

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210132Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: *Approval*

**NDA 210132
Review # 1**

BIJUVA (estradiol and progesterone) capsules

Drug Name/Dosage Form	Estradiol and Progesterone Capsules
Strength	(b) (4) 1 mg / 100 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	TherapeuticsMD Inc.
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original (0001)	12/28/17	Multi-discipline
Amendment (0003)	03/22/18	Process; Biopharm.
Amendment (0004)	03/29/18	Labeling
Amendment (0008)	05/31/18	Labeling
Amendment (0009)	06/26/18	Product; Process; Biopharm.
Amendment (0012)	07/18/18	Process
Amendment (0013)	07/30/18	Biopharm.
Amendment (0016)	08/10/18	Product; Biopharm.
Amendment (0017)	08/28/18	Product; Biopharm.
Amendment (0021)	09/13/18	Labeling
Amendment (0023)	10/05/18	Labeling; Biopharm. (PMC Agreement)
Amendment (0026)	10/22/18	Labeling
Amendment (0028)	10/24/18	Labeling

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Soumya Mitra	BII / DNDAPI / ONDP
Drug Product / Labeling / Environmental Assessment	Zhengfang Ge	BV / DNDPII / ONDP
Process / Facilities	Jingbo Xiao	PABV / DPAII / OPF
Microbiology	Denise Miller	BI / DMA / OPF
Biopharmaceutics	Sandra Suarez	BII / DB / ONDP



QUALITY ASSESSMENT



RBPM	Thao Vu / Florence Aisida	BI / DRBPM I / OPRO
Application Technical Lead	Mark Seggel	BV / DNDPII / ONDP
Laboratory (OTR)	N/A	DPA /OTR

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	MHaber 02/29/18 MAAnderson 05/24/18	
	II			Adequate	SMitra 05/21/18	
	II			Adequate	Jingbo Xiao, 08/02/18	
	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 114477	TXMD IND for estradiol and progesterone FDC in immediate-release soft gelatin capsule for oral administration

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, Inc.’s 505(b)(2) new drug application for BIJUVA (estradiol and progesterone) capsules, is recommended for APPROVAL from the OPQ perspective.

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 revised drug product labeling as submitted on October 24, 2018 is accurate, complete and complies with the requirements under 21 CFR 201.

The drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status.

The claimed categorical exclusion from the requirements to submit an environmental assessment based on ‘no increase in use’ is granted.

POSTMARKETING COMMITMENTS

PMC Description: In vitro studies to establish the appropriate dissolution method(s) and acceptance criteria. The Applicant has agreed to submit the final report by April 12, 2019.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	BIJUVA is intended to treat moderate to severe vasomotor symptoms (VMS) due to menopause, while protecting the endometrium from unopposed estradiol (i.e., menopausal women with a uterus)
Duration of Treatment	As needed.
Maximum Daily Dose	One capsule containing 1 mg estradiol and 100 mg progesterone
Alternative Methods of Administration	Not Applicable

BIJUVA (estradiol and progesterone) capsules is an immediate-release formulation of estradiol and progesterone in a soft gelatin capsule for oral administration. (b) (4)

[Redacted text block]

Estradiol is widely used in the treatment of vasomotor symptoms (VMS) due to menopause. However, treatment with estradiol alone is associated with endometrial hyperplasia and endometrial cancer. Addition of progesterone to the treatment provides protection to the endometrium from unopposed estradiol.

Progesterone alone is available in 100- and 200-mg oral formulations (e.g., Prometrium). Oral estradiol is approved in 0.5 mg, 1 mg and 2 mg strengths. Although a combination of conjugated estrogens and medroxyprogesterone acetate (e.g., Prempro) is approved for the treatment of moderate to severe VMS due to menopause, there are currently no approved combination products with estradiol and progesterone. The Applicant notes potential safety issues with the widespread use of compounded hormonal replacement therapy.

TherapeuticsMD evaluated four combinations of estradiol and progesterone:

- 1 mg estradiol/100 mg progesterone
- 0.5 mg estradiol/100 mg progesterone
- 0.5 mg estradiol/50 mg progesterone
- 0.25 mg estradiol/50 mg progesterone

(b) (4)
[REDACTED] 1 mg / 100 mg combination will be recommended for approval from the clinical perspective.

B. Quality Assessment Overview

BIJUVA (estradiol and progesterone) Capsules is an immediate-release formulation of estradiol and progesterone in a soft gelatin capsule for oral administration.

Drug Substance(s):

Estradiol and progesterone are well characterized and have long histories of use in medicinal products. The chemistry, manufacturing and controls (CMC) of estradiol and progesterone are documented in Type II DMFs # (b) (4) and # (b) (4), respectively. Both DMFs have been found adequate to support use of the drug substances in the manufacture of the drug product. Both drug substances are subjects of United States Pharmacopeia (USP) and European Pharmacopoeia (EP) monographs.

(b) (4)
[REDACTED]
[REDACTED] The levels of individual and total impurities in estradiol drug substance are adequately controlled and meet ICH requirements.

(b) (4)
[REDACTED] To ensure consistent product performance (i.e., dissolution of progesterone), the acceptance criteria include particle size controls. Levels of impurities

are controlled at levels specified in the EP monograph for progesterone. While the limits for EP Impurities B, C and I exceed the ICH Q3A threshold of 0.15%, the proposed limits are consistent with those established for progesterone drug substances used in other approved drug products.

This NDA is recommended for approval from the Drug Substance perspective. See IQA Chapter 1 for details.

Drug Product:

BIJUVA capsules consist of a soft gelatin capsule shell containing (b) (4) estradiol and (b) (4) progesterone. The soft gelatin capsule shell is prepared from (b) (4). The capsule fill is prepared with (b) (4).

(b) (4)

BIJUVA will be supplied in 30-count blister cards with an outer carton. (Initially, a (b) (4) count blister was proposed, but in the September 13, 2018 submission, with prior agreement from the Agency, the Applicant changed to a 30-count configuration (b) (4). A 5-count blister pack physician sample will also be available. See IQA Chapter 2 for details.

The product manufacturing process (b) (4)

The information in the NDA, as amended, regarding the batch formula, manufacturing process parameters, and in-process controls, is supportive of a robust process. See IQA Chapter 5, Process, for details.

Note that the manufacture of the proposed commercial scale batches by Catalent uses the same formulation, follows the same unit operations and sequence, utilizes equipment with the same design and operating principle used in the manufacture of the clinical batches by (b) (4).

The regulatory specification for the finished product includes tests for the identification, assay, and content uniformity of estradiol and progesterone, tests for estradiol and progesterone related compounds, (b) (4)%, and dissolution of estradiol and progesterone (see discussion below). The analytical procedures are adequately described and appropriately validated. See IQA Chapter 2 for details.

The Applicant proposed limit of NMT (b) (4)% for process impurity and degradant identified as EP Impurity M ((17 α)-pregn-4-ene-3,20-dione; 17-isoprogestosterone), stereoisomer of progesterone. It has been observed in drug product at levels up to (b) (4)%. Because this is above the ICH qualification threshold, the nonclinical review team was asked to assess any risk associated with (b) (4)% Impurity M. Dr. Frederic Moulin determined that, “[t]he no-more-than (NMT) (b) (4)% limit for EP Impurity M does not create a safety risk for patients and is therefore acceptable.” See Dr. Moulin’s nonclinical review dated 09/10/18 for details.

The drug product is also tested for Microbial Limits at release and on stability using methods consistent with USP Chapters <61> and <62> for non-sterile products. The acceptance criteria are consistent with USP Chapter <1111>. See IQA Chapter 8 for details.

The Applicant’s proposed dissolution test employs USP Apparatus III (reciprocating cylinder) at 30 dips per minute (DPM) and a medium consisting of 250-mL 3% w/v (b) (4) in 0.1 N HCl (b) (4). Acceptance criteria of $Q = (b) (4)\%$ at (b) (4) minutes were proposed. Sample work-up and analyses differ somewhat to accommodate (b) (4). Unfortunately, the proposed test conditions with (b) (4)% do not provide any discriminating power. Under these conditions, more than (b) (4)% of progesterone is dissolved within 15 minutes. Concerns about the test conditions and requests for additional data were conveyed to the Applicant on several occasions. The Applicant initiated development and validation of an improved dissolution test, the results of which will be reported under a PMC. While use of the current test conditions with an acceptance criterion of $Q = (b) (4)\%$ at 15 minutes and to which the Applicant has agreed to implement in the interim, is not ideal, it will ensure that the product meets minimum clinically-relevant performance criteria. See IQA Chapter 7, Biopharmaceutics, for details.

The lack of a discriminatory dissolution test method precludes use of dissolution data to bridge Phase 1 clinical materials to Phase 3 clinical materials (both manufactured by (b) (4)), and of the Phase 3 product to the commercial product manufactured by Catalent. The bioavailability of a 2 mg estradiol and 200 mg progesterone Phase 1 product was compared to Prometrium 200 mg capsule. While the Phase 1 and Phase 3 products manufactured by (b) (4) have similar composition, the absence of meaningful dissolution data precludes bridging of the 2 mg / 200 mg product to the 1 mg / 100 mg product used in the Phase 3 studies. During formulation development a change was made to the (b) (4)

(b) (4)

The manufacture of the investigational drug product by (b) (4) and the manufacture of the commercial product by Catalent are also considered sufficiently similar to, under usual circumstances, allow reliance on dissolution data to bridge the products. However, because of the deficiencies already noted, the available dissolution data are not useful in this context. Given the comparability of the formulations and manufacturing processes, significant differences in the performance of the Phase 1, Phase 3 and commercial product is not expected from the CMC perspective. Fortunately, this is borne out by the available pharmacokinetic data. See IQA Chapter 7 as well as Drs. Zou and Tran's Clinical Pharmacology Review dated September 7, 2018 for discussion of the pharmacokinetic bridge across products.

Verification of the analytical procedures by the CDER/OPQ/OTR laboratory in St. Louis (DPA) was not requested, as neither active ingredient is an NME, and the methods appear relatively straightforward and employ common analytical methodologies.

The Applicant initially proposed an expiration dating period of (b) (4) months based on up to 18 months of long-term data at 25°C/60% RH. (b) (4)

(b) (4). The Applicant has acknowledged the 18-month expiration dating period. Continued stability testing will be performed to confirm the current expiration dating period, and if appropriate, extension of the shelf-life. See IQA Chapter 2 for details.

Overall, TherapeuticsMD has provided adequate information on the drug product, including appropriate raw material controls, adequate manufacturing and in-process controls, a suitable regulatory specification, and suitable packaging, to assure the identity, strength, purity, quality and bioavailability throughout an 18-month expiration dating period when stored at 25°C/60%RH (b) (4).

The application as amended is recommended for APPROVAL from the Drug Product, Process, Microbiology, and Biopharmaceutics perspectives.

Facilities:

All manufacturing, packaging and testing facilities associated with the drug substances and drug product have acceptable CGMP status. The OPF Division of Inspectional Assessment issued an Overall Inspection Recommendation of *APPROVE* on August 13, 2018. No changes in facility status have been reported as of the date of this review. See IQA Chapter 6 for details.

Labeling: Based on the chemist's labeling review (see IQA Chapter 4, Labeling), and comments from DMEPA and ODPP, revisions to the labels (carton and blister) and Prescribing Information, were conveyed to the Applicant. Those changes include

corrections to nomenclature and formatting, and deletion of potentially promotional wording (e.g., [REDACTED] (b) (4)).

The carton and blister labels, and the Prescribing Information, as revised on October 24, 2018, are now adequate from the chemist's perspective. This conclusion supersedes the previous determination (Chapter 4) that, "this application is not ready for approval..."

C. Special Product Quality Labeling Recommendations

Not Applicable

D. Final Risk Assessment (see Attachment I)

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead Name:

Mark R. Seggel, Ph.D.

CMC Lead (acting)

{see electronic signature page}

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Environmental Assessment (*See Chapter 2*)

CHAPTER IV: Labeling

CHAPTER V: Process

CHAPTER VI: Facilities

CHAPTER VII: Biopharmaceutics

CHAPTER VIII: Microbiology

CHAPTER IX: Additional Quality Discipline (*Not Applicable*)

Attachment I: Final Risk Assessment / Life Cycle Management

Attachment II: List of Deficiencies for Complete Response (*Not Applicable*)

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment and Lifecycle Knowledge Management

a) Drug Product

Final 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	<ul style="list-style-type: none"> Manufacturing process Stability 	M	(b) (4)	Acceptable	
Identification	<ul style="list-style-type: none"> CGMPs 	L		Acceptable	
Assay – Progesterone (P)	<ul style="list-style-type: none"> Process parameters Scale/equipment Site 	L		Acceptable	
Assay – Estradiol (E2)	<ul style="list-style-type: none"> Process parameters Scale/equipment Site 	M		Acceptable	(b) (4)
Related Substances Impurities / Degradants	<ul style="list-style-type: none"> Formulation Raw materials Process parameters Scale/equipment Site 	M		Acceptable	(b) (4) appears to be shelf-life limiting. Impurity M in P adequately qualified per Tox.
(b) (4)	<ul style="list-style-type: none"> Manufacturing Process CCS 	L		Acceptable	
Uniformity of Dosage Units – Progesterone Estradiol	<ul style="list-style-type: none"> API Properties Formulation Process Scale / equipment Site 	M		Acceptable	(b) (4)
Product Performance / Dissolution	<ul style="list-style-type: none"> Formulation Raw materials Process parameters Scale/equipment Site 	M		Acceptable	Interim test and acceptance criteria; PMC to develop and validate more discriminating method
Microbial limits	<ul style="list-style-type: none"> Raw materials Equipment and handling Moisture content 	L		Acceptable	
Package Integrity	<ul style="list-style-type: none"> Raw materials Process parameters Scale/equipment Site 	L		Acceptable	

*Risk ranking applies to product attribute/CQA

**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

ATTACHMENT II: List of Deficiencies for Complete Response

Not Applicable.



Mark
Seggel

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LABEL FOR NDA 210132

I. PI

1. Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **TRADENAME** safely and effectively. See full prescribing information for **TRADENAME**.

TRADENAME (estradiol and progesterone) capsules, for oral use
Initial U.S. Approval: <<YYYY>>

WARNING: CARDIOVASCULAR DISORDERS, BREAST CANCER, ENDOMETRIAL CANCER, and PROBABLE DEMENTIA

See full prescribing information for complete boxed warning.

Estrogen Plus Progestin Therapy

- Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)
- The Women’s Health Initiative (WHI) estrogen plus progestin substudy reported increased risks of stroke, deep vein thrombosis (DVT), pulmonary embolism (PE), and myocardial infarction (MI) (5.1)
- The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.2)
- The WHI Memory Study (WHIMS) estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age or older (5.3)

Estrogen-Alone Therapy

- There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.2)
- Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)
- The WHI estrogen-alone substudy reported increased risks of stroke and DVT (5.1)
- The WHIMS estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age or older (5.3)

INDICATIONS AND USAGE (b) (4)

DOSAGE AND ADMINISTRATION
Take one capsule orally each evening with food. (2)

DOSAGE FORMS AND STRENGTHS
TRADENAME capsules: (b) (4) 1 mg estradiol/100 mg progesterone (3)

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4)
- Known, suspected, or history of breast cancer (4, 5.2)
- Known or suspected estrogen-dependent neoplasia (4, 5.2)
- Active DVT, PE, or history of these conditions (4, 5.1)
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions (4, 5.1)
- Known anaphylactic reaction or angioedema with **TRADENAME** (4, 5.15)
- Known liver impairment or disease (4, 5.10)
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)

(b) (4)

WARNINGS AND PRECAUTIONS

- Estrogens increase the risk of gallbladder disease (5.4)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia, or cholestatic jaundice occurs (5.5, 5.6, 5.9, 5.10)
- Monitor thyroid function in women on thyroid replacement hormone therapy (5.11, 5.18)

ADVERSE REACTIONS (b) (4)

To report **SUSPECTED ADVERSE REACTIONS**, contact TherapeuticsMD, Inc at 1-888-228-0150 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
Inducers and inhibitors of CYP3A4 may affect estrogen drug metabolism and decrease or increase the estrogen plasma concentration. (7.1)

USE IN SPECIFIC POPULATIONS (b) (4)

- Geriatric use: An increased risk of probable dementia in women over 65 years of age was reported in the Women’s Health Initiative Memory ancillary studies of the Women’s Health Initiative (5.3, 8.5)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling. Revised: <<insert month/year>>

Item	Information Provided in NDA	Reviewer’s Assessment
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))		
Proprietary name and established name	TRADENAME (estradiol and progesterone)	Adequate

Dosage form, route of administration	capsules, for oral use	Adequate
Controlled drug substance symbol (if applicable)	N/A	
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))		
Summary of the dosage form and strength	TRADENAME capsules; (b) (4) (b) (4) 1 mg estradiol/100 mg progesterone	Not Adequate “(b) (4)” should be revised to: “Tradename (estradiol and progesterone) capsules “

This section is not adequate.

- “(b) (4)” should be revised to:
 “Tradename (estradiol and progesterone) capsules “

2. Section 2 Dosage and Administration

2 DOSAGE AND ADMINISTRATION

(b) (4)

Use of estrogen, alone or in combination with a progestogen, should be limited to the lowest effective dose available and for the shortest duration consistent with treatment goals and risks for the individual woman. (b) (4) should be reevaluated periodically as clinically appropriate to determine if treatment is still necessary.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))		
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Should be taken orally each evening with food	Adequate

This section is adequate

3. Section 3 Dosage Forms and Strengths

3 DOSAGE FORMS AND STRENGTHS

(b) (4)

TRADENAME 1 mg estradiol/100 mg progesterone: oval shaped opaque (b) (4) light pink on one side and dark pink on the other side, printed with “1C1” in white ink.

Item	Information Provided in NDA	Reviewer’s Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))		
Available dosage forms	capsules	Not Adequate The TRADENAME should be revised to: “TRADENAME (estradiol and progesterone) capsules
Strengths: in metric system	(b) (4) 1 mg estradiol/100 mg progesterone	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	(b) (4) TRADENAME 1 mg estradiol/100 mg progesterone: oval shaped opaque (b) (4) capsules, light pink on one side and dark pink on the other side, printed with “1C1” in white ink.	Adequate

This section is not adequate.

- The TRADENAME should be revised to:
“TRADENAME (estradiol and progesterone) capsules

4. Section 11 Description

11 DESCRIPTION

(b) (4)

(b) (4)

TRADENAME 1 mg estradiol/100 mg progesterone: oval shaped, opaque, (b) (4) capsules, light pink on one side and dark pink on the other side, printed with "1C1" in white ink.

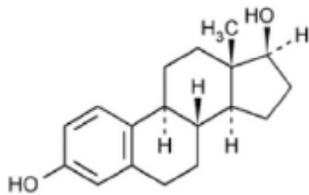
Estradiol (estra-1,3,5 (10)-triene-3,17 β -diol) has a molecular weight of 272.38, and the chemical formula C₁₈H₂₄O₂. (b) (4)

(b) (4)

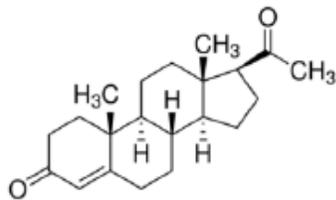
Progesterone (pregn-4-ene-3, 20-dione) has a molecular weight of 314.47, and the chemical formula C₂₁H₃₀O₂. (b) (4)

(b) (4)

The structural formulas are as follows:



Estradiol



Progesterone

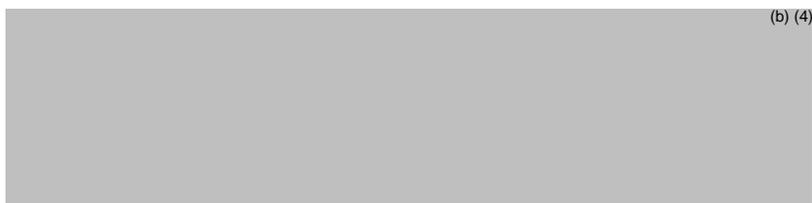
Each TRADENAME (b) (4) capsule contains the following inactive ingredients: medium chain mono and di-glycerides, lauroyl polyoxyl-32 glycerides, gelatin, glycerin, hydrolyzed gelatin, purified water, titanium dioxide, FD&C Red #40, ethanol, ethyl acetate, propylene glycol, polyvinyl acetate phthalate, isopropyl alcohol, polyethylene glycol, ammonium hydroxide, medium chain triglycerides and lecithin.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))		
Proprietary name and established name	TRADENAME	Not Adequate TRADENAME should be revised to TRADENAME (estradiol and progesterone) capsules.
Dosage form and route of administration	capsules	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	N/A	
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Each TRADENAME (b) (4) capsule contains the following inactive ingredients: medium chain mono and di-glycerides, lauroyl polyoxyl-32 glycerides, gelatin, glycerin, hydrolyzed gelatin, purified water, titanium dioxide, FD&C Red #40, ethanol, ethyl acetate, propylene glycol, polyvinyl acetate phthalate, isopropyl alcohol, polyethylene glycol, ammonium hydroxide, medium chain triglycerides and lecithin.	Adequate
Statement of being sterile (if applicable)	N/A	Adequate
Pharmacological/ therapeutic class	(b) (4)	Not Adequate Should be revised to: (b) (4)
Chemical name, structural formula, molecular weight	Provided	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	

Other important chemical or physical properties (such as pKa or pH)	TRADENAME contains a hormone regimen consisting of (b) (4) estradiol and (b) (4) progesterone.	Adequate
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This section is not adequate. The following revision should be made:

- TRADENAME in the beginning of the paragraph should be revised to TRADENAME (estradiol and progesterone) capsules



5. Section 16 How Supplied/Storage and Handling

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TRADENAME (estradiol and progesterone) is an oval-shaped opaque (b) (4) capsule, light pink on one side and dark pink on the other side. Each capsule is imprinted in white ink indicating the dosage strength (b) (4) 1C1. (b) (4) TRADENAME is provided in a blister package of (b) (4) capsules.

(b) (4)

TRADENAME 1 mg estradiol/100 mg progesterone NDC 50261-XXX-XX

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]

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))		
Strength of dosage form	(b) (4)	Not Adequate The drug name should include the dosage form, TRADENAMR (estradiol and progesterone) capsules
Available units (e.g., bottles of 100 tablets)	(b) (4) TRADENAME is provided in a blister package of (b) (4) capsules.	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	oval-shaped opaque (b) (4) capsule, light pink on one side and dark pink on the other side. Each capsule is imprinted in white ink indicating the dosage strength (b) (4) IC1 (b) (4)	Adequate
Special handling (e.g., Dispense in tight and light resistant container as defined in USP)	N/A	Adequate
Storage conditions	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature] (b) (4)	Adequate
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 after section 17 Patient Counseling Information	Adequate

This section is not adequate. The following revision should be made:

- The TRADENAME should be revised to:

TRADENAMR (estradiol and progesterone) capsules

II. Labels:

1. Immediate Container Label

5 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	Bijuva (b) (4)	<p>Not Adequate</p> <ul style="list-style-type: none"> Proprietary name is pending approval Proprietary name, established name, dosage form should be shown as the following: <p>TRADENAME (estradiol and progesterone) capsules</p>
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	(b) (4)	<p>Not Adequate Should be changed to</p> <p>(b) (4)</p> <p>TRADENAME (estradiol and progesterone) capsules, 1 mg mg/100 mg</p>
Net quantity of dosage form	(b) (4) capsules for commercial 5 capsules for samples	Adequate
"Rx only" displayed prominently on the main panel	Provided	Adequate
Lot number and expiration date	Provided	Adequate
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. (b) (4).	Adequate
Bar code (21CFR 201.25)	Provided	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Provided	Adequate
Manufacturer/distributor's name	Provided	Adequate

Quantitative ingredient information (injectables)	Contents: This package contains one blister card of (b) (4) capsules. Each BIJUVA™ (b) (4) capsule contains (b) (4) (b) (4), medium chain mono and di-glycerides, lauroyl polyoxyl-32 glycerides, gelatin, glycerin, hydrolyzed gelatin, purified water, titanium dioxide, FD&C Red #40, ethanol, ethyl acetate, propylene glycol, polyvinyl acetate phthalate, isopropyl alcohol, polyethylene glycol, ammonium hydroxide, medium chain triglycerides and lecithin.	Adequate
Statement of being sterile (if applicable)	N/A	
“See package insert for dosage information”	Dosage: Take one capsule each evening with food. See accompanying information.	Adequate
“Keep out of reach of children” (Required for OTC in CFR. Optional for Rx drugs)	Keep out of reach of children. Package is not child-resistant.	Adequate

This section is not adequate. The following revision should be made:

- The proprietary name, established name, dosage form and strength should be revised as following:

(b) (4)

TRADENAME (estradiol and progesterone) capsules, 1 mg/100 mg

List of Deficiencies:

A. Regarding PI

I. Highlights of Prescribing Information

- (b) (4) should be revised to:

“Tradename (estradiol and progesterone) capsules “

II. Full Prescribing Information

For section 3, “DOSAGE FORM AND STRENGTH”

- The TRADENAME should be revised to:
“TRADENAME (estradiol and progesterone) capsules

For Section 11, “DESCRIPTION”

1. TRADENAME in the beginning of the paragraph should be revised to
TRADENAME (estradiol and progesterone) capsules
2. Pharmacologic class should be added as following,



For Section 16, “HOW SUPPLIED/STORAGE AND HANDLING”

The TRADENAME should be revised to:
TRADENAME (estradiol and progesterone) capsules

B. Regarding Container/Carton Labels:

Immediate Container label

The TRADENAME should be revised to:
TRADENAMR (estradiol and progesterone) capsules

Carton Label

The proprietary name, established name, dosage form and strength should be revised as following:



Overall Assessment and Recommendation:

The labeling and labels are **not** deemed ready for approval in its present form per 21 CFR 314.125 (b)(6) from the CMC labeling perspective until the deficiencies are satisfactorily resolved.

Primary Labeling Reviewer Name and Date:

Zhengfang Ge, Ph. D.

*Reviewer, BRANCH V/DIVISION II
OFFICE OF NEW DRUG PRODUCT*

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

I agree with Dr. Ge's assessment on the labeling and labels, and concur with her recommendation that this application is **not** ready for approval as of this review.

Moo-Jhong Rhee, Ph. D.

*Branch Chief, BRANCH V/DIVISION II
OFFICE OF NEW DRUG PRODUCT*



Zhengfang
Ge

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Moo Jhong
Rhee

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BIOPHARMACEUTICS**Product Background:****NDA:** 210132 ORIG-1**Drug Product Name /Strength:** Estradiol and Progesterone Capsules, 1/100 (b) (4) (mg estradiol/mg progesterone)**Route of Administration:** Oral**Applicant Name:** TherapeuticsMD

The Applicant is seeking approval of Estradiol and Progesterone Capsules ((b) (4)) for the treatment of moderate to severe vasomotor symptoms associated with menopause in women with a uterus. The proposed drug product is a fixed-dose combination product consisting of a softgel immediate release formulation containing solubilized estradiol with micronized progesterone (b) (4)

(b) (4)

The drug product development program consists of several single dose PK studies (e.g. BA/BE studies), one multiple dose-PK study and one pivotal phase 3 efficacy and safety trial which evaluated several doses/strengths (b) (4). The multiple dose study characterized the PK (b) (4) and thus, along with the Phase 3 efficacy and safety data supersede dissolution testing and form the basis for supporting the approval (b) (4).

Review Summary:

Estradiol and Progesterone Oral Capsules is a fixed-dose IR combination drug product (b) (4) 1/100 mg estradiol/progesterone (b) (4).

An in vivo PK dose-proportionality and efficacy/safety data were included in the submission in support of (b) (4) approval. The qualification of these studies is under the purview of OCP and clinical review teams, respectively.

This 505(b)(2) submission relies on the previous findings of safety and efficacy for Estrace® (estradiol tablets USP) 2 mg and Prometrium® (progesterone USP) 200 mg capsules. Of note, the 505(b)(2) bridge was established via a BE study evaluating a higher strength (i.e., 2/200 mg) that is not being proposed for marketing. Since the 2/200mg and 1/100 mg are proportionally similar in composition, dissolution testing was originally proposed to establish the bridge between these two strengths. In general, this procedure for bridging relying on dissolution profile comparison is appropriate, given the nature of the drug product. However, the data provided were generated with a method that lack discriminating ability for these low solubility APIs. The reviewer requested that the Clinical Pharmacology review team rely on cross-study PK comparison between the data generated for the 1mg/100 mg strength manufactured at the (b) (4) (Phase 3 site) versus the data generated for the same strength at the Catalent site (commercial site) to support the bridge between the 200mg/2mg and the 100mg/1mg strengths (i.e., 505(b)(2) bridge). On an email communication, the Clinical Pharmacology review team concluded that based on sparse PK data analysis, the Cavg PK concentration for both APIs appears to be comparable between the two sites, providing the basis for bridging (refer also to the clinical pharmacology review by Drs. Tran and Zou). In addition, based on email communications with the CMC review team, the manufacturing changes implemented to the 1 mg/100mg and to the 2 mg/200mg strengths from the (b) (4) site compared to the 1/100 mg strength manufactured at the Catalent site are considered minor and are not expected to pose risk to the clinical performance of the drug product. It should be noted that these data analysis (e.g., PK cross study comparison and similarity in process/formulation) also support the change in site. Therefore, the proposed site change is acceptable from biopharmaceutics perspective.

The proposed dissolution method USP Apparatus 3 (see appendix for more detail) uses 0.1 HCl media containing 3% of surfactant (SLS). During the review cycle, the Applicant was informed via IR letters (see appendix for more detail) that the method is not discriminating, (b) (4) and that it should be revised. The Applicant followed the FDA's recommendation (b) (4). Based on a correspondence dated 7/30/18, the Applicant informed that the dissolution method development report supporting the new methods along with validation data would not be submitted until the end of September. Since there are no additional issues about 505 (b)(2) bridging and manufacturing site change bridging, the review team decided to accept the Applicant's proposal of submitting additional data supporting the dissolution method development and validation as PMC, provided the product receives approval recommendation. A PMC will be issued where the Applicant will have the opportunity to further investigate and establish adequate dissolution methods and acceptance criteria. Therefore, the following method and acceptance criterion are being approved on an interim basis (b) (4):

Parameter	Condition
Apparatus	USP 3 – Reciprocating Cylinders
Medium	3% (w/v) SLS in 0.1N HCl
Medium Volume	250 mL
Sample Volume	5-10 mL ^a
Screen Mesh Size	40 mesh
Dip Rate	30 dpm
Medium Temperature	37 ± 0.5 C
Sampling Time Points	5, 10, 15, 20, 30 minutes
Filters	Nylon, 0.45µm

^a Sample volume is 5 mL if collecting for a single active and 10 mL if collecting for both active components.

Dissolution acceptance criterion: Q (b) (4)% in 15 min.

On a submission dated Aug 28, 2018, the Applicant agreed upon the recommended acceptance criterion on an interim basis and with the commitment (PMC) to further revise the methods and acceptance criterion, accordingly. The recommended acceptance criterion will decrease the risk of releasing a non-conforming batch of the proposed drug product.

Reviewer's Assessment: ADEQUATE

From Biopharmaceutics perspective, NDA 210132 for **Progesterone and Estradiol Capsules**, (b) (4)

1/100mg is recommended for Approval with a PMC. The above dissolution method and acceptance criterion have been approved on an interim basis.

Under the PMC, the Applicant is being requested to develop a dissolution method and acceptance criterion (b) (4)

(b) (4)

A change in current dissolution specifications (i.e. method and acceptance criteria) set on an interim basis to final specifications should be requested via a PAS to the NDA.

Comments to the CMC Review Team

(b) (4)

- 1.
- 2.
- 3.

List Submissions being reviewed (table):

SUBMISSION(S) DATE	SEQUENCE NO.
12/28/17	0000
03/31/18	0004
06/25/18	0009
07/30/18	0013
08/28/18	0017

APPENDIX

Drug Product

The drug product is a fixed-dose combination product consisting of a softgel formulation containing solubilized estradiol with micronized progesterone, (Table 1). Catalent (the proposed commercial manufacturer) will use (b) (4), provided by (b) (4) and progesterone USP (micronized), provided by (b) (4). These active ingredients were also used in the manufacture of clinical supplies both at Catalent and (b) (4).

Table 1. Components and composition of the proposed drug product*.

Component [Compendial name (trade name)]	Quality Standard	Manufacturer	Function	Quantity/capsule (in mg)	
				(b) (4)	1 mg/100 mg
(b) (4)					

Drug Substance

BCS Designation

(b) (4)

(b) (4)

According to the Applicant both estradiol and progesterone ((b) (4)) can be classified as BCS class 2 drug substances.

Polymorphism

(b) (4)

(b) (4)

Dissolution Method and Acceptance Criterion

The following method and specification time point ((b) (4) min) were originally proposed for QC purposes (product release and stability testing) for both components of the drug product (estradiol and progesterone):

Table 4. (b) (4) **dissolution testing**

Parameter	Condition
Apparatus	USP 3 – Reciprocating Cylinders
Medium	3% (w/v) SLS in 0.1N HCl
Medium Volume	250 mL
Sample Volume	5-10 mL ^a
Screen Mesh Size	40 mesh
Dip Rate	30 dpm
Medium Temperature	37 ± 0.5°C
Sampling Time Points	(b) (4) minutes
Specification Time Point	(b) (4)
Filters	Nylon, 0.45µm

^a Sample volume is 5 mL if collecting for a single active and 10 mL if collecting for both active components.

(b) (4)

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Figure 1. Discriminating ability of the method toward variations in particle size distribution.

Therefore, the following comments were conveyed to the Applicant as part of the 74-day letter:

- 1. Your proposed dissolution method seems to be not adequate as a quality control for your drug product based on the following observations:*



(b) (4)

- 
2. *Submit the individual and mean in vitro dissolution profiles (in graphical and tabular form) for all batches tested in Phase 1 studies TXC17-02, TXC-16-01, (b) (4) PN0082-01 and the mean dissolution profiles for all batches tested in pivotal Phase 3 studies.*
 3. *Provide a side-by-side table listing all the changes implemented to the formulation tested in phase 3 pivotal batches in comparison to the to-be-marketed drug product.*

On a submission dated 3/21/18 the Applicant committed to:



(b) (4)

In response to this information, the following IR was submitted to the Applicant:

(b) (4)

(b) (4)

3. Note that since the methods are being revised, comparative dissolution profiles (with similarity testing) need to be provided for the following situations:
- Data supporting the manufacturing site change.
 - Data supporting the bridge between the formulation/strength used in pivotal BE study and the formulation/strengths proposed for marketing. To justify the use of dissolution data supporting the bridge, provide evidence that the strengths are proportionally similar in composition (e.g., 2mg/200mg vs. 1 mg/100mg strengths).
 - You are encouraged to submit any additional data (e.g., in vivo data) supporting the bridging between the 2mg/200mg and 1mg/100mg strengths.

On a submission dated 6/25/18 the Applicant provided an update on their efforts in developing dissolution methods (b) (4) with the following conclusions:

1.

(b) (4)

2.

As per latest correspondence, the Applicant committed to submit the final report containing all efforts invested (refer to submission dated 7/30/18)

<https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af803ac586>) including the validation of the method by end of September 2018. Briefly, the Applicant has evaluated several dissolution media, apparatuses, surfactant concentration, etc. and is still evaluating the discriminating ability of (b) (4) % SLS concentration towards critical attributes such as particle size distribution and crosslinking.

Dissolution Acceptance Criterion

Figures 2 and 3 summarize the dissolution performance of the clinical batches tested in Phase 3 pivotal clinical trials. It is demonstrated that more than (b) (4) % of the APIs (Figure 2 for estradiol) and Figure 3 for progesterone), dissolve within 15 min, supporting the dissolution acceptance criterion of $Q = (b) (4) \%$ in 15 min).

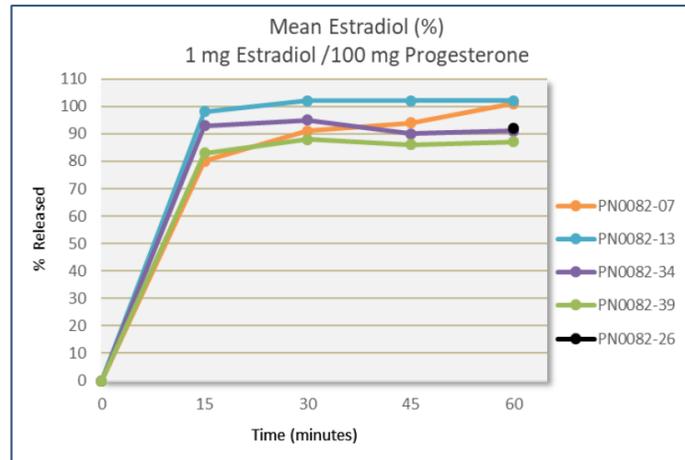


Figure 2. Mean Estradiol Dissolution Data for (b) (4) Batches 1 mg Estradiol and 100 mg Progesterone Softgel Capsules

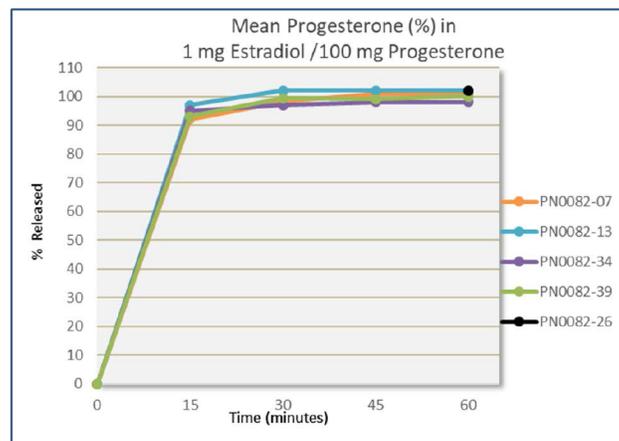


Figure 3. Mean Progesterone Dissolution Data for (b) (4) Batches 1 mg Estradiol and 100 mg Progesterone Softgel Capsules.

The Applicant was requested via IR to revise the dissolution acceptance criterion and consider the dissolution specifications with a PMC as follows:

1. Reference is made to your submission dated 07/30/18 where you outlined the timeline for submitting the data supporting the adequacy/validation of the proposed dissolution method (b) (4). Reference is also made to your submission dated 6/25/18, where you proposed submitting additional data supporting the adequacy and validation of the dissolution methods as post marketing commitment (PMC). We have further discussed your proposal internally and have made the decision to accept your proposal of submitting all data generated as part of method development and validation as PMC, provided your

product receives approval recommendation. Thus, the following method and dissolution acceptance criterion ((b) (4)) of your drug product will be accepted on an interim basis:

Dissolution Method:

Parameter	Condition
Apparatus	USP 3 – Reciprocating Cylinders
Medium	3% (w/v) SLS in 0.1N HCl
Medium Volume	250 mL
Sample Volume	5-10 mL ^a
Screen Mesh Size	40 mesh
Dip Rate	30 dpm
Medium Temperature	37 ± 0.5 C
Sampling Time Points	5, 10, 15, 20, 30 minutes
Filters	Nylon, 0.45µm

^a Sample volume is 5 mL if collecting for a single active and 10 mL if collecting for both active components.

Recommended Acceptance criterion for both components of the drug product:

NLT (b) (4)% (Q) dissolves within 15 min.

Please update the drug product specification table reflecting this recommendation and submit the revised drug product specification table by COB Aug 28, 2018.

Note that a postmarketing commitment proposal will be submitted to you for your review and mutual approval. The PMC will request you to develop and validate a discriminating dissolution test method suitable for the quality control of the drug product, and establish appropriate acceptance criteria.

On a submission dated 08/28/18, the Applicant agreed with the recommendations.

Reviewer’s Assessment: ADEQUATE

In summary, during the review cycle the Applicant was informed via IR letters that the method is not discriminating, (b) (4) and that it should be revised. The Applicant followed the FDA’s recommendation (b) (4). Based on a correspondence dated 7/30/18, the Applicant inform that the dissolution method development

report supporting the new methods along with validation data would not be submitted until the end of September 2018.

Since all review disciplines will be making an approval recommendation, the review team decided to issue a PMC where the Applicant will have the opportunity to further investigate and establish adequate dissolution methods and acceptance criteria. Therefore, the following method and acceptance criterion are being approved and agreed upon with the Applicant on an interim basis (b) (4) of the drug product. The revised dissolution acceptance criterion will add some discriminating ability to the method.

Parameter	Condition
Apparatus	USP 3 – Reciprocating Cylinders
Medium	3% (w/v) SLS in 0.1N HCl
Medium Volume	250 mL
Sample Volume	5-10 mL ^a
Screen Mesh Size	40 mesh
Dip Rate	30 dpm
Medium Temperature	37 ± 0.5 C
Sampling Time Points	5, 10, 15, 20, 30 minutes
Filters	Nylon, 0.45µm

^a Sample volume is 5 mL if collecting for a single active and 10 mL if collecting for both active components.

Dissolution acceptance criterion: $Q = \frac{(b)}{(4)}\%$ in 15 min

The PMC will request the Applicant to develop a dissolution method and acceptance criterion (b) (4)

A change in current dissolution specifications (i.e. method and acceptance criteria) set on an interim basis to final specifications should be requested via a PAS to the NDA.

Bridging of Formulations throughout the Phases of Drug Product Development: ADEQUATE

During the review cycle the Applicant was requested to submit a side-by-side table listing all the changes implemented to the formulation tested in phase 3 pivotal batches in comparison to the to-be-marketed drug product. According to the Applicant, the formulations of the Phase 3 pivotal batches (b) (4) and the to-be-marketed product (Catalent) are identical, with the exception of (b) (4) (see submission dated 3/21/18). The level of these changes (minor) were confirmed via

email by Dr. Ge Zhengfang on 05/30/18. Given the nature of the changes and as per SUPAC-IR dissolution profile comparison should be sufficient to support the change. Based on data generated with the method being approved on in interim basis, there are no significant difference in the release profile between manufacturing sites (e.g., more that (b) (4)% dissolves within 15 min or $t_2 > 50$).

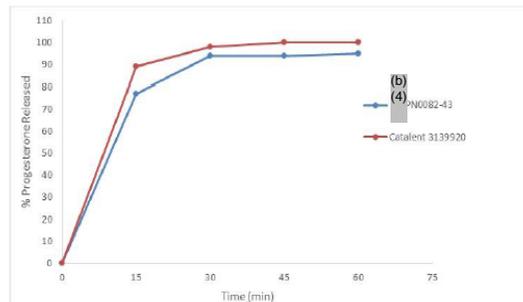


Figure 4. Dissolution profile comparisons (b) (4) vs. Catalent sites. (b) (4)

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Primary Biopharmaceutics Reviewer Name and Date:

Sandra Suarez Sharp, Ph.D. (Branch 2\DB\ONDP\OPQ), 08/10/18; 8/30/18

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

Vidula Kolhatkar, Ph.D., Acting Team Lead (Branch 2\DB\ONDP\OPQ) 8/13/18; 8/30/18



Sandra
Suarez

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Vidula
Kolhatkar

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MEMORANDUM



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

DATE: 15 May 2018

TO: NDA 210-132

FROM: Denise Miller
Sr. Microbiology Reviewer, OPF/DMA/Branch II

THROUGH: Bryan Riley, Ph.D.
Acting Branch Chief, OPF/DMA/Branch II

cc: Kimberly Shiley
OND Project Manger

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for
“Bijuva (estradiol and progesterone)” [Submission Date: 28 Dec 2017]

The Microbial Limits specification for “Bijuva” is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

“Bijuva (estradiol and progesterone)” is a capsule supplied in unit dose blister packs for oral administration. This is a soft capsule and is a non-aqueous product. (b) (4)

The drug product is tested for Microbial Limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The Microbial Limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use) and are as follows:

TAMC: (b) (4) CFU/g

TYMC: (b) (4) CFU/g

Absence of (b) (4)

The Microbial Limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>.

The drug product will also be tested for Microbial Limits annually as part of the post-approval

MEMORANDUM

stability protocol.

ADEQUATE

Reviewer Comments – The microbiological quality of the drug product is controlled via a suitable testing protocol.

END



Denise
Miller

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Bryan
Riley

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Mark
Seggel

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