

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208673Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # NDA 208673
Product Name: Soliqua 100/33 (insulin glargine and lixisenatide) injection, 100 units and 33 mcg per mL

PMC #1 Description: Stability analysis to assess maintenance of the essential performance requirements of the final finished combination product (i.e. dose accuracy, dispense force, etc.) through the intended expiration date of 18 months using primary registration stability batches.

PMC Schedule Milestones:	Final Protocol Submission:	n/a
	Study/Trial Completion:	n/a
	Final Report Submission:	01/30/2018
	Other:	n/a

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
- ☒ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

2. Describe the particular review issue and the goal of the study.

The Sponsor has not provided the results of essential performance requirement testing up to the labeled date of expiry for the combination product after real-time aging. The goal of the study is to ensure that the device maintains its essential performance requirements up to the labeled date of expiry after real-time aging.

3. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☒ Other

Describe the agreed-upon study:

The Sponsor has committed to testing the essential performance requirements of the device (i.e. dose accuracy, dispense force, etc.) up to the labeled date of expiry during the primary stability real-time aging studies to ensure that the combination product maintains its essential performance requirements up to the labeled date of expiry. The Sponsor agreed to submit the results of this testing to the NDA annual reports.

4. To be completed by ONDQA/OBP Manager:

- ☒ Does the study meet criteria for PMCs?
- ☒ Are the objectives clear from the description of the PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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/s/

JENNIFER R PIPPINS
11/21/2016

**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: November 15, 2016

To: Jean-Marc Guettier, MD
Director
Division of Metabolism and Endocrinology Products (DMEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Aman Sarai, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Ankur Kalola, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)

Drug Name (established name): SOLIQUA 100/33 (insulin glargine and lixisenatide injection)

Dosage Form and Route: Injection, for subcutaneous use

Application Type/Number: NDA 208673

Applicant: Sanofi-Aventis U.S. LLC

1 INTRODUCTION

On December 21, 2015, Sanofi-Aventis U.S. LLC submitted for the Agency's review an original New Drug Application (NDA) for insulin glargine/lixisenatide combination. The insulin glargine/lixisenatide combination is a fixed ratio combination product of a long-acting human insulin analog together with a glucagon like peptide-1 receptor agonist. The proposed indication for insulin glargine/lixisenatide fixed ratio combination is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment using both insulin glargine and lixisenatide is appropriate.

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 Metabolism and Endocrinology Products (DMEP) on December 28, 2015 and December 24, 2015, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instruction for Use (IFUs) for SOLIQUA 100/33 (insulin glargine and lixisenatide 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 October 6, 2016.

2 MATERIAL REVIEWED

- Draft SOLIQUA 100/33 (insulin glargine and lixisenatide injection) MG and IFU, received on December 21, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 8, 2016.
- Draft SOLIQUA 100/33 (insulin glargine and lixisenatide injection) Prescribing Information (PI) received on December 21, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 8, 2016.
- Approved ADLYXIN (lixisenatide) comparator labeling dated July 27, 2016.
- Approved TOUJEO (insulin glargine [rDNA origin] injection) comparator labeling dated February 25, 2015.

3 REVIEW METHODS

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 MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG 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 MG and IFU is 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 MG and IFU.

Please let us know if you have any questions.

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/s/

AMANPREET K SARAI
11/15/2016

MARCIA B WILLIAMS
11/15/2016

ANKUR S KALOLA
11/15/2016

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

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

Memorandum

Date: November 10, 2016

To: Martin White, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Request

NDA 208673 SOLIQUA™ 100/33 (insulin glargine and lixisenatide injection), for subcutaneous use

On December 24, 2015 OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI), Medication Guide, Instructions for Use (IFU), and Carton and Container labeling for Soliqua 100/33. OPDP's comments on the proposed draft PI and Carton and Container labeling are based on the versions sent via email by Martin White on November 8, 2016.

OPDP's comments on the PI are provided directly on the marked version below. We have no comments on the Carton and Container labeling at this time.

Additionally, OPDP will work collaboratively with DMPP to provide comments on the Medication Guide and IFU under separate cover.

Thank you for the opportunity to comment on these materials. If you have any questions, please contact Ankur Kalola at 301-796-4530 or Ankur.Kalola@fda.hhs.gov.

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/s/

ANKUR S KALOLA
11/10/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
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:	November 7, 2016
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208673
Product Name and Strength:	Soliqua 100/33 (insulin glargine and lixisenatide), injection, 33 units insulin glargine and 99 mcg lixisenatide per 3 mL pen (100 units insulin glargine and 33 mcg lixisenatide per mL)
Submission Date:	November 1, 2016
Applicant/Sponsor Name:	Sanofi-Aventis
OSE RCM #:	2015-2775-2
DMEPA Primary Reviewer:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader (Acting):	Hina Mehta, PharmD

1 PURPOSE OF MEMO

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container label, carton labeling, and medication guide for Soliqua 100/33 (Appendix A) to determine if it is 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 CONCLUSION

The revised container label, carton labeling, and medication guide for Soliqua 100/33 is unacceptable from a medication error perspective. This review identified deficiencies in the medication guide and we provide recommendations in Section 3. In addition, we identified

^a Conrad A. Review of Revised Label and Labeling Memorandum for Soliqua 100/33 (NDA 208673). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Oct 6. 9 p. OSE RCM No.: 2015-2775-1.

deficiencies in the container label and carton labeling and recommendations are provided in Section 4.

3 RECOMMENDATIONS FOR THE DIVISION

A. Medication Guide

1. Revise the title to correspond with the name approved for use on the final pen label and carton labeling for consistency across all product labeling noted below.

Soliqua 100/33 (insulin glargine and lixisenatide injection)
for subcutaneous use

4 RECOMMENDATIONS FOR SANOFI

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

A. Carton Labeling

1. Revise the presentation of the established name to include parenthesis as follows for consistency with other product labeling: "(insulin glargine and lixisenatide injection)".
2. Revise the statement "(b) (4)" as follows to remove the "(b) (4)" statement for improved clarity: "100 units/mL and 33 mcg/mL".

B. Container Label

1. Revise the presentation of the established name to include parenthesis as follows for consistency with other product labeling: "(insulin glargine and lixisenatide injection)".
2. Revise the statement "(b) (4)" as follows to remove the "(b) (4)" statement for improved clarity: "100 units/mL and 33 mcg/mL".

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/s/

ARIANE O CONRAD
11/07/2016

HINA S MEHTA
11/08/2016

**GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM**



ICC 1600655 / NDA 208673

Date: October 31, 2016
To: Martin White, RPM
Division of Metabolism and Endocrinology Products (DMEP),
Office of Drug Evaluation I (ODEI),
Office of New Drugs (OND),
Center for Drug Evaluation and Research (CDER)

From: John McMichael
General Hospital Devices Branch (GHDB),
Division of Anesthesiology, General Hospital, Respiratory,
Infection Control, & Dental Devices (DAGRID),
Office of Device Evaluation (ODE),
Center for Devices and Radiological Health (CDRH)

Through: CDR Alan Stevens, Branch Chief
General Hospital Devices Branch (GHDB),
Division of Anesthesiology, General Hospital, Respiratory,
Infection Control, & Dental Devices (DAGRID),
Office of Device Evaluation (ODE),
Center for Devices and Radiological Health (CDRH)

Subject: Sanofi has developed a pen-injector to insulin glargine and lixisenatide as a combination product and CDER has consulted CDRH to review the device constituent parts of the combination product for this new NDA.

Applicant	Sanofi-Aventis LLC
Indication for Use	An adjunct to diet and exercise to improve glycemic control in the treatment of adults with type 2 diabetes mellitus.
Drug / Biologic Constituent	LixiLan (Insulin glargine and 33 microgram/milliliter lixisenatide)
Device Constituent	Pen-injector and cartridge for 'Pen C'

Recommendation:

Device Constituent Parts of Combination Product are Approvable with (1) Post-Market Commitment.

Post-Market Commitment:

The Sponsor has committed to performing ongoing stability analysis to assess maintenance of the essential performance requirements of the final finished combination product through the intended expiration date of (b) (4) months using primary registration stability batches. The sponsor should submit evidence of completion of these activities to NDA annual reports

Digital Signature Concurrence Table		
Reviewer Sign-Off	John C. McMichael -S	Date: 2016.10.31 15:03:15 -04'00'
Branch Sign-Off	Alan M. Stevens -S	Alan M. Stevens -S 2016.10.31 15:40:53 -04'00'

I. Review Summary

The subject of this memo is to review information related to the Sponsor's newly updated 1 pen-injector presentation (Pen C) that supersedes the previous 2 pen-injector presentation (Pen A and Pen B) that was previously reviewed under ICC 1500701.

The device consultant authoring this review memorandum has performed a design review of submission materials intended to support the safety and functionality of the device constituent parts of the subject combination product. This memo covers review of design documentation for the final finished pen-injector combination product. This review did not cover manufacturing of the device constituent parts, sterility or biocompatibility of the primary container closure, or usability of the device constituent parts.

The review of submission documentation by CDRH/ODE found that the product components are of acceptable pedigree and that essential performance of the final finished device can be assured with a reasonable degree of certainty. Essential performance elements of the device under review by the consultants were considered to be:

- Dose accuracy of each dose presentation
- Connection and compatibility of components
- Sterility and biocompatibility of non-primary container closure components
- Functionality of the pen-injector
- Stability after exposure to preconditioning/aging and shipping conditions
- Risk management documentation of the device constituent parts

II. Review Interaction History

Below is a table denoting the CDRH/ODE review interaction to date for NDA 208673:

Review Interaction	Date
ICC 1500701 Initiated – Sponsor Submitted 2 Pen-Injector Presentation	12/24/2015
Information Requests Regarding ICC 1500701 Sent to Sponsor	03/02/2016, 03/15/2016, 03/22/2016, 04/26/2016
ICC 1500701 Completed – Approvable Recommendation Delivered to CDER	06/02/2016
ICC 1600655 Initiated – Sponsor Submitted New 1 Pen-Injector Presentation	09/19/2016
Information Request Sent to Sponsor Regarding New 1 Pen-Injector Presentation	09/27/2016
ICC 1600655 Completed – Approvable Recommendation Delivered to CDER	10/31/2016

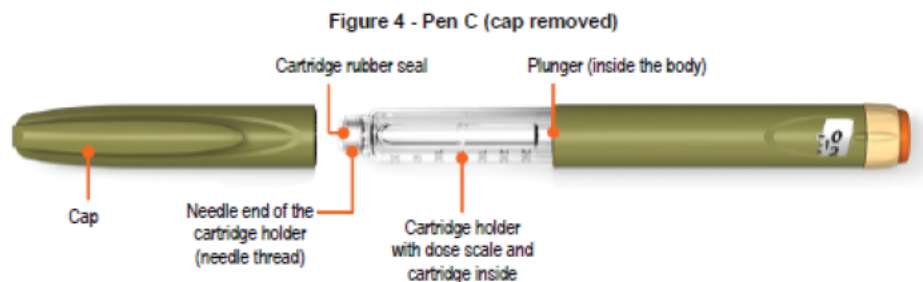
III. Device Constituent Parts Description

The final drug product, ie, insulin glargine/lixisenatide pen-injector pen C, is provided fully assembled and requires no further assembly before use (Figure 1). The design of pen C is based on the already marketed SoloStar® pen-injector, which contains insulin glargine 100 units/mL solution for injection (Lantus®, NDA 21-081) and which has been modified for the delivery of a fixed ratio of insulin. Pen C is a multi-use device designed to dispense variable doses of insulin glargine/lixisenatide solution for injection (in addition to a 'priming dose' which has to be dispensed before each regular dose for injection). The pen-injector is available in one dosage strength: 100 units/mL insulin glargine with 33 µg/mL lixisenatide. The body and cap of the pen are colored olive, while the dose selector is antique-white and the injection button is dark orange (Figure 1).

The design of the insulin glargine/lixisenatide pen-injector pen B that was originally submitted with NDA 208673 has been revised. The new pen design will be referred to as insulin glargine/lixisenatide pen-injector pen C for easy distinction. The new pen C retains almost all of the design features of the pen B upon which it is based, such as the materials of construction, dimensions, colors, mode of operation, formulation of the drug content (100 units/mL insulin glargine and 33 µg/mL lixisenatide) and the primary container (3 mL cartridge). The difference between Pen B and Pen C are described in Section VII below.

The pen-injector consists of (b) (4)

Pen C is (b) (4) not in contact with the insulin glargine/lixisenatide solution for injection. The fluid pathway is provided by the cartridge and the needle, which has to be attached to the threaded end of the cartridge holder prior to use. Needles are not part of the device, but sold separately.



Pen C consists of the following components (see also Figure 12):

- Cap
- Cartridge holder
- Cartridge (containing insulin glargine/lixisenatide solution for injection)
- Body
- Mechanism
- (b) (4)
- Dose selector
- Injection button

Figure 12 - Components of insulin glargine/lixisenatide pen-injector pen C



Please refer to ICC 1500701 for more details regarding the description of the device constituent parts.

IV. Design Review

The Verification and Validation information reviewed to support the to-be-marketed pen-injector presentation is provided under ICC1500701 completed and delivered to CDER on 06/02/2016. Please refer to ICC1500701 for specific design control review of the device constituent parts considered under this memo.

The Sponsor provided the following rationale for the functionality of Pen C:

The functionality of insulin glargine/lixisenatide pen-injectors pen B and pen C is identical, with the exception of the dose range. Pen B allows for dialing doses between 30 and 60 units, while the dosage range of pen C has been adapted to 15 to 60 units. The functionality of the pen-injector has been described in Section 3.2.P.7 “Container closure system – Disposable pen-injector” of NDA 208673. All functional elements as well as the steps necessary to prepare the pen for an injection and inject the dose are identical for pen B and pen C. The description of the container closure system has been updated to include information of pen C (see “Container closure system – Disposable pen-injector” in [QUA-FD-2016-25828]).

The Sponsor provided a comparison with Pen C, the final 1 pen-injector presentation, with the pen-injectors used during the clinical validation activities. The comparison is valid as Pen C and Pen B are identical in their functionality and only differ in colors and the numbers visible on the dial number sleeve. The lead reviewer finds the comparison acceptable and the rationale for the acceptability of the validation activities remains valid for Pen C as they did for Pen B.

The following tables represent the Verification / Validation activities that are supportive of Pen C:

Table 6 - Traceability of essential performance requirements for pen B and pen C

Pen operation step	Essential performance requirement	Specification	Traceability of verification
Remove the pen cap	Cap removal	The cap removal force has to range between (b) (4) N at ambient conditions	Sequence 0010 response document: [QUA-FO-2016-05990] Verification report: [QUA-FD-2016-06224]
Attach a needle	Needle attachment	The pen-injectors must be compatible with needles according to ISO 11608-2:2012	Sequence 0010 response document: [QUA-FO-2016-05990] Verification report: [QUA-FD-2016-06240]
Dose selection	Dial (b) (4)	The (b) (4) required to dial or back dial a dose shall be between (b) (4) Nmm	Sequence 0010 response document: [QUA-FO-2016-05990] Verification report: [QUA-FD-2016-06237]
	Dose number visibility	Dose numbers have to be readable at environmental lightning conditions of (b) (4) lx from a reading distance of (b) (4) cm	Information concerning the visual inspection was provided in NDA 208673. Please see "Pen-injector performance test – ISO 11608-1 – [QUA-FD-2015-01947]" and "Pen-injector performance test – ISO 11608-1 – Appendix – [QUA-FD-2015-10434]" for details
Dose injection	Dose accuracy	The pen-injectors must fulfill the dose accuracy requirements according to ISO 11608-1:2012	Information concerning the dose accuracy was provided in NDA 208673. Please see "Pen-injector performance test – ISO 11608-1 – [QUA-FD-2015-01947]" and "Pen-injector performance test – ISO 11608-1 – Appendix – [QUA-FD-2015-10434]" for details
	Dispense force	The maximum dispense force for the pen has to be (b) (4) N	Sequence 0010 response document: [QUA-FO-2016-05990] Verification report: [QUA-FD-2016-06238]
Attach the pen cap	Cap attachment	The cap attachment force must be (b) (4) N at ambient conditions	Sequence 0010 response document: [QUA-FO-2016-05990] Verification report: [QUA-FD-2016-06224]

Essential Performance Requirement	Specification	Verification	Validation	Aging (Y/N)	Shipping/Transportation (Y/N)	Lot Release Testing (Y/N)
Injection Depth	N/A – dependent on needle used	N/A – dependent on needle used	N/A – dependent on needle used	N/A – dependent on needle used	N/A – dependent on needle used	N/A – dependent on needle used
Injection Time	N/A -Dependent on dose	N/A -Dependent on dose	N/A - Dependent on dose	N/A - Dependent on dose	N/A - Dependent on dose	N/A - Dependent on dose
Dose Accuracy	(b) (4) According to ISO 11608-1:2012	Stability data CE dose accuracy - QUA-FR-2015-05894 and Pen injector performance test – ISO 11608-1 – QUA-FD-2015-01947	Clinical Trial	Yes (11-month in-use stability dose accuracy and 3 year accelerated aging at 55 degrees C)	Yes (Simulated shipping study – QUA-FD-2015-19978)	Yes – according to ISO 11608-1
Visual/Audible Feedback	Dialing a dose with the dose selector provides tactile and audible feedback (one click per unit of insulin glargine that can be heard and felt).	According to ISO 11608-1 Section 5.4.e for general design requirements	Human Factors Validation Study	No	No	Yes (as part of functional testing under dose accuracy)
Activation Force	(b) (4) N	Dispense Force Report – pen A and pen B – QUA-FD-2016-06238	Clinical Trial	No	No	Yes
Needle Length	N/A (see needle compatibility table)	N/A (see needle compatibility table)	N/A (see needle compatibility table)	N/A (see needle compatibility table)	N/A (see needle compatibility table)	N/A (see needle compatibility table)
Needle Gauge	N/A (see needle compatibility table)	N/A (see needle compatibility table)	N/A (see needle compatibility table)	N/A (see needle compatibility table)	N/A (see needle compatibility table)	N/A (see needle compatibility table)
Needle Connection Type	ISO 11608-2 thread	Needle Compatibility Report – pen A and pen B – QUA-FD-2016-06240	N/A	N/A	N/A	N/A
Cap Removal Force	(b) (4) N	Cap attachment and removal forces document number QUA-FD-2016-06224	Clinical Trial	No	No	Yes (as part of functional testing under dose accuracy)

V. Risk Assessment

The Sponsor provided an updated risk assessment in response to an information requested dated 09/27/2016.

The updated risk assessment is acceptable to the consultant reviewer – please see Section VII for more details.

VI. Labeling

The Sponsor provided updated device labeling in response to an information request sent on 09/27/2016.

The updated labeling of the pen-injector is adequate to the consultant reviewer. It is noted that the differences of the numbering sleeve are a result of communication with the Agency and the Sponsor prior to and after the Advisory Committee meeting. This labeling change is a review issue for the CDER human factors team in DMEPA. The numbering sleeve differences do not influence the functionality or biocompatibility of the pen-injector from the perspective of CDRH/ODE.

VII. Information Requests – Sent on 09/27/16

1. Detailed comparison of previous pen design and to-be-marketed pen design (i.e. engineering drawings, materials, functionality, labeling, etc.).

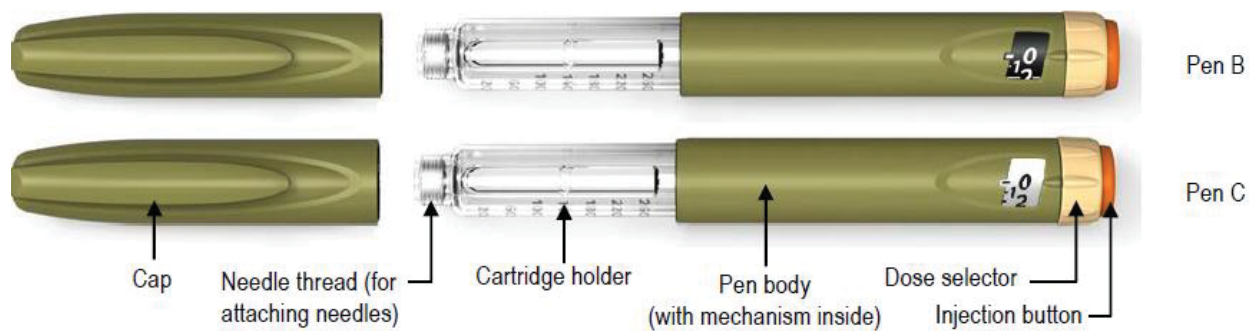
Sponsor Response:

The design of the insulin glargine/lixisenatide pen-injector pen B that was originally submitted with NDA 208673 has been revised according to FDA recommendations. The new pen design will be referred to as insulin glargine/lixisenatide pen-injector pen C in this response document to allow for easy distinction. The new pen C retains almost all of the design features of the pen B upon which it is based (Figure 1 and Figure 2), such as the materials of construction, dimensions, colors, mode of operation, formulation of the drug content (100 units/mL insulin glargine and 33 µg/mL lixisenatide) and the primary container (3 mL cartridge).

Figure 1 - Comparison of pen B and pen C outer appearance (cap on)

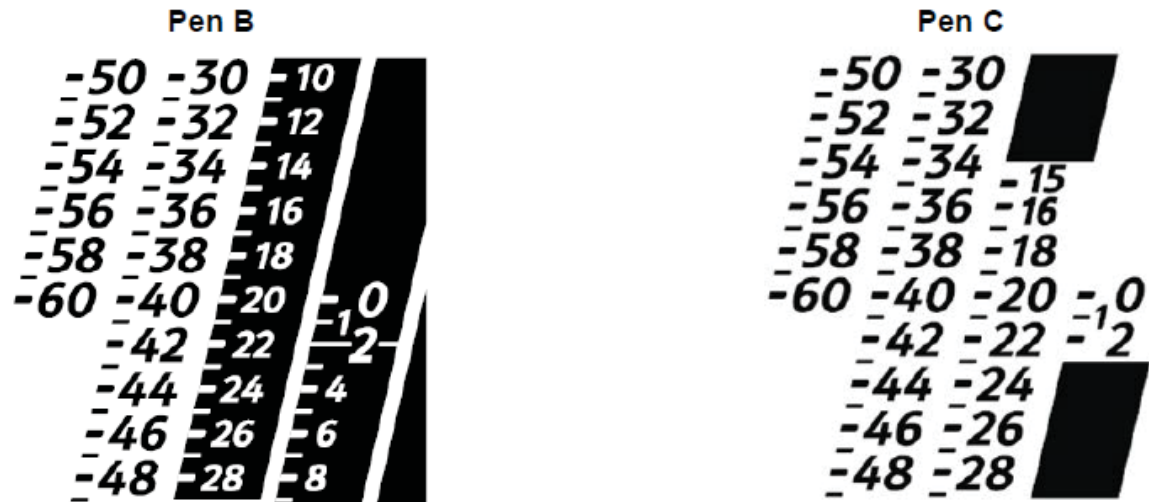


Figure 2 - Comparison of pen B and pen C outer appearance (cap off)



Changes were made to the number sleeve printing of pen C in order to reflect the new recommended dosing range of 15 – 60 units. A comparison of the printing designs is provided in Figure 3. The new printing design of the pen C features black printing without numbers in the dosing range of 3 – 14 units, as this range is not recommended for injections. This means it is not recommended to use the blackened region below the recommended dosing range, neither for regular injections nor for dose-splitting. The printing of pen C features black on white printing in the range of 2 units and below to allow priming the pen, as described in the instructions for use.

Figure 3 - Comparison of the number sleeve printing design of pen B and pen C



Recommended dosing range:

30 – 60 units

15 – 60 units

Black numbers on white background

Black numbers on white background

Non-recommended dosing range:

Below 30 units

Below 15 units up to 2 units

White numbers on black background

Black, no numbers

Engineering drawings:

Engineering drawings shown in Figure 4 are applicable to both pen B and the commercial design pen C. There are no differences between the pens with respect to their dimensions. All components of pen B and pen C are identical, with the exception of the printing on the number sleeve component (see Figure 3).

Materials of construction:

The materials of construction shown in Table 4 are identical for pen B and the commercial design pen C. Only the printing pattern on the number sleeve component is different (see Figure 3). Materials which may come into contact with the user were tested for biocompatibility and comply with the requirements of ISO 10993-1.

Biocompatibility of the pen-injector:

The biocompatibility of the pen-injector parts that may come into contact with the user has been investigated for pen B using a modified number sleeve printing pattern (Figure 5, left panel). As their components, dimensions and materials of construction are identical, successful biocompatibility studies conducted for pen B are valid for pen C as well. The difference in number sleeve printing between both pens has been evaluated with respect to the amount of printing dye used and the potential influence on the biocompatibility of pen C. The printing pattern of the commercial pen-injector pen C (Figure 5, right panel) uses approximately ^{(b) (4)} printing dye compared to pen B used in biocompatibility studies. Therefore, the printing on pen B can be regarded as a “worst case” that fully covers the commercial presentation of pen C with respect to biocompatibility.

Functionality of the pen-injector:

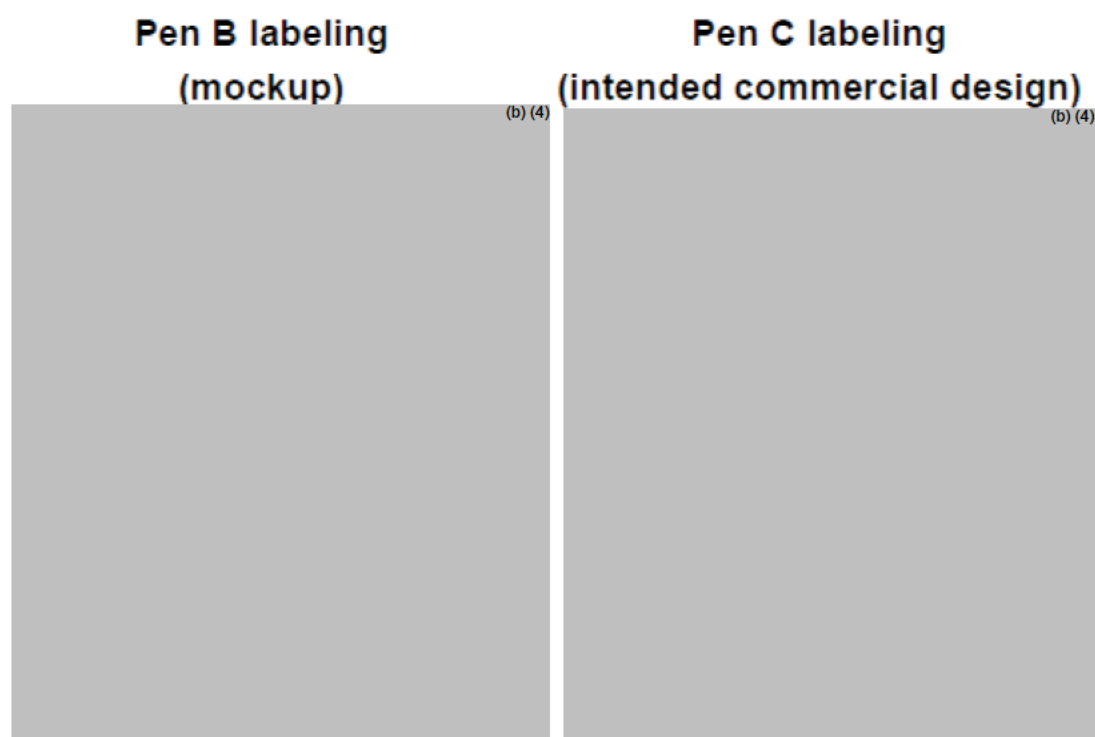
The functionality of insulin glargine/lixisenatide pen-injectors pen B and pen C is identical, with the exception of the dose range. Pen B allows for dialing doses between 30 and 60 units, while the dosage range of pen C has been adapted to 15 to 60 units. The functionality of the pen-injector has been

described in Section 3.2.P.7 “Container closure system – Disposable pen-injector” of NDA 208673. All functional elements as well as the steps necessary to prepare the pen for an injection and inject the dose are identical for pen B and pen C. The description of the container closure system has been updated to include information of pen C (see “Container closure system – Disposable pen-injector” in [QUA-FD-2016-25828]).

Labeling of pens and folding boxes:

The labeling applied to the pen-injector pen B and the to-be-marketed pen C is compared in Figure 6. Reference is made to the communication with the Agency on 2nd September 2016 recommending the numerical modifier “100/33” to be used after the brand name “Soliqua”. On 6th September 2016 Sanofi requested the Agency to review the numerical modifier such that the complete proprietary name for the product is “Soliqua 100/33”. The labeling on the folding boxes of pen B and the commercial pen C are compared in Figure 7.

Figure 6 - Comparison of pen labeling for pen B and pen C



Reviewer Comments:

- The biocompatibility information for Pen C was reviewed by Dr. Sarah Mollo (CDRH/ODE/DAGRID/GHDB) and determined to be adequate given the Sponsor’s rationale of Pen B as surrogate testing for Pen C.
 - The functionality of Pen C is identical to Pen B and therefore the verification / validation activities that were found acceptable under ICC 1500701 for Pen B remain undiminished for Pen C.
2. Comparison of the essential performance requirements/specifications between the previous pens and the to-be-marketed pen.
- a. Traceability from essential performance requirements/specifications to the associated verification testing and clinical validation of the to-be-marketed pen.
 - b. Rationale for the acceptability of any performance testing and/or clinical validation conducted with the previous pen design intended to support the new pen design.

Sponsor Response:

Essential performance requirements of insulin glargine/lixisenatide pen B and pen C:

The essential performance requirements are identical for insulin glargine/lixisenatide pen B and the to-be-marketed pen C. They are based on the steps that the user has to undertake to prepare the pen for an injection and successfully inject a dose. The essential performance requirements, acceptance criteria and data showing the successful verification of the requirements have previously been provided to the Agency in NDA 208673 Sequence 0010 [QUA-FO-2016-05990] for pen B. As explained below, all successful verification tests of essential performance requirements conducted for pen B remain valid for pen C.

An overview of essential performance requirements and traceability of the verification testing is provided in Table 6.

Rationales for the acceptability of performance testing:

Due to the similarities in design, all performance testing conducted for pen B remains valid for the to-be-marketed pen C, as explained hereafter:

1. **Cap attachment and removal:** the cap and the snap features needed to attach it to the cartridge holder are identical for pen B and pen C (see Figure 2). No changes have been made to the dimensions or materials of the cap and the cartridge holder. Therefore, the successful verification of cap attachment and removal for pen B remains valid for pen C.
2. **Needle attachment:** the cartridge holder component that houses the needle thread (see Figure 2) is identical for pen B and pen C. Therefore, the successful verification of needle attachment for pen B remains valid for pen C.
3. **Dial (b) (4):** the mechanism of the pen that is used for dialing doses is identical for pen B and pen C. The different printing on the number sleeve does not influence the dial (b) (4) needed to select a dose. Therefore, the successful verification of the dial (b) (4) for pen B remains valid for pen C.
4. **Dose number visibility:** the difference in number sleeve printing design is not expected to influence the dose number visibility requirements according to ISO 11608-1 Section 11.1 (ie, visual inspection at (b) (4) lx from a reading distance of (b) (4) cm). While the recommended dose range has been changed for pen C, the pen user is only allowed to set doses for injection using the non-blackened areas, which were also present in pen B (see Figure 3). Therefore, dose number visibility does not change from a user perspective and the successful verification of this essential performance requirement for pen B remains valid for pen C. To minimize the risk, a supplemental verification is being performed for the dose number visibility of pen C that does not challenge the validity of previous verification studies performed for pen B.
5. **Dose accuracy:** the change in number sleeve printing design does not influence the acceptance criteria for dose accuracy according to ISO 11608-1. Both pen B and pen C are subject to the same dose accuracy requirements and the same doses are used for testing, ie, (b) (4). The change in the dosing range from 30 – 60 units (pen B) to 15 – 60 units (pen C) does not influence the dose accuracy testing. Therefore, the successful dose accuracy verification of pen B remains valid for pen C.
6. **Dispense force:** the change in number sleeve printing design for pen C does not influence the force needed to dispense a dose from the pen. No components, materials or dimensions thereof have been changed for this pen. Therefore, the successful verification of the dispense force of pen B remains valid for pen C.

Clinical validation of the to-be-marketed pen:

The commercial design of insulin glargine/lixisenatide pen-injector (pen C) was not used in phase 3 clinical studies EFC12404 and EFC12405. In these trials, insulin glargine/lixisenatide solution for injection was administered using two pen-injectors called FRC pen A and FRC pen B. Both of these clinical pen-injectors are based on the SoloStar design, which is also the basis for the commercial pen-injector pen C (Figure 8). A detailed description of the clinical pen-injectors FRC pen A and FRC pen B, including a comparison to insulin glargine/lixisenatide pen-injectors and the marketed Lantus® SoloStar®, was provided in NDA 208673 Section 3.2.P.2 “Pharmaceutical development – Container closure system – Pen-injector comparison”. This comparison has been updated to compare the clinical pens and the marketed Lantus SoloStar to the commercial pen C. Please refer to “Container closure system - Pen-injector comparison” in [QUA-FD-2016-25845] for details.

In summary, the clinical pen-injector FRC pen B is highly similar to the commercial pen C, as they are both based on the same marketed pen design (SoloStar), are operated in the same way, conform to the same applicable standards and guidelines, and both dispense the same drug solution of 100 unit/mL insulin glargine and 33 µg/mL lixisenatide. Due to the low number of Product Technical Complaints (PTCs) recorded for the clinical pen-injectors and the absence of adverse events, it is evident that FRC pen B is safe and effective. The high similarity of FRC pen B and the commercial pen C leads to the conclusion that pen C is expected to perform according to its intended use and deliver doses of insulin glargine 100 units/mL and 33 µg/mL lixisenatide in a safe and effective manner.

Figure 8 - Comparison between clinical and commercial insulin glargine/lixisenatide pen-injectors, and marketed Lantus SoloStar

	Pen designation	Insulin glargine concentration	Lixisenatide concentration
Clinical designs of insulin glargine/lixisenatide pen-injectors:			
	FRC pen A	100 units/mL	50 µg/mL
	FRC pen B	100 units/mL	33 µg/mL
Commercial design of insulin glargine/lixisenatide pen-injector:			
	Pen C	100 units/mL	33 µg/mL
Marketed Lantus SoloStar:			
	Lantus SoloStar	100 units/mL	-

Reviewer Comment:

The lead reviewer finds the Sponsor's rationale and response to be adequate.

- Updated risk analysis for the new pen design, highlighting any differences in the previous pen design.

Sponsor Response:

Updated risk analysis:

The updated risk analysis for the commercial pen C is attached to this response document (please see "Risk management overview including verification & validation" in [QUA-FD-2016-27655]1). The list of changes that were made to the risk analysis in order to reflect the new design of pen C (compared to the previous designs of pen A and pen B) is provided hereafter. As Human Factors is closely linked to the risk analysis, the influence of the new pen C design on the validity of the Human Factors validation testing performed for pen B is also stated below.

Table 7 shows the items removed from the risk analysis for pen C. They were only applicable to the designs of pen A and pen B, ie, potential risks of mix-up between the two pens and dose splitting scenarios. As insulin glargine/lixisenatide solution for injection will only be marketed in one pen-injector (pen C) and dose-splitting is no longer an option with this pen, these items are no longer applicable.

Table 7 - Risk analysis items not applicable to the commercial insulin glargine/lixisenatide pen C

Risk analysis item	Description
(b) (4)	

Table 8 shows the items added to the risk analysis of pen C, which were not present in the previous risk analysis of pen A and pen B. They pertain to the absence of a dose-splitting scenario when using pen C. Verification of these items is currently ongoing and will be concluded before commercialization of the product.

Table 8 - Risk analysis items specific to the commercial insulin glargine/lixisenatide pen C

Risk analysis item	Description
Cause C086	User cannot select the full dose because not enough drug is remaining in the cartridge. To complete the dose, user takes a new pen and has to select a number of units that is not printed on the number sleeve.
Risk control measure E-M36	Patient information (leaflet): Inform patient to use a new pen if the patient cannot select her/his full prescribed dose
Risk control measure E-M37	Patient information (leaflet): Inform patients about the dose range of the pen and that only doses within the dose range of the pen shall be selected

Human Factors considerations:

The changes in pen design and name are not expected to affect the validity of the Human Factors validation testing previously performed for pen B, and the results, therefore, remain valid for pen C.

The design of pen C is highly similar to pen B, which was successfully validated in Human Factors validation testing. The few use errors that occurred during the Human Factors validation study for pen A and pen B are mitigated by the new design and name of the pen C, as explained in Table 9. Therefore, the change in pen design pertaining to the number sleeve printing and the change in product brand name are not expected to influence the validity of the results of the Human Factors validation testing performed for pen B.

The additional assessment of understanding of the product name modifiers (b) (4) by the intended users (ie, patients, nurses and pharmacists) is not relevant to pen C because the modifier has changed to "100/33" and only one pen is intended for commercialization.

Reviewer Comment:

The lead reviewer finds the Sponsor's rationale and response to be adequate in regards to the updated risk analysis.

VIII. Post-Market Commitment

The reviewer notes that within NDA 208673 the sponsor committed to performing ongoing stability analysis to assess maintenance of the essential performance requirements of the final finished combination product through the intended expiration date of (b) (4) months using primary registration stability batches. The sponsor should submit evidence of completion of these activities to NDA annual reports.

IX. Recommendation

The consulting reviewer recommends approval of the NDA in the context of device constituent parts for the combination product with the Post-Market Commitment noted in Section VIII above.

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

/s/

MARTIN L WHITE
10/31/2016



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Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: October 25, 2016 **Date Consulted:** January 25, 2016

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, M.D., M.S., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., Division Director,
Division of Pediatric and Maternal Health

To: Division of Metabolism & Endocrinology Products (DMEP)

Drug: Soliqua 100/33(insulin glargine and lixisenatide) injection

NDA: 208-673

Subject: Pregnancy and Lactation Labeling

Proposed Indication: Insulin glargine/lixisenatide fixed ratio combination is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both insulin glargine and lixisenatide is appropriate.

Applicant: Sanofi-Aventis U.S. LLC, A SANOFI COMPANY

Materials Reviewed:

- December 21, 2015, Applicants submission
- January 25, 2016, DMEP's request to DPMH-MHT for labeling review
- February 3, 2016 applicant's response to information request issued by DMEP on January 25, 2016
- April 7, 2016 DPMH Lixisenatide review by Christos Mastroyannis, M.D.
- July 18, 2016 Pharmacology/Toxicology review by Feleke Eshete, Ph.D.
- August 1, 2016, Applicant's proposed labeling

INTRODUCTION

The applicant, Sanofi Aventis, submitted a 505(b)(1) New Drug Application (NDA) for Soliqua 100/33 (insulin glargine and lixisenatide) injection, NDA 208-673, on December 21, 2015. The proposed indication is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both insulin glargine and lixisenatide is appropriate. The Division of Metabolism & Endocrinology Products (DMEP) consulted the Division of Pediatric and Maternal Health (DPMH) on January 25, 2016, to assist with reviewing the Pregnancy and Lactation subsections of labeling. This review provides recommended revisions and structuring of existing information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections in labeling in order to provide clinically relevant information for prescribing decisions and to comply with current PLLR regulatory requirements.

REGULATORY HISTORY

The applicant submitted the 505(b)(1) NDA 208-673 for Soliqua 100/33, a new fixed-dose combination product with insulin glargine and lixisenatide, on December 21, 2015. Prior to submission, on 28 August 2015, the applicant notified the FDA of their intent to use a Rare Pediatric Disease Priority Review Voucher (PRV NDA 205-750) with the NDA. In accordance with the Federal Register Notice (Vol. 79 page 59276, Section IV) dated 1 October 2014, the FDA issued an invoice for the PRV fee on 12 November 2015.

Insulin glargine has been marketed in the United States as parenteral hypoglycemic agent since April 20, 2000 (Sanofi-Aventis NDA 21-081-Lantus Recombinant 100 units/mL insulin glargine in 10 mL vials or 3 mL SoloStar prefilled pen) for once-daily subcutaneous administration to improve glycemic control in pediatric patients with Type 1 Diabetes Mellitus (T1DM) and in adults with Type 2 Diabetes Mellitus (T2DM). A more concentrated insulin glargine, (Sanofi-Aventis NDA 206-538- Toujeo SoloStar Recombinant 300 units/mL insulin glargine in 1.5 mL) was approved on February 25, 2015 for glycemic control in adult patients with Type 1 and Type 2 Diabetes Mellitus (T1DM and T2DM).

Marketing application (Sanofi-Aventis NDA 204-961) was filed for lixisenatide in 2012, but withdrawn with plans to resubmit when the final cardiovascular (CV) study-report (ELIXA) would be available. Lixisenatide (NDA 208-471) including the CV data was approved on July 27, 2016 for subcutaneous daily administration. It is indicated for glycemia control as an adjunct to diet and exercise in T2DM.

BACKGROUND

Drug Characteristics

The insulin glargine/lixisenatide combination is a fixed ratio combination product of a long-acting human insulin analog (insulin glargine, 100 Units/ml) together with a GLP-1 receptor agonist (lixisenatide) provided in 3 mL. It has been developed to be provided in two dose ratios for wide coverage:

- 10 to 40 pen: 3 mL solution for injection in fixed ratio 2U:1mcg – 100 units/mL (U-100) insulin glargine and 50 mcg/mL lixisenatide
- 30 to 60 pen: 3 mL solution for injection in fixed ratio 3U:1mcg – 100 units/mL (U-100) insulin glargine and 33 mcg/mL lixisenatide.

Insulin glargine is a recombinant long-acting human insulin analog that has a molecular weight of 6063 Da. Insulin glargine is 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. Plasma protein binding study was not conducted with insulin glargine, but it is not expected to bind plasma proteins since insulin is not known to do so.

Intravenous clinical testing has shown that the glucose-lowering effect of insulin glargine on a molar basis was similar to that of human insulin. Its metabolites are also similar to that of human insulin.¹

Lixisenatide is a selective dipeptidyl peptidase-4 (DPP-4) resistant, glucagon like peptide-1 (GLP-1) receptor agonist. Similar to endogenous GLP-1, the action of lixisenatide is mediated via a specific interaction with GLP-1 receptors, including those on pancreatic alpha and beta cells. Lixisenatide stimulates glucose dependent insulin secretion, and in parallel, glucagon secretion is suppressed. Lixisenatide also slows gastric emptying, thereby reducing the rate at which meal derived glucose appears in the circulation; slowing of gastric emptying is preserved with chronic dosing. Lixisenatide has a molecular weight of 4858.5 and in studies in humans showed plasma protein binding of 55%.^{2,3}

Disease Background

Diabetes Mellitus and Pregnancy

Adverse outcomes of diabetes during pregnancy relate to the onset of diabetes, its duration, and the degree of vasculopathy. Women with pregnancies complicated by diabetes mellitus may be separated into one of two groups:

- Gestational diabetes (GDM): women with carbohydrate intolerance of variable severity, with onset or first recognition during the present pregnancy. This means that the glucose intolerance may have antedated the pregnancy but was not recognized by the patient or the physician.
- Pregestational diabetes (PGD): women known to have diabetes before pregnancy.

Ninety percent of all pregnant diabetic women have gestational diabetes mellitus (GDM), whereas type 1 (insulin-dependent diabetes) and type 2 (non-insulin dependent diabetes) account for the remaining 10%.⁴

Gestational Diabetes

The incidence of GDM varies in different study populations and is estimated to occur in 3–5% of all pregnant women in the United States. The likelihood of developing GDM is significantly increased among certain subgroups, and these include women with a family history of type 2 diabetes, advancing maternal age, obesity, and nonwhite ethnicity. Infants born to women diagnosed with GDM do not have an increased risk of congenital anomalies when compared to infants born to women without GDM. GDM usually is diagnosed later in pregnancy when the risk of MCM has passed. PGD that is well under control is not associated with an increased risk either, however, infants of women with poorly controlled PGD have an increased risk of MCM.

Pregestational Diabetes

Poorly controlled PGD during pregnancy increases the risk for maternal complications, including diabetic ketoacidosis, preeclampsia, spontaneous abortions (SAB), preterm delivery, polyhydramnios, stillbirth and cesarean section due to fetal macrosomia. In addition, poorly controlled DM during pregnancy increases the risk for fetal malformations, including neural tube defects (anencephaly, open spina bifida, and holoprosencephaly), cardiovascular anomalies (ventricular septal defects and transposition of the great vessels), oral clefts, genitourinary abnormalities (absent kidneys, polycystic kidney, and double ureter), and sacral agenesis or caudal regression. Fetal complications include pyelonephritis, hypertensive disorders and macrosomia-related injuries (brachial plexus injury, hypoxia). Also directly related to metabolic

¹ Eshete F: Pharmacology/Toxicology review, July 18, 2016 in DARRTS

² Proposed labeling

³ Pharmacology Toxicology review by Feleke Eshete, Ph.D., July 18, 2016 in DARRTS. Reference ID: 3960523

⁴ Reece, EA, Hobbins, JC: Clinical Obstetrics, Third Edition, Chapter 38: Diabetes Mellitus in Pregnancy, pp: 292-305, Jan 14, 2008

control are fetal hyperglycemia and neonatal hypoglycemia, hypocalcemia, polycythemia, and hyperbilirubinemia.

Infants of diabetic mothers in unsatisfactory glycemic control often develop hypoglycemia during the first few hours of life. The reported incidence ranges from 25% to 40% of infants of diabetic mothers. Poor glycemic control during pregnancy and high maternal plasma glucose levels at the time of delivery increase the risk of hypoglycemia in the infant. Clinical studies suggest that euglycemia during organogenesis in pregestational pregnant diabetics is critical in the prevention of congenital anomalies.³ Achieving and maintaining maternal euglycemia prior to conception and throughout pregnancy decreases the risk of adverse outcomes for both the mother and the infant.^{5,6,7}

Poorly controlled pre-gestational Diabetes Mellitus (PGD) (before conception) and in the first trimester is associated with Major Congenital Malformation (MCM) (5-10%) and spontaneous abortion (15-20%).⁸ The higher the fasting serum glucose level is at diagnosis, the higher the incidence of MCM.⁹

The Micromedex database states that pregestational diabetes mellitus in pregnant women with poor control during organogenesis is associated with a 3-fold increase in congenital anomalies that include cardiac malformations, lumbosacral agenesis, hyperbilirubinemia, polycythemia, and renal vein thrombosis. Offspring of mothers with poorly controlled PGD during pregnancy have a mortality rate that is 5 times greater than that of non-diabetic mothers; the mortality rate is higher at all gestational ages.¹⁰

The American College of Obstetricians and Gynecologists (ACOG) in a statement issued in 2005 and reaffirmed in 2012 for PGD, states that HbA1c of 5-6% is associated with a fetal malformation rate close to what is seen in normal pregnancies. An HbA1c near 10% is associated with a fetal malformation rate of 20-25%.¹¹ Major malformations include: Hydrocephalus, meningomyelocele (lumbar), anencephaly, cleft palate, atresia of pulmonary valve, caudal regression syndrome, agenesis of a kidney, supernumerary toe, anomalous lumbar spine, aplasia of left diaphragm with hypoplasia of left lung, and omphalocele.¹²

Pregnancy and Lactation Labeling Rule (PLLR)

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”¹³ also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006

⁵ Mills JL. Malformations in infants of diabetic mothers. *Teratology*.1982;25:385-94

⁶ Persson, M. and Fadi, H. Perinatal outcome in relation to fetal sex in offspring to mothers with pre-gestational and gestational diabetes- a population-based study. *Diabetes Med*. 2014; 31(9): 1047-54.

⁷ www.cdc.gov. Problems of Diabetes in Pregnancy. Accessed 12/30/2015.

⁸ Ornoy, et al. Effect of Maternal Diabetes on the Embryo, Fetus, and Children: Congenital Anomalies, Genetic and Epigenetic Changes and Developmental Outcomes. *Birth Defects Research, Part C: Embryo Today: Reviews*. 2015; 105(1): 53-72.

⁹ Schaefer UM, Songster G, Xiang A, Berkowitz K, Buchanan TA, Kjos SL. Congenital malformations in offspring of women with hyperglycemia first detected during pregnancy. *Am J Obstet Gynecol*. 1997;177:1165–1171.

¹⁰ The Behrman RE, Kleigman RM, Nelson WE, et al: *Nelson Textbook of Pediatrics*, 14th. WB Saunders Company, Philadelphia, PA, 1992.

¹¹ ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. 2005; 60:675-685.

¹² Ylinen K, Aula P, Stenman UH, et. al. Risk of minor and major fetal malformations in diabetics with high haemoglobin A1c values in early pregnancy. *British Med. J*.1984;289:345-6

¹³ Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

Physicians Labeling Rule¹⁴ format to include information about the risks and benefits of using these products during pregnancy and lactation.

The current labeling for Lantus (insulin glargine)¹⁵ states:

8.1 Pregnancy

There are no well-controlled clinical studies of the use of LANTUS in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. In patients with diabetes or gestational diabetes, insulin requirements may decrease during the first trimester, generally increase during the second trimester, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients. Therefore, female patients should be advised to tell their physicians if they intend to become, or if they become pregnant while taking LANTUS.

Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m². In rabbits, doses of 0.072 mg/kg/day, which is approximately 2 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m², were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

The current labeling for Lixisenatide ¹⁶states:

8.1 Pregnancy

Risk Summary The limited available data with lixisenatide in pregnant women are not sufficient to inform a drug-associated risk of major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see Clinical Considerations]. Based on animal reproduction studies, there may be risks to the fetus from exposure to lixisenatide during pregnancy. ADLYXIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lixisenatide administered to pregnant rats and rabbits during organogenesis was associated with visceral closure and skeletal defects at systemic exposures that decreased maternal food intake and weight gain during gestation, and that are 1-time and 6-times higher than the 20 mcg/day clinical dose, respectively, based on plasma AUC [see Data].

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with a HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

¹⁴ Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, published in the Federal Register (71 FR 3922; January 24, 2006).

¹⁵ Lantus labeling approved July 17, 2015

¹⁶ Lixisenatide labeling approved July 27, 2016

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Animal Data

In pregnant rats receiving twice daily subcutaneous doses of 2.5, 35, or 500 mcg/kg during organogenesis (gestation day 6 to 17), fetuses were present with visceral closure defects (e.g., microphthalmia, bilateral anophthalmia, diaphragmatic hernia) and stunted growth. Impaired ossification associated with skeletal malformations (e.g., bent limbs, scapula, clavicle, and pelvis) were observed at ≥ 5 mcg/kg/day, resulting in systemic exposure that is 1-time the 20 mcg/day clinical dose, based on plasma AUC. Decreases in maternal body weight, food consumption, and motor activity were observed concurrent with the adverse fetal findings, which confounds the interpretation of relevance of these malformations to the human risk assessment. Placental transfer of lixisenatide to developing rat fetuses is low with a concentration ratio in fetal/maternal plasma of 0.1%.

In pregnant rabbits receiving twice daily subcutaneous doses of 2.5, 25, 250 mcg/kg during organogenesis (gestation day 6 to 18), fetuses were present with multiple visceral and skeletal malformations, including closure defects, at ≥ 5 mcg/kg/day or systemic exposures that are 6-times the 20 mcg/day clinical dose, based on plasma AUC. Decreases in maternal body weight, food consumption, and motor activity were observed concurrent with the fetal findings, which confounds the interpretation of relevance of these malformations to the human risk assessment. Placental transfer of lixisenatide to developing rabbit fetuses is low with a concentration ratio in fetal/maternal plasma of $\leq 0.3\%$. In a second study in pregnant rabbits, no drug-related malformations were observed from twice daily subcutaneous doses of 0.15, 1.0, and 2.5 mcg/kg administered during organogenesis, resulting in systemic exposures up to 9-times the clinical exposure at 20 mcg/day, based on plasma AUC.

In pregnant rats given twice daily subcutaneous doses of 2, 20, or 200 mcg/kg from gestation day 6 through lactation, decreases in maternal body weight, food consumption, motor activity were observed at all doses. Skeletal malformations and increased pup mortality were observed at 400 mcg/kg/day, which is approximately 200-times the 20 mcg/day clinical dose, based on mcg/m².

REVIEW

Pregnancy

Nonclinical experience

No prenatal- and postnatal development studies in animals have been conducted with insulin glargine and lixisenatide injection as a combination.

Reproductive toxicology studies were also not conducted with the combination of insulin glargine and lixisenatide. The reader is referred to July 18, 2016 Pharmacology/Toxicology review by Feleke Eshete, Ph.D. in DARRTS, Reference ID: 3960523.

Insulin glargine

Sanofi Aventis cross-referenced the nonclinical information from the approved insulin glargine (NDA 021-081) approved on April 20, 2000 and lixisenatide (NDA 208-471) approved on July 27, 2016 to support the marketing application for NDA 208-673. Nonclinical findings have suggested that the effects of human insulin and insulin glargine were additive.

Reproduction toxicology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses approximately 7 times the recommended human subcutaneous starting dose

of 10 Units/day (0.008 mg/kg/day), based on mg/m². In rabbits, doses of approximately 2 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m², were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits and are likely due to hypoglycemia. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.¹⁷

Lixisenatide

Lixisenatide administered to pregnant rats and rabbits during the period of organogenesis was associated with increased incidences of skeletal and visceral malformations, including closure defects, at systemic exposures that are 1- and 6-times the exposure (AUC) at the 20 µg human Q.D. dose in rats and rabbits, respectively. Maternal toxicity was observed at these exposures. “It is plausible that the brief interruption of nutritional status in the dams may have resulted in the adverse skeletal findings, because reduced food intake and weight gain was also noted during administration. There is very low placental transfer of lixisenatide (0.1% in rats, ≤0.5% rabbits).¹⁸

Carcinogenicity studies were conducted in CD-1 mice and Sprague Dawley rats with twice daily subcutaneous lixisenatide doses of 40, 200, or 1,000 µg/kg. Increase in thyroid C-cell adenomas were observed in male mice at >180-times the human. C-cell adenomas were seen at all doses in rats receiving lixisenatide, resulting in systemic exposures that are ≥15-times the human exposure. Increased incidence of endometrial adenocarcinoma of the uterus was also observed in mice at the mid-dose group only (~33-times exposure ratio to the recommended dose).

Because the weight loss and hypoglycemia, observed at low multiples of the proposed clinical doses, can harm the fetus, the lixisenatide and insulin combination bears potential risk to the fetus during pregnancy.

Summary

The nonclinical experience data on insulin glargine and lixisenatide have been previously reviewed and remain unchanged.

Review of Literature

No literature with the combined drug product of insulin glargine and lixisenatide use in pregnancy exists outside of the clinical trials performed.

Insulin glargine

Efficacy and safety of insulin glargine have been shown in more than 100,000 patients with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) in clinical studies. Post-marketing surveillance was gathered from approximately 79 million patient-years of clinical experience. However, there are no well-controlled clinical studies of the use of insulin glargine in pregnant women and there is no ongoing pregnancy exposure registry for insulin glargine.

A comprehensive literature search by the applicant was conducted in Medline (1966 to present) and Embase (1974 to present) for articles reporting or discussing insulin glargine (Lantus) and pregnancy. The databases were searched for articles published cumulative through August 12, 2015. There were 163 references retrieved from this search. No new safety issues related to pregnancy were identified as stated by the applicant.

DPMH searched PubMed, Embase, (b) (4) and (b) (4) databases for information regarding insulin

¹⁷ Existing labeling for Lantus (insulin glargine)

¹⁸ DPMH Lixisenatide review Aril 7, 2016 by Christos Mastroyannis, M.D.

glargine and use during pregnancy. No additional published safety information was identified.

A meta-analysis of eight observational clinical studies was performed to assess the safety of insulin glargine and neutral protamine hagedorn (NPH) insulin in gestational or pregestational diabetes. No significant differences in safety-related maternal or neonatal outcomes were seen between insulin glargine and insulin NPH during pregnancy.¹⁹

Other published observational studies consisted of case-control studies, cohort studies, or survey and participants were pregnant women with either type 1 or type 2 diabetes who used insulin glargine. Studies were excluded if they did not report obstetric or neonatal safety outcomes. There were a total of 12 original publications summarizing the results of observational studies. In eleven studies, insulin glargine was combined with lispro, aspart or human insulin. Nine studies included a comparison group, with women who used detemir, continuous subcutaneous insulin infusion, or NPH insulin in combination with lispro, aspart or human insulin.

With respect to the study participants, eight of the twelve studies included women with T1DM, while the remaining four studies examined women with both pregestational and/or gestational diabetes without further specifying the type of diabetes.^{20,21,22,23,24,25,26,27,28,29,30,31} Information on each study is presented in Table 1 below.

¹⁹ Pollex E, Moretti ME, Koren G, Feig DS. Safety of insulin glargine use in pregnancy: A systematic review and meta-analysis. *Ann Pharmacother*. 2011;45(1):9-16

²⁰ Pöyhönen-Alho M, Rönnemaa T, Saltevo J, et al. Use of insulin glargine during pregnancy. *Acta Obstetrica et Gynecologica Scandinavica* 2007; 86(10): 1171-1174.

²¹ Price N, Bartlett C, Gillmer MD. Use of insulin glargine during pregnancy: A case control pilot study. *An International Journal of Obstetrics and Gynaecology* 2007; 114(4):453-457.

²² Di Cianni G, Torlone E, Lencioni C, et al. Perinatal outcomes associated with the use of glargine during pregnancy. *Diabetic Medicine* 2008; 25(8): 993-996

²³ Egerman RS, Ramsey RD, Kao LW, et al. Perinatal outcomes in pregnancies managed with antenatal insulin Glargine. *American journal of perinatology* 2009; 26(8): 591-5

²⁴ Gallen IW, Jaap A, Roland JM, Chirayath HH. Survey of glargine use in 115 pregnant women with Type 1 diabetes. *Diabetic medicine* 2008; 25(2): 165-9.

²⁵ Imbergamo MP, Amato MC, Sciortino G, et al. Use of glargine in pregnant women with Type 1 diabetes mellitus: A case-control study. *Clinical Therapeutics* 2008; 30 (8): 1476-1484

²⁶ Fang YMV, MacKeen D, Egan J, et al. Insulin glargine compared with Neutral Protamine Hagedorn insulin in the treatment of pregnant diabetics. *Journal of Maternal-Fetal and Neonatal Medicine* 2009; 22(3): 249-253

²⁷ Lepercq J, Jacqueminet S, Hieronimus S, et al. Use of insulin glargine throughout pregnancy in 102 women with type 1 diabetes. *Diabetes and Metabolism* 2010; 36(3): 209-212

²⁸ Negrato CA, Rafacho A, Negrato G, et al. Glargine vs. NPH insulin therapy in pregnancies complicated by diabetes: an observational cohort study. *Diabetes research and clinical practice* 2010; 89(1): 46-51

²⁹ Bruttomesso D, Bonomo M, Costa S, et al. Type 1 diabetes control and pregnancy outcomes in women treated with continuous subcutaneous insulin infusion (CSII) or with insulin glargine and multiple daily injections of rapid-acting insulin analogues (glargine-MDI). *Diabetes & metabolism* 2011; 37: 426-31

³⁰ Ansar S, Milan S, Roth S, Hebdon GM, Aldasouqi S, Gossain VV. Safety of insulin Glargine in pregnancy. *J Diabetes Metab*. 2013; 4: 240. doi:10.4172/2155-6156.1000240.

³¹ Callesen NF, Damm J, Mathiesen JM, et al. Treatment with the long-acting insulin analogues detemir or glargine during pregnancy in women with type 1 diabetes: Comparison of glycaemic control and pregnancy outcome. *Journal of Maternal-Fetal and Neonatal Medicine* 2013;26(6): 588-592

Table 1. Published Observational Studies: Anti-diabetes Treatment during Pregnancy

Author (year)	Country	Sample size	Duration of diabetes (years) Mean (SD)*
Pöyhönen-Alho (2007)	Finland	Glargine: 45; NPH: 55	Glargine: 15 (1); NPH: 13 (1)
Price (2007)	UK	Glargine: 10; NPH: 10	Glargine: 15 (7) NPH: 14 (6)
Di Cianni (2008)	Italy	Glargine: 61; NPH: 46	Glargine: 17 (9) NPH: 16 (7)
Egerman (2008)	US	Glargine: 65; NPH: 49	Glargine: 5 (6) NPH: 5 (4)
Gallen (2008)	UK	Glargine: 115	Glargine: 15 (8)
Imbergamo (2008)	Italy	Glargine: 15; NPH: 15	Glargine: 14 (7) NPH: 16 (4)
Fang (2009)	US	Glargine: 37; NPH: 16	Not available
Lepercq (2010)	France	Glargine: 102	Not available
Negrato (2010)	Brazil	Glargine: 18; NPH: 38	Glargine: 7(6); NPH: 8 (5)
Bruttomesso (2011)	Italy	Glargine: 44; Continuous subcutaneous insulin infusion (CSII): 100	Glargine: 14 (8); CSII: 16 (7)
Ansar (2013)	US	Glargine: 92	Not available
Callesen (2013)	Denmark	Glargine: 46; Detemir: 67	Glargine: 13 (0-31)** Detemir: 15 (0.5-31)**
SUMMARY 10		TOTAL NUMBER OF PATIENTS: 558	

* Standard deviation

** Data are presented as median (range)

1) Neonatal outcomes:

There were a total of 25 newborns with congenital malformations identified among pregnancies exposed to insulin glargine vs NPH from eleven studies that reported the frequency of congenital malformation; two of these publications (Imbergamo 2008 and Fang 2009) found no congenital malformations. The frequency of congenital malformations ranged from 0 to 16%. No significant increased risk for congenital malformations associated with the use of insulin glargine was detected in any of the nine studies including a comparison group (see Table 2 below).

The frequency of other main neonatal outcomes, including macrosomia, large for gestational age birth weight (LGA), shoulder dystocia, preterm delivery and respiratory dysfunction syndrome are summarized in Table 2. There were no significant higher rates observed among pregnancies exposed to insulin glargine vs NPH.

2) Obstetric outcomes:

Six studies reported the risk of miscarriage in pregnancies exposed to insulin glargine. The rate ranged from 1.1% to 5%. The frequency of pre-eclampsia was reported in ten studies, ranging from 2 to 25%. No evidence has been documented for increased adverse obstetric outcomes with the use of insulin glargine in pregnancy compared to the use of NPH insulin or detemir among individual studies included for this review.

In some of the studies, the number of participants exposed to insulin glargine was as low as ten patients (see Table 1 above). Among the twelve studies included in the review, only two contained data for more than one hundred patients receiving insulin glargine treatment during pregnancy, none of which had a comparison group included in the study. None of the included studies provided the detailed information concerning diagnoses and classifications of congenital malformations.

Table 2. Neonatal Outcomes in Pregnant Women Using Insulin Glargine Among Published Observational Studies

Author (year)	Study groups	Congenital malformation	Macrosomia	Large for Gestational Age birth weight	Shoulder dystocia	Preterm delivery (<37 weeks)	Respiratory dysfunction syndrome
Pöyhönen- Alho (2007)	Glargine	2.2%	Not reported	Not reported	2.2%	Not reported	Not reported
	NPH	0	Not reported	Not reported	5.5%	Not reported	Not reported
Price (2007)	Glargine	10%	40%	Not reported	Not reported	Not reported	Not reported
	NPH	10%	30%	Not reported	Not reported	Not reported	Not reported
Di Cianni (2008)	Glargine	4.7%	20.9%	44.1%	Not reported	29.7% (of entire study participants)	Not reported
	NPH	5.2%	14.8%	41.3%	Not reported		Not reported
Egerman (2008)	Glargine	16%	Not reported	Not reported	0	Not reported	8%
	NPH	15%	Not reported	Not reported	8%	Not reported	10%
Gallen (2008)	Glargine	2.8%	Not reported	Not reported	Not reported	Not reported	7%
Imbergamo (2008)	Glargine	0	Not reported	46.7%	Not reported	Not reported	20%
	NPH	0	Not reported	26.7%	Not reported	Not reported	0
Fang (2009)	Glargine	0	Not reported	18.9%	Not reported	13.5%	0
	NPH	0	Not reported	50%	Not reported	18.8%	0
Lepercq (2010)	Glargine	2.0%	Not reported	30%	Not reported	23%	11%
Negrato (2010)	Glargine	5.5%	17%	50%	Not reported	Not reported	5.5%
	NPH	11%	21%	37%	Not reported	Not reported	8%
Bruttomesso (2011)	Glargine	2.7%	14.5%	45.5%	4.9%	34.2%	9.8%
	CSII	5.5%	14.0%	45%	1.1%	32.3%	9.9%
Ansar (2013)	Glargine	Not reported	12.3%	Not reported	2.1%	Not reported	Not reported
Callesen (2013)	Glargine	4.3%	Not reported	30%	Not reported	35%	Not reported
	Detemir	3.0%	Not reported	49%	Not reported	31%	Not reported

Pollex, et al. published results of a transplacental transfer study of insulin glargine. No insulin glargine was detectable in the fetal compartment with perfusions conducted at therapeutic insulin glargine concentrations. At supra-therapeutic concentrations, insulin glargine was detectable in the fetal compartment at low concentrations indicating low placental transfer. The authors concluded that insulin glargine is unlikely to cross the placenta when used at therapeutic concentrations.³²

Blumer, et al³³ in an Endocrine Society Clinical Practice Guideline of 2013, state “that insulin glargine is widely used in pregnancy and available evidence supports its safety for use during pregnancy”. The authors also recommend that “women successfully using insulin glargine may continue to use it prior to conception and during pregnancy”, an off-label use.

The (b) (4) database states that the “Magnitude of teratogenic risk to child born after exposure to insulin glargine during gestation is unlikely but the data are insufficient to state that there is no risk”.

Lixisenatide

The applicant performed a literature search in Medline and Embase. No relevant publications for pregnancy and lixisenatide were identified for any of the search terms: safety, adverse drug reactions, adverse effects, adverse events, toxicity, drug interactions, embryo-toxicity, feto-toxicity, repro-toxicity, genotoxicity. DPMH also conducted a review of PubMed for published literature with similar terms regarding lixisenatide and use in pregnancy, lactation and females of reproductive potential. No relevant articles were identified.³⁴

As per (b) (4) and (b) (4) databases, a single case of an infant exposed to lixisenatide during gestation was reported. There were no major congenital malformations identified.

Review of Pharmacovigilance Data

Because Soliqua has not yet been approved, no pharmacovigilance database has been established for Soliqua.

Insulin glargine

Spontaneous reports of exposed pregnancies from Post Marketing Surveillance including a large number (more than 1000 retrospective and prospective pregnancy outcomes) of exposed pregnancies indicate no specific adverse effects of insulin glargine use on pregnancy, or on the health of the fetus and newborn child. The overall estimated cumulative patient exposure to insulin glargine in the general population is 79,750,488 patient-years. The reporting rate for the adverse events of specific interest in the global pharmacovigilance database is 27.07 per 1,000,000 patient years.

A cumulative search up March 2,-2015 was performed in the Sanofi global pharmacovigilance database to identify all solicited and unsolicited cases for insulin glargine with the following Preferred Terms (PT's) using Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 and Standardized MedDRA Query (SMQ):

- Stillbirth: High Level Term (HLT) of Stillbirth and Fetal death
- Congenital Anomaly: SMQ Congenital, familial, and genetic disorders, and/or PT's with "repair"

³² Pollex E., Feig D., Lubetsky A., Yip P., Koren G. Insulin Glargine Safety in Pregnancy: A transplacental transfer study. Diabetes Care 2010; 33:29-33.

³³ Blumer I., Hadar E., Hadden D., Jovanovic L., Mestman J., Murad M., Yogeve Y. Diabetes and Pregnancy: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2013; 98:4227-49.

³⁴ DPMH review by Christos Mastroyannis, M.D. in DARRTS, April 7, 2016 Reference ID:391226)

(b) (4)

from the SMQ Neonatal disorders, Broad and Narrow, and/or seriousness criterion of "congenital anomaly"

- Spontaneous abortion: PT's with string text "abortion spontaneous": Abortion spontaneous, Abortion spontaneous complete complicated, Abortion spontaneous complicated, Abortion spontaneous incomplete complicated, Abortion spontaneous complete, Abortion spontaneous incomplete
- Induced abortion: All cases with HLT of Induced abortion
- Ectopic pregnancy: PT's with string text "ectopic pregnancy": Ectopic pregnancy, Ectopic pregnancy termination, Ectopic pregnancy with intrauterine device, Ruptured ectopic pregnancy, Abortion of ectopic pregnancy
- Preterm: PT's Premature baby, Premature delivery, Premature labor, Premature rupture of membranes, Premature separation of placenta
- Exposure via breast milk: Include all cases with SMQ of Neonatal exposures via breast milk
- Cases linked to pregnancy/neonatal: SMQ Pregnancy and Neonatal topics, and/or with seriousness criteria of "congenital anomaly" (includes all cases of pregnancy exposure including normal pregnancy/outcome)
- Cases linked to exposure via father: PT's Exposure via father, Paternal drugs affecting fetus

The search retrieved a total of 2174 exposures to insulin glargine in pregnancy, of which 229 cases were solicited and 1945 cases were unsolicited. Of the 1945 unsolicited cases, 1235 were medically confirmed by a healthcare professional (HCP) and 710 were not confirmed by a healthcare professional. Fifteen cases were reviewed but not included in the analysis because these cases were not found relevant to pregnancy.

Finally, 2159 exposures to insulin glargine in pregnancy are reviewed. The reporting rate was calculated by dividing the number of cases by the cumulative exposure (approximately 79,750,488 per 1,000,000 patient-years). The Proportional Reporting Rate/Percentage was calculated by taking the number of cases per category and dividing it by the total number of pregnancy cases (2159) (see Table 3).

Table 3: Insulin glargine: Case Overview – Cumulative through March 2, 2015^a

MedDRA search	Total	Reporting Rate ^b (per 1,000,000 patient-years)	Proportional Reporting Rate / Percentage ^c
Pregnancy and neonatal topics (Total cases)	2159	27.07	NA
Abortion Induced	12	0.15	0.006 / 0.6%
Abortion Spontaneous	101	1.27	0.047 / 4.7%
Congenital, familial, and genetic disorders	79	0.99	0.037 / 3.7%
Ectopic pregnancy	5	0.06	0.002 / 0.2%
Exposures via breast milk	63	0.79	0.029 / 2.9%
Premature birth	67	0.84	0.031 / 3.1%
Male mediated	4	0.05	0.002 / 0.2%
Stillbirth	20	0.25	0.009 / 0.9%
a Some cases may be counted more than once due to multiple events reported in one case			
b The reporting rate is based on cumulative exposure since there is no data by gender.			
c Percentage calculation is based on total number of pregnancy/lactation related cases and events			

From applicant's submission as response to IR February 3, 2016

Lixisenatide

Post-marketing surveillance was gathered from approximately 79 million patient-years of clinical experience.³⁶ In the lixisenatide clinical development program, there were 7 pregnancies confirmed while patients were on active treatment. Three pregnancies occurred in the lixisenatide group, 1 pregnancy occurred in each of the exenatide and sitagliptin groups, and 2 pregnancies occurred in the placebo group. The pregnancies had the following outcomes: 2 healthy babies (1 male (lixisenatide) and 1 female (placebo)) born, 2 stillbirths (1 sitagliptin and 1 lixisenatide), 1 pregnancy that was electively terminated (exenatide), 1 ectopic pregnancy (placebo), and 1 death in utero (lixisenatide) (patient narratives are presented in NDA 208-471, 2.7.4 Summary of Clinical Safety [5.3.5.3 ISS (Section 7.3.2)]) A report by the applicant confirms these 7 pregnancies (see Table 4).

Table 4: Lixisenatide: Case Overview – Cumulative through March 2, 2015^a

MedDRA search	Total	Reporting Rate ^b (per 10,000 patient-years)	Proportional Reporting Rate / Percentage ^c
Pregnancy and neonatal topics (Total cases)	7	1.84	NA
Abortion Induced	0	NA	NA
Abortion Spontaneous	0	NA	NA
Congenital, familial, and genetic disorders	0	NA	NA
Ectopic pregnancy	0	NA	NA
Exposures via breast milk	0	NA	NA
Premature birth	1	0.26	0.14 / 14%
Male mediated	2	0.53	0.29 / 29%
Stillbirth	1	0.26	0.14 / 14%
a Some cases may be counted more than once due to multiple events reported in one case			
b The reporting rate is based on cumulative exposure since there is no data by gender.			
c Percentage calculation is based on total number of pregnancy/lactation related cases and events			

Summary

Patients with diabetes and their fetus have an increased risk for pregnancy complications from the underlying disease. Poorly controlled PGD during pregnancy increases the risk for maternal complications, including diabetic ketoacidosis, preeclampsia, spontaneous abortions (SAB), preterm delivery, polyhydramnios, stillbirth and cesarean section due to fetal macrosomia. In addition, poorly controlled PGD (before conception and in the first trimester) is associated with an increased risk of MCM (5-10%). PGD in pregnant women with poor control during organogenesis is associated with a 3-fold increase in cardiac malformations, lumbosacral agenesis, hyperbilirubinemia, polycythemia, and renal vein thrombosis. Additional MCM observed include: Hydrocephalus, meningomyelocele (lumbar), anencephaly, cleft palate, atresia of pulmonary valve, caudal regression syndrome, agenesis of a kidney, supernumerary toe, anomalous lumbar spine, aplasia of left diaphragm with hypoplasia of left lung, and omphalocele.

There have been no randomized, well-controlled clinical studies of the use of insulin glargine or

³⁶ Mastroyannis, Christos: Lixisenatide review in DARRTS. April 7, 2016

lixisenatide in pregnant women. The available data suggest that there are no identifiable, consistent adverse maternal or fetal outcomes for specific malformations or other fetal/neonatal toxicity with the use of insulin glargine during pregnancy.

Based on the spontaneous global pharmacovigilance data, the proportion of pregnancies with congenital anomalies while on insulin glargine was 3.7%, and with miscarriage in patients on insulin glargine was 4.7%.

Based on literature review and the review of the Sanofi global pharmacovigilance database, there is currently insufficient information to evaluate the safety of lixisenatide in pregnant women. For lixisenatide, the reporting rate for the adverse events of specific interest is 1.84 per 10,000 patient years.

Overall, no additional information that would qualify for inclusion in Section 8.1 Pregnancy of the proposed labeling has been identified.

DPMH recommends the following language be included in the Soliqua 100/33 labeling:

Risk Summary: There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy. The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c > 7 and has been reported to be as high as 20-25% in women with HbA1c > 10.³⁷

Clinical consideration: Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, still birth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity. Insulin therapy and careful medical and obstetrical management are strongly recommended for diabetic women at the time of conception and throughout pregnancy to reduce the risk of diabetes related congenital malformations and other adverse fetal outcomes.^{38,39}

Lactation

Nonclinical Experience

It is not known if insulin glargine is present in animal milk. No studies have been conducted. A study in lactating rats showed low transfer of lixisenatide and its metabolites into milk within 24 hours following a single subcutaneous administration of a 1 mg/kg dose. Drug presence and accumulation in breast milk is species-specific; therefore, no direct relationship can be made about drug levels in human milk.

Review of Literature

Review of the literature by the applicant failed to produce any publications related to insulin glargine or lixisenatide and their presence in breast milk or on the effects on the breastfeeding infant or on lactation.

DPMH conducted a search of Medications and Mother's Milk⁴⁰, the Drugs and Lactation Database (LactMed)⁴¹, Micromedex⁴², and of published literature in PubMed using the search terms "insulin glargine and lactation," "insulin glargine and breastfeeding," "lixisenatide and lactation" and "lixisenatide and

³⁷ Jentadueto and ACTOS existing labeling

³⁸ Allen VM, Armson BA, Wilson RD, Allen VM, Blight C, Gagnon A, Johnson J-A, Langlois S, Summers A, Wyatt P, Farine D, Armson BA, Crane J, Delisle M-F, Keenan-Lindsay L, Morin V, Schneider CE, Van Aerde J: Teratogenicity associated with pre-existing and gestational diabetes. J Obstet Gynaecol Can 29(11):927-944, 2007.

³⁹ Mathiesen ER, Vaz JA: Insulin treatment in diabetic pregnancy. Diabetes Metab Res Rev 24(Suppl 2):S3-S20, 2008

⁴⁰ Hale, Thomas (2012) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing

⁴¹ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

⁴² Truven Health Analytics information, <http://www.micromedexsolutions.com/>.

breastfeeding”. No reports of clinical lactation studies or case reports of Soliqua or its components use in lactating women were found in published literature.

DPMH in review of insulin glargine and lactation including Hale’s Medication and Mother’s Milk, identified no records about insulin glargine. Dr. Hale states “while we have no studies of insulin glargine transfer into human milk, we are certain that small levels of insulin are present. However, most present in milk would likely be totally destroyed in the infant’s gastrointestinal tract prior to absorption. There are no contraindications to using insulin or its derivatives in breast feeding mothers”. A review of Toxnet revealed no records of insulin glargine and lactation.

A review of the literature by the Applicant regarding lixisenatide and lactation, failed to produce any publications. DPMH in review of lixisenatide and lactation including Hale’s Medication and Mother’s Milk, identified no records about lixisenatide. A review of Toxnet⁴³ revealed no records of lixisenatide and lactation.

It is not known whether lixisenatide is present in human milk.

Reviewer comment

Lixisenatide is a peptide and any amount present in human milk would most likely be degraded in the gastrointestinal system (GI) of the infant (as seen in rats). Half-life of lixisenatide is about 3 hours. Therefore, the amount a breastfed infant may be exposed to is likely to be low.

Summary

There were no adverse events observed when infants exposed to insulin glargine via breast milk.

(b) (4) and current labeling of lixisenatide and given the lack of lactation information for lixisenatide, DPMH recommends that the following statement appear in the “Risk Summary” section of Soliqua (insulin glargine and lixisenatide) labeling:

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Soliqua and any potential adverse effects on the breastfed infant from Soliqua or from the underlying maternal condition.

Females and Males of Reproductive Potential

Nonclinical Experience

No animal fertility studies were performed for either Soliqua or insulin glargine.

Lixisenatide

Non-clinical studies in which male and female rats received twice daily subcutaneous doses of 2, 29, or 414 mcg/kg/dose prior to pairing through gestation day 6 did not indicate any adverse effects on male or female fertility in rats up to the highest dose tested, 414 mcg/kg/dose, or approximately 300 times the clinical systemic exposure at 20 mcg/day based on plasma AUC.⁴⁵ No adverse effects of GLP-1 agonists on male or female fertility have been observed in animals (mice) even when the drug was administered in very high

⁴³ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

(b) (4)

⁴⁵ Pharmacology/Toxicology review on Lixisenatide by Feleke Eshete, Ph.D/Todd Bourcier, Ph.D. in DARRTS, April 8, 2016, Reference ID: 3914355 and DPMH review by Christos Mastroyannis, M.D. in DARRTS, April 7, 2016 Reference ID:391226

doses (over 300 times the clinical systemic exposure).

Review of Literature

The applicant, even though referring to literature search for “insulin glargine” and “lixisenatide” and “males and females of reproductive potential”, no references are identified.

DPMH performed a search of published literature in PubMed and Embase on insulin glargine and infertility as well as on lixisenatide, and did not identify any publications.

Summary

Animal reproductive studies of administration of lixisenatide did not show any adverse effects on fertility in animals (mice) even when the drug was administered in very high doses (over 300 times the clinical systemic exposure). Because there are no human data available on the effect of insulin glargine or lixisenatide on fertility, and no evidence of infertility in animal studies to inform a potential clinical risk, Section 8.3, Females and Males of Reproductive Potential, will not be included in Soliqua labeling.

CONCLUSION

The Pregnancy and Lactation, sections of Soliqua 100/33 labeling were structured to be consistent with the PLLR as follows:

- **Pregnancy, Section 8.1**
 - The “Pregnancy” section of Soliqua labeling was formatted in the PLLR format to include: “Risk Summary”, “Clinical Considerations” and “Data” sections.
- **Lactation, Section 8.2**
 - The “Lactation” section of Soliqua labeling was formatted in the PLLR format to include the “Risk Summary” and “Data” sections.
- **Females and Males of Reproductive Potential, Section 8.3**
 - Females and Males of Reproductive Potential, Section 8.3 is omitted because there is nothing to be reported.
- **Patient Counseling Information, Section 17**
 - The “Patient Counseling Information” section of labeling was updated to correspond with changes made to sections 8.1 of labeling.

RECOMMENDATIONS

DPMH revised sections 8.1, 8.2 and 17 of labeling for compliance with the PLLR (see below). The below recommendation include discussion with the Nonclinical and discussion from the October 4, 2016 labeling meeting and October 26, labeling edits. DPMH refers to the final NDA action for final labeling.

DPMH PROPOSED PREGNANCY AND LACTATION LABELING EDITS FOR SOLIQUA

-----USE IN SPECIFIC POPULATIONS-----

- Use during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1)

FULL PRESCRIBING INFORMATION: CONTENTS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

17 PATIENT COUNSELING INFORMATION

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data with Soliqua and lixisenatide in pregnant women are not sufficient to inform a drug-associated risk of major birth defects and miscarriage. Published studies with insulin glargine use during pregnancy have not reported a clear association with insulin glargine and major birth defect or miscarriage risk [see Data]. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see *Clinical Considerations*]. Based on animal reproduction studies, there may be risks to the fetus from exposure to lixisenatide, a component of SOLIQUA, during pregnancy. SOLIQUA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Lixisenatide administered to pregnant rats and rabbits during organogenesis was associated with visceral closure and skeletal defects at systemic exposures that decreased maternal nutritional intake and weight gain during gestation, and that are 1-time and 6-times higher than the exposure at the 20 mcg/day clinical dose, respectively, based on plasma AUC [see Data]. At these exposures, concomitant maternal toxicity was also observed in the animals.

(b) (4)

. The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c>7 and has been reported to be as high as 20-25% in women with HbA1c>10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, still birth and delivery complications.

Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

(b) (4)

Data

Human Data

Insulin glargine

Published data do not report a clear association with insulin glargine and major birth defects, miscarriage, or adverse maternal or fetal outcomes when insulin glargine is used during pregnancy. However, these studies cannot definitely establish the absence of any risk because of methodological limitations including small sample size and some with no comparative group.

Animal Data

Animal reproduction studies were not conducted with the combined products in SOLIQUA. The following data are based on studies conducted with the individual components of SOLIQUA.

Lixisenatide

In pregnant rats receiving lixisenatide twice daily subcutaneous doses of 2.5, 35, or 500 mcg/kg during organogenesis, from gestation day 6 to 17, fetuses were present with visceral closure defects (e.g., microphthalmia, bilateral anophthalmia, diaphragmatic hernia) and stunted growth. Impaired ossification associated with skeletal malformations (e.g., bent limbs, scapula, clavicle, and pelvis) were observed at ≥ 2.5 mcg/kg/dose, resulting in systemic exposures that are 1 time the 20mcg/d clinical dose, based on plasma AUC. Decreases in maternal body weight, food consumption, and motor activity were observed concurrent with the adverse fetal findings. Placental transfer of lixisenatide to developing rat fetuses is low with a concentration ratio in fetal/maternal plasma of 0.1%.

In pregnant rabbits receiving twice daily subcutaneous doses of 2.5, 25, 250 mcg/kg from gestation day 6 to 18 (organogenesis), fetuses were present with multiple visceral and skeletal malformations, including closure defects, at ≥ 5 mcg/kg/dose or systemic exposures that are 6-times the 20 mcg/day highest clinical dose, based on plasma AUC. Decreases in maternal body weight, food consumption, and motor activity were observed concurrent with the fetal findings. Placental transfer of lixisenatide to developing rabbit fetuses is low with a concentration ratio in fetal/maternal plasma of $\leq 0.3\%$. In a second study in pregnant rabbits, no drug-related malformations were observed from twice daily subcutaneous doses of 0.15, 1.0 and 2.5 mcg/kg administered during organogenesis, resulting in systemic exposures up to 9- times the clinical exposure at 20 mcg/day, based on plasma AUC.

In pregnant rats given twice daily subcutaneous doses of 2, 20, or 200 mcg/kg from gestation day 6 through lactation, decreases in maternal body weight, food consumption, and motor activity were observed at all doses. Skeletal malformations and increased pup mortality were observed at 400 mcg/kg/day, which is approximately 200-times the 20 mcg/day clinical dose, based on mg/m².

Insulin glargine

Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 2-times the recommended human subcutaneous high dose of 60 units/day (0.0364 mg/kg/day), based on mg/m². In rabbits, doses up to 0.072 mg/kg/day, which is approximately 1-times the maximum recommended human subcutaneous dose of 60 units/day (0.0364 mg/kg/day), based on mg/m², were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

8.2 Lactation

Risk Summary

There is no information regarding the presence of lixisenatide and insulin glargine in human milk, the effects on the breastfed infant, or the effects on milk production. Endogenous insulin is present in

human milk. Lixisenatide is present in rat milk;

(b) (4)

[see Data]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SOLIQUA 100/33 and any potential adverse effects on the breastfed infant from SOLIQUA 100/33 or from the underlying maternal condition.

Data

Lixisenatide

A study in lactating rats showed low (9.4%) transfer of lixisenatide and its metabolites into milk and negligible (0.01%) levels of unchanged lixisenatide peptide in the gastric contents of weaning offspring.

17 PATIENT COUNSELING INFORMATION

Pregnancy: Advice patients to inform their physicians if they are pregnant or intend to become pregnant [see *Use in Specific Populations (8.1)*].

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

/s/

CHRISTOS MASTROYANNIS
10/26/2016

TAMARA N JOHNSON
10/27/2016

LYNNE P YAO
10/27/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
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:	October 6, 2016
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208673
Product Name and Strength:	Soliqua 100/33 (insulin glargine and lixisenatide), injection, (b) (4) units insulin glargine and 99 mcg lixisenatide per 3 mL pen (100 units insulin glargine and 33 mcg lixisenatide per mL)
Submission Date:	August 11, 2016
Applicant/Sponsor Name:	Sanofi-Aventis
OSE RCM #:	2015-2775-1
DMEPA Primary Reviewer:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader (Acting):	Hina Mehta, PharmD
DMEPA Deputy Director:	Lubna Merchant, MS, PharmD

1 PURPOSE OF MEMO

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the prescribing information (PI), Medication Guide, Instructions for Use (IFU), carton labeling, and container label for Soliqua (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that were made during a previous label and labeling review^a and advice from DMEP^b. In addition, DMEP requested we provide additional comments regarding options considered to determine the most appropriate

^a Conrad A. Label and Labeling and Human Factors Results Review for Insulin Glargine and Lixisenatide (NDA 208673). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 April 12. 22 p. OSE RCM No.: 2015-2775 and 2015-2782.

^b White M. COR-MEET-08 (Late-Cycle Meeting Minutes) for insulin glargine and lixisenatide. Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2016 June 22. NDA 208673.

term of measure to communicate the dose of Soliqua in the labeling from a medication error prospective.

2 DISCUSSION

We considered various options for the term of measure that would be most appropriate to communicate the dose of Soliqua in the labeling. We discussed multiple options with DMEP and the Office of Policy for Pharmaceutical Quality (OPPQ) and these are outlined below:

1. Introduction of the novel term (b) (4) and others as proposed by Sanofi
 - a. Based on our experience, we determined that the introduction of a novel term for this product (and others in this class) would introduce confusion because the terms proposed do not indicate any of the product contents. In addition, we believe that electronic prescribing systems would have difficulty accommodating this non-standardized measure term.
2. Use of the term “units” as proposed by Sanofi
 - a. We acknowledge that this term may be considered misleading since it only references the insulin component and does not impart the presence of two medications. However, we determined that this term is the least problematic of the options available considering that the applicant has based the dosing strategy for Soliqua on the number of insulin units contained in the dose and designed the pen device to dial based on the units of insulin. In addition, healthcare practitioners and patients are familiar with the measure term “units” and electronic prescribing systems are already designed to accommodate this term.
3. Use of the terms “units/mcg” or “mcg” alone
 - a. The numbers on the current pen dial are designed to correspond to the dose of insulin. We determined that using terms such as “units/mcg” or “mcg” would be confusing for end users, especially considering that the pen design requires dialing the Soliqua dose based on units of insulin. In order to accommodate either of these options, the pen would have to be redesigned to indicate either the dose of both medications or the GLP-1 component alone on the pen dial.
4. No term of measure
 - a. We determined that this was not a viable option because expressing a dose without a term of measure would result in miscommunication of the dosing information and we anticipate that electronic prescribing systems would not be able to support a lack of a measure term.

These recommendations were discussed with DMEP and DMEP determined that use of the term “units” would be the least problematic strategy for communicating the dose for this product in the labeling. We acknowledge that there are some residual risks with the use of the measure term “units” in instances where prescribers do not read the prescribing information and are not familiar with the contents of Soliqua and assume that the product only contains insulin. Thus, we have provided recommendations to revise the product label and labeling to increase the clarity and prominence of critical dosing information. Furthermore, following discussion with DMEP, numerical modifiers were added to the proprietary name to help convey

to healthcare providers that the formulation contains two ingredients (i.e., Soliqua 100/33). This nomenclature is similar to that currently used for marketed insulin/insulin mixtures, where the numerical modifier conveys the percentage of each insulin in the mixture.

This review identified several areas that could be clarified within the proposed labels and labeling and we provide recommendations below. We have determined that follow-up human factors testing of the Instructions for Use (IFU) is not necessary since the recommended modifications do not alter the current content and are primarily for clarification of key information. In addition, the Division of Metabolism and Endocrinology Products (DMEP) recently provided recommendations^c to the sponsor for the labeling and pen dial (Appendix B) but the sponsor has not submitted updated labeling for review. Therefore, we may have additional comments upon review of that material.

3 CONCLUSION

This review identified several deficiencies in the prescribing information (PI), the Instructions for Use (IFU), and Medication Guide. We provide recommendations in Section 4 and recommend their implementation prior to approval of this NDA. In addition, we identified deficiencies in the container label and carton labeling and recommendations are provided in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)

1. Highlights of Prescribing Information: Dosage and Administration

- a. Add the following statement as (b) (4) bullet in this section for improved visibility of this information: “(b) (4) Soliqua pen (b) (4) deliver doses from 15 to 60 units (b) (4) injection (b) (4)”

2. Highlights of Prescribing Information: Dosage Forms and Strengths

- a. Revise the current statement as follows for improved clarity:
“Injection: 100 units (b) (4) insulin glargine and 33 mcg (b) (4) lixisenatide in a 3 mL (b) (4) pen.”

3. Full Prescribing Information: (b) (4)

- a. We recommend using bullets for the text in this section for improved readability.
- b. Revise the statement starting with (b) (4)

^c White M. COR-NDAIR-01 (Information Request) for insulin glargine and lixisenatide. Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2016 Sept 6. NDA 208673.

(b) (4)

4. Full Prescribing Information: Section (b) (4) Titration of Soliqua

- a. Modify this statement for improved clarity as follows:

(b) (4)

5. Full Prescribing Information: Section 3 Dosage Forms and Strengths

- a. Remove the statement

(b) (4)

from this section

(b) (4)

6. Full Prescribing Information: Section 16.1 How Supplied

- a. Modify the statement “(b) (4) to
“Soliqua (b) (4) supplied as a clear, colorless solution in a prefilled,
disposable, single-patient use, (b) (4) pen (b) (4)

7. Full Prescribing Information: Section 16.2 Storage

- a. Revise the statement (b) (4) as follows for
improved clarity: “Discard after the expiration date printed on the label

(b) (4)

B. Instructions for Use (IFU)

1. Revise the title to correspond with the name approved for use on the final pen label and carton labeling for consistency across all product labeling.
2. Remove the statement (b) (4) from the document title.
3. Following the statement “The drug combination in this pen is only for the daily injection of 15 to 60 units of Soliqua”, add the following: “Each unit dialed contains 1 unit insulin glargine/0.33 mcg lixisenatide.”.
4. Under “Important Information”, revise the bulleted statement (b) (4) as follows: “Perform a safety test before each injection”.
5. Under “Learn to Inject”, revise the bulleted statement that begins “(b) (4) as follows to increase prominence of the important information in the statement: “Read all of these instructions before using your pen. You may get too much or too little medication if you do not follow the instructions correctly.”
6. Under “(b) (4) you will need”, we recommend removing the bulleted statement “(see Step 2)” because it appears to be out of place and not

associated with an item. Also, we recommend revising the statement (b) (4) as follows to improve clarity: “(see “Throwing your pen away” (b) (4) at the end of these Instructions for Use)”.

7. For Step 1, we recommend improved differentiation (i.e., bolding and/or underlining) for the statement “Take a new pen out of the refrigerator at least 1 hour before you inject.”
8. For Step 1A, add the phrase “on the pen label” at the end of the bulleted statement “**Do not** use your pen after the expiration date.” for improved clarity.
9. Under Step 3B, we recommend revising the bulleted statement (b) (4) to improve clarity: “change the needle (see Step 6 to remove the needle and Step 2 to (b) (4) attach (b) (4) needle),”.
10. Under Step 4B (b) (4) we commend revising the bulleted statements as follows: (b) (4)
11. Under Step 4B “(b) (4)” add the following as a bulleted statement after the first bullet in this section: “Do not dial your dose by counting the clicks. You (b) (4) dial the wrong dose. Always check the number in the dose window to make sure you dialed the correct dose.”

C. Medication Guide

1. Revise the title to correspond with the name approved for use on the final pen label and carton labeling for consistency across all product labeling.
2. Under the “What is Soliqua?” section, revise the statement to include the concentration of lixisenatide as follows: “Soliqua is a prescription medicine (b) (4) that contains 2 diabetes medications, insulin glargine (b) (4) and lixisenatide (b) (4)”.

5 RECOMMENDATIONS FOR SANOFI

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

A. Carton Labeling

1. Revise the product name to correspond with the name approved for use on the final pen label and carton labeling for consistency across all product labeling.
2. Revise the statement “(b) (4)” to “See prescribing information” for improved clarity.
3. On the principal display panel, add the following statement immediately below the product concentration information: “With each unit of insulin glargine the pen also delivers 0.33 mcg of lixisenatide”.
4. On the principal display panel, remove the statement “Use within 14 days after (b) (4)”.

5. On the back panel, revise the statement “Use within 14 days after (b) (4) use” to read “Use within 14 days after (b) (4).” for improved clarity. In addition, revise the statement “(b) (4)” to read “Soliqua pen should be stored at room temperature after first use.”
6. On the back panel, change the statement (b) (4) to read “Date of First Use” for improved clarity.
7. On the back panel, revise the statement “(b) (4)” to read (b) (4) be refrigerated (b) (4) at 36°F to 46°F (2°C to 8°C).” for improved clarity.

B. Container Label

1. Add the following statement immediately below the product concentration information: “Each unit of Insulin (b) (4) pen also delivers 0.33 mcg of lixisenatide”. Consider minimizing the font size or relocating the statements “Only for doses from 15 to 60 units” and “3 mL prefilled pen” to provide space for the above statement.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

ARIANE O CONRAD
10/06/2016
updated

HINA S MEHTA
10/06/2016

LUBNA A MERCHANT
10/07/2016

Clinical Inspection Summary

Date	7/8/2016
From	Cynthia F. Kleppinger, M.D., OSI/DCCE/GCPAB Janice Pohlman, M.D., M.P.H., OSI/DCCE/GCPAB, Team Leader Susan Thompson, M.D. <i>for</i> Kassa Ayalew, M.D., M.P.H., OSI/DCCE/GCPAB, Branch Chief
To	Suchitra Balakrishnan, M.D., Ph.D., Clinical Reviewer William Chong, M.D., Team Leader Martin White, M.S., Regulatory Health Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA/BLA #	NDA 208673
Applicant	Sanofi-Aventis U.S. LLC
Drug	Insulin glargine and lixisenatide (HOE901/AVE0010)
NME (Yes/No)	No
Therapeutic Classification	Antidiabetic
Proposed Indication(s)	Treatment for type 2 diabetes mellitus
Consultation Request Date	1/21/2016
Summary Goal Date	7/15/2016
Action Goal Date	8/19/2016
PDUFA Date	8/21/2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA involved two domestic and two foreign clinical sites consisting of seven sites for two studies.

The classification for Dr. Larson is Voluntary Action Indicated (VAI). Although regulatory violations were noted (as described below), they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from this site is acceptable for use in support of the indication for this application. The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The classification for Drs. Vorokhobina, Zhdanova, and Frias is No Action Indicated (NAI). Data from these sites are considered reliable based on the available information. The full Establishment Inspection Report (EIR) for Dr. Frias was submitted for review. The EIR was not available for review for Drs. Vorokhobina and Zhdanova. Preliminary inspection results were communicated by the FDA ORA field investigator.

In general, based on the inspections of the four clinical sites, the inspectional findings support validity of data as reported by the Sponsor under this NDA.

All classifications are considered preliminary until the final communication letter is sent to the inspected entity. An inspection summary addendum will be generated if conclusions change upon receipt and review of the pending EIRs.

II. BACKGROUND

Sanofi-aventis U.S., LLC is seeking approval for insulin glargine/lixisenatide combination (HOE901/AVE0010), a fixed ratio combination product of a long-acting human insulin analog (insulin glargine, 100 Units/ml) together with a glucagon like peptide-1 (GLP-1) receptor agonist (lixisenatide). It is proposed to be used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both insulin glargine and lixisenatide is appropriate.

Insulin glargine has been registered and marketed in the U.S. since April 20, 2000 as Lantus® (insulin glargine [rDNA origin] injection, 100 Units/mL). The lixisenatide NDA (NDA 208471) was submitted to the FDA on July 27, 2015 and is currently under review for the treatment of adults with type 2 diabetes mellitus.

The combination has been developed with two different dose ratios in disposable pre-filled pens:

- The 10 to 40 pen delivers 10 to 40 Units at a ratio of 2 U glargine/1 µg lixisenatide. Doses from 10 to 40 U in steps of 1 unit allow administration of daily combination doses between 10 U glargine/5 µg lixisenatide and 40 U glargine/20 µg lixisenatide.
- The 30 to 60 pen delivers 30 to 60 Units at a ratio of 3 U glargine/1 µg lixisenatide. Doses from 30 to 60 U in steps of 1 unit allowing administration of daily combination doses between 30 U glargine/10 µg lixisenatide and 60 U glargine/20 µg lixisenatide.

Inspections were requested for the following two clinical studies:

- **EFC12404** “A randomized, 30-week, active-controlled, open-label, 3-treatment arm, parallel-group multicenter study comparing the efficacy and safety of insulin glargine/lixisenatide fixed ratio combination to insulin glargine alone and to lixisenatide alone on top of metformin in patients with Type 2 diabetes mellitus (T2DM)”

There were 240 centers in 23 countries involved. Of the 2457 patients screened, 1479 patients started the run-in phase, 1170 patients were randomized and 1085 patients completed the study. The first patient enrolled February 12, 2014 and the last patient completed on June 17, 2015. The primary efficacy endpoint was change in HbA1c (%) from baseline to Week 30.

- **EFC12405** “A randomized, 30-week, active-controlled, open-label, 2-treatment arm, parallel-group, multicenter study comparing the efficacy and safety of the insulin glargine/lixisenatide fixed ratio combination to insulin glargine with or without metformin

in patients with Type 2 diabetes mellitus (T2DM)”

There were 187 centers in 18 countries involved. Of the 1930 patients screened, 1018 patients entered the 6-week run-in phase, 736 patients were randomized, and 691 patients completed the study. The first patient enrolled January 27, 2014 and the last patient completed July 09, 2015. The primary efficacy endpoint was change in HbA1c (%) from baseline to Week 30.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 208673 in accordance with Compliance Program 7348.811. General instructions were also provided with the assignment.

Sites were chosen based on the Office of Scientific Investigation’s site selection tool. To expand coverage, priority was given to sites that enrolled in both studies and had never been inspected.

III. RESULTS (by Site):

Name of CI/ Address/ Site#	Protocol # and # of Subjects Randomized	Inspection Date	Classification*
Juan P. Frias, MD 2010 Wilshire Blvd., Suite 302 Los Angeles, CA 90057 Site 840044 Site 840581	EFC12404 12 subjects EFC12405 5 subjects	03/02 – 03/09/2016	No Action Indicated (NAI)
David C. Larsen, MD 4001 South 700 East, Suite 105 Salt Lake City, UT 84107 Site 840041	EFC12404 11 subjects	05/31 – 06/07/2016	Voluntary Action Indicated (VAI)
Natalia Vorokhobina, M.D., Ph.D. 14, Vavilovkykh Street St. Petersburg, 195257 Russia Site 643002 Site 643502	EFC12404 5 subjects EFC12405 9 subjects	04/10 – 04/19/2016	No Action Indicated (NAI)
Elena Zhdanova, M.D., Ph.D. Lenina Sq., 5a Voronezh, 394018 Russia		04/20 – 04/29/2016	No Action Indicated (NAI)

Site 643004	EFC12404 13 subjects		
Site 643509	EFC12405 10 subjects		

Key to Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations; data unreliable.

*Pending = Preliminary classification based on information in 483 (if applicable) and preliminary communication with the field; final classification is pending letter to site.

NOTE: Site inspections focused on 100% review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor's data line listings.

1. Juan Frias/ Site 840044 for Study EFC12404/ Site 840581 for Study EFC12405

For Study EFC12404, there were 26 subjects screened and 12 subjects enrolled into the study; 10 subjects completed the study. All subject records were reviewed.

For Study EFC12405, there were 8 subjects screened and 5 subjects enrolled into the study; 5 subjects completed the study. All subject records were reviewed.

The site files were well-organized, legible, and complete. There were no issues with informed consent. The institutional review board of record was (b) (4).

All subjects met inclusion/exclusion criteria. The primary efficacy endpoint was verifiable for both studies. There was no under-reporting of adverse events. Source records were compared to the sponsor data line listings and there were no discrepancies.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

2. David Larsen/ Site 840041 for Study EFC12404

There were 22 subjects screened and 11 subjects enrolled into the study; nine subjects completed the study. Subject 84004105 withdrew because of an adverse event; Subject

84004120 died of congestive heart failure. Both appeared to be appropriately reported. All 11 records of enrolled subjects and four screen failure records were reviewed. All 22 informed consent forms were reviewed.

The site files were well-organized, legible, and complete. There were no issues with informed consent.

There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable. Secondary efficacy endpoints were verifiable with the exception of Subject 84004121. This subject did not complete the required seven-point self-monitored plasma glucose (7-SMPG) prior to Visit 5, yet was enrolled.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. An investigation was not conducted in accordance with the investigational plan. Specifically, ineligible subjects were enrolled in the study.
 - a. On 05/02/2014 (Visit 4), study Subject 84004106's fasting plasma glucose level was 293 mg/dL. Despite meeting exclusion criteria (fasting plasma glucose > 250 mg/dL at Visit 4), the subject was enrolled, randomized, and administered study drug at Visit 5 on 05/09/2014.
OSI Reviewer Comment: This was an acknowledged oversight of the site. When they became aware of the oversight, they reported the deviation to their IRB.
 - b. On 04/10/2014, study Subject 84004112 was screened for study participation; no hypertension was noted. On 05/13/2014, the site sought clarification from the study's Medical Monitor regarding the subject's eligibility to participate and receive study drug as the diastolic blood pressure reading was high. On 05/21/2014 (Visit 5), the subject was enrolled, randomized, and administered study drug—despite the absence of clarification from the Medical Monitor. On 05/22/2014, the Investigator was informed that Subject 84004112 met exclusion criteria and should be a screen failure.
OSI Reviewer Comment: The subject did not have a history of hypertension, but had a reading of an elevated diastolic blood pressure of 99 mmHg and it was not clear if this qualified per protocol as being "uncontrolled or inadequately controlled hypertension". As there was a delay in the Medical Monitor response, the investigator determined that it did not. Source records show several blood pressure readings that were within normal limits.
 - c. Study mandated tasks were not completed for Subject 841004121 who failed to perform the required seven-point self-monitored plasma glucose (7-SMPG) sampling prior to receiving the first administration of study drug on 06/12/2014.
OSI Reviewer Comment: The PI acknowledged that he was aware that the subject was non-compliant but elected to enroll the subject within the

required window.

An adequate response to the observations with corrective actions was received June 23, 2016.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable.

3. Natalia Vorokhobina/ Site 643002 for Study EFC12404/ Site 643502 for study EFC12405

For study EFC12404, there were 11 subjects screened and 5 subjects enrolled into the study; 5 subjects completed the study. All subject records were reviewed.

For study EFC12405, there were 24 subjects screened and 9 subjects enrolled into the study; 9 subjects completed the study. All subject records were reviewed.

The primary efficacy endpoint was verifiable for both studies. There was no under-reporting of adverse events. Source records were compared to the sponsor data line listings and there were no discrepancies.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

4. Elena Zhdanova/ Site 643004 for Study EFC12404 / Site 643509 for Study EFC12405

For study EFC12404, there were 16 subjects screened and 13 subjects enrolled into the study; 13 subjects completed the study. All subject records were reviewed.

For study EFC12405, there were 11 subjects screened and 10 subjects enrolled into the study; 10 subjects completed the study. All subject records were reviewed.

The primary efficacy endpoint was verifiable for both studies. There was no under-reporting of adverse events. Source records were compared to the sponsor data line listings and there were no discrepancies.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
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Susan Thompson, M.D. *for*
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CC:

Central Doc. Rm./ NDA 208673
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DMEP /Deputy Director/Jim P. Smith
DMEP/Team Lead/William Chong
DMEP/Clinical Reviewer/Suchitra Balakrishnan
DMEP /Regulatory Project Manager/Martin White
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OSI/DCCE/GCPAB/Program Analyst/Joseph Peacock/Yolanda Patague
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CYNTHIA F KLEPPINGER
07/08/2016

JANICE K POHLMAN
07/08/2016

SUSAN D THOMPSON
07/08/2016

GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM



ICC 1500701 / NDA 208673

Date: June 2, 2016

To: Martin White,
Division of Metabolism and Endocrinology Products (DMEP),
Office of Drug Evaluation I (ODEI),
Office of New Drugs (OND),
Center for Drug Evaluation and Research (CDER)

From: John McMichael
General Hospital Devices Branch (GHDB),
Division of Anesthesiology, General Hospital, Respiratory,
Infection Control, & Dental Devices (DAGRID),
Office of Device Evaluation (ODE),
Center for Devices and Radiological Health (CDRH)

Through: CDR Alan Stevens, Branch Chief
General Hospital Devices Branch (GHDB),
Division of Anesthesiology, General Hospital, Respiratory,
Infection Control, & Dental Devices (DAGRID),
Office of Device Evaluation (ODE),
Center for Devices and Radiological Health (CDRH)

Subject: Sanofi has developed a pen-injector to insulin glargine and lixisenatide as a combination product and CDER has consulted CDRH to review the device constituent parts of the combination product for this new NDA.

Applicant	Sanofi-Aventis LLC
Indication for Use	An adjunct to diet and exercise to improve glycemic control in the treatment of adults with type 2 diabetes mellitus.
Drug / Biologic Constituent	LixiLan (Insulin glargine and 50 or 33 microgram/milliliter lixisenatide)
Device Constituent	Pen-injectors and cartridges: Pen A and Pen B

Recommendation:

Device Constituent Parts of Combination Product are Approvable with (1) Post-Market Commitment.

Post-Market Commitment:

The Sponsor has committed to performing ongoing stability analysis to assess maintenance of the essential performance requirements of the final finished combination product through the intended expiration date of (b) (4) months using primary registration stability batches. The sponsor should submit evidence of completion of these activities to NDA annual reports

Digital Signature Concurrence Table	
Reviewer Sign-Off	John C. McMicheal -S Date: 2016.06.02 15:16:25 -04'00'
Branch Sign-Off	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2016.06.02 15:20:07 -04'00'

I. Review Summary

The device consultant authoring this review memorandum has performed a design review of submission materials intended to support the safety and functionality of the device constituent parts of the subject combination product. This memo covers review of design documentation for the final finished pen-injector combination product. This review did not cover manufacturing of the device constituent parts, sterility or biocompatibility of the primary container closure, or usability of the device constituent parts.

The review of submission documentation by CDRH/ODE found that the product components are of acceptable pedigree and that essential performance of the final fished device can be assured with a reasonable degree of certainty. Essential performance elements of the device under review by the consultants were considered to be:

- Dose accuracy of each dose presentation
- Connection and compatibility of components
- Sterility and biocompatibility of non-primary container closure components
- Functionality of the pen-injector
- Stability after exposure to preconditioning/aging and shipping conditions
- Risk management documentation of the device constituent parts

Review of this information found that there are sufficient design control documentation and verification/validation activities for the device constituent part of the combination product to recommend approval.

II. Consult Purpose

The Center for Drugs Evaluation and Research (CDER) requested a consult from CDRH/ODE for device constituent part design review of NDA 208673, which is a combination product consisting of two pen injectors that deliver LixiLan (Insulin glargine and 50 or 33 microgram/milliliter lixisenatide) for the treatment of diabetes mellitus. This NDA has been submitted by Sanofi and this original NDA is being brought to Advisory Committee due to the unorthodox nature of combining the two drug products in relation to clinical practice and expected use conditions.

III. Coverage of Review / Review Team

CDRH/ODE reviews content related to the design of device constituent parts for combination product submissions. This review focuses on evaluation of design control documentation (21 CFR 820.30), which includes design requirements and verification/validation information to support the device constituent part, including essential performance of the device constituent part and reliability of the

device constituent part over time and after expected environmental exposures. Device risk analysis documentation is also evaluated as part of design validation activities.

Documents Reviewed:

- Container Closure System – Cartridge – QUA-FM-2014-20994
- Container Closure System – Pen-injector – QUA-FM-2014-01973
- Container closure system – pen-injector – QUA-FD-2015-13118
- Container closure system – cartridge – QUA-FG-2014-19612
- Description and composition of the pen-injector – QUA-FD-2015-02270
- Comparison of clinical pen-injector to commercial pen-injector – QUA-FD-2015-13644
- Pen injector performance test – ISO 11608-1 – QUA-FD-2015-01947
- Pen injector performance test – ISO 11608-1 – Appendix - QUA-FD-2015-10434
- Container closure system - Performance test (ISO 11608-3 and 13926-2) – QUA-FM-2014-22382
- Cartridge performance test – ISO 11608-3 and ISO 13926-2 – Appendix I – QUA-FM-2015-21250
- Simulated shipping study – QUA-FD-2015-19978
- Response to FDA request dated 02-March-2016 – CMC
- Dispense force report – pen A pen B – QUA-FD-2016-06238
- Dial (b) (4) report – pen A and pen B – QUA-FD-2016-06237
- Needle compatibility report – pen A pen B – QUA-FD-2016-06240
- Cap attachment and removal force report – pen A and pen B – QUA-FD-2016-06224
- Maximum dose stop report – pen A pen B – QUA-FD-2016-06302
- Pen-injector Risk Management Results – QUA-FD-2015-16111
- Pen-injector Risk Management Summary – QUA-FD-2015-15002
- Stability data CE dose accuracy – QUA-FR-2015-05894
- Stability summary and conclusions – dose accuracy – QUA-FR-2015-05889
- Initiation doses in clinical study EFC12405 – Appendix 2 – QUA-FD-2015-27134
- Pen-related events in clinical studies EFC12404 and EFC12405 – Appendix 1 – QUA-FD-2015-27132
- Pen-related events and initiation dose deviations observed in clinical trials – QUA-FD-2015-24611
- Insulin glargine/lixisenatide – Original NDA – 10to40units-1ct-SoloStar-container
- Insulin glargine/lixisenatide – Original NDA – 30to60units-1ct-SoloStar-container
- Insulin glargine/lixisenatide – Original NDA – 10to40units-1ct-SoloStar-carton
- Insulin glargine/lixisenatide – Original NDA – 30to60units-1ct-SoloStar-carton
- Response to FDA request dated 15-March-2016 – CMC
- Response to FDA request dated 26-April-2016 – CMC
- Response to FDA request dated 09-May-2016 – CMC

Note: Documents reviewed for the biocompatibility of the pen-injector are listed in Dr. Sarah Mollo's review attached to this memo.

Review Team:

Team Member	Role
John McMichael (CDRH/ODE/GHDB)}	Lead Reviewer – Engineering
Dr. Sarah Mollo (CDRH/ODE/GHDB)	Consultant – Biocompatibility (Consult Review Attached)
Dr. Patricia Beaston (CDRH/ODE/GHDB)	Consultant - Clinical

IV. Device Description

Cartridge:

Section 3.2.P.7 of the submission contains summary information on the design of the drug delivery system selected to administer the subject medication. The sponsor states that the device constituent part of the combination product is a cartridge and a pen-injector delivery system. The “primary container closure” system is composed of the following components:

Table 1 - Description of drug product packaging components				
Type	Material	Color	Remarks	Reference
(b) (4)				

The sponsor references several drug master files (DMFs) for the primary container closure:

Table 2 – Supplier(s) of the primary packaging components

Primary packaging	Supplier(s)	Reference
(b) (4)		

Pen-injectors:

The secondary container closure system of the combination product is the pen-injector. Note that there are two separate presentations of the pen-injector, “Pen A” and “Pen B,” representing two different concentrations and dose ranges. Pen A is intended for 50 µg/mL lixisenatide with 100 U/mL insulin glargine with a selectable dose range of 10-40 units. Pen B is intended for 33 µg/mL lixisenatide with 100 U/mL insulin glargine with a selectable dose range of 30-60 units. The pen-injectors are identical in their composition and materials and are composed of the following components:

Figure 2 – Insulin glargine/lixisenatide pen-injectors with different colors

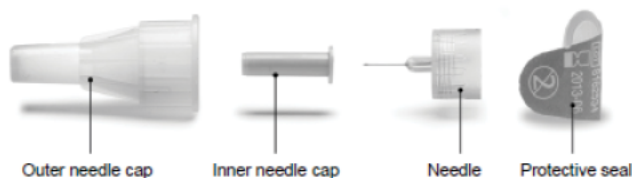
Pen designation	Pen A		Injection button color
Color of pen	Peach		
Concentration insulin glargine	100 U/mL		
Concentration lixisenatide	50 µg/mL		orange
Pen designation	Pen B		Injection button color
Color of pen	Olive		
Concentration insulin glargine	100 U/mL		
Concentration lixisenatide	33 µg/mL		dark orange

The Sponsor states that the needles are not provided with the pen-injectors and are supplied separately. The following is a description of the compatible needles:

A needle must be attached to the thread on the cartridge-end of the device by screwing it onto the cartridge holder. This thread was developed according to ISO 11608-2 (1) which defines the standard for needles and the related thread. A new needle should always be used for each injection to prevent contamination or possible needle blockage.

The insulin glargine/lixisenatide pen-injector is not marketed with needles (Figure 11). The pen-injector needles are supplied separately.

Figure 11 – Pen-injector needle (example)



The Sponsor has provided the following list of compatible needles for the pen-injectors:

Examples of needles compatible with the insulin glargine/lixisenatide pen-injector are provided in Table 4. All needles/brands manufactured by companies listed in Table 4 are compatible.

Table 4 - Examples of needles compatible with the insulin glargine/lixisenatide pen-injector

Brand	Needle type	Needle manufacturer
(b) (4)		

This list is provided for review purposes only and will not be maintained or updated as part of this submission

The Sponsor states that the final to-be-marketed presentation of the pen-injectors is slightly different than those that were used during clinical trials. In document QUA-FD-2015-13644 the Sponsor notes the specific differences as shown below:

Figure 1 - Insulin glargine/lixisenatide pen-injectors FRC pen A and FRC pen B, used in clinical trials EFC12404 and EFC12405

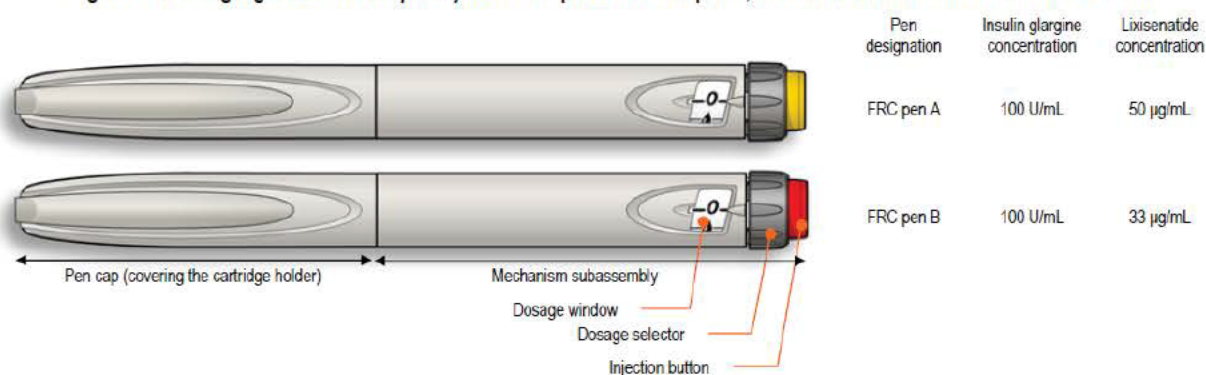


Figure 2 - Insulin glargine marketed pen-injector (Lantus SoloStar), used as comparator in clinical trials EFC12404 and EFC12405

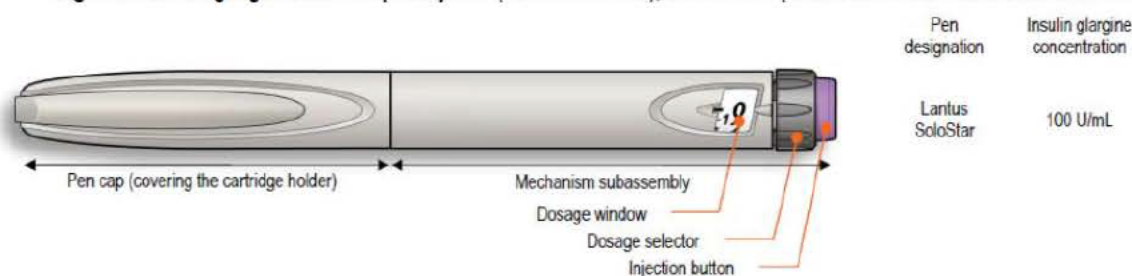


Figure 3 - Insulin glargine/lixisenatide pen-injector pen A and pen B, intended for commercial distribution

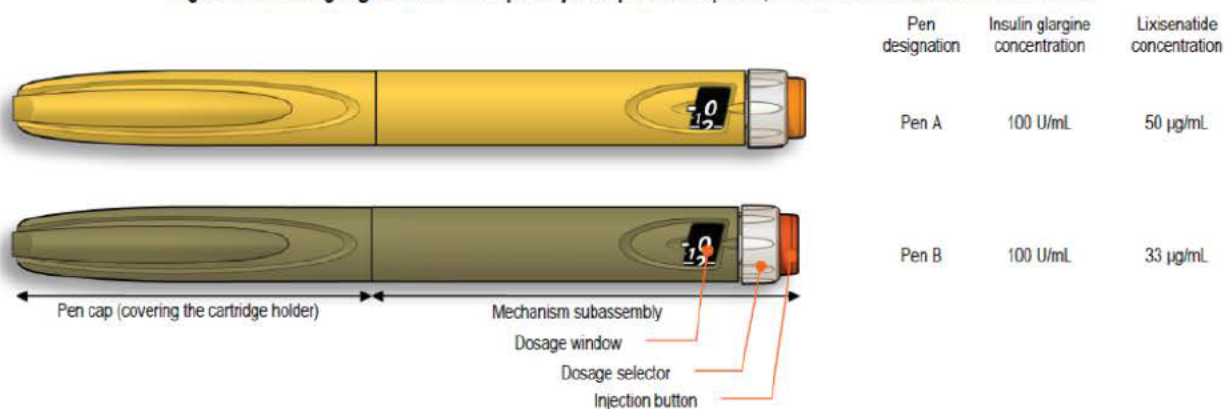


Figure 4 - Comparison of number sleeves

FRC pen A	FRC pen B	Pen A	Pen B	Lantus SoloStar
-30 -10	-50 -30	-30 -10	-50 -30 -10	-70 -50 -30 -10
-32 -12	-52 -32	-32 -12	-52 -32 -12	-72 -52 -32 -12
-34 -14	-54 -34	-34 -14	-54 -34 -14	-74 -54 -34 -14
-36 -16	-56 -36	-36 -16	-56 -36 -16	-76 -56 -36 -16
-38 -18	-58 -38	-38 -18	-58 -38 -18	-78 -58 -38 -18
-40 -20 -0-	-60 -40 -0-	-40 -20 -0-	-60 -40 -20 -0-	-80 -60 -40 -20 -0-
-22 -2	-42 -2	-22 -2	-42 -22 -2	-62 -42 -22 -2
-24	-44	-24 -4	-44 -24 -4	-64 -44 -24 -4
-26	-46	-26 -6	-46 -26 -6	-66 -46 -26 -6
-28	-48	-28 -8	-48 -28 -8	-68 -48 -28 -8

Figure 5 - Comparison of injection buttons

FRC pen A	FRC pen B	Pen A	Pen B	Lantus SoloStar
				
Yellow with added raised ring	Red with added four dots	Orange	Dark orange	Lilac

Below is a summary of the main differences between the various pen-injector presentations:

3.1 DIFFERENCES BETWEEN DEVICES

Beside the colors, differences related to the functionality of the devices are based on volume characteristics and the associated changes to the number sleeves:

- In clinical insulin glargine/lixisenatide pens, the dosage range of 10 to 40 units (FRC pen A) and 30 to 60 units (FRC pen B) is limited by label, not by design. Doses outside the intended range are not printed on the number sleeves. The priming dose is indicated by a droplet symbol on the number sleeves.
- In commercial insulin glargine/lixisenatide pens, the dosage range of 10 to 40 units (pen A) and 30 to 60 units (pen B) is limited by label and design. Special printing patterns on the number sleeves advice the user not to dial doses for injection below the intended limit. Additionally, the dosage range above the intended limit of 40 units (pen A) and 60 units (pen B) is physically blocked. The priming dose is indicated by a bold "2" on the number sleeves.
- In Lantus SoloStar pens the dosage range is not limited by label. Users may set doses in the range of 1 to 80 units. The entire dosage range is printed on the number sleeves. The priming dose is indicated by a bold "2" on the number sleeve.

Apart from dosage characteristics, the obvious difference between clinical and commercial variants of insulin glargine/lixisenatide pen-injectors and Lantus SoloStar lies in the use of a different drug substance, ie, Lantus SoloStar does not contain lixisenatide.

Table 1 - Comparison of main characteristics of FRC pen A, FRC pen B, pen A, pen B and Lantus SoloStar

	FRC pen A	FRC pen B	Pen A	Pen B	Lantus SoloStar
Concentration of insulin glargine	100 U/mL	100 U/mL	100 U/mL	100 U/mL	100 U/mL
Concentration of lixisenatide	50 µg/mL	33 µg/mL	50 µg/mL	33 µg/mL	-
Cartridge volume	3 mL	3 mL	3 mL	3 mL	3 mL
Insulin content per pen (cartridge)	300 U	300 U	300 U	300 U	300 U
Liixisenatide content per cartridge	150 µg	99 µg	150 µg	99 µg	-
Dose setting interval (units / volume per click)	1 U / 10 µL	1 U / 10 µL	1 U / 10 µL	1 U / 10 µL	1 U / 10 µL
Min single dose	10 U ^a	30 U ^a	10 U ^a	30 U ^a	1 U
Max single dose	40 U ^a	60 U ^a	40 U	60 U	80 U
Color pen cap/ pen body	grey	grey	peach	olive	grey
Color cartridge holder	transparent	transparent	transparent	transparent	transparent
Color dosage selector	dark grey	dark grey	antique white	antique white	dark grey
Color of injection button	yellow	red	orange	dark orange	illac
Scale on number sleeve	10 to 40 U	30 to 60 U	0 to 9 U (white on black background) 10 to 40 U (black on white background)	0 to 29 U (white on black background) 30 to 80 U (black on white background)	0 to 80 U
Use of device	Clinical trials EFC12404 and EFC12405	Clinical trials EFC12404 and EFC12405	Intended for commercial distribution	Intended for commercial distribution	Commercial use Used as comparator in clinical trials EFC12404 and EFC12405
Disposable device	yes	yes	yes	yes	yes
Dose accuracy according to ISO 11608-1 (2)	yes	yes	yes	yes	yes
Biocompatible according to ISO 10993-1 (3)	yes	yes	yes	yes	yes
Human Factors validation	yes	yes	yes	yes	Not required at the time of launch

^a Limited by label (b) (4)
Units (U) refer to insulin glargine 100 U/mL

Reviewer Comments:

- The CDRH/ODE raised the question of the differences in the numbering sleeves between those used in the clinical trials and those to-be-marketed to the CDER review team during the Mid-Cycle meeting on 03/21/16 and again via an email.
- During the Pre-Meeting for the Late-Cycle Meeting for NDAs 208471 and NDA 208673 the issue of the numbering sleeves was raised once more to the CDER review team. It was decided that the backgrounder document for the Advisory Committee meeting should include the issue on the numbering sleeve and possible user errors that may arise. OSE/DMEPA is also aware of the change in the numbering sleeve and has taken this into account during their review of the human factors validation study.

- In an information request dated May 2, 2016 the Sponsor was asked to provide verification testing for the new Maximum Dose Stop feature that has been added to the to-be-marketed version of the pen-injectors. Please see Section XIII for more details.

V. Device Constituent Part – Design Review

This review covers the following critical attributes related to functionality and safety of the device constituent parts of the combination product:

- 1) Statement of device inputs (system requirements and specifications), including:
 - a. Dimensional characteristics
 - b. Functional characteristics
 - c. Stability of dimension and functional characteristics
- 2) Evidence of verification/validation of device inputs (device testing/design output)
 - a. Dimensional characteristics
 - b. Functional characteristics
 - c. Connectivity of components
 - d. Sterility and biocompatibility of fluid path (deferred to CDER/OPQ)
 - e. Usability of device (deferred to CDER/DMEPA)
 - f. Stability and shipping

A. Essential Performance Requirements

The following Essential Performance Requirements were provided by the Sponsor in response to an information request dated 03/02/2016:

Essential performance requirement	Specification	Verification test report
Cap removal	The cap removal force has to range between (b) (4) N at ambient conditions	Verification report – Cap attachment and removal forces – document no. [QUA-FD-2016-06224]
Needle attachment	The pen-injectors must be compatible with needles according to ISO 11608-2:2012	Verification report – Needle compatibility – document no. [QUA-FD-2016-06240]
	The (b) (4) required to dial or back dial a dose shall be between (b) (4) Nmm	Verification report – Dial (b) (4) – document no. [QUA-FD-2016-06237]
Dose selection	Dose number visibility: dose numbers have to be readable at environmental lightning conditions of (b) (4) x from a reading distance of (b) (4) cm	Information concerning the visual inspection was provided in NDA 208673. Please see "Pen-injector performance test – ISO 11608-1 – [QUA-FD-2015-01947]" and "Pen-injector performance test – ISO 11608-1 – Appendix – [QUA-FD-2015-10434]" for details
	The maximum dispense force for pen A and pen B has to be (b) (4) N	Verification report – Dispense force – document no. [QUA-FD-2016-06238]
Dose injection	The pen-injectors must fulfill the dose accuracy requirements according to ISO 11608-1:2012	Information concerning dose accuracy was provided in NDA 208673. Please see "Pen-injector performance test – ISO 11608-1 – [QUA-FD-2015-01947]" and "Pen-injector performance test – ISO 11608-1 – Appendix – [QUA-FD-2015-10434]" for details
Cap attachment	The cap attachment force must be (b) (4) N at ambient conditions	Verification report – Cap attachment and removal forces – document no. [QUA-FD-2016-06224]

The steps necessary for testing the priming of the pen are assessed during the dose accuracy tests

The following table was substantiated from the above essential performance table provided by the

Sponsor as well as various test reports provided in the original NDA submission:

Essential Performance Requirement	Specification	Verification	Validation	Aging (Y/N)	Shipping/Transportation (Y/N)	Lot Release Testing (Y/N)
Injection Depth	N/A – dependent on needle used	N/A – dependent on needle used	N/A – dependent on needle used	N/A – dependent on needle used	N/A – dependent on needle used	N/A – dependent on needle used
Injection Time	N/A -Dependent on dose	N/A -Dependent on dose	N/A -Dependent on dose	N/A -Dependent on dose	N/A -Dependent on dose	N/A -Dependent on dose
Dose Accuracy	(b) (4) According to ISO 11608-1:2012	Stability data CE dose accuracy - QUA-FR-2015-05894 and Pen injector performance test – ISO 11608-1 – QUA-FD-2015-01947	Clinical Trial	Yes (11-month in-use stability dose accuracy and 3 year accelerated aging at 55 degrees C)	Yes (Simulated shipping study – QUA-FD-2015-19978)	Yes – according to ISO 11608-1
Visual/Audible Feedback	Dialing a dose with the dose selector provides tactile and audible feedback (one click per unit of insulin glargine that can be heard and felt).	According to ISO 11608-1 Section 5.4.e for general design requirements	Human Factors Validation Study	No	No	Yes (as part of functional testing under dose accuracy)
Activation Force	(b) (4) N	Dispense Force Report – pen A and pen B – QUA-FD-2016-06238	Clinical Trial	No	No	Yes
Needle Length	N/A (see needle compatibility table)	N/A (see needle compatibility table)	N/A (see needle compatibility table)	N/A (see needle compatibility table)	N/A (see needle compatibility table)	N/A (see needle compatibility table)
Needle Gauge	N/A (see needle compatibility table)	N/A (see needle compatibility table)	N/A (see needle compatibility table)	N/A (see needle compatibility table)	N/A (see needle compatibility table)	N/A (see needle compatibility table)
Needle Connection Type	ISO 11608-2 thread	Needle Compatibility Report – pen A and pen B – QUA-FD-2016-06240	N/A	N/A	N/A	N/A
Cap Removal Force	(b) (4) N	Cap attachment and removal forces document number QUA-FD-2016-06224	Clinical Trial	No	No	Yes (as part of functional testing under dose accuracy)

B. Design Verification Activities

The following verification activities were performed by the Sponsor.

1) Performance Testing:

APPEARS THIS WAY ON
ORIGINAL

a. Injection Depth

The Sponsor notes that the injection depth of the pen-injector is based upon the needle used. The Sponsor has provided a list compatible needles for use with the pen-injector. The reviewer notes that the length of the compatible needles range from (b) (4) mm. The Sponsor was asked in an information request to provide a rationale explaining that the listed compatible needles are capable of reaching and maintaining the subcutaneous injection depth throughout the duration of the largest reasonable foreseeable dose.

Below is the table of compatible needles including their length:

Examples of needles compatible with the insulin glargine/lixisenatide pen-injector are provided in Table 4. All needles/brands manufactured by companies listed in Table 4 are compatible.

Table 4 - Examples of needles compatible with the insulin glargine/lixisenatide pen-injector

Brand	Needle type	Needle manufacturer
(b) (4)		

This list is provided for review purposes only and will not be maintained or updated as part of this submission

This is adequate to the lead reviewer.

b. Injection Time

The Sponsor notes that injection time is based upon the dose selected by the user. The Sponsor was asked in an information request to provide a rationale for the acceptability of the average rate of delivery through the pen-injector. Please see Section XIII for more details.

The Sponsor provided the following response:

For the insulin glargine/lixisenatide pen-injector no specification for the injection time of minimum or maximum doses is established. (b) (4)

(b) (4)

Due to these non-uniform parameters that vary greatly between individuals, the IFU does not restrict the user to certain injection times. Instead, the user can adjust the injection time and speed himself/herself to a level that allows the least level of discomfort when injecting a dose.

Regardless of injection times, the IFU instructs the user to maintain pressure on the injection button for 10 s (with the needle inside the patient) after finishing an injection to allow for complete delivery of the dose.

Reviewer Comment:

The Sponsor has stated that the pen-injector (b) (4)

This response is adequate to the lead reviewer and the issue has been resolved.

c. Visual / Audible Feedback

The Sponsor provided the following in QUA-FD-2015-01947 in accordance with ISO 11608-1:

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All pens complied with the acceptance criterion.

Reviewer Comments:

- **The verification testing results provided by the Sponsor can be seen in Section VIII of this memo. The testing is adequate to the lead reviewer and the issue has been resolved.**

- Please see Section V.C.4 of this memo for information regarding lot release testing for audible/visual/tactile feedback. The Sponsor has stated that due to the invariable nature of the feedback mechanisms, re-testing during batch release tests or stability studies is not necessary. The lead reviewer finds the design verification testing of the audible/tactile/visual feedback adequate.

d. Activation Force

The Sponsor provided the following information in document titled 'Dispense force report – pen A pen B – QUA-FD-2016-06238' which is equivalent to activation/sustained injection force:

3.2 TEST RESULTS FR PEN A AND PEN B

(b) (4)

The lead reviewer finds this testing adequate to show that the dispensing force is less than or equal to (b) (4) N.

Additionally, the Sponsor has added injection force to their batch release testing and supplied the following results from their ongoing in-use stability testing:

Figure 3 - Trend analysis of dispense force data during stability studies – pen A

(b) (4)



Figure 4 - Trend analysis of dispense force data during stability studies – pen B

(b) (4)



Reviewer Comment:

The dispensing force verification testing is adequate to the lead reviewer.

e. Dose Accuracy

The Sponsor provided the following dose accuracy verification testing under document QUA-FD-2015-01947:

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Table 6 - Results of dose accuracy testing [μL] according to ISO 11608-1 (pen B)

Condition (determinations per V_{set})	Set dose V_{Set}	Min	Max	Mean value $\bar{x}$	Standard deviation s	LSL	USL	$\bar{x} - k \times s$	$\bar{x} + k \times s$	Test result ^a
Standard atmosphere (n=60)									(b) (4)	complies
										complies
										complies
Cool atmosphere (n=240)										complies
										complies
										complies
Warm atmosphere (n=60)										complies
										complies
										complies
Last dose (n=60)										complies
Preconditioning by free-fall (n=21)	complies									
	complies									
	complies									
Preconditioning in dry-heat (n=60)	complies									
	complies									
	complies									
Preconditioning in cold-storage (n=60)	complies									
	complies									
	complies									
Preconditioning by vibration (n=20)	complies									
	complies									
	complies									

^a Results are noted as "complies" if the test requirements according to ISO 11608-1 were fulfilled

LSL: lower specification limit

USL: upper specification limit

Reviewer Comment:

The above dose accuracy testing was completed after preconditioning according to ISO 11608-1. This testing is adequate to the lead reviewer. It should be noted that dose accuracy testing was also conducted after aging during the in-use stability studies shown below as well as after simulated shipping studies seen in Section V.C.3 of this memo.

The following dose accuracy testing results have been reported under the ongoing in-use stability study within document QUA-FR-2015-05894:

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Reviewer Comment:

The in-use stability dose accuracy test reports demonstrates that the pen-injectors can adequately meet their essential performance requirement of dose accuracy up to a time point of 11 months. This testing is adequate to the lead reviewer in order to demonstrate maintenance of the dose accuracy of the devices up to the labeled date of expiry of (b) (4) months based on the current trending dose accuracy data reported in Section V.A.1 under Verification after Aging/Preconditioning/Shipping.

f. Needle Length and Gauge

The Sponsor states in document QUA-FO-2016-05990 that test procedures were carried out in cooperation with the needle manufacturers in order to demonstrate the compatibility of the insulin glargine/lixisenatide pen-injector using dedicated pen needles of several commercially available needle brands. The instructions for use of the pen-injector provide guidance to the user when choosing compatible needles:

(b) (4)

Additionally, as noted in the Labeling Section of this memo, the Sponsor includes a statement on the proposed labeling of the carton of both pens stating “ (b) (4) ” and similarly “BD ultra-fine needles are compatible with [BRANDNAME] (b) (4) .”

The following is an excerpt from a test report within document QUA-FD-2015-10434 that demonstrates that dose accuracy testing was performed with the (b) (4) .

Needles:	(b) (4)
Name:	(b) (4)
Outer - Ø [mm]	(b) (4)
Length [mm]:	(b) (4)

The following table was provided by the Sponsor denoting all of the needles compatible with the glargine/lixisenatide pen-injector:

Table 4 - Examples of needles compatible with the insulin glargine/lixisenatide pen-injector		
Brand	Needle type	Needle manufacturer
(b) (4)		
This list is provided for review purposes only and will not be maintained or updated as part of this submission		

Reviewer Comments:

- The table of compatible needles is adequate to the lead reviewer for a description and control of the needle lengths and gauge that can be used with the pen-injectors.
- The reviewer notes that dose accuracy testing was conducted using the (b) (4) This is acceptable to the lead reviewer to justify that the listed needles are capable of accurately dispensing the correct dose.

g. Force to Separate Components

The Sponsor has provided testing for the force to separate the following components:

Cap Attachment/Removal

The following is taken from document QUA-FD-2016-06224,

OBJECTIVES

The report describes the results of the *Cap attachment and removal Force test* which was conducted on the Lixilan Fixed Ratio pen A & B in accordance with version 3.0 of the test protocol [3].

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Reviewer Comment:

The cap attachment/removal testing according to the performance requirements/specifications established by the Sponsor is acceptable to the lead reviewer.

Needle Attachment/Removal

Reviewer Comment:

See Section VI.B.1.h of this memo for details on this testing. This testing was found to be acceptable to the lead reviewer.

Cartridge Testing

The Sponsor performed testing on the cartridge according to ISO 11608-3 and ISO 13926-2 within document QUA-FM-2014-22382 including the following,

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Table 3 – Summary of test results

(b) (4)

Reviewer Comments:

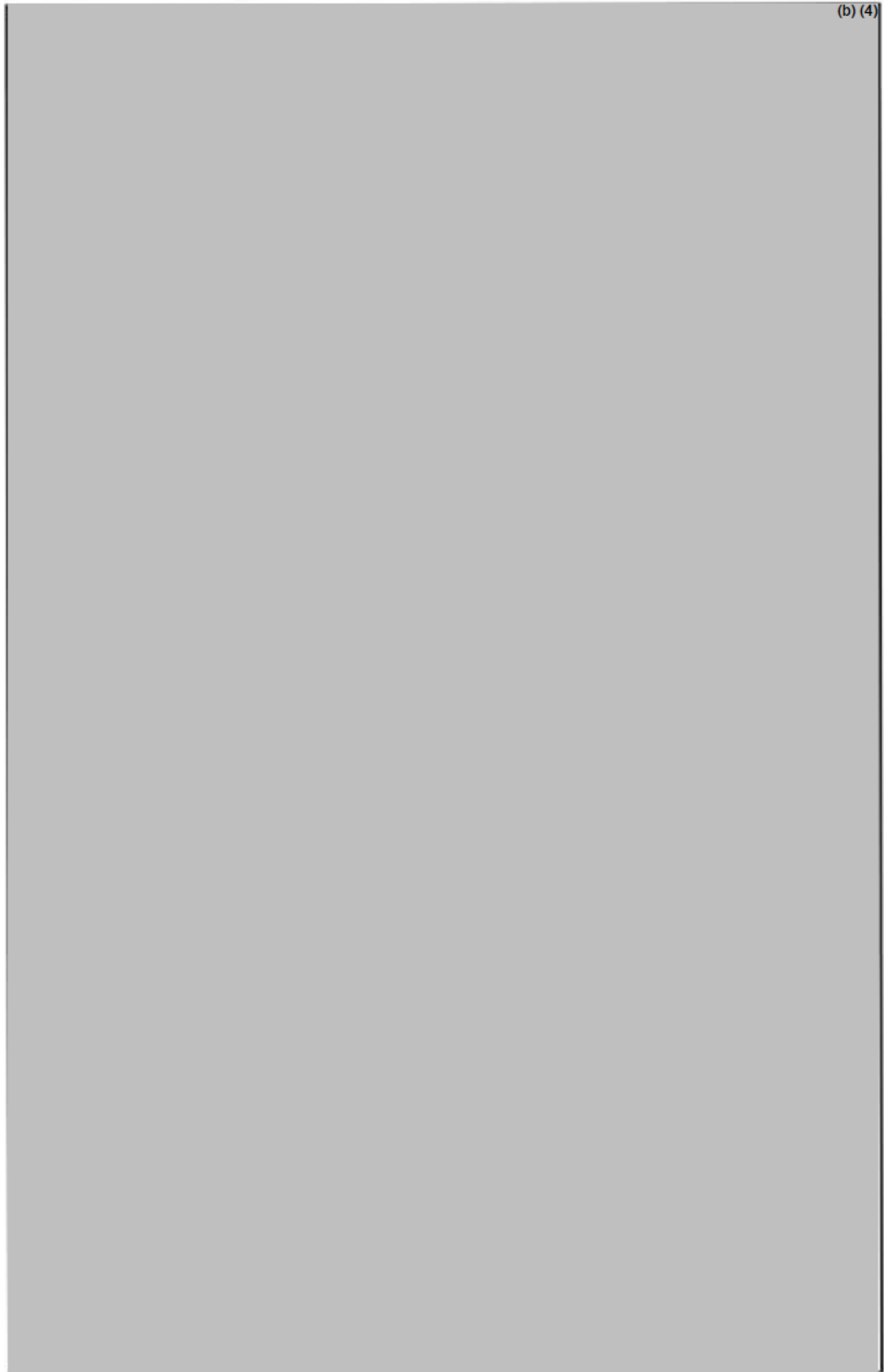
- The Sponsor has conducted force testing on the needle, cap, and cartridge of the combination product in order to establish that the force to separate components is acceptable.
- Testing included sliding characteristic of the cartridge, leakage of the cartridge, resealability of the cartridge, force to remove/attach the needle, and force to remove/attach the cap.
- The Sponsor also performed dose accuracy testing according to ISO 11608-1 which includes preconditioning such as free fall and vibration, as well as dose accuracy testing after simulated shipping studies. These tests demonstrate that the force to separate components is great enough to prevent separation of components resulting in a dose inaccuracy after expected use conditions.

h. Needle Connection Type

The Sponsor states that the requirements for compatible needles are controlled by the respective manufacturers of those needles and the needle manufacturers have to verify that their needles comply with requirements of

ISO 11608-2:2012, Section 11 "Test method for validating the compatibility of needles and injector systems."

The Sponsor provided document QUA-FD-2016-06240 that demonstrates the needle compatibility and connection to the pen-injectors:

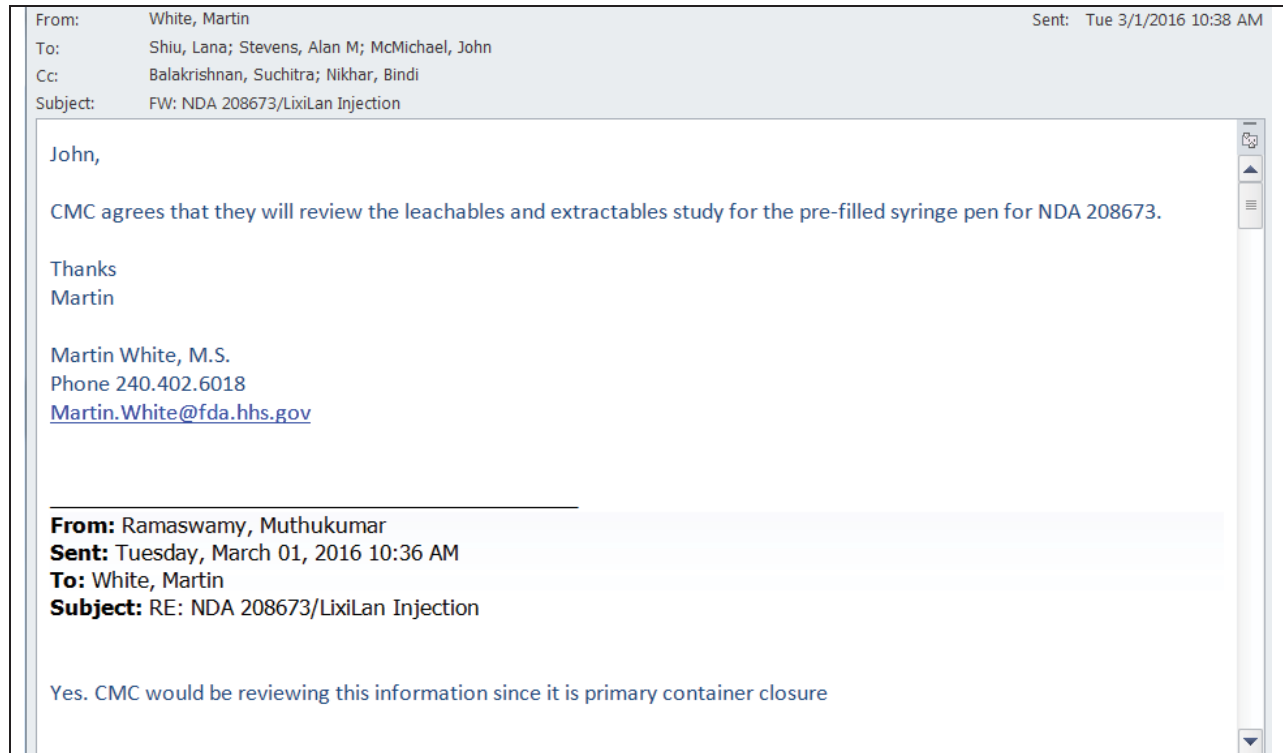


Reviewer Comment:

The Sponsor has completed adequate verification testing to demonstrate the needle connection meets the specification of (b) (4) Nm screw on torque, the needle removal torque is less than (b) (4) Nm, and subsequent dose accuracy testing meets the requirement of ISO 11608-2:2012. This testing is adequate to the lead reviewer.

2)Biocompatibility:

This review only covers the biocompatibility of the secondary, non-drug contacting, container closure parts of the combination product. In an email dated 03/01/2016 Muthukumar Ramaswamy (CDER/OPQ/ONDP/DNDPII/NDPBVI) confirmed that CMC would be completing a review of the biocompatibility of the primary container closure elements of the combination product:



The lead reviewer from CDRH/ODE, John McMichael, consulted the biocompatibility review of the secondary container closure parts of the combination product to Dr. Sarah Mollo (CDRH/ODE/DAGRID/GHDB). Her review memo is attached to this review. A summary of her conclusion is copied below:

The reviewer recommends approval based on the biocompatibility of the patient contacting components of the device.

Reviewer Comment:

The lead reviewer notes that the consultant, Dr. Sarah Mollo, found the biocompatibility to be adequate after receiving requested additional information. Please see Sections VI and VII of this memo for more details regarding information requests and Sponsor's responses. The lead reviewer concurs with the consultant's conclusion that the biocompatibility of the pen-injector is acceptable.

3)Sterility:

The pen-injector and cartridge are provided (b) (4) This is acceptable to the lead reviewer and there are no further comments.

4) Verification after Aging/Preconditioning/Shipping:

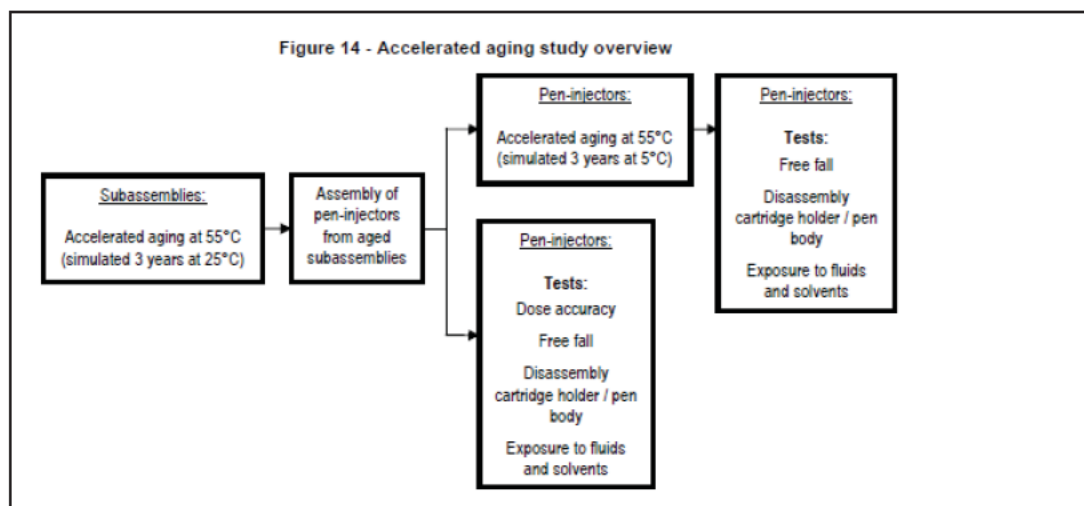
To support functionality of the combination product after aging, the sponsor has completed an assessment of system attributes after preconditioning by shipping and preconditioning by aging.

a. Aging

The Sponsor notes in QUA-FR-2014-24232 that the shelf-life of the combination product is (b) (4) months:

The presented stability results and the statistical evaluation support the proposed preliminary shelf life and storage directions of insulin glargine / lixisenatide solution for injection assembled in the pen-injector:	
Proposed shelf life:	(b) (4) months
Storage directions:	Prior to initial use, store between +2°C and +8°C, protected from light. Do not freeze.
Proposed in-use period:	14 days
In-use storage directions:	Store at room temperature (up to +30°C, protected from light).

The following represents the aging preconditioning that occurred prior to functional testing of the device:



The Sponsor notes that the aging study was conducted with the Lanus SoloStar pen and not the final finished to-be-marketed pen A and pen B. The Sponsor provided the following rationale for the acceptability of this testing:

The study was performed with Lantus SoloStar, which differs from insulin glargine/lixisenatide pen-injector device constituent parts only in colors and modifications to the number sleeves (ie, the dose stop for the maximum selectable dose). (b) (4)
(b) (4) therefore the mechanical properties are expected to be the same and modifications are not expected to affect device functionality.

Reviewer Comment:

This rationale for the acceptability of the aging study is acceptable to the lead reviewer.

In addition to completing 3-year accelerated aging on the subassemblies prior to performing dose accuracy, the Sponsor has provided in-use stability after 11 months with 14 days in-use period as well as

12 months long term storage within document QUA-FR-2015-05894. A summary of the results is copied here in response to an information request dated May 2, 2016:

Table 1 - Pen stability batches

Strength [lixisenatide]	Batch no. (pen)	Batch no. (cartridge)	Batch size	Stability study conditions	Data tables
50 µg/mL	C1046020 (4F001A)	C1044102 (4F002)	(b) (4)	Long term (initial results, 6 months, 12 months)	Table 2, Table 3
				In-use (5 months, 11 months)	Table 6, Table 7
33 µg/mL	C1046019 (4F001A)	C1044100 (4F002)		Long term (initial results, 6 months, 12 months)	Table 4, Table 5
				In-use (5 months, 11 months)	Table 8, Table 9

Table 3 - Statistical values of dose accuracy batch C1046020 (4F001A) – cartridge batch C1044102 (4F002, 50 µg/mL lixisenatide)

Strength [lixisenatide]	Batch no.	Time	Target dose [µL]	Mean value $\bar{x}$ [µL]	Standard deviation s [µL]	$\bar{x} - (k \times s)$ [µL]	$\bar{x} + (k \times s)$ [µL]	Test result ^a
50 µg/mL	4F002	Initial results						(b) (4) Complies
		6 month						Complies
		12 month						Complies

^a Test results are noted as "complies" if the test requirements according to ISO 11608-1 are fulfilled

Table 5 - Statistical values of dose accuracy batch C1046019 (4F001A) – cartridge batch C1044100 (4F002, 33 µg/mL lixisenatide)

Strength [lixisenatide]	Batch no.	Time	Target dose [µL]	Mean value $\bar{x}$ [µL]	Standard deviation s [µL]	$\bar{x} - (k \times s)$ [µL]	$\bar{x} + (k \times s)$ [µL]	Test result ^a
33 µg/mL	4F002	Initial results						(b) (4) Complies
		6 month						Complies
		12 month						Complies

^a Test results are noted as "complies" if the test requirements according to ISO 11608-1 are fulfilled

Table 7 - Statistical values of in-use dose accuracy batch C1046020 (4F001A) – cartridge batch C1044102 (4F002, 50 µg/mL lixisenatide)

Strength [lixisenatide]	Batch no.	Time	Target dose [µL]	Mean value $\bar{x}$ [µL]	Standard deviation s [µL]	$\bar{x} - (k \times s)$ [µL]	$\bar{x} + (k \times s)$ [µL]	Test result ^a
50 µg/mL	4F002	5 month						(b) (4)
								Complies
								Complies
		11 month						Complies
								Complies
								Complies

^a Test results are noted as "complies" if the test requirements according to ISO 11608-1 are fulfilled

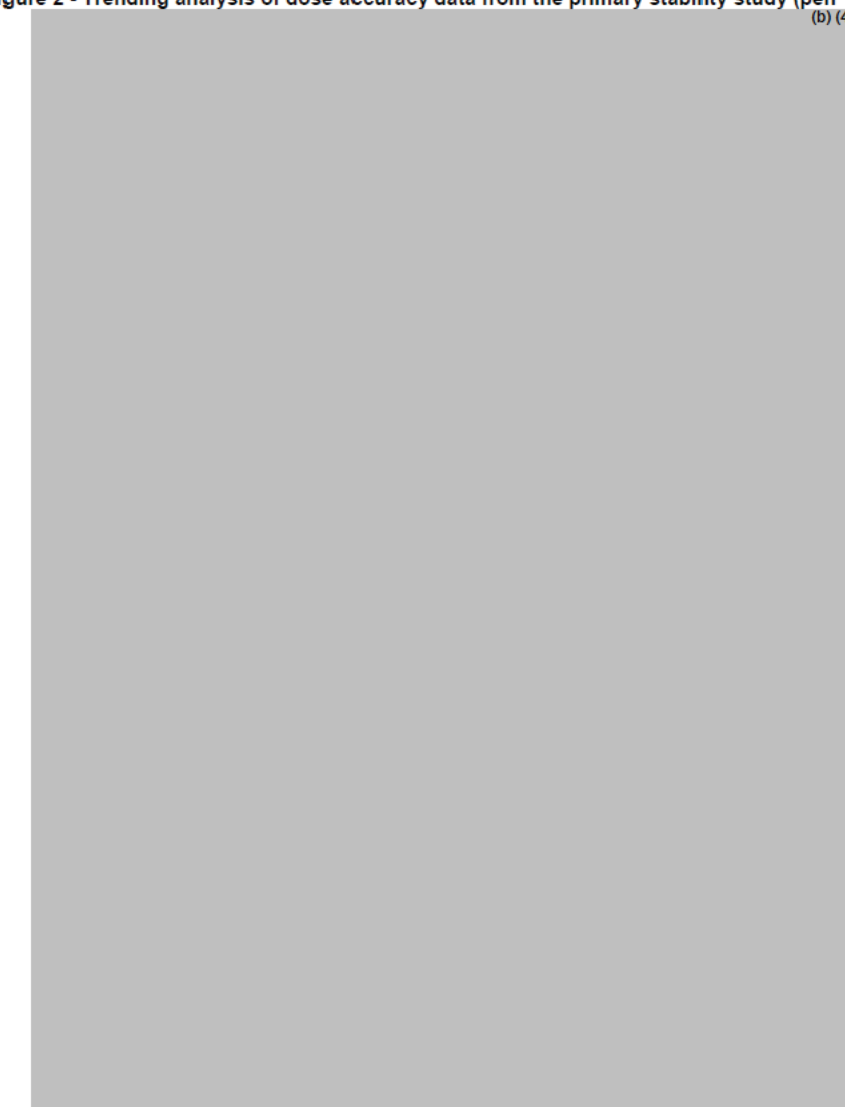
Table 9 - Statistical values of in-use dose accuracy batch C1046019 (4F001A) – cartridge batch C1044100 (4F002, 33 µg/mL lixisenatide)

Strength [lixisenatide]	Batch no.	Time	Target dose [μL]	Mean value $\bar{x}$ [μL]	Standard deviation s [μL]	$\bar{x} - (k \times s)$ [μL]	$\bar{x} + (k \times s)$ [μL]	Test result ^{a)}
33 μg/mL	4F002	5 month						(b) (4)
								Complies
								Complies
		11 month						Complies
								Complies
								Complies

^a Test results are noted as "complies" if the test requirements according to ISO 11608-1 are fulfilled

A trending analysis of the dose accuracy over time of stability was provided in response to an information request dated May 2, 2016:

Figure 2 - Trending analysis of dose accuracy data from the primary stability study (pen (b) (4))



USL = upper specification limit
LSL = lower specification limit

Reviewer Comment: The lead reviewer believes that the combination of accelerated aging (simulating 3 years of aging) and the results of 11-month (+14 days in-use) and 12 month long-term stability testing has shown that the pen A and pen B can adequately perform dose accuracy up to its proposed shelf life of (b) (4) months.

The following preconditioning activities performed on the device prior to performance testing according to ISO 11608-1:

- Standard atmosphere
- Cool atmosphere
- Warm atmosphere
- Last dose
- Free-fall
- Dry-heat
- Cold storage
- Vibration

The Sponsor states that the following tests have been completed after aging:

- Dose Accuracy
- Free Fall
- Disassembly cartridge holder / pen body
- Exposure to fluids and solvent

Additionally, the Sponsor stated the following in response to an information request dated May 2, 2016:

Certain design verification tests (eg, dose accuracy according to ISO 11608-1:2012) require preconditioning of the pen-injector in standard/warm/cold atmosphere, in dry heat/cold storage, as well as by free-fall and vibration. These tests are designed to simulate adverse conditions that the pen-injectors may be exposed to during storage, usage or transport. Compliance with the acceptance criteria of these tests (as demonstrated by the insulin glargine/lixisenatide pen-injector) therefore demonstrates the robustness of the device under adverse conditions.

In addition to design verification data presented here, functional tests of the pen-injector are performed as part of the primary stability study. Dose accuracy is assessed during long term storage and in-use up to the intended shelf-life of the combination product. These tests are performed according to ISO 11608-1:2012 and require full functional assessment of the pen, including steps to set up the pen for an injection and dispense the dose. They are therefore fully representative of the device functionality at the time of testing. Primary stability data is shown in Section 3.2.P.8.3 "Stability data – Dose accuracy of the pen-injector".

The following is taken from QUA-FD-2015-01947:



Reviewer Comment:

The Sponsor states that the tests performed during in-use and long term stability studies are performed according to ISO 11608-1:2012 and require full functional assessment of the pen-injector, including steps to set up the pen for an injection and dispense the dose. However, the Sponsor has not stated specifically what essential performance requirements were tested after aging besides dose accuracy. It seems that the Sponsor is asserting that a test for dose accuracy is a downstream effect of all functional characteristics of the pen-injector and therefore is representative of all other essential performance criteria. The Agency believes that certain essential performance requirements such as dispensing force, injection time, and visual/audible/tactile feedback should be tested after aging and preconditioning the device in order to establish that the device meets all essential performance requirements up to the labeled date of expiry for the device.

The Sponsor responded to an information request dated April 26, 2016 with the following:

The essential performance requirements defined by Sanofi for the insulin glargine/lixisenatide pen-injector represent the steps necessary to prepare the pen for an injection, inject the dose and subsequently prepare the pen for storage (Table 5; please see also response to question no. 3 (Doc No. [QUA-FO-2016-05990]) of the information request dated March 2, 2016 (Sequence 0010)).

Table 5 - Overview of insulin glargine/lixisenatide pen-injector performance parameter testing

Test item	Essential performance requirement	Tested during design verification	Tested during batch release	Tested during real time aging studies (primary stability)
Cap removal	x	x		x ^b
Needle attachment	x	x		x ^b
Dose selection	x	x	x ^b	x ^b
Audible/visual/tactile feedback		x		
Dispense force	x	x	x	x
Dose accuracy	x	x ^a	x ^a	x ^a
Cap attachment	x	x		x ^b

^a Includes a visual inspection of the pen-injectors (eg, for dose number visibility)

^b Implicitly tested during dose accuracy tests, which requires preparing the pen for dispensing the dose

To address the Agency's concerns regarding the assessment of essential performance requirements during aging studies, Sanofi is providing the results of dispense force tests from the ongoing real time aging study (primary stability). The Section 3.2.P.8 "Stability" of NDA 208673 has been updated accordingly. Please refer to the documents 3.2.P.8.1 "Stability summary and conclusion" ([QUA-FD-2016-12286]) and 3.2.P.8.3 "Stability data" ([QUA-FD-2016-12287]) for details. Dispense force data is available for the time points 0, 6 and 12 month of the long term stability study, as well as 5 and 11 month of the in-use stability study. Tests were performed in standard atmosphere with 38 pen-injectors each using the same batches that were used for the dose accuracy measurements reported in Section 3.2.P.8 "Stability" of NDA 208673. The dispense forces were measured using a tensile meter while the doses were being dispensed. All test items complied with the specification limit for the maximum dispense force ($F \leq \text{(b) (4)} \text{ N}$). This specification limit was set at the time of primary stability study initiation and is consistent with the limit set for design verification. As explained in the response to [AGENCY QUESTION / REQUEST FOR INFORMATION ITEM NO. 4](#), future stability study and batch release criteria for the dispense force will be based on the specification limit that resulted from Human Factors studies ($F \leq \text{(b) (4)} \text{ N}$).

A trending analysis of dispense force data from the stability study is provided in [Figure 3](#) for pen A and in [Figure 4](#) for pen B, showing the mean values of dispense forces and the accompanying standard deviation. This trend analysis takes into account stability data from available time point of long term and in-use stability studies. No discernible trend is visible in the trend analysis.

As explained in the response to [AGENCY QUESTION / REQUEST FOR INFORMATION ITEM NO. 4](#), verification tests for audible, visual and tactile feedback were performed during design verification but not as part of real time stability studies, because they are not expected to alter during storage. Similarly, injection times were not assessed during the real time stability

studies because they are not specified for the pen (see response to [AGENCY QUESTION / REQUEST FOR INFORMATION ITEM NO. 2](#)).

Figure 3 - Trend analysis of dispense force data during stability studies – pen A



Figure 4 - Trend analysis of dispense force data during stability studies – pen B



Reviewer Comment:

The Sponsor's response is acceptable to the lead reviewer. The essential performance requirements have been adequately verified after aging in the opinion of the lead reviewer based upon the rationale provided by the Sponsor.

b. Shipping

Please see Section V.C.3 of this memo for details regarding testing of essential performance requirements after shipping. This testing is adequate to the lead reviewer as verification of the essential performance requirements after shipping.

B. Combination Product Validation Activities

Validation Activities

1) Clinical Validation:

The Sponsor has provided the following comparison of the pen-injectors that have been clinically validated under Phase 3 trials, titled EFC2404 and EFC 2405, and the to-be-marketed versions of the pen-injectors in document QUA-FD-2015-13644:

Table 1 - Comparison of main characteristics of FRC pen A, FRC pen B, pen A, pen B and Lantus SoloStar					
	FRC pen A	FRC pen B	Pen A	Pen B	Lantus SoloStar
Concentration of insulin glargine	100 U/mL	100 U/mL	100 U/mL	100 U/mL	100 U/mL
Concentration of lixisenatide	50 µg/mL	33 µg/mL	50 µg/mL	33 µg/mL	-
Cartridge volume	3 mL	3 mL	3 mL	3 mL	3 mL
Insulin content per pen (cartridge)	300 U	300 U	300 U	300 U	300 U
Lixisenatide content per cartridge	150 µg	99 µg	150 µg	99 µg	-
Dose setting interval (units / volume per click)	1 U / 10 µL	1 U / 10 µL	1 U / 10 µL	1 U / 10 µL	1 U / 10 µL
Min single dose	10 U ^a	30 U ^a	10 U ^a	30 U ^a	1 U
Max single dose	40 U ^a	60 U ^a	40 U	60 U	80 U
Color pen cap/ pen body	grey	grey	peach	olive	grey
Color cartridge holder	transparent	transparent	transparent	transparent	transparent
Color dosage selector	dark grey	dark grey	antique white	antique white	dark grey
Color of injection button	yellow	red	orange	dark orange	lilac
Scale on number sleeve	10 to 40 U	30 to 60 U	0 to 9 U (white on black background) 10 to 40 U (black on white background)	0 to 29 U (white on black background) 30 to 80 U (black on white background)	0 to 80 U
Use of device	Clinical trials EFC12404 and EFC12405	Clinical trials EFC12404 and EFC12405	Intended for commercial distribution	Intended for commercial distribution	Commercial use Used as comparator in clinical trials EFC12404 and EFC12405
Disposable device	yes	yes	yes	yes	yes
Dose accuracy according to ISO 11608-1 (2)	yes	yes	yes	yes	yes
Biocompatible according to ISO 10993-1 (3)	yes	yes	yes	yes	yes
Human Factors validation	yes	yes	yes	yes	Not required at the time of launch

^a Limited by label (b) (4)
Units (U) refer to insulin glargine 100 U/mL

Figure 4 - Comparison of number sleeves

FRC pen A	FRC pen B	Pen A	Pen B	Lantus SoloStar
-30 -10 -32 -12 -34 -14 -36 -16 -38 -18 -40 -20 -0- -22 -2 -24 -26 -28	-50 -30 -52 -32 -54 -34 -56 -36 -58 -38 -60 -40 -0- -42 -2 -44 -46 -48	-30 -10 -32 -12 -34 -14 -36 -16 -38 -18 -40 -20 -0- -22 -2 -24 -4 -26 -6 -28 -8	-50 -30 -10 -52 -32 -12 -54 -34 -14 -56 -36 -16 -58 -38 -18 -60 -40 -20 -0- -42 -22 -2 -44 -24 -4 -46 -26 -6 -48 -28 -8	-70 -50 -30 -10 -72 -52 -32 -12 -74 -54 -34 -14 -76 -56 -36 -16 -78 -58 -38 -18 -80 -60 -40 -20 -0- -62 -42 -22 -2 -64 -44 -24 -4 -66 -46 -26 -6 -68 -48 -28 -8

Figure 5 - Comparison of injection buttons

FRC pen A	FRC pen B	Pen A	Pen B	Lantus SoloStar
				
Yellow with added raised ring	Red with added four dots	Orange	Dark orange	Lilac

3.1 DIFFERENCES BETWEEN DEVICES

Beside the colors, differences related to the functionality of the devices are based on volume characteristics and the associated changes to the number sleeves:

- In clinical insulin glargine/lixisenatide pens, the dosage range of 10 to 40 units (FRC pen A) and 30 to 60 units (FRC pen B) is limited by label, (b) (4). Doses outside the intended range are not printed on the number sleeves. The priming dose is indicated by a droplet symbol on the number sleeves.
- In commercial insulin glargine/lixisenatide pens, the dosage range of 10 to 40 units (pen A) and 30 to 60 units (pen B) is limited by label and design. Special printing patterns on the number sleeves advise the user not to dial doses for injection below the intended limit. Additionally, the dosage range above the intended limit of 40 units (pen A) and 60 units (pen B) is physically blocked. The priming dose is indicated by a bold "2" on the number sleeves.
- In Lantus SoloStar pens the dosage range is not limited by label. Users may set doses in the range of 1 to 80 units. The entire dosage range is printed on the number sleeves. The priming dose is indicated by a bold "2" on the number sleeve.

Apart from dosage characteristics, the obvious difference between clinical and commercial variants of insulin glargine/lixisenatide pen-injectors and Lantus SoloStar lies in the use of a different drug substance, ie, Lantus SoloStar does not contain lixisenatide.

The following information was provided by the Sponsor in document QUA-FD-2015-24611 titled "Pen-related events and initiation dose deviations observed in clinical trials":

Table 1 - Summary	
Summary	
Pen related events	
Following a request received from FDA in early 2014, the PRE-Q was created, in close collaboration with the agency, to evaluate pen-related events that occurred in the clinical trials. The evaluation of pen-related events in the ongoing Phase 3 trials using the PRE-Q was subsequently implemented in both studies per Amendment 1. During the treatment period in the clinical studies, a total of 70 patients (44/1169 patients in EFC12404 and 26/730 patients in EFC12405) reported 83 events related to the use of the pen-injectors; 44 of the 83 events were related to the use of the FRC pen-injectors (33 events in EFC12404 and 11 events in EFC12405). See Section 3.1. A total of 22 of the 44 FRC pen-related events (18 events in EFC12404 and 4 events in EFC12405) were related to the use of the pen-injector (either FRC pen A or FRC pen B) outside of its intended dose range; these are considered to be unique to this FRC relative to insulin glargine because insulin glargine does not have a defined dose range. None of the events was associated with a clinical event (ie, hypoglycemia or GI adverse event or hyperglycemic event). See Section 3.2. A number of mitigations to minimize the occurrence of these events were subsequently implemented in the design of the commercial pens (compared to the clinical FRC pens) and in the labeling (ie, IFU, pen label and pen package). For example, the pen mitigations were to add a mechanical stop to prevent users from dialing doses greater than the maximum for each pen, and to print the section of the number sleeve below the intended dose range in reverse colors (ie, white numbers on a black background). See Section 3.3 and Table 5.	
Table 4 - Root causes of Category 1 PRE in the FRC group	
Injection above the maximum intended dose range	
Number of events	n = 15 events (total) (n = 11 in EFC12404, n = 4 in EFC12405)
Description/Root Cause	All events were related to the use of FRC pen A, and administration of a dose above the maximum intended dose of 40 units. In a total of n = 5 events (3 in EFC12404 and 2 in EFC12405), the patients dialed the pen to greater than the maximum intended dose of 40 units by counting the clicking sound that the dose dial makes (1 "click" = 1 unit). This was possible because even though the numbers printed on the number sleeve in the dose window stopped at 40 units, the clinical trial pen was not engineered to prevent dialing beyond the upper end of the intended dose range. In a total of n = 8 events (6 in EFC12404 + 2 in EFC12405), the patients split the dose into two injections to deliver a dose higher than 40 units. In a total of 2 events (both in EFC12404), the details of the event were unclear; the patients injected 42 units and 46 units, respectively. For mitigations, see Table 5.
Injection below the minimum intended dose range	
Number of events	n = 6 events (all in EFC12404)
Description/Root Cause	In a total of 6 events (3 used FRC pen A and 3 used FRC pen B), the patients dialed the pen to a dose below the minimum intended dose (of 10 units for FRC pen A or 30 units for FRC pen B) by counting the clicking sound that the dose dial makes (1 "click" = 1 unit). Even though on the clinical pen the number sleeve in the dose window had no numbering in that range, the patients dialed a lower dose either by starting at 0 and dialing up or starting at 10 (for FRC pen A) or 30 (for FRC pen B) and dialing down to the dose they wanted to inject. For mitigations, see Table 5.
Other PRE	
Number of events	n = 1 (in EFC12404)
Description/Root Cause	One patient used both FRC pen A and FRC pen B to self-titrate and inject a dose above the intended maximum dose range. The patient used FRC pen B to inject 60 units and then FRC pen A to inject additional units. This was possible because the patient received investigational study kits for both FRC pen A and FRC pen B. For mitigations, see Table 5.

Table 5 - Mitigations implemented in the commercial product for Category 1 PRE

Mitigations

Mitigations for commercial product

Design mitigations

- To prevent users from dialing doses greater than the maximum intended dose for each pen, a mechanical stop was added at 40 units for commercial pen A and at 60 units for commercial pen B and the printing on the number sleeve stops at that point.
- To discourage users from dialing doses less than the minimum intended dose for each pen, the printing on the number sleeve was revised: in the intended dose range, the numbers are printed in black text on a white background, and in the range below the minimum intended dose, the numbers are printed in white text on a black background.¹

Labeling mitigations

- The IFUs were revised to support user understanding of the intended dose range of each pen.
- (b) (4)
- Wording on the IFU, (b) (4) were revised to emphasize that the pen should be used to deliver a "single daily dose" to support user understanding of correct pen use.

(b) (4)

(b) (4)

Table 11 - EFC12404: Number (%) of patients with events reported in pen-related event questionnaire during the on-treatment period - Safety population

	Fixed Ratio Combination (N=469)	Insulin Glargine (N=467)	Lixisenatide (N=233)
Any pen-related events	25 (5.3%)	10 (2.1%)	9 (3.9%)
Associated with a clinical event	0	0	0
Not associated with a clinical event	25 (5.3%)	10 (2.1%)	9 (3.9%)

Clinical event = symptomatic hypoglycemic event, hyperglycemic adverse event or other adverse event collected in pen-related questionnaire.

Table 12 - EFC12405: Number (%) of patients with events reported in pen-related event questionnaire during the on-treatment period - Safety population

	Fixed Ratio Combination (N=365)	Insulin Glargine (N=365)
Any pen-related events	11 (3.0%)	15 (4.1%)
Associated with a clinical event	0	0
Not associated with a clinical event	11 (3.0%)	15 (4.1%)

Clinical event = symptomatic hypoglycemic event, hyperglycemic adverse event or other adverse event collected in pen-related questionnaire.

Note: The on-treatment period is defined as the time from the first injection of open label IMP up to 3 days after the last injection of IMP, regardless of the introduction of rescue therapy.

Reviewer Comments:

- The lead reviewer notes that the FRC Pen A and FRC Pen B pen-injectors have been clinically validated under Phase 3 trials, titled EFC12404 and EFC12405, with no pen-related events leading to adverse events in the trials.
- The lead reviewer notes that the Sponsor developed the 'PRE-Q' questionnaire to capture any pen-related technical failures during the Phase 3 clinical trials at the advice of the Agency.
- The lead reviewer notes that the differences between the to-be-marketed versions of Pen A and Pen B versus the clinically validated FRC Pen A and FRC Pen B consist only of labeling, coloring, and the maximum dose stop design change.

- The lead reviewer finds the testing of the maximum dose stop acceptable as noted in the performance testing section of this memo. Furthermore, the lead reviewer finds this design change to be an adequate risk mitigation for the 'injection above maximum intended dose range' pen-related events seen in the clinical trials.
- The labeling and coloring changes form the clinically validated pen-injectors are being reviewed for adequacy under the Human Factors Validation Studies by CDER/OSE/DMEPA and a review of these changes are not within the scope of this review. See Human Factors Section of this memo below for more details.
- The lead reviewer finds the comparison of the to-be-marketed pen-injectors to the clinically validated pen-injectors to be adequate considering the performance testing that was completed on the to-be-marketed pen-injectors and the verification of the maximum dose stop design change. The adequacy of the numbering sleeve labeling and coloring changes is not within the scope of this review.

2) Human Factors:

CDER/OSE/DMEPA has reviewed the Human Factors Validation Study for this submission and it was confirmed via telephone conversation on 04/27/16 with Ariane Conrad (CDER/OSE/OMEPRM/DMEPA) that the DMEPA review team was aware of the changes between the pen-injectors used in the clinical trials and the to-be-marketed pen-injectors including, but not limited to:

- Numbering sleeve labeling changes
- Pen-injector cap coloring
- Injection button coloring

Reviewer Comment:

The lead reviewer notes that review of the human factors studies is not contained within the scope of this review and is confirmed to be covered by CDER/OSE/DMEPA.

3) Shipping/Transportation:

The Sponsor provided the following simulated shipping study in document number QUA-FD-2015-19978:

Pen-injectors manufactured by Sanofi Aventis Deutschland GmbH (SADG) are packaged (b) (4)

This report summarizes the results of a transport simulation study using vibration, impact and compression tests to assess these influences. Tests were carried out using the already marketed Lantus® SoloStar® instead of insulin glargine/lixisenatide pen-injectors, as explained in Section 3.

(b) (4). Above all, special attention was paid to the dynamic loads with respect to the individual folding boxes. After the transport simulation, additional tests were conducted on the packaging and pen-injectors to ensure that both comply with visual and functional requirements (eg, no unacceptable damages to packaging, no glass breakage or loosening of pen-injector components).

This shipping simulation study followed the standard ASTM D4169 (1).

After the simulation, visual and functional tests on the packaging and its content ensured that the effects of the shipping simulation were properly assessed.

Test Samples:

Due to the unavailability of the final commercial presentation of insulin glargine/lixisenatide peninjectors (including labeling and packaging) at the time of testing, an already marketed variant of the SoloStar pen-injector which is combined with insulin glargine 100 U/mL solution for injection (Lantus, NDA 21-081) has been used for the simulated shipping study instead.

The insulin glargine/lixisenatide pen-injector is based on the SoloStar design, which has been modified for the application of the insulin glargine/lixisenatide solution for injection. The modification comprises the color of the bodies, caps, injection buttons, dose selectors and the printing on the number sleeves. Additionally, the number sleeves have been modified with respect to the maximum doses that can be dialed. Apart from these modifications, the overall geometry and mechanical function of the insulin glargine/lixisenatide pen-injectors remain the same as Lantus SoloStar. Labeling and packaging are also of a similar nature, as the insulin glargine/lixisenatide pen-injector will use the same type of labeling and folding box as Lantus SoloStar. Thus, both pen-injectors and their packaging were judged to be similar enough so that Lantus SoloStar can be used to assess the influence of shipping on the insulin glargine/lixisenatide pen-injector.

The shipping simulation study was performed with one batch of SoloStar pen-injectors, using one type of folding box containing 5 pen-injectors each. The batch description of the packaged pen-injectors is listed in Table 1. An overview of the quantity of packaging material and pen-injectors used in this study is provided in Table 4.

Table 1 – Batch of packaged SoloStar pen-injectors used for shipping simulation

Pen Type	Drug content	Sanofi batch number (material number)
Lantus SoloStar	Insulin glargine 100 U/mL	5F1392A (b) (4)

Figure 1 - Packaging scheme of the individual shipping cartons



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8.2.2 Functional inspection and dose accuracy of pen-injectors

Pen-injectors underwent functional testing in accordance with Section 10.1 d) of ISO 11608-1 (11). Functionality of the pen-injectors was assessed as part of dose accuracy measurements. Dose accuracy of pen-injectors was tested in standard atmosphere according to the requirements of ISO 11608-1.

9.1.2 Visual Inspection of pen-injectors

The visual inspection of pens revealed no significant defects. All pens complied with acceptance criteria listed in Table 9.

9.2.1 Functional inspection and dose accuracy of pen-injectors

Of the 70 pen-injectors selected during sampling, 60 pens underwent functional inspection, including dose accuracy testing. Pen-injectors successfully passed the ISO 11608-1 Section 10.1 d) criteria for "functional inspection".

The results of dose accuracy tests performed on sampled pen-injectors are shown in Table 10. Results of the dose accuracy measurements complied with test requirements according to ISO 11608-1, ie, the upper ($\bar{x} + k \times s$) and lower ($\bar{x} - k \times s$) values of the tolerance interval were within the upper (USL) and lower (LSL) specification limits for the tested dosage volume V_{Set} .

Table 10 - Results of dose accuracy testing [μL] according to ISO 11608-1

Condition (determinations per V_{Set})	Set dose V_{Set}	Min	Max	Mean value $\bar{x}$	Standard deviation s	LSL	USL	$\bar{x} - k \times s$	$\bar{x} + k \times s$	Test result ^a
Standard atmosphere (n=60)									(b) (4)	complies complies complies

^a Results are noted as "complies" if the test requirements according to ISO 11608-1 were fulfilled

LSL: lower specification limit

USL: upper specification limit

Tolerance limit factor k : (b) (4)

Reviewer Comments:

- The Sponsor only performed dose accuracy testing after simulated shipping studies instead of all essential performance requirements. This deficiency was communicated via an information request on 04/26/16 to the CDER project manager. The project manager sent the information request to the Sponsor on 05/09/16. Please see Section VIII for more details.
- The Sponsor performed the simulated shipping study not with the final finished combination product, however the overall geometry and mechanical function of the pen-injectors were identical. The lead reviewer reviewed the differences between the test

samples and the final finished combination product and deemed the differences negligible in the context of the shipping study.

- The results of the shipping study, including the dose accuracy testing, are adequate to the lead reviewer.

4) Lot Release Testing:

The Sponsor has provided the following description of their lot release testing in response to an information request sent on 04/26/16:

Revised specifications for the pen-injector batch release:

Sanofi is providing the Agency with revised pen batch release specifications, which include the following test items:

- Identity;
- Appearance;
- Functional test and dose accuracy in standard atmosphere;
- Dispense force.

Please see [Table 2] of the updated document 3.2.P.5.1 "Specifications" (Doc. No. QUA-FR-2016-12014). The description of batch release methods for the pen-injector presented in [Section 9.3] of document 3.2.P.7 "Container closure system – Disposable pen-injector" (Doc. No. QUA-FD-2015-01973) has also been updated accordingly.

Dose selection:

The test for dose selection that is recommended by the Agency is performed (b) (4)

Dose selection is implicitly tested during the dose accuracy batch release test of the assembled pen, as the dose has to be accurately set for the test to succeed. Thus, no separate specification is provided for dose selection.

Audible, visual and tactile feedback:

Audible, visual and tactile feedback mechanisms are not considered to be essential performance requirements. Reference is made to Table 5 in the response to AGENCY QUESTION / REQUEST FOR INFORMATION ITEM NO. 5. The verification of audible, visual and tactile feedback was performed during design verification (please see the response to AGENCY QUESTION / REQUEST FOR INFORMATION ITEM NO. 3). Due to the invariable nature of these feedback mechanisms, re-testing during batch release tests or stability studies is not considered to be necessary. Design verification ensures that feedback mechanisms are adequately tested on a number of pens representative of the commercial product.

Dispense force:

It should be noted that a development target of (b) (4) N was set for dispense force limit tested during design verification, which provides a sufficient safety margin to the maximum acceptable dispense force limit of (b) (4) N based on Human Factor studies, which is set for routine batch release of commercial product. The batch release criterion for dispense force will also be applied to future stability studies of the pen-injector.

Injection time:

The injection time is not specified for the pen batch release test (please see the response to AGENCY QUESTION / REQUEST FOR INFORMATION ITEM NO. 2).

The following is taken from documents QUA-FR-2016-12014 and QUA-FD-2015-01973 that were updated per the information request of the Agency:

Table 1 and Table 2 list the tests to be performed for release. The tests have to be carried out with each batch unless periodic testing is indicated.

The acceptance criteria are valid for release and end of shelf life including in-use period, unless otherwise indicated.

References to pharmacopoeial analytical procedures and acceptance criteria are made to the current versions of the pharmacopoeias including their supplements. In cases where more than one pharmacopoeia is referred to, all requirements have to be fulfilled.

Table 2 - Specifications for insulin glargine/lixisenatide solution for injection, 100 U/mL insulin glargine with 50 or 33 µg/mL lixisenatide – performed with pen-injectors

Test	Analytical procedure reference	Acceptance criteria
Identification of pen-injector	Visual determination	Complies with internal requirements for pen identification.
Appearance of pen-injector	Visual determination	There must not be any manufacturing faults or damage which adversely affects the function and/or appearance of the insulin glargine/lixisenatide pen-injector system. All printed lettering must be legible.
Functional test and dose accuracy in standard atmosphere	Gravimetry/optical measurement	No problems in setting and dispensing the dose are admissible. The dose will be dispensed; - The expelled volume is measured gravimetrically. The calculated tolerance interval has to be within the upper and lower specification limits as defined by ISO 11608-1 Or alternatively - The (b) (4) is checked^a. The calculated tolerance interval has to be within the upper and lower specification limits as defined by ISO 11608-1 (using distance measurements instead of volumes)
Dispense force	Force measurement	The dose will be dispensed; the force measured must comply with the specification limit of $F \leq \frac{(b)}{(4)}N$

^a

(b) (4)

9.3.3 Functional test and dose accuracy in standard atmosphere

Functional testing of the pen-injector in standard atmosphere is performed as part of the dose accuracy measurements, as described hereafter.

9.3.3.1 Gravimetric test of dispensed volume

The dispensed volume is measured gravimetrically (expressed as mass m) and converted into volumes (V) using the density (ρ) of the solution: $V = m/\rho$. The tolerance interval for the dose accuracy test is calculated as shown in Table 6. The calculated tolerance interval has to be within the upper and lower specification limits according to ISO 11608-1.

9.3.3.2 (b) (4) test



9.3.4 Dispense force test

The pen is dialed to the maximum possible dose, after which the dose will be dispensed at a defined speed. The force necessary to dispense the dose is measured throughout the entire dose dispensing operation and has to be below the specification limit.

Reviewer Comment:

The lead reviewer accepts the Sponsor's response and notes that injection or 'dispense' force has been added to the lot release specifications in addition to the 'functional test and dose accuracy in standard atmosphere' which either implicitly or explicitly tests functional requirements of the device such as dial (b) (4) needle attachment, cap removal, audible/visual/tactile feedback, and dose accuracy.

C. Risk Analysis/Assessment

The Sponsor has provided Risk Management documentation under documents QUA-FD-2015-16111 and QUA-FD-2015-15002. The Sponsor states that they have identified all known and foreseeable causes leading to hazardous situations by analyzing the discrete functional steps of the entire product lifecycle from assembly to disposal. The Sponsor states that a project specific list of potential hazards has been created in cooperation with medical experts and global safety officers.

FMEAs (Failure Mode and Effect Analysis) were conducted to serve as bottom-up analysis to identify risks. The following is taken from QUA-FD-2015-15002 describing the FMEA approach:

As further mentioned in the risk management plan, due to the high similarity of the insulin glargine/lixisenatide pen-injectors to the Lantus SoloStar, the applicability of the Lantus SoloStar FMEAs was analyzed in the scope of the project.

In the D-FMEA, only a small number of items were identified where the insulin glargine/lixisenatide pen-injectors differ from the Lantus SoloStar. The risks associated with all of these items were scored very low, with an RPN below (b) (4) (an 'acceptable' rating). All other items remained unchanged from Lantus SoloStar which is a device representative of the "state of the art".

In the P-FMEA, the changes between the insulin glargine/lixisenatide pen-injectors and the Lantus SoloStar were evaluated as not having any impact on the Lantus SoloStar P-FMEA, which therefore is applicable without any changes.

Overall, it can be concluded that the residual risks identified in the bottom-up processes are either very low or identical to those of the Lantus SoloStar, which can be considered as being representative of the "state of the art". Therefore, when weighed against the treatment benefit described in Section 3.1, the residual risk / benefit analysis for the risks from the bottom-up analyses is in favor of the benefit.

Therefore the residual risk from the bottom-up analyses can be considered as being acceptable.

The following 'primary operating functions' in which the Sponsor analyzed if any risks could be introduced were as follows:

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The hazards identified by the Sponsor for a failure in each of these operating functions include:

- under/over dosing
- no injection possible
- virus/bacteria/contamination
- needle stick
- choking/inhalation of small parts
- exposure of medication to eyes
- injection of wrong insulin
- injection of non-insulin drug
- environmental hazard
- percutaneous exposure to contaminated fluid
- degradation of drug product

The Sponsor has committed to continuing surveillance and risk management activities for the marketed pen-injectors if approved according to ISO 14971.

Reviewer Comment:

The lead reviewer finds the risk management documentation, including identification of hazards and risk control measures, to be acceptable.

D. Labeling

The following was provided by the Sponsor in documents titled:

- Insulin glargine/lixisenatide – Original NDA – 10to40units-1ct-SoloStar-container
- Insulin glargine/lixisenatide – Original NDA – 30to60units-1ct-SoloStar-container
- Insulin glargine/lixisenatide – Original NDA – 10to40units-1ct-SoloStar-carton
- Insulin glargine/lixisenatide – Original NDA – 30to60units-1ct-SoloStar-carton

4 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS)
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The biocompatibility study for the insulin glargine/lixisenatide pen-injector was split into two parts: the first part was the investigation of the biocompatibility of the pen-injectors pen A and pen B, while the second part only assessed the biocompatibility of the new (b) (4) that will be used for the commercial product. Table 1 provides an overview of laboratory test reports associated with the biocompatibility studies of the pen-injector, while Table 2 provides the information for the new (b) (4). The (b) (4) is used for (b) (4), ie, the tests referred to in Table 2 are for those components only. Testing of components from different pens is not necessary (b) (4). Biocompatibility of the (b) (4) was tested on Lantus® SoloStar® pen components, which feature identical or very similar (b) (4) compared to insulin glargine/lixisenatide pen-injector components, as explained in NDA 208673. A comparative biocompatibility study was conducted to show that (b) (4) remains biocompatible after changing to the new (b) (4).

Conclusions drawn in these test reports confirm the summative description of biocompatibility test results that was provided in Section 3.2.P.2.4 "Container closure system - Biocompatibility of the pen-injector (ISO 10993-1)". The insulin glargine/lixisenatide pen-injector is biocompatible in accordance with ISO 10993-1.

Table 1 - Biocompatibility test reports for the insulin glargine/lixisenatide pen-injector

Test item	Test report pen A	Test report pen B
In vitro cytotoxicity (ISO 10993-5)	In vitro cytotoxicity report (ISO10993-5) - pen A – document no. [QUA-FD-2016-06212]	In vitro cytotoxicity report (ISO10993-5) - pen B – document no. [QUA-FD-2016-06215]
Irritation (ISO 10993-10)	Intracutaneous reactivity report (ISO10993-10) - pen A – document no. [QUA-FD-2016-06213]	Intracutaneous reactivity report (ISO10993-10) - pen B – document no. [QUA-FD-2016-06216]
Skin Sensitization (ISO 10993-10)	Skin sensitization report (ISO10993-10) - pen A – document no. [QUA-FD-2016-06214]	Skin sensitization report (ISO10993-10) - pen B – document no. [QUA-FD-2016-06217]

Table 2 - Biocompatibility test reports after change of (b) (4)

Test item	Test report ^a
In vitro cytotoxicity (ISO 10993-5)	In vitro cytotoxicity report (ISO10993-5) - (b) (4) - document no. [QUA-FD-2016-06243] In vitro cytotoxicity report (ISO10993-5) - (b) (4) - document no. [QUA-FD-2016-06248]
Chemical characterization by GC/MS fingerprint and ICP-OES investigation (ISO 10993-18)	Chemical characterization (ISO 10993-18) - (b) (4) - document no. [QUA-FD-2016-06250] Chemical characterization (ISO 10993-18) - (b) (4) - document no. [QUA-FD-2016-06252]

^a

GC/MS = Gas chromatography / Mass spectrometry

ICP-OES = Inductively coupled plasma optical emission spectrometry

Reviewer Comment:

This response was reviewed by the biocompatibility consultant Dr. Sarah Mollo. Please see her

attached memo for reference and acceptability of this response.

2. You note that a difference between the clinically used pen-injectors and the to-be marketed pen-injectors is that the dosage range above the intended limit of 40 or 60 units (depending on the model) is physically blocked for the to-be marketed pen-injectors. Please provide any verification/validation testing you have to support the functionality of this design feature.

Sponsor Response:

The specification of the physical max dose stops of the the insulin glargine/lixisenatide pen-injectors (at 40 units for pen A and at 60 units for pen B) is based on the specification of the physical max dose stop for the marketed Lantus SoloStar device (at 80 units). The (b) (4) for the max dose stop of the Lantus SoloStar and the insulin glargine/lixisenatide pen-injectors is specified with $\geq$ (b) (4) Nm and was found to be appropriate based on market data.

Therefore, the specification (robustness) of respective max dose stops for the insulin glargine/lixisenatide pen-injectors was not included into human factors validation as agreed with the Agency during human factors validation protocol review. The specification for the max dose stop (at 40 U and at 60 U) of the insulin glargine/lixisenatide pen-injectors was verified via technical verification testing to ensure the design is in accordance with the specification. The verification test report for the insulin glargine/lixisenatide pen-injectors is provided ("Verification report – Max dose stop", document no. [QUA-FD-2016-06302]).

Reviewer Comment:

The lead reviewer has reviewed the testing provided in document QUA-FD-2016-06302 and found the data to be adequate in verifying the functionality of the Max Dose Stop physical block on the to-be-marketed pen-injectors. The following is an excerpt from document QUA-FD-2016-06302:

TEST RESULTS LIXILAN FR PEN A AND PEN B

Test results show that the dial stop failure (b) (4) in standard atmospheric conditions of all samples are higher than (b) (4) Nm.

PenA:

(b) (4)

Pen B:

(b) (4)

3. Please provide a traceability matrix that lists the essential performance requirements of your pen-injector, the specification for each requirement, and the title of the provided test report that verifies your device to meet the specification. An example table can be seen below:

Essential Performance Requirement	Specification	Verification Test Report
Injection depth		
Injection accuracy		

Injection volume		
Injection time		
Activation force (initial and sustaining)		
Needle Connection Type		
Needle Length		
Needle Gauge		
....		

Please note that specifications should include performance up to the labeled date of expiry of the device (i.e. after preconditioning, aging, and shipping). If a requirement is controlled by another manufacturer (i.e. needle length/gauge) please provide the intended component specification (i.e. the pen-injector is intended for use with X needles) and how it is being controlled (i.e. labeling, warning statements, etc.) with reference to your risk assessment.

Sponsor Response:

The traceability matrix for the essential performance requirements of the insulin glargine/lixisenatide pen-injector that were tested during design verification is provided in [Table 3](#). These items are based on user requirements, ie, the steps necessary to safely operate the pen. The insulin glargine/lixisenatide pen-injector is operated manually; therefore essential performance requirements associated with automated features do not apply.

Certain design verification tests (eg, dose accuracy according to ISO 11608-1:2012) require preconditioning of the pen-injector in standard/warm/cold atmosphere, in dry heat/cold storage, as well as by free-fall and vibration. These tests are designed to simulate adverse conditions that the pen-injectors may be exposed to during storage, usage or transport. Compliance with the acceptance criteria of these tests (as demonstrated by the insulin glargine/lixisenatide pen-injector) therefore demonstrates the robustness of the device under adverse conditions.

In addition to design verification data presented here, functional tests of the pen-injector are performed as part of the primary stability study. Dose accuracy is assessed during long term storage and in-use up to the intended shelf-life of the combination product. These tests are

performed according to ISO 11608-1:2012 and require full functional assessment of the pen, including steps to set up the pen for an injection and dispense the dose. They are therefore fully representative of the device functionality at the time of testing. Primary stability data is shown in Section 3.2.P.8.3 "Stability data – Dose accuracy of the pen-injector".

Table 3 - Essential performance requirements of the insulin glargine/lixisenatide pen-injector

Essential performance requirement	Specification	Verification test report
Cap removal	The cap removal force has to range between (b) (4) N at ambient conditions	Verification report – Cap attachment and removal forces – document no. [QUA-FD-2016-06224]
Needle attachment	The pen-injectors must be compatible with needles according to ISO 11608-2:2012	Verification report – Needle compatibility – document no. [QUA-FD-2016-06240]
	The (b) (4) required to dial or back dial a dose shall be between (b) (4) mm	Verification report – Dial (b) (4) – document no. [QUA-FD-2016-06237]
Dose selection	Dose number visibility: dose numbers have to be readable at environmental lightning conditions of (b) (4) from a reading distance of (b) (4) cm	Information concerning the visual inspection was provided in NDA 208673. Please see "Pen-injector performance test – ISO 11608-1 – [QUA-FD-2015-01947]" and "Pen-injector performance test – ISO 11608-1 – Appendix – [QUA-FD-2015-10434]" for details
	The maximum dispense force for pen A and pen B has to be $\leq$ (b) (4) N	Verification report – Dispense force – document no. [QUA-FD-2016-06238]
Dose injection	The pen-injectors must fulfill the dose accuracy requirements according to ISO 11608-1:2012	Information concerning dose accuracy was provided in NDA 208673. Please see "Pen-injector performance test – ISO 11608-1 – [QUA-FD-2015-01947]" and "Pen-injector performance test – ISO 11608-1 – Appendix – [QUA-FD-2015-10434]" for details
Cap attachment	The cap attachment force must be $\leq$ (b) (4) N at ambient conditions	Verification report – Cap attachment and removal forces – document no. [QUA-FD-2016-06224]

The steps necessary for testing the priming of the pen are assessed during the dose accuracy tests

Requirements for needles are controlled by the respective manufacturers of those needles. The needle manufacturers have to verify that their needles comply with requirements of DIN ISO 11608- 2:2012 "Needle-based injection systems for medical use – Requirements and test methods – Part 2: Needles", section 11 ("Test method for validating the compatibility of needles and injector systems"). Therefore, test procedures were carried out in cooperation with the needle manufacturers in order to demonstrate the compatibility of the insulin glargine/lixisenatide pen-injector using dedicated pen needles of several commercially available needle brands. The instructions for use of the pen-injector provide guidance to the user when choosing compatible needles:

Only use needles that are compatible for use with *TRADENAME*,

(b) (4)

(b) (4)

Examples of needles compatible with the insulin glargine/lixisenatide pen-injector are provided in Table 4. All needles/brands manufactured by companies listed in Table 4 are compatible.

Table 4 - Examples of needles compatible with the insulin glargine/lixisenatide pen-injector

Brand	Needle type	Needle manufacturer
(b) (4)		

This list is provided for review purposes only and will not be maintained or updated as part of this submission

The trace matrix provided in Section 3.2.P.2.4 "Container closure system - Overview of the results of risk management" contains all risk management related actions and results with regard to needle compatibility and needle handling.

Reviewer Comment:

The lead reviewer accepted the Sponsor's response; however the lead reviewer sent follow-up information requests on 04/26/16. Please see Section IX of this memo for more details.

4. You note that you intend to continue in-use stability dose accuracy testing on your pen-injectors, however the Agency can not locate a requirement or statement of the intended shelf-life of your device.
 - a. Please provide information regarding the intended shelf-life of your device.

Sponsor Response:

- a) The proposed shelf life of the drug-device combination product is (b) (4) months. Please refer to Section 3.2.P.8.1 "Stability summary and conclusion" of NDA 208673, document titled "Stability summary and conclusions - solution for injection – QUA-FR-2014-24232", chapter ["Summary and recommended storage conditions and shelf life"].

Reviewer Comment:

This is acceptable to the lead reviewer.

- b. The Agency notes (b) (4) within your submitted stability data. Please provide a trend analysis of the dose accuracy of your device out to the labeled date of expiry with any available stability data you have acquired for both of your pen-injectors.

Sponsor Response:

- b) NDA 208673 was submitted containing in-use dose accuracy data after storage of the pen-injector for 5 months. All tested pen-injectors complied with dose accuracy requirements according to ISO 11608-1:2012. Updated in-use dose accuracy data containing the 11-month time point is provided with this response document. Reference is made to Section 3.2.P.8.3 "Stability data – dose accuracy of the pen-injector – [QUA-FR-2015-05894]". All pen-injectors complied with dose accuracy requirements according to ISO 11608-1:2012 after storage for 11 months plus an in-use period of 14 days.

A trending analysis of available dose accuracy data of the primary stability study is provided in Figure 1 for pen A and Figure 2 for pen B. This analysis takes into account both the long term stability and the in-use stability studies, as reported in Section 3.2.P.8 "Stability". All tested doses were within the upper and lower specification limits (USL and LSL) in accordance with ISO 11608-1:2012. (b) (4)

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Figure 2 - Trending analysis of dose accuracy data from the primary stability study (pen E (b) (4))



Reviewer Comment:

This response is acceptable to the lead reviewer and it is noted that the currently available stability data show (b) (4).

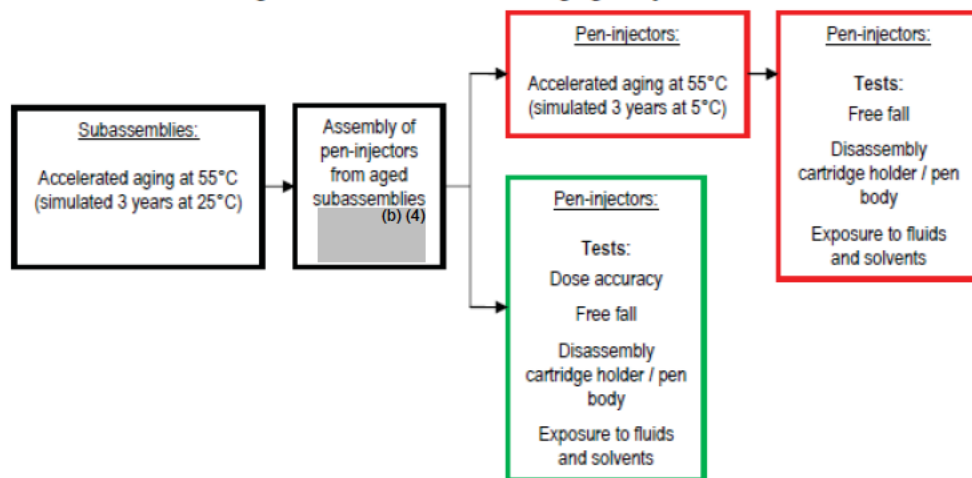
- c. You are proposing to leverage accelerated aging testing data acquired from the Lantus SoloStar pen-injector, (b) (4). Please clarify at what temperature the accelerated aging dose accuracy testing was completed for the Lantus SoloStar pen-injector. Furthermore, please clarify the corresponding shelf-life confirmed by the accelerated aging dose accuracy testing if performed at a lower temperature.

Sponsor Response:

c) For the accelerated aging study of SoloStar pen-injectors, pens were assembled from aged pen subassemblies (simulated 3 years). Cartridges used in these pens had not been exposed to accelerated aging conditions. According to the study protocol, pen-injectors were subsequently split into two groups:

1. One group of pen-injectors underwent dose accuracy testing in standard atmosphere according to ISO 11608-1 (see green box in Figure 3). (b) (4)
(b) (4) Additional tests were performed to ensure the physical robustness of the device, ie, resistance to damage from free-fall, unauthorized disassembly and exposure to fluids and solvents.
2. The second group of pen-injectors was not tested for dose accuracy but exposed to accelerated aging conditions (simulated 3 years). No dose accuracy was performed after completion of the study (b) (4) (see red boxes in Figure 3). To ensure the physical robustness of the device after accelerated aging, tests were conducted to show the resistance to damage from free-fall, unauthorized disassembly and exposure to fluids and solvents.

Figure 3 - SoloStar accelerated aging study overview



The shelf-life claim for the drug-device combination product is based on the stability data presented in Section 3.2.P.8 "Stability" of NDA 208673 and experience gained with other marketed SoloStar-based pen-injectors composed of the same materials. The accelerated aging data presented for the SoloStar device is indicating the stability of the device constituent part and as such is supportive of the overall stability of the drug-device combination.

Reviewer Comment:

The provided description is acceptable to the lead reviewer; however the lead reviewer sent follow-up information requests on 04/26/16 regarding the essential performance requirements that had been tested after preconditioning/aging. Please see Section XI of this memo below for more details.

5. The Agency notes that you performed functional testing on the pen-injector after preconditioning in dry-heat atmosphere for at least 96 hours. However, you state that the pen-injectors are intended to be stored for up to 14 days. Please provide a justification for why the preconditioning of your device is representative of the intended storage duration.

Sponsor Response:

The preconditioning referred to by the Agency is performed as part of the dose accuracy verification according to ISO 11608-1:2012. Preconditioning for 96 h in dry-heat atmosphere is a requirement of this standard and therefore tested accordingly.

The intended in-use period of the drug-device combination product (14 days) is supported by the stability data provided in Section 3.2.P.8.3 "Stability data" of NDA 208673. Stability data of the drug-device combination product is provided including dose accuracy after 6-month long term storage as well as 5-month storage followed by the 14 days in-use period.

Updated dose accuracy data after 12-month long term storage as well as 11-month storage followed by the 14 days in-use period is provided with this response document. Please see Section 3.2.P.8.3 "Stability data – dose accuracy – [QUA-FR-2015-05894]". All samples complied with the specifications.

Reviewer Comment:

The Sponsor's response is acceptable to the lead reviewer due to the ongoing stability testing.

vii. Information Requests – Sent 03/15/2016

1. In your response on March 2, 2016, you provided biocompatibility testing on the insulin glargine/lixisenatide pen-injector; however, a new (b) (4) will be used for the commercial product. You have provided test reports for cytotoxicity testing and chemical characterization by GC/MS fingerprint and ICP-OES investigation on another pen, the Lantus® SoloStar® pen components with that contains the (b) (4).
 - a. Provide a description of the materials in the Lantus® SoloStar® pen compared to the proposed device and provide a rationale as to why any difference in materials between the two pens would not result (b) (4) of the proposed device.
 - b. Provide a risk assessment using the potential exposure values obtained in the chemical characterization of the Lantus SoloStar pen that specifically address the irritation and sensitization endpoints not assessed directly by biocompatibility testing.

Alternatively, please provide the primary irritation and sensitization testing on the final finished device that will be marketed.

Sponsor Response:

Reviewer Comment:

This response was reviewed by the biocompatibility consultant Dr. Sarah Mollo. Please see her attached memo for reference and acceptability of this response.

VIII. Information Requests - Sent 03/22/2016

On March 2, 2016, you provided test reports for cytotoxicity testing and chemical characterization data on the Lantus SoloStar pen components, which contains the (b) (4) that will be used in the to-be marketed glargine/lixisenatide pen-injectors. On March 15, 2016, the Agency requested that you provide a comparison of the materials in the proposed glargine/lixisenatide pen-injector to the Lantus SoloStar, in order to determine that no additional (b) (4) of the proposed pen, resulting in a cytotoxic response that would not occur with the Lantus SoloStar pen. Additionally, the Agency requested information to address the sensitization and irritation endpoints. On March 18, 2016, you provided irritation and sensitization test reports on the to be marketed pen-injector (b) (4). However, you are still using the cytotoxicity testing from the Lantus Solostar pen to evaluate the cytotoxicity of the device. Please provide a description of the materials in the Lantus SoloStar pen compared to the to-be marketed glargine/lixisenatide pen-injector and provide a rationale as to why any difference in materials between the two pens would not result in increased amounts of (b) (4) of the to-be marketed device.

Sponsor Response:

(b) (4)

Reviewer Comment:

This response was reviewed by the biocompatibility consultant Dr. Sarah Mollo. Please see her attached memo for reference and acceptability of this response.

IX. Information Requests – Sent 04/26/2016

1.

(b) (4)

(b) (4)

Please provide a justification for why the vehicles you have used are appropriate for this test. Alternatively, please provide a method validation demonstrating that the extracts from the chosen vehicles are able to detect potential sensitizers. For more information, please refer to ASTM F2148: standard practice for evaluation of delayed contact hypersensitivity using the murine local lymph node assay.

Sponsor Response:

Sanofi agrees that it is essential to have adequate exposure over time in the LLNA.

(b) (4)

Sanofi is therefore convinced that the LLNA has been performed according to state-of-the-art methods and procedures.

Reviewer Comment:

This response was reviewed by consultant Dr. Sarah Mollo and was found to be adequate. Please see her attached memo for reference.

2. In response to an information request date March 2, 2016 you stated that the glargine/lixisenatide pen-injector is operated manually and therefore essential performance requirements associated with automated features do not apply. The Agency accepts this rationale for certain performance criteria, however the Agency notes that a specification should be developed for the injection time per unit dose so that the users have an expectation of how long it should take to inject given a maximum dispensing force of less than or equal to (b) (4) N. Please state the minimum time to inject (i.e. at a dispensing force of (b) (4) N) the minimum and maximum dose for both pen A and pen B. This minimum time to inject should be included in the labeling of the device to inform users the minimum time they must sustain the injection (independent of any audible/visual/tactile feedback for the end of injection). Alternatively, please provide a more detailed rationale for not including an estimated injection time for the minimum and maximum dose of the pen-injectors.

Sponsor Response:

For the insulin glargine/lixisenatide pen-injector no specification for the injection time of minimum or maximum doses is established.

(b) (4)

(b) (4)

Due to these non-uniform parameters that vary greatly between individuals, the IFU does not restrict the user to certain injection times. Instead, the user can adjust the injection time and speed himself/herself to a level that allows the least level of discomfort when injecting a dose.

Regardless of injection times, the IFU instructs the user to maintain pressure on the injection button for 10 s (with the needle inside the patient) after finishing an injection to allow for complete delivery of the dose.

Reviewer Comment:

The lead reviewer accepts the Sponsor's response and notes that the Sponsor has accounted for the various factors that may influence the injection time. The human factors validation study results determine if the 10 second hold after injection is validated.

3. The Agency notes that your pen-injectors include tactile/visual/audible feedback per ISO 11608-1. However, you have not provided any verification of this feedback. Please develop a specification for this feedback as a part of your essential performance requirements and provide verification that the feedback functions as intended.

Sponsor Response:

Sanofi does not define audible, visual and tactile feedback as essential performance requirements of the pen-injector. Reference is made to [Table 5](#) and the responses to [AGENCY QUESTION / REQUEST FOR INFORMATION ITEM NO. 4](#) and to [AGENCY QUESTION / REQUEST FOR INFORMATION ITEM NO. 5](#). However, these feedback mechanisms were verified during the design verification process. The following product design specifications were defined for the insulin glargine/lixisenatide pen-injector with regards to the audible, visual and tactile feedback mechanisms:

(b) (4)

Reviewer Comment:

The lead reviewer accepts the Sponsor's response and finds the data adequate to support the verification of the audible/visual/tactile feedback mechanisms of the pen-injectors.

4. The Agency notes that of your essential performance requirements you have only included extractable volume as a test of dose accuracy within your current batch release (document QUA-FR-2014-23122). The Agency notes that all essential performance requirements should be verified during batch release including dose selection, dispensing force, injection time (based on results of request for specification), audible/visual/tactile feedback, and dose accuracy. Please

provide documentation as evidence that you have included dose selection, dispensing force, and audible/visual/tactile feedback within your batch release testing.

Sponsor Response:

Revised specifications for the pen-injector batch release:

Sanofi is providing the Agency with revised pen batch release specifications, which include the following test items:

- Identity;
- Appearance;
- Functional test and dose accuracy in standard atmosphere;
- Dispense force.

Please see [Table 2] of the updated document 3.2.P.5.1 "Specifications" (Doc. No. QUA-FR-2016-12014). The description of batch release methods for the pen-injector presented in [Section 9.3] of document 3.2.P.7 "Container closure system – Disposable pen-injector" (Doc. No. QUA-FD-2015-01973) has also been updated accordingly.

Dose selection:

The test for dose selection that is recommended by the Agency is performed (b) (4)

Dose selection is implicitly tested during the dose accuracy batch release test of the assembled pen, as the dose has to be accurately set for the test to succeed. Thus, no separate specification is provided for dose selection.

Audible, visual and tactile feedback:

Audible, visual and tactile feedback mechanisms are not considered to be essential performance requirements. Reference is made to Table 5 in the response to AGENCY QUESTION / REQUEST FOR INFORMATION ITEM NO. 5. The verification of audible, visual and tactile feedback was performed during design verification (please see the response to AGENCY QUESTION / REQUEST FOR INFORMATION ITEM NO. 3). Due to the invariable nature of these feedback mechanisms, re-testing during batch release tests or stability studies is not considered to be necessary. Design verification ensures that feedback mechanisms are adequately tested on a number of pens representative of the commercial product.

Dispense force:

It should be noted that a development target of (b) (4)N was set for dispense force limit tested during design verification, which provides a sufficient safety margin to the maximum acceptable dispense force limit of (b) (4)N based on Human Factor studies, which is set for routine batch release of commercial product. The batch release criterion for dispense force will also be applied to future stability studies of the pen-injector.

Injection time:

The injection time is not specified for the pen batch release test (please see the response to [AGENCY QUESTION / REQUEST FOR INFORMATION ITEM NO. 2](#)).

Reviewer Comment:

The lead reviewer accepts the Sponsor's response and notes that injection force has been added to the lot release specifications in addition to the 'functional test and dose accuracy' which either implicitly or explicitly tests functional requirements of the device such as dial (b) (4) audible/visual/tactile feedback, and dose accuracy.

5. In response to an information request dated March 2, 2016 you stated that the tests performed during in-use and long term stability studies are performed according to ISO 11608-1:2012 and require full functional assessment of the pen-injector, including steps to set up the pen for an injection and dispense the dose. However, you have not stated specifically what essential performance requirements were tested post-aging besides dose accuracy. It seems that you are asserting that a test for dose accuracy is a downstream effect of all functional characteristics of the pen-injector and therefore is representative of all other essential performance criteria. The Agency believes that certain essential performance requirements such as dispensing force, injection time, and visual/audible/tactile feedback should be verified after aging and

preconditioning the device in order to establish that the device meets all essential performance requirements up to the labeled date of expiry for the device. Please provide this testing on a currently available batch within the long-term stability study in order to verify the essential performance requirements after aging. Alternatively, please provide greater detail regarding the full functional testing based on the instructions for use completed post-aging and if the functional testing included testing for the other essential performance requirements of your device besides dose accuracy.

Sponsor Response:

The essential performance requirements defined by Sanofi for the insulin glargine/lixisenatide pen-injector represent the steps necessary to prepare the pen for an injection, inject the dose and subsequently prepare the pen for storage (Table 5; please see also response to question no. 3 (Doc. No. [QUA-FO-2016-05990]) of the information request dated March 2, 2016 (Sequence 0010)).

Table 5 - Overview of insulin glargine/lixisenatide pen-injector performance parameter testing

Test item	Essential performance requirement	Tested during design verification	Tested during batch release	Tested during real time aging studies (primary stability)
Cap removal	x	x		x ^b
Needle attachment	x	x		x ^b
Dose selection	x	x	x ^b	x ^b
Audible/visual/tactile feedback		x		
Dispense force	x	x	x	x
Dose accuracy	x	x ^a	x ^a	x ^a
Cap attachment	x	x		x ^b

^a Includes a visual inspection of the pen-injectors (eg, for dose number visibility)

^b Implicitly tested during dose accuracy tests, which requires preparing the pen for dispensing the dose

These steps are aligned with the possible interactions between the user and the device interface, as reported in the human factors study (please see the human factors / usability report Doc. No. [QUA-FD-2015-14585] of NDA 208673). The dose accuracy measurements require the same sequence of steps to prepare the pen for the test and dispense the dose. In addition, preparing the pen and dispensing the dose involves the entire mechanism of the pen. Dose accuracy tests are therefore considered fully representative of pen performance at the time of testing, including during real time aging studies.

To address the Agency's concerns regarding the assessment of essential performance requirements during aging studies, Sanofi is providing the results of dispense force tests from the ongoing real time aging study (primary stability). The Section 3.2.P.8 "Stability" of NDA 208673 has been updated accordingly. Please refer to the documents 3.2.P.8.1 "Stability summary and conclusion" ([QUA-FD-2016-12286]) and 3.2.P.8.3 "Stability data" ([QUA-FD-2016-12287]) for details. Dispense force data is available for the time points 0, 6 and 12 month of the long term stability study, as well as 5 and 11 month of the in-use stability study. Tests were performed in standard atmosphere with 38 pen-injectors each using the same batches that were used for the dose accuracy measurements reported in Section 3.2.P.8 "Stability" of NDA 208673. The dispense forces were measured using a tensile meter while the doses were being dispensed. All test items complied with the specification limit for the maximum dispense force ($F \leq$ (b) (4) N).

This specification limit was set at the time of primary stability study initiation and is consistent with the limit

set for design verification. As explained in the response to [AGENCY QUESTION / REQUEST FOR INFORMATION ITEM NO. 4](#), future stability study and batch release criteria for the dispense force will be based on the specification limit that resulted from Human Factors studies ($F \leq \text{(b) (4) N}$).

A trending analysis of dispense force data from the stability study is provided in [Figure 3](#) for pen A and in [Figure 4](#) for pen B, showing the mean values of dispense forces and the accompanying standard deviation. This trend analysis takes into account stability data from available time point of long term and in-use stability studies. No discernible trend is visible in the trend analysis.

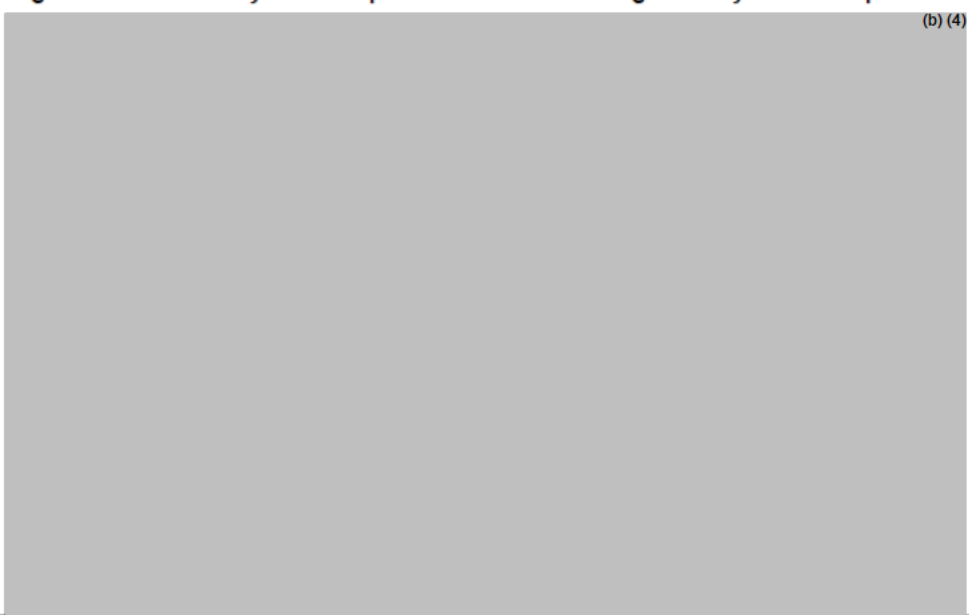
As explained in the response to [AGENCY QUESTION / REQUEST FOR INFORMATION ITEM NO. 4](#), verification tests for audible, visual and tactile feedback were performed during design verification but not as part of real time stability studies, because they are not expected to alter during storage. Similarly, injection times were not assessed during the real time stability studies because they are not specified for the pen (see response to [AGENCY QUESTION / REQUEST FOR INFORMATION ITEM NO. 2](#)).

Figure 3 - Trend analysis of dispense force data during stability studies – pen A



Figure 4 - Trend analysis of dispense force data during stability studies – pen B

(b) (4)



Reviewer Comment:

The lead reviewer accepts the Sponsor's response and notes that the reported injection force testing as part of the on-going stability testing is adequate according to the specification maintained under the NDA. The lead reviewer notes that the Sponsor makes the argument that cap removal, needle attachment, dose selection, and cap attachment are implicitly tested during the functional test of dose accuracy. The lead reviewer accepts this argument and notes that the dose accuracy test includes testing of the visual/audible/tactile feedback of the pen-injectors. Any testing deviations or observations during the functional steps required to accomplish the dose accuracy testing is recorded by the Sponsor.

6. In document QUA-FD-2015-19978 you executed a simulated shipping study and performed functional inspection and dose accuracy testing to confirm the pen-injectors maintained functionality after shipping. The Agency believes that certain essential performance requirements such as dispensing force, injection time, and visual/audible/tactile feedback should be verified after shipping in order to establish that the device continues to meet all essential performance requirements. Please provide this testing in order to verify the essential performance requirements after shipping. Alternatively, please provide greater detail regarding the 'functional testing' performed in accordance with ISO 11608-1 Section 10.1 d) and if the functional testing included testing for the other essential performance requirements of your device besides dose accuracy.

Sponsor Response:

Sanofi agrees that device functionality after simulated shipping has to be thoroughly investigated to assess the potential influence of transportation on pen performance. As part of the response to question no. 5 of Sequence 0023 (Doc. No. QUA-FO-2016-11977), the applicant provided the Agency with an overview ([Table 5]) of pen performance tests conducted at the various stages of development, primary stability and batch release testing. This table has now been extended to include an overview of performance tests performed after simulated shipping of the pens (please see Table 1, right column).

Functional assessment of the pen-injectors after simulated shipping:

As previously communicated to the Agency, the primary mode by which pen functionality is assessed is the test for dose accuracy. Pen-injectors sampled after the shipping simulation were therefore subjected

to dose accuracy tests in standard atmosphere according to the provisions of ISO 11608-1:2012. The dose accuracy test includes the functional assessment according to ISO 11608-1:2012 Section 10.1 d), which comprises of all steps to set up the pen for an injection, followed by dispensing the dose. These steps are based on the instructions for use. It is therefore not only an assessment of dose accuracy, but also implicitly includes tests of other essential performance requirements like cap removal, needle attachment, dose number visibility, dose selection and dispense force. These test items are monitored by the operator during the procedure and any observations are recorded in an observation sheet. It should be noted that without successful completion of these implicit test items, the dose accuracy test itself cannot be successfully completed, as they are an essential part of the procedure (see below).

A detailed explanation of the dose accuracy test procedure is provided hereafter. All pen test items listed for the shipping simulation in Table 1 were either explicitly or implicitly tested during this procedure.

(b) (4)

Considering the dose accuracy testing described above, all essential performance requirements were successfully addressed. No additional tests were considered necessary because the dose accuracy tests have shown that pens retained full functionality after the shipping simulation.

Injection time:

The injection time was not assessed after the shipping simulation. No injection time is specified for SoloStar-based pen-injectors, as SoloStar is a manually driven injector that depends on the injection speed the user feels most comfortable with. Please see the response to [question no. 2] of Sequence

0023 (Doc. No. QUA-FO-2016-11977) for an explanation.

Visual/audible/tactile feedback:

Visual/audible/tactile feedback mechanisms were not assessed after the shipping simulation. As detailed in the response to [question no. 3] of Sequence 0023 (Doc. No. QUA-FO-2016-11977), these feedback mechanisms are not regarded as essential performance requirements. Due to their invariant nature they have been tested during design verification of insulin glargine/lixisenatide pen-injector but not after aging or simulated shipping. Design verification data has been provided to the Agency for review.

Table 1 - Overview of insulin glargine/lixisenatide pen-injector performance parameter testing

Test item	Essential performance requirement	Tested during design verification	Tested during batch release	Tested during real time aging studies (primary stability)	Tested after shipping simulation ^c
Cap removal	x	x		x ^b	x ^b
Needle attachment	x	x		x ^b	x ^b
Dose selection	x	x	x ^b	x ^b	x ^b
Audible/visual/tactile feedback		x			
Dispense force	x	x	x	x	x ^b
Dose accuracy	x	x ^a	x ^a	x ^a	x ^a
Cap attachment	x	x		x ^b	

^a Includes a visual inspection of the pen-injectors (eg, for dose number visibility).

^b Implicitly tested during dose accuracy tests, which require preparing the pen for injection and dispensing the dose.

^c The shipping simulation was performed with marketed Lantus® SoloStar® pen-injectors, which are sufficiently similar to insulin glargine/lixisenatide pen-injectors regarding their form and function.

Reviewer Comment:

The lead reviewer accepts the Sponsor's response. The Sponsor has provided a more detailed description of the testing completed after the simulated shipping. The lead reviewer notes that essential performance requirements such as cap removal, needle attachment, dose selection, audible/visual/tactile feedback, and dispensing force are implicitly tested under functional testing of the pen-injectors. The Sponsor notes that after each step of delivering a set dose any observations from cap removal force, needle attachment force, dispensing force, dose selection, etc. were recorded. This is acceptable to the lead reviewer in order to validate that the pen-injectors maintained their essential performance requirements after shipping.

X. Outstanding Deficiencies

N/A

XI. Post-Market Commitment / Post-Market Requirements

The reviewer notes that within NDA 208673 the sponsor committed to performing ongoing stability analysis to assess maintenance of the essential performance requirements of the final finished combination product through the intended expiration date of (b) (4) months using primary registration stability batches. The sponsor should submit evidence of completion of these activities to NDA annual reports.

XII. Recommendation

The consulting reviewer recommends approval of the NDA in the context of device constituent parts for the combination product with the Post-Market Commitment noted in Section XI above.

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xiii. Attachments

Attached is Dr. Sarah Mollo's (CDRH/ODE/DAGRID/GHDB) biocompatibility review.

APPEARS THIS WAY ON
ORIGINAL

Consult Memo: ICC1500701/ NDA 208673

Date: May 9, 2016
From: Sarah Mollo, DAGRID/GHDB
To: John McMichael, Lead Reviewer, DAGRID/GHDB

Type of Product: pen injector

Product Name: Insulin glargine/lixisenatide pen injector
Intended Use: self-administration of Insulin glargine/lixisenatide
Sponsor: Sanofi
Consult Review: Biocompatibility of the Device Constituent

I. Scope of Consult

This consult is a review of the biocompatibility of the patient contacting components of the pen injector. The toxicological assessment of the primary container closure is reviewed by CDER.

II. Documents Reviewed

NDA 208673 container closure

Biocompatibility test reports:

- (b) (4) - cytotoxicity ISO 10993-5 - QUA-FD-2016-06243
- (b) (4) - leachables ISO 10993-18 - QUA-FD-2016-06250
- (b) (4) - cytotoxicity ISO 10993-5 - QUA-FD-2016-06248
- (b) (4) - leachables ISO 10993-18 - QUA-FD-2016-06252
- pen A - cytotoxicity ISO 10993-5 - QUA-FD-2016-06212
- pen A - irritation ISO 10993-10 - QUA-FD-2016-06213
- pen A - sensitization ISO 10993-10 - QUA-FD-2016-06214
- Pen A (b) (4) - cytotoxicity ISO 10993-5 - QUA-FD-2016-08710
- pen B - cytotoxicity ISO 10993-5 - QUA-FD-2016-06215
- pen B - irritation ISO 10993-10 - QUA-FD-2016-06216
- pen B - sensitization ISO 10993-10 - QUA-FD-2016-06217
- Pen B (b) (4) - cytotoxicity ISO 10993-5 - QUA-FD-2016-08712

III. Device Description

The design of the insulin glargine/lixisenatide pen-injector is based on the already marketed SoloStar® peninjector, which is combined with insulin glargine 100 U/mL solution for injection (Lantus®, NDA 21-081) and which has been modified for the application of the insulin glargine/lixisenatide solution for injection. The modification comprises the color of the bodies, caps, injection buttons, dose selectors and the scaling on the number sleeves. Additional modifications of the number sleeves define the maximum doses that can be dialed.

The insulin glargine/lixisenatide pen-injector is a pre-filled, disposable, manual pen-injector. It does not contain any electronic components. After dialing the desired dose, the injection button is pushed to deliver the medicinal product for subcutaneous injection. The device is irreversibly combined with a 3 mL cartridge filled with insulin glargine/lixisenatide solution for injection. By design, the pen-injector is a disposable device that cannot be reused after dispensing the labeled volume. The cartridge serves as reservoir for the drug product. No part of the pen-injector is in direct contact with the drug product solution or fluid pathway.

The insulin glargine/lixisenatide pen-injector is available for two different dosage strengths: 100 U/mL insulin glargine with 50 µg/mL lixisenatide (pen A) or 100 U/mL insulin glargine with 33 µg/mL lixisenatide (pen B). Body and cap are provided in 2 different colors; ie, in peach color for pen A and in olive color for pen B (Figure 2).

Figure 2 – Insulin glargine/lixisenatide

Pen designation	Pen A		Injection button color
Color of pen	Peach		
Concentration insulin glargine	100 U/mL		
Concentration lixisenatide	50 µg/mL		orange
Pen designation	Pen B		Injection button color
Color of pen	Olive		
Concentration insulin glargine	100 U/mL		
Concentration lixisenatide	33 µg/mL		dark orange

IV. Biocompatibility Summary

The sponsor states the patient contacting components include the following: the cap, cartridge holder, body, injection button, dose selector, number sleeve and thread insert. The pen-injector parts (including the printing on the cartridge holder and number sleeve) were tested for biocompatibility after removing the cartridge from the device. There are no drug-contacting components.

Materials

Table 3 - Materials of the pen-injector components

Component	Material	Color	Printing
(b) (4)			

The sponsor provided biocompatibility testing on pen A and pen B in accordance with ISO 10993-1 for intact skin contacting devices: cytotoxicity, sensitization, and irritation.

Due to a change (b) (4), an additional study was conducted to determine the biocompatibility (b) (4) used for the Lantus® SoloStar® pen instead of pen A and pen B. The sponsor stated that the studies performed on the (b) (4) using the alternative pen were acceptable for the following reasons:

Since the biocompatibility of pen A and pen B had already been investigated (see Section 3.1), components (b) (4) were subjected to a different complement of tests:

- Cytotoxicity testing according to ISO 10993-5;
- GC/MS fingerprint investigation according to ISO 10993-18 (5). (b) (4)
- ICP-OES investigation according to ISO 10993-18. (b) (4)

Interactive Review Summaries

- 1) March 2, 2016: An IR was sent to the sponsor requesting biocompatibility test reports for the pen injector. The sponsor provided the cytotoxicity, sensitization, and irritation test reports for the insulin glargine/lixisenatide pen-injector as well as biocompatibility information (b) (4) that will be used on the to-be marketed pen that was not included on the pen that underwent the biocompatibility testing submitted.
- 2) March 15, 2016: An IR was sent to the sponsor requesting a comparison of the materials in the proposed glargine/lixisenatide pen-injector to the Lantus SoloStar, in order to determine that (b) (4) of the proposed pen, resulting in a cytotoxic response that would not occur with the Lantus SoloStar pen as well as information to address the sensitization and irritation endpoints. The sponsor provided sensitization and irritation test reports for the insulin glargine/lixisenatide pen-injectors (b) (4). The sponsor stated that the tests were initiated in December 2015 and results became available recently. The sponsor did not address the request for information regarding the cytotoxicity testing.
- 3) March 22, 2016: An IR was sent to the sponsor requesting a description of the materials in the Lantus SoloStar pen compared to the to be marketed glargine/lixisenatide pen-injector and a rationale as to why any difference in materials between the two pens would not result in increased amounts of (b) (4) of the to-be marketed device. The sponsor provided the cytotoxicity test reports for the insulin glargine/lixisenatide pen-injectors (b) (4).
- 4) March 26, 2016: For the sensitization endpoint, the sponsor provided LLNA testing (b) (4)
An IR was sent to the sponsor to provide a justification for why the vehicles you have used are appropriate for this test.

Biocompatibility Testing

Test articles: LixiLan FR, Pen A; LixiLan FR, Pen B

Extraction ratio: (b) (4) g/ml

Endpoint	Test Method	Extraction and Test Method Acceptability	Test Result
Cytotoxicity	XTT cytotoxicity test	Acceptable	(b) (4)
Sensitization	LLNA in mice	Acceptable	
Irritation	ISO Intracutaneous (intradermal) Reactivity Test in Rabbit	Acceptable	
			Pass

Cytotoxicity testing

Results for Test Item and Controls after 24 Hours Extraction in Complete medium

		Microscopic Evaluation	Photometric Evaluation			
Test Group	Extract Conc. [% (v/v)]	Cytotoxicity	Mean Absorbance*	Standard-Deviation	Chem. Blanks	Absorbance in % of Medium Control
Medium Control	(b) (4)					(b) (4)
Test Item						
Negative Control						
Medium Control						
Positive Control						

Given absorbances are rounded values.

Relative absorbances are calculated using correct absorbance values.

* mean absorbance (absolute) of (b) (4)

Grey shaded test groups indicated cytotoxic effects in the microscopic evaluation.

Reviewer comment

(b) (4)

The reviewer agrees that the test extract appears to be non-cytotoxic.

LLNA testing (sensitization testing)

The sponsor provided the following response to the IR sent on March 26, 2016 regarding the LLNA method used to address the sensitization endpoint:

Sanofi response

Sanofi agrees that it is essential to have adequate exposure over time in the LLNA.

(b) (4)

Sanofi is therefore convinced that the LLNA has been performed according to state-of-the-art methods and procedures.

Reviewer Comment

The response is adequate; the deficiency is resolved.

VI. Review Summary

The reviewer recommends approval based on the biocompatibility of the patient contacting components of the device.

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

/s/

MARTIN L WHITE

06/02/2016

Signing on behalf of John McMichael (CDRH reviewer)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Drug Utilization Review

Date: April 27, 2016

Primary Reviewer: LCDR Justin Mathew, Pharm.D
Division of Epidemiology II (DEPI II)

Team Leader (Acting): Tracy Pham, Pharm.D
Division of Epidemiology II (DEPI II)

Deputy Director LCDR Grace Chai, Pharm.D
For Drug Utilization: Division of Epidemiology II (DEPI II)

Drug names: Insulin Glargine and Lixisenatide
Insulin Degludec and Liraglutide

Application Type/Number: NDA 208673, NDA 208583

Applicant/sponsor: Sanofi-Aventis, Novo Nordisk

OSE RCM #: 2016-221

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

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EXECUTIVE SUMMARY

New drug applications (NDAs) for combination antidiabetic products containing a basal insulin and a GLP-1 agonist have been submitted by two sponsors for approval by the FDA. Currently, there are no FDA approved combination anti-diabetic products that also include insulin. In order to determine the proportion of patients who concurrently use a GLP-1 agonist with a basal insulin, the Division of Metabolism and Endocrinology Products (DMEP) requested the Division of Epidemiology II (DEPI II) to provide the utilization patterns for GLP-1 agonists in combination with basal insulin from April 2010 through March 2015, annually. In support of DMEP's request, this review examined: 1) national cross-sectional outpatient retail data to assess the extent of use of GLP-1 agonists and 2) longitudinal healthcare plans claims data to assess the proportion of concurrent use of a GLP-1 agonist and basal insulin. In addition, this review also comments on the sponsor's submitted utilization study of the proposed product Lixilan, a fixed-dose insulin glargine and lixisenatide (a GLP-1 agonist) product.

The nationally estimated total number of unique patients who received dispensed prescriptions through the U.S. outpatient retail pharmacies for all GLP-1 agonists increased from approximately 535,000 patients in the 12-month period ending in March 2011 to 882,000 patients in the 12-month period ending in March 2015. The majority of patients were dispensed Victoza® and were adult patients aged 45 to 64 years in the 12-month period ending in March 2015. The patients who were dispensed GLP-1 agonists accounted for 5% of the total number of patients who received dispensed prescriptions for any OAD (oral anti-diabetic) and/or GLP-1 agonists in the 12-month period ending in March 2015.

For the concurrency analysis, patient data based on prescription claims for any OAD/GLP-1 agonists and basal insulin were obtained from a sample of the U.S. commercially insured population captured in the IMS Real World Data (RWD) Adjudicated Claims – US database. The number of patients who had prescription claims for any OAD and/or GLP-1 agonists and the patients on concurrent therapy with a GLP-1 agonist and basal insulin were obtained from this sample. The concurrency analysis are based on unprojected data and may not be nationally representative; therefore, the analysis focused on the proportion of patients rather than the absolute numbers in the sample. Among the patients who had a prescription claim for a GLP-1 agonist, the proportion of patients who had concurrent therapy with a GLP-1 agonist and a basal insulin increased from 17% of GLP-agonist patients in the 12-month period ending in March 2011 to 27% of GLP-agonist patients in the 12-month period ending in March 2015. However, the percentage of patients who were new to diabetes treatment and started on concurrent therapy with GLP-1 agonist and basal insulin was negligible ($\leq 0.1\%$) during the study period.

The sponsor conducted drug utilization analysis with three unrelated databases:

(b) (4)

The sponsor's study has numerous limitations and assumptions among the three databases to conclude Lixilan can meet the insulin demands of (b) (4) % of the intended patient population. (b) (4)

(b) (4) had a small sample size, the (b) (4)

(b) (4) data were not linked, and the use of (b) (4) data to determine accurate daily insulin dosing is difficult.

In summary, based on a sample population, it appears that about a quarter of commercially insured patients with prescription claims for GLP-1 agonist products concurrently had prescription claims for basal insulin. The sponsor's study concludes that their product will meet (b) (4)% of the insulin needs of their target population, however the studies used to reach that conclusion have limitations. Therefore, it is difficult to determine if a fixed dose combination product containing a basal insulin and GLP-1 agonist can meet the higher daily dose of insulin for many type 2 diabetic patients based on the studies provided.

1 INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists) "increase glucose-dependent insulin secretion, decreases inappropriate glucagon secretion, increases B-cell growth/replication, slows gastric emptying, and decreases food intake."¹ GLP-1 receptor agonists are indicated as "an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus."¹ There are currently five GLP-1 receptor agonist being marketed:

GLP-1 Agonists ²		
Product Name	Formulations/Strengths	Approval Date
Byetta [®] (exenatide)	Injectable: 300mcg/1.2mL; 600mcg/2.4mL	April 28, 2005
Victoza [®] (liraglutide)*	Injectable: 18mg/3mL	January 25, 2010
Bydureon [®] (exenatide)	Injectable: 2mg/vial; 2mg (pen)	January 27, 2012
Tanzeum [®] (albiglutide)	Injectable: 30mg (pen); 50mg (pen)	April 15, 2014
Trulicity [®] (dulaglutide)	Injectable: 0.75mg/0.5mL; 1.5mg/0.5mL	September 18, 2014

*Saxenda[®] (liraglutide) is indicated for weight loss only and was NOT included in the study.

Currently, no combination antidiabetic product has been approved with one of the components being insulin. According to clinical treatment standards for type 2 diabetes, it is recommended that newly diagnosed patients are started on one oral antidiabetic product (i.e. metformin). If the patient fails to achieve hemoglobin A1c (HbA1c) level goals, step up therapy is warranted. Step up therapy would consist of adding an additional one or two antidiabetic products (sulfonylureas, dipeptidyl peptidase 4 inhibitors (DPP-4

¹ "Facts & Comparisons[®] EAnswers." *Facts & Comparisons[®] EAnswers*. Wolters Kluwer Health, Inc, Mar. 2015. Web. 23 Mar. 2016. <<http://online.factsandcomparisons.com/index.aspx>>.

² Drugs@FDA: FDA Approved Drug Products." *Drugs@FDA: FDA Approved Drug Products*.. Web. 23 Mar. 2016. <<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>>.

inhibitors), sodium/glucose co-transporter 2 (SGLT2 inhibitor), and/or GLP-1 agonists). If patients' HbA1c still remains uncontrolled, insulin therapy is the last step.³

The Division of Metabolism and Endocrinology Products (DMEP) is reviewing new drug applications (NDA) submitted by Sanofi-Aventis (NDA 208673) and Novo Nordisk (NDA 208583) for approval. The two NDAs consist of combination products of a GLP-1 agonist and basal insulin. An advisory committee meeting is scheduled for May 24th and 25th to discuss the safety profiles of these NDAs and determine if these combination products have an unmet need. In support of DMEP's reviews of the NDAs and upcoming advisory committee meeting, this review from the Division of Epidemiology II (DEPI-II) provides: 1) national estimates of patients who were dispensed prescriptions for GLP-1 agonists from U.S. outpatient retail pharmacies, and 2) the proportion of patients who had concurrent prescription claims for a GLP-1 agonist and a basal insulin from a sample of U.S. commercially insured population for five 12-month time periods from April 2010 through March 2015. This review also comments on the sponsor's submitted utilization study of the proposed product Lixilan, a fixed-dose insulin glargine and lixisenatide (a GLP-1 agonist) product.

2 MATERIALS & METHODS

Proprietary drug utilization databases available to the Agency were used to conduct the analyses in this review. Full database descriptions are provided in Appendix 2 of the review.

2.1 NATIONAL CROSS-SECTIONAL UTILIZATION ANALYSES OF GLP-1 AGONISTS

2.1.1 DETERMINING SETTINGS OF CARE

The IMS Health, IMS National Sales Perspectives™ database were used to determine the various settings of care to which GLP-1 agonists were sold to. During year 2015, the sale of GLP-1 agonists by number of bottles sold from manufacturers indicated that approximately 76% of total sales were distributed to the outpatient retail pharmacy settings, 18% to the mail-order/specialty pharmacies, and 6% to the non-retail pharmacy setting.⁴ As a result, outpatient retail pharmacy utilization patterns were examined. Data from mail-order/specialty pharmacies and non-retail settings were not included in this review.

2.1.2 DATA SOURCES USED

The IMS, Total Patient Tracker (TPT) database was used to obtain the nationally estimated number of patients receiving dispensed prescriptions for an oral antidiabetic

³ "American Diabetes Association Standards of Medical Care in Diabetes D 2016." *Diabetes Care* 39.1 (2016): n. pag. Jan. 2016. Web. 23 Mar. 2016.

⁴IMS Health, IMS National Sales Perspectives™. 2015. Extracted March 2016. File: IMS DATA 2016-221 Lixilan AC.xlsx

(OAD) medication and/or a GLP-1 agonist from U.S. outpatient retail pharmacies. The nationally projected patient data for GLP-1 agonists were also stratified by molecule and patient age (0-17, 18-44, 45-64, 65 years and older) for five 12-month time periods from April 2010 through March 2015. Appendix 3 provides a list of selected OADs and GLP-1 agonists which were included in this analysis.

2.2 CONCURRENCY ANALYSIS OF GLP-1 AGONISTS AND BASAL INSULIN

In addition to the analysis of nationally estimated utilization trends of GLP-1 agonists in the outpatient retail setting, we examined a longitudinal patient-level database based on a sample of U.S. commercially insured patients to assess the concurrent use of GLP-1 agonists and basal insulins for five 12-month time periods from April 2010 through March 2015. These data were stratified by patient age groups (1-17, 18-44, 45-64, 65 years and older). These data particularly assessed: 1) the proportion of patients who filled a GLP-1 agonist and had a concurrent basal insulin therapy, and 2) the proportion of patients who were new to diabetes treatment and had a concurrent therapy of GLP-1 agonist and basal insulin as their first treatment.

2.2.1 DATA SOURCES USED

The IMS Health Real-World Data (RWD) Adjudicated Claims – US database (formerly known as “PharMetrics Plus”) was searched to obtain the number of commercially insured patients who had pharmacy prescription claims for any OAD and/or GLP-1 agonist from a sample of commercial health plans, as well as a sample of patients who had pharmacy prescription claims for basal insulin for five 12-month time periods from April 2010 through March 2015. The total number of patients in the database on any OAD and/or GLP-1 agonist for each examined time period served as a possible surrogate of treated Type 2 Diabetes patient population in the IMS RWD Adjudicated Claims – US database. From this sample of patients with OADs and/or GLP-1 agonist prescription claims, the number and proportion of patients on concurrent therapy of GLP-1 agonist and basal insulin were obtained for each examined time period. Appendix 3 provides a list of selected OADs, GLP-1 agonists, and basal insulins which were included in these analyses.

Patient-level summary information will be reported for five cohorts. Each cohort data time frame consists of a 1-year selection time period, a 1-year look-back period, and a 3-month washout period for allowable gaps in therapy. For each cohort, we require all patients to be continuously enrolled in their health plan throughout the corresponding data time frame in order to ensure a complete view of their claims history. Therefore, children less than one who are born between the look back periods are not captured.

The total number of patients on any OAD/GLP-1 agonist was defined as has having two or more prescription claims for any OAD/GLP-1 agonist. The more stringent definition of 2+ prescription claims were used for the total OAD/GLP-1 agonist patients to determine a conservative baseline population who were continuously on an OAD/GLP-1 agonist therapy. Patients with a prescription claim for GLP-1 agonist as well as a concurrent claim of basal insulin required a less stringent 1+ prescription claim during the look back period in order to allow for the capture of patients who received prescriptions for a GLP-1 agonist and basal insulin on the same day. Patients are

considered new if they have not received **ANY** OAD/GLP-1 agonist or basal insulin during the look back period.

Cohort Selection Time Frame
Year 1: April 1, 2010 – March 31, 2011
Year 2: April 1, 2011 – March 31, 2012
Year 3: April 1, 2012 – March 31, 2013
Year 4: April 1, 2013 – March 31, 2014
Year 5: April 1, 2014 – March 31, 2015

Concurrent use is defined as any prescription fill of GLP-1 agonist or basal insulin where, at the time of the fill, the patient is also on a continuous course of therapy of the other class (basal insulin or GLP-1 agonist). The following business rules will be used to determine if a patient is “on therapy” for the other class at the time of a given GLP-1 agonist or basal insulin fill.

1. Patient has a prescription for GLP-1 agonists

AND

 2. Patient has a fill for selected basal insulin during the reporting period and after the GLP-1 agonists fill

AND

 3. Patient has another fill of GLP-1 agonists after the basal insulin prescription (patient can change products within GLP-1 agonists, but as long as they are still filling within the class they will be considered “on therapy” of GLP-1 agonist at the time of the basal insulin fill)

AND

 4. The two GLP-1 agonists fills fall within an allowable “grace period”

OR

1. Patient has a prescription for basal insulin

AND

 2. Patient has a fill for selected GLP-1 agonist during the reporting period and after the basal insulin fill

AND

 3. Patient has another fill of basal insulin after the GLP-1 agonist prescription (patient can change products within basal insulin, but as long as they are still

filling within the class they will be considered “on therapy” of basal insulin at the time of the GLP-1 agonist fill)

AND

4. The two basal insulin fills fall within an allowable “grace period”

In addition, patients filling both a GLP-1 agonist and basal insulin on the same day will be considered to be using the classes concurrently. The “grace period” is the number of out-of-drug days allowed between the last day of supply for a given prescription and the fill date for the next prescription in the same class for the patient’s therapy to be considered continuous. The “grace period” will be 30 out-of-drug days.

The IMS RWD Adjudicated Claims – US database is a commercially insured health care claims database (not including Medicare and Medicaid claims) which captures commercially administered plans. The patient-level health plan claim analyses in this review were conducted using a sample of U.S. commercially insured population captured in this database. Healthcare plan pharmacy prescription claims were captured from outpatient retail and mail-order/specialty pharmacies. National estimates of these healthplan claim data are not available at the time of the analyses. Therefore, trending sample estimates of patient-level health plan claim data across time is not recommended because the number of contributed data may fluctuate over time and the true extent of use of these products is likely underestimated.

2.3 SPONSOR’S DRUG UTILIZATION STUDY OF LIXISENATIDE (GLP-1 AGONIST) AND INSULIN GLARGINE⁵

The sponsor submitted a drug utilization study of the proposed product Lixilan, a fixed-dose insulin glargine and lixisenatide (a GLP-1 agonist) product using the following databases: (b) (4)

The sponsor concluded that the combination lixisenatide/insulin glargine can meet the insulin requirements of a broad number of patients with type 2 diabetes. DMEP requested DEPI to provide comments on the data analysis of the study and the limitations of the databases used to come to their conclusion (section 3.3).

3 RESULTS

3.1 NATIONALLY ESTIMATED NUMBER OF PATIENTS RECEIVING OUTPATIENT RETAIL DISPENSED PRESCRIPTIONS FOR GLP-1 AGONISTS

Table 3.1 in Appendix 1 displays the nationally estimated number of unique patients who received dispensed prescriptions for any OAD and/or GLP-1 agonists from U.S. outpatient retail pharmacies for five 12-month time frames from April 2010 through March 2015. There were roughly 16-19 million total patients, annually, who received

⁵Sponsor Submission. Original New Drug Application: 208673. Submission Date: December 21, 2015, for NDA 208673

dispensed retail prescriptions for any OAD or GLP-1 agonists during the five year study period. Of these total patients who were dispensed any OAD and/or GLP-1 agonists, the proportion of patients who received a dispensed prescription for a GLP-1 agonist was small and slightly increased from 3% to 5%. In terms of absolute numbers, there was a 65% increase in the number of patients who received a dispensed prescription for a GLP-1 agonist from approximately 535,000 patients in the 12-month period ending in March 2011 to 882,000 patients in the 12-month period ending in March 2015.

For the most recent 12 month period from April 2014 through March 2015, Victoza® was the market leader, accounting for 68% of the total 882,000 GLP-1 patients, followed by Bydureon® with 20% and Byetta® with 12.5% of the total GLP-1 patients. Tanzeum® and Trulicity® were marketed in 2014 and accounted for 3% and 2%, respectively, of the total GLP-1 patients.

During the five-year study period, the majority of the patients receiving a dispensed prescription for a GLP-1 agonist were adult patients aged 18 years and older. In the recent 12-month period ending in March 2015, adult patients aged 45-64 years accounted for 58% of Victoza® patients, 62% of Bydureon® patients, 55.5% of Byetta® patients, 66% of Tanzeum® patients, and 65% of Trulicity® patients. The 65 years and older age group accounted for 29% of Victoza® patients, 24% of Bydureon® patients, and 33% of Byetta® patients, while the 18 to 44 years old age group accounted for 20% of Tanzeum® patients and 18% of Trulicity® patients.

3.2 CONCURRENCY ANALYSIS OF GLP-1 AGONISTS AND BASAL INSULIN (SAMPLE OF COMMERCIALY INSURED POPULATION)

Tables 3.2 and 3.3 in Appendix 1 provide the sample number of commercially insured patients who had prescription claims for an OAD and/or a GLP-1 agonist from April 2010 through March 2015. The number of unique patients with prescription claims for any OAD and/or GLP-1 agonist was used as the base population as a surrogate of treated type II diabetic patients in the sample dataset. During year one (April 2010 through March 2011), there were approximately 644,695 unique patients with pharmacy prescription claims for any OAD and/or GLP-1 agonists. By year five (April 2014 through March 2015) of the study period, the sample population in the dataset is 486,477 unique patients.

It is important to keep in mind the data are not projected and to focus on the percentage change between years rather than absolute patient counts. The number of total unique patients with prescription claims for any OAD and/or GLP-1 agonists **does not** reflect a decrease as is seen from year one to year five in table 3.2 and 3.3. Rather, there was a drop in enrolled patients available within data set. Therefore, trending these patient estimates is not recommended.

3.2.1 SAMPLE PATIENTS CURRENTLY ON A GLP-1 AGONIST THERAPY

Table 3.2 in Appendix 1 provides the sample and the proportion of patients on concurrent therapy with GLP-1 agonist and basal insulin. The percentage of patients who had prescription claims for a GLP-1 agonist was small and increased from approximately 7% in year one (April 2010 through March 2011) to 9.5% in year five (April 2014

through March 2015). Of these patients on GLP-1 agonists, the percentage of patients on concurrent therapy with basal insulin increased from 17% in year one to 27% in year five.

3.2.2 SAMPLE PATIENTS WHO WERE NEW TO DIABETES TREATMENT

Table 3.3 in **Appendix 1** provides the sample and the proportion of patients who were new to diabetes treatment and initiated on concurrent therapy with a GLP-1 agonist and basal insulin. The percentage of patients who were new to diabetes treatment and had prescription claims for any OAD and/or GLP-1 agonist remained steady (22-24%) throughout the study period. The percentage of patients who were new to diabetes treatment and initiated on concurrent therapy with a GLP-1 agonist and basal insulin was rare and accounted $\leq 0.1\%$ of patients throughout the five year study period.

3.3 ANALYSIS OF SPONSOR LIXISENATIDE (GLP-1 AGONIST) & INSULIN GLARGINE STUDY

The sponsor conducted drug utilization analyses incorporating several databases to estimate the percentage of patients who could potentially benefit/meet their daily insulin requirements from the fixed dose Lexilan product. (b) (4) was initially used by the sponsor to determine if Lexilan will meet the insulin requirements for the target population. This database is a prospective, cross-sectional survey of physicians conducted in a real-world clinical setting. The inclusion criteria using the (b) (4) database included patients identified as type 2 diabetic patients with an HbA1c value greater than 7%. From a total of (b) (4) physician surveys, (b) (4) patient records were collected and only (b) (4) records met the inclusion criteria for the analysis. The inclusion criteria contained patients who were on insulin glargine $\pm$ (with or without) an OAD (oral antidiabetic) and had an HbA1c value $>7\%$. The sponsor determined from the (b) (4) patient records, Lexilan would not meet (b) (4) of the patients or (b) (4) % of sample population's insulin requirements.

One possible limitation of this study is the inclusion of patients who are only using insulin glargine. Restricting to only insulin glargine limits the inclusion criteria and excludes the sample population of type 2 diabetic patients who are using other basal insulins. In addition, it appears that the sponsor findings are based on a small sample size in the context of the prevalence of type 2 diabetes. These data are likely not nationally representative or reflective of the target population.

The second database that the sponsor used in their analysis was (b) (4), an electronic healthcare database. The only inclusion/exclusion criteria the sponsor established in the (b) (4) was that if a diabetic patient is controlled (b) (4) % or uncontrolled (b) (4) % as determined by HbA1c values less than or greater than 7. In addition, the methods used in the (b) (4) does not appear to differentiate between type 1 vs type 2 diabetic patients. Within (b) (4), the sponsor does not state the underlying number of patients in the 2014 dataset as a whole nor does the (b) (4) have similar inclusion/exclusion criteria as used in the (b) (4), the third dataset used in the sponsor's analysis.

Within the third database, (b) (4), the sponsor includes the first inclusion/exclusion criteria as number of patients on basal insulin +/-

OAD (oral antidiabetic) followed by number of patients who have an average daily dose of 60 units of basal insulin. The first inclusion/exclusion criteria of the number of patients on basal insulin +/- OAD separates type 2 vs. type 1 diabetic patients from the basal patient level. The sponsor is assuming that only type 2 patients would be concurrently taking basal insulin and an OAD while excluding patients with prescriptions for rapid acting insulin as a surrogate marker for type 1 diabetes patients. This inclusion criterion nets (b) (4) patients in the study sample.

The second inclusion/exclusion criteria of number of patients who have an average daily dose of 60 units of basal insulin is based on the calculation of the dose dispensed over the number of days the prescription is written for. It is difficult to determine daily insulin dose in this manner. This inclusion criterion narrows the sample patient population to (b) (4) patients and assumes patients are using basal insulin exactly as written. The (b) (4) should have incorporated the time between refills to determine exactly how long the initial basal insulin prescription lasted for a patient instead of days of supply, which is often determined at the pharmacy and may take into account billing restriction, i.e. a “30 day supply for a vial” to meet insurance requirements. However, prescriptions are typically written as “use as directed” with no other specific instructions. It is also unknown if daily insulin doses are changed or titrated after dispensing based on prescription claims data. Due to these limitations, prescription claims data alone are insufficient to accurately determine daily insulin dose.

After the inclusion/exclusion criteria was established for (b) (4) 2014 and (b) (4) 2015, the sponsor combines the included patient population of the two separate databases to make one assumption. The sponsor concludes that of the (b) (4) patients who use greater than 60 units of basal insulin per day, approximately (b) (4) % of them or (b) (4) are uncontrolled. The (b) (4) sample patients or (b) (4) % ((b) (4) patients/ (b) (4) patients) of the population are whom the sponsor cannot meet the greater than 60 units per day of basal insulin criteria under their current formulations for the Lexilan product.

The sponsor’s claim that Lexilan can meet the insulin requirements of (b) (4) % of the targeted patient population from the (b) (4) is based on many assumptions and on data with numerous limitations. The sponsor did not link the (b) (4) with the patient population in the (b) (4). Any comparisons of the two databases require the assumptions that the (b) (4) databases have similar patient populations and inclusion criteria. However, the inclusion criteria used for the two databases were not similar and (b) (4) database did not differentiate between type 1 and 2 type diabetic patients.

4 DISCUSSION

To assist DMEP in their review of NDAs for combination products containing a GLP-1 agonist and basal insulin, this review examines: 1) national cross-sectional outpatient retail data to assess the extent of use of GLP-1 agonists, and 2) longitudinal healthcare plans claims data to assess the proportion of concurrent use of a GLP-1 agonist and basal insulin. In addition, this review also comments on the sponsor’s submitted utilization

study of the proposed product Lixilan[®], a fixed-dose insulin glargine and lixisenatide (a GLP-1 agonist) product.

The findings from the national level cross-sectional patient database (IMS Total Patient Tracker) shown in Table 3.1 suggest that the nationally **projected** number of patients who received a dispensed prescription for a GLP-1 agonist have increased by 65% during the study period. However, in the context of patients who received any OAD or GLP-1 agonists, the proportion of patients on GLP-1 agonists was small and accounted for 3-5% of total patients per year of those who received dispensed retail prescriptions for any OAD or GLP-1 agonists from U.S. outpatient retail pharmacies. It is important to note that the data are only representative of outpatient utilization trends, data from mail-order/specialty or inpatient settings were not included. The estimates provided in Table 3.1 are national estimates, but no statistical tests were performed to determine statistically significant changes over time. All changes over time should be considered approximate and may be due to random error.

Utilization of GLP-1 agonists used concurrently with basal insulin were further assessed in a commercial healthcare plans database. The findings from the longitudinal patient-level database (IMS RWD Adjudicated Claims – US) showed that out of the total number of patients with prescription claims for GLP-1 agonists, the proportion of patients on concurrent therapy with a GLP-1 agonist and basal insulin increased from 17% to 27% of total patients during the study period. However, the percentage of patients who were new to diabetes treatment and started on concurrent therapy with GLP-1 agonist and basal insulin was negligible ($\leq 0.1\%$ of patients new to OAD/GLP-1 agonist therapy). Basal insulin doses were not determined because dosing instructions or “signa” are not available in claims data and there are limitations to using days supply and dispensed vial sizes in claims data to calculate accurate dosing for insulin products.

The IMS RWD Adjudicated Claims – US (Tables 3.2 and 3.3) provide a **sample** (unprojected) number of patients on a GLP-1 agonist as well those on a concurrent therapy with a GLP-1 agonist and basal insulin. When interpreting the IMS RWD Adjudicated Claims – US data, the numbers should not be trended because each reporting time period is distinct. Between each distinct 12 month time periods within the study, the pool of patients and healthcare plans contributing to the data sample may change over time. Since the data was not projected, it is imperative to focus on the proportion of patients throughout the study period.

Patient-level data captured in the IMS RWD Adjudicated Claims – US were obtained from a **sample** of healthcare claims from a commercially insured U.S. population, not including Medicare and Medicaid patients. Therefore, these analyses do not estimate the utilization of concurrent GLP-1 agonist and basal insulin therapy in cash payers, elderly, and the Medicare and Medicaid populations.

The sponsor estimates Lexilan can meet the insulin needs of approximately 80-90% of the targeted patient population. However, the methods and databases the sponsor used for the estimates have limitations. The sponsor used three disparate data sources that were not linked to the same patient populations. Assumptions were made to link the findings from one database to the other. The Adelphi Real World – Disease Specific Programs had a limited sample size that is not nationally representative, while the IMS Health Lab and

Health APLD Lifelink Patient level data were not linked. The IMS Lifelink data from the sponsor also only calculated days' supply of insulin based on 30 day supply of what was dispensed, not when the patient actually refilled the prescription. Dosing information on insulin based solely on claims data are insufficient due to limitations described above.

5 CONCLUSION

In support of FDA's review of NDAs for novel combination GLP-1 agonist and basal insulin products, this review examined both national level data on extent of GLP-1 agonists use as well as longitudinal patient-level data on the concurrent use of GLP-1 and basal insulin. In addition, this review also comments on the sponsor's submitted utilization study of the proposed product Lixilan, a fixed-dose insulin glargine and lixisenatide (a GLP-1 agonist) product.

Based on the FDA's analysis of longitudinal health plan claims data, about a quarter of the commercially insured patients in the sample population on GLP-1 agonists also had a concurrent prescription claim for basal insulin per year. The proportion of patients who were new to diabetes therapy and initiated on concurrent therapy with a GLP-1 agonist and basal insulin was negligible.

Based on the nationally projected cross-sectional outpatient retail data, patients on GLP-1 agonists have increased to nearly 900,000 patients in the most recent 12 month study period. The sponsor's study concludes that they will meet (b) (4) % of the insulin needs of their target population; however, the studies used to reach that conclusion contain many limitations. The (b) (4) had a small sample size, using pharmacy claims data to determine insulin dose is difficult, and the patients in the two disparate data sources, (b) (4) were not linked. Therefore, it is difficult to determine if a fixed dose combination product containing basal insulin and GLP-1 agonist can meet the higher daily dose of insulin for many type 2 diabetic patients.

APPENDIX 1: TABLES

Table 3.1

NATIONALLY ESTIMATED NUMBER OF PATIENTS WHO RECEIVED A DISPENSED PRESCRIPTION FOR GLP-1 AGONISTS STRATIFIED BY AGE
FROM U.S. OUTPATIENT RETAIL PHARMACIES, APRIL 2010 - MARCH 2015, ANNUALLY

	Year 1		Year 2		Year 3		Year 4		Year 5	
	Apr. 2010 - Mar. 2011		Apr. 2011 - Mar. 2012		Apr. 2012 - Mar. 2013		Apr. 2013 - Mar. 2014		Apr. 2014 - Mar. 2015	
	Patient (n)	% Share	Patient (n)	% Share	Patient (n)	% Share	Patient (n)	% Share	Patient (n)	% Share
TOTAL OAD & GLP-1 AGONISTS	15,720,189	100.0%	16,563,386	100.0%	16,628,789	100.0%	17,198,977	100.0%	18,557,716	100.0%
TOTAL GLP-1 AGONISTS	535,159	3.4%	616,165	3.7%	703,459	4.2%	768,935	4.5%	881,919	4.8%
VICTOZA	228,855	42.8%	348,563	56.6%	445,531	63.3%	539,874	70.2%	601,381	68.2%
0 - 17 years	547	0.2%	720	0.2%	683	0.2%	687	0.1%	633	0.1%
18 - 44 years	44,958	19.6%	65,196	18.7%	75,186	16.9%	84,679	15.7%	90,543	15.1%
45 - 64 years	146,164	63.9%	221,051	63.4%	271,833	61.0%	319,404	59.2%	348,576	58.0%
65+ years	39,850	17.4%	68,251	19.6%	106,505	23.9%	145,420	26.9%	172,581	28.7%
Unknown Age	48	< 0.1%	--	--	2	< 0.1%	1,176	0.2%	4,819	0.8%
BYDUREON	--	--	10,361	1.7%	97,882	13.9%	134,813	17.5%	175,920	19.9%
0 - 17 years	--	--	15	0.1%	140	0.1%	133	0.1%	183	0.1%
18 - 44 years	--	--	1,812	17.5%	16,404	16.8%	22,060	16.4%	27,475	15.6%
45 - 64 years	--	--	6,458	62.3%	61,909	63.2%	84,420	62.6%	108,443	61.6%
65+ years	--	--	2,076	20.0%	20,702	21.2%	30,352	22.5%	42,230	24.0%
Unknown Age	--	--	--	--	--	--	237	0.2%	1,316	0.7%
BYETTA	343,180	64.1%	286,864	46.6%	205,650	29.2%	136,842	17.8%	110,219	12.5%
0 - 17 years	720	0.2%	604	0.2%	360	0.2%	217	0.2%	191	0.2%
18 - 44 years	53,088	15.5%	42,688	14.9%	27,906	13.6%	17,080	12.5%	13,820	12.5%
45 - 64 years	211,189	61.5%	171,154	59.7%	119,118	57.9%	76,513	55.9%	61,177	55.5%
65+ years	83,649	24.4%	77,900	27.2%	62,273	30.3%	45,565	33.3%	36,747	33.3%
Unknown Age	122	< 0.1%	3	< 0.1%	--	--	231	0.2%	907	0.8%
TANZEUM	--	--	--	--	--	--	--	--	26,797	3.0%
0 - 17 years	--	--	--	--	--	--	--	--	13	< 0.1%
18 - 44 years	--	--	--	--	--	--	--	--	5,243	19.6%
45 - 64 years	--	--	--	--	--	--	--	--	17,794	66.4%
65+ years	--	--	--	--	--	--	--	--	3,708	13.8%
Unknown Age	--	--	--	--	--	--	--	--	219	0.8%
TRULICITY	--	--	--	--	--	--	--	--	15,625	1.8%
0 - 17 years	--	--	--	--	--	--	--	--	20	0.1%
18 - 44 years	--	--	--	--	--	--	--	--	2,850	18.2%
45 - 64 years	--	--	--	--	--	--	--	--	10,191	65.2%
65+ years	--	--	--	--	--	--	--	--	2,504	16.0%
Unknown Age	--	--	--	--	--	--	--	--	113	0.7%

**Please note due to the possibility of double counting patients who are receiving treatments over multiple periods in the study, unique patient counts may not be added across time periods.

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months)

IMS Health Vector One® Total Patient Tracker. Extracted Mar. 2016. File DATA 2016-221 Combination GLP-1 Agonist & Insulin AC.xlsx

Table 3.2

Patients with concurrent prescriptions for a GLP-1 agonist and basal insulin from a sample of the commercially insured * U.S. population, stratified by patient age, by reporting years, April 2010 through March 2015

	Year 1		Year 2		Year 3		Year 4		Year 5	
	April 2010 - March 2011		April 2011 - March 2012		April 2012 - March 2013		April 2013 - March 2014		April 2014 - March 2015	
	Patients (n)	% Share	Patients (n)	% Share	Patients (n)	% Share	Patients (n)	% Share	Patients (n)	% Share
Total Number of Patients on OAD/GLP-1 Agonist	644,695	100.0%	664,629	100.0%	610,265	100.0%	578,363	100.0%	486,477	100.0%
Patients On A GLP-1 Agonist	45,647	7.1%	51,570	7.8%	55,343	9.1%	53,696	9.3%	46,216	9.5%
1-17 years	78	0.2%	68	0.1%	47	0.1%	25	0.0%	25	0.1%
18-44 years	7,286	16.0%	7,986	15.5%	8,266	14.9%	7,796	14.5%	6,945	15.0%
45-64 years	33,857	74.2%	38,333	74.3%	41,821	75.6%	41,045	76.4%	35,152	76.1%
65+ years	4,426	9.7%	5,183	10.1%	5,209	9.4%	4,830	9.0%	4,094	8.9%
Patients On Both GLP-1 Agonist & Basal Insulin	7,837	17.2%	9,799	19.0%	13,162	23.8%	13,807	25.7%	12,360	26.7%
1-17 years	4	0.1%	9	0.1%	6	0.0%	2	0.0%	6	0.0%
18-44 years	826	10.5%	1,050	10.7%	1,440	10.9%	1,515	11.0%	1,432	11.6%
45-64 years	6,054	77.2%	7,502	76.6%	10,264	78.0%	10,828	78.4%	9,606	77.7%
65+ years	953	12.2%	1,238	12.6%	1,452	11.0%	1,462	10.6%	1,316	10.6%

* Commercially insured excludes Medicare and Medicaid

Reporting Year rolling 12 month period (i.e. April 2010 through March 2011 = reporting year 1)

Due to the study being unprojected, the data should not be trended between years. Inference may be made on percentage changes between years. Age groups may not be representative of the population.

Source IMS LifeLink PharMetrics Plus. Reporting Time April 2010 Through March 2015 Extracted March 2015. File DATA 2016-221 Combination GLP-1 Agonist & Insulin AC.xlsx

Table 3.3

Patients with concurrent prescriptions for a GLP-1 agonist and basal insulin from a sample of the commercially insured * U.S. population, stratified by patient age, by reporting years, April 2010 through March 2015

	Year 1		Year 2		Year 3		Year 4		Year 5	
	April 2010 - March 2011		April 2011 - March 2012		April 2012 - March 2013		April 2013 - March 2014		April 2014 - March 2015	
	Patients (n)	% Share	Patients (n)	% Share	Patients (n)	% Share	Patients (n)	% Share	Patients (n)	% Share
Total Number of Patients on OAD/GLP-1 Agonist	644,695	100.0%	664,629	100.0%	610,265	100.0%	578,363	100.0%	486,477	100.0%
1-17 years	2,795	0.4%	2,716	0.4%	2,496	0.4%	2,564	0.4%	2,083	0.4%
18-44 years	89,949	14.0%	90,167	13.6%	86,267	14.1%	83,222	14.4%	74,572	15.3%
45-64 years	440,652	68.4%	455,106	68.5%	430,605	70.6%	414,367	71.6%	347,827	71.5%
65+ years	111,299	17.3%	116,640	17.5%	90,897	14.9%	78,210	13.5%	61,995	12.7%
Patients New To Any OAD/GLP-1 Agonist	147,679	22.9%	153,149	23.0%	135,148	22.1%	135,166	23.4%	114,694	23.6%
1-17 years	1,873	1.3%	1,803	1.2%	1,741	1.3%	1,712	1.3%	1,397	1.2%
18-44 years	39,191	26.5%	38,865	25.4%	37,142	27.5%	36,854	27.3%	33,042	28.8%
45-64 years	92,288	62.5%	96,380	62.9%	85,677	63.4%	86,316	63.9%	72,706	63.4%
65+ years	14,327	9.7%	16,101	10.5%	10,588	7.8%	10,284	7.6%	7,549	6.6%
Patients New To GLP-1 Agonist & Basal Insulin Concurrently	42	<0.1%	48	<0.1%	87	0.1%	76	0.1%	48	<0.1%
1-17 years	--	--	--	--	--	--	--	--	--	--
18-44 years	9	21.4%	13	27.1%	10	11.5%	17	22.4%	12	25.0%
45-64 years	29	69.0%	30	62.5%	70	80.5%	53	69.7%	32	66.7%
65+ years	4	9.5%	5	10.4%	7	8.0%	6	7.9%	4	8.3%

Reporting Year rolling 12 month period (i.e. April 2010 through March 2011 = reporting year 1)

** Commercially insured excludes Medicare and Medicaid*

Due to the study being unprojected, the data should not be trended between years. Inference may be made on percentage changes between years. Age groups may not be representative of the population.

Source IMS LifeLink PharMetrics Plus. Reporting Time April 2010 Through March 2015 Extracted March 2015. File DATA2016-221 Combination GLP-1 Agonist & Insulin AC.xlsx

APPENDIX 2: DRUG UTILIZATION DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS, Total Patient Tracker (TPT)

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

IMS Health Real-World Data (RWD) Adjudicated Claims – US

The IMS Health Real-World Data Adjudicated Claims - US Database is a health plan claims database representing approximately 101 managed care plans and covering approximately 65.8 million de-identified patients. The medical claims are captured from doctor's offices, retail and mail order pharmacies, patient visits to specialists and hospitalizations including diagnoses, ER visits, office visits, home care, diagnostic tests, procedures and injections. The data are not nationally projected; however, it represents approximately 9% of the United States commercially insured population based on year 2007 United States Census.

**APPENDIX 3: LIST OF SELECTED ANTIDIABETIC DRUGS OF INTEREST
AND GPI CODES**

Class	Drugs Included	GPI Code(s)
Basal Insulin	Lantus, Toujeo, Levemir, Humulin N, Novolin N, Other Basal (Insulatard NPH, Relion N, Humulin L, Novolin L, Humulin U)	27104003* 27104006* 27104020* 2710403* 2710405*
GLP-1	Byetta, Bydureon, Bydureon Pen, Victoza, Trulicity, Tanzeum EXCLUDES: Saxenda	27170020* 27170050* 27170015* 27170010*
DPP-IV	Onglyza, KombiGlyze Januvia, Janumet, Janumet XR, Juvisync Tradjenta, Jentadueto, Glyxambi Nesina, Oseni, Kazano	27550065*, 27992502607* 27550070*, 27992502700* 27992502707* 279930027* 27550050, 2799250240*, 2799650230 27550010* 279940021* 279925021*
Other OAD	Glyset, Miglitol, Precose, Acarbose Fortamet ER, Glucophage, Glucophage XR, Metformin HCl, Metformin HCl ER, Riomet, Prandin, Repaglinide, Starlix, Nateglinide, Acetohexamide, Amaryl, Glimepiride, Chlorpropamide, Diabinese, Diabeta, Dymelorm Glyburide, Glyburide Micro, Glycron, Glynase Prestab, Glipizide, Glipizide ER, Glipizide Cl, Glucotrol, Glucotrol Xl, Orinase, Tolbutamide, Sk-Tolbutamide, Tolazamide, Tolinase, Rosiglitazone (Actos), Pioglitazone (Avandia)	2750* 2725*, 279990025* 2728* 2720* 2760* 279970* 279980* 279978* 279950*

	Glipizide-Metformin, Glyburide-Metformin Pioglitazone HCl-Metformin, Rosiglitazone Maleate-Metformin Glimepiride-Rosiglitazone, Glimepiride-Pioglitazone Repaglinide-Metformin	2757402010*
SGLT2 Inhibitors	Invokana, Farxiga, Jardiance, Invokamet, Xigduo XR , Synjardy, Glyxambi	27700020* 27700040* 27700050* 2799600220* 2799600230* 2799600240* 2799650230*

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/s/

JUSTIN A MATHEW
04/27/2016

TRACY M PHAM
04/27/2016

GRACE CHAI
04/27/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Devices and Radiological Health

Office of Compliance, Division of Manufacturing & Quality

Orthopedic, Neurology, and Dental Device (POND) Branch

Date: March 15, 2016

To: Anika Lalmansingh, OPRO, CDER WO 75/4631
anika.lalmansingh@fda.hhs.gov

Office of combination products at combination@fda.gov

RPM: Anika Lalmansingh

Through: Matthew Krueger, Chief, POND, DMQ, OC, CDRH
Matthew C. Krueger -S
2016.04.15 16:00:58 -04'00'

From: Vesa Vuniqui, POND, DMQ, OC, CDRH

Applicant: Establishment (Applicant):
Contact: David Faunce, Director
Sanofi-Aventis, US LLC
55 Corporate Drive
Bridgewater, NJ 08807
Phone: (908) 981-5000
Fax: (877) 332-5512
FEI: 3003596612

Application # NDA 208673

Consult # ICC1500705

Product Name: Insulin glargine and lixisenatide pen-injector

Pre-Approval Inspection: No

Documentation Review: No Additional Information Required

Final Recommendation: **APPROVAL**

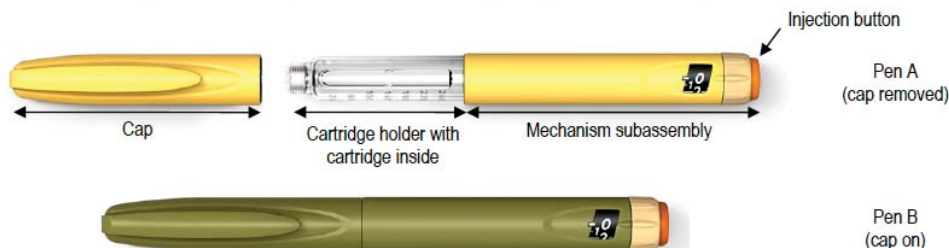
The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of Application # 208673.

PRODUCT DESCRIPTION

The firm manufactures a Class II combination product consisting of a pre-filled 3mL drug cartridge (insulin glargine/lixisenatide combination solution) assembled into multi-use, disposable pen-injectors. The final drug product-insulin glargine/lixisenatide pen-injector, is provided fully assembled and requires no further assembly before use. The design of the insulin glargine/lixisenatide pen-injector is based on the already marketed SoloStar® pen-injector which is combined with insulin glargine 100 U/mL solution for injection (NDA 21-081) which has been modified for the application of the insulin glargine/lixisenatide solution for injection. The modification comprises of the color of the bodies, caps, injection buttons and dose selectors as well as the scale on the number sleeves and the dose stop for the maximum dispensable doses.

The pen-injector is available in two different dosage strengths (see Figure 1): 100 U/mL insulin glargine with 50 µg/mL lixisenatide (pen A) or 100 U/mL insulin glargine with 33 µg/mL lixisenatide (pen B). The insulin glargine/lixisenatide pen-injector (b) (4) is not in contact with the insulin glargine/lixisenatide solution for injection. The fluid pathway is provided by the cartridge and the needle, which has to be attached to the threaded end of the cartridge holder prior to use. Needles are not part of the device, but sold separately.

Figure 1 - Insulin glargine/lixisenatide pen-injector in two different colors



REGULATORY HISTORY

The following facility was identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

Sanofi-Aventis Deutschland GmbH

Brüningstraße 50
Industriepark Höchst
65926 Frankfurt am Main, Germany
Phone: +49 0 69 305165
FEI: 3003195501

Responsibility –The firm is responsible for manufacturing, assembly of the disposable pen-injector, testing, primary and secondary packaging, labeling, stability testing, and release.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that an inspection was conducted from December 7, 2015 through December 10, 2015. The inspection covered medical device QS requirements and was classified VAI. Manufacturing of a similar product Lixisenatide (NDA pen-injector was covered during this inspection.

Inspection Recommendation:

An inspection is not required because a recent inspection of the firm was acceptable.

DOCUMENTATION REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

(b) (4)



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Documentation Review Recommendation

The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable Quality system Requirements showed no deficiencies. No additional information is required for the documentation review.

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

RECOMMENDATION

The application for Insulin glargine and lixisenatide pen-injector – NDA 208673 is approvable from the perspective of the applicable Quality System Requirements.

Vesa
Vuniqi -S

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DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People, cn=Vesa
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Vesa Vuniqi

Prepared: VVuniqui: 3/15/2016

Reviewed: MKrueger: 4/15/2016

CTS No.: ICC1500705

NDA 208673

Review Cycle Meeting Attendance:

3/11/2016

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

/s/

ANIKA A LALMANSINGH

04/21/2016

Uploading on behalf of Vesa Vuniqui.

LABEL AND LABELING AND HUMAN FACTORS RESULTS REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
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 12, 2016
Requesting Office or Division:	Division of Metabolic and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208673
Product Name and Strength:	Insulin glargine and lixisenatide injection, 300 units and 150 mcg per 3 mL pen (100 units and 50 mcg per mL) Insulin glargine and lixisenatide injection, 300 units and 99 mcg per 3 mL pen (100 units and 33 mcg per mL)
Product Type:	Multi-ingredient and Combination Product
Rx or OTC:	RX
Applicant/Sponsor Name:	Sanofi-Aventis
Submission Date:	December 21, 2015 and January 8, 2016
OSE RCM #:	2015-2775 and 2015-2782
DMEPA Primary Reviewer:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Yelena Maslov, PharmD
DMEPA Acting Associate Director:	QuynhNhu Nguyen, MS
DMEPA Deputy Director	Lubna Merchant, MS, PharmD
DMEPA Director	Todd Bridges, RPh

1 REASON FOR REVIEW

The Division of Metabolic and Endocrinology Products (DMEP) requested that DMEPA evaluate the human factors (HF) study report and proposed labels and labeling submitted under NDA 208673 for insulin glargine and lixisenatide pen injectors intended to treat type 2 diabetes.

2 BACKGROUND

Under IND 105157, DMEPA provided advice to the Applicant on several occasions (refer to Appendix F) regarding human factors considerations related to this product's development program. As part of our advice, we recommended that the Applicant conduct label comprehension studies to support the use of the proposed proprietary name modifiers, (b) (4) and ensure that these modifiers would be understood by end users as to their meaning and purpose. The applicant included label comprehension tasks as part of their HF study.

3 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	C
Other-Regulatory History	D
Labels and Labeling	E

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

For this product, DMEPA reviewed the human factors study design and results, and the proposed Prescribing Information (PI), Information for Use (IFU), and Medication Guide materials submitted by Sanofi on December 21, 2015. Sanofi also submitted updated proposals for container labels and carton labeling for review on January 8, 2016.

(b) (4)

4.1 PRODUCT DESIGN

Insulin glargine and lixisenatide is a multi-ingredient product that combines a long-acting insulin with a glucagon-like peptide-1 (GLP-1) receptor agonist into a single pen device. This product is intended for the treatment of patients with type 2 diabetes when simultaneous therapy would be clinically appropriate. Insulin glargine (under the proprietary name Lantus) is currently approved for the treatment of type 1 and type 2 diabetes. Lixisenatide (NDA 208471) is not currently FDA approved for the treatment of type 2 diabetes but the application is currently under review. The product is to be available in two pen device strengths containing two different fixed ratio dosing options of insulin glargine: lixisenatide (3:1 and 2:1) using the SoloStar pen injector device platform currently marketed for Lantus, Toujeo, and Apidra.

In the process of reviewing this product, we identified the following unique aspects of the product:

- It is a mixture of an insulin with a non-insulin active ingredient as a combination in a single container closure system. Importantly, unlike insulin-insulin mixtures, the two active ingredients in this proposed product are dosed using different units of measure (units vs. mcg). See discussion in Section 4.3 of this review.
- The two pen devices proposed contain different fixed ratios of the active ingredients that should not be substituted for one another. If the wrong pen was provided to a patient, the patient would receive the wrong dose of lixisenatide, possibly resulting in an increased risk of lixisenatide side effects and differences in glucose control. For example, if a patient received 40 units with Pen A³ (which contains a higher concentration of lixisenatide to the insulin glargine component) instead of Pen B, this could result in hypoglycemia, nausea, and other lixisenatide side effects.
- Pen A can deliver doses from 1 to 40 units and Pen B can deliver doses from 1 to 60 units, based on the insulin glargine component. The doses that are intended to be delivered from the two pen devices, as represented by the insulin glargine component, range from 10 to 40 units for Pen A and from 30 to 60 for Pen B. There is an overlap between Pen A and Pen B, as both are labeled to deliver doses ranging from 30 units and 40 units. (b) (4)

this overlap can create ambiguity as to which pen should be used for patients requiring doses within this range.

4.2 HUMAN FACTORS STUDY

The HF study for insulin glargine and lixisenatide pen injector was conducted with a total of 75 participants (15 prescribers, 15 pharmacists, 15 nurses treating and training diabetes patients, and 30 diabetes patients). The study was designed to simulate use tasks and provide data to support that intended users can prescribe, dispense, differentiate, and comprehend storage (refer to Appendix C). The study focused on these specific tasks and aspects of use, as these are unique and different from those for the currently marketed SoloStar pen injectors approved and marketed for the administration of single ingredient insulin products, including insulin

³ Pen A contains 2:1 ratio of insulin glargine: lixisenatide; Pen B contains 3:1 ratio of insulin glargine: lixisenatide

glargine (Lantus). We agreed with this approach as the Applicant was relying on the HF validation data and post-marketing information gathered from the currently marketed SoloStar pen injectors for the injection process (e.g., dialing and administering a dose).

We have provided a summary of the study results and our evaluation in the following sections.

1. Prescribing

For the prescribing component of the study, 15 physicians were presented with the PI along with four individualized patient case scenarios. After the physicians reviewed the PIs and case scenarios, the physicians were asked to provide specific prescriptions for each case scenario based on the PI. All 15 physicians correctly prescribed the correct insulin glargine/lixisenatide pen and dose when provided with individualized patient case scenarios. We note that the conditions employed in the study may not have adequately simulated actual use in several respects. In actual use, we would anticipate that prescribers may not read the PI in detail, which may have an effect on how well they interpret the information⁴. In addition, in the course of the study, prescribers in the study were specifically directed to answer questions based on the PI instead of using the PI as they would if they were actually planning to prescribe the product in clinical practice. We would anticipate that a prescriber may not have unlimited time to review the PI to direct the prescribing of the medication. Although the conditions tested may not simulate actual prescribing of a product, we would expect prescribers to familiarize themselves with important information about the product using the PI or other drug information resources prior to prescribing the product for the first time. Since this product is not marketed and our interest is to understand whether physicians can comprehend the information related to specific aspects of this intended use, we find this approach to be reasonable. Additionally, since the study was specifically designed to test the contents of the labeling, the results indicate that the physicians understood the information contained in the PI, and they were able to prescribe the correct dose and device.

In addition, the HF study evaluated physician understanding of the product name's modifiers, (b) (4) but the adequacy of those data are discussed in detail in the proprietary name review for Soliqua (b) (4). Our evaluation of the proprietary name found that the modifiers may cause medication error because the modifiers may be confused or misinterpreted by end users as ratios or a prescribed dose. In addition, the modifiers can be misleading because each of the proposed devices can deliver doses outside of the labeled dose range (i.e., (b) (4)). Thus we found the modifiers unacceptable⁵.

⁴ de Leon J. Highlights of Drug Package Inserts and the Website DailyMed: the Need for Further Improvements in Package Inserts to Help Busy Prescribers. *Journal of Clinical Psychopharmacology*. June 2011; 31(3): 263-265.

⁵ Conrad A. Proprietary Name Review of Soliqua (b) (4) (insulin glargine

2. Dispensing

For the dispensing component of the study, 15 pharmacists were presented with a prescription for either the (b) (4) *** (b) (4) ***⁶ product options. Fourteen of the 15 pharmacists selected the correct package. One pharmacist selected the wrong product when presented with the prescription because he misunderstood the task and selected a product that he dispenses often. We consider this error to be an artifact of the study. When the moderator clarified the task, the participant selected the wrong (b) (4) *** product because he did not consider the proprietary name modifier (e.g., (b) (4) when making his selection. During the root cause questioning, the moderator noted that the participant misunderstood the task which lead to the error. The Sponsor determined that overlooking the modifier was a study artifact; however, we are unable to determine that this is a study artifact as our evaluation did not find sufficient reason to characterize this as a study artifact because the participant had the task clarified by the moderator after the first error. Also, based on our experience with other marketed drug products, we note that overlooking modifiers and selecting the wrong product within a product line is a common source of error. However, since this error is related to the use of the proprietary name modifier, evaluation of this error is covered further in the aforementioned proprietary name review for this product.⁵

3. Pen differentiation and handling

All nurse and patient study participants for this task identified the correct pen (b) (4) and so we do not have any concerns regarding pen differentiation.

Forty-four out of 45 of the patient and nurse participants selected the correct pen to use when presented with different dose regimens. These participants were also asked to prepare an assigned dose using one of the pen injector devices. One patient participant that was inexperienced with using pen devices failed this task and prepared 10 units for the dose instead of the 20 units he was instructed to prepare. The participant reported confusing the name modifier (b) (4), with the specified dose.

4. Pen storage

All 45 of the patient and nurse participants were able to demonstrate understanding of the storage instructions provided in the IFU.

4.3 LABELS AND LABELING

and lixisenatide) NDA 208673. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Mar 31. RCM # 2016-2740671, 2016-2740673, 2016-2706472.

⁶These were mock proprietary names used in the simulation study for this insulin glargine/lixisenatide product

This review identified several areas that could be clarified within the proposed container labels, carton labeling, patient instructions for use (IFU), and the prescribing information (PI) labeling. Although the human factor study results evaluating the product labeling were positive overall, we noted that some areas could be improved. However, since we are not recommending content changes, re-testing in human factors studies will be unnecessary. We provide recommendations in sections 5.1 and 5.2 and recommend their implementation prior to approval of this NDA.

Of note, we have some concern regarding the proposal to communicate the dose using the term “units” in the labeling. This terminology may be misleading to users since it only references the insulin component (insulin glargine) and does not impart the presence of two drugs. However, this terminology was used in the HF validation study and users demonstrated the ability to understand the dosing. Therefore, we agree that this terminology may simplify the expression of doses and facilitate safe use of the product. In addition, if the dosing on the pen device were to express both active ingredients, the cumbersome nature of the expression may actually create confusion for end users.

5 CONCLUSION & RECOMMENDATIONS

The HF study report presented some data that the product’s proposed proprietary names may be confusing to practitioners and may lead to error. We communicated this finding to the Applicant on April 1, 2016 in the context of a decisional letter regarding their proposed proprietary names for this product.⁷ Because the two pens are designed to deliver specific doses to patients and should not be substituted for one another, it is important that the products are reliably identified in the prescribing, dispensing and administration process so that the patients receive the correct product. We recommend that the Applicant carefully reconsider the proprietary names employed for this product, which may serve as a useful identifier to distinguish the two pens. Product proprietary name modifiers may be useful to distinguish between the two pens but there is an inherent risk of medication errors associated with the use of modifiers.

The availability of two pens may still be associated with risk that may not be adequately mitigated through proprietary names or product labeling. Therefore, we recommend that Sanofi consider marketing only one pen for this combination product that could deliver the full range of labeled doses (b) (4) to minimize the risk of error and eliminate the need to distinguish between products. However, we defer to the clinical team to determine the clinical value of having two pen devices available for this multi-ingredient product.

⁷ Thomas T. Proprietary Name Denied for Soliqua (b) (4). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 April 1. NDA 208673.

Regarding the HF component of the submission, we find that the HF study report acceptable. We have identified some areas that could be clarified in the proposed labels and labeling and provide recommendations below.

5.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Highlights of Prescribing Information- Dosage Forms and Strengths

i.

(b) (4)

2. Highlights of Prescribing Information-Dosage and Administration

i. Clarify if the dose should be administered prior to the first meal of the day (b) (4) as noted in Section (b) (4)

(b) (4) Revise the statement to include (b) (4) if that is accurate for consistency.

ii. Consider removing the statement “ (b) (4) (b) (4) ” from this section since it does not apply to dosage and administration of the medication.

3. Section (b) (4)

i. It is unclear what you intend to convey with the following statement (b) (4)

(b) (4) Revise the statement to clarify the intended meaning.

ii. Rephrase the bulleted information provided in (b) (4) to read as follows for improved clarity:

- (b) (4)
- (b) (4)
- (b) (4)

⁸ TRADENAME to be updated after an acceptable name for the two pens is determined.

4. Section (b) (4)
 - i. The symbols “<” and “>” are on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations” because it has been mistaken for the opposite of the intended meaning. Therefore, we recommend that you replace these symbols with their intended meaning (e.g., less than) to prevent misinterpretation and confusion.
 5. Section (b) (4) titration of TRADENAME⁸
 - i. Replace the symbol “>” with its intended meaning to prevent misinterpretation.
 6. Section 16.2 Storage
 - i. Clarify that the product will not (b) (4). If it will only be available as a prefilled pen device, remove the words (b) (4) from the statement “(b) (4) TRADENAME⁸ (b) (4) pen should be stored in a refrigerator, 36°F – 46°F (2°C – 8°C)”.
- B. Medication Guide
1. Include the product proprietary names, (b) (4), in the title of the document. We recommend that you title the document to correspond with the language used for the final pen label and carton labeling to minimize confusion for end users.
- C. Instructions for Use (IFU)
1. Revise the titles of both IFUs to correspond with the names approved for use on the final pen label and carton labeling for consistency across all product labeling.

5.2 RECOMMENDATIONS FOR SANOFI

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

A. Container Labels

1. The dosage form “injection” should immediately follow the established name so that it reads “insulin glargine and lixisenatide injection”.
2. Revise the statement “insulin glargine + lixisenatide” to “insulin glargine and lixisenatide” to remove the abbreviation “+”. This abbreviation is on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations because it has been mistaken for the number “4” when written. Therefore, we recommend the removal of the abbreviation “+” from the carton labeling and replaced with “and” instead to reduce the risk of confusion.

3. Remove the statement “ (b) (4) ” because the statement of contents, “100 units/mL (b) (4) and (b) (4) 33 mcg/mL”, provides that information. In addition, removal will help to improve the readability of other information on the small label.
4. Please resubmit updated labels and labeling once a proprietary name is found to be conditionally acceptable.

B. Carton Labeling

1. The dosage form “injection” should immediately follow the established name so that it reads “insulin glargine and lixisenatide injection”
2. As recommended above, revise the statement “insulin glargine + lixisenatide” to “insulin glargine and lixisenatide” to remove the abbreviation “+” and replace with “and” to reduce the risk of confusion.
3. Revise the warning (b) (4) to state “Never remove medication using a syringe” for improved clarity.
4. Consider removing the statement (b) (4) from the middle of the primary display panel since this information is duplicated on the label in the statement “Five 3 mL prefilled pens.” Removal of this statement may improve readability of the other information on the label.
5. On the primary display panel, remove the statement “ (b) (4) (b) (4) ” because the statement of contents, “100 units/mL (b) (4)) and (b) (4) 33 mcg/mL”, provides that information.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for insulin glargine/lixisenatide that Sanofi submitted on December 21, 2015.

Table 2. Relevant Product Information for insulin glargine/lixisenatide	
Initial Approval Date	N/A
Active Ingredient	Insulin glargine and lixisenatide
Indication	Adjunctive therapy to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both insulin glargine and lixisenatide is appropriate
Route of Administration	Subcutaneous
Dosage Form	Solution
Strength	100 units/mL insulin glargine and 50 mcg/mL lixisenatide (10 to 40 pen); 100 units/mL insulin glargine and 33 mcg/mL lixisenatide (30 to 60 pen)
Dose and Frequency	Individualized dose administered once a day within the hour prior to the first meal of the day (b) (4)
How Supplied	Fixed ratio of insulin glargine and lixisenatide in 3 mL prefilled, disposable pen device; available as package of 5 pens
Storage	Unopened pens-refrigerate until expiration date (b) (4) (b) (4) opened pens-room temperature for 14 days

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On February 26, 2016, we searched the L:drive and AIMS using the terms, glargine lixisenatide, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 3 previous reviews, and we determined that the previous recommendations were implemented.

<u>Review Title</u>	<u>RCM Number</u>	<u>Full Citation</u>
Review of Human Factors Validation Protocol for Insulin glargine/Lixisenatide	2014-2586	Vee S. Review of Human Factors Validation Protocol for Insulin glargine/Lixisenatide (IND 105157). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 February 23. OSE RCM No.: 2015-2586.
Label Memo for Insulin glargine/Lixisenatide	2014-787	Vee S. Label Memo for Insulin glargine/Lixisenatide (IND 105157). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 May14. OSE RCM No.: 2014-787.
Human Factors Protocol Memo for Insulin glargine/Lixisenatide	2013-2642	Vee S. Human Factors Protocol Memo for Insulin glargine/Lixisenatide (IND 105157). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 November 25. OSE RCM No.: 2013-2642.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design

Human Factors Report for Prescribing Information:

7.3 PARTICIPANTS

A total of 15 participants participated in the HF validation study. The participants were representative of the intended users of the USPI (see [Table 5](#)).

Table 5 - Participants involved in the HF validation study

User group (n = # of participants)	Study tasks	
	Prescription	Identifier Assessment
Physicians (n=15) who prescribe insulin products	x	x

In this study, none of the participants (physicians) was trained.

Table 6 - Task to be performed by the study participants and definition of task success

Task No.	Task	Study task	Range of acceptable performance
1.1	Physician prescribes insulin glargine/lixisenatide pen-injector based on specific patients' needs	Physicians: Will be asked to prescribe the correct insulin glargine/lixisenatide pen-injector based on 4 different patient profiles	Physicians must be able to prescribe the correct insulin glargine/lixisenatide pen-injector and the appropriate starting dose for each patient profile (see Appendix B, Section 8.2).

Table 7 - Study result – study task

Task No.	Task	Results	Observations	Potential harm (associated with observation)	Severity	Root Cause/Comments
1.1	Prescription of correct insulin glargine/lixisenatide pen-injector related to patient needs	Pass 15/15 prescribers	N/A	N/A	N/A	N/A

7.9 CONCLUSION

The results of the Human Factors Validation Study demonstrate the following:

- The USPI was adequate to enable the physician participants to understand how to prescribe the pens correctly.
- The product name modifiers (identifiers) were found to be helpful for some physicians to understand how to prescribe the pens.

Human Factors/Usability Report:

7.4 STUDY MATERIALS

All materials used in the HF validation study were representative of the commercial product, with the exception of the brand name. (b) (4) was used as a dummy brand name for the insulin glargine/lixisenatide pen-injector in the HF validation study for the purpose of blinding the product identity from the study participants.

The following materials were used in the HF validation study:

- Pen packages for package differentiation session (for pharmacists, patients and nurses):
 - Pen package labeled as (b) (4) (Appendix D, Section 8.4)
 - Pen package labeled as (b) (4) (Appendix D, Section 8.4)
 - Packages for the comparators (Appendix B, Section 8.2)
- Pre-filled pens for pen differentiation session (for patients and nurses):
 - Pen labeled as (b) (4) (Appendix E, Section 8.5)
 - Pen labeled as (b) (4) (Appendix E, Section 8.5)
 - Pre-filled pens for the comparators (Appendix B, Section 8.2)
- Pre-filled pens for pen differentiation session (for patients and nurses):
 - Pen labeled as (b) (4) (Appendix E, Section 8.5)
 - Pen labeled as (b) (4) (Appendix E, Section 8.5)
 - Pre-filled pens for the comparators (Appendix B, Section 8.2)
- Materials for pen handling session (for patients and nurses)
 - Pen labelled as (b) (4) (Appendix E, Section 8.5)
 - Pen labelled as (b) (4) (Appendix E, Section 8.5)
 - Instructions for use (IFU) for pen for (b) (4) (Appendix C, Section 8.3)
 - Instructions for use (IFU) for pen for (b) (4) (Appendix C, Section 8.3)

7.6.1 Training

In this study, none of the participants (pharmacist, patient- and nurse-participants) was trained.

All the participants, including the nurses and pharmacists, were given only a high-level overview of the purpose of the therapy and the study.

Table 8 - User interface elements and user interactions with insulin glargine/lixisenatide pen-injector and Lantus SoloStar

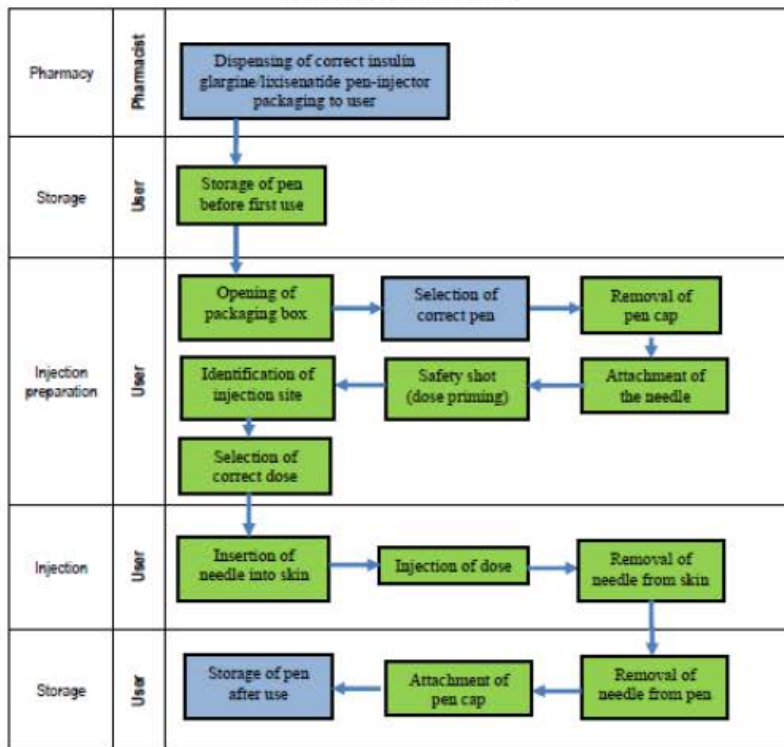


Table 12 - Tasks to be performed by the study participant groups and definitions of task success

Task No.	Task	Study task	Range of acceptable performance
1.1	Pharmacist dispenses product to the user.	Pharmacists: Were asked to identify the correct box from a set of boxes.	Pharmacists must be able to select the correct box from the set of boxes (including comparator boxes).
2.1	Select correct pen.	Patient and nurse participants: Were asked to identify the correct pen from a set of pens.	Patient and nurse participants must select the correct pen.
2.2	Select correct dose related to intended dose range of each insulin glargine/lixisenatide pen-injector.	Patient and nurse participants: Were asked to identify the respective intended dose range of each insulin glargine/lixisenatide pen-injector from a set of devices. Patients and nurse participants: Were asked how they would proceed in case they need a dose higher or below the intended dose range of an insulin glargine/lixisenatide pen-injector.	Patient and nurse participants must answer the correct intended dose range for each insulin glargine/lixisenatide pen-injector. Patients and nurse participants must answer: "Use the other pen" OR "Ask my HCP"
2.3	Store insulin glargine/lixisenatide pen-injector in correct conditions after first use and understand how long to use a pen	Patient and nurse participants: Were asked to provide the storage conditions after first use and how long a pen should be used.	Patients and nurse participants must answer: "Room temperature", "up to 30°C", (b) (4) "14 days after first use"

Table 13 - Study results - critical handling tasks

Task No.	Task	Results		Observations	Root Cause/Comments
1.1	Dispensing of correct pen package to user in pharmacy	Pass	14/15 pharmacists	N/A	N/A
		Use Error	1/15 pharmacists	One pharmacist initially chose the package for another medication and said it was a pen that he often dispensed. Because he seemed to have misunderstood the question, the study moderator clarified the question, but the pharmacist became nervous and, without paying attention to the modifier, chose an insulin glargine/lixisenatide package but the one for the wrong pen.	The study participant misunderstood the question asked by the moderator. This is considered an artifact of the artificial situation. When the question was clarified, the participant had no difficulty identifying the correct product. The selection of the package for the wrong pen is also considered to be associated with the artificial situation.
2.1	Select correct pen related to drug	Pass	30/30 patients 15/15 nurses	N/A	N/A
2.2	Select correct insulin glargine/lixisenatide pen for different doses; select correct dose	Pass	29/30 patients 15/15 nurses	N/A	N/A
		Use Error	1/30 patients	One patient (unexperienced in self-injection with a pen) selected an incorrect dose with pen A; he wrongly selected 10 units instead of the prescribed 20 units.	When asked about the error during the post-task interview, the patient said he mixed up the information in the identifier "10 to 40" with the dose written on the prescription slip. The study participant misunderstood the prescription slip used in the study, which is considered to be an artifact of the artificial situation.
2.3	Store pen in correct conditions after first use (temperature)	Pass	30/30 patients 15/15 nurses	N/A	N/A
	Store pen in correct conditions after first use (lifetime)	Pass	30/30 patients 15/15 nurses	N/A	N/A

Identifier assessment

	Dose Range (correct)	11/15 nurses 27/30 patients	Pharmacists were not asked the question before familiarization
Understanding of identifier prior to tasks/before insulin glargine/lixisenatide pen-injector interaction tasks	Ratio (incorrect)	2/15 nurses 2/30 patients	N/A
	Other (incorrect)	2/15 nurses 1/30 patients	1. Nurse07: The number of units the pen will dispense 2. Nurse09: Dose or strength – not sure 3. Patient29: How many times you can inject yourself
	Dose Range (correct)	15/15 pharmacists 15/15 nurses 30/30 patients	N/A
Understanding of identifier after tasks/after insulin glargine/lixisenatide pen-injector interaction tasks	Other (incorrect)	0/60 participants	N/A
Question: Is the identifier helpful?	Yes	15/15 pharmacists 14/15 nurses 29/30 patients	N/A
	No	0/15 pharmacists 1/15 nurses 1/30 patients	N/A

The main results of the HF validation study, which was conducted in the U.S. with U.S. citizens, are shown in [Table 1](#).

Table 1 - Summary of study results

Study item	Study results
Pen-injectors	The insulin glargine/lixisenatide pen-injectors were found to be safe and effective for the intended users.
IFU	The IFU were found to be understandable and effective in communicating the safety-critical information to the intended users.
Pen package	The pen package was found to be differentiable from other packages and enabled users to select the correct package based on a simulated prescription.
Modifier	The product name modifiers (identifiers) were found to be understood by the intended users and helpful for the users to identify the correct pen and understand the intended dose range.

7.9 CONCLUSION

The results of the Human Factors Validation Study demonstrate the following:

- The device is safe and effective for use by the intended users.
- The pens were found be differentiable from other pens.
- The package for each insulin glargine/lixisenatide pen-injector was found to enable users to recognize it and to differentiate it from other packages.
- The packaging and the insulin glargine/lixisenatide pen-injector for the two dose ranges were found to be differentiable from each other.
- The IFU was found to be understandable and effective in communicating to the intended users the safety-critical information.
- The product name modifiers (identifiers) were found to be understood by the intended users and helpful for the users to identify the correct pen and understand the intended dose range.

APPENDIX D. REGULATORY HISTORY

During the review process, Sanofi provided several submissions in relation to this review:

- December 18, 2014: Sanofi submitted the Human Factors Validation Study Protocol for insulin glargine/lixisenatide for review under IND 105157.
- February 27, 2015: In conjunction with the letter from the Division of Metabolism and Endocrinology Products (DMEP), DMEPA sent an (information request) IR asking for further clarification regarding the name descriptors (b) (4) intended for use on the labels and labeling. In addition, DMEPA provided recommendations for identified deficiencies noted in protocol relating to the user group scenarios and knowledge assessment.
- April 20, 2015: Sanofi sent a reply to the IR providing additional information regarding the name descriptors and human factors study protocol.
- June 22, 2015: DMEPA sent an IR requesting more clarification regarding the proposed modifiers (b) (4).
- July 7, 2015: Sanofi responded to the IR with further clarification.
- July 24, 2015: DMEPA sent an additional IR for clarification of the proposed modifiers.
- July 31, 2015: Sanofi sent an email reply to the IR and agreed to test the understandability of the proposed modifiers (b) (4).
- December 21, 2015: Sanofi submitted a NDA for insulin glargine/lixisenatide (NDA 208673), labels, labeling, and human factors validation study results for review.
- January 8, 2016: Sanofi submitted a request for proprietary name review for Soliqua***. They modified this request to include (b) (4)*** and (b) (4)*** on January 20, 2016.
- February 12, 2016: DMEPA sent an IR to Sanofi requesting sample pen devices to aid in the review process.
- February 19, 2016: DMEPA sent an IR to Sanofi requesting a full HF study report and additional information associated with the name's modifiers (b) (4).
- February 26, 2016: Sanofi replied to the IR and provided the requested information.
- March 2, 2016: DMEPA sent an IR to Sanofi requesting additional data for the IFU assessment questions in the HF study results. Additionally, we asked for more clarification regarding the dose ranges for the pens.
- April 1, 2016: DMEPA sent a decision letter to Sanofi denying the proposed proprietary name request for Soliqua (b) (4).

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

/s/

ARIANE O CONRAD

04/12/2016

updated links to supporting documents

QUYNHNNHU T NGUYEN

04/12/2016

YELENA L MASLOV

04/12/2016

LUBNA A MERCHANT

04/12/2016

TODD D BRIDGES

04/13/2016

HUMAN FACTORS STUDY REVIEW MEMORANDUM

Division of Medication Error Prevention and Analysis (DMEPA)
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: April 12, 2016

Requesting Office or Division: Division of Metabolic and Endocrinology Products (DMEP)

Application Type and Number: NDA 208673

Product Name and Strengths: Insulin glargine and lixisenatide injection, 300 units and 150 mcg per 3 mL pen injector (100 units and 50 mcg per mL)
Insulin glargine and lixisenatide injection, 300 units and 99 mcg per 3 mL pen injector (100 units and 33 mcg per mL)

Product Type: Multi-Ingredient Combination Product

Rx or OTC: Rx

Applicant/Sponsor Name: Sanofi-Aventis

OSE RCM # 2015-2775 and 2015-2782

Acting Associate Director for Human Factors: QuynhNhu Nguyen, MS

DMEPA Deputy Director: Lubna Merchant, MS, PharmD

DMEPA Director: Todd Bridges, RPh

1 PURPOSE OF MEMO

This memorandum is a response to DMEP's request to characterize the type of data that are typically captured from a human factors (HF) validation study¹, and discuss the limitations that are associated with these types of studies within the context of this combination product².

¹ HF validation study is typically conducted with representative users performing tasks under simulated conditions. For new combination products to be used by a wide range of users (e.g. prescribers, pharmacists, nurses, and patients) such as this product, we typically require that an HF validation study be conducted to demonstrate that the product can be used safely and effective under simulated use conditions.

² Insulin glargine and lixisenatide is a new multi-ingredient product that combines a long-acting insulin with a GLP-1 analog intended for the treatment of patients with type 2 diabetes when simultaneous therapies would be clinically appropriate. It is to be available in two peninjectors containing two different fixed ratio of insulin glargine: lixisenatide (3:1 and 2:1)

2 MATERIALS REVIEWED

- Human Factors Study Report for Soliqua submitted on December 21, 2015
- Draft instructions for use (IFU), prescribing information (PI), and label and labeling submitted on December 21, 2015 and January 8, 2016
- DMEPA Human Factors Study Results and Label and Labeling review authored by Dr. A. Conrad

3 DISCUSSION AND CONCLUSION

This combination product employs a new approach where the delivery device (pen injector) is designed to deliver a combination of insulin glargine and lixisenatide (non-insulin). It is worth noting that:

1. The Applicant intends to make available two pen injectors³ that are designed to deliver two different fixed ratios of insulin glargine and lixisenatide⁴.
2. The two active ingredients are dosed using different units of measure (units vs. mcg)⁵. The proposed dosing of this product focuses on one, but not both, active ingredients. This differs from other injectable mixtures of insulins where the two active ingredients are dosed using a single unit of measure (units) to represent both active ingredients.
3. There is an overlap in dosing between 30 and 40 units of insulin glargine between the two pen injectors that could result in an overdose of lixisenatide if the incorrect pen injector is prescribed and/or dispensed.

The clinical team has raised the following concerns regarding the potential of medication errors due to the design of this combination product:

1. Healthcare providers may not realize that each pen injector contains two drugs, one of which is a non-insulin.
2. Prescribers may not read the prescribing information (PI), or have time constraints to review the PI prior to prescribing the product for the first time. In such cases, healthcare providers may lack awareness and understanding that each pen injector contains two drugs, particularly since they are dosed relying on only a single unit of measure. This concern may also present an increased risk for medication errors when patients on this product are transitioning from an outpatient setting to an inpatient setting, or vice versa.
3. Potential of overdose on lixisenatide with multiple injections, for patients that may need larger doses of insulin glargine (>60 units). Prescribers may continue to prescribe for dosages larger than 60 units as they may be familiar with the practice for prescribing long acting insulin products, which do not have maximum dose. As a result, if the pen injector is prescribed for dosing that are higher than 60 units, the lixisenatide

³ Currently proposed proprietary names: Soliqua

(b) (4)

⁴ 2 units (of insulin):1 mcg (of lixisenatide) for the 10 to 40 peninjector and 3 units (of insulin):1 mcg (of lixisenatide) for the 30 to 60 pen injector.

⁵ Insulin glargine is expressed in units versus lixisenatide is expressed in mcg.

component that will be delivered would be higher than the maximum labeled recommendation for this component, which could lead to adverse events.

4. The two pen injectors have an overlap in the delivery of doses between 30 and 40 units. Since doses in this range could be achieved with either pen injector, it may be ambiguous to the prescribers as to which pen injector should be prescribed if the patient requires a dose of insulin glargine that falls within that range.

In the following sections, we will describe how we have utilized the HF validation data to inform our understanding of these potential risks as well as discuss some limitations associated with HF validation study.

1. We recognize that the introduction of a non-insulin component to what is traditionally been only insulin-based combination products presents a challenge to the Applicant and FDA with respect to product's proprietary naming strategy and labeling of the dose in order to ensure both pen injectors can be used appropriately. Specifically, the concerns surround the issue of the pen injector being labeled for the unit of measure for insulin glargine only (in units) when the unit of measure for other drug, lixisenatide, is in mcg. In our experience reviewing multi-ingredient products where the two ingredients have a different unit of measure, we note that the dosing has been conveyed using the common unit of measure or the dosage form to be administered. For example, multi-ingredient products such as Prepopik, which contains 10 mg sodium picosulfate, 3.5 g magnesium oxide, and 12 g citric acid is supplied as a powder in a packet for the dose and dosed as 1 packet. Similarly, Neosporin, which contains neomycin 3.5 mg, polymyxin B 10,000 units, and bacitracin 400 units per gram supplied as an ointment is usually prescribed with instructions such as "apply as directed" or "apply the ointment ...". Therefore in these instances, the specific dose of every single ingredient does not need to be specified on the order, which is not the case with the proposed product. Additionally, the concern noted by the clinical team with the use of units of insulin glargine to convey dosing of the proposed products was assessed from the perspective of the prescribing physicians and dispensing pharmacists within the HF validation study. The HF validation study demonstrated that users were able to understand the dosing of this multi-ingredient product. We also note that prior to conducting the validation study, the Applicant had conducted multiple formative studies to assess (1) the information related to the intended dose range, (2) the insulin glargine/lixisenatide pen injector label to facilitate device differentiation and correct use of both dose strengths, and (3) different pen injector packaging options to support differentiation of packaging boxes. The results of these formative evaluations were used to optimize the product design and to minimize use-related risks associated with dosing and differentiation. Therefore, we agree with the use of units to convey dosing of the proposed products.
2. With respect to the medication error risks related to prescribers' failure to recognize that the product is composed of two active ingredients, we note that the products active ingredients are clearly labeled in the proposed prescribing information, as well as on the container label and carton labeling. While we acknowledge that the simulated

use conditions employed in the HF study included conditions in which the physicians had liberal time to review the PI, in actual use, we would anticipate that prescribers may not read the PI in detail, which may have an effect on how well they interpret the information.⁶ Given that the HF validation study was designed with a specific focus to assess whether the PI is effective in communicating information regarding which insulin glargine/lixisenatide pen injector and initiation dose to prescribe to patients with different profiles, reviewing the PI prior to prescribing was necessary and reasonable. We recognize it is difficult to simulate in the context of a HF validation study what the prescribers would do prior to prescribing a new product and the amount of time some prescriber would take to review the PI. We accept this as a residual risk because prescribers may not always carefully read the prescribing information.

3. We note that the clinical team is also concerned that prescribers may prescribe this product for patients that require doses higher than 60 units. The product is not labeled for doses higher than 60 units because it would deliver doses higher than the maximum recommended dose of 20 mcg lixisenatide.. The pen injector can be dialed to a maximum of 60 units, which may limit the ability of patients to administer such doses. However, it remains possible that patients prescribed doses exceeding 60 units could do so by administering two injections. If patients administer doses of this product greater than 60 units, they would receive an overdose of lixisenatide which could result in adverse events. However, the HF validation study evaluated the prescribers' comprehension regarding the dose limitation of this product and the data showed that all prescribers were able to identify when the product is not appropriate for patients that need higher doses of insulin glargine based on a representative patient's profile.
4. Regarding the clinical team's concern about overlapping dose ranges between 30 and 40 units that could be achieved with either pen injector, (b) (4) and this was also evaluated in the HF study and the data indicated that physicians were able to prescribe the correct pen injector.

Because the two pen injectors are designed to deliver specific doses to patients and should not be substituted for each other, it is important that the products are reliably identified in the prescribing, dispensing and administration process so that the patients receive the correct product. We previously recommended that the Applicant carefully consider the proprietary name employed for this product, which may serve as a useful identifier to distinguish the two pen injectors. As part of the HF study, the Applicant evaluated physician understanding of the product name's modifiers, (b) (4) *** and (b) (4) ***, the adequacy of those data are discussed in detail in the proprietary name review for Soliqua (b) (4) ***. Our evaluation of the proprietary names found that these modifiers may cause medication errors; the modifiers may be confused or misinterpreted by end users as

⁶ de Leon J. Highlights of Drug Package Inserts and the Website DailyMed: the Need for Further Improvements in Package Inserts to Help Busy Prescribers. *Journal of Clinical Psychopharmacology*. June 2011; 31(3): 263-265.

ratios or dose. The modifiers can be misleading because each of the proposed devices can deliver doses outside of the labeled dose range. Thus we found the modifiers unacceptable.

Although acceptable proprietary names have not been identified for these products and we have some residual concerns that expressing the strength relying on one, but not both, active ingredients may have some residual risks of error, overall our evaluation of the data presented in the HF validation study report found that representative users were able to prescribe, differentiate, dispense, and use the pen injector without patterns of concerning use errors. We conclude that the HF validation study results showed that the product design can be reasonably expected to lead to appropriate use by the intended users including prescribers, pharmacists, nurses, and patients. We acknowledge that there are some residual risks in instances where prescribers do not read the PI, however that cannot be further reduced within the context of a human factors usability study.

We recommend that the Applicant carefully reconsider the proprietary names employed for this product, which may serve as a useful identifier to distinguish the two pens. Product proprietary name modifiers may be useful to distinguish between the two pens but there is an inherent risk of medication errors associated with the use of modifiers. We consider that the availability of two pens may still be associated with risk that may not be adequately mitigated through proprietary names and product labeling. Therefore, we recommend that the Applicant consider marketing only one pen injector for this combination product that could deliver the full range of labeled doses (b) (4) to minimize the risk of error and eliminate the need to distinguish between products. However, we defer to the clinical team to determine the clinical value of having two pen devices available for this multi-ingredient product. The approach of having one pen injector would absolve the other residual concerns about the overlapping dose ranges between 30 and 40 units that could be achieved with either pen injector, and the uncertainty of whether prescribers understand that there are two pen injectors with differing dose ranges.

Appendix A: Executive Summary of the HF Validation Study Review

The HF validation study for insulin glargine and lixisenatide pen injectors was conducted with 75 representative users including 15 prescribers, 15 pharmacists, 15 diabetes educating nurses, and 30 diabetic patients. The study was designed to focus on aspects of use that are unique from the currently marketed SoloStar pen injectors (approved for insulin glargine, and is manufactured by the same Applicant) which included prescribing, dispensing, differentiating, and comprehension of storage information contained in the Instructions for Use (IFU). The prescribers were given the PI and four patient's case profiles and were asked to write the prescriptions after they had a chance to review the PI and the profiles. The pharmacists were asked to dispense the pen injector according to prescriptions, and the nurses, and patients were asked to identify the correct pen injector and to prepare a dose, and identify critical information about storage from the Instructions for Use. The study results showed:

1. All 15 prescribing physicians understood the PI and were able to prescribe the correct dose and pen injector.
2. Fourteen (out of 15) pharmacists selected the correct product. For the one that failed to select the product, the root cause analysis attributed the error to overlooking the proprietary name modifier.
3. Forty-four (out of 45) patients and nurses selected the correct pen injector and prepared the correct dose using one of the pen injectors. For the one patient that failed to prepare the correct dose, the root cause analysis attributed the error to confusing the proprietary name modifiers. All 45 of the patient and nurse participants were able to demonstrate understanding of the storage instructions provided in the IFU.

The study results indicated that the prescribers were able to understand the information contained in the PI, and the pharmacists, nurses, and patients were to recognize and differentiate the pen injectors from other competitor's products and from each other, to prepare the correct dose, and to understand critical information from the IFU regarding storage.

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

/s/

QUYNHNNHU T NGUYEN
04/13/2016

LUBNA A MERCHANT
04/13/2016

TODD D BRIDGES
04/13/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208673		Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: soliqua Established/Proper Name: insulin glargine, lixisenatide Dosage Form: subcutaneous injection Strengths: 100 U/mL ins. glar. with 50 or 33 µg/mL lixi.		
Applicant: Sanofi Agent for Applicant (if applicable):		
Date of Application: December 21, 2015 Date of Receipt: December 21, 2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: August 21, 2016		Action Goal Date (if different): August 19, 2016
Filing Date: February 19, 2016		Date of Filing Meeting: January 21, 2016
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Insulin glargine/lixisenatide fixed ratio combination is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both insulin glargine and lixisenatide is appropriate.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
<i>If 505(b)(2): Draft the “505(b)(2) Assessment” review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		
Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		☐ 351(a) ☐ 351(k)

Review Classification: The application will be a priority review if: • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted		☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☒ Pediatric Rare Disease Priority Review Voucher		
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐		
Part 3 Combination Product? ☐ If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults		☐ Convenience kit/Co-package ☒ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)		
☐ Fast Track Designation ☐ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:		☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)		
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 062724, IND 105157, IND 049078, NDA 021081, NDA 206538, NDA 208471, DMF (b) (4), DMF (b) (4), DMF (b) (4), DMF (b) (4), DMF (b) (4), DMF (b) (4), DMF (b) (4)				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system?	☒	☐		
<i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>				
Are the established/proper and applicant names correct in tracking system?	☒	☐		
<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g.,	☒	☐	☐	

chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>				
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm If yes , explain in comment column.	☐	☒		
If affected by AIP , has OC been notified of the submission? If yes , date notified:	☐	☐		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (check daily email from UserFeeAR@fda.hhs.gov): ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: ☒ Not in arrears ☐ In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☒ Yes ☐ No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (Check the 356h form, cover letter, and annotated labeling). If yes , answer the bulleted questions below:	☐	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	☐	☐		

Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>	☐	☐																		
Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If yes, please list below: <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table> <i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													☐	☐		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
Exclusivity	YES	NO	NA	Comment																
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm	☐	☒																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	☐	☐	☒																	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	☐	☒	☐																	
If yes, # years requested:																				
Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.																				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐																	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per	☐	☐	☒																	

FDAAA Section 1113)?				
If yes, contact the Orange Book Staff (CDER-Orange Book Staff).				
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?	☐	☐	☒	
If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager				
<i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only)	☒	☐		
If no , explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	☐	☐	☐	

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included.</i> <i>Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	☒	☐		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	☒	☐		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	☒	☐		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	☒	☐	☐	
<i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>				
<i>Note: Debarment Certification should use wording in FD&C</i>				

Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	☐	☒	☐	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	☒	☐		July 6, 2016
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☒	☐	☐	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	☐	☐		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	☒	☐	☐	soliqua
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	☒	☐	☐	
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	☒	☐		
Is the PI submitted in PLR format?⁴ If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	☒	☐		
	☐	☐	☒	

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	☒	☐	☐	
Has a review of the available pregnancy and lactation data been included?	☐	☒	☐	IR sent to applicant on 1-25-2016
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	☒	☐	☐	CDRH 12-24-2015 PLLR to DPMH 1-25-2016

5

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 6-25-2010	☒	☐		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 9-28-2015	☒	☐		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	☐			
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 21, 2016

BACKGROUND:

The insulin glargine/lixisenatide combination (HOE901/AVE0010) is a fixed ratio combination product of a long-acting human insulin analog (insulin glargine, 100 Units/ml) together with a glucagon like peptide-1 (GLP-1) receptor agonist (lixisenatide).

The combination of insulin glargine and lixisenatide has been developed in a fixed-ratio presentation so that both components are delivered together to allow patient-centric treatment that targets optimal fasting and postprandial glycemic control. To maximize the range of insulin glargine and concomitantly deliver lixisenatide to approximate its maximum clinical dose in the majority patients, the combination has been developed with 2 different dose ratios. The combination has been formulated as a once daily subcutaneous injection available in disposable pre-filled pens which are based on the Solostar device platform.

Indication statement:

Insulin glargine/lixisenatide fixed ratio combination is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both insulin glargine and lixisenatide is appropriate.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Martin White	Y
	CPMS/TL:	Pam Lucarelli	Y
Cross-Discipline Team Leader (CDTL)	Bill Chong		Y
Division Director/Deputy	Jean-Marc Guettier		Y
Office Director/Deputy	Curtis Rosenbaugh		N
Clinical	Reviewer:	Suchitra Balakrishnan	Y
	TL:	Bill Chong	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Pharmacology	Reviewer:	Sury Sista	Y
	TL:	Manoj Khurana	Y
• Genomics	Reviewer:	N/A	N/A
• Pharmacometrics	Reviewer:	N/A	N/A
Biostatistics	Reviewer:	Jiwei He	Y
	TL:	Mark Rothmann	Y
Nonclinical	Reviewer:	Feleke Eshete	Y

(Pharmacology/Toxicology)	TL:	Todd Bourcier	N
Statistics (carcinogenicity)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Product Quality (CMC) Review Team:	ATL:	Muthukumar Ramaswamy	Y
	RBPM:	Anika Lalmansingh	Y
• Drug Substance	Reviewer:	N/A	N
• Drug Product	Reviewer:	Muthu Rmaswamy	Y
• Process	Reviewer:	Yuesheng Ye	N
• Microbiology	Reviewer:	Maria Cruz-Fisher	N
• Facility	Reviewer:	Vipul Dholakia	N
• Biopharmaceutics	Reviewer:	N/A	N/A
• Immunogenicity	Reviewer:	N/A	N/A
• Labeling (BLAs only)	Reviewer:	N/A	N/A
• Other (e.g., Branch Chiefs, EA Reviewer)	N/A		N/A
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Aman Sarai	N
	TL:	Shawna Hutchins	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Ankur Kalola	N
	TL:	N/A	N
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Ariane Conrad	Y
	TL:	Yelena Maslov	N
OSE/DRISK (REMS)	Reviewer:	Amarilys (Lisy) Vega	N
	TL:	Naomi Redd	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Klepplinger	Y
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Other reviewers/disciplines			
OSE DPV	Reviewer:	Christine Chamberlain	Y
		Ali Niak	Y
		Debra Ryan	Y
	TL:	Christian Cao	N
CDRH	Reviewer:	John McMichael and Patricia Beaton	Y
			N
	TL:	Alan Stevens	N
Other attendees	Bindi Nikhar		Y

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues: ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? If no, explain: Batch Records not in English, IR sent in Filing Communication	☐ YES ☒ NO
• Electronic Submission comments List comments:	☐ Not Applicable ☒ No comments
CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? If no, explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☒ YES Date if known: May 24, 2016 ☐ NO ☐ To be determined Reason:

If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u>	
Is the product an NME?	☒ YES ☐ NO
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? Comments:	☒ YES ☐ NO ☐ YES ☐ NO

<u>Facility Inspection</u> Establishment(s) ready for inspection? Comments:	☐ Not Applicable ☒ YES ☐ NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) - Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? - If so, were the late submission components all submitted within 30 days?	☐ N/A ☐ YES ☒ NO ☐ YES ☒ NO
What late submission components, if any, arrived after 30 days?	N/A
Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Curtis Rosenbaugh	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): March 21, 2016	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional): • Receipt date: Dec. 21, 2015 • Filing meeting: Jan 21, 2016 • Filing Date: February 19, 2016 • 74 day letter: March 4, 2016 • Mid cycle Meeting: March 21, 2016 • Mid Cycle Communication with the sponsor: March 29, 2016 • Labeling Meeting 1: April 11, 2016 • REMS Notification Letter: April 18, 2016 • AC Meeting: May 24, 2016 • PeRC Meeting: July 6, 2016 • Labeling Meeting 2: July 14, 2016 • Wrap-up Meeting: July 18, 2016 • Complete Primary Review: July 24, 2016 • Send proposed labeling to Applicant: July 22, 2016 • Complete Secondary Review: July 28, 2016 • Issue DR letters: July 31, 2016 • Complete CDTL review: July 31, 2016 • Complete DD Review: August 11, 2016 • Complete ODE Review: August 15, 2016 • PDUFA goal date: August 21, 2016	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☐ Standard Review ☒ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).

☐ N/A	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐ N/A	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☒	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAAs completed: September 2014

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

/s/

MARTIN L WHITE
02/18/2016

REGULATORY PROJECT MANAGER PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208673

Application Type: New NDA

Drug Name(s)/Dosage Form(s): insulin glargine and lixisenatide injection

Applicant: Sanofi Aventis

Receipt Date: December 21, 2015

Goal Date: August 21, 2016

1. Regulatory History and Applicant's Main Proposals

The insulin glargine/lixisenatide combination (HOE901/AVE0010) is a fixed ratio combination product of a long-acting human insulin analog (insulin glargine, 100 Units/ml) together with a glucagon like peptide-1 (GLP-1) receptor agonist (lixisenatide).

The combination of insulin glargine and lixisenatide has been developed in a fixed-ratio presentation so that both components are delivered together to allow patient-centric treatment that targets optimal fasting and postprandial glycemic control. To maximize the range of insulin glargine and concomitantly deliver lixisenatide to approximate its maximum clinical dose in the majority patients, the combination has been developed with 2 different dose ratios. The combination has been formulated as a once daily subcutaneous injection available in disposable pre-filled pens which are based on the Solostar device platform.

Indication statement:

Insulin glargine/lixisenatide fixed ratio combination is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both insulin glargine and lixisenatide is appropriate.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.
Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required

Selected Requirements of Prescribing Information

• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term

Selected Requirements of Prescribing Information

“**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- YES** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015** ”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "[see *Warnings and Precautions (5.2)*]."

Comment:

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

- YES** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

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6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

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8 USE IN SPECIFIC POPULATIONS

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8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

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11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

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14.1 Subsection Title

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15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

MARTIN L WHITE
02/18/2016