CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210605Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	April 15, 2020
To:	Michael G. White, PhD Senior Regulatory Project Manager **Division of Diabetes, Lipid Disorders, and Obesity (DDLO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Ankur Kalola, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name) and Dosage Form and Route:	SEMGLEE (insulin glargine injection) for subcutaneous use, prefilled pen (100 units/mL, U-100) SEMGLEE (insulin glargine injection) for subcutaneous use, 10 mL vial (100 units/mL, U-100)
Application Type/Number:	NDA 210605
Applicant:	Mylan

Reference ID: 4624597

1 INTRODUCTION

On December 16, 2019 Mylan submitted for the Agency's review a Resubmission-Complete Response (CR) Amendment (Facility, Labeling and Safety Information Provided) for SEMGLEE (insulin glargine injection), for subcutaneous use (NDA 210605). The purpose of this resubmission is to fully respond to facility and safety deficiencies outlined in the Agency's CR Letter dated August 28, 2019.

The proposed indication for SEMGLEE (insulin glargine injection), for subcutaneous use is to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. SEMGLEE (insulin glargine injection), for subcutaneous use is not recommended for treating diabetic ketoacidosis.

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 Diabetes, Lipid Disorders, and Obesity (DDLO) on December 19, 2019 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for SEMGLEE (insulin glargine injection), for subcutaneous use (prefilled pen and 10 mL vial).

DMPP conferred with the Division of Medication Error, Prevention and Analysis (DMEPA) and a separate DMEPA review of the IFUs was completed on March 5, 2020.

2 MATERIAL REVIEWED

- Draft SEMGLEE (insulin glargine injection), for subcutaneous use PPIs and IFUs received on December 16, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 6, 2020.
- Draft SEMGLEE (insulin glargine injection), for subcutaneous use Prescribing Information (PI) received on December 16, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 6, 2020.
- Patient Labeling Review for SEMGLEE (insulin glargine injection), for subcutaneous use dated August 20, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPIs and IFUs the target reading level is at or below an 8th grade level.

Additionally, 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.

In our collaborative review of the PPIs and IFUs we have:

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

4 CONCLUSIONS

The PPIs and IFUs 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 PPIs and IFUs 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 PPIs and IFUs.

Please let us know if you have any questions.

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

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

Memorandum

Date: April 10, 2020

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

Monika Houstoun, Associate Director for Labeling, (DMEP)

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

Subject: OPDP Labeling Comments for SEMGLEE™ (insulin glargine injection) for subcutaneous use

NDA: 210605

In response to DMEP's consult request dated December 19, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the NDA resubmission for SEMGLEE™ (insulin glargine injection) for subcutaneous use.

PI, PPI, and IFU: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DMEP on April 4, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DMEP April 4, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Ankur Kalola at (301) 796-4530 or Ankur.Kalola@fda.hhs.gov.

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ANKUR S KALOLA
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MEMORANDUM

REVIEW OF REVISED LABELS AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 13, 2020
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 210605
Product Name and Strength:	Semglee (insulin glargine) solution, 100 units/mL, 10 mL vial and 3 mL prefilled pen
Applicant/Sponsor Name:	Mylan GmbH (Mylan)
FDA Received Date:	March 11, 2020
OSE RCM #:	2017-842-4
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Mylan submitted revised container labels and carton labeling for NDA 210605 Semglee (insulin glargine) on March 11, 2020. The revisions are in response to recommendations that we made during a previous labeling review.[a]

2 CONCLUSION

Mylan implemented all of our recommendations for their proposed labels and labeling and we have no additional recommendations at this time.

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[a] Conrad A. Review of Revised Label and Labeling for Semglee (NDA 210605). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Mar 5. RCM No. 2017-842-3.

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/s/

ARIANE O CONRAD
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MEMORANDUM

REVIEW OF REVISED LABELS AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 5, 2020
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 210605
Product Name and Strength:	Semglee (insulin glargine) solution, 100 units/mL, 10 mL vial and 3 mL prefilled pen
Applicant/Sponsor Name:	Mylan GmbH (Mylan)
FDA Received Date:	December 16, 2019
OSE RCM #:	2017-842-3
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Mylan submitted their response to a complete response letter for NDA 210605 Semglee (insulin glargine) on December 16, 2019. We reviewed labels and labeling for Semglee (Appendix A) to determine if they are acceptable from a medication error perspective.

2 REGULATORY HISTORY

We evaluated Mylan's HF validation studies, submitted April 27, 2017 and February 28, 2019, in prior reviews[a,b]. The NDA received a complete response (CR) on May 17, 2018 and Mylan's response to the CR received a subsequent CR on August 28, 2019.

[a] Conrad A. Label and Labeling and Human Factors Results Review for Semglee (NDA 210605). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Apr 4. RCM No. 2017-842 and 2017-1868.
[b] Flint J. Label and Labeling and Human Factors Results Review for Semglee (NDA 210605). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Aug 15. RCM No.: 2017-842-1 and 2017-1868-1.

Reference ID: 4624097

Mylan submitted the response to CR on December 16, 2019. We reviewed the labels and labeling to determine that they were acceptable from a medication error perspective.

On June 18, 2019, a postmarket medication error review was completed to address medication errors related to the opening of insulin pen cartons and dispensing individual pens[c]. Thus, we provide a recommendation below to include a statement on the carton labeling for dispensing the carton sealed.

3 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed prescribing information, Instructions for Use, and container labels determined that they were acceptable from a medication error perspective. We did identify one area of vulnerability that may lead to medication errors and we provide one recommendation for the proposed carton labeling in Section 3.1.

3.1 RECOMMENDATIONS FOR MYLAN

A. Carton Labeling
   a. Add the statement "Dispense in this sealed carton" to the Principal Display Panel (PDP) to decrease the risk of improper dispensing of the product.

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[c] Lowery A. Postmarket Medication Error Review for Insulin Pens (TSI 1917). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Jun 18. OSE RCM No.: 2018-202.

Reference ID: 4624097

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ARIANE O CONRAD
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MEMORANDUM

REVIEW OF REVISED LABELS AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 21, 2019
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 210605
Product Name and Strength:	Semglee (insulin glargine) solution, 100 units/mL, 10 mL vial and 3 mL prefilled pen
Applicant/Sponsor Name:	Mylan GmbH (Mylan)
FDA Received Date:	August 2, 2019; August 7, 2019; August 16, 2019
OSE RCM #:	2017-842-2
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Millie Shah, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Mylan submitted revised labels and labeling for Semglee. The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised labels and labeling for Semglee (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Flint J. Label and Labeling and Human Factors Results Review for Semglee (NDA 210605). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Aug 15. RCM No.: 2017-842-1 and 2017-1868-1.

Reference ID: 4620697

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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:	August 20, 2019
To:	Lisa Yanoff, MD Acting Director **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Aman Sarai, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Ankur Kalola, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Inserts (PPIs) and Instructions for Uses (IFUs)
Drug Name (established name):	SEMGLEE (insulin glargine injection)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	210605
Applicant:	Mylan

Reference ID: 4479475

1 INTRODUCTION

On February 28, 2019, Mylan submitted for the Agency's review a resubmission in response to the Agency's Complete Response letter on May 17, 2018 for Insulin Glargine 100 Units/mL solution for subcutaneous Injection which cited major deficiencies. In addition to addressing the deficiencies to the Agency's Complete Response letter, Mylan has received email correspondence on February 13, 2019 confirming that the new functions (pen assembly, packaging, and testing, etc.) that the Malaysia site will perform can be included at the time of the resubmission (complete response).

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 March 12, 2019 and March 5, 2019, for DMPP and OPDP to review the Applicant's proposed Patient Package Inserts (PPIs) and Instructions for Uses (IFUs) for Semglee (insulin glargine injection), injection for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft Semglee (insulin glargine injection) PPIs and IFUs received on February 28, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 14, 2019.
- Draft Semglee (insulin glargine injection), Prescribing Information (PI) received on February 28, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 14, 2019.
- LANTUS (insulin glargine inection) comparator labeling dated May 9, 2019.
- BASAGLAR (insulin glargine inection) comparator labeling dated September 5, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPIs and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPIs and IFUs using the Arial font, size 10.

In our collaborative review of the PPIs and IFUs we:

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

4 CONCLUSIONS

The PPIs and IFUs 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 PPIs and IFUs are 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 PPIs and IFUs.

Please let us know if you have any questions.

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

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

Memorandum

Date: August 19, 2019

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

Monika Houstoun, Associate Director for Labeling, (DMEP)

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

Subject: OPDP Labeling Comments for SEMGLEE® (insulin glargine injection) for subcutaneous use

NDA: 210605

In response to DMEP's consult request dated March 5, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the NDA resubmission for SEMGLEE® (insulin glargine injection) for subcutaneous use.

PI, PPI, and IFU: OPDP's review of the proposed labeling is based on the draft PI received by electronic mail from DMEP (Michael White) on August 13, 2019, and we do not have any comments.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DMEP (Michael White) on August 13, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Ankur Kalola at (301) 796-4530 or Ankur.Kalola@fda.hhs.gov.

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LABEL AND LABELING AND HUMAN FACTORS RESULTS REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	August 15, 2019
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 210605
Product Name and Strength:	Semglee (insulin glargine) solution, 100 units/mL, 10 mL vial and 3 mL prefilled pen
Product Type:	Single Ingredient Product, Drug-Device Combination Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Mylan GmbH (Mylan)
FDA Received Date:	February 28, 2019
OSE RCM #:	2017-842-1 and 2017-1868-1
DMEPA Safety Evaluator (Human Factors):	Jason Flint, MBA, PMP
DMEPA Safety Evaluator (Label and Labeling):	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader (Acting):	Millie Shah, PharmD, BCPS
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS
DMEPA Associate Director:	Mishale Mistry, PharmD, MPH

Reference ID: 4624897

1 REASON FOR REVIEW

We reviewed the human factors (HF) validation study report and proposed labels and labeling from a medication error perspective for NDA 210605 for insulin glargine, submitted on February 28, 2019, as part of the evaluation of the 505(b)(2) resubmission. The listed drug is Lantus (insulin glargine, NDA 021081), which was approved on April 20, 2000.

1.1 PRODUCT INFORMATION

Mylan submitted NDA 210605 for Semglee, which will be supplied in a multiple dose vial and a disposable multiple dose pen injector containing 100 units/mL of insulin glargine, to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. The pen injector uses the (b) (4) (b) (4) Disposable Pen Device platform.

1.2 REGULATORY HISTORY

We evaluated Mylan's HF validation study results submitted April 27, 2017 in a prior review.[a] Our review determined that there were an insufficient number of pediatric untrained injection naïve patients in the study. In addition, we determined that the selection errors observed in the HF study results did not support that users would select the correct product. Thus, we advised that Mylan implement our recommendations for the Instructions for Use (IFU) and conduct an additional HF validation study with 15 untrained, injection naïve pediatric patients. In addition, we recommended that Mylan conduct a differentiation study after implementing the carton and container labeling recommendations to provide data to demonstrate that the products can be differentiated by all intended user groups.

The NDA received a complete response (CR) from the Agency on May 17, 2018 and our recommendations were communicated to Mylan as part of the complete response letter (CRL).[b] Thus, Mylan submitted additional HF and differentiation study data, and revised product labeling for review on February 28, 2019.

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.

Table 1. Materials Considered for this Label and Labeling Review

[a] Conrad A. Label and Labeling and Human Factors Results Review for Semglee (NDA 210605). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Apr 4. RCM No. 2017-842 and 2017-1868.

[b] White M. Complete Response for Semglee (insulin glargine). Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2018 May 17. NDA 210605.

Reference ID: 4624897

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information • Previous DMEPA Reviews • Human Factors Engineering Process	B
Human Factors Study Report	C
Review of Product Sample	D
Information Requests	E
Labels and Labeling	F

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The following sections provide a summary of the study design and methodology, use errors/close calls/use difficulties observed (Table 2), and our analysis to determine if the HF validation study results support safe and effective use of the proposed product by intended users in the intended use environments. We also provide our assessment of the differentiation study results (Table 3) and the proposed product labels and labeling.

3.1 SUMMARY OF STUDY DESIGN

The HF validation study was designed to assess the ability of pediatric patients (between 6 and 17 years old) to successfully use the Semglee (MYL-1501D) pre-filled pen (PFP) without any training or previous experience with PFPs (i.e., injection naïve). The study population included 15 participants, with 7 participants between the ages of 6 and 11 and 8 participants between the ages of 12 and 17.

The HF validation study design was the same as in the previously reviewed HF validation study[c]. However, the PFP label, carton labeling and IFU were amended in response to the Agency's feedback on labeling in the complete response letter (CRL). At the end of each participant session, the moderator conducted a root cause analysis to understand the participant's perception of the cause of any observed use errors, close calls, or use difficulties. After the participant tasks, the moderator assessed participant's response to three knowledge tasks.

The differentiation study was designed to confirm that the intended user population (including self-administering pediatrics and adolescents) can differentiate the Semglee PFP from the Humulin R U-500 KwikPen using the proposed to-be-marketed Semglee PFP labeling. The differentiation study follows the previous differentiation study design but incorporates the feedback and discussion from the Agency from the CRL (received

[c]Conrad A. Label and Labeling and Human Factors Results Review for Semglee (NDA 210605). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Apr 4. RCM No. 2017-842 and 2017-1868.

Reference ID: 4624897

May 17, 2018), General Advice letter[d] (received May 31, 2018), and Meeting Minutes[e] (received October 02, 2018). The study population included 63 trained and 63 untrained participants, including adults and pediatric patients. Mylan used four pens, the Semglee PFP, the Humulin R U-500 KwikPen, the Lantus SoloStar, and the Basaglar KwikPen in the differentiation study.

3.2 STUDY RESULTS

Table 2 describes the HF validation study results for critical tasks, Mylan's analyses of the results, and DMEPA's analyses and recommendations. Table 3 describes the differentiation study results, and DMEPA's analyses and recommendations.

[d] White M. General Advice Letter for Semglee (insulin glargine). Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2018 May 31. NDA 210605.

[e] White M. Meeting Minutes for Semglee (insulin glargine). Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2018 OCT 02. NDA 210605.

Reference ID: 4624897

3.2.1 ANALYSIS OF HUMAN FACTORS VALIDATION STUDY RESULTS

Critical Tasks Evaluated	Number and Description of Use Errors (UE), Close Calls (CC) and Use Difficulties (UD)	Participant's Feedback and Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Task UC4: User correctly attaches the needle to the pen	Use Errors: None UD: 1 [Use Difficulty; P15]: This participant initially attached the needle by pushing it onto the pen but not screwing it on. When she attempted to remove the inner needle cap, the needle detached from the pen. After pressing it on again, the participant screwed the needle onto the pen creating a secure connection.	Disposable Needle Design: The audible "click" heard by the participant after pressing the needle onto the pen led her to assume the needle had been securely attached to the pen prior to screwing it on.	N/A	We agree that this is a critical task because difficulty with correct needle attachment can lead to a delay in therapy, most likely with the first use of the product. We agree that the root cause of this use difficulty is related to the disposable needle design. However, since this design element is common among pen needles and insulin pens, changes to the product user interface (PUI) are unlikely to further reduce the occurrence of this use error. Furthermore, our review of the IFU concluded that we do not have any recommendations to mitigate the risk for this use difficulty and we find the residual risk acceptable.
Task UC5b: User removes	UE: 1 [Use Error; P5]: This participant pair (parent and	Disposable Needle Design: P5: The need to remove two caps from the disposable	This step represents standard practice for the use of all insulin needles and no	While the sponsor did not characterize this task as either Critical or Essential,

Reference ID: 4674897

Critical Tasks Evaluated	Number and Description of Use Errors (UE), Close Calls (CC) and Use Difficulties (UD)	Participant's Feedback and Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
inner needle cap	child participant) did not remove the inner needle cap prior to attempting the injection. The participant's parent correctly understood that the dose was not delivered to the foam pad during the first attempt, however, so the moderator assisted the pair with this step on the second injection in order to collect data on subsequent injection steps. UD: 1 [Use Difficulty, P11]: This participant's parent initially tried to remove the outer needle cap by pulling up on the needle base before realizing the inner cap separated from the base during removal.	needle was not intuitive for this participant pair. P11: This participant's parent stated that she pulled on the base of the needle while trying to remove the inner needle cap because the base of the needle was the same color as the inner needle cap (white) and thought the base was part of the cap.	reasonable further mitigation is possible.	we find that this is a critical task because failure to remove the inner needle cap prevents the user from delivering the medication. We agree that the root cause is related to the color of the plastic on the disposable needle. Our review of the IFU concluded that we do not have any recommendations to mitigate the risk for this use error and difficulty and we find the residual risk acceptable.
Task UC13: User holds the purple button down for 10 seconds	UE: 6 Participants 1, 3, 4, 6, 12, and 13 failed to hold the purple button down for 10 seconds after the dose	Device Design: P1: One participant's parent realized they did not hold the needle in the skin for 10 seconds after the task was	Clear written and pictorial instructions provided in IFU. The 10 second hold is more than double the average	We agree that this is a critical task because failure to hold the button for 10 seconds may result in incomplete dose delivery. We agree that the root cause

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Critical Tasks Evaluated	Number and Description of Use Errors (UE), Close Calls (CC) and Use Difficulties (UD)	Participant's Feedback and Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	window read zero. The longest hold time for this group of participants was 4 seconds, and the shortest was 0 seconds.	complete and suggested that they did not see this step until it was too late because of the step's location toward the end of the IFU. P3: One participant's parent stated that she assumed that the injection would be finished after hearing the final click of the injection P4: One participant saw this step in the IFU and verbalized an intent to hold for 10 seconds just before performing the injection, but only held the button for 4 seconds after the injection was complete. While the patient/child participant interpreted the instructions correctly after the simulation, the participant's parent remarked that she focused on the pictures in the IFU and gave contradictory answers/seemed unsure of whether she should start counting at the start of the	hold time required to ensure entire dose is administered. No reasonable further mitigation is possible.	of this use error is related to the design of the device and the IFU. In the previous review, we provided IFU recommendations to help mitigate this use error and to align with other similar insulin products. Mylan incorporated those changes and we note that there was a reduction in errors from the previous study, indicating that the changes may have helped to address this error. At this time, we do not have further recommendations.

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Critical Tasks Evaluated	Number and Description of Use Errors (UE), Close Calls (CC) and Use Difficulties (UD)	Participant's Feedback and Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
		injection or after the final click. IFU Design: P6: One participant's parent misinterpreted the IFU and stated that she thought she should start counting to 10 as she began pressing the dose button. However, on her second reading of the instructions, she appeared to understand that she should have started counting after the dose button reached 0. Device Design, IFU Design: P 12: One participant's parent stated that she thought the 10 second hold time specified in the IFU included the time it took for the dial to return to 0 because she assumed that once the dial returned to 0, all of the medication had been injected. The participant/child, however, understood the instructions during the simulation and verbalized her disagreement		

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Critical Tasks Evaluated	Number and Description of Use Errors (UE), Close Calls (CC) and Use Difficulties (UD)	Participant's Feedback and Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
		with her mother as her mother performed the injection. After the simulation, the participant/child indicated she and her mother both paid more attention to the images in the IFU. P 13: One participant pair performed the injection in real time as they read the IFU together. After the injection was complete, as they kept reading, the participant noted that his mother failed to count to 10 before removing the needle from the injection site. After the simulation, the participant's parent remarked that she believed that when the dial returned to 0, all of the medication had been injected. She did not remember reading about the 10 second hold period in the IFU.		
Knowledge Question	1 "Gave Up"	IFU Design and Study Artefact: During root cause	This information is clearly provided in IFU. No	We agree that this is a critical task, and that study

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Critical Tasks Evaluated	Number and Description of Use Errors (UE), Close Calls (CC) and Use Difficulties (UD)	Participant's Feedback and Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
UC19: User knows what the insulin solution looks like	[Gave Up; P1]: This participant's parent stated that she did not know what the medication should look like and that she did not remember reading about this topic in the IFU.	probing, she reported that the medication should be clear, but that she commented on the amount of new information she was processing and that if the scenario were real she would read the IFU several times. The participant's parent read the IFU during the familiarization period but reported not seeing the information about what the medication should look like in the cartridge.	reasonable further mitigation is possible.	artefact was the primary root cause. Our review of the IFU concluded that we do not have any recommendations to mitigate the risk for this use error and we find the residual risk acceptable.
Knowledge Question UC20: User knows that prior to first use the Pen should be refrigerated (stored between 37°F and 46°F)	UE: 1 [Use Error; P11]: This participant's parent stated they would store the unused pen in a drawer in a bathroom.	Study Artefact: The participant's parent reported assuming that they would be practicing using the pen and focused on related areas in the IFU and skipping over earlier sections. While answering the next question about where an in-use pen should be stored, the participant's parent read the information about storing the pen before use, and the participant/child reported	The storage requirements are clearly provided on carton and IFU. No reasonable further mitigation is possible.	We agree that this is a critical task and that the root cause was study artifact. Our review of the IFU concluded that we do not have any recommendations to mitigate the risk for this use error and we find the residual risk acceptable.

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Critical Tasks Evaluated	Number and Description of Use Errors (UE), Close Calls (CC) and Use Difficulties (UD)	Participant's Feedback and Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
		that the pen should be stored in the refrigerator before use.		
Knowledge Question UC21: User knows that after using the Pen for the first time the Pen should be stored at room temperature (under 86F)	UE: 2 [Use Error; P4]: This participant reported that an in-use pen should be stored in the refrigerator. [Use Error; P15]: This participant pair reported that an in-use pen should be stored in the refrigerator.	IFU Design: The participant stated that the IFU instructed them to put an in-use pen back into the refrigerator after using it. His parent remarked that she had not seen the phrase "Do NOT" before the phase "put the pen back into the refrigerator after using it" as she read the IFU. IFU Design, Negative Transfer: The participant pair stated that the IFU instructed them to put an in-use pen back into the refrigerator. The participant's parent remarked that she had skimmed the storage instructions and saw the before-use instruction to store the pen in the refrigerator and assumed she should store an in-use pen in the refrigerator	The storage requirements are clearly provided on pen label, carton and IFU. No reasonable further mitigation is possible.	We agree that this is a critical task, and the root cause of this error is related to design of the IFU. We provided recommendations to mitigate this use error in the previous review, which Mylan incorporated into the IFU. Therefore, we do not have additional recommendations to mitigate the risk for this error and find the residual risk is acceptable.

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Critical Tasks Evaluated	Number and Description of Use Errors (UE), Close Calls (CC) and Use Difficulties (UD)	Participant's Feedback and Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
		similarly. She also mentioned knowing that insulin should be stored in the refrigerator but remarked that she may have given the correct answer if the IFU instructed her not to "re-refrigerate" the pen in the before use storage section of the IFU.		
Knowledge Question UC22: User knows the Pen should be disposed of 28 days after first use regardless of number of units remaining	UE: 2 [Use Error; P6]: This participant pair answered that the pen could be used until it contained no more medication. [Use Error; P15]: This participant pair answered that the pen could be used until it contained no more medication (participant's parent) or until the expiration date was reached (participant/child)	IFU Design, Packaging Design: Despite reading the storage section of the IFU, the participant's parent did not remember reading the instructions regarding disposing of the pen 28 days after opening it. She also mentioned that the presence of the expiration date may have led to believe she could keep using the pen until the medication was used. IFU Design: The participant's parent remarked that she had only noticed the storage instructions for the pen before use and saw the instruction that it could be used up until its expiration	The storage requirements are clearly provided on pen label, carton and IFU. No reasonable further mitigation is possible.	We agree that this is a critical task, and that the use errors are related to IFU and packaging design. The storage requirements are available in the IFU, pen label, and carton. Our review of the labeling concluded that we do not have any recommendations to mitigate the risk for this use error and we find the residual risk acceptable.

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Critical Tasks Evaluated	Number and Description of Use Errors (UE), Close Calls (CC) and Use Difficulties (UD)	Participant's Feedback and Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
		date. She remarked that she had "skipped over" the section regarding an in-use pen but that she would probably have done the same at home.		

3.2.2 ANALYSIS OF ESSENTIAL TASKS

The HF validation study showed use errors, use difficulties, and close calls with six essential tasks that are common to other insulin glargine pre-filled pens. We have no recommendations for use errors, difficulties, or close calls related to the following tasks:

- Task UC1: User is able to open the carton and remove the pen
- Task UC3: User cleans the rubber seal with alcohol wipe
- Task UC6: User retains outer cap
- Task UC14a: User does not recap the needle with the inner needle cap
- Task UC14b: User removes the needle using the outer cap
- Task UC15: User discards the needle in the sharps container
- Task UC18: User correctly identifies the number of units remaining in the Pen

There were use errors associated with Task UC7; "User primes the pen" that may have been associated with the design of the IFU. This step in the IFU is split across two columns. We make a recommendation in Section 4.1, C1 to ensure that the instructions for priming the pen are not split up in the IFU.

There were two use errors associated with Task UC10 "User cleans the injection site with an alcohol wipe". While this is a common error, we noted that the instruction in the IFU is at the end of several lines of text. Increasing the prominence of this information may minimize the risk for this use error. We make a recommendation in Section 4.1, C2 to increase the prominence of important information in the IFU.

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We have determined that these changes can be implemented without additional validation testing.

3.2.3 ANALYSIS OF DIFFERENTIATION STUDY RESULTS

Table 3: Summary and Analyses of Differentiation Study Results for Task 1: Selection of the MYL-1501D PFP.
* Mylan refers to the Semglee PFP as MYL-1501D PFP throughout the results table.

Description of Use Errors (UE)	Description of Close Calls (CC)	Applicant's Root Cause Analysis (RCA) and Participant's Subjective Feedback on UEs, CCs, and UDs	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Use Errors: n=4 Use error # 1: One participant chose the Humulin R U-500 KwikPen and used it to simulate dose delivery. The participant was asked to deliver a dose of 6 units and when he couldn't find '6 units' on the dial he decided that 6 units must be depicted by '60' on the dial and this is the dose of Humulin R U-500 that he administered to the skinpad. Use error # 2: One participant read the task card aloud then asked:		UE 1: RCA: Device Color / Lack of familiarity with pens. "*I thought that was the one I just reviewed. Maybe it wasn't*." The participant picks up Semglee "*It could have been this one, I know it was a blue cap. Oh I guess it was this one I'm sorry I picked the wrong one. I didn't this it was this long though. I was confused given 4 different ones. Was I supposed to remember the one I just reviewed? I mean they kind of all look the same, but I thought it was this one*" the participant points to Humulin R U-500 KwikPen. *I didn't think it*	UE 1: The potential differentiation failure mode will only occur after a series of events including: • User or multiple users store multiple insulin PFPs together. • User does not follow the guidance of every insulin PFP IFU to check the medication label prior to use. • User has no association with the drug product name or insulin type. • User does not associate visual cues with a certain PFP (e.g. warning label on Humulin cartridge, purple button on MYL-1501D PFP, dose	UE 1 and 3: We agree with the root cause analysis provided, however, we disagree that hyperglycemia is the worst potential outcome for this use error. In this particular case (for Use error #1), a participant simulated delivery of a 10-fold higher dose of insulin using Humulin R U-500 KwikPen, which could lead to significant hypoglycemia. In the case of Use error #3, the participant selected an insulin glargine product (Lantus Solostar) which would produce the same therapeutic effect as Semglee (also insulin glargine).

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Table 3: Summary and Analyses of Differentiation Study Results for Task 1: Selection of the MYL-1501D PFP. * Mylan refers to the Semglee PFP as MYL-1501D PFP throughout the results table.				
Description of Use Errors (UE)	Description of Close Calls (CC)	Applicant's Root Cause Analysis (RCA) and Participant's Subjective Feedback on UEs, CCs, and UDs	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
"So, I can just use any pen?" The moderator asked her to do what the task card said so the participant looked at the card again and read: "Select the pen injector" She then selected Lantus SoloStar and performed the simulated injection. Use Error #3: This participant asked his mother for guidance on which pen to choose and she pointed to Lantus SoloStar. The participant proceeded to select Lantus SoloStar and use it to simulate dose delivery. Use Error #4: This participant chose the Humulin R U-500 pen, dialed a dose of 5 units and simulated injection.		*was this one (Semglee) because I didn't think it was this long that's why I picked that one"* the participant points to Humulin. This participant has no experience of the use of PFPs and no experience of the treatment of diabetes. He therefore had no understanding of the risk of mixing insulin medications or dialing the wrong dose. During the post task interview the participant spoke of how he would have been aided in his choice by a label on the medications stating his name or 'mealtime' and 'daily'. The moderator then asked what he would do if both pens had been prescribed to him and he responded:	increments on the dose setting knob of the PFP). This participant, who was unfamiliar with prefilled insulin pens and had no experience of the treatment of diabetes, reflected during post task interview that in real life he would have stored these pens in different locations. It is also feasible to suggest that he had formed a mental model that he should be able to achieve the task with the selected pen and he seemed determined to find a way to complete the task, thus overlooking the visual cues even when he was verbalizing them (for example when he spoke of not being able to dial '6' units, he persuaded himself that	UE 2 and 4: We agree that this error is associated with a test artifact. The task card contained the phrase "recently familiarized with" and participants interpreted this to mean "familiar with." We discuss our analysis of the differentiation further in Section 3.4.2.

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Table 3: Summary and Analyses of Differentiation Study Results for Task 1: Selection of the MYL-1501D PFP. * Mylan refers to the Semglee PFP as MYL-1501D PFP throughout the results table.				
Description of Use Errors (UE)	Description of Close Calls (CC)	Applicant's Root Cause Analysis (RCA) and Participant's Subjective Feedback on UEs, CCs, and UDs	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
		"*Well if I took this for a long acting daily dose I would put this (Semglee) up in my bathroom and keep it there. And this (Humulin) I would keep close to the dinner table because I would inject myself at dinner or only at mealtimes, so I definitely have these in different places*" The participant clearly would not find himself in the situation set out in this study if he were at home as he would be checking that the PFP was prescribed to him and if it were a different insulin type it would be stored in a different location. UE 2: RCA: Inattention.	'60' must equal '6'). There was therefore an element of study artefact in the outcome. Hyperglycemia with a severity of S4 is the worst-case scenario for this potential failure mode; the patient could experience increasing symptoms of hyperglycemia however they would be likely to recognize symptoms or become aware through glucose monitoring and be able to address the situation with an additional insulin dose before reaching the worst-case impact of this potential harm. The combination of the series of events required in order for the potential failure mode to occur plus the likelihood that the	

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Description of Use Errors (UE)	Description of Close Calls (CC)	Applicant's Root Cause Analysis (RCA) and Participant's Subjective Feedback on UEs, CCs, and UDs	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
		The participant selected the pen that stood out to her most because she assumed she could pick any pen. She commented that she was not paying attention when reading and she then identified Semglee as the pen she would have selected had she paid attention to the task. At the start of the root cause analysis the moderator asked the participant to read the card aloud again and as she read it the participant said: "Ah, so I should have used that one" and pointed to Semglee. The moderator asked why the participant had chosen Lantus and she said:	potential harm would be detected before becoming serious enough to require medical intervention supports the conclusion that no further mitigation is required. UE 2: There are 2 remote scenarios in which this risk could occur: 1. User incorrectly chooses pen prescribed to another patient in the household. This could lead to, at worst case, contamination with a blood borne virus (S4), if the pen had been incorrectly stored with a used needle and the (incorrect) user proceeded to use this needle. 2. User incorrectly choses a pen that was previously prescribed to them and	

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Table 3: Summary and Analyses of Differentiation Study Results for Task 1: Selection of the MYL-1501D PFP. * Mylan refers to the Semglee PFP as MYL-1501D PFP throughout the results table.				
Description of Use Errors (UE)	Description of Close Calls (CC)	Applicant's Root Cause Analysis (RCA) and Participant's Subjective Feedback on UEs, CCs, and UDs	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
		"I don't know I just grabbed one! Because I didn't read very carefully" The moderator asked for further clarification of why the participant chose Lantus and she said because of the bright color of the cap [this could be interpreted as the purple button although the participant didn't articulate or indicate that] but added that she now understood that she should have chosen the MYL-1501D PFP. The moderator asked the participant to explain what she thought she had to do when she first read the task card and she said: "Just take one of the pens but I should have taken the one I was familiarized with which was Semglee, but I chose that one" and	potentially injects insulin glargine that it is past its expiration date, which, in the worst case would lead to a harm categorized as Critical (S4) as defined in Table 3.2.P.2.4/ 62: Definition of Severity Classification Used in MYL-150D PFP Risk Management. In both cases the PFP(s) are not being used in their intended use and warnings associated with sharing pens and the reuse of needles are clearly presented in the labelling of all insulin PFPs. This risk is not specific to the MYL-1501D PFP and could occur between any PFPs where inattention leads to the user selecting and using the wrong PFP. Due to the remote likelihood of	

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Description of Use Errors (UE)	Description of Close Calls (CC)	Applicant's Root Cause Analysis (RCA) and Participant's Subjective Feedback on UEs, CCs, and UDs	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
		pointed to Lantus. The moderator asked whether the participant had any confusion between the two pens and she said: "No, I just should have paid more attention to what I was reading" UE 3: RCA: Study Artefact. During post task interview it became apparent that the participant pair misunderstood the task. The moderator asked the participant to read the task card again and when he read "recently familiarized" his mother said: "*Ahhh!! We did the wrong one sorry*" The moderator then asked the participant which one he recently familiarized himself with	occurrence of this risk and the series of events required to result in harm (at severity levels ranging from S2 to S4) there are no further mitigations required. UE 3: Whilst this use error is believed to be due to study artefact and therefore would not have occurred in a real-life scenario, the impact of the potential failure mode has been assessed and there are 2 scenarios in which this risk could occur: 1. User incorrectly choses pen prescribed to another patient in the household. This could lead to, at worst case, contamination with a blood borne virus (S4), if the pen had been incorrectly stored with a used needle and the	

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		and he pointed to the MYL-1501D PFP. The moderator asked what made the mother point to Lantus SoloStar and she said she was familiar with the name. The participant said: "*Mom! I was thinking about choosing that one*!" The moderator asked the participant for his thought process when thinking about choosing Semglee and he said: "*Because it said the one you recently familiarized with, so I was going to choose that (Semglee) but my mom picked the other one"* It seems clear that the participant understood and would have chosen the correct PFP but took the guidance of his mother who misunderstood the task.	(incorrect) user proceeded to use this needle. 2. User incorrectly choses a pen that was previously prescribed to them and at worst case injects insulin glargine that is past its use-by date leading to hyperglycemia (S2) from 1 missed dose (patient unaware) or hyperglycemia (S4) from multiple missed dose (patient unaware). In both cases the PFP(s) are not being used in their intended use and warnings associated with sharing pens, the reuse of needles and adherence to expiration date are clearly presented in the labeling of all insulin PFPs and therefore this is not a risk specific to the MYL-1501D	

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			PFP. No further mitigation is required.	
		UE 4: RCA: Study Artefact. The participant misunderstood the phrase on the task card "recently familiarized with" and interpreted it to mean the pen he is most familiar with. Once he truly understood the task there was no confusion in picking the MYL-1501D PFP. When asked why he picked Humulin R U-500 KwikPen the participant said: "I'm just familiar with it…." When asked to point out the pen that he'd looked at earlier the participant pointed to Semglee.		

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Description of Use Errors (UE)	Description of Close Calls (CC)	Applicant's Root Cause Analysis (RCA) and Participant's Subjective Feedback on UEs, CCs, and UDs	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	Close Calls – n=4 CC: 1 The participant expressed some confusion over reading the task card initially and was asked to reread it to herself to ensure she understood it prior to attempting the task. She initially selected Basaglar KwikPen before working with her parent and correcting to MYL-1501D PFP which she then used to simulate dosing. CC 2: This participant (16yo male) selected the Humulin R U-500 KwikPen and started to prepare the pen for dosing (uses alcohol wipe, starts to attach needle). At this point his mother intervened to say that she thought he had picked the	CC 1 RCA: Study Artefact. The participant picked up Basaglar (current medication) at which point her mother said: *"Would you re-select? Ask yourself….the recent one. The one that you just used"* The participant replied: "*Oh!!! Ok*" Then without any further discussion picked up the MYL-1501D PFP and proceeded to simulate dose delivery. During RCA she verbalized a misunderstanding of the phrase on the task card "recently familiarized with" and interpreted it to mean the pen she is most familiar with. Once she truly understood the task at hand, there was no	None given.	CC1: We agree that this close call is associated with a test artifact. The task card contained the phrase "recently familiarized with" and participants interpreted this to mean "familiar with." CC 2 and 3: We agree based on the participant's comments that these close calls may be due to a study artifact. In addition, based on subjective feedback, the participant might have initially chosen the Humulin R U-500 KwikPen because it was a meal-time insulin (the participant specifically stated that is what he would choose for meal time).

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	wrong pen. She looked to the moderator for assistance and the moderator asked them what they thought they had to do. The mother said she thought that he should pick the MYL-1501D PFP because that's the one they'd just looked at. The participant acknowledged the different dosing scale on the Humulin R U-500 KwikPen and he then selected the MYL-1501D PFP and used this to simulate dosing. CC 3: This participant initially selected the Lantus SoloStar before his mother intervened and pointed out that he was to choose the MYL-1501D PFP because that's the one they'd been trained	confusion in picking the MYL-1501D PFP. CC 2 RCA: Study Artefact. This close call was related to the study scenario and not to confusion between pens. After the mother intervened the moderator asked whether she would intervene in such a way at home and she said yes because he was about to use a pen that didn't belong to him. The participant was asked what was his thought process when selecting the Humulin R U-500 KwikPen and he explained that it was the first pen he saw and because the session was conducted at mealtime he associated the task instructions with his usual practice at home i.e., to go to the table at		CC 4: We disagree that this close call is related to "unfamiliarity with the PFP". The length of time that it took the participant to select between the Humulin KwikPen and the Semglee PFP indicates difficulty in differentiation between the two devices. In fact, the participant states that the primary reason for initially selecting the Humulin R U-500 KwikPen was the color of the pen. We discuss differentiation further in section 3.2.4.

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Description of Use Errors (UE)	Description of Close Calls (CC)	Applicant's Root Cause Analysis (RCA) and Participant's Subjective Feedback on UEs, CCs, and UDs	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	on. The participant then selected the MYL-1501D PFP and used this to simulate dosing. CC 4: This participant successfully selected the MYL-1501D PFP however due to the time taken to select the pen this is being reviewed as a close call. The participant quickly discounted Lantus SoloStar and Basaglar KwikPen but spent considerable time choosing between Humulin R U-500 KwikPen and MYL- 1501D PFP, eventually confirming her choice as MYL-1501D PFP and proceeding to simulate dose delivery using MYL-1501D PFP.	mealtime and select his Humalog pen in order to take a mealtime dose. He therefore thought that he should pick the Humulin pen (which he knew to be a mealtime insulin). Once the participant understood the task he selected the MYL-1501D PFP and simulated dose delivery. CC 3 RCA: Study Artefact. This participant experienced difficulty reading the task card and it is the moderator's opinion that he did not understand what the task was asking or fully internalize the task card instructions. During RCA the moderator asked the participant about his thought process when		

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		choosing the Lantus SoloStar and he said: "*I thought we had to do like one by one. But then I remembered we had to do the brand and I took that one. My mom told me."* On further investigation it became apparent that he used the physical setup of the pens next to each other as a cue to understanding what he was supposed to do, and since the pens were lined up next to each other, assumed he was going to try each one. He arbitrarily picked up a pen assuming he would be using all of them. This participant pair were naïve to the use of PFPs and therefore it is not possible to compare the mother's intervention to their usual process.		

Reference ID: 4674897

Table 3: Summary and Analyses of Differentiation Study Results for Task 1: Selection of the MYL-1501D PFP. * Mylan refers to the Semglee PFP as MYL-1501D PFP throughout the results table.				
Description of Use Errors (UE)	Description of Close Calls (CC)	Applicant's Root Cause Analysis (RCA) and Participant's Subjective Feedback on UEs, CCs, and UDs	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
		CC 4 RCA: Unfamiliarity with the PFP During RCA the participant was asked about her thought process when choosing between Humulin R U-500 KwikPen and MYL-1501D PFP and she replied: "*well the pen that I had yesterday was one of these, and so I chose the one with the color [i.e., not the quickly discounted Lantus and Basaglar] and as I was looking then I noticed one said Humulin and the other is the insulin, so I knew it must have been this one (Semglee)"* The participant then expressed that she had hesitated because she didn't recall the purple button on MYL-1501D PFP		

Reference ID: 4674897

Table 3: Summary and Analyses of Differentiation Study Results for Task 1: Selection of the MYL-1501D PFP. * Mylan refers to the Semglee PFP as MYL-1501D PFP throughout the results table.				
Description of Use Errors (UE)	Description of Close Calls (CC)	Applicant's Root Cause Analysis (RCA) and Participant's Subjective Feedback on UEs, CCs, and UDs	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
		from the training session. The participant was asked what she would typically do to reassure herself in this situation and she replied: *"I'd have to look it up. Look at my prescription and if I didn't have it I would call my doctor or some medical person to make sure I have the right one"* During the post task interview the participant demonstrated that she had the information and ability to make her selection and that she was walking through all the points that she recalled from the training to assure herself that she was making the right choice based on her limited familiarity with the pens.		

Reference ID: 4674897

3.2.4 DISCUSSION OF DIFFERENTIATION STUDY RESULTS

We note that the proposed Semglee (insulin glargine), 100 units/mL pen and Humulin R U-500 KwikPen (500 units/mL) are similar in appearance and may not be adequately differentiated (Figure 1). Post-marketing experience with products using similar color schemes has shown that product selection errors can occur when users rely on color as their primary indicator instead of reading the product's name.

MYL-1501D PFP	
Humulin R U-500 KwikPen	
Figure 1: Pen Comparison	

We acknowledge that there is the potential for serious clinical consequences, including hyperglycemia or hypoglycemia, if the proposed Semglee pen is confused with Humulin R U-500 KwikPen and the wrong drug was administered. Per further discussion with the DMEP Clinical Team, we note that it is unlikely for patients to be managed on both insulin glargine 100 units/mL (Semglee) and U-500 insulin (Humulin R U-500) because both products are available options for basal coverage. In addition, we note that the prescribing information (PI) for Humulin R U-500[f] states that it has both prandial and basal activity, which allows for the use of Humulin R U-500 as monotherapy. The PI labeling indicates that Humulin R U-500 may not be "safe and effective when used in combination with other insulins" due to an increased risk of hypoglycemia with concomitant insulin therapy. Thus, the clinical team anticipates that Semglee and Humulin R U-500 would likely be used as therapeutic alternatives, instead of being used concomitantly, and we can surmise that the risk of selection errors occurring in actual use may be minimal.

[f] Humulin R U-500 [Prescribing Information]. FDA Label Search. U.S. Food and Drug Administration. Nov 2018. [cited 2019 Aug 5]. Available from: https://www.accessdata.fda.gov/spl/data/01dcc798-7fba-4eb7-af12-001ab92dee6e/01dcc798-7fba-4eb7-af12-001ab92dee6e.xml.

Reference ID: 4624897

Furthermore, we sent an Information Request (IR) on July 26, 2019 to the Applicant requesting that they provide an assessment regarding the potential that Semglee and Humulin R U-500 would be prescribed concomitantly. Mylan's August 2, 2019 response concluded that it is "highly unlikely to be co-prescribed as Humulin R U-500 is intended for use as a monotherapy".[g] Of note, the Applicant indicates that the "unique prandial and basal activity profile allows Humulin R U-500 to be used as insulin monotherapy without concomitant use of basal insulins", which they point out is reflected in the approved PI and is supported by case reports (referenced in their response) and discussions with two leading clinical endocrinologists. In contrast, Semglee would require the use of supplemental insulin (short acting or rapid acting) to meet both basal and prandial insulin requirements, which is reflected in Section 2 of the proposed PI.

If a patient was taking Semglee and was then prescribed Humulin R U-500 (or vice versa), we foresee the potential for both products to be available to the patient for a limited time. We note in the differentiation study that there was one study participant who was asked to select the pen and administer a dose of 6 units. This participant incorrectly selected the Humulin R U-500 KwikPen, spoke of not being able to dial '6' units, and then persuaded himself that '60' must equal '6'. This study participant was unfamiliar with prefilled insulin pens and had no experience of the treatment of diabetes; therefore, it is unlikely that this participant would encounter such a scenario (prescribed both Humulin R U-500 and Semglee).

In considering the totality of the information provided, while we do not have strong evidence supporting a safety risk in actual use with Semglee and the Humulin R U-500 KwikPen for the reasons cited above, there remains a theoretical risk for selection errors between both products in instances where patients are switched from one product to the other. Therefore, we defer to the clinical team with respect to the acceptability of the residual risk associated with differentiation between Semglee and Humulin R U-500 KwikPen, and whether this residual risk should be addressed by the Applicant in the postmarket setting.

[g] Mylan. Response to Information Request for insulin glargine dated July 26, 2019. 2019 Aug 2. NDA 210605.

Reference ID: 4624897

3.3 LABELS AND LABELING

We reviewed the proposed labels and labeling from a medication error perspective. Our review determined that additional modifications are needed to improve the clarity and readability of important information on the proposed labeling and we provide recommendations in Sections 4.1 for the Prescribing Information (PI) and Instructions for Use (IFU) and in Section 4.2 for the container labels and carton labeling.

We have determined that our recommendations for the container labels and carton labeling can be implemented without additional validation testing.

4 CONCLUSION & RECOMMENDATIONS

The results of the HF validation study demonstrated use errors and close calls, but we do not have any additional recommendations to further address those errors.

The results of the differentiation study indicate that the product is not well differentiated from the Humulin R U-500 KwikPen. However, we discussed the differentiation study results with the DMEP Clinical team and defer to the Clinical Team with respect to the acceptability of the residual risk of selection errors.

Our evaluation of the proposed labels and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations for the proposed labeling in Section 4.1 and Section 4.2 to improve clarity.

The Division sent our recommendations for the container label and carton labeling to the Applicant on July 26, 2019; recommendations for the Prescribing Information, Patient Information, and Instructions for Use were sent to the Applicant on July 30, 2019.

4.1 RECOMMENDATIONS FOR THE DIVISION[h]

A. General Comments (Prescribing Information, Patient Information, and Instructions for Use)

   1. Ensure that the word “units” appears with a lower case “U” throughout the product labeling to minimize the risk of readers misinterpreting the “U” as the number zero in the product strength.

B. Prescribing Information

   1. Full Prescribing Information: Section 2 Dosage and Administration Section

      a. We recommend removing the statements “Use the Semglee prefilled pen with caution in patients with visual impairment.” from Section 2.1 and

[h] The Division sent our recommendations for the container label and carton labeling to the Applicant on July 26, 2019; recommendations for the Prescribing Information, Patient Information, and Instructions for Use were sent to the Applicant on July 30, 2019.

Reference ID: 4624897

(b) (4)

from Section 2.2 because these statements appear elsewhere in Section 2

C. Instructions for Use

1. We note that Step 3 Prime your Pen Needle is split across two columns in the PDF version of the IFU, which may have contributed to the priming errors in the HF study. We recommend revising the IFU so that the instructions within a step are grouped together for improved clarity.
2. For Step 5 Select and Clean the injection site, we note that the instructions to clean the injection site are in the last sentence of the paragraph, which may have contributed to a use error in the HF validation study. We recommend increasing the prominence of this instruction (for example, by moving this sentence to a separate line as Step 5B) to minimize the risk for this error.

4.2 RECOMMENDATIONS FOR MYLAN GMBH (MYLAN)[i]

Our review of your proposed container labels and carton labeling identified several areas that should be modified, and we recommend that the following revisions are implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

B. Carton Labeling

1. 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

[i] The Division sent our recommendations for the container label and carton labeling to the Applicant on July 26, 2019; recommendations for the Prescribing Information, Patient Information, and Instructions for Use were sent to the Applicant on July 30, 2019.

Reference ID: 4624897

the warning is in the same viewing angle and field as the drug name and less likely to be overlooked.

2. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.

3. We recommend revising the statement (b) (4) (b) (4) to read "Recommended dosage: see Prescribing Information".

4. We recommend revising the statement (b) (4) (b) (4) to read as follows for improved clarity (modify based on number of pens per carton):

"Discard unused portion of the pen 28 days after first opening.

Date of first opening: Pen 1: __/__/__.
Pen 2: __/__/__.
Pen 3: __/__/__.
Pen 4: __/__/__.
Pen 5: __/__/__."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Semglee received on February 28, 2019 from Mylan GmbH (Mylan), and the listed drug (LD).

Table 3. Relevant Product Information for Semglee and the Listed Drug (Lantus)		
Product Name	Semglee	Lantus (NDA 21081)
Initial Approval Date	n/a	April 20, 2000
Active Ingredient	insulin glargine	
Indication	improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus	
Route of Administration	subcutaneous	
Dosage Form	injection	
Strength	100 units/mL	
Dose and Frequency	Individualized dosage administered once daily at any time of day, but at the same time every day	
How Supplied	10 mL vials 3 mL prefilled pen (1 pen per carton, 3 pens per carton, or 5 pens per carton)	10 mL vials 3 mL SoloStar prefilled pen (5 pens per carton)
Storage	Unopened: Refrigerate (36°F -46°F [2°C -8°C]) until labeled expiration date; Room Temperature (below 86◦F [30◦C]) for up to 28 days Opened: for vial- 28 days Refrigerated or room temperature; for prefilled pen-28 days Room temperature only (Do not refrigerate)	

Reference ID: 4624897

APPENDIX B. BACKGROUND INFORMATION

B.1 Previous DMEPA Reviews

On March 18, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, insulin glargine, 105279, and 210605. Our search identified 4 previous reviews[j], and we confirmed that our previous recommendations were implemented.

B.2 Human Factors Engineering Process

The background information can be accessible in EDR via:

\\cdsesub1\evsprod\nda210605\0045\m1\us\12-cover-letters\resubmission-reviewers-guide.pdf

APPENDIX C. HUMAN FACTORS STUDY REPORT

The HF study results report can be accessible in EDR via:

\\cdsesub1\evsprod\nda210605\0045\m3\32-body-data\32p-drug-prod\insulin-bioc-bnglr\32p2-pharm-dev\container-closure-system-device-development.pdf

[j]Vee S. Memorandum Review of Revised Human Factors Validation Protocol for insulin glargine (IND 105279). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 January 12. RCM No. 2015-1823.

Vee S. Human Factors Protocol Review for insulin glargine (IND 105279). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 May 18. RCM No. 2016-919.

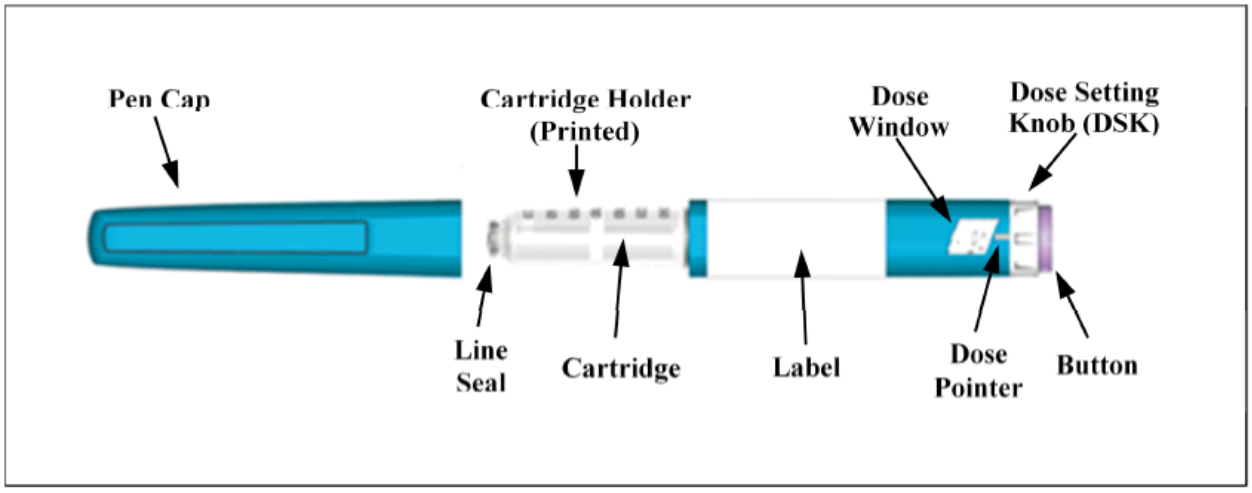
Conrad A. Label and Labeling and Human Factors Results Review for Semglee (NDA 210605). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Apr 4. RCM No. 2017-842 and 2017-1868.

White M. Final Written Response for Type C meeting for insulin glargine (MYL-1501D). Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2018 Jun 5. IND 105279.

Reference ID: 4624897

APPENDIX D. REVIEW OF PRODUCT SAMPLES

We received 5 product samples for evaluation and did not identify medication error concerns.



Reference ID: 4624897

APPENDIX E. INFORMATION REQUEST

1. We sent an information request on May 28, 2019 for the Applicant's analysis of postmarketing medication error cases, adverse event cases, and product complaints associated with product selection errors between Semglee and other insulin products, particularly Humulin R U-500, as we noted that Semglee was marketed in other countries. In addition, we requested clarification regarding the differences between the carton and container labels proposed for use in the US and those approved for use in other countries.

   Mylan's response was submitted to the EDR on June 4, 2019:

   - \\cdsesub1\evsprod\nda210605\0055\m1\us\111-information-amendment\safety-response-to-information-request-dated-may-28-2019.pdf
   - \\cdsesub1\evsprod\nda210605\0055\m1\us\111-information-amendment\appendix-1-summary-of-safety-cases-medication-errors.xlsx

2. We sent an information request on July 26, 2019 for the Applicant's analysis of the potential for patients to be prescribed Semglee and Humulin R U-500.

   Mylan's response was submitted to the EDR on August 2, 2019:

   - \\cdsesub1\evsprod\nda210605\0063\m1\us\111-information-amendment\cmc-response-to-information-request-dated-july-26-2019.pdf
   - \\cdsesub1\evsprod\nda210605\0063\m1\us\111-information-amendment\appendix-1-fault-tree-analysis.pdf

Reference ID: 4624897

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[k] along with postmarket medication error data, we reviewed the following Semglee labels and labeling submitted by Mylan GmbH (Mylan).

- Container Labels and Carton Labeling received on February 28, 2019
  - \\cdsesub1\evsprod\nda210605\0045\m1\us\114-labeling\draft\carton-and-container\draft-carton-and-container-labels-pdf.pdf
- Prescribing Information received on February 28, 2019
  - \\cdsesub1\evsprod\nda210605\0045\m1\us\114-labeling\draft\labeling\draft-labeling-text-clean-pdf.pdf
- Pen Instructions for Use received on February 28, 2019
  - \\cdsesub1\evsprod\nda210605\0045\m1\us\114-labeling\draft\labeling\draft-labeling-text-instructions-for-use-pen-clean-word.docx
  - \\cdsesub1\evsprod\nda210605\0045\m1\us\114-labeling\draft\labeling\draft-labeling-text-instructions-for-use-pen-clean-pdf.pdf
- Vial Instructions for Use received on February 28, 2019
  - \\cdsesub1\evsprod\nda210605\0045\m1\us\114-labeling\draft\labeling\draft-labeling-text-instructions-for-use-vial-clean-word.docx
  - \\cdsesub1\evsprod\nda210605\0045\m1\us\114-labeling\draft\labeling\draft-labeling-text-instructions-for-use-vial-clean-pdf.pdf
- Patient Information received on February 28, 2019
  - \\cdsesub1\evsprod\nda210605\0045\m1\us\114-labeling\draft\labeling\draft-labeling-text-patient-information-vial-clean-pdf.pdf
  - \\cdsesub1\evsprod\nda210605\0045\m1\us\114-labeling\draft\labeling\draft-labeling-text-patient-information-pen-clean-pdf.pdf

5 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[k] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Reference ID: 4624897

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JASON A FLINT
08/15/2019 12:02:28 PM

ARIANE O CONRAD
08/15/2019 12:34:44 PM

MILLIE B SHAH
08/15/2019 12:52:55 PM

MISHALE P MISTRY on behalf of QUYNHNHU T NGUYEN
08/15/2019 12:55:12 PM

MISHALE P MISTRY
08/15/2019 12:55:41 PM

OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH

INTERCENTER CONSULT MEMORANDUM

Device Constituent Review: CDER NDA210605 - CDRH ICC1900196

Date	July 26, 2019
To	Michael White
Requesting Division	CDER/OND/ODEII/DMEP
From	Rong Guo CDRH\OHT3\DHT3C\THT3C1
Through (Team Lead)	Sarah Mollo CDRH\OHT3\DHT3C\THT3C1
Through (Branch Chief)	CAPT Alan Stevens CDRH\OHT3\DHT3C
Subject	Device review for NDA210605
Combination product	insulin glargine (Semglee)
Recommendation	CDRH recommends **Approval** based on review of the device constituent of the combination product.

Digital Signature Concurrence Table	
Reviewer	Rong Guo -S Digitally signed by Rong Guo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rong Guo -S, 0.9.2342.19200300.100.1.1=2000718961 Date: 2019.07.29 09:53:54 -04'00'
Team Lead	
Branch Chief	Alan M. Stevens -S

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2019-04581
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=4934
ICC tracking # (Lead)	ICC1900196
Submission Number	NDA210605
Sponsor	Mylan
Drug	ICC1900196
Indications for Use	Indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
Device Constituent	Pen injector
Route of Administration	S.C.

Table 2. Important Dates	
Information Requests Sent	n/a
Review Checkpoints	**Meeting / Due Date**
Primary Review / Lead Device Review	

2. PURPOSE/BACKGROUND

2.1. Scope

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH) regarding NDA210605 insulin glargine (Semglee). The device consultant authoring this review memorandum has performed a review of device constituent part of the combination product.

3. BACKGROUND

NDA210605 was issued a CR letter on 05/17/2018. Device constitute part was reviewed in the original submission with no deficiency. Review memo was uploaded into DARRTS by Rong Guo on 03/27/2018. The Sponsor re-submitted NDA210605 in response to FDA's major deficiencies, labeling comments, an updated proprietary name request, a safety update and information that addresses the additional comments regarding product quality.

The pen injector has no change in the resubmission. In addition to addressing the deficiencies to the CR letter, Biocon Sdn. Bhd. Facility (FEI 3011248248) is added as a new facility for pen assembly in addition to Biocon Limited (Bangalore, India). This new facility is responsible for activities related to manufacturing, filling, primary packaging, quality control testing [Chemical/Physical, Microbiological (sterility and non-sterility) testing] of the 3 mL cartridges and pre-filled pen assembly (secondary packaging), quality control testing [Chemical/Physical] of the pre-filled pens and secondary packaging in carton box. A desk review of the quality system was performed and there was no issue. Review memo was uploaded into DARRTS by Rong Guo on 05/28/2019. After a desk review of the facility inspection, CDRH recommended a pre-approval inspection of the facility Biocon Sdn. Bhd. Facility (FEI 3011248248).

An inspection to Biocon Sdn. Bhd. Facility was performed 06/24-07/05/2019. An FDA 483 letter was issued with 12 items. Observation 12 is device related: (b) (4)

Reference ID: 4669996

(b) (4)

Sponsor submitted response to the 483 letter on 07/26/2019, and "promised to correct". The response is acceptable since this observation will not pose any significant safety concerns. CDRH review team recommends the inspection is acceptable. This recommendation is made without reading the EIR.

4. RECOMMENDATION

CDRH recommends Approval based on review of the device constituent of the combination product.

Reference ID: 4669996

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/s/

MICHAEL G WHITE
07/30/2019 01:19:01 PM
Filed on behalf of Rong Guo, CDRH reviewer, CDRH\OHT3\DHT3C\THT3C1

NDA 21605 Immunogenicity Review (Resubmission)

Application Type	NDA
Application Number	210605
Submit Date	February 28, 2019
Received Date	February 28, 2019
BsUFA Goal Date	7/17/2019 Primary Reviews due
Division/Office	Division IV/ OBP
Review Completion Date	July 14, 2019
Product Code Name	MYL-1501D
Proposed Proper Name[1]	Insulin glargine
Proposed Proprietary Name[1]	SEMGLEE
Pharmacologic Class	Insulin
Applicant	Mylan
Applicant Proposed Indication(s)	SEMGLEE is a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
Recommended Regulatory Action	There are no immunogenicity issues that would prevent approval

Immunogenicity Reviewers

Primary Reviewer(s)	Frederick Mills, Ph.D., Staff Scientist, Division IV, OBP
Secondary Reviewer(s)	Gerald Feldman, Ph.D., Chief, Laboratory of Immunobiology, Division IV, OBP
Tertiary Reviewer(s)	

[1] The proposed proper and proprietary names are conditionally accepted until such time that the application is approved.

Reference ID: 4624007

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Reference ID: 4624007

1. Summary Basis of Recommendation/Executive Summary

1.1 Immunogenicity Executive Summary and Recommendation

In the first review cycle, data from studies comparing Lantus with MYL-1501D (Semglee) manufactured with process V were provided and reviewed. These studies, were Study MYL-GAI-3001: T1D, conducted in a Type 1 diabetes population, and study MYL-GAI-3002:T2D, conducted in a Type 2 diabetes population. The immunogenicity data included ADA, anti-insulin, and HCP antibody data. The OBP immunogenicity review during the first review cycle indicated no significant immunogenicity differences between Lantus and MYL-1501D produced using process V. These studies are not discussed further in the current review of the sponsor's resubmission.

In summary, the immunogenicity assays are suitable for their intended purpose and support the conclusions that there are no significant immunogenicity differences between MYL-150D and LANTUS, or between MYL-150D Process V and MYL-150D Process VI. There are no immunogenicity concerns that would prevent approval.

1.2 Scientific Justification and Bridge to U.S.-licensed Reference Product (Lantus)

Appropriately validated immunogenicity assays indicate no significant immunogenicity differences between MYL-1501D and Lantus.

1.3 Deficiencies and Other Recommended Comments to Applicant

None

2. Review

Document Reviewed	Submission Date
NDA 21065, Amendment 45	February 28, 2019

2.1 Immunogenicity Risk Assessment

MYL-1501D is a long lasting insulin analogue and a follow-on product to Lantus, which is produced by Sanofi-Aventis. Both MYL-1501D and Lantus are designated as insulin glargine. Insulin glargine has a substitution of glycine for asparagine at position 21 in the insulin A chain, and addition of two arginine residues at position 30 of the insulin B chain. (b) (4)

(b) (4)

(b) (4)

Mylan has performed the majority of their clinical studies using a manufacturing process designated Process V. However, the proposed commercial material is manufactured at a different site by a somewhat different process, designated Process VI. Between Processes V and VI, there are some QA differences including (b) (4) glycosylated species and impurities for Process VI. In the original submission Mylan did not provide clinical immunogenicity data for Process VI.

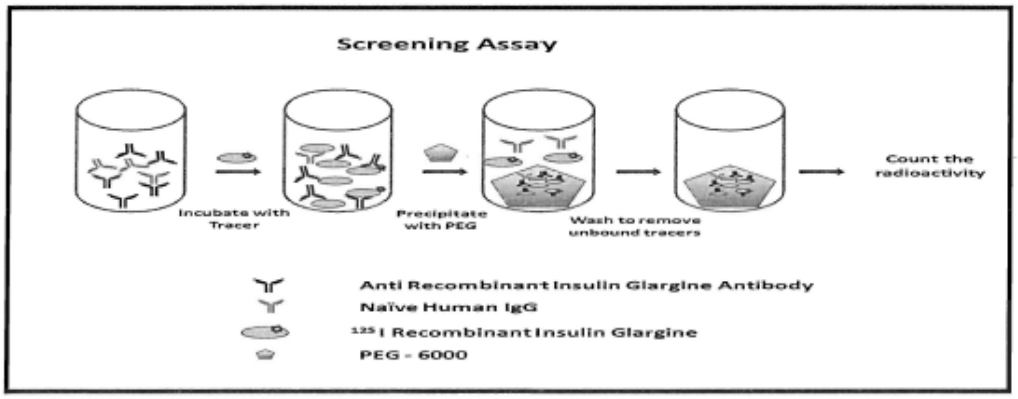
As part of the Complete response to the original submission, the FDA recommended that the Sponsor provide clinical PK and immunogenicity data demonstrating comparability for material prepared via Processes V and VI. This was necessary because there is no immunogenicity data for Process VI material], which will be used commercially, and because there are some differences in Quality attributes between Process V and Process VI, clinical performance, including immunogenicity, would be difficult to predict.

2.2 Validation of Anti-Drug Antibody Assay

2.2.1 Method Principle

The ADA screening and confirmatory assays utilize RadioImmuno Precipitation Assay (RIPA) methodology. Samples are treated with acid to release antibody from free drug, followed by charcoal adsorption of the free drug (either MYL-1501D (*designated MIG in this discussion*,) or Lantus). The samples are then neutralized and centrifuged to remove the charcoal and incubated overnight with ^{125}I labeled MIG or Lantus tracer under the following conditions.
RIPA assay buffer only
RIPA assay buffer with excess unlabeled MIG
RIPA assay buffer with excess unlabeled Lantus
RIPA assay buffer with excess unlabeled Novolin R (recombinant human insulin, native sequence)

After the overnight incubation, bovine IgG and PEG are added to precipitate the tracer-antibody complexes, which are then pelleted, and washed with PEG solution. Supernatants are removed and emissions are counted in a gamma-counter, as shown in the following schematic



The % binding (%B/T) is calculated as the ratio of the precipitated counts to total gamma counts for the uninhibited tube (RIPA assay buffer only) as well as for the tubes inhibited with competitor MIG, Lantus, or Novolin R. In this assay format, screening and confirmation are performed simultaneously; i.e. inhibition with

Reference ID: 4624007

MIG, Lantus, and Novolin R are included in the assessment of each sample so that specific binding (%SB is reported as the difference between uninhibited RIPA assay buffer only tube and the inhibited MIG, Lantus, or Novolin R tubes. Thus the assay captures specific reactivity to MIG and Lantus, as well as reactivity to native insulin as per the Novolin R tube. The native insulin reactivity is referred to as cross-reactivity.

To improve drug tolerance, prior to assay acid dissociation of insulin-ADA complexes is performed, followed by activated charcoal absorption of unbound insulin. Comparability between MIG tracers prepared from Process V and Process VI material was established, and a Process VI tracer was used for the ADA assays reported for the Process V vs. Process VI immunogenicity clinical immunogenicity study MYL-GAI-3004 (T1DM).

2.2.2 Validation Exercises

[Insert summary table(s) here.]

Table 2.1: Validation Results and Reviewer Assessment for ADA assay

Validation Parameter	**Study**: MYL-GAI-3004 (T1DM), **Validation Report:** (b) (4) GCL-601 sc-18-124-018 in NDA	**Reviewer Comment**
Contract Research Org	(b) (4)	
Assay principle	RadioImmunoPrecipitation (RIPA)	*Standard, sensitive assay for anti-insulin ADA*
Sample Pretreatment (Acid dissociation)	Samples are acid dissociated, followed by activated charcoal absorption of unbound insulin	*This procedure increases the signal across a range of PC concentrations in the presence of added drug, indicating improved drug tolerance*
MIG V vs MIG VI tracer	Assay comparability between MIG process V and process VI was determined by using labeled tracers from either MIG process V or process VI samples to run PC antibody dilution antibody curves of with data points at 500, 375, 250, 187.5, 125, 62.5, 31.25, and 15.6 ng/mL. All passing runs met the acceptance criteria with intra- and inter-assay precision of < 20%.	*I have examined the tabulated data for this MIG V and MIG VI tracer curves and find there reading show little difference at each concentration, indicating that MIG V and MIG VI material behave similarly in the ADA assay. The MIG VI tracer was used for the data in the current submission.*
Positive control (PC)	Guinea pig anti-Lantus/Mylan Insulin Glargine Antibody	*A polyclonal control antibody is appropriate, since the patient ADA are polyclonal*
PC Dose Curve and Hook Effect	The higher the antibody concentration, the higher the result. It does appear that antibody saturation is present at 10,000-20,000 ng/m, but no decreased signal with increasing PC (hook effect) was observed.	*No hook effect is observed, ensuring that signal will be in some way proportional to the level of ADA. The plateau at very high PC concentration is expected, and is likely beyond anticipated ADA levels*

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LPC	15 ng/ ml	*This is near the sensitivity of the assay, and is actually slightly below the 17. 9 ng/ ml sensitivity. However the precision for the LPC is narrow, indicating that this LPC is adequate for controlling the low range of the assay.*
HPC	500 ng / ml	*This HPC is near the upper end of the linear range for the assay, and is thus appropriate for controlling the upper range.*
Matrix and NC	Human serum (Normal healthy and T1DM)	*This is the appropriate matrix for an ADA assay on serum, and will provide stability for the ADA*
MRD	1 / 4	*This low dilution will promote sensitivity*
NC system suitability range	≤ 0.73 % SB MIG tracer/MIG competitor	*The NC should be < than the CP, ensuring that the background is always < the CP, allowing adequate detection of very low signals*
LPC system suitability range	0.85-4.58 %SB MIG tracer/MIG competitor	*The LPC concentration is very low (15 ng/ ml), suggesting potential for high variability. However, the actual LPC precision is narrow, indicating adequate control in the low range.*
HPC system suitability range	63.01-85.79 %SB MIG tracer/MIG competitor	*This specification corresponds to an ~ 8% range around a median, which should provide adequate control*
Antigenic Equivalence testing (MIG V vs. MIG VI)	PC was spiked into NC at the HPC level Analysis of the HPC sample was performed with MIG V and MIG VI to yield inhibition curves. All samples at each inhibitor level were acceptable and all of the %CVs were < 20%.	*Examination of the tabulated data for MIG V and MIG VI shows close similarity, supporting antigenic equivalence.*
Screening cut- point (SCP)	Screening and confirmation are in one assay; i.e. inhibition with MIG, Lantus, and Novolin R included in analysis of each sample so specific binding (%SB) is reported as the difference between uninhibited RIPA assay buffer only tube and the inhibited MIG, Lantus, or Novolin R tubes. This captures specific reactivity to MIG and Lantus, and native insulin (Novolin R). Cut points were determined from 51 individual human serum samples. Data was analyzed to determine cut points that would be expected to result in a false positive rate of approximately 5%. A fixed cut point of 0.73% SB was calculated for MIG tracer /MIG competitor and	*This is standard procedure for anti-insulin ADA assays. The cut points are both < 1%SB, ensuring that even low ADA responses will be reported.*

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	0.85% SB for MIG tracer /Novolin B competitor	
Confirmatory cut-point (CCP) Floating	NA-see above	
Titer Cut Point (TCP)	NA-for insulin RIPA, %SB is taken as a quantitative measure of ADA	*The use of % SB as a quantitative measure is appropriate for RIPA, as this method has a large linear range.*
Assay Drug tolerance	Positive control at 31.3 ng/mL can be detected in the presence of 100 ng/mL of either MIG or NOV	*The expected mean PK is <1 ng/ ml, so this drug tolerance is adequate*
Target tolerance	NA	*NA*
Sensitivity	17.9 ng/mL	*This represents a sensitivity that is in the low range for ADA assays, ensuring detection of low responses*
Repeatability/Intra-assay variability	MIG VI tracer /MIG VI competittor %CV Intra Inter NC -108.1 -168.6 LPC 13.2 15.4 HPC 3.6 3.6 MIG VI tracer / Novolin R competitor %CV Intra Inter NC 312.9 320.4 LPC 13.7 14.1 HPC 3.9 4.2	*<u>Explanation for the NC %CV values.</u> The % CV values appear large, but it is important to note that they are in fact based upon small assay values. For the MIG /MIG NC precision, the Intra and Inter-assay mean values were -0.36 % SB (slightly negative inhibition). The SD values were 0.39 and 0.61, so these yielded negative % CV based upon small values. Similarly, for the MIG/NOV NC precision, the intra and inter assay values were again small (0.10 and 0.10 % SB). The SD values were small, but larger that the means, so the intra and inter-assay % CVs were 312.9 and 320.4 Overall, the Precision ranges are narrow, indicating that the assay is likely to provide results that can be meaningfully compared across samples and between runs.*
Intermediate Precision (IP)/inter-assay variability	See above	
Selectivity	Criterion: Test serum lots spiked at the LPC level should exhibit an increase in %SB greater than the MIG VI tracer/MIG VI competitor cut point relative to the corresponding unspiked lot. Results: eighteen out of 20 (90%) of positive spikes met the acceptance criteria.	*The assay reproducibly shows a Low Positive Control signal detectable over background (assay cut point) demonstrating selectivity*
Stability	Stability confirmed for positive control s over the following conditions: Freeze/thaw	*The positive controls are stable over the expected range of storage conditions*

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	-70 °C 8 cycles -20 °C 8 cycles Short-term 20 to 25 °C 24 hours 2 to 8°C 48 hours, but limited to 24 housr because reduction in LPC signal	
Lipemia	LPC was assessed in 5 lots of lipemic serum. MIG tracer 5/5 ≥ CP Lantus tracer 4/5 ≥ CP	*These data demonstrate that serum lipid is expected to have little affect on the detection of positive ADA signals by this assay.*
Hemolysis	LPC was assessed in 5 lots of hemolyzed serum. MIG tracer 5/5 ≥ CP Lantus tracer 5/5 ≥ CP	*These data demonstrate that hemolysis in patient sera is expected to have no effect on the detection of positive ADA signals by this assay.*
ADA Assay Assessment	**Suitable for Intended purpose**	

Additional Reviewer Comments:

2.3 Facility Inspection (ND)

2.4 Analysis of Clinical Immunogenicity Results

2.4.1 Executive Summary

In the first review cycle, data from studies comparing Lantus with MYL-1501D manufactured with process V were provided and reviewed. These studies, which included immunogenicity data, were Study MYL-GAI-3001: T1D, conducted in a Type 1 diabetes population, and study MYL-GAI-3002:T2D, conducted in a Type 2 diabetes population. The OBP immunogenicity review during the first review cycle indicated no significant immunogenicity differences between Lantus and MYL-1501D produced using process V. These studies are not discussed further in the current review of the sponsor's resubmission.
The new data in the current submission provide further support for comparable immunogenicity between LANTUS and MYL-1501D, and also demonstrating comparable immunogenicity for MYL-1501D produced via Process V and Process IV.

2.4.2 Study Designs and Criteria for Process V and VI similarity

The resubmission contains data from Study MYL-GAI-3004 (T1DM), which was multicenter, double-blind, randomized, parallel-group Phase 3 study in subjects with T1DM to compare efficacy, immunogenicity, and safety of MYL-1501D from Process V and Process VI, given in combination with insulin lispro with T1DM. In this study, subjects were randomized to he following two arms: Process V or Process VI for 18 weeks of treatment.

The sponsor's resubmission also contained data from the MYL-GAI-3003:T1D study, which was an extension of the MYL-GAI-301:T1D study, with the following of randomization of subjects:
MYL-IG sequence : 12 weeks MYL-1501D, 12 weeks Lantus, weeks MYL-1501D
LANTUS sequence: 12 weeks Lantus, 12 weeks Lantus, 12 weeks Lantus

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2.4.3 Study Results

2.4.4 For study MYL-GAI-3004 (T1DM), the following is a summary of the immunogenicity data:

		Process V	Process VI
Incidence	**%**		
Total ADA			
	baseline	85.2	88.2
	18 weeks	86.1	86.3
Cross-reactive ADA			
	baseline	88.9	85.5
	18 weeks	86.1	84.3

Potential Neutralization : Subjects with > 10% cross-reactive ADA from baseline, ≥ 0.2% increase in HbA1c from baseline, and an increase in total insulin dose were identified.

	Process V	**Process**	**VI**
week 12	2		0
week 18	1		2

Hypersensitivity
For ADA positive subjects, no hypersensitivity was reported

For this study the sponsor captured Treatment Emergent: Responses (TEAR), with subjects receiving a positive TEAR assessment if they met either of the following two criteria:
Negative at baseline, and positive anytime during study
or
Positive at baseline, and an increase of ≥ 30 % SB anytime during study
The following table provides a TEAR summary.

	MIG assay	
	MYL-1501D Process VI (N=110) n (%)	**MYL-1501D Process V (N=108) n (%)**
Cross Reactive ADA	29 (26.4%)	28 (25.9%)
Difference	0.44%	
90% CI	(-9.35%, 10.23%)	
P value	0.941	
Total ADA	30 (27.3%)	32 (29.6%)
Difference	-2.35%	
90% CI	(-12.41%, 7.69%)	
P value	0.700	

Moreover, these TEAR differences were similar to or less than the TEAR differences between MYL-150D and LANTUS in the 3001, 3002, and 3003 studies (data not shown)
Reviewer comment

Reference ID: 4624007

Overall, the immunogenicity data from Study MYL-GAI-3004 show close similarity for subjects treated with either Process V and Process VI MYL-1501D.

For the MYL-GAI-3003 extension study, the summary immunogenicity results are as follows:

Total Insulin ADA %SB

Baseline

MYL-IG sequence		**LANTUS sequence**	
MYL-IG assay	**LANTUS assay**	**MYL-IG assay**	**LANTUS assay**
12.023	11.465	10.023	10.396
9.112 *wk 32*	9.146 *wk 16*	6.674 *wk 28*	6.801 *wk 25*

The incidences of total and cross-reactive were ADA similar ;i.e.

Cross Reactive ADA

18 (28.1%)	23 (35.9%)	24(38.1%)	24 (38.1%)

HCP incidence was also similar ; i.e.

92.2	%	95.2 %

Reviewer comments

Overall, Study MYL-GAI-3003 showed similar % SB, ADA incidence, and anti-HCP between the MYL-1501D and Lantus sequences, supporting the view that there are no important immunogenicity differences in subjects treated with MYL-1501D or Lantus, and consistent with the results of the MYL-GAI-3001 and MYL-GAI-3002 studies, which were reviewed in the first review cycle.

2.5 Information Requests Sent During Review

IR sent 6/24/2019, response received 7/02/2019

Your validation reports for ADA and anti-insulin antibody assays do not address the effects of hemolysis and lipidemia on the assays. Describe procedures used for immunogenicity assays on hemolyzed or lipidemic samples and discuss how hemolysis or lipidemia may have affected your assay results.

The 7/02/2019 response was adequate ; i.e. the data provided in the response indicates that the effects of hemolysis or lipidemia are not important.

Reference ID: 4624007

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/s/

FREDERICK C MILLS
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OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH

INTERCENTER CONSULT MEMORANDUM

Device Constituent Review: CDER NDA210605 - CDRH ICC1900196

Date	May 24, 2019
To	Leeza Rahimi
Requesting Division	CDER/OPQ/OPRO/DRBPMI/RBPMBI
From	Rong Guo CDRH\OHT3\DHT3C\THT3C1
Through (Team Lead)	Sarah Mollo CDRH\OHT3\DHT3C\THT3C1
Through (Branch Chief)	CAPT Alan Stevens CDRH\OHT3\DHT3C
Subject	Device review for NDA210605
Combination product	insulin glargine (Semglee)
Recommendation	No update. CDRH has no further comments.

Digital Signature Concurrence Table	
Reviewer	Rong Guo -S Digitally signed by Rong Guo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rong Guo -S, 0.9.2342.19200300.100.1.1=2000718961 Date: 2019.05.28 11:02:24 -04'00'
Team Lead	Sarah Mollo Digitally signed by Sarah Mollo DN: cn=Sarah Mollo, o=FDA, ou, email=sarah.mollo@fda.hhs.gov, c=US Date: 2019.05.28 11:43:39 -04'00'
Branch Chief	

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2019-04581
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=4934
ICC tracking # (Lead)	ICC1900196
Submission Number	NDA210605
Sponsor	Mylan
Drug	ICC1900196
Indications for Use	Indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
Device Constituent	Pen injector
Route of Administration	S.C.

Table 2. Important Dates	
Information Requests Sent	n/a
Review Checkpoints	**Meeting / Due Date**
Primary Review / Lead Device Review	

2. PURPOSE/BACKGROUND

2.1. Scope

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH) regarding NDA210605 insulin glargine (Semglee). The device consultant authoring this review memorandum has performed a review of device constituent part of the combination product.

3. ADMINISTRATIVE

3.1. Documents Reviewed

FDA 483 letter to Biocon Malaysia site
Biocon Malaysia EIR 2018

4. BACKGROUND

NDA210605 was issued a CR letter on 05/17/2018. Device constitute part was reviewed in the original submission with no deficiency. Review memo was uploaded into DARRTS by Rong Guo on 03/27/2018. The Sponsor re-submitted NDA210605 in response to FDA's major deficiencies, labeling comments, an updated proprietary name request, a safety update and information that addresses the additional comments regarding product quality.

The pen injector has no change in the resubmission.

In addition to addressing the deficiencies to the CR letter, Biocon Sdn. Bhd. Facility (FEI 3011248248) is added as a new facility for pen assembly in addition to Biocon Limited (Bangalore, India). This new facility is responsible for activities related to manufacturing, filling, primary packaging, quality control testing [Chemical/Physical, Microbiological (sterility

and non-sterility) testing] of the 3 mL cartridges and pre-filled pen assembly (secondary packaging), quality control testing [Chemical/Physical] of the pre-filled pens and secondary packaging in carton box.

3-mL Cartridges Manufacturing and Testing; Pre-filled Pen Assembly and Testing; and Secondary packaging

Site Address	**Biocon Sdn. Bhd. (930330-U),** No.1, Jalan Bioteknologi 1, Kawasan Perindustrian SiLC, 79200 Iskandar Puteri, Johor, Malaysia.	**Responsibilities:** The activities related to manufacturing, filling, primary packaging, quality control testing [Chemical/Physical, Microbiological (sterility and non-sterility) testing] of the 3 mL cartridges and pre-filled pen assembly (secondary packaging), quality control testing [Chemical/Physical] of the pre-filled pens and secondary packaging in carton box.
DUNS Number	865785591	
FEI Number	3011248248	

After a desk review of the facility inspection, the following IR was conveyed to the Sponsor on 03/28/2019:

After reviewing the provided documents related to 21 CFR Part 4 requirements during the documentation review of NDA210605 in reference to applicable 21 CFR 820 regulations of the finished combination product, the following deficiencies have been identified. Please provide the following information as well as where in the application we can find the information, if already provided.

1. Please provide a summary of your management structure with executive responsibility for those who manage, perform, and assess work affecting quality of the product and related controls to ensure that your quality policies are appropriately implemented and followed, and the product appropriately designed and manufactured in conformance with CGMP requirements, including quality system requirements met as per 21 CFR 820.20.

2. A summary of your design control system under 21 CFR 820.30 must be included for the device constituent part and combination product. The design control information should include initial design, planning and development, design input, design output, design review, design transfer, design verification, design validation that meets the proposed intended use of the final combination product, design changes, and design history file. For changes made to the device constituent part of the combination product, the impact of the design changes on the overall combination product performance should be considered and documented. All the design control activities must be documented in the Design History File (DHF) and subjected for design reviews. In addition, the location of DHF should be provided to the Agency for the facility inspection determination.

3. Please provide a summary of information pertaining to the Purchasing Control as per 21 CFR 820.50 to demonstrate controls and documentation for components, products, or services (e.g., sterilization) received at your facility for use in the manufacture of the combination product. The summary should include your evaluation process of your suppliers that meet the manufacturing acceptance criteria of the combination product specifications. Notification of changes by the suppliers should be considered in your Purchasing/Supplier agreement as changes to incoming specification that can impact the safety and effectiveness of the final combination product.

Reference ID: 4639693

4. Please provide a summary of information related to Corrective and Preventive Actions (CAPA) as per the requirement of 21 CFR 820.100. CAPA procedures are used to determine the cause of problems and non-conformances, and the appropriate measures used to correct and prevent such problems and non-conformances from recurring. The CAPA system must account for investigations into failures in the device constituent. CAPA activities for the analysis of sources of quality data to identify existing and potential cause of nonconformances, related investigations, and actions considered to correct and prevent recurrences of problems and non-conformances, including the verification or validation of the actions should be documented under your CAPA System as described in 21 CFR 820.100.
Please note that combination products manufactured under the CGMP drug operating system, the Applicant/Licensure must also fulfill the requirements under 21 CFR Part 4.4b to show compliance to 21 CFR Part 4 for the finished combination product. To assist in the preparation of the above summaries related to the 21 CFR 820.20, 21 CFR 820.30, 21 CFR 820.50 and 21 CFR 820.100, you may reference the FDA Guidance 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003) located at the link: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

For more information regarding cGMP requirements for combination products please refer to the FDA Guidance titled Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products issued in January 2017 (https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf).

The Sponsor responded that the information was provided in Sequence 0004 and submitted on June 9, 2017.

***Reviewer Comment**: The provided documentation covers Biocon Sdn. Bhd. Facility. CDRH compliance reviewer Habacuc Barrera reviewed the information in the first cycle and recommended a post-approval inspection for Biocon Bangalore site. See review memo uploaded into DARRTS by Anika Lalmansingh on 12/22/2017. There is no need to re-do the desk review of these information. The response form the Sponsor is acceptable.*

Biocon Sdn. Bhd. Facility was never inspected for medical device. The most recent drug inspection which ended on 02/15/2018 was OAI and an FDA 483 letter was issued. The 483 letter pointed out several deficiencies related to sterility of the DP and process validation (b) (4), and failure to explain some discrepancy. These deficiencies indicate (b) (4) the pen injector might have the same issues.

CDRH recommended a pre-approval inspection of site Biocon Sdn. Bhd. (FEI 3011248248). In addition to performing the medical device quality system inspection, CDER should ensure the 2/15/2018 OAI inspection has been addressed.

Upon communicating with OPQ team, the inspection has been scheduled in late June. There is no update on this at the time point when the device reviewer is drafting the memo.

5. RECOMMENDATION

There is no update on the device constitute part of the combination product. CDRH has no further comments.

Reference ID: 4639693

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/s/

RONG GUO
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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 07, 2019

TO: Lisa Yanoff, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Office of New Drugs

FROM: Sripal Reddy Mada, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Deputy Director
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Routine inspection of clinical site supporting clinical endpoint Study CEL-HI-200 Non-Responsive

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of ProSciento, Inc., Chula Vista, CA.

No objectionable conditions were observed, and Form FDA 483 was not issued at the close-out of the inspection. The final inspection classification for the inspected site is No Action Indicated (NAI).

1.1. Recommendation

After reviewing the inspectional findings, I conclude the data from the audited study CEL-HI-200 Non-Responsive are reliable to support a regulatory decision.

2. Inspected Study:

The following study was audited during the inspection:

Non-Responsive

Study Number: CEL-HI-200
Study Title: "A Double-Blind, Randomized, Crossover, Euglycemic Glucose Clamp Study to Test for Bioequivalence between Celerity's Premixed Regular Human Insulin (rDNA origin) Injection 1 USP unit/mL in 0.9% Sodium Chloride and Novolin® R in Healthy Subjects"
Dates of conduct: 05/22/2017 – 10/21/2017

Site:
Site Name: ProSciento, Inc.
Street Address: 855 3rd Avenue, Suite 4400
City, State: Chula Vista, CA, 91911
Investigator Name: Rachel Peterson, MD

3. Inspectional Findings

ORA investigators Lakecha N. Lewis, CSO (Lead) and Marilyn S. Babu, CSO inspected ProSciento, Inc., Chula Vista, CA from April 08-12, 2019.

The inspection included a thorough examination of study records, case report forms (CRFs), informed consent process, protocol deviations, institutional review board approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, and adverse events.

At the conclusion of the inspection, investigators Lakecha Lewis and Marilyn Babu did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site.

4. Conclusion:

After reviewing the inspectional findings, I conclude the data from the audited study are reliable. In addition, data from the study using a similar design submitted to a pending application (**Attachment 1**) should be accepted for further Agency review. Also, studies of similar design conducted at ProSciento before the end of the current surveillance interval should be considered reliable without an inspection.

Sripal Reddy Mada, Ph.D.
Pharmacologist

Reference ID: 4620102

Final Classification:

NAI - ProSciento, Inc.
Chula Vista, CA 91911
FEI#: 3004445267

cc:
OTS/OSIS/Kassim/Mitchell/Fenty-Stewart
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au/Mada
ORA/OMPTO/OBIMO/ORABIMOW.Correspondence@fda.hhs.gov

Draft: SRM 05/02/2019
Edit: YMC 05/03/2019; JAK 05/07/2019

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/ProSciento, Inc., Chula Vista, CA, USA

OSIS File #: Non-Responsive
BE 7633 (NDA 210605)

FACTS: 11888324

Reference ID: 4620102

Attachment 1

Study in support of Pending Application

Application #	Study #	Study Type	Drug Name	Dates of conduct
NDA 210605	MYL-1501D-1003	In vivo	MYL-1501D (Process V and Process VI)	December 7, 2017 – August 15, 2018

NDA 210605

Study Number: MYL-1501D-1003
Study Title: "A Glucose Clamp Study Investigating the Bioequivalence of MYL-1501D (Process V) and MYL-1501D (Process VI) with US Lantus Reference Product in Healthy Volunteers"

Site:
Site Name: ProSciento, Inc.
Street Address: 855 3rd Avenue
City, State: Chula Vista, CA, 91911
Investigator Name: Linda Morrow, M.D.

Reference ID: 4620102

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/s/

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JOHN A KADAVIL
05/08/2019 04:49:06 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 5/3/2019

TO: Division of Metabolism and Endocrinology Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 210605

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

PROFIL, Neuss, Germany: The Office of Regulatory Affairs (ORA) inspected the site in January 2018, which falls within the surveillance interval. The inspection was conducted under the following submission: NDA 210605. The previously inspected study was conducted within 1 year of the current study MYL-1501D-1004, utilized a similar test product (insulin glargine injectable), and involved the same Clinical Investigator-Dr. Oliver Klein.

The final classification for the inspection was No Action Indicated (NAI).

PROFIL, Mainz, Germany: The Office of Regulatory Affairs (ORA) inspected the site in January 2018, which falls within the surveillance interval. The inspection was conducted under the following submission: NDA 210605. The previously inspected study was conducted within 1 year of the current study MYL-1501D-1004, utilized a similar test product (insulin glargine injectable), and involved the same Clinical Investigator-Dr. Leona Plum-Morschel.

The final classification for the inspection was No Action Indicated (NAI).

(b) (4) **:** OSIS inspected the site in December 2017, which falls within the surveillance interval. The inspection was conducted under the following submissions: Non-Responsive and NDA 210605.

The final classification for the inspection was Voluntary Action Indicated (VAI) for the following observations related to Non-Responsive only:

Non-Responsive

Non-Responsive

OSIS recommended that all study date be accepted for Agency review but also recommended that the review division evaluate whether the ADA positive control stability data can be reliably interchanged among different animal species (from rabbit to goat to monkey) (OSIS EIR review – December 2017).

Based on the outcome of the previous inspection and the rationale described above, inspections are not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	PROFIL Institut für Stoffwechselforschung GmbH	Hellersbergstraße 9, D-41460 Neuss, Germany
Clinical	PROFIL Mainz GmbH & Co. KG	Rheinstraße 4c, 55116 Mainz, Germany
Analytical	(b) (4)	

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/s/

NICOLA M FENTY-STEWART
05/03/2019 05:30:03 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	May 11, 2018
To:	William Chong, M.D. Acting 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)** Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Aman Sarai, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI) and Instructions for Uses (IFUs)
Drug Name (established name):	SEMGLEE (insulin glargine injection)
Dosage Form and Route:	solution, for subcutaneous injection
Application Type/Number:	210605
Applicant:	Mylan Pharmaceuticals Inc.

Reference ID: 4204497

1 INTRODUCTION

On April 27, 2017, Mylan Pharmaceuticals Inc. submitted for the Agency's review a 505(b)(2) application for SEMGLEE (inslulin glargine). The proposed indication is for a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

On May 4, 2017, the Division of Metabolism and Endocrinology Products (DMEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Uses (IFUs) for SEMGLEE (inslulin glargine), solution for subcutaneous injection.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI and IFUs for SEMGLEE (inslulin glargine).

2 CONCLUSIONS

Due to outstanding clinical and CMC deficiencies, DMEP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A new review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

Reference ID: 4004497

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/s/

AMANPREET K SARAI
05/11/2018

SHARON W WILLIAMS
05/11/2018

NDA 210605
MYL-1501D insulin glargine follow-on
for treatment of Type 1 and Type 2 Diabetes

From: Frederick C. Mills, Ph.D., Staff Scientist, Division IV, OBP, OPQ, CDER, FDA

To: Gerald M. Feldman, Ph.D., Lab Chief, Division IV, OBP, OPQ

Subject: Immunogenicity assays, and immunogenicity testing

Sponsor: Mylan

Date: April 18, 2018
Revised: April 25, 2018

Comments to the File
This document contains the OBP review of the assay for detection of anti-drug antibodies (ADA) to Mylan's long lasting MYL-1501D insulin glargine product. This assay is also used to detect ADA to the comparator licensed Lantus product, as well as antibodies that react with insulin (cross-reactivity). MYL-150D is produced in yeast, and a yeast host-cell protein (HCP) antibody-based assay has also been reviewed. Both antibody assays are adequately validated.

These antibody assays have been used to evaluate immunogenicity in clinical studies that used Mylan's Process V MYL-1501D, and will be used in additional trials employing Process VI manufacturing, which the Sponsor plans to use for commercial release. The immunogenicity sampling plans for these proposed Process VI studies should be adequate to the immunogenicity time-courses and comparability in immune responses between Processes V and VI.

The review team is planning to issue a Complete Response letter for this review cycle. Because the assays are adequately validated and the proposed immunogenicity sampling plans appear adequate, there are no comments to the Sponsor at this time.

Reference ID: 4223492

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Reference ID: 4823492

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Executive Summary

NDA 210605 is for the proposed licensing of Mylan's MYL-1501D product for treatment of Type1 (T1D) and Type 2 (T2D) diabetes. MYL-1501D is a long-lasting insulin analogue (insulin glargine) and a follow-on product to Lantus, which is produced by Sanofi-Aventis. This NDA contains data on head-to-head trials for MYL-1501D versus Lantus in T1D and T2D patients.

Comparability data for MYL-1501D manufactured with the current Process V versus the proposed commercial Process VI indicates that there is no expected impact from the process change on factors critical for immunogenicity; i.e. overall impurity profile, higher order species (aggregation), amino acid sequence, and stability.

reviewed review of the validation documents for assays used to assess immunogenicity of MYL-1501D indicates that the assays for ADA and anti-Pichia antibodies are appropriate validated and have high sensitivity

ADA (Anti-Drug Antibodies) were assessed using a Radio Immuno Precipitation Assay (RIPA), and this assay will also be used in further proposed studies to support licensing. This assay appears to have high sensitivity of 4.2 ng/ml using the MYL-1501D (MIG) tracer and 4.7 ng/ml using the Lantus tracer, at a ¼ Minimal Required Dilution (MRD). The assay uses a Low Positive Control (LPC) of 50 ng/ ml, which is reasonably close to the sensitivity values. A drug tolerance has been determined as 500 ng/ ml. The other assay performance characteristics, as recommended by the 2016 FDA Guidance for Development and Validation of Immunogenicity Testing, are contained in the validation report; i.e. cutpoints, precision, specificity, hemoglobin and lipid interference, prozone effect, and reagent stability. Cutpoints for confirmation of specific reactivity using specific inhibition (MIG or Lantus) or for cross reactivity (Novolin R) are acceptable. The MYL-1501D and Lantus ADA assays can also detect ADAs reactive with native insulin (cross-reactivity), which is an important part of immunogenicity characterization in any insulin clinical development program. The RIPA assays allow quantitative assessment of ADA levels, and this quantitation is widely used in place of titer evaluation in insulin clinical evaluation.

During ADA assay validation, some assay cross reactivity was observed with G-CSF/filgrastim using the anti-drug antibody high positive control . This observation indicates a theoretical concern that high concentrations of ADA may potentially be reactive with G-CSF. Because some patients may be treated with G-CSF, this concern may need to be discussed in labeling discussions. However, labeling discussions will not occur in this review cycle, as the review team is planning to issue a Complete Response letter.

The Sponsor has also assessed patient antibodies specific for Host Cell Proteins (HCP) from the Pichia pastoris yeast used to produce MYL-1501D, and will use the assay in further studies to support licensing. The HCP assay utilizes an ElectroChemiLuminescence (ECL) methodology. This assay is also adequately validated according to the 2016 FDA guidance. The assay employs an MRD 1:2, which will facilitate detection of low-abundance antibodies. The assay is adequately validated for selectivity, screening and confirmatory cutpoint, precision, specificity, robustness, positive control stability, cross-reactivity to insulins (essentially drug tolerance),

sensitivity, titer assessment, and prozone effect. The assay sensitivity is 57 ng/ml, well within current guidance.

Finally, The Sponsor has obtained samples for antibody testing at the following time points: Screening, Randomization, 2 weeks, 4 weeks, 12 weeks, 24 weeks. These samples have been tested for ADA (anti-drug antibodies), neutralizing antibodies (Nabs), anti-HCP antibodies, and drug concentration (MYL-1501D or Lantus). The sampling time points are appropriate to capture antibody levels at baseline, as well as primary and secondary responses.
Testing for ADA, Nabs, and anti-HCP will provide a relatively complete picture of patient immune responses. Thus the sampling plan is adequate.

Introduction

NDA 210605 is a 505(b)(2) submission for the proposed licensing of Mylan's MYL-1501D product for treatment of Type1 (T1D) and Type 2 (T2D) diabetes. MYL-1501D is a long lasting insulin analogue and a follow-on product to Lantus, which is produced by Sanofi-Aventis. Both MYL-1501D and Lantus are designated as insulin glargine. Insulin glargine has a substitution of glycine for asparagine at position 21 in the insulin A chain, and addition of two arginine residues at position 30 of the insulin B chain. These modifications make insulin glargine soluble in a pH 4 formulation solution, (b) (4)

(b) (4)

MYL-1501D is produced in Pichia pastoris yeast by recombinant DNA technology. (b) (4)

(b) (4)

Process V vs. VI comparability: Potential Impact on Immunogenicity

The process used to make the DS used in the clinical trials for NDA 210605 is designated Process V. Subsequent to advice provide by the EMEA, Mylan made a number of modifications to the manufacturing process (b) (4), resulting in a new process designated Process VI, which Mylan proposes to use after US licensing of NDA 210605. The DS and DP for process VI are manufactured in, Johor, Malaysia.

Mylan has assessed the potential risks resulting from the Process V to Process VI change, including those that may impact immunogenicity

Table 3.2.S.2.6/ 31: List of Critical Quality Attributes Used to Demonstrate Comparability between MYL-1501D Process V and Process VI

Quality Attribute		Criticality	Potential impact
Product Variants			
Size variant	HMWP (high molecular weight impurities)	**High**	Safety, immunogenicity
Sequence variant (impurity profile)	(b) (4)	**Moderate**	Safety, immunogenicity
pI variant (impurity profile)		**Moderate**	Safety, immunogenicity
		Moderate	Safety, immunogenicity
Deamidation variant (impurity profile)		**Low**	Safety, immunogenicity
		Low	Safety, immunogenicity

Quality Attribute	Criticality	Potential impact
Product Attributes		
Protein content (assay)	**Very High**	Efficacy,
Amino acid sequence	**Very High**	Efficacy, safety and immunogenicity
Higher Order Structure	**Very High**	Efficacy, safety and immunogenicity
Zinc content	**Moderate**	Efficacy
Functional Attributes		
Metabolic Activity	**Very High**	Efficacy
Mitogenic Activity	**Very High**	Safety

.

Table 3.2.S.2.6/ 64: Comparability of DP using DS from Process V and VI: Batch Analysis Data

Batch No.	DS Manufacturing process	Parameters						
		pH	HMWP (%)	Zinc content (µg/100U)	Assay (%)	(b) (4)	Total impurities (%)	Any individual impurity (%)
C13DBBFHH-0002	Process V	(b) (4)	BQL					(b) (4)
C13DBBFHH-0004			BQL					
C13DBBFHH-0005			BQL					
BS15005866	Process VI		BQL					
BS15005867			BDL					
BS15006714			BQL					
BQL= Below Quantification limit (LOQ: 0.050%)								

Reviewer comment

There are substantially reduced levels of impurities for process VI relative to process V material, indicating reduced immunogenicity concern for process VI.

The summary data for factors most likely to have an impact on immunogenicity are reproduced below.

Amino acid sequence

Peptide mass fingerprinting under reducing conditions, using Glu-C enzyme-mediated digestion of the protein and subsequent reduction with DTT, was performed to confirm the primary sequence of DS and DP. The 6 expected peptide fragments that were obtained, from all batches of DP derived from DS manufactured by either Process V or Process VI, show masses comparable with those of the theoretical fragments:

Table 3.2.S.2.6/ 67: Expected Theoretical Fragments for Insulin Glargine Digestion Peptide Mass Fingerprinting by MS-MS under Reducing Conditions: Mass of Individual Peptides (Digest with Glu-C)

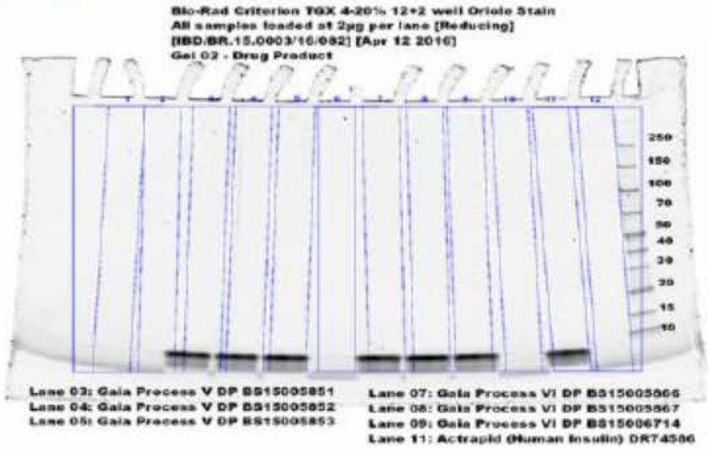
Fragment	Theoretical Mass Mono Da (M+H)	Sequence	Position
6	(b) (4)	NYCG	A(18-21)
5		GIVE	A (1-4)
4		RGFFYTPKTRR	B (22-32)
3		FVNQHLCGSHLVE	B (1-13)
2		ALYLVCGE	B (14-21)
1		QCCTSICSLYQLE	A (5-17)

Table 3.2.S.2.6/ 66: Comparability of DP from DS from Process V and VI: Primary Structure

Batch Number	BS15005866	BS15005867	BS15006714	BS15005851	BS15005852	BS15005853	Theoretical Mass*
DS Process	VI	VI	VI	V	V	V	
Tests	Results						
Intact molecular mass by LC-ESI-MS							
Observed mass	(b) (4)						(b) (4)
Reduced Molecular Mass by LC-ESI-MS							
Observed Mass of chain A	(b) (4)						(b) (4)
Observed Mass of chain B	(b) (4)						
Peptide mapping (reduced) by LC-ESI-MS							
Fragment 6	(b) (4)						(b) (4)
Fragment 5	(b) (4)						(b) (4)
Fragment 4	(b) (4)						
Fragment 3	(b) (4)						
Fragment 2	(b) (4)						
Fragment 1	(b) (4)						
* Acceptance criteria:	(b) (4)						

Lack of higher order species that could promote immunogenicity

Figure 3.2.S.2.6/ 44: SDS-PAGE under Non-reducing Conditions: Comparability of DP Batches from DS from Process V and Process VI



Reviewer comment

The non-reducing SDS PAGE shows no higher order species that could result from aggregation and promote immunogenicity

Stability profile is the same or better for Process VI

Table 3.2.S.2.6/ 85: Comparability of Process V and VI Drug Substance: Long-Term Stability Testing (-20°C ± 5°C)

Batch Number	BS15006908	BS15007170	BS15007049	ED-B13-01-001454	ED-B13-01-001594	ED-B13-01-001670
DS Process	VI	VI	VI	V	V	V
Testing Intervals (Months)	Total Impurities (%)					
Initial	(b) (4)					
1						
2						
3						
6						
9						
12						
18						
24						
Testing Intervals (Months)	Any Individual Impurity (%)					
Initial	(b) (4)					
1						
2						
3						
6						
9						
12						
18						
24						
Testing Intervals (Months)	High Molecular Weight Impurity (%)					
Initial	(b) (4)					
1						
2						
3						
6						
9						
12						
18						
24						

Reviewer comments

The comparability data for factors most likely to impact immunogenicity; i.e. amino acid sequence, impurities, aggregation, and stability, indicate no increased risk from DS manufacturing process VI.

Assessment of patient antibody data (using Process V material)

From Clinical Overview

Study MYL-GAI-3001: T1D/Type 1 diabetes population

Overall, the results of the immunogenicity profiles were comparable between MYL-1501D and Lantus-US treatment groups. Percentage specific binding profiles for total ADA were similar to insulin cross reactive antibody %SB regarding actual and change from baseline values. There was a statistically significant change in baseline in the Lantus treatment group at Week 52 but not in the MYL-1501D treatment group for the Lantus assay. There were no other statistically significantly changes from baseline at scheduled visits within each treatment group for either assays. There were no statistically significant differences between the 2 treatment groups for any type of insulin antibodies at any of the visits during the treatment periods. The incidence of total ADA and insulin cross reactive antibody were also comparable between 2 treatments and no statistically significant difference was found at any post-baseline visits and by either assay method. The proportion of patients with anti-HCP antibodies was comparable between the treatment groups, with 95.7% of the patients in the MYL-1501D group and 94.2% of the patients in the Lantus-US group having anti-HCP antibodies. The proportions of patients who tested positive for anti-HCP antibodies were similar between the treatment groups at all time points, with no statistically significant differences between them.

Study MYL-GAI-3002:T2D/Type 2 diabetes population

Overall, the results of the immunogenicity profiles were comparable between the MYL-1501D and Lantus-US treatment groups, with most patients showing negative responses for total ADA and insulin cross-reactive antibodies. The incidence of total ADA and insulin cross-reactive antibodies were also comparable between the 2 treatment groups. For both the MYL IG and Lantus assays, statistically significant increases in total insulin antibody were observed from Baseline to Weeks 12 and 24 within the MYL-1501D group. With regard to percentage binding profiles for drug-specific antibody, statistically significant changes from Baseline were observed between the treatment groups, with positive percentage binding changes in the MYL-1501D group versus negative changes in the Lantus-US group. Additionally, a statistically significant decrease from Baseline in drug-specific antibody %SB was observed in the Lantus-US group at Week 12. Among insulin-naïve and insulin non-naïve patient subgroups, there were no statistically significant differences in total antibody %SB or cross-reactive antibody %SB between the MYL-1501D and Lantus-US groups. The proportion of patients with anti-HCP antibodies was comparable between the treatment groups, with 93.5% of patients in the MYL-1501D group and 95.0% of patients in the Lantus-US group testing positive for anti-HCP antibodies at Baseline, and 87.3% of the MYL-1501D group and 86.9% of the Lantus-US group testing positive at Week 24.

Reviewer comments

The data from the clinical trials using process V material show good comparability for immunogenicity between the Mylan MYL-1501D product and the licensed Lantus product.

Protocol for MYL-1501-1003 (from IND 105279 / amendment 58)

A Glucose Clamp Study Investigating the Bioequivalence of MYL-1501D (Process V) and MYL-1501D (Process VI) with US Lantus® Reference Product in Healthy Volunteers

Table 1-1 Study Schedule

Study Period	Screening Period		Treatment Period		Follow-up
Visit no.	0	1	2	3 to 7	8
	Informed Consent	Screening	Dosing visit	Dosing visit	Final Examination
Approx. Duration	2 hours	2 hours	36 hours	36 hours	1 hour
Period between Visits		Up to 28 days	5-14 days	5-14 days	1-7 days
In-house Visit			X	X	
Informed consent	X[1]	X[1]			
Fasting		X	X	X	X
Inclusion/Exclusion criteria		X	X[2]		
Demographic data		X			
Smoking and alcohol consumption habits		X			
Concomitant illness and medical history		X			
Weight, height, BMI		X	X[3]	X[3]	X[3]
Alcohol breath test		X	X	X	
Physical examination		X			X
Vital signs		X	X[4]	X[4]	X
12-lead ECG		X	X[4]	X[4]	X
Hematology		X			X
Biochemistry		X			X
Coagulation		X			
Urinalysis		X			X
Infectious serology		X			
Fasting plasma glucose[9]		X			
Pregnancy test (females only)[10]		X	X	X	X
Urine drug screen[5]		X	X	X	
Standard of care for subjects[6]		X	X	X	X
Dosing day exclusion criteria			X	X	
Withdrawal criteria			X	X	
Randomization			X		
Study drug administration			X	X	
Euglycemic clamp			X	X	

Study Period	Screening Period		Treatment Period		Follow-up
Visit no.	0	1	2	3 to 7	8
	Informed Consent	Screening	Dosing visit	Dosing visit	Final Examination
Approx. Duration	2 hours	2 hours	36 hours	36 hours	1 hour
Period between Visits		Up to 28 days	5-14 days	5-14 days	1-7 days
In-house Visit			X	X	
Glucose monitoring for safety			X	X	
Immunogenicity sample		X	X[11]	X[11]	X
Blood sampling for PK			X[7]	X[7]	
Blood sampling for C-peptide		X[7]	X[7]	X[7]	
Adverse events		X	X	X	X
Local tolerability at injection site			X	X	
Drug accountability			X	X	
Concomitant medication		X	X	X	X
In-house meal[8]		X	X	X	X
End of study form					X

[1] Check of signed and dated informed consent. The actual signing must be performed prior to any study related activities (incl. fasting). It is permitted to combine visit 0 and visit 1 in case subject first signs the ICF and immediately thereafter, conducts all activities for visit 1.
[2] Re-check of subject eligibility; In case Visit 1 and 2 have been scheduled more than one week apart, an additional safety lab analysis (hematology, biochemistry and urinalysis) may be performed if deemed necessary by the investigator.
[3] Weight only. The dosing will be based on weight at each visit
[4] Body temperature, ECG, blood pressure, pulse rate and respiratory rate (all but body temperature are in supine position after at least 5 min rest) will be recorded pre-clamp and after end of the clamp
[5] Drug screen will be carried out locally at the study site
[6] Please refer to Section 4.4 specific diet and exercise restrictions
[7] See Table 1-2 for details on the timing of sampling at each dosing visit
[8] At the end of Visits 1 to 8, subjects will be offered a breakfast buffet or meal of their choice
[9] To be performed at the study site for inclusion using the YSI 2300 STAT device.
[10] A pregnancy test will be performed at the safety laboratory on a blood (serum) sample obtained at the screening and follow-up visit (Visit 1 and Visit 8). For Visits 2-7 it would be conducted at the study site using urine sample.
[11] The samples at V2 through V7 need to be taken prior to dosing and will be analyzed only for immune related safety concern or unusual PK data.

Visits with immunogenicity sampling

1 up to 28 days

2 5-17 days

3-7 5-14 days between visits,

For these visits, immunogenicity samples should be taken for each visit prior to dosing and will be evaluated only if there is immune related safety concern or unusual PK profile.

8 1-7 days after visit 7

Visit 1 – Screening Visit

The screening visit will take place up to 28 days prior to the first dosing. After the ICF has been signed, subjects will be asked to attend the screening visit in a fasting condition (abstinence from food and beverage consumption (other than water) for at least 10 hours). If subjects are fasting, all screening assessments may be done on the same day. If subjects are not fasting, they will be invited to return for a second screening visit (within 1-5 days) to complete any missing screening procedures (e.g. laboratory assessments). Immunogenicity samples should be taken during the visit that was preceded by fasting.

The interval between study visits 2-7 will be 5-14 days. Subjects who do not comply with all dosing day exclusion criteria, will be excluded from the dosing visit, but may be rescheduled later at the discretion of the Investigator. The subjects may only be rescheduled once per dosing visit.

Subjects will be instructed to comply with the dosing day exclusion criteria and the lifestyle guidelines for those visits. Immunogenicity samples should be taken for each visit prior to dosing and will be evaluated only if there is immune related safety concern or unusual PK profile.

Table 6-1: Blood Volume

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening	Study Period	Follow up Visit	
Safety Labs	15	1		1	30
Clamp PK + Glucose	60		6		360
Clamp C-peptide	24	1 (4 ml only)	6		148
Immunogenicity	5	1	6	1	40
TOTAL					**578**

*YSI- if 0.25mL taken every 120 minutes, for a 24-hour clamp, additional 4mL for glucose per visit to be considered.

The pharmacokinetic and immunogenicity samples will be stored for up to 1 year after finalization of the clinical trial report. All other samples will be destroyed at the latest after finalization of the clinical trial report.

Assessment of Immunogenicity

Blood samples (5 ml each) will be collected as per Study Schedule (Table 1) for potential analysis for the presence of anti-drug antibodies (ADA). The blood samples will be drawn via an indwelling intravenous catheter or by direct venipuncture into serum separator tubes, and the exact times of blood sampling will be recorded. The samples at V2 through V7 will be taken prior to dosing with study drug, and the sample taken at screening will be designated for method development and /or validation. Immunogenicity samples would only be analyzed, if deemed necessary (e.g., due an unexpected PK profile).

Reviewer comments regarding Study MYL-1501-1003

The Sponsor has proposed to perform immunogenicity testing at baseline, then at the first visit (5-17). These tests will be followed by a risk-based strategy for visits 3-7, which are spaced 5-14 days between visits, with testing only performed if there is an unusual PK profile (indicative of ADA mediated clearance). Immunogenicity testing will again be mandatory for visit 8, which is the final visit. This testing strategy is adequate because it will capture the potential early and

long-term development of ADA, and ADA development that may be causing increased insulin clearance. These features of the testing should also inform an assessment of whether the immunogenicity of Process V and VI MYL-1501D is similar.

Protocol for Study MYL-1501D-3004

A Randomized, Multi-center, Double-Blind, Parallel-Group Clinical Study Comparing the Efficacy and Safety of MYL-1501D Produced by Two Manufacturing Processes in Type 1 Diabetes Mellitus Patients

Table 1: Study Schedule of Activities

Study Periods	Screening	Run-in Period				Randomized Comparative Treatment Period									Follow-up
Study Visits[1]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 (EOT)	V15 (FU)
Study Week	-6 to -4	-4	-3	-2	-1	0	1	2	4	6	9	12	15	18	20
Study Days	-42 to -28	-28±3	-21±3	-14±3	-7±3	0±3	7±3	14±3	28±3	42±3	70±7	84±7	112±7	126±7	140±7
Informed Consent	x														
Inclusion/Exclusion Criteria Review	x					x									
History of previous insulin usage	x														
Dilated Ophthalmoscopy / retinal photography if not done in the last 6 months	x														
Standard-of-care specifics[2]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Age, Gender, Height, Race	x														
Body Weight and BMI	x					x		x		x		x		x	
Pregnancy Test[3]	x					x		x		x		x	x	x	
Medical History including concomitant illness	x														
Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vitals signs measurement (sitting)	x	x		x		x		x		x		x		x	

Study Periods	Screening	Run-in Period				Randomized Comparative Treatment Period									Follow-up
Study Visits[1]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 (EOT)	V15 (FU)
Study Week	-6 to -4	-4	-3	-2	-1	0	1	2	4	6	9	12	15	18	20
Study Days	-42 to -28	-28±3	-21±3	-14±3	-7±3	0±3	7±3	14±3	28±3	42±3	70±7	84±7	112±7	126±7	140±7
Physical examination	x					x								x	
12-lead ECG (supine)	x					x								x	
Randomization						x[8]									
Record AEs and SAEs (including local and systemic allergic reactions) and hypoglycemic events[4] due to medication, disposable pen or needle		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Record device safety information			x	x	x	x	x	x	x	x	x	x	x	x	
Fasting plasma glucose	x	x		x		x		x		x		x		x	
HbA1c Assay	x					x						x		x	
Fasting C-peptide, HIV, HBsAg, and HCVAb	x														
Sampling for hematology, blood chemistry and urinalysis[5]	x					x								x	
Fasting lipid profile	x					x						x		x	
Sampling for immunogenicity [9]	x					x		x		x		x		x	

Study Periods	Screening	Run-in Period				Randomized Comparative Treatment Period									Follow-up
Study Visits[1]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 (EOT)	V15 (FU)
Study Week	-6 to -4	-4	-3	-2	-1	0	1	2	4	6	9	12	15	18	20
Study Days	-42 to -28	-28±3	-21±3	-14±3	-7±3	0±3	7±3	14±3	28±3	42±3	70±7	84±7	112±7	126±7	140±7
Sampling for PK[6]						x		x		x		x		x	
Review 8-point SMBG Profile performed in the week before the visit [7]			x	x	x	x				x		x		x	
Dose review of Lantus, MYL-1501D and insulin lispro and instruction		x	x	x	x	x	x	x	x	x	x	x	x	x	
Dispense Study Medication and ancillary supplies		x				x				x		x			
Drug Accountability and Compliance				x		x		x		x		x	x	x	
Dispense subject diary		x				x				x		x			
Review subject diary				x		x				x		x		x	

1. Visits 3, 5, 7, 9 and 11 may be telephone contacts *(*grey columns represent telephone contacts).
2. Standard–of-care specifics includes assessment and documentation of the following - Training on self-management of diabetes, lifestyle modification measures (includes maintenance of appropriate body weight, following recommended physical activity, avoidance of smoking and following the recommended diet); and monitoring to prevent complications.
3. Serum pregnancy test for women of child bearing potential will be done during screening and randomization visit. During subsequent visits urine pregnancy test will be done. At the randomization visit, both urine and serum pregnancy tests will be done. Subject may be enrolled if the urine pregnancy test is negative.
4. Non-severe hypoglycemic events (which are not consider as SAE) occurring after the EOT visit will not be recorded at the follow-up visit.
5. A routine urine dipstick test will be performed by the site. A microscopic urinalysis will be performed by the central lab if the dipstick test result is abnormal.
6. The PK sample will be taken during the visit, preferably prior to the daily glargine dose. The timing of study drug administration from prior day should be collected along with the time of PK sample collection.
7. The 8-point SMBG profile, measurement will be done by the subject at home on 3 days (of which 2 are consecutive days) in the week before the next visit. Evaluation will be based on the measurements after each 6 weeks; thus during randomized period it would done at Week 6, 12 and 18, while SMBG would be done on 3 days during Weeks 5, 11 and 17.
8. Prior to randomization, Investigator is required to confirm subject eligibility into the study based on the data collected during the screening period, including the labs values recorded during screening. In case subject does not meet the eligibility re-screening need to be confirmed by the Sponsor or designee.
9. During the Randomized Comparative Treatment Period, the immunogenicity samples should be drawn immediately following the PK sample, as outlined under Footnote 6.

Visits with immunogenicity sampling

V1 -42 to -28

V6 0 ± 3

V8 14 ± 3

V10 42 ± 3
V12 84 ± 7
V14 126 ± 7

Blood samples of 5 mL each will be taken into serum separator tubes at each time point as outlined in Table 1. At Visits 1, 8, 10, 12, and 14, three blood samples will be drawn, whereas at Visit 6 (baseline) four blood samples will be drawn. The blood samples will be taken by direct venipuncture, and the exact times of blood sampling will be recorded in the CRF. Two of the samples will be used to determine the presence of anti-drug antibodies against insulin glargine using the approach outlined below. The other sample will be collected and stored in reserve for potential supplemental immunogenicity testing and/or characterization. Samples collected pre-dose at the randomization visit (Visit 6) will be considered as baseline. Samples collected at screening and the supplemental samples collected at baseline may also be used for method development and validation. Sample handling instructions are specified in the laboratory manual.

A conventional radioimmunoprecipitation assay (RIPA) will be employed for the assessment of anti-drug antibodies in clinical samples. In this assay, samples will undergo a pretreatment step that includes acid dissociation to release any anti-insulin antibodies complexed with free drug, followed by charcoal adsorption of the free insulin analog. The treated samples will be incubated with a fixed amount of ^{125}I-MYL-1501D, and anti-drug antibody complex formation with the tracer is measured via gamma counter and expressed as a percentage of bound to total radioactivity (%B/T).

Reviewer comments
The sampling plan provides adequate coverage to assess the time course of the immunogenicity response extending from baseline, through early responses, mid-course, and long term ADA development. The Sponsor has also clarified that there will be sufficient volumes for re-testing, as necessary, and that a protocol is in place to reduce drug interference in the ADA assay using acid dissociation of ADA-insulin complexes. Therefore, overall the protocol should be adequate to assess immunogenicity comparability between process V and VI for MYL-1501D

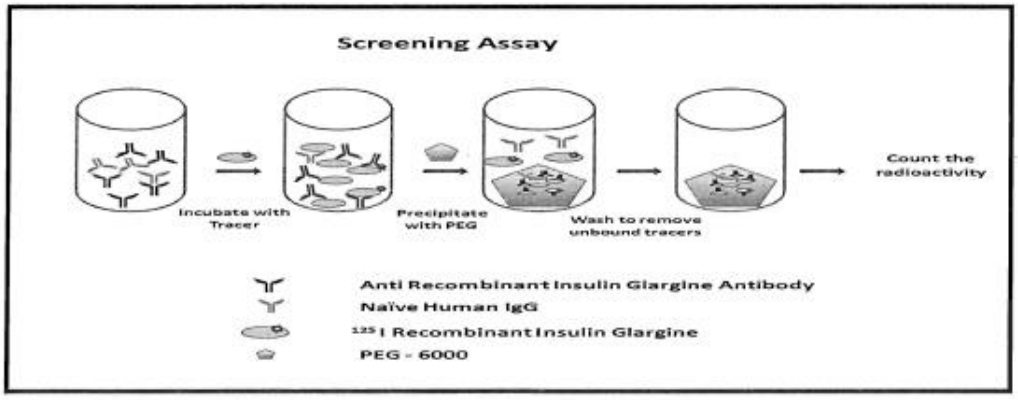
Validation of RadioImmunoPrecipitation Assay (RIPA) for anti-insulin glargine antibodies (NDA entry 15-124-002). The validation was performed by (b) (4), Validation report GCL-425, and was completed June 29, 2016

Assay description

The ADA screening and confirmatory assays utilize RadioImmuno Precipitation Assay (RIPA) methodology. Samples are treated with acid to release antibody from free drug, followed by charcoal adsorption of the free drug (either MYL-1501D (*designated MIG in this discussion*,) or Lantus). The samples are then neutralized and centrifuged to remove the charcoal, and incubated overnight with ^{125}I labeled MIG or Lantus tracer under the following conditions.

RIPA assay buffer only
RIPA assay buffer with excess unlabeled MIG
RIPA assay buffer with excess unlabeled Lantus
RIPA assay buffer with excess unlabeled Novolin R (recombinant human insulin, native sequence)

After the overnight incubation, bovine IgG and PEG are added to precipitate the tracer-antibody complexes, which are then pelleted, and washed with PEG solution. Supernatants are removed and emissions are counted in a gamma-counter, as shown in the following schematic



The % binding (%B/T) is calculated as the ratio of the precipitated counts to total gamma counts for the uninhibited tube (RIPA assay buffer only) as well as for the tubes inhibited with competitor MIG, Lantus, or Novolin R. In this assay format, screening and confirmation are performed simultaneously; i.e. inhibition with MIG, Lantus, and Novolin R are included in the assessment of each sample so that specific binding (%SB is reported as the difference between uninhibited RIPA assay buffer only tube and the inhibited MIG, Lantus, or Novolin R tubes. Thus the assay captures specific reactivity to MIG and Lantus, as well as reactivity to native insulin as per the Novolin R tube. The native insulin reactivity is referred to as cross-reactivity.

Minimum Required Dilution (MRD)

Pooled human serum samples were tested at different fold dilution (Neat, 2.SF, SF and 10F) to establish the MRD. The ULOQ and LLOQ concentrations were spiked in above mentioned fold dilution of pooled human sera. Acceptance Criteria: spiked samples should show a nominal recovery of 80- 120% compared to recovery in buffer. Five-fold dilutions of pooled human sera

showed a recovery of 80-120%. As a slightly more conservative practice, assays were performed at a four-fold MRD.

Reviewer comment

The modest four-fold MRD should capture all anti-glargine signals, without loss of signal that might occur at high dilutions. Thus, the MRD is acceptable.

Positive controls

The positive control antibody is a guinea pig anti-MIG/Lantus antibody. The LPC is 50 ng/ ml and the HPC is 500 ng/ ml.

Reviewer comment

The LPC is acceptable, being close to the sensitivity and resulting in a modest mean value of 11.24 % SB.

Cut Points

The cut point is the level of % specific binding at or above which samples are classified as positive. Sixteen individual serum samples from four different types of populations (Normal, T1DM, T2DM naïve, and T2DM treated) were included for determination of MIG/MIG, MIG/NOV, LAN/LAN, and LAN/NOV cutpoints. The 64 cut point samples were distributed into 4 groups, with equal numbers of each serum type per group. Each serum sample was analyzed in each assay 6 times across 6 different assays by 4 different analysts over 4 days using an unbalanced Latin Square design. The reported value for each test sample was the %SB value. All disease sera samples included for CP determination were pre-screened for absence of pre-existing anti-insulin antibody. Additional pruning was performed on the T1D set because the T1DM mean %SB was higher than the means from the other three populations. Hence specific binding (SB) cut point analysis was estimated. Cut points were calculated at a false positive rate of 1%, resulting in fixed cut points of 1.15% SB, 1.05% SB, 1.00% SB, and 1.06% SB for MIG/MIG, MIG/NOV, LAN/LAN, and LAN/NOV assays, respectively.

Reviewer comment

The sponsor has determined cutpoints that are appropriate for a confirmatory assay.

Sensitivity

Sensitivity of the method was determined using a %SB curve generated by serial dilution of anti-Lantus/MIG antibody in NC, with concentrations ranging from 20,000 ng/mL to 3.9 ng/mL. The data was fitted using a 5-parameter logistical fit algorithm, and the positive control antibody concentration that interpolated to the cut point was determined. This experiment was performed on 3 separate days. The mean of the 3 interpolated concentrations was 4.2 ng/mL for MIG/MIG assay and 4.7 ng/mL for LAN/LAN assay. The prozone samples yielded a %SB in the same range as the HPC which indicates no presence of prozone effect.

Reviewer comments

Sensitivities of 4.2 ng/mL for MIG/MIG assay and 4.7 ng/mL for LAN/LAN assay are very high, and well within the 100 ng/ml target recommended in the 2016 draft FDA guidance for development and validation of immunogenicity assays. In addition, this phase of the validation shows no prozone effect, supporting accuracy of the ADA assays at high antibody levels.

Selectivity

Forty (40) individual matrix samples were spiked with positive control antibody at the low PC

level. Ten samples were from normal donors, 10 from donors with type 1 diabetes mellitus (T1DM), 10 from donors with type 2 diabetes mellitus (T2DM) that are insulin naïve (T2DM Naïve), and 10 from donors with T2DM that have been treated with insulin (T2DM Treated). These samples were spiked with the LPC, and analyzed in the MIG/MIG and LAN/LAN assays. All the Normal, T1DM, and T2DM treated samples gave signals above the cutpoints for both assays, and 8/10 T2DM naïve samples were above the cutpoints.

Reviewer comments

These results indicate that low ADA signals are expected to be detectable in almost all samples from the target populations; i.e significant matrix inhibitory effects are not expected.

Specificity

NC, LPC, and HPC were analyzed with and without excess MIG, LAN, and NOV in each of the cut point runs using both the MIG and LAN tracers. This validation exercise showed that ≥ 96% of 288 results for NPC showed acceptable %CV and were less than the cutpoints. For the LPC ≥ 98% had acceptable %CV and were greater than the cutpoints, while for the HPC, ≥ 99% had acceptable %CV and were greater than the cutpoints.

Reviewer comments

These results show that the ADA assay can be expected to nearly always give the expected specificity results for the controls, and thus specificity is adequately validated.

Precision

Intra-assay precision was evaluated across all 24 runs for both the MIG and LAN assay and maximum individual intra-assay precision observed was 15.7% for the MIG assay and 23.1% for the LAN assay for the PC samples. Inter-assay precision across all 24 batches for MIG assay was 8.8% at LPC and 4.3% at HPC. Interassay precision across all 24 batches for LAN assay was 9.2% at LPC and 5.0% at HPC.

Reviewer comments

These precision results are within industry practice and FDA guidance for ADA assays, and are thus acceptable.

Cross Reactivity

Cross-reactivity of the method was tested using both the MIG and LAN tracers in conjunction with no inhibitor, MIG inhibitor, LAN inhibitor, NOV (native insulin) inhibitor or filgrastim (G-CSF, a non-specific inhibitor) at the same molarity. The %SB-MIG/MIG, %SB-MIG/LAN, %SB-LAN/LAN, and %SB-LAN/MIG of LPC and HPC levels of samples were greater than respective cut point (CP-MIG/MIG or CP-LAN/LAN), where "greater than respective cut point" means the % inhibition resulting from a given inhibitor was at least as great as a given cut point.

In terms of assessing cross reactivity, the %SB-MIG/NOV and %SB-LAN/NOV of LPC and HPC levels of samples were greater than the respective cut points (CP-MIG/NOV and CP-LAN/NOV) for all results, demonstrating that the assays can detect cross reactivity of native insulin with the MIG or LAN tracers.

Regarding the non-specific filgrastim inhibitor, although the %SB-MIG/Non-Specific Drug and %SB-LAN/Non-Specific Drug at the LPC level was less than the respective cut points for %SB-MIG/MIG and %SB-LAN/LAN, at the HPC level %SB-MIG/Non- Specific Drug was above the cut point for 2 out of 3 samples and the %SB-LAN/Non-Specific Drug was above the cut point

Reference ID: 4033492

for 1 of 3 samples. This indicates that at high ADA concentrations, there may be some cross reactivity with G-CSF.

Reviewer comments
The Sponsor has demonstrated that the MIG and LAN ADA assays can also detect ADAs reactive with native insulin (cross-reactivity). However, there is also potential for ADA cross reactivity with G-CSF/filgrastim, and this is a potential labeling issue.

Interference (hemoglobin and lipids)
Hemolyzed samples (5 lots) and lipemic samples (5 lots) were spiked with anti-Lantus/MIG LPC level. For unspiked hemolyzed samples, 4 out of 5 samples for MIG/MIG and 4 out of 5 samples for LAN/LAN assay gave %SB less than the respective cut points. All unspiked lipemic samples gave %SB less than the respective cut points for both MIG/MIG and LAN/LAN assays. Of the spiked samples, all 5 samples for MIG/MIG of both hemolyzed and lipemic serum exhibited %SB greater than the cut point. Of the hemolyzed samples for LAN/LAN, all of the spiked samples exhibited %SB greater than the cut point. Of the lipemic samples for LAN/LAN, 4 of the 5 spiked samples exhibited %SB greater than the cut point.
Reviewer comments
This aspect of the validation indicates that lysed RBCs or lipids do not cause important increases in negative sample signals, or important decreases in low ADA signals.

Stability
The positive control antibody was stable in matrix through 8 freeze/thaw cycles at -20 °C and and -70 °C and for at least 24 hours when stored at 20 - 25 °C. Extracted samples were found to be stable for up to 72 hours when stored at 2 - 8 °C).
Reviewer comments
I have reviewed the tabulated stability data and find the Sponsor's statements to be accurate. The data supports the storage times and freeze-thaw cycles that are likely to be used for the PC in routine practice.

Drug Interference
The method was tested for the ability to detect anti-MIG and anti-Lantus antibodies in the presence of pharmacological concentrations of free drug. Samples containing 0.125, 0.250 and 0.500 µg/mL MIG or LAN were pre-incubated with anti-Lantus/MIG antibodies at concentrations ranging from 0.00 to 1000.00 ng/mL prior to assay. The anti-Lantus/MIG antibody spiked PC at 15.6 ng/mL was detectable in the presence of 0.500 µg/mL of drug in both MIG/MIG and LAN/LAN assays. This tolerance is expected to cover the expected levels of drug during the analysis of antibody samples
Reviewer comment
A low level of positive control, near the assay sensitivity, is still detectable in the presence of 500 ng/ml MIG product, indicating adequate drug tolerance.

Validation of an ECL method for detection of anti-Pichia Host Cell Protein antibodies (NDA entry 15-124-011). The validation was performed by (b) (4), Validation report GCL-507, and was completed December 21, 2016

Reviewer comment

Overall I find this method to be appropriately validated with high sensitivity.

Method Description

The method uses a ligand binding assay based on the MSD electrochemiluminescence platform. In this format, the host cell protein pool obtained from *Pichia pastoris* null cells (referred to as HCP), is coated onto a 96-well MSD plate and then blocked using 3% BSA in PBS. Goat polyclonal Anti-MIG HCP antibody is used as the positive control. Human serum samples and the positive control samples (PCs prepared in rat plasma) undergo a minimum required dilution of 1:2 for the screening assay in assay buffer (1% BSA in PBS) and in confirmatory buffer (1% BSA in PBS containing 1mg/mL HCP) for confirmatory assays. Samples are incubated on the coated plate. The bound antibody is detected by the addition of HCP-Digoxin conjugate followed by Anti-Digoxin Antibody Sulfotag conjugate (Anti-DIG-Stag). Read buffer containing tripropylamine is added and the Sulfotag associated with the Anti-DIG Antibody produces a chemiluminescent signal when an electrical voltage is applied. This signal is directly proportional to the level of Anti-HCP antibodies present in the sample.

The assay was validated for three tiers:

Tier 1 (Screening): All samples will be subjected to an initial screening assay, and those falling at or above a plate specific screening cut point will be deemed positive.

Tier 2 (Confirmation): Samples scored positive in the screening tier will be subjected to a confirmatory assay, in which samples will be diluted 2-fold in buffer containing excess HCP, prior to analysis. Samples with a true positive antibody response will show a notable percentage inhibition (equal to or greater than the confirmation cut point) in the response for the sample with buffer containing excess HCP as compared to the sample with buffer alone.

Tier 3 (Titer): The confirmed positive samples may then undergo titer analysis where the sample is serially diluted with pooled rat plasma until it crosses the plate specific titer cut point, to allow semi-quantification.

Positive Controls

A polyclonal anti-MIG HCP antibody control antibody was raised in goat and used as a positive assay control. The HPC is 7.5 μg/ml, while the LPC is 0.75 μg/ml.

Reviewer comments

The LPC is considerably above the assay sensitivity of 57 ng/mL. However, examination of the tabulated data across all the validation runs shows low assay variability at low ECL levels which are near the sensitivity limit, indicating good control of assay reproducibility at low signals.

MRD

An MRD of 1:2 was used, where samples and PCs were diluted into rat serum

Reviewer comment

This modest MRD of 1:2 should be helpful in ensuring that ADA signals are not lost at high dilutions, as would be a concern at higher MRDs.

Selectivity (Matrix Effects)

Selectivity is the ability of an assay to detect the desired analyte in the presence of other matrix components. Forty individual matrix samples (10 from normal human donors, 10 from rat K2EDTA plasma, 10 from type I diabetes mellitus (T1DM) subjects, and 10 from type II diabetes mellitus (T2DM) subjects (9 of which were insulin naïve)) were spiked with positive control antibody at both Low and High PC levels. The assay responses in all cases showed that HPC response > LPC response > unspiked sample

Reviewer comments

Examination of the tabulated data shows that all the rat serum unspiked samples gave low values in the range 120-150 ECL supporting reproducibility of the assay at low signal values. All the human unspiked samples were higher, indicating exposure to yeast proteins, and also indicating that cutpoints should be established using samples from these populations. The 0.75 μg/ml LPC values were 600-900 ECL units above the unspiked sample for each serum sample, and the 7.5 μg/ml HPC values were 4000-6000 units above the LPC values for each sample, indicating a proportional, although not perfectly linear response. This non-linearity is acceptable because in the subsequent sensitivity phase of assay validation the response was fitted with a 5 PL non-linear regression equation.

Screening Cut Point

A cut point factor for this method was determined from the analysis of 48 serum samples. Each serum sample was analyzed in duplicate to generate 1 reportable result per run across 6 runs by 3 analysts over 10 days, using a balanced design. Log_{10} transformed ECL values showed a normal distribution, and cut point factor was calculated that would yield a false positive rate of approximately 5%. This screening cut point factor of 1.16, and in subsequent discussion, PSCP (Plate-Specific Cut Point) refers to the mean NC of a given plate multiplied by the cut point factor.

Reviewer comment

The methodology for screen cut point determination is as recommended in the 2016 FDA Draft Guidance for Development and Validation of Immunogenicity Assays, and is acceptable.

Confirmatory Cut Point

The confirmatory cut point is the level of percent inhibition caused by the presence of excess drug at and above which samples are classified as confirmed positives. The confirmatory cut point for this method was determined from the analysis of 48 individual samples, with and without the presence of 1 mg/mL MIG HCP. The same balanced design as the screening cut point was followed. The degree of inhibition by excess MIG HCP, expressed as a percentage, was calculated and the data analyzed. Untransformed % inhibition values were assessed by Shapiro-Wilkes and found to satisfy this criterion for normality. Therefore, a parametric estimate of the % inhibition that would give an ~ 1% false positive rate was calculated, yielding a confirmatory cut point of 38.1% inhibition.

Reviewer comment

The methodology for screen cut point determination is as recommended in the 2016 FDA Draft Guidance for Development and Validation of Immunogenicity Assays, and is acceptable on this

basis. Moreover, the 38.1% inhibition cut point is acceptable because it does not require excess (≥ 50%) inhibition, which might be expected to result in a true positive sample not being confirmed.

Precision

Each of the six cut point runs (18 plates) included 24 wells (12 sets of duplicates (4 sets per plate)) of negative control and 12 wells (6 sets of duplicates (2 sets per plate)) of each positive control level (LPC and HPC). Each ECL value was based on the average response from duplicate wells. The intra- and inter-assay statistics over these six runs indicate precision, with CVs of ≤ 8.0% for both levels of positive control, well within the ≤ 25%. acceptance criteria for intra- and inter-assay precision.

Reviewer comments

Examination of the tabulated precision data indicates tight clustering of the data for NC, LPC, and HPC samples, consistent with CVs of ≤ 8.0%, and well with industry standards for precision. Therefore, the precision results are acceptable.

Specificity

Samples using non-specific antibodies (anti-MIG, anti-E.*coli* HCP, and anti-S. *cerevisiae* HCP) were prepared at the assay LPC and HPC levels in the negative control pool and were analyzed in the assay both with and without excess HCP. The acceptance criteria were: LPC and HPC levels of samples prepared with non-specific antibody should be less than the respective cut points (PSCP as well as CCP). All non-specific antibody results were less than the respective cut points demonstrating a specificity of this method for the anti-MIG HCP antibody

Reviewer comments

Examination of the tabulated data shows that the anti-MIG, anti E.Coli, and anti-S cervesiae values were well within the range of the NCP or unspiked samples-100-150 ECL, indicating no non-specific reactivity.

Robustness

The ability of the method to perform adequately with minor variations in assay conditions was tested. Two assays were performed where each incubation step was tested at the minimum and maximum times allowed in the method. Both assays fulfilled the run acceptance criteria indicating that the method is robust within these ranges.

Table 8 Robustness Evaluation

	Incubation Times	
	Longest	Shortest
	Assay 16MSD40765	Assay 16MSD40760
Sample	ECL Units		Mean	%CV
NC	125	134	130	4.7
LPC (0.75 µg/mL)	706	825	765	10.9
HPC (7.5 µg/mL)	7170	7942	7556	7.2
	Response/NC Ratio			
LPC (0.75 µg/mL)	5.45	6.36		
HPC (7.5 µg/mL)	55.34	61.30		

Incubation Times

Assay ID	Plate Coating (hours:minutes)	Plate Blocking (minutes)	Sample Incubation (minutes)	MIG HCP Dig Incubation (minutes)	Anti-Dig Sulfo tag (minutes)	Read Buffer (minutes)
16MSD40765	20:01	65	125	125	65	04
16MSD40760	14:04	55	115	115	55	00

Reviewer comment

There is essentially no change in assay readout between the "shortest" and "longest" time frames, so the assay is robust if performed within these times.

Stability

Stability of the PC was demonstrated through 8 freeze/thaw cycles. The positive control antibody was also found to be stable for at least 24 hours at 2 to 8 °C or at 15 to 30 °C. The acceptance criterion for stability was: within ± 30% of Difference from Reference value.

Table 14

# of Freeze/Thaw Cycles	Assay Number	µg/mL	ECL Units		
1 (reference)	16MSD40645	0	140	138	134
		0.75	835	834	799
		7.50	8016	8511	8284
6	16MSD40645	0	136	139	134
		0.75	896	888	885
		7.50	8791	8448	8888
7	16MSD40645	0	137	138	132
		0.75	865	866	876
		7.50	8197	8521	8512
8	16MSD40645	0	143	139	133
		0.75	820	855	836
		7.50	7803	8374	8222

Table 15 Short-Term Stability Assessment in Rat K_2EDTA Plasma

Stability after:	Temp (°C)	Assay Number	Anti-HCP (µg/mL)	ECL units		
0 hours (reference)		16MSD40708	0.00	124	127	123
			0.75	775	736	
			7.50	7662	7200	
4 hours	2-8	16MSD40708	0.00	128	125	121
			0.75	758	744	723
			7.50	7229	7454	7570
	15-30	16MSD40708	0.00	122	118	128
			0.75	746	733	731
			7.50	7431	7321	7220
24 hours	2-8	16MSD40708	0.00	127	120	119
			0.75	703	683	719
			7.50	7249	6720	7170
	15-30	16MSD40708	0.00	124	130	128
			0.75	677	669	659
			7.50	6537	6510	6280

Reviewer comments

There is little or no loss of PC signal across 8 freeze-thaw cycles, incubation at 2-8 ^{0}C up to 24 hours, and incubation at 15-30 ^{0}C for 4 hours. For 24 hours at 15-30 ^{0}C, there was a 11.6 % loss of signal for the LPC, and a 13.3 % loss for the HPC. Although such prolonged storage of antibodies at RT is not recommended, these losses of signal are only in the range of 10%, and are thus not expected to affect incidence or titer determinations.

Cross Reactivity

The method was tested for the ability to detect anti-MIG HCP antibodies using MIG HCP, Novolin (NOV), Mylan's insulin glargine (MIG), and Lantus® (LAN) as inhibitors. The NC, LPC and HPC samples were analyzed both with and without each inhibitor. For acceptance, the response of LPC and HPC samples in the presence of excess MIG, LAN and NOV should be greater than PSCP and the % inhibition less than the CCP (no inhibition), and the %inhibition of the LPC and HPC samples should be greater than the CCP in the presence of excess MIG HCP.

Table 10 Cross-Reactivity Assessment

Assay Number 16MSD40659

Sample	Mean	%CV	% Inhibition	Result
NC	121	2.0		
LPC (0.75 µg/mL)	704	3.1		
HPC (7.5 µg/mL)	7240	0.3		
NC (+ HCP)	92	2.3	24.3	Negative
LPC (0.75 µg/mL) (+ HCP)	89	1.2	87.3	Positive
HPC (7.5 µg/mL) (+ HCP)	90	1.6	98.8	Positive
NC with NOV	114	2.9	5.7	Negative
LPC with NOV	741	0.9	-5.3	Negative
HPC with NOV	7464	2.2	-3.1	Negative
NC with MIG	117	4.5	3.6	Negative
LPC with MIG	733	2.4	-4.1	Negative
HPC with MIG	7011	10.1	3.2	Negative
NC with LAN	121	2.7	-0.4	Negative
LPC with LAN	728	4.2	-3.5	Negative
HPC with LAN	7419	4.0	-2.5	Negative

Reviewer comment

There is no change in PC signal with added NOV, MIG, or LAN, so there is no cross-reactivity of the assay with insulins.

Sensitivity and Titer

The sensitivity of the method was determined using the titration curves generated by a 2-fold serial dilution of goat anti-MIG host cell protein antibody in negative control pool, with concentrations ranging from 7500 to 15.0 ng/mL. The data was fitted using a 5-parameter logistical algorithm, and the concentration that corresponded to the cut point response was determined. The responses from the 3 curves in each batch were averaged and then regressed and the cut point interpolated from the curve. The mean of the 4 results was 57 ng/mL.

Reviewer comment

This value is considerably lower than the sensitivity recommended by FDA (100 ng/mL), and is therefore acceptable

The precision of the titration was estimated using the dilution curves from the sensitivity determination (4 runs, 12 curves). For each curve, the end point titer was calculated based on the titer cut point factor of 1.32. The intra-assay precision of titration was ≤ 4.5% and the inter-assay precision of titration was 2.8%

Reviewer comments

Examination of the tabulated data for titer validation shows tight clustering of triplicate ECL values at each dilution, supporting the stated high precision (intra-assay was ≤ 4.5% and inter-assay 2.8%). Moreover, the titer cut point factor of 1.36 is appropriately near the screening cut point factor of 1.16, so titer curves are expected to reach their true low asymptotes and provide accurate titer values.

Prozone Assessment

The prozone effect was not seen because all samples that were at or above the LPC concentration (0.75 µg/mL) yielded results which were at or above the PSCP.

Table 13 Prozone Assessment

Assay Number: 16MSD40644

Sample	Mean (ECL Units)
750 µg/mL PC	68312
75 µg/mL PC	37921
7.5 µg/mL PC	8567
0.75 µg/mL PC	902
0.075 µg/mL PC	196
0.0075 µg/mL PC	139

Reviewer comment

The assay response is monotonic even to very high (750 µg/ml) PC concentrations, so I agree with the validation report that there is no prozone effect.

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/s/

FREDERICK C MILLS
04/25/2018

GERALD M FELDMAN
04/25/2018

LABEL AND LABELING AND HUMAN FACTORS RESULTS REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	April 4, 2018
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 210605
Product Name and Strength:	Semglee (insulin glargine), solution, 100 units/mL, 10 mL vial and 3 mL prefilled pen
Product Type:	Single Ingredient, Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Mylan GmbH
Submission Date:	April 27, 2017, October 18, 2017
OSE RCM #:	2017-842 and 2017-1868
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD
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Associate Director (Acting):	Mishale Mistry, PharmD, MPH

Reference ID: 4243910
Reference ID: 4624497

1 REASON FOR REVIEW

The Division of Metabolic and Endocrinology Products (DMEP) requested that DMEPA review the human factors (HF) validation study report and proposed labels and labeling submitted under NDA 210605 for Semglee (insulin glargine) as part of the evaluation of the 505(b)(2) submission. The reference listed drug is Lantus (insulin glargine, NDA 021081), which was approved on April 20, 2000.

1.1 PRODUCT INFORMATION

Mylan submitted NDA 210605 for Semglee, which will be supplied in a multiple dose vial and a disposable multiple dose pen injector containing 100 units/mL of insulin glargine, to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. The pen injector uses the (b) (4) Disposable Pen Device platform.

1.2 REGULATORY HISTORY

We previously provided advice to Mylan during a Type B-End of Phase 2 meeting on March 7, 2014 recommending a human factors validation study be conducted. We evaluated their proposed HF validation study protocol submitted on August 7, 2015. We advised Mylan during a teleconference on February 18, 2016 to conduct a differentiation study with Lilly's Humulin R U-500 KwikPen. We evaluated their proposed HF differentiation study submitted on April 18, 2016. We confirmed that our recommendations were implemented.

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.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Information Request(s)	D
Previous FDA/Sponsor Interactions	E
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

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3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the human factors validation study results and we performed a risk assessment of the proposed labeling to identify areas of vulnerability that may lead to medication errors and other areas of improvement.

3.1 HUMAN FACTORS VALIDATION STUDY RESULTS

The sections below provide a summary of the study designs, errors observed with critical tasks (Table 2), and our analysis of the HF validation study results.

3.1.1 SUMMARY OF STUDY DESIGN

Usability Study

Mylan conducted two Human Factors validation studies (one in an adult population and one in a pediatric population) designed to provide data to support that intended users can use the Semglee pen injector to prepare and administer doses and comprehend the Instructions for Use (IFU).

The usability studies were conducted with 168 participants (48 pediatric patients with diabetes and their caregivers, 90 adult patients with diabetes, and 30 healthcare practitioners[a]) who were representative of the intended user groups. Half of the study participants (84) were trained to use the pen injector and the other 84 participants were untrained. The IFU was available if the participant chose to use it. Each participant was asked to simulate administering an injection from the Semglee prefilled pen into a simulated skin pad strapped to the intended injection sites (upper arm, thigh, abdomen, or buttock). After the administration tasks were completed, participants were asked knowledge assessment questions related to pen care and storage information provided in the IFU.

We reviewed the methodology for the adult validation study[b] but Mylan did not submit the protocol for the pediatric study for our review. We note that Mylan included 48 pediatric patients (8 trained and 8 untrained Lantus experienced patients, 8 trained and 8 untrained other insulin pen experienced patients, and 8 trained and 8 untrained insulin pen naive patients). As such, we found that the untrained pen naïve pediatric patient group did not have a minimum of 15 pediatric patients, which would be consistent with prior advice provided for the adult study (i.e., include a minimum of 15 participants per distinct user group).[c] Therefore, we will request data with additional pediatric users (See Section 4).

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[a] Healthcare practitioner group included 5 registered nurses, 11 registered nurses/certified diabetes educators, 1 pharmacy manager, 1 pharmacist/certified diabetes educator, 7 certified diabetes educators, 3 nurse practitioners, and 2 dieticians/certified diabetes educators.

[b] Vee S. Memorandum Review of Revised Human Factors Validation Protocol for insulin glargine (IND 105279). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 January 12. RCM No. 2015-1823.

[c] Whitehead R. Meeting Minutes for insulin glargine. Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2014 April 2. IND 105279.

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Differentiation Study

Our prior review of Mylan's human factors validation study protocol made note that "*the turquoise pen body color for your proposed Insulin Glargine pen is very similar to Lilly's Humulin R U-500 Kwikpen, which was approved on December 29, 2015. Thus, we are concerned that selection errors between the two products may occur. The selection error between the two products is particularly concerning as Insulin Glargine is a long acting insulin and Humulin U-500 is a concentrated intermediate-acting insulin. Thus, confusion between these two insulin pens may result in overdoses that can lead to severe hypoglycemia.*"[b] Therefore, we requested that Mylan conduct a differentiation study to support that intended users can differentiate between Semglee and Eli Lilly's Humulin R U-500 KwikPen[d] and we reviewed the study protocol for this differentiation study.[e] This study was conducted with 126 representative users (96 adult patients with diabetes and 30 healthcare practitioners) and half of the participants (63) received training on the pen injector the day before the study. Each participant had access to the Semglee pen and the IFU prior to completing study tasks.

3.1.2 STUDY RESULTS AND ANALYSIS

Failures observed in the usability HF validation studies involved critical, essential, and non-essential tasks. After evaluating the errors with the essential and non-essential tasks, we determined that no additional mitigations are necessary and the residual risk is acceptable.

Table 2 below summarizes and focuses on the results observed with critical tasks, including knowledge tasks, that were evaluated in the usability and differentiation HF validation studies along with the root cause analysis that Mylan provided for each failure or close call. The table also includes our assessment of the critical task failures and close calls. Of note, Mylan did not propose any further mitigation strategies to address the failures and close calls identified in the studies.

[d] White M. Memorandum of Teleconference for insulin glargine. Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2016 February 18. IND 105279.

[e] Vee S. Human Factors Protocol Review for insulin glargine (IND 105279). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 May 18. RCM No. 2016-919.

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Table 2: List of critical tasks where failures occurred and the assessment of the failures that occurred during the task			
Critical Task	**Use Errors and Close Calls**	**Root Cause Analysis**	**Additional Analysis and General Recommendations from DMEPA**
correctly attach the needle	<u>3 close calls:</u> -1 untrained, naive pediatric patient -1 trained, naive pediatric patient -1 trained, Lantus experienced adult patient These patients initially attempted to screw the needle on by turning it in the wrong direction then self-corrected.	Mylan's analysis indicated that these participants were initially confused about turning the needle right versus left but they determined that the instructions in the IFU were sufficient.	Difficulty with correct needle attachment can lead to a delay in therapy, most likely with the first use of the product; however, each participant self-corrected and successfully completed an injection. In addition, since this medication is for chronic use, we determined that the residual risk is minimal. Furthermore, our review of the IFU concluded that the instructions for this step are clear so we do not have any recommendations to mitigate the risk for these errors and we find the residual risk acceptable.
dial the correct dose	<u>1 close call:</u> -1 trained, naive adult patient This patient successfully primed the pen then inserted the needle into the simulated skin pad without dialing the dose to inject. Before attempting to press the dose button, the patient realized	Mylan's analysis noted that this participant inadvertently skipped the step in the IFU but they determined that the instructions were sufficient.	Inadvertent failure to dial the dose could result in a delay in dose administration; however, this participant was able to self-correct and dial the correct dose. We do not have any recommendations and we find the residual risk acceptable.

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Table 2: List of critical tasks where failures occurred and the assessment of the failures that occurred during the task			
Critical Task	**Use Errors and Close Calls**	**Root Cause Analysis**	**Additional Analysis and General Recommendations from DMEPA**
	the error without aid, removed the needle, dialed the dose, and administered the dose successfully.		
administer the full dose by completely depress the dose button to administer the medication)	<u>2 errors:</u> -1 untrained, other experienced pediatric patient -1 untrained, naive adult patient <u>2 close calls:</u> -1 untrained, naive pediatric patient -1 untrained, other pen experienced adult patient The patients that experienced errors stopped pressing the dose button before the dose counter read "0" or removed the needle from the simulated skin pad while pressing the dose button resulting in a wet injection. The patients with close calls either failed to press the dose button initially due to the simulated	Mylan determined that one participant's close call (i.e., initial failure to press the dose button) was a possible artifact of the study. Mylan's analysis of the other use errors determined the errors were due to user inattention and determined that the instructions associated with this task are sufficient.	Each of these participants experienced a wet injection. While this failure can result in an underdose, we note that the wet injection would alert users in subsequent injection given that the product for chronic use. In addition, our review of the IFU concluded that the instructions for this step is clear so we do not have any recommendations to mitigate the risk for these errors and we find the residual risk acceptable.

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Table 2: List of critical tasks where failures occurred and the assessment of the failures that occurred during the task			
Critical Task	**Use Errors and Close Calls**	**Root Cause Analysis**	**Additional Analysis and General Recommendations from DMEPA**
	nature of the study or had some initial difficulty due to the differences from their previously used pen.		
hold the button down for 10 seconds (i.e., continue holding the dose button down for 10 seconds after fully depressing the button to administer the medication)	<u>22 errors:</u> -3 trained, Lantus experienced pediatric patient -7 untrained, Lantus experienced pediatric patient -1 untrained, naive pediatric patient -5 untrained, other pen experienced pediatric patient -3 trained, other pen experienced pediatric patient -1 untrained, naive adult patient -1 untrained, Lantus experienced adult patient -1 untrained nurse practitioner Participants failed to hold the pen in the injection pad for the recommended 10 seconds after	Multiple participants assumed that the full dose was administered once the dose counter read "0" or that they were supposed to start counting as soon as they started pushing the dose button instead of waiting until the counter read "0". In response to our October 19, 2017 information request, Mylan indicated that the pen injectors are designed to deliver the labeled dose between 4 and 6 seconds after the dose counter reads "0". Mylan recommends 10 seconds for this task to minimize the risk of an underdose associated with this varied timeframe for delivery. Mylan determined that the instructions were sufficient.	Failure to wait the recommended hold time before removing the needle can result in an underdose if the user does not hold the needle in place at least 4 to 6 seconds after the dose button is pushed down to "0". We determined that these study participants did not rely on the visual cue (i.e., the dosing counter) or the IFU for this step. Our review of the IFU determined that the instructions regarding the recommended hold time to administer a dose (i.e., hold the dose button down for 10 seconds) after initially pressing the dose button down to "0" is unclear. We recommend modifications to the IFU to improve the clarity of this information. Please see our recommendations for the IFU in

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Table 2: List of critical tasks where failures occurred and the assessment of the failures that occurred during the task			
Critical Task	**Use Errors and Close Calls**	**Root Cause Analysis**	**Additional Analysis and General Recommendations from DMEPA**
	the dose window read "0". Some participants noted that they overlooked the time in the IFU and only held the button for a few seconds instead of counting to 10.		Section 4.1 (sub-bullet B6).
user recognizes that pen should be refrigerated prior to first use	<u>1 error:</u> -1 untrained, naive adult patient <u>1 close call:</u> -1 untrained, Lantus experienced pediatric patient Both patients assumed that unused pens could be stored at room temperature prior to first use.	These patients based their responses on memory but they were able to determine that the unused pens should be refrigerated after reading the information in the IFU and carton labeling. Mylan determined that the labeling was sufficient.	Participants were able to identify the proper storage information when they read the IFU and carton labeling. However, we note that improper storage of unused pens at room temperature could result in patient use of expired medication and decreased effectiveness of medication. Per the prescribing information, unused pens stored in the refrigerator have an expiration date consistent with that on the label but unrefrigerated pens expire within 28 days. Our review of the IFU determined that the instructions could be improved to improve the visibility of the storage information. Please see our recommendations for the IFU in

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Table 2: List of critical tasks where failures occurred and the assessment of the failures that occurred during the task			
Critical Task	**Use Errors and Close Calls**	**Root Cause Analysis**	**Additional Analysis and General Recommendations from DMEPA**
			Section 4.1 (sub-bullet B3).
user recognizes that pen should be stored at room temperature after first use	4 errors: -2 untrained, other pen experienced pediatric patient -1 untrained, naive pediatric patient -1 trained, naive adult patient 1 close call: -1 untrained, Lantus experienced pediatric patient These patients assumed that insulin pens should continue to be refrigerated after use.	Each of the patients that experienced errors or close calls made assumptions regarding the proper storage of a used insulin pen based on prior knowledge. In addition, two of these patients were noted to have possibly misread the information on the container label and IFU, which lead them to determine that the pens were to always be stored in the refrigerator. Mylan determined that the labeling was sufficient.	Failure to store the used pen at room temperature may result in some discomfort upon injection but there are no clinical consequences associated with this error. In addition, our review of the IFU concluded that the instructions for this step are clear. We do not have any recommendations and we find the residual risk acceptable.
user knows to dispose of pen 28 days after first use	8 errors: -3 untrained, Lantus experienced pediatric patient -1 untrained, naive pediatric patient -4 untrained, other pen experienced pediatric patient	Each of the study participants based their responses on prior experience with another insulin product or an assumption to determine the beyond-use date and did not refer to the IFU initially. Of note, one of the patients that answered	Use of insulin pens beyond the 28 beyond-use date may result in patient use of expired medication and decreased effectiveness of therapy. Our review of the IFU determined that the instructions could be improved to improve the visibility of the storage

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Table 2: List of critical tasks where failures occurred and the assessment of the failures that occurred during the task			
Critical Task	**Use Errors and Close Calls**	**Root Cause Analysis**	**Additional Analysis and General Recommendations from DMEPA**
	1 close call: -1 trained, naive pediatric patient Each of the patients that experienced errors or close calls with this knowledge question incorrectly determined that the pen could be used until it was empty, until the labeled expiration date, or for up to 30 days based on prior experience with insulin.	incorrectly assumed that the pen could be used for up to 45 days based on this patient's experience with Levemir (which can be used for up to 42 days). Mylan indicated that the patient making the close call error responded to the knowledge question correctly after consulting the pen's label. Therefore, Mylan determined that the labeling was sufficient.	information. Please see our recommendations for the IFU in Section 4.1 (sub-bullet B3).
user identifies the Mylan pen in the presence of the Humulin R U-500 KwikPen (differentiation task)	4 errors: -2 untrained, other pen experienced adult patient -1 trained, other pen experienced adult patient -1 untrained HCP 1 close call: - 1 trained, other pen experienced adult patient	Mylan classified two of the errors as study artifacts because these participants appeared to misunderstand the task. Two of the participants (an untrained healthcare provider and a trained pen experienced patient) noted the similarity in pen color and body shape as contributing factors to their selection errors. Mylan determined that this risk associated with this error was minimal; thus, they determined	Semglee is a long acting insulin containing 100 units/mL while Humulin R U-500 is a concentrated insulin containing 5 times more units per mL and a selection error could result in a potentially serious overdose of the wrong insulin product. Thus, we have a concern regarding the errors noted in this differentiation task as the risk for patient harm is significant should a mix-up occur.

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Table 2: List of critical tasks where failures occurred and the assessment of the failures that occurred during the task			
Critical Task	**Use Errors and Close Calls**	**Root Cause Analysis**	**Additional Analysis and General Recommendations from DMEPA**
	Each of these participants selected the Humulin R U-500 KwikPen when asked to select the test pen.	that no further mitigation is required.	We note that the issues of similarity in pen color and body shape are not unique to this product and we determined that improvements in the carton and container labeling could be improved to mitigate the risk of confusion between Semglee and the Humulin R U-500 KwikPen. Of note, we determined that the product information on the carton and container could be difficult for users to read and we have provided multiple recommendations to improve the clarity of the carton and container. Please see our recommendations for the sponsor in Section 4.2. We recommend that Mylan conduct another HF differentiation study to validate the updated carton and container labeling. We advise that Mylan implement the recommended carton and container labeling

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Table 2: List of critical tasks where failures occurred and the assessment of the failures that occurred during the task			
Critical Task	**Use Errors and Close Calls**	**Root Cause Analysis**	**Additional Analysis and General Recommendations from DMEPA**
			changes prior to commencing their supplemental HF study.

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3.2 LABELS AND LABELING

In addition to the human factors study evaluation, DMEPA reviewed the proposed labels and labeling to determine whether there are any significant concerns in terms of safety related to preventable medication errors. We noted several areas that could be clarified within the proposed container labels, carton labeling, instructions for use (IFU), and the prescribing information (PI). For the IFU, we recommend additional language for consistency with other similar insulin products. For example, we provide language for selecting the dose for increased clarity in dialing even and odd doses of Semglee.

We provide recommendations in section 4.1 for the Prescribing Information and Instructions for Use and in Section 4.2 for container label and carton labeling. Of note, we do not believe that the changes recommended for the PI and IFU require an additional HF validation study because the changes are intended to increase the clarity and prominence of information in the labeling and they do not change the critical tasks for product use.

4 CONCLUSION & RECOMMENDATIONS

Our review determined that there were an insufficient number of pediatric untrained injection naïve patients in the study. In addition, the selection errors noted in the Human Factors validation study results do not support that users will select the correct product. Our review of the proposed PI, IFU, carton and container labeling identified several areas of improvement, based on safety concerns and post-marketing experience with other insulin products.

The changes recommended for the PI and IFU do not require an additional HF validation study for all user groups because the changes are intended to increase the clarity and prominence of information. As such, we recommend Mylan conduct an additional human factors validation study with 15 untrained naive pediatric patients after implementing the changes recommended for the IFU. In addition, we recommend that Mylan conduct a differentiation study to provide data to demonstrate that the products can be differentiated by all intended user groups after implementing the carton and container labeling recommendations provided in Section 4.2.

Please see Sections 4.1 and 4.2 for our labeling recommendations.

4.1 RECOMMENDATIONS FOR THE DIVISION

We have the following recommendations:

A. Prescribing Information
   1. Dosage and Administration: Section 2.1 Important Administration Instructions
      a. We recommend replacing the word (b) (4) in the statement "administer Semglee subcutaneously into the abdominal area, thigh, or (b) (4) …" to "upper arm" as this corresponds to the instructions provided in the Instructions for Use (IFU). In addition, we recommend adding "buttocks" as an administration site to align with the information provided in the IFU.

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b. We recommend adding the statement "Use the Semglee prefilled pen with caution in patients with visual impairment." as the final bullet in this section.

2. Dosage and Administration: Section 2.2 General Dosing Instructions
   a. We recommend adding the statement "Semglee prefilled pens are designed to dial doses in 1 unit increments" as the final bullet in this section.
3. Dosage and Administration: Section 2.4 Changing to Semglee from Other Insulin Therapies
   a. We do not agree with removing the statement (b) (4) (b) (4). Therefore, we recommend adding the following statement as a new bullet this section: "In patients changing from once daily NPH insulin to once daily dose of Semglee, the recommended initial Semglee dose is the same as the dose of NPH that is being discontinued."
4. How Supplied/Storage and Handling: Section 16.1 How Supplied
   a. We recommend reformatting this section using the following table to present this information.

Semglee	Total Volume	Concentration	Total Units Available in Presentation	Dose Increment	NDC Number	Package Size
U-100 vial	10 mL	100 units/mL	1,000 units	n/a	(b) (4)	1 vial
U-100 prefilled pen	3 mL	100 units/mL	300 units	1 unit		1 pen
						3 pens
						5 pens

5. How Supplied/Storage and Handling: Section 16.2 Storage
   a. We recommend revising the temperature presentations in the table to present the Fahrenheit temperatures before the Celsius temperatures as this coincides with the temperature presentation in the IFU. In addition, Fahrenheit temperature is more likely to be understood by end users in the US.

B. Instructions for Use (IFU)-Pen
   1. We recommend that you revise the statement (b) (4) (b) (4) (b) (4) to read as follows for improved clarity: "Semglee™ is a prefilled disposable pen injector that contains a total of 300 units of insulin glargine. One pen contains multiple doses of medicine. You can select doses from 1 to 80 units in steps of 1 unit." In addition, we recommend adding the statement "If your prescribed dose is more than 80 units, you will need to give yourself more than 1 injection." to this paragraph.
   2. We recommend that you move the statement "**Do not** leave the needle attached to the Pen during storage or reuse needles." so that it is immediately following the statement "Always store the Pen with the cap on, to prevent

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contamination.": "Always store the Pen with the cap on, to prevent contamination. **Do not** leave the needle attached to the Pen during storage or reuse needles."

3. Due to the use errors involving the storage of Semglee observed in the HF study, we provide the following recommendations for the storage information. Under the Storage heading, we recommend adding section subheadings and bullet points to increase clarity and readability of the statements. In addition, we recommend modifications to the language as follows:

Storage

Unused Pens

- Before using the Pen, store the cartons containing the Pen in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Unused Pens may be used until the expiration date printed on the carton, if the Pen has been kept in the refrigerator.
- Do not freeze the Pen

In-use Pen

- Before first use, take a Pen out of the refrigerator, rest it on a flat surface, and wait for it to reach room temperature between 59°F to 86°F (15°C to 30°C).
- While using the Pen, store it at room temperature up to 86°F (30°C). Do not put the Pen back in the refrigerator after using it.
- Always store the Pen with the cap on, to prevent contamination. Do not leave the needle attached to the Pen during storage or reuse needles.
- The Pen that you are using should be thrown away 28 days after the first use, even if the Pen has insulin left in it. See disposal instructions in Step 8.

Keep your Pen and needles out of sight and reach of children.

Always use a new sterile needle for each injection as this helps stop blocked needles and prevents infections.

4. Step 4: Select your dose
   a. We recommend the addition of the following as bullet points under this heading: "-The Pen dials 1 unit at a time.", "-The Dose Knob clicks as you turn it.", "-**Do not** dial your dose by counting the clicks because you may dial the wrong dose.", "-The **even** numbers are printed on the dial. The odd numbers are shown as lines."
   b. We recommend the addition of an image of an odd dose dialed on the device pen to correspond with the language added to indicate that odd doses are shown as lines in the dose window.
   c. We recommend that you add the statement "If you need a dose greater than 80 units, you should give it as two or more injections." so that it

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immediately follows the statement "**Do not** force the dose knob to turn beyond 80 units.": "**Do not** force the dose knob to turn beyond 80 units. If you need a dose greater than 80 units, you should give it as two or more injections." In addition, we recommend that these statements are moved to immediately follow the statement (b) (4) by turning the dose knob in either direction until the correct dose lines up with the yellow dose pointer." to increase prominence of this information in the IFU.

5. Step 5: Select and clean the injection site
    a. We recommend revising the statement "Select the injection site as explained..." to read as follows:
    "Select the injection site as explained to you by your healthcare provider. Semglee is injected under the skin (subcutaneously) of your arms, hips, thighs, buttocks, or abdomen. You should change your injection site for each injection.
    Clean with a new alcohol wipe and let your skin dry before you inject your dose."
6. Due to the use errors with holding the dose button down to complete the injection observed in the HF study, we provide the following recommendation for Step 6: Inject your dose:
    a. Under step D, revise the statement "hold the purple injection button...is injected." as follows for improved clarity: "after the dose window shows "0", continue to hold the purple injection button down and slowly count to 10 to make sure that the full dose of insulin is injected."

4.2 RECOMMENDATIONS FOR MYLAN

Our review determined that there were an insufficient number of untrained injection naïve pediatric patients in each user group of the study. Our review of the instructions for use (IFU) identified several areas that should be modified. As such, we recommend that you implement those changes, and conduct an additional human factors validation study with 15 untrained injection naive pediatric patients.

In addition, we note that the results of product differentiation showed multiple study participants failed to select the Semglee pen. Our review of the proposed carton and container labeling identified multiple areas that can be modified to enhance product differentiation. Therefore, we recommend that you implement these modifications and conduct a differentiation study with all the intended user populations for the product with at least 15 users in each distinct user group.

A. Container Label-Pen
    1. The proprietary name, "Semglee," the established name, and the product strength lack prominence on the container label and are not readable. Thus, we request that you revise the label to remove the graphic matter (e.g., colors, banding, colored boxes) interfering with the readability of this information on the label in accordance with 21 CFR 201.10 (a) and 21 CFR 201.15 (a)(6).

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Consider presenting this text (proprietary name, established name, and product strength) on a white background with black letters in larger font to improve readability.

2. To improve readability of the proprietary name, we recommend increasing the font size of "Semglee" on the label.
3. To improve readability of the product NDC, we recommend using black font on a white background.
4. To improve the readability of the "Rx only" statement, we recommend removing the (b) (4) and using black font.
5. Increase the font of the "For Single Patient Use Only" statement to improve readability of this information.

B. Container Label-Vial

1. The product strength, 100 units/mL (U-100), is illegible and difficult to read due to the use of the (b) (4). We recommend that you consider placing this text on a white background with black letters in larger font for improved readability.
2. To improve the readability of the "Rx only" statement, we recommend removing the (b) (4) and using black font.

C. Carton Labeling-Pen

1. The product strength, 100 units/mL (U-100), is illegible and difficult to read on each of the carton presentations due to your use of the (b) (4) (b) (4). We recommend that you consider placing this text on a white background with black letters in larger font for improved readability. In addition, move the product strength statement so that it is directly below the proprietary name and established name on the principle display panel.
2. To improve the readability of the "Rx only" statement, we recommend removing the (b) (4) and using black font.
3. We recommend that you consider moving the statement (b) (4) (b) (4) from the PDP so that it is immediately above "Initial Use Date:" on the back panel. In addition, we recommend that you modify the statement to read "Use each pen within 28 days after initial use." for improved clarity of the statement.

D. Carton Labeling-Vial

1. The product strength is illegible and difficult to read on each of the carton presentations due to your use of the (b) (4). We recommend that you consider placing this text on a white background with black letters in larger font for improved readability.
2. To improve the readability of the "Rx only" statement, we recommend removing the (b) (4) and using black font.
3. To improve readability of the carton contents, we recommend moving the statement "One 10 mL vial" above the blue box area and changing "one" to black font.

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APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Semglee that Mylan submitted on April 27, 2017, and the listed drug (LD).

Table 3. Relevant Product Information for Semglee and the Listed Drug (Lantus)

Product Name	**Semglee**	**Lantus (NDA 21081)**
Initial Approval Date	n/a	April 20, 2000
Active Ingredient	insulin glargine	insulin glargine
Indication	improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus	improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus
Route of Administration	subcutaneous	subcutaneous
Dosage Form	injection	injection
Strength	100 units/mL	100 units/mL
Dose and Frequency	Individualized dosage administered once daily at any time of day, but at the same time every day	Individualized dosage administered once daily at any time of day, but at the same time every day
How Supplied	10 mL vials 3 mL prefilled pen (1 pen per carton, 3 pens per carton, or 5 pens per carton)	10 mL vials 3 mL SoloStar prefilled pen (5 pens per carton)
Storage	Unopened: Refrigerate (36°F - 46°F [2°C -8°C]) until labeled expiration date; Room Temperature (below 86◦F [30◦C]) for up to 28 days Opened: for vial- 28 days Refrigerated or room temperature; for prefilled pen- 28 days Room temperature only (Do not refrigerate)	Unopened: Refrigerate (36°F - 46°F [2°C -8°C]) until labeled expiration date; Room Temperature (below 86◦F [30◦C]) for up to 28 days Opened: for vial- 28 days Refrigerated or room temperature; for SoloStar pen- 28 days Room temperature only (Do not refrigerate)

Reference ID: 4243910
Reference ID: 4624497

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 6, 2017, we searched for DMEPA's previous reviews using the terms, "insulin glargine" and "105279". Our search identified two previous reviews[f], and we confirmed that our previous recommendations were implemented.

[f] Vee S. Memorandum Review of Revised Human Factors Validation Protocol for insulin glargine (IND 105279). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 January 12. RCM No. 2015-1823.

Vee S. Human Factors Protocol Review for insulin glargine (IND 105279). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 May 18. RCM No. 2016-919.

Reference ID: 4243910
Reference ID: 4624497

APPENDIX C. HUMAN FACTORS STUDY

The HF study can be accessible in EDR via:

\\cdsesub1\evsprod\nda210605\0000\m3\32-body-data\32p-drug-prod\insulin-bioc-bnglr\32p2-pharm-dev\container-closure-system-device-development.pdf

Reference ID: 4243910
Reference ID: 4624497

APPENDIX D. INFORMATION REQUESTS

- Information request sent on October 19, 2017 to request additional information to aid in our evaluation of the study results. Mylan's response was submitted to the EDR on November 14, 2017.
    - \\cdsesub1\evsprod\nda210605\0021\m1\us\111-information-amendment\response-to-cmc-ir-dated-october-19-2017.pdf
    - \\cdsesub1\evsprod\nda210605\0021\m1\us\111-information-amendment\myl-1501d-prefilled-pen-use-related-risk-assessment.pdf

- Information request sent on November 30, 2017 to request clarification regarding a previously completed differentiation study. Mylan's response was submitted to the EDR on December 4, 2017.
    - \\cdsesub1\evsprod\nda210605\0022\m1\us\111-information-amendment\response-to-cmc-ir-dated-november-30-2017.pdf

Reference ID: 4243910
Reference ID: 4624497

APPENDIX E. PREVIOUS FDA/SPONSOR INTERACTIONS

Interactions with sponsor under IND 105279

March 7, 2014 End of Phase 2 meeting with Mylan, DMEPA, DMEP, CDRH, and other members of the review team:

DMEPA provided multiple recommendations including the following: (1) conduct a "pen identification task" prior to the usability test on the device, (2) include a case-based protocol for differentiation between the study pen and other pens from product lines likely to be prescribed with it, and (3) evaluate the finalized commercial product including pen color, label, and labeling in a summative study.[g]

April 2014 meeting minutes.pdf

February 18, 2016 teleconference with Mylan, DMEPA, and DMEP:

Meeting to follow-up on recommendations provided to the sponsor January 2016. Mylan presented background information and their proposed mitigation strategy to minimize potential errors with Mylan's pen and Lilly's Humulin U-500 KwikPen. Recommended Mylan complete a differentiation study before submitting the NDA and submit the study protocol for review.[h]

Feb 2016 teleconference meetin

4 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[g] Whitehead R. Type B End-of-Phase 2 (EOP2) Meeting Minutes for insulin glargine. Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2014 April 4. IND 105279.

[h] White M. Memorandum of Teleconference for insulin glargine. Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2016 February 18. IND 105279.

Reference ID: 4243910
Reference ID: 4624497

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

/s/

ARIANE O CONRAD
04/04/2018

HINA S MEHTA
04/04/2018

QUYNHNHU T NGUYEN
04/04/2018

MISHALE P MISTRY
04/04/2018

OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH

INTERCENTER CONSULT MEMORANDUM

Date	March 19, 2018
To	Anika Lalmansingh CDER/OPQ/OPRO/DRBPMI/RBPMBI
Requesting Division	CDER/OND/ODEII/DMEP
From	Rong Guo CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	Carolyn Dorgan CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CAPT Alan Stevens CDRH/ODE/DAGRRID/GHDB
Subject	Consult for Submission # NDA 210605, SEMGLEE, MYL-1501D ICCR2017-01604 ICC1700398
Recommendation	Approval of the device constituent of the combination product

Digital Signature Concurrence Table	
Reviewer	Rong Guo -S 2018.03.22 15:09:03 -04'00'
Team Lead	Carolyn C. Dorgan -S Digitally signed by Carolyn C. Dorgan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001800814, cn=Carolyn C. Dorgan -S Date: 2018.03.23 09:04:48 -04'00'
Branch Chief	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: 2018.03.27 07:01:06 -04'00'

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2017-01604
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=1824
ICC tracking # (Lead)	ICC1700398
Submission Number	NDA210605
Sponsor	Mylan GmbH
Drug/Biologic	Insulin glargine
Indications for Use	Improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
Device Constituent	pre-filled pen
Related Files	NDA210605 EDR 3.2.P.2; 3.2.P.7

Table 2. Important Dates	
Filling	Sept 15, 2017
Mid-Cycle Meeting	January 8, 2018
Wrap up Meeting	April 11, 2018
Final Discipline Specific Memos Due	April 9, 2018
Final Lead Device Review Memo Due	April 17, 2018
PDUFA date	May 17, 2018

2. PURPOSE/BACKGROUND

2.1. Scope

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH) regarding NDA 210605, MYL-1501D, Insulin glargine. The device consultant authoring this review memorandum has performed a design review of submission materials intended to support the safety and functionality of the pre-filled pen injector. This review did not cover manufacturing of the pen injector nor the human factors study.

This review covers the essential performance elements of the device under review:

- Dose accuracy
- Functional Performance
- Biocompatibility of non-primary closure components

Topics not covered in this review:

- Human factors deferred to CDER/OSE/DMEPA
- Device manufacturing review deferred to CDRH/OC
- Final combination product benefit / risk assessment
- Review of the prefilled cartridge (primary container closure) including biocompatibility and sterility deferred to CDER/OPQ

Reference ID: 4240177
Reference ID: 4624497

2.2. Background

Insulin glargine (Anatomical Therapeutic Chemical [ATC] code A10AE04) is a long-acting analog of human insulin, and is classified under the ATC group "drugs used in diabetes, insulins and analogues for injection, long-acting". The primary sequence of insulin glargine differs from that of insulin by 3 amino acids: asparagine at position A21 instead of glycine and 2 arginines added to the C-terminus of the B chain. Lantus® (insulin glargine [rDNA origin] injection; NDA# 021081; Sanofi-Aventis) is the reference listed product. The sequence of MYL-1501D was shown to be identical to that of insulin glargine (Lantus). MYL-1501D is a clear, colorless solution for injection, at pH 4.0. It is supplied in a pre-filled disposable pen integrated with a 3 mL cartridge, containing 100 U insulin glargine per mL.

2.3. Prior Interactions

GHDB received ICC1700398 on May 8, 2017. Rong Guo was the reviewer. The submission contained sufficient data for the device constituent part of the combination product. Device recommended filing. This application was issued a Refuse to File on 6/26/2017. The applicant has Filed over Protest and therefore the review clock has been restarted.

2.3.1. Related Files

NDA 210605 Sequence 0000 submitted on 04/27/2017
Sequence 30 submitted on 02/28/2018
(b) (4) Disposable pen

2.4. Indications for Use

Combination Product	Indications for Use
Insulin glargine	Improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
(b) (4) Disposable pen	To deliver a maximum of 80 insulin glargine units (U) per injection and the total deliverable content of the MYL-1501D cartridge is 300 U

2.5. Dosage and Administration

- Individualize dosage based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, prior insulin use
- Administer subcutaneously once daily at any time of day, but at the same time every day.
- Do not dilute or mix with any other insulin or solution.
- Rotate injection sites to reduce the risk of lipodystrophy.
- Closely monitor glucose when changing to SEMGLEE and during initial weeks thereafter.

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Date - Version	Location
(b) (4)	(b) (4) Disposable pen Device Master File	CDRH Image

Reference ID: 4240177
Reference ID: 4624497

NDA 210605	Sequence 0000 submitted on 04/27/2017	CDER EDR
NDA 210605	Sequence 30 submitted on 02/28/2018	CDER EDR

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

The device constituent part of the MYL-1501D combination product is composed of the [redacted] (b) (4) Disposable Pen Body Subassembly, the [redacted] (b) (4) Disposable Pen Cartridge Holder and the [redacted] (b) (4) Disposable Pen Cap [redacted] (b) (4) are the Design Authority for the device and the holder of the device master file [redacted] (b) (4) Disposable Pen Device Master File).

Figure 3.2.P.2.4/ 1: An Illustration of the MYL-1501D Combination Product, as Received by the User[1]

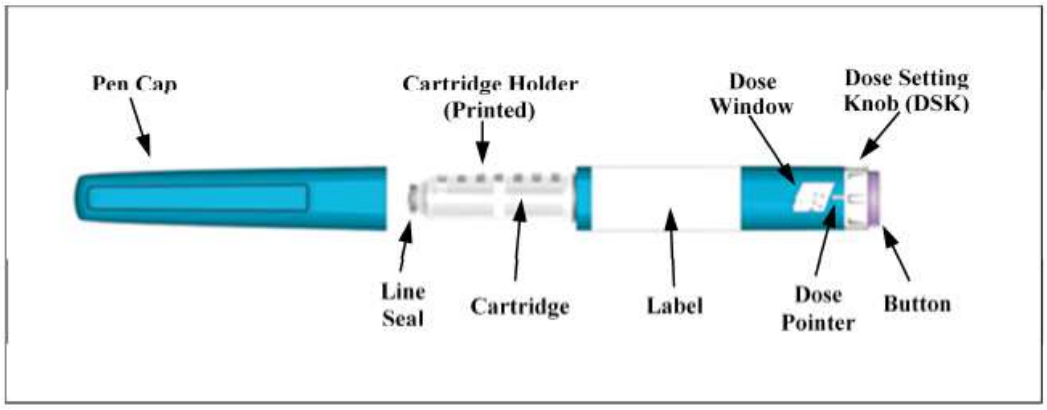

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Table 3.2.P.7/7: Overview of the MYL-1501D PFP Components

Device Component	Constituent Component	Material	DMF/MAF Reference	Supplier
Pen body subassembly	[redacted]	[redacted]	[redacted]	(b) (4)
Cartridge holder	Cartridge holder	(b) (4)		
Pen cap	Pen cap			

Principles of Operation

Each MYL-1501D PFP contains in total 300 insulin glargine units (U) (in 3 mL of 100 U/mL solution for injection). The MYL-1501D PFP is designed to deliver a maximum of 80 U per injection. Doses from 1 to 80 U can be set in increments of 1 U. These are consistent with the reference product Lantus

Prior to injection, the pen cap is removed and a new pen needle is attached to the front end of the cartridge holder. In its initial position, the DSK (located at the rear end of the device) is flush with the body and "0" is displayed in the dose window. The dose is pre-selected by rotating the DSK and the number of insulin glargine units (U) is displayed in the dose window. Numerals on the outside of the DSK are visible through the dose window of the body to indicate the selected dose. The dialing mechanism allows dosage increments of 1 U.

The injection is then performed by pushing the dose button. The user pushes on the button, which locks the set back and DSK, so that they rotate and translate together. The rotation of the set back is transmitted to the lead screw, and the rotation of the lead screw drives the plunger rod forward to push the cartridge plunger stopper and deliver the dose. During dose delivery, the DSK rotates, clicking down through each unit administered. Once the injection is complete, the dose button will have returned to its original position and "0" is displayed in the dose window. The display of "0" assures the user that the injection is complete.

Comparison between the RLD (Lantus® SoloSTAR®, Sanofi-Aventis) and the proposed MYL-1501D

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Table 3.2.P.2.4/ 1: Comparison of the User Interfaces for Lantus SoloSTAR and the MYL-1501D Combination Product

Company	Sanofi-Aventis	Mylan Inc
Name	Lantus SoloSTAR	MYL-1501D Combination Product
Composition	Lantus SoloSTAR is a disposable pre-filled pen (PFP) for the injection of insulin glargine. The PFP is approximately 16 to 17 cm in length with the pen cap attached. Each Lantus SoloSTAR contains in total 300 insulin glargine units (U) (in 3 mL of 100 U/mL solution for injection). Doses from 1 to 80 U can be set in increments of 1 U. An indicative scale is printed on the cartridge holder of the PFP with graduations (b) (4)	The MYL-1501D combination product is a disposable pre-filled pen (PFP) for the injection of insulin glargine. The PFP is approximately 16 to 17 cm in length with the pen cap attached. Each MYL-1501D PFP contains in total 300 insulin glargine units (U) (in 3 mL of 100 U/mL solution for injection). Doses from 1 to 80 U can be set in increments of 1 U. An indicative scale is printed on the cartridge holder of the PFP with graduations (b) (4)
Component Color	The Lantus SoloSTAR is grey with a purple injection button.	The MYL-1501D PFP is blue with a purple injection button.
Disposable Pen	 Image representative of Lantus SoloSTAR	 Image representative of the MYL-1501D PFP
Packaging Configuration	Provided in a package of 5 Lantus SoloSTAR PFP	Provided in a carton containing 1 MYL-1501D PFP.[2]

Company	Sanofi-Aventis	Mylan Inc
Package Insert	PIL and IFU	PIL and IFU
Carton	(b) (4)	
Storage		

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Reviewer Comment: *The device description is comparable to the reference product Lantus, and is acceptable.*

Device Characteristic	Description / Specification
Injector Name	(b) (4) Disposable pen
Injector Platform Name	n/a
Priming Dose / Volume	2 U
Dose accuracy	Comply with ISO 11608-1: 2014
Injection Time	User dependent; Hold 10 seconds after injection
Injection Site	subcutaneous injection
Injection tissue and depth of injection	Depends on the commercial needle used
Audible / visual feedback	yes
Cap Removal Force	(b) (4)
Activation Force	User dependent
Visibility of medication container	yes
Last Dose Specifications and Safety Features	Comply with ISO 11608-1: 2014
Needle Specifications • Length(s) • Gauge(s) • Connection type ○ ISO 11608-2:2012 ○ Prestaked	Commercial needle (BD Ultra-Fine™ needles are compatible with this pen). Comply with ISO 11608-2:2012
Type of Use (e.g. single use, disposable, reusable, other)	Multi-use, disposable

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Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Self-administer for adult patients with diabetes mellitus, or healthcare provider
Injection mechanism (e.g., manual piston, spring, gas, etc.)	manual piston
Method of actuation	Pressing the purple injection button
Automated Functions	n/a
Residual Medication	n/a
Delivered Volume (for single dose or selectable volume range for multidose pens)	Up to 80 U per injection
Drug Container Type	Clear, colorless, Type I (b) (4) glass cartridges
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	U
Environments of use	home
Storage conditions and expiry	Before using the Pen, store the cartons containing the Pen in the refrigerator between 36°F to 46°F (2°C to 8°C). After using the Pen, store it at room temperature up to 86°F (30°C). Do not put the Pen back in the refrigerator after using it The Pen should be thrown away after 28 days of first use, even if it still has insulin left in it
Graduation marks / fill lines	yes
Preparation and administration (describe all that are applicable) • Warm to room temp prior to injection • Assembling components • Prime steps • Setting dose • Skin preparation steps (e.g., pinch skin, inject through clothing, etc.) • Changing / disposing needles • Etc.	Rest the pen on a flat surface and wait for it to reach room temperature between 59°F to 86°F; Always prime a new Pen needle before each injection with 2 dose units; Turn the white dose knob until the yellow dose pointer lines up with your required dose; Clean skin with a new alcohol wipe and let it dry; Pinch skin; Change injection site for each injection; Do not re-use needles. Do not administer intravenously or via an insulin pump.
Safety Features • Needle safety	no

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Electronics / Data transmission • Display • Control functions • Data transmission technology • Data being transferred	n/a
Material composition of injector	(b) (4)

5. DESIGN CONTROL REVIEW

5.1. Design Review Summary

The device design, development, verification and validation data contained in this submission provide a summary of the device development conducted with a consideration of 21CFR Part 820.30 and EN ISO 13485:2012 – Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes.

5.1.1. Design Control Documentation Check

Design Control Requirement*	**Signed/Dated Document Present**		**Submission Location**
	Yes	**No**	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	x		EDR 3.2.P.5.1
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	x		EDR 3.2.P.2
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	x		EDR 1.11.1
Validation Data	x		EDR 3.2.P.2
• Human factors • Clinical data	x		EDR Module 5
Traceability Documentation	x		

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5.1.2. Design Control Review

Biocon and Mylan have collaborated with (b) (4) for the design, development and manufacture of the components of the PFP. The submission complies with the following guidance and standards:

21 CFR Part 820.30 – Design Controls
Guidance for Industry Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (FDA, June 2013)
Guidance for Industry – Container Closure Systems for Packaging Human Drugs and Biologics (FDA, May 1999)
Guidance for Industry and Food and Drug Administration Staff – Applying Human Factors and Usability Engineering to Medical Devices (FDA, February 2016)
Guidance for Industry and Food and Drug Administration Staff – Use of International Standard (ISO) 10993-1, "Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing within a Risk Management Process" (FDA, June 2016)
ISO 10993-1:2009 – Biological evaluation of Medical Devices – Part 1: Evaluation and Testing within a Risk Management Process
EN ISO 13485:2012 Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes
ISO 14971:2007 - Medical Devices – Application of Risk Management to Medical Devices
ISO 11608-1:2014 Needle-based Injection Systems for Medical Use – Requirements and Test Methods - Part 1: Needle-based Injection Systems
ISO 11608-2:2012 Needle-based Injection Systems for Medical Use – Requirements and Test Methods – Part 2: Needles
ISO 11608-3:2012 Needle-based Injection Systems for Medical Use – Requirements and Test Methods - Part 3: Finished containers
EN ISO 62366-1:2015 – Medical Devices. Application of Usability Engineering to Medical Devices

***Reviewer Comment**: The design control is acceptable.*

6. DESIGN VERIFICATION AND VALIDATION REVIEW

6.1. Summary of Design V&V Attributes

Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	x		
To-be-marketed device was used in the pivotal clinical trial?		x	
Selectable dose range on device matches the labeled dose range for the medication?	x		
Verification methods relevant to specific use conditions as described in design documents and labeling	x		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability	x		

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study)				
Traceability demonstrated for specifications to performance data		x		
Conformance to applicable standards demonstrated	ISO 11608-1:2014 – Needle based injection systems – Requirements and Test Methods	x		
	ISO 11608-2:2012 – Needles	x		
	ISO 11068-4:2006 – Electronic and Electromechanical Pen Injectors			x
	ISO 11608-5:2012 – Automated Functions	x		
Adherence to FDA Guidance: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products		x		
Stability and simulated shipping / transport data adequately verifies device will meet essential performance requirements at expiry		x		
Discipline -Specific Design Verification / Validation adequately addressed	Biocompatibility	x		
	Sterility			x
	Software / Cybersecurity			x
	Electrical Safety / EMC			x
	Human Factors	x		

6.2. Design Validation Review

Design Validation Attributes	**Yes**	**No**	**N/A**
Phase I/II/III Study utilized the to-be-marketed device		x	
Bioequivalence Study utilized to-be-marketed device	x		
Simulated Actual Use Study utilized to-be-marketed device	x		

Design changes between the clinical and commercial pen configurations:

- Optimization of the detailed design of the tower core component to reduce the risk of mechanical failure if excessive injection forces are applied, for example, during a potential misuse scenario such as use of a bent needle.
- Improvements to the pen cap, including resistance of the clip to breakage and optimizing the push-on/pull-off forces for ease of use, by adjusting the bump-offs on the pen cap which retain it to the cartridge holder.
- Moving the location datum of the cartridge in the cartridge holder from the shoulder to the tip. This minimizes the depth of the recess around the tip to ease cleaning of the rubber seal (lined seal).

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- As in other pre-filled pens, lubricant is used between the DSK and body. The lubricant minimizes friction, and enables free rotation between the button and double clicker. Note that the lubricant is contained within the pen body subassembly, remote from the cartridge.

Additional non-functional refinements were made which included minor alterations to tolerances, clearances and fits between mating components, tool design (b) (4) and assembly features. These are described in Section 3.2.P.2.4.2.3.1.1.2, Non-Functional Design Changes and Refinements from the Clinical Pen to the Commercial Pen.

An IR was sent on 01/10/2018:

You indicated that there are design changes between the clinical and commercial pen configurations. Please provide a comparison of the verification and validation between the to be marketed presentation and the clinical studied pen injector, and justify how the design changes will not impact the essential performance specifications through a risk analysis.

The Sponsor responded on 02/28/2018 and provided a comparison table.
The design changes and design refinements proposed included the following improvements related to use of the PFP:

- A reduction in the dose selection forces on operation of the Dose Setting Knob (DSK)
- A reduction of the plunger force during dose injection
- Improved resistance to freefall drop

All these changes did not impact the Device Requirement Specification (DRS) between the clinical and commercial pen configurations. Both clinical pen and commercial pen met the performance requirement specifications. The comparison table is provided in Response to CMC IR dated January 10 located in EDR Sequence 30 submitted on 02/28/2018

6.3. Design Verification Review

Essential Performance Requirement	Specification	Verification	Validation	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)	Lot Release Testing (Y/N)
Injection Depth	Injection depth is dependent on length of commercial needle selected.	n/a				
Injection Time	10 seconds	Y	Y	Y	Y	N
Dose Accuracy	Must comply with ISO 11608-1:2014 (b) (4)	Y	Y	Y	Y	Y
Visual/Audible Feedback	DSK movement starts at start of injection and stops at end of injection; Clicking starts at start of injection and	Y	Y	N	N	Y

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	stops at end of injection.					
Activation Force	Not more than (b) (4)	Y	Y	Y	Y	Y
Needle Length	dependent on the commercial needle selected	n/a				
Needle Gauge	dependent on the commercial needle selected	n/a				
Needle Connection Type	Comply with ISO 11608-2:2012	n/a				
Needle Resistance to Bend / Fracture	Not applicable. No inherent needle.	n/a				
Cap Removal Force	(b) (4)	Y	Y	Y	Y	N

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Table 3.2.P.2.4/ 35: Design Verification Test Rationale for MYL-1501D PFP (b) (4)

Input Design Requirement	Specification	Attribute Tested on (b) (4) MYL-1501D PFPs	Rationale
Dose accuracy in standard in-use conditions	(b) (4)	Yes	(b) (4)
Dose accuracy following freefall		Yes	
System resistance to freefall		Yes	
Cartridge holder removal force – axial load		Yes	
Cartridge holder removal force – side load		Yes	
Cap attachment force		Yes	
Cap detachment force		Yes	

Dose Accuracy

The MYL-1501D PFP contains 3 mL of 100 U/mL insulin glargine equating to 300 U (i.e. each 0.01 mL of 100 U/mL insulin glargine equates to 1 U). The lowest selectable dose is 1 U (i.e. a volume of 0.01mL) and the highest selectable dose is 80 U (i.e. a volume of 0.80mL).

Dose accuracy performance and functionality/robustness testing was performed in accordance with ISO 11608-1:2014. The MYL-1501D PFP was subjected to in-use cool, ambient (standard) and warm environmental conditions, cold and hot storage conditions, freefall and vibration robustness, each followed by both functional and performance (dose accuracy) assessment. The BD Ultra-Fine (b) (4) needle was used throughout the DVT as the "standard test needle".

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Table 3.2.P.2.4/ 10: Dose Accuracy and Device Functionality in Cool In-Use Conditions

DRS Requirement		The pen must maintain volumetric accuracy as per ISO 11608-1:2014 under the operating conditions 5°C ± 3°C/uncontrolled RH		Met requirements
Mechanical Function	Sample Size n = 60 pens	Functionality: Number of mechanical failures (for (b) (4)% reliability) = 0		Pass
		Requirement	Results (mL)	
Dose Accuracy (Needle BD Ultra-Fine (b) (4))	n = 60 pens (MYL-1501D cartridge) (Commercial pen configuration)	(b) (4)		Pass
				Pass

*Standard deviation reported to 3 decimal places for information

Table 3.2.P.2.4/ 15: Dose Accuracy in Warm In-Use Conditions

DRS Requirement		The pen must maintain volumetric accuracy as per ISO 11608-1:2014 under the operating conditions 40°C ± 2°C/50% ± 10% RH		Met requirements
Mechanical Function	Sample Size n = 60 pens	Functionality: Number of mechanical failures (for (b) (4)% reliability) = 0		Pass
		Requirement	Results (mL)	
Dose Accuracy (Needle BD Ultra-Fine (b) (4))	n = 60 pens (MYL-1501D cartridge) (Commercial pen configuration)	(b) (4)		Pass
				Pass

* Standard deviation reported to 3 decimal places for information

Table 3.2.P.2.4/ 16: Dose Accuracy Following Freefall

DRS Requirement		The pen must maintain volumetric accuracy as per ISO 11608-1:2014 following freefall testing		Met requirements
Mechanical Function	Sample Size n = 30 pens	Functionality: Number of mechanical failures (for (b) (4)% reliability) = 0		Pass
		Requirement	Results (mL)	
Dose Accuracy (Needle BD Ultra-Fine (b) (4))	n = 30 pens (MYL-1501D cartridge) (Commercial pen configuration - (b) (4))	(b) (4)		Pass
				Pass

* Standard deviation reported to 3 decimal places for information

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Table 3.2.P.2.4/ 17: Dose Accuracy Following Vibration (Needle BD Ultra-Fine [redacted])

DRS Requirement		The pen must maintain volumetric accuracy as per ISO 11608-1:2014 following vibration testing		Met requirements
Mechanical Function	Sample Size n = 20 pens	Functionality: Number of mechanical failures (for [redacted]% reliability) = 0		Pass
Dose Accuracy (Needle BD Ultra-Fine [redacted])	n = 20 pens (Water filled cartridge) (Commercial pen configuration)	Requirement	Results (mL)	Pass
		[redacted]		Pass

* Standard deviation reported to 3 decimal places for information

Table 3.2.P.2.4/ 18: Dose Accuracy Following Cold Storage Conditions (Needle BD Ultra-Fine [redacted])

DRS Requirement		The pen must maintain volumetric accuracy as per ISO 11608-1:2014 under storage at 5°C ± 3°C/uncontrolled RH conditions for 96 hours and allowed to equilibrate to Room Temperature (RT) for a minimum of 4 hours		Met requirements
Mechanical Function	Sample Size n = 60 pens	Functionality: Number of mechanical failures (for [redacted]% reliability) = 0		Pass
Dose Accuracy (Needle BD Ultra-Fine [redacted])	n = 60 pens (Water filled cartridge) (Commercial pen configuration)	Requirement	Results (mL)	Pass
		[redacted]		Pass

* Standard deviation reported to 3 decimal places for information

Table 3.2.P.2.4/ 19: Dose Accuracy Following Hot Storage Conditions (Needle BD Ultra-Fine [redacted])

DRS Requirement		The pen must maintain volumetric accuracy as per ISO 11608-1:2014 under storage at 40°C ± 2°C/50% ± 10% RH conditions for 96 hours and allowed to equilibrate to RT for a minimum of 4 hours		Met requirements
Mechanical Function	Sample Size n = 60 pens	Functionality: Number of mechanical failures (for [redacted]% reliability) = 0		Pass
Dose Accuracy (Needle BD Ultra-Fine [redacted])	n = 60 pens (Water filled cartridge) (Commercial pen configuration)	Requirement	Results (mL)	Pass
		[redacted]		Pass

* Standard deviation reported to 3 decimal places for information

Dose accuracy at last dose

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Table 3.2.P.2.4/ 20: Dose Accuracy at Last Dose, in Standard In-Use Conditions (Needle BD Ultra-Fine (b) (4))

DRS Requirement		The pen must maintain volumetric accuracy at last dose as per ISO 11608-1:2014 under the operating conditions 23°C ± 5°C/50% ± 25% RH		Met requirements
Mechanical Function	Sample Size n = 60 pens	Functionality: Number of mechanical failures (for (b) (4) % reliability) = 0		Pass
		Requirement	Results (mL)	
Dose Accuracy (Needle BD Ultra-Fine (b) (4))	n = 60 pens (Water filled cartridge) (Commercial pen configuration)	(b) (4)		Pass
				Pass

* Standard deviation reported to 3 decimal places for information

Volume expelled during dose selection

Table 3.2.P.2.4/ 22: Volume Expelled During Dose Selection

DRS Requirement		Volume expelled during dose selection is minimal			Met requirements
		Number of failures (for (b) (4) % reliability) = 0			Yes
		Requirement	Results (µL)		
Volume expelled during dose selection	Sample Size n = 30 pens (Water filled Cartridge in Commercial pen configuration)	(b) (4)	Average	(b) (4)	Yes
			Range		
			SD		

Reviewer Comment: *The dese accuracy testing complies with ISO 11608-1:2014, which is the same as the reference product Lantus, and another approved insulin glargine pen (* (b) (4) *. Per ISO 11608-1:2014, three dose sizes were used such that Vset is delivered from the front 1/3, middle 1/3 and rear 1/3 divisions of the container closure. The dose accuracy acceptance criteria were determined from ISO 11608-1:2014 requirements, the absolute error for the pen is 0.01 mL (minimum settable dose) and so the ISO 11608-1:2014 transition point (TP) dose between using the absolute error α and a relative error β, expressed as a percentage (5%) of the set dose, is determined by* $TP = \frac{100 \times \alpha}{\beta}$, *which is 0.20 mL. When the dose size is equal to or below TP, absolute error is equal to the minimum dialing resolution (0.01ml); when the dose size is above the TP, relative error is equal to 5% of the dose size.*

Dose accuracy testing was performed using drug product-filled cartridges for cool, ambient (standard) and warm conditions, and following freefall testing. Water was used within the cartridges in the dose accuracy assessment for vibration, dry heat and cold storage studies. As the density of insulin glargine is (b) (4) *at standard temperature [23°C] against water of 0.9975 g/mL at the same temperature, the two liquids have similar density and viscosity, the use of water in some of the dose accuracy testing (vibration, dry heat and cold storage studies) is acceptable.*

The reviewer agrees that the above dose accuracy performance of the pen following conditioning as prescribed by ISO 11608-1:2014 (in-use cool, storage in dry heat and cold conditions, free fall and vibration) and last dose all met the ISO 11608-1:2014 prescribed dose accuracy acceptance criteria, with no mechanical function failures. In use standard conditions testing with different commercial needles are shown under Needle compatibility testing, which also passed

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acceptance criteria. These demonstrate acceptable delivery performance of the commercial pen configuration MYL-1501D PFP.

Hold time Necessary after End of Injection

Injection time is largely user dependent, based upon applied force. The hold time following injection ensures that the entire dose is delivered once the plunger is pushed to the end of stroke and is within the time specified within the IFU.

Table 3.2.P.2.4/ 21: Hold Time Necessary After End of Injection (b) (4)

DRS Requirement		Hold time necessary after end of injection			Met requirements
Hold time after injection (b) (4)	Sample Size n = 60 pens (MYL-1501D cartridge) (Commercial pen configuration)	Number of failures (for (b) (4) % reliability) = 0			Yes
		Requirement	Results (seconds)		
		(b) (4)	Average	(b) (4)	Yes
			Range		
			SD		

Needle Compatibility Testing

Verification of the finished cartridge and needles suitability for use with the MYL-1501D PFP were conducted on the following specific commercialized pen needles:

- BD Ultra-Fine™ (b) (4)
- BD Ultra-Fine (b) (4) (b) (4)

Dose accuracy, cartridge compatibility, needle thread pitch, needle attachment and needle detachment torque were tested with these four commercial needles. All test passed acceptance criteria.

Table 3.2.P.2.4/ 11: Dose Accuracy in Standard In-Use Conditions (Needle BD Ultra-Fine (b) (4)

DRS Requirement		The pen must maintain volumetric accuracy as per ISO 11608-1:2014 under the operating conditions 23°C ± 5°C/50% ± 25% RH		Met requirements
Mechanical Function	Sample Size n = 60 pens	Functionality: Number of mechanical failures (for (b) (4) % reliability) = 0		Pass
		Requirement	Results (mL)	
Dose Accuracy (Needle BD Ultra-Fine (b) (4))	n = 60 pens (MYL-1501D cartridge) (Commercial pen configuration - (b) (4)	(b) (4)	(b) (4)	Pass
				Pass

* Standard deviation reported to 3 decimal places for information

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Table 3.2.P.2.4/ 12: Dose Accuracy in Standard In-Use Conditions (Needle BD Ultra-Fine [redacted])

DRS Requirement		The pen must maintain volumetric accuracy as per ISO 11608-1:2014 under the operating conditions 23°C ± 5°C/50% ± 25% RH		Met requirements
Mechanical Function	Sample Size n = 60 pens	Functionality: Number of mechanical failures (for [redacted]% reliability) = 0		Pass
		Requirement	Results (mL)	
Dose Accuracy (Needle BD Ultra-Fine [redacted])	n = 60 pens (MYL-1501D cartridge) (Commercial pen configuration - [redacted])	[redacted]		Pass
				Pass

* Standard deviation reported to 3 decimal places for information

Table 3.2.P.2.4/ 13: Dose Accuracy in Standard In-Use Conditions (Needle [redacted])

DRS Requirement		The pen must maintain volumetric accuracy as per ISO 11608-1:2014 under the operating conditions 23°C ± 5°C/50% ± 25% RH		Met requirements
Mechanical Function	Sample Size n = 60 pens	Functionality: Number of mechanical failures (for [redacted]% reliability) = 0		Pass
		Requirement	Results (mL)	
Dose Accuracy (Needle [redacted])	n = 60 pens (MYL-1501D cartridge) (Commercial pen configuration - [redacted])	[redacted]		Pass
				Pass

* Standard deviation reported to 3 decimal places for information

Table 3.2.P.2.4/ 14: Dose Accuracy in Standard In-Use Conditions (Needle [redacted])

DRS Requirement		The pen must maintain volumetric accuracy as per ISO 11608-1:2014 under the operating conditions 23°C ± 5°C/50% ± 25% RH		Met requirements
Mechanical Function	Sample Size n = 60 pens	Functionality: Number of mechanical failures (for [redacted]% reliability) = 0		Pass
		Requirement	Results (mL)	
Dose Accuracy [redacted]	n = 60 pens (MYL-1501D cartridge) (Commercial pen configuration - [redacted])	[redacted]		Pass
				Pass

* Standard deviation reported to 3 decimal places for information

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Table 3.2.P.2.4/ 6: External Component Suitability

Input Design Requirement	Device Requirement Specification	Rationale	Verification Type (Configuration)	Reliability	Met Requirement
Cartridge compatibility	Must be compatible with Biocon insulin glargine 3 mL cartridge	(b) (4)	Tolerance analysis (Commercial pen configuration)	(b) (4)	Yes
Needle thread pitch (on cartridge holder)	(b) (4)		Tolerance analysis (Commercial pen configuration)		Yes
Needle attachment	Needle attachment possible (b) (4) (b) (4)		Test protocol n = 60 (Commercial pen configuration)		Yes

Table 3.2.P.2.4/ 7: Needle Detachment Torque (BD Ultra-Fine (b) (4))

Test Requirement	Sample Size	Needle detachment torque (b) (4) (b) (4)		Met requirement
Needle detachment torque: BD Ultra-Fine (b) (4)	n = 60 needles (Commercial pen configuration)	Number of mechanical failures (for (b) (4)% reliability) = 0		Yes
		Requirement	Results (Nm)	
		(b) (4)		Yes

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Table 3.2.P.2.4/ 8: Needle Detachment Torque [redacted]

Test Requirement	Sample Size	Needle detachment torque [redacted]	Met requirement
Needle detachment torque: [redacted]	n = 60 needles (Commercial pen configuration)	Number of mechanical failures (for [redacted]% reliability) = 0	Yes
		Requirement: Results (Nm)	
		[redacted]	Yes

Table 3.2.P.2.4/ 9: Needle Detachment Torque [redacted]

Test Requirement	Sample Size	Needle detachment torque [redacted]	Met requirement
Needle detachment torque: [redacted]	n = 60 needles (Commercial pen configuration)	Number of mechanical failures (for [redacted]% reliability) = 0	Yes
		Requirement: Results (Nm)	
		[redacted]	Yes

Reviewer Comment: *The above data show that the four commercial needles tested (BD Ultra-Fine™ [redacted] passed ISO 11608-2:2012 requirement for general fit (as assessed by dose accuracy at minimum and maximum doses per ISO 11608-1:2014 at standard atmosphere) and attachment and removal torque.*

The following are **user-related forces testing**. All testing passed the functionality requirement.

Pen Cap Attachment Force

Table 3.2.P.2.4/ 25: Pen Cap Attachment Force

DRS Requirement		Pen Cap Attachment Force			Met requirements
Pen cap attachment force	Sample Size n = 30 pens (Commercial pen configuration - [redacted]	Number of failures (for [redacted]% reliability) = 0			Yes
		Requirement	Results (N)	Pen Cap Attachment Force	
		[redacted]			Yes

Pen Cap Detachment Force

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Table 3.2.P.2.4/ 26: Pen Cap Detachment Force

DRS Requirement		Pen Cap Detachment Force			Met requirements
Pen cap detachment force	Sample Size n = 30 pens (Commercial pen configuration - (b) (4)	Number of failures (for (b) (4)% reliability) = 0			Yes
		Requirement	Results (N)	Pen Cap Detachment Force	
		(b) (4)			Yes

Dose Selection Torque (Dose Increase and Dose Decrease)

Table 3.2.P.2.4/ 27: Dose Selection Torque (Dose Increase and Dose Decrease)

DRS Requirement		Dose selection torque (dose increase and dose decrease)				Met requirements
Dose selection torque (dose increase and dose decrease)	Sample Size n = 30 pens (each) (Commercial pen configuration)	Number of failures (for (b) (4)% reliability) = 0				Yes
		Requirement	Results (ozf.in)	Dose increase	Dose decrease	
		(b) (4)				Yes

Dose Selection Override Torque (at 0 Volume and at Last Dose)

Table 3.2.P.2.4/ 28: Dose Selection Override Torque (at 0 Volume and at Last Dose)

DRS Requirement		Dose selection torque (at 0 volume and at last dose)				Met requirements
Dose selection override torque (at 0 volume and at last dose)	Sample Size n = 30 pens (Commercial pen configuration)	Number of failures (for (b) (4)% reliability) = 0				Yes
		Requirement	Results (ozf.in)	at 0 volume	at last dose	
		(b) (4)				Yes

Dose Selection Override Torque (at Maximum Selectable Volume)

Table 3.2.P.2.4/ 29: Dose Selection Override Torque (at Maximum Selectable Volume)

DRS Requirement		Dose selection torque (at max volume)			Met requirements
Dose selection override torque (at max volume)	Sample Size n = 30 pens (Commercial pen configuration)	Number of failures (for (b) (4)% reliability) = 0			Yes
		Requirement	Results (ozf.in)	at max volume	
		(b) (4)			Yes

Clip Stiffness (when Lifting)

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Table 3.2.P.2.4/ 30: Clip Stiffness (when Lifting)

DRS Requirement		Clip stiffness (when lifting)		Met requirements
Clip stiffness (when lifting)	Sample Size n = 30 pens (Commercial pen configuration - (b) (4)	Number of failures (for (b) (4) % reliability) = 0		Yes
		Requirement	Results (N/mm)	
			(b) (4)	Yes

Injection Force (without Cartridge and Needle)

Table 3.2.P.2.4/ 31: Injection Force (without Cartridge and Needle)

DRS Requirement		Injection force (without cartridge and needle)		Met requirements
Injection force (without cartridge and needle)	Sample Size n = 30 pens (Commercial pen configuration – (b) (4) (b) (4)	Number of failures (for (b) (4) % reliability) = 0		Yes
		Requirement	Results (N)	
			(b) (4)	Yes

An IR was sent on 01/10/2018:

You provided design verification for Injection Force (without Cartridge and Needle) and mentioned that Injection Force (with Cartridge and Needle) are tested in the stability protocol. Please provide verification and validation for Injection Force (with Cartridge and Needle).

The Sponsor responded on 02/28/2018 and provided the injection force (with cartridge and needle) data generated at the initial timepoint and after storage of the MYL-1501D PFP at 5°C, 25°C and 40°C for 18 months. This data demonstrates that the force required to push down on the button (and dose setting knob) to make an injection (into air) is such that the user can administer the dose without having to use excessive force.

Device Requirement		Injection Force (with Cartridge and Needle)						Met Requirements
Injection Force (with Cartridge and Needle)	Sample Size n = 30 PFPs[6]	Number of failures (for (b) (4) % reliability) = 0						Yes
		Requirement	Results (N)	DVT (Initial T=0)	Stored at 5°C (18 months)	Stored at 25°C (18 months)	Stored at 40°C (18 months)	
		Injection force average (with cartridge and needle) ≤ average sustaining force of cartridge and needle at the same flow rate	Mean	(b) (4)				Yes
			Range					

[6] - Water filled cartridge; commercial pen configuration – (b) (4) injected into air

***Reviewer Comment**: Water was used in this testing, instead of the final drug product. As insulin glargine has similar density (b) (4) at room temperature) with water (0.9975 g/mL at room temperature), it's acceptable to use water in this testing.*

Cartridge Holder Removal Force

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Table 3.2.P.2.4/ 33: Cartridge Holder Removal Force – Axial Load

Test Requirement	Sample Size	Cartridge Holder Removal Force – Axial Load			Met Requirements
		Number of failures (for (b) (4)% reliability) = 0			
		Requirement	Results (N)		
Cartridge holder removal force – axial load	n = 30 pens (Water filled Cartridge) (Commercial pen configuration - (b) (4)	(b) (4)	Average	(b) (4)	Yes
			Range		
			SD		

Table 3.2.P.2.4/ 34: Cartridge Holder Removal Force – Side Load

Test Requirement	Sample Size	Cartridge Holder Removal Force – Side Load		Met Requirements
		Number of failures (for (b) (4)% reliability) = 0		
		Requirement	Results (N)	
Cartridge holder removal force – side load	n = 30 pens (Water filled cartridge) (Commercial pen configuration - (b) (4)	(b) (4)		Yes

Additional testing

The following physical attributes further demonstrate that the MYL-1501D PFP meets specific requirements of ISO 11608–1:2014 and ISO 11608-5:2012 – Needle-based Injection Systems for Medical Use – Requirements and Test Methods – Part 5: Automated Functions, as well as those attributes specific to the MYL-1501D PFP required in the DRS.

Table 3.2.P.2.4/ 32: Design Requirements of the MYL-1501D PFP Verified by Design Verification Tests

Design Requirement	Device Requirement Specification	Rationale	Verification Type	Sample Number	Reliability	Meets Criteria
Dose selection near end of use	The system does not allow a larger dose to be pre-set than is left in the cartridge	Compliance to ISO 11608-1:2014, General Requirements Part j.1	Design rationale	n/a	n/a	Yes
Product contact with device	There shall be no contact between the drug and the device with the exception of during drug delivery through the needle	ISO 11608-5:2012 4.1(d)	Design rationale	n/a	n/a	Yes
System with pen cap does not roll on a surface of ≥ (b) (4) degrees incline	Will not roll on a surface of ≥ (b) (4) degrees incline	The injector must include (b) (4)	Verification Test (Commercial pen configuration - (b) (4)	n = 60	(b) (4)	Yes
Ready for injection indicator: visual	Dose setting in dose window	Compliance to ISO 11608-1:2014, General Requirements Part f	Verification Test (Commercial pen configuration)	n = 120	(b) (4)	Yes

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Design Requirement	Device Requirement Specification	Rationale	Verification Type	Sample Number	Reliability	Meets Criteria
Ready for injection indicator: visual	DSK position visible	Compliance to ISO 11608-1:2014, General Requirements Part f	Verification Test (Commercial pen configuration	n = 120	(b) (4)	Yes
Start of injection indicator: visual and tactile	DSK movement starts	Compliance to ISO 11608-1:2014, General Requirements Part g	Verification Test (Commercial pen configuration)	n = 120		Yes
Start of Injection indicator: audible	Clicking starts	Compliance to ISO 11608-1:2014, General Requirements Part g	Verification Test (Commercial pen configuration)	n = 120		Yes
End of injection indicator: visual and tactile	DSK movement stops	Compliance to ISO 11608-1:2014, General Requirements Part h	Verification Test (Commercial pen configuration)	n = 120		Yes
End of injection indicator: visual	DSK markings at 0	Compliance to ISO 11608-1:2014, General Requirements Part h	Verification Test (Commercial pen configuration)	n = 120		Yes
End of injection indicator: audible	Clicking stops	Compliance to ISO 11608-1:2014, General Requirements Part h	Verification Test (Commercial pen configuration)	n = 60		Yes

Design Requirement	Device Requirement Specification	Rationale	Verification Type	Sample Number	Reliability	Meets Criteria
End of last dose injection indicator: visual and tactile	DSK increase movement stops	Compliance to ISO 11608-1:2014, General Requirements Part h	Verification Test (Commercial pen configuration)	n = 60	(b) (4)	Yes
Ready for injection and end of injection indicators different: visual	Dose setting in dose window changes	Compliance to ISO 11608-1:2014, General Requirements Part h	Verification Test (Commercial pen configuration)	n = 120		Yes
Ready for injection and end of injection indicators different: visual	DSK position changes	Compliance to ISO 11608-1:2014, General Requirements Part f	Verification Test (Commercial pen configuration)	n = 120		Yes
Remaining drug indicator: visual	Cartridge holder window enables indication of remaining doses	Compliance to ISO 11608-1:2014, General Requirements Part a	Verification Test (Commercial pen configuration)	n = 120		Yes
Dose selection increment indicator: visual	DSK marking present	Compliance to ISO 11608-1:2014, General Requirements Part e	Verification Test (Commercial pen configuration)	n = 120		Yes
Dose increment indicator: audible and tactile	Clicking during increment/decrement	Compliance to ISO 11608-1:2014, General Requirements Part e	Verification Test (Commercial pen configuration)	n = 60		Yes

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Design Requirement	Device Requirement Specification	Rationale	Verification Type	Sample Number	Reliability	Meets Criteria
Marking present on DSK and cartridge holder	No missing or partial markings	As specified in ISO 11608-1:2014, Section 11.1	Verification Test (Commercial pen configuration)	n = 60	(b) (4)	Yes
Marking legibility	No marred, blurred or smudged markings	As specified in ISO 11608-1:2014, Section 11.1	Verification Test (Commercial pen configuration)	n = 60		Yes
Marking permanency	Markings do not rub off	Compliance to ISO 11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration)	n = 60		Yes
Dose reset	Doses can be reset to 0	Compliance to ISO 11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration)	n = 120		Yes
Dose selection marking alignment	DSK: pointer misalignment accuracy (at rest): ± (b) (4) % of distance between scale intervals	Compliance to ISO 11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration)	n = 30		Yes
Pen cap attachment indicator	Audible feedback when pen cap is fully attached	Ensures user awareness of correct fitment of pen cap. The pen cap provides protection for the rubber seal prior to and during use	Verification Test (Commercial pen configuration)	n = 60		Yes
Font style	Sans serif	Compliance to ISO 11608-1:2014, Section 13.2.1	Design rationale	n/a	n/a	Yes

Design Requirement	Device Requirement Specification	Rationale	Verification Type	Sample Number	Reliability	Meets Criteria
DSK markings font character height	(b) (4)	Compliance to ISO 11608-1:2014, Section 13.2.1	Verification Test (Commercial pen configuration)	n = 30	(b) (4)	Yes
DSK markings font character height for minor increment		Compliance to ISO 11608-1:2014, Section 13.2.1	Design rationale	n/a	n/a	Yes
DSK markings font character stroke width to character height ratio		Compliance to ISO 11608-1:2014, Section 13.2.1	Verification Test (Commercial pen configuration)	n = 30	(b) (4)	Yes
DSK markings font character width to character height ratio		Compliance to ISO 11608-1:2014, Section 13.2.1	Verification Test (Commercial pen configuration)	n = 30		Yes
DSK font orientation	Font Orientation (during injection) is perpendicular to the skin	Compliance to ISO 11608-1:2014, General Requirements Part d	Design rationale	n/a	n/a	Yes
Dose window alignment	Dose window shows entire dose value	Compliance to ISO 11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration)	n = 60	(b) (4)	Yes
Marking contrast (all markings)	Marking contrast sufficient for legibility	Compliance to ISO 11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration - Mylan PMS 306C blue)	n = 60		Yes

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Design Requirement	Device Requirement Specification	Rationale	Verification Type	Sample Number	Reliability	Meets Criteria
Font spacing between charters to character width ratio	(b) (4)	Compliance to ISO 11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration)	n = 30	(b) (4)	Yes
Font spacing between lines to character height ratio		Compliance to ISO 11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration)	n = 30		Yes
Dose window width		Compliance to ISO11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration)	n = 30		Yes
Dose pointer marking	A pointer marking system for the dose is present on the body	Compliance to ISO 11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration)	n = 60		Yes
Dose pointer protrusion from surface of system	The dose pointer protrudes from the face of the PFP	Compliance to ISO 11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration)	n = 60		Yes
Dose pointer protrusion into window	The dose pointer protrudes into the dose window	Compliance to ISO 11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration)	n = 60		Yes

Design Requirement	Device Requirement Specification	Rationale	Verification Type	Sample Number	Reliability	Meets Criteria
Drug inspection window visibility: radial degrees	(b) (4)	Compliance to ISO 11608-1:2014, General Requirements Part a	Verification Test (Commercial pen configuration)	n = 60	(b) (4)	Yes

Biocompatibility

Assessment of the fluid path (the cartridge and the needle) is the scope of the CMC discipline and is not covered in this review memo as those are part of the container closure system.

Biocompatibility of the user contacts of the pen injector is provided in the submission and follows ISO 10993.

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Table 3.2.P.2.4/ 51: Biocompatibility Tests Conducted on the Skin Contacting Components of the MYL-1501D PFP Components

Component Description	Material	Color	Tests conducted	Result
Pen Cap	(b) (4)	(b) (4)	*In vitro*: Cell Cytotoxicity Elution, 48 hour single point	Pass Score = 0
			In vivo: Primary Dermal Irritation (saline, polyethylene glycol [PEG])	Negligible irritant (saline, PEG)
			Murine Local Lymph Node Assay (saline, PEG)	Non-sensitizer (saline, PEG)
Cartridge Holder		Clear (with black ink printing)	*In vitro*: Cell Cytotoxicity Elution, 48 Hour Single point	Pass Score = 0
			In vivo: Primary Dermal Irritation (saline, PEG)	Negligible irritant (saline, PEG)
			Murine Local Lymph Node Assay (saline, PEG)	Non-sensitizer (saline, PEG)
Body		(b) (4)	*In vitro*: Cell Cytotoxicity Elution, 48 hour single point	Pass Score = 0
			In vivo: Primary Dermal Irritation (saline, PEG)	Negligible irritant (saline, PEG)
			Murine Local Lymph Node Assay (saline, PEG)	Non-sensitizer (saline, PEG)
Dose Setting Knob (DSK)		White (with black ink printing)	*In vitro*: Cell Cytotoxicity Elution, 48 hour single point	Pass Score = 0
			In vivo: Primary Dermal Irritation (saline, PEG)	Negligible irritant (saline, PEG)
			murine local Lymph node Assay (saline, PEG)	Non-sensitizer (saline, PEG)
Button		Purple	*In vitro*: Cell Cytotoxicity Elution, 48 hour single point	Pass Score = 0
			In vivo: Primary Dermal Irritation (saline, PEG)	Negligible irritant (saline, PEG)
			Murine Local Lymph Node Assay (saline, PEG)	Non-sensitizer (saline, PEG)

saline: 0.9% sodium chloride (NaCl)

Reviewer Comment*: The user contact of the pen injector is categorized as surface contact with intact skin. The provided biocompatibility information to evaluate cytotoxicity, sensitization and irritation endpoints of the user contacts is appropriate and acceptable for the intended use of the user contacting of the combination product.*

Stability

Based on available long term stability data from DP, a shelf-life of 24 months is proposed for the DP when stored at 5°C±3°C.

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Table 3.2.P.2.4/ 46: Device Component Shelf Life and Use Life Storage Conditions

Type	Maximum Storage Period	Conditions
Component storage in warehouse prior to assembly	(b) (4)	
MYL-1501D PFP storage prior to first use		
MYL-1501D PFP in use storage		

Table 3.2.P.2.4/ 47: MYL-1501D PFP Stability Study

Type	Target Real Time		Accelerated Aging Equivalent	
	Time (Months)	At Temperature (°C)	Time (Months)	At Temperature (°C)
Component storage	36	5	3.2	40
	36	25	12.8	40
	36	30	18	40
PFP storage (unused)	60	5	5.3	40

Table 3.2.P.2.4/ 48: Functionality and Performance Tests Conducted During Devic Stability Studies

Design Input Requirement	Sample Number (n)	Reliability	Meets Criteria
Hold time necessary after end of injection	60	(b) (4)	Yes
Volumetric accuracy as per ISO 11608-1:2014 under the operating conditions 23°C ± 5°C/50% ± 25% RH	60		Yes
Volumetric accuracy as per ISO 11608-1:2014 following freefall testing	30		Yes
Volumetric accuracy as per ISO 11608-1:2014 following vibration testing	20		Yes
Volume expelled during dose selection is minimal	30		Yes
Cartridge holder removal force – Axial load	30		Yes
Cartridge holder removal force – Side load	30		Yes
Pen cap attachment and detachment force	30		Yes
Dose selection torque (dose increase and dose decrease)	30		Yes
Dose selection override torque (at 0 volume, at last dose and at maximum selectable volume)	30		Yes
Injection force (with cartridge and needle)	30		Yes
Dose reset	120		Yes
Dose selection play (prior to increment change)	30		Yes
Dose selection direction change hysteresis	30		Yes

***Reviewer Comment**: The stability testing includes the essential performance requirements of the pen injector. The provided stability information is adequate for device performance.*

Shipping Verification

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Shipping verification was performed according to ASTM D4169-16 DC13. Air (intercity) and motor freight (local, single package up to 150lb (61.8kg). Following distribution testing MYL-1501D PFPs were visually inspected and no failure were observed at any level of the consignment following shipper carton or device level inspection.

Table 3.2.P.2.4/ 42: ASTM D4169-16 DC13 Test Sequence

<table>
<tr><th>Sequence No.</th><th>Schedule</th><th>Description</th></tr>
<tr><td>1</td><td>Schedule A
Handling</td><td>First sequence of drops in various orientations from a drop height of 610 mm as per ASTM D5276-98(2009) – Standard Test Method for Drop Test of Loaded Containers by Free Fall</td></tr>
<tr><td>2</td><td>Schedule C
Vehicle stacking</td><td>Momentary compression test on the basis of mixed commodity shipping in a small package delivery environment, as per ASTM D642-15 – Standard Test Method for Determining Compressive Resistance of Shipping containers, Components, and Unit Loads</td></tr>
<tr><td>3</td><td>Schedule F
Loose-vibration load</td><td>Rotary vibration for a total of 60 minutes, with 50% of the time on the base, and the remaining time split across all the other faces, as per ASTM D999-08(2015) – Standard Test Method for Vibration Testing of Shipping Containers</td></tr>
<tr><td>4</td><td>Schedule I
Low pressure</td><td>Hold under a partial vacuum for 60 minutes equivalent to an altitude of 42 067 m (14 000 ft) as per ASTM D6653 / D6653M-13 – Standard Test Methods for Determining the Effects of High Altitude on Packaging Systems by Vacuum Method</td></tr>
<tr><td>5</td><td>Schedule E
Vehicle vibration</td><td>Random Truck Vibration between 1 and 200 Hz for the 60 minutes profile shown below spread equally across all faces, as per ASTM D4728-06(2012) – Standard Test Method for Random Vibration Testing of Shipping Containers
<table>
<tr><th>Vibration intensity</th><th>Overall g_{RMS}</th><th>Time at test intensity</th></tr>
<tr><td>Low</td><td>0.40</td><td>40 minutes</td></tr>
<tr><td>Medium</td><td>0.54</td><td>15 minutes</td></tr>
<tr><td>High</td><td>0.70</td><td>5 minutes</td></tr>
</table>
Random air vibration between 32 and 300 Hz for 120 minutes spread equally across all faces with an overall g_{RMS} of 1.49 as per ASTM D4728-06(2012)</td></tr>
<tr><td>6</td><td>Schedule J
Concentrated impact</td><td>5.4 J impact to each face with a cylindrical mass from 800 mm as per ASTM D6344-04(2009) – Standard Test Method for Concentrated Impacts to Transport Packages</td></tr>
<tr><td>7</td><td>Schedule A
Handling</td><td>Second sequence of drops in various orientations from a drop height of 610 mm as per ASTM D5276-98(2009)</td></tr>
</table>

7. RISK ANALYSIS

7.1. Risk Analysis Attributes

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	x		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	x		

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Mitigations are adequate to reduce risk to health	x		
Version history demonstrates risk management throughout design / development activities	x		

7.2. Summary of Risk Analysis

Risk management for the MYL-1501D combination product incorporates risk management relating to: design and molded component manufacture from (b) (4) as Design Authority and component supplier, final assembly from Biocon as manufacturer of the MYL-1501D combination product, and design and user risk management conducted by Mylan which considered the (b) (4) and Biocon risk management programs.

An IR was sent on 01/10/2018:

You only provided a user-related risk analysis per ISO 14971:2007. Risks should be categorized from a user and functional perspective (by outcome – over dose, etc. or by error type, user, device etc.). Please provide a complete risk analysis table which outlines each risk. In addition, the analysis should include traceability to associated risk mitigation validation/ verification.

The Sponsor responded on 02/28/2018 and provided a risk analysis table. In addition to the User-Related Risk Assessment (URRA) provided already, the Sponsor conducted a Preliminary Hazard Analysis (PHA) to confirm the suitability of the design of the delivery system as an element of the combination product. The Sponsor states that the output of the device risk management program confirmed the suitability of the PFP, with no new or increased risks when compared to the RLD, for its intended use, by intended users, in the intended use environment. Risk control measures were considered, where possible, through implementation in the device design intent or as subsequent risk mitigation.
Portion of the risk analysis is shown below:

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Table 2: Preliminary Hazard Analysis

Potential System Failure State or User Misuse Related to Design Feature (Leading to Hazardous Situation)	Outcome (Potential Harm Arising from System Failure)	Severity of Harm	Associated User Requirement(s)	Design Feature or PFP Component Contributing to System Failure	Is there a Misuse Scenario Contributing to System Failure? If so is it Foreseeable (F) or Deliberate (Del)?	Risk Control Measures: Inherent in Design (D) or Addressed Through Risk Mitigation (M).
Pen cap cannot be removed. (Missed dose – user aware)	Inconvenience	S1	The user shall be able to remove the cap without excessive force.	Pen cap	No	(D) Pen cap is designed to have sufficient retention features while maintaining usability.
Primary container cannot be inspected prior to injection. (Injection of foreign particulates – drug product)	Granuloma / pain / irritation	S2	The Pre-Filled Pen (PFP) shall allow the user to inspect the primary container contents prior to injection.	Cartridge holder	No	(D) Cartridge holder has windows to provide visibility of the cartridge contents.
Incompatible needle attached. (Multiple missed doses – user unaware)	Hyperglycemia	S4	The PFP shall be compatible with the following needles to allow for subcutaneous injection: BD Ultra-Fine™ (b) (4) BD Ultra-Fine™ (b) (4) (b) (4)	PFP interaction with needle	(F) User unintentionally selects an incompatible needle	(D) The Type A thread form on the cartridge holder is designed to be compatible with multiple needle options for subcutaneous injections in accordance with ISO 11608-1:2014 – Needle-based Injection Systems for Medical Use – Requirements and Test Methods – Part 1: Needle-based Injections Systems (D) Design of the Instructions For Use (IFU) ensure that the user is provided with clear information on appropriate needle choice.
Incompatible needle attached leading to multiple minor underdose. (Disease control incomplete but recoverable – inconvenience)	Hyperglycemia	S1			(F) User unintentionally selects an incompatible needle	
Incompatible needle attached. (Missed dose – user aware)	Inconvenience	S1			(Del) User intentionally selects an incompatible needle	
Needle cannot be attached to PFP. (Missed dose – user aware)	Inconvenience	S1			(Del) User intentionally selects an incompatible needle	
Needle cannot be attached to	Inconvenience	S1	The user must be able to	Cartridge holder	No – this is a	(D) The Type A thread form on the

Reviewer Comment: *The MYL-1501D device risks have been managed to the point where it is appropriate for moving forward into commercial supply from the device point of view.*

8. LABELING

Draft pen label

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Reference ID: 4240177
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9. DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

The following release specifications are included for the device constituent within eCTD Module 3.2.P.5:

8	Extractable volume	Based on Ph. Eur. method # 2.9.17 and USP <1>	Between (b) (4)
15	Friction force test		
	Initiating force	ISO 11608-3:2012	Not more than (b) (4)
	Sustained force		Not more than (b) (4)
16	Dimensions		
	G – Length of glass barrel assembled with crimp cap	ISO 11608-3:2012	(b) (4)
	I – Length between gauging diameter on top of cartridge to rear end of plunger (delivery position)		(b) (4)
	(G-I) – Start position of the plunger		(b) (4)

Table 3.2.P.5.1/ 2: Specifications for MYL-1501D Drug Product (Pre-filled pen)

Sr. No.	Parameter	Acceptance Criteria	Test Method Reference
1.	Description	Pre-filled pen containing insulin glargine, with purple injection button	In-house
2.	Functional tests		
	a. Zero position	The zero position in the window should be pointing to yellow pointer	In-house
	b. Audible click	Audible click should be heard on dialing each unit	In-house
	c. Dose accuracy	Must comply with ISO 11608-1:2014 (b) (4)	ISO 11608-1: 2014
3.	Cosmetic test: Printing check on DSK	Missing and not able to read numbers on DSK should not be present	In-house

***Reviewer Comment**: The lot release specifications include the device essential performance requirement. The proposed lot release for the drug product is appropriate and acceptable from device point of view.*

10.INTERACTIVE REVIEW

Agency Information Request (sent on 01/10/2018)

Reference ID: 4240177
Reference ID: 4624497

- *You only provided a user-related risk analysis per ISO 14971:2007. Risks should be categorized from a user and functional perspective (by outcome – over dose, etc. or by error type, user, device etc.). Please provide a complete risk analysis which characterizes and evaluates the risks of the pen injector to the user or patient both during normal use, reasonable foreseeable mis-use, and potential system failure states. The risk analysis should include any risk control/mitigations as well as the residual risk remaining after any risk controls/mitigations are implemented.*

- *You indicated that there are design changes between the clinical and commercial pen configurations. Please provide a comparison of the verification and validation between the to be marketed presentation and the clinical studied pen injector, and justify how the design changes will not impact the essential performance specifications through a risk analysis.*

- *You provided design verification for Injection Force (without Cartridge and Needle) and mentioned that Injection Force (with Cartridge and Needle) are tested in the stability protocol. Please provide verification and validation for Injection Force (with Cartridge and Needle).*

The Sponsor responded on 02/28/2018. All responses are incorporated in the review memo and found adequate.

11.RECOMMENDATION

CDRH recommends approval based on review of the device constituent of the combination product. Review of this information found that there are sufficient verification activities for the safety and functionality of the device constituent part of the combination product to recommend approval.

Reference ID: 4240177
Reference ID: 4624497

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/s/

RONG GUO
03/27/2018

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 22, 2018

TO: Badrul Chowdhury, M.D., Ph.D.,
Director
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Office of Drug Evaluation II
Office of New Drugs

Mary Thanh Hai, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Office of New Drugs

FROM: Gajendiran Mahadevan, Ph.D.
Pharmacologist
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

And

Ruben Ayala, Pharm.D.
Lead Pharmacologist
DNDBE/OSIS

THROUGH: Charles Bonapace, Pharm.D.
Director
DNDBE/OSIS

SUBJECT: Amended EIR review covering the surveillance inspection of (b) (4) (b) (4)

Note: This document amends the previous OSIS EIR review submitted to DARRTS by Dr. Gajendiran Mahadevan, Ph.D. on February 12, 2018.

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) audited the analytical portion of studies Non-Responsive , and MYL-1501D-1001 (NDA 210605) conducted at (b) (4) (b) (4).

Form FDA 483 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI).

Non-Responsive

Non-Responsive

The inspectional findings mentioned above were isolated in nature and do not impact the reliability of audited study MYL-1501D-1001 (NDA 210605). The stability assessments in this study included freshly-prepared comparators. Therefore, the data from study MYL-1501D-1001 and other studies of similar analytical methodology should be accepted for further review.

Inspected Studies:

Non-Responsive

NDA 210605

Study Number: MYL-1501D-1001
Study Title: "A glucose clamp trial investigating the Biosimilarity of two formulations of Mylan's

insulin glargine with US Lantus reference product."

Dates of Bioanalysis: January 19-March 18, 2017

Analytical Site: [redacted] (b) (4)

OSIS Pharmacologists Gajendiran Mahadevan, Ph.D. and Ruben Ayala, Pharm.D. audited the analytical portion of the above studies at [redacted] (b) (4) [redacted] (b) (4).

We thoroughly audited the study records, facility, laboratory equipment, method validation, sample analysis, and interviewed the firm's management and staff. As a part of surveillance approach, we selected and audited several key components across multiple studies that best represent [redacted] (b) (4) bioanalytical operations.

At the conclusion of the inspection, we issued Form FDA 483 to [redacted] (b) (4) (**Attachment-1**). The firm responded to Form FDA 483 on December 21, 2017 (**Attachment-2**). The firm also responded to DPARP's Information Request (IR) letter on March 9, 2018 (**Attachment-3**). The Form FDA 483 observations, the firm's response to Form FDA 483, the firm's response to DPARP's IR letter, and our evaluation follow.

[redacted] (b) (4)

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Non-Responsive

We also recommend that the data from study MYL-1501D-1001 (NDA 210605) and other studies of similar analytical methodology be accepted for further review (**Attachment-7**). The stability assessments in this study included freshly-prepared comparators.

Gajendiran Mahadevan, Ph.D.
Pharmacologist

Ruben Ayala, Pharm.D.
Lead Pharmacologist

Final Classification:

Analytical Site:
VAI: (b) (4)
FEI#: (b) (4)

cc:
OTS/OSIS/Kassim/Choe/Taylor/Haidar/CDER-OSIS-BEQ@fda.hhs.gov
OTS/OSIS/DGDBE/Cho/Kadavil/Skelly/Choi/Au
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Mahadevan

CDER/OND/DPARP/Chowdhury
CDER/OND/DMEP/Thanh Hai

Draft: RCA 3/20/2018; GM 3/20/2018; 3/22/2018
Edits: CB 3/22/2018

ECMS: (b) (4) /NDA 210606 Non-Responsive

OSIS File #: BE 7633 (NDA 210605); Non-Responsive
FACTS: 11778936 (NDA 210605); Non-Responsive

Reference ID: 4624497

Attachment-7

Studies in support of Pending Applications

Application #	Study #	Study Type (in vitro)	Drug Name	Dates of Analytical Conduct
NDA 210605	MYL-1501D-1001	In vivo	Insulin glargine	January 19-March 18, 2017

Non-Responsive

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/s/

GAJENDIRAN MAHADEVAN
03/22/2018

RUBEN C AYALA
03/22/2018

CHARLES R BONAPACE
03/22/2018

Clinical Inspection Summary

Date	3/14/2018
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader Susan D. Thompson, M.D. for Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Mitra Rauschecker, M.D., Clinical Reviewer Lisa B. Yanoff, M.D., Clinical Team Leader Michael G. White, Ph.D, Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA/BLA #	NDA 210605
Applicant	Mylan Pharmaceuticals, Inc.
Drug	insulin glargine injection (MYL-1501D)
NME (Yes/No)	No
Therapeutic Classification	Antidiabetic
Proposed Indication(s)	To improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus
Consultation Request Date	9/6/2017
Summary Goal Date	3/19/2018
Action Goal Date	5/17/2018
PDUFA Date	5/17/2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of three domestic sites and one foreign clinical site (representing seven total sites) as well as the sponsor. The inspection of the sponsor and the clinical investigators revealed no regulatory violations.

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

The classification for Drs. Klugh, Lane, Shaw, and Tildesley is No Action Indicated (NAI). Data from these sites is considered reliable based on the available information. The full Establishment Inspection Reports for all sites were submitted for review.

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The classification for the sponsor Mylan Pharmaceuticals, Inc. is NAI. Data from this sponsor are considered reliable based on the available information. The full Establishment Inspection Report was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

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

II. BACKGROUND

A new drug application (NDA) was submitted by Mylan Pharmaceuticals, Inc. for insulin glargine injection MYL-1501D, a long-acting human insulin analog proposed to be used to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. As a 505(b)(2) NDA, this application relies, in part, on FDA's finding of safety and effectiveness for Lantus® (insulin glargine [rDNA origin] injection; NDA# 021081; Sanofi-Aventis) used as the reference product to establish "a bridge" between MYL-1501D and Lantus®.

Two studies were chosen for inspection:

- **MYL-GAI-3001** An Open-label, Randomized, Multi-center, Parallel-Group Clinical Trial Comparing the Efficacy and Safety of Mylan's Insulin Glargine with Lantus® in Type 1 Diabetes Mellitus Patients.

  The study began August 18, 2014 and completed July 7, 2016. The study involved 164 study sites globally. A total of 832 patients were screened and 558 patients were randomized. Only patients who were on a stable dose of Lantus® for at least three months prior to screening were included in this study. The primary efficacy outcome was change in HbA1c from baseline to Week 24.

- **MYL-GAI-3002** An Open-label, Randomized, Multicenter, Parallel-Group Clinical Trial Comparing the Efficacy and Safety of Mylan's Insulin Glargine with Lantus® in Type 2 Diabetes Mellitus Patients

  The study began September 16, 2014 and completed December 24, 2015. The study involved 128 study sites globally. A total of 951 patients were screened and 560 patients were randomized. Patients were required to be either insulin-naïve or on a stable dose of Lantus® for three months. The primary efficacy outcome was change in HbA1c from baseline to Week 24.

A site selection tool was not provided by the Applicant. Many of the larger enrolling sites for both studies had recently been inspected for other applications with no significant findings; therefore, they were not chosen. Sites were chosen based on enrollment, involvement in both studies, inspectional history, no audit history by the sponsor, and protocol violations.

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III. RESULTS (by Site):

Name of CI/ Address	Protocol #/Site # and # of Subjects Randomized	Inspection Date	Classification
Hugh Tildesley, M.D.↘ ERS Endocrine Research Inc. Suite 410-1033, Davie Street Vancouver British Columbia Canada V6E IM7 ↘*Deceased 2016*	MYL-GAI-3001 Site 1008 11 subjects	01/29 – 02/02/2018	No Action Indicated (NAI)
Wendy Lane, M.D. Mountain Diabetes & Endocrine Center 1998 Hendersonville Rd., Bldg. 31 Asheville, North Carolina, 28803	MYL-GAI-3001 Site 11034 11 subjects MYL-GAI-3002 Site 32032 1 subject	12/12 – 12/15/2017	No Action Indicated (NAI)
Serena Ann Klugh, M.D. Palm Research Center, Inc. 3150 North Tenaya Way, Suite 415 Las Vegas, Nevada, 89128	MYL-GAI-3001 Site 11015 6 subjects MYL-GAI-3002 Site 32016 17 subjects	01/10 – 01/19/2018	No Action Indicated (NAI)
Stephanie Shaw, M.D. Texas Diabetes & Endocrinology, PA 110 Deer Ridge Drive Round Rock, TX, 78664	MYL-GAI-3001 Site 11023 8 subjects MYL-GAI-3002 Site 32029 11 subjects	12/12 – 12/18/2017	No Action Indicated (NAI)
Mylan Pharmaceuticals, Inc. 1000 Mylan Boulevard Canonsburg, PA 15317	MYL-GAI-3001 MYL-GAI-3002	02/26 – 03/01/2018	No Action Indicated (NAI)*

Key to Compliance Classifications
NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations; data unreliable.
*Pending = Preliminary classification based on information in 483 (if applicable) and preliminary communication with the field; final classification is pending letter to site.

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

1. Hugh Tildesley/ 3001 Site 1008

During the planning of the inspection, it was discovered that Dr. Tildesley had died (b) (6) (b) (6) *His research site has closed. Records from Dr. Tildesley's site were transferred* (b) (4) (b) (4) *for inspection. A Mylan representative was present to host the inspection and coordinate the retrieval of documents.*

There were 16 subjects screened and 11 subjects enrolled into the study; 10 subjects completed the study. Subject (b) (6) completed most of the study visits but chose to discontinue the study early. There were 11 subject records reviewed.

When Dr. Tildesley died on (b) (6), nine study subjects were still active at his site. There were two subinvestigators, Dr. Adam White and Dr. Monika Pawlowska. Dr. White and Dr. Pawlowska took on responsibilities for the study, remained at the site, and conducted follow-up visits until the study closed in June 2016.

The institutional review board (IRB) of record was (b) (4). The study site submitted an Unanticipated Problem Report to the IRB dated 6/17/16, informing them that Dr. Tildesley had died. The sponsor was notified on 3/15/16. The Mylan study team contacted the contract research organization (CRO), (b) (4). The CRO subsequently contacted the IRB.

There were five storage boxes of study records. All records in the storage boxes were in paper form. Only the case report forms were electronic. The files were legible, organized and available.

Dr. Tildesley's files included documentation of the qualifications of study staff as well as good clinical practice (GCP) training and protocol-specific training. Dr. Tildesley's initials or signature were on eligibility forms, laboratory reports, blood glucose print outs, adverse event forms and other medical records, documenting oversight. Source records were compared to the sponsor data line listings. There was no evidence of under-reporting of adverse events or serious adverse events. The primary/secondary efficacy endpoint data were verifiable.

During the inspection, it was found that the site often (but not always) made a printout of

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the eight-point self-monitored blood glucose levels. It appeared the site printed out these glucose levels so the site investigator could review them, make any changes to the dosages, and sign that he had reviewed them. The Mylan representative stated that the source document was not the printout from the glucose monitor but the patient diary, where the patient documented what they saw on the monitor. There were many discrepancies as the subjects were not always accurate with documenting what they saw on the glucose monitor. However, the sponsor data line listings did reflect what was placed in the diary entries.

Of note, all the sites had the same equipment (Accu-Chek meters) provided by the CRO (b) (4). The data from these glucose meters was not collected and was not stored at a central server. The sites were told to use the diary as the source. The study monitors did not cross-check the printouts versus the diaries for errors.

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.

2. Wendy Lane/ 3001 Site 11034 & 3002 Site 32032

For Study Protocol MYL-GAI-3001, there were 16 subjects screened and 11 subjects enrolled into the study; 10 subjects completed the study. One subject (b) (6) died. There were 16 subject records reviewed.

For Study Protocol MYL-GAI-3002, there were two subjects screened and one subject enrolled into the study; one subject completed the study. There were two subject records reviewed.

Dr. Lane is an employee of Mountain Diabetes and Endocrine Center, a small private endocrine clinic practice which performs human clinical studies. Dr. Lane is board certified in Internal Medicine and Endocrinology.

(b) (4) was the IRB of record.

Source documents were organized, complete, legible, and attributable. Source records were compared to the sponsor data line listings. There were no discrepancies. There was no evidence of under-reporting of adverse events or serious adverse events. The primary/secondary efficacy endpoint data were 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.

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Reference ID: 4624497

3. Serena Ann Klugh/ 3001 Site 11015 & 3002 Site 32016

For Study Protocol MYL-GAI-3001, there were eight subjects screened and six subjects enrolled into the study; six subjects completed the study. There were six subject records reviewed.

For Study Protocol MYL-GAI-3002, there were 26 subjects screened and 17 subjects enrolled into the study; 14 subjects completed the study. Two subjects discontinued (Subject (b) (6) - dropped out and Subject (b) (6) - withdrew consent). One subject was lost to follow-up (Subject (b) (6)). There were 10 subject records reviewed.

Palm Research Center (PRC) is a private research company that is part of the Palm Medical Group (PMG) that has two locations in Las Vegas, NV. Dr. Klugh is an endocrinologist and is affiliated with two local hospitals. Subjects were recruited via radio and television advertising and potential PMG patients.

(b) (4) was the IRB of record. Consent documents were in English and Spanish with appropriate translations.

The files were organized, legible and available. Source records were compared to the sponsor data line listings. There were no discrepancies. All SAEs and AEs were reported. The primary/secondary efficacy endpoint data were 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.

4. Stephanie Shaw/ 3001 Site 11023 & 3002 Site 32029

For Study Protocol MYL-GAI-3001, there were 12 subjects screened and eight subjects enrolled into the study; eight subjects completed the study. There were four subject records reviewed. No subjects went on to enroll in the 3003 study.

For Study Protocol MYL-GAI-3002, there were 12 subjects screened and eleven subjects enrolled into the study; 10 subjects completed the study (one was lost to follow-up and one terminated early). There were five subject records reviewed.

Dr. Stephanie Shaw was on leave; therefore, was not available during this inspection. The study coordinator and other staff were available for questions.

The institutional review board (IRB) for this clinical site was (b) (4).

The clinical records were legible, organized and available. Source records were compared to the sponsor data line listings and there was one discrepancy. For Subject (b) (6) a medication error (Humalog taken instead of insulin glargine) was reported as an adverse

Reference ID: 4234284
Reference ID: 4624497

event but not listed as a protocol deviation. All subjects were randomized in accordance with the randomization scheme and all hypoglycemic events were properly reported. There was no under-reporting of adverse events. The primary efficacy endpoint 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.

5. Mylan/ Sponsor

The inspection consisted of reviewing the organizational structure and responsibilities, transfer of obligations, contractual agreements, selection of sites, training, investigational product accountability, the evaluation of the adequacy of monitoring and corrective actions taken by the sponsor/monitor/CRO, deviations related to key safety and efficacy endpoints, quality assurance and audits, adverse events evaluation and reporting, 1572s and investigator agreements, the interactive voice/web response system, financial disclosures, standard operating procedures (SOPs), trial master file review, record retention, data management, escalation of issues, and clinical trial oversight.

All documents were available for inspection. There were no issues noted with the trial master file. Monitoring was properly performed and there was sufficient oversight.

It was confirmed at the sponsor inspection that the source document for glucose readings from the glucose monitor was the patient diary, where the patient documented what they saw on the monitor. As noted during the site inspections, there were many discrepancies with the glucose monitor printouts as the subjects were not always accurate with documenting what they saw on the glucose monitor. However, the sponsor data line listings did reflect what was placed in the diary entries.

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.

Data from this sponsor appear acceptable.

{See appended electronic signature page}

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

Reference ID: 4234284
Reference ID: 4624497

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

CC:

Central Doc. Rm./ NDA 210605
DMEP/Division Director/ Mary Thanh-Hai
DMEP /Deputy Director/Jim P. Smith
DMEP/Team Lead/Lisa B. Yanoff
DMEP/Clinical Reviewer/ Mitra Rauschecker
DMEP /Regulatory Project Manager/Michael G. White
OSI/DCCE/Division Director/Ni Aye Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Janice Pohlman
OSI/DCCE/GCPAB/Team Leader/Susan Thompson
OSI/DCCE/GCPAB Reviewer/Cynthia Kleppinger
OSI/DCCE/GCPAB/Program Analyst/Joseph Peacock/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

Reference ID: 4234284
Reference ID: 4624497

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/s/

CYNTHIA F KLEPPINGER
03/14/2018

JANICE K POHLMAN
03/14/2018

SUSAN D THOMPSON
03/14/2018

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 28, 2018

TO: James Smith, M.D., M.S.
Deputy Director
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II (ODEII)
Office of New Drugs (OND)

FROM: Li-Hong Yeh, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDBE, OSIS

SUBJECT: Surveillance inspection of Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany and Profil Mainz GmbH & Co. KG, Mainz, Germany.

Inspection Summary:

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of Study **MYL-1501D-1001**(**NDA 210605)** conducted at Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany and Profil Mainz GmbH & Co. KG, Mainz, Germany.

No significant deficiencies were observed and Form FDA 483 was not issued at the inspection close-out at each inspected site. The final inspection classification is No Action Indicated (NAI) for both sites.

After reviewing the inspectional findings, I found the data from the audited study (**MYL-1501D-1001**) reliable. Thus, I recommend that the data from Study **MYL-1501D-1001** and other studies of similar design (**Attachment-1**) conducted at Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany and Profil Mainz GmbH & Co. KG, Mainz, Germany be accepted for further Agency review.

Application	Study	Sponsor	Study Sites	Recommendation	Classification
NDA 210605	MYL-1501D-1001	Mylan GmbH, Zurich, Switzerland	(1) Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany (2) Profil Mainz GmbH & Co. KG, Mainz, Germany	Accept all data	**NAI** **NAI**

Inspected Study:

NDA 210605

Study Number: MYL-1501D-1001

Study Title: "A glucose clamp trial investigating the biosimilarity of two formulations of Mylan's insulin glargine with US Lantus reference product."

Dates of Study Conduct: 11/29/2016 – 03/04/2017

Clinical sites:

(1) Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany

(2) Profil Mainz GmbH & Co. KG, Mainz, Germany

ORA Investigator Matthew C. Watson (DBIMO-I) inspected Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany from 01/08/2018 - 01/12/2018. Mr. Watson inspected Profil Mainz GmbH & Co. KG, Mainz, Germany from 01/15/2018 – 01/16/2018.

The inspection included a thorough examination of study records (paper-based), subject records, informed consent process, protocol compliance, institutional review board approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and case report forms.

At the conclusion of the inspection, investigator Watson did not observe any objectionable findings at the inspected sites and did not issue Form FDA 483 to the sites.

Conclusion:

After reviewing the inspectional findings, I found the data from the audited study reliable. Thus, I recommend that the data from Study **MYL-1501D-1001** and other studies of similar design (**Attachment-1**) conducted at Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany and Profil Mainz GmbH & Co. KG, Mainz, Germany be accepted for further Agency review.

Li-Hong Yeh, Ph.D.
Chemical Engineer
DNDBE/OSIS

Final Classification:
Clinical sites
NAI- Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany
(FEI 3003421648)

NAI- Profil Mainz GmbH & Co. KG, Mainz, Germany
(FEI 3013981932)

CC:
OTS/OSIS/Kassim/Choe/Fenty-Stewart/Nkah/Miller/Johnson
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Yeh
OTS/OSIS/DGDBE/Cho/Kadavil/Skelly/Choi/Au
ORA/DBIMO-I/Watson

Draft: PY 2/26/2018
Edits: RCA 2/28/2018 AD 02/28/2018

ECMS:

http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f8815fb6c5
(Profil in Neuss, Germany)
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f8815fb51c
(Profil in Mainz, Germany)

BE File #: 7633 (NDA 210605)
FACTS: 11778929

Attachment 1
List of additional Studies

Application # (BE #)	Study #	Drug Name(s)	Dates of conduct
NA	HMR1964-BEQ13941	Insulin glulisine	NA
NA	MYL-1601D-1001	Insulin Aspart	NA
NA	MYL-1501D-1004	MYL_1501D	NA
NA	PDY15084	SAR341402 Mix 70/30	NA

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/s/

LI-HONG P YEH
02/28/2018

RUBEN C AYALA
02/28/2018

ARINDAM DASGUPTA
03/01/2018

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 12, 2018

TO: Badrul Chowdhury, M.D., Ph.D.,
Director
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Office of Drug Evaluation II
Office of New Drugs

Mary Thanh Hai, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Office of New Drugs

FROM: Gajendiran Mahadevan, Ph.D.
Pharmacologist
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

And

Ruben Ayala, Pharm.D.
Lead Pharmacologist
DNDBE/OSIS

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDBE/OSIS

SUBJECT: Surveillance inspection of (b) (4) (b) (4)

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the analytical portion of studies Non-Responsive Non-Responsive and MYL-1501D-1001 (NDA 210605) conducted at (b) (4) (b) (4)

Reference ID: 4624497

Form FDA 483 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI).

Non-Responsive

The inspectional findings were isolated in nature and do not impact the reliability of audited study MYL-1501D-1001 (NDA 210605). The stability assessments in this study included

freshly-prepared comparators. Therefore, the data from study MYL-1501D-1001 and other studies of similar analytical methodology should be accepted for further review.

Inspected Studies:

Non-Responsive

NDA 210605

Study Number: MYL-1501D-1001
Study Title: "A glucose clamp trial investigating the Biosimilarity of two formulations of Mylan's insulin glargine with US Lantus reference product."
Dates of Bioanalysis: January 19-March 18, 2017

Analytical Site: (b) (4)

OSIS Pharmacologists Gajendiran Mahadevan, Ph.D. and Ruben Ayala, Pharm.D. audited the analytical portion of the above

studies at (b) (4)
from (b) (4).

We thoroughly audited the study records, facility, laboratory equipment, method validation, sample analysis, and interviewed the firm's management and staff. As a part of surveillance approach, we selected and audited several key study components across multiple studies that best represent (b) (4) bioanalytical operations.

At the conclusion of the inspection, we observed objectionable conditions and issued Form FDA 483 to (b) (4) (**Attachment-1**). The firm responded to Form FDA 483 on December 21, 2017 (**Attachment-2**). The Form FDA 483, the firm's response to Form FDA 483, and our evaluation follow.

(b) (4)

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(b) (4)

Conclusion:

After reviewing the inspectional findings, there was evidence that significant deficiencies impacted the reliability of a portion of data from Non-Responsive Non-Responsive. The finding Non-Responsive Non-Responsive appears to be isolated in nature because it did not impact the reliability of study MYL-

1501D-1001 (NDA 210605) and other studies of similar analytical methodology conducted at (b) (4). The DPARP reviewer should pursue the following pending items.

Non-Responsive

We also recommend that the data from study MYL-1501D-1001 (NDA 210605) and other studies of similar analytical methodology be accepted for further review (**Attachment-6;** See at the end of this memo). The stability assessments in this study included freshly-prepared comparators.

Gajendiran Mahadevan, Ph.D.
Pharmacologist

Ruben Ayala, Pharm.D.
Lead Pharmacologist

Final Classification:

Analytical Site:
VAI: (b) (4)
FEI#: (b) (4)
cc:
OTS/OSIS/Kassim/Choe/Taylor/Haidar/CDER-OSIS-BEQ@fda.hhs.gov
OTS/OSIS/DGDBE/Cho/Kadavil/Skelly/Choi/Au
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Mahadevan
CDER/OND/DPARP/Chowdhury
CDER/OND/DMEP/Thanh Hai

Draft: GM 02/05/2018; 02/12/2018
Edits: RCA 2/07/2018, 2/09/2018; AD 02/09/2018

ECMS: (b) (4) /NDA 210606 Non-Responsive

OSIS File #: BE 7633 (NDA 210605); Non-Responsive
FACTS: 11778936 (NDA 210605); Non-Responsive

Attachment-6

Studies in support of Pending Applications

Application #	Study #	Study Type (in vitro)	Drug Name	Dates of Analytical Conduct
NDA 210605	MYL-1501D-1001	In vivo	Insulin glargine	January 19-March 18, 2017

Non-Responsive

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/s/

GAJENDIRAN MAHADEVAN
02/12/2018

RUBEN C AYALA
02/12/2018

ARINDAM DASGUPTA
02/12/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Premarket and Labeling Compliance (DPLC)
Abdominal and Surgical Devices Branch

Date:	September 6, 2017
To:	Muthu Ramaswamy, Ph.D., CDER/OPQ/OPF/DIA/IABIII vidya.pai@fda.hhs.gov
	Juandria Williams, Ph.D. Chief, CDER/OPQ/OPF/DIA/IABIII, Juandria.williams@fda.hhs.gov
	Office of Combination Products at combination@fda.gov
	RPM: Anika Lalmansingh, Senior Regulatory Health Program Manager, OPQ/OPRO/DRBPMI/RBPMBII
Through:	Nazia Rahman, Lead Consumer Safety Officer, CDRH/OC/DMQ Nazia Rahman -S 2017.12.21 14:54:09 -05'00'
From:	Habacuc Barrera, CSO, CDRH/OC/DMQ/ASDB
Applicant:	Mylan GmbH
	Thurgauerstrasse 40, Zurich, Switzerland, CH-8050
	FEI# 3007160792
Application #	NDA-210605
Consult #	ICC1700725
Product Name:	Insulin glargine (rDNA origin) - 100 U/mL - Solution for Subcutaneous Injection "Semglee"

Reference ID: 4199948
Reference ID: 4624497

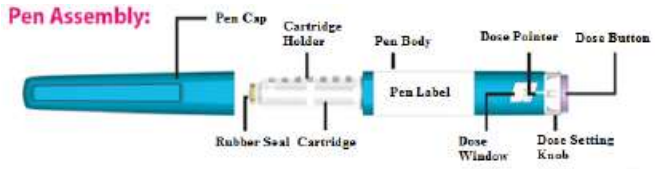
Combination Product

Intended Use:	SEMGLEE is a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
Pre-Approval Inspection:	No, Post-Approval Inspections are requested.
Documentation Review:	Additional Information Required
Final Recommendation:	**APPROVAL**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of NDA-210605.

PRODUCT DESCRIPTION

MYL-1501D drug product (DP) presented in pre-filled pen is a clear, colorless liquid, free from turbidity and foreign matter. It contains 100 units/mL of insulin glargine and is presented in a pre-filled pen integrated with 3 mL colorless tubular glass (United States Pharmacopeia [USP]/European Pharmacopeia [Ph. Eur.] Type I) cartridges that are sealed using lined seals and plugged with plunger stoppers. The pre-filled pen is intended to subcutaneously deliver measured doses of MYL-1501D using recommended, commercially available insulin pen needles. Each pre-filled pen is intended for use by a single user. The pre-filled pen is a manual use, disposable, multiple and variable dose injection device that comprises three main components: Pen body or dosing mechanism, Cartridge holder, and Pen cap.



Reference ID: 4199948
Reference ID: 4624497

REGULATORY HISTORY

The following facilities were identified as being involved in the manufacturing and/or development of the finished combination product Insulin glargine (rDNA origin) - 100 U/mL - Solution for Subcutaneous Injection "Semglee" in NDA-210605.

1. Responsibility –3-mL Cartridges Manufacturing and Testing Facility

Site Address	**Biocon Sdn. Bhd. (930330-U),** No.1, Jalan Bioteknologi 1, Kawasan Perindustrian SiLC, 79200 Iskandar Puteri, Johor, Malaysia.	**Responsibilities:** The activities related to manufacturing, filling, primary packaging, quality control testing [Chemical/Physical, Microbiological (sterility and non-sterility) testing] of the 3 mL cartridges.
DUNS Number	865785591	
FEI Number	3011248248	

Inspectional History – CDRH/OC Comments: No inspection history in the database. Inspection is not needed because it is a component.

2. Responsibility –Pre-filled Pen Assembly Facility

Site Address	**Biocon Limited,** Special Economic Zone Plot No: 2, 3, 4, 5, Phase – IV Bommasandra-Jigani Link Road Bommasandra Post Bangalore Karnataka, 560099 India	**Responsibilities:** Pre-filled Pen Assembly (Secondary Packaging), Quality Control Testing (Chemical/Physical) and Secondary Packaging in Carton Box. Analytical similarity assessment: Compilation (data from outsourced tests), analysis and assessment of analytical similarity.
DUNS Number	650501997	
FEI Number	3003981475	

Reference ID: 4199948
Reference ID: 4624497

Inspectional History – CDRH/OC Comment: Last inspection history 05/25/2017 06/03/2017 – compliance program 7356.002A, Sterile Drug Process Inspections. The current inspection utilized the systems approach and covered Quality, Facilities & Equipment, Materials, Production Packaging & Labeling and Laboratory Control systems. The inspection was conducted for profile class SVS and SVL. The previous FDA inspection was conducted October 19-29, 2015 and classified VAI.

Inspection Recommendation

A post-approval inspection is required because:

- A recent medical device inspection of the firm has not been performed

An inspection (pre-approval) is not required because:

- A recent drug inspection of the firm has been performed and the site is a foreign establishment.

3. Mylan GmbH Inspectional History –An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

Site Address	**Biocon Limited,** Mylan GmbH Thurgauerstrasse 40, Zurich, Switzerland, CH-8050	**Responsibilities:** Mylan has collaborated with (b) (4) for the design, development and manufacture of device constituent parts of the pre-filled pen. (b) (4): this incorporates the (b) (4) color on the pen cap and pen body intended for European markets. Site is responsible for design and development of device.
DUNS Number	370658091	
FEI Number	3007160792	

Reference ID: 4199948
Reference ID: 4624497

Inspection Recommendation:

A post-approval inspection is required because:

- The firm is responsible for major activities related to the development of the final combination involving the device constituent part; and,
- A recent medical device inspection of the firm has not been performed

DOCUMENTATION REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

Management Control, 21 CFR 820.20

Mylan is the applicant for the MYL-1501D product under NDA 210605, MYL-1501D submission and as such has overall responsibility for the combination product, with Biocon responsible for the development, manufacture and release of the combination product MYL- 1501D. All aspects of 21CFR part 820, as they relate to the requirements required to comply with 21CFRpart 4.4 (b) under the streamlined approach, are the responsibility of Biocon. Mylan oversees Biocon as a supplier. Figure 1 shows the Quality Organizational chart in Mylan, with the relationship with Biocon managed through the Quality Team identified on this chart. Biocon's ongoing responsibilities are defined and managed by Mylan through an approved Quality Technical Agreement (QTA), which undergoes periodic review to ensure activities and responsibilities are commensurate with current requirements.

Figure 1 Mylan Quality Team Organizational Structure

Quality Team (including Biologics) ➡ Head of Complex Products Quality ➡ Head of Global Quality Operations ➡ Head of Global Quality ➡ Mylan President ➡ Mylan CEO

The Quality Control and Quality Assurance organization structure at Biocon is presented in Annexure 2, with the Senior Vice President for Quality and National Regulatory Affairs reporting directly into the Chairman and Managing Director of Biocon, thus maintaining independence of function within the Biocon organization.

The design, development and manufacturing of the MYL-1501D combination product and its device constituent parts is the responsibility of Biocon. Biocon maintain an approved Quality Agreement with (b) (4) to support Biocon's responsibilities in the MYL-1501D program. The Quality and Technical teams input relevant technical information.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

Reference ID: 4199948
Reference ID: 4624497

Design Controls, General, 21 CFR 820.30

Mylan has collaborated with (b) (4) for the design, development and manufacture of device constituent parts of the pre-filled pen. Design and Development activities were conducted based on the principles of device development including the relevant requirements of Design Controls (21 CFR Part 820.30), Medical devices – Quality management systems (EN ISO 13485:2012); Needle-based injection systems for medical use – Requirements and test methods (ISO 11608-1 to 3); Biological Evaluation of Medical Devices (ISO 10993-1:2009); Risk Management (EN ISO 14971:2012); Guidance for Industry - Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (Food and Drug Administration [FDA], June 2013); Guidance for Industry – Container Closure Systems for Packaging Human Drugs and Biologics (FDA, May 1999).

Verification and validation of the design confirmed the suitability of the MYL-1501D device for its intended use as defined in the design inputs, encompassing the needs of the intended user.

Design outputs, which included an assessment of component materials, design drawings, and manufacture and control of device components, fed into design verification. Design Verification Testing (DVT) is appropriately performed. Both the DVT and the assessment of component materials demonstrated that the MYL-1501D device satisfied the relevant device requirements. Design validation demonstrated that the MYL-1501D device met the user requirements.

Device risk management considered all potential risks to the user from the design, intended use, and foreseeable misuse. A failure modes and effects analysis was conducted to review the acceptability of known and potential risks in consideration of the severity of potential harm to the user (as defined by the Medical Hazard List [MHL]). Risk mitigation was considered as part of the device component selection process such that the risk of user harm from intended or foreseeable misuse scenarios was reduced to a tolerable level.

Mylan provided design input requirements for the insulin glargine pen. Design reviews were conducted by (b) (4) and risk management procedures were followed to reduce risks to an acceptable level. Design Verification and usability studies were conducted throughout the device development program.

Two pen configurations have been used during the development process and are referred to as the following;

- Clinical Pen Configuration: the pen used in the phase 3 clinical studies (this pen was black in color)

- Commercial Pen Configuration: the pen that contains all of the design refinements resulting from the development program. This pen configuration is available in two colors:

Reference ID: 4199948
Reference ID: 4624497

o (b) (4): design verification testing was undertaken with this color of the commercial pen configuration (this color is not intended for European markets)

o (b) (4): this incorporates the (b) (4) color on the pen cap and pen body intended for European markets. This was used for biocompatibility, applicable verification testing to confirm that the color change did not impact functionality of the pen, and summative usability testing.

The clinical pen configuration met dose accuracy requirements of ISO 11608-1; subsequently, the commercial configuration pen incorporated refinements to the design to address a potential misuse scenario, where application of excessive injection force could cause mechanical failure and make the pen unusable. In addition, the opportunity was taken to make other refinements to improve the in-use and manufacturing robustness of the pen and enhance the user perception of quality.

An assessment was performed to determine whether the refinements made to the clinical pen could potentially impact function. Based on this assessment, it was concluded that these refinements do not change any parameters that would have an impact to the safety or effectiveness, or the ability to accurately deliver the dose. The clinical pen configuration met the dose accuracy requirements of ISO 11608-1. Therefore, the clinical data collected using the clinical pen configuration is representative of the commercial pen.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50

Evaluation of suppliers in Biocon is controlled through an approved supplier evaluation program. This program involves the following process to ensure that suppliers conform to specified requirement outlined by Biocon

New vendors for existing products/new products are qualified and approved by Quality Assurance (QA) as per the Biocon vendor approval process. The procurement and vendor qualification process can be summarized as below:

- Once potential vendors are identified Certificate of Analysis (CoAs) are requested for assessment and approval of these allow the supplier evaluation program to progress.
- Post approval of CoAs, samples from 3 different batches are sought from the vendor and submitted for further evaluation. In the case of existing products, the purchase team shares a specification with the prospective vendor.
- Relevant documents related to the product are produced as requested by the cross functional teams.
- A supplier questionnaire, approved by Biocon QA, is sent to the vendor for completion.
- An audit is scheduled at the vendor's facility if deemed necessary.
- Post approval of samples and verification of documents (including the audit report if required), the vendor is included into the Approved Vendor List (AVL). The AVL is unique

Reference ID: 4199948
Reference ID: 4624497

to each product and each site and is maintained by the QA department. Materials can only be procured from suppliers on the AVL.

- Procurement is done via a SAP® system generated purchase order which goes through multiple approvals. Purchase orders are raised on vendors listed in SAP, which in turn is linked to the AVL ensuring materials can only be procured from approved vendors.

Upon receipt of any product, the warehouse team consults the AVL before receipt of any goods. The quality control team samples the product and undertakes analysis in line with the approved specification.

The QA team enters Quality Agreements for critical suppliers and includes details related to the quality/regulatory requirements of the product including the change notification process, the acceptance process and standards to be applied to the product.

Biocon confirms the quality of the purchased product and services through an approved incoming inspection process, where the product is reviewed against approved specifications to ensure the quality of the product received is suitable for use. These records are stored in the document management system in Biocon.

For the MYL-1501D program in Biocon the above process outlined is adhered to when purchasing, receiving and accepting device components from (b) (4) (b) (4).

The agreements, as outlined in response to 2a of this information request, detail the quality agreements between Biocon and(b) (4) to control the supply of device components purchased from(b) (4) for MYL-1501D. Approved QTAs also detail the requirements of suppliers to notify Biocon of changes to purchased device components. Biocon shall perform an internal assessment of the change to classify the impact of the change before agreeing to any proposed changes.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100

Procedures and systems are in place for Corrective and Preventive Actions (CAPA) in Biocon. Biocon uses a CAPA process to manage non-conforming product and other quality events. This is implemented through an initial correction against the non-conformance with a corrective action plan to prevent recurrence. Changes to methods, procedures, equipment or processes are captured within the QMS. The CAPA assigned identifies the root cause and/ or observation and not just the symptoms of an event.

The CAPA process in Biocon is designed to ensure that customer complaints, customer returns, non-conformances (out of specification results), aberrant results (out of trend results),

Reference ID: 4199948
Reference ID: 4624497

deviations, investigations and non-conformances from approved procedures are thoroughly investigated and actioned as required.

Following implementation of the CAPA, verification may be required depending on the nature of the non-conformances to establish that the corrective action taken has eliminated the root cause of the event and has thereby prevented its recurrence. Additionally, preventive action can be taken to eliminate the causes of potential non-conformances.

Figure 2: Flow Chart of CAPA process

1. CAPA Identification:
   An event occurs requiring a CAPA which can be a customer complaint, customer returns, non-conformances (out of specification results), aberrant results (out of trend results), deviations, investigations or non-conformances from approved procedures.

2. CAPA Initiation:
   A CAPA is initiated by the user group within a defined timeframe, and a CAPA report is drafted. The CAPA report is forwarded by the user department to QA to log in to the system.

3. Review Comments by Cross Functional Team:
   CAPA log in will be performed by QA as per the standard operating procedure for management of CAPAs. After the logging in of the CAPA by QA, the CAPA should be reviewed by a cross-functional team prior to final approval.

4. CAPA Implementation:
   All agreed/approved CAPAs are implemented by the user department within the timeline detailed in the CAPA plan. Change controls are opened where necessary. After verification of implemented CAPA, QA close the CAPA report. As required, effectiveness monitoring for the CAPA shall be carried out as per procedure. CAPA

Reference ID: 4199948
Reference ID: 4624497

effectiveness verification details are recorded. Periodic trending of CAPAs is conducted to assess effectiveness of the corrective action.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.100.

Installation, 21 CFR 820.170

Installation is not required for this combination product. The information provided by the firm has **adequately** addressed the requirements of 21 CFR 820.170.

Servicing, 21 CFR 820.200

Servicing is not required for this combination product. The information provided by the firm has **adequately** addressed the requirements of 21 CFR 820.170.

MANUFACTURING

(b) (4)

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Reference ID: 4199948
Reference ID: 4624497

Acceptance Activities

Table 2.3.P/ 8: Specifications for MYL-1501D Drug Product (3 mL Cartridges)

Sr. No.	Parameter	Test Method Reference	Acceptance Criteria
1	Description	Visual inspection/In-house	A clear colorless liquid free from turbidity and foreign matter
2	Identification (by HPLC)	In-house (based on Ph. Eur. method # 2.2.29 and # 0838 and USP <621>)	The retention time of the principal peak of the sample obtained in assay chromatogram should be comparable with that of the standard
3	pH of the solution	In-house (based on Ph. Eur. method # 2.2.3 and USP <791>	Between (b) (4)
4	High molecular weight impurities (by size exclusion chromatography)	In-house (based on Ph. Eur. method # 2.2.30 and USP <621>)	Not more than (b) (4) %
5	Zinc content (by Atomic Absorption spectrometry)	In-house (based on Ph. Eur. method # 2.2.23 and USP <852>)	(b) (4) µg/100 U
6	(b) (4)	In-house (based on USP <621>)	Between (b) (4) (between (b) (4) % of label claim*)
7	Particulate matter (visible particulate)	Based on Ph. Eur. method #2.9.20 and USP <790>	Physical inspection should not show any evidence of foreign particles
8	Extractable volume	Based on Ph. Eur. method # 2.9.17 and USP <1>	Between (b) (4)
9	Assay (By HPLC) (content of insulin glargine)	In-house (based on USP <621>)	Between (b) (4) (between (b) (4) % of label claim**)
10	Related compound (by HPLC)		
	Total impurities	In-house (based on USP <621>)	Not more than (b) (4) %
	Any individual impurity		Not more than (b) (4) %
11	Seal integrity test	Based on self-sealing test as per Ph. Eur. # 3.2.9 and USP <381>	None of the cartridges should contain any trace of colored solution

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Sr. No.	Parameter	Test Method Reference	Acceptance Criteria
12	Particulate matter (sub-visible particulate)	Based on Ph. Eur. method #2.9.19 and USP <788>	≥ 10µm: NMT (b) (4) particles/container ≥ 25µm: NMT (b) (4) particles/container
13	Bacterial endotoxins	Based on Ph. Eur. method # 2.6.14 and USP <85>	Less than 80 EU/100 U of insulin glargine
14	Sterility	Based on Ph. Eur. method # 2.6.1 and USP <71>	Preparations for injection meet the requirements of sterility
15	Friction force test		
	Initiating force	ISO 11608-3:2012	Not more than (b) (4)
	Sustained force		Not more than (b) (4)
16	Dimensions		
	G – Length of glass barrel assembled with crimp cap	ISO 11608-3:2012	(b) (4)
	I – Length between gauging diameter on top of cartridge to rear end of plunger (delivery position)		(b) (4)
	(G-I) – Start position of the plunger		(b) (4)
* Label claim for (b) (4) ** Label claim for assay is 100 U/mL EU= endotoxin unit; NMT = Not more than			

Table 2.3.P/ 8: Specifications for MYL-1501D Drug Product (3 mL Cartridges)

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3	pH of the solution	In-house (based on Ph. Eur. method # 2.2.3 and USP <791>	Between (b) (4)
4	High molecular weight impurities (by size exclusion chromatography)	In-house (based on Ph. Eur. method # 2.2.30 and USP <621>)	Not more than (b) (4)%

Reference ID: 4199948
Reference ID: 4624497

Sr. No.	Parameter	Test Method Reference	Acceptance Criteria
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6	(b) (4)	In-house (based on USP <621>)	Between (b) (4) (between (b) (4) % of label claim*)
7	Particulate matter (visible particulate)	Based on Ph. Eur. method #2.9.20 and USP <790>	Physical inspection should not show any evidence of foreign particles
8	Extractable volume	Based on Ph. Eur. method # 2.9.17 and USP <1>	Between (b) (4)
9	Assay (By HPLC) (content of insulin glargine)	In-house (based on USP <621>)	Between (b) (4) (between (b) (4) % of label claim**)
10	Related compound (by HPLC)		
	Total impurities	In-house (based on USP <621>)	Not more than (b) (4) %
	Any individual impurity		Not more than (b) (4) %
11	Seal integrity test	Based on self-sealing test as per Ph. Eur. # 3.2.9 and USP <381>	None of the cartridges should contain any trace of colored solution
12	Particulate matter (sub-visible particulate)	Based on Ph. Eur. method #2.9.19 and USP <788>	≥ 10µm: NMT (b) (4) particles/container ≥ 25µm: NMT (b) (4) particles/container
13	Bacterial endotoxins	Based on Ph. Eur. method # 2.6.14 and USP <85>	Less than 80 EU/100 U of insulin glargine
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16	Dimensions		
	G – Length of glass barrel assembled with crimp cap	ISO 11608-3:2012	(b) (4)
	I – Length between gauging diameter on top of cartridge to rear end of plunger (delivery position)		(b) (4)
	(G-I) – Start position of the plunger		(b) (4)

Reference ID: 4199948
Reference ID: 4624497

Sr. No.	Parameter	Test Method Reference	Acceptance Criteria
* Label claim for (b) (4) ** Label claim for assay is 100 U/mL EU= endotoxin unit; NMT = Not more than			

Documentation Review Recommendation

This application was adequate overall.

RECOMMENDATION

The application for Mylan GmbH Insulin glargine (rDNA origin) - 100 U/mL, ANDA 210605 is approvable from the perspective of the applicable Quality System Requirements.

CDRH/OC had recommended post-approval inspections for the Biocon Limited sites in India and Switzerland.

CDRH/OC hereby finds NDA 210605 approvable from the perspective of the applicable Quality System Requirements.

Habacuc V. Barrera -S

Digitally signed by Habacuc V. Barrera -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001099118, cn=Habacuc V. Barrera -S
Date: 2017.12.22 11:34:50 -05'00'

Habacuc Barrera

Reference ID: 4199948
Reference ID: 4624497

Prepared: HBarrera: 12/21/17

Reviewed: NRahman: 12/21/17

CTS No.: ICC1700725

Application Number 210605

Reference ID: 4199948
Reference ID: 4624497

Inspectional Guidance

Firm to be inspected:

Site Address	**Biocon Limited,** Mylan GmbH Thurgauerstrasse 40, Zurich, Switzerland, CH-8050	**Responsibilities:** Mylan has collaborated with (b) (4) for the design, development and manufacture of device constituent parts of the pre-filled pen. (b) (4): this incorporates the (b) (4) color on the pen cap and pen body intended for European markets. Site is responsible for design and development of device.
DUNS Number	370658091	
FEI Number	3007160792	

CDRH recommends a post-approval inspection under the applicable Medical Device Regulations of Mylan GmbH, Thurgauerstrasse 40, Zurich, Switzerland, CH-8050, and FEI# 3007160792.

A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Reference ID: 4199948
Reference ID: 4624497

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Habacuc Barrera
CSO
Abdominal and Surgical Devices Branch
Office of Compliance, Division of Premarket and Labeling Compliance (DPLC)
Office of Compliance, WO66 RM 3614
Phone: 240-402-9678

Secondary Contacts (if Primary is unavailable and a timely answer is required)

LCDR Cesar A. Perez, PhD
Chief
Abdominal and Surgical Devices Branch
Office of Compliance, Division of Premarket and Labeling Compliance (DPLC)
Office of Compliance, WO66 RM 3626
Phone: 301-796-5476

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

Reference ID: 4199948
Reference ID: 4624497

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

/s/

ANIKA A LALMANSINGH
12/22/2017
Uploaded on behalf of Habacuc Barrera, CSO, CDRH/OC/DMQ/ASDB

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Premarket and Labeling Compliance (DPLC)
Abdominal and Surgical Devices Branch

Date:	September 6, 2017
To:	Muthu Ramaswamy, Ph.D., CDER/OPQ/OPF/DIA/IABIII vidya.pai@fda.hhs.gov
	Juandria Williams, Ph.D. Chief, CDER/OPQ/OPF/DIA/IABIII, Juandria.williams@fda.hhs.gov
	Office of Combination Products at combination@fda.gov
	RPM: Anika Lalmansingh, Senior Regulatory Health Program Manager, OPQ/OPRO/DRBPMI/RBPMBII
Through:	Nazia Rahman, Lead Consumer Safety Officer, CDRH/OC/DMQ Nazia Rahman -S 2017.12.14 12:41:21 -05'00'
From:	Habacuc Barrera, CSO, CDRH/OC/DMQ/ASDB
Applicant:	Mylan GmbH
	Thurgauerstrasse 40, Zurich, Switzerland, CH-8050
	FEI# 3007160792
Application #	NDA-210605
Consult #	ICC1700725
Product Name:	Insulin glargine (rDNA origin) - 100 U/mL - Solution for Subcutaneous Injection "Semglee"

Reference ID: 4196731
Reference ID: 4624497

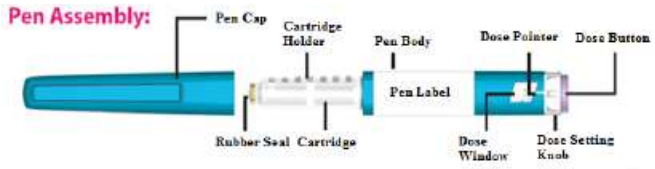
Combination Product

Intended Use:	SEMGLEE is a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
Pre-Approval Inspection:	No, A Post-Approval Inspection is requested.
Documentation Review:	Additional Information Required
Final Recommendation:	**DISAPPROVAL**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of NDA-210605.

PRODUCT DESCRIPTION

MYL-1501D drug product (DP) presented in pre-filled pen is a clear, colorless liquid, free from turbidity and foreign matter. It contains 100 units/mL of insulin glargine and is presented in a pre-filled pen integrated with 3 mL colorless tubular glass (United States Pharmacopeia [USP]/European Pharmacopeia [Ph. Eur.] Type I) cartridges that are sealed using lined seals and plugged with plunger stoppers. The pre-filled pen is intended to subcutaneously deliver measured doses of MYL-1501D using recommended, commercially available insulin pen needles. Each pre-filled pen is intended for use by a single user. The pre-filled pen is a manual use, disposable, multiple and variable dose injection device that comprises three main components: Pen body or dosing mechanism, Cartridge holder, and Pen cap.



Reference ID: 4196731
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REGULATORY HISTORY

The following facilities were identified as being involved in the manufacturing and/or development of the finished combination product Insulin glargine (rDNA origin) - 100 U/mL - Solution for Subcutaneous Injection "Semglee" in NDA-210605.

1. Responsibility –3-mL Cartridges Manufacturing and Testing Facility

Site Address	**Biocon Sdn. Bhd. (930330-U),** No.1, Jalan Bioteknologi 1, Kawasan Perindustrian SiLC, 79200 Iskandar Puteri, Johor, Malaysia.	**Responsibilities:** The activities related to manufacturing, filling, primary packaging, quality control testing [Chemical/Physical, Microbiological (sterility and non-sterility) testing] of the 3 mL cartridges.
DUNS Number	865785591	
FEI Number	3011248248	

Inspectional History – CDRH/OC Comments: No inspection history in the database. Inspection is not needed because it is a component.

2. Responsibility –Pre-filled Pen Assembly Facility

Site Address	**Biocon Limited,** Special Economic Zone Plot No: 2, 3, 4, 5, Phase – IV Bommasandra-Jigani Link Road Bommasandra Post Bangalore Karnataka, 560099 India	**Responsibilities:** Pre-filled Pen Assembly (Secondary Packaging), Quality Control Testing (Chemical/Physical) and Secondary Packaging in Carton Box. Analytical similarity assessment: Compilation (data from outsourced tests), analysis and assessment of analytical similarity.
DUNS Number	650501997	
FEI Number	3003981475	

Reference ID: 4196731
Reference ID: 4624497

Inspectional History – CDRH/OC Comment: Last inspection history 05/25/2017 06/03/2017 – compliance program 7356.002A, Sterile Drug Process Inspections. The current inspection utilized the systems approach and covered Quality, Facilities & Equipment, Materials, Production Packaging & Labeling and Laboratory Control systems. The inspection was conducted for profile class SVS and SVL. The previous FDA inspection was conducted October 19-29, 2015 and classified VAI.

Inspection Recommendation

An inspection is not required because:

- A recent drug inspection of the firm has been performed and the site is a foreign establishment.

3. Mylan GmbH Inspectional History –An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

Site Address	**Biocon Limited,** Mylan GmbH Thurgauerstrasse 40, Zurich, Switzerland, CH-8050	**Responsibilities:** Mylan has collaborated with (b) (4) for the design, development and manufacture of device constituent parts of the pre-filled pen. (b) (4) this incorporates the (b) (4) color on the pen cap and pen body intended for European markets. Site is responsible for design and development of device.
DUNS Number	370658091	
FEI Number	3007160792	

Inspection Recommendation:

A post-approval inspection is required because:

- The firm is responsible for major activities related to the development of the final combination involving the device constituent part; and,
- A recent medical device inspection of the firm has not been performed

Reference ID: 4196731
Reference ID: 4624497

DOCUMENTATION REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

Management Control, 21 CFR 820.20

Information regarding Management Controls was not provided in the submission **(see deficiency #1 below).** The information provided by the firm has **inadequately** addressed the requirements of 21 CFR 820.20.

Design Controls, General, 21 CFR 820.30

Mylan has collaborated with (b) (4) for the design, development and manufacture of device constituent parts of the pre-filled pen. Design and Development activities were conducted based on the principles of device development including the relevant requirements of Design Controls (21 CFR Part 820.30), Medical devices – Quality management systems (EN ISO 13485:2012); Needle-based injection systems for medical use – Requirements and test methods (ISO 11608-1 to 3); Biological Evaluation of Medical Devices (ISO 10993-1:2009); Risk Management (EN ISO 14971:2012); Guidance for Industry - Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (Food and Drug Administration [FDA], June 2013); Guidance for Industry – Container Closure Systems for Packaging Human Drugs and Biologics (FDA, May 1999).

Verification and validation of the design confirmed the suitability of the MYL-1501D device for its intended use as defined in the design inputs, encompassing the needs of the intended user.

Design outputs, which included an assessment of component materials, design drawings, and manufacture and control of device components, fed into design verification. Design Verification Testing (DVT) is appropriately performed. Both the DVT and the assessment of component materials demonstrated that the MYL-1501D device satisfied the relevant device requirements. Design validation demonstrated that the MYL-1501D device met the user requirements.

Device risk management considered all potential risks to the user from the design, intended use, and foreseeable misuse. A failure modes and effects analysis was conducted to review the acceptability of known and potential risks in consideration of the severity of potential harm to the user (as defined by the Medical Hazard List [MHL]). Risk mitigation was considered as part of the device component selection process such that the risk of user harm from intended or foreseeable misuse scenarios was reduced to a tolerable level.

Mylan provided design input requirements for the insulin glargine pen. Design reviews were conducted by (b) (4) and risk management procedures were followed to reduce risks

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to an acceptable level. Design Verification and usability studies were conducted throughout the device development program.

Two pen configurations have been used during the development process and are referred to as the following;

- Clinical Pen Configuration: the pen used in the phase 3 clinical studies (this pen was black in color)

- Commercial Pen Configuration: the pen that contains all of the design refinements resulting from the development program. This pen configuration is available in two colors:

o [redacted] (b) (4) design verification testing was undertaken with this color of the commercial pen configuration (this color is not intended for European markets)

o [redacted] (b) (4): this incorporates the [redacted] (b) (4) color on the pen cap and pen body intended for European markets. This was used for biocompatibility, applicable verification testing to confirm that the color change did not impact functionality of the pen, and summative usability testing.

The clinical pen configuration met dose accuracy requirements of ISO 11608-1; subsequently, the commercial configuration pen incorporated refinements to the design to address a potential misuse scenario, where application of excessive injection force could cause mechanical failure and make the pen unusable. In addition, the opportunity was taken to make other refinements to improve the in-use and manufacturing robustness of the pen and enhance the user perception of quality.

An assessment was performed to determine whether the refinements made to the clinical pen could potentially impact function. Based on this assessment, it was concluded that these refinements do not change any parameters that would have an impact to the safety or effectiveness, or the ability to accurately deliver the dose. The clinical pen configuration met the dose accuracy requirements of ISO 11608-1. Therefore, the clinical data collected using the clinical pen configuration is representative of the commercial pen.

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50

Information regarding Purchasing Controls was not provided in the submission **(see deficiency #2 below).** The information provided by the firm has **inadequately** addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100

Information regarding CAPAs was not provided in the submission **(see deficiency #3 below).** The information provided by the firm has **inadequately** addressed the requirements of 21 CFR 820.100.

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Installation, 21 CFR 820.170

Installation is not required for this combination product. The information provided by the firm has **adequately** addressed the requirements of 21 CFR 820.170.

Servicing, 21 CFR 820.200

Servicing is not required for this combination product. The information provided by the firm has **adequately** addressed the requirements of 21 CFR 820.170.

MANUFACTURING

(b) (4)

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Acceptance Activities

Table 2.3.P/ 8: Specifications for MYL-1501D Drug Product (3 mL Cartridges)

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10	Related compound (by HPLC)		
	Total impurities	In-house (based on USP <621>)	Not more than (b) (4) %
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	Initiating force	ISO 11608-3:2012	Not more than (b) (4)
	Sustained force		Not more than (b) (4)
16	Dimensions		
	G – Length of glass barrel assembled with crimp cap	ISO 11608-3:2012	(b) (4)
	I – Length between gauging diameter on top of cartridge to rear end of plunger (delivery position)		(b) (4)
	(G-I) – Start position of the plunger		(b) (4)
* Label claim (b) (4) ** Label claim for assay is 100 U/mL EU= endotoxin unit; NMT = Not more than			

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Sr. No.	Parameter	Test Method Reference	Acceptance Criteria
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10	Related compound (by HPLC)		
	Total impurities	In-house (based on USP <621>)	Not more than (b) (4) %
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16	Dimensions		
	G – Length of glass barrel assembled with crimp cap	ISO 11608-3:2012	(b) (4)
	I – Length between gauging diameter on top of cartridge to rear end of plunger (delivery position)		(b) (4)
	(G-I) – Start position of the plunger		(b) (4)

Reference ID: 4196731
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Sr. No.	Parameter	Test Method Reference	Acceptance Criteria
* Label claim (b) (4)			
** Label claim for assay is 100 U/mL			
EU= endotoxin unit; NMT = Not more than			

Documentation Review Recommendation

This application was deficient overall. Additional information is required for an adequate documentation review.

Deficiencies to be conveyed to the applicant

The following deficiencies have been identified while doing the documentation review of application Product Name, Application # 210605, in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product:

1. A summary of the firm's management structure with executive responsibility who manage, perform, and assess work affecting quality of the product and related controls to ensure that the firm's quality policies are appropriately implemented and followed, and the product appropriately designed and manufactured in conformance with CGMP requirements, including quality system requirements met as per 21 CFR 820.20.

2. Summary of information pertaining to the Purchasing Control as per 21 CFR 820.50 to demonstrate controls and documentation for components, products, or services (example sterilization) received at the sponsor's facility for use in the manufacture of the combination product. The summary should include the applicant's evaluation process of their suppliers that meet the manufacturing acceptance criteria of the combination product specifications. Notification of changes by the suppliers should be considered in the firm's Purchasing/Supplier agreement as changes to incoming specification can impact the safety and effectiveness of the final combination product.

3. Summary of information related to Corrective and Preventive Actions (CAPA) as per the requirement of 21 CFR 820.100. CAPA procedures are used to determine the cause of problems and non-conformances, and the appropriate measures used to correct and prevent such problems and non-conformances from recurring. The CAPA system must account for investigations into failures in the device constituent. CAPA activities for the analysis of sources of quality data to identify existing and potential cause of nonconformances, related investigations, and actions considered to correct and prevent recurrences of problems and non-conformances, including the verification or validation of the actions should be documented under the firm's CAPA System as described in 21 CFR 820.100.

Reference ID: 4196731
Reference ID: 4624497

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

RECOMMENDATION

The application for Mylan GmbH Insulin glargine (rDNA origin) - 100 U/mL, ANDA 210605 is not approvable from the perspective of the applicable Quality System Requirements.

CDRH/OC had recommended deficiencies to be communicated to the applicant, along with inspections for the Biocon Limited site.

CDRH/OC hereby finds NDA 210605 not approvable from the perspective of the applicable Quality System Requirements.

Habacuc V. Barrera -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001099118, cn=Habacuc V. Barrera -S
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Habacuc Barrera

Reference ID: 4196731
Reference ID: 4624497

Prepared: HBarrera: 11/6/17

Reviewed: FMLast name: Month/Day/Year

CTS No.: ICC1700725

Application Number 210605

Reference ID: 4196731
Reference ID: 4624497

Inspectional Guidance

Firm to be inspected:

Site Address	**Biocon Limited,** Mylan GmbH Thurgauerstrasse 40, Zurich, Switzerland, CH-8050	**Responsibilities:** Mylan has collaborated with (b) (4) for the design, development and manufacture of device constituent parts of the pre-filled pen. (b) (4): this incorporates the (b) (4) color on the pen cap and pen body intended for European markets. Site is responsible for design and development of device.
DUNS Number	370658091	
FEI Number	3007160792	

CDRH recommends a post-approval inspection under the applicable Medical Device Regulations of Mylan GmbH, Thurgauerstrasse 40, Zurich, Switzerland, CH-8050, and FEI# 3007160792.

A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

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Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Habacuc Barrera
CSO
Abdominal and Surgical Devices Branch
Office of Compliance, Division of Premarket and Labeling Compliance (DPLC)
Office of Compliance, WO66 RM 3614
Phone: 240-402-9678

Secondary Contacts (if Primary is unavailable and a timely answer is required)

LCDR Cesar A. Perez, PhD
Chief
Abdominal and Surgical Devices Branch
Office of Compliance, Division of Premarket and Labeling Compliance (DPLC)
Office of Compliance, WO66 RM 3626
Phone: 301-796-5476

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

Reference ID: 4196731
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/s/

ANIKA A LALMANSINGH
12/18/2017
Uploaded on behalf of Habacuc Barrera, CSO, CDRH/OC/DMQ/ASDB

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

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

Memorandum

Date: June 14, 2017

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

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

Subject: OPDP Labeling Consult Request

NDA 210605 Semglee™ (insulin glargine injection) solution for subcutaneous use

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OPDP acknowledges receipt of your May 4, 2017, consult request regarding the proposed labeling for Semglee™ (insulin glargine injection) solution for subcutaneous use. Final labeling negotiations were not initiated during this review cycle and DMEP plans to issue a Refuse to File letter. Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DMEP submit a new consult request during the subsequent review cycle.

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.

Reference ID: 4111424
Reference ID: 4624497

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/s/

ANKUR S KALOLA
06/14/2017