434 injection) and Humalog. The proposed product is 505(b)2 application a standalone product with clinical data. The analytical similarity exercise provides assurance quality characteristics are comparable between Humalog and Sanofi insulin lispro injections. The following quality characteristics were compared using multiple batches of product: structural comparison (b) (4) batch release profile, stability profile comparison (using data from real-time, in-use study, accelerated and forced degradation studies), and biological activity comparison using rabbit blood sugar assay. The biological activity comparison *(in vitro* pharmacology studies*)* between Humalog and SAR342434 is evaluated in the Pharmacology Toxicology review.

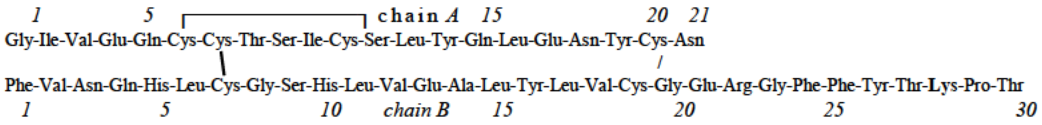
The number of batches tested in the analytical comparison between the originator and new product was variable. For example, structural comparison studies used at least one batch for each group. For higher order structures, at least 3 batches were used for comparison. For purity comparison a minimum of 3 batches of new product were compared with 30 batches of originator product. For potency, a minimum of 3 batches of the new product was compared against originator product label.

The NDA also includes data to show that there is no significant difference in strength, quality or purity between new product and Humalog and meet the standards set in the USP monographs. Biological activity (USP <121> Bioidentity) is part of the regulatory drug substance specification.

The product is intended for glycemic control in adults and children with diabetes. For maximum daily dose information, please refer to CDTL's memo.

Drug Substance Quality Summary

Dr. Xavier Ysern has reviewed CMC information for SAR342434 drug substance. Insulin lispro is produced by recombinant DNA technology utilizing *E.coli* (b) (4) strain as the production organism. Chemically SAR342434 is 28B-LYS, 19B-Pro human insulin. SAR342434 has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808 Da. SAR342434 has the same amino acid sequence and structure as the reference listed drug. SAR342434 has the following structural formula:



SAR342434 is manufactured from (b) (4)

(b) (4)

The structure of insulin lispro was confirmed based on amino acid sequencing, mass spectroscopy and peptide mapping. Per drug substance reviewer, (b) (4) with Ph. Eur. and USP reference standards did not display significant differences between Sanofi insulin and reference standards.

Drug substance used in Phase III clinical studies were manufactured by the from (b) (4)

(b) (4)

The applicant's stability data supported the proposed (b) month shelf life, when stored (b) (4)

(b) (4)

Drug substance review concluded that the information provided in the NDA supports approval of the NDA. For additional details, please refer to Dr. Ysern's CMC review in Panorama.

Drug Product

SAR342434 drug product (Insulin lispro injection) is a sterile, aqueous, clear, colorless solution filled in 10mL vial or as 3mL prefilled pen. The drug product composition and strength are the same as the referenced approved drug. The potency of the proposed formulation (100 Units/mL) is based on mass of insulin lispro in solution (b) (4) The proposed final formulation is the same as the one used in development and Phase 3 clinical studies.

Drug product contains (b) (4) mg of insulin lispro, glycerol (16 mg), metacresol (b) (4) zinc oxide (b) (4) disodium phosphate dehydrate USP (1.88 mg), and water for injection USP. Hydrochloric acid or sodium hydroxide may be added to adjust pH (b) (4) Zinc and metacresol are provided (b) (4) (b) (4) The pH and zinc content of the drug product (b) (4) (b) (4)

Excipients proposed for use in the drug product are known for use in pharmaceutical products (b) (4) (b) (4) The formulation proposed for commercial use is the same as the one used in clinical studies.

The drug product is filled in USP (b) (4) glass cartridge (3mL) vial sealed with a (b) (4) rubber disc on one end and a (b) (4) (b) (4) plunger on the other end. The drug product is also available in 10 mL vial sealed with a (b) (4) The proposed container closure system components are known for use or the same as in approved insulin products.

The compatibility of the drug product with the container closure components and insulin infusion pump was demonstrated by the available stability data. Extractable and leachable data are reported in the NDA with supporting safety information. Pharm. Tox. Reviewer was consulted on the safety for product related impurities and leachables. No safety concerns were identified. *Please refer to non-clinical review dated 7/20/17 in DARRTS.*

The NDA contains adequate manufacturing process description. The proposed drug product manufacturing process utilizes (b) (4) used for the insulin injectable dosage form. It includes (b) (4) (b) (4)

The manufacturing process was validated (b) (4) (b) (4)

The applicant provided validation information for hold time (b) (4) (b) (4) For detailed information on the manufacturing process description and process control, please refer Dr. Khalid Khan's review in Panorama dated 6/20/17. *Dr. Khan's review concluded that the proposed drug product manufacturing process description and controls are adequate to support the NDA.*

The Applicant utilized risk assessment techniques to identify the critical quality attributes (CQA) of product and assessed the impact of manufacturing process parameters on critical quality attributes. (b) (4) (b) (4)

The proposed drug product specification (b) (4) conforms to USP monograph for insulin lispro injection and is adequate to assure the quality, strength, and purity of the product. The specifications are based on batches used in pre-clinical, clinical and registration stability studies and are in accordance with ICH Q6B recommendations, pharmacopeial and/or regulatory guidelines. Analytical procedures proposed for potency and purity are improvements to monograph procedures. All non-compendial analytical procedures (b) (4) as well as the pharmacopoeial analytical procedures for sterility and bacterial endotoxins were validated.

The critical attributes of the product are controlled through (b) (4) (b) (4) (b) (4) The proposed control strategy is adequate to assure the quality of the product. *Please refer to Dr. Khan's review (Process) and Microbiology review.*

Finished product (Pen injector, (b) (4) specification includes a test for dose accuracy. Please refer to CDRH Review for additional information related to device evaluation.

Expiration Date & Storage Conditions: Shelf-life determination is based on real-time stability information for the following batches:

a) 36 months of real-time stability data for 4 stability batches packaged in cartridges (Primary: C1050125 and 1050126; Supportive - C1024625 and C1033467), and 1 supportive stability batch packaged in vials (SAR342434_12_0_042).
b) 18 months of real-time stability and in-use data for 3 vial batches (C1050629, C1050630, and C1050631).
c) 12-18 mo. real-time stability and in-use data for product in pen injector batches (C1051066, and C1051926).

Based on available data, an expiration period of 36 months is granted when stored at 2-8 °C for the finished product in vials and in prefilled pens with an in-use period of up to 28 days at room temperature (below 86° F (30 °C) after first use. Refer to CMC (Drug Product) review dated 7/07/17 in Panorama.

The applicant provided stability/compatibility data to support the continuous infusion of the drug product continuously for 7 days using Animas Vibe and Medtronic insulin pumps. Original ND NDA submission did not contain sub-visible particulate information for the product dispensed form infusion pump. Per FDA request, the applicant provided satisfactory information on the sub-visible particulate content of the dispensed product (Refer to July 14, 2017 NDA amendment). No occlusion of product was observed during infusion period. Available CMC information is adequate to support the 7 day pump in-use period. Infusion tubing change is recommended after every 3 day of use.

Manufacture of the drug product, assembly of the disposable pen-injector, testing, packaging, labeling, and release will be performed at Sanofi-Aventis Deutschland GmbH. Manufacturing facility compliance status of device assembly site was reviewed by CDRH compliance reviewer (*Ms. Crystal Lewis review dated 7/13/17) and concluded that it is acceptable*. Facility compliance information for drug product and drug substance manufacturing facilities was reviewed by Dr. Krishna Ghosh. Her review *concluded that there are no outstanding manufacturing or facility risks that prevent approva*l of this application. Please refer to *Dr. Ghosh's review dated 6/8/17 in Panorama for details.*

Microbiological controls associated with the drug product manufacturing process were reviewed by microbiology reviewer (*Dr. J. Chiaruttini*). Microbiology review covered (b) (4) (b) (4) (b) (4) *Refer to CMC (Microbiology) review by Dr. J. Chiaruttini dated 6/30/17 in Panorama.*

Microbiology review concluded that microbiological controls are adequate to support the NDA with the exception of the in-use period proposed for diluted product stored in infusion bag. *Microbiology review recommended that the hold times for infusion solution should be revised to not more than 4 hours at room temperature or 24 hours at 2°C - 8°C in the package insert.*

Labeling comments (related to Section 2 and 16) will be finalized during the multi-disciplinary review managed by OND.

C. Summary of Drug Product Intended Use: See CDTL's memo.

D. Life Cycle Knowledge Information

Final Risk Assessment - CMC Reviewer's risk assessment for critical attributes is shown at the end of the drug product review. The final risk assessment concluded that the final risk is low for the proposed product. No further mitigation necessary.

OVERALL ASSESSMENT AND SIGNATURES:

From CMC perspective, the proposed product is recommended for approval.

Muthukumar Ramaswamy, Ph.D. 7/25/17

Application Technical Lead Name and Date:

155 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

MICROBIOLOGY

Product Background:

NDA: 209196

Drug Product Name / Strength: Insulin lispro [rDNA origin] injection, 100 U/mL

Route of Administration: Subcutaneous and intravenous

Applicant Name: Sanofi-Aventis, US. LLC

Manufacturing Site: Sanofi-Aventis Deutschland GmbH
Brüningstaße 50
Industriepark Höchst
65926 Frankfurt am Main, Germany

Method of Sterilization: (b) (4)

Review Summary: Recommended for Approval after implementation of the labeling revisions indicated on the last page of this review.

List Submissions being reviewed: November 1, 2016, January 10, 2017 and April 03, 2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: The proposed in-use period for the drug product diluted into an infusion bag is not supported with microbiological data. (b) (4) See the last page of this review for more information.

Supporting/Related Documents: The review of DMF (b) (4) by M. Cruz-Fisher performed on 12/9/2015 (b) (4) and found adequate. The review of DMF (b) (4) by H. Ngai performed on 5/26/2016 (b) (4) found adequate.

Remarks Section: This is an eCTD submission. The drug product formulation (b) (4) as that found under NDA 20563 (Eli Lilly's Humalog); however, this NDA proposes a 3 mL prefilled pen injector and 10 mL vial presentation. The initial draft microbiology review was conducted by Z. Cusumano with J. Chiaruttini for secondary reviewer and an information request was sent on March 02, 2017. The April 03, 2017 information request response was reviewed by J. Chiaruttini with J. Metcalfe as secondary reviewer.

S Drug Substance

(b) (4)

P.1 Description of the Composition of the Drug Product

Description of drug product – the drug product is a sterile, preserved, clear and colorless solution for injection. The drug product is available in two presentations: a 3 mL cartridge (3 mL fill) to be used with a pen injector, and a 10 mL vial (10 mL fill) to be used in external insulin pumps and infusion bags.

Drug product composition – The drug product composition of the two presentations, 3 mL cartridge and 10 mL vial, are described in the two tables below, copied from p. 3/4 of the pdf "Description and composition of the drug product – 3 mL cartridge – (b) (4) and p. 3/4 of the pdf "Description and composition of the drug product - 10 mL vial – (b) (4) respectively. Both pdfs are located in section 3.2.P.1.

Table 1 - Composition of insulin lispro solution for injection in cartridges

Components [a]	Composition			Function	Reference to standards [b]
	Percentage [%]	Per mL [mg]	Per unit (3 mL cartridge) [mg]		
Insulin lispro *[equivalent to U of insulin]*	(b) (4)	*[100]*	*[300]*	Drug substance	Ph. Eur., USP
Metacresol [c]					Ph. Eur., USP
Glycerol					Ph. Eur.
Dibasic sodium phosphate					USP
Zinc oxide [d]					Ph. Eur., USP
Sodium hydroxide					Ph. Eur., NF
Hydrochloric acid					Ph. Eur., NF
Water for injection					Ph. Eur., USP
					Ph. Eur., NF

(b) (4)

Table 1 - Composition of insulin lispro solution for injection in vials

Components [a]	Composition			Function	Reference to standards [b]
	Percentage [%]	Per mL [mg]	Per unit (10 mL vial) [mg]		
Insulin lispro *[equivalent to U of insulin]*		*[100]*	*[1000]*	Drug substance	Ph. Eur., USP
Metacresol [c]					Ph. Eur., USP
Glycerol	1.88				Ph. Eur.
Dibasic sodium phosphate					USP
Zinc oxide [d]					Ph. Eur., USP
Sodium hydroxide					Ph. Eur., NF
Hydrochloric acid					Ph. Eur., NF
Water for injection					Ph. Eur., USP

(b) (4)

Description of container closure system – The description of the 3 mL cartridge is described in the table below, copied from p. 4/15 of the pdf "3 mL Cartridge – Container Closure System – (b) (4) located in section 3.2.P.7.

(b) (4)

The description of the container closure system for the 10 mL vial is described in the table below, copied from p. 4/10 of the pdf "10 mL vial – Container Closure System – (b) (4) (b) (4)

(b) (4)

Reviewer's Assessment: Example: The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

3 mL Cartridge

The integrity of the 3 mL cartridges was validated with both a microbial ingress and dye ingress test, which are described on p. 7/7 of the pdf "Container closure system- 3mL cartridge – (b) (4) (b) (4) located in section 3.2.P.2. For the microbial ingress test (b) (4)

10 mL vial

The integrity of the 10 mL cartridges was validated with both a microbial ingress and dye ingress test, which are described on p. 6/7 of the pdf "Container closure system- 10 mL vial – (b) (4) (b) (4) located in section 3.2.P.2. The integrity test methods for both the microbial and dye ingress test were identical to the 3 mL cartridge. For the microbial ingress test, no containers were positive for growth. For the dye ingress the primary stability data for the 10 mL vial was acceptable.

Information request dated 02 March 2017

We acknowledge the use of a dye ingress method for the container closure integrity test for the 3mL cartridge and 10 mL vial. Provide a brief description of the method, (b) (4) (b) (4)

Summary of 03 April 2017 response

(b) (4)

Reviewer's Assessment: The container closure integrity test is adequate. The detection level, while not ideal, is acceptable. (b) (4) However, the dye ingress method is still more sensitive than the microbial ingress method so no additional studies will be requested. Ideally, the leaks for vials and cartridges would be detected at the (b) (4) µm level. However, at this time the Agency does not have well-established scientific standards for container closure integrity testing and the provided data are consistent with current industry standards for both the vial and cartridge systems. The provided data would be acceptable until the Agency provides public guidance on this topic.

(b) (4)

50 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page