NDA 21-081

Aventis Pharmaceuticals Inc.
Attention: J. Michael Nicholas, Ph.D.
Director, US Regulatory Affairs
Marketed Products
P.O. Box 9627
Kansas City, MO 64134-0627

Dear Dr. Nicholas:

Please refer to your new drug application (NDA) dated April 9, received April 23, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lantus™ (insulin glargine [rDNA origin] injection).

We acknowledge receipt of your submissions dated May 13, June 4, 10, 15, and 18, July 6, August 24, September 2, October 4, 18, and 21, November 4 and 22, and December 2, 21, 22, and 29, 1999, and January 6 (2), 7, 10, 13, 14, 17, 18, and 31, February 4, 9, 24 (3), 28, and 29, March 2 (2), 3, 6, 8, 13, 14 (2), 15 (2), 16, 30, and 31, and April 10, 12, 18, and 20, 2000.

This new drug application provides for the use of Lantus™ (insulin glargine [rDNA origin] injection) for once-daily subcutaneous administration in the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

This new drug application also provides for the OptiPen™ One Insulin Delivery Device for use with Lantus™ cartridges.

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

The final printed labeling (FPL) must be identical to the submitted draft labeling ((1) package insert submitted April 20, 2000, (2) patient package inserts [for vials and cartridges] submitted April 20, 2000, (3) OptiPen™ One User Manual dated April 18, 2000, and (4) immediate container and carton labels [for 5 mL and 10 mL vials and 3 mL cartridges] submitted April 18, 2000). 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 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 21-081." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your clinical Phase 4 commitment specified in your submissions dated March 14, 2000, and chemistry, manufacturing, and controls Phase 4 commitment specified in your submission dated March 6, 2000. These commitments, along with any completion dates agreed upon, are listed below.

1. To compare the percentage of patients with type 2 diabetes with ≥ 3-step progression in the Early Treatment Diabetic Retinopathy Study scale during treatment with either once-daily Lantus™ or twice-daily NPH human insulin (March 14, 2000, submission):

   Final Protocol Submission: October 2000
   First patient randomized: January 2001
   Study end date: October 2004
   Final Report Submission: April 2005

2. To re-evaluate the [ ] for the insulin glargine content when the 24-month stability data on the primary stability lots of drug substance are available (March 6, 2000, submission):

   Protocol Submission: Submitted in the original NDA
   Study Start: Study on-going
   Final report submission: No later than May 31, 2000

3. To re-evaluate the [ ] related to the drug substance when the 24-month stability data on the primary lots of insulin glargine drug substance are available (March 6, 2000, submission).

   Protocol Submission: Submitted in the original NDA
   Study Start: Study on-going
   Final report submission: No later than May 31, 2000

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 these Phase 4 commitments should 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 note that you have fulfilled the pediatric study requirement at this time for children aged 6 or older. We are waiving the pediatric study requirements for children less than 6 years old for this action on this application.

In addition, 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 send one copy to the Division of Metabolic and Endocrine Drug Products 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, call Julie Rhee, Regulatory Project Manager, at (301) 827-6424.

Sincerely,

John K. Jenkins, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research