

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**206538Orig1s000**

**OTHER REVIEW(S)**

**REGULATORY PROJECT MANAGER  
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW  
OF THE PRESCRIBING INFORMATION**

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** [NDA206538](#)

**Application Type:** [New NDA](#)

**Name of Drug/Dosage Form:** [TOUJEO \(insulin glargine \[rDNA origin\] injection\) for subcutaneous injection, 300 Units/mL \(U-300\)](#)

**Applicant:** [sanofi-aventis U.S. LLC](#)

**Receipt Date:** [April 25, 2014](#)

**Goal Date:** [February 25, 2015](#)

**1. Regulatory History and Applicant's Main Proposals**

[Toujeo is a new NDA submission for a higher concentration of its currently approved insulin glargine product Lantus. This is the first review cycle of Toujeo.](#)

**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 for Prescribing Information (SRPI)" checklist (see the Appendix).

**3. Conclusions/Recommendations**

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in in labeling sent to the applicant. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format during labeling negotiations. The resubmitted PI will be used for further labeling review.

# Selected Requirements of Prescribing Information

## Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-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.

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## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

### 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:**

- NO** 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:** *it is greater than ½ page. We will grant waiver.*

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

**Comment:**

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

**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 A for a sample tool illustrating white space in HL.

**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. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required

## Selected Requirements of Prescribing Information

• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

**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

- NO** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit** year.

**Comment:** 2015 added (tentative date based on current PDUFA goal date)

#### 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 heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

## Selected Requirements of Prescribing Information

### Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading 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 heading 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 the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in 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) --- 9/2013”.

### Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

### Comment:

### Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

### Comment:

### Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

### Comment:

### Contraindications in Highlights

**YES**

## Selected Requirements of Prescribing Information

21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions in Highlights

- YES** 22. 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) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement in Highlights

- YES** 23. 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** 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

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: February 2015 added (tentative date based on current PDUFA goal date)

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- YES** 26. 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** 27. The same heading 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** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 29. 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 (through), articles (a, an, and the), or conjunctions (for, and)].  
*Comment:*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of 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** 32. 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.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- NO** 33. 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)*]” or “[*see Warnings and Precautions (5.2)*]”.

**Comment:** Change 6.1 Lipodystrophy cross-reference (b) (4)  
to [*see DOSING AND ADMINISTRATION (2.1)*].

## Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

*Comment:*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

*Comment:*

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

*Comment:*

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

*Comment:*

#### CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

*Comment:*

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“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** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), 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:*

#### PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

## Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) 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 A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

#### WARNING: [SUBJECT OF WARNING]

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

### DOSAGE AND ADMINISTRATION

- [text]
- [text]

### DOSAGE FORMS AND STRENGTHS

[text]

### CONTRAINDICATIONS

- [text]
- [text]

### WARNINGS AND PRECAUTIONS

- [text]
- [text]

### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- [text]
- [text]

### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

#### 6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

#### 7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 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

12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

#### 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/  
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RICHARD E WHITEHEAD  
02/23/2015

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

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

*Memorandum*

**Date:** February 23, 2015

**To:** Richard Whitehead, 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 206538 TOUJEO (insulin glargine [rDNA origin] injection) for subcutaneous injection

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On May 2, 2014, OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI), Patient Information (PPI), Instructions for Use (IFU), and Carton and Container labeling for Toujeo. OPDP's comments on the proposed draft PI and Carton and Container labeling are based on the versions available in Sharepoint and DARRTS, respectively, on February 23, 2015.

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

Additionally, OPDP worked collaboratively with DMPP to provide comments on the PPI 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](mailto:Ankur.Kalola@fda.hhs.gov).

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/s/  
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ANKUR S KALOLA  
02/23/2015

**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: February 17, 2015

To: Jean-Marc Guettier, M.D.  
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)**

Melissa Hulett, MSBA, MSN, FNP-BC, RN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Robin Duer, MBA, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Ankur Kaola, Pharm.D.  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and  
Instructions For Use (IFU)

Drug Name (established name): TOUJEO (insulin glargine [rDNA origin] injection)

Dosage Form and Route: for subcutaneous injection

Application Type/Number: NDA 206538

Applicant: Sanofi US Services Inc.

## 1 INTRODUCTION

On April 24, 2014, Sanofi US Services Inc. submitted for the Agency's review a New Drug Application (NDA 206538) for TOUJEO (insulin glargine [rDNA origin] injection) for subcutaneous injection, 300 units/mL (U-300), to be available in a 1.5 mL glass cartridge assembled on a in a disposable pen injector. TOUJEO is a long-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on May 2, 2014, respectively for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TOUJEO (insulin glargine [rDNA origin] injection) for subcutaneous injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on November 3, 2014.

## 2 MATERIAL REVIEWED

- Draft TOUJEO (insulin glargine [rDNA origin] injection) PPI and IFU received on April 24, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on February 9, 2015
- Draft TOUJEO (insulin glargine [rDNA origin] injection) PPI and IFU received on April 24, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on February 9, 2015
- Draft TOUJEO (insulin glargine [rDNA origin] injection) Prescribing Information (PI) received on April 24, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on February 9, 2015
- Draft TOUJEO (insulin glargine [rDNA origin] injection) Prescribing Information (PI) received on April 24, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on February 9, 2015
- Tentatively approved BASAGLAR (insulin glargine injection) comparator labeling dated August 18, 2014
- DMEPA labeling/IFU handling study review for TOUJEO (insulin glargine [rDNA origin] injection) dated November 3, 2014

## 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. The PPI and IFU documents are formatted using the Arial font, size 11.

In our collaborative review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The PPI and IFU are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU 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 PPI and IFU.

Please let us know if you have any questions.

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/s/  
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AMANPREET K SARAI  
02/17/2015

ANKUR S KALOLA  
02/17/2015

MELISSA I HULETT  
02/17/2015

LASHAWN M GRIFFITHS  
02/17/2015



Food and Drug Administration  
Office of Device Evaluation  
White Oak Building 66  
10903 New Hampshire Ave.  
Silver Spring, MD 20993

**Intercenter Consult Memorandum**

**ICC1400277/NDA206538**

Date: 1/20/2015

To: Richard Whitehead  
Division of Metabolism and Endocrinology Products (DMEP),  
Office of Drug Evaluation II (ODEII),  
Office of New Drugs (OND),  
Center for Drug Evaluation and Research (CDER)

From: Ryan McGowan  
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: Device Constituent Part Design Review  
Insulin glargine injection, 300 Units/mL  
NDA 206538; CDRH ICC1400277

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**I. Recommendation**

Based on the above CDRH/ODE evaluation of the design of the device constituent part of the combination product, the reviewer recommends NDA approval. If agreeable to the review division, two labeling recommendations have been made for consideration.

**II. Review Summary**

The CDRH reviewer performed an evaluation of the design of the device constituent parts of the insulin glargine U300 combination product. This evaluation covered the intended design and design control information for the subject device constituent part. This review did not cover the following elements:

- Review of drug product
- Review of primary container closure-drug product interaction or biocompatibility/toxicology
- Usability and Human Factors of the combination product
- Manufacturing of the drug product
- Manufacturing of the device constituent part of the combination product

This review did cover the following elements:

- Inspection of sponsor's design input activities
- Inspection of sponsor's design verification activities
- Confirmation of standards conformance where relied upon
- Inspection of test methods and results of bench top testing completed

- Inspection of stability testing completed on the device constituent part
- Review of risk analysis documentation and conclusions of safety
- Review of clinical and marketing experience of the device constituent part

Relevant finding within this review included:

- The sponsor completed adequate design control activities to characterize product requirements
- The sponsor provided sufficient documentation to verify implementation of product requirements with one exception. This exception is noted [REDACTED] (b) (4) [REDACTED]. This deviation is considered acceptable due to instructions for use indicating only a damp cloth should be used to clean the device.
- The device conforms with international and FDA-recognized consensus standards
- The device meets essential performance requirements, including device accuracy, in the following manner to a 95% confidence interval:
  - o If the dose is set to 1 unit (3.33  $\mu$ L), the device was never off more than .03 units (.1  $\mu$ L)
  - o If the dose is set to 40 units (133.33  $\mu$ L), the device was never off more than .16 units (.52  $\mu$ L)
  - o If the dose is set to 80 units (266.66  $\mu$ L), the device was never off more than .32 units (1.05  $\mu$ L)
- The device maintains essential performance after exposure to shipping conditions
- The device maintains essential performance after exposure to aging and in-use conditions equivalent to 12 months. However review of periodic real time test results and certification of ongoing accelerated and real-time aging studies qualify the device for an expiry of 36 months
- The sponsor has established and conducted appropriate device design risk management activities
- Prior clinical use and marketing history do not suggest an unacceptable rate of device constituent part malfunction. The sponsor has demonstrated that they are capable of monitoring and establishing corrective action plans related to device complaints.

Two recommendations for potential product labeling revisions include:

- 1) An explicit warning that the user should not use solvents other than water to clean the device. This is recommended [REDACTED] (b) (4) [REDACTED]
- 2) A statement of the brand/type of needles the device is permitted to be used with (currently only the needle manufacturers are listed). This is recommended as the device has only been verified to function with ISO11608-2 compatible insulin needles.

### III. Consult Purpose

The Center for Drugs Evaluation and Research (CDER) requested a consult from CDRH/ODE for device constituent part design review of NDA 206538, which is a combination product consisting of a pen injector that delivers insulin glargine solution (300 U/mL). This NDA has been submitted by Sanofi-Aventis.

### IV. Coverage of Review

CDRH/ODE reviews content related to the design of device constituent parts for combination product submissions. This review is limited to 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. This

review does not cover review of the primary “container closure” (i.e. cartridge), manufacturing or process validation of the device, nor usability studies for the device.

## V. Device Description

The sponsor has chosen a pen device constituent part based closed on the “Lantus SoloStar” pen injector configuration. The Lantus SoloStar combination product is currently marketed under NDA 021081 (S-024), which was approved on April 25, 2007. The subject product is changed from the “Lantus SoloStar” pen injector in the coloring, some molding changes, as well as changed in the dial incrementing system.

The injector is shown in the figure below.



(b) (4)

The pen injector consists of the following components: an irreversibly integrated 1.5 mL insulin cartridge which cannot be replaced, the cap, the cartridge holder and the dosing mechanism. The device is operated fully mechanically and does not contain electronics. The pen injector contains the 1.5 mL cartridge which serves as primary packaging for the insulin glargine solution for injection. The injection

system provides a maximum of 80 units in one dosing. The total content of the cartridge is 450 insulin units. For the convenience of the user, for safety and to protect the cartridge, a pen cap is part of the pen system.

The cartridge serves as the reservoir for the drug product. The cartridge is clear and colorless (glass type I), which is closed on the distal end with a plunger/stopper and closed on the proximal end with flanged caps and (b) (4) sealing discs.

The sponsor does not appear to have conducted clinical studies with the final finished combination product as described within the submission. Instead, two other device presentations were used. These devices are described as “Devices A and B” within the submission. Section 3.2.P.2.4 contains a comparison of the two devices studied clinically with the final finished system. This comparison concludes that the design of devices A and B is sufficiently similar to the to-be-marketed system to allow for clinical conclusions made with A and B to be translated to the to-be-marketed system.

From a device design/engineering perspective, the reviewer agrees with the sponsor that the functionality of devices A and B is sufficiently similar to the to-be-marketed system to allow for clinical conclusions made with A and B to be translated to the to-be-marketed system. However the reviewer wishes to acknowledge that this position does not include an assessment of device usability or other clinical concerns.

## **VI. Device Constituent Part – Design Review**

The submission indicates that functionality of the device is demonstrated through conformance to the requirements of ISO 13926-1 for glass cylinders, ISO 13926-2 and ISO 13926-3 for plungers, and ISO 11608-3 for needle-based injection systems. Additionally, the sponsor states that the final device design was verified to confirm the correct mechanical functionality through conformance to ISO 11608-1.

### **Essential Performance of the Combination Product**

The consultant performed a review of device requirements and specifications. This review, in combination with accepted performance aspects of pen injectors known to CDRH, yielded the following list of items for inspection and evaluation within this memorandum.

1. Adequate combination product design inputs
2. Adequate combination product verification activities
  - a. Accuracy
  - b. Compatibility with selected cartridge and labeled needles
  - c. Physical durability
  - d. Sterility
  - e. Biocompatibility
  - f. Stability
  - g. Shipping and storage
  - h. In-use testing
3. Adequate combination product risk analysis information
4. Evaluation of past performance and safety issues with combination product

### **Combination Product Design Inputs**

Section 3.2.P.7 of the submission contains a document titled “Insulin glargine - solution for injection - 300 U/mL 1.5 mL cartridges CONTAINER CLOSURE SYSTEM”. This document contains a listing of combination product system-level specifications. Select specifications are reproduced below:

Specification Name	Summary
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Material Biocompatibility	Patient contact materials – ISO10993-1 adherent Fluid contacting materials – None in pen (cartridge and needle create fluid path)
Dimensional	Length of the pen injector: 166.8±2 mm Width of the pen injector: 18.8±1 mm  Cartridge cap and plunger fitment Cartridge fitment into injector Needle fitment into injector
Component Attachment	Compatible with ISO 11608-2 insulin needle
Dose accuracy	Compliant with ISO 11608-1

The reviewer initially believed that the sponsor had not fully characterized the design of the system; however additional documents, located within 3.2.P.7, better characterizes the intent of the design:

- “Pen injector – insulin glargine 300U/mL – Material of Construction”
- “Pen injector – insulin glargine 300U/mL – Specifications and analytical methods assembled pen”
- “Pen injector – insulin glargine 300U/mL – Principles of operation”
- “Pen injector – insulin glargine 300U/mL – Engineering drawings”
- “Pen injector – insulin glargine 300U/mL – Dimensions”
- “1.5mL Cartridges – Container Closure System”

The documents present engineering/dimensional drawings, operational theory, proposed verification endpoints, and material formulations. Each of these documents was inspected and found to be adequate to characterize product function.

The sponsor also relies on a number of international consensus standards within their product design documentation. These are:

Consensus Document Number	Relevant Component(s)	Relevant Specifications/Findings
ISO10993-1	Pen injector	Biocompatibility of device constituent part – skin contacting, short duration
ISO 11608-2	Pen injector	Threading for needle compatibility
ISO 11608-1	Pen injector	Dose accuracy per “System Designation C”
European Pharmacopoeia, Chapter 3.2.1	Glass cartridge primary container system; glass composition	Cartridge conformance to “Glass Containers for Pharmaceutical Use” – type 1 glass
United States Pharmacopoeia, Chapter <660>	Glass cartridge primary container system; glass composition	Cartridge conformance to “Containers - Glass” – type 1 glass
ISO 11608-3	Flanged cap with (b) (4) sealing disk;	Dimensional characteristics  Materials used free from (b) (4)
ISO 13926-2	Flanged cap with (b) (4) sealing disk;  Plunger stopper	Dimensional characteristics  Materials compliance with comply with USP biological reactivity tests <87> and <88>
European Pharmacopoeia, Chapter 3.2.9	Flanged cap with (b) (4) sealing disk;  Plunger stopper	“Rubber Closures for Containers for Aqueous Parenteral Preparations, for Powders and for Freeze-dried Powders”; type I closure.

United States Pharmacopoeia, Chapter <381>	Flanged cap with (b) (4) sealing disk;	Elastomeric Closures for Injections", type I closure.
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Each of the FDA-reviewer nominated essential system requirements are detailed below:

High Level System Requirement	Statement of Requirement and Method of Verification
Accuracy	Sanofi test reports conducted per ISO 11608-1
Compatibility with selected cartridge and labeled needles	Sanofi test reports conducted per ISO 11608-3 and ISO13926-2 Use with ISO 11608-2 Needles under ISO 11608-1 Sanofi statement of compliance ISO 11608-2 in pen threading
Physical durability Repeated access Repeated use	Sanofi test reports conducted per ISO 11608-1 Sanofi test reports conducted per ISO 11608-3 Primary stability: In-use Testing
Sterility	Sterility of container closure assured by CDER review Sterility of non-supplied needle path assured by needle supplier
Biocompatibility	Sanofi test reports conducted per ISO 10993
Stability	Shipping and storage test reports provided within 3.2.P.8

This section is considered acceptable.

#### Combination Product Verification Activities

The sponsor has provided a number of test activities to verify the device constituent part of the combination product functions as intended, both after initial manufacturer and fill, as well as after exposure to conditions of use. These verification documents include, but are not limited to the following document, which were located within section 3.2.P.2 and 3.2.P.8 of the submission, and were categorized by the reviewer into two type: those verification tests intended to demonstrate the system behaves/functions as intended, as well as those activities which are intended to demonstrate dimensional or biological conformance.

##### 1. Functional Verification Activities

- Pen injector: performance test (ISO 11608-1)
- Pen injector: performance test (ISO 11608-3 and 13926-2) – cartridge
- Container closure system: pen injector – in-use study
- Stability - Dose accuracy pen injector after shipping and aging

##### 2. Dimensional or Biological Test Conformance

- Pen injector tissue contacting parts: biocompatibility (ISO 10993-1)
- Dimensional specifications - 1.5mL Cartridges – Container Closure System
- Dimensional specifications – Needle/Pen Interface

\*Reviewer note 1 – pen system dimensional properties are considered verified by successful completion of system functional verification activities

\*Reviewer note 2 – chemical/biological properties of the cartridge (biological reactivity, sterility, microbial ingress) are considered verified by CDER reviewers

\*Reviewer note 3 – functional properties of the cartridge (re-use and activation) are considered verified by system functional verification activities

## Functional Verification Activities

### ISO 11608-1 - Injector Performance Test:

Section 3.2.P.2.4 of the submission contains a test report for assessment of pen injector dose accuracy. The test method was based on FDA-accepted standard ISO 11608-1 "Needle-based injection systems for medical use – Requirements and test methods – Part 1: Needle-based injection systems". The test requirements under the standard change depending on the type of injector or "system designation" used. The sponsor has correctly declared their device as a "Type C" injector: *Needle-based injection device with integrated non-replaceable container. Each container holds multiple doses, the size of which may be fixed or variable (pre-set by the user).* As a type C injector, the sponsor is obligated to conduct dose accuracy after the following assessments:

1. Cool, standard, and warm preconditioning
2. Last dose accuracy
3. Free fall
4. Dry heat/cold storage
5. Vibration

The sponsor correctly identified the pre-conditioning tests required. The sample sizes and dose accuracy measurement techniques discussed within test report sections 3 and 7 are considered acceptable.

Dose accuracy was completed under the following methods:

Three dose sizes (Vset) were used (minimum Vmin, midpoint Vmid and maximum Vmax). Dosing was designed such that Vset was delivered equally from the front 1/3, middle 1/3 and rear 1/3 divisions of the cartridge.

For determination of the last dose accuracy Vmin was used (7.4.3) as described in section 10.2 of the standard. All doses delivered were recorded gravimetrically (m, expressed in milligrams) using an analytical balance. These recordings are converted to volumes (V) by using the density (ρ, expressed in milligrams per micro liter) for insulin glargine solution for injection 300 U/mL. The following equation was used to convert gravimetric measurements to volumetric:

$$V = \frac{m}{\rho}$$

Where V = calculated volume of a dose, m = mass of dose, ρ = density of product (changes to density over temperature were reported within the test report for preconditioning activities.

Assessments of dose accuracy were completed using the following standardized method: the two-sided statistical tolerance interval was calculated using the mean (x) plus or minus the uncertainty of the dose volume (sV) multiplied by the tolerance limit factor (k). This method is identical to the method as described in ISO 11608-1 section 7.4.5:

$$s_V = \sqrt{\left(\frac{s_m}{\rho}\right)^2 + \left(\frac{m}{\rho^2} s_\rho\right)^2}$$

Where: sV = uncertainty of the dose volume, Sm = standard deviation of measured dose mass, Sp = uncertainty of the used density.

According to the sponsor, the tolerance limit factor “k” was determined in accordance with table B.2 of ISO 11608-1, using the number of determinations performed, a confidence interval (Gamma) of 95% and probability content (p) of 0.950 or 0.975, respectively, as given in Table 1. The resulting values were required to be within the lower (LSL) and the upper (USL) specification limit.

Testing per the above method concluded that the U300 pen injector was able to deliver up to 80 units in 1 unit steps with a minimum of 1 U (1 U = 3.33 µL). The specification limits were calculated given the above constraints.

A summary of results were provided within the test report. These results showed that each administration after each precondition met the stated requirements of dose accuracy. According to the results provided, the pen dosing never exceeded the allowable under or over dose conditions. The deviations from set dose occurred in the following ways:

If the dose was set to 1 unit (3.33 µL), the device was never off more than .03 units (.1 µL)

If the dose was set to 40 units (133.33 µL), the device was never off more than .16 units (.52 µL)

If the dose was set to 80 units (266.66 µL), the device was never off more than .32 units (1.05 µL)

The above values are maximum dose deviations and most often occurred when the device had been subjected to an extreme pre-conditioning activity.

In addition to the dose accuracy requirement, the ISO 11608-1 standard also states a number of general requirements. These general requirements prescribe, for example, that the device shall have a viewing window to examine the remaining contents of the pen. Each of these general requirements were certified as properly implemented by the sponsor and checked by the reviewer.

**Additional Information Response Request:**

The sponsor provided a summary test report which described the general requirement and dose accuracy activities, but did not provide detailed test report information. This was requested of the sponsor within an additional information request, which was received under supplement 14. The low-level supporting test documentation was reviewed and found to be supportive of the test summary reported conclusions.

Within the low-level test report information provided, the sponsor conducted a number of independent verification activities normally associated with the design control process. These activities were conducted properly and were intended to demonstrate that detailed product requirements were satisfied.

After inspection of document “Final Design Verification”, the reviewer noticed that the device appeared to not meet one functional requirement (b) (4)

This test was conducted in order to challenge the device to cleaning solutions. The device was capable of retaining markings at 28 days after (b) (4) exposure, and was also capable of retaining markings after exposure to a number of other solvents. The reviewer examined product labeling for cleaning and found that product labeling recommends only wiping the device with a damp cloth. This, (b) (4) as well as continued device function after exposure to (u) (4) assisted in the determination that this verification deviation was acceptable.

This response to additional information was considered acceptable.

ISO 11608-3 and ISO 13926 - Cartridge Performance Test:

The sponsor provided reports of compliance with functional requirements for the primary container closure (cartridge) under ISO 11608-3 and ISO 13926. ISO 11608-3:2013 specifies the performance and test methods for multidose, single chamber prefilled cartridges used as primary containers in pen-injectors. ISO 13926-2:2012 specifies the design, dimension and material performance requirements and marking of plunger stops for medical pen systems.

The test report summary provided under “PHARMACEUTICAL DEVELOPMENT Pen injector: performance test (ISO 11608-3 and 13926-2) – cartridge” stated that the cartridge complied with the following requirements according to ISO 11608-3:

Requirement Name	Functional Requirement	Statement by Sponsor
Freedom from leakage	The cartridge shall be free from leakage at the plunger or disc	Compliant
Initiating and Sustaining force	The initiating force shall not exceed (b) (4) N The sustaining force shall not exceed (b) (4) N	Compliant
Eccentricity	Maximal eccentricity between axis of cap and axis of glass body of the filled cartridge shall meet the requirements in accordance with ISO11608-3	Compliant
Visibility of the medicinal product	The contents of the cartridge remain visible over the length of the deliverable volume	Compliant
Meniscus	The meniscus of the substance into the cartridge is not visible	Compliant
Resealability	No leakage after puncturing (according to ISO 11608-3) of the sealing disk	Compliant
Fragmentation	Not more than (b) (4)	Compliant
Lubrication	If the cartridge components are lubricated, the lubricant shall not, under normal or corrected to normal vision, be visible as droplet of fluid outside or inside of the surface of the components	Compliant
Dose accuracy	The dose accuracy of the cartridge shall meet the dose accuracy requirements in accordance with ISO 11608-1.	Compliant
Deliverable volume and last-dose accuracy	Deliverable volume and last dose accuracy of the cartridge shall meet the dose accuracy requirements in accordance with ISO11608-1	Compliant

The test report summary provided under “PHARMACEUTICAL DEVELOPMENT Pen injector: performance test (ISO 11608-3 and 13926-2) – cartridge” stated that the cartridge complied with the following requirements according to ISO 13926-2:

Requirement Name	Functional Requirement	Statement by Sponsor
Leakage	For this test item, product filled cartridges are prepared, using the plungers and/or the disks to be tested. (b) (4) Any observed leakage is recorded.	Compliant
Sliding Characteristics	Plungers to be tested for sliding characteristics (initiating and sustaining force) (b) (4) under well-defined conditions. Maximum and minimum force to sustain	Compliant

	continuous movement are determined	
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**Additional Information Response Request:**

The sponsor provided a summary test report which provided the above results, but did not provide detailed test report information. This was requested of the sponsor within an additional information request, which was received under supplement 14. The low-level supporting test documentation was reviewed and found to be supportive of the test summary reported conclusions.

Within the low-level test report information provided as “Testing of the 1,5 mL cartridge for Lantus U300 in accordance with ISO 13926 and ISO 11608 and SFI-PLAN-00301”, the sponsor conducted a number of verification activities to challenge the system. The test methods were conducted according to ISO 11608-3 ISO 13926, and found that the device primary container closure was capable of meeting functional requirements outlined within the table above. Some summary points are included below:

- Cartridge found to be leak-proof to (b) (4) N for (b) (4) seconds
- Cartridge found to not exhibit high movement/dispense forces
- Cartridge found to not produce unacceptable particulates after needle puncture
- Cartridge found to not product leakage after (b) (4) punctures, representing (b) (4) expected in-use amount

This response to additional information was considered acceptable.

Container closure system: pen injector – in-use study

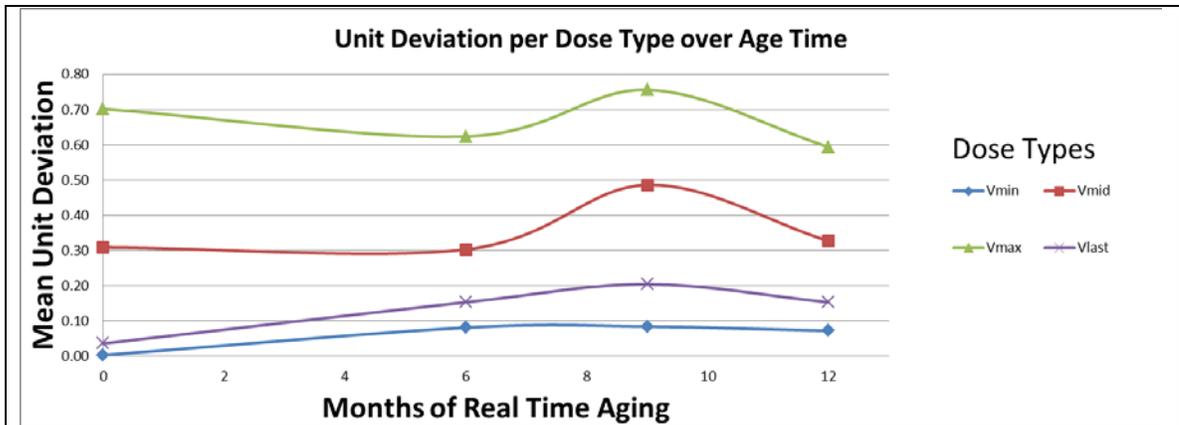
In order to demonstrate the pen injection system is capable of meeting its requirements during its period of use, Sanofi conducted an “in-use” study. After initial examination, the reviewer was not certain if this test demonstrated functionality of the pen injector in addition to being sensitive to drug activity and stability. The reviewer also desired to see the most updated copies of in-use testing completed after aging to the maximum real-time period available.

**Additional Information Response Request:**

In response to the Agency question, the sponsor responded in submission supplement 14 by stating that the in-use study conducted under “STABILITY DATA Primary stability: In-use” for the final finished injector did indeed include all essential device handling steps. This in-use assessment examined repeated exposure of the pen injector to ISO needles and repeated injections. This assessment required the test engineers to handle the device, dispense a dose, and examine the product for accuracy.

The sponsor also provided an updated copy of in-use testing results, this document summarized that the device performed accurately after in-use handling and preconditioning to a period of 12 months. Each of the time points sampled and the in-use results for device accuracy are shown below:

Vmin		Vmid		Vmax		Vlast	
Time (months)	Deviation (units)						
0	0.00	0	0.31	0	0.70	0	0.04
6	0.08	6	0.30	6	0.62	6	0.15
9	0.08	9	0.49	9	0.76	9	0.20
12	0.07	12	0.33	12	0.59	12	0.15



The above information shows that there does not appear to be a significant trend in dose accuracy deviation over time for the final finished pen injection system and after in-use testing. None of the individual time points deviate significantly from the intended dose, and none appear to deviate more than the values accepted under initial verification studies completed on un-aged product.

In addition to the real-time/in-use studies shown, the sponsor is completing in-house testing which will challenge the final finished device to a life-time of accelerated aging conditions with in-use assessments to assess device function. The sponsor will also continue to monitor device accuracy under the real time/in-use aging protocol.

The assessment of device function after 12 months of real time aging and (b) (4) days of use following (in-use), in addition to the ongoing internal aging controls the company is applying to the device supports a conclusion that the injector could be labeled for an expiration of 36 months.

The response is considered acceptable.

#### Stability - Dose accuracy pen injector after shipping and aging

Stability after Aging:

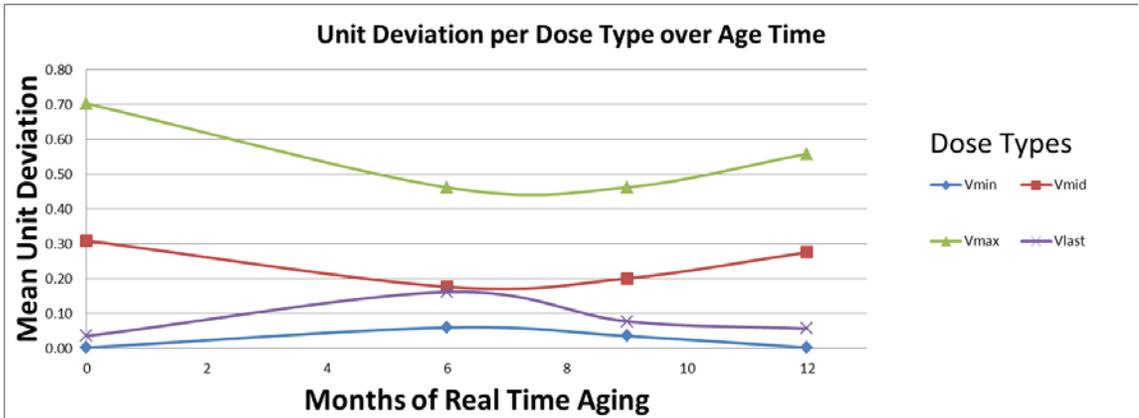
To support functionality of the combination product after aging, the sponsor has completed an assessment of essential performance after real-time aging to a period of 6 months. The dose accuracy conclusions drawn as part of those 6-month studies were intended to support functionality of the device after aging. Initially, the sponsor did not provide detailed test information on test protocols and device constituent part challenges conducted as part of the tests.

#### **Additional Information Response Request:**

The sponsor provided a summary test report which provided a summary of aging test results, but did not provide detailed test report information. The sponsor also did not provide an update to the file showing results of aging studies conducted while the file was under review. These items were requested of the sponsor within an additional information request, which was received under supplement 14. Specifically, a document titled "300UmL – primary stability – internal verification study (dose accuracy) – (b) (4) pen (CTD)" was provided to the file containing an update to the real time aging study of the final device, and supporting test reports were included for additional detail on the test methods used.

The update provided 12 months of device accuracy data under the document "300UmL – primary stability – internal verification study (dose accuracy) – (b) (4) pen (CTD)". Results of dose accuracy information as summarized and compiled by the reviewer are included below:

Vmin		Vmid		Vmax		Vlast	
Time (months)	Deviation (units)						
0	0.00	0	0.31	0	0.70	0	0.04
6	0.06	6	0.18	6	0.46	6	0.16
9	0.04	9	0.20	9	0.46	9	0.08
12	0.00	12	0.28	12	0.56	12	0.06



The above information shows that there does not appear to be a significant trend in dose accuracy deviation over time for the final finished pen injection system. None of the individual time points deviate significantly from the intended dose, and none appear to deviate more than the values accepted under initial verification studies completed on un-aged product.

In addition to the real-time studies shown, the sponsor is completing in-house testing which will challenge the final finished device to a life-time of accelerated aging conditions to assess device function. The sponsor will also continue to monitor device accuracy under the real time aging protocol.

The assessment of device function after 12 months of real time aging, in addition to the ongoing internal aging controls the company is applying to the device supports a conclusion that the injector could be labeled for an expiration of 36 months.

This response to additional information was considered acceptable.

#### Stability after Shipping:

Within the original submission, the sponsor did not adequately describe how the device was assured to be free from damage or functional impairment after shipping. A shipping study was included within section 3.2.P.8, however the protocol did not explicitly state if this study covered assessment of the device constituent part.

#### Additional Information Response Request:

The sponsor was requested to provide information on how the device was assessed after simulated shipping studies. These items were requested of the sponsor within an additional information request, which was received under supplement 14. The sponsor stated that product packaging was explicitly designed to prevent exposure of the product to shipping environmental forces, but that also that the functional characteristics under different environmental conditions, tests were conducted. These studies fulfilled internationally accepted standards like ISO 11608-1 and IEC 60068-2-6., covering vibration criteria (IEC 60068-2-6) and temperature criteria (ISO 11608-1). The sponsor states these tests were carried out within the ISO11608-1 verification

report and that the pen devices have been tested for dose accuracy following pre-treatment like temperature change (warm atmosphere (see answer to Question 2: U300sc\_R\_143 v1.0 section 4.5), cool atmosphere (U300sc\_R\_143 v1.0 section 4.4)), vibration (U300sc\_R\_143 v1.0 section 4.10) and free fall (U300sc\_R\_143 v1.0 section 4.7).

The reviewer agrees that ISO 11608-1 includes sub-assessments of device functionality and dose accuracy after pre-conditioning device to conditions that are similar to shipping conditions.

This response is considered acceptable.

#### Dimensional or Biological Test Conformance

##### Pen injector tissue contacting parts: biocompatibility (ISO 10993-1)

Per ISO 11608 and internal sponsor requirements, the injector must be biocompatible in a manner consistent with its intended use. The pen system is considered to have a degree of tissue contact as “intact skin”. The pen materials do not come into contact with subdermal tissues, as the subcutaneous needle is supplied separately. The pen materials do not come into contact with the drug constituent part of the combination product, as the primary closure is punctured by the needle to create the fluid path. The duration of contact is considered to be less than 24 hours, since the summed-time of patient exposure from a single device is fewer than 24 hours.

The sponsor classified the following components as short duration skin contacting, and has completed the biocompatibility assessments as shown:

Components	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	GC/MS fingerprint
Pen cap (pen body)	x	x	x	x
Cartridge holder	x	x	x	x
Dosage selector	x	x	x	x
Injection button	x	x	x	x
Number sleeve	x	x	x	x
Thread insert	x	x	x	x

To support the conclusion that the device components shown are biocompatible to the levels shown, the following test methods were employed:

- ISO 10993-1:2009; “Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management system (ISO 10993-1:2009)”
- ISO 10993-5:2009; “Biological evaluation of medical devices – Part 5: Tests for in vitro cytotoxicity (ISO 10993-5:2009)”
- ISO 10993-10:2010; “Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization (ISO 10993-10:2010)”;
- ISO 10993-12:2012; “Biological evaluation of medical devices - Part 12: Sample preparation and reference materials (ISO 10993-12:2012)”
- ISO 10993-18:2009; “Biological evaluation of medical devices – Part 18: Chemical characterization of materials (ISO 10993-18:2005)”;

A test summary was provided under “PHARMACEUTICAL DEVELOPMENT Pen injector: biocompatibility (ISO 10993-1)”, which showed the individual techniques used to test the device per 10993, as well as a summary of results of testing. This summary concluded that U300 pen injector is considered biocompatible per testing conducted. The sponsor further states that the U300 pen injector is considered biocompatible by pedigree. Specifically, the product is a

modification of SoloStar, using identical materials, whereas the modified components are differently colored. The SoloStar pen injector is a disposable insulin application device which has been marketed world-wide by Sanofi since 2007. The corresponding materials are used in SoloStar since 2007 and did not show any distinctive features.

**Additional Information Response Request:**

The sponsor provided a summary test report which generated the above results and conclusions, but did not provide detailed test report information. This was requested of the sponsor within an additional information request, which was received under supplement 14. The low-level supporting test documentation was reviewed and found to be supportive of the test summary reported conclusions.

This response to additional information was considered acceptable.

Dimensional specifications - "1.5mL Cartridges – Container Closure System"

ISO 11608-3 does not specify what the dimensional characteristics must be for a cartridge, simply that the dimensions must be recorded and repeatable for in process controls, and that fitment and verification of the interaction between the cartridge and intended pen injection system must be properly verified.

The sponsor provided the following information about the cartridge:



(b) (4)

Critical dimensions of the cartridge are reported by the sponsor to be inspected both before and after primary closure assembly to meet the above stated requirements.

This section is considered acceptable.

Dimensional specifications – Needle/Pen Interface

The sponsor explicitly states within product descriptions that they do not considered needles to be part of their marketed system; however the system does depend on the use of a needle. The sponsor states that a needle must be attached to the thread on the cartridge-end of the device by screwing it onto the cartridge. This thread was developed according ISO 11608-2 (1) which defines the standard for needles and the related thread. Additionally, although not explicitly cited as test evidence within the submission, the sponsor has promulgated device verification activities related to assurance that the system is capable of receiving standard needles. Further, all performance testing was completed with an 11608-2 compliant needle. Therefore, the submission is considered to have sufficient information to assure compatibility with an ISO-standard needle.

Adequate combination product risk analysis information

Within the original submission, the sponsor included documentation of a single risk management activity for the combination product. This was a “use failure mode effects analysis” and is created to identify system risks related to user interaction/the user interface.

This is a specialized document which is received by CDER human factors reviewers in order to evaluate and assess the appropriateness of mitigations deployed to help prevent mis-use of the product. However, in addition to this analysis, the Agency expects that system level or design level risk analysis activities will have been completed in order to assess risk from system design or implementation. This information could not be located within the file and so was requested via information request questions.

**Additional Information Response Request:**

The sponsor was asked to provide records of their risk management activities. This was requested of the sponsor within an additional information request, which was received under supplement 14.

In response, the sponsor provided a number of documents, including an overall risk management plan which described the overall risk management approach and phases as well as separate detailed documentation on the methods and output of the risk management plan.

Risks which were determined to be initially unacceptable by the sponsor were related to failure after a drop condition, biocompatibility, inability to visualize contents, blocked needle conditions, and incorrect device geometries. The firm implemented activities to mitigate the occurrence arm of the risk calculation for these items. These activities include changes to the manufacturing line, addition of labeling, or completion of tests to challenge the particular concern.

Some risks nominated by the sponsor were considered to be dependent on users and not principally controlled by design. These risks were considered and challenged within human factors assessments for the device.

The risk analysis approach used, as well as the sponsor's conclusion that the benefits of U300 outweigh system risks is considered supportable.

This response to additional information was considered acceptable.

**Device Constituent Part Clinical Use and Potential Failure Modes**

Clinical Use History within U300 Clinical Trials

The reviewer conducted a brief evaluation of clinical studies performed with the subject U300 device in order to understand if any clinical failures of the device were found to have occurred which were not accounted for within product testing or risk analysis activities.

Study Number/Name	Relevant Device Findings
PKD-10086; Bioequivalence of Lantus U100 and Lantus U300	Subject pen injector device does not appear to have been used within study
PKD-13560; Cross-over bioequivalence	Subject pen injector device does not appear to have been used within study
PKD-11627; 4-sequence Cross-over bioequivalence	Subject pen injector device does not appear to have been used within study
PKD-12270; 3-sequence 3-period Cross-over bioequivalence	Subject pen injector device does not appear to have been used within study
PKY-12335; 2-treatment Cross-over bioequivalence	1 report of "Malfunction injection device" under "special circumstances" description. No additional detail provided.
TDR-11626; Cross-over bioequivalence	No reported injector malfunctions within AE or safety event listings
PDY-12777; 16-week, open label, controlled	No reported injector malfunctions within AE or safety event listings
PDY-12456; 6-month, multicenter	No reported injector malfunctions within AE or safety event listings
PDY-11628; 6-month, multicenter	No reported injector malfunctions within AE or safety event listings
PDY-11628-ss; 6-month, admin sub-study	No reported injector malfunctions within AE or safety event listings
PDY-11629; 6-month, multicenter	No reported injector malfunctions within AE or safety event listings
PDY-11629-ss; 6-month, multicenter	No reported injector malfunctions within AE or safety event listings
PDY-12777; 6-month, multicenter	No reported injector malfunctions within AE or safety event listings

Within the “integrated summary of safety”, the sponsor collated reports of pen malfunctions reported within each of the studies. The sponsor states that reports or complaints about potential or alleged failure of the pens used in each of the studies were reported to the Sponsor via product technical complaint (PTC) form. For the subject device, two patients reported at least one device-related malfunction. The sponsor examined all reports of pen malfunctions and, if applicable, performed follow up. Five overdose events were experienced across three patients for each pen presentation studied (not all associated with the subject device). Upon follow-up, the sponsor found that the pen was not believed to have been a cause of the AE per the clinical site. For underdose, 18 events of hypoglycemia were reported to have been caused by device malfunction (not all associated with the subject device). Per the sponsor, after follow-up with each clinical site, relatedness of the hypoglycemic event to pen usage was excluded as reports were considered to result either from a transcription error, or from hypoglycemic events related to malfunction of device other than that of the study insulin, e.g. the malfunction occurred with the concomitant mealtime insulin pen or the commercial basal insulin pen used during the screening period.

Review of clinical study experience with the to-be-marketed device presentation did not raise questions of safety.

#### Clinical Use History within Similar Presentations

The sponsor provided a document for Agency review titled, “PERIODIC BENEFIT RISK EVALUATION REPORT/PERIODIC SAFETY UPDATE REPORT INSULIN GLARGINE” which contained listing of adverse event reports and safety issues for a number of products offered by Sanofi. This document was evaluated by the reviewer for events associated with the prior marketed Lantus SoloStar U100 version. This version was chosen for review as the device constituent part is substantially similar to the subject U300 pen device.

From April 2012 to April 2013, 2843 complaints regarding the SoloStar pen were received by Sanofi, however many of these events were reported to the firm as not being related to a serious adverse event or safety concern. Most events were reported as “without effect”, meaning that no symptoms or sequelae were reported. Additionally, in most instances, no conclusive root cause was able to be drawn from the reported complaint. The following is a listing of root causes which were not attributable to handling errors (i.e. the complaints listed below were caused by physical device malfunctions):

A total of 30 vents were related to manufacturing processes, including:

23 events related to mechanics separated from cartridge holder: corrective actions have been implemented to address the issue.

3 events related to out of specification administration forces: all devices were later found to be within specification

1 event (b) (4): The firm reports a corrective action in place to correct the issue

1 event (b) (4): The returned sample met all specifications

1 event of deformed dose selection grips: The firm reports this as a non-reproducible anomaly not related to the initial reported event.

1 event of soiled product: This report was caused by inadequate sealing of the product packaging

The above listing of complaints was evaluated by the reviewer and found to be acceptable given the following considerations:

- This premarket review is for device design only, the majority of above events appear to be related to product manufacturing. No deficiencies in product design have been raised after a review of

the complaints.

- The number of confirmed events is low in comparison to the number of devices manufactured and shipped by the sponsor
- The sponsor is engaged in ongoing improvement activities to address those findings which may lead to a future patient harm.

The above section is considered acceptable.

## VII. **CDRH Device Design Review Conclusions**

The CDRH reviewer performed an evaluation of the device constituent parts of the Insulin Glargine U300 combination product. The review was covered the following areas:

- Inspection of sponsor's design input activities
- Inspection of sponsor's design verification activities
- Confirmation of standards conformance where relied upon
- Inspection of test methods and results of bench top testing completed
- Inspection of stability testing completed on the device constituent part
- Review of risk analysis documentation and conclusions of safety
- Review of clinical and marketing experience of the device constituent part

Relevant finding within this review included:

- The sponsor completed adequate design control activities to characterize product requirements
- The sponsor provided sufficient documentation to verify implementation of product requirements with one exception. This exception is noted [REDACTED] (b) (4). This deviation is considered acceptable due to instructions for use indicating only a damp cloth should be used to clean the device.
- The device conforms with international and FDA-recognized consensus standards
- The device meets essential performance requirements, including device accuracy, in the following manner to a 95% confidence interval:
  - o If the dose is set to 1 unit (3.33 µL), the device was never off more than .03 units (.1 µL)
  - o If the dose is set to 40 units (133.33 µL), the device was never off more than .16 units (.52 µL)
  - o If the dose is set to 80 units (266.66 µL), the device was never off more than .32 units (1.05 µL)
- The device maintains essential performance after exposure to shipping conditions
- The device maintains essential performance after exposure to aging and in-use conditions equivalent to 12 months. However review of periodic real time test results and certification of ongoing accelerated and real-time aging studies qualify the device for an expiry of 36 months
- The sponsor has established and conducted appropriate device design risk management activities
- Prior clinical use and marketing history do not suggest an unacceptable rate of device constituent part malfunction. The sponsor has demonstrated that they are capable of monitoring and establishing corrective action plans related to device complaints.

Two recommendations for potential product labeling revisions include:

- 1) An explicit warning that the user should not use solvents other than water to clean the device. This is recommended [REDACTED] (b) (4)

- 2) A statement of the brand/type of needles the device is permitted to be used with (currently only the needle manufacturers are listed). This is recommended as the device has only been verified to function with ISO11608-2 compatible insulin needles.

**Recommendation:** Based on the above review results and considerations, the CDRH/ODE reviewer recommends **NDA approval**. If agreeable to the review division, two labeling recommendations have been made for consideration.

Digital Signature Concurrence Table		
Reviewer Sign-Off	Ryan J. Mcgowan -S	Digitally signed by Ryan J. Mcgowan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000352462, cn=Ryan J. Mcgowan -S Date: 2015.01.20 15:49:40 -05'00'
Team Lead 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: 2015.01.21 06:20:54 -05'00'
Branch Sign-Off	FDA	Digitally signed by Richard C. Chapman -A Date: 2015.01.21 10:16:16 -05'00'

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/s/  
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RYAN J MCGOWAN  
01/26/2015

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## 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)

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**Date of This Memorandum:** January 14, 2015  
**Requesting Office or Division:** Division of Metabolic and Endocrinology Products (DMEP)  
**Application Type and Number:** NDA 206538  
**Product Name and Strength:** Toujeo Solostar (insulin glargine [rDNA origin]) injection, 450 units per 1.5 mL (300 units per mL)  
**Submission Date:** January 8, 2015  
**Applicant/Sponsor Name:** Sanofi  
**OSE RCM #:** 2014-867-1  
**DMEPA Primary Reviewer:** Sarah K. Vee, PharmD  
**DMEPA Team Leader:** Yelena Maslov, PharmD

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#### 1 PURPOSE OF MEMO

Division of Metabolic and Endocrinology Products requested that we review the revised container label and carton labeling (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.<sup>1</sup>

#### 2 CONCLUSIONS

The revised container label can be improved from a medication error perspective. We recommend that the “Rx ONLY” statement be revised to be less prominent than other important information such as the “Subcutaneous use only” statement.

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<sup>1</sup> Vee, S. Label and Labeling Review for Toujeo Solostar (NDA 206538). 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 NOV 3. 32 p. OSE RCM No.: 2014-867.

**APPENDIX A. LABEL AND LABELING SUBMITTED ON JANUARY 8, 2015**

(b) (4)



2 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/  
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SARAH K VEE  
01/13/2015

YELENA L MASLOV  
01/16/2015

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**CLINICAL INSPECTION SUMMARY**

**DATE:** January 15, 2015

**TO:** Tania Condarco, M.D., Clinical Reviewer  
Lisa Yanoff, M.D., Clinical Team Leader  
Richard Whitehead, Regulatory Project Manager  
Division of Metabolism and Endocrinology Products (DMEP)

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

**THROUGH:** Janice Pohlman, M.D., M.P.H.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

Susan D. Thompson, M.D. for Kassa Ayalew, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 206538

**APPLICANT:** Sanofi-Aventis U.S. LLC

**DRUG:** Insulin glargine [rDNA origin] injection, 300 Units/mL

**NME:** No

**THERAPEUTIC CLASSIFICATION:** Standard Review

**INDICATIONS:** To improve glycemic control in adults with diabetes mellitus

CONSULTATION REQUEST DATE: June 12, 2014

CLINICAL INSPECTION SUMMARY GOAL DATE: January 25, 2015

DIVISION ACTION GOAL DATE: February 25, 2015

PDUFA DATE: February 25, 2015

## I. BACKGROUND

Sanofi-Aventis U.S. LLC is seeking approval of insulin glargine [rDNA origin] injection, 300 Units/mL (HOE901-U300) to be available in a 1.5 mL glass cartridge assembled in a disposable pen injector to improve glycemic control in adults with diabetes mellitus. Insulin glargine U300 (HOE901-U300) is a more concentrated formulation of insulin glargine U100 (HOE901), a recombinant analog of human insulin which has been marketed as Lantus<sup>®</sup> for more than 12 years. Studies requested for inspection are the following:

- **EFC12347** A 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus<sup>®</sup> in Insulin-Naïve Patients with Type 2 Diabetes Mellitus Not Adequately Controlled with Non-Insulin Antihyperglycemic Drugs with a 6-month Safety Extension Period

The study involved 249 centers in 15 countries. A total of 1396 patients were screened, and 878 patients with type 2 diabetes mellitus inadequately controlled with non-insulin antihyperglycemic drug(s) were randomized. The first patient was enrolled August 31, 2012 and the last patient completed September 11, 2013. The primary efficacy endpoint was change in HbA1c from baseline to endpoint (Month 6).

- **EFC12456** A 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus<sup>®</sup> Injected in the Morning or Evening in Patients with Type 1 Diabetes Mellitus with a 6-month Safety Extension Period

The study involved 147 active centers in 12 countries. A total of 846 patients were screened and 549 patients were randomized. The first subject was enrolled September 12, 2012. The last subject completed to Month 6 on September 11, 2013 (only data reported in the clinical study report). The primary efficacy endpoint was change in HbA1c from baseline to endpoint (Month 6).

- **EFC11628** A 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus<sup>®</sup> Both Plus Mealtime Insulin in Patients with Type 2 Diabetes Mellitus with a 6-month Safety Extension Period

The study involved 180 sites in 13 countries. There were 1177 patients screened and 806 patients randomized. The first patient was enrolled December 28, 2011 and the last patient completed January 30, 2013. The primary efficacy endpoint was change in HbA1c from baseline to endpoint (Month 6).

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 206538 in accordance with Compliance Program 7348.811. General instructions were also provided with this assignment.

## II. RESULTS (by Site):

<b>Name of CI/ Site #</b>	<b>Protocol # and # of Subjects Randomized</b>	<b>Inspection Date</b>	<b>Final Classification</b>
Mark P. Christiansen, M.D. Site 840002  Site 840115  Site 840223	EFC11628 3 subjects  EFC12456 12 subjects  EFC12347 12 subjects	10/20 – 31/2014	Pending No Action Indicated (NAI) <i>Interim</i>
Raymond Fink, M.D. Site 840004  Site 840123  Site 840235	EFC11628 6 subjects  EFC12456 10 subjects  EFC12347 4 subjects	7/22 – 25/2014	No Action Indicated (NAI)
Michael F. Jardula, M.D. Site 840243	EFC12347 12 subjects	8/11 – 13/2014	No Action Indicated (NAI)
Richard Bergenstal, M.D. (for Glen Matfin, M.D.) Site 840085	EFC11628 11 subjects	7/28 – 8/01/2014	No Action Indicated (NAI)
Michael Reeves, M.D. Site 840144  Site 840262  Site 840039	EFC12456 5 subjects  EFC12347 9 subjects  EFC11628 17 subjects	8/11 – 19/2014	Pending No Action Indicated (NAI)
Ronald Goldenberg Site 124209  Site 124105	EFC12347 8 subjects  EFC12456 8 subjects	10/06 – 10/2014	Pending No Action Indicated (NAI)

Site 124007	EFC11628 8 subjects		
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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, preliminary communication with the field, and review of EIR; final classification is pending letter to site.

**1. Mark P. Christiansen, M.D.**

Diablo Clinical Research, Inc.

2255 Ygnacio Valley Rd.

Suite M

Walnut Creek, CA 94598

- a. What was inspected:** The inspection focused on informed consent documents, credentials and training, IRB correspondence and approvals, randomization, case report forms (CRFs), delegation of duties, 1572s, financial disclosures, monitoring logs, source documents, adverse events, and drug accountability records. For Study EFC11628, there were nine subject records reviewed; for Study EFC12456, there were 12 subject records reviewed; for Study EFC12347, there were four subject records reviewed.
- b. General observations/commentary:** For Study EFC11628, there were nine subjects screened, three subjects enrolled, and three subjects who completed the study. For Study EFC12456, there were 20 subjects screened, 12 subjects enrolled, and eight subjects who completed the study. For Study EFC12347, there were 21 subjects screened, 12 subjects enrolled, and 10 subjects who completed the study.

The files were well organized and legible. There was no under-reporting of adverse events noted. The primary efficacy endpoint was verifiable for all three studies except for one subject. Under Study ERC12456, for Subject 840115004, a (b) (4) laboratory report indicated that the baseline (Visit 3) value for HbA1c was 8.5. This value is inconsistent with the data listings which indicated a baseline value of 9.5 for HbA1c for subject 840115004. The laboratory reports were directly uploaded into the database by (b) (4) laboratory and not the PI.

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.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not

available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

**2. Raymond Fink, M.D.**

8851 Center Dr.  
Suite 212  
La Mesa, CA 91942

- a. What was inspected:** The inspection focused on informed consent documents, credentials and training, IRB correspondence and approvals, randomization, case report forms (CRFs), delegation of duties, 1572s, financial disclosures, monitoring logs, source documents, and drug accountability records. All subject records were reviewed.
- b. General observations/commentary:** For Study EFC12347, five subjects were screened, four subjects were enrolled, and four subjects completed the study. One subject (003) moved to another state and transferred to another site. For Study EFC12456, 10 subjects were screened, 10 subjects enrolled, and seven subjects completed the study (Subjects 004 and 008 were terminated for poor compliance; Subject 010 withdrew for lack of efficacy). For Study EFC11628, seven subjects were screened, six subjects were enrolled and six subjects completed the study.

The files were well organized. Training on pen usage was documented in all the subject charts. After the study ended, a disc with all the reported data was given to the site by the sponsor. The staff was knowledgeable and able to answer questions and resolve any inconsistencies in the data. Subjects met eligibility criteria. Past medical records were retrieved if needed. There was no under-reporting of adverse events. The primary efficacy endpoint data was verifiable.

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.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

**3. Michael F. Jardula, M.D.**

Desert Oasis Healthcare Medical Group  
275 N. El Cielo Road  
Suite D-412

Palm Springs, CA 92262-6972

- a. **What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), institutional review board (IRB) correspondence, Form FDA 1572, financial disclosures, training records, subject training for the device, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria checklist, enrollment logs, subject source documents including medical history records, drug accountability, and adverse event reports. All 17 subject records were reviewed.
- b. **General observations/commentary:** Seventeen subjects were screened, 12 subjects were enrolled, and nine subjects completed the study. The first subject was screened on 12/17/2012 [REDACTED] (b) (4) Independent Review Board was the IRB of record.

There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable. Patients were trained on the use of the study drug pens/needles, glucose meters, and diaries by the study staff. There were no reported cases of pen device malfunctions at this site.

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.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

**4. Richard Bergenstal, M.D.**  
International Diabetes Center  
3800 Park Nicollet Blvd  
Minneapolis, MN 55416-2527\*

\* The initial inspection assignment was for Glen Matfin, M.D. Dr. Bergenstal was the initial principal investigator for the study. Dr. Matfin was a sub-investigator and then became the principal investigator. He is no longer employed at the Center [REDACTED] (b) (6)

- a. **What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), institutional review board (IRB) correspondence, Form FDA 1572, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria checklist, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. All 16 subject records were reviewed for informed consent. Six enrolled

subjects' records underwent full chart review (001, 004, 006, 009, 012, 014). All five screen failure charts were reviewed.

- b. General observations/commentary:** There were 16 subjects screened for the study and 11 subjects enrolled. The first subject was screened on 3/14/12. The (b) (4) Institutional Review Board was the IRB of record.

The study site dispensed the wrong batch numbers of insulin to five of the subjects. Initially, all investigational product (IP) kit numbers were labeled the same. The sponsor then changed the label and the IVRS system directed specific kit numbers to be dispensed to subjects. The sponsor was contacted when the discrepancy was identified. The subjects did not receive the wrong study medication and were able to remain in the study.

It was suspected that Subject 004 was not being honest about the recording of blood sugar levels in the diary as the HgA1C did not reflect the results. Subject 006 was not compliant with completing the diary. The primary efficacy endpoint for all subjects was verifiable.

There was no under-reporting of adverse events. There were two adverse events found that were reported on the eCRF but not in the sponsor data line listings. (Subject 009 had bronchitis and Subject 014 had basal cell carcinoma). The sponsor was contacted during the inspection and stated that the data cut-off was 1/20/2013 and both events occurred after the cut-off date.

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, was issued.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

**5. Michael Reeves, M.D.**  
725 Glenwood Drive  
Suite E-6  
Chattanooga, TN 37404

- a. What was inspected:** Informed consent forms were reviewed for all subjects. IRB approvals and correspondence, financial disclosures, 1572s, training records, and sponsor and monitor correspondences were reviewed. Source documents were reviewed for all subjects including medical histories, laboratory results, ECGs, adverse events, concomitant medications, efficacy data, and subject diaries. Source data was compared to sponsor reported data line listings. Drug accountability records were compared to source

documentation for three subject records for EFC11628, one subject record for EFC12347, and two subject records for EFC12456.

- b. **General observations/commentary:** For Study EFC11628, there were 20 subjects screened, 17 subjects enrolled, and 14 subjects that completed the study. For Study EFC12347, there were nine subjects screened, nine subjects enrolled, and eight subjects that completed the study. For Study EFC12456, there were five subjects screened, five subjects enrolled, and five subjects that completed the study. All subjects at this site in study EFC11628 randomized to the investigational product were signed informed consent for the optional sub-study in October 2012 using the obsolete substudy informed consent Version 1-0, rather than the current Version 2-0. However, all of the eligible subjects declined to participate in the sub-study.

All original informed consent documents for each of the three studies were reviewed. EFC11628 Subject 017 initially declined to notify their primary care physician (PCP) of their participation in the study; however, the site sent a notification letter to the PCP about the subject's participation. This discrepancy was not noted until after the closure of the site. Review of subject records found that the subject elected to notify the PCP in subsequent revisions of the informed consent document.

The studies were generally performed in accordance with the protocols. Subject records were noted to be complete, legible, and organized. Laboratory tests required by the protocol were conducted [REDACTED] (b) (4). The Principal Investigator delegated study tasks to the Study Coordinator and other study staff as permitted by the protocol; however, he retained sole responsibility for informed consent, determination of subject eligibility, review of laboratory reports, and dosing titration. Study involvement is documented by signatures on source documents.

All of the enrolled subjects met the eligibility criteria (inclusion/exclusion) for the three studies reviewed. All adverse events and/or inter-current illnesses appear to have been documented. Efficacy data points were verified for all subjects in all three studies against the data line listings provided by the sponsor.

There were a few protocol deviations noted. There were two instances of omitted concomitant medications that were identified between the source documents and the eCRF for Study EFC12347 (Z-pack and an herbal supplement *gymnena sylvestre*). During review of investigational product accountability records for Study EFC11628, it was noted that three subjects (004, 019, and 021) had log discrepancies (found during the inspection to be due to recording errors of the study coordinator) and one subject (021) had a kit which was not dispensed as directed by the IVRS system. In Study EFC12456, one subject record (004) lacked documentation of the initial dispensation of the

pen devices.

Temperature logs for the refrigerator used to store investigational product were reviewed. The site did document a weekly verification of temperatures and alarms; however those records do not document temperature checks for the weeks of 02/18/13, 02/25/13, and 03/04/13. It was discovered during the studies that the site had incorrectly toggled the Transit and Arrived buttons on the TempTale device, causing some data to be lost when the logs were downloaded. A Note to File dated 8/9/14 explained the site's temperature controls; the site recently began downloading the TempTale logs on a weekly basis.

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.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

**6. Ronald Goldenberg, M.D.**

LMC Diabetes and Endocrinology  
531 Atkinson Avenue, Suite 17  
Thornhill, Ontario L4J 8L7  
Canada

- a. What was inspected:** The inspection focused on informed consent documents, credentials and training, IRB correspondence and approvals, randomization, case report forms (CRFs), delegation of duties, 1572s, financial disclosures, monitoring logs, source documents, subject diaries, temperature logs, and drug accountability records. All subject records for all three studies were reviewed for informed consent; eight subject records from each study were reviewed for inclusion/exclusion and the primary efficacy endpoint. Approximately 50% of records were reviewed for secondary endpoints and adherence to protocol assessments.
- b. General observations/commentary:** For Study EFC11628, there were 17 subjects screened, eight subjects enrolled, and eight subjects who completed the study. For Study EFC12456, there were 13 subjects screened, eight subjects enrolled, and seven subjects who completed the study. For Study EFC12347, there were 11 subjects screened, eight subjects enrolled, and eight subjects who completed the study. A central IRB, Institutional Review Board Services (b) (4) had oversight of the studies. The CRO (b) (4) monitored the studies.

Records were well organized and legible. There were a small number of adverse

events and concomitant medications that were not included in the data listings for EFC12347 and EFC12456. It was clarified during the inspection that the data submitted to the application had a cut-off date of September 11, 2013. For all data prior to this date, there was no evidence of under-reporting of adverse events. The primary efficacy endpoint data was verifiable. Protocol deviations consisted primarily of out of window visits and study drug non-compliance. None were listed as the sponsor did not consider them significant.

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.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of five domestic clinical sites and one foreign clinical site.

Observations noted above for Drs. Fink, Jardula, Bergenstal, Reeves, and Goldenberg are based on the review of the Establishment Inspection Reports (EIRs). Observations noted above for Dr. Christiansen are based on communications from the field investigator. An inspection summary addendum will be generated if conclusions change upon OSI final classification.

No site was issued a Form FDA 483; the final classification for five sites is NAI (No Action Indicated). The preliminary interim classification for Dr. Christiansen's site is NAI, pending final review of the EIR. Data from these sites are considered reliable based on the available information.

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

*{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.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Susan D. Thompson, M.D. for  
Kassa Ayalew, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

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/s/  
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CYNTHIA F KLEPPINGER  
01/15/2015

JANICE K POHLMAN  
01/15/2015

SUSAN D THOMPSON  
01/15/2015



Food and Drug Administration  
Office of Device Evaluation  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**CDRH Human Factors Review**

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

DATE: October 17, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID  
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID  
TO: Hyon Kwon, Medical Officer, CDER/OND/OAP/DTOP  
Charlene Williamson, Regulator Project Manager, CDER/OND/ODEII/DMEP

SUBJECT: **NDA 206538**  
Applicant: Sanofi-Aventis LLC  
Drug: insulin glargine  
Device: peninjector  
Intended Use: diabetes  
CDRH CTS Tracking No. 1400610

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Date: 2014.10.22 14:02:50 -04'00'

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QuynhNhu Nguyen, Combination Products Human Factors Specialist  
(Human Factors Premarket Evaluation Team - HFPMET)

**Ronald D. Kaye**  
-S

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DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Ronald D. Kaye -  
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Ron Kaye, Human Factors and Device Use-Safety Team Leader (HFPMET)

## **CDRH Human Factors Review**

### ***Overview and Recommendation***

The Division of Metabolism and Endocrinology Products, Office of New Drugs, Center for Drugs Evaluation and Research requested a Human Factors (HF) consultative review of the insulin glargine peninjector under NDA 206538. CDRH HFPMET was previously consulted during the IND review, IND 112400, for a human factors validation study protocol in July 2013. The final human factors validation study protocol addressed all FDA comments.

Sanofi reported that they conducted 5 different usability studies to validate the safe and effective use of the U300 pen injector, the associated label and packaging as well as the instructions for use and additional information material. Notably, the human factors validation study included 74 patients and healthcare providers participants. Health care professionals did not receive formal training. Half of the patient participants received no formal training prior to using the pen for the first time. These participants were provided the U300 pen injector and IFU, but were not specifically instructed to review the IFU prior to their first assigned injection. The other half of the patient users were assigned to receive realistic, though minimal training with a training decay period of 24 hours. There were multiple reports of use errors for the tasks of performing safety test, injecting a full dose, holding the peninjector for 5 seconds at the injection site, and selecting the correct dose while dialing. It is worth noting that most of the participants performed the second injection successfully.

Upon further follow up with study participants and assessment of root cause, there was no specific implication of an inadequate user interface. Therefore, this human factors reviewer recommends that the human factors validation study should be found acceptable.

# CDRH Human Factors Review

## Combination Product Device Information

**Submission No: NDA 206538**  
Applicant: Sanofi-Aventis LLC  
Drug: insulin glargine  
Device: peninjector  
Intended Use: diabetes

## CDRH Human Factors Involvement History

- 5/2/2014: CDRH HFPMET was consulted to review human factors validation study report.
- 10/17/2014: CDRH HFPMET provided review recommendations to CDER/DMEP

## Summary of Human Factors Related Information

Sanofi reported that they conducted 5 different usability studies to validate the safe and effective use of the U300 pen injector, the associated label and packaging as well as the instructions for use and additional information material.

- IFU Readability and Comprehension:** The IFU design was equivalent to the commercial IFU, by having the final text, layout and images. This study included 15 representative adult participants. The participants were not provided with any training or other introduction to the device. No participant showed any lack of understanding related to any information given in the IFU, even if some participants took more than two minutes to find certain pieces of information or needed the questions to be explained to them again
- Prescribing Instructions Readability and Comprehension:** The study included 15 prescribers (1 Internal Physician, 2 General Practitioners, 3 Nurse Practitioners, 4 CDE, and 5 Endocrinologists). Participants were not provided with any training or other introduction to the device. No difficulties or failures had been observed.
- Dispensing Instructions Readability and Comprehension:** The study included 15 pharmacists (10 retail pharmacists and 5 hospital pharmacists) Participants were not provided with any training or other introduction to the device. Prior to answering the knowledge probes related to the information material, pharmacists completed some differentiation tasks

#	Question	Difficulty	Failure
1	What are the main differences between this insulin pen compared to other insulin pens?	None	None
2	How many units of insulin does one pen contain?	None	None
3	What do the materials say about the use of needles with this pen?	None	None
4	Why should a patient not re-use needles with this device?	None	None
5	How many pens would a patient need if they were taking 30 units a day, for 30 days?	None	1/15

Table 1: Summary of results for comprehension/readability study on dispensing

The one incorrect answer was from a hospital pharmacist, who stated 5 pens. The participant exhibited signs that he was unsure how to calculate the total. When debriefed

as to how he calculated the answer, the participant said he divided 150 by the total units (900). When asked why 150, he said he did not know where that number came from. The moderator then asked how many units for 30 days (at 30 units per day), and what is the total number of units delivered by each pen. The participant responded correctly with 900 units total and a total volume of 450 units. The consequence of this miscalculation would have resulted in patient receiving more pens than required for a month supply.

4. Differentiation Study: This study included 62 participants. See table 2 below.

Group	Sample Description
Patients (N=31)	Vial and syringe: 15 Pen users: 16
Nurses (N=16)	Certified Diabetes Educator: 1 Registered Nurse: 12 Licensed Practice Nurse: 3
Pharmacists (N=15)	Retail Pharmacists: 10 Hospital Pharmacists: 5

Table 2: differentiation study groups and subgroups.

All participants had been unfamiliar with the U300 pen injector and package prior to the study and received no formal training on the U300 pen injector and package, which they saw for the first time at the onset of their first differentiation tasks. Table 3 list of user tasks for the study.

Task Description	Completed by
Differentiation of pen in normal lighting conditions. The following competitor and Sanofi pen injection devices were included as comparators: - Apidra SoloStar (SoloStar) - Lantus SoloStar (SoloStar) - NovoLog FlexPen (Novo Nordisk) - Levemir FlexPen (Novo Nordisk) - Victoza <sup>(b)</sup> <sub>(4)</sub> Pen (Novo Nordisk) - Humalog KwikPen (Eli Lilly) - Humulin N (Eli Lilly)	Patients, Nurses, Pharmacists
Differentiation of pen in reduced lighting conditions.	Patients
Differentiation of package in normal lighting conditions.	Patients, Nurses, Pharmacists

Table 3: List of tasks covered by the differentiation study

No difficulties or failures had been observed.

5. Human Factors Simulated Use Study: Prior to the development and conduct of the Human Factors validation studies, Sanofi reported that several exploratory usability and

design optimization activities were performed. This study included 74 participants. See Table 4 and 5 for the breakdown of the study participants, and associated characteristics.

User Group (N: Number of Participants)	Distinct User Group (N: Number of Participants)	Sub-group (N: Number of Participants)	Training (N: Number of Participants)
Patients N = 60	Adult Patients with Diabetes Mellitus (aged 18 and older)	Vial-and-syringe-experienced N = 30	Trained N = 15
			Untrained N = 15
			Trained N = 15
		Pen-experienced N = 30	Trained N = 15
			Untrained N = 15
			Untrained N = 15
HCPs (Health Care Professionals) N = 15	RN (Registered Nurses) and CDE (Certified Diabetes Educators)	Pen-experienced N = 15	Untrained N = 15

Table 4: User Groups

Sample Characteristics	Description
Visual Impairment	Use of glasses or contact lenses: 48/60
	Diagnosed Retinopathy: 3/60
	Glaucoma: 2/60
	Cataracts: 1/60
	Color Blindness: 1/60
Manual impairment	Dexterity or strength issues: 12/60
	Neuropathy: 9/60
	Arthritis in hands or fingers: 16/60

Table 5: Associated Participants Characteristics

Health care professionals did not receive formal training. Half of the patient participants received no formal training prior to using the pen for the first time. These participants were provided the U300 pen injector and IFU, but were not specifically instructed to review the IFU prior to their first assigned injection. The other half of the patient users were assigned to receive realistic, though minimal training with a training decay period of 24 hours. Table 6 provides a summary of the study results according to study tasks.

Task	Risk	Trial 1	Trial 2	Overall
Open packaging. Safe removal from packaging.	MEDIUM	50/75	50/75	0/150
Knowledge of expiration date.	HIGH		0/75	
Open pen cap.	MEDIUM	0/75	0/75	0/150
Knowledge of how to identify empty pen/in-use device.	MEDIUM		72/75	
Attach needle after removing needle seal and needle caps.	MEDIUM	0/75	0/75	0/150
Perform safety test with any dose until insulin shows at the tip.	MEDIUM	2/75	1/75	3/150
Select correct dose.	HIGH	1/75	0/75	1/150
Dose dialing task	HIGH	3/75	0/75	3/150
Knowledge of correct injection site.	MEDIUM		0/75	
Injects correct dose - Number of units.	HIGH	2/75	0/75	2/150
Injects correct dose -Holding time	HIGH	2/75	0/75	2/150
Remove needle (avoiding needle blocking).	MEDIUM	0/75	0/75	0/150
Dispose needle.	MEDIUM	0/75	0/75	0/150
Close cap.	HIGH	0/75	0/75	0/150
Knowledge of pen storage. – Before use	HIGH		0/75	

Table 6: Summary of Study Results

#### Summary Discussion of Use Error, and Root Cause Analysis

- 3 participants failed to perform safety test during Injection (2 in trial 1 and 1 in trial 2).
  - One participant stated that they had apprehension about using the pen. When performing the injection the participant abandoned use of the instructions and began performing the injection without guidance. During the second injection the participant was able to correctly perform the safety.
  - One participant did not view the safety test as an important step because they currently do not perform the test at home with their current pen. During the second injection the participant was able to correctly perform the safety test.
  - One participant was under the impression that they only needed to do the safety test once instead of every time they perform an injection. The participant was able to correctly perform the safety test using the instructions during their first injection trial without error.

Sanofi stated that the instructions clearly state at the top of Step 3 to “Always do a safety test before each injection.” No design mitigation is required.

- 1 participant failed to select the correct dose during Injection 1 and dose dialing task. The participant was in a hurry, stopped reading the instructions after performing a safety test and did not make sure that the dose was dialed correctly. During the second injection and the dosing task at the end of the study the participant was able to correctly dial their

dose without error or difficulty. It should be noted that if the user selects wrong dose that leads to a clinically significant underdose or overdose. However, Sanofi reported that the instructions for use of this pen have devoted a large section and two images to instruct users on how to read the dose window correctly. Furthermore the pen window and dial are all clearly printed and distinguishes the difference between an odd and even number.

- 2 participants failed to inject the full dose during the first injection trial.
  - One participant was in a hurry and abandoned the IFU early on in the procedure and began performing the injection without guidance. The participant was able to correctly perform the procedure during the second trial by following the instructions.
  - One participant was over confident due to his experience injecting and did not have his glasses resulting in the participant not paying attention to the details of the procedure in the IFU. Participant stated that his vision was bad and that he had difficulty reading the instructions. The participant was able to correctly perform the procedure during the second trial by following the instructions.

It should be noted that if the user does not press the dose button all the way in before removing the needle from the skin; this leads to a clinically significant underdose. However, Sanofi reported no design mitigation is required because the analysis did not identify any issues associated with the device or IFU.

- 2 participants failed to hold for 5 seconds after pressing the injection button during the first injection trial. Both participants performed the procedure based on what they do with their pen at home instead of following the IFU during the procedure. When they removed the pen from the injection site there was no liquid on the pad signifying loss of drug, which is evidence that the participant was overall successful in receiving their full dose (even though they did not wait for 5 seconds).
- 2 participants failed to identify units of insulin remaining in pen.
  - One participant stated that there were 325 units remaining in the pen. This participant was not wearing their glasses and initially thought one of the lines on the plunger rod was the marking for measurement. Once the participant was able to identify the plunger they had no difficulty identifying that 75 units were left in pen. This participant was asked to identify several different levels of fluid, which the participant did so successfully.
  - One participant stated that there were 125 units remaining in the pen. The participant initially read the marks wrong and thought that the level was 25 units over the 100 unit mark instead of 25 units under the 100 unit mark. The participant got confused because they were initially holding the pen upside down.

It should be noted that if the user injects with empty pen which leads to a clinically significant underdose. Sanofi believes that no design mitigation is required, and stated that the insulin scale on the side of the cartridge is clearly labeled.

- 1 participant failed to identify concentration of insulin in pen. This participant identified the concentration of the insulin in the pen as 200 units/mL instead of 300 units/mL. The participant initially tried to compute the answer somehow because they were confused at how the labeling presented the units per milliliter as “units/mL” which is a standard form

of writing units per milliliter. The participant did not recalculate the dose. This participant struggled with several tasks during the trial and displayed lower than normal cognitive ability.

- 2 participants failed to select the correct dose during dose dialing task. One participant correctly dialed both doses during their injection trials but dialed 23 instead of 24 during their first dose dialing task. One participant correctly dialed both doses during their injection trials but dialed 37 instead of 38 during their first dose dialing task. Both participants were in a hurry and did not take the time to confirm that they had dialed correctly. The participant had already demonstrated that they could correctly dial their dose during both injection trials. Both participants were asked to perform two extra dose dial tasks for which, the participant was able to correctly select their dose. It should be noted that if user selects wrong dose which leads to a clinically significant underdose or overdose. However, Sanofi reported that the instructions for use of this pen have devoted a large section and two images to instruct users on how to read the dose window correctly. Furthermore the pen window and dial are all clearly printed and distinguishes the difference between an odd and even number.

**Appendix 1: Prior CDRH Human Factors Reviews of IND 112400 (by Chronological Order)**

APPEARS THIS WAY ON ORIGINAL



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration  
Office of Device Evaluation  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

DATE: July 29, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID

THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID

TO: Rich Whitehead, Regulatory Project Manager, CDER/OND/ODEII/DMEP  
Please see letter ready deficiencies (in blue) on pages 2 through 4.

SUBJECT: IND 112400  
Applicant: Sanofi US Services  
Drug: HOE901-U300 insulin glargine  
Device: Peninjector  
Intended Use: treatment of type I and II diabetes  
CDRH CTS Tracking: ICC1300283; CON1311783

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Date: 2013.07.30 13:31:18 -04'00'

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QuynhNhu Nguyen, Combination Products Human Factors Specialist

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Date: 2013.07.30 15:40:53 -04'00'

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Ron Kaye, Human Factors and Device Use-Safety Team Leader

## CDRH Human Factors Review

### *Overview and Recommendations*

The Division of Metabolism and Endocrinology Products, Office of New Drugs, Center for Drug Evaluation and Research requested a Human Factors consultative review of a draft human factors validation study protocol dated May 24, 2013 submitted under IND 112400 by Sanofi for HEO901-U300, insulin glargine, long acting human insulin and its peninjector delivery device. This product is intended for to treat type I and II diabetes. The review of the protocol identifies several areas that required additional information and/or clarification. Please transmit the following deficiencies to Sanofi:

1. On page 4 of the document titled “Human Factors Validation Study” you referred to a “differentiation validation study.” However, it is unclear if this “differentiation study” is a separate study. Additionally, there is no information in the study protocol that describes in detail how you plan to conduct this differentiation validation study. We expect that all representative users include healthcare providers, patients, pharmacists, etc. be included in this differentiation study. We also expect that the differentiation study is a component of the overall human factors validation study. Please provide additional information and clarification and revise the protocol (if needed).
2. On page 4 of the “Human Factors Validation Study” document, you stated that “It is therefore likely that patients and healthcare providers would already be familiar with the use of the U300 pen injector based on their experience with SoloStar. Nevertheless, it is planned to conduct a simulated use validation study only in the patient group since this group is more likely to have disease-inherent limitations that may affect their ability to handle the device. However, as the color of the U300 pen injector and packaging is different from the marketed SoloStar pens, we will include 15 health care professionals in the final differentiation validation study in order to support that pharmacists, doctors, and nurses are able to easily differentiate the U300 pen injector and packaging from the following marketed comparator devices.” However, on page 28 of the document titled “Human Factors Validation Master Study Plan” you stated that “...30 US participants, all of whom have been diagnosed with diabetes.”

Furthermore, you stated that “As color-blindness...does not impact handling tasks, it is not intended to specifically include color-blind users in the simulated use validation study....However, for differentiation tasks...color-blind users will be included in the final differentiation study...”

Please address the following:

- a. We are unclear who will be the study participants in your human factors validation study. We request that you revise the protocol to provide a clear and concise description of the intended user groups for the proposed product and their associated user characteristics i.e. injection experience, disease-related limitations (retinopathy and neuropathy) etc.

- b. We request that you clearly describe in the protocol potential use-related risks associated with color-blind users, and discuss whether they represent a unique user group for your proposed device color scheme.
  - c. We ask that your protocol provides the breakdown of the numbers of study participants and describe how the study participants are representative of the intended user groups.
  - d. Please plan to submit results of a study that includes minimum of 15 participants per group of distinct users consistent with your indicated population of users, and also describe sufficient demographic information to indicate how these participants are representative of the intended population of users. If users fall into distinct groups that are expected to interact differently with the device (different user tasks) or carry different risk profiles (e.g. level of disabilities/impairments) then the testing should include representative samples from each of these groups, divided roughly evenly but where the total could be no less than 25.
3. You proposed to include the following comparators pen for the final differentiation study:

Pen Name	Manufacturer
Apidra SoloStar	Sanofi
Lantus SoloStar	Sanofi
NovoLog FlexPen	Novo Nordisk
Victoza <sup>(b) (4)</sup> Pen	Novo Nordisk
Humalog KwikPen	Eli Lilly

Please provide a rationale for your selection of these comparators. You may include a discussion how your product can be differentiated from its comparators in terms of type of insulin; design features; color scheme for both delivery system, its container, and labeling, etc.

Regarding the document titled “Human Factors Validation Master Study Plan”, please address the following

- 4. You stated on page 7 that “the design of the device has been optimized...” You also provided a summary of preliminary studies in Appendix B of the document. It was not clear based on the summary how the device design has been optimized. Please add one column to the summary table, and provide information specifically on changes that were made to the product design, IFU, and/or training.
- 5. You provided on page 10 the main findings and conclusions from the training survey. However, we are not clear on the specific content of the training that will be provided as part of your human factors validation study. Please provide this information in your revised protocol. Also, please include a description of the training decay.
- 6. You stated on page 32 of the untrained participants must familiarize themselves using whatever means they would do at home before administering their first injection. We are

not clear the intent of this statement. We expect that you provide the device and its associated labeling to the study participants and allow them to use the product as they normally would use it in an actual use setting.

7. You provided in table 11 the tasks and associated study technique, performance, observed behavior, and subjective response. We are unclear on the information that you provided under the observed behavior column, and whether it is your intention to provide examples, or a complete listing of potential use errors associated with the tasks. We are unclear why some of the tasks have N/A listed in the observed behavior column. In addition, regarding the subjective response, we expect that you ask open-ended questions of participants at the end of a usability validation, such as, "Did you have any difficulty using this device? [If so] can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.
8. Related to comment 7, please also note that we expect your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. Every test participant who experiences a "failure" (does something that would have led to harm under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant.
9. You stated (b) (4)  
[REDACTED] We are unclear on the intent of this statement. (b) (4)  
[REDACTED] Please remove this word in this section and other sections in your protocol.
10. We ask that include all information about your human factors validation study in one document rather than providing it two separate documents, Human Factors Validation Study and Human Factors Validation Master Study Plan. Please consolidate the two documents and provide a single document that contains the revised human factors study protocol.

## Summary of Human Factors Related Information

The following table provides the highlights of the proposed human factors validation study:

Keyword	Description
Study Objective	The main objective of the proposed validation study is to validate that the new U300 prefilled insulin pen design, including associated Instructions for Use (IFU), can be correctly, safely and effectively used by the intended user audiences without patterns of (preventable) use errors that would result in harm to a patient or user.
Users/ Study Participants	A total of thirty (30) representative participants will complete the study with each participant performing two unaided simulated injections (60 injections total).
Use Cases/ Study Groups	All participants will be assigned to one of two groups: trained or untrained. Each group will consist of users with different degrees of experience. The trained group (N=15) will be trained by a Certified Diabetes Educator (CDE) or a trained moderator during their first session before returning for their second session to perform two unaided injections. The untrained group (N=15) will receive no training and will familiarize themselves using whatever means they would do at home before administering their first injection as an unaided injection. This represents all of the potential use cases for patients who are prescribed to use a new insulin pen, as patients of different degree of experience (see Section 8.1.1) may or may not be provided training before using the pen on their own.
User Training	Representative training will be provided to participants as identified in our diabetes training survey study.
User Tasks – Task Criticality	All critical tasks and contexts are evaluated in the study, and are based on a prior risk analysis.
User Tasks – Unanticipated Use Errors	Un-anticipated (off-nominal) use errors are also tracked in this study.
Data Collection – Objective and Subjective Data	Objective and subjective data will be obtained to evaluate effectiveness and safety of the injection procedure and the clarity of the IFU with respect to the performance of those tasks. Subjective data will be collected in narrative form.
Data Collection – Success and Failure	Success criteria (what constitutes success or failure in the behavior of a given task) for all critical tasks have been established. All failures will be followed by a formal debriefing

## Appendix 1: Device Information

The U300 pen injector is a disposable pen injector containing a total of 450 units of insulin. Doses can be set from 1 to 80 units in increments of 1 unit. It is a fully mechanical device, containing no electronic components.

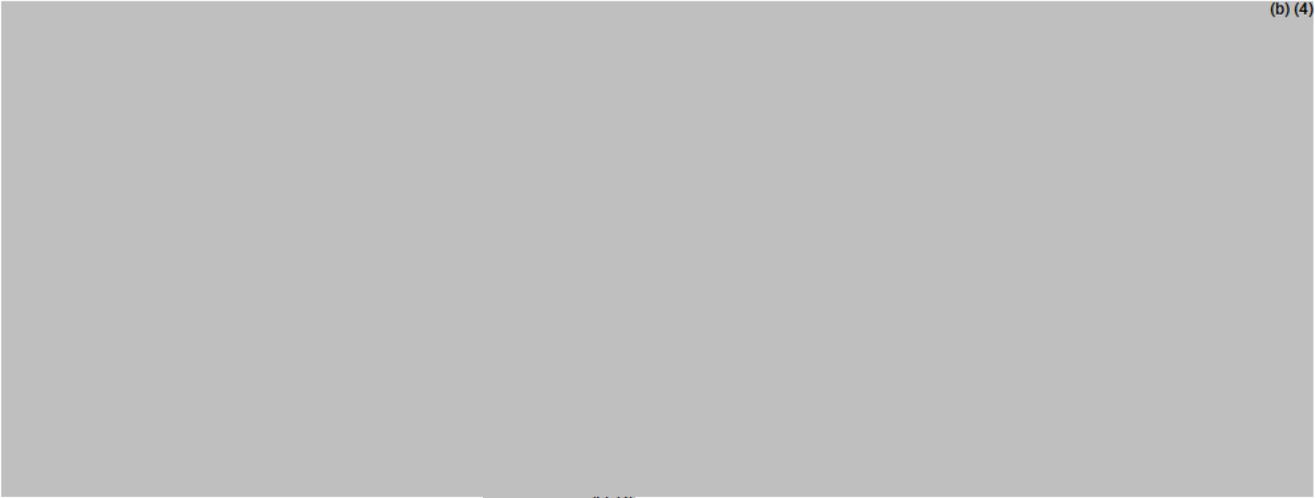


Figure 1 The U300 pen injector; (b) (4) is a provisional drug name.



Figure 2: Detailed Component Description



**DEPARTMENT OF HEALTH AND HUMAN SERVICES**      **MEMORANDUM**

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Food and Drug Administration  
Office of Device Evaluation  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

(b) (4)

[Redacted content]



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration  
Office of Device Evaluation  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

DATE: October 15, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID

THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID

TO: Rich Whitehead, Regulatory Project Manager, CDER/OND/ODEII/DMEP

SUBJECT: IND 112400  
Company: Sanofi Aventis US  
Drug: insulin glargine (U300)  
Device: pen injector (b) (4)  
CDRH CTS Tracking: ICC1300488

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Date: 2013.10.15 15:21:09 -04'00'

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ronald D. Kaye  
-S

Digitally signed by Ronald D. Kaye -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Ronald D. Kaye -S,  
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Date: 2013.10.15 17:36:26 -04'00'

Ron Kaye, Human Factors and Device Use-Safety Team Leader

## CDRH Human Factors Review

### *Overview and Recommendations*

The Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, Office of New Drugs, Center for Drugs Evaluation and Research requested a Human Factors consultative review of a meeting package for the IND 112400 submitted by Sanofi Aventis. The meeting package includes three questions (#10, 11, and 12) regarding the human factors study protocols for both device configurations peninjector (b) (4)

The following provides CDRH HF's proposed responses to those questions:

#### 11.4 Device – Peninjector

##### 11.4.1 Differentiation

10. As requested by the Division, Sanofi herein provides the pen differentiation study protocol and requests concurrence on the design and objectives of the proposed study (provided in Appendix Section 13.6), in particular with regard to the following:

- a) Study participants
- b) Comparator pen-device selection
- c) Task scenarios for each user group

CDRH HF's Proposed Response: We agree with your general proposal on study participants, comparator pen-device selection, and task scenarios for each user group included the U300 peninjector differentiation validation study protocol. We recommend that you recruit at least 15 users combined that have vision and manual impairments.

(b) (4)

## CDRH Human Factors Review

### Combination Product Device Information

Submission Number: IND 112400

Applicant: Sanofi-Aventis US Inc

Drug Constituent: insulin glargine (rDNA origin), long acting human insulin analog

Device Constituent: peninjector (b) (4)

Intended Use: improve glycemic control in adults with diabetes mellitus

Review Materials:

EDR Location: \\CDSESUB1\evsprod\IND112400\112400.enx

Supporting Document Number: 66

eCTD Sequence Number: 0064

Letter Date: 9/20/2013

Stamp Date: 9/20/2013

Cover Letter: <\\CDSESUB1\evsprod\IND112400\0064\m1\us\cover.pdf>

1571 Form: <\\CDSESUB1\evsprod\IND112400\0064\m1\us\fda-form-1571.pdf>

### CDRH Human Factors Involvement History

Date	Involvements
9/20/2013	CDRH HF team was requested to review HF related questions # 10, 11, and 12 in the meeting package
10/15/2013	CDRH HF team provided proposed responses to those questions.

### Summary of Review Materials

#### U300 Peninjector Differentiation Validation Protocol (Dated September 19, 2013, version 1.0).

Sanofi indicated that the differentiation study is a separate study from the human factors validation study and will be conducted to validate both the pen and package differentiation. The following sections provide a summary of the differentiation features of the U300 peninjector:

- green primary color
- unique pattern (see Figure 1, U300 Packaging)



Figure 1: U300 packaging, top view

- dose selector, window design, injection button, and cartridge holder

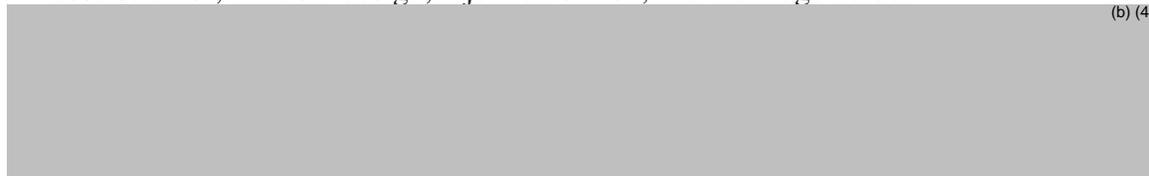


Figure 2: U300, Cartridge Holder, Dose Button, Window Design, and Cap Orientation

The following comparators will be used in the differentiation study:

1. Apidra SoloStar (SoloStar)
2. Lantus SoloStar (SoloStar)
3. NovoLog FlexPen (Novo Nordisk)
4. Levemir FlexPen (Novo Nordisk)
5. Victoza <sup>(b) (4)</sup> Pen (Novo Nordisk)
6. Humalog KwikPen (Eli Lilly)

The study will include 75 representative users (15 patients with vial and syringe experience, 15 patients with pen experience, 15 prescribers, 15 pharmacists, and 15 nurses). Of these users, 5 users will be with color vision deficiencies (deuteranomaly). No training will be provided to users.

The following table provides an evaluation of severity of clinical harm based on the potential mix-up of the U300 and the comparator devices.

Product Name	Manufacturer	Severity (Action Profile)	Probability of Mix-up due to Color, Form, and Function*	Selection Decision and Rationale
Apidra SoloStar	Sanofi	HIGH	Low, as pen body color and brand/insulin color are different.	Included, as all pen injector devices rated with high severity will be included.
Lantus SoloStar	Sanofi	LOW	Medium, as body color is of different in shade only, while brand/insulin color is different.	Included, as body color is similar and based on previous authority feedback.
NovoLog FlexPen	Novo Nordisk	HIGH	Medium, as body color is different. However, brand/insulin color could be seen as a shade similar to green by participants with color vision deficiencies.	Included, as all pen injector devices rated with high severity will be included.
NovoLog 70/30 FlexPen	Novo Nordisk	MEDIUM	Low, as both body color and brand/insulin color are different.	Not included as the probability of mix-up is very low and other pen injector devices of the same Novo Nordisk product portfolio (associated with higher severity) are already included.
Levemir FlexPen	Novo Nordisk	LOW	Medium, as body color is different, however, brand/insulin color is similar.	Included, as brand color is similar and based on previous authority feedback.
Victoza (b) (4) Pen	Novo Nordisk	HIGH	Low, as body color and brand/insulin color are different.	Included, as all pen injector devices rated with high severity will be included.
Humalog KwikPen	Eli Lilly	HIGH	Low, as body color and form different, very little color on small label, no tinted cartridge holder.	Included, as all pen injector devices rated high in with high medical risk medication.
Humalog Mix 75/25	Eli Lilly	MEDIUM	Low, as body color and form different, very little color on small label, no tinted cartridge holder.	Not included, as pen injector device is very similar to the Humalog KwikPen (associated with higher severity) already included in the study.
Humalog Mix 50/50	Eli Lilly	MEDIUM	Low, body color and form different, very little color on small label, no tinted cartridge holder.	Not included, as pen injector device is very similar to the Humalog KwikPen (associated with higher severity) already included in the study.
Byetta	Eli Lilly	MEDIUM	LOW, as different in function, form, body color and brand/insulin color.	Not included, due to the very low probability of mix-up based on different functional principle/handling concept, form, body color, and brand color.

Table 1: Evaluation of Severity of Clinical Harm Due to Potential Mix-Ups

Tables 4 and 5 of the protocol provided a list of tasks and scenarios for patients and healthcare providers, which basically included selecting packing, selecting device, and storing the device.

Human Factors Protocol for Summative Simulated Use Testing (Dated September 19, 2013 by

(b) (4)

[Redacted]

The protocol stated that differentiation between U- 300 insulin and other insulins on the market (including a variety of U-100 insulin brands and U-500 Humulin R [Redacted])

[Redacted] will be assessed. The comparator products are as follows:

- [Redacted]
- U-100 insulin to be included in testing are: Apidra, Lantus, Levemir, Novolog U-100 (Aspart), Humalog U-100 (Lispro), Novolog 70/30 (mix in vial), Humulin 70/30 (mix in vial), Humulin R, Humulin N, Humalog mix, Human insulin U100

The study will include 75 representative users. The following table provides a breakdown of the user groups:

	Lay users	Nurses and HCPs who inject	HCPs who teach	Pharmacists who dispense
Insulin injection experienced	15	15	15	15
Insulin injection inexperienced	15	N/A	N/A	N/A
Total = 75	30	15	15	15

Table 2: Syringe Human Factors Validation Study – Participant Breakdown

Representative training will be provided to patients. Patients will meet one-on-one with a Certified Diabetes Educator for a 30-minute session focused on teaching proper injection techniques. Period of at least one hour of potential learning decay will be scheduled between any participant training and testing session.

[Redacted]

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/s/  
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RICHARD E WHITEHEAD

11/12/2014

This review was added by RPM for QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID

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## **LABEL AND LABELING 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\*\*\***

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**Date of This Review:** November 3, 2014  
**Requesting Office or Division:** Division of Metabolic and Endocrinology Products (DMEP)  
**Application Type and Number:** NDA 206538  
**Product Name and Strength:** Toujeo Solostar (insulin glargine [rDNA origin]) injection, 300 units per mL  
**Product Type:** Combination (Drug + Device)  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Sanofi  
**Submission Date:** April 24, 2014  
**OSE RCM #:** 2014-867  
**DMEPA Primary Reviewer:** Sarah K. Vee, PharmD  
**DMEPA Team Leader:** Yelena Maslov, PharmD

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## 1 REASON FOR REVIEW

Sanofi submitted NDA 206538 on April 24, 2014 for review. DMEP requested that we review labeling for this NDA including human factors study results, container label, carton and package insert labeling, and instructions for use (IFU).

## 2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Human factors assessment of Toujeo SoloStar comprised of three parts (i.e. usability, differentiation, and comprehension questions) to ensure that the product is safe for use in each step of medication use process. This is especially important due to the fact that postmarketing reports show medication errors with concentrated insulin product (i.e. Humulin R U-500) where misunderstanding of the concentrated nature of the product resulted overdoses that led to patient harm, including death. Although U-500 insulin is available only in a vial presentation, the lessons learned from postmarketing experience with U-500 insulin applies to this product (i.e. calculation errors in prescribing and use of U-100 or volumetric syringes to administer U-500, dispensing wrong product).

### 3.1 READABILITY/COMPREHENSION STUDY: IFU, PRESCRIBING, DISPENSING

Overall, the three user groups were able to answer the readability and comprehension questions successfully using the materials provided to them. The aim of this part of the study was to ensure that patients and nurses are able to understand the contents of the IFU and

follow it, pharmacists are able to calculate the dose and dispense the correct number of pens, and prescribers are able to prescribe correctly without performing unnecessary calculations.

1. Prescriber Group: There were no failures reported for the prescriber user group (12 of 15 had U-500 experience). The information materials included the DHCP letter, the HCP Guide and the Patient Brochure.
2. Patient Group: There was at least one instance in answering Questions 3, 4, 5, and 9 where patients could not locate the information on the IFU and indicated that they would either contact their HCP or search online for the information. In addition, for Question 7 (“Imagine you have a sight problem which means it is difficult for you to handle the pen. What do the instructions advise you to do?”), several patients did not understand the question therefore answered incorrectly (i.e. thought the question was referring to injection site).
3. Pharmacist Group: One failure was reported for the pharmacist user group (7 of 15 had U-500 experience) where the pharmacist miscalculated the number of pens to be dispensed for the given scenario (30 units per day for 30 days) based on materials provided (i.e. DHCP letter, HCP Guide, and Patient Brochure). The pharmacist indicated that he usually relies on the computer system to calculate the correct unit and dose but did not indicate that he had difficulty with the information materials. This failure would not result in any dosing errors leading to patient harm.

### **3.2 DIFFERENTIATION**

There were no failures reported for the differentiation study for carton and pen (normal lighting and reduced lighting) across all user groups tested in the study.

### **3.3 USABILITY VALIDATION STUDY**

In terms of usability, human factors study results demonstrated that Toujeo prefilled pen can be used safely and effectively by trained users. However, some untrained users (11/14 errors were made by 9 different untrained users, with 5 of these 11 committed by participants who were untrained and use a needle and syringe) encountered difficulties while administering this product using the prefilled pen. The difficulties the untrained user group encountered have also been reported with the use of other similar marketed prefilled injection pen devices and have been managed reasonably well through labeling (e.g., Lantus, Apidra, Humalog, etc.). Additionally, the types of observed errors are not unique to the proposed pen (i.e. failure to perform safety test, failure to select correct dose, failure to hold button for 5 seconds, etc.). Failure to perform these tasks would result in underdoses in most instances and would not be

expected to cause serious harm acutely. Furthermore, the SoloStar pen-injector platform that is proposed for this product has been approved for Lantus and Apidra.

Overall, we find the results of the human factors study acceptable. The study results reported no observed calculation errors across all user groups (i.e. multiplying or dividing by 3, resulting in 3-fold over or under doses). The proposed labeling appears to have managed the risks. However, we recommend that training be provided before first use of the product to ensure safe and effective use of the device to deliver the dose of insulin glargine U-300 due to the new concentration of insulin as well as due to the postmarketing medication errors reported with the currently marketed U-500 concentrated insulin.

#### **4 CONCLUSION & RECOMMENDATIONS**

The Human Factors Study demonstrated that users are able to use the prefilled pen safely and effectively with no reported instances of calculation errors (i.e. multiplying or dividing by 3, resulting in 3-fold over or under doses). However, U-300 will be a new insulin concentration and misunderstanding of the concentration may result in serious harm to the patient, especially in cases of overdose. As a result, DMEPA concludes that proper education and training are provided prior to first injection to ensure that the users are able to safely use this product.

The proposed container label, carton and insert labeling can be improved to increase the readability and prominence of important information to promote the safe use of the product, to mitigate any confusion, and to clarify information.

##### **4.1 RECOMMENDATIONS FOR SANOFI**

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

- A. Physician Insert: Section 2.2 Initiation of TRADENAME therapy
  - 1. Add the statement: "Prior to initiation of TOUJEO, patients should be trained by their healthcare professional on proper use and injection technique. Training reduces the risk of administration errors such as needle sticks and incomplete dosing. Refer to the accompanying Instructions for Use for complete administration instructions with illustrations."
- B. Pen Label and Carton Labeling
  - 1. Add the statement "For Single Patient Use Only". The safety warning, "For Single Patient Use Only", should be placed immediately below the established name so that there is no intervening matter between the established name and the warning. This will ensure that the warning is in the same viewing angle and field as the drug name and less

likely to be overlooked. We also recommend using a red-shaded and bolded letters in a contrasting colored box to enhance visibility and prominence.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Toujeo Solostar that Sanofi submitted on April 24, 2014.

<b>Table 2. Relevant Product Information for Toujeo Solostar</b>		
<b>Initial Approval Date</b>	N/A	
<b>Active Ingredient</b>	insulin glargine [rDNA origin]	
<b>Indication</b>	a long- acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus.	
<b>Route of Administration</b>	Subcutaneous Injection	
<b>Dosage Form</b>	Solution	
<b>Strength</b>	300 units/mL	
<b>Dose and Frequency</b>	Individualized dosing once daily	
<b>How Supplied</b>	1.5 mL SoloStar® disposable prefilled pen	
<b>Storage</b>	<b>Not in-use (unopened)</b>	<b>In-use (opened)</b>
	<b>Refrigerated</b>	<b>(See Temperature Below)</b>
	Until expiration date	(b) (4) days Room temperature only (Do not refrigerate)
<b>Container Closure</b>	<p>The insulin glargine solution for injection 300 U/mL is packaged in a multidose container (cartridge) closed with a flanged cap with (b) (4) sealing disk and a plunger stopper.</p> <p>The U300 pen injector is composed of components (b) (4)</p>	

**APPENDIX B. HUMAN FACTORS STUDY**

**B.1 Study Design**

**Container Label and Carton Labeling Used in the Study**

(b) (4)



**B.1.1 Readability/Comprehension Study: IFU**

**Study Participants: Untrained**

**Table 15 - Sample description for the readability/ comprehension study.**

<b>Characteristics</b>	<b>Sample Description</b>
Gender	Female: 7 Male: 8
Age	34 – 71 with 6 participants aged > 64
Health Status	Type II Diabetes Mellitus: 13 Type I Diabetes Mellitus: 2
Device Experience	Pen users: 8 Vial and syringe users: 7
Educational Level	High school diploma: 5 Some college: 6 Bachelor or postgraduate degree: 4
Medicine Literacy Level (assessed by the REALM-SF test).	High school or equivalent: 10 Lower than high school: 5

**Questions**

1. What do the instructions advise you to do if you have any questions?
2. What advice do the instructions give about sharing your <sup>(b) (4)</sup> pen with somebody else?
3. Which needles can you use with this pen?

4. What advice do the instructions give about cleaning your (b) (4) pen?
5. You should check the insulin in your pen before injecting. How should the insulin look?
6. When should you use a new needle?
7. Imagine you have a sight problem which means it is difficult for you to handle the pen. What do the instructions advise you to do?
8. You should take care when handling needles. Why is this?
9. Imagine you think your (b) (4) pen is damaged. What advice do the instructions give?
10. Why must you never re-use a needle?
11. The instructions tell you to always carry a spare pen. Why should you do this?

### **B.1.2 Readability/Comprehension Study: Prescribing**

#### **Study Participants: Untrained**

15 prescribers (1 Internal Physician, 2 General Practitioners, 3 Nurse Practitioners, 4 CDE, and 5 Endocrinologists). 12 of 15 prescribers had U500 experience.

#### **Study Design**

Provided DHCP letter, the HCP Guide and the Patient Brochure.

Questions:

1. How many units would a patient, who is currently taking once daily 32 units of Lantus need when they switch to taking (b) (4) once daily?
2. What should you do after discontinuing (b) (4) U 300 insulin glargine and transferring the patient to another medication?
3. What do the materials say about the use of needles with this pen?
4. Why should a patient not re-use needles with this device?

### **B.1.3 Readability/Comprehension Study: Dispensing**

#### **Study Participants: Untrained**

The sample included 15 pharmacists (10 retail pharmacists and 5 hospital pharmacists). Seven of the pharmacists had previous experience with U500.

#### **Study Design**

Provided DHCP letter, the HCP Guide and the Patient Brochure.

Questions:

1. What are the main differences between this insulin pen compared to other insulin pens?
2. How many units of insulin does one pen contain?
3. What do the materials say about the use of needles with this pen?
4. Why should a patient not re-use needles with this device?
5. How many pens would a patient need if they were taking 30 units a day, for 30 days?

#### B.1.4 Differentiation

##### Study Participants: Untrained

**Table 18 - Sample description for the differentiation study: groups and subgroups.**

<b>Group</b>	<b>Sample Description</b>
Patients (N=31)	Vial and syringe: 15 Pen users: 16
Nurses (N=16)	Certified Diabetes Educator: 1 Registered Nurse: 12 Licensed Practice Nurse: 3
Pharmacists (N=15)	Retail Pharmacists: 10 Hospital Pharmacists: 5

**Table 20 - List of tasks covered by the differentiation study.**

<b>Task Description</b>	<b>Completed by</b>
Differentiation of pen in normal lighting conditions. The following competitor and Sanofi pen injection devices were included as comparators: <ul style="list-style-type: none"><li>- Apidra SoloStar (SoloStar)</li><li>- Lantus SoloStar (SoloStar)</li><li>- NovoLog FlexPen (Novo Nordisk)</li><li>- Levemir FlexPen (Novo Nordisk)</li><li>- Victoza <sup>(b) (4)</sup> Pen (Novo Nordisk)</li><li>- Humalog KwikPen (Eli Lilly)</li><li>- Humulin N (Eli Lilly)</li></ul>	Patients, Nurses, Pharmacists
Differentiation of pen in reduced lighting conditions.	Patients
Differentiation of package in normal lighting conditions.	Patients, Nurses, Pharmacists

### B.1.4 Human Factors Simulated Use Validation Study

The main objectives of the validation study were to:

- Validate that the new U300 pen injector including the associated material, can safely, effectively, efficiently and satisfyingly be used by the intended user audiences without patterns of (preventable) use errors that would result in harm to a patient or user.
- Validate that there are no remaining aspects of the new device design, package or instructions (see Section 9.1.1) that lead to confusion, failures, high-risk errors, or patient safety risks.

#### Study Participants:

**Table 22 - User Groups**

User Group (N: Number of Participants)	Distinct User Group (N: Number of Participants)	Sub-group (N: Number of Participants)	Training (N: Number of Participants)
Patients N = 60	Adult Patients with Diabetes Mellitus (aged 18 and older)	Vial-and-syringe-experienced N = 30	Trained N = 15
			Untrained N = 15
		Pen-experienced N = 30	Trained N = 15
			Untrained N = 15
HCPs (Health Care Professionals) N = 15	RN (Registered Nurses) and CDE (Certified Diabetes Educators)	Pen-experienced N = 15	Untrained N = 15

**Table 23 - Patient sample description for the Human Factors simulated use validation study.**

Sample Characteristics	Description
Diabetes Diagnosis	Type I Diabetes Mellitus: 18/60 Type II Diabetes Mellitus: 42/60
U500 Experience	At the time of protocol review (see also Section 2.2) the inclusion of U500 experienced patients was not explicitly requested by FDA; still, Sanofi made every reasonable effort in order to find U500 users willing to participate in this study. While this proved to be impossible, Sanofi managed to include an important number of HCPs with prior U500 experience in the sample of the information material validation study (see Section 8.3.2). This even seems more appropriate because HCPs are at the origin of the information chain and are considered the key factor when it comes to correct dosing of medication. Other than HCPs in a formative study (see Section 7.4) not a single patient or nurse in any of the formative (see Section 7.4) or summative studies (see Section 8.5.10) ever started to calculate doses.
Age	22 – 81 (median: 51 years)
Gender	Female: 31/60 Male: 29/60

## Training

**Table 24 - Description of Training Steps**

Step	Duration	Description
1	~4 minutes	Introduction: the Certified Diabetes Educator (trainer) introduced the patient to drug purpose, storage and dosing schedule, followed by general information and warnings.
2	~9 minutes	Review and Demonstration: together with the patient, the trainer reviewed the instructions for use (Steps 1-6) and demonstrated the use of pen. The patient was asked to follow along while viewing the instructions for use.
3	~5 minutes	Supervised Practice: the trainer observed the patient performing the injection procedure and corrected any errors.
4	~2 minutes	Knowledge Probes: the trainer probed participants on memory for key elements of the procedure.

## Session

**Table 25 - Session overview for trained group.**

Session 1	Session 2 (next day, that is a 24 h training-trial interval)			
Trained by CDE Supervised Injection	Injection #1: Unaided Injection (Odd or Even/Large or Small Dose)	Insulin Remaining Task	Injection #2: Unaided Injection (Opposite Dose)	Split Dose Task, Knowledge Probes, IFU feedback and Dial Dose Task
Context: Doctor's Office	Context: Home			

**Table 26 - Session overview for untrained group.**

Session 1			
Injection #1: Unaided Injection (Odd or Even/Large or Small Dose)	Insulin Remaining Task	Injection #2: Unaided Injection (Opposite Dose)	Split Dose Task, Knowledge Probes, IFU feedback, and Dial Dose Task
Context: Home (for patients) Context: Professional Environment (health care professionals)			

## User tasks in validation trial

**Table 28 - Anticipated user tasks with study technique and range of acceptable performance.**

Task	Risk	Study Technique	Range of Acceptable Performance
Open packaging. Safe removal from packaging.	MEDIUM	Participants were required to remove the pen from the packaging.	User had to open package without dropping the device.
Knowledge of expiration date.	HIGH	Participants were asked to identify the expiration date on a pen	User had to identify expiration date.
Open pen cap.	MEDIUM	Participants were observed regarding removal of the cap.	User had to remove cap.
Knowledge of how to identify empty pen/in-use device.	MEDIUM	Participants were presented a used pen and were asked to indicate the number of units remaining in the pen.	User had to identify the number of remaining units.
Attach needle after removing needle seal and needle caps.	MEDIUM	Participants were observed regarding attachment of needle (and removal of needle caps).	User had to attach needle correctly to the pen, including removing of needle caps and protective seal.
Perform safety test with any dose until insulin shows at the tip.	MEDIUM	Participants were observed regarding performance of a safety test until insulin appears	Performed with any dose and any number of repetitions until insulin shows at the needle tip.
Select correct dose.	HIGH	Participants were observed regarding the accuracy of their dose selection.	Had to dial to prescribed dose.
Knowledge of correct injection site.	MEDIUM	Participants were asked to indicate the allowable injection sites.	Had to identify the abdomen, arm or thigh.
Injects correct dose.	HIGH	Participants were observed regarding their injection technique.	Had to insert needle correctly. Had to press dose button all the way in. Had to hold pen in site and keep button pressed for 5 seconds. Had to remove needle from skin before removing needle from device.
Remove needle (avoiding needle blocking).	MEDIUM	Participants were observed regarding their removal of the needle.	Had to remove needle from pen.
Dispose needle.	MEDIUM	Participants were observed regarding disposal of the needle.	Had to dispose needle in puncture resistant container.
Close cap.	HIGH	Participants were observed regarding the replacement of the pen cap.	Had to replace pen cap.
Knowledge of pen storage.	HIGH	This was validated through two knowledge questions.	Had to identify storage conditions for new and in-use pen.

**Table 29 - Unanticipated user tasks with study technique and range of acceptable performance.**

<b>Task</b>	<b>Risk</b>	<b>Study Technique</b>	<b>Range of Acceptable Performance</b>
Knowledge about drug concentration.	HIGH	Participants were asked to identify the concentration of the insulin.	Participants had to know correct answer (300 units/mL).
Knowledge about dose splitting.	MEDIUM	Participants were asked to describe how to deliver a dose larger than their remaining units.	Had to describe process of using a new pen to deliver remaining units or full dose.
Knowledge about not withdrawing insulin via a syringe.	MEDIUM	Participants were asked to respond to a knowledge probe about what the instructions say regarding removing insulin with a syringe.	Participant had to know that insulin should not be withdrawn with a syringe.
Remove needle (avoiding needle stick injury)	HIGH	Participants were observed regarding their removal of the needle.	No needle sticks occur.

## B.2 Results

### B.2.1 Readability/Comprehension Study: IFU

For Questions 3, 4, 5, and 9 there had been single cases where a participant could not find some information, they all indicated that they would either call their HCP, call the hotline number given in the IFU, or look in the internet in order to get further assistance.

Three Participants were unable to find the information related to Question 7 (“Imagine you have a sight problem which means it is difficult for you to handle the pen. What do the instructions advise you to do?”). There had been a particular struggle with the understanding of the question as many participants thought it referred to injection site issues.

### B.2.2 Readability/Comprehension Study: Prescribing

**Table 16 - Summary of results for comprehension/readability study on prescribing.**

#	Question	Difficulty	Failure
1	How many units would a patient, who is currently taking once daily 32 units of Lantus need when they switch to taking (b) (4) once daily?	None	None
2	What should you do after discontinuing (b) (4) U-300 insulin glargine and transferring the patient to another medication?	None	None
3	What do the materials say about the use of needles with this pen?	None	None
4	Why should a patient not re-use needles with this device?	None	None

### B.2.3 Readability/Comprehension Study: Dispensing

**Table 17 - Summary of results for comprehension/readability study on dispensing**

#	Question	Difficulty	Failure
1	What are the main differences between this insulin pen compared to other insulin pens?	None	None
2	How many units of insulin does one pen contain?	None	None
3	What do the materials say about the use of needles with this pen?	None	None
4	Why should a patient not re-use needles with this device?	None	None
5	How many pens would a patient need if they were taking 30 units a day, for 30 days?	None	1/15

### B.2.4 Differentiation

**Table 21 - Summary of results for the differentiation tasks.**

ID	Task	Close calls	Error
R151v2.1.1	Differentiating Box	None	None
R151v2.1.2	Differentiating Pen – normal lighting	None	None
R151v2.1.3	Differentiating Pen – reduced lighting	None	None

### B.2.4 Human Factors Simulated Use Validation Study

An overall success rate of 99.4% (2236/2250) across all participant critical tasks (injection trials and knowledge probes) was observed. Also, a total of 95% (142/150) of all injection trials were performed without any form of failure.

**Table 30 - Summary of failures for the HF simulated use validation study (observations per total cases) – anticipated user tasks.**

Task	Risk	Trial 1	Trial 2	Overall
Open packaging. Safe removal from packaging.	MEDIUM	50/75	50/75	0/150
Knowledge of expiration date.	HIGH		0/75	
Open pen cap.	MEDIUM	0/75	0/75	0/150
Knowledge of how to identify empty pen/in-use device.	MEDIUM		72/75	
Attach needle after removing needle seal and needle caps.	MEDIUM	0/75	0/75	0/150
Perform safety test with any dose until insulin shows at the tip.	MEDIUM	2/75	1/75	3/150
Select correct dose.	HIGH	1/75	0/75	1/150
Dose dialing task	HIGH	3/75	0/75	3/150
Knowledge of correct injection site.	MEDIUM		0/75	
Injects correct dose - Number of units.	HIGH	2/75	0/75	2/150
Injects correct dose -Holding time	HIGH	2/75	0/75	2/150
Remove needle (avoiding needle blocking).	MEDIUM	0/75	0/75	0/150
Dispose needle.	MEDIUM	0/75	0/75	0/150
Close cap.	HIGH	0/75	0/75	0/150
Knowledge of pen storage. – Before use	HIGH		0/75	
Knowledge of pen storage.- In use	HIGH		0/75	

**Table 31 - Summary of failures for the HF simulated use validation study (observations per total cases) – unanticipated user tasks.**

Task	Risk	Trial 1	Trial 2	Overall
Knowledge about drug concentration.	HIGH		1/75	
Knowledge about dose splitting.	MEDIUM		0/75	
Knowledge about not withdrawing insulin via a syringe.	MEDIUM		0/75	
Remove needle (avoiding needle stick injury)	HIGH	0/75	0/75	0/150

**Table 33 - Summary of reported difficulties for the HF simulated use validation study (observations per total cases).**

<b>Task</b>	<b>Trial 1</b>	<b>Trial 2</b>	<b>Overall</b>
Did you have any trouble, or do you have concerns, with any part of the injection process? (Mentioned in Trial 1 were taking off the needle, safety shot, and a perceived awkward holding position.)	3/75	0/75	3/150
Q: Did you have any difficulty attaching the needle? (Mentioned in Trial 1 was screwing on the needle to be a little difficult.)	1/75	0/75	1/150
Q: Did you have any difficulty dialing your specified dose?	0/75	0/75	0/150
Q: Did you have any difficulty pressing the injection button to administer the full dose?	0/75	0/75	0/150
Q: Did you have any difficulty removing the needle after the injection? (Mentioned for Trial 2 was needle removal.)	0/75	1/75	1/150
Q: Did you have any difficulty determining the number of units remaining?		0/75	

## **APPENDIX C. LABELS AND LABELING**

### **C.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with postmarket medication error data, we reviewed the following Toujeo Solostar labels and labeling submitted by Sanofi on April 24, 2014.

- Container label
- Carton labeling
- Instructions for Use
- Medication Guide

### **C.2 Label and Labeling Images**



2 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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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.**  
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/s/  
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SARAH K VEE  
11/03/2014

YELENA L MASLOV  
11/03/2014