Roche Pharmaceuticals
A Member of the Roche Group

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

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

NOTE
ISI
[redacted]
2/7/97

February 5, 1997

CENTER FOR DRUG
REC'D
FEB 06 1997
HFD-510
EVALUATION AND RESEARCH

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

Re: NDA 20-766 Xenical®, 120 mg Capsules
Request for additional Biopharmaceutical Information

Reference is made to your teleconference on January 31 with Dr. Anthony Rhymer requesting additional biopharmaceutical data to be provided. You requested the batch sizes and certificates of analysis for each lot (30 mg, 60 mg, and 120 mg capsules) used in the following trials: BD14150, BM14119B, BD14119C, NM14161, NM14336, BD14419, and NM14280.

The requested information is provided herein for Protocols BD14419, NM14336, and ND14280, as follows:

Protocol Number	Clinical Lot Number	Original Lot Number	Capsule Dosage Strength	Batch Size
BD14419	C176983	PT 2157 T45	120 mg	110, 000 Capsules
NM14336	C171712	PT 2157 T10	120 mg	110,000 Capsules
	C174523	PT 2157 T30	120 mg	110,000 Capsules
	C176183	PT 2157 T38	120 mg	110,000 Capsules
	C176983	PT 2157 T45	120 mg	110, 000 Capsules
ND14280	C183305	DB-26453-018A	60 mg	666,666 Capsules
	C183295	DB-26453-020	30 mg	500,000 Capsules
	C177183	PT 2157 T02	30 mg	440,000 Capsules

Roche-Nutley certificates of analysis are included in this information. Certificates of analysis for lots manufactured in Basel (PT numbers) and the lots used in Protocols BD14150, BM14119B, BD14119C, and NM14161 are being obtained from Basel and will be submitted as soon as it arrives. For reference, the proposed commercial batch size for XENICAL is 666,666 capsules derived from 160 kilograms of excipient blend made into pellets.

If there are any questions concerning this submission, please contact the undersigned at (201) 235-4463 or Ms. Virginia A. Pate, Program Manager at (201) 562-3550 in my absence.

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Sincerely,

HOFFMANN-LA ROCHE INC.

Virginia A. Pate for

Margaret J. Jack
Program Director
Drug Regulatory Affairs

TH/LS:eh
HLR No. 1997-312
Desk Copy: Dr. Robert Shore

NDA ORIG AMENDMENT

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

/S/ [redacted]

2/4/97

February 4, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 0 5 1997
HFD-510

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

N20765

RE: Assay Validation Document for the Determination of Plasma β-Carotene (for Protocol NK14179B) and Serum Vitamins A and E (For Protocol NK14277A)

[redacted]

[redacted]

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J Jack

Margaret J. Jack
Program Director
Drug Regulatory Affairs

MJJ/LS:eh
Attachment
0204b.doc
HLR No. 1997-279
Desk Copy: Dr. Michael Fossler

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

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
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February 4, 1997

CENTER FOR DRUG
REC'D
FEB 05 1997
HFD-510
EVALUATION AND RESEARCH

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

Re: NDA 20-766 XENICAL® (orlistat) Capsules, 120 mg
Interactions Between FDA and Health Protection Branch

Reference is made to the above-mentioned NDA which was received by the US Food and Drug Administratation on November 27, 1996 and determined filable and designated priority review status on January 22, 1997 by the Division of Metabolic and Endocrine Drug Products. This NDA is scheduled for Advisory Committee on April 14, 1997.

This application was submitted simultaneously to the Health Protection Branch's Endocrinology, Metabolism and Allergy Division by Hoffmann-La Roche Limited, Canada.

The sponsor of NDA 20-766 has no objections to interactions between FDA and the Health Protection Branch concerning the review of this application.

If you have any questions concerning these interactions, 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:eh
HLR No. 1997-278
Desk Copy: Dr. Eric Colman

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) 562-3700/3554

February 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
ATTN: DOCUMENT CONTROL ROOM, 14B-19
5600 Fishers Lane
Rockville, MD 29857-1706

Ladies and Gentlemen:

Re: **NDA 20-766**
XENICAL® (orlistat) Capsules
Amendment to Pending NDA: Physical Evidence of
Absolute Configuration of Key Intermediate HBL (Ro 19-3052)

Hoffmann-La Roche herewith is submitting an amendment to the Chemistry, Manufacturing, and Controls section of the pending XENICAL® NDA. The amendment provides physical evidence to demonstrate that the key intermediate, Ro 19-3052, has the correct absolute configuration as described in the Original NDA submission of November 26, 1996 for XENICAL® (orlistat) Capsules. This information is being provided in response to requests that were made during a January 7, 1997 teleconference with FDA, and followed up in a January 9, 1997 telefax from Solomon Sobel, M.D., Director of the Division of Metabolism and Endocrine Drug Products.

[redacted]

In conformance with 21 CFR § 314.50(k)(3), 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 Metabolism and Endocrine Drug Products.

The information contained in this correspondence 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.

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:eh
Attachment
HLR No. 1997-261
Desk Copy: 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

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

January 31, 1997

CENTER FOR DRUG
REC'D
FEB 0 4 1997
HFD-510
EVALUATION AND RESEARCH

Dr. Eric Colman
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® 120 mg Capsules
Response to FDA Request for Additional Statistical Information

Enclosed please find a memorandum from John Mathieson regarding clarification of medical review questions and a brief summary of his notes at your meeting with him on January 30, 1997.

Sincerely,

HOFFMANN-LA ROCHE INC.

Trent Hughes

for Margaret J. Jack
Program Director
Drug Regulatory Affairs

TH/LS
HLR No. 1997-259
Desk Copy: Ms. Maureen Hess, CSO

HESS

Memorandum

To: Dr. Coleman

CC: Maureen Hess MPH,RD

From: John Mathieson /S/ [redacted]

Date: January 31, 1997

Re: Xenical:Clarification of Medical Review Questions

Dr. Coleman,

attached is a brief summary of my notes of our meeting on January 30th. They pertain to the questions that needed clarification before we could proceed with Statistical analyses and report generation. They reflect my understanding of your requirements, please review and let me know if anything is incorrect or if anything further is wanted.

As we complete each question, we will send directly to you our results and defer the official package until all questions are addressed.

APPEARS THIS WAY ON ORIGINAL

CC: NDA 20-766
HFD-510
HFD-510/MHess

Concurrence: EColman/2.3.97

VITAMINS AND β - CAROTENE

- **Of the subjects that had a reduction in a vitamin or beta-carotene value to below normal on two consecutive visits, how many had a reduction in more than one parameter. Please compare the percentages statistically: placebo vs. Orlistat.**

  The subjects should be restricted to those with normal baseline values for vitamins A,D, E and beta-carotene.

  Year one and two year analyses are required using the same pools of studies as reported in the NDA.

  Xenical 120 should be compared to Placebo.

- **Was there a particular pattern in the time to first occurrence of two consecutive low vitamin levels?**

  Compare Xenical to placebo with respect to time to occurrences of two consecutive low vitamins by life-table methods. The onset of the event, when it occurs, is at the first of the two low values.

  Year one and two year analyses are required using the same pools of studies as reported in the NDA.

- **In the integrated summary of safety data set please provide a statistical comparison of the percentages of patients in the orlistat vs. the placebo groups with at least two consecutive low vitamin or beta-carotene values. Please also provide for the patients with low vitamin levels on two consecutive occasions, the mean vitamin and beta-carotene values prior to supplementation.**

  The subjects should be restricted to those with normal baseline values for vitamins A,D, E beta-carotene and beta-carotene.

  Year one and two year analyses are required using the same pools of studies as reported in the NDA

  Xenical 120 should be compared to Placebo.

  The mean levels prior to supplementation should only be for the specific vitamins/ beta-carotene that had two consecutive lows prior to supplementation. Mean levels at baseline should be added for these cases.

BM14119C

- **Please provide the data on weight loss for the two groups. Please provide the DEXA data on those patients with outlier values for urinary excretion of calcium and hydroxyproline. Please also provide the change in plasma vitamin D levels in these subjects.**

  Xenical 120 should be compared to Placebo with respect to weight loss in the subpopulation with "outlier" values.

BM14149

- **Please provide the baseline demographic characteristics of the placebo and orlistat groups with statistical comparisons. Please also provide a statistical comparison of the BMDs at baseline and after 1 and 2 years of treatment. Were any of the women on ERT?**

  Xenical 120 should be compared to Placebo with respect to weight loss in the subpopulation with BMD values at baseline.

INTEGRATED SUMMARIES OF EFFICACY AND SAFETY

- **Please provide the results of subgroup analyses (age, gender, race, BMI) for efficacy and safety (adverse events and vitamin levels).**

  For age use the groups: < 40, 40 - 60, ≥60 years.

  Adverse events should be restricted to gastrointestinal.

  Vitamins should be compared with respect to mean changes over time and percentages with low values.

ORIGINAL

Roche Pharmaceuticals

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January 29, 1997

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 31 1997
HFD-510

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

Re: NDA 20-766 Xenical®, 120 mg Capsules
Request for additional Biopharmaceutical Information

Reference is made to your teleconference today with Dr. Anthony Rhymer requesting additional biopharmaceutical data to be provided. The purpose of this submission is to provide the requested information.

If there are any questions concerning this submission, please contact the undersigned at (201) 235-4463 or Ms. Tricia Hughes, Sr. Regulatory Affairs Officer at (201) 562-3726 in my absence.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Sincerely,

HOFFMANN-LA ROCHE INC.

Tricia Hughes for

Margaret J. Jack
Program Director
Drug Regulatory Affairs

TH/LS:eh
HLR No. 1997-239
Desk Copy: Dr. Robert Shore

/S/ [redacted]

BEST POSSIBLE

/S/ [redacted]

/S/ [redacted]

ORIGINAL

Roche Pharmaceuticals

A Member of the Roche Group

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

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Fax (201) 235-7771

January 29, 1997

Mr. David Moss
Food and Drug Administration
Center for Drug Evaluation and Research, HFD-70
Room 8B45, Parklawn
5600 Fishers Lane
Rockville, MD 20857-1706

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 30 1997
HFD-510

[redacted] 3/6/97

[redacted] 11 May 97

Dear Mr. Moss:

RE: NDA 20-766
XENICAL® (orlistat) Capsules, 120 mg
Delivery of Equipment

To facilitate the review of our application for XENICAL® in treatment of obesity, we are providing on loan the equipment listed below. These items will be provided for the use of Dr. Pain, Statistician, Division of Metabolism and Endocrine Drug Products to assist in the review of SAS datasets.

The equipment will be delivered to Dr. Pain as per mutual agreement on the morning of January 30, 1997. We have taken precautions to ensure that the equipment and files on it are free from computer viruses.

Equipment provided: (1) Microdisk 1030 external SCSI disk drive (1 GB) by Micropolis
Serial No.: MD 0006504
(1) SCSI Cable

Questions relating to the datasets should be addressed to:

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

Dr. Jain Chung
Xenical Project Statistician
Department of Biometrics
☎: (201) 235-7241
Fax: (201) 562-3411

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

January 29, 1997

Mr. David Moss
Food and Drug Administration
Center for Drug Evaluation and Research, HFD-70
Room 8B45, Parklawn
5600 Fishers Lane
Rockville, MD 20857-1706

CENTER FOR DRUG
REC'D
JAN 30 1997
HFD-510
EVALUATION AND RESEARCH

Dear Mr. Moss:

RE: NDA 20-766
XENICAL® (orlistat) Capsules, 120 mg
Delivery of Equipment

THIS IS A BACKUP SOLUTION TO THE MICROPOLIS DRIVE:

To facilitate the review of our application for XENICAL® in treatment of obesity, we are providing on loan the equipment listed below. These items will be provided for the use of Dr. Pain, Statistician, Division of Metabolism and Endocrine Drug Products to assist in the review of SAS datasets.

The equipment will be delivered to Dr. Pain as per mutual agreement on the morning of January 30, 1997. We have taken precautions to ensure that the equipment and the files on it are free from computer viruses.

Equipment provided:
(1) Digital Storage Works SCSI (2 GB) Removable External Drive
Model No. RZ28B, S/N CX42011614

(1) Digital Storage Works SCSI (2 GB) External Drive Receptacle
Model No.: BA353-AA S/N CX42710982

(1) SCSI Cable

Questions relating to the datasets should be addressed to:

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

Dr. Jain Chung
Xenical Project Statistician
Department of Biometrics
☎: (201) 235-7241
Fax: (201) 562-3411

Should you have any questions regarding this submission, please feel free to contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J. Jack
Program Director
Drug Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

MJ/LS:tg
uoebuso.doc
HLR No. 1997-237

Desk Copy: Dr. Colman, Medical Reviewer
Ms. Maureen Hess, CSO
Dr. L. Pain, Statistical Reviewer

NEW CORRES.

ORIGINAL

Roche Pharmaceuticals

A Member of the Roche Group

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

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RECD
JAN 29 1997
HFD-510
EVALUATION AND RESEARCH

January 28, 1997

JAN 29 1997
CENTER FOR DRUG EVALUATION AND RESEARCH

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

ISI [redacted]
03/24/97

Ladies and Gentlemen:

Re: NDA 20-766 Xenical®, 120 mg Capsules
Request for Human Pharmacokinetic Summary
To be Provided in Electronic Format - WordPerfect

Reference is made to Dr. Robert Shore (Pharmacokinetic Reviewer) request for the above-mentioned summary to be provided in electronic format, specifically WordPerfect for Windows. This summary was provided in Section 6 of the above-mentioned NDA via a publishing system [redacted] that is not compatible with WordPerfect. The purpose of this submission is to provide the requested information. A three-diskette electronic version of the above document (text plus appendices) in WordPerfect Window (V6.1) is herewith provided.

During the electronic conversion of this summary from the publishing system to WordPerfect, it was confirmed that a 100% conversion was not technically feasible. The document included in this submission is identical to the document in the NDA (except a few corrections of the original NDA errors) and the following stylistic differences :

1. No Title Page in the WordPerfect (WP) version
2. Instead, two front pages were added into the WP version; the abstract was similar to conclusions in the text.
3. In the WP version, references were cited in the order of appearance in the text. This was in accordance with the agreement with Dr. Shore in September of 1996.

4. No page numbers were assigned in Table of Content of the WP version.
5. Page numbers of the WP version are not in sequential order and are not the same as the INTERLEAF version.
6. Major appendix section numbers were either Roman or Arabic in the WP version.
7. No marginal notation of NDA Sec_Ref_Vol_Page appears in the WP version

Other format specifics such as fonts also exist.

We are providing the diskettes and hard copy of the WP version of this document. The core report is in the file NDA.SEC6.WPD, the synopses of the individual studies is provided in the file NDA.APP1.WPD, and the other appendices are included in the file NDA.APP2.WPD.

Dr. Shore has also requested the assay validation for the fecal fat analyses, and this validation report will be submitted under separate cover.

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

MMJ/LS:eh
HLR No. 1997-220