DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 018780/S-126
NDA 018780/S-134

SUPPLEMENT APPROVAL

Eli Lilly and Company
Attention: Ingrid Hensley, Ph.D.
Advisor, Global Regulatory Affairs- U.S. Diabetes
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Hensley:

Please refer to the following Supplemental New Drug Applications (sNDAs), and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Humulin R (insulin human injection) U-100 and U-500:

NDA Number	Supplement Number	Date of Receipt
18780	S-126	October 30, 2009
18780	S-134	December 15, 2011

The "Changes Being Affected" supplemental new drug application S-126 provides for addition of a 3mL vial presentation of U-100.

The Prior Approval supplemental new drug application S-134 provides for an update to the package insert to comply with the physician labeling rule (PLR) and pregnancy and lactation labeling rule (PLLR) for U-100, and for removal of "(b) (4)" from the non-proprietary name in all labeling for U-100.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions listed below.

Revision dates added to the prescribing information, patient package insert, and instructions for use.

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, text for the patient package insert, 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 include 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 immediate 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 — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3).* For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 018780/S-126 and NDA 18780/S-134**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

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}

William Chong, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Prescribing Information for U-100
Patient Package Insert for U-100
Instructions for Use Vial for U-100
Carton and Container Labeling for U-100
Prescribing Information for U-500 (version approved on July 8, 2016)
Patient Package Insert for U-500 (version approved on July 8, 2016)
Instructions for Use KwikPen for U-500 (version approved on December 29, 2015)
Instructions for Use Vial for U-500 (version approved on July 8, 2016)

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

/s/

WILLIAM H CHONG
05/25/2018