BLA 020563/S-202, BLA 021017/S-146, BLA 021018/S-132,
BLA 205747/S-028

SUPPLEMENT APPROVAL

Eli Lilly and Company
Attention: Ayana Rowley Henderson, Pharm.D.
Associate Director, Global Regulatory Affairs – North America
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Henderson:

Please refer to your supplemental biologics license applications (sBLAs) submitted under section 351(a) of the Public Health Service Act for the following:

BLA Number	Supplement Number	Product Name	Submitted/Receipt Date
020563	202	Humalog (insulin lispro) injection U-100	September 29, 2020
021017	146	Humalog Mix 75/25 (insulin lispro protamine and insulin lispro) injectable suspension	September 29, 2020
021018	132	Humalog Mix 50/50 (insulin lispro protamine and insulin lispro) injectable suspension	September 29, 2020
205747	028	Humalog (insulin lispro) injection U-200	September 29, 2020

These Prior Approval sBLAs provide for labeling revisions to ensure conformity with requirements for biological products regulated under section 351 of the PHS Act and updates to comply with the guidance for industry *Selection of the Appropriate Package*

Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single- Dose, and Single-Patient-Use Containers for Human Use[1].

APPROVAL & LABELING

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

- The revision dates have been updated in the highlights of the prescribing information (PI), on the patient package inserts (PPIs), and on the instructions for use (IFUs) to accurately reflect the month of approval.

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[2] that is identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert, Instructions for Use) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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 CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate these submissions "**Final Printed Carton and Container Labeling" for approved:**

- **BLA 020563/S-202**
- **BLA 021017/S-146**
- **BLA 021018/S-132**
- **BLA 205747/S-028**

Approval of these submissions by FDA is not required before the labeling is used.

For information on FDA's compliance policy for requirements related to BLA-specific labeling revisions, see guidance for industry, *The "Deemed to be a License" Provision of the BPCI Act: Questions and Answers*.[3]

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(s) 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.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the

[3] Available at: https://www.fda.gov/media/119274/download. For the most recent version of a guidance, check the FDA Guidance Documents Database at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.

If you have any questions, call Ajmal Mohmand, Regulatory Project Manager at 301-796-4951.

Sincerely,

{See appended electronic signature page}

Patrick Archdeacon, M.D.
Deputy Director
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

[4] For the most recent version of a guidance, check the FDA guidance web page athttps://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

ENCLOSURES:
Humalog U-100

- Content of Labeling (Branded)
  - Prescribing Information (shared PI with U-200)
  - Patient Package Insert
  - Instructions for Use (vial, KwikPen, KwikPen Junior, Tempo Pen)
- Content of Labeling (unbranded)
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use (vial, KwikPen, KwikPen Junior)
- Carton and Container Labeling (Branded)
- Carton and Container Labeling (Unbranded)

Humalog U-200

- Content of Labeling (Branded)
  - Patient Package Insert
  - Instructions for Use (KwikPen)
- Carton and Container Labeling (Branded)

Humalog Mix 75/25

- Content of Labeling (Branded)
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use (vial and KwikPen)
- Content of Labeling (unbranded)
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use (KwikPen)
- Carton and Container Labeling (Branded)
- Carton and Container Labeling (Unbranded)

Humalog Mix 50/50

- Content of Labeling (Branded)
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use (vial and KwikPen)
- Carton and Container Labeling (Branded)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PATRICK ARCHDEACON
07/21/2023 09:56:58 AM