CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205747Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Devices and Radiological Health

Office of Compliance, Division of Manufacturing and Quality

Respiratory, ENT, General Hospital, & Ophthalmic Devices Branch

---

Date:	May 12, 2015
To:	Callie, CappelLynch, CDER/OND/ODEII/DMEP, WO 22, Room 3362, Callie. CappelLynch@fda.hhs.gov
CC:	Office of combination products at combination@fda.gov
Through:	Rakhi Dalal, Ph.D., for Francisco Vicenty, Chief, CDRH/OC/DMQ/REGO, WO-66, Room 2642
	Rakhi M. Panguluri -S Digitally signed by Rakhi M. Panguluri -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300200210, cn=Rakhi M. Panguluri -S Date: 2015.05.13 13:54:46 -04'00'
From:	Bleta Vuniqi, Biomedical Engineer CDRH/OC/DMQ/REGO, WO-66, Room 2647
Applicant:	Eli Lilly and Company Center Drop Code 2543, Indianapolis, Indiana 46285 FEI: 1819470 Manufacturer: Eli Lilly and Company Center Drop Code 2543, 8645 Guion Rd. Indianapolis, Indiana 46268 FEI: 3006327424
Application #	NDA 205747
Product Name:	Humalog (insulin lispro) U-200

Consult Instructions:	Evaluate the Humalog (insulin lispro) U-200 documents provided by the applicant on quality system requirement 21 CFR 820, and determine if an inspection of the manufacturing facilities is required.

Background:
The Office of Compliance at CDRH received a consult request from CDER to evaluate NDA 205747 covering the medical device constituents of the combination product, and determine if an inspection of the manufacturing facilities is warranted.

Combination Product Description:
The Humalog® (b) (4) KwikPen™ (600 Unit KP) pen-injector has been designed for use with Insulin Lispro U-200. The components of the pen-injector do not contact the drug product. The drug remains in the primary container closure (cartridge) until a needle is attached to the Cartridge Holder and the drug is injected.

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

The firm noted that the development, design, and manufacturing of the Humalog (b) (4) KwikPen are compliant with the current Good Manufacturing Practice regulations for Combination Products, 21 CFR 4. Consistent with this regulation, during the development of this combination product the requirements of 21 CFR 820 are applied to the device constituent part. The Quality System covering the areas of the company responsible for the development and design of the device constituent part of the combination product includes requirements for Design Control (820.30), Purchasing Controls (820.50) and Corrective and Preventative Actions (820.100).

However, there was no information available for review regarding compliance with 21 CFR 820.20 (Management Controls) 21 CFR 820.30 (Design Controls), 21 CFR 820.50 (Purchasing Controls), and 21 CFR 820.100 (Corrective and Preventive Action).

With regards to information being provided to demonstrate compliance with applicable provisions of the Medical Device Quality System Regulation (21 CFR 820), this application was deficient. Additional information is required so that an appropriate review can be conducted.

Firm's Response:

The firm provided the following procedures which were reviewed and no observations noted.

- (b) (4)-SOP-(b) (4)0014 "Design Control" (Version 20)
- (b) (4)-SOP-(b) (4)4049 "DESIGN AND DEVELOPMENT PLANNING" (Version 24)
- (b) (4)-SOP-(b) (4)4128 "DESIGN INPUT" (Version 5)
- (b) (4)-SOP-(b) (4)4130 "DESIGN OUTPUTS" (Version 10)
- (b) (4)-SOP-(b) (4)4129 "DESIGN AND MANUFACTURABILITY REVIEWS" (Version 12)
- (b) (4)-SOP-(b) (4)4131 "DESIGN VERIFICATION AND DESIGN VALIDATION STUDIES" (Version 11)
- (b) (4)-SOP-(b) (4)0024 "RISK MANAGEMENT" (Version 13)
- (b) (4)-SOP-(b) (4)0010 "CHANGE MANAGEMENT" (Version 23)
- (b) (4)-SOP-(b) (4)4132 "DESIGN HISTORY FILE AND DESIGN HISTORY FILE INDEX" (Version 12)
- 001-003561 "Parenteral Site Quality Manual" (Version 15)
- 001-006077 "Material Supplier and GMP Service Provider Management" (Version 17)
- 001-002054 "Clothing and Hygiene Requirements for Parenteral Packaging (b) (4)" (Version 9)
- 001-003757 "Laboratory Equipment Maintenance and Retirement" (Version 10)
- 001-001651 "Process Validation for Parenteral Drug Product Manufacturing Operations
- 001-001654 Process Validation for Parenteral Drug Product Manufacturing Operations (Version 26)
- 001-001513 "Receipt and Inspection of Package Components" (Version 38)
- 001-008031 "Batch Release (b) (4) – (b) (4)/Reusable/Auto-Injector Devices (Version 9)
- 001-001147 "Managing Events, Non-conformances, and Complaint (b) (4) Investigations" (Version 37)
- (b) (4)-SOP-(b) (4)0042 "PRODUCT QUALITY COMPLAINT HANDLING" (Version 37)

Regulatory History Evaluation

After reviewing the application, the following facilities were potentially identified as being subject to applicable Medical Device Regulations under 21 CFR part 820:

Eli Lilly and Company Center
1555 S. Harding
Drop Code 2622
Indianapolis, Indiana 46285
FEI: 1819470

Firm is responsible form pen injector assembly, labeling and packaging, drug substance [redacted] (b) (4) Last FDA inspection covering medical device constituent parts was conducted on December 02-06, 2013. The inspection covered the firm's quality system regulations relating specifically to the firm's Humalog KwikPen (insulin lispro injection, USP) 200 U/mL (NDA 205747). A two-item FDA 483 Inspectional Observations form was issued for the following:

- Rework and reevaluation activities have not been documented in the device history record
- Procedures have not been adequately established to control product that does not conform to specified requirements.

In addition to the written observations, there were three verbal observations discussed with firm management. These observations included:

- Use of ambiguous acceptance criteria and actual results recorded in validation and design testing documents
- Design reviews have not been fully documented
- Corrective and preventive actions did not include a systemic corrective action to prevent recurrence of nonconforming product.

Eli Lilly and Company Center
Drop Code 2543,
8645 Guion Rd.
Indianapolis, Indiana 46268
FEI: 3006327424

Eli Lilly and Company Center is responsible for manufacturing, labeling, packaging, device assembly, and control testing. Last FDA inspection covering medical device constituent parts was conducted on December 02-06, 2013. The inspection covered the firm's quality system regulations relating specifically to the firm's Humalog KwikPen (insulin lispro injection, USP) 200 U/mL (NDA 205747). A two-item FDA 483 Inspectional Observations form was issued for the following:

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- Procedures have not been adequately established to control product that does not conform to specified requirements.

In addition to the written observations, there were three verbal observations discussed with firm management. These observations included:

- Use of ambiguous acceptance criteria and actual results recorded in validation and design testing documents

- Design reviews have not been fully documented
- Corrective and preventive actions did not include a systemic corrective action to prevent recurrence of nonconforming product.

The inspection was classified VAI and the corrective action addressing the observation noted above would have to be reviewed and verified during the next post-approval inspection.

CDRH Office of Compliance Recommendation

The Office of Compliance at CDRH has completed the evaluation of application NDA 205747 and recommends approval of Humalog (insulin lispro) U-200.

Bleta Vuniqi -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Bleta Vuniqi -S, 0.9.2342.19200300.100.1.1=2000554108
Date: 2015.05.13 13:51:37 -04'00'

Bleta Vuniqi

Prepared: BVuniqi: 05/12/2015

CTS No.: ICC1400729

NDA 205747

APPEARS THIS WAY ON ORIGINAL

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/s/

CALLIE C CAPPEL-LYNCH
05/13/2015
signing for Bleta Vuniqi

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

PATIENT LABELING REVIEW

Date:	May 11, 2015
To:	Jean-Marc Guettier, M.D. Director **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, MSN, FNP-BC, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Ankur Kalola, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	HUMALOG KwikPen (insulin lispro injection) 200 units/mL
Dosage Form and Route:	solution for subcutaneous use
Application Type/Number:	NDA 20-5747
Applicant:	Eli Lilly and Company

1 INTRODUCTION

On May 10, 2013, Eli Lilly and Company submitted for the Agency's review an original NDA for new insulin lispro U-200 formulation and associated KwikPen device. The inulin lispro U-200 formulation is a concentrated version of the existing insulin lispro U-100 formulation.

On March 10, 2014, the agency issued a Complete Response letter. On November 26, 2014, Eli Lilly and Company submitted for the Agency's review a Complete Response to the Complete Response letter issued on March 10, 2014, for HUMALOG KwikPen, (insulin lispro injection), 200 Units/mL for subcutaneous use. Humalog KwikPen, (insulin lispro injection) 200 Units/ml is a rapid-acting insulin indicated to improve glycemic control in adults and children 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 Metabolic and Endocrinology Products (DMEP) on November 4, 2014, for DMPP and OPDP to review the Applicant's proposed Patient Package Information (PPI) and Instructions for Use (IFU) HUMALOG KwikPen, (insulin lispro injection), 200 Units mL for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on March 12, 2015.

2 MATERIAL REVIEWED

- Draft HUMALOG KwikPen (insulin lispro injection), 200 Units mL, PPI and IFU received on November 26, 2014, and received by DMPP on May 4, 2015.
- Draft HUMALOG KwikPen (insulin lispro injection), 200 Units mL, PPI and IFU received on November 26, 2014, and received by OPDP on May 4, 2015.
- Draft HUMALOG (insulin lispro injection), 200 Units mL, Prescribing Information (PI) received on November 26, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on May 4, 2015.
- Draft HUMALOG (insulin lispro injection), 200 Units mL, Prescribing Information (PI) received on November 26, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on May 4, 2015.
- Approved TOUJEO (insulin glargine [rDNA origin] injection) comparator labeling dated February 25, 2015.

3 REVIEW METHODS

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

with vision loss. We have reformatted the PPI and IFU documents using the Arial font, size 10.

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

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

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

20 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

SHARON W WILLIAMS
05/11/2015

ANKUR S KALOLA
05/11/2015

MELISSA I HULETT
05/11/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Devices and Radiological Health

Office of Compliance, Division of Manufacturing and Quality

Respiratory, ENT, General Hospital, & Ophthalmic Devices Branch

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Date:	March 20, 2015
To:	Callie, CappelLynch, CDER/OND/ODEII/DMEP, WO 22, Room 3362, Callie. CappelLynch@fda.hhs.gov
CC:	Office of combination products at combination@fda.gov
Through:	Rakhi Dalal, Ph.D., for Francisco Vicenty, Chief, CDRH/OC/DMQ/REGO, WO-66, Room 2642
	Rakhi M. Panguluri -S Digitally signed by Rakhi M. Panguluri -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300200210, cn=Rakhi M. Panguluri -S Date: 2015.05.05 12:06:33 -04'00'
From:	Bleta Vuniqi, Biomedical Engineer CDRH/OC/DMQ/REGO, WO-66, Room 2647
Applicant:	Eli Lilly and Company Center Drop Code 2543, Indianapolis, Indiana 46285 FEI: 1819470 Manufacturer: Eli Lilly and Company Center Drop Code 2543, 8645 Guion Rd. Indianapolis, Indiana 46268 FEI: 3006327424
Application #	NDA 205747
Product Name:	Humalog (insulin lispro) U-200

Consult Instructions:	Evaluate the Humalog (insulin lispro) U-200 documents provided by the applicant on quality system requirement 21 CFR 820, and determine if an inspection of the manufacturing facilities is required.

Background:
The Office of Compliance at CDRH received a consult request from CDER to evaluate NDA 205747 covering the medical device constituents of the combination product, and determine if an inspection of the manufacturing facilities is warranted.

Combination Product Description:
The Humalog® (b) (4) KwikPen™ (600 Unit KP) pen-injector has been designed for use with Insulin Lispro U-200. The components of the pen-injector do not contact the drug product. The drug remains in the primary container closure (cartridge) until a needle is attached to the Cartridge Holder and the drug is injected.

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

The firm noted that the development, design, and manufacturing of the Humalog (b) (4) KwikPen are compliant with the current Good Manufacturing Practice regulations for Combination Products, 21 CFR 4. Consistent with this regulation, during the development of this combination product the requirements of 21 CFR 820 are applied to the device constituent part. The Quality System covering the areas of the company responsible for the development and design of the device constituent part of the combination product includes requirements for Design Control (820.30), Purchasing Controls (820.50) and Corrective and Preventative Actions (820.100).

However, there was no information available for review regarding compliance with 21 CFR 820.20 (Management Controls) 21 CFR 820.30 (Design Controls), 21 CFR 820.50 (Purchasing Controls), and 21 CFR 820.100 (Corrective and Preventive Action).

With regards to information being provided to demonstrate compliance with applicable provisions of the Medical Device Quality System Regulation (21 CFR 820), this application was deficient. Additional information is required so that an appropriate review can be conducted.

Regulatory History Evaluation
After reviewing the application, the following facilities were potentially identified as being subject to applicable Medical Device Regulations under 21 CFR part 820:

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1555 S. Harding
Drop Code 2622
Indianapolis, Indiana 46285
FEI: 1819470

Firm is responsible form pen injector assembly, labeling and packaging, drug substance [redacted] (b) (4) Last FDA inspection covering medical device constituent parts was conducted on December 02-06, 2013. The inspection covered the firm's quality system regulations relating specifically to the firm's Humalog KwikPen (insulin lispro injection, USP) 200 U/mL (NDA 205747). A two-item FDA 483 Inspectional Observations form was issued for the following:

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- Use of ambiguous acceptance criteria and actual results recorded in validation and design testing documents
- Design reviews have not been fully documented
- Corrective and preventive actions did not include a systemic corrective action to prevent recurrence of nonconforming product.

A medical device inspection must be conducted prior to approval of the submission. Drug base GMP inspections were conducted in 2013, 2014 and 2015. The inspection did not follow up on the device base observations noted above, in addition to, design controls and purchasing controls required under part 4 or the regulations.

Eli Lilly and Company Center
Drop Code 2543,
8645 Guion Rd.

Indianapolis, Indiana 46268
FEI: 3006327424

Eli Lilly and Company Center is responsible for manufacturing, labeling, packaging, device assembly, and control testing. Last FDA inspection covering medical device constituent parts was conducted on December 02-06, 2013. The inspection covered the firm's quality system regulations relating specifically to the firm's Humalog KwikPen (insulin lispro injection, USP) 200 U/mL (NDA 205747). A two-item FDA 483 Inspectional Observations form was issued for the following:

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In addition to the written observations, there were three verbal observations discussed with firm management. These observations included:

- Use of ambiguous acceptance criteria and actual results recorded in validation and design testing documents
- Design reviews have not been fully documented
- Corrective and preventive actions did not include a systemic corrective action to prevent recurrence of nonconforming product.

Deficiencies to be conveyed to the applicant

Joerg Pfeifer, PhD
Advisor - US Regulatory Affairs
Eli Lilly and Company Center
Drop Code 2543,
Indianapolis, Indiana 46285
T: 1-317-276-2146
EM: pfeifer_joerg@lilly.com

The following deficiencies were identified while conducting a desk review of NDA 205747, in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product, and it is requested that the below be communicated to the firm:

Because your product is a combination product, you are reminded that Combination Products are subject to 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for Combination Products accessible at https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products

A review of your submission found that documentation to demonstrate compliance with applicable 21 CFR 820 regulations was not provided. In your response to this letter, please provide information pertaining to manufacturing or assembly of the finished

combination product and documents necessary to demonstrate compliance with applicable 21 CFR part 820 regulations (i.e., Management Responsibility, Design Controls, Purchasing Controls, and Corrective and Preventive Actions).

Suggestions on the types of documents to submit for review related to the applicable 21 CFR Part 820 regulations can be found in the guidance document titled "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff," issued on February 3, 2003. The complete document may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

CDRH Office of Compliance Recommendation

The Office of Compliance at CDRH has completed the evaluation of application NDA 205747 and has the following recommendations:

NDA 205747 recommendation of approvability under the Medical Device Quality System Regulations should be delayed until the sponsor provides an adequate response to the deficiencies identified above, and a medical device inspection is conducted at Eli Lilly and Company Center (1555 S. Harding, Drop Code 2622, Indianapolis, Indiana 46285: FEI: 1819470) and Eli Lilly and Company Center (Drop Code 2543, 8645 Guion Rd. Indianapolis, Indiana 46268: FEI: 3006327424).

Bleta Vuniqi -S

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Date: 2015.05.06 20:13:34 -04'00'

Bleta Vuniqi

Prepared: BVuniqi: 02/27/2015

CTS No.: ICC1400553

NDA 205054

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/s/

CALLIE C CAPPEL-LYNCH
05/07/2015
signing for Vleta Vuniqi

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

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

Memorandum

Date: May 5, 2015

To: Calli Cappel-Lynch, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

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

Subject: OPDP Labeling Consult Request

NDA 205747 Humalog U-200 (insulin lispro injection, USP [rDNA origin] for injection)

On December 2, 2014, OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI) and Patient Information (PPI) for Humalog U-200 (insulin lispro injection, USP [rDNA origin] for injection) (Humalog). OPDP's comments on the proposed draft PI are based on the version sent via email by Calli Cappel-Lynch on May 4, 2015 and are provided below.

Additionally, OPDP will work collaboratively with DMPP to provide comments on the PPI under separate cover.

If you have any questions, please contact Ankur Kalola at 301-796-4530 or Ankur.Kalola@fda.hhs.gov.

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/s/

ANKUR S KALOLA
05/05/2015

M E M O R A N D U M

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

DATE: March 25, 2015

TO: Division of Metabolism and Endocrinology Products (DMEP)

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

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: NDA 205747

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting the data without an on-site inspection. The rationale for this decision is noted below.

The site listed below was inspected within the last year. The inspectional outcomes from the inspections were classified as No Action Indicated (NAI).

Requested Site Inspection

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

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/s/

SHILA S NKAH
03/26/2015

HUMAN FACTORS, LABEL AND LABELING REVIEW

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

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

Date of This Review:	March 12, 2015
Requesting Office or Division:	Division of Metabolic and Endocrinology Products (DMEP)
Application Type and Number:	NDA 205747
Product Name and Strength:	Humalog KwikPen (insulin lispro) for injection, 200 units/mL
Product Type:	Combination Product (Drug + Device)
Rx or OTC:	Rx
Applicant/Sponsor Name:	Eli Lilly
Submission Date:	November 26, 2014
OSE RCM #:	2014-1190
DMEPA Primary Reviewer:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Yelena Maslov, PharmD

1 REASON FOR REVIEW

Lilly resubmitted Humalog (insulin lispro) U-200 for review and DMEP requested that we review the container label, carton and insert labeling, instructions for use, and human factors study results to ensure they are acceptable from a medication error perspective. This submission is a response to Agency's complete response (CR) letter dated March 10, 2014.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

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

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Lilly conducted additional human factors study to address human factors deficiencies outlined in the CR letter as detailed in Appendix C. There were three main areas that were addressed:

1. Dose Dialing (not counting "clicks"): 2 participants dialed 1 unit more than the intended dose but were able to detect the use error and re-dial correctly during moderator probing. Both participants stated the intended dose when asked by the moderator and confirmed that they had dialed 1 unit more than the intended dose when asked to look at the dialed dose on the pen. First participant stated that it was "pure human error" and the second participant indicated that diabetic patients can adjust the dose according to blood glucose levels and didn't appear concerned with 1 unit overdose. They indicated that they dialed by looking at the dial, not by listening to the "clicks".

2. All patient and caregivers gave correct answers to jammed pen scenario and were able to find and state the printed warning on the pen about not transferring to a syringe and the warning in the IFU about not using auditory feedback when dialing a dose.
3. Prescribers: 1 prescriber misunderstood the task instructions and was able to provide the correct answer after having stated that he/she would cut the dose in half for U-200. The prescriber indicated that he/she did not read the full communication letter but was focused on the concentration.

The results indicate that the modified instructions for use and communication documents are acceptable.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that container label, carton labeling, and instructions for use are acceptable from a medication error perspective, but the proposed package insert and can be improved to promote the safe use of the product. We also have recommendations for the container label and carton labeling.

4.1 RECOMMENDATIONS FOR ELI LILLY

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

A. Prescribing Information

1. Highlight of Prescribing Information: Add the statement or similar: (b) (4)

2. Full Prescribing Information: Dosage and Administration Section 2.1 Dosage Considerations:

   Add the statement or similar: (b) (4)

B. Carton and Container Labels

1. Revise the proprietary name, established name and strength presentation to read:

   Humalog Kwikpen
   Insulin lispro injection, USP
   For Single Patient Use Only
   200 units/mL

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Humalog KwikPen U-200 that Eli Lilly submitted on November 26, 2014.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Humalog KwikPen U-200</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>Insulin lispro</td></tr>
<tr><td>Indication</td><td>HUMALOG® is a rapid acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.</td></tr>
<tr><td>Route of Administration</td><td>Subcutaneous injection</td></tr>
<tr><td>Dosage Form</td><td>Solution for injection</td></tr>
<tr><td>Strength</td><td>200 units/mL</td></tr>
<tr><td>Dose and Frequency</td><td>Individualized dose within 15 minutes before a meal or immediately after a meal</td></tr>
<tr><td>How Supplied</td><td>3 mL Humalog KwikPen</td></tr>
<tr><td>Storage</td><td>
<table>
<tr><th></th><th>Not In-Use (Unopened) Room Temperature (Below 86°F [30°C])</th><th>Not In-Use (Unopened) Refrigerated</th><th>In-Use (Opened) Room Temperature, (Below 86°F [30°C])</th></tr>
<tr><td colspan="4">HUMALOG U-200</td></tr>
<tr><td>3 mL Humalog KwikPen (prefilled)</td><td>28 days</td><td>Until expiration date</td><td>28 days, Do not refrigerate. Stability Summary and Conclusion 3.2.P.8.1</td></tr>
</table>
</td></tr>
<tr><td>Container Closure</td><td></td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

We searched the L: drive on February 20, 2015 using the terms, Humalog to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review[1]. The Application received a CR, thus the comments were not communicated to the Applicant.

[1] Agustin R. Label and Labeling Review for Humalog Kwikpen (Insulin Lispro) for Injection, U-200 (NDA 205747). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 May 10. 32 p. OSE RCM No.: 2013-1190 & 1194.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design

On May 7, 2014, Lilly had an End of Review Type A meeting with the FDA to discuss and gain alignment on the information required to address the FDA complete response letter. Details of the discussion are captured in the final version of the FDA minutes issued on July 14, 2014. As an outcome of the meeting, Lilly agreed to conduct a supplemental Summative Human Factors study with the following objectives:

- To conduct a performance-based assessment of the language in the IFU instructing patients to visually dial their dose, and
- To conduct knowledge-based assessments of:
  - the revised Patient Communication Document
  - the revised Healthcare Professional (HCP) Communication Document
  - the revised language in the Instructions for Use (IFU) instructing patients to not use auditory feedback (ie, count clicks) when dialing their dose

2.3 Study Subjects

The study population was representative of the Humalog KwikPen 200 units/mL intended user population, and included:

[n=10] Patients* with Type 1 or Type 2 diabetes mellitus who require injections of at least 20 units/day of mealtime insulin to maintain normal glucose homeostasis.

[n=6] Caregivers* (≥18 years of age) who administer insulin injections, in a nonprofessional capacity, to Patients with diabetes who require at least 20 units/day of mealtime insulin.

[n=15] Prescribers, i.e., Physicians, Nurse Practitioners (NPs), or Physician Assistants (PAs), who currently prescribe mealtime insulin to Patients with diabetes.

*Note: All Patients and Caregivers were required to complete all steps required for administering the injection including preparing the pen, dialing the dose, and injecting the dose.

Table 2.3-1 Recruiting Targets – Patients and Caregivers

Characteristic	Stratification	Minimum Target	Number Completed
Overall	N/A	15	16
Subject Type	Patient	5	10
	Caregiver	5	6
Impairments	Vision (VF-14 QOL ≤75)	3	2*
	Hand (M-SACRAH>30)	3	3

2.5 Study Materials

The Humalog 200 units/mL KwikPen is a mechanical, pre-filled insulin pen injector (Figure 2.5-1) intended for the subcutaneous injection of 200 units/mL Humalog insulin.

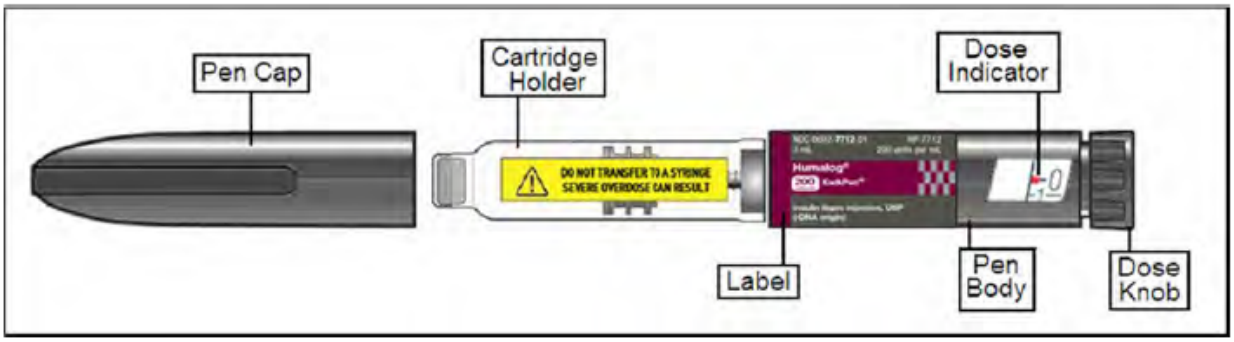

Figure 2.5-1 User Interface –U200 KwikPen

The test devices were equivalent to production devices with respect to the user interface. For safety, pens were filled with saline solution instead of insulin. An image of the pen label, as tested in the study, is shown in Figure 2.5-2 below.

Figure 2.5-2 Pen Label

Production-equivalent cartons were used. An image of the tested version of the carton is shown in Figure 2.5-3 below.

Figure 2.5-3 Carton

1.1 IFU changes

In response to FDA requests related to dose dialing, the IFU step for selecting the dose was revised to include statements to not count clicks and to check the number in the dose window, as indicated by the red box in Figure 1.1-1. Please note the red boxes are for providing clarity to the reviewer for purposes of this NDA resubmission only. (b) (4)

Figure 1.1-1 IFU Change –Selecting the Dose

To maximize the message effectiveness, the design of the added text conforms to basic principles of effective visual design (Williams, 1994):

- **Contrast:** The bolded font of the "check the number" message, slightly separated from the other text elements, increases its prominence within the section.
- **Repetition:** The "counting clicks" text uses the same bullet level as other elements of the step, to promote association with those elements.
- **Alignment:** The "check the number" text is aligned with the primary element of the section (i.e., "turn the dose knob") to emphasize its level of importance within the step.
- **Proximity:** The "counting clicks" text is placed with the other elements of the step to promote association with those elements. The "check the number" text is placed within the lines delineating the step section to indicate its association with the step.

1.2 Patient Communication Document Changes

In response to FDA requests related to important information for patients and caregivers, the Patient Communication Document (Figure 1.2-1) was revised in accordance with established principles of effective visual design to emphasize:

- the hazards associated with withdrawing with a syringe, and
- what to do if there are problems using the pen

Please note the red boxes are for providing clarity to the reviewer for purposes of this NDA resubmission only. (b) (4)

(b) (4)

1.3 HCP Communication Document Changes

In response to FDA requests related to important information for prescribers, the HCP Communication Document was revised (Figure 1.3-1) to emphasize the hazards associated with U200 insulin, including critical information regarding the dialed dose, the prescribed dose, and drug concentration.

Please note the red boxes are for providing clarity to the reviewer for purposes of this NDA resubmission only. (b) (4)

(b) (4)

Figure 1.3-1 HCP Communication Document Changes

1. Patient and Caregiver
    a. Simulated pharmacy scenario: received the patient communication document with carton of pens. Briefly went over key messages of the patient communication document.
    b. Dose Dialing Task: Instructed to follow the IFU while dialing their own typical mealtime insulin dose.
    c. IFU/Knowledge assessment:

Question Number	Question and Correct Response
1	It is time for your mealtime dose of insulin. If this pen becomes jammed, what would you do for your dose? (If study participant says "use a syringe", go to question #2; if participant does not mention a syringe, go to question #3.) **Correct response:** Must not mention a syringe.
2	If response to question #1 is "use a syringe": How would you use it? What if your dose was 20 units, what would you do? (Also ask what the pen instructions say about using a syringe.) **Correct response:** Must indicate filling the syringe to half the volume.
3	Is there a printed warning on this pen? [Yes, No, or I don't know] a. If "yes": What does it say? (If Participant says a different warning, ask if there is another warning on the pen). **Correct response:** Any variation of *"Do not transfer to a syringe, severe overdose can result"*. b. If "no": Pull off cap and show the pen to the participant and ask if they see the warning now. Also ask why they think they did not see it? c. If "I don't know": Show the pen to the participant and ask if they see the warning now. **Correct response:** Any variation of *"Do not transfer to a syringe, severe overdose can result"*.
4	Now I would like you to go to step 3 in the Instructions for Use. What does this step say about selecting your dose by counting clicks? (If other: Tell me more about that.) **Correct response:** Any variation of *"Do not dial your dose by counting clicks"*.

2. Prescribers
    a. Simulated clinical practice scenario: Provided with the HCP communication document and directed to read it.
    b. Knowledge Assessment:

#	Moderator Question
1	If your patient typically uses 10 units with the 100U/ ml Humalog KwikPen and you are switching them to the 200U/ml Humalog KwikPen, what would you tell them to dial on the new pen and why? (If other, show them the Communication Document and ask where in the materials they found that.) **Correct response:** 10.
2	If the pen becomes jammed, how would you tell your patient to get their mealtime dose? (If study participant says "use a syringe", go to question #3.) **Correct response:** Must not mention a syringe.
3	If response to question #2 is "use a syringe": How would you tell your patient to use it? What if your patient's dose was 20 units, what would you tell them to do? (Also ask what the documents say about using a syringe.) **Correct response:** Must indicate filling the syringe to half the volume.

C.2 Results

Table 4-1 provides a summary of the observed task failures.

Table 4-1 Task Failures Summary

Group	n	Task Failures	
		Task 1: Dose Dialing	Task 2: Instructional Materials Assessment
Patients and Caregivers	16	2	0
Prescribers	15	N/A	1
Total	31	2/16 (13%)	1/31 (3%)

4. Dose Dialing: 2 participants dialed 1 unit more than the intended dose but were able to detect the use error and re-dial correctly during moderator probing. Both participants stated the intended dose when asked by the moderator and confirmed that they had dialed 1 unit more than the intended dose when asked to look at the dialed dose on the pen. First participant stated that it was "pure human error" and the second participant indicated that diabetic patients can adjust the dose according to blood glucose levels and didn't appear concerned with 1 unit overdose.
5. All patient and caregivers gave correct answers to jammed pen scenario and were able to find and state the printed warning on the pen about not transferring to a syringe and the warning in the IFU about not using auditory feedback when dialing a dose.
6. Prescribers: 1 prescriber misunderstood the task instructions and was able to provide the correct answer after having stated that he/she would cut the dose in half for U-200.

APPENDIX D. LABELS AND LABELING

D.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[2] along with postmarket medication error data, we reviewed the following Humalog KwikPen U-200 labels and labeling submitted by Eli Lilly on November 26, 2014.

- Container label
- Cartridge Holder
- Carton labeling
- Instructions for Use

D.2 Label and Labeling Images

(b) (4)

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

10 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

SARAH K VEE
03/13/2015

YELENA L MASLOV
03/13/2015

M E M O R A N D U M

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

DATE: February 02, 2015

TO: Division of Metabolism and Endocrinology Products

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

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: NDA 205747

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

OSI inspected the site listed below within the last four years. The inspectional outcomes from the inspections were classified as No Action Indicated (NAI).

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Clinical	Lilly- NUS Centre for Clinical Pharmacology Pte Ltd,Level 6 Clinical Research Centre (MD 11), National University of Singapore	10 Medical Drive Singapore 117597

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/s/

SHILA S NKAH
02/02/2015

M E M O R A N D U M

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

DATE: February 02, 2015

TO: Division of Metabolism and Endocrinology Products

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

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: NDA 205747

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

OSI inspected the site listed below within the last four years. The inspectional outcomes from the inspections were classified as No Action Indicated (NAI).

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Clinical	Lilly- NUS Centre for Clinical Pharmacology Pte Ltd,Level 6 Clinical Research Centre (MD 11),National University of Singapore	10 Medical Drive Singapore 117597

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/s/

SHILA S NKAH
02/02/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICE MEMORANDUM

FDA/CDRH
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: January 4, 2015
From: Lana Shiu, M.D.
General Hospital Devices Branch, DAGRID,
ODE, CDRH

To: Callie Cappel-Lynch, RPM, CDER/OMPT/CDER/OND/ODEII/DMEP

Via: Ryan McGowan/Keith Marin,

Combination Products Team Leader, GHDB, DAGRID, CDRH

Rick Chapman

Branch Chief, General Hospital Devices Branch, DAGRID, ODE, CDRH

Subject: NDA 205747, ICC 1400729 (previously ICC 1300267 and last supplement reviewed was supplement 3) -- Insulin lispro 200 units/mL KwikPen™

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding NDA 205747. The device constituent of this combination product consists of a pen injector to deliver insulin lispro.

4/21/2014-ICC 1300276-Supplement 3:
Eli Lilly and Company (Lilly) is developing Insulin Lispro, 200 units/mL (U-200), which is a concentrated formulation of Humalog. The U-200 prefilled pen injector (KwikPen) device provides a total of 600 units of insulin lispro. The New Drug Application (NDA) 205747 for insulin lispro (rDNA origin) 200 units/mL KwikPen was submitted on 10 May 2013. Dr. Jackie Ryan did the initial review in which she identified five deficiencies that needed to be addressed by the sponsor. Bifeng Qian provided the biocompatibility consult. Recommendation at the end of ICC 1300267/S3 review was that 6 biocompatibility questions, #1 and #2 were adequately responded to but #3, 4, 5, 6 were not adequately addressed and further questions were posed to the sponsor and listed below.

☐It is noted [redacted] (b) (4) in the subject device. However, the MSDS provided does not clearly identify [redacted] (b) (4) Recommend that the sponsor clearly identify all [redacted] (b) (4) used in the subject device, including the chemical name, CAS reg. No., composition, and toxicological data.

☐The MSDS provided does not identify [redacted]. Recommend that the sponsor clearly identify all [redacted] used in the subject device, including the chemical
name, CAS reg. No., composition, and toxicological data.

☐The justification provided for not performing the chemical leachable analysis may be acceptable, if the biocompatibility testing provided in firm's future submission is adequate and appropriate to support the subject device.

☐Recommend that the sponsor provide a complete biocompatibility testing report that includes a detailed description of the test device and sample preparation, description of the test procedures, appropriate controls, summary of test results, test criteria, and conclusion. Our determination will be based on review of the final test report and data submitted.

Analysis of the Sponsor's Responses to the Biocompatibility Deficiencies for ICC 1400729

Biocompatibility Deficiency #1:

- Please clarify if the 3 mL Insulin Cartridge has been previously cleared or approved by the FDA. Please provide evidence to demonstrate that the Cartridge used is biocompatible and material compatible based on its intended use and patient contact classification.

Sponsor's Response #1:

- The rubber disc seal supplier [redacted] conducted biocompatibility testing of the disc seal and the results are found in the [redacted] Drug Master File (DMF) [redacted] (Type III), for which Lilly provided a Statement for Right of Reference in Section 1.4.2 of the initial NDA 205747 submission. Additionally, as agreed to in the End of Review meeting and documented in the FDA minutes dated 14 July 2014, Lilly is providing the Lilly test results [redacted] in Module 3.2.P.2.4.6 of this resubmission to address FDA CR Letter Comment 2.

Consultant Reviewer's Comment #1:

- Advised by LCDR Keith Marin, the Combination Product Team Leader of DAGRID/ GHDB, primary drug containers are reviewed by CDER. This question has been deferred to CDER/CMC after discussion with the CDER review team at the FDA pre-meeting for 7 May 2014 End of Review (Type A) Meeting.

Biocompatibility Deficiency #2:

In your study report of "Biological Evaluation of KwikPen Device Platform" submitted in the S002 response, you state "The KwikPen platform of prefilled insulin injection devices includes [redacted] This evaluation covers currently marketed devices [redacted].
On page 1 of the evaluation report, you have provided a Table which lists your final finished device models.

Please clearly identify all subject devices and device models or types included in this NDA. [redacted]

(b) (4)

Sponsor's Response #2:

- In the background materials submitted on 15 April 2014 for the End of Review meeting, Lilly provided the requested clarifications as below:

The subject device of NDA 205747 is the Humalog KwikPen 200 units/mL (U-200) only.

NDA 205747 for Humalog KwikPen 200 units/mL includes references to the marketed Humalog KwikPen (U-100). The references were used only to highlight the similarities and differences of the subject device to the marketed device.

The biological evaluation report submitted to FDA on 09 December 2013 provided a table on page 1 under "Scope" of all of the Lilly KwikPen products, (b) (4) Table 4.1 below was created for this briefing document to clarify the device models/types that have either been approved or have not been approved by FDA.

Table 4.1. Marketed Drug Products with KwikPen in the US

Product	Pen Color	Submission	Status
Humalog KwikPen 200 units/mL	Dark Gray	NDA 205747	Subject Device under FDA review
Humalog® KwikPen™ Humalog® Mix75/25 KwikPen™ Humalog® Mix50/50 KwikPen™	Blue	NDA 20563 NDA 21017 NDA 21018	Approved by FDA, marketed in the US, and not subject to this review
Humulin® N KwikPen™ Humulin® 70/30 KwikPen™	Beige	NDA 18781 NDA 19717	Approved by FDA, marketed in the US, and not subject to this review
(b) (4)		NDA 205692	Under FDA review and not subject to this review
		(b) (4)	Investigational and not subject to this review

Consultant Reviewer's Comment #2:

- The response is deemed adequate.

Biocompatibility Deficiency #3:

- Please clarify to the Agency if the materials identified in Table 1 of your biological evaluation report represent ALL materials used in the manufacturing process to construct the subject devices of this NDA (b) (4) If not, please provide a complete listing of ALL the manufacturing materials used and the associated Material Safety Data Sheets (MSDS).

Sponsor's Response #3:

- Lilly provided information in the background materials submitted on 15 April 2014 for the End of Review meeting. In FDA preliminary comments for

the End of Review meeting, FDA noted [redacted] in the subject device, yet the MSDS documents that Lilly provided did not clearly identify [redacted] The FDA recommended that Lilly clearly identify all [redacted] used in the subject device, including the chemical name, CAS reg. No., composition, and toxicological data. Lilly acknowledged that information was not provided [redacted] in the MSDS documents in the background materials for the End of Review meeting as they were deemed trade secrets by the suppliers. At the End of Review meeting, FDA agreed that the information could be provided either via a Master File or by providing the chemical name and identity, the percentage of the chemical used in the final device, health problems associated with the chemical, and available toxicological data (reference doses, LD50, NOAEL, and LOAEL) to justify that the safety concerns related to the use of the chemical in the device are negligible.

In this resubmission, Lilly is providing a table of all the manufacturing materials used in the external components of the subject device, [redacted] and either the MSDS documents or a reference to the Master File for each of the listed materials. These documents are provided in Module 3.2.R.2.7, Pen Attachment 4 of this resubmission.

Consultant Reviewer's Comment #3:

- The response is deemed adequate. Data presented in the MSDS reports do not indicate significant safety concerns for the chemicals under the intended use conditions.

Biocompatibility Deficiency #4:

- You state that the devices in the platform [redacted] Table 1 of your biocompatibility evaluation report [redacted] However, your MSDS provided does not clearly identify [redacted] Please provide a revised MSDS report which includes the chemical identity, composition, CAS number, and toxicological data [redacted] used in the subject devices.

Sponsor's Response #4:

- Lilly is providing a table of all the manufacturing materials used in the external components of the subject device, [redacted] and either the MSDS documents or a reference to the Master File for each of the listed materials in Module 3.2.R.2.7, Pen Attachment 4 of this resubmission.

Consultant Reviewer's Comment #4:

- The response is deemed adequate.

Biocompatibility Deficiency #5:

- Please provide chemical analysis of the leachables [redacted]

Sponsor's Response #5:

- In the background materials submitted on 15 April 2014 for the End of Review meeting, Lilly proposed that a separate chemical analysis of the leachables of the device [redacted] is not required if biocompatibility testing conducted per the ISO 10993 standard on the final finished device components that have user contact demonstrates acceptable results. The FDA agreed in the 02 May 2014 preliminary meeting comments to the End of

Review meeting (also captured in the 14 July 2014 FDA meeting minutes), that the justification provided for not performing the chemical leachable analysis may be acceptable, if the biocompatibility testing provided in the Lilly NDA resubmission is adequate and appropriate to support the subject device. As the biocompatibility testing (Module 3.2.R.2.7, Pen Attachment 4) demonstrated acceptable results per the ISO 10993 standard, Lilly asserts that the deficiency has been addressed.

Consultant Reviewer's Comment #5:

- The response is deemed adequate.

Biocompatibility Deficiency #6:

- In the study report of "Biological Evaluation of KwikPen Device Platform", you have included testing reports for in vitro cytotoxicity, irritation, and sensitization. The test devices used in the biocompatibility testing were described (b) (4) Based on this description, we are unclear if the testing was conducted on the subject devices that include all patient/user contact device components. In addition, the biocompatibility testing provided was completed in August, 2005, which was nearly 9 years ago. This is not acceptable. As risk analysis based on raw materials may have limitations and may not represent the final device components in the submission, FDA believes that safety assessments need to be done based on the final finished subject devices. Please provide current biocompatibility testing data, based on the final finished subject devices and a worst case condition. Please be advised all patient/user contact device components should be tested for biocompatibility (b) (4)

Sponsor's Response #6:

- The results of biocompatibility testing on the user contact components of the subject device are provided in Module 3.2.R.2.7, Pen Attachment 4 of this resubmission.

Consultant Reviewer's Comment #6:

- The sponsor has provided testing for in vitro cytotoxicity, skin irritation, and sensitization. The test device was identified as Humalog (Dark Gray) KwikPen PatientContact Components. The test extracts were prepared based on ISO 10993-12. The tests were conducted based on ISO 10993-5 and ISO 10993-10. The test results demonstrated that the test device did not induce cytotoxic response, skin irritation and sensitization. The testing provided is deemed appropriate and acceptable.

Recommendation:

The sponsor has adequately responded to all previous biocompatibility questions. No further issues from CDRH engineering perspective.

Digital Signature Concurrence Table	
Reviewer Sign-Off Lana Shiu, M.D.	Digitally signed by Lana L. Shiu -S Date: 2015.01.05 16:19:58 -05'00'
Branch Chief Sign-Off Richard Chapman	Digitally signed by Richard C. Chapman -A Date: 2015.01.05 16:32:02 -05'00'

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/s/

CALLIE C CAPPEL-LYNCH
01/06/2015
signed for Lana Shiu

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: August 12, 2014

TO: Jean-Marc Guettier, M.D.
Director, Division of Metabolism and Endocrinology Products, Acting
Office of Drug Evaluation II

FROM: Seongeun Julia Cho, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: Evaluation of a firm's response at the request of the Untitled Letter dated 4/18/2014

Background

At the request of the Division of Metabolism and Endocrinology Products (DMEP), Lilly-NUS Centre for Clinical Pharmacology, Singapore, the clinical site for the following bioequivalence study, was inspected.

Study F3Z-EW-IOPY: Evaluation of Bioequivalence of Two Formulations of Insulin Lispro in Healthy Subjects

Inspection: Inspection of Lilly-NUS Centre for Clinical Pharmacology, Singapore, was conducted during 11/7/2013 - 11/15/2013 by ORA investigator Kellia Hicks and OSI/DBGLPC scientist Seongeun Cho.

Form FDA 483 was issued at the close-out of the inspection for the following item.

1) Samples of the reference standard used in a bioequivalence study were not retained and released to FDA upon request as required by 21 CFR Part 320.138. Specifically, your firm failed to retain and provide samples of the reference standard Humalog 100U/ml, Lot A677287 used in Bioequivalence Study F3Z-EW-IOPY(a); Evaluation of the Bioequivalence of Two Formulations of Insulin Lispro in Healthy Subjects.

On November 26, 2013, in a written response to the observation, Dr. Danny Kwang Wei Soon, Managing Director & Principal Investigator, Lilly-NUS Center for Clinical Pharmacology, stated that Lilly-NUS has implemented a Standard Operating Procedure (SOP) titled "Management of investigational product samples for retention," which became effective on October 30, 2012.

On April 18, 2014, OSI issued an Untitled Letter to Dr. Soon for a regulatory violation, failure to retain bioequivalence reserve samples of the reference drug product at the clinical study facility [21 CFR 320.38].

Evaluation of the firm's response

OSI has received the site's written response, dated May 8, 2014 (Attachment 1). At the request of the Untitled Letter, Dr. Soon submitted the SOP that became effective on October 30, 2012, and also an updated version of the SOP that became effective on May 1, 2014. Per this current procedure, it is the sponsor's responsibility to inform the site if there is a requirement to retain investigational product samples for a BA/BE study. It also notes that the Clinical Project Specialist (CPS) and/or Principal Investigator (PI) are responsible for obtaining confirmation from the sponsor on the requirement and quantity of investigational product samples to be retained. The SOP also describes procedures for selection of reserve samples and their storage.

This reviewer finds the firm's updated procedure for retaining investigational product samples is adequate to prevent future occurrence properly. (b) (4) (b) (4) (b) (4) The firm's continued

compliance to its written procedure will be confirmed during OSI's next inspection.

Summary and Conclusion:

This reviewer finds the firm's response to the Untitled Letter adequate and recommends closing the case.

Seongeun (Julia) Cho, Ph.D.
Bioequivalence Branch, DBGLPC, OSI

Attachments:

Attachment 1: Response to the Untitled Letter by Lilly-NUS, dated 5/8/2014

CC:
OSI/Kassim/Taylor/Haidar/Bonapace/Skelly/Choi/Dasgupta/Biswas/Dejernett/Nkah/Fenty-Stewart/Johnson
OCP/DCP2/Suryanarayana Sista/Chandra Sahajwalla
OND/DMEP/Jean-Marc Guettier/Callie Cappel-Lynch

Emai c:
(b) (4) -DO/ (b) (4)

Draft: SC 8/12/14
Edit: MFS 8/12/14
OSI: BE 6474
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Inspections/BE Program/Clinical Sites/L S, Singapore
FACTS: (b) (4)

Attachment 1

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/s/

SEONGEUN CHO
08/12/2014

SAM H HAIDAR
08/20/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

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

CDRH Human Factors Consult Review

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

DATE: July 16, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID
TO: Callie Cappel-Lynch, Regulator Project Manager, CDER/OND/ODEII/DMEP

SUBJECT: **NDA 205747**
Applicant: Eli Lilly
Drug: Humalog
Device: U-200 peninjector
Intended Use: treatment of diabetes (types I or II)
CDRH CTS Tracking: ICC1400310

Digitally signed by Quynhnhu T. Nguyen -S
Date: 2014.07.17 14:03:44 -04'00'

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ronald D. Kaye -S
Digitally signed by Ronald D. Kaye -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ronald D. Kaye -S, 0.9.2342.19200300.100.1.1=1300110677
Date: 2014.07.17 14:25:38 -04'00'

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

CDRH Human Factors Review

Combination Product Device Information

Submission No.: NDA 205747
Applicant: Eli Lilly
Drug: Humalog
Device: U-200 peninjector
Intended Use: treatment of diabetes (types I or II))

CDRH Human Factors Involvement History

- 5/19/2014 – CDRH HFPMET was requested to review a human factors supplemental study protocol contained in a meeting package (sequence # 21, dated 4/15/2014). The request states: Please review the meeting request and briefing document (sequence # 25) for the type C meeting (briefing document due June 27, 2014) and provide comments in the sharepoint document by 7.20.14. If an internal meeting is necessary, please let me know.
  Cover Letter: \\CDSESUB1\evsprod\NDA205747\0021\m1\us\cover.pdf
  EDR Location: \\CDSESUB1\evsprod\NDA205747\0025
- 7/17/2014 – CDRH HFPMET provided feedback to CDER.

Overview and Recommendations

The Division of Metabolism and Endocrinology Products, Office of New Drugs, Center for Drugs Research and Evaluation requested a consultative review on the human factors supplemental study protocol contained in the meeting request under NDA 205747 (b) (4) The device constituent is the U-200 peninjector for delivery of humalog for treatment of diabetes mellitus.

NDA 205747 for insulin lispro (rDNA origin) 200 units/mL, was submitted on May 10, 2013. On March 10, 2014, a Complete Response letter was issued for this application. Subsequently, Lilly had a Type A meeting (teleconference) with FDA on May 7, 2014 to gain alignment with FDA on Lilly's response plan and contents of the resubmission to address FDA's concerns cited in the Complete Response Letter. In both the Complete Response Letter and the teleconference, FDA requested that Lilly conduct a supplemental Human Factors Study to test further mitigations for the KwikPen device to mitigate risks associated with overdose. The purpose of this meeting is to obtain written FDA comments on the supplemental study protocol.

The supplemental HF study protocol employs acceptable methodology for collecting and evaluation HF data. However, there are several concerns regarding the overall assessment of the modified user interface, mainly, the questions that are used for knowledge-based assessments of the intended users. These concerns are described in the proposed response to Question 1 (below).

Sponsor's Question 1: Does FDA agree with the study design as defined in the attached protocol, including the tasks and planned user groups to be evaluated?

CDRH HF's Proposed Response:

The supplemental HF study protocol includes general methodology that is adequate for collecting HF data. We have the following concerns regarding:

I. The questions intended to be used for knowledge-based assessments of the intended users. Your protocol outlined the following questions:

#	Moderator Question
1	What do the instructions say about removing insulin from the pen with a syringe? **Answer**: Do not transfer insulin from your pen to a syringe
2	What should you do if your pen does not work? **Answer**: Any of the following: Try a new needle, use a backup pen, call pharmacist, call HCP, call Lilly
3	What do the Instructions for Use tell you in Step 3 about selecting your dose by counting clicks? **Answer**: Do not dial your dose by counting clicks.

Figure 1: Instructional Materials Assessment - Patient and Caregiver Questions and Sample Answers

#	Moderator Question
1	If you had a patient taking 10 units with the 100U/ ml Humalog KwikPen and you are switching them to the 200U/ml Humalog KwikPen, what dose would you have them dial on the 200 U/ml Humalog KwikPen? **Answer**: 10 units
2	What does the document say about transferring insulin from the pen to a syringe? **Answer**: Do not transfer from the pen to a syringe.

Figure 2: Instructional Materials Assessment – Prescriber Questions and Sample Answers

While these questions are designed to assess the user's general knowledge about the use of your device, we do not believe that they provide adequate focus on the use-scenarios we are concerned about.

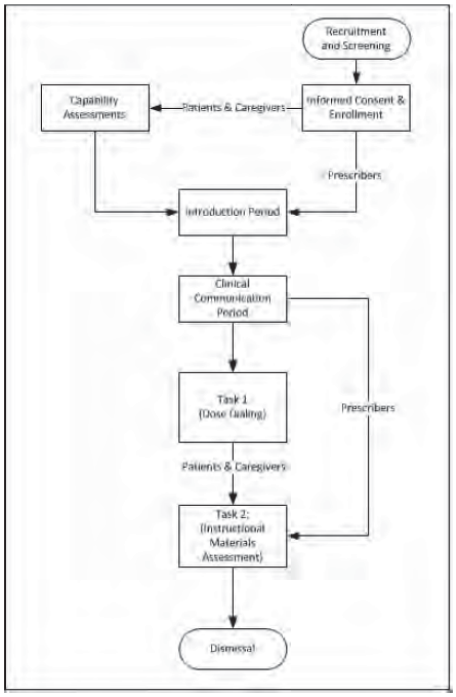
For patients and caregivers, we recommend that you use the following questions, in order, for your subjective data collections:

1. If this injector becomes jammed, how would you inject your insulin dose? (Note to moderator: collect all of the responses from study participants)
2. Would you use a syringe with this product? [Yes or No]
    a. If "yes": How would you use it? (Note to moderator: collect all of the responses from study participants)
    b. If "no": Why not? (Note to moderator: collect all of the responses from study participants)
3. Is there a printed warning on this peninjector? [Yes, No, or I don't know]
    a. If "yes": What does it say?
    b. If "no": Show the pen to the participant and ask if they see the warning now and ask why do you think you did not see it? (Note to moderator: collect all of the responses from study participants).
    c. If "I don't know": Show the pen to the participant and ask if they see the warning now. (Note to moderator: collect all of the responses from study participants).

For healthcare providers, i.e. prescribers, we recommend that you use the following questions, in order, for your subjective data collections:

1. If your patient typically uses 10 units with the 100U/ ml Humalog KwikPen and you are switching them to the 200U/ml Humalog KwikPen, what would you tell them to dial on the new peninjector?
2. If this injector becomes jammed, how would you inject your insulin dose? (Note to moderator: collect all of the responses from study participants)
3. Would you use a syringe with this product? [Yes or No]
    a. If "yes": How would you use it? (Note to moderator: collect all of the responses from study participants)
    b. If "no": Why not? (Note to moderator: collect all of the responses from study participants)
4. Is there a printed warning on this peninjector? [Yes, No, or I don't know]
    a. If "yes": What does it say?
    b. If "no": Show the pen to the participant and ask if they see the warning now and ask why do you think you did not see it? (Note to moderator: collect all of the responses from study participants).
    c. If "I don't know": Show the pen to the participant and ask if they see the warning now. (Note to moderator: collect all of the responses from study participants).

II. The study design with respect to the healthcare providers/prescriber. You provided the following flow diagram:



We are unclear why the prescribers are not expected to perform the dose dialing task.

Sponsor's Question 2: Does FDA agree that the supplemental HF study, if successful, will be adequate to address the FDA comments related to human factors provided in the 10 March 2014 CR letter?

CDRH HF's Proposed Response:

Provided that you satisfactorily address the issues raised in Question 1, and our review of the resulting data from your supplemental study in demonstrating that mitigations are effective, we should not have any further questions regarding the human factors component of the submission.

Appendix 1: Summary of Human Factors Validation Study Protocol

The supplemental HF validation study will include the following assessments, which are based on the discussion and agreements from the Type A meeting:

- A knowledge-based assessment of the revised patient communication document
- A knowledge-based assessment of the revised HCP communication document
- A knowledge-based assessment of the revised language in the Instructions for Use (IFU) instructing patients not to use auditory feedback (ie, count clicks) when dialing their dose
- A performance-based assessment of the language in the IFU instructing patients to visually dial their dose

As per FDA's request in the Type A meeting, the study will include 15 HCPs and 15 patients or caregivers.

Figure 1 below provides the design of the study:

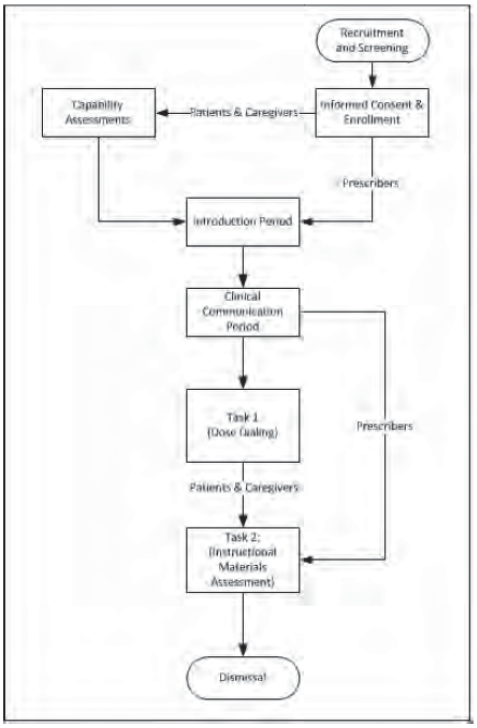


Figure 1: Study Design

This study is designed to evaluate modifications to the Patient Communication Document, HCP Communication Document and IFU. As such, the Patients and Caregivers participants will complete a simulated pharmacy scenario in which they will receive Patient Communication Document along with a carton of pens. The "pharmacist" (moderator) in the scenario will briefly walk participants through the key messages of the Patient Communication Document and refer them to the IFU inside the carton. Participants can review the messages or IFU as much or as little as they would at home. Participants will complete a dose dialing task and an assessment of the IFU and the Patient Communication Document. Participants will not complete a decay period prior to assessment since the tasks they are performing are either knowledge based assessments using the Communication Document and IFU, or are being performed using the IFU.

Similarly, the Prescribers participants will be provided with a HCP Communication Document, and will be asked to read it. Prescribers will complete an assessment of the HCP Communication Document. Patients and Caregivers will not complete a decay period prior to assessment since the tasks they are performing are either knowledge based assessments using the Communication Document and IFU, or are being performed using the IFU. The prescribers are not asked to perform a dose dialing task.

#	Moderator Question
1	What do the instructions say about removing insulin from the pen with a syringe? **Answer**: Do not transfer insulin from your pen to a syringe
2	What should you do if your pen does not work? **Answer**: Any of the following: Try a new needle, use a backup pen, call pharmacist, call HCP, call Lilly
3	What do the Instructions for Use tell you in Step 3 about selecting your dose by counting clicks? **Answer**: Do not dial your dose by counting clicks.

Figure 2: Instructional Materials Assessment - Patient and Caregiver Questions and Sample Answers

#	Moderator Question
1	If you had a patient taking 10 units with the 100U/ ml Humalog KwikPen and you are switching them to the 200U/ml Humalog KwikPen, what dose would you have them dial on the 200 U/ml Humalog KwikPen? **Answer**: 10 units
2	What does the document say about transferring insulin from the pen to a syringe? **Answer**: Do not transfer from the pen to a syringe.

Figure 3: Instructional Materials Assessment – Prescriber Questions and Sample Answers

Appendix 2: Description of Device User Interface and Modifications

The U200 KwikPen is a mechanical, pre-filled insulin peninjector intended for the subcutaneous injection of 200 units/mL Humalog insulin.

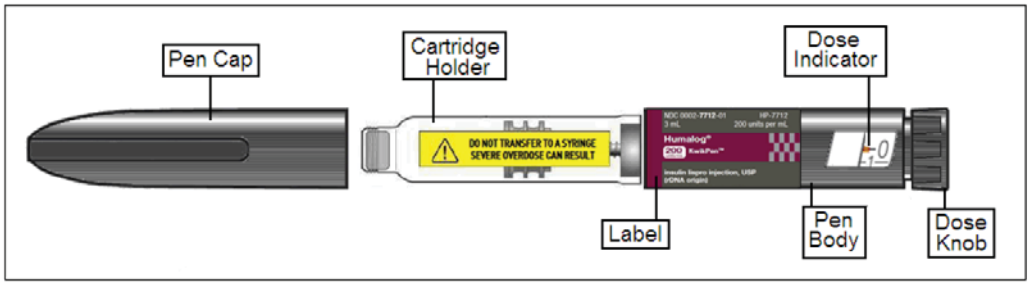


Figure 4: U200 KwikPen

The following sections provide comparison between the previous and updated version of the patient and HCP communications and the IFU that address specific FDA concerns mentioned in the CR letter and at the Type A meeting. These instructions and/or warnings are shown exactly as they appear in the respective documents, identical in both language and format (ie, bulleted, bolded, and underlined text).

1. In response to FDA requests related to dose dialing, the IFU step for selecting the dose was revised to include statements to not count clicks and to check the number in the dose window, as indicated by the red box in Figure 5 below:

Figure 5: IFU Change –Selecting the Dose

2. In response to FDA requests related to important information for patients and caregivers, the Patient Communication Document (Figure 6) was revised in accordance with established principles of effective visual design to emphasize the hazards associated with withdrawing with a syringe, and what to do if there are problems using the pen.

Figure 6: Patient Communication Document Changes

3. In response to FDA requests related to important information for prescribers, the HCP Communication Document was revised (Figure 7) to emphasize the hazards associated with U200 insulin, including critical information regarding the dialed dose, the prescribed dose, and drug concentration.

Figure 7: HCP Communication Document Changes

Appendix 3: Previous Correspondences

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205747

MEETING PRELIMINARY COMMENTS

Eli Lilly and Company
Attention: Sumitra Ghate
Consultant, Global Regulatory Affairs
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Ms. Ghate:

Please refer to your New Drug Application (NDA) dated and received May 10, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Humalog (insulin lispro [rDNA origin] injection) 200 units/mL.

We also refer to your correspondence dated and received April 15, 2014, requesting a meeting to discuss and gain alignment on the information required to address the FDA complete response letter issued March 10, 2014.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Callie Cappel-Lynch, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type A
Meeting Category: End Of Review

Meeting Date and Time: May 7, 2014 3:00pm-4:00pm
Meeting Location: Teleconference

Application Number: 205747
Product Name: Humalog Kwikpen 200units/mL
Indication: Improve glycemic control in adults and children with diabetes mellitus
Sponsor/Applicant Name: Eli Lilly

FDA ATTENDEES

CDER Participants:

Jean-Marc Guettier, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
Suchitra Balakrishnan, M.D.	Clinical Reviewer, DMEP
William Chong, M.D.	Team Leader, Acting, DMEP
Julie Van der Waag, M.P.H.	Chief, Project Management Staff, DMEP
Callie Cappel-Lynch, Pharm.D.	Regulatory Project Manager, DMEP
Sarah Vee, Pharm.D.	Safety Evaluator, Division of Medication Error and Prevention Analysis (DMEPA)
Yelena Maslov, Pharm.D.	Team Leader, DMEPA

CDRH Participants:

General Hospital Devices Branch, Division of Anesthesiology, General Hospital, and Infection

Lana Shiu, M.D.	Device Reviewer
Keith Marin, M.D.	Team Leader
Bifeng Qian, Ph.D.	Device Reviewer
Patricia Beaston, M.D.	Device Reviewer
Quynh Nguyen, M.S.	Human Factors Reviewer

SPONSOR ATTENDEES

Elizabeth Bearby, PharmD,	Senior Director, Global Regulatory Affairs, US-Diabetes
(b) (4)	Consultant, Technical and Manufacturing Services - Devices
LeeAnn Chambers, MBA,	Senior Research Scientist, Global Regulatory Affairs, US-Devices
Debra Conner, BS,	Research Scientist, Global Regulatory Affairs, US-Devices
(b) (4)	Consultant Engineer, Packaging Development
Sumitra Ghate, BS, BA,	Advisor, Global Regulatory Affairs, US-Diabetes
Robert Lew, MD,	Senior Director, Medical, Global Patient Safety
Jim Malone, MD,	Senior Director, Medical, Diabetes and Endocrinology, Insulin and Devices
Robert Metcalf, PhD,	Vice President, Global Regulatory Affairs, US
Tina Rees, PhD,	Senior Clinical Research Scientist, Devices
Anthony Schaff, BS,	Advisor, Delivery Device Research and Development
John Towns, PhD,	Senior Director, Global Regulatory Affairs, US-Devices)

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 7, 2014 3:00pm- 4:00pm between Eli Lilly and Company and the Division of Metabolism and Endocrinology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Humalog (insulin lispro) is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus. Humalog (insulin lispro) injection 100units/mL was approved under NDA 020563 on June 14, 1996.
On March 15, 2013 Eli Lilly submitted a new supplement to NDA 020563 proposing the addition of a new insulin lispro U-200 formulation and its associated device to various labeling documents of the currently approved Humalog U-100 formulation. It was determined by the

user fee staff and the division, that a new drug application with clinical data would be required in order to market this product. On May 10, 2013 Eli Lilly submitted NDA 205747 for insulin lispro U-200.
On March 10, 2014, FDA issued a Complete Response letter for NDA 205747. On April 15, 2014, Eli Lilly requested an End of Review Meeting to discuss and gain alignment on the information required to address the FDA complete response letter.

2.0 DISCUSSION

2.1. Device- Biocompatability

Question 1: Does the FDA agree that 3 mL cartridge rubber disc qualification testing conducted by (b) (4) Lilly and results of those tests described above, which will be provided in the NDA resubmission, are acceptable for addressing FDA's request in Comment 2 of the complete response letter?

FDA Response to Question 1: **Yes, we agree.**

Question 2: Does FDA agree that the information provided in Table 4.1 above to clarify the subject device in NDA 205747 versus other Lilly KwikPen devices satisfies FDA's request in Comment 3 of the complete response letter?

FDA Response to Question 2: **The response is adequate to address the deficiency.**

Question 3: Lilly intends to provide the information above and all aforementioned MSDS reports in the NDA resubmission. Does FDA agree that this satisfies the request in Comment 4 of the complete response letter?

FDA Response to Question 3: **It is noted (b) (4) in the subject device. However, the MSDS provided does not clearly identify (b) (4) We recommend that the sponsor clearly identify all (b) (4) used in the subject device, including the chemical name, CAS reg. No., composition, and toxicological data.**

Question 4: Lilly will provide the background information given above along with the MSDS reports for all of the materials used in the subject device in the NDA resubmission. Does FDA agree that this satisfies FDA's request from Comment 5 of the complete response letter?

FDA Response to Question 4: **The MSDS provided does not identify (b) (4) We recommend that the sponsor clearly identify all (b) (4) used in the subject device, including the chemical name, CAS reg. No., composition, and toxicological data.**

Question 5: Does FDA agree that a separate chemical analysis of the leachables of the device (b) (4) is not required if biocompatibility testing is conducted per the ISO 10993 standard on the final finished device components that have user contact?

FDA Response to Question 5: **The justification provided for not performing the chemical leachable analysis may be acceptable, if the biocompatibility testing provided in firm's future submission is adequate and appropriate to support the subject device.**

Question 6: Does FDA agree that submission of the results from the biocompatibility testing per the ISO 10993 standard using the final finished subject device components listed in Table 4.2 will meet FDA's request?

FDA Response to Question 6: **We recommend that the sponsor provide a complete biocompatibility testing report that includes a detailed description of the test device and sample preparation, description of the test procedures, appropriate controls, summary of test results, test criteria, and conclusion. Our determination will be based on review of the final test report and data submitted.**

2.2. Device- Human Factors

Question 7: Lilly asserts that an additional HF study is not warranted as: 1) the basic cartridge/advancing drive mechanism design is inherent in all insulin pen injectors and design modifications attempting to bar cartridge accessibility (to dissuade syringe extraction) is impractical and/or would cause a new set of failures, 2) IFU revisions would not likely mitigate FDA's cited use errors but could likely cause a new set of use errors, and 3) the key messages in the communication plan as described in the Risk Management program have in essence been validated in the summative human factors report and found to be effective. Further, the proposed communication plan would have its own post marketing assessments.
Does FDA agree that further mitigation and HF testing is not required and the information provided above addresses FDA's request in the complete response letter?

FDA Response to Question 7: **Your meeting package describes your proposal to utilize a post marketing risk minimization plan to address the use-related issues observed in your recent human factors validation study report (reference 32R2-KwikPen-VL7662-v001). This plan includes** (b) (4) [redacted]

We acknowledge your proposal; however, we remain concerned about the use-related issues that were observed in your HF study report. In the CR letter, we identified four areas of concerns, where we believe that performance observations and subjective feedback indicated the need for mitigations. Our list of issues, in order of priority, is as follows:

a. **Two use-related observations were noted that could result in overdose (FDA comment # 8d). One user, an adult patient, did not see the warning and withdrew and transferred U-200 insulin into a U-100 syringe. The other user, a Registered Nurse, stated that she understood the warning but when she had access to a U-100 syringe, she used the syringe to withdraw U-200 insulin from the peninjector. The RN did not correct for the difference in concentration, and if administered to a patient this would lead to a 2x**

overdose scenario which may lead to patient harm. Because healthcare provider (HCPs) and patients who use insulin have access to U-100 syringes, this use error represents a known risk that should be mitigated. While you developed the warning message that is placed directly on the peninjector and in the key messages to HCPs and patients, these observations indicate that the warning is not effective in preventing users from using U-100 syringe to withdraw the U-200 insulin in cases involving a jammed pen injector or other situations where users may need an alternative method to administer the U-200 insulin. The warning messages should be dramatically emphasized to successfully communicate this hazard and the danger associated with the use of a U-100 syringe in these situations. There is also a need to provide a clear description of the proper course of action a user should take. Please make the necessary modifications and provide data demonstrating that the additional mitigations are effective.

b. Three of 16 prescribers performed dose/units conversion in their heads which resulted in writing prescriptions that use ½ of the units specified in the tasks (FDA comment # 8a). These observations indicate that the key messages included in your HF study did not make users aware of critical information associated with the pen design and its drug concentration. The critical information regarding the dialed dose, the prescribed dose, and drug concentration contained in the messages to HCPs should be better emphasized to successfully communicate this hazard. Please make the necessary modifications and provide data demonstrating that the additional mitigations are effective.

c. One caregiver and four patients dialed the incorrect dose (FDA comment # 8b). One participant described confusion about the position of the zero in the dose window, another indicated that the error was based on counting the clicks, and the third said that she counted the clicks and performed visual confirmation. While you may not intend to have users use the clicks to determine the dialed dose, the clicks are auditory feedback to the users and many users might be accustomed to using an injector with audible clicks and use click counts when dialing a dose. Therefore, if you intend for users to focus on the visual feedback i.e. view/verify dialed dose via dose window, you need to emphasize the proper action in the instructions for use and clarify to the user that the auditory feedback should not be used for dialing dose. Please make the necessary modifications and provide data demonstrating that the additional mitigations are effective.

d. For use-related issues associated with pulling the pen injector out prematurely when the dialing window has not reset to zero (FDA Comment # 8c), we agree with your assessment and that no further action is needed given that the results were largely due to study artifacts.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new

routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of the criteria apply at this time to your application, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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

/s/

CALLIE C CAPPEL-LYNCH
07/18/2014
signing for Quynh Nguyen

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

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

Memorandum

Date: April 2, 2014

To: Calli Cappel-Lynch, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

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

Subject: OPDP Labeling Consult Request

NDA 205747 Humalog U-200 (insulin lispro injection, USP [rDNA origin] for injection)

OPDP acknowledges receipt of your May 23, 2013, consult request regarding the proposed labeling for Humalog U-200 (insulin lispro injection, USP [rDNA origin] for injection). Final labeling negotiations were not initiated during this review cycle and a Complete Response letter was issued on March 10, 2014. Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DMEP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these materials.

If you have any questions, please contact Ankur Kalola at 301-796-4530 or Ankur.Kalola@fda.hhs.gov.

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

/s/

ANKUR S KALOLA
04/02/2014

HUMAN FACTOR, LABEL, AND LABELING REVIEW

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

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

Application Type and Number:	NDA 205747
Date of Submission:	May 10, 2013
Established Name and Strength:	Humalog Kwikpen (Insulin Lispro) for Injection, U-200 (200 units/mL)
Product Type:	Single ingredient
Marketing Category:	Prescription
Applicant Name:	Eli Lilly and Company
OSE RCM #:	2013-1190 and 2013-1194
Date of This Review:	February 10, 2013
Reviewer:	Reasol Agustin, Pharm.D.
Team Leader:	Yelena Maslov, Pharm.D.

1. REASON FOR REVIEW

The Division of Metabolic and Endocrinology Products (DMEP) requested we evaluate the Applicant's Human Factor Validation Study Results as well as the container label, carton labeling, and Instructions for Use (IFU) associated with the proposed new product Humalog U-200 (Insulin Lispro), to ensure the intended population is able to use the product safely and effectively.

2. CONCLUSION

We conclude that the Human Factors Usability Study validated the safe use of the product during the following priority tasks 1) Differentiation among different pens, 2) Dialing the desired dose, 3) Delivering the desired dose and 4) Dispensing (Pharmacist).

However, in the Prescribing (HCP) task, three of the 15 prescribers failed to prescribe Humalog U-200 insulin correctly when switching from Humalog U-100 to Humalog U-200. This type of error would result in two-fold underdose and produce chronic hyperglycemia if not corrected. However, due to the fact that Humalog U-200 is a short-acting insulin and frequent blood glucose checks will rapidly identify underdose of the product, we find the results of the prescribing task acceptable, provided the prescribing information labeling will contain clear instructions regarding the fact that when prescribing or using the product, dose conversion must not be performed because the dose counter always shows the selected dose in units.

Additionally, we anticipate that learning over time will occur, thus, lessening this type of error over time.

As a result, although the overall results of the Human Factors Study are acceptable, revisions to the label and labeling as well as provider and patient education are still needed in order to ensure the product can be used by intended population safely and effectively.

3. RECOMMENDATIONS AND COMMENTS

Based on our evaluation, we recommend the following revisions be implemented prior to approval of this NDA:

3.1 Prescribing Information

3.1.1 Highlight of Prescribing Information:

Add the statement or similar (b) (4)

3.1.2 Full Prescribing Information

Add the following section under Dosage and Administration:

(b) (4)

- (b) (4)

3.2 Carton and Container Labels

a. Delete (b) (4) as this was found unacceptable for use.

b. Revise the proprietary name, established name and strength presentation to read:

Humalog Kwikpen

Insulin lispro injection, USP

(b) (4)

3.3 Instructions for Use (IFU)

In Step 2: Priming your Pen, increase the prominence of the statement “Prime before each injection” by using a different color font or increasing font size, in addition to bolding.

3.4 Prescriber Education

We recommend the Applicant performs education on proper prescribing for patients starting on Humalog Kwikpen U-200 and patients switching from Humalog Kwikpen U-100 to U-200.

If you have questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

4. DISCUSSION

Although we find the results of the Human Factors Usability Study acceptable, there are three types of failures that occurred during the following tasks: prescribing, priming, and use of jammed pen.

Three failures occurred when prescribers wrote for the incorrect number of units (cut the number of units in half) when switching from Humalog U-100 to Humalog U-200 insulin, which would result in two-fold underdose and chronic hyperglycemia if not corrected. However, due to the fact that Humalog U-200 is a short-acting insulin and frequent blood glucose checks will identify underdose of the product, we find the results of the prescribing task acceptable provided the prescribing information labeling will contain clear instructions regarding the fact that when prescribing or using the product, dose conversion must not be performed because the dose counter always shows the selected dose in units. Additionally, prescriber education and use of the product will help lessen this type of error over time.

Additionally, failures occurred with the task of priming the needle properly during each use of the product. However, other currently marketed Kwikpen devices (i.e., Humalog U-100, Humulin N Kwikpen, and Humulin 70/30 Kwikpen) also need to be primed during each use. As a result, the priming is not unique to this device. Additionally, according to the clinical team if the pen is not primed, it will not result in clinical harm because underdoing or overdosing by one to two units is insignificant considering the amounts of insulin of Humulin U-200 is prescribed and administered to the intended population.

Furthermore, several failures occurred during use of the jammed pen scenario, in which participants were asked what they would do in case the pen device was jammed. Participants were queried until they provided a response, specifically whether they would transfer the pen contents into a syringe. Some participants, who previously transferred contents of the pen into a syringe with other insulins, stated they would do the same thing. Although this error is concerning, we acknowledge that this is an abnormal scenario. For example, during the nurse response, the moderator incorrectly provided a syringe and requested the participant withdraw the dose, after the nurse already stated that transferring to a syringe is not a recommended practice, and preferred to wait for the pharmacy, which was a stop per the protocol. However, the moderator continued which prompted the participant to commit an error of transferring the drug content into a syringe, resulting in 100% overdose.

5. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. Section 6 provides the methods and results for each material reviewed.

Table 1. Materials considered for review of the Applicant's Human Factors Validation Study, proposed Prescribing Information, container labels, and carton labeling	
Section	**Material Reviewed**
6.1	Product Information/Prescribing Information
6.2	Human Factors/Usability Study
6.3	Container Label, Carton Labeling, and Instructions for Use

6. MATERIALS REVIEWED

6.1 Product Information

There are three Humalog Kwikpen currently marketed in the United States. The proposed product differs from those marketed in regards to concentration per mL and total amount of insulin per Kwikpen (see Table 1).

Table 1: Humalog Kwikpen Product Line Comparison				
Proprietary Name	**Humalog Kwikpen 200 units/mL (proposed name)**	Humalog Kwikpen	Humalog Mix 50/50 Kwikpen	Humalog Mix 75/25 Kwikpen
Established Name	**Insulin Lispro (Human)**	Insulin Lispro (Human)	Insulin Lispro Protamine and Insulin Lispro (Human)	Insulin Lispro Protamine and Insulin Lispro (Human)
Marketing Status	**Proposed**	Marketed		
Concentration (units per mL)	**200 units/mL**	100 units/mL		
How Supplied (total units per Kwikpen)	**600 units/3 mL**	300 units/3 mL		
Units/Click	**1 click=1 unit**	**(total of 60 units can be dispensed from any pen)**		

6.2 Human Factors Validation Study

We reviewed the Human Factors validation study entitled, "Attachment 1 – Humalog (b) (4) KwikPen Summative Human Factors Study Technical Report," and "Attachment 2 – Humalog (b) (4) KwikPen Human Factors Engineering and Usability Engineering Report (HFE/UE) that the Applicant submitted on May 10, 2013.

6.2.1 Study Participants

The summative usability test involved 130 participants which are representative of the intended users of the device.

Patient/Caregiver Group

	Injection Naïve	Vial and Syringe users	Pen Users	Pen users who transferred to a syringe	TOTAL **n=83**
Patient	15	16	20	16	67
Caregiver	0	11	5	0	16

Health Care Providers:

Nurse	15	6 LPN, 9 RN
Pharmacist	16	
Prescriber	16	4 Endocrinologist, 9 Primary Care, 2 Nurse Practitioners, and 1 Physician Assistant

6.2.2 Study Design

Test sessions were between 60 and 90 minutes, depending on the type of participant and the associated number of tasks participants were asked to perform.

1. Use Scenarios and Critical Tasks

Patients/caregivers:

- Scenario 1: Normal use of the Humalog [redacted] (b) (4) KwikPen device to deliver a dose into an injection pad placed against the abdomen, a commonly used injection location.
  - Priority tasks include dialing the desired dose and delivering the desired dose.
- Scenario 2: Differentiation of Humalog [redacted] (b) (4) KwikPen device by removing it from an insulated bag holding four commonly available pen injectors: Humalog [redacted] (b) (4) KwikPen, Humalog KwikPen, Lantus SoloStar, and Novolog FlexPen.
  - Priority task was selecting the correct pen.
- Scenario 3: Troubleshooting a jammed Humalog [redacted] (b) (4) KwikPen.
  - Priority task was troubleshooting the jammed pen without transferring an incorrect dose.

Nurses:

- Scenario 1: Sorting of Humalog [redacted] (b) (4) KwikPens from a bin containing commonly available pen injectors: Humalog [redacted] (b) (4) KwikPens, Humalog KwikPens, Lantus SoloStars, and Novolog FlexPens.
  - Priority task was sorting the pens correctly.
- Scenario 2: Normal use of the Humalog [redacted] (b) (4) KwikPen device to deliver a dose into an injection pad placed on the table to simulate injection into someone else.
  - Priority tasks include dialing the desired dose and delivering the desired dose.
- Scenario 3: Troubleshooting a jammed Humalog [redacted] (b) (4) KwikPen.
  - Priority task was troubleshooting the jammed pen without transferring an incorrect dose.

Pharmacists:

- Scenario 1: Sorting of Humalog [redacted] (b) (4) KwikPens from a bin containing commonly available pen injectors: Humalog [redacted] (b) (4) KwikPens, Humalog KwikPens, Lantus SoloStars, and Novolog FlexPens. (Scenarios 1 and 2 were randomized.)
  - Priority task was sorting the pens correctly.
- Scenario 2: Sorting of Humalog [redacted] (b) (4) KwikPen cartons from a bin containing cartons of commonly available pen injectors: Humalog [redacted] (b) (4) KwikPens, Humalog KwikPens, Lantus SoloStars, and Novolog FlexPens. (Scenarios 1 and 2 were randomized.)
  - Priority task was sorting the cartons correctly.
- Scenario 3: Filling a prescription for Humalog [redacted] (b) (4) KwikPen taken from a refrigerator containing multiple Lilly pen injector cartons and writing the patient label for the prescription.
  - Priority tasks were selecting the correct carton and writing the patient label without changing the number of units.

Prescribers:

- Scenario 1: Writing a prescription for a patient changing from the U-100 rapid acting insulin to the Humalog 600 Unit KwikPen. (Scenarios 1 and 2 were randomized.)
  - Priority task was writing prescription for proper product and number of units.
- Scenario 2: Writing a prescription for a patient starting on the Humalog 600 Unit KwikPen (Scenarios 1 and 2 were randomized).
  - Priority task was writing prescription for proper product and number of units.
- Scenario 3: Writing a hospital order for Humalog KwikPen (U-100) for a patient who normally uses the Humalog 600 Unit KwikPen.
  - Priority task was writing order for proper product and number of units.

6.2.3 Study Results

Selecting appropriate device (Differentiation Study)

- All 16 Pharmacist and 15 Nurse Participants were able to successfully differentiate between the devices.
- Eighty of 83 patients (96.4%) were able to successfully select the appropriate device. Of the three participants who failed, two self-corrected themselves.
  1) One trained, elderly insulin naïve patient with vision impairment selected the device based on shape. She noted [redacted] (b) (4) but did see "100" on it (referring to the U100). She thought she was unable to look back in the bag after reading the pen label. When she was told she could reopen, she selected correctly.
  2) One trained adult, vial/syringe user, without impairments reported only seeing 3 pens in the bag and identified pen based on "Humalog" and assumed it was correct. Self-corrected when he saw other pens.
  3) One untrained, elderly insulin naïve with vision impairment selected Humalog Kwikpen because saw "KwikPen" on the label.

Our evaluation indicates that these results are acceptable because two patients appear to have misinterpreted the task and one patient that failed this task did not realize there were two Humalog Kwikpen in the bag. Perhaps, if the pens were all laid out, this may have helped to prevent that failure.

Dialing the desired dose (10 units)

- All 15 nurse participants were able to successfully dial the desired dose.
- Seventy-six out of 83 patients (92%)

1. Twenty did not follow moderator instructions, and used pretend scenarios of what their blood sugar would be and what they plan to eat, and successfully dialed their desired dose.
   a. Patient error: 18% (15)
   b. Nurse error: 6% (5)

2. Dials incorrect dose- thinks they are dialing their target dose or the dose per the protocol, but dials a different dose than they are targeting.
    a. Patient error: 6% (5):
        1. Three participants thought they were dialing to 10 units but instead dialed to 9 units, with no further explanation.
        2. One participant dialed and primed but did not complete the prime stroke (stopped at 1) and then counted 10 clicks without verifying the dose window (dialed 11 units instead of 10 units)
    b. Nurse error: 0
3. Doesn't dial any dose- dialed prime dose and expelled prime dose but did not redial the pen.
    a. Patient error: 2.4% (2)
    b. Nurse error: 0

Although some failures occurred in this task, we acknowledge that this task is not unique to this particular pen; hence we find the results of this task acceptable. All currently marketed insulin pens require patients to dial to the prescribed dose and in addition, the currently marketed Humalog Kwikpen requires priming before each injection.

Deliver the desired dose

- Fourteen out of 15 nurse participants (93%) were able to successfully deliver the dose
- Seventy-five out of 83 patients were able to successfully deliver the dose.
    - Nine does NOT fully depress dose knob (zero in the dose window)
        - Depressed only until a 1 is seen in the dose window because the force had increased.

Although failures occurred in this task, we acknowledge that the errors that occurred are not unique to this particular product; hence we find the results of this task acceptable. All currently marketed insulin pens require patients to deliver the prescribed dose and in addition, the currently marketed Humalog Kwikpen requires priming before each injection.

Dispensing (Pharmacist)

1. All 16 Pharmacists were able to successfully select the carton.
2. Fifteen out of 16 Pharmacists were able to successfully select the appropriate number of cartons.
    a. One error occurred when Pharmacist dispensed 2 cartons (4 pens total). The pharmacist did the correct calculations for the number of units and devices needed, but thought there was only 1 pen per carton instead of 2.
3. All 16 Pharmacists were able to successfully write the sig codes.

Although one pharmacist failed to dispense the correct number of cartons, all 16 were able to successfully select the carton and write the sig codes. In addition, the pharmacist who made the

error of dispensing 2 cartons, instead of 1 calculated the number of units and device needed correctly. Therefore, the results of this task are acceptable.

Prescribing (HCP)

1) Forty out of 48 total prescriptions (83%) were successfully written by HCPs.
   (16 HCP x 3 prescriptions per prescriber = 48 total prescriptions. A success was considered if the HCP wrote the correct number of units and correct device name on the prescription order.
   a. Twelve out of 16 HCPS were able to successfully switch a patient from U100 insulin to Humalog U200.
      i. Four wrote for the wrong brand name using notations like 600 U/3mL, KwikPen 600, Humalog U600, or 200u/mL
   b. Thirteen out of 16 HCPS were able to successfully write a prescription for a patient starting on Humalog U200.
      i. Three wrote for the incorrect number of units (cut the number of units in half)
   c. Fifteen out of 16 HCPS were able to successfully switch a patient from U200 insulin to Humalog U100.
      i. One wrote for the incorrect product name (i.e. wrote for Humalog (b) (4) Kwikpen in the switching back to U100 scenario)

Abnormal Use (Jammed Pen) scenario

- Patients Response:
  - Five participants said they would transfer to a syringe. Four out of 5 were past extractors and untrained.
  - One participant saw the warning on the label and said would not withdraw, but they would call the pharmacy.
  - One respondent said they would need a U200 syringe and when told there is no U200, they would use U100 and perform dose calculation. Participant correctly calculated the dose.
  - One participant did not do the calculation correctly and withdrew a 100% overdose. (10 units on a U100 syringe)
- Nurses Response:
  - One of the 15 nurse participants recommended using a syringe to withdraw the insulin as her fourth response. Prior to this, nurse responded that transferring to a syringe is not a recommended practice and preferred to wait for the pharmacy, which was a stop per protocol. The moderator incorrectly provided a syringe and requested the nurse to withdraw the dose and the nurse withdrew a 100% overdose.

This specific scenario is unusual because it is not a recommended practice for any insulin pen device. This abnormal use (jammed pen) scenario was designed to promote the error of transferring the drug product from the pen into a syringe, as evidenced by the efforts made to

recruit participants with prior history as syringe extractors and the nurse error during the study. For example, the nurse participant first stated that transferring to a syringe is not a recommended practice and preferred to wait for the pharmacy which was a stop per the protocol. However, the moderator incorrectly provided a syringe and requested the respondent to withdraw the dose, thus resulting in the overdose.

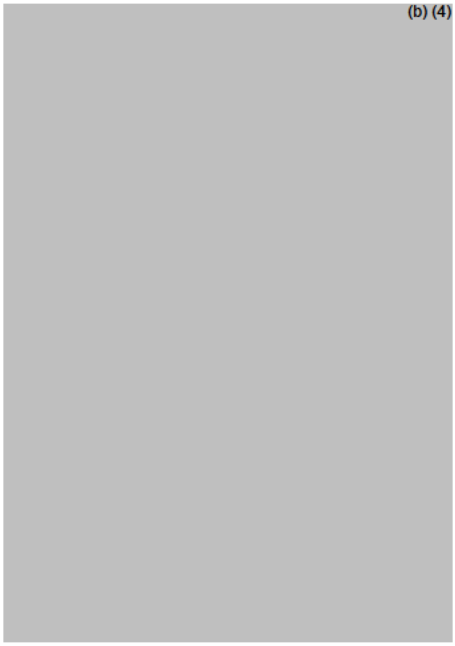
Therefore, despite the failures that occurred, we determined that this was an unfair task to the participants because of its design to promote the error of transferring to a syringe. Thus we find the results of this task acceptable.

6.3 Labels and Labeling Review

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarketing medication error data, we evaluated the following materials that the Applicant submitted on May 10, 2013:

- Humalog (b) (4) KwikPen container labels (section 6.3.1)
- Humalog (b) (4) KwikPen carton labeling (section 6.3.2)
- Humalog (b) (4) KwikPen Instructions for Use (section 6.3.3)
- Prescriber Information (Not included)

6.3.1 Container Labels



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

Cartridge Holder

6.3.2 Carton Labeling

(b) (4)

6.3.3 Instructions for Use (IFU)

(b) (4)

8 Pages 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 and this page is the manifestation of the electronic signature.

/s/

REASOL AGUSTIN
02/11/2014

YELENA L MASLOV
02/11/2014

KELLIE A TAYLOR
02/15/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: February 7, 2013
From: Jacqueline Ryan, Combination Products Team Leader, WO66, RM 1257
General Hospital Devices Branch, DAGID, ODE, CDRH

To: Callie Cappel-Lynch, RPM, CDER/OMPT/CDER/OND/ODEII/DMEP
Subject: CDRH Consult, CTS ICC 1300267/ S001, NDA 205747

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding NDA 205747. The device constituent of this combination product consists of a pen injector to deliver insulin lispro.

2. Previous Deficiencies and Sponsor Replies

FDA Question 1

Although the accuracy testing meets the standard (ISO 11608-1) of ± 0.005 mL for doses smaller than 0.1 mL and ± 5% for doses of 0.1 mL or greater. The results reported for 1U raise clinical concerns. (b) (4) [redacted] *Therefore, it is not unreasonable to expect that patients will use the pen to, at times, deliver smaller doses of insulin lispro. As such, it is important that patients and the healthcare providers prescribing and instructing the patient on the use of this product understand the performance at the lower end of the dose range. Provide additional accuracy testing in the lower claimed range. The results of accuracy testing should be reported in both volume and percentage error and presented in tabular form for inclusion into the product labeling.*

Lilly Response to Question 1

(b) (4)

(b) (4)

Reviewer's Comments:
Dr. Patricia Beaston was consulted regarding the sponsor's reply. Her comments are summarized below.

> **Lilly declined to provide the requested information in the labeling and does not consider the possible error to be of clinical concern. The Sponsor states that** (b) (4) **Contrary to the position of the Sponsor, patients manage their glucose based on the response to previous treatment attempts. If the device over or under delivers and the patient is unaware of this potential, then he or she, make and incorrect adjustment for the next dose. This is more likely to occur at the lower dose; however, the error in the expected dose is unknown because the Sponsor has not provided the requested information. The additional concern is that for convenience and or financial considerations patients with greater insulin sensitivity may want to use this insulin/device and would be at increased risk for harm.** (b) (4) **CDRH defers to the DMEP Medical Officer and the DMEPA team to determine if the Sponsor should address this identified risk in the labeling.**

FDA Question 2

You have not provided any biocompatibility data for the insulin lispro 200 units/mL KwikPen. (b) (4) *you have indicated that the color of the 200 unit/mL pen is different. Please provide a list of all materials of construction of the 100 unit/mL and 200 unit/mL KwikPens, biocompatibility testing for the 100 unit/mL pen and Materials Safety Data Sheets (MSDS) for* (b) (4) *the 200 unit/mL pen. We require this information by December 10, 2013.*

Lilly Response to Question 2

(b) (4)

Table 4.1 lists the materials of construction of the insulin lispro100 units/mL KwikPen and the insulin lispro 200 units/mL KwikPen. Biocompatibility testing for the current materials used in the 100 units/mL KwikPen will be submitted by FDA's requested date of 10 December 2013.

As stated in the Lilly response to the 74-day letter, (b) (4) have been updated. The MSDS sheets for the external components (b) (4) used in the 200 units/mL KwikPen are provided in Appendix 1 and Appendix 2. While the hazards listed on the MSDS sheets identify potential in-process or industrial hazards, these hazards do not apply to the final product (b) (4)

Reviewer's Comments:
Bifeng Qian, PhD was consulted regarding the sponsor's reply. Dr. Qian has the following information requests:

1. Please clarify if the 3 mL Insulin Cartridge has been previously cleared or approved by the FDA. Please provide evidence to demonstrate that the Cartridge used is biocompatible and material compatible based on its intended use and patient contact classification.

2. In your study report of "Biological Evaluation of KwikPen Device Platform" submitted in the S002 response, you state "The KwikPen platform of prefilled insulin injection devices includes (b) (4) **This evaluation covers currently marketed device** (b) (4) **. On page 1 of the evaluation report, you have provided a Table which lists your final finished device models. Please clearly identify all subject devices and device models or types included in this NDA.** (b) (4)

3. Please clarify to the Agency if the materials identified in Table 1 of your biological

evaluation report represent ALL materials used in the manufacturing process to construct the subject devices of this ND (b) (4) If not, please provide a complete listing of ALL the manufacturing materials used and the associated Material Safety Data Sheets (MSDS).

4. You state that the devices in the platform (b) (4) Table 1 of your biocompatibility evaluation report (b) (4) However, your MSDS provided does not clearly identify (b) (4) Please provide a revised MSDS report which includes the chemical identity, composition, CAS number, and toxicological data (b) (4) used in the subject devices.

5. Please provide chemical analysis of the leachables (b) (4)

6. In the study report of "Biological Evaluation of KwikPen Device Platform", you have included testing reports for *in vitro* cytotoxicity, irritation, and sensitization. The test devices used in the biocompatibility testing were described (b) (4) Based on this description, we are unclear if the testing was conducted on the subject devices that include all patient/user contact device components. In addition, the biocompatibility testing provided was completed in August, 2005, which was nearly 9 years ago. This is not acceptable. As risk analysis based on raw materials may have limitations and may not represent the final device components in the submission, FDA believes that safety assessments need to be done based on the final finished subject devices. Please provide current biocompatibility testing data, based on the final finished subject devices and a worst case condition. Please be advised all patient/user contact device components should be tested for biocompatibility (b) (4)

3. CDRH Recommendation

Based on our review, the following deficiencies should be conveyed to the Sponsor:

1. Clarify if the 3 mL Insulin Cartridge has been previously cleared or approved by the FDA. Provide evidence to demonstrate that the Cartridge used is biocompatible and material compatible based on its intended use and patient contact classification.

2. In your study report of "Biological Evaluation of KwikPen Device Platform" submitted in the S002 response, you state "The KwikPen platform of prefilled insulin injection devices includes (b) (4) This evaluation covers currently marketed device . On page 1 of the evaluation report, you have provided a Table which lists your final finished device models. Clearly identify all subject devices and device models or types included in this NDA. (b) (4)

3. Clarify if the materials identified in Table 1 of your biological evaluation report represent ALL materials used in the manufacturing process to construct the subject devices of this NDA, (b) (4) If not, provide a complete listing of ALL the manufacturing materials used and the associated Material Safety Data Sheets (MSDS).

4. You state that the devices in the platform (b) (4) Table 1 of your biocompatibility evaluation report (b) (4) However, your MSDS provided does not clearly identify (b) (4) Provide a revised MSDS report which includes the chemical identity, composition, CAS number, and toxicological data (b) (4) used in the subject devices.

5. Provide chemical analysis of the leachables (b) (4)

6. In the study report of "Biological Evaluation of KwikPen Device Platform", you have included testing reports for *in vitro* cytotoxicity, irritation, and sensitization. The test devices used in the biocompatibility testing were described (b) (4) Based on this description, we are unclear if the testing was conducted on the subject devices that include all patient/user contact device components. In addition, the biocompatibility testing provided was completed in August, 2005, which was nearly 9 years ago. This is not acceptable. As risk analysis based on raw materials may have limitations and may not represent the final device components in the submission, FDA believes that safety assessments need to be done based on the final finished subject devices. Provide current biocompatibility testing data, based on the final finished subject devices and a worst case condition. All patient/user contact device components should be tested for biocompatibility (b) (4)

Digital Signature Concurrence Table	
Reviewer Sign-Off Jacqueline Ryan	Jacqueline S. Ryan -S Digitally signed by Jacqueline S. Ryan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000570293, cn=Jacqueline S. Ryan -S Date: 2014.02.10 13:41:15 -05'00'
Branch Chief Sign-Off Richard Chapman	Digitally signed by Richard C. Chapman Date: 2014.02.10 15:17:28 -05'00'

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

/s/

CALLIE C CAPPEL-LYNCH
02/12/2014
signed for Jackie Ryan

M E M O R A N D U M

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

DATE: February 7, 2014

TO: Jean-Marc Guettier, M.D.
Director, Division of Metabolism and Endocrinology Products, Acting
Office of Drug Evaluation II

FROM: Seongeun Julia Cho, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: Review of EIR covering NDA 205747, Insulin Lispro U-200 injection, from Eli Lilly and Company

The Division of Metabolism and Endocrinology Products (DMEP) requested inspections of the clinical and analytical portions of the following study:

F3Z-EW-IOPY: "Evaluation of Bioequivalence of Two Formulations of Insulin Lispro in Healthy Subjects"

Clinical site inspection

Inspection of the clinical site, Lilly-NUS Centre for Clinical Pharmacology, Singapore, was conducted by ORA investigator Kellia Hicks and OSI/DBGLPC scientist Seongeun Cho from 11/7/2013 to 11/15/2013.

The inspection included a thorough review of study records, including case report forms, informed consent, adverse event

log, medical activity records, pharmacodynamic glucose measurements, and drug accountability, examination of facilities, and interviews and discussions with the principal investigator, firm's management and staff.

Following the inspection of Lilly-NUS Centre for Clinical Pharmacology, Form FDA 483 was issued (Attachment 1). The observation and our evaluation of the site's response follow.

1) **Samples of the reference standard used in a bioequivalence study were not retained and released to FDA upon request as required by 21 CFR Part 320.138. Specifically, your firm failed to retain and provide samples of the reference standard Humalog 100U/ml, Lot A677287 used in Bioequivalence Study F3Z-EW-IOPY(a); Evaluation of the Bioequivalence of Two Formulations of Insulin Lispro in Healthy Subjects.**

The study F3Z-EW-IOPY involved two formulations of Insulin Lispro, a test drug Insulin Lispro TRIS U-200 and a reference standard Insulin Lispro phosphate U-100. While the site retained reserve samples of the test drug, the site did not retain reserve samples of the reference standard. The reference standard used in study was Humalog purchased by Lilly-NUS (b) (4)

In the written response to the observation, Dr. Soon, Principal investigator and the Managing Director of the site, acknowledged a failure to retain reserve samples for the bioequivalence study (Attachment 2). He stated that prior to the start of study F3Z-EW-IOPY, Lilly-NUS corresponded with Lilly, Indianapolis, on the requirements and quantities of reserve samples for test and reference articles; however, Lilly's representative instructed Lilly-NUS site not to retain reference drug Humalog 100 units/mL.

Dr. Soon stated that effective October 30, 2012, Lilly-NUS implemented Standard Operating Procedure, Management of Investigational Product Samples for Retention, to address requirements and responsibilities of Lilly-NUS site personnel in the retention of reserve samples for BA/BE studies. Dr. Soon affirmed that Lilly-NUS will review this procedure following this inspection and on a periodic basis to ensure compliance with FDA regulations and Guidance with regard to BA/BE studies.

Lilly-NUS retained all documentation pertaining to Humalog 100 units/mL in the study binder, including the purchase request to the manufacturer, shipping receipts, dosing records for all subjects in the Trial Master File, and disposal records by a third party firm identifying quantities and lot numbers of all articles under destruction. Nonetheless, failure to retain the reference standard for a bioequivalence/bioavailability study is not compliant with 21 CFR 320.38 and the inspection could not confirm the identity of the reference product used in the study.

Bioanalytical site inspection

The findings from inspection at Lilly-NUS site were discussed with the application review team on December 5, 2013, and the at inspection of the bioanalytical site (b) (4) (b) (4) is not needed at this time, given the failure to retain reserve samples of the reference product at the clinical site.

Summary and Conclusion:

The audited study is subject to 21 CFR 320.38 and the site's failure to retain reserve samples is objectionable. Due to lack of reserve samples for the reference product, we were not able to authenticate the identity of the reference product used in the study. With regard to a requested audit of bioanalytical portions of the study (b) (4) OSI recommends cancelation of the inspection.

Seongeun (Julia) Cho, Ph.D.
Bioequivalence Branch, DBGLPC, OSI

Final Classifications:

OAI: Lilly-NUS Centre for Clinical Pharmacology, Singapore

Attachments:

Attachment 1: Form FDA 483
Attachment 2: Response to FDA 483 by Lilly-NUS

CC:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Skelly/Cho/Dejernett/CF
OCP/DCP2/Suryanarayana Sista/Chandra Sahajwalla
OND/ II/D
(b) (4) -DO/ (b) (4)
: SC 12/19/13
Edit: MFS 12/19/13, SHH 2/7/14
OSI: BE 6474; O:\Bioequiv\EIRCover\205747.Lil.Ins.doc
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Inspections/BE Program/Clinical Sites/L S, Singapore
FACTS: (b) (4)

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

/s/

SEONGEUN CHO
02/07/2014

SAM H HAIDAR
02/08/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

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

CDRH Human Factors Review

DATE: December 16, 2013

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

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

TO: Callie Cappel-Lynch, Regulatory Project Manager, CDER/OND/ODEII/DMEP

SUBJECT: NDA 205747
Applicant: Eli Lilly
Device Constituent: Kwik pen injector
Drug Constituent: Humalog 600
Intended Treatment: Diabetes
CDRH CTS Tracking No.: ICC 1300285

Digitally signed by QuynhNhu Nguyen
Date: 2013.12.19 18:28:02 -05'00'

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ronald D. Kaye -S
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Date: 2013.12.21 14:54:02 -05'00'

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

CDRH Human Factors Review

Combination Product Device Information

Submission No.: NDA 205747
Applicant: Eli Lilly
Device Constituent: Kwik pen injector
Drug Constituent: Humalog 600

Intended Treatment: DiabetesCDRH Human Factors Involvement History

- 5/10/2013 – CDRH HF was requested to review the human factors validation study report included in the NDA. Review Materials:
  EDR Location: \\CDSESUB1\EVSPROD\NDA205747\205747.enx

Overview and Recommendation

The Division of Metabolism and Endocrinology Products requested a consultative review from CDRH Human Factors team to review the human factors validation study report contained in the NDA 205747. This submission seeks FDA approval for a new insulin lispro U-200 formulation and its associated device under the proposed name "Humalog (b) (4) KwikPen."

The device is a prefilled pen injector designed to provide subcutaneous injection. The product may be used for self-administration by the patient or by health care providers or caregivers to administer the medicine. The product can be used more than once with the same drug cartridge (b) (4) The product may be used in health care, institutional, and home settings. The following are images of the carton and pen.

(b) (4)

The review of the human factors validation study identified the following deficiency that should be communicated to the Sponsor:

1. The results of your human factors validation study showed use errors were observed with high priority task of writing the prescription, dialing the dose, delivering the dose, and trouble-shooting jammed peninjectors. We are concerned with the following findings and residual risk analyses:
   a. Three prescribers, when asked to write a prescription for the U-200 insulin, wrote half of the units specified in the tasks, which would result in underdosing. You proposed a communication to providers about prescribing U-200 insulin i.e. the dose units are the same as the dialed dose from the pen.
   b. Four patients dialed one or two units less than the units specified in the tasks, which would result in underdosing. One patient dialed one unit more than the

units specified in the tasks, which would result in overdosing. You claimed that the Instructions for Use (IFU) does not encourage user to count the clicks for determining their dose. Our review of the IFU indicated that it does not provide any information to deter user from counting the clicks. In addition, the IFU does not instruct user to look and verify the dialed dose.

c. Nine patients/caregivers pulled the peninjector when the window did not reset to zero after counting to five. You indicated that 5mm needles were used and may have caused an increase in force encountered by the user. You asserted that the IFU provides needed information for delivering the dose. Review of the IFU showed that in users are instructed to hold the dose knob in and slowly counting to five in step 4b and users are instructed to look at the window after pulling the needle out in step 4c. Therefore, users may not be able to ensure that the window resets to 0 prior to pulling the device out of the skin.

d. There were two use errors observed when one patient and one registered nurse had to troubleshoot a jammed pen without transferring to a syringe. Both users ended up using a syringe with a U-100 scale and drew the dose of U-200 insulin, which resulted in a 2x overdose. We noted that the peninjectors has a warning affixed to the cartridge holder, which states (b) (4) However, given the two instances where users did not heed that warning, we believe that risk mitigation for potential overdosing has not been demonstrated to be effective. You proposed a (b) (4) communication to healthcare providers about the risk of overdosing.

In summary, the test results do not support a conclusion that the device as designed is safe and effective for the intended users. In addition, the report did not discuss implementation of additional risk mitigation strategies to address use related issues that could result in patient harm in actual use or subsequent testing and evaluation to demonstrate their effectiveness and the absence of additional unintended use-related hazards. We recommend that you implement additional risk mitigation strategies, and perform human factors validation testing with 15 representative users (healthcare providers and patients combined).

CDRH Human Factors Review

Prior to conducting the human factors validation study, Eli Lilly conducted three formative studies. The product design and associated instructions for use (IFU) were reported to have iteratively modified to address the issues seen in those studies.

The human factors validation study was conducted with 98 participants. Of those, there were 15 healthcare providers, and 83 patients/lay caregivers with half of these participants having varying levels of self-injection experience, and varying level of disease-related vision and hand impairments. Thirty eight participants received representative training. In addition, there were 16 pharmacists, who only performed the device differentiation task.

The differentiation tasks were set up to represent actual use settings with three competitive devices Humalog (b) (4) KwikPen (subject device), Humalog KwikPen, Novolog FlexPen, and Lantus SoloStar. The patient differentiation task includes making a selection from an insulated bag. The nurse differentiation task includes sorting devices into appropriate labeled bin. The pharamacist differentiation task includes sorting the pens into labeled bin, and dispensing from a refrigerator. There were three patients/caregivers who selected the Humalog KwikPen but not the Humalog (b) (4) KwikPen. Eli Lilly indicated that these use errors would not result in patient harm because time action profiles and dosing of the insulin are the same.

During the study, use errors were observed when the participants dialed and delivered the dose. The following tables provide a summary of the use errors:

Step	Type of error	Number of errors
Dialing desired dose	Dialed incorrect number of units based on target dose	5/98
	Did not dial any dose	2/98
Delivering desired dose	Depressed injection button before inserting needle	1/98
	Dial did not return to zero while injecting	9/98
	Moves pen around during injection	2/98

Table 1: Type of Use Errors

User groups	Number of use errors			
Scenario	Normal pen use		Differentiation	Jammed
Task	Dialing	Delivering	Differentiate	Jammed
Patients – injection naïve (n=15)	0	1	0	0
Patients – syringe and vial users (n=16)	2	6	0	0
Patients – pen injector users (n=19)	3	0	0	0
Patients – history of transferring from pen (n=17)	1	3	0	1
Caregivers who administer insulin (n=16)	1	1	0	0
Nurses (n=15)	0	1	0	1*
Total	**7**	**12**	**0**	**2***

Table 2: Breakdown of Use Errors by User Groups

The following section provides a brief analysis of the use errors.

- There were two use errors observed when one patient and one registered nurse had to troubleshoot a jammed pen without transferring to a syringe. These use errors would result in patient harm if occurred in actual use. The patient, instead of resolving the jammed pen condition, indicated that she would use a syringe to adminster the insulin. She subsequently used a syringe with a U-100 scale and drew the dose of U-200 insulin, which resulted in a 2x overdose. The registered nurse, after offering different alternative to resolve the situation, ended drawing the dose of U-200 insulin using the U-100 scale on the insulin syringe. The peninjectors has a warning affixed to the cartridge holder, which states (b) (4) Lilly proposed a pharmacy program with key messages regarding withdrawing using a syringe for the U-200 insulin, and a communication to healthcare providers about the risk of overdosing.
- Three prescribers, when asked to write a prescription for the U-200 insulin, wrote half of the units specified in the tasks, which would result in underdosing. The prescribers reported to have performed dose conversion while writing the prescriptions. Lilly proposed a communication to providers about prescribing U-200 insulin i.e. the dose units are the same as the dialed dose from the pen.
- Four patients dialed one or two units less than the units specified in the tasks, which would result in underdosing. One patient dialed one unit more than the units specified in the tasks, which would result in overdosing. Two patients reported to use the clicking sounds generated when they dialed to the dose to determine the dose. Lilly claimed that the Instructions for Use (IFU) does not encourage user to count the clicks for determining their dose. Review of the IFU indicated that it does not provide any information to deter user from counting the clicks. In addition, the IFU does not instruct user to look and verify the dialed dose.
- Nine patients/caregivers pulled the peninjector when the window did not to reset to zero after counting to five. Most of the dose window showed a value of 1, which would have resulted in underdosing of 1 unit. Lilly indicated that 5mm needles were used and shown to have required increase force near the end of the injection stroke due to the thickness of the outermost layer of the injection pad, and may have caused an increase in force encountered by the user. Lilly asserted that the IFU provides needed information for delivering the dose. Review of the IFU showed that in users are instructed to hold the dose knob in and slowly counting to five in step 4b and users are instructed to look at the window after pulling the needle out in step 4c.

The test results do not support a conclusion that the device as designed is safe and effective for the intended users. There are multiple use errors that can lead to misdosing or suboptimal therapy that can be clinically significant. This consultant believes that additional mitigations are necessary to effectively reduce the use errors that can result in patient harm.

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/s/

CALLIE C CAPPEL-LYNCH
02/06/2014
consult review for Quynh Nguyen

Clinical Consult

Date: December 18, 2013

From: Patricia Beaston, M.D., Ph.D., Medical Officer

To: Keith Marin, Reviewer

Device: Humalog® (b) (4) KwikPen™ (Pen-injector, piston syringe)

Drug: Insulin lispro (Humalog) U200

Sponsor: Lilly

Materials reviewed: NDA 205747 Response 4.1 FDA Question 1.

The Sponsor is proposing a new concentration of insulin lispro U200. The pen-injector is a modified version of the current insulin lispro U100.

The Sponsor was asked to respond to the following:
Your device is designed for delivery of insulin lispro in one unit increments from 1 unit to 60 units. Based on the reports of accuracy testing it appears that the dose error ranges from (b) (4)% to (b) (4)% at the 1 unit setting to less than (b) (4)% at the 30 unit setting. During therapy it is reasonable to assume that patients will use less than 30 unit injections. Therefore, it is important that patients and the Healthcare Providers prescribing and instructing the patient on the use of this product understand the performance at the lower end of the dose range. Please provide additional information on units (volumes) less than 30 units (b) (4) for example 5 units, 10 units, 20 units. The results of accuracy testing should be reported in both volume and percentage error and presented in tabular form for inclusion into the product labeling.

Lilly declined to provide the requested information in the labeling and does not consider the possible error to be of clinical concern. The Sponsor states that (b) (4) Contrary to the position of the Sponsor, patients manage their glucose based on the response to previous treatment attempts. If the device over or under delivers and the patient is unaware of this potential, then he or she, make and incorrect adjustment for the next

dose. This is more likely to occur at the lower dose, however, the error in the expected dose is unknown because the Sponsor has not provided the requested information. The additional concern is that for convenience and or financial considerations patients with greater insulin sensitivity may want to use this insulin/device and would be at increased risk for harm. (b) (4)

CDRH defers to the DMEP Medical Officer and the DMEPA team to determine if the Sponsor should address this identified risk in the labeling.

Digitally signed by Patricia R. Beaston -S
Date: 2013.12.18 15:48:26 -05'00'
Clinical Consultant

Digitally signed by Richard C. Chapman
Date: 2013.12.18 15:50:51 -05'00'
Branch Chief

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/s/

CALLIE C CAPPEL-LYNCH
12/19/2013
consult review for Patricia Beaston

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

REVIEW DEFERRAL MEMORANDUM

Date:	December 05, 2013
To:	Jean-Marc Guettier, MD Acting Director **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	HUMALOG (insulin lispro injection)
Dosage Form and Route:	For injection, for subcutaneous and intravenous use
Application Type/Number:	NDA 205-747
Applicant:	Eli Lilly and Company

1 INTRODUCTION

On May 10, 2013, Eli Lilly and Company, submitted for the Agency's review a New Drug Application (NDA-205747) for Humalog (insulin lispro injection), for injection, for subcutaneous and intravenous use. The purpose of the submission was to seek approval for a new insulin lispro U-200 formulation and its associated device under the proposed name "Humalog (b) (4) KwikPen." The key information in the submission was previously submitted to the FDA as a supplemental submission to the Humalog NDA (NDA-20563) on March 13, 2013. In a teleconference with Lilly on April 24, 2013, the FDA requested that an original NDA be submitted for this formulation. Humalog (insulin lispro injection, USP, [rDNA origin]) for injection (NDA-20563) was originally approved on June 14, 1996, and is indicated to improve glycemic control in adults and children with diabetes mellitus.

On May 23, 2013, the Division of Metabolism and Endocrinology Products (DMEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for Humalog (insulin lispro injection), for injection, for subcutaneous and intravenous use. This memorandum documents the DMPP review deferral of the Applicant's proposed PPI and IFU for Humalog (insulin lispro injection), for injection, for subcutaneous and intravenous use.

2 CONCLUSIONS

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

Please notify us if you have any questions.

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/s/

SHAWNA L HUTCHINS
12/05/2013

MELISSA I HULETT
12/05/2013

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

CDRH Office of Device Evaluation Consult Review

NDA 205747/ICC1300267

Date: October 2, 2013
To: Callie Cappel-Lynch (CDER/OND/DMEP)
From: Lana Shiu, M.D
Division: CDRH/ODE/DAGID/GHDB
Via: Richard Chapman, Branch Chief of GHDB
Jackie Ryan, M.D. (GHDB Combination Product Team Leader)

Application Number: NDA 205747
Product Name: Insulin Lispro U-200
Humalog® (b) (4) KwikPen™
(600 Unit KP) pen-injector as it has been designed for use with Insulin Lispro U-200.
Sponsor Name: Eli Lilly
Material Reviewed by CDRH/ODE: EDR submission 3.2.R dated 5/31/2013

RECOMMENDATION: → Request for Additional Information

The subject device is modified version of currently marketed Humalog KwikPen disposable pen injectors (NDAs 20-563, 21-017, and 21-018).

The 600 Unit KP device incorporates design changes to accommodate unit dose increment dosing of Insulin Lispro U-200, so the dialed dose is the same for the 600 Unit KP and the currently marketed Humalog KwikPen. Additional design changes were implemented to improve the differentiation of the 600 Unit KP from similar devices.

Device Description
600 Unit KP is a prefilled pen injector designed to provide subcutaneous injection of Insulin Lispro U-200 for treatment of diabetes mellitus. The product may be used for self-administration by the patient or by health care providers or caregivers to administer the medicine. The product can be used more than once with the same drug cartridge (b) (4) The product may be used in health care, institutional, and home settings.

The injection system consists of two main components: the filled 3 mL cartridge and the pen-injector. The KwikPen design was modified for use with insulin lispro U-200 (b) (4)

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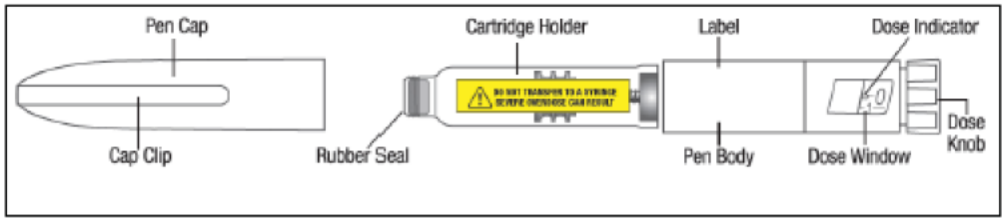
(b) (4)

The Dial continues to show 1 unit delivered per click. The exterior of the KwikPen was modified to provide space for a larger label and better differentiation from other similar devices.



The components of the pen injector do not contact the drug product. The drug product is contained in its primary container closure (cartridge) and the fluid path into the body is through an attached, disposable, single-use sterile needle. There are no concerns about interaction between the drug product and the device components because there is no contact between these components.

Key features of the 600 Unit KwikPen are:

- delivery of doses from 1 to 60 units (b) (4) as a single injection
- dosage amounts in 1-unit (b) (4) increments with audible or tactile clicks while setting dose
- ergonomic design to facilitate control and stability
- single-step dose setting; twist-to-set dose
- low injection force

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(b) (4)

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Feature	600 Unit KwikPen	Humalog KwikPen	Explanation if a change
General Information			
Intended Use	Intended for the use by patients with diabetes for insulin injection from 3 ml cartridges.	Intended for the use by patients with diabetes for insulin injection from 3 ml cartridges.	No change
Target Population	Target patients are persons with either Type 1 or Type 2 diabetes. Reserved for the treatment of patients with diabetes (b) (4) (b) (4) (b) (4)	Target patients are persons with either Type 1 or Type 2 diabetes.	(b) (4)

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Feature	600 Unit KwikPen	Humalog KwikPen	Explanation if a change
Design and Features			
Technology	Mechanical pen injector	Mechanical pen injector	No change
Label size	Width = 35 mm Length = 58 mm	Width= 25 mm Length = 58 mm	Width increased (40%) to allow for additional language and larger font for trade name.
Dial Printing	1 to 60 units in 1 unit increments.	1 to 60 units in 1 unit increments.	No change.
Dose Volume Increment	(b) (4) mL per dose increment	(b) mL per dose increment	(b) (4) (b) (4) Maintains consistency of the user interface with currently marketed pen
Dose Indicator	Length and Shape updated to be square and proud from the adjacent bezel surface. 	Dose indicator is slightly lower than the bezel surface and is more rounded. 	Updated to make the dose indicator more prominent.

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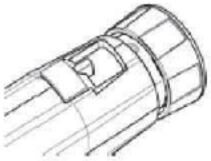
Feature	600 Unit KwikPen	Humalog KwikPen	Explanation if a change
Performance			
Key specifications met	Compliance with ISO 11608-1:2012	Compliance with ISO 11608-1:2000	Use of the currently approved standard during development.
Other			
Pen Body, Dose Knob, and Pen Cap color	Dark gray	Blue	Color changed to differentiate rapid-acting insulin portfolio from long acting insulin portfolio. Updates to the Pen Body, Dose Knob, and Pen Cap color are aligned with the KwikPen Differentiation Briefing Document, discussed with the FDA on July 22, 2011, NDA 20-563.
Bezel	5mm long without Lilly logo 	15mm long with Lilly logo 	Modified to allow for larger label.

Feature	600 Unit KwikPen	Humalog KwikPen	Explanation if a change
Cartridge Holder Markings	 Clear label with yellow box and warning statement, "DO NOT TRANSFER TO A SYRINGE – SEVERE OVERDOSE CAN RESULT.	 Gauge with numbers	Gauge removed in order to add a warning to deter the user from withdrawing the drug with a syringe. The warning is located near where the use error would occur.
Injector Life	The device will last for the user to inject 600 units of insulin or for 28 days.	The device will last for the user to inject 300 units of insulin or for 28 days.	The Insulin Lispro has a concentration of 200 units/mL.
Pen Cap Shape	The device Pen Cap is rounded at the end.	The device Pen Cap is square at the end.	Updates to the Pen Cap are aligned with the KwikPen Differentiation Briefing Document, discussed with the FDA on July 22, 2011, NDA 20-563. Cosmetic update to Cap design does not affect functionality.
Carton	Carton holds 2 devices	Carton holds 5 devices	Carton size decreased for differentiation.

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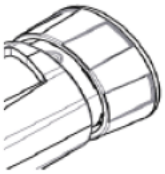
Feature	600 Unit KwikPen	Humalog KwikPen	Explanation if a change
Dose Knob features	Dose Knob side with cut outs. 	Scalloped Dose Knob side. 	Updates to the Dose Knob are aligned with the KwikPen Differentiation Briefing Document, discussed with the FDA on July 22, 2011. Cosmetic update to Dose Knob does not affect functionality.
	(b) (4)		

OPERATION OF THE PEN INJECTOR

The 600 Unit KP is used the same way as the currently marketed KwikPen. The injection mechanism allows the patient to set (dial) doses between 1 and 60 units in 1-unit increments. If the patient dials beyond the desired dose setting, the KwikPen allows the patient to dial backward to the correct setting without wasting insulin (that is, no special dose-correction method is required). By rotating the Dose Knob, the cartridge plunger displacement is set for the dose indicated.

After the dose-setting procedure has been completed, dose delivery is accomplished by depressing the Dose Knob, which causes the dial to turn back down into the mechanism while pushing the injection screw forward. The movement of the injection screw pushes the cartridge plunger and expels insulin through the needle.

Dose completion is confirmed when "0" appears in the dose window

MATERIALS

(b) (4)

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

Labeling – The KwikPen labeling was modified, including updates to the pen label, carton, and Instructions For Use (IFU). Modifications include the addition of syringe warnings and other information needed to use the device safely. The warning to not withdraw drug product with a syringe is repeated on the pen label, carton and IFU. This warning is the same as that provided on the Cartridge Holder and is repeated to mitigate the risk of using a syringe to withdraw drug product and calculating an incorrect dose.

Required Elements		Provided
User Manual (for both types of devices)		
	Labeling contains the prescribed statement from 21 CFR801.109 – "Caution: Federal law restricts…"	**N**
	Device name/model/Specification	Y
	Description of the device	**Y**
	Intended Use/Indications for Use	Y
	Relevant contraindications, warnings, precautions	Y
	Device operating principles, functions	Y
	Instructions for use	**Y**
	If for Home use, a copy of patient instruction included	Y
	Cleaning instructions (If not for single use. Consider possible damage of the cleaning solution to the device)	Y
	Troubleshooting and explanations of all error messages	Y

Sterilization –No sterilization information was included in the PDF document received. Autoinjector itself will be provided sterile to the patients.

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Shelf Life – No Shelf life was mentioned in the PDF document .

Biocompatibility--

(b) (4)

Biocompatibility as established in the currently marketed Humalog KwikPen disposable pen injectors (NDAs 20-563, 21-017, and 21-018)

Software: *Not applicable.*

Performance Testing – Bench

The autoinjector device conforms to the following ISO Standards:
ISO 11608-1:2012 Needle-based injection systems for medical use – Requirements and test methods – Part 1: Needle-based injection systems
ISO 14971:2007 Medical devices – Application of risk management to medical devices

General Requirements for Needle-Based Injection (NIS) Systems

Requirement 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.
Compliance	The Cartridge Holder allows viewing of the cartridge contents throughout the deliverable volume. The Cartridge Holder has no scale allowing for a warning label to mitigate the risk of using a syringe to withdraw and inject the therapeutic. The risk of syringe use was determined to be more severe than risks mitigated by the deliverable volume scale.
Requirement 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.
Compliance	The pen-injector is designed to deliver the labeled volume from the cartridge.
Requirement c)	Not applicable to 600 Unit KP, as this requirement applies to B1 systems.

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Requirement 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 (e.g. milliliters, milligrams, international units) or in a setting specified by the physician (e.g. number, letter, percentage) 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.
Compliance	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.
Requirement e)	There shall be an indication of the pre-setting by visual and either tactile and/or audible means
Compliance	The pen-injector visually indicates that it is ready for injection when the Dose Knob extends away/towards the pen injector as the dose is dialed up or down. Each dose increment has an audible click or tactile resistance associated with it
Requirement f)	The NIS shall indicate, at least by visual means, that is it ready for injection.
Compliance	When the pen-injector is ready to deliver a dose, the Dose Knob is extended with the pre-set dose in the Dose Window.
Requirement g)	The state of the NIS, when ready to deliver a dose, shall be different from its state when the dose has been delivered
Compliance	When the pen-injector is ready to deliver a dose, the Dose Knob is extended with the pre-set dose in the Dose Window. After delivering the dose, the Dose Knob remains down with zero in the Dose Window.
Requirement h)	The NIS shall indicate, by visual, audible or tactile means, or any combination of these, that the injection stroke has been completed
Compliance	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.

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Requirement i)	Not applicable to 600 Unit KP, as this requirement applies to D2 systems.
Requirement j)	Variable multi-dose NISs (system designations A and C) shall be designed so that they: Do not allow a larger dose to be pre-set that 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)
Compliance	The pen-injector will not allow the user to dial a dose that is larger than the amount of medicine remaining in the cartridge.
Requirement k)	Not applicable to 600 Unit KP, as the device has variable doses.
Requirement l)	The NIS shall be designed to function with its specified needles. ISO 11608-2 provides guidance for cartridge-based NISs.
Compliance	The pen-injector is designed, tested and in compliance with the ISO 11608-1 standard using BD pen needles. The BD needle labeling provides no information about the compliance of these pen needles with the ISO 11608-2 specifications.
Requirement m)	The NIS shall be designed to function with its specified containers. ISO 11608-3 provides guidance for containers.
Compliance	The pen injector is designed, tested, and in compliance with the ISO11608-1 standard using Lilly 3 mL drug cartridges.
Requirements n) through t)	Not applicable to 600 Unit KP, as the device is a mechanical NIS
Requirement u)	Adverse effects of the medicinal product contact with the NIS shall be assessed and mitigated through risk assessment
Compliance	Components of the pen injector do not contact the drug product.
Requirement v)	Biological requirements of the NIS shall be established in accordance with ISO 10993-1.
Compliance	The user contact materials selected for the pen-injector have been evaluated in accordance with ISO 10993-1:2009.
Requirement w)	Not applicable, all test methods for 600 Unit KP have acceptance criteria.

The ISO 11608-1 standard describes tests that should be conducted with new or revised pen injector designs. The standard defines the dose accuracy, visual and functional requirements that must be met when the pen injector is conditioned and tested under the various conditions described.

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The standard establishes dose accuracy specifications for design verification testing of ± 0.005 mL for doses smaller than 0.1 mL and ± 5% for doses of 0.1 mL or greater. The pen-injector must meet the following performance criteria at a 95% confidence level:

(b) (4)

[redacted]

Testing Conditions and Number of Pens Tested

(b) (4)

[redacted]

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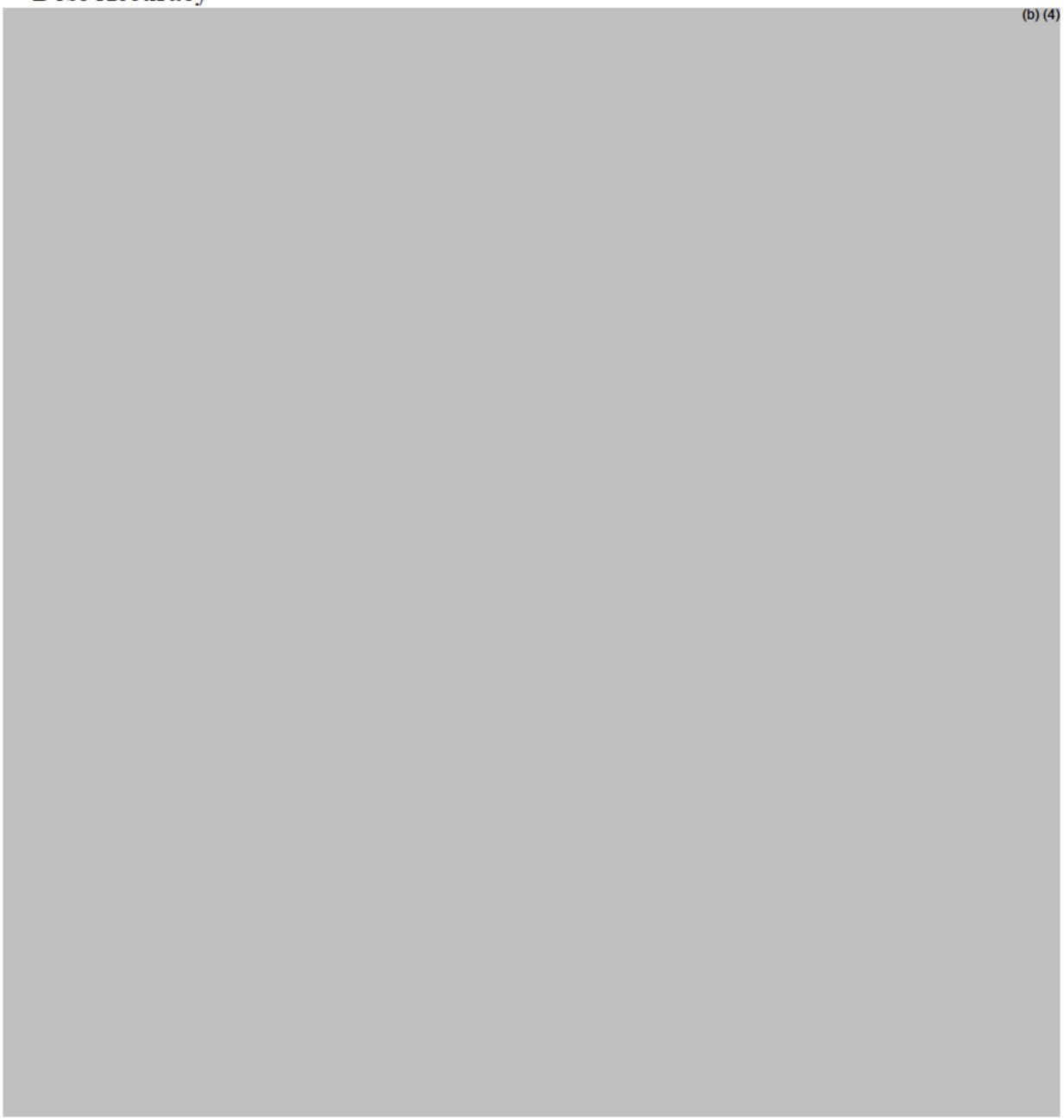
Dose Accuracy

(b) (4)



ISO 14971--Residual Risks Associated with the 600 Unit KP Device Design that are Similar to Other Pen Injectors

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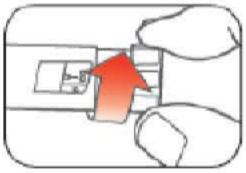
600 Unit KP Residual Risk	FMEA Potential Harm	Risk Mitigation
Risks that may result in Hypoglycemia		
User pushes and turns dose knob to 'dial up'	May Result in severe hypoglycemia	Instructions For Use: IFU informs the user how to dial a dose.  Design: (b) (4) (b) (4) Design: (b) (4) (b) (4) Validation: Formative and Summative Human Factors studies confirmed that representative users of the device were able to dial up the dose without activating this device state.

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600 Unit KP Residual Risk	FMEA Potential Harm	Risk Mitigation
User reads the dose number to the right of the dose window instead of the number inside of the dose window	May Result in severe hypoglycemia	Design: Length and Shape of the dose indicator updated to be square and raised from the adjacent bezel surface.  Instructions for Use: Similar to the current KwikPen manual, the IFU shows multiple examples of doses set within the dose window. (b) (4) [redacted] Validation: Formative and Summative Human Factors testing confirmed that users were able to dial the dose they intended without errors that would lead to clinically significant hyperglycemia or hypoglycemia.

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600 Unit KP Residual Risk	FMEA Potential Harm	Risk Mitigation
User attempts to use a broken device	May Result in severe hypoglycemia	Instructions for Use: Statement in IFU (b) (4) (b) (4) Design: (b) (4) (b) (4) Verification: Bench testing challenged the design features to prevent reasonably foreseeable device breakage. Production equivalent devices met the design specification requirements during design verification.
User cannot differentiate between odd and even numbers or cannot read the dose numbers or cannot identify dose indicator.	May Result in non-severe hypoglycemia	Design: Dose number size was maintained from KwikPen. Instructions for Use: The IFU shows multiple examples of doses set within the dose window, including one even and one odd number. (b) (4) Validation: Formative Human Factors testing were successful which included odd and even numbers to ensure users could select their intended dose. Formative and Summative Human Factors testing confirmed that users were able to dial the dose they intended without errors that would lead to clinically significant hyperglycemia or hypoglycemia.

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600 Unit KP Residual Risk	FMEA Potential Harm	Risk Mitigation
User attempts to use a broken device	May Result in severe hypoglycemia	Instructions for Use: Statement in IFU (b) (4) (b) (4) Design: (b) (4) (b) (4) Verification: Bench testing challenged the design features to prevent reasonably foreseeable device breakage. Production equivalent devices met the design specification requirements during design verification.
User cannot differentiate between odd and even numbers or cannot read the dose numbers or cannot identify dose indicator.	May Result in non-severe hypoglycemia	Design: Dose number size was maintained from KwikPen. Instructions for Use: The IFU shows multiple examples of doses set within the dose window, including one even and one odd number. (b) (4) Validation: Formative Human Factors testing were successful which included odd and even numbers to ensure users could select their intended dose. Formative and Summative Human Factors testing confirmed that users were able to dial the dose they intended without errors that would lead to clinically significant hyperglycemia or hypoglycemia.

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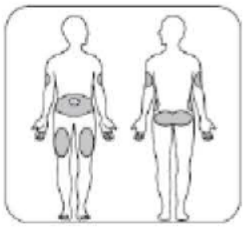
600 Unit KP Residual Risk	FMEA Potential Harm	Risk Mitigation
Part interferences cause dose number misalignment or confusion with dose number alignment.	May Result in non-severe hypoglycemia	Design: Database design and tolerance stacks to confirm dose number alignment. Verification: Production equivalent devices have met ISO11608-1:2012 dose accuracy requirements. Validation: Formative and Summative Human Factors testing confirmed that users were able to dial the dose they intended without errors that would lead to clinically significant hyperglycemia or hypoglycemia.
User uses incorrect injection technique including non-subcutaneous injection	May Result in non-severe hyperglycemia or non-severe hyperglycemia	Instructions for Use: Instruction to "Inject your insulin as your healthcare provider has shown you." Instructions for Use: Instructions that "HUMALOG is injected under the skin (subcutaneously) of your stomach area, buttocks, upper legs, or upper arms", including graphics of injection sites.  Validation: Human factors testing showed that when instructed to inject into an injection pad placed on their abdomen, they were able to perform the injection without errors that would result in a non-subcutaneous delivery.

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600 Unit KP Residual Risk	FMEA Potential Harm	Risk Mitigation
Interaction of cartridge and device causes the cartridge plunger to distort at the end of the dose, and recovers when the next dose is dialed - pulling air into the cartridge. The amount of air pulled in is dispensed on the next dose. Maximum observed overdose of 2 units	May Result in non-severe hypoglycemia	Manufacturing: cartridge release criteria of cartridge glide force and (b) (4) controls. Design: selection of (b) (4) material (b) (4) Design: selection of plunger material Verification: Production equivalent devices have meet ISO11608-1:2012 dose accuracy requirements.
Risks that may result in Hypoglycemia or Hyperglycemia		

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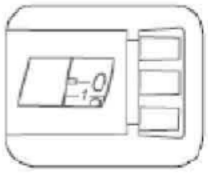
600 Unit KP Residual Risk	FMEA Potential Harm	Risk Mitigation
User does not complete full injection stroke	May result in non-severe hyperglycemia	Instructions for Use: IFU describes proper use in words and graphics, with confirmation step of checking for a zero in the dose window.  Validation: Human Factors Formative and Summative testing was successful, and no trends were observed with users not completing the full injection stroke which would result in clinically significant harm.
Insufficient (b) (4) inadequate strength of design features, or interference of parts results in an inoperable device.	May result in non-severe hyperglycemia	Design: Design specification challenges for the primary function and reasonably foreseeable misuse. Manufacturing (b) (4) Manufacturing (b) (4) (b) (4) Instructions for Use: Statement in IFU (b) (4) (b) (4) Verification: The device has met all design criteria to challenge the design, including free fall testing per ISO11068-1:2012.

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600 Unit KP Residual Risk	FMEA Potential Harm	Risk Mitigation
Risks that may result in Hyperglycemia		
Needle is improperly attached, partially clogged, or large air bubble in cartridge	May result in non-severe hyperglycemia	Design: threaded connection on the clear cartridge holder design has been successfully used in other pen devices with the same pen needles. Validation: Human factors testing were successful and no trends in needle attachment errors which would result in clinically significant harm were observed.
Pen is not primed or is not primed correctly or pressure is not maintained on the dose knob for full 5 seconds	May result in non-severe hyperglycemia	Instructions for Use: IFU describes proper priming techniques in words and graphics. IFU says, "**Prime before each injection.** Priming ensures the Pen is ready to use and removes air that may collect in the cartridge during normal use. If you do not prime before each injection, you may get too much or too little insulin." (b) (4) [redacted] (b) (4) [redacted] Validation: Human factors testing were successful, and no trends were observed with the priming steps that would result in clinically significant harm.

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600 Unit KP Residual Risk	FMEA Potential Harm	Risk Mitigation
Risks that may result in Infections		
Pen and/or needle is shared, handled or disposed of improperly.	Infection to another person	Instructions for Use: IFU includes instructions to dispose of used needles and pens in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and pens in your household trash. Labeling: Addition of "For Single Patient Use Only" to the pen label. Validation: Human factors summative testing was successful, and no trends in disposal errors leading to harm were observed.

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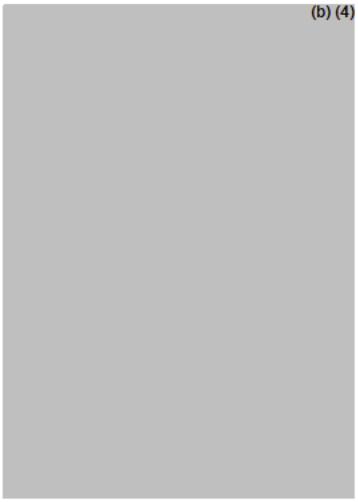
600 Unit KP Residual Risk	FMEA Potential Harm	Risk Mitigation
Risks that may result in incorrect dose		
User injects incorrect medication due to unclear prescription, pharmacy error, or patient removes or does not read pen label or user refills device with incorrect drug.	Unknown Injection	Design: Device and carton color is dark gray. The carton is a smaller size. Device was updated to allow for larger labeling area to enable the larger font for drug product and trade name. Labeling: Device label size and fonts for the identifying drug product and trade name increased. Checkerboard added to the Humalog brand color for differentiation. (b) (4)  Labeling: Carton is sized for two devices and is dark gray in color. Carton also includes same checkerboard pattern as the label. Validation: Formative and Summative Human Factors was successful which included tasks for patients, pharmacists, and nurses to differentiate from commonly available devices; Pharmacists also had to differentiate cartons and select the correct carton from a variety of options in a refrigerator.

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600 Unit KP Residual Risk	FMEA Potential Harm	Risk Mitigation
User injects incorrect medication due to label detachment without being peeled by the user	Unknown Injection	Design: Material selections for the label. Design: Contour design for the label adhesion portion of the housing. Instructions for Use: The instructions for use instructs to read the device and label Manufacturing: (b) (4) Manufacturing Validation: Equipment qualification and process validation will be completed (b) (4) (b) (4)

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600 Unit KP Residual Risks	FMEA Potential Harm	Risk Mitigation
User withdraws U-200 insulin with an insulin syringe AND converts dose incorrectly (4x)	May result in severe hypoglycemia	Design: It is not feasible to design a pen in which the insulin cannot be removed with a syringe. Protective Measures in the Medical Device or in the manufacturing process: Alarming is not feasible because the mechanical pen injector does not have alarming capabilities. Device Labeling: Warning statement added to the cartridge holder at the point of error in yellow warning box.  Carton, Device Label, and Instructions for Use: Yellow warning similar to the cartridge holder was added to the carton and IFU. Instructions for Use: Per the Risk Minimization Plan described in Section 2.5.6.2, Summary of Risk Minimization Plan, a statement of "Inject Humalog 200 units/mL ONLY with your Pen. Do not transfer insulin from your Pen to a syringe. (b) (4) (b) (4) (b) (4) A severe overdose can result, causing low blood sugar which may put your life in danger," has been added to the final IFU. Instructions for Use: (b) (4) (b) (4) Instructions for Use: (b) (4) (b) (4)

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600 Unit KP Residual Risks	FMEA Potential Harm	Risk Mitigation
User withdraws U-200 insulin with an insulin syringe AND converts dose incorrectly (4x), continued	May result in severe hypoglycemia	Communication: Per the Risk Minimization Plan described in Section 2.5.6.2 Summary of Risk Minimization Plan, direct communication to patients prescribed 600 Unit KP should occur at the time of prescription and at the time of first dispense from the pharmacy. A contact for troubleshooting will also be provided. Validation: This failure mode was tested in both Formative and Summative Human Factors testing. After removing the [redacted] (b) (4) in Formative Human Factors Study #2, this overdose amount was not observed. In the Summative Human Factors Study, even though some untrained respondents still withdrew with a syringe, the doses did not result in a 4x overdose.

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600 Unit KP Residual Risks	FMEA Potential Harm	Risk Mitigation
User withdraws U-200 insulin with a syringe and puts into a pump for off-label use.	May result in severe hypoglycemia	Design: It is not feasible to design a pen in which the insulin cannot be removed with a syringe. Protective Measures in the Medical Device or in the manufacturing process: (b) (4) Device Labeling: Warning statement added to the cartridge holder at the point of error in yellow warning box. DO NOT TRANSFER TO A SYRINGE SEVERE OVERDOSE CAN RESULT Carton, Device Label, and Instructions for Use: Yellow warning similar to the cartridge holder was added to the carton and IFU. Instructions for Use: Per the Risk Minimization Plan described in Section 2.5.6.2 Summary of Risk Minimization Plan, a statement of "Inject Humalog 200 units/mL ONLY with your Pen. Do not transfer insulin from your Pen to a syringe. (b) (4) (b) (4) (b) (4) A severe overdose can result, causing low blood sugar which may put your life in danger," has been added to the final IFU.
Incorrect label or label not applied to the cartridge holder to warn against syringe use	May result in severe hypoglycemia	Manufacturing: 100% inspection (b) (4) Manufacturing Validation: Equipment qualification and process validation will be completed (b) (4) (b) (4)

Performance Testing – Animal – No animal testing needed.

Performance Testing – Human Factors : Detailed Review of the HF testing will be addressed in a separate consult review memo by Quynh Nguyen of CDRH/ODE/DAGRID.

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Deficiencies

1. Your submission did not specify if your device is provided sterile to the end user and what is the method of sterilization and expected shelf life. Please also cite the appropriate ISO standards for the sterilization process [redacted (b) (4)] Please provide the information and testing per the ISO standards to include sterilant residuals, description of the [redacted (b) (4)] validation method for the sterilization cycle, and sterility assurance level (SAL).
2. Will your device be "non-pyrogenic"? If yes, then please provide a description of the verification method.
3. Please also provide a description of the device packaging and the integrity testing performed to verify that your device maintained sterility and functionality/operability after rough handling/shipping. Do you have any testing to show that the device maintained its functionality/operability right to deliver an accurate dose (w/o medication error or device malfunction) before its expected end-of-shelf life?
4. In your labeling you did not specify exactly how long the injector could be refrigerated. Please specify the maximum amount of time your combination product can be stored in the refrigerator and provide the test protocol/data using the final finished combination product (drug cartridge filled into the injector) to demonstrate that the performance of the combination product is not negatively impacted by the prolonged refrigeration in that the device is able to deliver the accurate drug dose w/o medication errors, leakage, device malfunctions or patient injuries.
5. In your patient labeling, please include a caution statement to warn the patient that if the injector is pulled out of the skin before counting to the last number, this can lead to significant under-dosing of the medication.

Recommendation –Request for Additional Information as outlined in the Deficiencies Section.

Lana L. Shiu -S
Digitally signed by Lana L. Shiu -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lana L. Shiu -S, 0.9.2342.19200300.100.1.1=1300389268
Date: 2013.10.02 17:43:53 -04'00'

Keith G. Marin -S
Digitally signed by Keith G. Marin -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Keith G. Marin -S, 0.9.2342.19200300.100.1.1=0011250397
Date: 2013.10.03 09:35:56 -04'00'

Richard C. Chapman
2013.10.03 09:42:09 -04'00'

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

/s/

CALLIE C CAPPEL-LYNCH
10/03/2013
Added to darrts for reviewer Lana Shiu

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: July 23, 2013

TO: Branch Chief,
Medical Products & Tobacco Trip Planning Branch
(MPTTPB)
Division of Medical Products and Tobacco Inspections
(DMPTI)
Office of Medical Products and Tobacco Operations
(OMPTO)

And

Director, District Office
(b) (4)

From: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: **FY 2013, High Priority, Pre-Approval Data Validation Inspection for Bioresearch Monitoring, Human Drugs, CP 7348.001**

RE: NDA 205-747
DRUG: Insulin Lispro U-200 injection
SPONSOR: Eli Lilly and Company

This memo requests that you arrange for inspections of the clinical and analytical portions of the following bioequivalence study. Please provide the name of the investigator, once identified, to the DBGLPC point of contact (POC) listed at the end of the assignment. The background material for the assignment is available in ECMS under ORA folder. **A DBGLPC scientist with specialized knowledge will participate in the inspection of clinical and analytical study sites to provide scientific and technical expertise. These inspections should be completed by November 20, 2013 to meet the PDUFA review due date.**

Please do not provide information about the application type or number, the studies to be inspected, the drug name, or the name of the study investigator prior to the start of inspection. The information will be provided to the site at the inspection opening meeting.

Please note that these inspections will be conducted under the Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigator). At the completion of inspection, please send a scanned copy of the completed sections A & B to the DBGLPC POC.

Study:	F3Z-EW-IOPY
Study Title:	"Evaluation of Bioequivalence of Two formulations of Insulin Lispro in Healthy Subjects."
Study Design:	Phase 1, single-center, open-label, 2-sequence, 4-period, randomized, crossover, 8-hour euglycemic clamp study.
Study Period:	May 17, 2010 to August 23, 2010 (45 subjects enrolled and 30 completed)
Clinical Site:	Lilly-NUS Centre for Clinical Pharmacology Pte Ltd Level 6 Clinical Research Centre MD 11, National University of Singapore 10 Medical Drive, Singapore 117597 (Tel) 65-6413-9811 (Fax) 65-6779-0587
Clinical Investigator:	Danny Soon, MD

Note: The glucose measurement during glucose clamp study was done at the clinical site.

SECTION A

RESERVE SAMPLES: These are bioequivalence studies subject to 21 CFR 320.38 and 320.63, and the site conducting the studies is responsible for randomly selecting and retaining reserve samples from each shipment of drug product provided by the sponsor for subject dosing.

Please note that the final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies (http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm)Please refer to CDER's Guidance for Industry, Handling and Retention of BA and BE Testing Samples (May 2004), which clarifies the requirements for reserve samples (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf).

Please follow the instructions below:

- **Verify if reserve samples were retained according to regulations.**
- **In an event reserve samples are not retained or not adequate in quantity; please notify the DBGLPC POC immediately.**
- Please obtain a written assurance from the investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence study, remained in custody of the investigator or the responsible person at the site, and were stored under conditions specified in accompanying records. Document the signed and dated statement (21 CFR 320.38(d, e, g) on the facility's letterhead, or Form FDA 463a, Affidavit.
- If the reserve samples were stored at a third party site, please verify and collect an affidavit to confirm that the alternative site is independent from the sponsor, packager or the manufacturer and that the sponsor was notified in writing of the location.

- Samples of the test and reference products **in their original containers** should be collected and shipped to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening at the following address:

  John Kauffman, Ph.D.
  Center for Drug Evaluation and Research
  Division of Pharmaceutical Analysis (DPA)
  Center for Drug Analysis (HFH-300)
  US Courthouse and Customhouse Bldg.
  1114 Market Street, Room 1002
  St. Louis, MO 63101
  TEL: (314)539-3869

SECTION B

Data Audit Checklist

- Any evidence of under-reporting of AEs identified? _____
- Any evidence of inaccuracy in data capture? _____
- Presence of 100% of signed and dated informed consent forms obtained according to regulations:_____
- Reports for 100% of subjects audited:_____
- Number of subjects screened at the site:_____
- Number of subjects enrolled at the site:_____
- Number of subjects completing the study:_____
- Confirm that the clinical assessments were conducted in a consistent manner and in accordance with protocol-defined requirements:_____
- Number of subject records reviewed during the inspection:_____
- Confirm that SOPs were strictly followed during study conduct:_____
- Review correspondence files for any sponsor- or monitor-requested changes to the study data or report:_____
- Include a brief statement summarizing your findings **(IRB approvals, study protocol, SOPs, protocol deviations, adverse events, concomitant medications, inclusion/exclusion criteria, adequacy of records, drug accountability documents, case report forms for dosing, whether the randomization schedule was strictly followed for dosing of subjects, etc.)**
- Other comments:

_____
_____

Collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

Analytical Site: (b) (4)

FEI: (b) (4)

Contact Person: (b) (4)
Director & Site Leader

Sample Analysis:

Methodology: Radioimmunoassay (RIA)
Analyte Assayed: Free Serum Lispro Insulin (LY275585)
Matrix: Human Serum

Please confirm the following during the inspection:

- Audit all pertinent items related to the analytical method used for the measurement of analyte concentrations in human serum.
- Compare the accuracy of analytical data provided in the NDA submissions by applicant against the original documents at the site.
- Determine if the validated analytical method was employed for the subject sample analysis.
- Compare the assay parameters (such as variability between and within assays, accuracy and precision, etc.) observed during the study sample analysis with those obtained during method validation.
- Determine if the subject samples were analyzed within the validated stability period.
- Confirm that freshly made calibrators and/or freshly made QCs were used for stability evaluations during method validation.
- Scrutinize the number of repeat assays of the subject samples, the reason for such repetitions, the SOP(s) for repeat assays, and if relevant stability criteria (e.g., number of freeze-thaw cycles) sufficiently covered the stability of reanalyzed subject samples.
- Examine correspondence files between the analytical site and the applicant for their content.

Additional instructions to ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to commencement of the inspection. Therefore, we request that the DBGLPC POC be contacted for any further instructions, inspection related questions or clarifications before the inspection and also regarding any data anomalies or questions noted during review of study records on site.

Please fax/email a copy of Form FDA 483 if issued, as soon as possible. If at close-out of the inspection, it appears that the violations may warrant an OAI classification, please notify the DBGLPC POC as soon as possible. At completion of inspection, please remind the inspected entity of the 15 business-day timeframe for submission of a written response to observations listed on Form FDA-483. Please forward written response as soon as you receive it to the DBGLPC POC.

DBGLPC POC: Arindam Dasgupta, Ph.D. (Foreign)
(301) 796-3326
Email: arindam.dasgupta @fda.hhs.gov

Gopa Biswas, Ph.D. (Domestic)
(301) 796-4167
Email: gopa.biswas@fda.hhs.gov

DARRTS CC:
CDER OSI PM TRACK
ORAHQ OMPTO DMPTI BIMO
OSI/DBGLPC/Taylor/Haidar/Biswas/Choi/Dejernett/Dasgupta/CF
ORAHQ/OMPTO/DMPTI/BIMO/Turner/Arline/Montemurro/Carrion
OMPT/CDER/OND/ODEII/DMEP/Callie Cappel-Lynch/Parks

Email CC:
OGROP/ORA/CE-FO/(b) (4)-DC (b) (4)

Draft: GB 07/11/2013
Edit: YMC 7/17/2013; SHH 7/17/2013
OSI: BE6474; O:\BE\assigns\bio205747.doc
FACTS: (b) (4)

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

/s/

GOPA BISWAS
07/23/2013

SAM H HAIDAR
07/24/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA #205747 BLA# N/A	NDA Supplement #:S- N/A BLA Supplement # N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Humalog (b) (4) KwikPen (under review) Established/Proper Name: Insulin Lispro (rDNA origin) Dosage Form: injection Strengths: 200U/mL		
Applicant: Eli Lilly and Company Agent for Applicant (if applicable): N/A		
Date of Application: May 10, 2013 Date of Receipt: May 10, 2013 Date clock started after UN: N/A		
PDUFA Goal Date:March 10, 2014	Action Goal Date (if different): N/A	
Filing Date: July 9, 2013	Date of Filing Meeting: June 25, 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 5		
Proposed indication(s)/Proposed change(s): improve glycemic controll in adults and children with diabetes mellitus		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☒ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☒ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other: N/A	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): N/A	
List referenced IND Number(s): (b) (4)	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			Standard Review
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	Not a 505(b)(2)
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***			X	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***		X		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			Not included in orginal submission but provided in an amendment on 6/6/13
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	X			Not included in original submission but provided in an amendment on 5/30/13

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	X			
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:			X	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		X		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☐ Medication Guide (MedGuide)			

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***			X	
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***			X	
If representative labeling is submitted, are all represented SKUs defined?			X	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X			CDRH and CDRH, Human Factors consulted 5/17/13 DMPP consulted 5/23/13
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** July 22, 2011 ***If yes, distribute minutes before filing meeting***		X		Type C Meeting under NDA 20563 to discuss development plans for insulin lispro U-200
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 25, 2013

BLA/NDA/Supp #: 205747

PROPRIETARY NAME: Humalog (b) (4) KwikPen (under review)

ESTABLISHED/PROPER NAME: Insulin Lispro

DOSAGE FORM/STRENGTH: Injection/ U-200

APPLICANT: Eli Lilly

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): improved glycemic control in adults and children with diabetes mellitus

BACKGROUND:
Humalog (insulin lispro) is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus. Humalog (insulin lispro) injection 100units/mL was approved under NDA 020563 on June 14, 1996. On March 15, 2013 Eli Lilly submitted a new supplement to NDA 020563 proposing the addition of a new insulin lispro U-200 formulation and its associated device to various labeling documents of the currently approved Humalog U-100 formulation. It was determined by the user fee staff and the division, that a new drug application with clinical data would be required in order to market this product. On May 10, 2013 Eli Lilly submitted this NDA for insulin lispro U-200.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Callie Cappel-Lynch	Y
	CPMS/TL:	Mehreen Hai	Y
Cross-Discipline Team Leader (CDTL)	Karen Mahoney		Y
Clinical	Reviewer:	Suchitra Balakrishnan	N
	TL:	Karen Mahoney	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (*for OTC*	Reviewer:	N/A	

products)			
	TL:	N/A	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Sury Sista	Y
	TL:	Lokesh Jain	N (Immo Zodezensky covering)
Biostatistics	Reviewer:	N/A	
	TL:	N/A	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Robert Maher	Y
	TL:	Karen Davis- Bruno	N
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Xavier Ysern	Y
	TL:	Danae Christodoulou	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Denis Miller	N
	TL:	Bryan Riley	N
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	N/A	
	TL:	N/A	
OSE/DMEPA (proprietary name)	Reviewer:	Reasol Agustin	N
	TL:	Lena Maslov	Y
OSE/DRISK (REMS)	Reviewer:	Joyce Weaver	Y
	TL:	Cynthia LaCivita	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:	N/A	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers	Quyhn Nguyen (CDRH-HF)		N
Other attendees	Jackie Ryan (CDRH)		Y
Other attendees	Minerva Hughes (BioPharm)		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: Clinical Team and OSI are in	☐ YES ☒ NO

agreement that no inspection is necessary.	
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Director- Division of Metabolism and Endocrinology Products

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): N/A

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Receipt date: May 10, 2013
Filing Date: July 9, 2013
74-Day letter must issue on July 23, 2013
Mid-Cycle Review meeting: October 10, 2013 (approximate)
PeRC meeting: Not needed
Team Meetings: As needed
Primary Reviews due: February 3, 2014
Labeling Meetings: As needed
Wrap-Up Meeting: February 4, 2014 (tentative)
Secondary Reviews due: February 10, 2014
Send proposed labeling/PMR/PMC to sponsor: February 10, 2014
CDTL Review due: February 17, 2014
Action package to Division Director: February 17, 2014
Sign Action letter: March 10, 2014 (PDUFA goal date)

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

CALLIE C CAPPEL-LYNCH
07/18/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Enforcement A
General Hospital Devices Branch

DATE: July 3, 2013

TO: Callie Cappel-Lynch, OND/ODEII/DMEP, CDER, WO22, Room 3362, callie.cappellynch@fda.hhs.gov

CC: Julie Marchick, OND/ODEII/DMEP, CDER, WO22, Room 3350, julie.marchick@fda.hhs.gov

Steven Hertz, OC/OMPQ/DGMPA/GDMAB, CDER, WO51, Room 4222, steven.hertz@fda.hhs.gov

Office of Combination Products at combination@fda.gov

THRU: Carl Fischer, Chief, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, WO66, Room 3526 7/3/13

FROM: Emre Genca, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, WO66, Room 3548

FIRMS: Eli Lilly & Company
Lilly Technology Center
Indianapolis, IN 46221
FEI No. 1819470

Lilly France
2, rue du Colonel Lilly
Fegersheim, France, 67640
FEI No. 3002807475

APPLICATION NUMBER NDA 205747

PRODUCT NAME: Humalog KwikPen (insulin lispro rDNA origin)

CONSULT INSTRUCTIONS: Evaluate the need for an inspection under the Medical Device Quality System Regulations of any of the facilities associated with this application.

The Office of Compliance at CDRH received a consult request from CDER to evaluate NDA 205747 and to assess whether any of the facilities associated with the NDA application need to be inspected under applicable 21 CFR Part 820 regulations.

The Humalog KwikPen is a rapid-acting human insulin analog indicated to improve glycemic control in patients with diabetes mellitus. The 3 mL cartridges are prefilled, assembled into pen injectors capable of delivering a total of 600 units of insulin lispro (200 units/mL), and administered as a series of subcutaneous injections.

Evaluation of Application Documents

The application was searched for documents pertaining to applicable 21 CFR Part 820 regulations for this combination product. Several deficiencies were noted:

- There was no information available for review regarding compliance with 21 CFR 820.30 design controls, 820.50 purchasing controls, and 820.100 corrective and preventive actions.

- The description of the manufacturing activities of the finished combination product was inadequate. The application did not include information on how the finished combination product would be assembled. No information was provided on acceptance activities.

Evaluation of Inspectional History

A drug and device inspection of the Indiana facility (PAC 82845B), conducted by DET-DO from August 9, 2011, through August 23, 2011, covered medical device manufacturing operations for Humalog. The inspection was classified VAI (483 observations were drug-related). No previous device-related inspections have been conducted at the French facility.

CDRH Office of Compliance Recommendation

The Office of Compliance at CDRH has the following recommendations regarding NDA 205747:

- Additional information addressing the deficiencies listed above is requested. The sponsor may find useful information regarding types of documents to provide in the following guidance document: 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm.

- An inspection of the Lilly facility located in Fegersheim, France (FEI No. 3002807475) under applicable medical device regulations (see attached inspectional recommendations).

Emre Genca

Prepared: EGenca: 7/2/13
Reviewed: ITejero: 7/2/13
Revised: EGenca: 7/3/13
Reviewed: CFischer: 7/3/13
Final:

cc:
WO66-3513 (DOE-A Firm File)
WO66-3513 (Division Chron. File)
WO66-3548 (EGenca)

CTS No.: ICC1300260

Inspectional Recommendations

Firm to be inspected:

Lilly France
2, rue du Colonel Lilly
Fegersheim, France, 67640
FEI No. 3002807475

CDRH recommends a baseline, Level 2 QSIT inspection under applicable medical device regulations of Lilly France located in Fegersheim, France (FEI No. 3002807475). The focus of this inspection should be Purchasing Controls (21 CFR 820.50), Corrective and Preventive Actions (21 CFR 820.100), and Design Controls (21 CFR 820.30) for the Humalog KwikPen (NDA 205747). Additionally, evaluate the manufacturing activities associated with the finished combination product, including in-process and final acceptance activities.

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CALLIE C CAPPEL-LYNCH
07/11/2013

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

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 205747

Application Type: New NDA

Name of Drug: Humalog (b) (4) KwikPen (insulin lispro [rDNA origin]) injection

Applicant: Eli Lilly and Company

Submission Date: May 10, 2013

Receipt Date: May 10, 2013

1.0 Regulatory History and Applicant's Main Proposals

The application provides for a Humalog U-200 prefilled pen device. Humalog U-100 was approved under NDA 20563 on June 14, 1996.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

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

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by July 13, 2013. The resubmitted PI will be used for further labeling review.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

NO 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required

• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

YES 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

YES 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

YES 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

YES 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

YES 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment: *Under subsection 2.5 Humalog U-200 (200 units/mL) the following is not in italics "[see Dosage and Administration (2.3, 2.4), Warnings and Precautions (5.3)".*

YES 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

YES 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

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