CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206538Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

Product Quality Microbiology Review

27 JAN 2015

NDA: 206538

Drug Product Name
Proprietary: Toujeo® SoloStar®
Non-proprietary: Insulin Glargine (rDNA origin) Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
25 APR 2014	25 APR 2014	28 APR 2014	29 APR 2014

Applicant/Sponsor
Name: Sanofi-Aventis U.S. LLC

Address: 55 Corporate Drive
Bridgewater, NJ 08807

Representative: Antonella Lozito
Telephone: 908-981-6997

Name of Reviewer: Neal J. Sweeney, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: 505 (b) (1) Original NDA

2. SUBMISSION PROVIDES FOR: Marketing of new drug product

3. MANUFACTURING SITE:

Sanofi-Aventis Deutschland GmbH
Brüningstraße 50
Industriepark Höchst
65926 Frankfurt am Main
Germany

Drug Establishment Registration #: 3003195501

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Multiple-dose insulin glargine [rDNA origin] (300 Units/mL), solution in 1.5 mL cartridges, for subcutaneous injection using the irreversibly integrated pen-injector.

5. METHOD(S) OF STERILIZATION:
(b) (4)

6. PHARMACOLOGICAL CATEGORY: Recombinant human insulin analog indicated to improve glycemic control in adults with diabetes mellitus.

B. SUPPORTING/RELATED DOCUMENTS:
Sanofi NDA 21-081 (LANTUS Insulin glargine [rDNA origin]).
NDA 21-081/S-047 (approved 5August 2010): (b) (4)
DMF (b) (4)
DMF (b) (4)

C. REMARKS:

(b) (4) are not included in the commercial cartridge/pen injection system.

File name: N206538R1.doc

Reference ID: 3713206

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for Approval.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product solution is (b) (4) filled into glass cartridges, which are irreversibly integrated in pen-injectors.

B. Brief Description of Microbiology Deficiencies – Based upon the information provided, no microbiology deficiencies were identified.

C. Contains Potential Precedent Decision(s)- ☐ Yes ☒ No

(If yes, provide a brief description and a reference to the page where the precedent is discussed in depth)

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O[3, 4, 5]	Severity of Effect (S)	Detect. (D)	Risk Priority Number[6] (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
Ster.	(b) (4)	10	9	5	5	225	Simulations and interventions conducted during media fills, Environmental monitoring
Endo		4	4	4	4	64	

(b) (4)

Reference ID: 3713206

(b) (4)

Reviewer's Note: (b) (4)

B. Final Risk Assessment -

(b) (4) Media fills include simulations, interventions and environmental monitoring. Formulation (b) (4) was validated by microbial retention validation studies. Additionally maximum (b) (4) hold time was validated, and container/closure integrity was demonstrated for the container/closure system. Therefore the applicant has mitigated the risk for drug product non-sterility.

IV. Administrative

A. Reviewer's Signature _____
Neal J. Sweeney, Ph.D.

B. Endorsement Block _____
John W. Metcalfe, Ph.D.

C. CC Block
N/A

Reference ID: 3713206

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE

The applicant referenced approved Sanofi NDA 21-081 (LANTUS Insulin glargine [rDNA origin]) and corresponding 2009/2010 Annual Report (SQ-0037, 14 Sept. 2010 submission) for drug substance information.

Microbial enumeration (TAMC and TYMC) and bacterial endotoxin testing are performed on a "batchwise" basis for insulin glargine drug substance, glycerol 85%, zinc (b) (4) and m-cresol. The following acceptance criteria were established for the drug substance and other components:

Table 1: Bioburden and Bacterial Endotoxins Acceptance Criteria for Drug Product Components

Starting material	TAMC [CFU]	TYMC [CFU]	Bacterial endotoxins [USP-EU]
Insulin glargine drug substance			(b) (4)
Glycerol 85%			
Zinc (b) (4)			
m-Cresol			

Table 1 was reproduced from applicant's Table 112 presented in Section 3.2.P.3.5, process-validation-2.pdf, page 98.

ADEQUATE

REVIEWER COMMENT – Microbiological quality acceptance criteria comply with those specified by USP (b) (4) for pharmaceutical use.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – The multiple-dose drug product contains (b) (4) solution of insulin glargine [rDNA origin] (300 Units/mL), in a 1.5 mL cartridge irreversibly integrated with a pen-injector.
- **Drug product composition** – Each 1 mL of drug product solution contains (b) (4) (300 Units) of insulin glargine, (b) (4) m-cresol (b) (4) (b) (4) Zinc (b) (4) and (b) (4) 85% glycerol (b) (4) in Water for Injection.
- **Description of container closure system** – The primary packaging consists of a 1.5 mL type I colorless glass cartridge (b) (4)

Reference ID: 3713206

[redacted] (b) (4) closed on one end with a [redacted] (b) (4) rubber stopper [redacted] (b) (4) and on the opposite end with a flanged aluminum cap [redacted] (b) (4) [redacted] The cartridge is irreversibly integrated into a disposable pen injector.

The design of the primary container components is schematically depicted in Figure 1 below:

Figure 1: Cartridge Container System

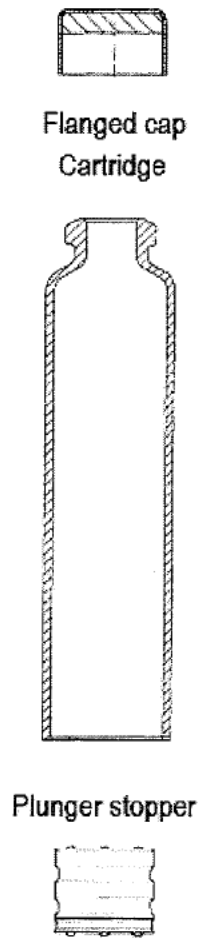

Figure 1 was reproduced in part from applicant's Table 1 presented in Section 3.2.P.7, container-closure-system.pdf, page 4.

The pen injector device provides a method of accurately injecting a selected dose of insulin through a single lumen hypodermic needle (not included). The pen injector consists of an irreversibly integrated 1.5 mL insulin cartridge which cannot be replaced, the cap, the cartridge holder and the

Reference ID: 3713206

dosing mechanism. The design of pen injector (with cap removed) is shown below in Figure 2:

Figure 2: Photo of Pen Injector with Cap Removed

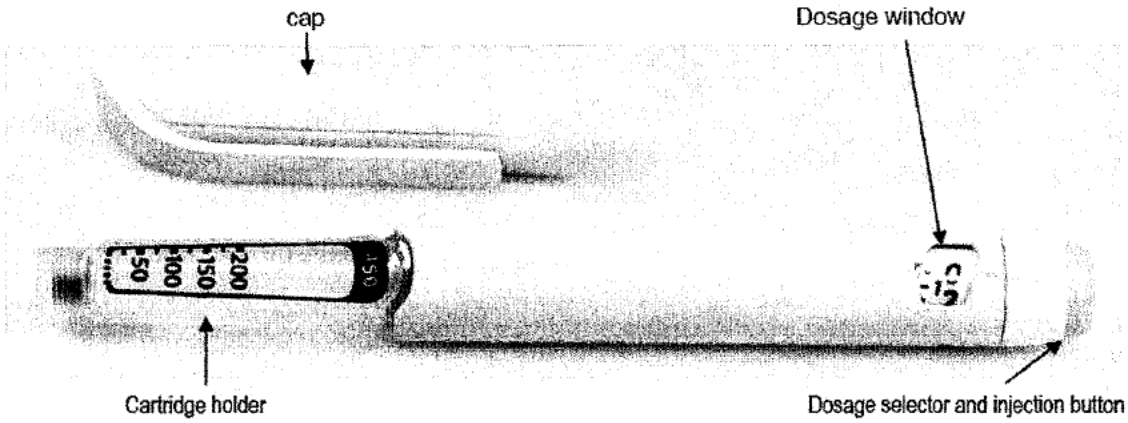

Figure was reproduced from applicant's Figure 1 presented in Section 3.2.P.7, description-and-composition-2.pdf, page 112.

The cartridge is positioned with the flanged cap end adjacent to the needle attachment, and the stopper end in contact with the pen dosage control mechanism.

The device is fully mechanical and does not contain electronics. When the insulin cartridge is empty the device must be discarded.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity -**
  Container/Closure integrity was validated by microbial ingress testing.
  (b) (4)

Reference ID: 3713206

- (b) (4)

(b) (4)

(b) (4)

- **Justification for not having a microbial limit specification for a non-sterile drug product** – N/A The drug product is sterile.

ADEQUATE

Reference ID: 3713206

REVIEWER COMMENT – Description of drug product and pharmaceutical development information were consistent with the FDA Guidances for Industry: (1) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, and (2) Q8(R2) Pharmaceutical Development.

P.3 Manufacture

P.3.1 Manufacturers

Drug product manufacture, packaging, release testing and stability testing will all be performed at the following cGMP facility:

Sanofi-Aventis Deutschland GmbH
Brüningstraße 50
Industriepark Höchst
65926 Frankfurt am Main
Germany

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4) **MANUFACTURING PROCESS (DRUG PRODUCT)**

- Building and facilities (floor plan, air quality, equipment locations) – Floor plans indicating the flow of materials, personnel and components, and room classifications of the rooms used for drug product manufacturing were provided. The drug product will be filled (b) (4) at the Sanofi-Aventis Deutschland GmbH facility. (b) (4)

The critical equipment used in manufacturing the drug product and corresponding room numbers are listed below in Table 3:

18 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Reference ID: 3713206

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

(b) (4) The drug product complies with the requirements of the note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev. 3).

The applicant referenced approved Sanofi NDA 21-081 (LANTUS Insulin glargine [rDNA origin]) and corresponding 2009/2010 Annual Report (SQ-0037, 14 Sept. 2010 submission) for drug substance information. .

R REGIONAL INFORMATION

R.1 Executed Batch Record

Executed batch records for batches 2F005 and 3F013.were provided for .

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT

The package insert states that unopened disposable prefilled pens should be stored in a refrigerator (2°C - 8°C), and opened-in-use units should be stored at room temperature for a maximum of (b) (4) days.

The multiple-dose disposable insulin pen injection system is for single patient use. Package insert instructions state that (1) the rubber seal must be wiped with an alcohol swab prior to needle attachment, (2) a new sterile needle must be attached to the pen before each injection, (3) needles should not be reused and (4) pen injectors should not be shared between patients. Additionally when the insulin cartridge is empty the device must be discarded.

Reviewer's Note: (b) (4) no (b) (4) data was provided to support the (b) (4) use period for opened-in-use units stored at room temperature. The Microbiology Reviewer recommends that the (b) (4) storage period specified in the package insert be changed to 28 days, and

Reference ID: 3713206

will participate in labeling discussions regarding the (b) (4) in-use time. The applicant's justification for the (b) (4) use period is based on (b) (4)

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

(none)

Reference ID: 3713206

Reviewer's Signature

Neal J. Sweeney -A

Digitally signed by Neal J. Sweeney -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300109587, cn=Neal J. Sweeney -A
Date: 2015.01.29 22:08:53 -05'00'

Neal J. Sweeney, Ph.D.

Endorsement Block

John W. Metcalfe -A

Digitally signed by John W. Metcalfe -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300198103, cn=John W. Metcalfe -A
Date: 2015.01.30 09:50:57 -05'00'

John W. Metcalfe, Ph.D.

Reference ID: 3713206

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 206538 **Applicant:** Sanofi-Aventis U.S. LLC **Letter Date:** 4/25/14

Drug Name: Insulin Glargine [rDNA origin] Injection **NDA Type:** 505(b)(1) Standard **Stamp Date:** 4/25/14

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		eCTD
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		(b) (4) filling in cartridges, and pen injector assembly. (3.2.P.3.3)
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		(b) (4) hold time, equipment and component (b) (4) and media fills. (3.2.P.3.5)
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	N/A
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		(b) (4)
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Sterility and endotoxin for release and stability (3.2.P.5.1), justification of endotoxin limit (3.2.P.5.6)
7	Has the applicant submitted the results of analytical method verification studies?	X		Sterility and endotoxin testing (3.2.P.5.3)
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	N/A	N/A	No product quality microbiology studies or information were requested during the 10/25/13 Pre-NDA meeting.
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?	N/A	N/A	Labeling indicates that the drug is not to be diluted or mixed with another insulin product.
10	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: (none)

Neal J. Sweeney, Ph.D., (Primary Reviewer) — 02 June 2014 Date

John W. Metcalfe, Ph.D., (Secondary Reviewer) — Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NEAL J SWEENEY
06/03/2014

JOHN W METCALFE
06/03/2014
I concur.