CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205931Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 23, 2014

To: Carmen DeBellas
Regulatory Project Manager
Division of Anti-Infective Products (DAIP)

From: Carrie Newcomer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA: 205931
doxycycline hyclate Tablets, 75 mg and 150 mg for Oral use

Background

On June 7, 2014, DAIP consulted OPDP to review the proposed package insert (PI) for doxycycline hyclate Tablets, 75 mg and 150 mg for Oral use.

Please note that OPDP has reviewed the proposed PI and our comments are based on the substantially complete version of the draft label received via e-mail from DAIP on June 7, 2014. Our comments are provided in the attachment.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at 6-1233, or carrie.newcomer@fda.hhs.gov.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CARRIE A NEWCOMER
06/23/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 20, 2014
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 205931
Product Name and Strength:	Acticlate (Doxycycline Hyclate) Tablets, 75 mg and 150 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Aqua Pharmaceuticals
Submission Date:	September 25, 2013
OSE RCM #:	2013-2653
DMEPA Primary Reviewer:	Aleksander Winiarski, PharmD
DMEPA Acting Team Leader:	Tingting Gao, PharmD, BCPS
DMEPA Acting Team Leader:	Julie Neshiewat, PharmD, BCPS

1 REASON FOR REVIEW

The Division of Anti-Infective Products (DAIP) requested that we review the submitted Acticlate labels and labeling for areas of vulnerability that may lead to medication errors. This is a 505(b)(2) application and the referenced drug is Doxycycline Hyclate tablets USP, 100 mg, [West-Ward pharmaceuticals] ANDA 065095. However, the Agency recommended that the Applicant base the Prescribing Information labeling on Doryx (Doxycycline Hyclate), NDA 050795, due to the similar dosage form (dual scored 150 mg tablet) and approved Prescribing Information labeling which is in the Physician's Labeling Rule (PLR) format. Additionally, the Applicant also considered the Prescribing Information labeling for the referenced drug and Vibramycin (Doxycyline Calcium), NDA 050007, per recommendation by the Agency.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D - N/A
ISMP Newsletters	E
Other	F - N/A
Proposed Labels and Labeling	G

N/A = Not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We identified one relevant medication error case from a previous review involving a patient who self-administered doxycycline without adequate fluid intake, which resulted in gastrointestinal ulcerations. However, we conclude that the submitted Acticlate Prescribing Information labeling provides adequate warnings and information to minimize the potential for this error (See Appendix C2 for further details).

We note that pediatric dosing is inconsistently expressed under different subsections of the Dosing and Administration section of the Prescribing Information. Under section 2.1 "Usual Dosage and Administration", pediatric doses are calculated on a 'mg per kg' per day basis divided into number of doses per day, and under section 2.3 the dose is calculated on a 'mg per kg' per dose basis, in this case administered twice-a-day, which may cause confusion. To decrease the chance for dose calculation errors, we recommend a standard approach to pediatric dosing, either using mg/kg/dose or mg/kg/day divided into appropriate number of doses per day, across all indications. However, given the marketing history with doxycycline products and use of both mg/kg/dose and mg/kg/day dosing, and that we did not identify previous cases of confusion regarding pediatric dosing; we plan to continue monitoring for this potential medication error. However, if the Division prefers to revise and standardize the pediatric dosing calculations, we defer to the Division for specific recommendations to address this potential issue.

The submitted Acticlate Prescribing Information labeling does not include patient labeling with instructions for use of the 150 mg dual scored tablets. A dual scored tablet is unusual because the dual scored tablet can be broken down into 3 pieces (each containing 50 mg dose). Given that patients may misinterpret oral instructions for use from the prescriber, we recommend the Applicant develop written instructions for use for this product to be distributed to patients, similar to that of the Doryx patient labeling and similar to section 17 "patient counseling information" of the Prescribing Information labeling.

The submitted 75 mg professional sample blisters contain 2 tablets. Per our discussion with our ONDQA colleagues, each blister card contains two blister wells (one for each tablet), but there is one label on the blister card covering both blister wells. The strength presentation, "75 mg", in conjunction with the net quantity statement, "2 tablets", may lead to confusion and indicate to the user that two tablets equal 75 mg. The FDA Guidance for Industry titled: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors,* states: "The product strength on the principal display panel and other panels of the blister carton labeling should describe the milligram amount of drug per single unit (e.g., tablet, capsule) so that there is no confusion as to how much product is contained in a single unit as compared to the total contents of the entire blister card." Therefore, we recommend the revision of the strength presentation to the following: "75 mg per tablet" and "150 mg per tablet" on the professional sample blister label and the professional sample carton labeling.

Also, in our review of the submitted container labels and carton labeling, we identified lack of prominence of important use/prescribing information and missing required content such as lot numbers and expiration dates on the carton labeling and container labels. We provide specific recommendations in sections 4.1 and 4.2 below.

4 CONCLUSION & RECOMMENDATIONS

The submitted labels and labeling for Acticlate may be improved to communicate important use information and to improve prominence of important product information. We recommend the following revisions be implemented prior to the approval of this NDA.

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA provides the following comments for the Division's consideration:

A. Dosage and Administration Section of the Prescribing Information

1. We note that pediatric dosing is inconsistently expressed under different subsections of the Dosing and Administration section. Under section 2.1 "Usual Dosage and Administration" pediatric doses are calculated on a mg/kg/day divided into number of doses per day. However, under section 2.3, the dose is calculated on a mg/kg/dose and administered twice-a-day, which may cause confusion. To decrease the chance for dose calculation errors, we recommend a standard approach to pediatric dosing, either using mg/kg/dose or mg/kg/day divided into appropriate number of doses per day, across all indications. However, given the marketing history with doxycycline products and use of both mg/kg/dose and mg/kg/day dosing, and that we did not identify previous cases of confusion regarding pediatric dosing; we plan to continue monitoring for this potential medication error. However, if the Division prefers to revise and standardize the pediatric dosing calculations, we defer to the Division for specific recommendations to address this potential issue.

B. Patient Package Insert

1. The submitted Acticlate Prescribing Information does not include patient labeling with instructions for use of the 150 mg dual scored tablets. For consistency with the Doryx Prescribing Information labeling, we recommend that the Applicant create a patient package insert (similar to section 17 "patient counseling information" of the Prescribing Information labeling and Doryx patient package insert).

4.2 RECOMMENDATIONS FOR THE APPLICANT

DMEPA recommends the following revisions prior to approval of this NDA:

A. All Container Labels and Carton Labeling

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[1]

B. Bottle Labels (75 mg and 150 mg)

1. The AQUA logo on the Principal Display Panel (PDP) draws attention to the eye and competes for prominence with important prescribing information, such as the established name and strength. Decrease the prominence of the logo by significantly reducing its size or consider removing the logo.

2. The net quantity statement on the Principal Display Panel (PDP) draws attention to the eye and competes for prominence with important prescribing information, such as the strength. Decrease the prominence of the net quantity statement by reducing its size or remove the color box surrounding the net quantity statement.

3. As per 21CFR 201.17 and 21CFR 201.18, please indicate where the required lot number and expiration date will appear on the labels.

C. Professional Sample Blister Carton Labeling (75 mg and 150 mg)

1. As per FDA Guidance for Industry titled *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* which states: The product strength on the principal display panel and other panels of the blister carton labeling should describe the milligram amount of drug per single unit (e.g., tablet, capsule) so that there is no confusion as to how much product is contained in a single unit as compared to the total contents of the entire blister card. We recommend the revision of the strength presentations to the following: “75 mg per tablet” and “150 mg per tablet”.

2. See B3 above.

D. Professional Sample Blister Labels (75 mg and 150 mg)

1. See C1 above.

2. For clarity and to minimize the chance for confusion with the strength, relocate the net quantity statements away from the strengths, such as to the lower right corner.

3. Increase the font size of the strength to improve strength differentiation.

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[1] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Acticlate from the submitted insert labeling and carton/containers, on February 14, 2014.

Table 2. Relevant Product Information for Acticlate	
Active Ingredient	Doxycycline Hyclate
Indication	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
Route of Administration	Oral
Dosage Form	Tablets
Strengths	75 mg and 150 mg (scored to deliver 3 doses of 50 mg)
Dose and Frequency	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 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.

How Supplied	60 count bottles and physician samples in blisters (2 count for 75 mg and 1 count for 150 mg)
Storage	Room Temperature
Container Closure	(b) (4) bottles and sample blisters in cartons

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on May 5, 2014 using the criteria in Table 3, and then individually reviewed each case. This was a gap analysis from a previous search from OSE review # 2011-557, NDA 050795, dated May 4, 2011. We limited our analysis to cases that described errors possibly associated with the labels and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[2]

Table 3: FAERS Search Strategy	
Search Date Range	April 18, 2011 (Date of last FAERS search in OSE Review # 2011-557, NDA 050795) to May 1, 2014
Drug Names	Doryx [product name]
MedDRA Search Strategy	**Medication Errors** [HLGT] **Product Packaging Issues** [HLT] **Product Label Issues** [HLT] **Product Quality Issues** (NEC)[HLT]

B.2 Results

Our search identified one case, which is excluded because it describes patient non-compliance, which is not associated with a medication error.

B.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:drive on May 1, 2014 using the terms Doxycycline to identify reviews previously performed by DMEPA.

C.2 Results

We identified two relevant reviews.

The first review OSE # 2011-557, NDA 050795, dated May 4, 2011 identified a medication error case which may be relevant to the submitted labels and labeling. The case described a patient who did not drink water when taking doxycycline which resulted in gastrointestinal ulceration. However, the submitted Acticlate insert labeling recommends administering the product with adequate amounts of fluid. The recommendation is listed in the "Dosage and Administration" and in the "Patient Counseling Information" sections of the insert labeling. Therefore, the proposed labeling is adequate to minimize this error.

The second review OSE # 2011-1137, NDA 050795, dated September 6, 2011 evaluated revised labeling for Doryx, which added instructions for use regarding how to break the dual scored tablet. The review did not identify any relevant post-marketing cases (The review conducted a FAERS search for Buspar cases which is another example of a dual scored tablet).

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on May 14, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
Newsletters	Acute Care, Community/Ambulatory Care
ISMP Newsletter Search Strategy	Match Exact word or phrase Match Any of the words
Search Terms	Doryx

E.2 Results

Our search did not identify any articles.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[2] along with postmarket medication error data, we reviewed the following Acticlate labels and labeling submitted by Aqua Pharmaceuticals on February 14, 2014.

G.2 Label and Labeling Images

Bottle Labels

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[redacted]

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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05/20/2014

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05/20/2014

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 16, 2014

TO: Sumathi Nambiar, M.D.
Director, Division of Anti-Infective Products
Office of New Drugs

FROM: Gopa Biswas, Ph.D., Pharmacologist
Hansong Chen, Ph.D, Pharmacologist
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations (OSI)

and

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs covering NDA 205-931, Doxycycline Hyclate Tablets-150 mg, sponsored by Aqua Pharmaceuticals

At the request of the Division of Anti-Infective Products, the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the clinical and analytical portions of the following bioavailability study:

Study Number: 11060203
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 Conditions"

Rebecca Davis (ORA, SAN-DO) audited records at Novum Pharmaceutical Research Services, Las Vegas, NV, from 2/19 to 2/25/2014.

(b) (4)

(b) (4)

The audits included a thorough review of study records, examination of facilities, equipment, interviews and discussions with the firm's management and staff.

At the conclusion of both the inspections, no objectionable conditions were observed and no Form FDA-483 was issued.

Conclusion:
Following review of the above inspections, the DBGLPC reviewers recommend that the clinical and analytical data from study 11060203 should be accepted for agency review.

Gopa Biswas, Ph.D.
Hansong Chen, Ph.D.
Bioequivalence Branch, DBGLPC, OSI

Final Classifications:

NAI- Novum Pharmaceutical Research Services, Las Vegas, NV
(FEI: 3004869520)

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CC:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Dejernett/CF
OSI/DBGLPC/BeB/Haidar/Choi/Biswas/Hansong Chen/Skelly
OSI/DBGLPC/GLPB/Bonapace/Mada
CDER/OND/OAP/DAIP/DeBellas/Sumathi Nambiar/Minerva Hughes

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GOPA BISWAS
04/16/2014

SAM H HAIDAR
04/17/2014

WILLIAM H TAYLOR
04/17/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 205931

Application Type: 505(b)(2)

Name of Drug/Dosage Form: Doxycycline Hyclate Tablets (USP) 75 mg and 150 mg

Applicant: Aqua Pharmaceuticals

Receipt Date: September 25, 2013

Goal Date: July 25, 2014

1. Regulatory History and Applicant's Main Proposals

This NDA is a 505(b)(2) for the same indications as the reference listed drug (RLD) doxycycline hyclate tablets USP, 100mg by West –ward Pharmaceuticals (ANDA 65095).

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

The review of the prescribing information was reviewed and found to be acceptable.

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES"** in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format

is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *The initial approval date will read July 25, 2014*

Selected Requirements of Prescribing Information

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment: *A boxed warning is not required*

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"*[*see Warnings and Precautions (5.2)*]".

Comment: *There are no cross references in the label*

NO 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: *This a new NDA*

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment: *The is an orginal NDA and has not been marketed yet.*

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

CARMEN L DEBELLAS
03/27/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 205931		
Proprietary Name: Established/Proper Name: doxycycline hyclate tablets, USP Dosage Form: tablets Strengths: 75 mg & 150 mg		
Applicant: Aqua Pharmaceuticals, Inc.		
Date of Application: September 25, 2013 Date of Receipt: September 25, 2013		
PDUFA Goal Date: July 25, 2014	Action Goal Date (if different): July 25, 2014	
Filing Date: November 24, 2013	Date of Filing Meeting: November 19, 2013	
Chemical Classification: 5S		
• Proposed indications • 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		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	X 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	X Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s):	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	X		
If yes, explain in comment column.			X	
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐	X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: X Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: X Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	X	☐	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	X	☐	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	X	☐	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	X	☐	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	X		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	X	☐	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	X	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☐	☐	X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) X All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	X	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	X	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	X	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	X	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	X	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☐		X	505(b)(2)
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with	X	☐	☐	

authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	X	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	X	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	x	☐		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☐	X	☐	

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	☐	X	☐	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☐	X	☐	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☐		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	x	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	x	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	X Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) X Carton labels X Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	x	☐		
Is the PI submitted in PLR format?[4]	x	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in	☐	☐	x	

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	x	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	x	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	x	☐	☐	
OTC Labeling	**X Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☐	☒	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	x		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	x		

Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	x		

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 19, 2013

ESTABLISHED/PROPER NAME: Doxycycline Hyclate

DOSAGE FORM/STRENGTH: 75mg and 150 mg Tablets

APPLICANT: Aqua Pharmaceuticals, Inc.

Proposed indications

- 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

BACKGROUND: This is a 505(b)(2) application referencing the Reference Listed Drug Doxycycline Hyclate Tablets USP, 100 mg by West-Ward Pharmaceuticals.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Carmen DeBellas	Yes
	CPMS/TL:	Frances LeSane	No
Cross-Discipline Team Leader (CDTL)	Dorota Matecka		Yes
Clinical	Reviewer:	Edward Weinstein	Yes
	TL:	John Alexander	Yes
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Kerian Grande	Yes
	TL:	Kerry Snow	Yes

Clinical Pharmacology	Reviewer:	Ryan Owen	Yes
	TL:	Kimberly Bergman	Yes
Biostatistics	Reviewer:	Mushfiqur Rashid	Yes
	TL:	Thamban Valappil	Yes
Nonclinical (Pharmacology/Toxicology)	Reviewer/ TL:	Wendelyn Schmidt	Yes
Biopharmaceutics	Reviewer:	Minerva Hughes	Yes
	TL:	Angelica Dorantes	No
Product Quality (CMC)	Reviewer:	Shikant Pagay	Yes
	TL:	Dorota Matecka	Yes
Quality Microbiology *(for sterile products)*	Reviewer:	Jessica Cole	Yes
	TL:	Bryan Riley	No
Facility Review/Inspection	Reviewer:	Steven Hertz	No
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☐ Not Applicable ☐ YES x NO X YES ☐ NO BA/BE studies
• Per reviewers, are all parts in English or English translation? **If no**, explain:	X YES ☐ NO
• Electronic Submission comments **List comments**:	X Not Applicable
CLINICAL **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: 505(b)(2) no clinical trials performed	☐ YES X NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the***	☐ YES Date if known: X NO ☐ To be determined Reason: Product is a 505(b)(2) application

drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease	
• Abuse Liability/Potential **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	X Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed? Inspection has been requested	X YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

PRODUCT QUALITY (CMC)	☐ Not Applicable X FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	X YES ☐ NO ☐ YES ☐ NO X YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable X YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable X YES ☐ NO X YES ☐ NO
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	X N/A ☐ YES ☐ NO ☐ YES ☐ NO

• What late submission components, if any, arrived after 30 days?	N/A
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	X YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	N/A
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	X YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Division Director

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): February 2014

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☐ Priority Review

ACTIONS ITEMS	
X	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
NA	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
X	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
NA	BLA/BLA supplements: If filed, send 60-day filing letter
NA	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
NA	Send review issues/no review issues by day 74
X	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
NA	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
NA	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]

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

/s/

CARMEN L DEBELLAS
01/29/2014