CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-216

Trade Name: Premarin Cream

Generic Name: Conjugated estrogens

Sponsor: Wyeth Pharms, Inc

Approval Date: October 16, 1978

Indications: For the treatment of Atrophic Vaginitis and Kraurosis Vulvae; Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-216

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-216

APPROVAL LETTER

13

NDA 83-273

OCT 16 1978

Ayerst Laboratories
Attention: Henry S. Perdue, Ph.D.
685 Third Avenue
New York, NY 10017

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Conjugated Estrogens Vaginal Cream, 0.625 mg./g.

Reference is also made to your amendments dated September 16, 1977, December 8, 1977, January 12, 1978, October 5, 1978 and October 12, 1978.

We have completed the review of this abbreviated new drug application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

Any significant change in the conditions outlined in this abbreviated new drug application, requires an approved supplemental application before the change may be made, except for changes made in conformance with other provisions of Section 314.8 of the new drug regulations.

This Administration should be advised of any change in the marketing status of this drug.

The requirement for adequate data to assure the biologic availability is being deferred at the present time. However, our action in approving this application is based upon an understanding that if this requirement is reinstated you will perform the appropriate procedures.

Promotion of a product marketed under an abbreviated new drug application must not convey the impression that the product is a new entity.

The enclosures summarize the conditions relating to the approval of this application.

Sincerely yours,

Marvin Seife 10/16/78

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
BUF DO

HFD-614
VVKarusaitis/JLMeyer/MAJarski
R/D init JLMeyer/MSeife 10/16/78
ps/10/16/78
approved MAJarski 10/16/78

Enclosures: JLMeyer 10/16/78
Conditions of Approval of a New Drug Application
Records and Reports Requirements

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 83-273

DATE APPROVAL LETTER ISSUED: OCT 16 1978

TO: Press Relations Staff (HFI-40)

FROM:
- [XX] Bureau of Drugs
- [ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION
- [ ] ORIGINAL NDA
- [ ] SUPPLEMENT TO NDA
- [XX] ORIGINAL ANDA
- [ ] SUPPLEMENT TO ANDA

ORIGINAL APPROVED

CATEGORY
- [XX] HUMAN
- [ ] VETERINARY

TRADE NAME *(or other designated name)* AND ESTABLISHED OR NONPROPRIETARY NAME *(if any)* OF DRUG

Conjugated estrogens

DOSAGE FORM

vaginal cream

HOW DISPENSED
- [XX] Rx
- [ ] OTC

ACTIVE INGREDIENT(S) *(as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)*

Conjugated estrogens 0.625 mg./g.

NAME OF APPLICANT *(Include City and State)*

Ayerst Laboratories
New York, NY 10017

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

estrogen

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME: majerski — DATE:

FORM APPROVED BY

NAME: JMeyer — DATE:

FORM FD 1642 (2/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-216

CHEMISTRY REVIEW(S)

CHEMIST's REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT	Statement Date:	NDA NUMBER: 83-273

NAME AND ADDRESS OF APPLICANT
Ayerst Laboratories
New York, NY 10017

ORIGINAL
AMENDMENT xxx
SUPPLEMENT
RESUBMISSION
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT/SUPPLEMENT
manufacturing and labeling
9-16,1977; 12-8,1977; 1-12, 1978; 10-5,78 and 10-12-78

DATE(s) of SUBMISSIO

PHARMACOLOGICAL CATEGORY	NAME OF DRUG	HOW DISPENSED
estrogen	conjugated estrogens	RX xxxx OTC
DOSAGE FORM(S)	POTENCY(IES)	RELATED IND/NDA/DMF
vaginal cream	0.625 mg./g.	
STERILIZATION	SAMPLES	

LABELING
see medical officer's reviews of

BIOLOGIC AVAILABILITY
not required

ESTABLISHMENT INSPECTION
satisfactory per HFD-322 memo of 10-11-77 based on inspection of 3-7-77

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS
satisfactory - firm makes commitments to further define priduct

PACKAGING
satisfactory

STABILITY
Protocol: satisfactory
Exp. Date: 24 mo.

REMARKS AND CONCLUSION: approval majarski

Mary Ann Jarski

CHEMIST'S REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT	Federal Register Statement Date	NDA Number 83-273

AF Number

Name and Address of Applicant (City and State)

ayerst labs
div. of american home products corp
new yorkm NY 10017

Original
Amendment
Supplement
Resubmission
Correspondance
Report
Other

Purpose of Amendment/Supplement

report + amend

Date(s) of Submission(

2/4/76(both)

Pharmacological Category	Name of Drug	
estrogens	premarin(conjugated estrogens)	
Dosage Form(s)	Potency(ies)	How Dispensed
topical vaginal cream	0.625 mcg per g.	R_x xx OTC
Packaging/Sterilization	Samples	Related IND/NDA/MF
requested	submitted & previously evlauated	

Labeling

as per MO(vvkarusaitis)

Biologic Availability

NC

Establishment Inspection

NC

Components, Composition, Manufacturing and Controls

as per letter to issue

Remarks

rev w/f

gmillar

Conclusion

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-216

OTHER REVIEW(S)

REVIEW OF AMENDMENT

DATE COMPLETED: 10-16-78 ANDA #: 83-273

CO. NAME: Ayerst Laboratories
685 Third Avenue
New York, NY 10017

NAME OF DRUG: Trade: Premarin Vaginal Cream

Generic: Conjugated Estrogens USP Vaginal Cream

TYPE OF SUBMISSION: Amendment

DATE OF SUBMISSION: 10-5-78

CLINICAL EVALUATION:

1. Review of Studies: Chemical and manufacturing data are to be reviewed by the chemist.

2. Review of Labeling:

Container labels: FPL's are satisfactory for the cartons (42.5 g. or 1.5 oz.) combination package and refill package.

b(4)

—— (tube) - 8 g. (0.28 oz.)
42.5 g (1.5 oz.) -- satisfactory

Instructions for Use of Applicator is satisfactory.

Package insert: FPL dated Sept. 1978, is satisfactory -- (paper is heavier or thicker and HOW SUPPLIED section has been shortened).

Patient Package Insert: FPL dated Sept. 1978, is satisfactory -- (HOW SUPPLIED section has been shortened).

CONCLUSION: FPL's are satisfactory.

RECOMMENDATIONS: Approval of the submission provided the manufacturing and chemical data are satisfactory.

Marvin Seife

Marvin Seife, M.D.

cc:dup
MS/wlh/10-16-78

REVIEW OF AMENDMENT RESUBMISSION

DATE COMPLETED: 4-3-78

ANDA#: 83-273

CO. NAME: Ayerst Labs.
ADDRESS: NY NY 10017

NAME OF DRUG: Trade: Premarin Vaginal Cream
Generic: Conjugated Estrogesn Vaginal Cream

DATE OF SUBMISSION: 9-16-77

TYPE OF SUBMISSION: Resubmission (Reply to FDA Letters 3-8-77: 5-9-77)

CLINICAL EVALUATION:

REVIEW OF STUDIES:

Pertinent Data is to be reviewed by the chemist
Bioavailability requiremnt: Not required
Full manufacturing information: Required

REVIEW OF LABELING:

a) Container Labels: Satisfactory
Net weigh 1 1/2 oz.: 42.5
Refill package

DRAFT Physician's complimentary Package NT WT. 0.28 oz.

b) Insert Labeling: Satisfactory
Date: 7-15-77

DRAFT Firm 9-16-77 Final printed labels will be forwarded when they become available.
4-3-78 Not available to date:

CONCLUSION: Labeling is satisfactory (Draft)
await FPL
Question: What is the PH of the product?

RECOMMENDATIONS: The firm is to be so notified.
Send PPI

V.V. Karusaitis, M.D.

cc:
DUP
VVKarusaitis/ps/4/13/78

REVIEW OF RESUBMISSION, FPL

DATE COMPLETED: 4-26-78 ANDA #: 83-273

CO. NAME: Ayerst Laboratories
NY, NY 10017

NAME OF DRUG: Trade: Premarin Vaginal Cream

Generic: Conjugated Estrogens USP Vaginal Cream

DATE OF SUBMISSION: 1-12-78

TYPE OF SUBMISSION: Resubmission

CLINICAL EVALUATION:

1. Review of Studies:
   Pertinent data is to be reviewed by the chemist.
   Bio requirement - required

2. Review of Labeling:

   Container labels: Satisfactory
   — tube of 8 g. (0.28 oz.)
   42.5 g (1 1/2 oz.)
   carton label box 1 1/2 oz. (42.5 g.)

   b(4)

   Insert labeling: Satisfactory
   date: 9-77

   Dec. 8, 1977 submission: Reply to FR 7-22-77
   PPI: Sept. 1977

CONCLUSION: Insert labeling is satisfactory. PPI and container labels are satisfactory.

RECOMMENDATIONS: The firm is to be so notified.

V.V. Karusaitis, M.D.

cc:dup
VVK/wlb/4-26-78

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-216

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 20-216

Wyeth-Ayerst Laboratories
Attention: Mr. Justin R. Victoria
Assistant Vice President, Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-1245

DEC 10 1991

Dear Mr. Victoria:

Reference is made to your approved Abbreviated New Drug Application for Premarin (conjugated estrogens) Vaginal Cream, ANDA 83-273.

The Division of Metabolism and Endocrine Drug Products is assuming responsibility for this application. In order to enter it into our document stream, it must be renumbered as a NDA. The official receipt date is September 10, 1991, and the new reference number is **NDA 20-216.**

As this drug product is already approved, and remains so, no filing date will be determined.

Please begin any communications concerning this application by citing the NDA number listed above. Address all correspondence to:

Solomon Sobel, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-510)
Attention: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857

Should you have any questions concerning this NDA, please contact Dr. James Cheever at (301) 443-3520.

Sincerely yours,

12/9/91

John R. Short
Supervisory Consumer Safety Officer
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

cc: NDA Arch
HFD-510
HFC-130/JAllen
HFD-600
HFD-510/SSobel/PCorfman/LGolden/YChiu/MBennett/AJordan
HFD-511/JCheever/11.29.91/N20216AK.001
Concurrences: JShort 12/2/91

ACKNOWLEDGE LETTER

12/3/91

Original

Ayerst

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

December 17, 1976

20-216

NDA ORIG AMENDMENT

FPL

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Scientific Evaluation
Bureau of Drugs HFD-530
Attn: DOCUMENT CONTROL ROOM 16-72
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

SUBJECT: NDA 83-273; PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream

Dear Dr. Seife:

In accord with the Administration's Notice published in the Federal Register on October 29, 1976 (41 FR 47573), we are submitting herewith, in triplicate, a supplemental application to provide for revised labeling which is substantially the same as that contained in the above Notice.

This labeling will be placed into effect by December 29, 1976. Twelve copies of the final printed package circulars are enclosed with this submission.

Sincerely,

AYERST LABORATORIES

for Henry S. Perdue, Ph.D.
Director
Regulatory Affairs

HSP
KGK:so
Enclosures

RECEIVED
DEC 17 1976
BUREAU OF DRUGS

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

Form Approved
OMB No. 57-R0003

NEW DRUG APPLICATION *(DRUGS FOR HUMAN USE)*

(Title 21, Code of Federal Regulations, § 130.4)

Name of applicant AYERST LABORATORIES

Address 685 Third Avenue, New York, New York 10017

Date December 17, 1976

Name of new drug PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream

- ☐ Original application (regulation § 130.4).
- ☒ Amendment to original, unapproved application (regulation § 130.7).
- ☐ Abbreviated application (regulation § 130.4(f)).
- ☐ Amendment to abbreviated, unapproved application (regulation § 130.7).
- ☐ Supplement to an approved application (regulation § 130.9).
- ☐ Amendment to supplement to an approved application.

The undersigned submits this application for a new drug pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. It is understood that when this application is approved, the labeling and advertising for the drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will contain the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant warnings, hazards, contraindications, side effects, and precautions, as that contained in the labeling which is part of this application in accord with §1.106(b) (21 CFR 1.106(b)). It is understood that all representations in this application apply to the drug produced until an approved supplement to the application provides for a change or the change is made in conformance with other provisions of §130.9 of the new-drug regulations.

Attached hereto, submitted in the form described in §130.4(e) of the new-drug regulations, and constituting a part of this application are the following:

1. Table of contents. The table of contents should specify the volume number and the page number in which the complete and detailed item is located and the volume number and the page number in which the summary of that item is located (if any).

2. Summary. A summary demonstrating that the application is well-organized, adequately tabulated, statistically analyzed (where appropriate), and coherent and that it presents a sound basis for the approval requested. The summary should include the following information: (In lieu of the outline described below and the evaluation described in Item 3, an expanded summary and evaluation as outlined in §130.4(d) of the new-drug regulations may be submitted to facilitate the review of this application.)

a. Chemistry.

i. Chemical structural formula or description for any new-drug substance.

ii. Relationship to other chemically or pharmacologically related drugs.

iii. Description of dosage form and quantitative composition.

b. Scientific rationale and purpose the drug is to serve.

c. Reference number of the investigational drug notice(s) under which this drug was investigated and of any notice, new-drug application, or master file of which any contents are being incorporated by reference to support this application.

d. Preclinical studies. (Present all findings including all adverse experiences which may be interpreted as incidental or not drug-related. Refer to date and page number of the investigational drug notice(s) or the volume and page number of this application where complete data and reports appear.)

i. Pharmacology (pharmacodynamics, endocrinology, metabolism, etc.).

ii. Toxicology, and pathology: Acute toxicity studies; subacute and chronic toxicity studies; reproduction and teratology studies; miscellaneous studies.

e. Clinical studies. (All material should refer specifically to each clinical investigator and to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found.)

i. Special studies not described elsewhere.

ii. Dose-range studies.

iii. Controlled clinical studies.

iv. Other clinical studies (for example, uncontrolled or incompletely controlled studies).

v. Clinical laboratory studies related to effectiveness.

vi. Clinical laboratory studies related to safety.

vii. Summary of literature and unpublished reports available to the applicant.

3. Evaluation of safety and effectiveness. a. Summarize separately the favorable and unfavorable evidence for each claim in the package labeling. Include references to the volume and page number in the application and in any documents incorporated by reference where the complete data and reports may be found.

b. Include tabulation of all side effects or adverse experience, by age, sex, and dosage formulation, whether or not considered to be significant, showing whether administration of the drug was stopped and showing the investigator's name with a reference to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found. Indicate those side effects or adverse experiences considered to be drug-related.

4. Copies of the label and all other labeling to be used for the drug (a total of 12 copies if in final printed form, 4 copies if in draft form):

a. Each label, or other labeling, should be clearly identified to show its position on, or the manner in which it accompanies, the market package.

b. If the drug is to be offered over the counter, labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to the layman. If the drug is intended or offered for uses under the professional supervision of a practitioner licensed by law to administer it, the application should also contain labeling that includes adequate information for all such uses, including all the purposes for which the over-the-counter drug is to be advertised to, or represented for use by, physicians.

c. If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purposes for which it is intended, including all the purposes for which it is to be advertised or represented, in accord with §1.106(b) (21 CFR 1.106(b)). The application should include any labeling for the drug intended to be made available to the layman.

d. If no established name exists for a new-drug substance, the application shall propose a nonproprietary name for use as the established name for the substance.

e. Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug.

f. No application may be approved if the labeling is false or misleading in any particular.

(When mailing pieces, any other labeling, or advertising copy are devised for promotion of the new drug, samples shall be submitted at the time of initial dissemination of such labeling and at the time of initial placement of any such advertising for a prescription drug (see §130.13 of the new-drug regulations). Approval of a supplemental new-drug application is required prior to use of any promotional claims not covered by the approved application.)

5. A statement as to whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

6. A full list of the articles used as components of the drug. This list should include all substances used in the synthesis, extraction, or other method of preparation of any new-drug substance, and in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

7. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed (for example, amount per tablet or per milliliter) and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

8. A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug. Included in this description should be full information with respect to any new-drug substance and to the new-drug dosage form, as follows; in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture, processing, and packing and the described facilities and controls to determine and preserve the identity, strength, quality, and purity of the drug:

a. A description of the physical facilities including building and equipment used in manufacturing, processing, packaging, labeling, storage, and control operations.

b. A description of the qualifications, including educational background and experience, of the technical and professional personnel who are responsible for assuring that the drug has the safety, identity, strength, quality, and purity it purports or is represented to possess, and a statement of their responsibilities.

c. The methods used in the synthesis, extraction, isolation, or purification of any new-drug substance. When the specifications and controls applied to such substance are inadequate in themselves to determine its identity, strength, quality, and purity, the methods should be described in sufficient detail, including quantities used, times, temperatures, pH, solvents, etc., to determine these characteristics. Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the substance may be specified.

d. Precautions to assure proper identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material.

e. Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

f. If the applicant does not himself perform all the manufacturing, processing, packaging, labeling, and control operations for any new-drug substance or the new-drug dosage form, his statement identifying each person who will perform any part of such operations and designating the part; and a signed statement from each such person fully describing, directly or by reference, the methods, facilities, and controls in his part of the operation.

g. Method of preparation of the master formula records and individual batch records and manner in which these records are used.

h. The instructions used in the manufacturing, processing, packaging, and labeling of each dosage form of the new drug, including any special precautions observed in the operations.

i. Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug package to assure their suitability for the intended use.

j. Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

k. Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and, if so, at what stage and by whom it is done.

l. Precautions to check the actual package yield produced from a batch of the drug with the theoretical yield. This should include a description of the accounting for such items as discards, breakage, etc., and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

m. Precautions to assure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling storage and inventory control.

n. The analytical controls used during the various stages of the manufacturing, processing, packaging, and labeling of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components. If the article is one that is represented to be sterile, the same information with regard to the manufacturing, processing, packaging, and the collection of samples of the drug should be given for sterility controls. Include the standards used for acceptance of each lot of the finished drug.

o. An explanation of the exact significance of the batch control numbers used in the manufacturing, processing, packaging, and labeling of the drug, including the control numbers that appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

p. A complete description of, and data derived from, studies of the stability of the drug, including information showing the suitability of the analytical methods used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new-drug substance, for the finished dosage form of the drug in the container in which it is to be marketed, including any proposed multiple-dose container, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed. State the expiration date(s) that will be used on the label to preserve the identity, strength, quality, and purity of the drug until it is used. (If no expiration date is proposed, the applicant must justify its absence.)

q. Additional procedures employed which are designed to prevent contamination and otherwise assure proper control of the product.

An application may be refused unless it includes adequate information showing that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity in conformity with good manufacturing practice and identifies each establishment, showing the location of the plant conducting these operations.)

9. Samples of the drug and articles used as components, as follows: a. The following samples shall be submitted with the application or as soon thereafter as they become available. Each sample shall consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the application to determine compliance with its control specifications for identity and assays:

i. A representative sample or samples of the finished dosage form(s) proposed in the application and employed in the clinical investigations and a representative sample or samples of each new-drug substance, as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

ii. A representative sample or samples of finished market packages of each dosage form of the drug prepared for initial marketing and, if any such sample is not from a commercial-scale production batch, such a sample from a representative commercial-scale production batch; and a representative sample or samples of each new-drug substance as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

iii. A sample or samples of any reference standard and blank used in the procedures described in the application for assaying each new-drug substance and other assayed components of the finished drug: *Provided, however,* That samples of reference standards recognized in the official U.S. Pharmacopeia or The National Formulary need not be submitted unless requested.

b. Additional samples shall be submitted on request.

c. Each of the samples submitted shall be appropriately packaged and labeled to preserve its characteristics, to identify the material and the quantity in each subdivision of the sample, and to identify each subdivision with the name of the applicant and the new-drug application to which it relates.

d. There shall be included a full list of the samples submitted pursuant to Item 9a; a statement of the additional samples that will be submitted as soon as available; and, with respect to each sample submitted, full information with respect to its identity, the origin of any new-drug substance contained therein (including in the case of new-drug substances, a statement whether it was produced on a laboratory, pilot-plant, or full-production scale) and detailed results of all laboratory tests made to determine the identity, strength, quality, and purity of the batch represented by the sample, including assays. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods used differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

e. The requirements of Item 9a may be waived in whole or in part on request of the applicant or otherwise when any such samples are not necessary.

f. If samples of the drug are sent under separate cover, they should be addressed to the attention of the Bureau of Medicine and identified on the outside of the shipping carton with the name of the applicant and the name of the drug as shown on the application.

10. Full reports of preclinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate preclinical tests by all methods reasonably applicable to a determination of the safety and effectiveness of the drug under the conditions of use suggested in the proposed labeling.

b. Detailed reports of the preclinical investigations, including all studies made on laboratory animals, the methods used, and the results obtained, should be clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short- or long-term administration or whether it is to be used in infants, children, pregnant women, or women of child-bearing potential.

c. Detailed reports of any pertinent microbiological and *in vitro* studies.

d. Summarize and provide a list of literature references (if available) to all other preclinical information known to the applicant, whether published or unpublished, that is pertinent to an evaluation of the safety or effectiveness of the drug.

11. List of investigators. a. A complete list of all investigators supplied with the drug including the name and post office address of each investigator and, following each name, the volume and page references to the investigator's report(s) in this application and in any documents incorporated by reference, or the explanation of the omission of any reports.

b. The unexplained omission of any reports of investigations made with the new drug by the applicant, or

submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, whether or not it would bias an evaluation of the safety of the drug or its effectiveness in use, may constitute grounds for the refusal or withdrawal of the approval of an application.

12. Full reports of clinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the labeling.

b. An application may be refused unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

c. Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, full information concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintains adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. An application for a combination drug may be refused unless there is substantial evidence that each ingredient designated as active makes a contribution to the total effect claimed for the drug combination. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

d. Attach as a separate section a completed Form FD-1639, Drug Experience Report (obtainable, with instructions, on request from the Department of HEW. Food and Drug Administration, Bureau of Drugs *(BD-200)* Rockville, Maryland 20852), for each adverse experience or, if feasible, for each subject or patient experiencing one or more adverse effects, described in Item 12c, whether or not full information is available. Form FD-1639 should be prepared by the applicant if the adverse experience was not reported in such form by the investigator. The Drug Experience Report should be cross-referenced to any narrative description included in Item 12c. In lieu of a FD Form 1639, a computer-generated report may be submitted if equivalent in all elements of information with the identical enumerated sequence of events and methods of completion; all formats proposed for such use will require initial review and approval by the Food and Drug Administration.

e. All information pertinent to an evaluation of the safety and effectiveness of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commerical marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application and related drugs. An adequate summary may be acceptable in lieu of a reprint of a published report which only supports other data submitted. Reprints are not required of reports in designated journals, listed in §130.38 of the new-drug regulations, about related drugs; a bibliography will suffice. Include any evaluation of the safety or effectiveness of the drug that has been made by the applicant's medical department, expert committee, or consultants.

f. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

g. The complete composition and/or method of manufacture of the new drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in Item 6, 7, or 8 of the application.

13. If this is a supplemental application, full information on each proposed change concerning any statement made in the approved application.
Observe the provisions of §130.9 of the new-drug regulations concerning supplemental applications.

AYERST LABORATORIES
(Applicant)

Per Henry S. Perdue, Ph.D.
(Responsible official or agent)

Director, Regulatory Affairs
(Indicate authority)

(Warning: A willfully false statement is a criminal offense. U.S.C. Title 18, sec. 1001.)

NOTE: This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States.

3 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

___√___ Draft Labeling (b5)

_____ Deliberative Process (b5)

Orig

Ayerst

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

December 15, 1976

NDA ORIG AMENDMENT

Marvin Seife, M.D.
Director
Generic Drug Staff
Bureau of Drugs - HFD 530
ATTENTION: DOCUMENT CONTROL ROOM #16-72
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

SUBJECT: NDA 83-273; PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream

Dear Dr. Seife:

We are submitting herewith, in triplicate, an amendment to our abbreviated new drug application for the above product. This amendment contains full manufacturing information as specified in Sections 6 (components), 7 (composition) and 8 (methods, facilities and controls) of the new-drug application form FD-356H.

Much of the information contained in this submission has been provided to the Administration in prior amendments, however, for your convenience it is included here as part of the full manufacturing information.

We would greatly appreciate the Administration's prompt attention to this application.

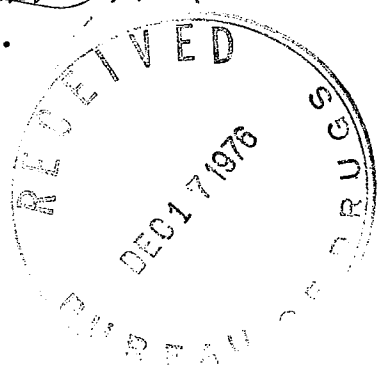
Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331(j).

Sincerely,

AYERST LABORATORIES

for Henry S. Perdue, Ph.D.
Director
Regulatory Affairs

HSP
KGK/jp
Encls.



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

Form Approved
OMB No. 57-R0003

NEW DRUG APPLICATION *(DRUGS FOR HUMAN USE)*

(Title 21, Code of Federal Regulations, § 130.4)

Name of applicant AYERST LABORATORIES

Address 685 Third Avenue, New York, New York 10017

Date December 17, 1976

Name of new drug PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream

- ☐ Original application (regulation § 130.4).
- ☒ Amendment to original, unapproved application (regulation § 130.7).
- ☐ Abbreviated application (regulation § 130.4(f)).
- ☐ Amendment to abbreviated, unapproved application (regulation § 130.7).
- ☐ Supplement to an approved application (regulation § 130.9).
- ☐ Amendment to supplement to an approved application.

The undersigned submits this application for a new drug pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. It is understood that when this application is approved, the labeling and advertising for the drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will contain the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant warnings, hazards, contraindications, side effects, and precautions, as that contained in the labeling which is part of this application in accord with §1.106(b) (21 CFR 1.106(b)). It is understood that all representations in this application apply to the drug produced until an approved supplement to the application provides for a change or the change is made in conformance with other provisions of §130.9 of the new-drug regulations.

Attached hereto, submitted in the form described in §130.4(e) of the new-drug regulations, and constituting a part of this application are the following:

1. Table of contents. The table of contents should specify the volume number and the page number in which the complete and detailed item is located and the volume number and the page number in which the summary of that item is located (if any).

2. Summary. A summary demonstrating that the application is well-organized, adequately tabulated, statistically analyzed (where appropriate), and coherent and that it presents a sound basis for the approval requested. The summary should include the following information: (In lieu of the outline described below and the evaluation described in Item 3, an expanded summary and evaluation as outlined in §130.4(d) of the new-drug regulations may be submitted to facilitate the review of this application.)

a. Chemistry.

i. Chemical structural formula or description for any new-drug substance.

ii. Relationship to other chemically or pharmacologically related drugs.

iii. Description of dosage form and quantitative composition.

b. Scientific rationale and purpose the drug is to serve.

c. Reference number of the investigational drug notice(s) under which this drug was investigated and of any notice, new-drug application, or master file of which any contents are being incorporated by reference to support this application.

d. Preclinical studies. (Present all findings including all adverse experiences which may be interpreted as incidental or not drug-related. Refer to date and page number of the investigational drug notice(s) or the volume and page number of this application where complete data and reports appear.)

i. Pharmacology (pharmacodynamics, endocrinology, metabolism, etc.).

ii. Toxicology and pathology: Acute toxicity studies; subacute and chronic toxicity studies; reproduction and teratology studies; miscellaneous studies.

e. Clinical studies. (All material should refer specifically to each clinical investigator and to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found.)

i. Special studies not described elsewhere.

ii. Dose-range studies.

iii. Controlled clinical studies.

iv. Other clinical studies (for example, uncontrolled or incompletely controlled studies).

v. Clinical laboratory studies related to effectiveness.

vi. Clinical laboratory studies related to safety.

vii. Summary of literature and unpublished reports available to the applicant.

3. Evaluation of safety and effectiveness. a. Summarize separately the favorable and unfavorable evidence for each claim in the package labeling. Include references to the volume and page number in the application and in any documents incorporated by reference where the complete data and reports may be found.

b. Include tabulation of all side effects or adverse experience, by age, sex, and dosage formulation, whether or not considered to be significant, showing whether administration of the drug was stopped and showing the investigator's name with a reference to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found. Indicate those side effects or adverse experiences considered to be drug-related.

4. Copies of the label and all other labeling to be used for the drug (a total of 12 copies if in final printed form, 4 copies if in draft form):

identified to show its position on, or the manner in which it accompanies, the market package.

b. If the drug is to be offered over the counter, labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to the layman. If the drug is intended or offered for uses under the professional supervision of a practitioner licensed by law to administer it, the application should also contain labeling that includes adequate information for all such uses, including all the purposes for which the over-the-counter drug is to be advertised to, or represented for use by, physicians.

c. If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purposes for which it is intended, including all the purposes for which it is to be advertised or represented, in accord with §1.106(b) (21 CFR 1.106(b)). The application should include any labeling for the drug intended to be made available to the layman.

d. If no established name exists for a new-drug substance, the application shall propose a nonproprietary name for use as the established name for the substance.

e. Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug.

f. No application may be approved if the labeling is false or misleading in any particular.

(When mailing pieces, any other labeling, or advertising copy are devised for promotion of the new drug, samples shall be submitted at the time of initial dissemination of such labeling and at the time of initial placement of any such advertising for a prescription drug (see §130.13 of the new-drug regulations). Approval of a supplemental new-drug application is required prior to use of any promotional claims not covered by the approved application.)

5. A statement as to whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

6. A full list of the articles used as components of the drug. This list should include all substances used in the synthesis, extraction, or other method of preparation of any new-drug substance, and in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

7. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed (for example, amount per tablet or per milliliter) and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

8. A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug. Included in this description should be full information with respect to any new-drug substance and to the new-drug dosage form, as follows, in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture, processing, and packing and the described facilities and controls to determine and preserve the identity, strength, quality, and purity of the drug:

a. A description of the physical facilities including building and equipment used in manufacturing, processing, packaging, labeling, storage, and control operations.

b. A description of the qualifications, including educational background and experience, of the technical and professional personnel who are responsible for assuring that the drug has the safety, identity, strength, quality, and purity it purports or is represented to possess, and a statement of their responsibilities.

c. The methods used in the synthesis, extraction, isolation, or purification of any new-drug substance. When the specifications and controls applied to such substance are inadequate in themselves to determine its identity, strength, quality, and purity, the methods should be described in sufficient detail, including quantities used, times, temperatures, pH, solvents, etc., to determine these characteristics. Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the substance may be specified.

d. Precautions to assure proper identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material.

e. Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

f. If the applicant does not himself perform all the manufacturing, processing, packaging, labeling, and control operations for any new-drug substance or the new-drug dosage form, his statement identifying each person who will perform any part of such operations and designating the part; and a signed statement from each such person fully describing, directly or by reference, the methods, facilities, and controls in his part of the operation.

g. Method of preparation of the master formula records and individual batch records and manner in which these records are used.

h. The instructions used in the manufacturing, processing, packaging, and labeling of each dosage form of the new drug, including any special precautions observed in the operations.

i. Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug package to assure their suitability for the intended use.

j. Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

k. Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and, if so, at what stage and by whom it is done.

l. Precautions to check the actual package yield produced from a batch of the drug with the theoretical yield. This should include a description of the accounting for such items as discards, breakage, etc., and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

m. Precautions to assure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling storage and inventory control.

n. The analytical controls used during the various stages of the manufacturing, processing, packaging, and labeling of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components. If the article is one that is represented to be sterile, the same information with regard to the manufacturing, processing, packaging, and the collection of samples of the drug should be given for sterility controls. Include the standards used for acceptance of each lot of the finished drug.

o. An explanation of the exact significance of the batch control numbers used in the manufacturing, processing, packaging, and labeling of the drug, including the control numbers that appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

p. A complete description of, and data derived from, studies of the stability of the drug, including information showing the suitability of the analytical methods used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new-drug substance, for the finished dosage form of the drug in the container in which it is to be marketed, including any proposed multiple-dose container, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed. State the expiration date(s) that will be used on the label to preserve the identity, strength, quality, and purity of the drug until it is used. (If no expiration date is proposed, the applicant must justify its absence.)

q. Additional procedures employed which are designed to prevent contamination and otherwise assure proper control of the product.

(An application may be refused unless it includes adequate information showing that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity in conformity with good manufacturing practice and identifies each establishment, showing the location of the plant conducting these operations.)

9. Samples of the drug and articles used as components, as follows: a. The following samples shall be submitted with the application or as soon thereafter as they become available. Each sample shall consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the application to determine compliance with its control specifications for identity and assays:

i. A representative sample or samples of the finished dosage form(s) proposed in the application and employed in the clinical investigations and a representative sample or samples of each new-drug substance, as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

ii. A representative sample or samples of finished market packages of each dosage form of the drug prepared for initial marketing and, if any such sample is not from a commercial-scale production batch, such a sample from a representative commercial-scale production batch; and a representative sample or samples of each new-drug substance as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

iii. A sample or samples of any reference standard and blank used in the procedures described in the application for assaying each new-drug substance and other assayed components of the finished drug: *Provided, however,* That samples of reference standards recognized in the official U.S. Pharmacopeia or The National Formulary need not be submitted unless requested.

b. Additional samples shall be submitted on request.

c. Each of the samples submitted shall be appropriately packaged and labeled to preserve its characteristics, to identify the material and the quantity in each subdivision of the sample, and to identify each subdivision with the name of the applicant and the new-drug application to which it relates.

d. There shall be included a full list of the samples submitted pursuant to Item 9a; a statement of the additional samples that will be submitted as soon as available; and, with respect to each sample submitted, full information with respect to its identity, the origin of any new-drug substance contained therein (including in the case of new-drug substances, a statement whether it was produced on a laboratory, pilot-plant, or full-production scale) and detailed results of all laboratory tests made to determine the identity, strength, quality, and purity of the batch represented by the sample, including assays. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods used differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

e. The requirements of Item 9a may be waived in whole or in part on request of the applicant or otherwise when any such samples are not necessary.

f. If samples of the drug are sent under separate cover, they should be addressed to the attention of the Bureau of Medicine and identified on the outside of the shipping carton with the name of the applicant and the name of the drug as shown on the application.

10. Full reports of preclinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate preclinical tests by all methods reasonably applicable to a determination of the safety and effectiveness of the drug under the conditions of use suggested in the proposed labeling.

b. Detailed reports of the preclinical investigations, including all studies made on laboratory animals, the methods used, and the results obtained, should be clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short- or long-term administration or whether it is to be used in infants, children, pregnant women, or women of child-bearing potential.

c. Detailed reports of any pertinent microbiological and *in vitro* studies.

d. Summarize and provide a list of literature references (if available) to all other preclinical information known to the applicant, whether published or unpublished, that is pertinent to an evaluation of the safety or effectiveness of the drug.

11. List of investigators. a. A complete list of all investigators supplied with the drug including the name and post office address of each investigator and, following each name, the volume and page references to the investigator's report(s) in this application and in any documents incorporated by reference, or the explanation of the omission of any reports.

b. The unexplained omission of any reports of investigations made with the new drug by the applicant, or

submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, whether or not it would bias an evaluation of the safety of the drug or its effectiveness in use, may constitute grounds for the refusal or withdrawal of the approval of an application.

12. Full reports of clinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the labeling.

b. An application may be refused unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

c. Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, full information concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintains adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. An application for a combination drug may be refused unless there is substantial evidence that each ingredient designated as active makes a contribution to the total effect claimed for the drug combination. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

d. Attach as a separate section a completed Form FD-1639, Drug Experience Report (obtainable, with instructions, on request from the Department of HEW. Food and Drug Administration. Bureau of Drugs *(BD-200)* Rockville, Maryland 20852), for each adverse experience or, if feasible, for each subject or patient experiencing one or more adverse effects, described in Item 12c, whether or not full information is available. Form FD-1639 should be prepared by the applicant if the adverse experience was not reported in such form by the investigator. The Drug Experience Report should be cross-referenced to any narrative description included in Item 12c. In lieu of a FD Form 1639, a computer-generated report may be submitted if equivalent in all elements of information with the identical enumerated sequence of events and methods of completion; all formats proposed for such use will require initial review and approval by the Food and Drug Administration.

e. All information pertinent to an evaluation of the safety and effectiveness of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commerical marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application and related drugs. An adequate summary may be acceptable in lieu of a reprint of a published report which only supports other data submitted. Reprints are not required of reports in designated journals, listed in §130.38 of the new-drug regulations, about related drugs; a bibliography will suffice. Include any evaluation of the safety or effectiveness of the drug that has been made by the applicant's medical department, expert committee, or consultants.

f. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

g. The complete composition and/or method of manufacture of the new drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in Item 6, 7, or 8 of the application.

13. If this is a supplemental application, full information on each proposed change concerning any statement made in the approved application.
Observe the provisions of §130.9 of the new-drug regulations concerning supplemental applications.

AYERST LABORATORIES
(Applicant)

Per **Henry S. Perdue, Ph.D.**
(Responsible official or agent)

Director, Regulatory Affairs
(Indicate authority)

(Warning: A willfully false statement is a criminal offense. U.S.C. Title 18, sec. 1001.)

NOTE: This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States.

Rec. w/c

Ayerst

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

September 28, 1976

No Reply
Sel Later documents
mdj 3/4/77

RESUBMISSION
NDA ORIG AMENDMENT

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Scientific Evaluation
Bureau of Drugs HFD-530
Attn: DOCUMENT CONTROL ROOM 16-72
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

SUBJECT: NDA 83-273; PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream

Dear Dr. Seife:

In response to your letter of March 31, 1976, we are submitting herewith, in triplicate, the requested information to amend the above ANDA.

The responses to your questions are given below and in the attached sections as described.

"1. For labeling:
a). Container labels: revise the ingredients section as per the above formulation change.

b). Package insert: a revised insert-as first requested in our letter of October 2, 1973---has not been submitted."

Draft labeling for the container labels and a revised package insert are included in the attached Section 1. The labeling revisions provide for the change in the formula in accordance with our amendment of February 4, 1976, and conformance with the Estrogen Labeling Guidelines as requested. Final printed labels will be submitted when they are available. This labeling is currently scheduled for implementation beginning October 1, 1976.

"2. For ingredients:
a). the active ingredients; an updating to USP XIX and submission of analytical results for same

b). others: an updating to USP XIX & NF XIV."

A memorandum by our Ms. H. Archibald which responds to the above question is attached as Section 2. The additional information described in that memorandum

RECEIVED
SEP 30 1976
BUREAU OF DRUGS

.../2

is contained in Section 3.

"3. For the drug dosage form: studies on its stability; and a proposal for expiration dating."

The proposal for expiration dating is contained in Ms. Archibald's memorandum (Section 2) and the related stability data are displayed in Section 4.

"4. Adequate information with respect to the characteristics of and the test methods employed for, the container, closure, or other component parts of the drug package to assure their suitability."

Descriptions of the product container and closure are given in the memorandum in Section 2. The suitability of the package for its intended use is determined by stability studies which insure that adequate protection is provided to the product. Results of these studies are shown in Section 5.

In addition, we are providing revised dosage form specifications in Section 6.

We would greatly appreciate your prompt attention to the material submitted in this amendment. We look forward to your reply at your earliest convenience.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331(j).

Sincerely,

AYERST LABORATORIES

Henry S. Perdue, Ph.D.
Director
Regulatory Affairs

HSP
KGK:so
Enclosures

REVIEW OF ANDA AMENDMENT

DATE COMPLETED: 4-22-76

ANDA #: 83-273

CO. NAME: Ayerst Labs.
New York, NY 10017

NAME OF DRUG: Trade: Premarin Vaginal Cream
Generic: conjugated estrogens vaginal cream

DATE OF SUBMISSION: resubmission (reply to FDA letter)

CLINICAL EVALUATION:

Review of studies: Pertinent data is to be reviewed by the chemist.
Bioavailability requirement: not required.

Review of Labeling: not submitted.

b(6)

** Letter of 4-1-76 = Firm states that L.M.D has been contacted for report on Mrs. [redacted]

CTED

CONCLUSION: Drug Experience report form FD-1639 has not been filed.

RECOMMENDATIONS: The firm is to be so notified.

V.V. Karusaitis, M.D.

cc:
Dup
VVKarusaitis/cjb/4-22-76

Orig

Ayerst

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

ORIG NEW CORRES

April 1, 1976

NOTED:
NO ACTION INDICATED
SIG:
DATE: 4/5/76

Marvin Seife, M.D.
Director
Generic Drug Monographs
Office of Scientific Evaluation
Bureau of Drugs HFD-530
Attn: DOCUMENT CONTROL ROOM 16-72
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

SUBJECT: NDA 83-273; PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream

Dear Dr. Seife:

On February 4, 1976, we submitted to the Administration a report we had received from Mrs. [redacted]. Mrs. [redacted] had reported that she experienced a rash and burning sensation while using PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream. We are transmitting herewith, in triplicate, a letter to Mrs. [redacted] physician, Dr. [redacted], requesting that she complete a Drug Experience Report Form FD-1639 regarding this occurrence, and we will forward it when received. b(6)

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331(j).

Sincerely,

AYERST LABORATORIES

for Henry S. Perdue, Ph.D.
Director
Regulatory Affairs

RECEIVED
APR 05 1976
BUREAU OF DRUGS

HSP
KGK:so
Enclosures

February 24, 1976

b(6)

Dear Doctor ———:

We have received a communication from your patient, Mrs. ———————, in which she has expressed b(6)
dissatisfaction with the results achieved with PREVENTH Vaginal Cream which you had prescribed for her. She asserts that the medication caused "a rash and burning" and, inasmuch as we are required to file with the Food and Drug Administration all reports of any adverse reactions to prescription drugs, I am enclosing herewith two copies of the standard Drug Experience Report Form #1639.

If you will be kind enough to complete these, returning one copy to me while retaining the other for your own files, it will materially assist us in keeping our records straight.

Thanking you for your cooperation, I am

Sincerely yours,

John B. Jewell, M. D.

JBJ:fb
Encl.

bcc: Dr.
Dr.
Mr.

b(6)

Ayerst®

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

January 28, 1976

b(6)

Dear Mrs. ———:

We have your letter of recent date in regard to your experiences with PREMARIN® Vaginal Cream.

Examination of our records on this product for the past five years shows that there have been only three complaints of a similar nature although there have been thousands of applications over this period. We do, however, wish to report your reaction to the F.D.A., and would appreciate it if you will kindly advise us of the name and address of your physician.

In regard to compensation, our company has a firm policy that there is no recompense for prescriptions which have been filled by the individual pharmacies.

We regret that you are unable to use the product, and hope that you will find appropriate measures for alleviating your condition.

Sincerely,

B. R. Bortolussi b(4)

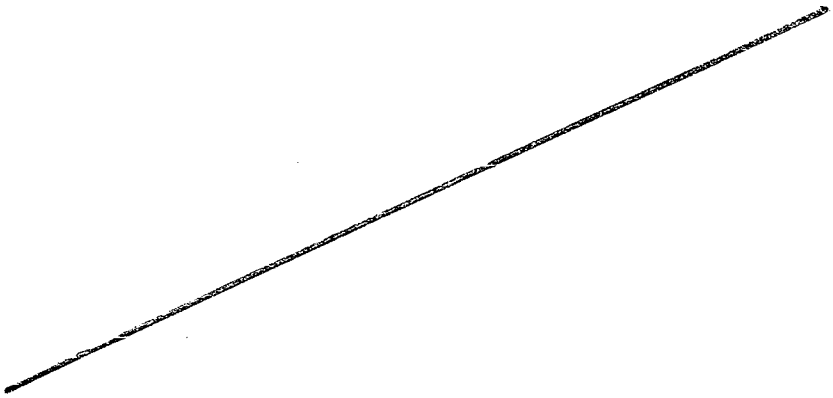
Director
Project Coordination

/cw

Dear Ser

I had to write to tell you that 2 years ago I got Premarin Vaginal cream from my doctor and got a rash and burning the first time I used it so I stopped it. I went to the doctor Monday and the doctor give me the same cream I didn't realize it was the same cream and got a rash and burning again. Something told me that was Premarin sure enough I find the same tube that was in the medicine chest I think I should be compensated for both tubes which was $5.95 each I am not a doctor but I think that cream

should not be sold it is supposed to make people feel better but it makes you feel miserable



b(6)

NDA 83-273

Aerst Laboratories
Division of American Home Products, Corp.
Attention: Dr. Henry S. Perdue
685 Third Avenue
New York, NY 10017

MAR 3 1 1976

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Premarin (conjugated estrogens) Vaginal Cream, 625 mcg. per g.

Reference is made to your communication dated February 4, 1976 amending the application with a drug experience report.

Reference is also made to your communication also dated February 4, 1976 which (a) enclosed a formulation revision whereby the _____ and (b) updated specifications for the drug dosage form. b(4)

We have re-reviewed this abbreviated new drug application. However, before we are able to reach a final conclusion, the following additional information is necessary:

1. For labeling:
   a). Container labels: revise the ingredients section as per the above formulation change.
   b). Package insert: a revised insert---as first requested in our letter of October 2, 1973---has not been submitted.

2. For ingredients:
   a). the active ingredients; an updating to USP XIX and submission of analytical results for same
   b). others: an updating to USP XIX & NF XIV.

3. For the drug dosage form: studies on its stability; and a proposal for expiration dating.

4. Adequate information with respect to the characteristics of, and the test methods employed for, the container, closure, or other componentsparts of the drug package to assure their suitability for the intended use.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife 3/31/76

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

NYC-DO
Dup
HFD-614, HFD-616
VVKarusaitis/JLMeyer/GMillar
R/D init. Jmeyer/MSeife 3-29-76
f typing/cjb/3-29-76
rev w/f
JMeyer 3/30/76

Chill 3/30/76

Chill 3/31/76

REVIEW OF RESUBMISSION *28 months to reply

DATE COMPLETED: 3-18-76

ANDA #: 83-273

CO. NAME: Ayerst Labs.
NY. NY 10017

NAME OF DRUG: Trade: Premarin Vaginal Cream

Generic: Conjugated Vaginal Cream, USP, 0.625 mg/g

DATE OF SUBMISSION: 2-4-76

TYPE OF SUBMISSION: Resubmission (reply to FDA letter 10-2-73) 28 mos. later.

CLINICAL EVALUATION:

1. Review of Studies:

Pertinent data is to be reviewed by the chemist.
Bioavailability requirement: Required.

2. Review of Labeling: b(4)

a) Container labels: Satisfactory (M.O.R. 5-10-73)

b) Firm proposes: 1. Elimination of [redacted].

2. Replacement of [redacted].

CONCLUSION: Labeling is satisfactory for container labels: Revised insert has not been submitted (Request 10-2-73: 6-9-75).

RECOMMENDATIONS: The firm is to be so notified.

V.V. Karusaitis, M.D.

cc:
Dup
VVKarusaitis/wlb/3-22-76

REVIEW OF ORIG. NEW CORRESPONDENCE

DATE COMPLETED: 3-11-76

ANDA #: 83-273

CO. NAME: Ayerst Labs.
NY,NY 10017

NAME OF DRUG: Trade: Premarin Vaginal Cream

Generic: Conjugated Vaginal Cream, USP

DATE OF SUBMISSION: 2-4-76

TYPE OF SUBMISSION: Report of adverse reaction (one)

CLINICAL EVALUATION:

Review of studies: Pt. reported vaginal rash and burning after using premarin cream prescribed by two M.D's.

Review of Labeling:

Container Labels: satisfactory

Insert Labeling: satisfactory

CONCLUSION: Adverse reaction reported of"rash and burning". Following use of premarin cream prescribed by two M.D's.
Firm has contacted one M.D. for information.

RECOMMENDATIONS: Will await report of adverse reaction; incomplete at present.

VVKarusaitis, M.D.

cc:
Dup
VVKarusaitis/cjb/3-11-76

Orig

Ayerst®

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

ORIG NEW CORRES

February 4, 1976

Marvin Seife, M.D.
Director
Generic Drug Monographs
HFD-530
Bureau of Drugs
ATTENTION: DOCUMENT CONTROL ROOM No. 16-72
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

SUBJECT: NDA 83-273; PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream

Dear Dr. Seife:

We are enclosing, in triplicate, information received from Mrs. ——— ——— regarding the development of a rash following the use of Premarin Vaginal Cream. b(6)

Also enclosed is a letter from our Mr. ——— requesting the name and address of Mrs. ——— physician. When further information regarding this experience is available we will forward it to the Administration. b(4)

Please include this submission in the Administration's files for NDA 83-273.

The material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331(j).

Sincerely,

AYERST LABORATORIES

for Henry S. Perdue
Director
Regulatory Affairs

HSP:
KGK:ms
Enclosures

K.G.K. JAN 28 1976

January 28, 1976

[redacted] b(6)

Dear Mrs. [redacted]

We have your letter of recent date in regard to your experiences with PREMARIN® Vaginal Cream.

Examination of our records on this product for the past five years shows that there have been only three complaints of a similar nature although there have been thousands of applications over this period. We do, however, wish to report your reaction to the F.D.A., and would appreciate it if you will kindly advise us of the name and address of your physician.

In regard to compensation, our company has a firm policy that there is no recompense for prescriptions which have been filled by the individual pharmacies.

We regret that you are unable to use the product, and hope that you will find appropriate measures for alleviating your condition.

Sincerely,

[redacted] b(4)

Director
Project Coordination

/cw
bcc: Dr. [redacted] b(6)
Dr. [redacted]

Dear Sir

I had to write to tell you that 2 years ago I got Premarin Vaginal Cream from my doctor and got a rash and burning the first time I used it. I stopped it. I went to the doctor Monday and the doctor gave me the same cream I didn't realize it was the same cream and got a rash and burning again. Something told me that was Premarin cream enough I find the same tube that was in the medicine chest I think I should be compensated for both tubes which was $5 each

I am not a doctor but I think that cream

should not be sold it is suppose to make people feel better but it makes you feel miserable

Yours truly

b(6)

Orig

Ayerst

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

Rev.

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

RESUBMISSION

February 4, 1976

NDA ORIG AMENDMENT

Marvin Seife, M.D.
Director
Generic Drug Monographs
HFD-530
Bureau of Drugs
ATTENTION: DOCUMENT CONTROL ROOM No. 16-72
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

SUBJECT: NDA 83-~~285~~ 273; PREMARIN® (Conjugated Estrogens, U.S.P.)
Vaginal Cream

Dear Dr. Seife:

We are enclosing, in triplicate, an amendment to our Abbreviated New Drug Application 83-273. This amendment proposes changes in the product formulation as suggested in your letters of October 2, 1973, and June 9, 1975. Namely, we have proposed eliminating b(4)

This submission consists of a memorandum from our Ms. H. Archibald, Ayerst Laboratories, Rouses Point, New York, revised Sections 6 and 7, an updated specifications section and stability and preservative challenge data supporting the proposed revision.

The material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331(j).

Sincerely,

AYERST LABORATORIES

for / Henry S. Perdue, M.D.
Director
Regulatory Affairs

RECEIVED FEB 9 1976 BUREAU OF DRUGS

HSP:
KGK:ms
Enclosures

AYERST LABORATORIES / Ayerst

Internal correspondence

K.G.K. JAN 28 19[illegible]

TO Dr. K. Kasses — LOCATION New York

FROM Ms. H. Archibald — LOCATION Rouses Point

SUBJECT PREMARIN® VAGINAL CREAM
ANDA 83-273 — DATE January 28, 1976

We are transmitting herewith revised qualitative and quantitative sections for the above subject dosage form [redacted]

An updated specification section is also included.

b(4)

Data on a formula with the new [redacted] and [redacted] in the current market product is attached. In our experience, this [redacted] does not interfere with the analysis.

This data includes U.S.P. Challenge Test for preservative effectiveness and accelerated stability in comparison to the current market formula.

Ayerst Laboratories agrees to test the stability of samples from representative production batches of the product and to submit the results as required for periodic records and reports. In the event that any batch is found to fall outside of specifications during the expected shelf life, Ayerst agrees to take appropriate action regarding such batch.

Please take whatever steps necessary to have this information submitted as part of our ANDA.

H. Archibald.
H. Archibald

HMA/mmm
Attach.

cc: Mr. B. Ferguson
Dr. H. Perdue
Dr. L. Schnell

AYERST LABORATORIES INCORPORATED,
ROUSES POINT, NEW YORK.

6.

A full list of the articles used as components of the drug. This list should include all substances used in the synthesis, extraction, or other method of preparation of any new-drug substance, and in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

ACTIVE INGREDIENT

Conjugated Estrogens, U.S.P.

INACTIVE INGREDIENTS

[redacted] N.F.

Cetyl Alcohol, N.F.

White Wax, U.S.P.

Glyceryl Monostearate, [redacted] b(4)

Propylene Glycol Mononstearate

Methyl Stearate

[redacted], N.F.

Sodium Lauryl Sulfate, U.S.P.

Glycerin, U.S.P.

Mineral Oil, U.S.P.

[redacted] U.S.P.

AYERST LABORATORIES INCORPORATED,
ROUSES POINT, NEW YORK.

7.

A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed, as for example, amount per tablet or per milliliter, and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

EACH GRAM OF CREAM CONTAINS

ACTIVE INGREDIENT	CLAIM	OVERAGE	INPUT	BATCH FORMULA FOR [redacted]
Conjugated Estrogens, U.S.P.	0.625 mg	[redacted]		

INACTIVE INGREDIENTS	INPUT/g	RANGE
[redacted], N.F.		
Cetyl Alcohol, N.F.		
White Wax, U.S.P.		
Glyceryl Monostearate, [redacted]		
Propylene Glycol Monostearate		
Methyl Stearate		
[redacted], N.F.		
Sodium Lauryl Sulfate, U.S.P.		
Glycerin, U.S.P.		
Mineral Oil, U.S.P.		
[redacted], U.S.P. [redacted]		

b(4)

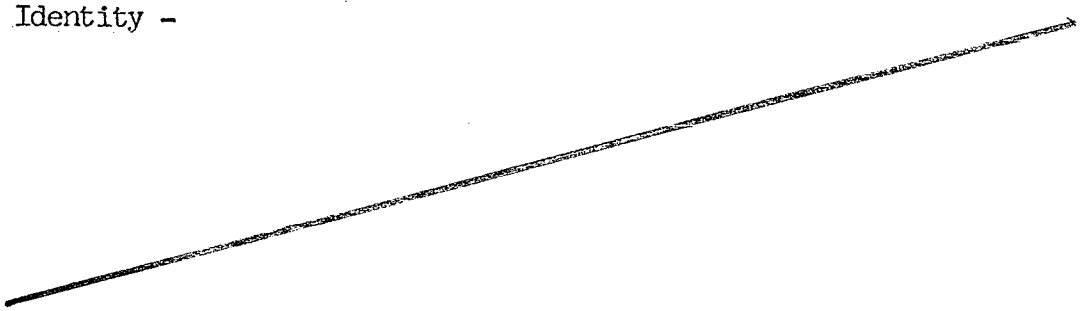
SPECIFICATIONS FOR THE DOSAGE FORM

The dosage form is not listed in the compendium. It will be tested by Ayerst Laboratories and conform to the following specifications.

Color - Shall be a white cream.

Appearance - Cream which is free from extraneous matter and lumps.

Identity -



b(4)

Bacteriological Examination - Not more than ═══ bacteria per gram at ═══ when tested by the U.S.P. procedure.

Strength - Total conjugated estrogens content shall be not less than ═══ mg/g and not more than ═══ mg/g when assayed by the attached method. b(4)

The test methods will not change from that in our ANDA 83-273.

2 Page(s) Withheld

√ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

REVIEW OF AMENDMENT

DATE COMPLETED: 8-19-75

ANDA #: 83-273

CO. NAME: Ayerst Laboratories
N.Y., NY 10017

APPROVAL DATE: NONE

NAME OF DRUG: Premarin Vaginal Cream
Conjugated Estrogens Vaginal Cream

DATE OF SUBMISSION: 7-29-75

TYPE OF SUBMISSION: Amendment - reply to FDA letter 6-9-75

CLINICAL EVALUATION:

1. Review of Studies: Firm's reply of 7-29-75 reiterates firm's letter of 7-21-75; no further information.

CONCLUSION: Adverse reaction report remains incomplete

RECOMMENDATIONS: Status Quo.

V.V. Karusaitis, M.D.

cc:
Dup
HFD-530
VVKarusaitis/wlb/8-19-75

Rev W/F

ORIG

Ayerst

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

July 29, 1975

NDA ORIG AMENDMENT
Submission
Noted NAI
Chle 8/20/75

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Scientific Evaluation
Bureau of Drugs HFD-107
Attn: DOCUMENT CONTROL ROOM 16-72
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

SUBJECT: NDA 83-273; PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream

Dear Dr. Seife:

Your letter of June 9, 1975 requested further information relative to a communication transmitted to the Administration on November 26, 1974 regarding

b(4)

We wish to advise that no further information was received. If further information is received, we will transmit it accordingly.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331(j).

Sincerely,

AYERST LABORATORIES

Henry S. Perdue, Ph.D.
Director
Regulatory Affairs

HSP
BEA:sa

RECEIVED
AUG 05 1975
BUREAU OF DRUGS

REVIEW OF AMENDMENT, RESUBMISSION

DATE COMPLETED: 8-6-75

ANDA #: 83-273

CO. NAME: Ayerst Laboratories
New York, NY 10017

NAME OF DRUG: Trade: Premarin[R] Vaginal Cream
&
Generic: Conjugated Estrogens U.S.P. Cream

DATE OF SUBMISSION: 7-21-75

TYPE OF SUBMISSION: Resubmission (reply to FDA letter 7-2-75)

CLINICAL EVALUATION:

1. Review of Studies: Pertinent data is to be reviewed by the chemist.
Bioavailability requirement: Not required

2. Adverse Reaction: Mrs. [redacted] *No information b(6)

CONCLUSIONS: Incomplete report
Firm states that if future information is received, same will be forwarded to FDA

RECOMMENDATIONS: the firm is to be so notified.

V.V. Karusatis, M.D.

cc:
Dup
HFD-530
VVKarusaitis/kim/8-6-75

ORIG

Ayerst

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

ORIG NEW CORRES

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

July 21, 1975

NAI: from notes
commit to submit - if/when it
receive relevant info
Chle 8/8/75

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Scientific Evaluation
Bureau of Drugs HFD-107
Attn: DOCUMENT CONTROL ROOM 16-72
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

SUBJECT: NDA 83-273; PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream

Dear Dr. Seife:

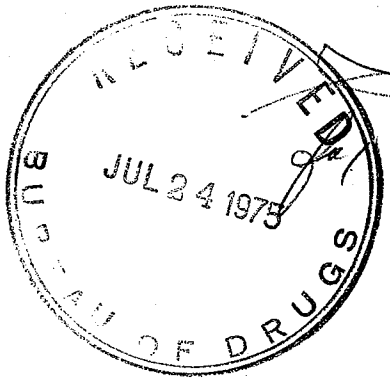
Your letter of July 2, 1975 requested further information relative to a communication transmitted to the Administration on March 31, 1975, regarding Ms. [redacted]. b(6)

We wish to advise that no further information was received. Neither the patient nor her physician made further contact with us. If further information is received, we will transmit it accordingly.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331(j).

Sincerely,

AYERST LABORATORIES



Henry S. Perdue, Ph.D.
Director
Regulatory Affairs

HSP
BEA:sa

NDA 83-273

AF 19-003

JUL 02 1975

Ayerst Laboratories
Division of American Home Products Corp.
Attention: Dr. Henry S. Perdue
685 Third Avenue
New York, NY 10017

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Premarin (conjugated estrogens) Vaginal Cream, 625 mcg. per g.

Reference is also made to your communication dated March 31, 1975, amending the application with an additional drug experience report.

We have reviewed the material submitted and note that the report is inconclusive; the rash cause has not been determined. We consider the material to be an inadequate adverse reaction reporting and suggest that additional information be submitted.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife 7/2/75

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
NYK-DO
Dup
HFD-530
HFD-614
HFD-616
VVKarusaitis/JLMeyer/CMillar/6-24-75 CMillar 6/24/75 JMeyer 7/1/75
R/D init. MSeife/JMeyer/6-26-75
Final typing/rt/6-26-75
ack.

ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT	Statement Date	NDA Number 83-273
		AF Number 19-003

Name and Address of Applicant (City and State)

ayerst laboratories
div. of american home products corp

Original ____
Amendment ____
Supplement ____
Resubmission ____
Correspondance ____
Report ____
Other ____

Purpose of Amendment/Supplement

adverse reaction report

Date(s) of Submission(s)
3/31/75

Pharmacological Category	Name of Drug	How Dispensed
estrogen	premarin(conjugated estrogens)	R_x xx OTC
Dosage Form(s)	Potency(ies)	
topical	0.625 mg. per g.	
Packaging/Sterilization	Samples	Related IND/NDA/MF
ma	ma	

Labeling

as per MO(vvkarusiatis)

Biologic Availability

na

Establishment Inspection

na

Components, Composition, Manufacturing and Controls

na

Remarks

as per letter to issue
NB: this is 2nd experienve report submitted

Conclusion ack

REVIEWER gmillar DATE 6/30/75

REVIEW OF RESUBMISSION

DATE COMPLETED: 6-11-75 ANDA #: 83-273

CO. NAME: Ayerst Laboratories
New York, NY 10017

NAME OF DRUG: Trade: "Premarin" Vaginal Cream

Gneric: Conjugated Estrogens U.S.P. Vaginal Cream

DATE OF SUBMISSION: 3-31-75

TYPE OF SUBMISSION: Report of adverse reaction: rash on thighs?

CLINICAL EVALUATION:

1. Review of Studies: Report is inconclusive: rash cause has not been determined.

CONCLUSION: Inadequate adverse reaction reporting.

RECOMMENDATION: The firm is to be so notified.

V. V. Karusaitis, M.D.

cc:
Dup
HFD-530
VVKarusaitis/rt/6-19-75

ORIG NEW CORRES

ORIG

Ayerst®

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

March 31, 1975

Edwin M. Ortiz, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Scientific Evaluation
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

SUBJECT: ANDA 83-273; PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream

Dear Dr. Ortiz:

We are enclosing information received from Ms. [redacted].

b(6)

Ms. [redacted] reports the occurrence of erythemia while receiving PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream. Mr. B. Mollov, Manager, Project Services, has written to Ms. Garvin; and a copy of his response is enclosed. We shall transmit further information if received.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331(j).

Sincerely,

AYERST LABORATORIES

Henry S. Perdue, Ph.D.
Director
Regulatory Affairs

HSP
BEA:sa
Enclosures

→ BCA

Patient Complaint

REC'D. M.M.F. MAR 10 1975

February 6, 1975

b(6)

Dear Ms. ———:

Reference is made to your letter of recent date regarding PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream. All the components of its formulation are listed on the package insert and the carton containing the tube.

With respect to the rash, we would suggest that you confer with your physician in order to determine the cause of this dermatological problem. Our Medical Department would welcome his inquiry in the event that he wishes to contact them.

Sincerely yours,

AYERST LABORATORIES

B. Mollov
Manager, Project Services

BM/mra

14/1/74

Gentlemen

Could you tell me whether

① Premarin Vaginal Cream contains [lanolin] ?

Ans.

② Whether all the ingredients are listed in the sheet enclosed

Ans.

③ If not, what other ingredients does it contain ?

Ans.

(over)

I have been using the cream & notice that my rash has now traveled from the pubis to the upper most side of the thighs.

Thank you.

b(6)

NDA 83-273

A F 19-003

Ayerst Laboratories
Division of American Home Products, Corp.
Attention: Dr. Henry S. Perdue
685 Third Avenue
New York, NY 10017

JUN 9 1975

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Premarin (conjugated estrogens) Vaginal Cream, 625 mcg. per g.

Reference is also made to your communication dated November 26, 1974, amending the application with a drug experience report.

1. The report of the adverse reaction is incomplete - undetermined.

2. That requested in our letter of October 2, 1973 pertaining to excipients.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife 6/9/75

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
NYK-DO
dup
HFD-530
HFD-614 HFD-616
VVKarusaitis/JLMeyer/GMillar 6/5/75
R/D init. JLMeyer, MSeife 6/2/75
Final typing bho 6/4/75
Rev. w/f

JLMeyer 6/6/75

NEW DRUG APPLICATION OR SUPPLEMENT	Statement Date	ORIGINAL ☐ SUPPLEMENT ☐
Name & Address of Applicant (City & State) ayerst labs div of american home products corp n.y. n.y. 10017		NDA Number 13-27
Name of Drug premarin	Nonproprietary Name (conjugated estrogens)	Amendment Date(s) 12/4/72 1/31+2/23+4/6+4/12/73 8/30/73
Purpose of Supplement		Other Date(s)
Pharmacological Category estrogen	How Dispensed Rx ☐ O.T.C. ☐	AF Number 19-003
Dosage Form(s) topical vaginal cream	Potency (ies) .625 mcg.	Related IND/NDA/NF(s) NDA 5 900

Satisfactory ☐ Labeling
Date Due as per MO's review(vvkarusaitis)

Satisfactory ☐ Components, Composition, Manufacturing and Controls
Date Due see below

Satisfactory ☐ Biologic Availability
Date Due
Is data on current formulation? YES ☐ NO ☐
as per biocommittee deferred 6/26/72

Satisfactory ☐ Probably or Possibly Effective Indications (if in labeling)
Date Data Due

Establishment Inspection	Recalls
in compliance: as per BD-340 memo	of 3/29/73

Is relabeling of drug in commercial channels required? YES ☐ No ☐
If so, what level?

Remarks

Request: 1. labeling, as per FDA guidelines(sent 5/17/73)
2. rationale for
3. removal-from formula) of
MO sees no need for same
Approval Ltr

b(4)

Conclusions

rev w/f

Chill 6/5/75
gmillar

REVIEW OF REPORT

DATE COMPLETED: 2-14-75

ANDA #: 83-273

CO. NAME: Ayerst Laboratories
New York, NY 10017

NAME OF DRUG: Trade: Premarin

Generic: Conjugated Estrogens Vaginal Cream, 625mcg per g.

DATE OF SUBMISSION: 11-26-74

TYPE OF SUBMISSION: Report of adverse reaction.

CLINICAL EVALUATION:

1. Review of Studies: Pertinent data is to be reviewed by the chemist.
Bioavailability requirement:

*report of adverse reaction is incomplete and of questionable value.

2. Review of Labeling:

a) Container labels: Satisfactory

b) Insert labeling: Satisfactory

CONCLUSION: Labeling is satisfactory.
*Incomplete advejse reaction - undetermined.

RECOMMENDATIONS: The firm is to be so notified.

V.V. Karusaitis, M.D.

cc:
Dup
HFD-530
VVKarusaitis/wlb/2-24-75

REPORTS

Ayerst
AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

November 26, 1974

Edwin M. Ortiz, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Scientific Evaluation
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

SUBJECT: NDA 83-273; PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream

Dear Dr. Ortiz:

We are enclosing information received from [redacted]. Dr. [redacted] reports the occurrence of irritation in a patient treated with PREMARIN® Vaginal Cream. He has completed a Form FD-1639 regarding this occurrence, and it is enclosed. b(6)

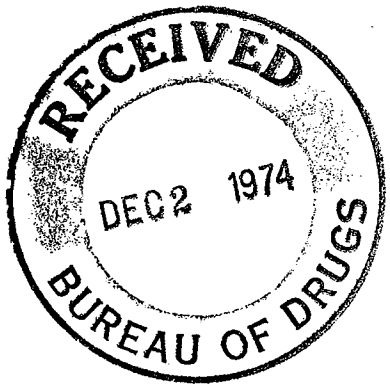
Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331(j).

Sincerely,

AYERST LABORATORIES

Henry S. Perdue, Ph.D.
Director
Regulatory Affairs

HSP
BEA:sa
Enclosures



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

DRUG EXPERIENCE REPORT

BUDGET BUREAU NO. 57-R0004
Approval Expires December 31, 1970

DATE SENT TO FDA (Mo, day, yr) | 1. ☐ INITIAL REPORT ☐ FOLLOW UP REPORT | 2. PATIENT INITIALS AND IDENTIFICATION NUMBER | 3. ACCESSION NO. (For FDA use only) 7502070100070 1

SECTION I. BASIC REACTION DATA

4. SEX	5. HEIGHT	WEIGHT	6. DATE OF BIRTH	7. ORIGIN	8. DATE OF REACTION ONSET
☐ M ☒ F	66 ins.	222 1/16 lbs.	mo ___ day ___ yr 1928	☐ CAUC ☒ NEGRO ☐ ORIENTAL ☐ AMERICAN INDIAN ☐ OTHER	mo 8 day 1 73

9. SOURCE OF REPORT (Mfg, Hospital, etc) (Name of reporting Physician is optional.)

10. ADDRESS OF SOURCE (Give Street, City, State, and Zip Code.) b(6)

11. DESCRIBE SUSPECTED ADVERSE REACTION(s) AND ANY POSSIBLE ASSOCIATION WITH THE DRUG(s) INVOLVED

SUBJECTIVELY LISTED IRRITATION, PT TREATED WITH #207 SAMPLE OF PREMARIN VAG CREAM; PT DID NOT RETURN FOR FOLLOW UP OR CONFIRMATION

12. OUTCOME OF REACTION TO DATE
- ☐ ALIVE WITH SEQUELAE
- ☐ RECOVERED
- ☐ STILL UNDER TREATMENT
- ☐ DIED (Give date and cause)

UNKNOWN

13. LIST ALL THERAPY IN ORDER OF SUSPICION (Manufacturer: List NDA or IND No.)

NAME OF DRUGS TRADE (Generic)	MANUFACTURERS CONTROL NO.	DOSAGE FORM (tab, cap, etc.)	TOTAL DAILY DOSE	ROUTE (po, im, iv, etc.)	DURATION OF THERAPY	DATES OF ADMINISTRATION	14. DISORDER OR REASON FOR USE OF DRUG
PREMARIN SAMPLE #207		VAG. APPL.	1 APP	P.V.	2 DAYS	31 July-1 Aug	VAGINAL IRRITATION

SECTION II. IMPORTANT MODIFYING DATA

15. SUBSTANTIATING LABORATORY STUDIES (Clinical Laboratory, Autopsy, X-Ray, etc.)
PT. DID NOT OBTAIN FOLLOW UP

CLINICAL LAB: ☐ DONE ☐ ATTACHED ☒ NOT DONE
BIOPSY/AUTOPSY: ☐ DONE ☐ ATTACHED ☒ NOT DONE

16. LIST POTENTIALLY NOXIOUS OR ENVIRONMENTAL FACTORS (Include household products, industrial and agricultural chemicals)
PT. DID NOT OBTAIN FOLLOWUP TO DETERMINE TYPE OR CAUSE

17. EXISTING OR PRIOR DISORDERS AND PAST DRUG REACTION OR ALLERGIC HISTORY
HX OF PENICILLIN ALLERGY

PREVIOUS EXPOSURE TO SUSPECTED DRUG OR RELATED COMPOUND ☐ YES ☒ NO

18. (a) IF FEMALE GRAVIDITY 0 PARITY 0 (b) IF PREGNANT WEEKS OF GESTATION NO

19. MAY THE SOURCE OF THIS REPORT BE RELEASED TO THE ARMED FORCES INSTITUTE OF PATHOLOGY? ☐ YES ☒ NO

FOR FDA USE ONLY

20. REACTION FACTORS (Check all applicable boxes)
☐ DECOMPOSITION OF DRUG ☐ INTERACTION OF TWO OR MORE DRUGS ☐ DRUG NOT USED ACCORDING TO LABELING ☐ DRUG OUTDATED
☐ DRUG MISUSED BY PATIENT ☐ OVERDOSAGE ☐ DRUG MISLABELED ☐ CONTAMINATION OF DRUG ☐ OTHER DRUG MISUSE (Specify)

FOR MFG USE ONLY

FORM FD-1639 (Rev 8/67) SEE INSTRUCTIONS ON REVERSE

NDA 83-273

AF 19-003

Ayerst Laboratories
Division of American Home Products, Corp.
Attention: Dr. Henry S. Perdue
685 Third Avenue
New York, NY 10017

OCT 02 1973

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Premarin (conjugated estrogens) Vaginal Cream, 625 mcg. per g.

Reference is also made to your communication dated August 22 and 30, 1973, amending the application.

We have completed our review of this abbreviated new drug application. However, before we are able to reach a final conclusion, the following additional information is necessary:

1. A revised package insert in accord with labeling guidelines transmitted to you on May 17, 1973.

2. Regarding the composition of the drug; it is recommended that you:

b(4)

Please let us have your response promptly.

Sincerely yours,

Marvin Seife 10/2/73

Marvin Seife, M.D.
Director
Generic Drug Staff
Office of Scientific Evaluation
Bureau of Drugs

cc:
NYK-DD
Dup
BD-69 BD-66
BD-106 BD-242
VVKarusaitis/JLMeyer/GMillar 9/26/73
R/D init. JLMeyer 9/26/73
Final typing bho 9/27/73
Rev. w/f

JLMeyer 10/1/73

NEW DRUG APPLICATION OR SUPPLEMENT	Statement Date	ORIGINAL ☐
		SUPPLEMENT ☐
Name & Address of Applicant (City & State) ayerst labs div of american home products corp n.y. n.y. 10017		NDA Number 83-273
Name of Drug premarin	Nonproprietary Name (conjugated estrogens)	Supplement Date and Number Amendment Date(s) 12/4/72 1/31+2/23+4/6+4/12/73 8/30/73
Purpose of Supplement		Other Date(s)
Pharmacological Category estrogen	How Dispensed Rx ☐ O.T.C. ☐	AF Number 19-003
Dosage Form(s) topical vaginal cream	Potency (ies) .625 mcg.	Related IND/NDA/MF(s) NDA 5 900

Satisfactory ☐ Labeling
Date Due as per MO's review(vvkarusaitis)

Satisfactory ☐ Components, Composition, Manufacturing and Controls
Date Due ~~see below~~

Satisfactory ☐ Biologic Availability
Date Due
Is data on current formulation? YES ☐ NO ☐
as per biocommittee deferred 6/26/72

Satisfactory ☐ Probably or Possibly Effective Indications (if in labeling)
Date Data Due

Establishment Inspection
in compliance: as per BD-340 memo of 3/29/73

Recalls

Is relabeling of drug in commercial channels required? YES ☐ No ☐
If so, what level?

Remarks

Request: 1. labeling, as per FDA guidelines(sent 5/17/73)
2. rationale for _____ b(4)
3. removal from formula) of _____
MO sees no need for sdme

Conclusions

rev w/f

gmillar 9/21/73

REVIEW OF RESUBMISSION

DATE COMPLETED: 9-20-73

ANDA #: 83-273

CO. NAME: Ayerst Laboratories
685 Third Ave.
New York, NY 10017

NAME OF DRUG: Trade: Premarin Vaginal Cream

Generic: Conjugated Estrogen

DATE OF SUBMISSION: August 22, 1973; August 30, 1973

TYPE OF SUBMISSION: August 22, 1973 Injury to patient using Premarin Cream
August 30, 1973 Resubmission to F.D.A. letter of 5-17-73

CLINICAL EVALUATION:

1. Review of Studies:

Pertinent data is to be reviewed by the chemist.

2. Review of Labeling:

Will be forwarded in a separate communication.

Submission: 8-22-73 Examination: Screw thread at the dispensing end of the applicator has been partially broken off.
Patient: History of "cut herself": Location and severity of cut unknown.

Conclusion: Report is incomplete: Area of cut unknown nor extent of same.

Rationale for using (1) [redacted] b(4)

Statement: [redacted]

CONCLUSION: Package circular will be submitted in a separate communication.

RECOMMENDATION: Recommend that [redacted] be removed from formulation. b(4)

V. V. Karusaitis, M.D.

cc:
Dup
BD-69
VVKarusaitis/rt/9-21-73

Rev. W IF E

RESUBMISSION

Original

NDA ORIG AMENDMENT

Ayerst®

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

August 30, 1973

Marvin Seife, M.D.
Director
Division of Actions Implementation
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

SUBJECT: NDA 83-273; PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream

Dear Dr. Seife:

The Administration's letter of May 17, 1973, requested additional manufacturing and control information with respect to our abbreviated supplemental new drug application for the product in caption. Accordingly, we are enclosing, in triplicate, the requested information. This is presented as a memorandum from our Ms. Hannah Archibald, Ayerst Laboratories, Rouses Point, New York, clarifying questions raised in the Administration's May 17th letter. Appropriate attachments to Ms. Archibald's memorandum are also enclosed.

The Administration's request for revision of the package circular for this product will be handled in a separate communication.

Please be advised that all material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C.A., Section 1905 and/or 21 U.S.C.A., Section 331 (j).

Sincerely,

AYERST LABORATORIES

Henry S. Perdue, Ph.D.
Director
Regulatory Affairs

HSP
BEA:jl
Encl.

RECEIVED
SEP 6 1973
BUREAU OF DRUGS

ORIG NEW CORRES

ORIG

Ayerst

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

August 22, 1973

Marvin Seife, M.D.
Director
Division of Actions Implementation
Drug Efficacy Study Implementation
Project Office
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

SUBJECT: NDA 83-273; PREMARIN® Vaginal Cream

Dear Dr. Seife:

We are enclosing, in triplicate, a report received from Dr. ———— ———————————. Dr. ———— reports that an unidentified patient "cut herself" while using PREMARIN Vaginal Cream. Enclosed is a copy of a letter to Dr. ———— from John B. Jewell, M.D., Medical Director, Ayerst Laboratories, and also an Ayerst Laboratory Work Request, No. 16713, explaining how this occurrence could have been possible. b(6)

Please add this information to the Administration's files for NDA 83-273.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C.A. Section 1905 and/or 21 U.S.C.A. Section 331 (j).

Sincerely,

AYERST LABORATORIES

Henry S. Perdue, Ph.D.
Director
Regulatory Affairs

RECEIVED
AUG 27 1973
BUREAU OF DRUGS

HSP
BEA:mo
Enc.

AYERST LABORATORIES

Product Complaint Form

Executed by

[illegible]
Name

4912
Territory No.

[illegible]
City, State

REC'D. B.M. JUN 29 1973

P.C. Nº 9401

Best Available Copy

Sheet No. 1 to New York Office.
Sheet No. 2 to Rouses Point with Complaint Material.
Sheet No. 3 for Sender's File.
Use label on No. 2 for return goods.

Date 6/25/73

Name and address

of complainant

b(6)

Product Name Premarin Vaginal Applicator Catalog No. 914 Lot Control No. ? Pkg. Size [illegible]

No. of units (Vials, Bottles, etc.) returned to Rouses Point 1 Applicator

Request for Credit has been issued. Yes ☐ No ☑ (Please indicate).

If customer is entitled to credit, Salesman should send completed Request for Credit Form to his Servicing Branch immediately.

REPORT

(Provide complete details) b(6) (Attach pertinent letters or memos to Sheet No. 1)

Dr. [redacted] reluctantly gave me this PVC applicator. He said that one of his patients cut herself while using this applicator. I advised him that it looked as if the woman did not remove the tube after inserting the cream & perhaps it broke off when she applied the cream. He seemed to agree, but requested that I send this to the proper department. He is expecting an answer. He refused to give any other information. They [illegible] [illegible] that no action will be taken!

Sheet No. 1 TO: — NEW YORK PROJECT SERVICES OFFICE

FOR NEW YORK OFFICE USE ONLY —

Quality Standard ☐

Untoward Action or Inaction ☐

Patient Complaint
[illegible]

REC'D. B. JUL 1 9 1973

July 19, 1973

Mr. [redacted]

[redacted]

P.C.: #9401

Dear Doctor [redacted]:

b(6)

Our Representative, Mr. [redacted], some time ago forwarded to our Rouses Point plant a PREMARIN Vaginal Cream applicator, the screw thread at the dispensing end of which had been partially broken off.

Mr. [redacted] further states that one of your patients "cut herself while using this applicator" but gives no indication whether it was a vaginal laceration or whether she may have cut finger in the process of unscrewing the applicator from the tube of cream.

Inasmuch as we had a 100% inspection program in effect before these applicators were packaged, one could not state with certitude as to how it may have become cracked, but it would be a possibility to have done so by screwing it too tightly onto the tube itself.

I might add that the current packaging of PREMARIN Vaginal Cream has a different type of applicator with which, hopefully, any possibility of such an occurrence has been removed.

Thanking you for having drawn this matter to our attention, and for your courtesies to Mr. [redacted] I am,

Sincerely yours,

JBJ:km

John B. Jewell, M.D.

bcc: Mr. Mollov
Mr. Anderson

WORK REQUEST FILE

NO. 16713

LABORATORY WORK REQUEST

COMPLAINT EVALUATION FORM

REPORT

Department Regulatory Office Date July 2, 1973 Batch No. Unknown

Product Premarin Vaginal Cream applicator

Additional Information

P.C. No. 9401
(one applicator returned)

Please examine

RESULTS

Physical Appearance

The product complaint consists of one Premarin® Vaginal Cream Applicator, batch number unknown. The screw thread at the dispensing end has been partially broken off.

Microscopic examination of the tip of the applicator shows minute fracture lines along the base of the screw threads. These small cracks are not apparent on a new barrel.

Conclusion:

Examination of the applicator indicates that undue stress during use may have caused the tip of the applicator to fracture.

Initiated by: I. Tetreault Performed by: A. Beath

OK'd by: D. E. Williams Time Required: 3 hours

Date Completed: 5 July 1973

Results Noted by: Approved by:

67-M-2-47

REVIEW OF ANDA, AMENDMENT, SUPPLEMENT, RESUBMISSION, FPL

DATE COMPLETED:
8/27/73

ANDA #: 83-273

F.R. DATE:

CO. NAME: Ayerst Laboratories
685 Third Ave.
N.Y., N.Y. 10017

NAME OF DRUG: Trade: Premarin Vaginal Cream

Generic: Conjugated Estrogen U.S.P. Vaginal Cream

DATE OF SUBMISSION: 8-10-73

TYPE OF SUBMISSION: Correspondence

CLINICAL EVALUATION:

1. Review of Studies:
Firm submits a complaint from a 70 year old woman who developed fissures and itching inher vulvo-vaginal area: Persisted for one year: Present at time of complaint. (7-5-73)

2. Review of Labeling:
Information is inadequate: No M.D. report.

CONCLUSION:
Information noted; inconclusive.

RECOMMENDATIONS:
No action ne cessary.

V.V.Karusaitis, M.D.

cc:
DUP
BD-69
V.V.Karusaitis/emb/8---28-73

Original

ORIG NEW CORRES

Ayerst

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

August 10, 1973

Submission Rec
NAI
8/28/73

Marvin Seife, M.D.
Director
Division of Actions Implementation
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

SUBJECT: NDA 83-273; PREMARIN® (Conjugated Estrogens, U.S.P.)
Vaginal Cream

Dear Dr. Seife:

b(6)

We are enclosing, in triplicate, correspondence from Mrs. ———— who complained of some discomfort experienced at the time of her use of PREMARIN Vaginal Cream.

Please add this information to the Administration's files for NDA 83-273.

Please be advised that all material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C.A., Section 1905 and/or Section 331 (j).

Sincerely,

AYERST LABORATORIES

Henry S. Perdue
Director
Regulatory Affairs

HSP
BEA:mo
Encl.

RECEIVED
AUG 15 1973
BUREAU OF DRUGS

Reply to Reg

Consumer Complaint

July 20, 1973

b(6)

Dear Mrs. ——:

We are in receipt of your recent letter regarding your long-term gynecological problem and would hasten to point out that we are manufacturers of medications, not practitioners of medicine. It would be improper for us to comment on a medical problem, which is the realm of physicians.

While it is unfortunate that you did not save the PREMARIN® Vaginal Cream for our examination, it is highly improbable that it was the positive factor in your malady. Certainly, it would be improper to store any medication where it would be subject to constant abnormal warmth as you describe your closet.

From the description of your medical problem we recognize the efforts you have put forth to seek relief and we sympathize with your discomfort. From the description you give us, may we recommend that you seek the medical attention of a gynecologist and/or dermatologist.

Sincerely yours,

AYERST LABORATORIES

B. Mollov
Manager, Project Services

BM/mra

b(6)

July 5th, 1973

Ayerst Laboratories,
Management
Dear Sirs.

About one year ago, when I went for a yearly Pap test — the doctor advised that I use Premarin a few times a week.

I am seventy years of age, incidentally,

Premarin is not unfamiliar to me as I've used it from time to time in the past & it has done very nicely for me.

I bought a tube from the drug store shortly after the doctor

advised that I use it.

I kept it in a closet that is a — my linen closet where I also keep other drug articles & creams & Condoms. This leads to an attic you can get to — a real insulated low ceiling attic. Although there is a wood cover at ceiling which closes off the attic — it is quite a warm, stuffy closet.

I don't know if the tube came defective from the drug store or it became defective in my closet.

It happens that when I went to get the premarin from the closet after a couple of weeks storage in the closet — I opened it up while getting it — right in the closet.

I applied it as usual in the past. It seems that same day — I don't remember how soon after using it, I got very itchy around the vaginal, vulva, clitoris, urethra & all along in the genital parts.

b(6)

I thought not too much of it at first as I could not connect it with the Premarin & thought it would just go away & paid no attention to it.

I still kept on using the Premarin & the itch got sharply. It seemed also to bite into the skin & cause soreness in the parts of the clitoris - urethra - vaginal & all in between the vulva. It has caused fissures.

It finally dawned on me to stop using the Premarin.

I kept thinking it would go away by itself & was embarrassed about going to the doctor with this.

After a number of months I finally went back to the doctor who gave me the Pap test - he felt sorry I was having this trouble but he sent me away with nothing to do for

it, I think he might have said apply some regular to it.

It's been about a year now that I have had this great discomfort.

Have been to a few doctors but have not been able to get any relief.

Was advised to use hydrocortatine but this makes it more itchy until it becomes unbearable. Regular routine it more itchy also.

I recently got a prescription from a doctor for "Procter Cream" and this does not help but only makes the itch greater.

At times when I use a lubricating cream, such as "K-Y", even this enhances the itch.

The doctor told me to take two warm baths a day + use the Procter Cream. The baths are so that the fissures in the skin will heal. Am continuing with the two warm baths a day as it seems to be helping

b(6)

with the fissures but not however with the itch & redness all around those parts. If the baths are helping the redness - it is slight, but the itchiness & condition in those parts still persists in spite of this.

All of the creams I've mentioned above & I've used Aquadan, Mycotatin, Lacorten, nothing has helped but only enhances the itch.

The two warm baths daily, I am doing this consistently & it does seem to be helping with the fissures.

I've had this difficulty almost one year now.

It occurred to me you might have an antidote to this.

Incidentally & unfortunately when I realized the Premarin

was causing the itch, after using it about three times, I threw the Plenoin out, just to make sure I would not use it again. I realize, it was a mistake to do this, as you would probably want to analyze it to try to know what in it, caused this malady.

However, it seems before I keep doctoring any more to no avail — you might be able to tell me what I may try as an antidote.

I would very much appreciate hearing from you and am only seeking help from this awful malady. It has caused me so much discomfort & worry.

Please, may I hear from you soon.

Yours very truly,
Mrs. [redacted]

b(6)

P.S.
Have been to a "Urologist doctor"! Have had a blood sugar test & a Urine culture but there is nothing wrong in that regard.

NDA ORIG AMENDMENT

E

Ayerst

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

SPECIAL NEW DRUG APPLICATION AMENDMENT/CHANGES BEING EFFECTED

January 31, 1973

Marvin Seife, M.D.
Acting Director
Division of Actions Implementation
Office of Scientific Evaluation
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Dear Dr. Seife:

SUBJECT: NDA 83-273; PREMARIN® (Conjugated Estrogens USP) Vaginal Cream

On October 3, 1972 Ayerst Laboratories submitted an Abbreviated Original New Drug Application (ANDA) for the subject product.

We are hereby amending that application and are submitting herewith, in triplicate, minor revisions to the instructions for use of the applicator. b(4)

We consider these revisions improvements that give increased assurance that the drug will have the characteristics of identity, strength, quality and purity which it possesses, and as provided by the regulations, they will be placed into effect on or before April 1, 1973.

This application contains copies of the revised labeling in draft form. Final printed labeling will be submitted to the Administration when it becomes available.

Material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C.A. §1905 and/or 21 U.S.C.A. §331 (j).

Sincerely,

AYERST LABORATORIES

Henry S. Perdue, Ph.D.
Director
Regulatory Affairs

RECEIVED
FEB 2 1973
BUREAU OF DRUGS

HSP
BEA:cs
Attachments

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

Form Approved
Budget Bureau No. 85-R0045

NEW DRUG APPLICATION *(DRUGS FOR HUMAN USE)*

(Title 21, Code of Federal Regulations, § 130.4)

Name of applicant AYERST LABORATORIES

Address 685 Third Avenue, New York, New York 10017

Date January 31, 1973

Name of new drug PREMARIN® (Conjugated Estrogens USP) Vaginal Cream

[X] Original application (regulation §130.4).
[ ] Amendment to original, unapproved application (regulation §130.7).
[ ] Supplement to an approved application (regulation §130.9).
[ ] Amendment to supplement to an approved application.

The undersigned submits this application for a new drug pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. It is understood that when this application is approved, the labeling and advertising for the drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will contain the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant warnings, hazards, contraindications, side effects, and precautions, as that contained in the labeling which is part of this application in accord with §1.106(b) (21 CFR 1.106(b)). It is understood that all representations in this application apply to the drug produced until an approved supplement to the application provides for a change or the change is made in conformance with other provisions of §130.9 of the new-drug regulations.

Attached hereto, submitted in the form described in §130.4(e) of the new-drug regulations, and constituting a part of this application are the following:

1. Table of contents. The table of contents should specify the volume number and the page number in which the complete and detailed item is located and the volume number and the page number in which the summary of that item is located (if any).

2. Summary. A summary demonstrating that the application is well-organized, adequately tabulated, statistically analyzed (where appropriate), and coherent and that it presents a sound basis for the approval requested. The summary should include the following information: (In lieu of the outline described below and the evaluation described in Item 3, an expanded summary and evaluation as outlined in §130.4(d) of the new-drug regulations may be submitted to facilitate the review of this application.)

a. Chemistry.

i. Chemical structural formula or description for any new-drug substance.

ii. Relationship to other chemically or pharmacologically related drugs.

iii. Description of dosage form and quantitative composition.

b. Scientific rationale and purpose the drug is to serve.

c. Reference number of the investigational drug notice(s) under which this drug was investigated and of any notice, new-drug application, or master file of which any contents are being incorporated by reference to support this application.

d. Preclinical studies. (Present all findings including all adverse experiences which may be interpreted as incidental or not drug-related. Refer to date and page number of the investigational drug notice(s) or the volume and page number of this application where complete data and reports appear.)

i. Pharmacology (pharmacodynamics, endocrinology, metabolism, etc.).

ii. Toxicology and pathology: Acute toxicity studies; subacute and chronic toxicity studies; reproduction and teratology studies; miscellaneous studies.

e. Clinical studies. (All material should refer specifically to each clinical investigator and to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found.)

i. Special studies not described elsewhere.

ii. Dose-range studies.

iii. Controlled clinical studies.

iv. Other clinical studies (for example, uncontrolled or incompletely controlled studies).

v. Clinical laboratory studies related to effectiveness.

vi. Clinical laboratory studies related to safety.

vii. Summary of literature and unpublished reports available to the applicant.

3. Evaluation of safety and effectiveness. a. Summarize separately the favorable and unfavorable evidence for each claim in the package labeling. Include references to the volume and page number in the application and in any documents incorporated by reference where the complete data and reports may be found.

b. Include tabulation of all side effects or adverse experience, by age, sex, and dosage formulation, whether or not considered to be significant, showing whether administration of the drug was stopped and showing the investigator's name with a reference to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found. Indicate those side effects or adverse experiences considered to be drug-related.

4. Copies of the label and all other labeling to be used for the drug (a total of 12 copies if in final printed form, 4 copies if in draft form):

a. Each label, or other labeling, should be clearly identified to show its position on, or the manner in which it accompanies, the market package.

b. If the drug is to be offered over the counter, labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to the layman. If the drug is intended or offered for uses under the professional supervision of a practitioner licensed by law to administer it, the application should also contain labeling that includes adequate information for all such uses, including all the purposes for which the over-the-counter drug is to be advertised to, or represented for use by, physicians.

c. If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purposes for which it is intended, including all the purposes for which it is to be advertised or represented, in accord with §1.106(b) (21 CFR 1.106(b)). The application should include any labeling for the drug intended to be made available to the layman.

d. If no established name exists for a new-drug substance, the application shall propose a nonproprietary name for use as the established name for the substance.

e. Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug.

f. No application may be approved if the labeling is false or misleading in any particular.

(When mailing pieces, any other labeling, or advertising copy are devised for promotion of the new drug, samples shall be submitted at the time of initial dissemination of such labeling and at the time of initial placement of any such advertising for a prescription drug (see §130.13 of the new-drug regulations). Approval of a supplemental new-drug application is required prior to use of any promotional claims not covered by the approved application.)

5. A statement as to whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

6. A full list of the articles used as components of the drug. This list should include all substances used in the synthesis, extraction, or other method of preparation of any new-drug substance, and in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

7. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed (for example, amount per tablet or per milliliter) and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

8. A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug. Included in this description should be full information with respect to any new-drug substance and to the new-drug dosage form, as follows, in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture, processing, packing and the described facilities and controls to determine and preserve the identity, strength, quality, and purity of the drug:

a. A description of the physical facilities including building and equipment used in manufacturing, processing, packaging, labeling, storage, and control operations.

b. A description of the qualifications, including educational background and experience, of the technical and professional personnel who are responsible for assuring that the drug has the safety, identity, strength, quality, and purity it purports or is represented to possess, and a statement of their responsibilities.

c. The methods used in the synthesis, extraction, isolation, or purification of any new-drug substance. When the specifications and controls applied to such substance are inadequate in themselves to determine its identity, strength, quality, and purity, the methods should be described in sufficient detail, including quantities used, times, temperatures, pH, solvents, etc., to determine these characteristics. Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the substance may be specified.

d. Precautions to assure proper identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material.

e. Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

f. If the applicant does not himself perform all the manufacturing, processing, packaging, labeling, and control operations for any new-drug substance or the new-drug dosage form, his statement identifying each person who will perform any part of such operations and designating the part; and a signed statement from each such person fully describing, directly or by reference, the methods, facilities, and controls in his part of the operation.

g. Method of preparation of the master formula records and individual batch records and manner in which these records are used.

h. The instructions used in the manufacturing, processing, packaging, and labeling of each dosage form of the new drug, including any special precautions observed in the operations.

i. Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug package to assure their suitability for the intended use.

j. Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

k. Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and, if so, at what stage and by whom it is done.

l. Precautions to check the actual package yield produced from a batch of the drug with the theoretical yield. This should include a description of the accounting for such items as discards, breakage, etc., and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

m. Precautions to assure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling storage and inventory control.

n. The analytical controls used during the various stages of the manufacturing, processing, packaging, and labeling of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components. If the article is one that is represented to be sterile, the same information with regard to the manufacturing, processing, packaging, and the collection of samples of the drug should be given for sterility controls. Include the standards used for acceptance of each lot of the finished drug.

o. An explanation of the exact significance of the batch control numbers used in the manufacturing, processing, packaging, and labeling of the drug, including the control numbers that appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

p. A complete description of, and data derived from, studies of the stability of the drug, including information showing the suitability of the analytical methods used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new-drug substance, for the finished dosage form of the drug in the container in which it is to be marketed, including any proposed multiple-dose container, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed. State the expiration date(s) that will be used on the label to preserve the identity, strength, quality, and purity of the drug until it is used. (If no expiration date is proposed, the applicant must justify its absence.)

q. Additional procedures employed which are designed to prevent contamination and otherwise assure proper control of the product.

(An application may be refused unless it includes adequate information showing that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity in conformity with good manufacturing practice and identifies each establishment, showing the location of the plant conducting these operations.)

9. Samples of the drug and articles used as components, as follows: a. The following samples shall be submitted with the application or as soon thereafter as they become available. Each sample shall consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the application to determine compliance with its control specifications for identity and assays:

i. A representative sample or samples of the finished dosage form(s) proposed in the application and employed in the clinical investigations and a representative sample or samples of each new-drug substance, as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

ii. A representative sample or samples of finished market packages of each dosage form of the drug prepared for initial marketing and, if any such sample is not from a commercial-scale production batch, such a sample from a representative commercial-scale production batch; and a representative sample or samples of each new-drug substance as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

iii. A sample or samples of any reference standard and blank used in the procedures described in the application for assaying each new-drug substance and other assayed components of the finished drug: *Provided, however,* That samples of reference standards recognized in the official U.S. Pharmacopeia or The National Formulary need not be submitted unless requested.

b. Additional samples shall be submitted on request.

c. Each of the samples submitted shall be appropriately packaged and labeled to preserve its characteristics, to identify the material and the quantity in each subdivision of the sample, and to identify each subdivision with the name of the applicant and the new-drug application to which it relates.

d. There shall be included a full list of the samples submitted pursuant to Item 9a; a statement of the additional samples that will be submitted as soon as available; and, with respect to each sample submitted, full information with respect to its identity, the origin of any new-drug substance contained therein (including in the case of new-drug substances, a statement whether it was produced on a laboratory, pilot-plant, or full-production scale) and detailed results of all laboratory tests made to determine the identity, strength, quality, and purity of the batch represented by the sample, including assays. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods used differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

e. The requirements of Item 9a may be waived in whole or in part on request of the applicant or otherwise when any such samples are not necessary.

f. If samples of the drug are sent under separate cover, they should be addressed to the attention of the Bureau of Medicine and identified on the outside of the shipping carton with the name of the applicant and the name of the drug as shown on the application.

10. Full reports of preclinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate preclinical tests by all methods reasonably applicable to a determination of the safety and effectiveness of the drug under the conditions of use suggested in the proposed labeling.

b. Detailed reports of the preclinical investigations, including all studies made on laboratory animals, the methods used, and the results obtained, should be clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short- or long-term administration or whether it is to be used in infants, children, pregnant women, or women of child-bearing potential.

c. Detailed reports of any pertinent microbiological and *in vitro* studies.

d. Summarize and provide a list of literature references (if available) to all other preclinical information known to the applicant, whether published or unpublished, that is pertinent to an evaluation of the safety or effectiveness of the drug.

11. List of investigators. a. A complete list of all investigators supplied with the drug including the name and post office address of each investigator and, following each name, the volume and page references to the investigator's report(s) in this application and in any documents incorporated by reference, or the explanation of the omission of any reports.

b. The unexplained omission of any reports of investigations made with the new drug by the applicant, or

submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, whether or not it would bias an evaluation of the safety of the drug or its effectiveness in use, may constitute grounds for the refusal or withdrawal of the approval of an application.

12. Full reports of clinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the labeling.

b. An application may be refused unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

c. Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, full information concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintains adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. An application for a combination drug may be refused unless there is substantial evidence that each ingredient designated as active makes a contribution to the total effect claimed for the drug combination. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

d. Attach as a separate section a completed Form FD-1639, Drug Experience Report (obtainable, with instructions, on request from the Department of HEW, Food and Drug Administration, Bureau of Drugs *(BD-200)* Rockville, Maryland 20852), for each adverse experience or, if feasible, for each subject or patient experiencing one or more adverse effects, described in Item 12c, whether or not full information is available. Form FD-1639 should be prepared by the applicant if the adverse experience was not reported in such form by the investigator. The Drug Experience Report should be cross-referenced to any narrative description included in Item 12c.

e. All information pertinent to an evaluation of the safety and effectiveness of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commerical marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application and related drugs. An adequate summary may be acceptable in lieu of a reprint of a published report which only supports other data submitted. Reprints are not required of reports in designated journals, listed in §130.38 of the new-drug regulations, about related drugs; a bibliography will suffice. Include any evaluation of the safety or effectiveness of the drug that has been made by the applicant's medical department, expert committee, or consultants.

f. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

g. The complete composition and/or method of manufacture of the new drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in Item 6, 7, or 8 of the application.

13. If this is a supplemental application, full information on each proposed change concerning any statement made in the approved application.
Observe the provisions of §130.9 of the new-drug regulations concerning supplemental applications.

AYERST LABORATORIES
(Applicant)

Per Henry S. Perdue, Ph.D.
(Responsible official or agent)

Director, Regulatory Affairs
(Indicate authority)

(Warning: A willfully false statement is a criminal offense. U.S.C. Title 18, sec. 1001.)

NOTE: This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States.

Original

ORIG NEW CORRES

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

PERSONALLY SUBMITTED BY
Burnside Anderson
Rec'd by B Owens
4-13-73

BY HAND

April 12, 1973

Mr. Jack Meyer
Division of Actions Implementation
DESI Project Office
Office of Scientific Evaluation
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

SUBJECT: ANDA 83-273; PREMARIN® (Conjugated Estrogens, USP) Vaginal Cream

Dear Mr. Meyer:

As per your recent request we are transmitting additional samples of Conjugated Estrogens U.S.P. for analytical purposes pertinent to the product in caption. Included with this transmittal is an accompanying memorandum from our Mr. Thomas R. Russillo, Ayerst Laboratories, Rouses Point, New York which discusses the need to perform the assay under dry conditions.

We look forward to an early reply to this submission as well as to our original submission of October 3, 1972.

Material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C.A. § 1905 and/or 21 U.S.C.A. § 331 (j).

Sincerely,

AYERST LABORATORIES

for Henry S. Perdue, Ph.D.
Director, Regulatory Affairs

HSP
BEA:cb
Encl.

RECEIVED
APR 13 1973
BUREAU OF DRUGS

Samples rec'd in DRSS 4-13-73

AYERST LABORATORIES

Ayerst

Internal correspondence

TO	Mr. Bernie Anderson	**LOCATION**	New York
FROM	T. R. Russillo	**LOCATION**	Rouses Point
SUBJECT	CONJUGATED ESTROGENS RAW MATERIAL USED IN PREMARIN® VAGINAL CREAM	**DATE**	April 2, 1973

We are forwarding to you under separate cover four vials of Conjugated Estrogens U.S.P., batch #F-596 and four vials of Conjugated Estrogens, U.S.P., batch #L-568 as requested by Dr. Perdue.

It is our understanding that the FDA had some difficulty with the raw material sent previously (batch #F-596) and requested additional samples as well as a different batch of material (L-568).

We have re-assayed F-596 and find it essentially identical in potency to the original assay. Our Estrogens Laboratory offers the following advice:

" This material does not contain the [redacted] that are found in the normal conjugated estrogens [redacted] of commerce, and as a result tends to be more [redacted]. It is our practice to maintain our sample under very dry conditions and to proceed rapidly through the [redacted] stages of the analytical method. Particular care is taken to [redacted] ."

b(4)

Please advise if we can be of further assistance.

T R Russillo

TR/it
cc: Dr. Perdue

Assay No.
Batch No. F596
Rec. No.

Date 30 March/73

LABORATORY CONTROL RECORD

Ayerst Laboratories Incorporated
Rouses Point, New York

Sample No.

Control No.

Quantity

Count

Sample of: Conjugated Estrogens, U.S.P.

Manufactured by: Ayerst Laboratories

Sample Size:

Other Information:

ARM 85-6506-1

Description	-	
Identification	-	
Conjugated Estrogens, Total	-	b(4)
Sodium Estrone Sulfate	-	
Sodium Equilin Sulfate	-	

Signed: B.F. Cliffe Date 30 Mar 73

/sl B. F. Cliffe, Supervisor, Dosage Form Release Section, Quality Control (US)

Assay No.
Batch No. L568
Rec. No.

Date 30 March/73

LABORATORY CONTROL RECORD

Ayerst Laboratories Incorporated
Rouses Point, New York

Sample No.

Sample of: Conjugated Estrogens, U.S.P.

Control No.

Manufactured by: Ayerst Laboratories

Quantity

Count

Sample Size:

Other Information:

ARM 85-6506-1

Description	-	
Identification	-	
Conjugated Estrogens, Total	-	b(4)
Sodium Estrone Sulfate	-	
Sodium Equilin Sulfate	-	

Signed: B.F. Cliffe Date 30 Mar '73

/sl B. F. Cliffe, Supervisor, Dosage Form Release Section, Quality Control (US)

11 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__√__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Original

ORIG NEW CORRES

Ayerst®

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

August 10, 1973

Submission Rec
NAI
8/28/73

Marvin Seife, M.D.
Director
Division of Actions Implementation
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

SUBJECT: NDA 83-273; PREMARIN® (Conjugated Estrogens, U.S.P.)
Vaginal Cream

Dear Dr. Seife:

We are enclosing, in triplicate, correspondence from Mrs. [redacted] who complained of some discomfort experienced at the time of her use of PREMARIN Vaginal Cream. b(6)

Please add this information to the Administration's files for NDA 83-273.

Please be advised that all material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C.A., Section 1905 and/or Section 331 (j).

Sincerely,

AYERST LABORATORIES

Henry S. Perdue
Director
Regulatory Affairs

HSP
BEA:mo
Encl.

RECEIVED
AUG 15 1973
BUREAU OF DRUGS

Consumer Complaint

July 20, 1973

b(6)

Dear Mrs. ——:

We are in receipt of your recent letter regarding your long-term gynecological problem and would hasten to point out that we are manufacturers of medications, not practitioners of medicine. It would be improper for us to comment on a medical problem, which is the realm of physicians.

While it is unfortunate that you did not save the PREMARIN® Vaginal Cream for our examination, it is highly improbable that it was the positive factor in your malady. Certainly, it would be improper to store any medication where it would be subject to constant abnormal warmth as you describe your closet.

From the description of your medical problem we recognize the efforts you have put forth to seek relief and we sympathize with your discomfort. From the description you give us, may we recommend that you seek the medical attention of a gynecologist and/or dermatologist.

Sincerely yours,

AYERST LABORATORIES

B. Mollov
Manager, Project Services

BM/mra

NDA ORIG AMENDMENT E

ORIG

Ayerst

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N.Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

PERSONALLY SUBMITTED BY
M. Reiss
Reid Lay Blevins
12-5-72

December 4, 1972

Mr. Jack Myer
Drug Efficacy Study Implementation Office
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Dear Mr. Myer:

Subject: ANDA 83-273 Premarin (Conjugated Estrogens USP) Vaginal Cream

In accordance with a recent telephone conversation held between you and our Dr. Henry S. Perdue, we are submitting the following:

1. Four market packages of the subject product, Control 3KVJ.

2. Four x 2gm. samples of Conjugated Estrogens USP, Batch No. F-596 used in manufacturing the above dosage form.

3. Four x ——. samples of Equilin reference standard, Batch No. 1282-23. b(4)

4. Four x ——. samples of Estrone reference standard, Batch No. 1282-69.

The above samples are for laboratory use, to validate the test methods described in the above ANDA.

Material and data contained in this submission is confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C.A. Section 1905 and/or Section 331 (j).

Sincerely,

for/ Henry S. Perdue, Ph.D.
Director
Regulatory Affairs

RECEIVED
DEC 05 1972
BUREAU OF DRUGS

HSP
BEA/jp

Samples rec'd in DRSS 12-5-72

NDA 83-273
AF 19-003

NOV 3 1972

Ayerst Laboratories
Division of American Home Products Corp.
Attention: Dr. Henry S. Perdue
685 Third Avenue
New York, New York 10017

Gentlemen:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NAME of DRUG: PREMARIN (Conjugated Estrogens) Vaginal Cream

DATE of APPLICATION: October 3, 1972

DATE of RECEIPT: October 5, 1972

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 NDA number shown above.

Sincerely yours,

Marvin Seife 11/3/72

Marvin Seife, M.D.
Director
Division of Actions Implementation
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs

cc:
NYK-DO
Dup
BD-69
BD-66
BD-106
BD-310 JLMeyer 11/2/72
JLMeyer/kim/11-2-72
Ack.

83 273 ABBREVIATED NEW DRUG APPLICATION

Ayerst®

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

October 3, 1972

Marvin Seife, M.D.
Chief, ANDA Review Group
DESI Project Office
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

SUBJECT: PREMARIN® (Conjugated estrogens U.S.P.) Vaginal Cream

Re: DESI 2238

Dear Dr. Seife:

In accordance with the Federal Register notice of July 27, 1972 (37 F.R. 145-15028 DESI 2239), we are submitting herewith, in triplicate, an abbreviated original new-drug application (ANDA). This application contains six copies of revised labeling in draft form and other information required for abbreviated NDAs in 21 CFR 130.4(f) with respect to components, composition, and methods, facilities and controls. Copies of the final printed labeling will be submitted as soon as they are available and will be placed into use prior to approval in accordance with 21 CFR 130.9(d).

As stated in our submission, Ayerst Laboratories certifies that the methods used in, and the facilities and controls used for, the manufacturing, processing, packaging and holding of PREMARIN Vaginal Cream are in conformance with current good manufacturing practice as specified in 21 CFR 133.

Ayerst Laboratories Inc. assures that the drug dosage form and components will comply with the specifications and tests described in the official compendia or specific testing methods mentioned in our submission and that the tests applied to the drug and its components are adequate to assure its identity, strength, quality and purity.

Material and data contained in this submission is confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C.A. §1905 and/or 21 U.S.C.A. §331 (j).

Sincerely,
AYERST LABORATORIES

for/ Henry S. Perdue, Ph.D.
Director, Regulatory Affairs

RECEIVED
OCT 5 1972
BUREAU OF DRUGS

HSP
BEA:cs
Attachments

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

Form Approved
Budget Bureau No. 85-R0045

NEW DRUG APPLICATION *(DRUGS FOR HUMAN USE)*

(Title 21, Code of Federal Regulations, § 130.4)

Name of applicant AYERST LABORATORIES - Division of American Home Products Corporation

Address 685 Third Avenue

Date October 3, 1972

Name of new drug PREMARIN® Vaginal Cream

☐ Original application (regulation §130.4). ☒ Abbreviated Application (130.4(f)).
☐ Amendment to original, unapproved application (regulation §130.7).
☐ Supplement to an approved application (regulation §130.9).
☐ Amendment to supplement to an approved application.

The undersigned submits this application for a new drug pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. It is understood that when this application is approved, the labeling and advertising for the drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will contain the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant warnings, hazards, contraindications, side effects, and precautions, as that contained in the labeling which is part of this application in accord with §1.106(b) (21 CFR 1.106(b)). It is understood that all representations in this application apply to the drug produced until an approved supplement to the application provides for a change or the change is made in conformance with other provisions of §130.9 of the new-drug regulations.

Attached hereto, submitted in the form described in §130.4(e) of the new-drug regulations, and constituting a part of this application are the following:

1. Table of contents. The table of contents should specify the volume number and the page number in which the complete and detailed item is located and the volume number and the page number in which the summary of that item is located (if any).

2. Summary. A summary demonstrating that the application is well-organized, adequately tabulated, statistically analyzed (where appropriate), and coherent and that it presents a sound basis for the approval requested. The summary should include the following information: (In lieu of the outline described below and the evaluation described in Item 3, an expanded summary and evaluation as outlined in §130.4(d) of the new-drug regulations may be submitted to facilitate the review of this application.)

a. Chemistry.

i. Chemical structural formula or description for any new-drug substance.

ii. Relationship to other chemically or pharmacologically related drugs.

iii. Description of dosage form and quantitative composition.

b. Scientific rationale and purpose the drug is to serve.

c. Reference number of the investigational drug notice(s) under which this drug was investigated and of any notice, new-drug application, or master file of which any contents are being incorporated by reference to support this application.

d. Preclinical studies. (Present all findings including all adverse experiences which may be interpreted as incidental or not drug-related. Refer to date and page number of the investigational drug notice(s) or the volume and page number of this application where complete data and reports appear.)

i. Pharmacology (pharmacodynamics, endocrinology, metabolism, etc.).

ii. Toxicology and pathology: Acute toxicity studies; subacute and chronic toxicity studies; reproduction and teratology studies; miscellaneous studies.

e. Clinical studies. (All material should refer specifically to each clinical investigator and to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found.)

i. Special studies not described elsewhere.

ii. Dose-range studies.

iii. Controlled clinical studies.

iv. Other clinical studies (for example, uncontrolled or incompletely controlled studies).

v. Clinical laboratory studies related to effectiveness.

vi. Clinical laboratory studies related to safety.

vii. Summary of literature and unpublished reports available to the applicant.

3. Evaluation of safety and effectiveness. a. Summarize separately the favorable and unfavorable evidence for each claim in the package labeling. Include references to the volume and page number in the application and in any documents incorporated by reference where the complete data and reports may be found.

b. Include tabulation of all side effects or adverse experience, by age, sex, and dosage formulation, whether or not considered to be significant, showing whether administration of the drug was stopped and showing the investigator's name with a reference to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found. Indicate those side effects or adverse experiences considered to be drug-related.

4. Copies of the label and all other labeling to be used for the drug (a total of 12 copies if in final printed form, 4 copies if in draft form):

a. Each label, or other labeling, should be clearly identified to show its position on, or the manner in which it accompanies, the market package.

b. If the drug is to be offered over the counter, labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to the layman. If the drug is intended or offered for uses under the professional supervision of a practitioner licensed by law to administer it, the application should also contain labeling that includes adequate information for all such uses, including all the purposes for which the over-the-counter drug is to be advertised to, or represented for use by, physicians.

c. If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purposes for which it is intended, including all the purposes for which it is to be advertised or represented, in accord with §1.106(b) (21 CFR 1.106(b)). The application should include any labeling for the drug intended to be made available to the layman.

d. If no established name exists for a new-drug substance, the application shall propose a nonproprietary name for use as the established name for the substance.

e. Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug.

f. No application may be approved if the labeling is false or misleading in any particular.

(When mailing pieces, any other labeling, or advertising copy are devised for promotion of the new drug, samples shall be submitted at the time of initial dissemination of such labeling and at the time of initial placement of any such advertising for a prescription drug (see §130.13 of the new-drug regulations). Approval of a supplemental new-drug application is required prior to use of any promotional claims not covered by the approved application.)

5. A statement as to whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

6. A full list of the articles used as components of the drug. This list should include all substances used in the synthesis, extraction, or other method of preparation of any new-drug substance, and in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

7. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed (for example, amount per tablet or per milliliter) and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

8. A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug. Included in this description should be full information with respect to any new-drug substance and to the new-drug dosage form, as follows, in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture, processing, and packing and the described facilities and controls to determine and preserve the identity, strength, quality, and purity of the drug:

a. A description of the physical facilities including building and equipment used in manufacturing, processing, packaging, labeling, storage, and control operations.

b. A description of the qualifications, including educational background and experience, of the technical and professional personnel who are responsible for assuring that the drug has the safety, identity, strength, quality, and purity it purports or is represented to possess, and a statement of their responsibilities.

c. The methods used in the synthesis, extraction, isolation, or purification of any new-drug substance. When the specifications and controls applied to such substance are inadequate in themselves to determine its identity, strength, quality, and purity, the methods should be described in sufficient detail, including quantities used, times, temperatures, pH, solvents, etc., to determine these characteristics. Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the substance may be specified.

d. Precautions to assure proper identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material.

e. Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

f. If the applicant does not himself perform all the manufacturing, processing, packaging, labeling, and control operations for any new-drug substance or the new-drug dosage form, his statement identifying each person who will perform any part of such operations and designating the part; and a signed statement from each such person fully describing, directly or by reference, the methods, facilities, and controls in his part of the operation.

g. Method of preparation of the master formula records and individual batch records and manner in which these records are used.

h. The instructions used in the manufacturing, processing, packaging, and labeling of each dosage form of the new drug, including any special precautions observed in the operations.

i. Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug package to assure their suitability for the intended use.

j. Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

k. Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and, if so, at what stage and by whom it is done.

l. Precautions to check the actual package yield produced from a batch of the drug with the theoretical yield. This should include a description of the accounting for such items as discards, breakage, etc., and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

m. Precautions to assure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling storage and inventory control.

n. The analytical controls used during the various stages of the manufacturing, processing, packaging, and labeling of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components. If the article is one that is represented to be sterile, the same information with regard to the manufacturing, processing, packaging, and the collection of samples of the drug should be given for sterility controls. Include the standards used for acceptance of each lot of the finished drug.

o. An explanation of the exact significance of the batch control numbers used in the manufacturing, processing, packaging, and labeling of the drug, including the control numbers that appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

p. A complete description of, and data derived from, studies of the stability of the drug, including information showing the suitability of the analytical methods used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new-drug substance, for the finished dosage form of the drug in the container in which it is to be marketed, including any proposed multiple-dose container, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed. State the expiration date(s) that will be used on the label to preserve the identity, strength, quality, and purity of the drug until it is used. (If no expiration date is proposed, the applicant must justify its absence.)

q. Additional procedures employed which are designed to prevent contamination and otherwise assure proper control of the product.

(An application may be refused unless it includes adequate information showing that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity in conformity with good manufacturing practice and identifies each establishment, showing the location of the plant conducting these operations.)

9. Samples of the drug and articles used as components, as follows: a. The following samples shall be submitted with the application or as soon thereafter as they become available. Each sample shall consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the application to determine compliance with its control specifications for identity and assays:

i. A representative sample or samples of the finished dosage form(s) proposed in the application and employed in the clinical investigations and a representative sample or samples of each new-drug substance, as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

ii. A representative sample or samples of finished market packages of each dosage form of the drug prepared for initial marketing and, if any such sample is not from a commercial-scale production batch, such a sample from a representative commercial-scale production batch; and a representative sample or samples of each new-drug substance as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

iii. A sample or samples of any reference standard and blank used in the procedures described in the application for assaying each new-drug substance and other assayed components of the finished drug: *Provided, however,* That samples of reference standards recognized in the official U.S. Pharmacopeia or The National Formulary need not be submitted unless requested.

b. Additional samples shall be submitted on request.

c. Each of the samples submitted shall be appropriately packaged and labeled to preserve its characteristics, to identify the material and the quantity in each subdivision of the sample, and to identify each subdivision with the name of the applicant and the new-drug application to which it relates.

d. There shall be included a full list of the samples submitted pursuant to Item 9a; a statement of the additional samples that will be submitted as soon as available; and, with respect to each sample submitted, full information with respect to its identity, the origin of any new-drug substance contained therein (including in the case of new-drug substances, a statement whether it was produced on a laboratory, pilot-plant, or full-production scale) and detailed results of all laboratory tests made to determine the identity, strength, quality, and purity of the batch represented by the sample, including assays. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods used differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

e. The requirements of Item 9a may be waived in whole or in part on request of the applicant or otherwise when any such samples are not necessary.

f. If samples of the drug are sent under separate cover, they should be addressed to the attention of the Bureau of Medicine and identified on the outside of the shipping carton with the name of the applicant and the name of the drug as shown on the application.

10. Full reports of preclinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate preclinical tests by all methods reasonably applicable to a determination of the safety and effectiveness of the drug under the conditions of use suggested in the proposed labeling.

b. Detailed reports of the preclinical investigations, including all studies made on laboratory animals, the methods used, and the results obtained, should be clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short- or long-term administration or whether it is to be used in infants, children, pregnant women, or women of child-bearing potential.

c. Detailed reports of any pertinent microbiological and *in vitro* studies.

d. Summarize and provide a list of literature references (if available) to all other preclinical information known to the applicant, whether published or unpublished, that is pertinent to an evaluation of the safety or effectiveness of the drug.

11. List of investigators. a. A complete list of all investigators supplied with the drug including the name and post office address of each investigator and, following each name, the volume and page references to the investigator's report(s) in this application and in any documents incorporated by reference, or the explanation of the omission of any reports.

b. The unexplained omission of any reports of investigations made with the new drug by the applicant, or

submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, whether or not it would bias an evaluation of the safety of the drug or its effectiveness in use, may constitute grounds for the refusal or withdrawal of the approval of an application.

12. Full reports of clinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the labeling.

b. An application may be refused unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

c. Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, full information concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintains adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. An application for a combination drug may be refused unless there is substantial evidence that each ingredient designated as active makes a contribution to the total effect claimed for the drug combination. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

d. Attach as a separate section a completed Form FD-1639, Drug Experience Report (obtainable, with instructions, on request from the Department of HEW, Food and Drug Administration, Bureau of Drugs *(BD-200)* Rockville, Maryland 20852), for each adverse experience or, if feasible, for each subject or patient experiencing one or more adverse effects, described in Item 12c, whether or not full information is available. Form FD-1639 should be prepared by the applicant if the adverse experience was not reported in such form by the investigator. The Drug Experience Report should be cross-referenced to any narrative description included in Item 12c.

e. All information pertinent to an evaluation of the safety and effectiveness of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commerical marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application and related drugs. An adequate summary may be acceptable in lieu of a reprint of a published report which only supports other data submitted. Reprints are not required of reports in designated journals, listed in §130.38 of the new-drug regulations, about related drugs; a bibliography will suffice. Include any evaluation of the safety or effectiveness of the drug that has been made by the applicant's medical department, expert committee, or consultants.

f. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

g. The complete composition and/or method of manufacture of the new drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in Item 6, 7, or 8 of the application.

13. If this is a supplemental application, full information on each proposed change concerning any statement made in the approved application.
Observe the provisions of §130.9 of the new-drug regulations concerning supplemental applications.

AYERST LABORATORIES
(Applicant)

Per By
(Responsible official or agent)
Henry S. Perdue, Ph.D.
Director, Regulatory Affairs
(Indicate authority)

(Warning: A willfully false statement is a criminal offense. U.S.C. Title 18, sec. 1001.)

NOTE: This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States.

Ayerst®

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

HENRY S. PERDUE, Ph. D.
VICE PRESIDENT, REGULATORY AFFAIRS

October 13, 1978

RESUBMISSION

NDA ORIG AMENDMENT

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Scientific Evaluation
Bureau of Drugs HFD-530
Attn: DOCUMENT CONTROL ROOM 16-72
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUBJECT: ANDA 83-273; Premarin®(Conjugated Estrogens, U.S.P.) Vaginal Cream

Dear Dr. Seife:

Reference is made to our submission of October 5, 1978 to the subject abbreviated New Drug Application. In that letter we indicated in Item 4 (g), temperature cycling, that final data will be submitted following the completion of the cycling study.

b(4)

We are submitting herewith analytical data on tubes of Premarin Vaginal Cream that were cycled two days at 4°C and two days at 40°C for six complete cycles. As can be seen from the attached report, there was no significant non-uniformity in either estrogens potency, pH, or concentration.

We trust that these data and our prior commitments will permit approval of ANDA 83-273.

Sincerely,

Joseph L Monn

Henry S. Perdue, Ph. D.

HSP
JLM/mf

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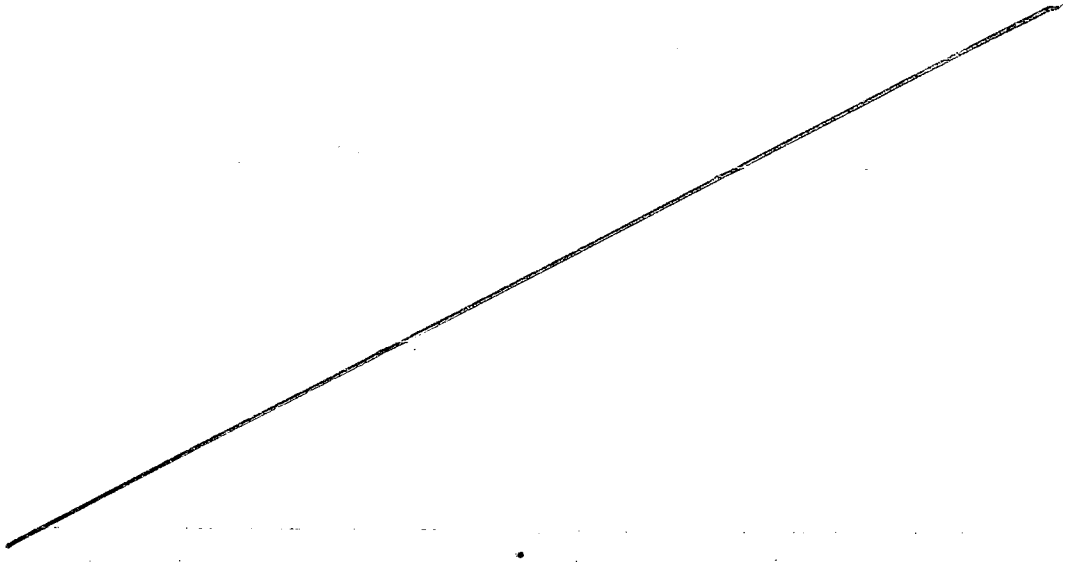
Effect of Temperature Cycling on the Physical Stability of Premarin® Vaginal Cream

Objective: To determine if exposure to alternating cold-hot temperatures will cause non-uniformity from dose to dose in estrogen potency, pH or phenylethyl alcohol.

Procedure: Tubes from batch 1FNH, manufactured July, 1977, were cycled two days at 4°C and two days at 40°C for six complete cycles. At the end of the six cycles, upright tubes were selected for analyses in order to accentuate phase separation if it occurred.



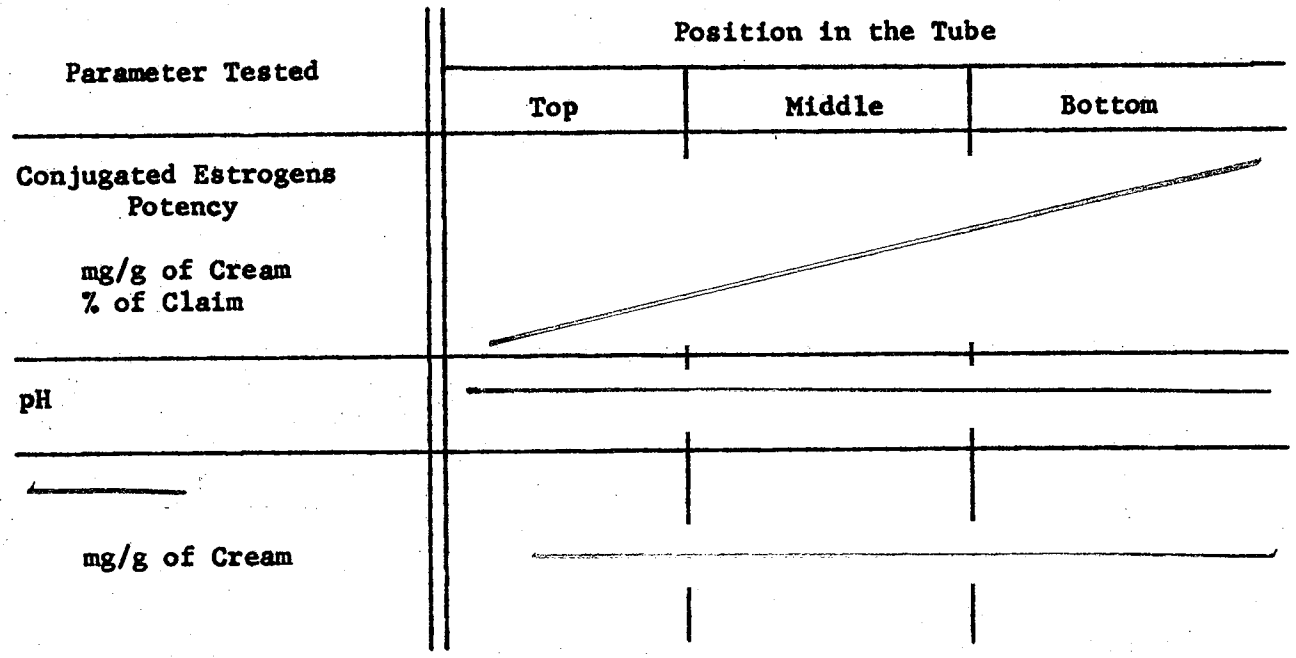
b(4)

Results: The results obtained are shown in Table 1, and demonstrate there was no significant non-uniformity of estrogen potency, pH or _____ developed in tubes exposed to six cold-hot temperature cycles.

b(4)

Table 1 - Uniformity Data Obtained on Premarin® Vaginal Cream Tubes Exposed to Six Cycles of Two Days at 4°C - Two Days at 40°C.

Batch 1FNH, Manufactured July, 1977



b(4)

Ayerst

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N. Y. 10017 / Tel: (212) 986-1000 / Cable: ALPHAMIN, New York

HENRY S. PERDUE, Ph. D.
VICE PRESIDENT, REGULATORY AFFAIRS

October 5, 1978

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Scientific Evaluation
Bureau of Drugs HFD-530
Attn: DOCUMENT CONTROL ROOM 16-72
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RESUBMISSION

NDA ORIG[illegible]CUMENT

FPL

SUBJECT: ANDA 83-273; Premarin®(Conjugated Estrogens, U.S.P.)
Vaginal Cream

Dear Dr. Seife:

We refer to your letters of March 8, 1977 and May 12, 1977 regarding the subject ANDA and our amendment of September 16, 1977 to that ANDA. We are at this time providing additional information on this product as follows:

1. Product specifications.

(a) pH specification

The pH specification for this product is ———— This change is presented in a revised controls section, Section 8 n (EXHIBIT I). Premarin Vaginal Cream is an ———— product which should rapidly equilibrate with the pH of the vagina; no pH adjustment is made during processing.

b(4

(b) estrogen specifications

The estrogens in Premarin Vaginal Cream were previously defined in Method 2E-0301, Identification of Conjugated Estrogens by Gas Chromatography, page 7, submitted to the Administration on September 16, 1977 as part of section 8 d. In this method we state that identity is positive if:

- the chromatogram exhibits distinct peaks for estrone and equilin and;
- the chromatogram exhibits a prominent peak for 17-alpha-dihydroequilin and;

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- additional minor peaks or shoulders correspond to 17-alpha-estradiol, 17-beta-dihydroequilin, equilenin, b(4)

. A copy of this method is reproduced in EXHIBIT II.

Ayerst agrees, however, to redefine the estrogens in Premarin Vaginal Cream following the validation and use of the gas chromatographic procedure indicated in Item 4 below. Unitl data to enable the redefining of these estrogens is available, Ayerst provides the following specifications:

Sodium estrone sulfate:
Sodium equilin sulfate: b(4)

These specifications are also included in the revised Section 8 n in EXHIBIT I.

The usual composition of Premarin Vaginal Cream is expected to be (within a few percentage points) similar to that of Premarin Tablets. The usual composition of Premarin Tablets is sodium estrone sulfate ———; b(4)
sodium equilin sulfate, ———; sodium 17-alpha-dihydroequilin sulfate ——— and the —— of sodium 17-alpha-estradiol sulfate, ———, sodium 17-beta-dihydroequilin sulfate ———. Ayerst agrees to characterize the estrogens in Premarin Vaginal Cream as soon as methodology and appropriate data are available.

2. ——— percent overage.

A —— overage is presently incorporated into the manufacture of this product for ——— purposes. Data indicate that we generally encounter a ———; the remainder of the overage is designed for ——— purposes. b(4)

we believe that the overage employed is not excessive. Should improved assay methods show an improved analytical recover, a reduction in overage will be made. This is specified in a revised composition section, Section 7 (EXHIBIT III).

3. Storage of estrogenic material prior to use.

b(4)

4. Relative to stability studies:

(a) stability of the conjugated estrogens concentrate

The data presented in EXHIBIT IV demonstrate that conjugated estrogens concentrate has a stability of at least — months. Ayerst agrees, however, to provide additional stability data on this material. b(4)

(b) stability data on individual estrogens

Ayerst Laboratories has encountered difficulties in developing analytical procedures which would enable the quantitative measurement of the individual estrogens specified in your letter of March 8, 1978. We believe, however, that we now have a suitable method for this purpose utilizing gas chromatography. This method is currently undergoing ruggedness testing. Ayerst agrees to provide quantitative data on each of the requested estrogens, i.e.,

sodium estrone sulfate
sodium equilin sulfate
sodium equilenin sulfate
sodium 17-alpha-dihydroequilin sulfate b(4)

as part of the stability program for Premarin Vaginal Cream.

(c) storage of stability samples

Samples for stability studies will be stored in the marketed container at both ambient and controlled elevated temperature.

(d) homogeniety of conjugated estrogens in the cream.

Ayerst Laboratories agrees to provide data on the uniformity (homogeniety) of conjugated estrogens in the cream as part of the stability program.

(e) stability data

We are providing at this time (see EXHIBIT V) additional stability data on 5 batches of Premarin Vaginal Cream. Initial and 6 month potency data were previously submitted in our ammendment of September 16, 1977.

(f) container —— compatability

EXHIBIT VI presents compatability data for 4 different container ——. Table #4 in this EXHIBIT provides data on the —— currently in use. These data show that each of these —— is compatable with the finished product. No change in package appearance or product appearance is evident after 52 weeks at room temperature. Compatability data at 4°, 40° and 51° are also presented. b(4)

(g) temperature cycling

Samples of Premarin Vaginal Cream in the marketed container (lot FNH) when frozen at -20° and then thawed showed no breaking of the cream emulsion. In addition to no change in the appearance of the cream, there was no change in the appearance of the container ——. The effect on the cream of temperature cycling between 4°C and an elevated temperature (48 hours at each temperature) is presently being determined. Final data will be submitted following the completion of the cycling study; an interim report is presented in EXHIBIT VII. b(4) b(4)

(h) release rate of estrogens from cream base

Premarin Vaginal Cream is an

——— b(4)

——— evidenced by the essentially quantitative analytical recovery of the estrogens in

——— (see EXHIBIT VIII).

The absorption of the estrogens from Premarin Vaginal Cream is documented by a recent publication (Rigg et al, New England J. Med. 298: 195-197, 1978) in which the authors indicate that conjugated estrogens (Premarin Vaginal Cream) are readily absorbed by the vaginal mucosa in estrogen deficient women. A copy of this manuscript is provided in EXHIBIT IX.

5. Final Printed Labeling.

Final printed labeling is presented in EXHIBIT X.

6. Microbial challenge test.

Microbial challenge test data on the current formulation was previously submitted to the Administration on February 4, 1976 in support of the use of ———. These data are reproduced in EXHIBIT XI. b(4)

7. "Typical" production batch record.

EXHIBIT XII provides a typical batch record for the production of batch F438-FJJ of Premarin Vaginal Cream. This record consists of typical forms used for batch F438 FJJ and contains a) amounts of individual ingredients used; b) the processing record; c) tank sanitation and sterilization records; d) packaging and labeling records; and e) quality control records for this particular batch. This batch record describes the production of batch F438 FJJ. It is to be understood that minor changes in the batch record which are not in conflict with the approved ANDA may occur with other batches.

8. Production flow diagram.

EXHIBIT XIII presents a process schematic of the manufacturing and in process controls for Premarin Vaginal Cream. The manufacturing procedure has been previously submitted in Section 8 h of our submission of September 16, 1977. Evidence for the uniformity of the distribution of the conjugated estrogens in the cream base is presented in EXHIBIT XIV. These data, generated on 10 randomly selected tubes from 10 batches of Premarin Vaginal Cream, show that the conjugated estrogens are uniformly distributed in the cream base during manufacture of the product.

We trust that this additional information and Ayerst's commitment to provide the requested stability and estrogen composition data will allow a rapid approval of ANDA 83-273.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331 (j).

Sincerely,

for/ Joseph L. Mauro

Henry S. Pennue, Ph. D.

HSP
JLM/mf

Ayerst

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December 8, 1977

Marvin Seife, M.D.
Director,
Division of Generic
Drug Monographs
Office of Scientific Evaluation
Bureau of Drugs HFD-530
Att: DOCUMENT CONTROL ROOM 16-72
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

NDA ORIG AMENDMENT

FPL

Subject: ANDA 83-273; PREMARIN(R) (Conjugated Estrogens,U.S.P.) Vaginal Cream

ANDA 83-488; Estrogenic Substance (Estrons) Aqueous Suspension

ANDA 85-515; PREMARIN(R) (Conjugated Estrogens, U.S.P.) with Methyltestosterone

Dear Dr. Seife:

In accord with the Administration's notice published in the Federal Register on July 22, 1977 (42FR37641), we are submitting herewith, in triplicate, an amendment to our application for the subject drugs to provide labeling directed to the patient. Please note that although several different code numbers are used for the patient labeling, the text is identical. The different code numbers are used to reflect different folding patterns, sizes, shapes or number of pieces included within the several sleeves used to bind groups of patient labeling pieces.

This labeling was put into effect on October 18, 1977 in accord with the extended effective date of the ruling. Twelve copies of each labeling piece and sleeve, when required, are enclosed.

Sincerely,

Henry S. Perdue, Ph.D.
Vice President
Regulatory Affairs

HSP
JLM:bnf
Encl.

RECEIVED
DEC 09 1977
BUREAU OF DRUGS

4 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

___√___ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)