DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-481

Hoffman-La Roche, Inc.
Attention: Robin L. Conrad
Program Director, Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Conrad:

Please refer to your new drug application (NDA) dated September 13, 2002, received September 16, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fuzeon™ (enfuvirtide) for injection, 90 mg.

We acknowledge receipt of your submissions dated June 24, 2002 (2), June 26, 2002 (3), July 1, 2002, July 16, 2002, July 24, 2002, July 30, 2002, August 13, 2002, August 22, 2002, September 10, 2002, September 13, 2002, September 27, 2002, October 7, 2002, October 11, 2002, October 23, 2002, October 24, 2002, October 31, 2002, November 1, 2002, November 12, 2002, November 15, 2002 (2), November 19, 2002, November 20, 2002, November 26, 2002, December 5, 2002, December 19, 2002, January 10, 2003, January 14, 2003 (2), January 17, 2003, January 21, 2003, January 22, 2003 (2), January 30, 2003, January 31, 2003, February 4, 2003 (2), February 5, 2003, February 6, 2003 (2), February 10, 2003 (3), February 11, 2003, February 14, 2003, February 21, 2003, February 27, 2003 (3), March 4, 2003, March 6, 2003, March 7, 2003, March 10, 2003, and March 12, 2003 (3).

This new drug application provides for the use of Fuzeon™ (enfuvirtide) for injection, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in treatment experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

We completed our review of this application, as amended, according to the regulations for accelerated approval. It is approved, effective on the date of this letter, for use as recommended in the agreed upon enclosed labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, text for the injection instructions, and immediate container and carton labels). 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 an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this

submission "**FPL for approved NDA 21-481**." Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your postmarketing study commitment specified in your submission dated September 13, 2002. This commitment, along with any completion dates agreed upon, is listed below.

- By December 31, 2003, please submit study reports for the 48 week data of the two ongoing Phase 3 studies, T20-301 and T20-302.

Submit final study reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing study commitment must be clearly designated "Subpart H Postmarketing Study Commitments."

In addition, we note your following postmarketing study commitments, specified in your submission dated March 12, 2003, which are not conditions of the accelerated approval. These commitments are listed below:

Clinical and Pharmacology/Toxicology

1. Please submit the complete protocol for the clinical cohort study you have described in outline form, *"Observational Cohort Study on the Incidence of Pneumonia in HIV-1 Infected Patients Treated with Fuzeon."* Following FDA review, this study will be initiated shortly after the product launch of enfuvirtide and completed in a time frame specified in the protocol.

   Protocol Submission: Within 4 months of the date of this letter
   Final Report Submission: Within 48 months of the date of this letter

2. Please conduct a general-purpose immune suppression screening assay, such as a T-cell dependent antibody-forming assay, and provide the results within 12 months of the date of this letter. If results of this study show evidence of impairment of immune response, a more specific host resistance assay using an appropriate animal model for upper-respiratory bacterial infections must be conducted.

   Protocol Submission: Within 3 months of the date of this letter
   Final Report Submission: Within 12 months of the date of this letter

3. Please submit the results of study T20-305, *"Intervention substudy: A Phase 3, Open-label Safety Study of T-20/Ro 29-9800 (HIV-1 fusion inhibitor) in combination with Oral Antiretrovirals, in Patients Who are Unable to Construct a Viable Regimen"*, with appropriate suggested changes to the package insert and all patient educational materials based on the results of this study. Additional follow-up studies may be needed to formally assess interventions that may reduce the occurrence or severity of local injection site reactions.

   Final Report Submission: Within 9 months of the date of this letter

Pharmacokinetics

4. Provide additional pharmacokinetic data in children less than six years old.

   Protocol Submission: Within 4 months of the date of this letter
   Final Report Submission: Within 28 months of the date of this letter

5. Evaluate the effect of impaired renal function (creatinine clearance less than 35 mL/minute) on enfuvirtide pharmacokinetics.

   Protocol Submission: Within 4 months of the date of this letter
   Final Report Submission: Within 24 months of the date of this letter

Microbiology

6. Please evaluate the effect of possible alterations in viral tropism on virulence. Submit the completed evaluation within 18 months of the date of this letter.

7. In patients who failed virologically in Studies T20-301 and T20-302, please sequence the entire gp160 sequence of paired isolates to identify the genetic determinants that contribute to the phenotypic resistance. Submit your results within 15 months of the date of this letter.

Chemistry, Manufacturing, and Controls

8. During the course of the next year, please make efforts to increase the purity of the enfuvirtide drug substance by changing the current synthesis and/or purification procedures and provide the results in the first annual report after marketing approval.

9. Per your amendments dated January 22, 2003 and February 27, 2003, please reevaluate the currently agreed-upon acceptance criteria for impurities in the drug substance specification and for degradation products in the drug product specification after manufacturing additional batches of the drug substance and drug product during the next year. Please submit your conclusions and any recommended changes to the acceptance criteria within 12 months of the date of this letter, using the submission recommendations in the Guidance on *"Changes to an Approved NDA or ANDA."*

The following is not a postmarketing commitment, but in your letter dated March 12, 2003, you agreed to include an integrated assessment of adverse reactions with each post approval quarterly mandated report. The assessment should include all reports of adverse events from ongoing clinical trials, postmarketing spontaneous reports, and literature reports. Particular attention should be paid to infectious complications, hypersensitivity reactions, and atypical injection site reactions. The assessment should also include any suggested changes to the product insert and all patient educational materials based on the integrated review. This requirement will be reassessed 36 months from the date of this letter.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected

summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

As required by 21 CFR 314.550, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of all promotional materials directly to:

Division of Drug Marketing, Advertising
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. A Written Request for Fuzeon was issued on January 19, 2001.

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Virginia L. Yoerg, Regulatory Health Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, M.D., M.P.H.
Director
Office of Drug Evaluation 4
Center for Drug Evaluation and Research

Enclosure: Package Insert, Patient Package Insert, and Injection Instructions

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

/s/

Mark Goldberger

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