

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

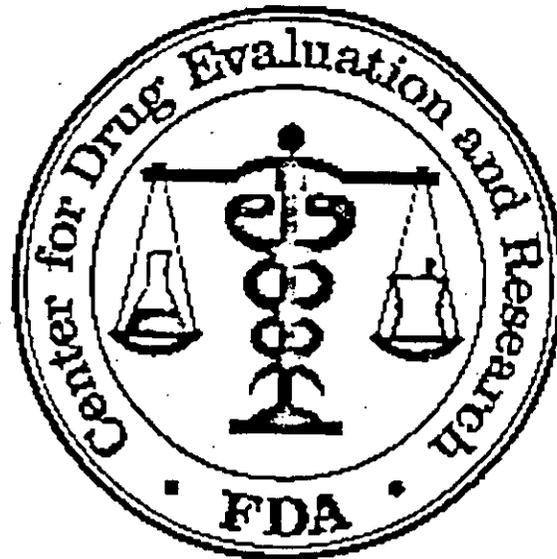
**APPLICATION NUMBER: 21-017
21-018**

CORRESPONDENCE

/S/

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: February 3, 1999



TO:

Name: Gregory Enas, Ph.D.

Fax No: (317) 276-1652

Phone No.: (317) 276-4038

Location: Eli Lilly

Pages (including this cover sheet): 3

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

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COMMENTS:

NDA 21-017 Humalog® Mix 25™

Microbiology review comments. Please submit your response to the NDA file.

cc: Orig NDA
HFD-510/DIV file
HFD-805/Hughes

Microbiology Review of NDA
NDA 21-017
Humalog® Mix 25™
Eli Lilly and Company

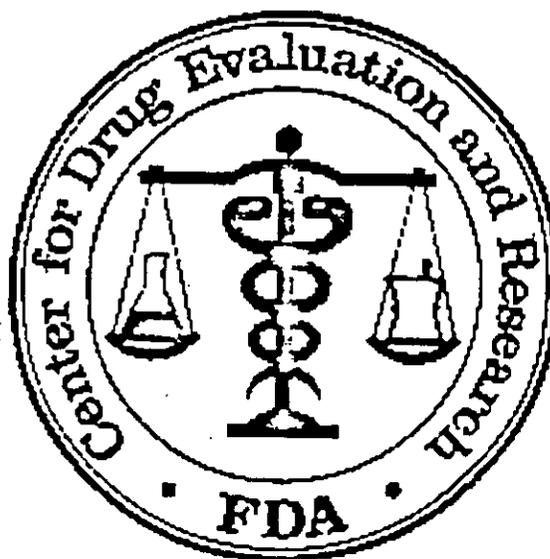
F. List of Microbiology Deficiencies and Comments:

Reference is made to the NDA 21- 017 for Humalog® Mix 25™. The information provided in the submission is incomplete from the standpoint of product quality microbiology. Please provide the following additional information:

- A. Information regarding the 10 mL Vials Insulin Lispro Low Mixture manufactured at Eli Lilly and Company, Indianapolis, Indiana
- 
- 
-

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: February 3, 1999



TO:

Name: Gregory Enas, Ph.D.

Fax No: (317) 276-1652

Phone No.: (317) 276-4038

Location: Eli Lilly

Pages (including this cover sheet): 3

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

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COMMENTS:

NDA 21-018 Humalog® Mix 50™

Microbiology review comments. Please submit your response to the NDA file.

Microbiology Review of NDA
NDA 21-017
Humalog® Mix25™
Eli Lilly and Company

B. Information regarding the 3.0 mL Cartridges of Insulin Lispro Low Mixture
manufactured at the Lilly France S.A. facility in France



Cleared for faxing by:

/S/

2/3/99

Peter Cooney, Ph.D., Microbiology Team Leader



Microbiology Review of NDA
NDA 21-018
Humalog® Mix 50™
Eli Lilly and Company

F. List of Microbiology Deficiencies and Comments:

Reference is made to the NDA 21- 018 for Humalog® Mix 50™. The information provided in the submission is incomplete from the standpoint of product quality microbiology. Please provide the following additional information:

- A. Information regarding the 10 mL Vials Insulin Lispro Mid Mixture manufactured at Eli Lilly and Company, Indianapolis, Indiana

Microbiology Review of NDA
NDA 21-018
Humalog® Mix50™
Eli Lilly and Company

B. Information regarding the 3.0 mL Cartridges of Insulin Lispro Mid Mixture
manufactured at the Lilly France S.A. facility in France

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Cleared for faxing by:

 / S /

2/3/99

Peter Cooney, Ph.D., Microbiology Team Leader

**Food and Drug Administration
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II (HFD-870)**

Memorandum

To: Julie Rhee, CSO (HFD-510)
NDA 21-017
NDA 21-018
Date: 20 August 1999
From: Mike Fossler
Re: Memo of a Telephone Conversation

ISI

8/20/99

Drs. James Woodworth and Ben Cerimele of Lilly called me today to inform me that some errors were found in the total glucose calculations in Study IOCM. Although the errors do not affect the overall conclusions of the study, they do affect some of the values in the summary tables. Although I do not consider IOCM a pivotal study in these applications, the errors should be corrected. Lilly readily agreed to supply these corrections as an amendment.

The discussion then turned to some of the linear regression plots in many of the PK/PD studies, particularly in IODJ. Although there are clear linear relationships between % soluble lispro and Rmax and total glucose infused, the r^2 values for these regression fits are low (e.g., 0.26, 0.45). This appears to be due (in the reviewer's opinion) to the presence of repeat runs in the data and the presence of pure error which can not be modeled by any statistical model. The reviewer then asked if a calculation of pure error had been entertained for any of these plots. Dr. Cerimele replied that they had not thought about doing these calculations, but that they were willing to do so if I felt they were needed. We agreed that Lilly would provide these calculations for Study IODJ only, and that this would be considered a minor amendment for administrative purposes.

**APPEARS THIS WAY
ON ORIGINAL**

CC:

- 2) The proposed proprietary name should appear more prominent, bolded and with a different color than black, to differentiate the proprietary name from the established name.
- 3) The quantity, "3.0 ml" contains a terminal zero. Often times, terminal zeros lead to medication errors. OPDRA recommends deleting all terminal zeros on the container labels, carton, and package insert labeling.
- 4) The statement, [REDACTED] on the carton labeling is confusing with the statement in the INFORMATION FOR THE PATIENT which reads, "invert it slowly 10 times". OPDRA recommends clarifying the directions.
- 5) The statement, "Each ml contains 50 units insulin lispro; 50 units insulin lispro protamine suspension", is inconsistent with the statement in the package insert which reads, "Each milliliter of Humalog [REDACTED] injection contains insulin lispro 100 Units." OPDRA recommends consistency in terms of stating the number of units per ml.
- 6) The strength, "100 units per ml" is hard to see, crowded near the established name. The strength should appear more prominently on the label.
- 7) The statement, [REDACTED] could be revised to read, "For subcutaneous injection only" to emphasize that it cannot be given intravenously. Furthermore, the statement should appear more prominently on the label.

▪ CONTAINER LABELS (Vial, cartridge, and disposable insulin delivery device)

- 1) The storage information should be on the label since the user may throw away the carton labeling and not know the storing directions for the vials, cartridge, and disposable insulin delivery device.
- 2) The INFORMATION FOR THE PATIENT for the cartridge reads, "not designed...for the cartridge to be reused." OPDRA recommends adding this information, in an abbreviated form, to the cartridge label so that a user will not reuse this product.
- 3) The disposable insulin delivery device label should clarify whether it can only be used one time or more before being disposed.
- 4) If the 3ml cartridge contains 300 units of the drug (100units /ml), the "scale measuring remaining volume of insulin", which is on the cartridge label, should reflect clear unit increments up to 3ml. If the cartridge net content is only 1ml in a 3ml cartridge, we would find the packaging design problematic because the remaining 2ml empty space or overfill would mislead a user to believe that other insulin can be added to Humalog Mix 25 and Mix 50, when it is not recommended in the labeling.

5) See comments under CARTON LABELING.

IV. RECOMMENDATIONS

- A. OPDRA does NOT recommend the approval of the proposed proprietary names, Humalog Mix 25 and Humalog Mix 50.
- B. OPDRA would not normally recommend a proprietary name to a manufacturer, since that puts the agency in the position of defending the name post-approval with problems due to name confusion. However, we have no objection at this time to the modifiers (50/50 and 75/25) as proposed. Timing constraints for this consult did not provide adequate time to conduct verbal and written analysis at this time for the names recommended by the Division. However, since there are medication error reports citing verbal miscommunication of the names for Humulin and Humalog products, OPDRA would consider conducting the verbal and written analysis, if requested by the Division.
- C. OPDRA recommends the above labeling revisions which might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

OPDRA would appreciate feedback of the final outcome of this consult (e.g. copy of the revised label/labeling/packaging). We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Lauren Lee, Pharm.D. at (301)827-3243.

Lauren Lee, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

**APPEARS THIS WAY
ON ORIGINAL**

Concur:

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

CC:

Office Files

HFD-510: Julie Rhee, Consumer Safety Officer, Division of Metabolic and Endocrine Drug Products

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B-03
Center for Drug Evaluation and Research

Evaluation of the proposed proprietary names, "Humalog Mix 50 and Humalog Mix 25"

DATE OF REVIEW: September 30, 1999

NDA#s: 21-017 & 21-018

NAME OF DRUGS: Humalog Mix 25
(25% insulin lispro injection and 75% insulin lispro protamine suspension [rDNA origin])

Humalog Mix 50
(50% insulin lispro injection and 50% insulin lispro protamine suspension [rDNA origin])

NDA HOLDER: Eli Lilly and Company

I. INTRODUCTION

This consult is in response to a request sent on September 17, 1999, from the Division of Metabolic and Endocrine Drug Products to review the proposed proprietary drug names, Humalog Mix 25 (25% insulin lispro injection and 75% insulin lispro protamine suspension [rDNA origin]) and Humalog Mix 50 (50% insulin lispro injection and 50% insulin lispro protamine suspension [rDNA origin]), regarding potential name confusion with existing proprietary/generic drug names. In addition, OPDRA was asked to review the container labels and carton labeling for possible interventions in minimizing medication errors.

The proposed proprietary names, Humalog Mix 25 and Humalog Mix 50, were previously reviewed by the Labeling and Nomenclature Committee (LNC) in April 1999 and were found to be unacceptable.

The Division of Metabolic and Endocrine Drug Products has recommended that the proposed proprietary names be changed to Humalog 75/25 and Humalog 50/50 in order to be consistent with the current nomenclature for insulin products.

PRODUCT INFORMATION

Humalog Mix 25 and Humalog Mix 50 are mixtures of insulin lispro solution, a rapid-acting blood glucose-lowering agent and insulin lispro protamine suspension (NPL, neutral protamine lispro), an intermediate-acting blood glucose-lowering agent. Insulin lispro is synthesized in a special nonpathogenic laboratory strain of *Escherichia coli* bacteria that has been genetically altered by the addition of the gene for insulin lispro.

NPL is a suspension of crystals produced from combining insulin lispro and protamine sulfate under appropriate conditions for crystal formation. The proposed drug products are indicated for the control of hyperglycemia in the treatment of patients with diabetes mellitus. The primary activities of these agents include regulation of glucose metabolism and several anabolic and anticatabolic actions on many tissues in the body. Studies in patients with type 1 (insulin-dependent) diabetes demonstrated that Humalog, the rapid-acting component of Humalog Mix 25 and Humalog Mix 50, is absorbed faster than regular human insulin. There are 2 phases of absorption. The early phase represents insulin lispro and its distinct characteristics of rapid onset, and the late phase represents the prolonged action of NPL. In patients with type 1 diabetes, peak serum concentrations were observed 30 to 240 minutes for Humalog Mix 25 and 45 to 120 minutes for Humalog Mix 50. Meaningful terminal phase half-life cannot be calculated after administration because of the prolonged NPL absorption. The effect of renal and hepatic impairment on the pharmacokinetics and glucodynamics have not been studied, but careful glucose monitoring and dose adjustments of insulin may be necessary in patients with hepatic and renal dysfunction. One unit of Humalog Mix 25 and of Humalog Mix 50 have been shown to have same glucose-lowering effect as one unit of Humulin 70/30 and of Humulin 50/50, respectively, but their effects are more rapid and of shorter duration. Humalog Mix 25 and Humalog Mix 50 are intended only for subcutaneous administration, and should not be administered intravenously. Dosage regimens will vary among patients and should be determined by the health care professional familiar with the patient's metabolic needs, eating habits, and other lifestyle variables. The proposed products will be available as 100 units per ml and supplied in vials, cartridges, and disposable insulin delivery devices.

II. RISK ASSESSMENT

A focus group of professional staff at OPDRA reviewed Lilly's proposed proprietary names for possible confusion with other drug names. In addition, we reviewed the enclosed Division's recommended proprietary names to the manufacturer and have the following comments:

HUMALOG MIX 25 & HUMALOG MIX 50 (proposed by the manufacturer)

- 1) The terms "Mix 25" and "Mix 50" may be confusing to a user in that they do not indicate the proportions of both insulin lispro injection and insulin lispro protamine suspension. The percentage of only insulin lispro injection is represented by the terms. Therefore, a user may not clearly understand that these products are mixtures.
- 2) The terms "Mix 25" and "Mix 50" utilize a new nomenclature system for insulin products which may be confusing to a user who is familiar with the long-used terms for insulin mixtures (i.e. 70/30, 30/70, and 50/50). Unfamiliarity with this new nomenclature system for these mixtures can create user error since the term, "Mix", is instructional in tone. When followed by a number, this combination may cause the user to wonder if adjustments need to be made in terms of dose or dosing methods. The term, "Humalog Mix 25" could be interpreted as an order to add 25 units of another insulin to Humalog.

HUMALOG 50/50 & HUMALOG 75/25 (proposed by the Division)

- 1) Humalog 50/50 could be confused with Humulin 50/50, since both products have similar names, labels, labeling, and packaging in addition to identical strengths and dosage forms. Furthermore, both products are used for similar indications. In addition, although Humalog 50/50 is a drug requiring a prescription and Humulin 50/50 is an OTC drug, these drugs may be stored close to together in the same refrigerator in most pharmacies.
- 2) From a search in AERS, there are five reports of medication errors involving Humalog and Humulin confusion, resulting in hypoglycemia and hospitalization. Two of these reports indicated verbal miscommunication of the proprietary names as the cause for these medication errors. In addition, there is one report from Great Britain of Humalog administration instead of Humalog Mix 25, leading to diabetic ketoacidosis.
- 3) Humulin insulin has many modifiers such as R, N, L, U, 70/30, and 50/50 in the proprietary name that describe the type of insulin in the product. There is no product associated with the name "Humulin" (without a modifier). However, Humalog is a rapid-acting insulin drug product that is currently on the market and has no modifier. Furthermore, Humalog is the name for the first component of the above proposed mixture and not for the second component. Therefore, when attaching the term "50/50" to "Humalog", it does not follow the current system of nomenclature as it was applied to Humulin 50/50. "Humulin" is not the name for the first component of Humulin 50/50.
- 4) OPDRA would not normally recommend a proprietary name to a manufacturer, since that puts the agency in the position of defending the name post-approval when problems due to the name arise.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the packaging and the labeling of Humalog Mix 25 and Humalog Mix 50, OPDRA has attempted to focus on safety issues relating to possible medication errors. Many of the items discussed in this consult involve issues normally reviewed by the chemist and the medical officer.

OPDRA has reviewed the current labeling and has identified several areas of possible improvement, which might minimize potential user error.

Humalog Mix 25 and Humalog Mix 50

- **CARTON LABELING** (vial, cartridge, and disposable insulin delivery device)
 - 1) Eli Lilly is the manufacturer for Humulin and Humalog products, and therefore, these products have very similar labeling and packaging that may have created confusion. OPDRA recommends that the carton labeling for the proposed Humalog mixtures appear distinctly different than the Humulin mixture products.



Memorandum

Date: 11/24/99



From: Saul Malozowski
Medical Team Leader

Subject: Humalog Mixture [redacted] (NDA 21-017). Team leader recommendations

7/5/25 71 11/30/99

To: Solomon Sobel
Division Director, DMEDP

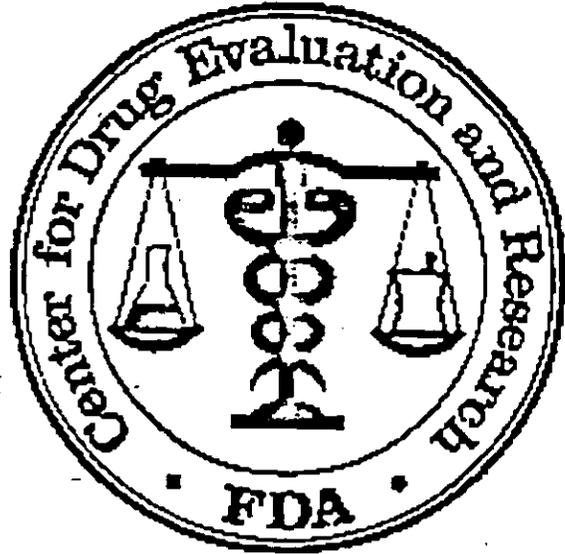
I second the primary reviewers' comments and recommendations for this product and recommend its approval pending changes in the proposed label in order to properly reflect the findings of the studies and to facilitate its use.

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ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: January 25, 1999



TO:

Name: Gregory Enas, Ph.D.

Fax No: (317) 276-1652

Phone No.: (317) 276-4038

Location: Eli Lilly

Pages (including this cover sheet): 2

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

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COMMENTS:

NDA's 21-017 and 21-018 Humalog Mixtures 25 and Humalog Mixtures 50

Requests from Biopharm. Please submit your response to the NDA files including a desk copy for the Biopharm reviewer. Thank you.

cc: Orig NDA's 21-017 + 21-018

HFD-510/Div Files

HFD-870/Fossler

ORIG AMENDMENT

SU

Lilly

Lilly Research Laboratories

A Division of Eli Lilly and Company

ORIGINAL

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

November 8, 1999



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolic and
Endocrine Drug Products, HFD-510
5600 Fishers Lane
Rockville, Maryland 20857

SAFETY UPDATE

Re: **NDA 21-017; Humalog® Mix 25™ [25% insulin lispro injection and 75% insulin lispro protamine suspension (rDNA origin)]**

NDA 21-018; Humalog® Mix 50™ [50% insulin lispro injection and 50% insulin lispro protamine suspension (rDNA origin)]

This letter is pursuant to a telephone conversation between Ms. Julie Rhee (FDA) and Dr. Jeffrey Winn (Lilly) regarding NDA 21-017 and NDA 21-018 on October 18, 1999. During the telephone call, Mr. Rhee requested the safety update required prior to approval of the two New Drug Applications. Lilly is herewith submitting the safety update pursuant to 21 CFR 314.50(d)(5)(vi)(b).

Lilly thanks you for your continued support and assistance. Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 276-4038 if you require additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Gregory G. Enas

Gregory G. Enas, Ph.D.
Director
U.S. Regulatory Affairs

*Imported into NDA to view 11/10/99
Need total # pregnancies*

IS/ 11/11/99

REVIEWS COMPLETED
REGISTRATION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS _____ DATE _____

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II (HFD-870)

Memorandum

To: Julie Rhee, CSO, HFD-510
NDA 21-017
NDA 21-018
From: Michael J. Fossler
Through: Hae-Young Ahn, Team Leader
Date: 22 January 1999
Re: Filing Memo for NDA 21-017 (25% insulin lispro and 75% insulin lispro protamine suspension) and NDA 21-018 (50% insulin lispro and 50% insulin lispro protamine suspension)

Handwritten notes: [Redacted] 1/25/99 [Redacted] 1/25/99

Eli Lilly has submitted NDAs 21-017 (Humalog Mix 25™ / 25% insulin lispro and 75% insulin lispro protamine suspension) and 21-018 (Humalog Mix 50™ / 50% insulin lispro and 50% insulin lispro protamine suspension) for marketing approval. The information in NDA 21-017 is completely cross-referenced to NDA 21-018, as both formulations were used in all clinical pharmacology studies.

A total of 8 clinical pharmacology studies were submitted to the NDA. Four studies were performed in healthy volunteers and were intended as proof-of-concept studies except for IOET, which was a bioequivalence study. Four studies were performed in Type 1 diabetic patients which examined the PK/PD of the two insulin lispro mixtures as compared with NPH and 70/30 human insulin. The firm's summary and proposed labeling are attached.

Plasma insulin and insulin lispro concentrations were measured by one of three assay methods: 1) a non-specific method which cross-reacts with both insulin and insulin lispro, 2) a non-specific method which incorporates an extraction step, resulting in the measurement of free insulin levels, and 3) a method which is specific to insulin lispro. Validation and QC data for all three methods were included in the submission.

Recommendation

The two submissions (NDAs 21-017 and 21-018) are filable from a clinical pharmacology/biopharmaceutics perspective. The comments below should be submitted to the firm.

Comments (to be sent to firm)

- 1) Please submit the study synopses for the following studies in Word format: IOBS, IOCM, IODJ, IODR, IODM, IOET, IOGI, IOFX. The proposed labeling should also be submitted electronically.
- 2) Please submit all PK/PD data for the following studies in either Excel files or ASCII format: IODJ, IOET, IOGI, IODM, IOFX.

CC: HFD-870 (M. Chen)

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Printed by Todd Sahlroot Electronic Mail Message

Subject: COMPANY CONFIDENTIAL

Date: 26-Aug-1999 12:00pm
From: Todd Sahlroot
SAHLROOTT
Dept: HFD-715 PKLN 14B45
Tel No: 301-827-6387 FAX 301-827-5875

TO: Saul Malozowski (MALOZOWSKIS)
TO: Elizabeth Koller (KOLLERE)

Subject: Statistical review of Humalog Mixes (21-017, 21-018)

Saul and Beth,

I've been looking at NDA's 21-017 and 21-018 for Humalog Mix25 (25% lispro injection, 75% lispro protamine suspension) and Humalog Mix50 (50% and 50%). My current thinking is that statistical reviews are unnecessary for several reasons:

1. The mixtures act essentially as depot versions of lispro. Biometrics has reviewed or is currently reviewing other depots (sandostatin, nutropin) but these involve (far) less frequent administrations of higher doses compared to the daily product where there might be a question of efficacy. If I'm not mistaken, the lispro mixtures involve the same quantity of lispro given with the same frequency, before meals, as regular lispro.

2. Lilly met with us on October 22, 1996, for a pre-NDA meeting. According to Lilly, FDA stated that "efficacy studies were not necessary in the clinical development plan for the humalog mixtures". Lilly's memo of the January 22, 1997, follow-up telecon state "FDA and Lilly agreed that pharmacokinetic (PK) studies in patients and safety data including antibody data were sufficient for the registration and approval of the Humalog mixtures". I cannot find any record anywhere of 510 disagreeing with this statement or any statement that controlled trials would be necessary for the evaluation of the mixtures.

3. Although the submission includes data from 4 active-controlled trials, none of these trials is referenced in the sponsor's proposed label.

4. Neither of the Humulin mixtures, 50/50 and 30/70, required a statistical review. Admittedly these are old submissions and we may do things differently now.

What do you think? Safety data may be another matter, e.g., antibody data.

Todd

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION REQUEST/RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE SENT: September 30, 1999

DUE DATE: N/A

OPDRA CONSULT #: 99-048

TO (Division): Solomon Sobel, M.D.
Director, Division of Metabolic and Endocrine Drug Products
(HFD-510)

PRODUCT NAMES:
Humalog Mix 25™
(25% insulin lispro injection and 75% insulin lispro protamine suspension [rDNA origin])

Humalog Mix 50™
(50% insulin lispro injection and 50% insulin lispro protamine suspension [rDNA origin])

MANUFACTURER: Eli Lilly and Company

NDA#s: 21-017 & 21-018

CASE REPORT NUMBER(S): N/A

SUMMARY:

In response to the request by the Division of Metabolic and Endocrine Drug Products, OPDRA conducted a review of the potential name confusion of the proposed proprietary names, Humalog Mix 50™ and Humalog Mix 25™ with other approved proprietary/generic names.

OPDRA RECOMMENDATION:

OPDRA does not recommend the approval of the proposed proprietary names, Humalog Mix 50™ and Humalog Mix 25™. See review.

Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 827-5189

Peter Honig, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

ELECTRONIC MAIL MESSAGE

Date: 06-Oct-1999 09:06am EST
From: Julie Rhee
RHEEJ
Dept: HFD-510 PKLN 14B04
Tel No: 301-827-6424 FAX 301-443-9282

TO: Roy Blay (BLAYR)
CC: Saul Malozowski (MALOZOWSKIS)
CC: Elizabeth Koller (KOLLERE)
Subject: NDA 21-017

Roy,

Dr. Koller just told me that DSI inspection will not be necessary for this NDA.

Julie

APPEARS THIS WAY
ON ORIGINAL

December 22, 1999

Memorandum

To: the file NDA 21-017 Humalog 75/25

NDA 21-018 Humalog 50/50

From: Solomon Sobel M.D. Director Division, of Metabolic and
Endocrine Drug Products

Subject: Approval of both NDAs

151/2-22-99

NDA 21-017 is for a 75% protamine insulin lispro suspension and 25% insulin lispro injection (Recombinant DNA origin) which will carry the trade name Humalog Mix75/25.

NDA 21-018 is for a 50% protamine insulin lispro suspension and 50% insulin lispro injection (Recombinant DNA origin) which will carry the trade name Humalog Mix50/50.

These mixtures utilize the more rapid onset of action of the lispro component while maintaining the duration of effect seen with similar humulin mixtures.

The NDAs rest primarily on pharmacodynamic studies (glucose infusion rates) that define the time course of action of these insulin mixtures. Such data are amply described in the labeling.

The chemistry review team found the chemistry, manufacturing and controls satisfactory.

The biopharmaceutics review team found the kinetic/dynamic studies performed in both healthy volunteers and diabetic patients to be satisfactory in both their design and execution.

Recommendation:

The Division recommends approval of both NDAs.

151
-Solomon Sobel

cc: Orig NDAs 21-017 + 21-018

HFD-510/Div Files 21-017 + 21-018

HFD-510/Malozowski/Koller

APPEARS THIS WAY
ON ORIGINAL

**RECORD OF TELEPHONE
CONVERSATION/MEETING**

Date:
December 7, 1999

Dr. Winn had faxed their proposed carton label (attached) for our comments. Dr. Stephen Moore asked me to check with OPDRA regarding the design code. I've discussed with Mr. Jerry Phillips at OPDRA and he suggested that we ask Lilly to remove the design code although he does not feel very strongly about it one way or the other.

When I called Dr. Winn to convey Mr. Phillips's recommendation, Dr. Winn informed me that other Humulin products have design codes as well and wanted to keep the proposed design codes for the Humalog mixtures.

After further discussion with Dr. Chiu, I informed Dr. Winn that we are amenable to the design code but asked to remove black background around the design code. Dr. Winn told me that he is going to discuss with their labeling people and asked me if it would be acceptable if they decide not to use any design code until color coding is finalized. I told him that would be acceptable.

I also asked him to remove terminal zero from 3.0 mL. Dr. Winn agreed to do so.

cc: OrigNDAs 21-017 and 21-018
HFD-510/DivFile 21-017 & 21-018
HFD-510/Moore

NDA#: 21-017 and
21-018

**Telecon/Meeting
initiated by:**

FDA

By: Telephone

Product Name:
Humalog Mix 75/25 and
Humalog Mix 50/50

Firm Name:
Eli Lilly

**Name and Title of Person
with whom conversation
was held:**
Jeffrey Winn, D.D.S.
Regulatory Affairs

Phone:
(317) 276-2098

/S/

Name: Julie Rhee

APPEARS THIS WAY
ON ORIGINAL



Memorandum

Date: 11/24/99



From: Saul Malozowski
Medical Team Leader

Subject: Humalog Mixture 50-50 (NDA 21-018). Team leader recommendations

To: Solomon Sobel
Division Director, DMEDP

I second the primary reviewers' comments and recommendations for this product and recommend its approval pending changes in the proposed label in order to properly reflect the findings of the studies and to facilitate its use.

APPEARS THIS WAY
ON ORIGINAL

ELECTRONIC MAIL MESSAGE

Activity: COMPANY CONFIDENTIAL

Date: 03-Dec-1999 09:05am EST
From: Lauren Lee
LEEL
Dept: HFD-400 PKLN 15B03
Tel No: 301-827-3243 FAX 301-480-8173

TO: Julie Rhee

(RHEEJ)

Subject: humalog

Hi Julie,

After I spoke with Jerry, I left you a message on your voicemail. Basically if the Division and the firm feel strongly about the symbol and coloring, we do not object to the use from a safety perspective. Please give me a call so that I can clarify our position.

Thanks,
Lauren (73243)

APPEARS THIS WAY
ON ORIGINAL

FACSIMILE TRANSMISSION

Eli Lilly and Company
Lilly Research Laboratories

U.S. Regulatory Affairs
Phone No. (317) 276-5185
FAX (317) 276-1652

CONFIDENTIAL

CONFIDENTIAL



TO: Julie Rhee

FROM: Jeff Winn

COMPANY: FDA

PHONE #: 317-276-2098

FAX #: 301-443-9282

DATE: 11/17/99

Number of Pages: 11
(Including cover sheet)

Message: "Draft" carton and container labels

IMPORTANT CONFIDENTIALITY NOTICE

The documents accompanying this telecopy transmission contain confidential information belonging to the sender which is legally protected. The information is intended only for the use of the individual or entity named below. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or the taking of any action in reliance on the contents of this telecopy information is strictly prohibited. If you have received this telecopy in error, please immediately notify us by telephone (collect) to arrange for return of the telecopied documents to us.

cc: Moore

14

Page(s) Redacted

Draft

Labeling

BEST POSSIBLE COPY

for the Applicant:

Product:

Please provide a Phase IV commitment to re-evaluate the lower Assay limit of []% when a sufficient number of lots have been analyzed to perform a suitable statistical analysis. A limit of []% appears to be more appropriate.

2. Please provide a justification for the proposed shelf-life limits for "Immediately Available Insulin Lispro" of []%.

Labeling:

1. The proposed proprietary name should appear more prominent, bolded and with a different color than black, to differentiate the proprietary name from the established name.
2. The references to other [] under the "How Supplied" section should be removed. *done*
3. In the "Information for the Patients" for both the cartridges and the disposable pens, under "Storage", the sentence referring to disposing of frozen Mix50 should be moved up to be the second sentence. *done*
4. The 'in-use' recommendation should be changed to read "Cartridges in use must be discarded after 10 days even if they still contain Humalog Mix50, however, cartridges may be kept for a total of 28 days without refrigeration". *done*
5. Lastly, as color-coding of insulins has not been formally accepted, please remove all references to the use of the [] at this time. *done*
6. The Trade-Name suffix "Mix50" remains in contention. The Division has proposed the use of "50/50". *done*
7. The Trade package should be differentiated from those of Humulin products, where feasible, in order to avoid medication errors.

Application Summary:

A. Drug Substance:

Drug Product:

- | | |
|---|------------------|
| 1/2. Components/Composition | Satisfactory |
| 3. Specifications and Methods for Ingredients | Satisfactory |
| 4. Manufacturer | Satisfactory |
| 5. Method of Manufacture | Satisfactory |
| 6. Regulatory Specifications/Analytical Methods | Not Satisfactory |
| 7. Container/Closure System | Satisfactory |
| 8. Microbiology | Satisfactory |
| 8. Drug Product Stability | Satisfactory |

C. Investigational Formulations Satisfactory

D. Environmental Assessment Satisfactory

E. Methods Validation Satisfactory

F. Labeling Satisfactory pending corrections

G. Establishment Inspection Satisfactory

- Although the general pattern of the PK/PD properties seen in healthy volunteers is preserved in Type 1 diabetics, lower levels of insulin lispro were seen in patients. This is likely a result of the [redacted] precipitation step used in the assay. The glucose infusion rates seen in patients are also significantly lower, suggesting that these Type 1 patients had a moderate degree of insulin resistance.
- 75/25 injected just before a standard meal gave a similar post-prandial glucose profile as compared with Humulin 70/30 given 30 minutes before eating. The conclusion is that Humalog 75/25, like Humalog R, may be given just prior to a meal.

VIII. Comments to firm

None at this time.

IX. Labeling Comments

The following comments apply to the labeling for both 75/25 and 50/50:

- 1) In Figures [redacted] the x-axes should be truncated at 12 hours post-dose in order to emphasize the relevant portions of the curves. *done*
- 2) Figures [redacted] should be combined into one graph, with all but the most relevant comparisons deleted. For 75/25, these would be 75/25 and Humulin 70/30. Similarly, for 50/50, these would be 50/50 and Humulin 50/50. It should be made clear that these are cross-study comparisons. *done*

stat fig. [redacted] (12/3 mtg)

X. Signatures

/S/ *12/2/99*

Michael J. Fossler, Pharm.D., Ph.D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

FT initialed by Hae-Young Ahn, Ph.D., Team Leader

/S/ *12/2/99*

version: Final
Recommendation: AP

Briefing held 12/2/99. Present: Chen, Hunt, Ahn, Johnson, Fossler

CC: NDA 21-017(orig., 1 copy), NDA 21-018 HFD-510(Koller, Rhee), HFD-850(Lesko), HFD-870(M. Chen, Fossler, Ahn), HFD-340(Vish), Central Document Room (Barbara Murphy)

**RECORD OF TELEPHONE
CONVERSATION/MEETING**

Date:
December 14, 1999

Re: 12/9/99 submission

NDA#: 21-017 and 21-018

I called Dr. Winn and acknowledged that we've received Lilly's 12/9/99 submission for carton label. However, I reminded him that terminal zero was not deleted on the 3.0 mL cartridges and Pen. He said it was an oversight but since they've already printed 7,000 labels for wholesaler, he asked if an approval is based on the 12/9/99 submission but agreed not to print anymore labels with terminal zero. He also committed that they will remove terminal zero when they re-print on 1/2/00. I told him I will check with OPDRA and would get back to him.

**Telecon/Meeting
initiated by:**

FDA

By: Telephone

Product Name:
Humalog Mix 75/25
Humalog Mix 50/50

I called Dr. Winn back and informed him that as long as Lilly promises not to print anymore labels with terminal zero, we will accept their 12/9/99 submission. I also asked Dr. Winn to submit a correspondence indicating their intention to delete terminal zero at the next printing. He agreed to submit the letter tomorrow (12/15).

Firm Name:

Eli Lilly

**Name and Title of Person
with whom conversation
was held:**

Jeffrey Winn, D.D.S.
Regulatory Affairs

cc: OrigNDAs 21-017 & 21-018
HFD-510/DivFiles 21-017 & 21-018

Phone:
(317) 276-2098

TS/

Name: Julie Rhee

11/30/99
MOR

absence of HgbA1c levels and sometimes insulin dose levels, as well as the small numbers of patients in the extension trials, restricts the conclusions that may be drawn about the long-term impact of antibody response.

g) The wide range of lispro permitted in the mixtures suggest that PK-PD profile may vary from batch to batch. Patients could experience unexpected hyperglycemia or hypoglycemia. This problem will be more clinically significant in patients with the best glycemic control. The chemists are addressing this wide specification range with the sponsor.

h) The addition of new mixtures to the widening array of insulin products potentially increases the risk for errors in dispensing and self-administration. The development of a self-explanatory label, unique packaging, and an educational program for professionals and patients will reduce problems.

13.--Regulatory Conclusions

a) The mid-mix and low mix lispro insulin mixtures appear to be approvable on the basis of the pharmacokinetic studies.

b) The sponsor did not meet the agreements for providing long-term safety data regarding antibodies.

RECOMMENDATION: APPROVABLE WITH CHANGES IN THE LABEL.

14.—Label Review

The labels are primarily pharmacokinetic-pharmacodynamic labels. The labels include glucose infusion rates for the family of human insulin products and the family of lispro insulin products. The graphs for the two insulin families of products are sequentially placed in the label, and the axes have the same scale. This does permit some direct comparisons by the prescribing physician, which will be utilitarian. The sponsor, however, did not do head-to-head comparisons of mid-mix with human insulin 50/50 except in a non-submitted study in a portion of patients in IODM. The sponsor states that:

It would be more correct for the sponsor to state that, although direct comparison studies have not been performed, it is likely that a) Humalog has a more rapid onset of glucose-lowering activity than Humulin 50/50 when dosed immediately before meals and b) the duration of activity of the two insulin products is similar. Similar statements were made in the low mix label. Although a head-to-head comparison study (IOFX) was conducted, that information was not included in the label. If adequate head-to-head information is available that should be included in the label.

In addition to the graphic data, it may be helpful for the sponsor to present PK-PD data in a tabular format with parameters that may better describe insulin, e.g. the time to insulin-AUC-25%, insulin-AUC-50%, insulin-AUC-75%, and insulin-AUC-100% as well as the

time to glucose-AUC-25%, glucose-AUC-50%, glucose-AUC-75%, and glucose-AUC-100%. Because t-max and C-max may not be very utilitarian in very short acting insulins and especially in very long-acting insulins, the AUC-derived parameters may better describe the temporal profile of insulin absorption and action and permit comparison between a broad range of insulins.

The sponsor should not include information from the Humalog trials when discussing special populations including age, gender, obesity, renal impairment, and hepatic impairment. Later in the label, under Precautions, the sponsor states that the mixtures have not been studied in pediatric patients and that the numbers of geriatric patients were insufficient to provide appropriate guidelines.

The sponsor indicates that cross-reacting antibodies increase. They do not indicate that the increase is typically greater in patients using lispro products (versus human insulin products). There are no-claims regarding temporal changes in the antibodies.

✓ 2
/S/

/S/
Elizabeth Koller, M.D.

/S/ 11/30/99

APPEARS THIS WAY
ON ORIGINAL

FACSIMILE TRANSMISSION

Eli Lilly and Company Lilly Research Laboratories

U.S. Regulatory Affairs

FAX (317) 276-1652

CONFIDENTIAL

CONFIDENTIAL



To: Ms Julie Rhee
 FAX #: (301) 443-9282
 Date: 22 DEC 99
 From: Jeffrey Winn, DDS
 Phone #: (317) 276-2098

Company: FDA

Re: NDA 20-563

Julie, here is the FAX with the acknowledgement letter as requested. Again, many thanks for your cooperation in the past and I certainly look forward to working with you in the new millennium.

Please let me know if there is anything else I need to do.

Have a Happy Holiday

Best Regards,
 Jeffrey L. Winn, DDS
 (317) 276-2098

A handwritten signature in black ink, appearing to read "Jeffrey".



Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

December 22, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolic and
Endocrine Drug Products, HFD-510
5600 Fishers Lane
Rockville, Maryland 20857

CORRESPONDENCE

**Re: NDA 21-017; Humalog® Mix 75/25™ [75% insulin lispro protamine suspension and 25% insulin lispro injection (rDNA origin)]
NDA 21-018; Humalog® Mix 50/50™ [50% insulin lispro protamine suspension and 50% insulin lispro injection (rDNA origin)]**

We acknowledge receipt of your letter via facsimile dated December 22, 1999. The letter notified Eli Lilly and Company that NDA 21-017 and NDA 21-018 were approved for distribution and sale in the United States.

Additionally we acknowledge the requirements that are stipulated; the need to submit final printed labeling and the phase 4 commitment as identified in the letter.

Lilly thanks you for your continued support and assistance. Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 276-4038 if you require additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY



Gregory G. Enas, Ph.D.
Director
U.S. Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF MEETING MINUTES

Meeting Date: November 5, 1999
Time: 1:30 - 2:30 pm
Location: Parklawn Bldg 3rd fl c/r "L"
Application: NDAs 21-017 and 21-018
Sponsor: Eli Lilly
Type of Meeting: General
Meeting Chair: Stephen Moore, Ph.D.
Meeting Recorder: Julie Rhee

Attendees:

FDA:

Elizabeth Koller, M.D., Medical Officer, DMEDP
Stephen Moore, Ph.D., Chemistry Team Leader
Jerry Phillips, Associate Director, Office of Post-Marketing Drug Risk Assessment
Leigh Hayes, General Counsel
Julie Rhee, Project Manager, DMEDP

Eli Lilly:

Khoso Baluch, Team Leader, Insulin Product Team
Jerry Buhler, Director, Insulin Product Team
Greg Enas, Ph.D., Director, U.S. Regulatory Affairs
John Holcombe, M.D., Senior Clinical Research Physician
Robert Lee Jr., Assistant General Patent Counsel
Thane Wettig, Director, U.S. Marketing
Jeffrey Winn, D.D.S., Regulatory Research Scientist
Thomas Copmann, Ph.D., Director, U.S. Regulatory Affairs

Background:

When Lilly submitted an NDA for Humalog mixtures, Lilly proposed the following name for the product:

- NDA 21-017 Humalog[®] Mix 25[™] (25% insulin lispro injection and 75% insulin lispro protamine suspension [rDNA origin])
NDA 21-018-Humalog[®] Mix 50[™] (50% insulin lispro injection and 50% insulin lispro protamine suspension [rDNA origin])

In 8/26/99 letter, the Agency proposed the following name:

- NDA 21-017 Humalog 75/25 (75% insulin lispro protamine suspension and 25% insulin lispro injection [rDNA origin])
NDA 21-018 Humalog 50/50 (50% insulin lispro protamine suspension and 50% insulin lispro injection [rDNA origin])

On 10/22/99, the sponsor requested a meeting to discuss the nomenclature further and to come to an agreement for the nomenclature of Humalog mixture.

Discussion Points:

1. Lilly wants to get away from using a ratio in the nomenclature because physicians tend to use the ratio only without specifying either Humulin or Novolin when they prescribe "70/30", for example.
 2. Since color coding should not be implemented until an FR notice is published, Lilly agreed to use black/white color on their Humalog mixture container.
 3. Lilly proposed the nomenclature of Humalog Mix 75/25* and Humalog Mix 50/50* as a counter proposal to Humalog Mixture 75/25 and Humalog Mixture 50/50. The Agency responded that they will get back to the sponsor after discussing the sponsor's new proposed nomenclature.
- * During my 11/10/99 telephone call with Dr. Jeffrey Winn, I informed him that the Agency will accept Humalog Mix 75/25 and Humalog Mix 50/50 with a post-marketing commitment to watch any error for one year after launch and then to take appropriate action, if necessary. Dr. Winn agreed to the post-marketing commitment request.

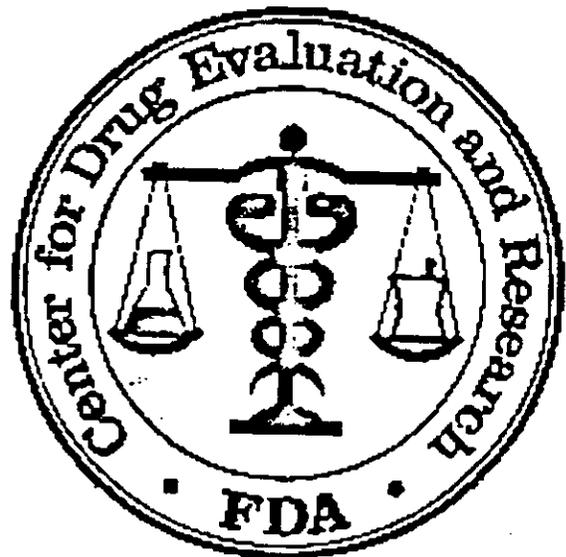
/S/ 11-17-99

Julie Rhee
Minutes Preparer

APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: October 21, 1999



TO:

Name: Jeffrey Winn, D.D.S.

Fax No: (317) 276-1652

Phone No.: (317) 276-2098

Location: Eli Lilly

Pages (including this cover sheet): 2

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

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COMMENTS:

NDA 21-018 Humalog Mix 50™

CMC review comments on 12/21/98 submission. Please submit your response by 11/5/99.

cc: Orig NDA

HFD-510/Div File

HFD-510/Moore

NDA 21-018 Humalog Mix 50

Date of Submission: December 21, 1998

Chemistry Review Comments

1. Please provide a Phase IV commitment to re-evaluate the lower Assay limit of [redacted] when a sufficient number of lots have been analyzed to perform a suitable statistical analysis. A limit of [redacted] appears to be more appropriate.

Please include the following information in the commitment:

- a) Protocol Submission: Within X months following (the NDA) approval
 - b) Study Start: Within Y months following approval
 - c) Final Report Submission: Within Z months following approval
2. Please provide a justification for the proposed shelf-life limits for "Immediately Available Insulin Lispro" of [redacted]

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Cleared for faxing by:

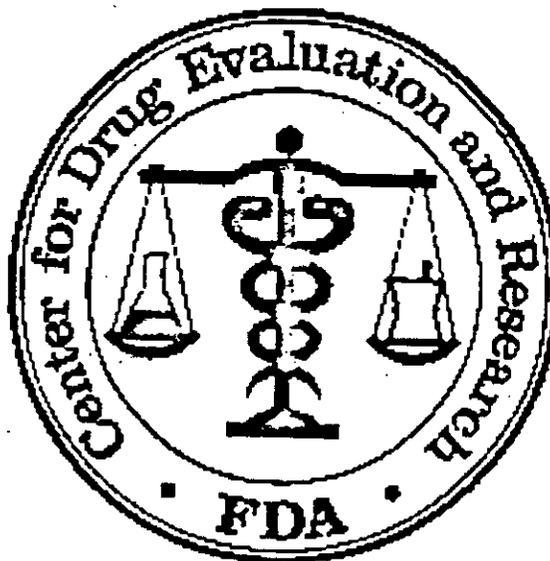
[redacted] /S/

10/21/99

Stephen Moore, Ph.D., Chemistry Team Leader, DMEDP

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: October 14, 1999



TO:

Name: Jeffrey Winn, D.D.S.

Fax No: (317) 276-1652

Phone No.: (317) 276-2098

Location: Eli Lilly

Pages (including this cover sheet): 2

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

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COMMENTS:

NDA's 21-017 and 21-018 Humalog Mixtures

Request from the Medical Officer.

cc: Orig NDAs 21-017 + 21-018
HFD-510/Div Files 21-017 + 21-018
HFD-510/Koller

For IODI, IODK, IODL, IODM, and IODN:

For the extension studies associated with the above clinical studies:

Please provide information on the patients whose insulin regimen (other than dose alone) was changed after randomization. ie number of doses of insulin or change to another insulin or addition of another insulin. Please provide information on the patients who used an insulin regimen not specified in the protocol. Please provide by study the patient-investigator identification number, the insulin modification made, the period and the treatment arm during which the modification was made, the number of days on the therapy during the treatment arm when modifications were made, and, if possible, the rationale for the change/modification.

Please provide information on the patients who discontinued after randomization. Please provide, by study, the patient-investigator identification number, the period and treatment arm during which discontinuation occurred, the number of days in the particular treatment arm before discontinuation occurred, and the reason for discontinuation.

/S/

/S/

10/13/99

APPEARS THIS WAY
ON ORIGINAL

**RECORD OF TELEPHONE
CONVERSATION/MEETING**

Date:
October 5, 1999

I called Dr. Winn to convey the following requests from Dr. Koller concerning studies IODI, IODK, IODM, and IODN:

NDA#: 21-017 & 21-018

1. Study IODI:

Provide data (t=0, t=6mon, & t=12mon) on HgbA1c, cross-reacting antibodies, total insulin dose/kg, and hypoglycemia rate and number of episodes using a hypoglycemia definition of <2 mmol glucose or requiring intervention.

**Telecon/Meeting
initiated by:**

FDA

By: Telephone

2. IODI-extension study:

Provide data (t=0 and each 6 mon) on HgbA1c, cross-reacting antibodies, and total daily insulin dose. Dr. Winn stated that they may not have data on total insulin daily dose. Dr. Winn mentioned that he has submitted an abbreviated report on this study on 9/24/99.

Product Name:
Humalog Mix 25
Humalog Mix 50

3. Studies IODK, IODM, and IODN:

If any of these studies have extension study, I asked the same information as the above item #2.

Firm Name:
Eli Lilly

4. I asked data from studies IODK, IODM, and IODN be sorted by patient and treatment and submit as EXCEL on a diskette.

5. I agreed to check with Dr. Koller whether or not she needs any additional information on studies IODM and IODN.*

**Name and Title of Person
with whom conversation
was held:**
Jeffrey Winn, D.D.S.
Regulatory Affairs

* Dr. Koller informed me that as long as the sponsor provides data (t=0 and every 3 mon until study completion) on HgbA1c, cross-reacting antibodies, total insulin dose/kg, and hypoglycemia rate and episodes, she does not need any additional information.

Phone:
(317) 276-2098

cc:OrigNDAs
HFD-510/DivFiles
HFD-510/Koller

/S/

Name: Julie Rhee

ORIGINAL

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: Sept 10, 1999
<p>I called Dr. Winn and asked for (1) insulin dose, (2) HgbA1c, and (3) cross-reacting antibodies data at baseline and at endpoint from Humalog and Humulin R before and after cross-over in Studies IODK, IODM, and IODN. I also requested a number of hypoglycemia events at endpoint for the above studies.</p> <p>I also asked data on the above parameters for Study IODL at baseline, 6-mon, 12-mon, 18-mon, and 24-months. Data on hypoglycemia is requested at endpoint (24-mon) only.</p> <p>I also informed Dr. Winn that Dr. Koller prefers either glucose value of ≤ 36 mg% or needing an assistance from another person as a criteria for hypoglycemia.</p> <p>I asked they provide the data either in EXCEL spreadsheet or SAS format on a-diskette. I informed him that Dr. Koller prefers EXCEL spreadsheet.</p> <p>cc: OrigNDA 21-017 & 21-018 HFD-510/DivFile 21-017 & 21-018 HFD-510/Koller</p> <p><u> /S/ </u> Name: Julie Rhee</p>	<p>NDA#: 21-017 & 21-018</p> <p>Telecon/Meeting initiated by:</p> <p>FDA</p> <p>By: Telephone</p> <p>Product Name: Humalog Mix 25 Humalog Mix 50</p> <p>Firm Name: Eli Lilly</p> <p>Name and Title of Person with whom conversation was held: Jeffrey Winn, D.D.S. Regulatory Affairs</p> <p>Phone: (317) 276-2098</p>

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

**RECORD OF TELEPHONE
CONVERSATION/MEETING**

Date:
Sept 10, 1999

Dr. Winn called and said Study IODL was a 6-mon study with 18-mon extension. They have 2 year safety data but not efficacy data such as HbA1c, insulin dose, or hypoglycemia with glucose level. They have qualitative hypoglycemia (by signs and symptoms). However, they do have antibody data and will submit the information they have.

cc: OrigNDAs 21-017 & 21-018
HFD-510/DivFiles21-017 & 21-018
HFD-510/Koller

APPEARS THIS WAY
ON ORIGINAL

NDA#: 21-017 & 21-018

**Telecon/Meeting
initiated by:**

● Applicant/Sponsor

By: Telephone

Product Name:
Humalog Mix 25
Humalog Mix 50

Firm Name:
Eli Lilly

**Name and Title of Person
with whom conversation
was held:**
Jeffrey Winn, D.D.S.
Regulatory Affairs

Phone:
(317) 276-2098

/S/

Name: Julie Rhee

WW file

**RECORD OF TELEPHONE
CONVERSATION/MEETING**

Date:
September 8, 1999

I called Dr. Winn and left a voice mail requesting patients' ID who were older than 65 years in Studies IODK, IODM, and IODN. This information was requested by Dr. Koller.

NDA#: 21-017 & 21-018

**Telecon/Meeting
initiated by:**

FDA

By: Telephone

Product Name:
Humalog Mixtures (75/25
and 50/50)

Firm Name:
Eli Lilly

**Name and Title of Person
with whom conversation
was held:**
Jeffrey Winn, D.D.S.
Regulatory Affairs

Phone:
(317) 276-2098

cc: Orig NDAs 21-017 & 21-018
HFD-510/DivFiles 21-017 & 21-018
HFD-510/Koller

APPEARS THIS WAY
ON ORIGINAL

/S/

Name: Julie Rhee

NDA 21-017
NDA 21-018

AUG 26 1999

Eli Lilly and Company
Attention: Gregory G. Enas, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Enas:

Please refer to your pending new drug applications dated December 21, 1998, received December 22, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

- NDA 21-017 Humalog Mix 25TM (25% insulin lispro injection and 75% insulin lispro protamine suspension [rDNA origin])
NDA 21-018 Humalog Mix 50TM (50% insulin lispro injection and 50% insulin lispro protamine suspension [rDNA origin])

We also refer to your correspondence dated July 8, 1999, in which you contested the recommendation of the Nomenclature Committee to reject your proposed trade names and requested a reversal of the Nomenclature Committee's decision by this Division.

We have reviewed your request and maintain our original decision not to accept the terms "Mix 25" and "Mix 50". The terms "75/25" and "50/50" should be utilized, instead, for the following additional reasons:

1. The latter terms should be utilized in order to avoid the risk of confusion by patients that could occur if the format is changed from the long-used and familiar symbols on related insulin products, i.e., "70/30" and "50/50".
2. Confusion would occur by the concurrent use of two different nomenclature systems for insulin products.

In order to be consistent with current nomenclature, we recommend that the following trade name be used:

- NDA 21-017: Humalog 75/25 (75% insulin lispro protamine suspension and 25% insulin lispro injection [rDNA origin])
NDA 21-018: Humalog 50/50 (50% insulin lispro protamine suspension and 50% insulin lispro injection [rDNA origin])

If you would like to pursue this matter further, please refer to the draft guidance document entitled "Formal Dispute Resolution: Appeals Above the Division Level" or contact Ms. Janice Sheehy, Dispute Resolution Project Manager, at (301) 594-5413 and submit a copy of your written request to the NDA file.

Sincerely yours,

/S/

Solomon Sobel, M.D.

Director

Division of Metabolic

and Endocrine Drug Products, HFD-510

Office of Drug Evaluation II

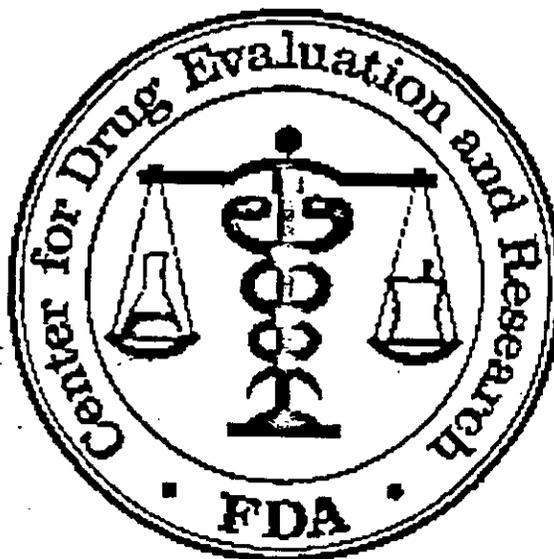
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

/S/

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: January 25, 1999



TO:

Name: Gregory Enas, Ph.D.

Fax No: (317) 276-1652

Phone No.: (317) 276-4038

Location: Eli Lilly

Pages (including this cover sheet): 2

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copy, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone (301-827-6430) and return it to us at the above the above address by mail. Thank you

COMMENTS:

NDA's 21-017 and 21-018 Humalog Mixtures 25 and Humalog Mixtures 50

Requests from Biopharm. Please submit your response to the NDA files including a desk copy for the Biopharm reviewer. Thank you.

cc: Orig NDA's 21-017 + 21-018

HFD-510/Div Files

HFD-870/Fossier

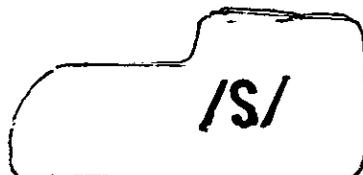
NDA 21-017 Humalog Mixtures 25
NDA 21-018 Humalog Mixtures 50

Date of Submission: December 22, 1998

Comments (to be sent to firm)

- 1) Please submit the study synopses for the following studies in Word format: IOBS, IOCM, IODJ, IODR, IODM, IOET, IOGI, IOFX. The proposed labeling should also be submitted electronically.
- 2) Please submit all PK/PD data for the following studies in either Excel files or ASCII format: IODJ, IOET, IOGI, IODM, IOFX.

Cleared for faxing by:



1/25/99

Hae-Young Ahn, Ph.D, Biopharm Team Leader

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dr. Daniel Boring, Chair, HFD-530, Corporate Building, Room N461

From: Division of Metabolism and Endocrine D. P./HFD-510
William K. Berlin 301-827-6370

Date:

1-26-99

Sent e-mail [redacted] /S/

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Humalog® Mix 25™ and Humalog® Mix 50™ NDA #: 21-01727018

Established name, including dosage form: 25% insulin lispro injection and 75% insulin lispro protamine suspension (rDNA origin) and 50% insulin lispro injection and 50% insulin lispro protamine suspension (rDNA origin)

Other trademarks by the same firm for companion products: Humalog for insulin lispro injection

Name and address of applicant: Eli Lilly and Co.
Lilly Technology Center
Indianapolis IN 46285

Indications for Use (may be a summary if proposed statement is lengthy):
Hyperglycemia from Diabetes Mellitus

Dosage Form: injection Strengths: 100 U/mL Route of Administration: injection Dispensed: B

Initial comments from the submitter (concerns, observations, etc.):

For human insulin, the corresponding trade names for the mixtures of soluble insulin and protamine sulfate suspension are Humulin® 70/30 and Humulin® 50/50.

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Oct. 1993

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION REQUEST/RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

*for con
date 3*

DATE SENT: September 30, 1999

DUE DATE: N/A

OPDRA CONSULT #: 99-048

TO (Division): Solomon Sobel, M.D.
Director, Division of Metabolic and Endocrine Drug Products
(HFD-510)

PRODUCT NAMES:
Humalog Mix 25TM
(25% insulin lispro injection and 75% insulin
lispro protamine suspension [rDNA origin])

Humalog Mix 50TM
(50% insulin lispro injection and 50% insulin
lispro protamine suspension [rDNA origin])

DA#s: 21-017 & 21-018

MANUFACTURER: Eli Lilly and Company

CASE REPORT NUMBER(S): N/A

SUMMARY:

In response to the request by the Division of Metabolic and Endocrine Drug Products, OPDRA conducted a review of the potential name confusion of the proposed proprietary names, Humalog Mix 50TM and Humalog Mix 25TM with other approved proprietary/generic names.

OPDRA RECOMMENDATION:

OPDRA does not recommend the approval of the proposed proprietary names, Humalog Mix 50TM and Humalog Mix 25TM. See review.

/s/

10/4/99

Jerry Phillips

Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

Phone: (301) 827-3246

Fax: (301) 827-5189

/s/

Peter Honig, M.D.

Deputy Director

Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

FACSIMILE TRANSMISSION

Eli Lilly and Company Lilly Research Laboratories

U.S. Regulatory Affairs
FAX (317) 276-1652

CONFIDENTIAL

CONFIDENTIAL



To: Ms. Julie Rhee
FAX #: (301) 443-9282
Date: 04MAY99
From: Jeffrey Winn, DDS
Phone #: (317) 276-2098

Company: FDA

Re: NDA 21-017; Humalog® Mix 25™ [25% insulin lispro injection and 75% insulin lispro protamine suspension (rDNA origin)]
NDA 21-018; Humalog® Mix 50™ [50% insulin lispro injection and 50% insulin lispro protamine suspension (rDNA origin)]

Lilly would like to request a meeting with the FDA regarding the trade names for the two formulations of Humalog that are currently being reviewed by the FDA. Following a telephone discussion with Dr. William Berlin (FDA) on October 4, 1999, Lilly was told that there is a lack of agreement within the FDA regarding the appropriate proprietary names to be used with these two formulations. Complicating this decision is the fact that Eli Lilly and Company will perform an additional

[Redacted] Due to the lack of agreement between various groups within the FDA, along with the fact that the two NDAs user fee date is only 2 months away, Lilly feels that it is imperative to resolve the issue regarding the proprietary names with the FDA.

I would am requesting a 1-hour meeting with the appropriate individuals from the FDA Division of Metabolism and Endocrine Drug Products.

See Next 1 Pages

Lilly attendees are anticipated to be:

Greg Enas, PhD
John Holcombe, MD
Jeffrey Winn, DDS
Khoso Baluch
Jerry Buhler, PhD
Thane Wettig

Director, US Regulatory Affairs
US Clinical Research Physician
Regulatory Research Scientist
Director, Insulin Product Team
Director, Insulin Product Team
Director, U.S. Marketing

Best Regards,
Jeffrey L. Winn, DDS
(317) 276-2098

**APPEARS THIS WAY
ON ORIGINAL**

/S/

Filing meeting minutes for NDAs 21-017 and 21-018

Date: January 25, 1999

NDA 21-017 Humalog® Mix 25™ (25% insulin lispro injection and 75% insulin lispro protamine suspension [rDNA origin])

NDA 21-018 Humalog® Mix 50™ (50% insulin lispro injection and 50% insulin lispro protamine suspension [rDNA origin])

Sponsor: Eli Lilly

Attendees:

Solomon Sobel, M.D., Director, DMEDP
Saul Malozowski, M.D., Acting Medical Team Leader, DMEDP
Elizabeth Koller, M.D., Medical Officer, DMEDP
William Berlin, Ph.D., Chemist, DMEDP
Todd Sahlroot, Ph.D., Statistical Team Leader, DOB II
Michael Fossler, Ph.D., Biopharm Reviewer, DPE II
Julie Rhee, Project Manager, DMEDP

Discussion:

Clinical:

1. The NDAs are fileable.
2. Dr. Koller will let me know of the additional information (i.e., information on antibodies) she needs in order for me to forward it to the sponsor.

Chemistry:

The NDAs are fileable. However, color coding and nomenclature might be problematic.

Pharmacology:

The NDAs are fileable.

Biometrics:

The NDAs are fileable.

Biopharm:

The NDAs are fileable.

**APPEARS THIS WAY
ON ORIGINAL**

Microbiology:

The NDAs are fileable.

General:

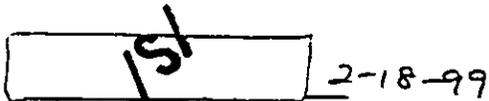
Since the 10-month UF goal date is 10/22/99, try to have a complete review by the end of September 1999.

Page 2

NDA's 21-017 & 21-018 filing meeting minutes

Decision:

1. The NDA's are filed.
2. Try to have the completed review by the end of September 1999.


Julie Rhee

cc: OrigNDA's 21-017 and 21-018

HFD-510/DivFiles 21-017 and 21-018

HFD-510/Koller/Steigerwalt/Berlin

HFD-715/Sahlroot

HFD-870/Fossler

R/D by: JRhee 2-2-99

Concurrence: Koller 2-5-99/Malozowski 2-3-99/Berlin 2-2-99/Steigerwalt 2-3-99/Sahlroot 2-5-99/Fossler 2-8-99

F/T by: JRhee 2-17-99

Minutes

APPEARS THIS WAY
ON ORIGINAL

ELECTRONIC MAIL MESSAGE

Activity: COMPANY CONFIDENTIAL

Date: 22-Jan-1999 10:50am EST
From: Ronald Steigerwalt
STEIGERWALTR
Dept: HFD-510 PKLN 14B04
Tel No: 301-827-6369 FAX 301-443-9282

TO: Julie Rhee

(RHEEJ)

Subject: HUMALOG FILING MEETING

Julie,
I would like to attend an important seminar that has been scheduled at the same time as the humalog filing meeting. There are no pharm/tox issues for the filing. The supplements are fileable for pharm/tox.
Thanks,
Ron

APPEARS THIS WAY
ON ORIGINAL

ELECTRONIC MAIL MESSAGE

Activity: COMPANY CONFIDENTIAL

Date: 25-Jan-1999 10:51am EST
From: Patricia Hughes
HUGHESP
Dept: HFD-160 PKLN 18B08
Tel No: 301-827-7340 FAX 301-443-9281

TO: Julie Rhee (RHEEJ)
CC: Peter Cooney (COONEY)
CC: Patricia Hughes (HUGHESP)

Subject: Re: Today's 1:30 filing meeting

Julie, I have just completed my first review of the two NDAs for Humalog. Peter Cooney needs to concur with my reviews and conclusions. The two NDAs are fileable from the product quality microbiology perspective. Some microbiology deficiencies have been noted and these should be resolved before recommending approval from the product quality microbiology standpoint. A deficiency list will be sent to you as soon as Peter concurs. I will not be able to attend the filing meeting.
Patricia

APPEARS THIS WAY
ON ORIGINAL

151

DEC 30 1998

Eli Lilly and Company
Attention: Gregory G. Enas, Ph.D.
Director, US Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Enas:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Humalog Mix 25 (25% insulin lispro and 75% insulin lispro protamine suspension [rDNA origin]) Injection, 100 U/mL
Therapeutic Classification: Standard (S)
Date of Application: December 21, 1998
Date of Receipt: December 22, 1998
Our Reference Number: 21-017

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 20, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 22, 1999, and the secondary user fee goal date will be December 22, 1999.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-017
Page 2

If you have any questions, contact Julie Rhee, Regulatory Health Project Manager, at (301) 827-6424.

Sincerely yours,

/S/

12.29.98

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

SEE THIS WAY
ON ORIGINAL

/S/

DEC 30 1998

Eli Lilly and Company
Attention: Gregory G. Enas, Ph.D.
Director, US Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Enas:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Humalog Mix 50 (50% insulin lispro and 50% insulin lispro protamine suspension [rDNA origin]) Injection, 100 U/mL

Therapeutic Classification: Standard (S)

Date of Application: December 21, 1998

Date of Receipt: December 22, 1998

Our Reference Number: 21-018

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 20, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 22, 1999, and the secondary user fee goal date will be December 22, 1999.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

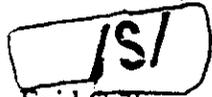
U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-018
Page 2

If you have any questions, contact Julie Rhee, Regulatory Health Project Manager, at (301) 827-6424.

Sincerely yours,

 12.29.78

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

FACSIMILE TRANSMISSION

Eli Lilly and Company
Lilly Research Laboratories
U.S. Regulatory Affairs
FAX (317) 276-1652

CONFIDENTIAL

CONFIDENTIAL



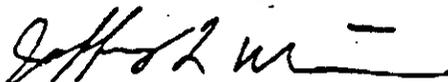
To: Ms Julie Rhoe
FAX #: (301) 443-9282
Date: 08 DEC 99
From: Jeffrey Winn, DDS
Phone #: (317) 276-2098

Company: FDA

Re: NDA 21-017, 21-018

Julie, here is the FAX with the statement you requested on December 7, 1999. I will mail the official response to you today. I should be able to mail the copies of the packaging to you on the 9th for the 10th delivery. I will verify this.

I will be out of the office all day today but please leave a voice mail with detail if you wish.


Best Regards,
Jeffrey L. Winn, DDS
(317) 276-2098

APPEARS THIS WAY
ON ORIGINAL



Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46205
317.276.2000

December 8, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolic and
Endocrine Drug Products, HFD-510
5600 Fishers Lane
Rockville, Maryland 20857

General Correspondence

Re: **NDA 21-017; Humalog® Mix 75/25™ [75% insulin lispro protamine suspension and 25% insulin lispro injection (rDNA origin)]**

NDA 21-018; Humalog® Mix 50™ [50% insulin lispro protamine suspension and 50% insulin lispro injection (rDNA origin)]

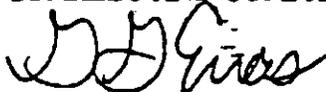
This letter is pursuant to a telephone conversation on December 7, 1999 between Julie Rhee, project manager in the Division of Drug Metabolism and Endocrine Drug Products and Dr. Jeffrey Winn (Lilly). Ms. Rhee requested the following statement for her records:

Eli Lilly and Company financially supported studies F3Z-MC-IODK, F3Z-MC-IODM, and F3Z-MC-IODN and indeed all pivotal and supportive studies presented in the New Drug Applications 21-017 and 21-018.

Lilly thanks you for your continued support and assistance. Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 276-4038 if you require additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY



Gregory G. Enas, Ph.D.
Director
U.S. Regulatory Affairs

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ORIGINAL

Lilly

ORIG AMENDMENT

3C

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000



November 22, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

AMENDMENT

Re: NDA 21-017, Amendment, Insulin Lispro Low Mixture

This amendment provides responses to chemistry questions communicated to Lilly on November 17, 1999.

Please call Ms. Barbara Mallett at (317) 276-8465 or me at (317) 276-4038 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory G. Enas

Gregory G. Enas, Ph.D.
Director
US Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS _____ DATE _____

Enclosure

Desk copies: Dr. Stephen Moore
Ms. Julie Rhee

Sales for Reg.
[S]
12/7/99

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

Eli Lilly and Company

DATE OF SUBMISSION

November 22, 1999

TELEPHONE NO. (Include Area Code)

317-276-2000

FACSIMILE (FAX) Number (Include Area Code)

317-276-1652

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

Lilly Corporate Center
Indianapolis, IN 46285

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, Country, ZIP Code, telephone and FAX number) IF APPLICABLE

Gregory G. Enas, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285 (317) 276-4038

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)

NDA 21-017

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

75% Insulin Lispro Protamine Suspension (rDNA Origin) and
25% insulin lispro injection

PROPRIETARY NAME (trade name) IF ANY

Humalog® Mix75/25

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)

CODE NAME (if any)

DOSAGE FORM: Injectable

STRENGTHS: 100 Units/mL

ROUTE OF ADMINISTRATION: Subcutaneous

PROPOSED INDICATION(S) FOR USE: Treatment of hyperglycemia

APPLICATION INFORMATION

APPLICATION TYPE

(check one) NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b) (1) 505 (b) (2) 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug: _____ Holder of Approved Application: _____

TYPE OF SUBMISSION

(check one) ORIGINAL APPLICATION AMENDMENT TO A PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT SUPAC SUPPLEMENT
 EFFICACY SUPPLEMENT LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

REASON FOR SUBMISSION Response to Questions

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED N/A

THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See Attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Stability Tests on the Finished Product

Stability Tests on 10 mL Vials Insulin Lispro Low Mixture

Addresses of Analytical Laboratories Performing Stability Studies

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 USA

Eli Lilly and Company
Lilly Technology Center
Indianapolis, Indiana 46285 USA

Stability Tests on 3.0 mL Cartridges Insulin Lispro Low Mixture

Address of Analytical Laboratories Performing Stability Studies

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 USA

Eli Lilly and Company
Lilly Technology Center
Indianapolis, Indiana 46285 USA

Lilly France S.A.
rue du Colonel Lilly
67640 Fegersheim, France

**Manufacturer of Cartridges Insulin Lispro Low Mixture,
100 U/mL, 3.0 mL**

Manufacturer of the Dosage Form

Cartridges Insulin Lispro Low Mixture, 100 U/mL, 3.0 mL will be manufactured at the following facility:

Lilly France S.A.
rue du Colonel Lilly
67640 Fegersheim, France

Packaging and Labeling

Packaging and labeling of Cartridges Insulin Lispro Low Mixture, 100 U/mL, 3.0 mL will be conducted by Eli Lilly and Company at the following facility:

Lilly France S.A.
rue du Colonel Lilly
67640 Fegersheim, France

Eli Lilly and Company
Lilly Technology Center
Indianapolis, Indiana 46285 USA

Control Facilities

Analytical laboratories conducting in-process, control and/or release testing of Cartridges Insulin Lispro Low Mixture, 100 U/mL, 3.0 mL will take place at the following facilities:

Lilly France S.A.
rue du Colonel Lilly
67640 Fegersheim, France

Eli Lilly and Company
Lilly Technology Center
Indianapolis, Indiana 46285 USA

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 USA

Manufacturer of Insulin Lispro Low Mixture

Manufacturer of Vials Insulin Lispro Low Mixture, 100 U/mL, 10 mL

Manufacturer of the Dosage Form

Vials Insulin Lispro Low Mixture, 100 U/mL, 10 mL will be manufactured at the following facility:

Eli Lilly and Company
Lilly Technology Center
Indianapolis, Indiana 46285 USA

Packaging and Labeling

Packaging and labeling of Vials Insulin Lispro Low Mixture, 100 U/mL, 10 mL will be conducted by Eli Lilly and Company at the following facility:

Eli Lilly and Company
Lilly Technology Center
Indianapolis, Indiana 46285 USA

Control Facilities

Analytical laboratories conducting in-process, control and/or release testing of Vials Insulin Lispro Low Mixture, 100 U/mL, 10 mL will take place at the following facilities:

Eli Lilly and Company
Lilly Technology Center
Indianapolis, Indiana 46285 USA

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 USA

Humalog® Mix 25:

Question 1

Please provide a Phase IV commitment to re-evaluate the lower Assay limit of [redacted] when a sufficient number of lots have been analyzed to perform a suitable statistical analysis. A limit of [redacted] appears to be more appropriate.

Please include the following information in the commitment:

- a) protocol Submission: Within X months following (the NDA) approval*
- b) Study Start: Within Y months following approval*
- c) Final Report Submission: Within Z months following approval*

Lilly Response

A protocol for the re-evaluation of the lower Assay limit of [redacted] for Humalog® Mix 25 and Humalog Mix® 50 will be submitted within six months following approval. A study will begin immediately following approval. Stability data which we are currently collecting, as well as, data from additional manufactured lots will be included in the study. When sufficient data are collected they will be statistically analyzed and a report will be submitted. A preliminary report will be provided at the first annual update, approximately [redacted] months following approval. Included in this report will be a commitment to the number of additional lots or the additional time necessary to complete the final report.

**APPEARS THIS WAY
ON ORIGINAL.**

BEST POSSIBLE COPY

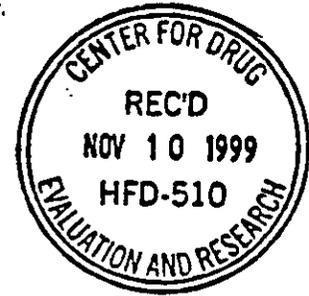
DUPLICATE

Lilly

BM

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000



November 9, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolic and
Endocrine Drug Products, HFD-510
5600 Fishers Lane
Rockville, Maryland 20857

General Correspondence

Re: ~~NDA 21-017~~; Humalog® Mix 25™ [25% insulin lispro injection and 75%
insulin lispro protamine suspension (rDNA origin)]

NDA 21-018; Humalog® Mix 50™ [50% insulin lispro injection and 50%
insulin lispro protamine suspension (rDNA origin)]

This letter is pursuant to a telephone conversation on November 4, 1999 between Julie Rhee, project manager in the Division of Drug Metabolism and Endocrine Drug Products and Dr. Jeffrey Winn (Lilly). Ms. Rhee indicated that the medical reviewing officer requested data concerning studies F3Z-MC-IODI, F3Z-MC-IODK, F3Z-MC-IODL, F3Z-MC-IODM, and F3Z-MC-IODN. The medical reviewing officer specifically wanted the number of patients who dropped out of the studies by treatment arm.

For your convenience, Lilly has attached a note to reviewer to this letter.

Lilly thanks you for your continued support and assistance. Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 276-4038 if you require additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Gregory G. Enas

Gregory G. Enas, Ph.D.
Director
U.S. Regulatory Affairs

Enclosure

Desk Copy: Dr. Elizabeth Koller HFD-510

*Already reviewed
in FAX to
NAI*

ISI 11/15/99

REVIEWS COMPLETED
CSO ACTION:
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<i>(S)</i>
CSO INITIALS
<i>11-17-99</i>
DATE

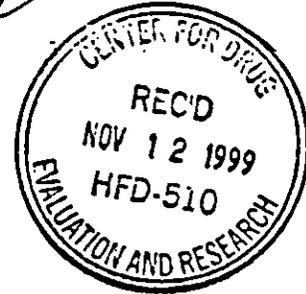
DUPLICATE

NEW
NV

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000



November 8, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attention: Division Document Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706

Re: NDA 21-018; Humalog® Mix 50™ [50% insulin lispro injection and 50% insulin lispro protamine suspension (rDNA origin)]

On this date a Safety Update document was submitted to NDA 21-017, Humalog® Mix 25™ [25% insulin lispro injection and 75% insulin lispro protamine suspension (rDNA origin)].

We request that this information be incorporated into the above file, NDA 21-018, by reference.

Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 276-4038 if you require any additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

A handwritten signature in cursive script, appearing to read "G. Enas".

Gregory G. Enas, Ph.D.
Director
U.S. Regulatory Affairs

Enclosure

**APPEARS THIS WAY
ON ORIGINAL**

ORIG AMENDMENT

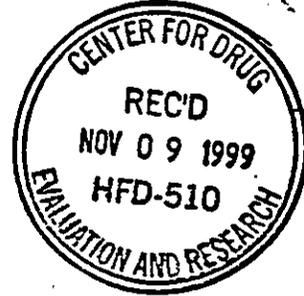
SU

Lilly

ORIGINAL

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000



November 8, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolic and
Endocrine Drug Products, HFD-510
5600 Fishers Lane
Rockville, Maryland 20857

SAFETY UPDATE

Re: NDA 21-017; Humalog® Mix 25™ [25% insulin lispro injection and 75% insulin lispro protamine suspension (rDNA origin)]

NDA 21-018; Humalog® Mix 50™ [50% insulin lispro injection and 50% insulin lispro protamine suspension (rDNA origin)]

This letter is pursuant to a telephone conversation between Ms. Julie Rhee (FDA) and Dr. Jeffrey Winn (Lilly) regarding NDA 21-017 and NDA 21-018 on October 18, 1999. During the telephone call, Mr. Rhee requested the safety update required prior to approval of the two New Drug Applications. Lilly is herewith submitting the safety update pursuant to 21 CFR 314.50(d)(5)(vi)(b).

Lilly thanks you for your continued support and assistance. Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 276-4038 if you require additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Gregory G. Enas

Gregory G. Enas, Ph.D.
Director
U.S. Regulatory Affairs

*Incorporated into NDA review 11/15/99
Need total # paragraphs*

ISI 11/15/99

REVIEWS COMPLETED	
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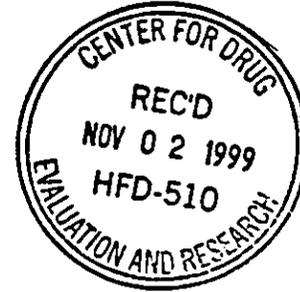
Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

ORIGINAL

NEW CORRESP
NC

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000



October 29, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolic and
Endocrine Drug Products, HFD-510
5600 Fishers Lane
Rockville, Maryland 20857

General Correspondence

Re: ~~NDA 21-018~~ Humalog® Mix 25™ [25% insulin lispro injection and 75% insulin lispro protamine suspension (rDNA origin)]

NDA 21-018; Humalog® Mix 50™ [50% insulin lispro injection and 50% insulin lispro protamine suspension (rDNA origin)]

This letter is pursuant to a FAX request (attached) from Julie Rhee, project manager in the Division of Drug Metabolism and Endocrine Drug Products, on October 4, 1999. The FAX correspondence indicated that the medical reviewing officer requested data concerning studies IODI, IODK, IODL, IODM, and IODN. The reviewing officer also requested information on the patients who discontinued after randomization.

For your convenience, Lilly has attached a note to reviewer to this letter.

Lilly thanks you for your continued support and assistance. Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 276-4038 if you require additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Gregory G. Enas
Gregory G. Enas, Ph.D.
Director
U.S. Regulatory Affairs

Enclosure

Desk Copy: Dr. Elizabeth Koller HFD-510

*FAXed previous
incorporated into NDA
11/10/99*

REVIEWS COMPLETED
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CSO INITIALS _____ DATE _____

/S/

BEST POSSIBLE COPY

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

October 27, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolic and
Endocrine Drug Products, HFD-510
5600 Fishers Lane
Rockville, Maryland 20857

General Correspondence

ORIGINAL

CDER APPROVALS

151



Re: ~~NDA 21-018~~ Humalog® Mix 25™ [25% insulin lispro injection and 75% insulin lispro protamine suspension (rDNA origin)]

NDA 21-018; Humalog® Mix 50™ [50% insulin lispro injection and 50% insulin lispro protamine suspension (rDNA origin)]

Not requested by MC

This letter is pursuant to a telephone request from Julie Rhee, project manager in the Division of Drug Metabolism and Endocrine Drug Products, on October 22, 1999. Ms. Rhee indicated that the medical reviewing officer requested a floppy disk with the physician and patient labeling in Microsoft Word® format.

A review copy of the aforementioned requested information is being provided to the medical reviewing officer on a single floppy disk as requested. The disk contains files in Word format. The archival copy of this data is included on a separate floppy disk being submitted to the document control room. All electronic media have been checked and verified to be free of known viruses. The virus checking software was McAfee VirusScan 4.0.2 using Virus Definitions 4.0.4038 created on 11 August 1999.

*Patent physician
diskette provided to
CSO previously
11/1/99*

REVIEWS COMPLETED	
CD	ONE:
[]	RE: Humalog Mix 25
	DATE: 11-3-99
CS	ASS
	DATE:

151

BEST POSSIBLE COPY

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

ORIGINAL

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

September 24, 1999



ISI

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolic and
Endocrine Drug Products, HFD-510
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-017; Humalog® Mix 25™ [25% insulin lispro injection and 75% insulin lispro protamine suspension (rDNA origin)]

NDA 21-018; Humalog® Mix 50™ [50% insulin lispro injection and 50% insulin lispro protamine suspension (rDNA origin)]

We are herewith submitting the following abbreviated report for F3Z-MC-IODI, "Clinical Study Abbreviated Report: Free Mixtures of Insulin Lispro Protamine Suspension (NPL) and Insulin Lispro in a twice Daily Regimen in the Treatment of Diabetes". The original Study Report was submitted with the original NDA 21-018 on December 22, 1998, this is the Abbreviated Report for the noncomparator, open label Extension phase of the study.

Lilly thanks you for your continued support and assistance. Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 276-4038 if you require additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Gregory G. Enas

Gregory G. Enas, Ph.D.
Director
U.S. Regulatory Affairs
Enc.

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

Patents called in to enter a 2nd/24 month extension study - but it appears that there were few patents of the study were truncated early. Only 12 months data was provided in the NDA submission paper.

11/1/99

ISI

BEST POSSIBLE COPY

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

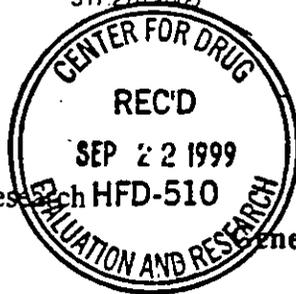
ORIGINAL

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

~~CONFIDENTIAL~~

151

September 21, 1999



Food and Drug Administration
Center for Drug Evaluation and Research HFD-510
Office of Drug Evaluation II
Division of Metabolic and Endocrine Drug Products, HFD-510
5600 Fishers Lane
Rockville, Maryland 20857
General Correspondence

Re: ~~NDA 21-017~~; Humalog® Mix 25™ [25% insulin lispro injection and 75% insulin lispro protamine suspension (rDNA origin)]

NDA 21-018; Humalog® Mix 50™ [50% insulin lispro injection and 50% insulin lispro protamine suspension (rDNA origin)]

This letter is pursuant to a telephone request from Julie Rhee, project manager in the Division of Drug Metabolism and Endocrine Drug Products, on September 10, 1999. Ms. Rhee indicated that the medical reviewing officer requested all data regarding insulin dose, HbA1c, cross-reactive antibodies at baseline and at endpoint for F3Z-MC-IODK, F3Z-MC-IODM, and F3Z-MC-IODN in SAS transport files or in an Excel spreadsheet on a floppy disk. Additionally, for these studies, Ms. Rhee requested the number of hypoglycemic events at endpoint for these studies. Hypoglycemia to be defined as \leq 36mg/dL or needing assistance. Ms. Rhee also indicated that the medical reviewing officer would like to have the same information for F3Z-MC-IODL at baseline, 6 month, 12 months, 18 months and at 24 months.

Dr. Winn called Ms. Rhee later that day to clarify that study F3Z-MC-IODL was a 6 month study with an 18 month extension and only the cross-reactive antibodies were available at points beyond 6 months. Also, the F3Z-MC-IODN protocol did not request or collect cross-reactive antibodies and these data would not be present in the response. Ms. Rhee indicated that Lilly should provide the information requested at baseline and at 6 months and the antibody data collected in the extension phase of F3Z-MC-IODL and all other requested information from study F3Z-MC-IODN.

A review copy of the aforementioned requested information is being provided to the medical reviewing officer on a single floppy disk as requested. The disk contains files in both Excel and SAS Transport format. The archival copy of this data is included on the

NC
151
11/17/99

CD-ROM being submitted to the document control room. For the agency's convenience, the archival copy contains a complete set of data for studies F3Z-MC-IODK, F3Z-MC-IODL, F3Z-MC-IODM, and F3Z-MC-IODN. The electronic archival copy of this data has been prepared in accordance with FDA guidance and occupies approximately 130MB of disk space for each of the two NDAs. All electronic media have been checked and verified to be free of known viruses. The virus checking software was McAfee VirusScan 4.0.2 using Virus Definitions 4.0.4038 created on 11 August 1999.

For your convenience, Lilly has also attached to this letter summary tables for the parent studies F3Z-MC-IODK, F3Z-MC-IODL, F3Z-MC-IODM, and F3Z-MC-IODN. The documents can be identified as HYLS17DK.DOC, HYLS17DL.DOC, HYLS17DM.DOC, and HYLS17DN.DOC. These tables present the response to the question "Able to Self Treat?" for each hypoglycemic episode that had a BG level \leq mmol/L.

Lilly thanks you for your continued support and assistance. Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 276-4038 if you require additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY



Gregory G. Enas, Ph.D.
Director
U.S. Regulatory Affairs

Enclosure

Desk Copy: Dr. Elizabeth Koller HFD-510

REVIEWS COMPLETED	
CSO ACTION:	
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<i>zm</i>	10-5-99
CSO INITIALS	DATE

*CDRom - Data in XPT files
Using EXCEL files
on diskette*

*ISI
9/30/99*

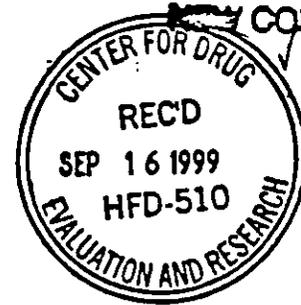
ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

(SI)



September 10, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolic and
Endocrine Drug Products, HFD-510
5600 Fishers Lane
Rockville, Maryland 20857

General Correspondence

Re: NDA 21-017; Humalog® Mix 25™ [25% insulin lispro injection and 75% insulin lispro protamine suspension (rDNA origin)]
NDA 21-018; Humalog® Mix 50™ [50% insulin lispro injection and 50% insulin lispro protamine suspension (rDNA origin)]

This letter is pursuant to a telephone request from Julie Rhee, project manager in the Division of Drug Metabolism and Endocrine Drug Products, on September 10, 1999. The request was for a list of all patients older than 65 years while enrolled in F3Z-MC-IODK, F3Z-MC-IODM, and F3Z-MC-IODN along with patient identifiers. Eli Lilly and Company also included those patients who meet this criterion from the study F3Z-MC-IODI for the reviewers information.

Lilly thanks you for your continued support and assistance. Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 276-4038 if you require additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Gregory G. Enas
Gregory G. Enas, Ph.D.
Director
U.S. Regulatory Affairs

Encl.

*Included in NDS
54 generic patients
later obtained by
spread sheet*

REVIEWS COMPLETED	
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CSO INITIALS	DATE

(SI) 7/11/99

BEST POSSIBLE COPY

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000



August 4, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

AMENDMENT
N-000-BC
ORIGINAL
ORIGINAL

Re: NDA 21-018, Amendment, Insulin Lispro Mid Mixture

This amendment provides updated stability data on lots previously provided in the initial NDA. Additionally, data are provided on drug product lots manufactured from bulk drug substance which has undergone changes to the "front-end" of the insulin lispro.

Please call Ms. Barbara Mallett at (317) 276-8465 or me at (317) 276-4038 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory G. Ehas
Gregory G. Ehas, Ph.D.
Director
US Regulatory Affairs

SEARCHED
SERIALIZED
INDEXED FILED
51 10-22-99

Enclosure

Desk copies: Dr. William Berlin
Dr. Peter Cooney
Ms. Julie Rhee

Received under Chem Res #1
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10/1/99

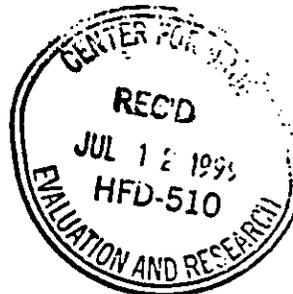
BEST POSSIBLE COPY

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

July 8, 1999



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolic and
Endocrine Drug Products, HFD-510
5600 Fishers Lane
Rockville, Maryland 20857

General Correspondence

NEW CORRESP
LC

Re: NDA 21-017; Humalog® Mix 25™ [25% insulin lispro injection and 75% insulin lispro protamine suspension (rDNA origin)]

NDA 21-018; Humalog® Mix 50™ [50% insulin lispro injection and 50% insulin lispro protamine suspension (rDNA origin)]

This letter is pursuant to a telephone conversation between Dr. William Berlin (FDA) and Dr. Jeffrey Winn (Lilly) on June 8, 1999. During the telephone conversation Dr. Berlin indicated that the Food and Drug Administration had decided to reject the proprietary names Humalog® Mix 25 and Humalog® Mix 50. The rationale for the rejection was that the proprietary names did not have the relative proportions of the ingredients identified (i.e. Humalog 25/75), although there was no indication that the potential for prescription errors was a concern.

The purpose of this communication is to contest the decision of the Nomenclature Committee and request a reversal of the decision by the Division of Metabolism and Endocrine Drug Products. The remainder of this letter will discuss the rationale for retaining the proprietary names of Humalog® Mix 25 and Humalog® Mix 50.

A review of all applicable regulations and guidelines has not produced any information relating to the requirement of providing the relative proportions of drug substances in the proprietary names of combination products. However, the generic names of all ingredients and their relative proportions must be prominently displayed alongside the trade name each time the proprietary name is used as noted in 21 CFR 201.10(g)(1-2). This will indeed be the case for Humalog Mix 25 and Humalog Mix 50, which will prominently display the precise ingredients and proportions thereof beside the proprietary name on all packaging and marketing materials. For example:

Proprietary name will address
ISI 8/5/99
ISI 8/5/99
ISI

25% Insulin Lispro
REVIEWS COMPLETED

CSO ACTION:
 LETTER N.A.I. MEMO

m
CSO INITIALS 8-26-99
DATE

injection and 75% insulin lispro protamine suspension (rDNA origin)]” will be prominently displayed in conjunction with the trade name, Mix25.

Analogous to Humalog Mix25 and Humalog Mix50 is the currently marketed product; the combination antihypertensive Maxzide® (triamterene/hydrochlorothiazide) has a “half-strength” dosage form that has as its proprietary name Maxzide-25. Other examples of combination products whose Proprietary name does not provide a proportion of the ingredients include: Augmentin® (amoxicillin/clavulanate), Primaxin® (imipenem/cilastatin), Combivent® (albuterol/ipratropium), Unasyn® (ampicillin/sulbactam), Timentin® (ticarcillin/clavulanate), and all oral contraceptives.

The products in question are currently under review by the FDA; however they have been reviewed and approved by the European Union, Canada, Mexico, and many other countries with the proprietary names Humalog Mix25 and Humalog Mix50. Eli Lilly and Company makes every effort to determine a proprietary name that is not confusing, and that will allow consistency around the world. The International Diabetes Federation, the Food and Drug Administration, and Industry has been successful in agreeing upon a standard color coding system to be used worldwide in an attempt to prevent confusion and allow for product identification by patients and health care workers. The addition of a standardized trade name for these products would greatly augment this system and further reduce the confusion for U.S. citizens who find themselves outside the United States, including in the neighboring countries Canada and Mexico.



Attached to this correspondence are copies of the “color-coded” packaging of the Humalog family that will use the Humalog designated color and a graphic representation of the amount of soluble Humalog contained within the mixture. The color is also used to differentiate the various formulations. As you will see, there is no ambiguity of the proprietary names. These will be formally submitted to the NDAs in the near future to be the first “color-coded” insulin packaging in the United States.

In conclusion, Lilly asks the Division of Metabolism and Endocrine Drug Products to reverse the decision to reject the names Humalog Mix25 and Humalog Mix75 for the reasons previously stated.

NDA 21-017; Humalog Mix 25
NDA 21-018; Humalog Mix50
Food and Drug Administration
July 8, 1999
Page 3

Lilly thanks you for your continued support and assistance. Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 276-4038 if you require additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Michael D. Clayman, MD
John
Gregory G. Enas, Ph.D.

Gregory G. Enas, Ph.D.
Director
U.S. Regulatory Affairs

Attch.

cc:

Dr. Solomen Sobel, MD (desk copy)
Dr. William Berlin, PhD (desk copy)

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

ORIG AMENDMENT

IS

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000



May 28, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

AMENDMENT

Re: NDA 21-018, Amendment, Insulin Lispro Mid Mixture

This amendment provides an additional response to the microbiology questions communicated to Lilly on February 3, 1999.

Please call Ms. Barbara Mallett at (317) 276-8465 or me at (317) 276-4038 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory G. Enas

Gregory G. Enas, Ph.D.
Director
US Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> MEMO
<i>m</i> <i>10-22-99</i>
MAILS DATE

Enclosure

Desk copies: Dr. William Berlin
Dr. Peter Cooney
Ms. Julie Rhee

Micro review completed 4/12/99

NAT for Chemistry
IS
10/22/99

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

April 20, 1999



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolic and
Endocrine Drug Products, HFD-510
5600 Fishers Lane
Rockville, Maryland 20857

SAFETY UPDATE

Re: NDA 21-017; Humalog® Mix 25™ [25% insulin lispro injection and 75% insulin lispro protamine suspension (rDNA origin)]

Eli Lilly and Company is herewith submitting a 4 month safety update pursuant to 314.50(vi)(b) for NDA 21-017. Although Lilly is submitting two documents, one for NDA 21-017 and NDA 21-018, these documents are identical due to the fact that the studies are integrated. Additionally, Lilly is supplying 1 copy to the medical reviewer and 2 copies for the file room.

Lilly thanks you for your continued support and assistance. Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 276-4038 if you require additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Gregory G. Enas
Gregory G. Enas, Ph.D.
Director
U.S. Regulatory Affairs

*Reviewed 5/20/99
The information was
incorporated into the NDA
review.*

ISI
10/1/99

Enc.

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Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

ORIGINAL

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

ORIG AMENDMENT

BEST POSSIBLE COPY

February 17, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

AMENDMENT

Re: NDA 21-017, Amendment, Insulin Lispro Low Mixture

This amendment provides the responses to the microbiology questions communicated to Lilly on February 3, 1999.

Please call Ms. Susan Lanham at (317) 277-2596 or me at (317) 276-4038 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory G. Enas

Gregory G. Enas, Ph.D.
Director
U.S. Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I.
<input type="checkbox"/> MEMO	
<input checked="" type="checkbox"/> (S)	10-22-99
	DATE

enclosure

desk copies: Dr. William Berlin
Dr. Peter Cooney
Ms. Julie Rhee

Micro review completed 4/12/99

NAI for Chemistry
IS/
10/22/99

BEST POSSIBLE COPY

CDRO AMT...

Lilly ISI

Lilly Research Laboratories
A Division of Eli Lilly and Company

ORIGINAL

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

February 8, 1999

WILL REVIEW
MT copy
ISI
General Correspondence
2/19/99

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolic and
Endocrine Drug Products, HFD-510
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-017; Humalog® Mix 25™ [25% insulin lispro injection and 75%
insulin lispro protamine suspension (rDNA origin)]

This letter is pursuant to a faxed request from the Division of Drug Metabolism and Endocrine Drug Products on January 25, 1999. Enclosed are two (2) CD-ROMs containing exactly the same information for both Humalog Mix25 (NDA 21-017) and Humalog Mix50 (NDA 21-018). One of the CD-ROMs is for Dr. Fossler who requested the information.

The files supplied in this response are contained on one CD-ROM and are approximately 60 megabytes in total size. Microsoft Word and Excel files were authored with Office 95. The contents of the CD-ROM are outlined in the table below.

All electronic media have been checked and verified to be free of known viruses. The virus checking software was McAfee VirusScan 3.2.0 using virus definitions 3.0.3201 created on 1/15/1999.

Folder\ Subfolder	File Name	Description (DOC files only)
	Readme.txt	
HUMALOG RESPONSES		
IOCM	Demegrap.xls	
	Iocmdata.xls	
	Mx0npd.xls	
	Mx100npd.xls	
	Mx25npd.xls	
	Mx50npd.xls	
	Nx75npd.xls	
	README IOCM.TXT	

NAI
ISI
4-20-99

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Lilly

Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

December 21, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolic and
Endocrine Drug Products, HFD-510
5600 Fishers Lane
Rockville, Maryland 20857

NOV 27 1998
NDA SUBMISSION

CENTER FOR DRUG
EVALUATION AND RESEARCH
REC'D
DEC 22 1998
CDR

REC'D
NOV 27 1998
HFD-510

Re: **NDA 21-017; Humalog® Mix 25™ [25% insulin lispro injection and 75% insulin lispro protamine suspension (rDNA origin)]**

This letter accompanies a submission by Eli Lilly and Company (Lilly) of an original New Drug Application (NDA) for Humalog® Mix 25™ [25% insulin lispro injection and 75% insulin lispro protamine suspension (rDNA origin)]. All sections of NDA 21-017 and 21-018 are identical except for items 2, 3 and 4.

This application is formatted and organized according to 21 CFR §314.50 and follows the "Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications". The clinical studies in the clinical and statistical sections of the NDA have been arranged not by study design as suggested in the guidelines, but rather by the value they add to the label in terms of label claims. This fact was highlighted in a letter sent to the FDA on April 15, 1998. Item 12 is being submitted as an electronic-only archival copy in accordance with the "Guidance for Industry: Archiving Submissions in Electronic Format—NDAs". The remaining documents will be available in both paper and electronic format.

The electronic archival copy of Item 12 is contained on one CD-ROM and is approximately 30 megabytes. The CD-ROM is included in the front of the first blue binder (archived copy). All files on each CD-ROM of the electronic submission are in Adobe PDF and can be viewed or printed by use of Adobe Acrobat Reader or Adobe Acrobat Exchange, version 3.x or later.

All electronic media have been checked and verified to be free of known viruses. The software utilized was McAfee VirusScan 3.11, scan engine 3.0.4 using virus definitions created on 11/11/1998.

Lilly has met with FDA personnel on a number of occasions to discuss the clinical development plans for Humalog Mix 25. The major outcomes and agreements from those meetings are outlined in the Note To Reviewers.

The archival copy is being sent to the Central Document Room in Rockville, Maryland. The review copy is being sent to the Review Division Document Room. As required by 21 CFR §314.50(k)(3) we hereby certify that a field copy is being provided simultaneously to our home FDA district office in Detroit, Michigan. This copy contains all appropriate sections, identical to those provided to the reviewing division. Lilly affirms that all manufacturing sites listed in this application that are involved in the manufacturing, packaging, and labeling of Humalog Mix 25 are available for pre-approval inspection.

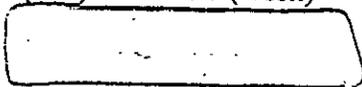
The User Fee (User Fee number 3563) due for this submission was paid to [redacted] on December 4, 1998 in the amount of [redacted]. The Patent certification, Debarment certification, and Field Copy certification have been provided.

To coordinate our activities with yours, we suggest that any facsimile (FAX) or other written communications, concerning this file, regardless of subject, be directed to:

Gregory G. Enas, Ph.D
Director
U.S. Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285
FAX number: (317) 276-1652

Telephone calls should be made between the hours of 7:30 a.m. and 4:15 p.m. (EST). Any calls dealing with general issues, clinical reports, labels, or literature should be made to:

Jeffrey L. Winn, D.D.S.
(317) 276-2098 (work)



or alternatively you may reach Dr. Winn via E-mail at WINN@LILLY.COM

In the case of Dr. Winn's absence, please contact:

Gregory G. Enas, Ph.D.
(317) 276-4038 (work)

On holidays and weekends, call Dr. Winn or Dr. Enas at home using the telephone numbers indicated.

Any calls relating to functionality of the CANDAs should be made to:

Steven T. Ward
(317) 276-2952 (work)

Any calls related to manufacturing and control issues should be made to:

Tobias Massa, Ph.D.
Director, Regulatory CM&C
(317) 276-0368(work)

or in his absence to:

Susan Lanham
Manager, Global Regulatory Affairs, CM&C
(317) 277-2596(work)

Any calls related to toxicology issues should be made to:

Michael A. Dorato, Ph.D., DABT
Director, Toxicology Projects & Environmental Sciences
(317) 277-4649 (work)

or in his absence to:

John L. Zimmerman, DVM, Ph.D., DACVP
(317) 277-4641 (work)



Close communication between the Lilly personnel listed above will result in any message being brought to the attention of all concerned parties.

Lilly thanks you for your continued support and assistance. Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 276-4038 if you require additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

A handwritten signature in cursive script that reads "Gregory G. Enas".

Gregory G. Enas, Ph.D.
Director
U.S. Regulatory Affairs

Enc.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

1/22/99

TO (Division/Office): Patricia Hughes, Ph.D., HFD-160
c/o Peter Cooney, Ph.D., HFD-160

FROM: HFD-510 (Division of Metabolic and Endocrine Drug Products) Julie Rhee

February 19, 1999

IND NO.:

NDA NO.:

21-018

TYPE OF DOCUMENT:
Response

DATE OF DOCUMENT:

February 17, 1999

NAME OF DRUG:
Humalog Mix 50

PRIORITY CONSIDERATION:

CLASSIFICATION OF DRUG:

DESIRED COMPLETION DATE:
April 30, 1999

NAME OF FIRM: Eli Lilly

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

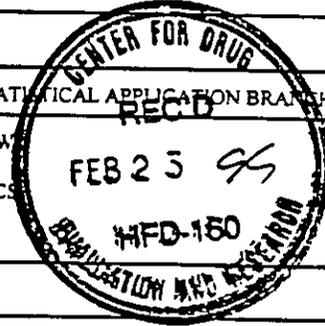
STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER:

ID: P. Hughes
File 3/1/99

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER:



III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> IN-VITRO AVAILABILITY STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Pat, this is Lilly's response to your requests. Please let me know if you need any additional information. Thanks.

cc: Original NDA 21-018
HFD-510/Div. Files

SIGNATURE OF REQUESTER:

METHOD OF DELIVERY (Check one):

MAIL

HAND

NATURE OF RECEIVER:

SIGNATURE OF DELIVERER:

IS/

IS/

REQUEST FOR CONSULTATION

ISI
12/31/98

TO (Division/Office): Peter Cooney, Ph.D., HFD-160

FROM: HFD-510 (Division of Metabolic and Endocrine Drug Products) Julie Rhee

DATE: December 31, 1998

IND NO.:

NDA NO.: 21-017

TYPE OF DOCUMENT: New NDA

DATE OF DOCUMENT: December 21, 1998

NAME OF DRUG: Humalog® Mix 25™ (25% insulin lispro injection and 75% insulin lispro protamine suspension [rDNA origin])

PRIORITY CONSIDERATION:

CLASSIFICATION OF DRUG:

DESIRED COMPLETION DATE: June 30, 1998

BEST POSSIBLE COPY

NAME OF FIRM: Eli Lilly

REASON FOR REQUEST

I. GENERAL

- NEW PROTOCOL
- PRE-NDA MEETING
- RESPONSE TO DEFICIENCY LETTER
- PROGRESS REPORT
- END OF PHASE II MEETING
- FINAL PRINTED LABELING
- NEW CORRESPONDENCE
- RESUBMISSION
- LABELING REVISION
- DRUG ADVERTISING
- SAFETY/EFFICACY
- ORIGINAL NEW CORRESPONDENCE
- ADVERSE REACTION REPORT
- PAPER NDA
- FORMULATIVE REVIEW
- MANUFACTURING CHANGE/ADDITION
- CONTROL SUPPLEMENT
- OTHER (SPECIFY BELOW):
- MEETING PLANNED BY

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
- END OF PHASE II MEETING
- CONTROLLED STUDIES
- TOCOTL REVIEW
- OTHER:

TO: P. Hughes
JAC
1/4/99

- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER:

III. BIOPHARMACEUTICS

- DISSOLUTION
- DEFICIENCY LETTER RESPONSE
- BIOAVAILABILITY STUDIES
- PROTOCOL-BIOPHARMACEUTICS
- PHASE IV STUDIES
- IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

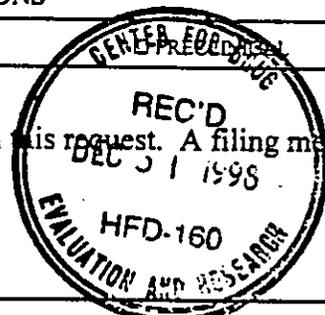
- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- SUMMARY OF ADVERSE EXPERIENCE
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- POISON RISK ANALYSIS
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Peter, this is a new NDA. Volumes 1.1, 1.3, and 1.46 are included with this request. A filing meeting is tentatively scheduled on 1/25 @1:30 pm. Thank you.



cc: Original NDA 21-017
HFD-510/Div. Files

SIGNATURE OF REQUESTER:

METHOD OF DELIVERY (Check one):

MAIL

HAND

SIGNATURE OF RECEIVER:

SIGNATURE OF DELIVERER:

ISI

TS/ 12/31/98

TO (Division/Office): Peter Cooney, Ph.D., HFD-160

FROM: HFD-510 (Division of Metabolic and Endocrine Drug Products) Julie Rhee

December 31, 1998

IND NO.:

NDA NO.: 21-018

TYPE OF DOCUMENT: New NDA

DATE OF DOCUMENT: December 21, 1998

NAME OF DRUG: Humalog® Mix 50/50™ (50% insulin lispro injection and 50% insulin lispro protamine suspension [rDNA origin])

PRIORITY CONSIDERATION:

CLASSIFICATION OF DRUG:

DESIRED COMPLETION DATE: June 30, 1998

BEST POSSIBLE COPY

NAME OF FIRM: Eli Lilly

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER: |
| OTHER: | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

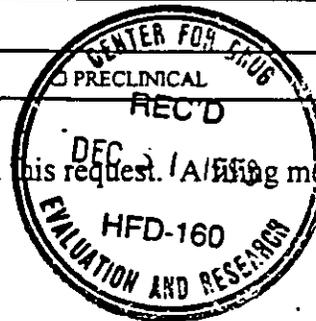
V. SCIENTIFIC INVESTIGATIONS

CLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Peter, this is another new NDA. Volumes 1.1, 1.3, and 1.21 are included with this request. A meeting is tentatively scheduled on 1/25 @ 1:30 pm. Thank you.

cc: Original NDA 21-018
HFD-510/Div. Files



NATURE OF REQUESTER:

METHOD OF DELIVERY (Check one):

MAIL

HAND

SIGNATURE OF RECEIVER: TS/

SIGNATURE OF DELIVERER: TS/

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

ISI

2/21/99

TO (Division/Office): Patricia Hughes, Ph.D., HFD-160
c/o Peter Cooney, Ph.D., HFD-160

FROM: HFD-510 (Division of Metabolic and Endocrine Drug
Products) Julie Rhee

DATE: February 19, 1999

IND NO.:

NDA NO.:
21-017

TYPE OF DOCUMENT :
Response

DATE OF DOCUMENT:
February 17, 1999

NAME OF DRUG:
Humalog Mix 25

PRIORITY CONSIDERATION:

CLASSIFICATION OF DRUG:

DESIRED COMPLETION DATE:
April 30, 1999

NAME OF FIRM: Eli Lilly

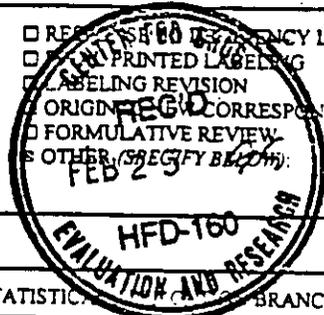
REASON FOR REQUEST

I. GENERAL

- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE/ADDITION
- MEETING PLANNED BY

- PRE-NDA MEETING
- END OF PHASE II MEETING
- RESUBMISSION
- SAFETY/EFFICACY
- PAPER NDA
- CONTROL SUPPLEMENT

- REQUEST FOR DEFICIENCY LETTER
- PRINTED LABELING
- LABELING REVISION
- ORIGINAL CORRESPONDENCE
- FORMULATIVE REVIEW
- OTHER (SPECIFY BELOW):



II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL EVALUATION AND RESEARCH BRANCH

- TYPE A OR B NDA REVIEW
- END OF PHASE II MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER:

P: Patricia Hughes
JMC 3/1/99

- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER:

III. BIOPHARMACEUTICS

- SOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
- PROTOCOL-BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Pat, this is Lilly's response to your information requests. Thanks.

cc: Original NDA 21-017
HFD-510/Div. Files

SIGNATURE OF REQUESTER:

ISI

METHOD OF DELIVERY (Check one):

MAIL

HAND

NATURE OF RECEIVER:

ISI

SIGNATURE OF DELIVERER:

ISI