CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-417

ADMINISTRATIVE DOCUMENTS

TIME SENSITIVE PATENT INFORMATION PURSUANT TO 21 C.F.R. 314.53
for NDA 21-417

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	PREMARIN®
Active Ingredient(s):	conjugated estrogens
Strength(s):	0.30 mg
Dosage Form:	Tablets, Oral
Approval Date:	To be determined

A. Information for each individual patent:

US Patent Number:	5,210,081
Expiration Date:	February 26, 2012
Type of Patent:	Drug Substance (Active Ingredient) - covers a sodium salt of delta-8,9-dehydroestrone-3-sulfate, a drug substance (ingredient) that is an active component of PREMARIN®.
Patent Owner:	American Home Products Corp., parent company of the Applicant

---

B. Declaration statement for listed patents which have Compostion/Formulation or Method of Use claims:

N/A

WYETH-AYERST LABORATORIES

By: _____
Arnold S. Milowsky, Ph.D.
Patent Counsel
Date: 11/20/01

TIME SENSITIVE PATENT INFORMATION PURSUANT TO 21 C.F.R. 314.53
for NDA 21-417

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	PREMARIN®
Active Ingredient(s):	conjugated estrogens
Strength(s):	0.45 mg
Dosage Form:	Tablets, Oral
Approval Date:	To be determined

A. Information for each individual patent:

US Patent Number:	5,210,081
Expiration Date:	February 26, 2012
Type of Patent:	Drug Substance (Active Ingredient) - covers a sodium salt of delta-8,9-dehydroestrone-3-sulfate, a drug substance (ingredient) that is an active component of PREMARIN®.
Patent Owner:	American Home Products Corp., parent company of the Applicant

---

B. Declaration statement for listed patents which have Compostion/Formulation or Method of Use claims:

N/A

WYETH-AYERST LABORATORIES

By: _____
Arnold S. Milowsky, Ph.D.
Patent Counsel
Date: 11/20/01

Amended Patent / Exclusivity Information

1)	Active ingredent(s)	Conjugated estrogens
2)	Strength(s)	0.30 mg
3)	Trade Name	PREMARIN®
4)	Dosage Form	Tablets, Oral
5)	Applicant Firm Name	Wyeth-Ayerst Laboratories
6)	NDA Number	21-417
7)	Approval Date	To be determined
8)	Exclusivity - Date first ANDA could be submitted or approved and length of exclusivity period	Pursuant to Section 505(j)(4)(D)(ii) and 505(c)(3)(D)(ii) of the Federal Food, Drug, and Cosmetic Act, no ANDA may be approved with an effective date which is prior to 3 years after the date of approval of this NDA Supplement
9)	Applicable patent numbers and expiration date of each	U.S. Patent No. 5,210,081 Expiration Date: February 26, 2012

Amended Patent / Exclusivity Information

1)	Active ingredent(s)	Conjugated estrogens
2)	Strength(s)	0.45 mg
3)	Trade Name	PREMARIN®
4)	Dosage Form	Tablets, Oral
5)	Applicant Firm Name	Wyeth-Ayerst Laboratories
6)	NDA Number	21-417
7)	Approval Date	To be determined
8)	Exclusivity - Date first ANDA could be submitted or approved and length of exclusivity period	Pursuant to Section 505(j)(4)(D)(ii) and 505(c)(3)(D)(ii) of the Federal Food, Drug, and Cosmetic Act, no ANDA may be approved with an effective date which is prior to 3 years after the date of approval of this NDA Supplement
9)	Applicable patent numbers and expiration date of each	U.S. Patent No. 5,210,081 Expiration Date: February 26, 2012

EXCLUSIVITY SUMMARY for NDA # 21-417 SUPPL # _____

Trade Name Premarin Tablets Generic Name conjugated estrogens

Applicant Name Wyeth Pharmaceuticals HF-510

Approval Date July 16, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? (**type 6 NDA**) YES/XX/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /XX/

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /XX/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

d) Did the applicant request exclusivity?

YES /___/ NO /**XX**/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /**XX**/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /**XX**/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /**XX?**/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /**XX**/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 4-782 Premarin

NDA # 10-402 Premarin

NDA # 20-216 Premarin

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /**XX**/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /<u>XX</u>/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /**XX**/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /**XX**/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /**XX**/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /**XX**/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 0713B-309-US

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /**XX**/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /XX/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____ _____

Signature of Preparer Date

Title:_____

_____ _____

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

David Orloff
7/16/03 01:36:44 PM

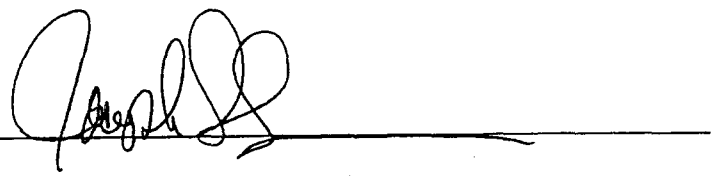
NDA 21-417

Premarin®
(conjugated estrogens tablets, USP)

Lower Doses: 0.45mg and 0.3mg
Indication: Prevention of Osteoporosis

Item 16: Certification Required by Generic Drug Enforcement Act of 1992

The undersigned certifies that Wyeth-Ayerst did not and will not knowingly use in any capacity the services of any person debarred under subsection (a) or (b) [section 306 (a) or (b)] of the Generic Drug Enforcement Act of 1992 in connection with NDA 21-417 for Premarin® (conjugated estrogens tablets, USP).

Signature 

Joseph S. Sonk, Ph. D.
Assistant Vice President
Worldwide Regulatory Affairs

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-417 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: December 17, 2001 Action Date: July 16, 2003

HFD 510 Trade and generic names/dosage form: Premarin (conjugated estrogens): 0.3 and 0.45 mg tablets

Applicant: Wyeth-Ayerst Therapeutic Class: 3S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Prevention of postmenopausal osteoporosis

Is there a full waiver for this indication (check one)?

XX Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
XX Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed

☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

____Patricia Madara__
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A
(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ☐ No: **Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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

/s/

Patricia Madara

7/21/03 04:14:38 PM

N021417

Premarin®
Conjugated Estrogens Tablets, USP

Lower Doses of 0.3mg and 0.45mg

Item 20: Pediatric Rule (Waiver Requested)

In accordance with 21 CFR §314.55, Wyeth-Ayerst believes that pediatric data is not required for inclusion within this application. This application is for the addition of lower doses of previously approved Premarin® products that are indicated for postmenopausal symptoms, i.e., treatment of vasomotor symptoms, treatment of vulvar and vaginal atrophy and the prevention of osteoporosis. This product is not indicated for any pediatric population.

Signature

Joseph S. Sonk, Ph.D.
Assistant Vice President
Worldwide Regulatory Affairs

K1.1

N21417

NDA 21-417

RCC-
09/24/03
2:28 PM

Premarin®

(conjugated estrogens tablets, USP)

0.3 mg and 0.45 mg

Wyeth-Ayerst Research

Goal Date$_{10}$: October 18, 2002
Project Manager: Samuel Y. Wu
Division of Metabolic and Endocrine Drug Products, HFD-510
Approved:

DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	NDA
Document Type:	NDA Letters
Document Group:	NDA Approval Letters
Document Name:	Approval letter based on enclosed/submitted labeling text
Shortcut ID Code:	NDA-I1
COMIS Decision Code	AP
Drafted by:	Pm/5/16/03; 5/23/03; 7/16/03
Revised by:	Kj/5/21/03; 7/16/03
Initialed by:	
Finalized:	
Filename:	
DFS Key Words:	
Notes:	

Version: 03/04/2003

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

TEAM LEADER MEMO

NDA: 21-417

DRUG: Conjugated estrogen (Premarin)

DOSES: 0.30mg and 0.45mg (tablets)

COMPANY: Wyeth Ayerst

INDICATION: Prevention of PMO

PRIMARY REVIEWER: Theresa Kehoe, MD

DATE OF MEMO: October 10, 2002

Background

With this supplemental NDA submission, Wyeth Ayerst is seeking approval of the 0.45 mg and 0.30 mg doses of conjugated estrogens (CE) for the prevention of postmenopausal osteoporosis (PMO) indication.

There are five dose strengths of CE currently approved: 0.30 mg, 0.625 mg, 0.9 mg, 1.25 mg, and 2.5 mg. The 0.625 mg dose of CE is the only dose approved for the prevention of PMO at this time. Other approved indications for CE include vasomotor symptoms (0.625 mg), vaginal atrophy (0.30 to 1.25 mg or more), hypogonadism (0.30 to 0.625 mg), breast cancer (10 mg TID), and advance androgen-sensitive prostate cancer (1.25 to 2.5 mg).]

HOPE Trial

The Health and Osteoporosis, Progestin and Estrogen (HOPE) study was a double-blind, randomized, placebo/active-controlled trial of healthy postmenopausal with an intact uterus. A total of 2,673 primarily Caucasian women with a mean age of 52 years and an average BMI of 24 kg/m^2 were randomized in equal fashion to one of eight regimens: [The combination of CE with medroxyprogesterone acetate (MPA) is known as Prempro or Premphase]

A: 0.625 CE + placebo
B: placebo + 0.625 CE/2.5 MPA
C: 0.45 CE + placebo
D: placebo + 0.45 CE/2.5 MPA
E: placebo + 0.45 CE/1.5 MPA
F: 0.30 CE + placebo
G: placebo + 0.30 CE/1.5 MPA
H: placebo + placebo

The primary objective of this study during Year 1 was to examine the efficacy of lower doses of CE and MPA in reducing the incidence of endometrial hyperplasia and in reducing the incidence of vasomotor symptoms and vulvar and vaginal atrophy. The one-year data are the focus of attention for DRUDP.

The primary objective of the study during Year 2 was to examine, in 822 women, the efficacy of lower doses of CE (0.45 mg and 0.30 mg) and CE plus MPA (0.45 mg CE/1.5 mg MPA and 0.30 mg CE/1.5 mg MPA) in the prevention of PMO and the maintenance of an acceptable metabolic profile (i.e., lipids, coagulation, and carbohydrate). This substudy is the focus of DMEDP's attention. The Division recently

issued an Approvable Letter for a [redacted] NDA seeking approval of the low doses of CE/MPA for the prevention of PMO.

Bone Mineral Density and Markers of Bone Turnover

After reviewing the appropriate data, Dr. Kehoe recommends that the 0.45 mg and 0.30 mg doses of CE be considered approvable for the prevention of PMO. Dr. Kehoe recommends that a final decision regarding approvability be made following the November 12 and 13 Reproductive Health Drugs Advisory Committee Meeting, which is being held to discuss the results of the recently published Women's Health Initiative (WHI) study.

Of the 822 women enrolled into the second year of the HOPE study, 749 received at least one dose of study drug and were considered evaluable for Year 2 analyses. The withdrawal rates ranged from 21% in the 0.30 CE/1.5 MPA group to 54% in the 0.625 CE group – with adverse event as the most common reason for discontinuation. A similar percentage of patients in each treatment group were taking similar types of concomitant medications at baseline.

The mean percent changes in bone mineral density (BMD) at the lumbar spine from baseline to Year 2 were approximately –2.0% for the placebo group and 2.3% and 1.5% for the 0.45 mg and 0.30 mg doses of CE, respectively ($p<0.001$) (Table). Similar positive and statistically significant effects on trochanteric, femoral neck, and total body BMD were also observed for the 0.45 mg and 0.30 mg doses relative to placebo.

The mean changes in markers of bone turnover, osteocalcin (formation) and NTX (resorption), support the changes noted in BMD.

Adjusted Mean Change in LS BMD from Baseline to Year 2 (evaluable population)			
Treatment Group	N	% change from baseline	P-value
0.625	66	2.8	<0.001
0.625/2.5	76	3.8	<0.001
0.45	77	2.3	<0.001
0.45/2.5	79	3.1	<0.001
0.45/1.5	75	2.5	<0.001
0.30	76	1.5	<0.001
0.30/1.5	82	1.8	<0.001
Placebo	78	-2.6	

Lipids

As expected, relative to treatment with placebo, the mean changes in total, LDL, and HDL cholesterol were favorable in the 0.45 mg and 0.30 mg dose groups. Also as expected, mean TG levels increased by a greater degree with active vs. placebo treatment.

Metabolic Variables

In the women who participated in the 2-year substudy, an evaluation was made of the effect of treatment on levels of plasma glucose, insulin, and a variety of standard coagulation factors. In short, no clinically meaningful changes were noted in any of the dose groups. Wyeth has not proposed that any of these data be included in the labeling.

Safety

Adverse Event Reporting

Deaths

There were no deaths in the 2-year substudy.

Serious Adverse Events

A total of 48 patients reported 50 serious adverse events (SAE). There were no obvious imbalances among groups in reporting rates for SAEs. Four women were diagnosed with breast cancer during the 2-year period: one each in the 0.625 mg, 0.45 mg, 0.45/1.5, and placebo groups. Two vascular thrombosis cases were reported: one in the 0.625/2.5 group and one in the 0.45 group. No vascular thrombotic events were reported during Year 2

Withdrawals Due to Adverse Events

The 0.625 CE group had a significantly higher percentage of patients who discontinued due to an adverse event (37%) compared with the other treatment groups including placebo (8-15%). A large portion of the patients in the 0.625 CE group discontinued because of endometrial hyperplasia and vaginal bleeding.

Treatment-Emergent Adverse Events

In an analysis of the percentage of patients reporting $\geq$ 5% treatment emergent adverse events, a number of comparisons were associated with a nominal p-value of $\leq$ 0.05. Some difference were expected, such as breast pain and endometrial hyperplasia, which were reported by a significantly greater percentage of women on unopposed estrogen vs. placebo. Other events such as bronchitis and ear disorder are nonspecific terms, they lack biological plausibility, and they are not serious, life-threatening events. Interpretation of these nominally significant results is particularly difficulty given the extremely large number of comparison that were made in the tabulation of adverse event reporting rates. In my opinion these findings do not warrant further analysis.

Clinical Chemistry

Some clinical chemistry parameters were affected by active treatment. As expected, therapy with estrogen (with or without progestin) was associated with small reductions in levels of mean plasma calcium (reduced bone resorption) and alkaline phosphatase (reduced bone formation). I do not believe that any of the statistically significant changes in clinical chemistry parameters in the active vs. placebo groups were of clinical significance.

Fractures

The HOPE trial was not designed to evaluate the efficacy of estrogen or estrogen plus progestin on risk for osteoporotic fracture. However, as safety data, 22 women sustained a fracture during the study. Although there were 5 women in the placebo group compared with 2 in the 0.625 CE group who had fractures, some of the fractures occurred following trauma and at skeletal sites not considered in an evaluation of osteoporotic fractures. There is certainly no evidence that treatment with estrogen had a detrimental affect on fracture risk in this population of early postmenopausal women.

Pediatric Rule: The sponsor should be issued a waiver for the requirement to study pediatric patients under the Pediatric Rule — postmenopausal osteoporosis is obviously not a condition that affects children or adolescents.

DSI: An audit by DSI was not requested for this supplemental NDA.

Conclusions and Recommendation

The BMD data submitted in this supplemental NDA support the efficacy of 0.45 mg and 0.30 mg of CE in the "prevention of PMO." If not for the recent publication of data from the WHI study, which reported an unacceptable risk – benefit profile of 0.625 mg CE/2.5 mg MPA in healthy postmenopausal women, I would recommend approval. However, during recent discussions among Office and Center-level personnel,

it was decided that any pending supplements for an estrogen and an estrogen + progestin product would be designated approvable pending outcome of an Advisory Committee meeting to be held in November, 2002.

I recommend that this application be considered **approvable**. A reassessment of its regulatory status should be made after:

1. An Advisory Committee meeting is held to discuss the full implications of the recently published data from the WHI study.
2. The Division and Wyeth Ayerst have agreed upon final labeling.

Eric Colman, MD
Medical Team Leader
HFD-510

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

/s/

Eric Colman
10/15/02 01:28:49 PM
MEDICAL OFFICER

David Orloff
10/15/02 02:55:50 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: October 18, 2002

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-417
Premarin (conjugated estrogen tablets, USP)
Prevention of postmenopausal osteoporosis

SUBJECT: NDA review issues and recommended action

Background

This is an application (Type 6 NDA) for approval of two lower doses of Premarin (conjugated equine estrogens), 0.45 and 0.30 mg, for the prevention of post-menopausal osteoporosis. The data submitted are from the HOPE trial, a double blind, randomized, placebo-controlled, parallel group study of 2673 post-menopausal women. The one-year data on vasomotor symptoms and vulvovaginal atrophy were reviewed by DRUDP. The year-two data from the substudy examining effects on BMD and metabolic parameters were reviewed by DMEDP. The reviews by Drs. Colman and Kehoe address the trial data in detail.

Clinical

Across the dosage range of Premarin and Prempro (premarin plus MPA), with 66-82 patients evaluable per group, there were changes in BMD at the lumbar spine from baseline to year 2 that were statistically significantly different from placebo. By and large, the effects of Prempro at each dose of the Premarin component were more effective, numerically, than Premarin alone at the same dose. This is consistent with previous data. No meaningful fracture data arose from this trial. The effects on plasma lipids were consistent with the data from previous investigations. There was a dose-related increase in total HDL-C and in the HDL2 subfraction. There were likewise small dose-related reductions in LDL-C and thus in the ratio of LDL-C to HDL-C, and dose-related increases in TG. The clinical significance with regard to impact on CHD risk of these effects is not known. While the premarin-only arms of the WHI study continue at this time, the data on cardiovascular outcomes associated with estrogen-progestin combination versus placebo in postmenopausal women from that part of the WHI support risk that exceeds benefit with HRT, at least at the doses studied. Certainly, the place in labeling (and the treatment of the data) of information on the lipid effects of these products bears further discussion and will be raised at the November 2002 meeting of the FDA advisory committee to discuss the WHI results.

There were no new safety concerns raised in these studies.

Labeling
Final labeling must still be negotiated.

Biopharmaceutics
Acceptable from the standpoint of OCPB. No deficiencies.

Pharmacology/Toxicology
No new pharm-tox data were submitted

Chemistry/ Microbiology
The chemistry, manufacturing, and controls are satisfactory and the application is approvable from the standpoint of ONDC, pending a satisfactory inspection of the Rouses Point, NY manufacturing site.
A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency.

DSI/Data Integrity
No audits of the BMD substudy were requested.

Financial disclosure
Dr. Kehoe addressed the submitted information on page 36 of her review and concludes that the integrity of the safety and efficacy data was not in question.

ODS/nomenclature
No issues

Recommendation
Concur with Drs. Colman and Kehoe. This application may be approved pending satisfactory establishment inspection with further guidance, particularly on labeling, to come from the upcoming FDA meeting on the WHI results.

NDA #
Drug:
Proposal:
10/19/02

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

/s/

David Orloff
10/19/02 11:04:32 AM
MEDICAL OFFICER

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-417	Efficacy Supplement Type SE-	Supplement Number
Drug: Premarin Tablets (0.3 and 0.45 mg)	Applicant: Wyeth Pharmaceuticals	
RPM: Patricia Madara	HFD- 510	Phone # 301-827-6416
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	July 16, 2003
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
Exclusivity Summary (approvals only)	X
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A

General Information	
Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE, October 18, 2002
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	NO
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	X
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	No
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	X
❖ Clinical review(s) *(indicate date for each review)*	October 10. 2002
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	Pg 31 of MOR; October 10, 2002
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) *(indicate date for each review)*	June 11, 2002
❖ Biopharmaceutical review(s) *(indicate date for each review)*	October 17, 2002
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	N/A
• Clinical studies	
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	May 12, 2003; October 7, 2002
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	N/A
• Review & FONSI *(indicate date of review)*	CMC review, 10/7/02, page 35
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: May 8, 2003 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	(X) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. Do NOT send this page with the letter.

Application #(s):	NDA 21-417
Document Type:	NDA Letters
Document Group:	NDA Approvable Letters
Document Name:	Approvable letter – Misc. deficiencies and labeling revisions listed in letter.
Shortcut ID Code:	NDA-H4
COMIS Decision Code	AE
Drafted by:	S. Wu/October 11, 2002
Revised by:	
Initialed by:	K. Johnson/October 16, 2002 E. Colman/October 16, 2002 D. Orloff/October 18, 2002
Finalized:	S. Wu/October 18, 2002
Filename:	AE-1-101802.doc
DFS Key Words:	
Notes:	

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Wyeth-Ayerst Laboratories
P O Box 8299
Philadelphia, PA 19101-8299

2. TELEPHONE NUMBER *(Include Area Code)*

(484) 865-3749

3. PRODUCT NAME

Premarin (conjugated estrogens tablets, USP)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-417

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4186

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See Item 8, reverse side if answered YES)*

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Jennifer D. Norman, R.Ph. Jennifer D Norman	Associate Director Worldwide Regulatory Affairs	December 13, 2001

FORM FDA 3397 (4/01)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

[X] (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	Premarin .45 mg & .3 mg	Study 309 - US
	(see attached lists)	

[X] (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

[X] (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Joseph S. Camardo, MD Mr. Robert Haller	Sr VP - Clinical R & D VP - R & D Finance
FIRM/ORGANIZATION	
Wyeth - Ayerst Research	
SIGNATURE	DATE
	September 27, 2001

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Created by: PSC Media Arts (301) 443-2454 ET

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 1

Premarin .45 mg & .3 mg
Study 309-US

The Clinical Investigators listed below include only those whose site enrolled patients in the above referenced study.

Last Name	First	MI
[redacted]		
r	Bruce	
[redacted]		

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 1

Premarin .45 mg & .3 mg
Study 309-US

The Clinical Investigators listed below include only those whose site enrolled patients in the above referenced study.

Last Name	First	MI
[redacted]		
Montgomery-Rice	Valerie	
[redacted]		

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 1

Premarin .45 mg & .3 mg
Study 309-US

The Clinical Investigators listed below include only those whose site enrolled patients in the above referenced study.

Last Name	First	MI
[redacted]		
Thorneycroft	Ian	
[redacted]		

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 1

Premarin .45 mg & .3 mg
Study 309-US

The Clinical Investigators listed below include only those whose site enrolled patients in the above referenced study.

Last Name	First	MI
[redacted]		

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 3

Premarin .45 mg & .3 mg
Study 309-US

Letters requesting Financial Disclosure were sent to the Clinical Investigators listed below as their site enrolled patients in the above referenced study. If no reponse was received from the initial request, additional attempts were performed (such as mail, phone, fax, e-mail) in order to meet the Financial Disclosure requirement. See comments below for explanation as to why Financial Disclosure forms could not be obtained.

Last Name	First	MI	Comments
[redacted]			No longer at site. Forwarding address not provided.
[redacted]			No longer at site. Forwarding address not provided.
[redacted]			No longer at site. Forwarding address not provided.
[redacted]			No longer at site. Forwarding address not provided.
[redacted]			Incapacitated.
[redacted]			No longer at site. Forwarding address not provided.
[redacted]			No longer at site. Forwarding address not provided.
[redacted]			No longer at site. Forwarding address not provided.
[redacted]			Has not responded to several requests.

PREMARIN .45 MG & .3 MG SUBMISSION

Amount Paid 2/99 thru 7/01

Investigator Name	Study #	Visiting Professors	CME	Honoraria/Travel	Consultant Meeting	Total
Carr, Bruce	309-US	[redacted]		[redacted]		[redacted]
Montgomery-Rice, Valerie	309-US	[redacted]		[redacted]		[redacted]
Thorneycroft, Ian	309-US	[redacted]		[redacted]		[redacted]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning Bruce Carr, MD (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study Premarin 045 mg & .3 mg (*Name of*) Study 309 - US (*clinical study*), is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Joseph S. Camardo, M.D. Mr. Robert Haller	Sernior Vice President - Clinical R & D Vice President - R & D Finance
FIRM/ORGANIZATION Wyeth-Ayerst Research	
SIGNATURE	DATE September 27, 2001

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

Created by Electronic Document Services USDHHS (301) FF

Attachment
FDA Form 3455 - Disclosure: Financial Interests and Arrangements of Clinical Investigators

Premarin/MPA (HOPE Study)

Bruce R. Carr, M.D., University of Texas Southwestern Medical Center, Dallas, TX was a Principal Investigator in the HOPE Study and has received from Wyeth-Ayerst Research a total of approximately [redacted] for his participation in the visiting Professor Program and for travel reimbursement. Payments for study-related procedures as defined by the Protocol were made to UT southwestern Grants Management as specified in the contract. Dr. Carr's specific role in the clinical program is outlined below.

Dr. Carr was listed as the Principal Investigator along with two other subinvestigators conducting the study at UT Southwestern. In this capacity, Dr. Carr was responsible for the clinical care and management of outpatients seeking treatment for menopausal symptoms. His center enrolled a total of 50 patients. The patients were randomly assigned to one of eight possible regimens of either Premarin alone (3 regimens), Premarin + medroxyprogesterone acetate (4 regimens) and placebo. The site was instructed to randomize patients in ascending order in sequence of their drug randomization codes. The Protocol requires numerous laboratory procedures and endometrial biopsies by outside laboratories, mammograms as well as other procedures to ensure the safety of the patients. Dr. Carr was not involved in the analysis of any safety and/or efficacy data nor is it anticipated that he will directly benefit from the sale of this product. Dr. Carr and his associates, the patients and Wyeth-Ayerst were blinded to the medication the patients were taking.

Therefore, the financial assets received by Dr. Carr were not likely to have influenced his medical assessment of the primary endpoints of the study (prevention of bone loss and reduction in the incidence of endometrial hyperplasia) or his assessment of key safety parameters (laboratory procedures, mammograms and physical and gynecologic exams)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning Valerie Montgomery-Rice (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study Premarin 045 mg & .3 mg (*Name of clinical study*) Study 309 - US, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Joseph S. Camardo, M.D. Mr. Robert Haller	Sernior Vice President - Clinical R & D Vice President - R & D Finance
FIRM/ORGANIZATION Wyeth-Ayerst Research	
SIGNATURE	DATE
	September 27, 2001

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

Created by Electronic Document Services (DSDHHS) (3/01) FF

Attachment
FDA Form 3455 - Disclosure: Financial Interests and Arrangements of Clinical Investigators

Premarin/MPA (HOPE Study)

Valerie Montgomery-Rice, M.D., University of Kansas Medical Center, Kansas City, KS was a Principal Investigator in the HOPE Study from September 1995 until July 1997 and as a Subinvestigator upon her return in 1998 to the University. Dr. Montgomery-Rice has received from Wyeth-Ayerst Research a total of approximately [redacted] for her participation in the visiting Professor Program and for travel reimbursement or honoraria for the period 2/99 through 7/01. Payments for study-related procedures as defined by the Protocol were made to the University of Kansas Medical Center Research Institute, Kansas City, KS as specified in the contract. Dr.Montgomery-Rice's specific role in the clinical program as both a Principal Investigator and Subinvestigator is outlined below.

Dr. Montgomery-Rice was listed as both a Principal Investigator and Subinvestigator along with approximately four other investigators who were filed at some time on the Form 1572 from the University of Kansas Medical Center. In this capacity, Dr. Montgomery-Rice was responsible for the clinical care and management of outpatients seeking treatment for menopausal symptoms. Her center enrolled a total of 72 patients (48 in the basic study and 24 in the substudy). The patients were randomly assigned to one of eight possible regimens of either Premarin alone (3 regimens), Premarin + medroxyprogesterone acetate (4 regimens) and placebo. The site was instructed to randomize patients in ascending order in sequence of their drug randomization codes. The Protocol requires numerous laboratory procedures and endometrial biopsies by outside laboratories, mammograms as well as other procedures to ensure the safety of the patients. Dr. Montgomery-Rice was not involved in the analysis of any safety and/or efficacy data nor is it anticipated that she will directly benefit from the sale of this product. Dr. Montgomery-Rice and her associates, the patients and Wyeth-Ayerst were blinded to the medication the patients were taking.

Therefore, the financial assets received by Dr. Montgomery Rice were not likely to have influenced her medical assessment of the primary endpoints of the study (prevention of bone loss and reduction in the incidence of endometrial hyperplasia) or her assessment of key safety parameters (laboratory procedures, mammograms and physical and gynecologic exams).

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning Ian Thorneycroft, MD (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study Premarin 045 mg & .3 mg (*Name of clinical study*), is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Joseph S. Camardo, M.D. Mr. Robert Haller	Sernior Vice President - Clinical R & D Vice President - R & D Finance
FIRM/ORGANIZATION Wyeth-Ayerst Research	
SIGNATURE	DATE
	September 27, 2001

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

Created by Electronic Document Services (HHS 4.0)

Attachment
FDA Form 3455 - Disclosure: Financial Interests and Arrangements of Clinical Investigators

Premarin/MPA (HOPE Study)

Ian Thorneycroft, M.D., University of South Alabama, Mobile, AL, was a Principal Investigator in the HOPE Study and has received from Wyeth-Ayerst Research a total of approximately [redacted] for his participation in the visiting Professor Program and for travel reimbursement. Payments for study-related procedures as defined by the Protocol were made to South Alabama Medical Science Foundation at the University of Alabama, Mobile, AL as specified in the contract. Dr. Thorneycroft's specific role in the clinical program is outlined below.

Dr. Thorneycroft was listed as the Principal Investigator along with ten other subinvestigators who were filed at some time on the Form 1572 from the University of South Alabama. In this capacity, Dr. Thorneycroft was responsible for the clinical care and management of outpatients seeking treatment for menopausal symptoms. His center enrolled a total of 29 patients. The patients were randomly assigned to one of eight possible regimens of either Premarin alone (3 regimens), Premarin + medroxyprogesterone acetate (4 regimens) and placebo. The site was instructed to randomize patients in ascending order in sequence of their drug randomization codes. The Protocol requires numerous laboratory procedures and endometrial biopsies by outside laboratories, mammograms as well as other procedures to ensure the safety of the patients. Dr. Thorneycroft was not involved in the analysis of any safety and/or efficacy data nor is it anticipated that he will directly benefit from the sale of this product.. Dr. Thorneycroft and his associates, the patients and Wyeth-Ayerst were blinded to the medication the patients are taking.

Therefore, the financial assets received by Dr. Thorneycroft were not likely to have influenced his medical assessment of the primary endpoints of the study (prevention of bone loss and reduction in the incidence of endometrial hyperplasia) or his assessment of key safety parameters (laboratory procedures, mammograms and physical and gynecologic exams).

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning [redacted], who participated as a clinical investigator in the submitted study Premarin 045 mg & .3 mg (*Name of clinical investigator*; *Name of clinical study*) Study 309 - US, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- [redacted] any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- [redacted] any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- [redacted] any proprietary interest in the product tested in the covered study held by the clinical investigator;
- [redacted] any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Joseph S. Camardo, M.D. Mr. Robert Haller	Sernior Vice President - Clinical R & D Vice President - R & D Finance
FIRM/ORGANIZATION Wyeth-Ayerst Research	
SIGNATURE	DATE September 27, 2001

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

Created by Electronic Document Services USDHHS (301) EF

Attachment
FDA Form 3455 – Disclosure: Financial Interests and Arrangements of Clinical Investigators

[redacted] M.D., was listed as a subinvestigator associated with [redacted] Ph.D., M.H.S., [redacted] Dr. [redacted] has admitted on his Financial Disclosure Form that he holds stock in American Home Products in an amount greater than [redacted]

Dr [redacted] was listed as a subinvestigator along with five other subinvestigators who participated in the study. Dr. [redacted] involvement in the study began approximately February 1999, roughly four months after enrollment had been completed. Dr [redacted] enrolled a total of 46 patients with 40 patients active in February 1999. Dr. [redacted] role was to assist with the management of outpatients seeking treatment for menopausal symptoms. The patients were randomly assigned to one of eight possible regimens of either Premarin alone (3 regimens), Premarin + medroxyprogesterone acetate (4 regimens) and placebo. The site was instructed to randomize patients in ascending order in sequence of their drug randomization codes. The Protocol requires numerous laboratory procedures and the analysis of endometrial biopsies by outside laboratories, mammograms as well as the procedures to ensure the safety of the patients. Dr. [redacted] was not involved in the analysis of any safety and/or efficacy data nor is it anticipated that he will directly benefit from the sale of this product. Dr. [redacted] Dr. [redacted] and all of the other subinvestigators, the patients, and Wyeth-Ayerst were blinded to the medication the patients are taking.

Therefore, the financial assets realized by Dr [redacted] are not likely to have influenced his medical assessment of the primary endpoints of the study (prevention of bone loss and reduction in the incidence of endometrial hyperplasia) or his assessment of key safety parameters (laboratory procedures, mammograms and physical and gynecologic exams).

NDA REGULATORY FILING REVIEW/MINUTES

NDA Number, Requested Trade Name, Generic Name and Strengths (modify as needed for an efficacy supplement and include type):

Applicant: Wyeth-Ayerst Research

Date of Application: December 17, 2001
Date of Receipt: December 18, 2001
Date of Filing Meeting: February 11, 2002
Filing Date: February 16, 2002

Indication(s) requested: Prevention of postmenopausal osteoporosis

Type of Application: Full NDA __X__ Supplement _____
(b)(1) __X___ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classifications: Osteoporosis-HRT
Review Status: Standard
Resubmission after a withdrawal or refuse to file: N/A
Chemical Classification: 3
Other (orphan, OTC, etc.): N/A

User Fee Status: Paid
Form 3397 (User Fee Cover Sheet) submitted: Yes
User Fee ID# 4186
Clinical data? YES
Date clock started after UN: N/A

User Fee Goal date: October 18, 2002

Action Goal Date (optional) _____

Note: If an electronic NDA: all certifications require a signature and must be in paper.

- Does the submission contain an accurate comprehensive index? YES

- Form 356h included with authorized signature? YES
  If foreign applicant, the U.S. Agent must countersign or submit a separate certification.

- Submission complete as required under 21 CFR 314.50? YES
  If no, explain:

- If electronic NDA, does it follow the Guidance? YES

- Patent information included with authorized signature? YES

- Exclusivity requested? NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES
  If foreign applicant, the U.S. Agent must countersign or submit a separate certification.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ..."

- Financial Disclosure included with authorized signature? YES
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign or submit a separate certification.

- Pediatric Rule appears to be addressed for all indications? YES

- Pediatric assessment of all ages? YES
  (If multiple indications, answer for each indication.)
  If NO, for what ages was a waiver requested? _____
  For what ages was a deferral requested? _____

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? YES
If not, have the Document Room make the corrections.

List referenced IND numbers: IND [redacted] and IND [redacted]

End-of-Phase 2 Meeting? NO
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? NO
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC?	NO
Trade name and labeling (PI) sent to ODS?	NO
Advisory Committee Meeting needed?	NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES_____ NO _____

Chemistry

• Did sponsor request categorical exclusion for environmental assessment?	YES
• EA consulted to Nancy Sager (HFD-357)?	NO
• Establishment Evaluation Request (EER) package submitted?	YES
• Parenteral Applications Consulted to Sterile Products (HFD-805)?	N/A

505(b)(2) N/A

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)?
Yes ____ No _____
(Normally, FDA will refuse-to-file such applications.)

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
Yes _____ No _____
If yes, the application must be refused for filing under 314.54(b)(1)

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?
Yes _____ No _____
If yes, the application must be refused for filing under 314.54(b)(2)

For a 505(b)(2) application, which of the following does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?
- Submit a statement as to whether the listed drug(s) identified have received a period of marketing exclusivity?
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

If the application is a 505(b)(2), has the Director, Div. of Regulatory Policy II, HFD-007 been notified? YES _____ NO _____

ATTACHMENT

FILING MEETING MINUTES

DATE: February 11, 2002

BACKGROUND:

This is a Type 6 NDA. The original NDA was approved in DRUDP (HFD-580). The application is for a new indication, prevention of postmenopausal osteoporosis, and an addition of a new low strengths, 0.45 mg tablet.

ASSIGNED REVIEWERS:

Discipline	Reviewer
Medical:	Eric Colman
Secondary Medical:	NN
Statistical:	Cynthia Liu
Pharmacology:	NN
Statistical Pharmacology:	NN
Chemist:	Yvonne Yang
Environmental Assessment (if needed):	Yvonne Yang
Biopharmaceutcal:	Johnny Lau
Microbiology, sterility:	NN
Microbiology, clinical (for antimicrobial products only):	NN
DSI:	NN
Project Manager:	Samuel Wu
Other Consults:	CMC to HFD-580 (David Lin)

Is the application affected by the application integrity policy (AIP) NO

Per reviewers, all parts in English, or English translation? YES

1. CLINICAL – File
   - Clinical site inspection needed: NO

2. STATISTICAL – File

3. BIOPHARMACEUTICS – File
   - Biopharm. inspection Needed: NO

4. CHEMISTRY – File
   - Establishment ready for inspection? Pending

REGULATORY CONCLUSIONS/DEFICIENCIES:

The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

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
9/11/02 11:15:40 AM
CSO

MEDICAL REVIEW OF COMPLETE RESPONSE to APRROVABLE LETTER

NDA: 21-417, N-000-50

DRUG: Conjugated estrogens (Premarin®) 0.3mg, 0.45mg

INDICATION: Prevention of Osteoporosis

COMPANY: Wyeth Pharmaceuticals

DATE OF SUBMISSION: January 15, 2003

DATE OF REVIEW: July 14, 2003

Wyeth Pharmaceuticals has submitted this complete response to the approvable letter dated October 18, 2002. Issues addressed include:

1) Chemistry – cGMP inspections were conducted at the Guayama, Puerto Rico site in March 2002 and at the Rouses Point, New York site in May 2002. Corrective actions were taken at the New York site and that site is now acceptable.

2) Labeling - The labeling changes proposed by the company have been reviewed in conjunction with the Division of Reproductive and Urologic Drug Products. The current submitted label is acceptable.

3) Safety data – The final study report for study 0731D2-309-US was submitted and was reviewed in the initial review of the Type 6 NDA 21-417. A four month safety update was submitted on April 17, 2002, and has been reviewed. For the period of March 2002 through December 2002, there have been no additional safety reports and therefore, no new patterns, trends or significant changes in the safety profile of Premarin 0.3mg and 0.45mg have been identified. At this time, there are no ongoing clinical trials for Premarin 0.3mg and 0.45mg. Premarin 0.3mg and 0.45mg has not been approved or labeled for the prevention of osteoporosis in any worldwide market.

Conclusion: No new safety issues have been identified.

Recommendation: Approval of Premarin 0.3mg and 0.45mg for the prevention of osteoporosis.

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

/s/

Theresa Kehoe
7/15/03 02:56:05 PM
MEDICAL OFFICER

Eric Colman
7/16/03 10:23:21 AM
MEDICAL OFFICER
Concur with Dr. Kehoe

MEMORANDUM

May 27, 2003

NDA: 21-417

DRUG: Premarin 0.3 mg and 0.45 mg

COMPANY: Wyeth Ayerst

DATE OF SUBMISSIONS: 04/17/02 and 01/15/03

INDICATION: Prevention of Postmenopausal Osteoporosis

RE: Safety Updates

In these two submissions, Wyeth Ayerst provides safety update information for the above referenced pending supplemental NDA.

In the April 2002 submission, two IND safety reports are included for subjects who received premarin + MPA. One event was coded as ischemic colitis and the other as transient ischemic attack.

There was no new safety information to report in the January 2003 submission.

Comment

No new safety information has been submitted that materially changes the risk-to-benefit profile for the 0.3 mg or 0.45 mg doses of premarin. I recommend approval of this supplement.

Eric Colman, MD

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

/s/

Eric Colman
5/27/03 12:20:24 PM
MEDICAL OFFICER

David Orloff
6/1/03 06:59:08 PM
MEDICAL OFFICER
Concur with Dr. Colman

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21417/000
Stamp: 18-DEC-2001
Regulatory Due: 16-JUL-2003
Applicant: WYETH AYERST LABORATORIES
8299
PHILADELPHIA, PA 191018299
Priority: 3S
Org Code: 510

Action Goal:
District Goal: 19-AUG-2002
Brand Name: PREMARIN(CONJUGATED ESTROGENS)0.3/0.45MG
Estab. Name:
Generic Name: CONJUGATED ESTROGENS

Dosage Form: (TABLET)
Strength: SEE COMMENTS

Application Comment: THE CURRENT APPROVED DOSAGE STRENGTHS ARE 0.3, 0.625, 0.9, 1.25, AND 2.5 MG. THIS NDA IS FOR THE APPROVAL OF THE 0.3 MG STRENGTH FOR A DIFFERENT INDICATION, AND THE 0.45 MG STRENGTH, WHICH WAS PREVIOUSLY SUBMITTED TO NDA 4-782, BUT WAS NOT APPROVED. (on 12-FEB-2002 by D. LIN (HFD-580) 301-827-4230)

FDA Contacts: S. WU (HFD-510) 301-827-6416 , Project Manager
D. LIN (HFD-580) 301-827-4230 , Review Chemist
S. MARKOFSKY (HFD-510) 301-827-6420 , Team Leader

Overall Recommendation: WITHHOLD on 30-MAY-2002 by P. LEFLER (HFC-130) 301-827-5636
ACCEPTABLE on 08-MAY-2003 by R. WOODS (HFD-322) 301-827-9011

Establishment: 9613692
AYERST ORGANICS INC
R7A 7H2
BRANDON, MANITOBA, CA

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CEX OAI Status: NONE
Estab. Comment: CONJUGATED ESTROGENS DRUG SUBSTANCE MANUFACTURER. DERIVED FROM A NATURAL SOURCE OF PREGNANT MARES' URINE. (on 12-FEB-2002 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	12-FEB-2002				LINDAV
OC RECOMMENDATION	12-FEB-2002			ACCEPTABLE BASED ON PROFILE	GARCIAM

Establishment: 2650135
AYERST WYETH PHARMACEUTICALS
STATE ROAD 3 KM 142.1
GUAYAMA, PR 00784

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: TTR OAI Status: NONE
Estab. Comment: DRUG PRODUCT MANUFACTURER. INCLUDES FINAL GRANULATION, COMPRESSION OF TABLETS. (on 12-FEB-2002 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	12-FEB-2002				LINDAV
SUBMITTED TO DO	12-FEB-2002	10D			DAMBROGIOJ
ASSIGNED INSPECTION	12-FEB-2002	PS			MTORRES
INSPECTION SCHEDULED	13-FEB-2002		18-MAR-2002		MTORRES
INSPECTION PERFORMED	19-MAR-2002		19-MAR-2002		MTORRES

The GMP and NDA pre-approval inspection of this Rx and OTC human drugs manufacturer was conducted as per District workplans and as per FACTS Assignment #1056262 for a pre-approval inspection of three NDA's. An NDA Post-Approval inspection was conducted to cover the process validation of [redacted] and [redacted]. Follow-up was given to

the firm's investigation regarding Premarin [redacted] dissolution failures, several NDA Field Alert Reports, DQRS complaints and one recall of [redacted]. Coverage was given under CP's 7356.002, 7346.832, and 7356.021.

The previous inspection dated 1/8-2/12/01 was conducted to follow-up the dissolution failures associated with Premarin Tablets, and a Class I Recall related to the [redacted]. The inspection identified the following objectionable conditions: failure to provide adequate justification for the in-process controls used during compression of Premarin cores; the Quality Control Unit failed to ensure the adequacy, accuracy and integrity of records; and inadequate operational qualifications of the [redacted] machines. The firm's response dated 2/28/01 was not considered adequate. On 4/21/01 SJN-DO held a regulatory meeting with the firm's officials, and the inspection was classified VAI.

The current inspection did not disclose any significant objectionable conditions and no FDA-483 was issued. Two verbal observations related to the use of [redacted] and the failure to meet the timeframes for [redacted] established in the Validation Master Plan were discussed with the firm's VP and General Manager. Mr. Martinez-Mora provided written documents with the proposed corrections. The current inspection confirmed correction to the previous inspection observations.

No samples were collected during this inspection.

INSPECTION PERFORMED	09-APR-2002	19-MAR-2002		MTORRES
DO RECOMMENDATION	09-APR-2002		ACCEPTABLE	MTORRES
			INSPECTION	

COMPREHENSIVE GMP INSPECTION FOUND NO DEVIATIONS; CORRECTIVE ACTIONS ASSOCIATED WITH PROCESS AT GUAYAMA HAVE BEEN IMPLEMENTED AND FOUND ADEQUATE; VALIDATION PENDING RESOLUTION OF ISSUES AFFECTING DISSOLUTION I PREMARIN PRODUCTS; PRODUCT IS CO-MAUFACTURED AT ROUSES POINT.

OC RECOMMENDATION	09-APR-2002	ACCEPTABLE	DAMBROGIOJ
		DISTRICT RECOMMENDATION	

Establishment: 1310337
WYETH LABORATORIES INC
64 MAPLE ST
ROUSES POINT, NY 12979

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER

Profile: CEX OAI Status: NONE

Estab. Comment: PERFORMS FINAL STEP IN MANUFACTURING BULK DRUG SUBSTANCE. (on 12-FEB-2002 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	12-FEB-2002				LINDAV
OC RECOMMENDATION	12-FEB-2002			ACCEPTABLE	DAMBROGIOJ
				BASED ON PROFILE	

Profile: TTR OAI Status: POTENTIAL OAI

Estab. Comment: DRUG PRODUCT MANUFACTURER. CAN PERFORM THE ENTIRE TABLETING PROCESS. (on 12-FEB-2002 by D. LIN (HFD-580) 301-827-4230)

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	12-FEB-2002				LINDAV
SUBMITTED TO DO	12-FEB-2002	10D			DAMBROGIOJ
DO RECOMMENDATION	15-FEB-2002			WITHHOLD	JPODSADO
				PREVIOUS DEVIATIONS PERSIST	

THE LAST GMP INSPECTION (2/1/2001) IN FACTS CLASSIFIES THE PROFILE CLASS "TTR" AS UNACCEPTABLE.

OC RECOMMENDATION	30-MAY-2002			WITHHOLD	ALCOCKP
				DISTRICT RECOMMENDATION	

CONTINUED CGMP PROBLEMS WITH PREMARIN [redacted] WARRANT WITHHOLD OF THIS APPLICATION. UNTIL CGMP ISSUES ARE RESOLVED - FIRM IS UNACCEPTABLE FROM GMP STANDPOINT FOR THESE 2 PRODUCTS.

OC RECOMMENDATION	08-MAY-2003			ACCEPTABLE	WOODSR
				CDER POLICY CHANGE	
				FIRM RESPONSE TO DEFIC.	
				ADEQUA	

THIS ACCEPTABLE RECOMMENDATION PERTAINS ONLY TO LOW DOSE STRENGTHS OF WYETH'S CONJUGATED ESTROGEN TABLETS, SUBJECT OF THIS APPLICATION. NOTE THE DISTRICT OFFICE AND PRIOR OC RECOMMENDATIONS OF WITHHOLD FOR THE GMP STATUS OF THIS APPLICATION BASED ON THE LAST GMP INSPECTION OF WYETH'S ROUSES POINT FACILITY. THE REMARKS SECTION OF THE PRIOR OC WITHHOLD RECOMMENDATION NOTES THAT THERE ARE CONTINUED CGMP PROBLEMS THAT WARRANT WITHHOLDING THIS APPLICATION UNTIL THE CGMP ISSUES ARE RESOLVED AT WYETH'S ROUSES POINT, NY FACILITY (CFN 1310337)
HOWEVER, CDER/OC HAS EVALUATED THE OUTSTANDING CGMP ISSUES AND PRIOR DO AND CDER/OC WITHHOLD RECOMMENDATIONS IN CONJUNCTION WITH THE FOLLOWING INFORMATION PROVIDED THROUGH HFD-300: IN LIGHT OF RECENT FINDINGS FROM THE WHI STUDY AND KNOWN DOSE-RESPONSE DATA FOR ESTROGEN-CONTAINING PRODUCTS, LOWER STRENGTHS OF PREMPRO AND PREMARIN CONTAINING PRODUCTS HAVE THEORETICAL PUBLIC HEALTH BENEFITS OVER HIGHER STRENGTHS. ADDITIONALLY, RECENT PRODUCT FAILURES ONLY INVOLVE [redacted] . BASED ON OUR EVALUATION OF THE ABOVE INFO AND DIRECTIONS FROM HFD-300, EES HAS BEEN UPDATED TO REFLECT AN ACCEPTABLE GMP STATUS FOR THIS APPLICATION. AGAIN, THIS ACCEPTABLE RECOMMENDATION ONLY APPLIES TO LOW DOSE STRENGTHS OF THIS APPLICATION. (I.E. LESS THAN .625 MG)

ENVIRONMENTAL ASSESSMENT — Satisfactory

The sponsor has requested a categorical exclusion under 21 CFR 25.31(a). In addition, the sponsor states that no "extraordinary circumstances" exist as defined in 21 CFR 25.15(d).