CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-275

CORRESPONDENCE

MINOR AMENDMENT

ORIG AMENDMENT

N/A M

December 7, 1998

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

Estradiol Tablets USP
0.5 mg, 1 mg, and 2 mg
ANDA #40-275

Dear Sir/Madam:

Reference is made to our abbreviated new drug application dated August 29, 1997, submitted pursuant to Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, for Estradiol Tablets USP, 0.5 mg, 1 mg, and 2 mg.

Reference is also made to our amendments dated March 31, May 1, and October 9, 1998 and your comment letter dated October 23, 1998. We understand that this response will be considered a Minor Amendment. Our reply is as follows:

A. Deficiency:

Comment: **The drug substance manufacturer, ecently submitted a revised DMF he DMF is inadequate. The updated DMF information is being requested from Schering AG. Please ensure a response to the DMF prior to amending your ANDA.**

REPLY: ne U.S. distributor for the estradiol drug substance, has notified us that submitted the requested updated DMF information on December 4, 1998.

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

The CGMP status of the firms referenced in the ANDA will be evaluated by our Office of Compliance and an adequate evaluation is required prior to approval.

REPLY: We acknowledge that the cGMP status of the firms referenced in the ANDA will be evaluated by the Office of Compliance and that an adequate evaluation is required for approval.

DEC 08 1998

401 North Middletown Rd., Pearl River, NY 10965-1299 Tel: (914) 732-5000

In accordance with 21 CFR 314.94(d)(5) requiring the submission by applicants of an additional copy of the chemistry, manufacturing and controls section of applications, we are providing a field copy of this amendment directly to the FDA Buffalo, New York District Office. We certify that the field copy is a true copy of this amendment to our application.

We trust that your concerns have been adequately addressed. We look forward to the swift approval of this application.

Sincerely,

Nicholas C. Tantillo
Director, Regulatory Affairs
914 732-4137

OCT 23 1998

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 40-275
APPLICANT: ESI Lederle, Inc.
DRUG PRODUCT: Estradiol Tablets USP, 0.5 mg,1 mg and 2 mg.

The deficiencies presented below represent Minor deficiencies.

A. Deficiency:

The drug substance manufacturer, recently submitted a revised DMF he DMF is inadequate. The updated DMF information is being requested from Schering AG. Please ensure a response to the DMF prior to amending your ANDA.

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

The CGMP status of the firms referenced in the ANDA will be evaluated by our Office of Compliance and an adequate evaluation is required prior to approval.

Sincerely yours,

/S/

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

FACSIMILE AMENDMENT

October 9, 1998

NEW CORRESP
NC

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

Estradiol Tablets USP
0.5 mg, 1 mg, and 2 mg
ANDA #40-275

Dear Sir/Madam:

We refer to our abbreviated new drug application dated August 29, 1997, submitted pursuant to Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, for Estradiol Tablets USP, 0.5 mg, 1 mg, and 2 mg.

Reference is also made to your comment letter dated September 10, 1998, and transmitted to us via facsimile on September 15, 1998, which listed deficiencies noted in our application. We understand that this response will be designated a Facsimile Amendment. Our reply is as follows:

A. DEFICIENCIES:

Page(s) 2

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemistry deficiencies

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

1. Please provide any additional stability data accrued to date.

REPLY: Stability reports presenting up to 12 months room temperature data for Estradiol Tablets USP, 0.5 mg, 1 mg, and 2 mg packaged in bottles of 100s are included in Section XVII of this amendment. A nine month room temperature report was included in our March 31, 1998 amendment. The data clearly show that the products are stable after 12 months when exposed to 25°C and 60% relative humidity.

2. **The CGMP status of the firms referenced in the ANDA will be evaluated by our Office of Compliance and an adequate evaluation is required prior to approval.**

REPLY: We acknowledge that the cGMP status of the firms referenced in the ANDA will be evaluated by the Office of Compliance and that an adequate evaluation is required for approval.

3. **Your bioequivalence data are under review and deficiencies, if any, will be communicated separately.**

REPLY: We received comments from the Division of Bioequivalence on February 26, 1998 and submitted a full response to the comments on May 1, 1998.

In accordance with 21 CFR 314.94(d)(5) requiring the submission by applicants of an additional copy of the chemistry, manufacturing and controls section of applications, we are providing a field copy of this amendment directly to the FDA Buffalo, New York District Office. We certify that the field copy is a true copy of this amendment to our application.

We trust that we have adequately addressed your comments. We look forward to a prompt review and approval of this application.

Sincerely,

Nicholas C. Tantillo
Director, Regulatory Affairs
914 732-4137

SEP 1 0

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 40-275
APPLICANT: ESI Lederle, Inc.
DRUG PRODUCT: Estradiol Tablets USP, 0.5 mg, 1 mg and 2 mg.

The deficiencies presented below represent Facsimile deficiencies.

A. Deficiencies:

1. We continue to believe that "NLT smaller or equal to for the particle size specification for the drug substance is appropriate. The data for the lot used in the biostudy is paramount as this is the only lot associated with drug product content uniformity and bioequivalence data.

2. Your release/stability specifications for "Individual Related Compounds" are excessive. Please tighten these limits in your release/stability specification. Actual data (not statistical analysis) are requested to justify any limit exceeding

3. The method for the *Method Validation for Assay, Content Uniformity, Blend Uniformity, and Purity Determination of Estradiol 0.5 mg, 1 mg and 2 mg Tablets, USP* was cited as different revisions. For example, *Method 4514-113* in Section XII in your 3/31/98 Amendment; *Method 4514-119* on page 6195 in the original submission; *Method* 4514-120 and 4514-120/Addendum #1 on pages 6235 and 6280 in the original submission. Please clarify.

4. As you mention that there are "small clumps" in the raw material (active drug substance), please clarify how you are going to control this matter in your manufacturing process.

5. The sample size for the blend uniformity analysis should be 1-3 dosage units equivalent removed from the blender or drums at multiple locations.

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

1. Please provide any additional stability data accrued to date.

2. The CGMP status of the firms referenced in the ANDA will be evaluated by our Office of Compliance and an adequate evaluation is required prior to approval.

3. Your bioequivalence data are under review and deficiencies, if any, will be communicated separately.

Sincerely yours,

/S/

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

BIOEQUIVALENCY AMENDMENT

May 1, 1998

Dr. D. Connor, Director
Division of Bioequivalence
Office of Generic Drugs
Food and Drug Administration, HFD 650
Metro Park II
7500 Standish Place
Rockville, MD 20855-2773

Estradiol Tablets USP
0.5 mg, 1 mg, and 2 mg
ANDA #40-275

Dear Dr. Connor:

We refer to our abbreviated new drug application dated August 29, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Estradiol Tablets USP, 0.5 mg, 1 mg, and 2 mg.

We also refer to your comment letter dated February 26, 1998 which outlined the following deficiencies in our studies.

COMMENT 1: **The information that you have provided in the submission regarding long term stability data for the three analytes (unconjugated estradiol, unconjugated estrone and conjugated estrogen) mentioned that unconjugated estradiol, and unconjugated estrone are stable for seven weeks and for conjugated estrogen the stability was six weeks. The stability data should cover a period equal to the time from the day each study started (blood sampling) to the day the last sample was analyzed.**

It is not clear from the submission if this period (6 or 7 weeks) covered the entire length of the bio-study. Please submit dates of the blood sampling and analytical assay for all subjects (preferred in tabulated formats, if possible).

REPLY: The stability information supplied in the analytical report did not cover the period from which the samples were collected to the day the last sample was analyzed. The longest duration of time for each analyte is listed below:

Analyte	Date Sample Collected	Date Sample Analyzed
Unconjugated estrone	26 April 1997	27 June 1997
17β-estradiol	3 May 1997	25 June 1997
Total estrone	26 April 1997	25 June 1997

Based on this information, nine weeks of stability is needed for this study. Prior to conducting this study, additional stability was performed on these

compounds to demonstrate approximately 13 months of stability for unconjugated estrone and 17β-estradiol and 6 months stability for total estrone. The results of these stability studies are presented in Attachment I, Tables 1-3.

A table listing the dates of the blood sampling and analytical assay for all subjects is included in Attachment II.

COMMENT 2: **The recovery data was not submitted for conjugated estrone. You should submit the recovery raw data for conjugated estrone. The recovery data should include the mean, range (high, low), the percentage of coefficient of variation (%CV) and the percentage of change from the quality control theoretical values. You should also submit the SOP for the recovery procedure**

REPLY:

COMMENT 3: **Spot checks for random calculated values of the analytes have shown different values as compared to your reported values in the submission. In particular for high concentration samples, the reported values of response ratios that are represented the division of response of analyte standard (or unknown sample) by the response of internal standard are not similar to the values calculated by the reviewer (see some examples on pages 335 and 381, volume C1.2).**

Please provide a summary of the method of calculation for the three analytes accompanied by a few examples of your calculations, especially examples for samples that reflect a different range of concentrations (low, medium and high).

REPLY: Due to the fact that an isotope abundance correction factor (IACF) is used for unconjugated estrone and total estrone, the following formula is used for these compounds:

The IACF used for unconjugated estrone is

The IACF used for total estrone is

An explanation of the isotope abundance correction factor can be found on pages 6 - 8 of the Method validation report (pages 570 - 572 of our original application). Examples of calculations of corrected response ratios taken from the validation report are included in Attachment V.

We trust that we have adequately addressed your comments. We look forward to a prompt review and approval of this application.

Sincerely,

Nicholas C. Tantillo
Director, Regulatory Affairs
914 732-4137

MAJOR AMENDMENT

March 31, 1998

ORIG AMENDMENT
N / A

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

Estradiol Tablets USP
0.5 mg, 1 mg, and 2 mg
ANDA #40-275

Dear Sir/Madam:

We refer to our abbreviated new drug application dated August 29, 1997, submitted pursuant to Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, for Estradiol Tablets USP, 0.5 mg, 1 mg, and 2 mg.

We also refer to your comment letter dated February 23, 1998 which outlined deficiencies noted in our application. We understand our response will be considered a Major Amendment. Our reply is as follows:

A. DEFICIENCIES:

Page(s) 3

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemistry deficiencies

B. GENERAL COMMENTS: - Please note and acknowledge the following:

1. Please provide any additional stability data accrued to date.

REPLY: Stability reports presenting up to 9 months room temperature data for Estradiol Tablets USP, 0.5 mg, 1 mg, and 2 mg are included in Section XVII of this amendment. Although we are withdrawing the bottles of 500s from this ANDA, the stability data accrued to date for the 500 tablet package size is included in the reports for informational purposes.

2. The CGMP status of the firms referenced in the ANDA will be evaluated by our Office of Compliance and an adequate evaluation is required prior to approval.

REPLY: We acknowledge that the cGMP status of the firms referenced in the ANDA will be evaluated by the Office of Compliance and that an adequate evaluation is required for approval.

COMMENT 9: **Please commit to test the largest and smallest package size of each strength of the products for the long-term stability. In this case, the firm should test both 100s and 500s container/closure systems.**

REPLY: For business reasons, we no longer wish to market bottles of 500 tablets and we therefore request that this package size be withdrawn from our application. Since we are requesting approval only for bottles of 100s of each strength tablet, the Marketed Product Stability Protocol included in Section XVII of this amendment is specific to this package size.

COMMENT 10: **Please include information for the "Physical Inspection" in the stability protocol, such as Appearance. No information was included in the accelerated stability testing report.**

REPLY: The Marketed Product Stability Protocol for Estradiol Tablets USP, 0.5 mg, 1 mg, and 2 mg included in Section XVII of this amendment has been modified to include a test for Description (Appearance) at each test interval. Information regarding tablet Description was included for each test station in the accelerated stability testing reports included on pages 6304 - 6327 of our original application. The Description for each strength tablet was included in the header on the Stability Summary Report pages. At all test intervals the results were reported as "Conforms".

B. GENERAL COMMENTS: - Please note and acknowledge the following:

1. **Please provide any additional stability data accrued to date.**

REPLY: Stability reports presenting up to 9 months room temperature data for Estradiol Tablets USP, 0.5 mg, 1 mg, and 2 mg are included in Section XVII of this amendment. Although we are withdrawing the bottles of 500s from this ANDA, the stability data accrued to date for the 500 tablet package size is included in the reports for informational purposes.

2. **The CGMP status of the firms referenced in the ANDA will be evaluated by our Office of Compliance and an adequate evaluation is required prior to approval.**

REPLY: We acknowledge that the cGMP status of the firms referenced in the ANDA will be evaluated by the Office of Compliance and that an adequate evaluation is required for approval.

3. **Your bioequivalence data are under review and deficiencies, if any, will be communicated separately.**

REPLY: We received comments from the Division of Bioequivalence on February 26, 1998. A separate response is being prepared.

4. **Your response must also address the labeling deficiencies.**

REPLY: Our labeling has been revised in accordance with your recommendations.

Please note that we will place four copies of the patient package insert with each bottle of 100 tablets. These will be placed in a printed carton with the bottle. Since we did not previously submit proposed labeling for the printed carton, we are doing so at this time and we are including a side-by-side comparison with the innovator's printed carton.

Labeling only for bottles of 100s is being submitted since we are withdrawing the bottles of 500s from the ANDA.

Attached for inclusion in SECTION V of our application are twelve (12) copies each of our final printed container labels (0.5 mg tablets, U5879-02; 1 mg tablets, U5880-02; 2 mg tablets, U5882-02), printed boxes (0.5 mg tablets, UK 22297; 1 mg tablets, UK 22298; 2 mg tablets, UK 22299), printed Professional Package Insert labeling (CI 5074-1, issued 3-16-98), and printed Patient Insert labeling (PI 5073-1, issued 3-16-98). We have also included a side-by-side comparison of the proposed container labels and physician and patient insert labeling as compared with the previously submitted labeling, and comparison of the proposed printed box labeling with the innovator printed box labeling. All differences have been annotated and explained.

5. **The USP analytical methods, as written, are considered regulatory for this product. Results from them shall prevail in event of a dispute.**

REPLY: We acknowledge that the USP analytical methods, as written, are considered regulatory for this product and that results from them shall prevail in the event of a dispute.

In accordance with 21 CFR 314.94(d)(5) requiring the submission by applicants of an additional copy of the chemistry, manufacturing and controls section of applications, we are providing a

field copy of this amendment directly to the FDA Buffalo, New York District Office. We certify that the field copy is a true copy of this amendment to our application.

We trust that we have adequately addressed your comments. We look forward to a prompt review and approval of this application.

Sincerely,

Nicholas C. Tantillo
Director, Regulatory Affairs
914 732-4137

(estrdef)

BIOEQUIVALENCY DEFICIENCIES

ANDA: #40-275 APPLICANT: ESI Lederle Inc.

DRUG PRODUCT: Estradiol Tablets

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

1. The information that you have provided in the submission regarding long term stability data for the three analytes (unconjugated estradiol, unconjugated estrone and conjugated estrogen) mentioned that unconjugated estradiol, and unconjugated estrone are stable for seven weeks and for conjugated estrogen the stability was six weeks. The stability data should cover a period equal to the time from the day each study started (blood sampling) to the day the last sample was analyzed.

   It is not clear from the submission if this period (6 or 7 weeks) covered the entire length of the bio-study. Please submit dates of the blood sampling and analytical assay for all subjects (preferred in tabulated formate, if possible).

2. The recovery data was not submitted for conjugated estrone. You should submit the recovery raw data for conjugated estrone. The recovery data should include the mean, range (high, low), the percentage of coefficient of variation (%CV) and the percentage of change from the quality control theoretical values. You should also submit the SOP for the recovery procedure.

3. Spot checks for random calculated values of the analytes have shown different values as compared to your reported values in the submission. In particular for high concentration samples, the reported values of response ratios that are represented the division of response of analyte standard (or unknown sample) by the response of internal standard are not similar to the values calculated by the reviewer (see some examples on pages 335 and 381, volume C1.2).
   Please provide a summary of the method of calculation for the three analytes accompanied by a few examples of your calculations, especially examples for samples that reflect a different range of concentrations (low, medium and high).

calculations, especially examples for samples that reflect a different range of concentrations (low, medium and high).

Sincerely yours,

/S/

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

October 31, 1997

U.S. Food and Drug Administration
Northeast Regional Laboratory
Attention: Ms Ella Walker
850 Third Avenue
Brooklyn, NY 11232

Estradiol Tablets USP
0.5 mg, 1 mg, and 2 mg
ANDA 40-275

Dear Ms. Walker:

Reference is made to your October 15, 1997 letter requesting Estradiol Tablet samples for method verification studies. As per your request, the following samples and information are included with this letter:

1) Three bottles containing 100 units each of Estradiol Tablets USP, 2 mg, Lot #R971645. This lot was used in our *in vivo* bioequivalence study against Estrace® 2 mg Tablets. The *in vivo* bioequivalence study was done by:

   PPD Pharmaco, Inc.
   2244 Dabney Rd.
   Richmond, VA 23230

2) A copy of our proposed Testing Specifications for Estradiol Tablets USP.

3) Copies of the following test methods:

   a)

   b)

   c)

4) Copies of the following Method Validation Reports:

   a)

   b)

5) A copy of our Certificate of Analysis (COA) for Estradiol Tablets USP, 2 mg, Lot #R971645. Attached to the COA is a representative calculation for the potency assay and representative HPLC chromatograms for the potency assay.

6) 3 x 500 mg Estradiol USP Reference Standard, Lot J.

7) 1 x 200 mg USP Reference Standard, Lot G. (Used as an internal standard for assay and content uniformity.)

8) 1 x 200 mg Estrone USP Reference Standard, Lot J. (Used for system suitability test, resolution factor for assay and content uniformity as well as urity test.)

9) 1 x 200 mg Wyeth-Ayerst Research 17 α-Estradiol Analytical Reference Standard #RS 636-5, Lot 3188-186. (Used for system suitability test, resolution factor for purity test.) Although the label states that this material should be stored in a freezer, it may be held at room temperature for at least a week since it is not being used for quantitative purposes.

10) Certificate of Analysis for 17 α-Estradiol Reference Standard #RS-636-5.

11) Material Safety Data Sheets for Estradiol, Alpha Estradiol, and Estrone.

4.6 x 150 mm column for performing dissolution analysis (Hewlett Packard).

13) 4.6 x 250 mm, 5 µm column for performing potency, content uniformity, and c purity testing (Phenomenex).

Should you have any questions, please contact us at 914-732-3191.

Sincerely,

Eric J. Messner for

Nicholas C. Tantillo
Director, Regulatory Affairs

cc: Document Control Room, OGD, ANDA #40-275

NEW CORRESPONDENCE

NEW CORRESP

October 31, 1997

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

Estradiol Tablets USP,
0.5 mg, 1 mg, and 2 mg
ANDA 40-275

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application dated August 29, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Estradiol Tablets USP, 0.5 mg, 1 mg, and 2 mg.

On October 31, 1997, we submitted samples of our drug product to the FDA Northeast Regional Laboratory in Brooklyn, New York for method verification studies. Attached is a copy of the October 15, 1997 request from the regional laboratory. Also attached is a copy of our letter to the laboratory listing the various samples and documents submitted in support of our application.

Sincerely,

Eric J Messner for

Nicholas C. Tantillo
Director, Regulatory Affairs

RECEIVED
NOV 3 1997
GENERIC DRUGS

401 North Middletown Rd., Pearl River, NY 10965-1299 Tel: (914) 732-5000 Fax: (914) 732-5114

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

October 15, 1997

Nicholas Tantillo
ESI Lederle, Inc.
401 North Middletown Road
Pearl River, New York 10965-1299

Dear Mr. Tantillo:

The U.S. Food and Drug Administration (FDA) will be performing method verification studies on Estradiol Tablets, 0.5mg, 1 mg and 2mg, in connection with your ANDA 40-275. With your cooperation, we can promptly complete this portion of our evaluation of your application.

In order to perform the necessary testing, please provide us with a sample from the reserve portion of the lot used to establish the bioequivalence or bioavailability of your product. Ideally, this sample should be within the proposed expiration date. If it is beyond this date and there is another pre-approval batch within expiration, send that instead. If no other batch is available, then the out-of-expiration batch is acceptable. If, however, a batch not in the ANDA is used, the batch record and Certificate of Analysis must be submitted as an unsolicited amendment to the application.

The sample should consist of the following:
300 units of the dosage used to establish the bioequivalence or bioavailability of your product.
A copy of the test method.
A copy of your worksheet for the analysis of the same lot with calculations, results and associated spectra and chromatograms.
Non-compendial reference standards that are needed to test the sample, including impurity and related compound standards. A non-compendial reference standard is one that is not available from the USP.
For new or unusual chemical compounds, safety or handling information that would be important in their laboratory use.

Please forward these materials within ten days of receipt of this letter via express or overnight mail to:

U.S. Food and Drug Administration
Northeast Regional Laboratory
850 Third Avenue
Brooklyn, NY 11232

1997

In addition, in connection with other work that needs to be completed regarding your application, please include in your sample package a letter indicating whether an in-vivo or in-vitro bioequivalence study was performed. If so, please provide the facility name and address. If no study was done, include a letter so stating nevertheless.

Thank you in advance for your cooperation. Please do not hesitate to call or fax if you have questions. You may contact me directly by telephone at (718) 965-5300 EXTENSION #5378 or by fax at (718) 965-5308.

Sincerely,

Ella S. Walker

Ella S. Walker
Supervisory Chemist

0-275

ESI Lederle Inc.
Attention: Nicholas C. Tantillo
401 North Middletown Road
Pearl River NY 10965-1299

OCT 15 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: Estradiol Tablets USP, 0.5 mg, 1 mg and 2 mg

DATE OF APPLICATION: August 29, 1997

DATE OF RECEIPT: September 2, 1997

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

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

Should you have questions concerning this application contact:

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

Sincerely yours,

/S/

Jerry Phillips 10/14/97
Director,
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

September 19, 1997

40-275

Office of Generic Drugs
Division of Bioequivalence
CDER FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

Estradiol Tablets USP,
0.5mg, 1mg and 2mg

checks received 9/22/97

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application which was submitted on August 29, 1997 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Estradiol Tablets USP, 0.5mg, 1mg and 2mg.

We have prepared an electronic submission of the bioequivalence data for the referenced product using FDA's Electronic Validation Application (EVA), and we are submitting the information for use during review of the bioequivalence portion of our ANDA for Estradiol Tablets USP, 0.5mg, 1mg and 2mg. Information regarding the following study is contained on two 3½" diskettes (1 original, 1 copy).

Protocol Number	Study Title
96-027-MA	2-Way Crossover Bioequivalence Study Comparing ESI-Lederle and Bristol-Myers (Estrace®) 2mg Estradiol Tablets in Fasting Subjects

Please note that data files were made for all baseline information. However, these files were not listed in the ESD document. Baseline data files (concentrations, PK parameters and Kel estimation) are mentioned in the companion document and are included on the diskettes (as suggested by UMBC).

Additionally, when entering the mean in PK parameters there was no category for least-squares means. Least squares arithmetic was chosen, but EVA was arbitrarily changing this designation to geometric.

We certify that the data that is submitted electronically is identical to the data contained in the hard copy submission. Attachment I contains a similar certification from PPD Pharmaco. PPD Pharmaco conducted the studies and performed the analytical work.

If you need any clarification of the information provided, or additional data, please feel free to contact either myself at (914) 732 - 4340 or Laurie Reynolds of PPD Pharmaco at (804) 359 - 1900 (ext. 5009).

Sincerely,

Linda O'Dea

Linda O'Dea
Manager
Regulatory Affairs

9/22/97

401 North Middletown Rd., Pearl River, NY 10965-1299 Tel: (914) 732-5000 Fax: (914) 732-5114

August 29, 1997

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

Estradiol Tablets USP,
0.5 mg, 1 mg, and 2 mg

Dear Sir/Madam:

We are submitting a complete Abbreviated New Drug Application pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Estradiol Tablets USP, 0.5 mg, 1 mg, and 2 mg.

This application provides for the manufacture, processing, labeling and packaging of the dosage form at our Rouses Point, New York facility. Documents contained in this application reference ESi Lederle, Wyeth-Ayerst Laboratories and Ayerst Wyeth Pharmaceuticals Inc., all of which are affiliated companies under common ownership and control of American Home Products Corporation.

This application, containing 19 unnumbered volumes, is organized in the format suggested in the April 1997 Guidance for Industry, entitled "Organization of an Abbreviated New Drug Application and an Abbreviated Antibiotic Application."

The reference drug product in this application is Estrace® Tablets 0.5 mg, 1 mg, and 2 mg manufactured by Bristol-Myers Squibb Company. The active ingredient, dosage form, strength and route of administration of the proposed product are the same as those of Estrace® Tablets 0.5 mg, 1 mg, and 2 mg. A side-by-side comparison of the proposed product labeling to the innovator drug product labeling is included in this application. The proposed product, like the innovator product, will be marketed as a prescription drug as stated in the labeling.

The reference drug is not entitled to a period of marketing exclusivity and there are no patents that claim the listed drug or that claim a use of the listed drug.

401 North Middletown Rd., Pearl River, NY 10965-1299 Tel: (914) 732-5000 Fax: (914) 732-5114

To demonstrate the bioequivalence of ESi Lederle's Estradiol Tablets USP, 0.5 mg, 1 mg, and 2 mg, a study entitled "2-Way Crossover Bioequivalence Study Comparing ESi Lederle and Bristol-Myers (Estrace®) 2 mg Estradiol Tablets in Fasting Subjects" was conducted. The completed study, included in Section VI of this application, demonstrates the in vivo bioequivalence of our proposed product to the reference product. The study was designed based on the agency's August 21, 1991 Conjugated Estrogens Tablets guidance document and the Division of Bioequivalence's letter to us dated July 23, 1996. Data for the study are contained on a diskette submitted with the orange review copy of this application. This data is in the format specified in the Division of Bioequivalence guidance titled, "Informal Guidance on the submission of Data for Bioequivalence Studies in Computer Format", dated 12/15/87.

We are using Estradiol USP drug substance manufactured by Germany. This application contains a letter from authorizing FDA to refer to their DMF behalf of ESi Lederle.

The submission batch sizes for Estradiol Tablets USP, 0.5 mg, 1 mg, and 2 mg were tablets, respectively. The anticipated production batch sizes are the same as the submission batch sizes.

The submission batches were packaged in the containers proposed for marketing. Estradiol Tablets USP, 0.5 mg, 1 mg, and 2 mg will be supplied in trade packages of 500 and unit of issue packages of 100. All operations will be performed at our Rouses Point, New York facility.

Since aspects related to our facilities will be evaluated by FDA's field investigational staff, and not by drug application reviewers, this application does not contain references to a Type I DMF, nor does it contain a description of our facilities related to the content of a Type I DMF. However, we are providing a brief, general description of our facilities, operations, and controls.

With respect to analytical methods, two copies of the method validation package are being submitted with this application.

In accordance with 21 CFR 314.94 requiring the submission of an additional copy of the chemistry, manufacturing and controls section of applications, we are providing a field copy directly to the Buffalo, New York District Office. We certify that the field copy is a true copy of the chemistry, manufacturing and controls section of our application.

This application contains a certification statement with respect to convictions or persons debarred under 21 USC 335a(a) or (b).

Please contact the undersigned if you need any additional information.

Sincerely,

Nicholas C. Tantillo
Director, Regulatory Affairs
ESi Lederle