CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-417

CORRESPONDENCE

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*** TX REPORT ***
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TRANSMISSION OK

TX/RX NO	0626
CONNECTION TEL	914848659214
CONNECTION ID	WYETH REG AFFAIR
ST. TIME	10/18 18:17
USAGE T	02'02
PGS. SENT	4
RESULT	OK

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: October 18, 2002

To: Jennifer Norman, R.Ph. Associate Director, Worldwide Regulatory Affairs	**From:** Samuel Y. Wu, Pharm.D. Regulatory Project Manager
Company: Wyeth-Ayerst Research	Division of Metabolic and Endocrine Drug Products
Fax number: 484-865-9214	**Fax number:** 301-443-9282
Phone number: 484-865-3749	**Phone number:** 301-827-6416

Subject: NDA 21-417 Premarin Action Letter

Total no. of pages including cover: 4

Comments:

Document to be mailed: ☑ YES ☐ NO

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3 Draft Labeling Page(s) Withheld

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-417

Wyeth-Ayerst Research
Attention: Jennifer D. Norman, R.Ph.
Associate Director, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Norman:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Premarin (conjugated estrogens tablets, USP)

Review Priority Classification: Standard (S)

Date of Application: December 17, 2001

Date of Receipt: December 18, 2001

Our Reference Number: NDA 21-417

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 16, 2002, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 18, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans

within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at 301-827-6416.

Sincerely,

{See appended electronic signature page}

Samuel Y. Wu, Pharm.D.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Samuel Wu
1/10/02 05:46:54 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-417

INFORMATION REQUEST LETTER

Wyeth-Ayerst Research
Attention: Jennifer D. Norman, RPh
Associate Director, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

FEB 28 2002

Dear Ms. Penhale:

Please refer to your December 17, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Premarin (conjugated estrogens tablets, USP) (CE).

We are reviewing the Human Pharmacokinetics and Bioavailability section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. *In vitro* dissolution methods and data for CE from various CE tablet formulations used in the clinical safety and efficacy as well as pharmacokinetic studies were provided. However, the proposed *in vitro* dissolution specifications for the 0.3 mg and 0.45 mg CE alone tablets are: [redacted] released after 2 hours, [redacted], after 5 hours and not less than (NLT) [redacted] in 8 hours for NDA 21-417 (Section 1.6 of the Human Pharmacokinetics and Bioavailability Summary). Therefore, these proposed *in vitro* dissolution specifications were the same as that for the lower doses PREMPRO™ (0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA; NDA 21-396). Please clarify the proposed *in vitro* dissolution specifications for NDA 21-417.

2. The formulations (CE and CE/MPA) tested in the clinical studies 0713D2-309-US, 0713D2-119-US, and 0713D2-120-US are identical to the marketed formulations in terms of scale of manufacture and composition except the color coat, which was [redacted] in the clinical formulation (Section 1.4 of the Human Pharmacokinetics and Bioavailability Summary). Comparisons of *in vitro* dissolution data based on the USP 24 method for the formulation tested in the clinical safety and efficacy study versus that of the to-be-marketed formulation were not provided. For the 0.3 mg CE alone tablet, please submit the individual *in vitro* dissolution data plus descriptive statistics (mean and range, etc.) for the clinical batches and to-be-marketed batches. Dissolution data on release, not stability data, are needed. These data are necessary to justify the lack of difference between the clinical batches and to-be-marketed batches, which are different in color. If the to-be-marketed 0.45 mg CE alone tablets are identical between NDA 04-782/S-115 and NDA 21-417, you can reference the submitted *in vitro* dissolution data between the clinical batches and to-be-marketed batches for the 0.45 mg CE alone tablet for NDA 04-782/S-115. If the to-be-marketed 0.45 mg CE

alone tablets are not identical between NDA 04-782/S-115 and NDA 21-417, you should submit the *in vitro* dissolution data for the 0.45 mg CE alone tablet as requested for the 0.3 mg CE alone tablet above.

If you have any questions, call Samuel Y. Wu, Pharm.D., Regulatory Project Manager, at 301-827-6416.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kati Johnson
2/28/02 03:21:10 PM