Roche

T-46341

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

Ladies and Gentlemen:

Re: NDA 20-766 XENICAL® (orlistat) Capsules, 120 mg
Withdrawal of the Unapproved Application

In accordance with 21 CFR 314.65, we are herewith notifying the Agency that we are withdrawing the above referenced New Drug Application. Also, as provided in 21 CRF 314.65, this application is being withdrawn without prejudice to refiling.

We consider this NDA and all information contained therein to be CONFIDENTIAL and not disclosable under the Freedom of Information Act (5 USC 552) and the Code of Federal Regulations (21 CFR 314.430). If for any reason the Agency should feel the need to disclose any information contained in this NDA to any member of the public, we expect that we will be consulted first on the issue of disclosure.

If you have any questions concerning this application or the withdrawal of the same, please contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J Jack

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

MJJ:LS/rp
HLR No. 1997-2098

T43065

Roche

August 21, 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
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706

Dear Ms. Hess:

Re: NDA 20-766 XENICAL® (orlistat) Capsules, 120 mg
Response to FDA Request of July 1, 1997

Reference is made to the teleconferences between the FDA and Roche on July 1, August 12 and August 19 of this year. Enclosed please find data and analyses that address questions raised by FDA on July 1. This submission includes the following major components:

1. an integrated summary that outlines the major components of the submission, the conclusions of the investigations and the inter-relationship between the findings,
2. a report from Dr. Gary Williams that addresses the biological plausibility of orlistat as an initiator or promoter of breast cancer as a result of his assessment of the nonclinical data,
3. two reports that discuss the lack of relationship between orlistat and estrogen disposition and metabolism,
4. an overall summary and individual reports from Drs. Feig (mammogram expert), McGee (pathologist), Rose (oncologist), Wright (pathologist), and Dr. Winer (oncologist) of their independent assessment of each individual breast cancer case. Dr. McGee's report will be sent under separate cover.
5. results (as of August 18) of the follow-up survey of women over 45 years of age participating in the phase 3 clinical program and an epidemiologic assessment of these data.

As discussed previously, the final updated tables from the survey, based on the stopping rules for each patient, and subsequent epidemiologic assessment of these data are scheduled for submission during the week of September 1. In addition, final assessments from the experts who conducted the independent assessments of each breast cancer case will be provided in the same submission.

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

In conclusion, all information available to date continues to support the position that there is no association of breast cancer with orlistat. Based on this preponderance of new evidence, the most likely explanations for the observation in the controlled clinical trials continue to be chance or a detection bias.

If FDA personnel have any questions or comments on this submission, please contact me directly at (973) 562-3710 or Ms. Peggy Jack at (973) 235-4463.

Sincerely,

HOFFMANN-LA ROCHE INC.

Daniel L. Zabrowski, PhD
Vice President and Global Head, Drug Regulatory Affairs
(973) 562-3710 (telephone)
(973) 562-3700/3554 (fax)

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

DZ:LS/mi
Attachments
HLR No. 1997-2031

T46432

ORIGINAL

Roche

August 21, 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
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706

Dear Ms. Hess:

Re: NDA 20-766 XENICAL® (orlistat) Capsules, 120 mg
Response to FDA Request of July 1, 1997: Information Not Included in a Previous Submission Also Sent to the Agency Today

Reference is made to the teleconferences between the FDA and Roche on July 1, August 12, and August 19 of this year. Enclosed please find the following information which was not included in our previous submission also sent to you today.

1. Prof. J. McGee's Interim Histopathology Report (Appendix B of our previous submission)

2. Table 2 - Prof. J. McGee's Summary of the Histopathology Assessment

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

Sincerely,

HOFFMANN-LA ROCHE INC.

Laurie Shaw

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

MJJ:LS/mi
Attachment
HLR No. 1997-2037

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

T45231

Roche

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
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 19 1997
HFD-510

August 15, 1997

Dear Ms. Hess:

RE: NDA 20-766 XENICAL® (orlistat) Capsules, 120 mg
Progress Report on Response to FDA Request of July 1, 1997

Reference is made to the teleconferences between members of FDA and Roche on July 1 and August 12 of this year. Attached please find a description of the work that the company is conducting to address questions that were raised by FDA on July 1. This work is currently being summarized for submission on August 21. This submission will be delivered to you by a Roche employee on that day.

Attachment #1 contains a progress report on the company's efforts to obtain additional follow-up information on patients in the controlled clinical trials. To date, we have responses from approximately 70% of patients. Through this survey, we have received reports of 3 additional cases of breast cancer (2 patients from the 120 mg orlistat group and 1 patient from the placebo group). In addition, approximately 78% of respondents in the survey have reported that they have received a mammogram since the end of the study. Based on our stopping rules for this survey, we anticipate to receive responses from 80-85% of patients in both US and Europe.

Attachment #2 contains a description of the basic analyses that are underway on the survey and trial data. We have calculated crude rates for the survey period, and they are reported in the following table.

Treatment Group	New Cases	Person Years of Follow-Up from Survey	Rate/1000 Years of Survey Follow-Up
placebo	1	929	1.07
30/60 mg orlistat	0	483	0
120 mg orlistat	2	1283	1.56
all orlistat	2	1766	1.13

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

Attachment #3 contains a brief summary of the independent assessments that are currently being conducted on each case of breast cancer that was reported during the study or survey. The curriculum vitae for each assessor is enclosed in attachment #4.

On August 21, a report will also be submitted from Dr. Gary Williams of the American Health Foundation (see attachment #4 for curriculum vitae). In this report, Dr. Williams summarizes his review of the relevant nonclinical data and provides his assessment on whether this product presents a hazard with respect to human cancer. He was specifically requested to determine whether orlistat has the characteristic features of an initiating-type carcinogen or demonstrates any promoting activity.

In conclusion, all information available to date provides further support that the breast cancer results in the controlled trials were due to chance.

If FDA personnel have any questions or comments on this submission or the submission that will be delivered on August 21, please contact me directly at (973) 562-3710.

Sincerely,

HOFFMANN-LA ROCHE INC.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

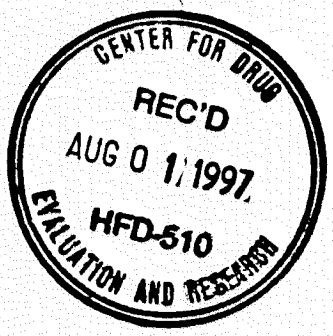
CSO INITIALS DATE

Daniel L. Zabrowski, PhD
Vice President and Global Head, Drug Regulatory Affairs
(973) 562-3710 (telephone)
(973) 562-3700/3554 (fax)

DZ:LS/rp
Attachments
HLR No. 1997-1969

Roche

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
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706



July 30, 1997

Dear Ms. Hess:

RE: NDA 20-766 XENICAL® (orlistat) Capsules
Market Exclusivity Information

Reference is made to Hoffmann-La Roche Inc's NDA 20-766 submitted November 27, 1997. Pursuant to Section 505 of the Federal Food, Drug and Cosmetic Act, the following Market Exclusivity Information supplements exclusivity information provided with the NDA and is submitted for inclusion in the above-noted NDA.

Since the New Drug Application has not yet been approved, this submission is considered as constituting trade secrets or commercial or financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552). It is requested that this submission not be published until the New Drug Application has been approved.

Additionally, as required, two copies of this information are also being submitted to the Central Document Room.

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

Sincerely,

Hoffmann-La Roche Inc.

Margaret J Jack

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

MJJ:LS/rp
Attachment
HLR No. 1997-1771

Copies (2): Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852

43982

MARKET EXCLUSIVITY INFORMATION

Re: Pending NDA 20-766 XENICAL® (orlistat) 120 mg Capsule
Patent Information/Market Exclusivity Request

Authority for Market Exclusivity Claim

Pursuant to the provisions of Section 505(c)(3)(D)(ii) and Section 505 (j)(4)(D)(ii) of the Federal Food, Drug and Cosmetic Act ("Act") as amended, we hereby claim the market exclusivity period as provided for under those Sections based upon the fact that no other active ingredient (including an ester or salt of the active ingredient) of which has been approved in any other application submitted under Section 505(b)(1). During this market exclusivity period, no other application may be accepted for submission by FDA which refers to orlistat before the expiration of 5 years from the date of the approval of the application for orlistat except that such an application could be submitted after the expiration of 4 years if the application contains a certificate of patent invalidity or non-infringement as further described in the Act.

In accord with the further amendments to the Act, when the approval is made by the Administration, it is our understanding that this market exclusivity information will be included at the same time in the Approved Prescription Drug Product List.

A copy of the patent information originally submitted on November 27, 1996 is herewith attached.

PATENT INFORMATION[1]

1.	Active Ingredient(s):	Orlistat
2.	Strength(s):	120 mg
3.	Trade Name:	Xenical®
4.	Dosage form and Route of Administration	capsule, oral
5.	Application Firm Name:	Hoffmann-La Roche Inc.
6.	NDA Number:	20-766
7.	First Approval Date:	None[2]
8.	Exclusivity:	Subject to patent rights, first ANDA can be submitted five years from date of pending NDA approval.
9.	Patent Information:	
	Patent Number and Expiration date:	4,598,089 6/18/2004[3]
	Type of Patent:	Drug
	Patent Owner:	Hoffmann-La Roche Inc.

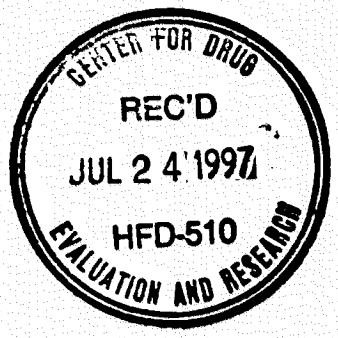
[1] While this submission was prepared in good faith, no warranty or guarantee is made regarding the accuracy or completeness of the information contained therein.

[2] Since the New Drug Application has not yet been approved, this submission is considered as constituting trade secrets or commercial or financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552). It is requested that this submission not be published until the New Drug Application has been approved.

[3] Subject to patent term extension provisions for 35 USC § 156 et seq.

Roche

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



July 23, 1997

Ladies and Gentlemen:

Re: NDA 20-766 XENICAL® (orlistat) Capsules, 120 mg
Revised Labeling
Response to FDA Fax Dated June 27, 1997

We are herewith providing a response to the Agency's comments on the XENICAL® labeling communicated to the sponsor in a fax dated June 27, 1997. This response includes the labeling changes suggested by the Division and any additional revisions to the label that the sponsor feels is appropriate. Also included in this submission is the sponsor's rationale for any changes made to the labeling previously provided by the Agency. This labeling does not however include breast cancer as this issue is still being addressed by the sponsor. Additional information will be available in the near future and will be addressed with the Agency at that time.

This submission consists of three parts:

1. **A Composite Label:**
This revised labeling incorporates the text recommended by the Agency and any additional text or changes to the Agency's suggested labeling are provided. The rationale for the sponsor's additions or changes to the label are also provided.

2. **The Revised Label**:
A copy of the above-mentioned label without any editorial designations

3. **Mineral Balance Study**
The final study report for this study is provided in volumes 2 of this submission.

In the very near future, we will also provide an electronic copy of the sponsor's suggested labeling in WordPerfect. This electronic copy will be sent under a separate cover.

The sponsor is of the opinion that the purpose of approved labeling is to provide medical practitioners with accurate and sufficient information for the safe and effective use of the drug in clinical practice. For a chronic, multifactorial disease such as obesity, physicians should be informed of the treatment effects on obesity-related risk factors in addition to the effects on weight management and weight regain. Other factors which can affect treatment outcomes, such as diet, should be presented in the label. The safety information should also be addressed adequately as well as accurately. To these ends, the sponsor believes that the enclosed label does provide the proper information to the medical practitioner.

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

The CLINICAL STUDIES section of the label has been reorganized as follows:

A. Year-one Results
   1. Weight Loss and Weight Maintenance information
   2. Risk Factors:
      Population as a Whole
      Population with Abnormal Baseline Risk Factor
   3. Quality of Life

B. Weight Regain

C. Two-Years Results
   1. Weight Loss and Weight Maintenance information
   2. Risk Factors:
      Population as a Whole
      Population with Abnormal Baseline Risk Factor
   3. Quality of Life

The sponsor will be happy to meet with the Agency concerning any other unresolved issues with the XENICAL® labeling if needed.

Please contact the undersigned if you have any questions concerning this submission.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J. Jack

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

MJJ/LS:lh
Enclosures
HLR No. 1997-1738
Desk Copies: Ms. Maureen Hess (6)

NZ0766

ORIGINAL

JUN 17 1997

16 April 1997

Memorandum of Telephone Conversation

tween: Margaret J. Jack (201) 235-4463
Dr. Jerry Kamm (201) 235-5035
Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110

and

David H. Hertig
Pharmacologist, HFD-510
(301) 443-3520; Fax (301) 443-0072

bject: Xenical (orlistat) Capsules NDA 20-766
Labeling and Preclinical studies.

BEST POSSIBLE

lled Peggy Jack; she suggested that since the questions were preclinical she uld have their toxicologist, Dr. Jerry Kamm, call me which he did.

l carcinogenicity studies must now be presented to the Executive CAC arcinogenic Assessment Committee). I am scheduled to present the mouse and rat rcinogenicity studies with Xenical (orlistat) to the committee on April 29, 97.

e following points and questions were posed to the sponsor:

1) With regard to the Precautions section of the labeling (Carcinogenesis, Mutagenesis, Impairment of Fertility and Pregnancy sections), multiples of the human dose were based on surface area (mg/m^2). How were these values derived? Could you please provide your method and calculations?
FDA normally bases calculations of surface area comparisons on a paper by Freireich, E.J. et al., (Cancer Chemother. Rep. 50:219-244, 1966.).

2) Could you also please provide us with the percent of drug in the diet of the mouse and rat carcinogenicity studies?

3) According to our statistician, the positive linear dose-response trend was found to be statistically significant ($p=0.0248$) for liver hemangiosarcoma in female mice [2 in the high dose (1500 mg/kg)]. Could you provide us with historical control data regarding hemangioma/hemangiosarcomas from studies with the strain of mice used in the carcinogenicity study (Han IBM: NMRI mouse, SPF). These studies should have been conducted at about the same time and under the same conditions as the mouse carcinogenicity study. In addition, references in the literature addressing the findings of hemangioma/hemangiosarcoma in mice, especially the Han strain would be helpful.

r. Kamm stated that he would try to answer the above questions and get the nformation to me as soon as possible.
Regarding questions:
1) He used Freireich, E.J., et al. for surface area calculations. He will send calculations.
2) He will calculate the amount of drug in the diet based on final bodyweights and targeted dose.
3) He will research this area.

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

[redacted] 6/17/97

. **Jerry Kamm returned my call.**

There are no reliable human data at clinical doses of 120 mg t.i.d. This s discussed with the agency during the course of the rat and mouse dose lection and it was agreed that a higher dose could be used in humans with trapolation (400 mg t.i.d.). [They do have data for orlistat and metabolites - e p.m. call below.]

♦In a Phase III clinical trial 80% of the plasma levels were undetectable. e highest single value seen was 8 ng/ml (parent drug, point data?).

♦They do have some data (C_{max} and C_{min}) from mouse and rat, parent and tabolites M1 and M3.

BEST POSSIBLE

♦With regard to the carcinogenicity studies the animals were bled over 24 urs at the end - we are seeing mean data.

♦There was no marked effect on transit time through the intestine.

♦The plasma assays were done in Basle, Switzerland.
. Kamm believes variability in part to be due to ad lib feeding.

♦Protein binding was high in all species. These analysis were done by other lab and he does not have the numbers readily at hand.

♦He has a later Expert Report which was sent to Europe. Does not believe at this was sent to the US. This report has various comparison tables. These will fax to me and send the full report by Federal Express.

m.: **Phone call** on voice mail from Dr. Kamm. He stated that their clinical harmacology group indicated that they do have human AUC data for orlistat and etabolites. He will fax when the data are obtained.

Received fax containing portions of Expert Report (Europe) as well as uman AUC data.

m.: **Call** from Dr. Kamm to see if fax had been received and to offer explanation f contents as follows:

♦Fax p. 007: The AUC given here for orlistat in humans is for total adioactivity. For M1 and M3, radioactivity is for the actual metabolite.

♦Notice that the AUC_{0-10} for Humans is 0-10 hrs while that of the AUC_{0-24} nimals is 0-24 hrs., therefore, one will have to multiply by 2.4. [This is not roper! See note below.]

♦The AUC for female rats and mice was greater than that for males.

♦By Dr. Kamm's calculation:
[These are not valid numbers! 2.4x was used in the calculations.]

MOUSE: The M1 ratio (mouse/human) is 29
The M3 ratio (mouse/human) is 68
Combined - add and calculate together = 55

RAT: M1 ratio (rat/human) is 63.5
M3 ratio (rat/human) is 14.4
Combined - add and calculate together = 29.9

DRUG
D
1997
510
RSEARCH

AMENDMENT ... ORIGINAL

Roche Pharmaceuticals
A Member of the Roche Group

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

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

ISI 6/19/97

ISI June 16, 1997

See Pharm Review of Labeling dtd 13,16 Jun 97. 19 Jun 97

CENTER FOR DRUG REC'D JUN 17 1997 HFD-510 EVALUATION AND RESEARCH

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

ISI 6/18/97

Dear Ms. Hess:

Re: NDA 20-766 Xenical® (orlistat) Capsules, 120 mg
Request for Additional Version of Labeling on Disk

As per your request, we have edited the June 2 version of the Xenical draft labeling and are herewith providing this edited version of the labeling electronically in WordPerfect, Version 6.1. For your convenience, we have enclosed a printed copy of the above and two computer disks which have been scanned for viruses.

June 2 Version of Label

Again, the June 2 label is a composite of the labeling recommended by the primary reviewers of this application. When the sponsor disagreed with "FDA reviewer-recommended text", then that latter text was designated with strikeout and "sponsor-suggested replacement text" was included and underlined.

June 16 Edited Labeling

This edited version of the labeling included electronically in this submission differs from the June 2 edited labeling in the following manner.

The June 16 version is identical to the June 2 version with the following exceptions. The editing tools, e.g., strikeouts and underlining are removed. As a result, some words will appear to be "run-on". However, all text that appeared as either a strikeout or underline in the June 2 version is provided.

June 13 Edited Labeling

As per our previous submission dated June 13 which included a disk, etc., the June 13 edited version of the label is the June 2 label with the struck-out text removed. The text that was underlined in the June 2 label appears as un-underlined text in this edited version of the label.

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Sincerely,

HOFFMANN-LA ROCHE INC.

Lorrie Sharon

FOR Margaret J. Jack
Program Director
Drug Regulatory Affairs

MJJ/LS:lh
Enclosures
HLR No. 1997-1368

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 13, 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 Additional Version of Labeling on Disk

June 2 Version

As per your request, we have edited the June 2 version of the Xenical draft labeling and are herewith providing this edited version of the labeling electronically in WordPerfect, Version 6.0, with the filename "clean.doc". For your convenience, we have enclosed a printed copy of the above and two computer disks which have been scanned for viruses.

June 2 Version of Label

Again, the June 2 label is a composite of the labeling recommended by the primary reviewers of this application. When the sponsor disagreed with "FDA reviewer-recommended text", then that latter text was designated with strikeout and "sponsor-suggested replacement text" was included and underlined.

June 13 Edited Labeling

This edited version of the labeling included electronically in this submission is identical to the June 2 labeling with the following exceptions:

1. All strikeout text is removed.

2. The underlining only was removed from the underlined text in the June 2 version. The text now appears un-underlined.

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
IND No. 1997-1354