

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208470Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

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

Date: November 16, 2016

From: Mark R. Seggel, Ph.D.
Application Technical Lead
Office of New Drug Products
Branch V/DNDP II

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Office of New Drug Products
Branch V/DNDP II

To: OPQ IQA #1 of NDA 208470

Subject: Final Recommendation - APPROVAL

The OPQ Integrated Quality Assessment (IQA) #1, dated October 20, 2016, concluded that this 505(b)(2) NDA was Not Ready for Approval in its present form per 21 CFR 314.125(b)(8). Specifically, it was noted that labeling (package insert, container/carton) negotiations had not been completed, and in its present form, the labeling did not comply with the requirements under 21 CFR 201.

The NDA was otherwise complete and adequate from the OPQ perspective.

On November 16, 2016 the NDA review team agreed to the labels and labeling as documented in Attachment 1 of this review.

As revised, all information required under 21 CFR 201 is adequately presented. The storage statement has been revised throughout for completeness and consistency. The labels and labeling will include the statement: Manufactured for Endoceutics Inc., Quebec City, Canada, G1V 4M7, rather than having multiple versions covering product (vaginal inserts) manufactured by (b) (4)

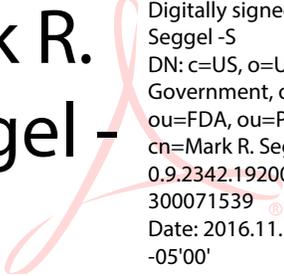
Recommendation:

This NDA is now recommended for **Approval** from the OPQ perspective.

Application Technical Lead Signature:

Mark R. Seggel, Ph.D.
CMC Lead (acting)

Mark R.
Seggel -
S



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Attachment 1:

1. Package Insert

(a) “Highlights” Section

INTRAROSA™
INTRAROSA™ (prasterone) vaginal inserts
Initial U.S. Approval: 2016

INDICATIONS AND USAGE

INTRAROSA™ is a steroid indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. (1)

DOSAGE AND ADMINISTRATION

One vaginal insert, once daily at bedtime. (2)

DOSAGE FORMS AND STRENGTHS

Vaginal Insert: 6.5 mg of prasterone. (3)

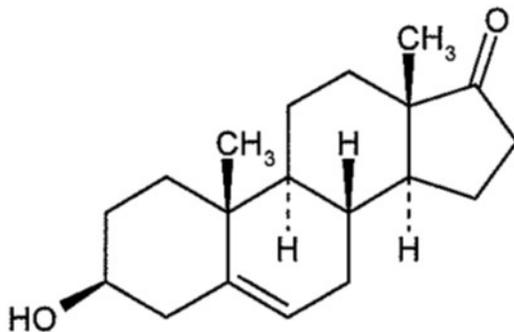
(b) “Full Prescribing Information” Section

#3. Dosage Form and Strength

Vaginal insert: 6.5 mg of prasterone, smooth, white to off-white solid fat bullet-shaped, measuring 28 mm in length, 9 mm in width at its wider end, and weighing 1.2 gram.

#11. Description

INTRAROSA (prasterone) vaginal insert is a vaginally administered steroid. Prasterone is identified chemically as 3β-hydroxyandrost-5-en-17-one. It has the empirical formula C₁₉H₂₈O₂ with a molecular weight of 288.424 g/mol. Prasterone is a white to off-white crystalline powder insoluble in water and soluble in sodium lauryl sulfate (SLS). The structural formula is:



Each INTRAROSA (prasterone) vaginal insert contains 6.5 mg of prasterone in 1.3 ml of off-white hard fat (Witepsol).

#16 How Supplied/Storage and Handling

16.1 How Supplied

INTRAROSA is supplied as white to off-white 1.3 mL solid fat bullet-shaped, smooth vaginal inserts (containing 6.5 mg of prasterone). INTRAROSA is available in small boxes of 4 blister packs containing 7 vaginal inserts (28 vaginal inserts per box). The small box (containing the vaginal inserts) is supplied inside a larger box containing 28 applicators (NDC 69110-001-01).

16.2 Storage and Handling

Store at 41°F to 86°F (5°C to 30°C). Can be stored at room temperature or in the refrigerator.

Manufactured for:
Endoceutics Inc.
Quebec City, Canada, G1V 4M7

© Endoceutics Inc.

Patient Package Insert

[Redacted content] (b) (4)

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



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Seggel

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Recommendation: *As of this review, this 505(b)(2) NDA is Not Ready for Approval in its present form per 21 CFR 314.125(b)(8).*

NDA 208470 Review #1

Drug Name/Dosage Form	Intrarosa™(prasterone) vaginal insert
Strength	6.5 mg
Route of Administration	Vaginal
Rx/OTC Dispensed	Rx
Applicant	EndoCeutics Inc.
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original (0000)	10/16/15	Multi-discipline
Amendment (0003)	12/08/15	“
Amendment (0004)	01/05/16	Drug substance
Amendment (0005)	02/12/16	Product; Facilities
Amendment (0006)	03/10/16	Multi-discipline
Amendment (0007)	03/16/16	Facilities
Amendment (0008)	03/23/16	Product
Amendment (0009)	03/24/16	Multi-discipline
Amendment (0011)	04/01/16	Multi-discipline
Amendment (0014)	05/03/16	Product; Process
Amendment (0019)	06/02/16	Product; Process
Amendment (0021)	06/28/16	Product; Process
Amendment (0024)	07/15/16	Product; Process
Amendment (0026)	08/08/08	CDRH
Amendment (0027)	08/12/16	Multi-discipline
Amendment (0028)	09/09/16	CDRH
Amendment (0029)	09/30/16	Facilities

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION / BRANCH
Drug Substance	Erika Englund	ONDP / New Drug API / Br. II
Drug Product	Caroline Strasinger	ONDP / DNDP II / Br. V
Process	Jingbo Xiao	OPF/DP/II/PABV
Microbiology	Jingbo Xiao	OPF/DP/II/PABV
Facility	Sherry Shen	OPF / DIA / Br. III
Biopharmaceutics	Kalpana Paudel	ONDP / DB / Br. II



CHEMISTRY REVIEW



Regulatory Business Process Manager	Thao Vu	OPRO / DRBPM I / Br I
Application Technical Lead	Mark Seggel	ONDP / DNDP II / Br. V
Environmental Assessment (EA)	James Laurenson	ONDP / EA Team
Laboratory (OTR/DPA)	Michael Hadwiger	OPQ/OTR/DPA

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	05/31/16	-
	Type II			-		DMF no longer active
	Type III			-		See NDA review
	Type III			-		See NDA review
	Type III			-		See CDRH-ODE review
	Type IV			Adequate	02-JUN-2016	-
	MAF			-		See CDRH review

* PRODUCTOS QUÍMICOS NATURALES SA DE CV

B. Other Documents: IND, RLD, or sister applications

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	78027	EndoCeutics ; Prasterone for vaginal atrophy, dyspareunia
(b) (4)		

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/ Toxicology	N/A			
CDRH-ODE	Completed	Approval	09/23/16	Sharon Andrews
CDRH-OC	Completed	Approval	10/03/16	Katelyn Bittleman, Francisco Vicenty
Other	N/A			

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

In its present form, EndoCeutics' 505(b)(2) New Drug Application #208470, for Intrarosa (prasterone) vaginal inserts, 6.5 mg per insert, is not ready for approval. Labeling (package insert, container/carton) negotiations have not been completed, and in its present form, the labeling does not comply with the requirements under 21 CFR 201.

Sufficient information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product. The drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status.

As a drug-device combination product, the device component (inserter) was reviewed by both CDRH-ODE and CDRH-OC. This NDA, as amended, is recommended for approval by both CDRH-ODE and CDRH-OC.

When manufactured as described in the amended NDA, prasterone vaginal inserts present minimal risks associated with product quality to the patients, who may benefit from this novel approach to the treatment of moderate to severe dyspareunia due to vulvovaginal atrophy associated with menopause.

An addendum to this review will be filed upon receipt and review of revised labeling.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable

II. Summary of Quality Assessments

Note: Although previously marketed as a dietary supplement, prasterone (dehydroepiandrosterone, DHEA) was initially considered a New Molecular Entity (NME) because there are no approved drug products or legally marketed prasterone drug products (i.e., those making drug claims). However, it subsequently determined that prasterone is not an NME. Office of Compliance records indicate that prasterone has been unlawfully marketed as a drug product. (See Dr. Norman Schmuff's memo dated 12/21/2015 for details.)

A. Drug Substance [prasterone] Quality Summary

Prasterone is an inactive endogenous steroid that is a precursor to androgens and estrogens. More commonly prasterone is known as DHEA (dehydroepiandrosterone), a widely promoted dietary supplement.

Prasterone is isolated as a white to yellowish white powder with a melting range of 146 to 151°C. It is practically insoluble in water, (b) (4)

The solubility of prasterone in Witepsol (W) (Hard Fat, NF), the only excipient present in the drug product, (b) (4)

The drug substance specification includes tests, and suitable acceptance criteria, to ensure the identity, quality, purity and potency of prasterone API.

A retest period (b) (4) has been established for drug substance stored at (b) (4).

This application is recommended for approval from a drug substance perspective.

B. Drug Product Quality Summary

Intrarosa (prasterone) vaginal inserts contain 6.5 mg prasterone in (b) (4) Hard Fat, NF (Witepsol (b) (4)). The drug load is only ca. 0.53% by weight. The tapered cylindrical inserts have a volume of ca. 1.3 mL and are designed to melt when introduced into the vaginal cavity. The inserts are ca. 28 mm in length and 9 mm at the widest end. At the narrowest end the insert is ca. 7 mm in diameter; this end fits into the tip of the accompanying disposal plastic applicator.

(b) (4)

Each carton of drug product consists of four blister strips of seven inserts (in a small box) and 28 applicators. (b) (4)



(b) (4)

A shelf-life of 36 months has been established for drug product stored at 25°C.

This NDA, as amended, is recommended for approval by both the drug product review and the process reviewer.

Biopharmaceutics

Release of the active ingredient from the product requires melting of the hard fat matrix and dissolution of prasterone. An in vitro dissolution method was developed by the applicant to assure quality control and consistent bioavailability of the drug product. The method employs USP Apparatus II (paddle) operated at 75 rpm. The dissolution medium consists of 1000 mL of 1% aqueous sodium lauryl sulfate (SLS) at 37.3°C. Additional data supporting the test conditions were submitted as requested. Because of the simple nature of the drug product

(API dissolved in hard fat), generation of data to demonstrate that the method is discriminatory was problematic.

(b) (4)

To confirm that the (b) (4) dissolution rate does not have an impact on the in vivo efficacy of the drug product in women, clinical study ERC-238 was conducted with product aged 17 to 28 months. Dr. Theresa H. van der Vlugt, Medical Officer, has confirmed that the study ERC-238 was adequate as one of the two confirmatory efficacy trials to support the efficacy of the DHEA insert for the proposed indication.

Agreement was eventually reached on the proposed acceptance criterion of Not Less Than (NLT) (b) (4) % (Q) dissolved in 180 minutes. This will ensure that a mean of at least (b) (4) % of the active ingredient will be dissolved in 180 minutes. A tighter acceptance criterion can be used by the applicant for batch release.

Comparative dissolution profiles of (b) (4) product (used in Phase 3 studies and stability studies) and (b) (4) product demonstrated adequate similarity (b) (4)

From the Biopharmaceutics perspective, this NDA is recommended for approval.

Product Quality Microbiology

Because the route of administration is intravaginal the product is not required to be sterile. The manufacturing process is not an aseptic process. Nevertheless, the product is tested per USP Microbial Limit Tests <61> and <62> at release and on stability to ensure adequate control of TAMC (Total Aerobic Microbial Count), and Yeasts and Molds, and to ensure the absence of specified organisms (*Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida albicans*). NDA 208470 is recommended for approval from the microbiology perspective.

Manufacturing Facilities

OPQ's Office of Process and Facilities, Division of Inspectional Assessment, determined that, "[t]here appears to be no significant risks to the drug product manufacturing based on the individual and composite evaluation of the listed facility's latest inspection results, inspectional history, and relevant experiences. All facilities are determined acceptable to support approval of NDA208470."

Analytical Methods Verification

The applicant's analytical procedures for drug substance identification, assay and impurities, and for drug product identification, assay, dissolution and impurities/degradants were verified and found acceptable for quality control and regulatory purposes by the FDA laboratory in St. Louis (OPQ/OTR/DPA) (see Methods Verification Report dated 07/27/2016).

Device Evaluation

The vaginal insert is administered using a (b) (4) applicator. The applicators consist of an applicator (b) (4). Four (b) (4) (b) (4) packages of seven applicators are supplied in a box with the 28 prasterone vaginal inserts. (b) (4)

The applicators were evaluated by Sharon Andrews, CDRH-ODE, who, based on the straight forward nature of the design and her review of samples of the newest version of the applicator, concluded that there were no safety or effectiveness concerns. She determined that, "the samples provided indicate that the applicator is sufficiently robust for its intended use and comparable to other marketed vaginal applicators." A specific shelf-life for the applicator has not been established, nor is one required.

While all three applicators have similar dimensions and function the same, concerns about "flimsiness" of the proposed and final commercial versions, and the potential to cause injury to the patient, have been raised by the clinical review team.

Katelyn Bittleman, CDRH Office of Compliance concluded that, "the application for Prasterone – NDA 208470 is approvable from the perspective of the applicable Quality System Requirements. The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies. The recommended inspections were conducted and deemed acceptable."

Environmental Assessment

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The required statement of no extraordinary circumstances was included. FDA requested additional information due to the hormonal activity of the API, per recent FDA guidance. The claim and supporting information were reviewed and the claim found to be acceptable.

Labeling

The primary labeling deficiency identified by the OPQ review team was the use of the dosage form (b) (4). The drug product should be referred to as ‘prasterone vaginal inserts.’ In addition, the cartons should list the inactive ingredient and should include a barcode. These recommendations have been conveyed to the OND review team in preparation for labeling negotiations.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	INTRAROSA (prasterone) vaginal inserts
Non Proprietary Name of the Drug Product	prasterone vaginal inserts
Non Proprietary Name of the Drug Substance	prasterone
Proposed Indication(s) including Intended Patient Population	Intrarosa is indicated for the treatment of moderate to severe dyspareunia (b) (4) a symptom of (b) (4) atrophy due to menopause (b) (4)
Maximum Daily Dose	6.5 mg (one vaginal insert) per day (b) (4) at bedtime (b) (4)

D. Biopharmaceutics Considerations

1. BCS Classification:
 - Drug Substance: not applicable
 - Drug Product: not applicable

2. Biowaivers/Biostudies
 - Biowaiver Requests: not applicable
 - PK studies: see Clinical Pharmacology review
 - IVIVC: not applicable

E. Novel Approaches

Not Applicable

F. Any Special Product Quality Labeling Recommendations

Per the USP, the dosage form is vaginal insert. The terms vaginal (b) (4) or (b) (4) should not be used.

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Mark R. Seggel, Ph.D.
CMC Lead (acting)

ASSESSMENT OF THE BIOPHARMACETICS

27. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

The Biopharmaceutics review is focused on the evaluation of the dissolution method development report to support the proposed method and acceptance criterion, and the in vitro dissolution comparability study of the drug product manufactured at the (b) (4) site ((b) (4) and the (b) (4) site (b) (4)

Dissolution Method and Acceptance Criterion

1. Composition of proposed drug product:

The quantitative composition and function of each component of commercial Prasterone (Dehydroepiandrosterone, DHEA) 6.5 mg vaginal (b) (4) are listed in the Table 1.

Table 1: Composition of Prasterone vaginal (b) (4)

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim)
		6.5 mg DHEA/ (b) (4)
		Quantity per unit (mg)
Prasterone, (b) (4)	Drug Substance	6.5
Hard Fat, NF (Witepsol (b) (4))	(b) (4)	
Total (mg):	(b) (4)	

2. In vitro dissolution method and acceptance criterion:

The proposed dissolution method and its acceptance criterion for Prasterone (b) (4) is shown below in Table 2.

Table 2. Dissolution method and acceptance criterion for the dissolution of Prasterone (b) (4)

Apparatus:	Apparatus II (paddle)
Medium:	1% SLS (Sodium Lauryl Sulfate)

Volume:	1000 mL
Temperature:	37.3°C ± 0.2°C
Speed:	75 rpm
Sampling time:	90 minutes
Specification:	Q= ^(b) ₍₄₎ % in 180 minutes

Justification of dissolution specification:

The Applicant noted that the dissolution specification was established at the 180 minute time point (b) (4)

(b) (4)


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FDA Information requests (IR):**Biopharmaceutics IR #1**

An IR from the Agency was sent to the Applicant on December 28, 2015, in the 74-day Filing letter. On February 12, 2016, the Applicant responded to the IR and provided the following response with the requested data.

1. We acknowledge your justifications for the proposed dissolution method (UCA135-M) as described in Module 3.2.P.5.2. Submit the following supportive information:

a. The complete dissolution profile data (individual, mean, standard deviation, profiles) that supports the selection of the paddle speed, dissolution medium, and SLS concentration. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's labeling claim).

Response from the Applicant:

The complete dissolution profile data is presented in the report entitled: [RD-2015-005-R Dissolution Method Development DHEA \(b\) \(4\)](#) in Module 3.2.P.5.2.

Reviewer's comments:

The Applicant provided complete dissolution profile data for the selection of paddle speed, dissolution medium, and SLS concentration. The Applicant also provided the details on solubility of the drug substance and sink condition. The related figures and data are provided in Dissolution Method Development below.

b. Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., (b) (4) % change to the specification ranges of these variables).

Response from the Applicant:

The discriminating ability of the dissolution method has been demonstrated during method development as shown in the Dissolution Method Development report [RD-2015-005-R](#) (in Module 3.2.P.5.2) and also during stability testing where a slowing dissolution profile was identified as shown in the report entitled: [DHEA 6.5 mg Ovules Dissolution Data Summary Report](#) in Module 3.2.P.5.6.

Reviewer's comments:

The Applicant did not provide any data to compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables. Hence, another IR (See IR #2 comment #2 below) was sent to the Applicant.

- 2. Provide the following information to support your proposed acceptance criterion:**
- The complete dissolution profile data (n=12) from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of your product (i.e., specification-sampling time point and specification value).**
 - The in vitro dissolution profile should encompass the timeframe over which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.**
 - The selection of the specification time point should be where $Q = \frac{(b)}{(4)}\%$ dissolution occurs.**

Response from the Applicant:

Complete dissolution profile data from the pivotal clinical batches and primary (registration) stability batches used for the setting of the dissolution acceptance is presented in the report entitled: [DHEA 6.5 mg Ovules Dissolution Data Summary Report](#) in Module 3.2.P.5.6.

The dissolution time point to ensure at least $\frac{(b)}{(4)}\%$ of the drug is dissolved for all batches has been established at 180 minutes to cope with the deceleration observed during stability that started around the $\frac{(b)}{(4)}$ month stability time point and reached a maximum at the $\frac{(b)}{(4)}$ month stability time point.

Reviewer's comments:

The Applicant has provided the complete dissolution profile data in the report: [DHEA 6.5 mg Ovules Dissolution Data Summary Report](#) in Module 3.2.P.5.6.

- 3. Submit the complete dissolution profile data for the comparative dissolution test results reported in "SN-1597-R - DHEA 6.5 mg $\frac{(b)}{(4)}$ - Dissolution Profile Comparison."**

Response from the Applicant:

The dissolution Profile Comparison report provided in Module 3.2.P.5.2 of Sequence 0000 of NDA has been updated to include the complete dissolution profile data: [SN-1597-R – DHEA 6.5 mg \$\frac{\(b\)}{\(4\)}\$ – Dissolution Profile Comparison](#).

Reviewer's comments:

The Applicant has provided the complete comparative dissolution data in the report: [DHEA 6.5 mg \$\frac{\(b\)}{\(4\)}\$ Dissolution Data Summary Report](#) in Module 3.2.P.5.6. The individual data is provided in Comparative Dissolution Profiles below.

Biopharmaceutics IR #2

On March 14, 2016, another IR from the Agency was sent to the Applicant that requested additional information. On April 01, 2016, the Applicant responded to the IR. The IR and the Applicant's response are provided below.

1. You proposed $Q = \text{(b) (4)}\%$ in 180 minutes as your dissolution specification. We recommend that the selection of the dissolution specification time point should be where $Q = \text{(b) (4)}\%$ dissolution occurs. Therefore, we recommend a specification of $Q = \text{(b) (4)}\%$ at (b) (4) minutes.

Response from the Applicant:

We agree with the recommended specification of $Q = \text{(b) (4)}\%$ at (b) (4) minutes for release.

have selected the drug product batches XB3064UA and XB306 manufactured at the (b) (4) site and used in Phase III efficacy study ERC-238. As can be seen in the Table below, the age of these two batches ranged between 17 and 28 months from initiation to the end of study.

Strength/ Batch Number	Batch Size	Manufacturer and Date	Manufacturing date	Phase III Trial	First Patient First Visit	Last Patient Last Visit	(b) (4)
(b) (4) 6.5 mg DHEA XB3064UA	(b) (4) kg	(b) (4)	Sep 2012	ERC-238	Feb 2014	Jan 2015	
6.5 mg DHEA XB3065FA	kg	(b) (4)	Sep 2012	ERC-238	Feb 2014	Jan 2015	

The (b) (4) dissolution profile was observed at the (b) (4) month time points for both batches, as can be seen in Figure 6 and Figure 7 of the report entitled "DHEA 6.5 mg (b) (4) dissolution data summary report", which concurs with their age during the clinical study.

The efficacy of the drug product has been demonstrated during study ERC-238 which supports the (b) (4) in vitro dissolution during storage does not have an impact on the in vivo effect of the drug product in women.

Therefore, a stability or storage shelf-life specification of $Q = \text{(b) (4)}\%$ at 180 minutes is being proposed in the revised Section 3.2.P.5.1 (b) (4) .

Reviewer's comments:

On April 06, 2016, the Medical Officer, Dr. Theresa H. van der Vlugt, was asked to confirm that the study ERC-238 was adequate, and there were no efficacy concerns based on this study. Dr. van der Vlugt confirmed via email on April 07, 2016 that the study ERC-238 was adequate as one of the two confirmatory efficacy trials to support the efficacy of the DHEA insert for the proposed indication. (see Appendix 2).

2. In the filing communication dated December 28, 2015, we requested that you provide data to support the discriminating ability of the selected dissolution method. You have not adequately evaluated the discriminating ability of the proposed method. We remind you that the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., (b) (4) % change to the specification-ranges of these variables).

Response from the Applicant:

In the case of (b) (4) where the drug substance is incorporated in a suitable base without additional excipients, the drug load is the most relevant parameter in evaluating the discriminating ability of the dissolution method. Batches of drug product have been manufactured with the target load of 0.50% as well as with 1.0% and 1.8% of DHEA in Witepsol (b) (4) for clinical study ERC-213 and with 0.25%, 0.50% and 1.0% of DHEA in Witepsol (b) (4) for clinical study ERC-210. The dissolution profiles generated indicate a (b) (4) dissolution profile for higher concentrations at initial collecting time points as presented in [Figure 1](#) and [Figure 2](#).

(b) (4)

From these data, along with the data generated during the development and validation of the analytical method UCA-135M where relevant parameters have been assessed, it can be concluded that the discriminating ability of the method has been demonstrated.

Reviewer's comments:

The Applicant did not adequately investigate the discriminating ability of the proposed method (i.e. by testing formulation or manufacturing process parameters with meaningful variations); however, the proposed dissolution method is acceptable due to the fact that Prasterone formulation is simple, and discriminatory data are not required by the Agency.

Biopharmaceutics IR #3

On May 26, 2016, the following IR was sent to the Applicant.

We recommend the dissolution specification of Q^{(b)(4)} % at 180 minutes for both release and stability. We also recommend that you incorporate tighter specifications into your internal controls. Please acknowledge your acceptance of the recommended dissolution specification. Update the drug product specification table and other relevant sections of your NDA accordingly.

Reviewer's comments:

In a Teleconference held on May 31, 2016, the Applicant requested clarification of the statement "*We also recommend that you incorporate tighter specifications into your internal controls*". The Agency recommended that the Applicant incorporate a tighter specification for internal quality control assessment at release for dissolution testing. The Applicant acknowledged their acceptance of the recommended specification Q^{(b)(4)} % at 180 minutes, and will revise the specifications table in 3.2.P.5.1. The meeting discussion is documented in Memorandum of Teleconference (dated June 13, 2016 in DARRTS).

3. Dissolution Method Development:

The Applicant has provided the complete data and profiles in response to the Agency IR #1 comment #1 (see details above) for justification of paddle speed, dissolution medium, and SLS concentration. The mean data and profiles are provided below. All individual data are provided in the report entitled: [RD-2015-005-R](#) Dissolution Method Development DHEA Suppositories in Module 3.2.P.5.2.

(b) (4)



(b) (4)



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4. Comparative Dissolution Profiles:

The batches of Prasterone manufactured at the (b) (4) were used in Phase 3 studies, ERC-238, and stability studies. The manufacturing process was later transferred to the (b) (4). The Applicant has submitted the results of comparative multi-point dissolution testing to demonstrate similarity of the drug product manufactured at the (b) (4) site and at the (b) (4) site. The Applicant has provided the complete dissolution profile data for the comparative dissolution test results reported in "SN-1597-R - DHEA 6.5 mg (b) (4) Dissolution Profile Comparison" in response to an IR sent to the Applicant (See IR #1 comment #3 above). The comparative dissolution profiles of prasterone vaginal (b) (4) manufactured at (b) (4) and the (b) (4) site are shown below. The individual data are provided in Appendix 1.

5. Analytical Method and Its Validation:

In vitro dissolution analytical method validation report for Prasterone 6.5 mg (b) (4) (Method UCA135-M) was submitted in M.3.2.P.5.3, which were validated in terms of specificity, linearity, precision, accuracy, solution stability, and robustness. The summary of validation is provided in Appendix 1.

Table 6. HPLC chromatographic conditions for prasterone

Column	Waters X-Bridge C ₁₈ , 4.6 mm x 150 mm, 5 μm or demonstrated equivalent
Mobile Phase	0.05 M Tris(hydroxymethyl)aminomethane, pH 7.00 ± 0.05 / Acetonitrile (85/15 v/v)
Column Temperature	45°C
Injection Volume	100 μL
Flow Rate	2.0 mL/min
Detection	280 nm

Reviewer’s Assessment:

- The Applicant’s dissolution method development report and the dissolution method are acceptable.
- The Applicant’s proposed dissolution acceptance criterion is Q^{(b) (4)}% at 180 minutes for both release and stability. The proposed dissolution acceptance criterion is acceptable based on the justification provided by the Applicant and confirmation by the Medical Officer, Dr. Theresa H. van der Vlugt, ^{(b) (4)}
^{(b) (4)} (see details in the IR above). As documented in the teleconference memorandum dated May 31, 2016, the Applicant acknowledged their acceptance of the recommended acceptance criterion Q^{(b) (4)}% at 180 minutes.
- Both the ^{(b) (4)} batches showed similar dissolution profiles. The similarity factor (f₂) calculated are >50. Therefore, the comparative dissolution profile data of Prasterone vaginal ^{(b) (4)} manufactured at the ^{(b) (4)} site and the ^{(b) (4)} site supports the transfer of the manufacturing process from ^{(b) (4)}.
- The analytical method and its validation report are reviewed and considered acceptable.
- The dissolution testing included the Prasterone lot XB3064UA and XB3065FA on which pivotal phase III studies were conducted.

28. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

Applicant’s Response:

Reviewer’s Assessment:NA

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

From the Biopharmaceutics perspective, this NDA is recommended for approval.

Kalpana Paudel, Ph.D. 06/21/16
BBII/DB/ONDP/OPQ

Secondary Review Comments and Concurrence:

I have reviewed the Biopharmaceutics assessment, and I concur with the recommendation for approval.

Kelly M. Kitchens, Ph.D.
Biopharmaceutics Quality Assessment Lead (Acting)
Division of Biopharmaceutics, Branch 2
June 21, 2016

Appendix 1

Comparative Dissolution Data

(b) (4)

Appendix 2

E-mail correspondence with Medical Officer

From: Van Der Vlugt, Theresa H
Sent: Thursday, April 07, 2016 8:10 AM
To: Paudel, Kalpana
Cc: Kitchens, Kelly; Vu, Thao; Slaughter, Shelley R; Dwyer, Kate
Subject: RE: NDA208470(Prasterone (b) (4))

Kalpana,

We have determined that Trial ERC-238 is adequate as one of the two confirmatory efficacy trials to support the efficacy of the DHEA insert for the proposed indication.

Theresa

Theresa H. van der Vlugt, M.D., M.P.H.
Medical Officer
Division of Bone, Reproductive and Urologic Products
HFD-580
Room 5362
Phone: 301-796-1014
theresa.vandervlugt@fda.hhs.gov

From: Paudel, Kalpana
Sent: Wednesday, April 06, 2016 4:31 PM
To: Van Der Vlugt, Theresa H
Cc: Kitchens, Kelly; Vu, Thao
Subject: NDA208470(Prasterone (b) (4))

Hi Theresa,

I am the Biopharm reviewer for this NDA. We recently received the following response from the Applicant for an Information Request regarding slower dissolution observed during long-term storage. The Applicant provided justification that the older/stored batches of the drug product do not have an impact on the in vivo effect as demonstrated in the Phase 3 clinical study ERC-238. Therefore, we would like to know if you have determined that study ERC-238 is adequate, and there are no efficacy concerns based on this study.

Information Request: You proposed $Q^{(b)(4)}$ % in 180 minutes as your dissolution specification. We recommend that the selection of the dissolution specification time point should be where $Q = \frac{(b)(4)}{(4)}$ % dissolution occurs. Therefore, we recommend a specification of $Q^{(b)(4)}$ % at $\frac{(b)(4)}{(4)}$ minutes. We have concerns about the slow dissolution of your drug product during long-term storage. Provide scientific justification that the slowing of dissolution during stability/storage will not impact the in vivo release and/or in vivo effect of the drug product.

Applicant’s response: In an attempt to verify the correlation of a slower in vitro dissolution behavior on in vivo efficacy, we have selected the drug product batches XB3064UA and XB3065FA manufactured at the (b) (4) site and used in Phase III efficacy study ERC-238. As can be seen in the Table below, the age of these two batches ranged between 17 and 28 months from initiation to the end of study.

Strength/ Batch Number (suppository)	Batch Size	Manufacturer and Date	Manufacturing date	Phase III Trial	First Patient First Visit	Last Patient Last Visit	(b) (4)
6.5 mg DHEA XB3064UA	(b) (4) kg	(b) (4)	Sep 2012	ERC-238	Feb 2014	Jan 2015	
6.5 mg DHEA XB3065FA	kg		Sep 2012	ERC-238	Feb 2014	Jan 2015	

The efficacy of the drug product has been demonstrated during study ERC-238 which supports the fact that the potential slowing of the in vitro dissolution during storage does not have an impact on the in vivo effect of the drug product in women.

Please feel free to contact us if you have any questions about our request.

Thank you,

Kalpana

ASSESSMENT OF MICROBIOLOGY

29. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant’s Response: Information Provided in Section 3.2.P.5 and Section 3.2.P.8.

The route of administration is intravaginal and the manufacturing process is not an aseptic process. Microbial limit test is proposed to be conducted on each commercial batch at release and during stability using harmonized methods of USP Chapters <61> and <62>. The following MLT specifications are proposed in compliance with USP Chapter <1111>.

Microbial Limit Tests		
- TAMC	NMT (b)(4) CFU/g	USP<61> and <62>
- Yeast and molds	NMT (b)(4) CFU/g	
- <i>Pseudomonas aeruginosa</i>	Absence in 1 g	
- <i>Staphylococcus aureus</i>	Absence in 1 g	
- <i>Candida albicans</i>	Absence in 1 g	

Assessment of Response to Information Request (IR#3) dated 03/14/2016:

Microbiology IR#3-19: Revise the acceptance criteria for test of Specified Microorganisms in Microbial Limit Tests (i.e., *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida albicans*) from “Absence” to “Absence in 1 g” in your drug product specifications at release and on stability to be in compliance with USP Chapter <1111> - Microbiological Examination of Nonsterile Products.

Response in an amendment dated 03/24/2016: The revised specification is provided in revised Section 3.2.P.5.1.

Evaluation: The firm’s response to microbiology IR#3-19 is adequate.

Microbiology IR#3-20: We acknowledge that Microbial Limit Tests are performed per USP General Chapters <61> and <62>. Provide a study report to demonstrate that suitability of the chosen methods for your drug product has been established.

Response in an amendment dated 03/24/2016: The study report entitled “Validation Report of the Microbial Contamination Test of (b)(4)” is included in Section 3.2.P.2.5.

Evaluation: The provided report should be relocated in Section 3.2.P.5.3. In addition, same type of report should be provided from (b)(4) site. The firm’s response to microbiology IR#3-20 is inadequate. Please reference the microbiology IR#4-8 per IR dated 04/26/2016.

Microbiology IR#3-21: Based on your stability protocol and stability commitment, please provide the results of Microbial Limit Tests for stability samples at 12-month and 24-month time points for batches XB3064UA, XB3065FA, and XB30651A under storage condition of 25°C/60% RH.

Response in an amendment dated 03/24/2016: Based on the approved stability protocol at the time of the study, microbial limit tests were not planned for batches # XB3064UA,

XB3065FA, and XB30651A under storage condition of 25°C/60% RH. However, microbial limit tests were conducted for these batches under storage conditions of (b) (4) °C/75% RH and 5°C/ambient. Results are presented in Section 3.2.P.8.3.

Evaluation: The firm’s response to microbiology IR#3-21 is adequate.

Assessment of Response to Information Request (IR#4) dated 04/26/2016:

Microbiology IR#4-8: We acknowledge you provided the study report entitled “Validation Report of the Microbial Contamination Test of (b) (4)” in Section 3.2.P.2.5. Please relocate this report to Section 3.2.P.5.3 – Validation of Analytical Procedures. In addition, please provide the same type of report from (b) (4) site in Section 3.2.P.5.3 to demonstrate that suitability of the Microbial Limit Tests for the drug product has been established.

Response in an amendment dated 05/03/2016: The study report entitled “Validation Report of the Microbial Contamination Test of (b) (4)” has been relocated to Section 3.2.P.5.3. The microbial validation report from (b) (4) site has also been added to Section 3.2.P.5.3.

Evaluation: The firm’s response to Microbiology IR#4-8 is adequate.

Reviewer’s Assessment: Adequate as amended

MLT Specifications for the Drug Product: Adequate as amended

Microbial Limit Test (MLT) is proposed in the drug product specifications at release and on stability for every commercial batch. The proposed MLT specifications are in compliance with USP Chapter <1111> - *Microbiological Examination of Nonsterile Products* for vaginal use of solid nonsterile dosage form products. MLT is performed per the current USP General Chapters <61> and <62>. Method suitability of the MLT for the drug product has been established at (b) (4) site and (b) (4) site.

MLT Test Protocols: Adequate

MLT is proposed to be conducted on each batch at release and at initial (T₀), 12-month, 24-month and 36-month time point during stability testing as shown in below table. This is acceptable.

Test	Method/Acceptance Criteria	Time Intervals (Months) ^a					
		0	6	12	18	24	36
Microbial Limit Tests - TAMC - Yeast and molds - <i>Pseudomonas aeruginosa</i> - <i>Staphylococcus aureus</i> - <i>Candida albicans</i>	USP<61> and <62> / NMT (b) (4) FU/g NMT (b) (4) FU/g Absence in 1g Absence in 1g Absence in 1g	x		x		x	x

MLT Test Results: Adequate as amended

Although MLT for specified microorganisms for clinical batches manufactured at (b) (4) are different from the proposed specifications for commercial batches as shown in below summarized table, it is acceptable since the MLT specifications for commercial batches and registration batches

manufactured at (b) (4) site and (b) (4) site are in accordance with USP <1111>.

(b) (4)			
- Total count - <i>Pseudomonas aeruginosa</i> - <i>Staphylococcus aureus</i> - <i>E. Coli</i> - <i>Salmonella</i> - <i>Candida albicans</i> - Yeast and molds	- Total count - <i>Pseudomonas aeruginosa</i> - <i>Staphylococcus aureus</i> - <i>E. Coli</i> - <i>Salmonella</i> - <i>Candida albicans</i> - Yeast and molds	- TAMC - <i>Pseudomonas aeruginosa</i> - <i>Staphylococcus aureus</i> - <i>E. Coli</i> - <i>Salmonella</i> - <i>Candida albicans</i> - Yeast and molds	- TAMC - Yeasts and molds - <i>Pseud. aeruginosa</i> - <i>Staph. aureus</i> - <i>Candida albicans</i>

In addition, all registration batches demonstrate compliance with their corresponding specifications. Below is the MLT test results of three registration batches manufactured at (b) (4) site for release as an example.

Test	Acceptance Criteria	XB3064UA	XB3065FA	XB30651A
		(b) (4)		
Microbial Limit				
- TAMC	(b) (4) cfu/g	(b) (4) cfu/g	(b) (4) cfu/g	(b) (4) cfu/g
- Yeasts and molds	(b) (4) cfu/g	(b) (4) cfu/g	(b) (4) cfu/g	(b) (4) cfu/g
- <i>Pseud. aeruginosa</i>	Absent	Absent	Absent	Absent
- <i>Staph. aureus</i>	Absent	Absent	Absent	Absent
- <i>Candida albicans</i>	Absent	Absent	Absent	Absent

All provided MLT results in stability tests meet the proposed criteria. The firm provided adequate explanation for excluding stability test results of MLT at 12-month and 24-month time points for batches # XB3064UA, # XB3065FA, and # XB30651A under storage condition of 25°C/60% RH.

Please reference the Assessment of Response to Information Request in above Applicant’s Response Section. The firm provided adequate information as amended for the microbial limit control of the drug product in this section.

2.3.P.7 Container/Closure System

30. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant’s Response: N/A

Reviewer’s Assessment: N/A

The drug product is in solid vaginal use dosage form and non-sterile in nature.

A APPENDICES**A.2 Adventitious Agents Safety Evaluation**

31. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: Information provided in Section 3.2.P.4.5.

The only excipient used in drug product 'Witepsol ^{(b) (4)}' is not an excipient of human or animal origin.

Reviewer's Assessment: N/A

32. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: N/A

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Adequate

Information provided for control of microbiology for the drug product is found adequate per microbiology review #1. Therefore, NDA 208470 is recommended for approval from the microbiology perspective.

Jingbo Xiao, Ph.D., Primary Reviewer, OPQ/OPF/DPAII/PABV, 06/14/2016.

Secondary Review Comments and Concurrence:

Concur with microbiology review #1.

Yubing Tang, Ph.D., Acting Branch Chief, OPQ/OPF/DPAII/PABV, 07/15/2016.

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The required statement of no extraordinary circumstances was included. FDA requested additional information due to the hormonal activity of the API, per recent FDA guidance. The claim and supporting information were reviewed and the claim found to be acceptable.

R Regional Information

Environmental Analysis

The applicant initially submitted a claim for a categorical exclusion from an environmental assessment (EA) for prasterone (dehydroepiandrosterone, or DHEA) in accordance with 21 CFR Part 25.31(e). This exclusion, however, is for investigational new drugs (INDs) and thus is not relevant to this NDA. Based on the explanation provided, it appeared the applicant was referring instead either or both to:

1. 21 CFR 25.31(b), which is for actions that increase the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb), or
2. 21 CFR 25.31(c), which is for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

These exclusions, however, were not stated, nor therefore were the relevant data specifically applied to them.

FDA responded to the categorical exclusion claim on December 28, 2015 by noting that the appropriate exclusion(s) must be cited and the relevant data specifically applied to the respective exclusion. FDA also requested supporting data using readily available environmental assessment literature and reports addressing both the active ingredient and substances with similar environmental toxicological modes of action (MoAs), including assessments submitted to other domestic and foreign agencies. The supporting data were noted as particularly important given this product has estrogenic and androgenic activity. FDA referenced its recently released draft guidance on hormonally active products, Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity (April 2015), which notes that drugs with such activity have the potential to cause developmental or reproductive effects in the aquatic environment at concentrations below 1 ppb. This guidance is now final, with minimal changes (March 2016).

On February 12, 2016, the applicant provided an updated claim for a categorical exclusion. This claim cited 21 CFR Part 25.31(b), since the action (new drug approval) would increase the use of the active moiety, prasterone, and the estimated concentration at the point of entry into the aquatic environment will be below 1 part per billion (ppb), in particular 0.088 ppb. The applicant also included the required statement of no extraordinary circumstances, per 21 CFR 25.21. The applicant supported their claim by

noting that the intracrine enzymes able to transform inactive prasterone into androgens and/or estrogens are not present in flora, insects, or fish, and that prasterone is an inactive compound by itself, requiring the appropriate enzymatic machinery to be transformed in an active molecule. In the vagina, through intracrine mechanisms, prasterone is noted as being transformed into active estrogens and androgens exclusively inside the cells where the sex steroids are also inactivated before being released in the circulation for elimination by the kidneys and liver as inactive compounds. The applicant also noted that humans and other primates are unique among animal species in having adrenals that secrete large amounts of the inactive precursor DHEA, which is converted at various levels into active androgens and/or estrogens in specific peripheral tissues via intracrine mechanisms. In addition, the applicant noted, the main glucuronidated and sulfated derivatives of metabolites do not have biological activity.

The applicant also referenced an [REDACTED] (b) (4)

[REDACTED] tating that prasterone and its metabolites are unlikely to represent a risk to the aquatic environment. Briefly, that assessment presented several conclusions, though for purposes of this review only the ratio of the predicted environmental concentration for water (PEC) to the predicted no-effect concentration (PNEC) is relevant. In particular, the assessment noted this ratio is less than 1, and thus the applicant indicated that prasterone and/or its metabolites are unlikely to represent a risk to the aquatic environment.

FDA responded on March 14, 2016 to the applicant's submission with four areas of questions. The following summarize these questions and the applicant's March 24, 2016 responses in an updated claim for a categorical exclusion and an amendment to CTD section 1.11.1:

1. FDA requested data or references to literature supporting the statement that the intracrine enzymes that are able to transform inactive into androgens and/or estrogens are not present in flora, insects, or fish. The applicant responded by clarifying that the intracrine enzymes that are able to transform inactive DHEA into androgens and/or estrogens are only unlikely to be—instead of not—present in flora, insects, or fish, based on information provided in Appendix 1 of the amendment to CTD section 1.11.1.
2. FDA noted that, in response to the applicant's statement that the sex steroids resulting from DHEA absorption and metabolism are inactivated before being released, such inactive compounds often are reactivated during wastewater treatment or in the environment and thus data or references supporting permanent deactivation should be provided. The applicant provided additional data supporting the argument that sex steroids resulting from DHEA absorption and metabolism are inactivated before being released.
3. FDA noted that the referenced environmental risk assessment submitted to EMA in turn referenced a study recommended by EMA—the OECD 210 Fish, Early Life Stage Toxicity Test—which would be particularly useful for supporting the

categorical exclusion. FDA asked whether the study results are available. The applicant noted that the OECD 210 Toxicity Test was cited under this section for reference purpose only, and that it is not under way and is not planned.

FDA noted two potential errors in the applicant's environmental submission, i.e., a $PNEC_{\text{water}}$ of (b) (4) rather than (b) (4) derived from a no observed effects concentration (NOEC) of (b) (4) (Section 1.4.1.3) and an estimated exposure of prasterone in groundwater as (b) (4) rather than (b) (4) (Section 1.4.1.4). The applicant concurred and has corrected these errors in the EA.

Reviewer's Assessment:

The prasterone EIC of (b) (4) ppb is more than an order of magnitude below the 1 ppb categorical exclusion value, per 21 CFR 25.31(b). The calculation appears accurate and reasonable. Therefore, the adequate statement of no extraordinary circumstances is now present.

As noted above, another relevant exclusion, 21 CFR 25.31(c), for substances that occur naturally in the environment, also might have been relevant for this application, since DHEA is naturally produced by humans, as well as other vertebrates (Norris and Carr, 2005). Based on data from Shackleton (1993), human males excrete approximately 490 $\mu\text{g}/\text{day}$ and human females excrete approximately 188 $\mu\text{g}/\text{day}$ of DHEA, which translates into approximately 39,000 kg/year of DHEA excreted by humans. Thus, the maximum release of DHEA into the environment due to this NDA—approximately (b) (4)—would be about (b) (4) % of the naturally excreted amount from humans. Removing from this prescribed amount the fraction lost from metabolism likely would reduce the percentage considerably. Similarly, adding the amount of DHEA from wildlife (Hartmann, 1998) to that from humans would reduce the prescription percentage further such that the action likely would meet this categorical exclusion's requirements to "not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment". If the use of DHEA in dietary supplements (Abbate et al., 2015) and the contribution from livestock (Hartmann, 1998) are also considered, the percent contribution due to this application would be reduced still further. The issue of hormonal activity and extraordinary circumstances noted above is addressed in part by the supporting information provided by the applicant. One of

the areas addressed in this supporting information is the claim that intracrine enzymes able to transform inactive prasterone into androgens and estrogens are not likely to be (significantly) present in flora, insects, or fish. After reviewing the referenced literature and other literature (Ankley et al., 2009), however, this claim appears to be only partly correct in that the extent to which prasterone is transformed or not to androgens and estrogens in fish is uncertain. In addition, as discussed below, data provided by the applicant and in the literature describe the transformation in humans of prasterone to other products that could then adversely affect aquatic organisms. Also, the data indicate there is the potential for adverse impacts directly from prasterone.

Another claim by the applicant was that the sex steroids resulting from DHEA absorption and metabolism are inactivated before being released, and that the inactivation process is irreversible. Several studies, however, show that reactivation and reversal to parent compound occur readily both in the human gut and during wastewater transport and treatment (Baronti et al., 2000; Gomes et al., 2009; Johnson and Williams, 2004). Furthermore, some transformation products have androgenic effects in fish, such as androstenedione (AD), which appears to be more potent in fish than testosterone (Yamazaki, 1983).

The assessment conducted by the applicant for EMA used the results of an OECD (b) (4) *Daphnia* sp. Acute Immobilization Test to develop a PNEC of (b) (4) based on a no-observed effects concentration (NOEC) of (b) (4) and an assessment factor (AF) of (b) (4). Another study was described that examined the acute toxicity of prasterone on algae and resulted in a (b) (4) percent effective concentration (EC50) of (b) (4). The report did not provide the rationale for why this lower effects concentration was not used to develop a PNEC. Furthermore, the short term nature of both tests would argue for a higher AF, typically (b) (4) or converting the short-term NOEC and (b) (4) for converting the short-term EC50, generally more for hormonally active drugs such as prasterone (USFDA, 2013) and for such limited data.

Given the limited data for developing PNECs, a simple margin of safety (MoS)

approach was used for purposes of this assessment. Thus, comparing the DHEA daphnia NOEC of (b) (4) to the EIC of (b) (4) results in an MoS of approximately (b) (4). Comparing the algae EC50 of 1 mg/L to the EIC results in an MoS of approximately (b) (4). These MoS values exceed the AF of (b) (4) noted above, indicating a sufficient level of protection for the EIC. Nevertheless, caveats include the lack of chronic data and the need for a broader range of taxa to make a more definitive determination of ecological risk, especially given that several species are known to be affected by DHEA (James, 2011; Orner et al., 1995; Wang and Croll, 2004; William, 2012).

Additional toxicity data can be derived from androstenedione (AD), which has been shown to be among the most potent transformation products from DHEA in fish (Yamazaki, 1983). A NOEC of 0.04 µg/L was obtained for AD for the mosquitofish (Stanko and Angus, 2007). While this value is lower than the prasterone EIC of 0.088 µg/L, the AD concentration would be substantially lower than this because not all prasterone transforms to AD. Also, wastewater treatment, environmental degradation, and dilution would result in additionally lower concentrations. Some studies indicate that the majority of AD is removed during conventional wastewater treatment, as well as the majority of DHEA (Esperanza et al., 2007; Liu et al., 2009). Thus, based on a review of the available data, FDA notes the following:

1. The API EIC meets the requirements of the 21 CFR 25.31(b) categorical exclusion, and an adequate statement of no extraordinary circumstances is now present. However, given recent concerns about hormonally active drugs in the environment, a more detailed review of this claim is warranted.
2. The API occurs naturally in the environment, and the action does not appear to significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. Thus, the categorical exclusion at 21 CFR 25.31(c) would appear to be relevant, although it was not claimed by the applicant.
3. The API and its by-products can result in adverse effects on the environment, depending on the environmental concentration. The concentrations from this

application are expected to be lower than the effects concentrations.

4. There is potential for cumulative impacts from the combination of this drug with other substances with similar MoAs, such as other drugs, dietary supplements, and other chemicals, both natural and synthetic, outside of this subject action.

FDA concludes that the claim for a categorical exclusion from and EA is acceptable. Additional monitoring is warranted outside of the subject action such as through future environmental assessments and/or requests of additional data from sponsors.

References:

Abbate, V., et al. (2015). "Anabolic steroids detected in bodybuilding dietary supplements – a significant risk to public health." *Drug Testing and Analysis* 7(7): 609-618.

Ankley, G. T., et al. (2009). "Endocrine disrupting chemicals in fish: Developing exposure indicators and predictive models of effects based on mechanism of action." *Aquatic Toxicology* 92(3): 168-178.

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Esperanza, M., et al. (2007). "Fate of sex hormones in two pilot-scale municipal wastewater treatment plants: Conventional treatment." *Chemosphere* 66(8): 1535-1544.

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Hartmann, S., et al. (1998). "Natural occurrence of steroid hormones in food." *Food Chemistry* 62(1): 7-20.

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fish.” Aquaculture, Volume 33, Issue 1, 1983, Pages 329-354

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer’s Assessment and Signature:

James Laurenson, EA Reviewer, OPQ/ONDP, July 19, 2016

Secondary Review Comments and Concurrence:

M. Scott Furness, Deputy Director, ONDP, July 21, 2016

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

NOTE: Because the drug substance has been designated a NCE, the Labeling Development Team (LDT)/OPQ reviewed the Labeling in its entirety. The recommendation by the LDT team were communicated to OND on 04/28/2016. Additional CMC edits were communicated to OND on 06/06/2016.

1. Package Insert

(a) “Highlights” Section (21CFR 201.57(a))

————— **DOSAGE FORMS AND STRENGTHS** —————
 Vaginal Inserts: 6.5 mg of prasterone (3)

Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Intrarosa Established Name: prasterone vaginal insert	Adequate
Dosage form, route of administration	Dosage: 6.5 mg of prasterone Route: Insert	Adequate
Controlled drug substance symbol (if applicable)	N/A	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Vaginal Insert: 6.5 mg of prasterone	Adequate

Conclusion: ADEQUATE

(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Vaginal inserts: 6.5 mg of prasterone, smooth, white to off-white solid fat bullet-shape, measuring 28 mm in length, 9 mm in width at its wider end, and weighing 1.2 grams.

Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	Vaginal Insert	Adequate
Strengths: in metric system	6.5 mg	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Smooth, white to off-white solid fat bullet-shape, measuring 28 mm in length, 9 mm in width at its wider end, and weighing 1.2 grams	Adequate

Conclusion: LDT communicated desired language to OND on 04/28/2016. OPQ concurs with LDT language.

#11: Description (21CFR 201.57(c)(12))



(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Intrarosa (praseterone) vaginal insert	Adequate
Dosage form and route of administration	Vaginal insert	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	NA	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(ii i)), listed by USP/NF names.	(b) (4)	Inadequate
Statement of being sterile (if applicable)	NA	Adequate
Pharmacological/therapeutic class	Therapeutic class is not provided.	Inadequate
Chemical name, structural formula, molecular weight	Chemical name is not appropriately presented.	Inadequate
If radioactive, statement of important nuclear characteristics.	NA	Adequate
Other important	Solubility,	Adequate

chemical or physical properties (such as pKa, solubility, or pH)		
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Conclusion: Inadequate

The description section should be revised as indicated above. (Communicated to OND on 06/06/2016)

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

INTRAROSA is supplied as white to off-white 1.3 mL solid fat bullet-shaped, smooth vaginal inserts (containing 6.5 mg of prasterone) measuring 28 mm in length and 9 mm in width at the wider end, and weighing 1.2 grams. INTRAROSA is available in small boxes of 4 blister packs containing 7 vaginal inserts (28 vaginal inserts per box). The small box (containing the vaginal inserts) is supplied inside a larger box containing 28 applicators. (NDC 69110-001-01)

16.2 Storage and Handling

Store at 5°C to 30°C (41°F to 87°F). Can be refrigerated.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	6.5 mg prasterone	Adequate
Available units (e.g., bottles of 100 tablets)	4 blister packs containing 7 inserts each (total 28 inserts per box). Supplied with 28 vaginal applicators.	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	White to off-white 1.3 mL solid fat bullet-shaped, smooth vaginal inserts measuring 28 mm in length and 9 mm in width at the wider end, and weighing 1.2 grams. NDC number included	Adequate
Special handling (e.g., protect from light, do not freeze)		
Storage conditions	Store at 5°C to 30°C (41°F to 87°F). Can be refrigerated.	Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Endoceutics	ADEQUATE

Conclusion: ADEQUATE

2. Labels

1) Immediate Container Label

(b) (4)

Reviewer's Assessment:

The individual inserts are small and therefore capturing all information in order (centered) on one insert packaging is difficult. The inserts are packaged in strips of 7 and therefore it can be expected that all information will be legible and visible throughout the use of the 7 day strip. Additionally, the spacing of the information is such that the strength, active ingredient and dosage form, will appear somewhere on every insert's immediate packaging. Though not shown in the picture, the lot number and expiry date will be imprinted at the base of each insert (currently designated by the blue square). Therefore, the only change to communicate for the primary packaging is that the dosage form should be changed to vaginal insert.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size and prominence) (21 CFR 201.10(g)(2))	Spacing is appropriate to permit appearance on all inserts in the strip. The dosage form should be changed to vaginal insert.	INADEQUATE
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Spacing is appropriate to permit appearance on all inserts in the strip.	ADEQUATE
Route of administration (21.CFR 201.100(b)(3))	Spacing is appropriate to permit appearance on all inserts in the strip. Vaginal (b) (4) needs to be changed to Vaginal Insert.	INADEQUATE
Net contents* (21 CFR 201.51(a))	NA	
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) (21CFR 201.100(b)(5)**	NA	
Lot number per 21 CFR 201.18	Located in blue box	ADEQUATE
Expiration date per 21 CFR 201.17	Located in blue box	ADEQUATE
"Rx only" statement per 21 CFR 201.100(b)(1)	Appears on Carton. Size restrictions prevent this on the immediate container closure.	ADEQUATE
Storage (not required)	N/A	
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	N/A	
Bar Code per 21 CFR 201.25(c)(2)***	N/A	
Name of manufacturer/distributor (21 CFR 201.1)	Endoceutics	ADEQUATE
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: INADEQUATE

- Vaginal ^{(b) (4)} should be changed to Vaginal Insert throughout the blister and carton/container.

2) Cartons

QUALITY ASSESSMENT

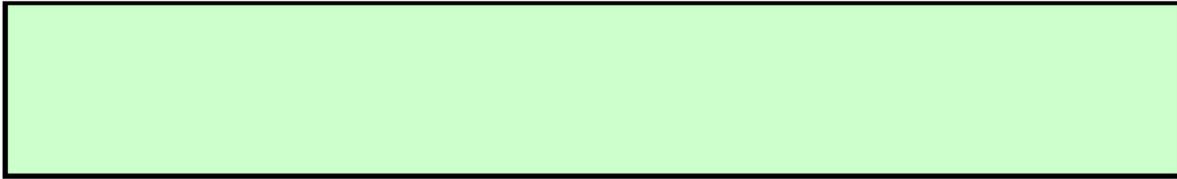


(b) (4)

Item	Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Intrarosa Prasterone vaginal (b) (4). Vaginal (b) (4) should be changed to vaginal insert	INADEQUATE
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	6.5 mg	ADEQUATE
Net contents (21 CFR 201.51(a))	28	ADEQUATE
Lot number per 21 CFR 201.18	Location designated	ADEQUATE
Expiration date per 21 CFR 201.17	Location designated	ADEQUATE
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables][201.10(a), 21CFR201.100(d)(2)]	Not present	INADEQUATE
Sterility Information (if applicable)	N/A	
“Rx only” statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)		ADEQUATE
Storage Conditions	<ul style="list-style-type: none"> • Room temperature below 86°F (30°C) • Can be refrigerated 	ADEQUATE
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Location designated	ADEQUATE
Bar Code per 21 CFR 201.25(c)(2)**	Not present	INADEQUATE
Name of manufacturer/distributor	Manufactured by (b) (4) for Endoceutics	ADEQUATE
“See package insert for dosage information” (21 CFR 201.55)	Dosage can be displayed on box, therefore not required	ADEQUATE
“Keep out of reach of children” (optional for Rx, required for OTC)	N/A	ADEQUATE
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Vaginally	ADEQUATE

Conclusion: INADEQUATE

- Per CFR 201.100(b)(5), include the inactive ingredients on the small box.
- Per CFR 201.25 (c)(2) include a bar code on the label.
- Additionally, replace the term vaginal (b) (4) with vaginal insert throughout the blister and cartons.



OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

- The **Highlight** section should be revised with a correct dosageform, vaginal insert
- The dosage form in the **Dosage form and Strength** (#3) section should be revised with vaginal insert.
- The **Description** (#11) section should be revised as follows:



(b) (4)

- Vaginal ^{(b) (4)} should be changed to Vaginal Insert throughout the blister and carton/container labels.
- Per CFR 201.100(b)(5), cartons should include the list of inactive ingredients on the
- Per CFR 201.25 (c)(2), carton labels should include a bar code.

All these comments were conveyed to the OND on 4/28/16 and 06/06/16.

From the LDT/OPQ perspective, this NDA is not recommended for approval until all

these deficiencies are satisfactorily resolved.

The reviewer's name: Caroline Strasinger, PhD

Secondary Review Comments and Concurrence:

(Secondary reviewer name should be here too).

II. List of Deficiencies To Be Communicated

Label/Labeling

- Per CFR 201.100(b)(5), include the inactive ingredients on the cartons
- Per CFR 201.25 (c)(2) include a bar code on the cartons
- Additionally, replace the term vaginal ^{(b) (4)} with vaginal insert throughout the package insert, blister and cartons.

III. ATTACHMENTS

Attachment A: Lifecycle Knowledge Management

a) Drug Product

Product Attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Physical Stability	Temperature control (a process operation parameter setting) for DS dissolution in Hard Fat is different between (b) (4)	M	M	L	M	(b) (4)
Content Uniformity	No particle size distribution control for DS	M	H	H	H	Low drug load, IPC for completion of drug dissolution in hard fat is via visible particulates. Effect of PSD variation in dissolution is unknown. (b) (4)
Chemical stability and micro-biological control	Failure of drug sealing step	M	H	H	H	(b) (4)
Microbiological control	Validity of micro limit testing method	L	M	L	M	No method suitability study report is provided.
Appearance	• Quality of Raw Materials • Process parameters	1	1	4	4	
Identification	• CGMPs	1	5	2	10	
Assay	• Formulation • Raw Materials • Process	3	5	2	30	Low drug load ((b) (4) % w/w)
Impurities/Degradants	• Process parameters	2	2	4	16	Exposure to heat
Drug Release	• Raw materials • Formulation • Process parameters	1	1	4	4	Drug release from hard fat upon melting in vaginal cavity

RPN Values: **Low Risk (1-25)**; **Moderate Risk (26-60)**; **High Risk (61-125)**

From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/Comments
Melt Temperature	• Raw material variation	L	Raw material controls	Acceptable (L)	Alternate sources of Hard Fat, NF should meet specification (especially Melting Point)
Particulates	• Raw material quality	M	Multiple visual inspections during manufacturing process when wax is clear	Acceptable (L)	

Broken Inserts	• Process parameters	M	Cooling profile optimization; weight check procedure modified; Proper training of personnel and updated AQL	Acceptable (L)	Any changes to process parameters (temperatures and cooling rates) should be evaluated carefully for impact on product integrity
Content Uniformity	• Raw material controls (API particle size) • Process parameters	H	In process controls. Added CU test after primary packaging.	Acceptable	(b) (4)
Physical Stability	(b) (4)	M	Process parameters used at (b) (4) adopted by (b) (4)	Acceptable	
Chemical stability and microbiological control	Failure of drug sealing step	H	In-process seal integrity testing	Acceptable	
Microbiological control	Validity of micro limit testing method	M		Acceptable	
Assay		M	Overall manufacturing controls	Acceptable	

Notes for Lifecycle Knowledge Management:

Process:

(b) (4)

Attachment B: CDRH Consult Reviews

Katelyn Bittleman reviewed the Applicant’s compliance with applicable Quality System Requirements. Her review is attached for detail and a summary of the conclusions follow. Note, that although the recommendation in the attached document is “delay” she stated that due to the low risk of the device component, post-market inspections would be acceptable if pre-approval inspections are unreasonable. Also note that a PAI was conducted at (b) (4) and no items related to 21 CFR part 4 were included in the EIR. (b) (4) does not intend to qualify their applicator supplier (b) (4) until after approval per their quality agreement with EndoCeutics.



ICC1500612_Review
Memo_KRB_AMENDED

Amendment Review:

EndoCeutics explains that the drug product manufacturer, (b) (4) will receive the finished applicators, conduct the final inspection of the devices, and release of the combination product.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.80.

Documentation Review Recommendation

The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable Quality system Requirements showed no deficiencies. No additional information is required for the documentation review.

RECOMMENDATION

The approvability of application Prasterone should be delayed for the following reasons:

- (1) The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies. However, a pre-approval inspection is recommended for:
 - a. EndoCeutics Inc.
2795 Laurier Boulevard
Suite 500
Quebec City, QC, Canada G1V 4M7
FEI#: 3012094463



Katelyn Bittleman -S
2016.06.24 11:21:06 -04'00'

Katelyn R. Bittleman

To: ORA

Inspectional Guidance

Due to the low risk of the device component, post-market inspections at the following facilities would be acceptable if pre-approval inspections are unreasonable.

Firm to be inspected:

EndoCeutics Inc.
2795 Laurier Boulevard
Suite 500
Quebec City, QC, Canada G1V 4M7
FEI#: 3012094463

CDRH recommends that the Pre-Approval Inspection (PAI) inspection of the firm listed above covers compliance with all the requirements of 21 CFR part 4, including the applicable Quality System (21CFR 820) requirements – Management Controls (21 CFR 820.20), Design Controls (21 CFR 820.30), Purchasing Controls (21 CFR 820.50), and CAPA (21 CFR 820.100). Emphasis should be placed on the contractual agreement with SRC Medical. The firm claims management controls, design controls, and CAPA are managed through their agreement with (b) (4)

(b) (4)

CDRH recommends that the Pre-Approval Inspection (PAI) inspection of the firm listed above covers compliance with 21 CFR part 820 with a focus on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30). (Comprehensive Baseline Level 2 inspection)

(b) (4)

CDRH recommends that the Pre-Approval Inspection (PAI) inspection of the firm listed above covers compliance with all the requirements of 21 CFR part 4, including the applicable Quality System (21CFR 820) requirements – Management Controls (21 CFR 820.20), Design Controls (21 CFR 820.30), Purchasing Controls (21 CFR 820.50), and CAPA (21 CFR 820.100).

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (the EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Katelyn R. Bittleman
 Consumer Safety Officer
 Physical Medicine, Orthopedics, Neurology, and Dental Devices Branch
 Division of Manufacturing and Quality
 Office of Compliance, WO66 RM 3451
 Phone: 240-402-1478

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Francisco Vicenty
 Chief
 Respiratory, ENT, General Hospital, & Ophthalmic Device Branch
 Division of Manufacturing and Quality
 Office of Compliance, WO66 RM 3426
 Phone: 301-796-5577

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

Attachment C: CDRH Consult Review

Sharon Andrews reviewed the Applicant’s applicator. She notes that the Applicant did not conduct biocompatibility testing on the applicator as requested in IND 78,027. Based on the short duration of contact of the applicator and its favorable marketing history, the CDRH reviewer agrees that no further biocompatibility testing is warranted, however noting that due to the changes in the applicator during the review cycle, the clinical studies previously conducted are not relevant to support biocompatibility. During the review cycle the applicator was changed including minor changes to the (b)(4) colorant, and surface changes. Sharon Andrews agreed that the changes are minor in nature and that the reduction in material ((b)(4) 3.7 g) are unlikely to cause failure since minimal force is needed for insertion and expelling the active insert. CDRH finds the applicator sufficiently robust for its intended use and comparable to other marketed vaginal applicators and the applicator is recommended for approval for the use described in NDA 208470. Her review is attached for further detail.



NDA208470_EndoCeutics_PrasteroneVagina

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