CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-371

Microbiology Review(s)

Product Quality Microbiology Review
Consult Review for HFD-580

04 April 2002

NDA: 21-371 BZ

Name of Drug: Estrasorb™

Review Number: 4

Submission Date: 21 March 2002

Applicant: Novavax

Name of Reviewer: Paul Stinavage

Product Quality Microbiology Data Sheet

A. 1. **NDA:** 21-371 BZ

2. **REVIEW NUMBER:** 4

3. **REVIEW DATE:** 04 April 2002

4. **TYPE OF SUPPLEMENT:** N/A

5. **SUPPLEMENT PROVIDES FOR:** N/A

6. **APPLICANT/SPONSOR:** Novavax, Inc.
12111 Parklawn Drive
Rockville, MD 20852

Name: Novavax
Representative: D. Craig Wright
Telephone: (301) 231- 0774 Ext. 23

7. **MANUFACTURING SITE:** [redacted]

8. **DRUG PRODUCT NAME:**
Proprietary: Estrasorb™
Non-proprietary: Estrogen
Drug Priority Classification: Standard

9. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Topical

10. **METHOD(S) OF STERILIZATION:** N/A

11. **PHARMACOLOGICAL CATEGORY:** Topical

B. 1. **DOCUMENT/LETTER DATE:** 21 March 2002
2. **RECEIPT DATE:** 27 March 2002
3. **CONSULT DATE:** 28 March 2002
4. **DATE OF AMENDMENTS:** 27 March 2002 (Subject of this Review)
5. **ASSIGNED FOR REVIEW:** 01 April 2002
6. **SUPPORTING/RELATED DOCUMENTS:** (none)

C. **REMARKS:** The submission provides data regarding antimicrobial preservative effectiveness testing conducted on the product formulation.

Executive Summary

I. Recommendations

Recommendation on Approvability – The submission is recommended for approval on the basis of antimicrobial effectiveness and microbial quality of the product.

B. Recommendation on Phase 4 Commitments and/or Agreements, if Approvable

Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology

The product is a non-sterile, topical preparation packaged in ← unit-dose C

B. Brief Description of Microbiology Deficiencies

C. Assessment of Risk Due to Microbiology Deficiencies-

III. Administrative

A. Reviewer's Signature /S/

B. **Endorsement Block**

Paul Stinavage/04 April 2002
P.H. Cooney/
D. Moore/

C. CC Block

cc:
Original NDA 21-371
HFD-580/Division File/NDA 21-371

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/s/

Paul Stinavage
4/16/02 07:35:29 AM
MICROBIOLOGIST
Met USP Category 2 criteria for preservative effectiveness.

Peter Cooney
4/16/02 10:52:00 AM
MICROBIOLOGIST

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

REQUEST FOR CONSULTATION

(Division/Office). ONDC Microbiology Team HFD-805: Attention: Dr. Peter Cooney, PKLN Room 18B-08

FROM. HFD-580 (Division of Reproductive and Urologic Drug Products) Diane Moore 17B-45

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 27, 2002		21-371	BC	February 20, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Estrasorb (estradiol topical emulsion)	Rush	Estrogen	March 14, 2002

NAME OF FIRM. **Novavax, Incorporated**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: (Previous reviews performed by Dr. Paul Stinavage.) Please review submission containing [redacted] Final Report, and microbial limit test data. Reference is made to January 25, 2002, teleconference with Novavax regarding microbiology deficiencies in the NDA submission.

'GNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Diane V. Moore
2/27/02 03:56:01 PM

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Product Quality Microbiology Review
Consult Review for HFD-580

01 March 2002

NDA: 21-371 BC

Name of Drug: Estrasorb™

Review Number: 3

Submission Date: 20 February 2002

Applicant: Novavax

Name of Reviewer: Paul Stinavage

Product Quality Microbiology Data Sheet

A. 1. **NDA:** 21-371 BC

2. **REVIEW NUMBER:** 3

3. **REVIEW DATE:** 01 March 2002

4. **TYPE OF SUPPLEMENT:** N/A

5. **SUPPLEMENT PROVIDES FOR:** N/A

6. **APPLICANT/SPONSOR:** Novavax, Inc.
12111 Parklawn Drive
Rockville, MD 20852

Name: Novavax
Representative: D. Craig Wright
Telephone: (301) 231- 0774 Ext. 23

7. **MANUFACTURING SITE:** [redacted]

8. **DRUG PRODUCT NAME:**
Proprietary: Estrasorb™
Non-proprietary: Estrogen
Drug Priority Classification: Standard

9. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Topical

10. **METHOD(S) OF STERILIZATION:** N/A

11. **PHARMACOLOGICAL CATEGORY:** Topical

B. 1. **DOCUMENT/LETTER DATE:** 20 February 2002
2. **RECEIPT DATE:** 21 February 2002
3. **CONSULT DATE:** 27 February 2002
4. **DATE OF AMENDMENTS:** 20 February 2002 (Subject of this Review)
5. **ASSIGNED FOR REVIEW:** 28 February 2002
6. **SUPPORTING/RELATED DOCUMENTS:** (none)

C. **REMARKS:** The submission provides data regarding antimicrobial preservative effectiveness testing [redacted]

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Executive Summary

I. Recommendations

Recommendation on Approvability – The submission does not alter the "Not Recommended for Approval" conclusion of the initial review. The submission provides data illustrating the preservative properties [ ]. The testing performed here was not performed with the product formulation and has no demonstrated correlation with product preservation.

B. Recommendation on Phase 4 Commitments and/or Agreements, if Approvable

Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology

The product is a non-sterile, topical preparation packaged in unit-dose — configurations.

B. Brief Description of Microbiology Deficiencies

[ ] The unit-dose formulation should be demonstrated to be bacteriostatic.

C. Assessment of Risk Due to Microbiology Deficiencies-

Unreasonably high risk of significant microbial product contamination which increases risk of clinical infection and/or degradation of product quality.

III. Administrative

/S/

A. Reviewer's Signature _____

B. Endorsement Block

Paul Stinavage/01 March 2002
P.H. Cooney/
D. Moore/

C. CC Block

cc:
Original NDA 21-371
HFD-580/Division File/NDA 21-371

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/s/

Paul Stinavage
3/26/02 02:28:03 PM
MICROBIOLOGIST

Peter Cooney
3/27/02 10:02:38 AM
MICROBIOLOGIST

Product Quality Microbiology Review
Consult Review for HFD-580

17 January 2002

NDA: 21-371 BC

Name of Drug: Estrasorb™

Review Number: 2

Submission Date: 29 June 2001

Applicant: Novavax

Name of Reviewer: Paul Stinavage

Product Quality Microbiology Data Sheet

A. 1. **NDA:** 21-371 BC

2. **REVIEW NUMBER:** 2

3. **REVIEW DATE:** 17 January 2002

4. **TYPE OF SUPPLEMENT:** N/A

5. **SUPPLEMENT PROVIDES FOR:** N/A

6. **APPLICANT/SPONSOR:** Novavax, Inc.
12111 Parklawn Drive
Rockville, MD 20852

Name: Novavax
Representative: D. Craig Wright
Telephone: (301) 231- 0774 Ext. 23

7. **MANUFACTURING SITE:** —

8. **DRUG PRODUCT NAME:**
Proprietary: Estrasorb™
Non-proprietary: Estrogen
Drug Priority Classification: Standard

9. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Topical

10. **METHOD(S) OF STERILIZATION:** N/A

11. **PHARMACOLOGICAL CATEGORY:** Topical

B. 1. **DOCUMENT/LETTER DATE:** 29 June 2001
2. **RECEIPT DATE:** 14 December 2001
3. **CONSULT DATE:** 18 December 2001
4. **DATE OF AMENDMENTS:** 14 December 2001 (Subject of this Review)
5. **ASSIGNED FOR REVIEW:** 4 January 2002
6. **SUPPORTING/RELATED DOCUMENTS:** (none)

C. **REMARKS:** The submission provides data indicating inadequate preservation of the formulation.

Executive Summary

I. Recommendations

A. Recommendation on Approvability – The submission does not alter the "Not Recommended for Approval" conclusion of the initial review. The submission provides data illustrating that [ ] does not meet USP criteria for antimicrobial preservative effectiveness. [ ]

Additionally, since the unit dose formulation only conforms to microbial limit specifications, the formulation should be demonstrated to be bacteriostatic. Microbial replication in the finished product may diminish the concentration of the active drug substance prior to patient use and/or result in hazardous levels of microorganisms in the product.

B. Recommendation on Phase 4 Commitments and/or Agreements, if Approvable

Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology

The product is a non-sterile, topical preparation packaged in — unit-dose [ ]

B. Brief Description of Microbiology Deficiencies

[ ] The unit-dose formulation should be demonstrated to be bacteriostatic.

C. Assessment of Risk Due to Microbiology Deficiencies- Unreasonably high risk of significant microbial product contamination which increases risk of clinical infection and/or degradation of product quality.

III. Administrative

A. Reviewer's Signature /S/

B. Endorsement Block

Paul Stinavage/17 January 2002
P.H. Cooney/
D. Moore/

C. CC Block

cc:
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/s/

Paul Stinavage
1/17/02 12:47:32 PM
MICROBIOLOGIST
Amendment demonstrating no preservation of product.

Peter Cooney
1/17/02 02:57:57 PM
MICROBIOLOGIST

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NDA 21-371
Estrasorb™ (estradiol topical emulsion)
Novavax, Inc.

Micro (validation of sterilization) Review(s) and Memoranda

This is not a sterile product. No microbiology review is required.

REVIEW FOR HFD-580
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1 OF NDA 21-371
25 October 2001

A. 1. NDA 21-371

APPLICANT: Novavax, Inc.
12111 Parklawn Drive
Rockville, MD 20852

2. PRODUCT NAMES: Estrasorb™

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is a nanoemulsion topical delivery system.

4. METHODS OF STERILIZATION:
The product is not a sterile product but, is subject to microbial limits specifications.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is to be used as estrogen replacement therapy in symptomatic post-menopausal women.

B. 1. DATE OF INITIAL SUBMISSION: 29 June 2001

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS: (none)

4. ASSIGNED FOR REVIEW: 31 July 2001

C. REMARKS: The application provides for the manufacture of the product at [redacted]. The product is to be packaged in [redacted].

D. CONCLUSIONS: The application is not recommended for approval. Specific comments are provided in "E. Review Notes" and "List of Microbiology Deficiencies".

/S/

Paul Stinavage, Ph.D.

cc: Original NDA 21-371
HFD-580/D. Moore
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 25 October 2001
R/D initialed by P. Cooney

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/s/

Paul Stinavage
11/7/01 05:20:08 AM
MICROBIOLOGIST
Topical estrogen replacement. No testing of topical pr
oduct.

Peter Cooney
11/7/01 10:39:02 AM
MICROBIOLOGIST

APPEARS THIS WAY
ON ORIGINAL