CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205747Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	May 21, 2015
From	William H. Chong
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA-205747
Applicant	Eli Lilly
Date of Submission	November 26, 2014
PDUFA Goal Date	May 26, 2015
Proprietary Name / Established (USAN) names	Humalog KwikPen (insulin lispro)
Dosage forms / Strength	Solution for injection (200 units of insulin per mL)
Proposed Indication(s)	1. To improve glycemic control in adults and children with diabetes mellitus
Recommended:	*Approval*

1. Introduction

Diabetes mellitus is a disease of impaired glucose metabolism. The primary aim of therapy in diabetes mellitus is to improve glucose control. This is based on evidence from large trials showing that better glycemic control improves outcomes (i.e., retinopathy). Insulin is the primary glucose regulatory hormone, and is absent in type 1 diabetes mellitus (T1DM) and insufficient in type 2 diabetes mellitus (T2DM). Exogenous administration of insulin is the mainstay of therapy in T1DM, and it also used to improve glycemic control in patients with T2DM.

The proposed NDA product is a concentrated insulin lispro. The currently approved insulin lispro is available at a concentration of 100 U/mL, and the Applicant is now proposing to market a 200 U/mL product as a pre-filled pen.

The NDA was originally submitted on May 10, 2013. The primary study supporting the NDA was a pharmacokinetic study designed to show bioequivalence to the approved insulin lispro 100 U/mL. A Complete Response letter was issued at the end of that review cycle due to an inspection failure of the study site. Reference samples were not retained, thus the inspection could not confirm the identity of the reference product. This in turn meant that the study results could not be validated resulting in no data to support approval. The Applicant is now resubmitting the NDA with a new bioequivalence study to support approval.

2. Background

To support this NDA, a new bioequivalence study was performed. The drug product is sufficiently similar to the reference that demonstration of bioequivalence was felt adequate to support approval without additional clinical studies. The most of the reviews were completed during the first review cycle and will not be discussed in detail here. The focus will be on the findings of the clinical pharmacology study, other issues identified from the first review cycle, and the Applicant's rationale for the NDA product.

The Complete Response letter issued on March 10, 2014 outlined the following deficiencies:

CLINICAL PHARMACOLOGY

1. The efficacy and safety for Humalog 200U/mL formulation was to have been supported by bridging this formulation with the approved Humalog 100U/mL formulation in a bioequivalence study (Study F3Z-EW-IOPY). The records of this 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 from November 7, 2013 to November 15, 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. Lilly- NUS Centre for Clinical Pharmacology, Singapore was issued FDA form 483 (FEI # 3004358483, dated November 15, 2013) noting this violation. The FDA form 483 was acknowledged by Lilly- NUS Centre for Clinical Pharmacology, Singapore in their letter to the Agency, dated November 26, 2013. 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, and therefore we are unable to validate the findings of the study.

   Submit adequate data to support the efficacy and safety for Humalog 200U/mL. If you repeat the bioequivalence study to bridge the efficacy and safety data from Humalog 100U/mL to Humalog 200U/mL, the study should be repeated ensuring that regulations as set in 21 CFR 320.38 and 320.63 are met (for details, see guidance "Handling and Retention of BA and BE Testing Samples", at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf). The conduct of the clinical study should adhere to regulations set in 21 CFR Part 50, 21 CFR Part 54 and 21 CFR Part 56. If the study is a foreign clinical trial not conducted under an IND, regulations set in 21 CFR 312.120 will apply. Per regulations set in 21 CFR 320.38 and 320.63, the clinical study site will have to retain the reserve sample for the Agency's inspectors to be able to collect and test the samples. The bioanalytical method associated with the study should be adequately validated (for details, see guidance "Bioanalytical Method Validation", at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf).

DEVICE

2. Clarify whether 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 that the material is compatible based on its intended use and patient contact classification.
3. 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] (b) (4) This evaluation covers currently marketed devices [redacted] (b) (4) . On page 1 of the evaluation report, you have provided a Table [redacted] (b) (4) Clearly identify all subject devices and device models or types included in this NDA. [redacted] (b) (4)
4. Clarify whether 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. Such materials would include [redacted] (b) (4) etc. If Table 1 does not identify all materials used, provide a complete listing of ALL the manufacturing materials used and the associated Material Safety Data Sheets (MSDS).
5. You state that the devices in the platform [redacted] (b) (4) Table 1 of your biocompatibility evaluation report [redacted] (b) (4) However, your MSDS provided does not clearly identify [redacted] (b) (4) Provide a revised MSDS report which includes the chemical identity, composition, CAS number, and toxicological data [redacted] (b) (4) used in the subject devices.
6. Provide chemical analysis of the leachables [redacted] (b) (4)
7. 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 [redacted] (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 [redacted] (b) (4)
8. The results of your human factors validation study showed that use errors were observed with high priority task of writing the prescription, dialing the dose, delivering the dose, and trouble-shooting jammed pen injectors. 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, stating in the communication that 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 under-dosing. 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) do not encourage the user to count the clicks for determining their dose. However, our review of the IFU indicated that they do not provide any information to deter the user from counting the clicks. In addition, the IFU do not instruct the user to look and verify the dialed dose.
c. Nine patients/caregivers pulled the pen injector 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 provide 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 dose window after pulling the needle out in step 4c. If the needle should be kept in place and the user should check for the dose window to display "0" prior to pulling the needle out of the injection site, ensure that is emphasized in the IFU.

9. 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 pen injector has a warning affixed to the cartridge holder, which states [redacted] (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 [redacted] (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).

3. CMC/Device

The Chemistry, Manufacturing and Controls (CMC) review was completed by Dr. Xavier Ysern during the first review cycle. The drug substance is identical to that used in the reference product, and there are only minor changes to the drug product (i.e., higher zinc:

insulin ratio, use of TRIS (b) (4) Based on his review of the submitted data, Dr. Ysern recommended approval. Dr. Ysern also agrees with the proposed shelf-life and storage conditions. No new CMC information was included in the resubmission.

The proposed drug product is to be dispensed as a prefilled pen delivery device. During the first review cycle, the Center for Devices and Radiological Health (CDRH) as well as the Division of Medical Error Prevention and Analysis reviewed the device and human factors studies. During the first review cycle, some concerns were raised with regard to biocompatibility as well as potential for medical errors.

Dr. Lana Shiu from the CDRH reviewed the responses to the biocompatibility issues. Evaluation of the biocompatibility of the rubber disc seal, specifically the results of the Applicant's in vitro test of the (b) (4) rubber disc was deferred to CMC. This was reviewed in Dr. Ysern's review and the rubber disc seal was felt to be adequate. Based on review of the responses to the other biocompatibility issues, Dr. Shiu has no further issues. The responses were felt to be adequate.

Dr. Sarah Vee from the DMEPA reviewed the additional data submitted in response to the human factors deficiencies. Based on her review of the additional data, Dr. Vee concludes that the container label, carton label, and instructions for use are acceptable.

In summary, all disciplines involved in review of the manufacturing, device, and human factors recommend approval.

4. Nonclinical Pharmacology/Toxicology

There is no nonclinical data submitted to support this NDA.

5. Clinical Pharmacology/Biopharmaceutics

The primary clinical pharmacology review was completed by Dr. Suryanarayana Sista. Based on his review of the data, he recommends approval.

As the reference samples from the original clinical pharmacology study were not retained, the Applicant performed a repeat study (Study F3Z-EW-IOQM: Evaluation of the bioequivalence of two formulations of insulin lispro in healthy subjects). In this study, the euglycemic clamp technique was used to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of insulin lispro 200 U/mL compared to insulin lispro 100 U/mL in healthy volunteers. Each subject was evaluated with four clamp procedures (two with insulin lispro 200 U/mL, two with insulin lispro 100 U/mL). For each clamp procedure, study subjects were administered 20 U of insulin followed by sampling over the 8-hour clamp procedure.

With the 20 U of insulin administered in this study, geometric mean ratios and confidence intervals for both the PK and PD parameters were within the pre-specified limits of 0.8-1.25 (see Figure 1 and Table 4 from Dr. Sista's review, excerpted below).

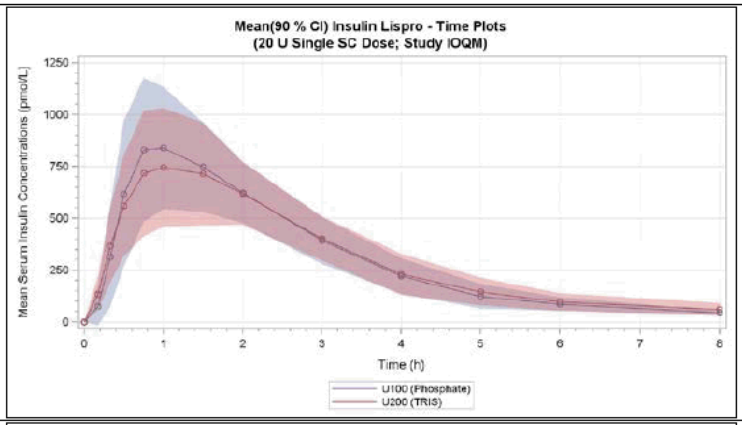
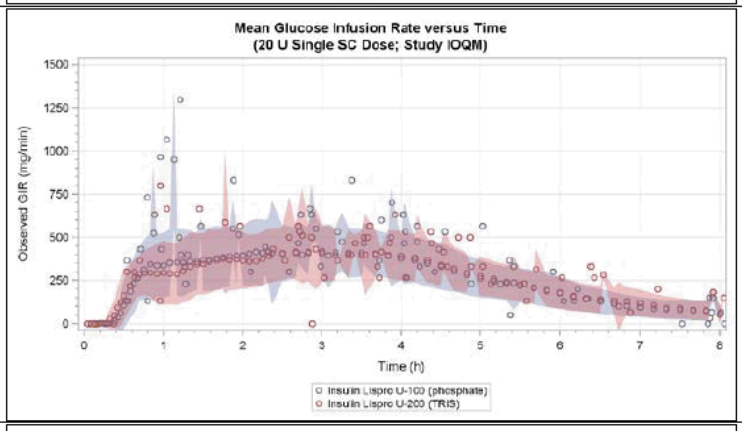
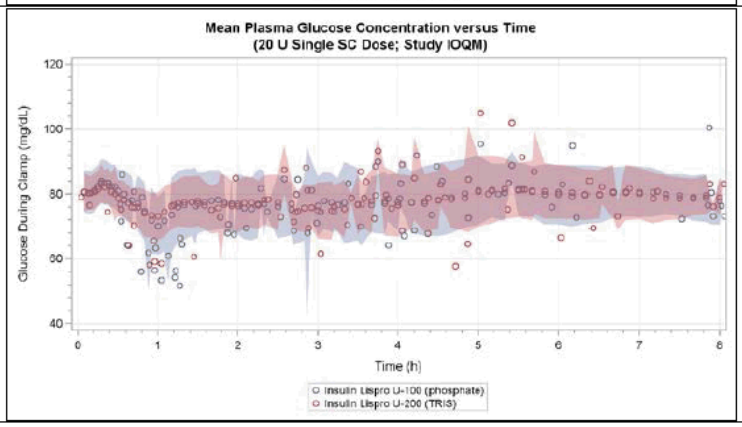
Insulin	
GIR	
Glucose	

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)**

Table 4Statistical analysis results for primary PK and PD parameters (Full Data)

Type	Parameter	GMR (90% CI)*
PK	C_{max} (pmol/L)	0.87 (0.83 – 0.92)
	$AUC_{0\text{-}t}$ (pmol·h/L)	0.99 (0.96 – 1.01)
PD	GIR_{max} (mg/min)	0.95 (0.90 – 1.00)
	$GIRAUC_{0\text{-}t}$ (mg)	0.98 (0.94 – 1.02)

Additionally, there was no apparent difference in time to peak insulin concentration, and there was no statistically significant difference in time to peak glucose infusion rate (see Table 3 of Dr. Sista's review, excerpted below).

Table 3 Summary statistics for primary PK and PD parameters (Full Data)

Type	Parameter	U-200 (Test)	U-100 (Reference)
PK	C_{max} (pmol/L)	794.5 ± 290.5	908.8 ± 340.9
	AUC_{0-t} (pmol·h/L)	2263 ± 395	2303 ± 408
	T_{max}* (h)	1.0 (0.5 – 3.0)	1.0 (0.5 – 2.0)
PD	GIR_{max} (mg/min)#	516.6 ± 1.41	558.8 ± 1.40
	$GIRAUC_{0-t}$ (mg)#	119426 ± 1.35	122671 ± 1.36
	$T_{GIR,max}$* (min)	154 (29 – 372)	121 (29 – 282)

*Median (Range); #Reported as R_{max} and G_{tot}, respectively in the sponsor's reports

Sensitivity analyses were performed to verify the robustness of these findings. These additional analyses supported the primary findings of the study (see Figure 7, Figure 8, and Figure 9, as well as Table 5, and Table 6 of Dr. Sista's review, not included here).

Based on the findings of this study, the PK and PD parameters of insulin lispro 200 U/mL appear comparable to the reference product (i.e., insulin lispro 100 U/mL).

6. Clinical Microbiology

Quality microbiology data was reviewed by Dr. Denise Miller during the first review cycle. No concerns were identified by Dr. Miller at that time and she recommended approval.

7. Clinical/Statistical- Efficacy

No clinical efficacy studies were performed to support this NDA. Thus there is no statistical review.

As the single study supporting this NDA is a phase 1 clinical pharmacology study in healthy volunteers, there is no relevant safety data to review. The safety information obtained from this study is of limited utility in evaluating risks. Dr. Suchitra Balakrishnan has submitted a memorandum discussing the clinical utility of a 200 U/mL insulin product in lieu of a clinical review which I will summarize here.

As noted in Dr. Balakrishnan's review, the Applicant has cited several potential benefits of the 200 U/mL insulin product. These include reductions in injection volume, decreased injection pain/discomfort, and easier manipulation/administration for patients with limited dexterity. The Applicant has also stated that with the increasing prevalence of obesity, higher insulin doses are needed for patients with T2DM. Dr. Balakrishnan does not disagree with any of these points, and notes that patients with higher doses of insulin may find the smaller injection volumes of some benefit with regard to tolerability and adherence to therapy. There is no data to suggest that this formulation will improve glycemic control more than the 100 U/mL. As noted by Dr. Balakrishnan, the Applicant has proposed (b) (4)

(b) (4)
Dr. Balakrishnan does not agree (b) (4) though she does agree with the proposed language (b) (4)

I agree with Dr. Balakrishnan that there is likely a population that will find some advantage from this 200 U/mL insulin product such as patients using higher doses of insulin. I also agree with her (b) (4) I do not agree with her recommendation to accept the proposed language (b) (4) for reasons which I will discuss further in section 8 below.

8. Safety

The clinical studies submitted in support of this NDA are limited to a single phase 1 clinical pharmacology study in healthy volunteers. As a result, there is limited safety information and it is unclear whether that information is particularly informative to safety. Safety of insulin lispro 200 U/mL is expected to be the same as that of the approved insulin lispro 100 U/mL.

Safety concerns unique to this product are related to the potential for medication errors (reviewed by Dr. Vee, briefly discussed above), and potential for dosing errors with the pen device. In the original review cycle, the reviewers from the CDRH noted that the variability in dose is higher at low doses compared to high doses (20-32% variability in volume delivered at 1 unit vs. < 1% variability in volume at 30 units). Due to concerns that patients using low doses of insulin may choose to use this product for convenience or financial reasons, the reviewers from CDRH (see Dr. Patricia Beaston's consult from December 18, 2013 [submitted to DARRTS on December 19, 2013 by Ms. Callie Cappel-Lynch] and Dr. Jacqueline Ryan's consult from February 7, 2013 [submitted to DARRTS on February 12, 2014 by Ms. Callie Cappel-Lynch]) have recommended that this product should be limited to those patients that need > 20 units of insulin daily and that labeling include a warning that patients using less than this threshold amount of insulin should not use this product. Dr. Balakrishnan agrees with this assessment.

I have considered the concerns of the reviewers from the CDRH as well as the thoughts outlined in Dr. Balakrishnan's review. I do not agree that this variability in delivery volume is a significant concern. Though the variability in volume delivered is higher percent-wise at low doses, I do not believe that this necessarily results in large variability in the amount of insulin delivered. My reason for concluding this is that the overall variability in the amount of insulin delivered is small across the range of doses tested and not likely to be clinically significant (see example calculations below).

Estimated variability in units of insulin delivered:

Table 3.2.R.2.3.1.2-2 Dose Accuracy Testing Results

Test Name	Number of observations	Dose Setting (units)	Mean Dose (ml)	Std. Dev. (ml)	Actual K	Minimum Target K	Test Result
Standard Atmosphere	60	1	0.0061	0.0008	5.094	2.670	Pass
	60	30	0.1494	0.0009	7.358	2.670	Pass
	60	60	0.2984	0.0012	11.017	2.670	Pass

Source: Excerpted from information submitted with original NDA on May 10, 2013 in module 3.2.R (pen.pdf)

# of units to deliver (U)	Intended volume of delivery (mL)
1	0.005
30	0.15
60	0.3
# of units to deliver (U)	**% variability in volume[1]**
1	16%
30	0.6%
60	0.4%
# of units to deliver (U)	**Variability in # of units delivered[2]**
1	0.16
30	0.18
60	0.24

[1] % variability = Std. Dev./Intended volume x 100; [2] Variability in # of units delivered = % variability in volume x # of units to deliver

Based on these estimates, the variability in absolute insulin dose is < 0.25 units across all doses tested. This variability appears to be reasonably consistent across the three doses tested, and I do not think that it will have a meaningful impact on glycemic control.

I believe that use of this 200 U/mL insulin product in the proposed pen device is reasonably safe across the range of doses that can be delivered by the device. (b) (4) I recommend removing any language (b) (4) I would note that this is consistent with the approach taken with the labeling for the recently approved 300 U/mL insulin glargine.

9. Advisory Committee Meeting

No Advisory Committee meeting was held to discuss this product.

10. Pediatrics

No data with regard to use in pediatrics are included in the NDA submission. The NDA product does not consist of a new active ingredient, new dosing form, or new route of administration. The Applicant also is not adding a new indication. Thus, the Pediatric Research Equity Act was not triggered and no Pediatric Study Plan was included (or necessary).

11. Other Relevant Regulatory Issues

No Financial Disclosure Template was completed for this NDA. The single study submitted to support the NDA is a PK/PD study which demonstrated bioequivalence for the 200 U/mL formulation with the approved 100 U/mL formulation. This study was performed at a single investigational site under a single investigator who is a full-time employee of the Sponsor. Though this raises the possibility of bias, I do not believe this is a concern as the outcome measures are based on objective analytical values for PK and PD, and these should not be influenced by the investigator.

12. Labeling

The Applicant has not submitted a separate label for this NDA, but has incorporated additional language into the approved insulin lispro 100 U/mL label. The majority of the changes to the label focused on identifying the specific information needed to inform the use of insulin lispro 200 U/mL. This includes a statement on when it is appropriate to use the 200 U/mL concentration, and separating information on use of insulin lispro in pumps and via intravenous administration (these routes were not studied with insulin lispro 200 U/mL, and are thus it is not labeled for administration via these routes). I agree with these additions. The Applicant has proposed (b) (4) As discussed in section 7 and 8 above, I do not agree with inclusion of this language. As the only study performed to support this NDA is a clinical pharmacology study, the main section with additional language is section 12. (b) (4) (b) (4) Applicant has been told to present the numerical results.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval of this NDA.

- Risk Benefit Assessment

The assessment of Risk-Benefit for insulin lispro 200 U/mL is essentially the same as that for the approved insulin lispro 100 U/mL. Based on the submitted clinical pharmacology study, the PK and PD characteristics of insulin lispro 200 U/mL is comparable to insulin lispro 100 U/mL. Thus, it is expected that the glucose lowering ability (and clinical benefit) of this product is also comparable. The drug substance is the same for the two products (b) (4) The safety profile of insulin lispro 200 U/mL is expected to be the same as the reference product (i.e., insulin lispro 100 U/mL).

My primary concern with approving this insulin product is the potential for dosing errors. This was reviewed as part of the human factors assessment, and it was concluded that there is adequate communication to mitigate this risk. Additionally, the 200 U/mL product will be marketed as a stand-alone pen device that displays the insulin dose to be delivered which should further limit dosing errors. Based on the review from the DMEPA, this risk appears to be minimal. Thus, I believe that this product has a benefit-risk profile that supports approval.

The utility of a 200 U/mL insulin product could be questioned, and I have considered this as part of my recommendation. Administration of larger volumes, as would be the case with high doses of insulin, can be associated with increased discomfort at the injection site. Additionally, patients with high insulin requirements will utilize the dispensed insulin more quickly necessitating more frequent prescription refills and incur greater cost. While higher concentration insulins are available (i.e., regular insulin 500 U/mL) the indication is for patients requiring more than 200 units of insulin per day. There may be a population of patients who could benefit from this intermediate concentration. The Applicant has proposed (b) (4) I do not find that argument particularly compelling, and disagree (b) (4) I recommend including no such language (b) (4) Thus, I favor not including any language (b) (4)

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

I do not recommend a Risk Evaluation and Management Strategy.

- Recommendation for other Postmarketing Requirements and Commitments

I do not recommend any Postmarketing Requirements or Postmarketing Commitments.

- Recommended Comments to Applicant

I do not have any additional comments to convey to the Applicant.

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/s/

WILLIAM H CHONG
05/21/2015

JEAN-MARC P GUETTIER
05/26/2015

Dr. Chong's memorandum serves as the divisional summary memorandum for this application. I concur with his review and recommendations and also recommend approval.
Briefly, Eli Lilly and Company submitted a new drug application pursuant to section 505(b)(1) of the Federal Food Drug and Cosmetic Act (FD&C Act) for Humalog U-200 on 10 May 2013. Humalog U-200 injection is a solution containing 200 units of insulin lispro per mL filled in a 3 mL (b) (4) cartridge pre-assembled in a dedicated auto-injector, multi-dose, pen-delivery device (i.e., KwikPen platform). The applicant is seeking to indicate Humalog U-200 to improve glycemic control in adults and pediatric patients with diabetes mellitus. The application received a Complete Response Letter on 10 March 2014 due to clinical pharmacology, device biocompatibility and device human factors deficiencies. A Complete Response addressing each of these deficiencies was received on 26 November 2014. In the response the applicant satisfactorily addressed each of these deficiencies. As summarized by Dr. Chong, the approval is based on new CMC, PK/PD, and Human Factors data. The applicant has demonstrated that Humalog U100 and Humalog U200 are bioequivalent at a given dose. The Humalog U-200 does not come in vial/syringe presentation. The drug product cartridge is irreversibly integrated in the pen device body and cannot be removed from the device. Furthermore the delivery device was specifically designed to deliver the U-200 formulation such that no dose calculations/volumetric conversions are required for correct dosing and administration. The above features will mitigate against the theoretical risk of over dosage due to medication errors. Labeling was enhanced to further mitigate against this risk. All disciplines including the Division of Medication Error Prevention and Analysis (DMEPA) have recommended approval.