CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-275

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 40-275

FIRM: ESI Lederle Inc.
P.O. Box 51502
Philadelphia, PA 19101

NAME OF RESPONSIBLE OFFICIAL OR AGENT:
Nicholas C. Tantillo
410 N. Middletown Road
Pearl River, NY 10965-1299

DOSAGE FORM: Tablets

STRENGTH: 0.5 mg, 1.0 mg, and 2 mg

DRUG: Estradiol Tablets, USP

EER acceptable by S. Ferguson on 12/21/98

CGMP STATEMENT/EIR UPDATED STATUS:
EER for all individual facilities listed in this ANDA (see section 33 of CR # 4) is pending per 12/15/98.

BIO STUDY:
The firm has met the requirements for in vivo bioequivalence and in vitro dissolution testing per bio acceptance letter dated 9-1-98. Bio review can be found in vol. 2.1.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
USP material. Methods Verification was acceptable.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?
Containers used in the stability studies are identical to those listed in container section.

LABELING:
Satisfactory per John Grace dated 4-20-98.

STERILIZATION VALIDATION (IF APPLICABLE):
N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
Bio/stability batches were manufactured at full scale production batches.

STRENGTH	0.5 mg	1 mg	2 mg
Batch size			
Batch lot #	R971663	R971646	R971645

Source of ~~NDS~~:
Referenced ~~DMF~~ was found satisfactory per review completed on 12-10-98 by this reviewer.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)
Stability batches are as follows:

STRENGTH	0.5 mg	1 mg	2 mg
Batch size			
Batch lot #	R971663	R971646	R971645

Bio/stability and stability batches are manufactured via same manufacturing process.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?
Intended production batch sizes are the same as bio batches for all three strengths(0.5 mg, 1.0 mg, and 2.0 mg), which is 0 tablets, correspondingly.

Manufacturing process for the intended production size is identical to that used for the bio/stability batch.

Bing Cai/12-15-98
Review Chemist
Division of Chemistry I
OGD/CDER
x:\new\firmsam\esileder\ltrs&rev\40275app.sum

BC 12/22/98
M Smela 12/22/98

Estradiol
0.5 mg, 1 mg and 2 mg Tablets
ANDA #**40-275**
Reviewer: Z. Wahba
File #40275a.598

ESI Lederle, Inc.
Philadelphia, PA
Submission Date:
May 01, 1998

REVIEW OF AN AMENDMENT

BACKGROUND

1. The firm has previously submitted an in vivo bioequivalence study under fasting conditions comparing its drug product Estradiol Tablets, 2.0 mg to the reference drug product Bristol-Myers Squibb's Estrace® Tablets, 2.0 mg.

2. The submission was reviewed and was found incomplete by the Division of Bioequivalence (review dated February 23, 1998, ANDA #40-275) due to problems cited in the deficiency comments.

3. In this submission, the firm has responded to the deficiency comments and included additional information in the current submission.

DEFICIENCY COMMENT #1:

The firm was asked to submit stability data covering the entire period of the clinical study.

THE FIRM'S RESPONSE TO THE DEFICIENCY COMMENT #1

The firm has provided stability data that have been obtained prior to the study. This stability study demonstrated that both unconjugated estrone and estradiol were stable for approximately 13 months. Total estrone was shown to be stable for 6 months. The results of these stability studies are presented on page #1, Attachment 1, Tables 1-3, Volume B2.1.

The firm's response to comment #1 is acceptable.

DEFICIENCY COMMENT #2:

The recovery data were not submitted for total estrone. The firm

was asked to 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.

THE FIRM'S RESPONSE TO THE DEFICIENCY COMMENT #2

A direct evaluation of recovery was not performed for total estrone during the validation study. Evaluation of recovery is normally a part of the validation process. However, in the case of total estrone, the compound and its internal standard must undergo enzymatic hydrolysis prior to analysis by The enzymatic hydrolysis converts the sulfate conjugates of estrone and its internal standard to the respective unconjugated forms. Because of this required process, there is no direct way to evaluate recovery of this compound. The recovery of total estrone after enzymatic hydrolysis relative to the unconjugated estrone internal standard can be estimated by the unconjugated method. This is the closest practical approximation that can be done to estimate recovery for total estrone. Relative recovery is determined by a comparison between samples in which the internal standard is added prior to extraction and samples in which the addition of the internal standard is delayed until just prior to derivatization. Attachment IV (pages #59-61, volume B2.1) shows data evaluating the completeness of the enzymatic hydrolysis used in the determination of total estrone. The data presented show that after 30 minutes, as required in the method for the total estrone determination, hydrolysis is complete. Since hydrolysis of total estrone is complete, the result is equivalent to the unconjugated form of estrone. Therefore, relative recovery of total estrone after hydrolysis is equivalent to that shown in the method of analysis of unconjugated estrone.

The firm's response to comment #2 is acceptable.

DEFICIENCY COMMENT #3:

Spot checks for random calculated values of the analytes have shown different values as compared to your reported values in the submission. 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).

THE FIRM'S RESPONSE TO THE DEFICIENCY COMMENT #3

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

An e
respo

The IACF used for unconjugated estrone was
The IACF used for total estrone was

Examples of calculations of corrected response ratios taken from the validation report were included in Attachment V (page #62, volume B2.1).

The firm's response to comment #3 is acceptable.

RECOMMENDATIONS

1. The in vivo bioequivalence study, single-dose under fasting conditions, conducted by ESI Lederle, Inc. on its drug product, Estradiol Tablets, USP, 2 mg (lot #R971645) and the reference product, Bristol-Myers Squibb's Estrace® Tablets, 2.0 mg (lot # K5K07A), have been found acceptable. The study demonstrates that under fasting conditions, ESI Lederle's Estradiol Tablets, USP, 2 mg is bioequivalent to the reference listed product, Bristol-Myers Squibb's Estrace® Tablets, 2.0 mg.

2. The dissolution testing conducted by ESI Lederle, Inc. on its drug product, Estradiol tablets, 2 mg (lot #R971645), 1 mg (lot #R971646) and 0.5 mg (lot #R971663) is acceptable. The waivers of the in vivo bioequivalence study requirements for the 1 mg and 0.5 mg strengths of the test product are granted. The Division of Bioequivalence deems the 1 mg and 0.5 mg strengths of the test product to be bioequivalent to the reference listed product, Bristol-Myers Squibb's Estrace® Tablets, 1 mg and 0.5 mg.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of in water, at 37°C using Apparatus #2 (Paddle) at 100 rpm. The test product should meet the following specifications:

Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in minutes.

The firm should be informed of the above recommendations.

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT 9.1.98
FT INITIALLED BDAVIT Barbara M Davit 9/1/98

Concur: /S/ Date: 9/19/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **40-275** Date of Submission: **March 31, 1998**

Applicant's Name: **ESI Lederle Inc.**

Established Name: **Estradiol Tablets USP, 0.5 mg, 1 mg and 2 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: **March 31, 1998** (100s - 0.5 mg, 1 mg and 2 mg)

Carton Labeling: **March 31, 1998** (1 X 100s - 0.5 mg, 1 mg and 2 mg)

fessional Package Insert Labeling: **March 31, 1998** (Rev. March 16, 1998)

Patient Package Insert Labeling: **March 31, 1998** (Rev. March 16, 1998)

Revisions needed post-approval:

1. CONTAINER/CARTON:

   Storage Temperature Recommendations - Delete the comma following "temperature".

2. INSERT

   Encourage the inclusion of the "Rx only" statement.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Estrace® Tablets

NDA Number: AND 81-295

A Drug Name: Estrace® Tablets

NDA Firm: Bristol-Myers Squibb

Date of Approval of NDA Insert and supplement #: 81-295/S-007
Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an NDA labeling guidance? YES - Class Labeling Guidance for Estrogen Drug Products

If yes, give date of labeling guidance: August 1992
Basis of Approval for the Container Labels:
Estrace labels in file folder.

VIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an AND or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
IV product packaged in syringe, could there be adverse patient outcome if given direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

beling (continued)	Yes	No	N.A.
es RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
lure to list the coloring agents if the composition statement lists e.g., acode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/AND dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does AND meet them?		X	
Is the product light sensitive? If so, is NDA and/or AND in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or mulative supplement for verification of the latest Patent or Exclusivity. List piration date for all patents, exclusivities, etc. or if none, please state.		X	

FOR THE RECORD:

1. Review based on the class labeling guidance for estrogen drug products and the labeling of the listed drug(Estrace®; Approved January 8, 1997, Revised September 1996).

2. Patent/ Exclusivities:

   There are no patents or exclusivities that pertain to this drug product.

3. Storage/Dispensing Conditions:

   NDA: Store at controlled room temperature 15° to 30°C (59° to 86°F).Dispense in a tight, light-resistant container as defined in the USP.

   ANDA: Store at controlled room temperature 15° to 30°C (59° to 86°F). Dispense in a tight, light-resistant container with a child-resistant closure.

   USP: Preserve in tight, light-resistant containers.

4. Scoring:

   NDA: ALL strengths SCORED.
   ANDA: ALL strengths SCORED.

5. Product Line:

   The innovator markets their product in bottles containing 100s (0.5 mg) and 100s and 500s (1 mg and 2 mg).

   The applicant proposes to market their product in bottles of 100s and 500s for all strengths(0.5 mg, 1 m g and 2 mg). The firm states 4 ppi's will be included in each bottle of 100. See cover letter to March 31, 1998 submission.

6. The tablet imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). See page 6065, Vol. 1.18.

7. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 5376, Vol. 1.16.

8. All manufacturing will be performed by **Wyeth-Ayerst Labs**. The firm explains that ESI and Wyeth Labs are affiliate corporations under common ownership of American Home products. No outside firms are utilized for any manufacturing. See pages 5431 and 5439, Vol. 1.16. The labels and labeling list ESI as the manufacturer. After discussion with John Grace this was determined to be acceptable. Apparently we have done this in the past with Sanofi Winthrop.

9. Container/Closure:

   This product will be packaged in HDPE bottles with the **100** count bottle having a **CRC** cap and the 500 count having a regular cap.

10. BIO

    500s is withdrawn H Sanchez 8/25/98

    Pending - The review dated 2/26/98. The package insert does NOT list any values in the CLINICAL PHARMACOLOGY section.

Date of Review: **April 16, 1998**

Date of Submission: **March 31, 1998**

Reviewer: Carol Holquist **Date:** 4-16-98

Team Leader: John Grace **Date:** 4/20/98

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cc

40-275

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Memorandum

DATE: December 3, 1997

FROM: Supervisory Chemist, Drug Chemistry Branch
Northeast Regional Laboratory, HFR-NE560

SUBJECT: ANDA 40-275: Estradiol Tablets
ESI Lederle Inc.; Pearl River, NY 10965
Sample No. 98-752-450

TO: ANDA Review Chemist
Office of Generic Drugs, CDER, HFD-600

The Northeast Regional Laboratory completed the method verification analysis on ANDA 40-275, estradiol tablets, using the USP method and the samples provided. The following is a summary of that analysis.

	Results	Specifications
Assay:	98.5%	90.0 - 115.0%
Content Uniformity:	94.6 - 98.9% ave = 96.8% RSD = 1.5%	85.0 - 115.0% RSD = or < 6.0%
Dissolution:	96.4 - 100.0%	NLT 75% (Q) in 60 minutes
Identification:	Complies	The Rf value and color of the principal spots from the sample and standard solutions corresponds

No analytical problems were encountered in performing this analysis. The USP method appears to be suitable for regulatory analysis of this product.

Ella S. Walker

Ella S. Walker

cc: HFC-140
HFD-354
HFR-NE1500

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **40-275** Date of Submission: **August 29, 1997**

Applicant's Name: **ESI Lederle Inc.**

Established Name: **Estradiol Tablets USP, 0.5 mg, 1 mg and 2 mg**

Labeling Deficiencies:

1. CONTAINER (100s and 500s)

   a. Please assure that the established name and strength appear as the most prominent items on the label.

   b. We encourage you to differentiate your product strengths with the use of boxing, contrasting colors or some other means.

   c. We note you have not proposed a carton for this drug product. How will the patient package insert be attached and how many inserts will accompany each container size?

2. INSERT

   I. PROFESSIONAL PACKAGE INSERT

      a. DESCRIPTION

         i. Revise to read "a molecular formula" rather than "an empirical formula".

         ii. To be in accord with USP 23, revise the molecular weight to read "272.39" rather than "272.37".

      b. CLINICAL PHARMACOLOGY

         Paragraph two - Capitalize the "F" in "Fallopian".

      c. INDICATIONS AND USAGE

         Delete "USP" from the first sentence.

      d. PRECAUTIONS

         i. General

A) ~~Addition~~ of a progestin - Revise to read as follows:

...progestin for ten or more...hyperplasia than would be induced by estrogen treatment alone...studies of endometria suggest...endometrium and to reduce the likelihood of hyperplastic changes.

There are possible risks which ...with the use of progestins...LDL) which could diminish the purported cardioprotective...tissue although few...point. (See PRECAUTIONS below.)

The choice...issues will require further study before they are clarified.

B) Insert the following text to appear as number two. In addition, renumber the remaining accordingly.

2. ***Cardiovascular risk.*** A causal relationship between estrogen replacement therapy and reduction of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the effect of added progestins on this putative benefit is not yet known.

In recent years many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy without added progestins and a decrease in cardiovascular disease in women. Although most of the observational studies which assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports:

(1) Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. In general, treated women were of higher socioeconomic and educational status, more slender, more physically active, more likely to have undergone surgical menopause, and less likely to have diabetes than the untreated women. Although some studies attempted to control for these selection factors, it is common for properly designed randomized trials to

fail to confirm benefits suggested by less rigorous study designs. Thus, ongoing and future large-scale randomized trials may fail to confirm this apparent benefit.

(2) Current medical practice often includes the use of concomitant progestin therapy in women with intact uteri (see PRECAUTIONS and WARNINGS). While the effects of added progestins on the risk of ischemic heart disease are not known, all available progestins reverse at least some of the favorable effects of estrogens on HDL and LDL levels.

(3) While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiological evidence suggests that progestins do not reduce, and may enhance, the moderately increased breast cancer incidence that has been reported with prolonged estrogen replacement therapy (see WARNINGS above).

Because relatively long-term use of estrogens by a woman with a uterus has been shown to induce endometrial cancer, physicians often recommend that women who are deemed candidates for hormone replacement should take progestins as well as estrogens. When considering prescribing concomitant estrogens and progestins for hormone replacement therapy, physicians and patients are advised to carefully weigh the potential benefits and risks of the added progestin. Large-scale randomized, placebo-controlled, prospective clinical trials are required to clarify these issues.

ii. Carcinogenesis, Mutagenesis, Impairment of Fertility - Delete "and" from the subsection heading.

iii. Insert the following text as the last subsection:

H. Pediatric Use. Safety and effectiveness in pediatric patients have not been established. Large and repeated doses of estrogen over an extended period of time have been shown to accelerate epiphyseal closure, resulting in short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. In patients in whom bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended.

Estrogen treatment of prepubertal children also induces

premature breast development and vaginal cornification, and may potentially induce vaginal bleeding in girls. In boys, estrogen treatment may modify the normal pubertal process. All other physiological and adverse reactions shown to be associated with estrogen treatment of adults could potentially occur in the pediatric population, including thromboembolic disorders and growth stimulation of certain tumors. Therefore, estrogens should only be administered to pediatric patients when clearly indicated and the lowest effective dose should always be utilized.

e. DOSAGE AND ADMINISTRATION

For prevention of osteoporosis - Delete "USP" from the first sentence.

II. INFORMATION FOR THE PATIENT INSERT

OTHER INFORMATION - Revise this section to read as follows:

1. Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Taking progestins, another hormone drug, with estrogens lowers the risk of developing this condition. Therefore, if your uterus has not been removed, your doctor may prescribe a progestin for you to take together with the estrogen.

   You should know, however, that taking estrogens <u>with</u> progestins may have additional risks. These include:

   - unhealthy effects on blood fats (especially the lowering of the HDL blood cholesterol, the "good" blood fat which protects against heart disease);
   - unhealthy effects on blood sugar (which might make a diabetic condition worse); and
   - a possible further increase in breast cancer risk which may be associated with long-term estrogen use.

   Some research has shown that estrogens taken <u>without</u> progestins may protect women against developing heart disease. However, this is not certain. The protection shown may have been caused by the characteristics of the estrogen-treated women, and not by the estrogen treatment itself. In general, treated women were slimmer, more physically active, and were less likely to have diabetes than the untreated women. These characteristics are known to protect against heart disease.

You are cautioned to discuss very carefully with your doctor or health care provider all the possible risks and benefits of long-term estrogen and progestin treatment as they affect you personally.

2. Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.

3. If you will be taking calcium supplements as part of the treatment to help prevent osteoporosis, check with your doctor about how much to take.

4. Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital or poison control center immediately.

5. This leaflet provides...

Please revise your container labels and insert labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

_____

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

ROVAL SUMMARY (List the package size, strength(s), and date of submission tor approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels:

Carton Labeling:

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Estrace® Tablets

NDA Number: AND 81-295

Drug Name: Estrace® Tablets

NDA Firm: Bristol-Myers Squibb

Date of Approval of NDA Insert and supplement #: 81-295/S-007
Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an NDA labeling guidance? YES - Class Labeling Guidance for Estrogen Drug Products

If yes, give date of labeling guidance: August 1992
Basis of Approval for the Container Labels:
Estrace labels in file folder.

VIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
s the package proposed have any safety and/or regulatory concerns?		X	
IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).	X		
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

beling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
s the term "other ingredients" been used to protect a trade secret? If so, is im supported?		X	
ailure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/AND dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does AND meet them?		X	
Is the product light sensitive? If so, is NDA and/or AND in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List xpiration date for all patents, exclusivities, etc. or if none, please state.		X	

ES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. Review based on the class labeling guidance for estrogen drug products and the labeling of the listed drug(Estrace®; Approved January 8, 1997, Revised September 1996).

2. Patent/ Exclusivities:

   There are no patents or exclusivities that pertain to this drug product.

3. Storage/Dispensing Conditions:

   NDA: Store at controlled room temperature 15° to 30°C (59° to 86°F).Dispense in a tight, light-resistant container as defined in the USP.

   AND: Store at controlled room temperature 15° to 30°C (59° to 86°F). Dispense in a tight, light-resistant container with a child-resistant closure.

   USP: Preserve in tight, light-resistant containers.

4. Scoring:

   NDA: ALL strengths SCORED.
   AND: ALL strengths SCORED.

5. Product Line:

   The innovator markets their product in bottles containing 100s (0.5 mg) and 100s and 500s (1 mg and 2 mg)

   The applicant proposes to market their product in bottles of 100s and 500s for all strengths.

6. The tablet imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). See page 6065, Vol. 1.18.

7. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 5376, Vol. 1.16.

8. All manufacturing will be performed by **Wyeth-Ayerst Labs**. The firm

explains that ESI and Wyeth Labs are affiliate corporations under common ownership of American Home products. No outside firms are utilized for any manufacturing. See pages 5431 and 5439, Vol. 1.16. The labels and labeling list ESI as the manufacturer. After discussion with John Grace this was determined to be acceptable. Apparently we have done this in the past with Sanofi Winthrop.

9. Container/Closure:

This product will be packaged in HDPE bottles with the 100 count bottle having a CRC cap and the 500 count having a regular cap.

Date of Review: October 24, 1997

Date of Submission: August 29, 1997

Reviewer: C Halquist **Date:** 10/30/97

Team Leader: John Grace **Date:** 11/4/97

cc:

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