

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213690Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

<input checked="" type="checkbox"/> Approval
<input type="checkbox"/> Approval with Post-Marketing Commitment
<input type="checkbox"/> Complete Response

NDA 213690 Assessment # 1

Drug Product Name	Zilxi (minocycline)
Dosage Form	Foam
Strength	1.5%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Foamix Pharmaceuticals Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original Submission	08/02/2019	All
General Correspondence	08/05/2019	All
Response to Clinical Information Request	09/11/2019	Clinical
Letter of Authorization for DMF (b) (4)	09/20/2019	OPQ-Drug Substance
Response to Clinical Information Request	10/07/2019	Clinical
Response to Clinical Information Request	10/15/2019	Clinical
Response to Quality Information Request	10/16/2019	OPQ-Drug Substance
Response to Clinical Information Request	10/28/2019	Clinical
Response to Clinical and Quality Information Request	10/29/2019	All
Proprietary Name Request	11/06/2019	All
Response to Quality Information Request	11/08/2019	OPQ-OPMA
Clinical Safety Update	12/13/2019	Clinical

Patent Exclusivity/Patent Certification	12/13/2019	Administrative-All
Patent Exclusivity/Patent Certification	12/19/2019	Administrative-All
Quality Information Amendment	12/30/2019	OPQ-OPMA
Proprietary Name Request for Review	01/21/2020	All
Response to Quality Information Request	01/23/2020	OPQ-OPMA
Response to Quality Information Request	01/31/2020	OPQ-ONDP-Biopharmaceutics
Response to Quality Information Request	02/14/2020	OPQ-ONDP-Drug Product
Response to Quality Information Request	02/21/2020	OPQ-ONDP-Biopharmaceutics
Draft Labeling	02/21/2020	All
Proprietary Name Request for Review	03/02/2020	All
Response to Quality Information Request	03/04/2020	OPQ-ONDP-Biopharmaceutics
Response to Quality Information Request	03/12/2020	OPQ-ONDP-Drug Product
Response to Quality Information Request	03/17/2020	OPQ-ONDP-Drug Product
Patent Exclusivity/Patent Information	04/01/2020	Administrative-All
Container and Carton Labels	04/06/2020	All
Draft Labeling	04/09/2020	OPQ-ONDP-Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Joseph Leginus, Ph.D.	Donna Christner, Ph.D.
Drug Product	Hailin Wang, Ph.D.	Moo-Jhong Rhee, Ph.D.
Manufacturing	Youmin Wang, Ph.D.	Yubing Tang, Ph.D.
Microbiology	Aditi Das, Ph.D.	Neal Sweeney, Ph.D.
Biopharmaceutics	Rajesh Savkur, Ph.D.	Vidula Kolhatkar, Ph.D.
Regulatory Business Process Manager	Bamidele (Florence) Aisida, Pharm. D., BCPS	
Application Technical Lead	Hamid Shafiei, Ph.D.	
Laboratory (OTR)	N/A	N/A
Environmental	Hailin Wang, Ph.D.	Moo-Jhong Rhee, Ph.D.

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)	Adequate	04/19/2019	Reviewed by Joseph Leginus, Ph.D.
	II			Adequate	09/19/2019	Reviewed by Joseph Leginus, Ph.D.

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

Document	Application Number	Description
NDA	50808	Cross referenced to SOLODYN® for nonclinical toxicology
IND	132239	Commercial IND for minocycline hydrochloride foam 4%
NDA	212379	AMZEEQ® (minocycline) Foam, 4% for topical use owned by the same applicant

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

[IQA NDA Assessment Guide Reference](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

- The applicant of this 505(b)(2) new drug application has provided **sufficient CMC information** to assure the identity, purity, strength, and quality of the drug substance, minocycline hydrochloride and the drug product, Zilxi (minocycline) Foam, 1.5% for topical use.
- Labels/labeling issues have been **satisfactorily** addressed.
- The Office of Process and Facility has made an overall **“Acceptable”** recommendation regarding the facilities involved in this NDA.
- The claim for categorical exclusion of the environmental assessment has been granted.

Therefore, from the OPQ perspective, this NDA is recommended for **APPROVAL** with expiration dating period of **18 months**.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Foamix Pharmaceuticals Inc. has submitted this 505(b)(2) new drug application for Zilxi (minocycline) Topical Foam, 1.5% indicated for the treatment of (b) (4) rosacea in adults.

The active ingredient, minocycline, is a semi-synthetic derivative of tetracycline antibiotic that has been approved as its hydrochloride salt, minocycline hydrochloride, since 1971. Multiple drug products containing minocycline have been approved and are currently being marketed as capsules, tablets, extended-release tablets, oral suspensions, injections, and periodontal systems. Recently a minocycline foam drug product at the strength of 4% with nearly identical formulation for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older, from the same applicant was approved on October 18, 2019 under NDA 212379 which is being marketed under the brand name AMZEEQ. The only difference between the quantitative compositions of Zilxi and AMZEEQ is that a lower amount of active ingredient is used in the composition of Zilxi foam. The decrease in the amount active ingredient in Zilxi is compensated by a very minor adjustment in the amount of light mineral oil in the formulation. Therefore,

except for the strength, differences in the formulations of Zilxi foam and AMZEEQ, for all practical purposes are deemed insignificant.

The foam formulation has been developed to ease the topical application to affected skin while limiting adverse effects associated with systemic absorption of minocycline.

Zilxi is an oil-based suspension packaged and marketed as 30g in pressurized aerosol aluminum upright canisters with (b) (4) propellant, (b) (4) (butane, isobutane, and propane) that facilitates the discharge the drug product as a foam for topical use. Each gram of Zilxi foam contains 15mg of minocycline provided as 16mg of micronized minocycline hydrochloride.

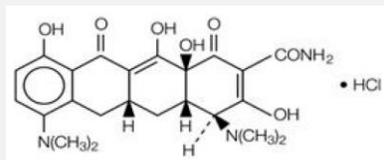
Proposed Indication(s) including Intended Patient Population	Treatment of (b) (4) rosacea in adults
Duration of Treatment	As prescribed by physicians
Maximum Daily Dose	Small amount of foam gently applied to the affected facial skin area on a day at the same time one hour before bedtime
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

Minocycline hydrochloride is a hydrochloride salt of minocycline, a semi-synthetic tetracycline antibiotic derivative. Oral drug products containing minocycline have shown to have antibacterial and anti-inflammatory effects.

Minocycline hydrochloride has the chemical name of 2-naphthacencarboxamide, 4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro- 3,10,12,12a-tetrahydroxy-1,11-dioxo-, monohydrochloride, molecular formula of C₂₃H₂₇N₃O₇·HCl, molecular weight of 493.94, and molecular structure below:



Minocycline hydrochloride is a yellow (b) (4) powder with a melting point of 210°C. It is soluble in solutions of alkali hydroxides and carbonates, sparingly soluble in water, slightly soluble in alcohol, and practically insoluble in chloroform and ether. (b) (4)

Micronized minocycline hydrochloride for this application is manufactured and supplied by (b) (4). The information regarding the manufacture of micronized minocycline hydrochloride by (b) (4) is provided in DMF (b) (4)

Minocycline hydrochloride is a compendial drug substance with USP and Eur monographs. It is tested and released according specification that complies with the compendial requirements. The release specification of minocycline hydrochloride intended for this application also includes (b) (4)

The information provided in DMF (b) (4) was reviewed by the Drug Substance reviewer, Dr. Joseph Leginus, on 04/18/2019 and 09/19/2019, respectively. Dr. Leginus has found both DMFs adequate to support this new drug application. Additionally, Dr. Leginus has found the information provided in the drug substance section of this application and the proposed retest date of (b) (4) adequate. Dr. Leginus's review is provided in the Drug Substance Chapter of the IQA.

Drug Product: Adequate

Zilxi (minocycline) Topical Foam, 1.5% has been developed for the treatment of (b) (4) rosacea in adults.

It is formulated as non-aqueous, oil-based, pre-foam suspension formulation containing micronized minocycline hydrochloride equivalent to 15mg of minocycline per gram of pre-foam formulation. The formulation of this drug product is the same as the formulation of the approved drug product AMZEEQ foam (NDA 212379 approved October 18, 2019). The only difference in the formulations of Zilxi and AMZEEQ is the reduced

amount of active ingredient in Zilxi which is compensated by a minor increase in amount of light mineral in the formulation. Therefore, except for the strength, formulations of the two drug product are considered identical.

The micronized minocycline hydrochloride pre-foam suspension formulation also contains soybean oil, coconut oil, light mineral oil, cyclomethicone (b) (4), cetostearyl alcohol, stearic acid, myristyl alcohol, hydrogenated castor oil, white wax (beeswax), stearyl alcohol, and docosanol (b) (4) as inactive ingredients. This drug product, similar to AMZEEQ, is packaged in an aluminum canister containing 30g of pre-foam formulation that is pressurized with the propellant, (b) (4) consisting of butane, isobutane, and propane that facilitates the discharge the product as a foam. Pressurized canisters containing 7g of Zilxi foam are also manufactured for use the physician samples. All inactive ingredient used in the composition of the drug product are either compendial materials or materials previously approved for use in AMZEEQ.

The drug product is tested and released according to a specification that includes testing and acceptance criteria for all physical and chemical attributes essential for assuring the identity, strength, purity, and quality of the drug product at release and throughout its proposed expiration dating period of 18 months. The applicant has provided sufficient stability data in support of the proposed drug product expiration dating period.

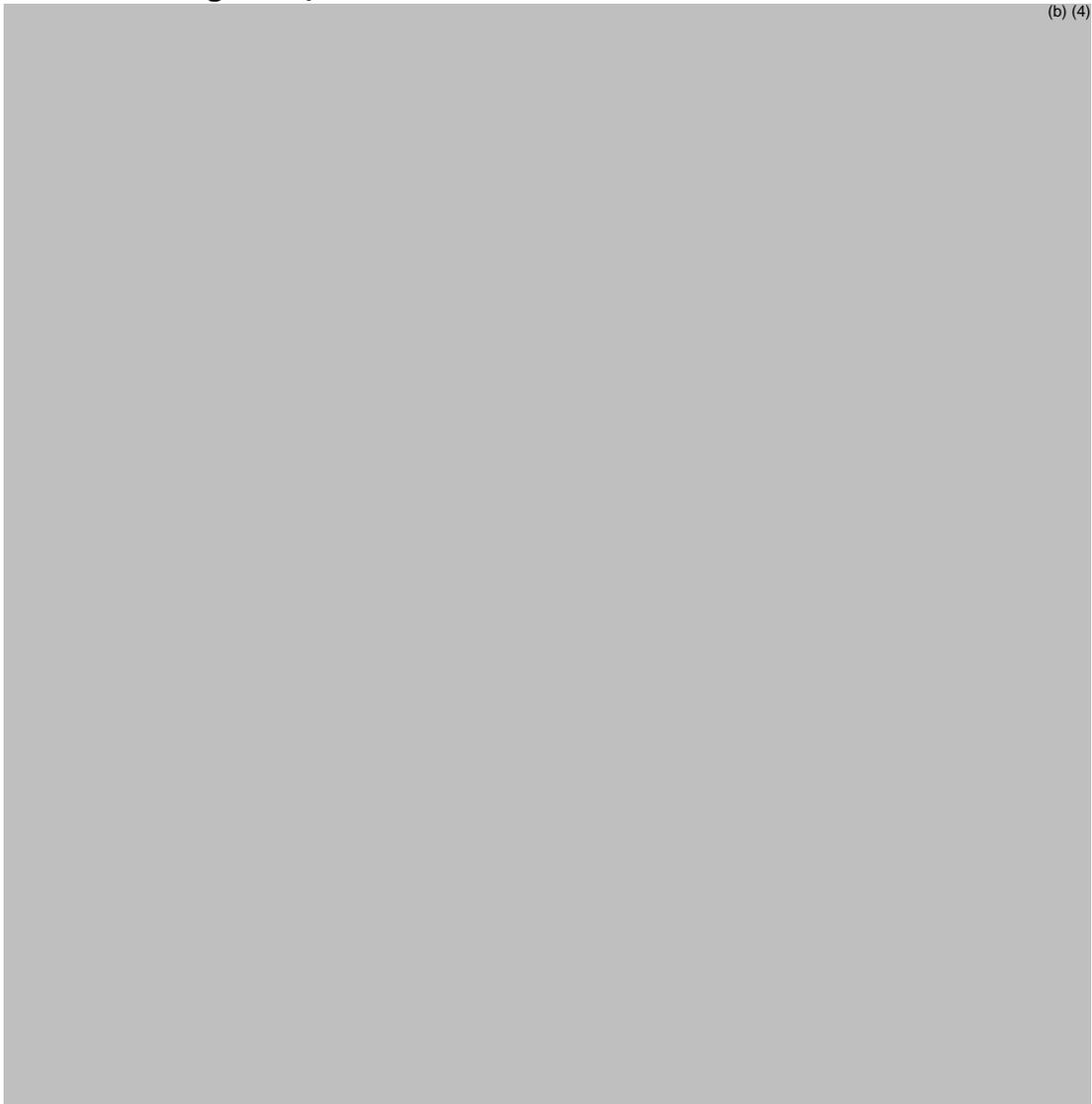
The drug product section of this application including the applicant's request for categorical exclusion from preparation of the environmental assessment has been reviewed by the Drug Product Reviewer, Dr. Hailin Wang. Dr. Wang has recommended the approval of this application with an expiration dating period of 18 months from the drug product perspective. Dr. Wang has also recommended granting the categorical exclusion for the preparation of environmental assessment for this application. Dr. Wang's review is provided in the Drug Product Chapter of the IQA.

Labeling: Adequate

The CMC sections of the Prescribing Information (PI) as well as the immediate container and carton labels have been reviewed by the Drug Product Reviewer, Dr. Hailin Wang. Dr. Wang has found that the final PI as well as immediate container and carton labels have satisfactorily addressed all outstanding issues noted in her Labeling Review #1, and therefore, she has recommended approval of this application from the CMC labeling/labels perspective (see Dr. Wang's addendum dated April 09, 2020 to her Labeling Review # 1).

Manufacturing: Adequate

(b) (4)



Biopharmaceutics: Adequate

The Biopharmaceutic review of this application was mainly focused on the proposed IVRT method, method validation, and the proposed IVRT acceptance criterion. It is concluded that the final proposed IVRT method and the proposed acceptance criterion of (b) (4) for testing of Zilxi foam are well-established based on the results from the pivotal clinical batches of drug product and therefore, considered adequate.

To bridge the bulk pre-foam formulation manufacturing of the Phase 3 clinical trial material at the scale of (b) (4) manufactured using (b) (4)

(b) (4)

(b) (4) It is concluded that IVRT data provided adequately bridges the manufacturing process of Phase 3 clinical batches to the manufacturing process intended for the commercial drug product.

The Biopharmaceutics section of this application has been reviewed by the Biopharm Reviewer, Dr. Rajesh Savkur. Dr. Savkur has found the information provided in the Biopharmaceutics section of this application adequate to support the approval of this application. Dr. Savkur's review is provided in the Biopharmaceutics Chapter of the IQA.

Microbiology (if applicable): Adequate

Zilxi (minocycline) topical foam, 1.5% is a non-aqueous, oil-based, suspension formulation filled in an aluminum canister with propellant that discharges the drug product as a foam. The formulation, manufacturing process, and container closure for this drug product is the same as the approved drug product, AMZEEQ foam with the exception of minor change in the composition to address the change in the strength from 4% to 1.5%. It is non-sterile drug product and is tested for bioburden according to USP <61> and USP<62>.

The applicant has also provided sufficient information in support of bulk formulation (b) (4) release and stability of the drug product. The microbiological attributes of this drug product have been reviewed by the Microbiology Reviewer Dr. Aditi Das. Dr. Das has concluded that the information provided in the application regarding the microbiological attributes and bioburden testing of the drug product is adequate to support this application. Dr. Das's review is provided in the Microbiology Chapter of the IQA.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Intra- container content uniformity	(b) (4)	M	(b) (4)	Acceptable	None

	(b) (4)		(b) (4)		
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D. List of Deficiencies for Complete Response

None

Application Technical Lead:

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



Hamid
Shafiei

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CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

TRADENAME™ (minocycline (b) (4) topical (b) (4)

Initial U.S. Approval: 1971

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Pending	
Established name(s)	minocycline (b) (4) Foam (b) (4)	Not Adequate Recommended change: “(minocycline) topical foam”. Per OPPQ recommendation* as referenced in the labeling review for NDA 212379
Route(s) of administration	Topical	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Foam, 1.5%	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	N/A
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.	N/A	N/A

* OPPQ recommended to name the Minocycline HCl-containing drug products based on the active moiety (minocycline) to be consistent with the strength expression.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

For topical use only, not for oral, ophthalmic or intravaginal use (b) (4)

After shaking the can well, a small amount of (b) (4) foam should be expressed from the can onto the fingertips of the hand and then applied as a thin layer over all areas of the face. Additional TRADENAME foam may be used as needed to ensure the entire face is treated. The foam should be applied (b) (4) at approximately the same time each day. The patient should not bathe, shower or swim for at least 1 hour after application of the product.

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)		Adequate from CMC perspective

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

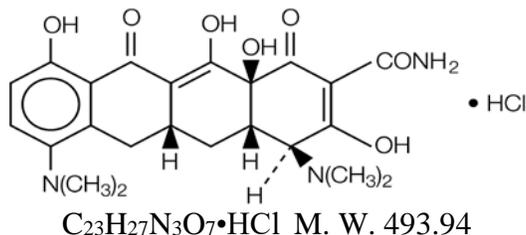
Foam, 1.5% (3)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Foam	Adequate
Strength(s) in metric system	1.5%	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Each gram of TRADENAME contains (b) (4) (b) (4) 15 mg of (b) (4) minocycline.	Not Adequate Recommended change: Each gram of TRADENAME (b) (4) contains 15 mg of minocycline equivalent to 16 mg of minocycline hydrochloride
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Not provided	Adequate The following revision has been made by OND labeling reviewer: Each gram of TRADENAME contains 15 mg of minocycline equivalent to 16 mg of minocycline hydrochloride and is supplied as a yellow suspension in a pressurized aluminum aerosol container.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
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.	N/A	N/A

1.2.4 Section 11 (DESCRIPTION)

Minocycline hydrochloride, a semi-synthetic derivative of tetracycline, is [4S(4α,4αα,5αα,12αα)]-

4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamide monohydrochloride. The structural formula is represented below:



Each gram of TRADENAME contains micronized (b) (4) 15 mg minocycline in a yellow suspension foam.

In addition, the TRADENAME (b) (4) 1.5% contains the following inactive ingredients: soybean oil, coconut oil, light mineral oil, cyclomethicone, cetostearyl alcohol, stearic acid, myristyl alcohol, hydrogenated castor oil, white wax (beeswax), stearyl alcohol, docosanol.

TRADENAME Foam aluminum (b) (4) container (can) (b) (4) pressurized (b) (4) propellant ((b) (4) butane, isobutane, and propane).

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	TRADENAME Foam (b) (4)	Not Adequate Recommended change: TRADENAME topical foam
Dosage form(s) and route(s) of administration	foam	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Each gram of TRADENAME contains micronized (b) (4) 15 mg minocycline in a yellow suspension foam.	Not Adequate Recommended change: Each gram of TRADENAME contains micronized minocycline 15 mg equivalent to 16 mg minocycline hydrochloride in a yellow suspension foam.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	soybean oil, coconut oil, light mineral oil, cyclomethicone, cetostearyl alcohol, stearic acid, myristyl alcohol, hydrogenated castor oil, white wax (beeswax), stearyl alcohol, docosanol,	Adequate from CMC perspective Includes 11 inactive ingredients for the suspension formulation, and 3 ingredients for the propellant mix. The sequence is arranged by function followed by amount.

	and propellant (butane, isobutane, and propane).	
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.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/Therapeutic class	Derivative of tetracycline	Adequate from CMC perspective
Chemical name, structural formula, molecular weight	<p>Minocycline hydrochloride, a semi-synthetic derivative of tetracycline, is [4S-(4α,4α,5α,12α)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide mono hydrochloride. The structural formula is represented below:</p> <p><chem>C23H27N3O7.HCl</chem> M.W. 493.94</p>	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	None	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”	(b) (4)	Adequate

1.2.5 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

1.1 How Supplied

TRADENAME™ (minocycline (b) (4)) Foam 1.5% is a yellow suspension supplied in a pressurized aluminum aerosol container (can), and is supplied as follows:

NDC 72356-103-03 30 g Can

1.2 Storage

TRADENAME must be stored at 2 °C – 8 °C (36 °F – 46 °F) until dispensed to the patient.

Once dispensed, the patient is to store TRADENAME at room temperature below 25 °C (77 °F) for 90 days. Do not store in the refrigerator.

1.3 Handling

Allow the can to warm to room temperature before first use.

Shake can well before use.

WARNING: Flammable. Avoid fire, flame, or smoking during and immediately following application. Contents under pressure. Do not puncture or incinerate. Do not expose to heat or temperatures above 49 °C (120 °F).

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	TRADENAME™ (minocycline (b) (4)) foam	Not Adequate Recommended change: TRADENAME (minocycline) topical foam
Strength(s) in metric system	1.5%	Adequate
Available units (e.g., bottles of 100 tablets)	30g	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yellow suspension foam NDC 72356-101-03 30g Can	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
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.	N/A	N/A

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.)	WARNING: Flammable. Avoid fire, flame, or smoking during and immediately following application. Contents under pressure. Do not puncture or incinerate. Do not expose to heat or temperatures above 49°C (120°F).	Adequate Warning information is provided due to presences of propellant in the formulation. This is consistent with propellant properties and is deemed adequate.
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."	N/A	N/A

Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	<p>TRADENAME must be stored at 2°C - 8°C (36°F - 46°F) until dispensed to the patient.</p> <p>Once dispensed, the patient is to store AMZEEQ at room temperature below 25°C (77°F) for 90 days. Do not store in the refrigerator.</p>	Adequate Storage condition and in-use condition is supported by stability data.
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."	N/A	N/A
Include information about child-resistant packaging	N/A	N/A

1.2.6 Other Sections of Labeling

None

1.2.7 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	<p>Manufactured by: ASM Aerosol-Service AG Mohlin, Switzerland</p> <p>Manufactured for: Foamix Pharmaceuticals, Inc. Bridgewater, NJ 08807</p> <p>Product of Portugal or Switzerland</p>	Adequate

2.0 PATIENT LABELING

The patient labeling comply with all regulatory requirements from a CMC perspective.

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	TRADENAME, (Minocycline (b) (4)	Not Adequate Recommended change: TRADENAME (minocycline) topical foam (b) (4) Both the established name (b) (4) Refer to deficiencies issued by DMEPA.
Dosage strength	(b) (4)	Adequate
Route of administration	Topical	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Each gram of TRADENAME contains micronized minocycline (b) (4) equivalent to (b) (4)	Not Adequate Recommended change: Each gram of TRADENAME contains minocycline 15 mg equivalent to 16 mg minocycline
Net contents (e.g. tablet count)	30 g, 7g (physician sample)	Adequate
"Rx only" displayed on the principal display	Yes	Adequate
NDC number	NDC 72356-103-03 NDC 72356-103-90	Adequate
Lot number and expiration date	Yes (bottom of carton)	Adequate

<p>Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.</p>	<p>Commercial Can 30g Store at 2°C - 8°C (36°F - 46°F) until dispensed to the patient. Once dispensed, the patient is to store TRADENAME at room temperature below 25°C (77°F) for 90 days. Do not store in the refrigerator. Allow the can to warm to room temperature before first use. Shake can well before use.</p> <p>WARNING: Flammable. Avoid fire, flame, or smoking during and immediately following application. Contents under pressure. Do not puncture or incinerate. Do not expose to heat or temperatures above 49°C (120°F).</p> <p>Physician’s can 7g Store TRADENAME at room temperature 68-77°F (20-25°C). Do not store in the refrigerator. Shake can well before use. WARNING: Flammable. Avoid fire, flame, or smoking during and immediately following application. Contents under pressure. Do not puncture or incinerate. Do not expose to heat or temperatures above 120°F (49°C).</p>	<p>Consistent with PI and supported by stability data. Adequate</p> <p>The storage temperature on the physician’s can label indicates refrigerated temperature which is not consistent with the room temperature storage indicated on the carton label or the proposed room temperature storage in P.8. Not Adequate</p>
<p>For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)</p>	<p>N/A</p>	<p>N/A</p>
<p>Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.</p>	<p>N/A</p>	<p>N/A</p>

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Yes	

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured by: ASM Aerosol-Service AG Mohlin, Switzerland Manufactured for: Foamix Pharmaceuticals Inc. Bridgewater, NJ 08807	Adequate
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap over seal	None	Adequate
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.	N/A	N/A
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling: {Not Adequate}

The container and carton labels, as of this review, do not comply with all regulatory requirements from a CMC perspective (see the List of Deficiencies).

ITEMS FOR ADDITIONAL ASSESSMENT

See the below.

Overall Assessment and Recommendation: Not Adequate

List of Deficiencies:

A. Regarding Prescribing Information

1. The established name in the proposed product title, “TRDADENANME™ (minocycline (b) (4) Foam”, is not acceptable. It should be revised to,

“TRDADENANME™ (minocycline) topical foam”
2. The equivalency statement, “Each gram of TRDADENANME contains 15 mg of minocycline equivalent to 16 mg of minocycline hydrochloride” should be added in the “**Dosage and Strength**”, “**Description**” as well as **How Supplied/Storage and Handling** sections.

B. Container and Carton Labels

1. The drug name, “TRDADENANME (minocycline (b) (4) foam”, in the labels should be revised to,

“TRDADENANME™ (minocycline) topical foam”
2. The following equivalency statement in the carton label should be revised to:

“Each gram of TRDADENANME contains 15 mg of minocycline equivalent to 16 mg of minocycline hydrochloride”
3. The storage temperature on the 7 g physician’s can label currently indicates refrigerated temperature, which should be revised to be consistent with the room temperature storage as described on the carton label and the proposed room temperature storage for the physician’s can in P.8.

Primary Labeling Assessor Name and Date: Hailin (Sheena) Wang, Ph.D. 02/13/2020

This application is not deemed ready for approval in its present form per 21 CFR314.125(b)(6) until the labeling/labels deficiencies delineated in the **List of Deficiencies** above are resolved satisfactorily.

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

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

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



Sheena Hailin
Wang

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Moo Jhong
Rhee

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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: April 09, 2020

TO: Review #1 of NDA 212379 Quality Assessment - Labeling

FROM: Hailin (Sheena) Wang, Ph.D.
Chemist, ONDP/DNDP II/OPQ

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

SUBJECT: **Final Recommendation on Labeling/Labels**

SUMMARY

The previous Quality Labeling Review #1 dated 02/18/2020, made a recommendation of not ready for approval of this NDA because of labeling deficiencies (see [N213690 IQA Labeling R1](#)). These labeling issues have been satisfactorily resolved based on the revisions made in SD 21 and SD 27.

RECOMMENDATION:

This application is now recommended for **Approval** from the Quality labeling/label perspective.

Assessment Notes

FDA labeling request and agency proposed labeling were communicated to the applicant on 02/19/2020 and 04/01/2020. Subsequently, the following amendments were submitted and assessed.

List Submissions being reviewed:

Document Reviewed (eCTD #)	Date Received
eCTD-0021 (SD-21)	02/21/2020
eCTD-0027 (SD-27)	04/06/2020

Review of the applicant's amendments is provided below:**IR request sent to the applicant on 02/21/2020:**

The Agency is requesting that you submit updated labeling for NDA 213690 minocycline (b) (4) foam, (b) (4) that is consistent with the approved labeling for your product AMZEEQ (NDA 212379), where appropriate/relevant.

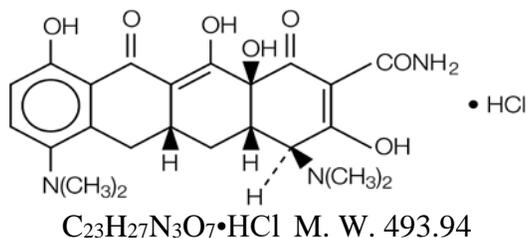
Related information/revisions provided in SD 21**HIGHLIGHTS OF PRESCRIBING INFORMATION****TRADENAME™ (minocycline) topical foam****SECTION 3 (DOSAGE FORMS AND STRENGTHS)**

Topical foam, 1.5%

Each gram of TRADENAME contains 15 mg of minocycline equivalent to 16 mg minocycline hydrochloride and is supplied as a yellow suspension in a pressurized aluminum aerosol container (can).

SECTION 11 (DESCRIPTION)

Minocycline hydrochloride, a semi-synthetic derivative of tetracycline, is [4S-(4 α ,4 $\alpha\alpha$,5 $\alpha\alpha$,12 $\alpha\alpha$)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamide mono hydrochloride. The structural formula is represented below:



Each gram of TRADENAME contains micronized 15 mg minocycline equivalent to 16 mg minocycline hydrochloride in a yellow suspension foam.

In addition, the TRADENAME topical foam 1.5% contains the following inactive ingredients: soybean oil, coconut oil, light mineral oil, cyclomethicone, cetostearyl alcohol, stearic acid, myristyl alcohol, hydrogenated castor oil, white wax (beeswax), stearyl alcohol, docosanol. TRADENAME topical foam is dispensed from an aluminum container (can) pressurized with propellant (butane + isobutane + propane).

SECTION 16 (HOW SUPPLIED/STORAGE AND HANDLING)

How Supplied

TRADENAME™ (minocycline) topical foam, 1.5% is a yellow suspension supplied in a pressurized aluminum aerosol container (can). Each gram of TRADENAME contains 15 mg of minocycline equivalent to 16 mg of minocycline hydrochloride, and is supplied as follows:

NDC 72356-103-03 30 g Can

Reviewer's Assessment: Adequate

The applicant has revised the established name and the equivalency statement to be consistent with approved labeling for AMZEEQ (NDA 212379) which is in line with USP salt policy.

On 04/01/2020

The Agency-proposed labeling for NDA 213690 minocycline (b) (4) foam for the prescribing information, patient information, instructions for use, and carton and container labeling was communicated to the applicant by Jennifer Harmon, PharmD via email.

Related information/revisions provided in SD 27 on 04/06/2020

CONTAINER LABEL

Trade Can Label 30 g

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

As shown above, the applicant has included the granted trade name “zilxi” on the C&C labels, revised the established name on the container label and the equivalency statement on the 30 g Trade and 7 g Physician Sample Cartons which is consistent with PI and approved container & carton labels for the approved AMZEEQ product.



Sheena Hailin
Wang

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Moo Jhong
Rhee

Digitally signed by Moo Jhong Rhee
Date: 4/09/2020 01:23:03PM
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BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA-213690-ORIG-1

Drug Product Name / Strength: FMX103 (Minocycline HCl) foam, 1.5%

Route of Administration: Topical

Applicant Name: Foamix Pharmaceuticals.

Review Summary: Adequate

FMX103 is a topical aerosol foam product containing 1.5% w/w micronized Minocycline HCl as the active ingredient. It is intended for the treatment of (b) (4) rosacea. The product is manufactured as a bulk pre-foam formulation (bulk PFF). The PFF is a liquid, (b) (4) aqueous, oil-based dispersion of Minocycline HCl that is filled into canisters and pressurized with a propellant. FMX103 is supplied in aerosol canisters to deliver 7 g and 30 g of FMX103 1.5%. The Applicant submitted this NDA (NDA-213690-ORIG-1) under section 505 (b)(2) to the Division of Dermatology and Dental Products for review on 8/2/2019. This 505 (b)(2) submission is based on the Listed Drug Solodyn® (Minocycline HCl), 80 mg Extended Release Tablets that was approved under NDA 50808 on 5/8/2006.

The Biopharmaceutics review focuses on the in vitro release (IVR) method development, the IVR data and the IVR acceptance criterion.

The final in vitro release method and acceptance criterion as agreed upon by the Agency and the Applicant are stated below:

Diameter of ring orifice:	15 mm
Release surface area:	1.7671 cm ²
Metal clamp size:	28
Stir bar size:	12.7 mm × 3 mm
Sample ring size:	15 mm diameter; 3.2 mm thickness
Membrane:	(b) (4)
Receptor medium:	DMSO:Isopropanol (10:90 v/v)
Temperature:	32 °C ± 0.5 °C
Stirring speed:	600 rpm
Cell volume:	12 mL
Aliquot volume:	0.5 mL, with medium replacement
Sampling intervals:	60, 90, 120, 150, 180 and 240 minutes
IVR Acceptance Criterion:	(b) (4)

From the Biopharmaceutics perspective, this Reviewer concludes that NDA-213690-ORIG-1 for Minocycline 1.5%, is **Adequate** for approval.

List Submissions being reviewed:

8/2/2019	Original Submission/Sequence 0001
10/29/2019	Information Request – Quality/Sequence 0009
11/8/2019	Information Request – Quality/Sequence 0011
12/30/2019	Information Request – Quality/Sequence 0015
1/31/2020	Information Request – Quality/Sequence 0018
2/21/2020	Information Request – Quality/Sequence 0020
3/4/2020	Information Request – Quality/Sequence 0023
3/17/2020	Information Request – Quality/Sequence 0025

Concise Description Outstanding Issues Remaining:

None

Solubility:

The solubility of Minocycline HCl (MCH) was demonstrated on the 4% FMX101 formulation (NDA-212379) and the saturated concentration of MCH in the receptor medium was determined to be (b) (4) the maximum concentration of MCH released at (b) (4) min of IVRT for (b) (4)% formulation (b) (4). This solubility achieved the receptor medium ‘sink’ condition which is greater than (b) (4) times the maximum concentration of the active during IVRT.

In vitro release (IVR): See the review below

In vitro Release Method and Acceptance Criterion

1. IVR method:

The Applicant has developed an in vitro release (IVR) method to evaluate the diffusion rate of FMX103 1.5% using a modified Franz cell apparatus. The IVR method conditions are stated below:

Apparatus Parameters:

Diameter of ring orifice:	15 mm
Release surface area:	1.7671 cm ²
Metal clamp size:	28
Stir bar size:	12.7 mm × 3 mm
Sample ring size:	15 mm diameter; 3.2 mm thickness
Membrane:	(b) (4)
Receptor medium:	DMSO:Isopropanol (10:90 v/v)
Temperature:	32 °C ± 0.5 °C
Stirring speed:	600 rpm
Cell volume:	12 mL
Aliquot volume:	0.5 mL, with medium replacement
Sampling intervals:	60, 90, 120, 150, 180 and 240 minutes

IVR method development:

Clinical relevance of dissolution method & acceptance criterion (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)**Reviewer's Assessment:**

The Applicant has not performed an in vitro-in vivo correlation. The IVR method proposed by Applicant is to ensure batch-to-batch consistency, and this is acceptable.

Bridging of Formulations

The Applicant has stated that all the clinical studies in the development program of the proposed product use the to-be-marketed FMX103 1.5% formulation.

In the IRs (IR1 and IR2) that were communicated to the Applicant, the Applicant was requested to identify the differences in manufacturing process for Phase 3 clinical batches and commercial batches, and submit the comparative in vitro release data for the batch(es) used in Phase 3 studies and commercial batch(es). The Applicant submitted their responses in Sequence 0009 (dated: 10/29/2019), Sequence 0011 (dated: 11/8/2019) and the comparative IVR data in Sequence 0015 (dated 12/30/2019). The Applicant's response is presented in Appendix 2.

The Applicant stated that the Phase 3 and registration (commercial) batches were manufactured at the same site: ASM Aerosol-Services AG, at their manufacturing facility at (b) (4), Möhlin, (b) (4) Switzerland. The Applicant also stated that due to the near identical formulations (differing only in Minocycline and Light Mineral Oil content) and the identical manufacturing procedures for FMX103 1.5% and FMX101 4% (NDA 212379) products, no formal transfer of FMX103 1.5% was required. However, the original process transfer was accomplished with FMX101 4% at ASM Aerosol-Services AG during the Winter of 2015/2016, and the manufacturing processes (b) (4) were assessed for any changes that were needed for FMX103 1.5% and no changes were necessary.

The Applicant has also stated that the batches used for in the clinical studies were produced using the same manufacturing process as used for the to-be-marketed registration batches. However, the batch size for the clinical trial batches were (b) (4), whereas the registration batch sizes were (b) (4). The differences in the manufacturing processes for the Phase 3 clinical and registration (commercial-scale) batches are detailed in the two tables presented in the response. The bulk pre-foam formulation (bulk PFF) for the clinical batches was manufactured (b) (4). The bulk PFF for the registration batches prepared at the proposed commercial (b) (4) were manufactured (b) (4), whereas the bulk PFF for the registration batches manufactured at the proposed (b) (4) commercial scale were prepared (b) (4). The Applicant's response is presented in the link below (see pages 1 – 4):

<\\cdsesub1\evsprod\nda213690\0009\m1\us\nda-213690-1114-multiple-module-amendment-seq0009-29oct1.pdf>

To demonstrate the bridging of the manufacturing differences in the Phase 3 clinical and the registration lots, the Applicant submitted IVR data on two Phase 3 clinical lots and three commercial lots listed below. The data is presented in the link below (see pages 1 – 2):

<\\cdsesub1\evsprod\nda213690\0015\m1\us\nda-213690-1111-quality-information-amendment-seq0015-30.pdf>

Phase 3 Clinical scale lots: 7061301 and 7061901
 Commercial scale lots: 7052901, 7053001 and 7101610

Lot Number	Use	Scale	Release Rate mean (range)	%RSD (n=6)
7061301	Phase 3 Clinical			(b) (4)
7061901	Phase 3 Clinical			
7052901	Registration			
7053001	Registration			
7101610	Registration			

Reviewer’s Assessment:

Based on the submitted information, all the clinical studies in the development program of the proposed product use the to-be-marketed FMX103 1.5% formulation.

Although the bulk PFF for the Phase 3 clinical and registration batches was manufactured at different sites, the Phase 3 clinical and registration (commercial) batches were manufactured at the same site - ASM Aerosol-Services AG, at their manufacturing facility at (b) (4) Möhlin, (b) (4) Switzerland. Hence, bridging of formulations due to a change in manufacturing site is not necessary.

Although the Phase 3 clinical and registration (commercial) batches were manufactured at the same site, there are differences in the manufacturing process. There was a change in equipment used to manufacture Phase 3 batches and registration batches. These changes are similar to the changes in the higher strength product (Minocycline foam 4%; NDA 212379). To assess the sameness between the clinical batches and the registration batches, as per the SUPAC-SS guidance, this Reviewer compared the reference batch (Phase 3 clinical batch# 7061301 - with the widest range of values from (b) (4)) to the test batch (Registration batch# 7053001 - with the widest range of values from (b) (4)). As per the SUPAC-SS guidance, the eighth and twenty-ninth ordered individual ratios (corresponding to 90% CI) are (b) (4), respectively - which in terms of percentages correspond to (b) (4) respectively. This 90% CI values fall within the limits of (b) (4) %.

Hence, this Reviewer considers the IVR rates between the Phase 3 clinical lots and the registration lots to be similar and the differences in manufacturing process for Phase 3 clinical batches and commercial batches to be satisfactorily bridged.

Stability Data

In the original submission (Sequence 0001), the Applicant has stated that the IVR test was not proposed to be performed on stability but would be tested only at release to give assurance that no significant issues are encountered during batch production.

In the IR (IR5) that was communicated, the Applicant was advised that the IVR test should be performed for all commercial batches at release and annually during stability including the first 3 commercial batches. The Applicant responded to the IR on 3/17/2020. The Agency’s IR comments

and the Applicant's response are presented in Appendix 2. The Reviewer's assessment is given below:

Reviewer's Assessment:

The Applicant has agreed to test the first three commercial batches for both 30 g and 7 g, as well as the annual stability batches of drug product for IVR at release, and will monitor results during stability in order to set an appropriate IVRT end of life stability criterion.

The Applicant's response to IR5 Item 3 is adequate and acceptable.

The proposed product in a non-aqueous, oil-based, dispersion of Minocycline HCl. The particle size distribution was identified as one of the critical quality attributes. Minocycline particle size is controlled, and the Applicant has proposed the following particle size specification to be tested at release and stability.

PSD specification at release:

Particle Size Determination Number of particles in range	(b) (4)
---	---------

PSD specification at stability:

Particle Size Determination Number of particles in range	(b) (4)
---	---------

Reviewer's Assessment:

The Applicant has submitted IVR data obtained from a batch manufactured with un-micronized particles. Based on this data, the IVR method has limited discriminating ability with respect to particle size. The Applicant has stated that the PSD will be controlled and maintained as described above.

This Reviewer finds the Applicant's approach to be acceptable. The adequacy of these will be reviewed by DP reviewer.

Biowaiver Request

There is only one strength of the test product – Minocycline 1.5%. The Applicant has not requested any waiver of in vivo bioavailability/bioequivalence studies.

Reviewer's Assessment:

There is only one strength of the proposed product. There is no request for any waiver of in vivo bioavailability/bioequivalence studies.

APPENDIX 1

Data Tables and Figures

Table 1A: The 6-unit IVR data for the phase 3 clinical lots - 7061301 and 7061901 and the registration lots – 7052901, 7053001, 7101610 and 9032110 in the proposed IVR method is presented in the link below:

<\\cdsesub1\evsprod\nda213690\0015\m1\us\nda-213690-ectd-seq0015-foamix-fmx103-release.xlsx>

Table 1B: The 6-unit IVR data for the phase 3 clinical lots – 7050401, 7082810 and 7102311 and the registration lot – 7101110 in the proposed IVR method is presented in the link below:

<\\cdsesub1\evsprod\nda213690\0018\m1\us\foamix-fmx103-release-rate-data.xlsx>

Table 1C: The 6-unit IVR data for the phase 3 clinical lot – 7102611 (3 data sets), the registration lots – 7052301, 7100910 (30 g and 7 g) and 9031911, and the development lot - 9120410 in the proposed IVR method is presented in the link below:

<\\cdsesub1\evsprod\nda213690\0023\m1\us\foamixfmx103ivrt-data-fda-format-02172020-seq0020-corre.xlsx>

APPENDIX 2

IR comments and Applicant's Response to IR:

On 10/16/2019, the following Information Request 1 (IR1) comments were communicated to the Applicant. On 10/29/2019, the Applicant responded to the Agency's IR comments (Sequence 0009). The Agency's IR comments, the Applicant's response to the IR, and the Reviewer's assessment are included below.

Information Request 1:

IR1 Item 1:

Provide in vitro release test (IVRT) method development report. The IVRT method development report should contain (but is not limited to) justification for the selection of the following methodology components:

- a. Diffusion apparatus
- b. Receptor medium selection
- c. Receptor medium stirring rate
- d. Membrane selection
- e. Sampling time points
- f. Temperature

We recommend that the IVRT method development report should contain data demonstrating the discriminating ability of the proposed method. That is, it should contain IVRT data demonstrating that the method is capable to discriminate for formulation variants that are

intentionally manufactured with meaningful variations for the identified critical relevant process/material/product attributes (e.g. drug substance particle size).

Applicant’s Response to the IR1 Item 1:

The Applicant stated that The development of the in vitro release test (IVRT) is detailed in module [3.2.P.5.3. Development of Analytical Procedures \(FMX103 1.5%, Foam\), Development Summary - In-Vitro Release Test \(IVRT\) method](#). Each of the parameters listed “a-e” are addressed in this section. The temperature of the system is set at (b) (4) and although the tolerance (b) (4), it is as described in USP chapter <1724> “Semisolid drug products – performance tests. The development summary detailed in module [3.2.P.5.3. Development of Analytical Procedures \(FMX103 1.5%, Foam\), Development Summary - In-Vitro Release Test \(IVRT\) method](#) also demonstrates the ability of the method to discriminate between product made with different particle size of the drug substance during the method development phase.

Reviewer’s assessment and conclusion:

This Reviewer has evaluated the IVR method development and the discriminatory ability of the IVR method in the text of the Review. The proposed IVR method possesses limited discriminatory ability against modified dosage strengths (b) (4) and also against a modified formulation (b) (4)

The Applicant’s response to IR1 Item 1 is adequate and acceptable.

IR1 Item 2:

Provide IVRT data and profiles for clinical and registration batch(es) in electronic format (e.g. MS Excel) as described below:

Chamber ID: # (identify each cell assignment)

Sample volume removed: mL

Diffusion cell area: cm²

Time (min, hr, etc.)	Sq. rt. Time	Concent ration in Cell (µg/mL)	Amount in Cell (µg)	Cumulat ive Amount in Cell (µg)	Cumulat ive Diffusion (µg/cm ²)
T1					
T2					
T3					
T4					
T5					
Tn					

Applicant’s Response to the IR1 Item 2:

The Applicant stated that they would submit this data by December 31, 2019.

Reviewer’s assessment and conclusion:

The Applicant has addressed the Reviewer’s concern and has stated that the data will be submitted by December 31, 2019.

The Applicant’s response to IR1 Item 2 is adequate and acceptable.

IR1 Item 3:

There were changes in manufacturing process during product development. Clearly identify the differences in manufacturing process for Phase 3 clinical batches and commercial batches. Provide comparative in vitro release data for the batch(es) used in Phase 3 studies and commercial batch(es).

Applicant's Response to IR1 Item 3:

In the Sequence 0009 response (dated 10/29/2019), the Applicant has stated that the Phase 3 clinical and registration (commercial-scale) batches were manufactured at the same site: ASM Aerosol-Services AG, at their manufacturing facility at (b) (4), Möhlin, (b) (4) Switzerland. Commercial manufacture will be undertaken at the same site.

The Applicant stated that the differences in the manufacturing processes for the Phase 3 clinical and registration (commercial-scale) batches are detailed in the two tables presented in the response. The bulk pre-foam formulation (bulk PFF) for the clinical batches was manufactured (b) (4). The response is presented in the link below (see pages 1 – 4):

<\\cdsesub1\evsprod\nda213690\0009\m1\us\nda-213690-1114-multiple-module-amendment-seq0009-29oct1.pdf>

Reviewer's assessment and conclusion:

Although the Phase 3 clinical and registration (commercial) batches were manufactured at the same site, there are differences in the manufacturing process. The Applicant has stated that the comparative IVR data for the batch(es) used in Phase 3 studies and commercial batch would be submitted before December 31, 2019. The bridging data will be reviewed upon submission of this information.

The Applicant's response to IR1 Item 3 is adequate and acceptable.

IR1 Item 4:

You have stated that the manufacturing process of the FMX103 1.5% product was successfully transferred to ASM Aerosol-Service AG. Clarify when the process transfer occurred and whether Phase 3 batches and commercial batches were manufactured at the same site. If Phase 3 and commercial batches were manufactured at different sites submit data to bridge the manufacturing site change.

Applicant's response to IR1 Item 4:

In the Sequence 0009 response (dated 10/29/2019), the Applicant stated that the Phase 3 and registration (commercial) batches were manufactured at the same site: ASM Aerosol-Services AG, at their manufacturing facility at (b) (4) Möhlin, (b) (4) Switzerland.

The Applicant stated that due to the near identical formulations (differing only in Minocycline and Light Mineral Oil content) and the identical manufacturing procedures for FMX103 1.5% and FMX101 4% (NDA 212379) products, no formal transfer of FMX103 1.5% was required. However, the original process transfer was accomplished with FMX101 4% at ASM Aerosol-

Services AG during the Winter of 2015/2016, and the manufacturing processes (b) (4) were assessed for any changes that were needed for FMX103 1.5% (no changes were needed).

Reviewer's assessment and conclusion:

The Phase 3 clinical and registration (commercial) batches were manufactured at the same site - ASM Aerosol-Services AG, at their manufacturing facility at (b) (4), Möhlin, (b) (4) Switzerland. Hence, bridging of formulations due to a change in manufacturing site is not necessary.

The Applicant's response to IR1 Item 4 is adequate and acceptable.

IR1 Item 5:

We are concerned with your proposed sample preparation procedures for your IVRT method. Pretreatment of the foam can alter the structure and rheological properties of the drug product. In general, the foam should be intact as in actual usage condition. Justification should be provided to support using the pretreatment and can include (but not limited to) data obtained using intact foam.

Applicant's response to IR1 Item 5:

In the Sequence 0009 response (dated 10/29/2019), the Applicant stated that a study was performed a study on the FMX101 4% formulation to demonstrate that the sample pre-treatment is an appropriate procedure to prepare the sample prior to applying to the IVRT vessels. The rationale for this sample pre-treatment (which is similar to FMX101 4% in NDA 212379; Sequence 0006) is described in detail in the link below (see pages 6 – 10)

<\\cdsesub1\evsprod\nda213690\0009\m1\us\nda-213690-1114-multiple-module-amendment-seq0009-29oct1.pdf>

Reviewer's assessment and conclusion:

The Applicant has submitted the rationale for the sample pre-treatment for FMX101 4% (NDA 212379). The Applicant has stated that the data for FMX103 1.5% will be submitted at a later date.

The Applicant's response to IR1 Item 5 is unsatisfactory and inadequate.

On 11/4/2019, the following Information Request 2 (IR2) comments were communicated to the Applicant. On 11/8/2019, the Applicant responded to the Agency's IR comments (Sequence 0011). The Agency's IR comments, the Applicant's response to the IR, and the Reviewer's assessment are included below.

Information Request 2:

IR2 Item 1:

Provide in vitro release test (IVRT) method development report. The IVRT method development report should contain (but is not limited to) justification for the selection of the following methodology components:

- a. Diffusion apparatus
- b. Receptor medium selection
- c. Receptor medium stirring rate
- d. Membrane selection
- e. Sampling time points
- f. Temperature

We recommend that the IVRT method development report should contain data demonstrating the discriminating ability of the proposed method. That is, it should contain IVRT data demonstrating that the method is capable to discriminate for formulation variants that are intentionally manufactured with meaningful variations for the identified critical relevant process/material/product attributes (e.g. drug substance particle size).

Applicant’s response to IR2 Item 1:

The Applicant has stated that they have provided a response to this question in eCTD Sequence 0009, dated October 29, 2019 (see Section 1.11.4 Question 3).

Reviewer’s assessment and conclusion:

The Applicant has submitted the response on 10/29/2019 (IR1 Item 1).

The Applicant’s response to IR2 Item 1 is satisfactory and acceptable.

IR2 Item 2:

Provide IVRT data and profiles for clinical and registration batch(es) in electronic format (e.g. MS Excel) as described below:

Chamber ID: # (identify each cell assignment)

Sample volume removed: mL

Diffusion cell area: cm²

Time (min, hr, etc.)	Sq. rt. Time	Concent ration in Cell (µg/mL)	Amount in Cell (µg)	Cumulat ive Amount in Cell (µg)	Cumulat ive Diffusion (µg/cm ²)
T1					
T2					
T3					
T4					
T5					
Tn					

Applicant’s Response to the IR2 Item 2:

The Applicant stated that they would submit this data by December 31, 2019.

Reviewer’s assessment and conclusion:

The Applicant has addressed the Reviewer’s concern and has stated that the data will be submitted by December 31, 2019.

The Applicant’s response to IR2 Item 2 is adequate and acceptable.

IR2 Item 3:

There were changes in manufacturing process during product development. Clearly identify the differences in manufacturing process for Phase 3 clinical batches and commercial batches. Provide comparative in vitro release data for the batch(es) used in Phase 3 studies and commercial batch(es).

Applicant’s Response to IR2 Item 3:

In the Sequence 0011 response (dated 10/29/2019), the Applicant has stated that they have provided a response to this in eCTD Sequence 0009, dated October 29, 2019 (see [Section 1.11.4 Question 1](#)). The Applicant has stated that they would provide the comparative IVRT data for the Phase 3 and commercial batches by 31st December 2019.

In the Sequence 0015 response (dated 12/30/2019), the Applicant stated they have performed IVR testing on the 2 Phase 3 Clinical lots and 3 Commercial lots listed below. The response is presented in the link below (see pages 1 – 2).

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The data demonstrates that the Phase 3 Clinical lots and the Commercial lots can be considered to be equivalent with respect to in-vitro release rates, mean and ranges along with %RSD. The data are presented in the table below:

Phase 3 Clinical scale lots: 7061301 and 7061901

Commercial scale lots: 7052901, 7053001 and 7101610

Lot Number	Use	Scale	Release Rate mean (range)	%RSD (n=6)
7061301	Phase 3 Clinical			(b) (4)
7061901	Phase 3 Clinical			
7052901	Registration			
7053001	Registration			
7101610	Registration			

Reviewer’s assessment and conclusion:

As stated in the assessment to IR1 Item 3, although the Phase 3 clinical and registration (commercial) batches were manufactured at the same site, there are differences in the manufacturing process. To assess the sameness between the clinical batches and the registration batches, as per the SUPAC-SS guidance, this Reviewer compared the reference batch (Phase 3 clinical batch# 7061301 - with the widest range of values from (b) (4)) to the test batch (Registration batch# 7053001 - with the widest range of values from (b) (4)). As per the SUPAC-SS guidance, the eighth and twenty-ninth ordered individual ratios (corresponding to 90% CI) are (b) (4), respectively - which in terms of percentages correspond to (b) (4)%, respectively. This 90% CI values fall within the limits of (b) (4)%. Hence, this Reviewer considers the IVR rates between the Phase 3 clinical lots and the registration lots to be similar and the differences in manufacturing process for Phase 3 clinical batches and commercial batches to be satisfactorily bridged.

The Applicant's response to IR2 Item 3 is adequate and acceptable.

IR2 Item 4:

You have stated that the manufacturing process of the FMX103 1.5% product was successfully transferred to ASM Aerosol-Service AG. Clarify when the process transfer occurred and whether Phase 3 batches and commercial batches were manufactured at the same site. If Phase 3 and commercial batches were manufactured at different sites submit data to bridge the manufacturing site change.

Applicant's response to IR2 Item 4:

In the Sequence 0011 response (dated 11/8/2019), the Applicant has stated that they have provided a response to this in eCTD Sequence 0009, dated October 29, 2019 (see [Section 1.11.4 Question 2](#)).

Reviewer's assessment and conclusion:

As stated in the assessment to IR1 Item 4, the Phase 3 clinical and registration (commercial) batches were manufactured at the same site - ASM Aerosol-Services AG, at their manufacturing facility at (b) (4) Möhlin, (b) (4) Switzerland. Hence, bridging of formulations due to a change in manufacturing site is not necessary.

The Applicant's response to IR2 Item 4 is adequate and acceptable.

IR2 Item 5:

We are concerned with your proposed sample preparation procedures for your IVRT method. Pretreatment of the foam can alter the structure and rheological properties of the drug product. In general, the foam should be intact as in actual usage condition. Justification should be provided to support using the pretreatment and can include (but not limited to) data obtained using intact foam.

Applicant's response to IR2 Item 5:

In the Sequence 0011 response, the Applicant has stated that they have provided a response to this question in eCTD Sequence 0009, dated October 29, 2019 (see [Section 1.11.4 Question 4](#)). The Applicant further commits to repeating the studies described in [Tables 1 and 2](#) in Section 1.11.4 Question 4 for FMX103 and will provide the data to the Agency by January 31st 2020.

The Applicant submitted the data on FMX103 in Sequence 0020 (dated 2/21/2020). The response is presented in the link below (see pages 1 – 3)

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Reviewer's assessment and conclusion:

The Applicant has submitted data on FMX103 1.5% to demonstrate that pre-treatment does not alter the structural and rheological properties of the product.

The Applicant's response to IR2 Item 5 is adequate and acceptable.

On 2/3/2020, the following Information Request 3 (IR3) comments were communicated to the Applicant. On 2/21/2020, the Applicant responded to the Agency's IR comments (Sequence 0020). The Agency's IR comments, the Applicant's response to the IR, and the Reviewer's assessment are included below.

Information Request 3:**IR3 Item 1:**

We acknowledge the information and data that you have submitted in your response dated December 30, 2019 (Sequence 0015). In this response you had also stated that data for the other clinical and registration lots (Clinical lots: 7050401, 7082810, 7102311, 7061501, and 7102611

Registration lots: 7052301 (30g), 7100910 (30g), 7101110 (30g), 7100910 (7g), 9031911 (7g)) will be provided when available.

We request that you to submit the data on these remaining Clinical and Registration to support the in vitro release acceptance criterion assessment.

Applicant's response to IR3 Item 1:

The Applicant has stated that reference is made to the prior responses to FDA requests for information dated October 29, 2019 (eCTD Sequence 009), December 30, 2019 (eCTD Sequence 0015) and January 31, 2020 (eCTD Sequence 0018). The remaining outstanding information to these prior CMC information requests are provided herein (see Module 1.11.1).

Reviewer's assessment and conclusion:

The Applicant has submitted the IVR data on all the batches. However, the Applicant submitted three data sets for lot# 7102610. This Reviewer notes that there is no lot listed as 7102610. This was clarified in the subsequent IR.

The Applicant's response to IR3 Item 1 is not satisfactory and unacceptable.

On 2/25/2020, the following Information Request 4 (IR4) comments were communicated to the Applicant. On 3/4/2020, the Applicant responded to the Agency's IR comments (Sequence 0023). The Agency's IR comments, the Applicant's response to the IR, and the Reviewer's assessment are included below.

Information Request 4:**IR4 Item 1:**

You have submitted the data for three batches that have been listed as 7102610 in the Excel sheet that you have submitted in module 1.11.1 on February 21, 2020. Provide the identity of each of the three batches listed as 7102610.

We also request that you submit the IVR data on remaining Clinical and Registration batches - 7050401, 7082810, 7102311 and 7101110 to further facilitate the assessment of the proposed in vitro release acceptance criterion.

We request that you respond by March 6, 2020.

Applicant’s response to IR4 Item 1:

The Applicant stated that in the response, [Sequence 0020](#) submitted on February 21, 2020, the Applicant incorrectly labeled Phase 3 clinical batch 7102611 as batch 7102610 in the text of the response letter and accompanying Excel spreadsheet. The Applicant has corrected the batch number to 7102611 in the Excel spreadsheet and provide the updated spreadsheet herein. Additionally, please note the following:

- For lot 7100910, which was packaged as both 30 g and 7 g, the 7 g lot has been distinguished in the list from the 30 g lot by addition of “7 g” notation following the sample number.
- For lot 7102611, three (3) data sets have been added as this batch was tested three times for the purposes of the SUPAC-SS comparison tested provided to the Agency on 31st January 2020.

The details of the batches and the submission is provided in the table below:

LOT NUMBER	USE	PACKAGE SIZE	SEQUENCE NUMBER
7061301	Phase 3 Clinical Lot	30 g	0015
7061901	Phase 3 Clinical Lot	30 g	
7052901	Registration Lot	30 g	
7053001	Registration Lot	30 g	
7101610	Registration Lot	30 g	
9032110	Registration Lot	7 g	
7050401	Phase 3 Clinical Lot	30 g	0018
7082810	Phase 3 Clinical Lot	30 g	
7102311	Phase 3 Clinical Lot	30 g	
7101110	Registration Lot	30 g	
7102611	Phase 3 Clinical Lot	30 g	0020/Corrected 0023
7052301	Registration Lot	30 g	
7100910	Registration Lot	30 g	
7100910	Registration Lot	7 g	
9031911	Registration Lot	7 g	
9120410	Development Lot	30 g	

Reviewer’s assessment and conclusion:

The Applicant has submitted the IVR data on all the clinical/registration/development batches in the format requested by the Agency. The acceptance criterion has been established based on the IVR data from all the clinical/registration/development batches.

The Applicant’s response to IR4 Item 1 is adequate and acceptable.

On 3/10/2020, the following Information Request 5 (IR5) comment was communicated to the Applicant. On 3/17/2020, the Applicant responded to the Agency’s IR comments (Sequence 0025). The Agency’s IR comments, the Applicant’s response to the IR, and the Reviewer’s assessment are included below.

Information Request 5:

IR5 Item 1:

We note the information that you have submitted in the “Development Summary of IVRT Method” (Module 3.2.P.5.3; Sequence 0001). Submit the particle size distribution for the (b) (4) %

LC, lot #MCH330(1.5)-190224S (1.5% MCH, w/w) and the altered formulation with the un-micronized API, lot# MCH330(1.5)-190512R (1.5% MCH, w/w).

Applicant’s response to IR5 Item 1:

The Applicant has submitted the API particle size distribution data for the following batches:

MCH330(1.5)-190224S (1.5% MCH, w/w) – micronized API lot number 05NY01-HQ00034
 MCH330(1.5)-190512R (1.5% MCH, w/w) – un-micronized API lot number 05NY01-HQ01157

The D₅₀ and D₉₀ results for the API lots are provided in the Table below:

Lot Number	D50 (µm)	D90 (µm)
05NY01-HQ00034		(b) (4)
05NY01-HQ01157		

Reviewer’s assessment and conclusion:

The Applicant has submitted the PSD of the target formulation (micronized API) lot and the modified formulation (un-micronized API) lot. This information has been taken into consideration when evaluating the discriminatory ability of the proposed IVR method used the modified formulation.

The Applicant’s response to IR5 Item 1 is adequate and acceptable.

IR5 Item 2:

Generally, the in vitro release (IVR) acceptance criterion is established based on the IVR data of clinical/exhibit batches at release and not from the method validation results. Based on the submitted IVR data from the clinical/registration/development lots, the mean IVR rate is (b) (4) with a standard deviation of (b) (4). Hence, your proposed acceptance criterion range of (b) (4) is (b) (4) unacceptable. We recommend that you revise the IVR acceptance criterion to (b) (4).

Update the drug product release specifications, and other relevant sections of your NDA submission, accordingly.

Applicant’s response to IR5 Item 2:

The Applicant has accepted that the acceptance criterion at release for in-vitro release proposed in the NDA (b) (4) the acceptance criterion for in-vitro release to the Agency recommended acceptance criterion to be the following:

(b) (4)

The response is presented in the link below (see pages 1 – 2)
<https://cdsesub1\evsprod\nda213690\0025\m1\us\nda-213690-1111-quality-information-amendment-seq0025-03.pdf>

Reviewer’s assessment and conclusion:

The Applicant has acknowledged the Agency’s recommended acceptance criterion.

The Applicant's response to IR5 Item 2 is adequate and acceptable.

IR5 Item 3:

We strongly recommend that you test the first three commercial batches as well as annual stability batches of drug product for in vitro release at release and during stability.

On 3/13/2020, the Applicant sent an email requesting a clarification to the above IR5 Item 3. The Agency responded on 3/16/2020 and clarified that the IVRT should be performed for all commercial batches at release and annually during stability including the first 3 commercial batches.

Applicant's response to IR5 Item 3:

The Applicant has agreed to test the first three commercial batches for both 30 g and 7 g, as well as the annual stability batches of drug product for IVR at release, and will monitor results during stability in order to set an appropriate IVRT end of life stability criterion. [Section 3.2.P.8.2](#) has been updated accordingly and is provided with this response.

The response is presented in the link below (see pages 1 – 2).

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Reviewer's assessment and conclusion:

The Applicant has acknowledged the Agency's comment and has agreed to test the first three commercial batches for both 30 g and 7 g, as well as the annual stability batches of drug product for IVR at release, and will monitor results during stability in order to set an appropriate IVRT end of life stability criterion.

The Applicant's response to IR5 Item 3 is adequate and acceptable.



Vidula
Kolhatkar

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Date: 3/30/2020 10:05:27AM
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Rajesh
Savkur

Digitally signed by Rajesh Savkur
Date: 3/30/2020 10:31:59AM
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MICROBIOLOGY

Product Information	
NDA Number	213690
Assessment Cycle Number	1
Drug Product Name / Strength	Minocycline foam, 1.5%.
Route of Administration	Topical
Applicant Name	Foamix Pharmaceuticals, Inc.
Manufacturing Site	ASM Aerosol-Service AG <div style="background-color: #cccccc; padding: 2px;">(b) (4)</div> <div style="background-color: #cccccc; padding: 2px;">(b) (4) Switzerland</div> FEI: 3005439256 DUNS: 480286111
Method of Sterilization	Nonsterile, non-aqueous drug product

Assessment Recommendation: Adequate

Theme:

<input type="checkbox"/> N/A	<input type="checkbox"/> Depyrogenation Validation Data
<input type="checkbox"/> Product Sterility Assurance	<input type="checkbox"/> Product Release and/or Stability Specifications
<input type="checkbox"/> Media Fill Data	<input type="checkbox"/> Validation for Product Release and/or Stability Test Method
<input type="checkbox"/> Validation of Product Test	<input type="checkbox"/> Other (Requires Division Director Approval)
<input type="checkbox"/> Due to Consult	

Justification: view justification statements found at: [Justification Statements](#)

N/A

Assessment Summary:

- The submission is recommended for approval.

List Submissions Being Assessed (table):

Submit	Received	Review Request	Assigned to Reviewer
08/02/2019	08/02/2019	N/A	08/14/2019

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues: NA

Supporting Documents:

NDA 212379 (Minocycline foam, 4%, Foamix Pharmaceuticals, Inc.) and associated product quality microbiology review, n212379mr01.doc (adequate) dated 4/16/2019

Select Number of Approved Comparability Protocols: 0

S DRUG SUBSTANCE

The drug substance is not sterile, and the applicant is not requesting reduced release/stability bioburden testing for the final drug product, therefore, a quality microbiology review of the drug substance is not necessary.

Drug substance: The drug substance is a broad-spectrum tetracycline antibiotic that inhibits the growth of many gram-positive and gram-negative bacteria as well as spirochetes, mycoplasmas, and *Entamoeba* sp. both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE (MINOCIN Package Insert 2018) section of the already approved Minocin® (minocycline hydrochloride pellet-filled capsules). Additionally, the drug substance will be stored at (b) (4) which will limit the potential for microbial growth.

Excipients: The excipients are predominantly oil-based (b) (4) and none of the excipients were found to promote microbial growth. The excipients are tested to USP and NF requirements (b) (4). The soybean oil and coconut oil were deemed potential risk based on the quantity used in the formulation. Therefore, these two excipients will be tested for microbiological attributes using the following specification limits:

Total aerobic microbial count (TAMC): (b) (4)

Total combined yeast/mold count (TYMC): (b) (4)

Specified microorganisms: Absence of *Pseudomonas aeruginosa* and *Staphylococcus aureus* per gram

Assessment:

Adequate

P DRUG PRODUCT

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product – The drug product, FMX103 1.5%, is an oil-based suspension of micronized minocycline hydrochloride (HCl) (equivalent to 1.5%

minocycline), developed as a (b) (4) propellant-driven aerosol foam for the topical treatment of (b) (4) rosacea. A smooth, stable, yellow foam is produced upon actuation from the aerosol canister, which collapses when rubbed onto the skin, delivering the minocycline. The product is to be provided in two configurations, a commercial package and a physician sample. The commercial package has a fill volume of 35 gm (product size 30 g) and the physician sample has a fill volume of 15 gm (product size 7 g).

- **Drug product composition -**
(3.2.P.1, Description and composition of the Drug Product)

The composition of FMX103 1.5% Topical Foam is reported from Table 1:

Component	Quality standard	Quantitative composition (% w/w)	Quantity per 30 g canister (g)	Quantity per 7 g canister (g)	Function
Bulk					
Minocycline HCl (expressed as minocycline) ^a	USP	1.50 ^a	0.45 ^a	0.105 ^a	Active Ingredient
Soybean Oil	Complies to USP	(b) (4)			
Coconut Oil	Complies to USP				
Light Mineral Oil ^b	NF				
Cyclomethicone (b) (4)	NF				
Cetostearyl Alcohol	NF				
Stearic Acid	NF				
Myristyl Alcohol	NF				
Hydrogenated Castor Oil	NF				
White Wax (Beeswax)	NF				
Stearyl Alcohol	NF				
Docosanol	NA				

(b) (4)					
Total Bulk		100.00	30.00	7.00	
Propellant (Butane+isobutane + propane) ^d	NA	(b) (4)			Propellant
	NA				
	NA				



Note to reviewer: The composition of FMX103 1.5% product is identical to that of FMX101 4%, reviewed in microbiology review n212579mr01.doc (adequate), with the exception of the content of minocycline HCl and corresponding adjustment of the content of light mineral oil. The manufacturing process is identical for both products. The potential (b) (4) of minocycline HCl was extensively monitored in the FMX101 4% product, both during manufacturing and during shelf life and no (b) (4) changes were detected. Therefore, the risk of potential (b) (4) change in FMX103 1.5% is considered to be negligible.

- **Description of container closure system**

(3.2.P.1., Description and composition; 3.2.P.7. Container-closure-system)

The drug product suspension is packaged in individual aluminum canisters with a valve/actuator assembly that is pressurized by the addition of a propellant. The FMX103 1.5% 30 g product is filled and crimped in a 35 x 88 mm aluminum canister while the FMX103 1.5% 7 g product is filled and crimped in a 35 x 65 mm aluminum canister. Drawings with specifications are provided for each device constituent in the container closure system (CCS). The CCS for both product sizes is shown in Table below:

Product size	Component	Part #	Description	Manufacturer
30 gm	Canister			
	Valve			
	Actuator			
7 gm	Canister			
	Valve			
	Actuator			

(b) (4)

Assessment:

Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

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/

HAMID R SHAFIEI
04/13/2020 04:13:05 PM