CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209627Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: ***Approval***

NDA 209627
Review # 1

ANNOVERA
(segesterone acetate and ethinyl estradiol vaginal system)

Drug Name/Dosage Form	segesterone acetate and ethinyl estradiol vaginal system
Strength	150 mcg/day segesterone acetate / (b) (4) mcg/day EE
Route of Administration	Vaginal
Rx/OTC Dispensed	Rx
Applicant	The Population Council, Inc.
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original (0001)	08/17/17	Multi-discipline
Amendment (0005)	10/31/17	Multi-discipline
Amendment (0006)	11/21/17	Process, Biopharm.
Amendment (0007)	12/05/17	OTR/DPA
Amendment (0008)	12/20/17	OTR/DPA
Amendment (0011)	02/06/18	Multi-discipline
Amendment (0012)	02/16/18	Multi-discipline
Amendment (0013)	02/23/18	Product, Biopharm., Process
Amendment (0014)	03/14/18	Multi-discipline
Amendment (0015)	04/05/18	Product Labeling
Amendment (0016)	04/11/18	Process
Amendment (0017)	04/20/18	Multi-discipline
Amendment (0018)	04/26/18	Multi-discipline
Amendment (0021)	05/18/18	Multi-discipline
Amendment (0023)	05/29/18	Product, Process, Biopharm.
Amendment (0025)	07/19/18	Product, Biopharm.
Amendment (0026)	07/27/18	Product, Product Labeling
-	07/31/18	Product Labeling

Quality Review Team

Discipline	Primary Reviewer / Secondary Reviewer	Branch / Division
Drug Substance	Soumya Mitra / Donna Christner	BII / DNDAPI /ONDP
Drug Product	Hong Cai / Moo-Jhong Rhee	BV / DNDPII / ONDP
Labeling	Hong Cai / Moo-Jhong Rhee	BV / DNDPII / ONDP
Process	James Norman / Yubing Tang	BVIII / DPAIII / OPF
Microbiology	Avital Shimanovich / Marla Stevens-Riley	BI / DMA / OPF
Facility	Vidya Pai / B.J. Ryan	BIII / DIA / OPF
Biopharmaceutics	Suneet Shukla / Vidula Kolhatkar / Sandra Suarez	BII / DB / ONDP
RBPM	Thao Vu & Florence Aisida	BI / DRBPM I / OPRO
Application Technical Lead	Mark Seggel	BV / DNDPII / ONDP
Laboratory (OTR)	Michael Hadwiger	DPA /OTR
Environmental Analysis (EA)	Jim Laurenson	ONDP EA Team

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	Adequate	Review #22 07/27/17	
	II			Adequate	Soumya Mitra 03/15/18	
	III			N/A		
	Device			Adequate	Hong Cai 05/25/18	

N/A: There is enough data in the application, therefore the DMF did not need to be reviewed.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND submissions and associated reviews	IND 49980	SA + EE IVR for Contraception

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	na			
Pharmacology/ Toxicology	na			
CDRH-ODE	Complete	Approval	03/08/18	Veronica Price
CDRH-OC	Complete	Defer to OPF/DIA	12/06/17 03/21/18	John Gomes
Clinical	na			
Other	na			

na: not applicable

Executive Summary

I. Recommendations and Conclusion on Approvability

The Population Council's 505(b)(2) new drug application for Annovera (segesterone acetate and ethinyl estradiol vaginal system) is recommended for APPROVAL from the OPQ perspective.

Annovera is a drug-device combination product. CDRH-ODE has determined that the mechanical and biocompatibility properties of the finished product have been adequately demonstrated. Sufficient chemistry, manufacturing and controls 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 revised drug product labeling as submitted on July 31, 2018 is accurate, complete and complies with the requirements under 21 CFR 201.

The drug substance manufacturing facilities have acceptable CGMP status. The finished product manufacturing site, QPharma AB, is acceptable from the CDRH-OC and CDER/OPQ/OPF perspectives. An Overall Inspection Recommendation of Approve was issued by the OPF Division of Inspectional Assessment on April 5, 2018.

The claimed categorical exemptions from the environmental assessment requirements are acceptable.

POSTMARKETING COMMITMENTS

The Applicant has agreed to a PMC to characterize the in vivo release rate (b) (4) (b) (4)

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	Annovera is an estrogen / progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy.
Duration of Treatment	One vaginal system is designed to deliver drug over thirteen (b) (4) cycles
Maximum Daily Dose	Average daily release over 273 days is 150 mcg/day segesterone acetate and 13 mcg/day EE (measured)
Alternative Methods of Administration	Not Applicable

Annovera (segesterone acetate and ethinyl estradiol vaginal system) is a flexible silicone elastomer vaginal ring designed to deliver approximately 150 mcg/day segesterone acetate (SA) and (b) (4) mcg/day ethinyl acetate (EE) over a total of 273 days. (Current data suggests an average of 13 mcg/day EE. The product strength will be labeled accordingly.) Each vaginal system contains 103 mg segesterone acetate and 17.4 mg ethinyl estradiol. The ring is worn for 21 days and then removed, rinsed and stored. After 7 days it is re-inserted for another (b) (4) cycle. After thirteen cycles, the ring is discarded.

The advantage of a contraceptive vaginal ring is associated with convenience, especially when compared to once-daily oral products. Drug is delivered locally, minimizing systemic exposure. Insertion and removal are easily performed by the user. This affords more flexibility to the user than intrauterine systems.

B. Quality Assessment Overview

ANNOVERA (segesterone acetate and ethinyl estradiol vaginal system) is combination hormonal contraceptive (CHC) product designed to deliver low levels of a progestin and an estrogen over thirteen (b) (4) cycles.

Each vaginal system, more commonly known as a vaginal ring, contains 103 mg segesterone acetate (SA) and 17.4 mg ethinyl estradiol (EE). When placed in the vagina, each ring releases, on average, 0.15 mg/day of segesterone acetate and 0.013 mg/day of ethinyl estradiol.

Segesterone acetate is a progestin chemically known as 19-norpregn-4-ene-3,20-dione, 17-hydroxy-16-methylene-, acetate and as 17-hydroxy-16-methylene-19-norpregn-4-ene-3,20-dione, acetate ester. The chemistry, manufacturing and controls (CMC) of segesterone acetate, a new molecular entity (NME), is adequately documented (b) (4)

Ethinyl estradiol has a long history and is a widely used component of CHC. The CMC for EE is adequately documented (b) (4)

ANNOVERA (segesterone acetate and ethinyl estradiol vaginal system) differs from the three FDA-approved vaginal rings, NuvaRing, Estring and Femring in several important ways. First, it is designed to be used for thirteen (b) (4) cycles. It is removed and stored for 7-days between each (b) (4) cycle. Second, rather than having a continuous drug-containing elastomeric core with or without a release-rate controlling membrane, two short drug-containing elastomeric (b) (4) are inserted and sealed in the Annovera ring body. (b) (4)

In addition to segesterone acetate and ethinyl estradiol, Annovera consists of several types of silicone elastomers (b) (4) and titanium dioxide, (b) (4) The silicone elastomer components are manufactured by (b) (4)
(b) (4)

There are three essential components of the Annovera vaginal system: a ring body with an overall outside diameter of 56 mm and a cross-sectional diameter of 8.4 mm, and two drug-containing (b) (4) cores. (b) (4) The ring body has two channels approximately 3.0 mm in diameter and 27 mm in length. Two drug-loaded cores are inserted and sealed in each channel with a silicone medical adhesive. Cores are 3 mm in diameter. One of the cores is 18 mm in length and contains (b) (4) SA and (b) (4) EE. The other core is 11 mm in length and contains (b) (4) SA.

The silicone elastomer ring bodies are manufactured (b) (4)
(b) (4)
(b) (4) Despite the complexity, the current manufacturing process and in-process controls are adequate to ensure product with the requisite quality and performance.

The essential performance characteristic of the vaginal system is the slow, controlled release of drug from the polymeric matrix. A fast release rate may result in safety concerns. Conversely, a slow release rate may result in delivery of levels of drug too low to support efficacy. To ensure the appropriate batch-to-batch performance characteristics of the product, two in vitro release tests were developed. An accelerated method was found in adequate for use. The other test method measures the in vitro release of drugs over a 30-day period. The biopharmaceutics review team performed extensive analyses to establish clinically relevant acceptance criteria. To ensure that the in vitro release criteria are met throughout the shelf-life as required by the regulatory specification, acceptance criteria for in vitro release testing for batch release was also established.

The Applicant's proposed in vitro in vivo correlation (IVIVC) was found unsuitable for use in providing a bridge to support formulation and manufacturing process changes.

The in vivo release rate of the active ingredients was determined by measuring residual drug levels in the rings after use for thirteen cycles. While this gives an idea of the average rate of in vivo release, it does not adequately capture the decrease in release rate

over time. The Applicant has agreed to further characterize the in vivo release rate (b) (4) as a post-marketing commitment.

In addition to in vitro release testing, the product specification includes tests for identity, dimensions, mass, (b) (4) hardness (b) (4), EE assay, SA assay, content uniformity, and related substances. Although vaginal rings are not manufactured as sterile products, they must meet requirements for microbial quality, and must be free of several specific microorganisms (e.g., E. coli). To minimize microbial contamination during the 7-day storage, the removed rings should be washed with mild soap and water and rinsed and patted dry.

Veronica Price, Biomedical Engineer in CDRH-ODE determined that the mechanical properties (e.g., (b) (4) hardness, elongation at break, compression strength) and biocompatibility of the finished combination were adequately characterized and documented, and that the vaginal ring was suitable for the intended use. In addition, it was determined that the vaginal system is compatible with condoms made from natural rubber latex, polyisoprene and polyurethane. The product should not be used with silicone-based personal lubricants. Consideration of potential interactions with tampons is deferred to the clinical and clinical pharmacology teams.

The stability of Annovera at 25°C for 18 months has been adequately demonstrated; an 18-month expiration dating period is therefore granted. (b) (4) Storage at elevated temperatures for long periods of time can adversely impact product performance. This applies to product before first use and when stored between (b) (4) cycles.

The drug substance manufacturing facilities have acceptable CGMP status. The product manufacturer, QPharma AB, Malmo, Sweden, was satisfactorily inspected for drug and medical device GMP compliance in December 2017. All ancillary facilities have acceptable CGMP status. An Overall Inspection Recommendation of Approve was issued by the OPF Division of Inspectional Assessment on April 5, 2018. The OPF review team recommends a post-approval inspection due to the complexity of the product and the likelihood of scale-up.

The applicant submitted a claim for a categorical exclusion from the requirement to prepare an environmental assessment (EA) for ethinyl estradiol (EE), pursuant to 21CFR25.31(a) (i.e., use will not increase) and for segesterone, per 21 CFR 25.31(b) (i.e., use will increase but the expected introduction concentration (EIC) will be <1 ppb), for this application. A statement regarding the applicant's knowledge of extraordinary circumstances was submitted, as required per 21 CFR 25.15(a).

Based on a review of the information provided by the applicant, and additional information obtained by FDA, the claims for categorical exclusions from EAs are acceptable. FDA also noted that because approval will result in expected concentrations of segesterone acetate that could approach environmental benchmarks, and because of the

potential for cumulative effects from other drugs and xenobiotics with similar mechanisms of action, FDA recommends a prudent use of label language that provides guidance regarding environmentally protective disposal practices.

Historically, drug-releasing elastomeric rings for vaginal administration have been referred to as either intravaginal rings (IVR) or vaginal rings. These are broadly understood and concise description of the products. The labeling of the approved products, NuvaRing, Estring and Femring, identifies them as 'vaginal rings.' The (b) (4) However, in keeping with current USP and OPQ/OPPQ recommendations, vaginal rings are to be labeled 'vaginal system.' The established name of the product is thus, 'segesterone acetate and ethinyl estradiol vaginal system.' This change has been made throughout the Annovera labeling. Note that, as confirmed by OPPQ, use of the term 'ring' as a descriptor in labeling text is acceptable.

A review of the product labeling from the OPQ perspective (see IQA Chapter IV) identified several deficiencies. These deficiencies have been communicated to the Applicant, and after several rounds of revisions, the product labeling is now acceptable from the OPQ perspective. The draft labeling (USPI, IFU, PPI, primary container (foil pouch), and secondary container (carton) as submitted on July 31, 2018 is complete and accurate from the OPQ perspective.

The product is supplied with a (b) (4) storage case to be used when the product is not worn. (b) (4)
(b) (4)

The Applicant proposed (b) (4) Comparability Protocols. The protocol covering minor changes (b) (4) and documentation via a CBE-30 supplement was accepted as revised. (b) (4)

Because there currently is limited understanding of the potential impact of various changes in raw materials and process conditions, for example, on product performance (i.e., drug release) and biocompatibility, future post-approval changes should be carefully evaluated from the product, process, biopharmaceutics and device perspectives. See Attachment 1.

C. Special Product Quality Labeling Recommendations

Not Applicable

D. Final Risk Assessment / Life Cycle Management (see Attachment I)

OVERALL ASSESSMENT AND SIGNATURE:

Application Technical Lead Name:
Mark R. Seggel, Ph.D.
CMC Lead (acting)

{see electronic signature page}

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance
CHAPTER II: Drug Product
CHAPTER III: Environmental Assessment
CHAPTER IV: Labeling
CHAPTER V: Process
CHAPTER VI: Facilities
CHAPTER VII: Biopharmaceutics
CHAPTER VIII: Microbiology
CHAPTER IX: Additional Quality Discipline *(Not Applicable)*
Attachment I: Final Risk Assessment / Life Cycle Management
Attachment II: List of Deficiencies for Complete Response (*Not Applicable*)

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Mark Seggel

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ENVIRONMENTAL

IQA Review Guide Reference

R Regional Information

The applicant submitted a claim for a categorical exclusion from the requirement to prepare an environmental assessment (EA) for ethinyl estradiol (EE), pursuant to 21CFR25.31(a) (i.e., use will not increase) and for segesterone, per 21 CFR 25.31(b) (i.e., use will increase but the expected introduction concentration (EIC) will be <1 ppb), for this application. A statement regarding the applicant's knowledge of extraordinary circumstances was submitted, as required per 21 CFR 25.15(a). The applicant provided additional information to support the claims for exclusion. FDA has determined that the applicant cited the appropriate exclusions and provided the required statement of no extraordinary circumstances. Based on a review of the information provided by the applicant, and additional information obtained by FDA, the claims for categorical exclusions from EAs are acceptable. FDA also noted that because approval will result in expected concentrations of segesterone that could approach environmental benchmarks, and because of the potential for cumulative effects from other drugs and xenobiotics with similar mechanisms of action, FDA recommends a prudent use of label language that provides guidance regarding environmentally protective disposal practices.

Environmental

During the investigational new drug (IND) phase, the applicant, in accordance with the draft (at the time) of FDA Guidance for Industry, "Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity", April 2015 (now USFDA, 2016), notified FDA that they planned to submit claims for categorical exclusions from an environmental assessment (EA) in the new drug application (NDA). The applicant also noted that they will state that no extraordinary circumstances exist under 21 CFR 25.21.

FDA responded that it concurs with the claim for a categorical exclusion from an EA for ethinyl estradiol (EE), assuming the exclusion to be claimed for this substance is pursuant to 21CFR25.31(a) (i.e., that EE will not increase in use), and that a rationale needs to be provided that includes an estimate of the amount of EE that will be used as a result of this application, along with the expected introduction concentration (EIC) and why the use of EE will not increase.

For segesterone, FDA responded to the claim for an EA exclusion that it was unclear whether the applicant was claiming an exclusion pursuant to 21CFR25.31(b) (i.e., use will increase but the EIC will be <1 ppb), and thus clarification would be needed. FDA also asked for additional information to assist in making a determination about whether the claim would be acceptable, per USFDA (2016). The information needed included (1) the expected use amount and associated EIC, with supporting calculations; (2) a summary of available data on measured or estimated concentrations and predicted no-effects

concentrations (PNECs) of similar substances in the aquatic environment (e.g., see Fent, 2015); and (3) a discussion of segesterone's potential for aquatic effects, including those relevant to USFDA (2016), taking into account the substance's EIC, mechanism of action, nonclinical and other toxicity data, plasma-based analysis (e.g., per Huggett et al., 2003), "read across" analysis, and any other relevant and available information or environmental risk assessments. FDA noted that submission of this information prior to the planned application would assist in the timely initiation of any needed assays should an EA be needed.

In response to the above, the applicant provided a July 10, 2017 document, Environmental Risk Assessment and Request for Categorical Exclusion. This document confirmed that the total amount of EE introduced into the environment is not expected to increase. The highest production amount expected through 5th year sales under this application is (b) (4) The document also noted that segesterone is projected to result in an EIC of (b) (4) based on (b) (4) production as the highest amount through 5th year sales. This concentration is less than 1 ppb, which satisfies the exclusion criterion.

The applicant noted that segesterone is a synthetic derivative of 19-nor-progesterone, which has strong and selective binding affinity to progestogen receptors (PRs). Segesterone also has been shown to be anti-estrogenic and, consequently, to have the potential for adverse reproductive activity. The applicant also noted that progestins, consistent with their therapeutic use, are often associated with decreased fecundity and other signs of reproductive and developmental toxicity in fish. Androgenic progestins such as levonorgestrel (LNG) and norethindrone (NET) are noted to be potent fish androgen receptor (AR) agonists and associated with decreased fecundity and skewed sex ratios in fish, with some lowest-observed-effect concentrations (LOECs) in the range of (b) (4) ng/L. In non-androgenic progestins, the applicant stated, comparable effects in fish are only seen starting at much higher concentrations ((b) (4) ng/L for progesterone and drospirenone, respectively). Indeed, segesterone is notable, according to the applicant, for being completely devoid of androgenic activity, even at high doses, and thus is not expected to cause AR agonism-related adverse reproductive effects in fish at concentrations comparable to those of androgenic progestins. As such, the applicant concluded, segesterone is unlikely to contribute to the total aquatic burden of androgenic progestins.

Overall, the applicant noted, the potential for segesterone to cause adverse reproductive and/or developmental effects on aquatic organisms cannot be excluded in the absence of definitive data. However, as a non-androgenic progestin, potential effects are predicted to occur at higher concentrations than those reported for approved, androgenic progestins.

Regarding environmental concentration factors, the applicant noted that studies with human hepatocytes and hepatic microsomes indicate that, compared to other progestins, systemically absorbed segesterone is rapidly metabolized. However, segesterone is also a hydrophobic steroid hormone that has a theoretical potential to bioaccumulate.

Reviewer's Assessment:

The claim for a categorical exclusion from an EA for EE per 21 CFR Part 25.31(a) is appropriate given no increase in use is expected. The calculation provided with the updated exclusion request appears accurate. An adequate statement of no knowledge of extraordinary circumstances per 21 CFR 25.15 is present. Similarly, the claim for a categorical exclusion from an EA for segesterone per 21 CFR Part 25.31(b) is appropriate for the anticipated amount of the drug to be used (< 1 µg/L EIC). An adequate statement of no knowledge of extraordinary circumstances per 21 CFR 25.15 is present.

The data submitted to support the claim for a categorical exclusion from an EA for segesterone is consistent with EA guidance on hormonally active drugs (USFDA, 2016) and the mechanism of segesterone as a selective progesterone modulator that has the potential to indirectly affect various estrogen effects (CTD section 2.4, Nonclinical Overview). FDA agrees that while LOECs for progestins exist in the range of (b) (4) ng/L, which is slightly above the segesterone EIC of (b) (4) ng/L. Non-androgenic progestins such as progesterone have been reported to cause reproductive adverse effects in fish at higher concentrations (b) (4) Nevertheless, there are data showing that non-androgenic progestins (progesterone) do affect the expression of vitellogenin and other markers at (b) (4) in fish embryos (Kumar et al., 2015), which would result in a risk ratio of (b) (4) Given the worst-case assumptions used—all residual drug in the ring is released, there is no metabolism, treatment, dilution, or degradation in the environment, and the LOEC is used for an endpoint (vitellogenin) that is not considered to be an apical endpoint—a ratio of less than 1 generally would indicate that approval of this application would not pose a significant risk to the environment. In this case, however, there is additional uncertainty not addressed, specifically the potential for undetected apical effects, given the lack of acceptable assays specifically on the molecule of concern (segesterone), and for cumulative effects from other drugs and xenobiotics with similar mechanisms of action, as highlighted by Runnalls et al. (2013) and Council on Environmental Quality guidance (CEQ, 2010). Therefore, similar to mitigation measures that would be developed for an EA (USFDA, 1998), FDA recommends a prudent use of label language that would enhance the current language and is consistent with the FDA label review tool (USFDA, 2017):

1. Current language in Section 16 of the label includes disposal language that could be enhanced as follows, "A compact case is provided with the drug product for storage of the SA/EE (b) (4) by patients during each 7 day (b) (4) out interval. The (b) (4) should be placed in the compact case after 13 cycles of use and discarded via a drug take-back option if one is available. If a take-back option is unavailable, then discard in a waste receptacle out of reach of children and pets. It should ~~not~~NOT be flushed down the toilet. See www.fda.gov/drugdisposal for more information about disposal of medicines."

2. In Patient Information:

   a. Under [redacted] (b) (4) after the SCHEDULE table on p. 6, in the bullet that begins "Do not use the RING for more than 13 cycles…", change the [redacted] (b) (4) sentence as follows: "Place the used ring in the compact case and discard via a drug take-back option if one is available. If a take-back option is unavailable, then ~~Y~~you can dispose of it in the trash out of reach of children and pets. Do ~~not~~NOT flush it down the toilet."

   b. [redacted] (b) (4)

3. On the carton and container, under "Storage", add "Do NOT flush used or unused product."

References:

CEQ, 2010. Final Guidance for Federal Departments and Agencies on Establishing, Applying, and Revising Categorical Exclusions under the National Environmental Policy Act. 75 Federal Register 75628.

Fent, K. 2015. Progestins as endocrine disrupters in aquatic ecosystems: concentrations, effects and risk assessment. Environment International, 84: 115-130.

Huggett, D. B., J. C. Cook, J. F. Ericson and R. T. Williams. 2003. A theoretical model for utilizing mammalian pharmacology and safety data to prioritize potential impacts of human pharmaceuticals to fish. Human and Ecological Risk Assessment: An International Journal, 9(7): 1789-1799.

Kumar, V., Johnson, A.C., Trubiroha, A., Tumová, J., Ihara, M., Grabic, R., Kloas, W., Tanaka, H. and Kroupová, H.K. 2015. The challenge presented by progestins in ecotoxicological research: a critical review. Environmental science & technology, 49(5), pp.2625-2638.

USFDA. 1998. Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications. Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD.

USFDA. 2016. Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity. Center for Drug Evaluation and Research. US Food and Drug Administration, Silver Spring, MD. Available at https://www.fda.gov/downloads/Drugs/Guidances/UCM444658.pdf

USFDA. 2017. Labeling Review Tool (Internal Use Only). Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD.

Primary Environmental Reviewer Name and Date: James Laurenson, April 16, 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Scott Furness, April 17, 2017

James Laurenson

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Michael Furness

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LABELING

I. Package Insert

Note: This review is based on the draft labeling submitted on 04-05-2018 (SN0015).

1. Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Annovera™ safely and effectively.
See full prescribing information for Annovera™.

Annovera™ (segesterone acetate and ethinyl estradiol) vaginal (b) (4)
Initial U.S. Approval: 2018

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS
See full prescribing information for complete boxed warning.
(b) (4) over 35 years old who smoke should not use Annovera™.
Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptive (CHC) use.
(b) (4)

----------INDICATIONS AND USAGE----------
Annovera™ is an estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by (b) (4) to prevent pregnancy. (1)

----------DOSAGE AND ADMINISTRATION----------
One Annovera™ is inserted in the vagina. The (b) (4) must remain in place continuously for three weeks (21 days) followed by a one-week (7 day) (b) (4)-free interval. One (b) (4) provides contraception for thirteen 28-day cycles (1 year).

----------DOSAGE FORMS AND STRENGTHS----------
Annovera™ is a silicone elastomer vaginal (b) (4) containing 103 mg segesterone acetate and 17.4 mg ethinyl estradiol, which releases on average 0.15 mg/day of segesterone acetate and (b) (4) mg/day of ethinyl estradiol.

Item	Information Provided in NDA	Reviewer's Assessment
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))		
Proprietary name and established name	Annovera™ (segesterone acetate and ethinyl estradiol) vaginal (b) (4)	**Not Satisfactory** Revise to "Annovera™ (segesterone acetate and ethinyl estradiol vaginal system).
Dosage form, route of administration	vaginal (b) (4)	**Not Satisfactory** Revise to "vaginal system".
Controlled drug substance symbol (if applicable)	N/A	NA

Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))		
Summary of the dosage form and strength	Annovera™ is a silicone elastomer vaginal (b) (4) containing 103 mg segesterone acetate and 17.4 mg ethinyl estradiol, which releases on average 0.15 mg/day of segesterone acetate and (b) (4) mg/day of ethinyl estradiol.	**Not Satisfactory** …vaginal (b) (4) should be revised to vaginal system containing… The release rate value should be revised to "0.15 mg/day of segesterone acetate and 0.013 mg/day of ethinyl estradiol" per in vivo release rate study.

2. FULL PRESCRIBING INFORMATION

Section 2 Dosage and Administration

See PI for the full details.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c) (12))		
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	N/A	Refer to CDRH review comments for special instruction regarding the compatibility with the lubricants.

3. *Section 3 Dosage Forms and Strengths*

3 DOSAGE FORMS AND STRENGTHS

Annovera™ (segesterone acetate and ethinyl estradiol) is a non-biodegradable, flexible, opaque white, contraceptive vaginal [redacted] containing [redacted] (SA: 103 mg), and [redacted] (EE; 17.4 mg). [redacted] Annovera™ is 56 mm in overall diameter and 8.4 mm in cross-sectional diameter. It contains two channels of approximately 3.0 mm diameter and approximately 27 mm length into which steroid-containing cores are inserted. The cores are 3 [redacted] mm in diameter. Contact between the cores and the ring body is fixed by coating the channels with silicone medical adhesive before introducing the cores. After insertion of the cores, the channels are sealed with the silicone medical adhesive. [redacted] core contains 40% SA and 12% EE and is 18 mm in length. The [redacted] core contains 50% SA and is 11 mm in length. [redacted] the steroids diffuse out of the [redacted] The inactive ingredients are silicone elastomer and titanium dioxide.

Each Annovera™ is designed to be used for up to 13 cycles (1 year).

Annovera™ is not made with natural rubber latex.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))		
Available dosage forms	Vaginal (b) (4)	**Not Satisfactory** Revise to "vaginal system".
Strengths: in metric system	(b) (4) the steroids diffuse out of the (b) (4)	**Not Satisfactory** Strengths should be expressed in the unit of mg to be consistent throughout PI. The values should be revised to 0.15 mg/day for SA and 0.013 mg/day for EE.
Active moiety expression of strength with equivalence statement (if applicable)	NA	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Annovera™ (segesterone acetate and ethinyl estradiol) is a non-biodegradable, flexible, opaque white, contraceptive vaginal (b) (4) containing (b) (4) (SA: 103 mg), and (b) (4) (EE; 17.4 mg). (b) (4) (b) (4) (b) (4) Annovera™ is 56 mm in overall diameter and 8.4 mm in cross-sectional diameter. It contains two channels of approximately 3.0 mm diameter and approximately 27 mm length into which steroid-containing cores are inserted. The cores are 3 (b) (4) mm in diameter.	**Satisfactory**. However, the following statement needs to be clarified: This reviewer recommends moving the following statement to Section #11, Description for better clarity: "Contact between the cores and the (b) (4) body is fixed by coating the channels with silicone medical adhesive before introducing the cores. After insertion of the cores, the channels are sealed with the silicone medical adhesive. (b) (4) core contains 40% SA and 12% EE and is 18 mm in length. The (b) (4) core contains 50% SA and is 11 mm in length."

4. ***Section 11 Description***

11 DESCRIPTION

Annovera™ (segesterone acetate and ethinyl estradiol)

(b) (4)

(b) (4) The (b) (4) body has an overall diameter of 56 mm and a cross-sectional diameter of 8.4 mm. (b) (4) 103 mg of SA is distributed throughout (b) (4) (b) (4) cores; and 17.4 mg of EE is distributed throughout one core. (b) (4)

(b) (4)

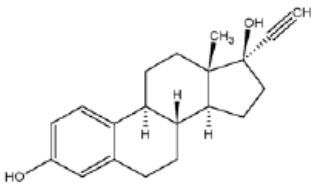
The structural formulas, (b) (4) for the active components are shown below:

(b) (4)

Segesterone acetate (SA)

$C_{23}H_{30}O_4$ **MW: 370.5**

Segesterone acetate is 16-methylene-17α-acetoxy-19-nor-pregn-4-ene-3,20-dione.



Ethinyl Estradiol (EE)

$C_{20}H_{24}O_2$ **MW: 296.4**

Ethinyl Estradiol is 19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol.

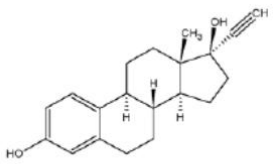
The steroids diffuse out of the (b) (4)

(b) (4) The daily release rates of SA and EE are higher during each initial (b) (4) hours of use achieving a somewhat lower steady-state with continued use over the subsequent (b) (4) days. The (b) (4) is designed to be used for 13 cycles (1 year) on a 21/7 days in/out schedule; the total in-use time with the 21/7 days in/out schedule over 13 cycles is 273 days. (b) (4)

(b) (4)

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c) (12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))		
Proprietary name and established name	Annovera™ (segesterone acetate and ethinyl estradiol)	**Not Satisfactory** Revise to "Annovera™ (segesterone acetate and ethinyl estradiol vaginal system)"
Dosage form and route of administration	The (b) (4) is designed…	**Not Satisfactory** Revise to "Annovera™ (segesterone acetate and ethinyl estradiol vaginal system)" (b) (4) needs to be changed to "vaginal system"
Active moiety expression of strength with equivalence statement (if applicable)	N/A	**N/A**
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	(b) (4) (b) (4)	**Not Satisfactory.** Revise to "The inactive ingredients are silicone elastomers and silicone medical adhesive."
Statement of being sterile (if applicable)	Not Provided.	**Satisfactory** Not Applicable. This is vaginal system which is not required to be sterile.

Pharmacological/ therapeutic class	(b) (4) [redacted]	**Not Satisfactory** Include the pharmacological class of EE.
Chemical name, structural formula, molecular weight	(b) (4) [redacted] **Segesterone acetate (SA)** $C_{23}H_{30}O_4$ Segesterone acetate is 16-methylene-17α-acetoxy-19-nor-pregn-4-ene-3,20-dione.  **Ethinyl Estradiol (EE)** $C_{20}H_{24}O_2$ Ethinyl Estradiol is 19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol.	**Not Satisfactory.** Specify the correct chirality of segesterone acetate in the structure.
If radioactive, statement of important nuclear characteristics.	Not Applicable	**Not Applicable**
Other important chemical or physical properties (such as pKa or pH)	Not provided.	**Not Satisfactory.** Provide the important chemical or physical properties of EE and SA, such as pH and solubility.

5. ***Section 16 How Supplied/Storage and Handling***

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Each Annovera™ (segesterone acetate and ethinyl estradiol) is individually packaged in an aluminum pouch. The pouch consists of a laminate from outside to inside of polyester, aluminum foil and polyethylene. A compact case is provided with the drug product for storage of Annovera™ by patients during each 7 day (b) (4)-out interval. The (b) (4) should be placed in the compact case after 13 cycles of use (b) (4) (b) (4) should not be flushed down the toilet.

(b) (4) 1 pouch. NDC xxxx-xxxx-xx

16.2 Storage Conditions

Prior to dispensing Annovera™ to the user, store Annovera™ at 25°C (77°F) with excursions permitted to 15° to 30° C (59° to 86° F) [See USP Controlled Room Temperature]. Protect Annovera™ from direct sunlight. Do not refrigerate or freeze and avoid excessive heat.

Manufactured for:
Population Council
One Dag Hammarskjold Plaza
New York, NY 10017
United States

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))		
Strength of dosage form	Not Provided.	**Not Satisfactory** Add the following: "When placed in the vagina, each system releases on average 0.15 mg/day of segesterone acetate and 0.013 mg/day of ethinyl estradiol over a 21 days in-use period of each cycle for up to 13 cycles (total of 273 days). Each cycle is 28 days with 21 days in and 7 days out. One vaginal system provides contraception for thirteen 28-day cycles (1 year)."
Available units (e.g., bottles of 100 tablets)	Each Annovera™ (segesterone acetate and ethinyl estradiol) is individually packaged in an aluminum pouch. (b) (4) 1 pouch.	**Not Satisfactory** Revise to "Each Annovera™ (segesterone acetate and ethinyl estradiol vaginal system) is individually packaged in an aluminum pouch. Each box contains one pouch."
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC xxxx-xxxx-xx	**Not Satisfactory.** There is no Identification characteristics provided. Revise to "Annovera™ (segesterone acetate and ethinyl estradiol vaginal system) is a non-biodegradable, flexible, opaque white, (b) (4) shaped vaginal (b) (4)"
Special handling (e.g., protect from light)	Protect Annovera™ from direct sunlight. Do not refrigerate or freeze and avoid excessive heat.	**Satisfactory.**

Storage conditions	Prior to dispensing Annovera™ to the user, store Annovera™ at 25°C (77°F) with excursions permitted to 15° to 30° C (59° to 86° F) [See USP Controlled Room Temperature].	**Not Satisfactory.** Revise the expression of the storage temperature per USP standard room temperature statement format: at 20°-25°C (68°-77°F) instead of "at 25°C (77°F)". Add "Do NOT flush used or unused product." (This is based on the recommendation from EA reviewer James Laurenson via email on 04/11/2018.)
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for: Population Council One Dag Hammarskjold Plaza New York, NY 10017 United States	**Satisfactory**

II. Labels:

1. ***Container Labels (Pouch)***

(b) (4)

(b) (4)

Item	Information provided in the container label	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	annovera (segesterone acetate/ethinyl estradiol vaginal (b) (4)	**Not Satisfactory** Revise to "Tradename (segesterone acetate and ethinyl estradiol vaginal system)" to be consistent with similar approved product on the markets. The size of established name should be at least 50% of the tradename.
Dosage strength	Delivers 0.150mg/ (b) (4) mg per day	**Not Satisfactory** The release values should be revised to 0.15 mg/0.013 mg per day.
Net contents	Contains 1 (b) (4)	**Not Satisfactory** Contains 1 vaginal system
"Rx only" displayed prominently on the main panel	Rx only	**Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	NDAXXXX-XXXX-XX	**Satisfactory** Place holder provided
Lot number and expiration date (21 CFR 201.17)	LOT: XXXX EXP: XX/XXXX MFG: XX/XXXX Product must be used prior expiration date	**Satisfactory** Place holder provided

Storage conditions	Storage: Prior to dispensing Annovera to the user, store Annovera at 25°C (77°F) with excursions permitted to 15-30°C (59 to 86°F) [See USP Controlled Room Temperature]. Protect Annovera from direct sunlight. Do not refrigerate or freeze and avoid excessive heat.	**Not Satisfactory** Revise the expression of the storage temperature per USP standard room temperature format: at 20°-25°C (68°-77°F) instead of "at 25°C (77°F)". Add "Do NOT flush used or unused product." (This is based on the recommendation from EA reviewer James Laurenson via email on 04/11/2018.)
Bar code (21CFR 201.25)	BARCODE	**Satisfactory** Place holder provided
Name of manufacturer/distributor	Manufactured by QPharma, Sweden Distributed by [COMPANY TO BE NAMED] [Address to be named] Product of Sweden Copyright ©XXXX, [COMPANY TO BE NAMED] All Rights Reserved	**Satisfactory**
And others, if space is available	For vaginal use Do not use if seal on pouch is broken	

2. ***Carton Label***

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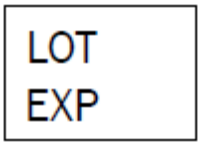
Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	annovera (segesterone acetate/ethynyl estradiol vaginal (b) (4)	**Not Satisfactory** Revise to: annovera (segesterone acetate and ethinyl estradiol vaginal system) Note: a space is needed between estradiol and vaginal The size of established name should be at least 50% of the tradename
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	Delivers 0.150mg/(b) (4) mg per day	**Not Satisfactory** The release values should be revised.
Net quantity of dosage form	Contains 1 (b) (4)	**Not Satisfactory** Contains 1 vaginal System
"Rx only" displayed prominently on the main panel	Rx only Rx (located at the back)	**Not Satisfactory** Revise **"Rx"** located at the back to "Rx only"
Lot number and expiration date		**Satisfactory** Place holder provided
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	**Storage:** Prior to dispensing Annovera to the user, store Annovera at 25°C (77°F) with excursions permitted to 15° - 30° C (59° to 86° F) [See USP Controlled Room Temperature]. Protect Annovera from direct sunlight. Do not refrigerate or freeze and avoid excessive heat.	**Not Satisfactory** Revise the expression of the storage temperature per USP standard room temperature statement format: at 20°-25°C (68°-77°F) instead of "at 25°C(77°F)". Add "Do NOT flush used or unused product. (This is based on the recommendation from EA reviewer James Laurenson via email on 04/11/2018.)

Bar code (21CFR 201.25)	BARCODE	**Satisfactory** Place holder provided
NDC number (21 CFR 207.35(b)(3)(i))	NDAXXX-XXXX-XX	Satisfactory Place holder provided
Manufacturer/distributor's name	Manufactured by QPharma, Sweden Distributed by [COMPANY TO BE NAMED] [Address to be named] Product of Sweden Copyright ©XXXX, [COMPANY TO BE NAMED] All Rights Reserved	**Satisfactory**
"See package insert for dosage information"	Dosage and Administration: (b) (4) see package insert (b) (4) (b) (4)	**Satisfactory**
Quantitative ingredient information (injectables)	Contents: Annovera contains 103 mg of segesterone acetate and 17.4 mg of ethynyl estradiol as active ingredients (b) (4) (b) (4)	**Not Satisfactory** The listed excipients should be consistent with the ones listed in Section 11 (Description) in PI.
Statement of being sterile (if applicable)	N/A	N/A
And others, if space is available	For Vaginal Use Only Do not use if seal on pouch is broken.	

List of Deficiencies:

A. Regarding PI

I. Highlights of Prescribing Information

1. Revise the drug product title to the following:

   Tradename (segesterone acetate and ethinyl estradiol vaginal system).

2. Revise the dosage form to vaginal system. The entire PI document should be updated accordingly.

3. For consistency, the strength should be expressed in "mg" for both segesterone acetate and ethynyl estradiol in the entire PI document. The values of the release rates of SA and EE should be revised to 0.15 mg/day and 0.013 mg/day, respectively.

4. Confirm the number value of the core diameter, 3.0mm or 3 (b) (4) mm in section #3 and/or #11.

II. Full Prescribing Information

For Section 11, "DESCRIPTION":

a) Add the established name and present the product as the following: "Annovera™ (segesterone acetate and ethinyl estradiol vaginal system) contains two active components, a progestin, segesterone acetate (SA), and an estrogen, ethinyl estradiol (EE). When placed in the vagina, each TRADENAME vaginal system releases an approximate average 0.15mg/day of segesterone acetate and 0.013mg/day of ethinyl estradiol over 21 days in-use period of each cycle for up to 13 cycles (total of 273 days). Each cycle is 28 days with 21 days in and 7 days out. (b) (4)

b) Revise the structure drawing to specify the correct chirality of segesterone acetate.
c) Add the important physical and chemical properties, such as solubility and pH of both SA and EE.
d) Include the list of the inactive ingredients. The inactive ingredients are silicone elastomers and silicone medical adhesive.
e) Include the pharmacological class of EE.

For Section 16 "HOW SUPPLIED/STORAGE AND HANDLING":

1) Add the drug product established name and the strength of both SA and EE (delivers 0.15 mg/day of SA and 0.013 mg/day of EE)

2) Add the drug product description and the characteristics

3) Revise the storage condition to the following: "Prior to dispensing Annovera™ to the user, store Annovera™ at 20°-25°C (68°-77°F) with excursions permitted to 15° - to 30° C (59° to 86° F) [See USP Controlled Room Temperature].
Protect Tradename from direct sunlight.
Do not refrigerate or freeze and avoid excessive heat.

4) Add the following instructions for the proper disposals of the used and unused drug product: "Tradename should be placed in the compact case after 13 cycles of use and discarded via a drug take-back option if one is available. If a take-back option is unavailable, then discard in the waste receptacle out of reach of children and pets. It should NOT be flushed down the toilet. See www.fda.gov/drugdisposal for more information about disposal of medicines."

B. Regarding Carton and Container Labels

1. To be consistent with the presentation in PI for the established name, Revise the product title to the following:

   "Tradename (segesterone acetate and ethinyl estradiol vaginal system)"

2. The size of the established name must be at least 50% of the tradename

3. Revise the dosage form to "vaginal system."

4. Revise the values of the strength (deliver rate) to 0.15 mg per day for segesterone acetate and 0.013 mg per day for ethinyl estradiol.

5. Under "Storage",

   a. add the disposal advice statement: "Do NOT flush used or unused product."

6. Revise the inactive ingredient list to be consistent with the description in section #11 of PI. The inactive ingredients are silicone elastomers and silicone medical adhesive.

7. Revise "Rx" to "Rx only" at the back side of the carton.

8. Revise the net content "Contains 1 (b) (4) to "Contains 1 vaginal system".

9. Provide the label for the black case container used for the storage of the drug product during 7-day non-use period of each cycle (total of 13 cycles) with the following:

Overall Assessment and Recommendation:

NDA209627 (segesterone acetate and ethinyl estradiol vaginal system) is a drug-device combination product. It is commonly known as a vaginal ring or intravaginal ring. Per advice from Yanna Mille (OPPQ), the established name is now [drug vaginal system] (See email from Dr. Mark Seggel dated May 30, 2018). This change is being made accordingly for the established name in the labeling/labels. A consultation to OPPQ for the guidance on whether the use of "vaginal ring" or "ring" is acceptable in some of the contexts in the labeling was sent on May 30, 2018 via email by ATL Dr. Mark Seggel. The response is pending at this time. Therefore, the final recommendation for use "vaginal ring" or "ring" as the description in labeling will be updated accordingly per OPPQ recommendation.

The comments for the direction of disposal of used and unused drug product is per EA reviewer James Laurenson recommendation via email on April 11, 2018.

From the ONDP perspective, this application is ***not*** ready for approval in its present form per 314.125(b) (6) until the deficiencies delineated above are satisfactorily resolved. It is also noted that the Proprietary name "Annovera™" is pending for approval at the time of this review.

Primary Labeling Reviewer Name and Date:

Hong Cai, Ph.D.
Reviewer, Branch V
DNDP II/ONDP

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I agree with Dr. Cai's assessment on the labels and labeling and concur with her recommendation that this application is not ready for approval as of this review.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP

Hong Cai

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Date: 7/11/2018 09:57:15AM
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Moo Jhong Rhee

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Date: 7/11/2018 12:36:07PM
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BIOPHARMACEUTICS

Product Background:

NDA: 209627

Drug Product Name / Strength: Segesterone acetate/ethinyl estradiol Vaginal Ring

Route of Administration: Vaginal

Applicant Name: The Population Council, Inc.

Review Summary:

The current submission is a New Drug Application (NDA) for Segesterone Acetate/Ethinyl Estradiol (SA/EE) contraceptive vaginal system (CVS) from The Population Council, Inc. SA (16-methylene-17α-acetoxy-19-nor-pregn-4-ene-3,20-dione) is a synthetic, nonandrogenic progestin, a derivative of 19-norprogesterone. Ethinyl estradiol (EE; 17α-ethynyl-1, 3, 5(10) estriene-3, 17β-diol) is an estrogen, a derivative of 17β-estradiol. EE is the active estrogen component of many approved combined hormonal contraceptives.

The SA/EE CVS is a nonbiodegradable, flexible, opaque white, combination contraceptive vaginal ring containing SA (103 mg) and EE (17.4 mg). When placed in the vagina, the steroids diffuse out of the CVS at a slow, steady rate to provide an approximate average daily dose of 150 µg of SA and 13 µg of EE. The inactive ingredients are silicone elastomer and titanium dioxide. SA/EE CVS releases SA and EE over a period of a year thereby providing cyclic contraception for an entire year. The 1 year of contraception is accomplished through 13 dosing intervals of 21 days each separated by 7 dose-free days. The above (b) (4) dosing/day applies not only to the 21 dosing days of the first 28-day hormonal contraceptive cycle, but to the 21 dosing days of the 12 subsequent cycles as well. The (b) (4) dosing begins and reaches a maximum concentration (Cmax) of SA and EE on Day 1 of each cycle; after the Cmax, serum levels decline until dosing is interrupted for 7 days beginning on Day 22.

The biopharmaceutics review is focused on evaluating the 30 -day in vitro release method, in vitro drug release acceptance criteria at 'release' and at 'stability' and determination of the in vivo dose delivered for the drug product labeling purpose. Further, in vitro in vivo correlation (IVIVC) studies proposed to bridge phase 2, phase 3 and to-be-marketed formulations of the CVS were also evaluated.

- **In vitro drug release method**: The following table summarizes the agreed upon in vitro drug release method for release and stability determination.

Apparatus	Speed	Medium/Temperature/	Volume	Sampling time

The in vitro release method was found acceptable based on its ability to discern in vitro drug release rate variations in drug product batches at 'release' vs. 'stability', including changes in (b) (4) release. In this regard, it should be noted that the method appears to be over-discriminating as batches showing similar efficacy and safety display different in vitro release rate.

- **In vitro drug release acceptance criteria:** Batches used in pivotal clinical studies demonstrated very different in vitro drug release for fresh batches compared to stability batches. Therefore, the decision was made to set two different acceptance criteria (fit for purpose) as 'release acceptance criteria' and 'stability acceptance criteria'. Based on the in vitro drug release rate observed with the batches used in the clinical studies, the following in vitro drug release acceptance criteria at 'release' and at 'stability' have been agreed upon with the Applicant (response received on July 19, 2018). It should be emphasized that the ranges recommended are considered clinically relevant as they are set based on batches that demonstrated acceptable efficacy and safety as per the clinical review team's assessment.

FDA recommended in vitro drug release acceptance criteria at 'RELEASE' for the SA component

Sampling time point	Mean Values (µg/24 hours)*
Day 1	(b) (4) *No individual values should be outside the range of (b) (4)
Day 9	(b) (4) *No individual values should be outside the range of (b) (4)

Day 17-18	(b) (4) *No individual values should be outside the range of (b) (4)
Day 29-32	(b) (4) *No individual values should be outside the range of (b) (4)

FDA recommended in vitro drug release acceptance criteria at 'RELEASE' for the EE component

Sampling time point	Mean Values (µg/24 hours)*
Day 1	(b) (4) *No individual values should be outside the range of (b) (4)
Day 9	(b) (4) *No individual values should be outside the range of (b) (4)
Day 17-18	(b) (4) *No individual values should be outside the range of (b) (4)
Day 29-32	(b) (4) *No individual values should be outside the range of (b) (4)

FDA recommended in vitro drug release acceptance criteria at 'STABILITY' for the SA component

Sampling time point	Mean Values (µg/24 hours)*
Day 1	(b) (4) *No individual values should be outside the range of (b) (4)
Day 9	(b) (4) *No individual values should be outside the range of (b) (4)

Day 17-18	(b) (4) *No individual values should be outside the range of (b) (4)
Day 29-32	(b) (4) *No individual values should be outside the range of (b) (4)

FDA recommended in vitro drug release acceptance criteria at 'STABILITY' for the EE component

Sampling time point	Mean Values (µg/24 hours)*
Day 1	(b) (4) *No individual values should be outside the range of (b) (4)
Day 9	(b) (4) *No individual values should be outside the range of (b) (4)
Day 17-18	(b) (4) *No individual values should be outside the range of (b) (4)
Day 29-32	(b) (4) *No individual values should be outside the range of (b) (4)

* Mean values (n=12 units) should be within the specified mean range and no individual value should be outside the specified range.

- **In vivo drug release rate determination:** The approach used to determine the in vivo drug release rate is considered not accurate to assess for the "true" in vivo drug release. Briefly, in vivo drug release rate was calculated based on residual drug collected at one time at the end of 13 cycles of use. Therefore, a post marketing commitment is agreed upon with the Applicant to collect additional data (b) (4) in in vivo drug release rate (b) (4) The Applicant is being requested to submit these studies within 24 months after approval. Based on the data available, e.g., residual amount of drug in rings collected at the end of 13 cycles, a total of 41.3 mg of Segesterone Acetate and 3.4 mg of Ethinyl Estradiol are released over 273 days. This translates to an approximate average daily dose of 0.15 mg of segesterone acetate and 0.013

mg of ethinyl estradiol with higher release rate expected at the beginning of dosing and a lower release rate towards the end.

- **IVIVC evaluation:** The Applicant submitted (b) (4) IVIVC to establish the biopredictive ability of the in vitro drug release method, to bridge the registration batches with the phase 3 pivotal batches (forward bridging) and to bridge the Phase 3 pivotal batches with the phase 2 batches (reverse bridging). However, the approach used to develop IVIVC was deemed not acceptable (b) (4) Further, the proposal to use IVIVC to bridge the formulations was not considered due to inadequacy of the IVIVC model.

- **Bridging of formulations:**
  - *Reverse bridging- Phase 2 to Phase 3 pivotal formulation:* The bridging analysis between phase 2 formulation (HC-02) with the Phase 3 formulation (GF991) using the IVIVC model was found not acceptable due to an inadequate IVIVC model. The clinical and clinical pharmacology teams were informed during the review cycle about the unacceptability of the IVIVC and that the formulations could not be bridged on the basis on in vitro drug release data.
  - *Forward bridging- Phase 3 pivotal formulation to TBM formulation:* Based on the Applicant's and FDA/OPQ reviewer's analyses, the changes implemented are considered minor requiring compliance with the recommended in vitro drug release acceptance criteria. Specifically, the TBM formulation meets the approved clinically relevant in vitro drug release acceptance criteria and thus, it is deemed similar to the clinical trial batch.

Recommendation: From Biopharmaceutics perspective, NDA 209627 for Segesterone acetate/ethinyl estradiol Vaginal System is recommended for ***approval*** with a PMC related to the in vivo drug release rate determination.

List Submissions being reviewed (table):

08/17/2017	NDA 209627/0001/Original submission
10/31/2017	NDA 209627/0005 (5)/Quality/Response to Information Request
11/21/2017	NDA 209627/0006 (6)/Quality/Response to Information Request
02/06/2018	NDA 209627/0011 (11)/Quality/Response to Information Request
02/16/2018	NDA 209627/0012 (12)/Quality/Response to Information Request
02/06/2018	NDA 209627/0012 (12)/Quality/Response to Information Request
02/23/2018	NDA 209627/0013 (13)/Multiple Categories/Subcategories
02/23/2018	NDA 209627/0013 (13)/Multiple Categories/Subcategories
03/14/2018	NDA 209627/0014 (14)/Multiple Categories/Subcategories

04/11/2018	NDA 209627/0016 (16)/Quality/Response to Information Request
04/20/2018	NDA 209627/0017 (17)/Multiple Categories/Subcategories
04/26/2018	NDA 209627/0018 (18)/Multiple Categories/Subcategories
05/02/2018	NDA 209627/0019 (19)/Multiple Categories/Subcategories
05/25/2018	NDA 209627/0022 (22)/ Quality/Response to Information Request
05/25/2018	NDA 209627/0023 (23)/ Quality/Response to Information Request
07/19/2018	NDA 209627/0025 (25)/ Quality/Quality information

Highlight Key Outstanding Issues from Last Cycle: This is first review cycle**.**

Concise Description Outstanding Issues Remaining: None

Comments for the Applicant: None

BCS Designation: The Applicant has not claimed BCS designation for their product, BCS classification is not pertinent.

Solubility: The solubility of SA and EE in water was tested in the range of pH from pH 1.1 to pH 7.8.

The following buffers were tested for evaluating the solubility.

Table 1. Buffer solutions used for test of SA and EE solubility at different pH (From 3.2.P.2.2 Drug Product)

Buffer solution	pH
0.1 M HCl	1.1
0.1 M citrate-HCl	2.0
0.1 M citrate-phosphate	3.1
0.1 M citrate-phosphate	4.1
0.1 M citrate-phophate	5.1
0.1 M phosphate	6.0
0.1 M phosphate	7.0
0.1 M phosphate	7.8

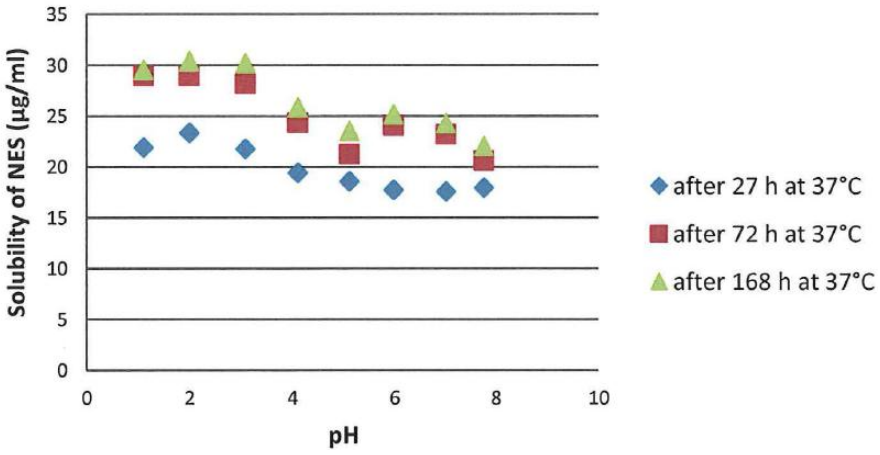
Solubility of SA

Maximal solubility of SA acetate after 27 hours was 23.3 µg/ml (at pH 2) (Table 3, Figure 1).

Table 2: Solubility of SA at different pH (From 3.2.P.2.2 Drug Product)

	Solubility NES µg/ml 27 h	Solubility NES µg/ml 72 h	Solubility NES µg/ml 168 h
pH	result set: 5801	result set: 6420	result set: 6544
1.11	21.862	28.944	29.500
2.00	23.298	28.950	30.341
3.08	21.753	28.156	30.174
4.10	19.412	24.344	25.819
5.11	18.549	21.260	23.505
5.98	17.700	24.068	25.139
7.01	17.562	23.213	24.261
7.76	17.936	20.635	22.041

Figure 1. Solubility of SA in water in the pH range 1.1-7.8 (From 3.2.P.2.2 Drug Product)



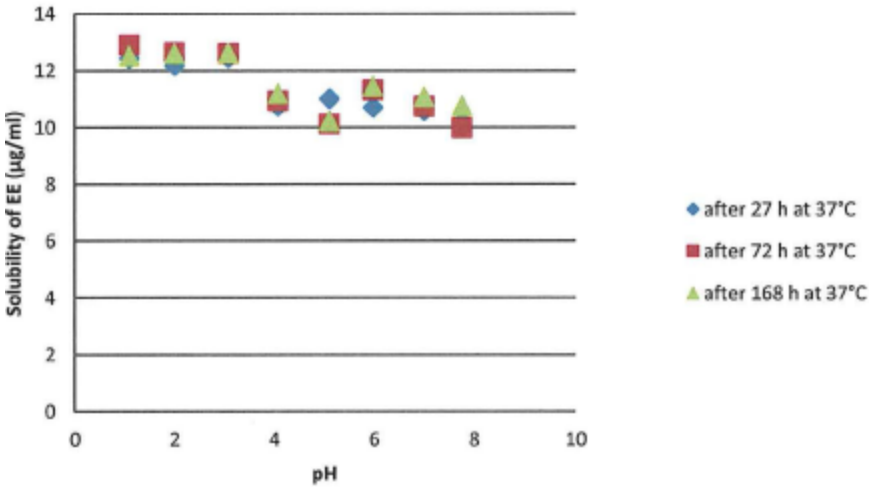
Solubility of EE

Maximal solubility of EE after 27 hours was 12.4 µg/ml (at pH range 1-3), respectively (Table 3, Figure 2).

Table 3: Solubility of EE at different pH (From 3.2.P.2.2 Drug Product)

	Solubility of EE 27 h	Solubility of EE, 72 h	Solubility of EE, 168 h
	27 h	72 h	168 h
	result set: 6159	result set: 6088	result set: 6481
pH	µg/ml	µg/ml	µg/ml
1.09	12.412	12.886	12.511
2.00	12.165	12.623	12.598
3.08	12.447	12.610	12.612
4.08	10.727	10.941	11.176
5.11	10.991	10.116	10.210
5.98	10.685	11.306	11.423
7.00	10.573	10.733	11.045
7.76	10.164	9.969	10.727

Figure 2. Solubility of ethynyl estradiol in water in the pH range 1.1-7.8 (From 3.2.P.2.2 Drug Product)



Reviewer's Assessment: Adequate

Solubility: The maximal solubility for both SA and EE is obtained in the pH range 1-3. However, the solubility in the pH range 5-7, (b) (4) is 18.5-17.6 µg/ml for SA and 11.0-10.5 µg/ml for EE after 27 hours. Further, at 168 hours, the saturation solubility of SA was determined to range from approximately 22 µg/mL (at pH 7.8) - 30 µg/mL (pH 1.1 to 3.1) with only a small effect of pH. At 168 hours, the saturation solubility of EE was

determined to range from approximately10 µg/mL (at pH 5.1) - 13 µg/mL (pH 1.2 to 3.1), with only a small effect of pH.
The above solubility data indicates that the two APIs, SA and EE can be considered low solubility drugs.

Permeability: No data provided

Dissolution: See 'Dissolution method and Acceptance Criteria' below.

In Vitro Drug Release Method development and Acceptance Criteria

The Applicant developed a 30-day In vitro drug release test to evaluate the drug release throughout the product development. The same 30-day in vitro drug release test was used in 13 cycles to simulate 'in-use 13-Cycle Release Rate'. Additionally, an accelerated in vitro drug release test was also developed on Agency's request and was used starting with the registration batches. Each of these methods are described below.

30-Day in vitro drug release test (b) (4)

The 30-Day in vitro drug release test is described as follows:

(b) (4)

30-Day In vitro drug release test method development studies

In vitro drug release test apparatus

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It should be noted that the method validation was reviewed in details by Drug Product reviwer Dr. Hong Cai, please refer to DP review for additional details.

Reviewer's Assessment: Adequate

The Applicant developed a 30-day in-house in vitro drug release test method for evaluation of in vitro drug release. The method development and validation is adequate with demonstration of the sink conditions. There were some deviations (explained above) observed in the validation reports but the applicant will take additional steps to rectify the deviations.

The suitability of the statistical approach employed by the Applicant to demonstrate differences in the release profiles of the variants used for demonstrating the discriminatory ability of the method was evaluated by Dr Meiyu Shen biostatistician, OTS. (review in DARRTS, submitted on 3/20/2018). Briefly, the statistical analysis was found inappropriate to reach a conclusion on the discriminating ability. Nevertheless, from biopharmaceutics perspective, the in vitro release method was found acceptable based on its ability to discern in vitro drug release rate variations in drug product batches at 'release' vs. 'stability', including changes in (b) (4) release. In this regard, it should be noted that the method appears to be over-discriminating as batches showing similar efficacy and safety display different in vitro release rate.

<u>30-Day accelerated in vitro drug release test (from 3.2.P.2.2.1.6):</u>

Since (b) (4)% in vitro drug release was observed in 30-day in vitro drug release test, the Agency recommended that the use of above 30-day in vitro drug release test for batch release, including stability studies, was not acceptable for quality control (QC) purposes and requested the

applicant to develop an accelerated in vitro drug release test that accounts for (b) (4)% of the labelled amount of drug.

The applicant developed the follwing accelarated method

(b) (4)

Establishment of linear correlation between 30-day in vitro drug release test with 30-day accelrated in vitro drug release test (3.2.P.2.2.A6)

In vitro drug release test for SA/EE CVS was conducted under non-accelerated (b) (4) (b) (4) as well as under accelerated conditions (b) (4) The accelerated in vitro drug release test (b) (4)

Reviewer's assessment: No Assessment done

The Applicant developed and validated 30-day accelerated in vitro drug release test in response to the Agency request earlier (the Agency had requested the Applicant to develop an accelerated method at IND stage) where a complete drug release was observed. Further, the Applicant submitted a report (Attachment 3.2.P.2.2-A6) establishing a linear correlation between 30-day in vitro drug release test with 30-day accelerated in vitro drug release test. The Agency further asked the applicant to provide the cross-validation of these two methods demonstrating the interchangeability and propose in vitro release acceptance criteria for the accelerated method. However, in their response on Feb 2, 2018, the applicant stated these studies could not be performed within the time-frame of the review cycle since the clinical batches which were manufactured in 2005 will not be available for such studies.

The Applicant decided to withdraw the 30-day accelerated in vitro drug release test (IR response received on 2/6/2018) as they did not propose the acceptance criteria for this method. (b) (4) Considering this, the reviewer did not review the method development and validation studies for 30-day accelerated in vitro drug release test.

30-Day in vitro drug release test acceptance criteria

A summary of the batches used in each clinical study are reported in Table 5.

Table 5: Batches used in Clinical Studies of SA/EE Contraceptive Vaginal Ring

Study	Delivery System	Manufacturer	NES (µg/day)	EE (µg/day)	Batch
			Phase 1 Formulation		
64	NES/EE CVR	PC CVR	100	5, 15, 30	NA
97	NES/EE CVR	PC CVR	100, 150	15, 30	FE-30, FE-15
			Phase 2 Formulation		
180	NES/EE CVR	PC CVR	150, 200	15, 20	NSE-150, NSE-152, NSE-200
181	NES/EE CVR	PC CVR	150	15	NSE-150
204	NES/EE CVR	PC CVR	50, 150	10, 15, 20	NS-10, NS-20, NE-150
317	NES/EE CVR	PC CVR	150	15	HC01
323	NES/EE CVR	PC CVR	150	15	HC-02
330	NES/EE CVR	PC CVR	150	15	HC-02
			Phase 3 Formulation		
300A	NES/EE CVR	QP CVR	150	15	GF993, GF994, GF995
300B	NES/EE CVR	QP CVR	150	15	GF992, GF993, GF994, GR995
300PK	NES/EE CVR	QP CVR	150	15	GF991
			Current Composition (Proposed Commercial) Formulation		
571	NES/EE CVR	QP CVR	150	(b) (4)	PE560

When doses are listed as "µg/day", the formulations were modified to achieve the target dose rate based on in vitro release studies.
CVR=contraceptive vaginal ring; EE=ethinyl estradiol; NA=not available; NES=Nestorone; PC=Population Council; QP=QPharma.
Source: Module 3.2.P.2.2.1.1, Table 2.

The summary of in vitro drug rlease data from CVS used in pivotal clinical studies is provided below.

Table 6: Summary of 30-Day In vitro drug release data of SA and EE from batches used in the pivotal clinical studies

(b) (4)

The raw data of all batches is provided in the batch analysis section of the submission at Application 209627 - Sequence 0001 - Batch Analyses and is shown in Appendix 1.

The applicant proposed the following in vitro drug release acceptance criteria in their initial submission. (Table 7).

Table 7: Proposed In vitro drug release accceptance criteria

(b) (4)

(b) (4)

The following registration batches and stability batches were manufactured by the Applicant (Table 8).

Table 8. Segesterone acetate/ ethinyl estradiol Vaginal Ring Batches Manufactured for Use as Supporting Stability Batches or Registration Batches

Finished product NSE/EE CVR Batch No.	Batch Use	Mfg NES Batch No. (QPharma No.)	Mfg EE Batch No. (QPharma No.)	NES/ EE Core Batch No.	NES Core Batch No.	Ring Body Batch No.	Batch size (rings)	Place of Drug Product Mfgr.	Date of Manufacture
PI569	Technical Batch (Supportive Stability Batch)	(b) (4)		PE566	PE567	PD554	728	QPharma AB	(b) (4)
QK584	Reg. 1			QI582	QI583	QH591	963	QPharma AB	
QL589	Reg. 2			QI587	QI588	QH586	1003	QPharma AB	
QL594	Reg. 3			QI592	QI593	QH591	835	QPharma AB	

DDI: drug-drug interaction clinical study; Mfg: Manufacturer; NA: Not Available; P3 CTM: Phase 3 clinical trial material; Reg.: Registration Batch

[a]Manufacturer name change only

The raw in vitro drug release data for 30-day in vitro drug release test for the registration batches is provided in the batch analysis section of the submission at Application 209627 - Sequence 0001 - Batch Analyses and is shown in Appendix 1

As shown in Appendix 1, a higher in vitro drug release on day 1 was observed in the registration batches (b) (4) and a supporting batch (b) (4) for EE when compared to the clinical batches used in Phase 3 studies (b) (4) The Applicant provided the following justification supporting that this increased in vitro drug release will not be a safety concern (supporting White Paper Report- PK and Specs Module 5.4).

Summary of justification supporting higher EE release

EE has been approved for use in the US since 1943. Currently, the highest approved oral dose of EE for contraception is 120 µg which is administered orally twice over the course of 12 hours. A linear and proportional relationship for EE between the oral dose and the Cmax and AUC has been justified by the Applicant based on published data. From this analysis, the Applicant concluded that the upper limit for Cmax and AUC associated with an FDA approved use of oral contraceptives containing EE is (b) (4) pg/mL and (b) (4) pg*hr/mL, respectively.

The Applicant stated that IVR rate for EE that corresponds to an in-vivo Cmax of (b) (4) pg/mL can be calculated based on the dose-response relationship for oral EE in the published literature since the bioavailability of EE from vaginal and oral dosing is similar. The IVR rate for EE that

corresponds to an in-vivo Cmax of (b) (4) pg/mL is (b) (4) µg/24 hours. Therefore, the Applicant claimed that the proposed highest specification for EE of (b) (4) µg /24 hours would result in a lower Cmax than was observed in a clinical study.

Summary of justification for SA

Segesterone acetate is a new chemical entity (NCE). The Applicant stated that data demonstrated a correlation of in-vivo Cmax and AUC of SA up to an in vitro release rate of (b) (4) µg/24 hours. Considering this correlation, the Cmax of (b) (4) µg/24 hours for SA will correspond to (b) (4) pg/mL. However, the Applicant did not have any in-vivo data for SA corresponding to an in vitro release rate of (b) (4) µg/24 hours. The Applicant referred to the QT study (Study 648) where the intravenous administration of SA produced a Cmax of 6092 pg/mL which was well tolerated with no serious or unexpected adverse events nor any increase in expected adverse events. (b) (4)

The proposed justification above also referenced to justify the higher in vitro drug release that was observed in the stability studies of clinical batches.

Reviewer's assessment: Adequate

Basis for determination of the final in vitro drug release acceptance criteria

The Applicant's proposed in vitro drug release acceptance criteria at 'RELEASE' and in vitro drug release acceptance criteria at 'STABILITY' for 30-day in vitro drug release was not acceptable. The Biopharm team evaluated the 30-day in vitro drug release data obtained from the clinical batches in batch analysis section. The team discussed the approach for determining the in vitro drug release acceptance criteria (see discussion below) with the Applicant in multiple IRs and via teleconference and reached an agreement with the Applicant for the final in vitro drug release acceptance criteria. It should be emphasized that the justification provided to support the limits relied on clinical efficacy/safety data for which the clinical review team provided input/qualification via email communication.

The following approach was employed to determine the mean upper bound, mean lower bound, individual upper bound and individual lower bound values.

Justification for setting the lower bound acceptance criteria:

The acceptance criteria for mean lower bound release rate was determined by considering the mean of the means for the observed release rate (with 10% variation) for the Phase 3 clinical batches. For example, the mean of the means at 29-32-day time point was (b) (4) µg/24 hour for EE and (b) (4) µg/24 hour for SA. Therefore, a 10% allowance in these values was added and the lower bound of mean in vitro release rate was recommended as below.

Mean lower bound in vitro drug release rate for in vitro drug release acceptance criteria at 'RELEASE' for day 1, day 9 and day 17.EE: (b) (4) µg/24 hour:

SA: (b) (4) µg/24 hour

It should be noted a 10% variation is included in above calculations for analytical and process variability.

Individual lower bound in vitro drug release rate for in vitro drug release acceptance criteria at 'RELEASE'

Further, the lowest individual value at batch release for a Phase 3 CTM batch was (b) (4) µg/24 hour for SA (batch GF992, Day 29-32), and (b) (4) µg/24 hour for EE (batch GF992, Day 29-32). Considering these above lowest individual values from phase 3 studies, the Agency recommended setting the acceptance criteria for individual units as below:

EE: (b) (4) µg/24 hour

SA: (b) (4) µg/24 hour

For the last time point 29-32 days, the lowest individual in vitro drug release of EE and SA was observed to be (b) (4) µg/24 hour and (b) (4) µg/24 hour, respectively. Additional 10% variation was considered for 29-32 day time-point as the Applicant justified that it is not expected to affect product performance.

Justification for setting the higher bound acceptance criteria:

The acceptance criteria for mean higher bound release rate was set on similar approach except that the higher bound acceptance criteria at each time point was based on the mean of the means for the observed release rate (with 10% variation) at the respective time points for the Phase 3 clinical batches. For example, the mean of the means for day 1 time point was (b) (4) µg/24 hour for EE and (b) (4) µg/24 hour for SA. Therefore, a 10% allowance in these values as lower bound of mean in vitro release rate is included as below

Mean lower bound in vitro drug release rate for 'release acceptance criteria'

EE: (b) (4) µg/24 hour

SA: (b) (4) µg/24 hour

It should be noted that a 10% variation was considered in above calculations for analytical and process variability.

The in vitro drug release data for the registration batches 'at release' was also evaluated.

Individual higher bound in vitro drug release rate for in vitro drug release acceptance criteria at 'RELEASE'

Further, the highest individual value at each time point was selected as the highest observed values amongst the samples tested for that time point. For example, the highest SA release on day 1 observed in batch GF994, sample 2 as (b) (4) µg/24 hour. Therefore, this value was selected initially as individual higher bound in vitro drug release rate for in vitro drug release acceptance criteria at 'RELEASE'. However, as allowed in mean values, the Applicant proposed adding a 5% variation to the individual ring boundaries proposed by the Agency to account for the variability that one would expect to observe for results from testing individual samples. The Agency considered the request and allowed it for ONLY day 1 for SA and EE.

The Biopharmaceutics team did not accept (b) (4) acceptance criteria for the proposed product. Instead, after considering a variation in the observed individual units based on experience with the clinical batches a range was recommended here according to individual mean values. In addition to mean range a range of individual units was specified in the acceptance criteria.

The Applicant should test n =12 units. Mean values (n=12 units) should be within the specified mean range and no individual value should be outside the specified range. In vitro drug release acceptance criteria as described in <USP 724> are not applicable in this case.

Similar approach was adopted to recommend the 'stability acceptance criteria'.

It should be noted that while the determination of the in vitro drug release acceptance criteria at 'RELEASE' were based on phase 3 clinical batch and registration batch data, the in vitro drug release acceptance criteria at 'STABILITY' were based on phase 3 clinical batch data. A 10% and 5% variation to the mean of the means for the observed release rate at the respective time points for 'RELEASE' and 'STABILITY' acceptance criteria, respectively was allowed. The lower variation allowed at stability was based on risk assessment and data provided. Individual values observed during the stability time points from 3-24 months for the clinical batches were also considered and those variations were included to account for analytical and process variabilities. Considering this, the following final in vitro drug release acceptance criteria were recommended based on clinical relevance and the justification/data provided throughout the review cycle.

The final in vitro drug release acceptance criteria as recommended by the Agency and agreed by the Applicant is below:

FDA recommended in vitro drug release acceptance criteria at 'RELEASE' for the SA component

Sampling time point	Mean Values (µg/24 hours)*
Day 1	(b) (4) *No individual values should be outside the range of (b) (4)
Day 9	(b) (4) *No individual values should be outside the range of (b) (4)
Day 17-18	(b) (4) *No individual values should be outside the range of (b) (4)
Day 29-32	(b) (4) *No individual values should be outside the range of (b) (4)

FDA recommended in vitro drug release acceptance criteria at 'RELEASE' for the EE component

Sampling time point	Mean Values (µg/24 hours)*
Day 1	(b) (4) *No individual values should be outside the range of (b) (4)
Day 9	(b) (4) *No individual values should be outside the range of (b) (4)
Day 17-18	(b) (4) *No individual values should be outside the range of (b) (4)
Day 29-32	(b) (4) *No individual values should be outside the range of (b) (4)

FDA recommended in vitro drug release acceptance criteria at 'STABILITY' for the SA component

Sampling time point	Mean Values (µg/24 hours)*
Day 1	(b) (4) *No individual values should be outside the range of (b) (4)
Day 9	(b) (4) *No individual values should be outside the range of (b) (4)
Day 17-18	(b) (4) *No individual values should be outside the range of (b) (4)
Day 29-32	(b) (4) *No individual values should be outside the range of (b) (4)

FDA recommended in vitro drug release acceptance criteria at 'STABILITY' for the EE component

Sampling time point	Mean Values (µg/24 hours)*
Day 1	(b) (4) *No individual values should be outside the range of (b) (4)
Day 9	(b) (4) *No individual values should be outside the range of (b) (4)
Day 17-18	(b) (4) *No individual values should be outside the range of (b) (4)
Day 29-32	(b) (4) *No individual values should be outside the range of (b) (4)

* Mean values (n=12 units) should be within the specified mean range and no individual value should be outside the specified range.

Reviewer's notes:

Since clinical evidence from Applicant's own studies supporting highest proposed IVR of (b) (4) *µg/24 hours for EE is absent, additional justification was needed to support such high values. Considering the history of the EE as a drug which is used for contraception since 1943, a higher limit was deemed acceptable, as per clinical team's input. Therefore, a 10% allowance in the IVR rate was included in the above recommended in vitro drug release acceptance criteria to account for normal variations during product manufacturing (see justification for setting up the in vitro drug release acceptance criteria).*

Since, a direct clinical evidence supporting the highest proposed IVR of (b) (4) *µg/24 hours for SA is absent, these IVR values cannot be allowed. However, considering the IVR observed in stability batches (24 months) and the fact that 24-month-old batches were also used in clinical studies, a higher limit can be allowed for both 'release acceptance criteria' and 'stability acceptance criteria'. Therefore, a 5% allowance in the IVR rate was included in the above recommended in vitro drug release acceptance criteria to account for normal variations during product manufacturing (see justification for setting up the in vitro drug release acceptance criteria).*

The justification provided by the Applicant suggests that an increased day 1 release of both EE and SA as observed in the registration batches and stability batches (during storage) will not be a safety concern. The above justification is because the Agency approved products containing EE demonstrate higher in vivo PK data based on published literature (for EE) and their own QT study (for SA). Therefore, a corresponding higher in vitro drug release especially on day 1 can be acceptable and used for quality control purposes for routine batch analyses. However, local exposure at the site of insertion (inside vagina) could be a safety concern. The reviewer communicated the concern to the Clinical and Clinical Pharmacology team. The clinical team responded that assessing safety due to high local exposure is not possible. In general, the clinical team is not as concerned with the progestin component (SA) when compared to estrogen.

Considering above justification, in vitro drug release data from the clinical batches and the registration batches was considered for setting the in vitro drug release acceptance criteria at 'release' time point. However, due to limited experience with the NME, SA and unique nature of this product, the in vitro drug release acceptance criteria at the 'stability' time point was determined based on data obtained from only clinical batches.

Justification for using 7-25-month-old rings for patient use: *The CVS used by subjects in the pivotal Phase 3 clinical trials were 7 to 25 months from manufacture at first use. The Biopharmaceutics team asked for a clarification about demonstration of the clinical efficacy and safety by 25 months old rings used in further 13 cycles (one additional year) of use. The Applicant confirmed that in pivotal Phase 3 clinical trials, 745 women used NES/EE CVS that*

were ≥ 24 months old at the start of administration (Table below from the Integrated Summary of Effectiveness report) showed that the number of pregnancies and Pearl indices were similar in each subgroup based on the age of ring at insertion.

Table 9: Pearl Indices by Age of Ring at Insertion -- All-Cycle Analysis Set

Age of Ring	Pregnancies	N	Cycles	Pearl Index	95% CI
2 years or greater	13	745	5261	2.47	(1.93, 3.16)
1.69 years thru 1.99 years	16	777	6598	2.96	(2.42, 3.61)
Less than 1.69 years	12	781	6199	2.31	(1.82, 2.92)
Age of Ring Tertiles (Ratio)	.	.	.	1.04	(0.88, 1.22)

The incidence of adverse events (AE) was also evaluated by age of the NES/EE CVS at insertion and reported by the applicant (Integrated Summary of Safety (ISS) (Module 5.3.5.3) and no meaningful differences were observed between the subgroups of interest. Taken together, one third of the subjects in the Phase 3 trials used a ring at least 24 months old at the start of dosing in the clinic with no meaningful differences in the number of pregnancies or AE/SAE incidence vs. the other groups; (b) (4)

(b) (4)

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

The Applicant submitted a validated (b) (4) vitro/in vivo correlation (IVIVC) to establish the bio relevance of the in vitro drug release method, to bridge the registration batches with the phase 3 pivotal batches (forward bridging) and to bridge the Phase 3 pivotal batches with the phase 2 batches (reverse bridging). (b) (4)

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(b) (4)

The Applicant responded on Feb 2, 2018 that the Agency's conclusion about inadequate/insufficient IVIVC has been noted.

In Vivo Drug Release/Dose determination

The CVS (batch# GF991) used in the Clinical Study 300 PK which were already used for 13 cycles, where the pharmacokinetics of SA and EE were also determined, were extracted to determine the amount of SA and EE remaining. The data were used to calculate the average release rate of SA and of EE over the thirteen cycles of use.

(b) (4)

Calculation of In Vivo Drug Release Rate by Ex vivo analysis

The calculation of SA and EE in vivo release rate was based on determining the amount of SA and EE released in vivo by subtracting the amount of SA and EE recovered from the starting content of SA and EE in the SA/EE CVS, and dividing that by the number of days of in vivo exposure to the SA/EE CVS. The amount recovered considered the sum of amount of the individual drugs released during the (b) (4) of in vitro drug release testing and the amount of the individual drug extracted. The starting content of SA and EE in the CVS was 103 mg and 17.4 mg. The calculations were performed as below.

In Vivo SA or EE Release (mg) = 103 mg for SA or 17.4 mg for EE – amount of SA or EE released during (b) (4) in vitro drug release testing – recovered SA or EE content (b) (4) .

The rings were used for 273 days of in vivo exposure to the ring (13 cycles x 21 days per cycle).

SA or EE in vivo release rate (µg/day) average over 13 cycles = In Vivo SA or EE Release (mg) / 273 days.

(b) (4)

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Reviewer's Assessment: Adequate with PMC

The in vivo drug release rate of SA and EE was calculated from (b) (4) randomly selected samples that have been used for complete 13 cycles from three clinics that participated in the 300 PK study. The SA and EE content was measured in these rings after (b) (4) of in vitro drug release testing and the amount of the individual hormone extracted was used to estimate the average in vivo drug release rate during the time the samples were used in vivo. This does not represent "true" in vivo release rate.

To accurately determine the strength of the product and for labeling purposes, the 'true' in vivo drug release should be calculated from data collected throughout the period of use. This issue could not be addressed during the review cycle since the data needed were not available.

Therefore, the Applicant was communicated that further studies will be needed (b) (4) (b) (4) and these studies should be submitted under a post marketing commitment as below.

(b) (4)

The PMC was communicated to the Applicant along with the approval letter and will be completed within the following timeline.

Final protocol submission: March 2019

Study completion date: April 2020

Final report submission date: Oct 2020

The biopharmaceutics team included the following in the label to Dosage and Strength section and section #3, #11 and #16 as below.

Dosage and Strength section: TRADENAME is a (b) (4) vaginal system containing 103 mg segesterone acetate (SA) and 17.4 mg ethinyl estradiol (EE), (b) (4)

Section #3: corrected the dose for EE from (b) (4) mg/day to 0.13 mg/day.

Section #11: The steroids diffuse out of the (b) (4) with release rates that vary over time. Based on in vitro data, the daily in vitro release rates of SA and EE are higher during each initial 24-48

hours of use achieving a somewhat lower steady-state with continued use over the subsequent days in each cycle. The (b) (4) is designed to be used for 13 cycles (1 year) on a 21/7 days in/out schedule. The total in-use time with the 21/7 days in/out schedule over 13 cycles is 273 days. Based on the residual amount of drug in (b) (4) used in clinical trials over 13 cycles, a total of 41.3 mg of SA and 3.4 mg of EE are released over this period. This translates to an approximate average daily dose of 0.15 mg of segesterone acetate and 0.013mg of ethinyl estradiol with higher release rate expected at the beginning of dosing and a lower release rate towards the end.

Section #16: changed the dose of EE from (b) (4) mg/day to 0.13 mg/day.

Dose determination based on in vitro drug release rate:

An in vitro drug release rate study of SA/ethinyl estradiol contraceptive vaginal rings (SA/EE/CVS) was conducted using 6 batches of product representing clinical, technical and regulatory batches (Table 12) to determine appropriate labeling regarding daily release rates and to compare the results from the clinical and pharmacokinetic (300PK) batches with the regulatory batches.

Table 13: Batches of the SA / EE CVS Tested

(b) (4)

The mean, minimum and maximum daily release rates were determined for each day and each cycle for each batch. In addition, the mean and maximum omitting the Cycle Day 1 results were also determined, because the release rate from the first Cycle Day 1 was always appreciably higher than the remaining days. An overall mean, minimum and maximum were also determined

for each drug. The mean, maximum and minimum release rate data for the completed in vitro studies arranged by batch, Cycle Day, and cycle for EE and SA are presented in Appendix 3.

The overall means, minimums, and maximums for both compounds are presented in Table 14.

Table 14: SA and EE Means, Minimums, and Maximums Expressed as µg/24 Hours for 6 Tested Batches

(b) (4)

Reviewer's Assessment:

It should be noted that the average mean release rates of SA and EE in this in vitro study were (b) (4) and (b) (4) µg/24 hours, respectively over a 13-cycle period after omitting the (b) (4) values of Cycle Day 1 of all cycles. However, the in vitro data cannot be used to make a determination of the in vivo dose delivered by the ring when used by the user. Therefore, these data will not be used to decide the in vivo dose of the ring but can be used as a supporting evidence to determine the in vivo drug release rate.

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment: N/A

In-Vitro Soft-food Interaction Study

Reviewer's Assessment: N/A

In-Vitro Release Testing (IVRT) for Semi-Solid Products

Reviewer's Assessment: N/A

In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products

Reviewer's Assessment: N/A

In-Vitro Dissolution Testing for Abuse-deterrent Products

Reviewer's Assessment: N/A

In-Vitro BE Evaluation for Pulmonary Products

Reviewer's Assessment: N/A

(b) (4)

Reviewer's Assessment: The CVS is a unique (b) (4) delivery system which releases contraceptive hormones for one year from a silicone vaginal ring. The clinical PK data demonstrated that during use, both EE and SA were consistently released by the ring during 13 cycles of use which spanned over 273 days. Further, the 13-cycle simulated in vitro drug release data also demonstrated that a prolonged release of the EE and SA was observed when the rings were used for 273 days simulating the in vivo conditions. (b) (4)

Bridging of Formulations

A comparison of the process and formulation changes between phase 2, phase 3 and TBM formulations is shown in Table 15 below:

Table 15: Comparison of SA/EE CVS 150 / (b) (4) µg Compositions Starting with Those Produced Using the Phase 2Process Through the Registration /Proposed Commercial Process

(b) (4)

Bridging of Phase 2 formulation to Phase 3 pivotal clinical trial formulation

The Applicant proposed IVIVC to bridge the formulation used in Phase 2 Process (HC-02) with the Phase 3 formulation (GF991). Since the IVIVC model is not acceptable IVIVC model cannot be used for bridging the phase 2 (HC-02) formulation with the phase 3 (GF991). The clinical and clinical pharmacology team was informed about the unacceptable IVIVC and that the phase 2 formulation cannot be bridged with phase 3 pivotal formulation based on similarity in in vitro drug release data or proposed IVIVC. Refer to Clinical Pharmacology review for details on bridging qualification based on clinical PK data.

Bridging of Phase 3 pivotal clinical trial formulation to Registration Batches

A (b) (4) IVIVC was submitted for bridging purposes and recommended as not acceptable as discussed above.

Changes in the Phase 3 product and TBM product are considered minor as described below. Therefore, the Applicant was asked to submit data demonstrating similarity in the in vitro drug release profile of the Phase 3 and TBM products. In their response to IR comments from April 5, 2018, the applicant submitted the following response for bridging the phase 3 formulation with the TBM formulation.

A general linear model (GLM), based on a completely balanced design, was used to compare the in vitro drug release data for SA and EE at batch release from the 5 clinical batches used in Phase 3 (GF991-995) to the in vitro drug release data for SA and EE at batch release for the 3 registration batches (QK584, QL589, QL594). There was a separate comparison for each day of in vitro drug release: day 1, day 9, day 17, and day 30. Six rings were tested from each of the five Phase 3 batches, for a total of 30 rings. Twelve rings were tested from each of the registration batches.

Similarity between the pivotal (Phase 3) clinical batches and registration batches, was evaluated using several different endpoints: means and standard deviations; Least Squares Means and standard errors; GLM P-values; percentage of single ring release rates beyond the Phase 3 batches reference mean +/- 2 SD; and percentage of single ring release rates either below (b) (4)% of the reference mean or above (b) (4)% of the reference mean.

All analyses were based on observed release rates and no logarithmic transformations or other transformations were performed. The complete analysis of the data using above approach is data submitted here: Application 209627 - Sequence 0018 - GLM SAS Output and the applicant's interpretation of individual data point is provided in Application 209627 - Sequence 0018 - Response to Request for Information

The Applicant concluded that GLM approach demonstrated that the Phase 3 batches are similar to the registration batches at Days 17 and 30. At Days 1 and 9, the deviations from similarity for SA are clinically safe and effective based on safety and efficacy data in the NDA (300PK, ISS, ISE), and the Day 1 and 9 deviations for EE are clinically safe and effective based on the safety and efficacy data in the literature as presented in the white paper. In addition, the (b) (4) (b) (4)IVIVC in the NDA also supports the similarity of the registration batches to the Phase 3 batches.

Reviewer's Assessment:

Reverse bridging- Phase 2 to Phase 3 pivotal formulation:

The bridging analysis between phase 2 formulation (HC-02) with the Phase 3 formulation (GF991) using the IVIVC model is not acceptable. Since, the formulation change between phase 2 and phase 3 formulations are considered major (Table 39), these formulations cannot be bridged based on comparison of in vitro drug release analysis. Therefore, the bridging of the

phase 2 (HC-02) formulation with the phase 3 (GF991) formulations cannot be established. The clinical and clinical pharmacology team was informed about the unacceptable IVIVC and that the formulations cannot be bridged on the basis on in vitro drug release data.

Forward bridging- Phase 3 pivotal formulation to TBM formulation:

The bridging of the formulations was established by the Applicant based on demonstration of similarity in the in vitro drug release profiles between the formulations used in the clinical development as below.

In response to the clarification sought by the Agency during the orientation meeting, the Applicant submitted a report (Application 209627 - Sequence 0006 - History of the Formulation and Process and Bridging to Support Changes , IR response received on 11/21/2017) stating that there are no significant differences between the materials and processes used to manufacture the CVS for the Phase 3 Process and the materials and processes used to manufacture the CVS in the Registration / Proposed Commercial Process. The change was in the supplier of the SA (b) (4) (b) (4) (b) (4) Considering the above justification, and based on input from process reviewer, the biopharmaceutics review team agreed that the changes in the composition and process between the phase 3 pivotal formulation and the TBM formulations are minor. Therefore, in the absence of IVIVC, above formulations can be bridged together by considering a similarity in the in vitro drug release profile between them.

The Applicant was asked (IR sent to the applicant on 4/5/2018) to provide an appropriate analysis demonstrating a similarity in the in vitro drug release profiles of the pivotal (Phase 3) clinical batches and TBM batches as below:

You proposed to the use of IVIVC to establish a bridge between the to-be-marketed (TBM) batches and the batches used in the pivotal clinical studies (Phase 3). However, as we communicated earlier, your proposed IVIVIC model is not acceptable. Therefore, to bridge the manufacturing changes implemented (e.g. minor process changes) provide an appropriate analysis (e.g. multivariate analysis) demonstrating the similarity in in vitro drug release profiles of the pivotal (Phase 3) clinical batches and TBM batches.

The Applicant provided a GLM model approach to demonstrate similarity analysis. However, the following differences in the in vitro drug release profiles were noted between the phase 3 pivotal formulations and the registration batches

1. For EE Day 1 – The Day-1 mean EE IVR for the registration batches was 18% higher compared to the Phase 3 clinical batches

2. For EE Day 9 - The Day-9 mean EE IVR for the for the two of the three registration batches was 20% higher for the registration batches compared to the Phase 3 clinical batches.

3. For SA Day 1 - The Day-1 mean SA IVR for the two of the registration batches was 16% and 5% lower than the Phase 3 clinical batches are significantly higher than the Day-1 mean SA IVR for two of the three registration batches.

4. For SA Day 9 - The Day-9 mean SA IVR for one of the three registration batches was 6% lower than the Phase 3 clinical batches.

The Applicant justified the deviations at Days 1 and 9 by referring to the white paper (as discussed above) and inferred that the release profile differences on Days 1 and 9 for EE are clinically safe and effective based on data in the literature as presented in the white paper safety and Days 1 and 9 deviations for SA are clinically safe and effective based on the efficacy data in the NDA (300PK, Integrated Summary of Efficacy (ISE) Integrated summary of safety(ISS)).

The reviewers (based on Clinical review team's input) agree with the totality of the safety and efficacy justification provided by the Applicant in the integrated summary of efficacy, safety and the white paper. Taken together, it can be inferred that even with the differences in the in vitro drug release values of phase 3 with the registration batches, there will be minimal effect on the safety and efficacy. Therefore, Phase 3 pivotal formulation will be considered bridged to the to-be-marketed formulation from Biopharmaceutics perspective.

Based on the Applicant's and FDA/OPQ reviewer's analyses, the changes implemented are considered minor requiring compliance with the recommended in vitro drug release acceptance criteria. Specifically, the TBM formulation meets the approved clinically relevant in vitro drug release acceptance criteria and thus, it is deemed similar to the clinical trial batch.

Biowaiver Request

Reviewer's Assessment: N/A

R Regional Information

Comparability Protocols

The Applicant submitted (b) (4) comparability protocols as below

1. The proposed changes to the manufacturing process for SA/EE CVS are described in Table 16

   Table 16. Proposed Changes to the SA/EE CVS Manufacturing Process

(b) (4)

(b) (4)

Reviewer's Assessment: The impact of the change (b) (4) was discussed with the OPQ team and it was decided that the change will be considered a minor change. Therefore, the following comments were communicated to the Applicant:

'With respect to the Comparability Protocol (b) (4), we requested data demonstrating similarity between the in vitro drug release profiles of the pre-change and post-change product using an appropriate statistical method for similarity analysis (e.g., multivariate analysis). Neither an appropriate statistical method nor a definition of 'statistical similarity' was provided. However, upon further review, we conclude that compliance with in vitro drug release acceptance criteria at release and on stability is sufficient and that a statistical assessment of profile similarity is not necessary (see also comments below).

In addition, you proposed to conduct a 13-cycle simulated in-use stability study on pre-change and post-change product (section 4.2). However, you did not provide a definition of 'qualitatively comparable.' Note that you should determine and justify what constitutes 'qualitatively comparable' prior to initiation of the study and provide this information in the proposed CBE-30 supplement.'

As noted above, the proposed change (b) (4) will be submitted as a CBE-30 supplement and will not require a similarity analysis between the in vitro drug release profiles of pre-change and post-change products.

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(b) (4)

Post-Approval Commitments

Reviewer's Assessment:

The Applicant will perform a prospective analysis to determine (b) (4) in vivo release rate of SA and EE (b) (4)

(b) (4)

The PMC was communicated to the applicant along with the approval letter and will be completed within the following timeline.

Final protocol submission: March 2019

Study completion date: April 2020

Final report submission date: Oct 2020

Lifecycle Management Considerations

As mentioned before, the in vitro release method was found acceptable based on its ability to discern in vitro drug release rate variations in drug product batches at 'release' vs. 'stability', (b) (4) Furthermore, the method appears to be over-discriminating as batches showing similar efficacy and safety display different in vitro release rate. Thus, similarity testing is not applicable for qualifying minor manufacturing changes. The assessment of the acceptability of the CMC changes should be based on the compliance to the approved in vitro drug release acceptance criteria for both components.

List of Deficiencies:

The PMC for (b) (4) in vivo release rate should be communicated to the Applicant as part of the approval letter.

Primary Biopharmaceutics Reviewer Name and Date: Suneet Shukla 07/19/18

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Vidula Kolhatkar, July 19, 2018

Tertiary Reviewer Name and Date: Sandra Suarez; 7/18/18

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Suneet Shukla

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Vidula Kolhatkar

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Sandra Suarez

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QUALITY ASSESSMENT

MICROBIOLOGY

IQA Review Guide Reference

Product Background:

NDA/ANDA: NDA 209627

Drug Product Name / Strength: segesterone acetate/ethinyl estradiol 150 (b) (4) vaginal ring (0.150 mg/0.0 (b) (4) mg per day)

Route of Administration: vaginal

Applicant Name: The Population Council, Inc.

Manufacturing Site:
QPharma AB
Agneslundvagen 27
212 15 Malmo, Scania, Sweden

Method of Sterilization: Non-sterile drug product

Review Recommendation: **Recommended for approval**

Review Summary: Estrogen and ethinyl estradiol vaginal ring is a non-sterile, non-aqueous product.

List Submissions Being Reviewed: 08/17/2017 (original submission) and 12/05/2017 (IR response to filing comments and updated labeling)

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None.

Supporting Documents: N/A

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance
The drug substance is not reviewed in this application as the final drug product is a non-sterile product.

S.2. Manufacture – N/A

S.2.1 Manufacturers – N/A

S.2.2 Description of the Manufacturing Process and Process Controls – N/A

S.2.5 Process Validation and/or Evaluation – N/A

S.4 Control of Drug Substance – N/A

S.6. Container Closure System – N/A

S.7. Stability – N/A

P.1 Description of the Composition of the Drug Product

- **Description of drug product:** The drug product is a flexible, opaque white ring that is inserted vaginally for 21 days and removed for 7 days for a total of thirteen 28-day menstrual cycles. The active pharmaceutical ingredients (API), Nesterone (NES) and ethinyl estradiol (EE) in the form of steroid containing (b) (4) cores are inserted into two channels of the vaginal ring.
- **Drug product composition:** Section 3.2.P.1-Table 1 reproduced below from submission describes API and excipients. Section 3.2.P.1-Tables 3 and 4 reproduced below from submission detail each core. There is no water used in the formulation of the drug product.

Table 1. Composition of Nestorone®/ Ethinyl Estradiol Contraceptive Ring Drug Product

Component	Quantity Per CVR	Percent Per CVR	Function	Quality Standard
- Drug substances:				
Nestorone®	103.00 mg	(b) (4)	Drug Substance	Section 3.2.S.4.1-NES
Ethinyl Estradiol	17.40 mg		Drug Substance	Section 3.2.S.4.1-EE
- Other components:				
Silicone elastomer (b) (4)	(b) (4)		(b) (4)	QPharma 421052 (b) (4)
Silicone elastomer (b) (4)				QPharma 421052 (b) (4)
Silicone elastomer (b) (4)				QPharma 421060 (b) (4)
Silicone elastomer (b) (4)				QPharma 421075 (b) (4)
Silicone elastomer (b) (4)				QPharma 421075 (b) (4)
Silicone medical adhesive (b) (4)				QPharma 421080 (b) (4)
Total		100		
(b) (4)				

Table 3. Composition of NES/EE Core

Component	Quantity Per Core	Function	Quality Standard
Nestorone®	(b) (4)	Drug Substance	Section 3.2.S.4.1-NES
Ethinyl Estradiol		Drug Substance	Section 3.2.S.4.1-EE
(b) (4)			
Core length	18 mm		
(b) (4)			

Table 4. Composition of NES Core

Component	Quantity Per Core	Function	Quality Standard
Nestorone®	(b) (4)	Drug Substance	Section 3.2.S.4.1-NES
(b) (4)			
Core length	11 mm		
(b) (4)			

- **Description of container closure system** – The drug product is packaged as an opaque white (b) (4) vaginal ring that is both flexible and non-biodegradable. It is packaged in an aluminum heat-sealed pouch, and a black (b) (4) case is provided for storage during non-use. The following figure is reproduced from submission Section 3.2.P.2.2.

(b) (4)

Reviewer's Assessment: ***Adequate***

The applicant provides an adequate description of the drug product and container/closure system.

P.2 Pharmaceutical Development
P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

Container closure integrity testing is not required as this is a non-sterile product. However, the applicant performs a pouch seal integrity test (b) (4)

(b) (4)

Reviewer's Assessment: ***Adequate***

The container closure is consistent with regulatory expectations for a non-sterile pharmaceutical product.

Antimicrobial Effectiveness Testing

N/A. Although the drug product is multiple-dose, it is a non-sterile, non-aqueous dosage form.

Reviewer's Assessment: N/A. Multiple dose, non-aqueous drug products are not required to be subjected to USP <51>.

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Marla Stevens Riley

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Attachment I: Final Risk Assessment / Life Cycle Management

Segesterone Acetate and Ethinyl Estradiol Vaginal System

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****
Appearance	• Process • Stability	Moderate	Process controls; established AQL	Adequate	
Dimensions	• Equipment • Process	Low		Adequate	
Mass	• Equipment • Process	Low	Material and process controls	Adequate	
Identification	• CGMPs	Low		Adequate	
Assay	• Raw materials • Formulation • Process parameters • Scale/equipment • Site	Moderate	Material and process controls; Assay	Adequate	
Related Substances Impurities/ Degradants	• Formulation • Process • Storage	Moderate	Material and process controls	Adequate	(b) (4)
Biocompatibility	• Formulation • Raw materials • Process	Moderate	Material and process controls	Adequate	Any changes that could impact biocompatibility should be consulted to CDRH-ODE (see Note 1)
Mechanical Properties	• Raw materials • Process	Low	Material and process controls	Adequate	Any changes that could impact mechanical properties should be consulted to CDRH-ODE
Uniformity of Dosage Units	• API Properties • Formulation • Process • Scale/equipment • Site	Moderate	(b) (4) Process controls	Adequate	
In Vitro Release	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	High	Established material and process controls; (b) (4)	Adequate	Controlled release of actives from the IVR is essential to product safety and efficacy. Impact of any changes on in vitro release must be evaluated. In vitro release rate profiles must meet clinical relevant accdeptance criteria. (b) (4)
Microbial Limits	• Raw materials •Equipment and handling • Moisture content	Low	Environmental controls; Micro. testing	Adequate	

*Risk ranking applies to product attribute/CQA

**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

Note 1

(b) (4)

Note 2

Principles of SUPAC-MR may be applied judiciously. Currently there is limited product and process knowledge, so the potential impact of any post-approval changes especially on biocompatibility and in vitro release rate must be carefully assessed.

#####

Mark Seggel

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