

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205931Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 205931

SUPPL #

HFD # 520

Trade Name Acticlate

Generic Name doxycycline hyclate

Applicant Name Aqua Pharmaceuticals, Inc.

Approval Date, If Known July 25, 2014

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

*The Applicant has completed the following studies:*

*Evaluate bioavailability of a new dosage strength of drug product relative to an equivalent dose of the RLD under fasted conditions*

*Evaluate bioavailability of a new dosage strength of drug product under fasted and nonfasted conditions*

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

## 2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

## **PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation

duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
IND # YES  ! NO   
! Explain:

Investigation #2 !  
IND # YES  ! NO   
! Explain:



Name of Division Director signing form: Sumathi Nambiar, MD  
Title: Director, Division of Anti-Infective Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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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.**  
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/s/  
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CARMEN L DEBELLAS  
07/25/2014

SUMATHI NAMBIAR  
07/25/2014

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 205931	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Acticlate Established/Proper Name: doxycycline hyclate Dosage Form: 75 mg and 150 mg Tablets		Applicant: Aqua Pharmaceuticals, Inc.
RPM: Carmen DeBellas		Division: Division of Anti-Infective Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>)            Date of check: _____</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>July 25, 2014</u></li> </ul>		<input checked="" type="checkbox"/> AP
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): 5S  
 (*confirm chemical classification at time of approval*)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Approval July 25, 2014
Labeling	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> </ul>	Acceptable 3/13/14 Review 3/7/14
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	<input checked="" type="checkbox"/> RPM: March 27, 2014 <input checked="" type="checkbox"/> DMEPA: May 20, 2014 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: June 23, 2014 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	January 29, 2014
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	June 11, 2014
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines should be filed with the respective discipline.

<ul style="list-style-type: none"> <li>• This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> No  <input checked="" type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC If PeRC review not necessary, explain: <u>The product is already labeled for Pediatric Patients</u></li> </ul> </li> </ul>	
<ul style="list-style-type: none"> <li>❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (<i>do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	Included
<ul style="list-style-type: none"> <li>❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	CMC July 29, 2013 Clinical May 21, 2103
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>❖ Advisory Committee Meeting(s)</li> </ul>	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
<ul style="list-style-type: none"> <li>❖ Office Director Decisional Memo (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	July 25, 2014
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	July 15, 2014
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
<ul style="list-style-type: none"> <li>❖ Clinical Reviews</li> </ul>	
<ul style="list-style-type: none"> <li>• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>• Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	June 12, 2014
<ul style="list-style-type: none"> <li>• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)</li> </ul>	505(b)(2) no clinical trials were performed
<ul style="list-style-type: none"> <li>❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A

❖ Risk Management	
<ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<p>N/A</p> <p>N/A</p> <p><input checked="" type="checkbox"/> None</p>
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	June 19, 2014
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	June 24, 2014
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	May 23, 2014
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
<ul style="list-style-type: none"> <li>ADP/T Review(s) (<i>indicate date for each review</i>)</li> <li>Supervisory Review(s) (<i>indicate date for each review</i>)</li> <li>Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)</li> </ul>	<p><input checked="" type="checkbox"/> No separate review</p> <p><input checked="" type="checkbox"/> No separate review</p> <p>January 13, 2014</p>
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i> • <i>Statistical Review for long term stability</i> • <i>Biopharmaceutics Review</i> • <i>Biopharmaceutics Inspection</i>	June 19, 2014 June 18, 2014 June 10, 2014 April 17, 2014
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	November 25, 2013
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	June 19, 2014- CMC Review Page 63
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i>	Date completed: July 21, 2014 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
• Finalize 505(b)(2) assessment	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/  
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CARMEN L DEBELLAS  
07/25/2014

**From:** [Kimberley Forbes-McKean](#)  
**To:** [Bhandari, Navdeep](#)  
**Cc:** [DeBellis, Carmen](#); [Sok Kang](#)  
**Subject:** FW: NDA 205931 - cmc information request  
**Date:** Wednesday, June 18, 2014 3:11:30 PM  
**Attachments:** [205931-0007-m1.11.1 Info amend 4 - CMC.docx](#)  
[205931-0007-m3r2p.docx](#)

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Dear Navi,

Thank you for the teleconference today with your team to discuss the statistical analysis of the stability data available to assign the shelf life of the proposed product.

As discussed, please find the Quality Information Amendment with the responses to the FDA comments and questions received by Aqua in the 10 June 2014 Information Request (Reference ID: 3520969). The updated comparability protocol for the [REDACTED] (b) (4) [REDACTED] is also attached here. These documents will be formally submitted to the FDA this Friday along with will the cover letter and FDA form 356h.

Please let us know if you have any questions or require additional information.

Thank you again for your assistance with this program.

Kind regards,  
Kim

*Kim Forbes-McKean, Ph.D.*

Vice President, Research & Development  
**Aqua Pharmaceuticals**  
158 West Gay Street, Suite 310  
West Chester, PA 19380

Office (610) 644-7000

[REDACTED] (b) (6)

4 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

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/s/  
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NAVDEEP BHANDARI  
06/19/2014

**From:** Bhandari, Navdeep  
**To:** "[Kimberley Forbes-McKean](#)"  
**Cc:** [DeBellas, Carmen](#); [Sok Kang](#)  
**Subject:** RE: CMC information request  
**Date:** Wednesday, June 11, 2014 2:22:00 PM  
**Importance:** High

---

Hello Kim,

Please see the response from my team:

We performed statistical analysis of 24 months or 12 months long-term stability data with multiple packaging types and multiple strengths. Our conclusions on the shelf life are summarized below.

-  (b) (4)

**A single shelf life of 12 months is recommended for both 75 and 150 mg strengths in  Blisters**

-  (b) (4)

**A single shelf life of 18 months is recommended for 150 mg and 75 mg strengths in 60 count bottles**

In summary, the proposed shelf life of  months is not supported by the long-term stability data. Typically a single shelf life is granted for different strengths and packaging configurations. At this time, to allow the maximum possible shelf-life based on available data, a shelf life of 18 months is granted for the commercial configuration of 60-count bottles for both strengths. A separate shelf of 12 months is granted for both strengths in  Blisters.

Thank you,  
Navi

---

**From:** Kimberley Forbes-McKean [mailto:[kimfmckean@aquapharm.com](mailto:kimfmckean@aquapharm.com)]  
**Sent:** Tuesday, June 10, 2014 2:52 PM  
**To:** Bhandari, Navdeep  
**Cc:** DeBellas, Carmen; Sok Kang  
**Subject:** FW: CMC information request

Dear Navdeep,

Thank you for your input in the recent information request which I have attached for your convenience. Before providing a response to the attached request, can you please provide information on what basis or product characteristic the suggested shelf life for each packaging configuration were assigned? Aqua would like to ensure we respond to your request based on the appropriate quality attribute.

Please note that we previously provided up to 24 months of stability data for the 75 mg tablets in HDPE bottles (commercial package) and (b) (4) (b) (4) Blisters, physician package) which fully support a (b) (4) month shelf life for the 75 mg tablet in both HDPE bottles and (b) (4) Blisters.

In addition, 12 months of stability data were submitted for the dual scored 150 mg tablets in HDPE bottles (commercial package) and (b) (4) blisters (physician package). The statistical analysis of the 12 month data, supporting a (b) (4) month shelf life for the dual scored 150 mg tablet in both packages is also attached for your reference.

Please let me know if this provides sufficient clarification to justify a (b) (4) month shelf life for our proposed product.

Thank you very much for your consideration.

Kim

*Kim Forbes-McKean, Ph.D.*

Vice President, Research & Development  
**Aqua Pharmaceuticals**  
158 West Gay Street, Suite 310  
West Chester, PA 19380

Office (610) 644-7000

(b) (6)

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**From:** DeBellas, Carmen [<mailto:Carmen.DeBellas@fda.hhs.gov>]

**Sent:** Tuesday, June 10, 2014 11:12 AM

**To:** Kimberley Forbes-McKean

**Subject:** CMC information request

Hi, Wanted to make sure you got this as soon as possible.

Carmen

Carmen DeBellas, PharmD, RPh  
Regulatory Project Manager  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Phone: 301-796-1203

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/s/  
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NAVDEEP BHANDARI  
06/11/2014

## 505(b)(2) ASSESSMENT

Application Information		
NDA # 205931	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Acticlate Established/Proper Name: doxycycline hyclate tablets USP Dosage Form: tablets Strengths: 75 mg and 150 mg		
Applicant: Aqua Pharmaceuticals, Inc.		
Date of Receipt: September 25, 2013		
PDUFA Goal Date: July 25, 2014		Action Goal Date (if different):
RPM: Carmen DeBellas		
<ul style="list-style-type: none"><li>Proposed Indication(s):</li><li>Rickettsial infections</li><li>Sexually transmitted infections</li><li>Respiratory tract infections</li><li>Specific bacterial infections</li><li>Ophthalmic infections</li><li>Anthrax, including inhalational anthrax (post-exposure)</li><li>Alternative treatment for selected infections when penicillin is contraindicated</li><li>Adjunctive therapy in acute intestinal amebiasis and severe acne</li><li>Prophylaxis of malaria</li></ul>		

## GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
<a href="#">50-533 Vibra tabs</a>	<a href="#">FDA previous finding of safety and effectiveness</a>

\*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies) The Sponsor has performed the following studies

*Evaluate bioavailability of a new dosage strength of drug product relative to an equivalent dose of the RLD under fasted conditions*

*Evaluate bioavailability of a new dosage strength of drug product under fasted and nonfasted conditions*

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO   
*If “NO,” proceed to question #5.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO   
*If “NO”, proceed to question #5.  
If “YES”, list the listed drug(s) identified by name and answer question #4(c).*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Vibra Tabs	NDA 50-533	Y

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES  NO

If "YES", please list which drug(s) and answer question d) i. below.  
If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

**This application provides for different strengths (75 mg and 150mg). The RLD is a 100 mg tablet.**

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

**(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).**

**Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.**

YES  NO

If "NO" to (a) proceed to question #11.  
If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent? N/A  YES  NO

If this application relies only on non product-specific published literature, answer "N/A"  
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO   
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)? N/A  YES  NO

If this application relies only on non product-specific published literature, answer "N/A"  
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

*the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s): NDAs- 50007, 50795, 50783 ANDAs- 65281, 62500, 65103, 62475, 91406, 65095, 90134 and others.

**PATENT CERTIFICATION/STATEMENTS**

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed  *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the*

*NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

*Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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/s/  
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CARMEN L DEBELLAS  
06/11/2014



NDA 205931

**INFORMATION REQUEST**

Aqua Pharmaceuticals  
Attention: Kimberley Forbes-McKean, Ph.D.  
Vice President, Research & Development  
158 West Gay Street Suite 310  
West Chester, PA 19380

Dear Dr. Forbes-McKean:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Doxycycline Hyclate Tablets, USP.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by June 11, 2014, in order to continue our evaluation of your NDA.

1. Please confirm the shelf life of the drug products (75 mg and 150 mg doxycycline hyclate tablets) begins from [redacted] (b) (4)
2. [redacted] (b) (4)
3. Based on the analysis of statistical data for doxycycline hyclate 75 mg round and 150 mg scored tablets stored in HDPE bottles (commercial package) and [redacted] (b) (4) blister (physician package), the assigned shelf life are as follows when stored at 20°C-25°C (USP Controlled room temperature):

Commercial HDPE bottles = 18 months  
[redacted] (b) (4) Blister Cards Physician Samples = 12 months

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402-3815.

Sincerely,

*{See appended electronic signature page}*

Rapti D. Madurawe, Ph.D.

Branch Chief, Branch V

Division of New Drug Quality Assessment II

Office of New Drug Quality Assessment

Center for Drug Evaluation and Research

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/s/  
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RAPTI D MADURawe  
06/10/2014

**From:** DeBellas, Carmen  
**Sent:** Friday, April 04, 2014 11:20 AM  
**To:** kimfmckean@aquapharm.com  
**Subject:** NDA 205931 Doxycycline Information Request

Hello, I have an information request from our Biopharmaceutics group below:

**Information Request**

(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 that indicates the NDA product being relied upon. Please 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.

(2) It is acknowledged that your proposed NDA product (b) (4) from ANDA 65095; however, as previously communicated to you under IND 113575 (17 April 2013 pre-NDA Meeting Minutes), optimal dissolution acceptance criteria need to be based on your NDA product's specific quality and performance attributes. (b) (4)

(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.

Thanks,  
Carmen

Carmen DeBellas, PharmD, RPh  
Regulatory Project Manager  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Phone: 301-796-1203

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CARMEN L DEBELLAS  
04/04/2014



NDA 205931

**INFORMATION REQUEST**

Aqua Pharmaceuticals  
Attention: Kimberley Forbes-McKean, Ph.D.  
Vice President, Research & Development  
158 West Gay Street Suite 310  
West Chester, PA 19380

Dear Dr. Forbes-McKean I:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Doxycycline Hyclate Tablets, USP.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Include a test for heavy metals test per USP<231> and propose an appropriate acceptance criterion. We recommend an acceptance criterion of NMT (b) (4).
2. The 2 major components in the formulation (b) (4) of the raw material is a critical quality attribute for batch to batch reproducibility of the drug product. Propose (b) (4) used to manufacture the registration and bio batches of doxycycline tablets.
3. The manufacturing process controls provided in 3.2.P.3.4 are (b) (4)
4. The development report (PVR12156.04) includes measurement of (b) (4). However, no data are presented in the report. Provide this data.
5. It is reported in the NDA (b) (4). Although this proposal is acceptable, please confirm that you will (b) (4)
6. Provide the batch size of the 150 mg scored tablets used in the splitting study.
7. Conduct a tablet splitting study similar to TTP-ARV-M0020 for the first three commercial scale batches and evaluate the content uniformity by assay of the split portions. This test may be included under the post-approval stability protocol at the initial time point (for the first 3 commercial batches). Submit the revised post-approval stability protocol.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402-3815.

Sincerely,

*{See appended electronic signature page}*

Rapti D. Madurawe, Ph.D.  
Branch Chief, Branch V  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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DOROTA M MATECKA  
03/27/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 205931

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Aqua Pharmaceuticals  
158 West Gay Street, Suite 310  
West Chester, PA 19380

ATTENTION: Kimberley Forbes-McKean, Ph.D.  
Vice-President, Research & Development

Dear Dr. Forbes-McKean:

Please refer to your New Drug Application (NDA), dated and received, September 25, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Doxycycline Hyclate Tablets, 75 mg and 150 mg.

We also refer to your February 13, 2014, correspondence, received February 14, 2014, requesting review of your proposed proprietary name, Acticlalte. We have completed our review of the proposed proprietary name, Acticlalte, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your February 13, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301)796-5413. For any other information regarding this application, contact Carmen DeBellas, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1203.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES on behalf of KELLIE A TAYLOR  
03/13/2014

## DeBellas, Carmen

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**From:** DeBellas, Carmen  
**Sent:** Tuesday, December 03, 2013 8:46 AM  
**To:** kimfmckean@aquapharm.com  
**Subject:** Information Request #2

Hi,

I have been asked to request submission of the packaging (containers and blister packs) that will be used for the to be marketed doxycycline product. I prefer to have these sent directly to me at the following address.

FDA/CDER/OND/OAP/DAIP  
Carmen DeBellas  
10903 New Hampshire Ave.  
Building #22 Room 6232  
Silver Spring, MD 20903

Thanks,  
Carmen

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/s/  
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CARMEN L DEBELLAS  
12/03/2013

From:DeBellas, Carmen  
Sent:Friday, November 15, 2013 10:31 AM  
To:kimfmckean@aquapharm.com  
Subject:NDA 205931 Information Request 1 -

Hello,

Please find information request from our quality microbiology group.

You propose waiving microbial limits release testing for your drug product. This proposal may be acceptable provided adequate upstream controls are established and documented. More information on your process is needed. Address the following points.

(b) (4)

2.You should minimally perform microbial limits testing at the initial stability testing time point. Provide an updated stability schedule to reflect this testing.

Carmen

Carmen DeBellas, PharmD, RPh  
Regulatory Project Manager  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Phone: 301-796-1203

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/s/  
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CARMEN L DEBELLAS  
11/15/2013



IND 113575

**MEETING MINUTES**

Aqua Pharmaceuticals

(b) (4)

Dear (b) (4) :

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Doxycycline Hyclate Tablets.

We also refer to the meeting between representatives of your firm and the FDA on June 6, 2013. The purpose of the meeting was to discuss the proposed NDA package supporting registration of Doxycycline Hyclate Tablets.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Carmen DeBellas, Regulatory Project Manager at (301) 796-1203.

Sincerely,

*{See appended electronic signature page}*

Sumathi Nambiar, MD, MPH  
Acting Director  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type A  
**Meeting Category:** Pre-NDA CMC  
**Meeting Date:** June 6, 2013

**Application Number:** 113575  
**Product Name:** Doxycycline Hyclate Tablets  
**Indication:** Multiple Indications  
**Sponsor/Applicant Name:** Aqua Pharmaceuticals/ [REDACTED] (b) (4)

**FDA ATTENDEES**

Division of Anti-Infective Products

Dr. John Farley	Acting Director
Dr. Katherine Laessig	Deputy Director
Dr. Sumathi Nambiar	Deputy Director for Safety
Dr. Dorota Matecka	Product Analysis Lead/CMC
Dr. Shrikant Pagay	Chemistry Reviewer
Dr. John Alexander	Clinical Team Leader
Dr. Dmitri Iarikov	Clinical Reviewer
Dr. Minerva Hughes	Biopharmaceutics Reviewer
Dr. Kimberly Bergman	Clinical Pharmacology Team Leader
Dr. Carmen DeBellis	Project Manager

**SPONSOR ATTENDEES**

Aqua Pharmaceuticals

Dr. Kimberley Forbes-McKean	Vice President, Research & Development
Mr. Skip Williams	Vice President, Product Development
[REDACTED] (b) (4)	[REDACTED] (b) (4) (Consultant)
[REDACTED] (b) (4)	[REDACTED] (b) (4) (Consultant)

## **BACKGROUND**

A Pre-NDA meeting was held on April 17, 2013 with the Agency to discuss the proposed NDA package for Doxycycline Hyclate Tablets. At the meeting the Agency agreed to listen to new information recently obtained from ongoing development work for discussion. The following information was submitted to the Agency in a Type A meeting background package for discussion:

- Justification for requesting a waiver from conducting an *in vivo* bioequivalence study of the 75 mg and dual-scored 150 mg tablets
- Justification for including the unscored 150 mg tablets in the NDA
- Stability data package to be included in the NDA

## **DISCUSSION**

The Sponsor received responses to the meeting background package questions prior to the meeting. The meeting was held to discuss any questions or clarifications the Sponsor had concerning the Agency responses. The discussion is described below.

**Question 1:** Does the Agency agree that the comparative dissolution studies in four media of the 75 mg tablets and dual-scored 150 mg tablets (rapidly dissolving formulations of BCS Class 1 drug substance), as well as data obtained for the unscored 150 mg tablets and the RLD, support the request for a waiver from conducting *in vivo* bioequivalence studies on the 75 mg tablets and the dual-scored 150 mg tablets?

**Preliminary FDA Response:** No, the data provided are not sufficient to support a waiver of bioequivalence studies for the 75 mg tablets and dual-scored 150 mg tablets. Although you have concluded that the slower dissolving, unscored 150 mg tablet is bioequivalent to the 100 mg RLD tablet and a faster dissolving product should not be less bioavailable, the issue is bioequivalence with respect to C<sub>max</sub> and AUC, not bioavailability. Your basis for concluding that the dissolution method is overly discriminating is also unclear given the absence of complete details on the method, corroborating *in vivo* data, or dissolution using biorelevant media as suggested in the Jantratid et al reference provided. That being said, we acknowledge the possibility that data variability may be contributing to some of the *in vitro* differences observed with the RLD and do recognize the breadth of studies characterizing doxycycline hyclate pharmacokinetics. Therefore, we request that you provide the following additional information as an amendment to your IND to better assess whether a biowaiver could be applicable for your 75 mg (unscored) and 150 mg scored tablets.

- Complete dissolution test method parameters used for each tested condition, with supporting justification. Please indicate which method is your intended regulatory method.

- Complete description of your multivariate, model-independent analysis, with a clear discussion on your protocol for determining the max MSD and MSD. We believe that the Mahalanobis Distance approach may be a better assessment of profile similarity given the observed data variability. However, this supplementary analysis was provided for only the 150 mg dual-scored and 75 mg tablets, which met the similarity limit by your f2 calculations. We request that you submit the MSD comparative analyses for each comparison summarized in Table 10-4 (page 14) of your package.
- Comparative dissolution data using (b) (4) possible, to strengthen your claim that the standard pH 1.2, 4.5, and 6.8 media are overly discriminating.

**Meeting Discussion:** The Sponsor clarified that the following dissolution parameters were used for dissolution profile analysis of Doxycycline Hyclate Tablets:



The Sponsor intends to rely on the USP dissolution method for Doxycycline Hyclate Tablets, noting that the methodology was monographed in the CFR up until 1998 and is one of the two dissolution tests listed in the USP for Doxycycline Hyclate Tablets. The Sponsor relied on their understanding that compendial standards are the official specification for immediate release products with the same active ingredient as per FDA's Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms. The Division clarified that dissolution methods are product specific, and while the USP method may be used as a starting point, the Sponsor needs to demonstrate that the proposed dissolution method is suitable for this new doxycycline hyclate formulation. It has been demonstrated that all doxycycline products do not provide the exact same dissolution performance. The Division also reminded the Sponsor that the information referenced from FDA's guidance pertains to generic products and is not applicable for an NDA

The Sponsor committed to submitting the complete dissolution method development and justification information for review.

In addressing the Division's concerns regarding the risk of bio-inequivalence for the 75 mg and scored 150 mg tablets, the Sponsor provided an overview of the available doxycycline pharmacokinetic (PK) studies to illustrate their position that the proposed dissolution method is overly discriminating and all formulations are expected to be bioequivalent. The Sponsor's key points were the following:

The Sponsor's bioequivalence study that compared the unscored 150 mg tablets to the reference listed drug (RLD) demonstrated virtually superimposable plasma concentration-time profiles and satisfied FDA's acceptance criteria for bioequivalence. Although formulations that have been shown to be bioequivalent in vivo are expected to have similar dissolution profiles to each other in all four dissolution media, the in vitro dissolution data comparing the unscored 150 mg tablets and the RLD in (b) (4) (Briefing Package Figure 11-3B) showed significantly different in vitro release rates and the  $f_2$  value was 29 (Table 2).

- The release rates of doxycycline from the oral doxycycline dosage forms in the stomach (i.e., acidic conditions represented by (b) (4)) are not critical since absorption of doxycycline primarily occurs in the duodenum. The data summarized in Table 1 demonstrate how different formulations of doxycycline result in similar pharmacokinetics. Thus, the (b) (4) dissolution media is overly discriminating as it showed a significantly different in vitro profile of two products that had identical in vivo performance.
- The prescribing information (PI) for Vibra-Tabs (the original RLD prior to marketing discontinuation) states that doxycycline is virtually completely absorbed after oral administration. This statement is identical to what is stated in the prescribing information of DORYX, a delayed release doxycycline hyclate tablet. In addition, the average peak serum levels in the PI are identical for Vibra-tabs and DORYX.
- A comparison of the pharmacokinetics of different doxycycline hyclate products obtained from publicly available information was provided, as summarized in Table 1. In addition, The Sponsor is the current Sponsor of the Monodox® (doxycycline monohydrate) Capsules. A study comparing Monodox® to various dosage forms and salts of doxycycline [i.e., Vibramycin® Hyclate (doxycycline hyclate capsules, USP) and Vibra-Tabs® (doxycycline hyclate tablets, USP) Film Coated Tablets and Vibramycin® Monohydrate (doxycycline monohydrate) for Oral Suspension] was submitted as a basis for approval and demonstrated bioequivalence. Despite the varied release mechanisms for these different doxycycline hyclate products, and the accompanying differences in their in vitro dissolution profiles, all of the doxycycline products produce comparable areas under the curve, peak concentrations and times to reach peak concentration in vivo. These data further demonstrate that different release rates of doxycycline from the oral doxycycline dosage forms in the stomach are not critical since absorption of doxycycline primarily occurs in the duodenum, and therefore ultimately, such differences do not significantly change the pharmacokinetics of the drug.

**Table 1: Comparison of the Pharmacokinetics of Different Doxycycline Hyclate Products**

Product	Dosage Form	Strength	Dose	N	Dose-Adjusted to 300 mg		
					AUC (ng-hr/mL)	C (ng/mL)	T (hours)
Aqua	IR Tablet Unscored	150	300 mg	24	73027	3044	3.0
Westward	IR Tablet	100	300 mg	24	70475	2979	3.0
				(b) (4) 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

Given this new information, the Sponsor posed the following new question to the Division:

Does the Agency agree that these scientific data and the in vivo data for the RLD vs. Aqua's unscored 150 mg tablets are adequate to support approval (i.e., biowaiver) of the dual-scored 150 mg tablets and 75 mg tablets?

The Division stated that it was unable to comment on the new information presented at the meeting and encouraged the Sponsor to submit a complete request for biowaiver package to the IND for Agency feedback.

The Sponsor and Agency agreed that the waiver submission would contain a front page executive summary and tabular summary of the key in vivo data and conclusions. The Sponsor mentioned that information concerning Monodox may be lacking since it is an older product and there may be some variability in data between the capsules and tablets but all inconsistencies will be explained.

In addition to the PK information, the Sponsor committed to providing the complete description of the multivariate, model independent analysis with a clear discussion on the protocol for determining the max MSD and MSD in the IND amendment.

The Sponsor expressed concerns regarding their planned timeline for submitting the NDA and asked whether including the biowaiver request in the NDA is an option. The Division noted that it is in the Sponsor's best interest to determine whether a biowaiver is applicable before submitting the NDA, but it is a business decision which option to pursue. The Division

recognized the importance of this issue to the Sponsor's development program and committed to expediting its review of the IND amendment, as resources allow. The Division also clarified that its request for additional dissolution data in [REDACTED]<sup>(b) (4)</sup> was to provide a more complete picture of the overly discriminating nature of the proposed method, but if these data are not available at this time, the Sponsor may proceed with updating the IND with their PK-based justification for a waiver to further expedite resolving the biowaiver issue.

### **PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Further, under the Food and Drug Administration Safety and Innovation ACT (FDASIA), sponsors must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012.

### **PRESCRIBING INFORMATION**

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, please note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.
- The preferred presentation for cross-references in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[see Warnings and Precautions (5.2)]".

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application

### **MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

**505(B)(2) Pathway**

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry Applications Covered by Section 505(b)(2) (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a

“duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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/s/  
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SUMATHI NAMBIAR  
07/29/2013



IND 113575

**MEETING MINUTES**

Aqua Pharmaceuticals

c/o [REDACTED] (b) (4)

Dear [REDACTED] (b) (4):

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for doxycycline hyclate tablets.

We also refer to the Pre-NDA meeting between representatives of your firm and the FDA on April 17, 2013.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Carmen DeBellas, Regulatory Project Manager at (301) 796-796-1203.

Sincerely,

*{See appended electronic signature page}*

John J. Farley, MD, MPH  
Acting Director  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date** April 17, 2013

**Application Number:** IND 113575  
**Product Name:** doxycycline hyclate  
**Sponsor/Applicant Name:** Aqua Pharmaceuticals

**FDA ATTENDEES**

Dr. John Farley	Acting Director
Dr. Katherine Laessig	Deputy Director
Dr. Carmen DeBellis	Project Manager
Dr. Kimberly Bergman	Clinical Pharmacology Team Leader
Dr. Ryan Owen	Clinical Pharmacology
Ms. Naseya Minor	Project Manager
Dr. Thamban Valappil	Statistical Team Leader
Dr. Kerry Snow	Acting Clinical Microbiology Team Leader
Dr. Wendelyn Schmidt	Pharmacology/Toxicology Team Leader
Dr. Scott Komo	Statistical Reviewer
Dr. Kerian Grande-Roche	Clinical Microbiology Reviewer
Dr. John Metcalfe	Product Quality Microbiology Reviewer
Dr. Dmitri Iarikov	Clinical Reviewer
Dr. John Alexander	Clinical Team Leader
Dr. Shrikant Pagay	Chemistry Reviewer
Dr. Rapti Madurawe	Chemistry Branch Chief VI
Dr. Minerva Hughes	Biopharmaceutics Reviewer

**SPONSOR ATTENDEES**

Aqua Pharmaceuticals

Dr. Kimberley Forbes-McKean	Vice President, Research & Development
Mr. Skip Williams	Vice President, Product Development

(b) (4)

## 1.0 BACKGROUND

The purpose of this meeting was to discuss the submission of a New Drug Application (NDA) for doxycycline hyclate tablets 75 mg and 150 mg. The Sponsor proposes to discuss the following items:

- eCTD format
- Chemistry, Manufacturing & Controls
- Clinical Microbiology
- Clinical Pharmacology

The Sponsor provided questions and received Agency responses before the meeting. The Sponsor asked to discuss responses to questions 3, 4, 5, 6 and 7.

## 2. DISCUSSION

### Question 3:

Does the Agency agree that the proposed drug substance specification, and analytical procedures are adequate to support the planned 505(b) (2) NDA?

### **Agency Response:**

No, we do not agree. While the specifications for the drug substance include USP information, USP testing is a minimum legal standard. Additional testing assures maintaining the quality and consistency from batch to batch. Please include the following additional tests in the drug substance specification:

- a) Heavy metals
- b) Residue on Ignition
- c) Total impurities
- d) Particle Size distribution
- e) Crystallinity

We also recommend you use ICH format for impurities specifications (i.e., specified, identified, specified unidentified, unspecified, total impurities) as recommended in the ICH Q3A (R2) guidance. Note that any new impurities present in your drug substance (or drug product) may require additional information, including qualification, depending on the type of impurity and amount present.

Note that the acceptability of the drug substance specifications will be determined during NDA review.

### **Meeting Discussion:**

The Sponsor agreed to include the additional testing per Agency's response. The Agency also asked to include in addition to the drug substance crystallinity test, tests for potential conversion of morphic forms during drug product manufacture and stability. The Agency stated that the sponsor should demonstrate that the process is controlled and that no new polymorph is formed in the drug product.

**Question 4:**

Does the Agency agree that the proposed drug product specification and analytical procedures are adequate to support the planned 505(b) (2) NDA?

**Agency Responses:**

No we do not agree. In addition to the proposed drug product specifications tests, we recommend you include a test for Total Impurities and use ICH Q3B (R2) format for impurities' specifications (i.e., specified identified, specified unidentified, unspecified, total degradation products).

**Additional Comments:**

a) Testing for the dual scored 150 mg tablets should include tests per Guidance for Industry "Tablet Scoring: Nomenclature, Labeling and Data for Evaluation." We also recommend you follow the FDA response in IND 113575 Study May Proceed letter dated July 6, 2012. Although (b) (4) % w/w, as it has dual score lines, we recommend content uniformity by assay for establishing uniformity of dosage units for each of the split 50 mg portions in the tablet splitting study recommended in the guidance. In addition, please present the content uniformity data for the middle 50 mg portions of the tablets separately as the middle portion with two broken edges may have increased risk of friability.

b) We recommend inclusion of the content uniformity by assay for the split 50 mg portions as part of the drug product specification.

c) Provide open dish data for tablets to gain an understanding of (b) (4).

d) Your proposed dissolution method and acceptance criterion of Q = 85% in 90 minutes is based on the USP monograph; however, please note that the dissolution method is product (i.e. formulation) specific, and the dissolution acceptance criterion should be based on the product's dissolution data from clinical and primary stability batches. Provide in your NDA submission, the data supporting the selection of the proposed dissolution method (i.e., selection of the equipment/apparatus, in vitro dissolution medium, agitation/rotation speed, pH, assay, sink conditions, etc.) and include the testing conducted to demonstrate the method's discriminating capability for your product (see USP<1092>). Additionally, provide the complete dissolution data (individual values, mean, RSD, and profiles) for the clinical and registration stability batches supporting the proposed specification-time point and specification-value. Note that for immediate release products, the selection of the specification time point should be where Q=80% dissolution occurs. For a slow dissolving, immediate release product, a two-point specification (i.e., early and late phase) is recommended for quality control.

**Meeting Discussion:**

a) The Sponsor stated that they would include a test for Total Impurities and use ICH Q3B (R2) format for impurities specifications. The Sponsor indicated that as the tablets (b) (4) They looked at left, middle and right portions after splitting tablets from 2 registration scored tablet batches. Other studies were performed on split tablets including composite assay, (b) (4), dissolution and friability and the studies met all the specifications for weight uniformity.

The Agency stated that as tablets are (b) (4), segregation could potentially occur (b) (4) and result in (b) (4) variation in the three split portions of the dual scored tablet. The Agency stated the sponsor should perform content uniformity testing by assay for the split 50 mg portions of the dual scored tablets instead of content uniformity by weight. The Agency agreed this test of 50 mg split tablet portions could be conducted as a one time study instead of the Agency's original recommendation to perform it as a release test. The Sponsor agreed to perform the Content Uniformity Test by assay of the split portions of the tablet.

b) The Sponsor agreed to perform the Content Uniformity Test on 2 lots of the scored tablets.

c) The Agency explained that the open dish study is a one time study to be conducted on split tablet portions stored under ambient conditions over a period of time. The Agency indicated that the rationale for this study is that a patient may split all the tablets in the prescription container at one time. The Agency stated that per current practice, the maximum number of drug dispensed for a prescription is a 90-day supply and the Sponsor could determine the appropriate test duration time depending on how their product is to be used. For example, the study could be for a week if the treatment period is for a week. The Agency said only the 150 mg scored tablet split pieces need be evaluated in this study.

d) The Sponsor acknowledged FDA's comments and indicated they plan to request a follow-up meeting to discuss the dissolution method and data supporting a future biowaiver request. Complete dissolution profile data will be collected and submitted to the NDA, as requested.

**Question 5:**

Does the Agency agree that Microbial Limits testing is not necessary for release or stability testing of commercial batches of Doxycycline Hyclate Tablets?

**Agency Response:**

Upon submission of the NDA, you may propose to omit finished product microbial limits testing for batch release and substitute in-process manufacturing controls, tests and acceptance criteria that provide assurance of the microbiological quality for each batch of your product. These process controls, tests and acceptance criteria should be identified in the batch release criteria, and include, for example:

- [REDACTED] (b) (4)

**Meeting discussion:**

The Sponsor stated that they decided to perform microbial limits testing at release of each batch of product. The Agency asked why the Sponsor arrived at this decision since the Agency's response will allow the Sponsor an option to forgo microbial limits testing on each product batch. The Sponsor responded that it was easier to test each batch for microbial limits that provide the information in the Agency response. The Agency clarified that the requested information would only need to be provided a onetime submission in the NDA. Upon review of the manufacturing process controls the Agency may determine that there is no need to perform microbial limits testing on each product batch. The Sponsor stated that they will use this information when determining whether to carry out microbial limits testing upon submission of the NDA.

**Question 6:**

Does the Agency agree that the stability data package for the planned 505(b) (2) NDA is adequate to support an initial expiry dating period of (b) (4) months in the commercial container closure systems?

**Agency Response:**

We are unable to provide a response as your NDA stability package is unclear and lacks sufficient detail.

It is our understanding that the commercial 150 mg tablet is scored while the commercial 75mg tablet is unscored. It is also our understanding the following packaging configurations are proposed for commercialization and the amount of stability data will be provided in the NDA. Please confirm.

- 75 mg Tablet in (b) (4) blister (2 count) – 6 months long-term (LT) and accelerated – 3 batches
- 75 mg Tablet in (b) (4) – 6 months LT and accelerated – 3 batches
- 75 mg Tablet in 60 CC HDPE (60 count) – 12 months LT and accelerated – 3 batches

- 150 mg dual-score Tablet (b) (4) blister (1 count) - 6 months LT and accelerated – 2 batches
- 150 mg dual-score Tablet in (b) (4) - 6 months LT and accelerated – 2 batches

150 mg dual-score Tablet in 60 cc HDPE (60 count) - 6 months LT and accelerated – 2 batches

To facilitate evaluation of your proposal, provide the rationale for each of these packaging configurations, in particular for the 75 mg: (b) (4) and 150 mg: (b) (4) configurations. Please also provide a scientific rationale for the amount of stability data proposed for each of these configurations, including any bracketing or matrixing approaches used.

Indicate if the three 75 mg batches represent (b) (4). Similarly, indicate if the two 150 mg batches are from (b) (4). We recommend stability batches be made from (b) (4).

We agree the following may be used as supportive, if the findings parallel the registration stability data:

75 mg in 2 count (b) (4) - 12 months LT, intermediate, and 1 month accelerated  
unscored 150 mg in 1 count (b) (4) - 12 months LT and intermediate, and 1 month accelerated  
unscored 150 mg in 30 count in 60cc HDPE bottle - 12 month LT and 6 months accelerated

It is our expectation that at least 12 months of long term registration stability data be provided at the time of NDA submission. Please refer to ICH stability guidelines given in Guidance for Industry, “Q1A (R2) Stability Testing of New Drug Substances and Products.”

Include in your NDA, the complete dissolution profile data (i.e., multi-point sampling at 15, 20, 30, 45, 60, 75 and 90 minutes) under long-term and accelerated storage conditions to assess dissolution profile changes on storage and to support setting a final acceptance criterion.

#### **Meeting Discussion:**

The Sponsor confirmed that they would be submitting stability data in the NDA for the 75 mg tablet and the 150 mg dual scored tablets as listed in the Agency’s response. These would include 3 batches each of 75 mg tablets (in 3 packaging configurations of 2 count (b) (4) (b) (4) and 60 count HDPE) and 2 batches each of 150 mg dual scored tablets (in 3 packaging configurations of 1 count (b) (4) (b) (4) and 60 count HDPE).

The Agency asked if (b) (4) are used for each of the 3 tablet batches in the Sponsor’s stability proposal. The Sponsor confirmed that (b) (4) are used to manufacture the three 75 mg and 150 mg unscored tablet batches. Also, (b) (4) are used to manufacture the two of the 150 mg dual-scored tablet batches.

There was discussion about the amount of data on the registration batches to be submitted in the NDA per ICH guidance which specifies 12 months data on long term storage conditions. The Sponsor plans to submit 12 month long term data for the 75 mg tablets and only 6 month long term data for the 150 mg scored tablets. The Sponsor pointed out their understanding from the previous meetings: “Aqua explained that the amount of data for the two batches of 150 mg dual-scored tablets (i.e., 6 months long-term and accelerated data at the time of NDA submission) was based on the Agency’s feedback in the Study May Proceed letter (Briefing Package, Page 80).” Since 150 mg unscored tablets were originally proposed for this application, the stability data for the 150 mg unscored tablets will be submitted as supporting data.

The Sponsor then asked if they could submit information for the 150 mg unscored tablet later as a supplemental application since they have performed all the bioequivalence work and it is equivalent to the Westward 100 mg tablet.

(b) (4)

The Agency replied that submitting the 150 mg unscored data in the NDA submission and the 150 mg scored information is a whole new question with many implications from Chemistry, Manufacturing & Controls standpoint. The Agency asked the Sponsor to submit a justification with questions in a meeting request to be reviewed concerning the 150 mg unscored proposal.

The Agency had asked for clarification on the packaging used in the stability studies. The Sponsor replied that originally the (b) (4) was intended for the drug sample package. This worked fine for the 12 month stability under long term storage but with the accelerated stability study, the (b) (4) after 1 month storage showed discoloration. The sponsor is monitoring this batch under 30°C/75% at the intermediate storage condition. The Sponsor then added a new packaging (b) (4) blister (b) (4). If the testing using (b) (4) didn't work out they would switch to bottles. The Sponsor reported that (b) (4) looked like it was going to be acceptable and bottles would not be needed.

The FDA asked if the Sponsor has considered bracketing or matrixing for stability data.

The Sponsor replied that it was difficult to propose such a design; instead, they will provide the stability data on batches, strengths and packages listed under the Agency's response above under Question 6.

The Agency stated that under PDUFA V it is expected that the Chemistry, Manufacturing & Controls package will be complete on submission because of the narrow timelines.

The Sponsor stated that they will collect complete dissolution profile data for future stability pulls and submit these data to the NDA. Multi-point dissolution sampling was not implemented at the start of the stability study, so only the later time points will be provided.

**Question 7:**

Does the Agency agree that with the removal of the indication for uncomplicated gonorrhea, no additional clinical microbiology information is required to support the planned 505(b) (2) NDA?

**Agency Response:**

The indication for uncomplicated gonorrhea will be included in the label. Prior to NDA submission, you should evaluate whether the content of your proposed labeling is consistent with the most recently approved labeling for Pfizer's doxycycline NDA.

**Meeting Discussion:**

The Sponsor stated that they will use the most recent Vibramycin and Doryx labels as examples for their labeling submission.

**3. PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Further, under the Food and Drug Administration Safety and Innovation ACT (FDASIA), sponsors must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012.

Because none of the criteria apply to your application, you are exempt from these requirements.

**4. PRESCRIBING INFORMATION**

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, please note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.
- The preferred presentation for cross-references in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[*see Warnings and Precautions (5.2)*]".

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

## **5 ACTION ITEMS**

In order to clarify and complete some chemistry issues, the Sponsor was advised to submit a meeting request with questions for response.

## **6 ATTACHMENTS AND HANDOUTS**

FDA Responses

## 9. SPECIFIC QUESTIONS

### 9.1. General

#### 9.1.1. Electronic Common Technical Document (eCTD) Format

This NDA will be submitted in eCTD format through the Agency's Electronic Submission Gateway (ESG) under [REDACTED]<sup>(b) (4)</sup> approved WebTrader account. The electronic submission will be prepared in accordance with the ICH eCTD Specifications, and all other pertinent and applicable FDA specifications/guidance.

The *in vitro* dissolution studies will be discussed and summarized in Module 1.12.15 (Request for Waiver of *In Vivo* Bioavailability Studies) and Module 3.2.P.2.2 (Pharmaceutical Development – Formulation Development), as applicable. The full dissolution studies will be published in Module 5.3.1.3 (*In Vitro-In Vivo* Correlation Study Reports and Related Information).

An eCTD content plan outlining the organization of the eCTD is provided in [Attachment 13-5](#).

**Question 1:** *Does the Agency agree with the proposed organization of the eCTD NDA?*

**Agency Response:**

**Yes, we agree.**

#### 9.1.2. Established Product Name

Aqua will separately request review and approval of a proprietary name. The proposed established name is Doxycycline Hyclate Tablets USP.

**Question 2:** *Does the Agency agree that the established name Doxycycline Hyclate Tablets USP is appropriate for Aqua's proposed product?*

**Agency Response:**

**Yes, we agree. The proposed established name is appropriate as per USP Monograph.**

## 9.2. Chemistry, Manufacturing and Controls

### 9.2.1. Control of Drug Substance

The proposed drug substance specification and overviews of the analytical procedures, validation and justification of the specification are provided in [Section 10.1.4](#). The proposed drug substance specification complies with the current USP monograph and includes additional noncompendial tests and acceptance criteria for two process related impurities <sup>(b) (4)</sup> as outlined in [Table 10-3](#).

***Question 3:*** *Does the Agency agree that the proposed drug substance specification and analytical procedures are adequate to support the planned 505(b)(2) NDA?*

#### **Agency Response:**

**No, we do not agree. While the specifications for the drug substance include USP information, USP testing is a minimum legal standard. Additional testing assures maintaining the quality and consistency from batch to batch. Please include the following additional tests in the drug substance specification:**

- a) Heavy metals
- b) Residue on Ignition
- c) Total impurities
- d) Particle Size distribution
- e) Crystallinity

**We also recommend you use ICH format for impurities specifications (i.e., specified, identified, specified unidentified, unspecified, total impurities) as recommended in the ICH Q3A (R2) guidance. Note that any new impurities present in your drug substance (or drug product) may require additional information, including qualification, depending on the type of impurity and amount present.**

**Note that the acceptability of the drug substance specifications will be determined during NDA review.**

### 9.2.2. Control of Drug Product

The proposed drug product specification and overviews of the analytical procedures, validation and justification of the specification are provided in [Section 10.2.5](#). The proposed drug product specification is based on the USP monograph for Doxycycline Hyclate Tablets. Additional tests for identification by high performance liquid chromatography (HPLC) and impurities/degradants are included. Acceptance criteria are based on the available stability data, and meet the USP monograph requirements for Doxycycline Hyclate Tablets.

***Question 4:*** *Does the Agency agree that the proposed drug product specification and analytical procedures are adequate to support the planned 505(b)(2) NDA?*

**Agency Response:**

**No we do not agree. In addition to the proposed drug product specification tests, we recommend you include a test for Total Impurities and use the ICF Q3B(R2) format for impurities specification (i.e, specified identified, specified unidentified, unspecified, total degradation products).**

**Additional Comments:**

**a) Testing for the dual scored 150mg tablets should include tests per Guidance for Industry “Tablet Scoring: Nomenclature, Labeling and Data for Evaluation.” We also recommend you follow the FDA response in IND 113575 Study May Proceed letter dated July 6, 2012. Although the drug load your tablets is greater than (b) (4), as it has dual score lines, we recommend content uniformity by assay for establishing uniformity of dosage units for each of the split 50 mg portions in the tablet splitting study recommended in the guidance. In addition, please present the content uniformity data for the middle 50 mg portions of the tablets separately as the middle portion with two broken edges may have increased risk of friability.**

**b) We recommend inclusion of the content uniformity by assay for the split 50 mg portions as part of the drug product specification.**

**c) Provide open dish data for tablets to gain an understanding of (b) (4) / (b) (4)**

**d) Your proposed dissolution method and acceptance criterion of Q = 85% in 90 minutes is based on the USP monograph; however, please note that the dissolution method is product (i.e. formulation) specific, and the dissolution acceptance criterion should be based on the product’s dissolution data from clinical and primary stability batches. Provide in your NDA submission, the data supporting the selection of the proposed dissolution method (i.e., selection of the equipment/apparatus, in vitro dissolution medium, agitation/rotation speed, pH, assay, sink conditions, etc.) and include the testing conducted to demonstrate the method’s discriminating capability for your product (see USP<1092>). Additionally, provide the complete dissolution data (individual values, mean, RSD, and profiles) for the clinical and registration stability batches supporting the proposed specification-time point and specification-value. Note that for immediate release products, the selection of the specification time point should be where Q=80% dissolution occurs. For a slow dissolving, immediate release product, a two-point specification (i.e., early and late phase) is recommended for quality control.**

### 9.2.3. Drug Product Microbial Limits Testing

Microbial limits testing was conducted during development on the registration batches of Doxycycline Hyclate Tablets. One of the approved generic products for doxycycline hyclate was sponsored by (b) (4). Aqua obtained the analytical technology from (b) (4) for their 100 mg dosage strength approved under (b) (4) as part of a licensing agreement. Microbial Limits testing according to USP <61> and <62> are not included in (b) (4). Doxycycline hyclate is an anti-microbial agent; therefore, microbial growth is not expected. Available stability data will be included in the NDA; these data demonstrate that no microbial growth occurs with Aqua's Doxycycline Hyclate Tablets. Therefore, Aqua proposes that Microbial Limits testing not be conducted for release or stability of commercial batches of Doxycycline Hyclate Tablets.

***Question 5:*** *Does the Agency agree that Microbial Limits testing is not necessary for release or stability testing of commercial batches of Doxycycline Hyclate Tablets?*

#### **Agency Response:**

**Upon submission of the NDA, you may propose to omit finished product microbial limits testing for batch release and substitute in-process manufacturing controls, tests and acceptance criteria that provide assurance of the microbiological quality for each batch of your product. These process controls, tests and acceptance criteria should be identified in the batch release criteria, and include, for example:**

- **Microbial limits data for critical raw materials,**
- **Microbiological monitoring data for critical processing steps that can be related to the batch, and**
- **In-process control parameters (e.g., heat, drying, washing) that may affect product quality microbiology.**

### 9.2.4. Stability Data Package

Initial development of Aqua's Doxycycline Hyclate Tablets included an unscored 150 mg dosage strength. As agreed with the Agency, the proposed commercial 150 mg dosage strength is a dual-scored tablet. As also agreed by the Agency in the pre-IND consultation review responses (27 January 2012 email; provided in [Attachment 13-3](#)) and in the IND 113575 Study May Proceed letter (Reference ID: 3155606; provided in [Attachment 13-6](#)), the initial NDA will include a minimum of 6- to 12-month stability data for the registration batches stored under long-term conditions ( $25^{\circ} \pm 2^{\circ}\text{C}/60\% \pm 5\% \text{RH}$ ) and a minimum of 6-month stability data for the registration batches stored under accelerated conditions ( $40^{\circ} \pm 2^{\circ}\text{C}/75\% \pm 5\% \text{RH}$ ).

Data will be provided in the NDA for the unscored 150 mg dosage strength [60 cc (30-count trade bottles)] used in the clinical studies through storage for 12 months under long-term conditions and through storage for 6 months under accelerated conditions. As agreed, the NDA will also include data for the 150 mg dual-scored tablets [60 cc (60-count trade bottles)] through storage for 6 months under long-term and accelerated conditions.

The proposed commercial container closure systems are outlined in [Table 10-5](#). The sample pack initially chosen for development was a (b) (4); however, significant changes were observed after storage of the (b) (4) pack for 1 month under accelerated conditions. Therefore, testing of (b) (4) samples stored under the intermediate storage conditions ( $30^{\circ} \pm 2^{\circ}\text{C}/65\% \pm 5\% \text{RH}$ ) was initiated. Stability data will be included in the NDA for the 75 mg dosage strength and the 150 mg unscored dosage strength packaged in the (b) (4) through storage for 12 months under long-term and intermediate conditions, as well as through storage for 1 month under accelerated conditions.

In order to ensure a more protective container closure system for samples for commercial distribution, Aqua initiated studies in two additional container closure systems: an (b) (4) blister and a (b) (4). Stability data from these sample package configurations for 75 mg tablets and dual-scored 150 mg tablets will be included in the NDA for samples stored through 6 months under long-term and accelerated conditions.

An overview of data for the registration batches (75 mg and 150 mg unscored tablets, and 150 mg dual-scored tablets) and the container closure systems (trade bottles, (b) (4), (b) (4) and (b) (4) sample blisters) to be included in the planned 505(b)(2) NDA is provided in [Table 10-18](#).

An initial expiry dating period of (b) (4) months for drug product stored in the commercial container closure systems [60 cc HDPE bottles, (b) (4) blisters and (b) (4) ([Table 10-5](#))] is proposed.

***Question 6:*** *Does the Agency agree that the stability data package for the planned 505(b)(2) NDA is adequate to support an initial expiry dating period of (b) (4) months in the commercial container closure systems?*

**Agency Response:**

**We are unable to provide a response as your NDA stability package in unclear and lacks sufficient detail.**

**It is our understanding that the commercial 150 mg tablet is scored while the commercial 75mg tablet is unscored. It is also our understanding the following packaging configurations are proposed for commercialization and the amount of stability data will be provided in the NDA. Please confirm.**

**75 mg Tablet in (b) (4) blister (2 count) – 6 months long-term (LT) and accelerated – 3 batches**

**75 mg Tablet in [REDACTED] (b) (4) – 6 months LT and accelerated – 3 batches**

**75 mg Tablet in 60 CC HDPE (60 count) – 12 months LT and accelerated – 3 batches**

**150 mg dual-score Tablet [REDACTED] (b) (4) blister (1 count) - 6 months LT and accelerated – 2 batches**

**150 mg dual-score Tablet in [REDACTED] (b) (4) - 6 months LT and accelerated – 2 batches**

**150 mg dual-score Tablet in 60 cc HDPE (60 count) - 6 months LT and accelerated – 2 batches**

**To facilitate evaluation of your proposal, provide the rationale for each of these packaging configurations, in particular for the 75 mg: [REDACTED] (b) (4) and 150 mg: [REDACTED] (b) (4) configurations. Please also provide a scientific rationale for the amount of stability data proposed for each of these configurations, including any bracketing or matrixing approaches used.**

**Indicate if the three 75 mg batches represent a [REDACTED] (b) (4). Similarly, indicate if the two 150 mg batches are [REDACTED] (b) (4). We recommend stability batches be made from [REDACTED] (b) (4).**

**We agree the following may be used as supportive, if the findings parallel the registration stability data:**

**75 mg in 2 count [REDACTED] (b) (4) - 12 months LT, intermediate, and 1 month accelerated**

**unscored 150 mg in 1 count [REDACTED] (b) (4) - 12 months LT and intermediate, and 1 month accelerated**

**unscored 150 mg in 30 count in 60cc HDPE bottle - 12 month LT and 6 months accelerated**

**It is our expectation that at least 12 months of long term registration stability data be provided at the time of NDA submission. Please refer to ICH stability guidelines given in Guidance for Industry, “Q1A (R2) Stability Testing of New Drug Substances and Products.”**

**Include in your NDA, the complete dissolution profile data (i.e., multi-point sampling at 15, 20, 30, 45, 60, 75 and 90 minutes) under long-term and accelerated storage conditions to assess dissolution profile changes on storage and to support setting a final acceptance criterion.**

### 9.3. Nonclinical

As agreed by the Agency during pre-IND correspondence ([Attachment 13-2](#) and [Attachment 13-3](#)), no nonclinical studies were conducted for Doxycycline Hyclate Tablets. Therefore, there are no nonclinical questions.

### 9.4. Clinical

#### 9.4.1. Clinical Microbiology

The IND 113575 Study May Proceed letter (Reference ID: 3155606; [Attachment 13-6](#)) included “Additional Microbiology Comments” requesting data that may be needed to update the proposed package insert for Aqua’s drug product. Based on the teleconference held on 22 May 2012 to discuss Aqua’s justification of the 150 mg dosage strength, Aqua agreed that the NDA would include an unscored 75 mg dosage strength and a dual-scored 150 mg dosage strength, and the indication for uncomplicated gonorrhea would be removed from the labeling. The Agency agreed (email 24 July 2012; [Attachment 13-7](#)) that although a final determination regarding removal of the indication for uncomplicated gonorrhea for the doxycycline products has not been reached, if the indication is removed from the labeling, Aqua would not need to provide the requested information.

***Question 7:*** *Does the Agency agree that with the removal of the indication for uncomplicated gonorrhea, no additional clinical microbiology information is required to support the planned 505(b)(2) NDA?*

#### Agency Response:

**The indication for uncomplicated gonorrhea will be included in the label. In previous communications, we indicated that at the time of NDA submission we may request providing recent (within the last 3 years) doxycycline susceptibility data for at least 100 *N. gonorrhoeae* isolates associated with the indication on uncomplicated gonorrhea. No additional microbiology data will be needed with your NDA submission. Prior to NDA submission, you should evaluate whether the content of your proposed labeling is consistent with the most recently approved labeling for Pfizer’s doxycycline NDA.**

#### 9.4.2. Clinical Pharmacology

At the pre-IND meeting for IND 111602 (Doxycycline Hyclate (b)(4)) the Agency noted that since the submission would be a NDA, labeling would be required in Physician's Labeling Rule (PLR) format. The Agency recommended that the labeling for DORYX<sup>®</sup> (Doxycycline Hyclate Delayed-Release Tablets, USP) be used as the template, as this is an approved PLR format for a doxycycline product. In addition to the changes to the package insert associated with the differences between the RLD and the proposed drug product (i.e., strengths, product names, manufacturers, etc.), Aqua proposes that the Clinical Pharmacology section of the labeling (DORYX<sup>®</sup> PLR Section 12.3) be updated to reflect the data obtained from Aqua's pharmacokinetic studies (Studies 11060203 and 11060204), (b)(4). These proposed changes to the content of the package insert are outlined in [Table 9-1](#). Synopses of Aqua's pharmacokinetic studies (Studies 11060203 and 11060204) are provided in [Attachment 13-8](#) and [Attachment 13-9](#), respectively.

***Question 8:*** *Does the Agency agree that the Clinical Pharmacology section of the package insert can be updated to reflect the data obtained from Aqua's pharmacokinetic studies (Studies 11060203 and 11060204)?*

**Agency Response:**

(b)(4)  
We agree that section 12.3 should be updated with the results from the completed studies. It is premature to discuss specific labeling statements prior to NDA submission."

#### 9.4.3. Clinical Data Package

The clinical data package to be included in the NDA is described in [Section 12](#) and outlined in the draft eCTD Content Plan provided in [Attachment 13-5](#).

***Question 9:*** *Does the Agency agree that the clinical data package is adequate to support the 505(b)(2) NDA?*

**Agency Response:**

The proposed clinical package appears adequate to support this NDA.

**Additional Comment:**

We have the following response to your February 28, 2013 submission, concerning PREA requirements.

**Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Further, under the Food and Drug Administration Safety and Innovation ACT (FDASIA), sponsors must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012.**

**Because none of the criteria apply to your application, you are exempt from these requirements.**

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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.**  
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/s/  
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JOHN J FARLEY  
05/21/2013