CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208253Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

NDA 208253
Review # 1

Drug Name/Dosage Form	Acticlate CAP doxycycline hyclate capsule
Strength	75 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Aqua Pharmaceuticals, LLC
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	June 26, 2015	All
Quality Amendment	September 4, 2015	Biopharmaceutics
Quality Amendment	November 19, 2015	Biopharmaceutics
Quality Amendment	December 28, 2015	Biopharmaceutics
Quality Amendment	February 2, 2016	Biopharmaceutics
Quality Amendment	February 16, 2016	Drug Product
Quality Amendments (2)	March 25, 2016	Drug Product

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sithamalli Chandramouli	ONDP/NDB1/DNDAPI
Drug Product	Shrikant Pagay	ONDP/DNDP I/Branch III
Process	Ying Wang	OPF/DPA II/Branch V
Microbiology	Ying Wang	OPF/DPA II/Branch V
Facility	Frank Wackes	OPF/DIA/Branch II
Biopharmaceutics	Gerlie Gieser	ONDP/DBP/Branch I
Regulatory Business Process Manager	Navi Bhandari	OPRO
Application Technical Lead	Dorota Matecka	ONDP/DNDP I/Branch III
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Assessment (EA)	Shrikant Pagay	ONDP/DNDP I/Branch III

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS [1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Doxycycline Hyclate	Adequate	07/15/2015	Reviewed for ANDA 90431
	Type III		(b) (4)	N/A		
	Type III			N/A		
	Type IV			N/A		
	Type III			N/A		
	Type III			N/A		
	Type III			N/A		
	Type III			N/A		
	Type III			N/A		

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

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	50007	Vibramycin (Doxycycline Hyclate Capsules), Company: Pfizer
ANDA	65095	Doxycycline Hyclate Tablets USP, Company: (b) (4)
IND	111602	Meeting minutes (pre-IND

		meeting dated July 12, 2011)

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

A. Recommendation and Conclusion on Approvability

NDA 208253 is recommended for approval by the Office of Pharmaceutical Quality. 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 on August 21, 2015.

Based on the overall stability information submitted in the NDA, 36 months and 24 months of expiration dating may be granted for the proposed drug product, doxycycline hyclate capsules, 75 mg, packaged in HDPE bottles and (b) (4) blisters, respectively, stored at 20° to 25°C (68° to 77°F) excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

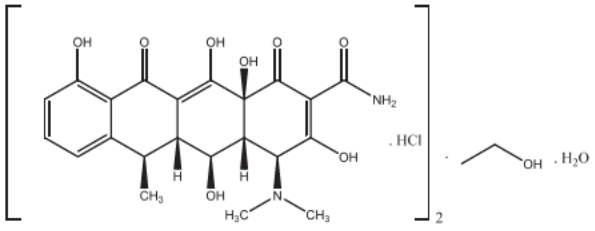
N/A

II. Summary of Quality Assessments

A. Drug Substance [doxycycline hyclate] Quality Summary

The chemical (IUPAC) name and structure of doxycycline hyclate are as follows:

(4S,4aR,5S,5aR,6R,12aS)-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide hydrochloride, compound with ethanol (1:0.5), (b) (4)



Doxycycline hyclate is a yellow to light yellow, crystalline powder (b) (4) It is freely soluble in water and methanol, but only sparingly soluble in ethanol and insoluble in organic solvents such as chloroform and ether.

Information regarding the chemistry, manufacturing and controls used in production of doxycycline hyclate, USP, is referenced to DMF Type II (b) (4) held by (b) (4), which has been reviewed and found adequate previously. The proposed specification for doxycycline hyclate meets the requirements of the respective USP monograph. The doxycycline hyclate drug substance, USP, supplied by (b) (4) is packaged in (b) (4)

B. Drug Product [doxycycline hyclate capsules] Quality Summary

Doxycycline hyclate capsules, 75 mg, are supplied as (b) (4) hard gelatin, navy blue opaque (b) (4) capsules (with a logo: Aqua 101C75) filled with yellow powder. The 75 mg doxycycline hyclate capsule is a size #2 hard gelatin capsule. Each capsule contains 86.6 mg doxycycline hyclate equivalent to 75 mg doxycycline. It should be noted that this NDA includes also some CMC information for 150 mg capsules, which were used in the bioavailability study conducted by the applicant to support the current NDA. Both 75 mg and 150 mg capsules contain microcrystalline cellulose and magnesium stearate. The formulation approach used (b) (4) for the two capsule strengths. However, the 150 mg doxycycline hyclate capsules are not proposed for marketing (b) (4)

The manufacturing process for the drug product, doxycycline hyclate capsules, 75 mg, is (b) (4) as described in the submission, have been found acceptable.

The drug product specification includes appearance, identification, dissolution, uniformity of dosage units, water, assay, impurities/degradation products and microbial limits. Most of the analytical procedures comply with the USP Monograph. The analytical procedure to be used for identification, assay, and impurities is an HPLC method, developed in-house. The residual solvents are controlled for the drug substance and excipients and no organic solvents are used in the drug product manufacture. The acceptance criteria for assay, water content, dissolution, and one of the impurities (b) (4) have been revised at the recommendation of the Agency.

The drug substance manufacturing site proposed via this NDA is (b) (4); the drug product manufacturing facility is (b) (4). There are several other facilities involved in testing and packaging of the proposed drug product and the drug substance. All manufacturing facilities were found acceptable by the Office of Process and Facilities.

The NDA includes a comparability protocol that proposes a post-approval submission (via a manufacturing supplement) of the [redacted] facility as an additional manufacturing site for the drug substance. Several revisions recommended by the Agency to the proposed comparability protocol were included and a revised protocol has been found acceptable.

The proposed container closure systems for the drug product include 60-count HDPE bottles (commercial packaging presentation) and 2-count [redacted] blisters (physician's samples).

Based on the available stability data in the NDA, the proposed expiration dating of 36 months and 24 months for the proposed drug product, doxycycline hyclate capsules, 75 mg, packaged in HDPE bottles and [redacted] blisters, respectively, has been found acceptable.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Acticlate CAP Capsule
Non Proprietary Name of the Drug Product	Doxycycline hyclate capsule
Non Proprietary Name of the Drug Substance	Doxycycline hyclate
Proposed Indication(s) including Intended Patient Population	Multiple antibacterial indications Adults and children > 8 years of age; [redacted]
Duration of Treatment	Multiple
Maximum Daily Dose	Multiple (weight-based dosing)
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Designation: (note: formal BCS-1 designation was not requested by the Applicant)
   - Drug Substance: high solubility, high permeability (absolute BA is 90 to 100%)
   - Drug Product: [redacted] drug release (NLT [redacted]% in [redacted] min) using USP dissolution method for doxycycline hyclate capsules, i.e., [redacted]

2. Biowaivers/Biostudies
   - Biowaiver Request: An *in vivo* BE waiver was requested for the proposed commercial, i.e., lower strength (75 mg) tablet. The biowaiver request is granted (see Biopharmaceutics Information section of this review).
   - PK studies – Refer to Clinical Pharmacology review of pivotal BA/BE study for the higher strength (150 mg) tablet

- IVIVC - none

E. Novel Approaches

F. Any Special Product Quality Labeling Recommendations

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

This NDA is recommended for approval from the Product Quality perspective.

Dorota M. Matecka -S

Digitally 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: 2016.03.25 15:11:29 -04'00'

Dorota Matecka, Ph.D., CMC Lead; Branch III; Division of New Drug Products I

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ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

The Biopharmaceutics review is focused on the evaluation of the proposed dissolution method and dissolution acceptance criterion and the Applicant's biowaiver request for the proposed commercial (lower strength) 75 mg doxycycline hyclate capsule.

1. **Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?**

The Applicant adopted the USP dissolution method and acceptance criterion for doxycycline hyclate capsules, as summarized below.

Table 38-1. Dissolution Method Parameters

Apparatus	USP Type 2 (Paddles)
Agitation Speed	75 rpm
Paddle Height[a]	4.5 ± 0.5 cm
Dissolution media	900 mL water (deaerated; purified or deionized)
Bath temperature	37 °C ± 0.5 °C
Sampling Times	Profile: 5, 10, 15, 20, 30, 60, 90, 120 minutes Routine QC: (b) (4) minutes
Method of Analyte Quantification	UV/Vis (276 nm)
Acceptance Criterion	Q = (b) (4) % in (b) (4) minutes

[a]distance between the blade and the inside bottom of the flask
Source: 3.2.P.5.3.

The Applicant claims that, based on the provided data (previously obtained by other laboratories and from the Applicant's supplementary method validation studies), the proposed USP dissolution method has satisfactory performance characteristics (i.e., in terms of accuracy, precision, linearity, specificity, recovery, filter suitability, solution stability, sink conditions) and was confirmed to be suitable for the proposed drug product. The Applicant reported that changes in the USP dissolution method conditions (e.g., alternate paddle speed [(b) (4)] and height [(b) (4)], alternative dissolution media [(b) (4)]) did not improve the accuracy and the variability of the dissolution results.

a. Is the Applicant's biowaiver request acceptable?

Yes. Based on prior agreement between FDA and the Applicant, the following information were submitted to support the biowaiver request for the proposed commercial 75 mg doxycycline hyclate capsules: (1) the side-by-side comparison of the chemical composition of the Applicant's Aqua (doxycycline) 75 mg and 150 mg capsules [Table 38.1-1], (2) the comparative *in vitro* dissolution profiles of the Applicant's Aqua (doxycycline) 75 mg and 150 mg capsules (as well as that of the Listed Drug) in 4 dissolution media: (b) (4) [Figure 38.1-1], and (3) the clinical study report of Study 11060201 which evaluated the comparative BA/BE between the Applicant's 150 mg capsule and the Listed Drug (Vibramycin (doxycycline) 100 mg capsule).

The *in vitro* dissolution profiles (n=12) in Figure 38.1-1 were generated using the USP dissolution method for doxycycline hyclate capsules; when appropriate, water was

replaced with the required (b) (4) as the dissolution medium. Three primary stability batches (Lots 1104136, 1104137, 1104138) of the Applicant's 75 mg capsule were compared to the batch of the Applicant's 150 mg capsule and the Vibramycin 100 mg capsule evaluated in the pivotal BA/BE study (Lots 1104141B and C111235 respectively, of Study 11060201). Since all test and reference formulations were (b) (4) dissolving, f_2 analysis was not considered appropriate.

Table 38.1-1.
Qualitative and Quantitative Composition of Doxycycline Hyclate Capsules

Ingredient	Function	Standard	Quantity (mg/Capsule)	
			75 mg	150 mg
Doxycycline Hyclate	Active	USP	86.6 mg[a]	173.2 mg[b]
Microcrystalline Cellulose	(b) (4)	NF	(b) (4)	
Magnesium Stearate		NF		
Total Fill Weight	---	---	202.3 mg	404.6 mg
(b) (4) Capsules (Blue Opaque Body (b) (4) (b) (4)	Capsule	(b) (4)	1 capsule	---
(b) (4) Capsules (Standard Blue Opaque Body/ (b) (4) (b) (4)	Capsule		---	1 capsule

[a] Equivalent to 75 mg doxycycline.
[b] Equivalent to 150 mg doxycycline.

Source: Attachment 1.12.15-1

Figure 38.1-1.
Comparative *In Vitro* Dissolution Profiles of Applicant's Aqua (doxycycline) 75 mg and 150 mg doxycycline capsules and Listed Drug Vibramycin (doxycycline) 100 mg capsule in water (b) (4) **(n=12)**

(b) (4)

[redacted]

Reviewer's Assessment:

BCS Classification

Although the Applicant did not formally request (and thus, did not officially receive) a BCS-1 designation for the proposed oral capsule, the known characteristics of the drug substance, and the observed *in vitro* dissolution profile of the proposed commercial doxycycline hyclate capsule suggest behavior consistent with an immediate release oral dosage form containing a BCS-1 compound. The reviewer notes that the International Pharmaceutical Federation had categorized doxycycline hyclate as a BCS-1 compound, and had published a corresponding biowaiver monograph for immediate release solid oral dosage forms containing doxycycline as the single active ingredient (http://onlinelibrary.wiley.com/doi/10.1002/jps.21954/pdf).

Dissolution Specification

The proposed USP Method for doxycycline hyclate capsules is appropriate for the routine QC of Aqua's proposed commercial 75 mg capsule. The dissolution data provided shows (b) (4) dissolution of Aqua's 75 mg strength capsule (as well as the Listed Drug Vibramycin® 100 mg capsule). Therefore, a dissolution acceptance criterion of Q = (b) (4)% in 15 minutes (instead of (b) (4) minutes) is recommended.

The following information request was sent to the Applicant on 01/19/2016:

Based on the cumulative dissolution information provided in the NDA, we recommend a dissolution acceptance criterion of Q= (b) (4)% at 15 minutes for Doxycycline Hyclate capsules, 75 mg. Therefore, update the drug product specification table and the stability protocol accordingly. In addition, submit to the NDA the 15-minute dissolution data for representative batches at the next/current stability time point.

In an email received by the FDA on 01/20/2016, the Applicant agreed to the FDA recommended dissolution acceptance criterion of Q= (b) (4)% at 15 minutes for Doxycycline Hyclate capsules (75 mg), and to update the Drug Product Specification Table and Stability Protocols accordingly. Based on the submitted Certificates of Analyses which included the full dissolution profiles for the three primary stability batches of the 75 mg capsules stored for 36 months under long-term storage conditions (25C/75%RH) in bottles, and 24 months under long-term storage conditions (25C/75%RH) in (b) (4) blisters, the FDA recommended dissolution specification time point (15 minutes) is justified.

Biowaiver Request

In a Pre-IND meeting (held in July 2011) to discuss the development of the Applicant's doxycycline hyclate 75 mg (b) (4)

In line with 21 CFR 320.22(d)(2), the Applicant's request to waive the requirement to conduct *in vivo* bioequivalence studies for the 75 mg doxycycline hyclate capsule is considered acceptable based on the following supportive information: (b) (4)

Therefore, the biowaiver request is granted.

2. **Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?**

Yes

Reviewer's Assessment:

On 11/10/2015, the following Biopharmaceutics Information Request was sent to the Applicant:

The proposed commercial drug product will be supplied as capsules with blue (b) (4) (b) (4)

Provide the in vitro dissolution profile(s) for at least one batch of the

doxycycline hyclate capsule (75 mg) in the proposed commercial blue (b) (4) capsule shell by November 30, 2015.

On 11/19/2015, the Applicant stated that the *in vitro* dissolution profile for the capsules with blue (b) (4) capsule (b) (4) is not available at this time but commits to obtain the requested information during their planned process validation work. The Applicant believes that the proposed commercial capsule with blue (b) (4) capsule (b) (4)

On 11/30/2015, the following FDA Information Request was sent to the Applicant:

Regarding your response to the Quality Information Request dated November 10, 2015
We acknowledge your commitment to determine (as part of process validation) the in vitro dissolution profile of the proposed commercial doxycycline hyclate product with blue opaque (b) (4) hard gelatin capsules. However, to facilitate our review of the NDA, this dissolution testing (b) (4) should be performed and the information should be submitted within 1 month of receiving this follow up information request.

On 12/28/2015, the Applicant submitted dissolution data for a laboratory scale batch of doxycycline hyclate capsules 75 mg (b) (4) The data confirm that the proposed commercial drug product exhibits (b) (4) dissolution (at least (b) (4)% of the labeled amount dissolved within 15 minutes) (b) (4) Therefore, the Applicant's response is acceptable and the provided dissolution data support the bridging between the drug product used during the product development and the proposed commercial drug product.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Recommendation and Signature:

From a Biopharmaceutics perspective, NDA 208253 for Doxycycline hyclate capsule, 75 mg is recommended for **APPROVAL**.

1/20/2016

Gerlie Gieser, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics/ONDP
Office of Pharmaceutical Quality

Secondary Concurrence and Signature:
I concur with Dr. Gieser's assessment and recommendation.

1/21/2016

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics/ONDP
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

The applicant proposes microbial limit tests according to USP <61> & <62> at release and during stability.

Reviewer's Assessment: Adequate

The proposed microbial test is adequate for solid oral dosage form.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Recommended for approval from microbiology perspective

Ying Wang 2/25/2016

Secondary Review Comments and Concurrence:

Upinder Atwal, Ph.D.
Branch Chief (Acting)
OPF/DPA I/Branch III

03/07/2016

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

The sponsor has claimed categorical exclusion as defined in 21 CFR25.31(a). The introduction of this new dosage form with the approval of the NDA will not increase the use of the active moiety since it will replace use of other marketed dosage strengths.

Also, the sponsor believes that there are no extraordinary circumstances exist as defined under 21CFR25.21 which would require EA submission.

Reviewer's Assessment: The categorical exclusion claim provided for this application is acceptable.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: Satisfactory

Shrikant Pagay, March 21, 2016

Secondary Review Comments and Concurrence:

I concur
Dorota Matecka, Ph.D.; CMC Lead; Branch III; Division of New Drug Products I
March 25, 2016

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

ACTICLATE® (doxycycline hyclate) tablets, for oral use
TRADENAME (doxycycline hyclate) capsules, for oral use
Initial U.S. Approval: 1967

----------DOSAGE FORMS AND STRENGTHS----------

- ACTICLATE Tablets: 75 mg and 150 mg (functionally scored) (3)
- TRADENAME Capsules: 75 mg **(Error! Reference source not found.)**

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	yes	Adequate for tablets
Dosage form, route of administration	yes	Adequate
Controlled drug substance symbol (if applicable)	yes	Adequate
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	yes	Adequate

Conclusion: Adequate

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

ACTICLATE Tablets:

ACTICLATE® (doxycycline hyclate) Tablets, 75 mg are round, convex, light-teal, film-coated, tablets with "75" debossed on one side of the tablet and "AQ101" debossed on the other (each tablet contains 75 mg doxycycline as 86.6 mg doxycycline hyclate).

ACTICLATE® (doxycycline hyclate) Tablets, 150 mg are oval-shaped, convex, mossy-green, film-coated tablets. Each side of the functionally scored tablet has two parallel score lines for splitting into 3 equal portions with "A" debossed on each portion of one side of the tablet, and no debossing on the other (each tablet contains 150 mg doxycycline as 173.2 mg doxycycline hyclate).

TRADENAME Capsules:

TRADENAME (doxycycline hyclate) Capsules, 75 mg have a navy blue opaque body and cap with the inscription "AQUA 101C75" in black (each capsule contains 75 mg doxycycline as 86.6 mg doxycycline hyclate).

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	yes	Adequate
Strengths: in metric system	yes	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	yes	Adequate

Conclusion: Adequate

#11: Description (21CFR 201.57(c)(12))

ACTICLATE® (doxycycline hyclate) Tablets and TRADENAME (doxycycline hyclate) Capsules contain doxycycline hyclate, a tetracycline class drug synthetically derived from oxytetracycline, in an immediate release formulation for oral administration.

The molecular formula of doxycycline hyclate is $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_6O \cdot H_2O$ and the molecular weight of doxycycline hyclate is 1025.87. The chemical name for doxycycline hyclate is:4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride, compound with ethyl alcohol (2:1), monohydrate.

The structural formula for doxycycline hyclate is:

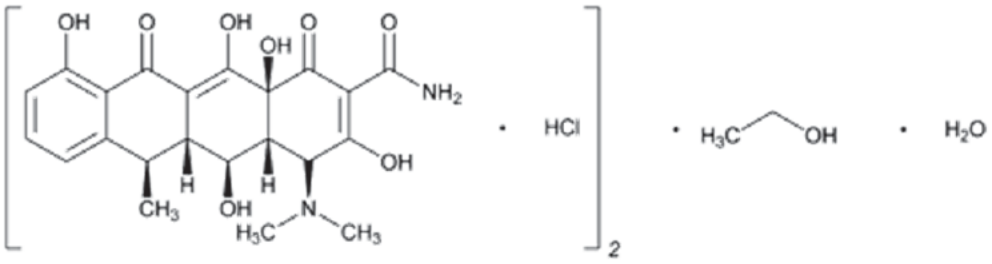

Figure 1: Structure of Doxycycline Hyclate

Doxycycline hyclate is a yellow crystalline powder soluble in water and in solutions of alkali hydroxides and carbonates.

ACTICLATE Tablet:
ACTICLATE is available as 75 mg and 150 mg tablets. Each 75 mg tablet contains 86.6 mg of doxycycline hyclate equivalent to 75 mg of doxycycline. Each 150 mg tablet contains 173.2 mg of doxycycline hyclate equivalent to 150 mg of doxycycline.

Inactive ingredients in the tablet formulation are: microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium and magnesium stearate. Film-coating contains: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, FD&C Blue #1 (75 mg Tablet), FD&C Blue #2 (150 mg Tablet) and yellow iron oxide (150 mg Tablet). ACTICLATE Tablets, 75 mg contain 0.34 mg (0.0146 mEq) of sodium. ACTICLATE Tablets, 150 mg contain 0.68 mg (0.0295 mEq) of sodium.

TRADENAME Capsule:
TRADENAME is available as 75 mg capsules. Each 75 mg capsule contains 86.6 mg of doxycycline hyclate equivalent to 75 mg of doxycycline.
Inactive ingredients in the capsule formulation are: microcrystalline cellulose, magnesium stearate, and a hard gelatin capsule which contains titanium dioxide, FD&C Red #40 and FD&C Blue #1. The capsules are printed with edible ink containing ammonium hydroxide, propylene glycol, isopropyl alcohol, N-butyl alcohol, black iron oxide, and shellac glaze in ethanol.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	yes	Adequate
Dosage form and route of administration	yes	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	yes	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	yes	Adequate
Statement of being sterile (if applicable)		Adequate
Pharmacological/ therapeutic class	yes	Adequate
Chemical name, structural formula, molecular weight	yes	Adequate
If radioactive, statement of important nuclear characteristics.		Adequate
Other important chemical or physical properties (such as pKa, solubility, or pH)	yes	Adequate

Conclusion: Adequate

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

How Supplied

ACTICLATE® (doxycycline hyclate) Tablets, 75 mg are round, convex, light-teal, film-coated, tablets with "75" debossed on one side of the tablet and "AQ101" debossed on the other. Each 75 mg tablet contains 86.6 mg of doxycycline hyclate equivalent to 75 mg of doxycycline.

Bottles of 60 tablets: NDC 16110-501-01

ACTICLATE® (doxycycline hyclate) Tablets, 150 mg are oval-shaped, convex, mossy-green, film-coated tablets. Each side of the functionally scored tablet has two parallel score lines for splitting into 3 equal portions with "A" debossed on each portion of one side of the tablet, and no debossing on the other. Each 150 mg tablet contains 173.2 mg of doxycycline hyclate equivalent to 150 mg of doxycycline.

Bottles of 60 tablets: NDC 16110-502-01

TRADENAME (doxycycline hyclate) Capsules, 75 mg, have a navy blue opaque body and cap with the inscription "AQUA 101C75" in black. Each 75 mg capsule contains 86.6 mg of doxycycline hyclate equivalent to 75 mg of doxycycline.

Bottles of 60 capsules: NDC 16110-601-01

Storage

Store at 20° to 25°C (68° to 77°F) excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Protect from light and moisture. Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	yes	Adequate
Available units (e.g., bottles of 100 tablets)	yes	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	yes	Adequate
Special handling (e.g., protect from light, do not freeze)	yes	Adequate
Storage conditions	yes	Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	yes	

Conclusion: Adequate

2. Container and Carton Labeling

1) Immediate Container Label (bottle)

(b) (4)

Reviewer's Assessment:

The following comment was forwarded to the Applicant:

Revise to add 86.6 mg in statement for doxycycline equivalency

The label was revised to add the following:

Each capsule contains doxycycline hyclate 86.6 mg equivalent to 75 mg of doxycycline

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	yes	
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	yes	
Route of administration 21.CFR 201.100(b)(3))	yes	
Net contents* (21 CFR 201.51(a))	yes	
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	NA	
Lot number per 21 CFR 201.18	yes	
Expiration date per 21 CFR 201.17	yes	
"Rx only" statement per 21 CFR 201.100(b)(1)	yes	
Storage (not required)	yes	
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	yes	
Bar Code per 21 CFR 201.25(c)(2)***	yes	
Name of manufacturer/distributor (21 CFR 201.1)	yes	
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: The proposed label was revised to include the amount of doxycycline hyclate as follows: "Each capsule contains 86.6 mg doxycycline hyclate equivalent to 75 mg doxycycline."

The remaining information provided on the container label is adequate.

2) Carton Labeling

(b) (4)

3) Blister Label:

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))	yes	
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	yes	
Net contents (21 CFR 201.51(a))	yes	
Lot number per 21 CFR 201.18	yes	
Expiration date per 21 CFR 201.17	yes	
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	NA	
Sterility Information (if applicable)	NA	
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	yes	
Storage Conditions	yes	
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	yes	
Bar Code per 21 CFR 201.25(c)(2)**	yes	
Name of manufacturer/distributor	yes	
"See package insert for dosage information" (21 CFR 201.55)	yes	
"Keep out of reach of children" (optional for Rx, required for OTC)	yes	
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))		

Conclusion:

The side panel was revised to include the amount of doxycycline hyclate as follows: "Each capsule contains 86.6 mg doxycycline hyclate equivalent to 75 mg doxycycline."

The remaining information provided on the carton label for physician's sample is adequate.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: Information provided for the package insert, carton and container from product quality perspective is satisfactory.

Shrikant Pagay, March 21, 2016

Secondary Review Comments and Concurrence:

I concur
Dorota Matecka, Ph.D.; CMC Lead; Branch III; Division of New Drug Products I
March 25, 2016

II. List of Deficiencies To Be Communicated

N/A

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

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	Factors identified in CQA will not affect the assay or stability (b) (4)	Acceptable	Changes in formulation or process should be assessed according to SUPAC Guidance
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	Adequate for solid oral dosage form; also, microbial limits included in both release and stability testing	Acceptable	
Dissolution	Formulation Raw materials Process parameters Scale/equipment	L	Characteristics of the drug substance (high solubility, high permeability)	Acceptable	Changes in formulation or process should be assessed according to SUPAC Guidance

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 9/11/2015

TO: Division of Anti-Infective Products
Office of Antimicrobial Products

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 208253

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Novum Pharmaceutical Research Services	3760 Pecos McLeod, Las Vegas, NV
Analytical		(b) (4)

Nicola M. Nicol -S

Digitally signed by Nicola M. Nicol -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001347020, cn=Nicola M. Nicol -S
Date: 2015.09.11 13:18:51 -04'00'

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/s/

NICOLA M FENTY-STEWART
09/11/2015