CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-788

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Duramed Pharmaceuticals, Inc., Subsidiary of Barr Pharmaceuticals, Inc.
New Drug Application
Synthetic Conjugated Estrogens, A, Vaginal Cream, 0.625 mg/g

ITEM 13. PATENT INFORMATION AND CLAIM OF EXCLUSIVITY

1. Patent Information

In accordance with Section 505 (b) of the Federal Food, Drug and Cosmetic Act and as specified by 21 CFR § 314.50 (h) and 21 CFR § 314.53 (c)(3), Duramed Pharmaceuticals, Inc., hereby declares that there are no patents which claim Synthetic Conjugated Estrogens, A, Vaginal Cream, 0.625 mg/g or which claim a method of using Synthetic Conjugated Estrogens, A, Vaginal Cream, 0.625 mg/g and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of Synthetic Conjugated Estrogens, A, Vaginal Cream, 0.625 mg/g.

2. Claim of Exclusivity

In accordance with Section 505(b) (1) of the Federal Food, Drug, and Cosmetic Act, and as specified by 21 CFR § 314.50(j) Duramed Pharmaceuticals, Inc. hereby claims three (3) years exclusivity pursuant to 21 CFR § 314.108 (b)(4). Duramed Pharmaceuticals, Inc. certifies that, to the best of its knowledge, each of the clinical investigations included in this new drug application (NDA 21-788) meets the definition of ``new clinical investigation`` set forth in § 314.108(a).

June 23, 2004

Frederick J. Killion **Date**
Senior Vice President and General Counsel

EXCLUSIVITY SUMMARY

NDA # 21-788 SUPPL # HFD # 580

Trade Name

Generic Name synthetic conjugated estrogens, A vaginal cream

Applicant Name Duramed Pharmaceuticals, Inc.

Approval Date, If Known

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

505(b)(1)

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 years

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# 20-992 Cenestin tablets

NDA#

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:

DR-CEN-302

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"):

DR-CEN-302

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 # 65,505	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
Title: Regulatory Health Project Manager
Date: 11-25-08

Name of Office/Division Director signing form: George Benson, M.D.
Title: Deputy Director

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/

George Benson
11/25/2008 03:32:44 PM

Lyght, George

From: Greeley, George
Sent: Thursday, September 11, 2008 3:18 PM
To: Lyght, George
Cc: Mathis, Lisa; Addy, Rosemary
Subject: NDA 21-788 PeRC Results

Importance: High

George,

As a follow-up to NDA 21-788, synthetic conjugated estrogens, the PeRC members agreed with the Division to grant a full waiver of pediatric studies in the 0-16 age group.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

Duramed Pharmaceuticals, Inc., Subsidiary of Barr Pharmaceuticals, Inc.
New Drug Application
Synthetic Conjugated Estrogens, A, Vaginal Cream, 0.625 mg/g

ITEM 16. DEBARMENT CERTIFICATION

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

This includes any person employed or contracted by Duramed Pharmaceuticals, Inc. and related subsidiaries of Barr Pharmaceuticals, Inc. or any of its outside contractors, and clinical investigators performing services pertaining to clinical research and manufacturing for this new drug application.

Joseph Carrado, M.Sc., R.Ph.
Senior Director, Regulatory Affairs

4 June 2004
Date

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: April 30, 2009.

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		
	Please see attached financial disclosure sheet	

☐ (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
Joseph A. Carrado, M.Sc., R.Ph.	Vice President, Global Regulatory Affairs
FIRM / ORGANIZATION	
Duramed Pharmaceuticals, Inc.	
SIGNATURE	**DATE**
	2/6/08

Paperwork Reduction Act Statement

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

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

FORM FDA 3454 (4/06)

PSC Graphics (301) 443-1090 EF

30 Page(s) Withheld

X Trade Secret / Confidential (b4) + b(6)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION		
NDA # 21-788 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Established/Proper Name: synthetic conjugated estrogens, A Dosage Form: vaginal cream		Applicant: Duramed Pharmaceticals, Inc. Agent for Applicant (if applicable):
RPM: George Lyght		Division: Division of Reproductive & Urologic Products (DRUP)

NDAs:	505(b)(2) Original 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 (include NDA/ANDA #(s) and 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: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	November 29, 2008 November 28, 2008
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None NA on April 25, 2005
❖ 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

The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

Application[2] Characteristics	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC 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 ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments:	
❖ Application Integrity Policy (AIP) http://www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP • If yes, exception for review granted *(file Center Director's memo in* Administrative/Regulatory Documents *section, with* Administrative Reviews*)* • If yes, OC clearance for approval *(file communication in* Administrative/Regulatory Documents *section with* Administrative Reviews*)*	☐ Yes ☒ No ☐ Yes ☐ Yes ☐ Not an AP action
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: ☐	Submitted 8-12-08 Response 9-11-08
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ 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 ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and 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:
• (b)(2) NDAs only: 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:
• (b)(2) NDAs only: 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:
• (b)(2) NDAs only: 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:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
Patent Information (NDAs 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 notice of certification? ☐ Yes ☐ No

  (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 the rest of the patent questions.*

  *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? (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 OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	9-11-08
Officer/Employee List	
List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/nonconsent by officers/employees	☐ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 11-28-08
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
❖ Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	11-17-08
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	11-19-08
❖ Original applicant-proposed labeling	03-13-08 & 9-29-08
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☒ None
❖ Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	

[3] ill in blanks with dates of reviews, letters, etc.

❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
❖ Original applicant-proposed labeling	
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
❖ Most-recent division proposal for (only if generated after latest applicant submission)	
❖ Most recent applicant-proposed labeling	
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEDP ☐ DRISK ☒ DDMAC ☐ CSS ☒ Other reviews SEALD
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	10-15-04
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If approval action, OC clearance for approval	☒ Not on AIP
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ 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 Requirement (PMR) Studies	☐ None
• Outgoing communications *(if located elsewhere in package, state where located)*	
• Incoming submissions/communications	
❖ Postmarketing Commitment (PMC) Studies	☐ None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	AP LTR
• Incoming submission documenting commitment	
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	yes
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☐ Not applicable
• Regulatory Briefing *(indicate date)*	☐ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg April 13, 2004
• EOP2 meeting *(indicate date)*	☐ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	Post action meeting-July 18, 2005

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None
Division Director Summary Review *(indicate date for each review)*	☐ None 09-12-08 & 11-28-08
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 09-11-08 & 11-26-08
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	09-11-08 & 11-26-08
• Clinical review(s) *(indicate date for each review)*	9-11-08
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	Financial Disclosure section
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
REMS • REMS Document and Supporting Statement *(indicate date(s) of submission(s))* • Review(s) and recommendations (including those by OSE and CSS) *(indicate location/date if incorporated into another review)*	☒ None
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
• Clinical Studies	
• Bioequivalence Studies	
• Clinical Pharmacology Studies	
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None 03-18-05
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None 09-02-08 & 11-25-08
Statistical Review(s) *(indicate date for each review)*	☐ None 08-26-08
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None 08-28-08 & 11-28-08

[5] iling reviews should be filed with the discipline reviews.

Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 08-27-08 & 11-28-08
DSI Clinical Pharmacology Inspection Review Summary	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 03-01-05 & 11-13-05
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 02-24-05 & 11-13-08
❖ 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	☐ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary	☐ None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None
• Branch Chief/TeamLeader Review(s) *(indicate date for each review)*	☐ None 09-11-08 &11-26-08
• CMC/product quality review(s) *(indicate date for each review)*	☐ None 09-11-08 &11-26-08
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date for each review)*	☐ None
❖ 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)*	04-22-05
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: 05-27-08 ☒ Acceptable ☐ Withhold recommendation
• BLAs: ➢ TBP-EER	Date completed: ☐ Acceptable ☐ Withhold recommendation
➢ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Requested ☐ Accepted ☐ Hold

NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-788

Duramed Research, Inc.
Attention: Charlene Bruno
Senior Manager, Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Ms. Bruno:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for synthetic conjugated estrogens A 0.625 mg/g vaginal cream.

We also refer to your September 26 and October 27, 2008, submissions addressing our concerns regarding your proposed proprietary name Bijuva.

We have reviewed the referenced material. Following consultation with the Division of Medication Error Prevention and Analysis (DMEPA), we continue to believe that the proprietary name Bijuva is unacceptable because of the potential for confusion with the marketed drug Enjuvia. The following were considered in reaching this decision.

1. Enjuvia and Bijuva share overlapping product characteristics such as active ingredient (synthetic conjugated estrogen), numerical strength (0.625 mg vs. 0.625 mg/gram), indications for use (vasomotor symptoms due to menopause or symptoms of vulvar and vaginal atrophy due to menopause), frequency of administration, and patient and prescriber population.

2. Depending on the handwriting, it is possible that a prescription written for "Enjuvia 0.625 mg, use as directed" may be misinterpreted as "Bijuva 0.625 mg/g, use as directed."

Therefore, we conclude that there is a potential for confusion between Bijuva and Enjuvia due to the overlapping product characteristics and orthographic similarities.

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}

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

APPEARS THIS WAY
ON ORIGINAL

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

/s/

George Benson
11/17/2008 04:40:54 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-788

Duramed Research, Inc
Attention: Charlene Bruno
Senior Manager, Regulatory Affairs
One Belmont Avenue, 11 Th. Floor
Bala Cynwyd, PA 19004

Dear Ms. Bruno:

We acknowledge receipt on September 29, 2008 of your September 26, 2008 resubmission to your new drug application for synthetic conjugated estrogens, A, vaginal cream, 0.625 mg/g.

We consider this a complete, class 1 response to our September 12, 2008 action letter. Therefore, the user fee goal date is November 29, 2008.

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 Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

George Lyght
10/6/2008 06:31:02 PM

MEMORANDUM

To: George Lyght
Division of Reproductive and Urologic Products

From: Iris Masucci, PharmD, BCPS
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: August 22, 2008

Re: Comments on draft labeling for synthetic conjugated estrogens, A vaginal cream
NDA 21-788

We have reviewed the proposed label for synthetic conjugated estrogens, A vaginal cream (FDA version dated 8/18/08) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the Division after a full review of the submitted data.

Please note that some of the comments provided here were also recommended for the Premarin Vaginal Cream label (NDA 20-216/S-060, review dated 6/3/08). We hope to discuss these with the Division at an upcoming meeting to see how they may be incorporated in light of the current draft guidance on labeling for these products.

b(4)

9 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Iris Masucci
8/26/2008 09:32:20 AM
DDMAC REVIEWER

Laurie Burke
8/27/2008 12:38:13 PM
INTERDISCIPLINARY

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	August 19, 2008
To:	Scott Monroe, MD, Acting Director, Division of Reproductive and Urologic Products, HFD-580
Through:	Kellie Taylor, Pharm D, MPH, Team Leader Denise Toyer, Pharm D, Deputy Director Division of Medication Error Prevention and Analysis, HFD-420
From:	Richard Abate, RPh, MS, Safety Evaluator Division of Medication Error Prevention and Analysis, HFD-420
Subject:	Label and Labeling Review for Bijuva
Drug Name(s):	Bijuva (Synthetic Conjugated Estrogens, A) Vaginal Cream
Application Type/Number:	NDA # 21-788
Applicant/sponsor:	Duramed Pharmaceuticals, Inc.
OSE RCM #:	2008-690

APPEARS THIS WAY
ON ORIGINAL

CONTENTS

EXECUTIVE SUMMARY

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed carton and container labels introduces vulnerability to confusion that could lead to medication errors. Specifically, we noted the lack of product strength on the container label and carton labeling as well as no route of administration on the carton labeling. The medication error prevention staff believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Reproductive and Urological Products for the assessment of the container label, carton, and insert labeling for the product, "Bijuva Vaginal Cream" (NDA- 21-788) for evaluation to identify areas that could lead to medication errors. We previously objected to the proposed proprietary name and the Division agreed with our objection. We requested the Division submit our comments to the Applicant from the previous reviews in an email ion July 2, 2008. The Division of Medication Error Prevention and Analysis has not received an alternative name to review for this product.

1.2 PRODUCT INFORMATION

Bijuva (synthetic conjugated estrogens, A) Vaginal Cream is indicated for the treatment of symptoms of vaginal atrophy. Each applicator will hold a gram of cream containing 0.625 mg of synthetic conjugated estrogens, A. One applicatorful of cream is to be inserted vaginally daily for one week followed by one applicatorful twice weekly. Bijuva Vaginal Cream will be packaged as a 30 gm tube along with eight re-usable applicators. The tube and applicators will be stored at room temperature.

2 METHODS AND MATERIALS

This section describe the methods and materials used by medication error prevention staff to conduct a label, labeling, and/or packaging risk assessment (see 2.2 Container Label and Carton and Insert Labeling Risk Assessment). The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The carton labels and container labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is

---

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because our staff analyzes reported misuse of drugs, we are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. The medication error prevention staff uses Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on March 12, 2008 the following labels and labeling for medication error prevention review (see Appendix A, B):

- Container label: 30 gram tube
- Carton labeling: 30 gram tube
- Prescribing Information (no image)

3 RESULTS

Upon review of the container label and carton labeling, the Division of Medication Error Prevention notes several vulnerabilities that may contribute to medication errors.

3.1 CONTAINER LABEL

We note the established name appears to be less than one half the font size of the proprietary name.

We also note that the strength is lacking on the primary display panel other than the description of the active drug content.

3.2 CARTON LABELING

We note that the strength is lacking on the primary display panel other than the description of the active drug content.

4 DISCUSSION

The font of the established name must be at least one half the font of the proprietary name per 21 CFR 201.10(g)(2).

The strength of this product, 0.625mg/g, does not appear on the either the container label or the carton labeling. The strength is described in Section 16 "HOW SUPPLIED/STORAGE AND HANDLING" of the Professional Information labeling. The medication error prevention staff

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

acknowledges that this product is only available in one strength (0.625 mg/g). However, we believe the inconsistant expression of the strength in the labels and labeling may be a source of confusion to healthcare providers and thus adds to the potential for medication errors.

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed carton and container labels introduces vulnerability to confusion that could lead to medication errors. The medication error prevention staff believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the medication error prevention staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the Applicant to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

5.1 COMMENTS TO THE DIVISION

The medication error staff would appreciate feedback of the final outcome of this review. The Division of Medication Error Prevention and Analysis requests an alternative name for this product be submitted for our review. We would be willing to meet with the Division for further discussion, if needed. Please copy the medication error staff on any communication to the applicant with regard to this review. If you have any questions or need clarification, contact Cherye Milburn, project manager, at 301-796-2084.

5.2 COMMENTS TO THE APPLICANT

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed carton and container labels introduces vulnerability to confusion that could lead to medication errors. The medication error prevention staff believes the risks we have identified can be addressed has provided recommendation below.

5.2.1 Container labels

1. Revise the font of the established name so that it is at least one half the proprietary name per 21 CFR 201.10 (g)(2).
2. Revise the presention of the Proprietary and established names to include the product strength, for example:

Proprietary name
(synthetic conjugated estrogens, A)
Vaginal Cream
0.625 mg/g

5.2.2 Carton labels

1. Revise the presention of the Proprietary and established names to include the product strength, for example:

Proprietary name
(synthetic conjugated estrogens, A)
Vaginal Cream
0.625 mg/g

5.2.3 Package Insert Labeling

1. No comments.

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Richard Abate
8/19/2008 09:40:11 AM
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor
8/19/2008 11:25:57 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
8/21/2008 03:52:55 PM
DRUG SAFETY OFFICE REVIEWER

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

FACSIMILE TRANSMITTAL SHEET

DATE: August 4, 2008

To: Charlene Bruno	**From:** George Lyght
Company: Duramed Pharmaceuticals, Inc	Division of Reproductive and Urologic Products
Fax number: 610-747-2979	**Fax number:** 301-796-9897
Phone number: 610-747-2737	**Phone number:** 301-796-0948

Subject: CMC information for NDA 21-788

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES ☑ NO

The following is information from the CMC reviewer. We understand you are reviewing you name options:

Your Data Listing Elements Table for 'Bijuva', included in the SPL labeling is still deficient. Please populate the table as described below. Note that the comments below address only wording, not formatting of the table.

b(4)

APPEARS THIS WAY
ON ORIGINAL

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
8/6/2008 07:29:12 PM
CSO

George Lyght
8/6/2008 07:30:00 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-788

INFORMATION REQUEST LETTER

Duramed Pharmaceuticals, Inc
Attention: Charlene Bruno, M.S.
Senior Manager, Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Ms. Bruno:

Please refer to your March 13, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for synthetic conjugated estrogens, A vaginal cream.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Proprietary name
We do not recommend the use of the proprietary name Bijuva. The potential for confusion with other proprietary names is a safety issue. We recommend that another name along with container labels, carton labeling and package insert labeling be submitted for review

CMC

1.

2.

b(4)

3.

4.

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 M. 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

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

/s/

Margaret Kober
7/8/2008 03:10:35 PM
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-788

Duramed Pharmaceuticals, Inc
Attention: Charlene Bruno, M.S.
Senior Manager, Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Ms. Bruno:

We acknowledge receipt on March 13, 2008 of your March 12, 2008 resubmission to your new drug application for synthetic conjugated estrogens, A vaginal cream.

We consider this a complete, class 2 response to our April 25, 2005 action letter. Therefore, the user fee goal date is September 13, 2008.

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}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Jennifer L. Mercier
4/3/2008 12:43:05 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-788

INFORMATION REQUEST LETTER

Duramed Research, Inc
Attention: Charlene Bruno
Senior Manager, Regulatory Affairs
One Belmont Avenue, 11 Th. Floor
Bala Cynwyd, PA 19004

Dear Ms. Bruno:

Please refer to your January 8, 2008 submission for your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bijuva® (synthetic conjugated estrogens, A) Vaginal Cream.

We have reviewed the Chemistry, Manufacturing and Controls section of your submission and have the following comments:

- For the 30 g tube: It is acceptable to submit the 18 months stability data for three batches in the Complete Response for review.
- [redacted]
- [redacted]

b(4)

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

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

/s/

Moo-Jhong Rhee
2/13/2008 08:56:16 AM
Chief, Branch III

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,505

Duramed Research, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph
Senior Director, Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for synthetic conjugated estrogens, A vaginal cream, 0.625 mg/g.

We also refer to your November 8, 2005, request, serial number 017, for a special clinical protocol assessment, received November 9, 2005. The protocol is entitled "A Randomized, Multicenter, Double-Blind, Placebo-Controlled Trial to Compare the Effects of 12 Weeks of Treatment with DR-2041 Vaginal Cream vs. Placebo Vaginal Cream on Vulvovaginal Atrophy in Healthy Postmenopausal Women.".

We have completed our review of your submission and, based on the information submitted, have the following comments and recommendations.

Clinical Comments and Recommendations

1. Findings from the investigator visual assessment of the vagina will not be considered in determining effectiveness of the drug product and no labeling claims will be allowed based on the reported results.

2. In the meeting held on July 18, 2005, you were advised to consider limiting the categories included in the self-assessment questionnaire to gynecologic symptoms likely to be the consequence of low estrogen levels (namely, vaginal dryness, irritation/itching, and pain with sexual activity) with exclusion of urinary symptoms (such as dysuria and frequency) that may not be a consequence of low estrogen levels. However, per the protocol submitted for Study DR-CEN-302, you propose to retain similar categories for self-assessment as utilized in the original NDA submission, which include the assessment of urinary symptoms. We advise you that the inclusion of urinary symptoms in the subject self-assessment questionnaire is still not recommended.

We have the following additional comments on the proposed questionnaire for "Patient Self Assessment of Vaginal Atrophy."

a. The general instructions for the patient may be confusing for some patients. For example, the patient may have to be instructed as to the visit number; the words "experience" and "asterisk" may not be understandable to all patients.
b. The instructions direct the use of an "asterisk" to indicate the most bothersome symptom. However, the instructions do not indicate where the "asterisk" is to be placed. We recommend that the form include clearer instruction as to how and where the patient is to identify the moderate to severe symptom that is most bothersome to her.
c. If the question regarding urinary symptoms is retained, we recommend that the word "urgency" be reconsidered. Urgency is a medical term that a non-medical patient may not understand.

In addition, please advise the Division whether non-English speaking patients will have access to a translated questionnaire form.

3. At the July 18, 2005 meeting, you were advised that the finding of plasma concentrations of estrone and equilin for the utilized vaginal dose(s) and dosing regimen(s) that exceeded those reported with oral administration of Cenestin® (synthetic conjugated estrogens, A) tablets approved for the treatment of vulvar and vaginal atrophy could be a review issue. However, per the protocol submitted for Study DR-CEN-302, no collection of pharmacokinetic parameters is proposed.

   We recommend that sparse sampling to determine C_{max} and AUC estimates for estrone and equilin (both baseline-adjusted and total) be collected in Study DR-CEN-302.

Statistical Comments and Recommendations

1. For mean change from baseline in the vaginal maturation index at end-of-treatment, the study should show a statistically significant increase in vaginal superficial cells and should show a statistically significant decrease in vaginal parabasal cells. Thus, sample size calculations should be done separately for these endpoints.

2. The protocol should specify the imputation plan for last observation carried-forward (LOCF). The division suggests that weekly average scores be based on non-missing values for that week, provided the week has no more than three missing days. A week that has four or more missing days should be considered missing altogether. The weekly score should then be carried forward from the previous week.

3. The proposed primary analysis for the two proposed doses does not control the Type I error rate at or below alpha = .05. If both dose-placebo groups are to be tested simultaneously then each group comparison can be done with alpha = .025 (two sided). If the groups can be tested sequentially, a step-down approach may be used. The higher dose comparison could then be tested first at alpha = .05, and only if this test rejects the null, can the lower dose group be tested.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our "*Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products*"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at http://www.fda.gov/cder/guidance/index.htm. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, call George Lyght, R.Ph., Regulatory Health Project Manager, at 301-796-2130.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Scott Monroe
12/22/2005 04:56:10 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-788

Duramed Research, Inc
Attention: Patricia Thomas
Director, Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Ms. Thomas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for synthetic conjugated estrogens, A vaginal cream, 0.625mg/gm.

We also refer to the meeting between representatives of your firm and the FDA on Monday, July 18, 2005. The purpose of the meeting was to discuss information needed for a "Complete Response" to the Not Approvable decision of April 25, 2005 for NDA 21-788.

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 Project Manager, at (301) 827-7517.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Clinical Team Leader
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	July 18, 2005
TIME:	1:30 PM
LOCATION:	Parklawn, Conference Room C
APPLICATION:	NDA 21-788
DRUG NAME:	Bijuva® Vaginal Cream, 0.625 mg/g (synthetic conjugated estrogens, A)
TYPE OF MEETING:	Type A
MEETING CHAIR:	Scott Monroe, M.D.
MEETING RECORDER:	George Lyght, R.Ph.

FDA ATTENDEES
Scott Monroe, M.D., Clinical Team Leader, Division of Reproductive & Urologic Drug Products, (DRUDP); HFD-580
Theresa van der Vlugt, M.D. Medical Reviewer, DRUDP; HFD-580
Margaret Kober, R.Ph., Chief, Project Management Staff, DRUDP; HFD-580
George Lyght, R.Ph., Project Manager; DRUDP; HFD-580

EXTERNAL CONSTITUENT ATTENDEES
Carole Ben-Maimon, M.D., President and Chief Operating Officer
Wayne Mulcahy, PhD., Vice-President, Clinical Operations
Kathleen Reaps, M.D., Director, Clinical Operations
Howard Hait, Vice-President, Data Management and Biostatistics and Marketing
Joseph Carrado, MS, R.Ph., Senior Director, RA and Clinical Quality Assurance
Patricia Thomas, MPH, Director, RA

BACKGROUND
Duramed Research, Inc submitted a new drug application (NDA) for synthetic conjugated estrogens, A vaginal cream on June 25, 2004. The application was filed on August 24, 2004. The indication was treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. Duramed Research, Inc. received a Not Approvable letter for NDA 21-788 on April 25, 2005.

MEETING OBJECTIVES
This meeting was requested by the Sponsor to discuss the steps needed to correct the deficiencies that resulted in non-approval of NDA 21-788.

DISCUSSION POINTS
After introductions, the Sponsor restated their request for guidance on how to correct the deficiencies that resulted in non-approval of NDA 21-788. The Sponsor also requested advice

regarding the submission of post-hoc reanalysis of data previously submitted in NDA 21-788. The Sponsor was advised that such a submission was permissible.

- The Division discussed this issue further after the meeting and discourages the Sponsor from pursuing this course of action as the primary component of a "Complete Response" to the "Not Approvable" decision.

DRUDP's advice regarding the information needed to correct the clinical deficiency

1. The Sponsor should submit the results of an adequate and well-controlled clinical trial that demonstrates statistically significant effectiveness of synthetic conjugated estrogens, A vaginal cream versus placebo (vehicle) vaginal cream in the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. The following are clinical trial designs that the Division would find acceptable:

   - An adequately powered, randomized, double-blind, parallel-group, placebo-controlled clinical trial of a study design similar to Study DP3-2002-002 incorporating the Division's three recommended co-primary endpoints (of which one is a most bothersome symptom endpoint).
     - It will not be necessary to include an active comparator. Sample size can be based on power estimates for the co-primary endpoint "subject self-assessment of most bothersome vulvar and vaginal atrophy symptom at baseline" using the treatment effects observed in Phase 3 Study DP3-2002-002.

   - An adequately powered, randomized, double-blind, parallel-group, placebo-controlled clinical trial of a study design similar to Study DP3-2002-002 incorporating the Division's three recommended co-primary endpoints without focusing on the most bothersome symptom endpoint.
     - The Sponsor can propose an alternative analysis plan to assess symptomatic improvement (e.g., composite analysis of symptoms).

   - An adequately powered, placebo vehicle run-in, randomized, double-blind, parallel-group, placebo-controlled clinical trial.
     - Subjects who do not have a satisfactory symptomatic response during the placebo run-in will be randomized to treatment with synthetic conjugated estrogens, A vaginal cream or placebo (vehicle) vaginal cream. A trial of this design would identify the study population most in need of treatment with a vaginal cream containing estrogen. Such a trial would provide data to support the indication "treatment of moderate to severe symptoms of vulvar and vaginal atrophy unresponsive to a non-estrogen topical vaginal product."

   The Sponsor also was told that they could develop new clinical trial instrument(s) for the assessment of symptomatic improvement. For example, the Sponsor could conduct focus group(s) with postmenopausal women to determine the vulvar and vaginal symptoms most commonly identified as bothersome. These focus group findings could be incorporated into the third co-primary endpoint (symptoms of vulvar and vaginal atrophy). The Sponsor also could develop a new instrument to assess symptomatic response to treatment.

2. Important study design elements for consideration by the Sponsor

   The study design should incorporate the recommended inclusion/exclusion criteria and safety monitoring assessments described in the Agency's 2003 draft Guidance on Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation.

   - If the Sponsor decides not to conduct focus groups, the Division recommends that the vaginal atrophy self-assessed questionnaire consist of gynecologic symptoms likely to be a consequence of low estrogen levels, namely: vaginal dryness, vaginal irritation/itching, and pain with sexual activity. The Division recommends that the Sponsor exclude urinary symptoms such as dysuria and frequency that may not be a consequence of low estrogens levels.
   - The clinical trial (or other supportive data) should provide justification that the proposed dosing regimen will result in exposure to the lowest effective dose.
   - If plasma concentrations of estradiol and estrone for the proposed vaginal dose(s) and dosing regimen(s) exceed those associated with oral administration of Cenestin® tablets for the treatment of vulvar and vaginal atrophy, this could be a review issue.

3. The Sponsor should submit the final protocol for review and comment under IND 65,505 prior to initiating the Phase 3 clinical trial.

Additional Comment to the Sponsor
After the meeting, the Division discussed further the need for the Sponsor to conduct a partner transfer/tolerability study in sexually active women. The Division concluded that such a study would not be required for product approval. The issue of potential transfer of synthetic conjugated estrogens, A to a partner could be addressed in product labeling if warranted.

Action Item
Meeting minutes to the Sponsor within 30 days.

APPEARS THIS WAY
ON ORIGINAL

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
8/17/2005 10:36:29 AM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-788 Supplement # SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: Cenestin Vaginal Cream
Generic Name: synthetic conjugated estrogens, A
Strengths: 0.625 mg/g

Applicant: Duramed Pharmaceuticals, Inc. (A subsidiary of Barr Pharmaceuticals, Inc.)

Date of Application: June 25, 2004
Date of Receipt: June 25, 2004
Date clock started after UN:
Date of Filing Meeting: August 11, 2004
Filing Date: August 24, 2004
Action Goal Date (optional): User Fee Goal Date: April 25, 2005

Indication(s) requested: Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.

Type of Original NDA: (b)(1) ___X_____ (b)(2) _____
OR
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 is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

____ NDA is a (b)(1) application OR ___ NDA is a (b)(2) application

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

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

User Fee Status: Paid ___x_____ 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. 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 an approved (b)(1) or (b)(2) application?

  YES NO

  If yes, explain:

NDA 20-992- Cenestin 0.3, 0.45, 0.625, 0.9 and 1.25 mg tablets, exclusivity expire June 21, 2005.

- 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

- Was form 356h included with an authorized signature? YES NO
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO

  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If in Common Technical Document format, does it follow the guidance? N/A YES NO

- Is it an electronic CTD? N/A YES NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO

- Exclusivity requested? YES, ____3__years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

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

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

Refer to 21 CFR 314.101(d) for Filing Requirements

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

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

- List referenced IND numbers: IND 65,505

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

- Pre-NDA Meeting(s)? Date(s) April 13, 2004 NO
If yes, distribute minutes before filing meeting.

Project Management

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

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

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

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?

  N/A YES NO

If Rx-to-OTC Switch application:

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

- Has DOTCDP been notified of the OTC switch application? 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 Florian Zielinski (HFD-357)? YES
  NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 11, 2004

BACKGROUND:
NDA 21-788 Cenestin Vaginal Cream (synthetic conjugated estrogens, A) 2 grams containing 0.625 mg synthetic conjugated estrogens, A per gram, is for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.
NDA 20-992 for Cenestin® tablets was approved on March 24, 1999 for the treatment of moderate to severe vasomotor symptoms (MSVS) associated with the menopause. The approved dosing regimen allowed for a range of doses including the 0.625 mg tablet, the 0.9 mg tablet, and 1.25 mg (2 x 0.625 mg tablets). The 0.3 mg tablet was approved on June 21, 2002 and the 0.45 mg tablet was approved on February 5, 2004, both for the same indication of MSVS.

ATTENDEES:
Brenda Gierhart, M.D., Team Leader, Division of Reproductive and Urologic Drug Products DRUDP (HFD-580)
Theresa van der Vlugt, M.D., M.P.H., Medical Officer, DRUDP (HFD-580)
George Lyght, R.Ph., Project Manager, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @DRUDP (HFD-580)
Sarah Pope, Ph.D., Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Moh-Jee Ng, M.S., Statistician, Division of Biometrics II (DBII; HFD-715)
Dhruba Chatterjee, Ph.D., Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Lynnda Reid, Ph.D., Pharmacologist Team Leader, DRUDP (HFD-580)

ASSIGNED REVIEWERS:

Discipline	Reviewer
Medical:	Theresa van der Vlugt, M.D., M.P.H., Medical Officer, DRUDP (HFD-580)
Statistical:	Moh-Jee Ng, M.S., Statistician, Division of Biometrics II (DBII; HFD-715)
Pharmacology:	Lynnda Reid, Ph.D., Pharmacologist Team Leader, DRUDP (HFD-580)
Chemistry:	Sarah Pope, Ph.D., Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Biopharmaceutical:	Stephan Ortiz, R.Ph., Ph.D., Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
DSI:	Roy Blay, Ph.D., Director, Regulatory Review Officer
Regulatory Project Management:	George Lyght, R.Ph., DRUDP (HFD-580)

Other Consults:

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

CLINICAL FILE __x____ REFUSE TO FILE _____

- Clinical site inspection needed: YES NO

- 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 NA _x___ FILE _____ REFUSE TO FILE _____

STATISTICS FILE __x____ REFUSE TO FILE _____

BIOPHARMACEUTICS FILE __x____ REFUSE TO FILE _____

- Biopharm. inspection needed: YES NO

PHARMACOLOGY NA _____ FILE __x____ REFUSE TO FILE _____

- GLP inspection needed: YES NO

CHEMISTRY FILE __x____ REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

___x___ 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.

___x___ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

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

2. 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.

3. Document filing issues/no filing issues conveyed to applicant by Day 74.

_George Lyght, R.Ph._____
Regulatory Project Manager, HFD-580

APPEARS THIS WAY
ON ORIGINAL

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
10/15/04 03:07:20 PM
CSO

George Lyght
10/15/04 03:10:31 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,505

Barr Research
Attention: Patricia Thomas
Director, Regulatory Affairs
109 Morgan Lane
Plainsboro, NJ 08536

Dear Ms. Thomas:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cenestin® (synthetic conjugated estrogens, A) vaginal cream, 0.625 mg/g.

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 Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Brenda Gierhart, M.D.
Medical Team Leader
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	April 13, 2004
TIME:	10: 30 AM to 12: 00 PM
LOCATION:	Parklawn Potomac Conference Room
SPONSOR:	Barr Research
APPLICATION:	IND 65,505
DRUG NAME:	Cenestin® (synthetic conjugated estrogens, A) Vaginal Cream, 0.625 mg/g
TYPE OF MEETING:	Pre-NDA
MEETING CHAIR:	Brenda Gierhart, M.D.
MEETING RECORDER:	George Lyght, R.Ph.

FDA ATTENDEES:

Daniel Shames, M.D. – Director, Division of Reproductive & Urologic Drug Products (DRUDP) HFD-580
Brenda Gierhart, M.D. - Medical Team Leader, DRUDP (HFD-580)
Theresa van der Vlugt, M.D. - Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Sarah Pope, Ph.D. - Chemist, (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetics Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Stephan Ortiz, R.Ph., Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Lynnda Reid, Ph.D. - Pharmacologist Team Leader, DRUDP (HFD-580)
Suzanne Thornton, Ph.D. - Pharmacologist, DRUDP (HFD-580)
Moh-Jee Ng, M.S. – Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
George Lyght, R.Ph. - Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Clinical and Biostatistics
Wayne Mulcahy, Ph.D. - Vice-President of Clinical Operations
Michele Sample, B.S.N., R.N. - Senior Clinical Program Manager
Howard Hait, M.S. - Vice-President, Biostatistics and Data Management
Gizelle Baker, Ph.D. - Statistician
Kathleen Reape, M.D. - Director of Clinical Operations

Clinical Pharmacology
Abdur Rashid, Ph.D. - Director

Chemistry, Manufacturing, and Controls
Emad Alkhawam, Ph.D. - Vice-President Analytical Research and Development

Toxicology
Keith Earle, D.V.M. - Senior Toxicologist

Regulatory Affairs
Joseph Carrado, R.Ph., M.Sc. - Senior Director
Patricia Thomas, M.P.H. - Director
Nicholas Tantillo - Director

BACKGROUND:
Barr Research completed their study to assess the pharmacokinetics of multiple doses of Cenestin vaginal cream. The phase 3 study compared doses of Cenestin vaginal cream, placebo vaginal cream, and an active comparator.

MEETING OBJECTIVES:
This Pre-NDA meeting was to seek guidance from the FDA on a NDA submission for Cenestin vaginal cream, the proposed Statistical Analysis Plan, the status of the Chemistry, Manufacturing and Controls, and the planned content and format of the NDA.

DISCUSSION POINTS:
The response to questions from the meeting package was supplied to the sponsor on April 9, 2004. This facilitated a discussion on issues that needed clarification. The following are additional comments:

Chemistry

- The revision of any acceptance criteria mid- or post-Phase III should be documented and well-justified. If undertaken, these revisions will be review issues for the NDA when submitted
- For pH testing, testing may be conducted only at release, with a justification provided for its exclusion during stability studies
- For content uniformity, USP guidelines should be followed

Clinical
The FDA expects the sponsor to clarify which symptoms will be selected and recommended review of the 2004 published draft guidance.

Statistics
DRUDP will provide Barr with a dataset format for ease of presentation.

Attached: April 9, 2004, response to questions in the meeting package.

Sponsor Questions:

1) *Does the Division agree that the 18 months of real time stability data generated from the three batches of Synthetic Conjugated Estrogens, A vaginal cream support the proposed —month expiration dating period for the to-be-marketed product?* b(4)

Division response:

- The amount of accelerated and long-term stability data proposed at the time of submission is acceptable. However, a final determination of the expiration dating period will be made during the

NDA review cycle. If additional stability data are available at the time of the NDA submission, the data should be submitted at that time.

2) *Does the Division agree with the proposed new specifications for the total of* _____ *to replace the current specification for the total of estrone, equilin and 17 α-dihydroequilin (3-component based)?*

b(4)

Division response:

- The proposed revisions are not acceptable. The approval of Cenestin (synthetic conjugated estrogens, A) Tablets included a regulatory specification for the Sum of 3 (estrone, equilin, and 17α-dihydroequilin). Accordingly, the proposed Cenestin (synthetic conjugated estrogens, A) vaginal cream should incorporate this same specification. The Sponsor was advised that the USP monograph for Conjugated Estrogens Tablets cannot be followed for the synthetic conjugated estrogens product(s).

3) *Does the Agency agree that the information referenced from the nonclinical pharm/tox information contained in submissions for previously approved drug products fulfill the necessary non-clinical requirement to file the proposed Cenestin® (synthetic conjugated estrogens, A) Vaginal Cream, 0.625 mg/g NDA?*

Division response:

Yes. In addition, we waive the conduct of an animal irritability study. This is in response to the waiver request submitted to IND 65,505 Serial No. 000 in the Cover Letter dated August 9, 2002 as follows:

1. Irritability Waiver: All of the excipients used in the Cenestin® Cream are either GRAS listed or listed in the FDA Inactive Ingredient Guide (IIG) for vaginal or topical use. Therefore, we are asking the agency to waive the conduct of an irritability study for this product.

4) *Does the Division agree that the proposed Statistical Analysis plan is acceptable?*

Division response:

- The Division concurs with the proposed Statistical Analysis plan Version 2.0 dated October 27, 2003.
- The statistical plan should include a procedure for handling dropout and missing data.
- All statistical tests should be 2-sided and performed at a 0.05 level of significance.
- If the residuals do not follow a normal distribution, tables should still show the mean change from baseline instead of the reported ranked value. However, p-values should be based on the non-parametric result.
- Please provide the datasets from which these tables were generated. Copies of the programs used to generate the tables would be helpful.
- Please clarify if tables for all three primary endpoints will be provided. Serial No. 010 only provided tables for the primary outcome analysis on the maturation index.
- Please provide additional details regarding the calculation of the mean change in the moderate to severe symptoms that has been identified by the patient as being the most bothersome between pretreatment (Week -4) and end of treatment (Week 12).
- Please provide a listing of the symptoms that patients could have selected as their most bothersome symptom. Table 4.4.4.1 does not list vaginal irritation or vaginal itching; however, the Vaginal Atrophy/Sexual Function Questionnaire provided in Version 5 of the protocol dated 1/10/03 has shaded this symptom as a potential "most bothersome" symptom selection. Please clarify if tables for the change from baseline to end of treatment in the most bothersome symptom for each treatment group will be provided.

- Please clarify if tables for the change from baseline to end of treatment for each specific bothersome symptom for each treatment group will be provided as a subgroup analysis.
- Please correct an apparent error with the Baseline Characteristics tables labeled as Week -2 in the SAP Version 1.0 and as Week -4 in SAP Version 2.0. Since Version 5 of the protocol dated January 10, 2003 states that screening occurs two weeks prior to randomization, the Division believes that the Baseline Characteristics tables should be labeled as Week -2.

5) *Does the Division agree that the Phase 3 clinical study, given a positive outcome, supports the planned Cenestin® (synthetic conjugated estrogens, A) Vaginal Cream, 0.625 mg/g NDA?*

Division response:

The Division is unable to respond to the stated question due to the following:

- It does not appear that any dose finding study was conducted to determine the lowest effective dose.

b(4)

. The "Guidance for Industry: Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms-Recommendations for Clinical Evaluation" dated January 2003 states that it is recommended that studies identify the lowest effective dose by including an ineffective dose as one of the doses evaluated. A Phase 4 commitment to conduct an additional study to determine the lowest effective dose may be required.

- It is unclear to the Division whether there will be sufficient data from the Investigator Assessment of Vaginal Atrophy questionnaire and vaginal/vulvar adverse event data to assess for patient tolerability. It appears that no specific assessment of patient tolerability, partner tolerability, or partner exposure to estrogen has been performed. Thus, it is unclear if clinical tolerability studies and/or a clinical transfer (to sexual partner) study should be performed. If so, there may need to be Phase 4 commitments to conduct the studies.
- In general, if a drug product is not considered to be a new molecular entity and does not pose an unexpected safety concern, Agency requirements for the VVA indication can be met by a single, adequately designed and powered, placebo-controlled study. The overall design of Protocol DP3-2002-002 is acceptable to the Division; however, whether Final Study Report for DP3-2002-002 will support the approval of Cenestin (synthetic conjugated estrogens, A) Vaginal Cream, 0.625 mg/g will be a review issue. You are advised that when the NDA is submitted, DP3-2002-002 subjects with protocol violations or deviations, subject dropouts, investigator financial disclosure statements, adverse event data, diary data, and blinding will be closely evaluated. The risk of performing only one Phase 3 study is that the execution of the study could be seriously flawed or an unexpected safety concern identified, resulting in a "not approval" decision for the NDA. You are referred to the "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products" dated May 1998.
- The proposed extent of population exposure to assess clinical safety may be inadequate. If only the daily regimen demonstrates efficacy, it appears that the entire safety population

exposed to that dose will be approximately 60 patients. Please clarify the number of subjects that will support the safety of each of the two regimens and their duration of exposure.

- The preliminary DP3-2002-002 safety information provided in Serial No. 010 is encouraging.

6) Does the Division concur with the proposed Cenestin Cream NDA contents and format?

Division response:

- The Division has no objection with the submitted 6-page proposed plan. We would have preferred a more detailed proposal.
- It is unclear whether the individual studies submitted in the electronic submission will be adequately indexed and linked.
- Please submit copies of all abnormal (ex. hyperplasia, carcinoma, atypical, disordered proliferative, or other abnormal) endometrial biopsy reports with the NDA.
- Please confirm that the NDA will contain either a claim for categorical exclusion of environmental impact or an environmental assessment.
- Copies of the individual case report forms for each patient who died or reported a serious adverse event during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug related or not, including patients receiving reference drugs or placebo should be submitted with the NDA.
- The Division anticipates submission of case report tabulations as line listings. If adequate line listings are provided, the Division would consider waiving the "Patient Profile" format tabulations, as submitted to IND 65,505 in Serial No. 011.

Additional Chemistry comments

1. Acceptance criteria should be developed and proposed for both viscosity and pH.
2. Please confirm with the drug substance DMF holder that DMFs — and — are current and up to date.
3. Provide the detailed calculations of the batch adjustment for — content in the drug substance.
4. Leachables/extractables testing should be provided for all primary packaging/plunger components in direct contact with the drug product.
5. According to the meeting package, a — has been changed. Be advised that the "equivalence" and suitability of the new — will be evaluated during the NDA review.
6. A detailed update on the container/closure problems reported in the 05-MAY-2003 information amendment should be provided. The NDA should include a clear depiction of the resolution of issues related to the noted — in the drug product and placebo).
7. Content uniformity should be included in the final specification for the drug product. Additionally, if any of the excipients perform as —, content uniformity and assay specifications should be developed for each. In all cases, the methods and criteria should confirm inter-tube and intra-tube consistency.
8. Homogeneity and phase separation should be addressed in the drug product specification. The visual assessment (Description) is not sufficient for these attributes.
9. The — in the drug product should be addressed.
10. In vitro release testing should be included in the final drug product specification.

b(4)

Additional Clinical comments:

1. We note two different Sponsor Proposed Indications in Serial No. 10 as follows:

- "Cenestin® (synthetic conjugated estrogens, A) Vaginal Cream is to be used as treatment of vulvovaginal atrophy in healthy postmenopausal women." (pg. 55)
- "Cenestin® (synthetic conjugated estrogens, A) Vaginal Cream, 0.625 mg/g is to be used as treatment of vulvovaginal atrophy in postmenopausal women." (pg. 4)

You should anticipate the approved Cenestin Vaginal Cream indication being identical to the approved indication for Cenestin 0.3 mg tablets, i.e. "treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause".

2. We note a request for a full waiver from the requirement to assess the safety and effectiveness of a new dosage form and new route of administration in pediatric patients in Serial No. 10 on pg. 55. Since the anticipated indication, i.e. "treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause", does not occur in pediatric patients, the Division anticipates that the Sponsor's request would be granted. We recommend submitting the request for a full waiver from the requirement to assess the safety and effectiveness of a new dosage form and new route of administration in pediatric patients with the NDA.
3. No labeling regarding the Premarin comparator arm in DP3-2002-002 should be anticipated.
4. The Division has a recommended format for submitting Financial Disclosure Information (attached).

FINANCIAL DISCLOSURE INFORMATION

Sponsor should submit Tables that include the following information for each study they are presenting to support safety and efficacy of their NDA. (This information will enable the Division to perform the Financial Disclosure Review more efficiently.)

Study # XXXXXX Study Start Date XX/XX/XXXX Study End Date XX/XX/XXXX

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

* If no information is provided by the investigator (principal or sub-investigator), then the sponsor must describe their efforts at due diligence in attempting to obtain this information, (i.e., sending certified letters, performing Internet searches, telephone calls, faxes, etc.)

** Any and all disclosable financial information must be explained.

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

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

Chair Concurrence: _____
Brenda Gierhart, M.D.
Team Leader, DRUDP

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

/s/

Daniel A. Shames
5/13/04 04:13:21 PM