CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201110Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	201110
Supporting document/s:	SDN 26; Class 2 resubmission SDN 29; Response to Information Request
Applicant's letter date:	10-29-2019
CDER stamp date:	10-29-2019
Product:	Progesterone vaginal ring (Milprosa®)
Indication:	Support of early pregnancy (up to 10 weeks post-embryo transfer) as part of an Assisted Reproductive Technology (ART) program
Applicant:	Ferring Pharmaceuticals
Review Division:	Division of Urology, Obstetrics and Gynecology
Reviewer:	Leslie McKinney, PhD
Supervisor/Team Leader:	Mukesh Summan, PhD, DABT Kimberly Hatfield, PhD
Acting Division Director:	Christine Nguyen, MD
Project Manager:	Nikia Morris

Disclaimer

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1 Executive Summary

1.1 Introduction

Indication: The proposed use of the Milprosa® vaginal ring is for support of early pregnancy (up to 10 weeks) for women undergoing Assisted Reproductive Technology (ART). The daily dose of progesterone released from the ring is 11 mg, and the ring is designed to be replaced after 7 days.

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

Related product: There are currently no approved products utilizing the silicone ring method of delivery for progesterone, however, there is an approved contraceptive device, Nuvaring®, that delivers synthetic estrogens to the uterus via a silicone ring.

1.3 Recommendations

1.3.3 Labeling

There were minimal changes to the sponsor's proposed labeling for nonclinical sections, and these consisted of deletions. There were no wording changes. The sponsor's proposed labeling is given by section below, with changes shown in strikethrough.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

MILPROSA is indicated to support embryo implantation and early pregnancy as part of an assisted reproductive technology treatment program for infertile women. Maternal risks are discussed throughout the labeling.

In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

MILPROSA has been used to support embryo implantation during the first trimester of pregnancy and to maintain clinical pregnancy as part of an ART regimen. (b) (4)

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.

(b) (4)

Reviewer's comment: This section is consistent with the labels for Endometrin and Crinone, two vaginally administered progesterone products (see Appendix below) (b) (4)

8.2 Lactation

Risk Summary

Detectable amounts of progesterone have been identified in the milk of nursing mothers. The effect of this on the nursing infant has not been determined. A published study reported no adverse effects of progesterone on milk production or infant growth during the first postpartum year.

12 CLINICAL PHARMACOLOGY

12.1Mechanism of Action

Progesterone is a naturally occurring steroid that is secreted by the ovary, placenta, and adrenal gland. In the presence of adequate estrogen, progesterone transforms a proliferative endometrium into a secretory endometrium. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain a pregnancy.

Reviewer's comment: This section is the same as Section 12.1 of the Endometrin label (see Appendix below).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Nonclinical toxicity studies to determine the potential of MILPROSA to cause carcinogenicity or mutagenicity have not been performed. The effect of MILPROSA on fertility has not been evaluated in animals.

Reviewer's comment: This statement is the same as Section 13.1 for Crinone and for Endometrin (see Appendix below).

(b) (4)

12. APPENDIX

Endometrin progesterone vaginal tablet – for ART (2008)

This label has not been updated according to the Pregnancy and Lactation Labeling Rule (PLLR)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Endometrin has been used to support embryo implantation and maintain clinical pregnancy in one clinical study. The livebirth outcomes of these pregnancies were as follows: (deleted)

Birth defects reported in the Endometrin three times daily group included: (deleted)
For additional information on the pharmacology of Endometrin and pregnancy outcome information *[see Clinical Pharmacology (12) and Clinical Studies Sections (14)]*.

8.3 Nursing Mothers

Detectable amounts of progesterone have been identified in the milk of nursing mothers. The effect of this on the nursing infant has not been determined.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Progesterone is a naturally occurring steroid that is secreted by the ovary, placenta, and adrenal gland. In the presence of adequate estrogen, progesterone transforms a proliferative endometrium into a secretory endometrium. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain a pregnancy.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Nonclinical toxicity studies to determine the potential of Endometrin to cause carcinogenicity or mutagenicity have not been performed. The effect of Endometrin on fertility has not been evaluated in animals.

Crinone progesterone vaginal gel – for ART (2013)
This label has not been updated according to the Physician's Labeling Rule (PLR) or PLLR

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy (See **CLINICAL STUDIES, Assisted Reproductive Technology**)
Crinone 8% has been used to support embryo implantation and maintain pregnancies through its use as part of ART treatment regimens in two clinical studies (studies COL1620-007US and COL1620-F01). In the first study (COL1620-007US), 54 Crinone-treated women had donor oocyte transfer procedures, and clinical pregnancies occurred in 26 women (48%). The outcomes of these 26 pregnancies were as follows: one woman had an elective termination of pregnancy at 19 weeks due to congenital malformations (omphalocele) associated with a chromosomal abnormality; one woman pregnant with triplets had an elective termination of her pregnancy; seven women had spontaneous abortions; and 17 women delivered 25 apparently normal newborns.

In the second study (COL1620-F01), Crinone 8% was used in the luteal phase support of women undergoing in vitro fertilization ("IVF") procedures. In this multi-center, open-label study, 139 women received Crinone 8% once daily beginning within 24 hours of embryo transfer and continuing through Day 30 post-transfer.

Clinical pregnancies assessed at Day 90 post-transfer were seen in 36 (26%) of women. Thirty-two women (23%) delivered newborns and four women (3%) had spontaneous abortions. Of the 47 newborns delivered, one had a teratoma associated with a cleft palate; one had respiratory distress syndrome; 44 were apparently normal and one was lost to follow-up.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Progesterone is a naturally occurring steroid that is secreted by the ovary, placenta, and adrenal gland. In the presence of adequate estrogen, progesterone transforms a proliferative endometrium into a secretory endometrium. Progesterone is essential for the development of decidual tissue, and the effect of progesterone on the differentiation of glandular epithelia and stroma has been extensively studied. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy. Normal or near-normal endometrial responses to oral estradiol and intramuscular progesterone have been noted in functionally agonadal women through the sixth decade of life. Progesterone administration decreases the circulatory levels of gonadotropins.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Nonclinical toxicity studies to determine the potential of Crinone to cause carcinogenicity or mutagenicity have not been performed. The effect of Crinone on fertility has not been evaluated in animals.

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/s/

LESLIE C MCKINNEY
04/23/2020 03:43:21 PM

KIMBERLY P HATFIELD
04/23/2020 03:50:47 PM

PHARMACOLOGY/TOXICOLOGY REVIEW

Date:	April 22, 2020
NDA #	201110 SDN 53
Sponsor:	Ferring Pharmaceuticals
Drug/Indication:	Progesterone vaginal ring (Milprosa®)
Indication:	Support of early pregnancy (up to 10 weeks post-embryo transfer) as part of an Assisted Reproductive Technology (ART) program
Reviewer:	Leslie McKinney, PhD

Background:

In mid-April, just a few weeks prior to the PDUFA date, this NDA was reclassified from a 505b1 to a 505b2 application. This was based on the finding by the Clinical Pharmacology team that the sponsor was going to have to rely on literature for a portion of the pharmacokinetic data needed for approval.

The 505b2 committee asked whether reliance on nonclinical literature was also necessary for approval of the NDA. The following text documents the scientific rationale for why no additional nonclinical information is necessary from literature to approve this application. We submitted the following to the CDTL for inclusion in the final approval memo, and now as an addendum to our review filed to DARRTS on 4-1-20.

Summary of nonclinical data:

NDA 201110 represents a novel route of administration and delivery for a well-studied endogenous hormone. Progesterone is produced by the corpus luteum of the ovary following ovulation. It supports early pregnancy until the placenta can produce enough progesterone to maintain the pregnancy.

To support the vaginal route of administration, nonclinical studies were conducted in the rabbit to assess the local response of vaginal tissue to the progesterone implant. The uterine and vaginal changes that were observed were deemed due to pharmacologic activity of progesterone.

Although literature was submitted to the NDA describing pharmacology and toxicology of progesterone, it was not needed to support approval of the NDA because the role of progesterone in maintaining pregnancy is well understood, and this product is mimicking the physiological role of progesterone in early pregnancy. The nonclinical literature that was submitted covered systemic effect of progesterone in nonclinical species by the

oral or injected route of administration, and involve large systemic exposures, which are informative but not relevant for this NDA.

Clinical experience with progesterone over many decades has established that progesterone is not fetotoxic. For that reason, it is not necessary to rely on nonclinical reproductive toxicity studies for approval. Also, total exposure to progesterone from Milprosa will not exceed 12 weeks, which is below the duration of use that would raise carcinogenicity concerns. For that reason, it is not necessary to have nonclinical data on carcinogenicity of progesterone to approve Milprosa.

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/s/

LESLIE C MCKINNEY
04/23/2020 11:43:21 AM

KIMBERLY P HATFIELD
04/23/2020 11:51:45 AM
I concur with Dr. McKinney.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	201110 505b1
Supporting document/s:	SDN 53; Class 2 resubmission
Applicant's letter date:	10-29-2019
CDER stamp date:	10-29-2019
Product:	Progesterone vaginal ring (Milprosa®)
Indication:	Support of early pregnancy (up to 10 weeks post-embryo transfer) as part of an Assisted Reproductive Technology (ART) program
Applicant:	Ferring Pharmaceuticals
Review Division:	Division of Urology, Obstetrics and Gynecology
Reviewer:	Leslie McKinney, PhD
Supervisor: Team Leader:	Mukesh Summan, PhD, DABT Kimberly Hatfield, PhD
Acting Division Director:	Christine Nguyen, MD
Project Manager:	Nikia Morris

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1 Executive Summary

1.1 Introduction

Regulatory issues: This NDA was initially submitted on April 30, 2010 by Teva Women's Health, Inc. It was reviewed by Krishan Raheja, DVM, PhD, and deemed approvable by PharmTox in a review dated July 16, 2010. The application received a complete response on Feb 28, 2011, based on product quality and clinical deficiencies.

Ownership of the product was subsequently transferred to Ferring Pharmaceuticals on Aug 5, 2015, who addressed the deficiencies and resubmitted the application in 2016. However, during the interim period when the application was being revised, vaginal ring products were reclassified as combination products, which means that review of this product is now shared between CDRH and CDER. CDRH is responsible for review of the device portion of the product (the ring) and CDER is responsible for review of the drug portion of the product (progesterone). Ferring was unaware of the reclassification and did not conduct the necessary biocompatibility testing required by CDRH, which led to a CR being issued in 2016. Ferring has now conducted the required biocompatibility testing and resubmitted the NDA.

Indication: The proposed use of the Milprosa® vaginal ring is for support of early pregnancy (up to 10 weeks) for women undergoing Assisted Reproductive Technology (ART). The daily dose of progesterone released from the ring is 11 mg, and the ring is designed to be replaced after 7 days.

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

Related product: There are currently no approved products utilizing the silicone ring method of delivery for progesterone, however, there is an approved contraceptive device, Nuvaring®, that delivers synthetic estrogens to the uterus via a silicone ring.

1.2 Brief Discussion of Nonclinical Findings

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, both 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

genetic toxicology, reproductive/developmental toxicology, or carcinogenicity studies were conducted for this product, and none were necessary.

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.

1.3 Recommendations

1.3.1 Approvability

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.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

Labeling will be reviewed separately.

11 Integrated Summary and Safety Evaluation

NDA 201110 represents a novel route of administration and delivery for a well-studied endogenous hormone, progesterone. Nonclinical studies conducted in the rabbit in support of the original submission were designed to assess the local response of vaginal tissue to the progesterone implant. As described in Dr. Raheja's review, neither the 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. Note that Dr. Raheja's review references a dose of (b) (4) mg/day, which was the dose tested in the Phase 1 trials.

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.

Based on concordance between the progesterone drug substance used in the original submission it can be concluded that the current submission is acceptable.

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/s/

LESLIE C MCKINNEY
03/31/2020 06:55:23 PM

KIMBERLY P HATFIELD
04/01/2020 10:15:19 AM
I concur with the review and conclusions of Dr. McKinney, and agree that this product is approvable from a nonclinical perspective.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	201110
Supporting document/s:	SDN 26; Class 2 resubmission SDN 29; Response to Information Request
Applicant's letter date:	02-25-2016 04-06-2016
CDER stamp date:	02-25-2016 04-06-2016
Product:	Progesterone vaginal ring (Milprosa®)
Indication:	Support of early pregnancy (up to 10 weeks post-embryo transfer) as part of an Assisted Reproductive Technology (ART) program
Applicant:	Ferring Pharmaceuticals
Review Division:	Division of Reproductive and Urologic Drugs
Reviewer:	Leslie McKinney, PhD
Supervisor/Team Leader:	Mukesh Summan, PhD, DABT
Division Director:	Hylton Joffe, MD
Project Manager:	Nikia Morris

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1 Executive Summary

1.1 Introduction

This NDA was initially submitted on April 30, 2010 by Teva Women's Health, Inc. It was reviewed by Krishan Raheja, DVM, PhD, and deemed approvable by PharmTox in a review dated July 16, 2010. (Dr. Raheja's review is appended to this document). The application received a complete response on Feb 28, 2011, based on product quality and clinical deficiencies. Ownership of the product was subsequently transferred to Ferring Pharmaceuticals on Aug 5, 2015, which has addressed the deficiencies and resubmitted the application. However, during the interim period when the application was being revised, vaginal ring products were reclassified as combination products, which the new sponsor was unaware of at the time of resubmission. Review of this product is now shared between CDRH and CDER. CDRH is responsible for review of the device portion of the product (the ring) and CDER is responsible for review of the drug portion of the product (progesterone).

The proposed use of the Milprosa® vaginal ring is for support of early pregnancy (up to 10 weeks) for women undergoing ART. The daily dose of progesterone released from the ring is 11 mg, which is designed to be replaced after 7 days.

Progesterone is a human hormone that has been approved under multiple NDAs in various formulations for use in treating amenorrhea (Progesterone), Assisted Reproductive Technology (ART) (Crinone®, Endometrin®), as a contraceptive (Progestasert® IUD - no longer marketed in the US), and for endometrial protection in women who are taking estrogen (Prometrium®). The daily dose of progesterone contained in the Milprosa® vaginal ring (11 mg) is less than the already approved doses. The duration of exposure (up to 10 weeks) is less than the duration of already approved products.

There are currently no approved products utilizing the silicone ring route of administration for progesterone, however, there is an approved contraceptive device, Nuvaring®, that delivers synthetic estrogens to the uterus via a silicone ring.

1.2 Brief Discussion of Nonclinical Findings

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 genetox, reprotox, or carcinogenicity studies were conducted for this 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.

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 engineer. The sponsor 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.

1.3 Recommendations

1.3.1 Approvability

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.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Labeling will be reviewed separately at a later date.

11 Integrated Summary and Safety Evaluation

NDA 201110 represents a novel route of administration for a well-studied hormone, progesterone. Nonclinical studies conducted in the rabbit in support of the original submission were designed to assess the local response of vaginal tissue to the progesterone implant. As described in Dr. Raheja's review, neither the 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.

12 Appendix/Attachments

Review of NDA 201110 by Dr. Krishan Raheja. Note that Dr. Raheja's review references a dose of (b) (4) mg/day, which was the dose tested in the Phase 1 trials.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	201-110
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	4/30/10
PRODUCT:	Progesterone vaginal ring (DR-2011), (b)(4)% w/w, 14 mg/day, 7day application. DR2011 is a progesterone –containing flexible silicone vaginal ring with a cylindrical-shaped hollow cavity that is filled with a progesterone silicone blend. (b)(4)™ as the proposed primary proprietary name.
INTENDED CLINICAL POPULATION:	To support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation
SPONSOR:	Teva Women's Health, Inc.
DOCUMENTS REVIEWED:	e-Submission
REVIEW DIVISION:	Division of Reproductive & Urologic Products (HFD 580)
PHARM/TOX REVIEWER:	Krishan L. Raheja, D.V.M., Ph.D.
PHARM/TOX SUPERVISOR:	Alex Jordan, Ph.D.
DIVISION DIRECTOR:	Scott E Monroe, M.D.
PROJECT MANAGER:	Celia, Peacock

Date of review submission to Division File System (DFS): 7-16-10

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Pharmacology/Toxicology recommends approval of NDA 201-110.

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

C. Recommendations on labeling: Labeling is in accord with PLR and presented in SLR format.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: 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.

B. Pharmacologic activity: Progestogenic effects

C. Nonclinical safety issues relevant to clinical use: None

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 201-110
Review number: 1
Sequence number/date/type of submission: 000/4-30-10/original submission
Information to sponsor: Yes ( ) No ( )
Sponsor and/or agent: Teva Women's Health, Inc. (b) (4)
Manufacturer for drug substance: (b) (4)

Reviewer name: Krishan L. Raheja, D.V.M., Ph.D.
Division name: Reproductive & Urologic Products
HFD #: 580
Review completion date: 7-15-10

Drug:

Trade name: none given. Sponsor has proposed proprietary name as (b) (4)
Generic name: Progesterone, UPS (b) (4)
Code name: DR-2011
Chemical name: pregn-4, ene-3-20-dione
CAS registry number: 57-83-0
Molecular formula/molecular weight: $C_{21}H_{30}O_2$/314.47
Structure:

Relevant INDs/NDAs/DMFs: IND 70,875; Organon DMF (b) (4)

Drug class: Progestin

Intended clinical population: To support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation.

Clinical formulation: Progesterone Vaginal Ring's formulation which was described under original IND 70,875 is as follows:

The ring's active ingredient is progesterone, USP (b) (4))

The ring's inactive ingredients are the following:

Silicone Elastomer, (b) (4).

(b) (4)

(b) (4)

Other inactive ingredient is Light mineral oil, NF

The progesterone vaginal ring releases (b) (4) mg progesterone/day.

Note: Silicone elastomers have been used under IND (b) (4)

(b) (4) conducted extensive toxicity studies on silicone elastomers, which consisted of the following:

- In vitro tissue cell culture
- Pyrogen test in rabbits
- Systemic injection in mice
- Intracutaneous test in rabbits
- Skin sensitization test in rabbits
- Hemolysis test
- 90-day implantation in rabbits
- 72 hour vaginal implantation in rabbits
- thrombogenicity test for silastic
- 2-year tissue implantation in Fisher 344 rats with (b) (4)

Thus the safety of (b) (4) silicone elastomer seems reasonably well established.

Studies conducted with silicone elastomers for biocompatibility and Ames mutagenicity assay were provided under original IND 70875 SS# 000 dated 10-6-04 and are presented in table below:

Summary of silicone biocompatibility and genotoxicity studies

Study type	Species/strain/sex	Animals/dose group	Test material	Findings
Sample extract cytotoxicity study	(b) (4)	**N/A**	**5% serum concentration of minimum essential medium**	**No evidence of cytotoxicity**
Systemic toxicology study	**Mice**	**5**	**Uncharged silicone extract with 0.9% sodium chloride and cotton seed oil administered intraperitoneally**	**No systemic toxicity observed. Acceptable body weight changes. No mortality. All animals appeared clinically normal throughout the observation period.**
Muscle implantation study	**Rabbits**	**3**	**6 uncharged implants placed in right paravertebral muscle and 4 control strips implanted in opposite muscle and housed for 90 consecutive days**	**Silicone extracts nonirritant as assessed by microscopic exam. Findings similar to control**
Intracutaneous toxicity study	**Rabbits**	**2**	**0.2 ml of extract injected intracutaneously into 5 sites on right side of back; 5 sites injected as controls on left side**	**No evidence of significant irritation or toxicity**
Ames mutagenicity study	**5 salmonella typhimurium tester strains**	**N/A**	**Extract prepared in 0.9% sodium chloride**	**Considered non-mutagenic**

Progesterone specifications: The following information was provided:

Impurities: Related substances as determined by PLC

(b) (4) equal or less than (b) (4)%
Any unspecified impurity equal or less than (b) (4)%
Total impurities equal or less than (b) (4)%.

(b) (4)

Particle size of (b) (4) progesterone

(b) (4)

Potential related substances originating from the route of synthesis or from degradation:

(b) (4) limit equal or less than (b) (4) %

The following are covered by the limit for unspecified impurities

(b) (4)

Route of administration: Intravaginal

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 201-110 are owned by Teva Women' Health, Inc. or are data for which Teva Women's Health, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 201-110 that Teva Women's Health, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Teva Women's Health, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 201-110.

Studies reviewed within this submission: The following 2 toxicology studies have been reviewed under this submission:

1. **10- Day intravaginal irritation study of progesterone in female New Zealand White rabbits. CR-DDS Argus Division Protocol number: HFE00006**

2. **An intravaginal safety assessment study of a surgically implanted progesterone vaginal capsule formulation for 30, 60, 75 and 90 days in mature New Zealand White female rabbits. Testing facility study No. (b) (4) and Sponsor Ref. No. DR-201-001.**

Studies <u>not</u> reviewed within this submission: No other toxicology studies are submitted in this submission.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary: Progesterone is progestational hormone of the placenta and corpus luteum.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Progestational effects

Drug activity related to proposed indication: Exogenous supplementation of progesterone in the absence of endogenous progesterone to support embryo implantation and early pregnancy.

2.6.2.3 Secondary pharmacodynamics: None given

2.6.2.4 Safety pharmacology: None conducted

2.6.2.5 Pharmacodynamic drug interactions: None submitted

2.6.3 PHARMACOLOGY TABULATED SUMMARY

None provided
[pivotal studies pertinent to the primary indication and core pharmacology studies relevant to the primary pharmacodynamic effect, as available and as provided by the sponsor]

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

TK data is provided and reviewed for the 90-day intravaginal toxicity study

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

None submitted
[pivotal studies pertinent to the primary indication and core pharmacology studies relevant to the primary pharmacodynamic effect, as available and as provided by the sponsor]

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: 10-day vaginal irritation and 90-day intravaginal toxicology studies are submitted and reviewed. The findings of these studies demonstrate that the preparation is well tolerated and did not cause significant drug-related toxicity.

Genetic toxicology: None submitted.
No genotoxic concerns because progesterone is an endogenous hormone.

Carcinogenicity: No carcinogenic concerns progesterone being an endogenous hormone. Silicone elastomer was negative in the Ames genotoxicity assay.

Reproductive toxicology: None submitted.

Special toxicology: None submitted

2.6.6.2 Single-dose toxicity

Study title: **10-Day intravaginal irritation study of progesterone in female New Zealand White rabbits**

Purpose of the study: The purpose of this study in female NZW rabbits was to determine the acute local and distant tolerability of vaginally administered progesterone formula prepared as a silicone matrix capsule insert.

Key study findings: Under the experimental conditions used, implantation of vaginal inserts containing (b) (4)% progesterone had no adverse effects in rabbits over 10 days observation period except hyperplasia of the endometrium in 4 of 5 rabbits and hyperplasia of cervix in one rabbit in this group. Also one of two rabbits examined in this group had hyperplasia of the inguinal lymph nodes.

Study no.: HFE00006
Volume #, and page #: e-Submission
Conducting laboratory and location: (b) (4)
Date of study initiation: 6-8-04
GLP compliance: Yes
QA report: yes (*) no ( )
Drug, lot #, and % purity: PC-017. Purity considered 100%
Methods

Doses: As shown in table 1 below:

Table 1

Dose group	Treatment	Concentration of progesterone (%)	Daily dose (mg/day)[a]	Number of rabbits
1	**Surgical sham control**	**NA**	**NA**	**5**
2	**Positive control (2% Nonxynol-9)[b]**	**0**	**20**	**5**
3	**Vaginal capsule matrix negative control**	**0**	**0**	**5**
4	**Vaginal capsule matrix formulation with progesterone**	(b) (4)	**5.3 +/- 0.05[c]**	**5**

The test, negative and positive control articles were considered 100% active/pure for the purpose of dose calculations.

a. The insertswere designed for release of progesterone at an approximate rate of 5.3 mg/day (determined by in vitro analytical methods)
b. Rabbits were administered 1.0 mL per day of a 20 mg/mL dose intravaginally for 10 consecutive days.

c. Rabbit dosage was approximately 1x the human dosage of 40 mg/day (on mg/m^2 basis)

Species/strain: New Zealand White rabbits/Hra☹NZW)SPF
Number/sex/group or time point (main study): 5/f/g
Route, formulation, volume, and infusion rate: Intravaginal, capsule insert, single application
Satellite groups used for toxicokinetics or recovery: None
Age: 5 months
Weight: 3.0 – 3.4 kg for group 2 and 3.3 – 3.7 kg for groups 1, 3 and 4.
Sampling times: At necropsy on DS 11
Unique study design or methodology (if any): These involved priming of the vagina and insertion of the article insert:

Priming of the vagina: External vaginal tissue of all rabbits was digitally primed from DSs -6 to 0 when vaginal suppositories were inserted in groups 1, 3 and 4 on DS 1. The clitoris of each rabbit in these groups was stimulated 4 – 5 times daily to produce engorgement and darkening of the vulva. The rabbits were primed to ensure that the vaginal canal size was adequate to accommodate the vaginal capsules.

Insertion of test article: The test and negative control article inserts were administered by surgical implantation in to the vagina under anesthesia. The surgical procedure involved the following:

A midline laparotomy incision was made, and the urinary bladder was separated from the anterior vaginal surface. The uterus was isolated and wet laparotomy sponges were placed underneath. After vagina was visualized, the capsule was lightly lubricated with K-Y brand lubricating gelly and then inserted through the exterior vaginal opening and advanced to the upper vaginal cavity. The capsule insert was anchored with 5-0 non-absorbable suture to the vaginal wall using a suture made approximately 1/8 inch deep from the outer capsule surface and knotted to the outer dorsal vaginal wall. The laparotomy incision was closed by suturing the multiple layers.

The test and negative control article inserts were weighed prior to surgical placement and then again on the day of necropsy examination i.e., DS 11.

Rationale for dose selection: The insert was formulated to release approximately 5.3 mg/day of progesterone. Based on rabbit's anatomy, the study was limited by the size of the capsule, and therefore, could not exceed the proposed doses. The dose administered to the rabbit was approximately 1x the anticipated human vaginal dose of approximately 40 mg/day (based on body surface area). The dose of the positive control article was stated as the standard dose in a standard 10 day vaginal irritation study.

Observations and times:

Mortality: Viability checked twice daily

Clinical signs: Clinical signed recorded daily. At each interval, the vulva and the surrounding tissues were evaluated for erythema, edema, discharge or other evidence of irritation. No internal vaginal examination was performed.
Body weights: Body weights were recorded on the day of arrival and then daily starting one week prior to the first day of dosing and continuing until sacrifice.
Food consumption: was recorded daily during the dosing period.
Ophthalmoscopy: none conducted
EKG: none conducted
Hematology: No hematology was performed.
Clinical chemistry: clinical chemistry was not performed
Urinalysis: Urine was not analyzed
Gross pathology: All surviving rabbits were sacrificed on DS 11, and a complete necropsy was performed. The necropsy included examination of the external surfaces and all orifices; external surfaces of the brain and spinal cord; the organs and tissues of the cranial, thoracic, abdominal and pelvic cavities and neck; and the reminder of the carcass. The vagina was removed in toto from the pubic symphysis (including the vulva) to the cervix and examined for signs of irritation and inflammation.
Organ weights (specify organs weighed if not in histopath table): The adrenal glands, brain, heart, kidneys, liver, ovaries and pituitary were weighed prior to fixation. The vaginal tissue as well as the ovaries, oviducts, uterus with cervix, paired inguinal lymph nodes were also retained in buffered formalin for histological examination.

Histopathology: Adequate Battery: yes (*), no ( )—explain
33 tissues were retained in buffered formalin for future histological examination.
Peer review: yes ( ), no (*)

Comment: Blood and endometrial tissue progesterone concentrations were not conducted, which are important to correlate blood and tissue concentrations with any adverse effects of treatment. This information will be requested from the sponsor.

Results

Mortality: One doe with a vaginal capsule matrix with progesterone was sacrificed on study day 3 in moribund condition.

Clinical signs: Except for the one doe that was moribund and sacrificed, all does appeared normal. For vaginal irritation scoring, taking number of observations/number of rabbits examined, erythema and edema is shown in table 2 below:

Table 2

Vaginal irritation scoring	Group 1 surgical sham control	Group 2 positive control 2% nonoxynol-9	Group 3 vaginal capsule matrix negative control	Group 4 vaginal capsule matrix formulation with progewterone
Vaginal observations:				
Appeared normal	55/5	51/5	24/5	39/5
Erythema grade 1	0/0	4/2	31/5**	6/3**
Edema grade 1	0/0	0/0	6/2	4/1
Yellow or clear discharge	0/0	0/0	1/1	1/1[a]

** Significantly different from the control group value ($p \leq 0.01$

[a] Rabbit 5998 was moribund sacrificed on day 3 of study.

Data in the table suggests that the erythema is due to presence of capsule and not due to progesterone. Vaginal irritation grading system is based on changes in epithelium, vascular congestion, leukocyte infiltration and edema, each graded at a scale of 0 – 4.

Vaginal evaluation criteria used was as shown in table 3 below:

Table 3

Composite score	**Vaginal irritation rating**	**Conclusion**
1 – 4	Minimal irritation	Acceptable
5 – 8	Mild irritation	Acceptable
9 – 11	Moderate irritation	Acceptable
12 – 16	Marked irritation	Acceptable

The composite score on microscopic examination of the vaginal sections were 0, 2.1, 0.2 and 0.53 for groups 1, 2, 3 and 4, respectively and thus all were classified as acceptable.

Body weights: There was no significant treatment effect on body weight or body weight gain. The terminal body weights of the positive control group, negative control group and the progesterone capsule group were 94.4%, 99.4% and 100% of the sham control group, respectively.

Food consumption: Absolute and relative feed consumption was similar in the 4 dosage groups. The absolute feed consumption for the study period were 104.3%, 97.2% and 93.8% of the sham control group value for the positive capsule control, negative capsule control group and the progesterone capsule group, respectively.

Gross pathology: The rabbit that was sacrificed in moribund condition on study day 3, exhibited signs of difficult breathing, decreased motor activity and a grade 1 clear vaginal

discharge. At necropsy all lobes of the lungs were mottled red, black and pink. The mucosal surface of the trachea was red and black and the lumen contained a white frothy material. Microscopically, the lungs showed multiple areas of necrosis and consolidation with suppurative inflammation and abscess. Based on these observations, it was considered as purulent bronchopneumonia of bacterial origin. There were no microscopic changes in the sections of the vagina that could be correlated with the gross observations.

Organ weights (specify organs weighed if not in histopath table): There was no significant treatment-related effect on the ratios of organ weight to terminal body weight for pituitary, brain, liver, kidneys paired, adrenals paired, ovaries paired, heart for the 4 treatment groups and for the vaginal capsule matrix negative control and vaginal capsule matrix formulation with progesterone.
Histopathology: There were no microscopic changes reported in tissues examined from the rabbits exposed to (b)(4)% concentration of progesterone via surgically implanted capsule that were considered to be related to exposure to the test article or the vehicle (implanted capsules without progesterone)
Microscopic changes observed in the vaginal mucosa of the rabbits in the positive control group, based on Vaginal Irritation Rating scale suggested minimal irritation and considered within acceptable limits.

It was concluded that all microscopic changes observed in sections of the vagina were related to the surgical implantation procedure and/or the physical presence of intravaginal implant. Moreover, no microscopic changes were reported in other organs or tissues to indicate any systemic effect of progesterone except on uterus where 4 of 5 rabbits had hyperplasia of the endometrium, and one had hyperplasia of cervical mucosa. One of the 2 rabbits examined in group 4, one had lymphoid hyperplasia. **(**of the inguinal lymph node)

Toxicokinetics: none conducted.

Other: none

2.6.6.3 Repeat-dose toxicity

Study title: An intravaginal safety assessment study of a surgically implanted progesterone vaginal capsule formulation for 30, 60, 75 and 90 days in the mature New Zealand White rabbits.

Key study findings: There was no progesterone-related effect on vaginal irritation scores. Platelet count was significantly increased at Day 30 determination only and serum triglycerides and urine volume at all sampling times in the progesterone treated group. The mean vagina and uterus absolute and relative to body/brain weights were reduced in progesterone capsule group at all study endpoints. Histological examination showed progesterone effects on vagina, uterus and inguinal lymph nodes. The uterus findings of decidual reaction and endometrium/myometrium atrophy and vaginal findings of epithelial atrophy were observed at all endpoints. Inguinal lymph node hyperplasia was

reported in one animal on day 75 endpoint. Urine volume was significantly higher in progesterone-treated animals at all determinations. Surgical implantation of progesterone vaginal capsule resulted in significant systemic exposure, which did not increase with duration of treatment. Endometrial progesterone concentrations were not determined.

Study no.: Testing facility study No. (b) (4); Sponsor reference No. DR-201-001
Volume #, and page #: e-Submission
Conducting laboratory and location: (b) (4)
Date of study initiation: 3-16-09
GLP compliance: Yes
QA report: yes (*) no ( )
Drug, lot #, and % purity: A9P13128A, purity not given **(check purity)**

Methods

Doses: as shown in study design in table 1 below:

Table 1

Group #	Identification	Number of animals[c]			
		Day 30 necropsy	Day 60 necropsy	Day 75 necropsy	Day 90 necropsy
1	Positice control (2% Nonoxynol-9 cream)[a]	4	4	4	4
2	Surgical sham control	4	4	4	4
3	Placebo control capsule	4	4	4	4
4	Progesterone ((b) (4)% w/w) capsule[b]	4	4	4	4

[a] Animals were administered 1 mL of 2% Nonoxynol-9 cream intravaginally (20 mg/day) daily for the first 10 consecutive days and then once weekly (beginning on Day 15) until scheduled necropsy.

[b] Anticipated average daily dose of PNG (based on in vitro release data) of approximately 2.9 mg/day

[c] Animals scheduled for necropsy on Days 30, 60, 75 or 90 were designed in the study records and report as Replicate 1, 2, 3 or 4, respectively.

Progesterone capsule description: (b) (4)% w/w progesterone, (b) (4)% silicone (b) (4), (b) (4)% light mineral oil matrix in the form of a 30 mm (long) x 8.5 mm (wide) capsule with (b) (4) mg of progesterone, (b) (4) mg light mineral oil, (b) (4) Silicone Elastomer, (b) (4)

Species/strain: Rabbit/NZW (Oryctologus cuniculus)
Number/sex/group or time point (main study): 4/f/g as shown in the table above
Route, formulation, volume, and infusion rate: intravaginal, capsule insert, once to last up to 90 days.
Satellite groups used for toxicokinetics or recovery: None. Blood was collected at various time points for determination of PGN plasma concentrations for TK analysis.

Age: 5 months
Weight: 2.8 – 3.5 kg
Sampling times: Experimental Days 30, 60, 75 and 90
Unique study design or methodology (if any): Method of implanting capsule inserts as described in the 10 day intravaginal toxicity under protocol HFE00006 reviewed above under this submission.

Observations and times:

Mortality: checked for mortality and for signs of ill health and/or reaction to treatment twice daily throughout the study.
Clinical signs: All animals observed for general condition on the day of surgery and daily throughout the in-life period. Cage-side observations were performed at the same time each day.
Body weights: Body weights were measured for all animals on day of randomization, prior to surgery and weekly throughout the treatment period and weighed (fasted) before scheduled necropsy.
Food consumption: recorded daily during the last week of pre-treatment period and throughout the treatment period.
Ophthalmoscopy: -
EKG: -
Hematology: Blood samples for hematology were collected once during the pre-treatment period and on all surviving animals (all replicates) prior to necropsy on Days 30, 60, 75 and 90. Blood samples were collected from the auricular artery/vein. Samples were analyzed for blood cell morphology, erythrocyte indices, hematocrit, hemoglobin mean platelet volume, platelet count, RBC count, reticulocyte count and WBC total count and % differential.
Clinical chemistry: Same time points as for hematology. Food was removed overnight prior to blood sampling. Samples were analyzed for A/G ratio, albumin, globulin, glucose, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, BUN, Ca, Cl, P, Na, cholesterol, creatinine, TG and bilirubin.
Urinalysis: Urine was collected on same occasions as for hematology and clinical chemistry for routine analysis.
Vaginal irritation scoring: Scoring of vaginal irritation was conducted once pretreatment, weekly throughout the treatment period and prior to necropsy. Vaginal irritation was qualitatively assessed using the Draize scoring system. At each interval, the vulva and the surrounding tissue were evaluated for erythema, edema and discharge. The erythema and edema scores ranged from 0 to 4 with a maximum possible score of 8. The cumulative irritation index was used to evaluate Draize scoring results. The severity was characterized using the following scale:

Response category	Mean score
Negligible	0 to 0.4
Slight	0.5 to 1.9
Moderate	2.0 to 4.9
Severe	5.0 to 8.0

Gross pathology: All animals were euthanized (as scheduled on Day 30, 60, 75 or 90 or unscheduled for humane reasons or if the animal was suspected of having expelled its capsule). Animals were fasted overnight before necropsy. The vaginal capsules were weighed before implantation and then again when found and retrieved.

Organ weights (specify organs weighed if not in histopath table): The following organs were dissected free of fat and weighed: adrenal glands, brain, heart, kidneys, liver, lungs, ovaries, pituitary gland, spleen, thymus, thyroid and parathyroid glands, uterus with cervix and vagina.

Histopathology: Adequate Battery: yes (*), no ( )—explain
Peer review: yes ( ), no ( )
Of all the tissues collected for microscopic examination were imbedded in paraffin but the following were processed and stained for microscopic examination:

Ovaries, uterus (body and cervix), vagina, liver, inguinal lymph nodes and abnormalities and gross lesions.

Toxicokinetics: Blood samples for progesterone determination were collected (approximately 1 mL) into test tubes containing K_2EDTA via an auricular artery. Blood was collected on day 1, pre-dose and then 1, 2, 4, 6, 8, 12, and 24 hours and then on Days 2, 3, 5, 8, 15, 22, 29 for a total collection of 8 blood samples. Day 30 scheduled necropsy was conducted at this time.
Bleeding was then conducted on Days 36, 43, 50 and 57 when Day 60 necropsy was conducted with total blood samples being 10. Further blood samples were collected on Day 64 and then Day 71 and animals scheduled for Day 75 were necropsied with total of 12 blood samples. Blood was then collected on Day 78 and then Day 90 when animals scheduled for Day 90 were necropsied with a total of 14 blood samples for TK.
At same time points blood samples were collected from the placebo control vaginal capsule animals.

Results

Mortality: No treatment-related deaths were reported during the course of the study. Two rabbits with placebo control capsules and one with progesterone capsule were preterminally euthanized on Days 24, 34 and 52 due to capsule expulsion. One rabbit in the placebo control capsule group was euthanized due to humane reasons on Day 9.

Clinical signs: There were no progesterone-related effects on vaginal irritation scores. Signs of irritation were reported amonst all groups including all 3 control groups. The mean irritation scores across groups were generally classified as slight to moderate and increased with time of treatment. Following week 5, animals in the placebo group had the highest mean irritation score.

Body weights: As shown in table 2 below, treatment had no significant effect on absolute body weight (kg) or body weight gains (kg) during the 12 week study.

Table 2

Treatment group/study week	Positive control (2% N-9 cream)	surgical sham control	Placebo control capsule	Progesterone ((b)(4) % w/w) capsule
Week 1	3.18	2.94	2.97	2.98
Week 12	3.75	3.83	4.00	3.73
Body wt gain +/- SD	0.05 +/- 0.058	0.10 +/- 0.000	0.5 +/- 0.058	0.03 +/-- 0.05

Food consumption: Feed consumption was not affected by treatment. The average feed consumption (g/animal/day) ranged from 110 to 120 amongst all treatment groups.

Ophthalmoscopy: Not conducted

EKG: None conducted

Hematology: As shown in table 3 below, only platelet count (+/- SD) was significantly increased at Day 30 determination and thereafter values in all groups appear similar.

Table 3

Treatment group/study Day	Positive control (2% N-9 cream)	surgical sham control	Placebo control capsule	Progesterone ((b)(4) % w/w) capsule
Day 30	414 +/- 91	418 +/- 95	422 +/- 109	5165 +/- 124
Day 60	410 +/- 154	426 +/- 101	413 +/- 97	505 +/- 100
Day 75	426 +/- 90	474 +/- 107	469 +/- 200	567+/- 112
Day 90	380 +/- 42	422 +/- 90	424 +/- 80	477 +/- 86

It was stated that other differences in hematology parameters, including those that reached statistical significance, were not considered related to the administration of progesterone due to their small magnitude, direction of change, comparability to sham, placebo control and/or baseline values and/or within biological variation.

Coagulation: There were no progesterone or nonoxynol-9-related effects on blood coagulation parameters.

Clinical chemistry: The only treatment-related change in serum chemistry involved increase in triglyceride values for the progesterone treated group at all sampling times. The TG values (mg/dL) for the 4 treatment groups are shown in table 4 below:

Table 4

Treatment group/study Day	Positive control (2% N-9 cream)	surgical sham control	Placebo control capsule	Progesterone (b) (4) % w/w) capsule
Pre-treatment	**38**	**36**	**36**	**32**
Day 30	**31**	**26**	**29**	**48**
Day 60	**30**	**28**	**26**	**45**
Day 75	**30**	**30**	**24**	**42**
Day 90	**25**	**23**	**23**	**38**

Urinalysis: As shown in table 5 below, mean urine volume (mL) was increased for animals with progesterone capsules on all sampling times compared to placebo controls and sham controls. Data is expressed as mean +/- SD.

Table 5

Treatment group/study Day	Positive control (2% N-9 cream)	surgical sham control	Placebo control capsule	Progesterone ((b) (4) % w/w) capsule
Pre-treatment	**62 +/61**	**56 +/- 52**	**72 +/- 54**	**72 +/- 45**
Day 30	**100 +/- 92**	**72 +/- 74**	**98 +/- 68**	**158 +/- 122**
Day 60	**92 +/- 47**	**70 +/- 55**	**65 +/- 27**	**150 +/- 122**
Day 75	**131 +/- 88**	**93 +/- 42**	**100 +/- 77**	**174 +/- 96**
Day 90	**90 +/- 71**	**46 +/- 37**	**151 +/- 165**	**176 +/- 107**

The urine specific gravity was not changed with treatment. It is not explained if increased urine volume was due to any hormonal changes. Water intake was not recorded and it likely could affect urine volume changes.

Gross pathology: There was no progesterone or N-9-related macroscopic changes reported. The occurrence of dark area was observed in the vagina and/or urinary bladder of a few rabbits and it correlated with microscopically with hemorrhage or inflammation and was attributed to experimental procedure. All other macroscopic findings were considered to be agonal, incidental or related to surgical procedure.

Organ weights (specify organs weighed if not in histopath table):

Progesterone capsule-related organ weight changes were noted in the vagina and uterus at all study endpoints. Table 6 below shows mean vagina and uterus absolute and relative to body/brain weights were reduced in the progesterone capsule group:

Table 6

Treatment group/study Day	Positive control (2% N-9 cream)	surgical sham control	Placebo control capsule	Progesterone ((b)(4)% w/w) capsule
Absolute organ weights (g)				
Day 30				
Uterus	**8.21 +/- 1.394**	**6.46 +/- 2.090**	**7.85 +/-2.119**	**5.38 +/-1.604**
Vagina	**7.27 +/- 1.433**	**7.29 +/- 1.317**	**7.74 +/- 1.043**	**4.04 +/- 0.457**
Day 60				
Uterus	**8.17 +/-1.496**	**7.80 +/-2.615**	**8.34**	**6.23+/-1.933**
Vagina	**8.77 +/- 3.560**	**9.58 +/- 3.370**	**8.30**	**7.23 +/- 3.002**
Day 75				
Uterus	**9.01 +/-2.737**	**7.34 +/- 1.608**	**8.96 +/-1.657**	**5.22 +/- 1.398**
Vagina	**9.20 +/-2.002**	**7.41 +/- 1.746**	**10.37 +/- 4.108**	**5.37 +/- 1.830**
Day 90				
Uterus	**8.72 +/- 3.320**	**10.87 +/-2.078**	**11.66 +/-1.151**	**4.88 +/- 0.504**
Vagina	**7.03 +/- 0.761**	**8.17 +/-1.189**	**12.43 +/- 2.125**	**4.74 +/- 1.302**
Organ weights relative to body weight (%)				
Day 30				
Uterus	**0.241 +/-0.0480**	**0.198 +/- 0.0596**	**0.240 +/- 0.0488**	**0.1`75 +/- 0.0505**
Vagina	**0.212 +/- 0.0438**	**0.223 +/- 0.0352**	**0.238 +/- 0.0314**	**0.131 +/- 0.0169**
Day 60				
Uterus	**0.228 +/- 0.0391**	**0.220 +/- 0.0771**	**0.232**	**0.1765 +/- 0.0458**
Vagina	**0.246 +/- 0.0962**	**0.267 +/- 0.0819**	**0.232**	**0.204 +/- 0.0739**
Day 75				
Uterus	**0.242 +/- 0.0754**	**0.201 +/- 0.0432**	**0.248 +/- 0.0519**	**0.142 +/- 0.0350**
Vagina	**0.247 +/- 0.0561**	**0.202 +/- 0.0453**	**0.287 +/- 0.1205**	**0.145 +/- 0.0424**
Day 90				
Uterus	**0.236 +/- 0.0836**	**0.291 +/- 0.0591**	**0.295 +/- 0.0263**	**0.130 +/- 0.0143**
Vagina	**0.193 +/- 0.0334**	**0.219 +/- 0.0422**	**0.315 +/- 0.0562**	**0.126 +/- 0.0331**
Organ weights relative to brain weight (%)				
Day 30				
Uterus	**84.64 +/- 17.07**	**71.45 +/- 26.96**	**81.05 +/- 19.96**	**59.59 +/- 18.96**
Vagina	**74.46 +/- 13.95**	**80.35 +/- 18.44**	**80.37 +/- 13.42**	**44.54 +/- 5.22**
Day 60				
Uterus	**90.77 +/- 16.51**	**84.34 +/- 33.48**	**95.53**	**66.30 +/- 23.89**
Vagina	**95.62 +/- 32.96**	**101.03 +/- 31.91**	**95.08**	**77.19 +/- 36.00**
Day 75				
Uterus	**86.09 +/- 22.00**	**79.00 +/- 15.37**	**95. 30 +/- 20.23**	**54.72 +/- 14.96**
Vagina	**88.20 +/- 15.39**	**79.80 +/- 17.94**	**109.38 +/- 41.97**	**56.14 +/- 18.07**
Day 90				
Uterus	**89.76 +/- 27.58**	**110.89 +/- 25.74**	**115.22 +/- 5.86**	**52.22 +/- 7.71**
Vagina	**73.54 +/- 9.07**	**83.15 +/- 15.03**	**124.01 +/- 27.87**	**50.82 +/- 15.63**

Histopathology: Adequate Battery: yes (*), no ( )—explain: Microscopic examination was performed on ovaries, uterus, vagina, liver, inguinal lymph nodes and abnormalities or gross lesions. Microscopic examination was performed on these tissues from all animals, including those euthanized prior to scheduled necropsy. It was stated that the remaining tissues were prepared by embedding in paraffin wax for potential microscopic examination if warranted by the Pathologist and/or Study Director.

Incidence of animals with microscopic findings by organ/group is shown in table 7 below:

Table 7

Treatment group/study week	Positive control (2% N-9 cream)	surgical sham control	Placebo control capsule	Progesterone ((b) (4) % w/w) capsule
Day 30				
Uterus				
Decidyual reaction	-	-	-	3
Atrophy:				
endometrium/myometriaum	-	-	-	4
Vagina				
Infiltration: heterophil	3	-	1	1
Atrophy:epithelial	-	-	1	4
Degeneration: epithelial	2	-	-	-
Vacuolation:epithelial	1	-	-	-
Hemorrhage	1	-	-	-
Day 60				
Lymph node-inguinal				
Hyperplasia: lymphoid	-	-	-	2
Uterus				
Decidual reaction				
Atrophy: endometrum/myometrium	-	-	-	2
	-	-	-	3
Vagina				
Infiltration:heterophil				
Atrophy: epithelial	1	-	-	-
	-	-	-	3
Day 75				
Lymph node inguinal				
Hyperplasia: lymphoid	-	-	-	1
Uterus				
Decidual reaction				
Atrophy:	-	-	-	4
endometrium/myometrium	-	-	-	4
Vagina				
Infiltration: heterophil	1	-	1	-
Atrophy:endometrium/myometrium	-	-	-	4
Hemorrhage	1	-	-	-
Day 90				
Uterus				
Decidual reaction				

Atrophy:endometrium/mypmetrium	**-**	**-**	**-**	**3**
	-	**-**	**-**	**4**
Vagina				
Infiltration: heterophil	**-**	**-**	**-**	**-**
Atrophy: epithelial	**-**	**-**	**-**	**4**
Vacuolation: epithelial	**4**	**-**	**-**	**-**
Hemorrhage	**-**	**-**	**1**	**-**

There were 4 animals in each group. One animal in group 4 necropsied on Day 90 had liver granuloma.
Results thus showed that the progesterone effects were observed in uterus, vagina and lymph node. The uterus findings involved decidual reaction and atrophy of endometrium and myometrium. The vaginal changes included epithelial atrophy. A few animals had lymphoid hyperplasia of the inguinal lymph nodes.

Peer review: yes ( ), no (*)

Toxicokinetics:

TK parameters of progesterone in female NZW rabbit plasma following surgical implantation of progesterone ((b) (4) % w/w) vaginal capsule for group 4 at four necropsy time interval is shown in table 8 below. Values are mean +/- SD for 4 animals:

Table 8

Animal subgroup	**T_{max} (h)**	**T_{last} (h)**	**C_{max} (ng/mL)**	**$AUC_{(0\text{-}672\ h)}$ (ng.h/mL)**
4501 – 4504	**16.0**	**672 (Day 29)**	**42.5 +/- 24.7**	**9118 +/- 2046**
4505 – 4508	**9.00**	**1260 (Day 57)**	**34.4 +/- 7.84 1**	**11976, 13077[a]**
4509 – 4512	**8.00**	**1680 (Day 71)**	**28.0 +/- 2.03**	**11573 +/- 1923**
4513 – 4516	**4.00**	**2136 (Day 90)**	**37.5 +/- 358**	**13716 +/- 1506**
Overall	**8.00**	**1512**	**35.6+/- 12.9**	

[a]Values for 2 animals were not reported because the $AUC_{(0\text{-}inf)}$ was extrapolated by more than 20% or R^2 was <0.8.
Anticipated average daily dose of progesterone (based on in vitro release data) was approximately 2.9 mg/day.
T_{max} and T_{last} are reported as median values

Percentage of progesterone exposure achieved in Days 29, 57, 71 vs Day 90 in female NZW rabbit plasma following a surgical implantation of progesterone ((b) (4) % w/w) vaginal capsule is given in table 9 below:

Table 9

Animal subgroup	Time of last sampling	Mean $AUC_{(0\text{-}t}^{*}$	Ratio ($AUC_{(0\text{-}t}^{*}/AUC_{(0\text{-}2136\ h)}$
4501 – 4504	**672 (Day 29)**	**9118**	**66.5**
4505 – 4508	**1344 (Day 57)**	**12526**	**91.3**
4509 – 4512	**1680 (Day 71)**	**11573**	**84.4**
4513 – 4516	**2136 (Day 90)**	**13716**	**100**

* Time of last sampling

Results thus showed that all animals in the progesterone capsule groups exhibited measurable increase in plasma progesterone concentration.

Concentrations of progesterone in female NZW rabbit plasma following surgical implantation of placebo control vaginal ring:

Endogenous progesterone concentrations ranged between below LLOQ (lower limit of quantification= 0.500 ng/mL) to 6.73 +/- 6.17 ng/mL at one sampling time. The endogenous progesterone concentrations exhibited high intra-day and inter-day fluctuations. Also animals implanted with progesterone capsules (group 4) had pre-dose concentrations comparable to endogenous progesterone levels measured in control group, with all values below LLOQ with the exception of 4 animals that had endogenous levels between 2.64 and 8.82 ng/mL.

Other:

Comparison of the 10 day and 90 day vaginal toxicity studies: Significant treatment-related differences involved hyperplasia of the endometrium/myometrium in 4/5 rabbits, hyperplasia of the cervix in one and that of inguinal lymph nodes in two rabbits in the 10 day study. In the 90-day toxicity study progesterone-related effects included decidual reaction in the uterus and atrophy of the endometrium/myometrium. There was atrophy of the vaginal epithelium. These findings were observed at all study endpoints. Lymphoid hyperplasia was reported in 2 rabbits on Day 60 and 1 on Day 75 determinations.

Comparison of the toxicokinetics for humans and rabbits: In a clinical study entitled "A bioavailability study to evaluate the single and steady state pharmacokinetics of a progesterone loaded vaginal ring (DR-2011) formulation in post menopausal females", sponsor reported mean +/- SD Cmax (0-168 h) of 9.33 +/- 2.80 ng/mL, Tmax of 134.80 +/- 49.17 hr and AUC of 1188.41 +/- 374.24 ng.hr/mL for first 7-day vaginal ring insertion (n=30). Similar values were observed during the second 7-day vaginal ring insertion (168 – 336 h).

In the present rabbit repeat-dose toxicity study on Day 29, mean +/-SD for Cmax was 42.5 +/- 24.7 ng/mL, Tmax 16.0 hr and AUC 9118 +/- 2046 ng.hr/mL. Values for Days 57, 71 and 90 were similar to those reported for Day 29 (n=4).

The dose in human is 14 mg i.e. about 0.28 mg/kg or 10 mg/m^2 and that of rabbit was 2.9 mg i.e. about 1 mg/kg or 12 $mg/m^{2.}$ Thus the progesterone dose as mg/m^2 used in the

rabbit study with (b)(4)% w/w progesterone was similar to that used in the human PK study. Steady state plasma concentrations of progesterone were reached during the first vaginal ring insertion in both humans and rabbits. However, the plasma progesterone concentrations were much higher in the rabbits than those reported for humans.

P/T comments: The significant different drug effects observed in the 10 Day and 90 Day studies, i.e., hyperplastic uterine and vaginal changes in the 10 Day study and atrophic changes in the 90 Day study. These could be possibly due to different progesterone concentrations used for the progesterone formulations i.e., (b)(4)% w/w in the 10-Day experiment and (b)(4)% w/w in the 90-Day study or these differences could be due to duration of treatment. Clinical significance if any of these observations is not explained.

Histopathology inventory (optional)

Study				
Species				
Adrenals				
Aorta				
Bone Marrow smear				
Bone (femur)				
Brain				
Cecum				
Cervix				
Colon				
Duodenum				
Epididymis				
Esophagus				
Eye				
Fallopian tube				
Gall bladder				
Gross lesions				
Harderian gland				
Heart				
Ileum				
Injection site				
Jejunum				
Kidneys				
Lachrymal gland				
Larynx				
Liver				
Lungs				
Lymph nodes, cervical				
Lymph nodes mandibular				
Lymph nodes, mesenteric				
Mammary Gland				
Nasal cavity				

Optic nerves				
Ovaries				
Pancreas				
Parathyroid				
Peripheral nerve				
Pharynx				
Pituitary				
Prostate				
Rectum				
Salivary gland				
Sciatic nerve				
Seminal vesicles				
Skeletal muscle				
Skin				
Spinal cord				
Spleen				
Sternum				
Stomach				
Testes				
Thymus				
Thyroid				
Tongue				
Trachea				
Urinary bladder				
Uterus				
Vagina				
Zymbal gland				

X, histopathology performed
*, organ weight obtained

2.6.6.4 Genetic toxicology: None submitted. See statement from Prometrium label below.

2.6.6.5 Carcinogenicity: None submitted. However citing literature the Prometrium label under the title "Carcinogenesis, mutagenesis, impairment of fertility" contains the following statement;

Progesterone has not been tested for carcinogenicity by the oral route of administration. When implanted into female mice, progesterone produced mammary carcinomas, ovarian granulosa cell tumors and endometrial stromal sarcoma. In dogs, long term intramuscular injections produced nodular hyperplasia and benign and malignant mammary tumors. Subcutaneous or intramuscular injections of progesterone decreased the latency and increased the incidence of mammary tumors in rats previously treated with a chemical carcinogen.

Progesterone did not show evidence of genotoxicity in in vitro studies for point mutations or for chromosomal damage. In vivo studies for chromosomal damage have yielded

positive results. Exogenously administered progesterone has been shown to inhibit ovulation in a number of species and it is expected that high doses given for extended duration would impair fertility until the cessation of treatment.

2.6.6.6 Reproductive and developmental toxicology: None submitted. See statement from Prometrium label above.

2.6.6.7 Local tolerance: Vaginal irritation evaluated in both the 10 day and 90 day studies.

2.6.6.8 Special toxicology studies: None submitted

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: 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.

Unresolved toxicology issues (if any): None

Recommendations: Pharmacology recommends approval of NDA 201,110 from the P/T perspective for progesterone vaginal ring (DR-2011) for the proposed indication "to support embryo implantation and early pregnancy by supplementation".

Suggested labeling: Labeling is in accordance with PLR and presented in SLR format and is acceptable to P/T.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

Appendix/attachments: None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201110	ORIG-1	TEVA WOMENS HEALTH INC	PROGESTERONE (VAGINAL RING)

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

/s/

KRISHAN L RAHEJA
07/16/2010

ALEXANDER W JORDAN
07/16/2010

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

/s/

LESLIE C MCKINNEY
06/10/2016

MUKESH SUMMAN
06/10/2016
Pharm Tox Supports AP

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	201-110
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	4/30/10
PRODUCT:	Progesterone vaginal ring (DR-2011), (b)(4)% w/w, 14 mg/day, 7day application. DR2011 is a progesterone –containing flexible silicone vaginal ring with a cylindrical-shaped hollow cavity that is filled with a progesterone silicone blend. (b)(4)™ as the proposed primary proprietary name.
INTENDED CLINICAL POPULATION:	To support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation
SPONSOR:	Teva Women's Health, Inc.
DOCUMENTS REVIEWED:	e-Submission
REVIEW DIVISION:	Division of Reproductive & Urologic Products (HFD 580)
PHARM/TOX REVIEWER:	Krishan L. Raheja, D.V.M., Ph.D.
PHARM/TOX SUPERVISOR:	Alex Jordan, Ph.D.
DIVISION DIRECTOR:	Scott E Monroe, M.D.
PROJECT MANAGER:	Celia, Peacock

Date of review submission to Division File System (DFS): 7-16-10

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Pharmacology/Toxicology recommends approval of NDA 201-110.

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

C. Recommendations on labeling: Labeling is in accord with PLR and presented in SLR format.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: 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.

B. Pharmacologic activity: Progestogenic effects

C. Nonclinical safety issues relevant to clinical use: None

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 201-110
Review number: 1
Sequence number/date/type of submission: 000/4-30-10/original submission
Information to sponsor: Yes ( ) No ( )
Sponsor and/or agent: Teva Women's Health, Inc. (b) (4)
Manufacturer for drug substance: (b) (4)

Reviewer name: Krishan L. Raheja, D.V.M., Ph.D.
Division name: Reproductive & Urologic Products
HFD #: 580
Review completion date: 7-15-10

Drug:

Trade name: none given. Sponsor has proposed proprietary name as (b) (4)
Generic name: Progesterone, UPS (b) (4)
Code name: DR-2011
Chemical name: pregn-4, ene-3-20-dione
CAS registry number: 57-83-0
Molecular formula/molecular weight: $C_{21}H_{30}O_2$/314.47
Structure:

Relevant INDs/NDAs/DMFs: IND 70,875; Organon DMF (b) (4)

Drug class: Progestin

Intended clinical population: To support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation.

Clinical formulation: Progesterone Vaginal Ring's formulation which was described under original IND 70,875 is as follows:

The ring's active ingredient is progesterone, USP (b) (4)

The ring's inactive ingredients are the following:

Silicone Elastomer, (b) (4)

(b) (4)

(b) (4)

Other inactive ingredient is Light mineral oil, NF

The progesterone vaginal ring releases (b) (4) mg progesterone/day.

Note: Silicone elastomers have been used under IND (b) (4)

(b) (4) conducted extensive toxicity studies on silicone elastomers, which consisted of the following:

- In vitro tissue cell culture
- Pyrogen test in rabbits
- Systemic injection in mice
- Intracutaneous test in rabbits
- Skin sensitization test in rabbits
- Hemolysis test
- 90-day implantation in rabbits
- 72 hour vaginal implantation in rabbits
- thrombogenicity test for silastic
- 2-year tissue implantation in Fisher 344 rats with (b) (4)

Thus the safety of (b) (4) silicone elastomer seems reasonably well established.

Studies conducted with silicone elastomers for biocompatibility and Ames mutagenicity assay were provided under original IND 70875 SS# 000 dated 10-6-04 and are presented in table below:

Summary of silicone biocompatibility and genotoxicity studies

Study type	Species/strain/sex	Animals/dose group	Test material	Findings
Sample extract cytotoxicity study	(b) (4)	**N/A**	**5% serum concentration of minimum essential medium**	**No evidence of cytotoxicity**
Systemic toxicology study	**Mice**	**5**	**Uncharged silicone extract with 0.9% sodium chloride and cotton seed oil administered intraperitoneally**	**No systemic toxicity observed. Acceptable body weight changes. No mortality. All animals appeared clinically normal throughout the observation period.**
Muscle implantation study	**Rabbits**	**3**	**6 uncharged implants placed in right paravertebral muscle and 4 control strips implanted in opposite muscle and housed for 90 consecutive days**	**Silicone extracts nonirritant as assessed by microscopic exam. Findings similar to control**
Intracutaneous toxicity study	**Rabbits**	**2**	**0.2 ml of extract injected intracutaneously into 5 sites on right side of back; 5 sites injected as controls on left side**	**No evidence of significant irritation or toxicity**
Ames mutagenicity study	**5 salmonella typhimurium tester strains**	**N/A**	**Extract prepared in 0.9% sodium chloride**	**Considered non-mutagenic**

Progesterone specifications: The following information was provided:

Impurities: Related substances as determined by PLC

(b) (4) equal or less than (b) (4)%
Any unspecified impurity equal or less than (b) (4)%
Total impurities equal or less than (b) (4)%.

(b) (4)

Particle size of (b) (4) progesterone

(b) (4)

Potential related substances originating from the route of synthesis or from degradation:

(b) (4) limit equal or less than (b) (4) %

The following are covered by the limit for unspecified impurities

(b) (4)

Route of administration: Intravaginal

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 201-110 are owned by Teva Women' Health, Inc. or are data for which Teva Women's Health, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 201-110 that Teva Women's Health, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Teva Women's Health, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 201-110.

Studies reviewed within this submission: The following 2 toxicology studies have been reviewed under this submission:

1. **10- Day intravaginal irritation study of progesterone in female New Zealand White rabbits. CR-DDS Argus Division Protocol number: HFE00006**

2. **An intravaginal safety assessment study of a surgically implanted progesterone vaginal capsule formulation for 30, 60, 75 and 90 days in mature New Zealand White female rabbits. Testing facility study No. (b) (4) and Sponsor Ref. No. DR-201-001.**

Studies <u>not</u> reviewed within this submission: No other toxicology studies are submitted in this submission.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary: Progesterone is progestational hormone of the placenta and corpus luteum.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Progestational effects

Drug activity related to proposed indication: Exogenous supplementation of progesterone in the absence of endogenous progesterone to support embryo implantation and early pregnancy.

2.6.2.3 Secondary pharmacodynamics: None given

2.6.2.4 Safety pharmacology: None conducted

2.6.2.5 Pharmacodynamic drug interactions: None submitted

2.6.3 PHARMACOLOGY TABULATED SUMMARY

None provided
[pivotal studies pertinent to the primary indication and core pharmacology studies relevant to the primary pharmacodynamic effect, as available and as provided by the sponsor]

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

TK data is provided and reviewed for the 90-day intravaginal toxicity study

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

None submitted
[pivotal studies pertinent to the primary indication and core pharmacology studies relevant to the primary pharmacodynamic effect, as available and as provided by the sponsor]

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: 10-day vaginal irritation and 90-day intravaginal toxicology studies are submitted and reviewed. The findings of these studies demonstrate that the preparation is well tolerated and did not cause significant drug-related toxicity.

Genetic toxicology: None submitted.
No genotoxic concerns because progesterone is an endogenous hormone.

Carcinogenicity: No carcinogenic concerns progesterone being an endogenous hormone. Silicone elastomer was negative in the Ames genotoxicity assay.

Reproductive toxicology: None submitted.

Special toxicology: None submitted

2.6.6.2 Single-dose toxicity

Study title: **10-Day intravaginal irritation study of progesterone in female New Zealand White rabbits**

Purpose of the study: The purpose of this study in female NZW rabbits was to determine the acute local and distant tolerability of vaginally administered progesterone formula prepared as a silicone matrix capsule insert.

Key study findings: Under the experimental conditions used, implantation of vaginal inserts containing (b) (4)% progesterone had no adverse effects in rabbits over 10 days observation period except hyperplasia of the endometrium in 4 of 5 rabbits and hyperplasia of cervix in one rabbit in this group. Also one of two rabbits examined in this group had hyperplasia of the inguinal lymph nodes.

Study no.: HFE00006
Volume #, and page #: e-Submission
Conducting laboratory and location: (b) (4)
Date of study initiation: 6-8-04
GLP compliance: Yes
QA report: yes (*) no ( )
Drug, lot #, and % purity: PC-017. Purity considered 100%
Methods

Doses: As shown in table 1 below:

Table 1

Dose group	Treatment	Concentration of progesterone (%)	Daily dose (mg/day)[a]	Number of rabbits
1	**Surgical sham control**	**NA**	**NA**	**5**
2	**Positive control (2% Nonxynol-9)[b]**	**0**	**20**	**5**
3	**Vaginal capsule matrix negative control**	**0**	**0**	**5**
4	**Vaginal capsule matrix formulation with progesterone**	(b) (4)	**5.3 +/- 0.05[c]**	**5**

The test, negative and positive control articles were considered 100% active/pure for the purpose of dose calculations.

a. The insertswere designed for release of progesterone at an approximate rate of 5.3 mg/day (determined by in vitro analytical methods)
b. Rabbits were administered 1.0 mL per day of a 20 mg/mL dose intravaginally for 10 consecutive days.

c. Rabbit dosage was approximately 1x the human dosage of 40 mg/day (on mg/m^2 basis)

Species/strain: New Zealand White rabbits/Hra☹NZW)SPF
Number/sex/group or time point (main study): 5/f/g
Route, formulation, volume, and infusion rate: Intravaginal, capsule insert, single application
Satellite groups used for toxicokinetics or recovery: None
Age: 5 months
Weight: 3.0 – 3.4 kg for group 2 and 3.3 – 3.7 kg for groups 1, 3 and 4.
Sampling times: At necropsy on DS 11
Unique study design or methodology (if any): These involved priming of the vagina and insertion of the article insert:

Priming of the vagina: External vaginal tissue of all rabbits was digitally primed from DSs -6 to 0 when vaginal suppositories were inserted in groups 1, 3 and 4 on DS 1. The clitoris of each rabbit in these groups was stimulated 4 – 5 times daily to produce engorgement and darkening of the vulva. The rabbits were primed to ensure that the vaginal canal size was adequate to accommodate the vaginal capsules.

Insertion of test article: The test and negative control article inserts were administered by surgical implantation in to the vagina under anesthesia. The surgical procedure involved the following:

A midline laparotomy incision was made, and the urinary bladder was separated from the anterior vaginal surface. The uterus was isolated and wet laparotomy sponges were placed underneath. After vagina was visualized, the capsule was lightly lubricated with K-Y brand lubricating gelly and then inserted through the exterior vaginal opening and advanced to the upper vaginal cavity. The capsule insert was anchored with 5-0 non-absorbable suture to the vaginal wall using a suture made approximately 1/8 inch deep from the outer capsule surface and knotted to the outer dorsal vaginal wall. The laparotomy incision was closed by suturing the multiple layers.

The test and negative control article inserts were weighed prior to surgical placement and then again on the day of necropsy examination i.e., DS 11.

Rationale for dose selection: The insert was formulated to release approximately 5.3 mg/day of progesterone. Based on rabbit's anatomy, the study was limited by the size of the capsule, and therefore, could not exceed the proposed doses. The dose administered to the rabbit was approximately 1x the anticipated human vaginal dose of approximately 40 mg/day (based on body surface area). The dose of the positive control article was stated as the standard dose in a standard 10 day vaginal irritation study.

Observations and times:

Mortality: Viability checked twice daily

Clinical signs: Clinical signed recorded daily. At each interval, the vulva and the surrounding tissues were evaluated for erythema, edema, discharge or other evidence of irritation. No internal vaginal examination was performed.
Body weights: Body weights were recorded on the day of arrival and then daily starting one week prior to the first day of dosing and continuing until sacrifice.
Food consumption: was recorded daily during the dosing period.
Ophthalmoscopy: none conducted
EKG: none conducted
Hematology: No hematology was performed.
Clinical chemistry: clinical chemistry was not performed
Urinalysis: Urine was not analyzed
Gross pathology: All surviving rabbits were sacrificed on DS 11, and a complete necropsy was performed. The necropsy included examination of the external surfaces and all orifices; external surfaces of the brain and spinal cord; the organs and tissues of the cranial, thoracic, abdominal and pelvic cavities and neck; and the reminder of the carcass. The vagina was removed in toto from the pubic symphysis (including the vulva) to the cervix and examined for signs of irritation and inflammation.
Organ weights (specify organs weighed if not in histopath table): The adrenal glands, brain, heart, kidneys, liver, ovaries and pituitary were weighed prior to fixation. The vaginal tissue as well as the ovaries, oviducts, uterus with cervix, paired inguinal lymph nodes were also retained in buffered formalin for histological examination.

Histopathology: Adequate Battery: yes (*), no ( )—explain
33 tissues were retained in buffered formalin for future histological examination.
Peer review: yes ( ), no (*)

Comment: Blood and endometrial tissue progesterone concentrations were not conducted, which are important to correlate blood and tissue concentrations with any adverse effects of treatment. This information will be requested from the sponsor.

Results

Mortality: One doe with a vaginal capsule matrix with progesterone was sacrificed on study day 3 in moribund condition.

Clinical signs: Except for the one doe that was moribund and sacrificed, all does appeared normal. For vaginal irritation scoring, taking number of observations/number of rabbits examined, erythema and edema is shown in table 2 below:

Table 2

Vaginal irritation scoring	Group 1 surgical sham control	Group 2 positive control 2% nonoxynol-9	Group 3 vaginal capsule matrix negative control	Group 4 vaginal capsule matrix formulation with progewterone
Vaginal observations:				
Appeared normal	55/5	51/5	24/5	39/5
Erythema grade 1	0/0	4/2	31/5**	6/3**
Edema grade 1	0/0	0/0	6/2	4/1
Yellow or clear discharge	0/0	0/0	1/1	1/1[a]

** Significantly different from the control group value ($p \leq 0.01$
[a] Rabbit 5998 was moribund sacrificed on day 3 of study.

Data in the table suggests that the erythema is due to presence of capsule and not due to progesterone. Vaginal irritation grading system is based on changes in epithelium, vascular congestion, leukocyte infiltration and edema, each graded at a scale of 0 – 4.

Vaginal evaluation criteria used was as shown in table 3 below:

Table 3

Composite score	**Vaginal irritation rating**	**Conclusion**
1 – 4	Minimal irritation	Acceptable
5 – 8	Mild irritation	Acceptable
9 – 11	Moderate irritation	Acceptable
12 – 16	Marked irritation	Acceptable

The composite score on microscopic examination of the vaginal sections were 0, 2.1, 0.2 and 0.53 for groups 1, 2, 3 and 4, respectively and thus all were classified as acceptable.

Body weights: There was no significant treatment effect on body weight or body weight gain. The terminal body weights of the positive control group, negative control group and the progesterone capsule group were 94.4%, 99.4% and 100% of the sham control group, respectively.

Food consumption: Absolute and relative feed consumption was similar in the 4 dosage groups. The absolute feed consumption for the study period were 104.3%, 97.2% and 93.8% of the sham control group value for the positive capsule control, negative capsule control group and the progesterone capsule group, respectively.

Gross pathology: The rabbit that was sacrificed in moribund condition on study day 3, exhibited signs of difficult breathing, decreased motor activity and a grade 1 clear vaginal

discharge. At necropsy all lobes of the lungs were mottled red, black and pink. The mucosal surface of the trachea was red and black and the lumen contained a white frothy material. Microscopically, the lungs showed multiple areas of necrosis and consolidation with suppurative inflammation and abscess. Based on these observations, it was considered as purulent bronchopneumonia of bacterial origin. There were no microscopic changes in the sections of the vagina that could be correlated with the gross observations.

Organ weights (specify organs weighed if not in histopath table): There was no significant treatment-related effect on the ratios of organ weight to terminal body weight for pituitary, brain, liver, kidneys paired, adrenals paired, ovaries paired, heart for the 4 treatment groups and for the vaginal capsule matrix negative control and vaginal capsule matrix formulation with progesterone.
Histopathology: There were no microscopic changes reported in tissues examined from the rabbits exposed to (b)(4)% concentration of progesterone via surgically implanted capsule that were considered to be related to exposure to the test article or the vehicle (implanted capsules without progesterone)
Microscopic changes observed in the vaginal mucosa of the rabbits in the positive control group, based on Vaginal Irritation Rating scale suggested minimal irritation and considered within acceptable limits.

It was concluded that all microscopic changes observed in sections of the vagina were related to the surgical implantation procedure and/or the physical presence of intravaginal implant. Moreover, no microscopic changes were reported in other organs or tissues to indicate any systemic effect of progesterone except on uterus where 4 of 5 rabbits had hyperplasia of the endometrium, and one had hyperplasia of cervical mucosa. One of the 2 rabbits examined in group 4, one had lymphoid hyperplasia. **(**of the inguinal lymph node)

Toxicokinetics: none conducted.

Other: none

2.6.6.3 Repeat-dose toxicity

Study title: An intravaginal safety assessment study of a surgically implanted progesterone vaginal capsule formulation for 30, 60, 75 and 90 days in the mature New Zealand White rabbits.

Key study findings: There was no progesterone-related effect on vaginal irritation scores. Platelet count was significantly increased at Day 30 determination only and serum triglycerides and urine volume at all sampling times in the progesterone treated group. The mean vagina and uterus absolute and relative to body/brain weights were reduced in progesterone capsule group at all study endpoints. Histological examination showed progesterone effects on vagina, uterus and inguinal lymph nodes. The uterus findings of decidual reaction and endometrium/myometrium atrophy and vaginal findings of epithelial atrophy were observed at all endpoints. Inguinal lymph node hyperplasia was

reported in one animal on day 75 endpoint. Urine volume was significantly higher in progesterone-treated animals at all determinations. Surgical implantation of progesterone vaginal capsule resulted in significant systemic exposure, which did not increase with duration of treatment. Endometrial progesterone concentrations were not determined.

Study no.: Testing facility study No. (b) (4); Sponsor reference No. DR-201-001
Volume #, and page #: e-Submission
Conducting laboratory and location: (b) (4)
Date of study initiation: 3-16-09
GLP compliance: Yes
QA report: yes (*) no ( )
Drug, lot #, and % purity: A9P13128A, purity not given **(check purity)**

Methods

Doses: as shown in study design in table 1 below:

Table 1

Group #	Identification	Number of animals[c]			
		Day 30 necropsy	Day 60 necropsy	Day 75 necropsy	Day 90 necropsy
1	Positice control (2% Nonoxynol-9 cream)[a]	4	4	4	4
2	Surgical sham control	4	4	4	4
3	Placebo control capsule	4	4	4	4
4	Progesterone ((b) (4)% w/w) capsule[b]	4	4	4	4

[a] Animals were administered 1 mL of 2% Nonoxynol-9 cream intravaginally (20 mg/day) daily for the first 10 consecutive days and then once weekly (beginning on Day 15) until scheduled necropsy.

[b] Anticipated average daily dose of PNG (based on in vitro release data) of approximately 2.9 mg/day

[c] Animals scheduled for necropsy on Days 30, 60, 75 or 90 were designed in the study records and report as Replicate 1, 2, 3 or 4, respectively.

Progesterone capsule description: (b) (4)% w/w progesterone, (b) (4)% silicone (b) (4), (b) (4)% light mineral oil matrix in the form of a 30 mm (long) x 8.5 mm (wide) capsule with (b) (4) mg of progesterone, (b) (4) mg light mineral oil, (b) (4) mg Silicone Elastomer, (b) (4)

Species/strain: Rabbit/NZW (Oryctologus cuniculus)
Number/sex/group or time point (main study): 4/f/g as shown in the table above
Route, formulation, volume, and infusion rate: intravaginal, capsule insert, once to last up to 90 days.
Satellite groups used for toxicokinetics or recovery: None. Blood was collected at various time points for determination of PGN plasma concentrations for TK analysis.

Age: 5 months
Weight: 2.8 – 3.5 kg
Sampling times: Experimental Days 30, 60, 75 and 90
Unique study design or methodology (if any): Method of implanting capsule inserts as described in the 10 day intravaginal toxicity under protocol HFE00006 reviewed above under this submission.

Observations and times:

Mortality: checked for mortality and for signs of ill health and/or reaction to treatment twice daily throughout the study.
Clinical signs: All animals observed for general condition on the day of surgery and daily throughout the in-life period. Cage-side observations were performed at the same time each day.
Body weights: Body weights were measured for all animals on day of randomization, prior to surgery and weekly throughout the treatment period and weighed (fasted) before scheduled necropsy.
Food consumption: recorded daily during the last week of pre-treatment period and throughout the treatment period.
Ophthalmoscopy: -
EKG: -
Hematology: Blood samples for hematology were collected once during the pre-treatment period and on all surviving animals (all replicates) prior to necropsy on Days 30, 60, 75 and 90. Blood samples were collected from the auricular artery/vein. Samples were analyzed for blood cell morphology, erythrocyte indices, hematocrit, hemoglobin mean platelet volume, platelet count, RBC count, reticulocyte count and WBC total count and % differential.
Clinical chemistry: Same time points as for hematology. Food was removed overnight prior to blood sampling. Samples were analyzed for A/G ratio, albumin, globulin, glucose, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, BUN, Ca, Cl, P, Na, cholesterol, creatinine, TG and bilirubin.
Urinalysis: Urine was collected on same occasions as for hematology and clinical chemistry for routine analysis.
Vaginal irritation scoring: Scoring of vaginal irritation was conducted once pretreatment, weekly throughout the treatment period and prior to necropsy. Vaginal irritation was qualitatively assessed using the Draize scoring system. At each interval, the vulva and the surrounding tissue were evaluated for erythema, edema and discharge. The erythema and edema scores ranged from 0 to 4 with a maximum possible score of 8. The cumulative irritation index was used to evaluate Draize scoring results. The severity was characterized using the following scale:

Response category	Mean score
Negligible	0 to 0.4
Slight	0.5 to 1.9
Moderate	2.0 to 4.9
Severe	5.0 to 8.0

Gross pathology: All animals were euthanized (as scheduled on Day 30, 60, 75 or 90 or unscheduled for humane reasons or if the animal was suspected of having expelled its capsule). Animals were fasted overnight before necropsy. The vaginal capsules were weighed before implantation and then again when found and retrieved.

Organ weights (specify organs weighed if not in histopath table): The following organs were dissected free of fat and weighed: adrenal glands, brain, heart, kidneys, liver, lungs, ovaries, pituitary gland, spleen, thymus, thyroid and parathyroid glands, uterus with cervix and vagina.

Histopathology: Adequate Battery: yes (*), no ( )—explain
Peer review: yes ( ), no ( )
Of all the tissues collected for microscopic examination were imbedded in paraffin but the following were processed and stained for microscopic examination:

Ovaries, uterus (body and cervix), vagina, liver, inguinal lymph nodes and abnormalities and gross lesions.

Toxicokinetics: Blood samples for progesterone determination were collected (approximately 1 mL) into test tubes containing K_2EDTA via an auricular artery. Blood was collected on day 1, pre-dose and then 1, 2, 4, 6, 8, 12, and 24 hours and then on Days 2, 3, 5, 8, 15, 22, 29 for a total collection of 8 blood samples. Day 30 scheduled necropsy was conducted at this time.
Bleeding was then conducted on Days 36, 43, 50 and 57 when Day 60 necropsy was conducted with total blood samples being 10. Further blood samples were collected on Day 64 and then Day 71 and animals scheduled for Day 75 were necropsied with total of 12 blood samples. Blood was then collected on Day 78 and then Day 90 when animals scheduled for Day 90 were necropsied with a total of 14 blood samples for TK.
At same time points blood samples were collected from the placebo control vaginal capsule animals.

Results

Mortality: No treatment-related deaths were reported during the course of the study. Two rabbits with placebo control capsules and one with progesterone capsule were preterminally euthanized on Days 24, 34 and 52 due to capsule expulsion. One rabbit in the placebo control capsule group was euthanized due to humane reasons on Day 9.

Clinical signs: There were no progesterone-related effects on vaginal irritation scores. Signs of irritation were reported amonst all groups including all 3 control groups. The mean irritation scores across groups were generally classified as slight to moderate and increased with time of treatment. Following week 5, animals in the placebo group had the highest mean irritation score.

Body weights: As shown in table 2 below, treatment had no significant effect on absolute body weight (kg) or body weight gains (kg) during the 12 week study.

Table 2

Treatment group/study week	Positive control (2% N-9 cream)	surgical sham control	Placebo control capsule	Progesterone ((b)(4) % w/w) capsule
Week 1	3.18	2.94	2.97	2.98
Week 12	3.75	3.83	4.00	3.73
Body wt gain +/- SD	0.05 +/- 0.058	0.10 +/- 0.000	0.5 +/- 0.058	0.03 +/-- 0.05

Food consumption: Feed consumption was not affected by treatment. The average feed consumption (g/animal/day) ranged from 110 to 120 amongst all treatment groups.

Ophthalmoscopy: Not conducted

EKG: None conducted

Hematology: As shown in table 3 below, only platelet count (+/- SD) was significantly increased at Day 30 determination and thereafter values in all groups appear similar.

Table 3

Treatment group/study Day	Positive control (2% N-9 cream)	surgical sham control	Placebo control capsule	Progesterone ((b)(4) % w/w) capsule
Day 30	414 +/- 91	418 +/- 95	422 +/- 109	5165 +/- 124
Day 60	410 +/- 154	426 +/- 101	413 +/- 97	505 +/- 100
Day 75	426 +/- 90	474 +/- 107	469 +/- 200	567+/- 112
Day 90	380 +/- 42	422 +/- 90	424 +/- 80	477 +/- 86

It was stated that other differences in hematology parameters, including those that reached statistical significance, were not considered related to the administration of progesterone due to their small magnitude, direction of change, comparability to sham, placebo control and/or baseline values and/or within biological variation.

Coagulation: There were no progesterone or nonoxynol-9-related effects on blood coagulation parameters.

Clinical chemistry: The only treatment-related change in serum chemistry involved increase in triglyceride values for the progesterone treated group at all sampling times. The TG values (mg/dL) for the 4 treatment groups are shown in table 4 below:

Table 4

Treatment group/study Day	Positive control (2% N-9 cream)	surgical sham control	Placebo control capsule	Progesterone ((b)(4) % w/w) capsule
Pre-treatment	38	36	36	32
Day 30	31	26	29	48
Day 60	30	28	26	45
Day 75	30	30	24	42
Day 90	25	23	23	38

Urinalysis: As shown in table 5 below, mean urine volume (mL) was increased for animals with progesterone capsules on all sampling times compared to placebo controls and sham controls. Data is expressed as mean +/- SD.

Table 5

Treatment group/study Day	Positive control (2% N-9 cream)	surgical sham control	Placebo control capsule	Progesterone ((b)(4) % w/w) capsule
Pre-treatment	62 +/61	56 +/- 52	72 +/- 54	72 +/- 45
Day 30	100 +/- 92	72 +/- 74	98 +/- 68	158 +/- 122
Day 60	92 +/- 47	70 +/- 55	65 +/- 27	150 +/- 122
Day 75	131 +/- 88	93 +/- 42	100 +/- 77	174 +/- 96
Day 90	90 +/- 71	46 +/- 37	151 +/- 165	176 +/- 107

The urine specific gravity was not changed with treatment. It is not explained if increased urine volume was due to any hormonal changes. Water intake was not recorded and it likely could affect urine volume changes.

Gross pathology: There was no progesterone or N-9-related macroscopic changes reported. The occurrence of dark area was observed in the vagina and/or urinary bladder of a few rabbits and it correlated with microscopically with hemorrhage or inflammation and was attributed to experimental procedure. All other macroscopic findings were considered to be agonal, incidental or related to surgical procedure.

Organ weights (specify organs weighed if not in histopath table):

Progesterone capsule-related organ weight changes were noted in the vagina and uterus at all study endpoints. Table 6 below shows mean vagina and uterus absolute and relative to body/brain weights were reduced in the progesterone capsule group:

Table 6

Treatment group/study Day	Positive control (2% N-9 cream)	surgical sham control	Placebo control capsule	Progesterone ((b)(4)% w/w) capsule
Absolute organ weights (g)				
Day 30				
Uterus	**8.21 +/- 1.394**	**6.46 +/- 2.090**	**7.85 +/-2.119**	**5.38 +/-1.604**
Vagina	**7.27 +/- 1.433**	**7.29 +/- 1.317**	**7.74 +/- 1.043**	**4.04 +/- 0.457**
Day 60				
Uterus	**8.17 +/-1.496**	**7.80 +/-2.615**	**8.34**	**6.23+/-1.933**
Vagina	**8.77 +/- 3.560**	**9.58 +/- 3.370**	**8.30**	**7.23 +/- 3.002**
Day 75				
Uterus	**9.01 +/-2.737**	**7.34 +/- 1.608**	**8.96 +/-1.657**	**5.22 +/- 1.398**
Vagina	**9.20 +/-2.002**	**7.41 +/- 1.746**	**10.37 +/- 4.108**	**5.37 +/- 1.830**
Day 90				
Uterus	**8.72 +/- 3.320**	**10.87 +/-2.078**	**11.66 +/-1.151**	**4.88 +/- 0.504**
Vagina	**7.03 +/- 0.761**	**8.17 +/-1.189**	**12.43 +/- 2.125**	**4.74 +/- 1.302**
Organ weights relative to body weight (%)				
Day 30				
Uterus	**0.241 +/-0.0480**	**0.198 +/- 0.0596**	**0.240 +/- 0.0488**	**0.1`75 +/- 0.0505**
Vagina	**0.212 +/- 0.0438**	**0.223 +/- 0.0352**	**0.238 +/- 0.0314**	**0.131 +/- 0.0169**
Day 60				
Uterus	**0.228 +/- 0.0391**	**0.220 +/- 0.0771**	**0.232**	**0.1765 +/- 0.0458**
Vagina	**0.246 +/- 0.0962**	**0.267 +/- 0.0819**	**0.232**	**0.204 +/- 0.0739**
Day 75				
Uterus	**0.242 +/- 0.0754**	**0.201 +/- 0.0432**	**0.248 +/- 0.0519**	**0.142 +/- 0.0350**
Vagina	**0.247 +/- 0.0561**	**0.202 +/- 0.0453**	**0.287 +/- 0.1205**	**0.145 +/- 0.0424**
Day 90				
Uterus	**0.236 +/- 0.0836**	**0.291 +/- 0.0591**	**0.295 +/- 0.0263**	**0.130 +/- 0.0143**
Vagina	**0.193 +/- 0.0334**	**0.219 +/- 0.0422**	**0.315 +/- 0.0562**	**0.126 +/- 0.0331**
Organ weights relative to brain weight (%)				
Day 30				
Uterus	**84.64 +/- 17.07**	**71.45 +/- 26.96**	**81.05 +/- 19.96**	**59.59 +/- 18.96**
Vagina	**74.46 +/- 13.95**	**80.35 +/- 18.44**	**80.37 +/- 13.42**	**44.54 +/- 5.22**
Day 60				
Uterus	**90.77 +/- 16.51**	**84.34 +/- 33.48**	**95.53**	**66.30 +/- 23.89**
Vagina	**95.62 +/- 32.96**	**101.03 +/- 31.91**	**95.08**	**77.19 +/- 36.00**
Day 75				
Uterus	**86.09 +/- 22.00**	**79.00 +/- 15.37**	**95. 30 +/- 20.23**	**54.72 +/- 14.96**
Vagina	**88.20 +/- 15.39**	**79.80 +/- 17.94**	**109.38 +/- 41.97**	**56.14 +/- 18.07**
Day 90				
Uterus	**89.76 +/- 27.58**	**110.89 +/- 25.74**	**115.22 +/- 5.86**	**52.22 +/- 7.71**
Vagina	**73.54 +/- 9.07**	**83.15 +/- 15.03**	**124.01 +/- 27.87**	**50.82 +/- 15.63**

Histopathology: Adequate Battery: yes (*), no ( )—explain: Microscopic examination was performed on ovaries, uterus, vagina, liver, inguinal lymph nodes and abnormalities or gross lesions. Microscopic examination was performed on these tissues from all animals, including those euthanized prior to scheduled necropsy. It was stated that the remaining tissues were prepared by embedding in paraffin wax for potential microscopic examination if warranted by the Pathologist and/or Study Director.

Incidence of animals with microscopic findings by organ/group is shown in table 7 below:

Table 7

Treatment group/study week	Positive control (2% N-9 cream)	surgical sham control	Placebo control capsule	Progesterone ((b)(4) % w/w) capsule
Day 30				
Uterus				
Decidyual reaction	-	-	-	3
Atrophy:				
endometrium/myometriaum	-	-	-	4
Vagina				
Infiltration: heterophil	3	-	1	1
Atrophy:epithelial	-	-	1	4
Degeneration: epithelial	2	-	-	-
Vacuolation:epithelial	1	-	-	-
Hemorrhage	1	-	-	-
Day 60				
Lymph node-inguinal				
Hyperplasia: lymphoid	-	-	-	2
Uterus				
Decidual reaction				
Atrophy: endometrum/myometrium	-	-	-	2
	-	-	-	3
Vagina				
Infiltration:heterophil				
Atrophy: epithelial	1	-	-	-
	-	-	-	3
Day 75				
Lymph node inguinal				
Hyperplasia: lymphoid	-	-	-	1
Uterus				
Decidual reaction				
Atrophy:	-	-	-	4
endometrium/myometrium	-	-	-	4
Vagina				
Infiltration: heterophil	1	-	1	-
Atrophy:endometrium/myometrium	-	-	-	4
Hemorrhage	1	-	-	-
Day 90				
Uterus				
Decidual reaction				

Atrophy:endometrium/mypmetrium	**-**	**-**	**-**	**3**
	-	**-**	**-**	**4**
Vagina				
Infiltration: heterophil	**-**	**-**	**-**	**-**
Atrophy: epithelial	**-**	**-**	**-**	**4**
Vacuolation: epithelial	**4**	**-**	**-**	**-**
Hemorrhage	**-**	**-**	**1**	**-**

There were 4 animals in each group. One animal in group 4 necropsied on Day 90 had liver granuloma.
Results thus showed that the progesterone effects were observed in uterus, vagina and lymph node. The uterus findings involved decidual reaction and atrophy of endometrium and myometrium. The vaginal changes included epithelial atrophy. A few animals had lymphoid hyperplasia of the inguinal lymph nodes.

Peer review: yes ( ), no (*)

Toxicokinetics:

TK parameters of progesterone in female NZW rabbit plasma following surgical implantation of progesterone ((b) (4)% w/w) vaginal capsule for group 4 at four necropsy time interval is shown in table 8 below. Values are mean +/- SD for 4 animals:

Table 8

Animal subgroup	**T_{max} (h)**	**T_{last} (h)**	**C_{max} (ng/mL)**	**$AUC_{(0\text{-}672\ h)}$ (ng.h/mL)**
4501 – 4504	**16.0**	**672 (Day 29)**	**42.5 +/- 24.7**	**9118 +/- 2046**
4505 – 4508	**9.00**	**1260 (Day 57)**	**34.4 +/- 7.84 1**	**11976, 13077[a]**
4509 – 4512	**8.00**	**1680 (Day 71)**	**28.0 +/- 2.03**	**11573 +/- 1923**
4513 – 4516	**4.00**	**2136 (Day 90)**	**37.5 +/- 358**	**13716 +/- 1506**
Overall	**8.00**	**1512**	**35.6+/- 12.9**	

[a]Values for 2 animals were not reported because the $AUC_{(0\text{-}inf)}$ was extrapolated by more than (b) (4)% or R^2 was <0.8.
Anticipated average daily dose of progesterone (based on in vitro release data) was approximately 2.9 mg/day.
T_{max} and T_{last} are reported as median values

Percentage of progesterone exposure achieved in Days 29, 57, 71 vs Day 90 in female NZW rabbit plasma following a surgical implantation of progesterone ((b) (4)% w/w) vaginal capsule is given in table 9 below:

Table 9

Animal subgroup	Time of last sampling	Mean $AUC_{(0\text{-}t}^{*}$	Ratio ($AUC_{(0\text{-}t}^{*}/AUC_{(0\text{-}2136\ h)}$
4501 – 4504	**672 (Day 29)**	**9118**	**66.5**
4505 – 4508	**1344 (Day 57)**	**12526**	**91.3**
4509 – 4512	**1680 (Day 71)**	**11573**	**84.4**
4513 – 4516	**2136 (Day 90)**	**13716**	**100**

* Time of last sampling

Results thus showed that all animals in the progesterone capsule groups exhibited measurable increase in plasma progesterone concentration.

Concentrations of progesterone in female NZW rabbit plasma following surgical implantation of placebo control vaginal ring:

Endogenous progesterone concentrations ranged between below LLOQ (lower limit of quantification= 0.500 ng/mL) to 6.73 +/- 6.17 ng/mL at one sampling time. The endogenous progesterone concentrations exhibited high intra-day and inter-day fluctuations. Also animals implanted with progesterone capsules (group 4) had pre-dose concentrations comparable to endogenous progesterone levels measured in control group, with all values below LLOQ with the exception of 4 animals that had endogenous levels between 2.64 and 8.82 ng/mL.

Other:

Comparison of the 10 day and 90 day vaginal toxicity studies: Significant treatment-related differences involved hyperplasia of the endometrium/myometrium in 4/5 rabbits, hyperplasia of the cervix in one and that of inguinal lymph nodes in two rabbits in the 10 day study. In the 90-day toxicity study progesterone-related effects included decidual reaction in the uterus and atrophy of the endometrium/myometrium. There was atrophy of the vaginal epithelium. These findings were observed at all study endpoints. Lymphoid hyperplasia was reported in 2 rabbits on Day 60 and 1 on Day 75 determinations.

Comparison of the toxicokinetics for humans and rabbits: In a clinical study entitled "A bioavailability study to evaluate the single and steady state pharmacokinetics of a progesterone loaded vaginal ring (DR-2011) formulation in post menopausal females", sponsor reported mean +/- SD Cmax (0-168 h) of 9.33 +/- 2.80 ng/mL, Tmax of 134.80 +/- 49.17 hr and AUC of 1188.41 +/- 374.24 ng.hr/mL for first 7-day vaginal ring insertion (n=30). Similar values were observed during the second 7-day vaginal ring insertion (168 – 336 h).

In the present rabbit repeat-dose toxicity study on Day 29, mean +/-SD for Cmax was 42.5 +/- 24.7 ng/mL, Tmax 16.0 hr and AUC 9118 +/- 2046 ng.hr/mL. Values for Days 57, 71 and 90 were similar to those reported for Day 29 (n=4).

The dose in human is 14 mg i.e. about 0.28 mg/kg or 10 mg/m^2 and that of rabbit was 2.9 mg i.e. about 1 mg/kg or 12 $mg/m^{2.}$ Thus the progesterone dose as mg/m^2 used in the

rabbit study with (b)(4)% w/w progesterone was similar to that used in the human PK study. Steady state plasma concentrations of progesterone were reached during the first vaginal ring insertion in both humans and rabbits. However, the plasma progesterone concentrations were much higher in the rabbits than those reported for humans.

P/T comments: The significant different drug effects observed in the 10 Day and 90 Day studies, i.e., hyperplastic uterine and vaginal changes in the 10 Day study and atrophic changes in the 90 Day study. These could be possibly due to different progesterone concentrations used for the progesterone formulations i.e., (b)(4)% w/w in the 10-Day experiment and (b)(4)% w/w in the 90-Day study or these differences could be due to duration of treatment. Clinical significance if any of these observations is not explained.

Histopathology inventory (optional)

Study				
Species				
Adrenals				
Aorta				
Bone Marrow smear				
Bone (femur)				
Brain				
Cecum				
Cervix				
Colon				
Duodenum				
Epididymis				
Esophagus				
Eye				
Fallopian tube				
Gall bladder				
Gross lesions				
Harderian gland				
Heart				
Ileum				
Injection site				
Jejunum				
Kidneys				
Lachrymal gland				
Larynx				
Liver				
Lungs				
Lymph nodes, cervical				
Lymph nodes mandibular				
Lymph nodes, mesenteric				
Mammary Gland				
Nasal cavity				

Optic nerves				
Ovaries				
Pancreas				
Parathyroid				
Peripheral nerve				
Pharynx				
Pituitary				
Prostate				
Rectum				
Salivary gland				
Sciatic nerve				
Seminal vesicles				
Skeletal muscle				
Skin				
Spinal cord				
Spleen				
Sternum				
Stomach				
Testes				
Thymus				
Thyroid				
Tongue				
Trachea				
Urinary bladder				
Uterus				
Vagina				
Zymbal gland				

X, histopathology performed
*, organ weight obtained

2.6.6.4 Genetic toxicology: None submitted. See statement from Prometrium label below.

2.6.6.5 Carcinogenicity: None submitted. However citing literature the Prometrium label under the title "Carcinogenesis, mutagenesis, impairment of fertility" contains the following statement;

Progesterone has not been tested for carcinogenicity by the oral route of administration. When implanted into female mice, progesterone produced mammary carcinomas, ovarian granulosa cell tumors and endometrial stromal sarcoma. In dogs, long term intramuscular injections produced nodular hyperplasia and benign and malignant mammary tumors. Subcutaneous or intramuscular injections of progesterone decreased the latency and increased the incidence of mammary tumors in rats previously treated with a chemical carcinogen.

Progesterone did not show evidence of genotoxicity in in vitro studies for point mutations or for chromosomal damage. In vivo studies for chromosomal damage have yielded

positive results. Exogenously administered progesterone has been shown to inhibit ovulation in a number of species and it is expected that high doses given for extended duration would impair fertility until the cessation of treatment.

2.6.6.6 Reproductive and developmental toxicology: None submitted. See statement from Prometrium label above.

2.6.6.7 Local tolerance: Vaginal irritation evaluated in both the 10 day and 90 day studies.

2.6.6.8 Special toxicology studies: None submitted

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: 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.

Unresolved toxicology issues (if any): None

Recommendations: Pharmacology recommends approval of NDA 201,110 from the P/T perspective for progesterone vaginal ring (DR-2011) for the proposed indication "to support embryo implantation and early pregnancy by supplementation".

Suggested labeling: Labeling is in accordance with PLR and presented in SLR format and is acceptable to P/T.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

Appendix/attachments: None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201110	ORIG-1	TEVA WOMENS HEALTH INC	PROGESTERONE (VAGINAL RING)

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

/s/

KRISHAN L RAHEJA
07/16/2010

ALEXANDER W JORDAN
07/16/2010

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

IND number: 70,875
Review number: 2
Sequence number/date/type of submission: 056/5-18-09/Type B Meeting (Pre-NDA-Clinical) Information Package
Information to sponsor: Yes ( ) No (*)
Sponsor and/or agent: Duramed Research, Inc. Bela Cynwyd, PA
Manufacturer for drug substance: not given

Reviewer name: Krishan L. Raheja, D.V.M., Ph.D.
Division name: DRUP
HFD #: 580
Review completion date: 5-28-09

Drug:

Trade name: not given
Generic name: Progesterone
Code name: DR-2011
Chemical name: Pregn-4-ene-3,20-dione
CAS registry number: 57-83-0
Molecular formula/molecular weight: $C_{21}H_{30}O_2$/314.47
Structure:

Relevant INDs/NDAs/DMFs: DMF # (b) (4) & DMF # (b) (4)

Drug class: Progestin

Intended clinical population: To support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteum function as part of Assisted Reproductive Technology (ART) treatment program for infertile women.

Clinical formulation: Progesterone Vaginal ring

The ring's active ingredient is progesterone, USP (b) (4)
The ring's inactive ingredients are:
Silicone Elastomer, (b) (4)

(b) (4)

(b) (4)

Other inactive ingredient is Light mineral oil, NF.

The progesterone vaginal ring releases (b) (4) mg progesterone/day

Note: Silicone elastomers have been used under IND (b) (4) .

(b) (4) conducted extensive toxicity studies on silicone elastomers, which consisted of the following:

- In vitro tissue cell culture
- Pyrogen test in rabbits
- Systemic injection in mice
- Intracutaneous test in rabbits
- Skin sensitization test in rabbits
- Hemolysis test
- 90-day implantation in rabbits
- 72 hour vaginal implantation in rabbits
- Thrombogenicity test for silastic
- 2-year tissue implantation in Fisher 344 rats with (b) (4)

Thus the safety of (b) (4) silicone elastomer seems reasonably well established.

Route of administration: Intravaginal

Dosing regimen: One vaginal ring inserted vaginally starting the day after oocyte retrieval. The vaginal ring is replaced weekly, continuing up to 10 weeks total duration.

Proposed clinical protocol: none submitted

Previous clinical experience: Clinical experience is based on the following 5 IND clinical studies for the progesterone vaginal ring:

Protocol 10716222: A Phase 1 study entitled "A bioavailability study to evaluate the single and steady state pharmacokinetics of a progesterone loaded vaginal ring (DR-2100) formulations in post-menopausal women". This study has been completed.

Protocol DR-201-102: A study entitled "A Phase 1, randomized, open-label, pharmacokinetic study to compare DR-2011 to a progesterone vaginal gel by evaluating progesterone concentration in endometrial issue and serum". This study is ongoing.

Protocol DR-PGN-201: A study entitled "A Phase 2, single-center, open-label, randomized, controlled, pharmacodynamic study to compare DR-2011 to a progesterone vaginal gel for luteal phase replacement". This study has been completed.

Protocol DR-PNG-202: A study entitled "A Phase 2, open-label, active-controlled, follow-up study to compare DR-2011 to a progesterone vaginal gel for clinical pregnancy rates in women undergoing donated oocyte in vitro fertilization". This study has been completed.

Protocol DR-PGN-302: A study entitled "A Phase 3, single-blind, randomized study to compare DR-2011 to a progesterone vaginal gel for luteal phase supplementation for in vitro fertilization". This study is ongoing.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission: none

Studies not reviewed within this submission: The following preclinical completed studies conducted in accordance with GLP regulations were reviewed under IND SS# 000 dated 10-6-04 on 10-4-04:

Summary of silicone biocompatibility and genotoxicity studies

Study type	Species/strain/sex	Animals/dose group	Test material	Findings
Sample extract cytotoxicity study	(b) (4)	N/A	5% serum concentration of minimum essential medium	No evidence of cytotoxicity
Systemic toxicology study	Mice	5	Uncharged silicone extract with 0.9% sodium chloride and cotton seed oil administered intraperitoneally	No systemic toxicity observed. Acceptable body weight changes. No mortality. All animals appeared clinically normal throughout the observation period.
Muscle implantation study	rabbits	3	6 uncharged implants placed in right paravertebral muscle and 4 control strips implanted in opposite muscle and housed for 90 consecutive days	Silicone extracts nonirritant as assessed by microscopic exam. Findings similar to control
Intracutaneous toxicity study	rabbits	2	0.2 ml of extract injected intracutaneously into 5 sites on right side of back; 5 sites injected as controls on left side	No evidence of significant irritation or toxicity

Ames mutagenicity study	**5 salmonella typhimurium tester strains**	**N/A**	**Extract prepared in 0.9% sodium chloride**	**Considered non-mutagenic**

Duramed Research conducted an additional study in rabbits to evaluate the acute local and distant tolerability of Progesterone VR. In this study silicone matrix capsules containing progesterone were surgically implanted vaginally to mimic the clinical route of administration.

The study was entitled as Study # HFE 00006: 10-day intravaginal study in rabbits (test article: progesterone in a silicone matrix capsule insert).

The results of this study are summarized in the following table:

Study title Testing facility (study number) Final report date GLP/non-GLP	**Strain /sex Supplier**	**Animals per dose group**	**Dail;y dose (mg/kg)**	**Significant findings**
10-day intravaginal study in rabbits (progesterone in a silicone matrix capsule insert) (b) (4) **(HFE00006)** (b) (4) **GLP**	**Hra: (NZW) SPF/females** (b) (4)	**5**	**0 (Sham surgery control)** **20 (Positive conrol: Nonoxynol-9) Gynol II clear gel lot # 4AM492, I g** **0 (Negative control:1 Empty clear capsule) Lot # PC-016** **5.3 +/- 0.05 mg (1 progesterone in silicone matrix capsule) Lot # PC-017** (b) (4) **% progesterone white capsules**	**No mortality or signs of systemic toxicity were attrributed to any test or control article in this study. All but one animal survived the duration of this study. This rabbit from progesterone group (1/5) was sacrificed in moribund condition due to apparent pneumonia that was not attributed to the test article. Clinical observations, body weight patterns, and food consumption values were comparable among control and treated groups. Necropsy findings including absolute and relative body weights were comparable for control and treated groups. Microscopic evaluation of the liver, reproductive organs ans inguinal lynph nodes indicated no effects of test article. Local signs of vaginal irritation were limited to Grade 1 erythema, edema and/or vaginal discharge in all but the surgical sham group. 5.3 mg/day delivered via vaginal route provided one-fold comparison to planned human progesterone VR dose of 40 mg/day (based on body surface area)**

Composite average vaginal irritation score was 0, 2.1, 0.2 and 0.53 for groups 1, 2, 3 and 4, respectively. The grading was done according to Draize score (0-4) for epithelium, vascular congestion, leukocytic infiltration and edema. Composite score of 1 –4 denoted minimal irritation and acceptable; 5 – 8 denoted mild irritation and acceptable; 9 – 11 denoted moderate irritation and considered borderline and 12 – 16 suggested marked irritation and considered unacceptable.

An additional intravaginal safety assessment study to support longer duration of exposure to vaginal ring matrix is currently ongoing at the (b) (4)

(b) (4) and planned for completion prior to NDA submission. Thee study is entitled "An intravaginal safety assessment study of a surgically implanted progesterone vaginal capsule formulation for 30, 60, 75 and 90 days in mature New Zealand White female rabbit: Testing facility study # (b) (4) and sponsor ref. No. DR-201-001. This study will be conducted in accordance with FDA GLP regulations.

The study design of the ongoing study DR-201-001/ (b) (4) is given in table below:

Group #	Identification	Number of animals used for necropsy on			
		Day 30	Day 60	Day 75	Day 90
1	Positive control (2%Nonoxynol-9 cream)[a]	4	4	4	4
2	Surgical sham control	4	4	4	4
3	Placebo control capsule (silicone vaginal capsule 30 mm x 8.5 mm)	4	4	4	4
4	Progesterone ((b) (4) % w/w) capsule[b]	4	4	4	4

[a] Animals are administered 1 ml of 2% Nonoxynol-9 cream intravaginally ((b) (4) mg/day) daily for the first 10 consecutive days and then weekly (beginning on Day 15) until necropsy.

[b]= Anticipated average daily dose of progesterone (based on in vitro release data) of approximately 2.9 mg/day or 11.6 mg/m^2 over a 90 day period, representing a dose of approximately 1.3 X the human clinical dose of 14 mg/day or 8.6 mg/m^2 based on body surface area.

The objectives of this study are to investigate the potential toxicity, vaginal tissue tolerability and toxicokinetics of an encapsulated progesterone formulation (30 mm long and 8.5 mm wide) after intravaginal surgical implantation.

Observations will include clinical examination, body weight, food consumption, vaginal irritation scoring using Draize scoring system, laboratory investigations (hematology, coagulation, clinical chemistry, and urinalysis) on all surviving animals, toxicokinetic evaluation, gross pathology (necropsy and macroscopic examination), organ weight assessment, and histopathology.

Comments : The sponsor has stated that due to the anatomical limitations of the test system, a vaginal ring is not feasible for nonclinical evaluation. Therefore, a surgically-implantable vaginal capsule that mimics a human vaginal ring's matrix composition, has been developed to enable tolerability assessment of the vaginal ring matrix formulation in rabbits.

Due to the magnitude of the implantation surgery (for animal welfare purposes0, the capsules can not be replaced: therefore, multiple necropsy endpoints (at 30, 60, 75, or 90 days post-implantation) have been implemented to capture any findings throughout the [declining progesterone-release] prolonged exposure period.

To support the safety of intravaginal progesterone administration the sponsor has referenced Ferring Pharmaceuticals NDA for Endometrin ® (progesterone) Vaginal Insert approved in 1974 for same indication as for the present Duramed submission.

This submission is reviewed for proposed Type B (Pre-NDA) meeting between Division representatives and Duramed Research scheduled for 6-16-09.

Specific preclinical question to the Division is as follows:

Sponsor's statement: Progesterone is a well-characterized drug that is widely marketed throughout the world. Also, the silicone elastomer (b) (4) component of the vaginal ring has met the biocompatibility and genotoxicity testing criteria of the ISO 10993 Part 10 guidelines and has been previously approved for use as a biological implant. Duramed is currently conducting study DR-201-001 entitled "An intravaginal safety assessment study of a surgically implanted progesterone vaginal capsule formulation for 30, 60, 75 and 90 days in the mature NZW female rabbit.

Sponsor's question: Does the Division concur that the nonclinical program (consisting of Study # 201-001, a 10-day intravaginal irritation study of progesterone in female New Zealand White rabbits (Study # HFE00006) and biocompatibility/genotoxicity results of the silicone elastomer (b) (4) is adequate to support NDA filing?

P/T response: YES

Based on the information available for Endometrin® on long term use of progesterone by the intravaginal route of administration for the same indication as for DR-2011, coupled with the safe use of DR-2011 formulation in sponsor's Phase 1 and Phase 2 clinical studies)

Linked Applications	Sponsor Name	Drug Name / Subject
IND 70875	DURAMED RESEARCH INC	PROGESTERONE (VAGINAL RING)

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

/s/

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06/01/2009

LYNNDA L REID
06/01/2009