CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-699/S-005

Name:	Effexor XR Extended-Release Capsules
Generic Name:	venlafaxine hydrochloride
Sponsor:	Wyeth Pharmaceuticals Inc.
Approval Date:	08/22/01
Indications:	For the treatment of depression and generalized anxiety disorder.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-699/S-005

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letter	X
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Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	X
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-699/S-005

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-699/SCM-005

Wyeth-Ayerst Laboratories
Attention: Patricia Foti Mann
Associate Director Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Mann:

Please refer to your supplemental new drug application dated August 2, 2001, received August 3, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EffexorXR 37.5 mg, 75 mg, 100 mg, 150 mg.

This supplemental new drug application provides for the following change: [ ] [ ] as an alternate manufacturing site of venlafaxine hydrochloride.

We have completed the review of this supplemental application, and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
(HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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

/s/

Robert H. Seevers
8/22/01 09:18:28 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-699/S-005

NON-APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-699/SCM-005

JUL - 1 1999

Wyeth-Ayerst Laboratories
Attention: Karel F. Bernady, Ph.D.
Director, Marketed Products, U.S. Regulatory Affairs
P. O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Bernady:

Please refer to your supplemental new drug application dated March 4, 1999, received March 5, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EffexorXR (venlafaxine HCl) Extended Release Capsules, 37.5mg, 75mg, 100mg, and 150mg.

This supplement proposes the following change(s): [ ] as an alternate manufacturing site of venlafaxine hydrochloride.

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

1. Please describe in detail the container closure system for venlafaxine HCl manufactured at [ ] and [ ]
2. Please state the retest date for venlafaxine HCl manufactured at [ ] and [ ]
3. Please inform the FDA what Wyeth-Ayerst has done to determine the cause of the unsatisfactory physical appearance test for 37.5mg Venlafaxine HCl Extended Release (ER) Capsule stability sample manufactured with drug substance made at [ ] It is noted that the physical appearance test for the 37.5mg Venlafaxine HCl ER Capsule stability sample manufactured with drug substance made at [ ] was satisfactory at 1 month (unpackaged) and 3 months (packaged) when exposed to fluorescent light.

Recently, our inspectors could not complete inspection of your manufacturing facilities for conformance with current good manufacturing practices (cGMP) because the facilities were not ready for inspection. A satisfactory inspection will be required before this application may be approved.

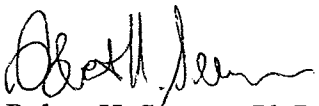
Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options

under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change prior to approval of this supplemental application.

If you have any questions, contact Paul David, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely,



Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
(HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 20-699
HFD-120/Div. Files
HFD-120/PDavid
HFD-120/RSeevers
HFD-120/LRocca
DISTRICT OFFICE

Drafted by: LR/June 30, 1999
Initialed by:
final:
filename: 20699SC2.WPD

NOT APPROVABLE (NA)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

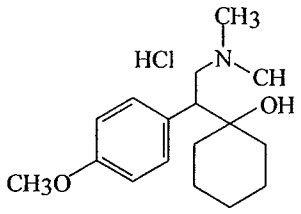
NDA 20-699/S-005

CHEMISTRY REVIEW(S)

JUN 30 1999

CHEMIST REVIEW
F **SUPPLEMENT**

1. ORGANIZATION: HFD-120
2. NDA Number: **20-699**
3. SUPPLEMENT NUMBERS/DATES: SCM-005
   Letter date: March 4, 1999
   Stamp date: March 5, 1999
4. AMENDMENTS/REPORTS/DATES: None
5. RECEIVED BY CHEMIST: March 9, 1999
6. APPLICANT NAME & ADDRESS: Wyeth-Ayerst Laboratories
   P. O. Box 8299
   Philadelphia, PA 19101-8299
7. NAME OF DRUG: Effexor®XR
8. NONPROPRIETARY NAME: venlafaxine hydrochloride
9. CHEMICAL NAME/STRUCTURE: (R/S)-1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride



10. DOSAGE FORM(S): Extended Release Capsules
11. POTENCY: 37.5mg, 75mg, 100mg, 150mg
12. PHARMACOLOGICAL CATEGORY: Treatment of Depression
13. HOW DISPENSED: X (R_x) _____ (OTC)
14. RECORDS & REPORTS CURRENT: X Yes _____ No
    REVIEW RECORDS & REPORTS CURRENT X Yes _____ No
15. RELATED IND/NDA/DMF: NDA 20-151, DMF [ ] (Type II), DMF [ ] (Type II), DMF 5387 (Type I)

16. SUPPLEMENT PROVIDES FOR: Alternate active pharmaceutical ingredient manufacturing site for Effexor®XR (venlafaxine hydrochloride) Extended Release Capsules 37.5mg, 75mg, 100mg, and 150mg.

17. COMMENTS:
NDA 20-699 Supplement SCM-005 (March 4, 1999) was submitted in accordance with 21 CFR 314.70(b) which refers to supplements requiring FDA approval before the change is made. The supplemental application provides for [ ] as an alternate manufacturing site of the Active Pharmaceutical Ingredient (API), venlafaxine HCl. The API manufactured at [ ] will be used to manufacture Effexor®XR (venlafaxine hydrochloride) Extended Release Capsules 37.5mg, 75mg, 100mg, and 150mg. The current approved source of the API for Effexor®XR is [ ] and [ ] are members of the same corporate entity. The API synthesis route is the same at both manufacturing sites.

DMF #[ ] describes the manufacture of API by [ ] DMF #[ ] describes manufacture of API at [ ] facilities. The amendment to DMF #[ ], submitted October 10, 1997, deals specifically with authorization to manufacture venlafaxine HCl at [ ]. DMF #[ ] Chemistry Review No. 1 (April 30 1999) found the April 10, 1997 amendment to DMF #[ ], adequate to support manufacture of venlafaxine HCl at [ ]

Site inspection was requested on March 19, 1999 for the API manufacturer ([ ] [ ]), and the drug substance release tester (Wyeth-Ayerst Laboratories, Rouses Point, NY). The Office of Compliance (OC) found the drug substance release tester acceptable (March 22, 1999). OC withheld their recommendation for the API manufacturer (March 31, 1999) for the reason "Firm Not Ready" for inspection. On June 22, 1999, a second inspection request was submitted to OC. As of June 29, 1999 [ ] has not received an acceptable review status for the manufacture of API at [ ]. The current EER Detail Report is appended to this review.

18. CONCLUSIONS & RECOMMENDATIONS:
Not Approvable. On March 19, 1999 this reviewer requested that [ ] facility be inspected for conformance with good manufacturing practices (CGMP). On March 31, 1999 the Office of Compliance withheld their decision because the firm was not ready for inspection. A satisfactory inspection will be required before this application may be approved. In addition, the following deficiencies are noted. A draft of the deficiency letter is appended to this review. Please address the following deficiencies:

- Please describe in detail the container closure system for venlafaxine HCl manufactured at [ ] [ ] and [ ]
- Please state the retest date for venlafaxine HCl manufactured at [ ] and [ ]
- Please inform the FDA what Wyeth-Ayerst has done to determine the cause of the unsatisfactory physical appearance test for the 37.5mg Venlafaxine HCl Extended Release (ER) Capsule stability sample manufactured with drug substance made at [ ] It is noted that the physical appearance test for the 37.5mg Venlafaxine HCl ER Capsule stability sample manufactured with drug substance made at [ ] was satisfactory at 1 month (unpackaged) and 3 months (packaged) when exposed to fluorescent light.

REVIEWER NAME	SIGNATURE	DATE COMPLETED
Lorenzo A. Rocca	Lorenzo Rocca	6/30/99

20. TEAM LEADER NAME	SIGNATURE	DATE COMPLETED
Robert H. Seevers	Robert H. Seevers	6/30/99

cc:
NDA 20-699/SCM005
HFD-120/Division File
HFD-120/RSeevers
HFD-120/LRocca
HFD-120/PDavid
F/T by: LRocca, File: C:\LR\Supplement\n20699\Scm-005Review.com

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information from

Chemistry Review #1

Appendix to Chemistry Review

NDA 20-699 Supplement SCM-005

I. Establishment Evaluation Report (EER)

29-JUN-1999 FDA CDER EES Page 1 of 1
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20699/005 Action Goal:
Stamp: 05-MAR-1999 District Goal: 31-MAY-1999
Regulatory Due: 05-JUL-1999 Brand Name: EFFEXOR XR E-R CAPS.(VENLAFAXINE HCL)
Applicant: WYETH AYERST LABS 8299 PHILADELPHIA, PA 191018299 Estab. Name:
Generic Name: VENLAFAXINE HCL
Priority: 3S
Org Code: 120 Dosage Form: (CONTROLLED RELEASE CAPSULE)
Strength: 37.5, 75, 100, 150 MG

Application Comment: THE ACTIVE PHARM INGRDIENT (API) WILL BE OBTAINED FROM THE FOLLOWING SOURCES: 1) [redacted] API WILL BE TESTED BY EITHER [redacted] OR WYETH-AYERST LABS ROUSES POINT, NY AND RELEASED AT WYETH-AYERST LABS ROUSES POINT, NY (DMF5387) (on 18-MAR-1999 by L. ROCCA (HFD-810) 301-594-2562)

FDA Contacts: P. DAVID (HFD-120) 301-594-2850 , Project Manager
L. ROCCA (HFD-810) 301-594-2562 , Review Chemist
R. SEEVERS (HFD-120) 301-594-2850 , Team Leader

Overall Recommendation: WITHHOLD on 31-MAR-1999 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]

DMF No: [redacted] AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: OAI ALERT
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-MAR-1999				ROCCAL
SUBMITTED TO DO	22-MAR-1999	10D			DAMBROGIOJ
DO RECOMMENDATION	31-MAR-1999			WITHHOLD FIRM NOT READY	NROLLI
WL ISSUED [redacted] TO [redacted] STATED [redacted] WOULD NOT BE READY FOR INSPECTION UNTIL MAY 15, 1999. [redacted] CORRECTIONS STILL PENDING.					
OC RECOMMENDATION	31-MAR-1999			WITHHOLD FIRM NOT READY	DAMBROGIOJ
SUBMITTED TO OC	22-JUN-1999				DAMBROGIOJ
SUBMITTED TO DO	22-JUN-1999	10D			DAMBROGIOJ

Establishment: 1310337
WYETH LABORATORIES INC
64 MAPLE ST
ROUSES POINT, NY 12979
DMF No: 5387 AADA:
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-MAR-1999				ROCCAL
OC RECOMMENDATION	22-MAR-1999			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

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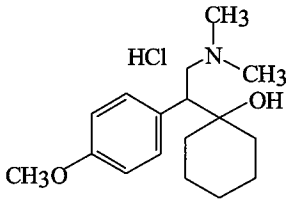
information from

Chemistry Review #1

CHEMIST REVIEW 2
OF **SUPPLEMENT**

1. ORGANIZATION: HFD-120
2. NDA Number: **20-699**
3. SUPPLEMENT NUMBERS/DATES: SCM-005 (BC)
   Letter date: June 19, 2000
   Stamp date: June 20, 2000
4. AMENDMENTS/REPORTS/DATES: None
5. RECEIVED BY CHEMIST: June 7, 2000
6. APPLICANT NAME & ADDRESS: Wyeth-Ayerst Laboratories
   P. O. Box 8299
   Philadelphia, PA 19101-8299
7. NAME OF DRUG: Effexor®XR
8. NONPROPRIETARY NAME: venlafaxine hydrochloride
9. CHEMICAL NAME/STRUCTURE: (R/S)-1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride



10. DOSAGE FORM(S): Extended Release Capsules
11. POTENCY: 37.5mg, 75mg, 100mg, 150mg
12. PHARMACOLOGICAL CATEGORY: Treatment of Depression
13. HOW DISPENSED: X (R_X) _____ (OTC)
14. RECORDS & REPORTS CURRENT: X Yes _____ No
    REVIEW RECORDS & REPORTS CURRENT _____ Yes X No
15. RELATED IND/NDA/DMF: NDA 20-151, DMF [redacted] (Type II), DMF [redacted] (Type II), DMF 5387 (Type I)

16. SUPPLEMENT PROVIDES FOR: Alternate active pharmaceutical ingredient manufacturing site for Effexor®XR (venlafaxine hydrochloride) Extended Release Capsules 37.5mg, 75mg, 100mg, and 150mg.

17. COMMENTS:
NDA 20-699 Supplement SCM-005 (March 4, 1999) was submitted in accordance with 21 CFR 314.70(b) which refers to supplements requiring FDA approval before the changes are made. The supplemental application provides for [redacted] facility as an alternate manufacturing site of the Active Pharmaceutical Ingredient (API), venlafaxine HCl. The API manufactured at [redacted] will be used to manufacture Effexor®XR (venlafaxine hydrochloride) Extended Release Capsules 37.5mg, 75mg, 100mg, and 150mg. The current approved source of the API for Effexor®XR is [redacted] and [redacted] are members of the same corporate entity. The API synthesis route is the same at both manufacturing sites.

DMF [redacted] describes the manufacture of API by [redacted] DMF [redacted] describes manufacture of API at [redacted] The amendment to DMF [redacted], submitted October 10, 1997, deals specifically with authorization to manufacture venlafaxine HCl at [redacted]. DMF [redacted] Chemistry Review No. 1 (April 30 1999)

found the April 10, 1997 amendment to DMF [ ], adequate to support manufacture of venlafaxine HCl at [ ]

Site inspection was requested on March 19, 1999 for the API manufacturer ([ ] [ ]), and the drug substance release tester (Wyeth-Ayerst Laboratories, Rouses Point, NY). The Office of Compliance (OC) found the drug substance release tester acceptable (March 22, 1999). OC withheld their recommendation for the API manufacturer (March 31, 1999) for the reason "Firm Not Ready" for inspection. On June 22, 1999, a second inspection request was submitted to OC. OC withheld their recommendation for the API manufacturer (July 28, 1999) for the reason "Firm Not Ready" for inspection. OC's recommendation was updated on March 24, 2000 following a cGMP inspection of the [ ] on [ ] The OC withheld their recommendation for the API manufacture due to "Inadequate QA Functions". On July 12, 2000, a third inspection request was submitted to OC following receipt of supplemental amendment SCM-005 (BC). OC withheld their recommendation for the API manufacturer (July 28, 2000) with the comment, "Firm continues to not be acceptable". In addition, OC has noted that the [ ] facility is under consideration for a warning letter. The current EER Detail Report is appended to this review.

At the time supplemental amendment SCM-005 was initially reviewed (see NDA20-699/SCM-005 Chemistry Review 1, June 30, 1999) three deficiency questions were submitted to the sponsor. In the current supplemental amendment SCM-005(BC), Wyeth-Ayerst has responded to each question. The sponsor's responses are satisfactory and are summarized in the Review Notes section.

18. CONCLUSIONS & RECOMMENDATIONS:
Not Approvable. On July 12, 2000, this reviewer requested that the [ ] facility be inspected for conformance with good manufacturing practices (cGMP). On July 28, 2000 the Office of Compliance withheld their decision because the firm continues to not be acceptable, at the same time the OC has noted that reinspection of the facility will be needed to determine adequate and acceptable corrective action. The sponsor has provided satisfactory responses to the deficiency questions raised when supplemental amendment SCM-005 was initially reviewed (see NDA20-699/SCM-005 Chemistry Review 1, June 30, 1999).

19. REVIEWER NAME	SIGNATURE	DATE COMPLETED
Lorenzo A. Rocca	_____	_____
20. TEAM LEADER NAME	**SIGNATURE**	**DATE COMPLETED**
Robert H. Seevers	_____	_____

cc:
NDA 20-699/SCM005(BC)
HFD-120/Division File
HFD-120/RSeevers
HFD-120/LRocca
HFD-120/PDavid
F/T by: LRocca, File: C:\data\LR\Supplement\n20699\Scm-005Review_2.com

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Chemistry Review #2

Appendix to Chemistry Review

NDA 20-699 Supplement SCM-005 (BC)

C. Establishment Evaluation Report (EER)

18-SEP-2000 FDA CDER EES Page 1 of 2
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20699/005
Stamp: 05-MAR-1999
Regulatory Due: 05-JUL-1999
Applicant: WYETH AYERST LABS
8299
PHILADELPHIA, PA 191018299
Priority: 3S
Org Code: 120

Action Goal:
District Goal: 31-MAY-1999
Brand Name: EFFEXOR XR E-R CAPS.(VENLAFAXINE HCL)
Estab. Name:
Generic Name: VENLAFAXINE HCL

Dosage Form: (CONTROLLED RELEASE CAPSULE)
Strength: 37.5, 75, 100, 150 MG

Application Comment: THE ACTIVE PHARM INGRDIENT (API) WILL BE OBTAINED FROM THE FOLLOWING SOURCES: 1) [redacted]
API WILL BE TESTED BY EITHER [redacted] OR WYETH-AYERST LABS ROUSES POINT, NY AND RELEASED AT WYETH-AYERST LABS ROUSES POINT, NY (DMF5387) (on 18-MAR-1999 by L. ROCCA (HFD-810) 301-594-5357)

FDA Contacts: P. DAVID (HFD-120) 301-594-2850 , Project Manager
L. ROCCA (HFD-810) 301-594-5357 , Review Chemist
R. SEEVERS (HFD-120) 301-594-2850 , Team Leader

Overall Recommendation: WITHHOLD on 31-MAR-1999 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 28-JUL-2000 by P. ALCOCK (HFD-324) 301-827-0062
WITHHOLD on 27-MAR-2000 by M. GARCIA (HFD-322) 301-594-0095

Establishment: [redacted]

DMF No: [redacted] AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: POTENTIAL OAI
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-MAR-1999				ROCCAL
SUBMITTED TO DO	22-MAR-1999	10D			DAMBROGIOJ
DO RECOMMENDATION	31-MAR-1999			WITHHOLD FIRM NOT READY	NROLLI
WL ISSUED [redacted] TO [redacted], CORRECTIONS STILL PENDING. [redacted] STATED [redacted] WOULD NOT BE READY FOR INSPECTION UNTIL MAY 15, 1999.					
OC RECOMMENDATION	31-MAR-1999			WITHHOLD FIRM NOT READY	DAMBROGIOJ
SUBMITTED TO OC	22-JUN-1999				DAMBROGIOJ
SUBMITTED TO DO	22-JUN-1999	10D			DAMBROGIOJ
DO RECOMMENDATION	28-JUL-1999			WITHHOLD FIRM NOT READY	SDELLAFA
FIRM RECEIVED A WRANING LETTER IN [redacted] THEY WILL NOT BE READY FOR A REINSPECTION UNTIL THE END OF AUGUST 1999. RECOMMENDATION WILL BE UPDATED AFTER THE RE-EI IF APPROPRIATE.					
ASSIGNED INSPECTION	23-SEP-1999	PS			RBROWN4
INSPECTION PERFORMED	10-JAN-2000		22-DEC-1999		RBROWN4
DO RECOMMENDATION	10-JAN-2000			WITHHOLD	RBROWN4
[redacted]					
EIR RECEIVED BY OC	14-FEB-2000				WOODSR

I. Establishment Evaluation Report (EER), continued

18-SEP-2000 FDA CDER EES Page 2 of 2
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

OC RECOMMENDATION	24-MAR-2000	WITHHOLD EIR REVIEW-CONCUR W/DISTRICT	WOODSR
SUBMITTED TO OC	12-JUL-2000		ROCCAL
SUBMITTED TO DO	13-JUL-2000 10D		FERGUSONS
DO RECOMMENDATION	18-JUL-2000	WITHHOLD PEND REG ACTION - WARNING LTR	RBROWN4

THE 12/99 EI IS STILL UNDER CONSIDERATION FOR A WARNING LETTER AND, AS YET, THE FIRMS WRITTEN RESPONSE IS PARTIAL.

OC RECOMMENDATION	28-JUL-2000	WITHHOLD DISTRICT RECOMMENDATION	ALCOCKP

MEMO SENT TO DNDCI (HFD-550) DATED 7/12/00 - FIRM CONTINUES TO NOT BE ACCEPTABLE. DISTRICT HAD [redacted] IN LIEU OF WARNING LETTER. REINSPECTION OF FACTILITY WILL BE NEEDED TO DETERMINE ADEQUATE AND ACCEPTABLE CORRECTIVE ACTION.

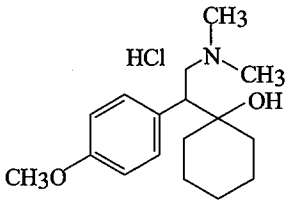
Establishment: 1310337
WYETH LABORATORIES INC
64 MAPLE ST
ROUSES POINT, NY 12979

DMF No: 5387 AADA:
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-MAR-1999				ROCCAL
OC RECOMMENDATION	22-MAR-1999			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

CHEMIST REVIEW 3
OF **SUPPLEMENT**

1. ORGANIZATION: HFD-120
2. NDA Number: **20-699**
3. SUPPLEMENT NUMBERS/DATES: SCM-005 (AC)
   Letter date: August 2, 2001
   Stamp date: August 3, 2001
4. AMENDMENTS/REPORTS/DATES: None
5. RECEIVED BY CHEMIST: August 20, 2001
6. APPLICANT NAME & ADDRESS: Wyeth-Ayerst Laboratories
   P. O. Box 8299
   Philadelphia, PA 19101-8299
7. NAME OF DRUG: Effexor®XR
8. NONPROPRIETARY NAME: venlafaxine hydrochloride
9. CHEMICAL NAME/STRUCTURE: (R/S)-1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride



10. DOSAGE FORM(S): Extended Release Capsules
11. POTENCY: 37.5mg, 75mg, 100mg, 150mg
12. PHARMACOLOGICAL CATEGORY: Treatment of Depression
13. HOW DISPENSED: X (R_X) _____ (OTC)
14. RECORDS & REPORTS CURRENT: X Yes _____ No
    REVIEW RECORDS & REPORTS CURRENT X Yes _____ No
15. RELATED IND/NDA/DMF: NDA 20-151, DMF [redacted] (Type II), DMF [redacted] (Type II), DMF 5387 (Type I)

16. SUPPLEMENT PROVIDES FOR: Alternate active pharmaceutical ingredient manufacturing site for Effexor®XR (venlafaxine hydrochloride) Extended Release Capsules 37.5mg, 75mg, 100mg, and 150mg.

17. COMMENTS:
NDA 20-699 Supplement SCM-005 (March 4, 1999) was submitted in accordance with 21 CFR 314.70(b) which refers to supplements requiring FDA approval before the changes are made. The supplemental application provides for [redacted] facility as an alternate manufacturing site of the Active Pharmaceutical Ingredient (API), venlafaxine HCl. The API manufactured at [redacted] will be used to manufacture Effexor®XR (venlafaxine hydrochloride) Extended Release Capsules 37.5mg, 75mg, 100mg, and 150mg. The current approved source of the API for Effexor®XR is [redacted] and [redacted] are members of the same corporate entity. The API synthesis route is the same at both manufacturing sites.

Site inspection was requested on March 19, 1999 for the API manufacturer ([redacted]), and the drug substance release tester (Wyeth-Ayerst Laboratories, Rouses Point, NY). The Office of Compliance (OC) found the drug substance release tester acceptable (March 22, 1999). OC withheld their recommendation for the API manufacturer (March 31, 1999) for the reason "Firm Not Ready" for inspection. On June 22, 1999, a second inspection request was submitted to OC. OC

withheld their recommendation for the API manufacturer (July 28, 1999) for the reason "Firm Not Ready" for inspection. OC's recommendation was updated on March 24, 2000 following a cGMP inspection of the [ ] on [ ]. The OC withheld their recommendation for the API manufacture due to "Inadequate QA Functions". On July 12, 2000 a third inspection request was submitted to OC following receipt of supplemental amendment SCM-005 (BC). OC withheld their recommendation for the API manufacturer (July 28, 2000) with the comment, "Firm continues to not be acceptable". In addition, OC has noted that the [ ] facility is under consideration for a warning letter. On August 16, 2001 a fourth inspection request was submitted to OC following receipt of supplemental amendment SCM-005 (AC). OC found the API manufacturer acceptable (August 16, 2001).

18. CONCLUSIONS & RECOMMENDATIONS:
Recommend issuing an approval letter. On August 16, 2001 the Office of Compliance found the [ ] [ ] facility acceptable (based on profile) as an alternate manufacturing site of the Active Pharmaceutical Ingredient (API), venlafaxine HCl.

19. REVIEWER NAME	SIGNATURE	DATE COMPLETED
Lorenzo A. Rocca	_____	_____

20. TEAM LEADER NAME	SIGNATURE	DATE COMPLETED
Robert H. Seevers	_____	_____

cc:
NDA 20-699/SCM005(AC)
HFD-120/Division File
HFD-120/RSeevers
HFD-120/LRocca
HFD-120/Pdavid

F/T by: LRocca, File: C:\data\LR\Supplement\n20699\Scm-005Review_3.com

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/s/

Lorenzo Rocca
8/21/01 10:14:49 AM
CHEMIST

Robert H. Seevers
8/22/01 09:13:11 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-699/S-005

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-699/S-005

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

MAR 16 1999

Attention: Karel F. Bernady, Ph.D., Director

Dear Dr. Bernady:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Effexor XR

NDA Number: 20-699

Supplement Number: S-005

Date of Supplement: March 4, 1999

Date of Receipt: March 5, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on May 4, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Attention: Document Control Room 4008
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

Robert W. Reese for

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-699/005
HFD-120/Div. Files
HFD-120/CSO/David

filename: C:\WPWIN61\TEMPLATE\FDA\20-699.005

SUPPLEMENT ACKNOWLEDGEMENT