EXHIBIT B

Roche Molecular Systems
A Member of the Roche Group

Roche Molecular Systems, Inc.
1080 U.S. Highway 202
Branchburg, New Jersey 08876-1760

Direct Dial 908-253-7540

March 8, 1996

Kathryn C. Zoon, Ph.D.
Director, Center for Biologics Evaluation and Research
Center for Biologics Evaluation and Research
Document Control Center (HFM-99)
Woodmont Office Center, Suite 200N
1401 Rockville Pike
Rockville, Maryland 20852-1448

Re: Amendment to PMA BP950005
Roche AMPLICOR HIV MONITOR™ Test

Dear Dr. Zoon:

Roche Molecular Systems, Inc., hereby submits this amendment to the Premarket Approval Application for the Roche AMPLICOR HIV MONITOR Test. The AMPLICOR HIV MONITOR Test is an in vitro diagnostic device intended for use in the quantitation of HIV-1 RNA in human plasma.

The information contained in this amendment is in support of the intended use of the AMPLICOR HIV MONITOR Test for monitoring the effects of antiretroviral drug therapy.

Please note that Section VI.C.16 of this amendment contains letters from two drug manufacturers, Hoffmann-La Roche Inc., and Merck & Co., Inc., authorizing CBER to cross-reference their protease inhibitor NDA submissions in support of PMA BP950005 sponsored by Roche Molecular Systems, Inc.

The information contained in this Premarket Approval Application constitutes trade secrets and/or is confidential within the meaning of the Federal Food, Drug and Cosmetic Act (21 USC 331 (j)), the Freedom of Information Act (5 USC 1002), or the Trade Secrets Act (18 USC 1905). This information may not be revealed or disclosed without the written consent of Roche Molecular Systems, Inc.

Please contact me directly at the number listed above with any questions on this amendment.

Very truly yours,

Alex Wesolowski
Director, Regulatory and Clinical Affairs

/aw
96-001
Enclosure

Roche Molecular Systems, Inc.
1080 U.S. Highway 202
Somerville, NJ 08876-3771

PMA BP950005

Premarket Approval Application for the
AMPLICOR HIV MONITOR™ TEST

Classification Name:	At the present time there is no official FDA classification for the product class which includes nucleic acid amplification-based *in vitro* diagnostic devices for the quantitative measurement of HIV RNA in human plasma or human serum.
Device Trade Name:	AMPLICOR HIV MONITOR™ TEST
Previous Submissions:	The AMPLICOR HIV MONITOR Test has not been the subject of any previous submissions or reclassification petitions to FDA.
Indications For Use:	The AMPLICOR HIV MONITOR™ *Test* is an *in vitro* nucleic acid amplification test for the quantitation of Human Immunodeficiency Virus (HIV) RNA in human plasma. The test ***is intended for use*** in conjunction with clinical presentation and other laboratory markers ***as an indicator of disease prognosis,*** as an aid in ***monitoring the effects of antiretroviral therapy on plasma HIV-RNA levels and as a surrogate marker for clinical endpoints in*** HIV infected individuals. The AMPLICOR HIV 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.
Site of Manufacture:	Roche Diagnostic Systems, Inc. 11 Franklin Avenue Belleville, New Jersey 07109-3597 Establishment Registration Number - 2250097
FDA Inspection Dates:	The latest FDA inspection was performed by the New Jersey District Office on ***November 20-21, 1995***.

TABLE OF CONTENTS

Amendment to
Premarket Approval Application BP950005
AMPLICOR HIV MONITOR™ Test

Vol. / Page

I. Cover Page ..... *i*

A. Name and Address of Applicant
B. Signature of Applicant or Authorized Representative
C. Classification (Genetic) Name of the Device (if applicable)
D. Device Trade Name
E. Identifying Numbers of All Previous Submissions for this Device
F. Indications for Use
G. Name and Address of Manufacturing Site(s)
H. FDA Inspection Information

II. Table of Contents ..... *ii*

III. Summary of Clinical Evaluations and Information in PMA *1 001*

A. Indications for Use - Revised Sections

1. Intended Use *1 002*
2. Intended Patient Population *1 003*
6.1 Viral Subtypes Detected - Effects on Quantitation *1 004*
7. Disease Associated with Human Immunodeficiency Virus (HIV) *1 007*
9. Relevant Medical and Public Health Issues *1 008*

D. Marketing History - Revised Sections *1 010*

1. Brief Description of US and Foreign Marketing History *1 011*
2. List of Countries in Which the Product is Being Marketed *1 012*
3. List of Countries in Which the Product has been Withdrawn *1 013*
4. Reports of Device Failures and Adverse Events *1 014*

E. Adverse Effects of the Device on Health - Revised Sections *1 015*

1.1 Relationship of HIV Viral Burden to Prognosis Therapeutic Efficacy *1 016*
3.1 References *1 017*

F. Summary of Studies - Revised Sections *1 019*

2.1 Summaries of Non-Clinical Laboratory Studies *1 020*
4.1 Summary of Clinical Investigations *1 023*

G. Conclusions Drawn from the Studies - Revised Sections 1 033

H. Summary of Safety and Effectiveness 1 040

IV. Device Characteristics on Manufacturing Section - Revised Section 1 073

C. Description of the Properties of the Device Relevant to the Diagnosis, Treatment,Prevention, Cure, or Mitigation of a Disease or Condition 1 074

E. Description of Methods, Facilities, and Controls Used in the Manufacture Processing, Packing, Storage and Installation of the Device 1 075

VI. Technical Sections

A. Non-Clinical Laboratory Studies - Revised Sections 1 077

5.1 Validation of Assay Specificity 1 078
6. Interference Studies 1 082

C. Clinical Evaluations 1 096

1. Comparison of AMPLICOR HIV MONITOR Kit Formats 1 097
Attachment VI.C.1 ..... 1 099
2. Clinical Protocols 1 111
3. Number of Investigators 1 132
4. Subject Selection and Exclusion Criteria 1 137
5. Study Population 1 142
6. Study Period 1 146
7. Safety and Effectiveness Data 1 149
8. Adverse Reactions and Complications 1 150
9. Patient Discontinuation 1 151
10. Patient Complaints 1 152
11. Device Failures and Replacements 1 153
12. Tabulations of Data 1 154
13. Copies of Subject Report Forms for each Subject who did not complete the investigation 1 157
14. Results of Statistical Analysis of Clinical Investigations 1 158
Attachment VI.C.14-1 ..... 1 202
15. Contraindications and Precautions 1 281
16. Other Appropriate Information 1 284
17. Compliance with 21 CFR 52 (IRB Regulations) and 21 CFR 50 (Informed Consent) 1 287
18. Compliance with 21 CFR 812 (IDE Regulation) 1 288
19. References 1 289

VII. One Investigator - Revised Section 1 292

VIII.Bibliography of All Published Reports - Revised Section 1 294

X. Labeling - Revised Section *1 303*

d) Draft Package Insert *1 304*

APPENDIX I - Study NV14255 Line Listings and Longitudinal Data Plots

APPENDIX II - Study NV14256 Line Listings and Longitudinal Data Plots

APPENDIX III - Study NV14255 - Data Tables (6 Books)

APPENDIX IV - Study NV14256 - Data Tables (9 Books)

VI. C. CLINICAL PROTOCOLS

1. *Comparison of AMPLICOR HIV MONITOR KIT Formats*
2. *Clinical Protocols*
3. *Number of Investigators*
4. *Subject Selection and Exclusion Criteria*
5. *Study Population*
6. *Study Period*
7. *Safety and Effectiveness Data*
8. *Adverse Reactions and Complications*
9. *Patient Discontamination*
10. *Patient Complaints*
11. *Device Failures and Replacements*
12. *Tabulations of Data*
13. *Copies of Subject Report Forms for each Subject who did not complete the investigation*
14. *Results of Statistical Analysis of Clinical Investigation Attachment VI.B.14-1*
15. *Contraindications and Precautions*
16. *Other Appropriate Information*
17. *Compliance with 21 CFR 52 (IRB Regulations) and 21 CFR 50 (Informed Consent)*
18. *Compliance with 21 CFR 812 (IDE Regulation)*
19. *References*

1. *COMPARISON OF AMPLICOR HIV MONITOR KIT FORMATS*

The HIV RNA viral load data presented in this Amendment to PMA BP950005 for the AMPLICOR HIV MONITOR Test were collected as part of a clinical program conducted by Hoffmann-La Roche Inc., Nutley, New Jersey, to establish the efficacy of saquinavir in HIV infection. Since the saquinavir phase II/III studies were initiated in March 1993, HIV RNA testing for these studies was performed using the Research Prototype version of the AMPLICOR HIV MONITOR™ Test. Non-clinical studies reported in the original PMA (see Section VI.B.1) have shown that the Research Prototype Test and the proposed commercial AMPLICOR HIV MONITOR Test perform in an equivalent manner. A detailed comparison of the reagent formulations and procedural steps for the Research Prototype and the AMPLICOR HIV MONITOR Test Kit was included in the original PMA (see Section VI.B.1) and is also included in Attachment VI.C.1.

HIV RNA quantitation for the saquinavir clinical studies was performed for Hoffmann-La Roche by Roche Biomedical Laboratories (RBL, now Laboratory Corporation of America, LabCorp), Research Triangle Park, North Carolina, using the Reseach Prototype version of the commercial AMPLICOR HIV MONITOR Test. The Research Prototype test used by RBL was identical to the Research Prototype Test used by RMS in the ACTG 116A and ACTG 116B/117 studies, with the two exceptions noted below. As stated above, the Research Prototype Test as used by both RMS and RBL have been shown to be equivalent to the commercial version of the HIV MONITOR Test.

- *Specimen Preparation*: In the RBL prototype test, the Quantitation Standard (QS) was added to the Specimen Lysis Reagent at an input of 80 copies per PCR reaction and was processed through the entire specimen preparation procedure in a manner identical to the specimen. This procedure is identical to that in the commercial test. In the RMS prototype test, the QS was added to the Resuspension Buffer in the final step of Specimen Preparation.

- *Calculation of HIV RNA Assay Results*: For the RBL prototype test, the external standard curve was extended to an absorbance of 2.2 OD units at 450 nm. For the RMS prototype kit and the commercial kit, the QS absorbance of the selected well must be ≤ 2.0 OD units. However, studies have confirmed that the QS standard curve is linear to at least 2.2 OD units.

The critical aspects of the test procedure and the basis of quantitation were identical for the prototype test used by RMS for the ACTG 116A and 116B/117 studies, the prototype test used by RBL for the saquinavir studies (NV14255 and NV14256), and the proposed commercial AMPLICOR HIV MONITOR Test kit. In addition, the equipment employed in both the Research Prototype test and the proposed commercial Test are equivalent. Data generated in comparative studies and presented in Section VI.A.10 of the original

PMA submission (and reproduced in Attachment VI.C.1 of this amendment) have shown that the Research Prototype and the AMPLICOR HIV MONITOR Tests perform in an equivalent manner. We are therefore confidant that data generated in the NV14255 and NV14256 clinical trials using the Research Prototype test reflect the clinical performance of the proposed commercial AMPLICOR HIV MONITOR Test.

3. *NUMBER OF INVESTIGATORS*

(a) Investigational Sites

Both NV14255 (ACTG 229) and NV14256 were multi-center clinical trials. A listing of the investigational sites by study is provided in Table VI.C.3-1 for NV14255 (ACTG 229) and Table VI.C.3-2 for NV14256.

(b) Patients Enrolled per Study

Study NV14255 was a US phase II double-blind randomized study in ZDV-pretreated patients with advanced HIV infection and included 295 patients (ITT population). Also included in this Amendment are data from a surrogate analysis of 423 patients who had completed at least 16 weeks of treaement (or who had withdrawn prematurely) in the US phase III study - Study NV14256. This study was conducted in ZDV-pretreated patients with advanced HIV infection.

TABLE VI.C.3-1
NV14255 (ACTG 229) STUDY SITES

CLINICAL SITE	*INVESTIGATOR*
Harborview Medical Center University of Washington, Seattle, WA	Ann C. Collier, MD
Ohio State University Hospitals Columbus, OH	Robert J. Fass, MD
Division of Infectious Diseases University of Pennsylvania Philadelphia, PA	Harvey Friedman, MD
Health Science Center University of Colorado, Denver, CO	Robert T. Schooley, MD Daniel Kuhitzkes MD
Stanford University Medical Center School of Medicine, Stanford, CA	Thomas C. Merrigan, Jr., MD
Northwestern University Medical School Chicago, IL	John Phair, MD
University of Texas Medical Branch Galveston, TX	Richard B. Pollard, MD
University of Rochester Medical Center Rochester, NY	Richard C. Reichman, MD
Veterans Administration Medical Center Birmingham, AL	Michael S. Saag, MD
New York University Medical Center Department of Medicine New York, NY	Fred T. Valentine, MD