CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208945Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality (OPQ) Review

NDA 208945

OPQ Review # 2

Review Date:	December 1, 2017
Submission:	NDA 208945 Resubmission (Class 2); SDN# 18
Submission date:	July 17, 2017
OND Division:	Division of Anti-Infective Products (DAIP)
Product Name:	Xepi (ozenoxacin) Cream, 1%
Applicant:	Ferrer Internacional S.A.

Executive Summary:

NDA 20895 originally submitted on June 23, 2016 was recommended for Complete Response (CR) by the OPQ Review Team due to significant cGMP deficiencies identified at the drug substance manufacturing site and the overall recommendation of "Withhold" for manufacturing facilities (refer to the Addendum to OPQ Review # 1 dated June 7, 2016 in Panorama, and the CR letter dated June 22, 2016 in DARRTS). The current NDA resubmission (Class 2) includes a response to the CR comment with no additional updates to other CMC sections. The drug substance facility (b) (4) and all other manufacturing facilities were found adequate by Dr. David Anderson during the review of the current NDA resubmission (refer to the Facilities Review, Attachment I, below). Based on this assessment and the overall recommendation of "Approve" entered by the Office of Process and Facilities (OPF) into Panorama on November 27, 2017, this NDA can be now recommended for approval.

Recommendation:

This NDA is recommended for **Approval** from the Product Quality perspective.

Application Technical Lead (ATL) Signature:

Dorota M. Matecka -S

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This NDA is recommended for approval from the Product Quality perspective.
On behalf of the OPQ Review Team
Dorota Matecka, Ph.D., ATL for NDA 208945

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Derek Smith

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David Dean Anderson

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NDA 208945

Addendum #1 to OPQ Review # 1

Date: June 7, 2017

Re: Final OPQ Recommendation for NDA 208945 (b) (4) (ozenoxacin) Cream]

Summary:

This NDA was recommended for Complete Response from the Product Quality perspective due to significant cGMP deficiencies identified at the drug substance manufacturing site and the overall recommendation of "Withhold" for manufacturing facilities entered in Panorama on March 3, 2017 (refer to the OPQ Review # 1 dated March 9, 2017 in Panorama). Also, there were several pending issues related to the equipment compatibility and holding times proposed in the drug product manufacturing process. In addition, insufficient information had been provided from the product quality microbiology perspective; specifically, validation data for the proposed *Burkholderia cepacia* complex (BCC) assay were not provided. However, these issues were addressed via subsequent NDA amendments, which provided additional information regarding the equipment compatibility and holding times in the manufacturing process, and validation protocol and data for the BCC assay (Quality Amendments dated March 27 and May 3, 2017, respectively). This information has been found to be adequate by the Process and Product Quality Microbiology Reviewers, respectively; therefore, these issues are considered to be now resolved (refer to the updated Process and Microbiology Reviews, Attachment I and II, respectively). In addition, the labeling revisions have been incorporated in the CMC sections of the package insert and the container, and carton labels, which are now considered acceptable from the CMC perspective (refer to Attachments IIIa and IIIb). However, due to the on-going unresolved issues at the drug substance facility and the Overall Recommendation for manufacturing facilities of "Withhold" in Panorama, this NDA continues to be recommended for Complete Response from the Product Quality perspective.

Recommendation:

NDA 208945 is recommended for **Complete Response** from the Product Quality perspective.

The following comment should be included in the Complete Response letter:

During a recent inspection of the (b) (4) manufacturing facility for this ANDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this application may be approved.

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David Dean Anderson

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Edwin Jao

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MICROBIOLOGY

Product Background:

NDA: 208945

Drug Product Name/ Strength: (b) (4) (Ozenoxacin) Cream 1% (10mg/g)

Route of Administration: Topical

Applicant Name: Ferrer Internacional, S.A.

Manufacturing Site: Teligent Pharma, Inc,
105 Lincoln Avenue, Buena NJ 08310

Method of Sterilization: Non-sterile drug product

Review Summary: The submission is **recommended** for approval on the basis of sterility assurance.

List Submissions being reviewed (table):

Submit*	Received	Review Request	Assigned to Reviewer
06/23/2016	06/23/2016	N/A	08/04/2016
09/20/2016*[1]	09/20/2016	N/A	N/A
12/21/2016*[2]	12/21/2016	N/A	N/A
02/27/2014*[2]	02/27/2017	N/A	N/A
03/27/2017*[2]	03/27/2017	N/A	N/A
05/03/2017*[2]	05/03/2017	N/A	N/A

* Submissions on 02/14/17 and 04/28/17 are noted but not reviewed as there are no relevant updates
*[1] Updated labeling
*[2] IR responses

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining:
There are no deficiencies identified based on the information submitted.

Supporting Documents: None

P.1 Description of the Composition of the Drug Product

Description of drug product –

Ozenoxacin Cream, 1% is a homogeneous, pale yellow cream packaged in aluminum tubes with (b) (4) caps. This formulation comprises of (b) (4) .

Drug product composition -

Ingredient	%w/w	Functional category
Ozenoxacin, IH	1.0	API
Benzoic Acid, USP	(b) (4)	
Octyldodecanol, NF		
Peglicol 5 Oleate, NF		
Pegoxol 7 Stearate , NF		
Propylene Glycol, USP		
Purified Water, USP		
Stearyl Alcohol, NF		

Description of container closure system – (b) (4)

Component	Description	Supplier
Tube	(b) (4)	
Cap		

3.2.P.7. Container Closure System.pdf, p2/8

Reviewer's Assessment: Acceptable

P.2 Pharmaceutical Development

(b) (4)

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Alifiya Ghadiali

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LABELING

R Regional Information

1.14 Labeling

(b) (4)

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Balajee Shanmugam

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LABELING

R Regional Information

1.14 Labeling

(b) (4)

(b) (4)

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(b) (4)

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Reviewer's Assessment: Acceptable

The Immediate Container Labels includes:

- Proprietary name, established name
- Strength
- Route of administration
- Net contents
- Name of all inactive ingredients (not on the physical sample label due to limited space)
- Lot number
- Expiration date
- "Rx only" statement
- Storage condition statement
- NDC number
- Bar Code (not on the physical sample label due to limited space)
- Name of manufacturer/distributor

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The Immediate Container Labels includes:

- Proprietary name, established name
- Strength
- Route of administration
- Net contents
- Name of all inactive ingredients
- Lot number
- Expiration date
- "Rx only" statement
- Storage condition statement
- NDC number
- Bar Code
- Name of manufacturer/distributor
- "See package insert for full prescribing information"
- "Keep out of reach of children"

Package Insert (SDN 16, eCTD 0014, submitted on 5/12/2017)

Highlights section

Product Title

XEPI™ (ozenoxacin) cream, for topical use

Reviewer's Assessment: Adequate

The product title line includes:
Proprietary name (non-proprietary name) dosage form, ROA
Per 21 CFR 201.57(a)(2)

Dosage Forms and Strengths (DFS) Heading

----------DOSAGE FORMS AND STRENGTHS----------
Cream: Each gram contains 10 mg of ozenoxacin (1%) (3).

Reviewer's Assessment: Adequate

The dosage forms and strengths (DFS) heading includes a concise summary of the information in Dosage forms and strengths section
Per 21 CFR 201.57(a)(8)

DOSAGE FORMS AND STRENGTHS Section (Section 3) of FPI

3 DOSAGE FORMS AND STRENGTHS

Cream: 1%, pale yellow cream. Each gram of XEPI contains 10 mg of ozenoxacin.

Reviewer's Assessment: Adequate

The dosage forms and strengths section includes:

- Dosage form
- Strength
- Description of identifying characteristics of dosage forms (parenteral dosage forms: color and other identifying characteristics)

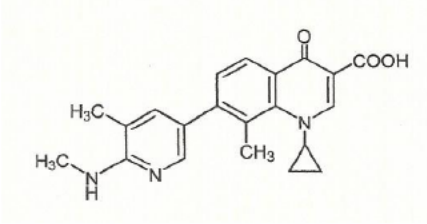
Per 21 CFR 201.57(c)(4)

DESCRIPTION Section (Section 11) of FPI

11 DESCRIPTION

XEPI contains ozenoxacin, a quinolone antimicrobial. It is intended for topical use only.

The chemical name of ozenoxacin is 1-Cyclopropyl-8-methyl-7-(5-methyl-6-methylamino-pyridin-3-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid. Ozenoxacin, a white to pale-yellow crystalline solid, has a molecular formula of $C_{21}H_{21}N_3O_3$, and a molecular weight of 363.41. The chemical structure is:



Each gram of cream contains 10 mg of ozenoxacin (1% w/w) and the following inactive ingredients: benzoic acid, octyldodecanol, peglicol 5 oleate, pegoxol 7 stearate, propylene glycol, purified water, stearyl alcohol.

Reviewer's Assessment: Adequate

The DESCRIPTION section includes:

- Proprietary name
- Established name or proper name

- Dosage form(s)
- Route(s) of administration
- Pharmacologic or therapeutic class
- Qualitative and quantitative ingredients
- Chemical name and structural formula

Per 21 CFR 201.57(c)(12)

HOW SUPPLIED/STORAGE AND HANDLING Section (Section 16) of FPI

16 HOW SUPPLIED/STORAGE AND HANDLING

XEPI cream, 1% is a pale yellow cream supplied in 10-, 30-, and 45-gram tubes. Each gram of cream contains 10 mg of ozenoxacin.

NDC 43538-320-10 (10-gram tube)

NDC 43538-320-30 (30-gram tube)

NDC 43538-320-45 (45-gram tube)

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

Reviewer's Assessment: Adequate

Storage statements made to be consistent between the PI and the container label and carton labeling. The container label and carton labeling statement is copied here.

The HOW SUPPLIED/STORAGE AND HANDLING section includes:

- Dosage form
- Strength
- Units in which dosage form is ordinarily available for prescribing by practitioners
- Description of identifying characteristics of the dosage forms (parenteral dosage forms: color and other identifying characteristics)
- National Drug Code (NDC) number(s)
- Storage statements

Per 21 CFR 201.57(c)(17)

Manufacturing Information at End of Labeling

MEDIMETRIKS PHARMACEUTICALS, INC.

Manufactured for :
Medimetriks Pharmaceuticals, Inc., Fairfield, NJ 07004 USA

QUALITY ASSESSMENT

Manufactured by:
Teligent Pharma, Inc., Buena, NJ 08310 USA

Reviewer's Assessment: Adequate

The manufacturing information at end of labeling includes the manufacturer/distributor name per 21 CFR 201.1.

List of Deficiencies:

None

Primary Labeling Reviewer Name and Date:

Yushi Feng, Ph.D.; Staff Fellow; Branch 3; Division of New Drug Product I.

Jun 7, 2017

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

Yushi Feng

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Balajee Shanmugam

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ATTACHMENT IV: Risk Assessment (*updated*)

From Initial Risk Identification			Review Assessment		
From Initial Risk Identification	**Review Assessment**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
		H, M, or L		Acceptable or Not Acceptable	
Assay /Stability	Formulation Raw materials Process parameters Scale/equipment Site	L		Acceptable	
Content Uniformity	Formulation Process parameters Scale/equipment Site	L		Acceptable	
Physical stability/ Homogeneity	Formulation Raw materials Process parameters Scale/equipment Site	L	*Particle size distribution acceptance criteria established;* (b) (4)	Acceptable	
Leachables	Formulation Container closure Scale/equipment Site	M		Acceptable	(b) (4)
Viscosity	Formulation Raw materials Process parameters Scale/equipment Site	L		Acceptable	
In-vitro release	Formulation Raw materials Process parameters Scale/equipment Site	L	*In-Vitro Release method was found to be adequately validated*	Acceptable	

Microbial Limits	Formulation Raw materials Process parameters Scale/equipment Site	L		Acceptable	
Manufacturing Facilities	Site	H	*Significant cGMP deficiencies identified at the DS site (WL issued)*	Not Acceptable	

This NDA is recommended for Complete Response from the Product Quality perspective.

Dorota M. Matecka -S

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Dorota Matecka, Ph.D. ATL for NDA 208945 *on behalf of OPQ Team*

Recommendation: *Complete Response*

NDA 208945
Review # 1

Drug Name/Dosage Form	(b) (4) (ozenoxacin) Cream
Strength	1%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Ferrer Internacional, S.A.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	6/23/2016	All
Quality Amendment	12/21/2016	Drug Product, Microbiology, Process, Biopharmaceutics
Quality Amendment	2/14/2017	Process
Quality Amendment	2/24/2017	Drug Substance, Drug Product, Microbiology

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Gene Holbert	Branch I/DNDAPI
Drug Product	Yushi Feng	Branch III/DNDP I
Process	David Dean Anderson	Branch VII/DPA
Microbiology	Alifiya Ghadiali	Branch II/DMA
Biopharmaceutics	Kaushalkumar Dave	Branch I/ DBP
Facility	David Dean Anderson	Branch II/DIA
Environmental Analysis (EA)*	Raanan Bloom	ONDP
Regulatory Business Process Manager	Luz Rivera	Branch I/DRBPM I
Application Technical Lead	Dorota Matecka	Branch III/DNDP I

**EA review captured in the Drug Product Chapter*

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status*	Date Review Completed	Comments
(b) (4)			Ozenoxacin	Adequate	03/07/2017	Reviewed in support of this NDA by Gene Holbert
			(b) (4)	*Active*	*03/20/1991*	(b) (4)
				N/A	Adequacy is demonstrated by data presented in NDA 208945	

**Adequate, Adequate with Information Request, Deficient, or N/A (there is enough data in the application, therefore the DMF did not need to be reviewed)*

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	105,567	

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	Complete	Adequate	*Email dated 2/21/2017*	Tessie Alapatt
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA has not provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, ozenoxacin cream. Significant cGMP deficiencies were identified at the drug substance manufacturing site during the most recent inspection (b) (4) and a Warning Letter for this facility was issued on (b) (4). Therefore, the overall recommendation of "Withhold" for manufacturing facilities has been entered in Panorama on March 3, 2017. In addition, insufficient information was provided from the product quality microbiology perspective; specifically, validation data for the proposed *Burkholderia cepacia* complex (BCC) assay were not provided. Also, there are several pending issues related to the equipment compatibility and holding times proposed in the manufacturing process, which need to be adequately resolved. In addition, the proposed package insert and the container and carton labels are presently under review by the NDA review team.

Therefore, this NDA is currently recommended for Complete Response from the Product Quality perspective.

II. Summary of Quality Assessments

A. Product Overview

Ozenoxacin is an antibacterial agent, a non-fluorinated quinolone with a potent dual inhibitory activity against bacterial DNA replication enzymes, DNA gyrase A and topoisomerase IV. Ozenoxacin has been developed as a topical cream, 1%, for the treatment of impetigo in adults, adolescents, children (b) (4) 2 months and older.

Proposed Indication(s) including Intended Patient Population	Treatment of impetigo in adults, adolescents, children (b) (4) 2 months and older.
Duration of Treatment	5 days (*cream applied to the affected area twice daily*)
Maximum Daily Dose	N/A
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Ozenoxacin (1-cyclopropyl-8-methyl-7-[5-methyl-6-methylamino-pyridin-3-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid) is a novel antibacterial agent with potent bactericidal activity against pathogens commonly involved in acute bacterial skin and skin structure infections (ABSSSI). Ozenoxacin, which is pharmacologically classified as a non-fluorinated quinolone is prepared via (b) (4) (b) (4). Ozenoxacin drug substance is a (b) (4) (b) (4), yellowish, crystalline (b) (4), which is insoluble in aqueous and acidic solutions, sparingly soluble in basic solution, and very slightly soluble in organic solvents. The CMC information for the (b) (4) drug substance has been provided via a reference to a DMF Type II (b) (4) held by (b) (4) DMF (b) (4) was reviewed and found adequate by Dr. Gene Holbert via a review dated 03/07/2017 (in DARRTS). In addition, information provided for the ozenoxacin drug substance in Module 3 of the NDA was also found acceptable. The stability information submitted for ozenoxacin drug substance in DMF (b) (4) was found adequate to support the retest period of (b) (4) months.

The proposed drug product, ozenoxacin cream, 1%, is a homogeneous, pale yellow cream containing 1% (w/w) of the drug substance ozenoxacin, and packaged in aluminum tubes with (b) (4) caps. The ozenoxacin drug substance is (b) (4). Inactive ingredients in the drug product include octyldodecanol, peglicol 5 oleate, pegoxol 7 stearate, propylene glycol, stearyl alcohol, purified water, and benzoic acid (b) (4) The finished drug product is (b) (4) 10 gram, 30 gram, and 45 gram aluminum tubes and packaged into unit cartons. The physician packaging configuration includes a 3 gram cream sample packaged into a 4 count sample (b) (4). As part of the product quality review, the need for the large size (45 gram) tube was questioned by the Drug Product Reviewer and consulted with the Medical Officer for this NDA who did not find it concerning. Therefore, the packaging configurations including the proposed container closure systems, as proposed in the NDA, were found acceptable.

The proposed drug product specification includes the following attributes relevant for the proposed dosage form (i.e., topical cream) such as: appearance, identification, pH, viscosity, particle size distribution, ozenoxacin assay, degradation products, benzoic acid assay, tube content uniformity, weight loss, package integrity, and microbial limits. Additional information and clarifications regarding the particle size distribution and viscosity testing and acceptance criteria were requested and provided by the Applicant during the NDA review. Based on the overall information provided in the original NDA and via the subsequent amendments, the drug product specification including the acceptance criteria for those quality attributes were found acceptable.

Stability information provided in the original NDA includes 18 months of long-term (25°C/60% RH) and 6 months of accelerated (40°C/75% RH) stability results for three drug product registration batches. Overall stability information provided in the NDA was found to be adequate to support the expiration dating of 36 months for the drug product to be stored at room temperature.

The drug product manufacturing process involves (b) (4) A number of comments were conveyed to the Applicant during the NDA review and additional information regarding the (b) (4) Some of these comments were adequately addressed by the Applicant. However, a resolution of issues related to the equipment compatibility and proposed holding times in the drug product manufacturing process is currently pending.

From the product quality microbiology perspective, several deficiencies have been identified during the NDA review and information requests to address issues related to microbial limits (b) (4) testing, were forwarded to the Applicant. Some of these comments have been adequately addressed; however, validation data for the *Burkholderia cepacia* complex (BCC) assay have not been yet provided. These deficiencies were conveyed to the Applicant; however, a response to these comments has not been yet submitted.

The biopharmaceutics review focused on the evaluation of In-Vitro Release Test (IVRT) method and the in vitro drug release data submitted in support of the drug product manufacturing site change. The proposed IVRT method was found adequately developed and validated by the Biopharmaceutics Reviewer. In addition, the comparative in vitro release data submitted for the drug product, ozenoxacin cream, manufactured at the Ferrer/Spain site (the manufacturer of the drug product used in the Phase III studies) and the drug product manufactured at the Teligent/USA site (the proposed commercial manufacturer) were reviewed and found to be adequate to support the proposed manufacturing site change.

The manufacturing facilities listed for this NDA include (b) (4), which is the drug substance facility, Teligent Pharma, Inc., the proposed drug product manufacturing site, and (b) (4), a testing site. The drug product manufacturing and testing facilities were found acceptable. However, multiple cGMP deficiencies were identified at the drug substance manufacturing site during the most recent inspection (in (b) (4) and a Warning Letter for this facility was issued on (b) (4). Therefore, the overall recommendation of "Withhold" for manufacturing facilities has been entered into Panorama for this NDA on March 3, 2017.

Based on the overall Product Quality assessment by the OPQ Review Team, this NDA is currently recommended for Complete Response. Several issues that need to be resolved before this NDA can be recommended for approval are listed in the Attachment II of this review.

C. Special Product Quality Labeling Recommendations (NDA only)

Labeling review is currently pending.

D. Risk Assessment (see Attachment I)

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David Dean
Anderson

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MICROBIOLOGY

Product Background:

NDA/ANDA: NDA 208945

Drug Product Name/ Strength: (b) (4) (Ozenoxacin) Cream 1% (10mg/g)

Route of Administration: Topical

Applicant Name: Ferrer Internacional, S.A.

Manufacturing Site: Teligent Pharma, Inc, 105 Lincoln Avenue, Buena NJ 08310

Method of Sterilization: Non-sterile drug product

Review Summary:

List Submissions being reviewed (table):

Submit	Received	Review Request	Assigned to Reviewer
06/23/2016	06/23/2016	N/A	08/04/2016
09/20/2016	09/20/2016	N/A	N/A
12/21/2016*	12/21/2016	N/A	N/A

* IR response

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining:
Micro deficiencies are: ☒ Major ☐ Minor
Deficiencies were found regarding microbial limit, (b) (4) and stability testing.

The submission is **not recommended** for approval on the basis of sterility assurance.

S. Drug Substance

Reviewer's Assessment: N/A

P.1 Description of the Composition of the Drug Product

Description of drug product –

Ozenoxacin Cream, 1% is a homogeneous, pale yellow cream packaged in aluminum tubes with (b) (4) caps. This formulation comprises of (b) (4)

Drug product composition -

Ingredient	Content/ (b) (4)	Functional category
Ozenoxacin	10.0	API
Benzoic Acid, USP	(b) (4)	
Octyldodecanol, NF		
Peglicol 5 Oleate		
Pegoxol 7 Stearate		
Propylene Glycol, USP		
Purified Water, USP		
Stearyl Alcohol, NF		

Description of container closure system – (b) (4)

Component	Description	Supplier
Tube	(b) (4)	
Cap		

3.2.P.7. Container Closure System.pdf, p2/8

Reviewer's Assessment: Acceptable

P.2 Pharmaceutical Development

(b) (4)

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Alifiya Ghadiali

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BIOPHARMACEUTICS REVIEW	
Application No.	NDA 208945
Type of Submission	505(b)(1)
Applicant/Sponsor	Ferrer Internacional, S.A.
Product Name	Ozenoxacin Cream, 1%
Dosage Form/Strength	Cream/1%
Route of Administration	Topical
Intended Use	Topical treatment of impetigo
Submission Date	06/23/2016
Review Date	02/21/2017
Primary Reviewer	Kaushalkumar Dave, Ph.D.
Secondary Reviewer	Elsbeth Chikhale, Ph.D.
Recommendation	Adequate

1. EXECUTIVE SUMMARY

Submission: NDA 208945 for Ozenoxacin Cream, 1% is a 505(b)(1) submission with ozenoxacin as a new molecular entity (NME). The proposed drug product is a topical cream containing 1% (w/w) of the drug substance ozenoxacin, and is packaged in aluminum tubes with (b) (4) caps. The formulation comprises of (b) (4) the active ingredient (ozenoxacin) (b) (4)

Review: The Biopharmaceutics review is focused on the evaluation of In-Vitro Release Test (IVRT) method and the in vitro drug release data supporting the proposed bridging studied. Development and validation of an in vitro drug release test is currently not required for approval of a semisolid product, nor is the in vitro release test currently required as a routine batch-to-batch quality control test. The in vitro drug release test was used in this submission to support the pre-approval manufacturing site change for the proposed product.

Assessment:

IVRT Method: The IVRT method was appropriately developed where experimental parameters including selection of the receiver fluid and the selection of the release membrane were investigated and adequately justified. Further the selected IVRT method was assessed for the operator repeatability and the day-to-day repeatability. The discriminating power of the selected dissolution method was studied using formulations with different drug concentrations, different viscosities, and different particle sizes. Overall, the proposed IVRT method was adequately developed and validated.

Bridging Studies: The Applicant developed an In-Vitro Release Test (IVRT) method, and submitted the IVRT reports supporting two bridging studies. The first comparative IVRT study was performed to bridge between Ozenoxacin Cream, 1%, batches manufactured at (b) (4)

(b) (4) which was used in early clinical studies (Phase 1 & 2 studies for safety and dose determination), and batches manufactured for phase 3 clinical studies at the manufacturing site at Ferrer/Spain. The second comparative IVRT study was performed to bridge between phase 3 clinical batches of the proposed product manufactured at Ferrer/Spain, and the registration batches of the proposed product manufactured at the commercial manufacturing site at Teligent/USA. Since, the pivotal clinical studies were performed at the manufacturing site in Ferrer/Spain, and the composition and the overall manufacturing process of the product did not change for any of the clinical and registration/exhibit batches, no bridging was required for the change in the manufacturing site (b) (4) to Ferrer/Spain. The current review evaluated the IVRT method and the data provided to support the bridge between the pivotal clinical study batches manufactured at Ferrer/Spain and the registration batches manufactured at the proposed commercial drug product manufacturing site in Teligent/USA.

The comparative in vitro release testing of ozenoxacin from the pre-change product (manufactured at Ferrer/Spain) and the post-change product (manufactured at Teligent/USA) was performed per the 'Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation' guidance for nonsterile semisolid dosage forms published by the FDA in May 1997. The in vitro drug release rate comparison data support the manufacturing site change from Ferrer/Spain to Teligent/USA.

Recommendation: The proposed IVRT method and the bridging studies are acceptable and the NDA 208945 is **recommended for Approval** from a Biopharmaceutics perspective.

1. List Submissions being reviewed (table):

eCTD sequence #	Received date	Document
0000	06/23/2016	Multiple categories
0006	12/21/2016	Quality/Response to Information Request

2. Highlight Key Outstanding Issues from Last Cycle: None

3. Concise Description Outstanding Issues Remaining: None

4. Background information

The proposed drug product, Ozenoxacin Cream, 1%, is (b) (4) indicated for the topical treatment of impetigo in adults, adolescents, (b) (4) and children 2 months and older. The product is packaged in aluminum tubes with (b) (4) caps. The composition of the product is:

Table 1: Composition of Ozenoxacin Cream, 1%

INGREDIENT	FUNCTION	%W/W
Ozenoxacin	Active Ingredient	1
Benzoic Acid, USP	(b) (4)	
Octyldodecanol, NF		
Peglicol 5 Oleate		
Pegoxol 7 Stearate		
Propylene Glycol, USP		
Purified Water, USP		
Stearyl Alcohol, NF		

5. Development of the In-Vitro Release Test (IVRT)

(b) (4)

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The finalized IVRT method used for the bridging studies has been summarized in Table 5.

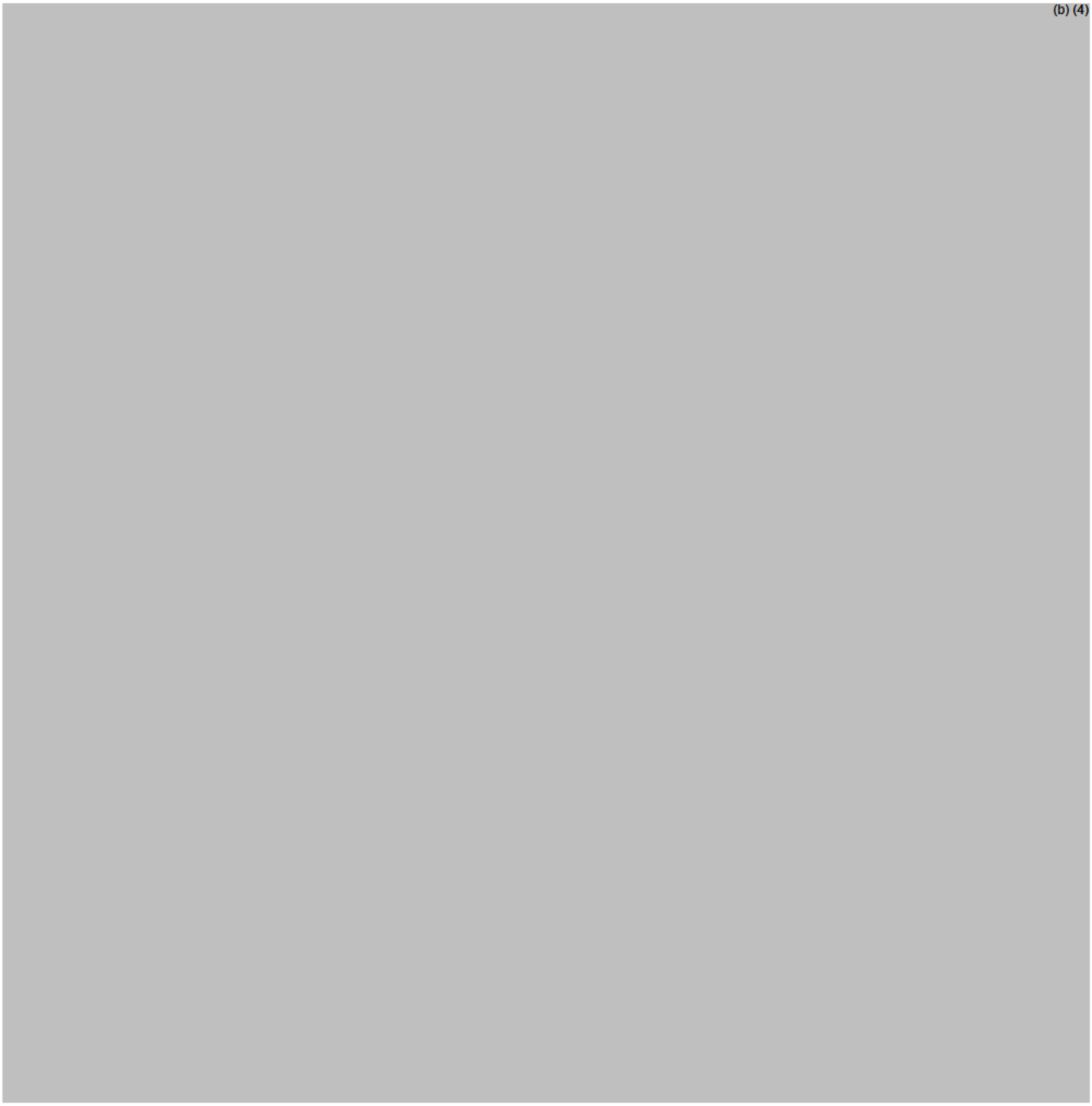
Table 5: The selected IVRT method for the bridging studies

Apparatus	Vertical Franz Diffusion Cell with an average surface area and volume of approximately 1.77 cm^2 and 10 mL, respectively
Receptor Fluid	50:50 v/v Transcutol P: water
Receptor Volume	10 mL
Bath Temperature	32°C
Speed	500 rpm
Sample Amount (Dosage)	300 mg
Sample Volume	1 mL
Time Points	0, 1, 2, 3, 4, 5 ,6, 8, and 24 hours
Filter Membrane	Polyethersulfone (PES) membrane with 0.45 µm pore size

Reviewer's assessment

(b) (4)

(b) (4)



6. Validation of the In Vitro Drug Release Method

On the basis of previous experience (IVRT Report Number RR-100864-01) and the above studies, the firm selected IVRT experimental conditions as shown in Table 2. Using this method, the following parameters were assessed for their effect on the ozenoxacin release rate for the validation of the IVRT method:

- Operator repeatability
- Day-to-day repeatability

- Sensitivity of the in vitro model to various concentrations of ozenoxacin
- Sensitivity of in vitro model to different drug particle size distribution (PSD) formulations
- Sensitivity of in vitro model to different viscosity formulations

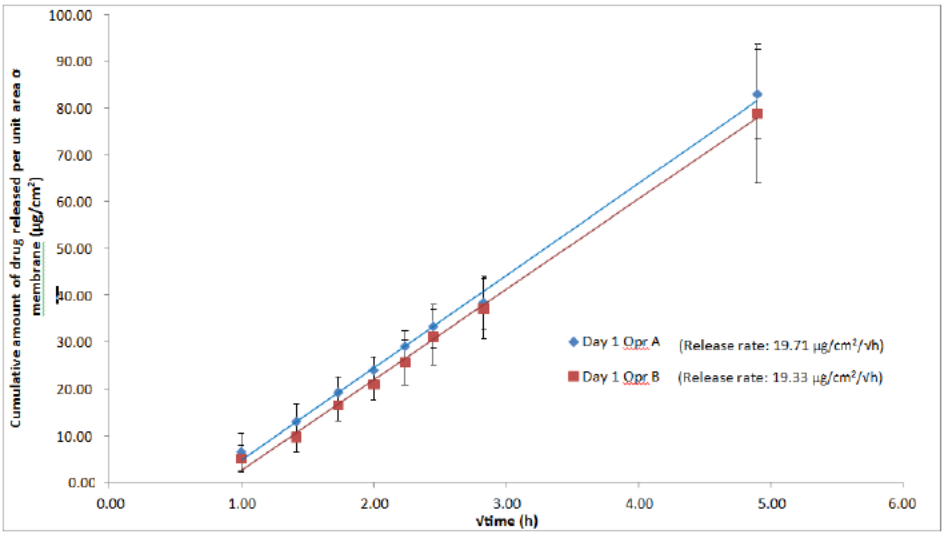


Figure 3: Total cumulative amount per unit area of ozenoxacin released from 1 % Ozenoxacin Cream (Batch No: 5137) through a PES membrane between 1 and 24 h, presented as a √time. The experiment was performed in parallel with two individual operators (operator A and operator B). Data is represented as Mean ± SD, n=6.

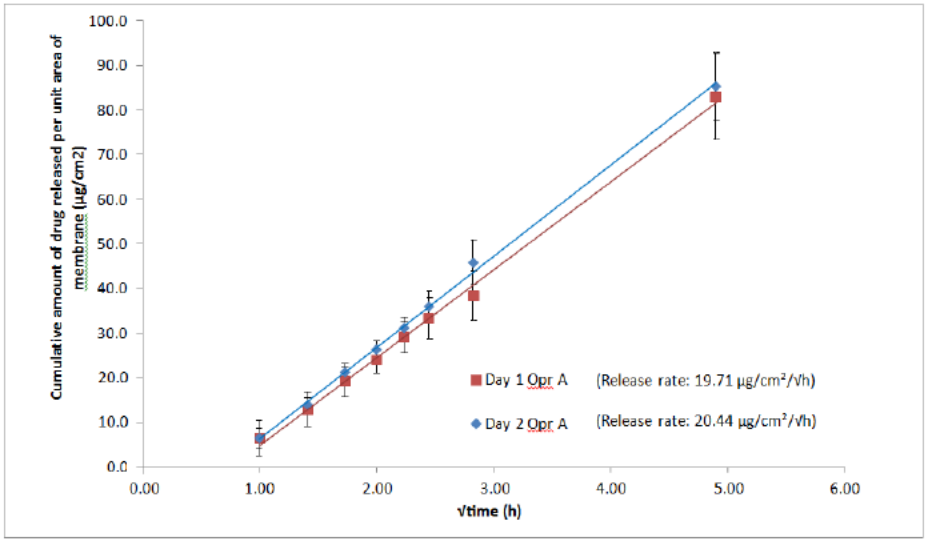


Figure 4: Total cumulative amount per unit area of ozenoxacin released from 1 % Ozenoxacin Cream (Batch No: 5137) through a PES membrane between 1 and 24 h, presented as a √time. The experiment was performed on two individual days (day 1 and day 2) using the same operator, data is represented as Mean± SD, n=6.

The discrimination ability of the method was studied by diluting the test product with a placebo cream to 90% or 80% of its original concentration by taking 9 g of cream and 1 g of placebo, or 8 g of cream and 2 g of placebo, respectively (Figure 5).

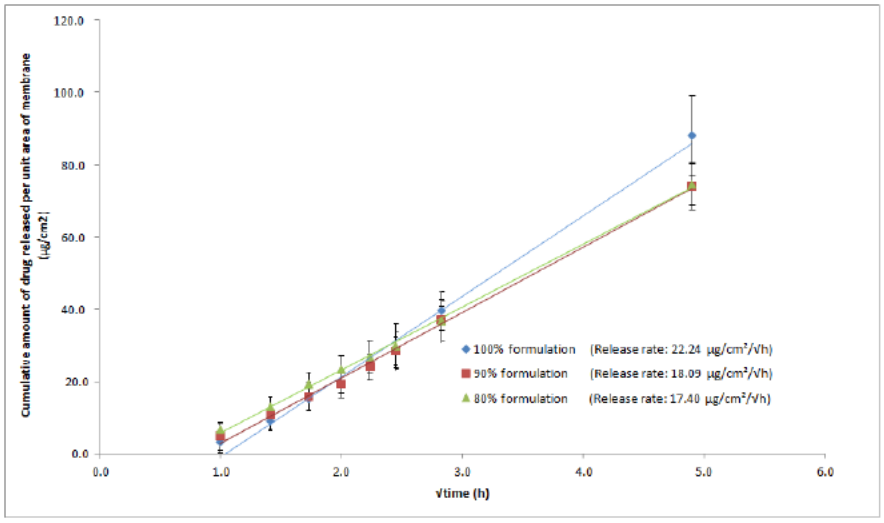


Figure 5: Total cumulative amount per unit area of ozenoxacin released from 100, 90 and 80 % formulations through a PES membrane between 1 and 24 h, presented as a √time. The data is represented as Mean ± SD, n=6.

The sensitivity of the IVRT model to different drug PSD formulations was evaluated by assessing two batches of 1% Ozenoxacin Cream containing (b) (4) (original formulation) and (b) (4) drug) (Figure 6).

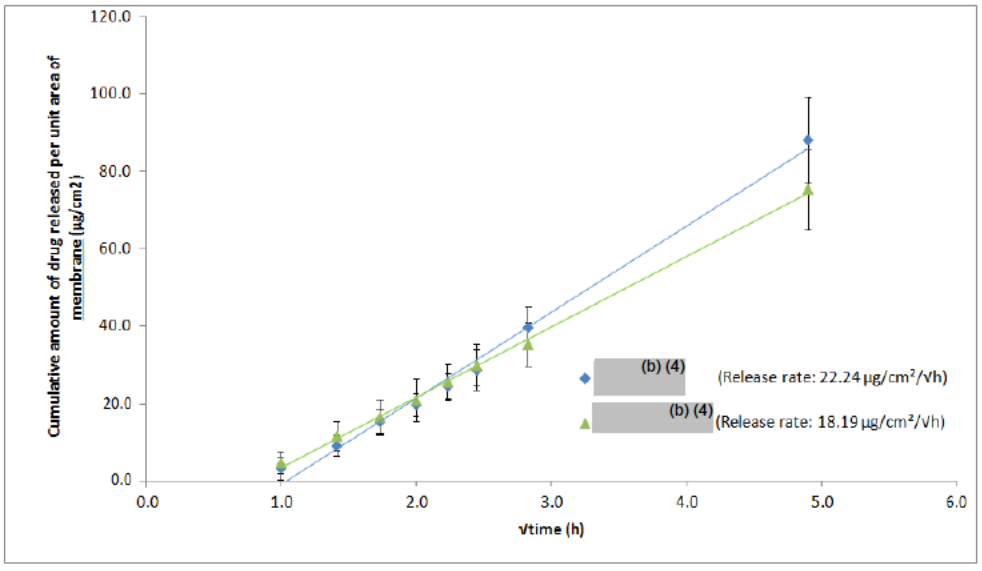


Figure 6: Total cumulative amount per unit area of ozenoxacin released from the (b) (4) (b) (4) drug formulations through a PES membrane between 1 and 24 h, presented as a √time. The data is represented as Mean ± SD, n=6.

Furthermore, to investigate the sensitivity of the in vitro model to formulations with different viscosities, the Applicant performed an in vitro release test assessing three different formulations including two batches of 1 % Ozenoxacin Cream with high and low viscosities, and the original formulation (Figure 7).

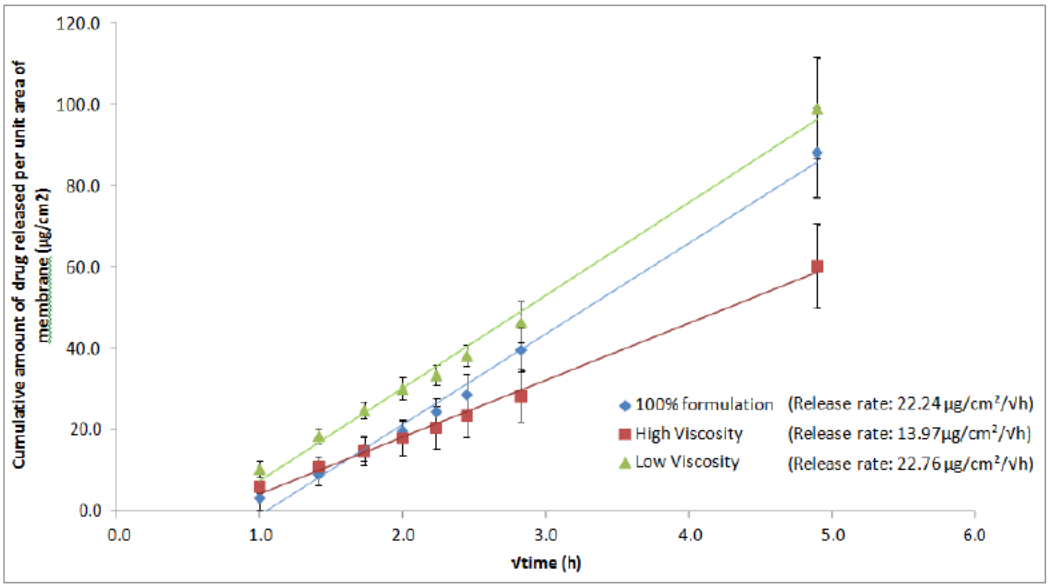


Figure 7: Total cumulative amount per unit area of ozenoxacin released from the different viscosity formulations through a PES membrane between 1 and 24 h, presented as a √time. The data is represented as Mean ± SD, n=6.

Reviewer's assessment

As can be seen in Figures 3 & 4, no significant change in results was observed between different operators and different days of the study. Sensitivity of the in vitro model to various concentrations of ozenoxacin was studied by diluting the cream to 80% and 90% using a placebo cream. The 'statistical analysis results' provided by the firm showed sameness between 80% and 90% formulations, and difference between 80% and 100%, and 90% and 100% formulations. The Applicant had not provided raw data for any of the in vitro release studies. Also the provided figures showing in vitro release of the drug from 80%, 90% and 100% formulations were of poor quality hence it was difficult to interpret the data. An IR was sent to the Applicant on 11/23/2016 (See Appendix I) asking the Applicant to provide all IVRT figures with better resolution, along with the raw data for all of the IVRT studies. In a response to the IR, the Applicant had provided raw data and higher resolution figures for all of the IVRT studies (Appendix I). The Statistical Analysis for the IVRT study results comparing batches with different drug concentrations was performed by the reviewer to verify the results provided by the Applicant.

IVRT studies with different drug PSD formulations showed that the formulations with higher viscosity and with (b) (4) drug had a lower drug release rates (18.27 µg/cm²/√h) compared to the original (b) (4) formulation (21.80 µg/cm²/√h) (Figure 6). The statistical analysis results provided by the Applicant showed that the drug release rates from these two formulations were different. However, the relative contribution of viscosity and PSD on the

release rate was unknown as the firm stated that the viscosity of the formulation containing the (b) (4) drug was much higher (b) (4) than the original formulation (b) (4) Hence, the results are inconclusive.

For the sensitivity of in vitro model to different viscosity formulations products with different viscosity (high viscosity and low viscosity) were prepared (Figure 7). However, the firm stated that the formulation with "high viscosity" was later found to be of similar viscosity of the original formulation. Also, the firm stated that the "high viscosity" formulation was physically unstable, possibly due to the change in the formulation (b) (4) The firm stated that a difference in steady state drug release was observed when the high viscosity formulation was compared with each of the other two formulations. However, no difference was observed between the low viscosity formulation and the original formulation. Since it is not clear whether a truly high viscosity formulation (which is stable) was used or not, the results of the study are inconclusive.

Reviewer's conclusion on the IVRT method development and validation: The proposed IVRT method is adequately developed and validated.

7. Bridging Studies

The Applicant submitted the IVRT reports supporting two bridging studies. The first comparative IVRT study was performed in 2011 by Ferrer/Spain to bridge between Ozenoxacin Cream, 1%, (b) (4) batches manufactured at (b) (4) (batches 001490 and 0376D) for early clinical studies (Phase 1 & 2 studies for safety and dose determination), and (b) (4) batches manufactured for the phase 3 studies at the manufacturing site at Ferrer/Spain (batches 1303D0105A, 1303D0106A and1303D0107A). The second comparative IVRT study was performed in 2015 by (b) (4) to bridge between Ozenoxacin Cream, 1%. (b) (4) batches manufactured at Ferrer/Spain (batches 1303E0101A and 13031I1102A1) for phase 3 clinical studies, and (b) (4) registration batches manufactured at Teligent/USA (batches 5137, 5138, and 5139). Batch 13001I2101A2 was a placebo. The IVRT report for this study was provided in Module 3.2.P.2.2 (Report Number 053-1501G-01). The IVRT method used in the second bridging study is described in Table 2, which was adequately developed and validated. The Applicant stated that the composition of the proposed product did not change during scale up or manufacturing site transfer and the same composition was used for all clinical and registration/exhibit batches of Ozenoxacin Cream, 1%. Similarly, No significant changes to the manufacturing process were implemented and equivalent equipment, operating principles and procedures were used for all clinical and registration/exhibit batches of Ozenoxacin Cream, 1%.

The results of the study are shown in Figure 8 and Figure 9, and the conclusion drawn by the Applicant from these results is shown in Table 6.

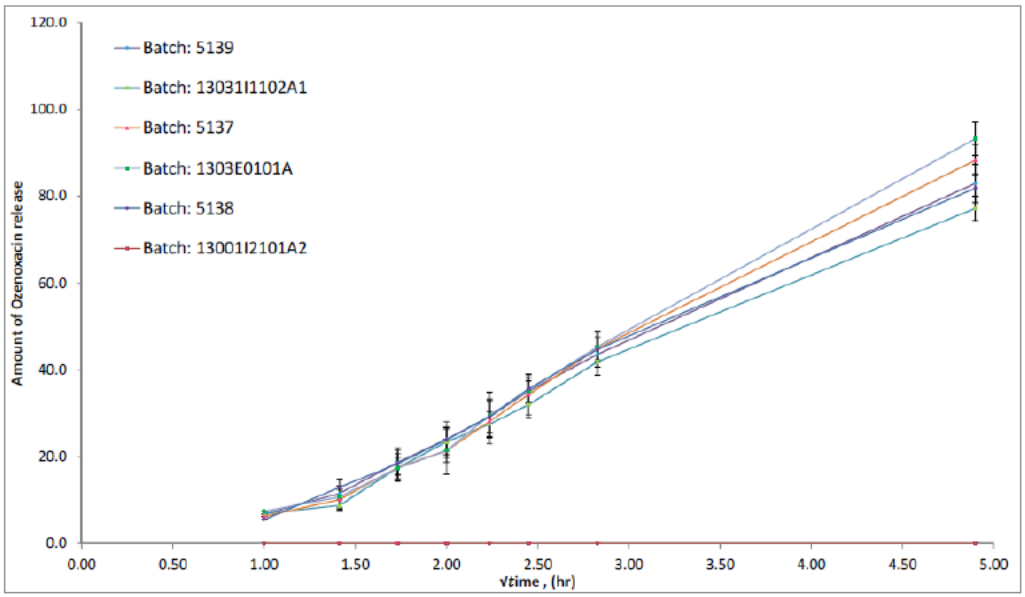


Figure 8: Total cumulative amount per unit area of ozenoxacin released from 6 formulations through a PES membrane between 1 and 24 h, presented as a √time. Data is represented as Mean ± SD, n=6.

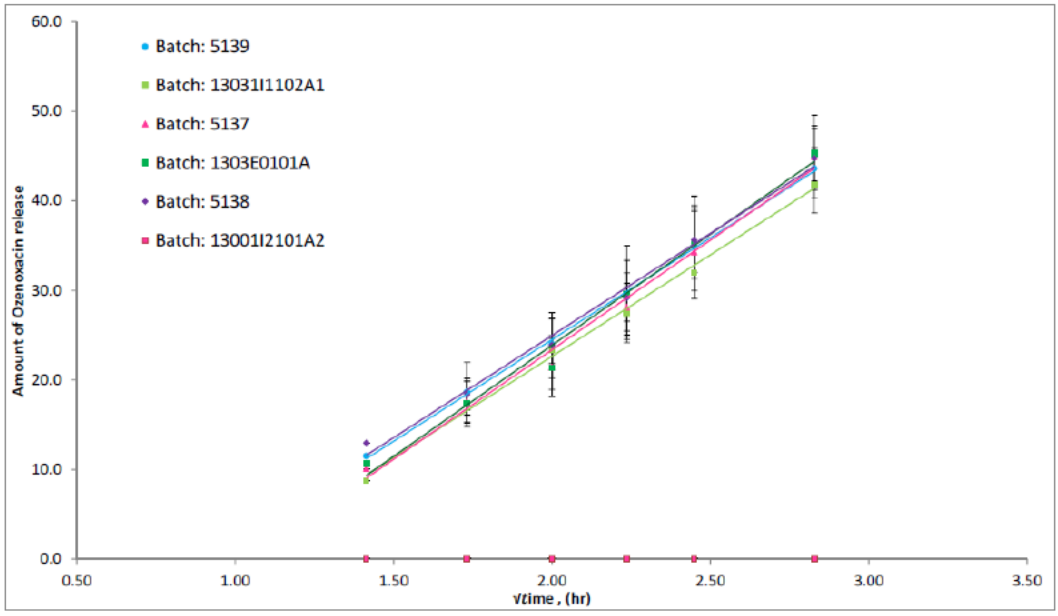


Figure 9: Total cumulative amount per unit area of ozenoxacin released from 6 formulations through a PES membrane between 2 and 8 h, presented as a √time. Data is represented as Mean ± SD, n=6.

Table 6. Statistical analysis of the slopes (illustrated in Figure 9) comparing the in vitro drug release profile (from 2 to 8 h) of ozenoxacin from the 5 active 1 % w/w ozenoxacin formulations. The 90 % confidence interval is determined according to the SUPAC guidelines, where limits ranging between 75 and 133.33% demonstrate sameness between the products.

Comparator A	Comparator B	90 % confidence interval	Result
Batch: 1303E0101A	Batch: 13031I1102A1	95.73 to 127.02	Sameness
Batch: 5137		95.54 to 124.34	Sameness
Batch: 5138		86.50 to 116.17	Sameness
Batch: 5139		84.30 to 125.72	Sameness
Batch: 5137	Batch: 1303E0101A	85.64 to 113.49	Sameness
Batch: 5138		79.45 to 105.38	Sameness
Batch: 5139		88.50 to 131.59	Sameness
Batch: 5138	Batch: 5137	82.32 to 106.62	Sameness
Batch: 5139		87.60 to 131.32	Sameness
Batch: 5139	Batch: 5138	84.00 to 123.62	Sameness

Reviewer's Assessment

Two pivotal Phase 3 studies (study # P-110880-01 with 464 subjects and study # P-110881-01 with 412 subjects) evaluating clinical efficacy and safety of Ozenoxacin Cream, 1% were performed using the product manufactured at the Ferrer/Spain site. Previous clinical study batches for Phase 1 clinical safety studies (study # P-100845-01 with 33 subjects and study # P-100846-01 with 32 subjects) and Phase 2 dose determination studies (study # P-080623-01 with 202 subjects) were manufactured at the (b) (4) site. Since, the pivotal clinical studies were performed at the manufacturing site in Ferrer/Spain, and the composition and the overall manufacturing process of the product did not change for any of the clinical and registration/exhibit batches, no bridging was required for the previous changes in the manufacturing site. However, the Applicant provided a comparative in vitro release rate data using Franz diffusion cells of Ozenoxacin Cream, 1% (b) (4) batches manufactured at the Clinical manufacturing site (Ferrer/Spain; batches 1303D0105A, 1303D0106A and1303D0107A) vs. prior Ozenoxacin Cream, 1% (b) (4) batch manufactured at (b) (4) (b) (4) (batch 001490 and 0376D). The report was provided in Module 3.2.P.2.2. From the results, the Applicant concluded that no difference existed between Ozenoxacin Cream, 1%, manufactured at (b) (4) and that manufactured at Ferrer/Spain. However, since it was determined by this reviewer that no bridging is required for these batches, the provided in vitro release study report RR-100864-01 was not evaluated.

Bridging proposed in IVRT report 053-1501G-01

The Applicant performed IVRT using products from two different manufacturing sites, to support the bridging. The Applicant determined that the in vitro release of ozenoxacin from these two products is same per the SUPAC Guidance for nonsterile semisolid dosage forms, as shown

in Table 6. To verify the claims made by the Applicant, this reviewer used IVRT raw data to verify the Applicant's results.

Reviewer-calculated slope data:

Table 7. Reviewer-calculated slopes for the in vitro drug release profiles (from 2 to 8 h) of ozenoxacin from the 5 active 1 % w/w ozenoxacin formulations

Replicates	Flux (µg/cm²/√h) from 6 time points √2-8 h				
	Pre-change lots (Reference)		Post-change lots (Test)		
	Batch 13031I1102A1	Batch 1303E0101A	Batch 5137	Batch 5138	Batch 5139
n=1	19.01	23.34	24.87	22.99	23.48
n=2	25.05	25.95	23.14	19.97	18.17
n=3	24.97	30.58	21.07	22.46	28.41
n=4	19.79	19.81	23.86	26.93	20.49
n=5	23.09	25.13	24.26	19.82	27.37
n=6	23.93	23.90	29.76	24.60	18.37

Table 8. Reviewer-calculated statistical analysis of the slopes (illustrated in Figure 9) comparing the in vitro drug release profile (from 2 to 8 h) of ozenoxacin from the 5 active 1 % w/w ozenoxacin formulations. The 90 % confidence interval is determined according to the SUPAC guidelines, where limits ranging between 75 and 133.33% demonstrate sameness between the products.

Comparison	90% confidence interval	Conclusion
13031I1102A1 Vs. 1303E0101A	95.74% to 127%	Sameness
13031I1102A1 Vs. 5137	95.55% to 124.36%	Sameness
13031I1102A1 Vs. 5138	86.49% to 116.17%	Sameness
13031I1102A1 Vs. 5139	79.54% to 118.61%	Sameness
1303E0101A Vs. 5137	88.12% to 116.79%	Sameness
1303E0101A Vs. 5138	79.44% to 105.36%	Sameness
1303E0101A Vs. 5139	75.99% to 113.00%	Sameness
5137 Vs. 5138	93.80% to 121.47%	Sameness
5137 Vs. 5139	87.58% to 131.33%	Sameness
5138 Vs. 5139	84.01% to 123.62%	Sameness

Reviewer's conclusion on the proposed bridging study: Per the 'Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation' guidance for nonsterile semisolid dosage forms published by the FDA in May 1997, the 90% confidence interval for the ratio of the median in vitro release rate for the post-change lot over the median in vitro release rate for the pre-change lot was found to be within the limits of 75% to 133.33%. Hence the studied products were found to be same in terms of their in vitro drug release profile. The IVRT study results and hence the proposed bridging —obtained using a properly developed and validated IVRT method—is acceptable.

Reviewer's Overall Conclusions:

The Biopharmaceutics review focused on the evaluation of In-Vitro Release Test (IVRT) method and the in vitro drug release data supporting the proposed bridging studied. Development and validation of an in vitro drug release test is currently not required for approval of a semisolid product, nor is the in vitro release test currently required as a routine batch-to-batch quality control test. The in vitro drug release test was used in this submission to support the pre-approval manufacturing site change for the proposed product.

- The Applicant's in vitro release test method development and validation are acceptable.
- The in vitro drug release rate comparison data support the drug product manufacturing site change from Ferrer/Spain to Teligent/USA.

Recommendation:

The in vitro drug release rate comparison data support the drug product manufacturing site change from Ferrer/Spain to Teligent/USA. From the Biopharmaceutics perspective, NDA 208945 for Ozenoxacin Cream, 1% is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date:

Kaushalkumar Dave, Ph.D., ***02/21/2017***

(electronic signature)

I concur with Dr. Dave's assessment and information requests.

Secondary Biopharmaceutics Reviewer Name and Date:

Elsbeth Chikhale, Ph.D., ***02/21/2017***

(electronic signature)

Appendix I

Information Request Sent to the Applicant on 11/23/2016

1. Regarding the In Vitro Release Test (IVRT) method development, provide the density of the receptor phase medium (50% Transcutol P in water) and evidence showing how the sink condition was maintained and ensured during all the IVRT studies mentioned in the report 053-1501G-01R.

Applicant's Response (Received on 12/21/2016)

(b) (4)

2. Explain the observed difference between the full replacement and (b) (4) described in IVRT report 053-1501G-01R (especially section 7.2.5 of the report; Figures 4 & 5). Justify your selection of (b) (4) instead of full replacement for the IVRT studies. Unless adequately justified, we recommend that you perform full replacement during the IVRT studies.

Applicant's Response (Received on 12/21/2016)

(b) (4)

(b) (4)

3. The provided figures/graphs of the IVRT studies are of poor quality and hence it is difficult to interpret the results. Provide images with better quality (higher resolution) for all the IVRT studies performed during method development, validation and the bridging studies mentioned in the report 053-1501G-01R. In addition provide individual (for each Franz diffusion cell) as well as average flux (slope) values for all the IVRT studies performed during method development, validation, and bridging studies. Also, provide all generated in vitro drug release data as described in the table below:

Time (min, hr., etc.)	Sq. rt. Time	Concentration in Cell (µg/mL)	Amount in Cell (µg)	Cumulative Amount in Cell (µg)	Cumulative Diffusion (µg/cm^2)
T1					
T2					
T3					
T4					
T5					
Tn					

Applicant's Response (Received on 12/21/2016)

The requested figures and raw data of the IVRT studies have been provided (Visit 'Sponsor Responses' in the Module 1.2. for the figures and the raw data of the IVRT studies.)

Elsbeth Chikhale

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Kaushalkumar Dave

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