CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75-256

CORRESPONDENCE

DURAmed

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The Science of Change

Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213

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

July 27, 1999

TELEPHONE AMENDMENT

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 #75-256 Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg/0.03 mg**
Subject: **COMMITMENT LETTER**

Dear Mr. Sporn,

Reference is made to a telephone conversation on Tuesday July 27, 1999 with Mr. Robert West, concerning field laboratory method validation testing on the referenced ANDA drug product. In that conversation I indicated to Mr. West that we have just received today (July 27, 1999) a letter from the FDA's Philadelphia Laboratory Branch requesting sample materials to complete their methods validation studies.

Given that our ANDA for Desogestrel and Ethinyl Estradiol tablets is in the final stage of review and the methods validation studies are expected to take approximately two (2) months to be completed (per Mr. Smith at the Philadelphia Laboratory) we now with this letter request a **waiver** of the thirty (30) day delay policy of the office concerning methods validation.

Specifically, Mr. West said this waiver could be accomplished by Duramed committing to resolve any remaining issues. **Thus, Duramed commits to resolving any issues uncovered by the FDA's Field Philadelphia Laboratory as part of their methods validation studies on Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg/0.03 mg.**

For completeness, I have included a copy of the letter received from Mr. Wayne Smith of the Philadelphia Laboratory requesting samples for validation studies.

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) 458-6007, or the undersigned at (513) 458-7274.

Sincerely,

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

Encl: completed FDA 356h

Copy faxed to Mr. West (301) 443-3847
Copy faxed to Document Control Room (301) 827-4337

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

July 15, 1999

TELEPHONE AMENDMENT

ORIG AMENDMENT

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 #75-256 Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg/0.03 mg**
Subject: **TELEPHONE AMENDMENT**

Dear Mr. Sporn:

Reference is made to a telephone call between Dr. Allen Rudman from the Office and Mr. Bill Stoltman from Duramed concerning minor deficiencies in our abbreviated new drug application (ANDA) #75-256 for Desogestrel and Ethinyl Estradiol Tablets. In this telephone conversation, Dr. Rudman requested that we modify our in-process testing specifications. In addition, he requested an update on available room temperature stability data. We now amend the application, having responded fully to this telephone request. Enclosed are the revised in-process testing specifications and an updated stability table.

This amendment is submitted in one (1) volume and includes two (2) copies, an archival copy and a review copy. A desk copy of the amendment was faxed to Dr. Rudman at 301-594-0180.

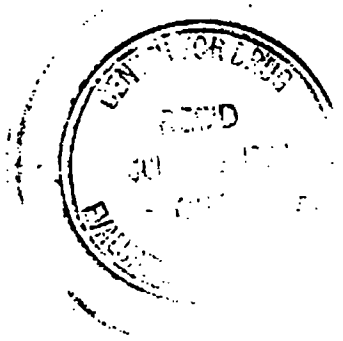
We certify that a true copy of the technical section as described in 21 CFR 314.50 (d)(5) has been provided to the Food and Drug Administration, Cincinnati, District Office in Cincinnati, Ohio.

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) 458-6007, or the undersigned at (513) 458-7274.

Sincerely,

Annette Arlinghaus /for

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



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

July 6, 1999

TELEPHONE AMENDMENT

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
N/AM

RE: **ANDA #75-256 Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg/0.03 mg**
Subject: **TELEPHONE AMENDMENT**

Dear Mr. Sporn:

Reference is made to a telephone call between Dr. Mujahid Shaikh, chemistry reviewer from the Agency and Mr. Bill Stoltman from Duramed concerning a minor deficiency in our abbreviated new drug application (ANDA) #75-256 for Desogestrel and Ethinyl Estradiol Tablets. In this telephone conversation, Dr. Shaikh indicated that the dissolution specifications filed in the ANDA for product release and stability do not match those stipulated in the recent letter from the Division of Bioequivalence (DOB). He requested that we change our documents to be consistent with the dissolution specifications specified by the DOB. We now amend the application, having responded to this telephone request. Enclosed are a revised Finished Product Specification Sheet and a Post Approval Stability Protocol.

This amendment is submitted in one (1) volume and includes two (2) copies, an archival copy and a review copy. In addition, a copy of the amendment was faxed to Dr. Shaikh at 301-443-3839.

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, Cincinnati, District Office in Cincinnati, Ohio.

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) 458-6007, or the undersigned at (513) 458-7274.

Sincerely,

Annette Arlinghaus /for

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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 07 1999
OGD

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

June 29, 1999

TELEPHONE AMENDMENT

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

[illegible] AMENDMENT

RE: **ANDA #75-256 Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg/0.03 mg**
Subject: **TELEPHONE AMENDMENT**

Dear Mr. Sporn:

[illegible] Huie, Reference is made to a telephone call between Lt. Denise Huie, project manager and Dr. Mujahid Shaikh, chemistry reviewer from the Agency and Mr. Bill Stoltman and Ms. Annette Arlinghaus from Duramed concerning a minor deficiency in our abbreviated new drug application (ANDA) #75-256 for Desogestrel and Ethinyl Estradiol Tablets. In this telephone conversation, Dr. Shaikh requested that we delete our proposal to reduce testing for post approval batch stability. We now amend the application, having responded to this telephone request.

This amendment is submitted in one (1) volume and includes two (2) copies, an archival copy and a review copy. In addition, a copy of the amendment was faxed to Dr. Shaikh at 301-443-3839.

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, Cincinnati, District Office in Cincinnati, Ohio.

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) 458-6007, or the undersigned at (513) 458-7274.

Sincerely,

Annette Arlinghaus /for

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

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

ORIG AMENDMENT
N/AC

December 29, 1998

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 #75-256 Desogestrel/Ethinyl Estradiol Tablets, 0.15 mg/0.03 mg
Subject Chemistry AMENDMENT

Dear Mr. Sporn:

Reference is made to our amendment dated September 17, 1998 in which we responded to major deficiencies in our abbreviated new drug application (ANDA) #75-256 for Desogestrel/Ethinyl Estradiol Tablets. In that amendment we stated that the drug substance manufacturer for desogestrel, has improved their manufacturing process.

In this amendment we provide an executed batch manufacturing record and accelerated stability data for a batch of Desogestrel and Ethinyl Estradiol Tablets manufactured using this "improved process" drug substance.

This amendment is submitted in one (1) volume and includes two (2) copies, an archival copy and a review copy.

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, Cincinnati, District Office in Cincinnati, Ohio.

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,

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

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DEC 30 1998

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

April 27, 1999

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

RE: ANDA #75-256 Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg/0.03 mg
Subject MINOR CHEMISTRY AMENDMENT

Dear Mr. Sporn:

Reference is made to your amendment dated March 25, 1999 concerning minor deficiencies in our abbreviated new drug application (ANDA) #75-256 for Desogestrel and Ethinyl Estradiol Tablets. 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 proposed labeling with our last submission.

This amendment is submitted in one (1) volume and includes two (2) copies, an archival copy and a review copy. In addition, two extra copies of the methods validation for a new Identification test is included.

We have enclosed final printed product labeling copy which does not include a trade name and is considered to be generic labeling. The trade name which we originally proposed for this product we now request be withdrawn for reasons of potential trademark infringement. We intend to market this product with a brand name and now submit four (4) new proposed trade names for this oral contraceptive product. This submission format was discussed and agreed to by Mr. Robert West of the Office.

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, Cincinnati, District Office in Cincinnati, Ohio.

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,

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

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

September 17, 1998

NDA UNG AMENDMENT
N/AC

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 #75-256 Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg/0.03 mg
Subject MAJOR AMENDMENT

Dear Mr. Sporn:

Reference is made to your facsimile correspondence dated July 20, 1998 concerning deficiencies in our abbreviated new drug application (ANDA) #75-256 for Desogestrel/Ethinyl Estradiol Tablets.

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 proposed labeling with our last submission. Desotrol™ is the new proposed trade-name for Duramed's brand of Desogestrel and Ethinyl Estradiol Tablets.

This **Major Amendment** is submitted in two (2) volumes and includes two (2) copies, an archival copy and a review copy. Two additional copies of the methods validation portion of this response (pages 01-017 through 01-019 and 01-103 through 01-133) are provided in red folders.

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, Cincinnati, District Office in Cincinnati, Ohio.

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,

A. Arlinghaus /for

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

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SEP 18 1998
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TABLE OF CONTENTS

Duramed Pharmaceuticals, Inc.
Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg/0.03 mg
ANDA # 75-256
September 17, 1998 Amendment

TABLE OF CONTENTS

Duramed Pharmaceuticals, Inc.
Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg/0.03 mg
ANDA # 75-256
September 17, 1998 Amendment

ANDA 75-256

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

FEB 20 1998

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 made to our "Refuse to File" letter dated January 16, 1998 and your amendment dated January 29, 1998.

Reference is also made to the telephone conversation dated February 11, 1998 and your correspondence dated February 18, 1998.

NAME OF DRUG: Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg/0.03 mg

DATE OF APPLICATION: November 19, 1997

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 9, 1998

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:

Sheila O'Keefe
Project Manager
(301) 827-5848

Sincerely yours,

/S/

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

ANDA
cc:

HFD-615/PRickman, Chief, RSB _____ date 2/19/98
HFD-615/GDavis, CSO _____ 2/18/98 date
HFD-625/MSmela, Sup. Chem. _____ date
WP File x:\new\firmsam\duramed\ltrs&rev\75256.ack
FT/njg/2/18/98
ANDA Acknowledgment Letter!

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

February 17, 1998

NEW CORRESP
NC

Mr. Jerry Phillips
Director, Division of Labeling and Program Support
Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North II, 7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-256 Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg / 0.03 mg
Subject: Change in Reference to Drug Product Listing

Dear Mr. Phillips:

Reference is made to a telephone conversation on Wednesday, February 11, 1998 with Mr. Gregory Davis, CSO, Regulatory Support Branch concerning the filing of Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg/0.03 mg ANDA. Mr. Davis informed us that the Office will accept this ANDA for filing; however, we will need to change the reference drug product from Desogen® to Ortho-Cept® in the applicable ANDA sections and re-state the certifications to Ortho-Cept®. Additionally, Mr. Davis requested that comparative dissolution profile testing on both Desogen® and Ortho-Cept® tablets be completed and submitted.

To expedite the official acceptance of this ANDA, we have prepared a table which lists the sections and pages in the original ANDA which have been affected by the change in the referenced drug product (Orange Book, 17th Edition) from Desogen® to Ortho-Cept®. In addition, we have included tables of data containing the dissolution profile results on 12 tablets of Desogen® and Ortho-Cept® as well as calculation of the F_2 similarity factor of these data.

We greatly appreciate the attention paid to this filing matter and administrative effort in resolution of acceptance of this ANDA.

This correspondence is submitted in three (3) volumes, an archival copy and two review copies. We certify that a true copy of this submission has been provided to the Food and Drug Administration, Cincinnati District Office, Cincinnati, Ohio.

If you have any questions, please contact Ms. Annette Arlinghaus at (513) 731-9900, by fax at (513) 731-6482 or the undersigned at (513) 458-7274.

Sincerely,

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

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

January 29, 1998

NEW CORRESP

Mr. Jerry Phillips
Director, Division of Labeling and Program Support
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 75-256
Desogestrel and Ethinyl Estradiol 0.15 mg/0.03 mg Tablets

Subject: Desogestrel and Ethinyl Estradiol Drug Listing

Dear Mr. Phillips:

Reference is made to your letter dated January 16, 1998, concerning ANDA 75-256 for Desogestrel and Ethinyl Estradiol 0.15 mg/0.03 mg tablets. In this letter you indicated that we had failed to reference in our ANDA filing the currently listed product in the Approved Drug Products with Therapeutic Equivalence Evaluations, 17th Edition, (Orange Book), Ortho-Cept®, manufactured by R.W. Johnson.

Duramed initiated the development of its generic equivalent drug product of Desogestrel and Ethinyl Estradiol 0.15 mg/0.03 mg tablets, (Desogen®-21), in 1995 with the purchase of drug substance in October, 1995. At that time the drug product Desogen®-21 was in the 15th Edition of the 1995 Orange Book as the referenced listed product. We purchased our innovator reference tablets from commercial distribution in December, 1995 and started our in-house development of a bioequivalent Desogen®-21 dosage form.

The FDA published the 8th Supplement to the 1995 Orange Book, in which they shaded both Desogen®-21 and Ortho-Cept® with no indication of their intent with regard to the listing and/or delisting of the products. In other words, Desogen®-21 was still listed as the reference product. In the 16th Edition of the 1996 Orange Book, Desogen®-21 was delisted and no other product was listed as the reference for Desogestrel and Ethinyl Estradiol 0.15 mg/0.03 mg tablets, although Desogen®-28 remained listed. The R.W. Johnson product, Ortho-Cept®, is listed; however, there is no indication of it being the reference drug. The listing of Ortho-Cept® as the reference

did not occur until the 8th Supplement, dated August, 1996, which was received at Duramed sometime in October, 1996. During this 1996 Orange Book period, *with no other product being referenced*, we continued to use the previously listed product, Desogen®-21 as the reference, and based our development decisions about the final formula and manufacturing process on that product. In July, 1996 we ordered the definitive bioequivalency clinical supplies based on the 1995 Orange Book listed reference product, Organon's Desogen®-21, and obtained a lot with an expiration dating of November, 1997. Final testing was completed on the tablets, as well as the developed formulation, with a planned biostudy scheduled for November, 1996. Biobatch manufacturing was delayed because of an analytical need for more reference standard. This being a non-USP drug substance, the reference standard, Desogestrel, was obtained from the drug substance manufacturer,

Work continued on the development of the product with the definitive biobatch being manufactured in March, 1997. The clinical bioequivalency study, utilizing Desogen®-21, started in May, 1997 and a complete report was issued by in November, 1997.

In support of the above chronology of product development events, we have prepared an overview, with key documents attached, verifying the time periods. This record clearly illustrates that Duramed had initiated its drug product development in 1995, and with the 1996 Orange Book not having any listed reference product, the project proceeded to final development with the biostudy scheduled for November, 1996.

Thus, ANDA 75-256 was filed with reference to Desogen®-21 as this was the listed reference drug to which Duramed developed an equivalent formulation. The official delisting of Desogen®-21 occurred after the formulation and development work had been completed and the biostudy pending. To have changed to a new reference listed product at that time would have caused the project to start over at a *significant* financial burden and loss of development time. Since Desogen®-21 was the officially listed drug product at the initiation of development and was delisted, *not for a safety issue*, but one of marketing, and that Desogen was AB rated to Ortho-Cept®, the drug product formulation continued. The ANDA development cost for this product is approximately $

Given the delisting of the original Desogestrel/Ethinyl Estradiol product, Desogen®-21, *at the end of the development of our formulation*, we request that our ANDA be granted a waiver and be accepted for filing under the current listed reference drug product Ortho-Cept®. We believe this development cost and loss of time should also be considered in your deliberation of our waiver.

In addition, since Desogen®-21 is no longer commercially distributed by Organon, we have prepared an amendment to the ANDA, if applicable, which includes a labeling section containing examples of Ortho-Cept® labeling, Duramed draft labeling, and side-by-side comparison of Duramed labeling versus Ortho-Cept® labeling.

In summary, we request that a waiver be granted for the filing of the ANDA 75-256 and that our labeling amendment, as applicable, be made part of the original ANDA file. In addition, we request that November 19, 1997, be considered the original filing date of this ANDA as our drug product was developed and bioequivalency tested to the commercially available listed product.

We respectfully request, now given the circumstances under which this ANDA was developed, that you urgently reconsider your decision and accept for filing our Desogestrel and Ethinyl Estradiol ANDA 75-256.

To expedite the review of this request, we have faxed the cover letter and applicable attachments, minus labeling, to you and the Document Control Room. Hard copies of this submission will be filed with the Document Control Room and consist of three (3) copies, an archival and two review copies.

If you have any questions, please feel freel to call me at (513) 458-7274.

Sincerely,

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

JRR/nam
Attachments
1) Completed FDA 356(h)
2) Chronology of Events
3) Labeling Amendment

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

ANDA 75-256

Food and Drug Administration
Rockville MD 20857

Duramed Pharmaceuticals, Inc.
Attention: John Rapoza
5040 Lester Road
Cincinnati, OH 45213

JAN 16 1998

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated November 19, 1997, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg/0.03 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)(2) for the following reasons:

> You have failed to properly identify the agency's designated reference listed drug in your application. Reference listed drug means the listed drug identified by the FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application [21 CFR 314.3(b)]. Please note that the reference listed drug identified in the Approved Drug Products with Therapeutic Equivalence Evaluations, 17th Edition is Ortho-Cept®, manufactured by R.W. Johnson, not Desogen®, manufactured by Organon, which is referred to in your application. Please provide a revised Form FDA 356h that cites the correct reference listed drug and application holder. In addition, please submit all the information required under 21 CFR 314.94, including new 505(j)(2)(A) information, and *in vivo* bioequivalence data revised to reflect the correct reference listed drug. New labeling comparisons to reflect the correct reference listed drug are required. You must submit four copies of draft labeling and a copy of the reference listed drug labeling. You must also provide a side-by-side comparison of the labeling of your proposed drug product with the approved labeling of the reference listed drug with all differences annotated and explained.

Your *in vivo* bioequivalence study was conducted against the wrong reference listed drug. Please submit an *in vivo* bioequivalence study using the reference listed drug, Ortho-Cept®, identified in Approved Drug Products with Therapeutic Equivalence Evaluations, 17th Edition. In addition, you must submit *in vitro* comparative dissolution profiles comparing your proposed drug product against the correct reference listed drug.

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. If you have any questions please call:

Gregory S. Davis
Project Manager
(301) 827-5862

Sincerely yours,

/S/

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 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

505(j)(1)(A)(iii) 2 OK
3/18/98
Mary S. Davis
CORRESP

February 3, 1998

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: Amendment to ANDA 75-256 for D-Estin™ -
(Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg / 0.03 mg)

Dear Mr. Sporn:

Duramed Pharmaceuticals, Inc. (Duramed) submits today, an amendment to ANDA 75-256 for D-Estin™ (Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg / 0.03 mg). Due to an oversight, the original application did not include moisture permeation results on the container/closure system specified in the application. This amendment now provides this information. For your convenience the attached page is numbered 08-0176a to fit into the applicable place in the original ANDA. In addition, page 08-176 of the original ANDA is revised to include reference to the moisture permeation study and is also attached.

This Amendment is submitted in one (1) volume, an archival copy and a review copy.

We certify that a true copy of this submission has been provided to the Food and Drug Administration, Cincinnati District Office, Cincinnati, Ohio.

If you have any questions, 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 /for

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

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

75-256

December 1, 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

Faxed 12/3/97 AHS

RE: EVA Amendment for ANDA for D-Estin™ -
(Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg / 0.03 mg)

Dear Mr. Sporn:

On November 19, 1997 Duramed submitted to the Office of Generic Drugs an original ANDA application for D-Estin™ (Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg / 0.03 mg). We now amend this application to provide for Entry and Validation Application (EVA) diskettes containing the *in vivo* bioequivalence data, *in vitro* dissolution results, assay and content uniformity test results, all of which have been included in the hardcopy ANDA submission.

We certify that the electronic data contained on the enclosed diskettes is the same as that data submitted on hardcopy in the ANDA submission of November 19, 1997. **Exceptions to this certification statement are found on the table enclosed.** These exceptions are due to the present limitations of the EVA software system. These system limitations have been communicated to Mr. Richard Sponaugle at the University of Maryland.

This **Bioequivalence Amendment** includes two copies, a archival (blue) copy and a review (orange) copy. Two (2) diskettes are enclosed with each copy; one diskette contains the EVA data files and the ESD; the other diskette contains the Companion Document. Two diskettes were necessary due to the large file size of the Companion Document.

If you have any questions, please contact Mr. Ken Phelps at (513) 731-9900, by fax (513) 731-6482, or the undersigned at (513) 458-7274.

Sincerely,

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

RECEIVED
DEC 4 1997
GENERIC DRUGS

ANDA 75-256

Duramed Pharmaceuticals, Inc.
Attention: John Rapoza
5040 Lester Road
Cincinnati, OH 45213

JAN 16 1998

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated November 19, 1997, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg/0.03 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)(2) for the following reasons:

> You have failed to properly identify the agency's designated reference listed drug in your application. Reference listed drug means the listed drug identified by the FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application [21 CFR 314.3(b)]. Please note that the reference listed drug identified in the Approved Drug Products with Therapeutic Equivalence Evaluations, 17th Edition is Ortho-Cept®, manufactured by R.W. Johnson, not Desogen®, manufactured by Organon, which is referred to in your application. Please provide a revised Form FDA 356h that cites the correct reference listed drug and application holder. In addition, please submit all the information required under 21 CFR 314.94, including new 505(j)(2)(A) information, and *in vivo* bioequivalence data revised to reflect the correct reference listed drug. New labeling comparisons to reflect the correct reference listed drug are required. You must submit four copies of draft labeling and a copy of the reference listed drug labeling. You must also provide a side-by-side comparison of the labeling of your proposed drug product with the approved labeling of the reference listed drug with all differences annotated and explained.

Your *in vivo* bioequivalence study was conducted against the wrong reference listed drug. Please submit an *in vivo* bioequivalence study using the reference listed drug, Ortho-Cept®, identified in Approved Drug Products with Therapeutic Equivalence Evaluations, 17th Edition. In addition, you must submit *in vitro* comparative dissolution profiles comparing your proposed drug product against the correct reference listed drug.

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. If you have any questions please call:

Gregory S. Davis
Project Manager
(301) 827-5862

Sincerely yours,

/S/

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

DURAmed

The Art of Leadership...
The Science of Change

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

November 19, 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: New ANDA for D-Estin™ -
(Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg / 0.03 mg)

Dear Mr. Sporn:

Duramed Pharmaceuticals, Inc. (Duramed) submits today, in accordance with 21CFR 314.94, an original abbreviated new drug application (ANDA) seeking approval to market D-Estin™ a brand of Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg / 0.03 mg that are bioequivalent to the reference drug, Desogen® Tablets, manufactured by Organon Pharmaceuticals pursuant to NDA # 20-071.

D-Estin™ is the proposed tradename for Duramed's brand of Desogestrel and Ethinyl Estradiol Tablets.

In accordance with the study protocol, Duramed conducted one definitive *in vivo* bioequivalence study for which we include the protocol and final report.

D-Estin™ Tablets are stable and a two year expiration dating is requested. The two year expiration dating is supported by six months accelerated stability testing.

This ANDA is submitted in eight (8) volumes. Duramed is filing an archival copy (blue folders) of the application that contains all the information required in the ANDA and a technical review copy (red folders) containing all the information in the archival copy with the exception of the Bioequivalence section. The Bioequivalence section (orange folders) contains the bioequivalence data as well as a computer disk containing ASCII files of the measured plasma concentrations of the drug analytes and the pharmacokinetic parameters for the bioequivalence study. Because this is a non-USP drug product, two additional copies of methods validation (Section XV) are provided in red folders.

For detailed information on the organization of this application, please refer to the following "EXECUTIVE SUMMARY - Organization of the ANDA".

We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1), the chemistry, manufacturing, and controls section of this submission, has been provided to the Food and Drug Administration, Cincinnati, District Office in Cincinnati, Ohio.

We have also prepared for submission an electronic validation application (EVA) for the bioequivalence section of this ANDA. This EVA and its certification will be filed as an amendment in the next few days.

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,

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

cc: E.T. Arington

Executive Summary - Organization of the ANDA

Duramed's Desogestrel/Ethinyl Estradiol Tablets, ANDA is organized in the manner recommended by the Office of Generic Drugs in its Policy and Procedure Guide #30-91, as modified by the October 14, 1994 letter to industry issued by FDA.

This ANDA is divided into 20 sections, each of which is designated by a roman numeral. A Table of Contents is provided that cross-references each section, as well as significant subparts of the individual sections, to the actual page number where the section or subpart begins. Tabbed divider sheets are provided for each section and subsection and bear the identity of the section to which the tab relates (e.g., "Section V - Labeling").

For ease of reference, each volume of the ANDA is numbered sequentially with the volume number and a dash followed by a three-digit page number in the lower center of each page so that both text and attachments bear consecutive numbering. Page numbers commence on the form 356h.

Whenever a section or subsection references either text or an attachment, a cross-reference will be provided to the location where the referenced text or attachment can be found in the ANDA. If an attachment is referenced more than once, it will only be physically included once in the submission.

Duramed is filing an archival copy (in blue folders) of the ANDA that contains all the information required in the ANDA and a technical review copy (in red folders) which contains all the information in the archival copy with the exception of the Bioequivalence section (VI). A separate copy of the Bioequivalence section is provided in orange folders.

ANDA 75-256

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

FEB 20 1998

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 made to our "Refuse to File" letter dated January 16, 1998 and your amendment dated January 29, 1998.

Reference is also made to the telephone conversation dated February 11, 1998 and your correspondence dated February 18, 1998.

NAME OF DRUG: Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg/0.03 mg

DATE OF APPLICATION: November 19, 1997

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 9, 1998

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.