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/s/

Diane V. Moore
9/24/01 06:26:09 PM

Susan Allen
9/25/01 01:55:47 PM

APPEARS THIS WAY
ON ORIGINAL

Filing Memorandum
Division of Reproductive and Urologic Drug Products

NDA 21-371/S-000

Trade Name:	ESTRASORB™
Generic Name:	Estradiol hemihydrate, USP
Sponsor:	Novavax Inc. 12111 Parklawn Drive Rockville, MD 20852
Submission Date:	June 29, 2001
Date Received:	June 29, 2001
Indication:	Treatment of moderate-to-severe vasomotor symptoms associated with the menopause.
Dose form:	[redacted]
Treatment Schedule:	7.5 mg of estradiol hemihydrate, USP applied daily with no interruption in therapy; systemic delivery of 50 mcg of estradiol per day.
Dosage Regimens:	1. Three 1.15 gram foil-laminated pouches each containing 2.875 mg estradiol hemihydrate, USP; each pouch delivers approximately 1 gram of ESTRASORB™ [redacted] containing 2.5 mg of estradiol: - first pouch applied to the top of the right thigh for two minutes - second pouch applied to the top of the left thigh for two minutes - ½ of the third pouch applied to the left calf for one minute; ½ of the third pouch applied to the right calf for one minute - any excess on either hand applied to buttock 2. Two 1.74 gram foil-laminated pouches each containing 4.35 mg estradiol hemihydrate, USP; each pouch delivers approximately 1.5 grams of ESTRASORB™ [redacted] containing approximately 3.75 mg of estradiol: - first pouch applied to the top of the right thigh for two minutes; any excess applied to the right calf for one minute - second pouch applied to the top of the left thigh for two minutes; any excess applied to the left calf for one minute - any excess on either hand applied to buttock 3. [redacted]
Related Submission:	IND 49,761
User Fee Goal Dates:	June 29, 2002
Division Goal Date:	April 29, 2002
Filing Meeting Date:	August 8, 2001
Medical Reviewer:	Theresa H. van der Vlugt, MD, M.P.H.

Submission Resume

ESTRASORB™ has been in development since 1996. IND 49,761/S-000, submitted on January 16, 1996, was a Phase 1, 10-day open design study of 10 postmenopausal women with moderate-to-severe vasomotor symptoms in which subjects applied topically, to the abdomen, 1 ml of micellar nanoparticles containing 2.5 mg of estradiol hemihydrate, USP. While the original Phase 1 safety study demonstrated no adverse skin reactions or other significant adverse events, the expected serum estradiol concentrations were not achieved. Higher doses of ESTRASORB™ (up to 10 mg) were subsequently studied. Topical application to one or more sites involving the lower extremities and buttocks were also investigated.

ESTRASORB™ (containing 2.5 mg of estradiol per gram —) is a topical delivery system consisting of surfactant stabilized micelles (micellar nanoparticles less than — in diameter) containing estradiol. — The components are then —

Early non-clinical studies and initial Phase 1 studies were conducted using a formulation containing — — water that required refrigeration. In 1997, a — formulation containing — water on a volume per volume basis was developed (ratio of pre-mixed materials to water is —). This new — — formulation was used to conduct a:

1) Phase 1 PK/PD study of single-site vs. split-site application of 7.5 mg ESTRASORB™ daily for 8 days in 10 subjects (Study E98-1);
2) Phase 2/3 double-blind, randomized, placebo-controlled dose-ranging study (2.5 mg, 5.0 mg, 7.5 mg of estradiol or placebo) of daily split-site applications over a four week period in 125 subjects for VMS (E98-2); and
3) Phase 3 double-blind, randomized, placebo-controlled study of daily split-site applications of 7.5 mg of ESTRASORB™ or placebo over a 12 week period in 200 subjects for VMS (E99-1).
4) Phase 1 open-label, single dose study in 12 subjects to determine the amount of residual ESTRASORB™ on the skin surface post application (2 and 8 hours) (E2000-1).

The efficacy data from Study E99-1 (12 weeks) is acceptable for review for the relief of moderate-to-severe vasomotor symptoms associated with the menopause. The data from the 4-week Phase 2/3 study (E98-2) is only supportive, as noted in the submission. The primary efficacy parameter for Study E99-1 is the change from baseline of the average daily count of moderate-to-severe hot flushes at both week 4 and week 12. Secondary efficacy parameters include the change from baseline in the severity of hot flushes, the absence of moderate-to-severe hot flushes in any seven-day dosing period, and trough serum levels of estradiol, estrone, and FSH. Trough serum levels of estrone sulfate were obtained in Study E98-2.

Integrated safety data from the three completed studies utilizing the to-be-marketed — formulation (E98-1, E98-2 and E99-1) is included in the submission and is acceptable. Safety data from the three completed studies utilizing the — formulation (N95-3, N96-1 and N97-3) and the residual estradiol study (E2000-1) were not integrated, but are included for review.

Fileability of NDA 21-371/S-000

NDA 21-371/S-000 is fileable.

Review Issues

1) Large variability in study site enrollment (20 original sites, 2 sites had no enrolled subjects and were closed due to non-performance, subjects enrolled in the 18 remaining sites ranged from 1 to 46).
2) Sponsor request approval of three dose administration configurations (felt to possible have less potential to bind large quantities of estradiol). These include: 1) three 1.15 gram foil-laminated pouches as used in the primary efficacy Study E99-1; 2) two 1.74 gram foil-laminated pouches; and 3) —

Request for Data

Sponsor is requested to submit a table entitled, "Summary of the Change from Screening for the Average Daily Severity Index by Age Category, Week, and Treatment Group, Protocol E99-1, Intent-to-Treat Population" that includes screening and weeks 4, 8, and 12. The requested table should be similar to Table 19.0 on page 157 of Volume Number 25 of the submission entitled, "Summary of the Change from Screening for the Average Daily Count of Moderate to Severe Hot Flushes by Age Category, Week, and Treatment Group, Protocol E99-1, Intent-to-Treat Population."

Recommendations for a Division of Scientific Investigations Audit

1. [redacted]
2. [redacted]

NDA: 21-371

45 Day Filing Meeting Checklist
CLINICAL

ITEM	YES	NO	COMMENT
1) Is the clinical section of the NDA clearly organized?	X		
2) Is the clinical section of the NDA adequately indexed and paginated?	X		
3) Is the clinical section of the NDA legible?	X		
4) Is there an adequate rationale for selection of dose and dosing schedule?	X		
5) Are the requisite number of adequate and well controlled studies submitted in the application?	X		
6) Are the pivotal efficacy studies of appropriate design and duration to assess approvability of this product for its proposed indication?	X		
7) Are electronic data sets (with adequate documentation for their use) provided for pivotal efficacy studies?	X		
8) Has the applicant submitted line listings in a format to allow review of individual patient data?	X		
9) Has the applicant submitted a rationale for assuming the applicability of foreign trial results to the U.S. population?	NA		
10) Has the applicant submitted all required case report forms (i.e., deaths, drop-outs due to ADEs and any other CRFs previously requested by the Division?	X		
11) If appropriate, have stratified analyses of primary safety and efficacy parameters been conducted for age, gender and race?	X		
12) Has the applicant presented the safety data in a manner previously agreed to by the Division?	X		
13) If approved in other countries, have a summary and assessment of foreign post-marketing experience been provided?	NA		
14) Has draft labeling been submitted?	X		
15) Have all special studies/data requested by the Division during pre-submission discussions with the sponsor been submitted?	X		Sponsor submitted data summarizing the change from screening by age group for the frequency of moderate-to-severe vasomotor symptoms but not for severity of vasomotor symptoms. This data will be requested.

16) From a clinical perspective, is this NDA fileable? If "no", please state in item #17 below why it is not.	X		
17) Reasons for refusal to file:			

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/s/

Theresa Van Der Vlugt
8/6/01 01:22:38 PM
MEDICAL OFFICER

Shelley Slaughter
8/6/01 02:21:18 PM
MEDICAL OFFICER
I concur

Division of Reproductive and Urologic Drug Products

ADMINISTRATIVE REVIEW OF APPLICATION

Application Number: **21-371**

Name of Drug: Estrasorb™ (estradiol micellar nanoparticles) emulsion

Sponsor: Novavax, Inc.

Material Reviewed: NDA 21-371

Submission Date: June 29, 2001

Receipt Date: June 29, 2001

Filing Date: August 28, 2001

User-Fee Goal Date(s): April 29, 2002 and June 29, 2002

Proposed Indication: For the treatment of vasomotor symptoms in post-menopausal women

Other Background Information: IND 49,761

Review

PART I: OVERALL FORMATTING[a]

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Cover Letter (original signature)	X		Volume 1.001
2. Form FDA 356h (original signature)	X		Volume 1.001
a. Reference to DMF(s) & Other Applications	X		Volume 1.001
3. Patent information & certification	X		Volume 1.001, pages 257-267 and page 268
4. Debarment certification (note: must have a definitive statement)	X		Volume 1.001, page 270
5. Financial Disclosure	X		Volume 1.001, pages 276-285

6. Comprehensive Index	X		Volume 1.001, page i- xxi
7. Pagination	X		throughout
8. Summary Volume	X		Volume 1.001
9. Review Volumes	X		Volumes 1.002-1.011; 1.012-1.013; 1.014-1.023; 1.024-1.052; 1.053
10. Labeling (PI, container, & carton labels)	X		Volume 1.001, pages 2-90
a. unannotated PI	X		Volume 1.001, pages 2-30
b. annotated PI	X		Volume 1.001, pages 50-90
c. immediate container	X		Volume 1.001, pages 32, 37, 42
d. carton	X		Volume 1.001, pages 33, 34, 35, 38, 39, 40, 43
e. foreign labeling (English translation)		X	This drug is not currently being marketed in any country
11. Foreign Marketing History	X		Volume 1.001, page 99
12. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		Volume 1.054
13. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X		Volume 1.054

Y=Yes (Present), N=No (Absent)

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PART II: SUMMARY[b]

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		Pharmacologic Class and Intended Use-- Volume 1.001, page 91 Scientific Rationale and Potential Clinical Benefit- Volume 1.001, page 92
2. Summary of Each Technical Section			
a. Chemistry, Manufacturing, & Controls (CMC)	X		Volume 1.002-1.011, pages
b. Nonclinical Pharmacology/Toxicology	X		Volume 1.012, page 18
c. Human Pharmacokinetic & Bioavailability	X		Volume 1.014, page 48
d. Microbiology		X	not submitted
e. Clinical Data & Results of Statistical Analysis	X		Volume 1.024-1.052, pages
3. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X		Volume 1.001, page 250
4. Summary of Safety	X		Volume 1.001, pages 214
5. Summary of Efficacy	X		Volume 1.001, page 195

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c]

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. List of Investigators	X		Volume 1.024, page 2
2. Controlled Clinical Studies	X		Volume 1.001, page 250 and Volume 1.024
a. Table of all studies	X		Volume 1.001, page 152; Volume 1.024 page 2
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		list of investigators -- Volume 1.024, page 2 Reports of individual studies—Volume 1.024, page 275 Clinical Pharmacology –Volume 1.024, page 41
c. Optional overall summary & evaluation of data from controlled clinical studies	X		Volume 1.001, page 256; Volume 1.024, page 11
3. Integrated Summary of Efficacy (ISE)	X		Volume 1.025
4. Integrated Summary of Safety (ISS)	X		Volume 1.026
5. Drug Abuse & Overdosage Information	X		Volume 1.027, page 342
6. Integrated Summary of Benefits & Risks of the Drug	X		Volume 1.027, page 343
7. Gender/Race/Age Safety & Efficacy Analysis Studies	X		Volume 1.014, page 72

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		X	Sponsor requested a waiver for pediatric studies
2. Diskettes	X		CD Rom of CRTs
a. Proposed unannotated labeling in MS WORD 8.0	X		
b. Stability data in SAS data set format		X	
c. Efficacy data in SAS data set format	X		
d. Biopharmacological information & study summaries in MS WORD 8.0		X	
e. Animal tumorigenicity study data in SAS data set format		X	
3. User-fee payment receipt	X		This NDA is exempt from user fees as it has a Small Business exemption

Y=Yes (Present), N=No (Absent)

[a]"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[b]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[c]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

Additional Comments:

Conclusions: This NDA can be filed from a regulatory perspective.

/S/

Regulatory Health Project Manager

/S/

Concurrence

cc:
Original NDA
HFD-580/Div. Files
HFD-580/PM/D.Moore/T.Rumble
HFD-580/S.Allen/D.Shames
HFD-580/ S.Slaughter/R.Bennett/M.Rhee/A.Jordan/K.Raheja/A.Parekh
draft: May 14, 2001
final: May 15, 2001

ADMINISTRATIVE REVIEW

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/s/

Diane V. Moore
7/20/01 11:47:47 AM
CSO

Terri F. Rumble
7/20/01 03:12:41 PM
CSO

Minutes of Teleconference

Date: June 22, 2001 **Time**: 1:00 - 2:15 PM **Location:** Parklawn; Room 17B-43

IND: 49,761 **Drug Name**: Estrasorb (micellar nanoparticles ; estradiol)

Indication: reduction of vasomotor symptoms (VMS) [redacted]

External Constituent: Novavax, Inc.

Type of Meeting: Chemistry Pre-NDA

FDA Lead: Dr. Moo-Jhong Rhee

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580) (via telephone)
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Archana Reddy – Project Manager, DRUDP (HFD-580)
Yuan-Yuan Chiu, Ph.D. - Director, Office of New Drug Chemistry (ONDC; HFD-800)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
John Hunt - Deputy Director, Division of Pharmaceutical Evaluation II (DPE II; HFD-870)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

External Participants:
D. Craig Wright, M.D. – Chief Scientific Officer, Novavax
Joan Brisker – Director of Regulatory Affairs and Quality Assurance, Novavax
Louis Reichel, Ph.D. – Director, Quality Assurance and Analytical Chemistry, Novavax
[redacted] Consultant,

Meeting Objective:
To discuss the Chemistry, Manufacturing and Quality Control questions posed in the May 4, 2001, meeting package from Novavax.

Background: The sponsor changed the manufacturing site from [redacted] because [redacted]

Discussion Items:
- the sponsor is proposing to use data utilizing the [redacted] to support the change in manufacturing sites; additional data using the [redacted] method should be provided in addition to the data from the method currently being used at [redacted] support the change in manufacturing sites

- in order to compare the products manufactured at the two different sites, the sponsor should follow the guidance entitled, "guidance for Industry, Nonsterile SemiSolid Dosage Forms, Scale-up and Post Approval Changes: Chemistry, Manufacturing, and Controls; In vitro Release Testing and in Vivo Bioequivalence Documentation"; it is a release rate test using with a
- the product is proposed to be marketed in packages 1.74 grams in a foil pouch, and
- the Division noted that in the May 4 submission on page 277, the composition and percentage of each component is given with the difference in percentages: in the June 18 submission, the sponsor again provided the composition of two components; the formulations at appear to be different based on the table on page 277; the sponsor clarified that there was no intent to change the composition; the numbers used in the submissions are both within the assigned specifications but in practicality, are slightly different since they were manufactured at different times

Decisions Reached:

- **Question #1:** Novavax would like to file an NDA on ESTRASORB in June or July of 2001. Due to the Regulatory and corporately required change in contract manufacture, Novavax would only have six months worth of data on the lots manufactured and packaged at Novavax would propose filing stability update within of our initial filing. Is worth of stability data on the ESTRASORB manufactured lots sufficient for acceptance of the proposed application for review?
  - **Answer to Question #1**: submission of of stability data for the 1.75 gm unit dose pouch with updated data during the review is acceptable; however, the shelf-life to be granted for the product depends on the quality of the stability data for all test attributes and the length of time of the stability data; the last amendment should not be after 3-months prior to the goal date
  - because the product is an emulsion, particle size and distribution of particles should be analyzed and the NDA should include the particle size distribution specifications
  - the expiration dating will be based on real-time data
  - the alcohol content of " ' is not acceptable unless supportive data is submitted that demonstrates efficacy at of theoretical should be utilized because alcohol is a penetration enhancer and a preservative
  - the sponsor suggested that because the concentration of ethanol is it is not acting as a penetration enhancer or a preservative, and the polysorbate 80 acts as the penetration enhancer; the Agency suggested that the sponsor provide either clinical data or literature references to support the conclusion that the ethanol is not a penetration enhancer nor a preservative at
  - the USP test for polysorbate 80 is a qualitative test; it is not adequate to address the lot-to-lot vairability in the penetration enhancement property of the surfactant; therefore, more quality control data is needed than that which is recommended by the USP; a high performance liquid chromatograph (HPLC) assay should be performed to determine the in the polysorbate 80 lots
  - the Agency recommends monitoring [ ] in lots of drug product (developmental batches) on batch release and stability and reporting the data to show that the polysorbate 80 is stable in the drug product
  - a cycling test to show no phase separation under stress conditions should be performed (store the sample at [ ] the final dosage product should be evaluated for one month using particle size, viscosity, homogeneity and separation parameters under stressed conditions

- the Agency recommended a release rate test as a regulatory specification for the drug product; the sponsor will respond to the Agency regarding the proposed frequency of testing
- interim specifications can be based on current data; the sponsor can propose final specifications at a later date with appropriate data and justifications
- preservative challenge testing should be performed on release and on stability testing
- the Agency will comment to the sponsor regarding the requirement of preservative challenge testing on release and on stability testing for the
- to demonstrate comparable rate of drug-release from the emulsion, the sponsor will submit data from — lots from — and — product from

- **Question #2**: We propose to use the to measure *in vitro* release of 17 β-Estradiol from the ESTRASORB lots manufactured at
  Is comparison of bulk lot release testing and comparison of the slopes of estradiol release sufficient data to assure the FDA that products manufactured at are equivalent?
  - **Answer to Question #2**:
  - *in vitro* release testing should be performed on bulk products; the sponsor should submit a proposal for their *in vitro* release testing protocol
  - the use of the ; should follow the guidance entitled, "Nonsterile Semisolid Dosage From Scale Up and Post Approval Changes: Chemistry, Manufacturing and Quality Control In Vitro Release Testing and In Vivo Bioequivalence" from the cell approach
  - performing the procedure as a comparison procedure could help validate Novavax's method; the sponsor should note if any seepage occurs in the —
  - references should be submitted for validation; more data regarding the number of samples used in the procedure is needed
  - the sponsor will follow the SUPAC guideline regarding the number of repetitions to be made
  - the sponsor was warned that if this method dose not demonstrate a valid comparison (similarity), a bioequivalence study may be needed
  - batches used in the comparison studies will be aged since no more batches can be made at the

- Novavax has also filled ESTRASORB from all into
  This fill solution is much less expensive than the present foil pouch unit dose system and contains approximately a 33 day supply of ESTRASORB.
  Question #3: In addition to stability testing and *in vitro* release testing, what additional information would be required by the FDA for Novavax to utilize this fill solution with ESTRASORB?
  - **Answer to Question #3**: additional stability data on the will be needed; this should be submitted as a post-approval supplemental application; the sponsor should follow the packaging guidance entitled, "Container Closure Systems for Packaging Human Drugs and Biologics, Chemistry, Manufacturing, and Controls Documentation"; the sponsor should submit Drug Master Files (DMFs) for the container closure systems with appropriate chemistry manufacturing and controls information, if the information is not included in the NDA

- **Question #4:** Would this new fill solution have to be a post-approval change submission or could information on this fill solution be included in this proposed NDA submission?
  - **Answer to Question #4:** changes in packaging should be submitted as a supplement to the NDA after approval as additional stability studies will be needed for the new packaging with the

submission; however, if sufficient stability data are available, [redacted] can be included in the original NDA submission

Action Items:

• **Item:**	**Responsible Person:**	**Due Date:**
• send sponsor final meeting minutes	DRUDP	1 month

/S/
Signature, minutes preparer

/S/
Concurrence, Chair

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

drafted: dm/7.3.01/I49761TC62201.doc

Concurrence:
T.Rumble 7.5.01/YYChiu 7.11.01/S.Slaughter, V.Jarugula, J.Hunt 7.12.01/A.Mitra 7.13.01
A.Reddy 7.18.01
Response not received from A.Parekh

cc:
HFD-580
HFD-580/Div. file/IND 49,761
HFD-580/SSlaughter/Tvan der Vlugt
HFD-580/DMoore/TRumble

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/s/

Diane V. Moore
7/20/01 12:36:18 PM

Moo-Jhong Rhee
7/23/01 09:19:08 AM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 49,761

5/24/01

Novavax
Attention: D. Craig Wright, M.D.
CSO
12111 Parklawn Dr.
Rockville, MD 20852

Dear Dr. Wright:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Estrasorb ([redacted] estradiol [redacted]

We also refer to your amendment dated April 26, 2001 (serial # 037), containing your request and background package for a pre-NDA meeting to discuss clinical development issues.

We have completed the review of your submission and have the following clinical and statistical comments and recommendations in response to the discussion questions incorporated in your submission.

Question 1. The NDA will be submitted in paper. However, Sections 11 & 12 will be submitted electronically per the electronic submission guidelines. Does this satisfy the agency's needs?

Answer to Question 1:

It is acceptable to submit the case report tabulations and case report forms in electronic format according to the electronic submission guidelines. In addition, electronic data sets for Study 99-1 should be submitted to the electronic document room per the electronic submission guidance entitled, "Providing Regulatory Submissions in Electronic Format – NDAs."

Question 2. Do the plans for the Integrated Summary of Efficacy (ISE), as presented, adequately present the data for efficient review of efficacy?

Answer to Question 2:

The proposed ISE is acceptable for filing. The Phase 3, 12-week VMS study (Study E99-1) will be accepted in support of the VMS indication. Please be advised that only the relief of vasomotor symptoms (VMS) indication will be considered, as only VMS data are presented in Study E99-1. Although Study E98-2 can be mentioned in support of the primary Study E99-1, it would have limited value in the ISE as it is of only four weeks duration; thus only Study E99-1 can be used to support efficacy.

In addition, an efficacy analysis by age group should be provided incorporating the following age groups: less than 50 years, 50 to 59 years, and 60 years and greater.

Question 3. Do the plans for the Integrated Summary of Safety, as presented, adequately present the data for efficient review of safety?

Answer to Question 3:
The proposed ISS is acceptable.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 324.55 (or 601.27), please submit your plans for pediatric drug development unless you believe a waiver is appropriate. If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 at the time of NDA submission

On February 2, 1998, FDA published a final rule requiring anyone who submits a marketing application of any drug, biological product or device to submit certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies covered by the rule. This requirement, which became effective on February 2, 1999, applies to any clinical study submitted in a marketing application that the applicant or FDA relies on to establish that the product is effective, and any study in which a single investigator makes a significant contribution to the demonstration of safety. This final rule requires applicants to certify to the absence of certain financial interests of clinical investigators or to disclose those financial interests. If the applicant does not include certification and/or disclosure, or does not certify that it was not possible to obtain the information, the agency may refuse to file the application. On December 31, 1998, FDA published an amended final rule that reduced the need to gather certain financial information for studies completed before February 2, 1999. On October 26, 1999, FDA published a draft guidance to provide clarification in interpreting and complying with these regulations. The burden hours required for Section 21 CFR Part 54 are reported and approved under OMB Control Number 0910 0396.

Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860), an applicant is required to submit to FDA a list of clinical investigators who conducted covered clinical studies and certify and/or disclose certain financial arrangements as follows:

1. Certification that no financial arrangements with an investigator have been made where study outcome could affect compensation; that the investigator has no proprietary interest in the tested product; that the investigator does not have a significant equity interest in the sponsor of the covered study; and that the investigator has not received significant payments of other sorts; and/or

2. Disclosure of specified financial arrangements and any steps taken to minimize the potential for bias.

Please submit tables to the NDA that include the following information for each study you are presenting to support safety and efficacy of the NDA.

Study #XXXXX

Site Name and Number	Number of Patients enrolled	Names of Investigators (principal and sub-investigators	*Certification and/or Disclosure for each Investigator (yes/no)	**Disclosable Information (yes/no)

*[If no information is provided by the investigator (principal or sub-investigator), then the efforts at due diligence in attempting to obtain this information, (i.e., sending certified letters, performing Internet searches, etc.) must be described]
** Any and all disclosable financial information must be elaborated upon.

For more detailed information, please refer to the **GUIDANCE FOR INDUSTRY: FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATORS** at www.fda.gov/oc/guidance/financialdis.html.

If you have any questions, call Diane Moore, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

/S/

Daniel Shames, M.D.
Deputy Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
5/24/01 05:00:12 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-371

7/9/01

Novavax Incorporated
Attention: D. Craig Wright, M.D.
CSO
12111 Parklawn Drive
Rockville, MD 20852

Dear Dr. Wright:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Estrasorb (17-beta-estradiol) —
Review Priority Classification:	Standard (S)
Date of Application:	June 29, 2001
Date of Receipt:	June 29, 2001
Our Reference Number:	NDA 21-371

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 28, 2001, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be April 29, 2002 and the secondary user fee goal date will be June 29, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Diane Moore, BS, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
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/

Jeanine Best
7/9/01 04:05:06 PM
signing for T. Rumble

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: August 13, 2001

From: Jeanine Best, M.S.N., R.N.
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: NDA 21-371

I have reviewed the financial disclosure information submitted by [redacted] in support of their NDA 21-371 for Estrasorb™ Transdermal[redacted] (estradiol topical emulsion).

Two pivotal studies were conducted to assess the safety and efficacy of Estrasorb™ Transdermal [redacted] (estradiol topical emulsion) for the relief of vasomotor symptoms in [redacted] symptomatic post-menopausal women. The study numbers and the results of the review of financial disclosure documents are summarized below:

Study Number/Title	Study Status	Financial Disclosure Review
Study E99-1/ "Evaluation of Daily Doses of Estrasorb™ 7.5 mg Compared to Placebo in the Treatment of Symptomatic Post-Menopausal Women"	Begun after 2/2/1999	Appropriate documentation received, no financial disclosure submitted
Study E2000-1/ "Residual Estrasorb™ Study in Post-Menopausal Women"	Begun after 2/2/1999	Appropriate documentation received, no financial disclosure submitted

Documents Reviewed:

- Financial Certification Information (Form FDA 3454) submitted June 29, 2001
- Financial Information: NDA Section 19.0 submitted June 29, 2001

Study E99-1

Study E99-1 started October 4, 1999 and completed February 9, 2001. There were 106 principal and subinvestigators (investigators) at 20 sites (200 subjects) in this trial.

- Site 4 had 2 subinvestigators for whom financial disclosure information was not received; this site was closed due to non-performance and no patients were consented.

Financial disclosure information was received for the remaining investigators; none had any disclosable information.

Study E2000-1

Study E2000-1 started September 5, 2000 and completed October 18, 2000. There were 8 principal and subinvestigators (investigators) at 2 sites (12 subjects) in this trial. Financial disclosure information was received for all investigators; none had any disclosable information.

Conclusion:
Adequate documentation was submitted to comply with 21 CFR 54. The documentation rate of return is acceptable. The sponsor performed due diligence in attempting to obtain certification/disclosure information from the two non-compliant subinvestigators in Study E99-1, Site 4. There was no disclosure of financial interests that could bias the outcome of the trials.

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

/s/

Jeanine Best
8/13/01 03:13:30 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

19.0 FINANCIAL INFORMATION

In accordance with 21 CFR §314.50(k), this item contains financial certification by the applicant, Novavax, Inc., as required under 21 CFR § 54, for all clinical investigators (as defined in 21 CFR § 54.2 (d)) who have enrolled patients into the covered clinical studies identified below (as defined in 21 CFR 54.2(e)) in support of NDA 21-371 for ESTRASORB™, for the treatment of vasomotor symptoms in post-menopausal women. No clinical investigator identified in this certification is a full-time or part-time employee of Novavax, Inc., the sponsor of each covered clinical study.

Covered Clinical Studies:

- Protocol No. E99-1, entitled: " Evaluation of Daily Dose of ESTRASORB™ 7.5 mg Compared to Placebo in the Treatment of Symptomatic Post-Menopausal Women"
- Protocol No. E2000-1, entitled: "Residual ESTRASORB™ Study in Post-Menopausal Women"

Disclosure Statements:
Disclosure statements are not applicable to this NDA. (As the applicant, Novavax certifies to the absence of financial interests and arrangements for all clinical investigators who have enrolled patients into the above covered clinical studies, or certifies that it acted with due diligence to obtain the information required under 21 CFR § 54 from all clinical investigators who have enrolled patients in the above covered clinical studies, that it was not possible to do so, and provides the reasons why this information could not be obtained).

Certification Statement:
Novavax, Inc. certifies to the absence of financial interests and arrangements regarding compensation affected by the outcome of clinical studies (as defined in 21 CFR 54.2(a)), financial interests and arrangements regarding significant equity interest in the sponsor of a covered study (as defined in 21 CFR 54.2(b)), proprietary interest in the tested product (as defined in 21 CFR 54.2 (c)), and significant payments of other sorts (as defined in 21 CFR 54.2(f)) for clinical investigators (Attachment) who have enrolled patients into the "Covered Clinical Studies" referenced above.

Novavax, Inc. acted with due diligence to obtain the information required under 21 CFR 54 from all clinical investigators who have enrolled patients in the above-referenced "covered clinical studies". If, however, it was not possible to obtain required disclosure; the reasons for this are noted (attachment).

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
JOHN A. SPEARS	PRESIDENT/CEO
FIRM/ORGANIZATION: NOVAVAX, INC.	
SIGNATURE	DATE: JUNE 14, 2001

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Created by Electronic Document Services/USDHHS (301) 443-2454 EF

Number of Pages Redacted 8

❖❖❖

Confidential,
Commercial Information

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**	
(Division/Office): Associate Director for Medication Error Prevention in OPDRA: Attention: Dr. Phillips/Sammie Beam HFD-400 PKLN bldg Room 15B-03	FROM: HFD-580 (Division of Reproductive and Urologic Drug Products) Diane Moore 17B-45	
DATE: August 8, 2001	IND NO.:	NDA NO.: 21-371
TYPE OF DOCUMENT: N	DATE OF DOCUMENT: June 29, 2001	
NAME OF DRUG: Estrasorb™	PRIORITY CONSIDERATION: Routine	CLASSIFICATION OF DRUG: estrogen
DESIRED COMPLETION DATE: December 20, 2001		
NAME OF FIRM: Novavax, Inc.		

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review tradename Estrasorb for estradiol emulsion. The goal date for this supplement is April 29, 2002. If you have any questions, please call Diane Moore at 7-4236.

cc: Original NDA 21-371
HFD-580/Div. Files
HFD-580/Diane Moore

SIGNATURE OF REQUESTER:	METHOD OF DELIVERY (Check one): MAIL HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

NDA 21-371
Estrasorb™ (estradiol micellar nanoparticles) 2.5 g/gm
Novavax, Inc.

User Fee Information

This NDA has a Small Business exemption granted May 22, 2001.

NOVAVAX
INCORPORATED

ATTACHMENT B – WAIVER OF APPLICATION FEE

Novavax has been granted a Small Business Waiver of the application fee. A copy of the letter granting the waiver dated 22 May 2001 is included in Section 18 of this NDA.

APPEARS THIS WAY
ON ORIGINAL

12111 Parklawn Drive, Rockville, MD. 20852 Ph:(301)231-0774 EXT. 23 Fax:(301)231-5366
Email:dcwright@EROLS.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	Form Approved. OMB No. 0910-0297 Expiration Date: February 29, 2004. **USER FEE COVER SHEET**

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Novavax Inc.
8320 Guilford Road, Suite C
Columbia, MD 21046

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021371

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW.

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

____
(APPLICATION NO. CONTAINING THE DATA)

2. TELEPHONE NUMBER *(Include Area Code)*

(301) 854-3900

3. PRODUCT NAME

Estrasorb (17-beta-estradiol)

6. USER FEE I.D. NUMBER

4160 (See #8, below)

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☒ YES ☐ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
'01 Rockville Pike
›ckville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
John A. Spears	President/CEO	June 14, 2001

FORM FDA 3397

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 2 2 2001

Marsha C. Wertzberger
Arent Fox Kintner Plotkin & Kahn, PLLC
1050 Connecticut Avenue, NW
Washington, DC 20036-5339

RE: Novavax Inc., Small Business Application Waiver Request
Estrasorb Topical —

Dear Ms. Wertzberger:

This responds to your request of March 23, 2001, to Beverly Friedman of my staff, on behalf of Novavax, Inc. (Novavax), requesting a waiver of the human drug application fee for new drug application (NDA) 21-371, Estrasorb (17-beta-estradiol) topical — under the small business waiver provision of section 736(d)(1)(E)[1] of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request 2001.027). For the reasons described below, the Food and Drug Administration (FDA) grants the request from Novavax for a small business waiver of the application fee.

According to your waiver request, Novavax currently employs fewer than 500 individuals and has several wholly owned subsidiaries: Fielding Pharmaceuticals, Inc., [redacted]. You state that Novavax is applying for the application fee waiver for the first NDA submitted to FDA by Novavax or any of its affiliates and that Novavax plans to submit that NDA to FDA by June 1, 2001. You note that although Novavax recently acquired Fielding Pharmaceuticals, the only prescription products that Novavax acquired as a result were prenatal vitamins. You also state that Novavax markets Gynodiol which is licensed from [redacted]. You claim Novavax does not market Gynodiol pursuant to its own or an affiliate's NDA.

Under the Act, a waiver of the application fee shall be granted to a small business for the first human drug application that a small business or its affiliate[2] submits to the FDA for review. The small business waiver provision entitles a qualified small business to a waiver when the business meets the following criteria: (1) a business must employ fewer than 500 persons, including employees of its affiliates, and (2) the marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

---

[1] 21 U.S.C. 379h(d)(1)(E).

[2] "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly - (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

FDA's decision to grant a small business waiver to Novavax is based on the following findings. First, the Small Business Administration (SBA) determined and stated in its letter dated April 26, 2001, that Novavax has fewer than 500 employees, including those of its affiliates, Fielding Pharmaceutical Company, . [redacted]
Second, according to FDA records, the marketing application for Novavax's Estrasorb (NDA 21-371), 17-beta-estradiol topical — will be the first human drug application, within the meaning of the Act, to be submitted to FDA by Novavax or its affiliates. Although Novavax holds approved NDA 6-530, it was submitted in April 1965 by a pharmaceutical company that is not affiliated with Novavax. Consequently, your request for a small business waiver of the application fee for Estrasorb, NDA 21-371, is granted.

FDA records show that NDA 21-371 has not yet been submitted in full. Please include a copy of this letter with your NDA when it is submitted in its entirety. If FDA refuses to file the application or Novavax withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, Novavax should contact this office approximately 90 days before it expects to resubmit its marketing application to determine whether Novavax continues to qualify for a waiver.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman or Michael Jones at 301-594-2041.

Sincerely,

/S/

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

BCC:
HFD-5 M. Jones
HFD-5 B. Friedman
HFD-5 Chronological File
HFD-5 Novavax Pharma, Inc. waiver file
HFD-510 E. Galliers
HFM-110 C. Vincent/R. Eastep
HFA-103 S. Farran
HFA-120 D. Simms
HF-20 F. Claunts

Drafted: B. Friedman 5/08/01
Reviewed: M. Jones 5/14/01
T. Brice 5/14/01
Edited: S. O'Malley 5/14/01
Revised: B. Friedman 5/15/01
Reviewed: J. Axelrad

\\CDS018\PDUFA\WAIVER\PENDING\Novavax\01A03232.DOC
May 15, 2001

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

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

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1. APPLICANT'S NAME AND ADDRESS

Novavax Inc.
8320 Guilford Road, Suite C
Columbia, MD 21046

2. TELEPHONE NUMBER *(Include Area Code)*

(301) 854-3900

3. PRODUCT NAME

Estrasorb (17-beta-estradiol)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021371

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW.

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4160 (See #8, below)

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☒ YES ☐ NO
(See Item 8, reverse side if answered YES)

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Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
John A. Spears	President/CEO	June 14, 2001

FORM FDA 3397 (3/01)

Created by: PSC Media Arts (301) 443-2454 EF

Number of Pages Redacted 159

Draft Labeling
(not releasable,

24 pages in pack
23
31
35
46

159

Minutes of Teleconference

Date: October 4, 2000 **Time:** 1:30 - 1:50 AM **Location:** Parklawn; Room 17B-43

IND: 49,761 **Drug Name:** Estrasorb [redacted] estradiol)

Indication: reduction of vasomotor symptoms (VMS) [redacted]

External Participant: Novavax, Inc.

Type of Meeting: Guidance

FDA Lead: Dr. Ameeta Parekh **External Participant Lead:** Dr. Craig Wright

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

External Constituents:
Craig Wright, Ph.D., Vice President, Regulatory Affairs
Joan Brisker, Director, Regulatory Affairs and Quality Control - Novavax

Meeting Objective:
To qualify the drug manufactured at the different site from the drug used in the clinical trial.

Discussion Items:
- the sponsor would like clarification as to what study might be needed to link the old and new manufacturing facilities
- [redacted] for Novavax
- validation lots are being made at that facility and the lots are being placed on stability
- only the site is being changed; there will be no changes in the formulation; the instrumentation will be [redacted] and will be dedicated to the manufacturer of this product only; the principles of operation of the instruments is identical to the previous instrumentation used to manufacturer the product used in the clinical trials
- the sponsor is currently looking at using a rabbit animal model for a linkage study
- the quality control of the product requires an *in vitro* release study, e.g., a standard flux release for QC to monitor the absorption of dosage per dosage time
- the section in the USP for transdermal *in vitro* release tests should be reviewed
- whether the rabbit study is applicable or necessary needs to be determined; an *in vitro* skin permeability may be more appropriate than a rabbit study
- the sponsor is having [redacted]
- microbial membrane is meant for viscous product and is not appropriate for release testing

- if no *in vitro* model is available for the transdermal product; a bioequivalence study may be preferable; this decision will be based on justification provided by the sponsor

Decisions Reached:

- the Agency will respond to the question regarding the need for a study to link the change in instrumentation and site after internal discussion
- a follow-up teleconference should be scheduled to include the FDA chemistry reviewer

- **Action Items:**

Item:	**Responsible Person:**	**Due Date:**
• set up follow-up teleconference	Ms. Moore	1-2 weeks
• provide meeting minutes to sponsor	Ms. Moore	1 month

/S/

Signature, recorder

/S/

Signature, Chair

Post Meeting Addendum:
On October 4, 2000, Diane Moore left a voice mail message asking Novavax how they perform particle size testing for quality control for release of clinical batches and suggested they look at the FDA Guidance for Industry for Non sterile Semisolid Dosage Forms posted May 1997. Another reference that might be helpful was the Scale up and Post Approval Chemistry and Manufacturing Changes for *in vitro* Release Testing and *in vivo* Bioequivalence Documentation.

On October 6, 2000, DRUDP requested the sponsor send a copy of the estradiol determination viscosity and pH lots release sheet. The sponsor agreed to submit a summary of what they are currently doing for clarification to the agency.

drafted: dm/10.15.00/I49761TC10400.doc

Concurrence:
TRumble 10.19.00/VJarugula 10.20.00/AParekh 11.6.00

cc:
HFD-580
HFD-580/Div. file/IND 49,761
HFD-580/LRarick/MMann/SSlaughter/Tvan der Vlugt
HFD-580/DMoore/TRumble

/s/

Diane V. Moore
11/6/00 05:47:07 PM

Ameeta Parekh
11/7/00 08:17:08 AM

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Date: July 19, 1999 **Time**: 2:30 - 4:00 PM **Location:** Parklawn; Potomac Conference Room

IND: 49,761 **Drug Name**: Estrasorb [redacted] estradiol)

Indication: reduction of vasomotor symptoms (VMS)

External Participant: Novavax

Type of Meeting: End of Phase 2

FDA Lead: Dr. Lisa Rarick

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)
Jeanine Best – Project Manager, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, DNDC II @ DRUDP (HFD-580)
Krishan Raheja, D.V.M., Ph.D. - Pharmacologist, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Soraya Madani, Ph.D. - Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
John Gibbs, Ph.D. - Division Director, DNDC II (HFD-820)

External Constituents:
[redacted] Medical Director, Consultant to Novavax
Richard Harwood, Ph.D. – Vice President of Pharmaceutical Development, Novavax
Bennett Kaufman, Ph.D. – Vice President of Regulatory Affairs
[redacted] - Contract biostatistician to Novavax
Dennis O Donnell, M.D. – Vice Chairman, Novavax
[redacted]
[redacted]

Meeting Objective: To discuss Novavax's proposed Phase 3 clinical trial (Protocol E99-1) and the questions in their pre-meeting package dated May 18, 1999.

Background: This is a topical estradiol cream to be applied on the anterior surface of both thighs and both calves over a 2-minutes time-span for each area for the reduction of vasomotor symptoms indication.

05 12/29/99

Discussion Items:

- Protocol Comments
  - eligibility criteria include women who have 7 – 8 hot flushes per day or 60 per week
  - the sponsor plans to include a 1-week run-in period; placebo responders will not be dropped from the study; seven days prior to treatment, all subjects will be given placebo to allow for laboratory results to be completed and to instruct patients on the use of the cream; baseline data will be data from seven days prior to dosing
  - the sponsor proposes to perform an initial biopsy to rule-out endometrial pathology as an entrance criteria
  - the sponsor proposed to use the last value carried forward from the intent-to-treat population; a 20% dropout rate is predicted
- Tolerance
  - after repeated administration (14 days in a row) of the Estrasorb — in the five completed studies, no local irritation problems were demonstrated; the sponsor maintains that there was adequate estradiol uptake with a demonstration of reduction of vasomotor symptoms (hot flushes) from Day 8 and maintained through Day 21
  - the sponsor performed a rabbit study to compare Estrasorb estradiol in 95% ethanol
  - the sponsor has seen no topical reactivity to the materials; only estradiol-related adverse events have been noted with the use of this product
- Formulation
  - because the previous formulation was [ ] the sponsor has revised the formulation
  - eventually, the sponsor may [redacted]
  - the sponsor is targeting September 2000 for NDA submission

Decisions Reached:

- **Question 1: General discussion of the content and design of Protocol E99-1, and its acceptability; is <u>one</u> "robust" trial adequate to support an NDA?**
  Answer:
  - the endpoints should be the mean change from baseline at Weeks 4, 8 and 12 for the reduction of VMS; the seven days of each week can be averaged; the drug must beat placebo at Week 4 and maintain efficacy through Week 12
  - one clinical trial is sufficient
  - eligibility criteria includes women who have had amenorrhea for more than one year; for patients who have been menopausal less than one year, FSH levels should be greater than 40 mIU/ml and estradiol levels should be less than 20 pg/ml
  - the exclusion criteria list should include acute or chronic liver disease, diabetics and cardiac patients
  - the proposed washout period of two months is acceptable, however, transdermals only require four weeks and vaginal preparations require one week washout period; injectables and implants require 3 to 6 months for washout; placebo responders should not be dropped from the study
  - estrone sulfate levels should be followed to formulate the pharmacokinetics (PK) of the drug; the phase 2 study that proposes to include estrone sulfate levels may be sufficient
  - thyroid stimulating hormone (TSH) screening should be added to the protocol
  - for patients aged 50 and above, pap smears and mammograms are recommended if these procedures have not been performed within the previous nine months
  - the sponsor should recruit additional subjects at the outset if a large number of dropouts are expected; the sentences referring to "replacing subjects" should be deleted from the protocol

- the seven days of data collected during the placebo period should not be used for excluding placebo-responders
- diaries should be kept to record relevant activities
- the inconsistencies in the protocol should be corrected regarding administration of the drug, recruitment vs. replacement of study subjects, inclusion criteria and the placebo run-in period
- the proposed ITT population is not defined correctly; a more appropriate analysis plan should be proposed

- **Question 2: Is there a need for a baseline vaginal sonogram for subjects entering the study?**
  Answer:
  - a baseline endometrial biopsy is recommended; if biopsies are being done at baseline, transvaginal ultrasounds (TVU) are not necessary; a TVU can be performed at the end of the 3-month period, and if the endometrium is >4 mm, a second biopsy can be performed
  - alternatively, a baseline vaginal sonogram may be performed with directed biopsies
  - FDA suggests that a progestin challenge be provided prior to performing TVU at the conclusion of the study (for example, 10 mg of MPA daily for 14 days)
  - times when biopsies will be performed or whether a progestin challenge will be given to all women with a uterus at the end of the study should be provided in the protocol

- **Question 3: Is the purpose of the baseline endometrial biopsy to compare with the end-of study biopsy (if required based on the end-of-study sonogram), or/and to detect uterine pathology as an exclusionary condition?**
  Answer:
  - a baseline endometrial biopsy is recommended to exclude women with uterine pathology; this is not a clinical endpoint
  - a local pathologist can be used to determine the results of the endometrial hyperplasia slides for entrance eligibility
  - a standard histology reading criteria should be provided for the local pathologist and should be added to the protocol; Blaustein's histology classification is recommended

- **Question 4: Is there a need for an independent, centralized panel to read baseline and/or final biopsies, or is an on-site pathologist adequate for this determination?**
  Answer:
  - the criteria for hyperplasia should follow Blaustein's classification; the histologists should agree upon the hyperplasia classifications to be used in the study in advance of study initiation; these classifications should be submitted to the IND and in the final study report

- **Additional FDA Comments**
  - the Agency recommends that sunscreen use be addressed
  - DMFs will be required for the drug substance and the foil pouch and laminate
  - [redacted] of stability data should be submitted; the degradation product should be monitored
  - changes in water content and emulsifiers such as polysorbate 80 in the formulation should be tabulated with batch numbers
  - the method for monitoring degradation products must be validated by demonstrating that the degradant can be separated from estradiol
  - [redacted] could be used to determine particle size (particles in oil)
  - upper and lower limits for particle size and viscosity specifications should be provided

- for content uniformity, the sponsor must demonstrate that the product does not have phase separation before packaging
- the drug product used in the clinical trials should ideally be the same as the to-be-marketed drug formulation or a bridging study may be needed
- photosensitization and delayed hypersensitivity should be monitored as soybean oil can be hyperallergenic; D-rays scoring should be considered

- **Action Items:** none

• **Item:**	**Responsible Party**	**Due Date:**
• sponsor to submit revised protocol	Novavax	1 month

/S/ 9/21/99
Signature, recorder

/S/ 9/22/99
Signature, Chair
U.D.
Deputy Director
/S/

drafted: dm/8.31.99/i49761MM71999.doc

cc:
HFD-580
HFD-580/Div. file/IND 49,761
HFD-580/LRarick/MMann/SSlaugher/Tvan der Vlugt/MRhee/AParekh/SMadani
HFD-580/LKammerman/KMeaker/DMoore/TRumble
HFD-820/JGibbs

Concurrence:
TRumble 09.03.99/SMadani, Tvan der Vlugt 09.08.99/KMeaker, KRaheja 09.9.99
LRarick, AParekh, JBest 09.10.99/MRhee 09.13.99/AMitra 09.15.99

Concurrence not received from JGibbs

APPEARS THIS WAY
ON ORIGINAL

Moore

Meeting Minutes

Date: July 6, 1999 **Time**: 1:00 AM - 1:35 PM **Location:** Parklawn; Rm. 17B-43

IND: 49,761 **Drug Name**: Estrasorb [redacted] estradiol)

Indication: reduction of vasomotor symptoms (VMS) [redacted]

Sponsor: Novavax

Type of Meeting: End of Phase 2 (Internal)

FDA Lead: Dr. Lisa Rarick

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Marianne Mann, M.D. - Deputy Director, DRUDP (HFD-580)
Shelley Slaughter, M.D., Ph.D. –Team Leader, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, DNDC II @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Soraya Madani, Ph.D. - Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
John Gibbs, Ph.D. - Division Director, DNDC II (HFD-820)
Saito Mitsuo – visiting Fellow

Meeting Objective: To discuss Novavax's proposed Phase 3 clinical trial (Protocol E99-1) and the questions in their pre-meeting package dated May 18, 1999.

Background: This is a topical estradiol [redacted] The 7.5 mg dose in 3 gms is the most consistent dose as determined in the dose-finding study. The application sites are the anterior surface of both thighs and one calf over a 2-minutes time-span for each area. Industry meeting is scheduled for July 19, 1999.

Discussion Items:
- the sponsor plans to propose only one dose for their Phase 3 study
- a 12-week vasomotor (VMS) study is proposed; although the inclusion and exclusion criteria are appropriate, the number of hot flushes in the inclusion criteria should be clarified, because the numbers differ in several sections of the protocol

Decisions Reached:

- **Question 1: General discussion of the content and design of Protocol E99-1, and its acceptability; is <u>one</u> "robust" trial adequate to support an NDA?**
  Answer:
  - a 2-month washout period should be utilized for subjects who have received oral hormone drugs prior to enrolling into the study
  - standard exclusion criteria should be added to the protocol
  - the inconsistencies in the protocol should be clarified regarding administration of the drug, recruitment vs replacement of study subjects, inclusion criteria and the placebo run-in period
  - the standard efficacy variable should be the mean number of hot flushes at weeks 4, 8 and 12 compared to baseline
  - placebo responders should not be dropped from the study
  - the proposed ITT population is incorrect; the sponsor should propose a more appropriate analysis plan
  - the sponsor may require guidance regarding the single- and multiple-dose studies
  - the degradation product should be monitored
  - the sponsor should verify whether the drug product used in the clinical trials is the to-be-marketed drug form

- **Question 2: Is there a need for a baseline vaginal sonogram for subjects entering the study?**
  Answer:
  - a baseline endometrial biopsy is recommended; a baseline vaginal sonogram may also be performed
  - the sponsor should propose when biopsies will be performed or whether a progesterone challenge will be given to all women with a uterus at the end of the study
  - the protocol suggests that women with a uterine thickness >4 mm upon transvaginal ultrasound receive a biopsy; sonograms are not needed if biopsies are routinely performed

- **Question 3: Is the purpose of the baseline endometrial biopsy to compare with the end-of study biopsy (if required based on the end-of-study sonogram), or/and to detect uterine pathology as an exclusionary condition?**
  Answer:
  - a baseline endometrial biopsy is recommended to exclude women with uterine pathology
  - a discussion regarding the need for baseline endometrial biopsies may be advisable at the meeting with the sponsor; it should be clarified whether the sponsor will provide a progesterone challenge at the end of the study for all women

- **Question 4: Is there a need for an independent, centralized panel to read baseline and/or final biopsies, or is an on-site pathologist adequate for this determination?**
  Answer:
  - the criteria for hyperplasia should follow Blaustein's classifications; the histologists should agree upon the hyperplasia classifications to be used in the study in advance of study initiation; these classifications should be submitted to the IND and in the final study report

- **Action Items:** none

/S/ 8/4/99
Signature, recorder

/S/ 8/9/99
Signature, Chair

drafted: dm/7.16.99/i49761PM7699.doc

cc:
HFD-580
HFD-580/Div. file/IND 49,761
HFD-580/LRarick/MMann/SSlaugher/Tvan der Vlugt/MRhee/AParekh/SMadani
HFD-580/LKammerman/KMeaker/DMoore/TRumble
HFD-820/JGibbs

Concurrences:
TRumble 07.20.99/MMann, Tvan der Vlugt, AParekh, KMeaker 07.28.99/LRarick 08.02.99
SSlaughter 08.04.99
Concurrence not received from MRhee/AMitra/SMadani/JGibbs/SMitsuo

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

Federal Register Notices

This application was not the subject of any Federal Register Notices.