M. 1-163.

FEB 3 1998

MEMORANDUM OF TELECON

DATE: February 2, 1998

APPLICATION NUMBER: NDA 20-766; Xenical

BETWEEN:

Name: Mr. Rudy Lucek, Dr. John Mathison and Ms. Peggy Jack
Phone: (973) 562-3688
Representing: Hoffmann-LaRoche

AND

Name: Maureen Hess and Dr. Lee Pian
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Statistical clarification

Teleconference to discuss the following:

1. Explanation of the discrepancy of 124 patient-years contributed to the 120 mg orlistat group from the placebo group during the survey period and the 106 patient-years as stated in the resubmission. The 106 patient-years was not previously reported in the 8/21/97 submission of the trial period.

   The firm could not explain the discrepancies and would have a response to the Division when they have looked into it.

2. The Division requested the firm to submit a table of the on-trial patient-year by study and treatment groups. The firm agreed to do so.

[redacted] /S/

Maureen Hess, MPH, RD
Consumer Safety Officer

cc: Original NDA 20-766
HFD-510/Div. File
HFD-510/EColman/LPian/MHess

TELECON

[redacted]

APPEARS THIS WAY ON ORIGINAL

Roche

January 30, 1998

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
Meeting Agenda for February 11, 1998 Meeting

We wish to confirm our meeting with the agency on Wednesday, February 11, 1998, at 2:30 PM to discuss the presentation of Xenical at the March 13,1998 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. In preparation for the February 11 meeting, we are submitting herewith a proposed agenda covering the purpose of the meeting, issues to be covered, attendees from Roche, and a listing of those individuals from the agency who we would request be in attendance.

1. General Purpose of the Meeting

To discuss and agree on all procedural aspects relating to the March 13 Xenical Advisory Committee Meeting and to outline the formal presentations to be made. To assure, through close collaboration between the sponsor and agency, that all substantive issues to be addressed are proactively identified so that they may be adequately presented, discussed, and resolved at the Advisory Meeting.

A meeting agenda and the specific issues to be discussed are outlined below.

2. Agenda and Specific Issues to be Discussed

A. Review of the NDA Resubmission

We wish to obtain feedback and reviewer comments from both the Metabolic and Oncology reviewers concerning their reviews of the November 1997 NDA resubmission.

B. New Data - Follow up Survey and Phase IIIB Clinical Studies

We wish to update the agency with all new information obtained from the second follow up survey and the ongoing Phase IIIB clinical trials. A complete presentation of this data will be provided in the Advisory Committee Briefing Document and the Four Month Safety Update.

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

C. Global Regulatory Update

Provide the agency with an update of the status of other health authority reviews of the Xenical dossier.

D. Advisory Meeting Presentations

We wish to review with the agency an outline of the sponsor's Advisory Committee presentation and gain agreement to meet in early March to review the presentations to be given by both the sponsor and the agency.

Is the FDA planning on making a presentation, and if so, what will be the subject and nature of the presentation and who will present for or on behalf of the FDA?

E. Advisory Committee Questions

We wish to discuss the questions the agency will pose to the committee concerning Xenical. A copy of these questions is requested; however, if they are not available by February 11, we wish to discuss their nature and scope. Will they be limited to the analysis of the breast cancer cases or will they cover other issues such as efficacy and general tolerability, including a specific question concerning benefit/risk?

F. Make Up of the Advisory Committee

We wish to discuss the make up of the Advisory Committee and who from the Oncology Advisory Committee will be represented.

Will the FDA be represented by additional experts, and if so, by whom? What will be the voting status of the Oncology members on the committee and outside experts?

G. Labeling

Establish a procedure and time frame for finalization of labeling.

3. Roche Attendees

Dr. Daniel Zabrowski	Project Leader
Dr. Jonathan Hauptman	Clinical Research
Dr. Martin Huber	Clinical Research
Dr. Timothy Anderson	Toxicology and Pathology
Dr. Susan Sacks	Epidemiology
Mr. Rudolph Lucek	Regulatory

4. Requested Participants from CDER

The attendance of the following representatives is requested:

Dr. James Bilstad	ODE II
Dr. Solomon Sobel	Division Director, DMEDP
Dr. Gloria Troendle	Deputy Director, DMEDP
Dr. Bruce Stadel	Epidemiology Reviewer
Dr. Eric Colman	Medical Reviewer
Dr. Lee Pian	Statistician
Ms. Maureen Hess	Consumer Safety Officer

In addition, we would also request the attendance of the reviewers from the Oncology Division who reviewed the NDA resubmission.

We are looking forward to meeting with you on February 11, and thank you for your time and consideration. Please feel free to contact the undersigned if I may be of further assistance.

Sincerely,

HOFFMANN-LA ROCHE INC.

Rudolph W. Lucek

Rudolph W. Lucek
Group Director
Drug Regulatory Affairs

Direct Dial: (973) 562-3688
Fax: (973) 562-3554/3700

RWL:tn
HLR No. 1998-282

Desk Copy: Ms Maureen Hess, Consumer Safety Officer

MEMORANDUM OF TELECON

DATE: January 26, 1998

APPLICATION NUMBER: NDA 20-766; Xenical (orlistat)

BETWEEN:

Name: Mr. Rudy Lucek and Dr. John Mathison
Phone: (973) 562-3688
Representing: Hoffmann-LaRoche

AND

Name: Maureen Hess and Dr. Lee Pian
Division of Metabolism and Endocrine Drug Products, HFD-510

SUBJECT: Clarification of information request

Hoffmann-LaRoche requested clarification of FDA's request to perform Kaplan-Meir Curves. Dr. Mathison questioned how they should handle the cross-over trials. Dr. Pian stated that they should depend on the first randomized treatment. Dr. Mathison inquired if they should ignore the fact that they cross-over. Dr. Pian agreed.

Dr. Mathison inquired about the presentation. Dr. Pian suggested rescaling the y-axis to 95-100%. Roche agreed to this.

Ms. Hess requested that the following information be submitted:

1. For each of the seven clinical trials, the month and year that the first patient was randomized and the month and year the final patient visit occurred.

2. Reference to the May 23, 1997, submission, Table 14E. Does the weight change column represent change in weight from randomization to breast cancer diagnosis or from the run-in period to diagnosis? If this does not represent change in weight from randomization to diagnosis, please provide that information.

[redacted]
/S/
Maureen Hess
Consumer Safety Officer

cc: Original NDA 20-766
HFD-510/Div. File
HFD-510/LPian/EColman/BStadel/MHess

TELECON

HESS

JAN 2 3 1998

MEMORANDUM OF TELECON

DATE: January 22, 1998

APPLICATION NUMBER: NDA 20-766; Xenical (orlistat)

BETWEEN:

Name: Ms. Peggy Jack
Phone: (973) 235-4463
Representing: Hoffmann-LaRoche

AND

Name: Maureen Hess
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Request for Information

Called Hoffman-LaRoche to request the following:

Reference is made to Table 3, Breast Cancer Epidemiology Report of the resubmission. Requested that two life tests are performed on the data from this table. One life test should be performed on the study cases and one on the cases from the follow-up survey with Kaplan-Meir Curves.

Reference is made to the Breast Cancer Reported in Phase 3 Trials section of the Executive Summary of the resubmission. This section states that the distribution of other cancers identified during treatment was similar between treatments. Requested information on all cancers by treatment group and within each treatment group, the data should be broken down by each organ system and within each organ system, the data should be broken down by histology.

Ms. Jack inquired how soon the information is needed. CSO responded that the information should be submitted as soon as possible.

[redacted] /S/

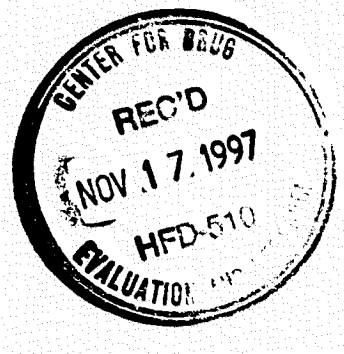
Maureen Hess, MPH, RD
Consumer Safety Officer

cc: Original NDA 20-766
HFD-510/Div. File
HFD-510/EColman/LPian/BStadel/MHess

TELECON

Roche

November 14, 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: Resubmission of NDA 20-766
XENICAL® (orlistat) Capsules, 120 mg

Reference is made to the sponsor's letter dated July 23, August 27 and September 30 of this year which included labeling, withdrawal of the application and a request for a meeting, respectively. In addition, reference is also made to the Agency's November 5 fax providing the minutes of the meetings between representatives of the sponsor and FDA which took place on August 25 and 26, 1997.

With this submission, Hoffmann-La Roche refiles NDA 20-766 for your review. This application provides additional information on the cases of breast cancer reported in female patients ≥ 45 years of age who participated in the phase 3 clinical studies of orlistat. As agreed during the meeting of August 26, 1997, it is the sponsor's understanding that this application will be granted priority review status and therefore, an action on this NDA will be determined by FDA within 6 months.

The available data on the reported breast cancer cases were extensively reviewed by the sponsor and independent experts in the fields of oncology, radiology, pathology and epidemiology. These experts reviewed the medical records for each patient, including pre- and post-study mammograms and histopathology slides. In addition, the preclinical safety assessment of orlistat was also reexamined both internally and externally to determine if there was any evidence to suggest a potential for an increased cancer risk in humans exposed to orlistat. This total weight of the clinical and preclinical data strongly suggest that there is no evidence that Xenical or its metabolites, either directly or indirectly, initiates, promotes, or enhances the growth of breast tumors. These conclusions are supported by the following findings:

a. Genotoxicity studies and carcinogenicity studies in animals with systemic exposures many multiples of that in humans, showed no evidence that Xenical treatment has any carcinogenic potential.
b. Histologic and mammographic review of the breast cancer cases provide unequivocal evidence that the vast majority of the breast cancer cases existed prior to study enrollment.
c. The histology of the tumors and surrounding breast ductal and lobular epithelium did not show evidence of enhanced or accelerated growth.

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Nutley, New Jersey 07110-1199

d. The histologic appearance of the tumors found in the Xenical studies were of several different pathologic types representative of what would be found in a general survey of a Western population.
e. There is no causal relationship between Xenical and breast cancer.

Components of the Submission:
Reports by these independent preclinical and clinical experts, as well as sponsor-issued reports are the basis of this submission.

Although we are re-submitting NDA 20-766, Volumes 1 through 672 of the NDA (dated Nov. 26, 1996) are already at the Agency. This re-submission consists of 22 additional volumes for Section 8/10 only. These 22 additional volumes are numbered 673 through 694. These volumes include the following information:

Volume 673	Administrative forms, cover letter, Index for the re-submitted volumes and a Reviewer's Guide to the Submission
Volume 674	**Executive Summary:** integrates all the data presented in the various reports included in this submission **Preclinical Section:** includes two summaries to reexamine the Sponsor's toxicology program for evidence to suggest a potential increase cancer risk in humans exposed to orlistat, a sponsor issued summary and a summary by Dr. Gary Williams, consultant. **Clinical Section:** includes Consensus of Expert Opinion Summary; Two pathology reviews of the 14 breast cancer cases, by the Armed Forces Institute of Pathology (Dr. Tavassoli) and Dr. J. O'D. McGee; A review of mammograms, both pre- and post-Xenical treatment by Dr. S. Feig.
Volume 675	**Clinical Section continued:** Two clinical oncology summaries of the 14 breast cancer cases by Drs. C. Rose and E. Winer respectively and a third pathology review of these cases by Dr. N. Wright; Final report of the survey and a final epidemiology report by the sponsor including analyses conducted by Dr. K. Rothman and associates; Revised Risk/Benefit Summary
Volume 676	**Clinical Section continued:** Integrated Summary of Efficacy and Safety (Female patients ≥ 45 years of age)
Volumes 677 - 690	Individual patient data including CRFs, case report tabulations; Medical records

Volume 691	Curriculum Vitae for Experts
Volume 692 - 694	References cited in reports included in volumes 674 and 675

For your information, the company is currently conducting a follow-up to our survey of female patients ≥ 45 years of age who participated in the phase 3 clinical studies of orlistat (see Attachment A for protocol). The objective of this activity is to obtain additional information on the risk factors for breast cancer in this patient population. This work will be completed by the end of January and the results reported to FDA in early February as part of the NDA safety update. Please note that the company has included the information on risk factors for the 14 women who were diagnosed with breast cancer in this resubmission.

Finally, the sponsor reiterates its request to meet with the Agency to discuss the review process for this NDA (see Attachment B) meeting request. Although Roche appreciates that the Agency will require time to conduct a preliminary review of this NDA, we are hopeful that the meeting can occur in mid-December or early January.

As stated in the Agency's letter dated August 27, 1997 and under section 736(a)(1)(c) of the PDUFA, the refiling of this application is not subject to fee.

If you have any questions or require further information, please feel free to contact the undersigned at (973) 235-4463 or as alternates, Mr. Rudy Lucek at (973) 562-3688 or Dr. Dan Zabrowski at (973) 562-3710.

We look forward to a close collaboration with the FDA during the review of this application.

Sincerely,

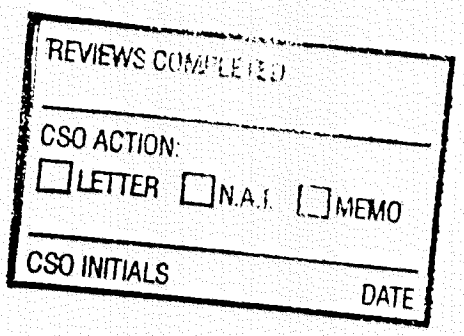
HOFFMANN-LA ROCHE INC.

Margaret J Jack

Margaret J. Jack
Program Director
(973) 235-4463 (telephone)
(973) 235-7771 (fax)

MJJ:LS/mi
Attachments
HLR No. 1997-2718

ORIGINAL



Roche

September 30, 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

N144

Ladies and Gentlemen:

Re: IND 31,617 XENICAL® (orlistat) Capsules, 120 mg / Ro 18-0647
Request for a Pre-NDA Meeting to Discuss Resubmission of NDA 20-766
Submission Serial No. 144

Reference is made to the Sponsor's letter indicating the withdrawal of NDA 20-766 on August 27, 1997 without prejudice to refiling and to previous discussions with the Agency on August 26, 1997 concerning the Sponsor's intent to refile this application in the near future. We are herewith requesting a meeting in October with the Agency to discuss the various topics related to the resubmission of NDA 20-766 and its subsequent presentation at an Advisory Committee (AC) meeting.

1. Purpose of the Meeting

The purpose of the meeting is to discuss the content and format of the resubmitted NDA and to obtain input from the Agency on the review process and timing of the future Advisory Committee meeting for this application.

2. Specific Objectives/Outcomes Expected from the Meeting

The Sponsor expects to obtain the Division's agreement on the format and content for this application and to identify the additional information/data that will be available for inclusion in the Advisory Committee briefing document and 4-month safety update.

In addition, the Sponsor wants to obtain input from the Division on the review process for this application, including the role in the review process of oncology experts outside the Division. Specifically, will the oncology consult include the Division of Oncology Drug Products? The Sponsor also requests a discussion on the format of the Advisory Committee meeting, the role of the oncology consultants at the Advisory Committee meeting, and the scope of the questions to be addressed at the AC meeting.

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

3. Proposed Agenda

1. **NDA Resubmission**: including timelines, format and content of NDA, additional information to be included in the AC briefing document and the 4-month safety update. — 20 minutes

2. **Regulatory Review Process**: including priority review process with oncology consultation and timelines, the role of the oncology consultants at the AC, format and Agency attendees at the AC meeting, and the scope of the questions for the Advisory Committee. — 40 minutes

4. Potential Roche Attendees

The possible Roche representatives may include:

Mr. Donald Cooper	Project Management
Dr. J. Hauptman	Clinical R&D
Ms. Peggy Jack	Regulatory
Mr. Rudy Lucek	Regulatory
Dr. John Mathieson	Biostatistics
Dr. R. Meibach	Clinical R&D
Dr. Susan Sacks	Epidemiology
D. Zabrowski	Project Leader

5. Potential Participants from CDER

The possible representatives from CDER may include:

Dr. James Bilstad	ODE II
Dr. Eric Colman	Medical Reviewer
Dr. Robert DeLap	Division of Oncology Drug Products
Ms. Maureen Hess	Consumer Safety Officer
Dr. Lee Pian	Statistician
Dr. Solomon Sobel	Division Director, Metabolic and Endocrine Drug Products
Dr. Bruce Stadel	Epidemiology Reviewer
Dr. Robert Temple	ODE I
Dr. Gloria Troendle	Deputy Director, Metabolic and Endocrine Drug Products

6. Proposed dates for the Meeting and Pre-Meeting Documents

Since we are planning to submit the NDA on November 14, 1997, we are requesting an October meeting. We are planning to send the pre-meeting documentation to the Division two weeks prior to the scheduled meeting.

ase feel free to contact the undersigned to discuss the scheduling of this meeting. Your rapid attention his meeting request would be appreciated.

cerely,

FFMANN-LA ROCHE INC.

Margaret J Jack

rgaret J. Jack
ogram Director
73) 235-4463 (telephone)
73) 235-7771 (fax)

JJ:LS/mi
R No. 1997-2377

T45415

ORIGINAL

Roche

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

CENTER FOR DRUG
REC'D
SEP 26 1997
HFD-510
EVALUATION AND RESEARCH

September 25, 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: IND [redacted]
Xenical® (orlistat) Capsules, 120 mg / Ro 18-0647
Other: Information Regarding Swedish Study - Protocol BM15421
Submission Serial No. 143

N143 GC

Reference is made to the submission to NDA 20-766 dated August 27, 1997 which included the Protocol BM15421 entitled "Weight reducing and NIDDM preventing effects of Xenical in obese patients" which is being conducted in Sweden. We indicated in that submission that clarification of the five-point grading system for mammograms will be provided in the near future. Reference is also made to the Agency's questions concerning Swedish Health Care system and the percentage of female patients with routine mammograms.

The purpose of this submission is to provide the clarification of the mammogram grading system and the exclusion criteria for the female patients to be included in Protocol BM15421 and to answer the inquires concerning the percentage of patients receiving routine mammograms in Sweden.

Protocol BM15421

The mammographies are coded from 1 to 5 by the radiologist utilizing the following grading system:

1. Normal
2. Benign findings
3. Malignancy cannot be ruled out
4. Probable malignancy
5. Malignancy

The exclusion criteria for Protocol BM15421 specifies that patients with mammography grades of 3 through 5 will not be entered into the study. It has also been clarified that carcinoma in situ (if visible on mammography) would be graded as a 3, and these patients will be excluded from the study population.

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

20-766/S-008

Roche

September 4, 1997

Maureen Hess, MPH, RD
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 14B-04
Rockville, Maryland 20857-1706

Dear Ms. Hess:

Re: NDA 20-766 XENICAL® (orlistat) Capsules, 120 mg
Request for Additional Copies of the Swedish Study Submission

As per your request, please find enclosed five (5) additional copies of a previous submission sent to the Agency on August 27, 1997. This submission was sent in response to an FDA request to review the Swedish study and questions concerning the Swedish health care system.

If you have any questions concerning this submission, please contact the undersigned at your convenience.

Sincerely,

HOFFMANN-LA ROCHE INC.

Laurie Skelton

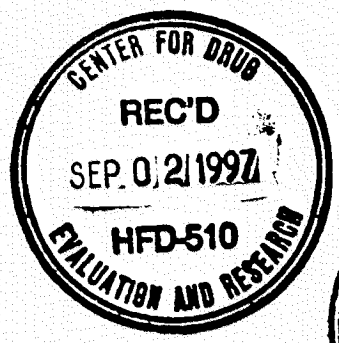
FOR Margaret J. Jack
Program Director
Drug Regulatory Affairs
(973) 235-4463 (Telephone)
(973) 235-7771 (Fax)

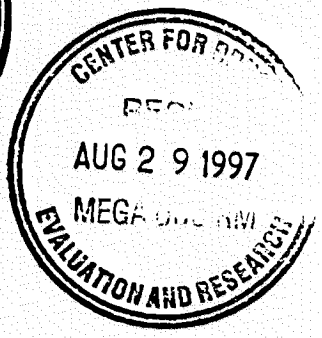
MJJ:LS/mi

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

NEW CORRESP.

Roche





August 27, 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

[redacted] 9/8/97

Ladies and Gentlemen:

Re: NDA 20-766 XENICAL® (orlistat) Capsules, 120 mg
Response to FDA Request to Review Swedish Study
and Questions Concerning Swedish Health Care System

[redacted] 9/11/97

As per our discussions with the Agency on August 25, 1997, we are herewith providing the Swedish Study protocol for review and comment. Enclosed please find Protocol BM15421B entitled, "Weight reducing and NIDDM preventing effects of Xenical in obese patients", see Appendix 1. This 2-year study is designed to include approximately 3,000 patients of which 1,800 are obese women between 30 to 60 years of age. Mammograms will be performed at baseline, year 1 and year 2. Protocol BM15421B will be initiated in September, 1997 and will not be conducted under the US IND [redacted]

[redacted]

As per the Exclusion Criteria for this study, women with a confirmed diagnosis of cancer or a patient history of cancer (including breast cancer) will not be allowed to participate in the study. In Sweden there is a standard, five point grading system of mammograms for which we are trying to obtain further clarification. Our preliminary information suggests that the grading system is as follows:

1. normal - free of any lesions
2. benign changes or findings
3. suspicious lesions
4. cancer
5. cancer

We are currently obtaining English translations for this scale and a clearer clinical differentiation between each of the five categories including which grade includes carcinoma in situ. It is our current understanding that only patients with baseline mammograms graded as 1 or 2 will be entered into Protocol BM15421B. As soon as further information on the grading scale and which patients will be entered into the study is available, it will be provided to the Agency.

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

The case report forms (CRFs) for the study will also request information on dates of menarche and menopause, pregnancies, breast feeding, use of oral contraception, use of hormone replacement therapy, family history of breast cancer and previous mammograms. A sample of this portion of the CRF is provided in Appendix 2.

We are requesting that the Agency review and provide comments on Protocol BM15421B as soon as possible, as this study is being initiated September, 1997. Again, we hope to provide further information on the Swedish standard mammography grading scale and which patients will be included in the study later this week or early next week.

In response to the Agency's additional requests concerning information on the Swedish Health Care system, we are currently trying to obtain information on the percent of Swedish women with routine mammograms, percent of obese women with routine mammograms and the percent of obese women over 45 years of age who have routine mammograms. This information should be available in the near future. The currently available information suggests that annual mammograms are not routinely done in Sweden, but are done every 2 to 5 years. However, the percent of female patients undergoing routine mammograms in Sweden is unknown.

If you have any questions or comments concerning this submission, please contact the undersigned at your convenience.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J Jack

REVIEWS COMPLETED

CSO ACTION:
☑ LETTER ☐ N.A.I. ☐ MEMO
MAN 9-21-97
CSO INITIALS DATE

Margaret J. Jack
Program Director
Drug Regulatory Affairs
(973) 235-4463 (Telephone)
(973) 235-7771 (Fax)

MJJ:LS/rp
Attachments
HLR No. 1997-2099