CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-072

CORRESPONDENCE

DURAmed

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Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

April 12, 1999

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

RE: **ANDA 75-072 Verapamil HCl ER Tablets, USP, 120 mg and 240 mg**

Subject: **FACSIMILE AMENDMENT**

Dear Mr. Sporn:

Reference is made to a facsimile amendment dated April 6, 1999 regarding chemistry and labeling deficiencies found on review of our ANDA #75-072 for Verapamil Hydrochloride Extended-Release Tablets, USP 120 mg and 240 mg. We have noted the deficiencies cited and are amending the application, having responded to all of the deficiencies. For each item we first restate the deficiency then present our response or explanation. As requested, we have included a side-by-side comparison of our final printed labeling with our last submission.

This amendment includes two copies, an archival (blue) copy and a review (red) copy. A copy of the response, minus the final printed labeling, was faxed to (301) 827-4337. In addition, a copy of the chemistry response, minus the label ng, was provided to Mr. Tim Ames. We certify that a true copy of the technical section as described in 21 CFR 314.50 (d)(5) has been provided to the Food and Drug Administration, North Brunswick Resident Post, North Brunswick, N.J.

Please direct any written communications regarding this ANDA to me at the above address. If you have any questions or require any additional information, please contact Ms. Annette Arlinghaus at (513) 731-9900, by fax at (513) 731-6482, or the undersigned at (513) 458-7274.

Sincerely,

Annette Arlinghaus /jar

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

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APR 13 1999
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Enclosures: completed 356h

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Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

ORIG AMENDMENT
N/AC

June 19, 1998

labeling reviewed 10.1.98 drafted aVyas

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JUN 22 1998
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Mr. Douglas L. Sporn
Director, Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Denied See Team B 6/29/98

Re: **ANDA 75-072**
Verapamil Hydrochloride Extended-Release Tablets USP, 120 mg, 180 mg and 240 mg

Subject: **Major Amendment Request for Consideration to Minor Amendment**

Dear Mr. Sporn:

Reference is made to a facsimile Major Amendment dated May 13, 1998, which included chemistry and labeling deficiencies found on review of our ANDA for Verapamil Hydrochloride Extended-Release Tablets USP, 120 mg, 180 mg and 240 mg.

In this amendment we respond fully to all of the deficiences listed in the referenced facsimile and request that the classification of this amendment be down-graded from a Major Amendment to a Minor Amendment.

The basis for this request is that there are no new deficiencies listed in the Major Amendment facsimile. The referenced facsimile lists clarification of previous chemistry deficiency responses for which the reviewer did not accept the proposed responses, in particular the definition of significant numbers, in-process controls and not providing a complete updated copy of the proposed master manufacturing batch record.

While the bulk of this response is the updated proposed batch record and updated stability tables, we do believe the responses to the reviewer's request for clarification can be reviewed within less than one hour. This application has been at the Office of Generic Drugs since February, 1997 and has undergone a very detailed review resulting in a previous Major Amendment for which we believe we had responded completely. This second Major Amendment is now requesting only minor additional clarifications and re-instatement of blend testing that was a disagreement with the reviewer in our previous response.

Mailed 6-22-98

We now believe we have answered the minor clarifications, have agreed to full in-process blend testing, and no substantive issues remain. Given this, we request that the Major Amendment be downgraded to a Minor Amendment and proceed to final review.

In addition, we request that the 180 mg strength tablet be withdrawn from the application and discontinue review. This decision is based on our on-going dialogue with the Division of Bioequivalence.

With regard to the format of this amendment, we have restated the question/comment followed by our response. As requested, we have included a side-by-side comparison of our final printed labeling with the proposed labeling in our last submission.

This amendment includes two copies, an archival (blue) copy and a review (red) copy. In addition a copy of the chemistry response, minus the batch records, was faxed to Mr. Tim Ames at 301-443-3839. We certify that a true copy of this submission has been provided to the Food and Drug Administration, North Brunswick Resident Post, North Brunswick, NJ.

Please direct any written communications regarding this request to me at the above address. If you have any questions, or require any additional information, please feel free to contact Ms. Annette Arlinghaus at (513) 731-9900 or myself at (513) 458-7274, or by fax at (513) 731-6482.

Sincerely,

Annette Arlinghaus /for

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

JRR/nam
Enclosures

1) Completed 356h
2) Desk copy - T. Ames (chemistry response only)

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Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

November 24, 1997

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

NDA ORIG AMENDMENT
AC

RE: **ANDA 75-072 Verapamil HCl ER Tablets, USP, 120 mg, 180 mg, 240 mg**

Subject: **ADDITIONAL CONTAINER/CLOSURE INFORMATION**

Dear Mr. Sporn:

Reference is made to our amendment dated October 24, 1997 regarding our Abbreviated New Drug Application (ANDA) 75-072 for Verapamil HCl ER Tablets, USP, 120 mg, 180 mg, 240 mg.

Deficiency A.5. of the October 24, 1997 amendment is in regards to USP <671> testing for "tight" containers. We now include water vapor permeation results for the container/closure systems used in the packaging of Verapamil HCl ER Tablets. This additional information has been paginated to be consistent with the October 24, 1997 amendment and is assigned page numbers 119a, 119b and 119c.

This **Amendment** includes two (2) copies, an archival (blue) copy and a review (red) copy.

We certify that a true copy of this submission has been provided to the Food and Drug Administration, North Brunswick Resident Post, North Brunswick, New Jersey.

If you have any questions, please feel free to contact Ms. Kala Patel, Somerset, N.J. at (908) 563-2245, or the undersigned at (513) 458-7274.

Sincerely,

Annette Arlington /for

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

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NOV 25 1997
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Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

ORIG AMENDMENT
N/AC

October 24, 1997

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

RE: **ANDA 75-072 Verapamil HCl ER Tablets, USP, 120 mg, 180 mg, 240 mg**

Subject: **MAJOR AMENDMENT**

Dear Mr. Sporn:

Reference is made to your correspondence dated August 20, 1997 concerning deficiencies in our Abbreviated New Drug Application 75-072 for Verapamil HCl ER Tablets, USP, 120 mg, 180 mg, 240 mg.

We have noted the deficiencies cited and are amending the application, having responded to all of the deficiencies. For each item we first restate the comment then present our response.

As requested, we have included a side-by-side comparison of our final printed labeling with the proposed labeling in our last submission.

This **Major Amendment** includes two (2) copies, an archival (blue) copy and a review (red) copy.

We certify that a true copy of this submission has been provided to the Food and Drug Administration, North Brunswick Resident Post, North Brunswick, New Jersey.

If you have any questions, please feel free to contact Ms. Kala Patel, Hallmark Division at (908) 563-2245, or the undersigned at (513) 458-7274.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

RECEIVED
OCT 27 1997
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Duramed Pharmaceuticals, Inc.
5040 Lester Road
Cincinnati, Ohio 45213
(513) 731-9900

June 13, 1997

Mr. Doug Sporn, 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

Re: ANDA 75-072 Verapamil HCl ER Tablets, USP
Telephone Amendment

Dear Mr. Sporn:

Reference is made to two telephone conversations on June 13, 1997 with Dr. Lizzie Sanchez and Mr. Makary in which the question was raised about the documentation of any deviations in the standard breakfast or meal schedule in the study of Verapamil HCl 240mg ER Tablets, USP under fed and fasted conditions. As was explained to Dr. Sanchez, there is no documentation of deviations to the meal schedule because there were no such deviations. Affirmative documentation that there were no deviations to the critical standard breakfast can be found in the Clinical Report on page 12-0122 of the original ANDA submission 75-072, wherein it is stated (paragraph 3):

"All subjects completed their breakfasts"

In the section of the Clinical Report under "Protocol Deviations" (pages 12-0122-3), there is no discussion of meal deviations because there were none.

For clarity and ease of reference, we have attached the referenced pages of the ANDA; this letter offers no new information.

Please contact the undersigned by telephone at 513-458-7325 or by FAX at 513-731-6482 should you have questions about this submission.

Sincerely,

Ken Phelps
Vice President Corporate Projects

Enclosure: completed FDA 356h
cc: Lizzie Sanchez (FAX letter only)

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Duramed Pharmaceuticals, Inc.
5040 Lester Road
Cincinnati, Ohio 45213
(513) 731-9900

June 2, 1997

Mr. Doug Sporn, 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

NC 3.

Re: ANDA 75-072 Verapamil HCl ER Tablets, USP

Dear Mr. Sporn:

Reference is made to a telephone conversation with Ms. Lizzie Sanchez on June 2, 1997 in which she informed Mr. Ken Phelps that the diskette containing the data from the 180 mg fasted bioequivalence study, the diskette containing the data from the 240 mg fed bioequivalence study, the diskette containing the data from the 240 mg steady state bioequivalence study, and the diskette containing the sponsor's summary of the bioequivalence study for Verapamil Hydrochloride ER Tablets, 120 mg, 180 mg and 240 mg, USP, were virus infected. Enclosed are two replacement sets of exact true copies (virus free) of the diskettes that were originally submitted on February 10, 1997.

Duramed is filing an archival copy (blue folders) and a review copy (orange folders), each containing four computer diskettes: three diskettes containing ASCII files of the measured concentrations of the drug substance, and the kinetic parameters for the bioequivalence study, and the fourth diskette containing the sponsor's summary of the bioequivalence study.

Please contact Ms. Annette Arlinghaus or the undersigned by telephone at 513-731-9900 or by FAX at 513-731-6482 should you have questions about this submission.

Sincerely,

Annette Arlinghaus /for

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

Enclosure: completed FDA 356h

cc: Lizzie Sanchez (FAX letter only)

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Duramed Pharmaceuticals, Inc.
5040 Lester Road
Cincinnati, Ohio 45213
(513) 731-9900

NEW CORR BIOAVAILABILITY
NC/BIO

April 10, 1997

diskette + printout removed

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 75-072 Verapamil HCl ER Tablets, USP

To whom it may concern:

Today, April 10, 1997, Mr. Larry Galvin of the Division of Bioequivalence, OGD, informed me that the diskette containing the data from the fasted bioequivalence study for the 120 mg strength of Verapamil HCl ER Tablets, USP, was missing from his copy of the ANDA submission. Herewith is an exact true copy of the diskette that was originally submitted on February 10, 1997 along with a printout of the data contained on the diskette.

Please contact Mr. Ken Phelps at 513-458-7325 or the undersigned should you have questions about this submission.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President Regulatory Affairs

cc: L Galvin via fax

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APR 11 1997
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ANDA 75-072

Duramed Pharmaceuticals, Inc.
Attention: John R. Rapoza, M.S., R.Ph.
5040 Lester Road
Cincinnati, OH 45213

MAY 8 1997

Dear Sir:

This letter is a correction to our "Refuse to File" letter dated March 31, 1997 and our letter acknowledging the receipt of your application dated April 7, 1997. In addition, we refer to your correspondence dated April 4, and April 10, 1997.

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: Verapamil Hydrochloride Extended-release Tablets USP, 120 mg, 180 mg, and 240 mg

DATE OF APPLICATION: February 10, 1997

DATE OF RECEIPT: February 10, 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:

Tim Ames
Project Manager
(301) 827-5798

Sincerely yours,

/S/

Jerry Phillips 5/8/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA
cc:

R Uhrhan date 5/8/97

ANDA 75-072

Duramed Pharmaceuticals, Inc.
Attention: John R. Rapoza, M.S., R.Ph.
5040 Lester Road
Cincinnati, OH 45213

APR 7 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.

Reference is also made to our "Refuse to File" letter dated March 31, 1997, and your amendment dated April 4, 1997.

NAME OF DRUG: Verapamil Hydrochloride Extended-release Tablets USP, 120 mg, 180 mg, and 240 mg

DATE OF APPLICATION: February 10, 1997

DATE OF RECEIPT: February 10, 1997

DATE ACCEPTABLE FOR FILING: April 4, 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:

Tim Ames
Project Manager
(301) 594-0305

Sincerely yours,

/S/ 4/7/97

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

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Duramed Pharmaceuticals, Inc.
5040 Lester Road
Cincinnati, Ohio 45213

(513) 731-9900
(800) 543-8338

NAI - Relabeling
J. Gilliland 7/25/97
NEW CORRESP
NC

April 04, 1997

Mr. Peter Rickman
Division of Labeling and Program Support
Office of Generic Drugs
7500 Strandish Place
Rockville, MD 20855-2773

Via Fax # 301-594-1174

Dear Mr. Rickman:

Ref: ANDA 75-072
Verapamil Hydrochloride Extended Release Tablets

Reference is made to our phone conversation Friday, April 4, 1997 concerning a FDA letter dated March 31, 1997 refusing to file our Verapamil Extended Release Tablets 120 mg, 180 mg, and 240 mg ANDA. In this conversation it was agreed if we provide via fax (hard copy will follow) the individual tablet dissolution data requested in the referenced letter, you would proceed to accept the filing of our ANDA.

Thus, please find attached three (3) tables containing individual tablet dissolution data as well as all the other analytical parameters mentioned in the referenced letter.

I would like to inform that, we will formally file a letter with the Office Director requesting that February 10, 1997 be the original filing date for acceptance of this ANDA. We beieve the data provided in our original submission was sufficient to allow for acceptance of filing of our ANDA.

If you have any questions please feel free to call Dr. Kamlesh Shah at 908-563-2245 or the undersigned at 513-458-7274.

Sincerely,

John Rapoza
Vice President, Regulatory Affairs

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APR 07 1997
GENERIC DRUGS

Enclosures:
1. Completed 356 h
2. Dissolution Tables

ANDA 75-072

Duramed Pharmaceuticals, Inc.
Attention: John R. Rapoza, M.S., R.Ph.
5040 Lester Road
Cincinnati, OH 45213

MAR 31 1997

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated February 10, 1997, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Verapamil Hydrochloride Extended-release Tablets USP, 120 mg, 180 mg, and 240 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 reasons:

> You have failed to provide complete comparative in vitro dissolution data between your proposed product and the reference listed drug. Comparative dissolution data profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for twelve tablets. The lot numbers of the tablets tested should be identified.

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

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(a)(3)If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference.