NOVAVAX
INCORPORATED

ATTACHMENT A – REQUEST FOR PEDIATRIC WAIVER

Per the *Guidance for Industry: Recommendations for Complying With the Pediatric Rule (21 CFR 314.55(a) and 601.27(a))* a waiver of Pediatric Studies may be requested if there is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups.

Novavax, Inc. is requesting a full waiver of Pediatric Studies. ESTRASORB™ qualifies under the Disease Specific waiver provision of the Guidance: *"FDA has developed a list of diseases that have extremely limited applicability to pediatric patients in that the signs and symptoms of these diseases occur for the most part in the adult population. Thus, products being developed for the treatment of these conditions in adults are likely to be granted a waiver. These include the following: ...Symptoms of menopause."*

A copy of the "Request for Waiver of Pediatric Studies" form follows.

APPEARS THIS WAY
ON ORIGINAL

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ATTACHMENT A — REQUEST FOR WAIVER OF PEDIATRIC STUDIES

ESTRASORB

IND No.: 49,761 NDA No: 21-371

Sponsor: Novavax,.Inc.

Indication(s):

"Treatment of Moderate & Severe [redacted] Symptoms Associated with Post-Menopause in Women"

1. What age ranges are included in your waiver request?

   ✔ All Pediatric Age Ranges (birth to 16 years)

2. Reasons for waiving pediatric studies:

   (a) No meaningful therapeutic benefit over existing treatments **and** is unlikely to be used in a substantial number of pediatric patients

   (b) Studies are impossible or highly impractical because the number of patients is so small or geographically dispersed

   (c) The product would be ineffective or unsafe in all pediatric age groups

   (d) Attempts to develop a pediatric formulation for a specific age group have failed

   ✔ (e) Disease-specific waiver indicated for the treatment of the condition in adults (please check)

_____ Alzheimer's disease	_____ Age-related macular degeneration
_____ Prostate Cancer	_____ Breast cancer
_____ Renal cell cancer	_____ Non-germ cell ovarian cancer
_____ Hairy cell cancer	_____ Pancreatic cancer, colorectal cancer
_____ Osteoarthritis	_____ Squamous cell cancers of the oropharynx
_____ Uterine cancer	_____ Basal cell and squamous cell cancer
_____ Endometrial cancer	_____ Small cell and non-small cell lung cancer
_____ Parkinson's disease	_____ Amyotrophic lateral sclerosis
_____ Arteriosclerosis	__X__ Symptoms of menopause
_____ Infertility	_____ Other (please state and justify)

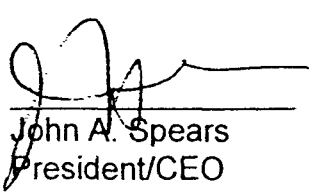
3. Justification for waiver (not necessary if category 2(e) is checked):

NOVAVAX
INC.

CERTIFICATION STATEMENT

Novavax, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

NOVAVAX, INC.



8/13/02

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Date

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NOVAVAX inc.

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NOVAVAX, INC.

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6/14/01
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13.0 PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG

Assignee	Patent No.	Expiration Date	Type
Novavax, Inc.	US 5,629,021 "Micellar nanoparticles"	January 31, 2015	Drug Drug Product Method of Use

The undersigned declares that Patent No. 5,629,021 covers the formulation, composition and/or method of use of ESTRASORB™. This product is the subject of this application for which approval is sought.

D. Craig Wright, MD
CSO, Novavax, Inc.

August 1, 2002
Date

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13.0 PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG

Assignee	Patent No.	Expiration Date	Type
Novavax, Inc.	US 5,629,021 "Micellar nanoparticles"	January 31, 2015	Drug Drug Product Method of Use

The undersigned declares that Patent No. 5,629,021 covers the formulation, composition and/or method of use of ESTRASORB™. This product is the subject of this application for which approval is sought.

D. Craig Wright, MD
CSO, Novavax, Inc.

6-29-01
Date: June 29, 2001

APPEARS THIS WAY
ON ORIGINAL

US005629021A

United States Patent [19]

Wright

[11] Patent Number: 5,629,021

[45] Date of Patent: May 13, 1997

[54] MICELLAR NANOPARTICLES

[75] Inventor: D. Craig Wright, Gaithersburg, Md.

[73] Assignee: Novavax, Inc., Rockville, Md.

[21] Appl. No.: 380,942

[22] Filed: Jan. 31, 1995

[51] Int. Cl.[6] A61K 9/14

[52] U.S. Cl. 424/489; 424/470

[58] Field of Search 514/3; 424/489, 424/470, 450; 252/312

[56] References Cited

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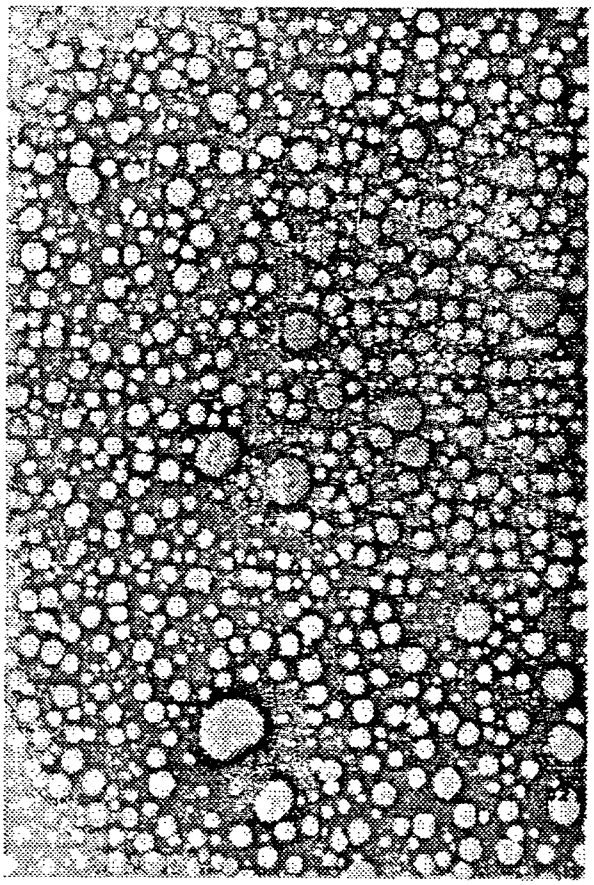
Primary Examiner—Thurman K. Page
Assistant Examiner—William E. Benston, Jr.
Attorney, Agent, or Firm—Lahive & Cockfield

[57] ABSTRACT

The present invention relates to micellar nanoparticles and methods of their production. Micellar nanoparticles are made by hydrating a mixture of an oil, a stabilizer/surfactant, and an alcoholic initiator with an aqueous solution. These micellar nanoparticles are normally less than 100 nanometers in diameter. The micellar nanoparticles are particularly advantageous in delivering materials such as estradiol topically through the skin because their small size allows easy penetration.

12 Claims, 3 Drawing Sheets



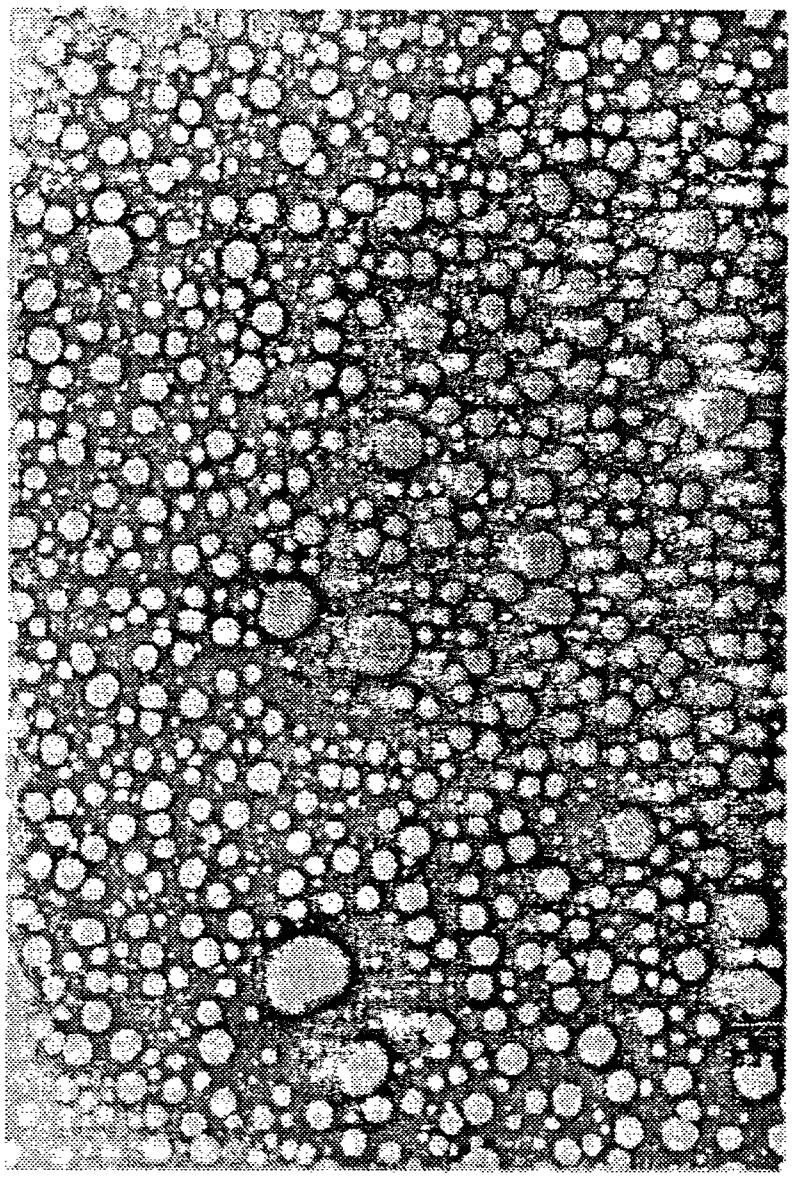


FIG. 1A

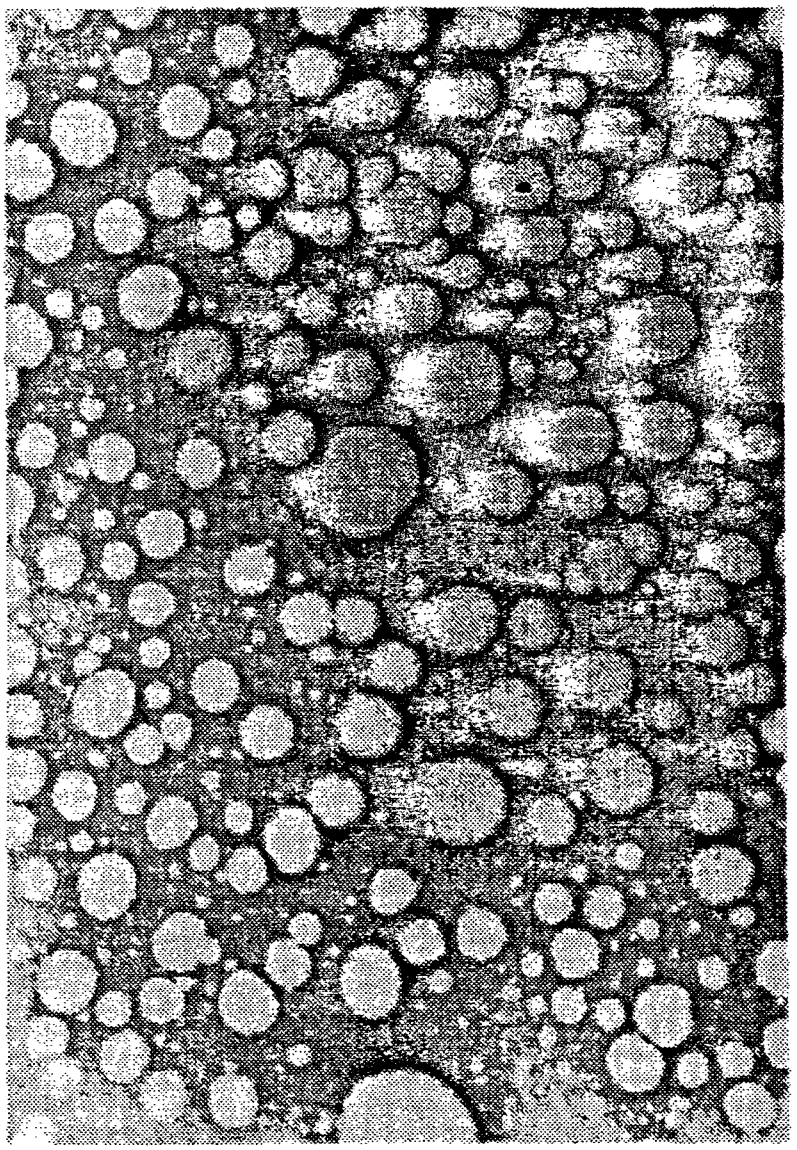


FIG. 1B

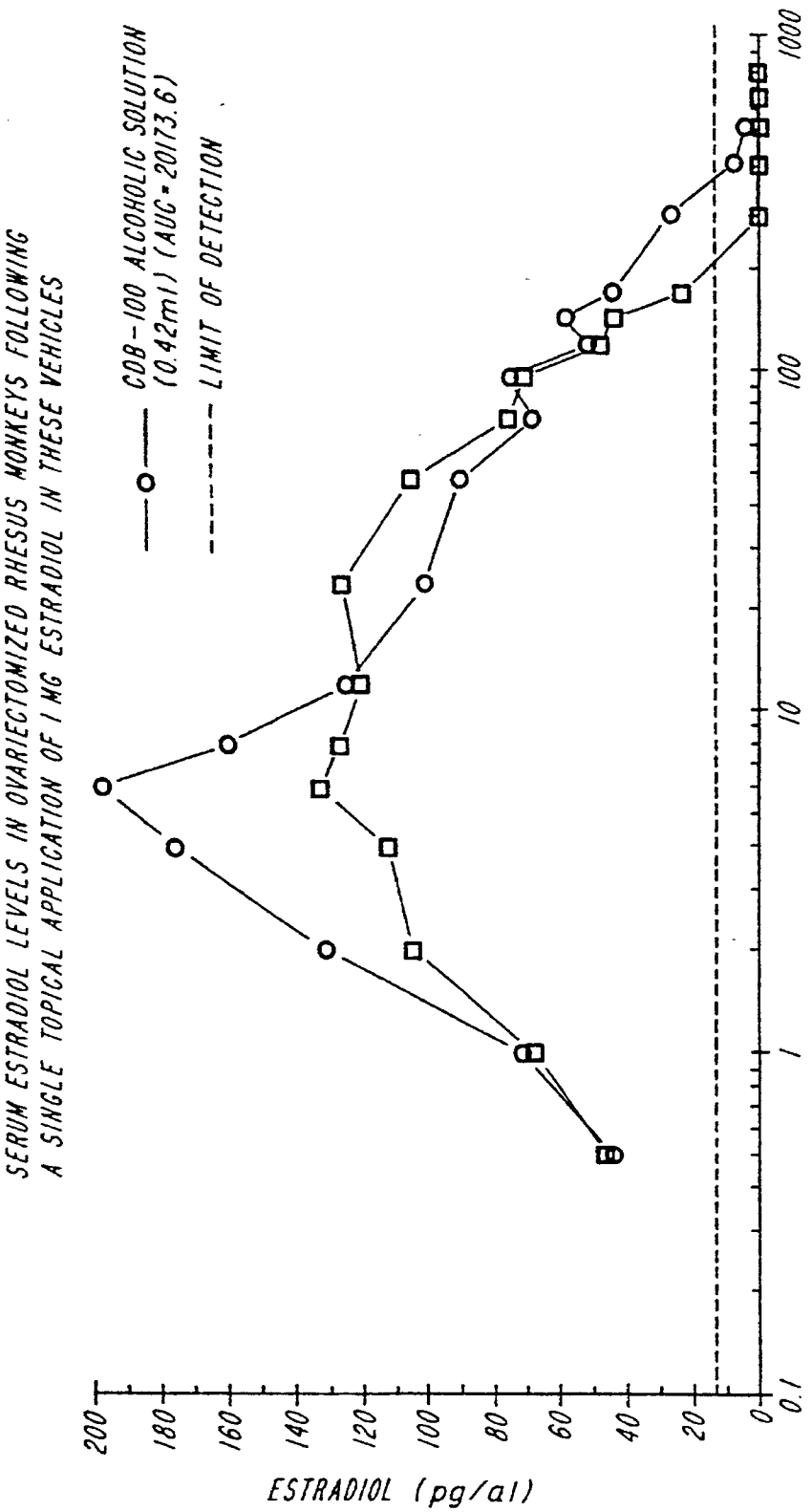


FIG. 2

MICELLAR NANOPARTICLES

BACKGROUND OF THE INVENTION

The present invention is concerned with the materials and methods for constructing "micellar nanoparticles," micelle-like particles with mean diameters less than 1000 nanometers (one micron). These micellar nanoparticles are submicron-sized, oil-based particles, the smallest of which are filterable through a 0.2 micron filter such as is standardly used for microbiological purification. The micellar nanoparticles of the invention may be formed into stable dispersions in aqueous solutions and buffers.

The micellar nanoparticles have a variety of uses because of their small size. Other synthetic particles such as liposomes, nonphospholipid lipid vesicles and microcapsules are normally a micron or larger. In contrast, it is possible to form the micellar nanoparticles of the invention in sizes less than 100 nanometers diameter. Unlike lipid vesicles, some of which can be engineered to carry an oil, see, e.g., U.S. Pat. No. 4,911,928 to Wallach, the present particles require at least an oil, a stabilizer/surfactant, an initiator, and water or another diluent in their manufacture. However, neither cholesterol nor phospholipids are used. In fact, these nanoparticles can be made using food grade, USP or NF grade materials suitable for human use applications. This is particularly important if these micellar nanoparticles are to be used for topical delivery of a material into the bloodstream. One specific use of this type of system is the delivery of natural or synthetic hormones such as estradiol. These materials often have solubility problems; e.g., they are often only soluble in materials such as ethanol which can be difficult to incorporate in stable particulate systems.

Micellar nanoparticles are unique in that they allow materials that are soluble in any of water, oil, or the initiator (i.e., ethanol or methanol) to be incorporated into stable particles with mean diameters between about 30 and 1000 nanometers. Most preparations have particle diameters between 30 to 500 nanometers, are mixable in water, and filterable through either 0.2 or 0.45 micron filters. They can be stored at between −20 and 25 degrees C°.

Utilizing the materials and methods describe, one can produce micellar nanoparticles that do the following:

1. Incorporate ethanol or methanol soluble drugs into the particles.

2. Incorporate ethanol or methanol soluble pesticides into the particles.

3. Incorporate adjuvants into the particles.

4. Incorporate proteins into the particles.

5. Incorporate whole viruses containing intact nucleic acids into the particles. It must be noted, however, that the smaller particles of the invention are about the same size as many viruses.

6. Incorporate ethanol-extracted flavors into the particles.

7. Incorporate volatile oils (flavors and fragrances) into the particles.

8. Incorporate a charge into the particles.

9. Create colored particles.

Of particular importance is the ability to transmit drugs topically. It has been known for many years that small particles, such as those below one micron in diameter, can more easily traverse the skin boundary than larger particles. However, the small amount of drug transmitted in small particles has often limited their usefulness In addition, most particles have only had limited classes of materials they could deliver.

Accordingly, an object of the invention is to produce submicron particles which can deliver a variety of classes of materials.

Another object of the invention is to produce submicron particles that can deliver materials that are soluble in ethanol or methanol but have limited or no solubility in aqueous and oil systems.

A further object of the invention is to produce particles below 100 nanometers in diameter that can be used for drug delivery.

A still further object of the invention is to produce a particle for topical delivery of hormones such as estradiol.

These and other objects and features of the invention will be apparent from the description and the claims.

SUMMARY OF THE INVENTION

The present invention features micellar nanoparticles and methods of their manufacture. These micellar nanoparticles have particular utility as drug delivery vehicles, with specific applications to topical delivery of materials that are soluble in ethanol and methanol. However, these micellar nanoparticles can also be used to deliver many different classes of drugs and other materials. The small size of the micellar nanoparticles and their compatibility with tissue render them applicable to numerous uses.

The micellar nanoparticles of the invention have diameters of about 10–1000 nanometers, with most of the particles having diameters of under 100 nanometers. This small particle size allows passage through a 0.2 micron filter. The nanoparticles are made of a lipophilic phase which includes an oil, a stabilizer (or surfactant) and an initiator such as ethanol or methanol. This lipophilic phase is hydrated by an aqueous solution such as water or a buffer. Preferred stabilizers are non-phospholipid surfactants, particularly the Tween (polyoxyethylene derivatives of sorbitan fatty acid esters) family of surfactants and the nonylphenol polyethylene glycol ethers. Most preferred surfactants are Tween 60 (polyoxyethylene 20 sorbitan monostearate) and Tween 80 (polyoxyethylene 20 sorbitan monooleate), and Tergitol NP-40 (Poly(oxy-1,2-ethanediyl), α-(4-nonylphenol)-ω-hydroxy, branched [molecular weight average 1980]) and Tergitol NP-70 (a mixed surfactant—AQ=70%). The high molecular weight of these surfactants appears to have advantageous properties in manufacture and stability of the resulting micellar nanoparticles.

The preferred initiators in the present invention are ethanol and methanol, but other short chain alcohols and or amides may be used in certain circumstances. While pure ethanol or methanol are preferred, mixtures of the two, and materials, blended or unblended, containing at least 50% alcohol, can be used. This group of initiators can include flavored initiators such as alcoholic extracts of flavors like peppermint, lemon, orange and the like.

In addition to the initiator and the surfactant of stabilizer, the micellar particles can be modified or custom manufactured by selection of the proper oil. While most oils seem to work, the preferred oils are selected from the group consisting of vegetable oils, nut oils, fish oils, lard oil, mineral oils, squalane, tricaprylin, and mixtures thereof.

A number of other materials may be added to the micellar nanoparticles to customize the particles. Volatile oils, such as volatile flavor oils, can be used in lieu of some the oil or can be added in addition to the other oil forming the particles. A coloring agent, such as a food coloring agent can also be used, preferably by adding it to the initiator. The

initiator or the oil can also carry actives which are incorporated into the final particle suspension. These actives can be dissolved, or suspended in the liquid. One preferred additive is a steroid or hormone such as estradiol, which can be dissolved in an ethanol initiator and incorporated into the particle. Since estradiol precipitates in aqueous solutions, the addition of the aqueous phase will precipitate the estradiol, which can then be released in a topical preparation. One interesting fact that appears is that the type of crystals formed using the methods of the present invention are different in shape than standard aqueous solution precipitates of estradiol.

The aqueous solution which is used to hydrate the lipophilic phase is preferably a physiologically compatible solution such as water or a buffer, e.g., phosphate buffered saline. The aqueous solution may have an active material dissolved or suspended therein for incorporation. The basic procedure for the manufacture of the micellar nanoparticles is blending the oil, the stabilizer/surfactant, and the initiator to form a lipophilic phase and blending an excess, preferably about a 4:1 ratio, of the lipophilic phase with an aqueous dilulent solution. The blending, or hydrating, of the lipophilic phase with the aqueous phase is preferably accomplished using a device which generates a relative velocity of about 50 m/s through an orifice diameter of 1/18,000 of an inch. This shear provides particles in the preferred size range while lower shear values, e.g., by using larger orifices or lower velocities, can cause larger particle size.

All of the different materials and processes described herein can be modified or selected to control the properties of the resulting micellar nanoparticles. Actives can be carried in the oil, the initiator, or the aqueous phase for incorporation into the particles. Although it appears that the particles are micelles, they may be in the form of reverse micelles without changing the scope of the invention. The invention is further illustrated by the following detailed description and the drawing.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1*a* and 1*b* are electromicrographs of the nanoparticles of the invention at two different magnifications; and

FIG. 2 is a graph of serum estradiol levels in ovariectomized Rhesus monkeys following topical administration of 1 mg of estradiol using three different types of vehicles.

DETAILED DESCRIPTION OF THE INVENTION

The present invention concerns micellar nanoparticles and methods of their production. Unlike microcapsules and liposomal systems, the present micellar nanoparticles have a significant size population under 100 nanometers in diameter, while still carrying significant quantities of active ingredients. These micellar nanoparticles are particularly useful as topical drug delivery vehicles because their small size and other characteristics which permit rapid dermal penetration. The micellar nanoparticles are also exceptionally versatile in that the active materials which can be carried include those which are suspendable or dissolvable in any of the oil, aqueous dilulent, or, preferable, the initiator. These properties allow this system to be used with actives that are difficult to use in other delivery systems.

Micellar nanoparticles are formed by first combining at least one oil, preferably an oil selected from Table 1, a stabilizer (surfactant), preferably a surfactant from Table 2, and an initiator, preferably ethanol or methanol. Most preferred stabilizers are Tween 60, Tween 80, Tergitol NP-40 and Tergitol NP-70. Additional possible initiators are shown in Table 3 (alcohols and related compounds) and Table 4 (alcohol flavored extracts). If any of the alcohol flavored extracts of Table 4 are used which are less than 50% ethanol, a 1:1 mixture of ethanol and the extract is used to ensure that at least 50% ethanol is used. Volatile oils can also be added to these chemical components (Table 5), and colors may also be added to the oil-stabilizer-initiator mixture (Table 6). A negative charge may be introduced by addition of oleic acid to the oil-stabilizer-initiator mixture. After pre-mixing these materials, water or a suitable buffer such as those shown in Table 7 is injected under a high velocity into this mixture. The preferred ratio of oil:stabilizer:initiator is 25:3:5, respectively, on a volume per volume basis. The preferred ratio of the pre-mixed oil containing phase to water is 4:1, respectively. Nanoparticles can be produced with reciprocating syringe instrumentation, continuous flow instrumentation, or high speed mixing equipment. Particles created at this 4:1 ratio range in diameters from 30 to 500 nanometers. These water miscible particles can then be filtered through either a 0.2 or 0.45 micron filter. Larger micellar particles can be created by simply increasing the water content, decreasing the oil-stabilizer-initiator content, or changing the shear in forming the particles. We have coined the name "micellar nanoparticles" for particles with mean diameters less than 1000 nanometers (one micron).

TABLE 1

Oils Utilized in Preparation of Micellar Nanoparticles.

Almond oil, sweet
Apricot seed oil
Borage oil
Canola oil
Coconut oil
Corn oil
Cotton seed oil
Fish oil
Jojoba bean oil
Lard oil
Linseed oil, boiled
Macadamia nut oil
Mineral oil
Olive oil
Peanut oil
Safflower oil
Sesame oil
Soybean oil
Squalane
Sunflower seed oil
Tricaprylin (1,2,3 trioctanoyl glycerol)
Wheat germ oil

TABLE 2

Stabilizers/Surfactants Utilized in Preparation of Micellar Nanoparticles.

Tween 60
Tween 80
Nonylphenol Polyethylene Glycol Ethers (alkylphenol-hydroxypolyoxyethylene)
1. Poly(oxy-1,2-ethanediyl), alpha-(4-nonylphenol)-omega-hydroy-, branched (i.e. Tergitol NP-40 Surfactant) Formula: $C_{95}H_{185}O_{40}$ MW (average) = 1980
2. Nonylphenol Polyethylene Glycol Ether mixtures (i.e. Tergitol NP-70 (70% AQ) Surfactant] Formula and MV: not applicable (mixture)

TABLE 3

Initiators Utilized in Preparation of Micellar Nanoparticles.

Ethanol
Methanol

TABLE 4

Flavored Initiators (flavored extracts*) Utilized in Preparation of Micellar Nanoparticles.

Pure Anise extract	(73% Ethanol)
Imitation Banana extract	(40% Ethanol)
Imitation Cherry extract	(24% Ethanol)
Chocolate extract	(23% Ethanol)
Pure Lemon extract	(84% Ethanol)
Pure Orange extract	(80% Ethanol)
Pure Peppermint extract	(89% Ethanol)
Imitation Pineapple extract	(42% Ethanol)
Imitation Rum extract	(35% Ethanol)
Imitation Strawberry extract	(30% Ethanol)
Pure Vanilla extract	(35% Ethanol)

*Extracts utilized are food grade materials (McCormick). Materials from other sources could be substituted.

TABLE 5

Volatile Oils or Fragrances Utilized in Preparation of Micellar Nanoparticles.

Balm oil
Bay oil
Bergamot oil
Cedarwood oil
Cherry oil
Cinnamon oil
Clove oil
Origanum oil
Peppermint oil

TABLE 6

Food Colors* Utilized in Preparation of Micellar Nanoparticles.

Green
Yellow
Red
Blue

*Food colors utilized are food grade materials (McCormick). Materials from other sources could be substituted.

TABLE 7

List of Diluents Utilized in Preparation of Micellar Nanoparticles.

Water for injection
Phosphate buffered saline

The following Examples will more clearly illustrate the invention and its usefulness.

EXAMPLE 1

Production of Uncharged Micellar Nanoparticles

Table 8 contains the materials used to produce micellar nanoparticles where water is the diluent. Sizing parameters using a Coulter L 130 Laser sizing apparatus are shown in Table 9.

TABLE 8

Preparation of Micellar nanoparticles utilizing water as the diluent.

Chemical Component	Amount
Soybean oil (Oil)	25 mL
Polysorbate 80 (Tween 80) (Stabilizer)	3 mL
Ethanol (Initiator)	5 mL

The above Oil-Stabilizer-Initiator components are mixed for 60 seconds. One mL of water is injected into four mL of the mixture using reciprocating syringe instrumentation. This instrumentation has two 5mL syringes connected together through a stainless steel Leurlok connector with a $\frac{1}{10,000}$ inch orifice. The solutions are driven between the syringes, through the connector, for about 100 seconds. The resulting particles were dried on EM grids, stained with uranyl acetate, and electron micrograph studies performed. FIG. 1*a* shows an electromicrograph of this preparation at a 60,000X magnification while FIG. 1*b* shows the same preparation at a 150,000X magnification. A brief description of the method of production of the micellar nanoparticles follows each table.

TABLE 9

Sizing of Micellar Nanoparticles using water as a Diluent

Preparation	LS-130 Mean Diameter (nanometers)	LS-130 Range (nanometers)
Micellar nanoparticles (SBO/Tw80/E/WFI)	312	193–455

One problem with using the LS 130 sizing device is that it cannot accurately size particles which are less than 200 nanometers in diameter. Using FIGS. 1*a* and 1*b*, it is determined that most of the particles are between 70 and 90 nanometers in diameter, with only 5% of particles be greater than 90 nanometers in diameter. Particles in the range of 20–30 nanometers are visible in the higher magnification shown in FIG. 1*b*.

EXAMPLE 2

Incorporation of Estradiol into Micellar Nanoparticles

Tables 10 and 12 contain the materials utilized to produce two lots of uncharged micellar nanoparticles into which estradiol has been incorporated at two different concentrations. Both preparations are made using water as the diluent. The higher estradiol concentration materials were used in the rhesus monkey studies described in Example 3 below. Either 50 or 100 mg of estradiol is solublized in the initiator (ethanol component) of the preparation prior to formation of the micellar nanoparticles. This is necessary since estradiol precipitates in the presence of water. In fact, the small amount of water in the reagent grade ethanol appears to be sufficient to precipitate the estradiol since the micellar particles formed using the materials and procedures described herein appear to have crystals of estradiol contained therein. However, these crystals appear to have a sheet-like form rather than the needle-like form standardly found in water precipitation.

TABLE 10

Preparation of Micellar Nanoparticles Containing Estradiol	
Chemical Component	Amount
Soybean oil (Oil)	25 mL
Polysorbate 80 (Tween 80) (Stabilizer)	3 mL
Ethanol (Initiator)	5 mL
Estradiol	50 mg

The micellar nanoparticles were made using procedures substantially identical to that described in Example 1, except the estradiol was dissolved (or suspended) in the ethanol initiator prior to the mixing of the initiator with the other components. The oil-stabilizer-initiator/estradiol components are hand mixed or can be mixed for 60 seconds using a vortex mixer. One mL of water is injected into four mL of the resulting mixture using reciprocating syringe instrumentation such as is described in Example 1.

TABLE 11

Sizing data on Estradiol containing Micellar Nanoparticles (50 mg)		
Preparation	LS-130 Mean Diameter (nanometers)	LS-130 Range (nanometers)
Micellar nanoparticles (SBO/Tw80/Etoh-estradiol/WFI)	289	174–459

Sizing data on these preparations, measured using a Coulter LS130 Laser sizing apparatus, is shown in Tables 11 and 13, respectively, for the two preparations. The LS130 sizing device cannot size particles accurately less than 200 nanometers in diameter. These materials were also dried on EM grids, stained with uranyl acetate and electron micrograph studies performed. Electron micrographs reveal that most of the particles are less than 200 nanometers. Particles in the range of 20–30 nanometers are visible. Crystallized estradiol is readily visible in the larger micelles. No free drug crystals are noted in any fields suggesting complete incorporation of drug into micelles.

TABLE 12

Preparation of Micellar Nanoparticles Containing Estradiol	
Chemical Component	Amount
Soybean oil (Oil)	25 mL
Polysorbate 80 (Tween 90) (Stabilizer)	3 mL
Ethanol (Initiator)	5 mL
Estradiol	100 mg

TABLE 13

Sizing data on Estradiol containing Micellar Nanoparticles (100 mg)		
Preparation	LS-130 Mean Diameter (nanometers)	LS-130 Range (nanometers)
Micellar nanoparticles (SBO/Tw80/Etoh-estradiol/WFI)	217	151–291

EXAMPLE 3

Rhesus Monkey Testing of Estradiol Containing Preparations

The 100 mg estradiol preparation of Example two was tested against a standard ethanol preparation of estradiol to show efficacy. One milligram of estradiol, in either ethanol (Table 14) or micellar nanoparticles (Table 15), was applied to the skin of groups of four ovariectomized rhesus monkeys. Serial blood samples were drawn and serum estradiol levels were determined over the next 32 days. The serum estradiol data is graphically depicted in FIG. 2. No additional drug was applied to skin of any animal. Animals were observed for the next 60 days to determine whether the time of occurrence, duration and severity of vaginal bleeding (Table 16).

TABLE 14

Serum Estradiol Levels in Ovariectomized Female Monkeys Following a Single Topical Application of Micellar Nanoparticles Equivalent to 1 mg Estradiol

	Monkey Number Serum Estradiol				
Sample Time	#19567 (pg/ml)	#21792 (pg/ml)	#22366 (pg/ml)	#22405 (pg/ml)	Group Mean ± S.E.
0 hour	0.0[b]	0.0[b]	0.0[b]	0.0[b]	0.0 ± 0.0[b]
0.5 hour	22.2	49.8	36.9	77.5	46.6 ± 11.7
1 hour	37.4	60.9	65.6	108.6	68.1 ± 14.8
2 hours	61.5	80.5	87.3	191.3	105.2 ± 29.2
4 hours	77.2	132.1	120.6	120.4	112.6 ± 12.1
6 hours	89.0	166.3	119.0	158.3	133.2 ± 18.0
8 hours	87.5	157.3	116.1	148.1	127.3 ± 15.9
12 hours	83.0	160.5	100.6	140.3	121.1 ± 17.8
day 1	90.7	178.0	105.7	132.6	126.8 ± 19.2
day 2	95.5	152.8	90.6	83.5	105.6 ± 15.9
day 3	81.9	122.6	51.1	47.2	75.7 ± 17.5
day 4	91.5	83.9	58.7	50.3	71.1 ± 9.9
day 5	41.6	74.7	35.1	40.0	47.9 ± 9.1
day 6	45.2	63.7	25.6	40.9	43.9 ± 7.8
day 7	18.3	25.9	21.9	27.0	23.3 ± 2.0
day 12	0.0[b]	0.0[b]	0.0[b]	0.0[b]	0.0 ± 0.0[b]
day 17	0.0[b]	0.0[b]	0.0[b]	0.0[b]	0.0 ± 0.0[b]
day 22	0.0[b]	0.0[b]	0.0[b]	0.0[b]	0.0 ± 0.0[b]
day 27	0.0[b]	0.0[b]	0.0[b]	0.0[b]	0.0 ± 0.0[b]
day 32	0.0[b]	0.0[b]	0.0[b]	0.0[b]	0.0 ± 0.0[b]

[a]CDB 3988 = 2.4 mg estradiol/ml of Tween/Oil. The dosing volume was 0.42 ml.
[b]0 = Not Detectable. The limit of detection (ED_{90}) for the assay was 13.3 ± 2.4 pg/ml (mean ± S.E., n = 4)

TABLE 15

Serum Estradiol Levels in Ovariectomized Female Monkeys Following a Single Topical Application of 1 mg Ethanol Containing Estradiol[a]

	Monkey Number Serum Estradiol				
Sample Time	#G-558 (pg/ml)	#G-603 (pg/ml)	#E-920 (pg/ml)	#E-924 (pg/ml)	Group Mean ± S.E.
0 hour	0.0[b]	0.0[b]	0.0[b]	0.0[b]	0.0 ± 0.0[b]
0.5 hour	17.7	97.1	44.8	19.5	44.8 ± 18.5
1 hour	53.2	44.1	88.3	99.9	71.4 ± 13.5
2 hours	144.3	89.4	138.5	155.1	131.8 ± 14.6
4 hours	143.7	202.3	165.1	193.6	176.2 ± 13.4
6 hours	155.8	257.8	173.1	203.7	197.6 ± 22.4
8 hours	114.2	266.1	130.7	130.0	160.3 ± 35.5
12 hours	80.8	219.5	86.4	115.9	125.7 ± 32.2
day 1	92.4	145.2	56.9	109.4	101.0 ± 18.4
day 2	74.1	124.2	55.3	107.2	90.2 ± 15.6
day 3	65.0	67.4	51.9	89.2	68.4 ± 7.7
day 4	70.5	79.6	57.8	90.0	74.5 ± 6.8
day 5	53.6	53.2	51.6	47.3	51.4 ± 1.4
day 6	60.1	59.0	59.4	53.0	57.9 ± 1.6
day 7	48.7	40.6	50.3	36.6	44.1 ± 3.3
day 12	28.5	24.2	53.3	0.0[b]	26.4 ± 10.9[b]
day 17	0.0[b]	0.0[b]	28.9	0.0[b]	7.2 ± 7.2[b]
day 22	0.0[b]	0.0[b]	13.8	0.0[b]	3.5 ± 3.5
day 27	0.0[b]	0.0[b]	0.0[b]	0.0[b]	0.0 ± 0.0[b]
day 32	0.0[b]	0.0[b]	0.0[b]	0.0[b]	0.0 ± 0.0[b]

[a]CDB 100 = 2.4 mg estradiol/ml of absolute ethanol. The dosing volume was 0.42 ml.
[b]0 = Not Detectable. The limit of detection (ED_{90}) for the assay was 13.3 ± 2.4 pg/ml (mean ± S.E., n = 4)

The data in Tables 14 and 15 and FIG. 2 show that therapeutic serum levels of estrogen are present in the blood stream of ovariectomized animals in both groups in one hour after a single application. Mean estradiol levels greater than 40 picograms/ml are maintained for 7 days with the ethanol preparation and for 6 days with the nanoparticle preparation. When estrogen levels remain low (see FIG. 2 and Table 16), vaginal bleeding occurs in both groups. Also of particular

interest is the shape of the curves in FIG. 2. The ethanol-estradiol preparation yields a "shark tooth" curve showing a high initial action and a sharp fall-off while the micellar nanoparticle preparation yields more of a "mesa" effect with a nearly flat level for several hours. This "mesa" effect is often preferred since some of the problems associated with peaking can be minimized.

TABLE 16

ESTROGEN WITHDRAWAL BLEEDING IN OVARIECTOMIZED RHESUS MONKEYS FOLLOWING A SINGLE TOPICAL APPLICATION OF ESTRADIOL IN ALCOHOL OR MICELLAR NANOPARTICLES

		WITHDRAWAL BLEEDING		
		DAYS		
CDB No.	ESTRADIOL ESTER	LATENCY	DURATION	INTENSITY[a]
100	Estradiol in alcoholic solution	19.5 ± 0.3	4.3 ± 0.9	1.6 ± 0.2
3988	Estradiol formulation[b]	16.5 ± 0.5[c]	7.3 ± 1.5	1.6 ± 0.1

[a]Mean intensity of bleeding (1 = scant, moderate, 3 = heavy) over bleeding period
[b]Novavax MN Suspension 11294-2
[c]Significantly different ($p < 0.01$) from estradiol in alcohol solution based on a one-way analysis of variance followed by a Student Neuman-Keuls multiple range test

Therefore, this Example demonstrates in a non-human primate that the micellar nanoparticles of the invention can be utilized to deliver estradiol through intact skin with maintenance of therapeutic serum estradiol levels for 6 days after a single application. This technology may have numerous therapeutic applications in medicine.

The estadiol preparation is also stable at a variety of temperatures. Table 17 shows thermal stability data for the micellar nanoparticle preparation of the Example 2 at −20° C., 25° C., and 65° C. As is clear, while the micellar nanoparticles are unstable at high temperatures, they are stable at room temperature and low temperatures.

TABLE 17

Thermal Stability of Micellar Nanoparticles

Preparation	LS-130 Mean Diameter (nanometers)	LS-130 Range (nanometers)
Micellar nanoparticles (SBO/Tw80/Etoh-estradiol/WFI) Storage at 25° C.	361	168–599
Micellar nanoparticles (SBO/Tw80/Etoh-estradiol/WFI) Storage at −20° C.	312	179–510
Micellar nanoparticles (SBO/Tw80/Etoh-estradiol/WFI) Storage at 65° C.	Unstable	

In addition, the micellar nanoparticles of the invention can be diluted with aqueous solutions without stability loss. This allows the possibility of using high concentration products which can be diluted for use as necessary.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

What is claimed is:

1. A micellar nanoparticle having a diameter of between about 25 and 1000 nm, said micellar nanoparticle comprising a lipophilic phase which includes an oil, a stabilizer and an alcohol-based initiator, hydrated with a suitable aqueous solution

wherein said stabilizer is selected from the group consisting of Tween 60, Tween 80, nonylphenol polyethylene glycol ethers, and mixtures thereof.

2. The micellar nanoparticle of claim 1 wherein said initiator is selected from the group consisting of alcoholic materials containing methanol, ethanol and mixtures thereof.

3. The micellar nanoparticle of claim 2 wherein said initiator is selected from the group consisting of alcoholic materials containing 50% or higher ethanol, methanol, and mixtures thereof.

4. The micellar nanoparticle of claim 1 wherein said oil is selected from the group consisting vegetable oils, nut oils, fish oils, lard oil, mineral oils, squalane, tricaprylin, and mixtures thereof.

5. The micellar nanoparticle of claim 1 wherein said aqueous solution comprises a physiologically compatible solution.

6. The micellar nanoparticle of claim 1 wherein said aqueous solution is selected from the group consisting of water, and phosphate buffered saline.

7. The micellar nanoparticle of claim 1 wherein said aqueous phase has an active material dissolved or suspended therein.

8. The micellar nanoparticle of claim 1 wherein said oil has an active material dissolved or suspended therein.

9. The micellar nanoparticle of claim 1 wherein said initiator has an active material dissolved or suspended therein.

10. The micellar nanoparticle of claim 9 wherein said active material comprises estradiol.

11. The micellar nanoparticle of claim 1 wherein said micellar nanoparticle is dispersible in aqueous solution.

12. The micellar nanoparticle of claim 1 wherein the diameter of said micellar nanoparticle allows passage through a 0.2 mm filter.

* * * * *

14.0 PATENT CERTIFICATION WITH RESPECT TO ANY PATENT WHICH CLAIMS THE DRUG

No certification is necessary because this application is for a drug for which investigations described in 21 U.S. C. §355(b)(1)(A) and relied upon by the applicant for approval of this application were conducted by or for the applicant, and this application is not an abbreviated application for a new drug.

Division Director Memorandum

From: Daniel Shames MD
Director, Division of Reproductive and Urologic Drug Products
CDER/FDA

To: File for NDA 21-371

Memorandum Completed: 10/9/03

Sponsor:	Novavax, Inc. 12111 Parklawn Drive Rockville, MD 20852
Drug Name:	
Generic:	Estradiol, USP as estradiol hemihydrate
Trade:	Estrasorb™
Pharmacologic category:	Estrogen
Route of Administration:	Transdermal
Dosage Form:	Topical emulsion
Strength:	3.48 grams of Estrasorb™ containing 8.7 mg of estradiol (2.5 mg of estradiol/gram), USP as estradiol hemihydrate applied daily
Proposed Indications:	Treatment of moderate to severe vasomotor symptoms associated with the menopause.
Related Submission:	IND 49, 761 (submitted on January 16, 1996) NDA 21-371/S-000 (submitted on June 29, 2001,
Related Documents:	NDA 21-371/S-000 Amendments dated 11/27/02, 12/5/02, 12/17/02, 1/13/03, 1/16/03, 1/28/03, 2/15/03, 4/30/03, 5/5/03, 5/19/03, 5/22/03, 6/5/03, 5/16/03, 7/11/03, 7/29/03, 7/31/03, 8/4/03, 9/5/03

1.0 BACKGROUND

Estrasorb™ is a topical drug delivery system containing estradiol USP, as estradiol hemihydrate, that utilizes micellar nanoparticle proprietary technology. A micellar nanoparticle is a sub-micron-sized nanoemulsion. Injecting water into a mixture of soybean oil, polysorbate 80 (a surfactant), and estradiol dissolved in ethanol produces the nanoemulsion [redacted] The components are then mixed using high speed mixing equipment, and have the consistency of an emulsion. ESTRASORB™ contains estradiol at a concentration of 2.5 mg of estradiol/gram.

Estradiol is an estrogen class hormone. Estrasorb™ is the first estradiol formulated in a topical nanoemulsion delivery system.

The Sponsor's proposed indication is the treatment of moderate to severe vasomotor symptoms associated with the menopause. A total of 3.48 grams of ESTRASORB™ containing 8.7 mg of estradiol (2.5 mg of estradiol/gram) is applied topically each day as follows: 1.74 grams split between the right anterior thigh and right calf areas, and 1.74 grams split between the left anterior thigh and left calf areas.

Estradiol has been used clinically for estrogen-alone therapy since the mid-1970s with the approval of generic oral 1 mg and 2 mg Estrace® Tablets (Estradiol tablets, USP) for the treatment of moderate to severe vasomotor symptoms (VMS), vulvar and vaginal atrophy (VVA), hypoestrogenism due to hypogonadism, castration or primary ovarian failure, and the palliative treatment of metastatic breast cancer and androgen-dependent carcinoma of the prostate. Estrace® 0.5 mg Tablets are approved for the prevention of postmenopausal osteoporosis. More recent efforts have centered on the approval of alternate delivery systems with estradiol, namely, estradiol vaginal tablets (Vagifem®), estradiol vaginal cream (Estrace® Cream 0.01%) estradiol vaginal ring (Estring® IVR) approved for the treatment of VVA, Femring® approved for the treatment of VMS and VVA, and estradiol transdermal systems approved for the treatment of VMS, VVA, and/or hypoestrogenism due to hypogonadism, castration or primary ovarian failure and the prevention of postmenopausal osteoporosis. Currently, six approved transdermal systems deliver daily estradiol: Estraderm®, Vivelle®, Vivelle-Dot®, Climara®, Alora®, and Esclim®.

There is one approved combination transdermal system, Combipatch™, containing 0.05 mg estradiol and 0.14 or 0.25 mg norethindrone acetate. No estradiol transdermal lotions/creams or emulsions are currently marketed in the US for the treatment of moderate to severe vasomotor symptoms associated with the menopause.

2.0 NDA DATA AND ANALYSIS

Nine studies were included in this submission. Six of them are particularly notable and are described in this section. Phase 3 Study E99-1, conducted to evaluate the safety and efficacy of 3.45 grams of Estrasorb™ containing 8.625 mg of estradiol (2.5 mg of estradiol/gram) versus placebo, was the single study submitted that met the Agency's

hormone therapy clinical evaluation guidance treatment duration (12 weeks) for a symptomatic indication. Other studies offered supportive evidence.

Phase 2/3 Study E98-2, which also evaluated the safety and efficacy of Estrasorb™, was 4 weeks in duration. Phase 1 Study E98-1 evaluated the pharmacokinetics and pharmacodynamics of single-site versus split-site application of 1.15 grams of Estrasorb™ daily for 8 days. Study E2000-1 was initiated at the recommendation of the Agency to evaluate the amount of residual estradiol on the skin after application of 1.15 grams of Estrasorb™ to each thigh. Studies E2002-1 and E2002-2, both initiated at the recommendation of the Agency, evaluated the transfer potential of estradiol to male partners and the effects of the application of sunscreen on the systemic absorption of estradiol, respectively.

Safety data submitted in the 4-Month Safety Update (dated January 13, 2003), in the Second Safety Update (dated May 5, 2003), and in the twelve-month Safety Update (dated September 5, 2003) were reviewed upon receipt.

2.1 Efficacy

Overall, the data demonstrated that the daily application of 3.45 grams of Estrasorb™ containing 8.625 mg of estradiol (2.5 mg of estradiol/gram) was effective in reducing the frequency and severity of moderate to severe hot flushes associated with the menopause in generally healthy postmenopausal women.

Two hundred (200) healthy postmenopausal women were randomized in the primary 12-week clinical trial (Phase 3 Study E99-1) conducted at 20 US investigational sites. One hundred subjects were randomized to the placebo treatment group and 100 subjects were randomized to the 3.45 gram Estrasorb™ treatment group. Seventy-six percent (76%) of the study population was white, 19% of the study population was black.

The daily application of 3.45 grams of Estrasorb™ containing 8.625 mg of estradiol (2.5 mg of estradiol/gram) was effective in reducing both the frequency and severity of moderate to severe hot flushes at weeks 4 and 12, the primary efficacy time points for a vasomotor symptoms indication ($p<0.001$ versus placebo at both time points).

2.2 Safety

In total, 425 postmenopausal women were included in the nine studies conducted during the development of ESTRASORB™. Three hundred thirty-five subjects (335) appear in the three studies included in the Integrated Summary of Safety (ISS, integrated Studies E98-1, E98-2, and E99-1), and 90 subjects appear in the six non-integrated studies (Studies N95-3, N96-1, N97-3, E2000-1, E2002-1, and E2002-2). There were no deaths reported during any of the clinical trials with ESTRASORB™. Safety evaluations and monitoring were adequate for the 335 subjects in the safety population.

3.0 NOTABLE ISSUES

3.1 Chemistry Manufacturing and Controls

Estrasorb™ consists of surfactant stabilized micelles containing estradiol. The micelles are produced by injecting water into a mixture of an oil, a stabilizer (surfactant polysorbate 80) and an initiator (ethanol in which the estradiol is dissolved). The components are then mixed with either a reciprocating syringe or continuous flow instruments or high speed mixing equipment. Since the particles are less than one micron in diameter, the preparation is therefore called micellar nanoparticles. The preferred ratio of the pre-mixed mixture of oil, surfactant and estradiol dissolved in ethanol to water is [ ]

Chemically, the active ingredient in Estrasorb™ is estradiol hemihydrate. The chemical name is (17β)-estra-1, 3, 5 (10)-triene-3, 17β-diol, hemihydrate. The molecular formula of estradiol hemihydrate is $C_{18}H_{24}O_2$, ½ H_2O and the molecular weight is 281.4.

3.11 Clinical trial and to-be–marketed formulations

The Estrasorb™ formulation utilized in the primary clinical trial (E-99-1) was prepared by [redacted] .. The to-be –marketed formulation of Estrasorb™ is manufactured by [redacted]

Study E99-1 was conducted using a drug formulation with **the identical composition** to that of the to-be-marketed formulation manufactured by [redacted] A bridging study was conducted between the two different sources of drug product supplies [redacted] for the Phase 3 clinical supplies and [redacted] for the to-be-marketed drug product) using an *in vitro* methodology recommended by SUPPAC-SS. Per the Clinical Pharmacology review dated April 24, 2002, adequate bridging between the clinical trial and the to-be-marked drug product was demonstrated.

3.12 [redacted]

The to-be-marketed drug product batches manufactured by [redacted] showed the presence of [redacted]

The drug product utilized in primary Phase 3 Study E99-1 was not tested for the presence [redacted] These clinical supplies are now 5 years old and unsuitable for testing. In addition, the clinical stability batches were not tested initially for the presence of [redacted] therefore, it is not certain whether the [redacted] form as a function of time or form during manufacture. The Sponsor's projected timetable for completion of method development validation for determination of [redacted] weight is January 26, 2004. This timetable is acceptable to the CMC reviewer.

Per the CMC review, the number of [redacted] per microliter of drug product should be set at [redacted] for arbitrary analytical variability) or at a maximum of [redacted]. These specifications are acceptable to the sponsor.

3.2 Clinical Pharmacology/ Formulation

Although the clinical trial and to-be-marketed formulations of Estrasorb were identical, the appearance of [redacted] in the to-be-marketed formulation raised some concerns among the CMC reviewer because similar data was no longer available for the clinical trial drug product and the original clinical trial product was not tested for [redacted]

However, pharmacokinetic parameters collected in Phase 1 Study E98-1 (which used the product manufactured at [redacted] the same drug formulation as Study E99-1) was compared with the pharmacokinetic parameters obtained during the Estrasorb™-only period in Study E2002-2 (first 7 days) which used the [redacted] manufactured product.

Table 1 Comparison of Serum Profile Estradiol Concentrations between Studies E98-1 and E2002-2.

	C_{max} (ng/dL)		$AUC_{(0\text{-}24h)}$ (ng-h/dL)	
	E98-1 3.2 ml Estrasorb™ (N = 4)	E2002-2 1.74 g Estrasorb™ (N = 14)	E98-1 3.2 ml Estrasorb™ (N = 4)	E2002-2 1.74 g Estrasorb™ (N = 14)
1st Dose	3.45 ± 2.66	2.5 ± 2.11	37.3 ± 25.1	38.91 ± 32.27
8th Dose	5.48 ± 1.40	5.54 ± 3.56	92.7 ± 28.9	92.35 ± 57.63

Source: NDA 21-371, Amendment-018 dated July 11, 2003, Table 11.4.1.1-1, page 55.

As shown in Table 1, the serum estradiol concentrations reported for Study E98-1 (the clinical trial formulation) and Study E2002-2 (the to-be marketed formulation) are comparable. This offers supportive evidence that these two identical formulations are similar pharmacokinetically, despite the presence of [redacted] in the to-be –market4d formulation..

3.3 Lowest Effective Dose

The Agency recommends that estrogen products be prescribed at the lowest effective dose (see **Boxed Warning** in the label). The division does not believe that data demonstrating the lowest effective dose for Estrasorb™ was included in this submission. Therefore, the division recommends that a second full 12-week adequately powered safety and efficacy study be conducted as a Phase 4 commitment to determine if lower doses of Estrasorb™ are effective for the treatment of moderate to severe vasomotor symptoms associated with the menopause. The Division recommends that the Sponsor consider the inclusion of the approved dose and one or more lower doses of Estrasorb™ in the clinical trial.

This recommendation is based on the data submitted for NDA 21-371. In a 4-week dose-ranging study (Study E98-2), 125 postmenopausal women were randomized to placebo or 1.15 grams (1 foil-laminated pouch), 2.30 grams (two 1.15 gram pouches), or 3.45 grams of Estrasorb™ (three 1.15 gram pouches) containing 2.5 mg of estradiol per gram per day. A linear reduction in vasomotor symptom relief was not demonstrated (e.g., more response to treatment as the dosage strength increases from 1.15 grams to 3.45 grams). Both the 1.15 gram and 3.45 gram ESTRASORB™ treatment groups showed a statistically significant reduction in the number of moderate to severe hot flushes at week 4. The 2.30 gram Estrasorb™ treatment group did not although this dose produced a

trough serum estradiol concentration of 34 pg/ml. In the Division's experience from reviews of other clinical trial data for a vasomotor symptoms indication, efficacious drug products produce serum estradiol concentrations that are increased at least 25 to 30 pg/ml above baseline.

3.4 Residual Estradiol after Time and Washing

The objective of Study E2000-1 was to assess the amount of residual estradiol on the skin surface at 2 and 8 hours after application of 1.15 grams of Estrasorb™ containing 2.5 mg of estradiol per gram (equivalent to 2.87 mg or 2875 micrograms of estradiol) to the anterior surface of the left and right thigh for 2 minutes (a 6 x 8 inch area was delineated using waterproof adhesive tape). Twelve postmenopausal women participated. The study nurse observed the application and the subject remained in the clinical site for 8 hours. Residual estradiol determinations were performed using a —— test developed by Novavax, Inc. The application areas were sampled prior to dosing and at 2 and 8 hours post-dosing. No subjects had detectable residual estradiol on the skin surface prior to application

At 2 hours post-dosing all 12 subjects had detectable residual estradiol on their left thighs. The amounts of estradiol detected at two hours post-application ranged from 220 micrograms (7.6% of 2875 micrograms applied) to 803 micrograms (28% of 2875 micrograms applied). At 8 hours post-dosing, all 12 subjects had detectable residual estradiol on their right thighs. The amounts detected at 8 hours post-application ranged from 74 micrograms (2.6% of 2875 micrograms applied) to 582 micrograms (20.2% of 2875 micrograms applied). Both thighs were then washed with soap and water and rinsed with water (8 hours post dosing) and again swiped for residual estradiol. Four of the 12 subjects (25%) still had detectable quantities of estradiol after washing that ranged from 17.8 micrograms (0.6% of 2875 micrograms applied) to 38.3 micrograms (1.3% of 2875 micrograms applied).

The results of Study E2000-1 indicate that the percent of residual estradiol detected varied between the 12 subjects at both time points, from 7.6% (220 micrograms) to 28% (803 micrograms) at 2 hours post-application and 2.6% (74 micrograms) to 20% (582 micrograms) at 8 hours post-application. After washing, these amounts were further reduced to none and 0.6% (17.8 micrograms) to 1.3% (38.3 micrograms) in 4 subjects.

However, if the correlate is considered based on the amount of estradiol applied to the skin surface (equivalent of 2875 micrograms applied to each thigh), the percent of estradiol no longer available for detection (i.e., "absorbed") on the skin surface also varied between the 12 subjects, from 72% to 92.4% at 2 hours post-application to 80% to 97.4% at 8 hours after application. Therefore, it appears from the available information that at least 72% of the applied dose at 2 hours and at least 80% at 8 hours was no longer detectable on the skin surface. In addition, washing after 8 hours appears to remove any remaining estradiol on the skin surface in the majority of subjects.

The variability in the amounts of estradiol detected on the skin surface 2 and 8 hours post-application in 12 subjects is not unexpected. Skin permeability, vigor of rubbing, the amount of drug products remaining on the hands after application, and clothing

contact are but a few of the possible contributing factors. This information will be conveyed in the label.

3.5 Skin Transfer

The primary objective of Study E2002-1was to determine if systemic absorption of estradiol occurred in a male subject after intentional contact exposure to the primary Estrasorb™ application sites of postmenopausal women. Study E2002-1 was an open-label Phase 1 study, conducted in 1 US center, in which 14 postmenopausal women (mean age 57.6 ± 8.7 SD) applied approximately 1.74 grams of Estrasorb™ containing 2.5 mg of estradiol/gram (equivalent of 4.35 mg or 4350 micrograms of estradiol) to each thigh and calf daily for two days. The contents of one 1.74 gram pouch was applied to the anterior left thigh and left calf areas for 3 minutes until thoroughly absorbed, and the contents of a second 1.74 gram pouch was applied to the anterior right thigh and right calf areas for 3 minutes until thoroughly absorbed. Any excess material remaining on the hands was rubbed on the buttocks. On completion of application, both hands were washed with soap and water. The pouches were weighed prior to and after application to determine the amount of product expressed by each subject.

Fourteen male partners (mean BMI of 28) attempted to transfer estradiol to his forearm by vigorously rubbing them against his female partner's thigh for 2 minutes, left forearm to left thigh at 2 hours and right forearm to right thigh at 8 hours.

Per the results reported for Study E2002-1, after two days of intentional exposure to Estrasorb™, the mean estradiol serum concentrations for the 14 male subjects were within the normal range of 0.8-3.5 ng/dL (day 0 results ranged from 1.76 to 2.41 ng/dL and day 1 results ranges from 1.74 to 2.80 ng/dL). Only 1 male subject (Subject 07M) with a baseline estradiol serum concentration within normal limits exceeded the normal range after exposure at 3 of the 14 sample time points (2 and 18 hours on day 0 and 18 hours on day 1).

Overall, the majority of individual male subjects in Study E2002-1 had serum estradiol concentrations on the two post-exposure days that ranged within the normal limits of 0.8-3.5 ng/dL. However, the mean $AUC_{(0\text{-}24h)}$ values on days 0 and 1 were statistically significantly higher (about 25%) than reported at screening with p-values of $p=0.017$ on day 0 and $p< 0.001$ on day 1.

The implication of these findings to children is of concern. Although limited, published literature reports indirect exposure to excessive amounts of topical estrogen with resulting gynecomastia, rapid changes in growth, and advanced bone age in prepubertal children.[1] Custom-compounded topical estrogen creams applied by mothers (9 mg of estradiol per 1 gram cream applied twice daily to thighs for 8 months and 24 mg of estradiol per 1 gram of cream applied twice daily to abdomen for 4 months) resulted in gynecomastia in 3 male children (33 months of age, 28 months of age, and 8 years). Serum estradiol concentrations were reported at 3.5 ng/dL, 4.8 ng/dL, and 10 ng/dL, respectively (normal values for age is < 1.5 ng/dL). Upon discontinuation of topical

[1] Felner, EI, White, PC. Prepubertal gynecomastia: indirect exposure to estrogen cream. J Pediatr. 2000;105(4):E55.

applications of cream, all 3 male children had regression of gynecomastia without recurrence and estradiol levels < 1.5 ng/dL. Although the exact route of transmission to each male child was not certain (application sites were normally clothed), the authors speculated that estrogen was spread from traces remaining on the mothers' hands after application, possibly via food preparation. Prepubertal gynecomastia has also been reported associated with estrogen-containing hair cream[2] and food ingested by children.[3]

In Study E2002-1, 2 of 14 male subjects had isolated sample time elevations of serum estradiol concentrations above the reported normal range of 0.8-3.5 ng/dL after 2 days of intentional exposure. From this information and the literature information on prepubertal gynecomastia attributable to exposure of topical estrogens, albeit larger doses applied that utilized in Study E2002-1, it appears prudent to recommend in labeling that topical applications sites be covered to prevent exposure, especially in children, and that hands be thoroughly washed after application. This information will be conveyed in labeling.

3.6 Sunscreen

Study E2002-2 entitled, "Estrasorb™ Sunscreen and Photosensitivity Study" was an open-label, non-randomized multiple-dose study in which 14 postmenopausal women applied two 1.74 gram foil-laminated pouches of ESTRASORB™ to the thighs and calves daily for 24 days and at various times applied sunscreen 10 minutes before or 25 minutes after the application of ESTRASORB. The objectives of Study E2002-2 were as follows:

a. To determine if systemic absorption of estradiol is significantly altered by application of sunscreen before or after Estrasorb™ application.
b. To determine if Estrasorb™ exposure causes photosensitivity reactions.
c. To determine the actual amount expressed from the packaging solution.

Comparison of estradiol AUC and C_{max} show significantly elevated AUC and C_{max} in the two "sunscreen" periods. The trough data suggest that use of sunscreen either before or after application of ESTRASORB™ enhances the absorption of ESTRASORB™ approximately 30% with little difference according to the order of application. This information will be conveyed in labeling.

4.0 Labeling (General Issues)

The trademark Estrasorb™ was submitted to the Office of Drug Safety, Division of Medication Errors and Technical Support (DMETS) for assessment of the proposed propriety drug name. DMETS has no objection to the use of the propriety name, Estrasorb™.

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[2] Edidin DV, Levitsky LL. Prepubertal gynecomastia associated with estrogen-containing hair cream. Am J Dos Child. 1982;136(7):587-8.

[3] Saenz de Rodriguez CA, Bongiovanni AM, Conde de Borrego L. An epidemic of precocious development in Puerto Rican children. J Pediatr. 1985;107(3):393-6.

The Labeling and Nomenclature Committee (LNC) was consulted concerning use of the established name ' . The LNC recommended the established name be revised to read, "estradiol topical emulsion". This revision has been incorporated into labeling.

The proposed labeling submitted has been modified in accordance with the Agency's 2003 draft labeling guidance entitled, "Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Prescribing Information for Healthcare Providers and Patient Labeling" (see Federal Register/ Volume 68/ Monday, February 3, 2003/Notices). Several major and minor changes are recommended. See the attached labeling in Appendix 1 of this review.

The PATIENT INFORMATION insert has been modified in compliance with the plain language initiative, recommendations from the Division of Drug Marketing, Advertising and Communications (DDMAC), and the Division of Surveillance, Research & Communication Support (DSRCS), and the Agency's 2003 draft labeling guidance.

5.0 Recommendations on Approvability

The data presented in this new drug application (NDA 21-371/000) provide substantial evidence to support the safety and efficacy of 3.48 grams of Estrasorb™ (two 1.74 gram foil-laminated pouches) containing 8.7 mg of estradiol (2.5 mg of estradiol/gram), applied topically each day, for the treatment of moderate to severe vasomotor symptoms associated with the menopause.

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

/s/

Daniel A. Shames
10/9/03 08:28:44 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

NDA 21-371

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 27, 2003

TIME: 3.00 – 4.00pm

LOCATION: Pkln 17B-43

APPLICATION: NDA 21-371

TYPE OF MEETING: 11-month status

SPONSOR: Novavax Inc.

DRUG: Estrasorb topical emulsion

MEETING CHAIR: Theresa van der Vlugt, M.D.

MEETING RECORDER: George Lyght, R.Ph.

Participants:
Theresa van der Vlugt, M.D. - Medical Officer, DRUDP
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)
Suzanne Thornton, Ph.D., Team Leader, Pharmacologist, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetics Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Sayed Al-Habet, Ph.D., Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Katherine Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
George Lyght, R.Ph. - Regulatory Project Manager, DRUDP (HFD-580)

MEETING OBJECTIVES:

To discuss the status of reviews for NDA 21-371

Background:
The clinical pharmacology review of the transfer potential and sunscreen studies for this NDA is ongoing. The information is to be shared with the chemistry reviewer in the hopes of resolving the issue of [redacted] found in the samples.

Discussion:

NDA 21-371

Clinical
- Review is complete except for the residual estradiol and transfer potential study information
- Remaining revisions to the label are dependent on chemistry and clinical pharmacology input

Chemistry
- The review is ongoing
- Unresolved issue: to be marketed product with [redacted] when there is no more clinical supplies for comparison
- The shelf life is to be limited to 2 years
- Chemistry and Clinical Pharmacology will decide if the data from the sunscreen studies is comparable or bioequivalent (using data from Lot.0038)

Clinical Pharmacology
- The transfer potential study shows a 15 to 25 percent transfer to a partner
- The sunscreen study shows minimal effects
- The pouch expression shows minimal difference in subjects (report pending)
- [redacted] did not appear to cause a problem

Pharm Tox
- Label under review

Statistics
- The Review is completed

Minutes Preparer: /S/
George Lyght, R.Ph., Project manager

Chair Concurrence: /S/
Theresa van der Vlugt, M.D.
Medical Reviewer

APPEARS THIS WAY
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NDA 21-371

cc: Original
HFD-580/Div. Files

Drafted by: gl/09.04.03
Initialed by: tv/09.26.03/km/09.26.03/am/09.29.03/ /mr/09.29.03/no other responses
final:

MEETING MINUTES

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/s/

Theresa Van Der Vlugt
10/9/03 05:10:50 PM
I concur with the meeting minutes.

APPEARS THIS WAY
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MEMORANDUM OF TELECON

MEETING DATE: September 29, 2003

TIME: 2: 00 PM

LOCATION: Parklawn Building Rm 17B-43

APPLICATION NUMBER: NDA 21-371 Estrasorb™ (estradiol topical emulsion)

SPONSOR: Novavax, Inc.

TYPE OF MEETING: Teleconference

Meeting Chairman: Amit Mitra, Ph.D., Chemistry Reviewer, DRUDP

Meeting Recorder: George Lyght, R.Ph., Regulatory Project Manager

FDA ATTENDEES
Amit Mitra, Ph.D., Chemist, Division of reproductive and Urologic Drug Products (DRUDP) (HFD-580)
George Lyght, R.Ph., Regulatory Project Manager (DRUDP) (HFD-580)

EXTERNAL ATTENDEES
Craig Wright, M.D., CEO, Novavax, Inc.
Joan Brisker, VP of Regulatory Affairs and Quality Assurance, Novavax, Inc.

BACKGROUND:
The FDA needed to give the sponsor clarification of the [redacted] ; commitment for the Estrasorb product.

MEETING OBJECTIVES:
To clarify to Novavax that the acceptance criteria for the number of [redacted] , for release and stability for all lots of Estrasorb is requested.

DISCUSSION

- DRUDP requested a change in the amendment dated 9-17-03. from "Novavax commits to set the specification criteria for the number of [redacted] in Estrasorb bulk lots as less than or equal to [redacted] to "Novavax commits to set the specification criteria for the number of [redacted] in Estrasorb bulk lots and stability lots as less than or equal to [redacted]
- The sponsor may seek guidance again if the sponsor is unable to meet the acceptance criteria.

DECISIONS:

- Novavax will send in the amendment as Amendment 23

ACTION ITEM:

- Official Minutes will be conveyed to the Sponsor

Minutes Preparer:

George Lyght, R.Ph., RPM

Chair Concurrence:

Amit Mitra, Ph.D., Chemist

APPEARS THIS WAY
ON ORIGINAL

cc: Original
HFD-580/Div. Files
HFD-580/Meeting Minutes files
HFD-580/RPM

Drafted by: gl/9/29/03
Initialed by: am/09.29.03/mr/09.30.03
final: 09.30.03

MEETING MINUTES

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/s/

Amit K. Mitra
10/9/03 01:05:21 PM

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NOVAVAX inc.

ORIGINAL

October 9, 2003

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fisher Lane
Rockville, Maryland 20857

RE: Amendment 026 to NDA Re-Submission 21-371 Phase IV Clinical Trial Commitment

Dear Dr. Shames:

Amendment 24 submitted to DRUDP on 10/7/03 contained a faithful commitment by Novavax to design a Phase IV clinical trial study to find the minimal effective dose of Estrasorb™. The following is the timeline for this commitment:

Protocol Submission:	Within 6 months of the date of receipt of the Estrasorb approval letter from DRUDP
Study Start:	Within 6 months of the protocol agreement with DRUDP
Final Report Submission:	Within 6 months of the study completion

If you have any questions, or require further information, please contact Ms. Joan Brisker, VP Regulatory Affairs and Quality Assurance at Novavax, Incorporated, 12111 Parklawn Drive, Rockville, Maryland, 20852, work phone (301)231-0774 EXT. 29 or cell phone 301-938-3989.

Respectfully yours,

Joan Brisker
VP Regulatory Affairs and Quality Assurance
Novavax, Inc.

Office of Drug Safety

Memo

To: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

From: Alina R. Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

CC: George Lyght
Project Manager
HFD-580

Date: October 9, 2003

Re: ODS Consult 01-0181-2; Estrasorb (Estradiol Topical Emulsion); NDA 21-371.

This memorandum is in response to a October 6, 2003 request from your Division for a re-review of the proprietary name, Estrasorb. Labels and labeling for the foil packets were submitted for review and comment.

DMETS has not identified any additional proprietary or established names that have the potential for confusion with Estrasorb since we conducted our initial review on March 11, 2002 (ODS consult 01-0181-1) that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name.

In review of the carton and package insert labeling, DMETS focused on safety issues relating to possible medication errors. We have identified the following areas of possible improvement which might minimize potential user error.

A. CARTON LABELING

1. The font of the "E" in ESTRASORB is larger and scripted in cursive. It differs from the rest of the word so much that it is possible to overlook it entirely and see only "strasorb". Modify the font style of the "E" in Estrasorb be consistent with the remaining letters of the name.

2. Revise the statement ' [redacted] ' to read "Each gram contains 2.5 mg of estradiol." In addition, relocate this statement to the side panel to avoid confusion with the total drug content.

3. Relocate the route of administration statement to the principal display panel.

4. Relocate the expression of total drug content to immediately follow the established name.

5. Relocate the net quantity statement to the bottom of the label to avoid confusion with the total drug content.

6. Include the milligrams/day of estradiol to be delivered systemically.

7. Since this package is to be dispensed to a patient, please assure that the packaging is child-resistant.

8. The manufacturers name on the back panel is prominent and may get confused as a product name. Please decrease prominence.

9. The directions on the side panel "Apply 2 pouches daily" should immediately follow the statement "Dosage and administration:".

10. The front panel utilizes the word "packets" yet the side panel utilizes the word "pouches". Please revise using one term to describe the package.

B. PACKAGE INSERT LABELING

1. DESCRIPTION

   a. Consider deleting the [redacted] from the US package insert. Although [redacted] ' is not considered a dangerous abbreviation by the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP), it may introduce confusion.

   b. To decrease confusion, consider using one term to describe the foil "packets" or "pouches." The cartons use "packet" and the insert uses "pouch" to describe the same item. Revise accordingly.

2. DOSAGE AND ADMINISTRATION

a. The statements [redacted] may be confusing. Please clarify whether excess material should be rubbed on the left calf or the buttocks.

b. Increase the prominence the following statement by using a bold font and moving it to the beginning of the section. "Any excess ESTRASORB [redacted] on either hand should be massaged into the buttocks. ESTRASORB [redacted] should not be applied to the breasts or other areas above the waist. Upon completion of ESTRASORB application, both hands should be washed with soap and water to remove any residual estradiol."

c. Please include a statement indicating the recommended usual dosage.

3. HOW SUPPLIED

a. The statement [redacted] should be revised to state "Estrasorb (estradiol topical emulsion) delivers 0.05 mg/day."

b. Please delete the daily dose statement in this section.

C. PATIENT PACKAGE INSERT

Consider using illustrations to facilitate patient understanding of instructions as done in the professional package insert.

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name and its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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/s/

Alina Mahmud
10/9/03 01:58:18 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/9/03 02:01:25 PM
DRUG SAFETY OFFICE REVIEWER

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420;PKLN Rm. 6-34
Attention: Sammie Beam, Project Manager
Carol Holquist, Deputy Director

FROM: George Lyght
Regulatory Health Project Manager
Division of Reproductive And Urologic Drug Products; HFD-580
301-827-4252

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
October 3, 2003		21-371	Resubmission	July 31, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Estrasorb (estradiol topical emulsion)	RUSH	estrogen	October 9, 2003

NAME OF FIRM: Novovax

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: The tradename ESTRASORB was found acceptable by DMETS in a review dated March 8, 2002.. Please do a quick re-evaluation of this tradename. The PDUFA goal date is OCTOBER 10, 2003. Please find the PI and carton labeling in EDR dated July 31 and August 4, 2003. Sorry for this late request.

Thanks.

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

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/s/

George Lyght
10/3/03 04:54:03 PM

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9/25/03

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-371 Supplement # SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: Estrasorb
Generic Name: estradiol
Strengths: 2.5 mg

Applicant: Novavax Inc.

Date of Application: June 29, 2001
Date of Receipt: June 29, 2001
Date clock started after UN: NA
Date of Filing Meeting: August 8, 2001
Filing Date: August 28, 2001
Action Goal Date (optional): User Fee Goal Date: 10/10/2003
Voluntary WD plus a Major Amendment changed the Goal date
Indication(s) requested: Treatment of moderate to severe vasomotor symptoms associated with the menopause

Type of Original NDA: (b)(1) X_____ (b)(2) _____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____
NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S ____x_____ P _____
Resubmission after withdrawal? ____x_____ Resubmission after refuse to file?
_____
Chemical Classification: (1,2,3 etc.) ____3_____
Other (orphan, OTC, etc.) _____

User Fee Status: Paid _____ Exempt (orphan, government) _____
Waived (e.g., small business, public health) __x_____

Form 3397 (User Fee Cover Sheet) submitted: YES NO
User Fee ID # _4160_____
Clinical data? YES _____ NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES NO

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO
- Was form 356h included with an authorized signature? YES NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
  If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A YES NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- If in Common Technical Document format, does it follow the guidance? N/A YES NO
- Is it an electronic CTD? N/A YES NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, _____years NO
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,

"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? YES NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: IND 49-761

- End-of-Phase 2 Meeting(s)? Date(s) July 19, 1999 NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) June 22, 2001 NO
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
  N/A YES NO

- Has DOTCDP been notified of the OTC switch application? NA YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? NA
  YES NO

Chemistry

• Did applicant request categorical exclusion for environmental assessment?		YES	NO
If no, did applicant submit a complete environmental assessment?		YES	NO
If EA submitted, consulted to Nancy Sager (HFD-357)?		YES	NO
• Establishment Evaluation Request (EER) submitted to DMPQ?		YES	NO
• If a parenteral product, consulted to Microbiology Team (HFD-805)?	NA	YES	NO

ATTACHMENT

MEMO OF FILING MEETING

Meeting Minutes

Date: August 8, 2001 **Time**: 1:00 - 1:35 PM **Location:** Parklawn; Room 17B-43
NDA: 21-371 **Drug Name**: Estrasorb (micellar nanoparticles containing estradiol)
Indication: reduction of moderate-to-severe vasomotor symptoms (VMS)
Sponsor: Novavax, Inc.
Type of Meeting: NDA Filing Meeting
FDA Lead: Dr. Susan Allen
Meeting Recorder: Ms. Diane Moore
FDA Participants:
Susan Allen, M.D., M.P.H. – Director, Division of Reproductive and Urologic Drug Products (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 – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Dornette Spell-LeSane, NP-C. – Project Manager, DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Paul Stinavage, Microbiologist, (ONDC; HFD-805)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Sayed Al-Habet, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Lisa Stockbridge, Ph.D. - Regulatory Reviewer, Division of Drug Marketing, Advertising and Communications (DDMAC; HFD-42)
Constance Lewin, M.D. -Pharmacologist, Division of Scientific Investigation (DSI), GCP Branch I (HFD-46)
Dianne Spillman, Regulatory Health Project Manager, Division of Oncology Drug Products (DODP; HFD-150)
Meeting Objective:
To discuss the fileability of NDA 21-371 for the — of moderate-to-severe vasomotor symptoms.
Background:
The NDA was received on June 29, 2001. The product is an emulsion of micelle nanoparticles containing estradiol hemihydrate. The NDA recommends the application of 7.5 mg of Estrasorb daily providing a dose of 50 ∝g/day of estradiol.

Decisions Reached:

Clinical

Fileable.NDA 21-371
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Page 2

in the clinical trial, subjects applied three foil laminated sachets of lotion (each delivering 2.5 mg of estradiol) for a total of 7.5 mg of estradiol to the top of the right thigh, top of the left thigh, right calf and left calf with the residual applied to the buttocks; the NDA also contains a package of two foil laminated pouches each delivering 3.75 mg of estradiol which needs to be rubbed into the skin for two minutes; clinical data from the two-pouch method of application were not included in the NDA

the product was reformulated in 1997 to increase the water content from to increase the stability of the product at room temperature; the pivotal trials used this new formulation; the sponsor did not submit bridging information for the multiple-dose applications to the clinical application

Division of Scientific Investigations (DSI)

all the study sites are in the United States; a request for clinical site audit will be forwarded to the DSI

Chemistry, Manufacturing and Quality Control

Fileable

there are some deficiencies in the NDA that were discussed at the Pre-NDA meeting with the sponsor on June 22, 2001; additional information was requested from the sponsor on August 2, 2001, including:

the polysorbate 80 and the particle size were not tested properly by the sponsor

the sponsor did not include a preservative challenge study in the NDA, as was requested in the Pre-NDA meeting

stability data for the ; was not submitted to the NDA

the sponsor did not submit the three validation packages and the Master Production batch record (this information was submitted on August 8, 2001)

Microbiology

Fileable

the sponsor should submit preservative efficacy testing data for the the current formulation may not pass preservative challenge for however, a preservative challenge test is not required for the single-dose packaging

Pharmacology

Fileable per the Pharmacology reviewer

Clinical Pharmacology and Biopharmaceutics

Fileable

the manufacturing site was changed because the former site received a warning letter from the Agency; it was determined that there was no need for a bioequivalence study for the new manufacturing site because the sponsor used *in vitro* release formulation data to bridge the clinical and new manufactured formulations

it needs to be determined whether a comparison study for the is needed

Biometrics

Fileable

one placebo-controlled clinical study was submitted; the study was randomized by strata for intact uterus

Regulatory
Fileable
Financial Disclosure information is adequate for review
Pediatric Waiver request was submitted for this application.NDA 21-371
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Page 3
Action Items: none

Signature, recorder Signature, Chair

Post Meeting Addendum:
The sponsor submitted the requested validation packages and the Master Production batch record on August 8, 2001. As of September 19, 2001, the sponsor has not submitted the requested stability data for the [redacted], data from polysorbate 80 [redacted] tests, or particle size preservative challenge study data. The sponsor indicated that it would take some time to generate the data. The requested information that has not been submitted will be review issues.
drafted: dm/8.29.01/N21371FM8801.doc
Concurrence:
T.Rumble 8.29.01/K.Meaker, C.Lewin, A. Parekh, L.Stockbridge, T.van der Vlugt 9.4.01
S.Slaughter, A.Mitra 9.18.01/ S.Al-Habet, Allen 9.19.01
Response not received from D.Spillman, P.Stinavage, D.Spell-LeSane,----------

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/s/

Diane V. Moore
9/24/01 06:26:09 PM
Susan Allen
9/25/01 01:55:47 PM
DATE:

Memo of Filing Meeting (Dated August 8, 2001) is attached The Electronic signed copy is in DFS
G. Lyght

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/s/

George Lyght
10/20/03 09:10:25 AM
CSO

George Lyght
10/20/03 09:16:04 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

9/25/03

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-371	Efficacy Supplement Type SE-	Supplement Number	
Drug:Estrasorb topical emulsion		Applicant:Novavax Inc.	
RPM:George Lyght		HFD-HFD-580	Phone # 7-5424
Application Type: (x) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): Estrasorb	

❖ Application Classifications:	
• Review priority	(x) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	October 10, 2003
❖ Special programs (indicate all that apply)	(x) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	( ) Paid
• User Fee waiver	(x) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (x) No
• This application is on the AIP	( ) Yes (x) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	( ) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted.	(x) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.	21 CFR 314.50(i)(1)(*i*)(A) ( ) I A ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (x) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	
General Information	
❖ Actions	
• Proposed action	(x) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	NA
• Status of advertising (approvals only)	(x) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(x) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None (x) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	10/08/2003
• Most recent applicant-proposed labeling	10/08/2003
• Original applicant-proposed labeling	09/04/2003
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS review 10.10.03
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Class labeling
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	10/08/2003
• Applicant proposed	10/08/2003
• Reviews	Yes
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Yes
• Documentation of discussions and/or agreements relating to post-marketing commitments	Yes
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Yes
❖ Memoranda and Telecons	Yes
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	July 19, 1999
• Pre-NDA meeting (indicate date)	June 22, 2001
• Pre-Approval Safety Conference (indicate date; approvals only)	NA
• Other	NA

Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	NA
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	January 31, 2003
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	10/09/2003
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	October 9, 2003
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	11/7/2001 & 1/17/ 2002, 4/4/2002
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	In clinical review p. 30
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	In clinical review p.4
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	
❖ Demographic Worksheet *(NME approvals only)*	NA
❖ Statistical review(s) *(indicate date for each review)*	04/22/2002
❖ Biopharmaceutical review(s) *(indicate date for each review)*	Final 10/08/2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	In clinical review
• Bioequivalence studies	NA
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	Last rev. 10/09/2003
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	July 29, 1997
• Review & FONSI *(indicate date of review)*	NA
• Review & Environmental Impact Statement *(indicate date of each review)*	02/13/2002
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	04/04/2002
❖ Facilities inspection (provide EER report)	Date completed: **(x)** Acceptable **( )** Withhold recommendation
❖ ❖ ❖ Methods validation	**(x)** Completed **( )** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ ❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	04/22/2002
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	NA
❖ ❖ CAC/ECAC report	NA