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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Clinical Review

Regina Zopf, MD, MPH

NDA 201110

MILPROSA (Progesterone vaginal ring/Progesterone, USP, (b) (4))

CLINICAL REVIEW

Application Type	505(b)(2) NDA Resubmission (Class 2)
Application Number(s)	201110
Priority or Standard	Priority
Submit Date(s)	October 29, 2019
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Division/Office	Division of Urology, Obstetrics and Gynecology [(DUOG), formerly the Division of Bone, Reproductive and Urology (DBRUP)]
Reviewer Name(s)	Regina Zopf, MD, MPH
Review Completion Date	April 24, 2020
Established/Proper Name	Progesterone vaginal ring/Progesterone, USP, (b) (4)
(Proposed) Trade Name	MILPROSA
Applicant	Ferring Pharmaceutical, Inc
Dosage Form(s)	Vaginal ring
Applicant Proposed Dosing Regimen(s)	One vaginal system inserted starting the day after oocyte retrieval, replaced weekly, continuing for up to 10 weeks total duration
Applicant Proposed Indication(s)/Population(s)	To support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteum function as part of an Assisted Reproductive Technology (ART) treatment for infertile women (under age 35)
Recommendation on Regulatory Action	APPROVAL
Recommended Population	Infertile women under the age of 35 who are undergoing ART

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
ART	assisted reproductive technology
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
DMEPA	Division of Medication Error and Prevention Analysis
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GnRH	Gonadotropin releasing hormone
GRMP	good review management practice
ICH	International Council for Harmonization
ICSI	Intracytoplasmic sperm injection
IM	Intramuscular
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety

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ITT	intent to treat
IVF	In vitro fertility
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAB	spontaneous abortion
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

MILPROSA (Progesterone vaginal ring/Progesterone, USP, (b) (4)) is combination drug-device product consisting of a flexible silicone vaginal system containing (b) (4) progesterone, as the active drug ingredient. MILPROSA is in the established pharmacologic class of progesterone. A previous (b) (4) progesterone product, vaginal gel, is approved as an adjunctive treatment for infertility of couples using Assisted Reproductive Technology (ART) such as invitro fertilization (IVF) to achieve pregnancy. For the proposed indication “To support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteum function as part of an Assisted Reproductive Technology (ART) treatment for infertile women (under age 35)”, the dosing regimen is one vaginal system (ring) placed weekly. Infertility is a worldwide problem affecting 20 percent of couples worldwide.

There are currently two approved progesterone products, Crinone and Endometrin, labeled to support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteal function as part of ART treatment for infertile women or progesterone replacement. Other progesterone products approved for different and unrelated indications are used off label for these indications (see Table 1) If approved, MILPROSA will be the first (b) (4) progesterone product delivered in the form of an intravaginal system in the United States.

The Division of Medication Error and Prevention Analysis (DMEPA) found the proprietary name, MILPROSA, to be acceptable (see DMEPA reviews in DARRTS archive dated February 2, 2011, March 10, 2016, and January 24, 2020).

This is the third review cycle for MILPROSA (NDA 201110). Following the first review cycle of the original New Drug Application submitted by Teva Women's Health Inc. on April 30, 2010, the application received a complete response due to failure to demonstrate in the phase 3 trial, efficacy in women ages 35 to 42 years of age as well as quality concerns related to (b) (4) particulate matter (b) (4) of the MILPROSA vaginal ring. The original (b) (4) process was thought to be responsible for the latter and a new (b) (4) process was developed by the sponsor. Teva Branded Pharmaceutical Products R&D, Inc. submitted the trial report for “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” to support the change in (b) (4) process. The Office of Clinical Pharmacology reviewed the trial report (see DARRTS archive September 7, 2016) and determined that bioequivalence of the new to-be marketed ring was established and would therefore bridge to the efficacy data of

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the original pivotal clinical trial to the to-be-marketed MILPROSA. After assuming ownership of MILPROSA (NDA 201110), Ferring Pharmaceuticals, Inc. submitted a Class 2 NDA resubmission on February 25, 2016, to address deficiencies listed in the original submission Complete Response letter, including particulate materials in the to-be-marketed product and failure to demonstrate efficacy of the progesterone vaginal system in women 35 to 42 years of age. The applicant proposed acceptance of a limitation of use in labeling, restricting the use of the MILPROSA vaginal system to the population of women evaluated, women less than age 35 and introduced a new (b) (4) method. On November 23, 2016, the Agency issued a Complete Response letter because of insufficient biocompatibility information to support permanent contact duration (cumulative single, multiple or repeated long-term use or contact exceeds 30 days) of the revised to-be-marketed MILPROSA and the need for an adequate clinical safety bridge between their legacy MILPROSA and the to-be-marketed MILPROSA. Subsequent to the second Complete Response determination, CDRH determined that biocompatibility testing was adequate and that Ferring Pharmaceuticals, Inc. had resolved MILPROSA quality issues (See consults in DARRTS archive dates December 13, 2016 and July 7, 2017).

On October 29, 2019, Ferring made a class 2 resubmission of NDA 20110 to address the need for an adequate clinical safety bridge to the new (b) (4) process of the to-be-marketed MILPROSA. Herein, the applicant submits results of a clinical safety trial with the intent of establishing a clinical safety bridge to phase 3 pivotal trial data for the to-be-marketed MILPROSA (progesterone vagina ring) for the indication, “to support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteum function as part of an Assisted Reproductive Technology (ART) treatment for infertile women (under age 35)”.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant has not submitted new phase 3 clinical trial data with this NDA resubmission. In the preliminary NDA submission, the clinical reviewer concluded that MILPROSA is efficacious in a subgroup of women less than 35 years of age (see DARRTS archive dated December 1, 2010). Trial SRR-PGN-302 was not sufficiently powered to conclude that MILPROSA is efficacious in women 35-42 years of age. Efficacy of MILPROSA in the older population cannot be extrapolated from that of the younger population. The applicant previously communicated their intent to perform a postmarketing trial powered to evaluate efficacy in women 35-42 years of age.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Infertility affects 15% of couples in the United States and can have emotionally devastating impacts on women and their families. Assisted Reproductive Technology (ART) including in vitro fertilization (IVF) and IVF plus intracytoplasmic sperm injection (ICSI) offer women/couples the opportunity to improve their chances of conceiving. Progesterone supplementation to support the luteal phase and early pregnancy (up to 10 weeks gestation) following IVF cycle and subsequent embryo transfer is necessary when a gonadotropin releasing hormone (GnRH) agonist has been used for pituitary suppression. Progesterone is currently available in 1) an oil for single injection, as needed (though not approved for the indication), 2) a vaginal gel for daily use or 3) a vaginal insert for daily use. MILPROSA provides for progesterone supplementation in the luteal phase and early pregnancy via local vaginal delivery from a silicon ring placed once weekly. This product may be of 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.

The risks associated with the use of some progestogens, primarily progestins, are well-defined with possible increases in the risk of stroke, myocardial infarction, deep vein thrombosis, and invasive breast cancer when used in conjunction with estrogens for hormone therapy. The overall risk of these serious outcomes is low as defined by the Women's Health Initiative trial of conjugated estrogens and conjugated estrogens plus progestins (2002). The risk profile associated with (b) (4) progesterone, including MILPROSA, may differ. Given that MILPROSA is a progesterone product, with shorter duration of use and potential lower level of serum exposure, the associated risk profile is expected to be different; however, 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.

Based on current evidence, the risk benefit profile of MILPROSA appears favorable. I recommend approval of MILPROSA for the proposed indication in women under 35 years of age.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Infertility is generally defined as 12 months of attempting to conceive without success in couples where the woman is less than 35 years of age. • The prevalence of infertility in couples in the United States is 15%. • 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. • Women ages 35-42, with an average age of 36 years, comprise 60% of women undergoing Assisted Reproductive Technology (ART) to attain pregnancy. • Progesterone is needed to support early pregnancy (up to 10 weeks gestation). Following the use of GnRH agonists for pituitary down-regulation as a part of an ART cycle with controlled ovarian stimulation (with menotropins, and/or gonadotropins,) there is resultant iatrogenic “luteal phase defect” characterized by low levels of progesterone.	Progesterone supplementation is necessary to attain pregnancy in women undergoing an ART cycle where GnRH agonist has been used to down-regulate the pituitary.
Current Treatment Options	• Progesterone is available as an FDA approved adjunctive therapy for women undergoing ART to attain pregnancy. ▪ (b) (4) progesterone is available in the following forms: - o Gel - o Vaginal insert • Progesterone in oil for intramuscular (IM) injection is used off-label for this purpose.	Progesterone is commercially available in the form of a gel, vaginal tablet or IM injection for women undergoing ART.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Progesterone administered as part of ART treatment provides support for embryo implantation and maintenance of early pregnancy in women undergoing ART who have also received pituitary-down regulation.	Progesterone is an FDA approved adjunctive treatment for progesterone supplementation as part of ART treatment for infertile women with progesterone deficiency.
Risk and Risk Management	• Progesterone products have been previously labeled as Contraindicated in women with liver disease, active or previous arterial or venous thromboembolism, known or suspected breast cancer, known missed abortion or ectopic pregnancy. • Labeled Warnings and Precautions indicate that progesterone should be discontinued if women have signs of myocardial infarction, cerebrovascular disorders, arterial or venous thromboembolism (venous thromboembolism or pulmonary embolism), thrombophlebitis, or retinal thrombosis. • Risks associated with synthetic progestin (note MILPROSA contains progesterone) use are well-defined with possible increases in the risk of stroke, myocardial infarction (MI), deep vein thrombosis, and invasive breast cancer. The Women's Health Initiative (WHI) estrogen plus progestin sub-study reported increased risks of deep vein thrombosis, pulmonary embolism, stroke and myocardial infarction in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg] combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo. The WHI estrogen plus progestin sub-study also demonstrated an increased risk of invasive breast cancer. The overall risk of these severe outcomes remains low as defined by the Women's Health Initiative study (2002). The WHI studied only one	The risk: benefit profile of short-term use of progesterone for the proposed indication appears to be acceptable in women less than 35 years of age.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	estrogen, conjugated estrogen (CE), and one estrogen plus progestin combination, CE plus medroxyprogesterone acetate (MPA) It is not known whether results of the WHI are applicable to other estrogens, other estrogen plus progestin/progestogen combinations and other dosages. • There is insufficient long-term safety information with exogenously administered progesterone to adequately characterized long-term risk. • Common side effects associated with short term progesterone use 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. • IM progesterone can be painful and associated with cellulitis, abscess and cannot be self-administered.	

1.4. Patient Experience Data

The applicant did not submit new patient experience data in this review cycle. In the original NDA submission, the applicant reported results from a Post-Trial Experience Questionnaire which was a questionnaire to measure satisfaction with treatment with progesterone; the questionnaire was administered to women post-pregnancy over the phone (See Table 1). Results were not reviewed in the original clinical review and are therefore reviewed briefly here. A copy of a sample questionnaire can be found in the Appendix of this review [Section 13.3].

The Post-Trial Experience Questionnaire data was collected on women from the safety population in MILPROSA and Crinone 8% arms. Results were similar between arms in most parameters of the questionnaire, however there were differences in women's experiences related to 1) the self-administration of MILPROSA and 2) notation by the woman or her partner of being "bothered" by the use of Crinone during intercourse .

A summary of the results shows that, the majority of women (~95%) reported that it was easy or somewhat easy to learn to use, remember, and use the progesterone medication as prescribed. The overall majority (~95%) reported that it was 'not a problem' or 'a little problem' to take the progesterone medication during daily activities, travel, allow for time to take the medication, or to store the medication. More women (8%) using MILPROSA found that it was 'somewhat', 'quite a bit' or 'a lot of a problem' to apply or administer the progesterone medication themselves vs. women using Crinone (1.3%). The majority of women in both MILPROSA and Crinone (~95%) arms found that it was a 'little stressful' or 'stressful' to remember to take the progesterone medication, use at the correct time, not forget, and use the correct number of times. However, more women using MILPROSA (7.2%) found that it was stressful to give themselves the progesterone medication versus women using Crinone (0.7%). Of women having intercourse, women using MILPROSA, 89% were 'not at all bothered' or a 'little bothered' by the progesterone medication as compared to 65% of women using Crinone. Women using Crinone and their partners were more likely to report being 'somewhat bothered' or more during intercourse with the progesterone medication than women using MILPROSA (35% versus 10%). More women using Crinone (19.5%) reported that the progesterone medication interfered with sexual comfort 'somewhat', 'quite a bit,' or 'a lot' than women using MILPROSA (7.7%). More women using Crinone (22.8%) also reported that the progesterone medication interfered with sexual desire 'somewhat', 'quite a bit', or a 'lot' compared to women using MILPROSA (12.3%). The majority of women (over 85%) in both arms reported that the progesterone medication did not interfere with daily activities, social or work/professional life.

Reviewer's Comment:

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The patient experience questionnaire is not a validated measure and will not be included in labeling. The majority of the patient experience questions reveal that the patient experience is similar with use of MILPROSA as compared to Crinone. Where they differ, the results reveal that while it may be slightly more stressful for women to self-administer MILPROSA as compared to Crinone, women having intercourse reported being less bothered by MILPROSA than Crinone.

Table 1 Patient Experience Data Relevant to this Application

☒	The patient experience data that was submitted as part of the application include:		Section where discussed, if applicable
☒	Clinical outcome assessment (COA) data, such as		
☐	Patient reported outcome (PRO)		
☐	Observer reported outcome (ObsRO)		
☐	Clinician reported outcome (ClinRO)		
☐	Performance outcome (PerfO)		
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
☐	Patient-focused drug development or other stakeholder meeting summary reports		
☒	Observational survey studies designed to capture patient experience data		See summary review of patient experience data [Section 1.4], and sample questionnaire [Section 13.3].
☐	Natural history studies		
☐	Patient preference studies (e.g., submitted studies or scientific publications)		
☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:		
☐	Input informed from participation in meetings with patient stakeholders		
☐	Patient-focused drug development or other stakeholder meeting summary reports		
☐	Observational survey studies designed to capture patient experience data		
☐	Other: (Please specify)		
☐	Patient experience data was not submitted as part of this application.		

2. Therapeutic Context

2.1. Analysis of Condition

Infertility is defined as the inability of a couple to conceive after 12 months of regular intercourse in women less than 35 years of age; and after six months of intercourse in women 35 years of age or older.¹ The prevalence of infertility in the US has been estimated in the National Survey of Family Growth (NSFG) as 6 percent when measured between 2006 and 2010. The incidence of infertility ranges from 12 to 18 percent.² There are many etiologies that can lead to infertility in couples and individuals, including factors attributed to the male and those attributed to the female or both. The incidence of infertility increases with advanced age of primarily the woman. Infertility can be emotionally devastating for couples or individuals that wish to have children.

Medical advances have been made in the field of ART to assist couples and individuals in attaining pregnancy. Progesterone is normally produced by the corpus luteum up to approximately 10 weeks of pregnancy when the placenta takes over progesterone production. In women undergoing treatment of infertility with ART, serum progesterone levels are lower than those needed to sustain implantation and continuation of pregnancy. GnRH, given as part of ART cycles result in a desensitization of the pituitary. This precludes normal function of the corpus luteum and leads to an iatrogenic “luteal phase defect” with lower than normal serum levels of progesterone. For women undergoing ART to attain pregnancy with procedures such as IVF/ICSI, treatment with progesterone is a well-established practice to improve rates of embryo implantation and to sustain early pregnancy.

2.2. Analysis of Current Treatment Options

FDA approved products for progesterone luteal supplementation as part of an ART regimen are currently available as (b) (4) progesterone in gel or vaginal insert form (Crinone and Endometrin). Progesterone in oil and Prometrium (vaginal insert containing (b) (4))

¹ Definitions of infertility and recurrent pregnancy loss. Fertil Steril. 2008 Nov;90(5 Suppl):S60. doi: 10.1016/j.fertnstert.2008.08.065. PubMed PMID: 19007647.

² Thoma ME, McLain AC, Louis JF, King RB, Trumble AC, Sundaram R, Buck Louis GM. Prevalence of infertility in the United States as estimated by the current duration approach and a traditional constructed approach. Fertil Steril. 2013 Apr;99(5):1324-1331.e1. doi: 10.1016/j.fertnstert.2012.11.037. Epub 2013 Jan 3. PubMed PMID: 23290741; PubMed Central PMCID: PMC3615032.

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progesterone) are both available as approved products which are used but are unlabeled for this indication. Refer to Table 2.

Progesterone products are administered from daily to up to three times daily. The injected form of progesterone in oil can be a very painful injection and is associated with injection site cellulitis. Additionally, it is less convenient to administer by women themselves. Per the applicant, MILPROSA offers the added convenience and ease of use over previously approved products because progesterone is delivered via a self-administered vaginal system placed once weekly. It may however, be associated with more vaginal discomfort than available therapies which may vary based on an individual woman's vaginal length and caliber.

Common side effects associated with available progesterone products are nausea, abdominal pain, breast tenderness, headache, abdominal distension, vaginal discharge, and non-specific muscle spasms. Warnings and precautions related to the pharmacologic activity of progestins include severe allergic reactions which may include anaphylaxis and anaphylactoid reactions. The most concerning serious adverse events (SAEs) associated with progesterone use are anaphylaxis, anaphylactoid reactions, and the discontinuation rate resulting from allergic reactions. These SAEs could potentially result in premature termination of treatment, and thus adversely affect clinical pregnancy outcome.

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Table 2 Products Used for the Proposed Indication

Products Approved for Progesterone Supplementation or Embryo implantation and Early Pregnancy Support						
Drug Name	Active Ingredient	Strength	Dosage (Form/Route)	Indication	Company	Date of Approval
Endometrin® NDA 22057	Micronized Progesterone	100 mg	Twice or Three Times Daily as a Vaginal Insert	Support embryo implantation and early pregnancy	Ferring Pharmaceuticals, Inc.	5/21/07
Crinone® 80%	Micronized Progesterone	90 mg	Once Daily as a Vaginal Gel	Progesterone supplementation or	Allergan Sales, LLC	5/13/77
Products Used Off-Label for Support of the Luteal Phase, or Implantation and Early Pregnancy Support						
Progesterone NDA 017362 (off label use)	Progesterone in oil	50 mg	Once Daily Intramuscular (IM)	Amenorrhea and abnormal uterine bleeding	Watson Labs	5/11/78
Prometrium® NDA 019781 NDA 020843 (off label use)	Oral Micronized Progesterone	200 mg	Three Times Daily as a Vaginal Tablet	Prevention of endometrial hyperplasia and secondary amenorrhea	Vitrus Pharmaceuticals	5/14/85
Prometrium® NDA 020843 (off label use)	Oral Micronized Progesterone	200 mg	Three Times Daily as a Vaginal Tablet	Prevention of endometrial hyperplasia and secondary amenorrhea	Abbvie, Inc.	12/16/98

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This is the third review cycle for the MILPROSA NDA. NDA 201110 for progesterone vaginal system was submitted on April 30, 2010, by Teva Women's Health Inc., a subsidiary of Teva Branded Pharmaceutical Products R&D, Inc. The Agency issued a Complete Response letter on February 28, 2011, followed by a General Advice letter on March 4, 2011. Ownership of NDA 201110 was transferred from Teva Branded Pharmaceuticals to Ferring Pharmaceuticals Inc. on August 5, 2015. A Class 2 Resubmission to address deficiencies listed in the original submission Complete Response letter (including particulate materials in the to-be-marketed product and failure to demonstrate efficacy of the progesterone vaginal system in women 35 to 42 years of age), was received from Ferring Pharmaceuticals on February 25, 2016. The applicant determined that the (b) (4) defects in the previously proposed to-be-marketed product was due to the (b) (4) process, which utilized (b) (4). To address this issue, the applicant replaced the (b) (4) process (legacy process) with a (b) (4) process (revised to-be-marketed process). The applicant also proposed to accept a limitation of use in labeling, restricting the use of the progesterone vaginal system to the population of women evaluated, women less than age 35. Bioequivalence of the new to-be-marketed ring to the legacy ring was established for efficacy data.

On November 23, 2016, a Complete Response letter was issued because of insufficient biocompatibility information to support permanent contact duration (cumulative single, multiple or repeated long-term use or contact exceeds 30 days) of the revised to-be-marketed progesterone vaginal ring. The Complete Response letter also advised that the applicant had not established an adequate clinical safety bridge between their legacy progesterone vaginal system used in the phase 3 clinical trials and their revised (new (b) (4) process) progesterone vaginal system product. The applicant was further advised to conduct a clinical trial to evaluate the clinical safety and tolerability of the revised to-be-marketed progesterone vaginal system over the entire duration of treatment (up to 10 weeks post-embryo transfer) in women who are undergoing Assisted Reproductive Technology (ART) procedures. Additional biocompatibility data of the to-be-marketed ring was also required to support approval prior to completing the clinical safety trial. Following the applicant's submission of biocompatibility test results, DBRUP communicated that there was no biocompatibility safety signal that would impact the design of the proposed clinical safety study and that biocompatibility testing requirements according to current CDRH guidance were met.

The current review cycle began with the class 2 resubmission of NDA 201110 on October 29, 2019. Herein, the applicant submits results of a clinical safety trial with the intent of

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establishing a clinical safety bridge to the to-be-marketed MILPROSA (progesterone vagina ring).

3.2. Summary of Pre-submission/Submission Regulatory Activity

The Agency's involvement in the drug development program for the progesterone vaginal system began in 2004. Since that time, there have been numerous meetings and written communications between the Applicant and the Agency. The following is an abbreviated summary of the regulatory history of the progesterone vaginal system presented in chronological order:

- October 7, 2004: Duramed Original Submission of IND 70875

A phase I single dose pharmacokinetic protocol for a vaginal system containing (b) (4) gm progesterone with a release rate of (b) (4) mg/day when used over a 1-week period

- December 7, 2004: Agency Advice Letter

The Division of Bone, Urologic, and Reproductive Products [(DBRUP) now the Division of Urology, Obstetrics and Gynecology (DUOG)] had the following recommendations:

- Choose progesterone doses that reach a pre-determined optimal serum progesterone level for the desired effect in phase 2 and 3 studies.
 - Duramed did not justify the dose selected in clinical studies. Thus, the Division expressed concern that the sponsor may not have evaluated adequate dose ranging in phase I.
- Women who require (b) (4) (b) (4) progesterone supplementation as part of in vitro fertilization (IVF). Therefore, progesterone treatment regimens (b) (4) .
 - Progesterone (b) (4) (b) (4) supplementation in IVF (b) (4) (b) (4)
 - Clinical trial data is necessary to support (b) (4) .
- The trial should include women up to 42 years of age.
 - Randomization and analyses should be stratified and powered by ovarian reserve as measured by Day 3 serum FSH and age of female partner.
 - Further sub-stratification of data based on BMI, type of insemination,

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and infertility diagnosis should be performed.

- o Studies should be powered to accommodate stratification.
- The primary endpoint should be clinical pregnancy as defined presence of a gestational sac and fetal heart beat beginning at six weeks following embryo transfer (ET).
- March 7, 2007: Agency Advice Letter
 - DBRUP reiterated concerns regarding the proposed single dose of (b) (4) mg progesterone/day for the progesterone vaginal ring. The dose is not well justified and may not be sufficient.
 - o Evaluate at least 2 dose levels of progesterone.
 - Progesterone (b) (4) supplementation (treating women undergoing assisted reproductive technology (ART) procedures, (b) (4))
- June 13, 2007: Type B End of Phase 2 (E-O-P 2) Meeting
 - The applicant initially proposed a progesterone-containing, silicone ring drug delivery system with an average in vitro release rate of (b) (4) mg progesterone/day. The applicant later changed the drug delivery system to decrease the in vivo release rate to an estimated (b) (4) when inserted vaginally for seven days.
 - Although the applicant reported that “its product provides the maximum amount at a consistent reliable dosing compared to the approved products, continued to stress that the applicant had not provided sufficient dose finding evidence to proceed into Phase 3.
 - The applicant proposed (b) (4) Trial DR-PGN-301 for luteal phase supplementation in IVF.
 - DBRUP recommended the following:
 - o The sponsor can proceed into phase 3 at their own risk.

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(b) (4)

- o The phase 3 trial should be double-blind or, at a minimum, the investigator and ultrasonographer should be blinded.
- o The primary efficacy analysis should be based on a two-sided 95% confidence interval.
 - It should include all subjects who completed oocyte retrieval and received at least one dose of progesterone (m-ITT cohort).
- o The sponsor's proposed lower non-inferiority (NI) limit of (b) (4) % is not acceptable for the progesterone vaginal ring. The NI limit for the Phase 3 trial should be equal to or greater than -10% of a two-sided 95% confidence interval (CI) when compared to an active progesterone comparator.
- o Report the percentages of the difference of the lower limit of the 95% CIs to the first decimal place.
- o The efficacy trial, in support of the progesterone vaginal ring, should demonstrate that its efficacy will be comparable to the 33% clinical pregnancy rate for fresh embryos as reported by the Centers for Disease Control (CDC) in 2004.
- o Stratify and power randomization and analyses by ovarian reserve [Day 3 follicle stimulating hormone (FSH) and age of female partner (<35 and 35-42 years of age)].
 - Further sub-stratification of data by BMI, type of insemination [IVF or intracytoplasmic sperm injection (ICSI)], and infertility diagnosis.
 - The analysis of sub-stratification data can be descriptive.
 - If specific claims are sought regarding sub-stratification groups, power studies to demonstrate differences in these groups.
 - Measure ovarian reserve at a central laboratory.
 - Evaluate serum FSH level on Days 2, 3, or 4. Exclude women with Day 2, 3, or 4 serum FSH levels ≥ 15 from the trial.
- o ART practices are significantly different in non-North American countries.

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Therefore, if one trial is performed for this indication, all sites should be U.S. sites, or the majority of women should be treated at U.S. sites.

- o Claims for Quality of life (QOL) are only acceptable if based on development of a validated instrument. Refer to the guidance entitled, "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims."
- October 29, 2007: Special Protocol Assessment (SPA) Request
- December 13, 2007: SPA Non-Agreement letter DBRUP made the following recommendations:
 - The recommended indication for the vaginal is: Progesterone vaginal system is a progesterone-containing device and is indicated to support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteum function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women.



- As practices of ART are significantly different in North American countries compared to Non-North American countries, the majority of women treated in the primary efficacy and safety trial should be from the US or Canada.
- DBRUP continued to express concerns that the proposed single dose of 14 mg/day (b) (4) for the progesterone vaginal system is not well supported. Therefore, if the sponsor proceeds with this single 14 mg/day dose, it is at their risk of failure to determine efficacy for this product.
- As randomization is planned after oocyte retrieval, the pregnancy rate will be calculated per retrieval. This will be clearly delineated in labeling.
- There may be significant differences in pregnancy rates when comparing subjects who have received embryo transfer on Day 3 compared to Day 5. To eliminate variability, we recommend using only Day 3 ET for this trial.

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- DBRUP made the following efficacy and statistical recommendations:
 - Assess the co-primary endpoints of viable pregnancy with documented fetal heartbeat at both, six weeks and ten weeks post-ET.
 - The analysis should be a non-inferiority comparison to Crinone®, which excludes a difference of greater than -10% in favor of Crinone®.
 - Stratify and power the primary analyses by ovarian reserve as measured by Day 3 serum FSH and age of women (age < 35 years and age > 35-42 years).
 - Further sub-stratification of data by BMI, type of insemination [IVF or intracytoplasmic sperm injection (ICSI)], and infertility diagnosis.
 - The analysis of sub-stratification data can be descriptive.
 - We recommend using only Day 3 embryo transfers. However, if both, Day 3 and Day 5 ETs are performed, sub-stratify based on transfer dates. If claims regarding these sub-groups are sought, power studies to demonstrate differences in these groups.
 - Provide a secondary analysis of the efficacy of progesterone that includes the clinical pregnancy rate in all subjects who initiated ovarian stimulation using gonadotropins prior to progesterone therapy (a per cycle analysis).
 - Report percentages of the difference between the confidence intervals to the first decimal point.
 - Results of the “Treatment Satisfaction Measure” questionnaire are considered exploratory and; therefore, are not acceptable for the purposes of labeling.
- Standardize the classification (grading) of ovarian hyperstimulation syndrome (OHSS) as an adverse event to allow standardization of reporting across sites.
 - Women, who require paracentesis as a result of OHSS, are classified as having severe OHSS.
- Calculate the rate of birth defects, in this trial, per live-birth for each treatment group.
- When reporting adverse events, use a single preferred term for all women with vulvovaginal candidiasis.
- December 13, 2007: Duramed’s Revised SPA Protocol Submission:
 - Enroll women 18 -42 years of age.

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- Stratify by age groups <35 and 35 – 42 years.
- Power the trial to demonstrate non-inferiority compared to Crinone® for women 35 – 42 years of age.
- Provide two efficacy analyses for the following groups:
 - Older age group (35 -42 years of age)
 - Entire trial population
- Provide descriptive summary analyses for women with FSH levels <10 IU/L and 10 – 15IU/L
- January 11, 2008: Agency SPA Non-Agreement/Advice Letter DBRUP response to Duramed's December 13, 2007 proposal included:
 - Stratify and power the trial for two age groups, 18 -34 and 35 – 42.
 - Base the primary efficacy analyses on the two age subgroups.
 - Perform a secondary sub-group analysis for women with a serum FSH<10 IU/L and FSH 10 – 15 IU/L.
 - DBRUP did not agree with an eligibility criterion to exclude women > 35 years of age with less than 2 oocytes retrieved. Eligibility criterion should be the same for all women. Women, who do not have any oocytes retrieved, should not be eligible to participate.
- August 27, 2008: Agency SPA Non-Agreement/Advice Letter
 - DBRUP does not agree that a trial powered only to demonstrate efficacy in a population of women <35 years of age is adequate for an indication of support of embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an ART treatment program for infertile women.
 - The proposed trial will not adequately address efficacy and safety in women > 35 years of age. Therefore, it is not acceptable if the sample size for this subgroup of older women is underpowered for assessing efficacy of the progesterone vaginal ring.
 - The Division is open to further discussion regarding powering Trial Dr- PGN-302 that would allow informative labeling for both age subgroups.
 - PK data from Trial 10716222 is for evidence of bioavailability, and not to infer efficacy or safety of DR-2011 in the target population.

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- March 3, 2009: Agency Advice Letter
 - Study DR-PGN-302 only has 200 subjects aged 35 – 42 years of age; and is therefore, is not adequately powered to assess efficacy in this population.
 - We continue to strongly recommend that randomization and primary analyses be stratified and powered for ovarian reserve as assessed by age (< 35 years and 35 – 42 years of age).
- June 16, 2009: Type B Clinical Pre-NDA Meeting
 - DBRUP indicated that, on multiple occasions since the June 13, 2007 EOP2 Type B Meeting, it had recommended that the phase 3 trial be stratified and powered to demonstrate efficacy in both, age groups < 35 years of age and 35 -42 years of age.
 - Duramed acknowledged the Division's recommendation to power the pivotal trial(s) to demonstrate efficacy in both age groups, women <35 years of age and women 35 – 42 years of age. However, due to internal constraints, they chose to power the trial only for women <35 years of age.
 - The sponsor noted an approved product whose primary trial was only powered for women <35 years of age.
 - Duramed would consider conducting a separate trial in women aged 35 - 42 years.
 - The Division continues to have concern regarding the formulation of DR- 2011- proegesterone vaginal system (release rate of 14 mg/day of progesterone) providing insufficient progesterone for supplementation of corpus luteum function and maintenance of early pregnancy.
 - The sponsor initially stated that progesterone vaginal system (DR-2011) has a release rate of (b) (4) mg/day. It was subsequently changed (b) (4) to 14 mg/day. It is not clear why the release rate changed without a reported corresponding change in formulation composition.
 - Release rate calculations should be based on the residual amount of progesterone remaining in DR-2011 following vaginal placement of the ring for 7 days.
 - The NDA should address the release rate changes.
 - The sponsor emphasized that the vaginal system design accommodates the maximum amount of progesterone possible; and the release rate is at the maximum.
 - DBRUP requested an additional safety table of women with OHSS categorized by

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- severity (mild, moderate, severe) using standardized criteria. They also asked the Sponsor to provide the definitions used to classify OHSS.
- DBRUP advised the sponsor that it was not in a position to determine whether the aforementioned studies are appropriate to be filed. This determination depends on results of the Division's review at the time of submission.
 - DBRUP reiterated its concern regarding the limited information for women in the older age group, 35 – 42 years of age.
- October 27, 2009: Type B Chemistry, Manufacturing and Control (CMC) pre-NDA Meeting
 - DBRUP informed the sponsor that the planned CMC information for Modules 2 and 3 appears adequate to file from the CMC standpoint.
 - DBRUP agreed agrees that the release data show no significant difference between the phase 3 clinical trial materials and the transfer batches. However, the stability data for all batches will need to be reviewed before we can agree that there is no meaningful difference with regard to the quality of the Progesterone Vaginal Rings manufactured at different facilities.
 - The sponsor provided a slide presentation outlining the manufacturing process. Per the sponsor, there have been no formulation changes from the phase 2 clinical trials to the proposed commercial product and the process is at the same scale (b) (4)
(b) (4)
 - For the current acceptance criteria and stability studies, DBRUP requested that the additional drug release time points (Days 9 and 14) be included in the future stability pulls for the phase 3 clinical supplies and that deletion of these time points be requested in the NDA.
 - DBRUP also asked for clarification on the results of the Durometer test on the phase 2 clinical supplies and the sponsor stated that they were approximately (b) (4)
(b) (4) of the transfer batches.
 - The analytical test information appears to be adequate to support the manufacturing site change.
 - The acceptability of the calculated release rate can only be concluded following the review of the full trial report and the method validation report. It is not clear why the average weight of the returned rings tested was a part of the equation to calculate the progesterone content of each returned ring.
 - DBRUP informed the sponsor that their calculation result indicates an apparent mean

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in vivo release rate of approximately 103 mg over 7 days or approximately 15 mg/24 hours. The variability was relatively high at 36.3% CV. The product labeling should reflect the known release rate and variability.

- The proposed method of estimating drug release calculated drug release over a 7- day use interval. The 24-hour release rate was calculated by dividing the 7-day release rate by 7. This calculation assumes that drug release is constant over the 7- day interval. The NDA should provide data to support this method of calculation.

- The sponsor presented a slide presentation on the following topics:

1. In vitro release rate calculation

- The sponsor acknowledged that average weight of the returned rings should not be used when calculating the drug content of each ring for drug release rate analysis.
- The sponsor proposed to assess the drug release rate using the rings (n=42) retrieved from a planned bioequivalence trial. More subjects will be enrolled to retrieve additional used rings if there is insufficient precision from the first 42 rings. The Division inquired if the additional rings may be needed. The sponsor stated that it may not be necessary to include additional rings, but they would like to have a plan to address high variability in the data, if this is seen.
- The sponsor proposed that labeling should utilize only the results from this new assessment for characterizing the drug release rate. The Division stated that this will be addressed, and a determination made during the NDA review, but all results including the previous trial need to be submitted. The sponsor should provide their rationale for choosing one set of results over the other at the time of NDA submission. In the trial report for the previous trial, there should be no adjustment based on the average weight of the returned rings. In addition, the raw data for each ring tested should be submitted.

2. Justification for dividing the 7-day release rate by 7 to calculate the average daily release rate

- DBRUP requested that justification for dividing the 7-day release rate by 7 to calculate the average daily release rate be included in the NDA.
- DBRUP commented that the rate being calculated based on the residual amount of drug remaining in the ring after use should be referred to as the apparent in vivo release rate instead of the delivery rate. The term delivery rate may be misinterpreted to mean delivery to the systemic circulation, which is not what is being determined.
- DBRUP agreed that with the demonstration of bioequivalence (BE) between the phase

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3 batch and the site transfer batch, sufficient support will be established to support the manufacturing site change.

- DBRUP provided the following comments:
 - Provide in the original NDA submission the raw and calculated pharmacokinetic parameters data files for the BE trial. Provide the files in SAS Transport (.XPT) format.
 - In addition to your proposed primary PK and statistical analyses based on baseline corrected progesterone concentration, we request that you calculate PK parameters and perform BE statistical analyses on baseline-uncorrected progesterone concentration as secondary analyses.
 - The trial report should include rationale to justify that the mean of 3 predose baseline samplings at -1, -0.5, and 0 hour would adequately capture the endogenous progesterone and could be used to perform baseline subtraction.
- The sponsor stated that the highest individual ratio of predose plasma concentration/post dose C_{max} (as determined from the 0-168 hours post dose interval) was 1.8% and the average baseline correction was 0.4% in one of their previous studies.
- DBRUP stated that if the data from the BE trial show a similar finding (i.e., endogenous progesterone concentration is low relative to the concentration from the progesterone vaginal ring), then the proposed predose sampling at -1, -0.5, and 0 hours should be acceptable.
- The sponsor agreed to submit PK results and BE statistical analyses based on both baseline corrected and uncorrected progesterone concentrations.
- DBRUP indicated that the proposed Overall Table of Contents and the Content Plan for Modules 2 and 3 appeared to be adequate to file the NDA from a CMC standpoint. The Division had the following additional comments:
 - In the NDA submission, provide a comprehensive table/list of all facilities involved in production of the drug substance and drug product with full street address of the actual manufacturing and/or testing site (not the corporate office), contact information of an individual at the site, detailed responsibilities of that facility and a date of when the facility was last inspected by FDA. This comprehensive table should be attached to the 356h. Full information should still be provided in the appropriate sections of Modules 2 and 3. Inspections cannot be requested unless all the above information is provided. If this information is not provided when the NDA is submitted, it will delay inspection

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requests and may adversely affect the outcome of a first cycle review decision.

- o Ensure that the stability data for the transfer batches includes the 6 month accelerated stability data.
- The sponsor inquired as to how the in vivo release rates would be presented in the labeling. DBRUP responded that they should use release rate, similar to other vaginal system products. The sponsor was referred to the labeling of ring products for contraception and hormone therapy.
- The sponsor's proposal on how the in vivo release rate is to be applied in labeling will be addressed during the NDA review.
- February 3, 2010: Agency Advice/Information Request:
 - DBRUP recommend the following inclusion criterion: All subjects should have a negative pretreatment mammogram (obtained at screening or within 3 months of trial enrollment) and a documented normal clinical breast examination prior to enrollment. Findings of suspicious significant breast pathology will result in exclusion of the subject from enrollment.
 - DBRUP recommend the following exclusion criteria:
 - o Dosage regimen changes of any concomitant medications during the trial.
 - o Current treatment with progesterone, other progestins, or estrogen (other than that required by the trial protocol).
 - DBRUP recommend that the sponsor fully document all vaginal examination findings both prior to and after treatment.
 - o Consider assessing the endometrial histology for progestational effects.
 - o DBRUP recommend that colposcopy be performed on all subjects with any abnormal findings on vaginal examination at trial termination or discontinuation. All colposcopic findings should be recorded using standardized reporting instruments such as those listed in the 2000 World Health Organization (WHO) manual for standardized colposcopy. If lesions or abrasions on the cervix or vagina are found at trial termination or discontinuation, DBRUP recommend that re-examination be performed within 2-4 days. Subjects should be followed until their lesions have resolved.
 - The outcomes of any pregnancies that occur during the trial should be followed and reported.

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- April 30, 2010: Submission of NDA 201110

Trial DR-PGN-302 was submitted to support efficacy and safety. However, Trial DR-PGN-302 was not powered to demonstrate non-inferiority of the progesterone vaginal ring, DR-2011, as compared to Crinone® 8% for the 35-42-year-old age group. This age group of women constitutes the largest percentage of women undergoing Art for treatment of infertility in the United States.

- October 12, 2010: Agency Information Request:
 - DBRUP suggest that microbial enumeration for the drug product be performed according to the USP 32-NF 27 Chapter <61> guidelines for testing transdermal patches. All results should be recorded as CFU/ring and not as CFU/g. Alternatively, provide a justification for the deviations from this method.
 - The process validation studies presented in ARD_RPT-2950 do not support your drug product testing method. Organisms should be inoculated directly onto the ring to show that the test method is capable of detecting the presence of microorganisms on the vaginal ring. These studies should reflect any changes made in response to comment #1.
 - Establish microbial limits (in CFU/ring) compliant with the recommendations in the USP 32-NF 27 General Chapter <1111> for vaginal products or provide rationale for any deviations from these recommendations.
 - Provide a justification for not following the current USP <62> recommendations on the test method for the absence of (b) (4)
 - Provide the results from the re-testing of site transfer and stability samples with the new validated microbial enumeration methods.
- November 30, 2010: Duramed. Submission - Quality Information Amendment to NDA 201110
- February 28, 2011: Complete Response (CR) Decisional Letter: Deficiencies and strategies for resolution of deficiencies were as follows:
 - 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.

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2. The progesterone vaginal system 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:
 - o Validate the accuracy of the HPLC test method for detection of impurity/degradation products in the drug substance.
 - o Validate the repeatability and intermediate precision of the drug product impurity test using samples spiked with the four known impurities at quantitation levels (QL).
 - o Revise the acceptance criteria of the relative standard deviation (RSD) (b) (4) for establishing the system suitability of the HPLC method.

■ CLINICAL

1. The sponsor has not provided sufficient evidence of efficacy for the progesterone vaginal 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. The sponsor has 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.
2. To address this concern, DBRUP continues to recommend that you conduct, prior to approval of your product, a randomized, active- controlled clinical trial to evaluate the efficacy of 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 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 trial.
3. It is also possible that appropriate labeling, which would include a statement on

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limitation of use, and a postmarketing commitment to conduct the clinical trial described above would be sufficient to support approval of the progesterone vaginal system for use in women less than 35 years of age.

■ LABELING

DBRUP reserves comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

■ FACILITY INSPECTIONS

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.

■ SAFETY UPDATE

Response to the above deficiencies should include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - o Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - o Present tabulations of the new safety data combined with the original NDA data.
 - o Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - o For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

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3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

In addition to the above deficiencies, the following issues should be addressed in your response to this letter:

■ PRODUCT QUALITY



(b) (4)

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■ MICROBIOLOGY

1. 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 listed in section 5.3. Revise ARD_RPT-5064 version 2.0 accordingly.
 2. Submit the results from microbial enumeration studies on the stability and site transfer batches using the revised test methods.
- March 4, 2011: Agency Advice Letter
 - We note the proprietary name is presented in all upper-case letters. Words set in upper- and lower-case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all-upper case. Therefore, we request you revise the proprietary name to appear in title case (i.e., 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.
 - DBRUP provided additional recommendations for labeling.
 - March 31, 2011: Teva Women's Health - Update to Microbiology Testing

The sponsor advised the DBRUP 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 (b) (4). The same type of container was used to test all five of the site transfer batches of Progesterone Vaginal Ring; therefore, results from all five batches are invalid.

- April 12, 2011: Agency Acknowledgement Regulatory Letter DBRUP acknowledged receipt of the sponsor's corporate name change from Duramed Research Inc., to Teva Women's Health, a division of Teva Branded Pharmaceutical Products R&D, Inc.
- May 31, 2011: Quality Information

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- Teva Women's Health Submission:

1. Results from re-testing of site transfer and stability samples of Progesterone Vaginal system (Batches 800354, 800356, 800357, 800358, and 800359 using the revised Finished Product Test Method (MTH- (b) (4)) for Microbiological Examination tests, which were performed after procurement of new, more suitable containers
2. Copy of OOS investigation report

- December 23, 2011: Quality Information Amendment

Teva Women's Health submitted an amendment, which addressed product quality deficiencies to determine the cause and remediate foreign particulate contamination in progesterone vaginal rings as outlined in the CR.

- February 28, 2012: Teva Women's Health Information Amendment Regarding Complete Response. The sponsor requested an extension in responding to the CR. The additional time 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 system manufacturing capability.
 - The sponsor initiated the first full-scale progesterone vaginal system batch manufacture on February 13, 2012; and completed manufacturing.
 - Safety update confirmed that there was not any new safety information on the progesterone vaginal ring.
 - The information amendment addressed product quality deficiencies.
 - Teva Womens Health proposed postponing discussion of the Post-marketing Commitment until fourth quarter 2012 with the final submission to the CR Letter.

- March 28, 2012: Agency Advice Letter

DBRUP informed Teva Women's Health 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: Corporate Name Change

Teva Women's Health R&D, a division of Teva Branded Pharmaceutical Products R&D, Inc. changed the corporate name to Teva Branded Pharmaceutical Products R&D, Inc.

- November 19, 2013: Teva Branded Pharmaceutical Products R&D, Inc. - Waiver Request

The sponsor requested a waiver to submit periodic Individual Case Safety Reports (ICSRs) on a

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rolling or ongoing basis throughout the reporting period via the Electronic Submissions Gateway.

- November 22, 2013: Agency Grants Waiver Request

Under 21 CFR 314.90(b), the Agency granted Teva Branded Pharmaceutical Products R&D, Inc. a waiver of the requirement to submit the non-expedited ICSRs obtained or otherwise received during the reporting interval of the postmarket periodic safety report in a single batch with that report. Instead, Teva should submit these non-expedited ICSRs electronically on an ongoing basis up until the due date of the descriptive portion of the postmarket periodic safety report.

- January 23, 2014: Teva Branded Pharmaceutical Products R&D - Submission of Bioequivalence Trial

The sponsor submitted a new clinical trial protocol for 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.” This is a phase 1 pharmacokinetic trial to evaluate for the bioequivalence (BE) of progesterone vaginal rings manufactured by a new (b) (4) process (information provided in the January 17, 2014 CMC amendment) and those manufactured by the legacy (b) (4) process (representative of the phase 3 clinical trial material) during a single 7-day application cycle in postmenopausal female subjects treated with estrogen. The legacy (b) (4) process was transferred from the manufacturing site used for the clinical trial material to that intended for commercial production and supported by a bioequivalence trial (Trial 10935036; provided in NDA 201110 sequence 0000 on April 30, 2010). Dr. Sandhya Apparaju reviewed Trial 10935036. See archived clinical pharmacology review dated February 2, 2011.

The “reference” material in the present trial is identical to the “test” material in the 10935036 trial.

- January 22, 2015: Teva Branded Pharmaceutical Products R&D - Submission of Bioequivalence Trial Report

Teva Branded Pharmaceutical Products R&D, Inc. submitted the trial report for “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 - Transfer of ownership

Teva Branded Pharmaceutical Products R&D, Inc. notified the Agency of transfer of ownership of NDA 201119 and IND 070875, and associated communications and documentation from the FDA to Ferring Pharmaceuticals Inc.

- August 6, 2015: Ferring Pharmaceuticals Inc. Acceptance of NDA Sponsorship

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In accordance with 21 CFR 314.72, Ferring accepted 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: Agency Acknowledgement of Change in Sponsorship for IND 070875.
- September 7, 2016: Division of Clinical Pharmacology 3 reviewed study results of “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”. According to the reviewer, Ferring Pharmaceuticals, Inc established the bioequivalence of the legacy (b) (4) process and the new (b) (4) process of the to-be marketed MILPROSA.
- October 8, 2015: Agency Acknowledgement Transfer of Ownership for NDA 20110.
- February 25, 2016: Ferring Pharmaceuticals, Inc class 2 resubmission of NDA 20110.
- November 23, 2016: CR Decisional Letter: Deficiencies and strategies for resolution of deficiencies are summarized as follows:

DEVICE

- Insufficient biocompatibility information was available to support the to-be-marketed combination drug-device product. To address biocompatibility, the applicant was advised to 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. It was noted that the applicant did provide acceptable data on irritation.

CLINICAL

- The applicant did not establish an adequate clinical safety bridge between the legacy progesterone vaginal system used in the phase 3 clinical trials and the new progesterone vaginal system product. DBRUP recommended the applicant conduct a study to evaluate the clinical safety of the new progesterone vaginal system to evaluate:
 1. 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
 2. Adverse events related to pregnancy outcomes, including miscarriage and ectopic pregnancy.
- DBRUP also continued to recommend that the applicant conduct, , a randomized, active-controlled clinical trial to evaluate the efficacy of your product in women 35-42 years of age prior to approval of MILPROSA but also advised of the possible alternative approach

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to label MILPROSA with a limitation of use only in women under 35 years of age along with a post-marketing commitment to conduct the clinical trial described above.

- March 7, 2017: Type A Meeting Minutes

The applicant requested a Type A meeting to discuss the design of a clinical safety study protocol to evaluate the to-be-marketed progesterone vaginal 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 biocompatibility testing was required prior to providing comment on design of the safety study, given potential implications of this information.
- DBRUP recommended the primary endpoint for the proposed safety trial 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) and advised that spontaneous abortion is the most relevant adverse event in this population.
- DBRUP recommendations were as follows:
 - 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 Visit10 (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.
- DBRUP recommended the following secondary safety endpoints:
 1. The cumulative rate of spontaneous abortion, including spontaneous clinically recognized pregnancy loss and blighted ovum, determined at 6- and 10-weeks post oocyte retrieval.
 2. The cumulative rate of biochemical abortions determined at 6- and 10-weeks post oocyte retrieval.
 3. Rates of ectopic and heterotopic pregnancy.
 4. Frequency, intensity, seriousness and relatedness of adverse events (AEs), including incidence of vaginal bleeding/spotting, vaginal hemorrhage, pain,

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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.

5. Rates of: 1) abnormal clinical laboratory findings and 2) abnormal vital sign determination.
 6. Frequency of and reason for progesterone vaginal system discontinuation.
 7. Rates of clinical pregnancy at 6- and 10-weeks post oocyte retrieval.
- August 24, 2017: Type C Meeting Minutes

Biocompatibility

- DBRUP agreed that the applicant complied with biocompatibility recommendations of 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) and determined that there was no biocompatibility safety signal that would impact the design of the proposed clinical safety study.

Clinical

- DBRUP agreed that given the 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 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, was reasonable. Using the point estimate of 8 and 10% with a 5% confidence interval (possible upper limit of the observed rate not exceeding 15%), DBRUP recommended the sample size should be between 544 and 658, respectively, adjusting for a potential 10% drop-out rate
- DBRUP agreed with the proposed primary endpoint, cumulative rate of spontaneous abortion occurring on or before 12 weeks following oocyte retrieval and proposed secondary endpoints.

Human Factors

- DBRUP recommended 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.

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- December 6, 2018: Type C Meeting Minutes WRO

Device

- DBRUP agreed that the completed biocompatibility testing on the combination product was adequate to resubmit your application.

Non-Clinical

DBRUP agreed that the format and content of the nonclinical information appeared acceptable.

Clinical

- DBRUP recommended a frequentist rather than a Bayesian model statistical approach given that the trial design of Trial 000293 differed from phase 3 Trial DR-PGN-302. Based on the assumptions in the statistical assessment plan, a sample size of 658 was recommended.

Human Factors

DBRUP reviewed the applicant's Use-Related Risk Analysis (URRA) and comparative analyses and determined that a human factors validation study was not required to support the proposed progesterone vaginal system combination product.

CMC:

DBRUP recommended the applicant provide and ensure following:

- 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: Applicant Response to Statistical Recommendations

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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.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

DUOG (formerly DBRUP) selected three clinical investigators (CIs): Drs. Park (Site USA09), Schnell (Site USA10) and Slater (Site USA12) for clinical inspections. The inspections verified the sponsor 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).

Findings at the individual sites were as follows:

Dr. Park (Site USA09): The inspection found adequate source documentation for all study subjects, 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. Two misfiled items were identified during the inspection that the source vitals worksheet labeled for Subject # (b) (6) was filed in the binder for Subject # (b) (6) at visit 5; while the information sheet labeled for Subject # (b) (6) was filed in the binder for Subject # (b) (6).

Dr. Schnell (Site USA10): The inspection found adequate source documentation for all inspected study subjects, 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.

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Dr. Slater (Site USA12): The inspection found adequate source documentation for all study subjects, 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. Subject # (b) (6)'s Visit 6 information was not signed by the person who recorded the information; and a comment on Subject # (b) (6)'s eligibility check list was not dated. The CI was working on making changes to prevent issues in the future.

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.

4.2. Product Quality

The manufacturing sites for NDA 201110 are approvable. There are no changes to CMC related information, facilities or compliance status since the last review cycle. Based on the submitted adequate stability data and CDRH's satisfactory assessment for the biocompatibility data, OPQ recommends approval from the drug product perspective with the requested 24-month expiration dating period when stored at 20°C to 25° (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). For more details see the original NDA and resubmission CMC reviews (dated February 7, 2011 and November 10, 2016 respectively).

4.3. Clinical Microbiology

The applicant did not submit new clinical microbiology data with this NDA resubmission. The applicant has addressed previous deficiencies outlined in the complete response to the original NDA submission (see clinical microbiology reviews dated February 8, 2011 and August 10, 2016 for full detail). Thus, the application is approvable from the product quality microbiology perspective.

4.4. Nonclinical Pharmacology/Toxicology

Pharmacology Toxicology deemed this combination drug product approvable in the original NDA submission and subsequent NDA resubmission on April 30, 2010 and November 25, 2016 respectively (See DARRTS archive dates July 16, 2010). Pharmacology Toxicology did not identify any new nonclinical concerns with this resubmission and the application is approvable.

4.5. Clinical Pharmacology

Clinical Pharmacology reviews of the original NDA application submitted on April 30, 2010 and the prior resubmission on February 25, 2016 can be found in the DARRTS archive (submissions dated February 2, 2011 and September 7, 2016 respectively). Clinical Pharmacology deemed

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prior submissions to be approvable and there are no new approvability issues in this resubmission from a Clinical Pharmacology standpoint. Clinical Pharmacology recommends approval of this NDA resubmission.

4.6. Devices and Companion Diagnostic Issues

On December 3, 2019, DUOG (Formerly DBRUP) requested a consult from CDRH/OPEQ/OHT3/DHTB/THT3B1 to evaluate the device aspects of MILPROSA. At that time, it was noted that the applicant had not completed mechanical testing on the new batches of the to-be-marketed MILPROSA. On February 7, 2020, an IR was sent to the applicant requesting mechanical testing on the new batches. The applicant performed mechanical testing as requested and the testing results were deemed to be acceptable from a CDRH perspective. They did however, recommend additional data collections related to ring thickness measurements and visual evaluation for signs of deterioration following compression testing as communicated in an IR on March 20, 2020. The applicant provided an acceptable response to these recommendations on March 24, 2020. There are no outstanding issues or deficiencies from a CDRH perspective.

4.7. Consumer Study Reviews

The applicant did not submit consumer study reviews with this NDA resubmission.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

In this review cycle, the applicant submits results from a single Trial 000293, entitled "SARA (Safety Assessment of Progesterone Vaginal System in Women Undergoing ART)". This is a prospective, multi-Center, non-comparative trial of the clinical safety of the progesterone vaginal system (ring) in women undergoing assisted reproductive technology (ART) specifically evaluating the to be marketed MILPROSA vaginal system (representing a different (b) (4) process from that in the original safety and efficacy trial).

For a prior presentation of the original safety and efficacy trial, the reader is referred to the clinical review archived in DAROTS on February 25, 2011.

5.2. Review Strategy

A single clinical safety trial (Trial 000293), which is to serve as a clinical bridge for the to-be-marketed product to the safety data of the original phase 3 trial, was submitted to support this class 2 resubmission. The primary outcome for this safety trial is the rate of spontaneous

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abortion up to week 12 following oocyte retrieval. This trial will be reviewed for primary and secondary safety outcomes using the to-be-marketed MILPROSA with an additional focus on vaginal pain, ulcerations, lesions and bleeding.

6. Review of Relevant Individual Trials Used to Support Efficacy

The applicant did not submit new efficacy data for this NDA. It was determined in the original review cycle that efficacy of MILPROSA for the proposed indication had been established in women under the age of 35. For the review of efficacy, the reader is referred to the original NDA clinical review (see DARRTS Archive, February 25, 2011).

7. Integrated Review of Effectiveness

See the immediately preceding paragraph, the applicant did not submit new efficacy data for this NDA.

8. Review of Safety

8.1. Safety Review Approach

For a prior presentation of controlled safety data and a full review of safety, the reader is referred to the original clinical review (DARRTS Archive, February 25, 2011). For this class 2 NDA resubmission, the applicant submits results from a single clinical trial entitled: "SARA (Safety Assessment of Progesterone Vaginal System in Women Undergoing ART)". Findings from this single arm, open label trial are reviewed to supplement the safety data from the pivotal phase 3 trial, specifically assessing the safety and tolerability of the to-be-marketed MILPROSA vaginal system (ring).

8.1.1. Study Design

Overview and Objective

Safety Assessment of Progesterone Vaginal System in Women Undergoing ART (SARA), Trial 000293 was designed and conducted to evaluate the safety of the to-be-marketed MILPROSA vaginal ring.

The primary objective was to estimate the cumulative rate of spontaneous abortion, defined as spontaneous clinically recognized pregnancy loss and blighted ovum during the trial (up to week 12 following oocyte retrieval), in women treated with MILPROSA following fresh embryo transfer.

The secondary objectives were as follows:

- To describe the cumulative rate of spontaneous abortions determined at 6- and 10-weeks post-oocyte retrieval, including spontaneous clinically recognized pregnancy loss and blighted ovum, in all subjects treated with MILPROSA.
- To describe the cumulative rate of biochemical abortions determined at 6- and 10-weeks post oocyte retrieval in all women treated with MILPROSA.
- To describe the rate of ectopic and heterotopic pregnancy in all women treated with MILPROSA following oocyte retrieval.
- To describe the safety of MILPROSA through the collection of clinical laboratory tests and vital signs in all women treated with MILPROSA.
- To assess the safety and tolerability of MILPROSA in all women treated with MILPROSA.
- To determine the positive β -hCG rate of women treated with MILPROSA following oocyte retrieval.
- To determine the clinical pregnancy rate of women treated with MILPROSA following oocyte retrieval

Trial Design

The trial was an open-label, single-arm, safety trial of the use of MILPROSA for luteal phase support in women aged 18-34 years undergoing IVF with fresh oocytes. The trial design was different than the original pivotal phase 3 trial in that it was a single arm study and there were changes in the way adverse events were collected in respect to vaginal tolerability and side effects including vaginal bleeding. This trial was conducted entirely in the US in a total of 14 investigational recruiting sites. The trial overview is presented in Table 3 below.

Table 3 Trial Overview

Screening	Study Phase

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Phase	Suppression Phase	Stimulation Phase		Treatment Phase	
Screening	Ovarian suppression	Ovarian stimulation	Oocyte retrieval	Treatment period	Post-treatment period
Consent and screening	Down-regulation	Visits 1 and 2	Visit 3	Visits 4-9: day after oocyte retrieval and ongoing pregnancy (~10 weeks) MILPROSA1 through MILPROSA10	Visit 10: end-of-trial visit (2 weeks after last exposure to MILPROSA)

This was an open-label, single-arm trial of progesterone supplementation (luteal phase support) in women undergoing IVF with fresh oocytes. Each trial center followed the trial center's standard practice for ART. On the day after oocyte retrieval, the participating woman began treatment with MILPROSA. Embryo transfer occurred 5 days after oocyte retrieval (Day 5). A serum pregnancy test was conducted 2 weeks after the oocyte retrieval. Subjects 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. There was a total of 254 women enrolled for a target of 240 evaluable women that underwent complete controlled ovarian stimulation cycle, oocyte retrieval, treatment with MILPROSA, and fresh embryo transfer.

Enrollment Criteria:

Inclusion Criteria

Women had to meet the following inclusion criteria to be eligible for participation in the trial:

- Informed consent signed and dated prior to any trial related procedures. Pre-menopausal female aged 18-34 years old at time of consent.
- Documentation of a normal uterine cavity by hysteroscopy, hydrosanogram, or hysterosalpingogram within 1 year of screening.
- Documentation of normal Pap smear test within 24 months of screening. Documentation of negative testing within 6 months of the start of screening for serum

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- Hepatitis B surface antigen, Hepatitis C antibody, human immunodeficiency virus antibody, rapid plasma reagent/venereal disease research laboratory.
- Documentation of rubella antibody, ABO grouping, Rho typing, and normal prolactin and thyroid function within 6 months of screening.
- At least 1 cycle without reproductive hormone medication prior to the screening follicle
- Follicle stimulating hormone (FSH) and estradiol blood draw.
- Tubal, idiopathic, male factor, ovulatory dysfunction, or endometriosis-linked infertility.
- For fresh sperm: sperm assessed for leukospermia (≥ 2 million white blood cells/mL or round cells/mL) was required within 2 months of pituitary down regulation OR male partner empirically treated with antibiotics prior to the IVF cycle.
- Semen analysis within 1 year of screening by standard World Health Organization and/or Kruger criteria. Frozen sperm, including donor sperm, could be used, as long as testing done at the time of freezing met standard criteria. Male partners with obstructive azoospermia were not required to have this semen analysis.
- Able to understand, read, and sign an informed consent after the nature of the trial has been fully explained.
- Able to complete all trial procedures.

Exclusion Criteria

- The presence of any of the following excluded a woman from trial enrollment:
- Contraindications to the use of progesterone, which included:
 - o Known sensitivity to progesterone or related drugs
 - o Undiagnosed vaginal bleeding
 - o Significant liver dysfunction or disease (including liver function tests > 2 times the upper limit of normal)
 - o Known or suspected malignancy of the breast or genital organs
 - o Active thrombophlebitis or thromboembolic disorders, or a history of hormone-associated thrombophlebitis or thromboembolic disorders

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- Significant psychiatric disease that was not well-controlled.
- Body mass index $>38 \text{ kg/m}_2$.
- Uncontrolled hypertension (systolic blood pressure $>160 \text{ mmHg}$ or diastolic blood pressure $>100 \text{ mmHg}$).
- FSH $>15 \text{ IU/L}$ during the early follicular phase (Day 2-4). For those subjects with polycystic ovarian syndrome, a Day 2-4 FSH level could be obtained following a progestogen withdrawal or spontaneous menses.
- Clinically significant gynecologic pathology, such as submucosal fibroids, intramural fibroids
- $>5 \text{ cm}$, communicating hydrosalpinx, uncorrected uterine septum, endometrial cancer or endometrial atypia, scar tissue inside the cavity or poorly developed uterine lining from prior uterine surgery, pelvic tuberculosis, or any other conditions that could adversely affect pregnancy success.
- Uncontrolled hyperprolactinemia or hypothyroidism.
- History of pelvic radiation. Women with a history of cancer within the last 5 years, except for squamous or basal cell cancer of the skin.
- Currently pregnant or breastfeeding.
- Current gonorrhea or chlamydia.
- History of human immunodeficiency virus/acquired immunodeficiency virus.
- Known hypersensitivity or previous intolerance to silicone or to any active ingredient or excipients in the medicinal products used in this trial.
- History of toxic shock syndrome.
- Known or suspected substance abuse within 1 year prior to screening.
- Use of any investigational drug or device within 30 days prior to screening.
- Undergoing donor oocyte cycle, embryo biopsy, or preimplantation genetic testing.
- History of more than 1 failed fresh IVF cycle. *Note:* an ART cycle is started when a woman begins taking medication to stimulate the ovaries to develop eggs or, if no drugs are given, when the woman begins ovarian follicular monitoring (using ultrasound

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or blood tests) for natural egg production. A failed cycle is defined as having started a cycle and not becoming pregnant or pregnancy loss prior to the 20th week of pregnancy.

- More than 2 consecutive clinical miscarriages (gestational sac observed on ultrasound).
- Insulin-sensitizing agents, ART cycle, or ovarian stimulation with gonadotropins within 30 days or clomiphene stimulation within 90 days prior to the screening FSH and estradiol blood draw.
- Tobacco use within 3 months prior to screening.
- For fresh sperm: male partners with non-obstructive azoospermia.
- Any abnormal finding or condition deemed clinically significant by the investigator on history, screening, physical examination, or pelvic examination that contraindicates pregnancy or the use of progesterone or a vaginal ring, including the presence of any vaginal or cervical abrasions/lesions.
- Any condition the investigator believed would interfere with the woman's ability to provide informed consent, to comply with trial instructions, or which might confound the interpretation of the trial results or put a woman at risk.

Reviewer's Comment:

The selection criteria differed slightly in Trial 000293 and the original pivotal phase 3 trial. In this trial, women with abnormal TSH or prolactin were excluded from participation. In the original trial, women with uncontrolled hyperprolactinemia or hypothyroidisms were excluded, but women with hyperthyroidism were not specifically identified as included. Women with hypothyroidism and hyperthyroidism are both at increased risk for spontaneous abortion. For this reason, DBRUP requested baseline TSH and prolactin levels from the original trial in an information request. The sponsor responded that they did not have this data available. A higher rate of participants with hyperthyroid in the original trial would bias toward the null in the evaluation of data from Trial 00023. Therefore, the clinical impact from this difference is not likely to affect the results in any clinically meaningful way.

Discontinuation Criteria

Women had to have at least 2 follicles ≥ 17 mm (mean of 2 dimensions) as measured by TVUS two days prior to oocyte retrieval to receive the hCG trigger (NOVAREL). Women who did not reach this threshold after 20 days of stimulation were discontinued from the trial. If the estradiol level was ≥ 5000 pg/mL, NOVAREL was not administered and the woman was

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discontinued from the trial.

A serum pregnancy test was conducted 2, 2.5, and 3 weeks after the oocyte retrieval. Women with a β -hCG level <5 mIU/mL were discontinued from the trial. A TVUS was performed to document the presence of an intrauterine gestational sac 4.5 weeks after oocyte retrieval. If it was determined that the woman had an ectopic pregnancy, the women was treated according to the site's standard protocol and was withdrawn from the trial.

Women who discontinued the trial were to complete an early withdrawal visit no later than 1 week after the last dose of the MILPROSA. An end-of-trial visit was required 2 weeks after the last dose of MILPROSA.

Women had the right to withdraw from the trial at any time for any reason, without the need to justify their decision. The investigator also had the right to withdraw participants.

Investigational Treatment Administered:

MILPROSA vaginal system releases an average of 11 mg progesterone/day consistently over 7 days. The progesterone is in a (b) (4) formulation and dispersed evenly throughout the ring.

Women inserted the first MILPROSA on the day after oocyte retrieval. A new MILPROSA was inserted every 7 days and each MILPROSA was to remain in place for a minimum of 23 hours/day. Depending on the woman's pregnancy assessments, MILPROSA treatment could be continued through week 12 of pregnancy (10 weeks post-oocyte retrieval).

Non-investigational Treatment Products Administered:

Non-investigational products used in this trial are listed in Table 4 below.

Table 4 Non-Investigational Treatment Products Employed in Trial 000293

NIMP	Trade name	Dose
Combined oral contraceptives	CYCLAFEM 1/35 (norethindrone [1 mg] and ethinyl estradiol [0.035 mg])	1 mg/0.035 mg (1 tablet) daily for at least 14 days but no more than 21 days during the downregulation period.

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GnRH agonist	LEUPROLIDE ACETATE (leuprolide acetate)	0.1 mL (500 µg)/day administered as subcutaneous injections during the downregulation period for at least 10 days but no more than 20 days, followed by 0.05 mL (250 µg/day) throughout the gonadotropin treatment period.
HP-hMG	MENOPUR (menotropin)	225 IU/day administered as subcutaneous injections for 5 days. Subsequent dosing was to be adjusted according to individual subject response. Dose adjustments were not to be made more frequently than once every two days and should not exceed 150 IU per adjustment. The maximum daily dose of MENOPUR should not exceed 450 IU and the minimum daily dose should not be lower than 75 IU. MENOPUR dosing could continue for maximum 20 days and coasting was not allowed.
hCG	NOVAREL (chorionic gonadotropin)	1 mL (2 x 5,000 IU) administered by intramuscular injection according to label as soon as 2 follicles of ≥17 mm were observed on TVUS.

Study Endpoints

Primary Endpoint:

The cumulative rate of any spontaneous abortion occurring on or before 12 weeks following oocyte retrieval in all women treated with MILPROSA and undergoing fresh embryo transfer. Spontaneous abortion was defined as two positive β -hCG tests occurring at least two days apart on or after 2 weeks post-oocyte retrieval but followed by observation of any empty intrauterine gestational sac (blighted ovum), intrauterine gestation without a fetal heartbeat, or absence of viable fetuses, as documented by transvaginal ultrasound (TVUS).

Secondary Endpoints:

- Cumulative rate of spontaneous abortions determined at 6- and 10-weeks post-oocyte retrieval in all subjects treated with PVR.
- Cumulative rate of biochemical abortions determined at 6- and 10-weeks post-oocyte retrieval in all women treated with MILPROSA. Biochemical abortion is defined as a positive β -hCG test between 2 weeks and 2 weeks + 3-4 days post-

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oocyte retrieval, followed by no observed gestational sac on a later TVUS or followed by a negative β -hCG test.

- Rate of ectopic and heterotopic pregnancies in all women treated with MILPROSA following oocyte retrieval.
- Rate of abnormal findings in clinical laboratory tests and vital signs for all women treated with MILPROSA.
- Frequency, intensity/grade, seriousness, and relatedness of adverse events for all women treated with MILPROSA.
- Frequency, intensity/grade of vaginal bleeding/spotting, vaginal hemorrhage, pain, vaginal infection, and vaginal irritation for all women treated with MILPROSA.
- Frequency, intensity/grade, seriousness, and relatedness of adverse events associated with vaginal and cervical abrasions and lesions and with vaginal adhesions for all women treated with MILPROSA.
- Frequency and reason for MILPROSA discontinuation.
- Positive β -hCG rate (positive serum β -hCG test) between 2 weeks and 2 weeks + 3-4 days post- oocyte retrieval in all women treated with MILPROSA.
- Clinical pregnancy rate (TVUS showing at least 1 intrauterine gestational sac with fetal heartbeat) at 6 and 10-weeks post-oocyte retrieval in all women treated with MILPROSA.

Reviewer's Comment:

Endpoints selected were clinically meaningful and consistent with DBRUP recommendations. Spontaneous abortion at 12 weeks gestational age (10 weeks post embryo transfer) is the most appropriate clinical endpoint for the desired indication. Secondary endpoints are adequate to evaluate the safety and tolerability of MILROSA with a specific focus on vaginal lesions, irritation, and bleeding.

Statistical Analysis Plan

The Division of Biometrics VII (DB7) concurred with the Statistical Analysis Plan (SAP) v.4.0 (submitted by Ferring Pharmaceuticals, Inc. August 12, 2019). This SAP outlined a statistical analysis plan that was a frequentist approach (as recommended by DB7) with a Bayesian sensitivity analysis. The proposed sample size of 240 women corresponds to 82% power and one-sided type I error of 0.025 for a test to rule out 15% spontaneous abortion rate, assuming a background rate of 9% (see Table 5). DB7 confirmed and concurred with power calculations. Calculations related to end points will reflect two-sided 95% confidence intervals.

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Table 5 Power Calculations for Trial 000293

Required Sample Size	Assumed "True" Spontaneous Abortion Rate		
	8%	9%	10%
180	80.3%	64.8%	46.1%
240	93.1%	81.8%	63.2%
365	98.9%	94.2%	80.9%

Source: SAP v4.0, p. 14

Analysis Sets:

Modified Intent to Treat (mITT) Cohort: All women who had successful oocyte retrieval, received at least 1 dose of MILPROSA and had completed fresh embryo transfer.

Safety Cohort: All women treated with MILPROSA

Eligible Subjects (ES) Cohort: All women deemed eligible for trial participation based on inclusion and exclusion criteria at screening and treated with oral contraceptives, leuprolide acetate, and MENOPUR

The analysis of the primary endpoint is based on the mITT population. The number and rate of any spontaneous abortions (occurring on or before 12 weeks following oocyte retrieval) for women in the mITT cohort will be summarized and the associated two-sided exact 95% confidence interval will be generated. Upon generating the two-sided exact 95% confidence interval, the upper bound of the interval will be assessed for whether it excludes or fails to exclude a spontaneous abortion rate of 15%. If it fails to exclude a spontaneous abortion rate of 15% then the trial is considered failed and a safety bridge will not be established between the to-be-marketed MILPROSA and the legacy MILPROSA.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

A total of 254 women were exposed to MILPROSA in Trial 000293. Table 6 presents exposures to MILPROSA in Trial 000293

Table 6 Progesterone Vaginal System Exposure in Trial 000293

Number of MILPROSA drug-devices used	
n	254
Mean (SD)	5.8 (3.77)

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Median (IQ-range)	4.0 [2.0; 10.0]
Duration of MILPROSA treatment (days)	
n	254
Mean (SD)	40.0 (27.21)
Median (IQ-range)	23.0 (14.0; 71.0)
Duration of MILPROSA treatment (weeks), n (%)	
<1 week	10 (3.9)
1-2 weeks	15 (5.9)
2-3 weeks	90 (35.4)
3-4 weeks	15 (5.9)
4-5 weeks	8 (3.1)
5-6 weeks	4 (1.6)
6-7 weeks	3 (1.2)
7-8 weeks	1 (0.4)
8-9 weeks	1 (0.4)
9-10 weeks	6 (2.4)
10-11 weeks	99 (39.0)
11-12 weeks	2 (0.8)
All	254 (100)
Total Cumulative Duration of MILPROSA treatment (weeks), n (%)	
<1 week	10 (3.9)
1-2 weeks	25 (9.8)
2-3 weeks	115 (45.2)
3-4 weeks	130 (51.1)
4-5 weeks	138 (54.2)
5-6 weeks	142 (55.8)
6-7 weeks	145 (57.0)
7-8 weeks	146 (57.4)
8-9 weeks	147 (57.8)
9-10 weeks	153 (60.2)
10-11 weeks	252 (99.2)
11-12 weeks	254 (100)
All	254 (100)
Number of MILPROSA drug-devices not inserted at least 23 hours per day, n (%)	
0	237 (93.3)
1	15 (5.9)
2	2 (0.8)
Number of MILPROSA drug-devices damaged during insertion or removal, n (%)	
0	254 (100)

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SD=Standard deviation, IQ-range=Interquartile range, n=number of women with observation, %= percentage of women with observation

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.

Reviewer's Comment:

The safety database of women exposed to MILPROSA is adequate for purposes of this class 2 NDA resubmission. Just over half of participating women stopped MILPROSA within one month of the first dose. This is expected from a clinical standpoint, as beta-human chorionic gonadotropin (β -hCG) testing occurs at 3 to 4 weeks following implantation and initiation of MILPROSA. There is no reason to continue the ring if women are not pregnant. An average duration of exposure of 40 days observed in this trial is adequate to evaluate the safety of the to be marketed version of MILPROSA given the current overall safety data available on progesterone for the proposed indication.

8.2.2. Relevant characteristics of the safety population:

Demographics of participating women in Trial 000293 is presented in Table 7.

Table 7 Demographics of Women in Trial 000293

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)

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Source, CSR 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 not Latina (88.2%) with the majority of the women enrolled greater than 30 years of age. Only 7% of trial participants were Black race.

Reviewer's Comment:

The overall demographics in the trial population are characteristic of infertility clinical trials given that infertility diagnosis and treatment increase with advancing age. The race distribution in the trial is overall reflective of the race distribution of women seeking infertility treatment in the United States.³

8.2.3. Adequacy of the safety database:

(b) (4) progesterone has an acceptable safety profile for the proposed indication and labeled population. This single arm clinical trial is adequate to allow for further evaluation of safety of the to-be-marketed MILPROSA vaginal system in the selected population beyond that of the pivotal phase 3 trial of the drug-device using legacy (b) (4) process. The sample size of 254 women treated with MILPROSA evaluating the primary safety outcome of spontaneous abortion provides adequate power to assess for a preselected spontaneous abortion rate at 12 weeks of 8 to 10 percent. DBRUP agreed that spontaneous abortion was the most important clinical safety outcome for evaluating the clinical safety of the proposed indication. The 12-week trial duration is consistent with the expected duration of use of this product. All women that were exposed to MILPROSA will be included in the safety analysis. The data presented in this class 2 resubmission is of adequate integrity to allow for a full safety evaluation. Additionally, the applicant complied with DBRUP recommendations related to collecting adverse events of special interest (AESI) related to vaginal bleeding/spotting, vaginal pain and irritation, vaginal or cervical abrasions and lesions, vaginal hemorrhage, vaginal infection and vaginal adhesions.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The data in this NDA submission was of adequate quality to allow for a thorough review of new safety data. There were no data integrity issues identified with this application.

³Dieke, AC, Boulet, SL, et al. Disparities in Assisted Reproductive Technology Utilization by Race and Ethnicity, United States, 2014: A Commentary. J Womens Health (Larchmt). 2017 June ; 26(6): 605–608.
doi:10.1089/jwh.2017.6467

8.3.2. Categorization of Adverse Events

The applicant coded adverse events using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0.

The applicant defined adverse event as any untoward medical occurrence including:

- Any unfavorable and unintended sign, symptom or disease temporally associated with the use MILPROSA, whether or not considered to be caused by MILPROSA.
- Adverse events commonly observed and adverse events anticipated based on the pharmacological effect of MILPROSA.
- Any laboratory abnormality, vital sign or finding from physical or gynecological examination assessed as clinically significant by the investigator [*note*: pre-existing conditions diagnosed through assessments and examinations at the screening visit or during the screening phase were not adverse events but were recorded as medical history].
- Accidental injuries, reasons for any change in medication (drug and/or dose), reasons for any medical, nursing or pharmacy consultation, or reasons for admission to hospital or surgical procedures.
- Overdoses and medication errors with and without clinical consequences.

The applicant defined Treatment Emergent Adverse Events (TEAE) as adverse events that occurred during the treatment phase or a pre-existing medical condition that worsened in intensity during the treatment phase. Adverse events were collected using open-ended questions by Investigators from screening throughout course of the entire trial.

8.3.3. Routine Clinical Tests

The following laboratory tests were performed:

- Screening and Visits 4, 9, and 10 (End-of-trial): serum chemistry: non-fasting glucose, blood urea nitrogen, creatinine, potassium, sodium, chloride, calcium, aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transferase
- Screening and Visits 4, 9, and 10 (End-of-trial): hematology: red blood cell count, white blood cell count, hematocrit, hemoglobin, platelet count, and differential count
- Screening and Visits 9 and 10 (End-of-trial): urinalysis: specific gravity, ketones, pH, protein, blood, and glucose
- Screening: (prior to start of ovarian suppression): AMH
- Screening (Cycle Day 3 $\pm$ 1 day): FSH
- Screening (Cycle Day 3 $\pm$ 1 day) and Visits 1, 2, 4, and 5: serum estradiol
- Screening and Visits 6, 6P, and 7: β -hCG
- Visits 4, 5, 6, and 9: progesterone

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All results were recorded in the eCRF. Investigators reviewed and determined the clinical significance of any abnormal results.

Reviewer's Comment:

The laboratory data collected for this trial was consistent with clinical practices in infertility and sufficient for evaluating the safety of MILPROSA. Laboratory results are further discussed in section 8.4.6.

8.4. Safety Results

8.4.1. Deaths

There were no deaths in Trial 000293.

8.4.2. Serious Adverse Events

Four women (1.5 percent of all participants) in Trial 000293 experienced serious adverse events (SAE). A listing of the SAEs experienced by women in the trial according to MedDRA System Organ Class (SOC) and Preferred Terms (PTs) is displayed in Table 8Error! Reference source not found..

Table 8 Treatment Emergent Serious Adverse Events, Trial 000293, MILPROSA N=254

System Organ Class	Serious Adverse Event	n	N=254 %
Pregnancy, puerperium and perinatal conditions	Ectopic pregnancy	1	0.4%
Psychiatric disorders	Suicidal ideation	1	0.4%
Reproductive system and breast disorders	Adnexal torsion	1	0.4%
	Ovarian cyst ruptured	1	0.4%
TOTAL		4	1.5%

Source: CSR, p. 93, n=number of women with observation,

Treatment Emergent SAE Narratives

Participant USA (b) (6): A 27-year-old woman experienced suicidal ideation during her enrollment in trial 000293. She had a medical history of hypothyroid, depression, and anxiety (disclosed after she reported suicidal ideation). She was taking SYNTHROID prior to enrollment. She started MILRPOSA in December 2018 and underwent embryo transfer 4 days later. In

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February 2019, she experienced suicidal thoughts and was attended by a psychiatrist. It was recommended that she discontinue MILPROSA (stopped 2 days later) and start ZOLOFT. She stopped the Zoloft due to abdominal pain after one day, was prescribed a new antidepressant but reported that she did not take it. She was still experiencing symptoms at the end of trial visit in February 2019 but was fully recovered in March 2019 (34 days after the onset of her symptoms).

Reviewer's Comment:

The participant had a medical history of depression. Progesterone can worsen depression symptoms and is currently labeled in the warnings and precautions section of approved labeling for other progesterone products with the same indication.

Participant USA (b) (6): A 33-year-old woman experienced ectopic pregnancy while enrolled in Trial 000293. Her medical history included bilateral salpingectomy, laparoscopy with bilateral neosalpingostomy, laser adhesiolysis, loop electrosurgical excision procedure, bilateral tubal hydrosalpinx, pelvic adhesions, and chlamydia. She started MILPROSA in December 2018 and underwent embryo transfer 4 days later. In January 2019, during her fourth MILPROSA ring, she was hospitalized due to abdominal pain and diagnosed with a urinary tract infection. Her quantitative β -hCG levels were increasing. Two days later, she was discharged from the hospital as the abdominal pain resolved. Three days later, during her fifth MILPROSA, transvaginal ultrasound revealed a heterogeneous mass (anterior superior to the uterus) and a non-viable pregnancy. She was prescribed methotrexate and advised to discontinue the MILPROSA as her β -hCG levels continued increasing. On the same day, she underwent diagnostic laparoscopy and was diagnosed with an ectopic pregnancy. Additionally, evacuation of the hemoperitoneum was performed. She was discharged from the hospital the day after the procedure. She fully recovered from the adverse event 5 days after the onset.

Reviewer's Comment:

This participant's medical history of extensive tubal surgery predisposed her to ectopic pregnancy. It is unlikely that MILPROSA was the cause of this SAE. Given this event in a participant with a medical history placing her at increased risk of ectopic pregnancy, this finding does not increase concern for the use of MILPROSA.

Participant USA (b) (6):

A 29-year-old woman experienced ovarian cyst ruptured while enrolled in Trial 000293. She has a medical history of 3 failed intrauterine inseminations (IUI). She started MILPROSA in November 2018 and underwent embryo transfer 4 days later. In December 2018, during her fifth MILPROSA treatment, her transvaginal ultrasound showed a viable intrauterine pregnancy with good fetal heartbeat. In addition, the ultrasound showed several ovarian cysts, with the largest on the left side. On the same day, the subject experienced significant pain in the lower left quadrant of the abdomen. A repeated transvaginal ultrasound showed multiple ovarian

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cysts, with the largest on the right side, and free fluid on the left side consistent with a ruptured ovarian cyst. The day after, she was admitted to the hospital for observation and pain management. She was prescribed pain medication and was discharged from the hospital on the same day. A week after, she reported persistent pain despite pain medication. The physical examination revealed tenderness in the left lower quadrant, but without signs of acute abdomen. The transvaginal ultrasound showed a single live intrauterine pregnancy with strong fetal cardiac activity, and bilateral enlarged ovaries with multiple cysts. She fully recovered from the adverse event 22 days after the onset, in January 2019.

Reviewer's Comment:

This SAE was singular in nature. Ruptured ovarian cysts are common in women undergoing ovarian stimulation from IUI and IVF. This information does not alter the expected safety profile of MILPROSA.

Participant USA (b) (6): A 29-year-old woman was diagnosed with adnexal torsion while enrolled in trial 000293. Her medical history included dilation and curettage secondary to elective abortion, colon resection, and 2 occurrences of letrozole/IUIs. No relevant concomitant medication was disclosed. The woman started MILPROSA in December 2018 and underwent embryo transfer 4 days later. In January 2019, during her fifth MILPROSA treatment, she went to the emergency room due to severe abdominal pain. The transvaginal ultrasound showed an ovarian torsion, and on the same day, the woman underwent right salpingo-oophorectomy. The woman was fully recovered from the adverse event the day after the onset. The end-of-trial visit took place in March 2019.

Reviewer's Comment:

Ovarian torsion is unlikely to be caused by progesterone supplementation. Enlarged ovarian cysts are common in women undergoing ovarian stimulation from IUI and IVF and can lead to ovarian torsion. This information does not alter the expected safety profile of MILPROSA.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

All discontinuations with the exception of a singular case of suicidal ideation were due to non-viable pregnancies. The SOC and adverse events associated with discontinuations are presented in below Table 9.

Table 9 Adverse Events Leading to Discontinuation in Trial 000293, MILPROSA N=254

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System Organ Class	Adverse Event	n	N=254 %
Pregnancy, puerperium and perinatal conditions	Biochemical abortion	25	9.8%
	Ectopic pregnancy	1	0.4%
	Spontaneous abortion	17	6.7%
Psychiatric disorders	Suicidal ideation	1	0.4%
TOTAL		44	17.3%

Source: NDA 201110, JMP Analysis Dataset ADAE, accessed February 12, 2020.

Reviewer's Comment:

With the exception of suicidal ideation, the observed AEs leading to discontinuation are not unanticipated given that progesterone supplementation is used to support pregnancy. In cases where the pregnancy is interrupted due to non-viability, progesterone supplementation should be stopped. As previously mentioned, depression is currently in progesterone labeling warnings and precautions, therefore the singular case does not alter the safety profile of MILPROSA.

8.4.4. Significant Adverse Events

8.4.4.1. Primary and Secondary Endpoints: Spontaneous Abortions

The primary endpoint for this safety trial was any spontaneous abortion occurring on or before 12 weeks following oocyte retrieval in all women treated with MILPROSA and undergoing embryo transfer. It was defined as two positive β -hCG tests occurring at least 2 days apart on or after 2 weeks post-oocyte retrieval, followed by 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 defined as 15% to bridge to safety data from the original phase 3 efficacy and safety trial.

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 and secondary endpoint analyses are present in Table 10.

Table 10 Results of Primary and Secondary Endpoints Analyses:

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)

Reviewer's Comment:

The total number of women experiencing the primary endpoint (spontaneous abortion at 12 weeks) was 18 out of 243 women in the MITT population (7.4%). The upper confidence interval for the primary endpoint (spontaneous abortion at 12 weeks) was 11.5%, which is well below the a priori determined cutoff of 15%, indicating that this safety data does not raise concerns with respect to the rate of spontaneous abortion in comparison to that in the original efficacy and safety Trial DR-PGN-302 for MILPROSA.

8.4.4.2. Adverse Events of Special Interest

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

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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.

Table 11 Adverse Events of Special Interest Occurring in the Treatment Phase, Trial 000293

System Organ Class	Adverse Event	n	MILPROSA 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 ring intended for commercial vaginal use, it was important to evaluate adverse event potentially resulting from direct contact with the ring. 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).

Reviewer's Comment:

The overall percentage of treatment emergent AESIs was low among women using MILPROSA in this trial. AESIs were focused on identifying vulvovaginal and cervical effects of MILPROSA. Based on these data, the MILPROSA vaginal system appears to be well-tolerated by women exposed to MILPROSA with few vulvovaginal or cervical side effects.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Overall, just under half of women in Trial 000293 experienced one or more TEAEs. Women in Trial 000293 experienced AEs that were overall consistent with other progesterone drug products. TEAEs (occurring in more than 2% of women) are displayed in Table .

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Table 12 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

Other less common reactions included vulvovaginal mycotic infection, dizziness, breast tenderness, abdominal distention, dysmenorrhea, and vaginal hemorrhage.

The majority of AEs were mild (102) or moderate grade (46). There were 9 AEs that were severe grade in nature, as shown in

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Table . Four of these were serious adverse events and are discussed in section 8.4.2 above.

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Table 13 Adverse Events Graded as Severe, Trial 000293

System Organ Class	Severe Adverse Event	n	N=254 %
Gastrointestinal disorders	Hyperemesis	1	0.4%
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	2	0.8%
	Cervical incompetence	1	0.4%
	Ectopic pregnancy	1	0.4%
Psychiatric disorders	Suicidal ideation	1	0.4%
Reproductive system and breast disorders	Adnexal torsion	1	0.4%
	Ovarian cyst ruptured	1	0.4%
TOTAL		9	3.5%

Source: NDA 201110, JMP Analysis Dataset ADAE, accessed February 13, 2020.

Reviewer's Comment:

The AE data observed in Trial 000293 are consistent with AE data in the phase 3 efficacy and safety Trial DR-PGN-302 as well as labeled adverse reactions in other progesterone drug products. The AEs are also expected in this population given that they are consistent with early pregnancy. This data does not affect labeling. Frequent AEs from the phase 3 efficacy and safety trial will be included in labeling.

8.4.6. Laboratory Findings

Laboratory values of the safety population were analyzed using shift tables to evaluate a change from baseline (visit 4) to abnormal values for liver enzymes (ALT, AST only as applicant did not collect Bilirubin), hematologic labs (hematocrit, hemoglobin), creatinine, and glucose at visit 9 and at the end of trial visit.

Pertinent findings are presented in Table below.

Table 14 Clinically Relevant Results of Laboratory Values from Trial 000293- Shift Table Analysis, Safety Population

Visit	Lab	Shift	N1	n	Percent
9	ALT	3 times the ULN	248	1	0.4
9	Creatinine	3 times the ULN	248	0	0
9	Glucose	High	235	1	0.4
9	Hematocrit	Low	220	21	9.5

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9	Hemoglobin	Low	223	27	12.1
EOT	AST	3 times the ULN	244	1	0.4
EOT	Hematocrit	Low	214	34	15.9
EOT	Hemoglobin	Low	214	37	17.1

ULN=Upper Limit of Normal, N1=women with lab drawn at baseline, n=number of women with the abnormal value, EOT=End of trial.

Participant USA (b) (6):

A 24-year-old woman with a body mass index of 29.07 kg/m² presented high alanine aminotransferase (ALT) levels during visit 9 while enrolled in Trial 000293. The participant did not disclose any relevant medical history. Relevant concomitant medication included FIORICET (which contains acetaminophen) as needed for migraine headaches. Additionally, she used acetaminophen 1000 mg for treatment of pain following embryo transfer. With regard to alcohol use, the participant reported consumption of 1-2 drinks per week during the 3 months prior to screening. The participant started PVR treatment on December 1, 2018 and underwent embryo transfer on December 5, 2018. At visit 9, on 08 February 2019, the participant presented high ALT levels. ALT levels increased from 10 U/L at screening to 91 U/L (normal range 6-29 U/L) at visit 9. This event was marked as abnormal not clinically significant by Dr. Doody, with the comment "repeat with OB MD". At visit 10 (end-of-trial visit), on February 22, 2019, ALT levels had decreased to 67 U/L. This event was marked as abnormal not clinically significant, with the comment "follow-up with OBGYN". The participant was pregnant with a twin pregnancy at the end-of-trial visit. No relevant adverse events were reported during the trial.

Participant USA (b) (6):

A 29-year-old woman with a body mass index of 35.61 kg/m² presented high aspartate aminotransferase (AST) levels during end-of-trial visit while enrolled in Trial 000293. The participant did not disclose any relevant medical history or concomitant medications. With regard to alcohol use, the participant reported consumption of 1-2 drinks per week during the 3 months prior to screening. The participant started PVR treatment on October 30, 2018 and underwent embryo transfer on November 3, 2018. At visit 10 (end-of-trial visit), on December 5, 2018, the participant presented high AST levels. AST levels increased from 19 U/L at screening to 93 U/L (normal range 10-30 U/L) at visit 10. This event was marked as abnormal not clinically significant with no comments. The participant discontinued PVR treatment on November 19, 2018 due to adverse event of biochemical abortion (15 November 2018). At visit 9, on November 20, 2018, the participant's AST levels were 17 U/L, i.e. within normal range. The participant was not pregnant and had discontinued PVR treatment at the time of the abnormal AST result. No other relevant adverse events were reported during the trial. Follow up after the trial revealed that LFTs returned to normal levels and the participant was asymptomatic. Concomitant medications at the time of oocyte retrieval and embryo transfer included acetaminophen.

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Reviewer's Comment:

The overall safety profile of MILPROSA appears favorable based on laboratory values observed. The highest percentage of shifts occurred in women that developed anemia however, this is consistent with early pregnancy which is associated with a physiologic anemia and can occur following blood loss secondary to spontaneous abortion. There were singular abnormal values related to liver function in 2 different women which is not significant for a liver signal with this product. Both cases that involved a transient rise in LFTs involved acetaminophen. Liver toxicity is a well-known side effect with acetaminophen. Labeling changes to MILPROSA based on this information are not warranted at this time.

8.4.7. Vital Signs

Vital signs were evaluated using a shift table analysis see Table 15.

Table 15 Vital Sign of Women Participating in Trial 000293- Shift Table Analysis, Safety Population

Condition	n	N=254
Systolic blood pressure (mmHg)		
Increase of ≥ 20 from baseline	47	18.5%
Increase of ≥ 20 from baseline and systolic blood pressure ≥ 130	28	11%
Increase of ≥ 20 from baseline and systolic blood pressure ≥ 160	1	0.4%
Decrease of ≥ 20 from baseline	21	8.3%
Diastolic blood pressure (mmHg)		
Increase of ≥ 20 from baseline	22	8.7%
Increase of ≥ 20 from baseline and diastolic blood pressure ≥ 80	22	8.7%
Increase of ≥ 20 from baseline and diastolic blood pressure ≥ 110	1	0.4%
Decrease of ≥ 20 from baseline	12	4.7%

n=number of women with condition

Participant USA (b) (6):

A 33-year-old woman with a body mass index of 34.28 kg/m² presented elevated systolic blood pressure (SBP) and diastolic blood pressure (DBP) while enrolled in Trial 000293. The event of elevated blood pressure was recorded in the medical history of the participant at screening visit. No other relevant medical history or concomitant medications were disclosed. With regard to alcohol use, the participant reported consumption of 3-5 drinks per week during the 3 months prior to screening. The participant started PVR treatment on January 18, 2019 and underwent embryo transfer on January 23, 2019. At screening, on October 11, 2018, the participant presented an SBP of 159 mmHg and a DBP of 105 mmHg. This event was marked as abnormal clinically significant and was recorded in the participant's medical history. At visit 4,

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on January 18, 2019, the participant presented an SBP of 144 mmHg and a DBP of 92 mmHg. This event was marked as abnormal not clinically significant by the investigator, who reported that the participant had a history of situational hypertension or white coat syndrome, and thus, was to monitor her blood pressure at home. At visit 6, on January 31, 2019, the participant presented an SBP of 164 mmHg and a DBP of 102 mmHg. This event was marked as abnormal not clinically significant by the investigator, who reported that the participant's SBP and DBP at home were 110 mmHg and 78 mmHg, respectively. At visit 10 (end-of-trial visit), on April 11, 2019, the participant presented an SBP of 141 mmHg and a DBP of 96 mmHg. The results were considered normal by the investigator as the participant's SBP and DBP at home were 122 mmHg and 78 mmHg, respectively.

Participant USA (b) (6):

A 31-year-old woman with a body mass index of 37.12 kg/m² presented elevated systolic blood pressure (SBP) and diastolic blood pressure (DBP) while enrolled in Trial 000293. The participant did not disclose any relevant medical history. Relevant concomitant medication included PROZAC (fluoxetine) administered daily for depression / anxiety. The participant reported no alcohol use during the 3 months prior to screening. The participant started PVR treatment on November 13, 2018 and underwent embryo transfer on November 17, 2018. At screening, on September 14, 2018, the participant presented an SBP of 128 mmHg and a DBP of 78 mmHg, which were marked as normal by the investigator. At visit 7, on December 3, 2018, the participant presented an SBP of 136 mmHg and a DBP of 114 mmHg. This event was marked as abnormal not clinically significant by the investigator, who reported that the participant was nervous for the laboratory results. At visit 10 (end-of-trial visit), on February 5, 2019, the participant presented an SBP of 156 mmHg and a DBP of 98 mmHg. This event was marked as abnormal not clinically significant by the investigator, who reported that the participant's SBP and DBP were elevated due to stress and asked the participant to monitor her blood pressure at home. The participant was pregnant with a singleton pregnancy at the end-of-trial visit. No adverse events were reported during the trial. Comorbidities included depression and anxiety.

Reviewer's Comment:

There was a singular case in severe range hypertension systolic and diastolic blood pressure readings in two separate women. Both women may have had untreated underlying hypertension.. These safety data do not raise concern for a signal related to blood pressure findings with MILPROSA.

8.4.8. Electrocardiograms (ECGs)

There were no ECG studies indicated or submitted in this class 2 NDA resubmission.

8.4.9. QT

There were no QT studies indicated or submitted in this class 2 NDA resubmission.

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8.4.10. Immunogenicity

There were no immunogenicity studies indicated or submitted in this class 2 NDA resubmission.

8.5. Analysis of Submission-Specific Safety Issues

There were no submission specific safety issues identified in this application.

8.6. Safety Analyses by Demographic Subgroups

The applicant did not perform safety analyses for demographic subgroups. An independent FDA analysis was performed to evaluate AEs by race and ethnicity. The percentages for the primary outcome spontaneous abortion are as follows: Asian 9.1% (2/22), Black/African American 17.6% (3/17), White 6.2% (13/210), Hispanic/Latina 6.7% (2/30), and Not Hispanic/Latina 7.1% (16/224).

Reviewer's Comment:

Given that this is a single arm trial that does not have a control, on-treatment subgroup differences cannot be separated from potential baseline subgroup differences; preventing meaningful conclusions.

8.7. Specific Safety Studies/Clinical Trials

The reader is referred to the original NDA review for a full discussion of safety studies/clinical trials.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

There were no carcinogenicity studies performed in this review cycle. According to the National Toxicology Program, 14th report on carcinogens, progesterone is "*reasonably anticipated to be human carcinogen*" based on sufficient evidence of carcinogenicity from studies in experimental animals. Progesterone implanted subcutaneously in female mice led to an increase in the incidence of mammary gland cancer (carcinoma) as well as ovarian tumors (granulosa cell) and tumors of the uterus (endometrial sarcomas). A number of case-control and cohort studies have been conducted to evaluate the risk of breast and endometrial cancer associated with prolonged use of progesterone only contraceptives. The International Agency for Research on Cancer (IARC) concluded that there was inadequate evidence of carcinogenicity in progesterone only contraceptives. However, an increased risk of breast cancer was observed

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in women over 40 years of age following prolonged progesterone only contraceptive use.⁴

One small study evaluated breast cancer risk in women with infertility treated with progesterone. A threefold increase of breast cancer was reported however other drugs were administered in addition to progesterone therefore it is unclear if progesterone led to the increased risk.

Reviewer's Comment:

There is insufficient evidence to determine the carcinogenicity of MILPROSA in humans at this time.

8.8.2. Human Reproduction and Pregnancy

Progesterone is routinely used to support the luteal phase, embryo implantation and clinical pregnancy maintenance.

Congenital anomalies in this safety trial included one case trisomy 18 identified in a 16-week fetus which ended in termination, and one case of renal aplasia identified in a 20-week fetus.

Congenital anomalies reported in the phase 3. double-blind, active, concurrently-controlled clinical trial included in the MILPROSA group: one fetus with arthrogryposis 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.

In the active comparator there were 17 congenital anomalies reported including: one fetus with abnormal karyotype (not specified), one fetus with acrania, one fetus with anencephaly, one fetus with atrial septal defect, one fetus with bilateral hernias, one fetus with cleft palate, two fetuses with congenital heart disease, one fetus with an enlarged clitoris, cardiac defect and hydrocephalus, one fetus with holoprosencephaly, two fetuses with hypospadias, one fetus with hypospadias and hydrocephalus, one fetus with multiple fetal anomalies, one fetus with spina bifida and hydrocephalus, one fetus with trisomy 16 and one fetus with Turner's Syndrome.

Reviewer's Comment:

Based on the available data there does not appear to be increased risks of congenital

⁴ National Toxicology Program, Report on Carcinogens, 14th Ed. Progesterone, CAS No. 57-83-0, <https://ntp.niehs.nih.gov/ntp/roc/content/profiles/progesterone.pdf>, accessed on February 24, 2019

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anomalies in the offspring of MILPROSA-exposed mothers.

8.8.3. Pediatrics and Assessment of Effects on Growth

Pediatric assessments and effects on growth were not performed in this NDA resubmission.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Progesterone is not a drug of abuse potential. Given the slow release of progesterone via vaginal ring, overdose is highly unlikely. There is no evidence of withdrawal following use of progesterone.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

The safety of progesterone in the postmarket setting is well established and the safety of MILPROSA is not expected to vary greatly given the results in this and the pivotal controlled trial previously reviewed in the original NDA.

8.9.2. Expectations on Safety in the Postmarket Setting

The safety information presented in this review is likely to be consistent with safety findings in the postmarket setting.

8.9.3. Additional Safety Issues From Other Disciplines

Safety issues from other disciplines are not relevant to this review.

8.10. Integrated Assessment of Safety

Ferring Pharmaceuticals, Inc. submitted only one Trial 000293 in this Class 2 NDA resubmission.

9. Advisory Committee Meeting and Other External Consultations

There is no indication for an advisory committee for this application given the well-established efficacy and safety profile of progesterone for the proposed indication.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Prescription drug labeling includes a presentation of safety and efficacy data findings for all age groups (18-42 years of age) as well as stratified efficacy data (18-34 years of age and 35-42 years of age) from the original pivotal clinical trial submitted on April 30, 2010.

Recommendations made to the sponsor include the following:

- Included the age range for approved subgroups in the Indications and Usage section (women up to and including 34 years of age). Limitation of use statement stating that efficacy in women 35 years of age and older has not been established.
- Updated formatting and content for consistency with the current FDA drug labeling recommendations.
- “(b) (4)” terminology changed to “vaginal system” terminology throughout the labeling.
- Updated Highlights and Clinical Study Experience to include all treatment related adverse reactions over 2%.
- “(b) (4)” updated to “severe hepatic impairment or disease” for more specificity in contraindications. Contraindication on breast cancer retained as supported by literature provided by the applicant to support the contraindication. A contraindication for genital organ malignancy was rejected given the protective benefits of progesterone on uterine cancer and the applicant did not provide literature to support the contraindication. The applicant deleted the contraindication for known missed abortion or ectopic pregnancy.
- Clarified General Dosing Information (Section 2.1) to clarify the duration of use of MILPROSA.
- Active comparator data was removed from labeling in Adverse Reactions and Clinical Trial Experience. Performance relative to active comparator beyond efficacy and a determination of safety is irrelevant to the users of the product.
- Pregnancy data was updated to include the following:

“In clinical trials, among 813 women less than 35 years of age who were treated with MILPROSA, 75 (9.2%) had a spontaneous abortion and 6 (0.7%) had an ectopic pregnancy. Of the 813 women less than 35 years of age, 559 (68.8%) were planned to be followed through birth. Among the 559 to be followed through birth, 263 (47.0%) had livebirths consisting of 154 (58.6%) singletons, 102 (38.8%) twins, and 7 (2.7%) triplets. In this same cohort of treatment, 10 (1.8%) had a second or third trimester loss. Neonatal birth defects were reported in 8 (2.1%) of infants based on 379 liveborn infants. In the 2.1% of live born infants with birth defects for women less than 35 years of age treated with MILPROSA the following were noted: Turner’s syndrome; Tetralogy of Fallot; and congenital anomalies including left foot deformity, hypospadias, pyloric stenosis, spina bifida, multiple congenital anomalies, and multiple congenital anomalies with VACTERL association.”
- Modified statement related to avoid “other vaginal products” *if possible* given that they

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were not studied with MILPROSA use.

- Clinical Studies was updated with additional efficacy data.
- Included information to clarify the association between Toxic Shock Syndrome and vaginal systems.
- Included an additional sentence in the Pediatric Use (section 8.4) to reflect that safety and effectiveness of MILPROSA in pediatric patients have not been established.
- Updated storage and handling (section 16) with the amount of progesterone release daily over 7 days of use. Dosage strengths were added to this section.
- Negative data was deleted from Nonclinical Toxicology section and updated to reflect that nonclinical studies to determine carcinogenicity or mutagenicity have not been performed and that fertility in animals has not been evaluated.

10.2. Nonprescription Drug Labeling

This product will not be used as an over-the-counter product at this time. Non-prescription drug labeling is not relevant to this application at this time.

11. Risk Evaluation and Mitigation Strategies (REMS)

There is no indication for REMS for this application given the well-established safety profile of progesterone for the proposed indication.

12. Postmarketing Requirements and Commitments

Ferring Pharmaceuticals, Inc. has committed to a full postmarketing trial to evaluate efficacy and safety in a phase 3 double-blind, placebo-controlled trial in women aged 35 to 44 years of age. The applicant reported that they will submit a clinical study protocol for FDA review and concurrence following this NDA review cycle.

13. Appendices

13.1. References

References documented in footnotes above.

13.2. Financial Disclosure

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Covered Clinical Study (Name and/or Number): Trial 000293

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>14</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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/s/

REGINA R ZOPF
04/24/2020 12:16:08 PM

SHELLEY R SLAUGHTER
04/29/2020 08:56:58 AM
I concur with Dr. Zopf's recommendation to approve.

Deputy Division Director Summary Review

Date	November 23, 2016
From	Audrey Gassman, MD
NDA #	201110
Applicant name	Ferring Pharmaceuticals Inc.
Date of submission	February 25, 2016
PDUFA goal date	August 25, 2016 (extended to November 2016)
Proprietary name/established name	Milprosa vaginal ring/progesterone vaginal ring
Dosage form/strengths/regimen	Silicone vaginal ring containing 1.78 grams of progesterone with average release rate of 11 mg/day
Proposed indication	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
Proposed regimen	One vaginal ring starting on the day after oocyte retrieval and replaced weekly for up to 10-weeks total use
Action	Complete Response

Material reviewed/consulted	Names of discipline reviewers
Project Regulatory Manager/Chief Project Regulatory Manager	Nikia Morris/Margie Kober
CDTL	Shelley R. Slaughter, MD, PhD
Medical Officer Reviewer	Rhonda Hearn-Stewart, MD
Statistical Review Team	Weiya Zhang PhD/Mahboob Sobhan, PhD
Pharmacology/toxicology Review	Leslie McKinney, PhD, Mukesh Summan PhD, DABT
Clinical Pharmacology Review	Peng Zou, PhD Doanh Tran, PhD
OPQ (CMC) Review Leads Drug Substance Drug Product Process Facility Biopharmaceutics Environmental Assessment	Mark Seggel, PhD Ben Stevens Bhavi Mittal James Norman Vipulchandra Kalpana Paudel James Laurenson
Product Quality Microbiology	Erika Pfeiler, PhD Jennifer Patro, PhD
DMEPA Tradename review Label and Labeling Review	Denise Baugh, PharmD, BCPS Danielle Harris, PharmD, BCPS Denise Baugh, PharmD, BCPS Lolita White, PharmD
CDRH Biomedical Engineer	Monica Garcia, PhD/Sharon Andrews
CDRH Division of Manufacturing and Quality	Pushya Potnis
Division of New Drug Bioequivalence Evaluation (DNDBE) In Vivo clinical site inspection Analytic site inspection	Yiyue Zhang, PhD Ruben Ayala, PhD Charles Bonapace, Pharm D Shila Nkah

OND=Office of New Drugs

CDTL=Cross-Discipline Team Leader

CMC = Chemistry, Manufacturing and Controls

OPQ = Office of Product Quality

OPDP= Office of Prescription Drug Promotion

DMPP=Division of Medical Policy Programs

DMEPA=Division of Medication Error Prevention and Analysis

OSI=Office of Scientific Investigations

CDRH= Center for Devices and Radiologic Health

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- 4. Nonclinical Pharmacology/Toxicology**
- 5. Clinical Pharmacology**
- 6. Clinical Microbiology**
- 7. Efficacy/Statistics**
- 8. Safety**
- 9. Advisory Committee Meeting**
- 10. Pediatrics**
- 11. Other Relevant Regulatory Issues**
- 12. Labeling**
- 13. Decision/Action/Risk Benefit Assessment**

1. Introduction

Ferring Pharmaceuticals, Inc. submitted a Complete Response to NDA 201110 to obtain marketing approval for Milprosa (Progesterone) Vaginal Ring for the proposed indication “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.” Currently, there are 2 vaginal progesterone products (Crinone® and Endometrin®) that are approved in the US for the same or a similar indication.

This progesterone vaginal ring (also referred to as the PVR in this review) is a non-biodegradable, flexible silicone ring with progesterone as the active drug substance. The ring is inserted vaginally, starting on the day after oocyte retrieval in women as part of an ART treatment program. The ring is replaced every 7 days, is used for up to 10 weeks, after which the placenta produces sufficient progesterone to support an on-going pregnancy.

The original application for NDA 201110 was submitted on April 20, 2010, by a previous Applicant (Teva Branded Pharmaceutical Products, Inc.). The NDA received a Complete Response letter on February 28, 2011, as a result of significant CMC and microbiology deficiencies. An additional deficiency outlined in the letter was related to a clinical concern that the Applicant failed to provide adequate data to support the safe and effective use of the product in women 35 to 42 years of age.

The current Applicant (Ferring Pharmaceuticals) submitted a Complete Response to address the deficiencies identified in the Agency’s February 2011 CR letter. The response contains updated CMC, microbiological and labeling information. The response also contains data from a bioequivalence study (DR201-BE-10021) conducted to support transfer to a new manufacturing site.

After an initial review of the current Complete Response, the progesterone vaginal ring was determined to be a drug device combination product under 21 CFR 3. The Center for

Devices and Radiologic Health (CDRH) review teams were consulted to review the engineering and manufacturing processes of the ring from a device perspective. The CDRH review teams evaluated the resubmission and sent an Information Request letter to the Applicant (see letter dated May 23, 2016). The May 2016 letter requested details on the mechanical properties, shelf-life evaluation, biocompatibility of the ring as well as a risk analysis that evaluates use of the progesterone vaginal ring with other intravaginal devices (such as intravaginal lubricants).

The Applicant's response to the CDRH review team's May 23, 2016 request was received on June 27, 2016. The June 2016 submission was determined to be a major amendment. As a result of the June 2016 submission, the goal date for the resubmission was extended for the Complete Response from August 10, 2016 to November 25, 2016.

The memorandum provides the basis of the regulatory action of this application.

2. Background

The active drug product in the vaginal ring, progesterone, is a Drug Efficacy Study Implementation (DESI) product. Development of this progesterone vaginal ring was initiated by a previous sponsor (Duramed Research) under IND 70,875 in 2004. During the development of the product, there were several interactions between the Division and Duramed Research. These interactions included an End-of-Phase 2 meeting (conducted on June 13, 2007) and a Special Protocol Assessment (SPA) received on October 26, 2007. The SPA submission resulted in a No Agreement letter sent on December 13, 2007 with a number of clinical and statistical comments. Further discussion of the phase 3 protocol was continued through 2008 through protocol amendments and a Type A meeting on January 18, 2008. During these discussions, the Agency found the overall design, endpoints and primary analysis of the proposed phase 3 trial generally acceptable.

During the original NDA review cycle, the following CMC and microbiologic deficiencies were conveyed to the applicant in the Complete Response letter:

- 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.
- 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.
- 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) ."

- Analytical methods for the drug product are inadequate. To address this deficiency:
 - o Validate the accuracy of the HPLC test method for detection of impurity/degradation products in the drug substance.
 - o Validate the repeatability and intermediate precision of the drug product impurity test using samples spiked with the four known impurities at quantitation levels (QL).
 - o Revise the acceptance criteria of the relative standard deviation (RSD) (b) (4) for establishing the system suitability of the HPLC method.

In addition, a clinical deficiency was outlined in the Complete Response letter regarding the lack of data in women 35 to 42 years of age. Of note, the Division Director stated in his summary review (dated February 28, 2011) that he believed that this could be handled through labeling and/or a postmarketing commitment to allow safe and effective use of the vaginal ring product.

After the Complete Response letter, the Applicant notified the Agency that the corporate name of the Applicant was changed to Teva Branded Pharmaceutical Products, Inc. on February 16, 2011. On August 5, 2015, the Applicant (Teva) notified the FDA that this NDA and the associated IND (070875) were transferred to the current Applicant (Ferring) – Refer to Agency acknowledgement letter sent October 8, 2015.

On February 25, 2016, Ferring submitted their response to the 2010 Complete Response letter.

Comment: No pre-NDA or guidance meeting was requested by the Applicant prior to submission of the February 2016 Complete Response.

After review of the Applicant's Complete Response, the progesterone vaginal ring was reclassified as a drug device combination. Intercenter consults were sent on March 3, 2016 to the Obstetrics/Gynecology Devices Branch and the Office of Compliance. The Obstetrics and Gynecology Devices Branch requested additional information from the Applicant in May 2016. A response to the May 26, 2016 Information Response letter was received on June 27, 2016. Details on the CDRH consults and conclusions reached by the CDRH reviewers are outlined in section 11 (Other Relevant Regulatory Issues) of this review.

3. CMC - OPQ

The active drug substance for this Application is progesterone, USP (b) (4) which has been used in previously approved drug products. The progesterone vaginal ring product is a non-biodegradable, flexible silicone ring containing solely progesterone as the active drug substance. The progesterone vaginal ring product consists of a mixture of a silicone elastomer (b) (4), light mineral oil, and progesterone, USP (b) (4). The active drug substance is present in a (b) (4) % w/w concentration (b) (4) dispersed

evenly within the ring. The ring has a cross-sectional diameter of (b) (4) mm and an outer diameter of 55 mm. Each ring contains 1.78 grams of USP grade progesterone.

The CMC review team assessed (b) (4) product used to produce the vaginal ring in the first review cycle and determined that it was suitable for use as a matrix material (See CMC review dated February 7, 2011).

The drug product was produced by (b) (4)

In the original review cycle, establishment evaluations were conducted. Visible (b) (4) particles were found on the finished drug products of all five site transfer batches. The Applicant conducted a root cause for the contamination and determined that the rings were not manufactured with adequate controls in the process, equipment and environment.

As a result of the contamination found at both the testing and manufacturing sites, the Office of Compliance recommended an overall “WITHHOLD” action on (b) (4). Based on the significant deficiencies related to manufacturing and product quality, the CMC review team determined that the Applicant had not provided sufficient information to assure the identity, strength, purity and quality of the drug product. The CMC review team also noted that the Office of Compliance had made an overall “WITHHOLD” recommendation for the facilities involved in the NDA. The CMC review team stated that in their review dated February 7, 2011, that, “...Therefore, from a CMC perspective, this NDA is not recommended for approval in its present form until all the pending issues are satisfactorily resolved.”

The CMC and facility deficiencies were summarized in the February 28, 2011 Complete Response letter and are outlined below:

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 the levels (QL).
 - Revise the acceptance criteria of the relative standard deviation (RSD) (b) (4) for establishing the system suitability of the HPLC method.

In addition, a number of other Product Quality and Microbiology comments related to the drug product manufacture were conveyed to the Applicant in the Complete Response letter. No postmarketing commitments or requirements were recommended by the OPQ review teams during the original review cycle.

In this second review cycle, the CMC review teams evaluated the resubmission and focused on manufacturing and product quality deficiencies identified in the original 2011 Complete Response. The Applicant had instituted corrective measures for the (b) (4) defects and also added testing for foreign particulate matter in the raw materials.

An Executive Summary from the Office of Product Quality was signed on November 10, 2016. In this review, the following was noted:

- Drug Substance review team – the team determined that the drug substance was well-controlled and product quality confirmed through several batch analyses at different stages of development. The team recommended approval of the application.
- Drug Product review team – the team focused their evaluation on the methodology the Applicant used to correct deficiencies in the original submission. The Applicant had used a (b) (4) method in the original submission and had changed this to a (b) (4) method. In addition, the Applicant added tests for foreign particulate matter in the raw materials and a complete (b) (4) visual inspection. Since the implementation of these methods, the Applicant had not identified foreign particle contamination in the drug product.

The Drug Product Reviewer also noted that the new process product contains (b) (4)

(b) (4) consists of ingredients of unknown acute toxicity. During the review cycle, the Center for Devices and Radiological Health (CDRH) reviewer was asked to evaluate the progesterone vaginal ring product from a device perspective.

The CDRH review raises concerns regarding absence of biocompatibility data on the to-be-marketed drug-device combination product using the new (b) (4) process. CDRH clarified to the sponsor through a series of information requests that biocompatibility evaluation on the final, finished (to-be-marketed) progesterone vaginal ring will be required to ensure that the device component of the ring is biocompatible and safe for use in humans. The CDRH biomedical engineer raised concerns regarding the lack of biocompatibility with the to-be-marketed drug-device combinations and discussed these issues with the Drug Product review team and Application Team Lead. The Drug Product review team stated in their review that, “The concerns expressed by CDRH are parallel to the concerns raised by ONDP. If the sponsor addresses the biocompatibility concerns by CDRH, they effectively address the concerns raised by ONDP as well. Also, the one-time thoroughly complete biocompatibility study would assure that the leachables do not need to be monitored during product stability testing. A follow-up teleconference was conducted with the applicant. The applicant agreed to the recommendations provided by the Agency regarding biocompatibility testing. This section of the application is not acceptable until the results of the biocompatibility testing are submitted and they are acceptable to CDRH.”

No other deficiencies were identified by the Drug Process, Biopharmaceutics or Environmental Assessment review teams. In the OPQ Integrated Quality Assessment review #1, dated November 10, 2016, the Application Team Lead concluded that the resubmission was Not Ready for Approval. This determination was primarily based on the biocompatibility issues for the drug-device vaginal ring product identified by the CDRH biomedical engineer. At the time of this memo, the device GMP inspection was outstanding.

In a supplemental memo dated November 22, 2016, the Application Technical Lead stated that the device GMP inspection was acceptable per a Facilities review dated November 22, 2016. He stated that the final OPQ recommendation remained Not Ready for Approval based on the recommendations from CDRH.

Comment: Although the majority of the deficiencies related to CMC issues that were outlined in the Complete Response letter were adequately addressed, the Applicant will be informed of the deficiencies in biocompatibility and sensitization identified by the Center for Devices and Radiologic Health reviewers (refer to section 11).

4. Nonclinical Pharmacology/Toxicology

The active drug substance in the vaginal ring is progesterone. Progesterone is a naturally occurring hormone and has been used for the proposed indication for decades. The safety profile for progesterone is well established. No new nonclinical studies or data were submitted with the complete response.

In the first review cycle, the pharmacology/toxicology reviewer evaluated the nonclinical toxicology findings, which included data from 2 nonclinical toxicology studies in rabbits; a 10-day vaginal irritation study and a 90-day intravaginal toxicology study. After review, the pharmacology/toxicology reviewer concluded that the studies were acceptable and recommended approval of the ring from the nonclinical standpoint (See review dated July 16, 2010).

In the second review cycle, the pharmacology/toxicology reviewer stated that there were no new nonclinical studies in the resubmission that required review. The submission did not contain any changes in drug substance from the original submission. The pharmacology/toxicology reviewer also confirmed that the impurity profile was the same in the DMF and current application as the profile listed in the original submission. As specifications for the impurity profile were consistent with ICH guidelines, a pharmacology/toxicology review was not necessary. (See Pharmacology/Toxicology memo dated June 10, 2016).

The Pharmacology/Toxicology reviewer stated in her review dated June 10, 2016, that, “From a CDER Pharm/Tox perspective, based on prior review and approval of the drug substance, which is unchanged in this resubmission, this application is approvable.” No postmarketing commitments or requirements were recommended by the Pharmacology/Toxicology review team during either the original review cycle or this resubmission.

Comment: I concur that there are no outstanding nonclinical issues for this resubmission.

5. Clinical Pharmacology

The Applicant conducted 7 clinical studies that assessed progesterone pharmacokinetics and pharmacodynamics. In addition, the NDA contained results of a bioequivalence study (Study 10936035). This study compared the clinical trial formulation of the progesterone vaginal ring to the proposed commercial formulation. After review, the original Clinical Pharmacology reviewer concluded that there were no outstanding clinical pharmacology issues other than labeling (See Clinical Pharmacology review dated February 2, 2011).

As previously mentioned, the current Applicant changed the manufacturing processes for the drug product. No changes were made to the drug substance formulation. Drug product changes included replacing the (b) (4) method for the ring from (b) (4). Because of these significant changes in manufacture of the drug product, the Applicant conducted a study to bridge the revised “to be marketed” progesterone vaginal ring and the progesterone vaginal ring used in the clinical trials. The Applicant bridged the new ring to the original clinical trial product by manufacturing progesterone vaginal rings using both the new and original processes. A clinical bioequivalence study (Study DR201-BE-10021) was then conducted using rings manufactured by the new and legacy processes. The BE study was a comparative open-label, 2-treatment, 2-period crossover study with 7 days washout in postmenopausal women. Women were randomized to

receive either the progesterone vaginal ring manufactured using the new manufacturing processes (Treatment A) or the original manufacturing processes (Treatment B).

During this second review cycle, the Clinical Pharmacology review focused on review of the results of Study DR201-BE-10021. The Applicant concluded that the point estimates for the ratio between products from the new process compared to legacy process for all three PK parameters, C_{max}, AUC_{0-t}, and AUC_{0-∞}, were between 96 - 100%, while the 90 % confidence intervals (CIs) surrounding these ratios were contained entirely within the BE limits of 80 - 125% when using baseline corrected data.

Based on these results and the results from baseline uncorrected data from Study DR201-BE-10021, the Clinical Pharmacology reviewer concluded that the data demonstrated that the revised progesterone vaginal ring was bioequivalent to the original clinical trial ring. In the review dated September 7, 2016, the Clinical Pharmacology concluded that, “The DR-201 progesterone vaginal ring produced from the new process was bioequivalent to the DR-201 progesterone vaginal ring produced from the legacy process. The overall Clinical Pharmacology information submitted to support this NDA is acceptable.”

No postmarketing commitments or requirements were recommended by the Clinical Pharmacology review team during the original review cycle or after review of this resubmission.

Comment: I concur with the Clinical Pharmacology reviewer’s assessment and recommendations regarding comparable efficacy of the progesterone vaginal ring. However, the Medical Officer and CDTL remain concerned that there could be outstanding safety issues with the new to-be-marketed ring. For additional discussion regarding this issue, refer to section 8 of this review.

6. Clinical Microbiology

The Microbiology review team was consulted during the original review cycle to evaluate the microbiological attributes of the progesterone vaginal ring product. After review, the microbiological review team concluded that they could not recommend approval on the basis of product quality microbiology. Issues identified by the microbiologic review team included unacceptable microbiological specifications for control of drug product to include absence of (b) (4), issues with method validation studies for total yeast and mold count, and data from re-testing of stability and site transfer batches with a revised microbial testing method. (See Microbiology review dated February 8, 2011). These microbiological deficiencies were conveyed to the Applicant in the Complete Response letter dated February 28, 2011).

In this resubmission, the Microbiology review team reviewed the specifications and analytic procedures related to microbial testing. Specifically, the review team focused on three outstanding recommendations from the original 2011 NDA submission: 1) Revise the specifications to include the absence of (b) (4), 2) Supply the correct

temperature for total yeast and mold count and 3) Provide microbial enumeration testing results for stability and site transfer batches.

After reviewing the information in the Applicant's complete response, the Microbiology reviewer concluded that there were no outstanding issues. In her review dated August 3, 2016, she stated in her review summary, "Recommended for Approval".

Comment: I concur with the Clinical Microbiology reviewer for the Complete Response resubmission that from a quality microbiology standpoint, there are no outstanding issues.

7. Efficacy/Statistics

Efficacy data was submitted during the initial review cycle. Clinical efficacy data for the progesterone vaginal ring was obtained from one multicenter, randomized, single-blind (investigator and sonographer), active-controlled, non-inferiority clinical trial of progesterone supplementation in women undergoing in-vitro fertilization (IVF) with freshly retrieved oocytes designed as Trial DR-PGN-302. This phase 3 trial was conducted at 22 sites in the US. Women were randomized 1:1 to receive either the progesterone vaginal ring or Crinone (progesterone vaginal gel) 8% once daily as luteal support. The treatment duration was one cycle beginning on the day of oocyte retrieval and continuing through week 12 of pregnancy if pregnancy occurred. Baseline characteristics and demographics (age, weight, race) were similar between the two treatment groups.

The primary efficacy endpoint for Trial DR-PGN-302 was the clinical pregnancy rate (defined as the proportion of subjects with visualization of a gestational sac and fetal heart motion by ultrasonography at:

- Week 8 of pregnancy (6-weeks post oocyte retrieval)
- Week 12 of pregnancy (10-weeks post oocyte retrieval)

The primary efficacy population was the modified Intent-to-Treat (mITT) cohort, defined as including any subject who had a successful oocyte retrieval, were randomized, and received at least one dose of study drug. An overview of the clinical pregnancy rates at weeks 8 and 12 are listed in Table 1 below:

Table 1: Clinical pregnancy rate per retrieval for Trial DR-PGN-302*

Age	Week of Pregnancy	PVR	Crinone	Treatment difference (PVR-Crinone)
All	8	310/646 (48.0%)	307/651 (47.2%)	0.8% (-4.6%, 6.3%)
	12	300/646 (46.4%)	294/651 (45.2%)	1.3% (-4.1%, 6.7%)
18 to <35 years of age	8	275/558 (49.3%)	269/560 (48.0%)	1.2% (-4.6%, 7.1%)
	12	269/558 (48.2%)	258/560 (46.1%)	2.1% (-3.7%, 8.0%)
35 to 42 years of age	8	35/88 (39.8%)	38/91(41.8%)	-2.0% (-16.4%, 12.4%)
	12	31/88 (35.2%)	36/91(39.6%)	-4.3%(-18.5%, 9.8%)

*Source: Adapted from Table 3.2.3 of the statistical review dated February 18, 2011.

Although the treatment with progesterone vaginal ring was statistically non-inferior to treatment with Crinone for the mITT population, the results are driven by the majority of population of subjects between 18 and < 35 who represented 86% of study subjects. Therefore, Trial DR-PGN-302 did establish that treatment with progesterone vaginal ring was non-inferior to Crinone for luteal support in an ART program for women under 35, but not for those over 35 years who represent a large proportion of the women who undergo ART in the US.

After reviewing the efficacy data from Trial DR-PGN-302, the statistical reviewer concluded in his review dated February 18, 2011, that, "From a statistical perspective, this application provided adequate data to support the non-inferiority of DR-2011 (the progesterone vaginal ring) to Crinone in supporting 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 treatment program for younger infertile women aged 18-34. However, no definitive efficacy conclusion can be made for the limited number of women aged 35-42 studied in this trial." The Medical Officer and CDTL stated similar efficacy conclusions in their reviews both dated February 25, 2011.

Concern was raised regarding use in women over 35. Subgroup analysis of the MITT population demonstrated that when the progesterone vaginal ring was compared to the progesterone gel using the primary endpoint of clinical pregnancy per retrieval at 12 weeks of pregnancy, the ring group failed to meet the predetermined non-inferiority limit of 10% at the (12 week CI -4.3 (-18.5%, 9.8%). CDTL further stated that, "The data submitted by the applicant failed to demonstrate efficacy of the progesterone vaginal ring for luteal support of implantation and maintenance of an early pregnancy in women age 35 and older; this population of women represents 60% of the population of infertile women (couples) who undergo Assisted Reproductive Technology (ART) to become pregnant. As the indication is maintenance of a pregnancy, failure to demonstrate efficacy (i.e. failure to maintain pregnancy) is also a safety concern (See Clinical/Statistical Efficacy and Safety discussion)."

The Division Director concurred with the CDTL's concerns regarding use of the progesterone vaginal ring in women 35 and older. Based on the clinical concern, the February 2011 Complete Response identified the following Clinical deficiency:

- You have not provided sufficient evidence of efficacy for the progesterone vaginal ring 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.

During this second review cycle, no new efficacy data was submitted that required review. The statistical reviewer evaluated the resubmission and stated the following, “Efficacy results in the label will remain the same, and, therefore no statistical review is needed for this resubmission.” (See Statistical Memo dated June 27, 2016). No postmarketing requirements or studies were recommended by the statistical reviewer.

The Medical Officer also evaluated bioequivalence Trial DR201-BE-10021. The BE study design was an open-label, single dose (7-day vaginal ring), multiple site, two-treatment, two-period, two-sequence, randomized crossover study in N= 56 postmenopausal women. Subjects received a single dose of once-weekly vaginal ring formulation – either Test (the formulation produced from the new process or Treatment A) or Reference (the legacy formulation or Treatment B) in period I or period II of the study separated by 7-day washout duration. The primary objective of this study was to evaluate the bioequivalence (through pharmacokinetic endpoints) of two progesterone vaginal rings (the to-be-marketed vaginal rings from the new process and the legacy process) during a single 7-day application cycle in postmenopausal female subjects treated with estrogen.

The Medical Officer and CDTL agreed with the Office of Clinical Pharmacology that bioequivalence Trial DR201-BE-10021 provides acceptable bioequivalence information to support reliance on the findings of efficacy from the single phase 3 Trial DR-PGN-302 conducted in women less than 35 years of age using the progesterone vaginal ring product, manufactured with the old (legacy) (b) (4) process.

The Medical Officer and CDTL both noted that the Applicant proposes to accept a limitation of use in labeling for women over 35 to respond to the Clinical Deficiency in the February 2011 Complete Response letter. The CDTL disagrees with the Applicant’s limitation of use in her review dated November 22, 2016 and recommends that the Applicant conduct a new trial in this population.

Comment: I concur with the previous decision in 2011 by the Division Director. I believe that labeling with a limitation of use for women over 35 years of age is an acceptable approach based on the February 2011 Complete Response letter.

Efficacy Summary:

The efficacy database for the progesterone vaginal ring was reviewed by the clinical and statistical review teams during the first review cycle. Both the statistical and clinical review teams determined that the data was adequate for approval for women less than 35 years of age.

The Applicant submitted bioequivalence Trial DR-201-BE-10021 to bridge the efficacy of the progesterone vaginal ring used in the phase 3 clinical trials to that of the new to-be-marketed ring using a different manufacturing process. The Clinical Pharmacology and Clinical teams have determined that the evidence was acceptable and I agree.

8. Safety

Safety data in the first review cycle was obtained from four phase 1 studies, two phase 2 studies and the phase 3 clinical Trial DR-PG-302. The key safety database for the progesterone vaginal ring was obtained from Trial DR-PG-302 as that was the sole safety data in the intended population of women undergoing ART. A brief summary of the safety findings from trial DR-PG-302 is outlined below:

Trial DR-PG-302 exposed 647 subjects to the progesterone vaginal ring and treated 650 subjects with an approved comparator progesterone gel (Crinone 8%). The mean exposure was 40.9 days for the progesterone vaginal ring and 41 for progesterone gel. Maximum allowed exposure to the ring or gel was 78 days which is one week longer than a complete cycle of use if pregnancy is supported through 12 weeks. In the original cycle, the Division Director summary memo dated February 28, 2011, stated that, "The size of the safety database is adequate for the proposed product and indication."

A total of 1234 women in Trial DR-PG-302 reported at least one AE with 622 of 648 (96%) in the progesterone vaginal ring group compared to 612 of 651 (94%) in the progesterone gel group. The most commonly reported treatment emergent AEs with a frequency over 15% were: nausea, headache, abdominal distention, and back pain. For these AEs, the percentages of subjects reporting them were similar across the two treatment groups.

The Medical Officer evaluated adverse vaginal events as this is the intended route of administration. Vaginal discharge was reported more commonly in the progesterone vaginal ring group (9.4%) as compared to the progesterone gel group (3.2%). However, percentages of subjects with reported vaginal infections and, urinary tract infections were clinically similar. An exploratory safety analysis by the Medical Officer of vaginal bleeding (all events combined that were reported using MedDRA terminology of vaginal hemorrhage and metrorrhagia) comparing the progesterone vaginal ring and progesterone gel showed a somewhat higher rate of bleeding in the progesterone gel group (5.8% in the progesterone gel compared to 5% in the progesterone ring group). However, when combining moderate and heavy bleeding adverse events, the rates were clinically similar (34.4% in the progesterone ring compared to 36% in the progesterone gel group). The Medical Officer determined that these bleeding rates did not represent a safety signal or trend and noted in his review dated February 28, 2011 that, "These types of adverse

events are not unreasonable for this type of trial. Some of them are not treatment related but may be due to concomitant treatments (i.e. IVF [in vitro fertilization]).”

Comment: I concur with the Medical Officer that the common AEs and potentially related vaginal AEs of interest in the phase 3 trial did not demonstrate a signal of concern for the progesterone vaginal ring. However, it is notable that the small sample size was likely unable to detect differences in adverse outcomes.

No maternal deaths were reported in the phase 3 trial and there were two neonatal deaths, one in each treatment group. No differences in congenital anomalies were reported between the two groups in the neonates and no safety signal or trend was identified in the neonatal safety data. At least one serious AE was reported in 83 of 647 subjects (12.8%) in the progesterone vaginal ring group and 72 of 640 (11.1%) in the progesterone gel group. Although anaphylaxis has been reported with other progesterone products, no SAEs or AEs of allergic or anaphylactic reactions were reported in the phase 3 trial.

Almost all of the serious AEs were related to either pregnancy loss or ovarian hyperstimulation syndrome (OHSS). The rate of OHSS and severe OHSS was roughly equivalent between the progesterone vaginal ring and progesterone gel groups (5.3% and 4.9%, 2.0% and 1.5%, respectively). Of importance, the CDTL noted that, “The Sponsor lists spontaneous abortion as 1.24% in the progesterone vaginal ring arm and 1.38% in the Crinone progesterone gel) arm. The rates in both arms appear low. However, when considering all of the capture terms indicating early pregnancy loss the rate is 6.5% in the progesterone vaginal ring arm and 6.1%. These rates are comparable and in the range of usual expectation for IVF trials.”

Comment: Although most early pregnancy loss is believed to result from chromosomal abnormalities, it is reassuring that there does not appear to be a difference in pregnancy loss or congenital anomaly rates that might raise concerns regarding inadequate luteal support from the progesterone vaginal ring.

The Medical Officer and CDTL also raised concerns that there was very limited safety data to inform whether the progesterone vaginal ring could maintain early pregnancy in women over 35.

After review of the safety data, the Division Director concluded that, “In summary, the overall safety profile for the progesterone vaginal ring, based on the data provided in the Application, was comparable to that of the approved active comparator Crinone (progesterone gel). There were no safety findings in the clinical development program for progesterone vaginal ring that raised any safety concerns or would preclude approval of the vaginal ring for the proposed indication.”

Comment: The concerns related to the lack of safety information (as well as efficacy) in women over 35 were considered by the Division Director during the first cycle and a decision was made to handle this through a limitation of use statement in the indication.

No other safety concerns or deficiencies were identified in the first cycle that required further evaluation by the Applicant.

In the resubmission, the Medical Officer and CDTL evaluated the safety data from the single bioequivalence trial (DR201-BE-10021). This trial was submitted to bridge the progesterone vaginal product used in the original phase 3 trial and the to-be-marketed progesterone vaginal ring product. In Trial DR201-BE-10021, no deaths, serious adverse events or withdrawal due to an adverse event were identified. The most frequently reported adverse events were in the reproductive and breast disorders systems and they were in a similar proportion of women in both treatment groups A (progesterone vaginal ring manufactured by the new process) and B (progesterone vaginal ring manufactured by the legacy process). All reported adverse events were mild except for one moderate case of withdrawal bleeding. The most frequently observed adverse event, withdrawal bleed, occurred in a similar proportion of women after each treatment. Pelvic pain, vaginal discharge and breast tenderness were also reported with similar rates in the treatment groups.

In her review dated November 21, 2016, the Medical Officer stated that, “The most common AE, withdrawal bleed, is not alarming in this trial. It is to be expected in this post-menopausal population that was pre-treated with estrogen, a withdrawal bleed would be expected after administration of progesterone. Vaginal discharge, cramping, and breast tenderness are common side effects associated with progesterone treatment.”

Both the Medical Officer and CDTL determined that the bioequivalence study was insufficient to determine if the newly manufactured progesterone vaginal ring would have the same safety profile, primarily in terms of local tolerance, as the previous ring product. The CDTL concluded in her November 22, 2016 review that, “this clinical reviewer has concerns that the safety of the to-be-marketed vaginal ring has not fully been assessed 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.” She also recommended that the safety (and possibly efficacy) of the to-be-marketed product be demonstrated pre-approval in both women less than 35 years of age with normal ovarian reserve and women 35 to 42 years of age with anticipated diminished ovarian reserve.

Comments:

- 1. As the Applicant is seeking a limitation of use in labeling, which is an acceptable path based on the 2011 Complete Response, I conclude there is no need to study the population of women 35 to 42 years of age at this time.*
- 2. As Clinical Pharmacology has determined that there is an adequate bioequivalence bridge to the legacy progesterone vaginal ring, I do not believe that additional trials to evaluate efficacy are needed.*
- 3. I do concur that there is an insufficient bridge for safety for the new progesterone vaginal ring as Applicant has only provided one week of safety data for a product that is intended for use up to 10 weeks post-embryo transfer. Therefore, I am recommending that the Applicant conduct a pre-market safety study. This study*

should be conducted to evaluate the clinical safety of the new progesterone vaginal ring. The study cohort should include women who are undergoing Assisted Reproductive Technology (ART) procedures as this is the intended population. This study should evaluate the safety and tolerability of the to-be-marketed ring over the entire duration of treatment (up to 10 weeks post-embryo transfer). In addition, data should be collected on the following:

- a. 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.*
- b. Adverse events related to pregnancy outcomes including miscarriage and ectopic pregnancy.*

The Applicant will be informed of the need for this study in the Complete Response letter.

Safety Summary:

In the first review cycle, the Division Director determined that the safety database was adequate from a clinical perspective to allow the vaginal ring product to be used in women under 35 years of age. In his Summary memo dated February 28, 2011, the Division Director stated that, "The deficiency identified by the primary clinical review team (failure of the Applicant to provide adequate data to support the safe and effective use of the product in women 35 to 42 years of age), however, could be addressed by (1) appropriate product labeling and (2) a postmarketing commitment by the Applicant to conduct an adequate and well-controlled clinical trial in women 35 to 42 years of age."

No new safety information regarding use of the progesterone vaginal ring in women over 35 years of age was submitted in the Applicant's Complete Response and labeling was proposed to respond to the February 2011 deficiency regarding adequate data in this population. However, as the Applicant intends to include a limitation of use statement for this population in labeling, no further data is needed for this resubmission.

In this resubmission, the safety database from a Bioequivalence Trial (DR201-BE-10021) were provided to support that safety of the to-be-marketed progesterone product can be bridged to the results in the phase 3 clinical trial with the original progesterone vaginal ring product. In my opinion, the Applicant has not provided an adequate safety bridge to the new progesterone vaginal ring product. The Applicant will need to provide additional clinical safety data in a study to evaluate the safety and tolerability of the new progesterone vaginal ring in the intended population with data over the entire treatment duration. This study should collect adverse event data that will be included in labeling for the product.

9. Advisory Committee Meeting

Two other vaginal progesterone products have been approved for this indication. This complete response was not presented to an Advisory Committee (AC); DBRUP did not believe that AC guidance was needed to make a regulatory decision concerning the approvability of the complete response.

10. Pediatrics

The Applicant requested a full waiver of pediatric studies. DBRUP concurred with the Applicant's request of a waiver of the pediatric requirement for studies in children because such studies would not be possible or highly impractical as the condition of infertility does not exist in children. The waiver request was also reviewed by the Pediatric Review Committee (PeRC) on May 25, 2016. PeRC concurred with DBRUP's decision to grant a full waiver.

11. Other Relevant Regulatory Issues

Division of Medical Policy Programs (DMPP):

Labeling recommendations were not requested from DMPP as it was determined that this Application would not be approved this cycle. Although the tradename Milprosa was found to be acceptable pending approval on June 10, 2016, the proposed proprietary name will need to be resubmitted with the response to the application deficiencies outlined above.

Office of Prescription Drug Promotion (OPDP):

Labeling recommendations were not requested from OPDP as it was determined that this Application would not be approved this cycle.

Office of Scientific Investigations (OSI):

As no new clinical studies or trials were conducted, the Office of Scientific Investigation was not consulted for this resubmission.

Division of Medication Error Prevention and Analysis (DMEPA):

The DMEPA review team also assessed the proposed tradename "Milprosa" and found it conditionally acceptable. (See DMEPA review dated June 3, 2016 and Letter to the Applicant from DMEPA dated June 10, 2016)

The DMEPA review team was also consulted to review the container label, carton labeling, instruction for use and prescribing information from a medication error perspective. In their review dated August 15, 2016. In this August 2016 review, the DMEPA reviewer noted that the presentation of the established name, dosage form and

statement of strength were cluttered on the carton and container labeling and needed to be revised. After the decision was made to provide a Complete Response to the Applicant, these comments will be provided to the Applicant in the next review cycle.

Financial Disclosures:

Financial disclosures were evaluated during the first review cycle for this NDA (See Medical Officer's review, section 3.3, dated February 25, 2011). No new issues related to financial interests for this application were identified in this cycle.

Comment: As no new clinical data was submitted in this response, there are no outstanding issues related to financial disclosures.

CDRH consult reviews:

In the first review cycle, the progesterone vaginal ring was reviewed by the CMC review team (See Section for details on the initial CMC team's findings). Upon review of the 2016 Applicant's Complete Response submission, the progesterone vaginal ring was reclassified as a drug device. Based on this determination, the Center for Devices and Radiologic Health (CDRH) Obstetric and Gynecologic Devices Branch and Office of Compliance in CDRH were consulted on March 21, 2016 to evaluate the progesterone vaginal ring from a device perspective.

On May 23, 2016, the Applicant was informed of the decision that the progesterone vaginal ring was a drug device combination in an Information Request letter. After an initial review, the Obstetric and Gynecologic Devices Branch identified a substantial number of deficiencies that the Applicant needed to address. An Information Request letter also requested complete assessment of the following device issues related to the vaginal ring (key issues summarized below):

- Mechanical properties testing to evaluate possible mechanical failure modes of the vaginal ring
- Shelf life testing evaluation that assessed the mechanical properties of the ring through stability testing
- Biocompatibility testing to evaluate the cytotoxicity, sensitization, genotoxicity and sub-acute toxicity to support a permanent contact duration of use for the progesterone vaginal ring based on CDRH guidance in ISO 10993
- Risk analysis that evaluates risks with the use of the progesterone vaginal ring with other intravaginal devices such as lubricants
- Justify the time limit at the appropriate storage conditions beyond which the polymer in the vaginal ring cannot be used in manufacturing
- Provide additional information on the manufacturing processes for the vaginal ring and final to be marketed progesterone vaginal ring product that include questions on lot numbers, changes in controlling foreign particulates, detecting surface defects, temperature set point, manufacturing process validation and specifications on the current master batch record for the molded products
- Provide summaries on the manufacturer's management structure, design control system for the constituent and combination product, purchasing controls and corrective and preventative actions (CAPA)

The Applicant's response to the May information request was received on June 27, 2016. After an initial review of the Applicant's information amendment, it was determined to be a major amendment. The goal date for the resubmission was extended to November 25, 2016,

The CDRH reviewer in the Obstetrics and Gynecology Device Branch determined there were still unresolved device issues related to biocompatibility testing. A teleconference was held on August 9, 2016, to discuss the outstanding biocompatibility issues of the to-be-marketed progesterone vaginal ring product. At this teleconference, the Applicant was informed that the information provided in the June 2016 response was inadequate to address the biocompatibility issues. During that teleconference, the Applicant agreed to conduct biocompatibility testing to support the safe use of the progesterone vaginal ring. The Applicant was informed that these tests needed to be conducted pre-approval and agreed to conduct subchronic and cytotoxicity testing. On October 14, 2016, the applicant provided a preliminary assessment of their sub-chronic systemic toxicity and cytotoxicity testing. The applicant concluded that the progesterone present in the final to-be-marketed ring interferes with appropriate biocompatibility testing due to the toxicity associated with the resultant progesterone concentrations in extracts of the final product.

On November 2, 2016, a teleconference was held between CDRH and the Applicant. The CDRH biomedical engineer requested additional testing (cytotoxicity and sensitization) using several dilutions of extracts derived from the final to-be-marketed product (with progesterone) as well as a chemical characterization followed by a toxicological risk assessment on extracts derived from the final to-be-marketed product.

Comment: The Applicant agreed to conduct these additional nonclinical studies.

The Obstetric and Gynecology Device Branch reviewer completed her review of the Applicant's major amendment on November 4, 2016. She concluded that, "CDRH does not agree that biocompatibility testing be performed on (b) (4) only. There is concern that the base (b) (4) device-material + drug could potentially interact with each other and may likely lead to different type and quantity of residuals and leachable substances being released from the final product as compared to that from the (b) (4) product. Another concern is that the process of application of the drug onto the (b) (4) product could potentially result in alteration of surface properties and chemical characteristics of the (b) (4) device-material, which could lead to changes in the biocompatibility response." The CDRH review stated that the biocompatibility testing to meet the device requirements were communicated and, "...the Sponsor seemed to have agreed on the test plan that was laid out to fulfill the biocompatibility requirements of the subject device."

After discussion with the CDRH review team, they determined that the following deficiency should be sent to the Applicant, "Your to-be-marketed combination drug-device product, progesterone vaginal ring, contacts the skin and mucosa 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." Additional comments and recommendations regarding this deficiency were also outlined in the Complete Response letter.

Comment: Although not specifically stated in the CDRH review, the OPQ Application team lead and I concur with the CDRH review teams that the Applicant will need to respond to the biocompatibility deficiencies identified by the CDRH reviewer in another Complete Response review cycle. These CDRH requirements must be met during the pre-approval cycle.

12. Labeling

As this Applicant will receive a Complete Response, labeling was not reviewed during this cycle.

13. Decision/Action/Risk Benefit Assessment

Decision:

I agree with the CDRH team, OPQ teams, and the Cross-Discipline Team Leader (CDTL) that this application should receive a Complete Response action detailing the deficiencies identified by CDRH. In addition, from a clinical perspective, the Applicant should provide pre-approval data to support use of the safety and tolerability of the new progesterone vaginal ring in the intended population of women undergoing ART procedures.

Risk Benefit Assessment:

The proposed indication for the progesterone vaginal ring is to support of 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. No new clinical safety or efficacy information was submitted in this resubmission. During this second review cycle, a determination was made that the progesterone vaginal ring was a drug device combination under 21 CDR part 3.

After review of the Complete Response submission and June 2016 Major Amendment, the following significant deficiencies precluding approval were identified by the CDRH review team:

- Biocompatibility testing including sub-chronic and cytotoxicity testing on the final, finished to-be-marketed progesterone vaginal ring product
- Sensitization testing per principles outlined in ISO 10993-10

Based on these outstanding device related deficiencies; I do not believe the risk-benefit assessment of the progesterone vaginal ring is satisfactory for approval this review cycle. The Applicant will need to respond to the deficiencies outlined by the CDRH review team as well as provide additional clinical safety data in the intended population.

Post-Marketing Requirement/Commitment and Risk Evaluation and Mitigation Strategies (REMS):

- No Risk Evaluation and Mitigation Strategies (REMS) program was recommended by any of the review teams during the review cycle for this supplemental application.
- No other postmarketing requirements or commitments were recommended by the review teams during this review cycle for this resubmission.

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/s/

AUDREY L GASSMAN
11/23/2016

Cross-Discipline Team Leader (CDTL) Review

Date	November 22, 2016
From	Shelley R. Slaughter, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	201110
Type of Submission	505(b)(1) Class 2 Resubmission
Applicant	Ferring Pharmaceuticals
Date of Submission	February 25, 2016
PDUFA Goal Date	Extended Goal Date: November 26, 2016 Original Goal Date: August 26, 2016
Proprietary Name / Established (USAN) names	MILPROSA™/progesterone vaginal ring
Dosage forms / Strength	Vaginal insert/ 1.78 g of progesterone in a silicone matrix with release rate of 11mg per day progesterone over a 7-day period
Proposed Indication(s)	(b) (4)
Recommendation:	Approval is not recommended.

1. Introduction and Executive Summary

NDA 201110 for progesterone vaginal rings was originally submitted by TEVA Women's Health R & D on April 10, 2010. The application received a complete response on Feb 28, 2011, based on product quality and clinical deficiencies (failure to establish efficacy and safety in women 35 to 42 years of age, who have reduced ovarian competency). Ownership of the product was subsequently transferred to Ferring Pharmaceuticals on August 5, 2015, who addressed the deficiencies in the February 28, 2011 Complete Response Letter and now resubmits the application for the indication of support of 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 for infertile women. Neither TEVA Women's Health R & D nor Ferring Pharmaceuticals attempted to meet with the Agency prior to resubmission. Progesterone vaginal ring is considered to be a combination drug-device product per 21 CFR Part 3. Because the applicant did not request a meeting with the Agency they were not directly informed by the Agency that upon resubmission, their product would be considered a combination drug-device and would have to meet requirements under 21 CFR Part 4 'Current Good Manufacturing Practice Requirements (cGMPs) for Combination Products'. That's said, it is the applicant's responsibility to stay informed of the regulations governing evaluation of their product.

Issues emerging during the review and consideration of this application were:

1. Combination Drug-Device Considerations for the To-be-Marketed Product

Progesterone vaginal ring is considered a combination drug-device and will need to meet requirements under 21 CFR Part 4. Following, the Agency's request, the applicant provided required information on dimensional analysis (per ISO 8009:2014, Annex A), thickness analysis, tensile strength (per ISO 8009:2014, Annex C), elongation at break (per ISO 8009:2014, Annex C), compression and fatigue resistance (per ISO 8009:2014, Annex E), and twisting during compression (per ISO 8009:14, Annex F). CDRH reviewed the information and found each to be acceptable.

The shelf life information provided by the applicant was also found to be acceptable. Biocompatibility evaluation on the final, finished (to-be-marketed) progesterone vaginal ring will be required to ensure that the device component of the ring is biocompatible and safe for use in humans. As a surface device that contacts mucosal membranes for a permanent contact duration, per the CDRH G95-1 guidance document, "Use of International Standard ISO 10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing'", it is required that the combination progesterone vaginal ring be evaluated for the following biocompatibility tests: cytotoxicity, sensitization, sub-chronic systemic toxicity and genotoxicity testing, per the guidelines outlined in 10993-1. Therefore, in order to ensure long-term safety of the progesterone vaginal ring device, the applicant was required to conduct a subchronic systemic toxicity study according to the principles

outlined in ISO 10993-11. The CDRH reviewer also clarified that in lieu of the sub-chronic systemic toxicity and genotoxicity testing, a toxicological risk assessment that is based on proper extractable and leachables (E & L) study of the final, finished to-be-marketed progesterone vaginal ring is acceptable.

CDRH has concluded upon final review of all information submitted by the applicant that with the exception of irritation and implantation testing, the complete battery of biocompatibility testing, **is still needed** to establish biocompatibility of the to-be-marketed product. The noted biocompatibility information is necessary and must be provided pre-approval for this NDA.

2. Chemistry, Manufacturing, and Controls (CMC)

The following chemistry, manufacturing and controls (CMC) issues from the original review cycle for the progesterone vaginal ring were noted as deficiencies in the Complete Response Letter of February 11, 2011. From a strictly CMC perspective, they have all been satisfactorily addressed, as noted:

- Particulate contaminations found in all five site transfer batches manufactured at the future commercial site.

The applicant determined that the (b) (4) defects in 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 (b) (4) process (Legacy process) with a (b) (4) (new to-be-marketed process). See Section 3 of this review.

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.*** See Section 3 of this review.

- 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.

The response to the deficiency requesting that the applicant amend the application to include a test for particle size distribution with acceptance criteria in the specification for the drug substance, has been incorporated in the drug substance specification (b) (4)

- 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).”

Information submitted by the applicant has satisfactorily addressed this deficiency. See Section 3 of this review.

- 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.

Information submitted by the applicant has satisfactorily addressed this deficiency. See Section 3 of this review.

- 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.

Information submitted by the applicant has satisfactorily addressed all noted deficiencies. See Section 3 of this review.

Even though the applicant satisfactorily addressed the CMC Quality issues as noted in the February 28, 2016 Complete Response Letter, by adopting the new to-be-marketed (b) (4) process, the applicant has effectively changed two variables simultaneously: time and temperature. Both of these variables are important to ensure the successful completion of the (b) (4) chemistry reaction. (b) (4)

None of the batches that were manufactured by the new to-be-marketed (b) (4) process were tested for extractables and leachables. Concerns regarding the absence of biocompatibility information on the to-be-marketed product as raised by CDRH (see Item 1 above and the CDRH-ODE Subsection of Section 3 of this

review) are parallel to the concerns raised by the Drug Product reviewer . If the sponsor addresses the biocompatibility concerns by CDRH, they effectively address the concerns raised by ONDP as well. Also, the one-time thoroughly complete biocompatibility study would assure that the leachables do not need to be monitored during product stability testing.

3. Information submitted to support Bioequivalence of New (b) (4) Process (To-Be-Marketed (b) (4) Method) to Original Legacy Process (b) (4) Process)

Results of bioequivalence 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) to reference (legacy progesterone vaginal ring) fall within the 80 – 125% acceptable range to establish bioequivalence.

4. Efficacy

Phase 3 efficacy and safety data were not submitted to this NDA. As noted in Item 3, the applicant submitted bioequivalence Trial DR201-BE-10021 [Test (new (b) (4) process):Reference (legacy (b) (4) process)] to support reliance on the findings of efficacy and safety for the previously submitted and reviewed single phase 3 Trial DR-PGN-302 conducted with the legacy (b) (4) process.

Trial DR201-BE-10021 provides acceptable bioequivalence information to support reliance on the findings of efficacy for the previously submitted and reviewed single phase 3 Trial DR-PGN-302 conducted in women less than 35 years of age using the progesterone vaginal ring product, manufactured with the legacy (b) (4) process.

As stated in the February 28, 2011 Complete Response decisional letter to TEVA Women's Health R & D, to the TEVA, the applicant did not provide in the original NDA sufficient evidence of efficacy for the progesterone vaginal ring in the subgroup of women 35 to 42 years of age. This subgroup represents approximately 50% of the infertile women for whom the drug is intended for use as part of an Assisted Reproductive Technology (ART) treatment program. In general, the subgroup of infertile women 35 to 42 years of age has diminished ovarian reserve relative to women under the age of 35. The applicant did 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, the Agency recommended that the applicant conduct, prior to approval of their product, a randomized, active-controlled clinical trial to evaluate the efficacy of progesterone vaginal ring in women 35 to 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.

The Agency also stated that it was also possible that appropriate labeling, which would include a statement on limitation of use, in addition to 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.

The Type 2 resubmission did not present any new efficacy and safety information on women 35 to 42 years of age. The applicant proposed instead to accept a limitation of use in labeling, restricting the use of this product to the population of women evaluated, women less than age 35.

As the application will again receive a complete response the recommendation to conduct a clinical trial in women 35 to 42 years of age will be repeated. In light of the failure to adequately characterize safety for the to-be-marketed product (See Item 5 below and Section 8 of this review), this reviewer believes that this should be the only recommendation put forth regarding the establishment of efficacy and safety in this age group.

5. Safety

Phase 3 efficacy and safety data were not submitted to this NDA. As noted in Item 3, the applicant submitted bioequivalence Trial DR201-BE-10021 [Test (new (b) (4) process):Reference (legacy (b) (4) process)] to support reliance on the findings of efficacy and safety for the previously submitted and reviewed phase 3 Trial DR-PGN-302 conducted with the legacy (b) (4) process. No new safety signals were identified in bioequivalence Trial DR201-BE-10021.

While there is acceptable evidence from the bioequivalence trial to support that the efficacy of the to-be-marketed progesterone vaginal ring can be assumed from the results of phase 3 clinical trial results of Trial DR201-BE-10021 with the legacy formulation of the progesterone vaginal ring, this clinical reviewer has concerns that the safety of the **to-be-marketed vaginal ring** has not fully been assessed 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. See discussion of absence of biocompatibility information on the to-be-marketed product under Item 1 above and Sub-Section CDRH-ODE, Section 3 of this review as well as Item 4 above.

6. Labeling

As the recommendation is for complete response, no labeling negotiations were pursued in this review cycle.

7. Deferred PREA Trial

Ferring requested a waiver of Pediatric Research Equity Act (PREA) requirements for children 0 to 17 years of age, because studies/trials are impossible or highly impractical to conduct. The waiver was granted.

2. Background and Regulatory History

Progesterone is produced by the 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 maintenance of pregnancy (and production of progesterone).

GnRH agonists or antagonists are used in ART programs to prevent premature luteinization of follicles as a result of premature LH surges. Unfortunately, suppression can continue into the luteal phase (despite the fact that agonist/antagonist therapy stops on 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 who may or may not require luteal supplementation in any given cycle, some form of luteal phase support is recommended for all ART (Speroff L and Fritz MA).

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, has also been compounded into a vaginal product by many local/university hospital-associated pharmacies and historically used “off-label” for luteal support.

Two products have been 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 document 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.”

The following is an abbreviated review of the regulatory history beginning with the original review cycle for progesterone vaginal ring.

- **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** – NDA 201110 received a Complete Response decisional action. 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 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** - Agency 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 (b) (4). The same type of container was used to test all five of the site transfer batches of Progesterone Vaginal Ring; 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 Ring 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 from TEVA Women's Health R & D.
 - Information addressed the cause of product quality deficiencies, foreign particulate contamination in progesterone vaginal rings, 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 requesting an extension to respond to the Complete Response Letter. The additional time requested was to allow for manufacture of additional full-scale progesterone vaginal ring batches and generation of release and stability data to confirm consistent progesterone vaginal ring manufacturing capability.
- **March 28, 2012** - Agency 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 notifies the Agency of its corporate name change to TEVA Branded Pharmaceutical Products R&D, Inc.
- **January 23, 2014** - TEVA Branded Pharmaceutical Products R&D submission the protocol for Bioequivalence 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."
- **January 22, 2015** - TEVA Branded Pharmaceutical Products R&D submission Trial Report for Trial DR201-BE-10021.
- **August 5, 2015** – Notification from TEVA Branded Pharmaceutical Products R&D of transfer of ownership of NDA 201110 and IND 070875, and associated communications and documentation from to Ferring Pharmaceuticals Inc.

- **August 6, 2015:** Ferring Pharmaceuticals Inc. notifies 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** – The Agency acknowledges change in sponsorship for IND 070875.
- **October 8, 2015** – The Agency acknowledges transfer of ownership for NDA 20110.

3. Chemistry, Manufacturing, and Controls (CMC), Biopharmaceutics and Device

The Chemistry and Biopharmaceutics data for this NDA were reviewed by Office of Pharmaceutical Quality (OPQ) with consultation to CDRH. The Office of Product Quality (OPQ) Review Team and CDRH consultants as listed in Tables 1 and 2, respectively.

Table 1: Office of Product Quality (OPQ) Review Team

DISCIPLINE	REVIEWER	DIVISION/BRANCH
Drug Substance	Ben Stevens	ONDP/DNDAPI/NDBII
Drug Product	Bhavi Mittal	ONDP/DNDPII/NDPBV
Process	James Norman	OPF/DPAII/PABV
Microbiology	Jennifer Patro	OPF/DPAII/MABI
Facility	Vipulchandra	OPF/DIA/IABIII
Biopharmaceutics	Kalpana Paudel	ONDP/DB/BII
Environmental Analysis (EA)	James Laurenson	ONDP/EA Team
Application Technical Lead	Mark Seggel	ONDP/DNDPII/NDPBV

Abbreviations: ONDP = Office of New Drug Products; DNDAP = Division of New Drug API; NDBII = New Drug Branch II; DNDPII = Division of New Drug Products II; NDPBV = New Drug Products Branch V; OPF = Office of Process and Facilities; DPAII = Division of Process Assessment II; PABV = Process Assessment Branch V; MABI = Microbiology Assessment Branch I; DIA = Division of Inspectional Assessment; IABIII = Inspectional Assessment Branch III; DBBII = Division of Biopharmaceutics/Branch II; EA – Environmental Analysis

Source: Adapted from OPQ Summary Review Table.

Table 2 CDRH Review Team

DISCIPLINE	REVIEWER	DIVISION / BRANCH
CDRH-ODE	Monica Garcia	CDRH/ODE/DRGRUD/OGDB
CDRG-OC		CDRH/ODE//DRGRUD/ULDP

Abbreviations: CDRH = Center for Devices and Radiological Evaluation; ODE = Office of Device Evaluation; DRGRUD = Division of Reproductive; Gastro-Renal and Urological Devices; OGDB = Obstetrics and Gynecology Devices Branch; ULDP = Urology and Lithotripsy Devices Branch

Source: Adapted from OPQ Summary Review.

In the Complete Response decisional letter issued February 28, 2011, the Agency identified the following major CMC Quality and Facilities deficiencies.

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) (b) (4) % for establishing the system suitability of the HPLC method.

FACILITY INSPECTIONS

5. 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.

The following information is adapted from the Executive Summary of the OPQ Quality Assessment Review (based on the applicant’s complete response), signed November 10, 2016 and the individual CMC discipline reviews.

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.

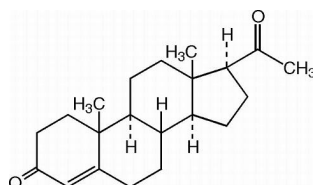
(b) (4)
Progesterone is practically insoluble in water but freely soluble in ethanol. It has a melting range of 126 to 131°C. See Figure 1

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:



The Complete Response deficiency requesting that the applicant amend the application to include a test for particle size distribution with acceptance criteria in the specification for the drug substance has been incorporated in the drug substance specification (b) (4)

Analytical methods used to confirm the drug substance quality have been validated and are adequate. Specifically, the concerns on the validation of the HPLC test method for detection of the impurity/degradation products in the drug substance are satisfactorily addressed by the applicant.

The applicant cites DMF (b) (4) for: 1) the drug substance manufacturing process; 2) progesterone raw material control strategy; 3) progesterone process validation; 4) progesterone manufacturing process development; 5) progesterone characterization data; and 6) discussion of progesterone impurities. All are acceptable. See also, reviews of DMF (b) (4).

See Drug Substance review for additional details regarding the DRUG SUBSTANCE process and method validation. Progesterone drug substance is the subject of a USP monograph.

Overall, the drug substance is well-controlled and the product quality has been confirmed through several batch analyses provided at different stages of development

Based on information (material) provided, this application is recommended for approval from the drug substance perspective.

Drug Product:

Milprosa™ (progesterone vaginal ring) is a white to off white, flexible silicone elastomer ring containing progesterone. Each ring contains 1.78 g of (b) (4) Progesterone, USP ((b) (4)), Light Mineral Oil, NF ((b) (4)), and silicone elastomer (b) (4). The composition of the progesterone vaginal ring is provided in Table 3

Table 3 Composition of the Progesterone Vaginal Ring

Ingredient	Composition Per Ring	
	Weight (g)	Percentage (w/w)
Progesterone, USP (b) (4)	1.7800	(b) (4)
Light Mineral Oil (b) (4)	(b) (4)	(b) (4)
Total per Ring		

Source: Adapted from CDRH Review Table 1.

The rings have an outer diameter of 55 mm and a cross-sectional diameter of 8.5 mm.

The rings, in which progesterone is uniformly dispersed throughout the elastomeric matrix, are manufactured by (b) (4). There are no welded or fused joints. Release of progesterone from the silicone matrix is diffusion controlled.

The drug product is supplied in boxes of two, individually wrapped (heat-sealed, foil laminate pouch) rings.



site, were the subject of the original cycle CMC review (see review of Dr. Nina Ni, archived October 7, 2011). The original cycle CMC review noted the following drug product deficiencies:

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.

The applicant determined that the (b) (4) defects in the proposed commercial product presented in the original review cycle were due to the (b) (4) process, which utilized (b) (4). To address this deficiency, the (b) (4) method used in the original drug product manufacturing process (legacy process) was replaced with a (b) (4) method. [(new to-be-marketed process) (b) (4) process was attributed to inadequate process, equipment and environmental controls. Corrective measures including tests for foreign particulate matter in the raw materials and a complete (b) (4) visual inspection were implemented. Foreign particulate contamination has not been observed in product manufactured after implementation of the corrective measures.

The Finished Product Specification was updated to include criteria for visible particles and the test for (b) (4). The amendment was submitted to the NDA on December 22, 2011 (SN0016). The revised specifications satisfactorily address the concerns.

The analytical methods were updated and provided as an amendment submitted to the NDA on December 22, 2011 (SN0016). Additional method validation has been performed to assess both accuracy and linearity of the impurities/degradation method for progesterone.

Validation results are provided in the Special Studies Report, "Progesterone, USP-Impurities/Degradation Products Test Procedure-Linearity and Accuracy," Version 1.0 (ARD_RPT-5105). All results met acceptance criteria, and demonstrate that the impurities/degradation products test procedure for Progesterone, USP is linear and accurate in the concentration range from about (b) (4) mcg per mL for all four impurities. The validation protocol ARD_PRT-4147, validation report ARD_RPT-5105 and section 3.2.P.5.3 are updated to include this new data. The concerns on the validation of the HPLC test method for detection of the impurity/ degradation products in the drug substance are satisfactorily addressed.

Additional parameters of repeatability and intermediate precision were successfully assessed as part of the validation of the drug product impurity method for progesterone. The four known impurities of progesterone were spiked into a progesterone sample at the quantitation levels. Results of this additional validation study met prescribed acceptance criteria, and are summarized in Section 9 of ARD_RPT-2866 version 5.0, "Progesterone Vaginal Ring, (b) (4) % w/w – Assay, Content Uniformity, and Impurity Method." The validation protocol ARD_PRT-4158, version 5.0 of validation report ARD_RPT-2866 and section 3.2.P.5.3 was updated to include reference to this new data. The request to validate

the repeatability and intermediate precision of the drug product impurity test using samples spiked with the four known impurities at quantitation levels was satisfactorily addressed.

The Assay test procedure for PGN, with a RSD of (b) (4)% for establishing system suitability for the HPLC method, has been revised to reflect a RSD of (b) (4)%. The change in RSD (b) (4)% for the Assay test procedure has been documented in MTH- (b) (4), version 10, "Finished Product Test Method Progesterone Vaginal Rings, (b) (4)% (w/w)." Version 10.0 of MTH- (b) (4) and section 3.2.P.5.2 was updated to include reference to this new method version. The request to the applicant to revise the acceptance criteria of the relative standard deviation (RSD) (b) (4) for establishing the system suitability of the HPLC method was satisfactorily addressed.

The applicant submitted drug release data for the three (3) validation batches manufactured with the new process [Batches 33805873, 33805874, and 33805875) and a phase 3 clinical batch data manufactured with the Legacy process (Batch 900214)]. Since the to-be-marketed (TBM) drug product is produced with the new (b) (4) process, only the data for that process was reviewed and summarized in this cycle. The new (b) (4) process drug product was placed on long term (25°C/60% RH) and accelerated (40°C/75% RH) stability. Stability samples were tested for appearance, assay, related impurities/degradants, microbial limits, in vitro drug release, and durometer. Based on the available data, including supporting data obtained on the clinical trials material and site transfer batches, the applicant's proposed 2 year expiration dating period is granted. CDRH-ODE concurs with the 2 year expiration dating period.

Even though the applicant satisfactorily addressed the CMC Quality issues as noted in the February 28, 2016 Complete Response Letter, by adopting the new to-be-marketed (b) (4) process, the applicant has effectively changed two variables simultaneously: (b) (4). Both of these variables are important to ensure the successful completion of the (b) (4) chemistry reaction. As a general observation, typically, (b) (4). Therefore, by using a (b) (4), it is quite likely that the reaction rate for (b) (4) chemistry reaction (of new to-be-marketed (b) (4) process) was significantly accelerated. However, since the time allowed for the reaction (b) (4) in the new process (b) (4) for the legacy process), it is possible that the new process could exhibit a different profile of volatile compounds and result in different sets of leachables and extractables.

None of the batches that were manufactured by the new to-be-marketed (b) (4) process were tested for extractables and leachables. An Information Request (IR) was drafted and sent to the applicant, dated July 6, 2016, to convey ONDP's concerns regarding the extractable and leachables testing: "The progesterone rings are manufactured (b) (4)



(b) (4) The ‘Addendum to the Product Development Report’, includes a summary of a mold leachable study, a ring extractable study, and a ring stressed leachables study of the ‘Legacy Process’ product. However, no data are provided for the ‘New Process’ product. Provide comparative leachables and extractables data for the rings manufactured by the legacy process and by the new process. Include details of the analytical methods used. Alternatively, provide your justification for not doing extractables/leachables studies on the product manufactured using the ‘New Process’.” The applicant responded that “the extractables and leachables study conducted on rings from the legacy process was considered a worst case scenario. The exposure times were (b) (4) for the legacy process vs. (b) (4) for the new process. The composition of the product between the legacy and new process is exactly the same. It was hypothesized that the exposure will be a worst case scenario at a longer exposure time. The (b) (4)

(b) (4) uring routine manufacturing processes. Therefore we did not foresee the need to study extractables and leachables for rings using the new process as worst case scenario for exposure time was already used in the legacy process.”

The drug product reviewer determined that, the applicant’s response to the Information Request Letter dated July 6, 2016 for extractables and leachables study was not acceptable. The reviewer acknowledges that the composition of the drug product is exactly the same between the legacy and new process. However, it is important to note that the drug product contains (b) (4) Based on the (b) (4) safety data sheet provided by the manufacturer of (b) (4) the mixture consists of ingredients of unknown acute toxicity. Since the new process which is significantly (b) (4) than the legacy process, the risks and concerns regarding product comparability (as demonstrated through a comparative extractables and leachables testing) between the new process and legacy process remain unchanged.

The CDRH review raises concerns regarding absence of biocompatibility data on the to-be-marketed drug-device combination product using the new (b) (4) process. CDRH clarified to the sponsor through a series of information requests that biocompatibility evaluation on the final, finished (to-be-marketed) progesterone vaginal ring will be required to ensure that the device component of the ring is biocompatible and safe for use in humans. As a surface device that contacts mucosal membranes for a permanent contact duration, per the CDRH G95- 1 guidance document, “Use of International Standard ISO 10993, ‘Biological Evaluation of Medical Devices Part 1: Evaluation and Testing’”, it is required that the device component of progesterone vaginal ring be evaluated for the following biocompatibility tests: cytotoxicity, sensitization, sub-chronic systemic toxicity and genotoxicity testing, per the guidelines outlined in 10993-1. Therefore, in order to ensure long-term safety of the progesterone vaginal ring device, the applicant was required to conduct a subchronic systemic toxicity study according to the principles outlined in ISO 10993-11. The CDRH reviewer also clarified that in lieu of the sub-chronic systemic toxicity and genotoxicity testing, a toxicological risk assessment that is based on proper Extractable and Leachable (E & L) study of the final, finished device

component of the progesterone vaginal ring is acceptable. See CDRH review for detailed comments.

The Drug Product reviewer concluded, “The concerns expressed by CDRH are parallel to the concerns raised by ONDP. If the sponsor addresses the biocompatibility concerns by CDRH, they effectively address the concerns raised by ONDP as well. Also, the one-time thoroughly complete biocompatibility study would assure that the leachables do not need to be monitored during product stability testing. A follow-up teleconference was conducted with the applicant. The applicant agreed to the recommendations provided by the Agency regarding biocompatibility testing. This section of the application is not acceptable until the results of the biocompatibility testing are submitted and they are acceptable to CDRH.

Center for Devices and Radiologic Health (CDRH)-ODE (Device Evaluation)
CDRH device evaluation was performed by Dr. Monica, Garcia,
DRH/ODE/DRGUD/OGDB.

The progesterone vaginal ring dimensions are described in the Table 4.

Table 4. Dimensions of Progesterone Vaginal Ring

Attribute	Dimension
Outer Diameter	55.0 ± 5.0
Inner Diameter	38.0 ± 5.0
Cross Sectional Diameter	8.5 ± 0.9

Source: Adapted from CDRH Review Table 2.

The dimensions of the progesterone vaginal ring device are similar to other intravaginal rings, and silicone elastomers are commonly used in intravaginal medical devices (intravaginal rings, diaphragms, pessaries).

The device specifications listed for the progesterone vaginal ring are as follows:

Description: White or off-white flexible silicone ring, free of visible particulates, in a heat-sealable pouch

Durometer: (b) (4)

These specifications are similar to other silicone intravaginal devices, and are acceptable.

A review of the silicone elastomer device master file MAF (b) (4) indicates that (b) (4) has been tested for durometer, tensile strength, elongation, energy and rupture, tear strength, stress at (b) (4) %, compression set, and tensile set at (b) (4) %. This testing was performed on (b) (4) at 3 different conditions:

(b) (4)

Results of these tests indicate that (b) (4) meets the device specifications listed in the product profile. However, these tests were performed on (b) (4) alone, not on the progesterone vaginal ring. Additionally, the (b) (4) process described in the master file is different than the process in the phase 3 studies ((b) (4)) and the current (b) (4)

process (b) (4). These differences in the (b) (4) process may result in different mechanical properties of the device. In the warning and disclaimer section of this master file, (b) (4) states “It is the user’s responsibility to adequately test and determine the safety and suitability for their application, and (b) (4) makes no warranty concerning fitness for any purpose. There has been no testing done by (b) (4) to establish safety of use in any medical application.” In a (b) (4) Information Request Letter, the applicant was asked to address the following in the to-be-marketed product:

- Dimensional analysis
- Tensile strength
- Elongation at break
- Compression strength
- Twisting during compression

The applicant responded with information on dimensional analysis (per ISO 8009:2014, Annex A), thickness analysis, tensile strength (per ISO 8009:2014, Annex C), elongation at break (per ISO 8009:2014, Annex C), compression and fatigue resistance (per ISO 8009:2014, Annex E), and twisting during compression (per ISO 8009:14, Annex F). CDRH reviewed the information and found each to be acceptable.

The shelf life information provided by the applicant was found to be acceptable.

CDRH has specific biocompatibility testing expectations for medical devices. Per ISO 10993-1:2009, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process, the progesterone vaginal ring 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). Therefore, per ISO 10993-1:2009, the applicant should assess cytotoxicity, sensitization, irritation, genotoxicity, and sub-acute toxicity potential of the final finished product. In addition, per the CDRH guidance document, “Use of International Standard ISO 10993-1, ‘Biological Evaluation of Medical Devices Part 1: Evaluation and testing within a risk management process’” issued on June 16, 2016, acute systemic toxicity, chronic toxicity, and implantation are optional tests.

A review of the device master file MAF (b) (4) indicates that (b) (4) has performed the appropriate biocompatibility testing for a permanent implant (cytotoxicity, sensitization, irritation, acute systemic toxicity, and genotoxicity). However, a review of these test reports indicates that the testing was performed using (b) (4) silicone elastomer, not the final finished product.

Per ISO 10993-1:2009, Clause 6.2.1, “the following shall apply when biological testing of medical devices is considered necessary as part of the overall risk management process:

- a) Testing shall be performed on the sterile final product, or representative samples from the final product, or materials processed in the same manner as the final product (including sterilization).”

In a May 23, 2016 Information Request Letter, CDRH recommended the applicant perform additional biocompatibility testing (cytotoxicity, sensitization, irritation, sub-acute systemic toxicity, and genotoxicity) on the final finished (to-be-marketed) progesterone vaginal ring per ISO 10993-1:2009 and the CDRH biocompatibility guidance document.

In response to this deficiency, the applicant provided the following justifications for the omission of the biocompatibility testing requirements for the to-be-marketed progesterone vaginal ring:

1. A previously approved product, PMA (b) (4)
2. Two GLP in vivo rabbit studies (HFE00006 and DR-201-001) had been conducted to assess vaginal irritation and macroscopic and microscopic pathology following 10-day and 90-day exposure periods.
3. The pivotal phase 3 Trial DR-PGN-302 was performed on 647 subjects that were randomized to receive the ring [This trial was conducted with drug product manufactured with the legacy (b) (4) process]. Adverse events were assessed to determine the impact of the progesterone vaginal ring when compared to a progesterone (b) (4) product on local vaginal tolerability.
4. The stability information provided in this submission demonstrated that the observed degradants were not known to be genotoxic or have been associated with biocompatibility issues.

The applicant maintained that the established safety of the progesterone and (b) (4) material alone, coupled with the results of the in vivo implantation studies discussed are sufficient for FDA biocompatibility requirements.

The applicant's response was reviewed by CDRH toxicologist Dr. Pushya Potnis (CDRH/ODE/DRGUD/ULDB). Following Dr. Potnis' review of the data provided in the master file and the applicant's response, he determined that the biocompatibility test data listed in the master file was not pertinent to the final to-be-marketed progesterone ring. In addition, the information provided for the cited referenced device (b) (4) was not sufficient to demonstrate the biocompatibility of the progesterone vaginal (absence of long-term systemic toxicity testing and inadequate genotoxicity testing). However, the GLP in vivo rabbit studies provided by the applicant were able to support intracutaneous irritation and implantation studies.

CDRH concluded that the complete battery of biocompatibility testing, with the exception of implantation and irritation testing, **is still needed** to establish biocompatibility of the to-be-marketed product.

The applicant was notified that additional biocompatibility testing was necessary (cytotoxicity, sensitization, sub-chronic systemic toxicity and genotoxicity testing, per the guidelines outlined in 10993-1) on the to-be-marketed product through an Information

Request letter sent on August 8, 2016. Additionally, the applicant was also notified in a teleconference on August 4, 2016 that biocompatibility information is necessary for approval of this NDA, and cannot be assessed post-approval.

On August 15, 2016, the applicant indicated that they were in the process of initiating the requested biocompatibility tests: cytotoxicity, sensitization, sub-chronic systemic toxicity and genotoxicity testing, per the guidelines outlined in 10993-1. In a correspondence with Agency dated October 14, 2016, the applicant provided a preliminary assessment of their sub-chronic systemic toxicity and cytotoxicity testing. In this preliminary assessment, the applicant concludes that the progesterone present in the final to-be-marketed ring interferes with appropriate biocompatibility testing due to the toxicity associated with the resultant progesterone concentrations in extracts of the final product. The observed toxicity of progesterone would require large dilutions to reduce the interference which would obviate the purpose of biocompatibility testing to detect toxicants present at low levels in the final product.

Based on the observed cytotoxicity and in vivo lethality of the high concentration of progesterone in the extracts of the to-be-marketed product, the applicant proposed that all further biocompatibility testing of the progesterone vaginal ring be performed on the placebo final product, which is produced by the same manufacturing process in the absence of progesterone. Dr. Potnis reviewed this information and determined that the proposed testing plan was not acceptable because the (b) (4) device-material plus drug could potentially interact with each other and may likely lead to different types and quantity of residuals and leachable substances being released from the final to-be-marketed product when compared to that from the progesterone-free placebo ring. Additionally, the process of application of the drug into the ring could potentially result in alteration of surface properties and chemical characteristics of the (b) (4) device-material, which could lead to changes in the biocompatibility response. Therefore, CDRH requests that the applicant perform additional testing (cytotoxicity and sensitization) using several dilutions of extracts derived from the final to-be-marketed product (with progesterone). In addition, CDRH recommends that the applicant perform a chemical characterization followed by a toxicological risk assessment on extracts derived from the final to-be-marketed product.

This recommendation was relayed to the applicant in a teleconference on November 2, 2016. Participants from the Agency included Monica Garcia (CDRH/DRGUD/OGDB), Pushya Potnis (CDRH/DRGUD/ULDB), and Thao Vu (CDER/OPQ/OPRO/DRBPMI/RBPMI). Applicant participants included Mason Diamond (Director of Regulatory Affairs Medical Devices), Brenda Marczl (Vice President of Regulatory Affairs), Jorge Montoya (Director of Medical Device Development), Anastasia Pavlovsky (Principal Scientist, Analytical Development), L. Bruce Pearce (Senior Consultant, Biologics Consulting), Giselle Rose (Director of Regulatory Affairs), and Richard Rymza (Senior Director of Project Management). For additional detail regarding the adequacy of the information provided in the October 14, 2016 correspondence, see Dr. Potnis' consult review memo dated November 3, 2016.

CDRH overall conclusion is that the biocompatibility information provided by the applicant is **NOT** acceptable. Should the application be approved in a future review cycle, CDRH believes that modification of proposed labeling provided by the applicant in response to the May 23, 2016 Information Request Letter and presented as follows, adequately addresses concomitant use in the intended population, of non-medicated intravaginal products, such as personal lubricants and condoms:

“MILPROSA™ is not recommended for use with other vaginal products (such as antifungal products, vaginal lubricants, diaphragms) as this concomitant use has not been studied and may alter the progesterone release and absorption from the vaginal ring [see Drug Interactions (7)]. Condoms should also not be used with MILPROSA™.”

For a detailed discussion of the requirement for biocompatibility information and the discussion of the applicant's responses, refer to the November 4, 2016 CDRH memorandum from Dr. Garcia and the consult memoranda from Dr. Potnis dated July 21, 2016 and November 3, 2016.

Process

(b) (4)

Product Quality Microbiology

MILPROSA™ is a non-sterile drug product. Nevertheless the drug product specification includes tests for microbial limits and the absence of (b) (4) (per USP<61> and <62>) at release and on stability. The microbiology deficiencies identified during the review of the original NDA and delineated in the February 28, 2011 Complete Response Letter have been adequately addressed.

The application is therefore recommended for approval from the product quality microbiology perspective.

Biopharmaceutics

The drug release method was previously reviewed and determined to be acceptable by Dr. Sandra Suarez-Sharp (see review dated February 4, 2011). The in vitro dissolution method uses USP Apparatus II (paddle) at 50 rpm, and 500 mL of 0.05 M sodium dodecyl sulfate (SDS). The acceptance criteria are: Day 1: 158-201 mg/day; Day 2: 67-83 mg/day; Day 7: 38-46 mg/day.

The current Division of Biopharmaceutics review focused on the impact of different injection ratios on the drug product release and the comparative drug release data of batches manufactured using the new to-be-marketed process and legacy processes.

Comparative drug release data and similarity factor metrics (f_2) values demonstrate that the drug products manufactured using the new to-be-marketed process and legacy processes have similar drug release profiles.

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

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.

Manufacturing Facilities

An FDA Form 483 was issued at the close out of the October 26 to November 10, 2016 device GMP inspection of TEVA. However, the inspection was classified as Voluntary Action Indicated. The OPF DIA concluded that, "Based on the risk assessment, compliance history, the current acceptable status, and recent inspection coverage, this facility is at low risk and is acceptable.

All other manufacturing, packaging and testing facilities have acceptable GMP status.

Based on their review of the application and inspectional documents, the Division of Inspectional Assessment concluded that, "there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities listed in NDA 201-110, Resub. 26 are found to be acceptable.

Office of Pharmaceutical Quality (OPQ) Overall Conclusions:

The Office of Pharmaceutical Quality (OPQ), concludes that the deficiencies noted in the February 28, 2011 Complete Response letter, have otherwise been adequately addressed. However, insufficient data to establish biocompatibility of the combination drug-device product under 21CFR 314.125(b)(1), which could have an impact on the safety of the product, precludes approval of the NDA.

4. Nonclinical Pharmacology/Toxicology

The non-clinical pharmacology and toxicology information presented in the application was reviewed by Leslie McKinney, Ph.D., Office of New Drugs (OND), Office of Drug Evaluations 3 (ODE 3), DBRUP.

There were no new nonclinical studies conducted in support of this resubmission. The original application was supported by a 10-day intravaginal irritation study and a 90-day intravaginal safety study conducted in the rabbit using a surgically implanted progesterone capsule. The uterine and vaginal changes that were observed were deemed due to pharmacologic activity of progesterone. No genotoxicity, reprotoxicity, or carcinogenicity studies were conducted for the drug product. For the purposes of this submission, the properties of the drug substance, (b) (4) progesterone, including the impurity profile, were reviewed.

In consultation with the product quality reviewers, it was determined that the drug substance was not changed from the previous submission. From the nonclinical studies conducted in the rabbit and included in the original submission, neither short-term (10-day) nor long-term (90-day) studies resulted in significant adverse effects. Tissue responses included endometrial hyperplasia in the short-term study and uterine and vaginal atrophy in the long-term study.

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 as listed under section 2.3.S. are the same, and that this is the same impurity profile described in the original submission. Specifications for limits on impurities follow ICH guidelines. Thus there were no changes to the progesterone drug substance that require further investigation.

Thus, based on concordance between the progesterone drug product used in the original submission, and the finding of safety in the originally used drug product, it can be concluded that the current submission is acceptable.

There were changes made to the manufacture of the silicone ring, which are now reviewed by the CDER product quality reviewer, and by the CDRH engineering reviewer.

The applicant was informed of CDRH requirements for nonclinical testing of the device portion of the product (the silicone ring) in a letter dated May 23, 2016.y

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review was performed by Peng Zhou, Ph.D., Office of Clinical Pharmacology (OCP)..

The following is based on information included in the OCP Review, archived October 14, 2016.

To address the CMC issues identified in the Complete Response letter to the original submission of NDA 201110 (See Section 3 of this review), the applicant replaced the (b) (4) method of the silicon ring used in the original drug product manufacturing process (legacy process) with a (b) (4) method for the to-be-marketed progesterone vaginal ring. 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 with the new (b) (4) process, were identical. To demonstrate bioequivalence between the to-be-marketed progesterone vaginal ring and the legacy progesterone vaginal ring, Ferring submitted results from Trial DR201-BE-10021, a clinical bioequivalence trial.

The trial was a multiple-site, open-label, single dose, randomized, two-treatment, two-period, crossover trial conducted in 56 healthy (no chronic diseases, no history of thromboembolic disease or thrombophlebitis and no contraindications to estrogen therapy) naturally postmenopausal non-hysterectomized women [mean age was 56.8 years pf age (range 47 to 65 years), the majority (54 [96%]) of participants were white, and mean (SD) subject weight was 68.7 (8.34) kg.) with a BMI within the range of 18.6-29.9 kg/m²]. No concomitant drug therapy, except 1 mg estradiol therapy. All concomitant medication use was documented.

Following an appropriate washout for prior oral, transdermal or vaginal estrogen or estrogen plus progestin therapy, progestin implant or estrogen or progestin injectable therapy, women received a single dose, once-weekly of the legacy (Reference) or to be-marketed progesterone vaginal ring (Test). Period 1 and period 2 treatment periods were separated by a 7-day washout period. All women received pre-treatment with 1 mg estradiol oral tablets for at least 28 days prior to the first dose of the progesterone vaginal ring, and also continued throughout the entire trial including the washout period (7 days), until after the final blood sailing in period 2. Trial entry and start of estradiol treatment occurred on day -28. Treatment with Treatment A (new to-be-marketed (b) (4) progesterone vaginal ring) or Treatment B (legacy (b) (4) progesterone vaginal ring) occurred for 7 days in treatment period 1, followed by a minimum 7-day washout period, and then the other treatment for 7 days in treatment period 2. The end of the trial was on day 10 of treatment period 2 or early termination, followed by a 12-day course of progesterone and a follow-up phone call (within 7 days). After completion of the trial, all women took a 12-day course of PROMETRIUM®. During each of the two (2) treatment periods, women checked into the trial center the evening of day -1, vaginal ring insertion occurred the following morning (day 1), and women remained confined to the study center until 24 hours after vaginal ring insertion (day 2). Women returned to the study center for outpatient visits at 48, 72, 96, 120, and 144 hours after vaginal ring insertion (Days 3 through 7) for pharmacokinetic blood sampling and ongoing safety evaluations. Women again checked into the trial center the evening of Day 7, vaginal ring removal occurred the following morning (Day 8, 168 hours after the vaginal ring was inserted), and women remained confined to the trial center until collection of the last pharmacokinetic sample at 216 hours (Day 10).

Blood samples for plasma progesterone analysis were collected at predose -1.0, -0.5 and 0 hours (within 10 minutes before ring insertion), after vaginal ring insertion at 1, 2, 3, 4, 6,

8, 12, 24, 48, 72, 96, 120, 144, 168 (before vaginal ring removal), 169, 170, 172, 174, 176, 180, 192, and 216 hours. Samples were analyzed by (b) (4)

using a validated LCMS/MS methodology. All post-dose samples were corrected for baseline by deducting the mean of three pre-dose values (-1, -0.5 and 0 hours).

Pharmacokinetic (PK) analyses were conducted on both baseline-corrected data and non-baseline corrected data. Baseline corrected data was considered primary, while non-baseline corrected data analysis is considered supportive data. One –hundred (100%) of enrolled women completed the trial. There were no drop-outs due to serious adverse events.

Bioequivalence was based on the 90 % confidence intervals of treatment mean ratios (T: R) for the analytes: AUC_{0-t} , AUC_{0-inf} and C_{max} . These data are summarized in Tables 5.

Table 5: Summary of Bioequivalence Analyses of Baseline Corrected Progesterone in Trial DR201-BE-10021

Analyte Parameter AUC_{0-t} (ng·hr/mL) AUC_{0-inf} (ng·hr/mL) C_{max} (ng/mL)	Geometric LS Mean		Ratio of Geometric Least Square Means (Test/Reference)	90% CI of ratio (Test:Reference)
	Test (new (b) (4) product) N=56	Reference (legacy (b) (4) product) N=5		
AUC_{0-t} (ng·hr/mL)	1106.188	1108.106	0.998	94.27% - 105.71%
AUC_{0-inf} (ng·hr/mL)	1101.701	1103.257	0.999	94.30 – 105.75
C_{max} (ng/mL)	8.166	8.442	0.967	92.63 – 101.02

Source: Adapted from OCP Review Table 6.

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) to reference (legacy progesterone vaginal ring) fall within the 80 – 125% acceptable range to establish bioequivalence. The Office of Clinical Pharmacology concludes 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 ring with the (b) (4) method to the legacy formulation of the progesterone vaginal ring with the (b) (4) method.

The above results suggest that the efficacy of the to-be-marketed progesterone vaginal ring can be assumed from the results of phase 3 clinical trial results of Trial DR201-BE-10021 with the legacy formulation of the progesterone vaginal ring. However, this clinical reviewer has concerns that safety of the to-be-marketed vaginal ring has not fully been assessed (See Sub-Section CDRH-ODE under Section 3 of this review.

6. Clinical Microbiology

See Section 3, Product Quality Microbiology Sub-section.

7. Clinical/Statistical – Efficacy

No new phase3 safety and efficacy data were submitted to support the progesterone vaginal ring. The Medical Officers' Review of Dr. Rhonda Hearn-Stewart evaluated the pharmacokinetic data from the bioequivalence Trial DR201-BE-10021, as noted under Section 5 of this review. The Clinical Review Team agrees with the Office of Clinical Pharmacology that bioequivalence Trial DR201-BE-10021 provides acceptable bioequivalence information to support reliance on the findings of efficacy for the previously submitted and reviewed single phase 3 Trial DR-PGN-302 conducted in women less than 35 years of age using the progesterone vaginal ring product, manufactured with the legacy (b) (4) process.

That said, the Agency's February 28, 2011 Complete Response Letter noted the following deficiency and potential pathways for remediation:

CLINICAL

1. You have not provided sufficient evidence of efficacy for the progesterone vaginal ring 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.

The Type 2 resubmission did not present any new efficacy and safety information on women 35 to 42 years of age. The applicant proposes instead to accept a limitation of use in labeling, restricting the use of this product to the population of women evaluated, women less than age 35. They appear to also accept performing a postmarketing requirement to evaluate women 35 to 42 years of age.

8. Safety

No new phase3 safety information was submitted in support of the progesterone vaginal ring.

No new safety signals were identified upon review of bioequivalence Trial DR201-BE-10021. There were no deaths, other serious adverse events, or withdrawals due to adverse events. Fifty [50 (89%) women reported at least 1 adverse event after receiving Treatment A (new to-be-marketed (b) (4) progesterone vaginal ring) and 48 (86%) women reported at least 1 adverse event after receiving Treatment B (legacy (b) (4) progesterone vaginal ring). The most frequently reported adverse events for both treatments occurred in the reproductive system and breast disorders system organ class. The most frequently observed adverse event, withdrawal bleed, occurred in a similar proportion of women after each treatment [39 (70%) women after receiving Treatment A and 41 (73%) women after receiving Treatment B]. Pelvic pain also occurred in a similar proportion of women after each treatment [8 (4%) women after receiving Treatment A and 9 (16%) women after receiving Treatment B]. Vaginal discharge was reported by 11 (20%) women after receiving Treatment A and 6 (11%) women after receiving Treatment B, and breast tenderness was reported by 7 (13%) women after receiving Treatment A and 4 (7%) women after receiving Treatment B. All adverse events for both treatments were reported as mild in severity, except for 1 moderate adverse event of withdrawal bleed. The majority of adverse events resolved without sequelae during the trial. The overall incidence of treatment-related adverse events was the same for Treatment A and Treatment B [47 (84%) women each].

While there is acceptable evidence from the bioequivalence trial to support that the efficacy of the to-be-marketed progesterone vaginal ring can be assumed from the results of phase 3 clinical trial results of Trial DR201-BE-10021 with the legacy formulation of the progesterone vaginal ring, this clinical reviewer has concerns that safety of the **to-be-marketed vaginal ring** has not fully been assessed (See discussion of absence of biocompatibility information with the to-be-marketed product Sub-Section CDRH-ODE under Section 3 of this review) 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.

This reviewer recommends that the complete response letter indicate that safety (and possibly efficacy) of the to-be-marketed product be demonstrated pre-approval in both 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.

9. Advisory Committee Meeting

Advisory Committee input was not sought for the decision on this application seeking approval of a revised formulation and dose of an approved product. .

10. Pediatrics

A full pediatric waiver for ages 0-11 (under age 12) was requested by Ferring with the rationale that progesterone vaginal ring “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 agreed with the Division to grant a full waiver as requested in pediatric patients.

11. Other Relevant Regulatory Issues

Inspections by the Office of Scientific Investigations (OSI)

As there were no phase 3 trials conducted specifically to support this NDA, only the clinical and analytical sites critical to the bioequivalence trial, 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”, were inspected:

Audrey Martinez, MD
SeaView Research
3898 NW 7th Street
Miami, FL 33126

The inspection was conducted May, 9-24, 2016. No discrepancies, significant issues, or under-reporting of adverse events (AEs) were observed. The final classification for this inspection is no action indicated (NAI).

The Office of Integrity and Surveillance (OSIS) recently inspected the following analytical site; and the inspection was classified as NAI.

(b) (4)

The Division of New Drug Bioequivalence Evaluation (DNDBE) recommends accepting data without an additional on-site inspection.

Financial Disclosure

Financial Certification and Disclosures are provided for investigators who participated in Trial DR201-BE-10021 entitled, “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.” List of Investigators:

- Martinez, Audrey E., MD – Principle Investigator
SeaView Research, Inc
3898 NW 7th St
Miami, FL 33126



The applicant indicated in the NDA, Financial Certification and Disclosure Form, “As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.29a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

A signed FORM FDA 1572 (2/13) is available in the application for the principal investigator and each sub-investigator.

Tradename Review

On June 10, 2016, the Division of Medication Error Prevention and Analysis (DMEPA) concluded that the tradename “MILPROSA™” was acceptable.

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

DMEPA has the following comments on the Container and Carton labeling for the applicant:

- As currently presented in your February 25, 2016 submission, the presentation of the established name, dosage form, and statement of strength are all on the same line, reducing the readability of this important drug-identifying information and giving the principal display panel a cluttered appearance on both the carton labeling and container label.

- We recommend you re-locate the statement of strength to the next line and increase the spacing between the letters of the established name and dosage form to improve their readability. This is in accordance with our Guidance, “Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors” <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

As labeling was not pursued for this review cycle, this recommendation was not further pursued with the applicant.

The Office of Prescription Drug Promotion (OPDP)

As labeling was not pursued for this review cycle, an OPDP consult review was not needed.

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

As labeling was not pursued for this review cycle, a DMPP consult review was not needed

12. Labeling

As the recommendation is to not approve, labeling negotiations were not pursued for this application

13. Conclusions/Recommendations/Risk Benefit Assessment

I concur with the primary review disciplines (OPQ, CDRH and Clinical) conclusions that NDA 201110 for MILPROSA™ should not receive approval.

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/s/

SHELLEY R SLAUGHTER
11/22/2016

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	201110
Priority or Standard	Standard/Resubmission
Submit Date(s)	February 25, 2016
Received Date(s)	February 25, 2016
PDUFA Goal Date	August 26, 2016 – original November 26, 2016 – following major amendment extension
Division / Office	Division of Bone, Reproductive, and Urologic Products (DBRUP)/Office of Drug Evaluation (ODE III)
Reviewer Name(s)	Rhonda Hearn-Stewart, M.D.
Review Completion Date	November 21, 2016
Established Name	Progesterone vaginal ring (Progesterone, USP), (b) (4)
(Proposed) Trade Name	Milprosa (Progesterone, USP) Vaginal Ring
Therapeutic Class	Progesterone
Applicant	Ferring Pharmaceuticals, Inc.
Formulation(s)	(b) (4) progesterone in a non-biodegradable (b) (4)
Dosing Regimen	One vaginal ring inserted vaginally starting the day after oocyte retrieval. The vaginal ring is replaced weekly for up to 10 weeks total duration.
Indication(s)	To support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteum function as part of an Assisted Reproductive Technology (ART) treatment for infertile women
Intended Population(s)	Infertile women undergoing ART

Template Version: March 6, 2009

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Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

We do not recommend approval of progesterone vaginal ring, Milprosa. The applicant did not perform a complete biocompatibility assessment of the final to-be-marketed (TBM) drug-device combination product and did not provide sufficient information to assess the risk of the (TBM) drug-device combination product. The manufacturing process, combination product drug-device design, clinical duration of exposure and the intended use of the progesterone vaginal ring are different from the reference product (b) (4) cited by the applicant. Additionally, different material handling & processing, manufacturing methods, and manufacturing residuals can affect biocompatibility. Thus, additional testing and biocompatibility evaluation on the final, finished TBM progesterone vaginal ring are necessary to ensure that the progesterone vaginal ring is safe for use in humans. Without the additional testing on the final TBM vaginal ring, the risk/benefit profile for this product cannot be determined.

1.2 Risk Benefit Assessment

Infertility affects approximately 10-15% of couples¹; and the use of Assisted Reproductive Technology (ART) doubled over the past decade. Preliminary 2014 data from the CDC National Art Surveillance System indicate that 404 US clinics performed 208,786 ART cycles². In 2013, the average age of women using ART services was 36 years of age. Women, aged 35-42 years, comprise 50% (20% in 35-37 years of age, 19% in 38-40 years of age, and 11% in 41-42 years of age) of women undergoing ART treatment. Women greater than 42 years of age comprise 12% (7% in 43-44 years of age and 5% in women greater than 44 years of age)³.

After ovulation and conception in natural cycles, the resultant corpus luteum, typically supports embryo implantation and pregnancy until the 10th week of gestation. However, during ART, the woman's pituitary gland is down-regulated (desensitized) generally utilizing Gonadotropin releasing hormone (GnRH) agonist/antagonist and the ovaries are stimulated with menotropins or gonadotropins to produce a greater number of mature oocytes, which can be retrieved for in vitro fertilization (IVF) and/or intracytoplasmic sperm injection (ICSI). Desensitization of the pituitary along with subsequent oocyte retrieval, result in corpus lutea which are unable to produce

¹ Zarinara A *et al.* Models Predicting Success of Infertility Treatment: A Systematic Review. J Reprod Infertil. 2016;17(2):68-81.

² Centers for Disease Control and Prevention. ART Success Rates. www.cdc.gov/art/reports/

³ Centers for Disease Control and Prevention. 2013 Assisted Reproduction Technology: Fertility clinic Success Rates Report. <http://www.cdc.gov/art/pdf/2013-report/art-2013-fertility-clinic-report.pdf>

Clinical Review

{Rhonda Hearn-Stewart, M.D.}

{NDA 201110}

{Milprosa (Progesterone, USP), (b) (4)}

sufficient progesterone to sustain the luteal phase, a “luteal phase defect”, and a subsequent pregnancy, should one occur. Additionally a low progesterone level may lower the chance of implantation. For all of the reasons, progesterone supplementation is necessary for women undergoing IVF/ICSI⁴.

Currently approved products for progesterone luteal supplementation, as part of an ART cycle, are administered daily up to three times per day intravaginally as a gel or an insert. However, unlike other progesterones marketed in the US, Milprosa is a solid vaginal ring containing approximately 1.8 grams of progesterone and a mixture of (b) (4) silicon elastomer and light mineral oil. The progesterone is present in a (b) (4) % w/w concentration dispersed evenly within the ring. The ring is inserted vaginally after oocyte retrieval and remains in place for one week. The ring is replaced weekly for up to 10 weeks. The Agency considers the proposed to-be-marketed progesterone vaginal ring to be a drug-device combination product with permanent contact duration (i.e., devices whose cumulative single, multiple or repeated long-term use or contact exceeds 30 days). Because of this and the fact that the final formulation has not been approved for any previously approved product, an additional major focus of the NDA safety evaluation was to assess the overall risk of the final “to be marketed (TBM)” product (progesterone vaginal ring). The progesterone vaginal ring is a drug-device combination product under 21 CFR Part 3, and is subject to 21 CFR Part 4 “Current Good Manufacturing Practice Requirements (cGMPs) for Combination Products”.

The February 25, 2016 resubmission for NDA 201110 does not include a complete assessment of the final (TBM) progesterone vaginal ring. (b) (4) performed testing on the previous product, which was referenced in the initial submission of NDA 201110 on April 30, 2010. (b) (4) performed biocompatibility testing for a permanent implant; but the testing was performed using (b) (4) silicone elastomer, not the final finished product (progesterone vaginal ring). The applicant did not perform testing on the final TBM product.

On May 23, 2016, the Agency sent Ferring Pharmaceuticals an IR letter which included the following comments:

“Neither your original April 30, 2010 NDA submission nor your February 25, 2016 class 2 resubmission provide certain information on the final to-be-marketed (TBM) progesterone vaginal ring that is required to allow a final determination of safety and efficacy for this product. For the final TBM product, you must provide information regarding a complete assessment of 1) mechanical properties, 2) shelf-life, 3) biocompatibility with skin and mucosal surface under conditions of permanent contact duration and 4) compatibility with other intravaginal devices for the final TBM progesterone vaginal ring.

⁴ Van der Linden M *et al.* Luteal phase support for assisted reproduction cycles. Cochrane Database System Review 2015 Jul 7;7:CD009154. Doi: 10.1002/14651858.CD009154.pub3.

You may provide this information from studies that you currently have or will conduct, or alternatively, from the published literature or reference to approved products, if materials used in the TBM product have been well characterized chemically and physically in the literature (with a long history of safe use) or have been previously approved.”” If you will rely on your own data or data for which you have the right-of-reference, we have the following recommendations:”

1. Mechanical Properties to include results of performance testing on the following parameters:
 - a. Dimension analysis
 - b. Tensile strength
 - c. Elongation at break
 - d. Compression strength and twisting during compression
2. Shelf-Life Evaluation including an evaluation of the mechanical properties of the ring in the stability validation for the progesterone vaginal ring.
3. Biocompatibility Testing to include the following:
 - a. Cytotoxicity
 - b. Sensitization
 - c. Irritation
 - d. Genotoxicity
 - e. Sub- acute, acute systemic, and chronic toxicity
 - f. Implantation
4. Compatibility with Other Intravaginal Devices including a risk analysis that evaluates risks associated with use of the vaginal ring other intravaginal devices that may be used concomitantly with the vaginal ring.

In response to the aforementioned deficiencies, the applicant provided acceptable mechanical testing for the requested parameters, acceptable shelf-life information on the subject ring, and acceptable mitigation methods for the concomitant use of other intravaginal devices. Although condom compatibility testing with the progesterone vaginal ring was not performed, alternatively stating in the label that the product should not be used with condoms is sufficient. The intended population is infertile women who are seeking conception and therefore, less likely to use condoms.

However, the applicant response did not provide acceptable biocompatibility information. The information was not sufficient to allow assessment of biocompatibility for the to-be-marketed progesterone vaginal ring in its final form. The manufacturing process, combination product drug-device design, clinical duration of exposure and the intended use of the progesterone vaginal ring are different from the reference product (b) (4) cited in the response. Furthermore, different material handling & processing, manufacturing methods (b) (4) and manufacturing residuals can affect biocompatibility. Thus, additional testing and

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{NDA 201110}

{Milprosa (Progesterone, USP), (b) (4)}

biocompatibility evaluation on the final, finished to-be-marketed progesterone vaginal ring are necessary to ensure that the progesterone vaginal ring is safe for use in humans.

On August 8, 2016, the Agency sent Ferring Pharmaceuticals an IR letter which included the following comments:

As the surface of the final finished Progesterone Vaginal ring (PVR) contacts mucosal membranes for a permanent contact duration, per the CDRH G95-1 guidance document, "Use of International Standard ISO 10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing'", provide the following biocompatibility tests to support the safe use of the PVR: cytotoxicity, sensitization, sub-chronic systemic toxicity and genotoxicity testing, per the guidelines outlined in ISO 10993-1.

- A detailed comparative Extractables & Leachable (E&L) study assessing chemical equivalence to determine whether the final, finished PVR manufactured by the 'new process', elutes the same type, and relative quantity of chemical compounds as compared to that manufactured by the 'legacy process'. It is important to make sure that the age of the products that are evaluated in the E&L study are within the established shelf life of the products as determined from the stability data.
- The chemical characterization of silicone-based product should include analysis for small molecular weight (b) (4). Note that the presence of these oligomers above their respective toxicologically acceptable levels would raise safety concerns regarding the use of the PVR.
- The chemical analysis should provide the total quantity or amount (in weight) of all identified compounds per PVR.
- The test sample preparation/extraction for chemical characterization should be performed as per the principles outlined in ISO 10993-12.
- The E&L study should be performed as per the principles outlined in ISO 10993-18.
- The toxicological risk assessment should be performed on all the identified known and unknown chemicals as per the principles outlined in ISO 10993-17.
- If data from the chemical characterization/risk assessment is used to leverage sub-chronic toxicity and genotoxicity testing, the toxicological risk assessment should be carried out by using the appropriately protective cancer-based Threshold of Toxicological Concern (TTC) values for those chemicals that are identified either as unknowns or have limited or no toxicological information available.

On October 14, 2016, the applicant provided preliminary results of cytotoxicity and sub-chronic systemic toxicity studies of the to-be-marketed progesterone vaginal ring. Based

on the initial test results and the observations that progesterone possibly interferes with the biocompatibility test assays, they proposed that all future biocompatibility testing of the progesterone vaginal ring be performed on the placebo final product vaginal rings, i.e., rings produced by the same manufacturing process, but without progesterone. The Agency does not agree that biocompatibility testing may be performed on progesterone-free vaginal ring placebo only.

Because biocompatibility deficiencies remain unresolved to date, approval cannot be recommended. To adequately evaluate and support biological safety of the subject product, the following testing paradigm is necessary to meet the biocompatibility requirements of the to-be-marketed product:

1. For products that are inherently cytotoxic or products that demonstrate cytotoxicity, additional testing using several dilutions of the extracts derived from the final, finished to-be-marketed progesterone vaginal ring product (with Progesterone) is necessary to determine the level at which cytotoxicity no longer occurs.
2. A chemical characterization followed by a toxicological risk assessment on extracts derived from the final, finished progesterone vaginal ring product (with Progesterone) will provide the overall leachable profile of the progesterone vaginal ring product and will be necessary to understand the breakdown products that are a result of progesterone vaginal ring silicone material + drug 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.
3. Sensitization testing per principles outlined in ISO 10993-10.
4. In your preliminary biocompatibility assessment, you state that you initiated a 14-day intraperitoneal (IP) study in female rats for sub-chronic toxicity testing. However, please note that a 14-day IP study does not represent sub-chronic systemic toxicity testing. For sub-chronic systemic toxicity testing, a 28-day IV and/or 90-day IP needs to be conducted to demonstrate potential systemic toxicity concerns following exposure to device extracts over a period that is considered to be longer than a typical sub-acute systemic toxicity test study, and not exceeding 10% of the animal species' life span. Therefore, additional rationale is needed for the selection of the 14-day duration of exposure and how the study period represents a sub-chronic systemic toxicity study.
5. On page 4 of the October 14, 2016 correspondence, you state that the progesterone dose-exposure calculation in rats is based on (b) (4) progesterone by IP route of administration. However, as the maximum injection dose volume limit via IP in rat species is 20 ml/kg, it is unclear how the dosage volume that is

(b) (4) times lower than the maximum recommended injection dose is representative of an exaggerated exposure dose for a systemic toxicity study. Additionally, in the information provided, the frequency of dose exposure is not clear (i.e., single, multiple, repeat, etc.). Therefore, additional rationale is needed for the dosage volume used in the study. Please address whether there are any adjustment factors such as surface area-to-body weight, exaggerated exposure conditions – dose, duration, frequency, route of exposure, physical-chemical and biological properties of the test sample, animal strain, etc. – that make up for the lower limit of the maximum dosage volume selected for test sample administration.

6. In the information provided, the exposure dosing is based on the drug potency of progesterone, rather than assessing the overall leachability profile of the final, to-be-marketed combination product. The objective of a sub-chronic systemic toxicity study is to evaluate the potential of leachable chemicals to induce systemic toxicity effects. Therefore, we recommend that exposure dosing be based on the leachability profile of the to-be-marketed product.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

We do not recommend approval. Postmarketing risk evaluation and mitigations strategies were not discussed.

1.4 Recommendations for Postmarket Requirements and Commitments

The applicant did not submit efficacy or safety data with this re-submission on April 30, 2010. Per archived NDA 201110 Clinical Review (February 14, 2011), no major safety issues were identified in women less than 35 years of age. However, because the largest group of women undergoing ART includes women greater than 35 years of age, a major focus of the NDA safety evaluation was to assess the overall risk of Milprosa in this age group. Pivotal Trial DR-PGN-302 was not powered to demonstrate efficacy in the subgroup of women aged 35-42 years and did not provide sufficient data to assess safety of the progesterone vaginal ring, Milprosa, in this age group. With this re-submission, the applicant proposed labeling with a limitation of use and a post marketing commitment (PMC) to evaluate efficacy and safety in women aged 35-42 years of age. The proposed limitation of use statement is, "Efficacy in women 35 years of age and older has not been clearly established". Milprosa was evaluated in a single trial of women age 18-42. The trial was not powered to demonstrate separately, efficacy in women less than age 35 and efficacy in women 35-42. The overwhelming majority of trial participants ranged in age from 20-42 years of age with a mean age of 31.6 years in the Crinone group and 31.7 years in the Milprosa group. Therefore, labeling should advise prescribers and patients that Milprosa was not adequately evaluated in women aged 35-42 years of age and efficacy and safety of use in this product has not been determined.

A woman's age is a significant predictor of SAB. There is a direct correlation of advanced age with miscarriage rate. The miscarriage rate increases as age increases. Sunkara *et al.* evaluated data from 1991 to June 2008 for 402,185 stimulated fresh IVF cycles and analyzed 124,351 pregnancy outcomes. In addition to identifying a strong association between the number of oocytes retrieved and miscarriage rate following IVF treatment, they also confirmed that the miscarriage rates gradually increased with increasing female age. The clinical miscarriage rate was 11.5% in women < 34 years of age, 15.2% in women 35 -37 years of age, 20.1% in women 38 - 39 years of age, and 29.3% in women 40 – 42 years of age⁵. With such an increase in miscarriage rates in women 35 – 42 years of age, it is imperative that the applicant demonstrate that Milprosa does in deed support early pregnancy (both an efficacy and safety endpoint) in this older population of women. Therefore, should the progesterone vaginal ring be approved at some point in the future without adequately powered clinical trial data in women 35-42 years of age and with a limitation of use in labeling, we recommend a post marketing requirement for a Phase 4 randomized, active-controlled non-inferiority comparator clinical trial, which is powered sufficiently for this major sub-group of older women. Results of such a trial should establish efficacy, the appropriate dosing regimen, and safety. Only after such results are known, should the limitation of use language be removed. A safe and effective dose of PVR for this indication cannot be extrapolated from the data from younger women.

2 Introduction and Regulatory Background

Epidemiological data indicate that infertility is a problem of global proportions, affecting one-fifth of couples trying to conceive worldwide (60-80 mln)-million⁶. Thus a great number of couples often seek infertility treatment, which often includes Assisted Reproductive Technology [(ART) specifically IVF and ICSI]. Administration of exogenous progesterone for luteal support is standard of care in IVF and ICSI. Intramuscular (IM) injection of progesterone in oil and vaginal administration of progesterone, in gel or insert form are the primary routes of administration. Traditionally, IM progesterone once daily has been the most common form of luteal phase support, but is associated with pain at the injection site, development of injection site cellulitis and abscesses, and inconvenience for patients who require another person to administer the injections. Vaginal administration of progesterone for luteal support has been shown to be efficacious, well tolerated and preferred by patients⁷.

⁵ Sunkara S *et al.* Association between response to ovarian stimulation and miscarriage following IVF: an analysis of 124, 351 IVF pregnancies. *Hum Reprod* 2014; 29(6):1218-1224.

⁶ Szkodziak P *et al.* Infertility in the light of new scientific reports - focus on male factor." *Annals of Agricultural and Environmental Medicine* 2016; 23(2): 227-230

⁷ Yanushpolsky E *et al.* Crinone vaginal gel is equally effective and better tolerated than intramuscular progesterone for luteal phase support in in vitro fertilization-embryo transfer cycles: a prospective randomized study. *Fertil Steril* 2010;94: 2596-9.

In a prospective randomized trial, Yanushpolsky *et al.* demonstrated that progesterone vaginal gel was better tolerated; and Beltsos *et al.* conducted a prospective patient survey, which suggests that progesterone vaginal insert is an easy to use method without the pain and inconvenience of daily IM progesterone⁸. Although daily IM progesterone, in oil, is accepted as a form of luteal support in ART; it is not approved for luteal phase support. Progesterone in oil is indicated in amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology such as submucosal fibroids or uterine cancer. There are two progesterone products, Endometrin® and Crinone®, approved for luteal support but none in the U.S. have been indicated as a weekly regimen (See Table 1). The Applicant suggests that once weekly insertion of the progesterone vaginal ring is sufficient for luteal support, thereby eliminating the need for painful injections or daily administration.

Reviewer Comment:

As the Yanushpolsky et al. trial was limited to women, under 40 years of age, the efficacy and safety results may not apply to the sub-population of women 40 years of age and older of women who undergo ART. Additionally, neither the investigators nor the study participants were blinded to the treatment. A double-blind, double-dummy trial design would be more appropriate to eliminate bias.

2.1 Product Information

The progesterone vaginal ring (established name) is in the class of drugs “Progestogens”, which includes progesterone. It is a vaginally inserted ring that contains the active drug ingredient (b) (4) progesterone. It is packaged individually in a sealed foil pouch. One carton contains 1 pouch or 2 pouches. The progesterone vaginal ring has similar pharmacologic effects as other progesterone products; but the active ingredient, (b) (4) progesterone, is delivered through a vaginal ring. The progesterone vaginal ring is manufactured (b) (4). The inactive ingredients are (b) (4) light mineral oil.

The Division of Medication Error and Prevention Analysis (DMEPA) previously reviewed the proprietary name, Milprosa and found it to be acceptable (archived OSE Review # 2010-2696 dated February 2, 2011). However, NDA 201110 received a complete response (CR) action February 28, 2011 due to multiple deficiencies. In their response to the CR on February 25, 2016, Ferring Pharmaceuticals (the new Applicant requested that the Agency re-review this name. DMEPA was consulted on March 10, 2016 to re-review the requested trade name, Milprosa. The name, Milprosa, was again found to be acceptable.

⁸ Beltsos A *et al.* Reproductive Health 2014; 11:78. Patients’ administration preferences: progesterone vaginal insert (Endometrin®) compared to intramuscular progesterone for luteal phase support.

The proposed indication is “to support embryo implantation and early pregnancy (up to 10 week post-embryo transfer) by supplementation of corpus luteum function as part of an Assisted Reproductive Technology (ART) treatment for infertile women”. Milprosa is a vaginal ring which contains, progesterone (a progestogen) intended for use, in women, who are less than 35 years of age. One vaginal ring is inserted vaginally starting the day after oocyte retrieval. The vaginal ring is replaced weekly for up to 10 weeks total duration.

2.2 Tables of Currently Available Treatments for Proposed Indications

Two progesterone products, Crinone® 8% and Endometrin®, are currently approved for luteal phase supplementation as part of Assisted Reproductive Technology (ART) treatment for infertile women. Prometrium® and Progesterone IM are used off label in ART. However, none of these products are indicated as a vaginal ring inserted or a weekly administration to sustain luteal support for one week. Current US progesterone treatment typically requires daily administration. See

Clinical Review
{Rhonda Hearn-Stewart, M.D.}
{NDA 201110}
{Milprosa (Progesterone, USP), (b) (4)}

Table 1.

APPEARS THIS WAY ON ORIGINAL

Table 1: Available drugs to support embryo implantation and early pregnancy (up to 10 weeks post- embryo transfer) by supplementation of corpus luteal function as part of ART treatment for infertile women

Products Approved for Support of the luteal phase, implantation and early Pregnancy						
Drug Name	Active Ingredient	Strength	Dosage (Form/Route)	Indication	Company	Date of Approval
Endometrin® NDA 22057	(b) (4) Progesterone	100 mg	Twice or Three Times Daily as a Vaginal Insert	Support embryo implantation and early pregnancy	Ferring Pharmaceuticals, Inc.	5/21/07
Crinone® 80%	(b) (4) Progesterone	90 mg	Once Daily as a Vaginal Gel	Progesterone supplementation or replacement as part of ART treatment	Allergan Sales, LLC	5/13/77
Un-Approved Products for support of the luteal phase, implantation and early Pregnancy						
Progesterone NDA 017362 (off label use)	Progesterone in oil	50 mg	Once Daily Intramuscular (IM)	Amenorrhea and abnormal uterine bleeding	Watson Labs	5/11/78
Prometrium® NDA 019781 NDA 020843 (off label use)	Oral (b) (4) Progesterone	200 mg	Three Times Daily as a Vaginal Tablet	Prevention of endometrial hyperplasia and secondary amenorrhea	Vitrus Pharmaceuticals	5/14/85
Prometrium® NDA 020843 (off label use)	Oral (b) (4) Progesterone	200 mg	Three Times Daily as a Vaginal Tablet	Prevention of endometrial hyperplasia and secondary amenorrhea	Abbvie, Inc.	12/16/98

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient, progesterone, is readily available in two drug products (Crinone® and Endometrin®) that are approved to support embryo implantation and early pregnancy (up to 10 week post-embryo transfer) by supplementation of corpus luteum function as part of an Assisted Reproductive Technology (ART) treatment for infertile women. Progesterone is also the active ingredient in two drug products (Progesterone in oil and Prometrium®) that are used off label to support embryo implantation and early pregnancy for luteal support in ART treatment for infertile women.

Reviewer Comment:

Although used off-label, for many years progesterone in oil was considered the “gold standard” for luteal support post-embryo transfer in ART. However, injection site pain, irritation, and redness are frequently reported with administration of IM progesterone. Therefore, many programs have switched to the vaginally administered progesterone products.

2.4 Important Safety Issues with Consideration to Related Drugs

Anticipated adverse events are likely to reflect known adverse events associated with available progesterone products. Common adverse events include disorders such as nausea, abdominal pain, breast tenderness, headache, abdominal distension, vaginal discharge, and non-specific muscle spasms⁹. Because the active ingredient, progesterone, is delivered through a vaginal ring, it is possible that like other vaginal ring products, less common AEs might include bladder perforation, vaginal irritation and discomfort from excipients in the drug product, dyspareunia, and vaginal discharge.

Warnings and precautions related to the pharmacologic activity of progestens include severe allergic reactions which may include anaphylaxis and anaphylactoid reactions. The most concerning serious adverse events (SAEs) associated with progesterone use are anaphylaxis, anaphylactoid reactions, and the discontinuation rate resulting from allergic reactions. These SAEs could potentially result in premature termination of treatment, and thus adversely affect clinical pregnancy outcome.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Agency’s involvement in the drug development program for the progesterone vaginal ring began in 2004. Since that time, there have been numerous meetings and written communications between the Applicant and the Agency. The following is a

⁹ Beltsos A et al. Reproductive Health 2014; 11:78. Patients’ administration preferences: progesterone vaginal insert (Endometrin®) compared to intramuscular progesterone for luteal phase support.

summary of the regulatory history of the progesterone vaginal ring numbered in chronological order:

- **October 7, 2004:** Duramed Original Submission of IND 70875

A phase I single dose pharmacokinetic protocol for a vaginal ring containing (b) (4) gm progesterone with a release rate of (b) (4) mg/day when used over a 1 week period

- **December 7, 2004:** Agency Advice Letter

The Division of Bone, Urologic, and Reproductive Products (DBRUP) had the following recommendations:

- Choose progesterone doses that reach a pre-determined optimal serum progesterone level for the desired effect in phase 2 and 3 studies.
 - Duramed did not justify the dose selected in clinical studies. Thus, the Division expressed concern that the sponsor may not have evaluated adequate dose ranging in phase I.
- Women who require (b) (4) progesterone supplementation as part of in vitro fertilization (IVF). Therefore, progesterone treatment regimens (b) (4)
 - Progesterone (b) (4) supplementation in IVF (b) (4).
 - Clinical trial data is necessary to support (b) (4).
- The trial should include women up to 42 years of age.
 - Randomization and analyses should be stratified and powered by ovarian reserve as measured by Day 3 serum FSH and age of female partner.

- Further sub-stratification of data based on BMI, type of insemination, and infertility diagnosis should be performed.
- Studies should be powered to accommodate stratification.
- The primary endpoint should be clinical pregnancy as defined presence of a gestational sac and fetal heart beat at six weeks or greater after embryo transfer (ET).
- **March 7, 2007:** Agency Advice Letter
 - DBRUP reiterated concerns regarding the proposed single dose of (b) (4) mg progesterone/day for the progesterone vaginal ring. The dose is not well justified and may not be sufficient.
 - Evaluate at least 2 dose levels of progesterone.
 - Progesterone (b) (4) supplementation (treating women undergoing assisted reproductive technology (ART) procedures, (b) (4)).
- **June 13, 2007:** Type B End of Phase 2 (E-O-P 2) Meeting
 - The applicant initially proposed a progesterone-containing, silicone ring drug delivery system with an average in vitro release rate of (b) (4) mg progesterone/day. The Applicant later changed the drug delivery system to decrease the in vivo release rate to an estimated (b) (4) when inserted vaginally for seven days.
 - Although the Applicant reported that “its product provides the maximum amount at a consistent reliable dosing compared to the approved products, continued to stress that the Applicant had not provided sufficient doe finding evidence to proceed into Phase 3.
 - The Applicant proposed (b) (4) Trial DR-PGN-301 for luteal phase supplementation in IVF.

- DBRUP recommended the following:
 - The sponsor can proceed into Phase 3 at their own risk.



- The phase 3 trial should be double-blind or, at a minimum, the investigator and ultrasonographer should be blinded.
- The primary efficacy analysis should be based on a two-sided 95% confidence interval.
 - It should include all subjects who completed oocyte retrieval and received at least one dose of progesterone (m-ITT cohort).
 - The sponsor's proposed lower non-inferiority (NI) limit of (b) (4) % is not acceptable for the progesterone vaginal ring. The NI limit for the Phase 3 trial should be equal to or greater than -10% of a two-sided 95% confidence interval (CI) when compared to an active progesterone comparator.
 - Report the percentages of the difference of the lower limit of the 95% CIs to the first decimal place.
 - The efficacy trial, in support of the progesterone vaginal ring, should demonstrate that its efficacy will be comparable to the 33% clinical pregnancy rate for fresh embryos as reported by the Centers for Disease Control (CDC) in 2004.
 - Stratify and power randomization and analyses by ovarian reserve [Day 3 follicle stimulating hormone (FSH) and age of female partner (<35 and 35-42 years of age)].
 - ❖ Further sub-stratification of data by BMI, type of insemination [IVF or intracytoplasmic sperm injection (ICSI)], and infertility diagnosis.

- ❖ The analysis of sub-stratification data can be descriptive.
- ❖ If specific claims are sought regarding sub-stratification groups, power studies to demonstrate differences in these groups.
- ❖ Measure ovarian reserve at a central laboratory.
- ❖ Evaluate serum FSH level on Days 2, 3, or 4. Exclude women with Day 2, 3, or 4 serum FSH levels ≥ 15 from the trial.
- ART practices are significantly different in non-North American countries. Therefore, if one trial is performed for this indication, all sites should be U.S. sites or the majority of women should be treated at U.S. sites.
- Claims for Quality of life (QOL) are only acceptable if based on development of a validated instrument. Refer to the guidance entitled, "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims."
- **October 29, 2007: Special Protocol Assessment (SPA) Request**
- **December 13, 2007: SPA Non-Agreement letter**

DBRUP made the following recommendations:

- The recommended indication for the vaginal is: Progesterone vaginal ring is a progesterone-containing device and is indicated to support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteum function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women.

(b) (4)

- As practices of ART are significantly different in North American countries compared to Non-North American countries, the majority of women treated in the primary efficacy and safety trial should be from the US or Canada.
- DBRUP continued to express concerns that the proposed single dose of 14 mg/day (b) (4) for the progesterone vaginal ring is not well supported. Therefore, if the sponsor proceeds with this single 14 mg/day dose, it is at their risk of failure to determine efficacy for this product.
- As randomization is planned after oocyte retrieval, the pregnancy rate will be calculated per retrieval. This will be clearly delineated in labeling.
- There may be significant differences in pregnancy rates when comparing subjects who have received embryo transfer on Day 3 compared to Day 5. To eliminate variability, we recommend using only Day 3 ET for this trial.
- DBRUP made the following efficacy and statistical recommendations:
 - Assess the co-primary endpoints of viable pregnancy with documented fetal heartbeat at both, six weeks and ten weeks post-ET.
 - The analysis should be a non-inferiority comparison to Crinone®, which excludes a difference of greater than -10% in favor of Crinone®.
 - Stratify and power the primary analyses by ovarian reserve as measured by Day 3 serum FSH and age of women (age < 35 years and age ≥ 35-42 years).
 - Further sub-stratification of data by BMI, type of insemination [IVF or intracytoplasmic sperm injection (ICSI)], and infertility diagnosis.
 - The analysis of sub-stratification data can be descriptive.
 - We recommend using only Day 3 embryo transfers. However, if both, Day 3 and Day 5 ETs are performed, sub-stratify based on transfer dates. If claims regarding these sub-groups are sought, power studies to demonstrate differences in these groups.
 - Provide a secondary analysis of the efficacy of progesterone that includes the clinical pregnancy rate in all subjects who initiated ovarian stimulation using gonadotropins prior to progesterone therapy (a per cycle analysis).

- Report percentages of the difference between the confidence intervals to the first decimal point.
 - Results of the “Treatment Satisfaction Measure” questionnaire are considered exploratory and; therefore, are not acceptable for the purposes of labeling.
 - Standardize the classification (grading) of ovarian hyperstimulation syndrome (OHSS) as an adverse event to allow standardization of reporting across sites.
 - Women, who require paracentesis as a result of OHSS, are classified as having severe OHSS.
 - Calculate the rate of birth defects, in this trial, per live-birth for each treatment group.
 - When reporting adverse events, use a single preferred term for all women with vulvovaginal candidiasis.
- **December 13, 2007:** Duramed’s Revised SPA Protocol Submission:
 - Enroll women 18 -42 years of age.
 - Stratify by age groups <35 and 35 – 42 years.
 - Power the trial to demonstrate non-inferiority compared to Crinone® for women 35 – 42 years of age.
 - Provide two efficacy analyses for the following groups:
 - Older age group (35 -42 years of age)
 - Entire trial population
 - Provide descriptive summary analyses for women with FSH levels <10 IU/L and 10 – 15IU/L
- **January 11, 2008:** Agency SPA Non-Agreement/Advice Letter
DBRUP response to Duramed’s December 13, 2007 proposal included:
 - Stratify and power the trial for two age groups, 18 -34 and 35 – 42.

- Base the primary efficacy analyses on the two age subgroups.
- Perform a secondary sub-group analysis for women with a serum FSH<10 IU/L and FSH 10 – 15 IU/L.
- DBRUP did not agree with an eligibility criterion to exclude women > 35 years of age with less than 2 oocytes retrieved. Eligibility criterion should be the same for all women. Women, who do not have any oocytes retrieved, should not be eligible to participate.
- **August 27, 2008:** Agency SPA Non-Agreement/Advice Letter
 - DBRUP does not agree that a trial powered only to demonstrate efficacy in a population of women <35 years of age is adequate for an indication of support of embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an ART treatment program for infertile women.
 - The proposed trial will not adequately address efficacy and safety in women > 35 years of age. Therefore, it is not acceptable if the sample size for this subgroup of older women is underpowered for assessing efficacy of the progesterone vaginal ring.
 - The Division is open to further discussion regarding powering Trial Dr-PGN-302 that would allow informative labeling for both age subgroups.
 - PK data from Trial 10716222 is for evidence of bioavailability, and not to infer efficacy or safety of DR-2011 in the target population.
- **March 3, 2009:** Agency Advice Letter
 - Study DR-PGN-302 only has 200 subjects aged 35 – 42 years of age; and is therefore, is not adequately powered to assess efficacy in this population.
 - We continue to strongly recommend that randomization and primary analyses be stratified and powered for ovarian reserve as assessed by age (< 35 years and 35 – 42 years of age).
- **June 16, 2009:** Type B Clinical Pre-NDA Meeting
 - DBRUP indicated that, on multiple occasions since the June 13, 2007 EOP2 Type B Meeting, it had recommended that the phase 3 trial be stratified and powered to demonstrate efficacy in both, age groups < 35 years of age and 35 -42 years of age.

- Duramed acknowledged the Division's recommendation to power the pivotal trial(s) to demonstrate efficacy in both age groups, women <35 years of age and women 35 – 42 years of age. However, due to internal constraints, they chose to power the trial only for women <35 years of age.
- The sponsor noted an approved product whose primary trial was only powered for women <35 years of age.
- Duramed would consider conducting a separate trial in women aged 35 - 42 years.
- The Division continues to have concern regarding the formulation of DR-2011-progesterone vaginal ring (release rate of 14 mg/day of progesterone) providing insufficient progesterone for supplementation of corpus luteum function and maintenance of early pregnancy.
 - The sponsor initially stated that progesterone vaginal ring (DR-2011) has a release rate of (b) (4) mg/day. It was subsequently changed (b) (4) 14 mg/day. It is not clear why the release rate changed without a reported corresponding change in formulation composition.
 - Release rate calculations should be based on the residual amount of progesterone remaining in DR-2011 following vaginal placement of the ring for 7 days.
 - The NDA should address the release rate changes.
- The sponsor emphasized that the vaginal ring design accommodates the maximum amount of progesterone possible; and the release rate is at the maximum.
- DBRUP requested an additional safety table of women with OHSS categorized by severity (mild, moderate, severe) using standardized criteria. They also asked the Sponsor to provide the definitions used to classify OHSS.
- DBRUP advised the sponsor that it was not in a position to determine whether the aforementioned studies are appropriate to be filed. This determination depends on results of the Division's review at the time of submission.

- DBRUP reiterated its concern regarding the limited information for women in the older age group, 35 – 42 years of age.
- **October 27, 2009:** Type B Chemistry, Manufacturing and Control (CMC) pre-NDA Meeting
 - DBRUP informed the sponsor that the planned CMC information for Modules 2 and 3 appears adequate to file from the CMC standpoint.
 - DBRUP agreed agrees that the release data show no significant difference between the Phase 3 clinical trial materials and the transfer batches. However, the stability data for all batches will need to be reviewed before we can agree that there is no meaningful difference with regard to the quality of the Progesterone Vaginal Rings manufactured at different facilities.
 - The sponsor provided a slide presentation outlining the manufacturing process. Per the sponsor, there have been no formulation changes from the Phase 2 clinical trials to the proposed commercial product and the process is at the same scale (b) (4)

 - For the current acceptance criteria and stability studies, DBRUP requested that the additional drug release time points (Days 9 and 14) be included in the future stability pulls for the Phase 3 clinical supplies and that deletion of these time points be requested in the NDA.
 - DBRUP also asked for clarification on the results of the Durometer test on the phase 2 clinical supplies and the sponsor stated that they were approximately (b) (4) of the transfer batches.
 - The analytical test information appears to be adequate to support the manufacturing site change.
 - The acceptability of the calculated release rate can only be concluded following the review of the full trial report and the method validation report. It is not clear why the average weight of the returned rings tested (b) (4) was a part of the equation to calculate the progesterone content of each returned ring.
 - DBRUP informed the sponsor that their calculation result indicates an apparent mean in vivo release rate of approximately 103 mg over 7 days or

approximately 15 mg/24 hours. The variability was relatively high at 36.3% CV. The product labeling should reflect the known release rate and variability.

- The proposed method of estimating drug release calculated drug release over a 7- day use interval. The 24 hour release rate was calculated by dividing the 7-day release rate by 7. This calculation assumes that drug release is constant over the 7- day interval. The NDA should provide data to support this method of calculation.
- The sponsor presented a slide presentation on the following topics:
 1. In vitro release rate calculation
 - a. The sponsor acknowledged that average weight of the returned rings should not be used when calculating the drug content of each ring for drug release rate analysis.
 - b. The sponsor proposed to assess the drug release rate using the rings (n=42) retrieved from a planned bioequivalence trial. More subjects will be enrolled to retrieve additional used rings if there is insufficient precision from the first 42 rings. The Division inquired if the additional rings may be needed. The sponsor stated that it may not be necessary to include additional rings, but they would like to have a plan to address high variability in the data, if this is seen.
 - c. The sponsor proposed that labeling should utilize only the results from this new assessment for characterizing the drug release rate. The Division stated that this will be addressed and a determination made during the NDA review, but all results including the previous trial need to be submitted. The sponsor should provide their rationale for choosing one set of results over the other at the time of NDA submission. In the trial report for the previous trial, there should be no adjustment based on the average weight of the returned rings. In addition, the raw data for each ring tested should be submitted.
 2. Justification for dividing the 7-day release rate by 7 to calculate the average daily release rate

- a. DBRUP requested that justification for dividing the 7-day release rate by 7 to calculate the average daily release rate be included in the NDA.
 - b. DBRUP commented that the rate being calculated based on the residual amount of drug remaining in the ring after use should be referred to as the apparent in vivo release rate instead of the delivery rate. The term delivery rate may be misinterpreted to mean delivery to the systemic circulation, which is not what is being determined.
- DBRUP agreed that with the demonstration of bioequivalence (BE) between the phase 3 batch and the site transfer batch, sufficient support will be established to support the manufacturing site change.
 - DBRUP provided the following comments:
 - Provide in the original NDA submission the raw and calculated pharmacokinetic parameters data files for the BE trial. Provide the files in SAS Transport (.XPT) format.
 - In addition to your proposed primary PK and statistical analyses based on baseline corrected progesterone concentration, we request that you calculate PK parameters and perform BE statistical analyses on baseline-uncorrected progesterone concentration as secondary analyses.
 - The trial report should include rationale to justify that the mean of 3 predose baseline samplings at -1, -.5, and 0 hour would adequately capture the endogenous progesterone and could be used to perform baseline subtraction.
 - The sponsor stated that the highest individual ratio of predose plasma concentration/post dose C_{max} (as determined from the 0-168 hours post dose interval) was 1.8% and the average baseline correction was 0.4% in one of their previous studies.
 - DBRUP stated that if the data from the BE trial show a similar finding (i.e., endogenous progesterone concentration is low relative to the concentration from the progesterone vaginal ring), then the proposed predose sampling at -1, -0.5, and 0 hours should be acceptable.

- The sponsor agreed to submit PK results and BE statistical analyses based on both baseline corrected and uncorrected progesterone concentrations.
- DBRUP indicated that the proposed Overall Table of Contents and the Content Plan for Modules 2 and 3 appeared to be adequate to file the NDA from a CMC standpoint. The Division had the following additional comments:
 - In the NDA submission, provide a comprehensive table/list of all facilities involved in production of the drug substance and drug product with full street address of the actual manufacturing and/or testing site (not the corporate office), contact information of an individual at the site, detailed responsibilities of that facility and a date of when the facility was last inspected by FDA. This comprehensive table should be attached to the 356h. Full information should still be provided in the appropriate sections of Modules 2 and 3. Inspections cannot be requested unless all the above information is provided. If this information is not provided when the NDA is submitted, it will delay inspection requests and may adversely affect the outcome of a first cycle review decision.
 - Ensure that the stability data for the transfer batches includes the 6 month accelerated stability data.
- The sponsor inquired as to how the in vivo release rates would be presented in the labeling. DBRUP responded that they should use release rate, similar to other vaginal ring products. The sponsor was referred to the labeling of ring products for contraception and hormone therapy.
- The sponsor's proposal on how the in vivo release rate is to be applied in labeling will be addressed during the NDA review.
- **February 3, 2010:** Agency Advice/Information Request:
 - DBRUP recommend the following inclusion criterion: All subjects should have a negative pretreatment mammogram (obtained at screening or within 3 months of trial enrollment) and a documented normal clinical breast examination prior to enrollment. Findings of suspicious significant breast pathology will result in exclusion of the subject from enrollment.
 - DBRUP recommend the following exclusion criteria:

- Dosage regimen changes of any concomitant medications during the trial.
 - Current treatment with progesterone, other progestins, or estrogen (other than that required by the trial protocol).
- DBRUP recommend that the sponsor fully document all vaginal examination findings both prior to and after treatment.
- Consider assessing the endometrial histology for progestational effects.
- DBRUP recommend that colposcopy be performed on all subjects with any abnormal findings on vaginal examination at trial termination or discontinuation. All colposcopic findings should be recorded using standardized reporting instruments such as those listed in the 2000 World Health Organization (WHO) manual for standardized colposcopy. If lesions or abrasions on the cervix or vagina are found at trial termination or discontinuation, DBRUP recommend that re-examination be performed within 2-4 days. Subjects should be followed until their lesions have resolved.
- The outcomes of any pregnancies that occur during the trial should be followed and reported.

• **April 30, 2010:** Duramed. **Submission of NDA 201110**

Trial DR-PGN-302 was submitted to support efficacy and safety. However, Trial DR-PGN-302 was not powered to demonstrate non-inferiority of the progesterone vaginal ring, DR-2011, as compared to Crinone® 8% for the 35-42 year old age group. This age group of women constitutes the largest percentage of women undergoing Art for treatment of infertility in the United States.

• **October 12, 2010:** Agency Information Request:

- DBRUP suggest that microbial enumeration for the drug product be performed according to the USP 32-NF 27 Chapter <61> guidelines for testing transdermal patches. All results should be recorded as CFU/ring and not as CFU/g. Alternatively, provide a justification for the deviations from this method.
- The process validation studies presented in ARD_RPT-2950 do not support your drug product testing method. Organisms should be inoculated directly onto the ring to show that the test method is capable of detecting the

presence of microorganisms on the vaginal ring. These studies should reflect any changes made in response to comment #1.

- Establish microbial limits (in CFU/ring) compliant with the recommendations in the USP 32-NF 27 General Chapter <1111> for vaginal products or provide rationale for any deviations from these recommendations.
 - Provide a justification for not following the current USP <62> recommendations on the test method for the absence of (b) (4).
 - Provide the results from the re-testing of site transfer and stability samples with the new validated microbial enumeration methods.
- **November 30, 2010:** Duramed. Submission - Quality Information Amendment to NDA 201110
 - **February 28, 2011:** **Complete Response (CR)** Decisional Letter:

Deficiencies and strategies for resolution of deficiencies were as follows:

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

1. The sponsor has not provided sufficient evidence of efficacy for the progesterone vaginal ring 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. The sponsor has 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.
2. To address this concern, DBRUP continues to recommend that you conduct, prior to approval of your product, a randomized, active-controlled clinical trial to evaluate the efficacy of progesterone vaginal ring 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 trial.
3. 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.

LABELING

DBRUP reserves comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

FACILITY INSPECTIONS

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.

SAFETY UPDATE

Response to the above deficiencies should include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

In addition to the above deficiencies, the following issues should be addressed in your response to this letter:

PRODUCT QUALITY



MICROBIOLOGY

1. 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 listed in section 5.3. Revise ARD_RPT-5064 version 2.0 accordingly.
 2. Submit the results from microbial enumeration studies on the stability and site transfer batches using the revised test methods.
- **March 4, 2011:** Agency Advice Letter
 - We note the proprietary name is presented in all-upper case letters. Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all-upper case. Therefore, we request you revise the proprietary name to appear in title case (i.e., 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.
 - DBRUP provided additional recommendations for labeling.

- **March 31, 2011:** Teva Women's Health - Update to Microbiology Testing

The sponsor advised the DBRUP 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 (b) (4)

The same type of container was used to test all five of the site transfer batches of Progesterone Vaginal Ring; therefore, results from all five batches are invalid.

- **April 12, 2011:** Agency Acknowledgement Regulatory Letter

DBRUP acknowledged receipt of the sponsor's corporate name change from Duramed Research Inc., to Teva Women's Health, a division of Teva Branded Pharmaceutical Products R&D, Inc.

- **May 31, 2011:** Quality Information

- Teva Women's Health Submission:

- Results from re-testing of site transfer and stability samples of Progesterone Vaginal Ring (Batches 800354, 800356, 800357, 800358, and 800359 using the revised Finished Product Test Method (MTH- (b) (4)) for Microbiological Examination tests, which were performed after procurement of new, more suitable containers
 - Copy of OOS investigation report

- **December 23, 2011:** Quality Information Amendment

Teva Women's Health submitted an amendment, which addressed product quality deficiencies to determine the cause and remediate foreign particulate contamination in progesterone vaginal rings.as outlined in the CR.

- **February 28, 2012:** Teva Womens Health Information Amendment Regarding Complete Response

- The sponsor requested an extension in responding to the CR. The additional time was to allow for manufacture of additional full-scale progesterone vaginal ring batches and generation of release and stability data to confirm consistent progesterone vaginal ring manufacturing capability.

- The sponsor initiated the first full-scale progesterone vaginal ring batch manufacture on February 13, 2012; and completed manufacturing.
- Safety update confirmed that there was not any new safety information on the progesterone vaginal ring.
- The information amendment addressed product quality deficiencies.
- Teva Womens Health proposed postponing discussion of the Post-marketing Commitment until fourth quarter 2012 with the final submission to the CR Letter.
- **March 28, 2012:** Agency Advice Letter

DBRUP informed Teva Women's Health 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:** Corporate Name Change

Teva Women's Health R&D, a division of Teva Branded Pharmaceutical Products R&D, Inc. changed the corporate name to Teva Branded Pharmaceutical Products R&D, Inc.
- **November 19, 2013:** Teva Branded Pharmaceutical Products R&D, Inc. - Waiver Request

The sponsor requested a waiver to submit periodic Individual Case Safety Reports (ICSRs) on a rolling or ongoing basis throughout the reporting period via the Electronic Submissions Gateway.
- **November 22, 2013:** Agency Grants Waiver Request

Under 21 CFR 314.90(b), the Agency granted Teva Branded Pharmaceutical Products R&D, Inc. a waiver of the requirement to submit the non-expedited ICSRs obtained or otherwise received during the reporting interval of the postmarket periodic safety report in a single batch with that report. Instead, Teva should submit these non-expedited ICSRs electronically on an ongoing basis up until the due date of the descriptive portion of the postmarket periodic safety report.

- **January 23, 2014:** Teva Branded Pharmaceutical Products R&D - Submission of Bioequivalence Trial

The sponsor submitted a new clinical trial protocol for 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.” This is a phase 1 pharmacokinetic trial to evaluate for the bioequivalence (BE) of progesterone vaginal rings manufactured by a new (b) (4) process (information provided in the January 17, 2014 CMC amendment) and those manufactured by the legacy (b) (4) process (representative of the phase 3 clinical trial material) during a single 7-day application cycle in postmenopausal female subjects treated with estrogen. The legacy (b) (4) process was transferred from the manufacturing site used for the clinical trial material to that intended for commercial production, and supported by a bioequivalence trial (Trial 10935036; provided in NDA 201110 sequence 0000 on April 30, 2010). Dr. Sandhya Apparaju reviewed Trial 10935036. See archived clinical pharmacology review dated February 2, 2011. The “reference” material in the present trial is identical to the “test” material in the 10935036 trial.

- **January 22, 2015:** Teva Branded Pharmaceutical Products R&D - Submission of Bioequivalence Trial Report

Teva Branded Pharmaceutical Products R&D, Inc. submitted the trial report for “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 - Transfer of ownership

Teva Branded Pharmaceutical Products R&D, Inc. notified the Agency of transfer of ownership of NDA 201119 and IND 070875, and associated communications and documentation from the FDA to Ferring Pharmaceuticals Inc.

- **August 6, 2015:** Ferring Pharmaceuticals Inc. Acceptance of NDA Sponsorship

In accordance with 21 CFR 314.72, Ferring accepted 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:** Agency Acknowledgement of Change in Sponsorship for IND 070875.
- **October 8, 2015:** Agency Acknowledgement Transfer of Ownership for NDA 20110.

2.6 Other Relevant Background Information

During the luteal phase of a normal menstrual cycle, an oocyte is released with spontaneous ovulation. The empty follicle, from which the oocyte was released, collapses and becomes a corpus luteum. The corpus luteum produces progesterone. Progesterone induces secretory transformation of endometrial tissue; and is therefore essential for embryo implantation. However, during controlled ovarian stimulation (COS) for IVF and ICSI cycles, administration of gonadotropin-releasing hormone (GnRH) agonists and antagonists compromise the production of progesterone by the corpus luteum¹⁰. Additionally, the oocyte retrieval process destroys the corpus luteum. Thus administration of exogenous progesterone for luteal support is standard of care for IVF and ICSI cycles. Progesterone supplementation is also standard of care in embryo recipients [ovum donation, embryo adoption, gestational surrogacy, or frozen embryo transfers (FETs)]. Progesterone is administered to initially align embryo recipient cycles with the stage of the embryos and to ultimately support embryo implantation until adequate production of progesterone by the placenta at approximately ten weeks of gestation.

3 Ethics and Good Clinical Practice

3.1 Submission Quality and Integrity

No new phase 3 clinical trials were conducted to support this re-submission. The majority of submissions were related to CDRH and CMC deficiencies.

3.2 Compliance with Good Clinical Practices (GCP)

The applicant reports that Trial DR201-BE-10021 was conducted in full accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP). Data handling, including data quality control, complied with ICH GCP guidelines: and

¹⁰ Beltsos A *et al.* Patient's administration preferences: progesterone vaginal insert (Endometrin®) compared to intramuscular progesterone for Luteal phase support. Reproductive Health 2014; 11:78.

the investigator agreed to conduct and administer this study in accordance with ICH GCP guidelines.

With this re-submission of NDA 201110, one site was identified for an in vivo bioequivalence inspection 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":

Audrey Martinez, MD
SeaView Research
3898 NW 7th Street
Miami, FL 33126

The inspection was conducted May, 9-24, 2016. No discrepancies, significant issues, or under-reporting of adverse events (AEs) were observed. The final classification for this inspection is no action indicated (NAI).

The Office of Integrity and Surveillance (OSIS) recently inspected the following site; and the inspection was classified as NAI.

(b) (4)

Therefore, the Division of New Drug Bioequivalence Evaluation (DNDBE) within DSI recommended accepting data without an on-site inspection.

No new phase 3 clinical trials were conducted to support this re-submission.

3.3 Financial Disclosures

Per archived clinical review dated December 1, 2010, adequate information was submitted to demonstrate compliance with financial disclosure requirements for previously submitted trials supporting efficacy and safety. Although, a new BE trial DR201-BE-10021 with data was submitted with this Class 2 Re-submission, the applicant did not submit additional/new financial disclosure information.

Reviewer Comment:

As Trial DR201-BE-10021 is a single investigator bioequivalence study supporting a new dosage form, this reviewer believes that corresponding financial disclosure information would have been appropriate. Because the applicant will receive a CR, the lack of new financial disclosure information will not have an impact on the review decision. However, if the applicant resolves

deficiencies and relies on BE Trial DR201-BE-10021 or any other trial to provide support for the effectiveness of the device-combination product or in which a single investigator makes a significant contribution to the demonstration of safety, is relied upon, disclosure of financial interests and arrangements is required (21 CFR §§ 54.2(e) and 54.3).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

Subsections 4.1.1, 4.1.2, 4.1.3 and 4.1.4 present deficiencies noted upon initial assessment of this Class 2 re-submission and the applicant's response to those deficiencies:

4.1.1 Drug Product Development

(b) (4)

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Clinical Review

{Rhonda Hearn-Stewart, M.D.}

{NDA 201110}

{Milprosa (Progesterone, USP), (b) (4)}

(b) (4)

The applicant's responses and justifications were deemed by the Office of Pharmaceutical Quality to adequately address the aforementioned deficiencies. Products manufactured by the legacy and new processes are bioequivalent and have similar in-vitro drug release profiles. However, leachables/extractables data are not available for the new ring.

Because changes to the (b) (4) process conditions (b) (4) and duration can impact the leachables/extractables profile and safety of the drug-device product, biocompatibility is necessary. Without biocompatibility testing, the application is not approvable from the drug product perspective.

For detailed information, see the CMC review.

4.1.2 Device Development

At the time of initial submission of NDA 201110 (April 30, 2010) by Teva Women's Health and the Agency's decision for complete response on the progesterone vaginal ring, the Agency had not yet issued its final rule on the current good manufacturing practice (CGMP) requirements applicable to combination products. However, when Ferring Pharmaceuticals, Inc., re-submitted NDA 201110 (February 25, 2016) it was considered a drug-device combination product under 21 CFR Part 3. Review of information provided in NDA 201110 identified deficiencies in mechanical testing of the ring, stability/shelf-life testing, and biocompatibility. On May 23, 2016, the applicant was advised that the progesterone vaginal ring is a drug-device combination product under 21 CFR Part 3 and subject to 21 CFR Part 4 'Current Good Manufacturing Requirement for Combination Products'. The following list of recommendations and information requests was also provided:

1. Provide a description of the progesterone vaginal ring which includes a list of components, dimensions, durometer specification, and appearance of the vaginal ring. However, you have not sufficiently evaluated the mechanical properties of the vaginal ring. 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.
2. Provide a full protocol, test report, and justification for the chosen acceptance criteria. (b) (4)

[Redacted content]

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 TBM progesterone vaginal ring is proposed to be inserted the day following oocyte retrieval and replaced weekly for up to 10 weeks total duration of use. Therefore, the TBM progesterone vaginal ring 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. To assist you in 1) planning new non-clinical studies that will provide this information or 2) evaluating the adequacy of previously conducted studies, 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.



4. Provide a risk analysis that evaluates the risks associated with the use of the vaginal ring 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 acceptable mechanical testing for the requested parameters, acceptable shelf-life information on the subject ring, and acceptable mitigation methods for the concomitant use of other intravaginal devices.

An August 8, 2016 Information Request Letter to the applicant outlined the following:

1. A detailed comparative Extractables & Leachable (E&L) study assessing chemical equivalence to determine whether the final, finished PVR manufactured by the 'new process', elutes the same type, and relative quantity of chemical compounds as compared to that manufactured by the 'legacy process'. It is important to make sure that the age of the products that are evaluated in the E&L study are within the established shelf life of the products as determined from the stability data.
2. The chemical characterization of silicone-based product should include analysis for small molecular weight (b) (4). Note that the presence of these oligomers above their respective toxicologically acceptable levels would raise safety concerns regarding the use of the PVR.
3. The chemical analysis should provide the total quantity or amount (in weight) of all identified compounds per PVR
4. The test sample preparation/extraction for chemical characterization should be performed as per the principles outlined in ISO 10993-12.
5. The E&L study should be performed as per the principles outlined in ISO 10993-18.
6. The toxicological risk assessment should be performed on all the identified known and unknown chemicals as per the principles outlined in ISO 10993-17.
7. If data from the chemical characterization/risk assessment is used to leverage sub-chronic toxicity and genotoxicity testing, the toxicological risk assessment should be carried out by using the appropriately protective cancer-based Threshold of Toxicological Concern (TTC) values for those chemicals that are identified either as unknowns or have limited or no toxicological information available.

On October 14, 2016, the applicant provided preliminary results of cytotoxicity and sub-chronic systemic toxicity studies of the to-be-marketed progesterone vaginal ring. Based on the initial test results and the observations that progesterone possibly interferes with the biocompatibility test assays, they proposed that all future biocompatibility testing of the progesterone vaginal ring be performed on the placebo final product vaginal rings, i.e., rings produced by the same manufacturing process, but without progesterone.

The Agency does not agree that biocompatibility testing may be performed on progesterone-free vaginal ring placebo only. To adequately evaluate and support biological safety of the subject product, the Agency requests the following testing paradigm to meet the biocompatibility requirements of the to-be-marketed product:

1. For products that are inherently cytotoxic or products that demonstrate cytotoxicity, additional testing using several dilutions of the extracts derived from the final, finished to-be-marketed progesterone vaginal ring product (with Progesterone) is necessary to determine the level at which cytotoxicity no longer occurs.
2. A chemical characterization followed by a toxicological risk assessment on extracts derived from the final, finished progesterone vaginal ring product (with Progesterone) will provide the overall leachable profile of the progesterone vaginal ring product and will be necessary to understand the breakdown products that are a result of progesterone vaginal ring silicone material + drug 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.
3. Sensitization testing per principles outlined in ISO 10993-10.
4. In your preliminary biocompatibility assessment, you state that you initiated a 14-day intraperitoneal (IP) study in female rats for sub-chronic toxicity testing. However, please note that a 14-day IP study does not represent sub-chronic systemic toxicity testing. For sub-chronic systemic toxicity testing, a 28-day IV and/or 90-day IP needs to be conducted to demonstrate potential systemic toxicity concerns following exposure to device extracts over a period that is considered to be longer than a typical sub-acute systemic toxicity test study, and not exceeding 10% of the animal species' life span. Therefore, additional rationale is needed for the selection of the 14-day duration of exposure and how the study period represents a sub-chronic systemic toxicity study.
5. On page 4 of the October 14, 2016 response, you state that the progesterone dose-exposure calculation in rats is based on (b) (4) progesterone by IP route of administration. However, as the maximum injection dose volume limit via IP in rat species is 20 ml/kg, it is unclear how the dosage volume that is (b) (4) times lower than the maximum recommended injection dose is representative of an exaggerated exposure dose for a systemic toxicity study. Additionally, in the information provided, the frequency of dose exposure is not clear (i.e., single, multiple, repeat, etc.). Therefore, additional rationale is needed for the dosage volume used in the study. Address whether there are any adjustment factors such as surface area-to-body weight, exaggerated exposure conditions – dose, duration, frequency, route of exposure, physical-chemical and biological properties of the test sample, animal strain, etc. – that make up for the lower limit of the maximum dosage volume selected for test sample administration.
6. In the information provided, the exposure dosing is based on the drug potency of progesterone, rather than assessing the overall leachability profile of the final, to-be-marketed combination product. The objective of a sub-chronic systemic

toxicity study is to evaluate the potential of leachable chemicals to induce systemic toxicity effects. Therefore, we recommend that exposure dosing be based on the leachability profile of the to-be-marketed product.

For additional details, see the CDRH review dated November 4, 2016.

Remaining device development deficiencies include:

1. For products that are inherently cytotoxic or products that demonstrate cytotoxicity, additional testing using several dilutions of the extracts derived from the final, finished to-be-marketed progesterone vaginal ring product (with Progesterone)
2. Chemical characterization followed by a toxicological risk assessment on extracts derived from the final, finished progesterone vaginal ring product (with Progesterone)
3. Sensitization testing per principles outlined in ISO 10993-10
4. A sub-chronic systemic toxicity study based on the leachability profile of the to-be-marketed product
5. Justification for the dosage volume used in rats during the progesterone dose-exposure study
6. Justification for the selection of the 14-day duration of exposure for sub-chronic toxicity testing

4.1.3 Conclusions

From an *Office of Pharmaceutical Quality (OPQ)* perspective, approval is not recommended.

Reviewers Comment:

The applicant has not performed sufficient biocompatibility testing on the proposed to-be-marketed progesterone vaginal ring product. Because changes to the process conditions such as (b) (4) duration can impact the leachable/extractable profile and safety of the drug, biocompatibility testing of the new drug is necessary. Additionally, because the progesterone vaginal ring acts locally on the endometrium, any changes to the progesterone vaginal ring could potentially impact efficacy as well. Therefore, biocompatibility testing on the proposed to-be-marketed progesterone vaginal ring is essential to accurately determine safety, efficacy, and the risk-benefit profile.

4.2 Clinical Microbiology

Milprosa is a non-sterile drug product. Nevertheless, the drug product specification includes tests for microbial limits and the absence of (b) (4) at release and on stability. The microbiology deficiencies identified during the review of the original NDA were delineated in the February 28, 2011 Complete Response letter:

1. 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) .”
2. 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 listed in section 5.3. Revise ARD_RPT-5064 version 2.0 accordingly.
3. Submit the results from microbial enumeration studies on the stability and site transfer batches using the revised test methods.

The applicant provided an adequate description of the drug product composition and the manufacturing process. The applicant identified facilities that perform release/stability testing for the subject drug product. Because the manufacturing facility was moved from Teva Pharmaceuticals (formerly Barr Laboratories) in Plainsboro and Northvale, NJ to Teva Pharmaceuticals USA in Cincinnati, OH, stability testing was reported from both sites to enable comparison of the processing and storage time for the new batches to the legacy batches. Data supports maintenance of microbiological quality during storage.

(b) (4) is included in the release product specification; and the specification limit is absent. All batches meet this specification. Thus, the drug product specification is adequate. Test methods, including microbial limits testing are adequate as well. The Microbiology deficiencies identified in the Complete Response letter dated February 28, 2011 have been adequately addressed. Thus the application is recommended for approval from the product quality microbiology perspective.

For detailed information, see the archived clinical microbiology review dated August 3, 2016.

4.3 Preclinical Pharmacology/Toxicology

The daily dose of progesterone in the Milprosa vaginal ring (11 mg), and the duration of exposure (up to 10 weeks) is less than that in approved progesterone containing products. No genotox, reprotox, or carcinogenicity studies were conducted for this

product. The applicant did not conduct any new non-clinical studies in support of this re-submission. Although there were changes made to the manufacture of the silicone ring, the drug substance was not changed from the previous submission.

Non-clinical rabbit studies conducted in support of the original submission assesses the local response of vaginal tissue to the progesterone implant. Neither, short term (10 day) or long term (90-day) studies resulted in significant adverse effects. Short term studies demonstrated endometrial hyperplasia; and long term studies demonstrated uterine and vaginal atrophy. A dose of (b) (4) mg/day was tested in Phase 1 trials. This dose is higher than the 11 mg/day dose proposed in this resubmission.

The impurity profile of the progesterone drug substance in the DMF and the current application are the same. This is also the same impurity profile described in the original submission. For detailed information see the preclinical pharmacology/toxicology archived reviews dated June 10, 2016 and July 16, 2010.

Recommendation: From the standpoint of drug pharmacology/ toxicity, the Pharmacology/Toxicology reviewer recommends approval of Milprosa. There are no non-clinical safety issues relevant to clinical use.

Reviewer Comment:

CDER's Pharmacology and Toxicology reviewer limited her discussion to the drug component of the to-be-marketed product. Carcinogenicity and Toxicity issues were also address by CDRH with respect to the device component of the to-be-marketed product. Refer to Section 4.1.2.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Progesterone is a naturally occurring steroid that is secreted by the ovary, placenta, and adrenal gland. During the luteal phase of a normal menstrual cycle, the corpus luteum secretes progesterone. In the presence of adequate estrogen, progesterone transforms a proliferative endometrium into a secretory endometrium. Progesterone also increases endometrial receptivity for embryo implantation. After establishment of embryo implantation, progesterone helps maintain the pregnancy.

In women undergoing ART, use of a gonadotropin releasing hormone (GnRH) agonist as part of the regimen causes a temporary suppression of pituitary luteinizing hormone (LH) secretion. Without the LH signal, the corpus luteum may be dysfunctional, and subsequent progesterone and estrogen secretion may be abnormal thereby compromising endometrial receptivity. This compromise in endometrial receptivity can potentially lead to decreased implantation and pregnancy rates. Additionally, helps

maintain early pregnancy. Thus the goal of progesterone supplementation in ART is to improve endometrial receptivity for embryo implantation and to support the early pregnancy until adequate placental support is established. Most treatment protocols advocate the use of progesterone through age of gestation 10 weeks because corpus luteum activity has been demonstrated up to week 10 of pregnancy.

4.4.2 Pharmacodynamics

Progesterone acts locally at the level of the endometrium by transforming proliferative endometrium into secretory endometrium, which increases endometrial receptivity for implantation of embryos. To assess the 'local' progesterone exposure from the vaginal formulation of Milprosa, tissue progesterone concentration in the endometrium and secretory transformation of the endometrium were assessed as pharmacodynamic (PD) outcomes in the following studies submitted with the initial submission of NDA, on April 30, 2010: (No new PD data was submitted with this submission.)

1. Trial DR-201-102 was a phase 1, randomized, open-label, active control, vs. no treatment control trial to assess endometrial tissue progesterone, systemic progesterone, and endometrial PD outcomes (% patients achieving successful secretory transformation of the endometrium). This study was conducted in 63 healthy females 18-40 years with regular menstrual cycles.
2. Trial DR-PGN-201 was a phase 2, randomized, open-label, active control trial in 21 females aged 18-50 years who are candidates for donor oocyte program; the study was a 'mock cycle' that evaluated the proportion of subjects with adequate endometrial transformation.
3. Trial DR-PGN-202 was a phase 2, randomized, open-label, active-control trial in 9 participants who had demonstrated successful endometrial transformation in earlier study DR-PGN-201. This trial assessed the clinical pregnancy rates (at 8 and 12 weeks of pregnancy).

Although successful secretory transformation of endometrium was observed, neither the correlation of tissue progesterone or endometrial transformation with the primary efficacy endpoint, clinical pregnancy, was established. Additionally, no trends were identified between serum progesterone concentrations and pregnancy outcome or endometrial transformation and pregnancy outcome.

For detailed information, see the clinical pharmacology review dated February 2, 2011.

4.4.3 Pharmacokinetics

The (b) (4) process and the vaginal progesterone ring used for phase 3 Trial DR-PGN-302 differ from the to-be-marketed product due to a change in manufacturing process. On February 25, 2016, the applicant submitted a new bioequivalence (BE) trial (#DR201-BE-10021) to demonstrate BE between the "to-be marketed" progesterone

vaginal rings manufactured using a new process and the legacy process. Only pharmacokinetic (PK) and in-vitro dissolution data were submitted for Trial #DR201-BE-10021. Trial #DR201-BE-10021 is an open-label, single-dose, single center, randomized, 2-treatment, 2-period crossover trial with a 7 day washout period.

The trial enrolled 56 naturally postmenopausal women ranging in age from 47-65 years with an intact uterus. The mean age was 56.8 years. Postmenopausal was defined as at least 12 months of natural spontaneous amenorrhea or at least 6 months of natural spontaneous amenorrhea with a follicle-stimulating hormone (FSH) level greater than 40 mIU/mL. Study participants had no clinically significant abnormal findings observed during pelvic, breast, and vaginal examination. Mammograms and Papanicolaou smear evaluations were normal. Fifty-four (96%) of study participants were white. The mean weight was 68.7 ± 8.34 kg; and the mean BMI was 27.5 ± 2.78 kg/m².

Study entry and start of estradiol treatment occurred on day -28. Treatment with Treatment A (new process) or Treatment B (legacy process) occurred for 7 days in treatment period 1, followed by a minimum 7-day washout period prior to a 7 day treatment in period 2. The end of the trial was on day 10 of treatment period 2 or early termination, followed by a 12-day course of progesterone and a follow-up phone call within 7 days. The following primary PK parameters were assessed: area under the plasma drug concentration by time curve from time 0 to the time of the last measurable drug concentration (AUC_{0-t}), area under the plasma drug concentration by time curve from time 0 to infinity (AUC_{0-∞}), and maximum observed plasma drug concentration (C_{max}). The following secondary PK parameters were also assessed: time to maximum observed plasma drug concentration (t_{max}), terminal elimination rate constant (λ_z), terminal elimination half-life (t_{1/2}). Blood sample collection was performed at -1, -0.5, and 0 hours before ring insertion and at 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168 hours before vaginal ring removal. Blood sample collection was also performed at 169, 170, 171, 172, 174, 176, 180, 192 and 216 hours.

Trial #DR201-BE-10021 is acceptable to establish BE of to-be-marketed formulations of the DR-201 vaginal ring manufactured from the new and legacy processes. BE analyses comparing the new process and legacy process indicate that the upper and lower bounds of the 90% confidence intervals (CIs) of the ratio of geometric least square (LS) means (Treatment A/Treatment B) for C_{max}, AUC_{0-t}, and AUC_{0-∞} for baseline corrected progesterone are within the BE boundaries of 0.80-1.25 and are consistent with results of the baseline non-corrected analysis. Thus, the DR-201 progesterone vaginal ring manufactured from the new process is bioequivalent to the DR-201 progesterone vaginal ring manufactured from the legacy process.

For more details on the clinical pharmacology evaluation, see Dr. Peng Zou's review, dated September 7, 2016.

Reviewer Comment:

Although BE has been established between the vaginal ring that was manufactured with the previous (b) (4) process and the vaginal ring (to-be-marketed product) manufactured with the new (b) (4) process, differences in (b) (4) processes may result in different mechanical properties of the device. Therefore, CDRH/ODE practice recommends that the following mechanical testing be performed on the to-be-marketed product using at least ten samples per test:

- Dimension analysis
- Tensile strength
- Elongation at break
- Compression strength
- Twisting during compression
- Seal strength at ring seal interface.

Mechanical testing was not performed on the to-be-marketed product. Thus approval cannot be recommended.

Additionally, PD outcome parameters were not assessed on the to-be-marketed product. Because, progesterone acts locally at the level of the endometrium by transforming proliferative endometrium into secretory endometrium, the 'local' progesterone exposure from the vaginal formulation of Milprosa should be assessed in the to-be-marketed product. This reviewer recommends a trial, which assesses PD outcomes, tissue progesterone concentration in the endometrium and secretory transformation of the endometrium.

5 Review of Efficacy

No new phase 3 clinical trial data was submitted with this resubmission. Per archived clinical review dated December 1, 2010, the clinical reviewer found Milprosa to be efficacious in the subgroup of women less than 35 years of age. Trial SRR-PGN-302 was not sufficiently powered to provide efficacy information on the subgroup of women 35-42 years of age. Efficacy of the older population cannot be extrapolated from that of the younger population.

6 Review of Safety

No new phase 3 clinical trial data was submitted with this resubmission.

The following information summarizes the safety findings from bioequivalence Trial DR201-BE-10021:

The number of study participants that reported an adverse event (AE) was similar in both treatment groups. Fifty (89%) of study participants reported at least one adverse event (AE) after receiving treatment A (new process); and 48 (86%) reported at least one adverse event (AE) after receiving treatment B (legacy process). The incidence of treatment-related AEs was equal, in both treatment groups, 47 (84%). All AEs were mild in severity with the exception of one moderate AE of withdrawal bleed reported in one (2%) study participant in Treatment A. This AE resolved without treatment or sequelae.

The most frequently reported AEs were within the Reproductive System and Breast Disorder System Organ Class (SOC) [45 (80%) and 44 (79%) in Treatment A and B, respectively]. The most frequently observed AE, withdrawal bleed, occurred with a similar incidence in treatment A and Treatment B with 39 (70%) and 41 (73%), respectively. The incidence of withdrawal bleed was followed by pelvic pain [Treatment A: 8 (14%); Treatment B: 9 (16%)], vaginal discharge [Treatment A: 11 (20%); Treatment B: 6 (11%)], and breast tenderness [Treatment A: 7 (13%); Treatment B: 4 (7%)].

No deaths, severe AEs, or discontinuations were reported.

Reviewer Comment:

The most common AE, withdrawal bleed, is not alarming in this trial. It is to be expected in this post-menopausal population that was pre-treated with estrogen, A withdrawal bleed would be expected after administration of progesterone. Vaginal discharge, cramping, and breast tenderness are common side effects associated with progesterone treatment.

7 Appendices

7.1 Literature Review/References

Literature references are included as footnotes in the appropriate sections of this review. Thus, a separate comprehensive review of the literature on progesterone for luteal supplementation for women undergoing ART is not necessary.

7.2 Labeling Recommendations

Approval is not recommended. Labelling negotiations did not take place during this review cycle.

7.3 Advisory Committee Meeting

There were no Advisory Committee meetings to discuss the progesterone vaginal ring.

Clinical Review

{Rhonda Hearn-Stewart, M.D.}

{NDA 201110}

{Milprosa (Progesterone, USP), (b) (4)}

APPEARS THIS WAY ON ORIGINAL

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

/s/

RHONDA M HEARNS-STEWART
11/22/2016

SHELLEY R SLAUGHTER
11/22/2016

I concur with Dr. Hearn-Stewart's recommendation for non-approval of this application. See also CDTL review for an overall presentation of the issues.

Summary Review for Regulatory Action

Date	February 28, 2011
From	Scott Monroe MD
Subject	Division Director Summary Review
NDA	NDA 201110
Applicant Name	Teva Women's Health, Inc.
Date of Submission	April 30, 2010
PDUFA Goal Date	February 28, 2011
Proprietary Name	Milprosa Vaginal Ring
Established (USAN) Name	Progesterone Vaginal Ring
Dosage Forms/Strengths	Silicone vaginal ring containing 1.78 grams of progesterone with average release rate of 11 mg/day
Proposed Indication	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
Proposed Regimen	One vaginal ring starting on the day after oocyte retrieval and replaced weekly for up to 10-weeks total use
Action	<i>Complete Response (see Section 13.1)</i>

Material Reviewed/Consulted	
OND Action Package, including:	Names of Discipline Reviewers
Medical Officer Review	Christos Mastroyannis MD (Clinical Reviewer)
Statistical Review	Xin Fang PhD/Mahboob Sobhan PhD
Pharmacology Toxicology Review	Krishan Raheja DVM PhD/Alexander Jordan PhD
CMC Review	Nina Ni PhD/Moo-Jhong Rhee PhD
Microbiology Review	Jessica Cole PhD/Stephen Langille PhD
Clinical Pharmacology Review	Sandhya Apparaju PhD/Myong-Jin Kim PharmD
DDMAC	Deferred
DSI	Roy Blay PhD/Tejashri Purohit-Sheth MD
CDTL Review	Shelley Slaughter MD PhD (also Clinical Team Leader)
OSE/DMEPA	L Sheneé Toombs PharmD/Irene Chan PharmD
OSE/DRISK	Deferred

OND=Office of New Drugs

CMC=Chemistry, Manufacturing and Controls

DDMAC=Division of Drug Marketing, Advertising, and Communication

DSI=Division of Scientific Investigations

CDTL=Cross Discipline Team Leader

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Errors Prevention and Analysis

DRISK=Division of Risk Management

DIVISION DIRECTOR SUMMARY REVIEW

1. INTRODUCTION

NDA 201110 was submitted by Teva Women's Health, Inc. to obtain marketing approval for Milprosa (Progesterone) Vaginal Ring for the proposed indication "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." Currently, there are 2 vaginal progesterone products (Crinone[®] and Endometrin[®]) that are approved in the US for the same or a similar indication. Intramuscular progesterone is also used off-label for this indication. The progesterone vaginal ring (also referred to as the PVR in this review) is inserted vaginally, starting on the day after oocyte retrieval in women as part of an ART treatment program. The ring, which is replaced weekly, is used for up to 10 weeks, after which the placenta produces sufficient progesterone to support an on-going pregnancy. The progesterone vaginal ring is not currently marketed in any country.

This Application included chemistry, manufacturing and controls (CMC), limited new preclinical toxicology, clinical pharmacology, and clinical safety and efficacy information to support approval. The Application included four Phase 1 pharmacokinetic (PK)/bioavailability studies, two Phase 2 pharmacokinetic/pharmacodynamic (PD) studies, and one randomized, single-blind Phase 3, active-controlled clinical trial (DR-PGN-302) that was the primary source of the clinical safety and efficacy data for the progesterone vaginal ring.

The primary CMC and microbiology reviewers, as well as the primary clinical review team, have concluded that there are significant deficiencies in this Application. These deficiencies are described fully in Section 3 (CMC), Section 6 (Microbiology), and Section 2.3 (Recommendations of primary Clinical Reviewer) of this Summary Review. Because of these deficiencies, the CMC and microbiology reviewers, and the primary clinical review team, have recommended that the Application not be approved at this time. I concur that the CMC/microbiology deficiencies preclude approval of NDA 201110 until such time as they are resolved. The deficiency identified by the primary clinical review team (failure of the Applicant to provide adequate data to support the safe and effective use of the product in women 35 to 42 years of age), however, could be addressed by (1) appropriate product labeling and (2) a postmarketing commitment by the Applicant to conduct an adequate and well-controlled clinical trial in women 35 to 42 years of age. Because of the Product Quality (CMC/Microbiology) deficiencies and the recommendation by the Office of Compliance of "WITHHOLD," based on inspections of the Applicant's facilities, this Application will not be approved during this review cycle and the regulatory action will be a Complete Response (Section 13.1).

2. BACKGROUND

2.1 Description of the Product

The progesterone vaginal ring is a non-biodegradable, flexible silicone ring containing progesterone as the active drug substance. The progesterone vaginal ring consists of a mixture of (b) (4) silicone elastomer, light mineral oil, and progesterone, USP (b) (4). The active drug substance is present in a (b) (4) % w/w concentration dispersed evenly within the ring. The ring has a cross-sectional diameter of (b) (4) mm and an outer diameter of 55 mm. Each ring

contains 1.78 grams of USP grade progesterone and releases an average of 11 mg progesterone/day over a 7-day period of use.

2.2 Regulatory History

The clinical development program for the progesterone vaginal ring was conducted under IND 70,875. During the clinical development of the product, there were several interactions between the Applicant and the Division of Reproductive and Urologic Products (DRUP). These interactions, which included an end-of-phase 2 meeting and a clinical Special Protocol Assessment (SPA) of the Applicant's single Phase 3 clinical trial (for which full agreement was not reached), are described in detail in Section 2.5 of the primary Clinical Review.

During these interactions, DRUP agreed that a single adequate and well-controlled clinical trial could be sufficient to support the efficacy and safety of the progesterone vaginal ring. The overall design, endpoints, and primary analysis of the Applicant's single Phase 3 clinical trial (Study DR-PGN-302), with one significant exception, were generally acceptable and for the most part followed DRUP's recommendations. The one exception was that Study DR-PGN-302 was not powered to assess adequately the efficacy of the progesterone vaginal ring in the subset of women 35 to 42 years of age. This deficiency in the design and conduct of Study DR-PGN-302 was conveyed to the Applicant on several occasions.

At the filing meeting for this Application, both the primary Clinical Reviewer and the Cross Discipline Team Leader (CDTL), who also was the Clinical Team Leader, recommended that this Application not be filed because of the absence of adequate data to assess the efficacy (and possibly the safety) of the progesterone vaginal ring in the subset of women 35 to 42 years of age. I concluded, however, that there were adequate clinical data to assess the safety and efficacy of the progesterone vaginal ring in women < 35 years of age. I also concluded that the product could possibly be labeled (depending on the outcomes of the discipline reviews) for safe and effective use in women < 35 years of age, and therefore the Application was filed.

2.3 Recommendations of Primary Clinical Reviewer and Cross-Discipline Team Leader regarding Approvability

The primary Clinical Reviewer, Christos Mastroyannis MD, stated the following in his Clinical Review signed on February 25, 2011:

"This reviewer recommends that the NDA not receive approval."

"....The analyses of the Milprosa vs. Crinone data in Study DR-PGN-302 for women <35 years yielded a lower bound of the 95% C.I. of the difference at 6 weeks post embryo transfer of -4.6% and at 10 weeks of -3.7%. The values at both 6 and 10 weeks post embryo transfer are within the predefined NI [non-inferiority] margin of -10%. In women ≥35 years, the lower bound of the 95% C.I. of the difference between Milprosa vs. Crinone was found to be -16.4% at 6 weeks and -18.5% at 10 weeks and thus did not demonstrate non-inferiority as assessed by the pre-defined and agreed upon NI margin of -10%. Study DR-PGN-302 was not sufficiently powered to allow demonstration of efficacy in this older age group."

"Given that the indication is luteal support and maintenance of early pregnancy, the efficacy is in a sense a safety endpoint. Failure to demonstrate that Milprosa was no worse than Crinone in sustaining the luteal phase and early pregnancy is concerning for the safe use of this product for the intended purpose in this older population of women. This aside, other safety parameters evaluated in Study DR-PGN-302 did not reveal any concerning signals."

“Given that the data does not support efficacy for an important subgroup, women age 35-42 years of age (comprising 60% of the intended population to be treated), this reviewer recommends that the NDA not receive approval until efficacy is demonstrated for this age group. I recommend that the Applicant conducts in the US, a trial to demonstrate efficacy and safety in this older age population. There is no need to provide additional data in the age sub-group of women less than age 35.”

“This reviewer recommends that efficacy data for women age 35-42 be obtained prior to approval of Milprosa for any age group. If this recommendation is not followed and the NDA receives approval, a condition of approval should be a post-marketing commitment to conduct a Phase 4 randomized active-controlled non-inferiority comparator clinical study in women age 35-42...”

The CDTL, Shelley Slaughter MD/PhD, stated the following in her Review signed on February 25, 2011:

“I am in complete concurrence with the Clinical and CMC reviewers that this application should not be approved.”

“Despite non-concurrence of the clinical team (medical officer and team leader), the application was filed. Upon full review of the application, both the clinical (see Medical Officer review dated February 25, 2011) and statistical team (see Statistical review dated February 18, 2011) have concurred that while efficacy has been demonstrated for the sub-group of subjects age less than 35, the application provides inadequate information to evaluate the efficacy in the age 35-42 subgroup. It is also my belief that we do not have sufficient information to inform women age 35-42 of appropriate and safe dosing if the drug were to be approved for women age less than 35. ... In short, I do not believe that we have sufficient information to solve the issue of insufficient efficacy and safety information of women age 35-42 with labeling.”

Dr. Slaughter recommends that the Applicant provide additional safety and efficacy data for women 35 to 42 years of age prior to approval of the progesterone vaginal ring. She recommends that these data be obtained from an adequately powered, randomized, blinded, active-controlled clinical trial.

Division Director's Comments

- I concur with Drs. Mastroyannis and Slaughter that it is important that the Applicant obtain information about the efficacy of the progesterone vaginal ring in women 35 to 42 years of age as this population constitutes approximately 50% of subjects who receive treatment via ART medical procedures. This information could be obtained by the Applicant conducting a well-designed and adequately powered non-inferiority study with the progesterone vaginal ring in women 35 to 42 years of age as a postmarketing commitment.
- I do not concur, however, with the recommendations of Drs. Mastroyannis and Slaughter that additional safety and efficacy data need to be obtained prior to approval of the progesterone vaginal ring. I believe that the progesterone vaginal ring could be approved for use by women < 35 years of age, after resolution of other approvability issues, with (1) appropriate product labeling that would include a statement on limitations of use and (2) a postmarketing commitment by the Applicant to conduct an adequate and well-controlled clinical trial in

women 35 to 42 years of age. See Section 7.5.2 for further discussion of the basis for my assessment of the approvability of the progesterone vaginal ring.

3. CMC

Active Drug Substance

The active drug substance for this Application is progesterone, USP (b) (4) which has been widely used in previously approved drug products. All information related to the manufacturing and controls for the active drug substance were referenced to (b) (4) Drug Master File (DMF) (b) (4). This DMF was previously found adequate. No changes were reported to the DMF since the last review. Consequently, DMF (b) (4) was considered adequate to support NDA 201110. The Applicant's proposed specification for the drug substance, however, was not deemed adequate because it lacked adequate controls for the particle sizes and the accuracy of the HPLC analytical method had not been validated.

Drug Product

The progesterone vaginal ring is a non-biodegradable, flexible silicone ring containing progesterone. The ring consists of a mixture of (b) (4) silicone elastomer, light mineral oil, and progesterone, USP (b) (4). The active drug substance is present in a (b) (4) % w/w concentration that is dispersed evenly within the ring. Each progesterone vaginal ring (total weight 8.9 grams) contains 1.78 grams of USP grade progesterone.

During the prior approval inspection by the FDA's Office of Compliance of the Applicant's intended commercial manufacturing site in Cincinnati, OH, foreign particulate contamination was found in all 5 site transfer batches of the drug product. (b) (4) foreign matter were identified, but not quantified. The Office of Compliance issued an overall "WITHHOLD" recommendation for the Application and WITHHOLD recommendations for 2 of the Applicant's facilities: Barr Laboratories Inc. Northvale, NJ, and Teva Women's Health, Cincinnati, OH.

The drug release profile of the progesterone vaginal ring at release and during stability studies was reviewed by Sandra Suarez-Sharp PhD. She concluded that the revised specification for the drug release profile were acceptable.

The primary CMC Reviewer, Dr. Ni, made the following overall recommendations in her primary CMC Review:

- This NDA has not provided sufficient information to assure the identity, strength, purity, and quality of the drug product.
- The Office of Compliance has made an overall "WITHHOLD" recommendation for the facilities involved in this NDA.
- Issues on labeling have not been resolved.
- Therefore, from the CMC perspective, this NDA is not recommended for approval in its present form until all the pending issues are satisfactorily resolved.

Based on the primary CMC/Microbiology Review, the following deficiencies regarding Product Quality will be communicated to the Applicant in the Complete Response Letter:

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 the system suitability of the HPLC method.

Based on the preapproval inspections of the Applicant’s facilities by the Office of Compliance, the following deficiency regarding the Facility Inspections will be communicated in the Complete Response Letter:

“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.”

Division Director’s Comments

- *I concur with the assessments and recommendation made by Dr. Ni that from a CMC perspective this NDA cannot be approved at this time.*
- *The findings of unidentified particulate matter in all 5 batches of drug product manufactured at the facility intended to manufacture the commercial product precludes approval of this Application until this issue is satisfactorily resolved.*

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

The active drug substance in the progesterone vaginal ring is progesterone. The inactive ingredients in the drug product are:

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

Progesterone is a naturally occurring hormone in women and has been used in clinically approved products in the US for decades. The safety profile for progesterone is well established.

According to the primary Toxicology Reviewer, Krishan Raheja DVM/PhD, (b) (4) has conducted extensive toxicity studies on the silicon elastomers. Dr. Raheja also states in his review “... the safety of (b) (4) silicone elastomer seems reasonably well established.”

The Applicant provided data from 2 nonclinical toxicology studies conducted in rabbits: a 10-day vaginal irritation and a 90-day intravaginal toxicology study. In both studies, the study drug product (progesterone in silicon elastomer) was well-tolerated and did not cause any significant drug-related toxicity. Dr. Raheja summarized the non-clinical toxicology findings as follows: “*Implantation of vaginal inserts containing (b) (4) % w/w progesterone induced uterine and vaginal changes known to be attributed to progesterone pharmacologic activity. The progesterone vaginal inserts were well tolerated.*”

Dr. Raheja made the following recommendations in his primary Review signed on July 16, 2010:

“Recommendations on approvability: Pharmacology/toxicology recommends approval of NDA 201110.

Recommendations for nonclinical studies: Required nonclinical toxicology studies submitted have been conducted in accordance with GLP regulations and are acceptable.”

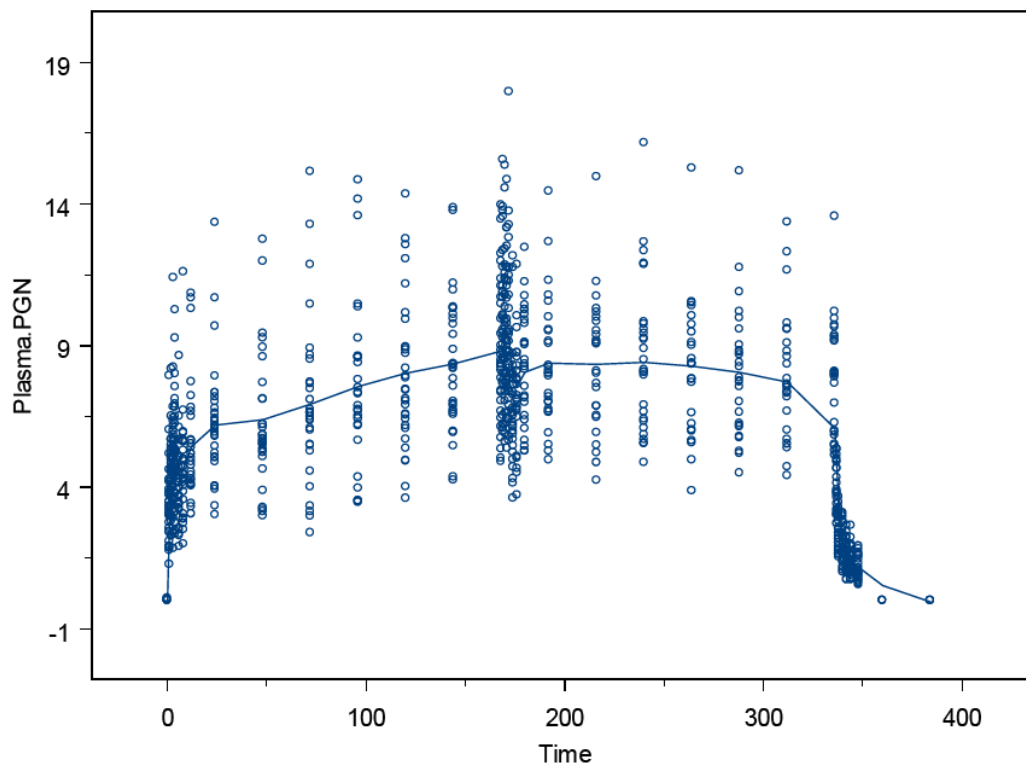
Division Director’s Comment

- *I concur with the conclusions and recommendations of Dr. Raheja.*

5. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

The Applicant conducted 4 PK/bioavailability studies and 2 PK/PD studies. Among these studies was Study 10716222 that evaluated the single-dose and steady-state PK of the progesterone vaginal ring. A total of 30 healthy post-menopausal volunteers used the vaginal ring for 2 consecutive 7-day treatment cycles. Subjects received pre-treatment one mg oral estradiol tablets once a day for 28 days prior to treatment with the progesterone vaginal ring and continued to receive estradiol treatment during the study period. Individual and average plasma progesterone concentrations in the subjects during and following the 2 consecutive once-weekly treatments with the progesterone vaginal ring are shown in Figure 1.

Figure 1 Scatter Plot of Plasma Progesterone (PGN) Concentrations (ng/mL) during and following Use of 2 Consecutive Weekly Vaginal Rings. The Solid Line Represents Mean Concentration Values.



Source: Figure 4 from the Clinical Pharmacology Review signed February 2, 2011.

According to the primary Clinical Pharmacology Reviewer, Sandhya Apparaju PhD, “the proposed vaginal ring formulation resulted in consistent release and absorption of progesterone via the vaginal mucosa into the systemic circulation.” The average steady-state plasma progesterone (C_{avg}) concentration during the second dose of the ring was 8.19 ng/mL.

Dr. Apparaju made the following overall assessment in her Review signed on February 2, 2011:

“NDA 201110 is acceptable from a Clinical Pharmacology perspective provided that a satisfactory agreement is reached between the sponsor and the Agency regarding language in the package insert.”

Dr. Apparaju did not request any Phase IV commitments.

Division Director's Comment

- *I concur with Dr. Apparaju's overall assessment and recommendation.*

6. CLINICAL MICROBIOLOGY

The primary Microbiology Reviewer, Jessica Cole PhD, recommended that the progesterone vaginal ring not be approved until the specification for final drug product was revised to include “the absence of (b) (4).”

Division Director's Comment

- This deficiency will be conveyed to the Applicant under Product Quality in the Complete Response Letter.*

7. CLINICAL/STATISTICAL-EFFICACY

7.1 Overview of Phase 3 Clinical Trial and Subject Demographics

The Applicant conducted a single Phase 3 clinical trial (Study DR-PGN-302) in support of the safety and efficacy of the progesterone vaginal ring. The primary objective of the study was to establish that the efficacy of the progesterone vaginal ring was not inferior to Crinone, an approved progesterone drug product, in terms of clinical pregnancy rates, based on a non-inferiority margin of -10%. Study DR-PGN-302 was a randomized, single-blind (investigator and sonographer), multicenter, active-controlled, non-inferiority clinical trial of progesterone supplementation in women undergoing in-vitro fertilization (IVF) with freshly retrieved oocytes and subsequent embryo transfer. The Study was conducted at 22 sites in the US. Eligible women were randomized in a ratio of 1:1 to one of the 2 treatment arms: (1) the progesterone vaginal ring (replaced every 7 days) or (2) Crinone 8% (a progesterone vaginal gel), which is an approved product that was applied once daily. The randomization was stratified by age (18 to < 35 years and 35 to 42 years). The treatment duration was one cycle beginning on the day of oocyte retrieval and continuing through the onset of menses or up to Week 12 of pregnancy (10 weeks post-embryo transfer) if pregnancy occurred. In this study, pregnancy was defined as beginning 2 weeks prior to oocytes retrieval.

The baseline characteristics of the subjects (e.g. age, body mass index, race, and having had a prior pregnancy) were similar between the 2 treatment groups (Table 1).

Table 1 Baseline Characteristics of Subjects in Study DR-PGN-302

Demographic Variable	PVR* (N=646)	Crinone (N=651)
Mean age (SD)	31.7 (3.73)	31.6 (3.86)
Mean Body Mass Index (SD)	25.3 (4.64)	25.7 (5.01)
Race [n (%)]:		
Caucasian/White	519 (80.3%)	507 (77.9%)
Black/African American	54 (8.4%)	48 (7.4%)
Hispanic/Latino	34 (5.3%)	51 (7.8%)
Asian	34 (5.3%)	37 (5.7%)
Other	5 (0.8%)	8 (1.2%)
Had a Prior Pregnancy	312 (48.3%)	335 (51.5%)

* Progesterone vaginal ring.

Source: Table 3.2.2 of the primary Statistical Review signed February 18, 2011.

Division Director's Comments

- The inclusion and exclusion criteria were acceptable and are described fully in the primary Clinical Review.*
- The racial distribution of the study population is fairly representative of the general US population and likely reflects the distribution of women who undergo ART procedures.*

- *Although it was recommended to the Applicant that the study be conducted under a double-blind design, employing a single-blind design is not likely to have affected the validity of the findings. The primary efficacy endpoint was clinical pregnancy based on the objective measurement of a gestational sac and a fetal heartbeat as determined by a sonographer who was blinded to the subject's treatment.*

7.2 Disposition of Subjects

Successful oocytes retrievals were obtained from 1,299 women. All were randomized, but 2 women never received study drug. Of the 1,297 subjects who were randomized and treated with at least one dose of study drug, 646 subjects were assigned to the progesterone vaginal ring group and 651 subjects were assigned to the Crinone group (Table 2). Of the subjects who received study drug, a total of 26 did not undergo embryo transfer.

Table 2 Disposition of Subjects in Study DR-PGN-302

Category	PVR * N (%)	Crinone N (%)
Randomized Subjects	647 (100%)	652 (100%)
Randomized and Received Study Drug (mITT Population)	646 (99.8%)	651 (99.8%)
Embryo Transferred	631 (97.5%)	640 (98.2%)
Discontinued Study Prematurely	347 (53.6%)	358 (54.9%)
Subject Never Pregnant or Spontaneously Aborted	284 (44.0%)	301 (46.2%)
Adverse Events	44 (6.8%)	36 (5.5%)
Non-compliance of Study Drug	4 (0.6%)	2 (0.3%)
Lost to Follow-up	4 (0.6%)	7 (1.1%)
Did Not Meet Protocol Requirements	3 (0.5%)	3 (0.5%)
Voluntary Withdrawal	2 (0.3%)	2 (0.3%)
Investigator Discretion	1 (0.2%)	2 (0.3%)
Other	5 (0.8%)	5 (0.8%)

* Progesterone vaginal ring.

Source: Table 3.2.1 of the primary Statistical Review signed February 18, 2011.

Division Director's Comments

- *As would be expected in this study, the majority of premature discontinuations were related to the subject never becoming pregnant or having a spontaneous pregnancy loss.*
- *The majority of adverse events leading to premature discontinuation were related to spontaneous losses of pregnancy as described in Section 8.3.*
- *The compositions of the mITT populations were slightly different from the compositions of the Safety populations due to 3 randomized subjects receiving the wrong treatment. The mITT populations were based on the subject's actual treatment assignment according to the randomization code, while the Safety populations were based on the treatment the subject actually received. Consequently, the safety population consists of 647 subjects in the progesterone vaginal ring cohort and 650 subjects in the Crinone cohort.*

7.3 Efficacy Findings

7.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the clinical pregnancy rate (defined as the proportion of subjects with visualization of a gestational sac and fetal heart motion by ultrasonography at:

- Week 8 of pregnancy (6-weeks post oocyte retrieval)
- Week 12 of pregnancy (10-weeks post oocyte retrieval)

The primary efficacy population was the modified Intent-to-Treat (mITT) cohort, defined as all subjects who had a successful oocyte retrieval, were randomized, and received at least one dose of study drug.

7.3.2 Primary Efficacy Findings

The clinical pregnancy rates at both Weeks 8 and 12 for all subjects and for the 2 age subgroups (18 to < 35 years and 35 to 42 years) are listed in Table 3. For all subjects, the differences in pregnancy rates in the subjects treated with the progesterone vaginal ring or Crinone (PVR - Crinone) were 0.8% and 1.3% at Weeks 8 and 12, respectively. The lower bounds of the 95% confidence intervals (CIs) for these rate differences were -4.6% and -4.1%, respectively, and were above the pre-specified non-inferiority margin of -10%. Therefore, for the overall mITT population, treatment with the progesterone vaginal ring was non-inferior to treatment with Crinone.

Table 3 Clinical Pregnancy Rate per Retrieval by Subject Age and Week of Pregnancy (MITT Population – Study DR-PGN-302)

Age (years)	Week of Pregnancy	PVR *		Crinone		Treatment Difference (PVR – Crinone) (95% C.I.)
		n/N	Percent	n/N	Percent	
All	8	310/646	48.0%	307/651	47.2%	0.8% (-4.6%, 6.3%)
	12	300/646	46.4%	294/651	45.2%	1.3% (-4.1%, 6.7%)
18 to <35	8	275/558	49.3%	269/560	48.0%	1.2% (-4.6%, 7.1%)
	12	269/558	48.2%	258/560	46.1%	2.1% (-3.7%, 8.0%)
35 to 42	8	35/88	39.8%	38/91	41.8%	-2.0% (-16.4%, 12.4%)
	12	31/88	35.2%	36/91	39.6%	-4.3% (-18.5%, 9.8%)

* Progesterone vaginal ring.

Source: Table 3.2.3 of the primary Statistical Review signed February 18, 2011.

For the subset of subjects 18 to < 35 years of age, the differences in pregnancy rates in the subjects treated with the progesterone vaginal ring or Crinone (PVR – Crinone) were 1.2% and 2.1% at Weeks 8 and 12, respectively. The lower bounds of the 95% CIs for these rate differences were -4.6%, and -3.7%, respectively, and they also were above the pre-specified non-inferiority margin of -10%. Therefore, for the subset of subjects 18 to < 35 years of age, treatment with the progesterone vaginal ring was non-inferior to treatment with Crinone.

For the subset of subjects 35 to 42 years of age, the differences in pregnancy rates in the subjects treated with the progesterone vaginal ring or Crinone (PVR – Crinone) were -2.0% and -4.3% at Week 8 and Week 12, respectively. The lower bounds of the 95% CIs for these rate differences (-16.4% and -18.5%, respectively), however, exceeded the pre-specified non-inferiority margin of -

10%. Therefore, Study DR-PGN-302 did not demonstrate that treatment with the progesterone vaginal ring was non-inferior to treatment with Crinone for the subset of subjects 35 to 42 years of age.

Division Director's Comments

- *Although treatment with the progesterone vaginal ring was statistically non-inferior to treatment with Crinone in the entire mITT population, this finding was driven by the subgroup of subjects 18 to < 35 years of age. Subjects in this subgroup comprised 86% of the mITT population.*
- *Study DR-PGN-302 has established that treatment with the progesterone vaginal ring is non-inferior to treatment with the approved drug product Crinone in women 18 to < 35 years of age for supporting embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an ART treatment program.*
- *The study was not powered for meaningful non-inferiority hypothesis testing for the subgroup of subjects 35 to 42 years as the sample size for this subgroup consisted of only 179 mITT subjects. Therefore, no conclusion can be made regarding the non-inferiority of the progesterone vaginal ring relative to Crinone in this older age group at this time.*

7.3.3 Secondary Efficacy Findings

The Applicant explored several secondary efficacy endpoints as described in the primary Clinical Review. Among these was an analysis of the live birth rates, which are of particular importance because this is the ultimate desired outcome of treatment of infertility. The live birth rate findings from Study DR-PGN-302 are presented in Table 4.

Table 4 Live Birth Rate per Retrieval by Subject Age (MITT Population – Study DR-PGN-302)

Age (years)	PVR *		Crinone		Treatment Difference (PVR – Crinone) (95% C.I.)
	n/N	Percent	n/N	Percent	
All	292/646	45.2%	282/651	43.3%	1.9% (-3.5%, 7.3%)
18 to <35	262/558	47.0%	249/560	44.5%	2.5% (-3.3%, 8.3%)
35 to 42	30/88	34.1%	33/91	36.3%	-2.2% (-16.2%, 11.8%)

* Progesterone vaginal ring.

Source: Table 3.2.4 of the primary Statistical Review signed February 18, 2011.

Division Director's Comment

- *The findings based on live birth rates are consistent with the findings based on clinical pregnancy rates at Week 8 and Week 12 of pregnancy. Treatment with the progesterone vaginal ring was shown to be non-inferior to treatment with Crinone in the subgroup of subjects 18 to < 35 years of age, but not in the subgroup of subjects 35 to 42 years of age.*

7.4 FDA Biostatistical Reviewer's Assessment of Efficacy

The primary Biostatistical Reviewer, Xin Fang PhD, stated the following in his Statistical Review, signed on February 18, 2011:

“There are no statistical issues in establishing the non-inferiority of DR-2011 [progesterone vaginal ring] to Crinone for younger women aged 18-34. But, the study was not designed to

show the non-inferiority of DR- 2011 to Crinone in the older women aged 35-42. A study with a larger sample size would be required to exclude a clinically meaningful lower bound in this group.”

“From a statistical perspective, this application provided adequate data to support the non-inferiority of DR-2011 to Crinone in supporting 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 treatment program for younger infertile women aged 18-34. However, no definitive efficacy conclusion can be made for the limited number of women aged 35-42 studied in this trial.”

7.5 Overall Assessment of Efficacy

7.5.1 Overall Assessment of Efficacy

The primary efficacy endpoint for study DR-PGN-302 was a comparison of the proportion of subjects in each treatment group with a clinical pregnancy (defined as the presence of both a gestational sac and fetal heart rate visualized on sonography) at Week 8 of pregnancy (6 weeks after oocytes retrieval) and Week 12 of pregnancy (10 weeks after oocytes retrieval) after one ART treatment cycle. The progesterone vaginal ring, replaced once weekly, was shown to be statistically non-inferior to the approved active comparator, Crinone 8% vaginal gel, dosed daily, in the overall mITT population and in the subset of subjects 18 to < 35 years of age. The finding of non-inferiority for the progesterone vaginal ring in the overall mITT population, however, was driven by the subset of subjects 18 to < 35 years of age because these subjects comprised 86% of the overall mITT population. For the subset of subjects 35 to 42 years of age, treatment with the progesterone vaginal ring did not meet the criteria for non-inferiority. The study, however, was not adequately powered for a meaningful assessment of non-inferiority in the older subset of subjects.

7.5.2 Does Demonstrated Efficacy Support Approval?

Both the primary Clinical Reviewer and the Clinical Team Leader have recommended that the progesterone vaginal ring not be approved until (1) all non-clinical deficiencies have been resolved and (2) the Applicant has conducted a well-designed and adequately powered non-inferiority study with the progesterone vaginal ring in women 35 to 42 years of age. It is my understanding that both the primary Clinical Reviewer and the Clinical Team Leader do not believe that the product could be adequately labeled for safe and effective use based on currently available clinical findings.

I concur with both the primary Clinical Reviewer and the Clinical Team Leader that it is important that the Applicant obtain information about the efficacy of the progesterone vaginal ring in women 35 to 42 years of age as this population constitutes approximately 50% of subjects who receive treatment via ART medical procedures. This information could be obtained by the Applicant by conducting a well-designed and adequately powered non-inferiority study with the progesterone vaginal ring in women 35 to 42 years of age as a postmarketing commitment.

I do not concur, however, with the primary clinical review team that the findings from Study DR-PGN-302 do not support approval of the progesterone vaginal ring. Both the primary Clinical Reviewer and the Clinical Team Leader and the Biostatistical Reviewer have stated in their respective reviews that the findings from Study DR-PGN-302 have demonstrated (1) that

treatment with the progesterone vaginal ring was non-inferior to treatment with Crinone in subjects 18 to < 35 years of age and (2) that the study successfully achieved its primary protocol-defined efficacy endpoint in this population. Furthermore, neither of the clinical reviewers identified any safety issues that would preclude approval of the progesterone vaginal ring in this younger age group. I believe that the progesterone vaginal ring could be labeled for safe and effective use in women < 35 years of age. This could be achieved by including in labeling that (1) the product is indicated for use in women < 35 years of age, either as part of the actual Indication or by a limitation of use statement, and (2) the efficacy of the product has not been demonstrated in women 35 to 42 years of age.

Lastly, approval of the progesterone vaginal ring, based on clinical data provided in the current Application, would provide another dosing option for women < 35 years of age who need supplementation of corpus luteal function as part of an ART treatment program. Many women might prefer a product such as the progesterone vaginal ring that requires only once weekly dosing instead of once daily dosing (Crinone) or more frequent dosing (Endometrin).

8. SAFETY

8.1 Overview

Safety data for the progesterone vaginal ring were obtained from four Phase 1, two Phase 2, and one Phase 3 clinical trials. The primary Clinical Reviewer (Dr. Mastroyannis) has provided a thorough review and discussion of the safety findings for the progesterone vaginal ring based on the data provided in NDA 201110. He did not identify any safety issues that would suggest that the overall safety profile for the progesterone vaginal ring is less acceptable than that for the approved active comparator Crinone. The following Summary Review of safety is focused on the findings from the single Phase 3 study conducted by the Applicant (Study DR-PGN-302) that was the primary source of safety data for the progesterone vaginal ring.

In Study DR-PGN-302, 647 subjects were treated with the progesterone vaginal ring. The maximum duration of exposure was 78 days, which is one week longer than a complete cycle of use if pregnancy were to be supported through Week 12 of pregnancy (10 weeks after oocyte retrieval). The average and median durations of treatment were 40.9 and 38 days, respectively.

Division Director's Comments

- The size of the safety database is adequate for the proposed product and indication. The active drug substance is progesterone. The pharmacology and toxicology of progesterone are well established and the systemic exposure to progesterone resulting from use of the progesterone vaginal ring is within physiologic concentrations for both non-pregnant reproductive-aged women and pregnant women.*
- In the following summary of safety findings, findings are presented in terms of 2 slightly different assessment periods. One period is the "study period," defined as the time from the subject's signing the Informed Consent Form until 14 days after the last dose of study drug. The other period is the "treatment period," a subset of the study period that included the time from the first dose of study drug until 14 days after the last dose. Both periods were of variable duration, depending on whether a successful pregnancy occurred.*

8.2 Deaths and Non-fatal Serious Adverse Events

8.2.1 Deaths

No deaths were reported in Study DR-PGN-302 or in the overall clinical development program. There were 2 neonatal deaths in Study DR-PGN-302, one in each treatment group.

8.2.2 Serious Adverse Events

During the study period, a total of 155 subjects (83 of the 647 [12.8%] subjects treated with the progesterone vaginal ring and 72 of 650 [11.1%] subjects treated with Crinone) reported experiencing one or more serious adverse events (SAEs). The SAEs reported in Study DR-PGN-302 are summarized in Table 5. Of the 162 SAEs that were reported, 144 were pregnancy-related. Intrauterine death, missed abortion, and blighted ovum accounted for the majority of the 144 pregnancy-related SAEs. Of the 18 SAEs that were not directly related to pregnancy, 11 (6.8%) were classified as Ovarian Hyperstimulation Syndrome (OHSS). The 5 SAEs in the progesterone vaginal ring treatment group that were not directly related to pregnancy or classified as OHSS were one case each of ovarian cyst, intra-abdominal hemorrhage (secondary to an accident), dehydration, bladder perforation, and pleural effusion.

**Table 5 Serious Adverse Events Occurring in Study DR-PGN-302
(DR-2011 = Progesterone Vaginal Ring)**

MedDRA System Organ Class and Preferred Term	DR-2011 (N=647)		Crinone[®] (N=650)	
	N	%	N	%
All SAEs	83	12.83	72	11.08
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS				
Total Disorders	76	11.75	63	9.69
INTRA-UTERINE DEATH	23	3.55	16	2.46
ABORTION MISSED	18	2.78	14	2.15
BLIGHTED OVUM	16	2.47	17	2.62
ABORTION SPONTANEOUS	8	1.24	9	1.38
ECTOPIC PREGNANCY	6	0.93	7	1.08
HYPEREMESIS GRAVIDARUM	4	0.62	1	0.15
CERVICAL INCOMPETENCE	1	0.15	0	0.00
RETAINED PRODUCTS OF CONCEPTION	1	0.15	0	0.00
RUPTURED ECTOPIC PREGNANCY	1	0.15	0	0.00
HETEROTOPIC PREGNANCY	0	0.00	1	0.15
REPRODUCTIVE SYSTEM AND BREAST DISORDERS				
Total Disorders	5	0.77	7	1.08
OVARIAN HYPERSTIMULATION SYNDROME	4	0.62	7	1.08
OVARIAN CYST	1	0.15	0	0.00
CONGENITAL, FAMILIAL AND GENETIC DISORDERS				
Total Disorders	1	0.15	4	0.62
FOETAL CHROMOSOME ABNORMALITY	1	0.15	2	0.31
CONGENITAL ANOMALY IN OFFSPRING	0	0.00	2	0.31
GASTROINTESTINAL DISORDERS				
INTRA-ABDOMINAL HAEMORRHAGE	1	0.15	0	0.00
METABOLISM AND NUTRITION DISORDERS				
DEHYDRATION	1	0.15	0	0.00
RENAL AND URINARY DISORDERS				
BLADDER PERFORATION	1	0.15	0	0.00
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
PLEURAL EFFUSION	1	0.15	0	0.00
INFECTIONS AND INFESTATIONS				
PELVIC INFLAMMATORY DISEASE	0	0.00	1	0.15
NERVOUS SYSTEM DISORDERS				
SYNCOPE	0	0.00	1	0.15

Source: Table 53, pg. 110, of Applicant's Final Report for Study DR-PGN-302.

Division Director's Comments

- The SAEs reported during the study period differed from those reported during the treatment period only by the inclusion of one additional SAE (a single case of pelvic inflammatory disease in the Crinone group) in the study period.
- The slightly higher percentage of subjects in the progesterone vaginal ring treatment group who reported a SAE (12.8%) compared to that in the Crinone group (11.1%) does not raise any safety concerns. The types of SAEs reported are expected in women undergoing ART medical procedures.

8.3 Discontinuations for Adverse Events

Adverse events (AEs) leading to discontinuation during the study period are summarized in Table 6. In Study DR-PGN-302, 44 of 647 (6.8%) subjects in the progesterone vaginal ring group and 36 of 650 (5.5%) subjects in the Crinone group discontinued prematurely because of an AE. All of the AEs leading to discontinuation, except for 5, were related to pregnancy loss (which would necessitate discontinuation from the study) or to OHSS.

Table 6 Adverse Events Leading to Discontinuation in Study DR-PGN-302 (DR 2011 = Progesterone Vaginal Ring)

MedDRA System Organ Class and Preferred Term	DR-2011 (N=647)		Crinone® (N=650)	
	N	%	N	%
ANY AE				
Total Disorders	44	6.80	36	5.54
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS				
Total Disorders	34	5.26	31	4.77
ABORTION MISSED	16	2.47	12	1.85
ABORTION SPONTANEOUS	6	0.93	6	0.92
ECTOPIC PREGNANCY	6	0.93	5	0.77
BLIGHTED OVUM	5	0.77	5	0.77
INTRA-UTERINE DEATH	2	0.31	3	0.46
REPRODUCTIVE SYSTEM AND BREAST DISORDERS				
Total Disorders	7	1.08	4	0.62
OVARIAN HYPERSTIMULATION SYNDROME	6	0.93	4	0.62
PELVIC PAIN	1	0.15	0	0.00
GASTROINTESTINAL DISORDERS				
INTRA-ABDOMINAL HAEMORRHAGE	1	0.15	0	0.00
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
ADVERSE DRUG REACTION	1	0.15	0	0.00
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
ECZEMA	1	0.15	0	0.00
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				
POST PROCEDURAL DISCOMFORT	0	0.00	1	0.15

Source: Table 58, pg. 119 of the Applicant's Final Report for Study DR-PGN-302.

Division Director's Comments

- One subject discontinued due to vaginal pain in the progesterone vaginal ring group (identified as “adverse drug reaction” in Table 6) after 4 days of use of the ring.
- The slightly higher percentage of subjects in the progesterone vaginal ring treatment group who discontinued from the study because of an adverse event (6.8% vs. 5.5%) does not raise any safety concerns.

8.4 Common Adverse Events

A total of 1,041 (80.3%) of the subjects in the safety cohort reported at least one AE during the treatment period. In the progesterone vaginal ring group, 81.0% of subjects reported at least one AE, compared to 79.5% of subjects in the Crinone group. The most commonly reported AEs (reported by $\geq 10\%$ of the total subjects) were nausea, headache, abdominal pain, post-procedural discomfort, abdominal distension, back pain, fatigue, and constipation.

Division Director's Comments

- The types and frequencies of the most commonly reported adverse events were similar across the 2 treatment groups.
- Vaginal discharge was reported more frequently in the progesterone vaginal ring group (9.43%) than in the Crinone group (3.23%).
- Potential mechanical effects of the vaginal ring on voiding could potentially predispose users to urinary tract infections. The incidence of urinary tract infections, however, in subjects who used the vaginal ring (4.0%) was numerically slightly lower than that in the Crinone group (5.38%).

8.5 Adverse Events of Special Interest

8.5.1 Early Pregnancy Losses

The CDTL noted in her review that “It is known that the rate of early pregnancy loss (typically losses occurring prior to Week 12 of pregnancy) increases with increased maternal age.” She therefore requested an analysis of the rate of early pregnancy loss by age subgroups to include the adverse events terms of abortion, fetal demise (early), missed abortion, spontaneous abortion, blighted ovum, and miscarriage. Table 7 presents the results of this analysis.

Table 7 Rate of Early Pregnancy Loss by Age: MITT Population

Age (years)	PVR *		Crinone		Treatment Difference (PVR – Crinone) (95% C.I.)
	n/N	Percent	n/N	Percent	
All	36/646	5.6%	38/651	5.8%	-0.3% (-2.8%, 2.3%)
18 to <35	28/558	5.0%	30/560	5.4%	-0.3% (-2.9%, 2.3%)
35 to 42	8/88	9.1%	8/91	8.8%	0.3% (-8.1%, 8.7%)

* Progesterone vaginal ring.

Source: Table 13 of the CDTL review signed February 25, 2011.

Division Director's Comment

- The rates of early pregnancy loss appeared to be similar in both treatment groups across both age subgroups (18 to < 35 years and 35 to 42 years).

8.5.2 Vaginal Adverse Events

Because both active treatments were administered intravaginal, and the vaginal ring was to remain in place continually (except for weekly replacement) for up to 10 weeks, rates of reported vaginal AEs were examined. The only notable difference in the incidence of vaginal-related AEs between the 2 treatment groups was that for vaginal discharge, which was reported more frequently in the progesterone vaginal ring group (9.43% of subjects) than in the Crinone group (3.23% of subjects). Other vaginal-related AEs were each reported in less than 2% of subjects and are listed in Table 8. The percentages of subjects reporting vaginal infections were low and were similar in both treatment groups. In addition to the AEs related to vaginal discharge and vaginal infections, there were a total of 22 additional AEs in the progesterone vaginal ring group and 26 AEs in the Crinone group.

Table 8 Vaginal Adverse Events that Were Reported in < 2% of Subjects in Study DR-PGN-302 (DR 2011 = Progesterone Vaginal Ring)

MedDRA System Organ Class and Preferred Term	DR-2011 (N=647)		Crinone® (N=650)	
	N	%	N	%
INFECTIONS AND INFESTATIONS				
VAGINAL INFECTION	11	1.70	8	1.23
VULVOVAGINAL MYCOTIC INFECTION	7	1.08	9	1.38
VAGINITIS BACTERIAL	2	0.31	1	0.15
VAGINITIS GARDNERELLA	1	0.15	1	0.15
VAGINAL CANDIDIASIS	0	0.00	1	0.15
REPRODUCTIVE SYSTEM AND BREAST DISORDERS				
VULVOVAGINAL DISCOMFORT	8	1.24	11	1.69
VAGINAL PAIN	4	0.62	1	0.15
VULVOVAGINAL DRYNESS	2	0.31	0	0.00
CERVIX DISORDER	1	0.15	2	0.31
DYSPAREUNIA	1	0.15	0	0.00
VAGINAL LACERATION	1	0.15	0	0.00
VAGINAL LESION	1	0.15	1	0.15
CERVICAL FRIABILITY	0	0.00	1	0.15
CERVIX ERYTHEMA	0	0.00	1	0.15
UTERINE CERVICAL EROSION	0	0.00	1	0.15
VAGINAL BURNING SENSATION	0	0.00	8	1.23
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
APPLICATION SITE DISCOMFORT	1	0.15	0	0.00
APPLICATION SITE IRRITATION	1	0.15	0	0.00
APPLICATION SITE REACTION	1	0.15	0	0.00
APPLICATION SITE WARMTH	1	0.15	0	0.00

Source: Modified from Table 47, pg 104 of the Applicant's Final Report for Study DR-PGN-302.

Division Director's Comments

- *The type of vaginal infection was not specified in approximately half of the cases; when specified, vaginal yeast infections were the most frequently reported infections.*
- *With the exception of the AE of vaginal discharge, the percentages of subjects reporting vaginal AEs were similar between the 2 treatment groups.*

8.6 Overall Assessment of Safety

The primary source of data supporting the safety of the progesterone vaginal ring was obtained from Phase 3 Study DR-PGN-302. A total of 1,041 (80.3%) of the subjects in the safety cohort reported at least one AE during the treatment period. In the progesterone vaginal ring group, 81% of subjects reported at least one AE, compared to 79.5% of subjects in the Crinone group. The most commonly reported AEs (reported by $\geq 10\%$ of the total subjects) were nausea, headache, abdominal pain, post-procedural discomfort, abdominal distension, back pain, fatigue, and constipation. For each of these commonly reported AEs, the percentages of subjects reporting them were similar across both treatment groups.

A total of 155 subjects (83 of the 647 [12.8%] subjects treated with the progesterone vaginal ring and 72 of 650 [11.1%] subjects treated with Crinone) reported experiencing one or more serious adverse events (SAEs). Almost all of the SAEs in both treatment groups were, as expected, related to pregnancy loss or OHSS. All but 4 of the AEs leading to discontinuation in the progesterone vaginal ring group were related to pregnancy loss or to ovarian hyperstimulation syndrome (OHSS). The 4 events were one case each of pelvic pain (unknown etiology), intra-abdominal hemorrhage (secondary to an accident), vaginal pain (related to the vaginal ring), and eczema (possibly related to the vaginal ring). The slightly higher percentage of subjects in the progesterone vaginal ring treatment group who discontinued from the study because of an adverse event (6.8% vs. 5.5%) does not raise any safety concerns.

Vaginal discharge was reported more frequently as an AE among those subjects randomized to the vaginal ring (9.4%) compared to those using Crinone, a vaginal gel (3.23%). However, the percentages of subjects reporting vaginal infections and other vaginal-related AEs were similar in the 2 treatment groups.

In summary, the overall safety profile for the progesterone vaginal ring, based on the data provided in the Application, was comparable to that of the approved active comparator Crinone. There were no safety findings in the clinical development program for the progesterone vaginal ring that raised any safety concerns or would preclude approval of the vaginal ring for the proposed indication.

9. ADVISORY COMMITTEE MEETING

Two other vaginal progesterone products have been approved for this indication. This Application was not presented to an Advisory Committee (AC) because the safety profile of progesterone for this indication is well established, and DRUP did not believe that AC guidance was needed to make a regulatory decision concerning the approvability of the Application.

10. PEDIATRICS

The Applicant requested a full waiver of pediatric studies. DRUP will recommend a full waiver of the pediatric requirement for studies in children because such studies would not be possible or

highly impractical as the condition of infertility does not exist in children. The request, however, was not consulted to the Pediatric Review Committee (PeRC) because it was determined that the Application would not be approved during the current review cycle.

11. OTHER RELEVANT REGULATORY ISSUES

Certification of Financial Interests

The primary Clinical Reviewer stated the following; “Financial Disclosure Information was obtained for the investigators (principal and sub-investigator) and all disclosable information is explained.”

Division of Scientific Investigation (DSI) Inspections

The Clinical Inspection Summary from the Division of Scientific Investigation stated the following:

“The clinical investigator sites of Drs. Foulk, Schnell, and Shamma were inspected in support of this NDA. Although regulatory violations were noted at the sites of Drs. Foulk and Shamma, the findings overall are unlikely to impact data integrity. The study appears to have been conducted adequately, and the data generated by these clinical sites appear acceptable in support of the respective indication.”

12. LABELING

The Division of Medication Errors Prevention and Analysis (DMEPA) found the proprietary name “Milprosa” Vaginal Ring acceptable.

Labeling negotiations were not conducted because it was determined that the Application would not be approved during this review cycle.

13. DECISION/ACTION/RISK BENEFIT ASSESSMENT

13.1 Regulatory Action

This Application will not be approved during this review cycle and the regulatory action will be a Complete Response.

There are several Product Quality deficiencies (see Section 3) that must be resolved before this Application could be approved. Among these deficiencies was the finding of foreign particulate contamination in all 5 site transfer batches of the product manufactured at the Applicant’s future commercial manufacturing facility. The Office of Compliance also has issued a WITHHOLD recommendation for 2 of the Applicant’s facilities.

Both the primary Clinical Reviewer and the Clinical Team Leader have recommended that this NDA not be approved until the Applicant has provided additional data to adequately assess the efficacy of the progesterone vaginal ring in the older subset of women (those 35 to 42 years of age) who would also use the product as part of an Assisted Reproductive Technology (ART) treatment program. This issue could be addressed by the Applicant conducting prior to approval a randomized, adequately powered, active-controlled clinical trial to evaluate the efficacy of the product in women 35 to 42 years of age. Alternatively, it is possible that (1) appropriate labeling, which would include a statement on limitation of use, and (2) 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.

13.2 Risk/Benefit Assessment

Efficacy Assessment: In the Applicant's single Phase 3 clinical trial, the progesterone vaginal ring, replaced once weekly, was shown to be statistically non-inferior to the approved active comparator, Crinone 8% vaginal gel, dosed daily, in the overall mITT population (subjects 18 to 42 years of age) and the subset of subjects 18 to < 35 years of age. The finding of non-inferiority for the progesterone vaginal ring in the overall mITT population, however, was driven by the subset of subjects 18 to < 35 years of age because these subjects comprised 86% of the overall mITT population. For the subset of subjects 35 to 42 years of age, treatment with the progesterone vaginal ring did not meet the criteria for non-inferiority. The study, however, was not adequately powered for a meaningful assessment of non-inferiority in the older subset of subjects.

Safety Assessment: The overall safety profile for the progesterone vaginal ring, based on the data provided in the Application, was comparable to that of the approved active comparator Crinone. There were no safety findings in the clinical development program for the progesterone vaginal ring that raised any safety concerns or would preclude approval of the vaginal ring for the proposed indication in the younger age group.

Overall Assessment: The subgroup of women 35 to 42 years of age represents approximately 50% of the infertile women in the US for whom the drug product is intended as part of an ART treatment program. In general, this subgroup of infertile women has diminished ovarian reserve relative to women under the age of 35. It is not known if efficacy data from women less than 35 years of age can be extrapolated to women in the older subgroup. I concur with the primary Clinical Reviewer and the Clinical Team Leader that it is important that the Applicant obtain information about the efficacy of the progesterone vaginal ring in these older women. I do not concur, however, with the recommendations of the primary Clinical Reviewer and the Clinical Team Leader that additional safety and efficacy data must be obtained prior to approval of the progesterone vaginal ring. I believe that the progesterone vaginal ring could be approved for use in women < 35 years of age, after resolution of the other approvability issues, with (1) appropriate product labeling that would include a statement on limitation of use and (2) a postmarketing commitment by the Applicant to conduct an adequate and well-controlled clinical trial in women 35-42 years of age.

In summary, I find the overall risk/benefit profile for the progesterone vaginal ring favorable for women < 35 years of age for the proposed indication and believe that the product could be labeled for safe and effective use in women < 35 years of age. Approval of the progesterone vaginal ring, based on clinical data provided in the current Application, also would provide another dosing option for women < 35 years of age. Many of these women might prefer a product such as the progesterone vaginal ring that requires only once weekly dosing instead of once daily dosing (Crinone) or more frequent dosing (Endometrin).

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS)

None at this time.

13.4 Recommendations for other Postmarketing Requirements and Commitments

Should this Application be approved during a subsequent review cycle, the Applicant will be requested to conduct a randomized, active-controlled, adequately powered clinical trial to evaluate the efficacy of the progesterone vaginal ring in women 35-42 years of age as a postmarketing commitment.

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

/s/

SCOTT E MONROE
02/28/2011

Cross-Discipline Team Leader Review

Date	February 25, 2011
From	Shelley R. Slaughter, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	201110
Supplement#	
Type of Submission	NDA 505 (b)(1)
Applicant	TEVA Women's Health R&D
Date of Submission	April 30, 2010
PDUFA Goal Date	February 28, 2011
Proprietary Name / Established (USAN) names	Milprosa/progesterone vaginal ring
Dosage forms / Strength	Non-biodegradable, (b) (4) vaginal ring containing approximately 1.8 grams (b) (4) progesterone USP and a mixture of (b) (4)-silicon elastomer (b) (4) and light mineral oil. Progesterone USP is present in (u) (4) 0% w/w concentration dispersed evenly within the ring.
Proposed Indication(s)	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 (cover letter)
Recommended:	Complete response is recommended

The main areas impacting the review and approvability of this submission for NDA 201110 for the progesterone vaginal ring are as follows:

1. Clinical Efficacy/Safety for Major Subgroup for which the product is intended to be used.
The data submitted by the applicant failed to demonstrate efficacy of the progesterone vaginal ring for luteal support of implantation and maintenance of an early pregnancy in women age 35 and older; this population of women represents 60% of the population of infertile women (couples) who undergo Assisted Reproductive Technology (ART) to become pregnant. As the indication is maintenance of a pregnancy, failure to demonstrate efficacy (i.e. failure to maintain pregnancy) is also a safety concern (See Clinical/Statistical Efficacy and Safety discussion).
2. Chemistry Manufacturing Concerns and Inspection Deficiencies
Prior approval inspections noted that the progesterone vaginal rings in the site transfer batches at the intended commercial site were found to have (b) (4) foreign particulate materials. The Office of Compliance has issued an overall “WITHHOLD” for the manufacturing facilities (See CMC discussion).

1. Introduction

TEVA Pharmaceuticals seeks approval for its (b) (4) progesterone product delivered via a vaginal ring for support of implantation and early pregnancy via corpus luteal support during ART. NDA 201110 was submitted and received by the Agency on April 30, 2010. The application was administratively filed on June 29, 2009. The major clinical deficiency and review issue noted in the 74-day Filing letter was failure to power the study to demonstrate efficacy in the important age subgroup of women age 35-42. The Sponsor ignored numerous recommendations from the Division during drug development to power the primary study to demonstrate efficacy in both age subgroups, age less than 35 and age 35-42. See Section 7 – Efficacy and Section 13 - Recommendations. The other major review issue arose during the course of the review and was related to inadequate controls in the process, equipments, and environment during manufacture of the progesterone vaginal ring. See Section 3 – CMC.

2. Background

Progesterone is produced by the 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 maintenance of pregnancy (and production of progesterone).

GnRH agonists or antagonists are used in ART programs to prevent premature luteinization of follicles as a result of premature LH surges. Unfortunately, suppression can continue into the luteal phase (despite the fact that agonist/antagonist therapy stops on 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 who may or may not require luteal supplementation in any given cycle, some form of luteal phase support is recommended for all ART (Speroff L and Fritz MA.)

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 was “off-label”. Prometrium approved under NDAs 019781 and 020843 for prevention of endometrial hyperplasia and treatment of secondary amenorrhea was also compounded into a vaginal product by many local/university hospital-associated pharmacies and historically used “off-label” for luteal support.

Two products have been 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 document 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.”

NDA 201110 for the progesterone vaginal ring was filed on June 29, 2010. The 74-day Filing Communications letter was sent to Duramed on July 13, 2010. The letter identified the following potential review issues:

Clinical

1. The single phase 3 study does not provide sufficient data to assess the efficacy or safety of your product in women age 35-42 years. Because this age group represents a large proportion of women seeking *in vitro fertilization* (IVF), this lack of data is a significant review issue.
2. There are no data reported for enrollment sites 5 and 16. Provide an explanation for this.
3. Provide an explanation for the non-sequential patient ID numbers.
4. Identify the reference for the classification of Ovarian Hyperstimulation Syndrome (OHSS) utilized in Study DR-PGN-302 and confirm that it was applied at all centers.

Clinical Pharmacology

1. We request that you submit the following information:
 - a. Systemic progesterone concentrations were assessed using either serum or plasma samples across the studies. Comment on the suitability of each of these fluids for assessment of progesterone concentrations and whether concentration values might vary when measured in serum or plasma.
 - b. Information regarding the clinical chemistry methods used for measuring progesterone concentrations during the phase 2 and 3 clinical trials could not be

located. Submit the missing information or, if already submitted, provide the location of the information in the electronic submission.

- c. Datasets for serum and tissue progesterone concentrations in study DR-201-102 could not be located. Submit the missing datasets in SAS transport file format or, if already submitted, provide the location of the datasets.
2. Estimation of the in vivo drug release rate and proposed labeling language will be a review issue.

Chemistry, Manufacturing, and Controls

Your Application does not contain enough information to reach a conclusion in terms of the acceptability of the proposed dissolution method and drug release specifications.

Submit the following information:

1. Dissolution method report including the complete dissolution profile data (individual, mean, SD, and profiles) collected during the development of the proposed dissolution method.
2. Complete dissolution profile data (raw data and mean values) from the clinical and primary stability batches supporting the selection of the drug release acceptance criteria (i.e., specification-sampling time point and specification value) for the progesterone vaginal ring.

3. CMC/Device

The drug substance proposed under this NDA is progesterone, USP (b) (4). All information related to the manufacturing and controls are referenced to (b) (4) Drug Master File (DMF) (b) (4). This DMF was previously found adequate to support the (b) (4) (b) (4). No changes are reported to the DMF since the last review. Based on this, DMF (b) (4) is considered adequate to support this NDA.

In addition to DMF (b) (4), the applicant has provided satisfactory batch data for the drug substances used in the manufacturing of the Phase 2 clinical trial, Phase 3 clinical trial, and site transfer batches of the drug product.

The Sponsor's proposed specification for the drug substance differs from that provided by the DMF holder and is not deemed adequate because it does not control for particle sizes and the accuracy of the HPLC analytical method has not been validated. (b) (4)

The drug product, Progesterone vaginal ring is a non-biodegradable, white to off-white, flexible silicone ring containing progesterone as the active ingredient. The progesterone vaginal ring consists of a mixture of (b) (4) silicone elastomer, light mineral oil, and progesterone, USP (b) (4). The active ingredient is present in (b) (4) % w/w concentration dispersed evenly within the ring. Each progesterone vaginal ring (8.9 grams) contains 1.78 grams of USP grade progesterone.

The drug product is prepared by (b) (4)

Approved Drug Products) for use in human. All information related to the manufacturing and controls of (b) (4) are referenced to (b) (4) MAF (b) (4). This MAF was reviewed and found to be adequate.

Appropriate in-process, release, and stability acceptance criteria have been established for the drug product to ensure consistency in quality. The in-process specification and the drug product specification were considered adequate as amended.

Stability data (accelerated and long term) are provided for two clinical batches (size: (b) (4) rings for Phase 2 study and (b) (4) rings for Phase 3 study) and five site transfer batches (size: (b) (4) rings) manufactured in the intended commercial manufacturing site. The stability data indicate that the drug product is physically and chemically stable with no significant change when stored at 25 (b) (4) °C/60 (b) (4) RH for up to 24 months (b) (4). All tested attributes are within the specification without significant trending. The stability data support the proposed expiration dating period of 24 months for progesterone vaginal ring when stored at 25°C (77°F), excursions permitted to 15 - 30°C (59 - 86°F).

The specification includes description, identification (HPLC), durometer, assay (HPLC), content uniformity (HPLC), related impurities (HPLC), drug release, and microbial limits. However, this specification needs to incorporate the test for foreign particulate matter for the following reason.

During prior approval inspection, foreign particulate contaminations were found for all five site transfer batches at the intended commercial site. (b) (4) foreign matters have been identified, but not quantified. The District Office (DO) issued “WITHHOLD” recommendation for the following two sites: Barr Laboratories Inc. Northvale, NJ (CFN #: 2225395) on December 02, 2010 and Teva Women’s Health, Cincinnati, OH (CFN #: 1526814) on November 09, 2010. The reader is referred to the CMC review of February 07, 2011 for a full description of the foreign particulate matter. Based on the preliminary report, the CMC reviewer concludes that the drug product rings were not manufactured with adequate controls in the process, equipments, and environment. Investigations of the root cause for the contaminations have been conducted and it has been concluded that the contamination originated (b) (4). Corrective measures have been proposed by the Sponsor to control for foreign particulates (b) (4). The applicant will have to submit test results from three new registration batches manufactured with the improved equipments and material controls. On January 05, 2011, the Office of Compliance issued an overall “WITHHOLD” recommendation for the facilities involved in the manufacture based on the findings and recommendations of the District which are as follows:

1. Failure of quality control unit to review batch record or its components for identifying the critical defect such as the presence of foreign material in the finished product.
2. Failure of biobatch demonstration batch to meet its specifications
3. No written procedure established for conducting tests on appropriate samples of in-processing materials of each batch
4. Lack of instructions for the responsibilities and procedures applicable to the quality control unit
5. Lack of training for production staff to perform visual inspection of the drug product.

The Office of New Drug Quality (ONDQA) assessment concludes that This NDA has **not** provided sufficient information to assure the identity, strength, purity, and quality of the drug product. ONDQA recommends that from a CMC perspective the application should not receive approval until pending issues are satisfactorily resolved.

ONDQA recommends that the following “Complete Response” deficiencies be communicated to the Sponsor.

1. The drug product ring contains (b) (4) % w/w concentration of the drug substance dispersed evenly within the ring and the particle size distribution of the drug substance is considered to be critical for the consistent drug release of the drug product. Implement a test for particle size distribution with its acceptance criteria to the drug substance specification.
2. During prior approval inspection (PAI) foreign particulate contaminations were found on all five site transfer batches manufactured at the future commercial site. Conduct thorough investigations to identify the root cause and propose corrective measures, and demonstrate that the root cause has been corrected by producing three production batches which show no particulates.
3. Revise the “Description” of the drug product specification by adding “Free of particulates by visual inspection”.
4. Revise the “Microbiological Examination” of the drug product specification by including “The absence of (b) (4) .”
5. Regarding analytical method for the drug product:
 - The accuracy of the HPLC test method for detection of impurity/degradation products in the drug substance should be validated.
 -  (b) (4)
 -
 -
6. The facilities involved are not compliant with cGMP requirements.

The following release rate specifications (Table 1) were agreed upon with the Sponsor in a teleconference on February 04, 2011. The Sponsor committed to providing a revised drug release specifications sheet reflecting these changes.

Table 1. Release Rate Specifications

Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume mL	Sampling Times	Specifications
Vaginal ring	II (Paddle)	50	0.05 M SDS	500	Days 1,2 and 7	Day 1: 158- 201 mg/day Day 2: 67 – 83 mg/day Day 7: 38 – 46 mg/day Meets USP <724> (b) (4) (b) (4)

4. Nonclinical Pharmacology/Toxicology

The progesterone vaginal ring's active ingredient is progesterone. The rings inactive ingredients are:

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

Silicon elastomers have been used under several INDs including several for combined contraceptive vaginal ring 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 for (b) (4)
- 2 year tissue implantation in Fisher 344 rats with (b) (4)

Studies for the biocompatibility and Ames mutagenicity assay were reviewed under the original IND (70875 dated October 06 2004). There was no evidence of cytotoxicity, irritation or systemic toxicity and the excipient is considered non-mutagenic. The Pharmacology Toxicology reviewer concluded that there was no safety concern raised for the (b) (4) excipient.

A 10-day vaginal irritation and 90-day intravaginal toxicology study demonstrated that the drug product is well tolerated and did not cause significant drug-related toxicity.

There are no unresolved toxicology issues. Pharmacology recommends approval from the pharmacology/toxicology perspective.

5. Clinical Pharmacology/Biopharmaceutics

Five Phase 1-2 studies were conducted to assess pharmacokinetics [(PK) both systemic and local tissue] and pharmacodynamics [(PD) secretory transformation] with the progesterone

vaginal ring formulation proposed. In addition because of a change in manufacturing site from that used in the Phase 3 study, the Sponsor conducted a bioequivalence study comparing the clinical trial and the to-be-marketed formulations

Study 1071622, was the primary systemic PK study evaluating progesterone from the proposed to be-marketed vaginal ring formulation. It was a Phase 1, open-label, single arm, single and multiple dose study in 30 healthy postmenopausal volunteering women. Extensive sampling for PK was conducted at various time points after the placement of first and second rings and following removal of the second ring for capturing the drug elimination. Pre-dose samples were obtained at -48, -24 and 0 hours for baseline progesterone determination. Baseline correction was done prior to analyses by subtracting the individual means of the three pre-dose samples from each of the post-dose concentrations.

The progesterone PK parameters determined in Study 1071622 are presented in Table 2

Table 2. Progesterone Pharmacokinetics (Baseline Corrected) Following the First and Second Vaginal Rings

Pharmacokinetic Parameter	Units	N	Mean	SD	Median	Min.	Max.
First DR-2011 vaginal ring insertion							
Cmax (0-168)	ng/ml	30	9.33	2.80	8.56	5.02	15.15
Tmax (0-168)	hr	30	134.80	49.17	144.00	4.02	168.00
AUC0-168	ng·hr/ml	30	1188.41	374.25	1135.60	606.20	2142.33
Second DR-2011 vaginal ring insertion							
Cmax (168-336)	ng/ml	27	10.66	2.72	10.36	6.63	17.96
Tmax (168-336)	hr	27	206.15	56.33	172.00	168.00	336.00
AUC168-336	ng·hr/ml	27	1377.59	362.00	1401.27	827.69	2427.82
Cmax (168-384)	ng/ml	27	10.66	2.72	10.36	6.63	17.96
Tmax (168-384)	hr	27	206.15	56.33	172.00	168.00	336.00
AUC168-384	ng·hr/ml	27	1402.18	367.08	1431.24	843.41	2460.29
AUC168-inf	ng·hr/ml	22	1382.62	387.81	1425.07	850.97	2476.21
Ke	hr ⁻¹	22	0.07	0.02	0.08	0.03	0.11
Elimhalf	hr	22	10.82	4.27	9.09	6.59	24.91

Source: Clinical Pharmacology Review Table 6, p13

Clinical Pharmacology concluded from the reviewed PK data:

- Plasma progesterone concentrations appear to have reached steady-state by the second dose of the progesterone vaginal ring at day 8.
- Based on AUC0-168h values after the first dose (day 1) and the second dose (day 7), some accumulation of progesterone in plasma was evident, with a mean value of 1.26 fold. Accumulation in individual subjects was varied and ranged between no accumulation to accumulation of up to 3-fold.
- Peak progesterone values (Cmax) after the first dose and second doses of the vaginal ring averaged at 9.3 ng/mL and 10.7 ng/mL, respectively. Median Tmax values for the first and second rings were 144 hours and 172 hours, respectively.

- The average value of steady-state plasma progesterone (C_{avg}) observed during the second dose of the ring was 8.19 ng/mL.
- The inter-individual variability (% CV) in plasma progesterone C_{max} and AUC following the vaginal ring product was approximately 25- 30 %.
- Progesterone concentrations in plasma declined with a terminal $T_{1/2}$ of approximately 11 hours following removal of the second ring at day 15.

Study DR-201-102 was a Phase 1, randomized, open-label, active control, vs. no-treatment control trial to assess endometrial tissue progesterone, systemic progesterone, and endometrial PD outcomes (percentage of subjects achieving successful secretory transformation of the endometrium). It was conducted in 63 healthy females [healthy pre-menopausal volunteers or healthy subjects with regular menstrual cycles intending to undergo In Vitro Fertilization (IVF)-embryo transfer (ET)] who were 18-40 years of age. Subjects were given pharmacologic doses of estrogen beginning on menstrual cycle day 1 in an attempt to minimize endogenous progesterone influence on the measured serum or tissue progesterone levels. After 14 days, subjects were randomized to: transdermal estrogen only, weekly progesterone vaginal ring (b)(4) % w/w or Crinone vaginal gel 8 % 90 mg once daily. Along with the transdermal estrogen, these treatments continued for 11-12 days. At the end of treatment, tissue progesterone levels were assessed. See Table 3 for results.

Table 3. Tissue Progesterone Concentrations Across Treatments in Study DR-201-102

Treatment	Tissue progesterone based on sample weight (ng/g)	Tissue progesterone – based on protein content (mg/g protein)
Estrogen only (n=21)	2.8 ± 8.2	0.11 ± 0.34
Vaginal ring (n=21)	52.5 ± 76.9	1.4 ± 2.12
Crinone vaginal gel (n= 21)	1437 ± 2370	34.7 ± 54.1

Source: Clinical Pharmacology Review Table 3, p10

As to be expected tissue progesterone levels were higher in both progesterone treatment groups with the levels in the group treated with Crinone substantially exceeding that of the progesterone vaginal ring. Several individuals in the Crinone group had tissue concentrations markedly higher than vaginal gel group. The Sponsor attributes high tissue concentrations in the vaginal gel group to sampling error wherein the bioadhesive, viscous progesterone gel retained in the vagina and near the cervix could've been inadvertently sampled while accessing the endometrium via the cervix for biopsy samples.

The histology results from Study R-201-102 are shown in Table 4.

Table 4: Histology Results (endometrial transformation status; PD) in Study DR-201-102

Endometrial status classification	Estrogen only (n=19)	Vaginal ring 20 % w/w (n=19)	Crinone vaginal gel 8 % (n=19)
Secretory	5 %	94.73 %	84.2 %
Other*	95 %	5.27 %	15.78 %
* proliferative, inactive, simple hyperplasia, abnormal			

Source: *Clinical Pharmacology Review Table 5, p11*

The group treated with the progesterone vaginal ring demonstrated 95% secretory transformation while the group treated with Crinone demonstrated 84% transformation compared to 5% in the group receiving no progesterone.

Study 10936057 was used to obtain used progesterone vaginal rings for assessment of residual drug content and calculation of in vivo drug release.

The average serum progesterone concentrations at the end of the study were 7.9 and 9.3 ng/mL, for the vaginal ring and Crinone groups respectively. Sponsors of non-systemically administered progesterone products have maintained that these products have their main effect locally and despite having serum progesterone levels that would appear to be inadequate, their local effects on the endometrium would be favorable for the ultimate desired outcome of pregnancy. The findings from this study would seem to be consistent with this position. Despite low serum progesterone levels the tissue progesterone levels were elevated and the endometrium was substantially converted to a secretory endometrium. However, caution must still be exercised in using endometrial histology and/or tissue progesterone as a clinical surrogate endpoint. The correlation between percentage of endometrial secretory conversion or tissue progesterone level and successful pregnancy has not been made and tissue progesterone levels remain an experimental measurement.

Two other studies assessed pharmacodynamic measures, Studies DR-PGN-201 and DR-PGN-202. Study DR-PGN-201 was a Phase 2, randomized, open-label, active control PD study in 21 females ages 18-50 years who were candidates for donor oocyte program; the study was a 'mock cycle' preceding study DR-PGN-202 (below) and served to evaluate the proportion of subjects with adequate endometrial transformation. Crinone 90 mg twice daily (Approved for replacement) was the comparator. The percentage of subjects achieving endometrial transformation was higher for the Crinone vaginal gel (100 %) compared to the ring (80 %). Two (out of ten) patients in the vaginal ring group who experienced an inadequate transformation of the endometrium had serum concentrations lower than 4 ng/mL.

Study DR-PGN-202 was a Phase 2, randomized, open-label, active-control PD study in 9 participants who had demonstrated successful endometrial transformation in earlier study DR-PGN-201. The study assessed clinical pregnancy rates (at 8 and 12 weeks of pregnancy). The clinical pregnancy rate determined by ultrasound at 8 weeks was 80 % for the vaginal ring treatment (4 out of 5 who underwent embryo transfer) and 25 % for the Crinone treatment arm (1 out of 4 who underwent embryo transfer). No discernible definitive trends could be made as to the 'desirable' threshold of serum progesterone concentrations with respect to positive pregnancy outcomes. Also, evidence of a successful endometrial transformation (PD) in the

earlier mock cycle (Study DR-PGN-201) using the same treatment regimen in the same patients did not ensure clinical success (i.e. pregnancy) in subsequent study 202 on the same regimen. The sample size is very small (n= 5 in vaginal ring group and n = 4 in the vaginal gel group) to make any definitive conclusions in this regard

Neither Study DR-PGN-201 nor PGN-202 would be acceptable to provide evidence of safety and efficacy for a progesterone replacement claim. Both Studies DR-PGN-201 and Study DR-PGN-202 were conducted with vaginal rings manufactured at a third site, Barr Lab's Plainsboro, NJ facility. No bridging bioequivalence information was provided for these rings.

Study 10936035 was a Phase 1, randomized, blinded, single-dose, two-treatment, two-period, two-sequence crossover trial in 31 healthy post-menopausal volunteers evaluating the bioequivalence of the proposed commercial formulation (manufactured at the Sponsor's Ohio commercial facility) to that of the Phase 3 clinical trial formulation (manufactured at the Sponsor's New Jersey Research & Development facility). There were no differences in the actual formulation or the equipment used across these two sites. However, during pre-NDA discussions with the Sponsor, the Office of New Drug Quality Assessment (ONDQA) recommended that the Sponsor should conduct a formal BE study to bridge the two manufacturing sites.

Subjects received a single dose of once-weekly vaginal ring formulation- either Reference (clinical trial formulation; manufactured at the R & D facility in NJ; batch number 900214) or Test (commercial formulation; manufactured at commercial facility in OH; batch number 800357) in period I or period II of the study separated by a 7-day washout duration. All subjects received pre-treatment with 1 mg estradiol oral tablets for at least 28 days prior to first dose and also continued with this treatment throughout the entire study including the washout period, until after the final blood draw in period II.

Blood samples for plasma progesterone analysis were collected at pre-dose (for baseline; -1.0, -0.5 and 0 h), extensively during the two treatment periods and after removal of the vaginal ring in the second period.

All post-dose samples were corrected for baseline by deducting the mean of three pre-dose values (-1, -0.5 and 0 hours). PK analyses were conducted on the baseline-corrected data. Non-baseline corrected data analysis is considered supportive data. Bioequivalence was based on the 90 % confidence intervals surrounding treatment mean ratios (T: R) for AUC0-t, AUC0-inf and Cmax. Results of Study 10936035 are provided in Table 5.

Table 5: Bioequivalence Analysis [Study 10936035]

	Test	Reference	Ratio [% Ref]	90 % CI range
Cmax (ng/mL)	7.14	7.54	94.62	89.37 - 100.18
AUC (ng h/mL)	949.35	1002.21	94.73	89.51 - 100.25
AUCinf (ng h/mL)	952.53	1005.53	94.73	89.52 - 100.24

Source: Clinical Pharmacology Review Table 15, p24

The point estimates (expressed as % reference B in the table above) for all three PK parameters above were approximately 95 %, while the 90 % confidence intervals surrounding

these ratios were contained entirely within the bioequivalence limits of 80-125 %. Thus the two treatments meet the bioequivalence criteria.

Bioequivalence analysis outcomes were also similar for the uncorrected progesterone data, with the point estimate for Test/Reference ratio of PK parameters C_{max}, AUC and AUC_{inf} close to 100 % and their associated 90 % CI ranges within 80-125 % bioequivalence bounds.

During BE Study 10936035 and follow-up ring exposure Study 10936057, progesterone vaginal rings were collected for residual drug content analysis after a one week use period from a total of 45 subjects. A control group of 45 rings from the same batch were used to derive the initial amount of drug in the vaginal rings. The overall data suggest that the ring releases approximately 75 mg (4.2 % of its 1.78 g drug load) over the 7 days of in vivo residence time. This translates to approximately 11 mg/day of in vivo drug release rate resulting in an average concentration (C_{avg}) of approximately 8 ng/mL per day at steady-state.

There is no established IVIVC for this drug product. The proposed in vitro release test is for quality control purposes and has no in vivo relevance.

The absorption and elimination characteristics of progesterone from the vaginal ring formulation are summarized as follows:

Absorption: Progesterone plasma concentrations steadily increased following the initial administration of the vaginal ring to healthy postmenopausal females once a week for two weeks. Steady state concentrations were attained by the end of the first ring with average plasma concentrations of progesterone of approximately 8 ng/mL. (b) (4)

Distribution: Progesterone is approximately (b) (4) % bound to serum proteins, primarily to serum albumin and corticosteroid binding globulin.

Metabolism: Progesterone is metabolized primarily by the liver largely to pregnanediols and pregnanones, which are conjugated to glucuronide and sulfate metabolites. Progesterone metabolites that are excreted in the bile may be deconjugated and may be further metabolized in the gut via reduction, dehydroxylation and epimerization.

Excretion: Progesterone undergoes both biliary and renal excretion. Following an injection of labeled progesterone, 50%-60% of the excretion of metabolites occurs via the kidney; approximately 10% occurs via the bile and feces. Overall recovery of the labeled material accounts for 70% of an administered dose. Only a small portion of unchanged progesterone is excreted in the bile. Following removal of the ring, plasma progesterone concentrations declined with a half-life of approximately 11 hours.

No specific drug-drug interaction studies were conducted for the progesterone vaginal ring formulation. The Phase 3 clinical trial did not allow concomitant use of other vaginal products such as anti-fungals while using the study drug. Labeling should indicate that concomitant vaginal formulations should be avoided while on this drug (for up to 10 weeks).

The Office of Clinical Pharmacology finds the application to be acceptable pending agreement on labeling.

6. Clinical Microbiology

Microbiology has determined that the application is not currently recommended for approval on the basis of product quality microbiology. The review lists the following deficiencies and comments to be included with a “Complete Response” action:

Deficiencies:

Revise the specification to include the absence of (b) (4).

Comments:



7. Clinical/Statistical- Efficacy

The major efficacy and (safety by extension) review issue for this drug product was based on the failure to establish efficacy of the progesterone vaginal ring based on the non-inferiority of progesterone vaginal ring to that of Crinone in the treatment of women age 35 years and older. This group is expected to constitute the majority of patients who will be treated with this product should it gain approval (based on the fact that the majority of subject who undergo ART procedures in the U.S. are age 35 years of age and older).

Highlights of the Regulatory History

- **October 07, 2004** - IND 70875 Opened by Duramed
A Phase 1 single dose pharmacokinetic protocol for a vaginal ring product containing (b) (4) gms of progesterone and release rate of (b) (4) mg/day when used over a 1 week period.
The Division in an
- **December 7, 2004** – Division of Reproductive and Urologic Products (DRUP) Advice Letter
Division provided its concern that adequate dose ranging may not have been evaluated in Phase 1 and it recommended that in Phase 1, the Sponsor choose progesterone doses that reach a predetermine optimal serum progesterone level for the desired effects in Phase 2 and 3 study. Relative to future Phase 3 study, the Division recommended that the ART study include subjects up to the age of 42 and that randomization and analyses be stratified and powered by ovarian reserve as measured by Day 3 FSH and the age of the female partner.

- **March 2007 – DRUP Advice Letter**
 - Division reiterated its concern that the proposed single dose of (b) (4) mg progesterone/day for the progesterone vaginal ring is not well justified and may not be sufficient.
 - Recommendation that the Sponsor evaluate at least 2 dose levels of progesterone.
 - Progesterone (b) (4) supplementation [treating women undergoing assisted reproductive technology (ART) procedures not involving oocyte donation] are considered as representing treatment (b) (4). (b) (4) progesterone supplementation should (b) (4) be supported by at least one adequate and well controlled study in the appropriate population.
- **June 13, 2007 - End-of-Phase 2 Meeting**
 - The Sponsor had changed the drug delivery system such that the in vivo release rate was estimated to be (b) (4) (a decrease from the initial proposal of (b) (4) mg/day) when vaginally inserted for 7 days.
 - DRUP commented that the Sponsor has not provided sufficient dose finding evidence to proceed into Phase 3. The Sponsor contended that “its product provides the maximum amount at a consistent reliable dosing compared to the approved products
 - DRUP recommended:
 - The Sponsor proceeds into Phase 3 at their own risk
 - Indication (b) (4) Pregnancy by progesterone supplementation as part of an Assisted Reproductive Technology (ART) treatment for infertile women. (b) (4)
(b) (4) The exact wording will be discussed at the time of labeling negotiations
 - Phase 3 study should be double-blind or at a minimum blinding of the investigator and ultrasonographer should occur.
 - The primary efficacy analysis should be based on a two-sided 95% confidence interval. A lower non-inferiority (NI) limit of (b) (4) % (as it was proposed by the Applicant) is not acceptable for the progesterone vaginal ring. The non-inferiority limit for the phase 3 study should be defined as equal to or greater than -10% of a two-sided 95% confidence interval when compared to an active progesterone comparator. The Sponsor should report the percentages of the difference of the lower limit of the 95% confidence intervals to the first decimal point. The live-birth per transfer rate in the 2004 CDC clinical pregnancy rate per cycle using fresh embryos is reported as 33% and the efficacy study in support of the progesterone vaginal ring should demonstrate that its efficacy will be comparable to this standard
 - The primary efficacy analysis should include all subjects who completed oocyte retrieval and have received at least one dose of progesterone (m-ITT cohort)
 - Randomization and analyses should be stratified and powered by ovarian reserve as measured by Day 3 serum FSH and age of female partner (< 35

years of age, and 35-42 years of age). The Division feels strongly that this information is critical in order to appropriately advise the physician who treats and the patient who falls in the age group greater than 35 years (up to 60% of the ART population for luteal supplementation). The Division further recommends a sub-stratification of data based on BMI, the type of insemination occurring [i.e. conventional IVF vs. intracytoplasmic sperm injection (ICSI)] and infertility diagnosis. The analysis of data relative to sub-stratification groups can be descriptive. Studies should be powered to demonstrate differences in these (sub-stratification) groups only if specific claims regarding these are sought

- DRUP recommends that ovarian reserve (serum FSH) be measured in a central laboratory. The entry criteria should include evaluation of a serum FSH level on Days 2, 3, or 4. Subjects with a serum FSH of 15 IU/L or greater obtained on cycle Day 2, 3 or 4 should be excluded
- DRUP recommends that if you choose to perform one study for this indication, either all of the sites or a majority of subjects be treated at US sites, as practices of ART are significantly different in non-North American countries
- **October 29, 2007** – Request for Special Protocol Assessment
- **December 13, 2007** – DRUP SPA Recommendations
 - Indication - Progesterone vaginal ring is a progesterone-containing device and is indicated to support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteum function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women.
 - Progesterone replacement for infertile women receiving donor oocytes and progesterone supplementation for infertile women undergoing Assisted Reproductive Technology as separate indication. Each indication would require a separate Phase 3 proof of efficacy study. (b) (4)
 - Study DR-PGN-302 could only be considered in the support of the indication (supplementation) as outlined above.
 - The majority of subjects treated in the primary efficacy and safety study should be from the US or Canada, as practices of ART are significantly different in North American countries compared to non-North American countries.
 - The proposed single dose of 14 mg/day (b) (4) for the progesterone vaginal ring is not well supported. The Sponsor proceeds with this single dose at its own risk of failure to demonstrate efficacy for this product.
 - As randomization is planned after oocyte retrieval, the pregnancy rate will be calculated per retrieval and not per cycle. This will be clearly delineated in labeling.
 - There may be significant differences in pregnancy rates when comparing subjects who have received embryo transfer on Day 3 compared to Day 5. This may complicate the findings. We recommend using only Day 3 transfer for this study to eliminate this variability.
 - Other efficacy and statistical recommendations:

- Assess the co-primary endpoints of viable pregnancy (with documented fetal heartbeat) at both six weeks and ten weeks post-embryo transfer. The analysis should be a non-inferiority comparison to Crinone®, which excludes a difference of greater than -10% in favor of Crinone®.
 - Randomization and the primary analyses should be stratified and powered by ovarian reserve as measured by Day 3 serum FSH and age of female subjects (age < 35 years and age ≥ 35 to 42 years)
 - Provide a descriptive sub-stratification of data based on Body Mass Index (BMI), the type of insemination occurring [i.e. conventional IVF vs. intracytoplasmic sperm injection (ICSI)] and infertility diagnosis. We recommend that only Day 3 embryo transfer be used. However, if both Day 3 and Day 5 transfers are retained, you should also sub-stratify based on the two transfer dates. Studies should be powered to demonstrate differences in these (sub-stratification) groups only if claims regarding these specific sub-groups are sought
 - Provide a secondary analysis of the efficacy of progesterone that includes the clinical pregnancy rate in all subjects who initiated ovarian stimulation using gonadotropins prior to progesterone therapy (a per cycle analysis).
 - Report the percentages of the difference between the confidence intervals to the first decimal point.
 - We consider results of the “Treatment Satisfaction Measure” questionnaire as exploratory and therefore not acceptable for the purposes of labeling.
 - Standardize the classification (grading) of ovarian hyperstimulation syndrome (OHSS) as an adverse event to allow standardization of reporting across sites.
 - Classify subjects who receive paracentesis as a result of OHSS as having severe OHSS.
 - For labeling purposes, calculate the rate of birth defects in this study as per live-birth for each treatment group and not per cycle
 - Use a single preferred term for all subjects with vulvovaginal candidiasis when reporting adverse events
- **December 13, 2007** – New Sponsor Proposal
 - Duramed will enroll subjects aged 18-42 and to stratify by age groups < 35 and 35-42. The study will be powered to show non-inferiority compared to Crinone® for subjects aged 35-42 years. “The Applicant acknowledges that this specific population is of interest to the Agency based on previous FDA minutes from the June 13, 2007 meeting. Evaluation of this population would provide currently unavailable, critically important clinical information for the treating physician, as this is the group with lower pregnancy rates in which efficacy has not been firmly established for the recently approved Endometrin® product.” Duramed will carry out two separate efficacy analyses, one of the older age group (35-42 years) and one of the entire study population. Descriptive data summaries will be provided for subjects with FSH levels < 10 IU/L and 10-15 IU/L
 - **January 11, 2008** – DRUP Comments on the December 13, 2007 Proposal

- Stratify and power based on two subgroups ages 18-34 and ages 35- 42. The primary efficacy analyses should be based on these two groups (18-34 and 35-42). Perform a secondary sub-group analysis of subjects with a serum FSH < 10 IU/L and those with an FSH 10-15 IU/L.
- DRUP does not agree with the addition of an eligibility criterion to eliminate subjects ≥ 35 of age who have less than 2 eggs retrieved. The eligibility criterion for subjects ≥ 35 years should be the same as subjects younger than age 35. Women who have no eggs retrieved should not be eligible to participate.
- **August 27, 2008 – Additional DRUP Comments**
 - DRUP does not agree that a study powered only to demonstrate efficacy in the population of women less than 35 years of age will be adequate for an indication of 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. The proposed study will not adequately address efficacy and safety in the population of women 35 years of age or greater. Such women represent approximately 50% of women undergoing ART procedures and would be expected to constitute approximately 50% of the potential users of the progesterone vaginal ring. Therefore, it is not acceptable if the sample size for the subgroup of older women is underpowered for assessing the efficacy of the progesterone vaginal ring. The Division is open to further discussion regarding the powering of Study DR-PGN-302 that would allow for informative labeling for both age subgroups.”
 - PK data obtained from Study 10716222 would be used for general evidence of bioavailability and not to infer efficacy or safety of DR-2011 in the target population.
- **March 3, 2009 – DRUP Advice Letter**
 - Study DR-PGN-302, with only 200 subjects in the age range of 35-42 years old, is inadequately powered to assess efficacy in this population. We continue to strongly recommend that randomization and the primary analyses be stratified and powered in terms of ovarian reserve as assessed by the age of the subject (subjects < 35 years old and subjects 35 to 42 years old)
- **June 16, 2009 - Pre-NDA Meeting**
 - DRUP reminds the Sponsor of the Agency’s recommendations made on multiple occasions during the drug development program (beginning with the June 13, 2007 end of Phase 2 Type B meeting and continuing into 2009) that the Phase 3 study be stratified and powered to demonstrate efficacy in each of the age groups represented by women less than 35 years of age and women 35-42 years of age.
 - Duramed acknowledged the Division’s recommendation to power the pivotal study(s) to demonstrate efficacy in women < 35 years old and women ≥ 35 to 42 years old, but clarified, that because of some “internal constraints”, they had made the choice to power their study only for women less than age 35. The Sponsor also noted an approved product whose primary study was powered only for subjects < 35 years of age.

- Duramed indicated that it would internally consider conducting a separate study in women age $\geq 35-42$.
 - DRUP continues to have concern that the formulation of the DR-2011-progesterone vaginal ring (release rate of 14 mg/day of progesterone) provides insufficient progesterone for supplementation of corpus luteum function and maintenance of early pregnancy. The issue of whether or not the progesterone vaginal ring provides sufficient supplementation is a review issue not only for efficacy, but for the safety (spontaneous abortion rate) of this product as well.
 - Duramed emphasized that the vaginal ring design has accommodated the maximum amount of progesterone possible and the release rate is at the maximum
 - The progesterone vaginal ring (DR-2011) was initially stated to release (b) (4) mg/day. It was subsequently changed to (b) (4) 14 mg/day. It is not clear how the release rates were calculated. It is also not clear why the stated release rate was changed twice without a reported change in formulation composition. The NDA should address these 2 comments. Release rate calculation should be based on the residual amount of progesterone remaining in DR-2011 following vaginal placement of the ring for 7 days.
 - Provide an additional safety table of all subjects who had a reported event of ovarian hyperstimulation syndrome (OHSS), categorized by severity (mild, moderate and severe) using standardized categorization criteria. In addition, provide the definitions used to classify OHSS
 - The Division relayed that it was not in a position to advise the Applicant as to whether or not an application with the above noted studies would be fileable; that determination would depend on the results of the Division's review at the time of submission. However, the Division again noted its concern regarding the very limited information on women in the older population.
- NDA 201110 filed on April 30, 2010

Individual Study Review of Primary Study –DR-PGN-302 ““A Phase 3, Single-Blind, Randomized Study to Compare DR-2011 to a Progesterone Vaginal Gel for Luteal Phase Supplementation for In Vitro Fertilization.”

Only one Phase 3 study was submitted in support of efficacy and safety of the progesterone vaginal ring.

Design:

The study was a prospective, multicenter (22 sites in the United States), investigator-blind, randomized, concurrent, active-control study of progesterone supplementation in women undergoing in-vitro fertilization (IVF) with freshly retrieved oocytes and subsequent embryo transfer. Two treatment groups were evaluated: DR-2011 [(progesterone vaginal ring); ring was replaced once weekly] and Crinone 8%-90 mg [(progesterone vaginal gel) administered once daily]. Treatment duration was one cycle beginning on the day of embryo retrieval and continued through the onset of menses or up to 12 weeks of pregnancy (10 weeks post-embryo transfer) should pregnancy occur.

Reviewer's Comments: Failure to have a double-blind design is an issue. Although Sponsor's have argued that double blind is less necessary with a truly objective criteria, the concern is that the patient is aware of her treatment assignment and during interactions

with care given it is not unexpected that the study medications might have been discussed. This in turn means that the investigator may not be truly blinded as well. Because most aspect of the IVF protocol can be manipulated by the physician, failure to have blinding could lead to substantial bias in favor of or against one of the two treatment arms. A solution to this would have been the double-blind, double dummy approach.

Entrance Criteria:

Inclusion Criteria

Women who were candidates for progesterone administration following gonadotropin stimulation and egg retrieval as part of an IVF program were enrolled with the following characteristics:

- ≥ 18 and ≤ 42 years old;
- Tubal, idiopathic, male factor, ovulatory dysfunction or endometriosis-linked infertility
- Documentation of a normal uterine cavity by hysteroscopy, hydrosanogram, or hysterosalpingogram (HSG) within 1 year of Screening
- Documentation of testing for serum Hepatitis B surface antigen, Hepatitis C antibody, HIV antibody, RPR/VDRL, rubella antibody, ABO grouping, Rho typing, prolactin and thyroid function within 6 months of Screening
- At least one cycle without reproductive hormone medication prior to the screening FSH and estradiol blood draw
- Semen analysis within 1 year of Screening by WHO and/or Kruger criteria. Frozen sperm, including donor sperm, could be used, as long as testing done at the time of freezing met standard criteria. Male partners with obstructive azoospermia were not required to have this semen analysis
- For fresh sperm: sperm assessed for leukospermia within two months of pituitary down-regulation, OR male partner empirically treated with antibiotics prior to the IVF cycle. If assessed, ≤ 2 million WBC/mL or round cells/mL were required for participation in this study
- Able to read and comprehend the English language
- Able to understand, read, and sign an informed consent after the nature of the study has been fully explained
- Able to complete all study procedures

Exclusion Criteria

Women who were candidates for progesterone administration following gonadotropin stimulation and egg retrieval as part of an IVF program were not enrolled if they had any of the following:

- Contraindications to the use of progesterone, which included:
 - Known sensitivity to progesterone or related drugs
 - Undiagnosed vaginal bleeding
 - Significant liver dysfunction or disease (including liver function tests > 2 times the upper limit of normal)
 - Known or suspected malignancy of the breast or genital organ
 - Active thrombophlebitis or thromboembolic disorders, or a history of hormone associated thrombophlebitis or thromboembolic disorders
- Significant psychiatric disease that was not well-controlled
- Body Mass Index (BMI) > 38 kg/ m²
- Uncontrolled hypertension (systolic blood pressure >160 mmHg; diastolic blood pressure >100 mmHg)
- Follicle stimulating hormone (FSH) > 15 mIU/mL during early follicular phase (day 2-4). For those subjects with polycystic ovarian syndrome (PCOS), a day 2-4 FSH level could be obtained following a progestogen withdrawal or spontaneous menses
- Clinically significant gynecologic pathology, such as submucosal fibroids, intramural fibroids > 5 cm, communicating hydrosalpinx, uncorrected uterine septum, endometrial cancer or endometrial atypia, scar tissue inside the cavity or poorly developed uterine lining from prior uterine surgery, pelvic tuberculosis, or any other conditions that could adversely affect pregnancy success
- Uncontrolled hyperprolactinemia or hypothyroidism
- History of pelvic radiation.
- Subjects with a history of cancer within the last 5 years, except for squamous or basal cell cancer of the skin
- Currently pregnant or breastfeeding
- Current Gonorrhea or Chlamydia
- History of HIV/AIDS
- Known hypersensitivity or previous intolerance to silicone
- History of toxic shock syndrome
- Known or suspected substance abuse within 1 year prior to screening
- Use of any investigational drug or device within 30 days prior to screening

- Low-grade squamous intraepithelial lesion (LSIL) or worse on screening Pap smear; any other abnormal finding on the Pap smear that the Investigator considers clinically significant [such as "atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (HSIL)" (ASCH), "atypical glandular cells" (AGC)]; or any Pap result that would necessitate further evaluation by biopsy and/or colposcopy. Any screening Pap with "atypical squamous cells of undetermined significance" (ASC-US) will have "reflex" human papilloma virus (HPV) testing done on the Pap sample. If the HPV testing is negative for high-risk types, the subject may be enrolled; if the HPV testing is positive for high-risk types, the subject will be required to have a colposcopy. If colposcopy shows dysplasia or cancer, the subject was NOT eligible for enrollment
- Undergoing donor oocyte cycle, blastomere biopsy or other experimental ART procedure
- History of more than one failed fresh IVF cycle. A prior ART cycle was considered started when a woman began taking medication to stimulate the ovaries to develop eggs or, if no drugs were given, when a woman began having her ovaries monitored (using ultrasound or blood tests) for natural egg production (CDC 2005). A prior failed cycle was defined as having started a cycle without becoming pregnant or a pregnancy loss prior to the 20th week of pregnancy
- More than 2 consecutive clinical miscarriages (gestational sac observed on ultrasound)
- Insulin-sensitizing agents, ART cycle or ovarian stimulation with gonadotropins within 30 days or clomiphene stimulation within 90 days prior to the screening FSH and estradiol blood draw
- Tobacco use 3 months prior to screening
- Male partners with non-obstructive azoospermia for couples using fresh sperm:
- Any abnormal finding or condition deemed clinically significant by the Investigator on history, screening, physical exam, or pelvic exam that contraindicates pregnancy or the use of progesterone or a VR

Reviewer's Comments: Should this product eventually be approved limitations with respect to FSH demonstration of ovarian reserve and BMI must be clearly labeled.

Study Conduct

Eligible subjects were started on an ovarian down-regulation protocol utilizing leuprolide acetate (Lupron) followed by an ovarian stimulation protocol utilizing a combination follicle stimulating hormone (FSH) and luteinizing hormone (LH)-containing product. Ovarian suppression was to begin during the cycle immediately prior to the embryo transfer cycle. Ovarian stimulation was begun once down-regulation was achieved. The length of stimulation depended on each subject, the investigational site's standard protocols, and/or the Investigator's clinical judgment. During stimulation, the subject was monitored to determine when to trigger ovulation with human chorionic gonadotropin (hCG). Egg retrieval was to occur approximately 35-37 hours after hCG administration.

On the day after egg retrieval, at the time of consent, eligible women were stratified by age (18-34 years of age or 35-42 years of age) and randomized in a 1:1 ratio to begin the progesterone vaginal ring or Crinone.

Embryo transfer occurred 3 to 5 days after egg retrieval. A serum pregnancy test was conducted 2 weeks after the egg retrieval. Subjects with a serum β -hCG <5 mIU were discontinued from the study. Those with a serum β -hCG >5 continued dosing with progesterone for up to a total of 10 weeks (i.e., through 12 weeks of pregnancy). Clinical pregnancy rates determined at 8 and 12 weeks of pregnancy (6 and 10 weeks post embryo transfer) by vaginal ultrasound were evaluated for each treatment group. All pregnancies were followed until completion to determine live birth rates. The overall study duration was approximately 12 months.

The study was conducted between the dates of February 04, 2008 (first subject enrolled) and concluded on January 08, 2009 (last subject completed.)

Study Disposition

Disposition of subjects in primary study, DR-PGN-302, is presented in Table 6.

Table 6. Disposition of Subjects in Primary Study, DR-PGN-302,

Disposition / Reason	
Screened	1752
Underwent Ovarian Stimulation	1383
•	
Underwent Egg Retrieval	1299
Randomized	1297
Progesterone vaginal ring	646
Crinone	651
Embryo Transfer	1271
Progesterone vaginal ring	631
Crinone	640

Primary Efficacy Variable:

- Clinical pregnancy (visualization on vaginal ultrasound of a gestational sac with fetal heart motion) at:
 - 8 weeks of pregnancy (6 weeks post oocyte retrieval)
 - 12 weeks of pregnancy (10 weeks post oocyte retrieval)

Primary Efficacy Analysis

- Non-inferiority of DR-2011, the progesterone vaginal ring, vs. Crinone. Please refer to the Statistical Review.

Secondary Efficacy Endpoints

- Live birth rate
- Cycle cancellation rate
- Rate of spontaneous abortion

- Rate of biochemical pregnancy
- Rate of ectopic pregnancy
- Safety and tolerability

Statistical Analysis Plan and Randomization

The Sponsor planned that a total of 1100 women aged 18-34 [550 per treatment group (See Table 7)] would provide at least 90% power based on the following assumptions:

- a one-sided non-inferiority test of the clinical pregnancy rate at a significance level of 2.5%,
- an estimated clinical pregnancy rate of 50% for both Crinone-treated and DR-2011-treated subjects, and
- a non-inferiority margin (maximum allowable difference in clinical pregnancy rate between the two treatment groups) of 10%.

In addition, the Sponsor would enroll to Study DR-PGN-302, approximately 200 women aged 35-42 for a total enrollment of 1300 women. See Table 7

Table 7. Subjects Planned and Randomized in Study DR-PGN-302

	progesterone vaginal ring	Crinone
Number planned		
18-34	550	550
35-42	100	100
Number randomized		
18-34	558	560
35-42	88	91

Source Statistical Analysis Review Table X

The primary efficacy analysis set was the modified intent-to-treat population (MITT), which included all subjects having successful egg retrieval and having at least one dose of progesterone. Subjects who terminated the study prior to 8 weeks of pregnancy (6 weeks after egg retrieval) were considered treatment failures at both 8 and 12 weeks.

The clinical pregnancy rates at Weeks 8 and 12 would be compared between the progesterone vaginal ring group and the Crinone group at one-sided alpha of 0.025. The 95% confidence interval (CI) for the difference in pregnancy rate was calculated using the normal approximation method. A non-inferiority margin of -8% was pre-specified in the statistical analysis plan although the study was powered with a margin of -10%. Treatment with the progesterone vaginal ring would be declared non-inferior to Crinone if the lower bound of the 95% CI for the difference in pregnancy rate was greater than -10% based on MITT population.

The two co-primary endpoints of the clinical pregnancy rate (Weeks 8 and 12) would also be evaluated in subgroups classified by two age groups: 18-34 and 35-42, embryo transfer day, ovarian reserve as measured by (day 2-4 serum FSH, BMI, the type of insemination, and infertility diagnosis. However, no formal statistical comparisons would be made between the two treatment groups within these subgroups.

Reviewer's Comments: *Despite hearing on numerous occasions (see regulatory history) the Division's recommendations that the study to demonstrate efficacy must be stratified and powered for subgroup analyses by age, 18-34 and 35-42 years of age, the Sponsor failed to power the primary study to demonstrate efficacy for the older age group nor was there a study conducted exclusively in this group.*

Primary Efficacy Results:

Sponsor analyses: (see Medical Officer Review)

The Sponsor's primary analysis of the clinical pregnancy rate at Week 8 (6 weeks post retrieval) and Week 12 (10 weeks post retrieval) by age subgroup is provided in Table 8.

Table 8: Clinical Pregnancy Rate per Retrieval by Age and Week: MITT Population

Age	Week	DR-2011		Crinone		Treatment Diff. (95% C.I.) (DR-2011 – Crinone)
		n/N	Percent	n/N	Percent	
18-34	8	275/558	49.3%	269/560	48.0%	1.2% (-4.6%, 7.1%)
	12	269/558	48.2%	258/560	46.1%	2.1% (-3.7%, 8.0%)
35-42	8	35/88	39.8%	38/91	41.8%	-2.0% (-16.4%, 12.4%)
	12	31/88	35.2%	36/91	39.6%	-4.3% (-18.5%, 9.8%)
All	8	310/646	48.0%	307/651	47.2%	0.8% (-4.6%, 6.3%)
	12	300/646	46.4%	294/651	45.2%	1.3% (-4.1%, 6.7%)

Sources: NDA Study DR-PGN-302 Clinical Report, Table 17, p76; Medical Officer Review Table 16

The Sponsor also presented the primary endpoint analyses by subgroup stratification of ovarian reserve (as determined by the Day 2 through 4 serum FSH levels), embryo transfer day (Day 3 vs. Day 5), BMI, type of insemination method (conventional IVF vs. ICSI), duration of infertility, and infertility diagnoses. As the study was not powered to demonstrate non-inferiority based on these parameters, no formal statistical comparisons were made between the two treatment arms within any subgroup. The reader is referred to Medical Officer Review for a full discussion of these subgroup analyses. This reviewer will only briefly touch on the analysis by ovarian reserve. The following Table 9 presents the Sponsor's analyses of the clinical pregnancy rate per retrieval by ovarian reserve.

Table 9. Clinical Pregnancy Rate per Retrieval by Ovarian Reserve- MITT Cohort^a

Age	Week	DR-2011		Crinone		Treatment Diff. (95% C.I.) (DR-2011 – Crinone)
		n/N	Percent	n/N	Percent	
FSH < 10 mIU/mL	8	297/618	48.1%	299/632	47.3%	0.7% (-4.8%, 6.3%)
	12	289/618	46.8%	286/632	45.3%	1.5% (-4.0%, 7.0%)
FSH 10-15 mIU/mL	8	12/22	54.5%	8/17	47.1%	-7.5% (-24.1%, 39.0%)
	12	10/22	45.5%	8/17	47.1.6%	-1.6% (-33.2%, 32.0%)
FSH 10-15 mIU/mL or Age ≥ 35	8	43/103	41.7%	46/106	43.4%	-1.6% (-15.1%, 11.8%)
	12	38/103	36.9%	44/106	41.5%	-4.6% (-17.8%, 8.6%)
FSH 10-15 mIU and Age ≥ 35	8	4/7	57.1%	0/2	0	57.1 (20.59, 93.8)
	12	3/7	42.9	0/2	0	42.9 (6.2, 79.5)

^aEight subject (6-progesterone vaginal ring, 2-Crinone) had no FSH level reported

Sources: NDA Study DR-PGN-302 Clinical Report, Table 18, p77; Medical Officer Review Table 18

Reviewer's Comments: Even though at first glance, the point estimate of the pregnancy rate in the elevated ovarian reserve group (FSH 10-15) appears to be very good (54 and 45%, respectively at Week 8 and Week 12), the number of individuals in this group is very small, such that no reliable conclusions can be drawn based on this study regarding the efficacy of this product in women with elevated FSH. As indicated, no effort was made to power for this subgroup analyses. The elevated ovarian reserve group (FSH 10-15) comprised only 3% of the subjects

FDA Analysis (See Statistical Analyses Review)

The Statistical reviewer's primary analysis of the clinical pregnancy rate at Week 8 (6 weeks post retrieval) and Week 12 (10 weeks post retrieval) by age subgroup is provided in Table 10.

Table 10: Clinical Pregnancy Rate per Retrieval by Age and Week: MITT Population

Age	Week	DR-2011		Crinone		Treatment Diff. (95% C.I.) (DR-2011 – Crinone)
		n/N	Percent	n/N	Percent	
18-34	8	275/558	49.3%	269/560	48.0%	1.2% (-4.6%, 7.1%)
	12	269/558	48.2%	258/560	46.1%	2.1% (-3.7%, 8.0%)
35-42	8	35/88	39.8%	38/91	41.8%	-2.0% (-16.4%, 12.4%)
	12	31/88	35.2%	36/91	39.6%	-4.3% (-18.5%, 9.8%)
All	8	310/646	48.0%	307/651	47.2%	0.8% (-4.6%, 6.3%)
	12	300/646	46.4%	294/651	45.2%	1.3% (-4.1%, 6.7%)

Sources: Statistical Analysis Review Table 3.2.3

Reviewer's Comments: In both the Sponsor's and the FDA's analysis of the subgroup analyses of women age 18-34, the lower bound of the 95% confidence interval of the difference between the progesterone vaginal ring and Crinone excludes a -10% difference (excludes that the progesterone vaginal ring is worse than Crinone by greater than 10 %) and thus non-inferiority can be declared with respect to pregnancy rates at both Weeks 8 and 10 of pregnancy,

In the subgroup analyses of women age 35-42, the lower bound of the 95% confidence interval of the difference between the progesterone vaginal ring and Crinone is -16.4 and -18.5% at Weeks 8 and 10, respectively. Thus it can not be conclude that the efficacy of the progesterone vaginal ring is no worse than 10% lower than that of Crinone and thus non-inferiority can not be concluded. As mentioned multiple times, the Sponsor did not adequately power for this analysis.

Secondary Efficacy Results:

This reviewer will only briefly touch on the secondary analyses of live birth rate because this is ultimate desired outcome of treatment of infertility. The reader is also referred to the Medical Officer Review for a full discussion of secondary efficacy parameters. Table 11 present the live birth rate data from Study DR-PGN-302.

Table 11. Live Birth Rate per Retrieval. MITT Population

Age	DR-2011		Crinone		Treatment Diff. (95% C.I.) (DR-2011 – Crinone)
	n/N	Percent	n/N	Percent	
18-34	262/558	47.0%	249/560	44.5%	2.5% (-3.3%, 8.3%)
35-42	30/88	34.1%	33/91	36.3%	-2.2% (-16.2%, 11.8%)
All	292/646	45.2%	282/651	43.3%	1.9% (-3.5%, 7.3%)
<i>Sources: Statistical Analysis Review Table 3.2.4</i>					

Reviewer's Comment: *The live birth rate point estimates in the less than age 35 age group for both the progesterone vaginal ring and Crinone are comparable (the lower bounds of the 95% confidence interval of the difference in pregnancy rates is -3.3) and both exceed 40% which is above the approximately 34% live birthrate per retrieval reported in the 2008 Centers for Disease Control and Prevention publication of "Assisted Reproductive Technology Success Rates" in clinical practice. In the age 35-42 years of age subgroup, the lower bounds of the 95% confidence interval of the difference in pregnancy rates is -16.2. The live birth rate results are consistent with those seen with clinical pregnancies.*

8. Safety

As only one primary efficacy and safety study was performed, an Integrated Summary of Safety was not done.

A serious adverse event (SAE) was one that met any one of the following criteria:

- Fatal or life threatening
- Required or prolonged inpatient hospitalization
- Resulted in persistent or significant disability/incapacity
- Congenital anomaly / birth defect
- Medically significant

Pregnancy outcomes that were classified as SAEs are as follows:

- Ectopic pregnancy
- Spontaneous abortion, which includes miscarriage and missed abortion
- Congenital anomaly/birth defect
- All neonatal deaths that occurred within one month of birth were reported, without regard to causality, as SAEs
- In addition, any infant death after one month that the investigator assessed as possibly related to the in utero exposure to IP.

For subjects who became pregnant during the study, SAEs were reported during the study period which encompasses enrollment through the first trimester. In the case of induced or spontaneous abortion, the aborted products of conception could be assessed by gross visual

inspection unless there were pre-abortion laboratory findings suggestive of a congenital anomaly that might necessitate further evaluation.

There were no maternal deaths during the conduct of Trial DR-PGN-302. There were 2 neonatal deaths, 1 in each treatment group.

In Study DR-PGN-302, a total of 155 subjects [83 of the 647 (12.8%) subjects randomized to the progesterone vaginal ring and 72 of 650 (11.1%) subjects randomized to Crinone 8%], representing 12.0% (155 of 1297) of subjects in the safety cohort, reported serious adverse events (SAEs). These 155 subjects reported a total of 162 SAEs. One hundred forty four [144 (89%)] SAEs were related to pregnancy and 18 SAEs (11%) were not pregnancy related. Table 12 presents the SAEs in Study DR-PGN-302.

Table 12. Incidence of Serious Adverse Events in Study Dr-PGN-302

MedDRA System Organ Class and Preferred Term	DR-2011 (N=647)		Crinone® (N=650)		Total (N=1297)	
	N	%	N	%	N	%
All SAEs	83	12.83	72	11.08	155	11.95
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS						
Total Disorders	76	11.75	63	9.69	139	10.72
INTRA-UTERINE DEATH	23	3.55	16	2.46	39	3.01
ABORTION MISSED	18	2.78	14	2.15	32	2.47
BLIGHTED OVUM	16	2.47	17	2.62	33	2.54
ABORTION SPONTANEOUS	8	1.24	9	1.38	17	1.31
ECTOPIC PREGNANCY	6	0.93	7	1.08	13	1.00
HYPEREMESIS GRAVIDARUM	4	0.62	1	0.15	5	0.39
CERVICAL INCOMPETENCE	1	0.15	0	0.00	1	0.08
RETAINED PRODUCTS OF CONCEPTION	1	0.15	0	0.00	1	0.08
RUPTURED ECTOPIC PREGNANCY	1	0.15	0	0.00	1	0.08
HETEROTOPIC PREGNANCY	0	0.00	1	0.15	1	0.08
REPRODUCTIVE SYSTEM AND BREAST DISORDERS						
Total Disorders	5	0.77	7	1.08	12	0.93
OVARIAN HYPERSTIMULATION SYNDROME	4	0.62	7	1.08	11	0.85
OVARIAN CYST	1	0.15	0	0.00	1	0.08
CONGENITAL, FAMILIAL AND GENETIC DISORDERS						
Total Disorders	1	0.15	4	0.62	5	0.39
FOETAL CHROMOSOME ABNORMALITY	1	0.15	2	0.31	3	0.23
CONGENITAL ANOMALY IN OFFSPRING	0	0.00	2	0.31	2	0.15
GASTROINTESTINAL DISORDERS						
INTRA-ABDOMINAL HAEMORRHAGE	1	0.15	0	0.00	1	0.08
METABOLISM AND NUTRITION DISORDERS						
DEHYDRATION	1	0.15	0	0.00	1	0.08
RENAL AND URINARY DISORDERS						
BLADDER PERFORATION	1	0.15	0	0.00	1	0.08
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
PLEURAL EFFUSION	1	0.15	0	0.00	1	0.08
INFECTIONS AND INFESTATIONS						
PELVIC INFLAMMATORY DISEASE	0	0.00	1	0.15	1	0.08
NERVOUS SYSTEM DISORDERS						
SYNCOPE	0	0.00	1	0.15	1	0.08

Sources: NDA Study DR-PGN-302 Clinical Report, Table 53, p110; Medical Officer Review Table 36

Of the 18 SAEs that were unrelated to pregnancy, 11 (6.8%) were related to OHSS [4 of 83 subjects (2.5%) with SAEs in the DR-2011 treatment group and 7 of 72 subjects (4.3%) with SAEs in the Crinone 8% treatment group]. 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. The subjects who constituted the 11 cases of SAEs secondary to OHSS were all hospitalized and recovered.

Intrauterine death, missed abortion and blighted ovum accounted for the majority of the 144-SAEs related to pregnancy. The Sponsor lists spontaneous abortion as 1.24% in the progesterone vaginal ring arm and 1.38% in the Crinone arm. The rates in both arms appear low. However, when considering all of the capture terms indicating early pregnancy loss the rate is 6.5% in the progesterone vaginal ring arm and 6.1%. These rates are comparable and in the range of usual expectation for IVF trials. However, this data does not inform regarding the ability to maintain early pregnancy in the older age subject. It is known that the rate of early pregnancy loss (typically losses occurring prior to Week 12 of pregnancy) increases with increased maternal age. This is mostly attributed to chromosomal abnormalities, but as the indication represents, early pregnancy loss can also result from inadequate progesterone production from the corpus luteum (or in the case of pregnancy's resulting from ART, inadequate exogenous progesterone support) before the placental production is fully achieved. Even though the study was not powered to look at differences in early pregnancy losses, this reviewer asked the primary statistical reviewer 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. Table 13 presents the results of these analyses. Similar analyses were performed by the Sponsor and can be found in the clinical report for Study DR-PGN-302, Table 28, page 85

Table 13. Rate of Early Pregnancy Loss by Age: MITT Population

Age	DR-2011		Crinone		Treatment Diff. (95% C.I.) (DR-2011 – Crinone)
	n/N	Percent	n/N	Percent	
18-34	28/558	5.0%	30/560	5.4%	-0.3% (-2.9%, 2.3%)
35-42	8/88	9.1%	8/91	8.8%	0.3% (-8.1%, 8.7%)
All	36/646	5.6%	38/651	5.8%	-0.3% (-2.8%, 2.3%)
<i>Sources: Prepared by the Statistical Reviewer at the request of the CDTL</i>					

Reviewer's comment: *Though the study was not prospectively powered for these analyses, the early pregnancy losses appear similar in both treatment groups across the 18-34 age subgroup (there are large numbers of subjects in both treatment groups). The rates were also similar for both treatments across the 35-42 age subgroup, although the numbers in this age subgroup are small. Besides lack of power (particularly for the 35-42 age group), interpretation of these results are also tempered by the fact that the Agency didn't verify early pregnancy losses by an independent evaluation of pregnancy cases.*

The common adverse events and treatment emergent adverse events profiles did not raise unexpected safety concerns. The most common treatment-emergent AEs reported during the treatment period were nausea, headache, abdominal pain, post-procedural discomfort, abdominal distension, back pain, fatigue, and constipation, all with a frequency of 10% or greater.

9. Advisory Committee Meeting

This section is not applicable to this review. No issues directly related to the review of data on urofollitropin, for injection purified were taken before an Advisory Committee.

10. Pediatrics

The Division will recommend a full waiver of the pediatric requirement for studies in children because such studies are not possible or are highly impractical because the condition of infertility does not exist in children. PeRC will consider the waiver during a subsequent review cycle.

11. Other Relevant Regulatory Issues

The Division of Scientific Investigations (DSI) conducted audits in 3 clinical sites in the US. The sites and findings are as follows:

Site 1: Dr. Schnell

Assessment of data integrity: The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.
NAI

Site 2: Dr. Foulk

Assessment of data integrity: Inspection noted omission of some dated and signatures from various data logs and some revisions to records without accompanying signatures and dates. A Form FDA 483 for minor deviations was issued.

Though minor deficiencies in documentation of drug accountability were noted, there appears to be no indication that data reliability was adversely affected by the omission of the signatures and dates. The study appears to have been conducted adequately, and the data appear acceptable in support of the respective indication.

Site 3: Dr. Shamma

Assessment of data integrity: Inspection noted that nine treated subjects had not signed the most recent revision of the consent form that noted the risk of toxic shock syndrome as a result of use of the investigational product. Other citations were failure to report concomitant medication that had been received and an error in documentation of dispensed and returned kits than actually received. The apparent dispensation and/or return of three kits of the comparator drug in excess of that actually received appears to be a matter of drug reconciliation rather than subjects not receiving the test article per protocol requirements. A Form FDA 483 for minor deviations was issued.

Although regulatory violations were noted, they are unlikely to affect data integrity in a substantive manner. The study appears to have been conducted adequately, and the data appear acceptable in support of the respective indication.

The Medical Officer determined that the Sponsor disclosed financial arrangements with clinical investigators were consistent with the recommendation by the Agency in the FDA Guidance for Industry on Financial Disclosure by Clinical Investigators. No clinical investigator disclosed any "proprietary interest in this product or a significant equity in the Sponsor as defined in 21 CFR 54.2(b)" and "no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

On February 04, 2011, the Division of Medication Error Prevention and Analysis (DMEPA) notified the Division that the proposed proprietary name Milprosa for NDA 201110 is acceptable after reviewing the product characteristics and safety profile. There were no "look alike" or "sound alike" concerns.

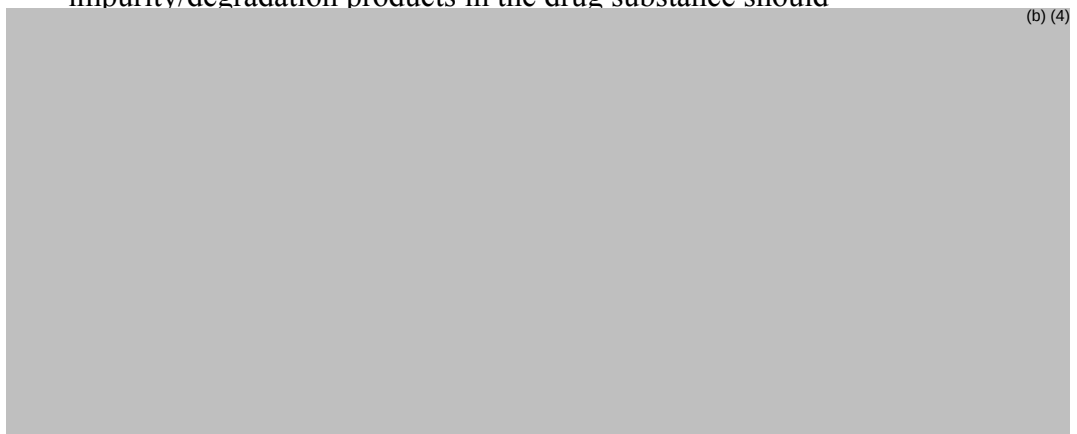
12. Labeling

Labeling negotiations were not pursued as the recommendation is to not approve. DDMAC will provide comments regarding labeling during a subsequent review cycle and requests that a new consult be issued at that time. DMEPA provided prescriber, patient, carton and container labeling comments in a report dated February, 10, 2011. Those recommendations will be addressed in a subsequent review cycle.

13. Recommendations/Risk Benefit Assessment

I am in complete concurrence with the Clinical and CMC reviewers that this application should not be approved. From a CMC standpoint, even if the Sponsor is able to satisfactorily address the Clinical/Statistical deficiencies (see below), the Sponsor will need to:

- Implement a test for particle size distribution with its acceptance criteria to the drug substance specification.
- Conduct thorough investigations to identify the root cause and propose corrective measures, and demonstrate that the root cause has been corrected by producing three production batches which show no particulates.
- Revise the “Description” of the drug product specification by adding “Free of particulates by visual inspection”.
- Revise the “Microbiological Examination” of the drug product specification by including “The absence of (b) (4).”
- With respect to the analytical method for the drug product:
 - Validate the accuracy of the HPLC test method for detection of impurity/degradation products in the drug substance should



- receive a satisfactory inspection of manufacturing facilities

In addition, the following comments should be provided to the Sponsor:

1. 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 listed in sections 5.3. Revise ARD_RPT-5064 version 2.0 accordingly.
2. Upon completion of the re-testing of stability and site transfer batches submit your final test results as a Special Report [21 CFR 314.81(b)(3)(ii)] to the NDA. In the cover letter clearly indicate what information is being provided. We note that you committed to provide these results by the end of the first quarter 2011. Alternately, you may submit the test results in the amendment which revises the specification as requested above.

According to information from the Centers for Disease Control and Prevention 2008 report on “Assisted Reproductive Technology Success Rates”, approximately 61.2 % of all ART occurs in women 35 years of age and older. From age 35 through age 42, approximately 79-94% of women use non-donor ART. Even at age 43-44, 63% of the cycles are non-donor cycles. This information clearly supports that the majority of users of gonadotropin products for controlled ovarian stimulation and progesterone products for luteal supplementation and maintenance of early pregnancy are between the ages of 35-44. Women over the age of 35 are clearly a distinct subset from their younger counterparts in that the older women have diminished

fertility secondary to diminished ovarian reserve. It is known that controlled ovarian stimulation and luteal supplementation is less efficacious in these women and it is important to appropriately inform physicians and the women themselves (and their partners) of the effectiveness and safety (including appropriate dosing and dosing regimens) of these products for them and not rely on extrapolation of information (that can not be done in an informed way) from younger women. For these reasons, DRUP's clinical team has held that efficacy of these products should be demonstrated in the older age group which for purposes of study is usually truncated at age 42. On no less than 7 separate occasions during the drug development process, the Division indicate to the Sponsor that the primary study (s) should be powered to adequately evaluate efficacy in the age subgroup of 35-42 years of age in addition to women of age less than 35. The Sponsor failed to follow recommendations and did not adequately study women in the age subgroup 35-42 years of age. This reviewer recommended against filing this NDA because the high level limited review conducted at the time of filing demonstrated clearly that efficacy was not established in this under-powered age sub-group. Based on my reading and understanding of the July 12, 1993, "New Drug Evaluation Guidance Document: Refusal To File", one of the criteria for refuse to file is: (3) "omission of critical data, information or analyses need to evaluate effectiveness and safety or provide adequate direction for use, for example:

- a. omission, without explanation, of animal carcinogenicity studies for a chronically administered drug;
- b. omission, without explanation, of animal reproduction studies for drugs that will be administered to people of reproductive age;
- c. total patient exposure (numbers or duration) at relevant doses that is clearly inadequate to evaluate safety;
- d. clearly inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age and racial subsets,
- e. absence of a comprehensive analyses of safety data, e.g. as recommended in the Clinical/Statistical Guideline;
- f. absence of an analysis of data supporting the proposed dose and dose interval; or
- g. absence of bioavailability/bioequivalence data comparing the product(s) proposed for marketing with the product(s) studied in clinical trials (if the to-be-marketed product is different)."

It is my opinion that a "refuse-to-file" action would have been supportable from a clinical standpoint based on item 3d. Women age 35-42 are clearly a "subset of women (based on age) who are intended to use this product". Refer to my discussion in the previous paragraph on ART use and age.

Despite non-concurrence of the clinical team (medical officer and team leader), the application was filed. Upon full review of the application, both the clinical (see Medical Officer review dated February 25, 2011) and statistical team (see Statistical review dated February 18, 2011) have concurred that while efficacy has been demonstrated- for the sub-group of subjects age less than 35, the application provides inadequate information to evaluate the efficacy in the age 35-42 subgroup. It is also my belief that we do not have sufficient information to inform women age 35-42 of appropriate and safe dosing if the drug were to be approved for women age less than 35. Simply ignoring the former group as unfortunately was done with a previous product or saying that it should not be used (the data does not really support this), in my opinion, will not adequately help the prescriber or the patient. In short, I do not believe that

we have sufficient information to solve the issue of insufficient efficacy and safety information of women age 35-42 with labeling.

I recommend that the following clinical/statistical comments be conveyed to the Sponsor in the regulatory action letter:

“There is insufficient evidence of efficacy and safety in the age subgroup of women age 35-42 to adequately inform the labeled use of this product in these women.”

To address this deficiency, you should conduct a randomized, blinded, active-controlled clinical trial powered sufficiently to evaluate efficacy and safety in this age-group. We recommend that you conduct a non-inferiority analysis to Crinone with a non-inferiority limit of -10%. Your study should demonstrate sufficient retention of efficacy in the progesterone vaginal ring arm when compared to the Crinone arm for the age subgroup of women age 35-42. You can propose for our review and concurrence/non-concurrence comparators other than Crinone or alternative analyses.”

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

/s/

SHELLEY R SLAUGHTER
02/25/2011

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	201,110
Priority or Standard	Standard
Submit Date(s)	4/30/2010
Received Date(s)	4/30/2010
PDUFA Goal Date	2/28/2011
Division / Office	Division of Reproductive and Urologic Products (DRUP)/Office of Drug Evaluation III (ODE III)
Reviewer Name(s)	Christos Mastroyannis, MD
Review Completion Date	12/1/2010
Proposed Established Name	Progesterone vaginal ring (Progesterone, USP), (b) (4)
(Proposed) Trade Name	Milprosa (progesterone, USP) Vaginal Ring
Therapeutic Class	Progesterone
Applicant	TEVA Women's Health R&D
Formulation(s)	(b) (4) progesterone in a non-biodegradable, (b) (4) vaginal ring
Dosing Regimen	One vaginal ring inserted vaginally starting the day after oocyte retrieval. The vaginal ring is replaced weekly, continuing for up to 10 weeks total duration
Dosage Form	The progesterone vaginal ring is a white to off-white, flexible, non-biodegradable, (b) (4) vaginal ring (cross-sectional diameter of (b) (4) mm and an outer diameter of 55 mm) containing approximately 1.8 grams of progesterone USP and a mixture of (b) (4) silicon elastomer (b) (4) and light mineral oil. Progesterone USP is present in (b) (4) % w/w concentration dispersed evenly within the ring.
Indication(s)	To support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteum function as part of an Assisted Reproductive Technology (ART) treatment for infertile women
Intended Population(s)	Infertile women undergoing ART

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends that the NDA not receive approval.
The rationale for the clinical recommendation is described below.

The primary efficacy and safety information is derived from the US Study DR-PGN-302, a randomized, investigator (single) blind, active controlled, multicenter (twenty two (22) centers in the US) study. The Applicant submitted this study with the intent to evaluate the clinical pregnancy rate using progesterone supplementation with DR-2011 (progesterone vaginal ring) compared to Crinone® 8% (progesterone vaginal gel) at two time points following egg retrieval:

- 8 weeks of pregnancy (6 weeks after egg retrieval) and
- 12 weeks of pregnancy (10 weeks after egg retrieval).

The Agency and the Sponsor prospectively agreed upon a non-inferiority (NI) margin [lower bound of the two-sided 95% confidence interval (CI) or one-sided 97.5% CI of the difference of Milprosa vs. Crinone® 8%] of -10%.

Despite the fact that facilitation of pregnancy through controlled ovarian stimulation (COS) and luteal phase/early pregnancy support is less successful in women ≥ 35 years, these women comprise approximately 60% of women treated with these agents as part of ART (mainly IVF) procedures. Taking this into account, the Division recommends that studies intended to demonstrate efficacy of gonadotropins products for COS and progesterone products for luteal phase/early pregnancy support be stratified and powered by the age sub-groups of women < 35 years of age and women ≥ 35 years. The analyses of the Milprosa vs. Crinone data in Study DR-PGN-302 for women < 35 years yielded a lower bound of the 95% C.I. of the difference at 6 weeks post embryo transfer of -4.6% and at 10 weeks of -3.7%. The values at both 6 and 10 weeks post embryo transfer are within the predefined NI margin of -10%. In women ≥ 35 years, the lower bound of the 95% C.I. of the difference between Milprosa vs. Crinone was found to be -16.4% at 6 weeks and -18.5% at 10 weeks and thus did not demonstrate non-inferiority as assessed by the pre-defined and agreed upon NI margin of -10%. Study DR-PGN-302 was not sufficiently powered to allow demonstration of efficacy in this older age group

Given that the indication is luteal support and maintenance of early pregnancy, the efficacy is in a sense a safety endpoint. Failure to demonstrate that Milprosa was no worse than Crinone in sustaining the luteal phase and early pregnancy is concerning for the safe use of this product for the intended purpose in this older population of women. This aside, other safety parameters evaluated in Study DR-PGN-302 did not reveal any concerning signals.

Given that the data does not support efficacy for an important subgroup, women age 35-42 years of age (comprising 60% of the intended population to be treated), this reviewer recommends that the NDA not receive approval until efficacy is demonstrated for this age group. I recommend

that the Applicant conducts in the US, a trial to demonstrate efficacy and safety in this older age population. There is no need to provide additional data in the age sub-group of women less than age 35.

1.2 Risk Benefit Assessment

The risk benefit assessment is found to be not favorable as efficacy was not established in a major population group which consists 60% of the intended to be treated population. There were no new or concerning safety signals demonstrated in the studies reviewed for safety.

1.3 Recommendations for Post-market Risk Evaluation and Mitigation Strategies

No post marketing risk evaluation and mitigation strategies are recommended for the progesterone vaginal ring at this time

1.4 Recommendations for Post-market Requirements and Commitments

For internal business reasons, the Applicant failed to comply with the Division's recommendation to study women in both age groups of <35 years of age and 35-42 years of age. In the single primary efficacy study, the age group of women 35 to 42 years of age was significantly underpowered. The Applicant has proposed to perform a study in women 35 to 42 years of age as a post-marketing commitment (PMC). This reviewer recommends that efficacy data for women age 35-42 be obtained prior to approval of Milprosa for any age group. If this recommendation is not followed and the NDA receives approval, a condition of approval should be a post-marketing commitment to conduct a Phase 4 randomized active-controlled non-inferiority comparator clinical study in women age 35-42. This clinical study is needed to establish efficacy, the appropriate dosing regimen, and safety in these women. Details of the study should be discussed with the Division and agreed upon before the study is initiated.

2 Introduction and Regulatory Background

2.1 Product Information

The progesterone vaginal ring, the subject of this NDA application, contains the active drug substance (b) (4) progesterone. The progesterone drug substance complies with the USP/EP compendia. Progesterone is a DESI product with no IND.

Barr Laboratories initiated a development program for a Progesterone Vaginal Ring ((b) (4) %w/w) in 2003 at Barr's Research and Development facility in Plainsboro, NJ. The clinical batches were produced at Barr's Plainsboro, NJ (Phase 2) and Northvale, NJ (Phase 3) R & D facilities. For the future commercial product, the manufacturing process was transferred to Barr's

Cincinnati, Ohio, cGMP commercial facility. Progesterone Vaginal Ring is manufactured

(b) (4)

As per the CMC reviewer, this NDA has **not** provided sufficient information to assure the identity, strength, purity, and quality of the drug product. Quality control for the drug substance and drug product is not deemed adequate because; 1) the controls for particle sizes of the drug substance have not been established; 2) the accuracy of the HPLC analytical method for drug substance has not been validated.

The Office of Compliance has made an overall “WITHHOLD” recommendation for the manufacturing facilities as they are provided in this NDA because of the presence of foreign particulate matter found in the vaginal ring (VR) and its removal has not been satisfactorily demonstrated (see the List of Deficiencies on p.111 of CMC Report). During PAI inspection, foreign particulate contaminations were found for all 5 site transfer batches at the intended commercial site. (b) (4) foreign matters have been identified, but not quantified. Based on the preliminary report, it seems to indicate that the drug product rings were not manufactured with adequate controls in the process, equipments, and environment. Investigations of the root cause for the contaminations have been conducted and it has been concluded that the contamination (b) (4)

Corrective measures have been proposed that foreign particulates will be controlled (b) (4)

. The applicant will have to submit test results from three new registration batches manufactured with the improved equipments and material controls prior to approval.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are two progesterone products currently approved for luteal phase supplementation as part of an Assisted Reproductive Technology (ART) treatment for infertile women, Endometrin® and Crinone® 8%. Progesterone IM is used off label. See Table 1.

Table 1: Available drugs 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 for infertile women

Drug Name	Active Ingredients	Strength	Dosage Form/Route	Company	Approval Date
Endometrin NDA 22057	Micronized Progesterone	100 mg	Twice or three times daily Vaginal Insert	Ferring Pharmaceuticals, Inc	June 21, 2007
Crinone NDA 20756	Micronized Progesterone	90 mg (Crinone 8%)	Once daily Vaginal Gel	Columbia research Laboratories, Inc	May 13, 1997

Clinical Review
{Insert Reviewer Name}
{Insert Application Type and Number}
{Insert Product Trade and Generic Name}

Progesterone NDA 017362 (Off label use)	Progesterone	50mg	Once daily Intramuscular (IM)	Watson labs	May 11, 1978

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient progesterone is contained in two approved drug products for the support of 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:

- 1) Crinone® 8% Vaginal Gel administered once daily for 10 weeks, and
- 2) Endometrin® Vaginal Insert administered two or three times daily for 10 weeks.

Progesterone is also the active component in a progesterone in oil product administered intramuscularly (used off label for luteal support) and the oral (b) (4) progesterone product Prometrium (which historically was compounded into a vaginal product and used off-label).

2.4 Important Safety Issues with Consideration to Related Drugs

The most concerning serious adverse events associated with progesterone therapy can be grouped into two areas: 1) adverse events resulting from the pharmacologic action of the drug (including severe allergic reactions), and/or 2) adverse events resulting from the presence of the gel, capsule, or ring in the vagina (resulting in vaginal irritation and discomfort) or vaginal inflammation from excipients in the drug product (such as the effervescence found with Endometrin®). These two serious adverse event groups could potentially result in premature termination of treatment, and consequently, adversely affect clinical pregnancy outcome. Anaphylaxis, anaphylactoid reactions, and the discontinuation rate resulting from allergic reactions are the most concerning pharmacologic adverse events associated with progesterone use.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In 2003, Duramed (a subsidiary of Barr Laboratories) initiated a development program for a progesterone vaginal ring. Duramed opened IND 70,875 on October 7, 2004 for a progesterone vaginal ring containing (b) (4) grams of progesterone, releasing (b) (4) mg of progesterone per day with weekly vaginal insertion. The proposed indication was progesterone supplementation of the corpus luteum for women undergoing embryo transfer as part of an in vitro fertilization procedure. Duramed proposed to support drug development with 5 studies (see Table 2).

Table 2: Proposed studies for the drug development of the progesterone vaginal ring

A. Phase I Pharmacokinetic Study	To determine the single dose pharmacokinetic profile of the progesterone vaginal ring

B. Phase II Feasibility Study (DR PGN-201):	To determine the efficacy of the progesterone vaginal ring administered in clinically agonadal women
C. Phase II Feasibility Study (DR PGN-202)	To determine the efficacy of the progesterone vaginal ring in women undergoing oocyte donation who previously demonstrated endometrial transformation in Study DR-PGN-201
D. Phase III Oocyte Donation Study:	To determine the efficacy of the progesterone vaginal ring in clinically agonadal women undergoing oocyte donation
E. Phase III Luteal Supplementation Study (DR-PGN-302)	To determine the efficacy of the progesterone vaginal ring in women undergoing embryo transfer as part of an IVF procedure.

Source: Communications between the Applicant and FDA

DRUP has been actively involved with the Sponsor and has on numerous occasions offered comments and recommendations during the development of this progesterone vaginal ring product. Interactions are summarized as follows:

December 7, 2004

Advice letter:

1. “We recommend that in Phase 1 you choose progesterone doses that reach pre-determined optimal progesterone levels for desired effect in Phase 2 and 3.
2. You have not adequately justified the reason for the dose selected in the clinical studies. Therefore, we recommend that you consider whether adequate dose ranging has been evaluated in Phase 1.
3.  (b) (4)
4. The Division recommends the primary endpoint be clinical pregnancy and be defined by the presence of a gestational sac and fetal heartbeat beginning six weeks or greater after embryo transfer
5. We recommend that randomization and analyses be stratified and powered by ovarian reserve as measured by Day 3 serum FSH and age of female partner. We further recommend a sub-stratification of data based on BMI, the type of insemination occurring [i.e. conventional IVF vs. intracytoplasmic sperm injection (ICSI)] and infertility diagnosis. Studies should be appropriately powered to accommodate stratification. The analysis of data relative to sub-stratification groups can be descriptive.
6. We recommend that you include patients for ART up to age 42.”

March 7, 2007

Advice letter:

1. “We continue to have concerns that your proposed single dose of (b) (4) mg progesterone/day for the progesterone vaginal ring is not well justified and may not be sufficient. We recommend that you evaluate at least 2 dose levels of progesterone.

2. (b) (4)

June 13, 2007

End-of-Phase 2 meeting:

The progesterone vaginal ring (henceforth to be referred to as DR-2011 in this review) discussed in 2007 was a progesterone-containing silicone ring drug delivery system that had an average *in vitro* release rate of (b) (4) over 5-7 days. The *in vivo* release rate was estimated to be (b) (4) (from initial proposal of (b) (4) mg/day) when vaginally inserted for 7 days. The Applicant proposed Study DR-PGN-301 for luteal phase replacement for oocyte donation; and Study DR-PGN-302 for luteal phase supplementation in IVF. Meeting minutes state:

1. The agency reiterated that Duramed had not provided sufficient dose finding evidence to proceed into Phase 3. “The results of study DR-PGN-201 appear to indicate that the decreased secretory transformation and the low serum progesterone levels seen, point towards inadequate progesterone delivery of the vaginal ring.” The Applicant contended that “its product provides the maximum amount at a consistent reliable dosing compared to the approved products. In addition, the Applicant believes that there will be success with this product based on clinical outcomes in the Phase 2 studies”, while the agency responded that “the Applicant may proceed to Phase 3 at their own risk.”
2. “The recommended indications will be for: 1. Pregnancy by progesterone supplementation as part of an Assisted Reproductive Technology (ART) treatment for infertile women. (b) (4)
The exact wording will be discussed at the time of labeling negotiations.”
3. Initial comments on Study DR-PGN-302 are listed below:
Study Design Issues:
 - a. “We recommend double-blinding or at a minimum investigator and ultrasonographer should be blinded.”
 - b. The primary efficacy analysis should be based on a two-sided 95% confidence interval. A lower non-inferiority (NI) limit of (b) (4) % (as it was proposed by the Applicant) is not acceptable for the progesterone vaginal ring. The non-inferiority limit for the phase 3 study should be defined as equal to or greater

than -10% of a two-sided 95% confidence interval when compared to an active progesterone comparator. You should report the percentages of the difference of the lower limit of the 95% confidence intervals to the first decimal point. We also remind you that the live-birth per transfer rate in the 2004 CDC clinical pregnancy rate per cycle using fresh embryos is 33% and your study should demonstrate that your product will be comparable to this standard.

- c. The primary efficacy analysis should include all subjects who completed oocyte retrieval and have received at least one dose of progesterone (m-ITT cohort).
 - d. **Randomization and analyses** should be **stratified** and **powered** by ovarian reserve as measured by Day 3 serum FSH **and age** of female partner (**< 35 years of age, and 35-42 years of age**). The Division feels strongly that this information is critical in order to appropriately advise the physician who treats and the patient who falls in the age group greater than 35 years (up to 60% of the ART population for luteal supplementation). The Division further recommends a sub-stratification of data based on BMI, the type of insemination occurring [i.e. conventional IVF vs. intracytoplasmic sperm injection (ICSI)] and infertility diagnosis. The analysis of data relative to sub-stratification groups can be descriptive. Studies should be powered to demonstrate differences in these (sub-stratification) groups only if specific claims regarding these are sought.
 - e. The Division recommends that ovarian reserve (serum FSH) be measured in a central laboratory. The entry criteria should include evaluation of a serum FSH level on Days 2, 3, or 4. Subjects with a serum FSH of 15 IU/L or greater obtained on cycle Day 2, 3 or 4 should be excluded.
 - f. The Division recommends that if you choose to perform one study for this indication, either all of the sites or a majority of subjects be treated at US sites, as practices of ART are significantly different in non-North American countries.
 - g. We remind you that these are not all the comments on the study design, and would recommend that the completed protocols be submitted for review.
4. Claims for QOL would only be acceptable based on development of a validated instrument. The Applicant should refer to the guidance entitled, *“Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.”*

October 29, 2007

Request for a Special Protocol Assessment.

December 13, 2007

DRUP’s comments on SPA:

1. “We recommend that the proposed indication for the vaginal ring be: Progesterone vaginal ring is a progesterone-containing device and is indicated to support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteum function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women.

2. [REDACTED] (b) (4)
3. If you choose to perform only one study for this indication, the majority of subjects treated should be from the US or Canada, as practices of ART are significantly different in North American countries compared to non-North American countries.
4. We continue to have concerns that your proposed single dose of 14 mg/day [REDACTED] (b) (4) [REDACTED] for the progesterone vaginal ring is not well supported. If you proceed with this single dose, you do so at your own risk of failure to demonstrate efficacy for this product.
5. As your randomization is planned after oocyte retrieval, the pregnancy rate will be calculated per retrieval and not per cycle. This will be clearly delineated in labeling.
6. There may be significant differences in pregnancy rates when comparing subjects who have received embryo transfer on Day 3 compared to Day 5. This may complicate the findings. We recommend using only Day 3 transfer for this study to eliminate this variability.
7. We have the following efficacy and statistical recommendations:
- Assess the co-primary endpoints of viable pregnancy (with documented fetal heartbeat) at both six weeks and ten weeks post-embryo transfer. The analysis should be a non-inferiority comparison to Crinone®, which excludes a difference of greater than -10% in favor of Crinone®.
 - Randomization and the primary analyses should be **stratified and powered** by ovarian reserve as measured by Day 3 serum FSH and **age of female subjects (age < 35 years and age ≥ 35 to 42 years)**.
 - Provide a descriptive sub-stratification of data based on Body Mass Index (BMI), the type of insemination occurring [i.e. conventional IVF vs. intracytoplasmic sperm injection (ICSI)] and infertility diagnosis. We recommend that only Day 3 embryo transfer be used. However, if both Day 3 and Day 5 transfers are retained, you should also sub-stratify based on the two transfer dates. Studies should be powered to demonstrate differences in these (sub-stratification) groups only if claims regarding these specific sub-groups are sought.
 - Provide a secondary analysis of the efficacy of progesterone that includes the clinical pregnancy rate in all subjects who initiated ovarian stimulation using gonadotropins prior to progesterone therapy (a per cycle analysis).
 - Report the percentages of the difference between the confidence intervals to the first decimal point.
 - We consider results of the “Treatment Satisfaction Measure” questionnaire as exploratory and therefore not acceptable for the purposes of labeling.
 - Standardize the classification (grading) of ovarian hyperstimulation syndrome (OHSS) as an adverse event to allow standardization of reporting across sites.

- h. Classify subjects who receive paracentesis as a result of OHSS as having severe OHSS.
- i. For labeling purposes, calculate the rate of birth defects in this study as per live-birth for each treatment group and not per cycle.
- j. Use a single preferred term for all subjects with vulvovaginal candidiasis when reporting adverse events.”

December 13, 2007

Duramed proposes to:

- “Enroll subjects aged 18-42 and to stratify by age groups < 35 and 35-42. The study will be powered to show non-inferiority compared to Crinone® for subjects aged 35-42 years. “The Applicant acknowledges that this specific population is of interest to the Agency based on previous FDA minutes from the June 13, 2007 meeting. Evaluation of this population would provide currently unavailable, critically important clinical information for the treating physician, as this is the group with lower pregnancy rates in which efficacy has not been firmly established for the recently approved Endometrin® product.
- Carry out two separate efficacy analyses, one of the older age group (35-42 years) and one of the entire study population. Descriptive data summaries will be provided for subjects with FSH levels < 10 IU/L and 10-15 IU/L.”

January 11, 2008

DRUP comments:

1. “We recommend that the study be stratified and powered based on the two subgroups ages 18-34 and ages 35- 42 and that the primary efficacy analyses be based on these two groups (18-34 and 35-42). We also recommend that you perform a secondary sub-group analysis of subjects with a serum FSH < 10 IU/L and those with an FSH 10-15 IU/L.
2. We do not agree with the addition of an eligibility criterion to eliminate subjects ≥ 35 of age who has less than 2 eggs retrieved. The eligibility criterion for subjects ≥ 35 years should be the same as subjects younger than age 35. Women who have no eggs retrieved should not be eligible to participate.”

August 27, 2008

DRUP comments :

1. “We do not agree that a study powered only to demonstrate efficacy in the population of women less than 35 years of age will be adequate for an indication 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. The proposed study will not adequately address efficacy and safety in the population of women 35 years of age or greater. Such women represent approximately 50% of women undergoing ART procedures and would be expected to constitute approximately 50% of the potential users of the progesterone vaginal ring. Therefore, it is not acceptable if the

sample size for the subgroup of older women is underpowered for assessing the efficacy of the progesterone vaginal ring. The Division is open to further discussion regarding the powering of Study DR-PGN-302 that would allow for informative labeling for both age subgroups.”

2. PK data obtained from Study 10716222 would be used for general evidence of bioavailability and not to infer efficacy or safety of DR-2011 in the target population.

March 3, 2009

Advice letter:

“Study DR-PGN-302, with only 200 subjects in the age range of 35-42 years old, is inadequately powered to assess efficacy in this population. We continue to strongly recommend that randomization and the primary analyses be stratified and powered in terms of ovarian reserve as assessed by the age of the subject (subjects < 35 years old and subjects 35 to 42 years old).”

June 16, 2009,

Pre-NDA

1. “We remind you of our recommendations made on multiple occasions during your drug development program (beginning with the June 13, 2007 end of Phase 2 Type B meeting and continuing into 2009) that your Phase 3 study be stratified and powered to demonstrate efficacy in each of the age groups represented by women less than 35 years of age and women 35-42 years of age.
2. The Division continues to have concern that the formulation of the DR-2011- progesterone vaginal ring (release rate of 14 mg/day of progesterone) provides insufficient progesterone for supplementation of corpus luteum function and maintenance of early pregnancy. The issue of whether or not the progesterone vaginal ring provides sufficient supplementation is a review issue not only for efficacy, but for the safety (spontaneous abortion rate) of this product as well.
3. Provide an additional safety table of all subjects who had a reported event of ovarian hyperstimulation syndrome (OHSS), categorized by severity (mild, moderate and severe) using standardized categorization criteria. In addition, provide the definitions used to classify OHSS.
4. The progesterone vaginal ring (DR-2011) was initially stated to release ^(b)₍₄₎ mg/day. It was subsequently changed to ^(b)₍₄₎ 14 mg/day. It is not clear how the release rates were calculated. It is also not clear why the stated release rate was changed twice without a reported change in formulation composition. The NDA should address these 2 comments. Release rate calculation should be based on the residual amount of progesterone remaining in DR-2011 following vaginal placement of the ring for 7 days.”

The Applicant emphasized that the vaginal ring design has accommodated the maximum amount of progesterone possible and the release rate is at the maximum.

The Applicant also acknowledged the Division's recommendation to power the pivotal study(s) to demonstrate efficacy in women < 35 years old and women ≥ 35 to 42 years old. The Applicant clarified, however, that because of some "internal constraints", they had made the choice to power their study only for women less than age 35. The Applicant also noted an approved product whose primary study was powered only for subjects < 35 years of age.

The Division relayed that it was not in a position to advise the Applicant as to whether or not an application with the above noted studies would be fileable; that determination would depend on the results of the Division's review at the time of submission. However, the Division again noted its concern regarding the very limited information on women in the older population.

The Applicant indicated that it would internally consider conducting a separate study in women age ≥ 35-42.

April 30, 2010

TEVA WOMENS HEALTH INC submitted the NDA 201-110 for review.

Submitted Studies:

PK studies:

Phase1

Protocol 10716222: Single dose and steady-state plasma PK in post-menopausal volunteers.

Study DR-201-102: Tissue and serum PK in healthy premenopausal women.

Phase2

Serum PK data using multiple doses were evaluated in Phase 2 and Phase 3 clinical trials:

DR-PGN-201 (Phase 2): Endometrial transformation assessment

DR-PGN-202 (Phase 2)

Protocol 10936035: Because of change in manufacturing site, the sponsor conducted a bioequivalence trial (BE) to bridge the formulation used in phase 3 and those proposed for commercial use.

Phase 3

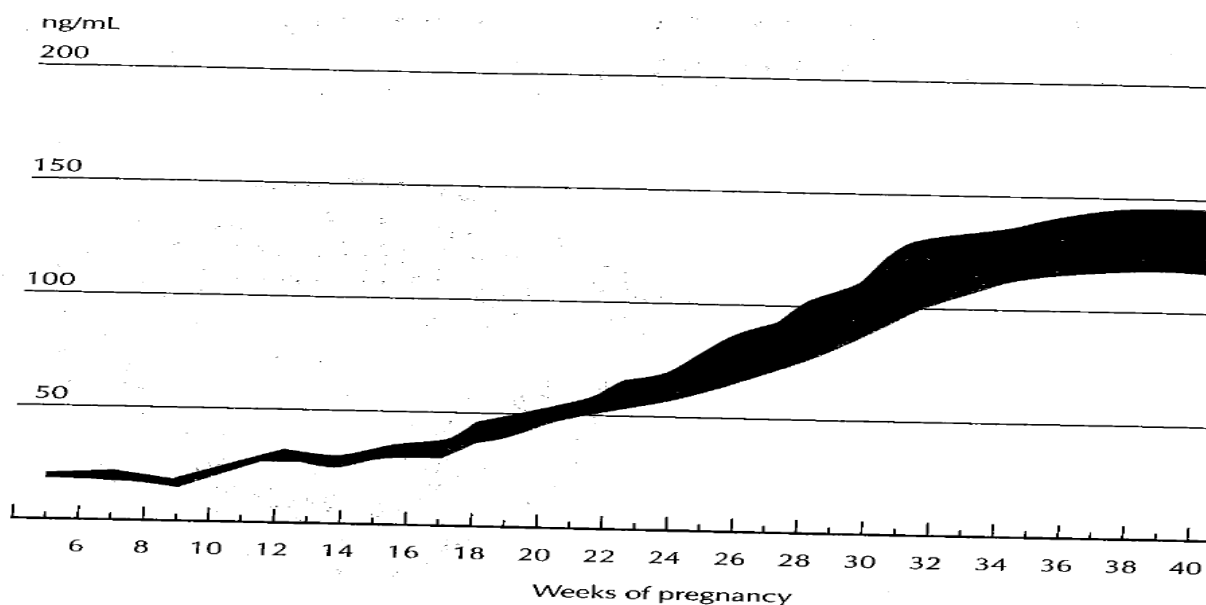
DR-PGN-302 (Phase 3): Study DR-PGN-302 is a Phase 3, randomized, single (assessor)-blind, parallel active-controlled trial that compared DR-2011 to a progesterone vaginal gel for luteal phase supplementation following In Vitro Fertilization. The primary endpoint is clinical pregnancy rate at 8 weeks of pregnancy (6 weeks after egg retrieval) and 12 weeks of pregnancy (10 weeks after egg retrieval)

2.6 Other Relevant Background Information

Until approximately the tenth week of gestation, the pregnancy is dependent on the presence of progesterone largely produced by the corpus luteum. Exogenous support for an early pregnancy (during the first 10 weeks) requires 100 mg of progesterone daily in addition to a maternal circulating level of approximately 10 ng/mL. Despite this requirement, patients pregnant after ovarian stimulation with one of the techniques of Assisted Reproductive Technology (ART) have had a successful pregnancy after experiencing extremely low progesterone levels. (Csapo et. al, Sultan et. al) Thus, individual variation is great, and very low circulating levels of progesterone can be encountered occasionally in women who experience normal pregnancies. Therefore, the predictive value, of progesterone measurements is limited (Speroff L and Fritz MA.)

Csapo AL, Pulkkinen MO, Wiest WG: Effects of luteectomy and progesterone replacement in early pregnancy patients, *Am J Obstet Gynecol* 115:759, 1973
Sultan KM, Davis OK, Liu H-C, Rosenwaks Z: Viable term pregnancy despite “subluteal” serum progesterone levels in the first trimester, *Fertil Steril* 60:363, 1993
Speroff L and Fritz MA: *Clinical Endocrinology and Infertility*, Seventh Edition, Lippincott Williams and Wilkins, Philadelphia, Baltimore etc, 2005, 260

Figure 1: Maternal Progesterone



Source: Adapted from: Speroff L and Fritz MA: *Clinical Endocrinology and Infertility*, Seventh Edition, Lippincott Williams and Wilkins, Philadelphia, Baltimore etc, 2005, p260

Progesterone is important in suppressing the maternal immunologic response to fetal antigens, thereby preventing maternal rejection of the trophoblast. Progesterone prepares and maintains the endometrium to allow implantation. The human corpus luteum makes significant amounts of estradiol and progesterone, but it is progesterone and not estradiol that is required for successful implantation (Rothchild.)

Rothchild I, Role of progesterone in initiating and maintaining pregnancy In Bardin CW, Milgrom E, Mauvais-Jarvis P, eds Progesterone and Progestins, Raven Press, New York, 1983, 219-229).

Recognition of the therapeutic potential of progesterone began in the 1930's with the extraction and purification of progesterone. The class of drugs "Progestogens" (which includes progesterone) was declared effective in the Federal Register Notice of October 10, 1973 for amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology. NDAs were submitted for progesterone injection to comply with a Federal Register publication of September 9, 1971 and to provide control data only. A memorandum dated June 20, 1972 from the Division of Metabolic and Endocrine Drug Products, determined that "preclinical and clinical trials are not necessary for progesterone injectables (as specified in the U.S.P monograph) for the two effective indications (amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology)".

Initial reports of successful clinical pregnancies resulting from the use of progesterone for luteal support after ovarian stimulation were first reported in the 1970's. In the 1980's, off-label use of progesterone intramuscular injection for luteal support post-embryo transfer was incorporated into the treatment regimen for in vitro fertilization (IVF) in the United States. Exogenous progesterone was presumed to prepare the endometrial lining to produce a favorable histology for implantation and to sustain the pregnancy after successful implantation. Exogenous progesterone was thought to be needed for the first ten weeks of pregnancy after which progesterone is produced by the placenta.

Controlled ovarian hyperstimulation with exogenous gonadotropins generally yields multiple corpora lutea that might well be expected to sustain supra-physiologic serum concentrations of estradiol and progesterone during the luteal phase of IVF cycles. Co-treatment with GnRH analogs for prevention of premature LH surges and luteinization effectively suppresses endogenous LH secretion, as intended. Unfortunately, even though agonists and antagonist treatment ends abruptly on the day of hCG administration, residual suppression of endogenous LH is not inhibited. Abnormally low levels of LH during the luteal phase can be insufficient to stimulate and maintain the level of luteal function required to promote timely endometrial maturation in preparation for implantation or to support an early pregnancy once established. Endogenous LH secretion can remain suppressed for as long as 10 days after treatment with a long-acting GnRH agonist ends, and luteal function is frequently inadequate in amount or duration.

Although antagonists have a much shorter duration of action, they often have the same consequence. Integrated estradiol and progesterone levels are abnormally low and luteal phase duration is grossly short in GnRH antagonist treatment cycles, particularly when a GnRH agonist

rather than hCG is used to stimulate the final stages of oocyte maturation. Because there is no way to predict who may or may not require luteal support in any given cycle, some form of treatment must be provided for all (Speroff L and Fritz MA.)

Numerous clinical trials have compared clinical, ongoing, or delivered pregnancy rates or spontaneous miscarriage rates between groups receiving treatment with different luteal phase support regimens, with varying results. Progesterone has been administered orally (300-800 mg daily), vaginally as an 8% gel (90 mg daily), cream or tablet (100-600 mg daily), and by intramuscular injection (25-50 mg daily; 17a-hydroxyprogesterone, 341 mg every 3 days). Supplemental doses of hCG have generally been administered every 3 days (1,500-2,500 IU.)

The population of women who will most frequently use these products are women 35 years of age and older. The most recently published CDC ART statistics reports that approximately 60% of women seeking ART services (IVF with their own oocytes- not donor oocytes) are 35 years or older. Therefore, it is important that products used for maintenance of pregnancy demonstrate efficacy and safety in these women with borderline ovarian reserve. With the clinical outcome of pregnancy, the issue is not just one of efficacy but safety as well, because failure to maintain the pregnancy, leading to spontaneous abortion, is a safety issue.

The proposed label for the progesterone vaginal ring states that the population studied was women 20-42 years. "In subjects under the age 35, the clinical pregnancy rates for subjects treated with Milprosa were non inferior to the clinical pregnancy rates for subjects treated with the active comparator. In women age 35 and older, the results did not meet the criteria for NI, because the number of subjects treated was too small to provide useful comparison."

This reviewer recommended that this NDA application not be filed based on the July 12, 1993 New Drug Evaluation Guidance document: Refusal to file, under 21 CFR 314.101 (d) (3) paragraph 3. The guidance document specifically states a refuse to file issue as: "Omission of critical data, information or analysis needed to evaluate effectiveness and safety or provide adequate directions for use," for example item d: "Clearly inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age and racial subsets".

The application clearly did not provide adequate evaluation of safety and efficacy in the 35 years or older subset. Despite my reservations, the application was accepted for filing, however, with the following clinical comments included in the 74-day letter.

"Women 35 years of age and older now represent approximately 55% of U.S. subjects who seek ART procedures and had their own fresh embryo transfer. We recommend that studies to demonstrate efficacy of progesterone for maintenance of pregnancy in women who have received In Vitro Fertilization, be **stratified** and **powered** for subgroup analysis of subjects <35 and 35-42 years of age. Study DR-PGN-302 provides insufficient data to assess the efficacy and safety of your product in women in the age range of 35 to 42 years; this will be a significant review issue and may impact upon approvability."

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Three sites were identified for a Division of Scientific Investigations (DSI) audit of the Sponsor's data and/or analyses. The following centers were proposed for audit based on:

1. Location: TX, MI and NV,
2. Largest number of subjects enrolled,
3. Pregnancy rates which appear higher than national average pregnancy rates (TX- 60.5%, NV- 47% and MI-57%),
4. Subject discontinuations, and
5. Protocol violations:

a) Russell Foulk, NV
The Nevada Center for Reproductive Medicine
645 Sierra Rose Drive, Suite 205
Reno, NV 89511
Site # 7

b) Vicki Schnell, MD
Center for Reproductive Medicine
1015 Medical Center Boulevard, Suite 2100
Webster, TX 77598
Site # 19

c) F. Nicholas Shamma, MD
IVF Michigan
3950 South Rochester Road, Suite 2300
Rochester Hills, MI 48307

DSI Report:

“The clinical investigator sites of Drs. Foulk, Schnell, and Shamma were inspected in support of this NDA. The site of Dr. Schnell had no violation. Although regulatory violations were noted at the sites of Drs. Foulk and Shamma, the findings overall are unlikely to impact data integrity. The study appears to have been conducted adequately, and the data generated by these clinical sites appear acceptable in support of the respective indication.”

3.2 Compliance with Good Clinical Practices

The clinical portion of Studies 10936035, 10936057, and 10716222 were monitored and audited for compliance with GCP Regulations by site by:

(b) (4)

The study procedures, study drug, regulatory aspects of study conduct, from documentation, and CRF transcription were monitored for accuracy and compliance with GCP regulations by the

(b) (4)

For clinical trial DR-201-102, Duramed performed an independent audit. The audit program, together with Duramed's internal quality control procedures, provided support that trial conclusions were based on valid procedures for data management and analysis, and that the clinical trial program was carried out in accordance with GCP guidelines.

For clinical trial DR-PGN-201, G. Frederick Wilkinson, President and Chief Operating Officer, Duramed Research, Inc., Bala-Cynwyd, PA certified that this study was conducted in accordance with regulations pertaining to Good Clinical Practice (GCP) (International Conference on Harmonization: Good Clinical Practice: Consolidation Guideline, Notice of Availability, Fed. Reg. 25692, May 6, 1997) and the Declaration of Helsinki (revised Edinburgh, Scotland 2000).

For clinical trial DR-PGN-202, Kathleen Z. Reape, MD, Vice President, Clinical Operations and Medical Affairs, Duramed Research Inc, Bala Cynwyd, PA 19004, declared that this study was conducted in accordance with regulations pertaining to Good Clinical Practice (GCP).

For Clinical trial DR-PGN-302, Kathleen Z. Reape, MD, Teva Branded Pharmaceutical Products R & D, Inc. certified that this study was designed and monitored in accordance with Sponsor procedures, which comply with the ethical principles of Good Clinical Practice (GCP) as required by the United States Food and Drug Administration (FDA), and in accordance with the Declaration of Helsinki.

3.3 Financial Disclosures

Form 3454, Certification of Financial Interests and Arrangements of Clinical investigators, dated 4/23/2010 was signed by Valerie Mulligan, Senior Director, Regulatory Affairs, TEVA Women's Health, Inc and submitted with the Application. Financial Disclosure Information was obtained for the investigators (principal and sub-investigator) and all disc losable information is explained.

Reviewer's Comment: Adequate information was submitted to demonstrate compliance with financial disclosure requirements.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See Section 2.1 of this report and CMC reviewer's report.

The revised specification of drug release profile is acceptable. The stability data support the proposed expiration dating period of 24 months for progesterone vaginal ring when stored at 25°C (77°F).

Deficiencies found with this submission:

1. This NDA has **not** provided sufficient information to assure the identity, strength, purity, and quality of the drug product.
2. Progesterone vaginal rings are designed to have a diffusion controlled drug release mechanism to release progesterone in a constant manner over a period of 7 days. The particle size distribution of the drug substance may have significant impact on the dissolution profile of the drug product. Unless developmental study data demonstrate that particle size of the drug substance is not a critical attribute, (this information is not provided in P.2 section of this submission), the applicant should incorporate controls of particle size based on batch data.
3. During prior to approval inspection (PAI), foreign particulate contaminations were found on all five site transfer batches manufactured at the future commercial site. Sponsor should conduct thorough investigations to identify the root cause and propose corrective measures, and demonstrate that the root cause has been corrected by producing three production batches which show no particulates.
4. Regarding analytical method for the drug product:
 - The accuracy of the HPLC test method for detection of impurity/degradation products in the drug substance should be validated.



4.2 Clinical Microbiology

The microbiology reviewer has identified several deficiencies in the review of Milprosa. These include:

1. Need to revise the specification to include the absence of (b) (4).
2. 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 listed in sections 5.3. The sponsor needs to revise ARD_RPT-5064 version 2.0 accordingly.
3. Upon completion of the re-testing of stability and site transfer batches the sponsor should submit the final test results as a Special Report [21 CFR 314.81(b)(3)(ii)] to the NDA. “We note that you committed to provide these results by the end of the first quarter 2011. Alternately, you may submit the test results in the amendment which revises the specification as requested above.”

Recommendation: Approvable pending resolution of product quality microbiology deficiencies.

4.3 Preclinical Pharmacology/Toxicology

Implantation of vaginal inserts containing (b) (4) % progesterone had no significant adverse effects in rabbits over a 10 days observation period. Four of five rabbits had hyperplasia of the endometrium and one had hyperplasia of the cervical mucosa. One rabbit had lymphoid hyperplasia. In a 90 day study, implantation of vaginal inserts containing (b) (4) % w/w progesterone, in rabbits resulted in decreased weight of the uterus and vagina at all time points. The uterus exhibited a decidual reaction and atrophy of the endometrium/myometrium and atrophy of the vaginal epithelium. The hyperplasia of the uterus observed in the 10-day study and atrophy in the 90-day study was not explained but could be due to inserts containing different amount of progesterone or the duration of treatment. In conclusion, implantation of vaginal inserts containing (b) (4) % w/w progesterone induced uterine and vaginal changes known to be attributed to progesterone pharmacologic activity. The progesterone vaginal inserts were well tolerated.

Recommendation: The Pharmacology/Toxicology reviewer recommends approval of Milprosa. There are no non-clinical safety issues relevant to clinical use

4.4 Clinical Pharmacology

NDA 201110 is acceptable from a Clinical Pharmacology perspective. Sponsor has conducted 7 phase 1, 2 & 3 clinical trials in order to assess progesterone pharmacokinetics (PK; systemic and tissue progesterone), pharmacodynamics (PD; successful secretory transformation of the

endometrium) and efficacy (clinical pregnancy rates) with the progesterone vaginal ring formulation. In addition, bioequivalence of the clinical vs. commercial formulations (change in site of manufacturing only) and estimation of in vivo drug release have been addressed. Neither formal pharmacokinetic drug-drug interaction studies have been conducted, nor PK in presence of renal or hepatic impairment has been assessed.

4.4.1 Mechanism of Action

The luteal phase of a natural cycle is characterized by the formation of a corpus luteum, which secretes steroid hormones, including progesterone (PGN). After fertilization and implantation, the developing blastocyst secretes human chorionic gonadotropin (hCG), which maintains the corpus luteum and its secretions. Normal luteal function is essential for maintaining pregnancy and data suggest that PGN is necessary for the maintenance of early pregnancy (Penzias 2002).

For many women who undergo ART, steps must be taken to prime the uterus for implantation, and to sustain the pregnancy after implantation. There have been many tools developed to aid in this process.

In the mid 1980s, gonadotropin releasing hormone (GnRH) agonists were incorporated into ovarian stimulation regimens and are associated with improved outcomes after In Vitro Fertilization (IVF) and other assisted reproductive technologies. GnRH agonists work by suppressing the pituitary and preventing premature surges of endogenous luteinizing hormone (LH) during IVF cycles and allows time for a larger number of oocytes to reach maturity prior to harvesting as well as increasing follicular growth. However, GnRH agonists inhibit the corpora lutea in these cycles and may create an iatrogenic luteal phase defect. Use of a GnRH agonist causes suppression of pituitary LH secretion for as long as 10 days after the last dose and pituitary function may not return completely until 2-3 weeks after the end of therapy. Without this LH signal, the corpus luteum may be dysfunctional, and subsequent progesterone and estrogen secretion may be abnormal, compromising endometrial receptivity, and potentially leading to decreased implantation and pregnancy rates (Pritts 2002).

Oral, vaginal, and intramuscular (IM) forms of progesterone have been used for luteal support in IVF cycles. However, oral administration has been found to be insufficient in several studies. Oral progesterone undergoes extensive first pass hepatic metabolism, is well recognized as a highly variable drug, undergoes little accumulation, has a substantial food effect, and consequently exhibits wide variation in plasma concentrations at steady state, which probably account for its poor efficacy for ART. IM progesterone administration is not associated with the preceding issues and, though not approved for this indication, it is generally recognized to be highly efficacious for ART. However, because IM administration does not benefit from a first uterine pass effect, high plasma concentrations may be needed to ensure maintenance of adequate endometrial concentrations. Based on the extensive clinical experience with IM progesterone, a serum concentration of 10 ng/mL has become a widely accepted as a target level to ensure efficacy. This is not an inherent physiological requirement, since lower endogenous

serum concentrations have been found to be correlated with secretory transformation (Chetkowski 1997).

Vaginal administration results in comparable (and efficacious) endometrial concentrations, albeit with lower systemic exposure, because of the well-established first uterine pass effect. However, the extent to which preferential delivery to the uterus occurs depends strongly on where the drug is delivered within the vagina, because the effect has only been observed from the upper third of the vagina, but not the lower third. Thus, for dispersible dosage forms with poor bioavailability that deliver drug throughout the length of the vagina, the extent of the first uterine pass effect may be incomplete. On the other hand, such dosage forms yield efficacious endometrial concentrations with less systemic exposure than via the IM route. While both IM and vaginal routes offer higher implantation rates than the oral route (Ludwig 2001, Penzias 2002, Tavaniotou 2000), vaginal dosing is less painful and more convenient to use than IM, with various dosage forms available. Vaginal progesterone gel (Crinone®/Prochieve®) and progesterone vaginal inserts (Endometrin®) require daily dosing like IM administration, and may be untidy to use, due to leakage.

Drug distribution of vaginally administered progesterone is influenced by what has been termed the “first uterine pass effect”, which amounts to preferential delivery of drug from the vagina to the uterus in a more direct manner than simply being distributed via the systemic circulation to the uterus. A number of mechanisms have been proposed to explain this effect, including direct migration of drug through the cervical and uterine lumina to the endometrium, passive diffusion of drug through the cervical and uterine tissues, venous or lymphatic circulatory systems, and countercurrent vascular transport (Cicinelli 1999). Cicinelli et al. measured a rapid hemodynamic response of uterine arteries to estradiol administered to either the upper or lower third of the vagina. A significant hemodynamic response was observed only when the estradiol was administered to the upper third of the vagina, but not when it was administered to the lower third of the vagina. According to the authors, this provided evidence of the countercurrent vascular transport mechanism of the first uterine pass effect, and furthermore, it demonstrated this effect only from drug administered to the upper third of the vagina (Cicinelli 2004). As per sponsor, the progesterone vaginal ring targets delivery to the upper part of the vaginal vault, thereby capitalizing on the first uterine pass effect.

Penzias AS. Luteal phase support. *Fertility and Sterility* 2002; 77(2): 318-323.

Pritts EA, Atwood AK. Luteal phase support in infertility treatment: a meta-analysis of the randomized trials. *Human Reprod.* 2002;17(9):2287-2299.

Chetkowski RJ, Kiltz RJ, Salyer WR., In premature luteinization, progesterone induces secretory transformation of the endometrium without impairment of embryo viability., *Fertil Steril.* 1997 Aug;68(2):292-7.

Ludwig M, Diedrich K. Evaluation of an optima luteal phase support protocol in IVF. *Acta Obstet Gynecol Scand* 2001; 80:452-466.

Tavaniotou A, Smits J, Bourgain C, Devroey P. Comparison between different routes of progesterone administration as luteal phase support in infertility treatments. *Human Reproduction Update* 2000; 6(2):139-148.

Cicinelli E, de Ziegler D., Transvaginal progesterone: evidence for a new functional 'portal system' flowing from the vagina to the uterus., *Hum Reprod Update.* 1999 Jul- Aug;5(4):365-72.

Cicinelli E, de Ziegler D, Bulletti C, Matteo MG, Schonauer LM, Galantino P., Direct transport of progesterone from vagina to uterus., *Obstet Gynecol.* 2000 March;95(3):403-6.

Cicinelli E, De Ziegler D, Morgese S, Bulletti C, Luisi D, Schonauer LM., First uterine pass effect" is observed when estradiol is placed in the upper but not lower third of the vagina., Fertil Steril. 2004 May;81(5):1414-6.

4.4.2 Pharmacodynamics

Tissue progesterone concentrations in the endometrium were assessed as one of the PD outcomes in this NDA [Study DR-201-102]. This was intended to assess the 'local' progesterone exposure from the vaginal formulation. The PD outcome of most interest however, was the successful secretory transformation of the endometrium. However, the correlation of either tissue progesterone or endometrial transformation with that of the primary efficacy outcome (i.e. clinical pregnancy) has not been established.

No trends were apparent between serum progesterone concentrations and the pregnancy outcomes in study DR-PGN-302. In women who became pregnant during the ART procedures, the endogenous progesterone concentrations continued to increase markedly thus confounding the contribution of exogenous progesterone. The serum concentrations in women who failed to become pregnant appeared to be within the expected range for this new ring formulation and therefore do not readily provide an explanation to the lack of efficacy.

4.4.3 Pharmacokinetics

Only a single dose strength of the vaginal ring (weekly) formulation was evaluated throughout this NDA [(b) (4) % w/w containing ~1.8 g of progesterone per ring]. The PK of progesterone from the proposed vaginal ring formulation were addressed in post-menopausal healthy volunteers during the definitive PK study 10716222 following single dose and steady state dosing. Mean progesterone concentration-time profiles are shown following the two doses:

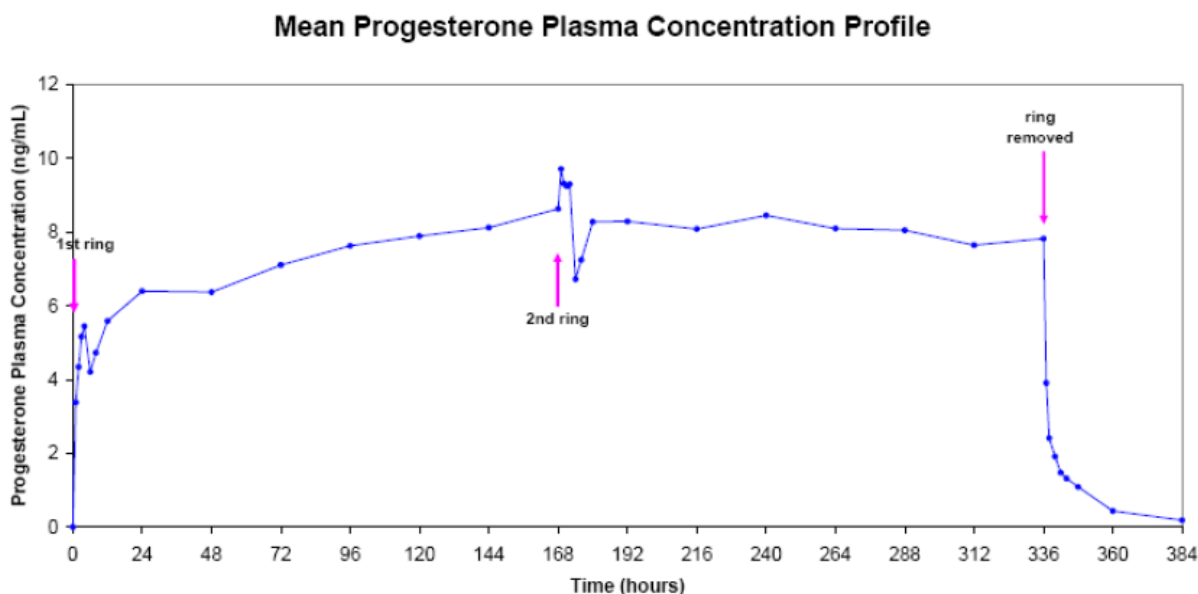


Figure 1 describes the average plasma progesterone concentration vs. time profiles following two consecutive weekly doses of progesterone vaginal ring formulation in post-menopausal volunteers. C_{max} values after the first dose and second dose of the vaginal ring averaged at 9.3 ng/mL and 10.7 ng/mL, respectively. The average value of steady-state plasma progesterone (C_{avg}) observed during the second dose of the ring was 8.2 ng/mL. The inter-individual variability (% CV) in plasma progesterone C_{max} and AUC following the vaginal ring product was ~25- 30 %.

The Clinical Pharmacology reviewer concluded that the proposed vaginal ring formulation resulted in consistent release and absorption of progesterone via the vaginal mucosa into the systemic circulation.

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5 Sources of Clinical Data

Tables 3 and 4 summarize the clinical studies conducted. The study DR-PGN-302 is the single primary study supporting efficacy and safety of the drug product.

5.1 Tables of Studies/Clinical Trials

Table 3: Studies/Clinical Trials

Study Country of conduct Start date-Completion date	Phase/Design	Investigational Products	Treatment duration	# subjects	Study outcome variable
Pivotal clinical safety and efficacy DR-PGN-302 USA February 2008-January 2009	Phase 3 Prospective/multicenter/randomized/ Single (investigator) blind/ Active control	DR-2011 vs Progesterone Vaginal Gel (Crinone 8%)	One treatment cycle 14 days for all treated subjects, up to 10 weeks post egg retrieval for those subjects who became pregnant	N Total: 1297 DR-2011: N=558 Age 18-34 N=88 Age 35-42 Crinone 8%: N=560 Age 18-34 N=91 Age 35-42	Clinical pregnancy defined as a gestational sac with fetal heart motion on vaginal ultrasound evaluation at 6 and 10 weeks post egg retrieval

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Table 4: Other studies performed during the drug development

Study Country of conduct Start date-Completion date	Phase/Design	Investigational Products	Treatment duration	# subjects	Study outcome variable
NOVUM-10716222 USA March 2008-April 2008	Phase 1 Bioavailability PK Open-Label, Single arm, Multicenter. Single and Steady State	Progesterone Vaginal Ring (DR-2011)	30 days One treatment, Two Dose (Two seven-day application)	30 enrolled-27 completed healthy post menopausal female volunteers who had been pre-treated with estrogen	Steady state plasma concentration of progesterone are reached during the first vaginal ring insertion. Following removal of the first ring and replacement with a second ring, no accumulation of progesterone is observed during the second treatment.
NOVUM-10936035 USA November 2009-December 2009	Phase 1 BE Open label, Single dose, Multi-center, Blinded, Randomized, Two treatment, Two period Cross-over	Progesterone Vaginal Ring (DR-2011) manufactured at Barr NJ facility and Barr OH facility	7 days per ring with a 7 day washout in between	32 enrolled 31 completed healthy post menopausal female volunteers who had been pre-treated with estrogen	To evaluate bioequivalence of DR- 2011 manufactured at NJ R&D facility and DR-2011 manufactured at OH commercial facility Bioequivalence was established
NOVUM 10936057 USA December 2009-January 2010	Phase 1 BE Open label, Single arm Single-center	Progesterone Vaginal Ring (DR-2011) from Barr OH facility	Single use 7 days	15 enrolled 15 completed healthy post menopausal	To obtain additional used DR-2011 for analysis of residual progesterone following

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				female volunteers	a single 7 day use period
DR-201-102 USA February 2009-August 2009	Phase 1 PK/PD Randomized, Open label, Active control, No-treatment Control (Estrogen only)(three arms) Single-center	Progesterone Vaginal Ring (DR-2011) Progesterone Vaginal gel (Crinone 8%)	11-12 days of progesteron e Overall 10 weeks for each subject. The study included three periods: a 14-day estrogen pretreatmen t period, an 11-12 day estrogen with or without progesteron e treatment period and a 14-day post treatment period.	63 randomized 1:1:1 21 per treatment arm 63 completed Healthy females age 18-40, with regular spontaneous menstrual cycles planning to undergo IVF/ET	To assess endometrial tissue PGN concentrations To compare systemic and endometrial PGN levels To compare safety and tolerability The mean endometrial tissue PGN concentration observed for the DR-2011 group was considerably higher than that found for the estrogen-only treatment group but lower than that observed with the vaginal gel. Systemic serum concentrations of PGN were substantially higher for the progesterone treatment groups than the estrogen-only group; serum PGN concentrations for DR- 2011 were similar to

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					the vaginal gel group. DR-2011 demonstrated a high rate of endometrial secretory transformation, with 18 of 19 subjects (94.7%) undergoing transformation to the secretory phase, compared to 16 of 19 subjects (84.2%) in the vaginal gel group
DR-PGN-201 USA July 2005-November 2006	Phase 2 PD Randomized, Open label, Active control Single-center	Progesterone Vaginal Ring (DR-2011) Progesterone Vaginal gel (Crinone 8%)	18 days DR-2011, used continuously from Cycle Day 14-31 (VR is replaced once in the treatment period, on Cycle Day 21.)	21 Randomized 20 Completed 1:1 10 per treatment arm. Females age 18-50, candidates for donor oocyte program	DR-2011 adequately transformed the endometrium to secretory phase in 8 out of 10 of patients while Crinone did so in 10 out of 10 patients. Progesterone serum levels in both treatment groups increased rapidly between Cycle Days 14 and 15 and remained fairly stable during treatment (up to Cycle Day 31).
DR-PGN-202 USA October 2005-September	Phase 2 Efficacy and Safety Randomized, Open	Progesterone Vaginal Ring (DR-2011) Progesterone Vaginal	10 Weeks DR-2011 was used	9 Treated 8 Completed DR-2011:5	Four out of five subjects who underwent an embryo

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2007	label, Active control Follow up	gel (Crinone 8%)	continuous y from the day of donor egg retrieval through 12 weeks of pregnancy, if subject became pregnant. The DR- 2011 was replaced every 7 days	Crinone 8%: 4 Participants in DR-PGN-201 who had successful endometrial transformation in Donor oocyte IVF	transfer using DR-2011 became pregnant (3 singleton and 1 twin delivery), compared to one pregnancy out of four subjects who received Crinone (1 singleton delivery). All pregnancies in both treatment groups led to live births. One of the DR-2011 subjects who became pregnant was withdrawn from the study after 8 weeks of pregnancy and was switched to IM progesterone due to the bleeding pattern after pregnancy was established.

5.2 Review Strategy

Sources used for preparing this review include the clinical studies listed in Tables 3 & 4. The primary study reviewed for both safety and efficacy is study DR-PGN-302, a US Trial. Only one Phase 3 clinical trial is evaluated for this application, as agreed between the FDA and the Applicant. See regulatory history on March 3, 2007 and June 13, 2007 in section 2.5 of this report.

Section 5.3.1 contains detailed information on Study DR-PGN-302.

5.3 Discussion of Individual Study/Clinical Trial

5.3.1 Primary trial-DR-PGN-302

5.3.1.1 Trial title/Coordinating Investigator/ Trial Dates

“A Phase 3, Single-Blind, Randomized Study to Compare DR-2011 to a Progesterone Vaginal Gel for Luteal Phase Supplementation for In Vitro Fertilization”.

The study coordinator/Applicant Signatory was Kathleen Reap, M.D. of Teva Branded Pharmaceutical Products R&D, Inc

The trial was initiated on February 4, 2008 and ended on January 8, 2009.

5.3.1.2 Ethics

The Applicant stated that a) this study met all local legal and regulatory requirements, b) this study was conducted in accordance with Good Clinical Practice (GCP), c) this study complied with ethical principles originating in the Declaration of Helsinki and the ICH-GCP guidelines of January 17, 1997, d) the study protocol and amendments were reviewed and approved by each study site’s Independent Ethics Committee (IEC) or Institutional Review Board (IRB) before the start of the study or before implementation of the protocol, and e) the study’s informed consent form was reviewed and approved by the IECs and IRBs prior to its issue.

5.3.1.3 Investigators and Trial Sites

The trial was conducted at 24 clinical trial sites. (see Table 6). As per Applicant:

Site #5 was assigned to Dr. Dumesic who received IRB approval on Dec 14, 2007 with the study initiation visit on Feb 6, 2008. The site consented zero subjects and was officially closed by the IRB on May 6, 2008. No subject data were generated.

Site #16 was assigned to Dr. Rosenwaks during pre-study activities. Dr. Rosenwaks subsequently declined participation. The site did not get to the point of seeking IRB approval. The site number was not re-assigned. No subject data were generated.

The absence of sequential numbers of subjects per center was explain by the Applicant as being screen failures. Subject number was assigned prior to screening, while randomization occurred later at Visit 4. Also within the same center with multiple satellite offices, each satellite maintained an address specific enrollment log that was later merged into one log for the investigator. Since randomization could occur at more than one office, at the study start Teva Women's Health, formerly Duramed Research, Inc. provided a specific numbering schema for each satellite. This was to ensure that no two subjects were assigned the same subject number for that investigator. Table 5 below, for example, demonstrates the numbering schema for sites 7 and 21 as explained by the Applicant.

Table 5: How subject number was assigned in centers with multiple satellite sites

Site #	Last 3 digits of subject # (b) (6)	PI last name	Institution and address
007		Foulk	Nevada Center for Reproductive Medicine 645 Sierra Rose Dr., Suite 205 Reno, NV 89511
007		Foulk	The Idaho Center for Reproductive Medicine 111 Main St., Suite 100 Boise, ID 83702
021		Shamma	IVF Michigan 3950 South Rochester Rd, Suite 2300 Rochester Hills, MI 48307
021		Shamma	IVF Michigan 5400 Mackinaw, Suite 4100 Saginaw, MI 48604
021		Shamma	IVF Michigan 6711 Monroe St., Bldg 3, Suite A Sylvania, OH 43560
021		Shamma	IVF Michigan Two Hurley Plaza, Suite 209 Flint, MI 48503

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Table 6: Clinical Site/Principal Investigator (PI)/Address

Site #	Last	First	Institution Name	Address	City	State	Zip
001	Bayer	Stephen	Boston IVF	130 Second Avenue	Waltham	MA	02451
002	Beltsos	Angeline	Fertility Centers of Illinois	767 Park Avenue West, Suite B400	Highland Park	IL	60035
003	Choe	Jung	Cooper Institute for Reproductive Hormonal Disorders	8002 E Greentree Commons	Marlton	NJ	08053
004	Doody	Kevin	The Center for Assisted Reproduction	1701 Park Place Avenue	Bedford	TX	76022
005	Dumesic	Daniel	Reproductive Medicine and Infertility Associates	2101 Woodwinds Drive, Suite 100	Woodbury	MN	55125
006	Feinman	Michael	Huntington Reproductive Center	1220 LaVenta Drive, Suite 103	Westlake Village	CA	91361
007	Foulk	Russell	The Nevada Center for Reproductive Medicine	645 Sierra Rose Drive, Suite 205	Reno	NV	89511
008	John L.	Frattarelli ¹	Reproductive Medicine Associates of New Jersey	111 Madison Avenue, Suite 100	Morristown	NJ	07960
009	Gibbons	William ²	Women's Center for Reproductive Medicine	9000 Airline Highway, Suite 670	Baton Rouge	LA	70815

¹ John Frattarelli, MD was originally the PI at this site. Richard T. Scott, Jr., MD took over as PI and was the PI at the end of the study.

² William E. Gibbons, MD was originally the PI at this site. Bobby Webster, MD took over as PI and was the PI at the end of the study.

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Site #	Last	First	Institution Name	Address	City	State	Zip
010	Ginsburg	Elizabeth	Brigham & Women's Hospital Dept. of Obstetrics and Gynecology	75 Francis Street	Boston	MA	02115
011	Kalra	Suleena	University of Pennsylvania, Penn Fertility Center	3701 Market Street, Suite 810	Philadelphia	PA	19104
012	Levy	Michael	Shady Grove Fertility Reproductive Science Center	15001 Shady Grove Road, Suite 400	Rockville	MD	20850
013	Miller	Charles	The Fertility Institute at Edward/ Charles E. Miller, MD & Associates	1900 E. Golf Road, Suite L-125	Schaumburg	IL	60173
014	Patrizio	Pasquale	Yale Fertility Center	150 Sargent Drive, 2 nd Floor	New Haven	CT	06511
015	Perloe	Mark	Georgia Reproductive Specialists, LLC	5445 Meridian Mark Road, Suite 270	Atlanta	GA	30342
017	Sanchez	Mark	Florida Fertility Institute	2454 McMullen Booth Road, Suite 601	Clearwater	FL	33759
018	Scheiber	Michael	Institute for Reproductive Health	3805 Edwards Road, Suite 450	Cincinnati	OH	45209
019	Schnell	Vicki	Center of Reproductive Medicine	1015 Medical Center Boulevard, Suite 2100	Webster	TX	77598
020	Schnorr	John	Southeastern Fertility Center	1375 Hospital Drive	Mount Pleasant	SC	29464
021	Shamma	F. Nicholas	IVF Michigan	3950 South Rochester Road, Suite 2300	Rochester Hills	MI	48307

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Site #	Last	First	Institution Name	Address	City	State	Zip
022	Silverberg	Kaylen	Texas Fertility Center	6500 North Mopac Expressway, Building 1, Suite 1200	Austin	TX	78731
023	Stadtmauer	Laurel	The Jones Institute Eastern Virginia Medical School	601 Colley Avenue	Norfolk	VA	23507
024	Uhler	Meike	Fertility Centers of Illinois, River North IVF	900 North Kingsbury, Suite RW6	Chicago	IL	60610

Reviewer's Comment: Assisted Reproductive Technology Surveillance-CDC- United States, 2006, by Saswati Sunderam, PhD, Jeani Chang, MPH et. al reveals that in 2006, ART use varied according to the patient's state of residence. Residents of California, New York, Illinois, New Jersey, Massachusetts, Florida, and Texas reported the highest number of ART procedures. These states also reported the highest number of infants conceived through ART. A review of success rates regarding pregnancies and deliveries of a live new born as per the above report revealed similar distributions among clinics in different states of the United States. Based on these findings, the data may be generalizable since Clinical Trial Sites were well distributed through out all USA. CVs of all PIs were reviewed and revealed they were well qualified to perform the trial. A sample informed consent for trial DR-PGN-302 was included in this NDA submission with the IRB approval and appeared adequate.

5.3.1.4 Trial objectives

The objective of Phase 3 Study DR-PGN-302 was to evaluate the clinical efficacy and general tolerability of two different progesterone preparations administered intravaginally (DR-2011, progesterone vaginal ring) by Teva versus Crinone® 8% (Progesterone Vaginal Gel) by (b) (4), when administered to patients undergoing ART to support and supplement the corpus luteum and early pregnancy. Crinone® 8% (Progesterone Vaginal Gel) will henceforth be referred to as Crinone 8% in this review. The Applicant states that Crinone 8% was used as the comparator through out the development program of DR-2011.

5.3.1.5 Trial Design

Study DR-PGN-302 was designed as a comparative Phase 3, prospective, active control, randomized, single-blind (investigator blind), multi-center study of progesterone supplementation (luteal phase support) in women undergoing In-Vitro Fertilization (IVF) with fresh oocytes over a single cycle of progesterone use until either menses occurred or a pregnancy

occurred (up to 10 weeks post embryo transfer). Eligible subjects were started on an ovarian down-regulation protocol utilizing leuprolide acetate (Lupron) followed by an ovarian stimulation protocol utilizing a combination follicle stimulating hormone (FSH) and luteinizing hormone (LH)-containing product. Ovarian suppression was to begin during the cycle immediately prior to the embryo transfer cycle. Ovarian stimulation was to begin once down-regulation was achieved. The length of stimulation depended on each subject, the investigational site's standard protocols, and/or the Investigator's clinical judgment. During stimulation, the subject was monitored to determine when to trigger ovulation with human chorionic gonadotropin (hCG). Egg retrieval was to occur approximately 35-37 hours after hCG administration. On the day after egg retrieval, at the time of consent, 1297 eligible women were stratified by age (18-34 years of age or 35-42 years of age) and randomized in a 1:1 ratio to begin the investigational product (IP), either DR-2011 once every week or Crinone 8% 90 mg once daily. Embryo transfer occurred 3 to 5 days after egg retrieval. A serum pregnancy test was conducted 2 weeks after the egg retrieval. Subjects with a β -hCG <5 mIU were discontinued from the study. Those with a β -hCG >5 continued dosing with progesterone for up to a total of 10 weeks (i.e., through 12 weeks of pregnancy). Clinical pregnancy rates at 8 and 12 weeks of pregnancy (6 and 10 weeks post embryo transfer) were evaluated for each treatment group. All pregnancies were followed until completion to determine live birth rates. The overall study duration was approximately 12 months.

The investigator and ultrasonographer were blinded from the subject's treatment assignments throughout the course of the study and remain blinded at the time of this study report. Each site utilized un-blinded study personnel to dispense investigational product, provide instructions for use and answer the subject's questions. The un-blinded personnel could reveal the treatment assignment to the Investigator only if it became necessary for the Investigator to know (e.g., in the event of a medical emergency or other reason determined by the investigator). Investigators were blinded by not allowing them to have any contact with the study medications (supplied in boxes labeled in a manner that did not reveal the content of the boxes), and requesting that patients not make any statements to the investigator that might indicate the treatment to which they were assigned.

Reviewer's Comments:

- 1. Sponsor did not choose the double blind, double dummy approach utilizing a placebo ring and vehicle for gel in Study DR-PGN-302, claiming that this approach could not be done. Sponsor's rationale for not having a double blind approach was that subjects were able to easily identify their assigned treatment group because DR-2011 was supplied in a ring format to be introduced by the patient into the vagina every 7 days, while Crinone 8% was supplied as a gel to be inserted into the vagina once every day. This reviewer believes that a double blind, double dummy approach utilizing a placebo ring and vehicle for gel could have been achieved and it would have been the preferred double blinding method. Despite this shortcoming, it appears that the single blinding approach did not compromise the validity of the trial since the end point was pregnancy and as such this approach is acceptable.***

2. ***The treatment of subjects prior to progesterone treatment initiation is compatible with the standard treatment for infertile patients undergoing IVF-ET and is considered acceptable.***

5.3.1.6 Inclusion Criteria

At Screening, subjects must have met the following criteria to participate:

1. Pre-menopausal females aged 18-42 years at time of consent
2. Documentation of a normal uterine cavity by hysteroscopy, hydrosanogram, or hysterosalpingogram (HSG) within 1 year of Screening
3. Documentation of testing for serum Hepatitis B surface antigen, Hepatitis C antibody, HIV antibody, RPR/VDRL, rubella antibody, ABO grouping, Rho typing, prolactin and thyroid function within 6 months of Screening
4. At least one cycle without reproductive hormone medication prior to the screening FSH and estradiol blood draw
5. Tubal, idiopathic, male factor, ovulatory dysfunction or endometriosis-linked infertility
6. For fresh sperm: sperm assessed for leukospermia within two months of pituitary down-regulation, OR male partner empirically treated with antibiotics prior to the IVF cycle. If assessed, ≤ 2 million WBC/mL or round cells/mL were required for participation in this study
7. Semen analysis within 1 year of Screening by WHO and/or Kruger criteria. Frozen sperm, including donor sperm, could be used, as long as testing done at the time of freezing met standard criteria. Male partners with obstructive azoospermia were not required to have this semen analysis
8. Able to read and comprehend the English language
9. Able to understand, read, and sign an informed consent after the nature of the study has been fully explained
10. Able to complete all study procedures.

5.3.1.7 Exclusion Criteria

At Screening, a subject was excluded from participating in the study for any of the following reasons:

1. Contraindications to the use of progesterone, which included:
 - Known sensitivity to progesterone or related drugs
 - Undiagnosed vaginal bleeding
 - Significant liver dysfunction or disease (including liver function tests > 2 times the upper limit of normal)
 - Known or suspected malignancy of the breast or genital organs
 - Active thrombophlebitis or thromboembolic disorders, or a history of hormone associated thrombophlebitis or thromboembolic disorders
2. Significant psychiatric disease that was not well-controlled
3. Body Mass Index (BMI) > 38 kg/ m²
4. Uncontrolled hypertension (systolic blood pressure > 160 mmHg; diastolic blood pressure > 100 mmHg)

5. Follicle stimulating hormone (FSH) > 15 mIU/mL during early follicular phase (day 2-4). For those subjects with polycystic ovarian syndrome (PCOS), a day 2-4 FSH level could be obtained following a progestogen withdrawal or spontaneous menses
6. Clinically significant gynecologic pathology, such as submucosal fibroids, intramural fibroids > 5 cm, communicating hydrosalpinx, uncorrected uterine septum, endometrial cancer or endometrial atypia, scar tissue inside the cavity or poorly developed uterine lining from prior uterine surgery, pelvic tuberculosis, or any other conditions that could adversely affect pregnancy success
7. Uncontrolled hyperprolactinemia or hypothyroidism
8. History of pelvic radiation. Subjects with a history of cancer within the last 5 years, except for squamous or basal cell cancer of the skin
9. Currently pregnant or breastfeeding
10. Current Gonorrhea or Chlamydia
11. History of HIV/AIDS
12. Known hypersensitivity or previous intolerance to silicone
13. History of toxic shock syndrome
14. Known or suspected substance abuse within 1 year prior to screening
15. Use of any investigational drug or device within 30 days prior to screening
16. Low-grade squamous intraepithelial lesion (LSIL) or worse on screening Pap smear; any other abnormal finding on the Pap smear that the Investigator considers clinically significant [such as "atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (HSIL)" (ASCH), "atypical glandular cells" (AGC)]; or any Pap result that would necessitate further evaluation by biopsy and/or colposcopy. Any screening Pap with "atypical squamous cells of undetermined significance" (ASC-US) will have "reflex" human papilloma virus (HPV) testing done on the Pap sample. If the HPV testing is negative for high-risk types, the subject may be enrolled; if the HPV testing is positive for high-risk types, the subject will be required to have a colposcopy. If colposcopy shows dysplasia or cancer, the subject was NOT eligible for enrollment
17. Undergoing donor oocyte cycle, blastomere biopsy or other experimental ART procedure
18. History of more than one failed fresh IVF cycle. A prior ART cycle was considered started when a woman began taking medication to stimulate the ovaries to develop eggs or, if no drugs were given, when a woman began having her ovaries monitored (using ultrasound or blood tests) for natural egg production (CDC 2005). A prior failed cycle was defined as having started a cycle without becoming pregnant or a pregnancy loss prior to the 20th week of pregnancy
19. More than 2 consecutive clinical miscarriages (gestational sac observed on ultrasound)
20. Insulin-sensitizing agents, ART cycle or ovarian stimulation with gonadotropins within 30 days or clomiphene stimulation within 90 days prior to the screening FSH and estradiol blood draw
21. Tobacco use 3 months prior to screening
22. For fresh sperm: male partners with non-obstructive azoospermia
23. Any abnormal finding or condition deemed clinically significant by the Investigator on history, screening, physical exam, or pelvic exam that contraindicates pregnancy or the use of progesterone or a VR

24. Any condition the Investigator believes would interfere with the subject's ability to provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the subject at risk
25. Any Duramed Research employee or relative of an employee, any Investigator Site employee or relative of employees working on the study.

Reviewer's Comment: The inclusion and exclusion criteria are generally acceptable. The Division recommended that women should be stratified by age as <35 years and 35-42 years. Therefore, women up to age 42 should have been enrolled in appropriate number capable to power the sub-stratification by age appropriately for non-inferiority analysis. TEVA has limited the numbers of women 35-42 and did not power for that age group while it did power for the age group <35 years. See Figure 2. The eligibility criteria adopted was to include only those patients with a reasonable likelihood of having a successful outcome, while excluding those who may have been at risk of a serious adverse events associated with one or more of the procedures common to IVF. While exclusion of individuals likely to be harmed by participation in the study is desirable and ethical, restriction of subjects to those "likely to succeed" represents pre-selection which introduces biases and limits generalizability of the study.

One additional comment, a mixed population of infertility subject were studied. This makes a determination of the background rate for pregnancy in the untreated subject difficult to determine.

5.3.1.8 Prior and Concomitant Therapy

Subjects were queried regarding concomitant use of medications at all study visits, as well as during the Post-Treatment phone call. All concomitant medication use (both prescription and over-the-counter) was reported during the study, and recorded on the CRF.

Allowed Medications:

The following medicines were permitted at any time during the study:

- Prenatal vitamins
- Antiemetics
- Other medication per the site's embryo transfer protocols and/or Investigator's discretion that was not prohibited by the protocol.

Prohibited Medications:

Use of the following medicines/therapies was prohibited at any time after signing consent and up until the post-treatment phone call:

- Vaginal medications other than the progesterone VR or progesterone vaginal gel as described in the protocol
- Estrogens or progestogens, other than those outlined in the protocol, administered by any route (oral, IM, vaginal). However, for those subjects with PCOS, a progestogen could

be used to induce a progestogen-withdrawal bleeding episode to obtain FSH on Cycle Days 2-4, prior to ovarian suppression

- Chronic, systemic corticosteroids
- Herbal remedies
- Aspirin
- Ovidrel® (choriogonadotropin alfa injection)
- The subject's partner was prohibited from using Viagra®, Cialis®, Levitra®
- Insulin-sensitizing agents (e.g., metformin)
- Any medications the Investigator believed could adversely affect endometrial thickness, embryo transfer, or pregnancy
- Acupuncture
- Smoking

Reviewer's Comment: Concomitant and disallowed medications were appropriate. It is not clear why Ovidrel is disallowed. This may become a label issue.

5.3.1.9 Study Procedures

A subject completed the study when all study visits/procedures were completed as designated by the protocol. A subject was considered completed if she was found not pregnant at any time following Visit 6, or if she was pregnant and reached Visit 9. A subject was considered completed if she was lost to follow-up between her final study visit (Visit 9 or Early Withdrawal Visit) and the Post-Treatment Phone Call. See Table 7.

Table 7: Study Flow Diagram

Pre-Study	Suppression	Stimulation	Treatment Period	Post Treatment Period		
			DR-2011 Crinone® 8%			
Consent and Screening	Pre-Medication	Visits 1 and 2	Visits 4-9: Day after Egg Retrieval and Ongoing Pregnancy (~10 weeks)	Ongoing Pregnancy (variable duration, continues until completion of pregnancy)		Post-Pregnancy (~ 2weeks)
				Post-Treatment Period (~ 2 weeks)		

Source: NDA Application DR-PGN-302 Clinical Study Report, Figure 1, p36

Pre-screening Visit

Women with tubal, idiopathic, male factor, ovulatory dysfunction or endometriosis-linked infertility, who agree to be considered for inclusion in the study were invited to be seen at the study site. At this visit, each potential study participant read the informed consent and all questions were addressed by study personnel. If the potential participant agreed to participate in

the study, she signed the consent form and it was documented that she read, expressed an understanding of, and was provided with a copy of the signed informed consent form. The consent form was signed prior to any study procedures being performed. If appropriate, the Pre-Screening Visit and the Screening Visit could occur on the same day. Subjects were given a reminder notebook to bring to each visit in which to record the following:

- I. Any AEs noted between visits
- II. Any concomitant medications taken between visits.

Visit 0: Screening

The Screening Period is intended to evaluate whether a subject is eligible for enrollment into the study. Visit 0 is the start of the Screening Period. The Screening Period may last up to 90 days from the time of signing the consent form to the start of ovarian suppression. Study personnel will determine subject eligibility based on the inclusion and exclusion criteria.

The following procedures were completed for subjects who appeared eligible for participation in the study (see Table 8):

- AEs that occurred after the informed consent was signed will be collected
- Physical exam, including a pelvic exam. The pelvic exam will include Gonorrhea/Chlamydia and a Pap smear. A Pap smear done within 6 months of Visit 0 is acceptable, provided the results are normal and a copy is obtained; any historical Pap done within 6 months prior to Visit 0 with atypical cells is NOT acceptable and the Pap should be repeated. LSIL or worse on screening Pap smear or any other abnormal finding that the Investigator considers clinically significant (such as ASC-H, AGC) would necessitate further evaluation by biopsy and/or colposcopy. Any screening Pap with ASC-US will have "reflex" HPV testing done on the Pap sample. If the HPV testing is negative for high-risk types, the subject may be enrolled; if the HPV testing is positive for high-risk types, the subject will be required to have colposcopy. If colposcopy shows dysplasia or cancer, the subject is NOT eligible for enrollment. See 5.3.1.6 and 5.3.1.7 (Inclusion/Exclusion Criteria)

If the subject's gonorrhea/chlamydia test is positive, the subject is no longer eligible for the study. However, the subject may be treated and rescreened for the study with a new subject number assigned.

- Medical/gynecological history, which will include any medication(s) taken within 30 days prior to Pre-Screening as well as a detailed past obstetrical and infertility history outlining gravidity, parity, previous miscarriages, abortions and ectopic pregnancies; duration of infertility, primary and concomitant causes of infertility and previous history of infertility therapies
- Vital signs (blood pressure, heart rate, temperature, weight and height), chemistry and hematology panels, urinalysis and serum levels of β -hCG

After meeting any applicable washout criteria indicated for Inclusion (reproductive hormones) and Exclusion (ART cycle, gonadotropins, insulin-sensitizing agents or clomiphene), blood will be drawn to measure FSH and estradiol serum levels on Cycle Days 2, 3, or 4 (prior to start of ovarian suppression treatment). The FSH serum will be sent to the central laboratory for analysis.

Clinical Review
 {Insert Reviewer Name}
 {Insert Application Type and Number}
 {Insert Product Trade and Generic Name}

Table 8: Study Schedule

Visit:	Pre-Screen	Screen (0) ³	Pre-Meds	1	2	3 ER	4	5 ⁴ ET		6	6P	7		7P		8					9	Post-Tx Call	Post-Preg Call
Egg Retrieval + X Weeks:					-2 days	0	+1 day	+3 days	1	2	2.5	3	4	4.5	5	6	7	8	9	10			
X Weeks of Pregnancy ⁵ :						2			3	4	4.5	5	6	6.5	7	8	9	10	11	12			
Informed Consent	X																						
Medical/gynecological history		X																					
Physical/pelvic exam		X																		X			
Vital signs		X				X	X	X		X		X				X				X			
Suppression treatment			X																				
Stimulation treatment ⁶				Start	Stop																		
HCG (ovulation induction)					X																		
Egg Retrieval (ER)						X																	
Randomization							X ⁹																
Embryo Transfer (ET)								X															
AEs/ConMeds/Vaginal Bleeding ⁸		X		X		X	X	X		X		X				X				X	X		
Treatment Satisfaction Measure questionnaire																				X			
SAEs and health outcome of infant																						X	
LABORATORY/DIAGNOSTIC TESTS																							
Pap smear ⁹		X																					
Chemistry and hematology panel		X					X													X			
Gonorrhea/chlamydia testing		X																					
Urinalysis		X																		X			
FSH serum levels		X ¹⁰																					
βHCG serum levels		X								X	X	X											
Progesterone serum levels							X			X										X			
Estradiol serum levels		X ⁹		X	X		X	X															
Transvaginal ultrasound (TVU)				X	X	X		X ¹¹						X		X				X ¹¹			
Abdominal ultrasound																							
PROGESTERONE VR TREATMENT																							
Ring placement							VR1		VR2	VR3		VR4	VR5		VR6	VR7	VR8	VR9	VR10				
Ring removal									VR1	VR2		VR3	VR4		VR5	VR6	VR7	VR8	VR9	VR10			
PROGESTERONE GEL TREATMENT																							
							Start													Stop			

Source: NDA DR-PGN-302 Clinical Study Report, Table 3, pp37-38

Ovarian Suppression Treatment

Suppression will take place during the cycle before the Embryo Transfer. All Screening procedures must be completed prior to the start of ovarian suppression. The subject may be enrolled in the study if the FSH and estradiol laboratory results are not available at Screening. However, the subject is considered no longer eligible to participate in the study if these results are exclusionary.

Ovarian suppression protocols will be determined individually for each subject by the Investigator's discretion based on the following protocol:

- Subjects will receive combination birth control pills (BCPs) Portia® [150 mcg levonorgestrel/30 mcg EE] provided by Duramed for no longer than 21 days.
- Subjects will start with 0.1 mL (500 µg)/day of Lupron 4 days prior to the last BCP; however, subjects should be taking BCPs 14-17 days unopposed.

Visit 1: Start of Ovarian Stimulation

Visit 1 will occur at the start of stimulation, which is defined as the day when the subject meets suppression criteria. Gonadotropin is started for controlled ovarian hyperstimulation as soon as

possible and no later than 1 week after meeting down-regulation documented by ultrasound and laboratory results. Stimulation will consist of a combination of FSH and LH according to the Investigator's discretion. At this visit, the following will occur for all subjects (see Table 8):

- Documentation of down-regulation includes serum estradiol level $< \frac{(b)}{(4)}$ pg/mL.
- A transvaginal ultrasound (TVU) will be performed for ovarian evaluation.
- Lupron will be reduced to 0.05 mL (250 µg)/day at the time stimulation begins.
- Ovarian stimulation protocols will be determined individually for each subject by the Investigator's judgment based on the following protocol: FSH (75-450 IUs) with a combination of any LH containing product (75-150 IUs).
- AEs and concomitant medication(s) recorded in the reminder notebook will be reviewed.
- During stimulation, the subject will be monitored to determine when to trigger ovulation for the subject with hCG; this will include a serum estradiol blood draw.

Reviewer's comment: Down-regulation with $E_2 < \frac{(b)}{(4)}$ pg/mL is in contradiction with the division's recommendation of $E_2 < 25$ pg/mL.

Visit 2: End of Ovarian Stimulation

Visit 2 will occur at the end of stimulation and 2 days prior to egg retrieval. At this visit, the following will occur for all subjects (see Table 8):

- Length of stimulation will be variable and dependent upon each subject, the site's standard protocols, and/or the Investigator's discretion.
- A TVU will be performed to measure follicle size. A subject must have at least 2 follicles ≥ 17 mm (mean of 2 dimensions) to receive the hCG induction. Subjects who do not reach this follicular threshold are considered no longer eligible to participate in the study.
- Serum estradiol levels (with or without serum LH levels, as appropriate) will be monitored to determine when to trigger ovulation with hCG. If the estradiol level is > 5000 pg/mL, hCG should not be administered. In cases where the rise of the estradiol level is too rapid, or the level is predicted to be above 5000 pg/mL when mature follicles develop, coasting (withholding both FSH and LH) up to 3 days is acceptable based on the Investigator's discretion.
- If after coasting the estradiol is still > 5000 pg/mL, the subject will no longer be eligible to participate in the study.
- HCG induction will include ≤ 10000 IUs of hCG IM administered 35-37 hours prior to the egg retrieval at the subject's home. Ovidrel® (choriogonadotropin alfa injection) use will NOT be permitted in this study.

Subjects may also be given additional medication consistent with the site's embryo transfer protocol and/or the Investigator's discretion, as long as it is not a prohibited medication as listed in 5.3.1.8.

Reviewer's Comment: It is not clear why Ovidrel is not allowed as part of the IVF in Trial DR-PGN-302. This may be a labeling issue.

Visit 3: Day of Egg Retrieval

Visit 3 will occur approximately 35-37 hours after ovulation induction with hCG. At this visit, the following will occur for all subjects (see Table 8):

- AEs and concomitant medication(s) recorded in the reminder notebook will be reviewed and subject instructed to bring the notebook with them to every visit
- Vital signs (blood pressure, heart rate, temperature) will be taken
- Egg retrieval will be performed under TVU guidance

The Intracytoplasmic Sperm Injection (ICSI) procedure was allowed in this study, however assisted hatching was prohibited.

Visit 4: Day of Randomization to Progesterone Treatment

Visit 4 will occur 1 day after egg retrieval. At this visit, the following will occur for all subjects (See Table 8):

- AEs and concomitant medication(s) recorded in the reminder notebook will be reviewed and subject instructed to bring the notebook with them to every visit
- Vital signs (blood pressure, heart rate, temperature) will be taken
- Before initiation of progesterone therapy, there will be a blood draw to assess the chemistry and hematology panels, and measure the levels of progesterone and estradiol in the subject's serum
- Subjects will be randomized to their assigned progesterone treatment by study personnel other than the blinded Investigator, to either DR-2011 or Crinone vaginal gel
- Ring replacement training/confirmation and vaginal gel administration training
- Subjects will be instructed to keep their study treatment blinded to the Investigator and the ultrasonographer
- Subjects will be asked to use sanitary napkins for any vaginal spotting or bleeding during the study, as tampons should NOT be used at any time
- Vaginal bleeding since the previous visit will be recorded after the start of progesterone administration until the post-treatment phone call
- Subjects will be given another reminder notebook to bring to each visit on which to record the following:
 - Any AEs noted between visits
 - Any concomitant medications taken between visits
 - Any vaginal bleeding/spotting noted between visits
 - Date of removal and insertion of progesterone VR and extended removal of VR (for those subjects in DR-2011 treatment group)
 - Missed doses of Crinone (for those subjects in vaginal gel treatment group.)

For subjects randomized to receive DR-2011:

- The first three VRs (VR1, VR2, and VR3) will be distributed

- Subjects will be instructed in the proper method for VR insertion and removal and given a copy of the Sample VR instructions to use at home if necessary
- Subjects will demonstrate the ability to insert and remove the VR. If the subject has difficulty inserting the ring, the ring may be rinsed with cool to lukewarm (not hot) water for lubrication before insertion; no other lubricant can be used
- Subjects will re-insert the VR. Study personnel (other than the blinded Investigator) will confirm that the VR is placed correctly. The date of the insertion will be recorded. From this point and on in the study, the subject will carry out all VR insertions and removals. The subject will be instructed to replace the VR every 7 days. The date of insertion/removal of all VRs must be recorded on the subject's reminder notebook and reported to the study site
- Subjects will be given isopropyl alcohol (IPA) wipes to clean used VRs and biohazard zip-lock bags to store used VRs before returning them to the study site at Visits 7, 8, and 9
- Subjects will be instructed to keep a VR in the vagina continuously during the progesterone treatment period, Visit 4 through Visit 9 (12th week of pregnancy). However, if the subject does not become pregnant or remain pregnant through the 12th week of pregnancy, she will be instructed to stop using the VR
- Subjects will be allowed to remove the VR for up to 1 hour per day; this includes removing the VR for sexual intercourse, although this is not necessary. If a VR is removed or expelled during the study, 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 VR should be replaced.

For subjects randomized to receive Crinone 8%:

Subjects will be distributed progesterone vaginal gel kits with adequate supply to last through Visit 7

Subjects will be instructed in the proper method for vaginal gel use

Subjects will administer their first vaginal gel dose in the morning, between 6 AM and 10 AM, and be instructed to continue dosing at approximately the same time every day for the remainder of the study. Daily dosing will continue until Visit 9 (12th week of pregnancy). However, if the subject does not become pregnant or remain pregnant through the 12th week of pregnancy, she will be instructed to stop using the progesterone vaginal gel

Ring replacement training/confirmation and vaginal gel administration training will take place at this time

Subjects will be instructed to return any used vaginal gel applicator wrappers and any unused applicators to the study site at Visits 7, 8, and 9 in the storage bag provided

Subjects will be instructed to withhold their daily dose of Crinone the morning of Visit 5 until after the embryo transfer is completed. Therefore, subjects will need to bring a dose of the vaginal gel applicator with them to Visit 5.

Visit 5: Day of Embryo Transfer

Visit 5 will occur 3 days after egg retrieval. PLEASE NOTE that transfers will be allowed up to 5 days after egg retrieval if the Investigator believes it is in the best interest of the subject's potential pregnancy. At this visit, the following will occur for all subjects (see Table 8):

- AEs, concomitant medication(s) and vaginal bleeding recorded in the reminder notebook will be reviewed and subject instructed to bring the notebook with them to every visit
- Vital signs (blood pressure, heart rate, temperature) will be taken
- There will be a blood draw to measure the levels of estradiol in the subject's serum
- The embryo transfer procedure will be completed per the study site's protocol. The embryo transfer will be guided by ultrasound (transabdominal or vaginal). The number of embryos to transfer must be guided by the 2006 American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) guidelines (SART/ASRM 2006)
- The number of embryos transferred will be recorded in the source documents. Embryos not used for the embryo transfer in this study may be frozen per the site's protocol
- Subjects will be instructed NOT to have intercourse from the time of embryo transfer until Visit 6 (Week 4 of pregnancy).

For subjects randomized to receive DR-2011:

- Subjects will remove VR1 before the embryo transfer and re-insert VR1 after the embryo transfer.
- Subjects will be reminded to insert VR2 at home 7 days following the initial insertion of VR1
- Used VRs should be returned to the study site at Visit 7 after being cleaned with an IPA wipe and placed in a biohazard zip-lock bag.

For subjects randomized to receive Crinone 8%:

Subjects will dose with one application of the vaginal gel after the embryo transfer. Subjects will be instructed to continue dosing with one application each day at approximately the same time every day, between 6 AM and 10 AM, and to return any used vaginal gel applicator wrappers and unused applicators to the study site at Visit 7 in the storage bag provided.

Visit 6: 2 Weeks after Egg Retrieval

Visit 6 will occur 2 weeks (14 ± 1 day) after egg retrieval. At this visit, the following will occur for all subjects (see Table 8):

- AEs, concomitant medication(s) and vaginal bleeding recorded in the reminder notebook will be reviewed and subject instructed to bring the notebook with them to every visit
- Vital signs (blood pressure, heart rate, temperature) will be taken
- There will be a blood draw to measure the levels of progesterone and β -hCG in the subject's serum
- Subjects may be contacted later with the β -hCG results
If the subject has a negative β -hCG (<5 mIU):
 - Treatment will be stopped
 - Subjects will be withdrawn from the study and all procedures required for an Early Withdrawal Visit will be carried out.

For subjects continuing in the study and randomized to receive DR-2011:

- Subjects will insert the next VR (VR3) either at the study site or while at home. Additional VR(s) will be provided to the subject at Visit 7. The date of removal and insertion of each VR will be recorded
- Used VRs should be returned to the study site at Visit 7 after being cleaned with an IPA wipe and placed in a biohazard zip-lock bag
- Subjects will be given additional isopropyl alcohol (IPA) wipes and biohazard zip-lock bags, as required, at this visit and at any subsequent visits.

For subjects continuing in the study and randomized to receive Crinone 8%:

- Subjects will be instructed to continue dosing with one application of the vaginal gel at approximately the same time every day, between 6 AM and 10 AM. and to return any used vaginal gel applicator wrappers and unused applicators to the study site at Visit 7 in the storage bag provided.

Visit 6P: Week 4.5 of Pregnancy (2.5 Weeks after Egg Retrieval)

Visit 6P is a Procedural Visit approximately 2-3 days after Visit 6. In this study, pregnancy is defined as beginning 2 weeks prior to egg retrieval. Blood will be drawn to measure the levels of β -hCG in the subject's serum. If it is determined that the subject is no longer pregnant (i.e., β -hCG <5 mIU, decreasing β -hCG), treatment will be stopped, the subject will be withdrawn from the study, and all procedures required for an Early Withdrawal Visit will be carried out.

Visit 7: Week 5 of Pregnancy (3 Weeks after Egg Retrieval)

Visit 7 will occur 21 ± 1 day after egg retrieval. At this visit, the following will occur for all subjects (see Table 8):

- AEs, concomitant medication(s) and vaginal bleeding recorded in the reminder notebook will be reviewed and subject instructed to bring the notebook with them to every visit. Vital signs (blood pressure, heart rate, temperature) will be taken
- There will be a blood draw to measure the level of β -hCG in the subject's serum.

For subjects randomized to receive DR-2011:

- Subjects will remove VR3 while at the study site
- VR4 will be distributed by study personnel and placed in the vagina by the subject
- Subjects will be given three additional VRs (VR5, VR6, and a replacement VR) to insert at home. Subjects will be instructed to replace the VR every 7 days. The date of removal and insertion of each VR will be recorded
- Subjects will be given one extra replacement VR to use if needed
- If a replacement VR is used, the subject should obtain another replacement VR as soon as possible from the study site
- Used VRs should be returned to the study site at Visit 8 after being cleaned with an IPA wipe and placed in a biohazard zip-lock bag.

For subjects randomized to receive Crinone 8%:

- Subjects will be instructed to continue dosing with one application of the vaginal gel at approximately the same time every day, between 6 AM and 10 AM, and to return any used

vaginal gel applicator wrappers and any unused applicators to the study site at Visit 8 in the storage bag provided

- Subjects will be distributed progesterone vaginal gel kits with adequate supply to last through Visit 8

If it is determined that the subject is no longer pregnant (e.g., decreasing β -hCG, miscarriage), treatment will be stopped, the subject will be withdrawn from the study, and all procedures required for an Early Withdrawal Visit will be carried out.

Visit 7P: Week 6.5 of Pregnancy (4.5 Weeks after Egg Retrieval)

Visit 7P is a Procedural Visit approximately 32 ± 1 day after egg retrieval. A TVU will be performed to document the presence of an intrauterine gestational sac.

- If it is determined that the subject has an ectopic pregnancy, the subject will be handled according to the site's standard protocol and/or the Investigator's discretion. The subject will be withdrawn from the study, and all procedures required for an Early Withdrawal Visit will be carried out.

For subjects randomized to receive DR-2011:

- The VR should be removed during the TVU to avoid any potential un-blinding of the Investigator or ultrasonographer.

Reviewer's comment: Sponsor didn't mention anything about how the blind will be maintained if the subject was randomized to the vaginal gel (Crinone 8%).

Visit 8: Week 8 of Pregnancy (6 Weeks after Egg Retrieval)

Visit 8 will occur 42 ± 1 day after egg retrieval. At this visit, the following will occur for all subjects (see Table 8):

- AEs, concomitant medication(s) and vaginal bleeding recorded in the reminder notebook will be reviewed and subject instructed to bring the notebook with them to every visit
- Vital signs (blood pressure, heart rate, temperature) will be taken
- A TVU will be done to determine the number of gestational sacs present with and without fetal heart motion
- Subjects will be instructed to bring any remaining clinical supplies (used and unused) with them to their next study visit (Visit 9) during their 12th week of pregnancy.

For subjects randomized to receive DR-2011:

- Subjects will remove VR while at the study site prior to the TVU to avoid any potential Un-blinding of the Investigator or ultrasonographer
- VR7 will be distributed by study personnel and placed in the vagina by the subject
- Subjects will be given three additional VRs (VR8, VR9, and VR10) to insert at home. Subjects will be instructed to replace the VR every 7 days. The date of removal and insertion of each VR should be recorded
- Used VRs should be returned to the study site at Visit 9 after being cleaned with an IPA wipe and placed in a biohazard zip-lock bag

For subjects randomized to receive Crinone 8%:

- Subjects will be instructed to continue dosing with one application of the vaginal gel at approximately the same time every day, between 6 AM and 10 AM, and to return any used vaginal gel applicator wrappers and any unused applicators to the study site at Visit 9 in the storage bag provided
- Subjects will be distributed progesterone vaginal gel kits with adequate supply to last through Visit 9

If it is determined that the subject is no longer pregnant, treatment will be stopped, the subject will be withdrawn from the study, and all procedures required for an Early Withdrawal Visit will be carried out.

Visit 9: Week 12 of Pregnancy (10 Weeks after Egg Retrieval)/Early Withdrawal

Visit 9 will occur 70 ± 1 day after egg retrieval. An Early Withdrawal Visit will occur as soon as possible and within 1 week after last dose of IP. At this visit, the following will occur for all subjects (see Table 8):

- AEs, concomitant medication(s) and vaginal bleeding recorded in the reminder notebook will be reviewed and the notebook collected
- Vital signs (blood pressure, heart rate, temperature, weight) will be taken
- Physical exam will be completed, including a pelvic exam. If any lesions or abrasions are found on the cervix or vagina, a re-examination will be performed in 2-4 days. Subjects will be followed until their lesions/abrasions resolve
- There will be a blood draw to measure the levels of progesterone in the subject's serum
- Chemistry and hematology will be assessed
- Urinalysis will be assessed
- If the subject is pregnant, an ultrasound (either transvaginal or abdominal) will be carried out after the physical/pelvic exam occurs to determine the number of gestational sacs present with and without fetal heart motion and the estimated gestational age. If the subject is not pregnant at the Early Withdrawal Visit, an ultrasound will not be conducted
- Any clinical supplies in the subject's possession will be collected by study personnel
- All subjects will be administered a Progesterone Treatment Satisfaction Measure questionnaire. A sample questionnaire is illustrated in Appendix 9.4.

For subjects randomized to receive DR-2011:

- The final VR should be removed prior to the ultrasound to avoid any potential un-blinding of the Investigator or ultrasonographer
- Subjects will be asked to report to study personnel the date of insertion and removal of any VR since their last subject visit
- Study personnel will collect any remaining used and unused VRs from the subject.

For subjects randomized to receive Crinone 8%:

- Study personnel will collect any remaining unused vaginal gel applicators or used vaginal gel applicator wrappers.

Post-Treatment Phone Call

Subjects will be called approximately 2 weeks after their final dose of progesterone. During this phone call, study personnel will ask the subject about any AEs, concomitant medication(s), and vaginal bleeding since their final study visit.

Post-Pregnancy Phone Call

If the subject remains pregnant through Week 12 of Pregnancy (10 weeks after egg retrieval), she will be called approximately 2 weeks after the end of her pregnancy. If a pregnant subject withdraws from the study prior to Week 12 of pregnancy, she will still receive a phone call approximately 2 weeks after the end of her pregnancy. During this phone call, the subject will be asked general questions about the outcome of the pregnancy, route of delivery and any Serious Adverse Events that may have occurred since the post-treatment phone call. If there was a live birth, the subject will also be asked about the health of the infant(s).

A subject may be withdrawn from the trial at any time for any reason.

Reviewer's Comment: The trial design and the schedule of assessments were adequate to study efficacy and safety of DR-2011 and had been previously reviewed and agreed to between the Division and the Applicant.

5.3.1.10 Primary Efficacy Variable

The primary objective of this study was to evaluate the clinical pregnancy rate (i.e., visualization of a gestational sac with fetal heart motion present on ultrasound) using progesterone supplementation with DR-2011 compared to progesterone vaginal gel (Crinone® 8%) at two time points following egg retrieval:

- 8 weeks of pregnancy (6 weeks after egg retrieval), and
- 12 weeks of pregnancy (10 weeks after egg retrieval).

Clinical pregnancy was defined as beginning two weeks prior to egg retrieval with a requirement of visualization of a gestational sac with fetal heart motion present on ultrasound.

Reviewer's Comment: This is acceptable and agreed to between the Division and the Applicant during the drug development program.

5.3.1.11 Secondary Efficacy Variables

The Applicant evaluated the following secondary efficacy endpoints:

- Live birth rate
- Cycle cancellation rate
- Rate of spontaneous abortion
- Rate of biochemical pregnancy
- Rate of ectopic pregnancy
- Safety and tolerability

Reviewer's Comment: Secondary Efficacy Variables are acceptable and in accordance with the agreement between the Division and the Applicant.

5.3.1.12 Statistical Analysis Plan

The following analysis cohorts were used for the analysis of safety and efficacy:

- Safety: This cohort consists of all treated subjects. No formal statistical analysis was conducted.

Summary tables are provided summarizing the incidence rate of adverse events and changes in continuous measures (vital signs and laboratory results).

- Efficacy:
 - a. The primary efficacy cohort was a Modified Intent-to-Treat (MITT) cohort, defined as all randomized subjects who had a successful egg retrieval at Visit 3, were randomized, and received at least one dose of progesterone.
 - b. The Per-Protocol (PP) Cohort, a subset of the MITT cohort, was defined as subjects who, in addition, met all of the criteria of clinical pregnancy status determined by TVU at 8 and 12 weeks of pregnancy, and did not have any major protocol violations/deviations determined prior to database lock.
 - c. The Eligible Subject (ES) cohort was defined as subjects who started ovarian stimulation treatment at Visit 1. This cohort served solely as the basis for the evaluation of cycle cancellation rate.
 - d. The prespecified non-inferiority margin of -10% of the lower bound of the two-sided 95% confidence interval for the difference in response rates between DR-2011 and the comparator.

Sample Size Determination

Data from previous studies showed that for the population of women aged 18-34, the clinical pregnancy rate at 8 weeks of pregnancy was approximately 50% for Crinone® 8% (90 mg/day)-treated subjects.

Per the application, a total of 1046 subjects (523 per treatment group) will achieve a power of no less than 90% based on the following assumptions:

- A one-sided non-inferiority test of the clinical pregnancy rate at a significance level of 2.5%
- An estimated clinical pregnancy rate of 50% for both Crinone-treated and DR-2011-treated subjects, and
- A non-inferiority margin (maximum allowable difference in clinical pregnancy rate between the 2 treatment groups) of -10%

To allow for a dropout rate of approximately 5%, multiple sites will randomize approximately 1300 eligible women stratified by age at the time of consent (1100 subjects [18-34 years of age] and 200 [35-42 years of age]) in a 1:1 ratio to either a progesterone VR or progesterone vaginal gel (Crinone ® 8% once daily, 90mg/day).

Number of subjects (planned and analyzed):

The protocol called for approximately 1300 subjects to be enrolled; 1297 subjects were randomized, treated and analyzed:

- DR-2011 progesterone vaginal ring (VR): N = 558, 18-34 years of age
N = 88, 35-42 years of age
- Crinone® 8% once daily, 90 mg/day: N = 560, 18-34 years of age
N = 91, 35-42 years of age

The Division communicated with the Applicant on numerous occasions (Refer to Section 2.5) that randomization and the primary analyses should be stratified and powered by ovarian reserve as measured by Day 3 serum FSH and age of female subjects (age < 35 years and age ≥ 35 to 42 years) but the applicant for internal reasons chose not to pursue the recommended path.

In the 74-day regulatory letter, the Division identified potential filing issues:

“The single phase 3 study does not provide sufficient data to assess the efficacy and safety of your product in women age 35-42 years. Because this age group represents a large proportion of women seeking in vitro fertilization (IVF), this lack of data is a significant review issue”.

Per the Applicant, Study DR-PGN-302 did, in fact, seek to enroll a representative number of subjects in the 35-42 year old age group, although a statistically-based minimum for the purpose of formal subgroup analysis was evidently not taken into account. The overall study sample size, and the sample size for the 18-34 year old age group, were each considered sufficient for formal statistical analysis and confidence interval estimation. While the sample size for the 35-42 year old group was not specifically chosen with the assumption that the same statistical approach would be taken for this sub-group as for the 18-34 age group, a substantial number of participants (N=88) was included so that reasonable estimates of response proportions and other efficacy endpoints for the older patient age group could be calculated. Therefore, the Applicant determined that the number of subjects in the 35-42 year old subgroup was adequate.

Reviewer’s Comment: The population of women who will most frequently use the progesterone vaginal ring are women 35 years of age and older. The most recently published CDC ART statistics support that approximately 60% of women seeking ART services (IVF with their own eggs- not donor oocytes) are 35 years or older. Therefore, it is important that products used for maintenance of pregnancy demonstrate efficacy and safety in these women with borderline ovarian reserve

5.3.1.13 Analysis of Safety

For this submission, the safety monitoring used in this protocol included:

- Medical and gynecological history (including subject report of signs and symptoms)
- Scheduled physical and pelvic examination
- Vital sign assessments
- Safety laboratory evaluations
- Adverse event reporting [coded using Medical Dictionary for Regulatory Activities (MedDRA) by Preferred Terms (PT) and System Organ Class (SOC) version 9.0].

The Safety cohort includes all subjects who were randomized and received at least one dose of study medication. Three subjects ((b) (6)) who were dispensed the incorrect study medication were evaluated for safety according to the treatment they actually received. A total of 647 subjects in the DR-2011 group and 650 subjects in the Crinone 8%® group were considered in the safety analysis. There were three distinct time periods in the study during which adverse events (AEs) and serious adverse events (SAEs) were collected: the study period (including the time from signing of informed consent through 14 days after the last dose of study medication), the treatment period (a subset of the study period which included the day of the first dose of study medication through 14 days after the last dose) and the follow-up period for those subjects who became pregnant (14 days from last dose of study drug through 30 days after the completion of the pregnancy). Only SAEs were collected during the follow-up period, and were classified as pregnancy-related (occurring in either the subject or the fetus during the pregnancy), neonatal or maternal (occurring in the subject after completion of the pregnancy). Spontaneous abortions and ectopic pregnancies were considered SAEs and were collected.

5.3.1.14 Protocol Amendments

The original protocol's final issue date was October 10, 2007.
Protocol Amendment's 1 final issue date was January 31, 2008
Protocol Amendment's 2 final issue date was August 15, 2008

Amendments include editorial changes for clarification purposes or to incorporate recommendations to the protocol made by the FDA.

Reviewer's Comment: The changes presented as amendments to the original protocol are acceptable. For word by word changes incorporated to the original protocol please refer to Appendix Section 9.5.

5.3.1.15 Disposition of Subjects

A total of 1,752 subjects were screened; 369 were considered screen failures, having not met the criteria for initiating ovarian stimulation. Of the 1383 subjects who began ovarian stimulation with gonadotropins, four were found to have not met Inclusion or Exclusion Criteria and were therefore not included in the Eligible Subjects Cohort. Successful egg retrievals were obtained from for 1299 subjects, 1297 were randomized to one of the two treatment groups at the 22 sites participating in the study and treated with at least one dose of study drug: 646 randomized to DR-2011 and 651 randomized to Crinone®. Two (2) subjects had an egg retrieval and were randomized (Subject (b) (6) to Crinone® and Subject (b) (6) to DR-2011) but did not take study drug. Of the randomized subjects a total of 26 did not undergo embryo transfer.

Table 9: Subject Disposition-MITT Cohort

	DR-2011	Crinone®	Total
Baseline:			
Total Subjects Screened			1752
Total Subjects with Ovarian Stimulation			1383 ^a
Eligible Subject (ES) Cohort			1379
Total Subjects with Egg Retrieval			1299
Randomized for the MITT Cohort (N=1297)	646	651	1297 ^b
Did not undergo embryo transfer	15 (2.3%)	11 (1.7%)	26 (2.0%) ^c
Discontinued from the MITT Cohort (N=1297) due to:			
Did Not Meet Protocol Requirements	3 (0.5%)	3 (0.5%)	6 (0.5%)
Non Compliance with the Protocol	4 (0.6%)	2 (0.3%)	6 (0.5%)
Investigator Discretion	1 (0.2%)	2 (0.3%)	3 (0.2%)
Subject Request to be Withdrawn	1 (0.2%)	2 (0.3%)	3 (0.2%)
Adverse Event	44 (6.8%)	36 (5.5%)	80 (6.2%)
Subject Not Pregnant or No Longer Pregnant	284 (44.0%)	301 (46.2%)	585 (45.1%)
Lost to Follow-Up	4 (0.6%)	7 (1.1%)	11 (0.8%)
Other	5 (0.8%)	4 (0.6%)	9 (0.7%)

Note: Numbers in parentheses are percentages of all treated (MITT) subjects for each and total treatment groups.

- ^a 2 subjects who began ovarian stimulation did not have their ovarian stimulation treatment recorded on the CRF. 4 subjects did not satisfy one or more Inclusion or Exclusion criteria, even though they started ovarian stimulation. Three were screen failures ((b) (6)), one subject ((b) (6)) was randomized to DR-2011, became pregnant and delivered at 39 weeks, 2 days.
- ^b 2 subjects had an egg retrieval and were randomized ((b) (6)) to Crinone® and ((b) (6)) to DR-2011) but did not take study drug, so were not included in the MITT cohort.
- ^c Randomized subjects who did not undergo embryo transfer were included in the MITT analysis but were classified as treatment failures.

MITT Cohort	DR 2011 N (%)	Crinone 8% N (%)	Total N (%)
Underwent Embryo Transfer	631 (97.7%)	640 (98.3%)	1271 (97.84%)
Completed Study	300 (46.4%)	294 (45.2%)	594 (45.8%)
Did not complete Study (Mostly not Pregnant)	346 (53.6%)	357 (54.8%)	703 (54.2%)

Source: NDA DR-PGN-302 Clinical Study Report, Table 7, p65

Table 10: Disposition of Subjects in Study DR-PGN-302

Category	DR-2011 N (%)	Crinone N (%)	Total
Subjects with Egg Retrieval	-	-	1299
Randomized Subjects	647 (100%)	652 (100%)	1299 (100%)
Completed Study	300 (46.4%)	294 (45.1%)	594 (45.7%)
Discontinued Study	347 (53.6%)	358 (54.9%)	705 (54.3%)
Adverse Events	44 (6.8%)	36 (5.5%)	80 (6.2)
Did Not Meet Protocol Requirements	3 (0.5%)	3 (0.5%)	6 (0.5%)
Non-compliance of Study Drug	4 (0.6%)	2 (0.3%)	6 (0.5%)
Investigator Discretion	1 (0.2%)	2 (0.3%)	3 (0.2%)
Patient not pregnant or no longer Pregnant	284 (44.0%)	301 (46.2%)	585 (45.0%)
Lost to Follow-up	4 (0.6%)	7 (1.1%)	11 (0.8%)
Voluntary Withdrawal	2 (0.3%)	2 (0.3%)	4 (0.3%)
Other	5 (0.8%)	5 (0.8%)	10 (0.8%)

Source: Adapted from Statistical Review, Table 3.2.1, p 8

Table 11: Subject Cohorts

	DR-2011 (N=647)	Crinone [®] (N=652)	Total (N=1299 ^a)
Modified Intend-to-Treat Cohort	646 (99.85%)	651 (99.85%)	1297 (99.85%)
Safety Cohort	647 (100.0%)	650 (99.69%)	1297 (99.85%)
Per-Protocol Cohort	602 (93.05%)	608 (93.25%)	1210 (93.15%)

^a Total number of subjects who had egg retrieval and were randomized; 2 of these subjects did not start study medication, one in each treatment group ((b) (6) in Crinone[®] and (b) (6) in DR-2011).

Source: NDA DR-PGN-302 Clinical Study Report, Table 8, p 66

5.3.1.16 Protocol Deviations

Four investigational sites (Sites 6, 15, 19, and 23) reported occasions of a study coordinator (one instance of a PI) inadvertently becoming unblinded, all during Visit 9 /Early Termination physical exams. Site 6 reported un-blinding for eight subjects (Subjects (b) (6), (b) (6), (b) (6), (b) (6), (b) (6), (b) (6), (b) (6), and (b) (6)), Site 15 did not specify the subject numbers, Site 19 reported one occasion of un-blinding for Subject (b) (6), and site 23 reported one occasion of the PI becoming unblinded for Subject (b) (6). These subjects were retained in the MITT and Safety cohorts because the deviation did not occur until the physical end of the study treatment.

Three randomized subjects were inadvertently dispensed the wrong study medication. For the efficacy analysis (MITT cohort), these subjects were included in the treatment group to which

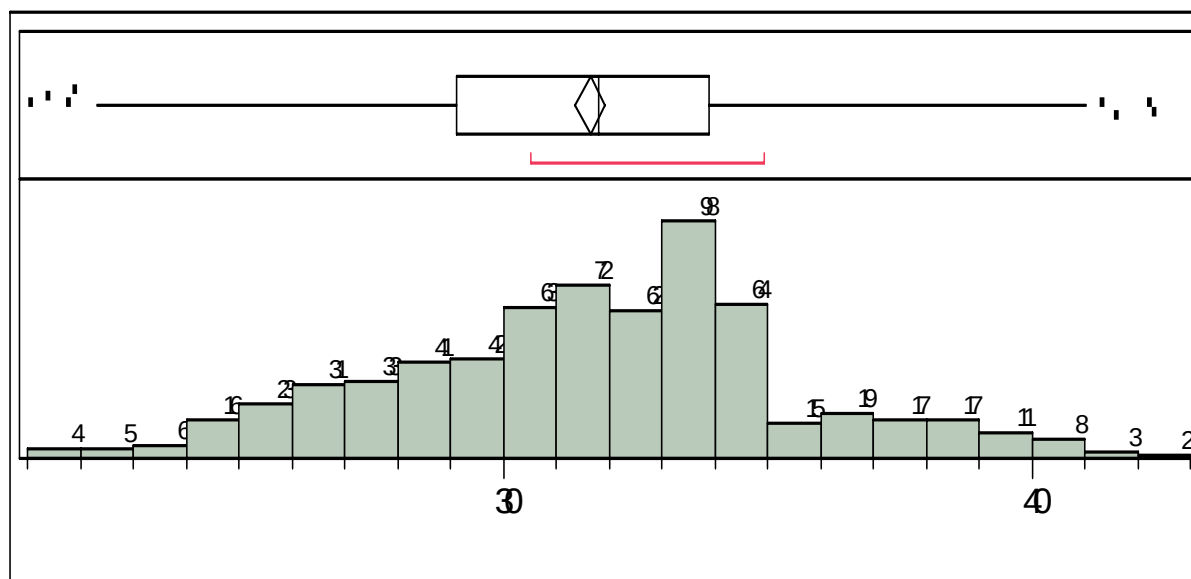
they were randomized. For the safety analysis (Safety cohort), they were included in the treatment group of the medication they actually received.
 A total of 12 subjects (4 in the DR-2011, and 8 in the Crinone8%) had an Inclusion or Exclusion Criteria violation. Nine of these subjects (all 4 in DR-2011, and 5 of the 8 in Crinone 8%) completed the study and all subjects were included in the efficacy analysis (MITT cohort). Twenty-eight (28) subjects reported at least one occurrence of non-compliance with investigational product. All but three of the non-compliant subjects (1 in the DR-2011 group, 2 in the Crinone 8% group) completed the study.

5.3.1.17 Demographics

Age

The subjects ranged in age from 21.05 to 42.31 years with a mean age of 31.64 and median age of 31.81 for the Crinone 8% group and 20.03 to 42.84 years with a mean age of 31.70 and median age of 31.71 for the DR-2011 group respectively. Figure 2 shows the age distribution.

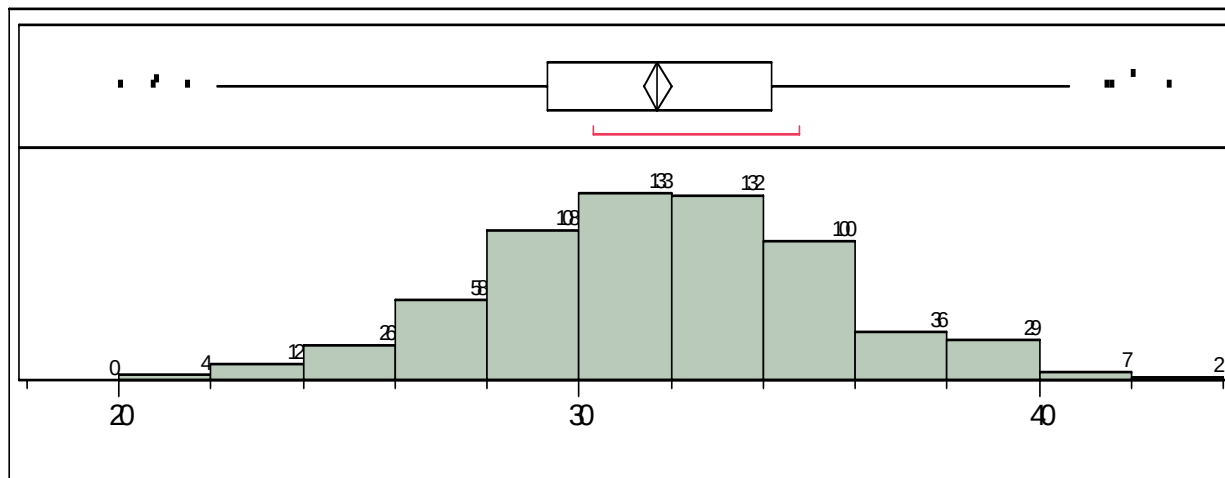
Figure 2: Age Distribution
 Crinone 8%



Age in Years

Maximum Age	42.3
Median Age	31.8
Minimum Age	21.0
Mean Age	31.6
N	652

DR-2011



Age in Years

Maximum Age	42.8
Median Age	31.7
Minimum Age	20.0
Mean Age	31.7
N	647

Source: Generated from NDA - "Demography Data Set"

Race

DR-2011

Table 12: Race/Ethnicity

Race/Ethnicity	N
African-American	55
Asian	34
Asian-Non Hispanic	1
Caucasian	519
Hispanic	34
Hispanic Asian Caucasian American Indian	1
Middle Eastern	1
Pacific Islander	1
Persian	1
Total	647

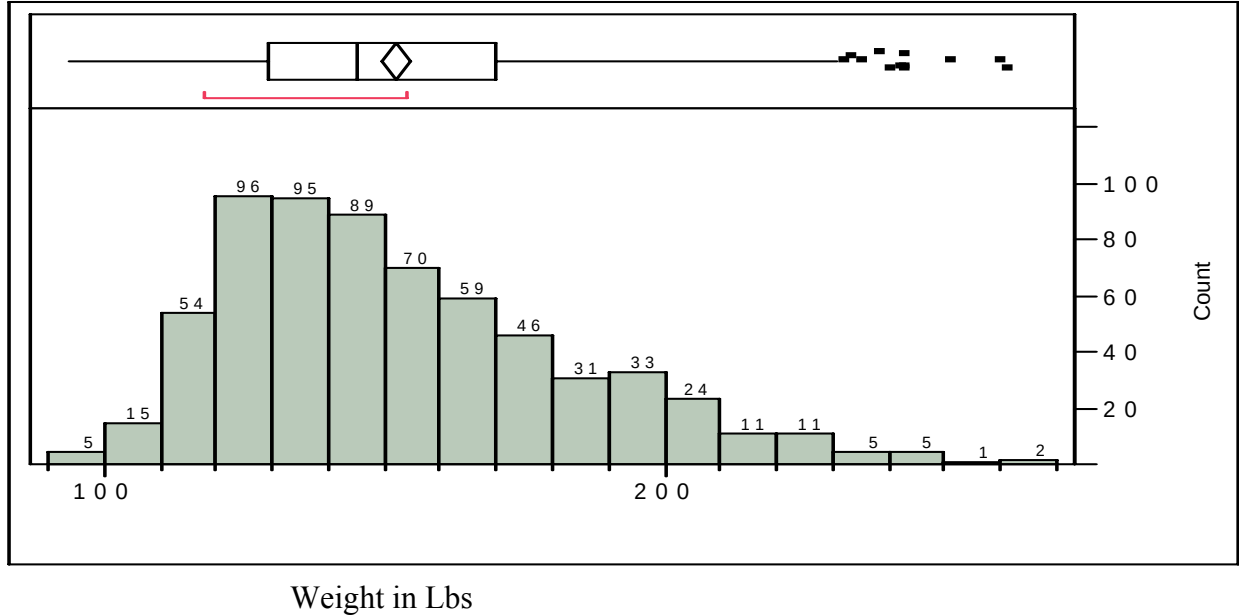
Source: Generated from NDA - "Demography Data Set"

Weight and BMI

The weight ranged from 97 to 264 lbs with a median of 147 and mean 154.5 lbs for the DR-2011 group and 94 to 261 lbs with median of 145 and mean 152.2 lbs for the Crinone 8% group while the BMI for the respective groups were: range from 16 to 38 with median 24.4 and mean 25.3 kg/m² and 15 to 38.2 with median 24.4 and mean 25.7 kg/m². Figure 4 shows the referenced distributions.

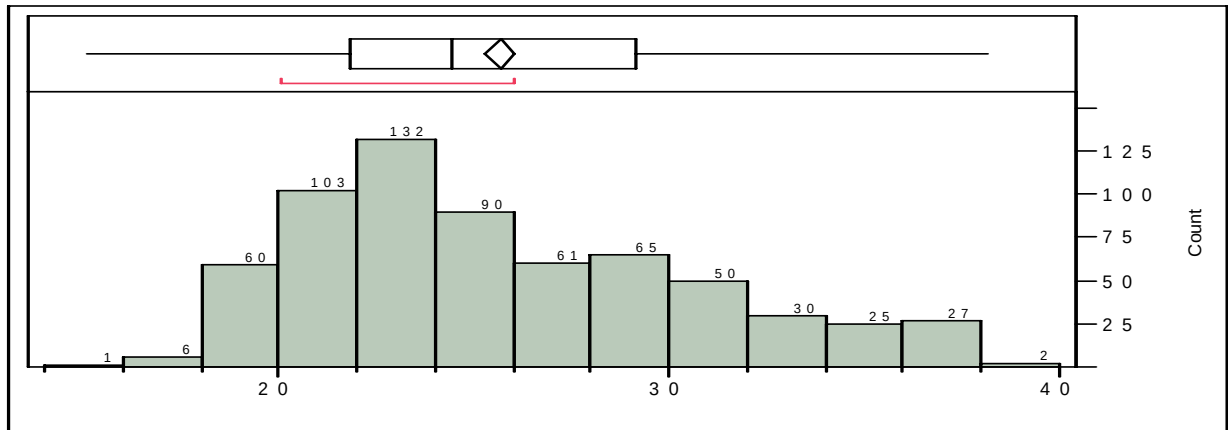
Figure 3: Weight and BMI distributions (Numbers on top of each bar represent subject numbers per arm)

WT for Crinone 8%



Maximum Weight in Lbs	261.0
Median Weight in Lbs	145.0
Minimum Weight in Lbs	94.0
Mean	152.2
N	652

BMI for Crinone 8%

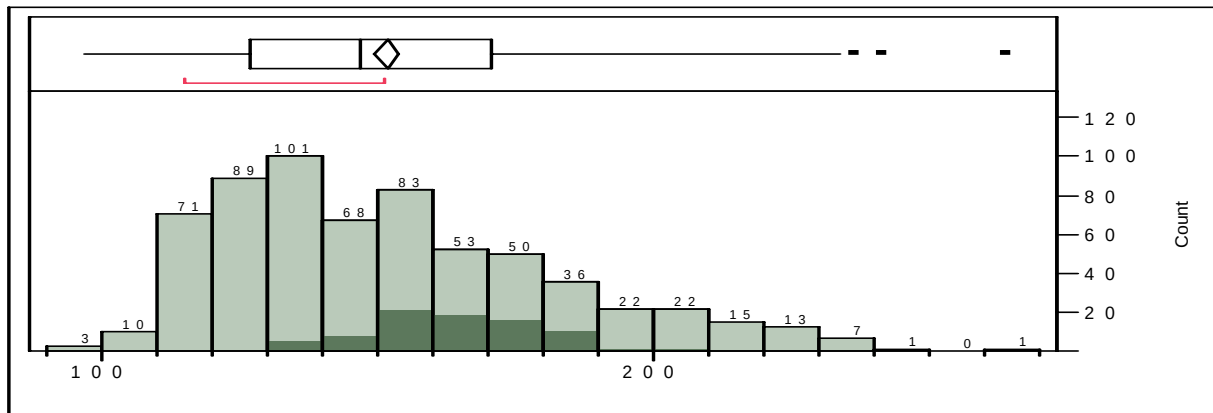


BMI in kg/m²

Maximum	38.2
Median	24.4
Minimum	15.1
Mean	25.7
N	652

Source: Generated from NDA - “Analysis Cohort Data Set”

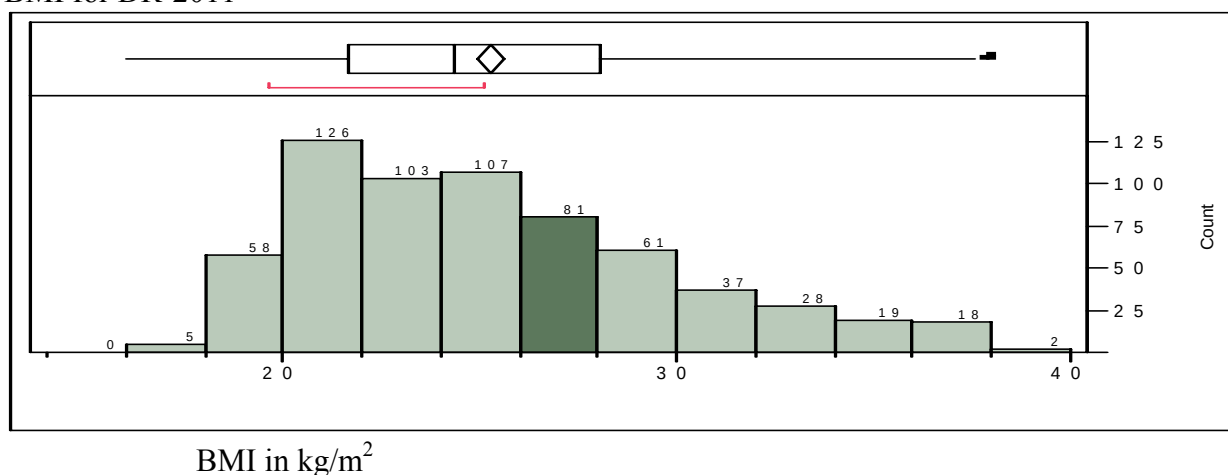
WT for DR-2011



Weight in lbs

Maximum	264.0
Median	147.0
Minimum	97.0
Mean	151.0
N	645

BMI for DR-2011



Maximum 38.01
 Median 24.37
 Minimum 16.01
 Mean 25.26
 N 645

Source: Generated from NDA - “Analysis Cohort Data Set”

Reviewer’s Comment: Overall, the study population adequately represents the target population in the US in regards to age, race and weight/BMI and groups are fairly balanced with respect to these parameters. This is in agreement with FDA’s recommendations.

Infertility Duration and Diagnosis

Almost half of the subjects had infertility for 3 years duration with the remainder of subjects divided equally between those with 1 year and those with 2 years duration.

Table 13: Duration of existing infertility

Treatment arm	<1 year N (%)	1 year N (%)	2 years N (%)	3 years N (%)
DR-2011	32 (4.9%)	138 (21.3%)	171 (26.4%)	306 (47.3%)
Crinone 8%	42 (6.4%)	184 (28.2%)	158 (24.2%)	268 (41.1%)

Source: Generated from NDA Application - “Duration of Infertility Data Set”

Table 14 Infertility Diagnoses by Treatment Group*

Specific Infertility Diagnosis	DR-2011 N(%)	Crinone N(%)
Male Factor	247 (38.2%)	259 (39.7%)
Ovulatory Dysfunction	193 (29.9%)	185 (28.4%)
Tubal Factor	165 (25.5%)	170 (26.1%)
Ideopathic (unexplained) Infertility	160 (24.7%)	138 (21.2%)
Endometriosis	146 (22.6%)	151 (23.2%)
Other	69 (10.7%)	74 (11.4%)

* Subjects in each category may have more than one infertility diagnosis

Source: Generated from NDA Application - "Duration of Infertility Data Set"

Reviewer's Comment: There were no differences in duration and diagnosis of infertility between the two treatment groups.

5.3.1.18 Treatment Compliance

Subjects maintained a study notebook for the duration of the study that was used to record the following:

- Any concomitant medications taken between visits
- For subjects randomized to the Crinone8% treatment group – subjects were expected to self-administer the gel at approximately the same time daily, beginning on the day of randomization. Subjects recorded missed doses in the study notebook. If the subject reported a missed dose, the site was instructed to contact the Duramed Study Manager to determine if the subject was still eligible to continue in the study.
- For subjects randomized to the DR-2011 treatment group – subjects were expected to place the progesterone vaginal ring (VR) on the day of randomization and self-replace with a new ring after seven days use or with the same ring in the event the ring was temporarily removed for any reason during the 7 day treatment duration. Subjects completed the Vaginal Ring Placement log with the date of insertion and removal of each new ring. Subjects were instructed to keep the VR in place (vaginally) for a minimum of 23 hours per day. The VR was not to be removed for longer than one hour over a 24-hour period. If a subject removed a ring for >1 hour at a time, they were to complete the Vaginal Ring Extended Removal log. If a subject reported having the VR out for more than 1 hour in a 24-hour period, the site was instructed to contact the Duramed Study Manager to determine if the subject was still eligible to continue in the study.

All subjects were expected to maintain dosing continuously through the 12th week of pregnancy (10 weeks after egg retrieval) if the subject became pregnant. If the pregnancy terminated before week 12, study medication was stopped.

To ensure compliance with these procedures and to assess the adequacy of quality control procedures, Duramed undertook an independent GCP audit program aimed at trial documentation, investigator sites data management, and clinical trial reports. Table 15 shows Study DR-PGN-302 treatment compliance.

Table 15: Treatment compliance

	DR-2011 (N=647)	Crinone® (N=650)	Total (N=1297)
Compliance			
≥ 90%	642 (99.2%)	641 (98.6%)	1283 (98.9%)
< 90%	3 (0.5%)	2 (0.3%)	5 (0.4%)
% Compliance			
N*	645	643	1288
Mean (Std)	99.9 (1.25)	99.7 (1.33)	99.8 (1.29)
Median	100.0	100.0	100.0
(Min, Max)	(79.4, 100.0)	(83.3, 100.0)	(79.4, 100.0)

*Nine subjects did not have valid values due to loss to follow-up

Source: Adapted from NDA, DR-PGN-302 Clinical Study Report, Table 16, p75

Reviewer's Comment: *Table 15 shows that the majority of subjects in Study DR-PGN-302 were compliant with study medication. Infertility subjects are highly motivated to take medication as directed because of their desire to have a successful pregnancy. The small number of total subjects (9 of 1297 [0.7%]) removed for reasons of compliance do not appear to have had any impact on the results of Study DR-PGN-302.*

5.3.1.19: Primary Efficacy Results

The primary efficacy variable was ongoing pregnancy, defined as identification of fetal heart movement on transvaginal ultrasound at approximately 6 and 10 weeks of gestation (6 and 10 weeks post-embryo transfer). The primary efficacy analysis was performed to determine whether the ongoing pregnancy rate for the progesterone vaginal ring applied vaginally once weekly was non-inferior to Crinone® 8% applied vaginally once daily. The analysis compared the 95% confidence interval for the ongoing pregnancy rate for each treatment group. Non-inferiority was demonstrated when the lower bound of the confidence interval excluded a difference of greater than 10% in favor of the comparator (Crinone®). As the subjects were randomized only after egg retrieval, pregnancy rates are reported per retrieval and not per cycle.

Total clinical pregnancy rates were approximately 45-49%, and similar across treatment groups for subjects aged 35-42 as well as for subjects aged 18-34. Within the 18-34 year age stratum, clinical pregnancy rates for both treatment groups were consistent with the specified rate of 50% used in the determination of the sample size. Success rates in the 35 to 42 years age stratum were somewhat lower at both Week 6 and Week 10 post embryo transfer compared to younger subjects, but the rates themselves were comparable across the treatment groups.

The lower bound of the 95% CI for subjects aged 18-34 was -4.6% at week 6 and -3.7% at week 10. This was above the 10% pre-specified in the protocol. For subjects within the 35-42 year age stratum, the sample size was not sufficient for the calculation of a 95% confidence interval that would not contain the same 10% bounds. The study was not powered to demonstrate non-inferiority for the 35 to 42 age subgroup. However, 179 women in this age range were

randomized and did receive treatment. Since the sample size of this subgroup was less than what would be required for a strict statistical inference regarding non-inferiority, the confidence intervals have been calculated and presented in this review primarily for reference. A summary of the ongoing pregnancy rates for the MITT population in the two treatment groups is shown in Table 16:

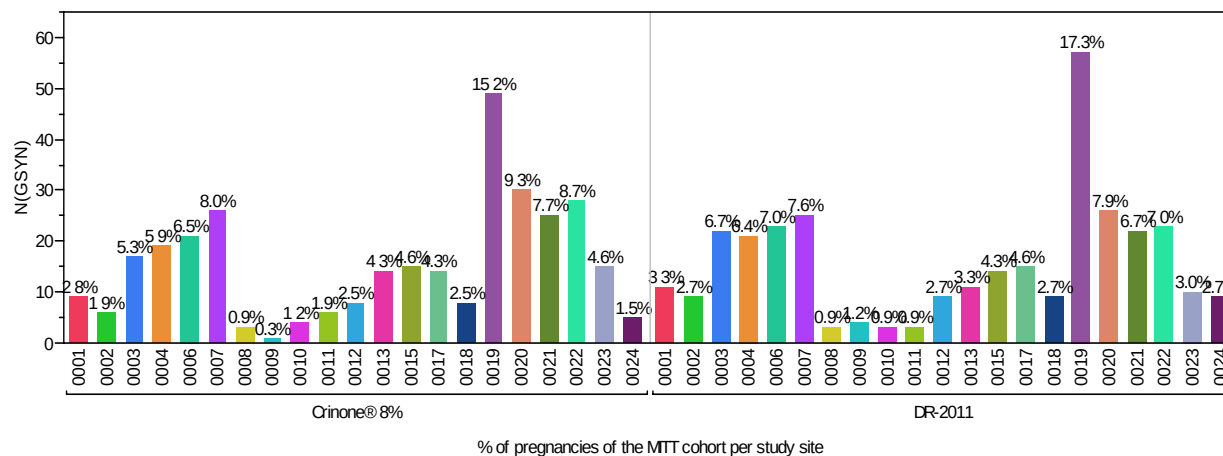
Table 16: Clinical Pregnancy Rate per Retrieval– MITT Cohort

	Weeks of Pregnancy	DR-2011 N=646		Crinone [®] N=651		DIFF (DR 2011- Crinone [®])	95% C.I. for DIFF
		N	%	N	%		
Ages 18-34	8	558	275 (49.3%)	560	269 (48.0%)	1.2%	(-4.6%, 7.1%)
	12		269 (48.2%)		258 (46.1%)	2.1%	(-3.7%, 8.0%)
All Ages (18-42)	8	646	310 (48.0%)	651	307 (47.2%)	0.8%	(-4.6%, 6.3%)
	12		300 (46.4%)		294 (45.2%)	1.3%	(-4.1%, 6.7%)
Ages 35-42	8	88	35 (39.8%)	91	38 (41.8%)	-2.0%	(-16.4%, 12.4%)
	12		31 (35.2%)		36 (39.6%)	-4.3%	(-18.5%, 9.8%)

Source: NDA DR-PGN-302 Clinical Study Report, Table 17, p76

Reviewer's Comment: Table 16 shows that DR-2011 administered vaginally once weekly treatment met the 10% non-inferiority criterion that was outlined in the protocol. As previously noted, however, the age group 35to 42 was not successful in meeting the efficacy statistical requirements, most probably because the Applicant elected to not power the study to demonstrate this predetermined non-inferiority limit, despite the repeated recommendations from the Division.

Figure 4: % of Pregnancies by treatment arm per clinical site

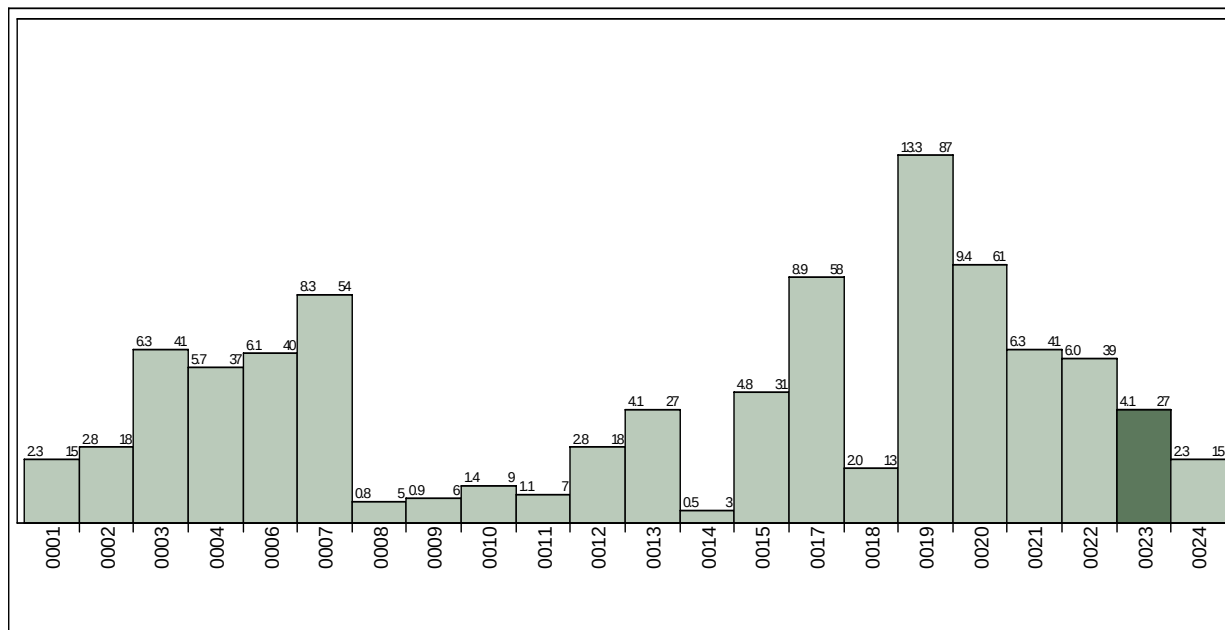


Source: Generated from NDA Application - "Pregnancy Data Set"

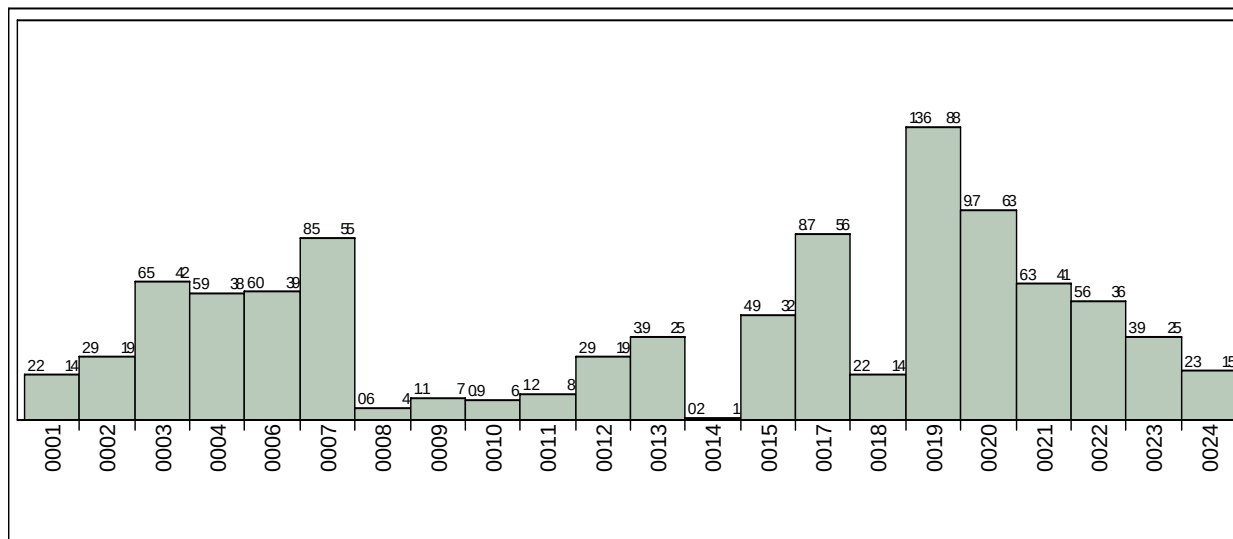
Reviewer's Comment: *Site # 19 had the most subjects and as such the most pregnancies among all sites.*

Figure 5: Number of subjects by treatment per site number (Number on the top of the bar on the left is % and the number on the right is the actual number of subjects)

Crinone® 8%



DR-2011



Source: : Generated from NDA Application - "Demography Data Set"

Reviewer's Comment: *Figures 4 and 5 show the subjects participating per site and their pregnancy success rates.*

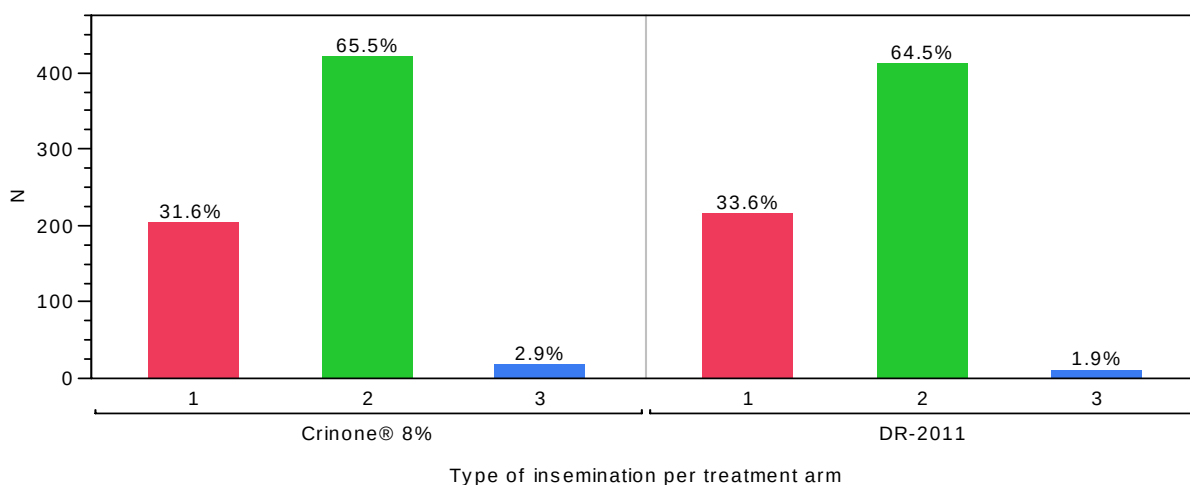
5.3.1.19.1 Additional Analyses Submitted by the Applicant

The clinical pregnancy rates at weeks 8 and 12 were also evaluated and compared between treatment groups after stratification of the MITT cohort based on type of insemination method (conventional IVF vs. ICSI), ovarian reserve (as determined by Day 2-4 serum FSH level), embryo transfer day (Day 3 or Day 5), BMI, duration of infertility, and infertility diagnosis. As the study was not powered to demonstrate non-inferiority based on these post-hoc-derived subgroup analyses, no formal statistical comparisons were made between the two treatment arms within any subgroup.

1. Type of insemination

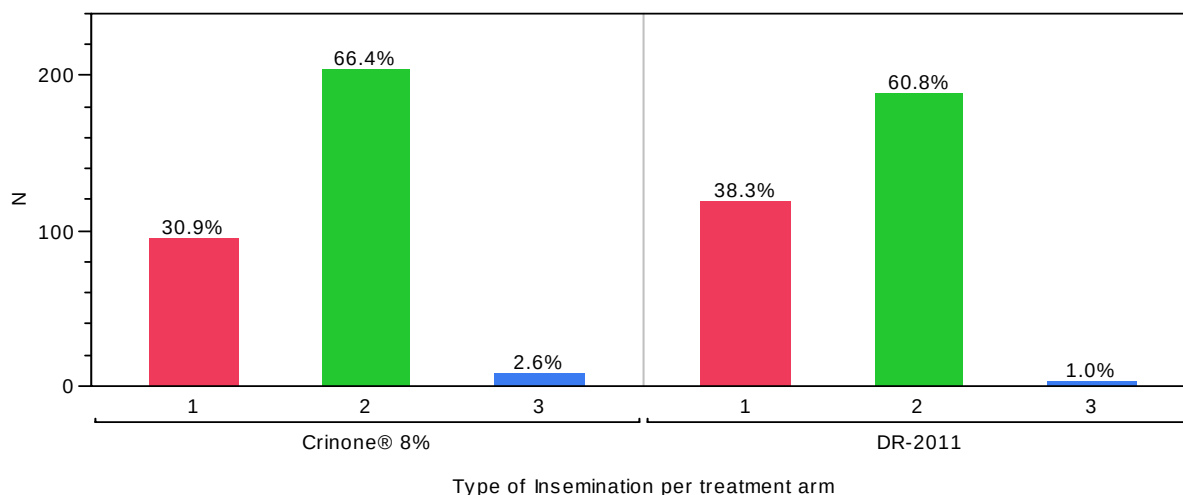
The MITT cohort was stratified and the clinical pregnancy rates at weeks 6 and 10 by type of insemination used with ART (conventional IVF versus ICSI procedures versus combined) was analyzed. In this trial, assisted hatching and experimental ART procedures were not permitted. The majority of subjects used ICSI (64.5% in the DR-2011 group and 65.5% in the Crinone® group). The distribution of insemination procedures was similar across the two treatment groups (see Figure 6). Slightly higher rates of pregnancy were observed with the DR-2011 when conventional IVF was used than with Crinone 8%, while slightly higher rates were observed with the vaginal gel when ICSI was used over the DR-2011 (see Table 17). Overall, pregnancy rates were similar among both treatment groups, regardless of which type of insemination was used. A small number of subjects utilized both methods.

Figure 6: Type of insemination per treatment arm (1=Traditional IVF, 2=ICSI, 3=Both)



Reviewer's Comment: *About 65% of subjects underwent ICSI, equally divided in both treatment arms, while 32% underwent traditional IVF*

Figure 7: Type of insemination of pregnant subjects per treatment arm (1=Traditional IVF, 2=ICSI, 3=Both)



Source: Generated from NDA Application – “Cohort and CP” data sets

Table 17: Clinical Pregnancy Rate by Type of Insemination – MITT

	Weeks of Pregnancy	DR-2011 N=646		Crinone® N=651		DIFF (DR 2011- Crinone®)	95% C.I. for DIFF
		N	%	N	%		
Conventional IVF	8	215	118 (54.9%)	203	95 (46.8%)	8.1%	(-1.5%, 17.6%)
	12		119 (55.3%)		90 (44.3%)	11.0%	(1.5%, 20.5%)
ICSI	8	414	189 (45.7%)	423	204 (48.2%)	-2.6%	(-9.3%, 4.2%)
	12		178 (43.0%)		196 (46.3%)	-3.3%	(-10.1%, 3.4%)
Both	8	12	3 (25.0%)	19	8 (42.1%)	-17.1%	(-50.2%, 16.0%)
	12		3 (25.0%)		8 (42.1%)	-17.1%	(-50.2%, 16.0%)

Source: NDA DR-PGN-302 Clinical Study Report, Table 22, p81.

Reviewer’s Comment: *There are some slight differences in the outcome data as depicted in Figures 6 and 7 and Table 17. These differences are the result of comparisons of different cohorts. As shown in Table 17, and Figure 7 slightly higher rates of pregnancy were observed in the DR-2011 treatment group when conventional IVF was used than in the Crinone 8% treatment group, while slightly higher rates of pregnancy were observed in the Crinone 8% treatment group when ICSI was used. Overall, pregnancy rates were similar among both treatment groups, regardless of which type of insemination was used. A small number of subjects utilized both methods. The study was not powered to show any differences.*

5.3.1.19.1.1 Ovarian reserve

Ovarian reserve was assessed by obtaining a serum FSH level during the early follicular phase (cycle days 2-4). Subjects with an FSH of >15mIU/mL were excluded. The vast majority of subjects had FSH levels of <10 mIU/mL, with less than 3% of subjects having an FSH in the range of 10-15 mIU/mL, indicative of diminished ovarian reserve. In the group with a FSH <10mIU/mL, clinical pregnancy rates are as high as 45-48% and comparable between treatment groups. See table 18.

Table 18: Clinical Pregnancy Rate per Retrieval by Ovarian Reserve – MITT Cohort

	Weeks of Pregnancy	DR-2011 N=646		Crinone® N=651		DIFF (DR 2011- Crinone®)	95% C.I. for DIFF
		N	%	N	%		
FSH<10 mIU/mL	8	618	297 (48.1%)	632	299 (47.3%)	0.7%	(-4.8%, 6.3%)
	12		289 (46.8%)		286 (45.3%)	1.5%	(-4.0%, 7.0%)
FSH 10-15+ mIU/mL	8	22	12 (54.5%)	17	8 (47.1%)	7.5%	(-24.1%, 39.0%)
	12		10 (45.5%)		8 (47.1%)	-1.6%	(-33.2%, 30.0%)
FSH 10-15+ or Age ≥35	8	103	43 (41.7%)	106	46 (43.4%)	-1.6%	(-15.1%, 11.8%)
	12		38 (36.9%)		44 (41.5%)	-4.6%	(-17.8%, 8.6%)
FSH 10-15+ and Age ≥35	8	7	4 (57.1%)	2	0 (0.0%)	57.1%	(20.5%, 93.8%)
	12		3 (42.9%)		0 (0.0%)	42.9%	(6.2%, 79.5%)

Source: NDA DR-PGN-302 Clinical Study Report, table 18, p77

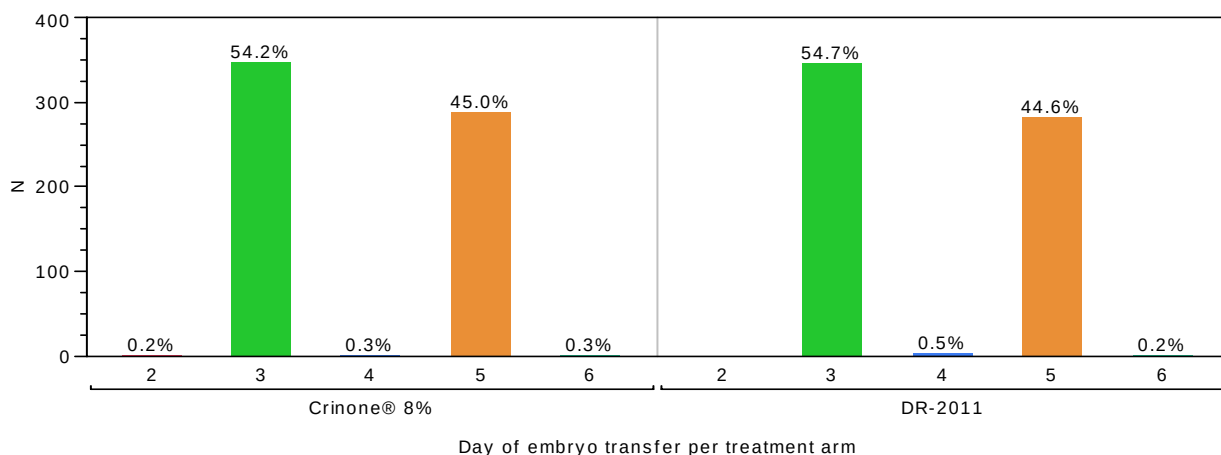
Reviewer's Comment: *Pregnancy success rates are very similar between the two treatment groups for FSH level <10mIU/mL at both 8 and 12 weeks of pregnancy. In a small subgroup of subjects (22 in the DR-2011 and 17 in the Crinone 8%) with diminished ovarian reserve (FSH 10 to 15+ mIU/mL) the pregnancy rate for the DR-2011 at 8 weeks gestation is 54.5%. Evaluating these subjects further, it was found that the majority of them had an age <34 years and FSH was <12 mIU/mL. This excellent pregnancy rate in the DR-2011 group, despite the somewhat diminished ovarian reserve, is higher than the Crinone group (54.5% vs 47.1% respectively) at 8 weeks. This difference almost disappears to similar levels for both groups at 12 weeks gestation. It is the opinion of this reviewer that no major conclusions may be drawn from these findings. The pregnancy point estimates are impressive, but the numbers are small. Additional studies, powered to demonstrate differences based on ovarian reserve would be needed to interpret the effects of diminished ovarian reserve on the efficacy of the drug product.*

Furthermore, when the analysis was done for combined FSH 10-15 mIU/mL and age ≥35, (only 9 subjects fulfilled these criteria, 7 in the DR-2011 and 2 in the Crinone group) the pregnancy point estimates are still as high as previously for the DR-2011. The subject number is very small for any meaningful conclusions. Further studies in this group of patients are needed to answer this question.

5.3.1.19.1.2 Day of Embryo Transfer

For most subjects (about 99%), embryos were transferred on either Day 3 or Day 5 after egg retrieval. There were 9 subjects who had an embryo transfer on days other than Day 3 or 5. No subject had an embryo transfer more than 6 days after egg retrieval. Clinical pregnancy rates at weeks 6 and 10 were similar between the treatment groups and ranged from between 51% and 59% for those who underwent embryo transfer on Day 5. Clinical pregnancy rates at weeks 8 and 12 of pregnancy were slightly lower for Day 3 transfers (approximate range 40%-43%), but similar between the treatment groups. A majority of subjects had their transfer on Day 3 (54.7% of subjects randomized to DR-2011 and 54.2% of subjects randomized to Crinone 8%, while 45% of subjects had day 5 transfer in both treatment arms (See Figure 8 and Table 19).

Figure 8: % of subjects by day of embryo transfer



Source: Generated from NDA Application - “Embryo Transfer” Data Set

Table 19: Pregnancy Rate by Day of Embryo Transfer Among Subjects in the MITT Cohort who Underwent Transfer on Either Day 3 or Day 5a

	Weeks of Pregnancy	DR-2011 N=646		Crinone® N=651		DIFF (DR 2011- Crinone®)	95% C.I. for DIFF
		N	%	N	%		
Day 3	8	346	143 (41.3%)	347	149 (42.9%)	-1.6%	(-9.0%, 5.7%)
	12		138 (39.9%)		144 (41.5%)	-1.6%	(-8.9%, 5.7%)
Day 5	8	281	167 (59.4%)	288	157 (54.5%)	4.9%	(-3.2%, 13.0%)
	12		162 (57.7%)		149 (51.7%)	5.9%	(-2.3%, 14.1%)

Source: NDA DR-PGN-302 Clinical Study Report, Table 19, p78

Similar results are also observed when subjects were randomized by age and day of embryo transfer (see Table 20).

Table 20: MITT Cohort who Underwent Transfer on Either Day 3 or Day 5^a

		Weeks of Pregnancy	DR-2011		Crinone [®]		DIFF (DR 2011- Crinone [®])	95% C.I. for DIFF
			N	%	N	%		
Day 3	Ages (18-34)	8	291	124 (42.6%)	290	128 (44.1%)	-1.5%	(-9.6%, 6.5%)
		12		122 (41.9%)		124 (42.8%)	-0.8%	(-8.9%, 7.2%)
	Ages (35-42)	8	55	19 (34.5%)	57	21 (36.8%)	-2.3%	(-20.0%, 15.4%)
		12		16 (29.1%)		20 (35.1%)	-6.0%	(-23.2%, 11.3%)
	All Ages	8	346	143 (41.3%)	347	149 (42.9%)	-1.60%	(-9.0%, 5.7%)
		12		138 (39.9%)		144 (41.5%)	-1.60%	(-8.9%, 5.7%)
Day 5	Ages (18-34)	8	253	151 (59.7%)	257	140 (54.5%)	5.2%	(-3.4%, 13.8%)
		12		147 (58.1%)		133 (51.8%)	6.4%	(-2.3%, 15.0%)
	Ages (35-42)	8	28	16 (57.1%)	31	17 (54.8%)	2.3%	(-23.1%, 27.7%)
		12		15 (53.6%)		16 (51.6%)	2.0%	(-23.6%, 27.5%)
	All Ages	8	281	167 (59.4%)	288	157 (54.5%)	4.90%	(-3.2%, 13.0%)
		12		162 (57.7%)		149 (51.7%)	5.90%	(-2.3%, 14.1%)

^a 26 subjects who had an egg retrieval did not have an embryo transfer. Nine subjects who had an embryo transfer (4 in DR-2011 group and 5 in Crinone[®] group) had the transfer on a day other than day 3 or day 5.

Source: NDA DR-PGN-302 Clinical Study Report, table 20, p79

Reviewer's Comment: Table 20 demonstrates that younger subjects, <35 years of age who had day 5 embryo transfer had the best successes for both treatment arms which is compatible with the CDC IVF success rates. Over all, DR-2011 and Crinone 8% treatment groups had similar success pregnancy rates when compared in same age groups and at the same day of transfer. However, Study DR-PGN-302 was not powered to demonstrate non-inferiority differences in subgroup analyses, and as such no claims may be made.

5.3.1.19.1.3 Body Mass Index

Subjects with BMI values in the range of 18.5 to 34 kg/m² had higher overall pregnancy rates than those at either extreme (see Tables 21 and 22).

In the clinical trial DR-PGN- 302, patients were to be included if they had a BMI less than 38 kg/m². Analysis of pregnancy (PR) outcome data based on [arbitrary] BMI categories suggests comparable pregnancy rates for BMI values up to <34.5 kg/m² with PR ranges from 46-48.5%. In the highest BMI category [34.5 – 38.5], the rates of pregnancy were lower with the progesterone vaginal ring formulation.

Table 21: Body Mass Index (BMI) Subgroup Results Based on MITT Population Clinical Pregnancy Rate per Retrieval

BMI	Pregnant Week	DR-2011		Crinone		Difference (DR-2011 – Crinone) (95% Confidence Interval)
		n/N	Percent	n/N	Percent	
<18.5	8	5/11	45.5%	9/18	50%	-4.5% (-42.0%, 32.9%)
	12	5/11	45.5%	9/18	50%	-4.5% (-42.0%, 32.9%)
18.5 ≤ BMI < 25	8	171/343	49.9%	161/331	48.6%	1.2% (-6.3%, 8.8%)
	12	165/343	48.1%	155/331	46.8%	1.3% (-6.3%, 8.8%)
25 ≤ BMI < 30	8	90/186	48.4%	78/168	46.4%	2.0% (-8.5%, 12.4%)
	12	89/186	47.8%	76/168	45.2%	2.6% (-7.8%, 13.0%)
30 ≤ BMI < 34	8	29/65	44.6%	35/80	43.8%	0.9% (-15.4%, 17.1%)
	12	27/65	41.5%	34/80	42.5%	-1.0% (-17.1%, 15.2%)
34 ≤ BMI < 38+	8	14/39	35.9%	24/54	44.4%	-8.5% (-28.6%, 11.5%)
	12	13/39	33.3%	20/54	37.0%	-3.7% (-23.3%, 15.9%)

Source: NDA DR-PGN-302 Statistical Review, Table A.4, p 14

Table 22: Clinical Pregnancy Rate per Retrieval by BMI – MITT

	Weeks of Pregnancy	DR-2011 N=646 ^a		Crinone [®] N=651		DIFF (DR 2011- Crinone [®])	95% C.I. for DIFF
		N	%	N	%		
BMI < 18.5 kg/m ²	8	11	5 (45.5%)	18	9 (50%)	-4.5%	(-42.0%, 32.9%)
	12		5 (45.5%)		9 (50%)	-4.5%	(-42.0%, 32.9%)
BMI ≥ 18.5 to < 25 kg/m ²	8	343	171 (49.9%)	331	161 (48.6%)	1.2%	(-6.3%, 8.8%)
	12		165 (48.1%)		155 (46.8%)	1.3%	(-6.3%, 8.8%)
BMI ≥ 25 to < 30 kg/m ²	8	186	90 (48.4%)	168	78 (46.4%)	2.0%	(-8.5%, 12.4%)
	12		89 (47.8%)		76 (45.2%)	2.6%	(-7.8%, 13.0%)
BMI ≥ 30 to < 34 kg/m ²	8	65	29 (44.6%)	80	35 (43.8%)	0.9%	(-15.4%, 17.1%)
	12		27 (41.5%)		34 (42.5%)	-1.0%	(-17.1%, 15.2%)
BMI ≥ 34 to < 38+ kg/m ²	8	39	14 (35.9%)	54	24 (44.4%)	-8.5%	(-28.6%, 11.5%)
	12		13 (33.3%)		20 (37.0%)	-3.7%	(-23.3%, 15.9%)

Source: NDA DR-PGN-302 Clinical Study Report, Table 21, p80

Reviewer's Comment: As shown in Tables 21 and 22, there are fluctuating, non-consistent differences between the two treatment groups across BMI. Steady decreasing

pregnancy rates are seen in both treatment groups as the BMI increases. The decrease of pregnancy rate is more profound in subjects with a BMI >34 kg/m² for the DR-2011 treatment group versus the Crinone 8% treatment group (35.9% vs 44.4% respectively at 6 weeks). This difference is also seen at 10 weeks post embryo transfer. No specific conclusion can be drawn from this observation except that heavier subjects may require more progesterone.

5.3.1.19.1.4 Duration and type of infertility

Pregnancy rates are comparable between the two treatment groups with a somewhat higher rate for DR-2011 over Crinone 8% when the duration of infertility is less than 3 years. This finding is reversed, however, when the duration of infertility is ≥3 years (see table 23).

Table 23: Clinical Pregnancy Rate per Retrieval by Duration of Infertility – MITT

	Weeks of Pregnancy	DR-2011 N=646		Crinone [®] N=651		DIFF (DR 2011- Crinone [®])	95% C.I. for DIFF
		N	%	N	%		
<1 year	8	32	18 (56.3%)	42	21 (50.0%)	6.3%	(-16.6%, 29.1%)
	12		17 (53.1%)		20 (47.6%)	5.5%	(-17.5%, 28.5%)
1<=years<2	8	138	72 (52.2%)	184	83 (45.1%)	7.1%	(-3.9%, 18.1%)
	12		68 (49.3%)		80 (43.5%)	5.8%	(-5.2%, 16.8%)
2<=years<3	8	170	91 (53.5%)	158	69 (43.7%)	9.9%	(-0.9%, 20.6%)
	12		88 (51.8%)		66 (41.8%)	10.0%	(-0.8%, 20.7%)
>= 3 years	8	306	129 (42.2%)	267	134 (50.2%)	-8.0%	(-16.2%, 0.1%)
	12		127 (41.5%)		128 (47.9%)	-6.4%	(-14.6%, 1.7%)

Source: NDA DR-PGN-302 Clinical Study Report, Table 23, p81

Reviewer's Comment: *As demonstrated in Table 23, the pregnancy rates for the DR-2011 treatment group follows the expectation that the longer the infertility, the less successful pregnancy rate. There is no explanation, however, why this does not hold true for the Crinone 8% treatment group. A decrease in the pregnancy rate is shown up to less than 3 years with a rebound after 3 years.*

When examined by type of infertility diagnosis, pregnancy rates differ. The most common infertility diagnosis influencing pregnancy rates for the DR-2011 treatment group appears to be male factor followed by ovulatory dysfunction. The most common infertility diagnosis influencing pregnancy rates for the Crinone 8% treatment group appears to be male factor followed by tubal factor. When idiopathic and other factors are considered, it appears that DR-2011 has a somewhat better pregnancy rate results.

Over all, it appears that infertility diagnosis did not have any significant impact upon the pregnancy rates between the two treatment groups (See Table 24).

Table 24: Clinical Pregnancy Rate per Retrieval by Infertility Diagnosis – MITT

	Weeks of Pregnancy	DR-2011		Crinone [®]		DIFF (DR 2011-Crinone [®])	95% C.I. for DIFF
		N	%	N	%		
Tubal Factor	8	164	69 (42.1%)	169	82 (48.5%)	-6.4%	(-17.1%, 4.2%)
	12		69 (42.1%)		78 (46.2%)	-4.1%	(-14.7%, 6.6%)
Ovulatory Dysfunction	8	193	103 (53.4%)	184	95 (51.6%)	1.7%	(-8.3%, 11.8%)
	12		100 (51.8%)		93 (50.5%)	1.3%	(-8.8%, 11.4%)
Endometriosis	8	146	72 (49.3%)	150	73 (48.7%)	0.6%	(-10.7%, 12.0%)
	12		69 (47.3%)		71 (47.3%)	-0.1%	(-11.4%, 11.3%)
Male Factor	8	247	123 (49.8%)	259	128 (49.4%)	0.4%	(-8.3%, 9.1%)
	12		117 (47.4%)		123 (47.5%)	-0.1%	(-8.8%, 8.6%)
Idiopathic Factor	8	160	73 (45.6%)	138	57 (41.3%)	4.3%	(-7.0%, 15.6%)
	12		69 (43.1%)		55 (39.9%)	3.3%	(-7.9%, 14.5%)
Other Factor	8	69	30 (43.5%)	74	24 (32.4%)	11.0%	(-4.8%, 26.9%)
	12		29 (42.0%)		23 (31.1%)	10.9%	(-4.8%, 26.7%)

Note: Subjects could have more than one infertility diagnosis

Source: NDA DR-PGN-302 Clinical Study Report, Table 25, p82

Reviewer's Comment: *As expected, the best pregnancy rates occurred in subjects with ovulatory dysfunction, followed by male factor and endometriosis. It is not surprise that idiopathic factor demonstrates the lowest pregnancy rates. Since the etiology is unknown, gonadotropin/progesterone support is not a directed treatment.*

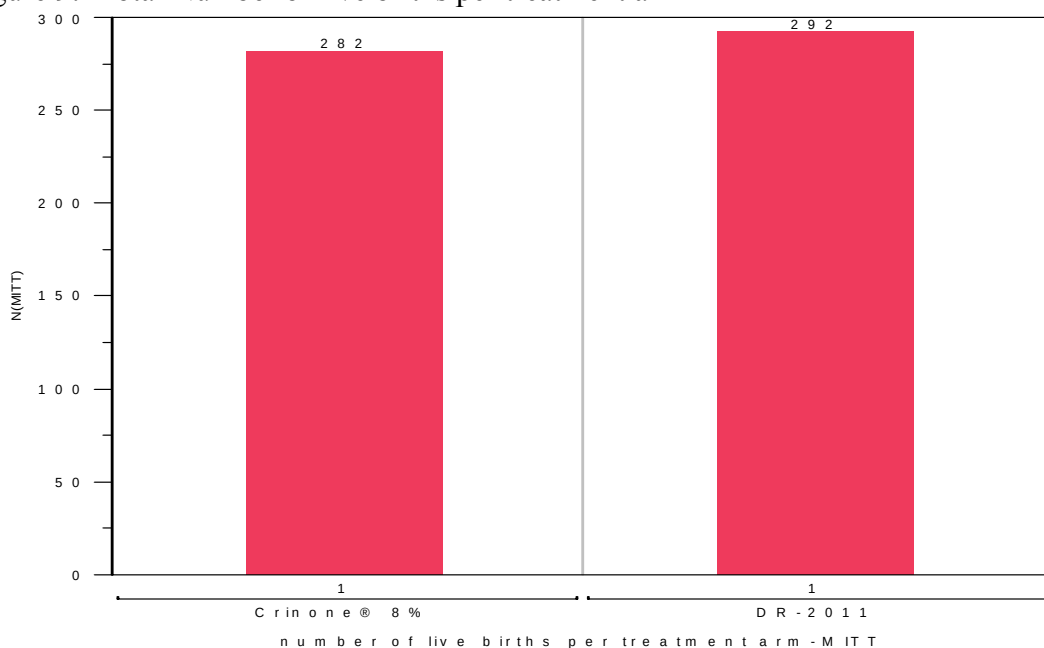
5.3.1.20 Secondary Efficacy Results

Secondary efficacy analyses included evaluations of live birth rate, cycle cancellation rate, rate of spontaneous abortion, rate of biochemical pregnancy, and rate of ectopic pregnancy for each treatment group.

5.3.1.20.1 Live Birth Rates

There were total 292 live births for DR-2011 and 282 for Crinone 8% in study DR-PNG-302 (see Figure 9).

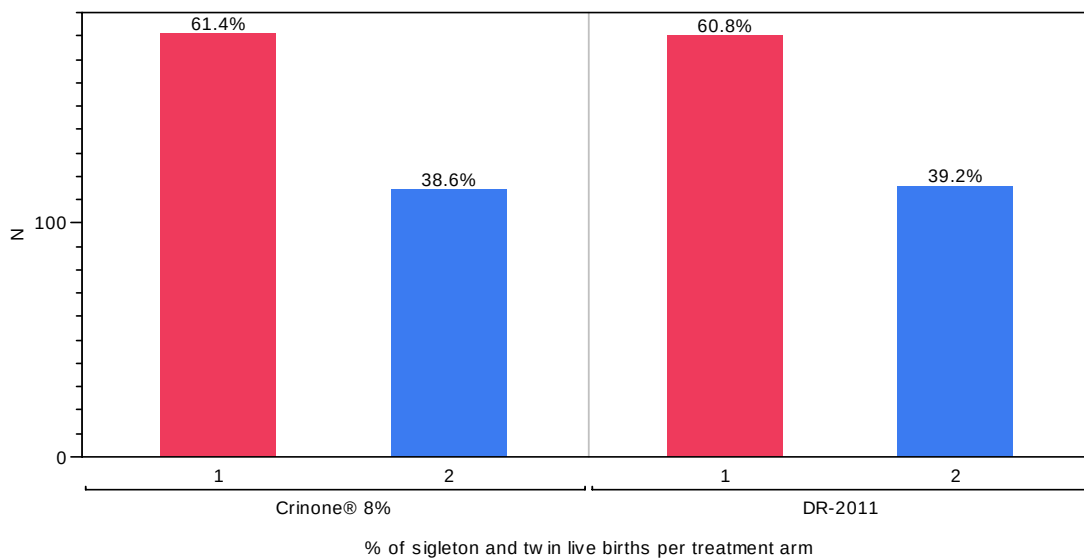
Figure 9: Total Number of live births per treatment arm-MITT



Source: Generated from NDA Application, “Cohort” Data Set

Figure 10 illustrates the percentage of singleton and twin live births. Both Figures 9 & 10 demonstrate very similar results.

Figure 10: Percentage of single and twin live birth



Source: Generated from NDA Application - “Post Pregnancy Phone Call” Data Set

Reviewer's Comment: The Figures above demonstrate the distribution of the categories of total, singleton and twin live births is very similar across the two treatment arms.

Table 25 shows live birth rates per retrieval for both treatment groups for all ages and for the 18-34 year old, and 35-42 year old age group. The live birth rate per retrieval for DR-2011 was 47% compared to 44.5% for Crinone 8% for the 18-34 year olds, 34.1% versus 36.3% for the 35 to 42 year olds, and 45.2% for the vaginal ring compared to 43.3% for Crinone 8% for all ages.

Table 25: Live Birth Rate per Retrieval – MITT Cohort

Age	DR-2011		Crinone		Difference (DR-2011 – Crinone) (95% Confidence Interval)
	n/N	Percent	n/N	Percent	
18-34	262/558	47.0%	249/560	44.5%	2.5% (-3.3%, 8.3%)
35-42	30/88	34.1%	33/91	36.3%	-2.2% (-16.2%, 11.8%)
All	292/646	45.2%	282/651	43.3%	1.9% (-3.5%, 7.3%)

Source: Statistical Analysis Review, Table 3.2.4, p10

5.3.1.20.2 Spontaneous Abortion Rates

Spontaneous abortion, typically defined as the loss of pregnancy prior to 12 weeks gestation, is often attributed to chromosomal abnormalities, but could also be an indicator of inadequate progestational support prior to the attainment of adequate levels of independent placental progesterone secretion. In this study, investigators used the Case Report form (CRF) to record spontaneous abortions. Adverse event listings were also reviewed and all related AE terms (spontaneous abortion, blighted ovum, fetal demise, missed abortion, miscarriage) that occurred during the treatment period were included in this analysis. Subjects with multiple gestational sacs and one of the AE terms listed above who maintained at least one viable fetus (resulting in a live birth), were not included in the calculation of spontaneous abortion rates. Table 26 shows that spontaneous abortion rates were similar for both treatment groups for all subjects and for those subjects <35 years. Overall, spontaneous abortion rates were approximately 5% regardless of treatment group, with higher rates observed in the older subjects.

Table 26: Spontaneous Abortion Rate per Retrieval – MITT Cohort

Spontaneous Abortion Rate	DR-2011 N=646		Crinone® N=651		DIFF (DR 2011- Crinone®)	95% C.I. for DIFF
	N	%	N	%		
Ages 18-34	558	27 (4.8%)	560	30 (5.4%)	-0.5%	(-3.1%, 2.1%)
All Ages (18-42)	646	35 (5.4%)	651	36 (5.5%)	-0.1%	(-2.6%, 2.4%)
Ages (35-42)	88	8 (9.1%)	91	6 (6.6%)	2.5%	(-5.4%, 10.4%)

Source: NDA DR-PGN-302 Clinical Study Report, Table 28, p85

Table 27: Spontaneous Abortion Rate per Retrieval – MITT Cohort

Age	DR-2011		Crinone		Difference (DR-2011 – Crinone) (95% Confidence Interval)
	n/N	Percent	n/N	Percent	
18-34	28/558	5.0%	30/560	5.4%	-0.3% (-2.9%, 2.3%)
35-42	8/88	9.1%	8/91	8.8%	0.3% (-8.1%, 8.7%)
All	36/646	5.6%	38/651	5.8%	-0.3% (-2.8, 2.3%)

Source: Generated from NDA-“AEs” Data Set

However, a review of adverse events (AEs) regarding spontaneous abortions under the MedDRA terms missed abortions, spontaneous abortions and blighted ovum reveals somewhat different results.

<i>Abortions</i>	<i>DR-2011 N = 646 n (%)</i>	<i>Crinone 8% N = 651 N (%)</i>
<i>Missed Abortions</i>	<i>18 (2.8%)</i>	<i>16 (2.4%)</i>
<i>Spontaneous Abortions</i>	<i>14 (2.2%)</i>	<i>14 (2.2%)</i>
<i>Blighted Ovum</i>	<i>16 (2.5%)</i>	<i>17 (2.6)</i>
<i>Total Abortions</i>	<i>48 (7.4%)</i>	<i>47 (7.3%)</i>

5.3.1.20.3 Biochemical Pregnancy Rates

Biochemical pregnancy, as defined in the protocol, was a clinical diagnosis described by the following criteria:

1. β -hCG level at Visit 6 reached at least 5 mIU;
OR
2. The β hCG ratio of any two consecutive visits (blood draws) occurring at least 2 days apart with a ratio less than 1.0 between the later visit and the earlier visit;
AND
3. No gestational sac was ever seen on ultrasound;
AND
4. The pregnancy was not identified as ectopic.

Using these definitions, the biochemical pregnancy rates were less than 10% and were similar for both treatment groups, for subjects of all ages as well as those aged 18-34 (See Table 28).

Table 28: Biochemical Pregnancy Rate – MITT Cohort

Biochemical Pregnancy Rate	DR-2011 N=646		Crinone® N=651		DIFF (DR 2011- Crinone®)	95% C.I. for DIFF
	N	%	N	%		
Ages 18-34	548	40 (7.2%)	551	47 (8.4%)	-1.2%	(-4.4%, 1.9%)
All Ages (18-42)	646	49 (7.6%)	651	52 (8.0%)	-0.4%	(-3.3%, 2.5%)

Source: NDA DR-PGN-302 Clinical Study Report, table 28, p85

5.3.1.20.4 Ectopic Pregnancy rates

The number and percentage of ectopic pregnancies as determined from the AEs Data Set provided by the Applicant are presented in Table 29. There were 7 ectopic pregnancies in the DR-2011 treatment group and 8 in the Crinone 8% treatment group representing 1.1% and 1.2% of the MITT cohort, respectively.

Table 29: Ectopic Pregnancy Rate – MITT Cohort

Ectopic Pregnancy Rate	DR-2011 N=646		Crinone® N=651		DIFF (DR 2011- Crinone®)	95% C.I. for DIFF
	N	%	N	%		
Ages 18-34	558	5 (0.9%)	560	6 (1.1%)	-0.2%	(-1.3%, 1.0%)
All Ages (18-42)	646	7 (1.1%)	651	8 (1.2%)	-0.1%	(-1.3%, 1.0%)
Ages (35-42)	88	2 (2.3%)	91	2 (2.2%)	0.1%	(-4.3%, 4.4%)

Source: NDA DR-PGN-302 Clinical Study Report, Table 31, p86

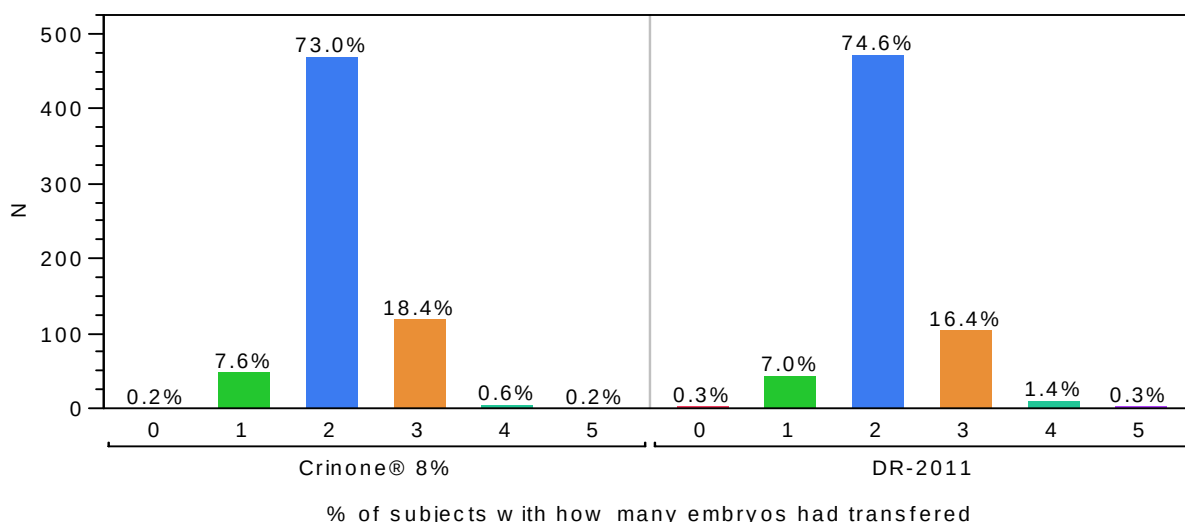
Reviewer's Comment: These findings are well within the expected range of ectopic pregnancies reported in the literature.

5.3.1.20.5 Additional Analyses:

5.3.1.20.5.1 Embryos transferred

There were no differences between the treatment groups in the distribution of the number of embryos transferred. Figure 11 shows the percent of subjects and the number of embryos transferred. About 80% of subjects in each treatment group had up to two embryos transferred while 16.5% in the Crinone 8% treatment group and 18.5% in DR-2011 treatment group had 3 embryos transferred. Furthermore, 0.8% of subjects in the Crinone 8% treatment group and 1.7% in the DR-2011 treatment group had 4 or 5 embryos transferred.

Figure 11: Percent of subjects with how many embryos had transferred



Source: Generated from NDA - “Egg Retrieval” Data Set

As shown in table 30, there were slightly more embryos transferred in the older age group compared to the younger age group (a mean of 2.48 for the DR-2011 treatment group and a mean of 2.42 for Crinone 8% treatment group in subjects aged 35-42., and a mean of 2.08 for both treatment groups combined in subjects aged <35).

Table 30: Mean Number of Embryos Transferred – by Age

	Mean (Std) of Embryos Transferred	
	DR-2011 (N=646)	Crinone® (N=651)
# of Embryo Transferred	631	640
All Ages	2.13 (0.550)	2.13 (0.534)
Ages (18-34)	2.08 (0.488)	2.08 (0.470)
Ages (35-42)	2.48 (0.771)	2.42(0.766)

Source: NDA DR-PGN-302 Clinical Study Report, Table 133, p192

Reviewer’s Comment: *The majority of subjects had one or most commonly 2 embryos transferred which is consistent with common clinical practice in the US.*

5.3.1.20.5.2 Multiple Pregnancy Rates

Table 31 displays the rates of singleton, twin, and triplet pregnancy at the weeks 8 and 12 time points for the two treatment groups and across all subjects. At both weeks 8 and 12,

approximately 60% of the pregnancies were singleton, 36-38% were twin gestations, and less than 3% were triplets. There were no higher order multiple gestations beyond triplets. The distribution of singleton, twin and triplet gestation was similar between the two treatment groups at both time points. The lower number of subjects (N) for week 12 represent twin gestations that were reduced naturally from twins to singletons.

Table 31: Number of Subjects and Distribution of Viable Fetuses as Seen on Ultrasound (All Ages) – MITT Cohort

	DR-2011	Crinone®	Total
Weeks of Pregnancy			
Week 8	N=310	N=307	N=617
Singleton	182 (58.7%)	185 (60.3%)	367 (59.5%)
Twins	120 (38.7%)	119 (38.8%)	239 (38.7%)
Triplets	8 (2.6%)	3 (1.0%)	11 (1.8%)
Week 12	N=300	N=294	N=594
Singleton	182 (60.7%)	183 (62.2%)	365 (61.4%)
Twins	110 (36.7%)	109 (37.1%)	219 (36.9%)
Triplets	8 (2.7%)	2 (0.7%)	10 (1.7%)

Source: NDA DR-PGN-302 Clinical Study Report, Table 34, p88

Table 32 provides the same information for the <35 year old age group. The proportions of singleton, twin, and triplet pregnancies are similar to the proportions observed with the entire study population. For the younger age group, age <35 years, at 8weeks gestation the singleton pregnancies were 56.4% for the DR-2011 treatment group and 60.2% for the Crinone 8% treatment group with twin pregnancies of 41.1% and 39.0% respectively. At 12 weeks gestation, the single pregnancies were 58.7% for the DR-2011 treatment group and 61.6% for the Crinone 8% treatment group, while twin gestations represented 38.7% and 37.6%, respectively.

Table 32: Number of Subjects and Distribution of Viable Fetuses as Seen on Ultrasound (Age 18-34) – MITT Cohort

	DR-2011	Crinone®	Total
Weeks of Pregnancy			
Week 8	N=275	N=269	N=544
Singleton	155 (56.4%)	162 (60.2%)	317 (58.3%)
Twins	113 (41.1%)	105 (39.0%)	218 (40.1%)
Triplets	7 (2.5%)	2 (0.7%)	9 (1.7%)
Week 12	N=269	N=258	N=527
Singleton	158 (58.7%)	159 (61.6%)	317 (60.2%)
Twins	104 (38.7%)	97 (37.6%)	201 (38.1%)
Triplets	7 (2.6%)	2 (0.8%)	9 (1.7%)

Source: NDA DR-PGN-302 Clinical Study Report, Table 35, p88

Of the 292 subjects who had a live birth after having been randomized to the DR-2011 treatment group, 61.3% had a singleton birth, 36.0% delivered twins and 2.7% had triplets (see 33).

Of the 282 subjects who had a live birth after being randomized to Crinone 8%, 63.8% had a singleton birth, 35.5% had twins and 0.7% delivered triplets (see Table 33). The rates of live births were similar between the two study drug groups.

Table 33: Distribution of Multiple Births Among All Subjects with a Live Birth

	DR-2011 (N=292)	Crinone® (N=282)	Total (N=574)
All Ages			
Singleton	179 (61.3%)	180 (63.8%)	359 (62.5%)
Twins	105 (36.0%)	100 (35.5%)	205 (35.7%)
Triplets	8 (2.7%)	2 (0.7%)	10 (1.7%)
	DR-2011 (N=262)	Crinone® (N=249)	Total (N=511)
Ages 18-34			
Singleton	154 (58.8%)	156 (62.7%)	310 (60.7%)
Twins	101 (38.6%)	91 (36.5%)	192 (37.6%)
Triplets	7 (2.7%)	2 (0.8%)	9 (1.8%)

Source: NDA DR-PGN-302 Clinical Study Report, Table 37, p91

Reviewer's Comment: Overall, approximately 37.4% of live births in this study resulted in the delivery of more than one infant. The rate of singleton deliveries (61.3%) in the DR-2011

group is much higher than the CDC 2006 report of 22.4% singletons per cycle or 24.5% singletons per transfer. Singleton deliveries are very much desired. The rate of multiple gestations is more likely to be directly determined by the number of embryos transferred and other factors (such as, maternal age, quality of embryos, etc.) rather than the use of supplemental progesterone.

Prematurity (preterm delivery) is defined as a delivery prior to 37 weeks of gestation. All ten pregnancies with triplets resulted in a preterm delivery; (see Tables 33 and 34), approximately 68% of all twin pregnancies resulted in a preterm birth (71.4% in the subjects randomized to DR-2011 and 65% in the subjects randomized to Crinone®), while 13.1% of all singleton pregnancies resulted in a preterm birth (14.5% for DR-2011 and 11.7% for Crinone®).

Table 34: Number (Percentage) of Live Births of Preterm Infants

	DR-2011 (N=292)	Crinone® (N=282)	Total* (N=574)*
Preterm Infants			
Singleton	26 (8.9%)	21 (7.4%)	47 (8.2%)
Twin	75 (25.7%)	65 (23.1%)	140 (24.4%)
Triplets	8 (2.7%)	2 (0.7%)	10 (1.7%)
Total	109 (37.3%)	88 (31.2%)	197 (34.3%)

*subjects with live birth

Source: NDA DR-PGN-302 Clinical Study Report, table 38, p91

5.3.1.21 Safety-Event Overview

The safety event overview is shown in Table 34. The total number of adverse events was 542, with 266 for DR-2011 and 276 for Crinone 8%.

Table 35: Trial DR-PGN-302 Overview of the Number (%) of Subjects with Adverse Events

Subject AE Description	DR-2011 N=647 n(%)	Crinone 8% N=650 n(%)	<u>Total</u> N=1297 n(%)
At least 1 AE	618 (95.5%)	610 (93.8%)	1228 (94.7%)
Non-fatal SAEs	83 (12.8%)	72 (11.1%)	155 (12.0%)
Maternal and Neonatal SAEs during the follow –up period	91 (14.1%)	79 (12.2%)	170 (13.1%)

Discontinuation of study drug due to an AE*	44 (6.8%)	36 (5.5%)	80 (6.2%)
Deaths	0 (0%)	0 (0%)	0 (0%)

*Most of the AEs leading to discontinuation were related to pregnancy loss and therefore are classified as serious adverse events (SAEs).

AE: Adverse event; SAE: Serious adverse event

Source: NDA DR-PGN-302 Clinical Study Report, pp98 & 109

5.3.1.22 Safety-Deaths

There were no maternal deaths during the conduct of Trial DR-PGN-302. There were 2 neonatal deaths, 1 in each treatment group.

5.3.1.23 Safety-Non Fatal Serious Adverse Events

In Study DR-PGN-302, a total of 155 subjects in the safety cohort (12.0%, 155 of 1297 subjects reported serious adverse events (SAEs) (83 subjects (12.8%) of the 647 subjects randomized to DR-2011 and 72 (11.1%) of 650 subjects randomized to Crinone 8%). For subjects who became pregnant during the study, SAEs were reported during the study period which encompasses enrollment through the first trimester. These 155 subjects reported a total of 162 SAEs. One hundred forty four [144 (89%)] SAEs were related to pregnancy; 18 SAEs (11%) were not pregnancy related.

Intrauterine death, missed abortion and blighted ovum accounted for the majority of SAEs related to pregnancy (see Table 36). Of the 18 SAEs that were unrelated to pregnancy, 11 (6.8%) were related to OHSS [4 (2.5%) of 83 subjects with SAEs in the DR-2011 treatment group and 7 (4.3%) of 72 subjects with SAEs in the Crinone 8% treatment group].

Table 36: Incidence of Serious Adverse Events (SAEs)

MedDRA System Organ Class and Preferred Term	DR-2011 (N=647)		Crinone® (N=650)		Total (N=1297)	
	N	%	N	%	N	%
All SAEs	83	12.83	72	11.08	155	11.95
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS						
Total Disorders	76	11.75	63	9.69	139	10.72
INTRA-UTERINE DEATH	23	3.55	16	2.46	39	3.01
ABORTION MISSED	18	2.78	14	2.15	32	2.47
BLIGHTED OVUM	16	2.47	17	2.62	33	2.54
ABORTION SPONTANEOUS	8	1.24	9	1.38	17	1.31
ECTOPIC PREGNANCY	6	0.93	7	1.08	13	1.00
HYPEREMESIS GRAVIDARUM	4	0.62	1	0.15	5	0.39
CERVICAL INCOMPETENCE	1	0.15	0	0.00	1	0.08
RETAINED PRODUCTS OF CONCEPTION	1	0.15	0	0.00	1	0.08
RUPTURED ECTOPIC PREGNANCY	1	0.15	0	0.00	1	0.08
HETEROTOPIC PREGNANCY	0	0.00	1	0.15	1	0.08
REPRODUCTIVE SYSTEM AND BREAST DISORDERS						
Total Disorders	5	0.77	7	1.08	12	0.93
OVARIAN HYPERSTIMULATION SYNDROME	4	0.62	7	1.08	11	0.85
OVARIAN CYST	1	0.15	0	0.00	1	0.08
CONGENITAL, FAMILIAL AND GENETIC DISORDERS						
Total Disorders	1	0.15	4	0.62	5	0.39
FOETAL CHROMOSOME ABNORMALITY	1	0.15	2	0.31	3	0.23
CONGENITAL ANOMALY IN OFFSPRING	0	0.00	2	0.31	2	0.15
GASTROINTESTINAL DISORDERS						
INTRA-ABDOMINAL HAEMORRHAGE	1	0.15	0	0.00	1	0.08
METABOLISM AND NUTRITION DISORDERS						
DEHYDRATION	1	0.15	0	0.00	1	0.08
RENAL AND URINARY DISORDERS						
BLADDER PERFORATION	1	0.15	0	0.00	1	0.08
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
PLEURAL EFFUSION	1	0.15	0	0.00	1	0.08
INFECTIONS AND INFESTATIONS						
PELVIC INFLAMMATORY DISEASE	0	0.00	1	0.15	1	0.08
NERVOUS SYSTEM DISORDERS						
SYNCOPE	0	0.00	1	0.15	1	0.08

Source NDA DR-PGN-302 Clinical Study Report, Table 53, p110

Table 37 shows SAEs for mothers and neonates observed during the follow up period (after 12 week of gestation until one month after delivery). An individual subject may have developed more than one SAE. A total of 170 of the 1297 subjects in the safety cohort (13.11%) reported SAEs (91 subjects [14.1%] in the DR-2011 treatment group and 79 subjects [13.1%] in the Crinone 8% treatment group).

Table 37: Summary of SAEs during follow up Period

	DR-2011 (N=647)	Crinone 8% (N=650)	Total (N=1297)
Total Number of			
All SAEs	204	162	366
Neonatal SAEs	127	107	234
Subject with			
All SAEs	91 (14.1%)	79 (12.2%)	170 (13.1%)
Neonatal SAEs	70 (10.8%)	54 (8.3%)	124 (9.6%)

Source: NDA DR-PGN-302 Clinical Study Report, Table 181, p403

Reviewer's Comment: The majority of SAEs reported in the follow-up period were pregnancy related. There were no differences observed in the rates of SAEs during the study period between the treatment groups. These findings are confirmed from the data sets provided (AE data set). Results are well within the expected established rates for the respective SAEs. No specific safety signal is observed.

Table 38 demonstrates the incidence of congenital anomalies reported during the follow-up period in Study DR-PGN-302.

Table 38: Serious Adverse Events During Follow-Up Period (Maternal and Neonatal)

MedDRA System Organ Class and Preferred Term	DR-2011 (N=647)		Crinone [®] (N=650)		Total (N=1297)	
	N	%	N	%	N	%
ANY AE						
Total Disorders	91	14.06	79	12.15	170	13.11
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS						
Total Disorders	80	12.36	66	10.15	146	11.26
PREMATURE BABY	56	8.66	40	6.15	96	7.40
PREMATURE LABOUR	12	1.85	12	1.85	24	1.85
PRE-ECLAMPSIA	10	1.55	5	0.77	15	1.16
PREMATURE RUPTURE OF MEMBRANES	6	0.93	1	0.15	7	0.54
NEONATAL DISORDER	5	0.77	5	0.77	10	0.77
PREGNANCY INDUCED HYPERTENSION	5	0.77	1	0.15	6	0.46
ABORTION SPONTANEOUS	3	0.46	2	0.31	5	0.39
HELLP SYNDROME	3	0.46	1	0.15	4	0.31
OLIGOHYDRAMNIOS	3	0.46	0	0.00	3	0.23
CONGENITAL, FAMILIAL AND GENETIC DISORDERS						
Total Disorders	9	1.39	10	1.54	19	1.46
CONGENITAL ANOMALY IN OFFSPRING	5	0.77	8	1.23	13	1.00
FOETAL CHROMOSOME ABNORMALITY	2	0.31	1	0.15	3	0.23
KLINEFELTER'S SYNDROME	1	0.15	0	0.00	1	0.08
MULTIPLE CONGENITAL ABNORMALITIES	1	0.15	0	0.00	1	0.08
HOLOPROSENCEPHALY	0	0.00	1	0.15	1	0.08

Source: NDA DR-PGN-302 Clinical Study Report, Table 54, p112-3

The rest are reported in frequencies of less than 0.5% each among the different organ system

Reviewer's Comment: *The incidence of congenital anomalies in this study are as expected in this population and do not raise any major concerns as a signal for SAEs.*

Table 39: Birth defects by treatment group

Treatment Group	Description of Fetal Anomalies
DR-2011 (N=647 subjects) N=413 infants born	N=12 total anomalies Trisomy 21 (n=2) Arthrogryposis akinesia Klinefelter's syndrome Left foot deformity Multiple congenital anomalies Multiple congenital anomalies-VACTERL association Hypospadias Pyloric stenosis Turner's syndrome Tetralogy of Fallot Spina bifida
Crinone® (N=650 subjects) N=386 infants born	N=17 total anomalies Abnormal karyotype Trisomy 16 Multiple fetal anomalies Acrania Hypospadias (n=2) Bilateral hernias Cleft palate Anencephaly Spina bifida/hydrocephalus Congenital heart disease (n=2) Atrial septal defect Holoprosencephaly Enlarged clitoris/cardiac defect/hydrocephalus Monosomy X Hypospadias/hydrocephalus

Source: NDA DR-PGN-302 Clinical Study Report, Table 57, p118

Reviewer's Comment: There were no differences observed in the rates of SAEs during the study period between the treatment groups. These findings are confirmed from the data sets provided (AE data set). Results are well within the expected established rates for the respective AEs and SAEs. No specific signal is observed.

Table 40 summarizes the pregnancy follow-up in Study DR-PGN-302

Table 40: Summary of Pregnancy Follow-up

Pregnancy Follow-up – MITT (% per retrieval)		
Pregnancy Outcome	DR-2011 (N=646)	Crinone 8% (N=651)
Selective Reduction	1 (0.2%)	2 (0.3%)
Miscarriage following chorionic villus sampling	0 (0%)	0 (0%)
Spontaneous Abortion ^a	35 (5.4%)	36 (5.5%)
Ectopic pregnancy	7 (1.1%)	8 (1.2%)
Elective Abortion ^b	2 (0.3%)	3 (0.5%)
2nd trimester fetal loss	7 (1.1%)	10 (1.5%)
3rd trimester fetal loss/Still Birth	4 (0.6%)	4 (0.6%)
Fetal/congenital anomalies	12 (1.9%)	17 (2.6%)

^a Spontaneous abortion was defined as first trimester complete loss of pregnancy (with 0 live births).

^b The number of elective abortions is anyone who reported a surgical or medical abortion at the post pregnancy phone call.

Source: NDA DR-PGN-302 Clinical Study Report, Table 113, p184

In Study DR-PGN-302, the following criteria were used to evaluate OHSS.

Table 41: OHSS Classification

Classification	Description
Mild Grade 1 Grade 2	Abdominal distention/discomfort Features of Grade 1 plus nausea, vomiting and/or diarrhea; ovaries enlarged to 5-12 cm.
Moderate Grade 3	Features of mild OHSS plus ultrasonographic evidence of ascites.
Severe Grade 4 Grade 5	Features of moderate OHSS plus clinical evidence of ascites and/or hydrothorax or difficulty in breathing All of the above plus change in blood volume, increased blood viscosity due to hemoconcentration, coagulation abnormalities, and diminished renal perfusion and function

From : Golan A, Ronel R, Herman A, et al. Ovarian hyperstimulation Syndrome: An update review. Obstet Gynecol Surv 1989;44:430-40

Table 42: Incidence of OHSS

	DR-2011 N=647 n(%)	Crinone 8% N=650 n(%)	Total N=1279 n(%)
OHSS	34(5.26%)	32(4.92%)	66(5.1%)

Source: NDA DR-PGN-302 Clinical Study Report, Table 157, p290

Table 43: Incidence of Severe OHSS

	DR-2011 N=647 n(%)	Crinone 8% N=650 n(%)	Total N=1279 n(%)
OHSS	13(2.0%)	10(1.54%)	22(1.7%)

Source: NDA DR-PGN-302 Clinical Study Report, Table 178, p388

See Table 44 for the incidence and severity of OHSS reported in Study DR-PGN-302

Table 44: Incidence and Severity of OHSS

OHSS	DR-2011 N=34 number of cases (%)	Crinone 8% N=32 number of cases (%)
Severity of OHSS		
Mild	11 (32.3%)	9 (28.1%)

Moderate	10 (29.4%)	13 (40.2%)
Severe	13 (38.2%)	10 (31.3%)

Source: NDA DR-PGN-302 Clinical Study Report, Table 42, p99

Reviewer's Comment: The classification of OHSS is appropriate and accepted. The reported incidence of OHSS (34 cases [5.26%] in the DR-2011 treatment group and 32 cases [4.92%] in the Crinone 8% treatment group) is acceptable and within the expected range for ART treatment and very similar between the two treatment groups.

5.3.1.24 Safety-Discontinuation due to Adverse Events

Overall, 80 subjects (6.2% of 1297 subjects) discontinued due to an AE in Study DR-PGN-302. The rates of discontinuation were similar between the treatment groups [44 (6.8% of 647 subjects) in the DR-2011 treatment group compared to 36 (5.54% of 650 subjects) in the Crinone 8% treatment group].

Approximately 75% of the AEs leading to discontinuation were related to pregnancy loss (which necessitated study withdrawal). Another 12.5% of AEs leading to discontinuation were due to OHSS (6 cases occurred in the DR-2011 treatment group and 4 cases occurred in the Crinone 8% treatment group). Eleven (11) subjects [(0.85% of 1297 subjects) 6 in DR-2011 treatment group and 5 in Crinone 8% treatment group] developed ectopic pregnancy (see Tables 45 and 46). Of those, 5 were treated with methotrexate, 3 with laparoscopic surgery, one with surgery (not specified), 1 had both methotrexate and laparoscopic surgery, and 1 subsequently developed tubal abortion without any treatment. One subject discontinued due to an adverse event of vaginal pain related to the vaginal ring after four days of use. There were no discontinuations due to vaginal bleeding in either treatment group.

Table 45: Adverse Events Leading to Study Discontinuation

MedDRA System Organ Class and Preferred Term	DR-2011 (N=647)		Crinone® 8% (N=650)		Total (N=1297)	
	N	%	N	%	N	%
ANY AE						
Total Disorders	44	6.80	36	5.54	80	6.17
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS						
Total Disorders	34	5.26	31	4.77	65	5.01
ABORTION MISSED	16	2.47	12	1.85	28	2.16
ABORTION SPONTANEOUS	6	0.93	6	0.92	12	0.93
ECTOPIC PREGNANCY	6	0.93	5	0.77	11	0.85
BLIGHTED OVUM	5	0.77	5	0.77	10	0.77
INTRA-UTERINE DEATH	2	0.31	3	0.46	5	0.39
REPRODUCTIVE SYSTEM AND BREAST DISORDERS						
Total Disorders	7	1.08	4	0.62	11	0.85
OVARIAN HYPERSTIMULATION SYNDROME	6	0.93	4	0.62	10	0.77
PELVIC PAIN	1	0.15	0	0.00	1	0.08
GASTROINTESTINAL DISORDERS						
INTRA-ABDOMINAL HAEMORRHAGE	1	0.15	0	0.00	1	0.08
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
ADVERSE DRUG REACTION	1	0.15	0	0.00	1	0.08
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
ECZEMA	1	0.15	0	0.00	1	0.08
INJURY, POISONING AND PROCEDURAL COMPLICATIONS						
POST PROCEDURAL DISCOMFORT	0	0.00	1	0.15	1	0.08

Source: NDA DR-PGN-302 Clinical Study Report, Table 51, p107

Table 46: Adverse Events leading to discontinuation by subject number and treatment arm

Ectopic Pregnancy				OHSS		Internal Bleeding
DR-2011 Subject #	Crinone 8% Subject #	Treatment		DR-2011 Subject #	Crinone 8% Subject #	Subject #
(b) (6)	(b) (6)	DR	Crin	(b) (6)	(b) (6)	(b) (6)
		Meth	Meth			
		Laparos	Meth			
		Meth	Laparos			
		Both	Meth			
		Surgery	No treat			
		Laparos				

DR= DR 2011, Crin=Crinone, Meth=Methotrexate, Laparos=Laparoscopic surgery,

No Treat=No Treatment, Surgery=Non defined

Source: Generated from NDA Case Report Forms

There were three subjects who were switched to alternate forms of progesterone. One subject randomized to DR-2011 (Subject # (b) (6)) withdrew from the study (subject requested to be withdrawn) because she felt uncomfortable with the ring. This was not classified as an AE. She withdrew on the day of embryo transfer, having removed the ring prior to the procedure. She was prescribed another form of vaginal progesterone (unspecified) and continued with her cycle, although not as a study subject. A second subject randomized to DR-2011 (Subject (b) (6)) developed a rash approximately 2-3 weeks after her first dose of study medication, discontinued the study and was switched to IM progesterone. One subject randomized to Crinone 8% (Subject (b) (6)) was switched to Endometrin® (progesterone vaginal insert) after 19 days of treatment due to abnormally increasing β -hCG levels and subsequently experienced a missed abortion.

Reviewer's Comment: The incidence of adverse events leading to study discontinuation is acceptable and not considered excessive this type of study..

5.3.1.25 Safety- Common Adverse Events

The percentage of subjects per treatment group, experiencing at least one adverse event (AE) in Study DR-PGN-302 were similar, (96% in Dr-2011 treatment group and 94% in Crinone 8% treatment group.) The analysis included an account of only those common AEs that exceeded 2%. They are coded by MedDRA v9-0 by preferred term and arranged by frequency of AEs experienced in the DR-2011 treatment group (See Table 47).

The most common treatment-emergent adverse events (TEAEs) reported during the treatment period were nausea, headache, abdominal pain, post-procedural discomfort, abdominal distension, back pain, fatigue, and constipation, all at a frequency of 10% or greater. Vaginal discharge was reported more frequently as a TEAE in those subjects randomized to the vaginal ring (9.9%) compared to subjects using the Crinone 8% gel (3.5%). Overall, the rates of vaginal infections were low, and no difference in rates was observed between the two treatment groups. The rate of urinary tract infections was not increased in the vaginal ring subjects relative to those using the vaginal gel. There was no difference in the rate of irritation between the two treatment groups. Rates of vaginal bleeding were similar between the treatment groups. No vaginal ring users discontinued due to a bleeding/ spotting event.

Table 47: Incidence of Adverse Events Occurring in 2% or More of Subjects in Either Treatment Group During the Study Period by Frequency: Safety Cohort

Preferred Term (MedDRA v9-0)	Treatment Group DR-2011 (N=648)	Treatment Group DR-2011 (N=648)	Treatment Group Crinone® 8% N(651)	Treatment Group Crinone® 8% N(651)
AT LEAST ONE EVENT	622	622 (96.0%)	612	612 (94.0%)
HEADACHE	288	288 (44.4%)	318	318 (48.8%)
NAUSEA	224	224 (34.6%)	208	208 (32.0%)
POST PROCEDURAL DISCOMFORT	194	194 (29.9%)	206	206 (31.6%)
ABDOMINAL PAIN	180	180 (27.8%)	197	197 (30.3%)
PROCEDURAL PAIN	156	156 (24.1%)	167	167 (25.7%)
ABDOMINAL DISTENSION	123	123 (19.0%)	113	113 (17.4%)
BACK PAIN	118	118 (18.2%)	128	128 (19.7%)
CONSTIPATION	95	95 (14.7%)	85	85 (13.1%)
FATIGUE	92	92 (14.2%)	88	88 (13.5%)
PELVIC PAIN	91	91 (14.0%)	101	101 (15.5%)
VOMITING	84	84 (13.0%)	82	82 (12.6%)
DYSPEPSIA	72	72 (11.1%)	87	87 (13.4%)
BREAST TENDERNESS	71	71 (11.0%)	62	62 (9.5%)
DYSMENORRHOEA	70	70 (10.8%)	54	54 (8.3%)
VAGINAL DISCHARGE	64	64 (9.9%)	23	23 (3.5%)
DIARRHOEA	59	59 (9.1%)	80	80 (12.3%)
PREMATURE BABY	56	56 (8.6%)	40	40 (6.1%)
NASOPHARYNGITIS	55	55 (8.5%)	48	48 (7.4%)
DIZZINESS	54	54 (8.3%)	49	49 (7.5%)
PHARYNGOLARYNGEAL PAIN	53	53 (8.2%)	40	40 (6.1%)
ABDOMINAL PAIN UPPER	48	48 (7.4%)	56	56 (8.6%)
URINARY TRACT INFECTION	36	36 (5.6%)	47	47 (7.2%)
OVARIAN HYPERSTIMULATION SYNDROME	34	34 (5.2%)	32	32 (4.9%)
UTERINE SPASM	34	34 (5.2%)	31	31 (4.8%)
UPPER RESPIRATORY TRACT INFECTION	32	32 (4.9%)	24	24 (3.7%)
INSOMNIA	32	32 (4.9%)	18	18 (2.8%)
METRORRHAGIA	27	27 (4.2%)	28	28 (4.3%)
SINUSITIS	27	27 (4.2%)	24	24 (3.7%)
RASH	26	26 (4.0%)	15	15 (2.3%)
PAIN IN EXTREMITY	24	24 (3.7%)	22	22 (3.4%)
ANOREXIA	24	24 (3.7%)	20	20 (3.1%)
INTRA-UTERINE DEATH	24	24 (3.7%)	19	19 (2.9%)
ARTHRALGIA	24	24 (3.7%)	15	15 (2.3%)

POST PROCEDURAL NAUSEA	23	23 (3.5%)	20	20 (3.1%)
ABDOMINAL DISCOMFORT	23	23 (3.5%)	19	19 (2.9%)
ABDOMINAL PAIN LOWER	22	22 (3.4%)	35	35 (5.4%)
COUGH	22	22 (3.4%)	17	17 (2.6%)
DYSPNOEA	22	22 (3.4%)	17	17 (2.6%)
SINUS HEADACHE	21	21 (3.2%)	19	19 (2.9%)
FLATULENCE	21	21 (3.2%)	16	16 (2.5%)
PYREXIA	20	20 (3.1%)	29	29 (4.5%)
MIGRAINE	18	18 (2.8%)	23	23 (3.5%)
PAIN	18	18 (2.8%)	19	19 (2.9%)
ABORTION MISSED	18	18 (2.8%)	16	16 (2.5%)
HYPERSENSITIVITY	17	17 (2.6%)	16	16 (2.5%)
ADNEXA UTERI PAIN	17	17 (2.6%)	15	15 (2.3%)
HOT FLUSH	16	16 (2.5%)	24	24 (3.7%)
BLIGHTED OVUM	16	16 (2.5%)	17	17 (2.6%)
SINUS CONGESTION	16	16 (2.5%)	17	17 (2.6%)
STOMACH DISCOMFORT	16	16 (2.5%)	10	10 (1.5%)
NASAL CONGESTION	15	15 (2.3%)	18	18 (2.8%)
MUSCLE SPASMS	15	15 (2.3%)	14	14 (2.2%)
ABORTION SPONTANEOUS	14	14 (2.2%)	14	14 (2.2%)
FUNGAL INFECTION	14	14 (2.2%)	14	14 (2.2%)
INFLUENZA	14	14 (2.2%)	12	12 (1.8%)
MYALGIA	13	13 (2.0%)	22	22 (3.4%)
NECK PAIN	13	13 (2.0%)	15	15 (2.3%)
BREAST PAIN	13	13 (2.0%)	14	14 (2.2%)
ACNE	13	13 (2.0%)	11	11 (1.7%)
SEASONAL ALLERGY	13	13 (2.0%)	8	8 (1.2%)
OVARIAN CYST	13	13 (2.0%)	7	7 (1.1%)

Source: Generated from the NDA – “Adverse Events” Data Set

Sixty-four (64)subjects (9.9%) developed vaginal discharge in the DR-2011 and 23 (3.5%) in the Crinone 8% group, while 22 (3.4%) in the DR-2011 and 26 (4%) in the Crinone 8% developed Vaginitis.

Per the protocol, any subject who reported moderate to heavy vaginal bleeding as an AE was to be evaluated for vaginal hemorrhage. The protocol defined vaginal hemorrhage as:

- blood loss of >500mLs or
- hemoglobin post-treatment <10 g/dL or
- blood loss requiring transfusion.

Although no subject met the protocol definition of vaginal hemorrhage, there were subjects who reported moderate to heavy bleeding at least for one day (see Table 48).

Table 48: Occurrence of Moderate to Heavy Bleeding – Treatment Period, Safety Cohort

	DR-2011 (N=647)	Crinone® (N=650)	Total (N=1297)
Total Number of Subjects Who Reported Moderate to Heavy Bleeding	184 (28.44%)	193 (29.69%)	377 (29.07%)
Visit 5 (Embryo Transfer - Visit 6)	83 (12.83%)	101 (15.54%)	184 (14.19%)
Visit 6 (Visit 6 - Visit 6P)	76 (11.75%)	66 (10.15%)	142 (10.95%)
Visit 6P (Visit 6P - Visit 7)	12 (1.86%)	8 (1.23%)	20 (1.54%)
Visit 7 (Visit 7 - Visit 7P)	9 (1.39%)	13 (2.00%)	22 (1.70%)
Visit 7P (Visit 7P - Visit 8)	7 (1.08%)	7 (1.08%)	14 (1.08%)
Visit 8 (Visit 8 - Visit 9)	11 (1.70%)	13 (2.00%)	24 (1.85%)
Visit 9 (Visit 9 - Post Treatment Phone Call)	6 (0.93%)	8 (1.23%)	14 (1.08%)

Source: NDA Application, Study Report Body, Table 49, P: 105

Reviewer's Comments:

- The overall rate of vaginal bleeding events (all events reported by MedDRA terminology of vaginal hemorrhage and metrorrhagia together) was somewhat higher in the Crinone® treatment group [38 subjects out of 651(5.8%)] compared to DR-2011[33 subjects out of 648 (5%).] The reason for this is unclear. When combining moderate and heavy vaginal bleeding, 223 (34.4%) subjects developed it in the DR-2011 group and 235 (36.1%) in the Crinone group. However, the lack of subjects that discontinued for vaginal bleeding or irritation after DR-2011 use is worth mentioning.***
- These type of adverse events are not unreasonable for this type of a trial. Some of them are not treatment related but may be related to concomitant treatments (i.e. IVF).***

5.3.1.26 Safety-Vital Signs

Descriptive statistics reported the change in vital signs and laboratory tests between baseline and end-of-study.

No major differences were observed between the two treatment groups in Study DR-PGN-302.

5.3.1.27 Safety – Labs

No clinically important differences were identified during the conduct of Study DR-PGN-302. No subjects were considered to have clinically significant abnormal laboratory values, and no subject was discontinued due to a significant laboratory adverse event.

Table 49: Progesterone Level: Change from Baseline to End of Treatment during Study Period - Safety Cohort

		DR-2011			Crinone 8%			Total		
	Change from	N	Mean (Std)	Min, Max	N	Mean (Std)	Min, Max	N	Mean (Std)	Min, Max
Safety Cohort	Change from Visit 4 to End of Study	622	3.6 (41.07)	(-190.1, 315.2)	620	3.9 (39.11)	(-139.4, 246.2)	1242	3.8 (40.09)	(-190.1, 315.2)
Subjects who were clinically pregnant at Week 12	Change from Visit 4 to End of Study	293	30.6 (34.18)	(-190.1, 209.5)	283	33.5 (33.11)	(-50.0, 246.2)	576	32.0 (33.66)	(-190.1, 246.2)
Subjects who were not clinically pregnant at Week 8 or 12	Change from Visit 4 to End of Study	318	-20.9 (30.71)	(-103.4, 315.2)	326	-21.3 (23.25)	(-139.4, 180.6)	644	-21.1 (27.17)	(-139.4, 315.2)

Source: NDA Application, Study Report Body, P: 437-8 and progesterone Data Set

Reviewer's Comment: In Study DR-PGN-302 progesterone levels fluctuated in both treatment groups suggesting the importance of an individual response to either DR-2011 or Crinone 8%. These variations occurred irrespective of the (b) (4) progesterone preparation. Table 49 shows that the serum progesterone level in the DR-2011 treatment group increased to higher levels in some individuals who were not pregnant over those who were pregnant, or decrease more even though they were pregnant versus those not pregnant. The Crinone 8% treatment group was more consistent with the status of pregnancy between visit 4 (one day after retrieval) and the end of the study. One easily would conclude, that individual's response variability is a significant factor. Based on my review of Table 49 (and review of similar data from other products), this reviewer believes that no conclusions regarding efficacy and safety of a vaginal progesterone product should be made based on serum progesterone concentrations (PK data)-alone.

5.3.2 Supportive study

None

5.3.3 Study 10716222, conducted in US

This was a Phase 1 bioavailability PK, open-label, single arm, multicenter study in single and steady state. The investigational product was DR-2011, Progesterone Vaginal Ring. The treatment duration was 30 days. Thirty (30) healthy postmenopausal females pre-treated with estrogen were enrolled (27 completed the study). The primary objective of this study was to evaluate systemic progesterone pharmacokinetics following intravaginal absorption, during two seven-day application cycles of the progesterone vaginal ring.

Adverse events were collected and tabulated but no formal statistical analyses were performed. Ninety (90) AEs were reported by 29 of the 30 subjects who were enrolled in the study. Eighty-eight (88) adverse events were considered mild; 74 resolved spontaneously prior to study completion, 12 resolved with treatment and 2 had not resolved by the end of the study. Two (2) adverse events were considered moderate; 1 resolved spontaneously and 1 resolved with treatment. The most frequent adverse events were metrorrhagia (73.3%), abdominal pain (36.7%), blood pressure decreased (16.7%), headache (10.0%), and generalized pruritus (10.0%). Based on the results of this study, it was concluded that steady state plasma concentration of progesterone are reached during the first vaginal ring insertion. Following removal of the first ring and replacement with a second ring, no accumulation of progesterone was observed during the second treatment.

5.3.4 Study 10936057, conducted in US

This was a Phase 1 bioequivalence (BE), open label, single dose, multi-center, blinded, randomized, two treatment, two period cross-over study evaluating progesterone vaginal ring (DR-2011) manufactured at Barr NJ facility and Barr OH facility. The treatment duration was 7 days per ring with a 7 day washout period in between ring insertion. Thirty-two (32) healthy postmenopausal women who had been pre-treated with estrogen were enrolled (31 completed the study). The primary objective of this study was to determine the BE between the new manufacturing site batch of the progesterone vaginal ring, (b) (4) % w/w (Test Product A) and the Phase 3 clinical trial progesterone vaginal ring, (b) (4) % w/w (Reference Product B), during a single seven day application cycle of the two products. The qualitative and quantitative composition for the Test Product A and the Reference Product B were identical (i.e. same formulation). The Test Product A was identified as the "to be marketed" formulation that is being evaluated to support the new manufacturing site for the intended commercial product. Data from subjects who completed both treatment periods of the study were used in the statistical determination of bioequivalence. Plasma samples were analyzed for progesterone concentrations.

One hundred sixty-seven (167) adverse events (all considered mild) were reported by all of the 32 subjects who participated in this study. Of these events, 73 occurred after receipt of Test product A and 94 occurred after receipt of Reference product B. One hundred sixty (160) adverse events were considered "mild" and resolved spontaneously prior to study completion, five (5) adverse events were considered "mild" and resolved with treatment, and two (2) adverse events were considered "mild" and had not resolved by the end of the study. The most frequently reported adverse event for both formulations was metrorrhagia (Test product A: 26

subjects, (83.9%), Reference product B: 27 subjects (84.4%), followed by abdominal pain (22.6% versus 34.4% respectively), blood pressure drop (12.9% versus 12.5%) and vaginal discharge [4 subjects (12.9%) in formulation A and 1 (3.1%) in formulation B.] The study concluded that “based on the statistical analysis of progesterone, the “to be marketed” formulation of progesterone vaginal ring, (b)(4)% w/w (Barr Laboratories, Inc.) meets the 90% CI for log transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} and is therefore considered bioequivalent to the “clinical trials” formulation (reference formulation), DR-2011 (progesterone vaginal ring), (b)(4)% w/w (Barr Laboratories, Inc.)”

The study also reported no serious adverse events.

Reviewer’s Comment: OCP accepted the findings and the safety profile is not concerning.

5.3.5 Study 10936057, conducted in US

This was a Phase 1, BE, open label, single arm single-center study of DR-2011 from Barr OH facility. The treatment duration was a single use of 7 days. Fifteen (15) out of 15 healthy postmenopausal women completed the study.

The purpose of this study was to analyze the amount of DR-2011 remaining in the new manufacturing site batch (Batch # 800357; Expiration Date: 07/12) of the progesterone vaginal rings, (b)(4)% w/w following a full 7 day use period in healthy postmenopausal women. All participants in this study were pre-treated with 1 mg estradiol oral tablets once a day for at least 28 days prior to having the vaginal ring inserted and continued with concomitant estradiol therapy during the study.

Twenty-nine (29) adverse events were reported by 11 of the 15 subjects who participated in this study. Twenty-four (24) adverse events were considered “mild” and resolved spontaneously prior to study completion, and five (5) adverse events were considered “mild” and had not resolved by the end of the study. The most frequently reported adverse events for the test product were back pain (3 subjects) and metrorrhagia (3 subjects). The study concluded that ANOVA estimates of the difference between the least squares mean drug content of the unused rings and the least squares mean drug content of the used rings was 75.44 mg released per 7 days with a 95% confidence interval about this difference of 68.84 – 82.05 mg released per 7 days. When divided by 7 to express the difference on a daily basis, results reported were 10.78 mg per day with a 95% confidence interval of 9.83 – 11.72 mg/day (which is 91.2% - 108.7% of the mean).

5.3.6 Study DR-201-102, conducted in US

This was a Phase 1, PK/PD, randomized, open label, active control, no-treatment control (Estrogen only)(three arms) single-center study. This study compared the progesterone vaginal ring (DR-2011) to progesterone vaginal gel (Crinone 8%). Sixty-three (63) subjects were randomized 1:1:1 (21 per treatment group). The third group was estrogen only. Progesterone was administered for 11-12 days to subjects in each group, with overall treatment for each subject about 10 weeks. The study included three periods: a 14-day estrogen pretreatment period, an 11-12 day estrogen with or without progesterone treatment period, and a 14-day post treatment period. Sixty-three (63) healthy females, age 18-40, with regular spontaneous menstrual cycles planning to undergo IVF/ET completed the study. The primary objective was:

- To assess endometrial tissue progesterone concentrations via endometrial biopsy specimens following 11-12 days of intravaginal administration of DR-2011 or a progesterone vaginal gel in females planning in-vitro fertilization (IVF) /embryo transfer (ET) cycles of healthy female volunteers.

The secondary objectives included:

- To compare systemic progesterone levels to endometrial tissue levels following 11-12 days of intravaginal administration of DR-2011 or a progesterone vaginal gel in females planning IVF embryo transfer cycles (IVF/ET) in healthy female volunteers.
- To compare endometrial tissue and serum progesterone levels of the DR-2011 and vaginal gel treatment groups to the estrogen-only control group.
- To compare safety and tolerability of DR-2011 to a progesterone vaginal gel.

Study findings:

Efficacy

1. The mean endometrial tissue progesterone (PGN) concentration observed for the DR-2011 group was considerably higher than that found for the estrogen-only treatment group but lower than that observed with the vaginal gel. However, probable contamination during the transcervical sampling process from the bioadhesive gel is very likely to have affected these results, rendering interpretation difficult.
2. Systemic serum concentrations of PGN were substantially higher for the progesterone treatment groups than the estrogen-only group; serum PGN concentrations for DR-2011 were similar to the vaginal gel group.
3. DR-2011 demonstrated a high rate of endometrial secretory transformation, with 18 of 19 subjects (94.7%) undergoing transformation to the secretory phase, compared to 16 of 19 subjects (84.2%) in the vaginal gel group.

Safety

Treatment-emergent and treatment-related AEs were few in number, and consistent with the known safety profile of PGN. There were no clinically significant changes in laboratory or clinical findings.

1. The percentages of subjects reporting any AE, treatment-emergent AEs, or treatment-related AEs, were slightly lower in the DR-2011 group compared to the other groups
2. There were no reports of vaginal bleeding or vaginal infections/irritation among users of DR-2011.
3. There were no deaths, serious AEs, (SAEs) leading to discontinuation, or other safety concerns noted in this study.

Conclusion as per Applicant:

“Overall, the results of this study demonstrated that the DR-2011 weekly progesterone vaginal ring application is safe and well tolerated and delivers a dose of PGN resulting in systemic serum PGN concentrations that are comparable to an FDA-approved comparator, with a high rate of endometrial secretory transformation. These findings suggest that DR-2011 provides a dose of PGN sufficient for luteal support in IVF cycles that is comparable to the Crinone® 8% vaginal gel.”

5.3.7 Study DR-PGN-201, conducted in US

This was a Phase 2, pharmacodynamic (PD), randomized, open label, active control, single-center study. It compared DR-2011 to Crinone 8% Vaginal Gel. The treatment duration was 18 days. DR-2011 was used continuously from Cycle Day 14-31 [vaginal ring (VR) was replaced once in the treatment period, on Cycle Day 21 (2 applications)]. Twenty-one (21) subjects were randomized and 20 completed the study (10 per treatment arm). Subjects were women aged 18-50 and candidates for donor oocyte program.

The objectives of this study were to determine in women with clinical or medically-induced agonadism:

1. The proportion of patients using DR-2011 (progesterone VR) with adequate endometrial transformation (on endometrial biopsy) as determined by histological dating of the endometrium
2. To describe progesterone and estradiol levels in the serum obtained from patients using DR-2011
3. The safety and tolerability of progesterone delivered by VR as compared with a progesterone vaginal gel

The Applicant concluded that: “DR-2011 adequately transformed the endometrium to secretory phase in 8 out of 10 of patients while Crinone did so in 10 out of 10 patients. Of the 2 VR patients that did not successfully transform:

- One subject had uterine fibroids with a non-datable endometrium; the endometrium was predominantly inactive with tubal metaplasia, but showing small foci of secretory exhaustion. These findings suggest an uneven end-organ response to the hormonal milieu (i.e. irregular ripening).
- One subject who had gonadal dysgenesis (streak ovaries and ovarian failure) developed a mixed inactive and exhausted secretory endometrium; these features favor late secretory phase, but no precise dating was possible.

Estradiol serum levels in the DR-2011 treatment group were comparable with those in the Crinone 8% treatment group. Mean progesterone serum levels in both treatment groups increased rapidly between Cycle Days 14 and 15 and remained fairly stable during treatment (up to Cycle Day 31).

In this study, DR-2011 was observed to have a safety profile similar to that of Crinone 8%. AEs were higher for the Crinone 8% treatment group than the DR-2011 treatment group. Nine patients in the DR-2011 treatment group reported mild vaginal bleeding and/or spotting, occurring primarily when a single VR was used for longer than 7 days.”

5.3.8 Study DR-PGN-202, conducted in US

This was a Phase 2, efficacy and safety, randomized, open label, active control, single center, follow up study comparing DR-2011 to Crinone 8% Vaginal Gel. Study DR-PGN-202 is a follow-up to Study DR-PGN-201. Subjects in Study DR-PGN-202 were participants in Study DR-PGN-201 who had successful endometrial transformation and who participated in a donor oocyte IVF cycle. The treatment duration was 10 weeks. DR-2011 was used continuously from the day of donor egg retrieval through 12 weeks of pregnancy, if subject became pregnant. The

progesterone vaginal ring was replaced every 7 days. 9 subjects were treated but 8 completed the study, 4 in each group.

The objectives of this study were to determine the clinical pregnancy rate in women with clinical or medically-induced agonadism:

Primary objective:

Clinical pregnancy rate (i.e., visualization of a gestational sac with fetal heart motion on ultrasound) at 8 weeks of pregnancy (6 weeks after embryo transfer) using DR-2011 or the progesterone 8% vaginal gel comparator, Crinone®

Secondary objectives included:

1. Biochemical pregnancy rate (i.e., transient increase in β -hCG levels, followed by a decrease), clinical pregnancy rate (i.e., visualization of a gestational sac with fetal heart motion on ultrasound) at 12 weeks of pregnancy (10 weeks after embryo transfer), and live birth rate using DR-2011 or Crinone 8% once a day
2. Serum progesterone and estradiol levels in subjects using DR-2011 or Crinone 8%
3. Safety and tolerability of progesterone delivered by VR or the vaginal gel comparator

The applicant concluded that: “DR-2011 was shown to effectively support pregnancy.

1. Four out of five subjects who underwent an embryo transfer using DR-2011 became pregnant (3 singleton and 1 twin delivery), compared to one pregnancy out of four subjects who received Crinone (1 singleton delivery).
2. All pregnancies in both treatment groups led to live births.
3. One of the DR-2011 subjects who became pregnant was withdrawn from the study after 8 weeks of pregnancy and was switched to IM progesterone due to the bleeding pattern after pregnancy was established.

The safety results revealed no clinically significant AEs, vital signs, laboratory findings, or any other untoward safety concern.”

Reviewer’s Comment:

In study DR-PGN-202 one subject was switched from DR-2011 to Crinone 8% at 8 weeks of gestation due to vaginal bleeding pattern she developed. No new or unexpected safety findings were observed in any of these studies.

This study would be considered as “proof of concept” and would not stand on its own as supporting an indication for luteal replacement in a donor oocyte program

The most common AEs reported in all of these studies, conducted with prior methodologies or formulations, were: abdominal /back pain, and metrorrhagia. There were no discontinuations due to any adverse events. No deaths were observed in any of these studies.

6. REVIEW OF EFFICACY

Efficacy Summary

This application seeks for the progesterone vaginal ring, an indication 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.

During the EOP-2 meeting on June 13, 2007, the Division advised the Applicant that one pivotal study, performed in the US or with the majority of centers in the U.S., would be sufficient for an NDA application. A US study is recommended because of the differences in the practice of ART in the U.S., and the superior success rate obtained in US studies primarily due to multiple embryo transfer protocols and, perhaps, an advantage in technique relative to that observed in Europe/South America.

The Division also strongly recommended that randomization and the primary efficacy analysis should be **stratified and powered** by ovarian reserve as measured by Day 3 serum FSH and **age of the female subjects (age < 35 years and age 35 to 42 years)**. The rationale for the sub-stratification by age group is based on Centers for Disease Control (CDC) 2006 report “ART Success Rates”, where more than 60% of women in the US who underwent ART for treatment of infertility were older than 35 years of age.

The Applicant’s analysis of this primary efficacy study, confirmed by the Agency’s statistical analysis (See Table 50 by Statistical Reviewer) for the two co-primary end points, reveals non-inferiority of DR-2011 in comparison to Crinone 8% for women less than 35 years of age and for the whole study population in Study Dr-PGN-302. The application fails, however, to demonstrate non-inferiority for the sub-group of women age 35-42 years of age. This failure is most probably due to the fact that Applicant did not power the trial for this sub-group analysis as the Division had strongly recommended on numerous occasions.

Table 50: Primary Efficacy Results Based on MITT Population; Clinical Pregnancy Rate per Retrieval

Age	Pregnant Week	DR-2011		Crinone		Difference (DR-2011 – Crinone) (95% Confidence Interval)
		n/N	Percent	n/N	Percent	
18-34	8	275/558	49.3%	269/560	48.0%	1.2% (-4.6%, 7.1%)
	12	269/558	48.2%	258/560	46.1%	2.1% (-3.7%, 8.0%)
35-42	8	35/88	39.8%	38/91	41.8%	-2.0% (-16.4%, 12.4%)
	12	31/88	35.2%	36/91	39.6%	-4.3% (-18.5%, 9.8%)
All	8	310/646	48.0%	307/651	47.2%	0.8% (-4.6%, 6.3%)
	12	300/646	46.4%	294/651	45.2%	1.3% (-4.1%, 6.7%)

Source: Statistical analysis report, Table 3.2.3.1, p10

Further attempts in evaluating the older population, namely women 35-42 years, failed again the predetermined NI limits of -10%.

Table 51: Primary Efficacy Results in Older Patients Based on MITT Population; Clinical Pregnancy Rate per Retrieval

Age	Pregnant Week	DR-2011		Crinone		Difference (DR-2011 – Crinone) (95% Confidence Interval)
		n/N	Percent	n/N	Percent	
35-37	8	21/50	42.0%	22/50	44.0%	-2.0% (-21.4%, 17.4%)
	12	20/50	40.0%	21/50	42.0%	-2.0% (-21.3%, 17.3%)
38-42	8	14/38	36.8%	16/41	39.0%	-2.2% (-23.6%, 19.2%)
	12	11/38	28.9%	15/41	36.6%	-7.6% (-28.3%, 13.0%)

Source: Statistical analysis report, Table A8, p15

6.1 Indication

This application seeks an indication 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 for the progesterone vaginal ring. The scientific rationale for the use of progesterone in the above clinical indication has been debated and extensively documented in the literature. With the advent of IVF, it has been established that the luteal phase of stimulated IVF cycles is abnormal (Edwards et al.,1980). Initially, it was thought that the removal of large quantities of granulosa cells during the oocyte retrieval (OR) might diminish the most important factor, progesterone synthesis by the corpora lutea, leading to a defect of the luteal phase. However, this hypothesis

was disproved when it was established that the aspiration of a preovulatory oocyte in a natural cycle neither diminished the luteal phase steroid secretion nor shortened the luteal phase (Kerin et al., 1981). Another proposal suggested that the prolonged pituitary recovery that followed the GnRH agonist co-treatment, designed to prevent spontaneous LH rise in stimulated cycles, resulted in lack of support of the corpus luteum. This would cause a luteal phase defect (Smitz et al., 1992a,b). It was also suggested that the hCG administered for the final oocyte maturation, in stimulated IVF cycles, could potentially cause a luteal phase defect by suppressing the LH production via a short-loop feedback mechanism (Miyake et al., 1979). However, the administration of hCG did not down-regulate the LH secretion in the luteal phase of normal, unstimulated cycles in normo-ovulatory women (Tavaniotou and Devroey, 2003). The introduction of GnRH antagonists in IVF raised speculations that a rapid recovery of the pituitary function (Albano et al., 1996) would obviate the need for luteal phase supplementation (Elter and Nelson, 2001). Preliminary observations in intrauterine insemination (IUI) cycles seemed to favor this contention. Ragni et al in 2001 explored the luteal phase hormone profiles in gonadotrophin stimulated cycles both with and without GnRH antagonist therapy for IUI. No deleterious effects of GnRH antagonist administration could be noted on either the luteal progesterone concentration or the duration of the luteal phase in that study. However, various studies of GnRH antagonist co-treatment in IVF have since revealed different results. Luteolysis is also initiated prematurely in antagonist co-treated IVF cycles, resulting in a significant reduction in the luteal phase length and compromising the chances for pregnancy (Albano et al., 1998; Beckers et al., 2003). Despite the rapid recovery of the pituitary function in GnRH antagonist protocols (Dal Prato and Borini, 2005), luteal phase supplementation remains mandatory (Taratzis et al., 2006). It can be postulated that one of the main causes of the luteal phase defect in stimulated IVF cycles is related to the supraphysiological levels of steroids secreted by a high number of corpora lutea during the early luteal phase, which directly inhibit the LH release via negative feedback actions at the hypothalamic-pituitary axis level (Fauser and Devroey, 2003). Studies in human and primates have demonstrated that the corpus luteum requires a consistent LH stimulus in order to perform its physiological function (Jones, 1991). LH support during the luteal phase is entirely responsible for the maintenance and the normal steroidogenic activity of the corpus luteum (Casper and Yen, 1979). As a result, withdrawal of LH, unnecessary causes premature luteolysis (Duffy et al., 1999.)

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Intramuscular (IM), and vaginal forms of progesterone are used extensively. Currently, a vaginal progesterone gel and a progesterone vaginal insert, administered once daily and two or three times daily, respectively, for 10 weeks are FDA-approved to support embryo implantation and early pregnancy as part of an Assisted Reproductive Technology (ART) program while the 50 mg IM administration of progesterone in oil one or twice daily is an off label use

6.1.1 Methods

See Subsections 5.3.1.5 to 5.3.1.11 for detailed information on the design of Study DR-PGN-302

6.1.2 Demographics

See Subsection 5.3.1.17 for detailed information on the demographics in Study DR-PGN-302

6.1.3 Subject Disposition

See Subsection 5.3.1.15 for detailed information on subject disposition in Study DR-PGN-302

6.1.4 Analysis of Primary Endpoint(s)

See Subsection 5.3.2.19 for the analysis of primary endpoints in Study DR-PGN-302. As it has been previously stated, the primary efficacy analysis should have been **stratified and powered by age of the female subjects (age < 35 years and age 35 to 42 years)**. Study DR-PGN-302 only revealed non-inferiority of DR-2011 in comparison to Crinone 8% , with a margin of -4.6% at 6 weeks post embryo transfer and -3.7% at 10 weeks, which is well within the prospectively agreed upon margin of -10%. This margin was maintained for the whole study population (ages 18-42 years) at -4.6 and -4.1% respectively. However, Study DR-PGN-302 failed to show non-inferiority for the sub-group of women 35-42 years of age. These margins were -16.4 and -18.5% respectively.. See table 16. See also previous tables 50 and 51.

Table 16: Clinical Pregnancy Rate per Retrieval– MITT Cohort

	Weeks of Pregnancy	DR-2011 N=646		Crinone® N=651		DIFF (DR 2011- Crinone®)	95% C.I. for DIFF
		N	%	N	%		
Ages 18-34	8	558	275 (49.3%)	560	269 (48.0%)	1.2%	(-4.6%, 7.1%)
	12		269 (48.2%)		258 (46.1%)	2.1%	(-3.7%, 8.0%)
All Ages (18-42)	8	646	310 (48.0%)	651	307 (47.2%)	0.8%	(-4.6%, 6.3%)
	12		300 (46.4%)		294 (45.2%)	1.3%	(-4.1%, 6.7%)
Ages 35-42	8	88	35 (39.8%)	91	38 (41.8%)	-2.0%	(-16.4%, 12.4%)
	12		31 (35.2%)		36 (39.6%)	-4.3%	(-18.5%, 9.8%)

Source: NDA Application, DR-PGN-302, Study Report Body, table 17, P 76

The non inferiority margin was also maintained when FSH was <10mIU/mL. Most of the subjects had an FSH less than 10mIU/mL. A proper statistical analysis was conducted. For FSH>10mIU/ml, the study was not appropriately powered, and non-inferiority could not be established.

Table 18 shows the analyses in reference to FSH value and a combination FSH and age. See subsection 5.3.1.19.2, Page 72

Reviewer's Comment: This reviewer has stated repeatedly in this review the importance of having a robust analysis of the two sub-groups regarding the age of the subjects studied and believes that the Applicant's explanation does not justify this significant omission.

6.1.5 Analysis of Secondary Endpoints(s)

See Subsection 5.3.2.20 for the analysis of secondary endpoints in Study DR-PRN-302.

6.1.6 Other Endpoints

See Subsections 5.3.1.19.1 and 5.3.1.20.6.1 and 5.3.1.20.6.2 for the analysis of other endpoints in Study DR-PRN-302.

6.1.7 Subpopulations

Not applicable

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant states that they have loaded the maximum amount of (b) (4) progesterone that the ring can hold. No other dosing studies were performed to demonstrate efficacy and safety of the progesterone vaginal ring.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

No data were combined in NDA 201-110 as only one Phase 3 study, Study DR-PGN-302, was submitted as the primary efficacy and safety study for DR-2011. This study was also used to estimate the incidence of adverse events in NDA 201-110.

Reviewer's Comment: Study DR-PGN-302 generally used the same study design that approved ART products have followed. It was one cycle clinical trial in down regulated subjects, who met all the inclusion criteria and had none of the exclusion criteria, who underwent an ART procedure and had a transfer. Despite multiple communications from the Division, recommending stratification and powering of Study DR-PGN-302 for the two age subgroups, <35 years and 35-42 years of age, the Applicant decided not to comply with this recommendation. As a result, Study DR-PGN-302 failed to show non-inferiority of DR-2011 as compared to Crinone 8% for the older group of women who constitute 60% of women who undergo ART for treatment of their infertility.

7 Review of Safety

Safety Summary

The safety assessments obtained during the development of DR-2011 generally followed the safety assessment obtained by progesterone products approved for the supplementation and support of corpus luteum and early pregnancy in association with ART. Exclusive of the failure to demonstrate maintenance of early pregnancy in the age 35 and older subject, the safety profile of DR-2011 is acceptable and raises no concerning safety signal.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

All seven (7) clinical trials performed under NDA 210-110 were included in evaluating the safety of DR-2011. These clinical trials were conducted either in postmenopausal women pre-treated with estrogen or healthy volunteers, age 18-50 years old who were planning to undergo ART (IVF/ICSI) with fresh oocytes, either their own or donor oocytes. All seven clinical trials were conducted in the US. All but one, DR-PGN-302, were conducted in a single center. Studies 10716622, 10936035, 10936057 and DR-201-120 were PK studies and safety information was collected. Study DR-PGN-201 and its follow-up Study DR-PGN-202 were PD trials and safety information was collected.

Per the application, the pivotal, primary Study DR-PGN-302 was conducted to support the use of DR-2011 in infertile women who undergo ART (IVF/ICSI) to achieve a pregnancy and require corpus luteum supplementation and support of the early pregnancy. In Study DR-PGN-302, subjects were treated only for one cycle. Since there was only one Phase 3 clinical trial, no pooled analysis has been conducted. No ISS or ISE analyses are provided with this application.

Safety was evaluated from signs and symptoms, and history reported by the subjects; vital signs assessments; scheduled physical examinations, transvaginal ultrasounds (TVUS), and laboratory testing. A follow up call in the post treatment period was conducted regarding the outcome of the pregnancy and neonatal evaluation. Adverse events were recorded throughout the clinical trials and were coded using the MedDRA (Medical Dictionary for Regulatory Activities) coding dictionary by Preferred Terms (PT) and System Organ Class (SOC), version 9.0. Adverse events and treatment-emergent adverse events (TEAE) were summarized by body system and treatment group. Incidence of OHSS, spontaneous abortion, and ectopic pregnancy data were analyzed. Laboratory assessments included:

1. Hormones: serum FSH, E₂, Progesterone and β -hCG;
2. Blood chemistry: AST, ALT, GGTP, total bilirubin, glucose, urea, creatinine etc;
3. Hematology: hemoglobin, hematocrit, RBC, WBC with differential, platelets;
4. STD testing for gonorrhea and chlamydia;

In study DR-PGN-302 each subject was treated with progesterone for one cycle of 14 days. If the subject achieved a pregnancy during this cycle, treatment continued up to 10 weeks post embryo transfer (12th week of pregnancy). If during this period a miscarriage occurred or an ectopic pregnancy was diagnosed, the treatment was discontinued. Monitoring and follow-up were adequate. No deaths were observed during the conduct of this study.

7.1.2 Categorization of Adverse Events

A total of 647 subjects in the DR-2011 treatment group and 650 subjects in the Crinone8% treatment group were considered in the safety analysis. There were three distinct time periods in the study during which AEs and SAEs were collected: the study period (including the time from

signing of the informed consent through 14 days after the last dose of study medication), the treatment period (a subset of the study period which included the day of the first dose of study medication through 14 days after the last dose), and the follow-up period for those subjects who became pregnant (14 days from the last dose of study drug through 30 days after the completion of the pregnancy). Only SAEs were collected during the follow-up period, and were classified as pregnancy-related (occurring in either the subject or the fetus during the pregnancy), and neonatal or maternal (occurring in the subject after completion of the pregnancy).

The following subgroups of adverse events were analyzed.

1. All adverse events.
2. Adverse events occurring after egg retrieval.
3. Severe adverse events occurring after initiation of ovulation induction.
4. Adverse events probably or definitely related to treatment occurring during and after progesterone treatment.
5. Serious adverse events.

In addition, various signs and symptoms of OHSS were assessed, and graded on a scale of None, Mild, Moderate or Severe.

Concomitant medications were coded using a modified WHO coding system and the following subgroups were analyzed.

1. All concomitant and prior medications.
2. Medications received prior to screening.
3. Medications received prior to progesterone treatment.
4. Medications received after ART treatment.

Tables of Treatment-Related and Treatment-Emergent Adverse Events are presented.

Treatment Related Adverse Events: The events that were judged by the investigator or applicant to be drug-related.

Treatment Emergent Adverse Event: A line listing of all reported treatment emergent adverse events, regardless of whether or not they were considered drug related, for all subjects participating in the trial.

Table 52 presents the Incidence of Treatment-Related Adverse Events >2% for- DR-PGN-302 while Table 53 shows the Incidence of Treatment-Emergent Adverse Events >2% for the same trial. In both tables. adverse events are presented by MedDRA System Organ Class and by Preferred Term

Table 52: Incidence of Treatment-Related Adverse Events >2%- Safety Cohort- DR-PGN-302

MedDRA System Organ Class and Preferred Term	DR-2011 (N=647)		Crinone® 8% (N=650)		Total (N=1297)	
	N	%	N	%	N	%
NERVOUS SYSTEM DISORDERS						
HEADACHE	44	6.80	39	6.00	83	6.40
REPRODUCTIVE SYSTEM AND BREAST DISORDERS						
VAGINAL DISCHARGE	26	4.02	13	2.00	39	3.01
BREAST TENDERNESS	24	3.71	14	2.15	38	2.93
PELVIC PAIN	19	2.94	23	3.54	42	3.24
GASTROINTESTINAL DISORDERS						
NAUSEA	25	3.86	21	3.23	46	3.55
ABDOMINAL DISTENSION	22	3.40	23	3.54	45	3.47
ABDOMINAL PAIN	19	2.94	25	3.85	44	3.39
CONSTIPATION	17	2.63	10	1.54	27	2.08
INJURY, POISONING AND PROCEDURAL COMPLICATIONS						
POST PROCEDURAL DISCOMFORT	24	3.71	25	3.85	49	3.78

Vaginal infections were less than 2% in both treatment groups (1.7% for DR-2011 and 1.2% for Crinone 8%)

From NDA Application, Body Study Report, table 171, p367

Table 53: Incidence of Treatment-Emergent Adverse Events >2%-Safety Cohort -DR-PGN-302

MedDRA System Organ Class and Preferred Term	DR-2011 (N=647)		Crinone® 8% (N=650)		Total (N=1297)	
	N	%	N	%	N	%
GASTROINTESTINAL DISORDERS						
NAUSEA	166	25.66	145	22.31	311	23.98
ABDOMINAL PAIN	131	20.25	150	23.08	281	21.67
ABDOMINAL DISTENSION	88	13.60	78	12.00	166	12.80
CONSTIPATION	74	11.44	69	10.62	143	11.03
VOMITING	66	10.20	55	8.46	121	9.33
DYSPEPSIA	52	8.04	68	10.46	120	9.25
DIARRHOEA	37	5.72	56	8.62	93	7.17
ABDOMINAL PAIN UPPER	29	4.48	30	4.62	59	4.55
ABDOMINAL PAIN LOWER	18	2.78	25	3.85	43	3.32
FLATULENCE	18	2.78	12	1.85	30	2.31
ABDOMINAL DISCOMFORT	16	2.47	12	1.85	28	2.16
NERVOUS SYSTEM DISORDERS						
HEADACHE	132	20.40	167	25.69	299	23.05
DIZZINESS	48	7.42	35	5.38	83	6.40
INJURY, POISONING AND PROCEDURAL COMPLICATIONS						
POST PROCEDURAL DISCOMFORT	102	15.77	98	15.08	200	15.42
PROCEDURAL PAIN	36	5.56	35	5.38	71	5.47
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
BACK PAIN	82	12.67	84	12.92	166	12.80
ARTHRALGIA	13	2.01	5	0.77	18	1.39
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
FATIGUE	81	12.52	80	12.31	161	12.41
PYREXIA	13	2.01	16	2.46	29	2.24
REPRODUCTIVE SYSTEM AND BREAST DISORDERS						
VAGINAL DISCHARGE	61	9.43	21	3.23	82	6.32
BREAST TENDERNESS	55	8.50	39	6.00	94	7.25
PELVIC PAIN	55	8.50	73	11.23	128	9.87
OVARIAN HYPERSTIMULATION SYNDROME	30	4.64	31	4.77	61	4.70
METRRORRHAGIA	24	3.71	20	3.08	44	3.39
UTERINE SPASM	23	3.55	25	3.85	48	3.70
DYSMENORRHOEA	14	2.16	10	1.54	24	1.85
PSYCHIATRIC DISORDERS						
INSOMNIA	27	4.17	14	2.15	41	3.16
INFECTIONS AND INFESTATIONS						
URINARY TRACT INFECTION	26	4.02	35	5.38	61	4.70

NASOPHARYNGITIS	13	2.01	11	1.69	24	1.85
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS						
INTRA-UTERINE DEATH	23	3.55	16	2.46	39	3.01
ABORTION MISSED	18	2.78	14	2.15	32	2.47
BLIGHTED OVUM	16	2.47	17	2.62	33	2.54
METABOLISM AND NUTRITION DISORDERS						
ANOREXIA	22	3.40	19	2.92	41	3.16
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
DYSпноEA	18	2.78	16	2.46	34	2.62
PHARYNGOLARYNGEAL PAIN	14	2.16	16	2.46	30	2.31
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
RASH	13	2.01	7	1.08	20	1.54

Source: NDA DR-PGN-302 Clinical Study Report, Table 166, p320-321

Reviewer's Comment: Treatment emergent adverse events (TEAEs) were generally similar between the two groups and accordant with the known profile of progesterone. The most common treatment-emergent AEs reported during the treatment period were nausea, headache, abdominal pain, post-procedural discomfort, abdominal distension, back pain, fatigue, and constipation, all with a frequency of 10% or greater. All reported TEAEs and treatment related AEs are similar to previously reported TEAEs and treatment related AEs to already approved progesterone products for support of embryo implantation and early pregnancy by supplementation of corpus luteum function.

See Subsections 5.3.1.21 to 5.3.1.25 for a complete discussion of the treatment emergent adverse events reported in Study DR-PGN-302.

7.1.2.1 Ancillary studies

Study 10716222

Table 54 shows the adverse events observed in study 1071622 and are presented by MedDRA System Organ Class and by Preferred Term

Table 54: Adverse Events Reported in Study 10716222

Body System/AE	DR-2011 N=30 n (%)
Gastrointestinal Disorders	
Abdominal Pain	11 (36.7%)
Investigations	
Blood Pressure decreased	5 (16.7%)
Nervous System Disorders	
Headache	3 (10%)
Reproductive System and Breast Disorders	
Metrorrhagia	22 (73.3%)
Vaginal Discharge	3 (10%)
Skin and Subcutaneous Tissue Disorders	
Pruritus Generalized	3 (10%)

Source: Generated from NDA, study Report

Study 10936035

Table 55 shows the adverse events observed in study 10936035 and are presented by MedDRA System Organ Class and by Preferred Term

Table 55: Adverse Events Reported in Study 10936035

Body System/AE	DR-2011 Test A N=31 n (%)	DR-2011 Test B N=32 n (%)
Gastrointestinal Disorders		
Abdominal Pain	7 (22%)	11 (34.4%)
Investigations		
Blood Pressure decreased	4 (12.9%)	4 (12.5%)
Nervous System Disorders		
Headache	3 (3.7%)	2 (6.25%)
Reproductive System and Breast Disorders		
Metrorrhagia	26 (83.9%)	27 (84.4%)
Vaginal Discharge	4 (12.9%)	1 (3.1%)

Source: Generated from NDA, study Report

Study 10936057

Table 56 shows the adverse events observed in study 10936057 and are presented by MedDRA System Organ Class and by Preferred Term

Table 56: Adverse events Reported in Study 10936057

Body System/AE	DR-2011 N=15
	n (%)
Musculoskeletal and Connective Tissue Disorders	
Back Pain	3 (20%)
Reproductive System and Breast Disorders	
Metrorrhagia	3 (20%)

Source: Generated from NDA, study Report

Study DR-201-102

Table 57 presents the Incidence of Treatment-Emergent Adverse Events for Study 201-102. Adverse events are presented by MedDRA System Organ Class and by Preferred Term

Table 57: Incidence of Treatment-Emergent Adverse Events - Safety Cohort in study DR-PGN-201-102

MedDRA System Organ Class and Preferred Term	DR-2011 (N=21)		Progesterone Gel (N=21)		Estrogen Only (N=21)		Total (N=63)	
	n	%	n	%	n	%	n	%
ANY AE								
Total Disorders ^a	14	66.67	17	80.95	17	80.95	48	76.19
INFECTIONS AND INFESTATIONS								
Total Disorders	6	28.57	4	19.05	4	19.05	14	22.22
UPPER RESPIRATORY TRACT INFECTION	4	19.05	0	0.00	1	4.76	5	7.94
DENTAL CARIES	1	4.76	0	0.00	0	0.00	1	1.59
INFLUENZA	1	4.76	0	0.00	1	4.76	2	3.17
NERVOUS SYSTEM DISORDERS								
Total Disorders	6	28.57	9	42.86	8	38.10	23	36.51
HEADACHE	5	23.81	8	38.10	8	38.10	21	33.33
REPRODUCTIVE SYSTEM AND BREAST DISORDERS								
Total Disorders	6	28.57	11	52.38	6	28.57	23	36.51
PELVIC PAIN	6	28.57	6	28.57	2	9.52	14	22.22
IMMUNE SYSTEM DISORDERS								
Total Disorders	4	19.05	2	9.52	1	4.76	7	11.11
SEASONAL ALLERGY	3	14.29	1	4.76	0	0.00	4	6.35
HYPERSENSITIVITY	1	4.76	1	4.76	0	0.00	2	3.17

Source: NDA, DR-201-102, Study Report, Table 15, p55

Table 58 presents the Incidence of Treatment-Related Adverse Events for Study 201-102. Adverse events are presented by MedDRA System Organ Class and by Preferred Term

Table 58: Incidence of Treatment-Related Adverse Events - Safety Cohort in study DR-PGN-201-102

MedDRA System Organ Class and Preferred Term	DR-2011 (N=21)		Progesterone Gel (N=21)		Estrogen Only (N=21)		Total (N=63)	
	n	%	n	%	n	%	n	%
NERVOUS SYSTEM DISORDERS								
Total Disorders	2	9.52	1	4.76	2	9.52	5	7.94
HEADACHE	1	4.76	1	4.76	2	9.52	4	6.35
REPRODUCTIVE SYSTEM AND BREAST DISORDERS								
Total Disorders	2	9.52	4	19.05	3	14.29	9	14.29
PELVIC PAIN	2	9.52	2	9.52	0	0.00	4	6.35
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS								
Total Disorders	1	4.76	0	0.00	1	4.76	2	3.17
APPLICATION SITE PRURITUS	1	4.76	0	0.00	0	0.00	1	1.59

Study DR-PGN-201

Table 59 presents the Incidence of Treatment-Emergent Adverse Events for Study 201. Adverse events are presented by MedDRA System Organ Class and by Preferred Term

Table 59: Incidence of Treatment-Emergent Adverse Events - Safety Cohort in study DR-PGN-201

MedDRA System Organ Class and Preferred Term	Progesterone VR (N=10)		8% Progesterone Vaginal Gel (N=11)		Total (N=21)	
	N	%	N	%	N	%
ANY AE						
Total Disorders	10	100.00	9	81.82	19	90.48
REPRODUCTIVE SYSTEM AND BREAST DISORDERS						
Total Disorders	10	100.00	6	54.55	16	76.19
METRORRHAGIA	9	90.00	0	0.00	9	42.86
DYSMENORRHOEA	1	10.00	1	9.09	2	9.52
VAGINAL DISCHARGE	1	10.00	0	0.00	1	4.76

Clinical Review
{Insert Reviewer Name}
{Insert Application Type and Number}
{Insert Product Trade and Generic Name}

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS

MYALGIA	1	10.00	0	0.00	1	4.76

SKIN AND SUBCUTANEOUS TISSUE DISORDERS

SKIN IRRITATION	1	10.00	0	0.00	1	4.76

Source: NDA, DR-201, Study Report, Table 8, p52

Study DR-PGN-202

Table 60 presents the Incidence of-Treatment-Related Adverse Events for Study 202. Adverse events are presented by MedDRA System Organ Class and by Preferred Term

Table 60: Incidence of Treatment-Related Adverse Events - Safety Cohort in study DR-PGN-202

MedDRA System Organ Class and Preferred Term	Progesterone Vaginal Ring (N=5)		8% Progesterone Vaginal Gel (N=4)		Total (N=9)	
	N	%	N	%	N	%
ANY AE						
Total Disorders	5	100.00	3	75.00	8	88.89
GASTROINTESTINAL DISORDERS						
Total Disorders	3	60.00	3	75.00	6	66.67
DYSPEPSIA	2	40.00	1	25.00	3	33.33
NAUSEA	2	40.00	1	25.00	3	33.33
ABDOMINAL PAIN LOWER	1	20.00	2	50.00	3	33.33
DIARRHOEA	1	20.00	0	0.00	1	11.11
VOMITING	1	20.00	0	0.00	1	11.11
REPRODUCTIVE SYSTEM AND BREAST DISORDERS						
Total Disorders	3	60.00	2	50.00	5	55.56
METRORRHAGIA	3	60.00	1	25.00	4	44.44
PELVIC PAIN	2	40.00	1	25.00	3	33.33
VAGINAL HAEMORRHAGE	1	20.00	0	0.00	1	11.11
PELVIC DISCOMFORT	0	0.00	1	25.00	1	11.11
INFECTIONS AND INFESTATIONS						
Total Disorders	2	40.00	3	75.00	5	55.56
UPPER RESPIRATORY TRACT INFECTION	1	20.00	2	50.00	3	33.33
VAGINAL CANDIDIASIS	1	20.00	0	0.00	1	11.11
HERPES SIMPLEX	0	0.00	1	25.00	1	11.11
NERVOUS SYSTEM DISORDERS						
Total Disorders	2	40.00	2	50.00	4	44.44
DIZZINESS	1	20.00	0	0.00	1	11.11
HEADACHE	1	20.00	2	50.00	3	33.33

Source: NDA, DR-PGN-202, Study Report, Table 16, p65

Reviewer's Comment: *The adverse events reported in each of the individual studies do not raise any safety concerns for the progesterone vaginal ring.*

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Nervous System Incidence

The most common nervous system AE across all studies was headache followed by dizziness. Pooling the data for treatment -related AEs in subjects who used DR-2011, headache was observed in 46 subjects out of 673 (6.8%), while for treatment -emergent AEs, headache was observed in 146 subjects out of 746 (19.6%) followed by Dizziness in 49 subjects (6.6%). See Table 61.

Table 61: Pool data across studies with Nervous System AEs

Treatment-Related AEs in Reference to Nervous System			
	DR-2011 N=673 n (%)	Crinone 8% N=675 n (%)	Total N=1348 n (%)
Headache	46 (6.8%)	42 (6.2%)	88 (6.4%)
Treatment-Emergent AEs in Reference to Nervous System			
	DR-2011 N=746 n (%)	Crinone 8% N=686 n (%)	Total 1432 n (%)
Headache	146 (19.6%)	178 (25.9%)	324 (22.6%)
Dizziness	49 (6.6%)	35 (5.1%)	84 (5.9%)

Reviewer's Comment: The incidence of headaches or dizziness is acceptable for this group of pharmaceutical products. Headache incidence ranges between 4-17% in the labels for the existing approved products.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The maximum duration of exposure was 78 days for the DR-2011 treatment group and 79 days for the Crinone 8% treatment group. This duration of exposure is consistent with one cycle of use, if pregnancy occurs. The overall exposure is adequate. See Table 62.

Table 62: Extent of Exposure in Days - Safety Cohort

Treatment Group	N	Mean (STD)	Min	Median	Max
DR-2011	647	40.9 (26.98)	0.5 ^a	38	78
Crinone 8%	650	41.0 (26.75)	1	30	79

^a *A half day of exposure was included in the calculation for two subjects who reported the same date for dispensing and removal of DR-2011.*

Source: NDA Application , Study DR-PGN-302 Clinical Study Report, Table 39, P: 95

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or in-vitro testing was undertaken.

7.2.4 Routine Clinical Testing

7.2.5 Metabolic, Clearance, and Interaction Workup

No metabolic, clearance, and interaction workup was completed.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The adverse events reported in Study DR-PGN-302 demonstrate the similarity between the progesterone vaginal ring and Crinone 8%.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in primary Study DR-PGN-302.

7.3.2 Nonfatal Serious Adverse Events

See Subsection 5.3.1.23 of this review for a complete discussion of nonfatal serious adverse events reported in Study DR-PGN-302.

7.3.3 Dropouts and/or Discontinuations

See Subsection 5.3.1.24 of this review for a complete discussion of dropouts and/or discontinuations reported in Study DR-PGN-302.

Subjects may have withdrawn From the time of consent until the end of the treatment period as

described in the protocol. Missing data in the co-primary endpoints due to early termination From the study were not imputed. That is, subjects who terminated prematurely From the study prior to 8 weeks of pregnancy (6 weeks after egg retrieval) were considered as “not pregnant” at both 8 weeks of pregnancy and 12 weeks of pregnancy (10 weeks after egg retrieval) in the efficacy analysis.

7.3.4 Significant Adverse Events

See Subsection 5.3.1.25 of this review for a complete discussion of significant adverse events reported in Study DR-PGN-302.

7.3.5 Submission Specific Primary Safety Concerns

Protocol Violations: There were no major protocol violations reported in Study DR-PGN-302, but numerous minor protocol deviations were reported during the conduct of this study. However, none of the reported minor protocol violations affect the evaluability of the subjects. These violations include inclusion/exclusion criteria (12 subjects), non-compliance with the investigational product (28 subjects-13 subjects in the DR-2011 group used the medication for more than 8 days [left the VR in the vagina for 9-12 days] and 15 subjects in the Crinone 8% group missed their dose 2-7 times), and using prohibited vaginal medications (18 subjects). One subject was randomized to Crinone 8% and received DR-2011, and two subjects were randomized to DR-2011 and received Crinone 8%.

There were 48 spontaneous abortions reported in the DR-2011 treatment group and 47 spontaneous abortions in the Crinone 8% treatment group (about 7.5% for each group). There were also 7 ectopic pregnancies in the DR-2011 treatment group and 8 ectopic pregnancies in the Crinone 8% treatment group (about 1.1% for each group).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

See Subsection 5.3.1.25 of this review for a complete discussion of common adverse events reported in Study DR-PGN-302. Six hundred twenty-two (622) subjects in the progesterone vaginal ring treatment group (96.0%) and 612 subjects in the Crinone 8% treatment group (94.0%) reported at least one adverse event in Study DR-PGN-302. The most common adverse reactions reported in the two treatment groups, occurring at an incidence of $\geq 10\%$ were: headache, nausea and post procedural pain, abdominal pain, procedural pain, abdominal distension, back pain, constipation, fatigue, pelvic pain, vomiting, dyspepsia, breast tenderness, dysmenorrhea, and diarrhea.

Reviewer’s Comment: All the common adverse reactions reported at an incidence of $\geq 10\%$ in Study DR-PGN-302 are well known side effects during ART treatment and with progesterone supplementation associated with ART. No significant increases in these AEs were reported.

7.4.2 Laboratory Findings

No significant changes in laboratory findings were observed during the time from screening to end-of-study, in Study DR-PGN-302.

7.4.3 Vital Signs

No significant changes in vital signs were observed between baseline and end-of-study, in Study DR-PGN-302.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed in Study DR-PGN-302.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were performed during the drug development process.

7.4.6 Immunogenicity

No human immunogenicity studies, data, or published literature were submitted in the NDA. FDA did not request any such studies.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No dose dependency studies were performed. In both Studies DR-PGN-202 and DR-PGN-302, only one dose was tested. The Applicant states that the vaginal ring was loaded with the maximum amount of progesterone. For safety results see Subsection 7.3, Major Safety Results, of this review. This drug is to be administered for conditions that occur only in women [female infertility in connection with ART (IVF/ICSI)] and is not indicated for use in pediatric patients. Safety and efficacy in such patients have not been established. Racial and ethnic differences are not likely to be of any significant concern regarding efficacy or safety of the drug product. The safety and efficacy of the drug in renal and hepatic insufficiency have not been studied.

7.5.2 Time Dependency for Adverse Events

There was no evidence of any time dependency for any adverse findings, and therefore, no exploration for time-dependent adverse events was undertaken in the NDA application.

7.5.3 Drug-Demographic Interactions

There was no evidence of drug-demographic interaction in the NDA Application.

7.5.4 Drug-Disease Interactions

There was no evidence of drug-disease interaction in the NDA application.

7.5.5 Drug-Drug Interactions

No drug-drug interactions were studied during the clinical development program.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity studies were performed.

7.6.2 Human Reproduction and Pregnancy Data

No preclinical studies were performed in humans on the effects of progesterone on reproduction or pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

The progesterone vaginal ring is not indicated for use in a pediatric population. Teva Women's Health, Inc. requested a full waiver for pediatric studies pursuant to 21 CFR 314.55 (c)(2) for the progesterone vaginal ring for the following reason:

The proposed indication for the progesterone vaginal ring is 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. This condition does not apply to the pediatric population.

Reviewer's Comment: This reviewer agrees with the sponsor's request for Pediatric waiver.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There are no overdose, drug abuse potential, withdrawal and rebound concerns with this drug product.

7.7 Additional Submissions / Safety Issues

The 4-Month Safety Update report states that there were no follow up reports received regarding any pregnancies or serious adverse events that occurred in the clinical trials submitted in the original NDA. There are no studies currently ongoing or recently completed, and the progesterone vaginal ring is not marketed in the United States or any other country.

Postmarket Experience

The progesterone vaginal ring, the subject of this NDA, is not approved in the United States or elsewhere

9 Appendices

9.1 Literature Review/References

Literature review/references are included as a footnote in the appropriate sections of this review. This reviewer determined that there was no need for a separate comprehensive review of the literature on progesterone for luteal supplementation for subjects who will be undergoing Assisted Reproductive Technology procedures.

9.2 Labeling Recommendations

9.3 Advisory Committee Meeting

There were no advisory committee meetings in which the progesterone vaginal ring was discussed.

9.4 SAMPLE Progesterone Treatment Satisfaction

As per the Applicant the Progesterone Treatment Satisfaction questionnaire is not a validated instrument. No claims can be made based on this instrument. It is only used by the Applicant to evaluate patient satisfaction.

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/s/

CHRISTOS MASTROYANNIS
02/24/2011

SHELLEY R SLAUGHTER
02/25/2011

I concur with the recommendatinn of Dr. Mastroyannis that this application should not be approved. See also the Cross Discipline Team Leader review.