

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**205747Orig1s000**

**MEDICAL REVIEW(S)**



## Center for Drug Evaluation and Research Division of Metabolism and Endocrinology Products

NDA205747-Class 2 Resubmission-insulin lispro (Humalog) U-200  
Clinical Review

**NDA: 205747**

**Name of Drug: LY275585, Humalog U 200 (200U/ml)**

**Formulation:** injection- subcutaneous in a KwikPen pre-filled device.

**Indication:** Treatment of Type 1, Type 2 diabetes mellitus (T1DM, T2DM)

**Applicant:** Eli Lilly and Co.

**Reviewer:** Suchitra Balakrishnan, MD, Ph.D.

**Team Leader:** William Chong, MD.

### **Background:**

On March 15, 2013, the applicant submitted a supplement to NDA 020563 proposing the addition of a new insulin lispro, 200U/mL (subsequently referred to as Humalog U-200) formulation in a KwikPen prefilled device to the approved labeling of insulin lispro 100U/mL (subsequently referred to as Humalog U-100). It was determined that a separate NDA would be required rather than a supplement. Therefore, on May 10, 2013, the applicant submitted NDA 205747 for Humalog U-200. This submission referenced the clinical efficacy and safety data available with Humalog U-100. The Humalog U-200 development program consisted of a pharmacokinetic bioequivalence (BE) study to show BE between the proposed commercial insulin lispro 200U/mL formulation and the approved insulin lispro 100U/mL formulation, and human factors studies. On March 10, 2014, the agency issued a complete response (CR) letter for NDA 205747. The main deficiency identified was in the pivotal BE study, as the FDA inspection found that the clinical site did not retain samples of the reference drug (i.e., insulin lispro 100U/mL). The applicant has now resubmitted to NDA 205747 with a new BE study to address FDA requests from the CR letter, as agreed to by FDA and the applicant at the End of Review meeting on May 7, 2014.

### **Deficiencies Identified in the CR Letter and Applicant Responses:**

#### **“Clinical Pharmacology:**

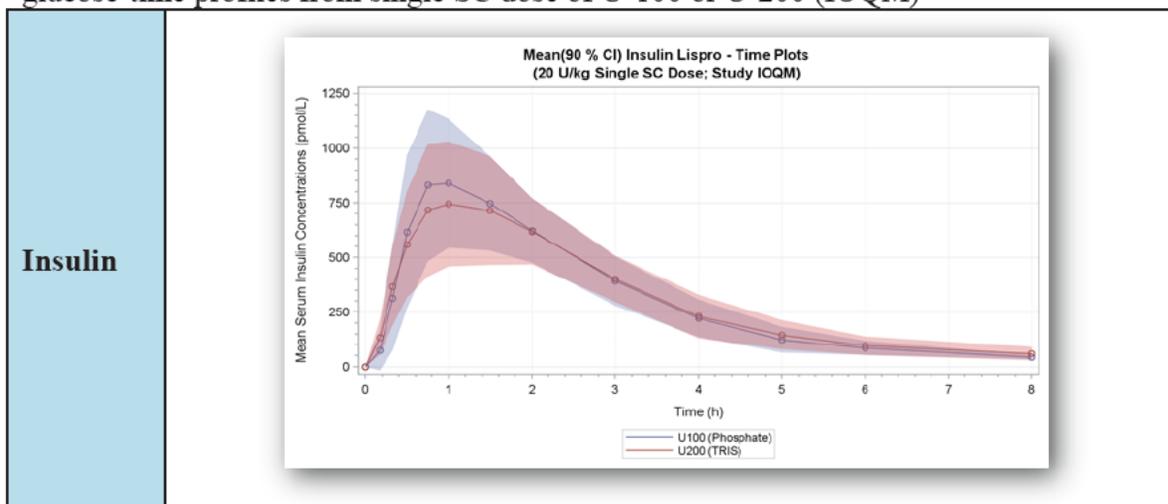
The records of the pivotal bioequivalence study entitled ‘Evaluation of Bioequivalence of Two formulations of Insulin Lispro in Healthy Subjects’ conducted at Lilly-NUS Centre for Clinical Pharmacology, Singapore were inspected by FDA inspectors in November, 2013. The inspection found that the clinical site did not retain samples of the reference drug Humalog 100U/mL, Lot A677287 used in the bioequivalence study, and did not release them to FDA upon request as required by 21 CFR Part 320.38. Due to lack of reserve samples for the reference product, the reviewers were not able to authenticate the

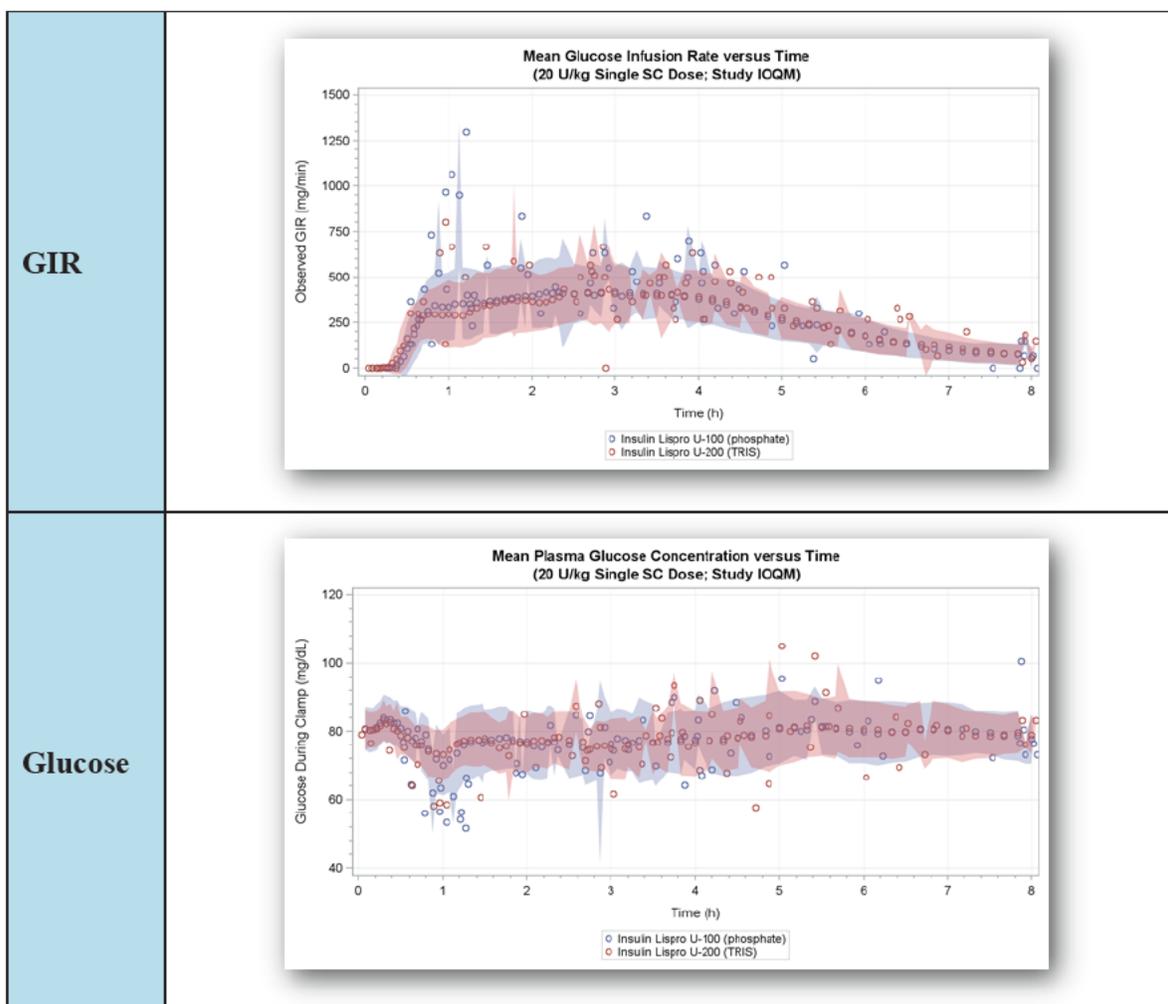
identity of the reference product used in the study, and therefore were unable to validate the findings of the study. The applicant was advised that if the bioequivalence study to bridge the efficacy and safety data from Humalog 100U/mL to Humalog 200U/mL was repeated, they should ensure that regulations as set in 21 CFR 320.38 and 320.63 are met.”

The applicant performed a new BE study (Study IOQM) evaluating the bioequivalence of insulin lispro TRIS U-200 formulation (test) relative to that of the marketed insulin lispro phosphate U-100 (reference) after subcutaneous (SC) administration of 20 units to healthy subjects.

The clinical pharmacology reviewer has concluded that evidence presented by the pharmacokinetic (PK)-pharmacodynamic (PD) study IOQM supports that the PK and PD (time-action) profile of U-200 is similar to that of U-100 (*refer to the Clinical Pharmacology review by Dr. Suryanarayana Sista in DARRTs dated May 1, 2015 for further details*). The results from study IOQM show that geometric mean ratios and confidence intervals for both PK and PD parameters were within the pre-specified limits of 0.80 to 1.25. In addition, there was no difference in time to peak plasma insulin concentration ( $T_{max}$ ) between the two treatments: median  $T_{max} = 1.0$  hour for both treatments, median difference for  $T_{max}$  showed no difference between the two treatments (95% CI: - 0.25 to 0, p-value=0.06) using Hodges-Lehmann method. The time to maximal glucose infusion rate ( $T_{GIR,max}$ ) revealed no statistically significant differences (p<0.001). The duration of action did not significantly differ between Humalog U-200 and Humalog U-100 (see Figure 1 below)

Figure 1 Mean serum insulin lispro, glucose infusion rate (GIR) and plasma glucose-time profiles from single SC dose of U-100 or U-200 (IOQM)





(Source- Figure 1 in Clinical Pharmacology review by Dr. Suryanarayana Sista)

The reviewer from the Center for Devices and Radiological Health (Dr. Jacqueline Ryan, CDRH consult dated February 7, 2013) did identify issues of concern in the last review cycle. She requested clarification about biocompatibility issues related to the proposed Humalog KwikPen device and the 3 ml insulin cartridge. The applicant was asked to provide current biocompatibility testing data based on the final finished device and in a worst case condition. In addition, all patient/user contact device components had to be tested for biocompatibility. (b) (4) CDRH also recommended that the applicant clearly identify all (b) (4) used in the device, including the chemical name, CAS reg. No., composition, and toxicological data. The applicant did provide further information and conduct the testing recommended by CDRH. The additional information has been included with the resubmission. This has been reviewed by CDRH and they have concluded that the applicant has adequately responded to all previous biocompatibility questions and have no approvability issues (CDRH consult review by Dr. Lana Shiu, Jan 6, 2015).

The Division of Medication Error Prevention and Analyses (DMEPA) had concerns about the human factors validation studies since use errors were observed with high

priority tasks of writing the prescription, dialing the dose, delivering the dose, and trouble-shooting jammed pen injectors. The reviewers felt that the test results did not support a conclusion that the device as designed was safe and effective for the intended users. They recommended that the applicant implement additional risk mitigation strategies, and perform human factors validation testing with 15 representative users (i.e., a combination of healthcare providers and patients). In response, the applicant revised the patient and health-care provider communications to significantly highlight the severe consequence of syringe extraction, along with providing the proper course of action in the pen malfunctions in the patient communication documents. The applicant tested these communication documents in a supplemental Summative Human Factors study with the following objectives:

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

The DMEPA reviewer has reviewed the revised documents and human factors study results and concluded that they are acceptable from a medication error perspective. She recommends approval (*For details, see the review by Dr. Sarah Vee, DMEPA in DARRTS, dated March 13, 2015*).

**Relevant review issues from other disciplines in this review cycle:**

There were no chemistry, manufacturing and controls (CMC) issues identified with the Humalog U-200 formulation. The proposed proprietary name (i.e., Humalog KwikPen) was found to be acceptable by the DMEPA. The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) have recommended accepting data from the repeat bio-equivalence study without an on-site inspection. The Office of Compliance at CDRH evaluated the application for quality system requirements to comply with applicable provisions of the Medical Device Quality System Regulation 21 CFR 820. They recommend approval of Humalog U-200.

**Clinical Issues:**

There are no clinical efficacy or safety studies to be reviewed with this submission. However it is worth discussing the rationale for this concentrated insulin product (i.e., medical need) and the benefit versus risk given the potential for medication error issues identified with the first review cycle.

The applicant has provided the following justifications as part of their product development rationale along with their benefit-risk conclusions with the initial submission, and in a response to an information request dated May 12, 2015:

- Possible improved treatment adherence when vial and syringe users transition to the Humalog KwikPen 200 U/mL

- The (b) (4) Humalog KwikPen 200 U/mL may be beneficial for patients with dexterity issues and reduce tissue trauma
- Societal (i.e., environmental) benefits of the Humalog KwikPen 200 U/mL as it may lead to less waste due to the need for fewer pens
- The applicant presented data on the increasing prevalence of obesity with parallel increase in diabetes, and increased insulin requirements with increasing BMI. They indicate that clinicians and patients have expressed a need for the development of insulin products formulated at higher concentrations to allow administration of insulin in lower volumes

Further, as discussed in the submission, the applicant justifies the proposed (b) (4)

[Redacted]

An issue of increased variability of the actual dose delivered with lower volumes has been raised by CDRH reviewers previously (CDRH consult dated February 7, 2013 by Dr. Jacqueline Ryan-question 1 to sponsor):

*“Although the accuracy testing meets the standard (ISO 11608-1) of  $\pm 0.005$  mL for doses smaller than 0.1 mL and  $\pm 5\%$  for doses of 0.1 mL or greater. The results reported for 1 [unit] 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.”*

The sponsor’s response was as follows:

[Redacted] (b) (4)

(b) (4)

(b) (4)

CDRH (Dr. Patricia Beaston) felt that the sponsor's response was inadequate but deferred to the DMEP and DMEPA review teams. Part of her response is included below to highlight her concerns:

“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)

***Reviewer's Assessment:***

Bioequivalence of Humalog U-200 to Humalog U-100 has been established, and Humalog U-100 has an established efficacy and safety profile. There appears to be some potential benefit from a more concentrated rapid-acting insulin being available for patients requiring high doses of a prandial insulin.

Overall, the benefits of this product in patients taking lower doses of rapid-acting insulin, e.g. < 60 U/day over 2-3 meals, are unclear. It is worth noting that there are approved concentrated insulin products (i.e., Humulin-R U-500, and Toujeo [insulin glargine U-300]). Humulin® R U-500 (500 Units/mL) is recommended for patients with diabetes requiring insulin doses of over > 200 Units per day. Toujeo (insulin glargine injection, U-300) has no minimal dose requirement specified<sup>1</sup>. There are notable differences between these products and the current proposed drug product. More patients might be expected to require daily doses of rapid-acting insulin covered by Humalog U-200 compared to Humulin-R-U-500. Given this larger potential population, I have concerns

<sup>1</sup> TOUJEO Solostar (insulin glargine U-300) and HUMULIN® R U-500 package inserts.

about the margin of error particularly with smaller volumes. . Compared to Toujeo (which is a once daily basal insulin), patients using this product are more likely to administer inject additional smaller doses to cover meals and snacks. This is of particular concern due to the variability noted by the CDRH reviewers at low volumes. Patients, especially those requiring prandial insulin at < 20 U/day are more likely to inject smaller doses for an unplanned meal or snack or due to reduced portion size with a regular meal.

In information presented in the original submission (Table 3.2.R.2.3.1.2-2-Dose accuracy testing results, page 18, Module 3.2.R.2- Medical Device- Prefilled Pen Injector) doses ranging from 1-60U were tested for accuracy. Significant safety concerns i.e. hypoglycemia due to increased dose delivered are more likely in patients with increased insulin sensitivity, as outlined by Dr. Beaston. The DMEPA reviewer has no concerns related to medication errors at the lower dose range. Hence I recommend approval of Humalog U-200 (b) (4)

#### **Clinical Recommendation**

I recommend approval of HumalogU-200 (b) (4)  
as  
discussed above.

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SUCHITRA M BALAKRISHNAN  
05/15/2015

WILLIAM H CHONG  
05/18/2015

See my memo/review for additional discussion with regard to this drug product.

## Division Director's Memorandum

**Date:** March 10, 2014

**From:** Jean-Marc Guettier, MD CM

**NDA#:** 205747

**Proprietary Name (established name):** Humalog <sup>(b) (4)</sup> KwikPen (insulin lispro injection). This is a twice concentrated version of currently marketed lispro (i.e., 200 units of insulin/mL).

**Submission Date:** May 10, 2013

**Goal Date:** March 10, 2014

**Applicant:** Hoffmann-La Roche Inc.

**Indication:** To improve glycemic control in adults and children with diabetes mellitus.

### **Regulatory Action: Complete Response**

This is a brief memorandum with my recommendation. Dr. Mahoney has summarized the issues in the application and the reader is referred to her memorandum for full details.

**Recommendation:** I concur with Dr. Mahoney's conclusions and also recommend a complete response. Briefly, to establish efficacy and safety of this twice concentrated version of insulin lispro, the applicant relies entirely on a pivotal bioequivalence study (i.e., F3Z-EW-IOPY). Inspection of the clinical study site where this study was conducted revealed that the study was not compliant with 21 CFR Part 320.38. This issue was discussed with leadership from the Office of Clinical Pharmacology (Dr. Sahajwalla), the office responsible for reviewing pivotal bioequivalent studies and DMEP learned that compliance with 21 CFR Part 320.38 has been an absolute requirement for pivotal bioequivalent studies. The division of medication error prevention and the CDRH human factors studies team also noted several potential use related risks and usability issues with the drug-device combination product and recommend additional mitigation strategies and testing. These will need to be addressed in a future re-submission. Clinical review of safety and review of the clinical rationale for this product was deferred until the next review cycle.

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JEAN-MARC P GUETTIER  
03/10/2014

## Cross-Discipline Team Leader Review

<b>Date</b>	February 14, 2014
<b>From</b>	Karen Murry Mahoney, MD, FACE Team Leader, Diabetes Team Division of Metabolism and Endocrinology Products (DMEP) Center for Drug Evaluation and Research (CDER)
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA # Supplement#</b>	NDA 205747
<b>Applicant</b>	Eli Lilly
<b>Date of Submission</b>	May 10, 2013
<b>PDUFA Goal Date</b>	March 10, 2014
<b>Proprietary Name / Established (USAN) names</b>	Proposed proprietary name: Humalog (b) (4) KwikPen (U-200 formulation) Established name: insulin lispro injection
<b>Dosage forms / Strength</b>	200 units insulin per mL
<b>Proposed Indication(s)</b>	To improve glycemic control in adults and children with diabetes mellitus
<b>Recommended:</b>	Complete Response

## 1. Introduction

On May 10, 2013, Eli Lilly submitted an application for a new formulation of insulin lispro. The currently approved insulin lispro contains 100 units of insulin per mL; the lispro proposed in this application contains 200 units per mL. A more concentrated formulation of lispro could allow injection of a smaller volume, which could be useful, particularly for patients who are insulin-resistant and require larger numbers of units of insulin. Lilly's proprietary name for lispro is Humalog®, hereafter referred to as Humalog or lispro.

The pivotal study submitted to support this application was Study F3Z-EW-IOPY, "Evaluation of the Bioequivalence of Two Formulations of Insulin Lispro in Healthy Subjects". This study was intended to compare the pharmacokinetic and glucodynamic parameters of lispro U-100 and lispro U-200. However, this study is inevaluable due to a failure (under CFR 21 Part 320.38) on inspection, by the FDA's Office of Scientific Investigations' (OSI's) Bioequivalence Branch, of the clinical site of the study. Please see Section 11 for a brief description of the inspection findings, and for details, please see Dr. Cho's review (DARRTS 8 Feb 2014).

Because of this lack of compliance with the requirement for retention of reference samples, the inspection could not confirm the identity of the reference product used in the study. Therefore,

the study results could not be validated, and there is no study upon which to base approval. Therefore, a Complete Response action is recommended.

Clinical and Clinical Pharmacology reviews could not be conducted for this application, because of invalidation of the sole pivotal study. This memo covers other discipline reviews which could be completed, and the inspection results.

## 2. Background

See Section 1.

## 3. CMC/Device

### 3.1. Chemistry, Manufacturing and Controls Review

Please see Dr. Ysern's review (DARRTS 10 Feb 2014). From a Chemistry standpoint, there were no issues which would have precluded approvability.

The drug substance is the same as that for Humalog® (insulin lispro).

The drug product is a pen delivery device containing lispro, 200 units/mL solution for injection prefilled into a 3 mL cartridge preassembled into a new pen injector capable of providing a total of 600 units of insulin lispro. The solution for U200 lispro has <sup>(b) (4)</sup>

The impurity profile was acceptable.

A refrigerated shelf life of 36 months, and an in-use shelf of 28 days at temperatures not exceeding 30 °C were supported.

Overall, Dr. Ysern found that the information on the drug substance, drug product, impurities, manufacture and stability were adequately documented and supported approval from a Chemistry standpoint.

### 3.2. Device Review

Please see the review by Dr. Ryan, Combination Products team leader, Center for Devices and Radiologic Health (CDRH) (DARRTS 12 Feb 2014).

Drs. Ryan and Qian identified several questions which the applicant will need to answer if the application is resubmitted. These questions begin on page 4 of Dr. Ryan's consult. In brief, CDRH has asked for the following:

- Clarification of whether the 3 mL insulin cartridge has been previously approved/cleared by FDA

- Clarification of the device models/types used in the NDA, and verification of their previous FDA approval(s)
- Clarification that all materials in the device were listed in the NDA
- Additional information (b) (4) used in the device
- Chemical analysis of the leachables (b) (4)
- Biocompatibility data for device components

### 3.3. Office of Surveillance and Epidemiology Human Factors Review

Please see the Human Factors Study review by Dr. Reasol of the Division of Medication Error Prevention and Analysis (DMEPA), Office of Medication Error Prevention and Risk Management (OMEPRM), Office of Surveillance and Epidemiology (OSE). Overall, DMEPA found the results of the Human Factors Study to be acceptable. However, Dr. Reasol notes the following issues:

- Three out of 16 prescribers wrote for the incorrect number of units. The pen device is marked in units, but three of the prescribers incorrectly wrote for half the correct dose, perhaps assuming that a conversion was needed to account for the fact that Humalog U200 is twice as concentrated as Humalog U100.
- In a device-jamming scenario, 16/67 participants incorrectly transferred insulin from the pen device to a syringe. However, a moderator error contributed to these occurrences.

Dr. Reasol recommended specific labeling changes in her consult; although labeling will not occur with this application, comments regarding the basis of her labeling recommendations can be conveyed to the applicant in the Complete Response letter, so that the applicant can modify the labeling for resubmission.

### 3.4. Center for Devices and Radiologic Health Human Factors Review

Please see Dr. Nguyen's review (DARRTS 6 Feb 2014). Dr. Nguyen also reviewed the Human Factors study, and felt that the study results did not support a conclusion that the device as designed is safe and effective for the intended users. Dr. Nguyen identified the following concerns:

- She mentioned the same concern identified by Dr. Reasol regarding prescribers inappropriately performing a dose conversion.
- She mentioned the error regarding transferring of the insulin contents of a jammed pen to a syringe.
- She noted four occurrences of patients underdosing by one or two units, and one occurrence of overdosing by one unit. She notes that, although the applicant states that the Instructions for Use (IFU) do not encourage users to count clicks to determine dosing, review of the IFU does not provide information to deter click-counting, and the IFU also does not instruct the user to visually verify the dialed dose.
- Users are supposed to ensure that a full dose is delivered by counting to five and then verifying that a window has reset to zero. Nine users pulled the injector when the window did not reset to zero after counting to five. Dr. Nguyen's review of the IFU found that the instructions do not make this procedure clear.

Dr. Nguyen notes that the applicant does not discuss implementation of additional risk mitigation strategies to address these issues. She asserts that implementation of such strategies is needed, followed by repeat Human Factors validation testing with 15 representative users (healthcare providers and patients combined).

I have considered Dr. Nguyen's recommendation regarding repeat Human Factors validation testing, and I concur. The errors mentioned could result in patient harm, due to underdosing, overdosing, or needle-stick injuries. In particular, significant under-dosing (half-dosing), or even double-dosing, could occur if patients or providers erroneously dose-convert in one direction or another. Therefore, the applicant not only needs to change the FPI and IFU, but also needs to validate that these changes result in fewer errors.

Please see Dr. Nguyen's recommended comments to the applicant, which begin on page 2 of her review. I have asked Dr. Nguyen (via email on 18 Feb 2014) for slight clarification of the language of her Comment C, but overall, I concur with communicating her comments to the applicant.

#### **4. Nonclinical Pharmacology/Toxicology**

No new nonclinical pharmacology/toxicology data were submitted with this application.

#### **5. Clinical Pharmacology/Biopharmaceutics**

Because the sole pivotal study was not acceptable due to the inspection failure discussed in Section 11, there were no data for Clinical Pharmacology to review. Dr. Sista discusses this in his memo in DARRTS (10 Feb 2014).

#### **6. Clinical Microbiology**

Please see Dr. Miller's Microbiology review (DARRTS 21 Jan 2014). No microbiology deficiencies were noted.

The product is a sterile [REDACTED] (b) (4)  
[REDACTED] Sterility and endotoxin testing were acceptable.

#### **7. Clinical/Statistical- Efficacy**

Because the sole pivotal study was not acceptable due to the inspection failure discussed in Section 11, there were no clinical data to review. Because the Cross-Discipline Team Leader is also the Clinical Team Leader and is filing this CDTL memorandum, no separate clinical review was filed.

## **8. Safety**

See Section 7.

## **9. Advisory Committee Meeting**

Not applicable.

## **10. Pediatrics**

No pediatric data were submitted.

## **11. Other Relevant Regulatory Issues**

### **11.1. Inspection Failure**

For details of the results of the inspection, please see Dr. Seongeun Cho's inspection report (DARRTS 8 Feb 2014). Dr. Cho and Kellia Hicks conducted a thorough inspection of the clinical site, Lilly-NUS Centre for Clinical Pharmacology, in Singapore, from 7-15 Nov 2013. Following that inspection, a Form FDA 483 was issued, with the following observation:

“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.”

It should be noted that, although the above quote references 21 CFR Part 320.138, the correct CFR passage is 21 CFR Part 320.38. The CDTL confirmed this in an email with the inspector, Dr. Cho, on 14 Feb 2014.

Because of this lack of compliance with the requirement for retention of reference samples, the inspection could not confirm the identity of the reference product used in the study. Therefore, the study results could not be validated.

On 5 Dec 2013, the review team, including DMEP (Drs. Guettier, Mahoney and Balakrishnan; and Ms. Cappel-Lynch), OSI (Dr. Cho) and the Office of Clinical Pharmacology (Drs. Sahajwalla, Jain, Khurana and Sista) met to discuss the inspection findings. The team concurred that, due to the failure to adhere to 21 CFR Part 320.38, the study results could not be validated and were therefore unacceptable. The team agreed that a Complete Response action was appropriate.

The applicant has been notified of the inspection findings, and stated that they are instituting appropriate corrective procedures for future studies.

#### 11.2. Financial Disclosure

The applicant provided financial disclosure data. However, because the pivotal study was inevaluable, these data are also not evaluable. Should the applicant choose to resubmit their application, the financial disclosure data for the repeat pivotal study will be evaluated during that review.

### **12. Labeling**

Labeling did not occur because the pivotal study was unacceptable.

On 14 Jan 2014, the FDA notified the applicant that the proposed proprietary name, Humalog KwikPen, was conditionally acceptable.

### **13. Recommendations/Risk Benefit Assessment**

The Cross Discipline Team Leader recommends a Complete Response action, due to a failed inspection (failure of the applicant to adhere to 21 CFR Part 320.38). Because of this lack of compliance with the requirement for retention of reference samples, the inspection could not confirm the identity of the reference product used in the study. Therefore, the study results could not be validated, and there is no study upon which to base approval. Therefore, a Complete Response action is recommended.

Should the applicant choose to resubmit their application using a repeat bioequivalence study to bridge the efficacy and safety data from lispro U100 to lispro U200, the repeat study must comply with all regulations, including 21 CFR Part 320.38.

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KAREN M MAHONEY  
02/20/2014

## 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. (b) (4)

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

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



## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	well-controlled studies in the application? <i>Pivotal Study #1</i> <i>F3Z-EW-IOPY-Evaluation of bioequivalence of two formulations of insulin lispro in healthy subjects</i> <i>Pivotal Study #2</i> <i>F3Z-LC-IMAB-Evaluate the effect of zinc on the pharmacokinetics and glucodynamics of insulin lispro in healthy subjects.</i> <i>Patient simulation studies:</i> 3.2.R.2.4 Attachment 1 - Humalog (b) (4) KwikPen Summative Human Factors Study Technical Report 3.2.R.2.5 Attachment 2 - Humalog (b) (4) KwikPen Human Factors Engineering and Usability Engineering Report (HFE/UE)				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			X	
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?			X	

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			Defer to Clinical Pharmacology and CDRH reviewer to confirm
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			As above
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			NA	
34.	Are all datasets to support the critical safety analyses available and complete?			NA	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				As above
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			NA	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all	X			

as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?				

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_\_Yes\_\_\_**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.- NA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.  
 Since primary review of these studies will be by the clinical pharmacology and CDRH reviewers, I defer to them for further comments

Suchitra Balakrishnan, MD, PhD. 5/13/13  
 \_\_\_\_\_  
 Reviewing Medical Officer Date

Karen Mahoney MD  
 \_\_\_\_\_  
 Clinical Team Leader Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUCHITRA M BALAKRISHNAN  
06/19/2013

KAREN M MAHONEY  
06/20/2013