

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209816Orig1s000

209817Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

**NDA 209816
Review 1**

Drug Name/Dosage Form	Omadacycline Tablet
Strength	150 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Paratek Pharmaceuticals, Inc.
US agent, if applicable	Randy Brenner

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
<i>Orig-1</i>	<i>02/02/2018</i>	<i>All</i>
<i>Quality Amendment</i>	<i>03/16/2018</i>	<i>Biopharm/Facilities</i>
<i>Quality Amendment</i>	<i>03/22/2018</i>	<i>Facilities</i>
<i>Quality Amendment</i>	<i>05/08/2018</i>	<i>Process</i>
<i>Quality Amendment</i>	<i>05/14/2018</i>	<i>Facilities</i>
<i>Quality Amendment</i>	<i>06/01/2018</i>	<i>Drug Product</i>
<i>Quality Amendment</i>	<i>06/07/2018</i>	<i>Facilities</i>

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Sharon Kelly	Charles Jewell
Drug Product	Milton Sloan	Balajee Shanmugam
Process	Arwa ElHagrasy	Upinder Atwal
Microbiology	Arwa ElHagrasy	Upinder Atwal
Facility	Arwa ElHagrasy	Ying Zhang/Derek Smith
Biopharmaceutics	Qi Zhang	Elsbeth Chikhale
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Yushi Feng	
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental	Raanan Bloom	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
Various	Type III	See DP review				

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	73431	IND for current NDA
NDA	209817	Omadacycline IV formulation; currently under review
IND	75928	IND for NDA 209817

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA is recommended for APPROVAL from the product quality perspective.

II. Summary of Quality Assessments

A. Product Overview

The drug product, omadacycline 150 mg, is an immediate release film-coated tablet indicated for Community-Acquired Bacterial Pneumonia (CABP) and Acute Bacterial Skin and Skin Structure Infections (ABSSSI). Omadacycline is being developed as both an oral tablet (NDA 209816) and as an IV formulation (NDA 209817).

Proposed Indication(s) including Intended Patient Population	Omadacycline 150 mg oral tablet is indicated for the treatment of patients 18 years of age or older with the following infections caused by susceptible microorganisms: Community-Acquired Bacterial Pneumonia (CABP) and Acute Bacterial Skin and Skin Structure Infections (ABSSSI).
Duration of Treatment	7 to 14 days
Maximum Daily Dose	Administer 450-mg of (b) (4) tablets orally, once a day for the first 2 days, followed by 300-mg orally once daily
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:

The route of synthesis of omadacycline starting with (b) (4) is unchanged from manufacturing of the initial preclinical toxicity study batches through the manufacture of the primary registration/stability batches. The synthesis consists of (b) (4)

(b) (4) Agreement was reached with the Agency at the pre-NDA meeting held July 26, 2017 regarding definition of the

primary stability batches. Additionally, the Agency agreed that the proposed Specification, acceptance criterion of \leq (b) (4) area % for individual unspecified impurities appears acceptable. The Sponsor solicited any additional feedback regarding the proposed control strategy and the Agency generally agreed with the strategy, with final determination a review issue. (b) (4)

The stability package at the time of NDA submission was also agreed upon. The Stability Protocol for the Primary Registration / Stability batches, timepoint 12 months, was the testing time point where the Sponsor bridged analytical method 2 for Assay and Related substances with the proposed regulatory method 3. The results indicate that the methods yield similar results with only three notable differences. The (b) (4) (b) (4) peak area is greater when it is quantified with Method #3 compared to the historical method due to better separation with a more robust integration with new analytical procedure. The improved separation from the main omadacycline peak and corresponding integration result in approximately 1% difference greater for Method #3. The assay of omadacycline may decrease slightly as well due to the improvement in integration and quantification. Lastly, (b) (4) (b) (4) peak area decreases slightly in the new method as this peak is better resolved in the new method allowing for better integration and more accurate quantification.

The results through 12 months at long term conditions (b) (4) and 6 months at accelerated conditions (b) (4) are consistent, remain unchanged and meet the acceptance criteria for appearance, polymorphic form, water, assay and related substances.

The drug substance is stable at the intended storage condition, (b) (4). The proposed retest period for omadacycline tosylate drug substance is (b) (4) months when stored at (b) (4). This is acceptable.

For additional details, see the Drug Substance review below.

Drug Product:

Omadacycline Tablets are available in a 150 mg strength, yellow colored, diamond shaped, and film-coated. The excipients utilized for omadacycline tablets, 150 mg include lactose monohydrate, microcrystalline cellulose, crospovidone, sodium bisulfite, col loidal silicon dioxide, sodium stearyl fumarate, (b) (4)

(b) (4) The formulation contains (b) (4)

The excipients used are commonly used pharmaceutical/compendia grade excipients (USP/NF] or Ph. Eur.) for the immediate release dosage formulation. The drug product excipients are all compendial except for the film coating. There are no novel excipients. The NDA submission proposes an HDPE bottle as the primary container closure system for omadacycline tablets, 150 mg. and (b) (4)

(b) (4) Please see Section P.7 for full discussion and details. The proposed HDPE bottle has a child resistant cap and is the primary container closure system. The drug product specification includes the critical quality attribute for the Omadacycline tablet dosage form.

The proposed drug product specification is adequate to ensure the quality of the drug product. The analytical procedures are appropriate for the intended use. The HPLC conditions are summarized in the DS review. Please refer to the DS review. The validation of the assay, and related substance analytical method validations are found in DS section of the NDA submission. A methods validation request was not made to the FDA laboratories to validate/verify the analytical methods. No impurities, beyond those identified and discussed in the drug substance sections of the NDA, have been identified in omadacycline tablets, 150 mg. The acceptance criteria are supported through the generated stability data on omadacycline tablets. The qualification of the impurities by P/T was concluded adequately done and support the tablet dosage form. The quality attributes monitored on stability were appearance, assay, related substances, (b) (4), and dissolution.

Evaluation of the stability data provided for up to 18 months long term and up to 24 months for the supportive data showed no issues. Forced degradation studies were done as part of development and are provided in the DS section (S.4.3.3.). The photostability studies for the tablet show no significant change upon light exposure conditions. The bulk hold time study showed for the (b) (4) through 12 months all attributes remained consistent. The applicant has proposed a 24 month shelf life when as follows: "Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15 - 30°C (59°F to 86°F)" [see USP Controlled Room Temperature]

Evaluation of the stability results indicates that omadacycline tablet is stable at long-term storage conditions and that no significant change occurs at accelerated conditions. Stability indicating analytical procedures are in place to monitor potential changes of the drug product on storage over time. Stability data for the three-primary registration/stability batches and the 2 supportive omadacycline tablet batches indicate that the drug product meets specifications through the time period tested. Based on the stability data, a 24-month shelf life at 20°C to 25°C is recommended.

For additional details, see the Drug Product review below.

Process:

(b) (4)

For additional details, see the Process review below.

Facilities:

There is no significant or outstanding risk to the manufacturing process or final product based on the individual and composite evaluation of the listed facilities and their previous inspection results, history, and relevant experience. No preapproval inspections were recommended for this NDA; the facilities supporting the submission are considered acceptable based on file review.



(b) (4)

For additional details, see the Facilities review below.

Biopharmaceutics:

The Biopharmaceutics review is focused on (1) the evaluation of the adequacy of the information/data supporting the proposed dissolution method and acceptance criterion, (2) bridging of formulations throughout product development.

Dissolution Method and Acceptance Criterion:

For the routine QC testing of the Omadacycline 150 mg Tablets, the proposed dissolution method and acceptance criterion for batch release and stability testing, shown in the table below, are acceptable.

USP Apparatus	Speed (RPM)	Medium	Volume/Temp (mL/°C)	Acceptance Criterion
II (Paddle)	60	0.1 N HCl	900/37 ± 0.5°C	Q = ^(b) ₍₄₎ 6 at 15 min

Bridging of Formulations:

The clinical formulation used in the pivotal clinical trial is the same as the proposed commercial drug product, except for minor changes in tablet color and shape. The manufacturing site of the drug product-batches used in the phase 3 clinical and registration-stability studies is the same as the proposed commercial site.

For additional details, see the Biopharmaceutics review below.

Environmental Assessment:

The claim of categorical exclusion is acceptable.

For additional details, see the Drug Product review below.

C. Special Product Quality Labeling Recommendations (NDA only)

Recommendations have been conveyed to the OND PM for consideration as the labeling is finalized.

D. Final Risk Assessment (see Attachment)



Yushi
Feng

Digitally signed by Yushi Feng
Date: 6/29/2018 01:51:08PM
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BIOPHARMACEUTICS

Product Background

NDA: 209816

Drug Product Name / Strength: (b) (4) (Omadacycline) Tablets, 150 mg

Route of Administration: Oral

Dosage Form: Immediate Release Tablet

Applicant Name: Paratek Pharmaceuticals, Inc.

Intended for Use: Acute Bacterial Skin and Skin Structure Infections (ABSSSI) Community-Acquired Bacterial Pneumonia (CABP)

Submission Type: 505(b)(1) (NME; rolling review (fast track), QIDP designation and Priority review)

PDUFA Goal Date: 10/02/2018

Biopharmaceutics Review Recommendation: Adequate

Review Summary: The Biopharmaceutics review is focused on (1) the evaluation of the adequacy of the information/data supporting the proposed dissolution method and acceptance criterion, (2) bridging of formulations throughout product development.

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List of Submissions being reviewed:

eCTD # (SDN #)	Received date	Document
0001 (2)	2/2/2018	New NDA
0009(10)	3/16/2018	Quality/Response to information request

BCS Designation

Reviewer’s Assessment: The Applicant reported omadacycline as a BCS Class III drug with high solubility and low permeability. However, no formal BCS designation request is submitted.

Aqueous Solubility: Omadacycline tosylate drug substance exhibits polymorphism. Per the Applicant, (b) (4)

(b) (4) Aqueous solubility of the proposed commercial polymorphic form, omadacycline tosylate salt (b) (4), was determined over physiological pHs ranging from pH 1 to pH 7 (Table 1).

Table 1: Omadacycline Tosylate Drug Substance Solubility

Media pH	Prep	Weight of drug substance (mg)	Concentration (mg/ml)
1.0	1	(b) (4)	(b) (4)
	2		(b) (4)
	3		(b) (4)
2.0	1		(b) (4)
	2		(b) (4)
	3		(b) (4)
3.0	1		(b) (4)
	2		(b) (4)
	3		(b) (4)
4.1	1	(b) (4)	
	2	(b) (4)	
	3	(b) (4)	
5.1	1	(b) (4)	
	2	(b) (4)	
	3	(b) (4)	
6.0	1	(b) (4)	
	2	(b) (4)	
	3	(b) (4)	
Media pH	Prep	Weight of drug substance (mg)	Concentration (mg/ml)
7.0	1	(b) (4)	(b) (4)
	2		(b) (4)
	3		(b) (4)

Permeability: In an *in vitro* bi-directional permeability study using the Caco-2 cell line, the apparent permeability coefficient (P_{app}) of omadacycline with concentrations of 2.0 μM and 12 μM was similar to that measured for mannitol (the low permeability marker); see **Tables 2 and 3**. At 12 μM, the A-to-B P_{app} in the presence of the P-gp inhibitor was 5.8 x 10⁻⁵ cm/min, as compared to 4 x 10⁻⁵ cm/min for mannitol.

Table 2: In vitro permeability of [¹⁴C]mannitol and [³H]propranolol across Caco-2 cell monolayers

Compound	Marker	P _{app} × 10 ⁻⁵	P _{app} × 10 ⁻⁵
		Ap → Bl ^b (cm·min ⁻¹)	Bl → Ap ^b (cm·min ⁻¹)
[³ H]-propranolol, 4.5 μM	High permeability	79.2 ± 6.0	110 ± 3.5
[¹⁴ C]-mannitol, 3.9 μM	Low permeability	4.0 ± 0.3	3.8 ± 0.7

Table 3: In vitro permeability of [¹⁴C]-omadacycline across Caco-2 cell monolayers in the presence and absence of transport protein inhibitors

Omadacycline Concentration, μM	Inhibitor ^a	$P_{app} \times 10^{-5}$		P_{app} Ratio (BI \rightarrow Ap/ Ap \rightarrow BI)
		Ap \rightarrow BI ^b ($\text{cm} \cdot \text{min}^{-1}$)	BI \rightarrow Ap ^b ($\text{cm} \cdot \text{min}^{-1}$)	
2.0	None	2.73 \pm 0.43	35.7 \pm 3.7	13.1 \pm 2.5
	LY335979	7.66 \pm 0.56	10. \pm 1.2	1.41 \pm 0.19
	MK571	3.97 \pm 0.76	35.1 \pm 1.7	8.83 \pm 1.7
	Ko143	3.71 \pm 0.99	36.9 \pm 2.3	9.94 \pm 2.7
12	None	2.10 \pm 0.14	26.6 \pm 2.4	12.7 \pm 1.4
	LY335979	5.80 \pm 0.22	6.99 \pm 0.26	1.21 \pm 0.06

^a Final concentrations for LY335979, MK571, and Ko143 were 1.0, 10, and 1.0 μM , respectively.

^b Values represent the average \pm standard deviation of four measurements

The oral bioavailability of 300 mg omadacycline is approximately 34.5% in healthy, fasted subjects. The relatively low oral bioavailability of omadacycline is mostly attributable to its low permeability in the GI tract. The rate of absorption is relatively rapid with peak plasma levels occurring 2 to 3 h after dosing. Oral exposure to omadacycline increases with increasing doses up to 600 mg, but the increase is not dose proportional.

Dissolution: Rapid dissolution (at least 85% drug release in 15 min) from the proposed Omadacycline Tablets is reported, using the proposed QC dissolution method. Refer to the section “Dissolution Method and Acceptance Criterion” below.

Dissolution Method and Acceptance Criterion

Reviewer’s Assessment: Adequate

Proposed Dissolution Method and Acceptance Criterion: The dissolution method and dissolution acceptance criterion proposed by the Applicant for the proposed drug product are presented below.

USP Apparatus	Speed (RPM)	Medium	Volume/Temp (mL/°C)	Acceptance Criterion Proposed by Applicant
II (Paddle)	60	0.1 N HCl	900/37 \pm 0.5°C	Q = $\frac{(b)}{(4)}$ % at 15 min

Dissolution Method Development:

(b) (4)

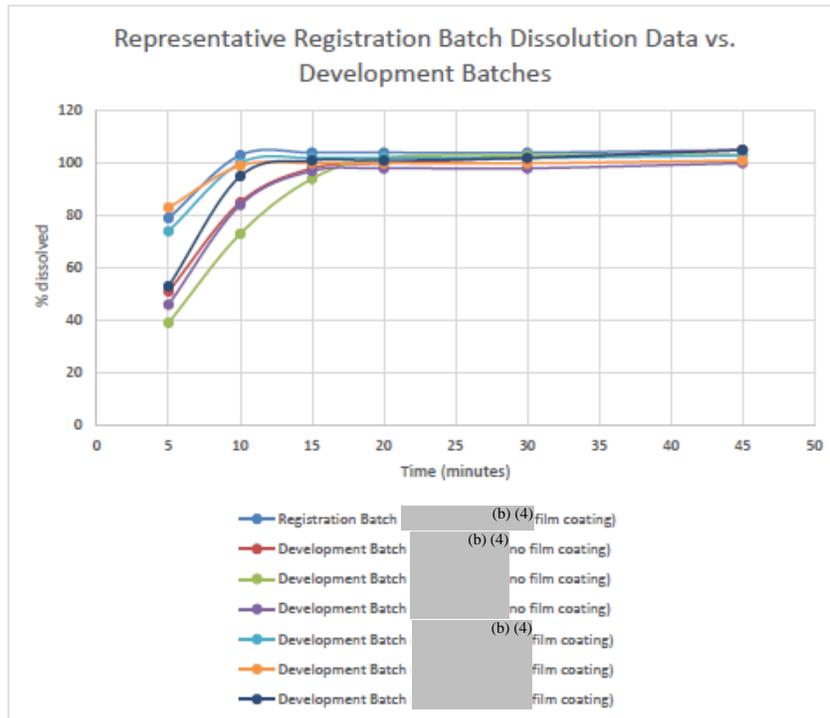
(b) (4)



Discriminating Capability:

The proposed QC dissolution method is expected to be lacking in discriminating power due to the very high solubility of the drug substance across the physiologic pH range, as well as the very rapid dissolution of the drug product in the proposed QC dissolution medium. The Applicant evaluated three (3) potential process/formulation parameters that could impact dissolution. As illustrated in the dissolution data, no noticeable change was observed in dissolution at 15 minutes for all batches evaluated (**Figure 6**).

Figure 6. Comparative Dissolution Profiles of Omadacycline Tablets, 150 mg



Method Robustness

An HPLC assay method (with UV detection at 280 nm) is used to quantify the drug in the dissolution samples. The HPLC method has been validated regarding specificity, linearity, accuracy, intermediate precision, system suitability and robustness. Refer to the Drug Product Review for the evaluation of the adequacy of the analytical HPLC method validation. The dissolution method robustness is validated with respect to dissolution media pH ((b) (4) M HCl), paddle speed ((b) (4) rpm) and degassing of the dissolution media.

Dissolution Acceptance Criterion

The proposed dissolution acceptance criterion is “Q= (b) (4) % of labeled amount at 15 min”, as the drug product dissolves very rapid and complete within 15 minutes. All historical omadacycline tablet batches including those used in the pivotal clinical studies (**Table 4**) and primary registration/stability batches (**Table 5**) (Refer to Section 3.2.P.5.4 Batch Analysis), have met this specification on release and throughout storage (Refer to Section P.8 Stability).

Overall, the proposed dissolution method is fully validated and is considered adequate for quality control purposes. The proposed dissolution acceptance criterion is supported by the complete dissolution data from the clinical and stability batches.

Table 4: Summary of *In Vitro* Dissolution data for Clinical Batches Containing Omadacycline Tosylate Salt (b) (4)

Batch Number/ Manufacturer/	Formulation	Used in Study Number	Strength (mg)	Conditions	No. of Dosage Units	% Dissolved, Mean (range)						Source
						5 min	10 min	15 min	20 min	30 min	45 min	
W025141/ (b) (4)	Omadacycline p-toluenesulfonate	PTK0796-15101 and PTK0796-ABSI-1108	150-mg tablets	USP<711> apparatus: Paddles (USP App. II) Dissolution media: 900 mL 0.1N HCl at 37 ± 0.5°C (b) (4) Rotation: 60 ± (b) (4) RPM Dissolution Time Point: 5, 10, 20 and 30 min, followed by 15 min infinity at 37 ± 0.5°C	6	42 (b) (4)	85 (b) (4)	108	110	110	111 (b) (4)	Section 3.2.P.5.4 (tablet)
W008825/ (b) (4)	Omadacycline p-toluenesulfonate	PTK0796A2 104	150-mg tablets	Same as above	6	42	74	81	86	86	86 (b) (4)	Section 3.2.P.5.4 (tablet)
W008824/ (b) (4)	Omadacycline p-toluenesulfonate	PTK0796A2 104	150-mg slower dissolving tablets	Same as above	6	20	44	63	78	85	88 (b) (4)	Section 3.2.P.5.4 (tablet)
W079407/ (b) (4)	Omadacycline p-toluenesulfonate	PTK0796-UUTI-15103 and PTK0796-MDPO-16105	150-mg tablets	Same as above	6	76	103 (b) (4)	104	104	104	105 (b) (4)	Section 3.2.P.5.4 (tablet)
W031519/ (b) (4)	Omadacycline p-toluenesulfonate	PTK0796-DDI-17106 and PTK0796-ABSI-16301	150-mg tablets	Same as above	6	79 (b) (4)	103	104	104	104	105 (b) (4)	Section 3.2.P.5.4 (tablet)
W077030/ (b) (4)	Omadacycline p-toluenesulfonate	PTK0796-CABP-1200 and PTK0796-ABSI-1108	150-mg tablets	Same as above	6	53 (b) (4)	84	101	101	102	102 (b) (4)	Section 3.2.P.5.4 (tablet)
W079408/ (b) (4)	Omadacycline p-toluenesulfonate	PTK0796-CABP-1200	150-mg tablets	Same as above	6	38	80	88	88	88	101 (b) (4)	Section 3.2.P.5.4 (tablet)

Batch Number/ Manufacturer	Formulation	Used in Study Number	Strength (mg)	Conditions	No. of Dosage Units	% Dissolved, Mean (range)						Source		
						5 min	10 min	15 min	20 min	30 min	45 min			
W032229/ (b) (4)		PTK0796-CABP-1200			6	48	(b) (4)	83	102	103	103	103	(b) (4)	Section 3.2.P.5.4 (tablet)

Study Number	Formulation	Batch Number/ Manufacturer	Strength (mg)	Conditions	No. of Dosage Units	% Dissolved, Mean (range)			Source	
						15 min	30 min	60 min		
W004305/ (b) (4)	Omadacycline p-toluenesulfonate	CPTK0796-A2103 and CPTK0796-A2201	150-mg tablets	USP<711> apparatus: Paddles (USP App. II) Dissolution media: 900 mL 0.1N HCl at 37 ± 0.5°C Rotation: 50 (b) (4) RPM Dissolution Time Point: 15, 30 and 60 min	6	104	104	104	(b) (4)	Section 3.2.P.5.4 (tablet)

HCl = hydrochloride, OMC = omadacycline, RPM = revolutions per minute, USP = United States Pharmacopeia.

Notes: Per the Applicant, when they started to change from utilizing omadacycline tosylate (b) (4) to utilizing (b) (4) there were some changes in the tablets including changing the (b) (4) (b) (4) (b) (4) (b) (4) Batches W008824 and W008825 manufactured in Aug 2010 were affected by these changes.

Table 5: Dissolution Profile Data of Omadacycline Tablets Primary Registration/Stability Batches Manufactured with The Omadacycline Tosylate (b) (4) Drug Substance

Time (Min)	% Dissolved												Mean	Max	Min	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12				
5	(b) (4)												79		(b) (4)	11.0
10	(b) (4)												103			1.6
15	(b) (4)												104			1.4
20	(b) (4)												104			1.3
30	(b) (4)												104			1.1
45	(b) (4)												105			0.9

Batch W031519

Time (Min)	% Dissolved												Mean	Max	Min	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12				
5	(b) (4)												61		(b) (4)	10.8
10	(b) (4)												92			4.0
15	(b) (4)												97			2.4
20	(b) (4)												97			2.1
30	(b) (4)												98			1.6
45	(b) (4)												100			0.9

Batch W031509

Time (Min)	% Dissolved												Mean	Max	Min	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12				
5	(b) (4)												64		(b) (4)	10.2
10	(b) (4)												98			4.5
15	(b) (4)												102			1.6
20	(b) (4)												103			1.3
30	(b) (4)												103			1.2
45	(b) (4)												106			1.0

Batch W031514

Bridging of Formulations

Reviewer's Assessment: Adequate

Three pharmaceutical forms of omadacycline API were used in the clinical development of the oral dose: (b) (4)

(b) (4)

Per the Applicant, all the forms are highly water-soluble. (b) (4) is used in all pivotal clinical studies and is the proposed commercial form of the drug substance. In addition, there appears to be adequate in vivo PK data to support bridging among different forms. The summary results of the relative and absolute BA studies among the (b) (4) are shown in **Table 6**. Refer to the Clinical Pharmacology Review for the final determination of the adequacy of PK bridging among those polymorphic forms. Additional comparative in vitro dissolution profile data are not deemed necessary, and so are not requested from the Applicant.

Table 47. Summary of Oral Bioavailability Results for the Three Omadacycline Formulations across Studies

Study No	Oral Omadacycline Dose (mg)/ (M/F)	iv Omadacycline Dose (mg)/ (M/F)	F (%)
PTK0796-BEQU-0801	200/ (8 M:8F)	100/ (6M:5F)	25.0
PTK0796-BEQU-0801	200/ (9M:7F)	100/ (6M:5F)	11.6
PTK0796-BAVA-0810 (Part B)	300/ (12M:4F)	100/ (12M:4F)	29.3
CPTK796-A2104	300/ (23M:1F)	100/ (23M:1F)	34.5

iv = intravenous, F (%) = bioavailability, F = female, M = male.

Notes: Per the Applicant's response (3/16/2018) to Biopharmaceutics IR Comments dated 3/8/2018, the most probable cause for the observed oral BA difference for the tablet batch TDHM020-001 utilized in Study BEQU-0801 was due to the difference of the drug product formulation composition. Batch TDHM020-001 was an early development formulation which included the use of (b) (4) (b) (4) the tablet batches (W002697 and W002696) utilized in the Study BAVA-0810 because of (b) (4) drug substance bioavailability.

The tablet color and shape were changed from (b) (4) shaped tablet" to "yellow, diamond shaped tablet with "OMC" on one side and "150" on the other side" during the phase 3 clinical studies, and the yellow, diamond shaped tablet is the proposed commercial image. The provided comparative dissolution profile data (**Table 4**) demonstrate that the dissolution profiles are similar with more than 85% drug release within 15 minutes (f_2 comparison is not required) for the phase 3 clinical and commercial batches, and therefore, support bridging of the images used in the phase 3 clinical studies and the commercial tablets.

List of Information Requests:

Refer to Appendix I for the Biopharmaceutics IR and the Applicant's responses.

Primary Biopharmaceutics Reviewer Name and Date:

Qi Zhang, PhD 6/11/2018

Secondary Reviewer Name and Date:

Elsbeth Chikhale, PhD 6/16/2018

Appendix I



response-to-request-
for-information-08m



Qi
Zhang

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Date: 6/18/2018 11:18:15AM
GUID: 547e178000007695c91eb10380b07939



Elsbeth
Chikhale

Digitally signed by Elsbeth Chikhale
Date: 6/18/2018 12:15:23PM
GUID: 50743ccc000031928b54eba1769a5df9

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

Final Risk Table

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations/ Comments
Assay, Stability (impurities/degradation products)		L		Acc	
Content uniformity		M	Controlled in the drug product specifications as uniformity of dosage units	Acc	
Physical stability		L		Acc	
Dissolution		L		Acc	
Microbial limits		L		Acc	



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Digitally signed by Yushi Feng
Date: 6/29/2018 10:08:07AM
GUID: 55916712002d8bbbf81fd3d0ab963187