CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40326

CORRESPONDENCE

ANDA 40-326

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

SEP 3 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.

NAME OF DRUG: Estradiol Tablets USP, 0.5 mg, 1 mg and 2 mg

DATE OF APPLICATION: August 13, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 14, 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:

Denise Huie
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Jerry Phillips 9/2/98
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

March 25, 1999

NDA ORIG AMENDMENT
N/FA

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

RE: ESTRADIOL TABLETS, USP 0.5MG, 1MG AND 2MG
ANDA #40-326
RESPONSE TO MARCH 25, 1999 TELEPHONE REQUEST

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review, and to a March 25, 1999 telephone conversation with Mr. Michael Smela of your Office regarding blend uniformity for Estradiol Tablets USP.

Mr. Smela requested that we provide a commitment to revise the blend uniformity acceptance criteria to % (mean of individual test values) with an RSD of NMT %. By way of this letter, Mylan acknowledges the Agency's request and hereby commits to revise the specifications for Estradiol Tablets USP, 0.5mg, 1mg and 2mg, accordingly.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned by phone at (304) 599-2595, ext. 6600, or by facsimile at (304) 285-6407.

Sincerely,

Marilyn A. Priddy for

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/tlr

RECEIVED
MAR 26 [illegible]
GENERIC DRUGS

G:\PROJECT\ANDA\ESTRADIOL-TABLETS\AGENCY-CALL-OF-032599.WPD

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

MAR 23 1999

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMEND
FA

TELEPHONE AMENDMENT

RE: ESTRADIOL TABLETS, USP 0.5MG, 1MG AND 2MG
ANDA #40-326
RESPONSE TO MARCH 23, 1999 TELEPHONE REQUEST

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review, and to a March 23, 1999 telephone conversation with Mr. Michael Smela and Mr. Mujahid Shaikh of your Office regarding related compounds for Estradiol Tablets USP.

Mr. Smela and Mr. Shaikh requested that we provide a commitment to revise the stability limits for and 'Any Other Individual Impurity' from Not More Than % to Not More Than %. By way of this letter, Mylan acknowledges the Agency's request and hereby commits to revise the specifications accordingly.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned by phone at (304) 599-2595, ext. 6600, or by facsimile at (304) 285-6407.

Sincerely,

Marilyn A. Friedly/for

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/tlr

RECEIVED
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GENERIC DRUGS

G:\PROJECT\ANDA\ESTRADIOL-TABLETS\AGENCY-CALL-OF-032399.WPD

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

MAR 10 1999

NDA ORIG AMENDMENT
N/AB

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE AMENDMENT

RE: ESTRADIOL TABLETS USP, 0.5MG, 1MG AND 2MG
ANDA #40-326
RESPONSE TO AGENCY CORRESPONDENCE DATED FEBRUARY 12, 1999

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review, and to the comments from the Agency pertaining to this application which were provided to Mylan in a facsimile dated February 12, 1999 from the Office of Generic Drugs' Division of Bioequivalence. In response to the Agency's comments of February 12, Mylan wishes to amend the application as follows:

A. REGARDING BIOEQUIVALENCE ISSUES:

FDA COMMENT 1. The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

You should include complete long term stability data in future applications.

Also, you did not report individual parameter test/reference ratios and individual AUCL/AUCI ratios. You should submit this information in future ANDAs.

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.

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

MYLAN RESPONSE: As requested, the dissolution testing for Estradiol Tablets USP, 0.5mg, 1mg and 2mg has already been incorporated into Mylan's stability and quality control programs. This testing is what was proposed in the original ANDA for the above referenced product which was submitted on August 13, 1998.

Additionally, Mylan commits to submit long term stability data as well as to report individual parameter test/reference ratios and individual AUCL/AUCI ratios in future applications.

It is also acknowledged and understood that the bioequivalency comments expressed in the correspondence dated February 12, 1999 are preliminary and may be revised after review of the entire application.

For your reference, a copy of the Agency correspondence dated February 12, 1999 is provided in Attachment 1. Responses to the chemistry comments contained in this correspondence along with revised labeling, also requested in the Agency's correspondence of February 12, 1999, have been forwarded in a separate amendment to this application, also submitted on March 10, 1999.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/tlr

enclosures

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

MAR 10 1999

NDA ORIG AMENDMENT
N/FA

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FACSIMILE AMENDMENT
(CMC INFORMATION ENCLOSED AND LABELING INFORMATION ENCLOSED)

RE: ESTRADIOL TABLETS USP, 0.5MG, 1MG AND 2MG
ANDA #40-326
RESPONSE TO AGENCY CORRESPONDENCE DATED FEBRUARY 12, 1999

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review, and to the comments from the Agency pertaining to this application which were provided to Mylan in a facsimile dated February 12, 1999. In response to the Agency's February 12, 1999 comments, Mylan wishes to amend this application as follows.

A. REGARDING CHEMISTRY ISSUES

FDA COMMENT 1. We note that the Reference Listed Drug, Estrace is manufactured scored tablet for all three strengths whereas Estradiol Tablets manufactured by you are not scored. Therefore, please provide a commitment to submit the following information for the first commercial batches of scored tablets:

a. Complete batch record;

b. Certificate of Analysis of the batch; and

c. Comparative dissolution data for the batch versus the biobatch.

Please include a statement that Mylan will not release this drug product to the market until the request information is reviewed and found satisfactory. We review the data on receipt. This data should be marked "Expedited Review Requested." If you have this data, then there is no need to submit this commitment. Either is acceptable.

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
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Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

MYLAN RESPONSE: In response to the Agency's comment regarding the reference listed drug's scored tablet configuration and, in accordance with CDER's Manual of Policies and Procedures (MAPP 5223.2), "Scoring Configuration of Generic Products", Mylan has added a score to our Estradiol Tablets, USP 0.5mg, 1mg and 2mg to match that of the innovator. The following documents are submitted in support of the revised tablet configuration:

- Revised blank Master Batch Records (production size) for all three strengths reflecting the scored tablet configuration (refer to Page 7 of each Master Batch Record) are provided in Attachment A.

- Executed batch records for Estradiol Tablets, USP 0.5mg (Lot #25E003G), 1mg (Lot #25E004G) and 2mg (Lot #25E005G) reflecting the manufacture of the scored tablets as well as the respective packaging records, batch reconciliations and in-process data are provided in Attachment B.

- Dissolution profiles for all three strengths comparing the scored and unscored tablet configurations are provided in Attachment C.

- Certificates of analysis for the scored Estradiol Tablets, USP 0.5mg (Lot #25E003G), 1mg (Lot #25E004G) and 2mg (Lot #25E005G) are provided in Attachment D.

- Revised finished product specifications for Estradiol Tablets, USP 0.5mg, 1mg and 2mg incorporating the scored tablet descriptions are provided in Attachment E.

FDA COMMENT 2. You have submitted your Procedure/SOP number for conducting but failed to submit the method description. Please provide your method description so that we get to know if the sample size for conducting is equivalent to 1-3 dosage size per current OGD requirements.

MYLAN RESPONSE: Regarding the size of the samples to be collected for testing of Mylan's Estradiol Tablets, USP 0.5mg, 1mg and 2mg, representative samples will be collected from specified locations throughout the and each sample will represent the equivalent of 1 to 3 dosage units.

FDA COMMENT 3. Please revise your release and stability specifications to include other known impurities and set their limit. Please also submit your limits for total impurities.

MYLAN RESPONSE: As requested by the Agency, Mylan has established release and stability specifications for the known impurities: Each known impurity will be controlled at the % level. It should be noted that these known impurities are also controlled in the raw material at the same %) level. Additionally, Mylan has established the total impurities limit for release and stability at % to accommodate the additional known impurities. The revised certificates of analysis, finished product specifications and post-approval stability protocols for all three strengths are provided in Attachments D, E and F, respectively. The revised related compounds procedure is also contained in Attachment E.

FDA COMMENT 4. We note that your proposed stability specification the limit for and the total impurities are excessive. Therefore, we ask for lower limits based on your stability data for your exhibit batches.

MYLAN RESPONSE: As requested by the Agency, Mylan has tightened the stability specifications for and total impurities. The specification limit for has been changed from NMT % to NMT % and the limit for total impurities has been changed from NMT % to NMT %. It should be noted that the stability specifications for total impurities has been tightened despite the requested addition of the aforementioned known impurities. Please refer to Attachment F for the revised post-approval stability protocols. Updated room temperature stability data is provided in Attachment G.

B. REGARDING MISCELLANEOUS ISSUES

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

FDA COMMENT 1. Please submit additional room temperature stability data for the executed batches, if available.

MYLAN RESPONSE: Accelerated and room temperature stability data for Mylan's scored Estradiol Tablets, USP 0.5mg (Lot #25E003G), 1mg (Lot #25E004G) and 2mg (Lot #25E005G) as well as updated room temperature stability data for Mylan's unscored Estradiol Tablets, USP 0.5mg (Lot #25D002E), 1mg (Lot #25D005E) and 2mg (Lot #25D004E) are provided in Attachment G.

FDA COMMENT 2. You must also address the labeling deficiencies with your response.

MYLAN RESPONSE: The labeling deficiencies presented in the February 12, 1999 correspondence have been addressed as follows:

C. REGARDING LABELING ISSUES

MYLAN RESPONSE: Regarding the labeling deficiencies, Attachment K contains twelve (12) copies of the following final printed bottle labels and outsert for Estradiol Tablets, USP 0.5mg, 1mg and 2mg:

BOTTLE LABELS

0.5mg
Code RM1452A - Bottles of 100 Tablets
Code RM1452B - Bottles of 500 Tablets

1mg
Code RM1454A - Bottles of 100 Tablets
Code RM1454B - Bottles of 500 Tablets

2mg
Code RM1458A - Bottles of 100 Tablets
Code RM1458B - Bottles of 500 Tablets

OUTSERT

Code ESTRT:R1, Revised February 1999

The enclosed labeling incorporates the revisions requested in the Agency's letter of February 12, 1999 including those related to the scored tablet configuration. A copy of this correspondence is provided in Attachment H for the convenience of the reviewer.

In order to facilitate the review of this labeling, Attachment I contains a side-by-side comparison of the final printed bottle labels to those previously submitted and Attachment J contains a side-by-side comparison of the final printed outsert (ESTRT:R1) to the outsert that was previously submitted. It is noted that prior to approval of this application, the agency reserves the right to request further changes in the Mylan labeling based upon the changes in the approved labeling of the listed drug or upon further review of the application.

As previously noted, a copy of the Agency correspondence dated February 12, 1999 is included in Attachment H, for the convenience of the reviewer. Responses to the Office of Generic Drugs' Division of Bioequivalence comments also contained in this correspondence have been forwarded in a separate amendment to this application, also submitted on March 10, 1999.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/tlr

enclosures

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

AUG 13 1998

ELECTRONIC DATA ENCLOSED
BIOEQUIVALENCE DATA ENCLOSED

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

505(j)(2)(a) OK
8/25/98

RE: ESTRADIOL TABLETS, USP
0.5MG, 1MG AND 2MG

Dear Mr. Sporn:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.92 and 314.94, we submit the enclosed abbreviated new drug application for:

Proprietary Name: None
Established Name: Estradiol Tablets, USP
This application consists of a total of 19 volumes.
Archival Copy - 8 volumes.
Review Copy - 9 volumes.
Technical Section For Chemistry - 3 volumes.
Technical Section For Pharmacokinetics - 6 volumes.
Analytical Methods - 2 extra copies; 1 volume each.
NOTE: The Technical Section for Pharmacokinetics of the review copy and the archival copy each contain a data diskette for the bioequivalence study conducted in support of this application.

This application provides for the manufacture of Estradiol Tablets, USP 0.5mg, 1mg and 2mg. All operations in the manufacture, packaging, and labeling of the drug product are performed by Mylan Inc., Road #172, Km. 13.4 El Jibaro Industrial Park, Cidra, Puerto Rico 00739.

As required by 21 CFR 314.94(d)(5) we certify that a true copy of the technical sections of this application, as submitted to the Office of Generic Drugs, has been forwarded to both the FDA's Baltimore and San Juan District Offices. The following Table of Contents and Reader's Guide detail the documentation submitted in support of this application.

RECEIVED
AUG 14 1998

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6600 and/or facsimile number (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/tlr