CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209844Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 209844

Addendum to OPQ Review #1

Date: June 12, 2018

Re: Listed Drug (LD) for NDA 209844 – correction to Biopharmaceutics Chapter

---

The purpose of this Addendum is to clarify the LD in the NDA. The original Biopharmaceutics Chapter noted that NDA 209844 had listed both Pfizer's NDA 50007, Vibramycin® (doxycycline hyclate) Capsules, 100 mg, and Pfizer's NDA 50533, Vibra-Tabs® (doxycycline hyclate) Tablets, 100 mg (discontinued) as the listed drug (LD) products in the Form 356h dated May 1, 2018. However, the 505(b)(2) committee decided that this NDA can/should rely only on NDA 50533. Therefore, the Applicant amended their Form 356h on June 1, 2018 removing Vibramycin Capsules (NDA 50007) and retaining Vibra-Tabs® (Doxycycline Hyclate) Tablets (NDA 50533) as the only LD for this NDA.

This change does not affect any other part of the original Biopharmaceutics Chapter. Also, it does not affect the conclusion of the original Biopharmaceutics review, as well as the overall Approval recommendation stated in the OPQ Review of this NDA dated May 10, 2018 (in Panorama).

Recommendation:

NDA 209844 continues to be recommended for **Approval** from the Product Quality perspective.

BIOPHARMACEUTICS REVIEW - ADDENDUM

Product Background:

NDA: 209844 (505(b)(2)).

Drug Product Name / Strength: LymePak (Doxycycline Hyclate) Tablets, 100 mg

Route of Administration: Oral

Applicant Name: Chartwell Pharma NDA B2 Holdings, LLC

Review Summary:

This 505(b)(2) application is submitted for LymePak (doxycycline hyclate) Tablets, 100 mg for treatment of early Lyme disease due to *Borellia Burgdorferi*.

The original Biopharmaceutics review (dated 5/7/2018) noted that NDA 209844 had listed both Pfizer's NDA 050007, Vibramycin® (Doxycycline Hyclate) Capsules, 100 mg and Pfizer's NDA 050533, Vibra-Tabs® (Doxycycline Hyclate) Tablets, 100 mg (Discontinued) as the listed drug (LD) products in the Applicant's 356h form dated May 1, 2018.

The 505(b)(2) committee decided that this application can/should rely only on NDA 050533, Vibratabs (Pfizer), and therefore, the Applicant amended the 356h form to remove Vibramycin Capsules (NDA 50007) as the LD on June 1, 2018. This Addendum to the original Biopharmaceutics review is noting that the listed drug product for NDA 209844 is Vibra-Tabs® (Doxycycline Hyclate) Tablets, 100 mg (NDA 050533) only. This change does not affect any other part of the original Biopharmaceutics review and does not affect the conclusion of the original Biopharmaceutics review. Therefore, per 21CFR 320.24(b)(6), based on the submitted information, the bridge has been established between the proposed LYMEPAK tablets and the drug products used in the 3 pivotal/key literature publications as well as the LD.

Recommendation:

From the Biopharmaceutics perspective, the recommendation for NDA 209844 for LymePak (Doxycycline Hyclate) IR Tablets, 100 mg remains **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date: Zhuojun Joan Zhao, Ph.D. 06/07/2018

Secondary Reviewer Name and Date: Elsbeth Chikhale, Ph.D. 06/11/2018

Zhuojun Zhao

Digitally signed by Zhuojun Zhao
Date: 6/11/2018 02:34:02PM
GUID: 508da6fd000284770cf4eecbae074722

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 6/12/2018 10:18:45AM
GUID: 50743ccc000031928b54eba1769a5df9

Recommendation: *Approval*

NDA 209844
Review # 1

Drug Name/Dosage Form	LYMEPAK (doxycycline hyclate) tablets
Strength	100 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Chartwell Pharma NDA B2 Holdings
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	August 18, 2017	All
Amendment (eCTD 003)	December 4, 2017	Drug Product
Amendment (eCTD 004)	December 4, 2017	Drug Product
Amendment (eCTD 005)	December 22, 2017	Biopharmaceutics
Amendment (eCTD 006)	February 16, 2018	Drug Product
Amendment (eCTD 008)	February 20, 2018	Biopharmaceutics
Amendment (eCTD 010)	March 30, 2018	Biopharmaceutics
Amendment (eCTD 012)	April 10, 2018	Drug Product, Process
Amendment (eCTD 013)	April 12, 2018	Microbiology
Amendment (eCTD 014)	April 20, 2018	Drug Product
Amendment (eCTD 015)	April 27, 2018	Drug Product
Amendment (eCTD 018)	May 1, 2018	Biopharmaceutics

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Haripada Sarker	Charles Jewell
Drug Product	George Lunn	Balajee Shanmugam
Process	Sateesh Sathigari	Steven Frisbee
Microbiology*	Sateesh Sathigari	Steven Frisbee
Facilities	Wenzheng Zhang	Ying Zhang
Biopharmaceutics	Zhuojun (Joan) Zhao	Elsbeth Chikhale
Environmental Assessment**	George Lunn	Balajee Shanmugam
Regulatory Business Process Manager	Luz Rivera	N/A
Application Technical Lead	Dorota Matecka	N/A

** The drug product microbiology assessment is part of the Process Chapter*

***The environmental assessment is covered 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)	II	(b) (4)	Doxycycline Hyclate	Adequate	8/25/2017	*Review by Wei Liu*
	II		Doxycycline Hyclate	Adequate	9/28/2017	*Review by Donglei Yu*

**A number of Type III and Type IV DMFs were also referenced in the NDA; however, sufficient information in support of the container closure system and excipients was provided in the NDA*

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	125184	

2. CONSULTS

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

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA, as amended, has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, doxycycline hyclate tablets. All information requests and review issues have been addressed and there are no pending approvability issues. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on May 9, 2018. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality.

II. Summary of Quality Assessments

A. Product Overview

Lyme borreliosis (Lyme disease) is one of the most common vector-borne zoonotic diseases in the United States. It is caused by the spirochete bacterium *Borrelia burgdorferi*, an obligate parasite, which is transmitted by the bite of the tick species *Ixodes scapularis* and *Ixodes pacificus*. The drug product, LYMEPAK (doxycycline hyclate) tablets, 100 mg, has been developed for the treatment of early Lyme disease as evidenced by erythema migrans (EM), due to *Borrelia burgdorferi*. Doxycycline, a broad spectrum anti-microbial drug, is a member of the tetracycline antibiotic class. Although doxycycline is currently not approved for the treatment of Lyme disease, it has been consistently used off-label, and is considered to be the current first-line therapy for the treatment of EM.

Doxycycline hyclate has been approved and marketed as tablets and capsules. The Applicant of the current NDA, markets immediate release doxycycline hyclate tablets under ANDA 62505. To support the efficacy and safety of LYMEPAK in treating Lyme disease, the Applicant is relying on published literature. The listed drugs (LD) are Vibramycin® (doxycycline hyclate) Capsules, 100 mg (approved via NDA 50007, held by Pfizer, Inc.) and Vibra- Tabs® (doxycycline hyclate) Tablets, 100 mg (approved via NDA 50533; currently discontinued).

Proposed Indication(s) including Intended Patient Population	Treatment of early Lyme disease in adults and pediatric patients 8 years of age and older weighing 45 kg and above
Duration of Treatment	One LYMEPAK tablet (100 mg), every 12 hours for 21 days
Maximum Daily Dose	200 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Doxycycline hyclate drug substance is described as yellow, crystalline powder soluble in water and in solutions of alkali hydroxides and carbonates, slightly soluble in alcohol, and practically insoluble in chloroform and in ether. There are two commercial suppliers of doxycycline hyclate drug substance proposed in the current NDA, (b) (4) The chemistry manufacturing and controls (CMC) information for doxycycline hyclate drug substance has been provided via a reference to the two Type II DMFs (b) (4) and (b) (4) held by these suppliers, (b) (4) respectively. Both DMFs have been recently reviewed in support of other applications in CDER and found to be adequate (as indicated in the above table). The overall information provided in the NDA in support of the drug substance, including the retest period of (b) (4) months, was found acceptable by the Drug Substance Reviewer.

The drug product is a round, green film-coated tablet engraved with "LP1" on one side and plain on the other. The tablets are packaged in a unit dose blister pack of 14 (7 x 2) tablets. The formulation of these tablets is the same as doxycycline hyclate tablets currently marketed under ANDA 62505 held by the current Applicant, Chartwell Pharma, except for the orange film coat and the engraving "3626" for the tablets marketed under ANDA 62505. The excipients are conventional for a product of this type. Apart from the (b) (4), the excipients are compendial. The (b) (4) film coat is made from (b) (4) The excipients have all been (b) (4) previously approved by CDER.

The drug product specification contains tests for appearance, identity (by HPLC and TLC), (b) (4) dissolution, assay, impurities, content uniformity, and mold growth. (b) (4) A satisfactory elemental impurities risk assessment, as described in USP <232> and Q3D, has also been provided. The proposed specification is conventional, generally matches the USP specification for doxycycline hyclate tablets, and is appropriate given the observed stability data. During the review, the proposed acceptance criteria for assay as (b) (4)% (consistent with the USP monograph for doxycycline hyclate tablets) were tightened at the FDA's request to the more conventional (b) (4)% based on the observed stability data. The acceptance criteria for impurities/degradation products are reasonable and supported by the data. The absence of routine microbial limits testing in the drug product specification was found adequately justified in course of the manufacturing process review. The analytical methods are described in reasonable detail and have been validated. Satisfactory batch analyses are provided for four (b) (4) batches. One batch was made with (b) (4) Other batches were manufactured using the (b) (4)

As noted above, the commercial drug product will be packaged in a unit dose blister pack of 14 (7 x 2) tablets. To obtain the stability data the tablets were packaged in blister cards having two rows of 5 tablets (2 x 5). Two film types, (b) (4)

(b) (4) will be used in the proposed commercial blisters. (b) (4) All components are covered by DMFs and comply with the 21 CFR food additive regulations.

Satisfactory stability data are provided for three batches packaged in blisters made with the (b) (4) and three batches packaged in blisters made with the (b) (4). Twelve months of data obtained at 25°C/60% RH are provided for the (b) (4) packaging and 9 months of similar data are provided for the (b) (4). Six months of accelerated data obtained at 40°C/75% RH are provided for all batches. Satisfactory supporting stability data out to 36 months have been provided for the tablets packaged in bottles and the very similar (b) (4) tablets packaged in bottles and blisters. No out of specification results or obvious trends for appearance, (b) (4) dissolution, or mold growth have been observed in these studies. There were no significant differences in stability behavior between the various packaging configurations. (b) (4) Based on these data, the proposed in the NDA expiration dating period of 12 months with the storage statement: "Store at 20°C to 25°C (68° to 77°F) [See USP Controlled Room temperature]" can be assigned for the drug product packaged in blisters, the proposed commercial container closure system. It should be noted that bottles are not proposed as a commercial packaging configuration under this NDA. The overall information provided in the NDA for the doxycycline hyclate tablets has been found to be adequate by the Drug Product Reviewer.

(b) (4) During the NDA review, the Applicant was requested to provide manufacturing process risk assessment and microbial data for registration batches. The responses and the overall information provided for the manufacturing process in the NDA have been found acceptable by the Process Reviewer.

The Biopharmaceutics review focused on the evaluation and acceptability of the proposed dissolution method, dissolution acceptance criterion and the evaluation of the bridging between LYMEPAK tablets and doxycycline products used in the publications supporting this NDA as well as the LD products. The dissolution acceptance criterion, as revised and agreed upon: NLT (b) (4)% (Q) in 30 minutes (USP II Paddle, 75 RPM, Deaerated Water, 900 mL) has been found acceptable by the Biopharmaceutics Reviewer. In addition, based on the information provided in the NDA (which included comparative dissolution profiles), the bridge has been established between the proposed LYMEPAK tablets and the drug products used in the three pivotal/key literature publications as well as the LD products.

The Applicant claims a categorical exclusion from the requirement to prepare an Environmental Assessment under 21 CFR 25.31 (a) on the grounds that this product will not increase the use of doxycycline. No extraordinary circumstances exist. The claim has been found acceptable by the Drug Product Reviewer.

The review of the labeling and container and carton labels are currently under review and discussion with the Applicant. The strength of the drug product is based on the content of the free base, doxycycline. However, the drug product established name includes "hyclate", which is consistent with the USP monograph (and other previously approved applications) for doxycycline hyclate tablets. Therefore, the equivalency statement will be incorporated in different areas of the labeling, to state: "Each tablet contains 100 mg of doxycycline (equivalent to 115 mg doxycycline hyclate)." The tablets are packaged in a unit dose blister pack of 14 (7 x 2) tablets that represents one week BID dosing. Three blister packs are packed in a carton and constitute a 21 day course as specified in the labeling.

The NDA includes two commercial drug substance manufacturers, (b) (4) Several other facilities are listed in the NDA as drug substance testing sites. The drug product manufacturer is Chartwell Pharmaceuticals LLC, NY; (b) (4) is responsible for unit dose packaging of the commercial batches. Following the review of the inspectional histories of the drug substance and drug product manufacturing and testing facilities listed in the NDA, no outstanding issues have been identified by the Facilities Reviewer and the overall manufacturing inspection recommendation of "Approve" was entered into Panorama on May 9, 2018.

C. Special Product Quality Labeling Recommendations (N/A)

D. Final Risk Assessment (see Attachment I)

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Process

CHAPTER IV: Biopharmaceutics

CHAPTER V: Facilities

CHAPTER VI: Labeling

ATTACHMENT I: Risk Assessment

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

BIOPHARMACEUTICS

Product Background:
NDA: 209844 (505(b)(2)).
Drug Product Name / Strength: LymePak (Doxycycline Hyclate) Tablets, 100 mg
Route of Administration: Oral
Applicant Name: Chartwell Pharma NDA B2 Holdings, LLC

Review Summary:
This 505(b)(2) application is submitted for LymePak (doxycycline hyclate) Tablets for treatment of early Lyme disease due to *Borellia Burgdorferi*. The listed drug (LD) products are Pfizer's NDA 050007, Vibramycin® (Doxycycline Hyclate) Capsules, 100 mg and NDA 050533, Vibra-Tabs® (Doxycycline Hyclate) Tablets, 100 mg (Discontinued). To support the efficacy and safety of LymePak in treating Lyme disease, the Sponsor is relying on the published literature.

The Biopharmaceutics review is focused on the evaluation and acceptability of the proposed dissolution method, dissolution acceptance criterion and the evaluation of the bridging between LymePak tablets and Doxycycline products used in the publications supporting this NDA as well as the LD products.

Based on the provided dissolution data, the following dissolution method (b) (4) for Doxycycline Hyclate tablet) and revised acceptance criterion are acceptable and agreed upon:

USP Apparatus	Speed (RPMs)	Medium	Volume	Cumulative % of Drug Dissolved (Label Claim)
USP II (Paddle)	75	Deaerated water	900 mL	NLT (b) (4)% (Q) in 30 minutes

Based on the provided information, the bridge has been established between the proposed LYMEPAK tablets and the drug products used in the 3 pivotal/key literature publications as well as the LD products.

List Submissions being reviewed:

Application Number	Submissions Reviewed	Document Date
IND 125184	BCS (b) (4) Designation Request	8/1/2017
NDA 209844	Original Submission	8/18/2017
	IR Response (Biowaiver amendment)	2/19/2018
	IR Response (Dissolution Acceptance Criterion)	3/30/2018
	IR Response (Additional Relied Upon LD)	5/1/2018

Recommendation:
From the Biopharmaceutics perspective, NDA 209844 for LymePak (Doxycycline Hyclate) IR Tablets, 100 mg is recommended for **APPROVAL**.

REVIEW

BCS Designation

The Applicant submitted a request for evaluation and classification of Doxycycline Hyclate Tablets as a BCS class (b)(4) drug product in IND 125184 (SD0017) dated August 1, 2017. However, the Applicant's request was denied, because the Applicant did not conduct drug substance solubility, drug substance permeability or drug substance gastric stability studies, but instead reference a published article[1]. In a Biopharmaceutics information request letter dated October 10, 2017[2] as well as Teleconference on October 16, 2017[3], the Applicant was requested to conduct drug substance solubility, drug substance permeability and drug substance gastric stability testing to support the BCS (b)(4) designation request.

The Applicant conducted drug substance solubility and gastric stability tests and provided the following drug substance solubility in the response dated February 19, 2018 (Appendix I). However, the Applicant still relies on literature for the permeability data of the drug substance and thus the request for designation of Doxycycline Hyclate tablets, 100 mg as a BCS class (b)(4) drug product remains as **Unacceptable.**

Drug Substance Solubility:

(b) (4)

[redacted]

Review Note: The drug substance is (b) (4) *per BCS guidance, when given at a dose of 100 mg. However, due to the insufficient information regarding the drug product permeability, the Applicant's BCS* (b)(4) *designation request remains as unacceptable (Appendix I).*

[1] DARRTS: IND 125184 REV-QUALBIOPHARM-21 (Primary Review), final date 10/3/2017.
[2] DARRTS: IND 125184 COR-INDAD-02 (Advice/Information Request), final date 10/10/2017
[3] DARRTS: NDA 209844 COR-NDAIR-01 (Information Request), final date 10/26/2017.
[4] \\cdsesub1\evsprod\nda209844\0008\m1\us\112-other-correspondence\sr-20180010-03.pdf

Permeability:

The Applicant refers to the approved label of Vibramycin® 100 mg Tablets which states that *Doxycycline is virtually completely absorbed after oral administration*. The Applicant also refers to permeability data reported in the literature[5].

Review Note: The approved label of Vibramycin® cannot be used to support the BCS designation of the proposed drug product, because the Vibramycin® label does not contain sufficient bioavailability data or a quantitative statement to support the (b) (4) *of Doxycycline Hyclate.*

Drug Substances:

Doxycycline hyclate, USP is the hyclate salt form of doxycycline, an antibacterial drug synthetically derived from oxytetracycline.

The molecular formula for doxycycline hyclate is $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \bullet C_2H_6O \bullet H_2O$ and the molecular weight is 1025.89. Doxycycline is a light-yellow crystalline powder. Doxycycline hyclate is freely soluble in water.

The Applicant has two API suppliers, (b) (4)

Formulation of the Proposed LymePak Tablets:

(b) (4)

[5] \\cdsesub1\evsprod\nda209844\0008\m1\us\111-information-amendment\quality-information.pdf

[6] \\cdsesub1\evsprod\anda062505\0002\m3\32-body-data\32p-drug-prod\doxycycline-hyclate-usp-tablets\32p3-manuf\manuf-process-and-controls-m-cw-3626-1a-3e.pdf

Table 2: Quantitative Formulation per Unit Dose of LymePak and ANDA 062505

Material	Quantity per unit (mg/tab) Proposed NDA	Quantity per unit (mg/tab) ANDA 062505
Doxycycline as Doxycycline Hyclate, USP		(b) (4)
Lactose Anhydrous, NF	(b) (4)	
Microcrystalline Cellulose, NF	(b) (4)	
Polyethylene Glycol, NF	(b) (4)	
Methylcellulose, USP	(b) (4)	
Sodium Starch Glycolate, NF	(b) (4)	
Stearic Acid, NF		
Colloidal Silicon Dioxide, NF		
Magnesium Stearate, NF		
Core Sub-Total		
(b) (4)		
(b) (4) *hypromellose (usp,Pheur, jp)*		
D&C yellow #10 (b) (4)		
Titanium Dioxide (USP,FCC, pheur, JP)		
(b) (4) *(NF, FCC, pheur, JECFA, JP)*		
FD&C blue #1/ (b) (4)		
(b) (4) *(jecfa, jsfa, jp mo)*		
FD&C Yellow #6/ (b) (4) *jecfa, jsfa, jp Mo)*		
FD&C Red # 40 (b) (4)		
-Coating Sub-total		
Final Tablet Total		

The ingredients in italics are ingredients in the (b) (4)

The Applicant provided comparative dissolution profiles between the proposed LymePak Tablets and Doxycycline Tablets (ANDA 062505) in Simulated Gastric Fluid, Acetate Buffer, Simulated Intestinal Fluid and Water (Appendix II) and the calculated similarity factors (f_2) listed in Table 4.

Table 3: Dissolution Similarity Between LymePak Tablets 100 mg and Doxycycline Tablet 100 mg (ANDA 062505)

Reference Batch # (ANDA) / product code	Test Batch # LYMEPAK / product code	Dissolution medium	pH	f_2
770020D / 3626	770171A / 5963	Simulated Gastric Fluid	1.2	76.39
770020D / 3626	770171A / 5963	Acetate Buffer	4.5	81.69
770020D / 3626	770171A / 5963	Simulated Intestinal Fluid	6.8	70.45
770020D / 3626	770171A / 5963	Water	7	59.47

Review Note: (b) (4)

Dissolution Method:

The Applicant proposes using the [redacted] for Doxycycline Hyclate tablets, which is also the approved QC dissolution method for ANDA 062505[7]. The method is summarized below:

Test Conditions	
Dissolution apparatus	USP Apparatus 2 (paddles)
Medium and volume	Deaerated water, 900 mL
Temperature	37 ± 0.5°C
Rotation speed	75 rpm
Distance from bottom	4.5 cm ± 0.5 cm
Sampling time	Code [redacted] - 30 minutes (single point) 5, 15, 30, 45, 60 minutes (dissolution profile Code [redacted] - 90 minutes (single point) 15, 30, 60, 90, 105 minutes (dissolution profile)
Analytical Conditions	[redacted]
[redacted]	[redacted]nm
	[redacted]m

Reviewer's Assessment of the Dissolution Method:

The proposed dissolution method is acceptable.

Dissolution Method Validation:

The analytical method for the quantitation of drug in the dissolution samples was validated for specificity, linearity, range, precision, and filter, which will be evaluated by the Drug Product reviewer (\\cdsesub1\evsprod\nda209844\0001\m3\32-body-data\32p-drug-prod\doxycycline-hyclate-tablets\32p5-contr-drug-prod\32p53-val-analyt-proc\validation-analyt-procedures-mvr2017-010.pdf).

Dissolution Acceptance Criterion:

The Applicant proposed a dissolution acceptance criterion of NLT [redacted] Based on the dissolution data of the proposed LymePak Tablets (see Appendix II), the revised recommended acceptance criterion of NLT [redacted]% (Q) in 30 minutes was found acceptable and agreed upon (Appendix III):

Reviewer's Assessment of the Dissolution Acceptance Criterion:

The revised dissolution acceptance criterion of "Q= [redacted]% at 30 minutes" is acceptable.

Bridging Request:

The Applicant relies upon information in the published scientific literature to support the efficacy of the proposed LymePak tablets for the treatment of early Lyme disease. The Clinical Team mainly reviewed the following three publications describing US clinical studies to support the efficacy and safety of the proposed LymePak Tablets:

[7] \\cdsesub1\evsprod\anda062505\0002\m3\32-body-data\32p-drug-prod\doxycycline-hyclate-usp-tablets\32p5-contr-drug-prod\32p52-analyt-proc\analytical-procedure-1-tm0022-02.pdf

Table 4: The pivotal/key clinical studies described in the literature publications used to support the safety and efficacy of Doxycycline

Amoxycillin plus probenecid versus doxycycline for treatment of erythema migrans borreliosis[8]	Dec 1990
Treatment of Early Lyme Disease[9]	April 1992
Ceftriaxone compared with doxycycline for the treatment of acute disseminated lyme disease[10]	July 1997

The doxycycline salt form nor the drug dosage form was specified in these publications, instead, only the active moiety "doxycycline" was noted. Therefore, those studies might use various formulations of doxycycline. Per orange book, the following doxycycline products were available on the US market and approved by FDA during the period that these clinical studies were conducted in the US:

Table 5: Oral Doxycycline Drug Products Approved by FDA Until 1997

API	NDA #	Dosage form	Strength	Brand name	Approved date	Applicant
Doxycycline Monohydrate	50006	Suspension	25 mg/5 mL	Vibramycin	12/5/1967	Pfizer
Doxycycline Hyclate	50007 (**LD**)	Capsules	100 mg	Vibramycin	12/5/1967	Pfizer
Doxycycline Calcium	50480	Suspension	50 mg/5 mL	Vibramycin	9/23/1974	Pfizer
Doxycycline Hyclate	50533 (DISCN)	Tablets	100 mg	Vibra-Tabs	12/18/1979	Pfizer
Doxycycline monohydrate	50641	Capsules	50, 75, 100 mg	Monodox	50 mg: 2/10/1992 100 mg: 12/29/1989	Aqua

It is noted that in the currently approved single Vibramycin® label (Appendix IV), the following four dosage forms/salt forms are listed: VIBRAMYCIN HYCLATE- doxycycline hyclate capsules (NDA 50007); VIBRAMYCIN MONOHYDRATE- doxycycline powder, for suspension (NDA 50006); VIBRAMYCIN CALCIUM- doxycycline calcium syrup (NDA 50480) ; VIBRA-TABS- doxycycline hyclate tablet, film coated (NDA 50533). These four drug products all have the same label with the same pharmacokinetic parameters described in Clinical Pharmacology Section, which indicates that these drug products are equivalent in pharmacokinetic parameters and efficacy when administered in equivalent dosing regimens. Therefore, the difference in salt form or dosage form (immediate release) of doxycycline does not result in any significant differences in the pharmacokinetic parameters of these drug products.

The proposed LymePak tablets, 100 mg has the same formulation (with exception of (b) (4) color coatings) as the marketed doxycycline hyclate tablets, 100 mg under ANDA 062505, which has demonstrated bioequivalence to Vibra-Tabs® (NDA 50533), one of the LD products. Based on the proposed formulation and the comparative dissolution profiles in Appendix II, the proposed LymePak tablets are expected to have comparable PK parameters to Vibra-Tabs® (NDA 50533) and other doxycycline drug products (including Vibramycin® Capsules, 100 mg (LD)) that were possibly used in the published literature article that this NDA is relying on.

Therefore, the bridge has been established between the proposed LYMEPAK tablets and the drug products used in the 3 pivotal/key literature publications as well as both LDs.

[8] \\cdsesub1\evsprod\nda209844\0001\m5\54-lit-ref\dattwyler-1990.pdf
[9] \\cdsesub1\evsprod\nda209844\0001\m5\54-lit-ref\massarotti-1992.pdf
[10] \\cdsesub1\evsprod\nda209844\0001\m5\54-lit-ref\dattwyler-1997.pdf

R Regional Information

Comparability Protocols: None

Post-Approval Commitments: None

Lifecycle Management Considerations: None

List of Deficiencies: None

Recommendations:
From the Biopharmaceutics perspective, NDA 209844 for LymePak (Doxycycline Hyclate) IR Tablets, 100 mg is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date: Zhuojun Joan Zhao, Ph.D. 05/03/2018

Secondary Reviewer Name and Date: Elsbeth Chikhale, Ph.D. 05/04/2018

APPENDIX I: *Biopharmaceutics Information Requests Dated October 10, 2017[2] and Applicant Response Dated February 19, 2018*

Biopharmaceutics Request Comments:

*Your request for a BCS-Class (b) (4) designation for the proposed Doxycycline Hyclate Tablets, 100 mg is **denied** at this time.*

You provided a published article by (b) (4) to support your BCS (b) (4) designation request for Doxycycline Hyclate tablets, 100 mg. Note that such published literature is considered inadequate to support your BCS designation request, because the drug substance solubility, drug substance permeability and drug substance gastric stability data from the literature cannot be fully verified by the Agency. With respect to permeability data, you may use information contained in the approved labeling of the reference drug product, but not peer reviewed articles.

Conduct and submit drug substance solubility, drug substance permeability and drug substance gastric stability tests as recommended in the current Biopharmaceutics Classification System (BCS) Guidance for Industry as well as the Question Based Approach attached to the FDA Meeting Request Written Response dated July 5, 2016.

Applicant's Response to Biopharmaceutics-IR Comment:

Chartwell has conducted drug substance solubility and drug substance gastric stability tests as recommended in the current Biopharmaceutics Classification System (BCS) Guidance for Industry as well as the Question Based Approach attached to the FDA Meeting Request Written Response dated July 5, 2016.

Chartwell has contracted a (b) (4) (b) (4) In support of this additional testing facility, this amendment contains a GMP Certification, Debarment Certification, and proof of good standing with FDA for the laboratory.

Drug Substance Permeability:

With respect to drug substance permeability data, we support our claim of Doxycycline Hyclate's (b) (4) permeability on two approaches:

(b) (4)

Reviewer Note:

The Applicant's response is not acceptable. The approved label of the listed drug product, Vibramycin® Capsules does not have sufficient bioavailability data or a quantitative statement to support the (b) (4) of Doxycycline Hyclate. Also, as stated in the IR letter dated October 10, 2017, the Agency does not accept published articles to support permeability. Therefore, the Applicant's request for designation of Doxycycline Hyclate tablets, 100 mg as a BCS class (b) (4) drug product remains as **Unacceptable.**

APPENDIX III: *Biopharmaceutics Information Requests Dated March 23, 2018 and Applicant Response Dated March 30, 2018*

Biopharmaceutics Request Comment:

Based on the provided dissolution data, a dissolution acceptance criterion of Q = (b)(4)% at 30 minutes is recommended for your drug product. Provide an updated drug product specification table and update all other sections of your NDA accordingly.

Be aware that setting of the dissolution acceptance criterion is based on S2 testing (n = 12) and therefore sometimes Stage 2 testing and occasional Stage 3 testing maybe needed.

Applicant's Response to Biopharmaceutics-IR Comment:

Chartwell has revised our dissolution acceptance criterion to Q = (b)(4)% at 30 minutes. Chartwell is aware that this dissolution acceptance criterion may require stage 2 and occasionally stage 3 dissolution testing.

Documentation has been revised and sections updated in the NDA as follows:

Section	Document updated	update
M2	**Quality Overall Summary**	Pg. 22 and 23 dissolution test method sample times updated to reflect 30 minutes
3.2.P.5.1 Specifications	**Specifications**	Specification table updated to NLT (b)(4)%(Q) doxycycline at 30 minutes
	FP-5963-02	Specification updated to NLT (b)(4)%(Q) doxycycline at 30 minutes
	STAB-5963-02	Specification updated to NLT (b)(4)%(Q) doxycycline at 30 minutes
3.2.P.5.2	**Analytical Procedures**	Listing of changes made to TM-022
	TM022-04	Pg 18 dissolution test method sample times updated to reflect 30 minutes for single point and 5, 15, 30, 45, and 60 for dissolution profile
3.2.P.8.1	**Stability Summary and Conclusions**	Table 4 updated to NLT (b)(4)%(Q) doxycycline at 30 minutes
3.2.P.8.2	**Post Approval Stability Commitment**	Specification updated to NLT (b)(4)%(Q) doxycycline at 30 minutes

Reviewer Note:

The Applicant's response is satisfactory.

APPENDIX IV: *VIBRAMYCIN® Label*[15]

VIBRAMYCIN MONOHYDRATE- doxycycline powder, for suspension
VIBRAMYCIN CALCIUM- doxycycline calcium syrup
VIBRAMYCIN HYCLATE- doxycycline hyclate capsule
VIBRA-TABS- doxycycline hyclate tablet, film coated
Pfizer Laboratories Div Pfizer Inc

Vibramycin®
Calcium
(doxycycline calcium oral suspension, USP)
oral suspension
SYRUP

Vibramycin®
Hyclate
(doxycycline hyclate capsules, USP)
CAPSULES

Vibramycin®
Monohydrate
(doxycycline monohydrate)
for ORAL SUSPENSION

Vibra-Tabs®
(doxycycline hyclate tablets, USP)
FILM COATED TABLETS

CLINICAL PHARMACOLOGY

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degree. They are concentrated by the liver in the bile, and excreted in the urine and feces at high concentrations and in a biologically active form. Doxycycline is virtually completely absorbed after oral administration.

Following a 200 mg dose, normal adult volunteers averaged peak serum levels of 2.6 mcg/mL of doxycycline at 2 hours, decreasing to 1.45 mcg/mL at 24 hours. Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal function (creatinine clearance about 75 mL/min.). This percentage excretion may fall as low as 1–5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 mL/min.). Studies have shown no significant difference in serum half-life of doxycycline (range 18–22 hours) in individuals with normal and severely impaired renal function.

Hemodialysis does not alter serum half-life.

Results of animal studies indicate that tetracyclines cross the placenta and are found in fetal tissues.

[15] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d6f98d3c-5a20-4cbf-9a9c-abef10b9e465

Zhuojun Zhao

Digitally signed by Zhuojun Zhao
Date: 5/04/2018 02:40:45PM
GUID: 508da6fd000284770cf4eecbae074722

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 5/04/2018 03:25:07PM
GUID: 50743ccc000031928b54eba1769a5df9

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

NDA 209844

LymePak (doxycycline hyclate, USP) Tablets

Review of Common Technical Document-Quality (Ctd-Q) Module 1 Labeling & Package Insert

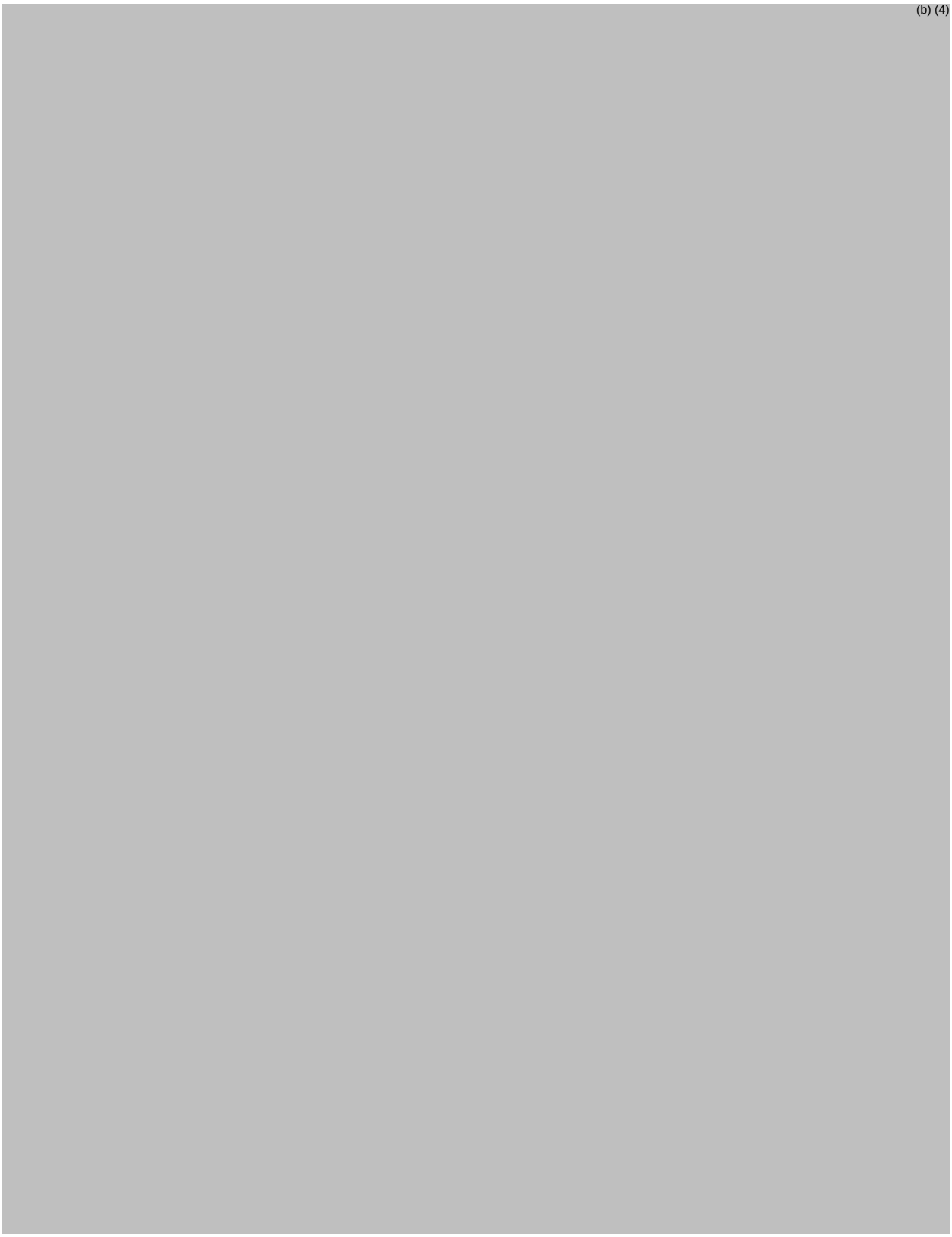
2. Container and Carton Labeling

Note: The blister cards and cartons were amended in the Amendment of 4/30/18 to accommodate the FDA-recommended dosing regimen of one tablet twice a day for 21 days, i.e., 3 blister cards of 14 tablets. This Amendment also describes a carton of 3 blister cards. Unprinted samples of the blister cards have been supplied.

1) Immediate Container Label (Blister Card)

Container front inside (Amendment of 4/30/18)


(b) (4)



Wording on cards as follows:

Blister card (outside)

NDC 62135-596-01
LymePak
(doxycycline hyclate (b) (4)
14 Tablets – 7 Day Supply
100 mg*
Rx Only

Blister card (inside)

Usual Dosage:
See package insert for full prescribing information.
Store at 20° to 25°C (68° to 77° F)
[See USP Controlled Room Temperature].
KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Manufactured by:
Chartwell Pharmaceuticals, LLC
Congers, NY 10920 USA

Manufactured for:
Chartwell RX, LLC
Congers, NY 10920

Made in USA

Bar code

LOT:
EXP:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	LymePak (doxycycline hyclate [redacted] (b) (4)	Adequate but remove USO
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4)) and salt equivalency statement (space permitting)	100 mg* [redacted] (b) (4)	Change to: Each tablet contains 100 mg of doxycycline (equivalent to 115 mg doxycycline hyclate).
Route of administration 21.CFR 201.100(b)(3))	None	Acceptable for oral
Net contents* (21 CFR 201.51(a))	14 tablets – 7 day supply	Adequate.
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Not present	Acceptable for reasons of space
Lot number per 21 CFR 201.18	Present inside	Adequate. Defer to DMEPA concerning location
Expiration date per 21 CFR 201.17	Present inside	Adequate. Defer to DMEPA concerning location
"Rx only" statement per 21 CFR 201.100(b)(1)	Present outside	Adequate
Storage (not required)	See package insert for full prescribing information. Store at 20° to 25° C (68° to 77°F) [See USP Controlled Room Temperature].	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Present	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Present inside	Adequate. Defer to DMEPA concerning location
Name of manufacturer/distributor (21 CFR 201.1)	Manufactured by: Chartwell Pharmaceuticals, LLC Congers, NY 10920 USA Manufactured for:	Adequate but would recommend addition of phone number or website. Particularly as two entities are

	Chartwell RX, LLC Congers, NY 10920	described.
Others	Opening instructions are provided Also contains: KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN	Adequate

2) Carton Labeling

Wording on Cartons as follows [Differences highlighted in yellow]

Top

NDC 62135-596-87
LymePak
(doxycycline hyclate (b) (4)
Contains 3 Cards
Each Card with:
14 Tablets (b) (4) day Supply

100 mg*
Rx Only

Front/back and side panels

NDC 62135-596-87
LymePak
(doxycycline hyclate [redacted])
Contains 3 Cards Each Card with 14 Tablets | [redacted] Day Supply

Bottom

*Each tablet contains:
[redacted]

Usual Dosage:
See package insert for full prescribing information.
Store at 20° to 25°C (68° to 77° F)
[See USP Controlled Room Temperature].

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.
Chartwell Pharmaceuticals logo

Manufactured by:
Chartwell Pharmaceuticals, LLC
Congers, NY 10920 USA

Manufactured for:
Chartwell RX, LLC
Congers, NY 10920

Made in USA

Red area: DO NOT PRINT UNVARNISHED (presumably for lot# and expiration)

Bar Code

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	LymePak (doxycycline hyclate (b) (4)	**Adequate but delete USP**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2)) and salt equivalency statement	100 mg* * (b) (4) (b) (4)	Change to: Each tablet contains 100 mg of doxycycline (equivalent to 115 mg doxycycline hyclate).
Net contents (21 CFR 201.51(a))	Contains 3 Cards Each Card with 14 Tablets Day Supply	**Adequate**
Lot number per 21 CFR 201.18	**Assuming that this is the red rectangle labeled "Do not print unvarnished".**	**Adequate**
Expiration date per 21 CFR 201.17	**Assuming that this is the red rectangle labeled "Do not print unvarnished".**	**Adequate**
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	**Not present**	Acceptable for reasons of space.
Sterility Information (if applicable)	NA	
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Present	**Adequate**
Storage Conditions	Store at 20° to 25° C (68° to 77°F) [See USP Controlled Room Temperature].	**Adequate**
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Present	**Adequate**
Bar Code per 21 CFR 201.25(c)(2)**	Present	**Adequate**
Name of manufacturer/distributor	Manufactured by: Chartwell Pharmaceuticals, LLC Congers, NY 10920 USA Manufactured for: Chartwell RX, LLC	Adequate but would recommend addition of phone number or website. Particularly as two entities are described.

	Congers, NY 10920	
"See package insert for dosage information" (21 CFR 201.55)	Usual Dosage: See package insert for full prescribing information. Store at 20° to 25°C (68° to 77° F) [See USP Controlled Room Temperature].	**Adequate**
"Keep out of reach of children" (optional for Rx, required for OTC)	KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN	**Adequate**
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Not present	**Adequate**

Overall Comments (apply to both card and carton):

Change doxycycline hyclate (b) (4) to doxycycline hyclate

Change "* (b) (4) " to "*Each tablet contains 100 mg of doxycycline (equivalent to 115 mg doxycycline hyclate)."

We recommend the addition of a phone number or website, particularly as two entities are designated, Chartwell Pharmaceuticals LLC and Chartwell RX, LLC.

George Lunn

Digitally signed by George Lunn
Date: 5/09/2018 11:49:07AM
GUID: 508da72000029f40833369b0a181e8b3

Dorota Matecka

Digitally signed by Dorota Matecka
Date: 5/09/2018 11:56:35AM
GUID: 508173530000859092c69506374d0011

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**
		H, M, or L		Acceptable or Not Acceptable	
Assay, stability	Formulation, Process parameters Raw materials Container closure system	L	Adequate container closure system Relatively short proposed expiration dating (12 months)	Acceptable	
Content uniformity	Formulation Raw materials Process parameters Scale/equipment	L	Adequate assay and in-process controls (b) (4)	Acceptable	
Microbial limits	Formulation Raw materials Process parameters	L	Low risk for microbial contamination (b) (4)	Acceptable	
Dissolution	Formulation Raw materials Process parameters Scale/equipment	L	Properties of the drug substance (b) (4)	Acceptable	

OVERALL RECOMMENDATION:
This NDA is recommended for Approval from the Product Quality perspective.
On behalf of OPQ Team
Dorota Matecka, ATL for NDA 209844

Dorota M. Matecka -S

Dig tally signed by Dorota M Matecka -S
DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0.9.2342.19200300.100.1.1=1300123291 cn=Dorota M Matecka -S
Date: 2018.05.10 21:25:31 -04'00'