CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208610Orig1s000
208611Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 208610
Review 1

Drug Name/Dosage Form	Baxdela (delafloxacin)
Strength	450 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Melinta Therapeutics, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission	10/19/2016	All Product Quality disciplines
Quality Amendment	02/01/2017	Drug product, Facilities, Process
Quality Amendment	02/02/2017	Drug product, Process
Quality Amendment	02/17/2017	Process
Quality Amendment	02/21/2017	Drug substance
Quality Amendment	02/23/2017	Drug substance, Drug product, Process
Quality Amendment	03/06/2017	Drug substance
Quality Amendment	03/13/2017	Drug substance, Process
Quality Amendment	03/17/2017	Drug substance, Process, Drug product
Quality Amendment	03/29/2017	Process, Drug product
Quality Amendment	04/27/2017	Process

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Monica Cooper	Kasturi Srinivasachar & Ben Stevens
Drug Product	Yushi Feng	Balajee Shanmugam
Process	Steven Frisbee	Upinder Atwal
Microbiology	Steven Frisbee	Upinder Atwal
Facility	Aditi Thakur	Christina Capacci-Daniels
Biopharmaceutics	Joan Zhao	Elsbeth Chikhale

Regulatory Business Process Manager	Luz Rivera	N/A
Application Technical Lead	Balajee Shanmugam	N/A
Laboratory (OTR)		
ORA Lead	-	-
Environmental	Yushi Feng	Balajee Shanmugam

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status*	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Adequate	Last reviewed 03/15/2013	
	Type III			Adequate	Last reviewed 08/09/2013	
	Type III			Adequate	Last reviewed 08/24/2012	
	Type III			Adequate	Last reviewed 3/05/2007	
	Type III			Adequate	Last reviewed 09/21/2012	
	Type III			Adequate	Last reviewed 04/16/2012	

* *Sufficient information was also submitted in the NDA*

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	76096	
IND	62772	

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA is recommended for **Approval** from Product Quality perspective. All major quality issues have been satisfactorily resolved. The outstanding issues mentioned below and discussed in detail in the appropriate sections of this review are of low-risk and not expected to significantly impact the quality of the drug product. These outstanding issues will be addressed, as agreed upon by the company via a post-marketing commitment (PMC) and a concurrent filing of a CBE-30. The PMC relates to establishing a validated analytical method for control of polymorphic form in the drug product specification and including a testing facility for this new method. The test will further enhance the quality of the product which at this time is addressed by way of robust controls. Recommendations on the proposed package insert and container and carton labels have been adequately resolved and the revised versions are acceptable from OPQ perspective. Evaluation of the manufacturing and testing facilities, as documented in the facilities review section, supports approval and the Overall Manufacturing Facility Status of "Approve" in Panorama. Therefore, the NDA is recommended **Approval** from OPQ perspective.

II. Summary of Quality Assessments

A. Product Overview

Delafloxacin is an anionic fluoroquinolone antibiotic with a broad spectrum antibacterial activity due to the inhibition of bacterial topoisomerase IV and DNA gyrase (topoisomerase II) the enzymes required for bacterial DNA replication, transcription, repair and recombination. Delafloxacin has been developed as an oral and IV formulations to treat acute bacterial skin and skin structure infections (ABSSSI). The NDA covered under this review provides for the oral formulation, BAXDELA (delafloxacin) tablet, 450 mg while NDA 208611 from the same applicant submitted to the same clinical division (DAIP) provides for the IV formulation, BAXDELA (delafloxacin) for injection, 450 mg/vial.

Proposed Indication(s) including Intended Patient Population	Treatment of acute bacterial skin and skin structure infections (ABSSSI)
Duration of Treatment	5 to 14 days
Maximum Daily Dose	450 mg
Alternative Methods of Administration	**N/A**

B. Quality Assessment Overview

(b) (4)

(b) (4) The applicant's proposed (b) (4) ***month retest date*** can be granted to delafloxacin meglumine drug substance stored in the commercial packaging at controlled room temperature.

The proposed drug product, delafloxacin tablet, 450 mg, is an immediate release, modified capsule-shaped (b) (4) tablet, of beige to mottled beige color. Each tablet contains the active ingredient 649 mg delafloxacin meglumine (equivalent to 450 mg delafloxacin) and the following inactive ingredients: citric acid, crospovidone, magnesium stearate, microcrystalline cellulose, povidone, sodium bicarbonate, and sodium phosphate monobasic monohydrate. All excipients are compendial and conform to the standards. The drug product specification includes tests for appearance, identification, assay, impurities, dissolution, uniformity of dosage units, water content and microbial tests. The proposed specifications and acceptance limits are appropriate. The control on drug substance polymorphic form is to be instituted in the drug product specifications through post-marketing commitment (PMC). The PMC includes establishing a validated XRD method and identify a GMP testing facility responsible for XRD testing. One analytical method is used for identification, assay and impurities. It was adequately validated for its intended use. The commercial delafloxacin tablets, 450 mg, will be packaged in 2 primary container closure systems: twenty tablets in a high density polyethylene (HDPE) bottle (b) (4) closed with an (b) (4) cap; and an unit dose in (b) (4) (b) (4) blisters (b) (4) Stability data are presented for 3 primary stability batches with tablet score (tablet without score is the commercial configuration), manufactured at the proposed commercial manufacturing site (b) (4) at varying batch sizes and package configurations (bottles (b) (4) to bracket the commercial presentation at 20 count, blisters at the commercial configuration), for up to 30 months at long-term

storage conditions (25°C/60%RH) and for 6 months at accelerated conditions (40°C/75% RH).
Based on currently available stability data the proposed shelf life for both the 20 count HDPE bottle and the (b) (4) blister is 36 months at 20 to 25°C (68 to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature] and can be granted.

The drug product specification includes a test for dissolution. The validated dissolution analytical procedure and the acceptance limit of NLT (b) (4)% (Q) in 10 minutes were found acceptable. The drug substance is highly soluble, and the drug product was formulated (b) (4) to provide immediate release. The proposed dissolution method (Apparatus 2; 500 mL of pH 4.5 sodium acetate buffer; 75 rpm) was able to differentiate formulations (b) (4) and is acceptable for the purpose of quality control for this rapidly dissolving drug product. The acceptance criterion was revised to Q= (b) (4)% in 15 minutes, which is supported by the dissolution data at release and on stability.

Delafloxacin 450 mg tablets are manufactured using standard manufacturing techniques (b) (4) (b) (4). The intended commercial scale for tablet compression is (b) (4) tablets. The drug is polymorphic, (b) (4) (b) (4) As a result of Information Requests, the level of in-process control during commercial manufacturing has been augmented by tightening the (b) (4) specification (b) (4) and performing further characterization (b) (4) in PPQ batches. In addition, the sponsor has made post marketing commitments (PMCs) to establish a validated XRPD limit test as part of drug product release and to update drug product release specifications accordingly. This information will be submitted as Changes Being Effected-30 Supplement and as part of the CMC.

The applicant has provided a claim for categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31 (b). The required statement of no extraordinary circumstances was included and the claim for categorical exclusion has been found acceptable for purposes of approval of the two currently reviewed NDAs for delafloxacin 208610 and 208611.

The manufacturing facilities for this NDA includes the API manufacturer (b) (4) (b) (4) the drug product manufacturer and testing facility (b) (4) and other testing facilities as detailed in the facilities review section of this IQA. The

assessment of all the facilities listed showed no significant outstanding manufacturing issues or risks and therefore deemed acceptable for manufacturing the proposed drug product.

C. Special Product Quality Labeling Recommendations (NDA only)

NA

D. Final Risk Assessment (see Attachment)

Provided in Attachment 1.

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CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Process

CHAPTER IV: Biopharmaceutics

CHAPTER VI: Facilities

CHAPTER VII: Environmental Analysis

ATTACHMENT I: Risk Assessment

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NDA 208610

Addendum #1

Product Name: BAXDELA (delafloxacin meglumine) 450 mg, Tablet

Addendum #1 to Drug Product Quality Review dated 3/06/2017

From: Yushi Feng, Drug Product CMC Reviewer, Branch 3, ONDPI

Date: May-15-2017

Re: Drug product quality assessment addendum

This addendum is to document the following updates for this NDA:

- Revised drug product specification on Appearance
- PMC on the drug substance polymorph control
- Updated container labels (revisions on the Package Insert and Medication Guide are in ongoing discussions)

The revised language for the drug product specification on Appearance is acceptable. Addressing the drug substance polymorph control as PMC is acceptable. The company has agreed to the proposed PMC (details provided in the review section below). The updated container labels are acceptable.

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

Please refer to the previous Drug Product Quality review for all other details.

____Yushi Feng, Ph.D._____
Drug Product CMC Reviewer

Revised drug product specification on Appearance

The drug product specification on Appearance was revised from (b) (4) to "modified capsule-shaped" for clarity (Table 1 in Appendix I. Drug Product Specifications).

Reviewer's Assessment: Acceptable

The revised language for the drug product specification on Appearance is acceptable.

PMC on the drug substance polymorph control

(b) (4)

(b) (4) the applicant claims that not instituting a control on the drug polymorphs does not adversely impact the quality of the drug product, and therefore routine testing for polymorphic form during commercial manufacturing of the tablets is not necessary.

Based on the information presented in the NDA, the polymorphic form of the drug substance in the drug product is expected to have a low probability to negatively impact the drug product quality. However, a drug substance polymorphic form control as part of the drug product specifications will provide additional assurance of quality for both the proposed manufacturing process and the drug product.

The goal of the proposed PMC study is to establish as part of the drug product specifications a validated analytical method (XRD) with well-justified acceptance limits on the polymorphic form of the drug substance in the drug product. Additionally, the applicant will also identify a GMP facility which will be responsible for polymorph testing.

In an amendment to the NDA (SDN 30, eCTD 0031, submitted on 03/17/2017), the Applicant commits to providing the following Product Quality information which will be submitted via NDA supplement(s):

1. Addition of the facility responsible for XRPD testing. The filing category will be selected based on FDA Guidance (See: Guidance for Industry Changes to an Approved NDA or ANDA).
2. Establish a validated XRPD limit test as part of product release. This information will be submitted as Changes Being Effected-30 Supplement.
3. Update drug product release specifications so commercial batches will have XRPD testing to confirm polymorphic form as a part of drug product final release testing. This information will be submitted as Changes Being Effected-30 Supplement.

Timeline for submission of reports:

Interim Report: 01 June 2017

Final Report: 01 September 2017

Refer to the PMC document in Panorama for additional details.

Reviewer's Assessment: Acceptable

Addressing the issue on the drug substance polymorphic form control as part of the drug product specifications as a PMC is appropriate.

Labeling

(b) (4)

Reviewer's Assessment: Acceptable

The immediate container (the blister pack) label includes:

- Proprietary name, established name
- Strength
- Lot number
- Expiration date
- "Rx only" statement
- Bar Code
- Name of distributor

These conform with the mandatory minimum requirements for small labels per 21 CFR 201.10 (i)(B). Additional required label information appears on the carton label.

Bottle lc

(b) (4)

Reviewer's Assessment: Acceptable

The immediate container (the bottle) label includes:

- Proprietary name, established name
- Strength, including a salt equivalency statement
- No route of administration statement – acceptable for oral tablets
- Net contents
- Names and amounts of all inactive ingredients
- Lot number
- Expiration date
- "Rx only" statement
- Storage condition statement – the statement is consistent with those in the Package Insert, and is supported by the stability data provided in the NDA
- NDC number
- Bar Code
- Name of distributor

Carton Labels

Blister pack carton for hospital use (SDN 39, eCTD 0041, submitted on 04/10/2017)

(b) (4)

Reviewer's Assessment: Acceptable

The carton labeling for the blister pack includes:

- Proprietary name, established name

- Strength, including a salt equivalency statement
- No route of administration statement – acceptable for oral tablets
- Net contents
- Names and amounts of all inactive ingredients
- Lot number
- Expiration date
- "Rx only" statement
- Storage condition statement – the statement is consistent with those in the Package Insert, and is supported by the stability data provided in the NDA
- NDC number
- Bar Code
- Name of distributor

Bottle carton (SDN 39, eCTD 0041, submitted on 04/10/2017)

(b) (4)

Reviewer's Assessment: Acceptable

The carton labeling for the bottle includes:

- Proprietary name, established name
- Strength, including a salt equivalency statement

- No route of administration statement – acceptable for oral tablets
- Net contents
- Names and amounts of all inactive ingredients
- Lot number
- Expiration date
- “Rx only” statement
- Storage condition statement – the statement is consistent with those in the Package Insert, and is supported by the stability data provided in the NDA
- NDC number
- Bar Code
- “See package insert for dosage instructions”
- Name of distributor

Appendix I. Drug Product Specifications

Table 1. Specifications and Analytical Methods for Delafloxacin Tablets, 450 mg (SDN 43, eCTD 0045, Submission Date 05/04/2017)

Test Attribute	Acceptance Criteria	Method
Appearance	Modified capsule-shaped tablet in beige to mottled[1] beige color with RX3341 debossed on one side.	Visual
Identification (HPLC)[2]	The retention time of the Delafloxacin peak from the Sample Solution corresponds to that of the Standard Solution in Assay Test.	TRX3341AUI
Identification (UV)[2]	The UV spectrum of the Delafloxacin peak from the Sample Solution corresponds to that of the Standard Solution.	TRX3341AUI
Assay	(b) (4) % of label claim	TRX3341AUI
Impurities (HPLC) (b) (4) Unspecified Impurities (each) Total Impurities[3]	 NMT (b) (4) % NMT % NMT %	TRX3341AUI
Dissolution	NLT (b) (4) % (Q) dissolved in 10 minutes.	TRX3341D4
Uniformity of Dosage Units[2]	Meets USP requirements	USP <905> Weight Variation
(b) (4)		
Microbial Testing Total aerobic microbial count Total yeasts and molds count *Escherichia coli*	 NMT (b) (4) cfu/g NMT (b) (4) cfu/g Absence in (b) (4) g	USP <61>,<62>

1. The mottled beige color comes from the active ingredient.
2. Identification and Uniformity of Dosage Units tests are for release testing only. They are not required for stability testing.
3. Sum of all known degradation products and unspecified impurities, excluding (b) (4), which are controlled in the drug substance specifications.

Yushi Feng

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Balajee Shanmugam

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BIOPHARMACEUTICS

Product Background:

NDA: 208610

Drug Product Name / Strength: Baxdela (delafloxacin) Tablet, 450 mg,

Route of Administration: Oral

Applicant Name: Melinta Therapeutics, Inc.

Review Summary:

The drug substance delafloxacin (a new molecular entity), is a novel anionic fluoroquinolone antibiotic with a broad spectrum of antibacterial activity.

Delafloxacin is being developed as a 450 mg tablet for oral administration in this NDA (208610) application, and under another NDA (208611) as a 300 mg powder for intravenous injection. Delafloxacin meglumine is a poorly soluble compound and the solubility increases with pH in aqueous buffers, while the proposed drug product is designed to be a *very rapidly disintegrating* dosage form.

This review evaluates the proposed dissolution method and acceptance criterion, and the need for bridging.

Based on the provided dissolution data, the following proposed dissolution method and acceptance criterion are acceptable.

Method	Using USP Apparatus II (Paddle) in 900 mL 0.05 mM Phosphate Buffer, pH 7.4 at 60 rpm
Acceptance Criterion	NLT (b) (4)% (Q) in 10 minutes

The Applicant provided comparable dissolution data to support the proposed (b) (4) (b) (4) commercial product. The bridging study between the scored tablets used in the clinical studies and the proposed unscored tablets for commercial distribution is acceptable.

From the Biopharmaceutics perspective, NDA 208610 for Dewlafloxacin Meglumine tablets, 450 mg is recommended for **APPROVAL**.

List Submissions being reviewed (table):

Submission(s) Reviewed	Document Date
Original Submission	10/19/2016

Highlight Key Outstanding Issues from Last Cycle: N/A (This is the 1st review cycle)

Concise Description of Outstanding Issues Remaining: None

BCS Designation

Reviewer's Assessment: The Sponsor did not submit an official BCS designation request. Delafloxacin meglumine exhibits low solubility and low permeability.

Drug Substance Solubility:

The solubility of delafloxacin meglumine in aqueous buffers increases with pH.

Table 1 Solubility of Delafloxacin Meglumine at 25°C (expressed as free acid)

Medium	Final pH	Solubility (mg/mL)
Water	6.75	0.038
0.1M HCl	0.8	0.00326
pH 4.0 citrate buffer	4.2	0.00344
pH 5.0 citrate buffer	5.1	0.00333
pH 6.8 phosphate buffer *	6.8	0.0668
pH 7.4 phosphate buffer	7.4	0.283
pH 8.0 phosphate buffer	7.8	0.651
pH 9.0 glycine buffer	8.2	2.49
0.01 M NaOH	8.4	3.40

* 37 °C

Table 2 Equilibrium Solubility of Delafloxacin Meglumine at 37°C (expressed as free acid)

Medium	Final pH	Solubility (mg/mL)
pH 1.0 (0.1M HCl)	1.1	0.00469
pH 4.5 Acetate buffer	4.3	0.00688
pH 6.8 phosphate buffer	6.8	0.135
pH 7.4 phosphate buffer	7.6	0.567

Table 3 Kinetic Solubility of Delafloxacin at 37°C (expressed as free acid)

Medium	Timepoint	Measured pH	Solubility (mg/mL)
pH 1.2 HCl	1 hr	0.89	0.0049
	2 hr	1.22	0.0058
	4 hr	1.24	0.0047
	24 hr	1.19	0.0047
pH 4.5 acetate buffer	1 hr	4.51	0.0072
	2 hr	4.52	0.0066
	4 hr	4.50	0.0067
	24 hr	4.52	0.0069
pH 6.8 phosphate buffer	1 hr	7.04	0.24
	2 hr	6.84	0.20
	4 hr	6.81	0.07
	24 hr	6.85	0.07
pH 7.4 phosphate buffer	1 hr	7.87	3.02
	2 hr	7.50	1.02
	4 hr	7.45	0.78
	24 hr	7.60	0.57

As shown in table 1-3, the solubility of the delafloxacin meglumine at pH 6.8-7.4 at 37 °C was higher than the solubility of the free acid.

Based on the commercial dose-strength of 450 mg, delafloxacin meglumine is considered to be a poorly soluble compound according to the Biopharmaceutics Classification System (BCS) as its minimum dose/solubility ratio over the physiological pH range is more than 250 mL.

Permeability:

Delafloxacin does not meet the criteria to be considered a high permeability compound (> 90% total dose absorbed). The absolute BA when administered as the 450 mg to-be marketed tablet is reported to be 58.8%.

Drug Substance

(b) (4)

Formulation:

The sponsor's selected the formulation J in Table 4 as the intended commercial formulation, which was evaluated in the Phase 3 clinical trial in patients.

Table 4 Composition of Delafloxacin Tablet, 450 mg,

	Tablet Composition Used in Clinical Trial RX-3341-114		Final Tablet Composition for BE Clinical Trial RX-3341-115, Phase 3, Registration Stability and Intended Commercial Use	
Formulation	**I(b)**		**J**	
Lot	13DE006		13DE009	
Ingredient	**mg/Tablet**	**% (w/w)**	**mg/Tablet**	**% (w/w)**
(b) (4)				
Delafloxacin meglumine[1]	649	(b) (4)	649	(b) (4)
Cellulose, Microcrystalline, NF (b) (4)				(b) (4)
Povidone, USP (b) (4)	33.8	(b) (4)	33.8	
Crospovidone, NF (b) (4)				(b) (4)
(b) (4)				
Sodium bicarbonate, USP	140.0	(b) (4)	140.0	(b) (4)
Sodium phosphate monobasic, monohydrate, USP	5.5		5.5	
Citric acid, Anhydrous, USP	5.5		5.5	
(b) (4)				
Magnesium stearate, NF		(b) (4)	10.0	(b) (4)
				(b) (4)

[1] Equivalent to 450 mg free acid
(b) (4)

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(b) (4)

R Regional Information

Comparability Protocols: None

List of Deficiencies: None

Recommendations:
From the Biopharmaceutics perspective, NDA 208610 for Delafloxacin Tablets, 450 mg is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date: Zhuojun Zhao, Ph.D. 2/12/2017

Secondary Reviewer Name and Date (and Secondary Summary):
I concur with Dr. Zhao's assessment and recommendation.

Elsbeth Chikhale, Ph.D.3/4/2017

Appendix

Table 8. Batch summary data for 5-minute dissolution time point

Batch	13DE009	13DE011	13DE012	14DE001	15DE005	NB1094-90	
n						n=1-12	n=13-24
1	74	91	74	96	58	52	65
2	92	77	77	98	58	59	55
3	85	74	71	98	59	61	60
4	78	70	68	91	56	61	63
5	83	82	85	93	58	66	54
6	86	68	81	95	49	73	58
7	89	81	71	96	48	67	61
8	85	87	74	94	49	60	49
9	80	73	76	93	56	68	68
10	80	54	77	91	63	63	55
11	83	75	67	96	54	63	49
12	80	76	71	93	58	58	60
max	92	91	85	98	63	73	
avg	83	76	74	95	56	60	
min	74	54	67	91	48	49	
RSD (%)	5.9	12.6	7.1	2.5	8.6	10.0	

Table 9. Batch summary data for 10-minute dissolution time point

Batch	13DE009	13DE011	13DE012	14DE001	15DE005	NB1094-90	
n						n=1-12	n=13-24
1	89	93	93	100	94	94	89
2	94	97	95	98	93	93	94
3	93	95	95	99	90	92	93
4	92	92	95	94	92	92	92
5	92	92	94	96	91	97	92
6	92	95	94	97	94	93	92
7	97	96	94	98	92	92	97
8	94	96	93	98	94	93	94
9	91	93	93	94	93	94	91
10	95	96	95	96	93	92	95
11	95	98	95	97	94	91	95
12	95	97	95	95	94	91	95
max	97	98	95	100	94	97	
avg	93	95	94	97	93	94	
min	89	92	93	94	90	91	
RSD (%)	2.3	2.2	0.9	2.0	1.4	1.7	

Table 10. Batch summary data for 15-minute dissolution time point

Batch	13DE009	13DE011	13DE012	14DE001	15DE005	NB1094-90	
n						n=1-12	n=13-24
1	91	94	95	101	96	96	95
2	96	99	97	99	95	96	97
3	94	96	98	99	93	94	96
4	94	94	97	95	94	95	97
5	94	93	96	97	93	99	96
6	93	97	96	98	96	95	97
7	98	97	96	98	96	94	95
8	96	97	96	99	97	94	98
9	93	95	95	95	95	95	97
10	96	98	96	97	95	94	97
11	96	99	97	97	96	93	97
12	97	98	97	96	96	93	95
max	98	99	98	101	97	99	
avg	95	96	96	98	95	96	
min	91	93	95	95	93	93	
RSD (%)	2.1	2.1	0.9	1.8	1.3	1.6	

Elsbeth Chikhale

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Zhuojun Zhao

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Lifecycle Management Considerations

The drug is polymorphic, and the sponsor [redacted] (b) (4)

[redacted] (b) (4)

[redacted] (b) (4) has made post manufacturing commitment (PMC) to establish a validated XRPD limit test and specification as part of drug product release.

Approvable for Process and Microbiology, based on review of submissions and Post Manufacturing Commitments made by sponsor.

Primary Process Reviewer Name and Date:

Steven Frisbee Ph.D. 03/03/2017, 03/14/2017, 05/04/2017

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

Upinder Atwal, Ph.D. 03/03/2017, 03/14/2017, 05/04/2017

Steven Frisbee

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Upinder Atwal

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(b) (4)

[redacted]

Reviewer's Assessment: N/A

Post-Approval Commitments

03/17/2017-The applicant has committed to provide addition of the facility responsible for XRPD testing as stated below:

The following information should be submitted via supplement(s):

PMC 1. Addition of the facility responsible for XRPD testing. The filing category should be selected based on FDA Guidance (See: Guidance for Industry Changes to an Approved NDA or ANDA).

Timelines:

Final Report: 1st September, 2017

Interim Report: 1st June, 2017

Reviewer's Assessment: Adequate. The filing category will be based on FDA guidance.

Lifecycle Management Considerations

N/A

List of Deficiencies: N/A

Primary Facilities Reviewer Name and Date:

Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities for NDA 208610 are found to be acceptable.

Aditi Thakur M.S. – 03/21/2017
Chemist, OPQ/OPF/DIA/IABII

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

I concur.

Christina Capacci-Daniel, PhD – 03/22/2017
Acting QAL, OPQ/OPF/DIA/IABII

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Aditi Thakur

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Christina Capacci-Daniel

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ATTACHMENT I: Final Risk Assessment

NDA 208610

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay/ Stability	Formulation, raw Materials, Process parameters, Scale & equipment, Site	L		Acceptable	
Physical stability	Formulation Raw materials Process parameters Scale/equipment Site	L	Polymorph control via: a) tightened IPC b) Monitor (b) (4) (b) (4) by XRD in the DP specification	Acceptable	PMC established to: a) develop validated XRD method b) Identify testing facility c) Add a test for polymorph to the DP specification
Content Uniformity	Formulation Raw materials Process parameters Scale/equipment Site	L	Adequate in-process controls	Acceptable	IPC for LOD and PSD will be finalized based on data from PPQ batches.
Microbial Limits	Formulation Raw materials Process parameters Scale/equipment Site	L		Acceptable	
Dissolution	Formulation Raw materials Process parameters Scale/equipment Site	L		Acceptable	
Facilities	cGMP Status	L		Acceptable	

OPQ Recommendation: The NDA is recommended for **Approval** from Product Quality perspective.

Balajee Shanmugam -S

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Date: 2017.05.16 15:07:37 -04'00'

Balajee Shanmugam, Ph.D. ATL for NDA 208610 on behalf of the OPQ team.

Recommendation: Approval

NDA 208611
Review 1

Drug Name/Dosage Form	Baxdela (delafloxacin) for injection
Strength	300 mg/vial
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Melinta
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission	10/19/2016	All Product Quality disciplines
Quality Amendment	01/06/2017	Drug Product
Quality Amendment	01/19/2017	Drug Product, Process
Quality Amendment	02/01/2017	Product Quality Microbiology
Quality Amendment	02/03/2017	Drug Product
Quality Amendment	02/17/2017	Process
Quality Amendment	02/23/2017	Drug Substance, Drug Product, Process
Quality Amendment	02/24/2017	Product Quality Microbiology
Quality Amendment	03/06/2017	Drug Substance
Quality Amendment	03/13/2017	Drug Substance, Process
Quality Amendment	03/17/2017	Drug Product
Quality Amendment	03/22/2017	Drug Product
Quality Amendment	03/28/2017	Process, Product Quality Microbiology
Quality Amendment	04/19/2017	Drug Product
Quality Amendment	04/27/2017	Drug Product

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Monica Cooper	Kasturi Srinivasachar & Ben Stevens
Drug Product	Danuta Gromek-Woods	Balajee Shanmugam

Process	Arwa El Hagrasy	Upinder Atwal
Microbiology	Jason God	Bryan Riley
Facility	Aditi Thakur	Christina Capacci-Daniels
Biopharmaceutics	Joan Zhao	Elsbeth Chikhale
Regulatory Business Process Manager	Luz Rivera	N/A
Application Technical Lead	Balajee Shanmugam	N/A
Laboratory (OTR)	Laura Pogue	Jason Rodriguez
ORA Lead	-	-
Environmental	Yushi Feng	Balajee Shanmugam

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status*	Date Review Completed	Comments
(b) (4)	Type IV		(b) (4)	Adequate	Last reviewed 7/22/2015	
	Type III			Adequate		
	Type V			Adequate	Last reviewed 8/26/2016	
	Type III			Adequate	Last reviewed 11/29/2016	

The NDA provided adequate information.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	76096	

2. CONSULTS

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

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA is recommended for **Approval** from Product Quality perspective. All product quality issues have been satisfactorily resolved. The company proposed to submit a CBE-30 to further refine two quality items which are of low-risk and is not expected to impact product quality. The first relates to an in-process control (b) (4) which is included in the NDA (b) (4). Process validation data to support a more suitable In-Process Control (IPC) limits (b) (4) will be submitted via CBE-30. Sterility test requalification data from the process validation batches is the second item which will be in the proposed CBE-30. As noted below and further detailed in the microbiology section of this IQA, the NDA provides adequate information on the manufacturing process including in-process controls and details on the validation of the sterilization/depyrogenation process to ensure sterility of the product. Facilities involved in the manufacturing and testing to support this NDA have been found acceptable and recommended "Approve".

II. Summary of Quality Assessments

A. Product Overview

Delafloxacin is an anionic fluoroquinolone antibiotic with a broad spectrum antibacterial activity due to the inhibition of bacterial topoisomerase IV and DNA gyrase (topoisomerase II) the enzymes required for bacterial DNA replication, transcription, repair and recombination. Delafloxacin has been developed as an oral and IV formulations to treat acute bacterial skin and skin structure infections (ABSSSI). The NDA covered under this review provides for the IV formulation BAXDELA (delafloxacin) for injection, 300 mg/vial while NDA 208610 also from the same applicant submitted to DAIP provides for the oral formulation, BAXDELA (delafloxacin) tablet, 450 mg.

Proposed Indication(s) including Intended Patient Population	Treatment of acute bacterial skin and skin structure infections (ABSSSI)
Duration of Treatment	5 to 14 days
Maximum Daily Dose	600 mg
Alternative Methods of Administration	NA

B. Quality Assessment Overview

The complete CMC information for the drug substance delafloxacin *N*-methyl-glucamine salt for the NDA under review is referenced to NDA 208610 which provides for the IV formulation containing the same active ingredient.

Delafloxacin for injection, 300 mg per vial, is a light yellow to tan colored cake provided in a (b) (4) clear (b) (4) glass vial. Prior to administration, the powder is reconstituted with sterile 5% dextrose solution or 0.9% saline solution for a final volume of 12(b) (4) mL. The reconstituted solution is further diluted to a total volume of 250 mL using either 5% dextrose solution or 0.9% sodium chloride to achieve a concentration of 1.2 mg/mL prior to administration. Drug product formulation contains the following inactive ingredients: meglumine (b) (4), Captisol® (b) (4), edetate sodium (b) (4) (b) (4) The quality of delafloxacin for injection, 300 mg, is controlled through a specification that includes tests for appearance for vial, identity, reconstitution time, appearance of reconstituted solution, pH, assay, content uniformity, purity, particulates, water content, sterility, and endotoxin. The applicant has submitted accelerated and long-term stability data from the drug product packaged in the proposed commercial configuration. The applicant in the Pre-NDA stages had discussed (b) (4) (b) (4) with the Agency and based on recommendations provided at these meetings had conducted several studies to address the concern from a manufacturing and stability stand point. Stability data from the non-conforming vials (b) (4) (b) (4) indicate the vials to be comparable to the conforming vials in all the quality attributes testing, including reconstitution. The study demonstrates that (b) (4) did not significantly impact product quality. For further details, refer to the drug product and facilities sections of this review. The data integrity issue (data management concerns and deviation investigations) was investigated during the recent inspection of the (b) (4) facility, (b) (4) (please see facilities review for details). This issue was also discussed prior to the submission of the NDA with Melinta and (b) (4). The impact of the data integrity issue and subsequent inspectional observations were considered in evaluating the stability data and granting the expiration date. The accelerated (40 ± 2°C/75 ± 5%RH) studies (6 months) have been completed. Thirty-six (36) months long-term (25 ± 2°C/60 ± 5%RH) data are available for batch 13DEL1 and 24 months long-term data are available for batches 14DEL1and 14DEL2. Based on statistical analysis of currently available stability data, an expiration date of 30 months at 20 to 25°C (68 to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature] can be granted.

The manufacturing process for Baxdela (delafloxacin meglumine), 300 mg, Injection involves (b) (4) (b) (4) (b) (4). The intended commercial batch will be

manufactured at a scale of (b) (4). In-process controls (b) (4) (b) (4) include bacterial endotoxin for WFI, appearance, pH, assay, bioburden. (b) (4) In-process control (b) (4) is included by (b) (4). Process validation data to support more suitable In-Process Control (IPC) limits (b) (4) will be submitted via CBE-30.

The drug product being sterile is (b) (4) (b) (4) filled. The microbiological aspects of the manufacturing process including in-process controls and validation of the sterilization/depyrogenation process is adequate to ensure sterility of the product. The sterility test requalification data from the process validation batches will be submitted via CBE-30. Container closure integrity (CCI) is assessed by dye ingress testing on three batches of finished drug product as part of stability testing. Data provided from stability testing showed all tested vials conform to CCI, endotoxin and sterility providing assurance for microbiological quality over the products expiration date.

(b) (4) manufactures the API for this NDA as well NDA 208610 which provides for the tablet dosage form. The other key facility which supports this NDA is the drug product manufacturing facility, (b) (4). Melinta pharmaceuticals had a number of regulatory meetings with the Agency to discuss the data integrity issues at this facility. A Pre-approval inspection by the Agency was necessitated due to the data integrity and the previously noted (b) (4) issues. During this inspection, besides examining the production operations, laboratory control and overall quality system, the third party report on the data integrity was also evaluated. It has been determined that the facilities involved in the manufacture and testing of NDA 208611 are acceptable.

C. Special Product Quality Labeling Recommendations (NDA only)

NA

D. Final Risk Assessment (see Attachment)

Please see attachment 1

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Process

CHAPTER IV: Microbiology

CHAPTER VI: Facilities

ATTACHMENT I: Risk Assessment

DRUG SUBSTANCE

NDA: 208611

The drug substance information for NDA 208611 was referenced to NDA 208610. Please see the drug substance review chapter for 208610 (M. Cooper) for a summary and evaluation of the delafloxacin meglumine API.

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Monica Cooper

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Ben Stevens

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Methods Verification Package

Reviewer's Assessment:

Method verification is in process at DPA/OTR, St. Louis Laboratories.

Comparability Protocols

Reviewer's Assessment:

NA

Post-Approval Commitments

Reviewer's Assessment:

NA

Lifecycle Management Considerations

Reviewer's Assessment:

Monitor analytical data integrity.

List of Deficiencies

None.

Primary Drug Product Reviewer Name and Date: Danuta Gromek-Woods, 02-Mar-2017

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

Danuta Gromek-Woods

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Balajee Shanmugam

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- NDA 208 611-
ADDENDUM TO REVIEW #1

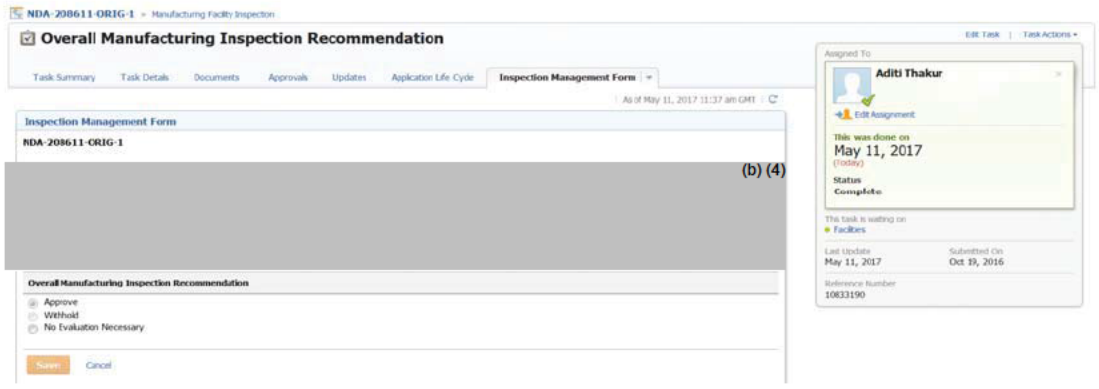
Product Name: BAXDELA (delafloxacin) 300 mg injection
From: Danuta Gromek-Woods, Ph.D., Drug Product Reviewer, Branch 3, DNDPI
Date: May-15-2017

CMC review #1, dated 16-Mar-2017, noted the following pending issues:

1. Final recommendation from the Office of Process and Facilities.
2. Due to data integrity issues, the drug product reviewer was awaiting recommendation from OPF to decide on appropriate expiration dating period for the drug product.
3. Method Verification
4. Labeling

Facility Recommendation

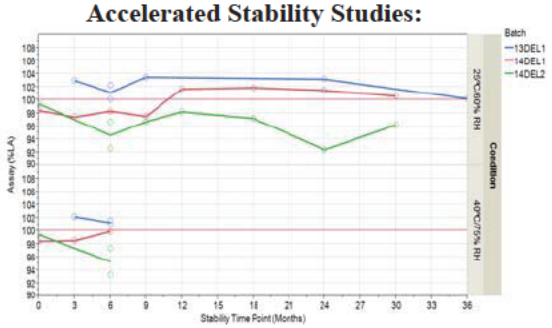
On May 11, 2017, the Office of Compliance issued the "Approve" recommendation for all facilities involved in the manufacturing and testing for NDA 208611.



Data Integrity

Summary of information submitted via amendments to NDA 208 611 subsequent to Review#1:

Location in EDR/date	Content	Comments/Evaluation
Seq. 0030/ 03/17/2017	**1.** Response to FDA Information Request received on 14 February 2017. This NDA amendment provides for 30-month stability time point data for registration batches 14DEL1 and 14DEL2.	The sponsor has included regression analysis and proposed expiration dating period of (b) (4) months for the injection formulation. **Evaluation:** All together, the applicant submitted the following long term stability data in the NDA: a) 36 months for batch 13DEL1 b) 30 months for batches 14DEL1 and 14DEL2

Location in EDR/date	Content	Comments/Evaluation
	2. In addition, this amendment also provided the following: a) accelerated stability data for 16DEL1 which the FDA requested on 10 March 2017 , b) updated stability impurity results and sterility results for 13DEL1, 14DEL1 and 14DEL2 based on the FDA PAI inspection (b) (4) (b) (4) completed on (b) (4)	c) 9 months for batch 16DEL1 **Assay Results Obtained during Long-term and Accelerated Stability Studies:**  Some of the stability time point were affected and invalidated due the data integrity issues (see DP Review#1, pages 52-53) impacting all the registration batches. The additional data provided indicate that the samples from different storage conditions comply with the proposed specification and no apparent trends were observed, This review also weighed in on the PAI findings, specifically on the data integrity issues. In conclusion, the requested expiration dating of (b) (4) months cannot be granted due to the lack of contiguous stability data set from the batches, but based on the available data a 30-month expiration dating period can be granted when stored at the recommended storage condition of 20° C to 25°C (68°C to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature] can be granted.
Seq. 0042/ 04/19/2017	**1)** This submission provides response to Information Request dated 27-Dec-2016 requesting data on vial content uniformity after reconstitution. A study to confirm the conc. after reconstitution in accordance with the reconstitution instructions was performed on delafloxacin commercial scale batch **17 DEL1,** with 0.9% Saline solution and 5% dextrose solution using BD syringes with a target volume of 10.5 mL of reconstitution fluid. **2)** Post-Approval CBE-30 commitments agreed to by FDA are also included. Per Agreement at Late Cycle Review Meeting on 07 April 2017, the sponsor will submit this data to NDA208611	**Delafloxacin Concentration in Vials (Batch 17DEL1) after Reconstitution with 0.9% Saline** (b) (4) * The theoretical cake weight is (b) (4) ** The diluent volume was measured in (b) (4) syringes ((b) (4) and delivered to the vial. The diluent weight was calculated by before and after weight. Diluent volume was calculated by using the density of 0.9% Saline solution of (b) (4) **Delafloxacin Conc. in Vials (Batch 17DEL1) after Reconstitution with 5% Dextrose**

Vial number	WEIGHT (mg)		VOLUME (mL)**	ASSAY	
	Diluent weight(mg)	Cake Weight* (mg)	Diluent volume introduced	mg/mL	%
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
average	11,591.26	2831.33	11.53	23.15	92.60
st dev	104.10	8.69	0.10	0.32	1.29
RSD %	0.90	0.31	0.90	1.40	1.40

<table>
<tr><th>Location in EDR/date</th><th>Content</th><th>Comments/Evaluation</th></tr>
<tr><td></td><td>based on completion of qualification testing from 3 runs as a CBE-30 (refer to the Quality Microbiology Review).</td><td>
<table>
<tr><th>Vial number</th><th colspan="2">WEIGHT (mg)</th><th>VOLUME (mL)**</th><th colspan="2">ASSAY</th></tr>
<tr><th></th><th>Diluent weight(mg)</th><th>Cake Weight* (mg)</th><th>Diluent volume introduced</th><th>mg/mL</th><th>%</th></tr>
<tr><td>1</td><td colspan="5" rowspan="10">(b) (4)</td></tr>
<tr><td>2</td></tr>
<tr><td>3</td></tr>
<tr><td>4</td></tr>
<tr><td>5</td></tr>
<tr><td>6</td></tr>
<tr><td>7</td></tr>
<tr><td>8</td></tr>
<tr><td>9</td></tr>
<tr><td>10</td></tr>
<tr><td>average</td><td>11,638.50</td><td>2,837.89</td><td>11.42</td><td>23.36</td><td>93.45</td></tr>
<tr><td>st dev</td><td>125.89</td><td>17.62</td><td>0.12</td><td>0.34</td><td>1.34</td></tr>
<tr><td>RSD %</td><td>1.08</td><td>0.62</td><td>1.08</td><td>1.43</td><td>1.43</td></tr>
</table>
The results demonstrate that an average of 92.6% and 93.45% of the theoretical conc. was obtained after reconstitution with 0.9% saline and 5% dextrose, respectively. Although the assay values are closer to the lower limit, all results are within the proposed specifications.
From a uniformity of dosage perspective, the results are within acceptable limits:
Reconstitution with 0.9% Saline: AV= (b) (4)
Reconstitution with 5% Dextrose: AV %</td></tr>
<tr><td>Seq. 0044/ 04/27/2017</td><td>This submission provides response to FDA's Information Request from 10 March 2017 requesting current stability data on commercial-scale delafloxacin batch 16DEL1. Stability data through 9 months is presented at long-term conditions.</td><td>All data are within the proposed specifications. The new data also augments for some of the missing data for the registration stability batches impacted by data integrity issue.</td></tr>
</table>

Method Verification:

In response to the method verification request (method MQC-733), the St. Louis Lab provided a few recommendations, including comments regarding:

- preparation of the system suitability solution for the impurity (b) (4) and
- stability of the sample solution with regard to impurity (b) (4)

The method verification report also communicates that the system solubility solution did not meet the recovery requirement of (b) (4) %. The method states that "if recovery is not met and the solution is older than 24 hours; prepare a fresh solution". The recommendations and concerns were shared with Melinta. The applicant reiterated that the NDA included data to demonstrate the stability of the sample for up to 9 days. The issue is considered resolved.

Labeling

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	

Item	Information Provided in NDA
Proprietary name and established name	BAXDELA Delafloxacin for Injection
Dosage form, route of administration	For Injection, for intravenous infusion
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	For Injection: 300 mg in a single dose vial

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	**Reconstitution and Dilution:** BAXDELA must be reconstituted under aseptic conditions, using 10.5 mL of sterile 5% Dextrose for Injection (D5W) or 0.9% Sodium Chloride Injection for each 300 mg vial. Shake the vial vigorously until contents are completely dissolved. The reconstituted vial contains 300 mg per 12 mL of BAXDELA as a clear yellow to amber colored solution. The reconstituted solution must then be diluted to a total volume of 250 mL using either 0.9% Sodium Chloride or D5W to achieve a concentration of 1.2 mg/mL, prior to administration.

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	For Injection
Strengths: in metric system	300 mg per vial
Active moiety expression of strength with equivalence statement	300 mg per vial
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	BAXDELA is supplied as a sterile, lyophilized powder in single-use vials of 300 mg which must be reconstituted and further diluted for intravenous infusion only.

4. *Section 11 Description*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	BAXDELA Delafloxacin for Injection
Dosage form and route of administration	For Injection
Active moiety expression of strength with equivalence statement (if applicable)	300 mg per vial
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Not included
Statement of being sterile (if applicable)	Not included
Pharmacological/ therapeutic class	Not included
Chemical name, structural formula, molecular weight	Yes
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	Not included

Section 16 How Supplied/Storage and Handling

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	300 mg per vial
Available units (e.g., bottles of 100 tablets)	Package of 300-mg single-dose vials
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	The lyophilized powder is a light yellow to tan cake, which may exhibit cracking and shrinkage and slight variation in texture and color.
Special handling (e.g., protect from light)	No
Storage conditions	Stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [*see USP Controlled Room Temperature*].
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Melinta Therapeutics, Inc. 300 Tri-State International Lincolnshire, Illinois, USA

Reviewer's Assessment of Package Insert: Inadequate, see deficiencies listed at the end of this review in the "List of Deficiencies". Adequacy of labeling will be discussed with the Review Team.

II. Labels:

1. *Container and Carton Labels*

2. *Carton Label*

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Adequate	Adequate
Dosage strength	300 mg/vial	300 mg/vial
Net contents	300 mg	300 mg
"Rx only" displayed prominently on the main panel	Yes	No
NDC number (21 CFR 207.35(b)(3)(i))	Yes	Yes
Lot number and expiration date (21 CFR 201.17)	Yes	Yes
Storage conditions	Yes	Yes
Bar code (21CFR 201.25)	No	No
Name of manufacturer/distributor	No	Yes
And others, if space is available		

To address labeling issues form the ONDP perspective, the following Information Requests were addressed to the applicant:

1. **In the HIGHLIGTHTS OF PRESCRIBING INFORMATION, section "Dosage Forms and Strengths" of the PI, change the name of the dosage form from (b) (4) to "For Injection" (addressed in the PI, coordinated by OND)**

2. **Please include the equivalency statement in the vial label, carton label and applicable sections of the Prescribing Information (PI) insert:**
   Baxdela
   delafloxacin for Injection
   300 mg per vial
   (equivalent to 433 mg of delafloxacin meglumine)

   Applicant's response: **Adequate**
3. **Revise the (b) (4) term that appears throughout the labels and labeling to the "single-dose" statement in the vial and carton labels and in all applicable sections of the PI.**

4. Applicant's response: **Adequate for vial and carton labels.**

   Addressed in the PI, coordinated by OND.

5. **Please include list of excipients along with their quantitative description in the vial and carton labels, as well as in section 11 of the PI.**

Applicant's Response:

Draft Vial carton:

(b) (4)

Draft Vial Label:

(b) (4)

Reviewer's Assessment of Labels: With regard to the Vial and Container labeling, the use of term "Inactive Ingredients" instead of "Excipients" seems to be more appropriate. The topic is still under discussion.

CMC related comments in the PI (Highlights of Prescribing Information, Section 2, Dosage and Administration, Section 11, Description, and Section 16, How Supplied/Storage and Handling) were sent to the applicant on 05-May-2017, along with comments issued from all other disciplines of the Review Team. Adequacy of labels and labeling will continue to be discussed with the Review Team.

Overall Labeling Assessment and Recommendation:

Adequacy of drug product labeling is under discussion with the Review Team.

Final Recommendation:

This NDA is recommended for Approval from ONDP perspective.

Primary Labeling Reviewer Name and Date: Danuta Gromek-Woods, Ph.D., 15-May-2017
Secondary Reviewer Name and Date: Balajee Shanmugam, Ph.D., 15-May-2017

Danuta Gromek-Woods

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Balajee Shanmugam

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MICROBIOLOGY

Product Background: The drug product is a (b) (4) **solution for injection,** (b) (4) **filled into** (b) (4) **vials.**

NDA: 208611

Drug Product Name / Strength: Baxdela (Delafloxacin meglumine), 300 mg, Injection

Route of Administration: IV

Applicant Name: Melinta Therapeutics, Inc.

Manufacturing Site: (b) (4)

Method of Sterilization: (b) (4)

Review Summary: Adequate. The Applicant has established microbiological manufacturing in-process controls and drug product controls, and has adequately validated sterilization/depyrogenation process. Therefore the applicant has adequately mitigated the drug product sterility and endotoxin risks.

List Submissions being reviewed (table):

Submit Received	Review Request	Assigned to Reviewer
10/18/2016	10/19/2016	11/01/2016
02/01/2016	02/01/2016	
02/24/2016	02/24/2016	

Highlight Key Outstanding Issues from Last Cycle:

Concise Description Outstanding Issues Remaining: None

SUPPORTING/RELATED DOCUMENTS: (b) (4) dated 6 November 2015, reviewed and found adequate DMF (b) (4) (b) (4).

P.1 Description of the Composition of the Drug Product

- Description of drug product – Delafloxacin for injection, 300 mg/vial, is provided as a light yellow to tan cake in a (b) (4) clear (b) (4) glass vial.

- Drug product composition –

Table 1: Composition of Delafloxacin for injection

Component and Quality Standard	Function	Strength (label claim)		
		mg/mL prior to lyophilization[a]	mg/dose	mg/vial
Delafloxacin meglumine (amount as free acid)[b]	Active	25.00	300	(b) (4)
Meglumine USP	(b) (4)		58.6	
Betadex Sulfobutyl Ether Sodium (Captisol®) NF			2400	
Edetate disodium (EDTA) USP			3.4	
			(b) (4)	

Table 1 was reproduced from the Applicant's Table 1, 3.2.P.1.2

- Description of container closure system

Table 2: Container closure system for Delafloxacin for Injection, 300 mg/vial

Component	Type/Description	Size	Color
Vial	Clear (b) (4) type I (b) (4) glass (b) (4). USP <660>; Ph. Eur. 3.2.1	(b) (4)	
Stopper	(b) (4) stopper. USP <381>; Ph Eur. 3.2.1		
Seal/ cap	(b) (4) (b) (4) cap		

Table 2 was reproduced from the Applicant's Table 3, 3.2.P.1.3

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

Container closure integrity is assessed by dye ingress testing on three batches of finished drug product as part of stability testing. (b) (4)

(b) (4)

(b) (4) Dye ingress into all vials was confirmed.

Antimicrobial Effectiveness Testing

N/A. Drug product is supplied lyophilized in a single use vial.

Reviewer's Assessment: Adequate.

Description of drug product and pharmaceutical development information were consistent with the FDA Guidances for Industry: (1) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, and (2) Q8(R2) Pharmaceutical Development.

P.3 Manufacture

P.3.1 Manufacturers

(b) (4)

P. 3.3 Description of the Manufacturing Process and Process Controls

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(b) (4)

P.8 Stability

P. 8.1 Stability Summary and Conclusion

Based on currently available stability data, a shelf life of (b) (4) months at 20-25°C has been proposed. Stability samples are stored under long-term (25+2°C /60+5% RH) and accelerated (40+2°C/75+5% RH) conditions. Three registration batches of drug product have been placed on primary stability: 13DEL1, 14DEL1, 14DEL2. Testing is performed as follows:

- Container Closure Integrity – Tested by dye intrusion at 12, 24 and 36 months for long-term stability samples and 6 months for accelerated stability samples.

- Endotoxin – Tested at 0, 12, 24 and 36 months for long-term stability samples and 0 and 6 months for long-term stability samples.

- Sterility – Tested at 0, 12, 24 and 36 months for long-term stability samples and 0 and 6 months for long-term stability samples.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

In addition to the batches currently on primary stability, a scale-up batch (16DEL1, commercial scale) and the first three production batches will be placed on stability under long-term and accelerated conditions. Additionally, one new lot per year will be placed under long-term storage. The scale-up batch and commercial production lots will be tested for sterility and endotoxin at 0 and 36 months for long-term samples and 0 and 6 months for accelerated samples.

P.8.3 Stability Data

Stability data, available through 36 months for 13DEL1 and 24 months for 14DEL1 and 14DEL2, conform to specifications.

Reviewer's Assessment: Adequate

The applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life. In addition, the stability data submitted to date support the microbiological quality of the subject drug product.

R Regional Information

Executed Batch Records

The executed batch record for batch 13DEL1 has been provided.

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

Product labeling indicates the vial as single-use. The product insert states that the lyophilized drug product is to be reconstituted with 10.5 mL of 5% Dextrose to a final volume of 12 mL. The reconstituted drug product is further diluted in a 250 mL IV bag of either 0.9% NaCl injection or D5W. It is stated that reconstituted drug product and diluted drug product may both be stored for up to 24 hours at 2-8°C or 20-25°C. The extended post-dilution storage time at 20-25°C was validated by microbiological challenge. IV bags containing diluted drug product were inoculated with challenge organisms to (b) (4) cfu/mL. Testing showed no increase from the initial count for up to 72 hours.

Reviewer's Assessment: Adequate

The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling.

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date: Jason M. God, Ph.D., 28 March 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Neal J. Sweeney, Ph.D., 28 March 2017

APPEARS THIS WAY ON ORIGINAL

Neal Sweeney

Digitally signed by Neal Sweeney
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Jason God

Digitally signed by Jason God
Date: 3/03/2017 11:27:03AM
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Following a review of the application, inspectional documents, and pre-approval inspection results, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities for NDA 208611 are found to be acceptable.

Aditi Thakur M.S. –5 May 2017
Chemist, OPQ/OPF/DIA/IABII

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

I concur with this acceptable recommendation.

Christina Capacci-Daniel, PhD – 11May2017
Acting QAL, OPQ/OPF/DIA/IABII

APPEARS THIS WAY ON ORIGINAL

Aditi Thakur

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Date: 5/11/2017 09:48:56AM
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Christina Capacci-Daniel

Digitally signed by Christina Capacci-Daniel
Date: 5/11/2017 10:12:58AM
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ATTACHMENT I: Final Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay /Stability	Formulation, Raw materials, Process parameters, Scale & equipment, Site	L		Acceptable	
Physical stability	Formulation Raw materials Process parameters Scale/equipment Site	L		Acceptable	
Uniformity of dose	Formulation Raw materials Process parameters Scale/equipment Site	L	Consistency of dosage across vials is monitored (b) (4) (b) (4) and tested as part of product release testing.	Acceptable	
Sterility	Formulation Raw materials Process parameters Scale/equipment Site	L		Acceptable	Sterility test requalification data from the process validation batches will be submitted via CBE-30
Reconstitution time*	Formulation Raw materials Process parameters Scale/equipment Site	L		Acceptable	
Facilities	cGMP Status	L		Acceptable	PAI inspection reviewed documents pertaining to data integrity issues. No facility risk identified.

* *Please see review for details on* (b) (4) *issue. The Non-conforming vials and conforming vials placed on stability showed no difference in the quality attributes tested (including reconstitution time).*

OPQ Recommendation: The NDA is recommended for **Approval** from Product Quality perspective.

Balajee Shanmugam -S

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Date: 2017.05.16 17:26:54 -04'00'

Balajee Shanmugam, Ph.D., ATL for NDA 208611on behalf of OPQ team.