

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208470Orig1s000**

**OTHER REVIEW(S)**

**505(b)(2) ASSESSMENT**

<b>Application Information</b>		
NDA # 208470	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: INTRAROSA™ Established/Proper Name: prasterone Dosage Form: inserts, intravaginal Strengths: 6.5 mg		
Applicant: Endoceutics Inc.		
Date of Receipt: October 16, 2015		
PDUFA Goal Date: November 16, 2016	Action Goal Date (if different):	
RPM: Kim Shiley		
Proposed Indication(s): Treatment of moderate to severe dyspareunia, a symptom of vulvovaginal atrophy due to menopause		

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published literature	<i>Nonclinical toxicology Section 13.1 of labeling</i>

\*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature<sup>1</sup>. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The Sponsor is relying on published literature that describes the carcinogenic effects of estrogen and testosterone. There are no long-term studies in animals evaluating the carcinogenic potential of prasterone. Prasterone is converted to estradiol and testosterone in the vagina, raising the local concentration of these hormones, with very little prasterone reaching the systemic circulation. Multiple studies show estradiol and testosterone are carcinogenic in animals; e.g. 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). The literature does not describe branded drugs. The carcinogenic risk from the literature is communicated in the prasterone label.

The data described in the submitted literature is scientifically relevant to the proposed product because the studies evaluate the two predominant and active metabolites of the active pharmaceutical ingredient in the Sponsor’s drug product, and the doses used in the reported animal studies are scientifically relevant to the proposed human dose.

**RELIANCE ON PUBLISHED LITERATURE**

<sup>1</sup>For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES  NO

*If "NO," proceed to question #5.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If "NO," proceed to question #5.*

*If "YES", list the listed drug(s) identified by name and answer question #4(c).*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

<sup>1</sup>For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES  NO

If “**YES**”, please list which drug(s) and answer question d) i. below.  
If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

***(Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

If “**NO**” to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent? N/A  YES  NO

If this application relies only on non product-specific published literature, answer "N/A"  
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO   
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)? N/A  YES  NO

If this application relies only on non product-specific published literature, answer "N/A"  
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

**PATENT CERTIFICATION/STATEMENTS**

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed  proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR

314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]? YES  NO

*If "NO", please contact the applicant and request the signed certification.*

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt. YES  NO

*If "NO", please contact the applicant and request the documentation.*

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

*Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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/s/  
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KIMBERLY A SHILEY  
11/16/2016

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: November 8, 2016

To: Hylton Joffe, MD  
Director  
**Division of Bone, Reproductive and Urologic Products (DBRUP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Marcia Williams, PhD  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Karen Dowdy, RN, BSN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Lynn Panholzer, PharmD  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)

Drug Name (established name): INTRAROSA (prasterone)

Dosage Form and Route: vaginal inserts

Application Type/Number: NDA 208470

Applicant: EndoCeutics Inc.

## 1 INTRODUCTION

On October 16, 2015, EndoCeutics Inc. submitted for the Agency's review New Drug Application (NDA) 208470 for INTRAROSA (prasterone) vaginal inserts with the proposed indication for the treatment of moderate to severe dyspareunia (or pain at sexual activity), a symptom of vulvovaginal atrophy due to menopause.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Bone, Reproductive and Urologic Products (DBRUP) on December 1, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for INTRAROSA (prasterone) vaginal inserts.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and DMEPA deferred to DMPP to provide IFU review comments.

## 2 MATERIAL REVIEWED

- Draft INTRAROSA (prasterone) vaginal inserts PPI received on October 16, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on November 4, 2016.
- Draft INTRAROSA (prasterone) vaginal inserts PPI received on October 16, 2015, revised by the Review Division throughout the review cycle, and received by OPDP on November 7, 2016.
- Draft INTRAROSA (prasterone) vaginal inserts IFU received on October 16, 2015 and received by DMPP on November 4, 2016.
- Draft INTRAROSA (prasterone) vaginal inserts IFU received on October 16, 2015 and received by OPDP on November 7, 2016.
- Draft INTRAROSA (prasterone) vaginal inserts Prescribing Information (PI) received on October 16, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 4, 2016.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU documents using the Arial font, size 10.

In our collaborative review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- The enclosed IFU review comments are collaborative DMPP and DMEPA.

#### **4 CONCLUSIONS**

The PPI and IFU are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI or IFU.

Please let us know if you have any questions.

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/s/  
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KAREN M DOWDY  
11/08/2016

LYNN M PANHOLZER  
11/08/2016

LASHAWN M GRIFFITHS  
11/08/2016

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** November 8, 2016

**To:** Kimberly Shiley  
Regulatory Project Manager  
Division of Bone, Reproductive and Urologic Products (DBRUP)

**From:** Lynn Panholzer, Pharm.D.  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** INTRAROSA (prasterone) vaginal inserts  
NDA 208470  
Labeling Consult Review

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### Background

This consult review is in response to DBRUP's December 1, 2015, request for OPDP's review of the draft package insert (PI), patient package insert (PPI), instructions for use (IFU), and carton/container labeling for INTRAROSA (prasterone) vaginal inserts.

OPDP reviewed the substantially complete version of the draft PI and carton/container labels sent from DBRUP via email on November 4, 2016. Our comments on the PI and carton/container labels are included directly on the attached copies of the labeling and labels. Our review of the PPI and IFU will be conducted jointly with the Division of Medical Policy Programs and filed under separate cover.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Lynn Panholzer at 301-796-0616 or [lynn.panholzer@fda.hhs.gov](mailto:lynn.panholzer@fda.hhs.gov).

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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

**Date:** September 23, 2016  
**From:** Sharon M. Andrews  
Biomedical Engineer/Branch Chief, CDRH/ODE/DRGUD/OGDB  
**Subject:** NDA 208,470 – Prasterone Vaginal Insert (EndoCeutics, Inc.)  
CDRH Consult Review  
**To:** Thao Vu  
Pharmacist, CDER/OPQ/OPRO/DRBPMI/RBPMBI

### **I. Background & Scope of Review**

EndoCeutics, Inc. (hereafter referred to as “the sponsor”) submitted NDA 208,470 for the Prasterone Vaginal Insert, also known as Intrarosa™, (hereafter referred to as “the drug product”). The drug product is indicated for “treatment of moderate to severe dyspareunia (or pain at sexual activity), a symptom of vulvovaginal atrophy due to menopause.” It is placed intra-vaginally using an applicator. The drug product and the applicator are considered a drug-device combination product.

The scope of this review is limited to a review of the vaginal applicator that is used to deliver the drug product.

### **II. Applicator Description**

The vaginal applicator is made of (b) (4) and includes a (b) (4). The applicator is manufactured by (b) (4). The sponsor provided a right of reference letter from the applicator manufacturer to Drug Master File (b) (4).

The applicator consists of an applicator body and a plunger. Both the applicator body and applicator plunger are made of (b) (4). The applicator body is 4.58 inches long and has an outer diameter of 0.405 inches at the widest part. The applicator plunger has a length of 4.745 inches. The sponsor provided dimensioned engineering drawings of the applicator body and plunger.

Seven applicators each are packaged in four (b) (4) packs. The four packs are packaged in a cardboard box containing 28 suppositories.

The drug product sits inside the distal end of the applicator body. The applicator plunger telescopes from the applicator body and pushes the drug product into the vagina.

### **III. Applicator Biocompatibility**

The sponsor did not conduct biocompatibility testing on the applicator as requested in IND 78,027. As stated in my review of the IND, the sponsor believes that biocompatibility testing on the applicator is not needed for the following reasons:

- The applicator has been used during clinical trials of more than 2000 women, including 435 women who used it daily for twelve months. The sponsor states that no adverse events have been reported related to the applicator and that physicians reported no observations related to the applicator from vaginal examinations performed during clinical trials.

- The sponsor states that the usability assessment of the device in 373 women did not report adverse events related to the applicator.
- The applicator has a short duration of patient contact, (i.e., few seconds).
- The sponsor provided a letter from the applicator manufacturer stating that similar applicators (same material and colorant and manufacturing process) have been used in other currently marketed vaginal applicators.

Based on the short duration of contact of the applicator and its favorable marketing history, I agree with the sponsor that no further biocompatibility testing is warranted. However, I will note that because of the subsequent changes made to the applicator (described in Section V of this review memo), the clinical studies are not a relevant to support biocompatibility.

#### **IV. Applicator Shelf Life**

The applicator is single use only and is not reusable.

The sponsor did not propose a shelf life for the applicator. A shelf life is not applicable to the applicator because it is provided and used non-sterile and has no functional requirements that are expected to change as a result of aging or storage conditions.

CDRH has not typically required a shelf life for vaginal applicators.

#### **V. Applicator Mechanical Performance**

While the NDA was under review, the sponsor stated that they had made changes to the applicator used in the clinical studies. As a result of these changes, we asked the sponsor in a July 14, 2016 IR letter to 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.). In a response, the sponsor described additional changes to the applicator, including minor changes to the (b) (4) colorant, surfaces changes to the applicator, etc. I agree with the sponsor that the changes made to the applicator are generally minor and likely not to lead to an increase in vaginal morbidity. However, more significantly, I noted that the new applicator incorporates much less (b) (4) compared to the first applicator proposed in the NDA. This is evidenced by the decrease in applicator weight from (b) (4) 3.7 g. I was concerned that the new applicator may be more “flimsy.” To that end, we asked the sponsor in an IR letter dated September 1, 2016 to 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.

In response, the sponsor stated that the designs of the applicator used in the clinical trials and the newly proposed applicator are similar enough to meet the requirement of the practical use of the applicator. They also stated that the reduction of material is unlikely to cause a failure since the use of the applicator requires little force for penetration into the vagina and the dispensing of the medical product requires minimal force to expel the insert.

I accept the sponsor’s response, and based on the information provided on the applicator in totality, I do not have any safety or effectiveness concerns. My view is primarily based on the straight forward nature of the design and my review of samples of the newest version of the applicator. I believe the samples provided indicate that the applicator is sufficiently robust for its intended use and comparable to other marketed vaginal applicators.

VI. **Recommendation**

I have no additional comments/concerns and recommend approval of the applicator.

Sharon M. Andrews -S  
2016.09.23 16:15:17 -04'00'

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THAO M VU  
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/s/  
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LYNN M PANHOLZER  
11/08/2016

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**LABEL, LABELING AND USE RISK ANALYSIS REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** July 22, 2016  
**Requesting Office or Division:** Division of Bone, Reproductive, and Urologic Products  
**Application Type and Number:** NDA 208470  
**Product Name and Strength:** Intrarosa (Prasterone) Vaginal Insert  
6.5 mg  
**Product Type:** Combination Product  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Endoceutics  
**Submission Date:** October 16, 2015  
**OSE RCM #:** 2015-2644  
**DMEPA Primary Reviewer:** Denise V. Baugh, PharmD, BCPS  
**Acting DMEPA Team Leader:** Lolita White, PharmD  
**DMEPA Deputy Director:** Lubna Merchant, PharmD, MS

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## 1 REASON FOR REVIEW

This review is in response to a request from the Division of Bone, Reproductive, and Urologic Products (DBRUP) to evaluate the blister label, carton labeling and prescribing information (PI) for Intrarosa (prasterone), NDA 208470 for vulnerabilities to medication errors. Additionally, this review evaluates Endoceutic's use related risk analysis submitted on October 16, 2015 and their conclusion that no human factors (HF) validation study is needed for the proposed product.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Endoceutics is proposing the combination product Intrarosa (prasterone) vaginal insert used in the treatment of moderate to severe dyspareunia, a symptom of vulvovaginal atrophy due to menopause. The vaginal inserts are placed intravaginally with the supplied applicator. The dose is one vaginal insert self-administered once daily at bedtime. The sponsor submitted carton labeling, blister label, PI and a use related risk analysis as part of this supplement.

## Use Related Risk Analysis Assessment

In response to our request for a use related risk analysis, Endoceutics submitted an article<sup>1</sup> which summarizes the findings from a patient questionnaire on product use submitted as part of a clinical study (titled “ERC-228”) to provide evidence that no human factors validation study is needed. The article describes the sponsor’s analysis of the data received from the patient questionnaire and how this data is used to estimate potential risk of use error and hazards. In the article, the participant questionnaire identified four potential use related risks which may occur with this combination product, however no unique or new risks were identified with the proposed Intrarosa combination product when compared to similar products available on the market.

Additionally, the Applicant states that their applicators are similar to those used with similar products (e.g., Premarin cream, Monistat and Vagifem) currently marketed and there is a low risk of medication errors associated with their use. Specifically, Intrarosa and Monistat are both inserted vaginally, share the same patient population, are administered via an applicator and have similar use tasks. Although Premarin Cream (NDA 020216) is available in a different dosage form, the indication, user population and user tasks are identical or very similar to that for Intrarosa.

Based on the data submitted from the patient questionnaire, the analysis of the identified use related risks and the comparison with similar products available on the market with no use related safety concerns, the applicant concludes that no HF validation study is needed.

We evaluated the applicants identified use tasks and use related risk analysis.. We agree that the proposed product is similar to already approved products and are not aware of any safety concerns with the existing products. Thus, we agree with Endoceutic’s conclusion that a HF validation study is not needed.

In a follow-up application review meeting, the clinical review team expressed concerns that changes to the ‘to-be-marketed’ device may pose a risk for vaginal injury and may require further validation. Specifically, the clinical team leader is concerned with the potential for damage to the vaginal wall with the modified applicator. DMEPA was asked to evaluate the appropriateness of a human factors (HF) study to address this concern. Although we acknowledge that modifications were made to the ‘to-be-marketed’ device, we determined that the concern with the potential for damage to the vaginal wall with the modified applicator

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<sup>1</sup> Montesino M, Labrie F, Archer, D et al. Evaluation of the acceptability of intravaginal prasterone ovule administration using an applicator. *Gynecol Endocrinol*, 2016:32(3): 240-245.

cannot be assessed via a simulated human factor study as these studies are designed to identify use-related issues and not adverse events. DMEPA conveyed this information via e-mail to the review team on June 15, 2016. We recommended the review team consider asking the Applicant to provide evidence that the modifications made to the applicator would not cause vaginal damage and evaluate their response. We defer to the division to request additional information from the Sponsor to alleviate concern of vaginal injury.

#### Blister Label and Carton Labeling Assessment

We reviewed the blister label, carton labeling and PI for risk of medication error and identified areas of improvement within the carton labeling and blister label to ensure product identification and increase readability. See Section 4.1 for our recommendations.

### **4 CONCLUSION & RECOMMENDATIONS**

Based upon the use risk analysis and the comparison of similar approved products on the market, we agree with the Applicant that a HF Validation Study is not required. However, based upon our review of the PI labeling, blister label and carton labeling, we find areas that can be revised to improve the presentation of drug identifying information, promote consistency and to increase readability. See Section 4.1 for specific recommendations.

#### **4.1 RECOMMENDATIONS FOR ENDOCEUTICS**

We recommend the following be implemented prior to approval of this NDA:

##### A. General Comments (Outer and Inner Carton Labeling)

1. The term 'insert' is the correct dosage form for this product. We recommend you revise the statement (b) (4) to read 'insert' wherever it appears on the carton labeling to be correctly state the approved dosage form and to be consistent with the prescribing information.
2. Increase the color contrast to improve readability of the established name and dosage form. The current presentation of the established name (prasterone) and dosage form (vaginal (b) (4)) is difficult to read because this information is stated in light pink font on a white background.
3. Revise the term (b) (4) to read 'usual dose' in accordance with 21 CFR 201.55.
4. To decrease risk of medication error with product identification, we request you add the product barcode to each individual carton and to increase

readability, we recommend you ensure that the barcode is surrounded by sufficient white space to allow scanners to read the bar code properly as required per 21 CFR 201.25(c)(2). Ensure that the bar code is placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation). The drug barcode is often used as an additional verification before drug administration and therefore it is an important safety feature that should be part of the label whenever possible.

## B. Blister Label

1. The term 'insert' is the correct dosage form for this product. We recommend you revise the statement (b) (4) to read 'insert' wherever it appears on the blister label to correctly state the approved dosage form and to be consistent with the prescribing information.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Intrarosa that Endoceutics submitted on March 30, 2016.

<b>Table 2. Relevant Product Information for intrarosa</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	prasterone
<b>Indication</b>	Treatment of moderate to severe dyspareunia, a symptom of vulvovaginal atrophy due to menopause
<b>Route of Administration</b>	intravaginal
<b>Dosage Form</b>	insert
<b>Strength</b>	6.5 mg
<b>Dose and Frequency</b>	One insert intravaginally once daily preferably at bedtime
<b>How Supplied</b>	Each blister pack has 7 inserts each and there are four blister packs in one carton (for a total of 28 inserts). A smaller box containing the (b) (4) is presented inside a larger box containing 28 applicators.
<b>Storage</b>	5°C to 30°C (41°F to 87°F); Can be refrigerated

## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

On June 3, 2016, we searched the L:drive and AIMS using the terms, “prasterone” to identify reviews previously performed by DMEPA.

### **B.2 Results**

Our search identified no previous reviews relevant to this review.

## **APPENDIX C. HUMAN FACTORS STUDY**

Not applicable.

**APPENDIX D. ISMP NEWSLETTERS**

Not applicable

**APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)**

Not applicable

**APPENDIX F. OTHER SOURCE**

Not applicable.

## APPENDIX G. LABELS AND LABELING

### G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>2</sup> along with postmarket medication error data, we reviewed the following Intrarosa labels and labeling submitted by Endoceutics on October 16, 2015.

- Carton labeling (referred to in the submission as “Big Box” and “Small Box”)
- Instructions for Use-no image
- Medication Guide-no image
- Prescribing Information (no image; submitted March 30 2016)
- Blister Labels

### G.2 Label and Labeling Images



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

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<sup>2</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/  
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DENISE V BAUGH  
07/22/2016

LOLITA G WHITE  
07/22/2016

LUBNA A MERCHANT  
07/22/2016

## Clinical Inspection Summary

<b>Date</b>	July 7, 2016
<b>From</b>	Roy Blay, Ph.D., Reviewer, GCPAB\OSI Janice K. Pohlman, M.D., M.P.H., Team Leader, GCPAB\OSI Susan D. Thompson, M.D., acting Branch Chief for Kassa Ayalew, M.D., M.P.H., Branch Chief, GCPAB\OSI
<b>To</b>	DBRUP\Project Manager\Kim Shiley DBRUP\Medical Officer\Theresa van der Vlugt DBRUP\Team Leader\Shelley Slaughter Division of Bone, Reproductive, and Urologic Products
<b>NDA/BLA #</b>	NDA 208470
<b>Applicant</b>	EndoCeutics Inc.
<b>Drug</b>	Intrarosa (prasterone )
<b>NME (Yes/No)</b>	No
<b>Therapeutic Classification</b>	Standard Review
<b>Proposed Indication(s)</b>	Treatment of moderate to severe dyspareunia (b) (4) (b) (4), a symptom of vulvovaginal atrophy due to menopause
<b>Consultation Request Date</b>	January 27, 2016
<b>Summary Goal Date</b>	July 15, 2016
<b>Action Goal Date</b>	August 16, 2016
<b>PDUFA Date</b>	August 16, 2016

### 1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Portman, Young, and Bouchard were inspected in support of this NDA and the final classification of these inspections was No Action Indicated (NAI). Based on the results of the clinical investigator inspections, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

### 2. BACKGROUND

The Applicant submitted this NDA to support the use of Intrarosa (prasterone) for the treatment of moderate to severe dyspareunia (or pain at sexual activity), a symptom of vulvovaginal atrophy due to menopause.

Protocols ERC-231, entitled “DHEA against vaginal atrophy (placebo-controlled, double-blind and randomized phase III study of 3-month intravaginal DHEA)” and ERC-238, entitled, “Intravaginal prasterone (DHEA) against vulvovaginal atrophy associated with menopause (placebo-controlled, double-blind and randomized phase III study)” were inspected in support of this application.

### **Protocol ERC-231**

The primary objective of this study was to confirm the efficacy of intravaginal DHEA on the symptoms and signs of vaginal atrophy in postmenopausal women suffering from vaginal atrophy.

This study randomized subjects in a 1:1:1 ratio to 0.25% DHEA (prasterone), 0.50% DHEA (prasterone), and placebo for a six week screening period and a 12-week treatment period. The primary endpoint was assessed at Week 12 and comprised a change in severity score of pain at sexual activity (dyspareunia) as a co-primary objective with changes in % of parabasal cells, % of superficial cells, and vaginal pH.

The study comprised 237 postmenopausal women in the ITT population. According to the sponsor, this trial confirmed the beneficial effects of intravaginal prasterone on dyspareunia and vaginal dryness.

### **Protocol ERC-238**

This protocol is very similar though not identical to Protocol ECR-231. The differences between the two, as summarized by the sponsor, include the following:

- Study ERC-231 evaluated 2 doses of prasterone, namely 0.25% (3.25 mg) and 0.50% (6.5 mg) compared to placebo in a study design in a 1: 1: 1 ratio between the 3 arms. Since one co-primary endpoint (dyspareunia) out of the 4 co-primaries did not reach statistical significance at the 0.25% prasterone dose in ERC-231, the second efficacy study, ERC-238, was conducted with only the 0.50% prasterone, the proposed dose for commercialization, and placebo.
- Study ERC-238 used a 2:1 ratio between prasterone:placebo in order to reach the total required number of subjects exposed overall to the drug product (1500 subjects). The total number of subjects enrolled in ERC-231 was smaller (255 women) than in ERC-238 (558 women).
- Study ERC-238 evaluated the usability of the vaginal applicator and the potential effect on the male partner. These two parameters were not evaluated in ERC-231.
- Study ERC-231 required endometrial biopsies at baseline and 12 weeks while Study ERC-238 required such biopsies only at baseline (as a safety assessment prior to enrollment).
- Study ERC-231 used the drug product manufactured by [REDACTED] (b) (4) while Study ERC-238 used the drug product manufactured by [REDACTED] (b) (4).

Dr. Portman's site was selected for inspection because it participated in the two primary 12-week safety and efficacy clinical trials (ERC-231 and ERC-238). In addition, Dr. Portman (Site #15) participated in the primary 52-week safety clinical trial (ERC-230). In the 12-week primary safety and efficacy Clinical Trial ERC-231, this site was ranked 4th among the top 4 sites demonstrating the largest mean change from placebo for dyspareunia severity (-1.00 for

0.50% DHEA versus -0.50 for placebo; -0.50 difference from placebo). Site #15 randomized a total of 46 subjects, reported a total of 11 discontinuations, and a total of 40 protocol deviations in the combined primary 12-week Clinical Trials ERC-231 and ERC-238.

Dr. Young's site was selected because it participated in the two primary 12-week safety and efficacy clinical trials (ERC-231 and ERC-238). In addition, Dr. Young's site (Site #21) participated in the primary 52-week safety clinical trial (ERC-230). In the 12-week primary safety and efficacy Clinical Trial ERC-238, this site demonstrated the largest mean change from placebo for dyspareunia severity (-1.76 for 0.50% DHEA versus -0.48 for placebo; -1.28 difference from placebo). Site #21 randomized a total of 52 subjects, reported a total of 9 discontinuations, and a total of 24 protocol deviations in the combined primary 12-week Clinical Trials ERC-231 and ERC-238.

Dr. Bouchard's site was selected because it participated in the two primary 12-week safety and efficacy clinical trials (ERC-231 and ERC-238). In addition, Dr. Bouchard's site (Site #02) participated in the primary 52-week safety clinical trial (ERC-230). In the 12-week primary safety and efficacy Clinical Trial ERC-238, this site was ranked 8th among the top 10 sites demonstrating the largest mean change from placebo for dyspareunia severity (-1.21 for 0.50% DHEA versus -0.59 for placebo; -0.62 difference from placebo). Site #2 randomized a total of 44 subjects, reported a total of 3 discontinuations, and a total of 21 protocol deviations in the combined primary 12-week Clinical Trials ERC-231 and ERC-238.

### 3. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
15/ David J. Portman, M.D., Columbus Center for Women's Health Research, 99 N. Brice Road, Suite 120, Columbus, OH 43213	ERC-231 and ERC 238/  22 in ERC-231 24 in ERC-238	7-17 Mar 2016	NAI
21/ Douglas Young, M.D., Northern California Research, 3840 Watt Ave., Bldg. E, Sacramento, CA 95821	ERC-231 and ERC-238/  10 in ERC-231 30 in ERC-238	9-13 May 2016	NAI
02/ Céline Bouchard, M.D., Clinique de Recherche en Santé des Femmes, 1000, chemin Ste-Foy, Suite 304, Quebec (QC) GIS 2L5, Canada	ERC-231 and ERC-238/  29 in ERC-231 15 in ERC-238	25-28 Apr 2016	NAI

### Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

#### **1. David J. Portman, M.D.**

At this site for Protocol ERC-231, 31 subjects were screened, 9 subjects failed screening, 22 subjects were enrolled, 7 subjects terminated early, and 15 subjects completed the study. For Protocol ERC-238, 44 subjects were screened, 20 subjects were screen failures, 24 subjects were enrolled, four subjects terminated early, and 20 subjects completed the study.

The records of all 31 screened subjects for Protocol ERC-231 and of 20 subjects randomized in Protocol ERC-238 were reviewed. Review of the records of these subjects for both studies included, but was not limited to, medical histories, physical examinations, randomization, laboratory assessments, endoscopy, mammography and pap smear results, adverse events, protocol deviations, IRB, sponsor, and monitor correspondence, and test article accountability and storage.

Review of these records indicated that informed consent forms were completed prior to any study-related testing. There was no evidence of under-reporting of adverse events and the primary efficacy endpoints were verifiable.

A Form FDA 483 was not issued at the conclusion of the inspection. The studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

#### **2. Douglas Young, M.D.**

At this site for Protocol ERC-231, 19 subjects were screened, 10 subjects were randomized, and 8 subjects completed the study. For Protocol ERC-238, 48 subjects were screened, 30 subjects were randomized, and 28 subjects completed the study.

The Case Report Forms (CRFs) for all 10 subjects in Protocol ERC-231 and for 12 randomly selected subjects in Protocol ERC-238 were reviewed. Review of these records included, but was not limited to, adverse events, serious adverse events, Institutional Review Board (IRB) approvals and reviews, sponsor monitoring and communications, study medication receipt, storage, and disposition, concomitant medications, personnel training, FDA 1572s, financial disclosure, protocol adherence, subject medical histories, laboratory results, physical exams, Female Sexual Function Index (FSFI), and Vaginal

Atrophy Symptoms questionnaires, and the primary efficacy endpoints of change in vaginal pain and pH.

The informed consent documents for all screened subjects for both studies were reviewed. All consent forms were completed prior to any study-related testing.

A Form FDA 483 was not issued at the conclusion of the inspection. The studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

### 3. Céline Bouchard, M.D.

At this site for Protocol ERC-231, 45 subjects were screened, 29 subjects were enrolled, and 27 subjects completed the study. For Protocol ERC-238, 42 subjects were screened, 15 subjects were randomized, and 14 subjects completed the study.

The records for all subjects screened and enrolled in Study ERC-231 were reviewed, in addition to all records for subjects enrolled in Study ERC-238. Review of these records included, but was not limited to, medical histories, physical examinations, laboratory assessments, endoscopy results, mammography and pap smear results, adverse events, protocol deviations, IRB and monitoring communications, randomization and blinding, and test article storage, administration and disposition.

The informed consent documents for all screened subjects for both studies were reviewed. All consent forms were completed prior to any study-related testing.

A Form FDA 483 was not issued at the conclusion of the inspection. The studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

*{See appended electronic signature page}*

Roy Blay, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Janice Pohlman, M.D., M.P.H.  
Team Leader,  
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Susan D. Thompson, M.D., for  
Kassa Ayalew, M.D., M.P.H  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CC:

Central Doc. Rm.\ NDA 208470  
DBRUP\Division Director\Hylton Joffe  
DBRUP\Team Leader\Shelley Slaughter  
DBRUP\Medical Officer\Theresa van der Vlugt  
DBRUP\Project Manager\Kim Shiley  
OSI\DCCE\Division Director\Ni Khin  
OSI\ DCCE\GCPAB\Branch Chief\Kassa Ayalew  
OSI\ DCCE\GCPAB\Team Leader\Janice Pohlman  
OSI\ DCCE\GCPAB\Reviewer\Roy Blay  
OSI\ DCCE\Program Analysts\Joseph Peacock\Yolanda Patague  
OSI\Database Project Manager\Dana Walters

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ROY A BLAY  
07/08/2016

JANICE K POHLMAN  
07/08/2016

SUSAN D THOMPSON  
07/08/2016



**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research**

**MEMORANDUM**

**Date:** 12/18/2015

**To:** Hylton V. Joffe, M.D., M.M.Sc.  
Division of Bone, Reproductive and Urologic Products (DBRUP)

**Through:** Michael Klein, Ph.D., Director  
Controlled Substance Staff (CSS)

**From:** Joshua Hunt, PharmD, Senior Regulatory Reviewer  
Controlled Substance Staff (CSS)

**Subject:** Consult for NDA 208470

**Description:** Prasterone (DHEA), 3 $\beta$ -hydroxy-5-androsten-17-one,  
Other Non-Proprietary Names: Dehydroepiandrosterone, DHEA,  
Dehydroisoandrosterone

**Proposed Indication:** Treatment of moderate to severe dyspareunia (b) (4)  
(b) (4) a symptom of vulvovaginal atrophy due to menopause

**Sponsor:** EndoCeutics Inc.

**Materials reviewed:** Controlled Substances Act (CSA) and Dietary Supplement Health and Education Act (DSHEA)

**Background**

DBRUP consulted CSS on 12/04/2015 to identify whether Prasterone is a controlled substance in the United States or if there are any import restrictions according to CSA.

21 CFR Part 1300 describes the definitions relating to controlled substances. Under Section 1300.01(b)(4), "*The term anabolic steroid means any drug or hormonal substance chemically and pharmacologically related to testosterone (other than estrogens, progestins, corticosteroids, and dehydroepiandrosterone)*"

DHEA is marketed as a *dietary supplement* in the United States. Due to its presence in the marketplace prior to 1994, the Dietary Supplement Health and Education Act treats DHEA as a "grandfathered" dietary ingredient under the law. The term "new dietary ingredient" means a

dietary ingredient that was not marketed in the United States in a dietary supplement before October 15, 1994. (See section 413(d) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), 21 U.S.C. 350b(d)). There is no authoritative list of dietary ingredients that were marketed in dietary supplements before October 15, 1994. Therefore, manufacturers and distributors are responsible for determining if an ingredient is a "new dietary ingredient" and, if not, for documenting either that a dietary supplement that contained the dietary ingredient was marketed before October 15, 1994, or that the dietary ingredient was marketed for use in dietary supplements before that date.

The Designer Anabolic Steroid Control Act (DASCA), which became effective on December 18<sup>th</sup> 2014, also noted that a drug or hormonal substance cannot be permanently designated as a Schedule III anabolic steroid if the drug or hormonal substance:

- Is an herb or other botanical
- Is a concentrate, metabolite, or extract of, or a constituent isolated directly from, an herb or other botanical;
- Is a combination of two or more herbs or other botanical, including a concentrate, metabolite, or extract of, or constituent isolated directly from, an herb or botanical
- Is a *dietary supplement* for purposes of the Federal Food, Drug & Cosmetic Act (21 U.S.C 301 et seq); and
- Is not anabolic or androgenic

## **Conclusions**

1. DHEA is specifically exempted from the definition of the term "anabolic steroid" as defined by the Anabolic Steroid Control Act of 1990 and 2004, which amended the CSA.
2. While all importation and exportation of any substance defined as an anabolic steroid must be in compliance with 21 CFR Part 1312, CSS finds no evidence that importation of DHEA is a violation of the CSA.

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JOSHUA S HUNT  
12/18/2015

MICHAEL KLEIN  
12/18/2015

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information	
NDA # 208470	<p>Efficacy Supplement Category:</p> <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: TBD (INTRAROSA submitted for review) Established/Proper Name: prasterone Dosage Form: insert Strengths: 6.5 mg	
Applicant: EndoCeutics Inc. Agent for Applicant (if applicable): Jann Kochel, Accenture, LLP	
Date of Application: 10-16-15 Date of Receipt: 10-16-15 Date clock started after UN:	
PDUFA/BsUFA Goal Date: 8-16-16	Action Goal Date (if different):
Filing Date: 12-15-15	Date of Filing Meeting: 12-2-2015
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input checked="" type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch	
Proposed indication(s)/Proposed change(s): treatment of moderate to severe dyspareunia [REDACTED] (b) (4), a symptom of vulvovaginal atrophy due to menopause.	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i></b> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> .	

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<b>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</b>	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<b>The application will be a priority review if:</b>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> <li>• <b>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</b></li> <li>• <b>The product is a Qualified Infectious Disease Product (QIDP)</b></li> <li>• <b>A Tropical Disease Priority Review Voucher was submitted</b></li> <li>• <b>A Pediatric Rare Disease Priority Review Voucher was submitted</b></li> </ul>	
Resubmission after withdrawal? <input checked="" type="checkbox"/> see 022463	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/>	<input checked="" type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): 078027, (b) (4)

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system?  <b>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system?  <b>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If yes, explain in comment column.</b>				
<b>If affected by AIP, has OC been notified of the submission?</b> <b>If yes, date notified:</b>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a></i> ): <input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application a 505(b)(2) NDA? ( <i>Check the 356h form,</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

cover letter, and annotated labeling). <b>If yes</b> , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>		
<b>Check the Electronic Orange Book at:</b> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a>					
<b>If yes</b> , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>	
Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
<b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>If yes</b> , # years requested: 5					
<b>Note:</b> An applicant can receive exclusivity without requesting it;					

<i>therefore, requesting exclusivity is not required.</i>				
<b>NDAs only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>If yes,</b> did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i>  <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<b>Format and Content</b>				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission,</b> which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission,</b> does it follow the eCTD guidance? <sup>1</sup> <b>If not,</b> explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		1.2 Reviewer Guide
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no</b> , explain.				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>If yes</b> , BLA #				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Updated 10-21-15
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Signed by Claude Dore, VP Finance, EndoCeutics, Inc.
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Sent consult 12-4-2015 (per AG request) to confirm that prasterone is <u>NOT</u> a CS in the US. Also asked if there are any import restrictions according to CSA.
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b>  Does the application trigger PREA?  <i>If yes, notify <a href="mailto:PeRC@fda.hhs.gov">PeRC@fda.hhs.gov</a> to schedule required PeRC meeting<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Per PeRC, send consult after mid-cycle meeting. (Full waiver per Agreed iPSP)

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

Version: 7/10/2015

7

<i>trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
<b>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<b>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Full waiver
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<b><u>BPCA:</u></b>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>				
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult submitted
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

4

	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>For applications submitted on or after June 30, 2015:</b> Is the PI submitted in PLLR format? <sup>5</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3 Females and Males of 24 Reproductive Potential of the USE IN SPECIFIC POPULATIONS missing
Has a review of the available pregnancy and lactation data been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Limited review
<b>For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Submitted
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	No REMS
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Submitted
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

5

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 4-27-2015	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 12-2-2015

**BACKGROUND:**

(b) (4)  
 EndoCeutics withdrew that application prior to the filing date. Since then, (b) (4) application have been performed under IND 078027. This New Drug Application (NDA) for Prasterone Vaginal insert is submitted for the indication “Treatment of moderate to severe dyspareunia (or pain at sexual activity), a symptom of vulvovaginal atrophy due to menopause.”

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kim Shiley	Y
	CPMS/TL:	Margie Kober	N
Cross-Discipline Team Leader (CDTL)			
Division Director/Deputy	Hylton Joffe/Audrey Gassman		N/Y
Office Director/Deputy	Julie Beitz/Amy Egan		N/N
Clinical	Reviewer:	Theresa van der Vlugt	Y
	TL:	Shelley Slaughter	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Jihong Shon	Y
	TL:	MJ Kim	Y

• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Kate Dwyer	Y
	TL:	Mahboob Sobhan	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Kim Hatfield/Leslie McKinney	Y/Y
	TL:	Lynnda Reid	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Mark Seggel	Y
	RBPM:	Thao Vu	Y
• Drug Substance	Reviewer:	Erika Englund/Donna Christner	N/N
• Drug Product	Reviewer:	Caroline Strasinger	N
• Process	Reviewer:	Jingbo Xiao/Yubing Tang	N/N
• Microbiology	Reviewer:	Jingbo Xiao/Yubing Tang	N/N
• Facility	Reviewer:	Sherry Shen	N
• Biopharmaceutics	Reviewer:	Kalpana Paudel/Kelly Kitchens	Y/Y
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer) Toxicology	Reviewer:	James Laurenson	Y
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Karen Dowdy	N
	TL:	Marcia Britt Williams	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Lynn Panholzer	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Denise Baugh	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:	Donella Fitzgerald	N
	TL:	Kimberly Lehrfeld	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Roy Blay	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
CDRH	Reviewer:	Sharon Andrews	Y
	TL:		
Other attendees	Patricia Love		Y
	Nneka McNeal-Jackson		Y
	Bindi Nikhar		Y
	Robin Duer		Y

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505 b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	<input type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no,</b> explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments

<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b> 505(b)(2) comments</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b><u>New Molecular Entity</u> (NDAs only)</b></p> <ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Review issues for 74-day letter
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<input checked="" type="checkbox"/> N/A  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Audrey Gassman, M.D.	
<b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): n/a	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):	
<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
<b>ACTION ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/> n/a	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/> n/a	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/> n/a	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/> n/a	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRA completed: September 2014

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KIMBERLY A SHILEY  
12/21/2015

MARGARET M KOBER  
12/22/2015

# REGULATORY PROJECT MANAGER PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**Application:** NDA 208470

**Application Type:** New NDA

**Drug Name(s)/Dosage Form(s):** INTRAROSA (prasterone), vaginal insert

**Applicant:** EndoCeutics Inc.

**Receipt Date:** 10-16-2015

**Goal Date:** 8-16-2016

## 1. Regulatory History and Applicant's Main Proposals

[REDACTED] (b) (4)  
[REDACTED] (b) (4)  
[REDACTED] . Since then, [REDACTED] (b) (4)  
[REDACTED] application have been performed under IND 078027. This New Drug Application (NDA) for Prasterone Vaginal insert is submitted for the indication "Treatment of moderate to severe dyspareunia (or pain at sexual activity), a symptom of vulvovaginal atrophy due to menopause."

## 2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

## 3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by January 19, 2016. The resubmitted PI will be used for further labeling review.

# Selected Requirements of Prescribing Information

## 4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

### Highlights

See Appendix for a sample tool illustrating Highlights format.

#### HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

**Comment:**

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

**Comment:**

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
  - TOC from the Full Prescribing Information (FPI).

**Comment:**

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

**Comment:**

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

**Comment:** *No white space present before each major heading.*

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:**

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required

## Selected Requirements of Prescribing Information

• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

**Comment:**

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

**Comment:**

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

**Comment:**

#### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:**

#### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

**Comment:**

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS**”

## Selected Requirements of Prescribing Information

**INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

**Comment:**

- N/A** 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning.***" This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

**Comment:**

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

**Comment:**

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

**Comment:**

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

**Comment:**

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

**Comment:**

### Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

**Comment:**

### Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

**Comment:**

## Selected Requirements of Prescribing Information

### Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

*Comment:*

### Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

*Comment:*

### Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

*Comment:*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.  
*Comment:*
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].  
*Comment:*
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS\***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Lactation</b> (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
<b>8.3 Females and Males of Reproductive Potential</b> (if not required to be in PLLR format, use "Nursing Mothers")
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- NO** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*].”

**Comment:** *No cross-references in FPI.*

## Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

*Comment:*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

*Comment:*

#### BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

*Comment:*

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

*Comment:*

#### CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

*Comment:*

#### ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

*Comment:*

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

*Comment:*

## Selected Requirements of Prescribing Information

### PATIENT COUNSELING INFORMATION Section in the FPI

- NO** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
  - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
  - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
  - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
  - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

***Comment:*** IFU incorrectly provided as 17.2; incorrect statement; should be option (Patient Information and Instructions for Use and not (Patient Information).

- NO** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

***Comment:*** IFU included as subsection 17.2

# Selected Requirements of Prescribing Information

## Appendix: Highlights and Table of Contents Format

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

**PROPRIETARY NAME** (non-proprietary name) dosage form, route of administration, controlled substance symbol  
Initial U.S. Approval: YYYY

#### WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

#### RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y  
Section Title, Subsection Title (x.x) M/201Y

#### INDICATIONS AND USAGE

**PROPRIETARY NAME** is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

#### DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

#### DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

#### CONTRAINDICATIONS

- Text (4)
- Text (4)

#### WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

#### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

#### USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

### FULL PRESCRIBING INFORMATION: CONTENTS\*

#### WARNING: TITLE OF WARNING

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

#### 6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

#### 7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

#### 9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\* Sections or subsections omitted from the full prescribing information are not listed.

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/s/  
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KIMBERLY A SHILEY  
12/18/2015

MARGARET M KOBER  
12/21/2015