CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205747Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205747

COMPLETE RESPONSE

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 acknowledge receipt of your amendments dated May 30 and 31, June 3, 5, 6, 20, and 27, August 8 and 29, September 6 (2), October 22 and 28, November 5, 18, and 20, and December 9, 2013, and February 7, 2014.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

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 (b) (4) This evaluation covers currently marketed devices. (b) (4) ". 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)

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 (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 (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.

6. Provide chemical analysis of the leachables (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 (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)

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 under-dosing. 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 does 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.

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 pen injector 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).

LABELING

9. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.

- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager, at (301) 796- 8436.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, MD
Director, Acting
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

JEAN-MARC P GUETTIER
03/10/2014