

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-527/s-017

CHEMISTRY REVIEW(S)

CHEMIST REVIEW #2
OF SUPPLEMENT

1. ORGANIZATION: DRUDP HFD-580
2. NDA NUMBER: 20-527/SE2-017
3. SUPPLEMENT NUMBERS/DATES:
Letterdate: 15-June-2000
Stampdate: 15-June-2000
4. AMENDMENTS/REPORTS/DATES:
Letterdate: See list on page 4
Stampdate: See list on page 4
5. RECEIVED BY CHEMIST: 18-Sept-2002

6. APPLICANT NAME AND ADDRESS:

Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299
(484)-865-3749

7. NAME OF DRUG:

Prempro™/Premphase® Tablets

8. NONPROPRIETARY NAME:

Conjugated estrogens/medroxyprogesterone acetate

9. CHEMICAL NAME/STRUCTURE:

Conjugated estrogens (CE) – Please refer to USP 24.
Medroxyprogesterone acetate (MPA) – Preg-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-, 6 α
(Please refer to USP 25 for structural formula.)

10. DOSAGE FORM(S):

Tablets

11. POTENCY:

0.625 mg CE/2.5 mg MPA or 0.625 mg CE/5 mg MPA (approved)
0.3 mg CE/1.5 mg MPA
0.45 mg CE/1.5 MPA

12. PHARMACOLOGICAL CATEGORY:

Estrogen/progestin, Hormone replacement therapy

13. HOW DISPENSED:

Rx

14. RECORDS & REPORTS CURRENT:

Yes

15. RELATED IND/NDA/DMF:

None

16. SUPPLEMENT PROVIDES FOR:

Two new lower dosage strength drug product tablets, 0.45 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate and 0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate.

17. **SPECIAL PRODUCTS:** YES X NO ___ (A form for this NDA has already been submitted).

18. **COMMENTS**

This efficacy supplement provides for two lower dosage strength tablets of conjugated estrogens (CE) and medroxyprogesterone acetate (MPA) [0.3 mg CE/1.5 mg MPA and 0.45 mg CE/1.5 MPA] in a continuous regimen for the treatment of moderate to severe vasomotor symptoms associated with menopause, and vulvar and vaginal atrophy. The drug substances are identical to those in the approved dosage strength tablets, and the drug product manufacturing process is identical to the approved process.

The 0.3 mg/1.5 mg dosage strength tablet was withdrawn from the supplement (see Chemist's Review #1 by David Lin, Ph.D., dated 12-Apr-2002).

This review covers materials submitted by the Sponsor (please refer to the list on page 4) as a complete response to the approvable letter issued by the Agency on 13-Apr-2001 for NDA 20-527/SE2-017.

NDA 20-527/SE2-017 was deemed approvable from a CMC standpoint, based on GMP compliance issues as well as minor proposed labeling changes. These items are discussed in the applicable sections of the attached review.

Based on data presented in the 28-Feb-03 and 5-Mar-03 amendments, an interim in-process, release, and stability dissolution acceptance criterion for CE at the five hour timepoint has been established. The in-process acceptance criterion is and the release and stability acceptance criterion is

The following are agreements that have been made with the Sponsor and need to be included in the Action Letter:

1. The Agency has agreed to an interim release and stability specification for CE dissolution at the 5 hour timepoint. This interim acceptance criterion is
2. The Sponsor has committed to the identification of additional/improved in-process controls at the and stages of conjugated estrogens tablet manufacture. Once these improvements have been identified, three revalidation batches will be manufactured and subjected to room temperature and accelerated stability studies. The Sponsor anticipates that the results from these studies will be reported in 4thQ03.
3.
4. The Sponsor has committed to Dissolution Surveillance Program for the dissolution of conjugated estrogens in the 0.45 mg/1.5 mg Premarin/MPA drug product. In this commitment, every packaged lot will be tested for CE dissolution at six-month intervals. This surveillance program will be performed through expiration of the product.

19. **CONCLUSIONS AND RECOMMENDATIONS:**

From a CMC standpoint, this supplement is acceptable and may be approved.

20.	REVIEWER NAME	SIGNATURE	DATE COMPLETED
	Sarah.Pope		7-Mar-2003

cc: Original: NDA 20-527/SE2-017
HFD-580/Division File
HFD-580/KSherrod
HFD-580/DLin/SPope

Filename: 2NDA20527SE2017.doc

**APPEARS THIS WAY
ON ORIGINAL**

**THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE**

8 pages

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 20527/017	Action Goal:	
Stamp:	15-JUN-2000	District Goal:	05-FEB-2003
Regulatory Due:	12-MAR-2003	Brand Name:	MINIFAL/PREMPHASE
Applicant:	WYETH AYERST LABS	Estab. Name:	
	8299	Generic Name:	CONJUGATED
	PHILADELPHIA, PA 191019299		ESTROGENS/MEDROXYPROGEST
Priority:	3S		ERONE
Org Code:	580	Dosage Form:	(EXTENDED-RELEASE TABLET
		Strength:	SEE COMMENTS

Application Comment: THE CURRENT DOSAGE STRENGTH IS 0.625 MG CONJUGATED ESTROGENS/2.5 MG OR 5 MG MEDROXYPROGESTERONE ACETATE. THIS SUPPLEMENT IS FOR TWO NEW DOSAGE STRENGTH TABLETS: 0.3 MG OR 0.45 MG CONJUGATED ESTROGENS/1.5 MG MEDROXYPROGESTERONE ACETATE. (on 30-JUN-2000 by D. LIN (HFD-580) 301-827-4230)

THESE SITES ARE BEING RESUBMITTED. THE SPONSOR HAS SUBMITTED A RESPONSE TO THE APPROVABLE LETTER (APRIL 13,2001), STATING THAT THE DEFICIENCIES IN THE GUAYAMA, PUERTO RICO SITE (WYETH-AYERST, #2650135, HAVE BEEN CORRECTED. THEREFORE, CURRENT CONFIRMATION IS NEEDED, THAT ALL SITES LISTED IN N20527, SE2-017 ARE IN COMPLIANCE. (on 23-OCT-2002 by S. POPE (HFD-580) 301-827-4260)

FDA Contacts: D. SPELL LESANE , Project Manager
S. POPE (HFD-580) 301-827-4260 , Review Chemist
D. LIN (HFD-580) 301-827-4230 , Team Leader

Overall Recommendation: ACCEPTABLE on 03-FEB-2003 by R. WOODS (HFD-322) 301-827-9011
WITHHOLD on 12-APR-2001 by P. LEFLER (HFD-324) 301-827-0062

Establishment: CFN 9613692 FEI 3002806438
AYERST ORGANICS INC
R7A 7H2
BRANDON, MANITOECA, CA

WF No. 1111

Profile:

CEX

OAI Status: NONE

Estab. Comment: . CONJUGATED ESTROGENS DRUG SUBSTANCE MANUFACTURER. (on 30-JUN-2000 by D.
LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-JUN-2000				LINDAV
SUBMITTED TO DO	03-JUL-2000				DAMBROGIOJ
ASSIGNED INSPECTION T	06-JUL-2000				EGASM
INSPECTION SCHEDULED	16-SEP-2000		08-NOV-2000		IRIVERA
INSPECTION PERFORMED	27-NOV-2000		31-OCT-2000		EGASM
DO RECOMMENDATION	19-DEC-2000			ACCEPTABLE INSPECTION	ADAMSS
OC RECOMMENDATION	21-DEC-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

APPEARS THIS WAY
ON ORIGINAL

15-FEB-2003

FDA FORM 322

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

OC RECOMMENDATION 18-NOV-2002 ACCEPTABLE DAMBROGIOJ
DISTRICT RECOMMENDATION

Establishment:

[REDACTED]

DMF No:

[REDACTED]

AADA:

Responsibilities:

[REDACTED]

Profile:

CSN

OAI Status: NONE

Estab. Comment:

[REDACTED]

(on 30-JUN-

2000 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-JUN-2000				LINDAV
OC RECOMMENDATION	03-JUL-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ
SUBMITTED TO OC	23-OCT-2002				POPES
OC RECOMMENDATION	23-OCT-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment:

[REDACTED]

Responsibilities: _____

Profile: CSN

OAI Status: NONE

Estab. Comment: _____

(on 30-JUN-

2000 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-JUN-2000				LINDAV
OC RECOMMENDATION	03-JUL-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ
SUBMITTED TO OC	23-OCT-2002				POPES
OC RECOMMENDATION	23-OCT-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment:

[REDACTED]

DMF No: [REDACTED]

AADA:

Responsibilities: [REDACTED]

Profile: CRU

OAI Status: NONE

Estab. Comment:

(on 12-JUL-2000

by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-JUL-2000				LINDAV
SUBMITTED TO DO	06-JUL-2000	GMP			EGASM
DO RECOMMENDATION	13-JUL-2000			ACCEPTABLE BASED ON FILE REVIEW	EGASM
OC RECOMMENDATION	14-JUL-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM
SUBMITTED TO OC	23-OCT-2002				POPES
OC RECOMMENDATION	23-OCT-2002			ACCEPTABLE BASED ON FILE REVIEW	DAMBROGIOJ

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

Estab. Comment: CONJUGATED ESTROGENS DRUG SUBSTANCE MANUFACTURER (on 30-JUN-2000 by D.
LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-JUN-2000				LINDAV
SUBMITTED TO DO	03-JUL-2000				DAMBROGIOJ
ASSIGNED INSPECTION	06-JUL-2000				JPODSADO
INSPECTION PERFORMED	25-JUL-2000		21-JUL-2000		JPODSADO
DO RECOMMENDATION	25-JUL-2000			ACCEPTABLE INSPECTION	JPODSADO
INSPECTION FOR CEX WAS CONDUCTED 7/10-21/2000. AN FDA 483 WAS ISSUED BUT THE FIRM WAS FOUND CAPABLE OF MANUFACTURING THE DRUG SUBSTANCE.					
OC RECOMMENDATION	25-JUL-2000			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS
SUBMITTED TO OC	23-OCT-2002				POPES

APPEARS THIS WAY
ON ORIGINAL

11-MAR-2001

15-APR-2001
WYETH AYERST LABS
3S
580

Priority:
Org Code:

Application Comment: THE CURRENT DOSAGE STRENGTH IS 0.625 MG CONJUGATED ESTROGENS/2.5 MG OR 5 MG MEDROXYPROGESTERONE ACETATE. THIS SUPPLEMENT IS FOR TWO NEW DOSAGE STRENGTH TABLETS: 0.3 MG OR 0.45 MG CONJUGATED ESTROGENS/1.5 MG MEDROXYPROGESTERONE ACETATE. (on 30-JUN-2000 by D. LIN (HFD-580) 301-827-4230)

EI OF 9/00 WAS CLASSED NAI; TWO SUBSEQUENT FOR-CAUSE INSPECTIONS AT THE FIRM HAVE FOUND DEFICIENCIES THAT AFFECT ALL PRODUCTS USING SAME MANUFACTURING AND LABORATORY CONTROL SYSTEMS AND EQUIPMENT.

OC RECOMMENDATION 12-APR-2001

WITHHOLD ALCOCKP
DISTRICT RECOMMENDATION

CGMP CONCERNS RE: PREMARIN ARE LINKED TO THE PREMPRO PRODUCT. PREMPRO HAS A PREMARIN TABLET CORE AND IS COATED WITH MEDROXYPROGESTERONE (MPA). THE FOR CAUSE INSPECTION OF PREMARIN FOUND SIGNIFICANT CGMP ISSUES SURROUNDING PREMARIN. IN THE PREMPRO APPLICATION, THE TABLETING OF THE PRE-COATED PREMPRO (WHICH IS ACTUALLY PREMARIN) IS CONDUCTED IN THE WYETH PUERTO RICO. UNTIL THE ISSUES SURROUNDING PREMARIN ARE ADDRESSED, THE TABELTING OF PREMARIN FOR PREMPRO IS ALSO UNACCEPTABLE. CONCUR WITH DISTRICT WITHHOLD RECOMMENDATION. MEMO FROM HFD-324 TO FOLLOW UPON FURTHER REVIEW OF THE DISTRICT'S INSPECTION REPORT. UF IS 4-15-01 - AND REVIEW DIVISION IS REQUESTING OC RECOMMENDATION TODAY (4-12-0).

Establishment: _____

DMF No: _____

AADA:

Responsibilities: _____

Profile: CSN

OAI Status: NONE

Estab. Comment: _____
JUN-2000 by D. LIN (HFD-580) 301-827-4230

(on 30-

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-JUN-2000				LINDAV
OC RECOMMENDATION	03-JUL-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: _____

DMF No: _____

AADA:

Responsibilities: _____

Profile: CSN

OAI Status: NONE

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
3/10/03 03:51:17 PM
CHEMIST

Eric Duffy
3/10/03 03:58:45 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

**THIS SECTION
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RELEASABLE**

2 pages

/s/

Moo-Jhong Rhee
4/13/01 12:34:20 PM
CHEMIST

**APPEARS THIS WAY
ON ORIGINAL**

**CHEMIST REVIEW
OF SUPPLEMENT**

1. **ORGANIZATION:** DRUDP HFD-580
2. **NDA NUMBER:** 20-527/SE2-017
3. **SUPPLEMENT NUMBERS/DATES:**
Letterdate: 15-JUN-2000
Stampdate: 15-JUN-2000
4. **AMENDMENTS/REPORTS/DATES:**
Letterdate: See list on page 5
Stampdate:
5. **RECEIVED BY CHEMIST:** 21-JUN-2000

6. APPLICANT NAME AND ADDRESS:

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

7. NAME OF DRUG:

Prempro/Premphase Tablets

8. NONPROPRIETARY NAME:

Conjugated estrogens/medroxyprogesterone acetate

9. CHEMICAL NAME/STRUCTURE:

- a. Conjugated estrogens (CE): see USP 24
- b. Medroxyprogesterone acetate (MPA): Pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-, (6 α)-
See USP for structural formula

10. DOSAGE FORM(S):

Tablets

11. POTENCY:

0.625 mg CE/2.5 or 5 mg MPA (approved), 0.3 mg CE/1.5 mg MPA, 0.45 mg CE/1.5 mg MPA

12. PHARMACOLOGICAL CATEGORY:

Estrogen, progestin/Hormone replacement therapy

13. HOW DISPENSED:

RX

14. RECORDS & REPORTS CURRENT:

Yes

15. RELATED IND/NDA/DMF:

none

16. SUPPLEMENT PROVIDES FOR:

Two new lower dosage strength drug product tablets, 0.45 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate and 0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate.

17. COMMENTS

This efficacy supplement provides for two lower dosage strength tablets of conjugated estrogens (CE) and medroxyprogesterone acetate (MPA) [0.3 mg CE/1.5 mg MPA and 0.45 mg CE/1.5 mg MPA] in a continuous regimen for the treatment of moderate to severe vasomotor symptoms associated with menopause, and vulvar and vaginal atrophy. The drug substances are identical to those in the approved dosage strength tablets and the drug product manufacturing process is identical to the approved process.

Before this supplement may be approved, it will be necessary to address the following:

- The Puerto Rico drug product manufacturing facility must have a satisfactory cGMP inspection.

18. CONCLUSIONS AND RECOMMENDATIONS:

From a Chemistry, Manufacturing and Controls point of view, this Efficacy Supplement may be approved pending satisfactory resolution of the deficiency below. **Issue an Approvable recommendation with the following statement. Before this application may be approved, it will be necessary to address the following:**

- **The Wyeth Ayerst Pharmaceuticals facility in Guayama, Puerto Rico must have a satisfactory cGMP inspection.**

19. REVIEWER NAME

David T. Lin, Ph.D.
Review Chemist

SIGNATURE

DATE COMPLETED

12-APR-2001

cc: Original: NDA 20-527/SE2-017
HFD-580/Division File
HFD-580/DMoore
HFD-580/MRhee/DLin

INIT by MJ Rhee

Filename: S20527.017 (doc)

**APPEARS THIS WAY
ON ORIGINAL**

**THIS SECTION
WAS
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NOT
TO BE
RELEASABLE**

40 pages

/s/

David T. Lin
4/13/01 10:51:24 AM
CHEMIST

Chemistry Review #1 for efficacy supplement. Approvable because of cGMP deficiencies.

Moo-Jhong Rhee
4/13/01 10:54:58 AM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

/s/

David T. Lin
4/13/01 10:51:24 AM
CHEMIST

Chemistry Review #1 for efficacy supplement. Approvable because of cGMP deficiencies.

Moo-Jhong Rhee
4/13/01 10:54:58 AM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

NDA 20-527/S-017

Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg and
0.45 mg/1.5 mg

Wyeth-Ayerst Laboratories, Inc.

Statistical Review Regarding Dissolution and/or Stability

No statistical review is needed regarding dissolution and/or stability.

**APPEARS THIS WAY
ON ORIGINAL**

**THIS SECTION
WAS
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20 pages

NDA 20-527/S-017

Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg and
0.45 mg/1.5 mg

Wyeth-Ayerst Laboratories, Inc.

Environmental Assessment

A categorical exclusion is claimed for this NDA in accordance with 21 CFR part 25.31 (b), as amended in the 29-Jul-1997 Federal Register. This was found to be satisfactory (see Chemistry Review dated April 13, 2001).

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-527/S-017

Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg and
0.45 mg/1.5 mg

Wyeth-Ayerst Laboratories, Inc.

Micro (validation of sterilization) review

No microbiology validation review is required for tablets.

**APPEARS THIS WAY
ON ORIGINAL**

Estab. Comment: (on 30-
JUN-2000 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-JUN-2000				LINDAV
OC RECOMMENDATION	03-JUL-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment:

DMF No: AADA:

Responsibilities:

Profile: CRU OAI Status: NONE

Estab. Comment: MEDROXYPROGESTERONE ACETATE DRUG SUBSTANCE MICRONIZER. (on 12-JUL-2000 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-JUL-2000				LINDAV
SUBMITTED TO DO	06-JUL-2000	GMP			EGASM
DO RECOMMENDATION	13-JUL-2000			ACCEPTABLE BASED ON FILE REVIEW	EGASM
OC RECOMMENDATION	14-JUL-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

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: CONJUGATED ESTROGENS DRUG SUBSTANCE MANUFACTURER (on 30-JUN-2000 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-JUN-2000				LINDAV
SUBMITTED TO DO	03-JUL-2000	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	06-JUL-2000	PS			JPODSADC
INSPECTION PERFORMED	25-JUL-2000		21-JUL-2000		JPODSADC
DO RECOMMENDATION	25-JUL-2000			ACCEPTABLE INSPECTION	JPODSADC
INSPECTION FOR CEX WAS CONDUCTED 7/10-21/2000. AN FDA 483 WAS ISSUED BUT THE FIRM WAS FOUND CAPABLE OF MANUFACTURING THE DRUG SUBSTANCE.					
OC RECOMMENDATION	25-JUL-2000			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

Profile: TCM OAI Status: NONE

Estab. Comment: DRUG PRODUCT MANUFACTURER. (on 30-JUN-2000 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
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FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

SUBMITTED TO OC	30-JUN-2000	LINDAV
SUBMITTED TO DO	03-JUL-2000 10D	DAMEROGIOJ
DO RECOMMENDATION	06-JUL-2000	ACCEPTABLE JPODSADO
OC RECOMMENDATION	07-JUL-2000	BASED ON FILE REVIEW
		ACCEPTABLE FERGUSONS
		DISTRICT RECOMMENDATION

APPEARS THIS WAY
ON ORIGINAL

NDA 20-527/S-017

Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg and
0.45 mg/1.5 mg

Wyeth-Ayerst Laboratories, Inc.

Methods Validation

The methods validation for this product have been completed and are acceptable (see Chemistry review dated April 13, 2001).

**APPEARS THIS WAY
ON ORIGINAL**