

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208470Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208470

SUPPL #

HFD #

Trade Name INTRAROSA™

Generic Name prasterone

Applicant Name Endoceutics Inc.

Approval Date, If Known November 16, 2016

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)(2)

b) 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:

c) Did the applicant request exclusivity?

YES NO

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

5

d) 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#

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:

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"):

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 #

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: Kim Shiley
Title: Regulatory Health Project Manager
Date: 11-16-2016

Name of Division Director signing form: Audrey Gassman
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

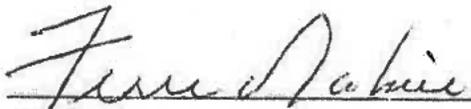
KIMBERLY A SHILEY
11/16/2016

AUDREY L GASSMAN
11/16/2016

1.3. Administrative Information

3. DEBARMENT CERTIFICATION

EndoCeutics 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.



Fernand Labrie, M.D., Ph.D.

President and CEO

EndoCeutics Inc.

Sept 18, 2015

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208470 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: INTRAROSA™ Established/Proper Name: prasterone Dosage Form: vaginal inserts		Applicant: Endoceutics Inc. Agent for Applicant (if applicable): Accenture, LLP, Attn: Raj Bandaru, Ph.D.
RPM: Kim Shiley		Division: Bone, Reproductive, and Urologic Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: 10-20-16</p> <p><i>Note: 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.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>11-16-2016</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation 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.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 2
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) 11-16-16
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 12-30-15 • Review(s) (<i>indicate date(s)</i>) 12-28-15 	
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input type="checkbox"/> None 12-21-15 DMEPA: <input type="checkbox"/> None DMPP/PLT (DRISK): <input type="checkbox"/> None 11-8-16 OPDP: <input type="checkbox"/> None 11-8-16 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input type="checkbox"/> None 11-16-16 Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	12-22-15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 10-24-16
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Completed
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>7-6-2016</u> If PeRC review not necessary, explain: _____ 	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 4-27-2015
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11-16-16
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11-16-16
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	

❖ Clinical Reviews		
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)		11-16-16
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)		See clinical review, page 26-27
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵		<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)		<input type="checkbox"/> N/A 12-18-15
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 		<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)		<input type="checkbox"/> None requested 7-8-16
Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Biostatistics		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 7-1-2016
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 10-24-16
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)		<input type="checkbox"/> None requested see OPQ

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8-9-2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	<input type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10-20-16/11-16-16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input type="checkbox"/> None 10-20-16
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	7-14-16/7-21-16
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	7-14-16/7-21-16
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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

/s/

KIMBERLY A SHILEY
11/17/2016



NDA 208470

ADVICE/INFORMATION REQUEST

EndoCeutics Inc.
Attention: Fernand Labrie, M.D., Ph.D.
c/o U.S. Agent, Accenture, LLP
Raj Bandaru, Ph.D.
Global Regulatory Affairs
1160 W. Swedesford Road, Building One
Berwyn, PA 19312

Dear Dr. Labrie:

Please refer to your New Drug Application (NDA) dated October 16, 2015, received October 16, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for prasterone.

We have the following comments regarding your new to-be-marketed combination device-drug product:

Your new applicator incorporates (b) (4) compared to the first applicator proposed in the NDA. This is evidenced by the (b) (4) g to 3.7 g. Accordingly, we are concerned that the newly proposed applicator may be less mechanically robust compared to both the initially proposed to-be-marketed applicator and the applicators used in the clinical trials.

Demonstrate, either through performance testing or a scientific justification, that the new applicator has comparatively similar mechanical characteristics to the applicator used during clinical trials. Provide results and/or a response by September 29, 2016.

If you have any questions, please contact Kim Shiley, R.N., B.S.N., Regulatory Project Manager, at (301) 796-2117.

Sincerely,

{See appended electronic signature page}

Shelley R. Slaughter, M.D., Ph.D.
Clinical Team Leader
Division of Bone, 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/

SHELLEY R SLAUGHTER
09/01/2016



NDA 208470

ADVICE/INFORMATION REQUEST

EndoCeutics Inc.
Attention: Fernand Labrie, M.D., Ph.D.
c/o U.S. Agent, Accenture, LLP
Raj Bandaru, Ph.D.
Global Regulatory Affairs
1160 W. Swedesford Road, Building One
Berwyn, PA 19312

Dear Dr. Labrie:

We refer to your New Drug Application (NDA) dated October 16, 2015, received October 16, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for prasterone.

We also refer to your July 22, 2016, submission containing your response to our July 18, 2016, Information Request letter.

We have the following comments:

- Section 13.1 of labeling will include the following information on carcinogenicity:

Long-term studies in animals to evaluate carcinogenic potential have not been conducted with prasterone. Two metabolites of prasterone, estradiol and testosterone, are carcinogenic in animals.
- We consider your application under the 505(b)(2) regulatory pathway because the labeling includes information about estradiol and testosterone that is based on submitted literature and your scientific justification for use of such literature. Submit a Form FDA 356h indicating that your NDA is a 505(b)(2) (see Box #17).
- Be aware that a 505(b)(2) application that relies for approval on published literature which does not specifically describe a brand name product(s), is not considered as relying on FDA's finding of safety and/or effectiveness for a listed drug(s).

If you have any questions, please contact Kim Shiley, R.N., B.S.N., Regulatory Project Manager, at (301) 796-2117.

Sincerely,

{See appended electronic signature page}

Shelley R. Slaughter, M.D., Ph.D.
Clinical Team Leader
Division of Bone, 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/

SHELLEY R SLAUGHTER
08/10/2016

**PeRC Meeting Minutes
July 6, 2016**

PeRC Members Attending:

Lynne Yao

Meshaun Payne

Gettie Audain

Robert "Skip" Nelson

Barbara Buch

Rosemary Addy

Wiley Chambers

Jackie Yancy

Thomas Smith

George Greeley NON-RESPONSIVE

Yeruk Mulugeta

Freda Cooner

Maura O'Leary NON-RESPONSIVE

Calipotriene)

Gilbert Burkhart

Gerri Baer

John Alexander

Peter Starke

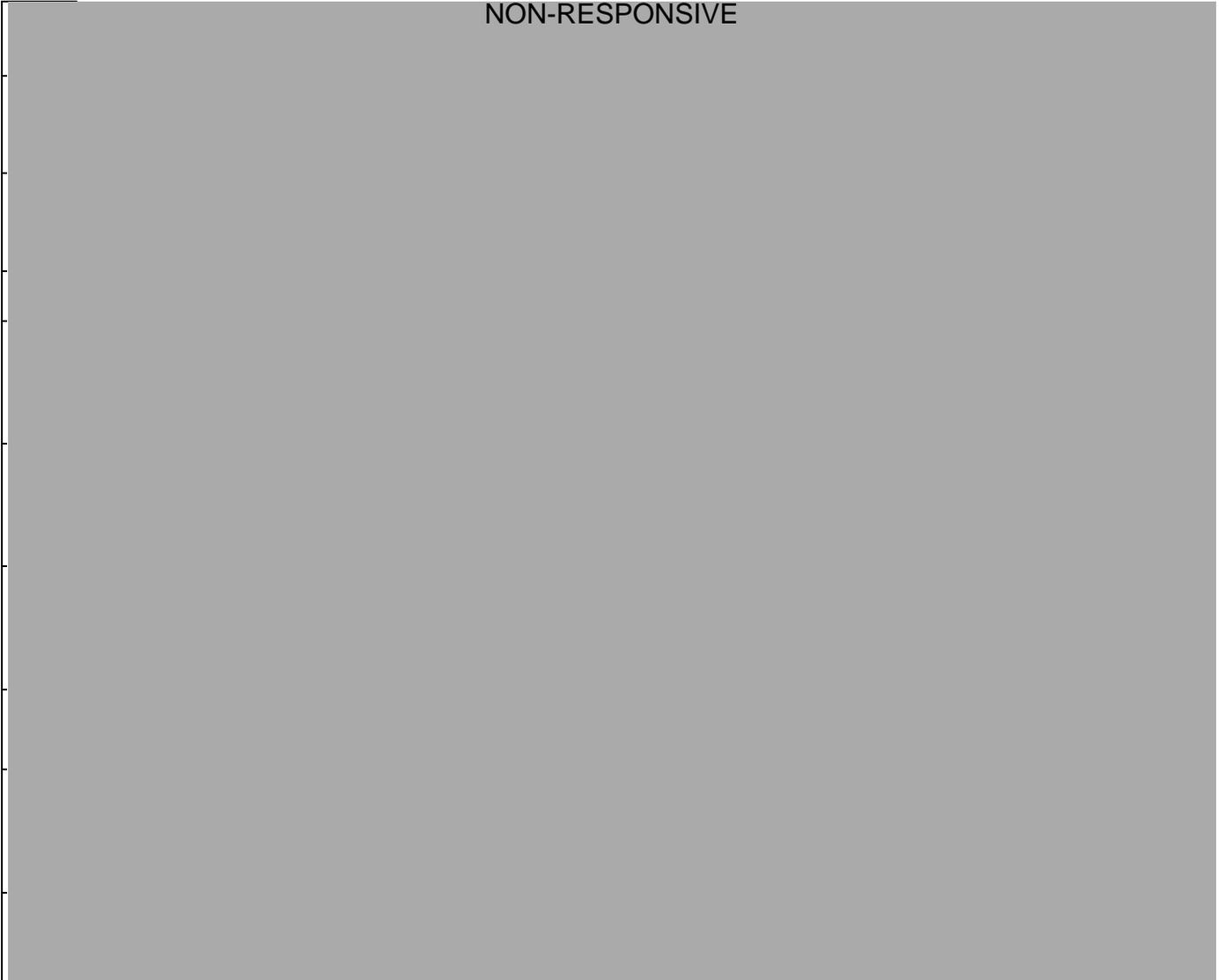
Julia Pinto NON-RESPONSIVE

Hari Sachs

Daiva Shetty

Agenda

NON-RESPONSIVE



	NDA 208470	Intratosa (prasterone) Full Waiver with Agreed iPSP	DBRUP	Kimberly Shiley	Treatment of moderate to severe dyspareunia, a symptom of vulvovaginal atrophy due to menopause
--	---------------	--	-------	-----------------	--

NON-RESPONSIVE



NON-RESPONSIVE



5 Page(s) have been Withheld in Full as NON-RESPONSIVE
immediately following this page

NON-RESPONSIVE

Intratosa (prasterone) Full Waiver with Agreed iPSP

- Indication: Treatment of moderate to severe dyspareunia, a symptom of vulvovaginal atrophy due to menopause
- *PeRC Recommendations:*
 - The PeRC concurred with the sponsor's plan for a full waiver.

NON-RESPONSIVE

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

/s/

MESHAUN L PAYNE
07/26/2016



NDA 208470

ADVICE/INFORMATION REQUEST

EndoCeutics Inc.
Attention: Fernand Labrie, M.D., Ph.D.
c/o U.S. Agent, Accenture, LLP
Raj Bandaru, Ph.D.
Global Regulatory Affairs
1160 W. Swedesford Road, Building One
Berwyn, PA 19312

Dear Dr. Labrie:

We refer to your New Drug Application (NDA) dated October 16, 2015, received October 16, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for prasterone.

We also refer to your June 20, 2016, submission containing your proposed labeling for Section 13.1 in response to our June 3, 2016, Information Request letter.

As stated in our June 3, 2016, letter, with use of your product, prasterone is converted to estradiol and testosterone in the vagina, raising the local concentration of these hormones. Postmenopausal estrogen therapy is considered to be carcinogenic in humans (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 72: 399-503, 1999) and testosterone is considered an animal and presumptive human carcinogen (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 21:519-547, 1979). Therefore, the possible risk for reproductive tract tumors should be communicated in labeling. We are recommending that Section 13.1 include the following information on carcinogenicity:

Long-term studies in animals to evaluate carcinogenic potential have not been conducted with prasterone. Two metabolites of prasterone, estradiol and testosterone, are carcinogenic in animals.

With this labeling recommendation, your application would be considered under the 505(b)(2) regulatory pathway, if you do not own or have a right of reference to data or literature which show estradiol and testosterone are carcinogenic in animals. If you accept this recommendation, you would need to submit a scientific rationale to support that reliance upon the literature is appropriate for your product. Alternatively for a 505(b)(2) application, you could rely on FDA's

finding of safety and effectiveness for a listed drug(s), provided you establish a “bridge” between your product and each listed drug to demonstrate that such reliance is scientifically justified.

If you still want your application to be considered under the 505(b)(1) regulatory pathway, you should: 1) submit data from carcinogenicity studies on prasterone or estrogen and testosterone that you have conducted; or 2) submit published literature documenting the relevant carcinogenicity of prasterone or estrogen and testosterone to which you own or have a right to refer.

Note that approval under the 505(b)(2) pathway does not preclude granting of 5-year new drug exclusivity for a new chemical entity. We are requesting that you respond no later than July 22, 2016, to inform of us of your final choice of the above alternative regulatory pathways. Failure to meet the criteria noted for the selected approach will influence approvability.

If you have any questions, please contact Kim Shiley, R.N., B.S.N., Regulatory Project Manager, at (301) 796-2117.

Sincerely,

{See appended electronic signature page}

Shelley R. Slaughter, M.D., Ph.D.
Clinical Team Leader
Division of Bone, 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/

SHELLEY R SLAUGHTER
07/18/2016



NDA 208470

ADVICE/INFORMATION REQUEST

EndoCeutics Inc.
Attention: Fernand Labrie, M.D., Ph.D.
c/o U.S. Agent, Accenture, LLP
Raj Bandaru, Ph.D.
Global Regulatory Affairs
1160 W. Swedesford Road, Building One
Berwyn, PA 19312

Dear Dr. Labrie:

Please refer to your New Drug Application (NDA) dated October 16, 2015, received October 16, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for prasterone.

We have the following comments regarding your combination device-drug product:

1. Your proposed to-be-marketed device component of your combination device-drug product is different from that used in the phase 3 clinical trials.
2. Provide evidence to support that the use of the to-be-marketed device is not expected to lead to an increase in vaginal morbidity (irritation, superficial tears, lacerations, hematoma, vaginal bleeding, etc.).

If you have any questions, please contact Kim Shiley, R.N., B.S.N., Regulatory Project Manager, at (301) 796-2117.

Sincerely,

{See appended electronic signature page}

Shelley R. Slaughter, M.D., Ph.D.
Clinical Team Leader
Division of Bone, 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/

SHELLEY R SLAUGHTER
07/14/2016



NDA 208470

INFORMATION REQUEST

EndoCeutics Inc.
Attn: Fernand Labrie, M.D., Ph.D.
c/o U.S. Agent, Accenture, LLP
Raj Bandaru, Ph.D., Global Regulatory Affairs
1160 W. Swedesford Road, Building One
Berwyn, PA 19312

Dear Dr. Labrie:

Please refer to your New Drug Application (NDA) dated October 16, 2015, received October 16, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for prasterone.

We have the following comments regarding your clinical amendment to protocol ERC-237, entitled "*Protocol for Second and Third Readings of End-of-Study Endometrial Biopsies from Postmenopausal Women with Vulvovaginal Atrophy (VVA) for Studies ERC-210, ERC-230, ERC-231 and ERC-234*", submitted June 1, 2016:

1. We concur with the selection of (b) (4) as the third reader. Provide (b) (4) with the slide sets obtained from the re-cut of paraffin blocks, including the slides sets that were previously read by (b) (4). Prior to providing slides to (b) (4), remove completely any markings previously made on the slides.
2. Provide the actual endometrial biopsy reports from each of the three independent pathologists (b) (4) as well as the individual subject data listings.

If you have any questions, please contact Kim Shiley, R.N., B.S.N., Regulatory Project Manager, at (301) 796-2117.

Sincerely,

{See appended electronic signature page}

Shelley R. Slaughter, M.D., Ph.D.
Clinical Team Leader
Division of Bone, 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/

SHELLEY R SLAUGHTER
06/15/2016



NDA 208470

ADVICE/INFORMATION REQUEST

EndoCeutics Inc.
Attention: Fernand Labrie, M.D., Ph.D.
c/o U.S. Agent, Accenture, LLP
Raj Bandaru, Ph.D.
Global Regulatory Affairs
1160 W. Swedesford Road, Building One
Berwyn, PA 19312

Dear Dr. Labrie:

Please refer to your New Drug Application (NDA) dated and received October 16, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for prasterone.

Section 505 of the Act describes three types of new drug applications:

1. an application that contains full reports of investigations of safety and effectiveness - section 505(b)(1);
2. an application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference - section 505(b)(2);
3. an application that contains information to show that the proposed product is identical in active ingredients, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things, to a previously approved product - section 505(j).

You have submitted this application as a 505(b)(1) application.

We disagree with your statement that estradiol and testosterone are not applicable to prasterone. With use of your product, prasterone is converted to estradiol and testosterone in the vagina, raising the local concentration of these hormones. Postmenopausal estrogen therapy is considered to be carcinogenic in humans (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 72: 399-503, 1999) and testosterone is considered an animal and presumptive human carcinogen (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 21: 519-547, 1979). Thus, there is a possible increased risk for reproductive tract tumors that should

be communicated in the labeling. To inform safety for product labeling, we propose that the carcinogenicity portion of section 13.1 read as follows:

Long-term studies in animals to evaluate carcinogenic potential have not been conducted with prasterone. Two metabolites of prasterone, estradiol and testosterone, are carcinogenic in animals. Systemic levels of estradiol and testosterone are not increased with intravaginal prasterone.

If you own or have the right of reference to data or literature which show estradiol and testosterone are carcinogenic in animals, submit them to the NDA. If you do not own or have a right of reference to such data or literature, then your application is considered to be a 505(b)(2) NDA.

We request your response to this letter by June 20, 2016.

If you have any questions, please contact Kim Shiley, R.N., B.S.N., Regulatory Project Manager, at (301) 796-2117.

Sincerely,

{See appended electronic signature page}

Shelley R. Slaughter, M.D., Ph.D.
Clinical Team Leader
Division of Bone, 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/

SHELLEY R SLAUGHTER
06/03/2016



NDA 208470

INFORMATION REQUEST

EndoCeutics Inc.
Attention: Fernand Labrie, M.D., Ph.D.
c/o U.S. Agent, Accenture, LLP
Raj Bandaru, Ph.D.
Global Regulatory Affairs
1160 W. Swedesford Road, Building One
Berwyn, PA 19312

Dear Dr. Labrie:

Please refer to your New Drug Application (NDA) dated October 16, 2015, received October 16, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for prasterone.

We have the following comments regarding your safety protocol for ERC-237 entitled "*Protocol for Second and Third Readings of End-of-Study Endometrial Biopsies from Postmenopausal Women with Vulvovaginal Atrophy (VVA) for Studies ERC-210, ERC-230, ERC-231 and ERC-234*" submitted on May 6, 2016:

1. With one exception, we generally concur with your proposal to conduct a re-read of the end-of trial endometrial biopsies specifically for 12-Week Trials ERC-210, ERC-231, and ERC-234 and 52-Week Trial ERC-230, as outlined in the above protocol.
2. We do not agree with the selection of five pathologists [REDACTED] (b) (4) [REDACTED] to participate as the "third reader" for the re-read of the slide set. Designate a single pathologist with expertise in gynecologic pathology to participate as the "third reader." Additionally, provide the actual endometrial biopsy reports from each of the three independent pathologists as well as the individual subject data listings.

If you have any questions, please contact Kim Shiley, R.N., B.S.N., Regulatory Project Manager, at (301) 796-2117.

Sincerely,

{See appended electronic signature page}

Shelley R. Slaughter, M.D., Ph.D.
Clinical Team Leader
Division of Bone, 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/

SHELLEY R SLAUGHTER
05/16/2016



NDA 208470

INFORMATION REQUEST

EndoCeutics Inc.
Attention: Fernand Labrie, M.D., Ph.D.
c/o U.S. Agent, Accenture, LLP
Raj Bandaru, Ph.D.
Global Regulatory Affairs
1160 W. Swedesford Road, Building One
Berwyn, PA 19312

Dear Dr. Labrie:

Please refer to your New Drug Application (NDA) dated October 16, 2015, received October 16, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for prasterone.

We have the following comments regarding endometrial assessments for ERC-210, ERC-231, ERC-234 and ERC-230:

1. Your evaluation of the endometrial biopsies conducted for assessment of the endometrium of participating women at Week 12 for trials ERC-210, ERC-231, and ERC-234 and Week 52 for ERC-230, were not conducted according to the Agency's 2003 draft Guidance for Industry, entitled "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation." Specifically you did not have three independent pathologists evaluate and provide an adequate endometrial histological diagnosis.

With one exception, a single pathologist, (b) (4), made the histological diagnosis for all endometrial samples obtained in the above trials as well as trial ERC-238. The exception involved the read of some of the baseline endometrial biopsies from ERC-210. (b) (4) read these slides.

2. Per the protocol for ERC-230, "endometrial biopsy will be evaluated based on the Guidance for Industry "Estrogen and Estrogen/Progestin Drug Product to Treat

Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluations as follows:”

- “The endometrial tissue obtained by endometrial biopsy at screening, during the conduct of the study, and at the end-of-study be processed in the same manner by a central laboratory.”
 - “A single pathologist reader (any one of the three blinded pathologists) initially assess the slides from the endometrial biopsies obtained at screening or because of participant bleeding while on study drug (safety reading).”
 - “Three independent expert pathologists, blinded to treatment group and to each other’s readings, determine the diagnosis for endometrial biopsy slides during the conduct of the study for all women who have an end-of-study biopsy or because of participant bleeding while on study drug safety reading.”
3. The protocols for ERC-231 and ERC-234 contain language similar to that noted in item 2 above.
 4. Failure to have three independent and blinded pathologists read the end-of-trial endometrial biopsies constitutes inadequate and insufficient endometrial assessment for your product.

To remedy the above situation, each endometrial biopsy for which endometrial tissue was obtained will need to be re-read by two additional independent and blinded pathologists. These pathologists should be located at different institutions and have no common fiduciary or reporting responsibilities. To conduct the re-read, adhere to the following:

- If possible, recut the block of tissue at the same level as that for the previous slide set to obtain new sets of slides for the re-read.
- If a recut is not possible because of insufficient tissue, the original slides may be re-used, but these should not contain any markings from the previous read. If there is insufficient tissue to perform a re-cut, you must state this in writing.
- A re-read of the original slides should be performed only under the specific circumstances noted in the preceding bullet.
- Slides should not be ordered by time or participant identifier and should be randomized without any other prior grouping.
- Known positive controls for endometrial hyperplasia (simple hyperplasia without atypia, simple hyperplasia with atypia, complex without atypia, and complex with

atypia) and endometrial carcinoma should be included in the slide set provided to each additional blinded pathologist.

- Known negative-controls of atrophic, inactive, proliferative (inactive, active and disordered), secretory and menstrual endometrium should be included in the slide set provided to each additional blinded pathologist.
- The two selected additional pathologists should be regarded and recognized as experts in gynecologic pathology.
 - Provide to the Agency, the curricula vitae for the additional participating pathologists.
- The additional two blinded pathologist, should not be informed that they are conducting a re-evaluation of a previously determined histological diagnosis.
 - The additional two blinded pathologists should have no connections (either by training or institution of practice) with (b) (4)
 - There should be no meetings or any other communications between the two additional pathologists or between either or both of the two additional pathologists and (b) (4).
- Follow, as recommended in the draft 2003 Guidance for Industry, standard criteria for histologic diagnosis as provided in Blaustein's pathology text (Pathology of the Female Genital Tract). For your convenience these are provided below:

Histologic Characteristics of the Endometrium:

0. No tissue
1. Tissue insufficient for diagnosis
2. Atrophic
3. Inactive
4. Proliferative
 - a. Weakly proliferative
 - b. Active proliferative
 - c. Disordered proliferative
5. Secretory
 - a. Cyclic type
 - b. Progestational type (including stromal decidualization)

6. Menstrual type
 7. Simple hyperplasia without atypia
 8. Simple hyperplasia with atypia
 9. Complex hyperplasia without atypia
 10. Complex hyperplasia with atypia
 11. Carcinoma (specify type)
- Include all additional and exploratory comments from the two additional blinded pathologists in addition to their diagnoses in line listings.
5. Provide the Agency with a safety protocol for conduct of the re-read of each endometrial biopsy for which endometrial tissue was obtained. Incorporate all of the elements required for assessing endometrial histology from the 2003 guidance into the protocol provided to the Agency.
 6. Provide the Agency with a time frame for completion of your proposed re-read of slides as described above.
 7. Failure to adequately assess endometrial safety is an approvability issue.

If you have any questions, please contact Kim Shiley, R.N., B.S.N., Regulatory Project Manager, at (301) 796-2117.

Sincerely,

{See appended electronic signature page}

Shelley R. Slaughter, M.D., Ph.D.
Clinical Team Leader
Division of Bone, 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/

SHELLEY R SLAUGHTER
03/29/2016



NDA 208470

INFORMATION REQUEST

From: jann.a.kochel@accenture.com [mailto:jann.a.kochel@accenture.com]

Sent: Tuesday, March 15, 2016 11:04 AM

To: Shiley, Kimberly

Subject: RE: NDA 208470, labeling revisions needed in 2 weeks

Hi Kim-

Thank you for the email. I have forwarded it to EndoCeutics.

Kind Regards,

Jann

From: Shiley, Kimberly [mailto:Kimberly.Shiley@fda.hhs.gov]

Sent: Tuesday, March 15, 2016 10:59 AM

To: Kochel, Jann A. <jann.a.kochel@accenture.com>

Subject: NDA 208470, labeling revisions needed in 2 weeks

Importance: High

Greetings Jann,

Draft labeling for NDA 208470 is attached. These are only high level comments and they do not convey any conclusions regarding the approvability of your product.

Provide revised labeling that responds to these comments and any other labeling comments (i.e. 74-day letter) by formally submitting revised labeling to the application no later than March 31, 2016. Provide a Word clean version and a redlined, track-changes version.

Provide confirmed receipt of this email.

Kim Shiley, RN, BSN

Regulatory Health Project Manager
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993
Bldg 22, Room 5377
office: 301-796-2117
fax: 301-796-9897
kimberly.shiley@fda.hhs.gov

This message is for the designated recipient only and may contain privileged, proprietary, or otherwise confidential information. If you have received it in error, please notify the sender immediately and delete the original. Any other use of the e-mail by you is prohibited. Where allowed by local law, electronic communications with Accenture and its affiliates, including e-mail and instant messaging (including content), may be scanned by our systems for the purposes of information security and assessment of internal compliance with Accenture policy.

www.accenture.com

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page

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

/s/

KIMBERLY A SHILEY
03/15/2016



NDA 208470

INFORMATION REQUEST

From: jann.a.kochel@accenture.com [mailto:jann.a.kochel@accenture.com]

Sent: Wednesday, February 03, 2016 3:25 PM

To: Shiley, Kimberly

Subject: RE: NDA 208470, ClinPharm Information Request

Hi Kim,

The data files in the xpt format for the serum concentrations of DHEA and its metabolites in the Studies ERC-213, ERC-231 and ERC-238 were submitted in the initial NDA package (sequence 0000).

Please find a summary table below indicating the location of those files for the serum concentrations:

Study ID	RAW DATASETS			Analysis DATASETS		
	Location	Dataset	Description	Location	Dataset	Description
ERC-213	m5/datasets/erc-213/tabulations/legacy/	STEROIDS.xpt	All Steroids (DHEA and its metabolites – FREE, Glucuronidated and Sulfated)	Not provided in the NDA package (sequence 0000)		
ERC-231	m5/datasets/erc-231/tabulations/legacy/	AD17G.xpt	Androstane-3 α , 17 β -diol 17-glucuronide	m5/datasets/erc-231/analysis/legacy/datasets/	adsters.xpt	DHEA and all its metabolites (FREE, Glucuronidated and Sulfated)
		ADTG.xpt	Androsterone glucuronide			
		DHEA.xpt	DHEA and its FREE Metabolites (5-diol, 4-dione, testo, DHT, E1 and E2)			
		SULFATE3.xpt	Sulfated metabolites (DHEA-Sulfate and Estrone-Sulfate)			
ERC-238	m5/datasets/erc-238/tabulations/legacy/	STEROIDS.xpt	All Steroids (DHEA and its metabolites - FREE, Glucuronidated and Sulfated)	m5/datasets/erc-238/analysis/legacy/datasets/	adsters.xpt	DHEA and all its Metabolites (FREE, Glucuronidated and Sulfated)

For the PK study ERC-213, the analysis dataset in the xpt format containing the calculated values of the pharmacokinetic parameters (AUC, Cmax) from serum steroid concentrations has not been included in the NDA package.

The analysis dataset for ERC-213 steroid concentrations and PK parameters will be provided by mid-next week under Sequence 0005 of NDA 208470 along with the additional information requested by the Agency in the filing communication dated 28-DEC-2015.

Thanks,
Jann

From: Shiley, Kimberly [<mailto:Kimberly.Shiley@fda.hhs.gov>]
Sent: Wednesday, February 03, 2016 8:10 AM
To: Kochel, Jann A. <jann.a.kochel@accenture.com>
Subject: NDA 208470, ClinPharm Information Request

Hi Jann,

Provide the following:

- data files in the xpt format for the serum concentrations of DHEA and its metabolites and (or) their pharmacokinetic parameters in the Study ERC-213, ERC-231 and ERC-238.
- If already submitted, indicate the location of those files in the NDA package.

Confirm receipt please.

Kim Shiley, RN, BSN

Regulatory Health Project Manager
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993
Bldg 22, Room 5377
office: 301-796-2117
fax: 301-796-9897
kimberly.shiley@fda.hhs.gov

This message is for the designated recipient only and may contain privileged, proprietary, or otherwise confidential information. If you have received it in error, please notify the sender immediately and delete the original. Any other use of the e-mail by you is prohibited. Where allowed by local law, electronic communications with Accenture and its affiliates, including e-mail and instant messaging (including content), may be scanned by our systems for the purposes of information security and assessment of internal compliance with Accenture policy.

www.accenture.com

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

/s/

KIMBERLY A SHILEY
02/03/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208470

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Endoceutics, Inc.
c/o Accenture, LLP
1160 W. Swedesford Road
Building One
Berwyn, PA 19312

ATTENTION: Jann A. Kochel
U.S. Agent

Dear Ms. Kochel:

Please refer to your New Drug Application (NDA) dated and received October 16, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prasterone Vaginal Insert, 6.5 mg.

We also refer to your correspondence, dated and received October 16, 2015, requesting review of your proposed proprietary name, Intrarosa.

We have completed our review of the proposed proprietary name, Intrarosa and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your October 16, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Shawnetta Jackson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-4952. For any other information regarding this application, contact Kimberly Shiley, Regulatory Project Manager in the Office of New Drugs, at 301-796-2117.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
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/

IRENE Z CHAN on behalf of TODD D BRIDGES
12/30/2015



NDA 208470

INFORMATION REQUEST

From: jann.a.kochel@accenture.com [mailto:jann.a.kochel@accenture.com]
Sent: Thursday, December 03, 2015 12:22 PM
To: Shiley, Kimberly
Subject: RE: question re: NDA 208470

Hi Kim,

I have checked with EndoCeutics and they own the data for the published literatures that they have submitted under Module 2 to support the pharmacology section of the preclinical package of NDA 208470. Occasionally, EndoCeutics is referring to other publications from the public domain to compare their own data with the published data from other researchers but all graphs, tables and detailed data described under the pharmacology summary of their NDA 208470 were obtained from studies conducted by or for EndoCeutics.

Thank you,

Jann

From: Shiley, Kimberly [mailto:Kimberly.Shiley@fda.hhs.gov]
Sent: Thursday, December 03, 2015 10:39 AM
To: Kochel, Jann A. <jann.a.kochel@accenture.com>
Subject: question re: NDA 208470
Importance: High

Greetings Jann,

Could you present and obtain the following information from Dr. Labrie and respond directly to this email?

Dr. Labrie:

We have the following questions for you regarding NDA 208470 for prasterone vaginal

(b) (4) :

Do you own the data for the published literature that you submitted to support the pharmacology section of your preclinical package? If the answer to this question is no, do you have the right-of-reference to this data? If the answer to this question is yes, provide the documentation of right-of-reference.

We request that you respond to our questions and provide the applicable documentation by close-of-business, December 4, 2015.

Thank you,

Kim Shiley, RN, BSN

Regulatory Health Project Manager
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993
Bldg 22, Room 5377
office: 301-796-2117
fax: 301-796-9897
kimberly.shiley@fda.hhs.gov

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

/s/

KIMBERLY A SHILEY
12/03/2015



IND 078027

MEETING MINUTES

EndoCeutics Inc.
c/o Accenture, LLP, U.S. Agent
Attention: Jann A. Kochel
Associate Director, Regulatory Affairs
1160 W. Swedesford Road
Building One
Berwyn, PA 19312

Dear Ms. Kochel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for EM-760 (prasterone, DHEA) vaginal

(b) (4).

We also refer to the meeting between representatives of your firm and the FDA on April 27, 2015. The purpose of the meeting was to discuss the format and content of your proposed NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kim Shiley, R.N., B.S.N., Regulatory Project Manager at (301) 796-2117.

Sincerely,

{See appended electronic signature page}

Shelley R. Slaughter, M.D., Ph.D.
Clinical Team Leader
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: April 27, 2015, 11:00 a.m. – 12:00 p.m.
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1417
Silver Spring, Maryland 20903

Application Number: 078027
Product Name: EM-760 (prasterone, DHEA) vaginal (b) (4)
Proposed Indication: Treatment of moderate to severe dyspareunia, a symptom of vulvovaginal atrophy, due to menopause

Sponsor/Applicant Name: EndoCeutics Inc. (EndoCeutics)

Meeting Chair: Shelley R. Slaughter, M.D., Ph.D.
Meeting Recorder: Kim Shiley, R.N.

FDA ATTENDEES

Division of Bone, Reproductive, and Urologic Products

Audrey Gassman, M.D., Deputy Director
Shelley R. Slaughter, M.D., Ph.D., Clinical Team Leader
Theresa van der Vlugt, M.D., M.P.H., Clinical Reviewer
Alexander Jordan, Ph.D., Pharmacology Team Leader
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
Kim Shiley, R.N., B.S.N., Regulatory Health Project Manager
Nneka McNeal-Jackson, M.D., Clinical Reviewer
Regina Zopf, M.D., M.P.H., Clinical Reviewer

Office of Clinical Pharmacology

Myong-Jin Kim, Pharm.D., Clinical Pharmacology Team Leader
Jihong Shon, M.D., Ph.D., Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality, Office of New Drug Products

Division of New Drug Products II

Moo Jong Rhee, Ph.D., Branch Chief
Mark Seggel, Ph.D., Acting CMC Lead
Raanan A. Bloom, Ph.D., EA Team

Division of Biopharmaceutics

Vidula Kolhatkar, Ph.D., Biopharmaceutics Reviewer

Office of Biometrics

Mahboob Sobhan, Ph.D., Biometrics Team Leader

Jia Guo, Ph.D., Statistician

Office of Scientific Investigations (OSI)

Roy Blay, Ph.D., Reviewer

Office of Combination Products

Bindi Nikhar, M.D., Associate Clinical Director

Office of Business Informatics

DDMSS\eData

Lisa Lin, M.B.A., Senior Regulatory Analyst

Rui Li, M.D., M.S.

Center for Devices and Radiological Health

Division of Reproductive, Gastro-Renal, and Urological Devices

Obstetrics and Gynecology Devices Branch

Sharon Andrews, Biomedical Engineer

SPONSOR ATTENDEES

EndoCeutics Inc., Quebec, Canada

Fernand Labrie, M.D., Ph.D. C.E.O.-C.S.O.

Jaâfar Zerhouni, M.Sc, M.Eng, M. Mgt., V.P., Quality & CMC

Céline Martel, Ph.D., Regulatory Affairs/Data Analysis

(b) (4)

Jann A. Kochel, Accenture LLP, U.S. Agent, Regulatory Affairs

1.0 BACKGROUND

The purpose of this meeting was to discuss the format and content of EndoCeutics' anticipated NDA submission for EM-760 (prasterone, DHEA) vaginal (b) (4). EndoCeutics seeks advice regarding the presentation of data, the dataset structure, and the acceptability of their data. Additionally, the acceptability of items related to CMC, namely specifications, stability data, and qualification of an additional commercial manufacturing site is also sought by EndoCeutics. The drug product is a vaginal (b) (4) containing 6.5 mg (0.50%; w/v) of prasterone (b) (4) in (b) (4) hard-fat base (Witepsol (b) (4)(NF)). Previous meetings include a Guidance meeting held in March, 2009 and Written Responses in lieu of a guidance meeting provided in July, 2013.

FDA sent Preliminary Comments to EndoCeutics on April 24, 2015.

2. DISCUSSION

A. NONCLINICAL

1. *For the Module 4 of the NDA, is it acceptable for the Agency that we include in the NDA the new study report on CYP inhibition but that cross-reference be made to the previously submitted and unchanged non-clinical study reports (Module 4.2.2.6), or if all nonclinical reports (toxicity and analytical reports) should be re-submitted in the NDA. The schematic presentation of the drug metabolism pathway will be included in the summary of clinical pharmacology (Module 2.7.2).*

Does the Agency agree that with the additional CYP study performed all preclinical requirements are met to support the NDA?

FDA Response:

Yes, you have met all nonclinical requirements to support the NDA.

For ease of review, we ask that all nonclinical study reports that will be used to support the nonclinical portion of your current NDA submission be resubmitted in Module 4 of the NDA. We also ask that you provide a tabular listing of titles of studies from all INDs or NDAs that you intend to use to support the nonclinical portion of your current NDA submission. This can be included in Module 2 under Nonclinical Overview.

2. *Does the Agency agree with the proposed wording in section 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility) of the proposed draft labeling included in Section 10.6?*

FDA Response:

No. It is premature to discuss labeling in detail. However, the wording proposed for Section 13.1 should be significantly simplified, and have minimal, if any, reference to figures or literature. As communicated previously in our letter addressing the waiver for carcinogenicity studies, we recommend similar product labeling to Sections 13.1 of Premarin vaginal cream and topical androgen products such as Androgel and Fortesta.

We also refer you to Section 3.0, *Discussion of the Content of a Complete Application - PRESCRIBING INFORMATION*. Section 8 of your proposed prescribing information does not conform to the Pregnancy and Lactation Labeling Rule (PLLR). Section 8 of prescribing information, submitted with the NDA, will need to conform to the PLLR.

B. CLINICAL

3. *Does the Agency agree with the proposed data and population to be used for the integrated efficacy analysis?*

FDA Response:

No, we do not agree with your proposal to integrate efficacy data from 12-week Trial ERC-231 and 12-week Trial ERC-238 with your post-hoc analysis of Trial (b) (4) to support the indication of treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

We consider DHEA to be a new molecular entity (NME). This NME should be supported by two confirmatory adequate and well-controlled 12-week, phase 3 clinical trials for safety and efficacy. As previously conveyed to you, we do not agree that (b) (4) can be considered as one of the confirmatory 12-week clinical trials to support the effectiveness of 0.50% prasterone (DHEA) for the indication as noted above. Our consideration of the efficacy of your product will be based on the results of Trial ERC-231 and Trial ERC-238, analyzed separately. Your proposed post-hoc analysis of Trial ERC-210 could be submitted as supportive of your two confirmatory clinical trials.

The primary efficacy analyses in Trial ERC-231 and Trial ERC-238 should be based on women who meet all three of the baseline inclusion criteria: 1) less than 5% superficial cells on a lateral-wall vaginal smear, and 2) a vaginal pH greater than 5, and 3) a most bothersome moderate to severe symptom of vulvar and vaginal atrophy (defined as dyspareunia in Trials ERC-231 and ERC-238).

We agree with your definition of the ITT population as all women who have 1) a baseline (Day 1) evaluation which meets the study entrance criteria, and 2) received at least one dose of medication (based on the woman's diary card).

Discussion:

EndoCeutics requested confirmation as to whether or not an integrated summary of efficacy (ISE) is required for their proposed NDA for prasterone. If an ISE is required, should Trials ERC-231 and ERC-238 be the studies included?

The Agency stated that Trials ERC-231 and ERC-238 should each be analyzed separately to provide confirmation of each other. DHEA is considered to be a NME and, as such, two confirmatory trials are recommended. The Agency stated that if so desired, EndoCeutics could also submit as supportive, an ISE with both studies included.

4. *As indicated above, the (b) (4) clinical study report (granular format) and its four amendments as well as the corresponding datasets and programs have already been submitted to the Agency under different sequences of IND 078027 (serial 0007, 0009, 0010, 0032 and 0040; refer to Section 10.1.1). Instead of re-submitting in the NDA the already submitted documents (report, appendices, etc)/datasets and additional information regarding study (b) (4), except as part of the integrated set of data, we would suggest to cross-reference to the submitted documents.*

Does the Agency agree?

FDA Response:

No, we do not agree. For ease of our review, in addition to your proposal to submit the clinical study reports for Trials ERC-230, ERC-231, ERC-234, and ERC-238, we also recommend that you submit the complete clinical study reports for Trials ERC-210 and ERC-213 in your NDA.

5. *Does the Agency agree with the proposed datasets and populations to be used for the integrated safety analysis?*

FDA Response:

Yes, we agree with the inclusion in the Integrated Summary of Safety (ISS) of all women who took at least one dose of study medication in the six (6) clinical trials in the DHEA development program.

We recommend that you submit individual clinical study reports, including all safety data, for each of the six (6) clinical trials completed in your development program. See also our response to Question 4.

MedDRA version 16.1 is acceptable.

Additionally, provide details on the approximately 50 postmenopausal women who participated in more than one of the clinical trials for the DHEA development program. For each participating woman, provide the trial number, the dose and dosing regimen, the duration of use, and each adverse event reported.

6. *Is this plan for data presentation and content acceptable for the Agency?*

FDA Response:

Yes, we concur with your proposal to submit complete clinical study reports for Trials ERC-230, ERC-231, ERC-234, and ERC-238 in your NDA. We also recommend that you submit complete clinical study reports for Trials ERC-210 and ERC-213 in your NDA. See also our responses to Questions 4 and 5.

We recommend that you provide the individual subject listings and subject case report forms (CRFs) in each completed clinical study report submitted.

We concur with your proposal to submit both individual CRFs for subjects who experienced fatal and non-fatal serious adverse events (SAEs) and for subjects who discontinued due to adverse events.

7. *Does the Agency agree with our proposed draft labeling and consider that there is no need to include a REMS in our NDA submission?*

FDA Response:

No. It is premature to discuss labeling in detail or make a decision on the need for a Risk Evaluation and Mitigation Strategies (REMS). Both of these will be addressed following

our review of your NDA. We refer you to Section 3.0 for information on the Physician Labeling Rule (PLR) Requirements for Prescribing Information and Pregnancy and Lactation Labeling Rule (PLLR) Requirements for Prescribing Information.

8.

(b) (4)

Additional FDA Comments:

We have the following additional comment on your Clinical Pharmacology development. As previously recommended during Advice (Type-C) Meetings on July 12, 2013 and April 30, 2009, provide at the time of the NDA submission, scientific justification to support: 1) dosing consideration for specific populations, such those with hepatic or renal impairment and; 2) safety in the exposed partner of the treated woman.

C. CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

9. *Does the Agency agree with this approach to support qualification of the (b) (4) site as an alternate commercial manufacturing site?*

FDA Response:

Yes, your proposed approach to support qualification of the (b) (4) site as an alternate commercial manufacturing site is acceptable. See also our response to Question 12.

10. *The Sponsor believes that additional extractables and leachables studies are not necessary. Does the Agency agree?*

FDA Response:

No. While it appears that the need for additional extractables and leachables studies is unlikely, a final determination cannot be made until the studies provided in DMF (b) (4) have been reviewed in the context of the proposed drug product.

Discussion:

EndoCeutics sought clarification that if the Agency determines that additional Extractable and Leachables studies are required, at what point in the review process would the Agency notify EndoCeutics of this finding.

The Agency stated that this information will be reviewed during the NDA. Typically some feedback will be provided at the time of the 74 day letter. For applications under "The Program", feedback will be provided no later than the mid-cycle meeting. The commitment to complete any additional studies needed, may be made a post-approval requirement.

11. *The limits of known and unknown impurities were established in accordance with ICH Q3B and the total impurities limit was established at NMT (b) (4) % to cover the new limits of individual known impurities. Does the Agency agree with these limits?*

FDA Response:

No. The acceptability of the acceptance criteria for individual and total impurities in the drug product will be determined during the NDA review.

12. *The specification for dissolution testing is established at Q (b) (4) % in 180 minutes (b) (4)*
Does the Agency agree with this specification?

FDA Response:

No. You have provided insufficient information about your dissolution method development and validation in the briefing document. Therefore, it is premature to answer this question. Provide a complete dissolution development and validation report. The final determination on the acceptability of the dissolution method is a review issue to be made following review of the data. Likewise, the acceptability of the dissolution acceptance criterion will be determined during the review process and will be based on the totality of the provided dissolution data on pivotal clinical batches and primary stability batches.

13. *The Sponsor believes that stability data from batches manufactured at (b) (4) should support the drug product proposed shelf life because the presence of a (b) (4) mL in the primary packaging can be considered as a worst case condition for the drug product stability. Does the Agency agree to submit data generated from batches manufactured at (b) (4) to support the product shelf-life?*

FDA Response:

Yes, supporting stability data on product manufactured at (b) (4) can be submitted in the NDA to support the product shelf-life.

14. *The Sponsor believes that additional stability studies on batches manufactured at the (b) (4) Site at (b) (4) are not necessary to support the claim that the product could be refrigerated. Does the Agency agree?*

FDA Response:

No. At least one batch of drug product manufactured at the (b) (4) site should be placed on stability at (b) (4). Drug substance (b) (4) should be evaluated.

Discussion:

EndoCeutics noted that they planned to submit the 3-month stability data for suppositories manufactured at (b) (4) no later than 30 days after NDA submission and asked if this was acceptable to the Agency.

The Agency stated that this was acceptable.

15. *The Sponsor considers submitting in the NDA drug product section 3.2.P.3.1 only the sites listed in Table 3 that will be used for the manufacture of commercial drug product. Does the Agency agree?*

FDA Response:

No. Include Table 2, which identifies the manufacturing, packaging and testing facilities of the clinical trial materials, as well as of the supporting stability batches. Note, however, that only those sites listed in Table 3, which are involved in the manufacturing, packaging and testing of commercial product should be included in the FDA Form 356h. The facilities involved in the commercial manufacturing, packaging and testing of the applicator should be included in 3.2.P.3.1 Table 3 and on the 356h.

Discussion:

EndoCeutics asked if the manufacture of drug product used in the clinical trials should be documented in separate 3.2.P Drug Product modules.

The Agency explained that the manufacturing development history should be discussed in section 3.2.P.2 Pharmaceutical Development.

Additional Chemistry Manufacturing and Control Comments:

We have the following additional comments:

- Prasterone is the International Nonproprietary Name (INN) for dehydroepiandrosterone (DHEA).

- A United States Adopted Name (USAN) designation for DHEA should be established. A USAN application form is available as a MS-Word document at the USAN Program website, www.ama-assn.org/go/usan.
- The NDA should include a Letter of Authorization for the US DMF covering the CMC for Witepsol (b) (4) hard fat supplied by (b) (4)

Additional Information Regarding Environmental Impact Requirements:

In the April 30, 2009, Memorandum of Meeting Minutes (Meeting Date: March 31, 2009), we advised that the claim for categorical exclusion under 21 CFR 25.31(b) appears to be appropriate for this application. We requested that you calculate and submit the Expected Introduction Concentration (EIC) as outlined in the *Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications* (July 1998)¹ along with the appropriate claim for categorical exclusion. To submit a claim for categorical exclusion a sponsor must provide: (1) a statement that the action requested qualifies for a specific categorical exclusion, citing the particular categorical exclusion that is claimed; and (2) a statement that, to the applicant's knowledge, no extraordinary circumstances exist (21 CFR 25.15(d)). Since drugs with endocrine-related activity have been shown to have potential developmental or reproductive effects in aquatic organisms at environmentally relevant concentrations², we request additional information to determine whether extraordinary circumstances exist³. Specifically, provide information on introductions of the active moiety or its metabolic products into the environment due to use of the drug product; information on endogenous DHEA production and excretion as compared to the drug product; and/or information demonstrating that DHEA would not be expected to produce developmental or reproductive effects in aquatic organisms at expected levels of exposure. If the statement of "no extraordinary circumstances" cannot be supported, an Environment Assessment (EA) will be required. Contact the EA Team for additional information.

16. *The Sponsor intends to submit in the drug product NDA under module 3.2.P.7 the following documents for each source:*
- the drawing of the applicator
 - the specifications of the (b) (4) and colorant used
 - the applicator certification provided by the manufacturer.

16.a. *Do these documents fulfill the Agency requirements for the NDA?*

¹ <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm088969.htm>

² For example, see Section II.C (pp. 7-13) of USFDA, 2013, "Response to Citizen Petition to the FDA Commissioner under the National Environmental Policy Act and Administrative Procedure Act Requesting an Amendment to an FDA Rule Regarding Human Drugs and Biologics," Docket No. FDA-2010-P-0377; U.S. Environmental Protection Agency (USEPA), Endocrine Disruptor Screening Program (EDSP), last accessed February 17, 2015 at <http://www.epa.gov/endo>; and Organisation for Economic Co-operation and Development (OECD), OECD Work Related to Endocrine Disrupters, last accessed February 17, 2015 at <http://www.oecd.org/env/ehs/testing/oecdworkrelatedtoendocrinedisrupters.htm>.

³ 21 CFR 25.21: Extraordinary circumstances

FDA Response:

The data may be submitted under Module 3.2.P.7; however, note that the proposed prasterone (b) (4) drug product that is to be co-packaged with a vaginal applicator is a drug-device combination product and as such is subject to 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for Combination Products accessible at:

<https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>.

While the vaginal applicator is approved as a Class I exempt device, in your proposed use, it is part of a drug-device combination product. As such it will need to satisfy the data requirements for NDA submission of a drug-device combination product. The details on those requirements will be provided during the meeting or as post-meeting comments to this document. See also our response to Question 17 for eCTD comments for combination products.

Clarify the package configuration for the applicators (describe how the box of applicators will be wrapped and/or attached to the box of (b) (4), and whether both boxes are to be placed in in a single carton).

16.b. *The applicator has been successfully qualified (b) (4) as per agreed protocol with FDA (ref: written response July 12, 2013 in Section 10.1.2.2). The Sponsor considers to submit the (b) (4) qualification protocol and report in the drug product NDA under module 3.2.P.7. Does the Agency agree?*

FDA Response:

Yes, the (b) (4) qualification protocol and report can be submitted in the NDA under module 3.2.P.7.

Additional comments on the (b) (4) qualification protocol will be provided during the meeting or as post-meeting comments.

Discussion:

Three issues were discussed:

1. EndoCeutics asked the Agency for its recommendations regarding packaging of the (b) (4) “with” or separately from the applicator (a class 1 exempt device).

The Agency clarified that it would be better from the patient’s viewpoint if the (b) (4) and applicators are in their respective packaging and co-packaged together in one box. The co-packaged product would be a combination product and the vaginal applicator would not retain its Class I exempt status per se, but would be considered the device constituent part of a combination product. The entire combination product would be expected to meet cGMP requirements per 21 CFR Part 4; however the cGMP requirements for the vaginal applicator would not be expected to be onerous.

2. EndoCeutics agreed overall with the combination product configuration, but indicated that they were still uncertain of their final commercial presentation (specifically, the number of applicators to be provided with the 28-day supply of (b) (4))

The Agency indicated that EndoCeutics should justify the ratio of supplied applicators to (b) (4) in their commercial presentation.

3. EndoCeutics asked if it was acceptable to submit information regarding the drug product secondary packaging within 30 days of the NDA submission.

The Agency stated that this was not acceptable. The to-be-marketed commercial product packaging presentation should be finalized before the NDA submission.

D. ELECTRONIC SUBMISSION

17. *Do we need to submit an eCTD pilot (and/or a cross-reference eCTD pilot if we are allowed to use this functionality) with the electronic document control room prior to the NDA filing?*

Please confirm that no paper archival copies are needed for any item with original signature (e.g. cover letter, Form FDA 356h, etc) these documents are planned to be submitted electronically (fillable form and scanned PDF copy of signed documents) in the NDA.

FDA Response:

Yes. We recommend that you submit a sample, prior to submitting cross application links. Additionally, no paper archival copies are needed for any item with electronic signature.

Additional eCTD comments for Combination Products:

Other than data analogous to batch records, all device constituent and combination product information data should be integrated in the eCTD with conceptually similar drug constituent information. The data should be organized based on the following principles:

- A. Do not use "node extensions" to create new elements. Although this is described in the eCTD specification, and may be acceptable in some regions, it is not acceptable in submissions to FDA.
- B. For eCTD format and use of the electronic submission system, please adhere to eCTD headings as defined per ICH and FDA specifications. In the specifications, these may be identified as leaf nodes or elements. Specifically, any title that is associated with a numerical item should not change; i.e., Item 3.2.P.7 should say "Container Closure System."

When including and referencing device information, we recommend the following:

- a. You may reference files under 3.2.P.7, which are not currently listed as numerical items in ICH and FDA specifications and guidance.

- b. In Module 3.2.P.7, you could include a leaf titled similar to the following, “Table of Contents for Vaginal Applicator. This leaf/document could provide reference links to the other files in module 3.2.P.7.
 - c. The leaf titles should be clear, concise, and indicative of the document's content.
- C. Module 1.4.4 “Cross-reference to other applications” is a location where you can provide references to other applications and you can include copies of an application’s table of contents, reference tables, or other similar documents. If you are cross referencing another company's application or master file, include the appropriate letters of authorization from the other companies in modules 1.4.1 - 1.4.3 (1.4.1 “Letter of authorization”, 1.4.2 “Statement of right of reference”, 1.4.3 “List of authorized persons to incorporate by reference”). If there are standards you will reference in the Performance Specifications which also meet these criteria, then put them in module 1.4.4. The Performance Specifications section should link to this information.
- D. All device information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with 21CFR Part 4 and the applicable 21 CFR part 820 regulations should be located in Section 3.2.P.3.
- a. The list of manufacturing facilities provided on the Form FDA 356h, or as an attachment to the form, should explicitly describe the manufacturing, assembly, or testing processes taking place at each site involved with the device constituent part.
 - b. Suggestions on the types of documents to submit for review of required sections of 21 CFR Part 820 (based upon the combination product 21 CFR Part 4 GMP operating system at the facility) can be found in the guidance document titled “Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,” issued on February 3, 2003. The complete document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>
- E. We recommend that you provide an “Information Guide” document in Module 1.2 Cover letters. This document would be separate from the cover letter and placed after the cover letter and should provide a high level overview (with reference links) of the submission’s content and list where the information is located in the eCTD. For example, it should identify where drug, device, and combination product is located.
18. *For the NDA to be submitted should we send the application as a follow-up sequence*
 ^{(b) (4)} *NDA number?*

FDA Response:

For ease of our review, we recommend that you obtain and use a new NDA number.

19. *Does the Agency agree with this plan for the submission of datasets? Does the Agency agree with proposed NDA format and content?*

FDA Response:

Review the current version of the *Study Data Technical Conformance Guide* for conformance to FDA's current thinking on dataset logistics in order to improve and expedite the review process. All datasets need to be submitted in xpt format. For legacy raw data and analysis data, please submit define.pdf and reviewer guide with them. We strongly recommend submitting both Define.xml and Define.pdf files for standardized data (including SDTM and ADAM data), as some internal processes rely on metadata from the .xml version.

From a technical standpoint (not content related), the proposed format for the planned NDA is acceptable. However, see the following additional comments.

Providing a linked reviewer's aid/ reviewer's guide in module m1.2, as a separate document from the cover letter, to briefly describe where information can be found throughout the application, would be helpful to reviewers. For archival purposes, also submit a pdf file of the labeling document submitted in word. When you submit word documents, make sure the leaf title includes "word", so reviewers could quickly identify the word version of the document.

Do not include placeholder stating "N/A", for sections without documents (e.g. m2.1). Only provide eCTD sections that have documents.

The study STF.xml file (e.g. stf-lrem-1276.xml) should be referenced in the index.xml file but should not be submitted as a file.

Use leaf titles that are clear and indicative of the content (e.g. study report 12345, protocol 12345, or something similar).

The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5.

Cross Referencing

Your options for cross referencing information submitted to another application (if any), would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (paper and/or non- eCTD format) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic

folder, file name, etc.) of the referenced document along with a hypertext link to the location of the information, when possible.

To use the second option (cross application links), both applications would need to be in eCTD format. The applications need to include the appropriate prefix in the href links (e.g. NDA, IND). In the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross reference to" and the application number (e.g. Cross Ref to NDA XXXXXX). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application.

Prior to using cross application linking in an application, we recommend that you submit an "eCTD cross application links" sample, to ensure successful use of cross application links. To submit an eCTD cross application links sample, you would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov. For more information on eCTD sample, refer to the Sample Process web page which is located at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM315023.pdf>

Discussion:

EndoCeutics asked for clarification as to whether they would need to provide define.pdf/xml and reviewer's guide for the legacy raw data. Additionally, they asked if analysis datasets and the define.pdf have to be provided for the three pivotal studies only (ERC-230, ERC-231, and ERC-238). EndoCeutics does not intend to submit SDTM data.

The Agency clarified that EndoCeutics would need to have define.pdf for all the datasets, including raw data and analysis data. Study Data Reviewer's Guide (SDRG) and Analysis Data Reviewer's Guide (ADRG) are recommended as integral part of study data submission. EndoCeutics should describe any special considerations or directions that may facilitate an FDA reviewer's use of the submitted data and may help the reviewer understand the relationships between the study report and the data.

EndoCeutics should refer to Study Data Technical Conformance Guide at Study Data Standards Resources website.

3. DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our March 19, 2015 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to

begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation

conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

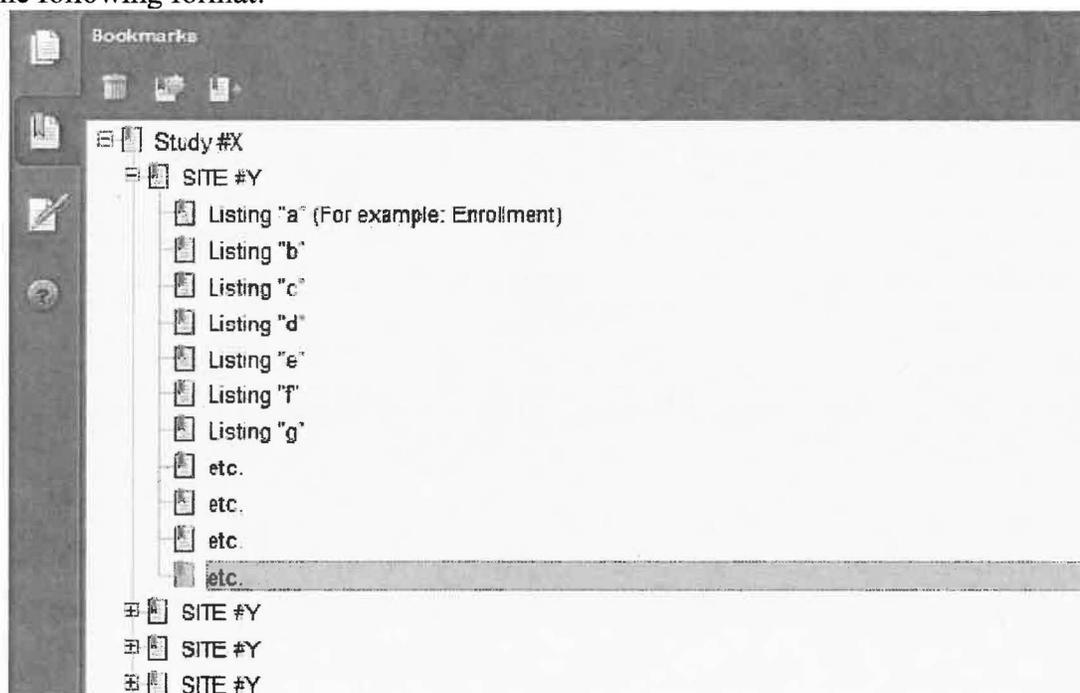
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Discussion:

EndoCeutics sought confirmation that Trials ERC-231, ERC-238 and one-year safety Trial ERC-230 are the major trials for which they would need to submit the items required by OSI.

The Agency stated the site selection tool is optional but strongly encouraged for Trials ER-231 and ER-238.

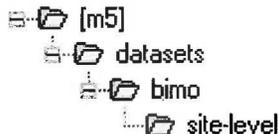
Attachment 1**Technical Instructions:****Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item⁴	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

⁴ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4. ISSUES REQUIRING FURTHER DISCUSSION

EndoCeutics asked for “priority review” for their NDA.

The Agency stated it was not prepared to address this issue at the meeting. EndoCeutics should formally submit their request for “priority review” before their NDA submission.

5. ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	May 26, 2015

6. POST-MEETING COMMENTS

The following additional comments in response to Question 16.a. were provided by CDRH after the meeting.

The referenced documents are not sufficient to fully characterize the proposed applicators. For both proposed applicators, provide the following information:

- A dimensioned engineering drawing of the applicator.

- The material composition of the applicator, including any colorants. Certain colorants are toxic (e.g., mutagens, carcinogens, etc.), and they may require additional biocompatibility/toxicity evaluation and/or be subject to specific regulations (e.g., 21 CFR 73). Therefore, if the applicator contains any colorants, then please provide the following information for those colorants:
 - chemical name and the Chemical Abstract Services (CAS) number of each colorant in the formulation;
 - purity level of colorant;
 - estimated absolute amount of colorant (in weight) per device;
 - Material Safety Data Sheet (MSDS) for each colorant;
 - identification of other US-marketed medical devices by device name, manufacturer, submission no., where the colorants have been previously used, if known;
 - toxicity risk assessment of this colorant that is preferably based on the eluted amount of colorant from your device under intended use, instead of the absolute total amount of the colorant; and
 - whether the colorant is subject to a specific FDA regulation (if known).
- The applicator will contact the vaginal mucosa of patients for a limited contact duration (i.e., ≤ 24 hours); therefore, per ISO 10993-1:2009, the cytotoxicity, sensitization, and vaginal irritation potential of the applicator should be assessed. Provide the protocol and results of the following biocompatibility testing conducted on the final, finished version of the applicator. For these tests, evaluate both polar and non-polar extracts of the applicator as described in ISO 10993-12:2012.
 - Cytotoxicity per ISO 10993-5:2009;
 - Guinea Pig Maximization Sensitization per ISO 10993-10:2010; and
 - Vaginal irritation per ISO 10993-10:2010.

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

/s/

SHELLEY R SLAUGHTER
05/20/2015