CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201110Orig1s000

PRODUCT QUALITY REVIEW(S)

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

Date: **April 28, 2020**

From: **Mark R. Seggel, Ph.D.**
Application Technical Lead
Office of New Drug Products
DNDP II / Branch 4

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch 4
Office of New Drug Products
DNDP II / Branch 4

To: **OPQ IQA #3 for NDA 201110**
MILPROSA (progesterone) vaginal system

Subject: **Final Recommendation - APPROVAL**

Summary:

The OPQ Integrated Quality Assessment (IQA) dated April 13, 2020, recommended a Complete Response for the second resubmission of 505(b)(2) NDA 201110. It was noted that labeling negotiations had not been completed and that the labeling did not comply with the requirements under 21 CFR 201. It was also noted that a final recommendation from CDRH-OPEQ on the adequacy of the device quality system was pending. The NDA was otherwise complete and adequate from the OPQ and CDRH (engineering, biocompatibility) perspectives.

Labeling: Deficiencies in the proposed labeling included use of incorrect nomenclature. Throughout labeling the product was referred to as a "ring." While this nomenclature was appropriate when the NDA was first submitted on April 30, 2010, per USP's 2016 'Nomenclature Guidelines,' USP<1151> Dosage Forms, and FDA's 'Product Title and Initial U.S. Approval' draft guidance, the correct term is "vaginal system." Other deficiencies in Sections 3, 11 and 16 were identified. See Hong Cai's labeling review in IQA # 3 for details.

Recommended revisions to the prescribing information and to the container (foil laminate pouch) and carton labels were conveyed to the applicant. The revised pouch and carton labels submitted April 17, 2020 (sn 0059) adequately incorporate all of ONDP recommendations. The previously identified deficiencies in the prescribing information have been adequately addressed in the labeling submitted April 24, 2020 (sn 0060). See Hong Cai's Labeling Review Addendum dated April 26, 2020 (Attachment 1 of this IQA

Addendum) for details. The revised labeling submitted April 28, 2020 (sn 0061) is also acceptable from the ONDP perspective.

CDRH Quality System Review: As part of the assessment of certain types of drug-device combination products, CDRH evaluates compliance with medical device GMPs including applicable quality system requirements. In the CDRH consult (ICC1901047) review dated April 15, 2020, CDRH reviewer Klara Jenkins confirmed that the finished product manufacturing site, Teva Women's Health, Cincinnati, Ohio, had acceptable GMP status and that the quality system documentation provided in the NDA was adequate. CDRH concluded that this NDA is approvable from the perspective of the applicable Quality System Requirements. See Klara Jenkins' consult review for details. [Note: The consult review refers to an inspection of Teva completed February 8, 2020 and classified as Official Action Indicated (OAI). This inspection was completed in 2019, and while the initial decision was OAI, the final decision was NAI.]

Additional Comments:

Product Description: The IQA #3 Executive Summary inadvertently identified the cross-sectional diameter of MILPROSA as (b)(4) mm. The diameter is in fact 8.5 mm.

Facility Status: All manufacturing facilities continue to be *Compliant* (see Attachment 2, Facility Status Report as of 04/28/2020). See also the OPMA Facilities assessment in IQA #3.

######

Recommendation:

This NDA is now recommended for **Approval** from the OPQ perspective.

Application Technical Lead Signature:

Mark R. Seggel, Ph.D.,
CMC Lead (acting)

{see digital signature page}

ATTACHMENTS

Attachment 1. Labeling

Attachment 2. Facility Status Report

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

Date: **April 26, 2020**

From: **Hong Cai, Ph.D.**
Drug Product Reviewer
Office of New Drug Products
Branch IV/DNDP II

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch IV
Office of New Drug Products
Branch IV/DNDP II

To: **Drug Product/Labeling Review #2 of NDA201110**
for MILPROSA™ (progesterone) vaginal system

Subject: **Final Recommendation**

The Labeling Review #1 has recommended that NDA 201110 is not ready for approval in its present form on April 2, 2020 from the CMC perspective. Consequently, the applicant, Ferring Pharmaceuticals Inc., has submitted the revised carton labeling and container labels on April 17, 2020 (SN0059) and the prescribing information (PI) on April 24, 2020 (SN0060), respectively, and incorporated FDA comments. In these submissions, the applicant has resolved all the CMC related deficiencies (Highlight of Prescribing Information, Section #3, #11 and #16 of PI, and Carton Labeling and Container Labels). Therefore, CMC related information is now deemed satisfactorily resolved from the CMC labeling perspective (See the Appendix-I for CMC relevant sections in Prescribing Information (PI) and Appendix-II for the mockup of the container/carton labeling/labels).

It is noted that the disposal instruction statement in Section 16 of PI has been modified from OPQ EA reviewer James Laurenson initial recommendation captured in the Labeling Review #1. This current version is acceptable from drug product labeling perspective and confirmed by James Laurenson via email on April 22, 2020. Although James Laurenson has recommended to include the disposal instruction in both Patient Package Insert (PPI) and Instructions for Use (IFU), the disposal instruction has been added to IFU only per Patient Labeling Reviewer Maria Nguyen, MSHS, BSN, RN (Refer to the Patient Labeling Review dated April 17, 2020 in DARRTS). Both PPI and IFU are part of the information to be distributed to the patients, this is acceptable.

Recommendation:
This application is recommended for **approval** from the CMC labeling perspective.

Hong Cai, Ph.D.
Drug Product Reviewer
Branch IV, Division II, ONDP

Moo-Jhong Rhee, Ph.D.
Branch Chief
Branch IV, Division II, ONDP

Attachment-1:

Sections related to CMC in Prescribing Information submitted on April 24, 2020 (SN0060):

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MILPROSA safely and effectively. See full prescribing information for MILPROSA.

MILPROSA™ (progesterone) vaginal system
Initial U.S. Approval: 1974

DOSAGE FORMS AND STRENGTHS

Vaginal system: 1.78 grams of progesterone in a white to off-white, flexible, non-biodegradable silicone ring (toroidal-shape). Releases an average of 11 mg/day progesterone over 7-days. (3)

Full Prescribing Information:

3 DOSAGE FORMS AND STRENGTHS

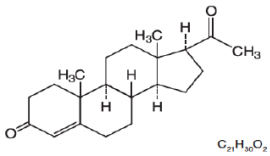
Vaginal system: 1.78 grams of progesterone in a white to off-white, flexible, non-biodegradable silicone ring (toroidal-shape). MILPROSA has a cross-sectional diameter of approximately 8.5 mm, and an outer and inner diameter of approximately 55 mm and 38 mm, respectively. Each MILPROSA releases an average of 11 mg/day of progesterone when placed in the vagina over a 7-day period.

11 DESCRIPTION

MILPROSA (progesterone) vaginal system is a white to off-white, flexible, non-biodegradable silicone ring (toroidal-shaped) containing 1.78 grams of progesterone. MILPROSA has a cross-sectional diameter of approximately 8.5 mm, and an outer and inner diameter of approximately 55 mm and 38 mm, respectively.

The chemical name for progesterone is pregn-4-ene-3,20-dione. It has an empirical formula of $C_{21}H_{30}O_2$ and a molecular weight of 314.5. Progesterone has a melting point of 126-131°C.

The structural formula is:



When placed in the vagina, each vaginal system is estimated to provide an average release rate of 11 mg/day of progesterone over 7 days.

The inactive components of the vaginal system are light mineral oil and silicone elastomer.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each MILPROSA (progesterone) vaginal system is a white to off-white, flexible, non-biodegradable silicone ring (toroidal-shaped), which contains 1.78 grams of progesterone and releases an average of 11 mg/day of progesterone over a 7-day period of use. MILPROSA vaginal system has an inner and outer diameter of approximately 38 mm and 55 mm, respectively, and a cross-sectional diameter of approximately 8.5 mm.

Each MILPROSA is packed individually in a sealed foil pouch. These pouches are available in cartons packed:

- 2 vaginal systems per carton (NDC 55566-9400-1)

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Do not refrigerate or freeze and avoid excessive heat.

After use, place in pouch and discard via a drug take-back option if available; otherwise, mix with something undesirable, such as used coffee grounds, dirt, or cat litter to make it less appealing to children and pets. Place the mixture in something that can be closed (a re-sealable zipper storage bag, empty can, or other container) and discard in the household trash. DO NOT flush down toilet. See drug disposal information at www.fda.gov/drugdisposal for more information.

MANUFACTURED FOR:
Ferring Pharmaceuticals Inc.
100 Interpace Parkway
Parsippany, NJ 07054 USA

FERRING
PHARMACEUTICALS

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

Hong Cai

Digitally signed by Hong Cai
Date: 4/27/2020 10:19:16AM
GUID: 55919d6500e16bdaad5825645e4f22ff

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 4/27/2020 10:35:44AM
GUID: 502d0913000029f9798ca689a802fa55

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 201110
MILPROSA (progesterone vaginal system)
Assessment #3

Drug Product Name	progesterone vaginal system
Dosage Form	vaginal system (formerly "vaginal ring")
Strength	Avg. 11 mg per day, for 7 days (1.78 g progesterone per system; (b)(4)% w/w)
Route of Administration	Vaginal
Rx/OTC Dispensed	Rx
Applicant	Ferring Pharmaceuticals
US agent, if applicable	-
Application Type	505(b)(2)
NDA Classification Code*	Type 3, New Dosage Form
Combination Product	Drug-device combination product (Type 2)

* Previously referred to as the "Chemistry Classification Code."

Submission(s) Assessed	Document Date	Discipline(s) Affected
		CDRH (biocompatibility)
Class 2 Resubmission (0047)	10/29/2019	Drug substance, drug product, labeling, and manufacturing; CDRH
Response to Info. Req. (0053)	02/25/2020	CDRH (mechanical testing)
Labeling (0055)	03/17/2020	Labeling
Response to Info. Req. (0056)	03/24/2020	CDRH (mechanical testing)
Labeling (0057)	04/02/2020	Labeling

Correspondence and meeting materials were submitted in the period between the 11/23/2016 CR Letter and the 10/29/2019 resubmission and were evaluated during that period. Included was the Biocompatibility Report, submitted 06/09/2017. See Section D, Regulatory History.

QUALITY ASSESSMENT TEAM

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

* Per Jennifer Patro, resubmission is NAI for Microbiology

** Per Okpo Eradiri, ONDP/DB Branch Chief, a Biopharmaceutics reviewer was not assigned this review cycle. Last reviewed by K. Paudel and Kelly Kitchens (November 1, 2016).

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

In its present form, Ferring Pharmaceutical's second Class 2 resubmission of 505(b)(2) New Drug Application 201110 for Milprosa (progesterone vaginal system), a drug-device combination product, is not ready for approval. Labeling (prescribing information and container/carton labels) negotiations have not been completed, and in its present form, the labeling does not comply with the requirements under 21 CFR 201.

CDRH-OPEQ has determined that the mechanical and biocompatibility properties of the finished product have now been adequately demonstrated. However, a final recommendation from CDRH-OPEQ on the adequacy of the 'device' quality management system and compliance with medical device GMPs is pending.

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

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

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

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

All issues identified in the previous Complete Response Letters have been adequately addressed.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Product Description:
Milprosa is a white to off-white, flexible, non-biodegradable, (b) (4) silicone vaginal system (formerly referred to as a vaginal ring) containing 1.78 g progesterone, with a cross-sectional diameter of (b) (4) mm and an outer diameter of 55 mm. The product releases an average of 11 mg/day progesterone, as determined by measuring residual drug in product after removal from the vagina. The vaginal system is to remain in place for 7 days after which it will be replaced with a new product.

This new dosage form of progesterone is intended to support embryo implantation as part of an Assisted Reproductive Technology (ART) treatment program for infertile women.

Background: See Section E, Regulatory History, below, for a partial timeline of application submissions, meetings, reviews and regulatory actions.

Teva Women's Health submitted NDA 201110 for their progesterone vaginal ring ten years ago on April 30, 2010. From the chemistry, manufacturing and controls (CMC) perspective, the application was deemed not adequate for approval, primarily because of manufacturing issues that were identified during a pre-approval inspection of the Teva Cincinnati, OH product manufacturing site. During the inspection product contaminated with foreign particulate matter was observed. A Complete Response Letter was issued on February 28, 2011.

While a root cause analysis of the foreign particulate matter contamination lead to improvements in manufacturing (b) (4) defects in the product were also identified. This was attributed to (b) (4) process was subsequently developed. See Section F, Batch History, below, for an overview of batches manufactured by the 'Legacy' and 'New' processes since 2009.

The NDA was resubmitted on February 25, 2016. It was subsequently determined that the progesterone vaginal ring was then to be considered a drug-device combination product under 21 CFR part 3. The NDA resubmission was therefore consulted to both CDRH-ODE and CDRH-OC. The Division of Reproductive, Gastro-renal and Urological Devices in CDRH's Office of Device Engineering determined that there were insufficient data to support the biocompatibility of the combination product, especially after the change in (b) (4) process, which could have impacted the extractables / leachables (i.e., impurities) profile of the finished product. A second Complete response Letter was issued on November 23, 2016.

Biocompatibility testing was performed in accordance with ISO 10993. After a determination that there were no biocompatibility safety signals, a clinical trial (SARA 000293) was conducted using product manufactured using the 'New' process (i.e., with the to-be-marketed product) to establish a 'clinical safety bridge'.

The October 29, 2019 resubmission includes documentation of the biocompatibility testing program as well as additional batch and stability data.

No changes have been made to the finished product formulation or manufacturing process since OPQ Quality Assessment #2, November 10, 2016, was completed.

Adequate drug release, mechanical performance and biocompatibility are critical to the safety and efficacy of Milprosa (progesterone vagina system). The control strategies incorporated in the manufacturing process, and in the finished product release and stability testing programs are adequate to mitigate risks to product performance.

Proposed Indication(s) including Intended Patient Population	MILPROSA is a progesterone vaginal system indicated to support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women.
Duration of Treatment	Each vaginal system is to remain in place for 7 days, after which the system is to be replaced with a new system, for up to a total of 10 weeks.
Maximum Daily Dose	Average release rate of 11 mg progesterone per day over 7 days. Each system contains 1.78 g progesterone.
Alternative Methods of Administration	Not applicable.

B. Quality Assessment Overview

Note: Please refer to Nina Ni's 2011 CMC Review #1 and to the November 10 and 23, 2016 OPQ Quality Assessment #2, and associated Addendum for detailed reviews of product CMC.

Drug Substance: Adequate

Progesterone drug substance CMC is documented in (b) (4) Type II DMF (b) (4) for progesterone. The DMF was most recently reviewed and found adequate on January 16, 2020. No drug substance information was provided in this NDA resubmission. See the attached Drug Substance review and the Drug Substance review in OPQ Quality Assessment #2, November 10, 2016, for additional notes on progesterone drug substance CMC.

Drug Product: Adequate

The October 29, 2019 resubmission includes batch analyses for the three batches of to-be-marketed product used in the clinical safety study SARA 000293 obtained at release and upon of the completion of the study. Stability data for the registration stability batches completed through 36 months.

Based on the totality of stability data submitted to the NDA, a 24-month expiration dating period is granted for product stored in the foil laminate pouch when stored at 20ºC to 25ºC (controlled room temperature).

No new drug product quality concerns have been identified. Please refer to the OPQ Quality Assessment #2 and the attached Drug Product review for details.

Environmental Assessment: Adequate

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

Labeling: Inadequate

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

Because deficiencies have been identified and labeling negotiations have not been completed, final labeling is not yet available. From the ONDP perspective this application is therefore deemed *NOT* ready for approval in its present form per 21 CFR 31.125(b)(6).

Manufacturing: Adequate

Process:
No significant changes to product manufacturing process since the application was last reviewed in 2016.

In this 2019 resubmission, new clinical data was submitted to support a process change that was reviewed in 2016. The manufacturing process was approvable in 2016 and no significant changes were made by the applicant. The manufacturing process remains ADEQUATE in this resubmission.

Facilities:
There are no changes to the facilities or their compliance status since the last review cycle. See attached Manufacturing Review (Facilities) for details. See also OPQ Quality Assessment #2, November 10, 2016.

Biopharmaceutics: Adequate

Adequate based on previous review. See the Biopharmaceutics review in OPQ Quality Assessment #2 dated November 10, 2016 for details.

Drug Release per USP <724>. The in vitro dissolution method uses USP Apparatus II (paddle) at 50 rpm, and 500 mL of 0.05 M sodium dodecyl sulfate (SDS). The acceptance criteria are: Day 1: 158-201 mg/day; Day 2: 67-83 mg/day; Day 7: 38-46 mg/day.

Microbiology (if applicable): Adequate

Adequate based on previous review. See the Microbiology review in OPQ Quality Assessment #2 dated November 10, 2016 for details.

CDRH-OPEQ: Pending

Engineering / Mechanical:
The 'device' specification includes: description, dimensions, and durometer (b) (4) As requested by CDRH, the Applicant has added tests for tensile strength, elongation at break, compression strength, and twisting during compression, to the mechanical testing protocol. Note that compression strength and twisting during compression are the most relevant of the parameters, as these forces will most commonly be encountered during the use of the vaginal system.

CDRH concludes that all mechanical testing provided in the application, as amended, is acceptable. All issues have been resolved and recommendations incorporated into the mechanical testing protocol. See Reginal Avery's March 27, 2020 review for details.

Biocompatibility:
As requested by CDRH during the previous review cycle, biocompatibility testing was performed in accordance with ISO 10993-1:2009, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process. Results were submitted in 2017 at which time they found acceptable. No changes to the finished product have been made since that time so the results remain valid. See Avery Reginald's review dated February 24, 2020 for details.

Quality System:
An assessment of the device quality management system by Klara Jenkins is pending.

C. Risk Assessment

From "Initial" Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
Appearance	• Process • Stability	Moderate	Process controls; Release testing	Adequate	
Dimensions	• Equipment • Process	Low		Adequate	
Mass	• Equipment • Process	Low	Material and process controls	Adequate	
Identification	• CGMPs	Low		Adequate	
Assay	• Raw materials • Formulation • Process parameters • Scale/equipment • Site	Moderate	Material and process controls; Assay	Adequate	
Related Substances Impurities/ Degradants	• Formulation • Process • Storage	Moderate	Material and process controls	Adequate	Avoid exposure to heat!
Biocompatibility	• Formulation • Raw materials • Process	Moderate	Material and process controls	Adequate	Any changes that could mpact biocompatibility should be consulted to CDRH-ODE
Mechanical Properties	• Raw materials • Process	Low	Material and process controls. Mechanical property testing protocol established	Adequate	Any changes that could mpact mechanical properties should be consulted to CDRH-ODE
Uniformity of Dosage Units	• API Properties • Formulation • Process • Scale/equipment • Site	Moderate	API particle size controls; Process controls	Adequate	Vaginal system contains (b) (4) % w/w progesterone (b) (4)
In Vitro Release	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	High	Established material and process controls; in vitro release test (days 1, 2 and 7) at release and on stability. Storage at 20ºC to 25ºC	Adequate	Controlled release of progesterone from the vaginal system is essential to product safety and efficacy. Impact of any changes on in vitro release must be evaluated. Avoid excessive heat (or freezing)
Microbial Limits	• Raw materials • Equipment and handling • Moisture content	Low	Environmental controls; Micro. testing Storage in foil laminate pouch at 20ºC to 25ºC	Adequate	Pouch seal integrity

*Risk ranking applies to product attribute/CQA
**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval,
etc.

Note 1. Factors such as (b) (4) process parameters (b) (4) may result in different extractable / leachable compounds in the final,

finished vaginal system which could impact its biocompatibility. A chemical analysis followed by toxicological risk assessment should be performed to demonstrate that new ring elutes leachable compounds of the same type and relative quantity as the old one. If differences are noted, additional biocompatibility testing may be necessary.

Note 2. Principles of SUPAC-MR may be applied judiciously. Currently there is limited product and process knowledge, so the potential impact of any post-approval changes especially on biocompatibility and in vitro release rate must be carefully assessed.

See James Norman's risk assessment included in OPQ Quality Assessment #2, November 11, 2016 (reproduced below for reader convenience) for detailed assessment of risk to critical quality attributes associated for each unit operation.

Excerpt from OPQ Quality Assessment #3, 11/10/2016

The following initial and updated risk assessments, and lifecycle management considerations were prepared by James Norman, Ph.D., Primary Process Reviewer (see review Chapter V: Process). They are repeated here as they thoroughly capture the risks associated with the manufacturing process and provide guidance for the review of any post-approval changes.

(b) (4)


(b) (4)

D. Regulatory History

Regulatory / Review History (Partial Listing)

Event	Date	Notes
IND 70875 (sdn 000)	10/06/2004	Original IND submitted by Duramed Research, Inc. (a subsidiary of Barr Pharmaceuticals)
New NDA 201110	04/30/2010	Original-1 (Type 3-New Dosage Form) Teva Women's Health Product Mfg.: Duramed, Cincinnati, OH Duramed and Barr are subsidiaries of Teva Pharmaceuticals
Chemistry Review #1 Nina Ni	02/07/2011	NDA "not recommended for approval" • Foreign particulate matter in site transfer batches… (see comments under Batch History below)
Complete Response #1	02/28/2011	Manufacturing issues cited
Product manufactured using 'New' process	06/30/2013	Changes previously had been implemented to prevent foreign particulate matter, however, other (b) (4) defects were noted in process validation and commercial launch batches manufactured by the 'Legacy' process. 'Legacy' process replaced by 'New' process (b) (4)
Transfer of Ownership (sn 0022)	08/25/2015	Ownership transferred from Teva to Ferring Note: Teva continues to manufacture product at Cincinnati, OH facility
Class 2 Resubmission #1	02/25/2016	Includes Teva final investigation report dated 09/05/2013
Advice	05/23/2016	Ferring formally advised that the product is a drug-device combination product under 21 CFR Part 3. Biocompatibility testing required along with additional mechanical testing.
Response to 05/23/2016 advice	06/27/2016	Ferring response to device information request (incomplete)
Amendment 07/27/2106 (further response to 05/23/2016 IR)	08/10/2016	Extension to 11/25/2016 due to Major Amendment
CDRH-ODE Review (M.Garcia)	11/04/2016	Deficiencies in biocompatibility testing noted
OPQ Quality Assessment #2	11/10/2016	New manufacturing process parameters identified. Impact on (b) (4) noted. Precludes direct link between phase 3 materials and TBM product. CDRH determines that lack of adequate biocompatibility testing precludes approval.
Addendum to Assessment #2	11/22/2016	• Labeling incomplete • Biocompatibility testing needed
Complete Response #2	11/23/2016	• Biocompatibility testing needed • Clinical study with TBM product needed
Type A End of Review Meeting	02/21/2017	
Biocompatibility Report submitted to IND 070875 / SN 0015	05/18/2017	
Biocompatibility Report to NDA 201110 (sn 0039)	06/09/2017	

CDRH Review (M. Garcia)	07/17/2017	
CDRH Biocompatibility Review (P.Potnis)	07/17/2017	
WRO	08/24/2017	CDRH agrees that biocompatibility issues have been addressed. Agency states that, “there is no biocompatibility safety signal that would impact the design of the proposed clinical safety study.”
Type C Meeting Package	10/23/2018	Does the Agency concur that the completed biocompatibility testing on the combination product is adequate for the NDA resubmission? (ref. to IND 070875 / SN 0015)
Written Response to Type C Mtg Request	12/06/2018	Agency agrees that the completed biocompatibility testing on the combination product is adequate to support resubmission of the application.
Class 2 Resubmission #2	10/29/2019	

E. Manufacturing Process and Batch History

Manufacturing Process and Batch History

Batch	Process	Mfg. Date	Expiry	Use
Resubmission 02/25/2016 (0024)				
900214	Legacy (Northvale, NJ)	08/28/2007		(b) (4)
800354	Legacy [a]	06/17/2009		
800356	Legacy [a]	07/14/2009		
800357	Legacy [a]	07/27/2009		
800358	Legacy [a]	08/17/2009		
800359	Legacy [a]	09/01/2009		
B2PO13181	Legacy	02/14/2012		
C2PO13183	Legacy	03/08/2012		
33803619	Legacy [c]	08/29/2012		
33803684	Legacy [c]	09/13/2012		
33803694	Legacy [c]	10/9/2012		
33804188	Legacy [c]	11/14/2012		
33804189	Legacy [c]	?		
33804190	Legacy [c]	?		
F3P013196A	New [d]	06/30/2013		
F3P013197A	New	7/10/2013		
G3P013198A	New	7/18/2013		
33805873	New	10/4/2013		
33805874	New	10/11/2013		
33805875	New	10/18/2013		
Resubmission 10/29/2019 (0047)				
33812534	New	01/12/2017	12/2018	
33814060	New	11/01/2017	10/2019	
33815243	New	05/21/2018	04/2020	

[a] Per Nina Ni's Chemistry Review #1, 02/07/2011, "During PAI inspection, foreign particulate contaminations were found for all 5 site transfer batches at intended commercial site. (b) (4) Based on the preliminary report, it seems to indicate that the drug product rings were not manufactured with adequate controls (b) (4). Investigations of the root cause for the contaminations have been conducted (b) (4) orrective measures have been proposed that foreign particulates will be controlled for (b) (4) finished drug product. The applicant will have to submit test results from three new registration batches (b) (4) "

[b] Manufacturing process transferred from Northvale, NJ to Cincinnati, Ohio.

[c] (b) (4) validation batches and in intended commercial batches.

[d] The "new" process incorporates an alternate operation (b) (4). The 'legacy' (b) (4) process has been replaced (b) (4).

F. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

na

2. Drug Substance Deficiencies

na

3. Drug Product Deficiencies

na

4. Labeling Deficiencies

See Labeling Review (currently under negotiation with Applicant)

5. Manufacturing Deficiencies

na

6. Biopharmaceutics Deficiencies

na

7. Microbiology Deficiencies

na

8. Other Deficiencies (Specify discipline, such as Environmental)

na

Application Technical Lead Name and Date:

Mark R. Seggel, Ph.D. April 13, 2020
CMC Lead (acting)

{see electronic signature page}

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	Progesterone	Adequate	Gaetan Ladouceur 01/16/2020	Amend. #118
	III		(b) (4)	N/A	-	-
	MAF			Adequate	*	See previous CMC and CDRH reviews

N/A: There is enough data in the application, therefore the DMF did not need to be reviewed during the current review cycle.

* See CMC reviewer Nina Ni's review of MAF (b) (4) dated 02/07/2011.

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document(s)	Application Number	Description
Original commercial IND, amendments, meeting packages and associated Agency reviews and communications.	IND 70875	progesterone vaginal ring

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	na			
Nonclinical	na			
CDRH OPEQ Device Review	Complete	Adequate for Biocompatibility and Mechanical Testing	02/24/2020 and 03/27/2020	Reginald Avery
CDRH OPEQ Quality System Review	*Pending*			Klara Jenkins
Clinical	na			
Other	na			

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Environmental Assessment (Not applicable)

CHAPTER IV: Labeling

CHAPTER V: Manufacturing (Process/Facilities)

CHAPTER VI: Biopharmaceutics (Not applicable)

CHAPTER VII: Microbiology (Not applicable)

CHAPTER VIII: Additional Quality Disciplines (Not applicable)

Mark Seggel

Digitally signed by Mark Seggel
Date: 4/13/2020 01:39:05PM
GUID: 507572b5000036176969356148025bae

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

Review of Prescribing Information (PI) is based on the resubmission #2 on October 29, 2019. This review precedes previous labeling review dated October 26, 2016 by Dr. Bavishy Mittal based on resubmission #1 on February 25, 2016. The CMC related information reviewed in PI (submitted on October 29, 2019, SN0047) are the following sections:

Highlights:

1. Product title
2. Dosage Forms and Strengths

Full Prescribing Information

Section 3: Dosage Forms And Strengths
Section 11: Description
Section 16: How Supplied/Storage And Handling
Manufacturing Information after Section 17

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MILPROSA safely and effectively. See full prescribing information for MILPROSA.

MILPROSA™ (progesterone) Vaginal Ring
Initial U.S. Approval: XXXX

INDICATIONS AND USAGE

MILPROSA is a progesterone [redacted] indicated to support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women. (1)

DOSAGE AND ADMINISTRATION

The dose of MILPROSA is one vaginal [redacted] inserted [redacted] the day after oocyte retrieval. [redacted] replaced weekly, continuing for up to 10 weeks total duration. [redacted] (2.1)

DOSAGE FORMS AND STRENGTHS

[redacted] progesterone releas [redacted] an average of 11 mg/day progesterone over a 7-day [redacted] (3)

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	**MILPROSA™**	**Satisfactory**
Established name(s)	(progesterone) [redacted]	**Not Satisfactory** Revise to "(progesterone) vaginal system"
Route(s) of administration	Vaginal	**Satisfactory**
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	[redacted] (3)	**Not Satisfactory** Include the dosage form: vaginal system. Revise to: Vaginal system: Each MILPROSA vaginal system contains 1.78 grams

		of progesterone and releases an average of 11 mg/day progesterone over 7-days.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	Not applicable	**Not Applicable**
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Not applicable	**Not Applicable**

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

2. DOSAGE AND ADMINISTRATION

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	See above	**Not Satisfactory** "(b) (4) should be replace by "vaginal system" Defer to the clinical team for further revision.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

3. DOSAGE FORMS AND STRENGTHS

(b) (4) a white to off-white, flexible, silicone vaginal ring (b) (4) a cross-sectional diameter of approximatel (b) (4) mm and an outer diameter of approximately 55 mm. (b) (4) eleases an average of 11 mg/day of progesterone over a 7-day period of use.

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	(b) (4)	**Not Satisfactory** The dosage form should be revised to "vaginal system".
Strength(s) in metric system	(b) (4) a white to off-white, flexible, silicone vaginal ring containing (b) (4) (b) (4) releases an average of 11 mg/day of progesterone over a 7-day period of use	**Satisfactory**
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Not Applicable	**Not Applicable**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	(b) (4) off-white, flexible, silicone vaginal ring (b) (4) a cross-sectional diameter of approximately (b) (4) mm and an outer diameter of approximately 55 mm.	**Not Satisfactory** Revise the following: 1. the amount of progesterone (b) (4) (b) (4) to 1.78g. 2. add the following identifying characteristics of the drug product: a. toroidal-shaped (ring), non-biodegradable b. the cross-sectional diameter from (b) (4) mm to 8.5 mm. c. add the inner diameter of 38 mm.

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not Applicable	**Not Applicable**
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Not Applicable	**Not applicable**

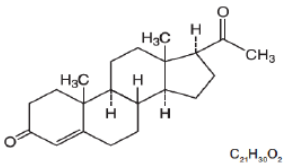
1.2.3 Section 11 (DESCRIPTION)

11. DESCRIPTION

(b) (4)

MILPROSA (b) (4) progesterone (b) (4) The chemical name for progesterone is pregn-4-ene-3,20-dione. It has an empirical formula of $C_{21}H_{30}O_2$ and a molecular weight of 314.5. (b) progesterone (b) (4) has a melting point of 126-131°C.

The structural formula is:

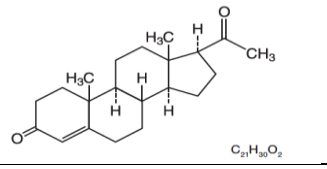


$C_{21}H_{30}O_2$

When placed in the vagina, each (b) (4) is estimated to provide an average release rate of 11 mg/day of progesterone over 7 days (b) (4) *(12.3)]*.

The inactive components in the (b) (4) are light mineral oil and silicone elastomer.

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Not provided	**Not satisfactory** Add the established name: "(progesterone) vaginal system"
Dosage form(s) and route(s) of administration	Not provided	**Not satisfactory** Add dosage form and route of administration: vaginal system.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Not applicable.	**Not Applicable** .
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	The inactive components in the (b) (4) are light mineral oil and silicone elastomer.	**Not Satisfactory** Revise (b) (4) to "vaginal system"
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Not Applicable	**Not Applicable**
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not Applicable	**Not Applicable**
Statement of being sterile (if applicable)	Not Applicable	**Not Applicable**
Pharmacological/ therapeutic class	(b) (4)	**Not Satisfactory** (b) (4)

Chemical name, structural formula, molecular weight	The chemical name for progesterone is pregn-4-ene-3,20-dione. It has an empirical formula of $C_{21}H_{30}O_2$ and a molecular weight of 314.5. The structural formula is: 	**Satisfactory**
If radioactive, statement of important nuclear characteristics.	Not Applicable	**Not Applicable**
Other important chemical or physical properties (such as pKa or pH)	(b) (4) progesterone (b) (4) (b) (4) has a melting point of 126-131°C.	**Not Satisfactory** Revise "(b) (4) progesterone (b) (4) (b) (4) has a melting point of 126-131°C." to "The progesterone has a melting point of 126-131°C." Remove (b) (4) from the statement.

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	Not Applicable	**Not Applicable**
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	(b) (4)	**Not Satisfactory** This statement sounds promotional and is not needed.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

16. HOW SUPPLIED/STORAGE AND HANDLING

Each MILPROSA is a white to off-white flexible silicone vaginal ring. Each MILPROSA is packed individually in a sealed foil pouch. These pouches are available in cartons packed:

- 2 vaginal (b) (4) (NDC 55566-9400-1)

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Not provided	**Not Satisfactory** Include the dosage form: "vaginal system"
Strength(s) in metric system	Not provided	**Not Satisfactory** Include the daily release rate: "releases an average of 11 mg/day of progesterone over a 7-day period of use"
Available units (e.g., bottles of 100 tablets)	2 vaginal (b) (4)	**Not Satisfactory** Revise to "2 vaginal systems per carton"
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Each MILPROSA is a white to off-white, flexible, silicone vaginal ring.	**Not Satisfactory** 1. Add the strength of releasing an average of 11 mg/day of progesterone over a 7-day period of use. 2. Add the characteristics and dimensions of MILPROSA. See the comments in Section of Dosage Forms and Strengths (Section 3).
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not Applicable	**Not Applicable**
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Not Applicable	**Not Applicable**

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Not Provided	**Not Satisfactory** 1. Add the following: "Do not refrigerate or freeze and avoid excessive heat. 2. Add the following disposal instruction per EA reviewer James Laurenson (Appendix I): "After use, place in pouch and discard via a drug take-back option if available; otherwise, discard in waste receptacle out of reach of children and pets. DO NOT flush down toilet. See www.fda.gov/drugdisposal for more information."
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	Not Applicable	**Not Applicable**
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].	**Satisfactory**
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	Not Applicable	**Not Applicable**
Include information about child-resistant packaging	Not Applicable	**Not Applicable**

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients (b) (4) Please notify the prescription drug division if the product contains any of these inactive ingredients.

Reviewer comments: There is no above-mentioned inactive ingredients in this drug product.

1.2.6 Manufacturing Information After Section 17 (for drug products)

MANUFACTURED FOR:
Ferring Pharmaceuticals Inc.
Parsippany, NJ 07054 USA

FERRING
PHARMACEUTICALS

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	MANUFACTURED FOR: Ferring Pharmaceuticals Inc. Parsippany, NJ 07054 USA FERRING PHARMACEUTICALS	**Not Satisfactory** Add the street address of the business per 21 CFR201.1.

2.0 PATIENT LABELING

Review is based on the PPI and IFU submitted on October 29, 2019 (SN0047). Only disposal instruction for the used drug product is commented. Per the request from Dr. James Laurenson in EA team, the instruction for proper disposal of MILPROSA after use should be included in the (b) (4)

(b) (4) Information for Use (IFU). Details see Appendix I and the related comments in “List of Deficiencies”.

3.0 CARTON AND CONTAINER LABELING

Review of Carton and Container labeling is based on the resubmission #2 dated October 29, 2019. This review precedes previous labeling review dated October 26, 2016 by Dr. Bavishy Mittal based on resubmission #1 dated February 25, 2016.

The content reviewed is based on the Carton and Container labeling submitted on March 17, 2020 (SN0055).

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

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Milprosa™ (progesterone) Vaginal (b) (4)	**Not Satisfactory** Dosage from should be revised to "vaginal system"
Dosage strength	Releases 11 mg per day	**Satisfactory**
Route of administration	For vaginal use only	**Satisfactory**
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not applicable	Not applicable
Net contents (e.g. tablet count)	Pouch: (b) (4) CONTAINS 2 VAGINAL RINGS	**Not Satisfactory** (b) (4) 2. Revise to the following: "Contains 2 vaginal systems with each individually packed in a pouch."

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

ITEMS FOR ADDITIONAL ASSESSMENT

LIST OF DEFICIECIES*:*

A. Prescribing information

The Highlights Section:

1. The dosage form should be revised [redacted] (b) (4) to "vaginal system" in the entire PI.
2. Revise the product title to "MILPROSA™ (progesterone) vaginal system"
3. Dosage Forms and Strengths in Highlights: Add the dosage form "vaginal system".

Full Prescribing Information Section:

1. Dosage Forms and Strengths (Section 3):

i. Replace the dosage [redacted] (b) (4) to vaginal system;

ii. Revise the following:

1. the amount of progesterone [redacted] (b) (4) to 1.78g.
2. add the following identifying characteristics of the drug product:
   a. toroidal-shaped (ring), non-biodegradable
   b. the cross-sectional diameter [redacted] (b) (4) to 8.5 mm.
   c. add the inner diameter of 38 mm.
   d. Revise [redacted] (b) (4) to 8.5 mm for the cross-sectional diameter to be consistent with the claim in the NDA.

2. Description (Section #11):

i. Add the drug product established name with the dosage from "progesterone vaginal system"

ii. Add the following description of the identifying characteristic of the dosage forms: “toroidal-shaped (ring)”, “non-biodegradable”;

iii. Revise the amount of progesterone (b) (4) to 1.78 grams;

iv. Add the description of the (b) (4): MILPROSA has a cross-sectional diameter of approximately 8.5 mm, and an outer and inner diameter of approximately 55 mm and 38 mm, respectively.

v. Remove the potential promotional statement (b) (4)

vi. (b) (4)

3. How Supplied/Storage And Handling (Section 16):

i. Add the drug product established name with the dosage from “progesterone vaginal system”;

ii. Add the strength of the drug product: releases an average of 11 mg/day of progesterone over a 7-day period when placed in vagina.

iii. Add the additional description of the identifying characteristic of MILPROSA: Refer to the relevant comments in Description (Section 11).

iv. Revise the content per carton statement (b) (4) to “2 vaginal systems per carton”.

v. Add the following statement in addition to the storage condition: “Do not refrigerate or freeze and avoid excessive heat.”

vi. Add the following disposal instruction: “After use, place in pouch and discard via a drug take-back option if available; otherwise, discard (b) (4) of children and pets. DO NOT flush down toilet. See www.fda.gov/drugdisposal for more information.”

vii. Provide the street address of the business in the manufacturing information after Section 17.

Patient Labeling:

I. Add the following disposal instruction statement in the Patient Information and Instructions for Use.

For IFU:

Under the following the step below:

For Step 1: Revise the disposal instruction [redacted] to "(see "To remove" below for disposal guidance)."

Revise Step [redacted]

to the following:

"Place the [redacted] *foil pouch* [redacted] *throw it away in your household trash out of the reach of children and pets. Do not flush* [redacted] *down the toilet. See www.fda.gov/drugdisposal for more information."*

For PPI:

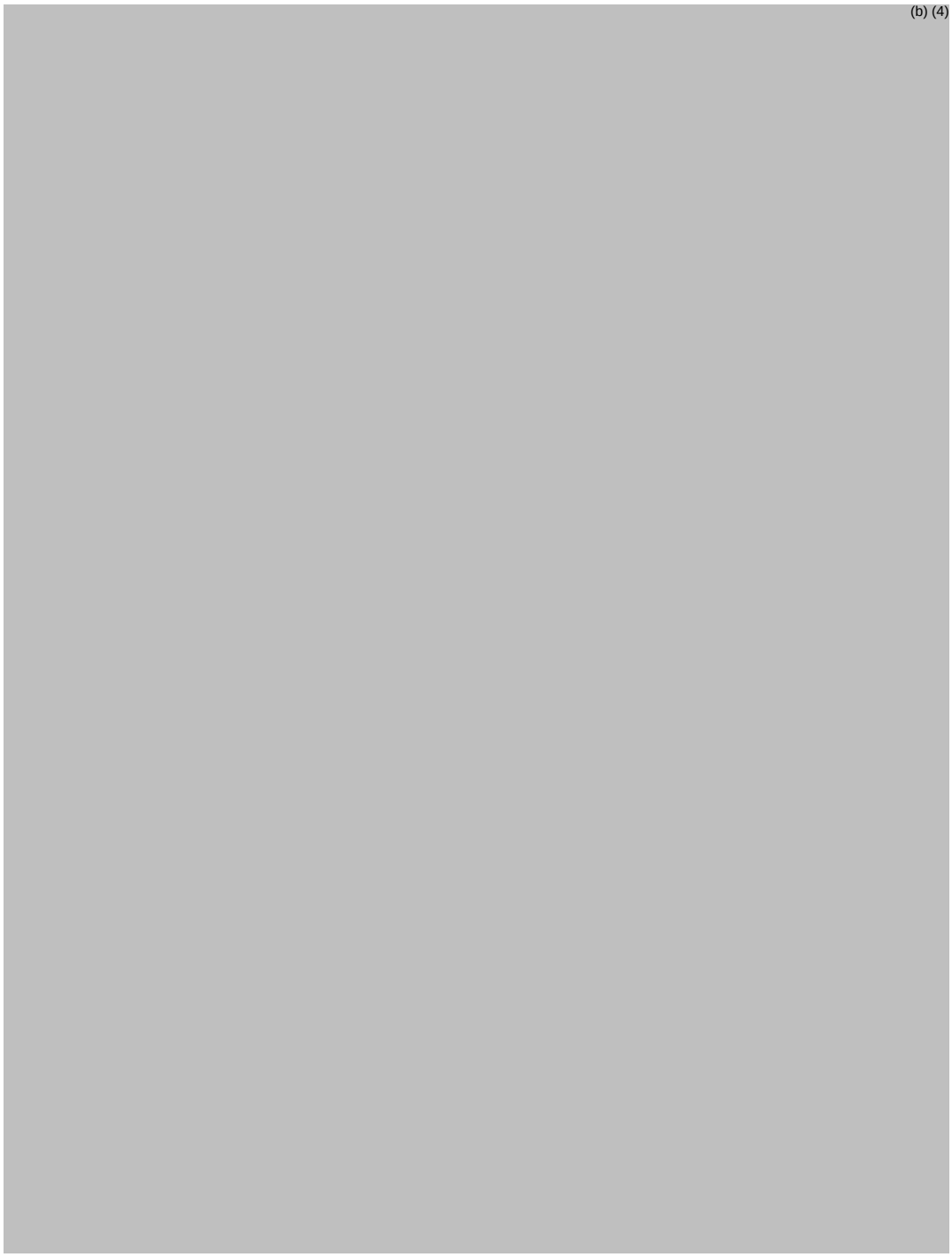
[redacted]

Container Labels and Carton Labeling:

1. The dosage form of MILPROSA is "vaginal system". Therefore, the product title presentations should be as follow:

MILPROSA

(b) (4)



Overall Assessment and Recommendation:

This CMC labeling review is based on the information provided in the Prescribing Information (PI) submitted on October 29, 2019 (SN0047) and the proposed labels for the carton and container on March 17, 2020 (SN0055), respectively. Per 21 CFR Part 201 as well as the FDA Labeling Review Tool (October 2018 version), deficiencies are noted as delineated in the above "**List of Deficiencies**". Therefore, from the ONDP perspective, this application is ***not*** deemed ready for approval in its

present form per 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Hong Cai, Ph.D.
Drug product Reviewer
Branch IV/DNDP II/ONDP/OPQ
April 2, 2020

Secondary Assessor Name and Date (and Secondary Summary, as needed):

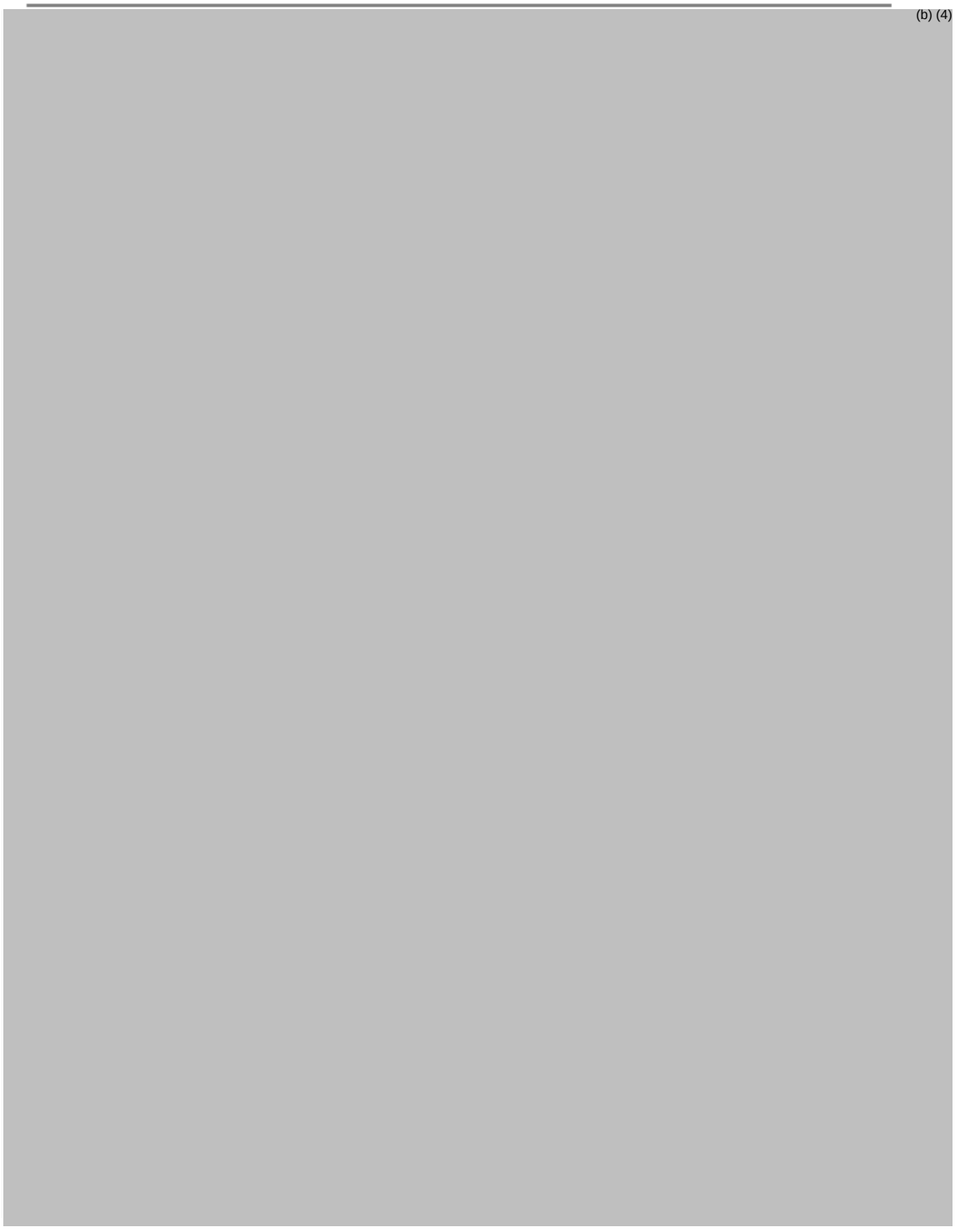
I agree with Dr. Cai's assessment on the labeling and labels, and therefore, I concur with her recommendation that this application is not ready for approval in its present form until the deficiencies delineated in the **List of Deficiencies** are satisfactorily resolved.

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
DNDPII/ONDP/OPQ
April 2, 2020

Appendix I:

From: Laurenson, James
To: Cai, Hong
Cc: Seggel, Mark R
Subject: RE: NDA 201110 Disposal Instruction on Labeling
Date: Wednesday, March 25, 2020 1:05:09 PM

(b) (4)



(b) (4)

Thanks.
Hong

Hong Cai

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Moo Jhong Rhee

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Date: 4/02/2020 03:26:36PM
GUID: 502d0913000029f9798ca689a802fa55

Product Quality Microbiology Review

07 FEB 2011

NDA: 201-110

Drug Product Name
Proprietary: Milprosa (proposed)
Non-proprietary: Progesterone

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
30 APR 2010	30 APR 2010	24 AUG 2010	30 AUG 2010
31 JAN 2011	31 JAN 2011	N/A	N/A

Applicant/Sponsor
Name: Teva Women's Health Inc.
Address: 425 Privet Rd
Horsham, PA 19044
Representative: Jennifer Norman
Telephone: 215-293-7227

Name of Reviewer: Jessica G. Cole, Ph.D.

Conclusion: Approvable pending resolution of product quality microbiology deficiencies.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original 505(b)(1) NDA.

2. SUBMISSION PROVIDES FOR: New drug product.

3. MANUFACTURING SITE: Duramed Pharmaceuticals, Inc.
5040 Duramed Road
Cincinnati, Ohio 45213

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Vaginal ring
- Release rate of 11 mg/day
- 7 day ring placement

5. METHOD(S) OF STERILIZATION: Non-sterile.

6. PHARMACOLOGICAL CATEGORY: Hormone for support of embryo implantation.

B. SUPPORTING/RELATED DOCUMENTS: None.

C. REMARKS: During the pre-approval inspection, (b) (4) particles were found in the stability batches. These particles (b) (4) the NDA will not be recommended for approval at this time due to GMP violations.

The following information request was sent to the ONDQA project manager on 21 September 2010.

Microbiology Comment:

Please provide the following information or a reference to its location in the subject submission.

1. We suggest that microbial enumeration for the drug product be performed according to the USP 32-NF 27 General Chapter <61> guidelines for testing transdermal patches. All results should be recorded as CFU/ring and not as CFU/g. Alternately, provide a justification for deviations from this method.
2. The process validation studies presented in ARD_RPT-2950 do not support your drug product testing method. Organisms should be inoculated directly onto the ring to show that the test method is capable of detecting the presence of microorganisms on the vaginal ring. These studies should reflect any changes made in response to comment #1.
3. Establish microbial limits (in CFU/ring) compliant with the recommendations in the USP 32 –NF 27 General Chapter <1111> for vaginal products or provide a rationale for any deviations from these recommendations.
4. Provide a justification for not following the current USP <62> recommendations on the test method for the absence of (b) (4).
5. Provide the results from the re-testing of site transfer and stability samples with the new validated microbial enumeration methods.

A follow-up call to the sponsor occurred on 22 December 2010 and on this call the sponsor was asked to provide a timeline for submission of the above information. The

sponsor committed to submit everything except the re-test (request #5) by the end of January 2011. The results from the re-testing of samples will be submitted by the end of the first quarter 2011.

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Executive Summary

I. Recommendations

A. Recommendation on Approvability – Not currently recommended for approval on the basis of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – Not applicable.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – This is a non-sterile vaginal ring (b) (4). The ring is non-biodegradable.

B. Brief Description of Microbiology Deficiencies – The specification was altered to remove the absence of (b) (4) in the 31 January 2011 amendment.

C. Assessment of Risk Due to Microbiology Deficiencies – There is a low risk of microbial infection as (b) (4) is not part of the normal vaginal microbial flora.

III. Administrative

A. Reviewer's Signature _____
Jessica G. Cole, Ph.D.

B. Endorsement Block _____
Stephen Langille, Ph.D.
Senior Microbiology Reviewer

C. CC Block
N/A

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

/s/

JESSICA COLE
02/08/2011

STEPHEN E LANGILLE
02/08/2011

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 201-110	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DRUP		
Sponsor:	Teva Women's Health Research Inc. (TWH)	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	Mirproa	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Progesterone Vaginal Ring	**Date Assigned:**	May 14, 2010
Indication:	To support embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an ART treatment program for infertile women.	**Date of Review:**	December 19, 2010
Formulation	Vaginal Ring		
Route of Administration	Vaginal		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA Date
April 30, 2010 Aug 13, 2010	May 4, 2010	May 14, 2010	Jan 2011
Type of Submission:	Original NDA		
Type of Consult:	Dissolution method and drug release specifications		

REVIEW SUMMARY:

Mirproa (Progesterone Vaginal Ring) has been developed by Teva Women's Health Division to support the embryo implantation by progesterone supplementation delivered by a weekly progesterone-releasing silicone vaginal ring in conjunction with Assisted Reproductive Technology (ART) treatment in early pregnancy for infertile women. Progesterone Vaginal Ring is a non-biodegradable, flexible silicone ring containing progesterone as the active ingredient. The Progesterone Vaginal Ring consists of a mixture of (b) (4) light mineral oil and Progesterone, USP (b) (4) The active ingredient is present in (b) (4) % w/w concentration dispersed evenly within the ring. Each Progesterone Vaginal Ring contains approximately 1.8 grams of USP grade progesterone.

In support of this NDA the sponsor included the results of a total of seven studies, four phase 1 BA/BE studies, including a BE study linking the clinical and to-be-marketed formulation, and three phase 2/3 PD/clinical studies. The bioequivalence study will be reviewed by OCP.

The sponsor's proposed dissolution method and drug release specifications for progesterone vaginal ring are as follows:

Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Sampling times	Specifications
Vaginal ring	II (Paddle)	50	0.05 M SDS	500	Days 1,2 and 7	**Day 1:** (b) (4) **Day 2:** **Day 7:** Meets USP <724> L1, L2 or L3 criteria as

						appropriate

The proposed dissolution method is acceptable. However, it is noted that the sponsor set the release specifications based on 3 batches only, namely Batch # 900214 (Phase 3 clinical study batch) and batches # 800357 and 800358 (site transfer batches) and did not consider all the 5 site transfer batches put under stability testing. In addition, it is noted that the drug release pattern overtime for site transfer batch number 800358 is different from that observed for all the other batches. In fact, some of the mean values fall outside the mean (b) (4) variation.

This reviewer considered all the site transfer batches and the clinical batch produced for setting the drug release specifications instead of just 3 batches as the sponsor did. The drug release specifications were initially set based on the mean drug release (at release and up to 6 months stability testing) of all the batches (b) (4) variation as follows:

Specifications
Day 1: 158-(b) (4) mg/day **Day 2:** 67-83 mg/day **Day 7:** 38-46mg/day Meets USP <724> L1, L2 or L3 criteria as appropriate

The lower bound of drug release means for batch number 800358 was not considered for setting the range of proposed specifications because this is the only batch out of the 5 transfer batches that presents a different release profile. In addition, there is no clinical data testing the efficacy of rings with a low bound of drug release as that observed for this batch.

The following comments were conveyed to the sponsor on Jan 10, 2011:

1. The proposed drug release method is acceptable. However, The following drug release specifications and time points are recommended for Progesterone Vaginal Ring (b) (4)% :

Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Sampling times	Specifications
Vaginal ring	II (Paddle)	50	0.05 M SDS	500	Days 1,2 and 7	**Day 1:** 158- (b) (4) mg/day **Day 2:** 67 – 83 mg/day **Day 7:** 38 – 46 mg/day Meets USP <724> L1, L2 or L3 criteria as appropriate

a) The setting of the recommended specification-ranges is based on the mean drug release

(b) (4) variation. Data from all site transfer batches (800354, 800356, 800357, 800358, and 800359) and the clinical trial batch (900214) were used for the setting of these ranges. Note that the lower bound of mean drug release for batch 800358 was not included in the setting of these ranges, because from out of the 5 transfer batches, this was the only batch that presented a very different release profile. Also, there is no clinical data supporting the efficacy of rings with a lower bound of drug release similar to the one observed for this batch.

b) Please revise the drug release specifications and testing times accordingly and submit and updated sheet of specifications.

In an email communication received on Jan 21, 2011, the sponsor stated that the proposed Agency's specifications (b) (4) and appear skewed to the lower end of the range. The sponsor requested additional clarification.

The following release rate specifications were agreed upon in a telecom dated Feb 04, 2011:

Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Sampling times	Specifications
Vaginal ring	II (Paddle)	50	0.05 M SDS	500	Days 1,2 and 7	**Day 1:** 158- 201 mg/day **Day 2:** 67 – 83 mg/day **Day 7:** 38 – 46 mg/day Meets USP <724> L1, L2 or L3 criteria as appropriate

The upper limit for the Day 1 release rate specification was agreed upon to be +12.5% (the maximum allowed by the IVIVC guidance). This upper bound is acceptable because this higher release rate on Day 1 will be of minimal clinical consequence. The sponsor committed to submit a revised drug release specifications sheet reflecting these proposed changes.

RECOMMENDATION:

The ONDQA/biopharmaceutics team has reviewed NDA 201-110 submitted on April 30, 2010 and Aug 13, 2010. The NDA is acceptable from the Biopharmaceutics perspective. The sponsor agreed with the Agency's proposed release rate specifications as follows:

Dosage	USP	Speed	Medium	Volume	Sampling	Specifications

Vaginal ring	II (Paddle)	50	0.05 M SDS	500	Days 1,2 and 7	**Day 1:** 158- 201 mg/day **Day 2:** 67 – 83 mg/day **Day 7:** 38 – 46 mg/day Meets USP <724> L1, L2 or L3 criteria as appropriate

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
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Background

Drug Product

Progesterone Vaginal Ring is a non-biodegradable, white to off white, flexible silicone ring containing Progesterone as the active ingredient. The Progesterone Vaginal Ring consists of a mixture of (b) (4) light mineral oil and Progesterone, USP (b) (4).

The active ingredient is present in (b) (4)% w/w concentration dispersed evenly within the ring. Each Progesterone Vaginal ring contains approximately 1.8 grams of USP grade progesterone.

The unit formula is presented in Table 1. The Progesterone Vaginal Ring dimensions are outlined below in Table 2. A schematic of the Progesterone Vaginal Ring is shown below in Figure 1.

Table 1: Composition of Progesterone Vaginal Ring

Ingredient	**Composition Per Ring**	
	Weight, g	Percentage, w/w
Progesterone, USP (b) (4)	1.7800	(b) (4)
Light Mineral Oil (b) (4)	(b) (4)	
Total per Ring	8.9000	

Table 2: Dimensions of Progesterone Vaginal Ring

Attribute	**Dimension (mm)**
Outer Diameter	55.0 (b) (4)
Inner Diameter	38.0 (b) (4)
Cross Sectional Diameter	8.5 (b) (4)

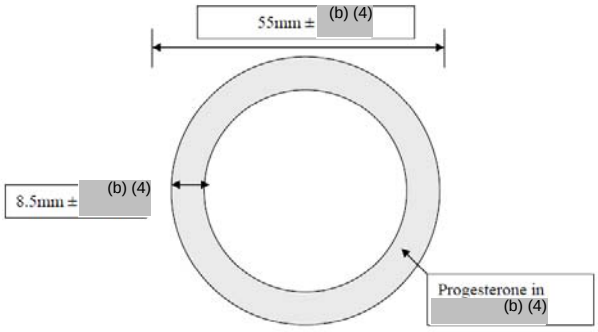

Figure 1: Schematic Representation of the Progesterone Vaginal Ring

The Phase 2 and 3 clinical batches were manufactured in Barr's R&D facilities in Plainsboro and Northvale, respectively. The site transfer batches, one of which was used in a bioequivalence study, were manufactured in Barr's proposed commercial manufacturing site in Cincinnati, Ohio. A summary of the Phase 3 and site transfer batches is provided in Table 3.

Table 3. Summary of Progesterone Vaginal Ring Phase 3 and Site Transfer Batches Used in Stability Studies

Batch Numbers	900214	800354	800356	800357	800358	800359
Batch Size (rings)	(b) (4)					
Phase of Development	Phase 3 Clinical	Submission	Submission	Submission Bioequivalence Study	Submission	Submission
Site of Manufacture	Northvale, NJ	Cincinnati, Ohio	Cincinnati, Ohio	Cincinnati, Ohio	Cincinnati, Ohio	Cincinnati, Ohio
Date of Manufacture	08/28/2007	06/17/2009	07/14/2009	07/27/2009	08/17/2009	09/01/2009
Container Closure Description	Pouch - Code 08-4033	Pouch - Code 08-4033	Pouch - Code 08-4033	Pouch - Code 08-4033	Pouch - Code 08-4033	Pouch - Code 08-4033

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(b) (4)

d) Please revise the drug release specifications and testing times accordingly and submit and updated sheet of specifications.

In an email communication received on Jan 21, 2011, the sponsor stated that the proposed Agency's specifications (b) (4) (b) (4). The sponsor added that the specifications originally proposed to the Agency included data available at the time of NDA submission and they are currently gathering additional data from our ongoing stability studies in order to determine whether the data supports an adjustment to the specifications. The sponsor committed to conduct the following analysis and report the findings in a timely manner:

1. TWH will assemble all the available data from release and long term stability for the PGN Vaginal Rings and analyze it.
2. TWH will provide the Agency with all results used to tabulate our findings.
3. TWH will propose new acceptance criteria for Days 1, 2, and 7 for PGN Vaginal Ring.

The following release rate specifications were agreed upon on a telecom dated Feb 04, 2011:

Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Sampling times	Specifications
Vaginal ring	II (Paddle)	50	0.05 M SDS	500	Days 1,2 and 7	**Day 1:** 158- 201 mg/day **Day 2:** 67 – 83 mg/day **Day 7:** 38 – 46 mg/day Meets USP <724> L1, L2 or L3 criteria as appropriate

The sponsor committed to submit a revised the drug release specifications sheet reflecting these changes.

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

/s/

SANDRA SUAREZ
02/04/2011

PATRICK J MARROUM
02/04/2011