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RESEARCH**

APPLICATION NUMBER:

205931Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 205931	Reviewer: Minerva Hughes, Ph.D.	
Submission Date:	25 September 2013		
Division:	Division of Anti-infective Products	Team Leader: Angelica Dorantes, Ph.D.	
		Acting Supervisor: Richard Lostritto, Ph.D.	
Sponsor:	Aqua Pharmaceuticals	Secondary Reviewer: Team Leader	
Trade Name:	Acticlate	Date Assigned:	1 Oct 2013
		Primary Review:	20 June 2014
		PDUFA Date:	25 July 2014
Generic Name:	Doxycycline hyclate	Date of Review:	10 June 2014
Indication:	Various microbial infections	Type of Submission: 505(b)(2) (Listed Drug – NDA 050533, Vibra-Tabs)	
Dosage Form/Strengths	Oral Tablets/ 75 mg and 150 mg		
Route of Administration	Oral		

Biopharmaceutics Review Focus:

- 505(b)(2) Bioequivalence Study under fasted conditions,
- Biowaiver Request,
- Dissolution Method and Acceptance Criterion

EXECUTIVE SUMMARY

NDA 205931 seeks approval under Section 505(b)(2) for two new strengths of Doxycycline Hyclate Tablets, 75 mg and 150 mg, with reliance on the Agency's previous findings of efficacy and safety for NDA 050533 (Vibra-Tabs). The proposed new strengths are intended to provide flexibility and ease of dosing and fall within the approved dosing regimens for the approved listed drug. The Applicant is seeking approval of the 75 mg and 150 mg dosage strengths for the same indications as the currently approved listed drug.

Doxycycline is a broad-spectrum antibiotic that is synthetically derived from oxytetracycline and available as doxycycline hyclate (doxycycline hydrochloride hemiethanolate hemihydrate) capsules and tablets for oral administration. The proposed 75 mg tablet product is unscored and the 150 mg tablet is a dual-scored product. The finished tablet includes a blend of the active and the following excipients: microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium, magnesium stearate, and (b) (4) film coating.

The Applicant completed two pharmacokinetic studies (Study 11060203 and Study 11060204) to establish a clinical bridge to the Agency's findings of efficacy and safety for the listed drug (i.e., 505(b)(2) NDA requirements) and to evaluate the effect of food on

systemic absorption.

- **Study 11060203** – Evaluated the comparative bioavailability of the proposed new drug product (150 mg tablet, 300 mg dose) relative to an equivalent dose of the reference product under fasted conditions.

It is noted that a generic doxycycline hyclate product approved under ANDA 065095 by West-ward Pharmaceuticals was used as the reference listed drug product in this study.

- **Study 11060204** – Evaluated the comparative bioavailability of the proposed new drug product (150 mg tablet) under fasted and fed conditions to evaluate the food effect.

It is noted that this study was reviewed by the Office of Clinical Pharmacology.

A third pharmacokinetic study was submitted in support of a biowaiver request for the 75 mg and dual-scored 150 mg tablet. The pivotal bioequivalence study was conducted with a 150 mg unscored tablet, and additional information was needed to support the requested biowaiver.

-  (b) (4)

SUMMARY OF IMPORTANT BIOPHARMACEUTICS FINDINGS

- The results from Study 11060203 demonstrated acceptable bioequivalence between the listed drug product and the 150 mg unscored tablets.
- A waiver of the requirement for bioavailability/bioequivalence data to support approval of the proposed lower strength (75 mg tablet) and dual-scored 150 mg tablet is granted.
- The following proposed dissolution method and acceptance criterion are acceptable for regulatory purposes.

Parameter	Criterion
Apparatus	USP 2 (Paddles)
Medium	900 mL purified water
Paddle Rotation	75 rpm
Temperature	37 °C
Assay	UV/Vis
Acceptance Criterion	$Q = \frac{(b)}{(d)}$ % at 30 min

- The proposed pharmacokinetic information is the label is acceptable from the Biopharmaceutics perspective.

CONSULTS

An OSI inspection was completed for the pivotal bioequivalence testing and analytical facilities (DARRTS 17 April 2014 report by Dr. Gopa Biswas). The inspection team found the clinical and analytical data acceptable.

PHASE 4 COMMITMENTS

None.

RECOMMENDATION

NDA 205931 for Doxycycline Tablets is recommended for approval from the Biopharmaceutics perspective.

Administrative Block {See Appended Electronic Signature Page}

Minerva Hughes, Ph.D.

Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.

Biopharmaceutics Team Leader
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Table of Contents

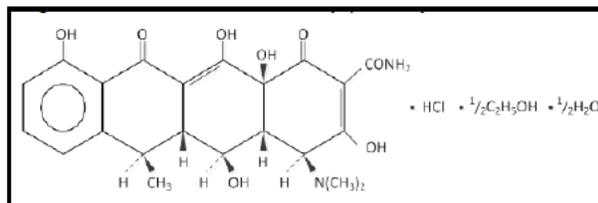
1	GENERAL ATTRIBUTES	5
2	GENERAL BIOPHARMACEUTICS (IN VIVO)	7
3	GENERAL BIOPHARMACEUTICS (IN VITRO).....	13
4	DISSOLUTION APPLICATIONS	19
5	LABELING	26
6	INFORMATION REQUESTS DURING THE REVIEW	26

BIOPHARMACEUTICS REVIEW

1 GENERAL ATTRIBUTES

1.1 *What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?*

The drug substance is doxycycline hyclate (USAN) or doxycycline hydrochloride (INN), a synthetically derived oxytetracycline with the following chemical structure and formulation.



Molecular formula: $C_{22}H_{24}N_2O_8 \cdot HCl \cdot \frac{1}{2}C_2H_6O \cdot \frac{1}{2}H_2O$

The drug substance is freely soluble in water and in methanol, sparingly soluble in ethanol (96%), practically insoluble in chloroform and ether, and readily dissolves in aqueous solutions of alkali, hydroxides and carbonates.

No polymorphs of doxycycline hyclate have been reported.

The Applicant is proposing to market two tablet strengths, Doxycycline Hyclate Tablets USP 75 mg and 150 mg, to provide flexibility and ease of dosing. The proposed tablet formulations are provided in the table below.

Table 2.3.P.1-1: Qualitative and Quantitative Composition of Doxycycline Hyclate Tablets USP, 75 mg and 150 mg

Ingredient	Standard	Function	Quantity (mg/Tablet)	
			75 mg	150 mg
Cores				
Doxycycline Hyclate	USP	Active	(b) (4)	
Microcrystalline Cellulose	NF	(b) (4)		
Sodium Lauryl Sulfate	NF			
Croscarmellose Sodium	NF			
Magnesium Stearate	NF			
TOTAL				
Film Coating				
(b) (4)				
TOTAL TABLET WEIGHT			166.76	333.51
(b) (4)				

The 150 mg tablet is a dual-scored tablet (i.e., 3 X 50 mg doses) and the 75 mg tablet is unscored.

1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Doxycycline is a broad-spectrum antibiotic. The proposed microbiology labeling reflects the most recent prescribing information for doxycycline hyclate (Vibramycin, doxycycline hyclate). Labeling was also updated to align with the DORYX (doxycycline hyclate delayed release) tablet label.

Doxycycline is indicated for:

- Rickettsial infections
- Sexually transmitted infections
- Respiratory tract infections
- Specific bacterial infections
- Ophthalmic infections
- Anthrax, including inhalational anthrax (post-exposure)
- Alternative treatment for selected infections when penicillin is contraindicated
- Adjunctive therapy in acute intestinal amebiasis and severe acne
- Prophylaxis of malaria

1.3 What are the proposed dosage(s) and route(s) of administration?

The doxycycline tablets are intended for oral administration. The dose is adjusted for the amount of doxycycline (the active moiety) and intended for the following dosage regimen:

Adults – usually, 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg daily. The dosing regimen may be adjusted based on the infection as per the full dosage and administration information in the label.

Children (8 years and above) - weighing 45 kg or less is 4.4 mg per kg of body weight divided into two doses on the first day of treatment, followed by 2.2 mg per kg of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections, up to 4.4 mg per kg of body weight may be used. For children over 45 kg, the usual adult dose should be used.

1.4 Is there any information on BCS classification? What claim does the applicant make based on BCS classification? What data are available to support this claim?

The Applicant notes that Doxycycline hyclate is a BCS Class 1 drug substance (i.e., high solubility/high permeability) with a wide therapeutic range. The absolute bioavailability of doxycycline administered orally at a dose of 100 to 200 mg is 90% to 100%. Several literature references were provided in support of the BCS Class 1 claim. In particular, reference is made to the Jantratid et al's commentary *Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Doxycycline Hyclate*, which compiled the published literature on the drug substance's physicochemical properties and

pharmacokinetics. In addition, the article also includes a survey of immediate release formulations marketed in Germany, Denmark, Finland, France, the Netherlands, Spain, the United Kingdom, and the United States and bioequivalence (BE) study results.

However, referencing the FDA BCS I database, doxycycline hyclate is not listed as a BCS I drug.

Information on the BCS classification was provided to support a biowaiver request for the 75 mg tablet and 150 mg dual-scored tablet (the pivotal BE study used the unscored 150 mg tablet). However, this information is specific to providing an understanding of the doxycycline kinetics from a risk-based perspective and is not presented as an application of *FDA Guidance for Industry – Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*. Such an approach is not applicable for this NDA because the requested waiver is for a change relative to the 150 mg unscored tablet (not intended for market), which does not meet BCS Class I criteria for rapidly dissolving (or >85% in 30 minutes).

The Applicant has not requested a BCS I designation for their product and the information was not referred to the FDA BCS committee for review given the purpose of the data.

See Section 4.2 for additional discussion on the biowaiver request.

2 GENERAL BIOPHARMACEUTICS (IN VIVO)

2.1 CLINICAL STUDIES

2.1.1 *What are the design features of the biopharmaceutics studies used to support the proposed to-be-marketed formulation? Summary of individual study reviews provided.*

The Applicant completed two pharmacokinetic (bioequivalence) studies (Study 11060203 and Study 11060204) to provide a clinical bridge to the Agency's findings of efficacy and safety for the listed drug, support the 505(b)(2) NDA for the new dosage strengths and evaluate the effect of food on systemic absorption.

Study 11060203: This study was a randomized, single-dose, two-treatment, two-period, two-sequence, crossover study conducted in 26 healthy volunteers. In each study period, a single 300 mg dose of doxycycline hyclate tablets was administered to subjects following an overnight fast of at least 10 hours. The subjects received Aqua's Doxycycline Hyclate Tablets USP (2 x 150 mg tablets) and West-ward's Doxycycline Hyclate Tablets USP (3 x 100 mg tablets) according to the randomization schedule.

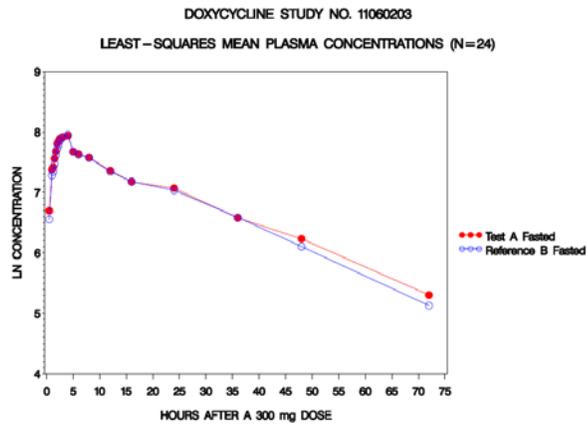
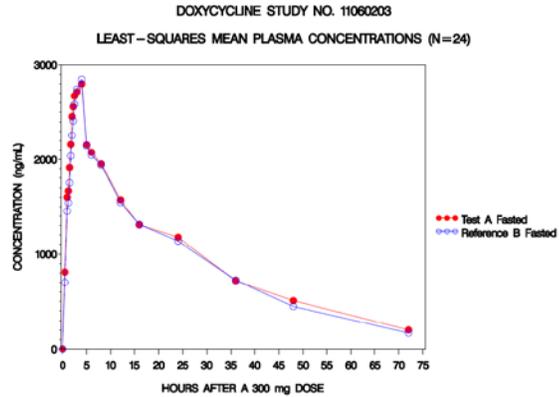
A brief synopsis of Study 11030203 is as follows.

STUDY 11030203 (FASTING BE)	
STUDY TITLE:	A Study to Evaluate the Relative Bioavailability of a New Formulation of Doxycycline Hyclate Tablets 150 mg (AQUA Pharmaceuticals) compared to an Equal Dose of Doxycycline Hyclate Tablets, USP 100 mg (Manufactured by: West-ward Pharmaceutical Corp.) in Healthy Volunteers under Fasted

STUDY 11030203 (FASTING BE)	
	Conditions
DESIGN:	Single-dose, randomized, two-treatment, two-period, two-sequence, crossover study, under fasting conditions.
METHODOLOGY:	<p>The test formulation was doxycycline hyclate tablets, 150 mg (AQUA Pharmaceuticals, Lot 1104146) and the reference formulation was doxycycline hyclate tablets, USP 100 mg (manufactured by: West-ward Pharmaceutical Corp., Control No. 69358B, Exp Sep 2013). Subjects received the test product as 2 x 150 mg tablets in one of the study periods and the reference product as 3 x 100 mg tablets in the other study period, according to the randomization schedule. Subjects were confined at the clinical facility from at least 10 hours before dosing until after the 24 hour blood collection and returned to the clinical facility for pharmacokinetic sampling at 36, 48 and 72 hours. The interval between doses was 14 days.</p> <p>Statistical analysis using average bioequivalence methodology was performed to evaluate the bioavailability of the test formulation relative to that of the reference product under fasted conditions.</p>
NUMBER OF SUBJECTS:	A total of 26 healthy, adult subjects were enrolled, and 24 subjects completed the study.
SUMMARY OF RESULTS	<p>Twenty (20) blood samples were collected from each subject during each period of the study: prior to dosing, then at 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36*, 48* and 72* hours after dosing (* return samples) for analysis of plasma doxycycline concentrations. The analytical data were used to calculate the pharmacokinetic parameters: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, Kel and T_{1/2}. The t in AUC_{0-t} is the time at which the last measurable concentration was recorded. Confidence intervals (90%) for the comparison of test and reference area and peak results were constructed to test two, one-sided hypotheses at the $\alpha = 0.05$ level of significance.</p> <p>Twenty-six (26) subjects were dosed in Period I, and twenty-four (24) subjects completed both periods of the study. Subjects 15 (b) (6) and 24 (b) (6) did not complete both periods of the study and therefore did not have plasma samples sent for bioanalysis.</p> <p>Mean plasma concentration versus time plots (linear and ln-linear) are presented below for doxycycline.</p>

STUDY 11030203 (FASTING BE)

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The confidence intervals are presented for the ratio of the test-to-reference treatment means and the geometric mean ratios (obtained from logarithmic transformation) for AUC0-t, AUC 0-inf, and Cmax.

Parameter	Test A	Reference B	Ratio	CI**	Intra-Subject %CV
AUC0-t (ng·hr/mL)	63406.95	61658.57	1.0284	0.9251 - 1.1432	21.6027
AUC0-inf (ng·hr/mL)	70192.79	68169.99	1.0297	0.9122 - 1.1622	24.1870
Cmax (ng/mL)	2897.18	2856.30	1.0143	0.9219 - 1.1160	19.4510

** Equivalent if confidence intervals are within 0.8000-1.2500 (80.00 to 125.00%) limits.
* N = 23 for AUC0-inf for Test A.
Test A: 2 x 150 mg Doxycycline Hyclate Tablets (AQUA Pharmaceuticals)
Reference B: 3 x 100 mg Doxycycline Hyclate Tablets, USP (manufactured by: West-ward Pharmaceutical Corp.)

SUMMARY OF SAFETY

A total of sixty-one (61) adverse events (1 prior to dosing in Period I with Reference B, 34 in Test A, 26 in Reference B) were reported by 21 of the 26 subjects who participated in this study. All reported adverse events were considered “mild”. Sixty (60) adverse events resolved spontaneously prior to study completion and one (1) had not resolved prior to study completion. The most frequently reported adverse event for both the test and reference products was nausea (Test A: 12 subjects; Reference B: 9 subjects). See attached supplemental tables and figures for a listing of adverse events.

Reviewer’s Evaluation: ADEQUATE

The study design was adequate to evaluate bioequivalence. There were no protocol deviations during the study. According to the study protocol, subjects who experienced emesis within 4 hours (based on approximately 2 x the anticipated Tmax of around 1.5-2 hours for doxycycline) of dosing were withdrawn from the study. The two (2) subjects not included in the analysis, Subjects 15 (b) (6) and 24 (b) (6), experienced emesis within this timeframe and were discontinued from further study participation. Pharmacokinetic sampling was not continued for these patients and the reason for excluding is acceptable. Although the Applicant notes that data were collected and analyzed for the remaining 24 subjects, the analysis for the Test A group included only 23 subjects for AUC0-inf because the terminal phase was not well characterized for one subject.

An independent assessment of the pharmacokinetic data demonstrated acceptable compliance with the standard bioequivalence criteria.

Reviewer’s BE Reanalysis Results (all subjects):

Parameter	Test	Reference	Ratio (Geometric)	90% CI
Cmax	2897.18	2856.30	101.43	92.19-111.60
AUCt	63406.95	61658.57	102.84	92.50-114.32
AUCi	69941.26	68169.99	102.60	91.07-115.59

A reanalysis of the data excluding all of Subject 16’s data (i.e., subject with incomplete AUCi information) showed no impact on the study’s conclusions.

It is noted that a generic doxycycline hyclate product approved under ANDA 65095 was used as the reference listed drug product in the pivotal BE study. However, the listed drug for the purposes of this 505(b)2 application is Vibra-Tabs NDA 50533. The innovator product is no longer on the market and it was agreed previously by FDA that the selected generic drug product would provide an acceptable bridge to the innovator NDA in support of the proposed 505(b)2 application. It is also noted that the generic doxycycline hyclate product (ANDA 065095) used for this NDA is also the reference listed drug for ANDA applications.

Study 11060204, was a randomized, single 150 mg dose, two-treatment, two-period, two-sequence, crossover study evaluating the effect of food on drug absorption. This food-effect study was reviewed by Dr. Ryan Owen, Office of Clinical Pharmacology and is not covered in this review. Refer to the link below for Dr. Owen’s ClinPharm review. <http://darrrts.fda.gov:9602/darrrts/ViewDocument?documentId=090140af80334765>

2.1.2 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

Not applicable. Bioequivalence was adequately demonstrated under fasting conditions.

2.1.3 *What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?*

The food effect study was reviewed by Dr. Ryan Owen, Office of Clinical Pharmacology, as per the current division of review responsibilities between the Biopharmaceutics and Clinical Pharmacology review staff. The results of this study showed that pharmacokinetics of doxycycline was altered when administered with food. Please refer to Dr. Owen's review for full details on the food effect study (Study 11060204) that was submitted in support of NDA 205931.

2.2 BIOANALYTICAL METHOD SECTION

2.2.1 *How are the active moieties and/or metabolites identified and measured in the plasma in the biopharmaceutics studies?*

Doxycycline is the only analyte measured in the bioequivalence study. Plasma samples (100 µL aliquots) were diluted and treated with acetonitrile, followed by 1.0% formic acid to precipitate proteins. The clarified supernatant was then analyzed by LC/MS/MS. Oxytetracycline was used as an internal standard for analysis only.

2.2.2 *What bioanalytical methods are used to assess concentrations?*

An LC-MS/MS method (positive electrospray ionization tandem mass spectrometry) was developed for the analysis of doxycycline in human EDTA plasma samples. The method, CTS-CHROM-SOP-318 was adequately validated for its intended use.

2.2.2.1 *What is the range of the standard curve? How does it relate to the requirements for the clinical studies? What curve fitting techniques are used? What are the lower and upper limits of quantification (LLOQ/ULOQ, and assay validation parameter: accuracy, precision, selectivity, sample stability, etc.?*

The method validation was performed over a range of 100 – 5000 ng/mL. The slope, intercept, and correlation coefficient (r) were determined by a 1/concentration weighted regression using a linear model.

The validation includes the following experiments: linearity, weighting scheme, LLOQ, intra-run and inter-run precision and accuracy, recovery, applicability of dilutions, selectivity, interferences, assay specific interferences, suppression / matrix effects, instrument precision, carry-over, robustness, hemolysis, room temperature stability, refrigerated stability, freeze-thaw stability, frozen stability, whole blood stability, processed sample stability, and processed batch stability.

A tabular summary of the validation parameters is provided below.

	Data System K
Analyte	Doxycycline
Internal Standard (IS)	Oxytetracycline
Method Description	Protein precipitation with acetonitrile and 1% formic acid dilution and reverse phase UPLC-MS/MS analysis.
Limit of Quantitation, Precision, Accuracy	100.00 ng/mL, 4.9%, 94.9%
Average Recovery of Drug (%)	88.5
Average Recovery of IS (%)	84.2
Standard Curve Concentrations (ng/mL)	100.00 – 5000.00
QC Concentrations (ng/mL)	300.00, 800.00, 4000.00
QC Intra-Run Precision Range (%)	4.5, 2.9, 3.1
QC Intra-Run Accuracy Range (%)	97.3, 100.3, 99.6
QC Inter-Run Precision Range (%)	5.0, 9.3, 6.3
QC Inter-Run Accuracy Range (%)	97.2, 104.4, 101.5
4°C Temperature	24 hours
Ambient Temperature	24 hours
Stock Stability @ 4°C	213 days
Auto Sampler @ 10°C Processed Stability	4 days
Freeze-Thaw Stability	3 cycles
Frozen Stability -20°C	5 days
Frozen Stability -80°C	5 days
Dilution Integrity 5-Fold and 10-Fold (% Accuracy)	104.3, 96.3
Selectivity	No interfering peaks noted in blank plasma samples
Instrument Precision (%)	1.7

The quantitation range used for validation is appropriate for analyzing the bioequivalence samples.

2.2.2.2 What is the QC sample plan?

A bioanalytical run is acceptable if two-thirds (2/3) of the total number of controls are acceptable and at least one-half (1/2) of the QCs at each level (low, mid, high) are acceptable. The analyte to internal standard response ratio in at least 2/3 of the zero blanks (matrix blank containing internal standard) may not exceed 20% of the mean response ratio in the accepted LLOQ calibration standard(s).

During the conduct of the study, zero (0) plasma samples for doxycycline were re-analyzed for pharmacokinetic (out-of-trend) reasons and four (4) samples were re-analyzed due to failure of an acceptance criteria due to an incorrect injection volume.

Repeat Analysis, Doxycycline

Accession Number	Subject ID	Period, Time Point	Run ID	Concentration (ng/mL)	Reason for Re-analysis	Reported Result (ng/mL)	Reason for Reported Result
F4502198	008	P2, 24 HR	5	960.1	1	917.1	a
			11	917.1	-		
F4502203	008	P2, 36 HR	5	524.2	1	534.4	a
			11	534.4	-		
F4502209	008	P2, 48 HR	5	437.1	1	441.4	a
			11	441.4	-		
F4502218	008	P2, 72 HR	5	343.7	1	349.0	a
			11	349.0	-		

Reason for Re-analysis:

1. Fails Internal Standard acceptance criterion due to incorrect injection volume.

Reason for Reported Result:

- a. The initial value was invalid and not reportable due to being an OOS result. The re-analysis result met all acceptance criteria and was reported.

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Additionally, three plasma sample were re-analyzed by dilution due to being greater than the assay's validated linear range (>ULOQ).

2.2.2.3 Are the Inspection reports of the BE study acceptable?

The clinical testing facilities and bioanalytical portion of the study were inspected and reviewed by the Office of Scientific investigations (OSI) and found acceptable. Refer to the 17 April 2014 review in DARRTS by Dr. Gopa Biswas in the link below.

<http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af8032a4f2>

3 GENERAL BIOPHARMACEUTICS (IN VITRO)

3.1 DISSOLUTION INFORMATION

3.2 DISSOLUTION METHOD

3.2.1 What is the proposed dissolution method?

The Applicant proposed to test the proposed doxycycline hyclate tablets according to the USP monograph procedures. The proposed dissolution method is as follows.

Parameter	Criterion
Apparatus	USP 2 (Paddles)
Medium	900 mL purified water
Paddle Rotation	75 rpm
Temperature	37 °C
Assay	UV/Vis

3.2.2 What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?

The method development report TTP-ARV-M0032 includes a summary of the verification testing to support the use of the USP method for the proposed tablet.

Medium selection



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(b) (4)



The Applicant also refers to the test methods used in the Watson Pharmaceuticals approved ANDA 62421 for doxycycline hyclate tablets, 100 mg. A valid letter of authorization was provided for reference to the CMC and bioavailability information in ANDA 62421 in support of NDA 205931.

The tablet formulation under this NDA was licensed from Watson Pharmaceuticals. No changes were made to the formulation (b) (4)

(b) (4) However, in response to the Agency's expressed concern over the intended use of the proposed 150 mg dosage strength, the Applicant agreed to develop dual-scored 150 mg tablets in order to match currently marketed 150 mg doxycycline products.

The (b) (4) information under ANDA 62421 was confirmed by this Reviewer as (b) (4) to the subject NDA's product.

3.2.3 What data are available to support the discriminating power of the method?

A formal method discriminating study was not completed. (b) (4)

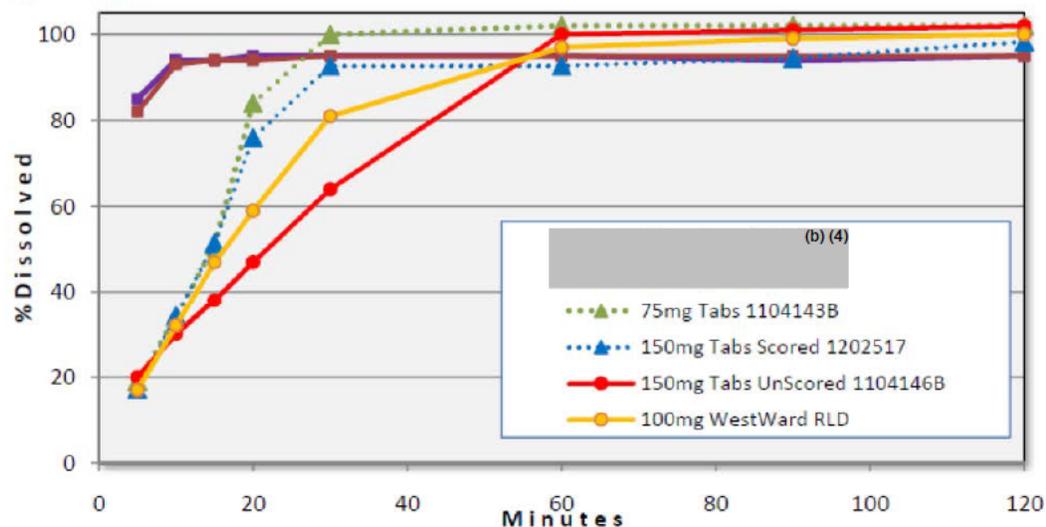


Table 1.12.15-12: Core Tablet Hardness Data

Product	Target Hardness
Unscored 150 mg Tablets	(b) (4)
Dual-Scored 150 mg Tablets	(b) (4)
75 mg Tablets	(b) (4)

The mean dissolution profiles are illustrated below for the 150 mg scored and unscored tablets, 100 mg RLD tablet (BE reference), and 75 mg tablet.

A: Water



(b) (4)

3.2.4 What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?

The dissolution assay method was validated with respect to linearity, accuracy/recovery, precision, selectivity, filter use, and robustness. The method and validation data are the same as approved by FDA under the Watson ANDA; however, the acceptability of these data to support this NDA will be addressed by the assigned CMC Reviewer, Dr. Shrikant Pagay.

3.2.5 Is the proposed dissolution method biorelevant? What data are available to support this claim?

No, the dissolution method is NOT biorelevant.

3.2.6 Is the proposed method acceptable? If not, what are the deficiencies?

Yes, the proposed method is acceptable. Using the USP monograph as a starting point, the Applicant verified that the selected test conditions would be appropriate for their product given the manufacturing changes (e.g., tablet scoring) employed. The proposed method is also the same method previously approved for the 100 mg RLD tablet, (b) (4). The proposed

dissolution method (b) (4) an important attribute of the new tablets. Although reference was made to a BCS 1 designation for the drug substance, the product's dissolution data do not correlate with rapid dissolution to support a BCS 1 claim for the finished product.

3.3 ACCEPTANCE CRITERIA

3.3.1 *What are the proposed dissolution acceptance criteria for this product?*

The proposed dissolution acceptance criteria are summarized below.

Dissolution (UV) USP <711> Apparatus 2 (paddles; height 4.5±0.5 cm) 75 RPM 900 mL of Water	USP, Test 1	NLT (b) (4) (Q) of the labeled amount of doxycycline is dissolved in (b) (4) minutes. NLT (b) (4) (Q) of the labeled amount of doxycycline is dissolved in (b) (4) minutes.
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3.3.2 *What data are available to support the criteria?*

The approved criteria for the referenced Watson ANDA were selected without modification. These criteria include the USP acceptance criterion of $Q = (b) (4)$ in 90 minutes and an FDA criterion of $Q = (b) (4) \%$ in (b) (4) minutes.

3.3.3 *Is the setting of the dissolution acceptance criteria based on data from clinical and registration batches?*

No, the criteria were based on what was used for the referenced ANDA.

3.3.4 *Are mean (n =12) dissolution profile data used for the setting of the acceptance criteria?*

No, the criteria were based on what was used for the referenced ANDA.

3.3.5 *Are the acceptance criteria acceptable? If not, what are the recommended criteria?*

The proposed acceptance criteria of NLT (b) (4) % (Q) at (b) (4) minutes and NLT (b) (4) (Q) at (b) (4) minutes are not supported by the dissolution data. The acceptance criteria are based on the approved Watson ANDA specification without any justification. Referencing ANDA 62421, this Reviewer notes that the dissolution criteria include an FDA criterion (i.e., NLT (b) (4) % (Q)) of unknown origin and the USP monograph criterion (NLT 85% (Q)). However, the mean dissolution data indicate that neither criterion is data driven and aligned with the capability of the manufacturing process to provide for meaningful quality control.

Reviewer's Recommended Criterion:

This Reviewer recommendation was made based on the available dissolution data for the to-be-marketed products.

Stability data are available for three batches each of the unscored 75 mg and 150 mg strength tablets through 12 months storage under long-term conditions (25° ± 2°C/60% ± 5% RH) and through 6 months storage under accelerated conditions (40°

$\pm 2^{\circ}\text{C}/75\% \pm 5\%$ RH in the intended primary packaging. In addition, data are submitted for two batches of 150 mg scored tablets after storage for 6 months under long-term and accelerated conditions in the primary packaging. Multi-point dissolution information was collected after initiating the stability study and data were submitted for the 6 month pull and subsequent pull points (*see the 11 April 2014 NDA Amendment*).

Regarding the physician sample pack, stability data are provided for the unscored 75 mg strength and 150 mg strength tablets (b) (4) stored under long-term ($25^{\circ} \pm 2^{\circ}\text{C}/60\% \pm 5\%$ RH) and intermediate conditions ($30^{\circ} \pm 2^{\circ}\text{C}/65\% \pm 5\%$ RH) for 12 months and accelerated ($40^{\circ} \pm 2^{\circ}\text{C}/75\% \pm 5\%$ RH) conditions for 6 months. In addition, stability data are provided for the unscored 75 mg strength and dual-scored 150 mg strength tablets packaged in (b) (4) blisters and in (b) (4) HDPE bottles stored under long-term and accelerated conditions for 6 months. The (b) (4) were the initial packaging, but after one month of storage under accelerated conditions, the tablets changed color and (b) (4) results were elevated. Consequently, (b) (4) blisters were implemented with a (b) (4) as an alternative if there is a supply problem with the blister material. Multi-point dissolution profile was included in the NDA for the later stability pulls under the 11 April 2014 Amendment.

Overall, the mean dissolution profile across all lots intended for marketing using the primary packaging, (b) (4) blister or alternate bottle configuration was (b) (4) at 30 minutes. A result that is consistent with an acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 30 minutes. Further, a decrease in mean dissolution at 30 minutes was noted by this Reviewer (b) (4), but not the later time points, suggesting better sensitivity at 30 minutes to detect product quality issues. This Reviewer does not consider it appropriate to use the (b) (4) dissolution results to widen the limits as the Sponsor implies; rather, the results indicate instability that should be detectable with appropriate controls.

The 30 minute sampling time point is also most correlated to (b) (4) as discussed in Section 3.2 above, which is an important tablet quality attribute. The (b) (4) used for the dual-scored 150 mg tablets was optimized to produce a durable tablet suitable for commercial distribution that would allow reproducible, consistent dosing from each of the split portions of the tablet. A consequence of producing a tablet with two functional scores was that the dual-scored 150 mg tablets have (b) (4) than the unscored 150 mg tablet. The (b) (4) is an important attribute of the dual-scored tablet.

It is acknowledged that the dissolution data for the 150 mg unscored tablets do not support an acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 30 minutes, rather $Q = \frac{(b)}{(4)}\%$ at $\frac{(b)}{(4)}$ minutes, and this was the product used in the BE study. However, per the direction of Biopharmaceutics leadership, the optimal dissolution acceptance criterion should be based on the performance of the to-be-marketed products, and from a manufacturing perspective, the different tablet strengths have different physical properties (e.g., size, scoring, etc.) that are relevant for overall finished quality. The discriminating ability of a dissolution method is not only determined by the dissolution method settings but also by the selected specification-sampling time point and specification value.

Therefore, in this instance, it was considered appropriate to define optimal criteria for commercial product based on the product intended for commercial distribution.

FDA's recommendation of Q = (b)(4)% at 30 minutes was accepted by the Applicant in the 6 May 2014 NDA Amendment.

A meeting was held with the Applicant on 29 April 2014 to discuss the recommended dissolution acceptance criterion issue. At the meeting, FDA indicated that product development is an ongoing process and any concerns regarding the dissolution acceptance criterion post approval should be handled through the NDA supplement process.

4 DISSOLUTION APPLICATIONS

4.1 FORMULATION CHANGES

4.1.1 *Is the to-be-marketed formulation the same as the formulation used in the pivotal clinical or bioequivalence studies? If not, is dissolution used to bridge the data?*

The to-be-marketed formulation is the same as the formulation used in the pivotal bioequivalence studies; however, to accommodate the score line on the to-be marketed 150 mg scored tablet, the manufacturing equipment and process was adjusted. Further, the 75 mg strength was not evaluated in the BE study. Comparative dissolution data are provided for all strengths and a waiver of BA/BE studies requested (see Section 4.2).

4.1.2 *Is the finished tablet scored? Do the dissolution data comparing the split versus whole tablet support tablet splitting?*

Yes, the 150 mg finished tablet is dual scored (i.e., 3 x 50 mg). A 90- day tablet splitting stability study was completed, which included an assessment of dissolution on split tablet portions (50 and 100 mg) by both mechanical and manual splitting techniques (180 tablets, white HDPE Bottle with (b)(4) Cap, stored at 25°C/60% RH).

The mean dissolution after 30 minutes at release is as follows.



Only the 50 mg data are provided; however, from the biopharmaceutics perspective, this represents a worst case scenario. The 100 mg split portion is not expected to perform any worse than the 50 mg split portion or the whole tablet on stability.

The dissolution data show a slowing of the dissolution rate for the 50 mg split portion after 90 days storage. The mean dissolution at 30 minutes is >10% reduced and the overall profiles are not similar; similarity f2 metric is 38, as determined by this Reviewer. However, adequate stability is considered demonstrated based on performance relative to the regulatory specification of $Q = \frac{(b)}{(4)}\%$ at 30 minutes and not profile similarity across time points for an immediate release dosage form. Thus, the tablet splitting data are supportive of splitting from the biopharmaceutics perspective.

4.2 BIOWAIVERS

4.2.1 *Is there a waiver request for in vivo BA or BE data (Biowaiver)? If yes, what is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s? Is the biowaiver request acceptable?*

Yes, the Applicant is requesting a waiver of the requirement to conduct bioequivalence studies on the 75 mg and 150 mg dual-scored tablet. The pivotal bioequivalence study was completed using a 150 mg unscored tablet, which is not intended for marketing.

All tablet strengths are manufactured from (b) (4). Initially, the Applicant intended to support the biowaiver request based on in vitro dissolution similarity. However, the results from the dissolution profiles using four media (water, (b) (4)) failed to demonstrate acceptable similarity using either the similarity (f2) metric or multivariate analysis (see appended tables).

The Applicant's request for a biowaiver is supported by the following:

- *Comparable pharmacokinetics (PK) from clinical studies conducted by the Applicant*

(b) (4)

Table 1.12.15-1: Statistical Analyses Based on LS Geometric Means from Ln-Transformed Capsules Study Values (N=22)

Parameter	(b) (4)	Vibramycin [®] Capsules	Ratio	90% Confidence Interval		%CV (b) (4)
				Lower Limit	Upper Limit	
AUC _{0-t} (ng·hr/mL)	57155	55588	1.028	0.950	1.113	15.3
AUC _{0-inf} (ng·hr/mL)	63017	61526	1.024	0.940	1.116	16.5
C _{max} (ng/mL)	2756	2734	1.008	0.938	1.084	13.9

Table 1.12.15-2: Statistical Analyses Based on LS Geometric Means from Ln-Transformed Tablets Study Values (N=24)

Parameter	Aqua Tablets	West-ward Tablets	Ratio	90% Confidence Interval		%CV (b) (4)
				Lower Limit	Upper Limit	
AUC _{0-t} (ng·hr/mL)	63407	61659	1.028	0.925	1.143	21.6
AUC _{0-inf} (ng·hr/mL)	70193	68170	1.030	0.912	1.162	24.2
C _{max} (ng/mL)	2897	2856	1.014	0.922	1.116	19.5

The ln-transformed data are summarized in this review for reference; however, cross study comparisons were completed for the mean and median PK data. The capsules to tablet ratio results are illustrated below.

Table 1.12.15-6: Capsule-to-Tablet Ratios for (b) (4) and Reference Products

Pharmacokinetic Parameter	(b) (4) Capsules/Tablets)	Reference (Capsules/Tablets)
	<i>LS Geometric Means</i>	
AUC _{0-t}	0.901	0.902
AUC _{0-inf}	0.898	0.903
C _{max}	0.951	0.957
<i>LS Arithmetic Means</i>		
AUC _{0-t}	0.883	0.899
AUC _{0-inf}	0.876	0.896
C _{max}	0.931	0.938
<i>Medians</i>		
AUC _{0-t}	0.938	0.901
AUC _{0-inf}	0.925	0.950
C _{max}	0.937	0.950

- *Comparable pharmacokinetics of marketed doxycycline dosage forms*

Table 1.12.15-7: Comparison of the Pharmacokinetics of Different Doxycycline Hyclate Products

Product	Dosage Form	Strength	Dose	N	Dose-Adjusted to 300 mg		
					AUC _{0-inf} (ng-hr/mL) ^a	C _{max} (ng/mL)	T _{max} (hours)
Aqua	IR Tablet Unscored	150	300 mg	24	73027	3044	3.0
West-ward	IR Tablet (b) (4)	100	300 mg	24	70475	2979	3.0
		150	300 mg	22	64019	2806	2.5
Vibramycin [®]	IR Capsule	100	300 mg	22	63116	2793	2.5
Oracea [®] IR/DR	MR Capsule	40	40 mg	17	59715	3923	2.0
			40 mg	13	-	4395	2.5
			40 mg	30	69203	3825	3.0
DORYX [®]	DR Tablet	100	100 mg	15	63108	3333	2.6
	DR Capsule	100	100 mg	15	60486	3051	2.4

IR: Immediate Release
DR: Delayed Release
MR: Modified Release
^a Arithmetic means

- *Literature information regarding the pharmacokinetics, physicochemical properties of the drug substance*

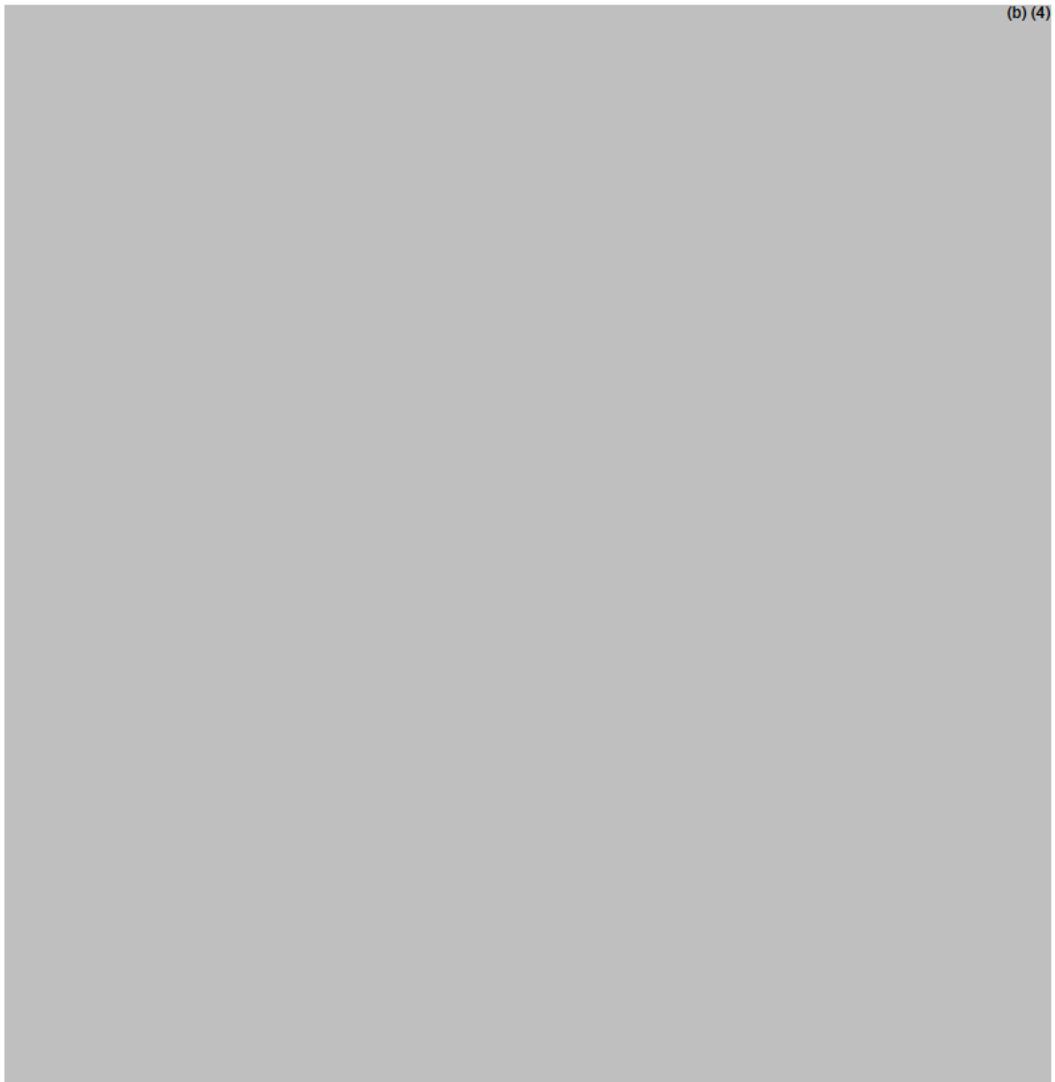
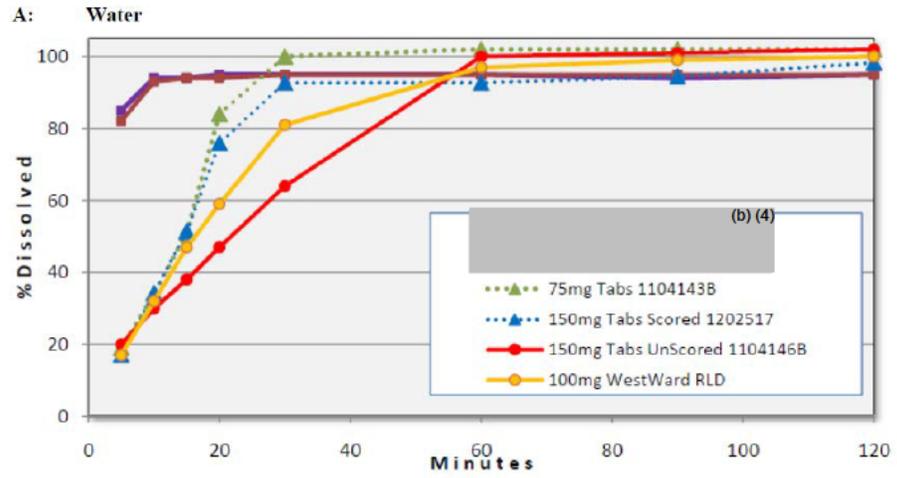
- Reference is made to several literature studies using doxycycline, and individual summaries are provided in the NDA.
 - Studies illustrate high drug solubility (50 mg/mL) and high permeability (using Caco-2 cells, doxycycline has an apparent permeability constant of 17.5×10^{-6} cm/sec (Jantratid et al. 2010))
 - Absorption occurs primarily in the duodenum.
 - Comparable PK across different dosage forms and salts, despite difference in in vitro dissolution profiles
 - High absolute bioavailability (90% to 100%)

- (b) (4)
The unscored 150 mg tablets (which were shown to be bioequivalent to the reference product in Study 11060203) (b) (4)



- *Dissolution profile testing summary*

The disparity among the dissolution profiles for the different doxycycline hyclate products is illustrated below.



(b) (4)

Based on the overall PK and scientific data, the Applicant concludes that the totality of the data support the bioequivalence of the reference product, unscored 150 mg tablets, dual-scored 150 mg tablets and 75 mg tablets, and in vivo studies for the dual-scored 150 mg tablets and 75 mg tablets are not required. The dissolution rates for the products included in the Applicant's relative bioavailability studies (unscored 150 mg tablets, 100 mg RLD tablets and 150 mg capsules) represent the extremes with respect to dissolution rates (i.e., the unscored 150 mg tablets and the RLD 100 mg tablets are the slowest dissolving formulations while the 150 mg capsules are the fastest dissolving formulation in all media studied). The dual-scored 150 mg tablets and 75 mg tablets have dissolution rates between these extremes. Thus, despite the observed in vitro dissolution dissolutions, no difference is expected in vivo.

Reviewer's Evaluation: ADEQUATE

In general, bioequivalence studies are recommended and often required when the test and reference products fail to demonstrate comparative similarity by using in vitro dissolution, as in this case. However, doxycycline is an old drug with a wide therapeutic index, and the review standard for an NDA is not necessarily bioequivalence, as is the case for ANDAs, but clinical equivalence. There is a significant amount of clinical and pharmacokinetic information available on doxycycline products, as well as vast product expertise within FDA to support applying a clinical risk assessment-benefit analysis in the context of the biowaiver request. Such flexibility is permitted through 21 CFR 314.90.

Although the submitted evidence suggest that doxycycline is a BCS 1 drug, the slow dissolution rate of the 150 mg unscored tablet does not support a BCS 1 claim for the product. That being said, this Reviewer agrees with the Applicant that the risk of suboptimal therapy from a faster dissolving product is negligible for doxycycline. Varying dosage forms with faster or modified release profiles demonstrate similar or acceptable in vivo PK. Further, this Reviewer accessed the referenced listed drug (Vibra-Tabs) NDA reviews and noted comparative BA studies across different dosage

forms (i.e., tablet vs. capsule vs. suspension) that showed acceptable clinical performance among the different products. Through consultation with the clinical team, and with consideration for the site of drug absorption, it is expected that that a faster dissolution rate could affect the rate of exposure, but not likely the extent. Based on the exposures observed with solution and fast dissolving capsule formulation, these differences, if present would not be clinically significant. Therefore, from a patient protection perspective, additional clinical studies are not warranted. A waiver is granted for the conduct of bioequivalence studies.

Granting the Applicant's waiver request does not mean agreement with the Applicant's claim that all strengths are bioequivalent, but rather that the clinical risk of bio-inequivalence is low and any differences, even if present, are not expected to affect clinical performance. Thus, all strengths are considered clinically equivalent and no additional studies are needed from a clinical risk assessment-benefit perspective.

4.2.2 *Is there any IVIVR or IVIVC information submitted? What is the regulatory application of the IVIVR/IVIVC in the submission? What data are provided to support the acceptability of the IVIVR or IVIVC model?*

Not applicable.

4.3 SURROGATES IN LIEU OF DISSOLUTION

4.3.1 *Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data are available to support the approval of the proposed surrogate test?*

No.

4.4 DISSOLUTION AND QBD

4.4.1 *Does the application contain QbD elements? If yes, is dissolution identified as a CQA for defining design space?*

No.

4.4.2 *Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment been performed to evaluate the criticality of dissolution?*

Not applicable.

4.4.3 *What biopharmaceutics information is available to support the clinical relevance of the proposed design space?*

Not applicable.

4.4.4 *Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?*

Not applicable.

5 LABELING

The proposed labeling information in the pharmacokinetic section is provided below.

12.3 Pharmacokinetics

Doxycycline is virtually completely absorbed after oral administration. Following administration of a single 300 mg dose to adult volunteers, average peak plasma doxycycline levels were 3.0 mcg per mL at 3 hours, decreasing to 1.18 mcg per mL at 24 hours. The mean C_{max} and $AUC_{0-\infty}$ of doxycycline are 24% and 15% lower, respectively, following single dose administration of ACTICLATE, 150 mg tablets with a high fat meal (including milk) compared to fasted conditions. (b) (4)

Tetracyclines are concentrated in bile by the liver and excreted in the urine and feces at high concentrations and in a biologically active form. Excretion of doxycycline by the kidney is about 40% per 72 hours in individuals with a creatinine clearance of about 75 mL per minute. This percentage may fall as low as 1% per 72 hours to 5% per 72 hours in individuals with a creatinine clearance below 10 mL per minute.

Studies have shown no significant difference in the serum half-life of doxycycline (range 18 to 22 hours) in individuals with normal and severely impaired renal function. Hemodialysis does not alter the serum half-life.

Reviewer's Evaluation: ADEQUATE

This Reviewer has no recommended edits. The information is consistent with the clinical PK results from the BE study.

6 INFORMATION REQUESTS DURING THE REVIEW

The following information requests were issued during the NDA review cycle. Responses are incorporated into the QBR above. There are no outstanding review issues.

- (1) We note that you have indicated reliance on ANDA 65095 on Form 356h as the basis for your 505(b)(2) NDA. However, reliance on FDA's previous findings of safety and efficacy should refer to an appropriate NDA product. You need to identify the NDA product that was the basis for submission of the ANDA product as the listed drug relied upon to support your application (i.e., NDA 50533 Vibra-Tabs (doxycycline hyclate))

Tablets). Provide a revised 356h and accompanying patent certification or statement indicated the NDA product being relied upon. Note also that reliance on FDA's finding of safety and/or effectiveness for a discontinued listed drug is contingent on FDA's finding that the drug was not withdrawn for reasons of safety or effectiveness.

Adequate responses were received on 15 April 2014.

- (2) It is acknowledged that your proposed NDA product is based on licensed technology from ANDA 065095; however, as previously communicated to you under IND 113575 (17 April 2013 pre-NDA Meeting Minutes), optimal dissolution acceptance criteria should be based on your NDA product's specific quality and performance attributes. Your proposed (b) (4) are not supported by the dissolution data and are not acceptable. We recommend an acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 30 minutes for your 75 mg and 150 mg scored doxycycline tablets based on the available data. Provide a revised drug product specification with the recommended changes to the dissolution acceptance criterion or a suitably alternate proposal for the dissolution acceptance criterion that is data and science-based for review.

Adequate responses were received on 6 May 2014.

SUPPLEMENTAL TABLES AND FIGURES

Table 1.12.15-14: Similarity Factor (f_2) Results and Multivariate (MV) Analyses Conclusions

Reference Product	Test Product	Media	f_2 Results	Figure	MV Analyses Demonstrate Similarity? (Yes/No)
Unscored 150 mg Tablets (Batch No. 1104146)	Dual-Scored 150 mg Tablets (Batch No. 1202517)	Water (b) (4)	37	Figure 1.12.15-3A	No
			31	Figure 1.12.15-3B	No
			34	Figure 1.12.15-3C	No
			30	Figure 1.12.15-3D	No
Unscored 150 mg Tablets (Batch No. 1104146)	75 mg Tablets (Batch No. 1104143)	Water (b) (4)	33	Figure 1.12.15-4A	No
			29	Figure 1.12.15-4B	No
			29	Figure 1.12.15-4C	No
			28	Figure 1.12.15-4D	No
RLD 100 mg Tablets (Batch No. 69358B)	Unscored 150 mg Tablets (Batch No. 1104146)	Water (b) (4)	51	Figure 1.12.15-5A	Yes
			29	Figure 1.12.15-5B	No
			70	Figure 1.12.15-5C	Yes
			68	Figure 1.12.15-5D	Yes
RLD 100 mg Tablets (Batch No. 69358B)	Dual-Scored 150 mg Tablets (Batch No. 1202517)	Water (b) (4)	53	Figure 1.12.15-6A	No
			65	Figure 1.12.15-6B	Yes
			37	Figure 1.12.15-6C	Yes
			35	Figure 1.12.15-6D	No
RLD 100 mg Tablets (Batch No. 69358B)	75 mg Tablets (Batch No. 1104143)	Water (b) (4)	44	Figure 1.12.15-7A	Yes
			66	Figure 1.12.15-7B	No
			31	Figure 1.12.15-7C	No
			33	Figure 1.12.15-7D	No

Summary of Adverse Events by MedDRA System Organ Class (SOC) and Preferred Term

MedDRA SOC	MedDRA Preferred Term	Treatment ¹	
		Test A N ² = 25	Reference B N = 25
		n ³ (% ⁴)	n (%)
Cardiac disorders	Dizziness	3 (12.0)	2 (8.0)
Gastrointestinal disorders	Abdominal discomfort	0 (0.0)	1 (4.0)
Gastrointestinal disorders	Abdominal pain upper	2 (8.0)	3 (12.0)
Gastrointestinal disorders	Diarrhoea	2 (8.0)	0 (0.0)
Gastrointestinal disorders	Dyspepsia	1 (4.0)	1 (4.0)
Gastrointestinal disorders	Faeces hard	1 (4.0)	0 (0.0)
Gastrointestinal disorders	Nausea	12 (48.0)	9 (36.0)
Gastrointestinal disorders	Vomiting	1 (4.0)	1 (4.0)
General disorders and administration site conditions	Fatigue	0 (0.0)	1 (4.0)
General disorders and administration site conditions	Feeling cold	1 (4.0)	0 (0.0)
General disorders and administration site conditions	Feeling hot	1 (4.0)	0 (0.0)
General disorders and administration site conditions	Vessel puncture site inflammation	0 (0.0)	1 (4.0)
Investigations	Blood glucose abnormal	1 (4.0)	1 (4.0)
Investigations	Blood pressure decreased	2 (8.0)	1 (4.0)
Investigations	Full blood count abnormal	0 (0.0)	1 (4.0)
Investigations	Glucose urine present	0 (0.0)	1 (4.0)
Investigations	Heart rate decreased	1 (4.0)	0 (0.0)
Metabolism and nutrition disorders	Increased appetite	0 (0.0)	1 (4.0)
Nervous system disorders	Headache	2 (8.0)	1 (4.0)
Nervous system disorders	Paraesthesia	1 (4.0)	1 (4.0)

MedDRA SOC	MedDRA Preferred Term	Treatment ¹	
		Test A N ² = 25	Reference B N = 25
		n ³ (%) ⁴	n (%)
Nervous system disorders	Sinus headache	0 (0.0)	1 (4.0)
Psychiatric disorders	Euphoric mood	2 (8.0)	0 (0.0)

¹ **Test A:** Two (2) 150 mg Doxycycline Hyclate Tablets, AQUA Pharmaceuticals

Reference B: Three (3) 100 mg Doxycycline Hyclate Tablets, USP (manufactured by: West-ward Pharmaceutical Corp.)

² N = number of subjects who dosed with respective treatment

³ n = number of subjects reporting Adverse Event

⁴ % calculated as (number of subjects reporting Adverse Event / number of subjects who dosed with respective treatment) times 100

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MINERVA HUGHES
06/10/2014

ANGELICA DORANTES
06/10/2014

CLINICAL PHARMACOLOGY REVIEW

NDA: 205-931	Submission Date(s): 9/25/2013
Drug	Doxycycline
Trade Name	ACTICLATE
OCP Reviewers	Ryan P. Owen, Ph.D.
OCP Team Leader	Kimberly L. Bergman, Pharm.D.
OCP Division	DCP4
OND division	DAIP
Sponsor	Aqua Pharmaceuticals
Relevant IND(s)	113,575
Submission Type; Code	505(b)(2)
Formulation; Strength(s)	75 mg and 150 mg doxycycline hyclate tablets
Indication	All approved doxycycline indications
Dosage and Administration	<p>Adult dose: Usual dose: 200 mg on the first day of treatment (administered 100 mg every 12 hours), followed by a maintenance dose of 100 mg daily. Maintenance dose may be administered as a single dose or as 50 mg every 12 hours.</p> <p>Pediatric dose: For pediatric patients >8 years of age: the recommended dosage schedule for children weighing 45 kg or less is 4.4 mg/kg of body weight divided into two doses on the first day of treatment followed by 2.2 mg/kg of body weight given as a single daily dose or divided into two doses on subsequent days.</p>

1. EXECUTIVE SUMMARY

The Sponsor (Aqua Pharmaceuticals) is seeking approval for 75 mg and 150 mg immediate release doxycycline hyclate tablets via a 505(b)(2) NDA. The Sponsor intends for the label of their product to contain all indications that are currently labeled in the approved doxycycline products already on the market. In support of their NDA, the Sponsor has submitted three clinical studies:

- 1) A pivotal BA/BE study comparing 300 mg (two 150 mg tablets) of the proposed product to 300 mg (three 100 mg tablets) of West-ward Pharmaceuticals Doxycycline Hyclate Tablets, USP 100 mg (the RLD). Per the memorandum of understanding (MOU) between the Office of Clinical Pharmacology (OCP) and the Office of New Drugs Quality Assessment (ONDQA), ONDQA will be responsible for the primary review of this study.
- 2) A food effect study to compare the relative bioavailability of the new formulation of doxycycline hyclate tablets 150 mg under fed and fasted conditions. This study will be reviewed by OCP.
- 3) A study to evaluate the relative bioavailability (b) (4)) compared to an equal dose of Vibramycin capsules in healthy volunteers under fasted conditions. Since this NDA is only seeking the approval of the doxycycline hyclate tablets,

this BA/BE study involving doxycycline hyclate capsules will not be reviewed by OCP or ONDQA.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the clinical pharmacology components of this NDA and is recommending the approval of this application.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics

Findings:

The following study was reviewed by OCP to support approval of NDA 205-931: Study 11060204: A Study to Compare the Relative Bioavailability of a New Formulation of Doxycycline Hyclate Tablets 150 mg under Fasted and Non-Fasted Conditions.

Using a crossover design, a single dose of the 150 mg doxycycline hyclate tablet was given to subjects in a fed and fasted state. When doxycycline hyclate tablets were given with food, the C_{max} and AUC_{0-inf} were significantly reduced (see Figure 1.3.1 for the mean plasma concentration-time profile and Table 1.3.1 for the mean pharmacokinetic parameters of doxycycline in the fed and fasted state in healthy subjects). The lower bound of the 90% confidence intervals around the point estimates fell below the pre-specified no-effect boundary for C_{max} , AUC_{0-t} , and AUC_{0-inf} (see Table 1.3.2); therefore, the pharmacokinetics of doxycycline were altered when co-administered with food. However, the clinical significance of such a decrease is unknown. The Reviewer recommends the following with regard to the product labeling:

1. The decrease in C_{max} and AUC_{0-inf} will be specified in Section 12.3
2. A statement regarding the uncertainty of the clinical significance of these findings will also be included in Section 12.3
3. The label will NOT state that this product can be administered without regard to food.
4. The label WILL state that the co-administration of doxycycline with food may improve the GI tolerability of doxycycline hyclate tablets.

Figure 1.3.1: Mean plasma concentration-time profile of doxycycline in Fed and Fasted Healthy Subjects

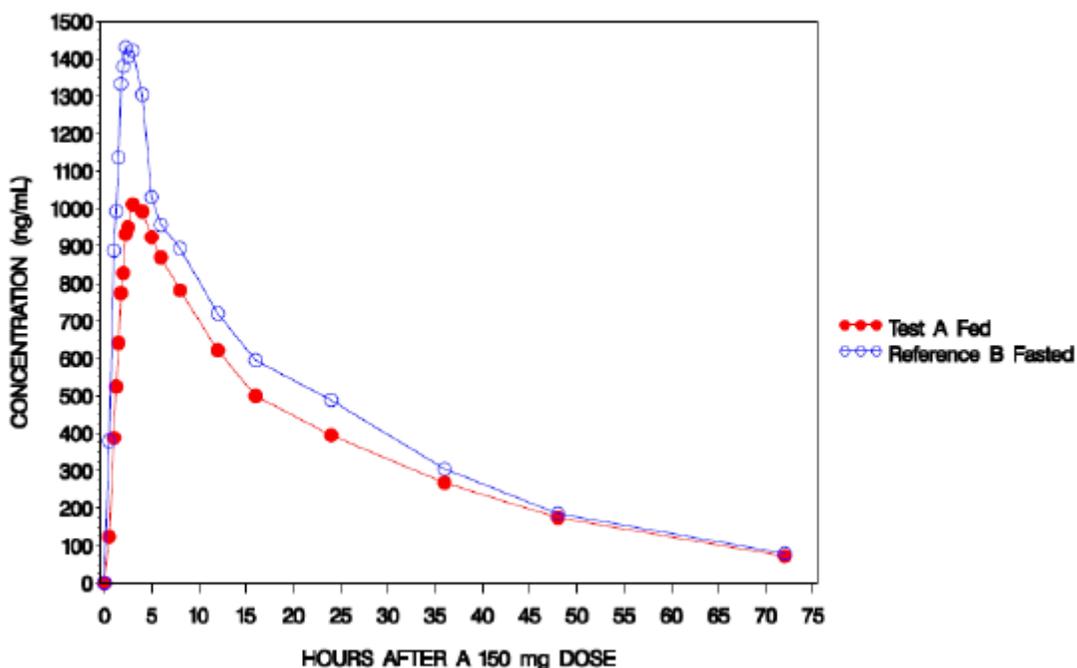


Table 1.3.1: Summary of Doxycycline Pharmacokinetic Parameters in a Fed and Fasted State

Pharmacokinetic Parameter	Arithmetic mean \pm SD (%CV)	
	Test A (fed)	Reference B (fasted)
AUC _{0-t} (ng·hr/mL)	24176.4844 \pm 5916.1385 (24.4706)	29444.9912 \pm 7356.6593 (24.9844)
AUC _{0-inf} (ng·hr/mL)	27003.8896 \pm 6955.7078 (25.7582)	31969.1695 \pm 8322.9684 (26.0344)
AUC _{0-t} /AUC _{0-inf} ratio	0.8959	0.9219
C _{max} (ng/mL)	1162.6800 \pm 298.2726 (25.6539)	1585.7440 \pm 622.9844 (39.2866)
T _{max} (hr)	2.5813 \pm 1.1559 (44.7810)	2.3900 \pm 0.6127 (25.6365)
Median T _{max} (hr) (Min – Max)	2.25 (1.50 – 6.00)	2.25 (1.50 – 4.00)
K _{el} (1/hr)	0.0376 \pm 0.0104 (27.6004)	0.0397 \pm 0.0099 (24.9652)
T _{1/2} (hr)	20.5168 \pm 9.2640 (45.1530)	18.9459 \pm 6.8037 (35.9113)

Test A (fed): 1 x 150 mg Doxycycline Hyclate Tablet (AQUA Pharmaceuticals) after high fat breakfast
Reference B (fasted): 1 x 150 mg Doxycycline Hyclate Tablet (AQUA Pharmaceuticals) after an overnight fast

Table 1.3.2: Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Ln-Transformed Data

Parameter	Test A (fed)	Reference B (fasted)	Ratio	CI*	Intra-Subject %CV
AUC _{0-t} (ng·hr/mL)	23474.16	28527.92	0.8229	0.7700 - 0.8793	13.7420
AUC _{0-inf} (ng·hr/mL)	26122.48	30850.36	0.8468	0.7955 - 0.9013	12.9265
C _{max} (ng/mL)	1130.86	1491.77	0.7581	0.6997 - 0.8213	16.6165

* Equivalent if confidence intervals are within 0.8000-1.2500 (80.00 to 125.00%) limits.

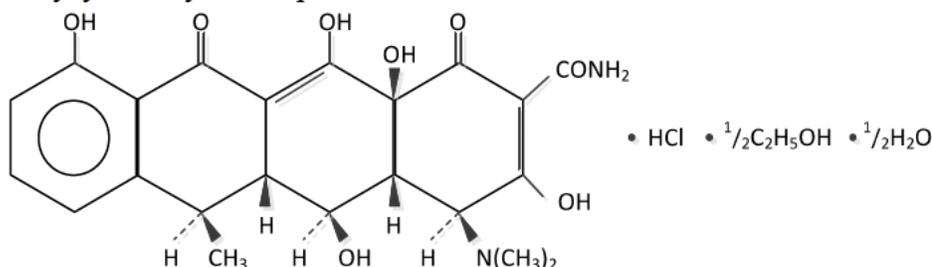
Test A (fed): 1 x 150 mg Doxycycline Hyclate Tablet (AQUA Pharmaceuticals) after high fat breakfast

Reference B (fasted): 1 x 150 mg Doxycycline Hyclate Tablet (AQUA Pharmaceuticals) after an overnight fast

2. QUESTION-BASED REVIEW

2.1 General Attributes of the Drug

Doxycycline is a tetracycline antibacterial marketed in multiple strengths and formulations including capsules, tablets, and injectables. The molecular formula for doxycycline hyclate is $C_{22}H_{24}N_2O_8 \cdot HCl \cdot \frac{1}{2}C_2H_5OH \cdot \frac{1}{2}H_2O$. The chemical structure of doxycycline hyclate is provided below.



2.1.1 *What is the formulation of the drug product?*

The proposed dosage forms are 75 mg and 150 mg tablets.

2.1.2 *What are the proposed mechanism(s) of action and therapeutic indication(s)?*

Doxycycline is a tetracycline antibacterial which inhibits protein synthesis by binding reversibly to the 30S unit of bacterial ribosome and preventing the addition of amino acids to the growing peptide.

The proposed therapeutic indications for this doxycycline product are as follows:

- Rickettsial infections
- Sexually transmitted infections
- Respiratory tract infections
- Specific bacterial infections
- Ophthalmic infections
- Anthrax, including inhalational anthrax (post-exposure)
- Alternative treatment for selected infections when penicillin is contraindicated
- Adjunctive therapy in acute intestinal amebiasis and severe acne
- Prophylaxis of malaria

2.1.3 *What are the proposed dosage(s) and route(s) of administration?*

For adults: the usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg daily. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended.

For children above eight years of age: the recommended dosage schedule for children weighing 45 kg or less is 4.4 mg per kg of body weight divided into two doses on the first day of treatment, followed by 2.2 mg/kg of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections, up to 4.4 mg/kg of body weight may be used. For children over 45 kg, the usual adult dose should be used.

2.2 General Clinical Pharmacology

Doxycycline is almost completely absorbed following oral administration. Tetracyclines as a class have varying degrees of protein binding. Doxycycline is excreted in both the urine and the feces. Excretion of doxycycline by the kidney is about 40% in 72 hours in individuals with a creatinine clearance of about 75 mL/min. The half-life of doxycycline is 18-22 hours. Hemodialysis does not alter the serum half-life of doxycycline.

The mean C_{max} and AUC_{0-inf} of doxycycline were 24% and 15% lower, respectively, following single dose administration of doxycycline hyclate 150 mg immediate release tablets with a high fat meal (including milk) compared to fasted conditions. The T_{max} of doxycycline was not affected by food.

2.3 Intrinsic Factors

Not applicable.

2.4 Extrinsic Factors

Not applicable.

2.5 General Biopharmaceutics

2.5.1. **What is the effect of food on the bioavailability (BA) of the drug form the dosage form? What dosing recommendations should be made, if any, regarding administration of the product in relation to meals or meal types?**

Study 11060204 was a single-dose, randomized, two-treatment, two-period, two-sequence, crossover study in fasted and non-fasted healthy subjects. In one period of the study, a single doxycycline hyclate 150 mg tablet was administered after an overnight fast of at least 10 hours. In the other period, a single doxycycline hyclate 150 mg tablet was administered following a standardized high fat breakfast. The order of administration followed a two sequence randomization schedule. Each dose was separated by a 14 day interval.

The mean plasma concentration-time profiles of doxycycline in the fasted and fed subjects are shown in Figure 2.5.1. The lower bound of the 90% confidence interval fell below 80.00% for the C_{max} , AUC_{0-t} , and AUC_{0-inf} when the 150 mg doxycycline hyclate tablets were administered with food (see Table 2.5.1). Therefore, the pharmacokinetics of doxycycline were altered by co-administration with food. However, the clinical significance of the decrease in C_{max} and AUC is unknown. The label will NOT state that the doxycycline tablets can be administered without regard to food, but it will state the magnitude of the interactions, and include a statement indicating that the clinical significance of such a decrease is unknown.

Figure 2.5.1: Mean Plasma Concentration-Time Profile of Doxycycline Following a Single 150 mg Dose in Fed and Fasted Healthy Subjects

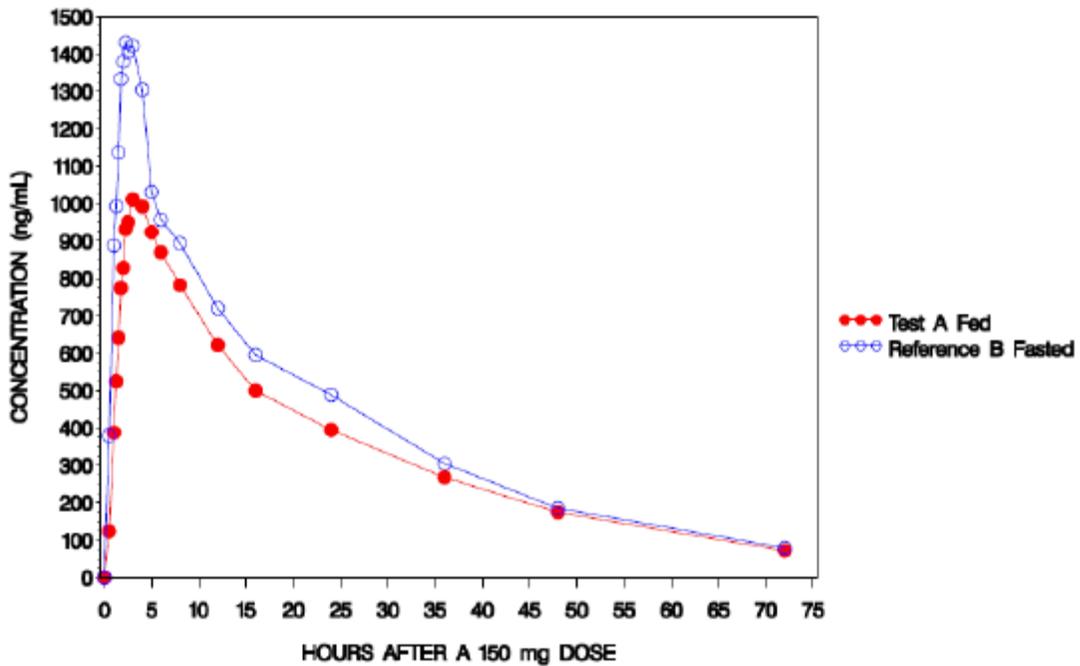


Table 2.5.1: Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Ln-Transformed Data

Parameter	Test A (fed)	Reference B (fasted)	Ratio	CI*	Intra-Subject %CV
AUC_{0-t} (ng·hr/mL)	23474.16	28527.92	0.8229	0.7700 - 0.8793	13.7420
AUC_{0-inf} (ng·hr/mL)	26122.48	30850.36	0.8468	0.7955 - 0.9013	12.9265
C_{max} (ng/mL)	1130.86	1491.77	0.7581	0.6997 - 0.8213	16.6165

* Equivalent if confidence intervals are within 0.8000-1.2500 (80.00 to 125.00%) limits.
 Test A (fed): 1 x 150 mg Doxycycline Hyclate Tablet (AQUA Pharmaceuticals) after high fat breakfast
 Reference B (fasted): 1 x 150 mg Doxycycline Hyclate Tablet (AQUA Pharmaceuticals) after an overnight fast

2.6 Bioanalytical Section

2.6.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Plasma concentrations of doxycycline were measured using a validated high performance liquid chromatography followed by positive electrospray-ionization tandem mass spectrometry (LC ESI/MS/MS).

2.6.2. Which metabolites have been selected for analysis and why?

No metabolites were selected for analysis. Doxycycline is not thought to be significantly metabolized.

2.6.3. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total doxycycline concentrations were measured. No specific justification is provided.

2.6.4. What bioanalytical method is used to assess concentrations?

Plasma concentrations of doxycycline were measured using a validated high performance liquid chromatography followed by positive electrospray-ionization tandem mass spectrometry (LC ESI/MS/MS).

2.6.4.1. What is the range of the standard curve? How does it relate to the requirement for clinical studies? What curve fitting techniques are used?

The standard curve ranged from 25 to 2,000 ng/mL. Linear regression was used with $1/x^2$ weighting. This range was adequate to cover the concentrations of doxycycline observed in the clinical studies.

2.6.4.2. What are the lower and upper limits of quantification (LLOQ/ULOQ)?

LLOQ: 25 ng/mL

ULOQ: 2,000 ng/mL

2.6.4.3. What are the accuracy and precision at these limits?

The accuracy ranged from 93.4.0% to 102.8%; and the precision (%CV) ranged from 1.7% to 11.6% for doxycycline.

2.6.4.4 What is the sample stability under the conditions used in the study (long term freeze-thaw, sample-handling, sample transport, autosampler)?

The long term storage stability was 23 days at -20°C and 241 days at -80°C. The samples were stable for four freeze/thaw cycles. The stock stability and the working sampler stability were for 39 days. The autosampler processed stability was for five days.

2.6.4.4. What are the QC samples?

The following Quality Controls were used:

Low: 75 ng/mL

Mid: 500 ng/mL

High: 1,600 ng/mL

Dilution: 4,000 ng/mL

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4. APPENDIX

Study Report Title: A Study to Compare the Relative Bioavailability of a New Formulation of Doxycycline Hyclate Tablets 150 mg (AQUA Pharmaceuticals) under Fasted and Non-Fasted Conditions (Study No. 11060204)

Dates: 8/4/12 to 8/21/12

Investigator: Darin Brimhall, D.O.

Novum Pharmaceutical Research Services

Las Vegas, NV

Analysis: [REDACTED] (b) (4)

OBJECTIVE: The purpose of this study was to evaluate the relative bioavailability of a test formulation of doxycycline hyclate tablets, 150 mg under fasted and non-fasted conditions in healthy volunteers.

BACKGROUND:

AQUA Pharmaceuticals is seeking approval in the US for a new strength of doxycycline hyclate tablets, 150 mg for which the FDA recommends a comparison of the bioavailability of the formulation under both fasted and fed conditions.

STUDY DESIGN:

This was a randomized, single-dose, two-treatment, two-period, two-sequence, crossover study under fasting and non-fasting conditions. The study was conducted with 26 (25 completing) healthy adult subjects. In one period of the study, a single doxycycline hyclate 150 mg tablet was administered after an overnight fast of at least 10 hours. In the other period, a single doxycycline hyclate 150 mg tablet was administered following a standardized high fat breakfast. The order of administration followed a two sequence randomization schedule. The test formulation was doxycycline hyclate tablet, 150 mg (AQUA Pharmaceuticals). Subjects were confined at the clinical facility from at least 10.5 hours before dosing until after the 24 hour blood collection and returned to the clinical facility for pharmacokinetic sampling at 36, 48, and 72 hours. The interval between doses was 14 days.

The plasma samples from all subjects who completed the study were shipped to the [REDACTED] (b) (4) for measurement of doxycycline concentrations.

Statistical analysis using average bioequivalence methodology was performed to evaluate the relative bioavailability of the test formulation when taken after food compared to when taken in the fasted state. The effect of food was determined based on the confidence intervals for the major pharmacokinetic parameters, log transformed AUC_{0-t} , AUC_{0-inf} , and C_{max} , for doxycycline.

METHODS AND ASSAY METHODOLOGY:

Plasma concentrations of doxycycline were measured using a validated high performance liquid chromatography followed by positive electrospray-ionization tandem mass spectrometry (LC ESI/MS/MS).

Criterion	Doxycycline	Comments
Concentration Range	25 – 2,000 ng/mL	Satisfactory
LLOQ	25 ng/mL	Satisfactory
Linearity	0.998	Satisfactory
Accuracy	98.0 – 102.8%	Satisfactory
Precision	1.7 – 6.1% (%CV)	Satisfactory

Twenty blood samples were collected from each subject during each period of the study: prior to dosing, then at 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.5, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours after dosing for analysis of plasma doxycycline concentrations. The analytical data were used to calculate the following pharmacokinetic parameters: AUC_{0-t} , AUC_{0-inf} , T_{max} , K_{el} , and half-life. The t in AUC_{0-t} is the time at which the last measurable concentration was recorded. SAS (Version 9.2) was used for all pharmacokinetic and statistical calculations.

The pharmacokinetic parameters were determined from the plasma concentration data using a non-compartmental model. The terminal elimination rate constants were estimated from the plasma doxycycline data for all subjects using the plasma concentrations of the terminal elimination phase as best as could be determined from the semi-logarithmic concentration-time plots for the individual subjects.

Analyses of Variance were performed using the General Linear Model (GLM) procedure of SAS with hypothesis testing for the treatment effects at $\alpha = 0.05$. The statistical model contained main effects of sequence, subject within sequence, treatment, and period. Sequence effects were tested against the Type III mean square term for subjects within sequence. All other main effects were tested against the mean squared error term. Least squares means for the treatments (LSMEANS statement), the differences between adjusted treatment means, and the standard errors associated with these differences (ESTIMATE statement) were calculated.

Confidence intervals (90%) for the comparison of test and reference area and peak results were constructed to test two, one-sided hypotheses at the $\alpha = 0.05$ level of significance. The confidence intervals are presented for the ratio of the test-to-reference treatment means and the geometric mean ratios (obtained from logarithmic transformation).

The effect of food on the test formulation was based on the log-transformed data by comparing Test A (fed) vs. Reference B (fasted). If the 90% confidence intervals for the test:reference ratio for AUC_{0-t} , AUC_{0-inf} , and C_{max} for doxycycline all fell within the range 80.00-125.00% in the fed state compared to the fasted state, then food was considered not to have any effect on the bioavailability of the test formulation.

RESULTS:

A total of 26 subjects were enrolled into the study, and 25 subjects completed the study. Subject 14 voluntarily withdrew from the study approximately 14 hours after dosing in Period I with Reference B (fasted) due to the adverse event of abdominal pain which was first reported at the time of withdrawal from the study. The subject declined to remain at

the clinical facility for monitoring but later returned and completed end of study safety evaluations with no clinically significant findings. As this subject did not complete both periods of the study, his samples were not sent for bioanalysis.

Demographics

Table 1 summarizes the subject demographics for this study.

Table 1: Subject Demographics

SUBJECTS INCLUDED IN THE STATISTICAL ANALYSIS (N = 25)	
Age (years)	
Mean ± SD	44.9 ± 12.6
Median	48.0
Range	21 - 63
Age Groups	
< 18	0 (0.00%)
18 – 40	7 (28.00%)
41 – 64	18 (72.00%)
65 – 75	0 (0.00%)
> 75	0 (0.00%)
Gender	
Males	22 (88.00%)
Females	3 (12.00%)
Ethnicity	
Not Hispanic/Latino	23 (92.00%)
Hispanic/Latino	2 (8.00%)
Race	
American Indian or Alaskan Native	0 (0.00%)
Asian	1 (4.00%)
Black or African American	11 (44.00%)
Native Hawaiian or Other Pacific Islander	0 (0.00%)
White	11 (44.00%)
Other	2 (8.00%)
Weight (lb)	
Mean ± SD	171.7 ± 23.4
Median	170.0
Range	121 - 216
Height (in)	
Mean ± SD	69.0 ± 3.0
Median	69.0
Range	62 - 75
BMI (kg/m²)	
Mean ± SD	25.2 ± 3.0
Median	24.9
Range	19.4 – 29.9

Pharmacokinetic Analysis

Figure 1 shows the mean concentration-time profile of doxycycline in the test and reference arms. Table 2 shows the summary of pharmacokinetic parameters (untransformed data) for doxycycline in the fed and fasted state. Table 3 shows the least squares means, ratio of means, and 90% confidence intervals based on ANOVA of untransformed data. Table 4 shows the least squares geometric means, ratio of means, and 90% confidence intervals based on ANOVA of ln-transformed data.

Figure 1: Mean plasma concentration-time profile of doxycycline following a 150 mg single dose in Fed and Fasted Healthy Subjects

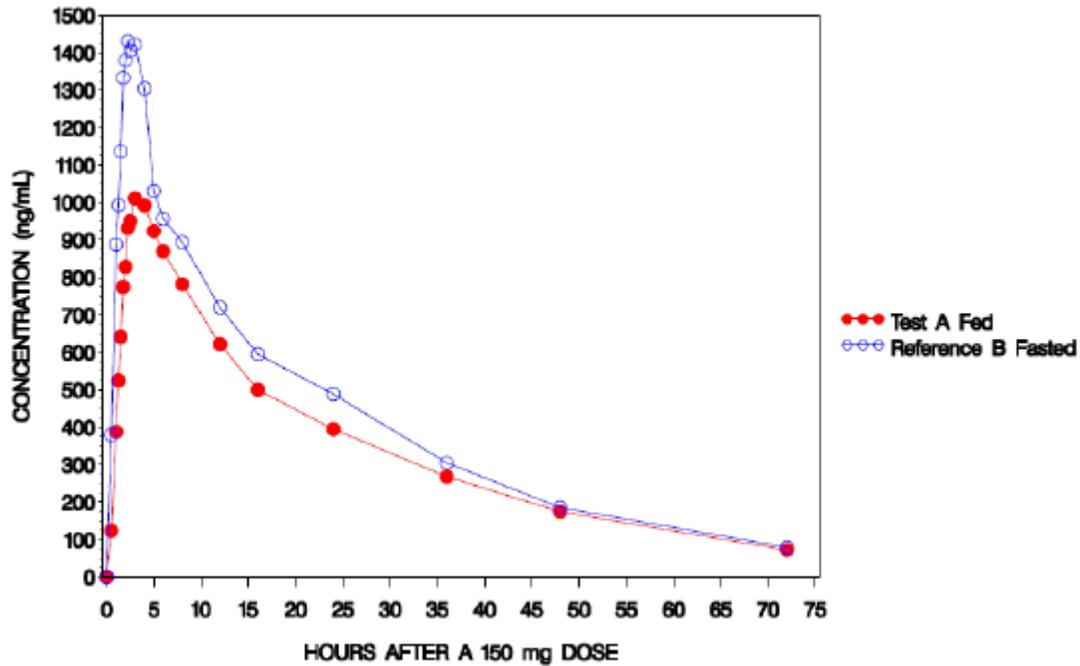


Table 2: Summary of Pharmacokinetic Parameters Untransformed Data: Doxycycline (N=25)

Pharmacokinetic Parameter	Arithmetic mean \pm SD (%CV)	
	Test A (fed)	Reference B (fasted)
AUC _{0-t} (ng·hr/mL)	24176.4844 \pm 5916.1385 (24.4706)	29444.9912 \pm 7356.6593 (24.9844)
AUC _{0-inf} (ng·hr/mL)	27003.8896 \pm 6955.7078 (25.7582)	31969.1695 \pm 8322.9684 (26.0344)
AUC _{0-t} /AUC _{0-inf} ratio	0.8959	0.9219
C _{max} (ng/mL)	1162.6800 \pm 298.2726 (25.6539)	1585.7440 \pm 622.9844 (39.2866)
T _{max} (hr)	2.5813 \pm 1.1559 (44.7810)	2.3900 \pm 0.6127 (25.6365)
Median T _{max} (hr) (Min – Max)	2.25 (1.50 – 6.00)	2.25 (1.50 – 4.00)
K _{el} (1/hr)	0.0376 \pm 0.0104 (27.6004)	0.0397 \pm 0.0099 (24.9652)
T _{1/2} (hr)	20.5168 \pm 9.2640 (45.1530)	18.9459 \pm 6.8037 (35.9113)

Test A (fed): 1 x 150 mg Doxycycline Hyclate Tablet (AQUA Pharmaceuticals) after high fat breakfast
Reference B (fasted): 1 x 150 mg Doxycycline Hyclate Tablet (AQUA Pharmaceuticals) after an overnight fast

Table 3: Least Squares Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Untransformed Data: Doxycycline (N=25)

Parameter	Test A (fed)	Reference B (fasted)	Ratio	CI
AUC _{0-t} (ng·hr/mL)	24216.52	29405.64	0.8235	0.7670 - 0.8800
AUC _{0-inf} (ng·hr/mL)	27029.84	31898.40	0.8474	0.7945 - 0.9003
C _{max} (ng/mL)	1164.03	1586.98	0.7335	0.6358 - 0.8312
K _{el} (1/hr)	0.04	0.04	0.9460	
Elimhalf (hr)	20.50	18.87	1.0862	

Test A (fed): 1 x 150 mg Doxycycline Hyclate Tablet (AQUA Pharmaceuticals) after high fat breakfast
Reference B (fasted): 1 x 150 mg Doxycycline Hyclate Tablet (AQUA Pharmaceuticals) after an overnight fast

Table 4: Least Squares Geometric Means, Ratio of means, and 90% Confidence Intervals Based on ANOVA of Ln-Transformed Data: Doxycycline (N=25)

Parameter	Test A (fed)	Reference B (fasted)	Ratio	CI*	Intra-Subject %CV
AUC _{0-t} (ng·hr/mL)	23474.16	28527.92	0.8229	0.7700 - 0.8793	13.7420
AUC _{0-inf} (ng·hr/mL)	26122.48	30850.36	0.8468	0.7955 - 0.9013	12.9265
C _{max} (ng/mL)	1130.86	1491.77	0.7581	0.6997 - 0.8213	16.6165

* Equivalent if confidence intervals are within 0.8000-1.2500 (80.00 to 125.00%) limits.

Test A (fed): 1 x 150 mg Doxycycline Hyclate Tablet (AQUA Pharmaceuticals) after high fat breakfast

Reference B (fasted): 1 x 150 mg Doxycycline Hyclate Tablet (AQUA Pharmaceuticals) after an overnight fast

Safety

There were no serious adverse events reported during this study. Both the test and reference treatments were well-tolerated during the study.

Twelve adverse events were reported by 9 of the 26 subjects who participated in this study. Of these events, 1 occurred prior to dosing in Period I with Test A (fed), 4 occurred after administration of Test A (fed), and 7 occurred after administration of Reference B (fasted). All reported adverse events were considered mild. The most frequently reported adverse events were abdominal discomfort (2/26, 7.7%) and nausea (2/26, 7.7%).

APPLICANT'S CONCLUSION:

When dosing doxycycline hyclate tablet, 150 mg (Aqua Pharmaceuticals) after a high fat breakfast, C_{max} was reduced by approximately 24% compared with the fasted state, but the median T_{max} remained the same (2.25 hours). The overall bioavailability as measured by AUC was decreased by about 15-18% when doxycycline hyclate tablet was administered after a high fat meal compared to administration in the fasted state. As this drug is intended for chronic rather than acute usage, this decrease in maximum exposure after a single dose is likely to be insignificant with respect to clinical efficacy. Therefore, it is proposed that doxycycline hyclate tablets, 150 mg (Aqua Pharmaceuticals) (b) (4)

There were no serious adverse events reported during this study. Both the test and reference treatments were well-tolerated during the study.

REVIEWER ASSESSMENT:

The administration of doxycycline in a fasted state led to an increased C_{max} and increased exposure relative to doxycycline in a fed state. The lower bound of the 90% CI for AUC_{0-t}, AUC_{0-inf}, and C_{max} all fell below the pre-determined threshold of 80.00% indicating that the pharmacokinetics of doxycycline were altered by co-administration with food. It is unknown whether the decrease in doxycycline C_{max} or AUC caused by co-administration with food is clinically significant. The Sponsor has acknowledged the decrease in C_{max} and AUC in section 12.3 of the proposed label, followed by the statement: The clinical significance of these decreases is unknown. This is an acceptable approach.

In their study report conclusions, the Sponsor proposes that their tablet can be administered without regard to food since doxycycline is intended for chronic use. However, in the label, the Sponsor has left the wording present in the DORYX label pertaining to food: If gastric irritation occurs, doxycycline may be given with food or milk. The proposed label does not contain the “without regard to food” language.

While no serious adverse events were observed in the trial, the incidence of AEs was somewhat higher in the fasted state. This result is consistent with the DORYX labeling which states that gastrointestinal-related adverse events may be improved by taking doxycycline with food or with a meal.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RYAN P OWEN
05/22/2014

KIMBERLY L BERGMAN
05/23/2014