DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

March 2, 1999

Alex Wesolowski
Roche Molecular Systems, Inc.
1080 US Highway 202
Branchburg, NJ 08876

Re: BP950005\3
Product: Roche AMPLICOR HIV-1 MONITOR™ Test

Date Received: 24-Jun-97
Amended: 10-Apr-98

Dear Mr. Wesolowski:

The Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA) has completed its review of your response of April 10, 1998 to our comments. We are pleased to inform you that your premarket approval application (PMA) supplement for the AMPLICOR HIV-1 MONITOR™ Test intended to be used as an aid in management of patients on anti-viral therapy for HIV disease is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The post-approval conditions to which you have agreed in your December 14, 1998 faxed letter include the following:

The Intended Use Statement should be modified to read as follow:

The AMPLICOR HIV-1 MONITOR™ Test is an in vitro nucleic acid amplification test for the quantitation of Human Immunodeficiency Virus Type 1 (HIV-1) RNA in human plasma. The test is intended for use in conjunction with clinical presentation and other laboratory markers of disease progress for the clinical management of HIV-1 infected patients. The test can be used to assess patient prognosis by measuring the baseline HIV-1 RNA level or to monitor the effect of antiviral therapy by serial measurement of plasma HIV-1 RNA levels during the course of antiviral treatment. Monitoring the effects of

antiviral therapy by serial measurement of plasma HIV-1 RNA has been validated for patients with baseline viral loads ≥25,000 copies/mL.

The AMPLICOR HIV-1 MONITOR™ Test is not intended to be used as a screening test for HIV or as a diagnostic test to confirm the presence of HIV infection.

The Procedure Limitations should be modified to read as follows:

Monitoring the effects of antiviral therapy by serial measurement of plasma HIV-1 RNA has only been validated for patients with baseline viral loads ≥25,000 copies/mL.

1. The AMPLICOR HIV-1 MONITOR™ Test can be used to accurately detect a 0.5 $\log_{10}$ (3-fold) or greater change in HIV-RNA for patients whose viral load is ≥1000 copies/mL. The test can accurately detect a 0.78 $\log_{10}$ (6-fold) or greater change in HIV-1 RNA for patients whose viral load is below 1000 copies/mL. Changes in viral load below this level may not be clinically relevant.

2. Reliable results are dependent on adequate specimen collection, transport, storage and processing procedures.

3. This test has been validated for use only with human plasma anticoagulated with EDTA or ACD. Heparin inhibits PCR; specimen collected using heparin as the anticoagulant should not be used with the AMPLICOR HIV-1 MONITOR Test.

4. The presence of AmpErase® in the AMPLICOR HIV-1 MONITOR Master Mix reduces the risk of amplicon contamination. However, contamination from HIV positive controls and HIV- positive clinical specimens can be avoided only by good laboratory practices and careful adherence to the procedures specified in this insert.

5. Use of this product should be limited to personnel trained in the techniques of PCR.

6. Only the Perkin-Elmer Gene Amp PCR System 9600 or Gene Amp PCR System 2400 thermal cyclers can be used with this protocol.

7. As with any diagnostic test, results from the AMPLICOR HIV-1 MONITOR Test should be interpreted with consideration of all clinical laboratory findings.

CBER will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

Document Control Center (HFM-99)
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852-1448

If you have any questions concerning this approval order, please contact Dr. Sayah Nedjar at (301) 827-3524.

Sincerely,

for Mark Heintzelman

Jay S. Epstein, M.D.
Director
Office of Blood Research and Review
Center for Biologics
Evaluation and Research

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to Document Control Center (HFM-99), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, Maryland 20852-1448

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the **addition** of, but **not the replacement** of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment

by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." **This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.**

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual post-approval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the changes. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POST-APPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of post-approval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Post-approval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the Document Control Center (HFM-99), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, Maryland 20852-1448. The post-approval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

   (a) Unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

   (b) Reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report

identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to Medwatch (HF-2), Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20852-9787 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) Has not been addressed by the device's labeling or

(b) Has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Post-approval Reports" above unless specified otherwise in the conditions of approval to this PMA. This post-approval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990, which became effective on July 31, 1996, and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

(1) May have caused or contributed to a death or serious injury; or

(2) Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the

malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10 (c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc.

Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
P. O. Box 3002
Rockville, MD 20847-3002

Copies of the MDR Regulation (FOD # 336 & 1336) and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD #509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at 800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers Assistance (DSMA) at 301-443-8818.