

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208352Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

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

NDA 208352 OPQ Assessment #2

Drug Product Name	PHEXXI (lactic acid, citric acid, and potassium bitartrate) vaginal gel			
Dosage Form	vaginal gel			
Strength		<u>lactic acid</u>	<u>citric acid</u>	<u>potassium bitartrate</u>
	% (w/w)	1.8%	1%	0.4%
	mg / gram	18 mg	10 mg	4 mg
	5-g dose	90 mg	50 mg	20 mg
Route of Administration	Vaginal			
Rx/OTC Dispensed	Rx			
Applicant	-			
US agent, if applicable	-			
Application Type	505(b)(2)			
NDA Classification Code*	Type 3, New dosage form; Type 4, New combination (physical)			
Combination Product	Type 2, Pre-filled Drug Delivery Device			

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

Submission(s) Assessed	Document Date	Discipline(s) Affected
Class 2 Resubmission after Complete Response (0034)	11/25/2019	All
Labeling (0037)	02/03/2020	ONDP Labeling
Reviewer Guide Update (0039)	03/06/2020	Product, Facilities
Labeling (0040)	04/06/2020	ONDP Labeling
Labeling (0042)	04/08/2020	ONDP Labeling
Response (0043)	04/13/2020	OPMA Process
Labeling (0044)	04/14/2020	ONDP Labeling
Labeling (0047; 0048)	05/01/2020	ONDP Labeling
Labeling (0050)	05/05/2020	ONDP Labeling
Labeling (0051)	05/20/2020	ONDP Labeling
Labeling (0052)	05/21/2020	ONDP Labeling

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Jeff Medwid	Donna Christner
Drug Product / Labeling	Venkat Pavuluri	Moo-Jhong Rhee
Manufacturing	Cassandra Abellard	Joanne Wang
Microbiology	Jesse Wells	Yarery Smith
Biopharmaceutics	_*	-
RBPM	Marquita Burnett	
ATL	Mark Seggel	
Laboratory (OTR)	-	-
Environmental	-	-

* Per email 12/05/2020 from Okpo Eradiri, ONDP/DB Branch Chief, "There are no Biopharmaceutics issues to assess in this resubmission; therefore, a Reviewer will not be assigned." The Biopharmaceutics task can be removed from Panorama. Until then, the Biopharmaceutics task will be marked N/A.

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Evoform's 505(b)(2) New Drug Application 208352 for PHEXXI (lactic acid, citric acid, and potassium bitartrate) vaginal gel, as resubmitted on November 25, 2019, is recommended for APPROVAL from the OPQ perspective.

Although several minor changes were reported in the resubmission, the chemistry, manufacturing and controls information, and supporting data provided in accordance with 21 CFR 314.50 remain adequate to ensure the identity, strength, quality, and purity of the drug product.

The revised drug product labels (aluminum foil overwrap and carton) and labeling (PI, PPI, IFU) as submitted on May 21, 2020 comply with the requirements under 21 CFR 201 and are adequate from the ONDP CMC perspective.

All drug substance and product-related manufacturing, packaging and testing facilities, including the new drug product manufacturer, have acceptable drug CGMP status. An overall manufacturing inspection recommendation of APPROVE was issued on March 30, 2020. The recommendation remains current as of this review. Note that the (b) (4) cited as deficient in the April 28, 2016 Complete Response Letter has been withdrawn from the application and a new supplier of potassium bitartrate has been identified.

PHEXXI is supplied in a 5-gram vaginal applicator and is thus a drug-device combination product under 21 CFR Part 3. CDRH-OPEQ has determined that all device-related deficiencies identified in the 2016 Complete Response Letter have been adequately addressed and that the information provided is sufficient to support approval of the proposed applicator for delivery of the drug product.

The proposed 30-month expiration dating period for drug product stored at 20°C to 25°C is supported by the available stability data.

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

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

PHEXXI (previously referred to as Amphora Gel) is a nonsterile vaginal gel containing 1.8% lactic acid, 1% citric acid and (b) (4)% potassium bitartrate in a gel base consisting of alginic acid and xanthan gum (gelling agents), benzoic acid (preservative), glycerin (humectant), sodium hydroxide (to adjust pH) and purified water. It is supplied in 5-gram, single-dose, pre-filled (b) (4) applicators for vaginal administration prior to vaginal intercourse.

Because of the alkalinity of semen, introduction into the vagina results in an increase in vaginal pH to above 6. Neutralization of the normally acidic vaginal environment contributes to the survival of spermatozoa. PHEXXI is an acid-buffering gel formulation which buffers the vaginal pH so that it remains below 5.0 when ejaculate is introduced. Low vaginal pH (ca. 3.5-4.5) is thought to immobilize spermatozoa and reduce sperm survival.

No significant product quality risks have been identified. The manufacturing process is straightforward and robust. All active and inactive ingredients are GRAS and are suitable for vaginal administration at the proposed levels. Degradation of alginic acid on storage may result in some discoloration of the gel. Sufficient benzoic acid is present to provide adequate antimicrobial effectiveness throughout the product shelf-life and to compensate for any loss due to adsorption on the (b) (4) barrel. The physico-chemical compatibility of the formulation with the (b) (4) plastic applicator has otherwise been demonstrated. No leachables compounds over the Safety Concern Threshold (SCT) of 1.5 µg/day have been observed.

In addition to tests to ensure identity, strength, and purity, the finished product specification includes tests for pH (b) (4), acid neutralization (a measure of buffering capacity) ((b) (4) mEq/g), viscosity, minimum fill, and preservative content. Drug product microbiological quality is adequately ensured by control of raw material quality, manufacturing process environmental controls, the presence of effective levels of preservative (benzoic acid) as demonstrated by antimicrobial effectiveness testing (AET), and by microbial quality testing, at release and on stability, that conforms to the requirements of USP <1111> for nonsterile, vaginally administered drug products. Weight loss is monitored on stability to ensure that loss of water from the product does not exceed (b) (4)% by weight. Because product activity does not depend on release of the active ingredients from the gel, in vitro release testing is not required.

(b) (4)	
The product is dispensed in a carton of 12 individually wrapped pre-filled applicators. The product is stored at controlled room temperature.	
Satisfactory device performance (mechanical function) requisite for easy user activation of the applicator has been demonstrated via break loose force and glide force testing. Biocompatibility was demonstrated in accordance with ISO 10993.	

Proposed Indication(s) including Intended Patient Population	PHEXXI is indicated for the prevention of pregnancy in females of reproductive potential who are seeking an on-demand method of contraception.
Duration of Treatment	As needed; self-administered before each episode of vaginal intercourse.
Maximum Daily Dose	Each pre-filled single-dose vaginal applicator delivers 5 g of gel containing lactic acid (1.8%), citric acid (1%), and potassium bitartrate (0.4%).
Alternative Methods of Administration	Not applicable.

B. Quality Assessment Overview

Note: The chemistry, manufacturing and controls (CMC) for lactic acid, citric acid, and potassium bitartrate vaginal gel was previously reviewed in 2016 (see OPQ Quality Assessment #1 dated April 11, 2016 and Addendum dated April 25, 2016). With the exception of the deficiencies associated with the (b) (4) potassium bitartrate drug substance manufacturing site, unresolved labeling issues, and device-related deficiencies identified by CDRH, it was concluded that, “[t]he applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substances and of the gel formulation. While efficacy (prevention of pregnancy) of the product has not been unequivocally demonstrated, the product quality attributes (pH, buffering capacity, and viscosity) requisite for spermicidal activity are adequately controlled.”

Several changes to the drug substance and drug product CMC are reported in the November 25, 2019 resubmission. See Attachment 2 of this Executive Summary for an applicant-provided list of changes made since the April 2016 Complete Response. Of note are: new potassium bitartrate drug substance and citric acid drug substance manufacturers, a new drug product

manufacturer, and a change in the lactic acid content of the gel from 1.76% (w/w) to 1.8% (w/w).

The following assessment summaries focus on the new information provided in the NDA resubmission and associated amendments, and resolution of labeling issues.

Drug Substance: Adequate

Lactic Acid: (b) (4)

(b) (4)
(b) (4)
(b) (4)
(b) (4)

Citric Acid: (b) (4)

(b) (4)
(b) (4)
(b) (4)

Potassium Bitartrate: (b) (4)

(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)

Overall, the CMC information for the three active ingredients is adequate. NDA 208352 is recommended for Approval from the drug substance CMC perspective (see attached IQA Chapter I).

Drug Product: Adequate

Each pre-filled 5-gram PHEXXI vaginal applicator contains 1.8% lactic acid, 1% citric acid and (b) (4)% potassium bitartrate in a gel base. In the time since the application was previously reviewed, the formulation has been revised slightly. The percent of lactic acid has been increased slightly from 1.76% (w/w) to 1.8% (w/w). This change was reportedly made in 2014 due to a change in the target assay acceptance criterion for lactic acid solution (b) (4). This difference is considered minor,

(b) (4)
(b) (4) the target pH of the formulation (b) (4) and acid neutralization test, a measure of buffering capacity, (b) (4) mEq/g) are unchanged.

To support a change in drug product manufacturer from (b) (4) to (b) (4) the Applicant submitted 3 months stability on

Overall, adequate drug product CMC information has been provided and the application as resubmitted is recommended for Approval from the ONDP Drug Product perspective. See IQA Chapter II, attached, for additional details.

Evoform has requested a categorical exclusion from the requirements to prepare an environmental assessment. The applicant knows of no extraordinary circumstance associated with the active ingredients in product. In addition, the expected introduction concentration (EIC) of each active moiety into the aquatic environment is not more than (b) (4) ppb, below the 1 ppb threshold. On this basis, the requested categorical exclusion is granted. Note that the EIC of (b) (4) ppb is a (b) (4) old increase over the EIC of (b) (4) ppb identified in the original submission.

Numerous deficiencies with the proposed labels and labeling were identified as documented in Chapter IV of this IQA. These deficiencies included incomplete information about product strength, missing dosage form statements, missing barcodes, inclusion of terms such as “naturally occurring,” and other issues related to formatting. From the CMC perspective the most problematic labeling issue associated with this application was the Applicant’s proposal to use ‘L-lactic acid’ throughout the labels and labeling, including in the established name of the drug substance and drug product. Note that the Applicant had not proposed such use in the labeling provided in the 2015 submission. (b) (4)

Reference ID: 4614920

references to lactic acid stereochemistry. With extensive input from Carol Holquist, DMEPA, all other labeling issues were adequately resolved. The labels and labeling as submitted on May 21, 2020 are acceptable for the ONDP CMC perspective.

See the attached ONDP Labeling Review (Chapter IV) and associated Labeling Review Addendum, for additional details.

Manufacturing: Adequate

Process:

A new drug product manufacturer, (b) (4), replaces the previous manufacturer, (b) (4). The manufacturing process is substantially equivalent to the original (b) (4) process, but the batch size has been scaled up from (b) (4) kg. Minor process changes have been made; these are considered improvements (additional critical process parameter and in process testing requirements). The (b) (4) site process is supported by appropriate exhibit batches manufactured with materials sourced from the new drug substance manufacturers. Accelerated stability data from 3 lots manufactured at (b) (4) provide further support. Concerns regarding bulk holding and process yield have been adequately addressed by the Applicant.

Facilities:

The (b) (4) cited in the April 28, 2016 Complete Response Letter, has been withdrawn. All current drug substance and drug product manufacturing, packaging and testing sites, including the new drug product manufacturer, (b) (4), (b) (4) and the citric acid manufacturer, (b) (4) have acceptable CGMP status.

An Overall Manufacturing Inspection Recommendation of Approve was issued on March 30, 2020 and remains current as of the date of this review.

Biopharmaceutics: Adequate

As noted in the April 11, 2016 Quality Assessment, because product activity does not depend on the release of the active ingredients from the gel, further assessment of the product from the Biopharmaceutics perspective was not warranted. Development of an in vitro release test was not requested. A Biopharmaceutics assessment of the 2019 resubmission was also found to be unnecessary.

Microbiology (if applicable): Adequate

Product quality microbiology was found adequate following review of the original submission. The current Product Quality Microbiology assessment (Chapter VII) considered information relevant to the new commercial drug product manufacturing site, (b) (4) including results from microbial limits testing of product manufactured at (b) (4)

Overall, drug product microbiological quality is adequately ensured by control of raw material quality, manufacturing process environmental controls, the presence of effective levels of preservative (benzoic acid) as demonstrated by antimicrobial effectiveness testing (AET), and by microbial quality testing, at release and on stability, complying with the requirements of USP <1111> for nonsterile, vaginally administered drug products.

CDRH: (if applicable): Adequate

The device constituent part of the proposed pre-filled vaginal applicator consists of an (b) (4) plastic applicator body (barrel) with an internal rubber piston, and an (b) (4) plunger. The applicator orifice is fitted with a removable cap. Prior to administration, the user must insert the plunger into the rubber piston.

Several device-related deficiencies were identified in Veronica Price's March 21, 2016 review of the device constituent. These approvability issues were conveyed to the Applicant in the April 2016 Complete Response Letter. Inadequate characterization of the components of the device and inadequate characterization of the performance (mechanical function) of the device were noted, as was the absence of adequate biocompatibility testing. Characterization of device function (break loose force and glide force) was necessary to ensure that the devices can be readily actuated by the user over the lifetime of the product.

As noted in Veronica Price's April 9, 2020 review of the resubmission, the Applicant has adequately addressed all of the device-related deficiencies identified in the Complete Response Letter. There are no device-related issues that would preclude approval of this NDA.

Per current internal policies and procedures, "applicators or inserters (including those for obstetrical and gynecological products) are considered technologically simplistic device constituent parts. A CDRH-OPEQ device quality system review is not necessary."

C. Risk Assessment

The following Risk Assessment / Lifecycle Knowledge Management table is from Quality Assessment #1, 04/11/2016. See Quality Assessment #1 for the Initial Risk Assessment. None of the changes reported in the resubmission affect this 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	- Quality of raw materials - Stability	L	(b) (4)	Acceptable	Degradation of alginic acid may contribute to discoloration, which may in turn impact patient compliance
Identification	CGMPs	L		Acceptable	
Assay	- Formulation - Raw materials - Process parameters - Scale/Equipment	L		Acceptable	
Related Substances Impurities / Degradants	- Raw materials - Stability	L		Acceptable	No acceptance testing or limits for degradants established.
Uniformity of Dosage Units	- Formulation - Process parameters	L		Acceptable	
Microbial limits	- Preservative - Container/closure system (CCS)	L		Acceptable	Benzoic acid level decreases due to absorption by pre-filled applicator materials.
Viscosity	Formulation	L		Acceptable	Critical Quality Attribute! Any changes that could impact viscosity should be carefully evaluated.
pH and buffering capacity	Formulation	L		Acceptable	Critical Quality Attribute! Any changes that could impact pH and buffering capacity should be carefully evaluated.

*Risk ranking applies to product attribute/CQA

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

D. List of Deficiencies for Complete Response

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

na

2. Drug Substance Deficiencies

na

3. Drug Product Deficiencies

na

4. Labeling Deficiencies

na

5. Manufacturing Deficiencies

na

6. Biopharmaceutics Deficiencies

na

7. Microbiology Deficiencies

na

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

na

#####

Application Technical Lead Name and Date:

Mark R. Seggel, Ph.D. May 22, 2020
CMC Lead (acting)

{see electronic signature page}

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Adequate	D. Ghosh 01/08/2016	No updates reported since last assessed
	II			Adequate	D. Yu 10/18/2019	
	III			N/A		No updates since 08/24/2015
	III			N/A		
	III			Adequate	See Quality Assessment #1	No relevant updates identified
	III			Adequate	See Quality Assessment #1	No relevant updates identified

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

Note: Other DMFs previously cited in Quality Assessment #1, 04/11/2016, are no longer applicable because the (b) (4) has been withdrawn from the application.

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

Application Number	Document(s)	Description
K033776 (Personal Lubricant; Class II device)	510(k)	Instead Intimate Lubricant; Instead Inc. Determination of <i>Substantially Equivalent</i> 6/24/04
IND 64623	Original IND	Investigational use of Acidform Gel (aka Amphora Gel) as a contraceptive gel; Sponsor: The CONRAD Program
IND 109300	Original IND	Investigational use of Amphora Gel as a vaginal contraceptive; Sponsor: Evofem, Inc.

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	na			
Nonclinical	na			
CDRH-ODE	Review completed	Information is insufficient. Deficiencies noted and information request drafted. See darfts Reference ID: 3905514	03/21/2016	Veronica Price
CDRH-OPEQ	Review completed	Firm has adequately addressed the CDRH engineering review concerns with the applicator	04/09/2020	Veronica Price
Clinical	na			
Other	na			

na Not Applicable

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Environmental Assessment (not applicable)

CHAPTER IV: Labeling

CHAPTER V: Manufacturing Integrated Assessment

CHAPTER VI: Biopharmaceutics (not applicable)

CHAPTER VII: Microbiology

CHAPTER VIII: Additional Quality Disciplines (not applicable)

Attachment 1. Complete Response Letter, April 28, 2016: CMC Issues

Attachment 2. Summary of CMC Changes in Resubmission

Attachment 1. Complete Response Letter: CMC

In addition to Clinical approvability issues, deficiencies related to a manufacturing facility and to the device (vaginal applicator) were identified in the April 28, 2016 Complete Response Letter:

FACILITY INSPECTIONS

During a recent inspection of the [REDACTED] (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

The CR Letter includes an long list of deficiencies from the CDRH device engineering perspective. The deficiencies are related to Device Description, Biocompatibility, Bench Testing, and Stability/Shelf Life.

ADDITIONAL COMMENTS (non-approvability issues)

Numerous specific revisions to the carton and container labeling were provided for the Applicant.

Attachment 2. Summary of CMC Changes Included in NDA Resubmission

Reviewer's Guide (0039 03/06/2020) (original reviewer's guide 0034 11/25/2019)

CTD Section:	Changes Made:
3.2.S Drug Substance	(b) (4)
3.2.P Drug Product	
3.2.P.1 Description and Composition of the Drug Product	- Update from (b) (4) raw material to (b) (4) raw material. - Removal of (b) (4) presentation.
3.2.P.2 Pharmaceutical Development	- Addition of (b) (4) as the commercial manufacturer - Addition of compounding and packaging processes comparability evaluation between (b) (4) - Addition of drug product release and stability comparability evaluation between (b) (4) - Summary of manufacturing changes introduced in 2017 - Removal of (b) (4)
3.2.P.3 Manufacturer	- Addition of (b) (4) as the commercial manufacturer and withdrawal of (b) (4) as a manufacturer - Scale up from (b) (4) kg - Manufacturing process differences in scale up from (b) (4) - Addition of critical process parameters and in process testing (b) (4) - Removal of (b) (4)
3.2.P.4 Control of Excipients	(b) (4)
3.2.P.5 Control of Drug Product	
3.2.P.6 Reference Standards of Materials	- Reference standard provided for Lactic acid (non-USP) - CoA provided for primary reference standards used in testing drug product**
3.2.P.7 Container Closure System	- Removal of (b) (4) - Addition of primary packaging component drawings, a description of secondary packaging, and carton serialization.
3.2.P.8 Stability	- Removal of (b) (4) - Addition of (b) (4) batches, (b) (4) batches, bulk hold stability data - Recommended shelf life increased to 30 months***

Review Notes

* As noted in the April 28, 2016 CR Letter, deficiencies were identified during an inspection of the American (b) (4) facility.

** "(b) (4)

"

*** To support (b) (4) Applicant submitted 3 months stability data on 3 drug product batches manufactured at (b) (4)



Mark
Seggel

Digitally signed by Mark Seggel

Date: 5/22/2020 06:56:14PM

GUID: 507572b5000036176969356148025bae

CHAPTER I: DRUG SUBSTANCE

[IQA NDA Assessment Guide Reference](#)

Drug Substance Name	Citric Acid, Lactic Acid, and Potassium Bitartate
NDA Number	208352
Assessment Cycle Number	1
DMF Number (If Applicable)	DMF (b) (4) DMF (b) (4)
DMF Status	Adequate
Applicant Name	Evoform Biosciences, Inc. 12400 High Bluff Drive, Suite 600 San Diego, CA 92130
DMF Holder	DMF (b) (4)
DMF Holder	DMF (b) (4) (b) (4)
Potassium Bitartrate Manufacturer	(b) (4)

Assessment Recommendation: Adequate

Assessment Summary:

The following changes were made to the API information in the current resubmission:

1. (b) (4) was withdrawn as a supplier of Potassium Bitartrate
2. (b) (4) was withdrawn as a supplier of Citric Acid
3. (b) (4) was added as a supplier of Citric Acid under DMF (b) (4)
4. (b) (4) was added as the supplier of Potassium Bitartrate, with information included in the NDA
5. An updated summary of Lactic Acid from (b) (4) was provided in the NDA. Full information is provided in DMF (b) (4)

Information on the L-Lactic Acid API is provided in the cross-referenced DMF (b) (4) which was found adequate on 08-January-2016 by Debasis Ghosh, PhD. There have been no updates that need review since that time.

Information on the Potassium Bitartrate API is provided in this NDA 208352 which was found adequate on March 3, 2020 J. Medwid, Ph.D.

Information on the Citric Acid API is provided in the cross-referenced DMF (b) (4) which was found adequate on October 18, 2019 by Donglei Yu, PhD.

Primary Drug Substance Reviewer Name and Date:

Reviewer's Assessment and Signature:

This **NDA 208352** is recommended for approval from the CMC drug substance perspective.

The CMC review #1 of DMF (b) (4) for L-lactic acid, submitted on July 27, 2007 was completed by Debasis Ghosh, PhD, on January 08, 2016 and approved by Donna F. Christner, Ph.D., Chief, Branch II, Division of New Drug API January 08, 2016. The final recommendation was adequate.

All CMC information for Potassium Bitartrate was provided in this NDA 208352 and was found adequate.

The CMC review #7 of DMF (b) (4) for Citric Acid, amendment 16, submitted on April 14, 2019 was completed by Donglei Yu, PhD, on October 18, 2019 and approved by Wei Liu, Ph.D., October 18, 2019. The final recommendation was adequate.

Jeffrey B. Medwid, PhD., Senior Review Chemist, Branch II, Division of New Drug API. March 4, 2020

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

Secondary Review Comments and Concurrence:

I concur with Dr. Medwid's assessment that the information on all three drug substances is adequate to support their use for NDA 208352.

**Donna F. Christner, Branch Chief, Branch II, Division of New Drug API.
March 4, 2020**



Jeffrey
Medwid

Digitally signed by Jeffrey Medwid

Date: 3/04/2020 08:32:07AM

GUID: 508da72000029f64e69d3df87ae5bd3e



Donna
Christner

Digitally signed by Donna Christner

Date: 3/04/2020 08:45:56AM

GUID: 502d0913000029cd728469a6a8a14427

CHAPTER II: DRUG PRODUCT

[IQA NDA Assessment Guide Reference](#)

Product Information	
NDA Number	208352
Assessment Cycle Number	02
Drug Product (DP) Name / Strength	Phexxi™; Lactic acid, citric acid, and potassium bitartrate gel; 1.8 %, 1%, and 0.4%
Route of Administration	Vaginal
Drug Product Manufacturer	(b) (4) for Evofem, Inc. (applicant)
RLD Information (Brand Name of Product, Applicant)	Filed as 505(b)(2) but no RLD was used.
RLD/RS Number	Not Provided
Proposed Indication	Prevention of pregnancy in women who choose to use an on-demand method for their contraceptive needs.

Assessment Recommendation: Adequate

Assessment Summary:

Phexxi™ (lactic acid, citric acid and potassium bitartrate) Gel, is an off-white to tan uniform gel, proposed to be supplied in 5 g single-use prefilled vaginal applicator for self-administration, indicated for birth control. Each gram of gel contains lactic acid 18 mg (1.8%), citric acid 10 mg (1%), and potassium bitartrate 4 mg (0.4%) as active ingredients.

Assay values for lactic acid (C₃H₆O₃) content as defined in Lactic acid, USP, has been revised (b) (4) resulted in change of labeling claim for lactic acid in the gel, from 1.76 to 1.8%. (b) (4)

(b) (4) Weight loss test was added to stability specification of the gel. CoAs for reference standards used in testing of drug product were included. Stability studies were launched on three new drug product batches, of (b) (4) kg each, manufactured at (b) (4) following withdrawal of (b) (4), original manufacturing and testing site. Proposed shelf life of 30 months is adequately supported by stability data for generated using samples of 3 registration batches manufactured earlier at (b) (4) up to 24 months at 25°C/40% RH and up to 6 months at 40°C/<25%RH, and up to 3 months at 25°C/40% RH and 40°C/<25%RH for 3 batches manufactured at (b) (4) using APIs from commercial sources. Supporting stability data is also available up to 37 months

at 25°C/40% RH and up to 6 months at 40°C/<25%RH for batches manufactured with Potassium Bitartrate from (b) (4), sourced for development.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Benzoic Acid Assay	Medium	Benzoic acid is known to degrade and / or migrate to plastic packaging components used	Low	Met set acceptance criteria of (b) (4) % at 24 months' time point for all batches, and the extrapolated values reached (b) (4) % at 33 months.
Viscosity of the gel	Medium	Gel is likely to lose its homogeneity / consistency up on storage.	Low	Met set acceptance criteria for appearance and viscosity of (b) (4) (cP) up to 24 months' time point.
Assay	Low	The active ingredients are known excipients with reasonable chemical stability.	Low	Met set acceptance criteria of (b) (4) % at 24 months' time point.

List Submissions being assessment (table):

Document(s) Assessed	Date Received
SN# 0034 Resubmission following Complete Response.	25-NOV-2019

Highlight Key Issues from Last Cycle and Their Resolution: None.

There were no deficiencies identified in previous review cycle in sections evaluated by the drug product reviewer.

Concise Description of Outstanding Issues (List Bullet Points with Key Information and Update as Needed): None

Reviewer's Note:

The review titled NDA 208352_DP_R02 covers evaluation of new or revised quality information submitted to module 3.2.P. Drug Product, in SN #0034 (Dt. 25-NOV-2019) and subsequently in response to Agency's request for information. This review specifically evaluates the stability data provided for additional drug product batches made at new manufacturing site (b) (4) and any updated drug product quality information provided in response to deficiencies identified in Agency's complete response letter (CRL) Dt. 28- APR-2016.

Refer to the original drug product review for complete information on overall equality valuation of the drug product.

P.1 DESCRIPTION AND COMPOSITION

Component/Composition Table

Table 1. Quantitative Composition of Amphora Gel (5 g Dose)

Component	Quality Standard	Function	Composition (% w/w)	Quantity per 5 g Dose (mg)
Lactic acid	USP	Drug substance	(b) (4)*	(b) (4)
Citric acid	USP	Drug substance	1.00	50
Potassium bitartrate	USP	Drug substance	0.40	20
Glycerin	USP	Humectant	(b) (4)	
Alginic acid	NF	Gelling agent		
Xanthan gum	NF	Gelling agent		
Sodium hydroxide	NF	pH adjustment		
Benzoic acid	USP	Preservative		
Purified water	USP	Solvent		
Total			100.0	5,000

NF = National Formulary; USP = United States Pharmacopeia.

* (b) (4) Actual lactic acid concentration in the formulation is 1.80%.

End of applicant material

The drug product composition remains same as in the earlier submission, with following minor changes.

1. The lactic acid content used in drug product composition changed from (b) (4) and meets current USP requirement of not less than (NLT) 88.0% and not more than (NMT) 92.0%, by weight, of lactic acid (C₃H₆O₃). Due to this change in specification for Lactic Acid, content of lactic acid in the drug product was revised as 1.8 % from earlier stated 1.76 % in the labels and labeling material, and on form 356h.

2. Potassium bitartrate manufactured at (b) (4)
is used in place of drug substance from (b) (4)
that had cGMP compliance issues.

Assessment: Adequate.

The changes made to specification of Lactic acid USP, used in the drug product has little or no impact on overall product quality of the gel. The three selected active ingredients (lactic acid, citric acid, and potassium bitartrate) are otherwise widely used inactive ingredients, in drug products for various routes of administration including vaginal route and meet the respective compendial monograph specifications (USP).

Though gelling agents, alginic acid and xanthan gum were not listed in the IID for vaginal delivery, they were approved for most other non-parenteral routes of administration. Safety of these excipients for vaginal administration was evaluated by applicant in toxicity study (Vaginal Irritation Test, Study Number 37795).

Refer to drug substance(s) review for evaluation of quality of lactic acid and potassium bitartrate from new manufacturers.

Refer to non-clinical evaluation for safety of the inactive ingredients used in the drug product composition.

P.2 PHARMACEUTICAL DEVELOPMENT

Formulation Development and Product Design



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

Post-Approval Stability Protocol and Commitment

Applicant provided the following commitments for stability testing and monitoring of commercial batches, post approval:

- To complete the ongoing stability studies on primary batches and submit results from the required stability studies following approval, in annual reports as provided in 21 CFR 314.70(d)(5).
- To initiate stability studies on first three commercial batches at 40°C/≤ 25% RH and 25°C / 40 % RH and at least one commercial batch annually on stability at 25°C / 40 % RH.
- To withdraw from the market any batch that fails to meet approved specifications within the expiration period and report the occurrence to FDA.

Assessment: Adequate.

The post approval commitments provided are acceptable.

R REGIONAL INFORMATION

Environmental Assessment

Applicant requested exemption earlier, from submitting an environmental assessment, pursuant to 21 CFR 25.31(b); stating that the estimated concentration of the substance(s) at the point of entry into the aquatic environment will be below 1 part per billion and no extraordinary circumstances exist to require the need for an environmental assessment.

Assessment: Adequate.

Acceptable in previous review cycle.

Methods Validation or Verification Package

No new methods requiring validation were developed following CRL.

Comparability Protocols

No new comparability protocols were submitted following the CRL.

Post-Approval Commitments

None

Lifecycle Management Considerations

Not applicable

DRUG PRODUCT LIST OF DEFICIENCIES

None

Primary Drug Product Assessor Name and Date:

Venkateswara R. Pavuluri, Ph. D., R. Ph.; 15-APR-2020

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

I agree with Dr. Pavuluri's assessment on this resubmission and concur with his recommendation of approval of this application from the drug product perspective with the proposed expiration dating period of 30 months.

Moo-Jhong Rhee, Ph. D.;
Chief, Branch IV
DNDPII/ONDP/OPQ
16-APR-2020



Venkateswara
Pavuluri

Digitally signed by Venkateswara Pavuluri
Date: 4/16/2020 10:00:19AM
GUID: 551eb409003b6d46b8d5dfa7699e4742



Moo Jhong
Rhee

Digitally signed by Moo Jhong Rhee
Date: 4/16/2020 10:19:06AM
GUID: 502d0913000029f9798ca689a802fa55

CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

This CMC review of prescribing information is based on submission provided in SN0037 dated 02/03/2020.

(b) (4)

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TRADENAME not included	Not Acceptable. • Include PHEXXI™ as Trade name
Established name(s)	(L-lactic acid, citric acid, and potassium bitartrate)	Not Acceptable. • Revise it as “(lactic acid, citric acid, and potassium bitartrate)”
Route(s) of administration	Vaginal	Acceptable
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s)	Vaginal Gel; L-lactic acid (1.8%),	Not Acceptable

in metric system.	citric acid (1%), and potassium bitartrate (0.4%)	Specify the strength as; “18mg lactic acid (1.8%), 10mg citric acid (1%), and 4mg potassium bitartrate (0.4%)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	Not applicable	Not applicable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Not a parenteral drug product. Pre-filled Single-dose Vaginal Applicator.	Acceptable

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Not applicable	Acceptable. No special preparation is required, other than inserting the plunger in to the prefilled applicator, after removing from the aluminum foil overwrap, per IFU.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Start of Applicant material

(b) (4)

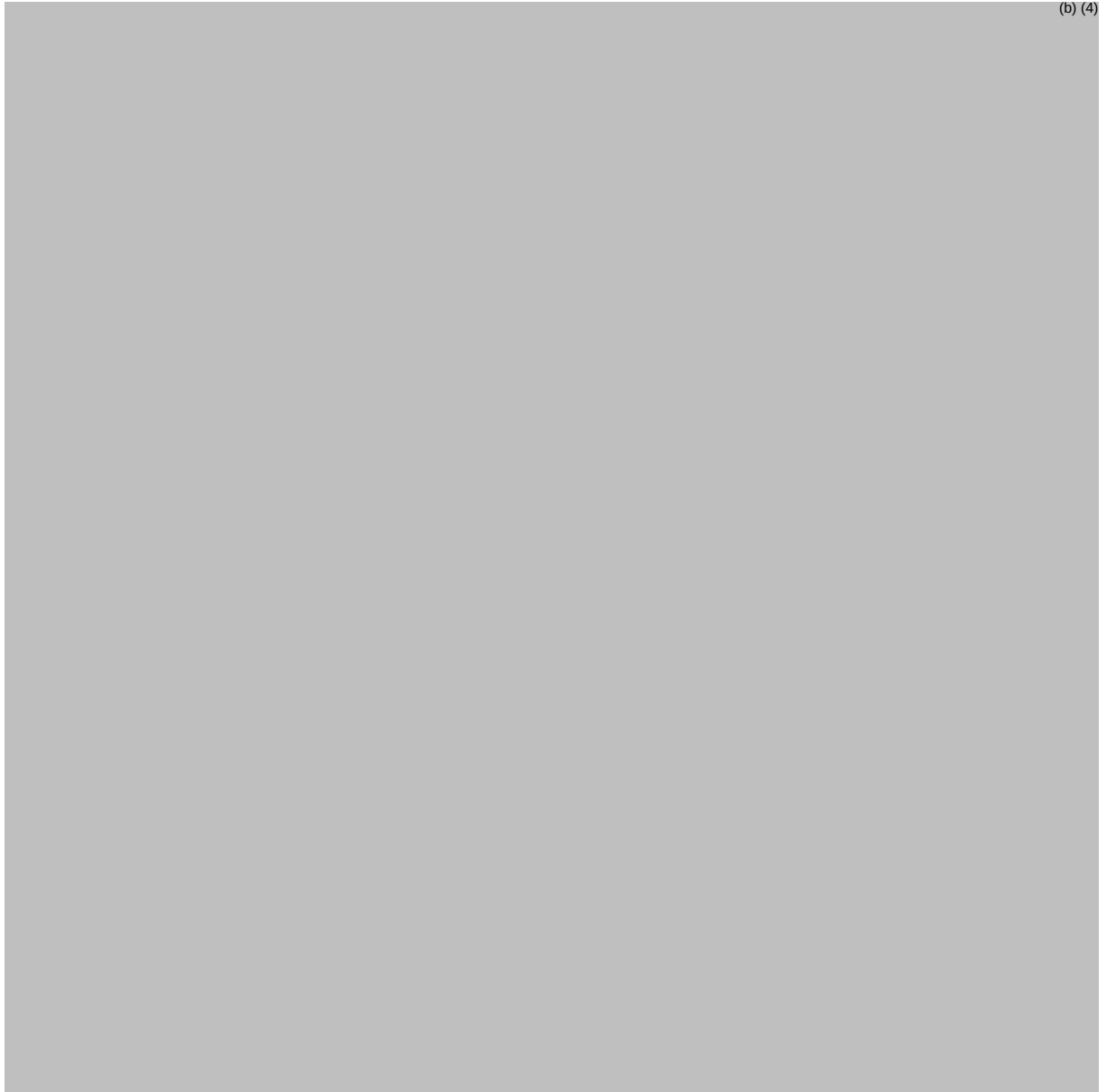
End of Applicant material

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	No dosage form is given	Not Acceptable • “Tradename” should be revised to “PHEXXI™ (lactic acid, citric acid, potassium bitartrate) vaginal gel”
Strength(s) in metric system	L-lactic acid (1.8%), citric acid (1%), and potassium bitartrate (0.4%)	Not Acceptable. • Revise the statement, “(b) (4) to “vaginal gel containing 18 mg Lactic acid (1.8%), 10 mg citric acid (1%), and 4 mg potassium bitartrate (0.4%) “
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Not applicable.	Simple inorganic compounds are not subject to salt policy.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	(b) (4)	Not Acceptable. • Revise as “Each pre-filled single-dose vaginal applicator of Tradename (lactic acid, citric acid, potassium bitartrate) vaginal gel delivers 5 g of off-white to tan color gel. • Bioadhesive, naturally occurring, should be removed • L-lactic acid should be changed to lactic acid

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	Not applicable to semisolid dosage form	Not applicable
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Not a parenteral drug product; but a “Pre-filled Single-dose Vaginal Applicator”	Acceptable

1.2.3 Section 11 (DESCRIPTION)

Start of Applicant material



End of Applicant material

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	TRADENAME No established name is stated.	Not Acceptable - Insert PHEXXI™ as trade name - The established name should be followed by the "PHEXXI™ (lactic acid, citric acid, and potassium bitartrate) vaginal gel"
Dosage form(s) and route(s) of administration	Not provided	Not acceptable Dosage form, vaginal gel, should be stated as above.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Not applicable	The simple inorganic compounds are not subject to salt policy.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	(b) (4)	Not Acceptable. - L-lactic acid, USP should be changed to "lactic acid, USP" - Separate the list of active ingredients from inactive ingredients as follows. "Each 5 g dose is provided in a pre-filled single-dose applicator containing lactic acid, citric acid, potassium bitartrate as active ingredients, and also glycerin, alginic acid, xanthan gum, sodium hydroxide, benzoic acid, and purified water as inactive ingredients"
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Not an injectable.	Not applicable

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not applicable	Not applicable
Statement of being sterile (if applicable)	Not a sterile product	Not applicable
Pharmacological/therapeutic class	vaginal pH regulator	Acceptable
Chemical name, structural formula, molecular weight	Information included for each of the active ingredients as copied above	Acceptable
If radioactive, statement of important nuclear characteristics.	Not applicable	Not applicable
Other important chemical or physical properties (such as pKa or pH)	None	Acceptable
For oral prescription drug products, include gluten statement if applicable	Not applicable	Not applicable
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	No promotional statement is made	Acceptable

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Start of Applicant material



(b) (4)

End of Applicant material

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	No information provided	Not acceptable. Include the word “vaginal gel” after “TRADENAME is off-white to tan in color”
Strength(s) in metric system	No information provided	Not acceptable. Include the text “containing three active ingredients: lactic acid 1.8%, citric acid 1%, and potassium bitartrate 0.4%,”
Available units (e.g., bottles of 100 tablets)	Box of 12	Not acceptable. Revise text as “Box of 12 single use applicators”.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4)	Not acceptable. - Revise text as follows: “TRADENAME is supplied as individually wrapped 5 g pre-filled single-dose vaginal applicators along with a plunger in sealed foil pouches and are available as follows: NDC 69751-100-12 Each gram contains; -LLactic acid (1.8%), -CCitric acid (1%), and -Potassium bitartrate (0.4%) supplied as individually wrapped 5 g pre-filled single-dose vaginal applicators along with a plunger in sealed foil pouches:”
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	Not applicable	Not applicable

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Not applicable for pre-filled single-dose vaginal applicators	Not applicable
---	---	----------------

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

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	None; pre-filled single-dose vaginal applicators are opaque.	Acceptable
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	Not applicable for water based semisolid product.	Not applicable
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	at room temperature 20°C to 25°C (68°F to 77°F); excursion permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].	Acceptable
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	Not applicable	Not applicable
Include information about child-resistant packaging	None	Acceptable.

1.2.5 Other Sections of Labeling:

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for Evofem, Inc., a wholly owned subsidiary of Evofem Biosciences, Inc., San Diego, CA 92130	Not acceptable. To include street address.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Not applicable

IFU and Patient Information documents doesn't have any text related to quality or composition statements.

3.0 CARTON (PHARMACY BOX) AND CONTAINER LABELING

This CMC review of Carton and Container is based on submission provided in SN0042 dated 04/08/2020.

3.1 Container Label (Applicator Foil, TRADE Name and Unbranded V2) :



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

Item	Information Provided in the NDA	Assessor's Comments about Applicator Foil and Carton
Proprietary name, established name, and dosage form (font size and prominence)	phexxi™, (L-lactic acid, citric acid, and potassium bitartrate) Vaginal Gel	Not Acceptable. Font size for established name is acceptable. However, established name should be revised as (lactic acid, citric acid, and potassium bitartrate) vaginal gel.
Dosage strength	1.8%, 1%, 0.4%	Acceptable
Route of administration	Vaginal	Acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not applicable; Potassium bitartrate is itself a buffering agent	
Net contents (e.g. tablet count)	"Net contents: 5 g" on the applicator foils, branded and Unbranded V2	Acceptable
"Rx only" displayed on the principal display	Yes	Acceptable
NDC number	NDC 69751-100-12	Acceptable
Lot number and expiration date	LOT XXXX EXP XX/XXX	Acceptable
Storage conditions. If applicable, include a space on the carton (Pharmacy Box) labeling for the user to write the new BUD.	Store at 15°C to 30°C (59°F-86°F) (see USP Controlled Room Temperature).	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Not a parenteral drug product; but it is a "Pre-filled Single-dose Vaginal Applicator"	Acceptable

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	Not applicable	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not applicable	
Bar code	Bar code not included	Not acceptable. Bar code is required on immediate container, in accordance with 21 CFR 201.25(c)(2)

Item	Information Provided in the NDA	Assessor's Comments about Applicator Foil and Carton
Name of manufacturer/distributor	Manufactured for Evofem, Inc., a wholly owned subsidiary of Evofem Biosciences, Inc., 12400 High Bluff Drive, Suite 600 San Diego, CA 92130	Acceptable.
Medication Guide (if applicable)	Not applicable	
No text on Ferrule and Cap overseal	No information provided	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	Not a compendial drug. Label contains adequate information about the quantity of each the three active ingredients	Acceptable
And others, if space is available	“For Vaginal Use Only” on applicator foil and carton.	Acceptable.

Assessment of Carton (Pharmacy Box) and Container Labeling: Not Acceptable

*The following deficiencies on carton and container labels were communicated to the applicant on 4/1/20.

- a) *Revise the font sizes for proprietary and established names on the TRADENAME foil, to be in accordance with 21 CFR 201.10 (g)(2), the established name should be at least ½ the size of the proprietary name and have commensurate prominence taking into consideration typography, layout, contrast and other printing features.*
- b) *Revise dosage strength on TRADENAME foil to 1.8%, 1%, and 0.4% (separated by “,” instead of “/”) to be consistent with the style used for active ingredients in drug product.*
- c) *Include statement of “Net contents: 5 g” on the applicator foil, separated from rest of the text, per 21 CFR 201.51(d)*
- d) *If space on the primary container (applicator foil) allows, modify the text to “Store at 20°–25° (68°–77° F) with excursions permitted between 15°C to 30°C (59°F - 86°F) (see USP Controlled Room Temperature).*
- e) *On secondary packaging component and applicator foil (if space allows for), Under “Name of manufacturer/distributor” Include street address as well along with the text “Manufactured for Evofem, Inc., a wholly owned subsidiary of Evofem Biosciences, Inc., San Diego, CA 92130, per 21 CFR 201.1(i).*
- f) *Include statement “**For Vaginal Use Only**” to appear prominently on the applicator foil.*
- g) *Include the following text on Prefilled Intimacy Wrap (Secondary packaging): “Each foil pouch contains one Prefilled Single-dose Vaginal Applicator and one Plunger”.*
- h) *The outer carton (Pharmacy Box) should include the following statements:*
 - i) *Each Single-dose pre-filled applicator contains: 5 g Vaginal Gel;*
 - j) *Active ingredients: Lactic acid 1.8%, citric acid 1% and Potassium bitartrate 0.4%*
 - k) *Net Contents: 12 individually wrapped foil pouches; each containing one Prefilled single dose Vaginal Applicator and one Plunger.*

In response to the requests above, the applicant submitted an amendment with draft **carton and container labels** on 08-APR-2020, and resolved satisfactorily except for two comments (see the **List of Deficiencies**):

ITEMS FOR ADDITIONAL ASSESSMENT

List of Deficiencies:

The following specific deficiency item is relevant, if applicable, to all Labels and Labeling Text (PI, applicator foil, intimate foil wraps and 12-unit carton).

- The proposed established name for L-Lactic acid is not acceptable per FD&C act 502 which stipulates that the established name for drug be the title of USP monograph, unless it obtains new USAN name per 21 CFR 299.4 as a new active ingredient.

(b) (4)

Therefore, the title of the drug should be **Tradename (lactic acid, citric acid, potassium bitartrate) vaginal gel**.

A. Regarding Full Prescribing Information:

1. Highlight Section

- The established name in the **title** should be revised to “(lactic acid, citric acid, and potassium bitartrate)”
- The strength in “**Dosage form and Strength**” section should be revised to “18mg lactic acid (1.8%), 10mg citric acid (1%), and 4mg potassium bitartrate (0.4%)”
- “(b) (4)” should be removed from “**Dosage Form and Administration**” section

2. Section 3 (DOSAGE FORMS AND STRENGTHS)

- “Tradename” should be revised to “Tradename (lactic acid, citric acid, potassium bitartrate) vaginal gel”
- Revise statement, (b) (4) to “vaginal gel containing 18 mg Lactic acid (1.8%), 10 mg citric acid (1%), and 4 mg potassium bitartrate (0.4%)”
- Revise statement, (b) (4) to “Tradename (lactic acid, citric acid, potassium bitartrate) vaginal gel delivers 5 g of off-white to tan color gel.
- (b) (4) should be removed.
- “L-lactic acid” should be changes to “lactic acid”

3. Section 11 (DESCRIPTION)

- The established name should be followed by “TRADENAME as (lactic acid, citric acid, and potassium bitartrate) vaginal gel”
- “L-lactic acid, USP” should be changed to “lactic acid, USP”
- Separate the list of the active ingredients from the inactive ingredients as follows:

“Each 5 g dose is provided in a pre-filled single-dose applicator containing lactic acid, citric acid, potassium bitartrate as inactive ingredients, and also glycerin, alginic acid, xanthan gum, sodium hydroxide, benzoic acid, and purified water as inactive ingredients”

4. Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

- Revise the statement,

(b) (4)

to,

“TRADENAME (lactic acid, citric acid, potassium bitartrate) vaginal gel is supplied as individually wrapped 5 g pre-filled single-dose vaginal applicators along with a plunger in sealed foil pouches and a box of 12 single use applicators are available as follows:

NDC 69751-100-12

Each gram of contains;

- 18mg lactic acid (1.8%),
- 10mg citric acid (1%), and
- 4mg potassium bitartrate (0.4%)

5. Section 17

- Full street address should be stated after the business place.

B. Regarding Carton (Pharmacy Box) and Container Labeling submitted in SN 0042, Dt 08-APR-2020

- If space is allowed on the container label, revise the storage condition to “Store at 20°–25° (68°–77° F) with excursions permitted between 15°C to 30°C (59°F - 86°F) [see USP Controlled Room Temperature].
- Include Bar code on immediate container, required per 21 CFR 201.25(c)(2)

Overall Assessment and Recommendation:

As of this review, this application is not deemed ready for approval in its present form per 21 CFR 314.125(6) from the CMC labeling/labels perspective until the remaining deficiencies delineated in the **List of Deficiencies** above are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Venkateswara R. Pavuluri, Ph. D, R. Ph.; 16-APR-2020

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

I agree with Dr. Pavuluri's assessment on the labeling and labels, and therefore, I concur with his recommendation that this application is not deemed ready for approval from the CMC labeling/label perspective until the current deficiencies listed in the **List of Deficiencies** are satisfactorily resolved.

Moo-Jhong Rhee, Ph. D.

Chief, Branch IV

DNDC II/ONDP/OPQ

17-APR-2020

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



Venkateswara
Pavuluri

Digitally signed by Venkateswara Pavuluri
Date: 4/17/2020 03:25:49PM
GUID: 551eb409003b6d46b8d5dfa7699e4742



Moo Jhong
Rhee

Digitally signed by Moo Jhong Rhee
Date: 4/17/2020 04:20:53PM
GUID: 502d0913000029f9798ca689a802fa55

Memorandum

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

Date: May 21, 2020

From: Venkateswara R. Pavuluri, Ph.D., R. Ph.
Drug Product Reviewer
Office of New Drug Products
Branch IV/DNDP II

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

To: CMC Labeling Review #2 of NDA 208352
for Phexxi™ (lactic acid, citric acid and
potassium bitartrate) Vaginal Gel

Subject: Final Recommendation - APPROVAL

At the time when Labeling Review of NDA208352 was completed on 16-APR-2020, this NDA was not recommended for approval per 21 CFR 314.125(6). Specifically, it was noted that labeling (Prescribing Information, container/carton labels) were not acceptable as presented and did not comply with the requirements under 21 CFR § 201.25(c)(2) and 21 CFR § 299.4. The NDA for this drug product was otherwise complete and adequate from the drug product perspective.

This addendum is to document the most updated Prescribing Information of the CMC related sections: the product title in Highlights of Prescribing Information Section and Section #3, #11, #16 and #17 in Full Prescribing Information (**Attachment-1**) and container/carton labels (**Attachment-2**) as submitted on May 21, 2020. The labeling and labels are now acceptable from the CMC labeling perspective.

Recommendation:

The outstanding CMC label/labeling issues have been satisfactorily resolved. This application is now recommended for **approval** from the CMC labeling/label perspective.

Venkateswara R. Pavuluri, Ph. D., R. Ph.
Drug Product Reviewer
Branch IV, Division II, ONDP

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



Venkateswara
Pavuluri

Digitally signed by Venkateswara Pavuluri
Date: 5/21/2020 04:24:28PM
GUID: 551eb409003b6d46b8d5dfa7699e4742



Moo Jhong
Rhee

Digitally signed by Moo Jhong Rhee
Date: 5/21/2020 04:27:34PM
GUID: 502d0913000029f9798ca689a802fa55

PROCESS

(b) (4)



P. 8.2 Post-Approval Stability Protocol and Stability Commitment

Two commercial size engineering batches and three registration batches have been manufactured at (b) (4). The three registration batches (b) (4) have been placed on stability.

- Microbial Limits – Unchanged

Microbial Limits	Method	Limit
Total aerobic microbial count	USP (b) (4)	NMT (b) (4) CFU/g
Total yeast and mold count	(b) (4)	NMT (b) (4) CFU/g
<i>Candida albicans</i>		Absent
<i>Pseudomonas aeruginosa</i>		Absent
<i>Staphylococcus aureus</i>		Absent

Testing Schedule for Gel Pre-filled Applicators

Condition	Testing Required at Time Point (months)								
	0	1	3	6	9	12	18	24	36
25°C/40% RH	X					X		X	X

Post Approval Stability Commitment

The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program.

P.8.3 Stability Data

The applicant stated that microbial limit testing remained within the acceptance criteria for all batches manufactured (b) (4).

R Regional Information

Executed Batch Records

Executed batch records were provided for lot #s (b) (4).

Comparability Protocols - No CP was included in the application.

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q)

MODULE 1

2.A. Package Insert – Unchanged

The drug product is supplied as individually wrapped 5 g pre-filled single-dose vaginal applicators. Store in the original foil pack at room temperature 20°C to 25°C (68°F to 77°F); excursion permitted between 15°C to 30°C (59°F to 86°F).

Post-Approval Commitments: N/A

MICROBIOLOGY LIST OF DEFICIENCIES – None identified

Primary Microbiology Reviewer Name and Date: Yarery Smith, Ph.D., 01/23/2020

Secondary Reviewer Name and Date (and Secondary Summary, as needed): I
concur. Jesse Wells, Ph.D., 01/23/2020

END



Jesse
Wells

Digitally signed by Jesse Wells

Date: 1/23/2020 03:27:58PM

GUID: 508da70b00028ea901ac6652677f7d00



Yarery
Smith

Digitally signed by Yarery Smith

Date: 1/23/2020 03:50:54PM

GUID: 508da70d00029036ac4e081b955894d3

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARK R SEGCEL
05/22/2020 07:17:45 PM

Memorandum

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

Date: April 25, 2016

From: Mark R. Seggel
CMC Lead (Acting) / ATL
Office of New Drug Products
Branch V / DNDP II

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

To: OPQ Integrated Quality Assessment #1 of NDA 208352 for Amphora
(lactic acid, citric acid, and potassium bitartrate) Vaginal Gel

Subject: Final Recommendation

Background: OPQ's Integrated Quality Assessment #1 for NDA 208352, dated 11-APR-2016, noted, "[a]s of this review, this 505(b)(2) NDA for a Combination Product is Not Ready for Approval in its present form per 21 CFR 314.125(b)(1), 21 CFR 314.125(b)(8) and 21 CFR 314.125(b)(13)." Specifically:

- A final recommendation from the Office of Process and Facility (OPF) was pending.
- CDRH-ODE identified deficiencies related to the characterization of these components (e.g., mechanical function and stability; biocompatibility). Until the device quality attributes are fully characterized, there is no assurance that the applicators will perform safely and effectively throughout the shelf-life.
- Label/labeling deficiencies were identified, precluding approval in accordance with 21 CFR 314.125(b)(8).

Current Status: Significant quality and cGMP deficiencies were identified during the March 2016 inspection of [REDACTED] (b) (4) the manufacturer of the active ingredient potassium bitartrate. All other facilities are adequate for the operations proposed in this NDA. OPQ's OPF therefore has issued an overall Withhold recommendation for this application (see Facilities Review (FR) Addendum, dated April 25, 2016; see also Attachment 1 of this review addendum for the cover page from the FR Addendum).

The issues identified by CDRH-ODE will be conveyed to the applicant in the CR letter.

Labeling issues were not resolved during this review cycle due to the pending Complete Response (CR) action for this application, but will be addressed following resubmission of the application. Preliminary labeling comments will be conveyed to the applicant in the CR letter.

Recommendation:

A ***Complete Response*** for Evofem Inc.'s NDA 208352, Amphora (lactic acid, citric acid, and potassium bitartrate) Vaginal Gel, is recommended from the OPQ perspective, and in accordance with 21 CFR 314.125(b)(1), 21 CFR 314.125(b)(8) and 21 CFR 314.125(b)(13).

APPLICATION TECHNICAL LEAD SIGNATURE:

Mark R. Seggel, Ph.D.
CMC Lead (Acting)
ONDP / DNDP II / Branch V

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

Recommendation: *As of this review, this 505(b)(2) NDA for a Combination Product is Not Ready for Approval in its present form per 21 CFR 314.125(b)(1) 21 CFR 314.125(b)(8) and 21 CFR 314.125(b)(13).*

NDA 208352

Review #1

Drug Name/Dosage Form	Amphora Gel (lactic acid, citric acid, and potassium bitartrate vaginal gel)
Strength	1.76% (88 mg), 1 % (50 mg), 0.4% (20 mg) per 5 g
Route of Administration	Vaginal
Rx/OTC Dispensed	Rx
Applicant	Evoform Inc.
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	07/02/15	Multi-discipline
Quality/Response to Information Request (sn0001)	08/17/15	Facilities
Quality/Response to Information Request (sn0002)	08/19/15	Facilities/Microbiology
Quality/Response to Information Request (sn0008)	10/29/15	Product/Process
Labeling/Container-Carton Draft (sn0014)	11/24/15	Product
Quality/Response to Information Request (sn0016)	12/28/15	Product
Quality/Response to Information Request (sn0017)	01/22/16	CDRH-OC/Facilities
Quality/Response to Information Request (sn0020)	02/04/16	Product
Quality/Response to Information Request (sn0021)	02/05/16	Substance
Quality/Response to Information Request (sn0022)	02/29/16	CDRH-OC/Facilities

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Debasis Ghosh	OPQ/ONDP/DNDAP/Branch II
Drug Product	Sarah Ibrahim	OPQ/ONDP/DNDPII/Branch V
Process	Kelly Forney-Stevens	OPF/DPA3/Branch VIII
Microbiology	Yarery Smith	OPF
Facility	Tony Wilson	OPF
Biopharmaceutics	Vidula Kolhatkar	ONDP
Regulatory Business Process Manager	Thao Vu	OPRO
Application Technical Lead	Mark Seggel	ONDP
Environmental Assessment (EA)	Mark Seggel	ONDP

Table of Contents

Table of Contents	2
Quality Review Data Sheet	3
Executive Summary	5
Primary Quality Review	14
ASSESSMENT OF THE DRUG SUBSTANCE	14
2.3.S DRUG SUBSTANCE [Lactic Acid] 14	
2.3.S DRUG SUBSTANCE [Potassium Bitartrate, American Tartaric Products]	17
2.3.S DRUG SUBSTANCE [Citric Acid, Advantar Laboratories]	21
ASSESSMENT OF THE DRUG PRODUCT	33
2.3.P DRUG PRODUCT	33
R.2 Comparability Protocols	54
ASSESSMENT OF THE PROCESS	58
2.3.P DRUG PRODUCT	58
R.2 Comparability Protocols	74
ASSESSMENT OF THE PROCESS - MICROBIOLOGY	79
ASSESSMENT OF THE FACILITIES	85
2.3.S DRUG SUBSTANCE	85
2.3.P DRUG PRODUCT	85
ASSESSMENT OF THE BIOPHARMACEUTICS	87
ASSESSMENT OF MICROBIOLOGY	89
2.3.P.7 Container/Closure System	89
A APPENDICES	89
ASSESSMENT OF ENVIRONMENTAL ANALYSIS	91
I. Review of Common Technical Document-Quality (Ctd-Q) Module 1	93
Labeling & Package Insert	93
II. List of Deficiencies To Be Communicated	112
III. Attachments	113

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	Adequate	01/08/2016	Reviewed by Debasis Ghosh in support of this NDA. No amendment is submitted to the DMF since last review.
	II			Adequate	02/03/2016	Reviewed by Debasis Ghosh in support of this NDA. Since last review, an amendment in response to IR is submitted to the DMF on 2/24/2016 (DARRTS SD#3). Based on preliminary review of SD#3, the DMF is adequate.
	III			N/A		Adequate
	III			N/A		Adequate
	III			N/A		On August 24, 2015 the CDER/FDA received an Amendment dated August 15, 2015 for the closed Drug Master File (b) (4). This DMF was closed on June 30, 2015 due to no response to the Overdue Notice Letter (January 16, 2015) within 90 days with the submission of an Annual Report.

(b) (4)	III	(b) (4)	dequate		Last reviewed 02/03/2012 by GENE W HOLBERT
	III		dequate		Last reviewed 04/29/2015 by LU, YONG DE
	III		dequate		Last reviewed 01-Oct-2013 by RAVINDRA K KASLIWAL
	III		dequate		Last Reviewed 28-Jun-2011 by GEORGE LUNN
	III		dequate		Last Reviewed 14-May-2012 by ZEDONG DONG
	III		/A		Adequate
	III		/A		Adequate

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
510(k)	K033776 (Personal Lubricant; Class II device)	Instead Intimate Lubricant; Instead Inc. Determination of <i>Substantially Equivalent</i> 6/24/04
Original IND	IND 64623	Investigational use of Acidform Gel (aka Amphora Gel) as a contraceptive gel; sponsor: The CONRAD Program
Original IND	IND 109300	Investigational use of Amphora Gel as a vaginal contraceptive; sponsor: Evofem, Inc.

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	Review Completed	Information is insufficient. Deficiencies noted and information request drafted. See darfts Reference ID: 3905514	03/21/16	Veronica Price
CDRH-OC	Final	Approval CTS No.: ICC1500610	3/1/16	Jamie Kamon-Brancazio Viky Verna
Clinical	N/A			
Other	-			

N/A Not Applicable

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and of the gel formulation. While efficacy (prevention of pregnancy) of the product has not been unequivocally demonstrated, the product quality attributes (pH, buffering capacity, and viscosity) requisite for spermicidal activity are adequately controlled.

On the other hand, in their review of the device components (pre-filled applicator and disposable applicator) of this Combination Product, CDRH-ODE identified deficiencies related to the characterization of these components (e.g., mechanical function and stability; biocompatibility). Until the device quality attributes are fully characterized, there is no assurance that the applicators will perform safely and effectively throughout the shelf-life.

A final recommendation regarding manufacturing facility CGMP status from the Facilities review team within the Office of Process and Facility is pending as of this review. A review addendum will be filed when a final recommendation regarding facility acceptability is issued.

On March 23, 2016, DBRUP issued a “Deficiencies Preclude Discussion” letter notifying the applicant that deficiencies had been identified that preclude discussion of labeling and PMC/PMRs at this time. These deficiencies are related to conduct of the clinical trials and analysis of the clinical study results (see 02/26/16 Memorandum to File). Therefore labeling (package insert, container/carton labels) issues have not been resolved.

From the OPQ perspective, this NDA is therefore not ready for approval in its present form per 21 CFR 314.125(b)(1), 21 CFR 314.125(b)(8) and 21 CFR 314(b)(13).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable

II. Summary of Quality Assessments

“Evofem, Inc. (Evofem) is seeking approval of a New Drug Application (NDA) for Amphora™ (88 mg [1.76%] lactic acid, 50 mg [1.00%] citric acid, 20 mg [0.40%] potassium bitartrate in a 5 g dose [equivalent to 5 mL]), a prescription non-hormonal topical contraceptive spermicidal gel for the prevention of pregnancy, under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Amphora gel is an acid-buffering

gel formulation which buffers the vaginal pH so that it remains below 5.0 when ejaculate is introduced. Typically, the introduction of semen into the vagina causes a rise in pH above 6.0 due to the alkalinity of the ejaculate, which neutralizes the normally acidic vaginal environment, allowing the survival of spermatozoa. The properties of the acidifying Amphora gel maintain low vaginal pH (pH = 3.5-4.5) even in the presence of semen, immobilizing spermatozoa and making Amphora gel spermicidal”

A. Drug Substance Quality Summaries

The three active ingredients in Amphora Gel, lactic acid, potassium bitartrate and citric acid, function together to provide pH buffering capacity within the vagina. Citric acid and potassium bitartrate also have metal chelation and anti-oxidant activity. All actives are extremely well characterized substances, widely occurring, widely used, and are Generally Recognized as Safe (GRAS) [for use as direct food additives]. Each is the subject monographs in the USP and Food Chemical Codex (FCC). All are of suitable quality and purity for the intended use and route of administration.

Chemistry, manufacturing and controls (CMC) documentation provided in support of the use of the active ingredients meets the requirement of 21 CFR 314.50(d)(1)(i). Adequate manufacturing and testing controls have been established to assure the identity, strength, quality, and purity of each drug substance.

From the perspective of the Drug Substance review team, the NDA is recommended for approval.

(b) (4)

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

B. Drug Product Quality Summary

Amphora Gel (lactic acid, citric acid and potassium bitartrate vaginal gel), 1.76% / 1.00% / 0.40% contains 88-, 50- and 20-mg, of the active ingredients respectively, per 5 gram dose [equivalent to 5 mL]. Inactive ingredients include purified water (b) (4) and glycerin (b) (4) (as a humectant). Sodium hydroxide is used to adjust the formulation to pH (b) (4). Benzoic acid (b) (4) is added as a preservative. Alginic acid (b) (4) and xanthum gum (b) (4) provide viscosity and mucoadhesive properties sufficient to allow product retention in the vagina.

The gel will be supplied in two packaging configurations: a unit-dose (5 mL equivalent to 5 g) pre-filled vaginal applicator (b) (4)

Leachables and extractables testing was conducted on all components. No leachables compounds over the Safety Concern Threshold (SCT) of 1.5 µg/day were observed. The pre-filled applicators are packaged in a foil overwrap.

Efficacy is directly linked to the pH and buffering capacity of the drug product. (b) (4)

The drug product specification also includes tests for identification of each of the active ingredients, physical appearance, minimum fill, preservative (benzoic acid) content and microbial limits. Note that the specification does not include tests for content uniformity and related substances (degradants). The test for content uniformity is considered unnecessary due to the demonstrated homogeneity of the bulk product and the control on fill weight. The three small-molecule organic acids that are the active ingredients are extremely stable, even under accelerated conditions and typical forced degradation conditions. Relevant degradation pathways have not been identified. As such, further routine testing for degradants for release and on stability is not warranted.

During stability testing, discoloration of the gel was noted in some samples. This was ultimately attributed to degradation of alginic acid. While the level of degradation is considered insignificant from a safety perspective, there is concern that loss of pharmaceutical elegance would lead to user non-compliance and customer complaints. Storage at elevated temperatures should therefore be avoided.

The proposed (b) (4) expiration dating period for drug product in either presentation when stored at 20° - 25°C is supported by the available stability data.

C. Manufacturing Process



The Manufacturing Process review team within the OPQ Office of Process and Facilities (OPF) has concluded that the drug product manufacturing processes and controls, as revised, are adequate.

D. Biopharmaceutics

The Biopharmaceutics review team notes that the proposed product's activity does not depend on release of APIs from the drug product but on the overall buffering ability of the product. In vitro release testing is not required. No further Biopharmaceutics review was conducted.

E. Microbiology

The drug product is a non-sterile formulation for topical administration. Nevertheless, the formulation contains benzoic acid antimicrobial preservative. Drug product testing includes microbial limits (NMT (b) (4) cfu/g total aerobic microbial count, nmt (b) (4) cfu/g total yeasts and mold count) and tests for absence of indicator organisms (*C. albicans*, *P. aeruginosa*, and *S. aureus* absent).

While the level of benzoic acid decreases due to absorption by the plastics of the pre-filled applicator, the level remaining has been found to be adequate.

The product quality Microbiology team notes that, “*Burkholderia cepacia* complex (BCC) testing is not required because the drug product is semi-aqueous and has a pH of (b) (4) making growth of BCC in this drug product highly unlikely.”

The Office of Process and Facilities product quality Microbiology review team has concluded that there are “no microbiology deficiencies” (see review section covering the Assessment of the Process – Microbiology for details).

F. Facilities

An overall recommendation from the Division of Inspectional Assessment, OPQ Office of Process and Facilities, is not available as of this review. Upon receipt of that recommendation, an addendum to this review will be filed. No approvability issues with respect to facility CGMP status are anticipated at this time.

Therefore, in its present form, this NDA may not be ready for approval in accordance with 21 CFR 314.125(b)(13).

G. Device Summary

Because the drug product is supplied as gel in pre-filled applicators (b) (4) Amphora Gel is considered a Combination Product. As such, CDRH was consulted with regard to device (i.e., applicator, which are considered Class 1 devices) engineering and with regard to device GMPs.

CDRH-ODE

This consult to CDRH/ODE/DRGUD/OGDB was initiated by DBRUP. In V. Price’s review dated 3/21/16 (darrrts Reference ID 3905514), the CDRH biomedical engineer identified deficiencies related to the description of device components, biocompatibility testing, bench testing (forces required to deliver gel and to remove the plunger and condom compatibility), and device stability (i.e., impact of aging on performance).

CDRH-ODE concludes that, “the firm has not provided sufficient information on the applicators proposed for use with the Amphora® gel.”

Therefore, in its present form, this NDA is not ready for approval in accordance with 21 CFR 314.125(b)(1).

CDRH-OC

This consult was initiated by OPQ to (1) evaluate the applicant’s compliance with Quality System Requirements and to (2) determine if any ‘medical device’ inspections were required.

Based on the recent inspectional history of (b) (4) (site of manufacturing and packaging of the combination product), it was concluded that a medical device inspection was not required. However, it noted that, “[t]he firm is responsible for activities related to the manufacturing and development of the final combination product therefore the next inspection at the firm should cover compliance with applicable Quality System (QS – 21 CFR 820) requirements.”

During the initial documentation review, J. Kamon-Brancazio noted deficiencies related to Management Control (21 CFR 820.20), Design Control, General (21 CFR 820.30), Purchasing Controls (21 CFR 820.590) and Corrective and Preventative Action (CAPA) (21 CFR 820.100). After two rounds of information requests, Evofem provided adequate documentation demonstrating compliance with the relevant sections of 21 CFR 820. The CDRH Compliance Officer concluded, “[t]he application for NDA-208352 for Amphora Gel is approvable from the perspective of the applicable Quality System Requirements.”

See consult reviews dated 1/5/16, 2/16/16 and 3/1/16 (for consult CTS No.: ICC1500610) for details.

H. Environmental Assessment

Evofem has requested a categorical exclusion from the requirements to prepare an environmental assessment. The applicant knows of no extraordinary circumstance associated with the active ingredients in Amphora Gel. The expected introduction concentration (EIC) of each active moiety into the aquatic environment is not more than (b) (4) ppb, well below the 1 ppb threshold. On this basis, the requested categorical exclusion is granted.

I. Labeling

Numerous deficiencies in the labeling (package insert, container and carton labels) have been identified (see review notes below; see also DMEPA’s review dated 12/10/15). As noted above, labeling negotiations with the applicant have not been initiated. The deficiencies noted below in this review will be conveyed to the applicant at a future date.

Therefore, in its present form, this NDA is not ready for approval in accordance with 21 CFR 314.125(b)(8).

J. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Amphora™ Gel
Non Proprietary Name of the Drug Product	lactic acid, citric acid, and potassium bitartrate vaginal gel

Non Proprietary Names of the Drug Substances	• Lactic acid • Citric acid • Potassium bitartrate
Chemical Names of the Drug Substances	• 2-Hydroxypropanoic acid • 2-Hydroxypropane-1,2,3-tricarboxylic Acid • Potassium (2R, 3R) - 2,3,4-trihydroxy-4-oxobutanoate
Proposed Indication(s) including Intended Patient Population	Amphora™ gel is a non-hormonal vaginal contraceptive gel indicated for use in preventing pregnancy.
Duration of Treatment	N/A (Amphora Gel is to be administered prior to sexual intercourse)
Maximum Daily Dose	N/A
Alternative Methods of Administration	None

K. Biopharmaceutics Considerations

1. BCS Classification:

Not Applicable

- Drug Substance:
- Drug Product:

2. Biowaivers/Biostudies:

Not Applicable

- Biowaiver Requests
- PK studies
- IVIVC

L. Novel Approaches*Not Applicable***M. Any Special Product Quality Labeling Recommendations***Not Applicable. See below for review of labeling for additional comments.***N. Life Cycle Knowledge Information (see Attachment A)****OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY****Application Technical Lead Signature:**

In its current form, this new drug application is not ready for approval.

Mark R. Seggel, CMC Lead (Acting) for DBRUP
Application Technical Lead

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

(b) (4)

Due to outstanding clinical and statistical deficiencies, DBRUP plans to issue a Complete Response (CR) letter. Therefore, we defer deficiencies on the Applicant's labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter.

**Sarah Ibrahim, Ph.D.
Reviewer, Branch V
DNDP II/ONDP**

Sarah
Ibrahim -S

Digitally signed by Sarah Ibrahim -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Sarah Ibrahim -S
0.9.2342.19200300.100.1.1=2001591303
Date: 2016.04.06 11:25:07 -04'00'

Secondary Review Comments and Concurrence:

These labeling issues will be resolved in the next review cycle.

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

A. Labeling & Package Insert

a) DESCRIPTION section

- i) Is the information accurate? ☐ Yes ☐ No

If "No," explain.

- ii) Is the drug product subject of a USP monograph? ☐ Yes ☐ No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

Reviewer's Assessment:

b) HOW SUPPLIED section

- i) Is the information accurate? ☐ Yes ☐ No
If "No," explain.
- ii) Are the storage conditions acceptable? ☐ Yes ☐ No
If "No," explain.

Reviewer's Assessment:

c) DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☐ N/A
If "No," explain.

Reviewer's Assessment:

d) For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No
If "No," explain.

Reviewer's Assessment:

e) For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code

f) Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

Reviewer's Assessment:

For NDA only

II. List of Deficiencies To Be Communicated

OPQ has no deficiencies to be communicated to the applicant at this time. Labeling deficiencies will be communicated at a later date.

Several deficiencies were noted in the CDRH-ODE review.

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

Initial Risk Assessment for NDA 208353, Amphora Gel, a spermicidal contraceptive indicated for the prevention of pregnancy. Functions by maintaining low vaginal pH in the presence of semen.

Product Attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Appearance	- Quality of raw materials - Stability	1	4	1	4	
Identification	cGMPs	1	5	2	10	
Assay	- Formulation - Raw materials - Process parameters - Scale/Equipment	1	3	2	6	
Related Substances Impurities / Degradants	- Raw materials - Stability	1	1	4	4	APIs have good chemical stability
Uniformity of Dosage Units	- Formulation - Process parameters	1	1	4	4	
Microbial Limits	- Preservative - Container/closure system (CCS)	2	2	4	16	Non-sterile formulation, microbial limits plus absence of indicator organisms
Viscosity	Formulation	1	5	1	5	Critical for retention of gel
pH and Buffering capacity	Formulation	1	5	1	5	Critical for efficacy

RPN Values: Low Risk (1-25); Moderate Risk (26-60); High Risk (61-125)

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	- Quality of raw materials - Stability	L	(b) (4)	Acceptable	Degradation of alginic acid may contribute to discoloration, which may in term impact patient compliance
Identification	cGMPs	L		Acceptable	
Assay	- Formulation - Raw materials - Process parameters - Scale/Equipment	L		Acceptable	

Related Substances Impurities / Degradants	- Raw materials - Stability	L	(b) (4)	Acceptable	No acceptance testing or limits for degradants established.
Uniformity of Dosage Units	- Formulation - Process parameters	L		Acceptable	
Microbial limits	- Preservative - Container/closure system (CCS)	L		Acceptable	Benzoic acid level decreases due to absorption by pre-filled applicator materials.
Viscosity	Formulation	L		Acceptable	Critical Quality Attribute! Any changes that could impact viscosity should be carefully evaluated.
pH and buffering capacity	Formulation	L		Acceptable	Critical Quality Attribute! Any changes that could impact pH and buffering capacity should be carefully evaluated.

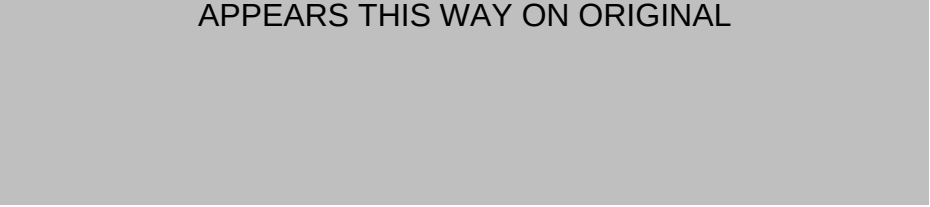
#####

Facilities Inspection Recommendation

APPEARS THIS WAY ON ORIGINAL

Other Product Quality Documents

APPEARS THIS WAY ON ORIGINAL



This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KIMBERLY A SHILEY
05/27/2020 02:40:44 PM