CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-813

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

14. PATENT CERTIFICATION

Patent information and certification statements (Forms FDA 3542a) for Bio-E-Gel are included in Item 13.

BioSante considers this to be a 505(b)(1) application.

In the opinion and to the best knowledge of BioSante, there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

In the document that follows, BioSante is requesting 3-year exclusivity for the prescription marketing of Bio-E-Gel.

EXCLUSIVITY SUMMARY

NDA # 21-813 SUPPL # HFD #

Trade Name Elestrin

Generic Name estradiol gel 0.06%

Applicant Name BioSante Pharmaceuticals Inc.

Approval Date, If Known December 15, 2006 (goal)

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-371 Estrasorb

NDA# 21-166 Estrogel

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study # EST005

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study # EST005

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 51,229	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: George Lyght, R.Ph
Title: Regulatory Health Project Manager
Date: October 30, 2006

Name of Office/Division Director signing form: Scott Monroe, M.D.
Title: Acting Division Director, Division of Reproductive and Urologic Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Scott Monroe
12/15/2006 05:07:54 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : N 21-813 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: February 16, 2006 PDUFA Goal Date: December 16, 2006

HFD 580 Trade and generic names/dosage form: Bio-E-Gel (estradiol gel 0.06%)

Applicant: BioSante Pharmaceuticals Inc. Therapeutic Class: Estrogen

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- ☐ Yes. Please proceed to the next question.
- X No. PREA does not apply. Skip to signature block.

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) *previously approved* (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): [ ]

Indication #1: Treatment of moderate to severe vasomotor symptoms associated with menopause

Is this an orphan indication?

- ☐ Yes. PREA does not apply. Skip to signature block.
- X No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- X Yes: Please proceed to Section A.
- ☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- X Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

George Lyght_
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- X **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- X **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- X **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

George Lyght
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

George Lyght
10/30/2006 11:04:24 AM

19. FINANCIAL INFORMATION

Appears This Way
On Original

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

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		
	See attached lists of 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
Stephen M. Simes	Vice Chairman, President, and Chief Executive Officer
FIRM/ORGANIZATION: BioSante Pharmaceuticals, Inc.	
SIGNATURE: Stephen M. Simes	DATE: 1/5/06

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

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of trade secret and/or

confidential commercial

information from

Administrative Documents - Clinical Investigator/Financial Disclosure

ACTION PACKAGE CHECKLIST

Application Information			
BLA # NDA # 21-813	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type	
Proprietary Name: Elestrin Established Name: estradiol gel Dosage Form: gel		Applicant: BioSante Pharmaceuticals, Inc.	
RPM: George Lyght		Division: DRUP	Phone # 301-796-0948

NDAs:	505(b)(2) NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	December 16, 2006 December 15, 2006
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☒ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 5

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☒ Included
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☐ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	12-15-2006
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	Division & applicant agreed
• Original applicant-proposed labeling	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	NA
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	X
• Original applicant-proposed labeling	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	NA
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	NA
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	NA
• Original applicant-proposed labeling	NA
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	X
• Most recent applicant-proposed labeling	Division & applicant agreed
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☒ DMETS 9-13-06 & 12-7-06 ☒ DSRCS 10-12-06 ☒ DDMAC 9-13-06 ☐ SEALD NA ☐ Other reviews ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	12-07-06 & ☐ Memo 12-14-06
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	NA
❖ Pediatric Page (all actions)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☒ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	
❖ Internal memoranda, telecons, email, etc.	NA
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg
• EOP2 meeting *(indicate date)*	☐ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	April 24, 2003
❖ Advisory Committee Meeting	☒ No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	12-14-06
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☒ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	NA
• ☐ Review & FONSI *(indicate date of review)*	
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	☐ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 09-22-06 ☒ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	August 9, 2006
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	☐ None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	October 16, 2006
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☐ None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☐ Not needed 10-12-2006
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☒ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) *(indicate date for each review)*	☐ None
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 10-16-2006

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/s/

George Lyght
12/22/2006 12:56:33 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-813

Bradley Pharmaceuticals, Inc.
Attention: Ralph Landau
Vice President, Chief Scientific Officer
383 Route 46 West
Fairfield, NJ 07004-2402

Dear Mr. Landau:

We acknowledge receipt on January 30, 2007 of your, January 29, 2007 correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

Name of Drug Product:	Elestrin™
NDA Number:	21-813
Name of New Applicant:	Bradley Pharmaceuticals, Inc.
Name of Previous Applicant:	BioSante Pharmaceuticals, Inc.

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate Bradley Pharmaceuticals, Inc. as the applicant of record for this application

All changes in the NDA from those described by the original owner, such as manufacturing facilities and controls, must be reported to us prior to implementation except that changes in the drug product's label or labeling to change the product's brand or the name of its manufacturer, packer, or distributor may be reported in the next annual report. Refer to the *Guidance for Industry: Changes to an Approved NDA or ANDA* for information on reporting requirements. We request that you notify your suppliers and contractors who have DMFs referenced by your application of the change in ownership so that they can submit a new letter of authorization (LOA) to their Drug Master File(s).

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81. In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call me at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

George Lyght, R.Ph.
Sr. Regulatory Health Project Managemer
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Cc: BioSante Pharmaceuticals, Inc.
Attention: Stephen M. Simes
Vice Chairman, President, and Chief Executive Officer
111 Barclay Boulevard
Lincolnshire, IL 60069

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/s/

George Lyght
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-813

Biosante Pharmaceuticals, Inc.
Attention: Joanne Zborowski
Project Manager
111 Barclay Blvd., Suite 280
Lincolnshire, IL 60069

Dear Ms. Zborowski:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bio-E-Gel (estradiol topical gel) 0.06%

We also refer to the meeting between representatives of your firm and the FDA on December 5, 2006. The purpose of the meeting was to clarify information sent to your firm in an Advice Letter dated November 22, 2006.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call George Lyght, R.Ph, Regulatory Health Project Manager, at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

Shelley R. Slaughter, MD., PhD.
Medical Team Leader
Division of Reproductive & Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	December 5, 2005
TIME:	3: 00 PM
LOCATION:	WO 5394
APPLICATION:	NDA 21-813
DRUG NAME:	Estradiol gel
TYPE OF MEETING:	Teleconference
MEETING CHAIR:	Shelley R. Slaughter, MD., PhD.
MEETING RECORDER:	George Lyght, R.Ph.

FDA ATTENDEES: (Title and Office/Division)
Scott Monroe, M.D., Acting Director Division of Reproductive & Urologic Products (DRUP)
Shelley R. Slaughter. M.D., Ph.D. – Medical Team Leader, (DRUP)
Theresa van der Vlugt, M.D. – Medical Reviewer, DRUP
George Lyght, R.Ph., - Sr. Regulatory Health Project Manager, DRUP

EXTERNAL CONSTITUENT ATTENDEES:
Biosante Pharmaceuticals, Inc.:
Stephen Simes, President and CEO
Michael C. Snabes, MD. PhD, Clinical Development, Consultant
Joanne Zborowski, Senior Project Manager

Bradley Pharmaceuticals:
Tom Brigliadoro, Senior Product Manager

BACKGROUND:
NDA 21-813 Estradiol gel was submitted to the FDA seeking [redacted] indications: (1) Treatment of moderate-to-severe vasomotor symptoms associated with the menopause [redacted]

On November 22, 2006, the Division sent an Advice letter to the Sponsor with the following comments:

> The endometrial safety of the 2.6 gram/day dose of estradiol gel has not been demonstrated.
>
> The findings in 12-week Study EST005 of 5 cases of hyperplasia upon scheduled end-of study endometrial biopsy in subjects receiving the 2.6 gram/day dose of estradiol gel raises concerns regarding the endometrial safety of this dose of estradiol gel.

BioSante Pharmaceutical Inc. requested a meeting to get clarification of the FDA's comments.

MEETING OBJECTIVE:
To answer the Sponsor's question:
Why would our 2.6 g/day dose of Bio-E-Gel be required to show endometrial safety in an estrogen-only study when it would be used clinically with concomitant progestin every month?

DISCUSSION POINTS:
Division comments:

- That the Agency's 74 day letter to BioSante had advised on potential serious safety review issues, specifically, the reported findings of one case of atypical endometrial hyperplasia at the 1.7 gm per day estradiol gel dose (1.05%, 1 case per 95 subjects with a uterus), and 5 cases of simple hyperplasia at 2.6 gm per day estradiol gel dose (11.1%, 5 cases per 45 subjects with a uterus).
- The Division acknowledges that the June 13, 2005 response presented a thorough review of the published literature and a thorough review of FDA approved products for the treatment of Vasomotor Symptoms (VMS) and Vulvar and Vaginal Atrophy (VVA).
- The Division made reference to the Agency's Draft Estrogen Class Labeling Guidance for estrogen only products including the:
    a) Black Box warning regarding the importance of close surveillance of women with a uterus receiving estrogens.
    b) The Warning Section of recommended estrogen class labeling that states that unopposed estrogens in women with a uterus has been associated with an increased risk of endometrial cancer. Most studies show no significant risk of endometrial cancer with estrogen use for less than 1 year.
    c) The Precautions Section of recommending estrogen class labeling points out that studies of addition of a progestin for 10 or more days to estrogen use have reported a lowered incidence of endometrial hyperplasia which may be a precursor to endometrial cancer.
- The Division stated that the Draft Guidance does not mandate the specific use of progestin therapy with estrogen use in women with a uterus as to do so would be considered an influence on the practice of medicine.

Sponsor's comments:

FDA comments

- The Division looks closely at safety in 12 week clinical trials, including endometrial safety. Review decisions regarding endometrial safety are made based on endometrial biopsy results.

ACTION ITEMS:
Official minutes will be conveyed to the Sponsor.

Signature, minutes preparer

George Lyght, R.Ph.
Regulatory Health Project Manager

Signature, Chair

Shelley R. Slaughter, MD., PhD.
Medical Team Leader, DRUDP

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/s/

Shelley Slaughter
1/4/2007 03:04:07 PM

NDA [ ]

NDA 21-813

Drug name:	Elestrin (Estradiol gel) 0.87 g, 1.7 g[ ]
Sponsor:	BioSante Pharmaceuticals Inc.
Stamp date:	February 16, 2006
PDUFA Date:	December 16, 2006
Indications:	Treatment of moderate to severe vasomotor symptoms associated with menopause[ ]

[ ] [ ]

Background/Action: This NDA was submitted with the Trade name of Bio-E-Gel with the [ ] doses for the [ ] indications. As a result of our review, it was decided to (1) change the name to Elestrin™ (estradiol gel)

[ ] [ ]

[ ] [ ]

[ ] NDA 21-813 Elestrin (estradiol gel) 0.87 g, 1.7 g
Indicated for the Treatment of moderate to severe vasomotor symptoms associated with menopause.

[ ] [ ]

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/s/

George Lyght
12/14/2006 05:17:33 PM
CSO

George Lyght
12/14/2006 05:20:46 PM
CSO

MEMORANDUM OF TELECON

DATE: December 12 and 13; 2006

APPLICATION NUMBER: NDA 21-813

BETWEEN:

Name: Joanne Zborowski, RN
Phone: 847-478-0500 ext. 104
Representing: BioSante Pharmaceuticals, Inc.

AND

Name: George Lyght, R.Ph.
Division of Reproductive & Urologic Products, HFD-580

SUBJECT: Elestrin™ (estradiol gel) Labeling

The Division provided revisions to Physician Package Insert (PPI), Patient Insert (PI), and the carton and container labeling (mock-up) for Elestrin™ (estradiol gel). Additionally, the manufacturing companies' names were updated in the PPI, PI, and mock-up. The Division requested that the Sponsor submit (1) A letter of acceptance of all changes discussed, and (2) Submit a clean copy of the labeling and mock-ups.

George Lyght, R.Ph.

SIGNER'S NAME
Regulatory Health Project Manager

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/s/

George Lyght
12/13/2006 05:48:44 PM
CSO

George Lyght
12/13/2006 05:51:37 PM
CSO

NDA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

NDA # 21-813 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Bio-E-Gel
Established Name: Estradiol topical gel
Strengths: 0.06%

Applicant: Biosante Pharmaceuticals Inc.
Agent for Applicant (if applicable):

Date of Application: February 16, 2006
Date of Receipt: February 16, 2006
Date clock started after UN:
Date of Filing Meeting: April 4, 2006
Filing Date: April 17, 2006
Action Goal Date (optional): User Fee Goal Date: December 16, 2006

Indication(s) requested: Treatment of moderate to severe vasomotor symptoms associated with menopause.

Type of Original NDA: (b)(1) ☑ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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 or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 5
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☑ NO ☐

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

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☑ NO ☐
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- 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 ☑

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- 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 ☐
  If no, explain:

- 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:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☑
   This application is: All electronic ☐ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☑ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?
   - All Labeling (SPL format and Microsoft Word version in addition to the paper copy)
   - Item, Case Report Tabulations
   - Item 12, Case Report Forms (CRF's)

   Additional comments: All paper forms & certifications have been signed.

3. This application is an eCTD NDA. YES ☐

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☑ NO ☐
- Exclusivity requested? YES, ☑ 3Years ☑
  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 . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☑ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☐ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☑

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☑ NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

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

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

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 51,229

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☑ NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) April 24, 2003 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO ☑
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☑
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☑ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☑ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☑ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☑ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☑ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☑ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☑ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☑

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☑

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  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 EA officer, OPS? YES ☑ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☑ NO ☐
- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☑

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 4, 2006

NDA #: 21-813

DRUG NAMES: Bio-E-Gel

APPLICANT: Biosante Pharmaceuticals Inc.

BACKGROUND: The Sponsor submitted Bio-E-Gel (estradiol gel) as a NDA is with indications for:

(1) Treatment of moderate-to-severe vasomotor symptoms associated with menopause [redacted]

The proposed presentation is for Bio-E-Gel to be in a Metered Dose Pump and is intended for once a day application.

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Slaughter, Shelley R; Van Der Vlugt, Theresa H; Christner, Donna; Tran, Doanh; Parekh, Ameeta; Sobhan, Mahboob; Reid, Lynnda L

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	**Reviewer**
Medical:	Theresa van der Vlugt, M.D.
Secondary Medical:	Shelley R. Slaughter, M.D., Ph.D.
Statistical:	Mahboob Sobhan, Ph.D.
Pharmacology:	Lynnda Reid, Ph.D.. Krishan Raheja, Ph.D.
Statistical Pharmacology:	
Chemistry:	Zhengfang Ge, Ph.D., Donna Christner, Ph.D.
Environmental Assessment (if needed):	
Biopharmaceutical:	Doanh Tran, Ph.D., Ameeta Parekh, Ph.D.
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Khairy Malek, Ph.D.
OPS:	
Regulatory Project Management:	George Lyght, RPh., Margaret Kober, RPh., M.P.A.
Other Consults: DMETS	Laura Pincock, Pharm.D
DSRCS	Nancy Clark

Per reviewers, are all parts in English or English translation? YES ☑ NO ☐
If no, explain:

CLINICAL FILE ☑ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☑ NO ☐

If no, explain:

- Advisory Committee Meeting needed? YES, date if known _____ NO ☑

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A ☑ YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A ☑	FILE ☐	REFUSE TO FILE ☐
STATISTICS	N/A ☐	FILE ☑	REFUSE TO FILE ☐
BIOPHARMACEUTICS		FILE ☑	REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☐ NO ☑
  YES

PHARMACOLOGY/TOX	N/A ☐	FILE ☑	REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☑

CHEMISTRY	FILE ☑	REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☑ NO ☐
- Sterile product? YES ☐ NO ☑
  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☑ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☑ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☑ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☑ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☑ Convey document filing issues/no filing issues to applicant by Day 74.

George Lyght
Regulatory Project Manager

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/s/

George Lyght
12/7/2006 04:36:38 PM
CSO

George Lyght
12/7/2006 04:42:40 PM
CSO

MEMORANDUM OF TELECON

DATE: December 7, 2006

APPLICATION NUMBER: NDA 21-813

BETWEEN:

Name: Joanne Zborowski
Phone: 847-951-9531
Representing: BioSante Pharmaceuticals Inc.

AND

Name: George Lyght, R.Ph.
Division of Reproductive & Urologic Products, HFD-580

SUBJECT: Container Labels

- The Sponsor was notified that the line between the trade name and the established name should be removed.
- A new mock up must be sent in as soon as possible.

George Lyght

_____

SIGNER'S NAME
Regulatory Project Manager

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/s/

George Lyght
12/7/2006 03:31:44 PM
CSO

George Lyght
12/7/2006 03:38:18 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: December 4, 2006

To: Joanne Zborowski	**From:** George Lyght
Company: Biosante Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 847-478-9260	**Fax number:** 301-796-0948
Phone number: 847-478-0500 x104	**Phone number:** 301-796-0948

Subject: Urgent Statistical Information Request

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☑ NO

December 4, 2006

NDA 21-813 Estradiol gel - Additional statistical information request.

"Re-analyze the change from baseline to last visit in vaginal dryness, irritation, pain with sexual activity, bleeding with sexual activity, and pain passing urine similar to Table 2, dated 4/8/2006 in subjects who had at least 1 moderate-to-severe symptom of vaginal atrophy identified as most bothersome to her, and who had PH>5.0 and superficial cells <=5% on a vaginal smear".

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/s/

George Lyght
12/4/2006 05:20:44 PM
CSO

George Lyght
12/4/2006 05:24:20 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-813

Biosante Pharmaceuticals, Inc.
Attention: Joanne Zborowski
Project Manager
111 Barclay Blvd., Suite 280
Lincolnshire, IL 60069

Dear Ms. Zborowski:

Please refer to your February 16, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for estradiol topical gel 0.06%.

We also refer to your November 29, 2006, correspondence, requesting a meeting to discuss item 2 of our Advice Letter dated November 22, 2006, regarding endometrial safety of [ ] 2.6 g/day dose for estradiol gel.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date:	December 5, 2006
Time:	3:00 PM to 4:00 PM
Phone Arrangements:	The Division will call you at 1-866-314-9633 and enter passcode 8474780500
CDER Participants:	Scott Monroe, M.D., Acting Director Division of Reproductive & Urologic Products (DRUP) Shelley R. Slaughter. M.D., Ph.D. – Medical Team Leader, (DRUP) Theresa van der Vlugt, M.D. – Medical Reviewer, DRUP Mahboob Sobhan, Ph.D., - Statistics Team Leader, Division of Biometrics II (DBII) @ DRUP Margaret Kober, R.Ph., M.P.A. – Chief, Project Management Staff, DRUP George Lyght, R.Ph., - Sr. Regulatory Health Project Manager, DRUP

If you have any questions, call George Lyght, R.Ph., Sr. Regulatory Health Project Manager, at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
12/1/2006 01:29:49 PM
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-813
Biosante Pharmaceuticals, Inc.
Attention: Joanne Zborowski
Project Manager
111 Barclay Blvd., Suite 280
Lincolnshire, IL 60069

Dear Ms Zborowski:

Please refer to your February 16, 2006, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for estradiol gel.

We are reviewing the Clinical and Statistical sections of your submission and have the following comments. At this stage in our review, we have identified the following concerns regarding the [ ] of this product:

1. [ ]

The January 2003 Draft Guidance for Industry, entitled "Estrogen and Estrogen/Progestin Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation" recommends that trials of drug products [ ] of treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy enroll subjects who meet the minimum criteria of a pH greater than 5, no greater than 5% superficial cells on a vaginal smear, and at least one moderate-to-severe symptom of vulvar and vaginal atrophy that the subject has self-identified as most bothersome to her. The Guidance further recommends that the results from studies [ ] demonstrate a statistically significant improvement versus placebo from baseline to week 12 of treatment in all four co-primary parameters:

1. Decrease of parabasal vaginal cells and increase in superficial vaginal cells
2. Lowering of the vaginal pH
3. The moderate to severe symptom identified by the subject as being most bothersome to her.

Study EST005 did not enroll only subjects who at baseline each met all of the three recommended criteria of a pH greater than 5, no greater than 5% superficial cells on a vaginal smear, and at least one moderate-to-severe symptom of vulvar and vaginal atrophy that the subject has self-identified as most bothersome to her. Therefore, subset analyses of subjects meeting these criteria were performed. [ ]

[redacted]

2. The endometrial safety of the 2.6 gram/day dose of estradiol gel has not been demonstrated.

   The findings in 12-week Study EST005 of 5 cases of hyperplasia upon scheduled end-of study endometrial biopsy in subjects receiving the 2.6 gram/day dose of estradiol gel raises concerns regarding the endometrial safety of this dose of estradiol gel.

If you have any questions, call George Lyght, R.Ph., Sr. Regulatory Health Project Manager, at 301-796-0948.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Acting Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Scott Monroe
11/22/2006 04:16:10 PM

MEMORANDUM OF TELECON

DATE: October 10, 2006 and October 16, 2006

APPLICATION NUMBER: NDA 21-813

BETWEEN:

Name: Joanne Zborowski & Stephen Simes
Phone: 847-478-0500, Ext. 104
Representing: BioSante Pharmaceuticals, Inc.

AND

Name: George Lyght,R.Ph., Regulatory Health Project Manager
Division of Reproductive & Urologic Products, HFD-580

SUBJECT: 2nd name for NDA 21-813 (Bio-E-Gel)

The Sponsor was also advised to send at least two more names for review. Mr. Stephen Simes indicated on October 16, 2006 that BioSante was working on the selections and will send them as soon as possible.

George Lyght, R.Ph.

SIGNER'S NAME
RPM

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/s/

George Lyght
11/15/2006 06:04:30 PM
CSO

George Lyght
11/15/2006 06:07:05 PM
CSO

MEMORANDUM OF TELECON

DATE: April 13, 2006

APPLICATION NUMBER: NDA 21-813

BETWEEN:

Name: Joanne Zborowski
Phone: 847-478-0500, Ext. 104
Representing: BioSante Pharmaceuticals, Inc.

AND

Name: George Lyght,R.Ph., Regulatory Health Project Manager
Division of Reproductive & Urologic Products, HFD-580

SUBJECT: 2nd name for NDA 21-813 (Bio-E-Gel)

The Sponsor was informed that a second name for the NDA should be submitted for review. [redacted]

George Lyght, R.Ph.

SIGNER'S NAME
RPM

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/s/

George Lyght
11/15/2006 05:58:40 PM
CSO

George Lyght
11/15/2006 06:01:28 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: November 8, 2006

To: Joanne Zborowski	**From:** George Lyght
Company: Biosante Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 847-478-9260	**Fax number:** 301-796-9897
Phone number: 847-478-0500 x104	**Phone number:** 301-796-0948

Subject: CMC Information request

Total no. of pages including cover: 2

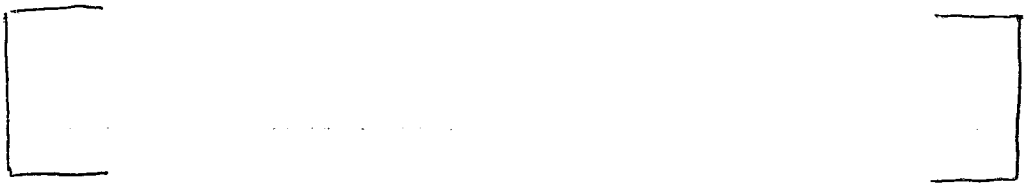
Comments:

Document to be mailed: ☐ YES ☑ NO

NDA 21-813
Chemistry Information Request

Provide updated mock-up of cartons and immediate labels with the following changes:

- The established name should be "estradiol gel". The dose strength 0.06% should be displayed immediately [ ] the established name. The size of the established name should be at least half of the trade name.
- Lot number should be included in the immediate container label.



Appears This Way
On Original

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/s/

George Lyght
11/9/2006 02:53:17 PM
CSO

George Lyght
11/9/2006 02:59:23 PM
CSO

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

CLINICAL INSPECTION SUMMARY

DATE: November 1, 2006

TO: George Lyght, Senior Project Manager
Theresa van der Vlugt, M.D., Clinical Reviewer
Division of Reproductive and Urologic Products, HFD-510

FROM: Khairy W. Malek, Medical Officer

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: #21-813

APPLICANT: Biosante Pharmaceuticals, Inc.

DRUG: Bio-E-Gel TM (estradiol topical gel 0.06%)

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of moderate to severe vasomotor symptoms associated with menopause [redacted]

CONSULTATION REQUEST DATES: April 4, 2006 & August 25, 2006

DIVISION ACTION GOAL DATE: November 27, 2006

PDUFA DATE: December 16, 2006

I. BACKGROUND:

At menopause, there is a decrease in estrogen concentration. Often this is accompanied with vascular instability in the form of hot flashes and night sweats, vulvo-vaginal

atrophy and an increase in bone loss. The new drug is a topical estradiol formulation for use in postmenopausal women as hormone replacement therapy for delivery of estradiol to the bloodstream. The drug is a hydroalcoholic gel which contains 0.06% estradiol.

The inspected study is a Phase III clinical trial which is double-blind and placebo-controlled to evaluate the efficacy and safety of Bio-E-Gel in two doses, 2.6 g/day which contain 1.56 mg estradiol and 1.7 g/day which contains 1.02 mg estradiol administered daily. Subjects were randomized into 3 equal groups: one received 2.6 g of the gel, second group received 1.7 g and the third received matching placebo gel.

The Review Division initially chose two sites for inspection: Center 21 of Dr. Stephan Swanson in Lincoln, NE; and Center 24 of Dr. Douglas Young in Carmichael, CA. Then on August 25, 2006, the Review Division chose another site, Center 10 of Dr. Michele Moreau in Montreal, Quebec, Canada. All centers used the same protocol (EST005)

Summary Report of U.S. and Foreign Inspections

II. RESULTS (by protocol/site):

Name of CI (MD) and Center #	City, State	Country	Protocol	Inspection Date	EIR Received Date	Final Classification
Stephen Swanson Center 21	Lincoln, NE	U.S.A	EST005	8/8-8/10/06	8/21/06	VAI
Douglas Young Center 24	Carmichael CA	U.S.A	EST005	7/11-7/17/06	8/7/06	NAI
Michele Moreau Center 10	Montreal, Quebec	Canada	EST005	10/23-10/27/06	Pending	NAI*

* = Preliminary Classification

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

1. Stephen Swanson, M.D., Lincoln, NE, Center 21

a. The field investigator reviewed the records of 20 subjects out of 37 enrolled.

b. There was no limitation of the inspection.

c. General Observations:

1. The CI did not maintain adequate and accurate case histories:

- The "Vaginal Maturation Index" data of all subjects in the study were not kept at the site after the study was completed and un-blinded. As a result, the field investigator could not verify the data of this efficacy parameter.

- Subject # 689 was using "Premarin Cream" according to the pre-screening telephone interview. This was not recorded in the pre-screening medication list and there was no information about when or if it was discontinued. A protocol exclusion criteria is use of estrogen hormone therapy within 8 weeks prior to the first screening visit.

d. Apart from one of the efficacy parameters (Vaginal Maturation Index) which could not be verified, and the un-certainity regarding use of "Premarin Cream" by subject # 869, the remaining data can be used in support of the NDA.

2. Douglas Young, M.D., Carmichael, CA, Center 24

a. The field investigator reviewed the records of 15 subjects out of 38 enrolled at this site.

b. There was no limitation of the inspection.

c. General Observations: There were no violations observed of FDA regulations and there was no under reporting of adverse events observed at this site.

d. The data from this site can be used in support of the NDA #21-813.

3.Michele Moreau, M.D., Montreal, Quebec, Canada-Center 10

I received a telephone call from the field investigator, that her inspection revealed no violations and that the recommended classification is "NAI".
I did not receive the EIR yet and if after reviewing the EIR, I find any violations, it will be reported to you in an addendum.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Except for one efficacy parameter (Vaginal Maturation Index) which could not be verified at Dr. Swanson's site, the data from these sites can be used in support of NDA# 21-813.

Khairy W. Malek
Medical Officer

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Khairy Malek
11/6/2006 02:08:53 PM
MEDICAL OFFICER

Constance Lewin
11/6/2006 03:08:07 PM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: September 27, 2006

To: Joanne Zborowski	**From:** George Lyght
Company: Biosante Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 847-478-9260	**Fax number:** 301-796-9897
Phone number: 847-478-0500 x104	**Phone number:** 301-796-0948

Subject: Clinical/Stts information request

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES ☑ NO

Information request:

For the ITT-Observed population for the subjects in Study EST005:

Provide a table for women who meet the no greater than 5% superficial cells inclusion criteria.

(Use Stat. Table 1 from your April 10, 2006 submission with data for superficial, intermediate, and parabasal cells as the model for this table).

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/s/

George Lyght
10/3/2006 03:26:47 PM
CSO

George Lyght
10/3/2006 03:30:15 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: September 22, 2006

To: Joanne Zborowski	**From:** George Lyght
Company: Biosante Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 847-478-9260	**Fax number:** 301-796-9897
Phone number: 847-478-0500 x104	**Phone number:** 301-796-0948

Subject: Clinical Information Request

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES ☑ NO

We are requesting the following information as soon as possible:

We need another VVA table.

- The table should show the mean change at week 12 for these three symptoms = vaginal dryness, vaginal irritation/itching, and vaginal pain with sexual activity for each treatment group in Study EST005.

- The table should show the **baseline** mean (SD) (day 7) for each of these symptoms identified as **moderate to severe at baseline AND most bothersome**, the week 12 mean (SD), the mean change from baseline, and the p-value versus placebo for these subjects.

- Confirm that Stat. Table 2 sent on April 10, 2006 representing mean change from screening (day -7) represents subjects who identified the symptom as moderate to severe at screening AND most bothersome.

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/s/

George Lyght
9/25/2006 02:43:53 PM
CSO

George Lyght
9/25/2006 02:50:34 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: September 20, 2006

To: Joanne Zborowski	**From:** George Lyght
Company: Biosante Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 847-478-9260	**Fax number:** 301-796-9897
Phone number: 847-478-0500 x104	**Phone number:** 301-796-0948

Subject: Clinical Information Request

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES ☑ NO

The following information is being requested:

1. A line listing of the 38 subjects in Study EST005 who had only a TVUS performed at baseline by treatment group, subject number, and TVUS result.

2. A line listing of the 36 subjects who had only a TVUS performed at end-of-study by treatment group, subject number, and TVUS result.

3. Where do we find this information in Section 8.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-813

INFORMATION REQUEST LETTER

Biosante Pharmaceuticals, Inc.
Attention: Joanne Zborowski
Project Manager
111 Barclay Blvd., Suite 280
Lincolnshire, IL 60069

Dear Ms Zborowski:

Please refer to your February 16, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bio-E-Gel (transdermal estradiol gel).

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following preliminary comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Additional comments on labeling/labels including trade name and established name will follow as we continue with our review.

Drug Substance:

- The drug substance specifications have several standards for each test including your own specification, USP, and EP. Clarify whether you will conduct all the tests for acceptance of the drug substance.

Drug Product:

- The color acceptance criteria for the drug product from colorless [ ] [ ]
- The description of acceptance criteria for the content uniformity specification is unclear. Clarify what the acceptance criteria is for the / tier test. Also, the / tier test should be no more than [ ] is outside the range of 85% to 115% of the label claim and no unit is outside the range of 75% to 125%, refer to USP <905>.
- The acceptance criteria for prime specification is NMT / actuations. The 1st failure after the initial priming is discarded as described in your actuation performance test method. However, in the patient information of the labeling, the patient is instructed that the initial priming of the pump is / depressions. Clarify the inconsistency and make changes accordingly.
- Acceptance criteria for assays of ethanol (/%- /%), DGME (/%- /%) and propylene glycol (/%- /%) are too broad. They should be [ ] to

/%- / % to ensure the quality and efficacy of the drug product. Otherwise, justification should be provided for the efficacy and quality of the drug product with the assays of ethanol, DGME and propylene glycol at the border of their acceptance criteria.

- Provide clarification if degradation products are identified during the development of the drug products. Provide impurity profile including specified and unspecified degradation products. The impurity specification should list individual specifications for the specified degradation products.
- Provide acceptance criteria for the impurities expressed as percentage of estradiol label claim instead of percentage of finished product. The acceptance criteria of /% for individual impurities and /% for total impurities are too broad and should be [ ] to / % and / % respectively. Provide an updated regulatory specification.
- For the test method 73.4779 of viscosity test, provide measurement procedures, test conditions and validation report for the method used specifically for the drug product. The validation of the test procedure should include validation data to justify your conclusion, refer to ICH Q2.
- For the test method 73.5504 of related substance assay, provide a table of relative retention time for estradiol and relative substances.
- For the analytical method and validation of the drug products, provide purity and source information of the reference standards for estradiol, 17α-estradiol, Δ-9,11-estradiol, estrone, ethanol, DGME and propylene glycol.
- Clarify whether the HPLC peaks found in the MDP [ ] components extractable test, leachable test and 12 –month stability test are the same peak. Provide the retention time and quantity for the peak found for the extractable and leachable tests. Clarify if identification has been attempted for this peak.

If you have any questions, call George Lyght, R.Ph., Sr. Regulatory Health Project Manager, at 301-796-0948.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
9/15/2006 12:47:06 PM
Chief, Branch III

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/s/

George Lyght
9/25/2006 02:35:17 PM
CSO

George Lyght
9/25/2006 02:41:23 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-813

ADVICE LETTER

Biosante Pharmaceuticals, Inc.
Attention: Joanne Zborowski
Project Manager
111 Barclay Blvd., Suite 280
Lincolnshire, IL 60069

Dear Ms. Zborowski:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bio-E-Gel (estradiol topical gel) 0.06%.

We also refer to your June 13, 2006, response to our Clinical Pharmacology comment No. 2 – nominal delivery rate for 2.6 g/day dose in our April 27, 2006 correspondence.

We have reviewed your submission and have the following comments:

We agree that in study EST008, the appropriate baseline estradiol correction is the Subject's own baseline measurement. However, we do not agree with combining the results from studies EST008 (drug applied to the upper arm) and EST003 (drug applied to the thigh). The current data is not sufficient to demonstrate bioequivalence between applications to the upper arm and thigh areas. Additionally, the current data suggest that bioavailability may differ when applied to the two different sites.

We recommend that only data from study EST008 be used to calculate the nominal delivery rate of Bio-E-Gel 2.6 g/day dose, which results in a rate of 0.077 mg/24 hours.

If you have any questions, call George Lyght, Regulatory Health Project Manager, at 301-796-0948.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Acting Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Scott Monroe
8/11/2006 06:54:12 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-813

BioSante Pharmaceuticals, Inc.
Attention: Stephen M. Simes
Vice Chairman, President, and Chief Executive Officer
111 Barclay Boulevard
Lincolnshire, IL 60069

Dear Mr. Simes:

Please refer to your February 16, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bio-E-Gel (estradiol gel).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on April 17, 2006 in accordance with 21 CFR 314.101(a).

We note that you have requested a priority review. We do not concur that this application qualifies for a priority review. Therefore, the user fee goal date for this application is December 16, 2006.

In our filing review, we have identified the following potential review issues:

Clinical
We are concerned, with the data inconsistency reported in Study EST005, for the Bio-E-Gel 0.87 gram/day, 1.7 gram/day, and 2.6 gram/day dose for the individual vaginal symptoms included on the subjects' self-assessment questionnaire for the vulvar and vaginal atrophy co-primary efficacy variable "mean change from baseline to week 12 in the moderate to severe symptom that has been identifies as being most bothersome to her." Provide a rational for these observed inconsistencies between the [ ] Bio-E-Gel doses.

The reported findings of one case of atypical endometrial hyperplasia by scheduled endometrial biopsy at the Bio-E-Gel 1.7 gram/day dose (incidence rate of 1.05%, 1 case per 95 subjects with a uterus), and 5 cases of simple hyperplasia by scheduled endometrial biopsy at the Bio-E-Gel 2.6 gram/day dose (incidence rate of 11.1%, 5 cases per 45 subjects with a uterus) in 12-week Study EST005 raises extremely serious safety concerns.

Chemistry Manufacturing and Controls
Provide a side-by-side comparison of the manufacturing processes used at [ ] and DPT, outlining any differences. A flow chart would be acceptable.

For the [ ], demonstrate that the product manufactured at DPT is similar to that manufactured at [ ] by performing comparative in-vitro releasing testing as per our SUPAC-SS guidance. Because it will not be possible to have similarly aged samples in [ ], it may be possible to compare stability samples in [ ] to stability samples in the MDP to show that the drug itself is similar.

Extractable/leachable testing could be performed on the [ ] held on stability to provide assurance that this packaging configuration is compatible with the drug product. USP testing should be performed prior to the decision on which therapeutic dose is efficacious in order to provide assurance that the [ ] is adequate prior to an action on the NDA.

Color mock-ups for the carton and immediate container labels should be provided, in order to allow full review of these labels. Prototype [ ] labels should be submitted.

Clinical Pharmacology

1. Regarding Study EST008, we are concerned with the increased estradiol exposure in the group where Bio-E-Gel was applied after sunscreen (mean increase of 55% with individual increase as high as [redacted] % relative to Bio-E-Gel alone) and the increased estradiol exposure in all groups in the second crossover period (mean increase of [ ] [redacted] fold relative to the first period).

   - [redacted]
   - Provide rationale for the higher exposure to estradiol in the second crossover period (i.e., days 37 and 44) as compared to the first period (i.e., days 15 and 22) in study EST 008. Specifically, address whether this was related to the application of sunscreen on days 16-22 or other factors that may be responsible for this observation (e.g., change in SHBG and estradiol binding).

2. The nominal delivery rate estimate for the 2.6 gram dose appears to be low. For calculations of the nominal delivery rate for the 2.6 gram dose, you used data from Study EST003, where 2.5 grams of gel was applied to the front and inner thigh area, to estimate a nominal delivery rate of 0.064 mg/day. The mean unadjusted average estradiol concentration (C_{avg}) in this study was 52.4 pg/ml. We noted that in Study EST008, where 2.6 grams was applied to the upper arm (i.e., same dose and application site as in the proposed labeling), the mean unadjusted C_{avg} for estradiol on day 15 were 74 and 75 pg/ml for group 1 and 2, respectively. Considering baseline mean estradiol levels of 4-8.1 pg/ml in your studies EST007 and EST003 and applying the same equation that you used,

the estimate nominal delivery rate would be approximately in the range of 0.084 to 0.091 mg/day. [ ]

We are providing the above comments to give you preliminary notice of review issues. Our filing review is only a preliminary evaluation of the application. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call George Lyght, R.Ph., Regulatory Project Manager, at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

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

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/s/

Daniel A. Shames
4/27/2006 04:31:32 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-813

NDA ACKNOWLEDGMENT

Biosante Pharmaceuticals, Inc.
Attention: Stephen M. Simes
Vice Chairman, President, and Chief Executive Officer
111 Barclay Boulevard
Lincolnshire, IL 60069

Dear Mr. Simes:

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: Bio-E-Gel™ (transdermal estradiol gel)

Date of Application: February 16, 2006

Date of Receipt: February 16, 2006

Our Reference Number: NDA 21-813

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 17, 2006 in accordance with 21 CFR 314.101(a). We acknowledge receipt of your request for a Priority review, which was submitted in serial #043 to your IND 51,229 on February 10, 2006. Final determination of the review priority classification for your application will be a filing issue. If we file the application, the user fee goal date will be determined at that time.

We acknowledge receipt of your request for a waiver of pediatric studies for this application. If we file the application, we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call George Lyght, R.Ph., Regulatory Project Manager, at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
3/7/2006 10:38:21 AM
Chief, Project Management Staff

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	April 24, 2003
TIME:	10;30 am – 12:00 pm
LOCATION:	Parklawn Potomac Room
APPLICATION:	IND 51,229 Bio-E-Gel (estradiol transdermal gel)
SPONSOR:	BioSante Pharmaceuticals, Inc.
TYPE OF MEETING:	End of Phase II
MEETING CHAIR:	Shelley R.Slaughter, M.D. Ph.D., Medical Team Leader Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
MEETING RECORDER:	Kassandra Sherrod, R.Ph.

FDA ATTENDEES:
Theresa van der Vlugt, M.D., Medical Reviewer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. Chemistry Team Leader, DRUDP (HFD-580)
Su Tran, Ph.D., Chemistry Reviewer, DRUDP (HFD-580)
Venkat Jarugular, Ph.D., Pharmacokinetic Reviewer, DRUDP (HFD-580)
Sayed Al-Habet, Ph.D., Pharmacokinetic Reviewer, DRUDP (HFD-580)
Krishan Raheja, Ph.D., Pharmacology, DRUDP (HFD-580)
Katherine Meaker, Ph.D., Statistics Reviewer, Reviewer, DRUDP (HFD-580)

EXTERNAL ATTENDEES:
Stephen Simes, President & CEO, BioSante Pharmaceuticals
Leah Lehman, Ph.D., Vice President of Clinical Development, BioSante Pharmaceuticals
Lisa McChesney-Harris, Director, Pharmaceutical Development, BioSante Pharmaceuticals
Joyce Helland, RN, Clinical Project Manager, BioSante Pharmaceuticals

Meeting Objective:
1. To discuss the Sponsor's Phase II lowest effective dose study results.
2. To discuss Clinical specific questions for development plans for Bio-E-Gel.
3. To discuss Chemistry specific questions.

Background:
Bio-E-Gel [(estradiol transdermal gel) 0.06% estradiol in a hydroalcholic gel formulation] is being proposed for an indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause. On August 8, 2001, in a Pre-IND teleconference, DRUDP recommended that the Sponsor consider conducting a Phase II dose-ranging, placebo-controlled clinical trial of 4 weeks duration to determine the lowest effective dose of Bio-E-Gel for the treatment of moderate to severe vasomotor symptoms associate with menopause.

On August 15, 2001 a Pre-IND meeting was held to discuss development plans. On recommendation of the Division Director, a decision was reached to do a phase II clinical trial identifying the lowest effective dose and demonstrating preliminary efficacy for the proposed indication, prior to proceeding to a phase III clinical trial, alternatively a phase III trial could be conducted provided it identified the lowest effective dose and address the pharmacokinetics issues.

Discussion:
Clinical Questions:
The data from the phase 2 dose-ranging study clearly identifies the Bio-E-Gel 2.5 gm (1.5 mg estradiol) dose as the lowest effective dose. Does the FDA concur?

Clinical Response:

- Per the Agency's 2003 draft guidance for industry regarding recommendations for clinical evaluation for estrogen alone drug product intended to treat moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause, the Division recommends that prior to initiating phase 3 development that adequate dose ranging studies be conducted to identify the doses to be studies in the proof of efficacy clinical trials. One controlled dose ranging study, usually of 12-week duration, can be adequate to identify the lowest effective dose by demonstrating an ineffective dose as one of the doses evaluated.

- In Study EST004, three dosage strengths of Bio-E-Gel were investigated: 0.625 g/day (delivering 37.5 mcg estradiol/day), 1.25 g/day (delivering 75 mcg estradiol per day) and 2.5 g/day (delivering 150 mcg estradiol per day). Dose selection was based on the findings in phase 2 Study EST[ ]that showed a C_{avg} serum estradiol concentration after 7 days of treatment of 24.2 pg/ml with 75 mcg estradiol/day and a C_{avg} serum estradiol concentration after 7 days of treatment of 50.7 pg/ml with 150 mcg estradiol/day), and on dosage strengths in similar approved gel products (dose range from 50mcg to 150 mcg estradiol/day).

- The preliminary/final data presented in the pre-meeting package that reports the adjusted mean change from baseline in the frequency and severity of moderate to severe hot flushes per day for the ITT population with LOCF using an ANCOVA model analysis (testing differences in the least squares means) demonstrates that the 150 mcg estradiol/day dosage strength is the most

effective dosage strength in relieving moderate to severe hot flushes. The 75 mcg estradiol/day dosage strength (the next lowest dosage strength utilized in Study EST004) does not appear to be different than placebo.

- Based on this data reported for Study EST004, you have proposed the use of [ ] mcg estradiol/day dosage strength in the phase 3 clinical trial. My concern is:

- The [ ] mcg/day dosage strength appears to be a high daily starting dose for the relief of moderate to severe vasomotor symptoms [ ] associated with the menopause based on the currently US approved transdermal products, Dosage strengths range from as low as 25 mcg estradiol/day to as high as 100 mcg estradiol/day.

- You may wish to consider conducting a phase 3 clinical trial that incorporates one or more lower doses of Bio-E-Gel to more clearly identify the lowest effective dose.

Question
Does the agency agree that no further PK is necessary to characterize the 2.5 g/day Bio-E-Gel dose, other than the collection of trough levels for estradiol, estrone, and estrone sulfate?

Clinical Response:

- Refer below to response from Clinical Pharmacology and Biopharmaceutics .

Question
Does the agency agree that the proposed phase 3 study is adequate to serve as the single pivotal clinical trial to support registration of Bio-E-Gel for the indications of VMS [ ]?

Clinical Response:

- The proposed draft phase 3 study design meets, with a few exceptions, the recommendations of the draft clinical trial guidance:
- The proposed inclusion and exclusion criteria are appropriate for VMA [ ] .
- The proposed study visits and procedures are appropriate
- The proposed clinical laboratory tests are appropriate
- The proposed adverse events monitoring and reporting are appropriate

The one element in the draft phase 3 protocol that is not appropriate is:

- The use of hot flush frequency and severity data obtained during the proposed single-blind placebo lead-in period (day –7 to day-1 of double-blind study medication) as the baseline assessment.

Question
Does the agency agree that using the hot flash data collected during the first two weeks of the screening period as the baseline is appropriate?

Clinical Response:

- You have proposed an approximate 4-week screening period. Subjects eligible on the basis of preliminary assessments (medical history, menopausal history and medication history, will receive daily diary records for recording the number and severity of hot flushes for a 14 day period Those subjects who experience 60 or more moderate-to-severe hot flushes during each week would be eligible to begin screening assessments.

- Hot flush frequency and severity reported in daily diaries during the first two week period could serve as the baseline assessment. Per the draft clinical trials guidance, subjects who have a minimum of 7 to 8 moderate to severe hot flushes per day, or 50 to 60 per week at baseline could be considered for enrollment.

Question
Does the agency agree that performing a transvaginal ultrasound instead of a biopsy is adequate safety monitoring of the uterus, if an endometrial biopsy cannot be performed at screening due to urogenital atrophy, small introitus, or stenotic cervical os?

Clinical Response:

- The Agency's draft clinical trial guidance recommends that all subjects with a uterus have an endometrial biopsy performed at screening, and that a finding of endometrial hyperplasia or cancer results in exclusion from study participation. The proposed inclusion criteria # 7, "No evidence of endometrial hyperplasia or dysplasia, as evidenced by an endometrial biopsy. If the specimen results at Screening (Visit 1) indicate that there was insufficient endometrial tissue for diagnosis, a transvaginal ultrasound must be performed prior to or at Visit 2 (Day-7), and the results must indicate (prior to placebo administration) that the endometrial double-wall thickness is ≤ 4 mm" is appropriate.

Question
Does the agency concur that the inclusion of additional coagulation tests (specifically antithrombin III, factor V Leiden, protein-C and protein-S) (PT/PTT coagulation testing is performed at screening and end-of-study) are not necessary and do not need to be collected?

Clinical Response:

- Per the draft clinical trial guidance, we recommend that safety assessments of lipids and of carbohydrate and coagulation parameters be conducted as recommended.

Question
Does the agency agree that no additional transfer studies are necessary for Bio-E-Gel?

Clinical Response:

- Refer below to response from Clinical Pharmacology and Biopharmaceutics

Question
The Sponsor is planning on studying the[ ] bottle dosage as the lowest effective dose in phase 3. Is this plan acceptable to the FDA?

Clinical Response:

- We recommend that you consider conducting a phase 3 clinical trial that incorporates one or more lower doses of Bio-E-Gel to more clearly identify the lowest effective dose.

Statistics Comments To The Clinical Questions:

- For the primary analyses, the baseline period used in the calculations of change from baseline variables should be clearly specified as the same baseline period used to determine eligibility for inclusion in the study.

- The sponsor needs to increase the planned enrollment to account for potential dropouts and ensure sufficient sample size. It is not appropriate to "replace" dropouts as currently described in Section 11.4.2.

Clinical Pharmacology and Biopharmaceutics Questions:

Question
Does the agency agree that no further PK is necessary to characterize the 2.5 g/day Bio-E-Gel dose, other than the collection of trough levels for estradiol, estrone, and estrone sulfate?

Biopharmaceutics Response:

- Based on the earlier studies, there was a high variability in the PK data. Therefor, the sponsor must ensure that there is sufficient PK data with sufficient number of subjects.

- The sponsor may consider additional PK study using the to-be-marketed product [ ]either in a subgroup of subjects in Phase III study or in a separate study.

- The proposal for collecting blood samples for trough estradiol level in Phase III study is acceptable.

- The sponsor must ensure to link any changes in formulation to the to-be-marketed.

Question
Does the Agency agree with the plan to include a statement in the label to reflect the potential transfer of estradiol to another individual upon skin contact? This statement will be similar to that in the AndroGel label. The sponsor is not planning to conduct transfer study on this product Does the agency agree that no additional transfer studies are necessary for Bio-E-Gel?

Biopharmaceutics Response:
The sponsor is advised to conduct the following studies:

- Partner transfer
- Effect of sunscreen
- Effect of washing

- The sponsor may consider using any of these studies to characterize the full PK of the to-be-marketed product in a sufficient number of subjects.
- The sponsor is advised to submit a draft protocol for each of the above studies for comments.

Question
Do the Agency agree with the sponsor's plan to use in Phase III study, a gel dispensing bottle that produces[ ]gram of gel per actuation rather than [ ]?

Biopharmaceutics Response:

- The sponsor may need to conduct in vitro study to determine the difference between the delivery via[ ] and the bottle.

Question:
The data from the phase 2 dose-ranging study clearly identifies the Bio-E-Gel[ ]gm ([ ]mg estradiol) dose as the lowest effective dose. Does the FDA concur?

Biopharmaceutics Response:
See Clinical comments addressing the lowest effective dose.

Chemistry Specific Questions:
The following questions were based on previous correspondence with DRUDP.

Question
All USP requirements for purified water should be met, including testing for pH, conductivity and

oxidizable substances. Please confirm that only Organic Carbon and water Conductivity are required for purified water.

CMC Response:

- Only Total Organic Carbon and Water Conductivity are required for Purified Water, USP.

Question
Per FDA's request at the pre-IND meeting, provide long-term and accelerated stability results for the drug product in the [ ] packaging. The results should include testing for content uniformity (estradiol content), phase separation, drug release, and water content. Please confirm that content uniformity is only required at release in terms of drug release and water content.

CMC Response:

- For the drug product in [ ], Content Uniformity is only required at release. Refer to the discussion on page 700 for the drug product in [ ]. Water Content is not necessary.
- Implement release and stability testing and establish acceptance criteria for In Vitro Drug Release

Question
The sponsor proposes to study the container/closure systems per USP. Is the proposed strategy acceptable to the FDA?

CMC Response:

- Acceptable strategy but in addition to the proposed studies, perform extraction studies on all product-contact surfaces of the [ ] as described in the "Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics, May 1999".

Question
Please confirm that this [ ] water soluble, drug product is not suitable for this type of evaluation.

CMC Response:

- See the response to the second Chemistry question.

Sponsor's Comment
The sponsor believes it is not necessary to conduct an in vitro release study for the following reasons:

- The gel is quite soluble in aqueous media (i.e, dissolves rapidly and completely).
- The sponsor believes that the drug is deposited within the skin and the skin releases the active

ingredient over time.

CMC Response:

- The sponsor must attempt to conduct in vitro release study.

New CMC Specific Questions.
These questions are based on the data provided in the end-of-phase II information package supporting the chemistry, manufacturing, and controls of the Bio-E-Gel drug product.

Question
Prior to MDP [ ] acceptance, chemical and physical compatibility studies will be conducted in addition to delivery performance tests under accelerated conditions. Is the proposed strategy acceptable to the FDA?

CMC Response:

- The Division accepts the strategy to study the [ ] and in addition to the proposed tests in the drug product characterization studies, implement Assay of estradiol, ethanol, [ ], and propylene glycol.

Question
If the MDP [ ] is found to be compatible, batch release will include Content Uniformity testing conducted according to Attachment 2 (in package). Is the proposed strategy acceptable to the FDA?

CMC Response:

- The Division accepts the proposed strategy. Also, implement Assay of estradiol, ethanol, [ ], and propylene glycol. Testing of the gel in the bottom portion of the [ ] should include the very last three actuations. Content Uniformity over the entire container [ ] should be part of the stability specification and include the same Assay of estradiol, ethanol, [ ], and propylene glycol.

Question
Meter-dose actuator performance will be monitored according to criteria outlined in the package. Is the proposed strategy acceptable to the FDA?

CMC Response:

- The proposed studies are acceptable.

Question
If the MDP [ ] is selected as the commercial package, the sponsor proposes studies to be conducted. Is the proposed strategy acceptable to the FDA?

CMC Response:

- The proposed studies are acceptable.

Question
If the MDP[ ] is selected as the commercial package, stability studies will be done with the [ ] in the inverted or horizontal orientation. Does the FDA concur?

CMC Response:

- Conduct stability studies of the drug product packaged in the[ ] both in the inverted and horizontal orientations.

ACTION ITEMS:

- Meeting minutes to be conveyed to the sponsor within 30 days.

Minutes Preparer: _____
George Lyght, R.Ph.
Regulatory Project Manager

Chair Concurrence: _____
Shelley R. Slaughter, M.D., Ph.D.
Medical Team Leader

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.

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

/s/

Theresa Van Der Vlugt
6/6/03 04:19:54 PM