

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209627Orig1s000

OTHER REVIEW(S)



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency
Version: 2018-01-24**

Date: 8/2/2018

Reviewer(s): Wei Liu, PhD, MSc
Division of Epidemiology II

Team Leader: Jie (Jenni) Li, PhD
Division of Epidemiology II

Division Director: CAPT David Moeny, RPh, MPH, USPHS
Division of Epidemiology II

Subject: ARIA Sufficiency Memo

Drug Name(s): Segesterone acetate and ethinyl estradiol vaginal system

Application Type/Number: NDA 209627

Applicant/sponsor: Population Council

OSE RCM #: 2017-1711



EXECUTIVE SUMMARY (*place "X" in appropriate boxes*)

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

Population Council (the sponsor) is seeking FDA approval for a contraceptive vaginal ring (CVR) indicated for use by females of reproductive age to prevent pregnancy. The product contains segesterone acetate/ethinyl estradiol (SA/EE) and is designed to release approximately 150 µg of SA and 15 µg of EE daily. Efficacy evaluation based on two Phase 3 open-label trials involving 2,308 healthy women between the age of 18 and 40 showed that the CVR is effective for 12 months (13 menstrual cycles) when used continuously for 3 weeks followed by a CVR-free week in each cycle. The sponsor submitted an original new molecular entity (NME) application (NDA 209627) for the CVR on August 17, 2017. The PDUFA goal date is August 17, 2018.

Currently, there's only one FDA-approved combined progestin-estrogen CVR available in the US market (NuvaRing, NDA 021187). NuvaRing, approved in October 2001, releases about 120 µg of etonogestrel (ENG) and 15 µg of EE per day and is for monthly use (3 weeks in vagina continuously, remove for a week, and a new ring inserted 1 week later), compared to a yearly use of SA/EE. Systematic review of controlled clinical trial data suggests that the efficacy and safety profile of NuvaRing are comparable to combined oral contraceptives (COCs).^{1,2,3}

Compared to other commonly used contraceptive methods, the main advantages of CVRs include lower estrogen release rate (compared to oral pills⁴), convenience of use (e.g., only need to replace the ring annually or once a month), reduced dysmenorrhea, and good cycle control.⁵

1.2. Describe the Safety Concern

For combined hormonal contraceptives (CHCs), an increased risk (2- to 3-fold increase, compared to non-use of CHCs) of venous thromboembolism (VTE) is well established.⁶ Epidemiological data on the risk of arterial thrombotic events (ATE) such as acute myocardial infarction (AMI) and stroke are sparse and most published studies lack statistical power to detect small effects on ATE due to rare nature of these conditions in young women.⁷

Concern for an even higher increased risk of VTE (higher than other progestin types) was identified in the NDA review for the SA/EE CVR. Four investigator-confirmed VTEs (2 deep venous thrombosis [DVT], 1 pulmonary embolism [PE], 1 cerebral venous thrombosis [CVT]), occurring during cycle 2, 3, 6, and 7 of the CVR use, were reported in the Phase 3 trials. The crude incidence rate for VTE was 24.1 (95% CI: 6.6-61.7) per 10,000 woman-years for SA/EE CVR in Phase 3 trials; the incidence rate for VTE observed in trials was 5.35 per 10,000 woman-years for NuvaRing; 16.7 and 11.3 per 10,000 woman-years for combined oral contraceptives (COCs) containing norethisterone acetate/EE or levonorgestrel/EE, respectively.^a

^a <http://wayback.archive-it.org/7993/20170113093209/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterial/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM282462.pdf>



Because two of the 4 cases (1 PE and 1 DVT) had a body mass index (BMI) of > 29, the Data Safety Monitoring Board (DSMB) recommended against further enrollment of new subjects with a BMI >29. Subsequently, the sponsor decided to withdraw all subjects enrolled in Phase 3 trials whose BMI was > 29. The sponsor proposed (b) (4)

However, the Division of Bone, Reproductive and Urologic Products (DBRUP) believes (b) (4)

To obtain better data about the VTE risk and its relationship to BMI among SA/EE users, DBRUP is intending to request more safety data with BMI measured and controlled for in an observational study to further quantify the increase of the risk by BMI. DBRUP requests a prospective observational study with primary data collection or medical record linkage post-marketing requirement (PMR) to determine the BMI value for safe use of SA/EE.

Randomized trials are generally designed for prespecified efficacy endpoints. Trials are usually underpowered even for anticipated safety outcomes such as VTE and ATE. In her medical officer's review, Dr. Abby Anderson from DBRUP commented that "[a]lthough the VTE risk (24.1 per 10,000 woman-years; 95% CI: 6.6-61.7) based on 2,308 healthy women contributing 21,590 cycles for SA/EE CVR is higher than any other CHC products approved by the FDA in the past 10 years^b, this increased risk is attributable to one additional VTE event only. The wide 95% confidence interval (CI) reflects the uncertainty of the VTE rate based on the integrated safety analysis population. This means that clinical studies of this size are not powered to provide a concise estimate of incidence of uncommon events including VTE and ATE. A postmarketing requirement to evaluate the VTE risk with an appropriately powered study will provide a more accurate risk assessment."

Because of concerns over the higher-than-expected VTE risk observed in the clinical trials and the need for further study post-marketing, DBRUP requested the Division of Epidemiology (DEPI) to determine whether active surveillance in Sentinel (ARIA) is sufficient to ascertain the risk of VTE and ATE in patients exposed to the SA/EE CVR. DEPI held a signal assessment meeting (SAM) on May 31, 2018; FDA colleagues from DBRUP, DEPI, and the OSE Sentinel team attended the meeting. Together, the group determined that ARIA was not sufficient. Using an observational approach would be challenging without data on important potential confounders such as smoking and BMI. The purpose of this ARIA memo is to document DEPI's current thinking and recommendations following the SAM.

Role of BMI in VTE studies of the CHCs:

Many studies have been published on the risk for VTE with the use of newer versus old generations of progestin, and the study results are inconsistent. In the administrative claim-based studies with less or no measure or adjustment for BMI and other key confounders, new generations of COC appear to be associated with a small, elevated risk (2-fold increase) which may be due, at least in part, to residual confounding. Yet in large prospective studies, usually conducted in Europe and with better measurement of and adjustment for BMI, patient medical history and other lifestyle factors, the VTE risk seems to be consistent across progestin types; and baseline BMI appears to be independently associated with a higher VTE risk. See detailed literature in Section 5. Therefore, DEPI has determined that ascertainment of BMI is critical in controlling confounding in VTE studies. In this particular NDA, BMI has shown to be a potential key factor in determining whether SA/EE is safe to be used among women with a higher BMI

^b The VTE incidence rate with CHC products acceptable to the agency is approximately 3-9 per 10,000 WYs.

value. There is a need to identify a safe BMI cut-point (b) (4) for women to use the new progestin type, if one exists. Since VTE is a known risk for CHCs, a higher level of evidence is needed for further informing labeling for this NDA.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	X
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	

1.4. Statement of Purpose

The purpose is to conduct an inferential analysis in Sentinel to quantify the risks of VTE and ATE in users of SA/EE CVR compared to users of other commonly used hormonal contraceptives (e.g., NuvaRing, oral pills). This study should control for all well-known confounding factors of the association between CHCs and VTE/ATE.

1.5. Effect Size of Interest or Estimated Sample Size Desired

Because the purpose of the study is to quantitatively assess the risk of known safety outcomes for a NME CVR relative to other marketed CHC products (e.g., *versus* an active-comparator rather than nonuse), and because the expected increase in risk between contraceptive types is generally low (less than 2) and the risk compared to non-use is 2-3, FDA requires post-marketing studies designed to exclude a minimum 1.5- to 2-fold excess VTE risk from SA/EE CVR.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The study population should include women 18-45 years of age with medical and pharmacy data available through a baseline period of 183 days, with no prior exposure to a hormonal contraceptive product and who initiate the SA/EE CVR or a control product.

2.2 Is ARIA sufficient to assess the intended population?

Yes. Ascertaining the intended population is not a limiting factor. Many observational studies aimed to assess the risks of VTE and/or ATE with use of hormonal contraceptive products (e.g., COCs, intrauterine device, transdermal patch, and vaginal ring) have been conducted using healthcare administrative claims databases in the US.^{7,8} Thus, we anticipate that ARIA is sufficient to capture SA/EE CVR users and the control population using other hormonal contraceptives.

3 EXPOSURES

3.1 Treatment Exposure(s)

The exposure of interest is SA/EE CVR. The exposure would be incident, i.e., no previous exposure to hormonal contraception of any form during a washout period of 6 months (183 days).

3.2 Comparator Exposure(s)

For post-marketing safety studies, an active comparison group is preferred because this could make the treatment groups more similar (e.g., increase the overlap of baseline characteristics), hence mitigating the confounding bias via study design. The primary control group is new users of NuvaRing. The secondary control group is new users of other commonly prescribed CHC products (e.g., grouped CHC comparators) containing other progestins.

3.3 Is ARIA sufficient to identify the exposure of interest?

Yes. ARIA permits identification of patients dispensed outpatient prescriptions. Administrative claims data available for ARIA should be sufficient for defining exposure to SA/EE CVR, NuvaRing or other CHCs using coded information.

In a prior Sentinel assessment of VTE risk associated with continuous- (e.g., Lybrel®) or extended- cycle versus cyclic use of levonorgestrel-containing COCs, prescription claims for hormonal contraception of various forms including oral pills, vaginal ring, transdermal patches, subdermal implants, or intrauterine devices were identified in administrative claims data using coded information (Jenni Li. Risk of venous thromboembolism with low-dose extended and continuous-cycle combined oral contraceptives – a safety study in the Sentinel system⁹). From these data, it appears that a Sentinel analysis could capture SA/EE CVR, NuvaRing and other CHC dispensing. However, prescription data only indicates that a prescription is filled, not necessarily administered. Also, another potential bias is differential adherence and discontinuation between different forms of contraceptive product. Despite these limitations, the risk of measurement bias would be likely low, so ARIA should be sufficient for defining exposures.

4 OUTCOME(S)

4.1 Outcomes of Interest

The outcomes of interest include hospitalization for VTE (including DVT, PE) and ATE (AMI, stroke).

4.2 Is ARIA sufficient to assess the outcome of interest?

Yes. ARIA is determined sufficient to ascertain hospitalized VTE and ATE events. In a prior Sentinel assessment of VTE risk following quadrivalent human papillomavirus (HPV4) vaccination, the investigators validated the International Classification of Diseases, 9th Version, Clinical Modification (ICD-9-CM) codes 415.1x (pulmonary embolism and infarction) and 453.x (other venous embolism and thrombosis) used to identify VTE events in emergency department and inpatient records. Using patient medical records as the reference (“gold standard”), the



positive predictive value (PPV) for this coding algorithm was 65%.¹⁰ Assuming misclassification between groups is approximately equal (e.g., non-differential), this will bias the relative risk (RR) estimate towards the null (e.g., RR is close to 1). In the aforementioned Sentinel Lybrel-VTE study, a secondary analysis was added which included VTE events (mainly DVT) diagnosed in the outpatient setting using the ICD-9-CM diagnosis codes in conjunction with prescriptions for an anticoagulant during the 30-day period subsequent to the VTE diagnosis.

ARIA also permits adequate identification of fatal or nonfatal AMI and stroke, if occurrence results in hospitalization. The Sentinel Working Group for identifying hospitalized AMI patients using ICD-9-CM codes 410.x1 and 410.x0 in the principal or primary position showed an overall positive predictive value (PPV) of 86% (95% CI: 79.2% to 91.2%). PPVs ranged from 76.3% to 94.3% across the 4 data partners involved in this assessment.¹¹ Acute stroke (ischemic or hemorrhagic) was an outcome evaluated as part of Sentinel's Health Outcome of Interest Validation and Literature Reviews.¹² The review found that the PPV for algorithms to identify stroke was > 80% using inpatient claims (in principal position) with ICD-9-CM diagnosis codes 430, 431, 433.x, 434.x, or 436. ARIA is currently unable to ascertain immediate fatal out-of-hospital AMI or stroke.

5 COVARIATES

5.1 Covariates of Interest

Confounding arises in observational studies when the factors that influence physician treatment decision and patient medication use are also independent determinants of the health outcome of interest. Covariates of interest typically include demographic variables, comorbidities, concomitant medications, and indicators of healthcare utilization. Specific covariates of interest for the proposed study are noted in the following section^{c,d}:

- 1) *Demographic variables*: age, calendar year
- 2) *Typical cardiovascular risk factors*: hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, chronic kidney disease, heart failure, myocardial infarction, stroke, obesity or overweight, smoking status
- 3) *Additional coexisting conditions*: gynecological conditions (uterine leiomyoma, endometriosis, ovarian cyst, menorrhagia, infertility, polycystic ovaries, polycystic ovarian syndrome related symptoms, other disorders of female genital tract), inflammatory conditions (rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, Crohn's disease, ulcerative colitis), migraines, sickle cell disease, malignancy, surgery, and recent hospitalization.
- 4) *Concomitant or recent treatments with*: beta blocker, ace inhibitors, non-steroidal anti-inflammatory drugs, statins, hormonal contraceptives, and non-hormonal contraceptives.
- 5) *Health service utilization*: number of ambulatory encounters, number of emergency room encounters, number of hospitalizations, number of non-acute institutional encounters, number of drug dispensing, number of unique generic drugs dispensed, number of unique drug classes dispensed, and number of preventive serviced.

^c Eworuke E, Thelus R, Lee JY, et al. Risk factors associated with an increased risk of venous thromboembolic events among combined oral contraceptive users. (b) (4)

^d Hotoleanu C. Genetic risk factors in venous thromboembolism. *Adv Exp Med Biol* 2017; 906: 253-272.



- 6) *Other covariates*: immobility, personal history of cardiovascular disease, family history of thrombotic disease, genetic risk factors (e.g., factor V Leiden, Protein C deficiency, Protein S deficiency, antithrombin deficiency)

5.2 Is ARIA sufficient to assess the covariates of interest?

No. We don't believe ARIA is sufficient in this domain because ARIA currently lacks credible methods for measuring BMI and smoking which are well-established risk factors for ATE/VTE.¹³⁻¹⁵ BMI might be an important effect modifier and/or confounding factor particularly for this new contraceptive, because its clinical trials identified VTE cases with BMI > 29 which raises concern over a potential higher VTR risk among women with a higher BMI. Smoking, BMI, personal and family history of thrombotic disease, and genetic risk factors are not completely ascertainable with ARIA.

For CHC/VTE studies, the importance of measuring and controlling for BMI was highlighted in the literature:

1. The European Active Surveillance Study (EURAS) was a multinational, prospective, noninterventional cohort study of new users of drospirenone (DRSP), levonorgestrel (LNG) and other progestin-containing COCs. Semiannual follow-up was based on mailed questionnaires collecting data on BMI and other key covariates, with additional follow-up procedures when needed. A total of 58,674 women were followed for 142,475 women-years of observation. At baseline, the percentage of obese (BMI >30.0) women was higher in the DRSP-containing COC cohort than in the other-COC cohort and the LNG-containing COC cohort (rate ratios, approx. 1.5). See Table 2 below. Since an elevated BMI is a well-known risk factor for VTE, the DRSP cohort had a higher baseline risk for VTE, compared to the other two COC cohorts. See the Figure below. This study suggests preferential prescribing patterns which could lead to an overestimate of VTE risk with DRSP. After adjusting for the predefined confounder variables, such as BMI and age, the hazard ratio for LNG (DRSP as reference group) decreased from 1.1 (95% CI: 0.7-2.0) to 1.0 (95% CI: 0.6-1.8) for VTE.¹⁶

Table 2

User cohorts: number of women (proportion of study population), and mean age, mean weight and mean body mass index (SD) at baseline

	Drospirenone	Levonorgestrel	Other OCs	NOHC	Total
No. of users (%)	16,534 (28.2)	15,428 (26.3)	26,341 (44.9)	371 (0.6)	58,674 (100)
Mean age (SD)	25.9 (8.1)	25.1 (8.7)	24.8 (7.8)	27.5 (8.0)	25.2 (8.2)
Mean weight (SD)	65.2 (12.9)	62.6 (11.9)	62.0 (11.5)	62.1 (10.7)	63.1 (12.1)
Mean BMI (SD)	22.9 (4.4)	22.0 (4.0)	21.7 (3.8)	21.7 (3.7)	22.1 (4.1)

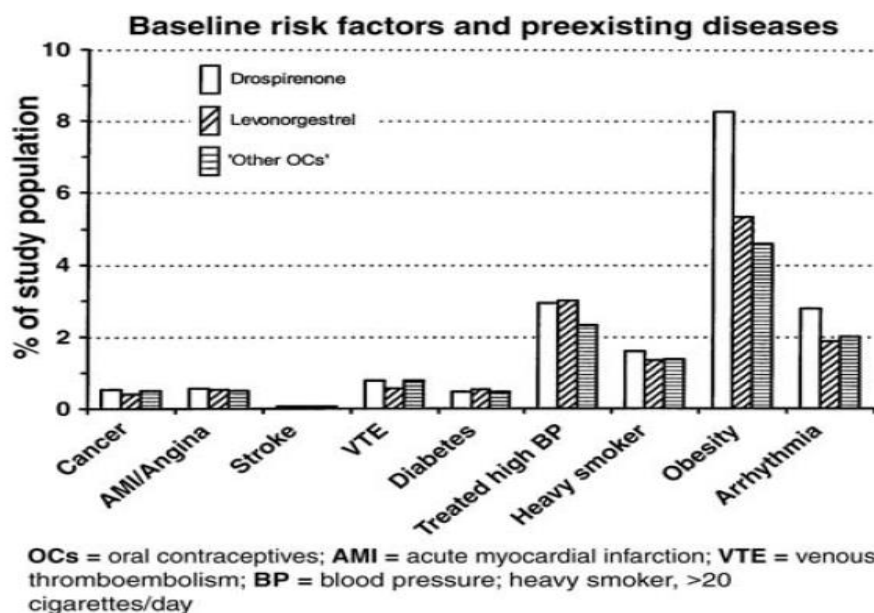


Fig. 1. Selected baseline risk factors and preexisting diseases per OC user cohort.

(Data source: page 348, Figure 1, in the publication Dinger et al. 2007)

2. In a case-controlled study in Germany, 680 VTE cases and 2,720 controls were identified. A higher percentage of cases had a BMI > 30 kg/m² than the controls (21.2% vs. 13.3%), and had a family (30.6% vs. 12.9%) or personal history of VTE (7.4% vs. 2.1%). The study did not find a higher VTE risk for dienogest (DNG) or DRSP, compared to LNG use (older generation of the progestin), after controlling for BMI, personal and family history of VTE, duration of COC use, and other covariates. Further, the use of any COC, compared to non-use of COC, was associated with a two-fold increased risk for VTE (adjusted odds ratio=2.4, 95% CI: 1.8-3.2). The authors believed that "The study was able to make use of information on personal/family history of VTE and BMI. These risk factors for VTE are probably the most important potential confounders to account for the specific risk associated with the DNG/EE and DRSP/EE user populations."¹⁷
3. Another nested case-control study in the UK General Practice Research Database included women aged 15-44 years without major risk factors for VTE who started a new episode of use of an oral contraceptive containing 30µg estrogen in combination with either DRSP or LNG between May 2002 and September 2009. A total of 61 cases of idiopathic VTE and 215 matched controls were identified. In the case-control analysis, current use of the DRSP-containing contraceptives was associated with a three-fold higher risk (odds ratio=3.3, 95% CI: 1.4-7.6) of non-fatal idiopathic venous thromboembolism compared with LNG use after adjusting for BMI as a continuous variable. The table below showed a clear association between BMI and VTE risk, with a higher BMI associated with a higher risk for VTE.¹⁸



Table 1 | Characteristics of cases and controls. Values are numbers (percentages) unless stated otherwise

Characteristic	Cases (n=61)	Controls (n=215)	Unadjusted matched odds ratio (95% CI)
Mean (SD) age (years)	32.2 (7.2)	31.8 (7.4)	–
Body mass index category (kg/m ²):			
<20	2 (3)	27 (13)	0.4 (0.1 to 1.7)
20-24.9	20 (33)	101 (47)	1.0
25-29.9	20 (33)	42 (20)	2.4 (1.2 to 4.8)
≥30	15 (25)	15 (7)	5.5 (2.1 to 14.0)
Unknown	4 (7)	30 (14)	0.7 (0.2 to 2.4)
History of varicose veins	3 (5)	9 (4)	1.2 (0.3 to 4.4)
Smoking status:			
Current smoker	11 (18)	47 (22)	0.7 (0.3 to 1.5)
Former smoker	9 (15)	39 (18)	0.7 (0.3 to 1.5)
Non-smoker	41 (67)	124 (58)	1.0
Unknown	0	5 (2)	–

(Data source: page 4, Table 1, in the publication of Parkin et al. 2011.)

In summary, residual confounding, due to failure to control for important VTE risk factors such as smoking and BMI in study design or statistical analysis may bias results to over- or under-estimate the VTE risk. Lacking information on these important confounders in the administrative claims data and with the understanding that DBRUP is seeking high quality evidence to definitively answer the safety question, DEPI deemed that ARIA is not sufficient. Sufficiency in this domain requires prospective data collection (e.g., direct patient questionnaire) or access to medical records to measure differences in frequency of those confounding factors between exposure groups.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

The Statement of Purpose requires inferential analysis, with sufficient confounding control, for VTE/ATE risk after exposure to SA/EE CVR or comparators.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes. ARIA currently includes modular programs for inferential analysis, including Cox proportional hazards regression with confounding control achieved by means of propensity score (PS) matching or stratification. DEPI determined that ARIA analytic tools should be sufficient to assess the question of interest. However, there might be one remaining caveat:

It has long been hypothesized that “healthy user bias” might be the cause of the observed increase in VTE risk associated with a newly marketed CHC product when compared to an older agent (e.g., comparator CHC) in some published observational studies.¹⁹ VTE risk tends to be



higher among naïve users and restarters (e.g., after an intake break of at least 4 weeks) of a CHC, particularly for the first 3-6 months of CHC use. Women who develop VTE symptoms while taking a CHC may terminate their treatment (e.g., “depletion of the susceptible”), therefore, the cohort of continuous users of a CHC tend to have a lower VTE risk compared to naïve users or restarters. It is likely that the cohort of ‘new users’ of SA/EE CVR may contain a larger proportion of women who are true naïve users or restarters (e.g., switchers from an old CHC product to SA/EE), compared to ‘new users’ of comparator CHC who often contain women who continue the older, established product. Further worsening the issue is the fact that physicians may prefer to prescribe the newer generation CHC agent over the older ones for those patients with a higher risk of thrombotic disorders if they think the newer product is safer.²⁰⁻²¹ Such thinking will result in channeling the higher risk women to the newer CHC product (e.g., selective prescribing) and ultimately overestimate the VTE risk for the new product. Since DBRUP does not intend to label the increased VTE risk due to BMI observed in Phase 3 trials, this may increase the likelihood of “differential prescribing.”

Study design or analytic options used to attempt to at least partially control for these biases include the use of propensity score enhanced sequential analytic methods (e.g., new user design, use active control, plus repeated PS matching within consecutive 3-/6-month follow-up windows),²²⁻²⁵ and the selection of a comparator cohort containing new users of CHCs with different generations of progestins (combined CHC comparators).²⁶ The sequential analytic tool described above is available in Sentinel recently. Details of this new surveillance tool are presented in Section 7 below.

7 NEXT STEPS

We deem ARIA is insufficient; FDA will issue a post-marketing requirement (PMR) to the Sponsor to evaluate the VTE and ATE risks following the SA/EE CVR exposure. (b) (4)

We request data collection in the US and other countries where the product will be marketed. The following PMR language is proposed and will be sent to the sponsor:

‘A controlled, non-interventional, long term cohort study that follows a series of cohorts comprising new users of your ring [Segesterone Acetate (SA) and Ethinyl Estradiol (EE) contraceptive vaginal system], new users of other ring contraceptives, new users of any intrauterine systems, and new users of contraceptives containing other progestins. The primary objective of the study is to assess the risk for venous thromboembolism (VTE)c risks of short term and long term use of your product in a study population representative of actual users of the product in the United States and other countries where your ring is prescribed. The study should be sufficiently powered to rule out a 1.5 to 2-fold risk for venous thromboembolism (VTE). (b) (4)

In addition, due to the timeline required for the proposed prospective study which may take a couple of years before the interim or final study results are available to the FDA^e, DEPI recommends active surveillance using Sentinel's sequential safety monitoring tool, which may allow for early detection of a grossly increased risk of VTE in the US population. This prospective surveillance tool allows the FDA to conduct sequential analyses to evaluate accumulating safety data of newly marketed medical products. The intent of sequential analysis is to quickly and effectively detect signals of excess risks that can be further investigated in clinical trials or by other available epidemiological methods. Prospective signal detection via periodic evaluation of routinely collected data is not a substitute for confirmatory studies and is not intended to imply a causal relationship. Ideally, prospective sequential monitoring using electronic healthcare data will only be useful for assessing risk of those signals that arise from pre-licensure trials, or are of particular biologic relevance.²⁷ Compared with conventional retrospective or prospective cohort studies, the advantage of the sequential monitoring is that it may obtain safety information earlier, hence may reduce time to signal detection.²²

To demonstrate the usefulness of the sequential analytic tool in the postmarketing drug safety surveillance, the FDA/Sentinel team conducted a pilot project to monitor the potential risk of acute myocardial infarction (AMI) associated with saxagliptin use, right after the drug's approval in 2009. The investigators conducted a total of 7 sequential assessments comparing use of saxagliptin versus selected comparators, and applied disease risk score stratification and propensity score matching to control for potential confounding. Meantime, per FDA's guidance, the sponsor conducted a postmarketing cardiovascular outcome trial (CVOT) starting in 2010. Five years after drug approval, both the trial and the observational study concluded that there is no suggestion of an increased risk of AMI with saxagliptin use. Interestingly, the observational study reached the conclusion earlier than the randomized trial. The interim results from the first 5 sequential analyses were available to FDA before the publication of the trial results in September 2013.²⁸

One obvious limitation of the sequential monitoring is that it is conducted in the same administrative claims data, hence, residual confounding due to missing information on BMI and smoking is still a caveat of the analysis. But we could roughly assess the potential impact of residual confounding using the concept of "E-value" that is introduced by VanderWeele and Ding.^{29,30} Briefly, E-value measures the minimum strength of association that an unmeasured confounder would need to have with the exposure and the outcome to completely explain away the observed association conditional on all measured confounders. A large E-value implies that considerable unmeasured confounding would be needed to nullify the observed association. For the VTE study, to be conservative, we could assume that the hazard ratio (HR) that we would like to rule out is 3 (e.g., compared with users of other CHCs, users of SA/EE CVR have a threefold increased risk of VTE). For an observed HR of 3, the corresponding E-value is 5.5. This means the observed HR of 3 can be explained away by an unmeasured confounder that is associated with both the treatment (e.g., SA/EE) and the outcome (e.g., VTE) by a factor of 5.5 each, beyond the measured confounders. Thus, a strong and relatively common unmeasured confounder would be needed to completely explain away the treatment-outcome association of 3. This is unlikely to be realistic for the case of BMI and smoking in the VTE/ATE study for SA/EE.

Finally, although we recommend using the active surveillance/sequential monitoring tool in Sentinel to rule out a HR of 3, this recommendation is pending a more detailed analysis of the

^e Per the current action plan and timeline proposed by the applicant for this PMR.



potential impact of the biases on the surveillance design. For example, to further quantify the effect of bias due to outcome misclassification using claims data, DEPI is planning to conduct a bias analysis to explore the range of positive predictive value (PPV) and how that may affect the effect estimates using the matrix adjustment method of bias analysis.

References:

1. Roumen FJ, Mishell DR Jr. The contraceptive vaginal ring, NuvaRing, a decade after its introduction. *Eur J Contracept Reprod Health Care*. 2012 Dec;17(6):415-27.
2. Oddsson K, Leifels-Fischer B, de Melo NR, et al. Efficacy and safety of a contraceptive vaginal ring (NuvaRing) compared with a combined oral contraceptive: a 1-year randomized trial. *Contraception*. 2005 Mar;71(3):176-82.
3. Ahrendt HJ, Nisand I, Bastianelli C, et al. Efficacy, acceptability and tolerability of the combined contraceptive ring, NuvaRing, compared with an oral contraceptive containing 30 microg of ethinyl estradiol and 3 mg of drospirenone. *Contraception*. 2006 Dec;74(6):451-7.
4. van den Heuvel MW, van Bragt AJM, Alnabawy AKF, et al. Comparison of ethinyl estradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. *Contraception* 2005;72:168-74.
5. Brache V, Payán LJ, Faundes A. Current status of contraceptive vaginal rings. *Contraception*. 2013 Mar;87(3):264-72.
6. Plu-Bureau G, Maitrot-Mantelet L, Hugon-Rodin J, et al. Hormonal contraceptives and venous thromboembolism: an epidemiological update. *Best Pract Res Clin Endocrinol Metab*. 2013 Feb;27(1):25-34.
7. <https://www.fda.gov/downloads/Drugs/DrugSafety/ucm277384.pdf>
8. <http://reaganudall.org/sites/default/files/Bate%202016%20VTE%20OCs%20IMEDS%20evaluation%20formatted%20poster.pdf>
9. Li J, Panucci G, Moeny D, et al. Risk for venous thromboembolism with low-dose extended- and continuous-cycle combined oral contraceptives – a safety study in the Sentinel system. *JAMA Internal Medicine* 2018, In Press.
10. Yih WK, Greene SK, Zichittella L, et al. Evaluation of the risk of venous thromboembolism after quadrivalent human papillomavirus vaccination among US females. *Vaccine*. 2016 Jan 2;34(1):172-8.
11. Cultrona SL, Toh S, Iyer A, et al. Validation of acute myocardial infarction in the Food and Drug Administration's Mini-Sentinel program. *Pharmacoepidemiol Drug Saf*. 2013 Jan;22(1):40-54.
12. <https://www.sentinelinitiative.org/sentinel/surveillance-tools/validations-lit-review>
13. Sweetland S, Parkin L, Balkwill A, et al. Smoking, surgery, and venous thromboembolism risk in women: United Kingdom cohort study. *Circulation* 2013; 127(12): 1276-82.
14. Pomp ER, Rosendaal ER, Doggen CJ. Smoking increase the risk of venous thromboembolism and acts synergistically with oral contraceptive use. *Am J Hematol* 2008; 83(2): 97-102.
15. McDaid A, Logette E, Buchillier V, et al. Risk prediction of developing venous thromboembolism in combined oral contraceptive users. *PLoS One* 2017; 12(7):eD0182041.
16. Dinger JC1, Heinemann LA, Kühl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. *Contraception* 2007; 75(5): 344-54.
17. Dinger J, Assmann A, Möhner S, et al. Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study. *J Fam Plann Reprod Health Care* 2010; 36(3): 123-9.
18. Parkin L, Sharples K, Hernandez RK, et al. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on

- UK General Practice Research Database. *BMJ*. 2011 Apr 21;342:d2139. doi: 10.1136/bmj.d2139.
19. Lewis MA. The Transnational Study on Oral Contraceptives and the Health of Young Women. Methods, results, new analyses and the healthy user effect. *Hum Reprod Update* 1999; 5(6): 707-20.
 20. Heinemann LA, Lewis MA, Assmann A, et al. Could preferential prescribing and referral behavior of physicians explain the elevated thrombosis risk found to be associated with third generation oral contraceptives? *Pharmacoepidemiol Drug Safety* 1996; 5:285-294.
 21. Jamin C, de Mouzon J. Selective prescribing of third generation oral contraceptives (OCs). *Contraception* 1996; 54(1):55-56.
 22. Cook AJ, Tiwari RC, Wellman RD, et al. Statistical approaches to group sequential monitoring of postmarket safety surveillance data: current state of the art for use in the Mini-Sentinel pilot. *Pharmacoepidemiol Drug Saf*. 2012 Jan;21 Suppl 1:72-81.
 23. Li, L., Kulldorff, M., Nelson, J.C. et al. A propensity score-enhanced sequential analytic method for comparative drug safety surveillance. *Stat Biosci* (2011) 3: 45.
 24. Brown JS, Kulldorff M, Petronis KR, et al. Early adverse drug event signal detection within population-based health networks using sequential methods: key methodologic considerations. *Pharmacoepidemiol Drug Saf*. 2009 Mar;18(3):226-34.
 25. Seeger JD, Loughlin J, Eng PM, et al. Risk of thromboembolism in women taking ethinyl estradiol/drospirenone and other oral contraceptives. *Obstet Gynecol* 2007; 110(3): 587-93.
 26. Sidney S, Cheetham TC, Connell FA, et al. Recent combined hormonal contraceptive (CHCs) and the risk of thromboembolism and other cardiovascular events in new users. *Contraception* 2013; 87:93-100.
 27. Brown JS, Kulldorff M, Chan KA, et al. Early detection of adverse drug events within population-based health networks: application of sequential testing methods. *Pharmacoepidemiol Drug Saf*. 2007 Dec;16(12):1275-84.
 28. Toh S, Reichman ME, Graham DJ, et al. Prospective Postmarketing Surveillance of Acute Myocardial Infarction in New Users of Saxagliptin: A Population-Based Study. *Diabetes Care*. 2018 Jan;41(1):39-48.
 29. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-Value. *Ann Intern Med* 2017; 167(4): 268-274.
 30. Ding P, VanderWeele TJ. Sensitivity analysis without assumptions. *Epidemiology* 2016; 27:368-377.

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/

WEI LIU
08/07/2018

JIE J LI
08/07/2018

DAVID G MOENY
08/07/2018

MICHAEL D BLUM
08/07/2018

MICHAEL D NGUYEN
08/07/2018

ROBERT BALL
08/07/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	August 6, 2018
Requesting Office or Division:	Division of Bone, Reproductive and Urologic Products (DBRUP)
Application Type and Number:	NDA 209627
Product Name and Strength:	segesterone acetate and ethinyl estradiol vaginal system, 0.15 mg/0.013 mg per day
Applicant/Sponsor Name:	Population Council
FDA Received Date:	August 2, 2018
OSE RCM #:	2017-1712-3
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Lolita G. White, PharmD

1 PURPOSE OF MEMORANDUM

Division of Bone, Reproductive and Urologic Products (DBRUP) requested that we review the proposed labels and labelings for Annovera (segesterone acetate and ethinyl estradiol) to determine if it is acceptable from a medication error perspective (see Appendix A). The revisions are in response to recommendations that we made in a previous review^a and also as part of negotiations between the sponsor and the Office of Pharmaceutical Quality (OPQ) made via e-mail to the DBRUP clinical team on July 30th and July 31st, 2018.

2 CONCLUSION

We acknowledge that the sponsor incorporated our previous recommendations in the revised container label and carton labeling for Annovera (segesterone acetate and ethinyl estradiol

^a Baugh D. Label, Labeling, and Packaging Review for SEGESTERONE ACETATE AND ETHINYL ESTRADIOL VAGINAL SYSTEM (NDA 209627). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2018 June 08. RCM No.: 2017-1712-2.

vaginal system). However, we identified a concern with the strength statement which may pose a risk of confusion due to decreased readability. We note that the space between the numerical dose and the unit of measure is absent, making the strength statement on the container label and carton labeling difficult to read. See our recommendation in Section 3.

3 RECOMMENDATIONS FOR POPULATION COUNCIL

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

As you currently propose, there is no space in the strength statement between the numerical dose and the unit of measure on the container label and carton labeling. This presentation makes the strength statement difficult to read. We recommend you add a space between the numerical dose and the units of measure. Specifically, revise the strength statement from '0.15mg/0.013mg' to now read '0.15 mg/0.013 mg' on the container label and carton labeling.

4 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

DENISE V BAUGH
08/06/2018

LOLITA G WHITE
08/06/2018

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

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

Memorandum

Date: June 27, 2018

To: Charlene Williamson, Regulatory Project Manager
Division of Bone, Reproductive, and Urologic Products (DBRUP)

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for segesterone acetate and ethinyl estradiol vaginal system

NDA: 209627

In response to DBRUP's consult request dated November 13, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for segesterone acetate and ethinyl estradiol vaginal system.

PI and PPI/IFU: OPDP's comments on the proposed labeling are based on the draft PI and PPI/IFU received by electronic mail from DBRUP on June 13, 2018. Our comments on the draft PI are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review of the draft PPI/IFU will be completed, and comments on the proposed PPI/IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labels received by electronic mail from DBRUP on June 13, 2018, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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

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

/s/

LYNN M PANHOLZER
06/27/2018

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

PATIENT LABELING REVIEW

Date: June 27, 2018

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

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Sharon W. Williams, MSN, BSN, RN
Senior Patient Labeling Reviewer, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Lynn Panholzer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name): TRADENAME (segesterone acetate and ethinyl estradiol)

Dosage Form and Route: vaginal-system

Application Type/Number: NDA 209627

Applicant: The Population Council, Inc.

1 INTRODUCTION

On August 17, 2017, The Population Council, Inc. submitted for the Agency's review a New Drug Application (NDA) 209627 for TRADENAME (segesterone acetate and ethinyl estradiol) vaginal-system. TRADENAME (segesterone acetate and ethinyl estradiol) is a New Molecular Entity (NME) with a proposed indication for use by females of reproductive age to prevent pregnancy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Bone, Reproductive and Urologic Products (DBRUP) on November 13, 2017 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TRADENAME (segesterone acetate and ethinyl estradiol) vaginal-system.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and separate DMEPA reviews of the PPI and IFU were completed on March 7, 2018 and May 14, 2018.

2 MATERIAL REVIEWED

- Draft TRADENAME (segesterone acetate and ethinyl estradiol) vaginal-system PPI and IFU received on August 17, 2017, revised by the Review Division throughout the review cycle, and received by DMPP on June 13, 2018.
- Draft TRADENAME (segesterone acetate and ethinyl estradiol) vaginal-system PPI and IFU received on August 17, 2017, revised by the Review Division throughout the review cycle, and received by OPDP on June 22, 2018.
- Draft TRADENAME (segesterone acetate and ethinyl estradiol) vaginal-system Prescribing Information (PI) received on August 17, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 13, 2018.
- Approved LILETTA (levonorgestrel-releasing intrauterine system) comparator labeling dated August 3, 2017.
- Approved NuvaRing (etonogestrel/ethinyl estradiol vaginal ring) comparator labeling dated February 12, 2018.

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication*

Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10 and the IFU document using the Arial font, size 11.

In our collaborative review of the PPI and IFU we:

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

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

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

/s/

KAREN M DOWDY
06/27/2018

LYNN M PANHOLZER
06/27/2018

SHARON W WILLIAMS
06/27/2018

LASHAWN M GRIFFITHS
06/27/2018

LABEL, LABELING, AND PACKAGING REVIEW

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

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

Date of This Review:	June 8, 2018
Requesting Office or Division:	Division of Bone, Reproductive and Urologic Products (DBRUP)
Application Type and Number:	NDA 209627
Product Name and Strength:	segesterone acetate and ethinyl estradiol vaginal system, 0.15 mg/0.0 (b) (4) mg per day
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription
Applicant/Sponsor Name:	Population Council
FDA Received Date:	April 5, 2018
OSE RCM #:	2017-1712-2
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Lolita G. White, PharmD

1 REASON FOR REVIEW

The Division of Bone, Reproductive, and Urologic Products (DBRUP) consulted the Division of Medication Error Prevention and Analysis (DMEPA) to evaluate the container label, carton labeling, and prescribing information (PI) for NDA 209627 to determine if they are acceptable from a medication errors perspective

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the container label, carton labeling and prescribing information (PI) identified the following areas of concern which may contribute to medication errors with this product:

- The label and labeling include the proposed proprietary name which is still under review by the Agency;
- The established name lacks prominence which is not in accordance with 21 CFR 201.10(g)(2);
- The NDC number is denoted by a placeholder on all label and labeling;
- As presented on the container label and carton labeling, the expiration date is not defined which may pose vulnerability to a 'degraded drug' medication error.
- Section 17 (Patient Counseling) in the PI lacks a statement to inform the patient to label the product with the discard date.
- The carton labeling can be improved to instruct the user when to discard the product. We are concerned this lack of instruction may pose risk of degraded product medication error.

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the container label and carton labeling where additional information should be added, revised, or removed to help ensure the safe use of this product. See our recommendations in Sections 4.1 and 4.2

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. How Supplied/Storage and Handling Section
 - a. Ensure that the intended NDC numbers are included in the 'How Supplied' (Section 16) section of the PI and in alignment with the NDC numbers as presented on the product packaging.
2. Patient Counseling
 - a. We note that there is a compact case provided to store the product for thirteen 28 day cycles. We recommend adding a statement to counsel the patient to label the product with the discard date at first use to minimize the risk that they will use the product beyond 13 cycles.

4.2 RECOMMENDATIONS FOR POPULATION COUNCIL

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

A. Container Label and Carton Labeling

1. We note the use of the proposed proprietary name, 'Annovera' throughout the label and labeling. Since this proprietary name has not been found to be acceptable, the proposed name, 'Annovera' should be revised to read 'Trade Name' throughout the label and labeling.
2. The established name ('segesterone acetate and ethinyl estradiol') lacks prominence commensurate with the proprietary name ('Trade Name'). The established name should be at least half the size of the proprietary name. Thus, we request you increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
3. The expiration date is absent or identified by a placeholder (e.g. 'xxxxx-xxxx-xx'). To minimize confusion and reduce the risk of 'deteriorated drug' medication errors, identify the format you intend to use. We recommend choosing one of the following formats:

DDMMYYYY (e.g., 31JAN2013)

MMYYYY (e.g., JAN2013)

YYYY-MM-DD (e.g., 2013-JAN-31)

YYYY-MM-DD (e.g., 2013-01-31)

4. As presented, the NDC numbers are indicated by place holders (e.g., 'xxxx-xxxx-xx'). Indicate the NDC numbers for our review and comment.

B. General Comment

1. We note that you provide a compact case for product storage when the vaginal ring is not in use. We are concerned that the information pertaining to when to discard the product may not be available to the user during the 13 cycles of repeated use and contribute to risk of degraded product medication error. To ensure safe and efficient use of the product, we recommend you consider a strategy to label the compact case at the time of first-use. For example, consider a peel-off label on the carton labeling which can be removed and placed on the compact case. The label may state "Discard after __/__/__" (instead of "Date opened" since "Discard after" is an affirmative statement, and has been shown to result in the desired action). Additionally, the "__/__/__" statement will alert the healthcare providers to write a complete date (month, day, and year) on the container label. This may help inform the user when 13 cycles have been completed.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for segesterone acetate and ethinyl estradiol vaginal system received on April 5, 2018 from Population Council.

Table 2. Relevant Product Information for segesterone acetate and ethinyl estradiol vaginal system	
Initial Approval Date	N/A
Active Ingredient	Segesterone acetate and ethinyl estradiol
Indication	Pregnancy prevention
Route of Administration	vaginal
Dosage Form	Vaginal system
Strength	103 mg segesterone acetate and 17.4 mg ethinyl estradiol, which releases on 0.15 mg/day of segesterone acetate and 0.0 (b) (4) mg/day of ethinyl estradiol
Dose and Frequency	Insert one ring vaginally and allow to stay in place for three consecutive weeks, followed by a one week ring-free period. Repeat this regimen for thirteen 28-day cycles.
How Supplied	One vaginal system is packaged in an aluminum pouch; one box contains 1 pouch
Storage	A compact case is used for storage during each 7-day ring-free interval. After 13 cycles of use, the ring should be placed in the compact case and discarded in the waste receptacle out of the reach of children and pets. It should not be flushed down the toilet.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 8, 2018, we searched DMEPA's previous reviews using the terms, 'segesterone' and '209627'. Our search identified no previous relevant reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following segesterone acetate and ethinyl estradiol labels and labeling submitted by Population Council.

- Container label received on April 5, 2018
- Carton labeling received on April 5, 2018
- Prescribing Information (Image not shown) received on April 5, 2018

G.2 Label and Labeling Images

Container label (front and back)



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

^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

LOLITA G WHITE on behalf of DENISE V BAUGH
06/08/2018

LOLITA G WHITE
06/08/2018

Clinical Inspection Summary

Date	5/31/2018
From	Cara Alfaro, Pharm.D., Clinical Analyst Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Charlene Williamson, Regulatory Project Manager Abby Anderson, M.D., Medical Officer Division of Bone, Reproductive, and Urologic Products
NDA #	209627
Applicant	Population Council
Drug	Segesterone acetate and ethinyl estradiol vaginal ring
NME	Yes
Proposed Indication	For use by women to prevent pregnancy
Consultation Request Date	10/5/2017
Summary Goal Date	6/17/2018
Action Goal Date	8/17/2018
PDUFA Date	8/17/2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Barnhart, Thomas, Gilliam, Darney, Brache, and the sponsor, Population Council, were inspected in support of this NDA. Although regulatory compliance violations were noted at Dr. Barnhart's and Dr. Darney's sites, the findings are unlikely to significantly impact data reliability. The studies appear to have been conducted adequately and the data generated by these sites and submitted to the sponsor appear acceptable in support of the respective indication.

Dr. Brache's site was chosen due to a higher than expected number of pregnancies compared to other sites participating in Protocol 300B. Per protocol, test article was to be stored at room temperature, though there were no requirements for temperature monitoring outlined in the protocol. The test article packaging indicated that the test article was to be stored in a "cool, dry place". This site did not monitor temperature or humidity, therefore, contribution of the test article (product failure) to the increased number of pregnancies at this site cannot be determined.

Four venous thromboembolic (VTE) events occurred in these studies, three in Protocol 300A and one in Protocol 300B. The sponsor inspection noted communication between the sponsor and Data Safety Monitoring Board (DSMB) to evaluate the benefit/risk for enrollment and continued participation of subjects in these studies. The sponsor appeared to provide requested

materials and analyses as requested by the DSMB relevant to these deliberations. Based on the VTE events and risk calculations, the DSMB recommended against further enrollment of new subjects with body mass index (BMI) $> 29 \text{ kg/m}^2$. In discussions with the sponsor, this was later changed to exclude all subjects, new and currently enrolled, with BMI $> 29 \text{ kg/m}^2$.

The sponsor used baseline BMI to analyze VTE event incidence in the studies. Baseline BMI (BMIBASE) was defined as “the maximum BMI recorded at any point prior to enrollment and first contraceptive vaginal ring (CVR) use”. In these studies, two VTE events occurred in subjects with BMIBASE $\geq 29 \text{ kg/m}^2$ and two events occurred in subjects with BMIBASE $< 29 \text{ kg/m}^2$. This sponsor inspection followed up on a complaint received from a former employee of the sponsor alleging that the definition of baseline BMI was changed after completion of the studies and database lock, and use of baseline, rather than time of event BMI for VTE incidence analysis. The inspection did not find evidence confirming this. We recommend that the review division perform analyses using whichever BMI is considered most appropriate to evaluate VTE risk within this application and for comparison of VTE risk with similar products and ask the sponsor to provide documentation of BMI at time of event.

The compliance classification of the inspections of Drs. Thomas, Gilliam, Brache, and the sponsor, Population Council, is No Action Indicated (NAI). The compliance classification of the inspections of Drs. Barnhart and Darney is Voluntary Action Indicated (VAI).

II. BACKGROUND

The segesterone acetate/ethinyl estradiol 150/15 contraceptive vaginal ring (CVR) is being developed for the prevention of pregnancy in women under NDA 209627. This is a progestin/estrogen combination hormonal contraceptive that is “user-controlled”, meaning that women insert and remove the product on a 21 day in and 7 day out regimen. It is designed to be reusable for up to one year (13 treatment cycles). The sponsor has submitted two Phase 3 studies, Study 300A and 300B, to support the efficacy and safety of segesterone acetate/ethinyl estradiol CVR for the prevention of pregnancy.

Protocol 300A

Title: “A multicenter, open-label study on the efficacy, cycle control and safety of a contraceptive vaginal ring delivering a daily dose of 150 μg of Nestorone® and 15 μg of ethinyl estradiol (150/15 NES/EE CVR)”

Subjects: 1129 enrolled

Sites: 15 sites in the United States

Study Initiation and Completion Dates: 12/19/2006 to 10/7/2009

This was an open-label study of the segesterone/ethinyl estradiol CVR. Included were healthy, sexually active women with a history of regular menstrual cycles when not using hormonal contraceptives, and 18 to ≤ 40 years of age. During the conduct of the study, the DSMB recommended exclusion of women with a BMI $> 29 \text{ kg/m}^2$.

A single CVR was used by each subject for up to 13 cycles (1 year). Each cycle included 21 dosing days where the CVR was in the vagina (ring-in days) followed by 7 non-dosing days when the CVR was not worn (ring-out days). After completion of the study, subjects who intended to use non hormonal contraceptives or who intended to become pregnant were entered into a 6-month post CVR follow-up to monitor the return to fertility and pregnancies.

Subjects were provided diary cards and were asked to record times when the CVR was in or out, dates of any bleeding/spotting, whether they had intercourse, condom or other contraceptive use, complete expulsions/partial expulsions, any problems with the CVR, medical problems, and concomitant medications. No other forms of contraceptive were allowed during the study.

The primary efficacy analysis was the Pearl Index, the number of pregnancies per 100 woman years, in subjects ≤ 35 years of age. The Pearl Index and 95% Confidence Interval (CI) for this study was 3.02 (1.80, 4.69) which, according to the sponsor, provided evidence of efficacy. There were three venous thromboembolic (VTE) events occurring in this study.

Protocol 300B

Title: “A multicenter, open-label study on the efficacy, cycle control and safety of a contraceptive vaginal ring delivering a daily dose of 150 µg of Nestorone® and 15 µg of ethinyl estradiol (150/15 NES/EE CVR)”

Subjects: 1135 enrolled

Sites: 12 sites; United States (5 sites), Latin America (3 sites), Europe (3 sites), and Australia (1 site)

Study Initiation and Completion Dates: 11/1/2006 to 7/2/2009

The study design was the same as Protocol 300A. The Pearl Index and 95% Confidence Interval (CI) for this study was 3.01 (1.90, 4.48) which, according to the sponsor, provided evidence of efficacy. There was one venous thromboembolic (VTE) event occurring in this study.

Rationale for Site Selection

The clinical sites were chosen primarily based on high subject enrollment, adverse events of special interest (venous thromboembolism [VTE]), numbers of pregnancies occurring at the site, and prior inspectional history. The sponsor, Population Council, was also inspected as part of a data audit inspection and a complaint related to the protocols under review for this NDA submission.

III. RESULTS (by site)

Site #, Name of CI, Address, Country if non- U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Dates	Classification
Site #12 Kurt Barnhart, M.D. Univ. of Pennsylvania 3701 Market Street Suite 810 Philadelphia, PA 19104	Protocol 300A Subjects: 135	11 – 15 Dec 2017	VAI
Site #21 Michael Thomas, M.D. Holmes Hospital Room 4028 200 Albert Sabin Way Cincinnati, OH 45267	Protocol 300A Subjects: 99	18 Dec 2017 – 5 Jan 2018 (6 days)	NAI
Site #9 Melissa Gilliam, M.D. University of Chicago Hospitals 5801 S. Ellis Street Room 421 Chicago, IL 60637	Protocol 300B Subjects: 73	12/7/2017 to 12/14/2017	NAI
Site #23 Philip Darney, M.D. University of California 625 Potrero Avenue San Francisco, CA 94110	Protocol 300B Subjects: 125	11/27/2017 to 12/01/2017	VAI

Site #, Name of CI, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Dates	Classification
Site #3 Vivian Brache, Lic. PROFAMILIA, Socorro Sánchez #160, Zona 1, Apartado 1053 Santo Domingo, Dominican Republic	Protocol 300B Subjects: 69	3/13/2018 to 3/16/2018	NAI
Sponsor Population Council 1230 York Avenue New York, NY 10065	Protocols 300A, 300B	3/6/2018 to 3/14/2018	NAI

Compliance Classifications

NAI = No Action Indicated, no deviation from regulations.

VAI = Voluntary Action Indicated, deviation(s) from regulations.

OAI = Official Action Indicated, significant deviations from regulations. Data may be unreliable.

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

1. Clinical Investigator: Kurt Barnhart, M.D.; Philadelphia, PA; Site #12

For Protocol 300A, 187 subjects were screened, 135 subjects were enrolled and randomized, and 79 subjects completed 13 cycles. There were 56 subject discontinuations including 22 subjects lost to follow-up and nine subjects who discontinued due to adverse events. The EIR did not contain enough information to verify the reasons for all subject discontinuations, including the specific adverse events leading to discontinuation. Reasons for subject discontinuation are included in sponsor listings (Listing 16.2.1 Subject Disposition).

An audit of the study records for 45 of the 135 subjects enrolled (33%) was conducted. Records reviewed included but were not limited to informed consent forms, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, subject home diaries, protocol deviations, and primary efficacy endpoint (pregnancy).

A Form FDA 483 was issued at the conclusion of the inspection. Dr. Barnhart provided a response to the Form FDA 483 on 12/21/2017. Inspectional observations included:

1. Investigation not conducted in accordance with the signed statement of the investigator.

An excluded concomitant medication was continued in one of 45 subject records reviewed:

Subject # (b) (6) notified the clinical investigator three months after enrollment that she had started taking clonazepam during the study. The study coordinator contacted the clinical research associate (CRA) and was told that the subject must be discontinued since clonazepam is an exclusionary medication per protocol (anticonvulsant medications are excluded concomitant medications). The subject continued in the study and continued to take clonazepam until she was contacted by the study coordinator approximately 7 months later and was told to discontinue the study medication. Use of this excluded concomitant medication is noted in protocol violation line listings.

Screening labs were not reviewed prior to enrollment for 3 of 45 (6.7%) subject records reviewed:

Subject # (b) (6) was screened on (b) (6) and enrolled on (b) (6) but culture results for chlamydia and gonorrhea were not reviewed prior to enrollment. When the site realized that the labs had not been reviewed, the site accessed the lab report on (b) (6) (presumably after the subject visit was completed). The results showed that *Chlamydia trachomatis* RNA was detected. The site monitor was informed. The subject was treated, with proof of cure, and the subject remained in the study.

Subject # (b) (6) had a screening visit, with labs drawn, on (b) (6). The subject was enrolled on (b) (6) however, the screening lab results were not reviewed prior to enrollment. The lab results were faxed to the site on (b) (6) and signed by the clinical investigator on (b) (6), approximately 6 months after the subject was enrolled.

Subject # (b) (6) had a screening visit, with labs drawn, on (b) (6). The subject was enrolled on (b) (6), however, the screening lab results were not reviewed prior to enrollment. On the CRF for the enrollment visit (b) (6), the site added a late note, dated (b) (6) that "blood results unknown at the time of enrollment".

Dr. Barnhart provided a response, dated 12/21/2017, to the inspectional observations. He agreed with the observations noted in the Form FDA 483 and outlined corrective action plans that were put into effect during and after this clinical study as well as staff additions and infrastructure changes that have occurred in the eight years since the study concluded. The response document did not comment on the continued participation of the subject taking concomitant clonazepam.

Reviewer Comments

The site failed to discontinue participation of a subject taking an excluded concomitant medication, clonazepam. In Section 10 (Concomitant Treatment) of the protocol, anticonvulsant therapies are listed as exclusionary concomitant medications. Email communications between the site and CRA explain that this exclusion is because anticonvulsant drugs are Category D (risk to fetus). This subject continued taking clonazepam and was not discontinued from the study until 7 months after the site was aware of the protocol deviation and had contacted the CRA.

Screening labs were not reviewed prior to enrollment in some subjects, in one case the subject had been participating in the study for > 6 months. The root cause of this oversight was not adequately discussed in Dr. Barnhart's response. It does appear that steps have been taken to prevent recurrence of this finding.

2. General requirements for informed consent were not met.

For the 45 subject records reviewed, 3 subjects (6.7%) were not re-consented using the most recent ICF which included additional risk factors related to the risk of thrombosis. ICF version 2.0 was approved by the IRB on 1/28/2008. Three subjects ((b) (6) and (b) (6)) signed an ICF between (b) (6) to (b) (6) and continued participation in the study until (b) (6), but were not reconsented with ICF version 2.0.

The site sent a letter, dated 1/3/2008, to all participating subjects informing them of blood clots that had developed in three study participants at other study sites. This letter outlined clinical symptoms of concern (e.g. leg pains, shortness of breath, sudden changes in vision, chest pain, weakness, or sudden severe headache) and included directions to contact the study coordinator or seek immediate medical attention if subjects experienced these symptoms. There is no documentation available to indicate that all subjects received this letter. Although the IRB approved a revised ICF on 1/28/2008, this letter (dated 1/3/2008) does not comment on a revised ICF or the need for re-consenting.

In his response, Dr. Barnhart stated that ICFs was amended twice to add detailed information regarding risk, specifically the increased prevalence of thrombosis. With the first amended ICF, the clinical investigator sent a letter to all subjects actively participating in the study and reconsented subjects at their next study visit. With the second amended ICF (version 2.0, 1/28/2008), the plan was to reconsent subjects at the next study visit. During routine monitoring of the study (date not specified), it was noted that reconsenting was not obtained for 3 subjects. The site established a corrective action plan that involved sending a certified letter to subjects informing them of the changes to the ICF and the need to contact the site. However, the limitation of that process was lack of a tracking system for re-consenting. A tracking system is now in place.

Reviewer comments:

Based on the screening, enrollment, and participation of these three subjects, it is assumed that they were initially consented using the original IFC (IRB approved 1/5/2007) and

reconsented using the first amended ICF (version 1.0) which was approved by the IRB in 11/27/2007.

This reviewer compared the two ICF versions (version 1 vs. version 2). There were two significant changes between these two ICFs. Version 2 of the ICF included information on VTEs occurring in this study (rather than only mentioning it as a class risk). Version 2 also included a more prominent section “Contact the study doctor or staff if you experience any of the following symptoms” which listed 12 clinical symptoms. Version 1 of the ICF included most of these symptoms, but in other sections of the ICF (e.g. very rare side effects) and not as prominently. Of note, those adverse events consistent with VTEs (leg pain, shortness of breath, sudden changes in vision, new chest pain/weakness) were included in version 1 of the ICF in bold font at the end of the “What are the possible side effects” section with instructions to contact the study doctor.

ICF version 2 included new information regarding VTEs occurring in this study. Since these three subjects were not reconsented using version 2, there is no documentation that subjects were informed of this new safety information. From the investigator response, it is not clear if the certified letter sent to these subjects is the letter dated 1/3/2008 which was sent to all participants. If so, this 1/3/2008 letter did include an update regarding VTE events occurring in this study, but did not mention changes to the ICF. This letter did not mention reconsenting and asked participants to contact the site only if they experienced clinical symptoms outlined in the letter. Dr. Barnhart did not mention whether there were attempts to contact subjects by telephone. Subjects should have been re-consented in a timely manner with the most recent version of the ICF.

No pregnancies occurred at this site. For one of 45 subject records reviewed, there was one instance of under-reporting of adverse events. In email communications (10/10/2007) regarding Subject (b) (6) pertaining to concomitant use of clonazepam, the clinical coordinator notes that the subject had been experiencing breakthrough bleeding for nine days and excessive bruising on legs. Excessive bruising on legs was also mentioned in the waiver request form which was completed requesting to continue the subject despite concomitant use of clonazepam. The adverse event, cramps, was also noted in a progress note (10/10/2007). None of those adverse events were included in the sponsor’s adverse event line listing.

Reviewer Comments: The regulatory compliance violations identified are unlikely to significantly impact data reliability.

2. Clinical Investigator: Michael Thomas; Cincinnati, OH; Site #21

For Protocol 300A, 175 subjects were screened, 99 subjects were randomized, and 53 subjects completed the study. Forty-six subjects discontinued: withdrew consent/personal reasons (15), adverse events (9), lost to follow-up (8), pregnancy (5), BMI > 29 (5), and non-compliance (4). The EIR did not include details regarding the discontinuations due to adverse events. Per sponsor line listings, these adverse events included pulmonary

embolism (an SAE), vulvovaginal pruritis, vaginal bleeding, acne, lower abdominal pain, back pain, vaginal pain, left leg pain, deep vein thrombosis (an SAE), and genital burning sensation.

An audit of the study records for 35 of the 99 subjects enrolled (35%) was conducted. Records reviewed included but were not limited to informed consent forms, source documents, staff training, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, concomitant medications, waivers, protocol deviations, and primary efficacy endpoint data (pregnancy). The site had submitted several waivers for subjects with menstrual cycle irregularity or elevated screening lipids, these waivers were granted prior to subject enrollment.

There were five pregnancies in subjects enrolled at this site. Two pregnancies resulted in spontaneous termination and three resulted in live births. For all pregnancies, the clinical investigator reviewed the records, determined the likely cause (e.g. user failure vs. method failure), and collected complete pregnancy and neonatal outcome.

There were two VTE events in subjects enrolled at this site. Subjects (b) (6) experienced a pulmonary embolism and Subject (b) (6) experienced deep vein thrombosis. These SAEs were reported to the sponsor within two days of knowledge of the event, as specified by protocol. The FDA field investigator was asked to verify subject height and weights, start and end date for VTE event, and description of the VTE event. The FDA field investigator was able to verify these data from sponsor line listings with source documents at the site.

A Form FDA 483 was not issued at the conclusion of the inspection. There was no evidence of underreporting of adverse events and SAEs were reported according to protocol.

Reviewer Comments:

The height, weight, and BMI data included in the sponsor line listings (Listing 16.2.4.2) include these data only for scheduled study visits. The FDA field investigator verified these data with source documents at the site for the two subjects with VTE events (Subject (b) (6) and (b) (6)). The narrative for Subject (b) (6) provided in the NDA submission states that the BMI upon admission to the hospital on (b) (6) for the VTE event was 30.2 kg/m² which was verified with hospital records included with the sponsor inspection. The narrative for Subject (b) (6) does not include a BMI (or weight) at the time of the VTE event. Medical records for this subject were included with the EIR for the sponsor inspection, but the weight could not be deciphered and BMI could not be calculated.

3. Clinical Investigator: Melissa Gilliam; Chicago, IL; Site #23

For Protocol 300B, 112 subjects were screened and 73 subjects were enrolled. According to the sponsor data listings, 30 subjects completed 13 cycles.

An audit of the study records for 37 of the 73 (51%) enrolled subjects was conducted.

Records reviewed included but were not limited to informed consent forms, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (pregnancy). No pregnancies occurred at this site.

One subject, Subject (b) (6), experienced the VTE event cerebral thrombosis at this site. The SAE was reported to the sponsor within two days of knowledge of the event, as specified by protocol. There was no evidence of under-reporting of adverse events.

A Form FDA 483 was not issued at the conclusion of the inspection. Several inspection findings were discussed with the clinical investigator including enrollment of three subjects who may have met exclusion criteria. One subject had reported a history of substance use/abuse, one subject had a history of depression, and one subject had a history of pituitary tumor. Documentation was lacking at the site for the latter subjects; subjects with a history of depression could be enrolled based on clinical judgment and subjects with a history of tumors could be enrolled if the tumors were not carcinogenic.

The protocol deviation data listing noted that heights for 10 subjects were “measured incorrectly” at screening at this site; four of these subjects had completed early termination before this was discovered. The FDA investigator noted that the heights had not been obtained during the screening visit as was required by protocol. For subjects who continued to participate in the protocol, heights were obtained at a later visit. The subject with the VTE event (Subject (b) (6)) was not one of the subjects listed in the protocol deviations log with incorrectly measured height.

4. Clinical Investigator: Philip Darney, M.D.; San Francisco, CA; Site #23

For Protocol 300B, 191 subjects were screened, 125 subjects were enrolled and randomized, and 100 subjects completed the study. Twenty-five subjects discontinued the study, four were discontinued by the sponsor (BMI > 29 [n = 2], slippage/expulsions, and smoker/ >35 years old). The most common reasons for subject discontinuation were adverse events (depression, spotting, discharge, bloating, migraine, yeast infections) occurring in 10 subjects and “did not like vaginal ring” occurring in 5 subjects.

An audit of the study records for 31 of 125 (24.8%) enrolled subjects was conducted. Records reviewed included but were not limited to informed consent forms, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, subject home diaries, protocol deviations, and primary efficacy data (pregnancy).

A Form FDA 483 was issued at the conclusion of the inspection for obtaining consent using an informed consent form (ICF) that was not approved by the IRB. The University of California San Francisco IRB had approved ICF version 6/29/2007 on 8/9/2007. An amended ICF, version 8/20/2007, was approved by the IRB on 10/16/2007. Nine subjects

signed ICF version 8/20/2007 between 8/30/2007 and 9/28/2007, prior to IRB approval of this amended ICF.

Dr. Darney submitted a response to the inspectional findings on 12/15/2017. He stated that subject's signing of an ICF that was not IRB approved was due to an oversight and that all but one subject was reconsented with the approved IRB ICF. Due to an oversight, one subject was not contacted for reconsenting with the IRB approved ICF. Dr. Darney outlined changes in the IRB practices that help to reduce ICF version issues including a new online system that automatically adds a stamp with the date of IRB approval for every modification and renewal.

There was no evidence of under-reporting of adverse events. Two pregnancies occurred at this site and these data were verified.

Reviewer Comments: All but one of the 9 subjects were reconsented approximately 5 months later using the IRB approved version of the ICF. At the time this study was conducted, a paper system was in place and ICFs were not stamped with IRB approval. Inspectional findings were appropriately addressed in the clinical investigator's response. The regulatory compliance violations identified are unlikely to significantly impact data reliability.

5. Clinical Investigator: Vivian Brache, Lic.; Dominican Republic; Site #3

Vivian Brache, Lic. is a medical technologist by training. The Form FDA 1572 includes five physician subinvestigators for Protocol 300B. For this protocol, 96 subjects were screened, 69 subjects were enrolled, and 46 subjects completed the study. Twenty-three subject discontinued: pregnancy (9), withdrawal of consent (5), lost to follow-up (3), not sexually active (2), adverse events (vaginal complaints [2], lower abdominal pain [1]), and BMI > 29 (1).

An audit of the study records for all enrolled subjects was conducted. Records reviewed included but were not limited to informed consent forms, source documents, case report forms (paper), monitoring documents, ethics committee/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, subject home diaries, protocol deviations, and primary efficacy data (pregnancy).

A Form FDA 483 was not issued at the conclusion of the inspection. There was no evidence of under-reporting of adverse events. During an interim monitoring visit conducted by the sponsor, it was noted that some adverse event CRFs and SAE CRFs were signed by the clinical investigator or the study coordinator but it was not clear whether a medical doctor had reviewed them at that time. A physician subinvestigator retrospectively reviewed adverse event information for these subjects.

Seven SAEs occurred at this site and all but one were reported to the sponsor within the

time frame, 2 calendar days, specified by protocol. One SAE (amebiasis/Subject # (b) (6)) was reported to the sponsor 8 days after the site became aware of the SAE. Site personnel did not specify the reason for the late reporting.

At this site, there was a higher number of pregnancies compared to other sites. The Pearl Index for this site was 0.009 compared to Pearl Index scores of 0.00 to 0.006 for the other 11 clinical sites. At this site, nine of 69 (13%) enrolled subjects became pregnant while using the contraceptive vaginal ring (CVR). The FDA investigator was asked to evaluate conditions of test article storage and any other factors that could have contributed to product failure.

The FDA investigator was able to confirm the date of last menstrual period and the date of the last use of the CVR in the data listings with source documents (CRFs, subject diaries) at the site. Per protocol, test article (CVR) was to be stored “at room temperature in a locked storage area away from sunlight”. The outer foil package containing the test article states “store in a cool, dry place”. At night, all the air conditioners in the entire facility are turned off except the air conditioners in the laboratory and clinical supply storage room. However, the test article was not stored in either of these two areas. The clinical site did not record room temperatures in the room where the test article was stored during the study. There were manual temperature recordings for an adjacent room available for two unrelated studies that overlapped the dates for Protocol 300B. Manual temperature recordings for this adjacent room, but not the room in which test article was stored for Protocol 300B, recorded a maximum temperature of 28°C on two days between 3/23/2007 and 4/12/2007. A note added to the record indicated that there was a problem with the air conditioner at the time. Humidity was also recorded with readings ranging from 34 to 72% humidity. An interim monitoring letter from the sponsor stated that test article storage was reviewed and found adequate.

During the sponsor inspection (see Population Council inspection summary section of CIS), the FDA investigator asked about the higher rate of pregnancies occurring at this site. The FDA investigator was told by the Medical Director of Population Council that the subjects at this site did not reinsert the ring within the allowable “ring out” window during the 21-day treatment period. The Medical Director did not provide any documentation to support his comments. Additionally, this issue was not addressed during any of the monitoring visits conducted at this site.

Reviewer Comments:

The protocol states that the test article should be stored at room temperature and the outer foil packet containing the test article states that it should be stored in a cool, dry place. The instructions for use appended to the sample ICF submitted by the sponsor states that the CVR should be stored in the package it came in at room temperature defined as 15 to 30 °C. The protocol does not require that the conditions of test article storage be monitored. The temperature of the room in which the test article was stored was not monitored. The temperature of the adjacent room was monitored and temperatures up to 28 °C were recorded. However, these are not the actual temperatures in the room where test article was stored. Additionally, the adjacent room had humidity

recordings that reached 72%. Although these recordings are for an adjacent room, if humidity was similar in the room where test article was stored, 72% humidity would not be considered a dry condition. Since we do not have any information regarding the actual temperature or humidity of the room where test article was stored, and we have knowledge that air conditioning is turned off at night, we have no documentation regarding whether storage conditions were acceptable for this product. Therefore, we cannot rule out contribution of storage conditions to product failure at this site.

Although the Medical Director of Population Council posited user-failure as a reason for the higher number of pregnancies at this site, there is no documentation to support this rationale.

6. **Sponsor:** Population Council; 1230 New York Avenue; New York, NY; 10065

This inspection covered sponsor practices related to Protocols 300A and 300B and to investigate a complaint. The complainant, a former employee of the sponsor, alleged that during analysis of the safety data after database lock (specifically, the combined studies 300A and 300B for the Integrated Summary of Safety, VTE), the definition of baseline BMI was changed to allow use of screening and immediate pretreatment visit (not just the immediate pretreatment) BMI $> 29 \text{ kg/m}^2$, to link incidence and conclusions related to probability of VTE with BMI $\geq 29 \text{ kg/m}^2$ for this investigational drug. The allegation also stated that this revised definition of baseline BMI use in analysis of incidence of VTE instead of actual BMI at the time of event was decided upon after the sponsor's medical director noted that three of the four subjects with VTEs had BMI $\leq 29 \text{ kg/m}^2$ at the time of event. This revised definition of baseline BMI was also used when it was noted that three of the four subjects with VTEs had baseline (defined as immediate pretreatment) BMI $\leq 29 \text{ kg/m}^2$.

Sponsor and study-specific documents reviewed include, but were not limited to, organizational charts, material transfer agreements, CRO contract (Protocol 300A), Form FDA 1572s, financial disclosure forms, SOPs, selection of monitors (Protocol 300B), monitoring plan, quality assurance, adverse event reporting, reporting of pregnancies, medical records for subjects with VTE events, DSMB meeting minutes, and (b) (4) /DSMB correspondence.

Protocol 300A was contracted to the (b) (4) and was conducted in collaboration with the (b) (4) per a (b) (4) transferred clinical monitoring responsibility for Protocol 300A to (b) (4), a CRO. Population Council was responsible for the clinical monitoring for Protocol 300B.

Financial disclosure forms were signed by clinical investigators participating in Protocol 300A *prior* to study initiation and for Protocol 300B *after* study initiation. The sponsor explained that financial disclosure forms were not signed prior to initiation of Protocol 300B as staff incorrectly interpreted the regulations and concluded that financial

disclosure requirements would not apply to Population Council because of its status as a non-profit organization. In 2011, an outside auditor noted the lack of financial disclosure information and contacted FDA for advice regarding this issue. The sponsor stated that, in conversations with FDA, financial disclosure forms could be collected post-hoc and proposed a program of due diligence including written, telephone, and personal contacts. Financial disclosure information for Protocol 300B was submitted with the NDA.

Protocol 300A was completed on 10/7/2009 with a database lock on 11/17/2011 and Protocol 300B was completed on 7/2/2009 with a database lock on 11/1/2011 (dates of database locks were provided in CSRs). The FDA investigator reviewed documentation of database locks and noted that the database lock for Protocol 300A was 11/15/2011 and the initial database lock for Protocol 300B was 9/12/2011. For Protocol 300B, the database was unlocked on or about 10/26/2011 and relocked on 11/1/2011. Comments on sponsor documents indicate that changes that appear to be minor (e.g. deletion of duplication of AE hyperlipidemia). The Senior Statistical and Data Quality Manager for Population Council stated that no study data was changed. The CSR does not mention the unlocking and relocking of the study database.

A DSMB was established by (b) (4) and conducted regular reviews of subject pregnancy and safety data. Four VTE events occurred in these studies, three events in Protocol 300A and one event in Protocol 300B (in chronological order):

- Subject # (b) (6) 23 YOBF; PE. Per subject narrative, screening BMI = 29.1, BMI at hospitalization = 30.2. Date of event ~ (b) (6).
- Subject # (b) (6) 26 YOBF; DVT. Per subject narrative, screening BMI = 30.8. Date of event (b) (6).
- Subject # (b) (6) 28 YOBF; cerebral venous thrombosis. Per subject narrative, BMI (not defined) = 25.2. Date of event (b) (6) (headache), to ER on (b) (6).
- Subject # (b) (6) 39 YOWF; DVT. Per subject narrative, baseline BMI = 24.7. Date of event ~3/7/2008.

The FDA investigator collected DSMB meeting minutes or associated correspondence for five meetings occurring on 8/22/2007, 12/17/2007, 1/27/2008, 4/18/2008, and 8/29/2008. These meeting minutes were reviewed. Of note:

During the DSMB Meeting on 8/22/2007, there was discussion about two VTE events occurring in Subject # (b) (6) and # (b) (6), both with BMI = 29.3 (meeting minutes did not specify which BMI this was [screening, baseline, time of event]). Discussion regarding expected rate of thrombosis is 1 per 1000 women years in young women compared to these two cases in 96 women years of exposure; not likely attributable by chance. The study included heavier women and smokers < 35 years in order to represent the present US population (the sponsor stated that this was based on request

from review division). Possible explanations of the apparent excess of thrombotic events are 1) an increase in risk of thrombosis with increased BMI and the apparent synergism between high BMI and contraceptive steroids causing thrombosis 2) higher than expected serum ethinyl estradiol levels with the study ring during initial cycles.

The DSMB inquired about what had been done to explore ways to mitigate the (b) (4) ethinyl estradiol effect occurring during the initial cycles of use.

The DSMB recommended:

1. Against further enrollment of new subjects with BMI > 29
2. Considered acceptable risk to continue existing subjects of BMI > 29 and age < 35 as these subjects will have already passed the time of greatest risk from possibly elevated estrogen levels. The study consents for these subjects should be reviewed to be sure there is adequate disclosure of possibly increased thrombosis risk.

In addition to not enrolling new subjects with BMI > 29, the sponsor decided to withdraw subjects currently enrolled with BMI > 29 (post meeting note)

3. Requested that the DSMB receive reports of SAEs at the same time as they are reported to the IRB and regulatory bodies when applicable.

The minutes from the second DSMB meeting on 12/17/2007 were not available, but a memo dated 1/10/2008, referenced this meeting. At this time, the number of thrombotic events was of concern to the DSMB (a third VTE event, cerebral venous thrombosis, had occurred ~12/4/2007).

The DSMB asked the sponsor to provide additional information about event rates for comparable products and an analysis of the probability of additional events during the remainder of the trial. The DSMB recommended that, in the interim, should another DVT or embolism occur among study participants, enrollment should be temporarily suspended but only after (b) (4) notified site investigators of the suspension. The study would not be stopped during this time and active subjects may continue their study participation.

1/17/2008 Population Council response to DSMB:

Population Council provided DSMB with reassessment of expected event rates. Using probabilities in the analyses they provided, the sponsor stated that stopping rules would suggest 5 or 6 VTE events.

A follow-up DSMB meeting to that of 12/17/2007 was held on 1/23/2008. The DSMB commented that the VTE rates for 300A and 300B trials thus far are 4.03 events per 1000 women years for all subjects and 1.49 per 1000 women years for subjects with BMI ≤ 29. Information available for Yasmin, OrthoEvra, and NuvaRing were reviewed. The highest rates of VTE were 1.5 per 1000 women years for Yasmin. Protocols 300A and 300B no longer include subjects with BMI > 29, so the VTE rate of 1.49/1000 women years is more relevant to the current study population. Based on

probability calculations, the DSMB stated that if 3 more serious VTE events occurred (which would exceed 1.5/1000 women years), the study will be stopped.

The third regular, planned DSMB meeting was held on 4/18/2008 to review efficacy/safety after a total of 800 women years of experience in both studies. The recent occurrence of a fourth VTE event, DVT in Subject # (b) (6), occurring ~ (b) (6) was discussed. Subject # (b) (6) was found to be heterozygous for Factor V Leiden which conveys increased risk of thrombosis and is found in ~5% of Caucasians. The DSMB reaffirmed the decision to impose a stopping order if 6 thrombosis cases and requested any additional follow-up information for Subject # (b) (6) (cerebral venous thrombosis).

The fourth regular, planned DSMB meeting was held on 8/29/2008. During this meeting, a discussion of a subject with phlebitis but no thrombosis (VTE) was discussed.

Complaint Follow-Up

During the conduct of Protocols 300A and 300B, a DSMB reviewed safety data and recommended that eligibility criteria be revised to exclude subjects with a BMI > 29 kg/m² due to an increased risk of venous thromboembolic (VTE) events. According to the sponsor, the DSMB made this recommendation on 8/22/2007. Exclusion criteria were modified via Amendment 1.1 (10/2007) to Protocol 300A and Amendment 8 (9/2007) to Protocol 300B.

A detailed complaint was filed (b) (4) by a former employee of the sponsor. The complaint alleges that, during analysis of the safety data after completion of the studies and after database lock, the definition of baseline for BMI was changed several times. The complainant was concerned that changes in the definition of baseline BMI and use of this baseline BMI rather than BMI at time of event may underestimate the risk of VTE events in subjects with BMI < 29 kg/m².

Reviewer Comments:

During the conduct of the studies, it appears that the DSMB regularly reviewed and addressed the VTE events and that the sponsor was responsive to most requests for information.

The FDA investigator did not find evidence of changes in baseline BMI definitions during the inspection. The definition of baseline BMI (denoted BMIBASE in the database) used by the sponsor in the Combined 300A and 300B analysis is defined as the maximum BMI before first CVR insert. This definition of "baseline" is not used elsewhere in the submission for any other variables, including in the other ISS parameters.

Table 1 includes BMI data available prior to VTE events and, where available, at the time of VTE event in the four subjects with these events. For these subjects, BMIBASE is very close to BMI on Day 1, the largest difference is for Subject # (b) (6) in which BMIBASE is >29 kg/m² while the BMI on Day 1 is < 29 kg/m². The BMI at the time of the VTE events

is only available for two of the four subjects via medical records included with the EIR.

Table 1. BMI for Subjects with VTE Events

Subject	BMIBASE*	BMI Screening	BMI Day 1	BMI Prior to Event	BMI Prior to Event	VTE Event Date	BMI at Time of Event
(b) (6)	29.1	29.1 4/11	28.5 5/10	-	-	(b) (6)	30.2
	30.8	30.3 1/5	30.8 2/9	30.1 4/12	-		29.3
	24.7	24.1 12/12	24.7 12/28	24.8 2/22	-		NA**
	25.2	25.2 5/3	25 5/25	23.5 7/24	24.4 10/22		NA**

*Per sponsor, maximum BMI before first CVR insert

**Subject # (b) (6): Weight in progress notes could not be deciphered; Subject # (b) (6): medical records not included with EIR

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Document Room/NDA #209627
DBRUP/Division Director/Hylton Joffe
DBRUP/Medical Team Leader/Catherine Sewell
DBRUP/Medical Officer/Abby Anderson
DBRUP/Project Manager/Z. Charlene Williamson
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Janice Pohlman
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
OSI/ GCPAB Program Analyst/Yolanda Patague
OSI/Database Project Manager/Dana Walters

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

/s/

CARA L ALFARO
05/30/2018

JANICE K POHLMAN
05/30/2018

KASSA AYALEW
05/31/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	May 14, 2018
Requesting Office or Division:	Division of Bone, Reproductive, and Urologic Products
Application Type and Number:	NDA 209627
Product Name and Strength:	Segesterone Acetate and Ethinyl Estradiol Vaginal System, 103 mg/17.4 mg
Applicant/Sponsor Name:	Population Council
FDA Received Date:	April 5, 2018
OSE RCM #:	2017-1712-1
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Lolita G. White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested that we review the revised 'patient package insert' and 'instructions for use' for segesterone acetate and ethinyl estradiol vaginal system (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised 'patient package insert' and 'instructions for use' for segesterone acetate and ethinyl estradiol vaginal system is acceptable from a medication error perspective. We have no further recommendations at this time.

.

^a Baugh D. Label, Labeling, and Label Comprehension Study Results for SEGESTERONE ACETATE AND ETHINYL ESTRADIOL VAGINAL SYSTEM (NDA 209627). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2018 Mar 07. RCM No.: 2017-1712.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON APRIL 5, 2018^b

HOW SHOULD I USE ANNOVERA™?

(b) (4)



^b The proposed proprietary name, 'Annovera' is currently under review and the acceptability of the name has not been determined.

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

/s/

DENISE V BAUGH
05/14/2018

LOLITA G WHITE
05/15/2018

REVIEW OF LABEL, LABELING, AND LABEL COMPREHENSION STUDY RESULTS

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

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

Date of This Review:	March 7, 2018
Requesting Office or Division:	Division of Bone, Reproductive, and Urologic Products
Application Type and Number:	NDA 209627
Product Name and Strength:	Segesterone and Ethinyl Estradiol Vaginal System, 103 mg/17.4 mg
Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Population Council
Submission Date:	August 17, 2017
OSE RCM #:	2017-1712
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Lolita G. White, PharmD
Associate Director for Human Factors:	QuynhNhu T. Nguyen, M.S.

1 REASON FOR REVIEW

The Division of Bone, Reproductive, and Urologic Products (DBRUP) consulted the Division of Medication Error Prevention and Analysis (DMEPA) to evaluate the label comprehension study results for NDA 209627 to determine if they are acceptable from a medication errors perspective.

PRODUCT BACKGROUND

This proposed Segesterone and Ethinyl Estradiol (103 mg/17.4 mg) Vaginal System combination product is indicated for pregnancy prevention and consists of a long acting, reusable hormonal birth control in the shape of a ring. The contraceptive vaginal ring (CVR) is self-inserted into the vagina and used for 3 out of 4 weeks every month for 13 consecutive months. This product will be prescribed by a healthcare provider (HCP) for women of child bearing age based upon the body mass index (BMI).

REGULATORY HISTORY

On October 21, 2016, we reviewed the use-related risk analysis and label comprehension protocol submitted July 22, 2016 for IND (b) (6) a. The Sponsor submitted their label comprehension study results to NDA 209627 on August 17, 2017.

On November 3, 2017, the Applicant responded to our October 24, 2017 Information request to clarify the correct response to knowledge task question # 6 and to provide a summary of the results to this question. Additionally, we requested the Applicant submit the 'intend to market' container label and carton labeling for our review and comment. At that time, the Applicant stated that they were actively seeking a licensee who would develop the 'intend to market' labeling and submit a proprietary name at a later date. However, at a teleconference held with the Agency on January 18, 2018, the Applicant decided to submit a proprietary name along with updated container labels, carton labeling, and prescribing information (PI). These submissions were pending at the time of this review and will be reviewed separately.

See Appendix F for more details of our communication with the Applicant.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A

^a Baugh, D. Review of Use-Related Risk Analysis and Label Comprehension Study Protocol for Segesterone acetate/ethinyl estradiol Contraceptive Ring. IND 049980. Silver Spring, MD: Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (United States); 2016 October 21. OSE RCM # 2016-1932.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Previous DMEPA Reviews	B
Label Comprehension Study	C
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Information Request	F
Labels and Labeling	G

N/A=not applicable for this review

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Population Council completed a label comprehension study to evaluate the patient labeling (e.g. Instructions for Use [IFU] and the Patient Package Insert [PPI]) for their proposed product. Of the knowledge task questions evaluated in the study, seven were found in the IFU and three were found to the PPI.

3.1 Labeling Comprehension Study – Summary of Results

Fifteen patient participants representative of the intended users of the product participated in this labeling comprehension study. The participants reviewed the IFU independently, then answered a series of knowledge task questions. The questions were aimed at assessing participants' understanding of critical or essential aspects of use, any aspects of the IFU that may have been difficult to understand or interpret, and the root causes of any difficulties participants may have had with understanding the use of the CVR.

The Sponsor identified 12 critical tasks in the use of this product and we agree that 10 of them are critical. The two tasks that we categorize as non-critical are: “User takes medication that reduces effectiveness of ring without using back up contraception” and “User gains weight and is above BMI threshold for ring and continues use of ring”. Our rationale is as follows:

- We note that the labeling for this drug class (hormonal contraceptive drug products) routinely mentions the hazards of ingesting other medications which could compromise the efficacy of hormonal products intended to prevent pregnancy. Therefore, this user population is familiar with the significance of drug-drug interactions and this hazard is not unique to this product. As such, we disagree with the Applicant's determination that this task is critical and conclude that this task is essential to the use of this product.
- At the time of the original submission, the Applicant proposed (b) (4)

Since gaining weight beyond a certain threshold leads to a compromise in efficacy and

safety, this task was identified as a critical (user) task. In discussion with the clinical review team, we find the requirement for a patient to determine if they have gained weight outside of the acceptable BMI range to be a task for the prescriber. We do not expect the patient to calculate BMI and subsequently make a clinical decision to alter their contraceptive therapy. Additionally, we note that a BMI calculation is part of the normal workflow for a health care provider. As such, we do not require it to be included as part of this label comprehension study. However, we acknowledge that the prescriber may not see the patient for 13 months while on this therapy and a substantial increase in weight during this time may lead to decreased clinical efficacy of this product and result in unwanted pregnancy or lead to safety issues. Thus the use of this product may require the patient to self-report significant weight gain. We provide a recommendation to the division below to address this concern.

Thus, Tables 2 and 3 below provides a summary of critical tasks and an analysis of 5 failures that occurred with two critical tasks.

Table 2: Summary of Critical Tasks Use Errors (n=8)	
Critical Tasks	Use Errors
Task 1.1 - Determine appropriate date for initial insertion	0
Task 2.1 - Ring is removed early (n = 1); late (n = 3)	4
Task 3.1 - Bleach is used to clean the ring	0
Task 5.1 – Ring is re-inserted too late (> 7 days from removal)	1
Task 6.1 – Ring is used beyond 13 cycles	0
Task 7.1 – Use of vaginal products such as oil-based suppositories, creams or gels while the ring is in place	0
Task 7.1 – Use of vaginal products such as douches while the ring is in place	0
Task 7.1 – Use of lubricants such as silicone while the ring is in place	0
Task 7.1 – User takes medication which reduces effectiveness of ring	Not validated; See section 3.1 for details.
Task 7.1 – Ring is removed mid-cycle and re-inserted after more than 2 hours without using back-up contraception	0
Task 7.1 - Ring is removed mid-cycle and not re-inserted	0
Task 7.1 - User gains weight and is above the threshold for the body mass index, but continues use of ring	Not validated; see Section 3.1 for details
Task 7.1 - User unintentionally expels ring and does not replace ring or use back up method	0

Our assessment of the label comprehension study results and the patient labeling are as follows:

Table 3: Analyses of Critical Tasks Use Errors and Operational Difficulties

Critical Tasks Description	Description of Failure	Participants' Subjective Feedback	Applicant's Root Cause Analysis	DMEPA's Analysis and Recommendation																				
Task 1 Ring is removed early (n=1)	Participant 04 stated she would remove the ring on day 21;	The participant states she read you should leave your ring in the entire 21 days or three weeks. The participant did not offer any mitigation.	Per the Sponsor, the participant assumed that leaving the ring in for 3 weeks meant it should be removed on day 21. She did not refer to the information in the PPI which states to remove the ring on day 22.	<p>We reviewed the table (titled 'schedule') for insertion and removal of the ring in the PPI and reviewed the narrative preceding the table. (see screen shot below).</p> <table><tr><th colspan="4">SCHEDULE</th></tr><tr><td>Cycle 1</td><td>Put RING in</td><td>Day 1</td><td>WEEKS 1, 2, and 3 Days 1-21</td></tr><tr><td></td><td>Take RING out</td><td>Day 22</td><td>WEEK 4 Days 22-28</td></tr><tr><td>Cycle 2</td><td>Put RING in</td><td>Day 1</td><td>WEEKS 1, 2, and 3 Days 1-21</td></tr><tr><td></td><td>Take RING out</td><td>Day 22</td><td>WEEK 4 Days 22-28</td></tr></table> <p>We also referred to the clinical reviewer for their expertise regarding the consequences of early removal of the ring. Per the clinical reviewer, removing the ring a day early would not result in a clinically significant consequence if it were replaced within 7 days of its removal. Although there is no clinically significant consequence to this use error, we determined that the language which precedes the table as well as the table itself could be a source</p>	SCHEDULE				Cycle 1	Put RING in	Day 1	WEEKS 1, 2, and 3 Days 1-21		Take RING out	Day 22	WEEK 4 Days 22-28	Cycle 2	Put RING in	Day 1	WEEKS 1, 2, and 3 Days 1-21		Take RING out	Day 22	WEEK 4 Days 22-28
SCHEDULE																								
Cycle 1	Put RING in	Day 1	WEEKS 1, 2, and 3 Days 1-21																					
	Take RING out	Day 22	WEEK 4 Days 22-28																					
Cycle 2	Put RING in	Day 1	WEEKS 1, 2, and 3 Days 1-21																					
	Take RING out	Day 22	WEEK 4 Days 22-28																					

Table 3: Analyses of Critical Tasks Use Errors and Operational Difficulties				
Critical Tasks Description	Description of Failure	Participants' Subjective Feedback	Applicant's Root Cause Analysis	DMEPA's Analysis and Recommendation
				of confusion and can be improved to more accurately determine the correct 'Ring Change Day' for the product. See Sections 4.2 (A) and 4.2 (B) for specific recommendations.

Table 3: Analyses of Critical Tasks Use Errors and Operational Difficulties

Critical Tasks Description	Description of Failure	Participants' Subjective Feedback	Applicant's Root Cause Analysis	DMEPA's Analysis and Recommendation																				
Task 1 Ring is removed late (n = 3)	Participant # 08, #12, and #13 - Removed ring on day 23.	<p>Participant # 08 stated she understood to keep the ring in days one through 21 and then take it out on day 23.</p> <p>Participant # 12 – intended to remove the ring on day 22, but when asked to indicate the removal day, chose day 23.</p> <p>Participant # 13 – The participant counted 3 whole weeks and then indicated she would remove the ring the next day. She was also focused on the schedule provided in the PPI and not on the “ring change day”. The participant commented it is easier with oral birth control</p>	<p>Participant # 08 understood that the ring should be removed on day 22, but made a mistake in counting and chose to remove it on day 23. She assumed that counting 3 weeks on the calendar from Saturday to Saturday would equal 21 days. When she got to the final Saturday, she added another day, choosing the Sunday to remove the ring. By doing this, she had intended to bring the day count to day 22, but actually brought it to day 23.</p> <p>Participant # 12 – assumed that counting 3 weeks on the calendar from Saturday to</p>	<p>We reviewed the table (titled ‘schedule’) for insertion and removal of the ring in the PPI and we referred to the clinical reviewer for their expertise regarding the consequences of late removal of the ring. Per the clinical reviewer, removing the ring a day late would not result in a clinically significant consequence.</p> <p>Our review of the schedule table notes the table does not refer to specific days of the week for removal. It instead states to put the ring in on day ‘1’ and take the ring out on day ‘22’ (see screen shot below).</p> <table><tr><th colspan="4">SCHEDULE</th></tr><tr><td>Cycle 1</td><td>Put RING in</td><td>Day 1</td><td>WEEKS 1, 2, and 3 Days 1-21</td></tr><tr><td></td><td>Take RING out</td><td>Day 22</td><td>WEEK 4 Days 22-28</td></tr><tr><td>Cycle 2</td><td>Put RING in</td><td>Day 1</td><td>WEEKS 1, 2, and 3 Days 1-21</td></tr><tr><td></td><td>Take RING out</td><td>Day 22</td><td>WEEK 4 Days 22-28</td></tr></table> <p>In addition to the subjective feedback from the three participants that experienced use errors, subjective feedback from three participants (P01,</p>	SCHEDULE				Cycle 1	Put RING in	Day 1	WEEKS 1, 2, and 3 Days 1-21		Take RING out	Day 22	WEEK 4 Days 22-28	Cycle 2	Put RING in	Day 1	WEEKS 1, 2, and 3 Days 1-21		Take RING out	Day 22	WEEK 4 Days 22-28
SCHEDULE																								
Cycle 1	Put RING in	Day 1	WEEKS 1, 2, and 3 Days 1-21																					
	Take RING out	Day 22	WEEK 4 Days 22-28																					
Cycle 2	Put RING in	Day 1	WEEKS 1, 2, and 3 Days 1-21																					
	Take RING out	Day 22	WEEK 4 Days 22-28																					

Table 3: Analyses of Critical Tasks Use Errors and Operational Difficulties				
Critical Tasks Description	Description of Failure	Participants' Subjective Feedback	Applicant's Root Cause Analysis	DMEPA's Analysis and Recommendation
		pills because the tablets have colors to indicate what day to take your tablets.	<p>Saturday would equal 21 days. She also pointed out that the PPI states to "leave the ring in for the whole three weeks". She interpreted this to mean that the ring should remain in place the full 24 hours of the final 'ring change day'. She stated the removal would take place the following day.</p> <p>Participant # 13 – counted 3 whole weeks, then indicated she would remove the ring the next day. She was focused on the schedule provided in the PPI and not on the 'ring change day'. This participant was familiar with birth control pills and found counting days on a</p>	<p>P03, P13) commented on some confusion relating to the schedule for ring insertion and removal. Two participants (P01, P06) suggested showing an example on a calendar rather than the schedule shown in the PPI. Although these participants did not fail this task, they commented on some confusion relating to the schedule for ring removal and insertion. They suggested that showing an example on a calendar would be more clear.</p> <p>In our post-marketing and front line experience, counting the days on a calendar or providing an example in the IFU can both be misinterpreted and lead to an error. Additionally, removing the ring late would not result in a clinically significant consequence. Despite this, we determined that the language which precedes the table as well as the table itself can be a source of confusion and should be improved to more accurately determine the correct 'Ring Change Day' for this product. See Sections 4.2(A) and 4.2(B) for specific recommendations.</p>

Table 3: Analyses of Critical Tasks Use Errors and Operational Difficulties

Critical Tasks Description	Description of Failure	Participants' Subjective Feedback	Applicant's Root Cause Analysis	DMEPA's Analysis and Recommendation																				
			calendar to be confusing.																					
Task 5.1. Ring is re-inserted too late. (n=1)	Participant #15 stated that the ring should be reinserted after a week, but then chose a day that was 8 days later (i.e., Sunday), when the ring change day was Saturday.	Participant #15 went back and forth on her day selection while flipping pages in the calendar, and was prompted by the moderator to reference the PPI. She focused on the statement "let it stay out for 1 week" rather than the schedule or the ring change day. She concluded that if the ring were removed on a Saturday, in order to stay out for one week, it should be reinserted on the following Sunday.	According to the Sponsor, like other participants who had difficulty selecting the correct ring removal date, this participant was confused when interpreting the meaning of "one week". She did not focus on a "ring change day" or using the example in the PPI.	<p>We reviewed the table (titled 'schedule') for insertion and removal of the ring in the PPI and we referred to the clinical reviewer for their expertise regarding the consequences of late re-insertion of the ring. The schedule does not refer to specific days of the week for removal. It merely states to put the ring in on day '1' and take the ring out on day '22' (see screen shot below).</p> <table><tr><th colspan="4">SCHEDULE</th></tr><tr><td>Cycle 1</td><td>Put RING in</td><td>Day 1</td><td>WEEKS 1, 2, and 3 Days 1-21</td></tr><tr><td></td><td>Take RING out</td><td>Day 22</td><td>WEEK 4 Days 22-28</td></tr><tr><td>Cycle 2</td><td>Put RING in</td><td>Day 1</td><td>WEEKS 1, 2, and 3 Days 1-21</td></tr><tr><td></td><td>Take RING out</td><td>Day 22</td><td>WEEK 4 Days 22-28</td></tr></table> <p>Per the clinical reviewer, reinserting the ring too late may result in pregnancy which is a clinically significant outcome.</p>	SCHEDULE				Cycle 1	Put RING in	Day 1	WEEKS 1, 2, and 3 Days 1-21		Take RING out	Day 22	WEEK 4 Days 22-28	Cycle 2	Put RING in	Day 1	WEEKS 1, 2, and 3 Days 1-21		Take RING out	Day 22	WEEK 4 Days 22-28
SCHEDULE																								
Cycle 1	Put RING in	Day 1	WEEKS 1, 2, and 3 Days 1-21																					
	Take RING out	Day 22	WEEK 4 Days 22-28																					
Cycle 2	Put RING in	Day 1	WEEKS 1, 2, and 3 Days 1-21																					
	Take RING out	Day 22	WEEK 4 Days 22-28																					

Table 3: Analyses of Critical Tasks Use Errors and Operational Difficulties				
Critical Tasks Description	Description of Failure	Participants' Subjective Feedback	Applicant's Root Cause Analysis	DMEPA's Analysis and Recommendation
				<p>We note that this participant experienced confusion relating to the schedule for ring re-insertion.</p> <p>Our review of the "Schedule" finds specific statements can be improved to reinforce the intent of the table. Specifically, the statement which begins with "For example, if Day 1 of your "RING IN" day is Monday at 9:00 in the morning, your first . . . " can be improved. Based on the severity of the outcome of re-inserting the ring late, we find cause for further mitigation See Section 4.2 (A) for specific recommendations.</p>

APPEARS THIS WAY ON ORIGINAL

3.2 Instructions for Use (IFU)

We reviewed the information in the IFU for risk of medication errors and areas of needed improvement. We identified the following concerns:

- The IFU does not include important information about the use of the product (e.g. insertion, removal, re-insertion instructions)
- The IFU does not include information about what chemicals to avoid in cleaning and the impact of using other medications is important.

We provide recommendations to address our concerns below in Section 4.2 (C).

4 CONCLUSION & RECOMMENDATIONS

We conclude that the label comprehension study results identify users who are confused by the removal and re-insertion time frames for this product. This poses a risk for wrong technique medication errors that may increase the risks of an unwanted pregnancy. Our review of the IFU and PPI find areas which can be improved to ensure the safe and effective use of the proposed product. We provide recommendations in section 4.1 for the division and for the Sponsor below in section 4.2 to address our concerns. We recommend these recommendations be implemented prior to the approval of this NDA and we conclude that the revisions do not need re-validation.

4.1 RECOMMENDATIONS FOR THE DIVISION

- A. The Sponsor states in their use related risk analysis that should a user gain weight which is above the threshold for the recommended body mass index, but continues use of the ring, this may result in decreased efficacy and result in an unwanted pregnancy. Consider moving this language to section 2 of the PI as this will require calculation and clinical decision support on the appropriateness of therapy. Additionally, since the user may not see their health care provider for 13 months, consider adding language to the IFU instructing the user to report significant weight gains to their provider.

4.2 RECOMMENDATIONS FOR POPULATION COUNCIL

We recommend the following be implemented prior to approval of this NDA and the revisions do not require re-validation:

- A. In your PPI, the table (titled “Schedule”) lacks clarity and is a source of confusion for participants in your labeling comprehension study. This lack of clarity may lead to unwanted pregnancy. We recommend you include the terminology “Ring Change Day” in the table to better guide the user to accurately count the days. See the following as an example:

SCHEDULE FOR RING CHANGE DAY			
Cycle 1	Put Ring In (RING CHANGE DAY)	Day 1	Weeks 1, 2, and 3 Days 1 through 21
	Take Ring out (RING CHANGE DAY)	Day 22	Week 4 Days 22 through 28
Cycle 2	Put Ring In (RING CHANGE DAY)	Day 1	Weeks 1, 2, and 3 Days 1 through 21
	Take Ring out (RING CHANGE DAY)	Day 22	Week 4 Days 22 through 28

- B. After internal discussion, we find that the language which precedes the table (under the heading “(b) (4)”) lacks clarity and consistency with information presented within the table. Our specific recommendations for revision of this language is as follows:

You first start using the RING between days 2 and 5 of your menstrual period (while bleeding). The day of the week you first insert BRANDNAME (referred to as “Day # 1”) is your RING CHANGE DAY.

For each cycle, you put the RING into your vagina and let it stay there 3 weeks (21 days). REMEMBER to keep the ring in for the whole 3 weeks (21 days).

You take the Ring out on your RING CHANGE DAY and let it stay out for 1 week (7 days). Note that your ring should be stored in the case provided, away from extreme temperatures and pets”.

Then you start over again for another 4 weeks. This time you may not be bleeding when you put the RING in.

Always put the RING in or take it out on your RING CHANGE DAY at about the same time of day. For example, if you put your RING in on Monday at 9:00 in the morning, always take it out or put it back in on Monday at about 9:00 in the morning.

You do not have to take the Ring out when you have sex. However, if you decide to remove it, remember to re-insert it within 2 hours or you may not be protected from pregnancy.

- C. As currently presented, the schedule provided in the PPI includes critical use tasks for insertion, removal and re-insertion of the proposed product that are not included in

the IFU. To decrease risk of confusion and to maintain consistency ensure that the insertion, removal, re-insertion and final disposal tasks in the Patient Package Insert (PPI) are also included in the Instructions for Use (IFU) to maximize the opportunity for the safe and effective use of your product.

The specific tasks that should be added to the IFU are:

- a. When to insert the ring for the first time (relative to the menstrual cycle);
- b. When to remove the ring;
- c. When to re-insert the ring;
- d. The number of 28 cycles for which the ring can be used;
- e. State that the ring should be disposed of after 13 cycles;
- f. Proper disposal of the ring after 13 cycles; and
- g. Products which should be avoided for cleaning the ring.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for segesterone acetate and ethinyl estradiol vaginal system that Population Council submitted on August 17, 2017.

Table 2. Relevant Product Information for Segesterone Acetate and Ethinyl Estradiol Contraceptive Vaginal Ring	
Initial Approval Date	N/A
Active Ingredient	Segesterone acetate and ethinyl estradiol
Indication	Pregnancy prevention
Route of Administration	vaginal
Dosage Form	ring
Strength	103 mg/17.4 mg
Dose and Frequency	Insert one ring vaginally and allow to remain in place for 3 weeks followed by a 1 week ring-free interval. Repeat this regimen for 13 cycles
How Supplied	Carton contains one ring
Storage	59°F to 86°F (15°C to 30°C)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 6, 2017, we searched DMEPA's previous reviews using the terms, 'segesterone'. Our search identified one previous review^b, and we confirmed that our previous recommendations were implemented or considered.

^b Baugh, D. Review of Use-related Risk Analysis and Label Comprehension Protocol for Segesterone acetate/ethinyl estradiol Contraceptive Ring. IND 049980. Silver Spring, MD: Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (United States); 2016 October 21. OSE RCM # 2016-1932.

APPENDIX C. LABEL COMPREHENSION STUDY

\\cdsesub1\evsprod\nda209627\0001\m1\us\114-label\1141-draft-label\label-comprehension-pop-2016-cvr-vt-503.pdf

APPENDIX F. INFORMATION REQUEST (excerpted from response submitted November 3, 2017)

knowledge assessment portion of the study. Please confirm both questions were asked and, if so, please forward the correct answer to the question (b) (4) and a summary of the results for our review.

Response: Both questions were asked during the study. All participants correctly indicated that they would no longer use the ring after 13 cycles.

3. RESPONSES TO INFORMATION REQUEST DATED OCTOBER 24, 2017 (FROM REGULATORY PROJECT MANAGER)

3.1 REQUEST 1:

Your knowledge assessment questionnaire is incomplete. Specifically, we note on page 21. (Table 5. Knowledge Task Question # 6) that the 2nd question (b) (4) does not have a correct response stated.

Response: The correct response to the second question is: (b) (4)

3.2 REQUEST 2:

We note in on page 25 (Table 6. Participant performance on knowledge task questions), the results report that all responses were correct to knowledge task question #6. It is unclear if one or both questions were asked during the

knowledge assessment portion of the study. Please confirm both questions were asked and, if so, please forward the correct answer to the question (b) (4) and a summary of the results for our review.

Response: Both questions were asked during the study. All participants correctly indicated that they would no longer use the ring after 13 cycles.

3.3 REQUEST 3:

We also note the submitted container label and carton labeling presents the name and product information in black and white. This presentation does not appear to be representative of your ‘intend-to-market label and labeling. To allow for a complete assessment of your submission, please submit the ‘intend to market’ version of your label and labeling for our review. In addition, please confirm whether the “intend-to-market” container label and carton labeling was used in your study.

Response: Population Council, as a non-profit research organization, will not be marketing the product. We are actively seeking a licensee who will develop the “intend to market” product labeling and identify a product name. The submitted container label and carton labeling is intended to serve as a placeholder until a licensee is identified. Once the product is licensed, the licensee will submit the “intend-to-market” label and carton labeling along with a proprietary name for review. Our intention was that these placeholder materials would allow for the review of the file, with the understanding that the labeling and name would still require review after they were submitted. Rings for the Phase 3 trial were packaged in an individual foil pouch only (no secondary packaging) with the below label:



APPEARS THIS WAY ON ORIGINAL

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with post-market medication error data, we reviewed the following Segesterone and Ethinyl Estradiol Vaginal System labels and labeling submitted by Population Council on August 17, 2017.

- Image of Product alone
- Image of Product in carrying case
- Instructions for Use (image not shown)
- Patient Package Insert (image not shown)
- Prescribing Information (Image not shown)

^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

G.2 Label and Labeling Images

Image of product alone and in its carrying case (excerpted from pages 11 and 15 of document titled “Results of CFR Label Comprehension Validation Test”)

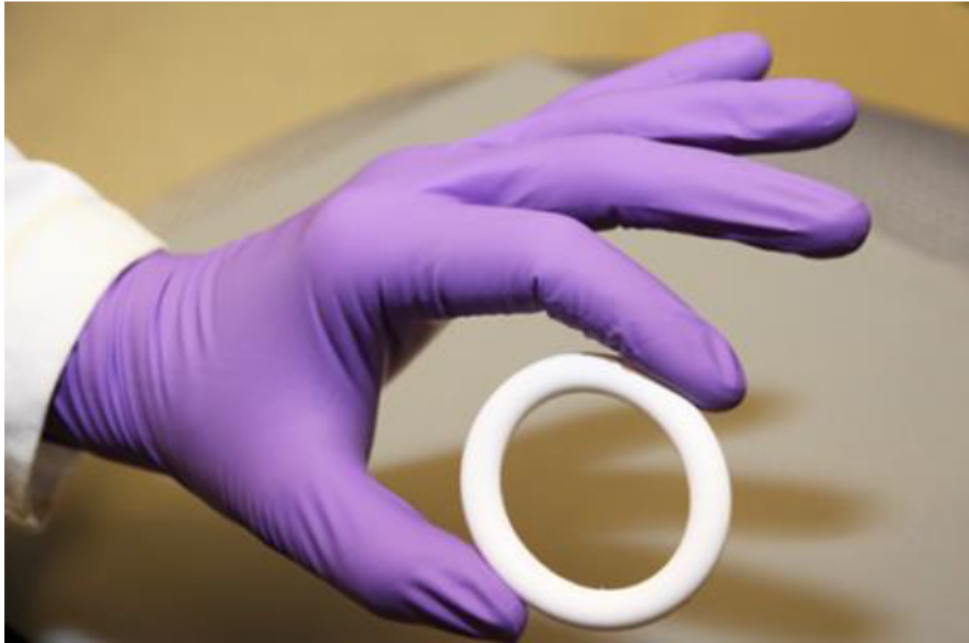


Figure 1. The Contraceptive Vaginal Ring

(b) (4)

Figure 3. Sample CVR in its carrying case.

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

/s/

DENISE V BAUGH
03/07/2018

LOLITA G WHITE
03/07/2018

QUYNH NHU T NGUYEN
03/07/2018