CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE

APPLICATION NUMBER(S)

21-371

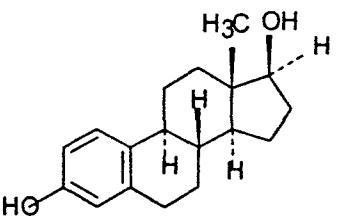
CHEMISTRY REVIEW(S)

NDA 21-371

Estrasorb

Novavax

Amit K. Mitra, Ph.D
Division of Reproductive and Urologic Drugs



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Chemistry Review Data Sheet

1. NDA 21-371

2. REVIEW # 3

3. REVIEW DATE: 1-OCT-2003

4. REVIEWER: Amit K. Mitra, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	29-Jun-2001
Amendment	29-Jun-2001
Amendment	08-Aug-2001
Amendment	14-Dec-2001
Amendment	20-FEB-2002
Amendment	01-MAR-2002
Amendment	07-MAR-2002

All previous documents

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Orignial Resubmission	12- SEP-2002
Amendment	20-NOV-2002
Amendment	01-APR-2003
Amendment	05-MAY-2003
Amendment	27-MAY-2003

Amendment	06-JUN-2003
Amendment	17-SEP-2003
Amendment	30-SEP-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Novavax, Inc.
Address:	12111 Parklawn Drive, Rockville, MD 20852
Representative:	D. Craig Wright, M.D
Telephone:	301-231-0774 x 23

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Estrasorb
b) Non-Proprietary Name (USAN): Estradiol topical emulsion
c) Code Name/# (ONDC only):N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Relief of vasomotor symptoms in symptomatic post-menopausal women

11. DOSAGE FORM: Emulsion [redacted]

12. STRENGTH/POTENCY: 2.5 mg/g; The drug is supplied in one unit dose package (1.74 g/pouch)

13. ROUTE OF ADMINISTRATION: Transdermal

[redacted]

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: Estradiol hemihydrate; $C_{18}H_{24}O_2$. ½ H_2O; 281.4

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: See Chemistry Review #1, dated 13-FEB-2002. Satisfactory.

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	8-OCT-2003	Ms. S. Ferguson
Methods Validation	Will be initiated		

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-371

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application may be approved with respect to CMC.

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

Novavax has made the following Phase 4 commitments to address the quality issues associated with the presence [redacted] in the Estrasorb drug product.

1. Novavax commits to count the number of [redacted] and make quantitative determination of free estradiol in [redacted] consecutive commercial batches including the stability lots and report the data in the annual report.
2. Novavax commits to notify the agency if the total [redacted] weight during annual stability monitoring is greater than or equal to [redacted] of the label claim for Estrasorb.

II. Summary of Chemistry Assessments

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

The drug product "Estrasorb" , is an emulsion at a concentration of 2.5 mg/g for the drug substance, estradiol. The drug product is available in 1.74 g unit dose pouch, For desired efficacy, the patient needs to apply contents of two 1.74 g pouch. The drug product is indicated for the relief of vasomotor symptoms in [redacted] symptomatic post-menopausal women.

The drug substance is estradiol, USP and it is used in the hemihydrate form. The Chemistry Manufacturing and Control information of the drug substance is located in the [redacted] DMF [redacted] and it is deemed adequate to support the NDA (See Chemistry Reviews #1 for the Original NDA).

All excipients used in the drug product are compendial. However, polysorbate 80 is a known penetration enhancer in vitro, and the compendial specification does not include an assay for polysorbate 80. Therefore, an assay specification of polysorbate 80 was sought. The sponsor developed an assay method for polysorbate 80 and adopted an acceptance criteria for assay. The critical in-process parameters are particle size of the emulsion, homogeneity or content uniformity, fill weight, and leak test. The sponsor was

requested to adopt in-process controls for particle size and content uniformity or homogeneity to assure uniformity of the amount of estradiol and particle size throughout the batch and the sponsor adopted all in-process controls adequately. The pre-clinical batches were manufactured using a — and packaged in syringes. The composition of the batches were different from the to-be-marketed formulation with respect to the oil to water ratio. The Phase III clinical trial was conducted using a formulation with the identical composition to that of the to-be-marketed formulation but manufactured at a different manufacturing site with different equipment of same operating principles. The bridging between the Phase III clinical supplies and the to-be-marketed formulation was conducted using an in vitro methodology recommended by SUPAC-SS. The adequacy of this test method and the test data was reviewed by the clinical pharmacologist. The clinical pharmacologist suggested adequate bridging between the clinical and the to-be-marketed product (see Clinical Pharmacology review, dated 24-APR-2002) .

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

The recommended dose for the drug product is — grams/per day. Only one formulation (2.5 mg of estradiol/gram of drug product) is available in one packaging configuration. The recommend dose is content of two pouches of 1.74 g/ pouch containing 2.5 mg of estradiol/gram per day . — The recommended dose per day is the maximum daily dose. The drug product is recommended to be applied on thigh and calf area for systemic absorption. Upon application of the recommended dose, — of estradiol is delivered to the systemic circulation per day.

So far, the sponsor has provided 24 months stability data. Based on the satisfactory stability data, a tentative expiration date of 24 months is granted. The shelf life of the drug product should not be extended beyond 24 months until stability of polysorbate 80 in the drug product is established. The drug product is to be stored at controlled room temperature at 25°C (77°F); excursions permitted to 15-30 °C (59-86°F).

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has adequately addressed all the deficiencies recorded as indicated in the Chemistry Assessment Section. The reviewer recommends approval of the application with respect to CMC.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

A. K. Mitra, Ph.D/
Moo-Jhong Rhee, Ph.D/
G. Lyght/

C. CC Block

NDA 21-371/Division File

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ON ORIGINAL

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page(s) of trade secret and/or confidential commercial information (b4)

CHEMISTRY REVIEW

Chemistry Assessment Section

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application	NDA 21371/000	Sponsor:	NOVAVAX INC
Org Code	580		12111 PARKLAWN DR
Priority	3S		ROCKVILLE, MD 20852
Stamp Date	29-JUN-2001	Brand Name :	ESTRASORB 2.5 MG/G —
PDUFA Date	12-OCT-2003	Estab. Name:	
Action Goal		Generic Name:	ESTRASORB
District Goal	13-AUG-2003	Dosage Form:	(EMULSION, —
		Strength :	2.5 MG/G

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

Overall Recommendation: ACCEPTABLE on 08-OCT-2003by S. FERGUSON(HFD-322) 301-827-9009

WITHHOLD on 01-JUL-2003by J. D AMBROGIO(HFD-322) 301-827-9049

WITHHOLD on 13-JAN-2003by J. D AMBROGIO(HFD-322) 301-827-9049

WITHHOLD on 23-APR-2002by HARTMANB

Establishment : — FEI —

—

—

DMF No: AADA:

Responsibilities: —

Profile	:	CTL	OAI Status:	NONE
Last Milestone	:	OC RECOMMENDATION		
Milestone Date	:	13-DEC-02		
Decision	:	ACCEPTABLE		
Reason	:	BASED ON PROFILE		

Establishment : [redacted] FEI : [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile	:	CTL	OAI Status:	NONE
Last Milestone	:	OC RECOMMENDATION		
Milestone Date	:	13-JAN-03		
Decision	:	ACCEPTABLE		
Reason	:	BASED ON PROFILE		

Establishment : [redacted] FEI : [redacted]

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ON ORIGINAL

08-OCT-2003 FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE

Last Milestone : OC RECOMMENDATION

Milestone Date : 08-OCT-03

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : FEI :

DMF No: AADA:

Responsibilities:

Profile : OIN OAI Status: NONE

Last Milestone : OC RECOMMENDATION

Milestone Date : 13-DEC-02

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : FEI

DMF No: AADA:

Chemistry Assessment Section

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 13-DEC-02
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : [redacted] FEI [redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 13-DEC-02
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI :

08-OCT-2003 | FDA CDER EES | Page 3 of 4

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

NOVAVAX INC
12111 PARKLAWN DRIVE
ROCKVILLE, MD 20852

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 31-DEC-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :
NOVAVAX INC
3001 RED LION ROAD
PHILADELPHIA, PA 19114

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : OIN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 10-JAN-03
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : FEI :

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile	CTL	OAI Status:	NONE
Last Milestone	OC RECOMMENDATION		
Milestone Date	16-DEC-02		
Decision	ACCEPTABLE		
Reason	BASED ON PROFILE		

Establishment [redacted] FEI : [redacted]

DMF No: [redacted] AADA:

Responsibilities: [redacted]

08-OCT-2003 | FDA CDER EES | Page 4 of 4

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile	CSN	OAI Status:	NONE
Last Milestone	OC RECOMMENDATION		
Milestone Date	16-DEC-02		
Decision	ACCEPTABLE		
Reason	BASED ON PROFILE		

Establishment : [redacted] FEI : [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile	CTL	OAI Status:	NONE
Last Milestone	OC RECOMMENDATION		
Milestone Date	13-DEC-02		
Decision	ACCEPTABLE		
Reason	BASED ON PROFILE		

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ON ORIGINAL

[redacted]

APPEARS THIS WAY ON ORIGINAL

580) 301-827-4238)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-SEP-2001				MITRAA
OC RECOMMENDATION	06-SEP-2001			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ
REQUEST CANCELLED	29-APR-2002			WITHDRAWN	EES_PROD
SUBMITTED TO OC	12-DEC-2002				MITRAA
OC RECOMMENDATION	13-DEC-2002			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	08-OCT-2003				MITRAA
OC RECOMMENDATION	08-OCT-2003			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: [redacted] FEI [redacted]

[redacted]

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

/s/

Amit K. Mitra
10/9/03 09:17:28 AM
CHEMIST

Moo-Jhong Rhee
10/9/03 10:08:44 AM
CHEMIST
I concur

METHODS VALIDATION

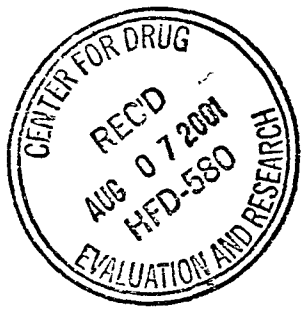
Three copies of the Methods Validation information from this NDA submission follow. The information included comes from the following volumes:

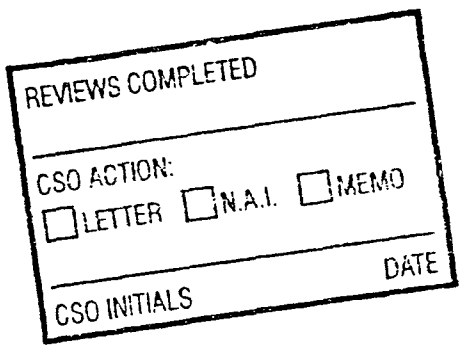
Volume 1.002 pp. 62-72, 237
Volume 1.007 Appendix 5: Analytical Methods and Validation
Volume 1.009 Appendix 6: Testing

ORIG AMENDMENT

BC

ORIGINAL





NDA 21-371

Estrasorb

Novavax

Amit K. Mitra, Ph.D
Division of Reproductive and Urologic Drugs

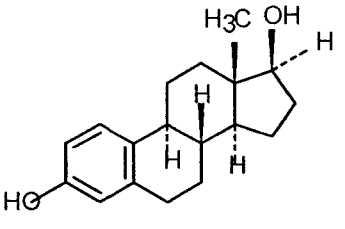


Table of Contents

Chemistry Review Data Sheet

1. NDA 21-371

2. REVIEW # 2

3. REVIEW DATE: 15-APR-2002

4. REVIEWER: Amit K. Mitra, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	29-Jun-2001
Amendment	29-Jun-2001
Amendment	08-Aug-2001
Amendment	14-Dec-2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	20-FEB-2002
Amendment	01-MAR-2002
Amendment	07-MAR-2002

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Novavax, Inc.
Address:	12111 Parklawn Drive, Rockville, MD 20852
Representative:	D. Craig Wright, M.D
Telephone:	301-231-0774 x 23

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Estrasorb
b) Non-Proprietary Name (USAN): Estradiol topical emulsion
c) Code Name/# (ONDC only):N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Relief of vasomotor symptoms in — symptomatic post-menopausal women

11. DOSAGE FORM: Emulsion (cream)

12. STRENGTH/POTENCY: 2.5 mg/g; The drug is supplied in — unit dose package [redacted] 1.74 g/pouch), [redacted]

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note24]:

_____SPOTS product – Form Completed

__x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: Estradiol hemihydrate; $C_{18}H_{24}O_2$. ½ H_2O; 281.4

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: See Chemistry Review #1, dated 13-FEB-2002. Satisfactory.

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Withhold	23-APR-2002	Mr. B. Hartman
Methods Validation	Will be initiated		
Microbiology	Satisfactory	04-APR-2002	Dr. P. Stinavage

The Chemistry Review for NDA 21-371

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is not-approvable from Chemistry, Manufacturing, and Controls point of view.

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

II. Summary of Chemistry Assessments

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

The drug product "Estrasorb" , is a water-in-oil emulsion at a concentration of 2.5 mg/g for the drug substance, estradiol. The drug product is proposed to be available in — — packaging configurations. — 1.74 g unit dose pouch, — — For desired efficacy, the patient needs to apply contents of two 1.74 g pouch, The drug product is indicated for the relief of vasomotor symptoms in — symptomatic post-menopausal women.

The drug substance is estradiol, USP and it is used in the hemihydrate form. The Chemistry Manufacturing and Control information of the drug substance is located in the , DMF — and it is deemed adequate to support the NDA. The sponsor of the NDA conducts a UV identification test according to the USP for acceptance of the drug substance. Since UV method does not give a finger print of the drug substance, a more discriminatory identification test such as Infrared Absorption (USP Identification test A) was recommended for acceptance of the drug substance in the Chemistry Review #1, dated 13-FEB-2002. The sponsor agreed with the recommendation and adopted an IR specification for the drug substance.

All excipients used in the drug product are compendial. However, polysorbate 80 is a known penetration enhancer in vitro, and the compendial specification does not include an assay for polysorbate 80. Therefore, an assay specification of polysorbate 80 is being sought. The sponsor agreed on developing an assay method but did not propose a time table when the analytical test method including the validation and the acceptance criteria will be implemented. Therefore, this item is yet to be clarified. The critical in-process

parameters are particle size of the emulsion, homogeneity or content uniformity, fill weight, and leak test. The sponsor was requested to adopt in-process controls for particle size and content uniformity or homogeneity to assure uniformity of the amount of estradiol and particle size throughout the batch but the sponsor was not able to adopt the homogeneity of estradiol as an in-process control, and it remains to be established. The pre-clinical batches were manufactured using a —— and packaged in syringes. The composition of the batches were different from the to-be-marketed formulation with respect to the oil to water ratio. The Phase III clinical trial was conducted using a formulation with the identical composition to that of the to-be-marketed formulation but manufactured at a different manufacturing site with different equipment of same operating principles. The bridging between the Phase III clinical supplies and the to-be-marketed formulation was conducted using an in vitro methodology recommended by SUPAC-SS. The adequacy of this test method and the test data is under review by the OCPB reviewer.

The sponsor provided partial response to the Information Request letter. The sponsor still needs to address the unresolved issues regarding the drug product Manufacturing and Controls described under "Basis for Approvability or Not-Approval Recommendation" below.

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

The recommended dose for the drug product is — grams/per day. Only one formulation (2.5 mg of estradiol/gram of drug product) is available in [redacted] packaging configuration. The recommend dose is content [redacted] of two pouches of 1.74 g/ pouch [redacted] with the same formulation containing 2.5 mg of estradiol/gram per day. The recommended dose per day is the maximum daily dose. The drug product is recommended to be applied on thigh and calf area for systemic absorption. Upon application of the recommended dose, – microgram of estradiol is delivered to the systemic circulation per day.

So far, the sponsor has provided — stability data. The decision on the shelf life is pending a satisfactory response from the sponsor regarding stability indicating nature of the analytical method for assay of estradiol, and satisfactory content uniformity (homogeneity).

C. Basis for Approvability or Not-Approval Recommendation

The facilities are not acceptable according to the CGMP Moreover, The quality of the drug product is not adequately established in terms of the methods used for analysis, and control used for the manufacture, processing or holding of the drug products.

To correct the deficiencies, the sponsor should address the following:

1. The deficiencies provided in the Form 483 by the inspector.
2. Content uniformity of estradiol in the drug product in the unit-dose packages should be established
3. [redacted]
4. Stability indicating HPLC assay method should be established. Estradiol impurities and related substances assay in the drug product should be conducted adequately.
5. Specific reason and remedy for assay failures [redacted] should be provided.
6. The delivery accuracy beyond — of the delivery in the — dose container should be established.
7. An assay specification for the surfactant polysorbate 80 should be adopted.
8. The in-process control for estradiol homogeneity in various portions of bulk estradiol emulsion should be established.
9. The drug product batches should be examined for the presence of estradiol — under a microscope. If — of estradiol form as a function of time during storage, a specification for the number — allowed per unit dose should be adopted. The test method should be provided.
10. Since this drug product is a topical product for systemic absorption, a specification for in vitro release rate should be adopted.
11. The extractable and leachable information for the foil laminate should be provided according to the "Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics, May 1999" for review.
12. Respond to all labeling comments cited in the Information Request letter, dated 01-FEB-2002 should be provided.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

A. K. Mitra, Ph.D/
M. J. Rhee, Ph.D/
D. Spell-lesanee/

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page(s) of trade secret and/or confidential commercial information (b4)

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

/s/

Amit K. Mitra
4/23/02 02:22:54 PM
CHEMIST

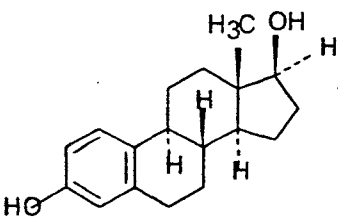
Moo-Jhong Rhee
4/23/02 02:46:19 PM
CHEMIST
I concur

NDA 21-371

ESTRASORB

NOVAVAX INC.

AMIT K. MITRA, Ph.D
REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS



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APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. NDA 21-371

2. REVIEW #: 1

3. REVIEW DATE: 13-FEB-2002

4. REVIEWER: Amit K. Mitra, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	29-Jun-2001
Amendment	29-Jun-2001
Amendment	08-Aug-2001
Amendment	14-Dec-2001

7. NAME & ADDRESS OF APPLICANT:

Name: Novavax, Inc.

Address: 12111 Parklawn Drive, Rockville, MD 20852

Executive Summary Section

Representative: D. Craig Wright, M.D

Telephone: 301-231-0774 x 23

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Estrasorb
b) Non-Proprietary Name (USAN): Estradiol topical emulsion
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Relief of vasomotor symptoms in symptomatic post-menopausal women

11. DOSAGE FORM: Emulsion

12. STRENGTH/POTENCY: 2.5 mg/g; The drug is supplied in unit dose packages 1.74 g/pouch),

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)

_____SPOTS product – Form Completed

__x____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: Estradiol hemihydrate; $C_{18}H_{24}O_2$. ½ H_2O; 281.4

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	24-AUG-1999	Reviewr: Dr. R. Trimmer
	III			1	Adequate	13-FEB-2002	Reviewr: Dr. A. K. Mitra
	III			7	Adequate	09-FEB-2001	The DMF was reviewed by Dr. D. Klein on 9-FEB-2001 and was found adequate for (part of DMF task force review). The item referred by the sponsor of the NDA (is included in the review.
	III			1	Adequate	08-FEB-2002	Reviewer: Dr. A. K. Mitra

[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: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending		
Pharm/Tox	NA		
Biopharm	NA		
LNC	The established name is recommended to be "Estradiol topical emulsion"	07-DEC-2001	Dr. D. Boring
Methods Validation	Will be initiated		
OPDRA	Trademark "Estrasorb" satisfactory. The other pertinent OPDRA comments were incorporated in the review of the labeling section	03-JAN-2002	Ms. Marci Lee
EA	Categorical exclusion granted		
Microbiology	Not satisfactory	25-OCT-2001 and 17-JAN-2002	Dr. P. Stinavage

The Chemistry Review for NDA 21-371

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable pending resolution of all the deficiencies recorded in the Draft Deficiency letter.

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

The sponsor should commit to monitor the ——— on batch release and during stability for three lots and report the data to show that the polysorbate 80 is stable in the drug product. This commitment is necessary, since the sponsor may extend the shelf life via annual report and it is not known whether the drug product would be efficacious at the extended shelf life.

II. Summary of Chemistry Assessments

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

The drug product "Estrasorb" , is a water-in-oil emulsion at a concentration of 2.5 mg/g for the drug substance, estradiol. The drug product is proposed to be available in — packaging configurations. — 1.74 g unit dose pouch, — For desired efficacy, the patient needs to apply contents of two 1.74 g pouch, — — once daily. — — The drug product is indicated for the relief of vasomotor symptoms in symptomatic post-menopausal women.

The drug substance is estradiol, USP and it is used in the hemihydrate form. The Chemistry Manufacturing and Control information of the drug substance is located in the — DMF — and it is deemed adequate to support the NDA. The sponsor of the NDA conducts a UV identification test according to the USP for acceptance of the drug substance. Since UV method does not give a finger print of the drug substance a more discriminatory identification test such as Infrared Absorption (USP Identification test A) is recommended for acceptance of the drug substance. All excipients are compendial. However, polysorbate 80 is a known penetration enhancer in vitro, and the compendial specification does not include an assay for polysorbate 80. Therefore, an assay specification of polysorbate 80 is being sought. The drug product is a water-in-oil emulsion stabilized with a surfactant polysorbate 80. The average particle size of the emulsion is approximately 1 micron.

The critical in-process parameters are particle size of the emulsion, homogeneity or content uniformity, fill weight, and leak test. The sponsor is being asked to adopt in-process controls for particle size and content uniformity or homogeneity to assure uniformity of the amount of estradiol and particle size throughout the batch. The pre-clinical batches were manufactured using a [redacted] and packaged in syringes. The composition of the batches were different from the to-be-marketed formulation with respect to the oil to water ratio. The Phase III clinical trial was conducted using a formulation with the same composition to that of the to-be-marketed formulation but manufactured at a different manufacturing site with different equipment of same operating principles. The bridging between the Phase III clinical supplies and the to-be-marketed formulation was conducted using an in vitro methodology recommended by SUPAC-SS. The adequacy of this test method and the test data will be determined by the OCPB reviewer. Several deficiencies are recorded in the Chemistry Review #1 and those are listed in the draft deficiency letter. The validity of the test method for assay of estradiol is being questioned by the reviewer. The sponsor is asked to provide data to support the claim that the test method is stability indicating and capable of measuring the impurities and related substances.

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

The recommended dose for the drug product is [redacted] grams/per day. Only one formulation (2.5 mg of estradiol/gram of drug product) is available [redacted] packaging configuration. The recommend dose is [redacted] content of two pouches of 1.74 g/ pouch [redacted] containing 2.5 mg of estradiol/gram per day. The recommended dose per day is the maximum daily dose. The drug product is recommended to be applied on thigh and calf area for systemic absorption. Upon application of the recommended dose, [redacted] of estradiol is delivered to the systemic circulation per day.

The expiration date is not yet established due to inadequacy of the stability data and the analytical method. So far, the sponsor has provided [redacted] stability data. The sponsor plans to provide [redacted] stability data in the future. Since the assay values for estradiol are extremely variable, resulting in failures for the assay of estradiol during the stability studies, decision on expiration dating is deferred until a satisfactory response on the assay failures is received.

C. Basis for Approvability or Not-Approval Recommendation

The NDA is approvable pending satisfactory response to the Information Request presented at the end of the review. The major deficiencies with the application is a lack of assay for the surfactant, polysorbate 80. Since polysorbate 80 is penetration enhancer for the drug product, an assay for polysorbate 80 is necessary. The analytical method for estradiol assay appears to be not stability indicating. Therefore, the sponsor must provide information regarding stability indicating nature of the assay method. The content uniformity or homogeneity of estradiol has not been evaluated; therefore, the sponsor needs to establish those attributes and

implement those in the drug product specification. The sponsor also needs to include related substances as a part of the drug product specification, unless justified, and explain the reason for estardiol assay failures during stability studies.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

A. K. Mitra, Ph.D/
M. J. Rhee, Ph.D/
D. Moore/

C. CC Block

NDA 21-371/Division File

APPEARS THIS WAY
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page(s) of trade secret and/or confidential commercial information

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14-JAN-2002

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Page 1 of 3

Application: **NDA 21371/000** Priority: **3S** Org Code: **580**
Stamp: **29-JUN-2001** Regulatory Due: **29-APR-2002** Action Goal: District Goal: **28-FEB-2002**
Applicant: **NOVAVAX** Brand Name: **ESTRASORB 2.5 MG/G** [redacted]
12111 PARKLAWN DR Established Name:
ROCKVILLE, MD 20852 Generic Name: **ESTRASORB**
Dosage Form: **EMC (EMULSION,** [redacted]
Strength: **2.5 MG/G**

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

Overall Recommendation:

Establishment: [redacted] DMF No:
AADA No:

[redacted]

Profile: **CTL** OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **06-SEP-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: [redacted] DMF No:
AADA No:

[redacted]

Profile: **CTL** OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **06-SEP-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: [redacted] DMF No:
AADA No:

[redacted]

Profile: **CTL** OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **06-SEP-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: [redacted] DMF No:

14-JAN-2002

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

AADA No:

[redacted]

[redacted]

Profile: **CTL** OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **06-SEP-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment:
NOVAVAX INC
12111 PARKLAWN DRIVE
ROCKVILLE, MD 20852

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE RELEASE TESTER**
Last Milestone: **ASSIGNED INSPECTION TO IB** **FINISHED DOSAGE STABILITY TESTER**
Milestone Date: **07-SEP-2001**

Establishment: [redacted]

DMF No:
AADA No:

[redacted]

Profile: **OIN** OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **ASSIGNED INSPECTION TO IB**
Milestone Date: **17-OCT-2001**

Establishment: [redacted]

DMF No: [redacted]
AADA No:

[redacted]

Profile: **CTL** OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **07-SEP-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: [redacted]

14-JAN-2002

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

AADA No:

[redacted]

[redacted]

Profile: **CSN** OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **24-SEP-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: [redacted] DMF No:
AADA No:

[redacted]

Profile: **CTL** OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **06-SEP-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

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14-JAN-2002 FDA CDER EES Page 1 of 3
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21371/000 Action Goal:
Stamp: 29-JUN-2001 District Goal: 28-FEB-2002
Regulatory Due: 29-APR-2002 Brand Name: ESTRASORB 2.5 MG/G
Applicant: NOVAVAX Estab. Name:
12111 PARKLAWN DR Generic Name: ESTRASORB
ROCKVILLE, MD 20852
Priority: 3S Dosage Form: (EMULSION
Org Code: 580 Strength: 2.5 MG/G

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

Overall Recommendation:
Establishment:

DMF No: AADA:
Responsibilities:
Profile: CTL OAI Status: NONE
Estab. Comment: (on 06-SEP-2001 by A. MITRA (HFD-580) 301-827-4238)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-SEP-2001				MITRAA
OC RECOMMENDATION	06-SEP-2001			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment:

DMF No: AADA:
Responsibilities:
Profile: CTL OAI Status: NONE
Estab. Comment: (on 06-SEP-2001 by A. MITRA (HFD-580) 301-827-4238)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-SEP-2001				MITRAA
OC RECOMMENDATION	06-SEP-2001			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment:

DMF No: AADA:
Responsibilities:
Profile: CTL OAI Status: NONE
Estab. Comment:

(HFD-580) 301-827-4238)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator

SUBMITTED TO OC	06-SEP-2001		MITRAA
OC RECOMMENDATION	06-SEP-2001	ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile: CTL OAI Status: NONE

Estab. Comment: [redacted] (on 06-SEP-2001 by A. MITRA (HFD-580) 301-827-4238)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-SEP-2001				MITRAA
OC RECOMMENDATION	06-SEP-2001			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment:
NOVAVAX INC
12111 PARKLAWN DRIVE
ROCKVILLE, MD 20852

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: PARTICLE SIZING, ANALYTICAL TESTING OF THE FINISHED PRODUCT, RAW MATERIAL TESTING (on 06-SEP-2001 by A. MITRA (HFD-580) 301-827-4238)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-SEP-2001				MITRAA
SUBMITTED TO DO	06-SEP-2001	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	'07-SEP-2001	GMP			BBARGO

Establishment: [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile: OIN OAI Status: NONE

Estab. Comment: [redacted]

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-SEP-2001				MITRAA
SUBMITTED TO DO	06-SEP-2001	PS			DAMBROGIOJ
ASSIGNED INSPECTION	'17-OCT-2001	PS			DPAGANO

Establishment: [redacted]

14-JAN-2002 FDA CDER EES Page 3 of 3
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

[redacted]

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

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-SEP-2001				MITRAA
OC RECOMMENDATION	07-SEP-2001			ACCEPTABLE BASED ON PROFILE	GARCIAM

CSN

Establishment: [redacted]

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

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-SEP-2001				MITRAA
SUBMITTED TO DO	07-SEP-2001	10D			GARCIAM
DO RECOMMENDATION	24-SEP-2001			ACCEPTABLE BASED ON FILE REVIEW	GARCIAM
OC RECOMMENDATION	24-SEP-2001			ACCEPTABLE DISTRICT RECOMMENDATION	GARCIAM

Establishment: [redacted]

DMF No: [redacted] AADA:
Responsibilities: [redacted]
Profile: CTL OAI Status: NONE
Estab. Comment: USP<661> AND USP<88> [redacted] (on 06-SEP-2001 by A. MITRA (HFD-580) 301-827-4238)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-SEP-2001				MITRAA
OC RECOMMENDATION	06-SEP-2001			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

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/s/

Amit K. Mitra
2/13/02 10:23:31 AM
CHEMIST

Moo-Jhong Rhee
2/14/02 02:04:55 PM
CHEMIST
I concur

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