CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-179

CORRESPONDENCE

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

May 1, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

ORIG AMENDMENT
N/AF
FPL

ANDA #75-179
NABUMETONE TABLETS, 500 mg and 750 mg
LABELING AMENDMENT

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced tentatively approved ANDA as a result of a telephone contact between Jim Braw of the Office of Generic Drugs and Deborah Jaskot, Senior Director of Regulatory Affairs at TEVA on April 14, 2000. Mr. Braw requested revision of our package insert labeling such that all reference to Nabumetone Tablets, 500 mg be deleted.

Per Mr. Braw's request, package insert labeling has been revised to delete all reference to the 500 mg strength, and twelve copies of final print labeling are provided herein. Please note that as TEVA Pharmaceuticals recently acquired Copley Pharmaceuticals, a request to revise the labeling for the TEVA USA product (ANDA # 75-189) to remove all reference to the 750 mg strength was also made. Therefore, revised labeling for ANDA # 75-189 is being submitted today in an amendment under separate cover.

Should you have any further questions or concerns regarding ANDA # 75-179, please contact me by telephone at (215) 256-8400, extension 5249 or by facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot

Deborah A. Jaskot
Authorized Agent

Enclosures
jpb

CENTER FOR DRUG
REC'D
MAY 02 2000
C&D
EVALUATION AND RESEARCH

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

Direct Tel: (781) 575-7318
Fax: (781) 575-7362

April 6, 2000

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: **Nabumetone Tablets, 500 mg and 750 mg**
ANDA 75-179
Minor Amendment

Dear Mr. Buehler:

Reference is made to Copley's ANDA 75-179 submitted August 4, 1997 for Nabumetone Tablets, 750 mg, to our Amendment dated October 27, 1997 providing for the 500 mg potency, and to the Agency's Minor Deficiency Letter dated March 27, 2000 (copy enclosed).

The Agency's comment has been restated and our response follows.

1. **The e was reviewed in connection with your amendment, and was found deficient. has been notified.**

   Please do not respond to this MINOR amendment letter until you have been informed by at they have submitted a complete response to the Agency.

Enclosed is a copy of a letter dated April 4, 2000 from notifying us that has responded to the deficiencies in Drug Master

We trust that our Minor Amendment satisfactorily addresses the Agency's concerns.

Please contact Deborah A. Jaskot, MS, RAC, Sr. Director, Regulatory Affairs at 215-256-8400 ext. 5249 or the undersigned at 781-575-7318 should you require any additional information.

Sincerely,

Vincent Andolina

Vincent Andolina, RAC
Sr. Manager, Product Registration

VA:va
Enclosures

cc: Deborah A. Jaskot, MS, RAC
Sr. Director, Regulatory Affairs, Teva Pharmaceuticals USA Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 07 2000
OGD

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38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-179 APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Nabumetone Tablets, 750 mg and 500 mg

The deficiency presented below represent a MINOR deficiency.

The File for Nabumetone was reviewed in connection with your amendment, and was found deficient. has been notified.

Please do not respond to this MINOR amendment letter until you have been informed by nc. that they have submitted a complete response to the Agency.

Sincerely yours,

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

38. **Chemistry Comments to be Provided to the Applicant:**

ANDA: 75-179 APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Nabumetone Tablets, 750 mg and 500 mg

The deficiency presented below represent a MINOR deficiency.

The Drug Master File for Nabumetone was reviewed in connection with your amendment, and was found deficient. nc. has been notified.

Please do not respond to this MINOR amendment letter until you have been informed by that they have submitted a complete response to the Agency.

Sincerely yours,

s/rm/cc

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

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

Direct Tel: (781) 575-7318
Fax: (781) 575-7362

February 29, 2000

NDA ORIG AMENDMENT

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: **Nabumetone Tablets, 500 mg and 750 mg**
ANDA 75-179
Minor Amendment

Dear Mr. Sporn:

Reference is made to Copley's ANDA 75-179 submitted August 4, 1997 for Nabumetone Tablets, 750 mg, to our Amendment dated October 27, 1997 providing for the 500 mg potency, and to the Agency's Not Approvable Letter dated September 28, 1999 (copy enclosed).

The Agency's September 28, 1999 letter stated that the Division of Manufacturing and Product Quality had recommended that approval of this ANDA be withheld until CGMP-related issues raised by the FDA New England District with regard to the active ingredient manufacturer, Napp Technologies, were resolved.

Enclosed is a copy of a letter dated February 10, 2000 from the FDA New England District to Rhodes Technologies (the current name of manufacturing site), stating that the District has recommended to CDER that the application is approvable.

We have now fulfilled all requirements for tentative approval, and request tentative approval of this ANDA.

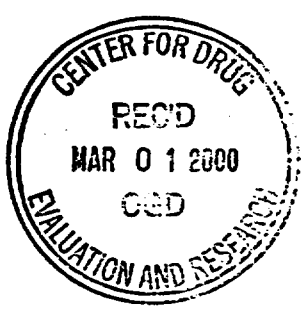
We believe that this ANDA should be eligible for final approval for the 750 mg potency on March 15, 2000, or on the date of the court decision finding that the patent is invalid, whichever occurs sooner. We anticipate that the District Court will find that the patent is invalid, and Copley will submit a copy of the Decision promptly upon receipt.

Please contact Gail Shamsi, RAC, Sr. Regulatory Associate at 781-575-7828 or the undersigned at 781-575-7318 should you require any additional information.

Sincerely,

Vincent Andolina

Vincent Andolina, RAC
Sr. Manager, Product Registration



VA:va
Enclosures

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V. 3. 1.

Gregory Davis
2 pages

NEW CORRESP
NC

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

Direct Tel: (781) 575-7318
Fax: (781) 575-7362

February 23, 2000

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: **Nabumetone Tablets, 500 mg and 750 mg**
ANDA 75-179
Patent Amendment

Dear Mr. Sporn:

Reference is made to Copley's ANDA 75-179 submitted August 4, 1997 for Nabumetone Tablets, 750 mg, to our Amendment dated October 27, 1997 providing for the 500 mg potency, to our Patent Amendments dated October 2, 1997 and February 9, 2000, and to § 505(j)(4)(B)(iii) of the Federal Food, Drug and Cosmetic Act.

Copley's February 9, 2000 Patent Amendment indicated that legal proceedings had been initiated by SmithKline Beecham Corporation and Beecham Group p.l.c. on October 27, 1997.

Mr. Gregory Davis, OGD spoke to Ms. Gail Shamsi of Copley on February 22, 2000, regarding the February 9 Patent Amendment which refers only to the Nabumetone Tablets, 750 mg strength. He asked whether Copley had notified SmithKline Beecham Corporation of the Nabumetone Tablets, 500 mg strength. Notification that ANDA 75-179 was amended to include the 500 mg strength Nabumetone Tablets was provided to the patent and NDA holder, SmithKline Beecham Corporation and received on November 11, 1997. Copies of the letter which was sent via certified mail and the return receipt card are enclosed.

We apologize for the delay in submitting this information. We believe that Copley's ANDA 75-179 should be eligible for final approval for the 750 mg potency on March 15, 2000, or on the date of the court decision finding that the patent is invalid, whichever occurs sooner. We anticipate that the District Court will find that the patent is invalid, and Copley will submit a copy of the Decision promptly upon receipt.

Please contact Gail Shamsi, RAC, Sr. Regulatory Associate at 781-575-7828 or the undersigned at 781-575-7318 should you require any additional information.

Sincerely,

Vincent Andolina

Vincent Andolina, RAC
Sr. Manager, Product Registration

Enclosures

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Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

Direct Tel: (781) 575-7318
Fax: (781) 575-7362

February 23, 2000

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: **Nabumetone Tablets, 500 mg and 750 mg**
ANDA 75-179
Patent Amendment

Dear Mr. Sporn:

Reference is made to Copley's ANDA 75-179 submitted August 4, 1997 for Nabumetone Tablets, 750 mg, to our Amendment dated October 27, 1997 providing for the 500 mg potency, to our Patent Amendments dated October 2, 1997 and February 9, 2000, and to § 505(j)(4)(B)(iii) of the Federal Food, Drug and Cosmetic Act.

Copley's February 9, 2000 Patent Amendment indicated that legal proceedings had been initiated by SmithKline Beecham Corporation and Beecham Group p.l.c. on October 27, 1997.

Mr. Gregory Davis, OGD spoke to Ms. Gail Shamsi of Copley on February 22, 2000, regarding the February 9 Patent Amendment which refers only to the Nabumetone Tablets, 750 mg strength. He asked whether Copley had notified SmithKline Beecham Corporation of the Nabumetone Tablets, 500 mg strength. Notification that ANDA 75-179 was amended to include the 500 mg strength Nabumetone Tablets was provided to the patent and NDA holder, SmithKline Beecham Corporation and received on November 11, 1997. Copies of the letter which was sent via certified mail and the return receipt card are enclosed.

We apologize for the delay in submitting this information. We believe that Copley's ANDA 75-179 should be eligible for final approval for the 750 mg potency on March 15, 2000, or on the date of the court decision finding that the patent is invalid, whichever occurs sooner. We anticipate that the District Court will find that the patent is invalid, and Copley will submit a copy of the Decision promptly upon receipt.

Please contact Gail Shamsi, RAC, Sr. Regulatory Associate at 781-575-7828 or the undersigned at 781-575-7318 should you require any additional information.

Sincerely,

Vincent Andolina

Vincent Andolina, RAC
Sr. Manager, Product Registration

Enclosures

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Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

Direct Tel: (781) 575-7318
Fax: (781) 575-7362

February 9, 2000

NEW CORRESP
NC

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: **Nabumetone Tablets, 500 mg and 750 mg**
ANDA 75-179
Patent Amendment

Dear Mr. Sporn:

Reference is made to Copley's ANDA 75-179 submitted August 4, 1997 for Nabumetone Tablets, 750 mg, to our Amendment dated October 27, 1997 providing for the 500 mg potency, to our Patent Amendment dated October 2, 1997, and to § 505(j)(4)(B)(iii) of the Federal Food, Drug and Cosmetic Act.

Copley's October 2, 1997 Patent Amendment indicated that the patent and NDA holder, SmithKline Beecham Corporation, received our Patent Notification on September 15, 1997.

Please be advised that SmithKline Beecham Corporation and Beecham Group p.l.c. initiated legal proceedings against Copley Pharmaceutical Inc., Civil Action No. 97CV12416RCL dated October 27, 1997 in the United States District Court for the District of Massachusetts. A copy of the Complaint is attached (pages 4-11).

Therefore, Copley's ANDA 75-179 should be eligible for final approval on March 15, 2000, or on the date of the court decision finding that the patent is invalid, whichever occurs sooner. We anticipate that the District Court will find that the patent is invalid, and will submit a copy of the Decision promptly upon receipt.

Please contact Gail Shamsi, RAC, Sr. Regulatory Associate at 781-575-7828 or the undersigned at 781-575-7318 should you require any additional information.

Sincerely,

Vincent Andolina

Vincent Andolina, RAC
Sr. Manager, Product Registration

VA:va
Enclosures

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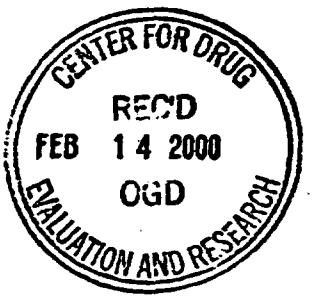

ANDA 75-179

Copley Pharmaceutical, Inc.
Attention: Isidoro Nudelman
25 John Road
Canton, MA 02021

SEP 28 1999

Dear Sir:

This is in reference to your abbreviated new drug application dated December 7, 1993, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Nabumetone Tablets, 500 mg and 750 mg.

Reference is also made to your amendments dated March 5, and July 16, 1998; and August 2, August 6, August 27, and September 22, 1999.

This application is deficient and, therefore, not approvable under 21 CFR 314.125(b)(13) because the Center for Drug Evaluation and Research (CDER) is unable to find that the methods used in, and the facilities and controls used for, the manufacture, processing, packaging or holding of the new drug product comply with current good manufacturing practice (CGMP) regulations.

Our conclusion is based upon the findings revealed during a CGMP inspection of by representatives of the United States Food and Drug Administration on December 9, 1998. During the inspection and as reported in recent telephone calls, this firm is not ready for inspection. Upon review of the inspectors' report and observations, we have received a recommendation from our Division of Manufacturing and Product Quality (DMPQ), Office of Compliance, to withhold approval of your abbreviated application.

Until such time as it can be demonstrated to the Agency that the CGMP-related issues associated with this facility have been corrected and the Agency's concerns are otherwise satisfied, your application cannot be approved.

You should amend this application when you have been informed by the New England District that the CGMP-related issues have been satisfactorily resolved. Your amendment, submitted in response to this not approvable letter, will be considered as a MINOR AMENDMENT provided that the amendment contains no significant additional information necessary to remedy the CGMP deficiencies

or to address concerns identified by the investigators. If, as a result of follow-up inspections related to the ongoing evaluation of this or other applications, it is necessary for you to significantly revise your procedures, controls or practices to correct the deficiencies, then the amendment will be considered to represent a MAJOR AMENDMENT.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

9/27/99

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

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

September 22, 1999

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: **Nabumetone Tablets, 500 mg and 750 mg**
ANDA # 75-179
Telephone Amendment to a Pending Application

Dear Mr. Sporn:

Reference is made to Copley's ANDA for Nabumetone Tablets, 500 mg and 750 mg, and to the telephone deficiency transmitted on September 22, 1999 by Ms. Ruby Yu, OGD Project Manager.

The Agency's comment has been restated and our response follows:

> **Submit a revised Post-Approval Stability Commitment with the phrase "if deemed appropriate" removed from the last paragraph.**

Enclosed is a revised Post-Approval Stability Commitment in which the last paragraph has been replaced with the commitments from Page 27, lines 907-912 of the Agency's June 1998 Draft Guidance for Industry "Stability Testing of Drug Substances and Drug Products."

We are submitting a hard copy of this Telephone Amendment via Federal Express, as well as transmitting it via facsimile.

We have now fulfilled all requirements for approval, and request the Agency's tentative approval of this ANDA.

Please contact Vincent Andolina, Senior Manager, Product Registration at 781-575-7318 or the undersigned at 781-575-7695 should you require any additional information.

Sincerely,

L. Nudelman, RAC
Director, Regulatory Affairs

IN:va
Enclosures

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NEW CORRESP
NC-

Copley Pharmaceutical Inc.
25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

August 27, 1999

(3.1)

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: **Nabumetone Tablets, 500 mg & 750 mg**
ANDA # 75-179
Telephone Amendment to a Pending Application

Dear Mr. Sporn:

Reference is made to Copley's ANDA for Nabumetone Tablets, 500 mg & 750 mg, and to our telephone conversation of August 20, 1999 with Ms. Ruby Yu, OGD Project Manager and Dr. Devinder S. (Dave) Gill, OGD Team Leader, Team 4.

The Agency's comment has been restated and our response follows:

> **Submit revised specifications for the active ingredient including the same limits for Residual Solvents as the DMF holder uses.**

Enclosed are revised specifications for the active ingredient, Document Number QC18-8277, Rev. Date 8/27/99, including a limit for Residual Solvents (Not More Than 0.2% isopropyl alcohol).

We are submitting a hard copy of this Telephone Amendment via Federal Express, as well as transmitting it via facsimile.

We have now fulfilled all requirements for approval, and request the Agency's tentative approval of this ANDA.

Please contact Vincent Andolina, Senior Manager, Product Registration at 781-575-7318 or the undersigned at 781-575-7695 should you require any additional information.

Sincerely,

I. Nudelman, RAC
Director, Regulatory Affairs

Enclosures

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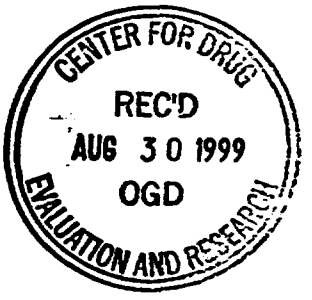

NEW CORRESP

NC

Copley Pharmaceutical Inc.
25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

August 6, 1999

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center For Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

(301) F

MINOR AMENDMENT
Nabumetone Tablets, 500 mg and 750 mg
ANDA # 75-179

Dear Mr. Sporn

Reference is made to our pending Abbreviated New Drug Application No.75-179 submitted August 5, 1997 for Nabumetone Tablets, 500 mg and 750 mg.

Further reference is made to our amendment of August 2, 1999 which responded to the Agency's deficiency Fax of May 24, 1999.

We have been informed by k, NJ, that their June 29, 1999 response to the deficiencies cited in DMF had the incorrect date rectified their response with the corrected date, July 29, 1999 (attached).

We believe that this information satisfactorily addresses the Agency's concern.

Please contact the undersigned at 1-781-575-7695 should you have any questions or require clarification.

Thank you.

Sincerely

L. Nudelman, RAC
Director, Regulatory Affairs

enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 09 1999
OGD

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

August 2, 1999

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center For Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/AM

MINOR AMENDMENT
Nabumetone Tablets, 500 mg and 750 mg
ANDA # 75-179

Dear Mr. Spōrn

Reference is made to our pending Abbreviated New Drug Application No.75-179 submitted August 5, 1999 for Nabumetone Tablets, 500 mg and 750 mg.

Further reference is made to our amendment of April 22, 1999 and to the Agency's deficiency Fax of May 24, 1999 (attached).

We have been informed by , that a response addressing all deficiencies cited in DMF was submitted to the FDA on June 29, 1999 (attached).

We believe that this information satisfactorily addresses the Agency's concern.

Please contact the undersigned at 1-781-575-7695 should you have any questions or require clarification.

Thank you.

Sincerely
Vincent Andolina for
I. Nudelman, RAC
Director, Regulatory Affairs

enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 03 1999
OGD

8-4-99

MAY 24 1999

38. **Chemistry Comments to be Provided to the Applicant:**

ANDA: 75-179 APPLICANT: Copley Pharmaceutical, Inc.

DRUG-PRODUCT: Nabumetone Tablets, 750 mg and 500 mg

The deficiency presented below represent a MINOR deficiency.

The response (dated April 2, 1999) to the deficiencies of Drug Master File (DMF) for Nabumetone was reviewed in connection with your submission, and was found deficient. has been notified.

Please do not respond to this MINOR amendment letter until you have been informed by hat they have submitted a complete response to the Agency.

Sincerely yours,

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

Copley Pharmaceutical Inc.
25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

April 22, 1999

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center For Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

MINOR AMENDMENT
Nabumetone Tablets, 500 mg and 750 mg
ANDA # 75-179

Dear Mr. Sporn

Reference is made to our pending Abbreviated New Drug Application No. 75-179 for Nabumetone Tablets, 500 mg and 750 mg.

Further reference is made to our amendment of September 18, 1998 and to the Agency's deficiency Fax of November 3, 1998.

The purpose of this submission is to respond to the Agency's deficiency letter of November 3, 1998. We have been informed by , that a response addressing all deficiencies cited in DMF was submitted to the FDA on April 2, 1999.

Included, please find revised copies of the following documents:
1. Finished Product Specification for Nabumetone Tablets 500 mg, Document Number: QC95-325
2. Finished Product Specification for Nabumetone Tablets 750 mg, Document Number: QC95-510

These documents include the revised specifications for dissolution, as requested in the above referenced Agency Fax.

Should you have any questions regarding this minor amendment, please contact the undersigned at 1-781-575-7695.

Thank you.

Sincerely

I. Nudelman, RAC
Director, Regulatory Affairs

NOV 3

38. **Chemistry Comments to be Provided to the Applicant:**

ANDA: 75-179 APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Nabumetone Tablets, 750 mg and 500 mg

The deficiencies presented below represent MINOR deficiencies.

1. The es' response (dated September 17, 1998) to the deficiencies of Drug Master File (DMF) No for Nabumetone was reviewed in connection with your submission, and was found deficient. . has been notified.

   Please do not respond to this MINOR amendment letter until you have been informed by Inc. that they have submitted a formal response to the Agency.

2. Please provide revised copies of Document No. QC95-510 and QC95-325 to include the revised specifications for dissolution.

Sincerely yours,

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

38. **Chemistry Comments to be Provided to the Applicant:**

ANDA: 75-179 APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Nabumetone Tablets, 750 mg and 500 mg

The deficiencies presented below represent MINOR deficiencies.

1. The response (dated September 17, 1998) to the deficiencies of Drug Master File (DMF) 5 for Nabumetone was reviewed in connection with your submission, and was found deficient. has been notified.

   Please do not respond to this MINOR amendment letter until you have been informed by Inc. that they have submitted a formal response to the Agency.

2. Please provide revised copies of Document No. QC95-510 and QC95-325 to include the revised specifications for dissolution.

Sincerely yours,

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

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

September 18, 1998

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center For Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/AM
9/28/98

MINOR AMENDMENT
Nabumetone Tablets, 500 mg and 750 mg
ANDA # 75-179

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application No. 75-179 for Nabumetone Tablets, 500 mg and 750 mg.

Further reference is made to our amendment of March 2, 1998 and to the Agency's deficiency letter of August 4, 1998 (attached).

The purpose of this submission is to respond to the Agency's deficiency letter of August 4, 1998. We have been informed by that a response addressing all deficiencies cited in DMF will be submitted to the FDA within the next several weeks. We have also revised our test specifications and methods for dissolution as recommended by the Division of Bioequivalence and provided this information in Attachment 1. In addition, dissolution test data for Nabumetone Tablets 500 mg and 750 mg, packaged in 100s and 500s stored for three months at accelerated conditions are provided in Attachment 2. All dissolution data are within specifications for the product.

We acknowledge that the firms listed in our application for Nabumetone Tablets, 500 mg and 750 mg must be in compliance with cGMPs at the time of approval.

Should you have any questions regarding this supplemental application, please contact the undersigned at (781) 575-7695 or Mr. Gary Lewis, Manager, Regulatory Affairs at (781) 575-7363.

Sincerely,

I. Nudelman, RAC
Director, Regulatory Affairs
Copley Pharmaceutical, Inc.

Enclosures:
Archive Copy (blue folder): 1 copy
Chemistry, Manufacturing, Controls Copy (red folder): 1 copy

RECEIVED
SEP 21 1998
GENERIC DRUGS

AUG 4 1998

38. **Chemistry Comments to be Provided to the Applicant:**

ANDA: 75-179 APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Nabumetone Tablets, 750 mg and 500 mg

A. The deficiencies presented below represent MINOR deficiencies.

1. Drug Master File (DMF) for Nabumetone was reviewed again in connection with your submission, and was found deficient. The holder of the DMF, has been notified of the deficiencies.

2. Please refer to the comments provided by the Division of Bioequivalence, and submit the following information

   a. Revised specifications and methods for finished product release and stability.

   b. Third month accelerated stability dissolution test data for both strengths packaged in 100s and 500s. The test results should meet the specifications recommended by the Division of Bioequivalence

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

The firms listed in your application must be in compliance with CGMP at the time of approval.

Sincerely yours,

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #75-179 APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Nabumetone Tablets, 750 mg and 500 mg.

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 ml of 2% w/v sodium laurel sulfate (SLS) in water, at 37°C using Apparatus #2 (Paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less than of the labeled amount of the drug in the tablet is dissolved in 45 minutes.
>
> Note: You are advised to submit dissolution testing profiles for your drug product and the reference listed drug (for the 750 mg and 500 mg strengthes). The dissolution testing data should compare your drug product to the reference listed drug using validation batches. Using the above-mentioned dissolution method at dissolution time points, 15, 30, 45 and 60 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

3.1

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #75-179 APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Nabumetone Tablets, 750 mg and 500 mg.

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 ml of 2% w/v sodium laurel sulfate (SLS) in water, at 37°C using Apparatus #2 (Paddle) at 50 rpm. The test product should meet the following specifications:

Not less than of the labeled amount of the drug in the tablet is dissolved in 45 minutes.

Note: You are advised to submit dissolution testing profiles for your drug product and the reference listed drug (for the 750 mg and 500 mg strengthes). The dissolution testing data should compare your drug product to the reference listed drug using validation batches. Using the above-mentioned dissolution method at dissolution time points, 15, 30, 45 and 60 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

July 20, 1998

NEW CORRESP
NC

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center For Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Bioequivalency Amendment
Nabumetone Tablet, 500 mg and 750 mg
ANDA No. 75-179

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application for Nabumetone Tablet, 500 mg and 750 mg, ANDA NO. 75-179, and to the Bioequivalency Amendment submitted on July 16, 1998.

We have inadvertently omitted the FDA 356h Form in the July 16, 1998 submission for the Bioequivalency Amendment. Please insert the attached FDA 356h forms in the referenced submission (one copy for the archival folder, and one copy for the chemistry review folder). For the reviewer's convenience, we are also providing a complete copy (including the FDA 356h form) of the Bioequivalence Amendment dated July 16, 1998 in the bioequivalence review folder (orange folder).

We apologize for any inconvenience that may have caused to your document control personnel. Please contact the undersigned at (781) 575-7695 should you have any question. Thank you!

Sincerely,

Linda Nudelman, RAC
Director, Regulatory Affairs

RECEIVED
JUL 21 1998
GENERIC DRUGS

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #75-179 APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Nabumetone Tablets, 750 mg and 500 mg.

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 ml of 2% w/v sodium laurel sulfate (SLS) in water, at 37°C using Apparatus #2 (Paddle) at 50 rpm. The test product should meet the following specifications:

Not less than of the labeled amount of the drug in the tablet is dissolved in 45 minutes.

Note: You are advised to submit dissolution testing profiles for your drug product and the reference listed drug (for the 750 mg and 500 mg strengthes). The dissolution testing data should compare your drug product to the reference listed drug using validation batches. Using the above-mentioned dissolution method at dissolution time points, 15, 30, 45 and 60 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

N/AB

July 16, 1998

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center For Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 1507500 Standish Place
Rockville, MD 20855-2773

BIOEQUIVALENCY AMENDMENT
Response to Telephone Deficiency of July 2, 1998
Nabumetone Tablets, 500 mg and 750 mg
ANDA No. 75-179

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application for Nabumetone Tablets, 500 mg and 750 mg, ANDA No. 75-179, to the amendment submitted on March 5, 1998, and to the telephone request from the Bioequivalence Division dated July 2, 1998.

The telephone deficiency dated July 2 , 1998 required Copley to clarify the expiration dating relative to the analytical data submitted in our March 5, 1998 amendment. The attached Bioequivalency Amendment prepared by Ms. Ellen Milano, Director of Analytical Development at Copley Pharmaceutical, Inc. addresses the Agency's request.

The attached amendment was submitted via facsimile to Ms. Nancy Chamberlin, Project Manager at the Division of Bioequivalence on July 16, 1998. We are now providing a hard copy via Federal Express mail service.

Please contact the undersigned at (781) 575-7695 should you have any question.

Sincerely,

I. Nudelman, RAC
Director, Regulatory Affairs

Enclosures

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

March 5, 1998

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center For Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 1507500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT

BIOEQUIVALENCY AMENDMENT
Response to Bioequivalency Deficiency Letter of February 5, 1998
Nabumetone Tablets, 500 mg and 750 mg
ANDA # 75-179

Dear Mr. Sporn:

Reference is made to the above Abbreviated New Drug Application submitted August 4, 1997, to the amendment submitted October 24, 1997 for the addition of the Nabumetone Tablets, 500 mg, and to the Agency's Bioequivalency Deficiency letter dated February 5, 1998 (copy attached). Enclosed in Attachment 1 is the requested dissolution data for the test products (Copley's Nabumetone Tablets, 500mg, lot # 325Z03 and 750mg, lot # 510Z05) and the reference products (SmithKline Beecham's RELAFEN®, 500mg, lot # 9775R51, and 750mg, lot # 17995R52) generated under the following conditions:

USP 23 apparatus # 2 (paddles), 50 rpm
in 900 mL of 2% w/v sodium lauryl sulfate (SLS) in water
at 37°C

Please note that the lots of Nabumetone Tablets, 750 mg used in the dissolution testing for this amendment are identical to the ones used in the in-vivo bioequivalency study submitted in the original ANDA. Copley will revise the current finished product test methods and specifications should the Agency requests Copley to adopt the dissolution testing and a new dissolution specification using the requested conditions.

RECEIVED
MAR 0 6 1998
GENERIC DRUGS

We believe that the data enclosed in this submission adequately address the Agency's request. Please contact the undersigned at (781) 575-7695 if you require clarifications.

Sincerely,

J. Nudelman, RAC
Director, Regulatory Affairs

Enclosures:
Archive Copy (blue folder): 1 copy
Pharmacokinetic Copy (orange folder): 1 copy

FEB 5 1998

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: #75-179 APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Nabumetone Tablets, 750 mg and 500 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

Please submit the dissolution data using USP 23 apparatus #2 (Paddle) at 50 rpm in 900 mL of 2% w/v sodium lauryl sulfate (SLS) in water at 37°C.

The dissolution testing should be conducted for both the test and reference products, performed simultaneously. The lot number of the dissolution testing should be identical to the one used in the in vivo bioeqivalence study.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

COPLEY PHARMACEUTICAL, INC.

BIOEQUIVALENCY AMENDMENT
Response to Bioequivalency Deficiency Letter of February 5, 1998
Nabumetone Tablets, 500 mg and 750 mg
ANDA # 75-179

Field Copy Certification

This is to certify that the field copy submitted in accord with 21 CFR § 314.96 (b) of the Code of Federal Regulations is a true copy of our bioequivalency amendment for Nabumetone Tablets, 500 mg and 750 mg, ANDA 75-179.

Regina S. Yeh

3/5/98

Regina S. Yeh, MS, RAC
Senior Regulatory Affairs Associate
Copley Pharmaceutical, Inc.

Date

COPLEY PHARMACEUTICAL, INC.
25 John Road
Canton, MA 02021

Fax to Number: 1-301-594-0180	From: Vincent Andolina
Recipients' Phone Number: 1- 301-827-5848	Date: November 24, 1999
Sender's Phone Number: 781-575-7318	Pages: 1 (including cover)
To: **Ms. Ruby Yu** Project Manager, Division of Chemistry I, Team 4	

RE: **Correspondence — ANDA 75-179**
Question for Dr. Devinder S. (Dave) Gill

Dear Ms. Yu:

On August 20, 1999, you and Dr. Gill called Copley to inform us of a telephone deficiency for our ANDA 75-179 for Nabumetone Tablets, 500 mg & 750 mg.

My notes show that as part of the conversation, Dr. Gill indicated that if we had any difficulty obtaining information on residual solvents limits from the holder of we should give him a call.

I am sending this facsimile to request information as to the specifications for all impurities and residual solvents currently provided for under because the DMF holder has not supplied this information to us.

If you have any questions, please call me at the number indicated above.

Thank you for your assistance.

Vincent Andolina

Vincent Andolina
Sr. Manager, Product Registration

38. **Chemistry Comments to be Provided to the Applicant:**

ANDA: 75-179 APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Nabumetone Tablets, 750 mg and 500 mg

A. The deficiencies presented below represent MINOR deficiencies.

1. Drug Master File (DMF) for Nabumetone was reviewed again in connection with your submission, and was found deficient. The holder of the DMF, Napp Technologies, Inc. has been notified of the deficiencies.

2. Please refer to the comments provided by the Division of Bioequivalence, and submit the following information

   a. Revised specifications and methods for finished product release and stability.

   b. Third month accelerated stability dissolution test data for both strengths packaged in 100s and 500s. The test results should meet the specifications recommended by the Division of Bioequivalence

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

The firms listed in your application must be in compliance with CGMP at the time of approval.

Sincerely yours,

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

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

March 2, 1998

FPL

AC

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center For Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 1507500 Standish Place
Rockville, MD 20855-2773

MAJOR AMENDMENT
Response to Deficiency Letter of January 12, 1998
Nabumetone Tablets, 500 mg and 750 mg
ANDA # 75-179

Dear Mr. Sporn:

Reference is made to the above Abbreviated New Drug Application submitted August 4, 1997, to the amendment submitted October 24, 1997, and to the Agency's Major Deficiency letter dated January 12, 1998 (copy attached). Enclosed are full responses and supporting documents to the chemistry, manufacturing and controls, and labeling comments listed in the January 12, 1998 letter.

As part of our response to the deficiency letter, we have also provided copies of the revised finished product and stability specifications, as well as the finished product test procedures in Attachment 1 of this amendment. In addition, we have amended the document RD09-510 - "Comparison of assay content uniformity, and dissolution data for bioequivalency studies" presented in the original ANDA by correcting a typographical error and providing re-tested dissolution data in Attachment 2 of this amendment. Lastly, copies of the revised proposed master production records for Nabumetone Tablets, 500 mg and 750 mg, which include the revised tablet hardness specifications based on our response to the Agency's comment are provided in Attachment 3 of this amendment.

Also enclosed is the response to the labeling deficiencies listed in the above referenced deficiency letter, including 12 copies of final printed container labels and insert labeling, as well as the annotated side-by-side comparison with the final printed labeling of the previous version.

Since this amendment pertains to the chemistry, manufacturing, and controls, and labeling, it is organized in the following manner for ease of review:

Chemistry, manufacturing, and controls (CMC):
A: Responses 1-11: Responses to section A:CMC questions 1-11
B: Responses 1-7: Responses to Section B: comments 1-7

Labeling:

1. Final printed container labels
2. Final printed insert labeling
3. Side-by-side comparison

Attachment 1:
Revised finished product specifications and test methods

Attachment 2:
Amendment to document RD09-510 - "Comparison of assay content uniformity and dissolution data for bioequivalency studies"

Attachment 3:
Revised proposed master production records for Nabumetone Tablets, 500 mg and 750 mg

We believe that the information enclosed in this submission adequately addresses the CMC and labeling comments pertaining to this ANDA and we look forward to an expeditious review of this amendment.

For any question on this submission, please contact Regina S. Yeh (Senior Regulatory Affairs Associate) at (781) 575-7828 or the undersigned at (781) 575-7695.

Sincerely,

I. Nudelman, RAC
Director, Regulatory Affairs

Enclosures:
Archive Copy (blue folder): 1 copy
Chemistry, Manufacturing, Controls Copy (red folder): 1 copy

FEB 5 1998

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: #75-179 APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Nabumetone Tablets, 750 mg and 500 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

Please submit the dissolution data using USP 23 apparatus #2 (Paddle) at 50 rpm in 900 mL of 2% w/v sodium lauryl sulfate (SLS) in water at 37°C.

The dissolution testing should be conducted for both the test and reference products, performed simultaneously. The lot number of the dissolution testing should be identical to the one used in the in vivo bioeqivalence study.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JAN 12 1998

ANDA: 75-179 APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Nabumetone Tablets, 750 mg and 500 mg

A. The deficiencies presented below represent MAJOR deficiencies.

1. Drug Master File (DMF) for Nabumetone was reviewed in connection with your submission, and was found deficient. The holder of the DMF, Hoechst Celanese has been notified of the deficiencies.

2. Please provide a consolidated list of Drug Master Files (DMFs) that are referenced in the submission. In the original submission, the list was not included. The DMF list provided in the amendment does not include the bottle used for the 750 mg strength product under DMF . There is also an error for Corporation's DMF number.

3. According to the composition table (Section VII, p. 114),the amount of active ingredient for the manufacture of the production batch will yield a product of higher strength. Please revise the amount to reflect the correct value. Also, please revise the amount of Starch to reflect the correct amount.

4. Amount of an ingredient per unit and the theorectical units yield for the two R & D Batch Records (p. 2674 and p. 285), will yield product beyond the scope of this application. Please clarify the reason for listing this information on the granulation record.

5. Please provide average tablet weight (ten tablets) for the actual compression for both strengths.

6. Please provide the test method for the Identification test in the Certificate of Analysis (COA) for the polystyrene liner (p. 364 and 365).

7. Your proposed in-process hardness range of 8-16 kp is too wide. Please revise the hardness range based on the observed values for both strengths. Alternatively, you may provide dissolution data at the high and low end of the proposed range.

8. Please establish and add specifications for individual related substances (known and unknown) to the finished drug product release and stability.

9. Please clarify which document (QC83-510/325 dated 02/06/97 or QC83-510 dated 07/10/97) is the official document for the 750 mg strength product.

10. Please justify why you propose a limit for total related substances at no more than when your accelerated stability test result indicated that no related substances were detected.

11. You mentioned two alternate drug substance suppliers in your submission, please be advised that if you intend to use the drug substance from the alternate sources, you must file an amendment to the application and provide manufacturing, packaging, and stability data on the drug product to support the use of alternate bulk drug substance suppliers.

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

1. Acceptability of your dissolution method and specifications will be determined by the Division of Bioequivalence.

2. We recommend that you provide revised component and composition tables to include the total amount of Sodium Glycolate per tablet.

3. A satisfactory CGMP compliance evaluation for the firms referenced in the ANDA is required for approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

4. We require a satisfactory methods validation prior to approval of the ANDA. We will schedule the validation with the District Office once the test and specification issues are resolved.

5. Please be advised that review of your Scale-up/Validation Overview (p. 2635) is the responsibility of the FDA investigators.

6. Acceptance of your expiration dating period is contingent upon the results of bioequivalence review.

7. Please be advised that when a new version of a document is prepared, such as replacing several pages of a document, you should enter the proper revision date on the entire revised document, and submit the entire document in full. We are referring to document QC14(VAL)-827, entitled "Validation of the Stability Indicating Procedure for the Assay and Purity of Nabumetone Raw Material".

Sincerely yours,

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

ANDA: 75-179 APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Nabumetone Tablets, 750 mg and 500 mg

A. The deficiencies presented below represent MAJOR deficiencies.

1. Drug Master File (DMF) for Nabumetone was reviewed in connection with your submission, and was found deficient. The holder of the DMF, has been notified of the deficiencies.

2. Please provide a consolidated list of Drug Master Files (DMFs) that are referenced in the submission. In the original submission, the list was not included. The DMF list provided in the amendment does not include the bottle used for the 750 mg strength product under DMF There is also an error for DMF number.

3. According to the composition table (Section VII, p. 114), the amount of active ingredient for the manufacture of the production batch will yield a product of higher strength. Please revise the amount to reflect the correct value. Also, please revise the amount of Starch to reflect the correct amount.

4. Amount of an ingredient per unit and the theorectical units yield for the two R & D Batch Records (p. 2674 and p. 285), will yield product beyond the slope of this application. Please clarify the reason for listing this information on the granulation record.

5. Please provide average tablet weight (ten tablets) for the actual compression for both strengths.

6. Please provide the test method for the Identification test in the Certificate of Analysis (COA) for the liner (p. 364 and 365).

7. Your proposed in-process hardness range of 8-16 kp is too wide. Please revise the hardness range based on the observed values for both strengths. Alternatively, you may provide dissolution data at the high and low end of the proposed range.

8. Please establish and add specifications for individual related substances (known and unknown) to the finished drug product release and stability.

9. Please clarify which document (QC83-510/325 dated 02/06/97 or QC83-510 dated 07/10/97) is the official document for the 750 mg strength product.

10. Please justify why you propose a limit for total related substances at no more than when your accelerated stability test result indicated that no related substances were detected.

11. You mentioned two alternate drug substance suppliers in your submission, please be advised that if you intend to use the drug substance from the alternate sources, you must file an amendment to the application and provide manufacturing, packaging, and stability data on the drug product to support the use of alternate bulk drug substance suppliers.

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

1. Acceptability of your dissolution method and specifications will be determined by the Division of Bioequivalence.

2. We recommend that you provide revised component and composition tables to include the total amount of Sodium per tablet.

3. A satisfactory CGMP compliance evaluation for the firms referenced in the ANDA is required for approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

4. We require a satisfactory methods validation prior to approval of the ANDA. We will schedule the validation with the District Office once the test and specification issues are resolved.

5. Please be advised that review of your Scale-up/Validation Overview (p. 2635) is the responsibility of the FDA investigators.

6. Acceptance of your expiration dating period is contingent upon the results of bioequivalence review.

7. Please be advised that when a new version of a document is prepared, such as replacing several pages of a document, you should enter the proper revision date on the entire revised document, and submit the entire document in full. We are referring to document QC14(VAL)-827, entitled "Validation of the Stability Indicating HPLC Procedure for the Assay and Chromatographic Purity of Nabumetone Raw Material".

Sincerely yours,

11/7/98

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

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

October 24, 1997

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center For Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Amendment to ANDA # 75-179
Nabumetone Tablet 750 mg
Addition of 500 mg Tablet Strength

Dear Mr. Sporn:

Reference is made to our above Abbreviated New Drug Application for Nabumetone 750 mg Tablet which was submitted to the Agency on August 4, 1997. We are submitting this amendment to ANDA # 75-179 (Nabumetone 750 mg Tablet), to add 500 mg tablet strength.

Enclosed are copies of the technical sections of this application, including all technical segments pertaining to the 500 mg tablet strength, as well as an executive summary, FDA form 3439, and complete table of contents for the entire application. Please direct any written communication regarding this ANDA to me at the above address, or contact me via phone or fax by the following numbers:

(781) 575-7520 (direct dial)
(781) 575-7362 (fax)

Thank you for your prompt review of this submission.

Sincerely,

William Brochu, Ph.D.
Director, Regulatory Affairs

Enclosures:
Archive Copy (blue folder): 1 copy
Chemistry, Manufacturing, Controls Copy (red folder): 1 copy

10-3-97
1.1

Copley Pharmaceutical Inc.
25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

10/2/97

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

NEW CORRESP
NC

Application Amendment
Nabumetone Tablets 750mg ANDA#75-179

Dear Mr. Sporn:

Reference is made to Copley's Nabumetone ANDA # 75-179 dated 8/5/97 which contains a paragraph IV certification [21CFR314.94(a)(12)(i)(A)(4)].

Copley is hereby amending its application as required by 21CFR314.95(e) to provide certification that the patent holder has been notified of the filing of the referenced application, the fact that it contains a paragraph IV certification claiming 4,420,639 is invalid and unenforceable, and providing the information required under 21CFR314.95(c). This amendment includes a copy of Copley's cover letter to Mr. Jan Leschly, Chief Executive Officer of SmithKline Beecham and a copy of the return receipt from the US Postal Service (notice received by SKB on 9/15/97).

Please direct any written communication regarding this ANDA to me at the above address. If you need to call or fax, my telephone numbers are as follows: 781-575-7520 (direct dial), 781-575-7362 (fax); telephone area codes have recently been changed in certain Boston area cities.

Sincerely,

W.E. Brochu, Ph.D.
Director, Regulatory Affairs

RECEIVED
OCT 0 3 1997
GENERIC DRUGS

Nadine 10-7-97

ANDA 75-179

Copley Pharmaceutical, Inc.
Attention: William E. Brochu, Ph.D.
Canton Commerce Center
25 John Road
Canton, MA 02021

SEP 5 1997

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Nabumetone Tablets, 750 mg

DATE OF APPLICATION: August 4, 1997

DATE OF RECEIPT: August 5, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Jim Wilson
Project Manager
(301) 827-5848

Sincerely yours,

9/4/97

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

505(j)

Copley Pharmaceutical Inc.
25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

8/4/97

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

RE: ANDA for Nabumetone Tablets 750mg.
Original Submission

Dear Mr. Sporn:

Copley Pharmaceutical, Inc submits today an original abbreviated new drug application ("ANDA") seeking approval to market a 750mg nabumetone tablet product that is bioequivalent to the listed drug, Relafen 750mg, manufactured by SmithKline Beecham pursuant to NDA#19-583. This application is submitted under section 505(b)(1) of the Food Drug and Cosmetic Act and contains a "paragraph IV" patent certification as described in 21CFR314.94(a)(12)(i)(A)(4).

This application consists of 9 volumes. Copley is filing a complete archival copy of the ANDA (in blue binders) which contains all the information required in such an application. In addition we are filing the following segments:

- Technical Review Copy - red folders
- Bioequivalence Section - orange folders
- Analytical Methods Section (2 copies) - black folders
- Technical Section - New England District Office - burgundy folders.

All segments include a copy of the cover letter, 356h form, and complete table of contents for the entire application.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax, my telephone numbers are as follows: 617-575-7520 (direct dial), 617-575-7362 (fax).

We look forward to your notification of acceptance for filing of this application and to its prompt review.

Sincerely

W.E. Brochu, Ph.D.
Director, Regulatory Affairs