DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209627

NDA APPROVAL

The Population Council, Inc.
Attention: Daniel C. Loeven
Associate Director, Regulatory Affairs
1230 York Avenue
Weiss Building 6th Floor
New York, NY 10065

Dear Mr. Loeven:

Please refer to your New Drug Application (NDA) dated and received August 17, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Annovera (segesterone acetate and ethinyl estradiol vaginal system).

This new drug application provides for the use of Annovera (segesterone acetate and ethinyl estradiol vaginal system) for prevention of pregnancy in females of reproductive potential.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information, text for the patient package insert, instructions for use). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels submitted on August 8, 2018, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3). For administrative purposes, designate this submission "Final Printed Carton and Container Labels for approved NDA 209627." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Annovera (segesterone acetate/ethinyl estradiol vaginal system) was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

SENTINEL/ARIA NOTIFICATION

The Food and Drug Administration Amendments Act of 2007 (FDAAA) required FDA to establish a national electronic system to monitor the safety of FDA-regulated medical products. In fulfillment of this mandate, FDA established the Sentinel System, which enables FDA to proactively monitor drug safety using electronic health data from multiple data sources that contribute to the Sentinel Distributed Database.

FDA plans to evaluate Annovera in the Sentinel System as part of the implementation of section 505(o) of the FDCA. We have determined that the new pharmacovigilance system, Sentinel's Active Risk Identification and Analysis (ARIA) System, established under section 505(k)(3) of the FDCA, is sufficient to conduct sequential safety monitoring for early detection of a large increase in the risk of non-fatal venous thromboembolism/arterial thromboembolism in the United States population.

The ARIA safety assessment will be posted to the Sentinel website at this location: https://www.sentinelinitiative.org. Once there is sufficient product uptake to support an analysis, an analysis plan will be posted online. After the analysis is complete, FDA will also post the results on the Sentinel website. FDA will notify you prior to posting the analysis plan and prior to posting the results.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an

assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for premenarcheal females from birth to 11 years and all males because studies are impossible or highly impractical. We note that you have fulfilled the pediatric study requirement by assessing the product in pediatric females aged 12 years and older.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of serious risk of venous thromboembolism and arterial thromboembolism associated with exposure to Annovera, and safety outcomes associated with co-administration of Annovera and cytochrome P4503A (CYP3A) inducers and inhibitors, and concurrent usage of tampon with Annovera.

Furthermore, the new pharmacovigilance system (ARIA) that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks. ARIA is insufficient to assess an elevated risk for fatal or non-fatal venous thromboembolism and arterial thromboembolism with sufficient measure and adjustment for covariates of interest due to long-term use of your product.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3454-1 A controlled, non-interventional, long-term cohort study that follows a series of cohorts comprising new users of your product (segesterone acetate and ethinyl estradiol vaginal system), new users of other vaginal ring contraceptives, new users of any intrauterine system, and new users of combined oral contraceptives containing other progestins. The primary objective of the study is to assess the risk for fatal and non-fatal venous thromboembolism and arterial thromboembolism associated with short-term and long-term use of your product in a study population representative of actual users of the product in the US and other countries where your vaginal system is prescribed. The study should be

sufficiently powered and have adequate confounding control to rule out a 1.5 to 2-fold risk for venous thromboembolism.

The timetable you submitted on July 20, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	08/2019
Study Completion:	08/2029
Final Report Submission:	08/2030

3454-2 A clinical drug-drug interaction trial to evaluate the effects of strong CYP3A induction and inhibition on the pharmacokinetics (PK) of segesterone acetate and ethinyl estradiol from your vaginal system.

The timetable you submitted on July 20, 2018, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	08/2019
Study Completion:	08/2020
Final Report Submission:	03/2021

3454-3 A clinical trial to evaluate the effect of tampon co-usage on systemic exposure to segesterone acetate and ethinyl estradiol from your vaginal system.

The timetable you submitted on July 20, 2018, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	08/2019
Study Completion:	08/2020
Final Report Submission:	02/2021

Submit clinical protocol(s) to your IND 049980 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to

report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

3454-4 A study to characterize the in vivo release rate of Annovera.

The timetable you submitted on July 20, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 03/2019
Study/Trial Completion: 04/2020
Final Report Submission: 10/2020

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at: http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Victor Crentsil, M.D., M.H.S.
Acting Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VICTOR CRENTSIL
08/10/2018