CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761109Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 5, 2020
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	BLA 761109
Product Name and Strength:	Lyumjev (insulin lispro-aabc) injection, 100 units/mL Lyumjev KwikPen (insulin lispro-aabc) injection, 100 units/mL and 200 units/mL Lyumjev Junior KwikPen (insulin lispro-aabc) injection, 100 units/mL Lyumjev Tempo Pen (insulin lispro-aabc) injection, 100 units/mL
Applicant/Sponsor Name:	Eli Lilly and Company
OSE RCM #:	2019-1741-1
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

Lilly submitted revised container labels and carton labeling received on May 27, 2020 and June 4, 2020 for Lyumjev. We reviewed the revised container labels and carton labeling for Lyumjev (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] Lilly responded to each of our labeling recommendations and they confirmed implementation.[b] Of note, they did not submit updated carton and container labels for their Tempo Pen professional samples as they have removed these samples from their application.

[a] Purcell J. Human Factors Study Results and Label and Labeling Review for Lyumjev (BLA 761109). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 May 6. RCM No.: 2019-1742 and 2019-1741.
[b] Eli Lilly and Company. Regulatory Response: Container and Carton Label Comments for BLA 761109. Submitted to FDA May 27, 2020. Available via: \\cdsesub1\evsprod\bla761109\0036\m1\us\response.pdf.

2 CONCLUSION

Our review determined that the Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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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 Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	May 21, 2020
To:	Callie Cappel-Lynch, PharmD, RAC Senior Regulatory Health 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 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):	LYUMJEV (insulin lispro-aabc)
Dosage Form and Route:	injection, for subcutaneous or intravenous use
Application Type/Number:	BLA 761109
Applicant:	Eli Lilly and Company

1 INTRODUCTION

On August 15, 2019 Eli Lilly and Company submitted for the Agency's review an Original Application- Biologics License Application (BLA) 761109 for LYUMJEV (insulin lispro-aabc) injection, for subcutaneous or intravenous use. The proposed indication for LYUMJEV (insulin lispro-aabc) injection, for subcutaneous or intravenous use is to improve glycemic control in adults with diabetes mellitus.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) on August 22, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for LYUMJEV (insulin lispro-aabc) injection, for subcutaneous or intravenous use.

On March 14, 2020, DDLO and DMPP made the agreement that DMPP will retain the current track changes as appropriate to the LYUMJEV patient labeling review so that all proposed edits to the PPI and IFUs are maintained in one version of the patient labeling.

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

2 MATERIAL REVIEWED

- Draft LYUMJEV (insulin lispro-aabc) injection, for subcutaneous or intravenous use PPI and IFUs received on August 15, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 14, 2020.
- Draft LYUMJEV (insulin lispro-aabc) injection, for subcutaneous or intravenous use Prescribing Information (PI) received on August 15, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 14, 2020.

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.

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 PPI and IFUs we have:

- simplified wording and clarified concepts where possible

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

4 CONCLUSIONS

The PPI 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 PPI 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 PPI 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: May 19, 2020

To: Callie Cappel-Lynch, Regulatory Project Manager
Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Monika Houstoun, Associate Director for Labeling, (DDLO)

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

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for LYUMJEV™ (insulin lispro-aabc) injection, for subcutaneous or intravenous use

BLA: 761109

In response to DDLO's consult request dated August 22, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and Instructions for Use (IFU) for the original BLA submission for LYUMJEV™ (insulin lispro-aabc) injection, for subcutaneous or intravenous use.

PI, PPI, and IFU: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDLO on May 13, 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.

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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HUMAN FACTORS STUDY RESULTS AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	May 6, 2019
Requesting Office or Division:	Division of Diabetes, Lipid Disorders and Obesity (DDLO)
Application Type and Number:	BLA 761109
Product Type:	Prefilled Biologic Delivery/Device System
Drug Constituent Name and Strength	Lyumjev KwikPen (insulin lispro-aabc) injection, 100 units/mL and 200 units/mL Lyumjev Junior KwikPen (insulin lispro-aabc) injection, 100 units/mL Lyumjev Tempo Pen (insulin lispro-aabc) injection, 100 units/mL
Device Constituent:	Prefilled Pen Injector (PPI)
Rx or OTC:	Rx
Applicant/Sponsor Name:	Eli Lilly and Company (Lilly)
FDA Received Date:	August 15, 2019
OSE RCM #:	2019-1742 and 2019-1741
DMEPA Human Factors Evaluator:	Janine Purcell, MS
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA Team Leader:	Lolita White, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS
DMEPA Associate Director:	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

This review evaluates the human factors (HF) differentiation study results and labels and labeling submitted under BLA 761109 for Lyumjev (insulin lispro-aabc) Pre-filled Pen Injector (PPI), 100 units/mL and 200 units/mL for areas of vulnerability which may increase the risk for medication errors. This is a combination product with a proposed prefilled pen device constituent part that is intended to improve glycemic control in patients with Type 1 or Type 2 diabetes mellitus.

1.1 PRODUCT DESCRIPTION

The Lyumjev KwikPens are intended for subcutaneous administration of insulin lispro-aabc. The proposed product is available as the Lyumjev KwikPen 3 mL 100 units/mL; Lyumjev KwikPen 3 mL 200 units/mL; and Lyumjev Junior Kwikpen 3 mL, 100 units/mL. The proposed product is supplied in a carton containing five 3 mL prefilled pens. See Appendix A.

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

- On April 17, 2017 we provided the Applicant guidance to submit a comprehensive risk analysis or plans for a Human Factors (HF) Validation Study.[a]
- On September 22, 2017, the Applicant submitted a human factors (HF) differentiation study protocol for Agency review.
- On December 14, 2017 we provided recommendations for the HF differentiation study protocol and requested that the Applicant address the identified areas of concern prior to commencing the HF differentiation study.[b]
- On August 15, 2019, the Applicant submitted a HF differentiation study report, which is the subject of this review.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	**Appendix Section (for Methods and Results)**

[a] Cappel-Lynch, C. Preliminary Meeting Minutes for (b) (4) (COR-MEET-05). Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2017 APR 17. IND 127210.

[b] Conrad, A. Human Factors Study Protocol Review for (b) (4) Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 DEC 14. RCM No.: 2017-1965.

Table 1. Materials Considered for this Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Background Information Previous HF Interactions (DMEPA and CDRH)	B
Human Factors Differentiation Study Report	C
Information Requests Issued During the Review	D
Labels and Labeling	E

3 OVERALL ASSESSMENT OF HUMAN FACTORS DIFFERENTIATION STUDY

The sections below provide a summary of the study design and our analysis of the observed use errors to determine if the differentiation study results support the safe and effective use of the proposed product.

3.1 SUMMARY OF THE HUMAN FACTORS DIFFERENTIATION STUDY DESIGN

This HF differentiation study sought to demonstrate that the Lyumjev (insulin lispro-aabc) pre-filled pens can be differentiated from other products that users may take concurrently, thus demonstrating that Lyumjev (insulin lispro-aabc) PPIs can be used safely and effectively by the intended users for intended use in the intended environments of use.

The HF differentiation study sample included 66 participants:

- 17 pediatric participants aged 10 – 17 years of age: 7 participants with type 1 or type 2 diabetes mellitus who either take only basal insulin or take less than 30 units of mealtime insulin per meal, and 10 lay users without diabetes.
- 15 adult patients / lay caregivers: Adult (18 years or older) patients and caregivers of patients with type 1 or type 2 diabetes mellitus who either take only basal insulin or take less than 30 units of mealtime insulin per meal.
- 15 nurses: Home healthcare, long term care, hospital or school nurses who administer insulin injections to others at least once per month in a professional capacity.
- 15 retail pharmacists who currently dispense insulin.
- 4 colorblind consumers without diabetes.

All participants were untrained. Each participant completed three differentiation scenarios in which he or she was asked to select a specific KwikPen device or carton when presented with a group of products similar in appearance. Pharmacists differentiated cartons; all other participants differentiated pens. After all differentiation scenarios were completed,

the moderator investigated root cause for all observed differentiation errors, close calls and requests for assistance from the perspective of the participant.

We compared the HF differentiation study methodology under review to the Human Factors Protocol Review recommendations provided on December 14, 2017 for the proposed product. To clarify the discrepancies, on December 26, 2019, FDA requested additional information regarding the justification for lay user participants without diabetes; screening questionnaires and demographic data; and the moderator script. The Applicant submitted their response to the information request on January 3, 2020 and provided the following:

Justification for Pediatric Lay Users without Diabetes

We requested data to support that 10 lay users in the pediatric user group are representative of the intended user group for the proposed product. In response, the Applicant described the effort to recruit 15 pediatric patients with diabetes per the HF protocol recommendation, including included advertising locally, sending faxes to local pediatricians and endocrinologists, use of social media, use of referrals from previous research studies, and direct emails to over 40,000 potential respondents. The totality of these efforts resulted in seven pediatric participants with diabetes completing the data collection process, so the pediatric user group was supplemented with 10 pediatric patients from the general population without diabetes. The Applicant further stated that the actual test results for the participants with and without diabetes were the same. We discussed the Applicant's justification internally and consulted with the clinical reviewer from DDLO to confirm the difficulty in recruiting pediatric participants with diabetes due to the prevalence of the disease state among this age group and concluded that this good faith effort is reasonable for the purposes of the HF differentiation study.

Screening Questionnaires and Demographic Data

To further determine if the study participants were adequately representative of the intended users of the proposed product, we requested the screening questionnaires and demographic data for each participant, documenting their disease state (e.g., type 1 diabetes mellitus, type 2 diabetes mellitus, no diabetes diagnosis); experience with insulin types (e.g., basal or mealtime insulin); insulin dosage forms (e.g., vial, insulin pump, pen injector); and pen experienced versus pen inexperienced (e.g., has taken or administered any drugs with pre-filled pen injectors). The Applicant provided the screening questionnaires and demographic data for each participant's diabetes status and experience with types of insulin. The Applicant stated that experience with pen injectors was not captured since the study did not include an injection task; and the study was not designed to collect data on insulin dosage forms in the context of vial, pump, or pen injector. The Applicant noted that the inclusion of both patient and lay users in the pediatric group in essence represented a blended group of pen injection experience and pen injection naïve participants. After internal discussion of the additional information provided by the

Applicant, we found the Applicant's justification for the participant recruitment criteria and the resulting participants to be reasonable.

Moderator Script

We requested the Moderator Script to determine if our HF protocol review recommendation had been implemented to remove leading language. The Applicant provided a rationale based on data artifacts that arose in prior studies when they had removed the question. Based on this data and in an effort to address the Agency's recommendation, the Applicant modified the language. After internal discussion of the additional information provided by the Applicant, we found the Applicant's justification to modify the language reasonable.

Distractor Pens

On January 29, 2020, FDA requested additional information regarding the use of distractor pens used in the differentiation scenarios in the HF differentiation study to clarify why they had not followed the recommendations we provided in our review of their HF differentiation study protocol. The Applicant submitted their response on January 31, 2020. The Applicant described the differentiation scenarios used for the current proposed product testing were based on scenarios used for testing their Humalog Junior KwikPen which in turn were designed to allow for clear differentiation results while avoiding bias due to sequencing effects, learning effects or study artifacts. In our internal discussion, we considered the rationale provided by the Applicant and find it reasonable that in the study every patient and caregiver participant completed a differentiation scenario using the distractor group C6 which included all three variants (Lyumjev KwikPen U-100, Lyumjev KwikPen U-200, and Lyumjev Junior KwikPen U-100

3.2 RESULTS AND ANALYSES OF HUMAN FACTORS DIFFERENTIATION STUDY DATA

Table 2 presents the summary and analysis of the errors that occurred in the differentiation study, the Applicant's analyses of the results, and DMEPA's analyses and recommendations.

Table 2: Summary and analyses of errors

Description of Task and Number of Errors	Description of Incorrect Pen Chosen and Participant Demographics	Participant's Subjective Feedback	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Differentiation Task 1: Select (b) (4) U100 from Cup C6 containing the three different (b) (4) pens 1 Use error	Use Error: (b) (4) Junior chosen instead of (b) (4) U100 PP01 - 11-year-old male type 1 diabetes	*"I just guessed."* (See page 25 of the report for full interview.)	Inattention (not design related) PP01 acknowledged that he simply guessed, demonstrating a lack of effortful attention in the task. He successfully completed the other two scenarios and had no difficulty correctly identifying the three variants in posttest interview. Taken together the results indicate that the root cause of the observed failure was unrelated to the KwikPen design.	No mitigation proposed: Little to no clinical consequence, as it would not prevent successful delivery of (b) (4) rapid insulin. The results and participant feedback do not suggest changes to the design are necessary.	The subjective feedback and root cause analysis provided by the Applicant did not attribute this selection error to specific aspects of the user interface. In addition, the same type of insulin was selected (i.e., Lyumjev insulin lispro) but the participant selected the wrong presentation. In an instance where a patient inadvertently selects the Junior Pen instead of the intended U-100 KwikPen, we note that the patient would still be able to achieve their dose when they dial the pen to the desired number of units (the difference is that the Junior KwikPen dials in half-unit increments and the U-100 KwikPen dials in whole-unit increments). Therefore, in this particular instance, we do not have any additional recommendations to address this error.
Differentiation Task 1: Select (b) (4) U200 from Cup C2 containing Novolog & Lantus pens 1 Use Error	Use Error: Novolog pen chosen instead of (b) (4) U200 PP02 - 13-year-old male type 1 diabetes Novolog user	*"I was just looking for...I don't know."* (See page 26 of the report for full interview.)	Inattention (not design related) PP02's statements and actions indicate that he was less than fully engaged during the task. The participant was unable to articulate any specific reason for choosing the Novolog pen and had no difficulty correctly identifying the (b) (4) U200 pen when the task was repeated in the post test interview. Taken together the results indicate that the root cause of the observed	No mitigation proposed: Little to no clinical consequence, as it would not prevent successful delivery of mealtime insulin. The results and participant feedback do not suggest changes	The subjective feedback and root cause analysis provided by the Applicant did not attribute this selection error to specific aspects of the user interface. In addition, a short acting meal time insulin was selected, and therefore, does not introduce any clinical risks. In evaluating the product user interface, we note that the proposed pen body color is (b) (4) with (b) (4) label (shown below): (b) (4) The Novolog pen body color is dark blue with orange (shown below):  From our expert heuristic evaluation between the proposed pen's product

			failure was unrelated to the KwikPen design.	to the design are necessary.	user interface design compared to the Novolog pen, we do not have any recommendations to further differentiate the proposed product. Therefore, in this particular instance, we do not have any additional recommendations to address this error.
Differentiation Task 1: Select (b) (4) U200 From Cup C1 containing Humalog U100 & Basaglar pens 1 Use Error	Use Error: Basaglar chosen instead of (b) (4) U200 PP11 – 10-year-old female lay user	PP11 was not able to articulate why she chose Basaglar. (See page 28 of the report for full interview.)	Task confusion, unlikely to be design related PP11 was unable to articulate any specific reason for choosing the Basaglar pen. She appeared confused by the moderators questions, and provided conflicting information during the post test interview. The Applicant attributes her state of cognitive development per her age as the rationale for her inability to articulate why she chose the pen.	No mitigation proposed: Giving basal insulin in place of mealtime insulin may result in moderate symptomatic hyperglycemia similar to underdose. The results and participant feedback do not suggest changes to the design are necessary.	We note that despite multiple attempts by the study moderator during the debriefing period, the participant did not attribute this selection error to specific aspects of the user interface. In addition, we note that Basaglar is a basal insulin whereas the (b) (4) is a mealtime insulin. As these two insulins have different onsets of action and different durations, substituting basal insulin when meal time insulin is intended may result in moderate symptomatic hyperglycemia similar to underdose. In evaluating the product user interface, we note that the proposed pen body color is (b) (4) with (b) (4) label (shown below): (b) (4) The Basaglar pen body color is light grey with neon green (shown below):  From our expert heuristic evaluation between the proposed pen's product user interface design compared to the Novolog pen, we do not have any recommendations to further differentiate the proposed product. Therefore, we do not have any additional recommendations to address this error.
Differentiation Task 1: Select (b) (4) t U200 from Cup C6 containing the three different (b) (4) pens 1 Use Error	Use Error: (b) (4) U100 chosen instead of (b) (4) U200 PP14 – 12-year-old female lay user REALM-Teen=41 below age-appropriate	*"I didn't ask if I was allowed to read the pens, so I wasn't sure of it. So, I basically just chose the first one that I saw."* (See page 29 of the report for full interview.)	Artifact (not design related) PP14 stated that she did not initially understand that she was allowed to examine the pens prior to making a selection and chose the first pen she saw in the first scenario. She successfully completed the other two scenarios, selected the correct pen during the second attempt during the post test interview, and had no difficulty correctly identifying the (b) (4) U100 and U200 pens in	No Mitigation proposed: Little to no clinical consequence, as it would not prevent successful delivery of (b) (4) rapid insulin. The results and participant feedback do not suggest changes	The subjective feedback and root cause analysis provided by the Applicant did not attribute this selection error to specific aspects of the user interface. In addition, the same type of insulin was selected (i.e., Lyumjev insulin lispro) but the participant selected the wrong presentation. In an instance where a patient inadvertently selects the U-100 KwikPen instead of the intended U-200 KwikPen, we note that the patient would still be able achieve their dose when they dial the pen to the desired number of units. Therefore, do not have any additional recommendations to address this error.

			posttest interview. Taken together the results indicate that the root cause of the observed failure was unrelated to the KwikPen design.	to the design are necessary.	
Differentiation Task 1: Select (b) (4) U100 from Cup C6 containing the three different (b) (4) pens 1 Use error	Use Error: (b) (4) U200 chosen instead of (b) (4) U100 PP16 – 13-year-old female lay user	"*I don't know. I thought it was it, but I guess not*." (See page 30 of the report for full interview.)	Root causes include confusion over the task, task instructions and a complicated and novel task. PP16 selected the correct pen during the second attempt during the post test interview and had no difficulty correctly identifying the three variants in posttest interview. The (b) (4) variants allow for a high transfer of learning and that the error would not be likely be repeated. Unlikely to be design related.	Little to no clinical consequence, as it would not prevent successful delivery of (b) (4) rapid insulin. The results and participant feedback do not suggest changes to the design are necessary.	The subjective feedback and root cause analysis provided by the Applicant did not attribute this selection error to specific aspects of the user interface. In addition, the same type of insulin was selected (i.e., Lyumjev insulin lispro) but the participant selected the wrong presentation. In an instance where a patient selects the U-200 KwikPen instead of the intended U-100 KwikPen, we note that the patient would still be able to achieve their dose when they dial the pen to the desired number of units. Therefore, we do not have any additional recommendations to address this error.
Differentiation Task 2: Select (b) (4) U100 from Cup C6 containing the three different (b) (4) pens 1 Use error	Use Error: (b) (4) U200 chosen instead of (b) (4) U100 PP02 – 13-year-old male type 1 diabetes patient currently using Novolog	PP02 picked the first pen he touched, did not look at the other pens in the cup. When asked why in the interview he stated *"It says (b) (4) there."* (See page 27 of the report for full interview.)	In the second scenario, the term (b) (4) met PP02's decision-making threshold, and resulted in his selecting (b) (4) Junior (the first pen he looked at) without attempting to gain any additional detail by looking at the pen label. Not design related.	Little to no clinical consequence, as it would not prevent successful delivery of (b) (4) rapid insulin. The results and participant feedback do not suggest changes to the design are necessary.	The subjective feedback and root cause analysis provided by the Applicant did not attribute this selection error to specific aspects of the user interface. In addition, the same type of insulin was selected (i.e., Lyumjev insulin lispro) but the participant selected the wrong presentation. In an instance where a patient selects the U-200 KwikPen instead of the intended U-100 KwikPen, we note that the patient would still be able to achieve their dose when they dial the pen to the desired number of units. Therefore, we do not have any additional recommendations to address this error.

3.3 LABELS AND LABELING

Tables 3 and 4 below include the identified medication error issues with the submitted labels and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 3: Identified Issues and Recommendations for DDLO			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Full Prescribing Information			
1.	We note that the instructions provided under Section 2.1 Important Administration Instructions describing the doses dialed by the U-100 and U-200 pens could be improved for clarity.	The approved Humalog prescribing information contains additional language and this label should be revised for consistency and improved clarity to decrease risk of underdose or overdose medication error.	Under Section 2.1 Important Administration Instructions, modify the bulleted statement "The dose window…" to read as follows: "Do not perform dose conversion when using any LYUMJEV U-100 or U-200 prefilled pens. The dose window of LYUMJEV prefilled pens shows the number of units of LYUMJEV to be injected."
2.	We note that the Section 2.1 Important Administration Instructions does not contain a warning that this product should not be administered via continuous subcutaneous infusion pump (i.e., insulin pump).	We are concerned that this label as presented may pose risk of wrong route medication error.	Add the following statement to Section 2.1 Important Administration Instructions: "Do NOT administer LYUMJEV using a continuous subcutaneous infusion pump (i.e., insulin pump)."
3.	We note that the instructions provided under Section 2.2 General Dosage Instructions are not consistent with Humalog because they do not include the language required in the labels of other insulin products, which clarifies dialing increments for each pen device.	These statements should be included to decrease risk of overdose and underdose medication error.	Add the following statements to Sect 2.2 General Dosage Instructions under the "Subcutaneous Injection" subheading, immediately following the "During changes to a patient's insulin regimen…" bulleted statement: • "The LYUMJEV U-100 KwikPen, LYUMJEV U-100 Tempo Pen and LYUMJEV U-200 KwikPen each dial in 1 unit increments and delivers a maximum dose of 60 units per injection. • The LYUMJEV U-100 Junior KwikPen dials in 0.5 unit

Table 3: Identified Issues and Recommendations for DDLO			
	Identified Issue	**Rationale for Concern**	**Recommendation**
			increments and delivers a maximum does of 30 units per injection."
4.	We note that Section 16.1 How Supplied lacks sufficient information to aid users to distinguish between the multiple formulations.	The additional information should improve users' ability to distinguish between the multiple formulations to decrease risk of product selection medication error.	Under Section 16.1 How Supplied, add the "Concentration" and "Total Units Available in Presentation" as column headings and populate each row.
Instructions for Use (IFU) for U-100 KwikPen, U-100 Junior KwikPen, U-200 KwikPen, and Tempo Pen			
1.	The images of the pen injector appear to be dark gray instead of the taupe color noted in the "How to recognize your LYUMJEV KwikPen (Junior KwikPen or Tempo Pen)" section.	The label should be revised for consistency.	Please revise these images of the pen injectors for consistency with the product description and to accurately represent the product.
Instructions for Use (IFU) for U-200 KwikPen			
1.	The label description could be improved for accuracy.	Lack of clarity may lead to confusion for some users.	Under "How to recognize your LYUMJEV KwikPen", we recommend revising the label description ("white with a blue color bar and checkerboard design") to read as follows: "White with a blue color bar and checkerboard design with "200 units per mL (U-200)" in a yellow stripe."

Table 4: Identified Issues and Recommendations for ELI LILY AND COMPANY (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
General Comments for Carton Labeling and Container Labels			
1.	We note that the use of graphic interferes with the proprietary name, Lyumjev, on your proposed labels and labeling.	The use of images or logos immediately before or after the proprietary name may lead to misinterpretation of the proprietary name. In this instance, the name may be misinterpreted as	We recommend that you revise the presentation of the proprietary name and the graphic so that the graphic does not interfere with the presentation of the proprietary name.

Table 4: Identified Issues and Recommendations for ELI LILY AND COMPANY (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
	(b) (4)		
2.	We note that your labeling does not appear to contain a barcode on the smallest sellable units.	The Drug Supply Chain Security Act (DSCSA) requires certain prescription drugs to have a human-readable and machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (usually the carton) for tracking and tracing purposes.	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 human-readable and machine-readable 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. For example, we noted that your labels do not contain machine readable product identifiers on the smallest sellable units. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.
3.	As currently presented, the format for the expiration date is not defined on your product labeling.	Lack of clarity may lead to confusion for some users and pose risk of deteriorated drug medication error.	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,

Table 4: Identified Issues and Recommendations for ELI LILY AND COMPANY (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
			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.
4.	The usual dose statements are not consistent with the prescribing information and is not in alignment with 21 CFR 201.55	The labeling should be revised to decrease risk of overdose or underdose medication error.	Revise the statements, (b) (4) to read "Recommended Dosage: See prescribing information."
Carton Labeling for Cartridges			
1.	The full product strength (i.e., 100 units per mL) is not displayed on the PDP.	Omission of this information may lead to confusion for some users due to inconsistent phrasing of the product strength.	We recommend revising the product statement (b) (4) to read "100 units per mL (U-100)" for improved clarity and prominence on the label.
2.	The route of administration is not displayed on the PDP per 21 CFR 201.100(b)(3).	Omission of this information may lead to confusion for some users and lead to wrong route medication error.	Add the route of administration to the principal display panel.
3.	Product expiration changes after first use and the post-opening date are not stated on the labeling.	The lack of this information may pose risk of degraded drug product medication error.	We recommend adding the following statement to the carton for clarity: "Discard unused portion of the cartridge 28 days after first opening. Date of first opening: 1: __/__/__. 2: __/__/__. 3: __/__/__. 4: __/__/__. 5: __/__/__.
Container Label for Cartridges			

Table 4: Identified Issues and Recommendations for ELI LILY AND COMPANY (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
1.	The net quantity statement is in close proximity to the product strength statement.	From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.	Relocate the net quantity statement away from the product strength; for example, you can consider moving the net quantity to the top of the PDP near the NDC number.
Carton Labeling for U-100 KwikPen and Tempo Pen			
1.	The net quantity statement is in close proximity to the product strength statement on the PDP and/or side panels for multiple carton and container labels.	From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.	Relocate the net quantity statement away from the product strength; for example, you can consider moving the statement to the top or bottom of the PDP.
Container Labels for U-100 KwikPen, U-200 KwikPen, and Tempo Pen			
1.	The net quantity statement is in close proximity to the product strength statement on the PDP and/or side panels for multiple carton and container labels.	From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.	Relocate the net quantity statement away from the product strength; for example, you can consider moving the statement to the top or bottom of the PDP.
Carton Labeling for the U-100 KwikPen and Tempo Pen Professional Samples			
1.	The product strength is not prominently displayed on the PDP.	Lack of prominence may lead to confusion for some users and may pose risk of underdose or overdose medication error.	We recommend relocating the product strength statements (b) (4) "100 units per mL" (b) (4) for improved visibility of this information. In addition, we recommend revising the statements to read "100 units per mL (U-100)" for improved prominence on the label per 21 CFR 201.15(a)(6).

Table 4: Identified Issues and Recommendations for ELI LILY AND COMPANY (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Container Label for the U-100 KwikPen and Tempo Pen Professional Samples			
1.	The net quantity statement is in close proximity to the product strength statement on the PDP and/or side panels for multiple carton and container labels.	From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.	Relocate the net quantity statement away from the product strength; for example, you can consider moving the statement to the top or bottom of the PDP.

4 CONCLUSION AND RECOMMENDATIONS

Our review of the human factors differentiation study showed that in six instances, patients selected the wrong pen injector. Four of the six selection errors would result in no clinically significant harm, since they involved choosing a different pen presentation of Lyumjev (e.g., U-100 KwikPen was selected instead of U-200 KwikPen). One of the selection errors would also result in no clinically significant harm because the incorrect product was also a short acting, mealtime insulin and would be metabolized in the same way. The remaining selection error involved the selection of a basal insulin instead of the intended Lyumjev. This error may result in moderate symptomatic hyperglycemia similar to underdose.

However, based on the participants' subjective feedback and the Applicant's root cause analysis, it does not appear that any of these selection errors were attributed to aspects of the user interface. Therefore, our review of the HF differentiation study results determined that no changes to the user interface are needed.

Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 3 for the Division and Table 4 for the Applicant. We ask that the Division convey Table 4 in its entirety to the Applicant so that recommendations are implemented prior to approval of this NDA. In this particular instance, we have determined that that these changes can be implemented without additional validation testing to be submitted for review.

4.1 RECOMMENDATIONS FOR ELI LILY AND COMPANY

Our evaluation of the proposed packaging, label, and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 4, and we recommend that you implement these recommendations prior to approval of this NDA. In this particular instance, we have determined that that these changes can be implemented without additional validation testing to be submitted for review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Lyumjev that Eli Lilly submitted on August 28, 2019.

Table 5. Relevant Product Information	
Initial Approval Date	n/a
Therapeutic Drug Class	Insulin
Active Ingredient	Insulin lispro
Indication	To improve glycemic control in adults with diabetes mellitus
Route of Administration	subcutaneous or intravenous[c]
Dosage Form	injection
Strength	100 units/mL and 200 units/mL
Dose and Frequency	Individualize dosage based on route of administration, the individual's metabolic needs, blood glucose monitoring results and glycemic control goal Subcutaneous injection: (b) (4) within 20 minutes after starting a meal
How Supplied	• 100 units/mL (U-100) is available as: o 10 mL multiple-dose vial o 3 mL single-patient-use KwikPen® o 3 mL single-patient-use Junior KwikPen® o 3 mL single-patient-use Tempo Pen™ o 3 mL single-patient-use cartridges • 200 units/mL (U-200) is available as: o 3 mL single-patient-use KwikPen®
Storage	Not in-use (unopened) LYUMJEV vials, pens, and cartridges should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C), but not in a freezer. In-use (opened) LYUMJEV pens and cartridges should be stored at room temperature, below 86°F (30°C) and must be used within 28 days or be discarded
Intended Users	Patients with diabetes mellitus, lay caregivers and healthcare providers, pharmacists for dispensing
Intended Use Environment	Home and healthcare setting

[c] most patients will administer subcutaneously; however, it can also be administered intravenously in a hospital setting under medical supervision.

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS AND COMMUNICATION TO THE APPLICANT

B.1.1 Methods

On November 6, 2019, we searched the L:drive and AIMS using the terms (b) (4) "127210," and "761109" to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified two previous interactions with the Applicant regarding the proposed product:

- On April 17, 2017 we provided the Applicant guidance to submit a comprehensive risk analysis or plans for a Human Factors (HF) Validation Study in preliminary meeting minutes.[d]
- On December 14, 2017 we provided a review with recommendations for a HF validation study protocol and requested that the Applicant address the identified areas of concern prior to commencing the HF validation study.[e]

[d] Cappel-Lynch, C. Preliminary Meeting Minutes for (b) (4) (COR-MEET-05). Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2017 APR 17. IND 127210.

[c] Conrad, A. Human Factors Study Protocol Review for (b) (4) Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 DEC 14. RCM No.: 2017-1965.

APPENDIX C. HUMAN FACTORS DIFFERENTIATION STUDY RESULTS REPORT

\\cdsesub1\evsprod\bla761109\0018\m3\32-body-data\32r-reg-info\medical-device-pen-hf-validation.pdf

APPENDIX D. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On December 26, 2019, FDA requested additional information regarding the recruited pediatric participants, demographic data for the participants, and the moderator guide. The Applicant submitted their response on January 3, 2020.

\\cdsesub1\evsprod\bla761109\0018\m1\us\response.pdf

On January 29, 2020, FDA requested additional information regarding the HFE report regarding the distractor pens used in the differentiation scenarios. The Applicant submitted their response on January 31, 2020.

\\cdsesub1\evsprod\bla761109\0024\m1\us\response.pdf

APPENDIX E. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[6] along with postmarket medication error data, we reviewed the following Cabenuva labels and labeling submitted by Eli Lilly.

- Container labels received on March 12, 2020
- Carton labeling received on March 12, 2020
- Professional Sample Container labels received on August 15, 2019
- Professional Sample Carton Labeling received on August 15, 2019
- Instructions for Use received on March 12, 2020
    - Vial: \\cdsesub1\evsprod\bla761109\0029\m1\us\proposed-ifu-10ml-vial-clean.docx
    - U-100 KwikPen: \\cdsesub1\evsprod\bla761109\0029\m1\us\proposed-ifu-u100-kwikpen-clean.docx
    - U-200 KwikPen: \\cdsesub1\evsprod\bla761109\0029\m1\us\proposed-ifu-u200-kwikpen-clean.docx
    - U-100 Junior KwikPen: \\cdsesub1\evsprod\bla761109\0029\m1\us\proposed-ifu-u100-junior-kwikpen-clean.docx
    - U-100 Tempo Pen: \\cdsesub1\evsprod\bla761109\0029\m1\us\proposed-ifu-u100-tempo-pen-clean.docx
- Prescribing Information received March 12, 2020
    - \\cdsesub1\evsprod\bla761109\0029\m1\us\proposed-uspi-clean.docx

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

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

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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/

JANINE A PURCELL
05/06/2020 02:14:03 PM

ARIANE O CONRAD
05/07/2020 08:10:27 AM

LOLITA G WHITE
05/07/2020 08:28:57 AM

QUYNHNHU T NGUYEN
05/07/2020 09:43:27 AM

MISHALE P MISTRY
05/07/2020 10:40:46 AM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	9/23/2019		
To:	Callie CappelLynch, Senior Regulatory Program Manager		
Requesting Center/Office:	CDER/OND	**Clinical Review Division:**	DMEP
From	David Wolloscheck, PhD, Senior Staff Fellow OPEQ/OHT3/DHT3C		
Through (Team)	Rumi Young, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject	BLA 761109 (b) (4) Rapid Insulin Lispro ICC1900710 00012268		
Recommendation	**Filing Recommendation Date: 9/24/2019** ☐ CDRH did not provide a Filing Recommendation ☑ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: 1/15/2020 ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☑ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 4/13/2020 ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
David Wolloscheck -S Digitally signed by David Wolloscheck -S Date: 2020.04.16 13:46:40 -04'00'	Rumi Young -S Rumi Young -S c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rumi Young -S, 0.9.2342.19200300.100.1.1=2002467913 2020.04.16 15:49:51 -04'00'	

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761109
Sponsor	Eli Lilly
Drug/Biologic	(b) (4) Rapid Insulin Lispro
Indications for Use	Treatment of Type 1 and Type 2 Diabetes Mellitus
Device Constituent	Pen-Injector
Related Files	IND 127210/ICC1900239

Review Team		
Lead Device Reviewer	*David Wolloscheck, PhD*	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**
N/A		

Important Dates	
Discipline-Specific Review Memos Due	4/15/2020
Final Lead Device Review Memo Due	05/04/2020
Interim Due Dates	**Meeting/Due Date**
Filing	10/14/2019
74-Day Letter	10/28/2019
Mid-Cycle	01/15/2020
Primary Review	05/04/2020
Internal Meeting(s)	09/24/2019 CMC Kickoff, 09/25/2019 Filing Meeting; 05/06/2020 Wrap-Up

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☑ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	X			No deficiencies
Labeling	X			No deficiencies
Design Controls	X			No deficiencies
Risk Analysis	X			No deficiencies
Design Verification	X			No deficiencies
Consultant Discipline Reviews			X	Not applicable
Clinical Validation	X			No deficiencies
Human Factors Validation			X	Deferred to CDER
Facilities & Quality Systems	X			No deficiencies

2.1. Comments to the Review Team

☐ CDRH does not have any further comments to convey to the review team.

☑ CDRH has the following comments to convey to the review team:

Comment #1: This review pertains to the Prefilled Autoinjectors only (i.e., 100 U Pen, 100 U half-dose Pen, 100 U Tempo Pen, and 200 U Pen). The standalone cartridge is not in scope of this review. Note that Lilly stated that plunger breakloose and glide forces are tested on the cartridges at release (3.2.R.4.1). We defer to CDER regarding the stability data of single cartridges.

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

TABLE OF CONTENTS

3. PURPOSE/BACKGROUND

3.1. Scope

Eli Lilly is requesting approval of (b) (4) Rapid Insulin Lispro. The device constituent of the combination product is a Pen-Injector.

CDER/OND has requested the following consult for review of the device constituent of the combination product:

A new BLA for (b) (4) rapid insulin lispro has been received. This product will be available via a prefilled pen device. Please review device details in the BLA and provide a recommendation for approval of the marketing application. This product was reviewed under IND 127210.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

Device performance, Biocompatibility of the pen-injector

This review will not cover the following review areas:

Biocompatibility of the container closure/fluid path, Human factors

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

CDRH has reviewed Lilly's KwikPens before under the Humalog NDA. The Sponsor stated that the devices are the same in terms of the mechanics responsible for the performance of the device.

3.2.1. Related Files

NDA 020563/ICC1900299

3.3. Indications for Use

Combination Product	Indications for Use
(b) (4) Rapid Insulin Lispro	Treatment of Type 1 and Type 2 Diabetes Mellitus
Pen-Injector	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
001 (original submission)	3.2.P, 3.2.R
0012 (Response to IR#1)	Whole Sequence
0026 (Response to IR#2 – 7)	Whole Sequence
0032 (Removal of Connectivity Comparability Protocol)	Whole Sequence

4. DEVICE DESCRIPTION

4.1. Device Description

Eli Lilly is proposing a set of four pen-injectors for the subcutaneous injection of (b) (4) rapid insulin lispro in two different drug strengths. The injectors are based on the KwikPen platform also used in Humalog and Humulin. The following presentations are proposed:

- 100 U/mL Pen-Injector, 10 µL Dose Increments
- 100 U/mL Junior Pen-Injector, 5 µL Dose Increments
- 200 U/mL Pen-Injector, 10 µL Dose Increments
- 100 U/mL Tempo Pen-Injector, 10 µL Dose Increments

Eli Lilly stated that the intended use and indications for use for the 100 U/mL Pen-Injector and 100 U/mL Tempo Pen-Injector are identical and that *Lilly does not intend to add any indications to the USPI other than listing Tempo Pen as another product presentation.* In a recent meeting request (IND 127210/ICC1900239), the Sponsor introduced a (b) (4) Pen (also referred to as Tempo Pen) that may be used with an external data transfer module. However, this data module is not included in this submission. Notably, Lilly included several Comparability Protocols in this submission (b) (4)

(b) (4)

Lilly stated that, as a stand-alone device, the tempo pen confers no new features and may be used interchangeably with the 100 U/mL Pen.

Lilly provided the following flowchart of the Container Closure Presentations:

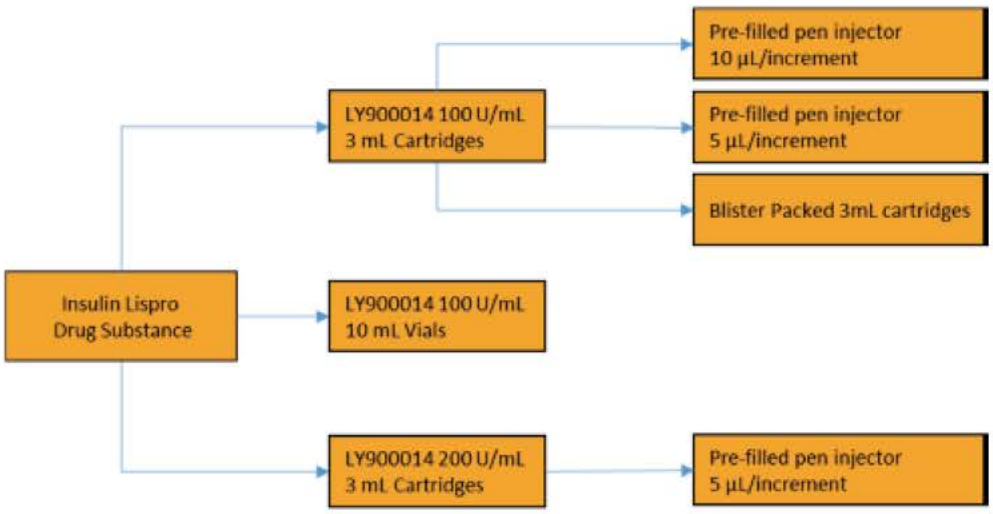


Figure 2.3.I-1 Container Closure System and Presentation

The following images of the Pen-injectors were included in 2.3.R:

In addition to the above images, Lilly also provided an exploded view of the Pen-Injector:

Figure 2.3.R.3-5 LY900014 Injection External Patient Contact Components

The Pen-Injectors are filled with 3 mL clear, glass cartridges. The device is used with "compatible Needles" with Lilly recommending needles from Becton, Dickinson and Company. Lilly provided the following list of materials for the pens and the respective patient contact classification for each material:

Table 3.2.R.2.3-1 LY900014 Injection U-100 Pre-Filled Pen Component Materials

	Component	Material/Base Resin
External Patient Contact Components	Dose Knob	(b) (4)
	Pen Cap	
	Cartridge Holder	
	Dial	
	Housing	
Internal Components		

UPDATE 03/26/2020: Lilly filed a new sequence for the NDA that removes the comparability protocol (b) (4) Sequence 0032 effectively removed this comparability from the submission.

4.2. Steps for Using the Device

The following description of the mechanism of operation was provided by the Sponsor in 2.3.R of the submission:

The LY900014 Injection pre-filled pens are used the same way as all other marketed KwikPens. Prior to injection, the user installs a pen needle to the cartridge holder. The user dials the intended dose by twisting the dose knob until the intended dose number is visible in the device window. If the patient dials beyond the desired dose setting, the pen allows the patient to dial backward to the correct setting. The user inserts the needle into the skin and injects by depressing the dose knob all the way in and holding for 5 seconds. Dose completion is confirmed by the "0" appearing in the dose window. The needle is then removed from the pen and discarded.

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The Sponsor has provided a full description of the device. No further deficiencies are identified.		

CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No

5. FILING REVIEW

CDRH performed Filing Review ☑ **Finalize Filing Review Section**	☑
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Filing Review Checklist				
Description		**Present**		
		Yes	**No**	**N/A**
Description of Device Constituent		X		
Device Constituent Labeling		X		
Letters of Authorization				X
Essential Performance Requirements defined by the application Sponsor		X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing		X	
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)			X
	Reliability			X
	Biocompatibility	X		
	Sterility			X
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors	X		
	Shelf Life, Aging and Transportation	X		
	Clinical Validation	X		
	Human Factors Validation	X		
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		
	CAPA Procedure	X		
	Control Strategy provided for EPRs	X		

Reviewer Comment

Eli Lilly has provided summary level information of all design verification activities. Additional test reports may be necessary during the review (i.e., dose accuracy test reports, activation force testing, biocompatibility test reports, etc.). These should be available from the Sponsor and should not be a filling issue. The Sponsor identified the essential performance requirements of the device as dose accuracy and needle compatibility. Per the submission, other specifications, like injection force, dial torque, etc., are identical to the already marketed KwikPens and do not require additional verification testing. However, as noted below, the data for these performance attributes should still be provided in the submission or leveraged from another submission with a rationale (including a LoA and exact location of test result).

5.2. Facilities Information

Firm Name:	Eli Lilly and Company
Address:	Lilly Corporate Center, Indianapolis IN, 46285 USA
FEI:	1819470
Responsibilities:	Drug Substance: Fermentation, Granule Recover, Concentrate, Purification, Control Facility. Drug product manufacturing process for 10 mL vials and 3 mL cartridges: formulation, primary packaging, in-process testing, final drug product testing, stability testing. Assembly of pre-filled pen device with 3 mL cartridge; final packaging of device, device testing.

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☑ Inspection was conducted 3/5/2019 to 3/5/2019. The inspection covered medical device QS and was classified NAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☐ A choose an item inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm Choose an item.

☑ An inspection is not required because A recent medical device inspection of the firm was acceptable.

Firm Name:	Lilly France
Address:	Z.A - Centre de production, 2 rue du Colonel Lilly, Fegersheim, 67640 France
FEI:	3002807475
Responsibilities:	Blister packaging of 3 mL cartridge product, pre-filled pen assembly, final packaging of device, device testing.

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☑ Inspection was conducted 2/11/2019 to 2/19/2019. The inspection covered drug CGMP and was classified VAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☑ A pre-approval inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm has not been performed.

☐ An inspection is not required because Choose an item.

5.3. Quality System Documentation Triage Checklist

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☑ No ☐ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☑ No ☐ UNK
Is the final combination product meant for emergency use?	☐ Yes ☑ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☐ Yes ☑ No ☐ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☑ No ☐ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☐ Yes ☑ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☑ No ☐ UNK
cGMP Risk:	
☑ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☐ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

Reviewer Comment

Lilly stated that it uses a drug based cGMP streamlined approach for compliance with the quality systems. Summary level information of management controls, design controls, purchasing controls, and CAPA are provided by the Sponsor in 3.2.P.3. The product is not intended as an emergency use drug for hyperglycemia. However, adverse events may still occur if the device does not deliver the intended dose.

5.4. Filing Review Conclusion

FILING REVIEW CONCLUSION

Acceptable for Filing: ☑ Yes ☐ No (Convert to a RTF Memo) ☐ N/A

Facilities Inspection Recommendation:
☑ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance
☐ No Inspection ☐ N/A

Site(s) needing inspection: Lilly France, FEI: 3002807475
Reviewer Comments The BLA is acceptable for filing. From the information provided, Lilly is leveraging the majority of the V&V data from the previously approved KwikPens (e.g., Humalog) and should have any missing test reports readily available. The Sponsor has identified the EPRs as dose accuracy and needle compatibility and provided summary test results that suggest that the pens meet ISO 11608. The Sponsor is relying on a completed phase 3 study with the subject pen and the commercial history of other KwikPen products for the design validation. 74-day letter deficiencies will be sent to the Sponsor to request full test reports for the design verification activities.
Refuse to File Deficiencies: ☐ Yes ☑ No ☐ N/A **74-Day Letter Deficiencies:** ☑ Yes ☐ No ☐ N/A

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors			X
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X

MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments

The labeling contains all relevant sections/symbols. (b) (4) The labeling is acceptable.

6.2. Device Specific Labeling Review

Device Specific Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Injector description including name	X		
Intended use and indications for use	X		
Type-of-use for the injector	X		
Intended patient population	X		
Contraindications	X		
Warnings, limitations, and precautions	X		
Safety and effectiveness data accrued with use of the injector	X		
Areas of the body appropriate for injection	X		
Target tissue and injection sites	X		
Directions for use	X		
Assembly instructions and diagrams	X		
Maintaining sterility during injector assembly			X
Dose setting and administering an injection	X		
How to ensure that the full dose is delivered	X		
How to ensure that a full dose remains in a reusable prefilled injector	X		
Prevention of or remedy for incomplete or partial dosing or overdosing events	X		
The correct amount of pressure needed for an injection			X
Information about injection depth			X
Labeling recommendations for sharps injury prevention features	X		
Environment conditions of use and storage	X		
Reuse, cleaning, servicing			X
Proper safe biomedical sharps waste disposal instructions	X		
Troubleshooting	X		
Life of the injector and critical components	X		

Reviewer Comments

The labeling includes the recommended information per the 2013 FDA guidance *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products*. The Sponsor recommends the use of BD pen needles with the device, hence the exact injection depth will depend on the chosen needle.

6.3. Clinical Labeling Review

The following Clinical Labeling Review was completed by
- ☐ Insert Consultant Name ; The full memo is located in Appendix B.
- ☑ The Lead Reviewer

Below is a summary of the review & recommendation:

The device does not warrant any specific clinical labeling.

6.4. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

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	
Mitigations are adequate to reduce risk to health		X	
Version history demonstrates risk management throughout design / development activities		X	
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)	X		
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		
Bioequivalence Study utilized to-be-marketed device			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 study)	X		
Traceability demonstrated for specifications to performance data	X		

Reviewer Comments
The Sponsor has not provided a risk analysis (dFMEA) for the device. Though the device has a history of safe use, the functional components are the same as in the Humira Kwikpen, it is premature to comment on the overall design control process without additional documentation. Please see IR#2 for details.

7.2. Design Inputs and Outputs

Essential Performance Requirements

Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)
Dose Accuracy	Comply with ISO 11608-1
Needle Compatibility	Assessed through dose accuracy testing. This was agreed on in a prior meeting request. The Pen Injectors are labeled for use with BD needles which are ISO 11608-2 compliant.
Glide Force/Actuation Force	Average (b) (4) lb-f; NLT (b) (4) and NMT (b) (4) lb-f

Reviewer Comments

The Design inputs cover the device attributes that are typically associated with essential performance requirements of pen injectors. The design outputs appear reasonable and are similar to specifications used in other Lilly KwikPen products. This is acceptable.

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Used ISTA 3A – Acceptable per ISO 11607-1
IEC 60601-1-2:2014	NA
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	N
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	NA
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	NA
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	N

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
ISO 13485:2016 ***Medical devices – Quality management systems – Requirements for regulatory purposes***	**N**	**Y**

Compliance to ISO 11608-1:

The Sponsor provided the following design requirements and a rationale of how these demonstrate compliance to ISO 11608-1:

Table 3.2.R.3.2-1 ISO 11608-1:2014 General Design Requirements for Needle-Based Injection (NIS) Systems

ISO 11608-1:2014 General Design Requirements	Compliance	Verification Data
a The container holder shall allow visibility of the deliverable volume. The manufacturer shall determine, by risk analysis, if a residual scale is required and how much of the deliverable volume shall be visible.	The cartridge holder is molded in clear (b) (4) and allows viewing of the cartridge contents throughout the deliverable volume.	This requirement is verified by virtue of successful visual inspection.
b With the exception of system designations B2 and D2, NISs shall be designed in such a way that they are able to accurately deliver the entire labeled volume from the container for which they are designed.	The pen injector is designed to deliver the labeled volume from the cartridge.	This requirement is verified by virtue of successful design verification testing, including dose accuracy testing.
d When the injection system requires the user to pre-set the dose, the injector shall provide an indication of the dose that has been set. This information can be displayed in drug-specific units or in a setting specified by the physician as appropriate for the drug to be delivered. When the dose has been pre-set by the manufacturer, the dose can be indicated by the device or the system labeling, as appropriate.	The pen injector displays the dose that has been pre-set by the user in international units. The pre-set dose is displayed in the Dose Window.	This requirement is verified by virtue of successful dose accuracy testing.
e There shall be an indication of the pre-setting by visual and either tactile and/or audible means.	The pen injector visually indicates that it is ready for injection by displaying the pre-set dose in the dose window. Each dose increment has an audible click and tactile resistance.	This requirement is verified by virtue of successful dose accuracy testing, and the inherent design of the device platform.
f The NIS shall indicate, at least by visual means, that it is ready for injection.	The pen injector visually indicates that it is ready by displaying the pre-set dose in the dose window.	This requirement is verified by virtue of successful dose accuracy testing.
g The state of the NIS, when ready to deliver a dose, shall be different from its state when the dose has been delivered. The difference shall be visible.	When the pen injector is ready to deliver a dose, the Dose Knob is extended. After delivering the dose, the Dose Knob returns to the undialed position with “0” in the dose window.	This requirement is verified by virtue of successful dose accuracy testing.

ISO 11608-1:2014 General Design Requirements	Compliance	Verification Data

h The NIS shall indicate by visual, audible, or tactile means, or any combination of these, that the injection stroke has been completed.	As the Dose Knob is manually pushed toward the pen injector and the dose is completed, a "0" is visible in the dose window when the Dose Knob's travel stops.	This requirement is verified by virtue of successful dose accuracy testing
j Variable multi-dose NIS (system designations A and C) shall be designed so that they: Do not allow a larger dose to be pre-set than is left in the container, or Do not allow dose delivery if the pre- set amount exceeds the amount of medicinal product left in the container, or Indicate the amount of medicinal product delivered, or Indicate the amount of medicinal product not delivered (of the pre-set dose).	The pen injector will not allow the patient to dial a dose that is larger than the amount of medicine remaining in the cartridge.	This requirement is verified by virtue of successful last dose dose accuracy testing.
l The NIS shall be designed to function with its specified needles. ISO 11608-2 provides guidance for needles.	The pen injector is designed, tested, and in compliance with the ISO 11608-1 standard using Becton Dickinson (BD) pen needles, which are compliant to ISO 11608-2.	This requirement is verified by virtue of successful dose accuracy testing.
m The NIS shall be designed to function with its specified containers. ISO 11608-3 provides guidance for containers.	The pen injector is designed, tested, and in compliance with the ISO 11608-1 standard using Lilly 3 mL drug cartridges, which are compliant to ISO 11608-3.	This requirement is verified by virtue of successful dose accuracy testing.
u Adverse effects of the medicinal product contact with the NIS shall be assessed and mitigated through risk assessment.	Components of the pen injector do not contact the drug product.	Device functionality is confirmed after contact with drug product.
v Biological requirements of the NIS shall be established in accordance with ISO 10993-1. Note: It is preferable that the design process incorporate environmentally conscious design.	User contact materials have been evaluated in accordance with ISO 10993-1.	This requirement is verified by virtue of successful biocompatibility testing.

General requirements c, i, k, n, o, p, q, r, s, t, and w do not apply and are not listed in the table.

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments Though the Sponsor said a risk analysis was conducted on the device, Lilly has not provided any documentation. Hence, an IR will be issued to provide the completed dFMEA. See Risk Analysis Section below for details.		

CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No

8. RISK ANALYSIS

8.1. Risk Management Plan

Lilly provided residual risk reports in Sequence 0026 as a response to IR#6. The Sponsor stated that the risk assessments are conducted according to ISO 14971:2012 as well as two internal documents. FMEAs are used for the risk management process. The FMEA items were evaluated according to the following:

- *Risks in the green region (referred to as "low risk") are generally considered to have a positive risk/benefit ratio and to be acceptable from the perspective of patient safety. Line items with SEV ≤ 2 are generally considered low risk (may cause discomfort or minor harm).*
- *Risks within the yellow region (referred to as "medium risk") are undesirable; reasonable efforts must be made to reduce them as low as possible, based on the state-of-the-art technology. When this is not possible, present the risks to the Device Safety Lead Team (DSLT) and provide justification of why the risk cannot be mitigated further and why the medical benefit outweighs it. The risks may be accepted at the discretion of the DSLT.*
- *Risks within the red region (referred to as "high risk") are considered unacceptable; make every effort to reduce them. However, if risk reduction is impossible, risks may be accepted at the discretion of the DSLT provided a medical risk benefit analysis indicates that the medical benefits outweigh the associated risks.*

Table 7.2 Risk Acceptability Criteria Matrix

Probability of Harm							
	Frequent (Prob. 5)	AFMEA	0	0	0	0	0
		DFMEAs	0	0	0	0	0
		PFMEAs	0	0	0	0	0
	Probable (Prod. 4)	AFMEA	0	0	0	0	0
		DFMEAs	0	0	0	0	0
		PFMEAs	2	0	0	0	0
	Occasional (Prob. 3)	AFMEA	2	0	3	0	0
		DFMEAs	12	0	0	0	0
		PFMEAs	11	4	0	0	0
	Remote (Prob. 2)	AFMEA	8	3	35	7	0
		DFMEAs	272	0	149	1	0
		PFMEAs	166	28	233	5	0
	Improbable (Prob. 1)	AFMEA	0	3	18	1	4
		DFMEAs	36	0	35	25	6
		PFMEAs	254	35	415	56	76
			Negligible (SEV 1)	Minor (SEV 2)	Moderate (SEV 3)	Major (SEV 4)	Severe (SEV 5)
			Severity of Harm				

Reviewer Comments

The overall risk management approach utilized by the Sponsor is acceptable. ISO 14971 *Medical Devices – Applications of Risk Management to Medical Devices* is an FDA recognized standard and the use of FMEAs in the risk assessment is commonly utilized for similar products. Note that an SAC is not necessary for this type of medical device.

8.2. Hazard Analysis and Risk Summary Report

The following residual risk summary table was provided:

Table 7.1. Residual Risk Summary Table

FMEA		Number of Low Risk Residual Risks	Number of Medium Risk Residual Risks	Number of High Risk Residual Risks
AFMEA	(b) (4) Rapid Insulin (URI) KwikPen AFMEA_2	70	14	0
DFMEA	(b) (4) Rapid Insulin (URI) U100 KwikPen DFMEA_2	263	4	0
	(b) (4) Rapid Insulin (URI) U200 & HU KwikPen DFMEA_2	266	3	0
PFMEA	A1 – A2 Wet PFMEA_9	265	22	0
	A1 – A2 Pen Inspection System pFMEA_3	32	17	0
	A1 Packaging (TenPack) pFMEA_3	16	0	0
	A1 – A2 Packaging PFMEA_4	174	0	0
	A1 – A2 Labeler PFMEA_3	45	19	0
	(b) (4) 1 Cap Cartridge Holder Labeler pFMEA_4	63	1	0
	Dry Side PFMEA All Stature_5	422	18	0
	Dial Printing PFMEA U100/U500/Extend_3	102	0	0
	(b) (4) Dial Printing at (b) (4) and (b) (4) _3	85	4	0
Total		1803	102	0

In Section 9 of the residual risk report, the Sponsor summarized that the majority of risks of the subject devices are identical to the risks reported for other KwikPens. Section 9.2 highlights unique risks to the LY900014 pens. These unique risks are related to the device label, housing, cap, dose knob color, dose knob geometry, and differences in the drug products. A brief summary of the evaluation is included below:

- Lilly concluded that the change in color of the device does not produce any additional risks. The biocompatibility of the new colorant was evaluated per ISO 10993-1 and an analysis demonstrated that the new colorant did not affect the performance of the device.
- The drug product includes a new constituent treprostinil that is, per the submission, (b) (4) This results in a new risk if the wrong product is delivered that was classified as low risk (severity 2) mainly because of the low probability of occurrence as several mitigations are implemented for this risk.

The following unique risk was identified that represents a moderate risk compared to other KwikPen products:

Use Step	Use Error	Potential Harm	SEV-Prob of Harm	Comments	Risk Mitigation
Give injection – Press dose knob until dose window shows "0"	User administers dose at wrong time.	Dosage: Mismatch between subject glucose levels and PK profile of drug SEV=4. May Result in SEVERE HYPOGLYCEMIA requiring the assistance of a third party	4-2	DSLT Reviewed and approved 04-Oct-2018. DSLT and Lilly medical support updating OCC to 2 for this risk based on Phase 3 Clinical data from PRONTO-T1D (I8B-MC-ITRM) and PRONTO-T2D (I8B-MC-ITRN).[5]	Prevention: Dosing instructions in the drug labeling

This risk is related to the fast acting nature of this drug product and was determined to be acceptable based on a risk-benefit analysis.

Risk assessment of the Temp Pen

The Sponsor submitted a separate risk management plan for the tempo pen. The Sponsor stated that design differences between this pen and the other KwikPens result in new risks related to (b) (4) Lilly stated that all unique risks were classified as low risks. One concern is the (b) (4) (b) (4)

(b) (4) The device was found acceptable. Hence, the additional risk related to the (b) (4) appears acceptable.

Reviewer Comments

The Sponsor provided risk management documentation in response to IR#6. The Sponsor highlighted new and modified risks as a result of design changes between the subject device and the Humalog KwikPens. Overall, it appears that the Sponsor has adequately assessed and mitigated the risks posed by the device.

8.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments Lilly has not provided a risk analysis for the device. Please see IR#6 for details. **Update:** Lilly provided risk management documentation in response to IR#6. The documentation was reviewed and found acceptable.		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent: 1/14/2020	**Date/Sequence Received:** 2/24/2020
Information Request #6	You have not included a risk analysis for the device constituent parts of the combination product. Provide a risk analysis (e.g., FMEA) for the pen-injectors.	
Sponsor Response	**Lilly Response to Question 5** Residual risk reports will be submitted as part of this sequence. **Table Q5-1 Residual risk reports**	

LY900014 Pen Type	**Applicable Residual Risk Report**
U-100 KwikPen, U-200 KwikPen, KwikPen Junior	PDS-DHF_DMR-01314 v0
Tempo Pen	PDS-DHF_DMR-01479 v0

Reviewer Comments	The Sponsor provided a risk analysis for the four device presentations. This is acceptable. Please see section 8 of this memo for a review of the provided information.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

9.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Dose Accuracy	Compliance with ISO 11608-1 ± the dialing resolution (1 Unit for U-100, U-100 tempo, and U-200; 0.5 Units for U-100 Junior) Or ± 5% of target dose whichever is greater.	Yes Testing was done on preconditioned devices by measuring gravimetrically the amount of expelled drug at different target doses. Test volumes: U-100 and U-100 Tempo 0.01 mL, 0.30 mL, and 0.60 mL U-200 and U-100 Junior 0.005 mL, 0.15 mL, and 0.30 mL	Yes Same Dose accuracy specifications used for pen injector in phase 3 clinical studies.	Yes Data was provided for pre-filled Humalog Kwikpens. **Update 4/12/2020:** The Sponsor provided stability data in the response to IR#3.	Yes Testing was done after preconditioning per ISTA 3A. In addition, testing per ISO 11608-1 includes preconditioning similar to simulated shipping.
Needle Compatibility	ISO 11608-2 compliant needles are compatible with the injector.	Yes Lilly stated that needle compatibility is an essential performance requirement, since dose accuracy is dependent on it. However, needle compatibility testing was not done apart from dose accuracy testing. The Sponsor stated that testing was done on different BD needles, but the test	Same as dose accuracy	Same as dose accuracy	Same as dose accuracy

		reports were not included in this submission. **Update 4/13/2020:** The Sponsor provided dose accuracy testing with different needles in response to IR#4.			
Glide Force (Device Actuation Force)	Average glide force (b) (4) lbs and glide force is NLT (b) (4) bs and NMT (b) (4) lbs	Yes Testing was done on preconditioned devices. Glide force measurements are taken concurrently with dose accuracy measurements and are provided for devices that underwent the same pre-conditioning.	Yes Specifications are identical to the cleared Humalog Kwikpen and the intended use population is the same.	Yes, provided in 3.2.P.8.3	Same as dose accuracy

Reviewer Comment

9.1.2. Verification of Design Inputs Evaluation

Design Input	Design Output	Verification Method	Results/Deviations	Adequately Verified (Y/N)	Validated through Clinical, Human Factors or Other	Adequately Validated (Y/N)
Dose Accuracy	Compliance with ISO 11608-1 ± the dialing resolution (1 Unit for U-100, U-100 tempo, and U-200; 0.5 Units for U-100 Junior)	Yes Testing was done on preconditioned devices by measuring gravimetrically the amount of expelled drug at different target doses. Test volumes: U-100 and U-100 Tempo 0.01 mL, 0.30 mL, and 0.60 mL	Results show that the Pens meet the dose accuracy specifications of ISO 11608 including last dose and service/use life (84 injections).	Yes	Yes Same Dose accuracy specifications used for pen injector in phase 3 clinical studies.	Yes

	Or ± 5% of target dose whichever is greater.	U-200 and U-100 Junior 0.005 mL, 0.15 mL, and 0.30 mL				
Needle Compatibility	ISO 11608-2 compliant needles are compatible with the injector.	Yes, method is identical to dose accuracy testing. Lilly stated that needle compatibility is an essential performance requirement, since dose accuracy is dependent on it. However, needle compatibility testing was not done apart from dose accuracy testing. The Sponsor stated that testing was done on different BD needles, but the test reports were not included in this submission.	Provided in response to IR#4. A representative KwikPen met dose accuracy requirements per ISO 11608-1 with a 29Gx12.7mm needle, 31Gx5mm needle, and 32Gx4mm needle.	Y	Same as dose accuracy	Yes
Cap removal force	NLT (b) (4) N; NMT (b) (4) N	Yes, see below for a review of the method.	Devices meet the specifications (mean force was 9.36 ± 0.86 N)		Sponsor stated that the specifications are identical as for the commercially available Humalog KwikPens and that the design is functionally the same between the two pens.	Yes
Dialing torque	The maximum average dialing torque is (b) (4) N*mm	Yes, see below for a review of the method.	Devices meet the specification (results reported between 14.55 and 19.04 N*mm)		Sponsor stated that the specifications are identical as for the commercially	

					available Humalog KwikPens and that the design is functionally the same between the two pens.	
Glide Force	Average glide force (b) (4) lbs and glide force is NLT (b) (4) lbs and NMT (b) (4) lbs (**Reviewer Comment:** Force should be designated as lbf not lbs).	Yes, see below for a review of the method.	Devices meet specification (results reported between 1.94 lbf and 4.51 lbf)		Sponsor stated that the specifications are identical as for the commercially available Humalog KwikPens and that the design is functionally the same between the two pens.	

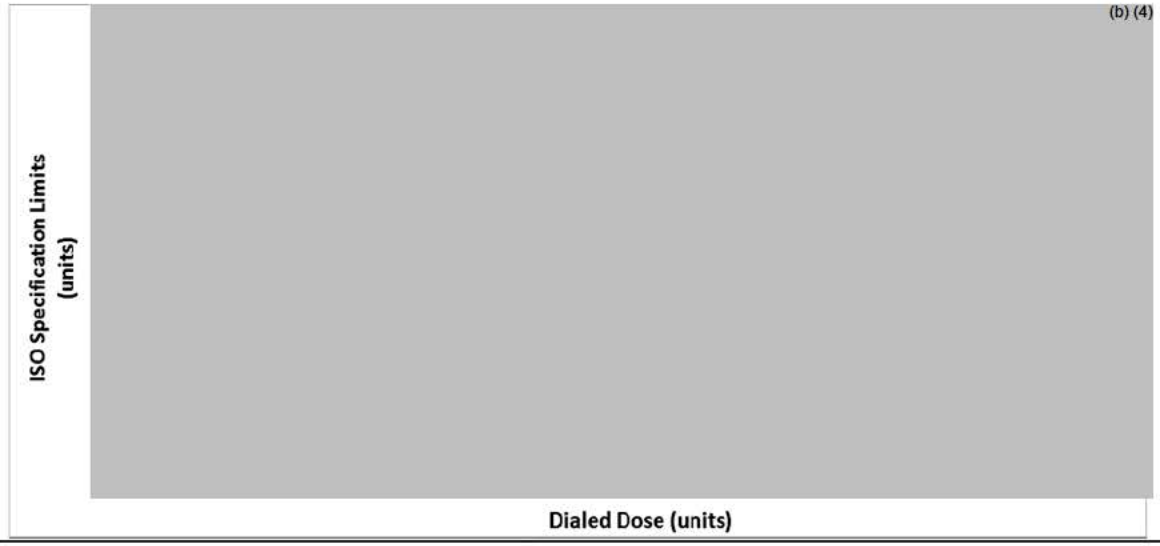
Lilly stated that the mechanical portions of the device are identical to other KwikPens and all share the same specifications. Since the approved Humalog and the subject product have the same intended patient population, this is an acceptable validation rationale.

Reviewer Comment

Lilly is not assessing the force required to successfully administer an injection. This performance attribute is normally considered an essential performance requirement and should be assessed. Based on a review of stability and release testing protocols, the Sponsor is assessing glide force of the primary container closure (cartridge). It is possible that this force directly translates to the injection force of the assembled, final product. An IR will be issued to request that injection force be tested or a rationale with supporting data that the cartridge glide force directly corresponds to the injection force. Please see IR#2 for additional information.

9.1.3. Evaluation of Test Methods

Title:	Dose Accuracy

Scope/Objective & Acceptance Criteria:	The objective of the method is to determine that the dose accuracy of the injector is compliant with ISO 11608-1. In addition, the Sponsor uses this test to verify compatibility with BD pen needles. The following was provided by the Sponsor regarding the acceptance criteria: *The ISO 11608-1:2014 specification limits are ± the dialing resolution (DR) or ±5%, whichever is greater. Because the LY900014 Injection U-100 pre-filled pen has a 1-unit DR, the standard establishes dose accuracy specification limits of (b) (4) mL (1 unit) for doses at or less than (b) (4) An illustration of the ISO 11608-1:2014 specification limits applied to this pen is shown in Figure 3.2.R.3.2-1.* 
Methods	*Visual and Functional Testing* *After the assembled pens were conditioned as described in Table 3.2.R.3.2.-2, the pens underwent the following visual/functional inspection. The pens passed the visual/functional inspection requirements described in ISO 11608-1:2014.* *Visual inspection was done under normal or corrected-to-normal vision to ensure any markings on the device essential for the safe use of the device are visible, easily legible and indelible after preconditioning. Additionally, devices were inspected for the following significant defects:* • *markings (that impact the safe functioning) no longer visible or easily legible;* • *cracks in the body and/or component of the device that may impact safe functioning;*

- *compromised assembly bonds, joints and alignments that may impact safe functioning.*

Basic pen functionality was tested by performing the following actions:

- *removing the cap*
- *dialing up to maximum dose*
- *dialing down to zero*
- *attaching the cap*

Dose Accuracy Testing Method

After conditioning and the visual/functional inspection, pens were prepared according to the instructions in the test method, which are derived from the proposed Instructions for Use (IFU), which describe the procedure for attaching a needle and priming. ISO 11608-2 compliant Becton Dickenson & Company needles were used. The pens were "dosed" by expelling fluid into a pan. The mass of the expelled fluid was measured gravimetrically in grams.

As outlined in Section 6.1 of ISO 11608-1:2014, all doses were converted to volumes by using the density, ρ, of the test fluid at environmental conditions. Once the data was collected and converted to volume, the mean, x_{bar}, and standard deviation, s, were calculated for each data set.

As described in Section 4 of ISO 11608-1:2014, the, k value, or tolerance limit factor, was, "determined from the confidence level (95%), probability content, p, and number of accuracy measurements, n, conducted at each dose setting." The tolerance intervals were calculated as described in Section 7.4.5 of ISO11608-1:2014 using the formula $x_{bar} \pm k\,s$ and compared to the specification limits.

Results:

Table 3.2.R.3.2-3 ISO 11608-1:2014 Dose Accuracy Testing Results

Dose Setting (units)	Test Description	*n*	Observed Mean[a], x_{bar}	Standard Deviation[a], *s*	Specification Limits	Tolerance Interval[c] $x_{bar} \pm k\,s$	Confidence/ Probability, p[b]
1	Standard (23°C)	60	1.08	0.08	(b) (4)	0.9 - 1.3	95%/0.975
1	Cool (5°C)	60	1.06	0.05		0.9 - 1.2	95%/0.975
1	Warm (40°C)	60	1.11	0.09		0.9 - 1.4	95%/0.975

					(b) (4)		
1	Free Fall	21	1.12	0.07		0.9 - 1.3	95%/0.95
1	Cold Storage	60	1.08	0.08		0.9 - 1.3	95%/0.975
1	Vibration[d]	19	1.11	0.10		0.8 - 1.4	95%/0.95
20	Last Dose	60	19.70	0.15		19.3 - 20.1	95%/0.975
30	Standard (23°C)	60	29.91	0.21		29.3 - 30.5	95%/0.975
30	Cool (5°C)	60	29.95	0.17		29.5 - 30.4	95%/0.975
30	Warm (40°C)	60	29.74	0.20		29.2 - 30.3	95%/0.975
30	Free Fall	21	29.92	0.17		29.5 - 30.4	95%/0.95
30	Cold Storage	60	29.91	0.21		29.3 - 30.5	95%/0.975
30	Vibration[d]	19	29.94	0.19		29.4 - 30.5	95%/0.95
60	Standard (23°C)	60	59.83	0.36		58.9 - 60.8	95%/0.975
60	Cool (5°C)	60	59.90	0.31		59.1 - 60.7	95%/0.975
60	Warm (40°C)	60	59.45	0.38		58.4 - 60.5	95%/0.975
60	Free Fall	21	59.78	0.37		58.8 - 60.8	95%/0.95
60	Cold Storage	60	59.80	0.37		58.8 - 60.8	95%/0.975
60	Vibration[d]	19	59.71	0.37		58.7 - 60.7	95%/0.95

[a] For ease of review, volumetric data has been converted to units by multiplying the fluid volumes by 100 units/mL.
[b] Corresponding k value is 2.670 for all testing except for Free Fall (k = 2.731) and Vibration (k = 2.793).
[c] Tolerance Interval is a function of confidence and probability content. For example, the first result in the table indicates that with 95% confidence, 97.5% of doses would be between 0.9 and 1.3 units.
[d] During vibration conditioning, one device escaped the fixture and was not assessed for dose accuracy.
The k-value of 2.793 corresponds to 95% confidence/0.95 probability content for n = 19.

Conclusions/ Reviewer Comments:	Testing was conducted on devices with the intended drug product. The testing included the recommended pre-conditioning and sample sizes per ISO 11608-1 table 3 – Test Matrix. ISO 11608-1 requires that dose accuracy testing be done to assess different "zones" of the cartridge. The Sponsor provided the following testing data to assess the dose accuracy at different zones and (b) (4) (b) (4) This rationale does not appear to be adequate. ISO 11608-1 specifically states that multi-dose injectors should assess dose accuracy at different regions within the cartridge. The summary test data provided does not account for free fall or vibration preconditioning. In addition, the rationale does not assess the 1 unit per click device (the tempo and 100U pen share the same functional design, in addition the 200U and 100U junior pen share the same functional design). Hence an IR will be sent to the Sponsor to provide dose accuracy data at different regions of the cartridge for the pen injectors. **Update:** Lilly has responded to this in IR#4. Please see the discussion in the IR below for details.

Acceptable:	☒Yes ☐No

Title:	Cap Removal Force
Scope/Objective & Acceptance Criteria:	*This method will provide the Cap Removal Force testing procedure for the KwikPen Platform.* *Pass if:* *The k-values are greater than or equal to (≥) the target k-value in Table 1. If the k-value is less than the target k-value, the Responsible Engineer must be contacted to determine if corrective action is required. The decision of the Responsible Engineer must be documented.* Specification: NLT (b) (4) N; NMT (b) (4) N
Methods	*The KwikPen Cap Removal Force Test method measures the amount of force required to remove the cap from cartridge holder by pushing a rod against the inside of the cap until the force drops. (b) (4) 2031070-2010-001 (b) (4) established the parameters and fixture for this test method. This method was transferred based on this development to our Contract Manufacturing Operations (CMOs) for release of CCH assemblies (both (b) (4) variants) and has successfully been used as release criteria for these products.*
Results:	**Table 17 Cap Detach** **Number of samples** | **Mean** | **Std Dev** | **LSL** | **USL** | **k-value** | **Target k** | $\bar{x} - k \times s$ | $\bar{x} + k \times s$ | **Conclusions from study:** 20 | 9.36 | 0.86 | (b) (4) | 6.233 | (b) (4) | 7.04 | 11.68 | Pass Reference: eLN: KwikPen-2017-001-032, Taupe KwikPen CCH Cap Removal Testing 842693 The Sponsor stated that this data is representative of all KwikPens.
Conclusions/ Reviewer Comments:	The test method an test results are acceptable. The results show an average cap removal force of 9.36 N with a standard deviation of 0.86 N. The calculated K-vale exceeds the target value for 95%/95% confidence/reliability. This is acceptable.
Acceptable:	☒Yes ☐No

Title:	Dialing Torque Test

Scope/Objective & Acceptance Criteria:	*This method will provide the procedure for measuring the dialing torque for KwikPen Platform devices. This test demonstrates the device can dial up and down while the maximum torque values (in each direction) remain within specification limits defined by design specifications. (Dialing torques of (b) (4) in-oz ((b) (4) Nmm) have shown to be acceptable to users of KwikPen Platform devices)* *The average of the maximum dialing up and dialing down torques shall be less than (b) (4) in-oz ((b) (4) N-mm).* ***Note:*** *Maximums are defined by the torque peaks associated with each click. The maximum torque for both dial up and dial down will be measured for each device. The average refers to the maximum dialing torque measured over the set of the devices tested. Positive and Negative values reported by the test system refer to the direction of the test (Positive values indicate dial up (clockwise), negative values indicate dial down (counterclockwise)).* *Information for Sample Size Selection and Target k-value (one-sided spec):* *☐ Mean Dialing Torque: Variables Data* *☐ Minor Defect Level* *☐ LQ = (b) (4) %* *Pass if Dial Up Average and Dial Down Average K are ≥ Target K* *Fail if Dial Up Average and/or Dial Down Average K are < Target K*
Methods	*The KwikPen Dialing Torque test method measures the maximum torque values in both the dial up and dial down directions. Torque readings are measured by a calibrated torque cell. Peaks are observed at each click during the dialing process.*
Results:	**200 U/mL Device Presentation (0.005 mL/click, 60 clicks max):** **Table 16 Dialing Torque**

Test	Number of Samples	Avg Max(|torque|) (Nmm)	Std dev Max (Nmm)	K-value	Target K-value	$\bar{x} - k \times s$	$\bar{x} + k \times s$	Conclusions from study:
Dial Up Torque	20	15.61	0.98	16.52	(b) (4)	13.32	17.90	Pass
Dial Down Torque	20	19.04	0.99	12.89		16.73	21.35	Pass

Reference: eLN: KwikPen -2017-001-020, (b) (4) U200 KwikPen w/ (b) (4) Cartridges Dialing Torque 828892

100 U/mL Device Presentation (0.010 mL/click, 60 clicks max):

Table 27 Dialing Torque

Test	Number of Samples	Avg Max(|torque|) (Nmm)	Std dev Max (Nmm)	K-value	Target K-value	$\bar{x} - k \times s$	$\bar{x} + k \times s$	Conclusions from study:
Dial Up Torque	20	14.55	1.59	10.85	(b) (4)	10.84	18.26	Pass
Dial Down Torque	20	16.54	2.09	7.30		11.66	21.42	Pass

Reference: eLN: KwikPen -2017-001-060, (b) (4) U100 KwikPen w/ (b) (4) Cartridges Dialing Torque 858872

Conclusions/ Reviewer Comments:	The force measurements are made using a Zwick Axial/Torsion system with a 2 Nm Torsion Cell. The test method appears to be acceptable and similar to methods used by other manufactures. Measurements were made of the 200 U/mL device and the 100 U/mL device to be representative of both the 0.005 mL/click and the 0.010 mL/click device designs. The Sponsor did not report any failures during the testing and met the k-value for a 95%/95% confidence/reliability for both device designs and both dialing directions. This is acceptable.
Acceptable:	☒Yes ☐No

Title:	Glide Force (Actuation Force) Testing
Scope/Objective & Acceptance Criteria:	*This method will provide the procedure for Dose Accuracy and Glide Force (DAGF) testing for the 10 microliter (uL) 60 click maximum (max) KwikPen Functional Attribute and Design Verification Testing.* *The injection force specification of the final finished device has two acceptance criteria:* *☐ mean glide force (b) (4) lbs.* *☐ individual glide force values between (b) (4) lbs. with 95% confidence and 95% p-content* *Note: the lower glide force limit specification is not applicable for Tempo Pen; however, it does meet this specification.* The acceptance criteria are identical to the Humalog Kwikpen device presentation.
Methods	*The 10 uL 60 click max DAGF test method characterizes the fluid volume expelled by device and the force required to actuate the dose delivery. Forces are applied by compressive movement of the CADI test system with the gravimetric readings measured by a precision balance. These gravimetric readings are then converted to volumetric readings by factoring in the density of the liquid dispensed. The glide force is measured by a force load cell attached to the linear actuator.*

Results:

Glide force measurements are taken concurrently with all dose accuracy measurements. The Sponsor stated in 3.2.R.2.5 that all measurements were taken with a 31Gx5mm needle. The following are examples from dose accuracy testing under standard atmosphere conditions (23°):

200 U/mL Device Presentation (0.005 mL/click, 60 clicks max):

Table 7 ISO Standard Atmosphere

Specification Requirement	Number of Samples	Mean (mL) or (lbs.)	Std Dev (mL) or (lbs)	LSL (mL) or (lbs)	USL (mL) or (lbs)	K-value	Target K-value	$\bar{x} - k \times s$	$\bar{x} + k \times s$	Conclusion from Study
(b) (4)	60	0.0062	0.0008	(b) (4)		4.750	(b) (4)	0.004	0.008	Pass
	60	0.1496	0.0010			7.100		0.147	0.152	Pass
	60	0.2993	0.0011			13.000		0.296	0.302	Pass
	60	1.98	0.22			8.545		1.47	2.49	Pass
Post conditioning Visual & Functional										Pass

Reference: eLN: KwikPen-2017-001-013, (b) (4) U200 KwikPen w/ (b) (4) Cartridges ISO Standard 827797

100 U/mL Device Presentation (0.010 mL/click, 60 clicks max):

Table 18 ISO Standard Atmosphere

Specification Requirement	Number of Samples	Mean (mL) or (lbs.)	Std Dev (mL) or (lbs)	LSL (mL) or (lbs)	USL (mL) or (lbs)	K-value	Target K-value	$\bar{x} - k \times s$	$\bar{x} + k \times s$	Conclusion from Study
(b) (4)	60	0.0108	0.0008		(b) (4)	11.500	(b) (4)	0.009	0.013	Pass

(b) (4)	60	0.2991	0.0021	(b) (4)	6.714	(b) (4) 0.293	0.305	Pass
	60	0.5983	0.0036		7.861	0.589	0.608	Pass
	60	3.57	0.26		13.346	2.96	4.18	Pass
Post conditioning Visual & Functional								Pass

Reference: eLN: KwikPen-2017-001-047. (b) (4) U100 KwikPen w/ (b) (4) Cartridges ISO Standard 857973

Conclusions/ Reviewer Comments:	The test protocol provided by the Sponsor in response to information request #2 indicates that the measured "glide force" of the pen is the actuation force of the pen. In addition, the Sponsor stated that the specification for this attribute are identical to the previously approved Humalog pen. The provided test data indicates that the devices meet the predetermined acceptance criteria.Testing was conducted with a 31Gx5mm needle. The pen injector is not labeled to be used with a specific pen needle but Lilly recommends the use of BD needles. BD offers pen needles in various gauges and lengths ranging from 29G to 32G with needle lengths between 4 to 8 mm. One of the major contributors with regard to injection force testing is the gauge of the needle. Generally, the higher the gauge (smaller diameter needle) the higher the injection force is expected to be. The needle tested does not represent the highest available gauge by BD, but is the second highest. Although the testing did not use the needle with the highest gauge, the results are very well below the specifications set by Lilly. It is not expected that going up 1 gauge would cause a more than 50% increase in the injection force. Hence, the provided data is acceptable.
Acceptable:	☒Yes ☐No

Reviewer Comment

The Sponsor has provided protocols for each conducted performance test of the device. The protocols were reviewed and found acceptable. The results indicate that the device performs according to the pre-determined acceptance criteria. This is acceptable.

9.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☑ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The Sponsor has sufficiently addressed all device verification related information requests. There are no further design verification issues identified.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent:	**Date/Sequence Received:**
Information Request #1	10/8/2019	11/8/2019 Seq 0012
Sponsor Response		

(b) (4)

	(b) (4)
Reviewer Comments	Lilly provided the requested test data for cap removal force, dose accuracy, dialing torque, and glide force. However, the Sponsor has not provided the test protocols for each conducted test. Furthermore, it is unclear how glide force of the cartridge translates to the injection force of the device. Hence, a follow-on deficiency will be sent to the Sponsor. The provided biocompatibility protocols were reviewed to ensure that the device complies with ISO 10993-1. Lilly conducted cytotoxicity testing per ISO 10993-5 and irritation and sensitization testing per ISO 10993-10. Some biocompatibility information (Dial and black Ink printing as well as Cartridge Holder) were leveraged from previous testing. The Sponsor stated that these components remain equivalent for biocompatibility purposes from the previous testing. For cytotoxicity, devices were extracted for 24 hours at 37°C in MEM with 10% Fetal Bovine Serum. Irritation and Sensitization were conducted with saline and cotton seed oil extracts from a 72 hours extraction at 50°C. The Sponsor stated that the extracts were not further manipulated and used within 24 hours. The following results were reported: Cytotoxicity: **Table 7. Test results from L929 MEM Elution Testing for Taupe test articles.**

Description	Maximum Grade	Acceptance Criteria	Pass/Fail (b) (4)
Dose Knob (Button)	0	(b) (4)	Pass
Dial and Black Printing Ink*	1		
Pen Body / Housing	0		
Cartridge Holder*	1		
Cap	0		

*Evaluated in previous testing instance with data reported in PDS-REPORTS-02806. Please refer to Reference 7 for further detail.

Irritation:

Table 8. Indirect Primary Skin Irritation maximum reaction scores from Taupe test articles (across all extractant medias)

Description	Maximum PII	Acceptance Criteria	Pass/Fail (skin reaction score (b) (4)
Dose Knob (Button)	0	(b) (4)	Pass
Dial and Black Printing Ink*	0		
Pen Body / Housing	0		
Cartridge Holder*	0		
Cap	0		

*Evaluated in previous testing instance with data reported in PDS-REPORTS-02806. Please refer to Reference 9 for further detail.

Sensitization:

Table 9. Sensitization classification test results from Taupe test articles

Description	Maximum Sensitization Reaction Score	Acceptance Criteria	Pass/Fail (Sensitization Grade (b) (4)
Dose Knob (Button)	0	(b) (4)	Pass
Dial and Black Printing Ink*	0		
Pen Body / Housing	0		
Cartridge Holder*	0		
Cap	0		

*Evaluated in previous testing instance with data reported in PDS-REPORTS-02806. Please refer to Reference 10 for further detail.

The results are acceptable.

Response Adequate: ☐ **Yes** ☑ **No, See IR #2 Sent on 1/14/2020**

Follow-On Deficiency	Date Sent: 1/14/2020	Date/Sequence Received: 2/24/2020 Seq 0026

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	(b) (4)
Reviewer Comments	Lilly has provided the requested test protocols for cap removal force, dose accuracy, dialing torque, and gliding force in sequence 0026. In addition, the Sponsor stated that the term glide force is used when referring to the actuation force of the final finished device. The test methods were reviewed under the design verification section of this memo and found acceptable. This response is adequate.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

	Date Sent: 1/14/2020	**Date/Sequence Received:** 2/24/2020
Information Request #3	(b) (4)	
Sponsor Response		

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	(b) (4)
Reviewer Comments	Lilly provided stability data of the final finished devices with the to be marketed drug product. No failures were reported, and the reported k-values indicate that the devices continue to meet the 95%/95% confidence and reliability. Module 3.2.P.8.3 were updated accordingly. This is acceptable.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

	Date Sent:	**Date/Sequence Received:**
	10/8/2019	**2/24/2020 Seq 0026**
Information Request #4	(b) (4)	
Sponsor Response		

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Reviewer Comments	Lilly provided dose accuracy data of another KwikPen that shares the same mechanical device design, similar materials, and *comparable drug product properties (viscosity and density)*. The greatest reported differences in the mean delivery is between the 31Gx5mm and the 23G4mm needle with a 1.98% difference at the low dose. Likewise, these two needles also had the lowest percent difference of 0.14% at the high dose. The 29Gx12.7mm needle and the 32Gx4mm needle show a percent difference of 0.98% at the low dose and 0.16% at the high dose. Dose accuracy results from the subject device submitted in Sequence 0012 shows that the variability of the pen is higher at the low dose settings compared to the high dose settings. Hence, seeing a slightly higher variability for the low dose when comparing different types of needles is consistent with this observation. Overall, the device performs within the acceptance criteria set in ISO 11608-1 and the reported K-values (even at low doses) are well above the target k-values. Based on this, it appears that the difference in the used needle does not result a significantly different mean dose accuracy result that would result in the injector being out of specification (OOS). The response to the information request is adequate.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

	Date Sent: 1/14/2020	**Date/Sequence Received:** 2/24/2020 Seq 0026
Information Request #5	(b) (4)	
Sponsor Response		

	(b) (4)
Reviewer Comments	Lilly stated that the data collection was done in compliance to the standard and that different zones of the cartridge were sampled as outline in the standard. The cartridge position analysis was conducted in addition to the tests prescribed in ISO 11608-1. This response is acceptable.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

9.3. Discipline Specific Sub-Consulted Review Summary

☑ No Additional Discipline Specific Sub-Consults were requested
☐ The following additional Discipline Specific Sub-Consults were requested:

10.CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

☐ There is no device related clinical studies for review
☑ There are clinical studies for review
This information was obtained from the following **documents**:

Study Name	
Study Type	Safety and Efficacy Study Phase III
Objectives/Endpoints	***Primary Objective:*** *To test the hypothesis that LY900014 was noninferior to Humalog on glycemic control (noninferiority*

	margin [NIM]=0.4% for hemoglobin [HbA1c]) in patients with type 1 diabetes (T1D), when administered *as prandial insulin (0 to 2 minutes prior to the meal), in combination with basal insulin glargine or insulin degludec* *for 26 weeks.* ***Multiplicity-Adjusted Objectives:*** *To test the hypothesis that LY900014 was:* *□ superior to Humalog in controlling 1-hour postprandial glucose (PPG) excursions (mixed-meal tolerance* *test [MMTT]), when administered as prandial insulin at Week 26 (H2)* *□ superior to Humalog in controlling 2-hour PPG excursions (MMTT), when administered as prandial insulin* *at Week 26 (H3)* *□ superior to Humalog for improving glycemic control when administered as prandial insulin (change from* *baseline to Week 26 in HbA1c) (H4)* *□ noninferior to Humalog for improving glycemic control (NIM=0.4% for HbA1c) when administered* *20 minutes after the start of a meal (LY900014+20) (H5)* ***Other Secondary Objectives:*** *To compare LY900014, LY900014+20, and Humalog for the following (only data up to and including Week 26 are* *presented in this clinical study report [CSR] for patients in the Humalog and LY900014 arms and Japanese patients* *in the LY900014+20 arm, and data up to and including safety follow-up for non-Japanese patients in the* *LY900014+20 arm):* *□ 1-hour and 2-hour PPG excursions (MMTT) at Week 26* *□ rate of severe hypoglycemic events at Week 26 and Week 52* *□ incidence and rate of documented symptomatic postmeal hypoglycemia from Week 12 through Week 26,* *Week 0 through Week 26, Week 26 through Week 52, and Week 0 through Week 52* *□ incidence and rate of documented symptomatic hypoglycemia from Week 12 through Week 26, Week 0* *through Week 26, Week 26 through Week 52, and Week 0 through Week 52* *□ 1,5-Anhyrdroglucitol (1,5-AG) (change from baseline at Week 26 and Week 52)* *□ 10-point self-monitored blood glucose (SMBG) profiles (10 SMBG measurements on the same day at* *premeal; 1 hour and 2 hours after the start of the morning, midday, and evening meals; and at bedtime)* *□ total, basal, and prandial insulin dose at Week 26 and Week 52* *□ diabetes treatment satisfaction as measured by the Insulin Treatment Satisfaction Questionnaire (ITSQ) at* *Week 26 and Week 52* *□ proportion of patients achieving HbA1c targets (<7% and ≤6.5%) at Week 26 and Week 52* *To compare LY900014 with LY900014+20 for the following:* *□ glycemic control (change from baseline HbA1c at Week 26)* *To compare LY900014 and Humalog for the following:* *□ glycemic control (actual and change from baseline to Week 52 in HbA1c)*
Drug/Device Studied	Unclear whether it was the same KwikPen was used. The Sponsor stated that the pen used complied with ISO 11608-1.
Number and Type of Subjects	*Planned: Approximately 1199 patients* *Randomized: 1222 total (LY900014, 451 patients; Humalog, 442 patients; LY900014+20, 329 patients)*

	Treated (at least 1 dose): LY900014, 451 patients; Humalog, 442 patients; LY900014+20, 329 patients *Entered safety follow-up or long term maintenance period: LY900014, 443 patients; Humalog, 424 patients;* *LY900014+20, 318 patients*
Brief description of protocol	*This was a Phase 3, prospective, randomized, outpatient, multinational, multicenter, 3-treatment group, parallel,* *active-controlled study conducted in patients with T1D currently using a multiple daily injections (MDI) regimen.* *In 2 of the treatment groups, LY900014 and Humalog were administered immediately (0-2 minutes) prior to each* *meal in a double-blind manner. A third open-label treatment group consisted of LY900014 administered 20 minutes* *after the start of a meal (LY900014+20). It was not possible to blind this treatment group with different injection* *timing. The study was designed to demonstrate noninferiority of LY900014 when compared with Humalog in* *change from baseline to Week 26 in HbA1c, when both were administered at the start of the meal. For patients in* *the 2 double-blind arms, the study included a 1-week screening period and an 8-week lead-in period followed by a* *52-week treatment period and a 4-week safety follow-up period. For patients in the open-label treatment group, the* *treatment period ended after 26 weeks (except in Japan where patients continued open-label treatment for an* *additional 26 weeks), which was followed by a 4-week safety follow-up period. The double-blind treatment groups* *continued in the study for 52 weeks to provide additional safety and efficacy data. All patients who completed the* *4-week safety follow-up visit (Visit 801) and had treatment-emergent insulin lispro antibodies that had not returned* *to the prespecified baseline range (Visit 2) were asked to participate in follow-up to monitor insulin lispro antibody* *levels for up to 26 weeks after Visit 801. The purpose of the lead-in period was to titrate basal insulin, obtain* *preliminary diagnostic laboratory tests, and determine baseline hypoglycemia rates. The results of the continuous* *glucose monitoring (CGM) substudy are summarized separately in a CSR addendum. The allowed basal insulin* *regimens during the study included: insulin glargine U-100 twice daily, insulin glargine U-100 once daily (either in* *the morning or evening), or insulin degludec U-100 once daily as determined by the investigator.* *At Visit 8, patients were randomized in a 4:4:3 ratio to either LY900014 administered at the start of the meal,* *Humalog administered at the start of the meal, or LY900014 administered 20 minutes after the start of a meal* *(LY900014+20). During the initial 12 weeks after randomization (intensive titration period), prandial insulin dose* *was adjusted as necessary in order to meet the target SMBG levels based on recommended titration algorithms* *provided in the protocol. Basal insulin could be titrated as needed to facilitate optimal prandial dosing or for safety* *reasons such as hypoglycemia or unacceptable hyperglycemia. Thereafter, during the maintenance period (Weeks*

	12-26 of treatment), it was expected that adjustments to prandial and basal insulin doses would be to maintain glycemic control or for safety reasons such as hypoglycemia or unacceptable hyperglycemia. The basal insulin dose may have been influenced by other clinical circumstances and safety considerations known to the investigator; thus, the prescribed basal insulin dose during the study was determined by, and the responsibility of, the investigator. For patients continuing into the 26-week long term maintenance period (2 double-blind arms) for a total of 52 weeks of treatment, adjustments to both prandial and basal insulins were made in order to maintain or further optimize glycemic control, as appropriate.
Device Related Comments	The study was reviewed for adverse events related to the use of the pen injector. Once medical device site inflammation was reported for the Humalog comparator and once device occlusion for the subject drug. Overall, the number of AEs related to the device were low. An evaluation of the PK data to assess the appropriateness of the dose accuracy specification is deferred to CDER.
Reviewer Comments	It's unclear whether the same device was used during the study as is subject of the marketing application. The Sponsor stated that the pen-injector used complied with ISO 11608-1, hence, given that the PK and efficacy data of the study are found acceptable by the relevant review divisions, this specification appears reasonably validated for the subject combination product.
Reviewer Conclusion	The study validates the acceptability of the dose accuracy specification.

Reviewer Comment

The clinical studies indicate that the device design outputs appear adequate to meet the design inputs. This is acceptable.

10.2. Clinical Validation Review Conclusion

CLINICAL VALIDATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A

Reviewer Comments

The Sponsor's conducted clinical studies using a pen injector that complies with ISO 11608-1 appear to adequately validate the dose accuracy specification. All other specifications (e.g., cap removal force, dialing torque, etc.) are identical to the already approved Humalog KwikPen. As the patient population and use environment of the already marketed Humalog pen are the same/similar to the subject combination, the Sponsor has provided sufficient information to validate the specifications of the device.

It is to note that the Sponsor has conducted a formative and summative human factors study with the device. The main goals of this study were to evaluate the following design specifications:

(b) (4)

As the HF study evaluated the labeling of the device and not a specific device performance attribute, the review of this human factors study is deferred to the relevant review division in CDER.

CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☑

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☑
CDRH Facilities Inspection Review was not conducted	☐

Facility Regulatory History Review	
Firm Name:	Lilly France S.A.S
Address & FEI:	Fegersheim, Bas Rhin, 67640 France; FEI: 3002807475
Responsibilities:	Blister packaging of 3 mL cartridge product, pre-filled pen assembly, final packaging of device, device testing.
Site Inspection Recommendation:	NAI.

Reviewer Comments

A medical device inspection was conducted for the facility from 01/13/2020 to 01/16/2020. The inspection covered medical device reports of corrections and removals, unique device identifier (UDI) requirements monitoring, and medical device level II (Baseline) inspection. The inspection was classified as NAI – No Action Indicated. The investigator noted that one single item was covered at inspection closeout. Executive management failure to attend

management review meetings on three occasions. Lilly France promised to correct the issue and modified the management review procedures to include required participants for the meetings. The investigator noted that these modifications were completed prior to the inspection closeout. The facility report is acceptable and supports the approval of this submission.

Facilities Review Conclusion		
The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable.	☑ Yes	☐ No

12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☑
CDRH Quality Systems Documentation Review was not conducted	☐

12.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the combination product, including the drug product/biologic and device constituent parts:

The following information was provided in 3.2.P.3.3:

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(b) (4)

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

12.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The Sponsor provided additional QS information in the response to IR#7. The information was reviewed and found acceptable.		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

(b) (4)

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/s/

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signing on behalf of David Wolloscheck

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: April 16, 2020

TO: Lisa Yanoff, MD
Director (Acting)
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
Office of New Drugs Clinical (OND Clinical)
Office of New Drugs

FROM: Srinivas R. Chennamaneni, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles R. Bonapace, Pharm.D.
Director
DNDSI, OSIS

SUBJECT: Routine inspection of Lilly Centre for Clinical Pharmacology Pte. Ltd., Synapse, Singapore.

1 Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of study NON-RESPONSIVE conducted at Clinical Pharmacology Pte. Ltd., Synapse, Singapore.

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

1.1. Recommendation

After reviewing the inspectional findings, I conclude the data from the audited study are reliable.

2 Inspected Study:

NON-RESPONSIVE

Clinical site: Lilly Centre for Clinical Pharmacology Pte. Ltd
3 Biopolis Drive, #02-11
Synapse, Singapore

ORA investigator Andrea A. Branche (BIMOW) inspected Lilly Centre for Clinical Pharmacology Pte. Ltd., Synapse, Singapore from February 3-7, 2020. This was the first FDA inspection of the firm.

The inspection included a thorough examination of study records, subject records, informed consent process, protocol compliance, PK sampling procedure, glucose clamp assessments, sponsor correspondence, concomitant medications, test article accountability and storage, randomization, adverse events, and case report forms.

3 Inspectional Findings

At the conclusion of the inspection, Investigator Branche did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site. However, one item was discussed at inspection close out. The discussion item, site's response at the inspection closeout meeting and my evaluation follow.

Discussion item:
Subject # (b) (6) reported an AE (adverse event) of pain in the right eye. Evaluation of the right eye pain was not documented in the clinic notes by the clinical investigator.

Firm's response:
The clinical investigator acknowledged the finding in discussion item. He stated that he did not document his evaluation of the AE in clinic notes because of an oversight on his part as the pain in right eye of subject # (b) (6) was a minor AE.

OSIS Evaluation:
The firm documented the AE in the adverse event form. Although the investigator did not describe his evaluation in the source document, the investigator assessed the AE as "mild" and unrelated to the study drug in the adverse event form. Subject # (b) (6) did not receive any concomitant medications and the AE resolved without further intervention. The firm communicated the AE to the sponsor and the AE was included in the adverse event listing submitted to the Agency. Thus, the discussion item has no impact on subject safety or study outcome.

4. Conclusion:

After reviewing the inspectional findings, I conclude the data from study NON-RESPONSIVE are reliable. Based on the inspectional findings, studies of similar design conducted by the end of the current surveillance interval should be considered reliable without an inspection.

Srinivas R. Chennamaneni, Ph.D.
Staff Fellow

Final Classification:

NAI - Lilly Centre for Clinical Pharmacology Pte. Ltd.
Synapse, Singapore
FEI#: 3014479753

cc:
OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/
Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas/Chennamaneni
OTS/OSIS/DGDSI/Cho/Choi/Skelly/Au
ORA/OMPTO/OBIMO/FDAInternational BIMO@fda.hhs.gov

Draft: SRC 4/9/2020, 4/13/2020, 4/16/2020
Edit: GB 4/12/2020, 4/13/2020, 4/16/2020; CRB 4/14/2020, 4/15/2020, 4/16/2020

ECMS:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f881cf5536

OSIS File #: BE 8731
FACTS: 11963535

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/s/

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04/17/2020 01:47:07 AM

CHARLES R BONAPACE
04/17/2020 07:22:14 AM

Clinical Inspection Summary

Date	4/7/2020
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Min Lu, M.D., M.P.H., Team Leader 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	Dolly Misra, M.D., Clinical Reviewer Patrick Archdeacon, M.D., M.Phil., Clinical Team Leader Callie Cappel-Lynch, Pharm.D., RAC Senior Regulatory Project Manager Division of Diabetes, Lipid Diseases, and Obesity (DDLO)
BLA	761109
Applicant	Eli Lilly and Company
Drug	(b) (4) rapid lispro
NME	Yes
Therapeutic Classification	Antidiabetic Agents, Insulin
Proposed Indication	Treatment of type 1 and type 2 diabetes mellitus
Consultation Request Date	10/4/2019
Summary Goal Date	4/13/2020
Action Goal Date	6/15/2020
PDUFA Date	6/15/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this biologics license application (BLA) consisted of two domestic and three foreign clinical sites in addition to the sponsor.

The inspection of one clinical investigator revealed regulatory deficiencies, which are unlikely to have a significant impact on overall safety and efficacy results. The inspection of the remaining clinical investigators and the sponsor revealed no regulatory violations.

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

II. BACKGROUND

Eli Lilly and Company (Lilly) has submitted an initial biologics license application (BLA) for LY900014, a new formulation of insulin lispro, the same active ingredient used in Humalog®, that has demonstrated accelerated insulin absorption compared to Humalog®. LY900014 has been developed by Lilly for subcutaneous (SC) and intravenous (IV) use to improve glycemic control in patients with diabetes mellitus.

Inspections were requested for two studies:

- Protocol **I8B-MC-ITRM** entitled, "A Prospective, Randomized, Double-Blind Comparison of LY900014 to Insulin Lispro with an Open-Label Postprandial LY900014 Treatment Group, in Combination with Insulin Glargine or Insulin Degludec, in Adults with Type 1 Diabetes (PRONTO-T1D)"
- Protocol **I8B-MC-ITRN** entitled, "A Prospective, Randomized, Double-Blind Comparison of LY900014 to Insulin Lispro, Both in Combination with Insulin Glargine or Insulin Degludec in Adults with Type 2 Diabetes (PRONTO-T2D)"

I8B-MC-ITRM
This was a Phase 3, prospective, randomized, outpatient, multinational, multicenter, 3-treatment group, parallel, active-controlled study conducted in patients with type 1 diabetes mellitus (T1D) currently using a multiple daily injections (MDI) regimen. Subjects had to have been continuously using insulin for at least 1 year at screening and been on MDI therapy for at least 90 days.

There was an 8-week lead-in period (prior to randomization) to titrate basal insulin, obtain preliminary diagnostic laboratory tests, and determine baseline hypoglycemia rates. All subjects at screening were transferred to Humalog® (insulin lispro) at Visit 2 so that all subjects were using Humalog® during the lead-in period.

At Visit 8, subjects were randomized in a 4:4:3 ratio to either LY900014 administered at the start of the meal, Humalog® administered at the start of the meal, or LY900014 administered 20 minutes after the start of a meal (LY900014+20). For the first two groups, LY900014 and Humalog® were administered in a double-blind manner. Subjects in these groups completed a 52-week treatment period (with primary endpoint at 26 weeks), and a 4-week safety follow-up period. The third open-label treatment group consisted of LY900014 administered immediately after completion of a meal or 20 minutes after the start of a meal (LY900014+20), whichever occurred first. Subjects in this treatment group completed a 26-week treatment period and a 4-week safety follow-up period. Assignment to treatment groups was determined by a computer-generated random sequence using an interactive web-response system (IWRS).

During the initial 12 weeks after randomization (intensive titration period), prandial insulin dose was adjusted as necessary to meet the target self-monitored blood glucose (SMBG) levels based on recommended titration algorithms provided in the protocol.

The double-blind treatment groups continued in the study for 52 weeks to provide additional safety and efficacy data. For subjects in the open-label treatment group, the treatment period ended after

26 weeks (except in Japan where subjects continued open-label treatment for an additional 26 weeks), which was followed by a 4-week safety follow-up period.

The primary efficacy measure was change from baseline to Week 26 in HbA1c.

This study was conducted at 166 study sites in 18 countries. A total of 1621 subjects were screened, 1222 subjects were randomized, and 1135 subjects completed the study; 265 subjects completed long-term safety follow-up. The first subject visit was July 17, 2017 and the first randomized subject was September 12, 2017. The third version of the Statistical Analysis Plan (SAP) was approved on August 14, 2018, prior to the official unblinding of the data on September 14, 2018. Data cutoff date is March 6, 2019.

NOTE: In Study I8B-MC-ITRM, an issue was identified globally early in the study and reported in the Clinical Study Report, which caused a loss of data for some subjects at multiple sites. The electronic Clinical Outcome Assessment (eCOA) diary (eDiary) wirelessly received all glucose data directly from the blood glucose (BG) meters. Hypoglycemic events were captured throughout the clinical study in eCOA along with date and time of the BG level, if measured, and hypoglycemia treatment and outcome data. The site had access via the eCOA portal (secure web-based site) to the ongoing near real-time updating of the BG readings, insulin doses administered, hypoglycemic events, and dosing time relative to the meal.

Study glucometers and eDiaries were connected using Bluetooth technology. At times, devices required re-pairing following the initial connection between the two devices in the system. (e.g., one was damaged, lost, or connection lost). The eCOA system cleared the glucometer memory during pairing of devices; therefore, BG readings not previously transferred to the eDiary were deleted. The potential existed for any subject to experience the problem of cleared BG readings from the glucometer if the subject repaired the devices. The issue was detected August 2017 and it was corrected with software updates released in September 2017 after randomization began September 12, 2017.

This necessitated a replacement of some of the glucometers for subjects at different sites and in some cases early missing data.

I8B-MC-ITRN
This study was a Phase 3, prospective, double-blind, randomized, outpatient, multinational, multicenter, 2-group, parallel, active-controlled study conducted in patients with type 2 diabetes mellitus (T2D) currently treated with basal insulin in combination with at least 1 prandial insulin injection or premixed insulin with at least 2 injections daily. Subjects had to have a diagnosis of T2D for at least 1 year, a HbA1c value $\geq 7.0\%$ and $\leq 10.0\%$, and a body mass index (BMI) of ≤ 45.0 kg/m^2.

The study included a 1-week screening period and an 8-week lead-in period followed by a 26-week treatment period and a 4-week safety follow-up period. Subjects may have been treated with up to 3 types of oral antihyperglycemic medications (OAMs) prior to screening and may have continued the use of 2 OAMs (metformin and/or a sodium glucose cotransporter 2 [SGLT-2] inhibitor) during the lead-in and treatment periods.

The purpose of the lead-in period (prior to randomization) was to titrate basal insulin, obtain preliminary diagnostic laboratory tests, and determine baseline hypoglycemia rates. Subjects were required to use the same basal insulin regimen throughout the study.

At Visit 8, subjects were randomized to double-blind treatment with either LY900014 or Humalog® at each meal. During the initial 12 weeks after randomization (intensive titration period), prandial insulin doses were titrated as necessary to meet the target SMBG levels based on recommended titration algorithms provided in the protocol.

The primary efficacy measure was the change from baseline to Week 26 in HbA1c.

This study was conducted at 131 study sites in 15 countries. A total of 673 subjects were randomized and 639 subjects completed the study. The date of the first subject visit was July 14, 2017 and the date the first subject was randomized was September 19, 2017. The data cutoff date was August 14, 2018. Unblinding of the study (to the main cohort) occurred on August 17, 2018. The third version of the SAP was approved on July 24, 2018 prior to unblinding.

III. RESULTS (by Site)

NOTE: Site inspections focused on 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.

FDA inspectors were also asked to evaluate the functioning of the eDiaries at the site and note any issues with missing data.

1. **Alberto Aliaga Verdugo, MD**
   Clinica Nuevas Tecnologias En Diabetes Y Endocrinologia
   Calle Alejo Fernandez, 9, Local 4
   Seville 41003
   Spain
   Site: 750 **Study**: I8B-MC-ITRM

Dates of inspection: January 20 – 24, 2020

There were 22 subjects screened and 19 subjects enrolled into the study; 4 subjects participated in the 26-week open arm part of the study. Nineteen subjects completed the study. There were 19 subject records reviewed.

Translation services were supplied by an independent provider contracted by the sponsor.

The translator interpreted all communications during the inspection and translated documents.

The institutional review board of record was (b) (4) This was a non-IND site.

Dr. Verdugo is an independent contractor at the site and has been conducting clinical studies as a sub-investigator for the past 6 years. Study I8B-MC-ITRM was his first study as site investigator. Dr. Verdugo additionally works at a private hospital. Dr. Cuesta Mayor, sub-investigator for the study, is the sole owner of the specialty clinic located at the address above for the last 10 years. Most subjects were recruited from within the patient population of the clinic and from the hospitals where both doctors work part-time. No advertisements or brochures were utilized for recruitment.

As noted earlier, an issue was identified in the study that caused a loss of data for some subjects at multiple sites. The patch and instructions were provided by the sponsor to study sites; the instructions were available for review. At the inspected site, there were no required devices replaced but data was lost for two subjects: Subjects (b) (6).

Source records were organized, available, and usually legible, although there were some written notes that were difficult to read. A review of subjects' ECG tracings showed that only a few had an imprinted date on the top of the paper tracing; most dates were handwritten along with the investigator's signature on the day it was reviewed. The site staff explained that the ECG tracings were not properly aligned when printed and the misalignment cut off the printed dates for some subjects.

Source records were compared to the sponsor data line listings. There were a few minor discrepancies. 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.

2. **Jose Gerardo Gonzalez Gonzalez, MD**
   Hospital Univ. Jose Eleuterio Gonzalez
   Serv. Endocrinologia-Gerardo Gonzalez
   Av. Francisco I.
   Madero Pte S/n Y Av. Gonzalitos
   Col. Mitra Centro
   Monterrey, Nuevo Leon 64460
   Mexico
   Site: 601 **Study**: I8B-MC-ITRM
   Site: 601 **Study**: I8B-MC-ITRN

Dates of inspection: January 13 – 16, 2020

For Study I8B-MC-ITRM, there were 16 subjects screened and 10 subjects enrolled into the study; 10 subjects completed the study. There were 10 subject records reviewed (plus 2 subjects in the maximized extended enrollment [MEE] were checked for informed consent and eligibility).

For Study I8B-MC-ITRN, there were 20 subjects screened and 15 subjects enrolled into the study; 15 subjects completed the study. There were 14 subject records reviewed (plus 2 subjects in the MEE were checked for informed consent and eligibility).

Source records were organized and available. During the inspection, it was noted that there were additional subjects at the site that were not on the sponsor data line listings. Communications were sent to the sponsor for an explanation. Both studies had an addendum to the protocols for maximized extended enrollment (MEE) to satisfy regulators in other countries (including Mexico). Once enrollment closed for the global cohort, the countries participating in the MEE continued enrollment until the required number of local subjects was reached for each country. At Site 601, 4 subjects were enrolled in the MEE addendum for both studies (Study ITRM: Subjects (b) (6); Study ITRN: Subjects (b) (6) All analyses of any MEE country-specific cohort are for submission only to that country and are not incorporated into the analysis of the global cohort.

Source records were compared to the sponsor data line listings. There was one unreported mild, self-limited gastroenteritis in Study ITRM that was not reported due to human error. Otherwise, there was no additional under-reporting of adverse events. Neither study had severe hypoglycemic events that resulted in a serious adverse event (SAE). The sub-investigators discussed hypoglycemic events with subjects at each visit and reviewed data at each visit from the online portal to check for hypoglycemic events and subject compliance with glucose checks.

The primary efficacy endpoint for both studies 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.

The full Establishment Inspection Report is not available for review at the present time.

3. Beata Lachova, MD
Diab s.r.o., Diabetologick a ambulancia
Namestie 1. Maja 11
048 01 Roznava
Slovakia
Site: 728 **Study**: I8B-MC-ITRM
Site: 728 **Study**: I8B-MC-ITRN

Dates of inspection: January 13 – 16, 2020

For Study I8B-MC-ITRM, there were 6 subjects screened and 5 subjects enrolled into the study; 5 subjects completed the study. There were 6 subject records reviewed.

For Study I8B-MC-ITRN, there were 10 subjects screened and 10 subjects enrolled into the study; 9 subjects completed the study (one subject died unrelated to study). Subject (b) (6) was discontinued from investigational product (IP) use on (b) (6) but remained in the study. There were 10 subject records reviewed.

No subjects participated in the open arm at this site for either protocol study.

The institutional review board of record was (b) (4) This was a non-IND site.

Most of the inspectional information was obtained through a translator as the site was limited in English. Translation services were supplied by an independent provider chosen by a service contracted by the sponsor. Those also present were two representatives from the Slovakian State Institute for Drug Control, who acted as observers of the FDA inspectional procedures.

Dr. Lachova established her practice at a local hospital in 1995 and moved to the current location in 2011. She established her practice as an LLC, named DIAB s.r.o., and has participated in multiple research studies. The sub-investigator Dalibor Sosovec, MD is her son, shares office space, and performed most study duties. Subjects were recruited without advertisements and from within their clinic as they have a database of over 6,000 diabetic patients.

As noted earlier, an issue identified globally caused a loss of data for some subjects at multiple sites. This necessitated a replacement of some of the glucometers for subjects at different sites and in some cases early missing data. At the site, two subjects required device replacement and re-pairing with the Bluetooth connection (Subjects (b) (6) in Study ITRN).

Source records were available and organized. Notes were lacking in explanation for some actions and in explanation for some corrective changes made. Not all efforts to contact subjects were recorded in the source records. It was noted that ECG tracings had no identifying machine-generated name or Subject ID, or date/time imprinted on the tracings but all information was hand-written as the ECG machine was set to manual mode.

Source records were compared to the sponsor data line listings. Deviations and actions taken were reported at the site and were well documented. There were a few minor out of window visits that were found upon review but not reported as protocol deviations (Study ITRM - Subjects (b) (6)).

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.

4. Wendell R. Miers, MD
Kentucky Diabetes Endocrinology Center
1760 Nicholasville Road, Suite 502
Lexington, KY 40503-1471
Site: 131 **Study**: I8B-MC-ITRM

Dates of inspection: February 7 – 20, 2020

There were 19 subjects screened and 16 subjects enrolled into the study; 16 subjects completed the study. There were 19 subject records reviewed.

The institutional review board of record was (b) (4)

Dr. Miers has been a practicing physician since 1987 and has been conducting clinical trials since 2001, focusing predominately on diabetes studies. The private practice is co-owned by Lyle C. Myers, M.D. Subjects were recruited from the practice; there was no advertisement used.

Source records were well organized, legible, and in good condition. All subjects' electronic diaries were monitored by the site and all hypoglycemic events were captured and reported to the sponsor. The sponsor sent a CD-ROM of the case report forms and the e-COA device information for the study subjects to the site after the study was completed.

Subject (b) (6) did not meet inclusion criterion #4 at the time of screening on (b) (6) The subject's basal insulin was switched to Tresiba (insulin degludec) on (b) (6) The subject was on insulin degludec for 24 days instead of 30 days as specifie ocol prior to screening. There was documentation in the site regulatory binder that the sponsor gave permission for the subject to continue in the study. This protocol deviation was reported to the sponsor.

Source records were compared to the sponsor data line listings. There were minor discrepancies regarding concomitant medications.

- Subject (b) (6) reported at the Week 801 Safety Follow Up Visit on (b) (6) treatment with glucagon IV for an assisted hypoglycemic event. The use of this concomitant medication was not recorded in the eCRF or on the data line listings provide by the sponsor; however, the adverse event was reported.
- Subject (b) (6) reported the use of naproxen sodium 220 mg prn 4 to 5 times per documentation dated (b) (6). This concomitant medication was not recorded in

the eCRF or on the data line listing provided by the sponsor.

There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation. Specifically, the ECG tracing for Subject (b) (6) dated (b) (6) was not consistent with the time planned for this screening activity and appears to be the tracing of a subject involved in another study. Subject (b) (6) signed the informed consent form on (b) (6) at 11:05 a.m. and the ECG was stamped as being performed on (b) (6) at 09:27 a.m.

This was brought to the attention of the study coordinator during the inspection. The study coordinator investigated the issue and discovered there was another Subject X who was participating in another diabetes study that was at the site for a study visit and required to have an ECG the same day. This ECG was done prior to Subject (b) (6) Subject X was scheduled for a 4-hour appointment at 08:30 a.m. and Subject (b) (6) was scheduled for a 1-hour appointment at 11:00 a.m. on (b) (6). Review of the ECG for Subject (b) (6) shows it to be identical to Subject X's ECG. There was no other identifying information such as initials, age, or gender listed on the ECG, only the subject number.

It was noted that preventative maintenance was performed on the Bionet Cardio Care-200 EKG equipment on 3/22/17 and there were no complaints of any malfunction. All study subject ECGs were then reviewed against the time the informed consent forms were signed by each subject and there were no other discrepancies found. The study only required one ECG to be performed at screening unless the investigator felt another one was clinically necessary.

OSI Reviewer Comment: Site staff were unaware of this observation until it was brought to their attention. It appears that there had been human error involved. No fraud is suspected. This was an isolated occurrence. Dr. Miers responded to the inspectional findings on February 27, 2020. His response was determined to be acceptable.

5. **Betsy M. Palal, MD**
   Palm Research Center
   9280 West Sunset Rd, Suite 306
   Las Vegas, NV 89148-4861
   Site: 139 **Study**: I8B-MC-ITRM
   Site: 139 **Study**: I8B-MC-ITRN

Dates of inspection: January 16 – 30, 2020

For Study I8B-MC-ITRM, there were 15 subjects screened and 10 subjects enrolled into the study; 9 subjects completed the study (one subject withdrew due to pregnancy). There

were 9 subject records reviewed.

For Study I8B-MC-ITRN, there were 21 subjects screened and 15 subjects enrolled into the study; 13 subjects completed the study (one subject died, and one subject withdrew). There were 13 subject records reviewed.

The institutional review board of record was (b) (4)
Approved translations of consent documents from English into Spanish were on file, along with letters certifying the accuracy of the translations and back translations.

Palm Research Center (PRC) is a private research company established in 2008 by Dr. Samer Nahkle. PRC is part of the Palm Medical Group (PMG) that has two locations in Las Vegas, NV. Dr. Samer Nahkle is the Medical Director. Dr. Palal has been with PRC since 2008 and has 15 years of research experience. The clinical site used advertising in recruiting study participants. In addition, potential subjects were recruited from the PMG medical practice patients.

Source records were organized and legible. At the completion of the studies, a CD-ROM of CRFs and e-COA device information were sent to the site by the sponsor.

Source records were compared to the sponsor data line listings. Subject (b) (6) in Study ITRN reported a urinary tract infection on (b) (6) that was not reported as an AE. There were no other discrepancies or under-reporting of adverse events.

The primary efficacy endpoint was verifiable for both studies.

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.

6. Eli Lilly and Company/ Sponsor
Lilly Corporate Center
839 South Delaware Street
Indianapolis, IN 46285-1782

Study: I8B-MC-ITRM
Study: I8B-MC-ITRN

Dates of inspection: March 16 – 20, 2020

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, selection criteria for all committee members, oversight of committees, data management, escalation of issues, and clinical trial oversight.

During the inspection, the FDA inspector also verified issues disclosed in the Clinical Study Report (CSR) and in follow-up responses to regulatory questions along with the corrective actions.

The inspection had limitations as Eli Lilly implemented social distancing measures for their US-based employees due to the COVID-19 Pandemic. Staff was brought into the building as needed and staff was also interviewed remotely.

(b) (4) had the responsibility for clinical monitoring and site management. Sites were monitored using a risk-based monitoring plan. Monitoring included 100% of critical data such as inclusion/exclusion criteria and informed consent forms. Source data verification (SDV) was to be performed every 1st, 6th, 11th subject and then every 5th subject thereafter.

Monitor coverage and frequency appeared to be adequate. In reviewing the monitoring reports, it was noted that Site 139 did not meet 20% of source data verification review per the monitoring plan. In addition, in some instances the monitor did not review the correct subject per the monitoring plan. Site 139 was also audited by the sponsor. The monitor for Site 116 (Study ITRN) and Site 122 (Study ITRM) as sampled the incorrect subjects; however, the 20% sampling was met per the monitoring plan.

Monitoring correspondence was reviewed and well documented. The firm appeared responsive to monitoring observations and requests.

Site 118 (Dr. Satish Garg) had site escalation procedures due to non-compliances identified during a routine Quality Compliance Visit (QCV) conducted by (b) (4) on 6/7/18. For all subjects, the total daily dose (TDD) of insulin was not captured at the screening visit; the site's temperature alarm for IP was set outside the limits; the site investigator Trial Master File was incomplete; subject screening ECGs did not contain information identifying the specific subject; and the concomitant medication log information was inaccurate. Corrective actions took place and all issues were resolved. An enrollment hold was not enacted, and no non-compliance letter was sent to the site. The site was not terminated.

Site 585 (Dr. Moon-Kyu Lee) had site escalation procedures due to non-compliance. Many of the Korean sites had deviations related to not switching to study allowed basal insulin at Visit 2, adding a new OAM at Visit 2, or not discontinuing non-allowed OAMs at Visit 2. Screening was paused for all Korean sites and all were allowed to resume enrollment after retraining except for Site 585 due to additional detected data issues that did not improve with retraining. No subjects were ever randomized at the site.

There appeared to be no sites unblinded throughout the duration of both studies. The firm

also provided a listing of names and titles of sponsor staff who were unblinded to treatment codes in accordance to the blinded/unblinded plan. This list included Demand Forecasters and Clinical Supply Coordinators for both studies, on-going Global Support Helpdesk staff, and IWRS support staff. There were no issues noted.

The CSRs for Study I8B-MC-ITRM and Study I8B-MC-ITRN state that 33 sites in 11 countries and 19 sites in 9 countries had site-level important protocol deviations for a significant delay in safety mailing review. As a part of the sponsor's obligation to distribute safety mailings to site investigators, the firm utilizes the electronic Safety Report Notification System (SAFR NS) whereby safety letters are sent to clinical investigators for their review. The timeliness of these reviews is verified during monitoring visits. The SAFRNS Safety Mailing Reports were reviewed for each site. The sponsor noted that some sites were not always reviewing safety reports in a timely manner, which involved a new process begun in March 2018 for signing into the system. As a result, some investigators did not understand how to access the reports. The monitoring process saw an influx of safety reports that were not being reviewed. It was confirmed that mailings were sent to the sites several times about the change before it occurred. The site monitors also retrained the sites that were non-compliant and followed up with the delays. Although there were late reviews by the sites, there were no 7- or 15-day IND safety reports that required FDA notification for either study.

When Lilly locked the data for Study ITRM Week 52, it was reported in the CSR that there were 34 subjects at sites with the wrong information in the eCRFs regarding the date the subject took their last dose (treatment date). The trial design was that there was still a 4-week safety follow-up, so sites inadvertently put in dates that were after the 52-week time. There were actually 24 subjects that had the wrong dates entered (21 sites had at least one subject with the wrong information). Lilly recognized the mistake and queried each site; each site corrected the actual treatment date. The corrected information is in the data base. The audit trails reviewed reflected that a change was made.

The FDA inspector also verified the firm's corrective actions regarding the use of the eDiary that wirelessly received all glucose data directly from the blood glucose meters. This issue was detected August 2017 and it was corrected with software updates released in September 2017. For context of missing BG data, this issue was present for the first three months of the trial and was remedied with the patch. The sponsor assessed BG data from the impacted time frame and concluded missing BG values of approximately 1% for ITRM and approximately 2% for ITRN of all BG data points across all sites and subjects.

The FDA inspector reviewed relevant documents and samplings of data line listings to confirmed that subjects involved in the Maximum Extended Enrollment (MEE) for Study ITRM were not part of the 26-week analyses.

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.

{See appended electronic signature page}

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

CONCURRENCE: *{See appended electronic signature page}*

Min Lu, 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}*

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./ BLA 761109
DMEP/Acting Division Director/ Lisa Yanoff
DMEP /Acting Deputy Director/William Chong
DMEP/Team Lead/Patrick Archdeacon
DMEP/Clinical Reviewer/ Dolly Misra
DMEP /Regulatory Project Manager/Callie Cappel-Lynch
OSI/DCCE/Division Director/Ni Aye Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Min Lu
OSI/DCCE/GCPAB Reviewer/Cynthia Kleppinger
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

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/s/

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KASSA AYALEW
04/08/2020 05:02:34 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: 10/18/2019

TO: Division of Metabolism and Endcrinology Products
Office of Drug Evaluation II

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

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

RE: BLA (b) (4)

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

Rationale

OSIS inspected the site in March 2018, which falls within the surveillance interval. The inspection was conducted under the following submission: BLA 761063.

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

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

FOLAREMI ADEYEMO
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