

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
206538Orig1s000

CHEMISTRY REVIEW(S)

NDA 206-538

Toujeo (insulin glargine U-300)

Insulin Glargine Injection 300 units/mL in 1.5 mL SoloStar® Disposable Prefilled Pen

Sanofi US Services Inc.

**Xavier Ysern, PhD
ONDQA/ DNDQA III/ Branch VII**

(Clinical Review Division: DMEP)

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Chemistry Review Data Sheet

1. **NDA:** 206-538
2. **Review #:** 1
3. **Review Date:** 08-Jan-2015
4. **Reviewer:** Xavier Ysern, PhD

5. Previous Documents:

<u>Previous Documents</u>	<u>Document Date</u>
--	

6. Submission(s) Being Reviewed:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
SND # 1 eCTD: 0000	25-Apr-2014 (Original)
SND # 2 eCTD: 0001	30-Apr-2014 (Proprietary Name)
SND # 8 eCTD: 0007	08-Oct-2014 (Response to CMC IR)

7. Name and Address of Applicant:

Name: Sanofi US Services Inc. (Sanofi)
Address: 55 Corporate Dr MS 55D 215A
Bridgewater, New Jersey 08807
United States
Representative: Antonella Lozito, Associate Director
Telephone: 908 981-6997
Fax: 908 981-7903
e-mail: antonella.lozito@sanofi.com

8. Drug Product Name/Code/Type:

- a) Proprietary Name: Toujeo (drug product)
b) Non-Proprietary Name: Insulin Glargine (drug substance)
c) Code Name: HOE901-U300
d) Chem. Type/Submission Priority: Chemical Type: 5 (New Formulation)/ Submission Priority: S

9. **Legal Basis For Submission:** 505(b)(1)

10. **Pharmacological Category:** Hormone. Long-acting human insulin analog indicated to improve glycemic control in adults with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

11. **Dosage Form:** Solution [for Injection]

12. **Strength/Potency:** 300 U/mL

13. **Route of Administration:** Subcutaneous Injection

14. **Rx/OTC Dispensed:** Rx

15. **SPOTS (Special Products On-Line Tracking System):** SPOTS product

16. Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:

Insulin glargine; 21A-Gly-30Ba-Arg-30Bb-Arg *human* Insulin C₂₆₇H₄₀₄N₇₂O₇₈S₆ MW = 6063



17. Related/Supporting Documents:

A. DMFs:

DMF #	Holder	Item Referenced	Code ^a	Status ^b	Date Review Completed	LOA Date
Type III		(b) (4)	4	Adequate		09-Oct-2013
			4	Adequate		08-Oct-2013
			4	Adequate		10-Jul-2013
			4	Adequate		08-Oct-2013
			4	Adequate		14-Feb-2013
Type V		(b) (4)				09-Oct-2013

^a Action codes for DMF Table:

1- DMF Reviewed.

2- Type 1 DMF;

5- Authority to reference not granted;

Other codes indicate why the DMF was not reviewed, as follows:

3- Reviewed previously and no revision since last review;

6- DMF not available;

4- Sufficient information in application;

7- Other (explain under "Comments")

^b Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Document	Application #	Description
IND	112400	Sanofi's HOE901-U300 insulin glargine [rDNA origin] injection
NDA	021081	Sanofi's LANTUS; insulin glargine [rDNA origin]

18. Status:

Consults	Recommendation	Date	Reviewer
EES	Pending		
Pharm/Tox	--		
Biopharm	N.A (No Biopharm review needed – as no biowaiver involved)	20-Apr-2014	Tapash Gosh, PhD
DMEPA	"Toujeo SoloStar" tradename Acceptable	03-Aug-2014	Kellie Taylor, PharmD, MPH
Methods Validation	Revalidation by Agency laboratories will not be requested		Part of this review
OPDRA			
EA	Satisfactory		Part of this review
Microbiology	Pending in Panorama		

*The Executive Summary***I. Recommendations****A. Recommendation and Conclusion on Approvability**

This application can be approved from the CMC perspective. At this time, the final Quality recommendation is pending the recommendations from CDRH for the acceptability of the [Toujeo] SoloStar® prefilled pen injector (b)(4). In addition, an overall recommendation for the commercial manufacturing and testing facilities listed in the NDA is pending in Panorama.

- Shelf life prior to first use of the drug product: 30 months at the recommended storage condition: store between 2 °C and 8 °C protected from light, do not freeze.
- In-use period: (b)(4) days stored at room temperature (up to 30 °C) protected from light.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

- **Drug Substance** [Insulin Glargine (HOE901)]

The drug substance, Sanofi's Insulin glargine [rDNA origin] (HOE901), is a human insulin analog produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12) as the production organism. Insulin glargine differs from human insulin by having a substitution of glycine for asparagine at N21 (Asn^{A21}→Gly) and two arginines added to the carboxy terminal of B chain (Arg^{B31}-Arg^{B32} tag). (b)(4)

The drug substance is the same than the one described by the Sponsor in their approved NDA 21-081(Lantus®). All CMC information is referred by cross-reference to the drug substance section of Sanofi's NDA 21-081. Due to the usage of prokaryotic cells no viral contamination is expected.

- **Drug Product** [Insulin Glargine 300 U/mL (HOE901-U300)]

HOE901-U300 has the same composition as the current commercial formulation of insulin glargine 100 U/mL, with adjustment of 3-times the amount of active pharmaceutical ingredient (300 U/mL insulin glargine) and corresponding zinc content (b)(4)

The manufacturing process (b)(4) correspond to those approved for the marketed insulin glargine solution for injection 100 U/mL process (NDA 21-081). The manufacturing procedure is based on (b)(4)

(b)(4) Cartridges are finally assembled into disposable delivery pen devices (1.5 mL SoloStar®)

Drug product specifications are similar to those for approved insulin glargine solution for injection 100 U/mL (NDA 21-081) with expected acceptance criteria modified for Assay and Zinc content. Tests and acceptance criteria are typical for parenteral protein solutions.

The CMC review team performed risk assessment on the factors that can impact product quality and concluded that the potential risk to overall product quality is acceptable (low risk, see table below for an executive summary of the risk assessment).

Executive Summary Risk Assessment						
From Initial Quality Assessment			Review Assessment			
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation approach	Risk evaluation Not acceptable or acceptable	Life cycle considerations/ comments	
Assay (protein)	Formulation Container closure Raw materials Process parameters Scale/ equipment	L	(b) (4)	Acceptable (Low risk)	Potency (300 U/mL) is based on mass based assay. 3.6378 mg = 100 U	
Assay (b) (4)	Site	M		Acceptable (Low risk)		
Product-related size variants – Soluble aggregates, HMWP)		H		Acceptable (Low risk)	HMWP has the potential to be immunogenic	
Other product-related variants		H		Acceptable (Low risk)		
Sterility		H		Acceptable (Low risk)		
Endotoxin		L				
Appearance		L		Existing process control and stability data support the notion that product appearance is maintained during storage and handling	Acceptable (Low risk)	
Uniformity of dose		L		Dose accuracy is part of specification for pen injector	Acceptable (Low risk)	
Particulate matter		M	Existing process control and component control assures the quality. Tested per USP <788>	Acceptable (Low risk)		
Leachables/ extractables		L	Components used in manufacturing are appropriately characterized.	Acceptable (Low risk)		
pH		L	Adequate (b) (4) to control pH.	Acceptable (Low risk)		

The drug product Toujeo® is supplied as solution for injection 300 unites per mL (U-300) in 1.5 mL SoloStar® disposable prefilled pen. The suitability of the packaging materials (cartridges and closures) was substantiated by the extractables and leachables studies and the results of the stability tests.

Based on the provided long-term, accelerated, stress, in-use, and photostability stability data, and their statistical evaluation, the proposed **30 months shelf life** for the drug product (shelf life storage directions: prior first use store between 2 °C and 8 °C protected from light, do not freeze), and the proposed **in-use period of (b) (4) days** (in-use storage directions: store at room temperature (up to 30 °C) protected from light), are both fully supported by the data and are granted.

B. Description of How the Drug Product is Intended to be Used

The drug product Toujeo® is insulin glargine HOE901 supplied as a sterile, non-pyrogen, clear, colorless, solution for injection available in the 300 U/mL formulation (HOE901-U300) in 1.5 mL SoloStar® disposable prefilled pen. Toujeo® is indicated for the treatment of diabetes mellitus in adults. Toujeo® is to be injected subcutaneously once daily.

C. Basis for Approvability or Not-Approval Recommendation

The information on the quality of the drug substance (reference to insulin glargine HOE901 drug substance under approved NDA 21-081) and drug product, including additional information requested by the Agency, has been adequately provided. Based on the evaluation of the submitted information, from a CMC perspective the NDA is recommended for Approval. There are no pending CMC issues.

At this time, the Quality final recommendation is pending the recommendations from CDRH for the acceptability of the 1.5 mL SoloStar® disposable (b) (4) injector for the proposed use. In addition, no overall recommendation for the commercial manufacturing and testing facilities listed in the NDA has been issued in Panorama.

III. Administrative

- | | | |
|--------------------------------|--------------------------|---|
| A. Reviewer's Signature | Xavier Ysern, PhD | Chemist/ CDER/ ONDQA/ DNDQA III/ Branch VII |
| B. Endorsement Block | Danae Christodoulou, PhD | Acting Branch Chief/ ONDQA/ DNDQA III/ Branch VII |
| C. CC Block | Callie Cappell Lynch | Project Manager/ CDER/ OND/ ODE II/ DMEP |

P Drug Product [Toujeo® SoloStar® (insulin glargine U-300)]**P.1 Description and Composition of the Drug Product***Satisfactory*

Insulin glargine is available as solution for injection containing 10.91 mg/mL insulin glargine [equivalent to 300 U (units) of insulin glargine] in 1.5 mL cartridges. The composition of the insulin glargine solution for injection is given in Table P.1-1.

Table P.1- 1. Composition of insulin glargine solution for injection 300 U/mL in cartridges

Components ^a	Reference ^b	Function	Percentage (%)	Per mL (mg/mL)	mg Per unit (1.5 mL cartridge)
Insulin glargine ^c	In-house	Drug substance	1.1	10.91 [300 U]	(b) (4) [450 U]
Metacresol ^d	Ph. Eur., USP				(b) (4)
Zinc (b) (4)	Ph. Eur., USP				(b) (4)
Glycerol (85 per cent)	Ph. Eur.				
Sodium hydroxide	Ph. Eur., NF				
Hydrochloric acid, concentrated	Ph. Eur., NF				
Water for injection	Ph. Eur., USP				
Nitrogen	Ph. Eur., NF				

^a Components are listed according to their Pharmacopeial names. If more than one monograph exists, other names are given in brackets, along with the compendial origin.

^b Reference is made to the current edition of the Pharmacopoeia.

^c [equivalent to U (units) of insulin glargine], 1 U is equivalent to 36.378 µg insulin glargine.

^d For metacresol, the common chemical name "m-cresol" is also used within this document.

^e Composition gives total zinc (b) (4) from drug substance and from the manufacturing of the drug product.

Comment: The composition of insulin glargine solution for injection 300 U/mL is similar to that of approved insulin glargine solution for injection 100 U/mL (Lantus NDA 21-081). However, insulin glargine solution for injection 300 U/mL contains insulin glargine and zinc (b) (4) a three-fold amount compared to the commercially available drug product insulin glargine solution for injection 100 U/mL.

The primary packaging material for insulin glargine solution for injection in 1.5 mL cartridges consists of clear and colorless glass cartridges (glass type I) closed on one end with plunger stoppers (b) (4). The cartridge is irreversibly integrated into a disposable pen injector (U300 pen injector shown in Figure P.1-1). The drug product is to be administered subcutaneously.



Figure P.1-1. U300 pen injector with cap removed

The U300 pen injector is a device that provides a method of accurately injecting a selected dose of insulin through a single lumen hypodermic needle. The device has to be discarded when the insulin container is empty. The pen injector consists of the following components: an irreversibly integrated 1.5 mL insulin cartridge which cannot be replaced, the cap, the cartridge holder and the dosing mechanism. The device is operated fully mechanically and does not contain electronics. The pen injector contains the 1.5 mL cartridge which serves as primary packaging for the insulin glargine solution for injection. The injection system provides a maximum of 80 units in one dosing. The total content of the cartridge is 450 insulin units. For the convenience of the user, for safety and to protect the cartridge, a pen cap is part of the pen system. Pen needles are not included in the commercial pen injection system and therefore are not part of this submission.

Comment: The pen injector, as a device, will be reviewed by the CDRH review team.

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

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling and Package Insert *Pending*

The review of the Container and Carton Labeling and of the Package insert is still ongoing (multidisciplinary review). Some initial assessments are mentioned below (to be discussed during labeling internal meetings and potentially subjected to change).

· Labeling

Draft carton container labels for insulin glargine U300 1.5 mL SoloStar® injection containing either 3 or 5 pen delivery devices (SoloStar®) have been submitted, as well the individual SoloStar® container label. As representatives of the labeling the carton containing 3 prefilled pens is shown and the SoloStar (individual prefilled pen) are shown in Figures II.A-1 and II.A-2.

(b) (4)



(b) (4)

**Package insert**

Although the Physician Package Insert (PI) is still under review (several disciplines involved), the three sections of the PI that rely mainly in Chemistry input, “Dosage Forms and Strengths”, “Description”, “How Supplied/Storage and Handling”, appear adequately described.

3. DOSAGE FORMS AND STRENGTHS *Adequate - No change recommended*

The following information provided under “Section 3. Dosage Forms and Strengths” is consistent with information provided under drug product section:

(b) (4)

**11. DESCRIPTION** *Adequate - No change recommended*

(b) (4)



16. HOW SUPPLIED/STORAGE AND HANDLING *Adequate - No change recommended*

16.1 How Supplied

(b) (4)

Dosage Unit/Strength	Package size	NDC #
1.5 mL SoloStar [®] disposable prefilled pen 300 Units/mL	package of 3	x
1.5 mL SoloStar [®] disposable prefilled pen 300 Units/mL	Pack of 5	x

Needles are not included in the packs of TRADENAME SoloStar[®] disposable prefilled pen. BD Ultra-Fine™ needles‡ to be used in conjunction with TRADENAME SoloStar[®] disposable prefilled pen are sold separately and are manufactured by BD.

Section 16.2 Storage:

TRADENAME SoloStar[®] disposable prefilled pen should not be stored in the freezer and should not be allowed to freeze. Discard TRADENAME SoloStar[®] disposable prefilled pen if it has been frozen.

Unopened SoloStar[®] disposable prefilled pen:

Unopened TRADENAME SoloStar[®] disposable prefilled pen should be stored in a refrigerator, 36 F – 46 F (2 C – 8 C). Discard after the expiration date.

Open (In-Use) SoloStar[®] disposable prefilled pen:

The opened (in-use) TRADENAME SoloStar[®] disposable prefilled pen should NOT be refrigerated but should be kept at room temperature (below 86 F [30 C]) away from direct heat and light. The opened (in-use) TRADENAME SoloStar[®] disposable prefilled pen must be discarded (b) (4) days after being opened.

These storage conditions are summarized in the following table:

	Not in-use (unopened)	In-use (opened)
	Refrigerated	(See Temperature Below)
1.5 mL SoloStar [®] disposable prefilled pen	Until expiration date	(b) (4) days Room temperature only (Do not refrigerate)

16.3 Preparation and handling

Parenteral drug products should be inspected visually prior to administration whenever the solution and the container permit. TRADENAME must only be used if the solution is clear and colorless with no particles visible.

Mixing and diluting: TRADENAME must NOT be diluted or mixed with any other insulin or solution (b) (4)

If TRADENAME SoloStar[®] disposable prefilled pen, malfunctions, TRADENAME must not be drawn from the TRADENAME pen into any syringe and injected (b) (4)

Needles must not be re-used. A new sterile needle must be attached before each injection. Re-use of needles increases the risk of locked needles which may cause underdosing or overdosing. Using a new sterile needle for each injection also minimizes the risk of contamination and infection (b) (4)

LANTUS and TRADENAME are registered trademarks of sanofi-aventis U.S. LLC.

‡The brands listed are the registered trademarks of their respective owners and are not trademarks of sanofi-aventis U.S. LLC.

Comment: As previously mentioned, the review of the labelling submissions is multidisciplinary and is still ongoing. Some of the initial assessments could be subjected to change. "Toujeo"[SoloStar] is the current accepted tradename for the proposed drug product.

B. Environmental Assessment or Claim of Categorical Exclusion *Satisfactory*

The Applicant is claiming Categorical Exclusion from preparation of an Environmental Assessment for a New Drug Application for insulin glargine, solution for subcutaneous injection provided Toujeo SoloStar 300 IU/mL. Compliance with the categorical exclusion criteria is made pursuant to 21 CFR §25.31 (b): “The classes of actions listed in this section are categorically excluded and, therefore, ordinarily do not require the preparation of an EA or an EIS: Action on an NDA, or a supplement to such applications, if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.”

A Categorical Exclusion is claimed since approval of this action for insulin glargine, solution for subcutaneous injection (provided in two strengths: LANTUS® 100 IU/mL and Toujeo SoloStar 300 IU/mL) would result in an insulin glargine concentration from sales of all insulin glargine products in the aquatic environment below 1 part per billion. Extraordinary circumstances per 21 CFR §25.21 are stated not to exist since no adverse or other significant effect on the quality of the human environment is predicted from this submission.

Comment: In general the use of a protein that is administered (e.g. subcutaneous, intravenously) is not expected to result in any environmental exposure to the intact protein due to physiological degradation. Categorical exclusion requirements are met and no adverse or other significant effect on the quality of the human environment is predicted from this NDA submission. Consequently, the Applicant is exempt of the preparation of an Environmental Assessment.

C. Establishment Inspections *Satisfactory*

The sites involved in the manufacture, testing and packaging of the drug substance (TableS.2.1-1) and drug product (Table P.3.1-1) were requested for inspection. The overall evaluation of these sites by the Office of Compliance is still pending (Panorama).

Comments to the Applicant (Not Approvability)

To include in the Action Letter as a recommendation:

The acceptance criteria for drug product specification for related substances are limited to current test method capabilities. Improvement of the HPLC test method (in particular LOQ) would allow the inclusion of known identified impurities as part of the DP specification. We expect that you will continue efforts to improve your analytical methodology and to provide updated specifications for identified impurities post-approval.

Xavier J.
Ysern -S

Digitally signed by Xavier J. Ysern
-S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300
065477, cn=Xavier J. Ysern -S
Date: 2015.01.22 11:35:34 -05'00'

Danae D.
Christodoulou -A

Digitally signed by Danae D. Christodoulou -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300132624,
cn=Danae D. Christodoulou -A
Date: 2015.01.22 12:41:35 -05'00'

ONDQA Initial Quality Assessment (IQA) and Filing Review for new NDA

1. NEW DRUG APPLICATION NUMBER: 206538
2. DATES AND GOALS:

Letter Date: 4/25/2014	Submission Received Date : 4/25/2014
PDUFA Goal Date: 2/25/2015	NDA is not part of "The Program"

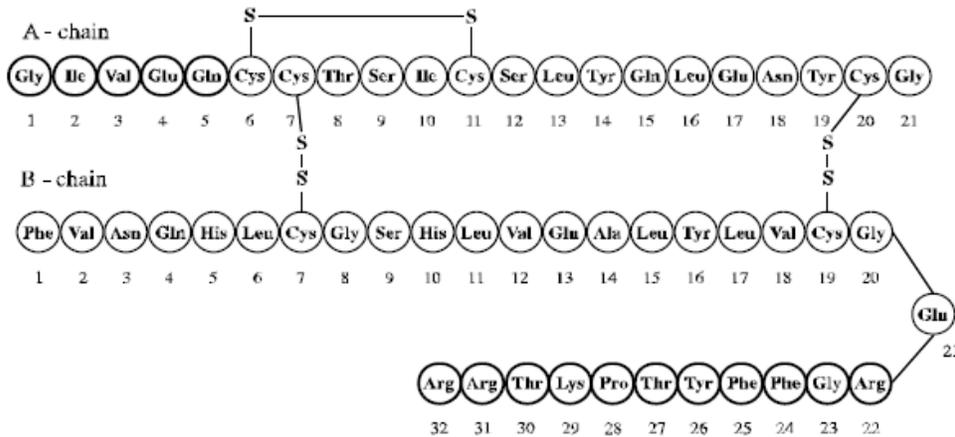
3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	None proposed
Established Name (USAN):	Insulin glargine [rDNA origin]
Dosage Form:	Solution
Route of Administration	Subcutaneous injection
Strength/Potency	300 Units/mL
Rx/OTC Dispensed:	Rx

4. INDICATION: Improvement of glycemic control in adults with diabetes

5. DRUG SUBSTANCE STRUCTURAL FORMULA:

Insulin glargine [rDNA origin] is a human insulin analog produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12) as the production organism. Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines remain at the C-terminus of the B-chain. Chemically, insulin glargine is 21^A-Gly-31^B-32^B-Di-Arg -human insulin and has the empirical formula C₂₆₇H₄₀₄N₇₂O₇₈S₆ and a molecular weight of 6063. Insulin glargine has the following structural formula:



6. NAME OF APPLICANT (as indicated on Form 356h): Sanofi-Aventis

7. SUBMISSION PROPERTIES:

Review Priority (select one)	Standard
Submission Classification:	5
Application Type:	505(b)(1)
Breakthrough Therapy	No
Clinical Division	Division of Metabolism and Endocrinology Products CMC Lead: Suong (Su) Tran

8. CONSULTS:

	YES	NO	COMMENTS:
Biometrics		x	
Establishment Evaluation Request (EER)	x		To be sent by the ONDQA PM
Pharmacology/Toxicology		x	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDA**

Methods Validation			To be determined by Primary Reviewer
Environmental Assessment			Claim of categorical exclusion to be reviewed by Primary Reviewer
CDRH	x		Review of pen injector
Other			

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes
Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? No

Biopharmaceutics: not applicable

From: [Ghosh, Tapash](#)
To: [Tran, Suong T](#); [Christodoulou, Danae D](#); [Kumar, Privanka](#)
Cc: [Ghosh, Tapash](#); [Lostritto, Richard T](#)
Subject: RE: please send assignments FW: New NDA 206538 - insulin glargine U300
Date: Monday, April 28, 2014 9:07:46 AM

No biopharm review needed – as no biowaiver involved. Thanks,

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes
Are there potential Microbiology review issues to be forwarded to the Applicant with the 74-Day letter? See Microbiology Filing Review in DARRTS for details and for any potential Microbiology review issues

**CMC Summary:
Critical Issues and Complexities**

Summary of Critical CMC Issues Previously Discussed with the Applicant:			
None			
Critical CMC Issues or Complexities			
None			
Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	No	No	No

Is a team review recommended?		
Yes	No	Suggested expertise for team
x		CMC (drug product) Microbiology (sterile product)

Summary or Highlights of the Application

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDA**

- This new NDA is for a higher concentration of the approved Lantus product of NDA 21081. Both NDAs have the same applicant. The approved product is 100 Units/mL, and the new product is 300 Units/mL. The two products share the same drug substance and the same composition for excipients (qualitative and quantitative) and only differ in the amount of the drug substance and zinc (b) (4) in the formulation.
- The drug product is packaged in a type I glass cartridge with a rubber stopper and a rubber plunger. This primary container closure system containing 1.5 mL of product (or 450 Units) is pre-assembled into a pen injector. The complete delivery system will be marketed as multi-dose and disposable.
- All aspects of the pen injector (design, functionality, manufacture, dose accuracy, etc.) will be reviewed by CDRH (consult request to be sent by DMEP).

Drug Substance

Reference is made by the applicant to the approved NDA 21081 (same applicant) for all CMC information on the drug substance.

Drug Product

Composition. A copy of the product composition is included in Attachment 1 of this review. As already mentioned, compared to the approved 100 Units/mL product, this new 300 Units/mL product has the same composition for excipients (qualitative and quantitative) and only differs in the amount of the drug substance and zinc (b) (4) in the formulation. The commercial formulation is the same as the formulation used in clinical studies. The fill volume of the commercial product is 1.5 mL/cartridge, while the volume of the clinical product was 3 mL/cartridge.

- 300 Units/mL is equivalent to 10.91 mg/mL of insulin glargine, which corresponds to the approved conversion factor of 1 Unit = 0.0361 mg in NDA 21081.
- Metacresol. Each product cartridge will be for multiple doses. (b) (4)

Manufacture. The manufacturing process of the drug product is based on the approved process for the 100 Units/mL product and is standard for this dosage form (sterile solution). (b) (4)

(b) (4)
Batches used in the clinical studies were manufactured at the commercial site, by the commercial process (b) (4) and at production scale. All sterility assurance information will be evaluated by the Microbiology reviewer. The NDA includes results from the process validation of three consecutive production scale batches.

Drug product specification. A copy of the drug product specification is included in Attachment 2 of this review. It includes standard attributes for an injectable solution product and is based on the approved drug product specification for the 100 Units/mL product. The specification includes testing for sub-visible particles, antimicrobial identity and assay, zinc assay, high molecular weight proteins, among other standard attributes. Proposed acceptance criteria will be evaluated by the primary reviewer. Per ICH Q6B, all acceptance criteria for impurities/degradants will be finalized based on actual levels present in clinical and nonclinical batches.

Container closure system. The list of Type III DMFs is included in the Filing Checklist of this review. The drug product is packaged in a USP Type I glass cartridge, sealed with a rubber disc and a rubber plunger. The rubber components are stated to comply with USP <381>, <87> and <88>. A report on the extractables and leachables is provided in the NDA, to be reviewed in

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDA**

consultation with the toxicology reviewer. The container closure integrity information and the sterility assurance of the components will be evaluated by the Microbiology reviewer.

Stability. The primary stability batches were manufactured at the commercial site, commercial scale, and packaged with the commercial container closure system. The batches include 3 batches of “naked” cartridges (without pen injectors) and 2 batches of pre-assembled pens. The NDA includes 18-month long term (2-8 °C) data for the “naked cartridges” and 12-month long term data for the pre-assembled pens, as well as 6-month accelerated data (25 °C). Other data are: thermal stress (b) (4) photostability, temperature cycling, and in-use (up to (b) (4) days at 30 °C). The reviewer will consider all available data and determine a proposed expiry based on actual data (no extrapolation) per ICH Q5C.

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a potential filing issue or a potential review issue.				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.	x		

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	Parameter	Yes	No	Comment
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		

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	Parameter	Yes	No	Comment
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	x		

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D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?			Referencing quality information in approved NDA 21081
13.	Does the section contain identification and controls of critical steps and intermediates of the DS			Referencing quality information in approved NDA 21081
14.	Does the section contain information regarding the characterization of the DS?			Referencing quality information in approved NDA 21081
15.	Does the section contain controls for the DS?			Referencing quality information in approved NDA 21081
16.	Has stability data and analysis been provided for the drug substance?			Referencing quality information in approved NDA 21081
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	

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E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	x		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment

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30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	x		
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H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED (b) (4)	LOA DATE
	III			14-FEB-2013
	III			10-JUL-2010
	III			09-OCT-2013
	III			09-OCT-2013
	III			08-OCT-2013

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

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Appendix 1. Composition of Drug Product

Table 1 - Composition of insulin glargine solution for injection 300 U/mL in cartridges

Components ^a	Composition			Function	Reference to standards ^b
	Percentage [%]	Per mL [mg]	Per unit (1.5 mL cartridge) [mg]		
Insulin glargine [equivalent to U (units) of insulin glargine]	1.1	10.91 [300]	16.37 [450]	Drug substance	In-house
Metacresol ^c	(b) (4)				Ph. Eur., USP
Zinc (b) (4)					Ph. Eur., USP
Glycerol (85 per cent)					Ph. Eur.
Sodium hydroxide					Ph. Eur., NF
(b) (4)					Ph. Eur., NF
[Hydrochloric acid]					NF
Water for injection					Ph. Eur., USP
(b) (4)					Ph. Eur., NF

^a Components are listed according to their pharmacopoeial names. If more than one monograph exists, other names are given in brackets, along with the compendial origin.

^b Reference is made to the current edition of the Pharmacopoeia.

^c For metacresol, the common chemical name "m-cresol" is also used within this document.

^d Composition gives total zinc (b) (4) from drug substance and from the manufacturing of the drug product.

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Appendix 2. Drug Product Specification

Table 20 - Specifications for insulin glargine solution for injection 300 U/mL

Test	Analytical procedure	Acceptance criteria
Appearance		
- Clarity	Visual Ph. Eur.	Not more opalescent than reference suspension I (Ph.Eur.)
- Color	Visual Ph. Eur.	Colorless to almost colorless, not more colored than reference solution B9 (Ph.Eur.)
Identification insulin glargine	HPLC	Retention time of sample corresponds to retention time of reference (b) (4)
Identification insulin glargine	HPSEC	Retention time of sample corresponds to retention time of reference (b) (4)
Identification m-cresol	HPLC	Retention time of sample corresponds to retention time of reference (b) (4)
Assay	HPLC	(b) (4)
Related impurities/degradation products	HPLC	(b) (4)
- Largest single related impurity/degradation product		
- Sum of related impurities/degradation products		
High molecular weight proteins	HPSEC	
pH (potentiometry)	Ph. Eur. / USP	Complies
Sterility	Ph. Eur. / USP	
Bacterial endotoxins	Ph. Eur. / USP	(b) (4)
Particulate matter (visible particles)	Ph. Eur.	Clear and practically free from particles
Particulate matter (subvisible particles)	Ph. Eur. / USP	(b) (4)
Number of particles per container (b) (4)		
Number of particles per container (b) (4)		
(b) (4)		
- m-cresol	HPLC	(b) (4)
Assay zinc (AAS)	Ph. Eur.	
Extractable volume	Ph. Eur. / USP	
(b) (4)		

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

/s/

SUONG T TRAN
06/02/2014

DANAE D CHRISTODOULOU
06/02/2014