DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 019717/S-098
NDA 019717/S-101

SUPPLEMENT APPROVAL

Eli Lilly and Company
Attention: Joerg Pfiefer, PhD
Advisor, US Regulatory Affairs
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Pfeifer:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received March 17, 2010 (S-098), and December 15, 2011 (S-101), submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Humulin 70/30 (70% human insulin isophane suspension/30% insulin human [rDNA origin]) injection, 100 Units/ml.

We acknowledge receipt of your following amendments:

S-098: March 2 and September 22, 2011, May 4 and June 8, 2012, January 30, March 22, and November 4, 2013

The January 30, 2013, submission constituted a complete response to our October 11, 2011, action letter.

S-101: January 18, 2012, and March 22 and November 4, 2013

The Prior Approval supplemental new drug application, S-098, proposes the addition of an additional disposable insulin delivery device (KwikPen) to the labeling for Humulin 70/30 (70% human insulin isophane suspension/30% insulin human [rDNA origin]).

The Prior Approval supplemental new drug application, S-101, proposes the creation of a package insert which conforms to the Physicians Labeling Rule (PLR) format.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the Package Insert, the Patient Package Insert, and Instructions for Use), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 019717/S-098 and NDA 019717/S-101**." Approval of this submission by FDA is not required before the labeling is used.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Humulin 70/30 (70% human insulin isophane suspension/30% insulin human [rDNA origin]) was approved on April 25, 1989, we have become aware of the results of the Human Factors Studies that were submitted with your resubmission of S-098, that identified task failures/use errors with the Humulin KwikPen, including errors in pen selection, insulin mixing, pen device priming, dose dialing, and dose injection. These task failures/use errors have the potential to result in hypoglycemia or hyperglycemia. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of medication errors (task failures/use errors) with resultant risks of hypoglycemia or hyperglycemia.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of medication errors (task failures/use errors) with resultant risks of hypoglycemia or hyperglycemia.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

2098-1 A human factors trial of the modified Instructions for Use (IFU) manual for the Humulin KwikPen including, but not limited to, assessment of pen selection, insulin mixing, pen-device priming, dose dialing, and dose injection.

The timetable you submitted on November 1, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	December 2013
Trial Completion:	June 2014
Final Report Submission:	August 2014

Submit the protocol to your IND 030225, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

ENCLOSURES:
- Package Insert
- Patient Package Insert
- Instructions for Use
- Carton and Container Labeling

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
11/07/2013