CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-390

CORRESPONDENCE

Telephone Conversation Memorandum

ANDA: 75-390

DRUG: Naproxen Delayed-release Tablets, 375 mg and 500 mg

FIRM: Alphapharm PTY Ltd

PERSONS INVOLVED: Christine Markus, U.S. Agent, King & Spaulding
Tim Ames, Raj Bykadi, FDA

PHONE NUMBER: 202-626-2926

DATE: March 9, 2001

Called firm to request updated finish product release and stability protocol specification reflecting the Div of Bioequivalence recommended dissolution method and specifications as per the January 28, 2000 fax communication. Ms Markus indicated she would convey the request and fax in the information as a Telephone amendment.

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem. I, Team 1, OGD

cc:

alphapharm

R&D Fax No. +61-7-300-6398

27th March 2001

Dr Rashmikant M. Patel
Director, Division of Chemistry I,
Office of Generic Drugs - HFD-620,
Centre for Drug Evaluation and Research,
Food and Drug Administration,
Metro Park North II,
7500 Standish Place, Room 150,
ROCKVILLE, MD 20855-2773, USA

N/AM

ORIG AMENDMENT

Re: **ANDA # 75-390**
Telephone Amendment for Naproxen Delayed-Release Tablets 375 mg and 500 mg

Dear Dr Patel,

Further to a telephone request on 9th March 2001 to update our finished product and stability specifications to reflect a dissolution specification recommended by the Division of Bioequivalence in a facsimile dated January 28, 2000, we enclose a Telephone Amendment for Naproxen Delayed-Release Tablets 375 mg and 500 mg ANDA #75-390.

This amendment is submitted on our behalf by our Agent, King and Spalding. Three complete copies of the amendment are enclosed – an Archival copy (Blue Folder), a Chemistry section (Red folder) and a Field Copy (Burgundy Folder). A signed Certification of the Field Copies (Red and Burgundy Folders) as true copies of this amendment has also been included.

A copy of this amendment was forwarded by facsimile on March 27, 2001 to Tim Ames.

We request that all information in this file be treated as confidential within the meaning of CFR § 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorised member of your office.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAR 29 2001
OGD

First for quality and value medicines

Alphapharm Pty Limited
ABN 93 002 359 739
PO Box 36 Camperdown NSW 1450

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Manufacturing / Research & Development
15 Garnet Street Carole Park QLD 4300
T 07 3000 6344 F 07 3000 6395

Customer Service
T 1800 077 421 F 1800 358 199
www.alphapharm.com.au

Should you have any questions regarding the information in this amendment, please do not hesitate to contact our agent, King and Spalding.

Yours sincerely,

Alphapharm Pty Ltd

Georgina Napier-Munn.

Regulatory Affairs Manager - Research and Development

Encl.

alphapharm

R&D Fax No. +61 7 3000-6398

February 16th, 2001.

Dr R. M. Patel,
Director, Division of Chemistry I,
Office of Generic Drugs,
Centre for Drug Evaluation and Research,
MPN-II, HFD-600, 5600 Fishers Lane,
ROCKVILLE, MD 20857 U.S.A.

NDA ORIG AMENDMENT

Re: ANDA #75-390
Minor Amendment for Naproxen Delayed-release Tablets 375 mg and 500 mg

Dear Dr Patel,

In response to the deficiency letter dated February 2nd, 2001, please find enclosed a Minor Amendment for Naproxen Delayed-release Tablets 375 mg and 500 mg ANDA #75-390. This amendment addresses the comments and deficiencies pertaining to the above ANDA raised in the Not Approvable letter.

Please find enclosed three complete copies of this amendment; an Archival copy (Blue folder), a Chemistry section (Red folder) and a Field copy (Burgundy folder). A signed certification of the Field copies as true copies of this amendment has also been included.

12 copies of the final package inserts and 4 copies of the side by side comparison with annotated changes have been included in the Archival Copy (Blue Folder).

Copies of the FDA deficiency correspondence and the Form FDA 356h, signed by our U.S. Agent, King and Spalding, are also included.

Yours sincerely,
Alphapharm Pty Ltd

G Napier Munn

Georgina Napier-Munn
Regulatory Affairs Manager (R&D)

CENTER FOR DRUG EVALUATION AND RESEARCH
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FEB 20 2001
OGD

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FEB 2 2001

38. Chemistry Comments to be provided to the Applicant

ANDA: 75-390 APPLICANT: Alphapharm Pty. Ltd.

DRUG PRODUCT: Naproxen Delayed-Release Tablets, 375 mg and 500 mg

The deficiencies presented represents MINOR deficiencies:

1. You have revised the hardness limits to 4-12 kP units from 6-14 kP units. What is the impact of lowering the hardness limits on the breakage of tablets during shipping and handling and storage? Please justify your revised hardness limits by providing the friability test results. Please provide the in-process specs and test results for your process validation batches also.

2. The DMF is presently deficient. The DMF holder has been notified of the deficiencies. Please do not respond to this deficiency until the DMF holder has informed you that they have responded to their deficiencies.

Sincerely yours,

Paul S. Lee

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ALPHAPHARM

PHARMACEUTICALS

12/22/00 AM noted. To CDRC Par waiver for review.

December 14th, 2000.

Dr R. M. Patel,
Director,
Division of Chemistry I,
Office of Generic Drugs,
Centre for Drug Evaluation and Research,
MPN-II, HFD-600,
5600 Fishers Lane,
***ROCKVILLE**, MD 20857*
U.S.A.

NDA ORIG AMENDMENT

Re: ***Minor Amendment for Naproxen Delayed-release Tablets 375 mg and 500 mg ANDA #75-390.***

Dear Dr Patel,

In response to the deficiency letter dated July 31st 2000, please find enclosed a Minor Amendment for Naproxen Delayed-release Tablets 375 mg and 500 mg ANDA #75-390. This amendment addresses the comments and deficiencies pertaining to the above ANDA raised in the Not Approvable letter.

Please find enclosed two complete copies of this amendment; an Archival copy (Blue folder) and a Chemistry section (Red folder). Three copies of our revised methods, Part B, Response 1, bound in Burgundy folders, have also been included for use by the district laboratory. A signed certification of these Field copies as true copies of this amendment has also been included.

Alphapharm wishes to change agent from Par Pharmaceutical Inc. to King and Spalding. A letter appointing King and Spalding as our U.S. Agent is included in this application. Copies of the deficiency letter and the form FDA 356h, signed by our U.S. Agent, King and Spalding, are also included.

Yours sincerely,
Alphapharm Pty Ltd

Mooney

Brett Mooney, Ph.D.,
Senior Manager
Research and Development

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
DEC 19 2000
OGD

12/22/00

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December 14th, 2000

Dr R. M. Patel,
Director,
Division of Chemistry I,
Office of Generic Drugs,
Centre for Drug Evaluation and Research,
MPN-II, HFD-600,
5600 Fishers Lane,
***ROCKVILLE**, MD 20857*
U.S.A.

Re: Minor Amendment for Naproxen Delayed-release Tablets 375 mg and 500 mg ANDA #75-390.

Dear Dr Patel,

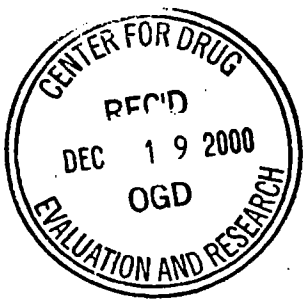
This is to advise that Alphapharm Pty Ltd has now nominated and appointed King and Spalding, 1730 Pennsylvania Avenue, Washington D.C. 20006-4706, as its U.S. Agent and that Eugene Pfeifer and Christina Markus are authorised to personally represent Alphapharm Pty Ltd in connection with this application and regulatory matters until further notice.

Alphapharm Pty Ltd will no longer use Par Pharmaceutical Inc., One Ram Ridge Road, Spring Valley NY 10977, as their agent for the above ANDA.

Yours sincerely,
Alphapharm Pty Ltd

Mooney

Brett Mooney, Ph.D.,
Senior Manager
Research and Development



ALPHAPHARM
PHARMACEUTICALS

D foreign
D

May 5th, 2000.

ORIG AMENDMENT
N Am

Dr. R. M. Patel,
Director,
Division of Chemistry I,
Office of Generic Drugs,
Centre for Drug Evaluation and Research,
MPN-II, HFD-600,
5600 Fishers Lane,
***ROCKVILLE**, MD 20857*
U.S.A.

Re: Minor Amendment for Naproxen Delayed-release Tablets 375 mg and 500 mg ANDA # 75-390.

Dear Dr. Patel,

Further to the deficiency letter dated March 23rd, 2000, detailing comments and deficiencies pertaining to the above ANDA, enclosed in the Minor Amendment for Naproxen Delayed-release Tablets 375 mg and 500 mg.

Please find enclosed two complete copies of this amendment; an Archival copy (Blue folder) and a Chemistry section (Red folder). A signed certification of the Field copy as a true copy of this amendment has also been included.

Copies of the deficiency letter and the form FDA 356h, signed by our U.S. agent, Par Pharmaceutical Inc., are included.

Should you have any further questions regarding the information in this amendment, please do not hesitate to contact our agent, Par Pharmaceutical Inc..

Yours sincerely,
Alphapharm Pty. Ltd.

PER. RPT#

Brett Mooney

Brett Mooney, Ph.D.,
Research and Development Manager

DSS

MAY 18 2000

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JUL 31 2000

38. Chemistry Comments to be provided to the Applicant

ANDA: 75-390 APPLICANT: Alphapharm Pty. Ltd.

DRUG PRODUCT: Naproxen Delayed-Release Tablets, 375 mg and 500 mg

The deficiencies presented represents a MINOR deficiencies:

1. We have reviewed the latest information provided by Drugs Ltd, the holder DMF . DMF is currently deficient and the DMF holder has been notified of the deficiencies. Please do not respond until you have been notified that all the deficiencies have been addressed by the DMF holder.

2. You have established a specification of NMT for 'Weight Gain' for the coated tablets. Please establish the minimum and maximum weight gain for the coated tablets at the completion of the coating operation. Establish your specification specifically for the coating materials considering that water may be a significant part of the weight gain.

3. Please review and update as necessary the specifications for Organic Volatile Impurities in your drug substance and applicable excipients to meet the current USP requirements.

4. Please update your finished product and stability specs and data sheets to show the revised dissolution specification as recommended by the Division of Bioequivalence. Additionally, please provide available long term room temperature stability data for the ANDA exhibit batches.

   In addition to responding to this deficiency, please note and acknowledge the following in your response.

   We have received the method validation report for the drug product from our District Laboratory. We note that the District Lab has made a recommendation to use a mobile phase to prepare the standard and sample solutions in your assay method. This recommendation is made to improve the peak shape and symmetry. Please contact Mr. Jay Santos at the following address for any additional information regarding the recommendation.

Food and Drug Administration
Philadelphia District Science Branch
200 Chestnut Street
Room 200
Philadelphia, PA 19106

Tel: (215)597-4390

Sincerely yours,

7/28/00

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ALPHAPHARM
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D Foreign
D

May 5th, 2000.

ORIG AMENDMENT
N Am

Dr. R. M. Patel,
Director,
Division of Chemistry I,
Office of Generic Drugs,
Centre for Drug Evaluation and Research,
MPN-II, HFD-600,
5600 Fishers Lane,
***ROCKVILLE**, MD 20857*
U.S.A.

Re: Minor Amendment for Naproxen Delayed-release Tablets 375 mg and 500 mg ANDA # 75-390.

Dear Dr. Patel,

Further to the deficiency letter dated March 23rd, 2000, detailing comments and deficiencies pertaining to the above ANDA, enclosed in the Minor Amendment for Naproxen Delayed-release Tablets 375 mg and 500 mg.

Please find enclosed two complete copies of this amendment; an Archival copy (Blue folder) and a Chemistry section (Red folder). A signed certification of the Field copy as a true copy of this amendment has also been included.

Copies of the deficiency letter and the form FDA 356h, signed by our U.S. agent, Par Pharmaceutical Inc., are included.

Should you have any further questions regarding the information in this amendment, please do not hesitate to contact our agent, Par Pharmaceutical Inc..

Yours sincerely,
Alphapharm Pty. Ltd.

PER. RPT#

Mooney

Brett Mooney, Ph.D.,
Research and Development Manager

DSS

MAY 18 2000

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MAR 23 2000

38. Chemistry Comments to be provided to the Applicant

ANDA: 75-390 APPLICANT: Alphapharm Pty. Ltd.

DRUG PRODUCT: Naproxen Delayed-Release Tablets, 375 mg and 500 mg

Deficiency:

We have reviewed the Drug Master File for Naproxen and found it to be deficient. The holder of the DMF has been notified of the deficiencies. Please do not respond to this deficiency until you have been notified by the DMF holder that they have responded to their deficiency letter.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Reseat

ALPHAPHARM
PHARMACEUTICALS

February 24th, 2000.

ALPHAPHARM
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NEW CORRESP
NC to
Fax

Dr. R. M. Patel,
Director,
Division of Chemistry I,
Office of Generic Drugs,
Centre for Drug Evaluation and Research,
MPN-II, HFD-600,
5600 Fishers Lane,
***ROCKVILLE**, MD 20857*
U.S.A.

Re: Facsimile Amendment for Naproxen Delayed-release Tablets 375 mg and 500 mg ANDA # 75-390.

Dear Dr. Patel,

Further to the facsimile received from your agency pertaining to Naproxen Delayed-release Tablets 375 mg and 500 mg ANDA # 75-390, please find enclosed the following response.

The comments in the Chemistry and Labelling sections have been addressed in the enclosed facsimile amendment.

Please find enclosed two complete copies of this facsimile amendment; an Archival copy (Blue folder) and a Chemistry section (Red folder). Included in the Archival copy (Blue folder) are 12 copies of the final printed carton labels and package inserts and 4 copies of the side by side comparison with annotated differences.

A copy of this amendment was forwarded by facsimile on February 24th 2000 to Bonnie McNeal.

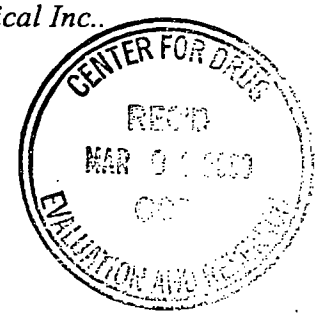
A signed certification of the Field copy as a true copy of this facsimile amendment has also been included.

Copies of the deficiency letter and the form FDA 356h, signed by our U.S. agent, Par Pharmaceutical Inc., are included.

Should you have any further questions regarding the information in this amendment, please do not hesitate to contact our agent, Par Pharmaceutical Inc..

Yours sincerely,
Alphapharm Pty. Ltd.

Brett Mooney, Ph.D.,
Research and Development Manager



75-390

NDC 57315-029-04

NAPROXEN DELAYED-RELEASE TABLETS 375 mg

℞ only

Unit dose 100 tablets

10 blister strips of 10 tablets

CHILD RESISTANT PACKAGE

Usual Adult Dosage: See package insert for full prescribing information.

Store at 15° to 30°C (59° to 86°F).

Protect from light.

Use this carton to protect contents from light.

310/3

Manufactured by:
ALPHAPHARM PTY. LTD.
Cnr Garnet & Antimony Sts.,
Carole Park, QLD. 4300
Australia

Call 1-800-661 3429

APPROVED

APR 19 2001

ALPHAPHARM

Lot No.:

Exp.:

NDC 57315-030-04

NAPROXEN DELAYED-RELEASE TABLETS 500 mg

℞ only

Unit dose 100 tablets

10 blister strips of 10 tablets

CHILD RESISTANT PACKAGE

Usual Adult Dosage: See package insert for full prescribing information.

Store at 15° to 30°C (59° to 86°F).

Protect from light.

Use this carton to protect contents from light.

312/3

Manufactured by:
ALPHAPHARM PTY. LTD.
Cnr Garnet & Antimony Sts.,
Carole Park, QLD. 4300
Australia

Call 1-800-661 3429

APPROVED

APR 19 2001

ALPHAPHARM

Lot No.:

Exp.:

ALPHAPHARM
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August 12th 1999.

ALPHAPHARM
Pty Limited
ACN 002 359 739

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Dr. Nasser Mahmud,
Office of Generic Drugs,
Document Control Room,
Metro Park North-II,
7500 Standish Place, Room 150
***Rockville**, Maryland 20855*
USA

ORIG AMENDMENT

AB

Re: Bioequivalence Amendment for Naproxen Delayed-release Tablets 375 mg and 500 mg, A.N.D.A. #75-390

Dear Dr Mahmud,

The comments and deficiencies of August 10th 1999 have been addressed in the enclosed Bioequivalence Amendment for Naproxen Delayed-release Tablets 375 mg and 500 mg.

Please find enclosed 2 copies of the Bioequivalence Amendment - an Archival copy (Blue folder) and Pharmacokinetic section (Orange folder) both with signed 356h forms included.

A copy of this bioequivalence amendment was forwarded by facsimile, on the 12th August, 1999, to Jennifer Pan.

A signed Certification of the Field Copy (Orange Folder) statement as a true copy of the Bioequivalence Amendment response is also included.

Should there be any questions regarding this application, please do not hesitate to contact our agent, Par Pharmaceutical, Inc.. A letter appointing Par as our agent is included.

Thank you for your assistance with our application.

Yours sincerely,
Alphapharm Pty. Ltd.

Mooney

Brett Mooney, Ph.D.,
Research and Development Manager

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 17 1999
OGD

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July 19th, 1999.

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Dr. Mark Anderson,
OFFICE OF GENERIC DRUGS
Document Control Room,
Metro Park North II,
7500 Standish Place, Room 150
***Rockville,** MD 20855-2773,*
USA

NDA ORIG AMENDMENT

Re:** **Major Amendment for Naproxen Delayed-release Tablets 375 mg and 500 mg: A.N.D.A. #75-390

Dear Dr Anderson,

Further to your correspondence of December 28th 1998 detailing comments and deficiencies pertaining to the above ANDA, enclosed is the Major Amendment for Naproxen Delayed-release Tablets 375 mg and 500 mg.

The comments and deficiencies in the Chemistry section and Labelling section have been addressed in the enclosed Major Amendment.

Please find enclosed two complete copies of this amendment - Archival copy (Blue Folder) and Chemistry section (Red folder). A signed Certification of the Field copy (Red Folder) as a true copy of the Major Amendment is also included.

Also enclosed are 3 copies of the Maroon Folder - Field Submission Chemistry section which contains the updated/revised assay method validation data for use at the FDA Laboratories.

In a separate Archival copy (Blue Folder) there is a secure copy of each of the following: final printed labels, final package insert, the side by side comparison of Alphapharms' revised package insert and the original package insert with annotated differences. Also attached to this folder (in plastic sleeves) are 12 copies of the final printed labels and final package inserts and 4 copies of the side by side comparison with annotated differences.

Copies of the deficiency letter and the FDA Form 356h, signed by our U.S. agent, Par Pharmaceutical Inc., are included. A letter appointing Par as our agent follows this letter.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 26 1999
OGD

Should you have any further questions regarding the information in this Major Amendment, please do not hesitate to contact our agent, Par Pharmaceutical, Inc..

Yours sincerely,
Alphapharm Pty. Ltd.

Brett Mooney, Ph.D.,
Research and Development Manager

Encl.

ALPHAPHARM
PHARMACEUTICALS

July 19th, 1999.

NDA ORIG AMENDMENT
AB

Dr. Nasser Mahmud,
Office of Generic Drugs,
Document Control Room,
Metro Park North-II,
7500 Standish Place, Room 150
***Rockville**, Maryland 20855*
USA

Re: Bioequivalency Amendment for Naproxen Delayed-release Tablets 375 mg and 500 mg, A.N.D.A. #75-390

Dear Dr. Mahmud,

Please find enclosed 2 copies of the Bioequivalency Amendment - an Archival Copy (Blue Folder) and Pharmacokinetic Section Copy (Orange Folder) in response to correspondence from Dr. Dale P. Conner, Director, Division of Bioequivalence OGD dated November 30th 1998.

A signed Certification of the Field Copy (Orange Folder) statement as a true copy of the Bioequivalency Amendment response is also included.

The comments and deficiencies in the Bioequivalence Section have been addressed in the enclosed Bioequivalency Amendment.

Should there be any questions regarding this application, please do not hesitate to contact our agent, Par Pharmaceutical, Inc.. A letter appointing Par as our agent is included.

Thank you for your assistance with our application.

Yours sincerely,
Alphapharm Pty. Ltd.

Brett Mooney, Ph.D.,
Research and Development Manager

CENTER FOR DRUG
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JUL 26 1999
OGD
EVALUATION AND RESEARCH

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DEC 2 8 1998

38. Chemistry Comments to be Provided to the Applicant

ANDA: _75-390_____ APPLICANT: _Alphapharm Pty. Ltd._____

DRUG PRODUCT: ___Naproxen Delayed-Release Tablets, 375 mg and 500 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. Please certify that does not use the solvents as identified in US Pharmacopeia's Chemical Test <467> - Organic Volatile Impurities in the manufacture of Naproxen.

2. You have omitted the "Batch Total Yield Calculation Sheet" for the four exhibit batches, PM109, PM108, RJ213 and RJ121 in your application. Please submit copies of these documents.

3. Your Letter of Authorization for Drug Master File held by dated December 17, 1991, is not valid. Sections 1 and 103 do not apply to updated information in this DMF. Furthermore, lacquers designated as and (page 04981 of your application) do not agree with Section 103 information submitted in 1991. Please update the referenced information with so that the foil information shown in your Q.A. document agrees with information from Drug Master File

4. Your finished product Certificates of Analysis identify related impurities observed in the at "rt 17.30" and "rt 22.29" for the exhibit lots PM109 and PM108 respectively. Since these two lots of drug product are made from the same lots of drug substance and a common granulate, please discuss the reason for the two different retention times.

5. Please supply a detailed description for the manufacture of (R,S)-Naproxen. This description should include starting materials, method of synthesis including applicable flow charts, in-process controls, analytical methods used, final specifications, etc.

6. Please supply a detailed description of the process for Naproxen and ethyl alcohol.

7. How many times is the step repeated for each batch (lot number) of drug substance. Please explain how the various "yields" of (S)-Naproxen are mixed or how a uniform mixture of drug substance is obtained from the processes.

8. Please supply the acceptance/release specifications for the used in your drug substance manufacturing process.

9. There are large differences of Total Impurities limits for the drug substance when analyzed by) and by . Please provide compatability data to demonstrate that the two methods yield comparable results.

10. The specification for residual should be reduced to "no more than to agree with the acceptance specifications used by Alphapharm.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The data supplied by has been supplied directly to your application, rather than the more usual manner of constructing/maintaining a separate Drug Master File. Because of this manner of drug substance information submission, it now becomes the responsibility of Alphapharm to monitor and periodically update this information of drug substance manufacture; i.e., manufacturing changes, annual reporting, stability testing, etc. You may want to consult with to change to a more traditional manner of drug substance manufacture/supply information, i.e., a Drug Master File held by

2. Your lead page of the Stability Test documentation identify the site of manufacture as Alphapharm whereas data pages of the Stability documentation show as the new drug manufacturer. Please clarify this observation. If this is a "third party" contract laboratory whereby manufacturing, analytical methods developed, packaging, stability testing, etc., was performed, please provide the address, responsible parties and functions performed at

3. The bioequivalence information which you have provided is under review. After this review is completed, any deficiencies found will be communicated to you under a separate cover.

4. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval.

5. Your drug products are not compendial drug products. The agency's district laboratory will request samples of the drug substance and the finished dosage forms for methods validation at the appropriate time.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ALPHAPHARM
PHARMACEUTICALS

5th October, 1998

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Fax 07 3271 5037

Dr. D.L. Sporn,
Director of Generic Drugs,
Centre for Drug Evaluation and Research,
MPN-II, HFD-600,
5600 Fishers Lane,
***ROCKVILLE**, MD 20857*
U.S.A.

NDA ORIG AMENDMENT
N/AC

RE: NAPROXEN DELAYED-RELEASE TABLETS 375 mg AND 500 mg ANDA #75-390, REFUSAL TO FILE LETTER.

Dear Dr Sporn,

Further to the FDA refusal to file letter of 26th June 1998 pertaining to Naproxen Delayed-release Tablets 375 mg and 500 mg, please find enclosed the following response.

The comments in the Chemistry section and Labelling section have been addressed in the enclosed amendment.

Please find enclosed four complete copies of this amendment-

1) *an Archival copy (Blue Folder)*
2) *a Chemistry section (Red Folder)*
3) *a Field Submission copy (Maroon Folder)*
4) *a Pharmacokinetic section (Orange Folder)*

Also enclosed in a separate Archival copy (Blue Folder) are the additional 4 copies of the draft proposed labelling.

A signed Certification of the Field copy as a true copy of the Amendment has also been included.

Copies of the refusal to file letter and the FDA Form 356h, signed by our U.S. agent, Par Pharmaceuticals Inc., are included.

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OCT 13 1998
GENERIC DRUGS

Should you have any further questions regarding the information in this Amendment, please do not hesitate to contact our agent, Par Pharmaceuticals.

Yours sincerely,
ALPHAPHARM PTY. LTD.

Brett Mooney, Ph.D.,
RESEARCH AND DEVELOPMENT MANAGER

Encl.

ANDA 75-390

Lipha Pharmaceuticals, Inc.
U.S. Agent for: Alphapharm Pty. Ltd.
Attention: Anita M. Goodman, M.D.
9 West 57th Street, Suite 3825
New York, NY 10019-2701

JUN 26 1998

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated May 14, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Naproxen Delayed-release Tablets USP, 375 mg and 500 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

1. Since you were unable to obtain a letter from the DMF holder, authorizing the FDA to review their DMF for the drug substance, please withdraw all reference to

2. Since your bioequivalence studies were conducted on the unauthorized source of drug substance, you are required to submit new *in* vivo studies on the drug substance from limited.

3. You have failed to completely package your exhibit batch in containers proposed for marketing. Partial packaging, packaging into bulk storage containers, or a packaging configuration for which you are not seeking approval is not acceptable unless a protocol has been submitted and approved prior to submission of the application. For example, packaging records for the 375 mg and 500 mg strengths show an yield respectively. But you appear to have packaged ablets of the 375 mg strength and tablets of the 500 mg strength, less than the minimum packaging required. Please refer to the letters to the industry from the Director, Office of Generic Drugs,

dated November 8, 1991 and August 4, 1993. Also, we refer you to the Office of Generic Drugs' Policy and Procedure Guide #41-95 dated February 8, 1995.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In addition, to be in compliance with 314.50(e)(2)(ii), you must provide four copies of the draft proposed labeling. Please provide two additional copies of the draft package insert for both the archival and review copies of the application.

In the future submissions, please refer to Policy and Procedure Guides #30-91, attachment B(2) for guidance on ANDA fasteners (hinges). A copy of this guidance maybe obtained from the Drug information Branch (301) 827-4573 or from the following Internet site:

http://www.fda.gov/cder/guidance/index.htm

In addition, we recommend an updated form 356h. A revised copy of this form can be found on the following Internet site:

http://aosweb.psc.dhhs.gov/forms/fdaforms.htm

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call.

Saundra T. Middleton
Project Manager
(301) 827-5862

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ALPHAPHARM
PHARMACEUTICALS

RTF 6/15/98 Addendum

ALPHAPHARM
Pty Limited
ACN 002 359 739

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Tel. 02 9692 9777
Fax 02 9566 4686

Manufacturing
15 Garnet Street
CAROLE PARK
QLD 4300
Tel. 07 3271 3244
Fax 07 3271 5037

14th May, 1998

Dr. D.L. Sporn,
Director of Generic Drugs,
Centre for Drug Evaluation and Research,
MPN-II, HFD-600,
5600 Fishers Lane,
***ROCKVILLE**, MD 20857*
U.S.A.

ORIGINAL ABBREVIATED NEW DRUG APPLICATION FOR NAPROXEN DELAYED-RELEASE TABLETS 375 mg AND 500 mg

Dear Dr. Sporn,

Pursuant to Section 505 (j) of the Food, Drug and Cosmetics Act, Alphapharm Pty. Ltd. herewith submits an Abbreviated New Drug Application for Naproxen Delayed-Release Tablets 375 mg and 500 mg. This Application is submitted on our behalf by our agent Lipha Pharmaceuticals Inc.. A letter appointing Lipha Pharmaceuticals Inc. as our Agent in the United States immediately follows this cover letter.

In support of this Application, the information outlined below is provided:

1) *Patent Certification.*

2) *356h Form, signed by our Agent, Lipha Pharmaceuticals Inc.*

3) *Index.*

4) *Chemistry, Manufacturing and Controls Information.*

5) *Draft labels/labelling and patient information leaflets. (The copies of the draft labels/labelling and patient information leaflet are presented in an Archival folder labelled accordingly).*

6) *Methods Validation Package (one copy in the Archival (Blue folder), one copy in the Review (Red) Folder, one copy in the Field Submission Chemistry (Maroon). The Analytical Methods and Methods Validation for Naproxen Delayed-Release Tablets contained in Section 16 of the ANDA is also presented in 3 copies (1 volume of each Maroon Folder - Field Submission Chemistry Section) for use at FDA Laboratories.*

7) *Bioavailability Studies of Naproxen Delayed-Release Tablets 375 mg and 500 mg*

A Two-Way Single-Dose Open-Label Fasting Bioavailability Study of Naproxen 375 mg Enteric-Coated Tablets In Normal Healthy Non-Smoking Male Volunteers, Biovail Study No. 1843.

A Two-Way Single-Dose Open-Label Fasting Bioavailabilty Study of Naproxen 500 mg Enteric-Coated Tablets in Normal Healthy Non-Smoking Male Volunteers, Biovail Study No. 1805-1.

A Three-Way Single-Dose Open-Label Food-Effect Bioavailability Study of Naproxen 500 mg Enteric-Coated Tablets In Normal Healthy Non-Smoking Male Volunteers, Biovail Study No. 1806.

Also find enclosed an Archival folder containing diskettes with plasma Naproxen concentration and pharmacokinetic data from these studies. This information can be found in the files entitled ' " and A hard copy of this data, as written on the diskette, is also enclosed.

Alphapharm had intended to use s the manufacturer of Naproxen Drug Substance. Naproxen Delayed-Release Tablets 375 mg and 500 mg (Batches PM109 and PM108) were manufactured using aterial. These two batches were used in the above mentioned bioavailability studies and placed on a stability programme in the proposed market packs.

hen failed to adequately support the ANDA and were not forthcoming with a Letter of Access to their USA DMF. Consequently, Alphapharm changed to : the manufacturer of the Naproxen Drug Substance.

Naproxen Delayed-Release Tablets 375 mg and 500 mg (Batches RJ213 and RJ121) were manufactured using aw material and placed on a stability programme in the proposed market packs.

This application contains complete details of

(1) The Drug Substance from both

(2) The Naproxen Delayed-Release Tablets 375 mg and 500 mg batches manufactured using the v material and batches manufactured using the aw material.

Enclosed please find three copies of this application. An Archival copy (Blue Folder), a Review copy divided into two parts: a Chemistry, Manufacturing and Controls data part (Red Folder), a Bioavailability/bioequivalence data part (Orange Folder); and a Field Submission copy (Maroon Folder) of the Chemistry, Manufacturing and Controls Information for use prior to Preapproval Inspections.

Three copies of Section 16 of the ANDA are also included in Field Submission Chemistry Section Folder (Maroon Folder).

We request that all information in this file be treated as confidential within the meaning of 21 CFR section 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorised member of your Office.

If you should have any questions regarding the information in this submission, please do not hesitate to contact our Agent, Lipha Pharmaceuticals Inc.

Yours Sincerely,
ALPHAPHARM PTY. LTD.

Mooney

Brett Mooney, Ph.D.
RESEARCH AND DEVELOPMENT MANAGER