CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-396

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

NDA 21-396

Prempro™/Premphase®
(conjugated estrogens/medroxyprogesterone acetate tablets)

Wyeth-Ayerst Laboratories

Sarah C. Pope, Ph.D.
Division of Metabolism and Endocrine Drug Products
(HFD-510)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-396

2. REVIEW #2:

3. REVIEW DATE: 10-MAR-2003

4. REVIEWER: Sarah C. Pope, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	24-SEP-2001
Amendment	25-JAN-2002
Amendment	17-JUN-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Complete response to AE action	03-DEC-2002
Amendment	02-APR-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Wyeth-Ayerst Laboratories
Address:	P.O. Box 8299 Philadelphia, PA 19101-8299
Representative:	N/A
Telephone:	484-865-3743

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Prempro™/Premphase®
b) Non-Proprietary Name (USAN):conjugated estrogens/medroxyprogesterone acetate tablets
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 6
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Hormone, for the prevention of osteoporosis

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 0.3 mg CE/1.5 mg MPA, 0.45 mg/CE/1.5 mg MPA

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
___X___SPOTS product – Form Previously Submitted

_____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

a. Conjugated estrogens (CE): see USP 26

b. Medroxyprogesterone acetate (MPA): Pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-, (6α)- (See USP for structural formula)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	Medroxyprogesterone acetate	1	Adequate	23-FEB-2003	Reviewed by Dr. S. Pope
[redacted]	II	[redacted]	Medroxyprogesterone acetate	1	Adequate	21-MAY-2002	Reviewed by Dr. D. Lin
[redacted]	III	[redacted]	[redacted]	3	Adequate	29-JUL-1999	Reviewed by Dr. D. Klein
[redacted]	III	[redacted]	[redacted]	3	Adequate	23-APR-1998	Reviewed by Dr. A. Al-Hakim
[redacted]	III	[redacted]	[redacted]	3	Adequate	27-SEP-2000	Reviewed by Dr. R. Lostritto
[redacted]	III	[redacted]	[redacted]	3	Adequate	27-MAR-2001	Reviewed by Dr. D. Lin
[redacted]	III	[redacted]	[redacted]	7	N/A	N/A	The relevant information has been transferred to DMF [redacted]
[redacted]	III	[redacted]	[redacted]	7	N/A	N/A	The relevant information has been transferred to DMF [redacted]
[redacted]	III	[redacted]	[redacted]	3	Adequate	25-MAR-2001	Reviewed by Dr. D. Lin
[redacted]	III	[redacted]	[redacted]	3	Adequate	26-MAR-2001	Reviewed by Dr. D. Lin
[redacted]	III	[redacted]	[redacted]	3	Adequate	9-FEB-2001	Reviewed by Dr. D. Klein
[redacted]	III	[redacted]	[redacted]	3	Adequate	28-SEP-2000	Reviewed by Dr. D. Klein
[redacted]	III	[redacted]	[redacted]	3	Adequate	24-MAR-2000	Reviewed by Dr. D. Klein
[redacted]	III	[redacted]	[redacted]	3	Adequate	31-MAR-	Reviewed by

Chemistry Review Data Sheet

					2001	Dr. D. Lin
	III		3	Adequate	2-MAR-2000	Reviewed by Dr. D. Christodoulou
	III		3	Adequate	3-AUG-2001	Reviewed by Dr. S. Peri
	III		3	Adequate	11-AUG-2000	Reviewed by Dr. R. Trimmer
	III		3	Adequate	20-APR-2000	Reviewed by Dr. S. Markovsky
	III		3	Adequate	31-MAR-01	Reviewed by Dr. D. Lin

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Original NDA	NDA 4-782	Approved NDA for Premarin Tablets, the core tablet for the Prempro drug product
Patent	36,247	Drug substance, drug product formulation, method of use. Expiration date: 2-May-2006. Patent owner: Wyeth-Ayerst Laboratories
Patent	5,547,948	Drug substance, drug product formulation, method of use. Expiration date: 17-Jan-2015. Patent owner: Wyeth-Ayerst Laboratories
Patent	5,210,081	Drug substance, drug product formulation, method of use. Expiration date: 26-Feb-2012. Patent owner: Wyeth-Ayerst Laboratories

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	3-FEB-2003	M. Garcia
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Methods previously validated for approved strengths		
OPDRA	N/A		
EA	Categorical exclusion granted		David T. Lin, Ph.D. (see Chemistry Review #1)
Microbiology	N/A		

The Chemistry Review for NDA 21-396

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing and controls standpoint, this NDA may be **Approved.**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

1. The Agency has agreed to an interim release and stability specification for CE dissolution at the ——— timepoint. This interim acceptance criterion is ———
2. The Sponsor has committed to the Dissolution Surveillance Program for the dissolution of conjugated estrogens in the 0.3 mg/1.5 mg and 0.45 mg/1.5 mg Premarin/MPA drug product. In this commitment, every packaged lot will be tested for CE dissolution at ——— intervals. This surveillance program will be performed through expiration of the product.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:
Prempro is an solid oral tablet and is currently approved in three dosage strengths for the treatment of vaginal and vulvar atrophy associated with menopause. The approved Prempro dosages include 0.625 mg of conjugated estrogens (CE), USP, combined with either 2.5 mg or 5 mg of medroxyprogesterone acetate (MPA). An additional lower dose (0.45 mg CE/1.5 mg MPA) was recently approved by the Agency (12-Mar-2003).

This NDA proposes the addition of two new Prempro dosage strengths, 0.3 mg CE/1.5 mg MPA and 0.45 mg CE/1.5 mg MPA for the prevention of post-menopausal osteoporosis. The 0.3/1.5 mg dosage strength is a cream-colored, ——— coated tablet. The 0.45/1.5 mg dosage strength is a gold-colored, ——— coated tablet. Both tablets will be marketed in one continuous dosing regimen consisting of 28 consecutive tablets of the prescribed dosage.

The Prempro tablet consists of a core Premarin tablet containing Conjugated Estrogens, USP. The Premarin core is coated with a ——— The other active component, MPA, is incorporated into an outer ——— to yield the finished drug product.

Executive Summary Section

The drug product is co-manufactured at the [redacted] and the Wyeth Pharmaceuticals facility in Guayama, Puerto Rico. Acceptable specifications have been provided to ensure product quality at release.

Once released, the drug product will be packaged in [redacted] configurations: [redacted] 28-count polystyrene dial dispensers will be the marketed packaging configurations. The relevant DMFs for [redacted] container/closure systems have been reviewed and determined to be adequate for this drug product.

Based on the stability data provided in the first review cycle for this NDA, a 24-month expiry has been granted for storage at 25 °C/60% RH (controlled room temperature).

Drug Substance:
The conjugated estrogens (CE) drug substance is a mxture of conjugated estrogens derived from [redacted] All of the pertinent CMC information is cross-referenced to NDA 4-782 (Premarin Tablets).

Medroxyprogesterone acetate (MPA) is a well-characterized and compendial progestin manufactured by [redacted] The DMFs for these two sources of MPA have been reviewed and found to be acceptable for use in the drug product. The manufactured MPA is tested and released in accordance with criteria outlined in the current USP monograph. The proposed release specifications are adequate to control the quality of the drug product.

Stability data to support the retest period for MPA have been provided in the corresponding DMFs.

B. Description of How the Drug Product is Intended to be Used

Prempro is administered as a single tablet, once daily, for the prevention of bone loss in postmenopausal women with intact uteri.

The drug product expiry is 24 months when stored at 20-25 °C (controlled room temperature).

C. Basis for Approvability or Not-Approval Recommendation

From a CMC standpoint, this NDA may be Approved. This recommendation is based on the satisfactory resolution of the previous cGMP non-compliance of the [redacted] facility. As of 3-FEB-2003, this NDA has been given an overall acceptable recommendation from the Office of Compliance.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: YYang/SPope/19-MAR-2003
ChemistryTeamLeaderName/Date: DLin/20-APR-2003
ProjectManagerName/Date: KJohnson/20-APR-2003

C. CC Block

HFD-510/Division File/NDA 21-396
HFD-580/DLin/SPope
HFD-580/KSherrod
HFD-510/KJohnson

5 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Chemistry Assessment Section

D(s0FO&k4SO&17.27c66F 24-MAR-2003
5

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 21396/000	Action Goal:	
Stamp:	25-SEP-2001	District Goal:	26-MAY-2002
Regulatory Due:	04-JUN-2003	Brand Name:	[redacted] (CONJUG
Applicant:	WYETH-AYERST	Estab. Name:	ATED ESTROGENS/M
	NO CITY, , XX	Generic Name:	CONJUGATED
	3S		ESTROGENS/MEDROXYPROGEST
Priority:	510		ERONE
Org Code:		Dosage Form:	(TABLET)
		Strength:	SEE COMMENTS

Application Comment: THE CURRENT DOSAGE STRENGTH IS 0.625 MG CONJUGATED ESTROGENS/2.5 MG OR 5 MG MEDROXYPROGESTERONE ACETATE FOR A OSTEOPOROSIS INDICATION. THIS SUPPLEMENT IS FOR TWO NEW DOSAGE STRENGTH TABLETS: 0.3 MG OR 0.45 MG CONJUGATED ESTROGENS/1.5 MG MEDROXYPROGESTERONE ACETATE. (on 26-NOV-2001 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: ACCEPTABLE on 03-FEB-2003by R. WOODS (HFD-322)301-827-9011
WITHHOLD on 04-JUN-2002by J. D AMBROGIO(HFD-322)301-827-9054

Establishment: [redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile: CEX OAI Status: NONE

LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-NOV-2001				LINDAV
OC RECOMMENDATION	27-NOV-2001			ACCEPTABLE BASED ON PROFILE	GARCIAM

Establishment: CFN 2650135 FEI 3003108339

AYERST WYETH PHARMACEUTICALS

STATE ROAD 3 KM 142.1

GUAYAMA, PR 00784

DMF No: AADA:

APPEARS THIS WAY
ON ORIGINAL

24-MAR-2003 FDA CDER ERS

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TTR OAI Status: NONE

Estab. Comment: DRUG PRODUCT MANUFACTURER (on 26-NOV-2001 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-NOV-2001				LINDAV
SUBMITTED TO DO	27-NOV-2001	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	07-DEC-2001	PS			MTORRES
INSPECTION SCHEDULED	13-FEB-2002		18-MAR-2002		MTORRES
INSPECTION PERFORMED	09-APR-2002		10-MAR-2002		MTORRES
DO RECOMMENDATION	09-APR-2002			ACCEPTABLE INSPECTION	MTORRES

COMPREHENSIVE GMP COVERAGE FOUND CORRECTIVE ACTIONS HAVE BEEN IMPLEMENTED FOR PORTIONS OF PROCESS PERFORMED AT SITE. VALIDATION NOT COMPLETED PENDING RESOLUTION OF DISSOLUTION ISSUES RELATED TO PROCESS AT [redacted]. THIS PRODUCT IS CO-MANUFACTURED AT BOTH LOCATIONS. INSPECTION IS ASSIGNED AND PENDING RECOMMENDATION FROM MTK-DO.

OC RECOMMENDATION	09-APR-2002			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: [redacted] FEI [redacted]

[redacted]

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile: CSN OAI Status: NONE

Estab. Comment: [redacted] (on 26-NOV-2001 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator

CHEMISTRY REVIEW

Chemistry Assessment Section

SUBMITTED TO OC	26-NOV-2001		LINDAV
SUBMITTED TO DO	27-NOV-2001 GMP		GARCIAM
DO RECOMMENDATION	29-NOV-2001	ACCEPTABLE BASED ON FILE REVIEW	GARCIAM
8/03/01			
OC RECOMMENDATION	29-NOV-2001	ACCEPTABLE DISTRICT RECOMMENDATION	GARCIAM

Establishment: [redacted] FEI [redacted]

DMF No: [redacted] AADA:

APPEARS THIS WAY
ON ORIGINAL

24-MAR-2003 FDA CDER ESS Page 3 of 5

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

Estab. Comment: [redacted] (on 26-NOV-2001 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-NOV-2001				LINDAV
SUBMITTED TO DO	27-NOV-2001	10D			GARCIAM
DO RECOMMENDATION	29-NOV-2001			ACCEPTABLE BASED ON FILE REVIEW 2/21/01	GARCIAM
OC RECOMMENDATION	29-NOV-2001			ACCEPTABLE DISTRICT RECOMMENDATION	GARCIAM

Establishment: [redacted]

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile: CRU OAI Status: NONE

Estab. Comment: [redacted] (on 26-NOV-2001 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-NOV-2001				LINDAV
SUBMITTED TO DO	27-NOV-2001	10D			GARCIAM
DO RECOMMENDATION	29-NOV-2001			ACCEPTABLE BASED ON FILE REVIEW	GARCIAM

Establishment: CFN 1310337 FEI 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

APPEARS THIS WAY
ON ORIGINAL

24-MAR-2003 FDA CDER EES Page 4 of 5

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Estab. Comment: CONJUGATED ESTROGENS DRUG SUBSTANCE MANUFACTURER (on 26-NOV-2001 by D. LIN (HFD-580) 301-827-4236)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-NOV-2001				LINDAV
OC RECOMMENDATION	27-NOV-2001			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Profile: TTR OAI Status: POTENTIAL OAI

Estab. Comment: DRUG PRODUCT MANUFACTURER. (on 26-NOV-2001 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-NOV-2001				LINDAV
SUBMITTED TO DO	27-NOV-2001	10D			DAMBROGIOJ
DO RECOMMENDATION	07-DEC-2001			WITHHOLD PREVIOUS DEVIATIONS PERSIST	JPODSADO

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

OC RECOMMENDATION	30-MAY-2002			WITHHOLD DISTRICT RECOMMENDATION	ALCOCKP

DUE TO CONTINUED CGMP ISSUES WHICH HAVE YET TO BE RESOLVED RE: PREMARIN AND PREMPRO PRODUCTS FIRM IS STILL UNACCEPTABLE FROM CGMP STANDPOINT FOR PREMARIN AND PREMARIN PRODUCTS.

OC RECOMMENDATION	03-FEB-2003			ACCEPTABLE BASED ON PROFILE	WOODSR

THIS CDER/OC ACCEPTABLE RECOMMENDATION ONLY APPLIES TO LOW DOSE STRENGTHS OF WYETH-SQUA PREMPRO (CONJUGATED ESTROGENS/MEDROXYPROGESTERONE ACETATE TABLET) THAT ARE PART OF THE FOLLOWING APPLICATIONS:

NDA 20-527/S-017 (0.45 MG PREMARIN/1.5 MG MEDROXYPROGESTERONE ACETATE (MPA); GOAL DATE OF 03/01/03

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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

/s/

Sarah Pope
4/22/03 01:27:56 PM
CHEMIST

David T. Lin
4/22/03 01:47:03 PM
CHEMIST
I concur.

July 10, 2001

Environmental Assessment

Statement of Compliance

Wyeth-Ayerst Pharmaceuticals states that an Environmental Assessment (EA) for the proposed action, the New Drug Application (NDA 21-396) for the use of Prempro® (conjugated estrogens/medroxyprogesterone acetate combination tablets, 0.3 mg/1.5 mg and 0.45 mg/1.5 mg strengths) for a new indication for the treatment of osteoporosis, is categorically excluded according to 21 CFR 25.31(b).

The aforementioned regulation states that a categorical exclusion is permitted for "Action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph, if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion." The Expected Introduction Concentration (EIC) of conjugated estrogens is below one part per billion. The EIC of medroxyprogesterone acetate is also below one part per billion.

To the best knowledge of Wyeth-Ayerst Pharmaceuticals, no extraordinary circumstances exist associated with the proposed action.

Craig F. Seyfried
Senior Director
Environmental Health & Safety
Wyeth-Ayerst Pharmaceuticals

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

ication:	NDA 21396/000	Action Goal:	
Stamp:	25-SEP-2001	District Goal:	26-MAY-2002
Regulatory Due:	25-JUL-2002	Brand Name:	[redacted] (CONJUG
Applicant:	WYETH-AYERST	Estab. Name:	ATED ESTROGENS/M
	NO CITY, , XX	Generic Name:	CONJUGATED
	3S		ESTROGENS/MEDROXYPROGEST
Priority:	510		ERONE
Org Code:		Dosage Form:	(TABLET)
		Strength:	SEE COMMENTS

Application Comment: THE CURRENT DOSAGE STRENGTH IS 0.625 MG CONJUGATED ESTROGENS/2.5 MG OR 5 MG MEDROXYPROGESTERONE ACETATE FOR A OSTEOPOROSIS INDICATION. THIS SUPPLEMENT IS FOR TWO NEW DOSAGE STRENGTH TABLETS: 0.3 MG OR 0.45 MG CONJUGATED ESTROGENS/1.5 MG MEDROXYPROGESTERONE ACETATE. (on 26-NOV-2001 by D. LIN (HFD-580) 301-827-4230)

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

Overall Recommendation: WITHHOLD on 04-JUN-2002by J. D AMBROGIO(HFD-324)301-827-0062

blishment: [redacted]

DMF No: AADA:
Responsibilities:

Profile: CEX OAI Status: NONE

Estab. Comment: [redacted] (on 26-NOV-2001 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-NOV-2001				LINDAV
OC RECOMMENDATION	27-NOV-2001			ACCEPTABLE BASED ON PROFILE	GARCIAM

Establishment: CFN 2650135 FEI 3003108339
AYERST WYETH PHARMACEUTICALS
STATE ROAD 3 KM 142.1
GUAYAMA, PR 00784

No: AADA:
onsibilities: FINISHED DOSAGE MANUFACTURER

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

File: TTR OAI Status: OAI ALERT

Estab. Comment: DRUG PRODUCT MANUFACTURER (on 26-NOV-2001 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-NOV-2001				LINDAV
SUBMITTED TO DO	27-NOV-2001	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	07-DEC-2001	PS			MTORRES
INSPECTION SCHEDULED	13-FEB-2002		18-MAR-2002		MTORRES
INSPECTION PERFORMED	09-APR-2002		10-MAR-2002		MTORRES
DO RECOMMENDATION	09-APR-2002			ACCEPTABLE INSPECTION	MTORRES

COMPREHENSIVE GMP COVERAGE FOUND CORRECTIVE ACTIONS HAVE BEEN IMPLEMENTED FOR PORTIONS OF PROCESS PERFORMED AT SITE. VALIDATION NOT COMPLETED PENDING RESOLUTION OF DISSOLUTION ISSUES RELATED TO PROCESS AT [redacted] THIS PRODUCT IS CO-MANUFACTURED AT BOTH LOCATIONS. INSPECTION IS ASSIGNED AND PENDING RECOMMENDATION FROM NYK-DO.

OC RECOMMENDATION	09-APR-2002			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: [redacted] FEI [redacted]

No: [redacted] AADA:

Responsibilities: [redacted]

Profile: CSN OAI Status: NONE

Estab. Comment: [redacted] (on 26-NOV-2001 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-NOV-2001				LINDAV
SUBMITTED TO DO	27-NOV-2001	GMP			GARCIAM
DO RECOMMENDATION	29-NOV-2001			ACCEPTABLE BASED ON FILE REVIEW	GARCIAM
8/03/01 OC RECOMMENDATION	29-NOV-2001			ACCEPTABLE DISTRICT RECOMMENDATION	GARCIAM

Establishment: [redacted] FEI

No: [redacted] AADA:

onsibilities:

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

File: CSN OAI Status: NONE

Estab. Comment: [redacted] (on 26-NOV-2001 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-NOV-2001				LINDAV
SUBMITTED TO DO	27-NOV-2001	10D			GARCIAM
DO RECOMMENDATION	29-NOV-2001			ACCEPTABLE BASED ON FILE REVIEW	GARCIAM
2/21/01 OC RECOMMENDATION	29-NOV-2001			ACCEPTABLE DISTRICT RECOMMENDATION	GARCIAM

Establishment: [redacted] FEI

DMF No: AADA:
Responsibilities: [redacted]

Profile: CRU OAI Status: NONE

Comment: [redacted] (on 26-NOV-2001 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-NOV-2001				LINDAV
SUBMITTED TO DO	27-NOV-2001	10D			GARCIAM
DO RECOMMENDATION	29-NOV-2001			ACCEPTABLE BASED ON FILE REVIEW	GARCIAM
4/14/00 OC RECOMMENDATION	29-NOV-2001			ACCEPTABLE DISTRICT RECOMMENDATION	GARCIAM

Establishment: CFN 1310337 FEI 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

Comment: CONJUGATED ESTROGENS DRUG SUBSTANCE MANUFACTURER (on 26-NOV-2001 by D. LIN (HFD-580) 301-827-4230)

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-NOV-2001				LINDAV
OC RECOMMENDATION	27-NOV-2001			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Profile: TTR OAI Status: POTENTIAL OAI

Estab. Comment: DRUG PRODUCT MANUFACTURER. (on 26-NOV-2001 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-NOV-2001				LINDAV
SUBMITTED TO DO	27-NOV-2001	10D			DAMBROGIOJ
DO RECOMMENDATION	07-DEC-2001			WITHHOLD PREVIOUS DEVIATIONS PERSIST	JPODSADO

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

OC RECOMMENDATION	30-MAY-2002			WITHHOLD DISTRICT RECOMMENDATION	ALCOCKP

DUE TO CONTINUED CGMP ISSUES WHICH HAVE YET TO BE RESOLVED RE: PREMARIN AND PREMPRO PRODUCTS - FIRM IS STILL UNACCEPTABLE FROM CGMP STANDPOINT FOR PREMARIN AND PREMARIN PRODUCTS.

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21396/000** Priority: **3S** Org Code: **510**
Stamp: **25-SEP-2001** Regulatory Due: **04-JUN-2003** Action Goal: District Goal: **26-MAY-2002**
Applicant: **WYETH-AYERST** Brand Name: [redacted] **(CONJUGATE D ESTROGENS/M**

NO CITY, , XX

Established Name:
Generic Name: **CONJUGATED ESTROGENS/MEDROXYPROGESTERONE**
Dosage Form: **TAB (TABLET)**
Strength: **SEE COMMENTS**

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:

ACCEPTABLE on 03-FEB-2003 by R. WOODS (HFD-322) 301-827-9011
WITHHOLD on 04-JUN-2002 by J. D AMBROGIO (HFD-322) 301-827-9054

Establishment [redacted]

DMF No:
AADA No:

Profile: **CEX** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **27-NOV-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

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

DMF No:
AADA No:

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **09-APR-2002**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment: [redacted]

DMF No: [redacted]
AADA No:

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Profile: **CSN** OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **29-NOV-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: [redacted] DMF No: [redacted]
AADA No:

Profile: **CSN** OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **29-NOV-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: [redacted] DMF No: [redacted]
AADA No:

Profile: **CRU** OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **29-NOV-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **1310337**
WYETH LABORATORIES INC
64 MAPLE ST
ROUSES POINT, NY 12979
DMF No:
AADA No:

Profile: **CEX** OAI Status: **NONE** Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
Last Milestone: **OC RECOMMENDATION** **DRUG SUBSTANCE OTHER TESTER**
Milestone Date: **27-NOV-2001** **FINISHED DOSAGE MANUFACTURER**
Decision: **ACCEPTABLE** **FINISHED DOSAGE RELEASE TESTER**
Reason: **BASED ON PROFILE**

Profile: **TTR** OAI Status: **POTENTIAL OAI**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **03-FEB-2003**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
FIRM RESPONSE TO DEFIC. ADEQ
