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APPLICATION NUMBER:

205931Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 14, 2014
From	Angelica Dorantes, Ph.D. Biopharmaceutics Team Leader, ONDQA
Subject	Cross-Discipline Team Leader Review
NDA	NDA 205931
Type of Submission	505(b)(2)
Applicant	Aqua Pharmaceuticals LLC
Date of Submission	September 25, 2013
PDUFA Goal Date	July 25, 2014
Proprietary Name / Established (USAN) names	Acticlate Tablets Doxycycline Hyclate Tablets, USP
Dosage forms / Strength	Immediate Release Oral Tablets, 75 mg and 150 mg
Proposed Indication(s)	To reduce the development of drug-resistant bacteria and maintain the effectiveness of doxycycline hyclate and other antibacterial drugs. Acticlate Tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. Acticlate is a tetracycline-class antibacterial 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
Recommendation:	**APPROVAL** is recommended with labeling changes, provided CMC, which recommendation is pending recommends approval

This secondary CDTL review is based, on the primary reviews/memos of:

DICIPLINE	PRIMARY REVIEWER	FINAL REVIEW DATE
Pharmacology/Toxicology	Wendelyn Schmidt, Ph.D.	1/13/2014
Chemistry/Manufacturing/ Controls	Shrikant N. Pagay, Ph.D.	6/19/2014
Quality Microbiology	Jessica G. Cole, Ph.D.	11/25/2013
Quality Statistics (Biometrics)	Xiaoyu (Cassie) Dong, Ph.D.	6/18/2014
Biopharmaceutics	Minerva Hughes, Ph.D.	6/10/2014
Clinical Pharmacology	Ryan P. Owen, Ph.D.	5/23/2014
Clinical	Edward A. Weinstein, MD, Ph.D.	6/12/2014
Clinical Microbiology	Kerian K Grande Roche, Ph.D.	6/19/2014
Clinical Statistics	Mushfiqur Rashid, Ph.D.	6/24/2014
Medication Error Prevention and Analysis	Aleksander P. Winiarski, Pharm.D.	3/7/2014 (proprietary name) 5/20/2014 (labels & labeling)
Prescription Drug Promotion	Carry Newcomer, Pharm.D.	6/23/2014
Regulatory Project Manager	Carmen L. DeBellas	6/11/2014

Cross Discipline Team Leader Review

1. Introduction

On September 25, 2013, the Applicant, Aqua Pharmaceuticals LLC submitted NDA 205031 under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act Act (21 U.S.C. 355), seeking authorization to market Doxycycline Hyclate, 75 mg and 150 mg immediate release tablets.

The Listed Drug Product (LDP) is Vibra-Tabs (doxycycline hyclate 100 mg oral tablets, NDA 50533) manufactured by Pfizer and approved by FDA on January 15, 1980. This product was discontinued for reasons not involving safety or efficacy, and a number of presently marketed doxycycline hyclate tablets rely upon the Vibra-Tabs NDA 50533 as the LDP. As a result, West-ward Pharmaceuticals doxycycline hyclate 100 mg tablets (ANDA 065095), approved by FDA on July 2, 2003 is used as the reference drug product for the bioequivalence study in this application.

2. Background

The drug substance doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline, and is available as doxycycline hyclate (doxycycline hydrochloride hemiethanolate hemihydrate) capsules and tablets for oral administration.

Doxycycline is a tetracycline-class antibacterial drug and is generally considered bacteriostatic. Tetracycline-class antibacterials inhibit protein synthesis in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains. The antibacterial spectrum of doxycycline includes Gram-positive and Gram-negative organisms (including aerobic and anaerobic species), including methicillin-resistant *Staphylococcus aureus* (MRSA*),* and some Mycobacteria. Cross-resistance of these organisms to tetracycline is common.

Doxycycline is almost completely absorbed following oral administration. Tetracyclines as a class have varying degrees of protein binding. Doxycylcine 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 proposed 75 mg tablet product is unscored and the 150 mg tablet is a dual-scored product. 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 that are currently labeled in the approved doxycycline products already on the market. All other attributes, such

as active ingredient, dosage form, route of administration, conditions of use, indications and dosing regimens are the same as the LDP.

The basis of approval of this NDA for Doxycycline Hyclate Tablets are; 1) three clinical pharmacokinetic studies conducted by Novum Pharmaceutical Research Services, and 2) previous finding of safety and efficacy for the Listed Drug Product (LDP). The application did not utilize any published literature as a source of clinical data. The submitted pharmacokinetic studies are summarized in the table below.

Summary of Clinical Bioequivalence Studies

Study No.	Study Objectives	Test Product(s) Dosing Regimen Route of Administration	Number of Subjects	Treatment Duration
11060203	Evaluate bioavailability of new dosage strength of drug product relative to an equivalent dose of the RLD under fasted conditions.	Doxycycline Hyclate Tablets, 150 mg (unscored) 300 mg Dose Oral	26 (24 included in statistical analysis)	Single Dose
11060204	Evaluate bioavailability of new dosage strength of drug product under fasted and non- fasted conditions.	Doxycycline Hyclate Tablets, 150 mg (unscored) 150 mg Dose Oral	26 (25 included in statistical analysis)	Single Dose
11060201	Evaluate bioavailability of a new dosage strength of drug product relative to an equivalent dose of the RLD under fasted conditions.[a]	Doxycycline Hyclate Capsules, 150 mg300 mg Dose Oral	26 (22 included in statistical analysis)	Single Dose

1 ***Study No. 11060203:*** 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 listed drug product).
Per the Memorandum of Understanding (MOU) between the Office of Clinical Pharmacology (OCP) and the Office of New Drugs Quality Assessment (ONDQA), ONDQA's Biopharmaceutics conducted the primary review of this study.

2 ***Study No. 11060204:*** 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 was reviewed by OCP.

3 ***Study No. 11060201:*** A study to evaluate the relative bioavailability of a new formulation of doxycycline hyclate capsules 150 mg (Aqua Pharmaceuticals) compared to an equal dose of Vibramycin® capsules in healthy volunteers under fasted conditions.
Since this NDA was only seeking the approval of the doxycycline hyclate tablets, this BA/BE study involving doxycycline hyclate capsules was not reviewed by OCP or ONDQA.

3. Quality CMC

- **General Quality Considerations**

Drug Substance: The Applicant provided sufficient information on the raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug product. The DMFs for doxycycline hyclate drug substances are adequate.

Drug Product: The proposed strengths for the drug products are 75 mg and 150 mg doxycycline immediate release tablets. (b) (4) The 75 mg tablet contains (b) (4) mg doxycycline hyclate and is a round, light teal (b) (4) tablet debossed with "75" on one side and "AQ101" on the other side.

The 150 mg tablet contains (b) (4) mg doxycycline hyclate. It is an oblong capsule-shaped, mossy-green tablet with two parallel score lines on both upper and lower side to provide flexible dosing of 50 and 100 mg.

Full Tablet Top View

Full Tablet Side View

Each 50 mg split portion is debossed with "A" on one side while the other side is unmarked. Since 300 mg dose is approved only for gonorrhea the clinical division (DAIP) has agreed to accept a dual-scored 150 mg tablet. The scored tablets upon splitting also meet the quality requirements for content uniformity, loss of mass, friability, dissolution, (b) (4) and assay for each split portion of the tablet.

Since pharmacies can provide up to 90 days supplies of medications, stability studies were performed for this in-use period. The split tablets are stable when stored at room temperature for up to 90 days. The tablets meet the USP Monograph.

- **Stability:**

The NDA provided sufficient stability information on the drug product to assure identity, strength, purity, and quality of the drug product through the approved shelf life. A separate Biopharmaceutics review covers the acceptability of the dissolution test method and the test results, and recommends approval of the NDA. The drug product shelf life (for both strengths)

granted for the commercial tablet in HDPE (60 tablets/ bottle) is 18 months and for Physician sample in Aclar blisters 12 months when stored at 20°C to 25°C. (b) (4) The overall conclusion from a CMC perspective is that the manufacturing and controls appear to be sufficient and risks are adequately mitigated to maintain adequate product quality through the life cycle (with required regulatory changes).

- **Facilities Review/Inspection:**

Doxycycline Hyclate Tablets, USP are for oral administration and will be manufactured at Catalent Winchester, KY. The drug substance is manufactured in (b) (4) Doxycycline hyclate CMC information is referenced to DMF (b) (4). The DMF was last reviewed on 9/30/2013 and found to be acceptable. A Letter of Authorization is provided.

Inspection by Office of Compliance was requested for the manufacturing site of drug product at the Catalent Winchester, KY. At the time of this review the Office of Compliance has not provided a recommendation for the manufacturing and testing facilities.

- **CMC Overall Recommendation:**

Based on the CMC information provided in this submission and the quality microbiology and Biopharmaceutics reviews recommending approval, from the product quality perspective the application is satisfactory to assure the identity, strength, purity and quality of the drug product. All product quality issues have been satisfactorily resolved. For full details refer to the CMC review by Dr. Shrikant Pagay dated June 19, 2014.

Since the Office of Compliance has not yet made an overall recommendation for the manufacturing and testing facilities, CMC cannot recommend approval until an overall acceptable recommendation is received from the Office of Compliance. Therefore, the CMC overall recommendation on the approvability of this NDA is PENDING.

4. Quality Microbiology

The Quality Microbiologist, Dr. Jessica G. Cole in her review dated 11/14/2013, states that the Applicant provided acceptable information to support the proposed microbial control strategy to eliminate microbial limit testing at release and during shelf life studies and the microbial testing requirements were waived for this drug product.

Dr. Cole concluded in her review that the Microbial Limits specification for Doxycycline Hyclate Tablets, USP are acceptable from a Product Quality Microbiology perspective and APPROVAL is recommended for this application.

5. Quality Statistics

The Office of Biometrics (OB) was consulted by ONDQA-CMC to perform the statistical analysis of the proposed drug product 24 months and 12 months long-term stability data with multiple packaging types and multiple strengths. The following table extracted from the statistical review summarizes the estimated shelf-life for the multiple packaging types and strengths.

FDA Statistics Reviewer's Estimated Shelf Life for each Package and Strength using Long-term Stability Data

	75 mg Tablets	150 mg Tablets	150 mg Dual Scored Tablets
[redacted]			(b) (4)
60cc Bottle			(b) (4)
(b) (4) Blister			(b) (4)
(b) (4)			

The Statistical reviewer concludes that the proposed shelf life of (b) (4) months is not supported by the long-term stability data. For full details refer to Dr. Cassie Dong's statistical review dated 6/18/2014.

It is noted that based on this statistical analysis, the CMC Reviewer is recommending a shelf life of 18 months for the commercial HDPE bottle and a shelf-life of 12 months for the (b) (4) blister package when stored at 20°C-25°C.

6. Nonclinical Pharmacology/Toxicology

No new pharmacology/ toxicology data were submitted to this NDA. The labeling information for the relevant pharmacology/toxicology sections is identical to previously approved labels. The excipient profile is within levels previously approved for compounds administered by the oral route.

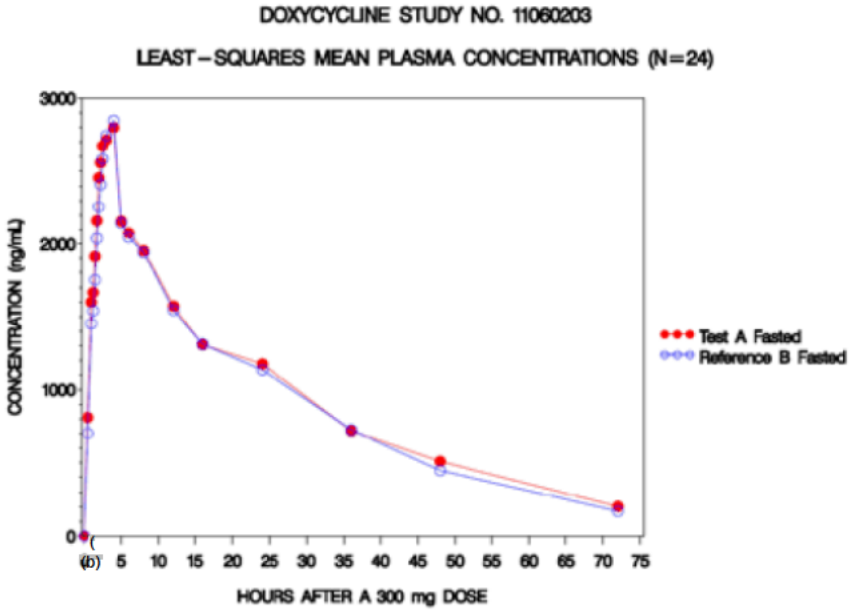
The pharmacology/toxicology Reviewer, Dr. Wendelyn Schmidt mentions that there are no pharmacology/toxicology issues with this compound and APPROVAL is recommended.

7. Biopharmaceutics

The Biopharmaceutics primary basis in support of this new drug application comes from; 1) the evaluation of bioequivalence study 1106023 conducted under fasted conditions, 2) the biowaiver request for the lower 75 mg strength tablets, and 3) the proposed dissolution method and acceptance criterion.

1) Study 1106023 was a single-dose, randomized, two-treatment, two-period, two-sequence, crossover study conducted under fasting conditions. Twenty four subjects completed the study. 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).

The Mean plasma concentration vs. time for Doxycycline is presented below.



The table below presents the confidence intervals for the ratio of the test-to reference treatment means and the geometric mean ratios for AUC0-t, AUC 0-inf, and Cmax.

Least Squares Geometric Means, Ratio of Means, and 90% CI Based on ANOVA of Ln-Transformed Data

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.)

The results from this study demonstrated acceptable bioequivalence between the listed drug product and the 150 mg unscored tablets. The inspection by the Office of Scientific

Investigation of the analytical and clinical facilities of this pivotal BE study was conducted and the clinical and analytical data were acceptable (report dated 4/17/2014).

2) The provided data supported the Applicant's request of a biowaiver for the proposed lower strength (75 mg tablet) and dual-scored 150 mg tablet and the biowaiver for this strength was granted.

3) The following proposed dissolution method and acceptance criterion were found acceptable for Quality Control (QC) 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 = (b) (4)% at 30 min

The Biopharmaceutics Reviewer is recommending APPROVAL of this NDA for Doxycycline Tablets. For full details refer to the Biopharmaceutics review by Dr. Minerva Hughes dated 6/10/2014.

8. Clinical Pharmacology

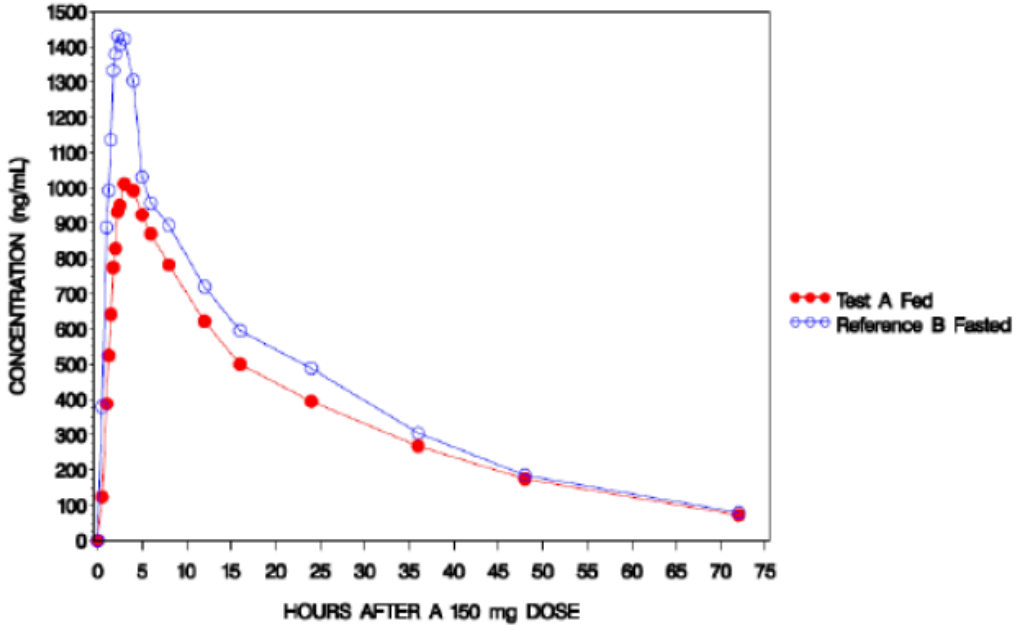
The Office of Clinical Pharmacology reviewed Study 11060204 assessing the effect of food.

Study 11060204 was a single-dose, randomized, two-treatment, two-period, two-sequence, crossover design evaluating the relative bioavailability of the proposed formulation of Doxycycline Hyclate Tablets 150 mg under fasted and fed conditions. 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. Each dose was separated by a 14 day interval. Twenty-five healthy subjects completed the study.

The study results showed that when doxycycline hyclate tablets were given with food, the Cmax and AUC0-inf were significantly reduced.

The mean plasma concentration-time profiles in the fed and fasted state are illustrated in the next Figure.

Mean Plasma Concentration-Time Profile of Doxycycline Following a Single 150 mg Dose under Fed and Fasted Conditions



The 90% confidence intervals for Cmax, AUC0-t, and AUC0-inf are presented in the Table below.

Least Squares Geometric Means, Ratio of Means, and 90% CI Based on ANOVA of Ln-Transformed Data

Parameter	Test A (fed)	Reference B (fasted)	Ratio	CI*	Intra-Subject %CV
AUC0-t (ng·hr/mL)	23474.16	28527.92	0.8229	0.7700 - 0.8793	13.7420
AUC0-inf (ng·hr/mL)	26122.48	30850.36	0.8468	0.7955 - 0.9013	12.9265
Cmax (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

The mean Cmax and AUC0-inf of doxycycline are 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 Tmax of doxycycline was not affected by food.

The Clinical Pharmacology Reviewer states that the clinical significance of such a decrease in doxycycline levels when co-administered with food is unknown and the following labeling changes are recommended:

- *The decrease in Cmax and AUC0-inf will be specified in Section 12.3*

- *A statement regarding the uncertainty of the clinical significance of these findings will also be included in Section 12.3*
- *The label will NOT state that this product can be administered without regard to food*
- (b) (4)

It is noted that the above labeling recommendations were incorporated in the Division's final revised labeling. The Clinical Pharmacology review recommends APPROVAL of this application. For full details refer to the Clinical Pharmacology review by Dr. Ryan Owen dated 5/23/2014.

9. Clinical

There were no clinical studies conducted for the purpose of evaluating efficacy and safety. The Applicant is relying on FDA's previous findings of safety and effectiveness for the listed drug product, Vibra-Tabs (doxycycline hyclate tablets 100 mg). However, the clinical review included the evaluation of the safety assessments of adverse events for pharmacokinetic studies No. 11060203 and 11060204 conducted to demonstrate bioequivalence of the Applicant's Doxycycline Hyclate to listed drug and the effect of food, respectively. No deaths or serious adverse events were reported in these pharmacokinetic studies. For full details on the safety assessments refer to the Clinical review dated 6/12/2014 by Edward Weinstein, MD, Ph.D.

The following labeling changes for the Warning section 5.5 for Intracranial Hypertension were recommended in the clinical review.

(b) (4)

(b) (4)

Since intracranial pressure can remain elevated for weeks after drug cessation patients should be monitored until they stabilize. Concomitant use of isotretinoin and doxycycline should be avoided because isotretinoin, a systemic retinoid, is also known to cause pseudotumor cerebri.

It is noted that the above highlighted recommended changes were not incorporated in the Division's final revised labeling. Dr. Weinstein in his review recommends APPROVAL of this 505 (b)(2) application for doxycycline hyclate for the same indications as the Listed Drug Product.

10. Clinical Microbiology

No new micro studies were submitted in the NDA and the Applicant is relying on previous findings of efficacy and safety. This proposed doxycycline new strengths fall within the approved strengths and the same indications will be used as the approved product.

The clinical microbiology review mentions that the name *Calymmatobacterium granulomatis* is old taxonomy that should be associated with the new taxonomy *Klebsiella granulomatis* in the indications and usage section and list of organisms, since the bacteria has been renamed. Updates to Quality control have been made to agree with recent Clinical and Laboratory Standards Institute documents (M100-S24).

The clinical microbiology review recommends APPROVAL for the proposed product, with recommended updates to the drug product's labeling. For full details on the recommended labeling updates, refer to the Clinical Microbiology review by Dr. Kerian Grande Roche dated 6/19/2014.

11. Clinical Statistical

There were no clinical studies conducted for the purpose of evaluating efficacy and safety. The Applicant is relying on previous findings of the efficacy and safety for the listed drug.

The Biostatistics review dated 6/24/2014, by Dr. Mushfiqur Rashid, Statistical Reviewer reports that this submission did not require statistical evaluation because there were no clinical studies provided in the submission.

12. Safety

There were no clinical studies conducted for the purpose of evaluating efficacy and safety. The Applicant is relying on FDA's previous findings of safety and effectiveness for the listed drug product. However, the safety of the clinical pharmacokinetic studies No. 11060203 and 11060204 was evaluated in the clinical review. No deaths or serious adverse events were reported in these studies.

Doxycycline has a safety profile that is similar to other tetracyclines whose major safety issues include permanent discoloration of the teeth and bone if administered during development, the development of *Clostridium difficile* associated diarrhea, photosensitivity, overgrowth of non-susceptible organisms, benign intracranial hypertension, and antianabolic activity. The clinical

review indicates that no additional safety concerns are expected to be associated with 75 mg and 150 mg tablets.

13. Advisory Committee Meeting

Current submission did not go to an Advisory Committee Meeting.

14. Pediatrics

Doxycycline Hyclate commercial products are currently approved for pediatric patients >8 to 18 years of age and may be used in younger children for some indications.

The clinical review by Dr. Weinstein mentions that the proposed tablet strengths of 75 mg and 150 mg may be of limited use because the dosing regimen for most indications in adults and in children weighing over 45 kg is 100 mg twice daily. In adults the 150 mg tablet may potentially be used in an alternative treatment regimen for gonorrhea consisting of two 300 mg doses administered one hour apart although this regimen is rarely utilized. The 75 mg tablet and a 50 mg portion of the dual scored 150 tablet may potentially be used in some children weighing 45 kg or less who are dosed at 2.2 mg/kg once or twice daily.

15. Other Relevant Regulatory Issues

- **505(b)(2) Assessment:** The required assessment for 505(b)(2) NDA submissions was already completed and filed in DARRTS on 6/11/2014 by Mr. Carmen DeBellas, RPM.

- There are no other additional relevant regulatory issues with this application.

16. Labeling

- **Proprietary Name:** The Applicant's proposed proprietary name Acticlate (Doxycycline Hyclate) Tablets has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and found acceptable from both promotional and safety perspectives. For details refer to the DMEPA review by Dr. Aleksander Winiarski dated 3/7/2014.

- DMEPA also evaluated the Product Information/Prescribing Information, FDA Adverse Event Reporting System (FAERS), Previous DMEPA Reviews, ISMP Newsletters, and Proposed Labels and Labeling. The review concludes that the submitted labels and labeling for Acticlate Tablets may be improved and recommends several revisions. For full details refer to the DMEPA review by Dr. Aleksander Winiarski dated 5/20/2014.

- **Labeling Revisions:** Several revisions were recommended for the proposed labeling by CMC, Clinical Pharmacology, Clinical, Clinical Microbiology, and DMEPA. For the specific recommendations refer to the individual reviews from these disciplines. It

is noted that the recommended revisions by the different disciplines were discussed and incorporated in the proposed labeling as appropriate during the labeling meetings.

- On 6/7/2014, DAIP consulted the Office of Prescription Drug Promotion (OPDP) for the review of the Division's revised version of the labeling for Doxycycline Hyclate Tablets. The review from OPDP by Dr. Carrie Newcomer was completed on 6/23/2014 and it includes several labeling comments for the Division's consideration.

- **Conclusion:** At the time of this review, a draft proposal labeling in the PLR format for labeling changes that include the overall DAIP's recommendations have been conveyed to the Applicant. A final agreement with the Applicant should be reached on the recommended labeling changes before a regulatory action is taken for this NDA.

17. Recommendations/Risk Benefit Assessment

- ***Recommended Regulatory Action:*** **APROVAL** with labeling changes is recommended for NDA 205931 for Acticlate (Doxycycline Hyclate) Tablets, provided CMC recommends approval. It is noted that at the time of this review, the CMC recommendation is PENDING because the Office of Compliance has not yet made their overall recommendation for the manufacturing and testing facilities.

- ***Risk Benefit Assessment:*** Doxycycline is effective for the approved indications and remains a preferred treatment option against pathogens such as *Chlamydia*, *Rickettsia*, *Vibrio* and *Mycoplasma* species. The doxycycline label adequately informs providers on risks and benefits associated with doxycycline use. This application for doxycycline hyclate tablets relies on FDA's previous findings of safety and effectiveness for the reference drug, Vibra-Tabs (doxycycline hyclate tablets 100 mg). No additional safety concerns are expected to be associated with 75 mg and 150 mg tablets.

- ***Recommendation for Postmarketing Risk Evaluation and Management Strategies***: Based on the information available in the current submission and the understanding of Doxycycline Hyclate approved therapy, there are no specific recommendations for post-market risk evaluation and mitigation strategies.

- ***Recommended Comments to Applicant:*** No comments need to be conveyed to the Applicant in the regulatory action letter. However, it is noted that the Applicant has been asked to revise the product's labeling as recommended by the Division.

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/s/

ANGELICA DORANTES
07/15/2014