

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208564Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: *Approval*

NDA 208564

Review # 2

IMVEXXY (estradiol vaginal inserts)

Drug Name/Dosage Form	Estradiol Vaginal Insert
Strength	4 mcg and 10 mcg (b) (4)
Route of Administration	Vaginal
Rx/OTC Dispensed	Rx
Applicant	TherapeuticsMD (TXMD)
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission Following Complete Response (0034)	11/29/17	Team
Amendment (0035)	01/12/18	Stability Update / Team
Amendment (0037)	04/26/18	Labeling
Amendment (0039)	05/18/18	Labeling

SUBMISSION(S) PREVIOUSLY REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original (0001)	07/07/16	Multi-discipline
Response (0004)	09/23/16	Biopharmaceutics
Response (0008)	12/20/16	Drug Product; Biopharmaceutics;
Information (0009)	12/27/16	Drug Product
Response (0011)	01/19/17	Multi-discipline
Response (0014)	02/23/17	Biopharmaceutics
Response (0017)	02/08/17	Multi-discipline
Response (0018)	03/22/17	Drug Product; Biopharmaceutics

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Martin Haber	BII / DNDAPI / ONDP
Drug Product	Hamid Shafiei	BV / DNDPII / ONDP
Labeling	Hamid Shafiei	BV / DNDPII / ONDP
Process	Jingbo Xiao	BVIII / DPAPIII / OPF
Microbiology	Stephen Langille	BI / DMA / OPF
Facility	Vidya Pai	BIII / DIA / OPF
Biopharmaceutics	An-chi Lu	BII / DB / ONDP
RBPM	Thao M. Vu	BI / DRBPM I / OPRO
Application Technical Lead	Mark Seggel	BV / DNDPII / ONDP
Laboratory (OTR)	Laura Pogue	DPA / OTR
Environmental Analysis (EA)	Hamid Shafiei	BV / DNDPII / ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	Adequate	12/16/16; 02/28/18	
	II		Adequate	03/09/17; 03/23/17	Reviews cover formulation and process	
	IV		N/A	-		
	III		N/A	-		
	III		N/A	-	Used for clinical materials; will not be used for commercial product	
	III		N/A	-		
	III		N/A	-		
	III		N/A	-		

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

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND submissions and associated reviews	IND 118439	TXMD IND for estradiol vaginal inserts

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	na			
Pharmacology/Toxicology	na			
CDRH	na			
Clinical	na			
Other	na			

na: not applicable

Executive Summary

I. Recommendations and Conclusion on Approvability

TherapeuticsMD's 505(b)(2) New Drug Application #208564, for Estradiol Vaginal Inserts, 4 mcg and 10 mcg per vaginal insert, as resubmitted in response to the May 5, 2017 Complete Response Letter, is recommended for APPROVAL from the OPQ perspective.

Agreement has been reached on the final labeling (package insert, container/carton) (see Information Request dated May 18, 2018 and labeling submitted on the same date). The labeling now complies with the requirements under 21 CFR 201.

Sufficient 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. The commercial drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status. The claimed categorical exclusion from the environmental assessment requirements is granted.

Because there is a USP drug product monograph for Estradiol Vaginal Inserts, 10 mcg and 25 mcg per insert, there is an expectation that the TherapeuticsMD (TXMD) product will meet the compendial monograph requirements. However, because the TXMD product is a soft gelatin capsule formulation that is quite distinct from the tablet formulation (i.e., Vagifem) upon which the USP monograph is based, and because a new, lower strength (4 mcg) is proposed, the USP monograph is not a suitable public standard for TherapeuticsMD's new drug product. TherapeuticsMD has been advised to petition the USP with proposed revisions to the monograph in order to accommodate TXMD's new drug product.

POST-MARKETING COMMITMENTS

In response to Additional Comments provided in the May 5, 2017 Complete Response Letter and to discussions with the OPQ review team on September 19, 2017, TherapeuticsMD post-marketing commitments (PMC) (per email correspondence dated January 23, 2018; see Attachment IV). Further clarification of the PMCs was provided during a teleconference with the applicant on April 25, 2018. These PMCs are acceptable from the OPQ perspective.

1. Develop and validate a new regulatory method capable of detecting known and unknown estradiol-related impurities in the drug product (see Attachment V).
2. Perform a revalidation of the dissolution method TxMD-003 in accordance with requirements of USP using one batch of each strength of the for-market formulations manufactured by the proposed commercial manufacturer (see attachment VI).

II. Summary of Quality Assessments

A. Product Overview

TherapeuticsMD’s new drug product, estradiol vaginal inserts, consists of estradiol, an estrogen, (b) (4) and encapsulated in a soft gelatin capsule for vaginal administration. The manually administered soft gelatin capsule formulation provides an easy to use alternative to the Vagifem estradiol vaginal insert, a tablet formulation administered with a plastic applicator.

The TherapeuticsMD (TXMD) product may offer other advantages over topical estradiol and Vagifem (and generic equivalents). TXMD suggests that, “the expected advantages of the formulation are: (1) immediate release of estradiol from the softgel capsule should enhance local delivery in the vagina and (2) the estradiol (b) (4) should increase the estradiol permeation through the vaginal wall and thus improve local action with minimal systemic estrogen absorption.” Note that these potential advantages have not been evaluated in any comparative studies.

Two strengths, 10 mcg and 25 mcg, of Vagifem estradiol vaginal inserts were approved, although only the former is currently being marketed. TXMD originally proposed marketing 4 mcg, 10 mcg (b) (4) the 4 mcg and 10 mcg products.

Proposed Indication(s) including Intended Patient Population	Estradiol vaginal insert is indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.
Duration of Treatment	One (b) (4) inserted (b) (4) daily for (b) (4) twice weekly (b) (4)
Maximum Daily Dose	10 mcg
Alternative Methods of Administration	(b) (4) vaginal inserts should be administered intravaginally only.

B. Quality Assessment Overview

See OPQ IQA #1.

Drug Substance:

(b) (4)

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/s/

MARK R SEGCEL
05/03/2018

HAMID R SHAFIEI
05/03/2018

MOO JHONG RHEE
05/04/2018
Chief, Branch V

ERIC P DUFFY
05/14/2018

MEMORANDUM

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

DATE: May 7, 2018

FROM: **Hamid R. Shafiei, Ph.D.**
Review Chemist (Branch V/DNDP II/ONDP)

Moo-Jhong Rhee, Ph.D.
Branch Chief (Branch V/DNDP II/ONDP)

TO: **Package Insert (PI), Immediate Container,
and Carton Labeling/Label review # 1 for NDA 208564**

SUBJECT: **Final ONDP Recommendation from the Labeling/Label Review
Perspective**

In the review #1 of NDA 208564, the application was not recommended for approval in the form it was presented due to the CMC deficiencies noted in PI labeling as well as immediate container (blister) and carton labels.

The CMC labeling-label deficiencies identified during the review # 1 of NDA 208564 were conveyed to the applicant (see the **Attachment**) on May 5, 2017 with the CR letter (clinical perspective). Therefore, the CMC labeling-label deficiencies were not addressed during the first review cycle.

On April 26, 2018, the application was resubmitted with the revised PI labeling and the revised container and carton labels to address deficiencies conveyed in the CR letter. (b) (4)

. The revised PI labeling as well as the revised immediate container and carton labels are presented below with brief evaluations:

A. PI

a) Highlight Section

IMVEXXY™ (estradiol vaginal inserts)
Initial U.S. Approval: 1975

DOSAGE FORMS AND STRENGTHS
IMVEXXY (b) (4) inserts contain 4 mcg or 10 mcg (b) (4) estradiol. (3)

Evaluation: It was agreed by the applicant and the Agency to use the USP established name for this drug product. Therefore, (estradiol vaginal inserts) has been used as the established name for this drug product throughout PI labeling as well as on the container and carton labels. It was also agreed to change the drug product physical description from (b) (4) " to (b) (4) " in the PI labeling and packaging labels.

Conclusion: The **Highlight Section** of the PI is now considered **satisfactory**.

b) Full Prescribing Information

#3: Dosage Forms and Strengths

IMVEXXY are small, light pink, tear shaped (b) (4) inserts for manual placement (b) (4) into the vagina. IMVEXXY inserts contain 4 mcg or 10 mcg of (b) (4) estradiol. Each insert is imprinted in white ink on one side with "04" or "10" corresponding to the insert's dosage strength.

Evaluation: Since the (b) (4) in section 11 of the PI, the (b) (4) is no longer needed.

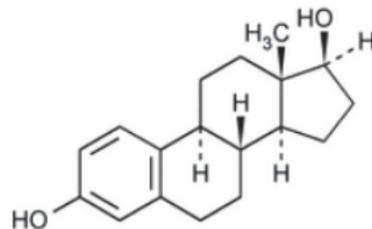
Conclusion: The revised **Dosage Form and Strengths** section of the **Full Prescribing Information** of the PI are now considered **satisfactory**.

#11: Description

IMVEXXY (estradiol vaginal inserts) are small, light pink, tear-shaped, (b) (4) (b) (4) inserts for manual placement (b) (4) into the vagina. Inserts contain 4 mcg or 10 mcg of (b) (4) estradiol, (b) (4) an estrogen. Each insert is imprinted in white ink on one side with "04" or "10" corresponding to the insert's dosage strength. IMVEXXY vaginal inserts are used intravaginally. When the (b) (4) insert comes in contact with the vaginal mucosa, (b) (4) estradiol is released into the vagina.

Estradiol is chemically described as estra-1,3,5 (10)-triene-3,17 β -diol. The chemical formula is C₁₈H₂₄O₂ with a molecular weight of 272.38.

The structural formula is:



IMVEXXY (estradiol vaginal inserts) contain the following inactive ingredients: Medium chain triglycerides, polyethylene glycol stearates, ethylene glycol palmitostearate, gelatin, hydrolyzed gelatin, sorbitol-sorbitan solution, purified water, glycerin, FD&C Red #40, ethanol, ethyl acetate, propylene glycol, titanium dioxide, polyvinyl acetate phthalate, isopropyl alcohol, polyethylene glycol, and ammonium hydroxide, and lecithin. FDA approved acceptance criteria for assay, organic impurities, and dissolution tolerances differ from the USP test.

Evaluation: Since the (b) (4) (b) (4) is no longer needed. Estradiol vaginal inserts has been agreed as the established name for this drug product based on the current USP monograph.

Conclusion: The revised **Description** section of the **Full Prescribing Information** of the PI is now considered **satisfactory**.

#16: How Supplied/Storage and Handling

16.1 How Supplied

IMVEXXY (estradiol vaginal inserts) are small, light pink, tear-shaped, (b) (4) (b) (4) inserts for manual placement (b) (4) into the vagina. Inserts contain 4 mcg or 10 mcg of (b) (4) estradiol. Each insert is imprinted in white ink on one side with “04” or “10” corresponding to the insert’s dosage strengths.

IMVEXXY (estradiol vaginal inserts), 4 mcg and 10 mcg, are provided in opaque push-through blisters and are packaged in cartons containing either 18 inserts for the starter pack or 8 inserts for the maintenance pack.

IMVEXXY 4 mcg	8 inserts	NDC 50261-104-08
IMVEXXY 4 mcg	18 inserts	NDC 50261-104-18
IMVEXXY 10 mcg	8 inserts	NDC 50261-110-08
IMVEXXY 10 mcg	18 inserts	NDC 50261-110-18

Keep out of reach of children. Packages are not child-resistant.

16.2 Storage and Handling

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.]

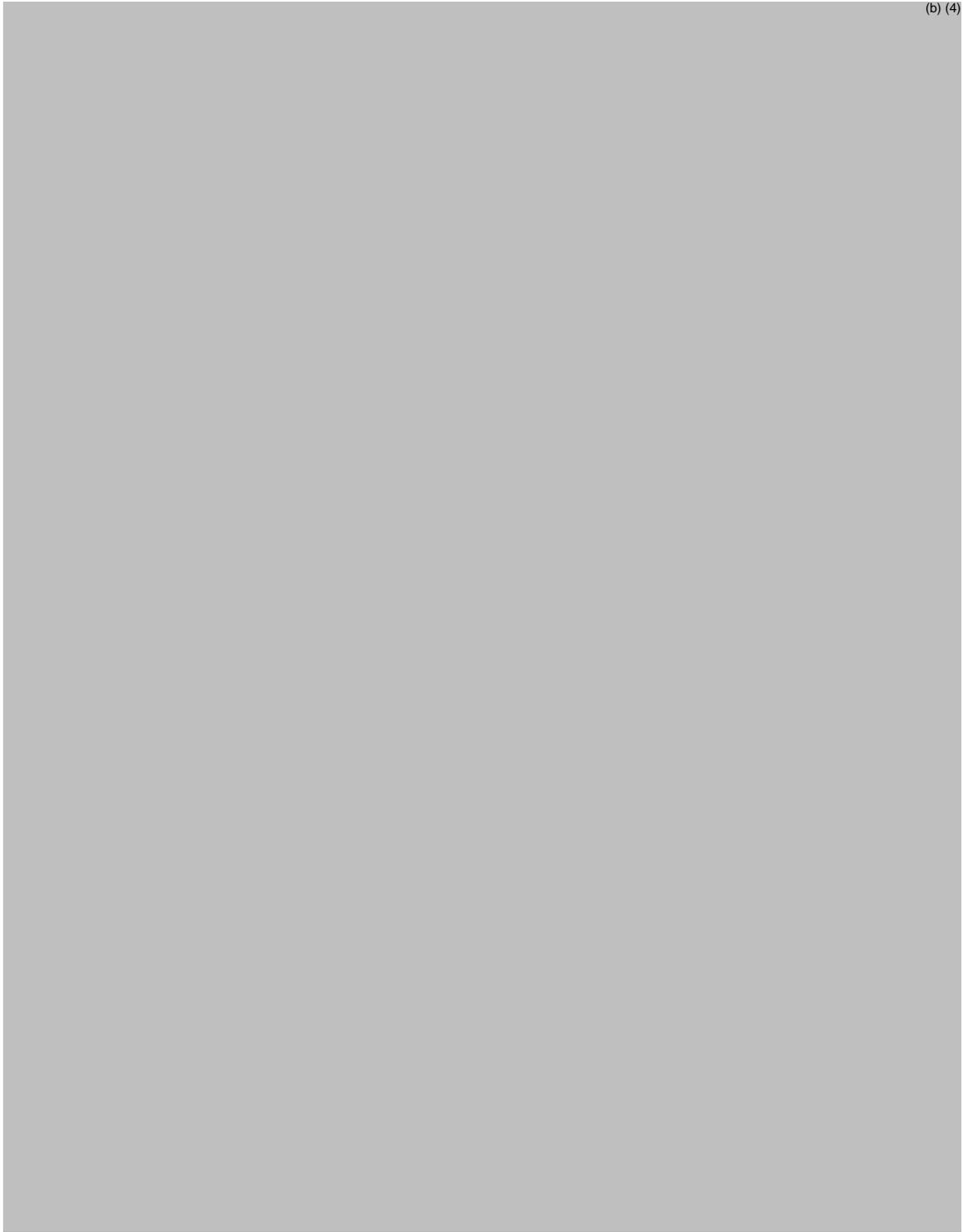
Evaluation: Since the [REDACTED] (b) (4) [REDACTED] is no longer needed. Estradiol vaginal inserts has been agreed as the established name for this drug product based on the current USP monograph.

*Conclusion: The revised **How Supplied/storage** and **Handling** section of the **Full Prescribing Information** of the PI is now considered **satisfactory**.*

B. Container/Carton Labels:

a. Immediate container labels: Blisters:

APPEARS THIS WAY ON
ORIGINAL



Evaluation: The proprietary name, established name (as agreed), dosage strengths, net content, Rx, NDC numbers, bar code, lot number, expiration date, storage conditions, and the manufacturer/distributor name have been appropriately added to the blister labels for both 4mcg and 10mcg strength. (b) (4)

Conclusion: *The revised blister labels are now considered adequate.*

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

Evaluation: The proprietary name and established name (as agreed) are properly presented on the carton labels. (b) (4) have been replaced by (b) (4) on the carton labels. (b) (4)

(b) (4)

***Conclusion:** The revised blister labels are now considered adequate.*

Recommendation: This application now considered ready for **approval** from the PI, immediate container, and carton labeling-label perspective.

Attachment: The deficiencies previously noted in the Review #1 and conveyed to the applicant via the CR letter on May 5, 2017

A. Regarding PI

a) Highlight Section

- 1) The title should be revised to "Tradename (estradiol) Vaginal Inserts"
- 2) The dosage forms and strengths should be revised to "Tradename (estradiol) Vaginal Inserts (b) (4)

b) Full Prescribing Information

#3: Dosage Forms and Strengths

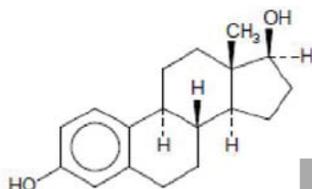
This section should be revised as suggested below:

Dosage Form and Strength should be revised to "Tradename are small, light pink, tear shaped (b) (4) for manual (b) (4) into the vagina. Tradename inserts contain (b) (4) 4mcg, 10mcg, (b) (4) estradiol, (b) (4) Each insert is imprinted in white ink on one side with "04", "10" (b) (4) corresponding to the insert's dosage strength.

#11: Description

This section should be revised as suggested below:

Tradename (estradiol) Vaginal Inserts are small, light pink, tear-shaped, (b) (4) for manual (b) (4) into vagina. Inserts contain (b) (4) 4mcg, 10mcg, (b) (4) of estradiol (b) (4) an estrogen. Each insert is imprinted in white ink on one side with "04", "10" (b) (4) corresponding to the insert's dosage strength. (b) (4) (b) (4) the chemical formula (b) (4) $C_{18}H_{24}O_2$ (b) (4) molecular weight of (b) (4), (b) (4)



(b) (4)

Tradename vaginal inserts contain (b) (4)
(b) (4)
ingredient (b) (4) medium chain triglycerides,
polyethylene glycol stearates, ethylene glycol palmitostearate, gelatin,
hydrolyzed gelatin, sorbitol-sorbitan solution, water, glycerin, titanium
dioxide, FD&C Red #40, ethanol, ethyl acetate, propylene glycol, polyvinyl
acetate phthalate, isopropyl alcohol, polyethylene glycol, and ammonium
hydroxide (b) (4) (b) (4)
lecithin (b) (4)

#16: How Supplied/Storage and Handling

This section should be revised as suggested below:

Tradename (estradiol) Vaginal Inserts are small, light pink, tear-shaped,
(b) (4) for manual (b) (4) into vagina. Inserts contain (b) (4)
(b) (4) 4mcg,
10mcg, (b) (4) of estradiol. Each insert is imprinted in white ink on (b) (4)
side with (b) (4) 04, 10, (b) (4)
YUVVEXY vaginal inserts are provided in opaque push-through blisters and
are packaged in cartons containing either 18 inserts for the starter pack or 8
inserts for maintenance pack.

Tradename 4 mcg	8 inserts	NDC 50261	(b) (4)
Tradename 4 mcg	18 inserts	NDC 50261	
Tradename 10 mcg	8 inserts	NDC 50261	
Tradename 10 mcg	18 inserts	NDC 50261	

Keep out of reach of children.

Storage and Handling:

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.]

B. Regarding the Container/Carton Labels:

a) **Immediate container labels: Blisters:**

Add the following information to the blisters:

- 1) Proprietary name and established name: Tradename (estradiol) Vaginal Inserts
- 2) Dosage strength: 4mcg, 10mcg, (b) (4)
- 3) Not content: 18 inserts or 8 inserts
- 4) Rx
- 5) Corresponding NDC numbers
- 6) Corresponding bar codes to 18-insert blisters

- 7) Lot number and expiration date
- 8) Storage conditions
- 9) Name of manufacturer/distributor

b) Carton labels:

4mcg strength carton:

- 1) Revise the drug product proprietary and established name to “Tradename (estradiol) Vaginal Inserts.
- 2) Replace the (b) (4) to vaginal inserts throughout the label
- 3) Revise the content to “each (b) (4) insert contains (b) (4) (b) (4) 4 mcg estradiol (b) (4)

10mcg strength carton:

- 1) Revise the drug product proprietary and established name to “Tradename (estradiol) Vaginal Inserts.
- 2) Replace the (b) (4) to vaginal inserts throughout label
- 3) Revise the content to “each (b) (4) insert contains (b) (4) (b) (4) 10 mcg estradiol (b) (4)

(b) (4)





Hamid
Shafiei

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Moo Jhong
Rhee

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MICROBIOLOGY

16 February 2018

Product Background**NDA:** 208564**Drug Product Name / Strength:** Estradiol Vaginal (b) (4) Capsules, 4, 10 (b) (4)**Route of Administration:** Vaginal**Applicant Name:** TherapeuticsMD, Inc.**Manufacturing Site:** Catalent Pharma Solutions, LLC
2725 Scherer Drive North
St. Petersburg, FL**Method of Sterilization:** Non-sterile drug product**Review Summary:** Recommended for Approval**List Submissions Being Reviewed** 7 July 2016, 29 November 2017**Highlight Key Outstanding Issues from Last Cycle:** The drug product is a non-sterile (b) (4) capsule for vaginal administration. The drug product has a microbial release specification consistent with compendial recommendations and is tested regularly on stability for microbiological quality. The original NDA was submitted to the agency on 7 July 2017. A complete Response letter was provided to the applicant on 5 May 2017. The NDA resubmission was sent to the agency on 29 November 2017. There is only one minor change to the microbiology information submitted in the resubmission.**Concise Description Outstanding Issues Remaining:** No deficiencies were identified based upon the information provided.**Supporting/Related Documents:** Not applicable**Remarks Section:** The application was provided in eCTD format.**S Drug Substance**

The drug substance is not sterile and thus will not be covered as part of the product quality microbiology review. Section 4.3.4 of the 29 September 2017 NDA resubmission states that the drug substance specification has been updated with a footnote stating that (b) (4)

(b) (4)

Reviewer's Assessment: Adequate

The applicant's proposed change to the drug substance specification is satisfactory since each lot of drug product is subjected to microbial enumeration testing at release.

P.1 Description of the Composition of the Drug Product

- Description of drug product –
Estradiol (b) (4) gelatin capsules contain 4, 10, (b) (4) of estradiol. Each capsule is formulated as a (b) (4) fill then encapsulated.
- Drug product composition –
The composition of the 4, 10, (b) (4) (b) (4) capsules is provided in tables 1-3 respectively of section 3.2.P.1. Because the only difference between the (b) (4) (b) (4) is the amount of estradiol in each capsule, only the 4 ug capsule composition is provided in this section.

Ingredient	Quality Standard	Manufacturer	Function	mg/Capsule	% w/w ^a
Softgel Fill Material					
(b) (4) estradiol (b) (4)					(b) (4)
(b) (4) (medium chain triglycerides)					
(b) (4) PEG					
stearate ethylene glycol palmitostearate and PEG (b) (4) stearate					
<i>Total Fill Material</i>					(b) (4)
Softgel Shell Material					
Gelatin, (b) (4)					(b) (4)
Hydrolyzed Gelatin					
(b) (4)					
(Sorbitol sorbitan solution)					
Glycerin (b) (4)					
Purified Water (b) (4)					
ethanol, ethyl acetate, propylene glycol, titanium dioxide, polyvinyl acetate phthalate, purified water, isopropyl alcohol, polyethylene glycol ammonium hydroxide)					
Ethanol (b) (4)					
medium chain triglycerides)					
<i>Total Shell Material</i>					(b) (4)
Total					(b) (4)

- Description of container closure system – The (b) (4) capsules will be packaged in (b) (4) 8-count, or 18-count blister strips.

Reviewer’s Assessment: Adequate

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain microbiological quality of the product.

P.2.5 Microbiological Attributes

Not applicable

P.3 Manufacture

P.3.1 Manufacturers

Catalent Pharma Solutions, LLC
 2725 Scherer Drive North
 St. Petersburg, Florida (FL) 33716-1016
 United States (USA)

P. 3.3 Description of the Manufacturing Process and Process Controls

Not applicable

P. 3.5 Process Validation and/or Evaluation

Not applicable

P.5 Control of Drug Product

P. 5.1 Specification

The drug product specification for microbial limits was provided in table 1 of section 3.2.P.5 of the application and has been reproduced in the table below:

Microbial limits			
Total Aerobic Plate Count		(b) (4)	USP <61> <62>
Total Yeast/Mold			
<i>Pseudomonas aeruginosa</i>			
<i>Candida albicans</i>			
<i>Staphylococcus aureus</i>			

The microbial limits specification is consistent with the limits provided in USP <1111> for vaginal use products.

P.5.2 Analytical Procedures

The use of USP chapter <61> and <62> methodology is appropriate for this product.

P.5.3 Validation of Analytical Procedures

Microbial enumeration testing verification is covered in report OET-10275407 provided in section 3.2.P.5.3 of the application. Verification testing was conducted according to USP <61> and <62>. The results of USP <62> verification testing were provided in table 2 located on p. 5 of report OET-10275407. The results of USP <61> verification testing (conducted in triplicate) were provided in table 3 located on pp. 6-7 of report OET-10275407.

Reviewer's Assessment: Adequate

The applicant confirmed that the compendial verification test was conducted according to USP <61/62> methodology and provided satisfactory results of verification testing.

P.7 Container Closure

See section P.1 of this review.

P.8 Stability

The stability protocol was provided in section 3.2.P.8.1 of the application. Microbial limits testing will be conducted on product stored at 25°C/60% humidity at time 0 and 6, 12, 24, and 36 months. This test protocol deviates slightly from that proposed in ICH Q1a but given that this is a relatively low risk product, this stability test schedule is acceptable. Intermediate stability conditions consist of a storage temperature of 30°C/60% humidity (test intervals of time 0, 6 months, and 12 months). Accelerated stability lots will be held at 40°C/75% RH and tested at time 0, 3 and 6 months. The applicant proposes an expiry of 24 months for commercial batches. The results of stability studies were provided in section 3.2.P.8.3 of the application and found to be satisfactory.

Reviewer's Assessment: Adequate

The applicant provided a satisfactory summary of the stability program and stability results.

A Appendices

Not applicable

R Regional Information

Not applicable

List of Deficiencies:

No product quality microbiology deficiencies were identified based upon the information provided.

Primary Microbiology Reviewer Name and Date: 16 February 2018

Stephen E. Langille, Ph.D. – Acting Branch Chief – Branch 3, DMA

Secondary Reviewer Name and Date (and Secondary Summary, as needed): 16 February 2018

John Metcalfe – Acting Quality Assessment Lead – Branch 3, DMA



Stephen
Langille

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John
Metcalf

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Date: 2/26/2018 03:00:59PM

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Comments: I concur.



Mark
Seggel

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Recommendation: *As of this review, this 505(b)(2) NDA is Not Ready for Approval in its present form per 21 CFR 314.125(b)(8).*

**NDA 208564
Review # 1**

Drug Name/Dosage Form	Estradiol Vaginal Insert
Strength	4 mcg, 10 mcg (b) (4)
Route of Administration	Vaginal
Rx/OTC Dispensed	Rx
Applicant	TherapeuticsMD (TXMD)
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original (0001)	07/07/16	Multi-discipline
Response (0004)	09/23/16	Biopharmaceutics
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	IV		N/A	-		
	III		N/A	-		
	III		N/A	-	Used for clinical materials; will not be used for commercial product	
	III		N/A	-		
	III		N/A	-		
	III		N/A	-		

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

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND submissions and associated reviews	IND 118439	TXMD IND for estradiol vaginal inserts

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	na			
Pharmacology/Toxicology	na			
CDRH	na			
Clinical	na			
Other	na			

na: not applicable

Executive Summary

I. Recommendations and Conclusion on Approvability

In its present form, TherapeuticsMD's 505(b)(2) New Drug Application #208564, for Estradiol Vaginal Inserts, 4 mcg, 10 mcg, and (b)(4) per vaginal insert, is not ready for approval. Labeling (package insert, container/carton) negotiations have not been completed, and in its present form, the labeling does not comply with the requirements under 21 CFR 201. For labeling deficiencies, see Attachment II (p.11). *Note: Labeling deficiencies and comments will not be conveyed to the applicant during the current review cycle.*

Although numerous deficiencies were noted during a recent inspection of the manufacturer (b)(4) of the phase 3 clinical trials materials, the totality of information indicates that those materials were of suitable quality for investigational use. The quality of the investigational product is consistent with the commercial product manufactured by Catalent.

Sufficient 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. The commercial drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status. The claimed categorical exclusion from the environmental assessment requirements is granted.

Because there is a USP drug product monograph for Estradiol Vaginal Inserts, 10 mcg and 25 mcg per insert, there is an expectation that the TherapeuticsMD (TXMD) product will meet the compendial monograph requirements. However, because the TXMD product is a soft gelatin capsule formulation that is quite distinct from the tablet formulation (i.e., Vagifem) upon which the USP monograph is based, and because a new, lower strength (4 mcg) is proposed, the USP monograph is not a suitable public standard for TherapeuticsMD's new drug product. TherapeuticsMD, should therefore petition the USP with proposed revisions to the monograph in order to accommodate TXMD's new drug product.

COMMENTS FOR ACTION LETTER:

We remind you that the current USP includes a monograph for Estradiol Vaginal Inserts. We understand that the current USP monograph may not be a suitable public standard for your new drug product. However, there is an expectation that your product will conform to the compendial monograph requirements. Alternatively, deviations from the monograph requirements should be identified on your product labels. We recommend that you petition the USP with proposed revisions to the monograph in order to accommodate your new drug product. Please see the following link for more information about that USP process: <http://www.usp.org/usp-nf/pending-monographs>.

Specifically, we note differences in assay test method and acceptance criteria, the dissolution test method and acceptance criteria, and in the procedure for determining related substances.

The proposed analysis of estradiol related compounds and degradation impurities by HPLC-MS may be acceptable for quality control purposes in the firm’s laboratory but is currently unacceptable for regulatory purposes because the method does not work with a similar mass spectrometer in two different locations. It is therefore incumbent upon you to propose methods that are suitable for regulatory purposes.

With regard to the dissolution test method, we recommend that you perform dissolution method validation in accordance with US<1092>, *The Dissolution Procedure: Development and Validation*, and adopt appropriate acceptance criteria.

II. Summary of Quality Assessments

A. Product Overview

TherapeuticsMD’s new drug product, estradiol vaginal inserts, consists of estradiol, a naturally occurring estrogen, (b) (4) and encapsulated in a soft gelatin capsule for vaginal administration. The manually administered soft gelatin capsule formulation provides an easy to use alternative to the Vagifem estradiol vaginal insert, a tablet formulation administered with a plastic applicator.

The TherapeuticsMD (TXMD) product may offer other advantages over topical estradiol and Vagifem (and generic equivalents). TXMD suggests that, “the expected advantages of the formulation are: (1) immediate release of estradiol from the (b) (4) capsule should enhance local delivery in the vagina and (2) the estradiol (b) (4) should increase the estradiol permeation through the vaginal wall and thus improve local action with minimal systemic estrogen absorption.”

Two strengths, 10 mcg and 25 mcg, of Vagifem estradiol vaginal inserts were approved, although only the former is currently being marketed. TXMD proposes marketing 4 mcg, 10 mcg (b) (4) strengths.

Proposed Indication(s) including Intended Patient Population	Estradiol vaginal insert is indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.
Duration of Treatment	One (b) (4) inserted (b) (4) daily for (b) (4) twice weekly (b) (4)
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	(b) (4) vaginal inserts should be administered intravaginally only.

ATTACHMENT II: List of Deficiencies for Complete Response

A. Drug Substance Deficiencies

Not applicable.

B. Drug Product Deficiencies

Not applicable.

C. Environmental Analysis Deficiencies

Not applicable.

D. Labeling Deficiencies

A. Regarding PI

a) Highlight Section

- 1) The title should be revised to "Tradename (estradiol) Vaginal Inserts"
- 2) The dosage forms and strengths should be revised to "Tradename (estradiol) Vaginal Inserts" (b) (4)

b) Full Prescribing Information

#3: Dosage Forms and Strengths

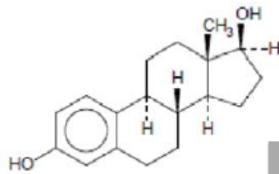
This section should be revised as suggested below:

Dosage Form and Strength should be revised to "Tradename are small, light pink, tear shaped, (b) (4) manual (b) (4) into the vagina. Tradename inserts contain (b) (4) 4mcg, 10mcg (b) (4) (b) (4) estradiol (b) (4) Each insert is imprinted in white ink on one side with "04", "10" (b) (4) corresponding to the insert's dosage strength." (b) (4)

#11: Description

This section should be revised as suggested below:

Tradename (estradiol) Vaginal Inserts are small, light pink, tear-shaped, (b) (4) for manual (b) (4) into vagina. Inserts contain (b) (4) 4mcg, 10mcg, (b) (4) of estradiol (b) (4), an estrogen. Each insert is imprinted in white ink on one side with "04", "10" (b) (4) corresponding to the insert's dosage strength. (b) (4) (b) (4) estro1,3,5 (10)-triene-3,17 β -diol (b) (4) the chemical formula (b) (4) 18H24O2 (b) (4) molecular weight of (b) (4) (b) (4) presented below: (b) (4)



Tradename vaginal inserts contain (b) (4) ingredient (b) (4) medium chain triglycerides, polyethylene glycol stearates, ethylene glycol palmitostearate, gelatin, hydrolyzed gelatin, sorbitol-sorbitan solution, water, glycerin, titanium dioxide, FD&C Red #40, ethanol, ethyl acetate, propylene glycol, polyvinyl acetate phthalate, isopropyl alcohol, polyethylene glycol, and ammonium hydroxide (b) (4) lecithin (b) (4) (b) (4).

#16: How Supplied/Storage and Handling

This section should be revised as suggested below:

Tradename (estradiol) Vaginal Inserts are small, light pink, tear-shaped, (b) (4) for manual (b) (4) into vagina. Inserts contain (b) (4) 4mcg, 10mcg. (b) (4) of estradiol. Each insert is imprinted in white ink on (b) (4) side with (b) (4) (04, 10, (b) (4)).

Tradename (estradiol) vaginal inserts are provided in opaque push-through blisters and are packaged in cartons containing either 18 inserts for the starter pack or 8 inserts for maintenance pack.

Tradename 4 mcg 8 inserts NDC 50261- (b) (4)
 Tradename 4 mcg 18 inserts NDC 50261 (b) (4)
 Tradename 10 mcg 8 inserts NDC 50261
 Tradename 10 mcg 18 inserts NDC 50261- (b) (4)
 (b) (4)

Keep out of reach of children.

Storage and Handling:

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.]

B. Regarding of the Container/Carton Labels:

a) Immediate container labels: Blisters:

Add the following information to the blisters:

- 1) Proprietary name and established name: Tradename (estradiol) Vaginal Inserts
- 2) Dosage strength: 4mcg, 10mcg (b) (4)
- 3) Not content: 18 inserts or 8 inserts
- 4) Rx
- 5) Corresponding NDC numbers
- 6) Corresponding bar codes to 18-insert blisters
- 7) Lot number and expiration date
- 8) Storage conditions
- 9) Name of manufacturer/distributor

b) Carton labels:**4mcg strength carton:**

- 1) Revise the drug product proprietary and established name to "Tradename (estradiol) Vaginal Inserts.
- 2) Replace the (b) (4) to vaginal inserts throughout the label
- 3) Revise the content to "each (b) (4) insert contains (b) (4) 4 mcg estradio (b) (4)
- 10mcg strength carton:
- 4) Revise the drug product proprietary and established name to "Tradename (estradiol) Vaginal Inserts.
- 5) Replace the (b) (4) to vaginal inserts throughout label
- 6) Revise the content to "each (b) (4) insert contains (b) (4) 10 mcg estradiol (b) (4)

(b) (4)

E. Process Deficiencies

Not applicable.

F. Facilities Deficiencies

Not applicable

G. Biopharmaceutics Deficiencies

Not applicable

H. Microbiology Deficiencies

Not applicable.

#####



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Seggel

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LABELING

R. Regional Information

1.14 Labeling

I. Package Insert

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

1) Title

(b) (4) (estradiol (b) (4) VAGINAL (b) (4)
Initial U.S. Approval (b) (4)

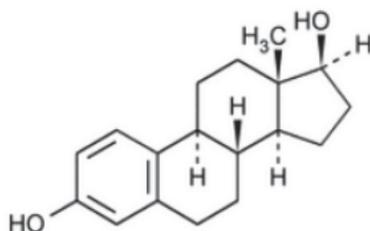
2) DOSAGE FORMS AND STRENGTHS

(b) (4) vaginal (b) (4) contain 4 mcg, 10 mcg (b) (4)
(b) (4) estradiol.

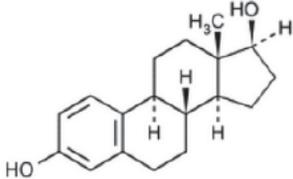
Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	(b) (4) (estradiol) (b) (4)	The use of the trade name (b) (4) for this drug product has already been declined but it has been placed appropriately. Established name, (estradiol) (b) (4), should be revised to (estradiol) vaginal inserts. Unsatisfactory
Dosage form, route of administration	(b) (4) VAGINAL (b) (4)	The accepted dosage form is "vaginal inserts" Unsatisfactory
Controlled drug substance symbol (if applicable)		N/A
Dosage Forms and Strengths (201.57(a)(8))	(b) (4) vaginal (b) (4) contain 4 mcg, 10 mcg, (b) (4) estradiol. (3)	This should be revised to, (b) (4) vaginal inserts (b) (4) (b) (4) 4mcg, 10mcg, (b) (4) (b) (4) " Unsatisfactory
Whether the drug product is scored	.Not applicable	Not applicable

Each (b) (4) (b) (4) capsule contains the following excipients: medium chain triglycerides, polyethylene glycol stearates, ethylene glycol palmitostearate, gelatin, hydrolyzed gelatin, sorbitol-sorbitan solution, water, glycerin, titanium dioxide, FD&C Red #40, ethanol, ethyl acetate, propylene glycol, polyvinyl acetate phthalate, isopropyl alcohol, polyethylene glycol, and ammonium hydroxide. (b) (4) lecithin (b) (4). (b) (4) the vaginal mucosa, (b) (4) estradiol is released into the vagina. (b) (4) (b) (4) estra-1,3,5 (10)-triene-3,17β-diol. The chemical formula is C₁₈H₂₄O₂ with a molecular weight of 272.38.

The structural formula is:



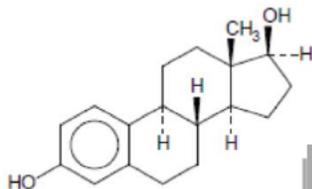
Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	(b) (4)	(b) (4) should be revised to "Tradename (estradiol) vaginal insert". The use of trade name (b) (4) for this drug product has already been declined. Unsatisfactory
Dosage form and route of administration	Vaginal (b) (4) (b) (4)	Should be revised to vaginal inserts Unsatisfactory
Active moiety expression of strength with equivalence statement (if applicable)	Not provided	Unsatisfactory
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	medium chain triglycerides, polyethylene glycol stearates, ethylene glycol palmitostearate, gelatin, hydrolyzed gelatin, sorbitol-sorbitan solution, water, glycerin, titanium dioxide, FD&C Red #40, ethanol, ethyl acetate, propylene glycol, polyvinyl acetate phthalate, isopropyl alcohol, polyethylene glycol, and ammonium hydroxide. (b) (4) lecithin (b) (4)	Provided. Satisfactory
Statement of being sterile (if applicable)	Not applicable	Not applicable
Pharmacological/ therapeutic	Not provided	

class		Unsatisfactory
Chemical name, structural formula, molecular weight	<p>5</p> <p>(b) (4)</p> <p>chemically described as <i>estra-1,3,5 (10)-triene-3,17β-diol</i>. The chemical formula is $C_{18}H_{24}O_2$ with a molecular weight of 272.38.</p> <p>The structural formula is:</p> 	<p>Provided</p> <p>(b) (4)</p>
If radioactive, statement of important nuclear characteristics.	Not applicable	Unsatisfactory Not applicable
Other important chemical or physical properties (such as pKa or pH)	Estradiol is (b) (4)	Provided Satisfactory

This section should be revised as suggested below:

Tradename (estradiol) Vaginal Inserts are small, light pink, tear-shaped. (b) (4) for manual (b) (4) into vagina. Inserts contain (b) (4) 4mcg, 10mcg, (b) (4) of estradiol. (b) (4) (b) (4), an estrogen. Each insert is imprinted in white ink on one side with "04", "10", (b) (4) corresponding to the insert's dosage strength. (b) (4)

(b) (4) *estra-1,3,5 (10)-triene-3,17β-diol* (b) (4) the chemical formula (b) (4) $C_{18}H_{24}O_2$ (b) (4) molecular weight (b) (4)



(b) (4)

Tradename vaginal inserts contain the following inactive ingredients: Medium chain triglycerides, polyethylene glycol stearates, ethylene glycol palmitostearate, gelatin, hydrolyzed gelatin, sorbitol-sorbitan solution, water, glycerin, titanium dioxide, FD&C Red #40, ethanol, ethyl acetate, propylene glycol, polyvinyl acetate phthalate, isopropyl alcohol, polyethylene glycol, and ammonium hydroxide. (b) (4)
 lecithin (b) (4).

3) #16: HOW SUPPLIED/STORAGE AND HANDLING

(b) (4) estradiol vaginal (b) (4) are small, light pink, tear-shaped (b) (4) 4 mcg, 10 mcg, (b) (4) Each (b) (4) is imprinted in white ink on (b) (4) side (b) (4)
 (b) (4) estradiol vaginal (b) (4) are provided in opaque push-through blisters. (b) (4) 18 (b) (4) (starter pack) or 8 (b) (4) (maintenance pack).
 (b) (4) 4 mcg NDC 50261- (b) (4)
 4 mcg NDC 50261-
 10 mcgNDC 50261-
 10 mcgNDC 50261- (b) (4)

Storage and Handling:

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 NDA	Reviewer's Comment and Recommendations
Strength of dosage form	vaginal (b)(4) are small, light pink, tear-shaped (b)(4) 4 mcg, 10 mcg, (b)(4) estradiol	The proper dosage form is "vaginal insert". Strengths are appropriately provided Unsatisfactory
Available units (e.g., bottles of 100 tablets)	(b)(4) estradiol vaginal (b)(4) are provided in opaque push-through blisters. (b)(4) either 18 (b)(4) (starter pack) or 8 (b)(4) (maintenance pack).	Provided with the exception that as stated above the dosage form should be revised to vaginal inserts. Unsatisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Small, light pink, tear-shaped (b)(4) Each (b)(4) is imprinted in white ink on (b)(4) side (b)(4) (04, 10 (b)(4)	Provided with the exception that as stated above the dosage form should be revised to vaginal inserts. Unsatisfactory
Special handling (e.g., protect from light)	Not applicable	Not applicable
Storage conditions	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.]	Provided. Satisfactory
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for: TherapeuticsMD, Inc. Boca Raton, FL 33487 Manufactured by: Catalent Pharma Solutions, LLC St Petersburg, FL 33716	Provided at the end of the PI. Satisfactory

The revision is suggested below:

Tradename (estradiol) Vaginal Inserts are small, light pink, tear-shaped, (b)(4) capsules for manual (b)(4) n into vagina. Inserts contain (b)(4) 4mcg, 10mcg. (b)(4) of estradiol. Each insert is imprinted in white ink on (b)(4) side with (b)(4) (04, 10. (b)(4)

(b)(4) vaginal inserts are provided in opaque push-through blisters and are packaged in cartons containing either 18 inserts for the starter pack or 8 inserts for maintenance pack.

Tradename 4 mcg	8 inserts	NDC 50261	(b)(4)
Tradename 4 mcg	18 inserts	NDC 50261	
Tradename 10 mcg	8 inserts	NDC 50261	
Tradename 10 mcg	18 inserts	NDC 50261	(b)(4)

Keep out of reach of children.

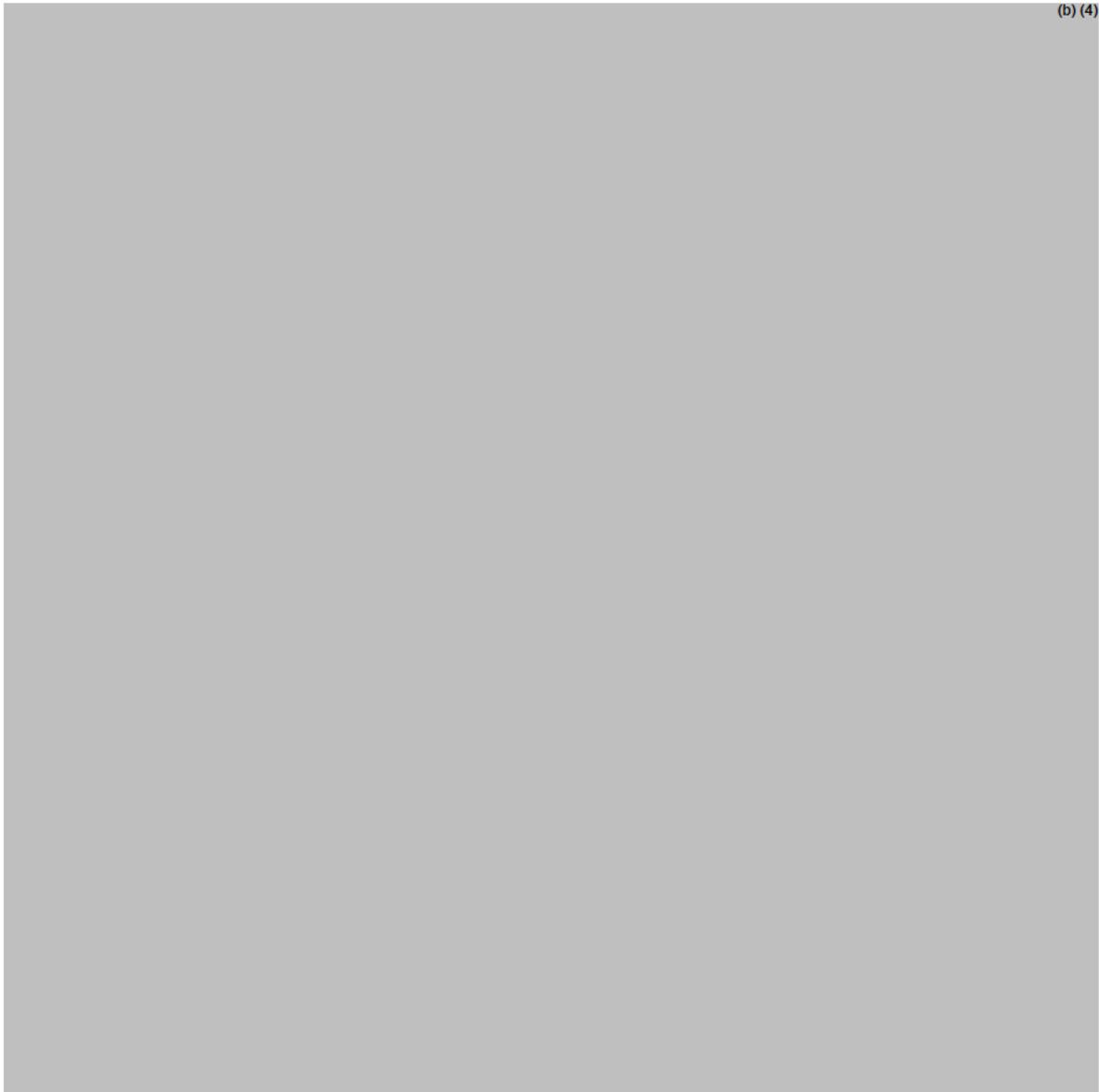
Storage and Handling:

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.]

II. Labels

1. IMMEDIATE CONTAINER

Blister label for 4mcg strength starter pack containing 18 inserts



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Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Not displayed.	Unsatisfactory
Dosage strength	Not displayed.	Unsatisfactory
Net contents	Not displayed.	Unsatisfactory
“Rx only” displayed prominently on the main panel	Not displayed.	Unsatisfactory
NDC number (21 CFR 207.35(b)(3)(i))	Not displayed.	Unsatisfactory
Lot number and expiration date (21 CFR 201.17)	Not displayed.	Unsatisfactory
Storage conditions	Not displayed.	Unsatisfactory
Bar code (21CFR 201.25)	Not displayed.	Unsatisfactory
Name of manufacturer/distributor	Not displayed.	Unsatisfactory
And others, if space is available	Not displayed.	Not required.

Revise the immediate containers, blisters to display the following information:

- 1) Proprietary name and established name: Tradename (estradiol) Vaginal Inserts
- 2) Dosage strength: 4mcg, 10mcg, (b) (4)
- 3) Not content: 18 inserts or 8 inserts
- 4) Rx
- 5) Corresponding NDC numbers
- 6) Corresponding bar codes to the 18-insert blisters
- 7) Lot number and expiration date
- 8) Storage conditions
- 9) Name of manufacturer/distributor

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Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	(b) (4)	Trade name and established name are provided. However, the agency did not accept the proposed trade name, (b) (4). The applicant has been requested to submit a new trade name Satisfactory
Dosage strength	Vaginal (b) (4)	The proper dosage form is "vaginal insert". Unsatisfactory
Net contents	18 and 8 vaginal (b) (4)	The net contents are provided. But the dosage form should be revised to "vaginal inserts". Satisfactory
"Rx only" displayed prominently on the main panel	Displayed	Provided. Satisfactory
NDC number (21 CFR 207.35(b)(3)(i))	Displayed	Provided. Satisfactory
Lot number and expiration date (21 CFR 201.17)	Displayed	Provided. Satisfactory
Storage conditions	Displayed	Provided. Satisfactory
Bar code (21CFR 201.25)	Displayed	Provided. Satisfactory
Name of manufacturer/distributor	Displayed	Provided. Satisfactory
And others, if space is available	Components of each (b) (4) are provided.	The dosage form (b) (4) should be revised to vaginal insert. The content of the inserts should also be revised to include the equivalency statement (see below). Satisfactory

The following changes should be made to the carton labels:

4mcg strength carton:

- 1) Revised the drug product proprietary and established name to "Tradename (estradiol) Vaginal Inserts.
- 2) Replace the (b) (4) to vaginal inserts throughout the label
- 3) Revise the content to "each (b) (4) insert contains (b) (4) (b) (4) 4 mcg estradiol (b) (4)

10mcg strength carton:

- 1) Revise the drug product proprietary and established name to “Tradename (estradiol) Vaginal Inserts.
- 2) Replace the (b) (4) to vaginal inserts throughout label
- 3) Revise the content to “each (b) (4) insert contains (b) (4) 10 mcg estradiol (b) (4)



III. LIST OF DEFICIENCIES:

A. Regarding PI

a) **Highlight Section**

- 1) The title should be revised to “Tradename (estradiol) Vaginal Inserts”
- 2) The dosage forms and strengths should be revised to “Tradename (estradiol) Vaginal Insert (b) (4)

b) **Full Prescribing Information**

#3: Dosage Forms and Strengths

This section should be revised as suggested below:

Dosage Form and Strength should be revised to “Tradename are small, light pink, tear shaped, (b) (4) for manual (b) (4) into the vagina. Tradename inserts contain (b) (4) of (b) (4) 4mcg, 10mcg, (b) (4) estradiol, (b) (4). Each insert is imprinted in white ink on one side with “04”, “10”, (b) (4) corresponding to the insert’s dosage strength.

#11: Description

This section should be revised as suggested below:

Tradename (estradiol) Vaginal Inserts are small, light pink, tear-shaped, (b) (4) for manual (b) (4) into vagina. Inserts contain (b) (4) 4mcg, 10mcg, (b) (4) of estradiol (b) (4)

Keep out of reach of children.

Storage and Handling:

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.]

B. Regarding of the Container/Carton Labels:

a) Immediate container labels: Blisters:

Add the following information to the blisters:

- 1) Proprietary name and established name: Tradename (estradiol) Vaginal Inserts
- 2) Dosage strength: 4mcg, 10mcg (b) (4)
- 3) Not content: 18 inserts or 8 inserts
- 4) Rx
- 5) Corresponding NDC numbers
- 6) Corresponding bar codes to 18-insert blisters
- 7) Lot number and expiration date
- 8) Storage conditions
- 9) Name of manufacturer/distributor

b) Carton labels:

4mcg strength carton:

- 1) Revise the drug product proprietary and established name to “Tradename (estradiol) Vaginal Inserts.
- 2) Replace the (b) (4) to vaginal inserts throughout the label
- 3) Revise the content to “each (b) (4) insert contains (b) (4) (b) (4) 4 mcg estradiol (b) (4)

10mcg strength carton:

- 4) Revise the drug product proprietary and established name to “Tradename (estradiol) Vaginal Inserts.
- 5) Replace the (b) (4) to vaginal inserts throughout label
- 6) Revise the content to “each (b) (4) insert contains (b) (4) (b) (4) 10 mcg estradiol (b) (4)

(b) (4)

IV. OVERALL ASSESSMENT AND RECOMMENDATION:

- Multiple PI labeling deficiencies have been noted.
- Blister labels as provided do not display the required immediate container information.
- The carton labels require revisions.

Recommendation:

From the ONDP perspective, this application is *not* recommended for approval per (314.1259b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Reviewer Name and Date:

Hamid Shafiei, Ph.D.
Reviewer, Branch V
DNDP II/ONDP/OPQ

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

I concur with Dr. Shafiei's assessment and his statement 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 V
DNDP II/ONDP/OPQ



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Rhee

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Shafiei

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BIOPHARMACEUTICS**Product Background:****NDA: 208564****Drug Product Name / Strength: To be determined (estradiol)/ 4 µg, 10 µg** (b) (4)**Route of Administration: Vaginal insert****Applicant Name: TherapeuticsMD*****Review Recommendation:* Recommend approval from Biopharmaceutics perspective. We have following recommendation for the applicant:**

- 1. We recommend that you petition the USP to incorporate your dissolution method and specifications (as recommended by the Agency and acknowledged and accepted by you) into the USP monograph following the approval of your application.**
- 2. We recommend that you perform dissolution method validation per USP <1092> and adopt appropriate acceptance criteria.**

Review Summary:

The Applicant submits an NDA for estradiol vaginal (b) (4) capsules 4, 10 (b) (4) for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. The estradiol vaginal (b) (4) capsule strengths are formulated with (b) (4) (b) (4) 4, 10, (b) (4) estradiol. The (b) (4) capsule formulation was designed for easy insertion, without the need for an applicator, and formulated to dissolve completely and quickly, without requiring vaginal secretions to activate the formulation, minimizing vaginal discharge following administration. The Applicant intends to seek approval of this product via the 505(b)(2) pathway.

Formulation Development:

The composition of Estradiol vaginal (b) (4) capsules, 4 µg is listed in Table 1 below. The composition for 10 (b) (4) are the same as the 4 µg capsule, except for the (b) (4) (b) (4), which is (b) (4) % for 10 µg and (b) (4) for (b) (4) µg.

Table 1: Composition – Estradiol Vaginal (b) (4) Capsules, 4 µg

Ingredient	Quality Standard	Manufacturer	Function	mg/Capsule	% w/w *
Softgel Fill Material					
(b) (4)-estradiol	(b) (4)				(b) (4)
(b) (4)					
(b) (4) medium chain triglycerides					
(b) (4) PEG	(b) (4)				
stearate	(b) (4)				
palmitostearate	(b) (4)				
and PEG	(b) (4)				
stearate	(b) (4)				
Total Fill Material					(b) (4)
Softgel Shell Material					
Gelatin,	(b) (4)				(b) (4)
Hydrolyzed Gelatin					
(b) (4)					
(Sorbitol sorbitan solution)					
Glycerin	(b) (4)				
Purified Water	(b) (4)				
ethanol, ethyl acetate, propylene glycol, titanium dioxide, polyvinyl acetate phthalate, purified water, isopropyl alcohol, polyethylene glycol ammonium hydroxide)					
Ethanol	(b) (4)				
medium chain triglycerides)					
Total Shell Material					(b) (4)
Total					(b) (4)

Dissolution Testing

The proposed dissolution method is as follows:

(b) (4)

The applicant accepted the following Agency recommended acceptance criterion:

NLT (b) (4) % (Q) of the labeled content in 60 minutes.

Comparative Dissolution Study to compare manufacturing site of Catalent and (b) (4)

(b) (4) strengths of estradiol vaginal (b) (4) capsules are manufactured using an identical manufacturing process. To demonstrate that the manufacturing process used by Catalent for the registration / stability batches and the process used at (b) (4) for clinical and registration/ stability batches produces equivalent product, a comparison of the dissolution profiles for two batches of (b) (4) estradiol strength capsules; one manufactured at Catalent (batch 1553489) and one

manufactured at (b) (4) batch PN0089-15) was performed. The two-sample T-test concludes that the means at the 30, 60, 90, and 120 minute time points do not differ from each other for Lots (b) 1553489 and PN0089-15. Data provided for 4 µg and 10µg products demonstrate that about (4)% or more API is dissolved at the first few time points, similarity factor f2 cannot be calculated and in vitro release profiles are considered comparable.

List Submissions being reviewed (table):

[Application 208564 - Sequence 0001 - 0001 \(1\) 07/07/2016 ORIG-1 /Multiple Categories/Subcategories](#)

[Application 208564 - Sequence 0004 - 0004 \(4\) 09/23/2016 ORIG-1 /Quality/Response To Information Request](#)

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining:

There are no outstanding issues but we have following recommendations for the Applicant:

1. We recommend that you petition the USP to incorporate your dissolution method and specifications (as recommended by the Agency and acknowledged and accepted by you) into the USP monograph following the approval of your application.
2. We recommend that you perform dissolution method validation per USP <1092> and adopt appropriate acceptance criteria.

BCS Designation

Reviewer’s Assessment: No BCS designation was requested by the Applicant

Solubility: (b) (4)
(b) (4)

Permeability: Not provided

Dissolution:

Please see below:

Reviewer’s Assessment:

{Assess method development, method robustness, and criteria; modeling approach}

Drug Product

Dissolution Method and Acceptance Criteria

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: n/a

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: n/a

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment: the product is not administered orally, so an in vitro alcohol dose dumping study is not needed.

In-Vitro Soft-food Interaction Study

Reviewer's Assessment: n/a

In-Vitro Release Testing (IVRT) for Semi-Solid Products

Reviewer's Assessment: n/a

In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products

Reviewer's Assessment: n/a

In-Vitro Dissolution Testing for Abuse-deterrent Products

Reviewer's Assessment: n/a.

In-Vitro BE Evaluation for Pulmonary Products

Reviewer's Assessment: n/a

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment: n/a

Bridging of Formulations

Reviewer's Assessment: n/a

Biowaiver Request

Reviewer's Assessment:

R Regional Information

Comparability Protocols

Reviewer's Assessment: n/a

Post-Approval Commitments

Reviewer's Assessment: n/a

Lifecycle Management Considerations

Reviewer's Assessment: n/a

List of Deficiencies:

We have following recommendations for the Applicant:

3. We recommend that you petition the USP to incorporate your dissolution method and specifications (as recommended by the Agency and acknowledged and accepted by you) into the USP monograph following the approval of your application.
4. We recommend that you perform dissolution method validation per USP <1092> and adopt appropriate acceptance criteria.

Primary Biopharmaceutics Reviewer Name and Date: An-chi (Angela) Lu, Pharm D. 3/1/2016

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

Vidula Kolhatkar, Ph.D., March 24, 2017



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Kolhatkar

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MICROBIOLOGY

9 January 2017

Product Background**NDA:** 208564**Drug Product Name / Strength:** Estradiol Vaginal (b) (4) Capsules, 4, 10 (b) (4)**Route of Administration:** Vaginal**Applicant Name:** TherapeuticsMD, Inc.**Manufacturing Site:** Catalent Pharma Solutions, LLC
2725 Scherer Drive North
St. Petersburg, FL**Method of Sterilization:** Non-sterile drug product**Review Summary:** Recommended for Approval**List Submissions Being Reviewed** 7 July 2016**Highlight Key Outstanding Issues from Last Cycle:** The drug product is a non-sterile (b) (4) capsule for vaginal administration. The drug product has a microbial release specification consistent with compendial recommendations and is tested regularly on stability for microbiological quality.**Concise Description Outstanding Issues Remaining:** No deficiencies were identified based upon the information provided.**Supporting/Related Documents:** Not applicable**Remarks Section:** The application was provided in eCTD format.**S Drug Substance**

The drug substance is not sterile and thus will not be covered as part of the product quality microbiology review.

P.1 Description of the Composition of the Drug Product

- Description of drug product –
Estradiol (b) (4) gelatin capsules contain 4, 10, (b) (4) of estradiol. Each capsule is formulated as a (b) (4) fill then encapsulated.
- Drug product composition –
The composition of the 4, 10, (b) (4) (b) (4) capsules is provided in tables 1-3 respectively of section 3.2.P.1. Because the only difference between the (b) (4) (b) (4) is the amount of estradiol in each capsule, only the 4 ug capsule composition is provided in this section.

Ingredient	Quality Standard	Manufacturer	Function	mg/Capsule	% w/w ^a
Softgel Fill Material					
(b) (4) estradiol (b) (4)					(b) (4)
(b) (4) (medium chain triglycerides)					
(b) (4) PEG (b) (4)					
stearate (b) (4) ethylene glycol palmitostearate (b) (4) and PEG (b) (4) stearate (b) (4)					
<i>Total Fill Material</i>					(b) (4)
Softgel Shell Material					
Gelatin, (b) (4)					(b) (4)
Hydrolyzed Gelatin					
(b) (4)					
(Sorbitol sorbitan solution)					
Glycerin					
(b) (4)					
Purified Water					
(b) (4)					
ethanol, ethyl acetate, propylene glycol, titanium dioxide, polyvinyl acetate phthalate, purified water, isopropyl alcohol, polyethylene glycol ammonium hydroxide)					
Ethanol					
(b) (4)					
(b) (4)					
medium chain triglycerides)					
<i>Total Shell Material</i>					(b) (4)
Total					(b) (4)

- Description of container closure system –
The (b) (4) capsules will be packaged in (b) (4) 8-count, or 18-count blister strips.

Reviewer’s Assessment: The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain microbiological quality of the product.

P.2.5 Microbiological Attributes

Not applicable

P.3 Manufacture

P.3.1 Manufacturers

Catalent Pharma Solutions, LLC
 2725 Scherer Drive North
 St. Petersburg, Florida (FL) 33716-1016
 United States (USA)

P. 3.3 Description of the Manufacturing Process and Process Controls

Not applicable

P. 3.5 Process Validation and/or Evaluation

Not applicable

P.5 Control of Drug Product

P. 5.1 Specification

The drug product specification for microbial limits was provided in table 1 of section 3.2.P.5 of the application and has been reproduced in the table below:

Microbial limits		
Total Aerobic Plate Count	(b) (4)	USP <61> <62>
Total Yeast/Mold		
<i>Pseudomonas aeruginosa</i>		
<i>Candida albicans</i>		
<i>Staphylococcus aureus</i>		

The microbial limits specification is consistent with the limits provided in USP <1111> for vaginal use products.

P.5.2 Analytical Procedures

The use of USP chapter <61> and <62> methodology is appropriate for this product.

P.5.3 Validation of Analytical Procedures

Microbial enumeration testing verification is covered in report OET-10275407 provided in section 3.2.P.5.3 of the application. Verification testing was conducted according to USP <61> and <62>. The results of USP <62> verification testing were provided in table 2 located on p. 5 of report OET-10275407. The results of USP <61> verification testing (conducted in triplicate) were provided in table 3 located on pp. 6-7 of report OET-10275407.

Reviewer's Assessment: The applicant confirmed that the compendial verification test was conducted according to USP <61/62> methodology and provided satisfactory results of verification testing.

P.7 Container Closure

See section P.1 of this review.

P.8 Stability

The stability protocol was provided in section 3.2.P.8.1 of the application. Microbial limits testing will be conducted on product stored at 25°C/60% humidity at time 0 and 6, 12, 24, and 36 months. This test protocol deviates slightly from that proposed in ICH Q1a but given that this is a relatively low risk product, this stability test schedule is acceptable. Intermediate stability conditions consist of a storage temperature of 30°C/60% humidity (test intervals of time 0, 6 months, and 12 months). Accelerated stability lots will be held at 40°C/75% RH and tested at time 0, 3 and 6 months. The applicant proposes an expiry of 24 months for commercial batches. The results of stability studies were provided in section 3.2.P.8.3 of the application and found to be satisfactory.

Reviewer's Assessment: The applicant provided a satisfactory summary of the stability program and stability results.

A Appendices

Not applicable

R Regional Information

Not applicable

List of Deficiencies:

No product quality microbiology deficiencies were identified based upon the information provided.

Primary Microbiology Reviewer Name and Date:

Stephen E. Langille, Ph.D. – Acting Branch Chief – Branch 3, DMA

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

John Metcalfe – Acting Quality Assessment Lead – Branch 3, DMA



John
Metcalf

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