DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-304/S-001

Hoffman-La Roche Inc.
Attention: Charles Lee
Sr. Program Manager
Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Mr. Lee:

Please refer to your supplemental new drug application dated November 11, 2002, received November 12, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Valcyte™ (valganciclovir hydrochloride) 450 mg Tablets.

We acknowledge receipt of your submissions dated:

November 11, 2002 (2)	March 6, 2003	July 18, 2003	August 29, 2003
January 17, 2003	April 11, 2003 (2)	July 21, 2003 (2)	September 4, 2003 (6)
January 29, 2003 (2)	April 17, 2003	August 1, 2003	September 5, 2003 (3)
February 5, 2003	April 22, 2003	August 8, 2003 (2)	September 9, 2003 (3)
February 10, 2003	May 7, 2003	August 11, 2003	September 10, 2003
February 11, 2003	May 9, 2003	August 21, 2003	September 11, 2003 (4)
February 14, 2003	May 23, 2003	August 22, 2003	
February 28, 2003	July 3, 2003	August 27, 2003	

This supplemental new drug application provides for the use of Valcyte™ (valganciclovir hydrochloride) 450 mg Tablets for the prevention of cytomegalovirus (CMV) disease in kidney, heart, and kidney-pancreas transplant patients at high risk (Donor CMV seropositive/Recipient CMV seronegative).

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert submitted September 10, 2003).

Please submit the FPL electronically 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, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-304/S-001." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated September 11, 2003. These commitments are listed below.

1. Perform UL54 gene sequencing for all day 100 and suspected CMV disease samples from study PV16000, previously analyzed by UL97 sequencing and not found to contain UL97 resistance or novel mutations.

Study Start:	Ongoing
Submission of sequencing results:	Within 10 months of the date of this letter

2. Analyze the six novel UL97 mutations observed in study PV16000 via marker transfer experiments.

Study Start:	Ongoing
Submission of experimental results:	Within 18 months of the date of this letter

3. Perform resistance testing in an open randomized study to evaluate the efficacy and safety of oral valganciclovir versus intravenous ganciclovir for the treatment of CMV disease in adult solid organ transplant recipients. Samples for the investigation of emergence of drug resistance will be collected pre-treatment, at end-of-treatment (pre-maintenance) and at end of maintenance therapy.

Protocol Submission:	Within 2 months of the date of this letter
Study Start:	Within 5 months of the date of this letter
Final Report Submission:	Within 40 months of the date of this letter
Submission of Resistance Analysis:	Within 51 months of the date of this letter

4. Perform resistance testing in a study to assess the safety and pharmacokinetics of valganciclovir syrup formulation when administered as prophylaxis for CMV disease in pediatric solid organ transplant recipients. Samples for the investigation of emergence of drug resistance will be collected from all patients on day 100 (end of study drug prophylaxis) and from those patients presenting with suspected CMV disease.

Protocol submission:	Within 2 months of the date of this letter
Study start:	Within 5 months of the date of this letter
Final study report:	Within 30 months of the date of this letter
Submission of Resistance Analysis:	Within 34 months of 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."

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. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. We also remind you of the amended Pediatric Written Request issued on November 6, 2001.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send 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-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

As stated in your submission dated September 11, 2003, we expect that you will distribute the agreed-upon “Dear Health Care Provider” letter within three weeks of the date of this letter. We request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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

If you have any questions, please call Nitin Patel, R.Ph., Regulatory Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosures: Final Printed labeling (product package insert and patient package insert)

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See next page

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/s/

Debra Birnkrant
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