DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-628/S-020

Hoffmann-LaRoche, Inc
Attention: Matthew W. Lamb
Program Manager, Global Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Mr. Lamb:

Please refer to your supplemental new drug application dated February 20, 2003 and received February 24, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for INVIRASE® (saquinavir mesylate) 200 mg Capsules.

We acknowledge receipt of your submissions dated:

August 8, 2003	September 11, 2003
August 21, 2003	October 2, 2003
September 5, 2003	October 15, 2003
September 8, 2003	December 16, 2003

This supplemental new drug application provides for the use of INVIRASE (1000 mg twice daily) coadministered with ritonavir (100 mg twice daily) and in combination with other antiretroviral drugs, for the treatment of HIV infection. This new dosing regimen replaces the previously approved regimen for INVIRASE.

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 attached labeling (text for the package insert and text for the patient package insert) dated December 24, 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 20-628/S-020**". Approval of submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated December 23, 2003. These commitments are listed below.

1. Conduct a drug interaction study with the 1000 mg saquinavir plus 100 mg ritonavir twice-daily regimen and ketoconazole (400 mg daily) and provide dosing recommendations for both ketaconazole and saquinavir plus ritonavir.

Protocol Submission Date:	September 2004
Study Start Date:	November 2004
Final Study Report Submission Date:	November 2005

2. Conduct a drug interaction study with the 1000 mg saquinavir plus 100 mg ritonavir twice-daily regimen and methadone and provide dosing recommendations for both methadone and saquinavir plus ritonavir.

Protocol Submission Date:	June 2004
Study Start Date:	August 2004
Final Study Report Submission:	August 2005

3. Conduct a drug interaction study with the 1000 mg saquinavir plus 100 mg ritonavir twice-daily regimen and rifampicin and provide dosing recommendations for both rifampicin and saquinavir plus ritonavir.

Protocol Submission Date:	September 2004
Study Start Date:	November 2004
Final Study Report Submission:	November 2005

4. Conduct a drug interaction study with the 1000 mg saquinavir plus 100 mg ritonavir twice-daily regimen and efavirenz and provide dosing recommendations for both efavirenz and saquinavir plus ritonavir.

Protocol Submission Date:	September 2004
Study Start Date:	November 2004
Final Study Submission Date:	November 2005

5. Conduct a study to assess the saquinavir plus ritonavir combination regimen in subjects with hepatic impairment.

Protocol Submission Date:	June 2004
Study Start Date:	September 2004
Final Study Submission:	March 2006 (assuming a one-year recruitment period)

6. Submit the final study report containing both safety and efficacy data from the MaxCmin 2 study.

Final Study Report Submission Date:	July 2004

7. Submit phenotypic and genotypic data from the MaxCmin1 and MaxCmin 2 studies. The data should include phenotypic susceptibility and HIV-1 genotypes at baseline and sequential changes during treatment with ritonavir boosted saquinavir.

MaxCmin 1 Protocol:

Final Study Report Submission Date:	July 2004

MaxCmin 2 Protocol:

Final Study Report Submission Date:	July 2004

8. Submit data on the *in vitro* combination effects (*e.g.* additive, synergistic, or antagonistic) of saquinavir with all approved antiretroviral agents.
   Final Report Submission Date: September 2004

9. Submit pharmacokinetic analyses and data from study PACTG 397.
   Final Report Submission Date: September 2004

(b)(4)

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final study 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, the 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**."

In addition, please 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

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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, please call Marsha Holloman, Regulatory Health Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Jeffrey S. Murray, MD, MPH
Deputy Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure Marked-up printed labeling (product package insert and patient package insert)

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

/s/

Jeffrey Murray

12/24/03 03:42:23 PM