NDA 21-017
NDA 21-018

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

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

We acknowledge receipt of your submissions dated February 8 and 17, April 20, May 28, July 8, August 4, September 10, 21, 24, 30 (2), October 22, 25 (2), 27, 29 (3), and November 8 (2), 9 (2), 10, and 22, and December 1, 8, 9, 16, and 21, 1999.

New drug application NDA 21-017 provides for the use of Humalog Mix 75/25 (75% insulin lispro protamine suspension and 25% insulin lispro [rDNA] injection) for the treatment of patients with diabetes mellitus for the control of hyperglycemia.

New drug application NDA 21-018 provides for the use of Humalog Mix 50/50 (50% insulin lispro protamine suspension and 50% insulin lispro [rDNA] injection) for the treatment of patients with diabetes mellitus for the control of hyperglycemia.

We have completed the review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert for Humalog Mix 75/25 and Humalog Mix 50/50 submitted December 21, 1999, patient package insert

(for vials and pens) for Humalog Mix 75/25 submitted December 16, 1999, patient package insert (for cartridges) for Humalog Mix 75/25 submitted December 21, 1999, patient package insert (for vials, cartridges, and Pens) submitted December 16, 1999, immediate container and carton labels submitted December 9, 1999). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL for each NDA as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-017 or NDA 21-018." Approval of these submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitment specified in your submission dated November 22, 1999. This commitment, along with any completion dates agreed upon, is listed below.

For both NDAs, you will re-evaluate the lower assay limit [ ] when a sufficient number of lots have been analyzed to perform a suitable statistical analysis. A limit of [ ] appears to be more appropriate. In your November 22, 1999, submission, you have committed the following time lines to meet your Phase 4 commitment:

Protocol Submission:	Within six months following approval.
Study Start:	Immediately following approval of the protocol. The study will include stability data that you are currently collecting as well as data from additional manufactured lots.
Final Report Submission:	Based on a preliminary report that will be included in the first annual report, a commitment to the number of additional lots or the additional time necessary to complete the final report will be provided.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitment, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to this Phase 4 commitment must be clearly designated "Phase 4 Commitment."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the

Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

Please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.
We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

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