Larry P. Bell, M.D.
Senior Director
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August 14, 1998

Mr. David M. Moss
Acting Director, Technology Support Service Staff
Office of Information Technology
Center for Drug Evaluation & Research
Food & Drug Administration
5600 Fishers Lane, 8B-11
Rockville, Maryland 20857

MERCK
Research Laboratories

NDA 19-643/S-055: MEVACOR™ (Lovastatin)

Amendment to a Pending Application
Electronic Submission

Dear Mr. Moss:

By copy of this letter, Merck Research Laboratories (MRL) is providing one (1) CD which contains corrections to the electronic copy of the Supplemental New Drug Application/S-055, Lovastatin-AFCAPS/TexCAPS contained in the Compact Disk (CD) delivered to the Technology Support Service Staff (TSSS) on May 12, 1998.

These corrections were previously submitted in hard copy to NDA 19-643 as an Amendment to a Pending Application on August 10, 1998.

The information on this CD [redacted] is to be added on the [redacted] currently installed on the MRL-dedicated network server at the Agency.

Please notify MRL's Regulatory Agency Relations (RAR) Office (301/881-9000) when the file replacement has been successfully completed.

The information submitted in electronic form on this CD may be retained indefinitely by the Agency as an archival copy.

There are three attachments to this letter:

Attachment 1 Installation Instructions detailing how to copy the information on the CD to the [redacted]

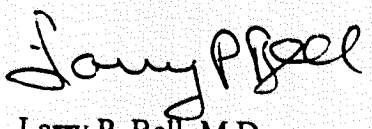
Attachment 2 Documentation regarding the development procedures performed at MRL For this electronic submission.

Attachment 3 A complete list of file names contained on the CD.

During the time that the electronic submission is actively being used, MRL will provide technical support. Any questions relating to this electronic submission should be addressed to me (610/397-2310) or, in my absence, Marie A. Dray (301/881-9000).

Please direct questions or need for additional information to Larry P. Bell, M.D. (610/397-2310) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely,



Larry P. Bell, M.D.
Senior Director
Regulatory Affairs

Attachments and CD (Serial No. 8083 2047 4029)
Federal Express # 1

cc (cover letter only):
Mr. J. D'Ambrosia, Division of Infrastructure Management & Services, HFD-080
Federal Express #2
Mr. K. Edmunds, Division of Technology Support Services Staff, HFD-70
Federal Express #3

cc (cover letter only):
LIST OF REVIEWERS

Dr. D. Orloff, HFD-510, Room 14B-04, Federal Express # 4
Dr. M. Park, HFD-510, Room 14B-04, Federal Express # 4
Dr. J. Mele, HFD-715, Room 14B-45, Federal Express #5
Ms. M. Simoneau, HFD-510, Room 14B04, Federal Express #4

cc (cover letter with attachments): NDA 19-643: MEVACOR™
Dr. Sobel, HFD-510, Room 14B-04 (2 copies), Federal Express #4

q\robinson\murakami\elecsub

Charles L. Hyman, M.D.
Director
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August 10, 1998

DESK COPY

MERCK
Research Laboratories

Solomon Sobel, M.D. - Director
Division of Metabolism and Endocrine
Drug Products HFD-510, Room 14B-04
Office of Drug Evaluation II (CDER)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Sobel:

Supplemental New Drug Application: NDA 19-643/S-055
MEVACOR™ (Lovastatin)

Reference is made to the Supplemental New Drug Application 19-643/S-055 for MEVACOR™ (Lovastatin) submitted on April 28, 1998. Reference is also made to a telephone conversations on July 31, 1998 between Dr. Charles Hyman, Merck Research Laboratories (MRL) and Drs. David Orloff and Mary Parks, and Ms. Margaret Simoneau, FDA, regarding this supplemental application.

Merck has identified an error in an appendix to the Clinical Study Report (CSR) for the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS, Protocol No. 042). Appendix 4.6.3 is an Adverse Event (AE) Counts production table entitled "Patient Counts of Adverse Experiences (AE Summary)." Appendix 4.6.3 was provided as a data source for Tables 62, 64 and 66 of the AFCAPS/TexCAPS CSR. However, it is not possible to recreate these three CSR tables from the AE Counts production table as it is currently represented by Appendix 4.6.3.

The AE Counts production table represented by Appendix 4.6.3 in the April 28, 1998 filing was generated using AEs reported during baseline, treatment and follow-up periods, and also pooled AEs that were serious, lead to discontinuation and drug-related. However, in the CSR the AE Counts Tables reported only AEs occurring during the treatment and follow-up periods and separated counts for serious (Table 62), drug-related (Table 64), and leading to discontinuation for AEs (Table 66) occurring in > 0.2% of either the lovastatin or placebo groups.

With this letter, MRL is correcting this error by submitting three additional and individual AE Counts production tables generated from data accrued during the treatment and follow up period (Serious AE Counts, Drug Related AE Counts, and Resulting in Discontinuation AE Counts). With these AE Count production tables the reviewer will be able to recreate Tables 62, 64 and 66 reported in the AFCAPS/TexCAPS CSR. These three additional production tables are to be inserted in Appendix 4.6.3. between the cover page for Appendix Category 4 Data for Appendix 4.6 Adverse Events and the Adverse Event (AE) Counts production table entitled "Patient Counts of Adverse Experiences (AE Summary)."

A Table of Contents is also included for Appendix 4.6.3 as it will now contain four AE Counts production tables as follows:

1. **SERIOUS ADVERSE EXPERIENCE COUNTS** - Number (%) of Participants With Serious Adverse Experiences

2. **DRUG RELATED ADVERSE EXPERIENCE COUNTS** - Number (%) of Participants With Drug-Related Adverse Experiences

3. **RESULTING IN DISCONTINUATION ADVERSE EXPERIENCE COUNTS** - Number (%) of Participants With Adverse Experiences Leading to Discontinuation From Therapy

4. **COMBINED TABLE** - PATIENT COUNTS OF ADVERSE EXPERIENCES THAT ARE ONE OF THE FOLLOWING: SERIOUS, DRUG-RELATED, RESULTING IN DISCONTINUATION OR CONFIRMED ENDPOINT RELATED AES (As originally provided with the April 28, 1998 Submission)

The AFCAPS/TexCAPS CSR and its appendices appear twice in the SNDA/S-055 for MEVACOR™ (Lovastatin) submitted on April 28, 1998. Appendix 4.6.3 is found under Clinical Documentation (hard copy Volume 3, starting page 1207) and under Statistical Documentation (hard copy Volume 7, starting page 1258). Therefore, two copies of the Table of Contents for Appendix 4.6.3 and the three new AE Counts production tables are attached for insertion in the April 28, 1998 filing as follows:

Item 8	Volume number	Affected Document	Revision	Pages to be Inserted
Clinical Documentation A. MRL Clinical Study Report: A Randomized Double-Blind, Placebo-Controlled Trial of the Effect of Lovastatin on the Incidence of Primary Coronary Heart Disease in Patients With Mild to Moderate Elevations in Total and LDL-Cholesterol in Combination With Low HDL-Cholesterol (Protocol 042).	3	Appendix 4.6.3	Insert Table of Contents for Appendix 4.6.3 and three additional AE Counts production tables: 1. Serious AE Counts 2. Drug Related AE Counts 3. Resulting in Discontinuation AE Counts	After page 1206 insert 1206.1 through 1206.32 1206.2-1206.17 1206.18-1206.23 1206.24-1206.32

Table of Contents for Appendix 4.6.3 and the three new AE Counts production tables are attached for insertion in the April 28, 1998 filing as follows (Continued):

Item 10	Volume number	Affected Document	Revision	Pages to be Inserted
Statistical Documentation A. Reference Documents 2. MRL Clinical Study Report: A Randomized Double-Blind, Placebo-Controlled Trial of the Effect of Lovastatin on the Incidence of Primary Coronary Heart Disease in Patients With Mild to Moderate Elevations in Total and LDL-Cholesterol in Combination With Low HDL-Cholesterol (Protocol 042).	7	Appendix 4.6.3	Insert Table of Contents for Appendix 4.6.3 and three additional AE Counts production tables: 1. Serious AE Counts 2. Drug Related AE Counts 3. Resulting in Discontinuation AE Counts	After page 1257 insert 1257.1 through 1257.32 1257.2-1257.17 1257.18-1257.23 1257.24-1257.32

Additional copies are being submitted to Ms. M. Simoneau for distribution to the appropriate Agency personnel for insertion in the review copies of the SNDA/S-055 for MEVACOR™ (Lovastatin) submitted on April 28, 1998.

We apologize for any inconvenience the addition of these pages may have caused to your personnel.

Corrections to the electronic submission associated with the above referenced documentation will be incorporated in to the [redacted] that contains the original electronic submission version of the SNDA/S-055 for MEVACOR™ (Lovastatin) submitted on April 28, 1998. These electronic corrections will be submitted to the Technology Support Service Staff (TSSS) in approximately one week.

As required by Section 306(k)(1) of the Generic Enforcement Act [21 U.S.C. 335a(k)(1)], we hereby certify that, in connection with this application, Merck & Co., Inc. did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.