

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201110Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	April 29, 2020
From	Shelley R. Slaughter, MD PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 201110 Class 2 Resubmission
Applicant	Ferring Pharmaceuticals
Date of Submission	October 29, 2019 (receipt date)
PDUFA Goal Date	April 29, 2020
Proprietary Name	MILPROSA™
Established or Proper Name	Progesterone vaginal system
Dosage Form(s)	Vaginal system
Applicant Proposed Indication(s)/Population(s)	Support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women
Applicant Proposed Dosing Regimen(s)	1.78 gram of progesterone in a silicone matrix with release rate of 11mg per day progesterone over a 7-day period
Recommendation on Regulatory Action	<i>Approval</i>
Recommended Indication(s)/Population(s) (if applicable)	To support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women up to and including 34 years of age Limitation of Use Efficacy in women 35 years of age and older has not been established.
Recommended Dosing Regimen(s) (if applicable)	Insert one MILPROSA vaginal system starting on the day after oocyte retrieval. Leave in place continuously

(for a minimum of 23 hours per day) for 7 days, then remove the used vaginal system and insert a new vaginal system. Replace MILPROSA weekly for up to 10 weeks

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Progesterone is currently approved in the form of a vaginal gel and a vaginal insert for use in supplementation of the luteal phase (beginning after oocyte retrieval) and maintenance of early pregnancy as part of an Assisted Reproductive Technology [(ART) mostly in vitro fertilization with or without intracytoplasmic sperm injection (ICSI) and fresh embryo transfer (ET)] cycle, for which a gonadotropin releasing hormone (GnRH) agonist is started in the menstrual cycle before for pituitary down regulation, and gonadotropins are used for controlled ovarian stimulation to produce multiple follicular development. Crinone was approved under NDA 020701 on July 31, 1997 for treatment of secondary amenorrhea and under NDA 020756 on May 13, 1997 “for progesterone supplementation or replacement as part of an ART treatment for infertile women with documented or suspected progesterone deficiency.” Endometrin was approved June 21, 2007 for “support of embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women.” A progesterone in oil product for intramuscular injection is also used off-label in the same manner as the approved progesterone products. MILPROSA provides for progesterone supplementation in the luteal phase and early pregnancy via local vaginal delivery from a silicon, toroidal-shaped (ring) system placed once weekly. The applicant proposes that MILPROSA will provide additional benefit to women through avoidance of the risks associated with injection including pain and cellulitis or those associated with vaginal gels including vaginal discharge, discomfort, and irritation.

Progesterone is an endogenous C-21 steroid produced under normal circumstance by the Corpus Luteum structure in the ovary that forms following ovulation. In the luteal phase and early pregnancy, progesterone has the following roles:

- Conversion to a thickened secretory endometrium allowing for the implantation, nourishment and maintenance of the early implanted embryo.
- Influence changes to the vaginal epithelium and cervical mucus, such that the latter becomes impenetrable to sperm.
- Suppression of the maternal immunologic response to fetal antigens thus preventing recognition of the trophoblasts as foreign and rejection of the pregnancy.

GnRH agonists (or antagonists) are used in ART programs to prevent premature luteinization of follicles as a result of premature LH surges. However, the pituitary suppression resulting from the use of GnRH agonists may continue into the luteal phase (even though agonist/antagonist therapy stops prior to hCG administration) resulting in insufficient progesterone levels. Therefore, exogenous administration of progesterone may be necessary to supplement endogenous progesterone.

Progesterone use in Art is for short-term use until the role of producing progesterone in early pregnancy is taken over by the fetal placenta around 10-Weeks post-embryo transfer (12th Gestational Week). MILPROSA should be used with cautions in women with cardiovascular or cerebrovascular disorders and depression. Cases of toxic shock syndrome (TSS) have been reported in women using vaginal systems with and without tampon use. No causal relationship between the use of MILPROSA and TSS has been established. Concomitant use of MILPROSA with other vaginal products (such as antifungal products, vaginal lubricants, diaphragms and condoms) has not been studied; these products may alter progesterone release and absorption from MILPROSA. If possible, avoid use of other vaginal products with MILPROSA.

There are insufficient long-term safety data to adequately characterize long term risks of progesterone alone. Common side effects associated with progesterone can include bloating, abdominal pain or cramps, headache, dizziness, nausea, vomiting, breast pain, vaginal discharge, genital pruritis, perineal pain, constipation, diarrhea, depression, decreased libido, nervousness, somnolence, dyspareunia, breast enlargement, nocturia.

Overall the Benefit:Risk profile is anticipated to be favorable for the limited, non-chronic use of MILPROSA in the intended population of women 18 to 34 years of age.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • Infertility is a condition resulting in failed or delayed ability to conceive a child. • Infertility is recognized by the American Society of Reproductive Medicine as a disease (disease defined as “any deviation from or interruption of the normal structure or function of any part, organ, or system of the body as manifested by characteristic symptoms and signs; the etiology, pathology, and prognosis may be known or unknown’’, defined by the failure to achieve a successful pregnancy after 12 months or more of 	ART is an increasingly common treatment of the female partner in couples with infertility who have not conceived with other treatments. Supplementation with exogenous progesterone is needed in women undergoing an ART cycle when that cycle is preceded with a GnRH agonist for the purpose of down-regulation of pituitary. Such luteal phase exogenous progesterone supplementation improves

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>appropriate, timed unprotected intercourse or therapeutic donor insemination. Earlier evaluation and treatment may be justified based on medical history and physical findings and is warranted after 6 months for women over age 35 years [Practice Committee of the American Society for Reproductive Medicine, Definitions of infertility and recurrent pregnancy loss: A Committee Opinion Fertil Steril 2013;99:63].</p> <ul style="list-style-type: none"> • The data support a prevalence of 15% infertility in U.S. couples. • Infertility increases with several demographic characteristics including, but not limited to, age, lower education, nulliparity, and history of gynecologic disorders in women as well as defects in sperm quality and quantity in men. • Progesterone is currently approved in the form of a vaginal gel and a vaginal insert for use in supplementation of luteal phase (beginning after oocyte retrieval and maintenance of early pregnancy support as part of an Assisted Reproductive Technology [(ART) mostly in vitro fertilization with or without intracytoplasmic sperm injection (ICSI) and fresh embryo transfer (ET)] cycle for which a gonadotropin releasing hormone (GnRH) agonist is started in the menstrual cycle before for pituitary down regulation, and gonadotropins are used for controlled ovarian stimulation to produce multiple follicular development. <ul style="list-style-type: none"> ▪ Progesterone supplementation is necessary in ART cycles because the use of GnRH agonists may result in pituitary downregulation and resultant insufficient corpus luteum production of endogenous progesterone to support endometrial implantation and maintenance of the early eutopic pregnancy. 	<p>endometrial implantation</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	<p>Crinone was approved under NDA 020756 on May 13, 1997 “for progesterone supplementation or replacement as part of an ART treatment for infertile women with documented or suspected progesterone deficiency.” Endometrin was approved June 21, 2007 for “support of embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women.” A progesterone in oil product for intramuscular injection is also used off-label in the same manner as the approved progesterone products.</p>	<p>Exogenous progesterone is approved as a vaginal gel and a vaginal insert as part of an ART treatment program. MILPROSA will offer an additional form of administration.</p>
Benefit	<p>Approved exogenous progesterone has been demonstrated to be efficacious in the support of embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women.</p> <p>MILPROSA is recommended for this indication in infertile women up to and including 34 years of age. Labeling for MILPROSA will include:</p> <p>Limitation of Use Efficacy in women 35 years of age and older has not been established.</p>	<p>MILPROSA is recommended to support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women up to and including 34 years of age.</p> <p>Efficacy of MILPROSA in women 35 years of age and older has not been established.</p>
Risk and Risk Management	<p>Exogenous progesterone use is contraindicated in women with:</p> <ul style="list-style-type: none"> • Known sensitivity to progesterone or any of the ingredients of the progesterone product. • Undiagnosed vaginal bleeding • Severe hepatic impairment or disease • Known or suspected malignancy of the breast • Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events. <p>Exogenous progesterone should be used with caution (Warning and Precautions) in women with:</p>	<p>The risk: benefit profile of short-term, non-chronic use of MILPROSA in the intended population of women 18 to 34 years of age is anticipated to be favorable.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> • Cardiovascular or Cerebrovascular Disorders Be alert to early signs of myocardial infarction, cerebrovascular disorders, arterial or venous thromboembolism (venous thromboembolism or pulmonary embolism), thrombophlebitis, or retinal thrombosis. Discontinue if any of these are suspected. • Depression Observe closely women with a history of depression who use exogenous progesterone. Discontinue if symptoms of depression worsen. <p>In addition, MILPROSA will receive additional Warnings and Precautions for:</p> <ul style="list-style-type: none"> • Toxic Shock Syndrome Cases of toxic shock syndrome (TSS) have been reported in women using vaginal systems with and without tampon use. No causal relationship between the use of MILPROSA and TSS has been established. Warning signs of TSS include fever, nausea, vomiting, diarrhea, muscle pain, dizziness, faintness or a sunburn-like rash on face and body. Discontinue MILPROSA if TSS is suspected. and initiate appropriate medical evaluation and treatment. • Use of Other Vaginal Products Concomitant use of MILPROSA with other vaginal products (such as antifungal products, vaginal lubricants, diaphragms and condoms) has not been studied; these products may alter progesterone release and absorption from MILPROSA [see Drug Interactions (7)]. If possible, avoid use of other vaginal products with MILPROSA. <p>The following common adverse drug reactions were seen in 2% or greater of women using MILPROSA for the intended indication:</p>	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>headache, vaginal discharge, nausea, breast tenderness, post procedural discomfort, abdominal distension, abdominal pain and pelvic pain.</p> <p>There are insufficient long-term safety data to adequately characterize long term risks of progesterone alone. The proposed indication is a limited, non-chronic use indication.</p>	

2. Background

Progesterone is a C-21 steroidal hormone produced by the ovarian corpus luteum following ovulation. In the luteal phase and early pregnancy, progesterone has the following roles:

- Conversion to a thickened secretory endometrium allowing for the implantation, nourishment and maintenance of the early implanted embryo.
- Influence changes to the vaginal epithelium and cervical mucus, such that the latter becomes impenetrable to sperm.
- Suppression of the maternal immunologic response to fetal antigens thus preventing recognition of the trophoblasts as foreign and rejection of the pregnancy.

Between the 6th and 10th week of pregnancy, a luteal placental shift takes place such that by Week 10 of pregnancy, the placenta takes over the function of production of progesterone and maintenance of pregnancy.

GnRH agonists or antagonists are used in Assisted Reproductive Technology [(ART), primarily in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI)] programs to prevent premature luteinization of follicles as a result of premature luteinizing hormone (LH) surges. Unfortunately with GnRH agonist use, suppression can continue into the luteal phase (even though agonist therapy has stopped prior to the day of hCG administration) resulting in insufficient progesterone levels. Therefore, exogenous administration of progesterone may be necessary to supplement endogenous progesterone. Because there is no way to predict which woman may or may not require luteal supplementation in any given cycle, some form of luteal phase support is recommended for all ART (Speroff L, Glass R and Kase Clinical Gynecologic Endocrinology and Infertility, Williams and Wilkins).

For many years, progesterone-in-oil, 50 mg administered intramuscularly, was considered the gold standard for luteal phase support. Progesterone-in-oil is approved (May 11, 1978) under NDA 017362 for the treatment of amenorrhea and abnormal uterine bleeding and its use in infertility treatment is “off-label”. Prometrium approved under NDAs 019781 and 020843 for prevention of endometrial hyperplasia and treatment of secondary amenorrhea, respectively, was/is also compounded into a vaginal product by many local/university hospital-associated pharmacies and historically used “off-label” for luteal support.

Two products are approved specific to the ART indication. Crinone was approved under NDA 020701 on July 31, 1997 for treatment of secondary amenorrhea and under NDA 020756 on May 13, 1997 “for progesterone supplementation or replacement as part of an ART treatment for infertile women with documented or suspected progesterone deficiency.”

Endometrin was approved June 21, 2007 for “support of embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women.”

This is the third review cycle for NDA 201110 for MILPROSA™ (progesterone) vaginal system. The following is an abbreviated review of the regulatory history of this product, beginning with the original review cycle.

- **April 30, 2010** - TEVA Women’s Health R & D submitted NDA 201110 for the progesterone vaginal ring. The application was filed on June 29, 2010.
- **February 28, 2011** – The Division of Bone, Reproductive, and Urologic Drug Products [(DBRUP) now the Division of Urology, Obstetrics and Gynecology (DUOG)] issued a Complete Response decisional letter for NDA 201110. The following deficiencies and discussion of resolution of each deficiency were provided in the letter to TEVA Women’s Health R & D:

PRODUCT QUALITY

1. During the prior approval inspection (PAI) of your facility, foreign particulate contaminations were found in all five site transfer batches manufactured at the future commercial site. Conduct a thorough investigation to identify the root cause. Propose corrective measures and demonstrate that the root cause has been corrected by producing three production batches which show no particulates.
2. The progesterone vaginal ring contains (b) (4) % w/w concentration of progesterone dispersed evenly within the ring. The particle size distribution of progesterone is considered to be critical for the consistent release of progesterone. Amend your application to include a test for particle size distribution with acceptance criteria in the specification for the drug substance.
3. The drug product specification is incomplete. Revise the “Description” of the drug product specification by adding “Free of particulates by visual inspection” and revise the “Microbiological Examination” of the drug product specification to include “The absence of (b) (4) .”
4. Analytical methods for the drug product are inadequate. To address this deficiency:
 - Validate the accuracy of the HPLC test method for detection of impurity/degradation products in the drug substance.
 - Validate the repeatability and intermediate precision of the drug product impurity test using samples spiked with the four known impurities at quantitation levels (QL).
 - Revise the acceptance criteria of the relative standard deviation (RSD) (b) (4) for establishing the system suitability of the HPLC method.

CLINICAL

5. You have not provided sufficient evidence of efficacy for the progesterone vaginal ring [system] in the subgroup of women 35-42 years of age. This subgroup represents approximately 50% of the infertile women for whom your drug is intended for use as part of an Assisted Reproductive Technology (ART) treatment program. In general, the subgroup of infertile women 35-42 years of age has diminished ovarian reserve relative to women under the age of 35. You have not demonstrated that information obtained from the subgroup of women less than 35 years of age can be extrapolated to women in the older subgroup.
 - To address this concern, we continue to recommend that you conduct, prior to approval of your product, a randomized, active-controlled clinical trial to evaluate the efficacy of your product in women 35-42 years of age. The trial should be adequately powered to demonstrate sufficient retention of efficacy in the progesterone vaginal ring arm when compared to the active comparator. Details of the trial should be agreed upon with the Agency prior to the conduct of the study.
 - It is also possible that appropriate labeling, which would include a statement on limitation of use, and a postmarketing commitment to conduct the clinical trial described above would be sufficient to support approval of the progesterone vaginal ring for use in women less than 35 years of age.

FACILITY INSPECTIONS

6. During recent inspections of the Northvale, NJ, testing facility and the Cincinnati, OH, manufacturing facility, our field investigator(s) conveyed deficiencies to the representatives of the facilities. Satisfactory resolution of these deficiencies is required before this application may be approved.

Additionally, the applicant was asked to address the following in their response to the letter:

PRODUCT QUALITY



(b) (4)

MICROBIOLOGY

4. The method validation studies for total yeast and mold count included an incubation temperature of (b) (4) °C, while the proposed test method has an incubation temperature of (b) (4) °C. This appears to be an error based on information found later in the method validation package. The error occurs in section 5.2.1(i) and the correct temperature is list in section 5.3. Revise ARD_RPT-5064 version 2.0 accordingly.
 - Submit the results from microbial enumeration studies on the stability and site transfer batches using the revised test methods.
- **March 4, 2011** -The Agency provided an Advice Letter noting provisional approval of the proprietary name, MILPROSA™.
 - “We have completed our review of the proposed proprietary name, MILPROSA™, and have concluded that the name is acceptable. However, the name will be re-reviewed 90 days prior to the approval of the NDA following resubmission. If we find the name unacceptable following the re-review, we will notify you.”
- **March 31, 2011** - TEVA Women’s Health R & D advised the Agency that the out of specification (OOS) testing for batches 800354 and 800356 resulted from bacterial contamination. At this time, the investigation had not been finalized; but an integrity issue was identified with containers (b) (4). The same type of container was used to test all five of the site transfer batches of progesterone vaginal ring [system]; therefore, results from all five batches are invalid.

- **May 31, 2011** - TEVA Women's Health R & D submitted the following "Quality" information.
 - Results from re-testing of site transfer and stability samples of progesterone vaginal system for:
 - Batches 800354, 800356, 800357, 800358, and 800359 using the revised Finished Product Test Method (MTH-(b) (4)) for Microbiological Examination tests, performed after procurement of new, more suitable containers.
 - Copy of OOS investigation report.
- **December 23, 2011** - Quality Information Amendment received from TEVA Women's Health R & D.
 - Information addressed the cause of product quality deficiencies, foreign particulate contamination in progesterone vaginal rings [system], as outlined in the Complete Response Letter, as well as the proposed and remediation.
- **February 28, 2012** - TEVA Women's Health R & D Information Amendment requested an extension to respond to the Complete Response Letter. The additional time requested was to allow for manufacture of additional full-scale progesterone vaginal system batches and generation of release and stability data to confirm consistent progesterone vaginal ring [system] manufacturing capability.
- **March 28, 2012** - DBRUP provided an Advice Letter informing TEVA Women's Health R & D that their request for an extension to submit all final responses to the Agency's Complete Response Letter by fourth quarter 2012, is acceptable.
- **February 28, 2013** – TEVA Women's Health R & D notified the Agency of its corporate name change to TEVA Branded Pharmaceutical Products R&D, Inc.
- **January 22, 2015** - TEVA Branded Pharmaceutical Products R&D submitted the Trial Report for Trial DR201-BE-10021, "An Open-Label, Single-Dose, Randomized, 2-Treatment, 2- Period Crossover Pharmacokinetic Study to Evaluate the Bioequivalence of 2 Progesterone Vaginal Rings (b) (4) % (w/w) in Postmenopausal Women."
- **August 5, 2015** –TEVA Branded Pharmaceutical Products R&D notified the Agency of transfer of ownership of NDA 201110 and IND 070875, and associated communications and documentation from TEVA to Ferring Pharmaceuticals Inc. (henceforth referred to in this review as Ferring).

- **August 6, 2015:** Ferring notified the Agency of its acceptance of NDA sponsorship of NDA 201110 and IND 070875 as of August 5, 2015, and committed to the agreements, promises, and conditions made by the former owner and contained in the application, as well as to compliance with all NDA requirements and obligations set forth in 21 CFR Part 314.
- **August 8, 2015** – DBRUP acknowledged change in sponsorship for IND 070875.
- **October 8, 2015** – DBRUP acknowledged transfer of ownership for NDA 201110.
- **February 25, 2016** – The Agency received from Ferring, a Class 2 Resubmission of NDA 201110.
- **November 23, 2016:** DBRUP issued a Complete Response decisional letter to Ferring: The deficiencies and strategies for resolution of deficiencies are summarized as follows:

DEVICE

1. Your to-be-marketed combination drug-device product, progesterone vaginal ring [system], contacts the skin and mucosal surface for a permanent contact duration (cumulative single, multiple or repeated long-term use or contact exceeds 30 days), and you provided insufficient biocompatibility information to support this contact duration. To address biocompatibility, you must provide acceptable data on cytotoxicity, sensitization, irritation, genotoxicity, and sub-acute toxicity to support permanent contact duration of use, and thus safety of your to-be-marketed product. You have provided acceptable data on irritation. However, the remaining biocompatibility tests (cytotoxicity, sensitization, genotoxicity, and sub-acute toxicity) are still needed to support your to-be-marketed product.
 - We do not agree that biocompatibility testing may be performed on the progesterone-free vaginal ring [system (placebo)] only. This determination is based on our concern that the base (b) (4) progesterone vaginal ring [system] silicone material plus drug (progesterone) could interact with each other, likely resulting in release of different types and quantities of residuals and leachable substances for the final to-be-marketed combination product compared to the progesterone-free (placebo) vaginal ring [system] product. Additionally, the process of application of the drug onto the vaginal ring [system] product could result in alteration of surface

properties and chemical characteristics of the (b) (4) vaginal ring silicone material, leading to changes in the biocompatibility response. To meet the biocompatibility requirements and adequately evaluate and support safety of the to-be-marketed progesterone vaginal ring [system] product, satisfactorily address the following testing paradigm:

- For products that are inherently cytotoxic or products that demonstrate cytotoxicity, perform additional testing using several dilutions of the extracts derived from the final, finished, to-be-marketed combination progesterone vaginal ring [system] product to determine the level at which cytotoxicity no longer occurs.
 - A chemical characterization followed by a toxicological risk assessment on extracts derived from the final, finished, to-be-marketed combination progesterone vaginal ring [system] product will provide the overall leachable profile of the progesterone vaginal ring product and will be necessary to understand the breakdown products that result from progesterone vaginal ring silicone material and progesterone interaction. The toxicological risk assessment can serve as an alternative to the chronic systemic toxicity and genotoxicity testing requirements for the to-be-marketed progesterone vaginal ring [system].
 - Sensitization testing that fulfills the principles outlined in the Center for Devices and Radiological Health (CDRH) G95-1 guidance document, “Use of International Standard ISO 10993-10, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing.”

CLINICAL

2. You have not established an adequate clinical safety bridge between your legacy progesterone vaginal ring [system] used in the phase 3 clinical trials and your new progesterone vaginal ring [system] product. We recommended that you conduct a study to evaluate the clinical safety of the new progesterone vaginal ring [system]. The study should include women who are undergoing Assisted Reproductive Technology (ART) procedures, which is the intended population. This study should evaluate the safety and

tolerability of the to-be-marketed ring [system] over the entire duration of treatment (up to 10 weeks post-embryo transfer). In addition, collect data on women who discontinue use of the new progesterone ring. Data collected in this study should include:

- Adverse events (AEs) such as pain, vaginal bleeding, vaginal irritation, vaginal infection, and other more serious adverse events that may be related to the progesterone vaginal ring
- Adverse events related to pregnancy outcomes, including miscarriage and ectopic pregnancy.

3. We remind you of the deficiency in our Complete Response letter dated February 28, 2011, that you have not provided sufficient evidence of efficacy for the progesterone vaginal ring [system] in the subgroup of women 35-42 years of age. To address this concern, we continue to recommend that you conduct, prior to approval of your product, a randomized, active-controlled clinical trial to evaluate the efficacy of your product in women 35-42 years of age. The trial should be adequately powered to demonstrate sufficient retention of efficacy in the progesterone vaginal ring [system] arm when compared to the active comparator. Details of the trial should be agreed upon with the Agency prior to the conduct of the study. We also stated in the February 28, 2011 Complete Response letter that a possible alternative approach would be appropriate labeling, which would include a statement on limitation of use along with a post-marketing commitment to conduct the clinical trial described above.

- **March 7, 2017:** The Agency held a Type A Meeting with Ferring to discuss the design of a clinical safety study protocol to evaluate the to-be-marketed progesterone vaginal ring [system] along with a statement on limitation of use in labeling and a post-marketing commitment to perform a randomized, active- controlled clinical trial to evaluate the efficacy and safety of MILPROSA in women 35-42 years of age.
 - DBRUP advised the applicant that while we agree that an open-label, non-comparative simple safety trial is acceptable, we currently do not have sufficient information to reach a decision on this question because the results from your biocompatibility testing are not yet available. Those results could potentially impact aspects of the design of this safety study, such as the proposed sample size. In a teleconference on November 2, 2016, and in a Complete Response Letter dated November 23, 2016, we informed you that the following remaining biocompatibility tests are required to support your to-be-marketed product: cytotoxicity, sensitization, genotoxicity, and sub-acute toxicity. To date, biocompatibility testing is not complete. We recommend that

you complete biocompatibility testing and submit those results together with your proposed safety study protocol for the Agency's review. We recommend that you incorporate the following when you prepare your study protocol:

- The primary endpoint as the overall cumulative rate of spontaneous abortion, including spontaneous clinically-recognized pregnancy loss and blighted ovum, determined at end of the study (Week 12 following oocyte retrieval). Spontaneous abortion is the most relevant adverse event in this population.
 - The DBRUP (DUOG) agreed that the rate of spontaneous abortion (including blighted ovum) occurring anytime within the first 12 weeks post-retrieval will be defined as the number of such events divided by the number of enrolled women treated who received fresh embryo transfer.
- Amend the protocol to include a speculum examination for visual inspection of the cervix and vagina to assess for abrasions, lesions, etc. during the following visits: Screening, Visit 7P (Week 4.5 following oocyte retrieval), Visit 8 (Week 6 following oocyte retrieval), Visit 9 (Week 10 following oocyte retrieval), and Visit 10 (end of trial, Week 12 following oocyte retrieval).
- Characterize and report cervical and vaginal abrasions, lesions and bleeding/spotting on a predefined and standardly-applied (across all participating centers) scale.
 - Ferring indicated that they were not aware of a published predefined scale(s) used to characterize and report cervical and vaginal abrasions, lesions, and bleeding/spotting and asked if DBRUP had a recommendation for predefined scale(s).
 - DBRUP recommended that the sponsor propose a scale for reporting vaginal and cervical abrasions and lesions. The proposed scale should be medically and scientifically justified based on the literature. The literature on colposcopy evaluation of the vagina and cervix may provide some guidance. A grading of the abrasions and lesions by assigned point scale is acceptable. To ensure uniform compliance and reporting across all participating centers, the protocol should specifically define how investigators evaluate and grade abrasions/lesions. Upon receipt of the final

- protocol, DBRUP will review and comment on the proposed scale.
- DBRUP recommended that, in addition to an assessment of the number of pads per day used, the sponsor should employ a more quantitative scale, such as a pictorial scale. DBRUP referred Ferring to the literature on menorrhagia to guide their proposal. Upon receipt of the final protocol, DBRUP will review and comment on the proposed scale.
 - DBRUP proposed that Ferring consider a scale similar to that used for dermal irritation to evaluate vaginal irritation. Upon receipt of the final protocol, DBRUP will review and comment on the proposed scale.
- DBRUP recommended the following secondary safety endpoints:
- The cumulative rate of spontaneous abortion, including spontaneous clinically recognized pregnancy loss and blighted ovum, determined at 6- and 10-weeks post oocyte retrieval.
 - The cumulative rate of biochemical abortions determined at 6- and 10-weeks post oocyte retrieval.
 - Rates of ectopic and heterotopic pregnancy.
 - Frequency, intensity, seriousness and relatedness of adverse events (AEs), including incidence of vaginal bleeding/spotting, vaginal hemorrhage, pain, vaginal infection, and vaginal irritation. Vaginal bleeding, vaginal pain, and vaginal irritation should be graded as mild, moderate or severe. The criteria for the grading should be prospectively provided in the protocol and the Investigator's brochure.
 - Rates of: 1) abnormal clinical laboratory findings and 2) abnormal vital sign determination.
 - Frequency of and reason for progesterone vaginal system discontinuation.
 - Rates of clinical pregnancy at 6- and 10-weeks post oocyte retrieval.

- **August 24, 2017:** Ferring submitted a request for a Type C Meeting - Written Response Only (WRO) to obtain the Agency's concurrence on the clinical safety study design to support a future resubmission.
 - Biocompatibility – On the results of the biocompatibility testing the Agency agreed that Ferring had complied with the Center for Devices and Radiological Health guidance Use of International Standard ISO 10993-1, “Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process” (2016). Therefore, the Agency determined that there is no biocompatibility safety signal that would impact the design of the proposed clinical safety study.
 - Clinical –
 - With respect to Ferring’s proposed sample size, DBRUP does not agree with your proposed sample size. You cite a miscarriage rate of 11.6% in women less than 35 years of age undergoing Assisted Reproductive Technology (ART) in the U.S., based on the 2014 Society for Assisted reproductive Technology National Summary Report. Based on this information and the spontaneous abortion rate of 6.5% (total of missed abortion, blighted ovum, and spontaneous abortion) in the same age group in Trial DR-PGN-302, an assumption of 8% to 10% spontaneous abortion rate, as defined in the protocol, is reasonable. Additionally, because the proposed trial is open-labeled, a tight confidence interval is also appropriate. Using the point estimate of 8 and 10% with a 5% confidence interval (possible upper limit of the observed rate not exceeding 15%), the sample size should be between 544 and 658, respectively, adjusting for a potential 10% drop-out rate.

We refer you also to our response to Question 7 that the proposed safety trial should evaluate women in the same age group, 18 to 34 years of age, as evaluated in phase 3 Trial DR-PGN-302.

- With respect to Ferring’s proposals regarding the primary and secondary endpoints have been properly implemented, DBRUP is in agreement with the proposed primary endpoint, cumulative rate of spontaneous abortion occurring on or before 12 weeks following oocyte retrieval. We are also in agreement with the proposed secondary endpoints.
- With respect to Ferring’s proposals regarding criteria for grading and reporting vaginal pain irritation, DBRUP is in agreement that the proposed criteria are acceptable.

- With criteria for grading and reporting vaginal bleeding/spotting, the Division is not in full agreement. Amend the protocol to describe how the number of pads used daily will be used in conjunction with the pictorial assessment to quantitate bleeding with the product. To ensure standardized grading and recording across all sites, provide to all study participants for their use throughout the duration of the safety trial, identical (same brand and size) sanitary napkins.
- Additional Clinical Comments:
 - We do not agree with the proposed age group. We recommend that the safety protocol evaluate women in the same age group, 18 to 34 years of age, as evaluated in phase 3 trial, DR-PGN-302.
 - We remind you that labeling will have a limitation of use statement because efficacy has not been established in women 35 years of age and older.
 - Amend the protocol to include the following:
 - Detailed study stopping criteria
 - Detailed drug accountability assessment:
 - Criteria for the adverse event (AE) clinically significant bleeding
 - Human Factors – The Agency recommends a comprehensive risk analysis or plans for a Human Factors (HF) validation study including a comprehensive and systematic evaluation of all the steps involved in using the product.
- **December 6, 2018:** DBRUP responded to a Type C Meeting – WRO request from Ferring.
 - Device
DBRUP agreed that the completed biocompatibility testing on the combination product was adequate to resubmit NDA 201110.
 - Non-Clinical
DBRUP agreed that the format and content of the nonclinical information appeared acceptable.
 - Clinical
 - With respect to the statistical analysis plan (SAP), the Agency stated, we cannot agree at this time. The application of sound Bayesian model assumptions is critical to the implementation of the proposed analysis of phase 3b Trial 000293. Reassess the robustness

of the model assumptions for their influence on statistical power. If the trial is underpowered, the probability of not ruling out a spontaneous abortion rate of 15% increases. As a point of reference for your proposed sample size of 215 subjects, our August 24, 2017, Meeting Written Response recommended a sample size of 658 to rule out a spontaneous abortion rate of 15%, assuming a 10% spontaneous abortion rate under a frequentist approach. We have the following statistical comments and recommendations for Trial 000293:

- For the Bayesian method to be appropriately utilized, the study design [population, treatment regimen (including non-investigational medicinal products), outcome definition, follow-up time, etc.] of phase 3 Trial DR-PGN-302 should be similar to Trial 000293. Provide an assessment of the similarities in study design and primary outcome definition between the two trials and provide justification of any dissimilarities.
- The definition of spontaneous abortion from Trial DR-PGN-302 determines the prior data (currently 55/549 (10%)) used in the Bayesian analysis, which directly influences the power of Trial 000293. Discuss the definition of spontaneous abortion used in Trial DR-PGN-302 to arrive at 55/549 and any differences relative to the definition of spontaneous abortion used in Trial 000293. If the true spontaneous abortion rate is greater than 10%, then this study is underpowered.
- We simulated power and type 1 error estimates that are lower than your estimates (power: (b) (4) 81%, type 1 error: 4.8% vs. 9%). A power of (b) (4) is not acceptable. Provide the simulation code or program used to generate the power, type 1 error, and estimated rates in the tables on page 38, Appendix 2 of the SAP.
- The priors have impact on the study power. Therefore, justify the prior distribution specifications $\mu \sim \text{Normal}(- (b) (4))$ and $\tau^2 \sim \text{Inverse Gamma}((b) (4))$. Derive the mean and variance for the inverse gamma distribution.
- Provide a reference or explanation for the formula (b) (4) used to calculate the effective number of borrowed subjects.

- Calculate the exact frequentist 95% confidence interval (CI) for spontaneous abortion and 95% CI in the secondary analyses (not (b) (4) CD).
- Clarify whether demographics and prior/concomitant medication are summarized for the safety cohort in addition to the proposed mITT and eligible subjects (ES) cohorts. SAP Sections 7.1.2-7.1.5 and 7.3 did not specify the safety cohort.
- With respect to the format and content of the clinical sections of the eCDT, the Agency indicated that we cannot answer definitively at this time. The format and the content of the clinical sections of the eCTD according to the eCTD Index provided as an attachment to the meeting package, appear reasonable, however, we request that you respond to the following requests for clarification:
 - Are data for completed phase 3 Trial DR-PGN-302 intended to be included under controlled phase 3 trials?
 - How are you classifying single arm, non-comparative Trial 000293? Under what subsection of Module 5 do you propose to provide the trial report for Trial 000293 given that it is not a controlled trial?
- Human Factors
 - With to the need for additional Humans Factors information, the Agency stated, following our review of your Use-Related Risk Analysis (URRA) and comparative analyses, we have determined that a human factors validation study is not required to support your proposed progesterone vaginal ring combination product.
- General with respect to the overall format and content appears reasonable. The submission should address the following:
 - CMC – Provide:
 - A tabulation of any updates or changes made to the to-be-marketed combination product manufacturing, packaging and controls after the November 23, 2016, Complete Response Letter.
 - Batch analyses and stability data for the to-be marketed combination product used in the clinical safety study.
 - Updated stability data from the registration stability batches, if available.

- That the Establishment Information provided in the Form FDA 356h is complete and current, and that all facilities are ready for inspection.
- Device:
 - Changes to the to-be-marketed combination product may require additional biocompatibility evaluation.
- **August 12, 2019:** Ferring responded to the Agency's statistical recommendations.
 - The applicant agreed to use a frequentist statistical approach as the primary analysis for the clinical trial with a Bayesian model sensitivity analysis. They also communicated the sample size calculation of 240 evaluable women based on a spontaneous abortion rate of 8-10% as suggested by DBRUP.
 - The Division of Biometrics VII reviewed the applicant's revised statistical analysis plan and concurred with the frequentist approach and proposed sample size in an email to DBRUP Deputy Director and Team Leader dated August 30, 2019.

3. Product Quality

Review of the Chemistry, Manufacturer and Controls [(CMC), Product Quality] was performed as follows (see Table 1):

Table 1: CMC Review Team for Cycle 3 Class 2 Resubmission of NDA 201110

Discipline	Primary Reviewer	Secondary Reviewer
Drug Substance	Gaetan Ladouceur	Donna Christner
Drug Product	Hong Cai	Moo-Jhong Rhee
Manufacturing	James Norman	Yubing Tang
Microbiology	Jennifer Patro (NAI)	Jessie Wells (NAI)
Biopharmaceutics	Kalpana Paudel (Reviewed Previous Cycle)	Kelly Kitchens (Reviewed Previous Cycle)
Regulatory Business Process Manager	Marquita Burnett	
Application Technical Lead	Mark Seggel	
Laboratory (OTR)	NA	NA
Environmental	James Laurenson	Scott Furness

Drug Substance

The drug substance is progesterone (pregn-4-ene-3,20-dione) (see Figure 1). Progesterone is a well-known member of the progestogen class of steroid hormones. Progesterone is produced

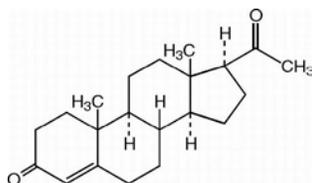
(b) (4)

Progesterone is practically insoluble in water but freely soluble in ethanol. It has a melting range of 126°C to 131°C. See Figure 1 for presentation of USAN Name, Chemical Name, and Molecular Weight.

Figure 1 Progesterone (USAN) Chemical Name and Structure

Chemical and USAN Name: Progesterone (USAN), Pregn-4-ene-3,20-dione (Chemical Name)

Structural Formula:



No drug substance information was provided in the October 29, 2019 Cycle 3 Class 2 resubmission for NDA 201110. The complete information regarding the drug substance can be found in the cross-referenced Drug Master File (DMF), which was last reviewed by the Agency on December 09, 2019 (DMF (b) (4), Adequate); there has been no new DMF amendment since then. A retest period for the drug substance of (b) (4) was originally granted and is still valid. From a drug substance perspective, this NDA is recommended for approval.

Drug Product

The proposed drug product is MILPROSA™(progesterone) vaginal system. MILPROSA™ is a non-biodegradable, white to off white, flexible silicone ring (toroidal-shaped) containing 1.78 g progesterone ((b) (4) % w/w drug load). It also consists of (b) (4) silicone elastomer (total of (b) (4) % w/w) and light mineral oil (b) (4) % w/w).

Particulate contaminations were found in all five site transfer batches manufactured at the future commercial site during the original review cycle for the progesterone vaginal system, which were noted as deficiencies in the Complete Response letter of February 11, 2011.

The applicant subsequently determined that (b) (4) the proposed commercial product presented in the original review cycle was due to the (b) (4) process, which utilized (b) (4). To address this issue, the applicant replaced the original (b) (4) process (Legacy process) with a (b) (4) process (new to –be-marketed process). The applicant instituted corrective measures including tests for foreign particulate matter in the raw materials and a complete (b) (4) visual inspection were implemented. ***No foreign particulate contamination has been observed in product manufactured after implementation of the corrective measures.***

Additionally, information provided in this resubmission include:

1. Batch analyses data for three clinical batches acquired at release as well as at the end of Trial 000293. Trial 000293 was conducted to establish an adequate clinical safety bridge between the progesterone vaginal system manufactured with “the legacy process” (b) (4) used in the original phase 3 trial and “a new (b) (4) process” (b) (4) for the to-be-marketed product. With the use of (b) (4) the review noted that the issue of particulate matter in the original product was resolved, per the Drug Product Review #2 of Dr. Bhavishya Mittal, dated October 26, 2016, of the Cycle 2 Class 2 NDA Resubmission, dated February 25, 2016,
2. A 36-month long term stability data from the three registration batches with a proposed 24-month expiration dating period.

No other changes to the Chemistry, Manufacturing, and Controls (CMC)-related information have been made since the Agency issued the November 23, 2016 Complete Response letter.

Per Dr. Cai, based on the submitted adequate stability data and CDRH’s satisfactory assessment for the biocompatibility data, this application is now recommended for approval from the drug product perspective with the requested 24-month expiration dating period when

stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Do not refrigerate or freeze and avoid excessive heat.

Facilities

The drug product manufacturer is (b) (4). There have been three inspections at this site since the end of cycle #2:

- (b) (4)
- (b) (4)
- (b) (4)

There are no alerts for this site. This site remains acceptable as the drug product manufacturer for NDA 201110.

There is one testing site requiring evaluation – (b) (4). There has been one inspection at this site since the end of Cycle 2 – an NAI surveillance inspection in (b) (4). There are no alerts for this site. It remains acceptable.

The corporate headquarters for the applicant, Ferring, was inspected from the device perspective in the last review cycle. There are no new inspections or alerts for this site. It remains acceptable from the device perspective.

The FDA Form 356h included two sites for which no evaluation was necessary.

- (b) (4)
- (b) (4)

These sites were not documented in the Cycle 2 IQA document. Updates on these “Other” sites was update January 24, 2020.

Environmental Assessment

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The required statement of no extraordinary circumstances was added during an update. Additional information also was provided to support the claim. The claim and supporting information were reviewed and the claim was found to be acceptable. See the Environmental Analysis in OPQ Quality Assessment #2, November 10, 2016.

Device

The Cycle 2 Class 2 NDA Resubmission/CDRH device evaluation was performed by Dr. Monica Garcia, CDRH/ODE/DRGUD/OGDB. The Cycle 3 Class 2 NDA Resubmission CDRH device evaluation was performed by Dr. Reginald Avery CDRH/OPEQ/OHT3/DHT3B/THT3B1.

After a review of the Cycle 2 Class 2 NDA Resubmission, Dr. Garcia, determined that the progesterone vaginal system information was deficient regarding mechanical testing of the ring, stability/shelf-life testing, biocompatibility, and compatibility with other intravaginal products which may be used concomitantly. These deficiencies, provided to the applicant in an Information Request letter, dated May 23, 2016, are summarized at a high level as follows:

1. You have not sufficiently evaluated the mechanical properties of the vaginal system. This information is necessary to evaluate the possible mechanical failure modes of the vaginal ring. At a minimum, provide the results of performance testing on the following parameters:
 - Dimensional analysis
 - Tensile strength
 - Elongation at break
 - Compression strength and twisting during compression.
 - Compression strength and twisting during compression are the most relevant of the required parameters, as these forces will most likely commonly be encountered during the use of the intravaginal ring.

Evaluate at least ten samples per each test. Provide justification for the chosen acceptance criteria for each of the tests. Refer to ISO 8009-14, *Mechanical contraceptives – Reusable natural and silicone contraceptive diaphragms – Requirements and tests*, for additional guidance regarding evaluation of some of the parameters listed above.

2. Provide a full protocol, test report, and justification for the chosen acceptance criteria. You propose a shelf-life of 24 months for the progesterone vaginal ring when stored at 25°C. Section P.8.3 (Stability Data) of the application presents tabular presentations of all pivotal and supportive drug product stability data (accelerated and real time) for the progesterone vaginal ring. However, the physical and mechanical properties you evaluated during these studies only include durometer and appearance. In order to assess signs of degradation following storage, include an evaluation of the mechanical properties of the ring in the stability validation for the progesterone vaginal system.

Repeat the mechanical tests identified in the above Comment 1 on samples that have undergone simulated shipping, handling, and storage for the proposed shelf-life of the device.

We recommend that you evaluate samples at various intervals throughout the intended shelf- life (e.g., 3 months, 6 months, etc.).

3. The to-be-marketed progesterone vaginal system is proposed to be inserted the day following oocyte retrieval and replaced weekly for up to 10 weeks total duration of use. Therefore, the to-be-marketed progesterone vaginal system is a surface device that contacts the skin and mucosal membranes for a permanent contact duration (i.e., devices whose cumulative single, multiple or repeated long-term use or contact exceeds 30 days). Your submission does not contain evaluation of cytotoxicity, sensitization, irritation, genotoxicity, and subacute toxicity potential to support permanent contact duration of use for the TBM product. We refer you to ISO 10993-1:2009, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process for information on the type and conditions of testing. We also request that you evaluate acute systemic toxicity, chronic toxicity, and implantation. We refer you to CDRH G95-1 guidance document, “Use of International Standard ISO 10993, ‘Biological Evaluation of Medical Devices Part 1: Evaluation and Testing’” issued on May 1, 1995. In Module 1.4, you state that (b) (4) has provided authorization to reference DMF# (b) (4) silicone elastomer. We have provided to the DMF holder, comments regarding the biocompatibility testing, which was conducted on the (b) (4) silicone elastomer.
4. Provide a risk analysis that evaluates the risks associated with the use of the vaginal ring [system] with other intravaginal devices (for example, vaginal lubricants) that may be used concomitantly with the vaginal ring. Propose mitigation methods to ensure that there is no negative impact/effect on the vaginal ring or other intravaginal device. Perform condom compatibility testing or alternatively state in the labeling that the product should not be used with condoms.

The applicant provided a response to the Information Request letter on June 27, 2016. Ferring committed to the same mechanical testing on the next 10 batches of to-be-marketed progesterone vaginal system. Dr. Garcia’s review noted additional deficiencies with respect to the to-be-marketed product remained and these were identified for the applicant in an Information Response letter on August 8, 2016 and in the November 23, 2016 (Cycle 2) Class 2 NDA Resubmission Complete Response decisional letter. A high-level summary of the remaining device deficiencies at that time of the Cycle2 Class 2 NDA Resubmission decisional letter are presented as follows (See also Section 2 of this review):

1. You do not have sufficient biocompatibility information to support a permanent contact duration. To address biocompatibility, you must provide acceptable data on cytotoxicity, sensitization, irritation, genotoxicity, and sub-acute toxicity to support permanent contact duration of use, and thus safety of your to-be-marketed product.
 - We do not agree that biocompatibility testing may be performed on the progesterone-free vaginal ring [system (placebo)] only. This determination is based on our concern that the base (b) (4) progesterone vaginal ring [system] silicone material plus drug (progesterone) could interact with each other, likely resulting in release of different types and quantities of residuals and leachable substances for the final to-be-marketed combination product compared to the progesterone-free (placebo) vaginal ring [system] product. Additionally, the process of application of the drug onto the vaginal ring

[system] product could result in alteration of surface properties and chemical characteristics of the (b) (4) vaginal ring [system] silicone material, leading to changes in the biocompatibility response. To meet the biocompatibility requirements and adequately evaluate and support safety of the to-be-marketed progesterone vaginal ring [system] product, satisfactorily address the following testing paradigm:

- For products that are inherently cytotoxic or products that demonstrate cytotoxicity, perform additional testing using several dilutions of the extracts derived from the final, finished, to-be-marketed combination progesterone vaginal ring [system] product to determine the level at which cytotoxicity no longer occurs.
 - A chemical characterization followed by a toxicological risk assessment on extracts derived from the final, finished, to-be-marketed combination progesterone vaginal ring [system] product will provide the overall leachable profile of the progesterone vaginal ring [system] product and will be necessary to understand the breakdown products that result from progesterone vaginal ring [system] silicone material and progesterone interaction.
 - The toxicological risk assessment can serve as an alternative to the chronic systemic toxicity and genotoxicity testing requirements for the to-be-marketed progesterone vaginal ring [system].

For this (Cycle 3) Class 2 NDA Resubmission, it was noted that mechanical testing, that was requested in the May 23, 2016 IR letter, was not performed on the three new batches included in the submission. In an Information Request letter, dated February 7, 2020, the applicant was requested to perform the same mechanical testing on the new product batches. On February 25, 2020, Ferring replied with the information requested. Dr. Avery reviewed and found it to be acceptable and indicated that there were no remaining mechanical testing deficiencies. However, Dr. Avery made two recommendations related to data collection for future batches relative to the ring thickness measurements and visual evaluation for signs of deterioration following compression testing. These recommendations were not considered to be approvability issues and, thus, could be addressed by the applicant postmarketing.

An Information Request letter outlining these recommendations was provided to Ferring on March 20, 2020. Ferring responded on March 24, 2020 with a mechanical testing protocol including the recommended additional testing and acceptance criteria. Dr. Avery determined that the revisions to the mechanical testing protocol are acceptable. There are no remaining mechanical testing deficiencies or recommendations. CDRH-OPEQ has determined that the mechanical and biocompatibility properties of the finished product have now been adequately demonstrated.

Labeling

Deficiencies in the prescribing information (PI) and container/carton labels have been identified by Hong Cai, Product Quality reviewer. For example, per USP the dosage form “vaginal system” should be used instead of the previously used “vaginal ring.” Product strength should be expressed in terms of the average release rate, 11 mg/day. The OPQ/ONDP Environmental Assessment Team has provided recommended language regarding disposal of the used product. See attached Labeling Review for details. See also OPQ Quality Assessment #2, November 10, 2016.

Summary

CDER OPQ has concluded that sufficient chemistry, manufacturing and controls information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product.

All drug substance and product-related manufacturing, packaging and testing facilities have acceptable drug CGMP status.

An expiration dating period of 24 months for product stored in its foil laminate pouch at 20°C to 25°C is granted.

The claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) is acceptable.

All issues identified in the Cycle 1 (original submission) February 28, 2011- and the Cycle 2 Class 2 NDA Resubmission November 23, 2016 Complete Response letters have been adequately addressed.

Pending agreement on final labeling, the application is approvable from a CDER OPQ perspective/.

3. Nonclinical Pharmacology/Toxicology

Review of the nonclinical pharmacology and toxicology information for this (Cycle 3) Class 2 Resubmission was provided by Drs. Leslie McKinney and Kimberly Hatfield.

The progesterone vaginal ring’s active ingredient is progesterone, which is an endogenous human hormone. Progesterone has been approved under multiple NDAs in various formulations for use in treating amenorrhea (Progesterone), ART (Crinone[®], Endometrin[®]), as a contraceptive (Progestasert[®] IUD - no longer marketed in the US), and for endometrial protection in women who are taking estrogen (Prometrium[®]). The daily dose of progesterone contained in the MILPROSA[®] vaginal ring [system (11 mg)] is less than the already approved dosage strengths. The duration of exposure (up to 10 weeks) is also less than the duration of already approved products.

The vaginal system (ring) inactive ingredients are:

- silicon elastomer, (b) (4)
- light mineral oil, NF

There are currently no approved products utilizing the silicone ring [system] method of delivery for progesterone. However, silicon elastomers have been used under several INDs including several for combined contraceptive vaginal ring [system] products. (b) (4) has conducted extensive toxicity studies on the silicon elastomers including: in vitro tissue cell culture, pyrogen test in rabbits, systemic injection in mice, intracutaneous test in rabbits, hemolysis tests, 90-day implantation in rabbits, 72-hour vaginal implantation in rabbits, thrombogenicity test (b) (4)

(b) (4) Studies for the biocompatibility and Ames mutagenicity assay were reviewed under the original IND ((b) (4)). There was no evidence of cytotoxicity, irritation or systemic toxicity and the excipient is considered non-mutagenic. A 10-day vaginal irritation and 90-day intravaginal toxicology study in rabbits (with a surgical-implanted progesterone capsule) demonstrated that the drug product is well tolerated and did not cause significant drug-related toxicity. No genetic toxicology, reproductive/developmental toxicology, or carcinogenicity studies were conducted for this product, and none were considered necessary. The original (Cycle1) Pharmacology Toxicology reviewer, Krishan Raheja, DVM, PhD, concluded that there was no safety concern raised for the (b) (4) excipient and the drug product was approvable. However, the application received a complete response (Feb 28, 2011), due to product quality (See Section 3 of this review) and clinical deficiencies of failure to adequately evaluate safety and efficacy in women 35 years of age and older (See Sections 2 and 7 of this review).

Following a Class 2 Resubmission by new owner, Ferring Pharmaceutical (February 25, 2016) and a second cycle of review, the NDA received a second Complete Response [November 23, 2016 (extended Goal Date: November 26, 2016)] based on failure to demonstrate adequate biocompatibility of the drug-device combination.

Ferring has conducted the required compatibility testing and has made a second Class 2 Resubmission (October 29, 2019) for a third cycle of review. For the purposes of the current review cycle, the properties of the drug substance, progesterone, including the impurity profile, were reviewed. Regarding the impurity profile of the progesterone drug substance, it was verified by referencing the DMF in consultation with the product quality reviewers that the impurity profile in the DMF and the current application are the same, and that this is the same impurity profile described in the original submission. Specifications for limits on impurities follow ICH guidelines. Therefore, in consultation with the product quality reviewers, it was determined that the drug substance was not changed from the previous submission.

From a CDER Pharmacology/Toxicology perspective, based on prior review and approval of the drug substance, which is unchanged in this resubmission, Drs. McKinney and Hatfield recommend that this application is approvable.

4. Clinical Pharmacology

Review of this Cycle 3 Class 2 resubmission clinical pharmacology information was provided by Drs. Peng Zou and Yanhui Lu.

The original application and resubmission of NDA 201110 submitted on April 30, 2010 was reviewed by the Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 and

found acceptable from a Clinical Pharmacology perspective. For details, refer to the Clinical Pharmacology review of Dr. Sandhya Apparaju, archived February 02, 2011

The Cycle 2 Class 2 resubmission (February 25, 2016) was reviewed by Dr. Peng Zou, archived September 07, 2016 in DARRTS. In Cycle 2, to address the CMC issues identified in the Complete Response letter to the original submission of NDA 201110 (See Sections 2 and 3 of this review), the applicant replaced the (b) (4) method of the silicon ring [system] used in the original drug product manufacturing process (legacy process) with a (b) (4) method for the to-be-marketed progesterone vaginal ring [system]. The formulation of the combination drug-device product was not changed. The qualitative and quantitative composition of the legacy and the to-be-marketed progesterone vaginal ring [system] with the new (b) (4) process, were identical. To demonstrate bioequivalence between the to-be-marketed progesterone vaginal ring [system] and the legacy progesterone vaginal ring [system], Ferring submitted results from Trial DR201-BE-10021, a clinical bioequivalence trial.

Results of Trial DR201-BE-10021 demonstrate that the 90% confidence interval of the ratio of geometric least square means of test (to-be-marketed progesterone vaginal ring [system]) to reference (legacy progesterone vaginal ring [system]) fall within the 80 – 125% acceptable range to establish bioequivalence. The Office of Clinical Pharmacology concluded that desirable features of the trial design such as the two-way cross-over treatments, use of a washout period between test and reference, and use of pre-treatment with estradiol support acceptability of the overall information and, therefore, the trial is acceptable to establish bioequivalence of the to-be marketed formulation of the progesterone vaginal system (b) (4) to the legacy (clinical trial) formulation of the progesterone vaginal system (b) (4). Based on the bioequivalence trial, the Clinical Pharmacology and Clinical Review Teams were in agreement in acceptance of efficacy for the to-be-marketed progesterone vaginal ring [system] based on the efficacy results of phase 3 clinical Trial DR201-BE-10021 with the legacy formulation of the progesterone vaginal system. However, the Clinical Review Team had concerns that the safety of the to-be-marketed progesterone vaginal system had not fully been assessed by information provided in Cycle 2 (see Sections 3 and 8 of this review).

No new approvability issues were identified in this Cycle 3 resubmission. In this resubmission, the applicant provided literature information to support the labeling language for Distribution, Metabolism, and Excretion under Section 12.3 Pharmacokinetics of the Full Prescribing Information and changed the regulatory pathway from 505(b)(1) to 505(b)(2). This literature was found to be acceptable. Therefore, the Clinical Pharmacology review team in DCEP recommends approval from the clinical pharmacology standpoint.

5. Clinical Microbiology

No Clinical Microbiology review was required for this Cycle 3 Class 2 NDA Resubmission.

6. Clinical/Statistical- Efficacy

Review of clinical efficacy information for this Cycle 3 Class 2 NDA Resubmission was reviewed by Dr. Regina Zopf.

The applicant did not submit new efficacy data to support progesterone vaginal system.

Effectiveness is based on the establishment in Trial DR201-BE-10021 of bioequivalence of the to-be marketed formulation of the progesterone vaginal system (b) (4) to the legacy (clinical trial) formulation of the progesterone vaginal system (b) (4) providing the bridge to the efficacy data of phase 3 Trial DR-PGN-302, reviewed in Cycle 1. The reader is encouraged to read the Clinical Pharmacology Review of Dr. Peng Zou (archived September 07, 2016), the Clinical Review of Dr. Rhonda Hearn-Stewart (archived, November 22, 2016) and this reviewer's CDTL Review (archived, November 22, 2016) for assessment of the bioequivalence data provided in Trial DR201-BE-10021.

The reader is also encouraged to read the review of the efficacy data as provided in the Clinical Review of Dr. Christos Mastroiannis (archived February 25, 2011) and this reviewer's CDTL Review (archived February 25, 2011) of single, randomized, active-controlled, phase 3 Trial DR-PGN-302 conducted primarily in women 18 to 34 years of age using the progesterone vaginal system, manufactured with the legacy (b) (4) process. Trial DR-PGN-302 results in women 18 to 34 years of age randomized to MILPROSA demonstrated a clinical pregnancy rate of 49.3% and 48.2% at 6- and 10-weeks post-embryo transfer, respectively while results in women randomized to the active progesterone comparator demonstrated pregnancy rates of 48.0% and 46.1% at 6- and 10-weeks post-embryo transfer, respectively. At 6 weeks post-embryo transfer the point estimate (lower bound of the 95% confidence interval) of the difference of MILPROSA – active progesterone comparator was 1.2% (-4.6%) and at 10 weeks post-embryo transfer the point estimate (lower bound of the 95% confidence interval) of the difference of MILPROSA – active comparator was 2.1 (-3.7%). The lower bound of the 95% confidence interval of the difference between the progesterone vaginal ring and active progesterone comparator, excluded the prespecified non-inferiority limit of -10% difference (i.e., excluded that the progesterone vaginal system is worse than active progesterone comparator by greater than 10%) and thus non-inferiority was declared with respect to the co-primary endpoints of the pregnancy rates at both 6 weeks post-embryo transfer (Gestational Weeks 8) and 10 weeks post-embryo transfer (Gestational Weeks 12).

It was also determined that phase 3 Trial DR-PGN-302 was insufficiently powered to provide statistically meaningful results on the co-primary endpoints for women 35 to 42 years of age.

To date, the protocol for a phase 3 trial to support efficacy in women 35 to 42 years of age has not been submitted to the Agency.

7. Safety

Review of the clinical safety information for this Cycle 3 Class 2 NDA Resubmission was performed by Drs. Regina Zopf and Thanh Van Tran, Division of Biometrics VII, Office of

Surveillance and Epidemiology. No new phase 3 clinical trial safety data were submitted to support the safety profile of MILPROSA vaginal system 1.78 gram to deliver 11 mg progesterone per day.

The reader is encouraged to read the review of the safety data as provided in the Clinical Review of Dr. Christos Mastroyannis (archived February 25, 2011) and this reviewer's CTDL Review (archived February 25, 2011) of single, randomized, active-controlled, phase 3 Trial DR-PGN-302 conducted primarily in women 18 to 34 years of age using the progesterone vaginal system, manufactured with the legacy formulation (b) (4).

The safety profile of the legacy progesterone vaginal system was considered to be acceptable. There were no maternal deaths and 2 neonatal deaths (1 in each treatment group). Of the 18 SAEs that were unrelated to pregnancy, 11 (6.8%) were related to ovarian hyperstimulation syndrome [(OHSS), 4 of 83 women (2.5%) with SAEs in the legacy progesterone vaginal system group and 7 of 72 subjects (4.3%) with SAEs in the active comparator group]. The women who constituted the 11 cases of SAEs secondary to OHSS were all hospitalized and recovered. The 7 non-pregnancy-, non-OHSS-associated SAEs were 1 case each of: ovarian cyst, intra-abdominal hemorrhage, dehydration, bladder perforation, pleural effusions pelvic inflammatory disease and syncope.

Intrauterine death, missed abortion and blighted ovum accounted for the majority of the 144 SAEs related to pregnancy. The applicant listed spontaneous abortion as 1.24% in the legacy progesterone vaginal system arm and 1.38% in the active progesterone comparator arm. However, with a broader capture of terms the spontaneous abortion rate was 6.5% in the legacy progesterone vaginal system arm and 6.1% with the active progesterone comparator. These rates are comparable and in the range of usual expectation for IVF trials. The primary statistical reviewer was asked to do a "post-hoc" analysis of the rate of early pregnancy loss by age subgroup to include the adverse events terms of abortion, fetal demise (early) missed abortion, spontaneous abortion, blighted ovum and miscarriage. Results of these analyses demonstrated an overall 5.6% early pregnancy loss rate in the legacy progesterone vaginal system arm and 5.8% early pregnancy loss rate in the active progesterone comparator. Rates in women 18 to 34 years of age were comparable to the overall, while rates in women 35 to 42 years of age were 9.1% with use of the legacy progesterone vaginal system arm and 8.8% with the active progesterone comparator. Similar analyses were performed by the applicant and can be found in the clinical trial report for Trial DR-PGN-302, Table 28, page 85. In phase 3 Trial DR-PGN-302, congenital anomalies reported in the MILPROSA treatment arm included: one fetus with arthrogyriposis akinesia, two fetuses with Down's syndrome, one fetus with Klinefelter's syndrome, one fetus with a foot deformity, one fetus with multiple congenital anomalies, one fetus with multiple congenital anomalies – VACTERL association, one fetus with hypospadias, one fetus with pyloric stenosis, one fetus with spina bifida, one fetus with Turner's syndrome, and one fetus with Tetralogy of Fallot.

While the Cycle 2 Class 2 NDA Resubmission Clinical Review considered that there was acceptable evidence from the bioequivalence trial to support that the efficacy of the to-be-marketed progesterone vaginal system based on the bioequivalence efficacy bridge from Trial DR201-BE-10021 to the phase 3 clinical trial efficacy results with the legacy formulation of the progesterone vaginal system, this Clinical Reviewer had concerns that safety of the to-be-

marketed vaginal ring had not fully been assessed (based on the absence of biocompatibility information with the to-be-marketed product as assessed by CDRH) in the clinical development program for either major populations of expected users of this product, women less than 35 years of age with anticipated normal ovarian reserve and women 35 to 42 years of age with anticipated diminished ovarian reserve. The November 23, 2016 Class 2 Resubmission Complete Response letter identified the clinical deficiency of failure of the applicant to establish an adequate clinical safety bridge between their legacy progesterone vaginal system [REDACTED] (b) (4) of the silicon device] used in the phase 3 clinical trials and their new progesterone vaginal system [REDACTED] (b) (4) product. To satisfy this deficiency the Agency recommend that the applicant conduct a study to evaluate the clinical safety of the new progesterone vaginal system. The study should include women who are undergoing Assisted Reproductive Technology (ART) procedures, which is the intended population and should evaluate the safety and tolerability of the to-be-marketed system over the entire duration of treatment (up to 10 weeks post-embryo transfer). In addition, collect data on women who discontinue use of the new progesterone ring. Data collected in this study should include adverse events (AEs) such as pain, vaginal bleeding, vaginal irritation, vaginal infection, and other more serious adverse events that may be related to the progesterone vaginal system; as well as adverse events related to pregnancy outcomes, including miscarriage and ectopic pregnancy.

Over multiple formal meeting between DBRUP and the applicant/sponsor and numerous written responses to the applicant/sponsor, DBRUP agreed that the study 1) should evaluate women 18 to 34 years of age, as evaluated in phase 3 Trial DR-PGN-302; 2) could have an open-label, non-comparative simple safety design; and 3) evaluate as the primary endpoint the overall cumulative rate of spontaneous abortion, including spontaneous clinically-recognized pregnancy loss and blighted ovum, occurring on or before 12 weeks following oocyte retrieval; defined as the number of such events divided by the number of enrolled women treated who received fresh embryo transfer. Based on the 2014 Society for Assisted Reproductive Technology National Summary Report (applicable at the time of the discussion) and the spontaneous abortion rate of 6.5% (total of missed abortion, blighted ovum, and spontaneous abortion) in the same age group in Trial DR-PGN-302, an assumption of 8% to 10% spontaneous abortion rate was considered reasonable. Additionally, because the proposed trial is open-labeled, a tight confidence interval is also appropriate; use the point estimate of 8 and 10% with a 5% confidence interval (possible upper limit of the observed rate not exceeding 15%). Use a frequentist statistical approach as the primary analysis for the clinical trial with a Bayesian model sensitivity analysis. The agreed to sample size based on a spontaneous abortion rate of 8-10%, was 240 evaluable women. Secondary safety endpoints were to include:

- The cumulative rate of spontaneous abortion, including spontaneous clinically recognized pregnancy loss and blighted ovum, determined at 6- and 10-weeks post oocyte retrieval.
- The cumulative rate of biochemical abortions determined at 6- and 10-weeks post oocyte retrieval.
- Rates of ectopic and heterotopic pregnancy.
- Frequency, intensity, seriousness and relatedness of adverse events (AEs), including incidence of vaginal bleeding/spotting, vaginal hemorrhage, pain, vaginal infection,

and vaginal irritation. Vaginal bleeding, vaginal pain, and vaginal irritation should be graded as mild, moderate or severe. The criteria for the grading should be prospectively provided in the protocol and the Investigator's brochure.

- Rates of: 1) abnormal clinical laboratory findings and 2) abnormal vital sign determination.
- Frequency of and reason for progesterone vaginal ring discontinuation.
- Rates of clinical pregnancy at 6- and 10-weeks post oocyte retrieval.

This (Cycle 3) Class 2 NDA Resubmission contains the results of the “Safety Assessment of Progesterone Vaginal Ring in Women Undergoing ART (SARA)” Trial 000293 which was conducted to evaluate the safety of the to-be-marketed MILPROSA vaginal system and to serve as the clinical safety bridge between the to-be marketed MILPROSA (progesterone) vaginal system [redacted] (b) (4) and the legacy formulation [redacted] (b) (4) [redacted] of the silicon device] of the progesterone vaginal system used in the phase 3 clinical trial. As agreed-to by the Agency, Trial 000293 was an open-label, single-arm, safety trial, conducted exclusively in U.S. (14 investigational sites), to evaluate the safety of MILPROSA in women 18-34 years of age who were undergoing IVF with fresh oocytes. Each trial center followed their own standard practice for IVF. Enrollment criteria were similar to Trial DR-PGN-302. On the day after oocyte retrieval, participating women began treatment with MILPROSA. Embryo transfer occurred 5 days after oocyte retrieval (Day-5). Embryo transfer occurred on Day-3, but up to Day-5 in Trial DR-PGN-302. A serum pregnancy test was conducted 2 weeks after the oocyte retrieval. Women with a β -hCG level <5 mIU/mL were discontinued from the trial. Those with a β -hCG level ≥ 5 mIU/mL continued dosing with MILPROSA for up to a total of 10 weeks.

Demographics of participating women in Trial 000293 is presented in the following Table 2.

Table 2 Demographics of Women in Trial 000293 – Safety Population

Age	
n	254
Mean (SD)	30.8 (2.72)
Median (IQ-range)	31.0 [29.0;33.0]
Min; max	22; 34
Age Group, n (%)	
< 25	6 (2.4)
25– 30	71 (28.0)
≥ 30	177 (69.7)
Race, n (%)	
American Indian or Alaska Native	3 (1.2)
Asian	22 (8.7)
Black or African American	17 (6.7)
Native Hawaiian or other Pacific Islander	2 (0.8)
White	210 (82.7)
Ethnicity	
Hispanic or Latina	30 (11.8)
Not Hispanic or Latina	224 (88.2)

Source, Clinical Study Report, Table 7-4, p 72. n = Number of women with observation, % = Percentage of women with observation.

The majority of participating women in the Trial 000293 were White (82.7%) and non-Latina (88.2%) and greater than 30 years of age (age enrollment upper limit is 34 years of age).

As agreed to, the primary endpoint for safety Trial 000293 was any spontaneous abortion occurring on or before 12 weeks following oocyte retrieval in all women treated with MILPROSA and undergoing embryo transfer. Spontaneous abortion was defined by two positive serum β -hCG tests occurring at least 2 days apart on or after 2 weeks post-oocyte retrieval, followed by clinical observation of blighted ovum, intrauterine gestation without a fetal heartbeat, or absence of viable fetuses, as documented by transvaginal ultrasound (TVUS).

The primary analysis was performed to identify the proportion of any spontaneous abortion with 95% exact confidence interval (CI). The predetermined cutoff level of the upper bound of the 95% CI was agreed to as 15% to bridge the safety of the to-be-marketed formulation (b) (4) to the safety data from the Trial DR-PGN-302 conducted with the legacy formulation (b) (4). The primary outcome was analyzed for the modified intent-to-treat (mITT) population, defined as all women who were treated with MILPROSA and completed embryo transfer.

There was a total of 254 women enrolled for a target of 240 evaluable women who completed controlled ovarian stimulation cycle, oocyte retrieval, treatment with MILPROSA, and fresh embryo transfer. Among 254 women treated with MILPROSA (safety population), 243

women were eligible for the mITT population. By the end of the trial, 239 subjects had complete information to determine their status for spontaneous abortion. The remaining four women with incomplete information were as follows: one woman withdrew consent, one woman was lost to follow-up, two women exited the trial after β -hCG testing but before transvaginal ultrasounds were completed.

Secondary endpoints related to spontaneous abortion included the following:

- Spontaneous abortions determined at 6- and 10-weeks post-oocyte retrieval
- Biochemical abortions determined at 6- and 10-weeks post-oocyte
- Ectopic and heterotopic pregnancies
- Positive β -hCG tests at 2 weeks and 2 weeks + 3-4 days post-oocyte retrieval
- Clinical pregnancy at 6- and 10-weeks post-oocyte

The results of the primary (bolded) and secondary endpoint analyses are present in Table 3.

Table 3 Results of Primary and Secondary Endpoints Analyses in Trial 000293

Endpoints	mITT-Number of events (N=243)	mITT-Percentage (95% CI)	Safety-Number of events (N=254)	Safety-Percentage (95% CI)
Spontaneous abortion 12 weeks (primary)	18	7.4 (4.4, 11.5)	-	-
Spontaneous abortion 10 weeks	18	7.4 (4.4, 11.5)	18	7.1 (4.3, 11.0)
Spontaneous abortion 6 weeks	14	5.8 (3.2, 9.5)	14	5.5 (3.0, 9.1)
Biochemical abortion 10 weeks	25	10.3 (6.8, 14.8)	25	9.8 (6.5, 14.2)
Biochemical abortion 6 weeks	25	10.3 (6.8, 14.8)	25	9.8 (6.5, 14.2)
Ectopic pregnancy	1	0.4 (0.0, 2.3)	1	0.4 (0.0, 2.2)
Heterotopic pregnancy	0	0.0 (0.0, 1.5)	0	0.0 (0.0, 1.4)
Clinical pregnancy 10 weeks	105	43.2 (36.9, 49.7)	105	41.3 (35.2, 47.7)
Clinical pregnancy 6 weeks	109	44.9 (38.5, 51.3)	109	42.9 (36.7, 49.2)

There were 18 spontaneous abortion events at 12 weeks in 243 women in the mITT population. The percentage of spontaneous abortion was 7.4% (95% CI 4.4, 11.5). The upper confidence interval for spontaneous abortion at 12 weeks was 11.5%, which is below the a priori determined upper limit of the 95% C.I. cutoff of 15%. Therefore, as prospectively agreed-to with the applicant, the safety bridge is considered to be established.

The Biometric Review implemented the sponsor's Bayesian hierarchical model for sensitivity analyses. This resulted in a posterior mean of 8.3% and 95% credible interval (5.3, 11.3) for spontaneous abortion, similar to the sponsor's estimates. The effective number of borrowed women was approximately 81, or 25% ($81/(243+81)$) of the effective sample size. These posterior estimates should be interpreted with care given that the proposed study sample size ($N = 240$) corresponded to an inflated type I error of 0.08, which was more than 3 times the error probability of ruling out 15% for a frequentist non-inferiority test (0.025). Because the Bayesian hierarchical model is more appropriate for borrowing from many studies, it cannot reliably estimate between-study variability when borrowing from only one study. Additionally, posterior distribution inference, power, and type I error were sensitive to the specification of the between trial variation hyperprior distribution.

For the secondary endpoints, estimates in the mITT population were slightly greater with less precision compared to the safety population because the mITT population had 11 subjects less. The percent of biochemical abortion at 6 or 10 weeks, 10.3% (CI 6.8, 14.8), was higher than other adverse secondary pregnancy outcomes, but this is expected from a clinical standpoint. There was one ectopic pregnancy and no heterotopic pregnancies. Congenital anomalies in this safety trial included one case of trisomy 18 identified in a 16-week fetus which ended in termination, and one case of renal aplasia identified in a 20-week fetus

On average, the duration of MILPROSA exposure was 40.0 days, with women using an average of 5.8 MILPROSA drug-devices. The majority of discontinuers stopped MILPROSA at 2-3 weeks after treatment initiation. Nearly all women used MILPROSA for at least 23 hours per day and no rings were damaged during insertion or removal.

There were no deaths in Trial 000293. Four women (1.5 percent of all participants) in Trial 000293 experienced serious adverse events (SAE). By MedDRA System Organ Class (SOC) and Preferred Terms (PTs), under pregnancy, puerperium and perinatal conditions there was one case of ectopic pregnancy; under reproductive system and breast disorders, there was one case each of adnexal torsion and rupture ovarian cyst; under psychiatric disorders, there was one case of suicidal ideation.

Adverse events of special interest (AESI) identified included vaginal bleeding/spotting, vaginal pain and irritation, vaginal or cervical abrasions and lesions, vaginal hemorrhage, vaginal infection and vaginal adhesions. The Grading scale for genitourinary and vaginal adverse events was adapted from the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies), dated November 2007. A visual bleeding log was employed as a patient directed measure of vaginal bleeding. This log was adapted from published literature by Wyatt KM and colleagues, entitled Determination of total menstrual blood loss as published in the peer review medical journal Fertility and Sterility volume 76, issue 1, pages 125 to 31, 2001. Refer to Table 11 for a presentation of AESI in Trial 000293. AESI in Trial 000293 are shown in Table 4.

Table 4 Adverse Events of Special Interest Occurring in the Treatment Phase, Trial 000293

System Organ Class	Adverse Event	n	MILPROS A N=254	Number of events
TEAE of Special Interest		5	2.0%	10
Reproductive system and breast disorders	Vaginal hemorrhage	4	1.6%	6
	Vulvovaginal pain	2	0.8%	3
	Cervix lesion	1	0.4%	1

Note: A participant can have more than one event type.

Source: NDA 201110, JMP Analysis Dataset ADAE, accessed February 12, 2020. TEAE=Treatment emergent adverse event.

Given that MILPROSA is a drug-device combination of progesterone in a silicon system intended for commercial vaginal use, it was important to evaluate adverse event potentially resulting from direct contact of the device with the vaginal wall. Observed AESIs included cervicovaginal abrasions lesions, pain and vaginal bleeding. The majority of AESIs were mild in nature. The sponsor reports 2 AESIs were moderate (vulvovaginal pain and vaginal hemorrhage) AESIs and 1 was severe (vaginal hemorrhage). Overall, MILPROSA (progesterone) vaginal system appears to be well-tolerated by women with few vulvovaginal or cervical side effects.

In the safety population, 49% (124/254) of women had 312 treatment emergent adverse events (TEAEs), with 0 events leading to death, 44 events leading to discontinuation in 44 (17%) women, and 53 adverse drug reactions in 25 (10%) women.

TEAEs (occurring in more than 2% of women) are displayed in Table 5.

Table 5 Frequently occurring TEAEs by Participant ($\geq 2\%$ of participants), Trial 000293

System Organ Class	Preferred Term	n	N=254 %
Endocrine disorders	Hypothyroidism	7	2.8
Gastrointestinal disorders	Nausea	22	8.7
	Abdominal pain	22	8.7
	Constipation	9	3.5
	Vomiting	9	3.5
General disorders and administration site conditions	Fatigue	6	2.4
Infections and infestations	Nasopharyngitis	5	2
	Urinary tract infection	5	2
Nervous system disorders	Headache	13	5.1
Pregnancy, puerperium and perinatal conditions	Biochemical pregnancy	25	9.8
	Abortion spontaneous	18	7.1
	Subchorionic hematoma	11	4.3
	Vomiting in pregnancy	7	2.8
Reproductive system and breast disorders	Pelvic pain	8	3.1
	Vaginal discharge	7	2.8
	Ovarian hyperstimulation syndrome	6	2.4

Source: NDA 201110, JMP Analysis Dataset ADAE, accessed February 13, 2020. Note: combined AEs with preferred terms abdominal pain, abdominal discomfort and abdominal pain lower

Overall TEAEs were consistent with other progesterone drug products.

8. Advisory Committee Meeting

Advice from the Bone, Reproductive and Urologic Drugs Advisory Committee was not deemed necessary for a decision on the approvability of this Class 2 NDA Resubmission.

9. Pediatrics

Ferring requested a full pediatric waiver for ages 0-11 (under age 12) and “a waiver is also requested in children 12 to 17 years of age on the grounds studies/trials are impossible or highly impractical.” The Pediatric Research Committee (PeRC)/Pediatric Research Equity Act (PREA) Subcommittee met on May 25, 2016 and PeRC agreed with DBRUP (DUOG) to grant a full waiver in pediatric patients because the disease/condition does not exist in children.

10. Other Relevant Regulatory Issues

Clearance by 505(b)(2) Committee

NDA 201110 was discussed at the April 20, 2020 505(b)(2) clearance meeting. The application was cleared for action from a 505(b)(2) perspective. It was noted that the only literature reliance is that submitted to support Pharmacokinetic ADME information in Section 12.3 of the Full Prescribing Information. There was some discussion of whether there was a broader need for literature reliance to support the nonclinical safety of this application.

DUOG indicated that NDA 201110 represents a novel route of administration and delivery for a well-studied endogenous hormone. Progesterone is produced by the corpus luteum of the ovary following ovulation. It supports early pregnancy until the placenta can produce enough progesterone to maintain the pregnancy. To support the vaginal route of administration, nonclinical studies were conducted in the rabbit to assess the local response of vaginal tissue to the progesterone implant. The uterine and vaginal changes that were observed were deemed due to pharmacologic activity of progesterone. Although literature was submitted to the NDA describing pharmacology and toxicology of progesterone, the nonclinical team did not deem it necessary to support approval of the NDA because the role of progesterone in maintaining pregnancy is well understood, and this product is mimicking the physiological role of progesterone in early pregnancy. The nonclinical literature that was submitted by the applicant covered systemic effect of progesterone in nonclinical species by the oral or injected route of administration, and involve large systemic exposures, which are informative but were not considered relevant for this NDA.

Progesterone is an endogenous hormone produced by the corpus luteum in nonpregnant reproductive women and the placenta in pregnant women. Additionally, clinical experience with exogenous progesterone over many decades has established that progesterone is not fetotoxic. For these reasons, it is not necessary to rely on nonclinical reproductive toxicity studies for approval. Also, total exposure to progesterone from MILPROSA will not exceed 12 weeks, which is below the duration of use that would raise carcinogenicity concerns. For that reason, it is not necessary to have nonclinical data on carcinogenicity of progesterone to approve MILPROSA.

Financial Disclosure

Financial Certification and Disclosures are provided for investigators who participated in Trial 000293. Fourteen (14) Investigators were identified. No investigators had disclosable financial interests/arrangements (Form FDA 3455).

Inspections by the Office of Scientific Investigations (OSI)

Three clinical investigators (CIs): Drs. Park (Site USA09), Schnell (Site USA10) and Slater (Site USA12) were selected for clinical inspections. Drs. Park and Slater were selected because of their relatively high subject enrollments and lack of previous inspection. Dr. Schnell was selected because the site enrolled the largest number of subjects and had the second highest spontaneous abortion rate.

The inspections verified that Ferring Pharmaceutical Inc. submitted clinical data with source records at the CI sites. Only minor issues were found at each clinical site and all three sites appeared to be compliant with Good Clinical Practice (GCP). Based on the results of these CI

inspections, Trial 000293 appears to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the indication.

The following is a high-level summary of the individual site findings:

1. **Dr. John Park, Site USA09**

2601 Lake Drive, Suite 301
Raleigh, NC 27607

This site was inspected on January 15-21, 2020. This was the initial inspection for Dr. Park.

The study site screened a total of 26 women and enrolled 22 women. The records for each of the 22 enrolled women were reviewed. Source records reviewed during the inspection included the study protocol, informed consent forms (ICFs), documentation of eligibility criteria, medical records, adverse events (AEs) and serious adverse events (SAEs), the investigational product (IP) accountability records, visit data, laboratory results, electronic case report forms (eCRF), and related regulatory documents [e.g., institutional review board (IRB) approvals and communications, staff training, financial disclosures and delegation of authority].

The first woman was enrolled on August 14, 2018 and the follow-up on the last woman to be enrolled occurred on July 01, 2019. Nineteen (19) women completed the study and 3 women had abortions (2 women had biochemical abortions and 1 woman had a spontaneous abortion). Of the 19 women who completed the study, 14 women had an ongoing pregnancy at their final study visit and 5 women did not conceive.

The inspection found adequate source documentation for all women, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy data source was verified. There was no evidence of underreporting of AEs or SAEs. In general, this clinical site appeared to be in compliance with Good Clinical Practices (GCP). Data submitted by this clinical site appear acceptable in support of this specific indication. At the end of the inspection, no Form 483 (Inspectional Observations) was issued.

2. **Dr. Vicki Schnell, Site USA10**

1015 Medical Center Blvd., Suite 2100
Webster, TX 77598

This site was inspected on January 21-24, 2020. Dr. Schnell was previously inspected in 2006 and 2010.

For the current study, the site screened a total of 40 women and enrolled 31 women. The records were reviewed for 15 (50%) of the 31 enrolled women. The first woman was enrolled on July 26, 2018

Source records reviewed during the inspection included the study protocol and amendments, ICFs, documentation of eligibility criteria, AEs and SAEs reporting, lab results, the IP accountability records, visit data, laboratory results, eCRF, monitoring

log, and related regulatory documents (e.g., IRB approvals and communications, staff training, financial disclosures and delegation of authority).

The inspection found adequate source documentation for all inspected study participants, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy data source was verified. There was no evidence of underreporting of AEs or SAE.

The inspection identified two protocol deviations which have already been reported in the study report: 1) Subject # (b) (6) had a Menopur dose decrease of 225 IU from 450 IU that exceeded the 150 IU as recommended per protocol on Visit 2; and 2) Subject # (b) (6) received one dose of prohibited medication (aspirin) for non-cardiac chest pain. There were also a couple of subjects with out of window visits. These protocol deviations were discussed with the CI at the end of the inspection.

This clinical site appeared to be in compliance with GCP except the protocol deviations noted above. Data submitted by this clinical site appear acceptable in support of this specific indication. At the end of the inspection, no Form 483 was issued.

This reviewer agrees that the above noted protocol deviations do not affect the reliability of the data collect.

3. Dr. Cristin Slater, Site USA12

1000 E Park Blvd., Suite 110
Boise, ID 83712

The site was inspected on February 3-6, 2020. This was the first inspection for Dr. Slater.

Source records reviewed during the inspection included the study protocol and amendments, ICFs, documentation of eligibility criteria, AE reporting, the IP accountability records, visit data, laboratory results, efficacy endpoint data, eCRF, and related regulatory documents (e.g., IRB approvals and communications, staff training, financial disclosures and delegation of authority).

The study site screened a total of 28 women and all 28 women were enrolled. Nineteen (19) women completed the study. The first woman was enrolled on August 09, 2018 and the last visit for the last woman enrolled occurred on June 11, 2019. Records were reviewed for each of the 19 women who completed the study.

The inspection found adequate source documentation for all women studied, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy data source was verified. There was no evidence of underreporting of AEs.

There were a couple of minor issues identified during inspection. Visit 6 information for Subject # (b) (6) was not signed by the person who recorded the information; and a comment on the eligibility check list for Subject # (b) (6) was not dated. This reviewer

agrees that the above noted minor issues do not affect the reliability of the data collect.

In general, this clinical site appeared to be in compliance with GCP. Data submitted by this clinical site appear acceptable in support of the specific indication. At the end of the inspection, no Form 483 was issued.

Office of Surveillance and Epidemiology (OSE)/Division of Medication Error Prevention and Analysis (DMEPA)

Dr. Justine Kalonia conducted, the Division of Medication Error Prevention and Analysis (DMEPA), archived on March 04, 2020 and March 20, 2020. The review identified areas of the Prescribing Information, Container and Carton labeling and Professional Sample labeling for MILPROSA that could be improved to minimize the risk of medication errors.

The following recommendations, to be implemented prior to approval of the supplement, were provided to the applicant on March 10, 2020.

Container (Pouch) Label and Carton Labeling (for both Trade and Sample):

- The strength statement (11 mg/day) can be improved. The presentation of the strength may not make it clear exactly how much progesterone is expected to be released per day. Revise the strength presentation from “11 mg/day” to read: “releases 11 mg per day”. Consider relocating the revised strength statement to appear directly below the established name.
- Pouch labels and carton labeling do not contain a placeholder for the lot number and expiration date. The lot number and expiration date are required per 21 CFR 01.10(i)(1) and 21 CFR 211.137, respectively. Ensure that the lot number and expiration date are present on the pouch labels and carton labeling in accordance with 21 CFR 201.10(i)(1) and 21 CFR 211.137.
- The format for expiration date is not defined on the pouch labels and carton labeling. Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
- The strength of 11 mg lacks a space between the number and unit of measure (i.e. 11mg) on the pouch labels and carton labeling. Lack of space between numerical dose and unit of measure may contribute to errors. To improve readability, place adequate space between the numerical dose and unit of measure (i.e. 11 mg instead of 11mg) on the pouch labels and carton labeling.
- The “(b) (4)” statement can be improved on the pouch labels and carton labeling. To ensure consistency with Physician Labeling Rule (PLR) formatted Prescribing Information labeling. We recommend you revise the usual dose statement: “(b) (4)”

(b) (4). See complete Prescribing Information” to read: “Recommended Dosage: Insert 1 (b) (4) vaginally and replace every 7 days. See Prescribing Information.”

- The statement “Replace every 7 days” lacks prominence on the pouch labels and carton labeling. We are concerned the statement “replace every 7 days” lacks prominence and may therefore be missed by the patient. Additionally, the patient may forget what day MILPROSA was inserted. Consider increasing the prominence of the instruction to “replace in 7 days” on the pouch labels and the carton labeling (e.g. bold font, larger font, add space between that and other information, etc.). Also, consider implementing strategies to help patients remember when Milprosa was inserted and when it should be removed and replaced (e.g., including a space on the pouch label and carton labeling for the patient to write the date inserted, including reminder stickers). Or, address this concern by other means.

Container (Pouch) Label

- Images of the back of the pouch labels (trade and sample) were not submitted. Clarify if there is information printed on the pouch backing and submit images of the pouch backing label for our evaluation.

Carton Labeling

- As currently presented, there is no product identifier on the trade box carton labeling. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and packagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product’s labeling. ¹The draft guidance is available from: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugsgen/documents/document/ucm621044.pdf>. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product’s labeling. The DSCSA guidance on product identifiers recommends that the human-readable portion be located near the 2D matrix barcode and recommends the following format: NDC: [insert product’s NDC] SERIAL: [insert product’s serial number] LOT: [insert product’s lot number] EXP: [insert product’s expiration date].
- The Prescribing Information labeling instructs not to use other vaginal products with MILPROSA. However, this warning is not conveyed on the carton labeling. We are concerned that users may mistakenly use other vaginal products concurrently with MILPROSA, which may alter the release and absorption of progesterone from the MILPROSA vaginal system. Consider adding a warning to the carton labeling to advise patients against use of other vaginal products with MILPROSA.
- It is unclear whether pouches are intended for individual dispensing. The carton labeling contains important safety information that may not be available to users if pouches are dispensed individually. Clarify whether pouches are intended for individual dispensing or whether they should be dispensed in the sealed carton. If the

later, consider revising the carton labeling to state “Dispense in this sealed carton” on the principal display panel, or address this concern by other means.

- The net quantity statement lacks prominence. May contribute to wrong quantity dispensing errors. Consider improving the readability of the net quantity statement.

In a memorandum dated March 20, 2020, Dr. Kalonia noted:

- The applicant submitted revised container (pouch) labels and carton labeling received on March 17, 2020 for Milprosa (progesterone) vaginal ring. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised pouch labels and carton labeling for Milprosa (progesterone) vaginal ring (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review. The applicant implemented all of our recommendations and we have no additional recommendations at this time.

DUOG agrees with the DMEPA regarding the Ferring response.

The following recommendations were provided from DMEPA to DUOG for its consideration of the Prescribing Information and Patient Information labeling:

Prescribing Information (PI) – Section 1 Indications and Usage:

- Section 2 (Dosage and Administration) states “Efficacy in women 35 years of age and older has not been clearly established.” However, this limitation of use is not described in Section 1 (Indications and Usage) of the PI. The labeling can be optimized to reduce the risk of use in women 35 years of age and older. We defer to the Review Team to determine whether this limitation of use should be moved to Section 1 (Indications and Usage) of the PI.

PI – Section 16 How Supplied/Storage and Handling:

- Section 16 does not list the strength of MILPROSA. Per 21 CFR 201.57(c)(17), Section 16 must contain the strength or potency of the dosage form in metric system. We recommend adding the strength “11 mg/day” to Section 16. For example, may reflect the language used in Section 3: “It releases an average of 11 mg/day of progesterone over a 7- day period of use.”

Instructions for Use (IFU)

- The IFU do not contain information about when to replace the vaginal system. The IFU is missing a description on when it is necessary to remove and replace the vaginal system. We recommend adding this information to the IFU. For example: “replace in 7 days” and “If the vaginal system is expelled, it should be rinsed with cool to lukewarm (not hot) water and reinserted as soon as possible, except if fecally-contaminated. If fecally-contaminated, the vaginal ring should be replaced.”

The above noted DMEPA recommendations were incorporated with or without revisions, as thought to be appropriate, in the final labeling negotiated with the applicant on April 28, 2020.

APPEARS THIS WAY ON ORIGINAL



The Office of Prescription Drug Promotion (OPDP)

In a consult review response, dated April 17, 2020, Jina Kwak, Pharm D. stated that OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DUOG on April 10, 2020 and has no comments for the DUOG or the applicant.

Office of Medical Policy/Division of Medical Policy Programs (DMPP)

Ms. Maria Nguyen, Dr. Marcea Williams and Ms. LaShawn Griffiths from DMPP and Dr. Jina Kwak from OPDP performed a joint review, dated April 17, 2020, of the Patient Information. In general, the intent of their comments was:

- 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.
- 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 and IFU document using the Arial font, size 10.

In DMPP's collaborative review of the Patient Package Insert (PPI) and Instructions for Use (IFU). The reviewers intended to:

- Simplify wording and clarify concepts (for patients) where possible.
- Ensure that the PPI and IFU is consistent with the Prescribing Information (PI).
- Remove unnecessary or redundant information.
- Ensure that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language.
- Ensure that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

DMPP and OPDP recommendations for the final Patient Information and Instructions for use were incorporated with final labeling negotiated with the applicant on March 28, 2019.

11. Labeling

Exchange of labeling recommendations between DUOG and Ferring occurred on the following dates:

- March 10, 2020, the Carton and Container labeling recommendations provided by the DMEDP to Ferring.
- March 17, 2020, Ferring accepts the Agency's Carton and Container labeling recommendations.
- April 9, April 22, April 23, April 24, 2020, and April 27, 2020, DUOG provided labeling recommendations for the Prescribing Information and/or Patient Information to Ferring.

- April 17, April 24 and April 25, 2020, Ferring provided response to DUOG revisions. On April 28, 2020, Ferring responded with Final agreed-to labeling.

Input from OPQ-CMC, Pharmacology and Toxicology, Clinical Pharmacology, Clinical, Biometrics, Office of Prescription Drug Promotion (OPDP), Division of Medication Error Prevention and Analysis (DMEPA) and Division of Medical Policy Programs (DMPP) contributed to the April 28, 2020 final-agreed to labeling.

FDA-Approved Patient Labeling

See recommendations provided by DMPP and OPDP, as provided in **Section 11 of this review**.

Carton and Container Labeling

See recommendations provided by DMEPA for the container and carton labeling as well as the Professional Sample labeling for the (b) (4) strength, as provided in **Section 11 of this review**.

12. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Risk minimization strategies beyond the product labeling were not necessary for this efficacy supplement.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

No Postmarketing Required (PMR) trial were sought. As specified in both the February 28, 2011 and the November 23, 2016 Complete Response letters, Postmarketing Commitment (PMC) for a safety and efficacy trial of MILPROSA in women 35 to 42 years of age was sought for approval of this Class 2 NDA Resubmission.

On April 28, 2020, the following was provided to Ferring:

As indicated to you in our February 28, 2011 and our November 23, 2016 Complete Response letters, along with appropriate labeling, including a limitation of use statement, a postmarketing commitment to conduct a prospective, randomized, appropriately-blinded, concurrent- and parallel-arm, active-controlled, U.S. clinical trial to evaluate efficacy and safety of your product in women 35 to 42 years, will be sufficient to support approval of MILPROSA (progesterone vaginal system) for use in women 34 years of age and under. Therefore, we request that you agree to the following postmarketing commitment by close of business today:

“Conduct a prospective, randomized, appropriately-blinded, concurrent- and parallel-arm, active-controlled, U.S. clinical trial to evaluate efficacy and safety of MILPROSA in women 35 to 42 years”

The trial should be adequately powered to demonstrate sufficient retention of efficacy in the MILPROSA arm when compared to the active comparator arm. Details of the trial

should be agreed upon with the Agency prior to conduct of the trial. You will need to address this commitment and timetable for draft protocol submission, final protocol submission, study completion, and submission of final report for the postmarketing commitment trial described within a reasonable timeframe.”

The exact language of the PMC will be included in the decisional letter.

13. Recommended Comments to the Applicant

Chemistry, manufacturing and control, biocompatibility, and clinical approvability deficiencies identified in Cycle 1 and Cycle 2 of this NDA review have all been adequately addressed with exception of the recommendation to conduct, prior to approval, a randomized, active-controlled clinical trial to evaluate the efficacy of the progesterone vaginal system in women 35-42 years of age. The trial should be adequately powered to demonstrate sufficient retention of efficacy in the progesterone vaginal ring arm when compared to the active comparator. Instead, the applicant has decided to accept the alternative path forward of accepting appropriate labeling for use in women less than 35 years of age, which includes a statement on limitation of use, and agree to a postmarketing commitment to conduct the recommended clinical trial. The following Postmarketing Commitment was agreed to:

“Conduct a prospective, randomized, appropriately-blinded, concurrent- and parallel-arm, active-controlled, U.S. clinical trial to evaluate efficacy and safety of MILPROSA in women 35 to 42 years”

The trial should be adequately powered to demonstrate sufficient retention of efficacy in the MILPROSA arm when compared to the active comparator arm. Details of the trial should be agreed upon with the Agency prior to conduct of the trial. You will need to address this commitment and timetable for draft protocol submission, final protocol submission, study completion, and submission of final report for the postmarketing commitment trial described within a reasonable timeframe.”

Consistent with the approvability recommendation of all review disciplines participating in the review of this Class 2 NDA Resubmission, I recommend that NDA 201110 for MILPROSA (progesterone) vaginal system be approved.

Appendix I – Recommended Prescribing Information and Patient Information

12 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/

SHELLEY R SLAUGHTER
04/29/2020 09:11:29 AM

CHRISTINE P NGUYEN
04/29/2020 09:19:23 AM