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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-717/S-035

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 supplemental new drug application dated January 28, 2002, received January 29, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Humulin® N/R Mixture 70/30 (70% human insulin [rDNA origin] isophane suspension and 30% human insulin [rDNA origin] injection).

We acknowledge receipt of your submission dated January 31, 2002.

This supplemental new drug application provides for the importation and distribution of three lots (FF1CS7, FFICS8, and FF1CC7) of Humulin® N/R Mixture 70/30 vials produced at the Fegersheim, France facility.

We have completed the review of this supplemental application, and it is approved.

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, call Julie Rhee, Regulatory Project Manager, at (301) 827-6424.

Sincerely,

{See appended electronic signature page}

Stephen K. Moore, Ph.D.
Chemistry Team Leader I
Division of Metabolic
and Endocrine Drug Products, HFD-510
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
	DMEDP II, HFD-510	19-717
3. NAME AND ADDRESS OF APPLICANT		4.SUPPLEMENT NUMBER, DATE
Eli Lilly and Co. Lilly Corporate Center Indianapolis IN 46285		19-717, SCS-035, 28-Jan-02
5. NAME OF THE DRUG	6. NONPROPRIETARY NAME	7. AMENDMENTS, REPORT, DATE
Humulin® 70/30 N/R Mixture	70% human insulin isophane suspension and 30% human insulin injection, rDNA origin	19-717, SCS-035 BC, 31-Jan-02

8. SUPPLEMENT PROVIDES FOR:

The importation and distribution of three lots (FF1CS7, FF1CS8 and FF1CC7) of Humulin N/R Mixture 70/30 vials produced at the Fegersheim, France facility.

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Hyperglycemia treatment	OTC	
12. DOSAGE FORM	13. POTENCY	
Injection	100 U/ml	
14. CHEMICAL NAME AND STRUCTURE		
See Chemistry Review #1		

15. COMMENTS

This supplement was submitted and filed as a PAS-Expedited Review Requested. The applicant is requesting to import three lots of Humulin N/R Mixture 70/30 vials manufactured at the Fegersheim, France facility because of the ongoing cGMP deficiencies at their Indianapolis fill/finish plant. The lot numbers for the import batches are FF1CS7, FF1CS8 and FF1CC7. The Fegersheim facility is approved to manufacture 1.5 and 3.0 mL cartridges and Humulin N and Humalog vials but not 70/30 vials.

The sponsor provided a side-by-side summary outlining the differences between vials manufactured at Fegersheim vs Indianapolis. The salient differences are the pH of the drug product, the lack of testing for nitrogen and an HPLC-identity testing at the Indianapolis site. Indianapolis manufactures the product to meet a pH range between 7.0-7.8 and Fegersheim between 6.9-7.5. Once the lots have been transported to the U.S., the applicant will test for identity and total nitrogen then notify the agency in writing of results of this test for all three lots, which must meet the approved specifications. The COA was provided for the three lots and all test results were within the approved NDA specifications for Humulin 70/30. The three lots were tested for pH and the results were 7.31, 7.34, and 7.37, which meet specifications. Continued.

16. CONCLUSION AND RECOMMENDATION

The sponsor has satisfactorily provided assurance that the 3-lots of 70/30 drug product meets the U.S. approved NDA specifications. Issue and Approval letter.

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
JANICE T. BROWN		04-Feb-02

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15. Continued

At the agency request, in-process control results were submitted for the three lots, side-by-side identification of methods used for testing at release, and clarification of test used for filling uniformity. In-process control results were within the approved specifications, lot release methods were either identical or the approved alternate test. The three lots were analyzed for uniformity of filling by the biuret test. The range of individual vials results were as follows: lot FF1CS7: 98.5-100.6%; lot FF1CS8: 98.8-100.9%, and lot FF1CC7: 97.6-101.6% and is acceptable.

The applicant also provided a side-by-side comparison of Fegersheim and Indianapolis batch formula (500-L), approved specifications, manufacturing process, in-process controls, packaging components, process flow chart, and transport information and labels. The transport between facilities to and from the airport is by a controlled temperature truck. Vials are transported between countries by airline in a insulated air container with a temperature recorder. The temperature is monitored by a recording device, which is reviewed by appropriate Lilly personnel. The product must stay between 2-24°C for no more than 72-hours or 2-8°C without any time limitations. The 2-24°C temperature range is within the approved "in-use" stability period and 2-8°C is an approved storage temperature. Upon reciept, an HPLC identity and nitrogen test will be performed at the Indianapolis facility. Vials will be labeled with the currently approved NDA label and cartoned in the Indianapolis facility. Vials will bear the 24-month expiry.

The sponsor has committed to put one lot of Humulin N/R Mixture 70/30 vials manufactured at Fegersheim into their approved stability program. There are no other issues that would prevent approval of this supplement.

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

/s/

Janice Brown
2/4/02 05:18:15 PM
CHEMIST

Stephen Moore
2/4/02 05:24:16 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL