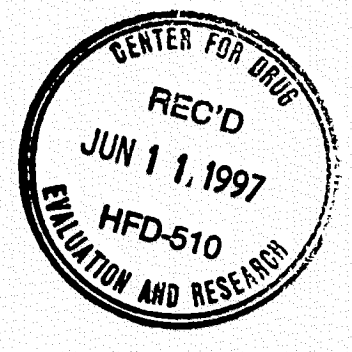
Roche Pharmaceuticals
A Member of the Roche Group

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial (201) 235-4463
Fax (201) 235-7771

June 10, 1997

Ms Maureen Hess, CSO
Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane, Room 14B04
Rockville, MD 20857-1706



Dear Ms. Hess:

Re: NDA 20-766 Xenical® (orlistat) Capsules, 120 mg
Request for Electronic Copy of Draft Labeling

With reference to your request for the above, please find enclosed two computer disks, each containing a copy of the proposed draft labeling for Xenical capsules. The draft labeling provided is a Microsoft Word Version 6.0 file which was converted to WordPerfect Version 6.0, and the filename is 060997.wpd.

We have taken the precaution of scanning each disk for viruses.

If there are any questions concerning this submission, please contact the undersigned at (201) 235-4463.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J Jack

Margaret J. Jack
Program Director
Drug Regulatory Affairs

MJJ/LS:lh
Enclosures
HLR No. 1997-1339

Roche

June 3, 1997

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Attention: Document Control Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20850

Ladies and Gentlemen:

Re: NDA 20-766 - XENICAL® (orlistat) Capsules, 120 mg
Response to FDA Request for Comments of Draft Labeling

Reference is made to the three faxes received from the Agency recommending changes to the draft labeling for Xenical previously submitted in NDA 20-766. These faxes dated March 27, 1997, April 28, 1997 and April 29, 1997 included labeling recommendations from the following reviewers: chemistry, biopharmaceutics, pharmacology and medical. The purpose of this submission is to respond to the labeling recommendations previously provided in these faxes by the Agency review team and to provide a rationale and supporting documentation for labeling text remaining to be resolved between the Sponsor and the Agency.

The draft labeling included in this submission is a composite label of both the recommendations provided by the Agency's review team in the previously cited faxes and labeling text included in the original NDA which was not recommended for change by the same FDA review team. Additions and deletions to this composite label are designated with new or added text having a double underscore and text that the Sponsor feels should be deleted or replaced is struckthrough.

The following section of the labeling have been updated by the Sponsor for the Agency's consideration: CLINICAL PHARMACOLOGY, CLINICAL STUDIES, INDICATIONS AND USAGE, CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION. As previously stated, a brief rationale for the Sponsor's recommendations is also provided. A brief rationale for many of the Sponsor's changes and recommendations to the labeling are also provided.

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

If you have any questions concerning this submission, please contact the undersigned at 201-235-4463 or via fax at 201-235-7771.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J Jack

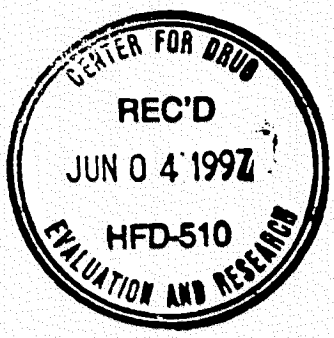
Margaret J. Jack
Program Director
Drug Regulatory Affairs
(201) 235-4463
(201) 235-7771

MMJ/JMD
HLR No. 1997-1260
june3pi.doc

Desk Copies: Ms. Maureen Hess (5)

June 3. 1997

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Attention: Document Control Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20850



Ladies and Gentlemen:

Re: NDA 20-766 - XENICAL® (orlistat) Capsules, 120 mg
Response to FDA Request for Supporting
Documentation for Quality of Life Data In NDA 20-766

Reference is made to the Agency's request for copies of the references cited in the Quality of Life development section of the above-mentioned NDA and for the validation study supporting these data. We are herewith providing the following information in this submission:

1. Complete set of references as outlined in the QOL development section, NDA 20-766, Section 8/10, volume 453, pages 100-101. (These references are located in volume one of this submission.)

2. A copy of the validation study acceptance letter from *Quality of Life Research*, see volume 2.

3. A copy of the validation study manuscript entitled, "Assessing Health-Related Quality-Of-Life and Health State Preference In Persons with Obesity: A Validation Study". The page proofs from the journal are also provided, see volume 2.

4. Copies of the references for the validation study in 3 which were not previously included in volume 1 of this submission are contained in volume 2. Please note that references 10, 12, 20, 25, 28 and 29 were not readily retrievable and will be provided at a latter date. References 1, 3, 4, 8, 9, 13, 14, 15, 16, 17 and 18 are included in volume 1 of this submission.

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

If you have any questions concerning this submission, please contact the undersigned at 201-235-4463 or via fax at 201-235-7771.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J Jack

Margaret J. Jack
Program Director
Drug Regulatory Affairs
(201) 235-4463
(201) 235-7771

MMJ/JMD
HLR No. 1997-1262
qofisub.doc

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340 Kingsland Street
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Direct Dial (201) 235-4463
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ORIGINAL

[redacted] 5/27/97

May 23, 1997

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766
Xenical® (orlistat) Capsules
Information Request for Breast Cancer Patients

Reference is made to the fax from the Agency dated May 16, 1997 and the teleconference between the sponsor and the Agency held on May 19, 1997. The purpose of these communications was to discuss and request additional information regarding patients with breast cancer.

The purpose of this submission is to provide the following information regarding the breast cancer patients:

1. **Response to the FDA fax dated May 16, 1997**
2. **Expert Report on Breast Cancer Requested at the Advisory Committee Meeting, May 14, 1997**
3. **Hoffmann-LaRoche Inc. Proposal for Post-Marketing Surveillance Re: Breast Cancer**
4. **Minutes of Meeting with Dr. Alfred Neugut (Epidemiologist - Columbia University)**
5. **Epidemiology Report from Dr. Pavel Napalkov**

1. Response to FDA fax Dated May 16, 1997

The response to the above-mentioned fax is included in this submission. The data provided is from the Phase 2 and 3 studies only. The Phase 1 studies were less than six weeks in duration with the majority of the subjects receiving orlistat for 7 to 15 days. The orlistat Phase 1 safety population was 1025 with approximately 15% of the subjects being female.

The ongoing studies were also reviewed, however, most studies were short-term (4 wks duration) and the long-term studies which have been initiated are blinded and cannot provide meaningful exposure data at this time.

2. Expert Report on Breast Cancer Requested at the Advisory Committee Meeting, May 14, 1997

The minutes of this meeting are provided in this submission. This panel is considered an independent expert panel, as these scientists were consulting for a third party group on the issue, and their conclusions on these eleven cases of breast cancer are provided. The curriculum vitae of the members of this panel will also be provided upon request.

3. Hoffmann-LaRoche Inc. Proposal for Post-Marketing Surveillance Re: Breast Cancer

The above-mentioned proposal is included in this submission. This proposal consists of both clinical trials and an obesity registry program to be initiated to assess the incidence of breast cancer in a large, heterogeneous population.

4. Minutes of Meeting with Dr. Alfred Neugut (Epidemiologist)

In addition to the expert panel discussed in 2, the breast cancer cases were also reviewed by two other epidemiologists, Dr. Alfred Neugut and Dr. Pavel Napalkov. The minutes of the meeting with Dr. Neugut are provided in herewith. The minutes of the March 27, 1997 meeting with Dr. Neugut were based on original exposure tables which did not include all the exposure data for orlistat. These exposure tables were subsequently revised and provided to Dr, Neugut. The document entitled "Updated Epidemiologic Data" is based on the revised exposure data. Dr. Neugut reviewed and approved both documents included in this submission. Dr. Neugut is Associate Professor of Medicine and Public Health, Breast Cancer Unit at Columbia University, NY.

5. Epidemiology Report from Dr. Pavel Napalkov

Dr. Pavel Napalkov is an epidemiologist with F. Hoffmann LaRoche in Basel Switzerland who also reviewed the breast cancer cases. Dr. Napalkov's report is also provided in this submission.

Sponsor's Comments

The expert panel reviewed the breast cancer data as a group, while Dr. Neugut and Dr. Napalkov reviewed the data independently. However, all these scientists reached similar conclusions concerning the data. In summary, the difference in breast cancer occurrence between the orlistat and placebo groups are probably due to a selection bias or chance.

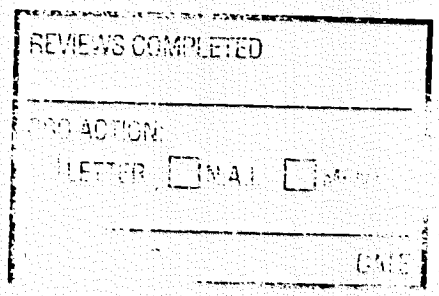
It is interesting to note that 5 cases occurred during the conduct of Study M14149, a two-year, double-blind, placebo-controlled trial conducted in Europe (Austria, Finland, France, Germany, Netherlands, Sweden and Switzerland) at doses of 120 mg, 60 mg and placebo administered tid. Seven hundred patients were projected to participate in M14149. Another two-year study, M14119C, was also conducted in Europe in the same seven countries (plus Denmark). M14119C was also a double-blind, placebo controlled study conducted at doses of 120 mg tid vs placebo with 700 patients also projected to participate in the study. There were no cases of breast cancer reported in M14119C.

In reviewing the database, there are two other examples of serious events occurring preferentially in one treatment group. For example, there were 7 spontaneous abortions reported during the conduct of the orlistat clinical program, 6 in the placebo group, and 1 in the orlistat group while both groups had a similar number of pregnancies, 21 vs 20 for the placebo and orlistat-treated groups respectively. Similarly, 4 placebo patients died in motor vehicle accidents vs no patient in the orlistat treated groups. Such findings also cannot be readily explained.

The proposed surveillance program includes prospective clinical studies and a physician-based registry. It is the sponsor's opinion that such a program will provide a acceptable tool for the assessment of breast cancer incidence rates in a large, heterogeneous population.

This submission consists of 12 volumes. Volume 1 includes the five items previously discussed in the letter. Volumes 2 through 12 (one volume for each patient) include the actual patient data such as case report forms, biopsy reports etc.

If you have any questions concerning this submission or need additional information related to the topics contained herein, please contact the undersigned at (201) 235-4463 or via fax at (201) 235-7771.



Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J Jack

Margaret J. Jack
Program Director
Drug Regulatory Affairs

MJJ/LS:rp
HLR No. 1997-1202
Desk Copies: (2) Maureen Hess, CSO

JUN 17 1997 ORIGINAL

20, 21 May 97

Memorandum of Telephone Conversation

etween: Dr. Jerry Kamm
Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110
(201) 235-5035

[redacted] and

David H. Hertig
Pharmacologist, HFD 510
(301) 443-3520; Fax (301) 443-9282

ubject: Xenical (orlistat) Capsules NDA 20-766
Precautions Section of the Labeling

0 May 97:
r. Kamm left a message on my Voice Mail requesting that I call him.

eturned Dr. Kamm's call.

1) He wished to know why the Agency had included the following statements n the labeling: "The incidence of dilated cerebral vesicles [later corrected to "ventricles"] was increased in the mid- and high-dose groups of the rat eratology study. These doses were 6 and 23 times the daily human dose calculated, on a body surface area (mg/m^2) basis for the mid- and high-dose levels, respectively. This finding was not reproduced in two additional rat teratology studies or in the rabbit teratology study at doses up to 23 and 47 times, respectively, the daily human dose calculated on a body surface area (mg/m^2)."

He indicated that the sponsor felt that this may have been a developmental finding and that the statement could be misleading.

I indicated that an increased incidence did appear and that it was in everyone's best interest that the finding should be covered in the labeling. This was, however, followed by the statement that the finding was not reproduced in additional teratology studies, two in rats and one in rabbits.

2) Dr. Kamm also wished to know how the Agency had derived the multiples of the human dose (mg/M2 based on surface area) for the preclinical studies in the Precautions section of the labeling. [According to their calculations (using a complicated formula for the derivation of Km), the multiples were approximately 6 fold greater.]

It was explained to him that these multiples were based on calculations from the paper by Freireich, E.J. et al. [Cancer Chemother Rep. 50:219-244, 1966]. [He claimed that their calculations were also based on this paper.]

We used the following formula:
mg/M^2 = Km x dose in mg/kg/day
Km's used by us were: 70 kg human = 40 mouse = 3 rat = 6 rabbit = 12

[redacted]

21 May 97: Call from Dr. Kamm

He stated that they had made a mistake in calculations and that our numbers were correct.

cc: Original NDA 20-766; HFD-510 NDA 20-766, RSteigerwalt, MHess, DHertig

[redacted] 6/17/97
David H. Hertig
Pharmacologist

[redacted]

JUN 17 1997

ORIGINAL

BEST POSSIBLE

16 May 97

Memorandum of Telephone Conversation

tween: Dr. Jerry Kamm
Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110
(201) 235-5035

and

David H. Hertig
Pharmacologist, HFD 510
(301) 443-3520; Fax (301) 443-9282

bject: Xenical (orlistat) Capsules NDA 20-766
Metabolites - Mouse and Rat Carcinogenicity Studies

all to Dr. Kamm Tuesday, 13 May 1997. Left message to call me.

6 May 97: [He had attended Advisory Committee Meeting on Xenical.]
The following questions were posed to Dr. Kamm:

1) Were the AUCs 0-24h for the animal studies extrapolated calculations?
Ans: Yes

2) Were there any metabolites found in humans that were not found in animals.
Ans: Not to the best of his knowledge.
Metabolites other than those given as major metabolites were mostly theoretical and not found.

Dr. Kamm believes the metabolic pathway to be the same in humans and animals.

APPEARS THIS WAY ON ORIGINAL

cc: Original NDA 20-766; HFD-510 NDA 20-766, RSteigerwalt, MHess, DHertig

/S/ 6/17/97
David H. Hertig
Pharmacologist

ORIGINAL
SUPPL NEW CORRES

Roche Pharmaceuticals
A Member of the Roche Group

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial (201) 562-3710
Fax (201) 562-3700/3554

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 12 1997
HFD-510

Ms. Kathleen Reedy
Health Science Administrator
HFD 21
HHS/FDA/CDER/ACS
Room 200 Chapman Building
1901 Chapman Avenue
Rockville, Maryland 20852

Dear Ms. Reedy:

Re: NDA 20-766, XENICAL® (orlistat) Capsules
Endocrinologic and Metabolic Advisory Committee Meeting - May 14, 1997
Sponsor Opposition to Release of Confidential Information to A Third Party and
Opposition to Any Modification of the Previously Published Meeting Agenda

We understand that an external organization has requested the FDA to release trade secret and confidential information contained in the New Drug Application NDA 20-766 for orlistat.

To date, only very limited clinical data regarding orlistat, essentially partial data from one of the seven Phase 3 studies, has been communicated to the public. We regard all information submitted to the FDA to be confidential and constitute a trade secret, disclosure of which could cause irreparable harm to Roche. This position is supported by FDA's own Freedom of Information regulations which specifically designate a new drug application to be confidential.

Our first disclosure of the overall development program will take place at the Endocrinologic and Metabolic Drugs Advisory Committee meeting on May 14, 1997. Therefore, we oppose any effort that would result in the premature disclosure of selective safety and efficacy data from our NDA. The disclosure of selective and perhaps incomplete information does not demonstratably benefit the public interest.

We understand that regulations permit the Commissioner to exercise discretion in the premature release of selected safety and efficacy summary information; however, we do not regard the current request for information to resemble in any way the kind of situation for which this regulation was originally established. We know of no previous situation in which confidential information was released by the Agency for no demonstratable public safety benefit. The disclosure of our trade secrets and confidential information would create an ominous precedent for the FDA. It would mean that external organizations could expect to receive confidential information from FDA prior to Advisory Committee meetings.

In addition to our concerns regarding the release of confidential information by FDA, the sponsor is also opposed to any modification to the published agenda for the Advisory Committee meeting that would move the open public session of the meeting from its current time slot at the beginning of the committee meeting to a time slot after the presentations by the sponsor and the Agency reviewers. The currently established agenda was published in the Federal Register on April 22, 1997 in compliance with FDA regulations (21CFR 14.20). The Federal Register notice appropriately provided sufficient notification to all interested persons and adequately established the time set aside for oral statements and other public participation.

Modifications to a published agenda for the purpose of accommodating the request of one external organization not only sets a bad precedent for future meetings, it is also unfair and without regard for the schedules, travel plans and convenience of others attending the Advisory Committee meeting, including others participating in the open public session. Past Endocrinologic and Metabolic Drugs Advisory Committee meetings routinely scheduled the open public hearing at the beginning of the meeting. The expectations of those testifying in the public session has been to present their case independent of the presentations of the sponsor or FDA. We are unaware of any public concern that was not adequately addressed with the public session at the beginning of the meeting. If the Agency feels that the Advisory Committee would be better served by having the open public hearing after the sponsor and FDA presentations, then the published agenda should have reflected such a schedule. Such a change in the previously published agenda would pose an unnecessary burden on all meeting attendees regardless if they are participants or not.

Should the Agency decide to either release confidential information to external parties or decide to make changes to the meeting agenda, then the sponsor formally requests the opportunity to meet with senior officials within the Agency to discuss these issues before these conclusions are communicated to the public.

We would like to thank you in advance for your attention to this matter. If you have any questions concerning this communication or wish clarification on any information contained herein, please contact Ms. Peggy Jack via telephone at (201) 235-4463 or via fax at (201) 235-7771 or contact the undersigned at (201) 562-3710 or via fax at (201) 562-3700/3554.

Sincerely,

HOFFMANN-LA ROCHE INC.

Peggy Jack for

Daniel Zabrowski
Vice President
Pharma Development Regulatory

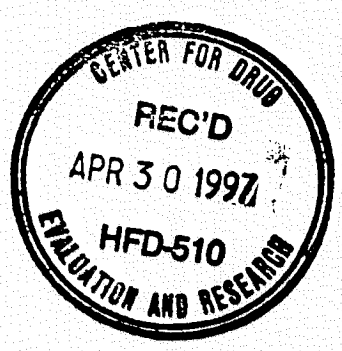
MJJ/ls
HLR No. 1997-1081
Desk Copies: Dr. James Bilsted
Ms. Kathleen Reedy
Dr. S. Sobel
Dr. R. Wykoff

Roche Pharmaceuticals
A Member of the Roche Group

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial (201) 235-4463
Fax (201) 235-7771

April 29, 1997



Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM, 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766 XENICAL® (orlistat) Capsules, 120 mg
Response to FDA's Request for Additional Data on DEXA;
Correction of Previously Submitted Bone Metabolism Data

Reference is made to the Agency's request for additional data and analyses of the patients with DEXA measurements during the Phase 3 clinical program. Such measurements were done at two study sites, one study site for Protocol BM14149 and one for Protocol BM14119C. These measurements were done by the investigators and were not part of the sponsor's database. The data for Dr. Sjostrom's study site (Protocol BM14149) was provided to the Agency in a submission to this NDA dated March 24, 1997. The purpose of this submission is to provide both the bone metabolism and DEXA data for Dr. Anderson's site (Protocol BM14119C, Center 6653). Although Protocol BM14119C was a two-year study, DEXA data was collected during year one only.

We are herewith providing the following data for study center 6653:

1. Demography for the Study Site Population, see Table 1
2. Summary Table of Year One Weight Change, see Table 2
3. Summary Statistics of Vitamins D, A, E, and Beta Carotene and Calcium, seeTables 3 - 7
4. Estrogen Replacement Data, see Tables 8 and 9
5. Bone Metabolism Markers: Baseline and Year One Mean Data for placebo and orlistat 120 mg treatment groups, see Table 10
6. Individual Patient Data for Bone Metabolism Markers, see Table 11
7. Statistical Analyses of the Bone Metabolism Markers, see Table 12

VOI

A report entitled "Changes in Calcium Metabolism and Bone Mineral Content" which presents the data for Dr. Anderson's site was provided in NDA 20-766, see Section 8/10, Volume 453, page 70-74. **It has now been clarified that ratios for both hydroxy-proline/creatinine and calcium/creatinine were incorrectly calculated in the report. These ratios have been corrected and are included in this submission.**

The DEXA data and statistical comparisons between treatment groups for the body as a whole, spine and forearm are presented in Tables 13 - 15 respectively.

If you have any questions concerning this submission, please contact the undersigned at (201) 235-4463 or via fax at (201) 235-7771.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J. Jack

Margaret J. Jack
Program Director
Drug Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

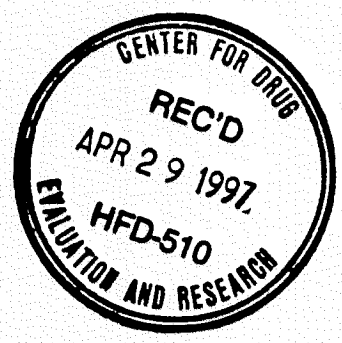
MMJ/LS:lh
Attachments
HLR No. 1997-991

Roche Pharmaceuticals
A Member of the Roche Group

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial (201) 562-3550
Fax (201) 562-3554/3700

April 28, 1997



Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766 Xenical® (orlistat) Capsules
Amendment to Pending Original NDA:
Chemistry, Manufacturing and Controls -
Response to FDA Letter of March 27, 1997 Requesting
Additional Information Regarding the Chemistry Section

Reference is made to Hoffmann-La Roche Inc.'s Original New Drug Application 20-766 for Xenical (orlistat) Capsules, submitted on November 26, 1996. In accordance with 21 CFR §314.60, we submit herewith a Chemistry, Manufacturing, and Controls amendment to the subject pending Original NDA. The amendment includes a response to the Chemistry questions in the March 27, 1997 letter from FDA regarding comments and requests pertaining to information submitted in the Original NDA.

The FDA letter of March 27, 1997 is included in Attachment 1. The Roche responses to the FDA's comments and requests for information are included in Attachment 2. Attachment 3- 11 provide supportive information referenced in the responses.

In addition to the responses to FDA's comments and requests, revised specifications and directions for testing the drug product are included in Attachment 12. The document was revised to correct a typographical error in the calculation for the Uniformity of Dosage Units. Updated stability test results are also provided in support of the proposed 24-month expiration dating period (Attachment 13). Data is included for Xenical® (orlistat) Capsules stored in the proposed market package configurations for up to 18 months.

The information contained in this amendment is **CONFIDENTIAL** and is not to be disclosed to any person outside the Food and Drug Administration without prior notification and written consent from Hoffmann-La Roche Inc.

In conformance with 21 CFR §314.71(b), and as indicated at the end of this letter, an identical field copy of this supplement has been prepared for simultaneous submission to the New Jersey District Office of the FDA. The undersigned hereby certifies that the copy submitted to the District Office is identical to that submitted to the Division of Metabolic and Endocrine Drug Products.

Hoffmann-La Roche Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under 21 U.S.C. 306 (a) and (b), in connection with this application.

Please feel free to contact the undersigned at (201) 562-3550 if you have any questions concerning this amendment.

Sincerely,

HOFFMANN-LA ROCHE INC.

Virginia A. Pate

Virginia A. Pate
Program Manager
Drug Regulatory Affairs

VAP/ls:lh
Attachments
HLR No. 1997-983

Desk Copies (2): Ms. Maureen Hess, MPH, RD

Field Copy: Ms. Regina Brown
Pre-Approval Program Director
Food and Drug Administration
120 North Central Drive
North Brunswick, NJ 08902