CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-048

CHEMISTRY REVIEW(S)

Summary of Chemistry Reivew

A. Drug Substance

1. Description and characterization: Satisfactory; See DMF (Chemistry Rev. # 4 and 5)
2. Manufacturing: Satisfactory; See DMF (Chemistry Rev. # 4 and 5).
3. Synthesis: Satisfactory; See DMF (Chemistry Rev. # 4 and 5).
4. Specifications/Analytical Methods: Satisfactory; See DMF (Chemistry Rev. # 4 and 5).
5. Containers/Closure System: Satisfactory; See DMF (Chemistry Rev. # 4 and 5).
6. Stability: Satisfactory, See DMF (Chemistry Rev. # 4 and 5).

B. Drug Product

1. Components/Composition: Satisfactory; See Chem. Rev #1 and 2, DMF
2. Specifications and Methods for Drug Product Ingredients: Satisfactory: See Chem. Rev #1 and 2, DMF
3. Manufacturer: Satisfactory; See Chem. Rev #1 and 2, DMF
4. Manufacturing and Packaging: Satisfactory; See Chem. Rev #1 and 2, DMF
5. Specifications and Test Methods: Satisfactory, See Chem. Rev #1 and 2, DMF
6. Container/Closure System: Satisfactory; See Chem. Rev #1 and 2, DMF
7. Stability: Satisfactory; See Chem. Rev #1 and 2, DMF

C. Investigational Formulations: Satisfactory, See Chem. Rev #1 and 2, DMF

D. Environmental Assessment: Satisfactory, See Chem. Rev #1, NDA 21-048

E. Labeling: Satisfactory, The tradename was not provided, See Chem. Rev #1, NDA 21-048

F. Establishment Inspections: Satisfactory, See Chem. Rev #1, NDA 21-048

G. Method Validation: Will be initiated.

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS (HFD-580)
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA # 21-048 **Chemistry Review # 1** **Review Date**: 9-15-99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	11-20-99	11-24-99	11-30-99

NAME AND ADDRESS OF APPLICANT
Wyeth-Ayesrst Laboratories
P.O. Box 8299, Philadelphia, PA 19101

DRUG PRODUCT NAME
Proprietary: None given
Non-proprietary/USAN: Estradiol Transdermal System
Compendium: does not apply
Code name/number:None
Chem. Type/Ther. Class: 3 S

ANDA SUITABILITY PETITION/DESI/PATENT STATUS: N/A

PHARMACOL. CATEGORY/INDICATION: Estrogen, Hormone replacement in postmenopausal women.

DOSAGE FORM: Transdermal Delivery System

STRENGTHS: 1) 2.6 mg (50 mcg/day, 13.5 cm2); 3.9 mg (75 mcg/day, 20 cm2); 5.3 mg (100 mcg/day, 27 cm2)

ROUTE OF ADMINISTRATION: Transdermal (Once weekly application)

Dispensed: By prescription

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT.:
Estradiol- Estra-1,3,5(10)-triene-3, 17-diol (17β); Estra-1,3,5(10)-triene-3, 17β-diol;

$C_{18}H_{24}O_2$ (Estradiol)
272.39

SUPPORTING DOCUMENTS

Type/No.	Subject	Holder	Status	Review Date	Letter Date
II/DMF			IR letter sent Response received and deemed adequate	7-13-99 9-10-99	7-16-99
IV/DMF			Adequate	8-24-88	NA
IV/DMF			IR letter sent Response received and deemed adequate	7-8-99 9-12-99	7-28-99
III/DMF			Adequate	7-29-99	NA
III/DMF			IR letter sent Response received and deemed adequate	7-13-99 9-12-99	7-30-99
III/DMF			Adequate	8-26-99	NA
III/DMF			Not reviewed since the drug product manufacturer does not plan to use it commercially. See Chemistry Review #2 for DMF	NA	NA

RELATED DOCUMENTS
None

CONSULTS
The EER was sent on 1-6-99. The inspection results are satisfactory.

REMARKS/COMMENTS
1. No trademark was submitted for the drug product. Therefore, there is nothing to send to the LNC as far as the trademark is concerned.
2. The CMC information is provided in the DMF —— and it was reviewed separately. The DMF is adequate to support the NDA 21-048.
3. The labeling of the of the Packaging Insert (Description and How Supplied Sections) was reviewed here. The deficiencies on the labeling were given to the project manager and corrected in subsequent draft labels.

CONCLUSION AND RECOMMENDATION
With respect to chemistry, manufacturing and controls, the application can be approved.

DRAFT DEFICIENCY LETTER:
None

9-15-99

Amit K. Mitra, Ph.D

cc: NDA 21-048
HFD-580/A. K. Mitra
HFD-580/M.J. Rhee
HFD-580/D. Spell-lesane
R/D. Init. By- for M.J. Rhee 9/17/99

2 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21048/000
Stamp: 23-NOV-1998
Regulatory Due: 23-SEP-1999
Applicant: WYETH AYERST LABS
8299
PHILADELPHIA, PA 191018299
Priority: 3S
Org Code: 580

Action Goal:
District Goal: 25-JUL-1999
Brand Name: ESTRADIOL TRANSDERMAL SYSTEM (E2 III TS)
Estab. Name:
Generic Name: ESTRADIOL TRANSDERMAL SYSTEM (E2 III TS)

Dosage Form: (TRANSDERMAL PATCH)
Strength: 50, 75 AND 100 MCG/DAY

Application Comment: CYGNUS RELEASES THE DRUG SUBSTANCE. THE DRUG PRODUCT IS MANUFACTURED, PACKAGED AND RELEASED BY CYGNUS. THE LOCATION OF THE MANUFACTURING FACILITY IS 701 GALVESTON DRIVE, REDWOOD CITY, CA 94063 WHICH IS AT THE SAME CAMPUS AS THE HEADQUARTER LISTED ABOVE (on 06-JAN-1999 by A. MITRA (HFD-580) 301-827-4238)

FDA Contacts: A. MITRA (HFD-580) 301-827-4238 , Review Chemist

Overall Recommendation: ACCEPTABLE on 15-SEP-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment:
CYGNUS THERAPEUTIC SYSTEMS
400 PENOBSCOT DR
REDWOOD CITY, CA 94063

DMF No: —— AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: TDP OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-JAN-1999				MITRAA
SUBMITTED TO DO	06-JAN-1999	10D			FERGUSONS
DO RECOMMENDATION	06-AUG-1999			ACCEPTABLE BASED ON FILE REVIEW	MEDWARDS
OC RECOMMENDATION	06-AUG-1999			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

Establishment: [redacted]

DMF No: —— AADA:
Responsibilities: [redacted]
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-JAN-1999				MITRAA
OC RECOMMENDATION	06-JAN-1999			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: [redacted]

DMF No: AADA:
Responsibilities: [redacted]
Profile: CTL OAI Status: NONE

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-JAN-1999				MITRAA
SUBMITTED TO OC	06-JAN-1999				MITRAA
OC RECOMMENDATION	06-JAN-1999			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: [redacted]

DMF No: AADA: [redacted]

Responsibilities:

Profile: CTL OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-JAN-1999				MITRAA
SUBMITTED TO DO	06-JAN-1999	GMP			FERGUSONS
ASSIGNED INSPECTION	30-MAY-1999	PS			MEDWARDS
INSPECTION SCHEDULED	06-AUG-1999		27-AUG-1999		MEDWARDS
INSPECTION PERFORMED	13-SEP-1999		24-AUG-1999		MEDWARDS
THIS WAS A TEAM INSPECTION CONDUCTED BY MYSELF AND TODD BOZICEVICH, MICROBIOLOGIST					
DO RECOMMENDATION	13-SEP-1999			ACCEPTABLE INSPECTION	MEDWARDS
OC RECOMMENDATION	14-SEP-1999			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21048/000
Priority: 3S
Org Code: 580
Stamp: 23-NOV-1998 Regulatory Due: 23-SEP-1999
Action Goal:
District Goal: 25-JUL-1999
Applicant: WYETH AYERST LABS
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Brand Name: ESTRADIOL TRANSDERMAL SYSTEM (E2 III TS)
Established Name:
Generic Name: ESTRADIOL TRANSDERMAL SYSTEM (E2 III TS)
Dosage Form: TDP (TRANSDERMAL PATCH)
Strength: 50, 75 AND 100 MCG/DAY

FDA Contacts: A. MITRA (HFD-580) 301-827-4238 , Review Chemist

Overall Recommendation:

ACCEPTABLE on 15-SEP-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: [redacted]
CYGNUS THERAPEUTIC SYSTEMS
400 PENOBSCOT DR
REDWOOD CITY, CA 94063
DMF No: [redacted]
AADA No:

Profile: TDP
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 06-AUG-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: FINISHED DOSAGE MANUFACTURER

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

Profile: CSN
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 06-JAN-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: CTL
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 06-JAN-1999
Decision: ACCEPTABLE
Responsibilities: [redacted]

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Reason: **BASED ON PROFILE**

Establishment: [redacted]

DMF No:

AADA No:

Profile: **CTL** OAI Status: **NONE**

Responsibilities: [redacted]

Last Milestone: **OC RECOMMENDATION**

Milestone Date **14-SEP-1999**

Decision: **ACCEPTABLE**

Reason: **DISTRICT RECOMMENDATION**

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___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling