

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208253Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208253

Trade Name Acticlate CAP

Generic Name Doxycycline Hyclate capsules, 75 mg

Applicant Name Aqua Pharmaceuticals, LLC

Approval Date, If Known April 26, 2016

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)

b) 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.

Bioequivalence study conducted

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

c) Did the applicant request exclusivity?

YES NO **X**

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

n/a

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

YES NO **X**

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 **X**

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 **X** NO

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

NDA# 50-007 Doxycycline Hyclate Oral Capsule

NDA# 205931 Doxycycline Hyclate Oral Tablet

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 **X**

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:

(b) For each investigation not carried out under an IND or for which the applicant was

not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

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

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

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Maureen Dillon-Parker
Title: Chief, Project Management Staff
Date: *{See Electronic Signature}*

Name of Division Director signing form: Sumathi Nambiar, MD, MPH
Title: Director
Date: *{See Electronic Signature}*

Form OGD-011347

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

/s/

MAUREEN P DILLON PARKER
04/26/2016

SUMATHI NAMBIAR
04/26/2016

ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION ¹ | | |
|--|--------------------------------------|--|
| NDA # 208253 | 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 CAP Established/Proper Name: doxycycline hyclate 75 mg Dosage Form: Capsules | | Applicant: Aqua Pharmaceuticals LLC |
| RPM: Maureen Dillon-Parker | | Division: 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>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p>X No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: 4/25/16</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"> • Proposed action • User Fee Goal Date is <u>April 26, 2016</u> | | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR |
| <ul style="list-style-type: none"> • Previous actions <i>(specify type and date for each action taken)</i> | | <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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____ | | N/A |
| ❖ Application Characteristics ³ | | |

¹ 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.

² For resubmissions, 505(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).

³ 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.

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 | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

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: n/a

| | |
|--|---|
| ❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| ❖ Public communications (approvals only) | |
| • Office of Executive Programs (OEP) liaison has been notified of action | <input type="checkbox"/> Yes <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)? | <input checked="" type="checkbox"/> No |
| • If so, specify the type | |
| ❖ 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. |

CONTENTS OF ACTION PACKAGE

Officer/Employee List

| | |
|--|------------|
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only) | X Included |
| Documentation of consent/non-consent by officers/employees | X Included |

| Action Letters | |
|--|--|
| ❖ Copies of all action letters (<i>including approval letter with final labeling</i>) | Approval 4/26/2016 |
| Labeling | |
| ❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>) | |
| • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) | <input checked="" type="checkbox"/> Included 3/2/2016 |
| • Original applicant-proposed labeling | <input checked="" type="checkbox"/> Included 6/26/2015 |
| ❖ 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 |
| • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) | N/A |
| • Original applicant-proposed labeling | N/A |
| ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) | |
| • Most-recent draft labeling | <input checked="" type="checkbox"/> Included See Above Labeling 3/2/2016 |
| ❖ Proprietary Name | Denial 9/15/2015 Granted 3/25/2016 Review #1 9/02/2015 Review #2 3/22/2016 |
| • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) | |
| • Review(s) (<i>indicate date(s)</i>) | |
| ❖ Labeling reviews (<i>indicate dates of reviews</i>) | RPM: PM Label Rev 07/23/2015 PLR Format 07/23/2015 DMEPA: Rev#1 01/05/2015 Rev#2 12/23/2015 Rev#3 04/12/2016 PLT: 03/08/2016 OPDP: 02/16/2016 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None |
| ❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>) | 09/02/2015 |
| ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee | 04/08/2016 |
| ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) | <input checked="" type="checkbox"/> Included |
| ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |
| • Applicant is on the AIP | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

| | |
|---|---|
| <ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No N/A N/A |
| ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>n/a</u> If PeRC review not necessary, explain: Exempt from <u>PREA per May 2013 Pre-NDA meeting/ minutes; application provides for a new strength; does not trigger PREA.</u> | Application did not trigger PREA. |
| ❖ Breakthrough Therapy Designation | <input checked="" type="checkbox"/> N/A |
| <ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) | N/A |
| <ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) | N/A |
| <ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <u>MPC SharePoint Site</u></i>)</p> | N/A |
| ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>) | Included |
| ❖ 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) | n/a |
| ❖ Minutes of Meetings | |
| <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> N/A |
| <ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) | 05/21/2013 |
| <ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> No mtg |
| <ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> N/A |
| <ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> N/A |
| <ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) | N/A |
| ❖ Advisory Committee Meeting(s) | <input checked="" type="checkbox"/> No AC meeting |
| <ul style="list-style-type: none"> • Date(s) of Meeting(s) | |
| Decisional and Summary Memos | |
| ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Division Director Summary Review (<i>indicate date for each review</i>) | 04/21/2016 |
| Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) | 04/04/2016 |
| PMR/PMC Development Templates (<i>indicate total number</i>) | <input checked="" type="checkbox"/> None |

| Clinical | |
|--|--|
| ❖ Clinical Reviews | |
| • Clinical Team Leader Review(s) (indicate date for each review) | <input checked="" type="checkbox"/> No separate review |
| • Clinical review(s) (indicate date for each review) | 2/26/2016 |
| • Social scientist review(s) (if OTC drug) (indicate date for each review) | <input checked="" type="checkbox"/> None |
| ❖ 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 (indicate date of review/memo) | See Page 5 of Division director Summary Review |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) ⁵ | <input checked="" type="checkbox"/> None |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review) | <input checked="" type="checkbox"/> N/A |
| ❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) • REMS Memo(s) and letter(s) (indicate date(s)) • Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review) | N/A <input checked="" type="checkbox"/> None |
| ❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators) | <input checked="" type="checkbox"/> None requested |
| Clinical Microbiology <input type="checkbox"/> None | |
| ❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review) | <input checked="" type="checkbox"/> No separate review |
| Clinical Microbiology Review(s) (indicate date for each review) | 03/02/2016 |
| Biostatistics <input type="checkbox"/> None | |
| ❖ Statistical Division Director Review(s) (indicate date for each review) | <input checked="" type="checkbox"/> No separate review |
| Statistical Team Leader Review(s) (indicate date for each review) | <input checked="" type="checkbox"/> No separate review |
| Statistical Review(s) (indicate date for each review) | 03/22/2016 |
| Clinical Pharmacology <input type="checkbox"/> None | |
| ❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review) | <input checked="" type="checkbox"/> No separate review |
| Clinical Pharmacology Team Leader Review(s) (indicate date for each review) | <input checked="" type="checkbox"/> No separate review |
| Clinical Pharmacology review(s) (indicate date for each review) | 01/08/2016 |
| ❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters) | 09/11/2015 |

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

| Nonclinical <input type="checkbox"/> None | |
|--|--|
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| • ADP/T Review(s) <i>(indicate date for each review)</i> | <input checked="" type="checkbox"/> No separate review |
| • Supervisory Review(s) <i>(indicate date for each review)</i> | <input checked="" type="checkbox"/> No separate review |
| • Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i> | 11/04/2015 & 01/15/2016 |
| ❖ 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 Included in P/T review, page |
| ❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i> | <input checked="" type="checkbox"/> None requested |
| Product Quality <input type="checkbox"/> None | |
| ❖ Product Quality Discipline Reviews ⁶ | |
| • Tertiary review <i>(indicate date for each review)</i> | <input checked="" type="checkbox"/> None |
| • Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i> | <input checked="" type="checkbox"/> None |
| • Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i> | 03/25/2016 |
| ❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <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> | See page 54 of OPQ Review |
| <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 type="checkbox"/> Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> | <input checked="" type="checkbox"/> Acceptable 09/11/2015 Memo Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable |

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

| Day of Approval Activities | |
|---|---|
| <ul style="list-style-type: none"> ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) | X No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>) |
| <ul style="list-style-type: none"> • Finalize 505(b)(2) assessment | X Done |
| <ul style="list-style-type: none"> ❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager | n/a (<i>Send email to CDER OND IO</i>) |
| <ul style="list-style-type: none"> ❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications | n/a |
| <ul style="list-style-type: none"> ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email | X Done |
| <ul style="list-style-type: none"> ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter | n/a |
| <ul style="list-style-type: none"> ❖ 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 | X Done |
| <ul style="list-style-type: none"> ❖ Ensure Pediatric Record is accurate | n/a |
| <ul style="list-style-type: none"> ❖ Send approval email within one business day to CDER-APPROVALS | X Done 4/27/16 |



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208253

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Aqua Pharmaceuticals, LLC
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, June 26, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Doxycycline Hyclate Capsules, 75 mg.

We also refer to your correspondence, dated and received January 13, 2016, requesting review of your proposed proprietary name, Acticlate CAP.

We have completed our review of the proposed proprietary name, Acticlate CAP and have concluded that it is conditionally acceptable.

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

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

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 Maureen Dillon Parker, Regulatory Project Manager in the Office of New Drugs, at 301-796-0706.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
03/25/2016



NDA 208253

LABELING PMR/PMC DISCUSSION COMMENTS

Aqua Pharmaceuticals
Attention: Kimberley Forbes-McKean, PhD
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) dated June 26, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for doxycycline hyclate capsules, 75mg.

We also refer to our September 2, 2015, letter in which we notified you of our target date of March 2, 2016, for communicating labeling changes and/or postmarketing requirements/commitments (PMRs/PMCs) in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

On January 8, 2016, we received your January 8, 2016, revised labeling to this application. We have completed the preliminary review of the proposed labeling and have additional revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by March 11, 2016. The resubmitted labeling will be used for further labeling discussions.

Additionally, at this time we have not identified any PMRs/PMCs.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

If you have any questions, call me at (301)796-0706.

Sincerely,

{See appended electronic signature page}

Maureen Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE: Labeling

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/s/

MAUREEN P DILLON PARKER
03/02/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208253

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

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

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

Dear Dr. Forbes-McKean:

Please refer to your New Drug Application (NDA) dated and received, June 26, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Doxycycline Hyclate Capsule, 75 mg.

We also refer to your correspondence, dated and received, June 29, 2015, requesting review of your proposed proprietary name, (b) (4)

We have completed our review of the proposed proprietary name, (b) (4) and have concluded that this name is unacceptable for the following reasons:

(b) (4)

A large rectangular area of the document is completely redacted with a solid grey fill, obscuring the reasons for the unacceptable proprietary name. The redaction is labeled with "(b) (4)" in the top right corner.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

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 Mona Atkinson, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4215.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
09/15/2015



NDA 208253

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Aqua Pharmaceuticals, LLC
Attention: Kimberley Forbes-McKean, PhD
Vice President, Research & Development
158 West Gay Street
Darlington Commons, Suite 310
West Chester, PA 19380

Dear Dr. Forbes-McKean:

Please refer to your New Drug Application (NDA) dated June 26, 2015, received June 26, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for doxycycline hyclate capsules, 75mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is April 26, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by March 2, 2016.

We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues:

1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.
2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.
3. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval.
4. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.
5. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.
6. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).
7. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
8. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics*

and enclosed within brackets. For example, “[see Warnings and Precautions (5.2)]” or “[see Warnings and Precautions (5.2)]”.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by October 2, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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.

We reference the waiver granted on May 21, 2013, for the pediatric study requirement for this application.

If you have any questions, call Mona Atkinson, Regulatory Project Manager, at (301) 796-4215.

Sincerely,

{See appended electronic signature page}

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

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/s/

SUMATHI NAMBIAR
09/02/2015



NDA 208253

NDA ACKNOWLEDGMENT

Aqua Pharmaceuticals, LLC
Attention: Kimberley Forbes-McKean, PhD
Vice President, Research & Development
158 West Gay Street
Darlington Commons, Suite 310
West Chester, PA 19380

Dear Dr. Forbes-McKean:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Doxycycline Hyclate Capsules USP, 75 mg

Date of Application: June 26, 2015

Date of Receipt: June 26, 2015

Our Reference Number: NDA 208253

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 25, 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Mona Atkinson, Regulatory Project Manager, at (301) 796-4215.

Sincerely,

{See appended electronic signature page}

Maureen Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAUREEN P DILLON PARKER
07/24/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 113575

MEETING MINUTES

Aqua Pharmaceuticals
c/o B & H Consulting, Inc.
Attention: Elizabeth N. Dupras, RAC
Associate Director, CM&C and Regulatory Affairs
50 Division Street, Suite 206
Somerville, NJ, 08876

Dear Ms. Dupras:

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 DeBellis, 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)

| | |
|------------------------------|---|
| Ms. Elizabeth N. Dupras, RAC | Associate Director, CM&C and Regulatory Affairs, B & H Consulting Services, Inc. (Consultant) |
|------------------------------|---|

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 the drug load of your tablets is greater than (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 (b) (4).

d) Your proposed dissolution method and acceptance criterion of Q = (b) (4)

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 = (b) (4) % dissolution occurs. For a (b) (4) immediate release product, (b) (4) 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 are (b) (4) % weight/weight, content uniformity testing of split tablets was performed on a weight basis. They looked at left, middle and right portions after splitting tablets from 2 registration scored tablet batches. Other studies were performed on split tablets (b) (4) and the studies met all the specifications for weight uniformity.

The Agency stated that as tablets (b) (4)

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:

- 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 (b) (4) that may affect product quality microbiology.

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 (b) (4)

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 (b) (4)

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) 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 (b) (4) We recommend stability batches (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) blisters - 12 months LT, intermediate, and 1 month accelerated
(b) (4) 150 mg in 1 count (b) (4) blister - 12 months LT and intermediate, and 1 month accelerated
(b) (4) 150 mg in (b) (4) 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) and 60 count HDPE) and 2 batches each of 150 mg dual scored tablets (in 3 packaging configurations of 1 count (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) used to manufacture the three 75 mg and 150 mg (b) (4) tablet batches. (b) (4)

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 (b) (4) tablets were originally proposed for this application, the stability data for the 150 mg (b) (4) tablets will be submitted as supporting data.

The Sponsor then asked if they could submit information for the 150 mg (b) (4)

(b) (4)

(b) (4)

The Agency had asked for clarification on the packaging used in the stability studies. The Sponsor replied that originally the (b) (4) package was intended for the drug sample package. (b) (4)

The Sponsor then added a new packaging (b) (4) blister to protect from moisture. 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 (b) (4) 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 B&H Consulting Services Inc.'s 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 ((b) (4)), 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) % 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 (b) (4)

d) Your proposed dissolution method and acceptance criterion of Q = (b) (4)

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= (b) (4) % dissolution occurs. For a (b) (4) immediate release product, (b) (4) 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 ANDA 062421 as part of a licensing agreement. Microbial Limits testing according to USP <61> and <62> are not included in ANDA 062421. 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 (b) (4) that may affect product quality microbiology.**

9.2.4. Stability Data Package

Initial development of Aqua's Doxycycline Hyclate Tablets included an (b) (4) 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° ± 2°C/60% ± 5% RH) and a minimum of 6-month stability data for the registration batches stored under accelerated conditions (40° ± 2°C/75% ± 5% RH).

Data will be provided in the NDA for the (b) (4) 150 mg dosage strength (b) (4) 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) blister pack; however, significant changes were observed after storage of the (b) (4) blister pack for 1 month under accelerated conditions. (b) (4)

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) HDPE bottle. 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 (b) (4) and 150 mg dual-scored tablets) and the container closure systems (trade bottles, sample bottles, (b) (4) sample blisters 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 (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 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

(b) (4)
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

(b) (4)
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)/HDPE and 150 mg: (b) (4)/HDPE 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 (b) (4). Similarly, indicate if the two 150 mg batches (b) (4). We recommend stability batches (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) blisters - 12 months LT, intermediate, and 1 month accelerated
(b) (4) 150 mg in 1 count (b) (4) blister - 12 months LT and intermediate, and 1 month accelerated
(b) (4) 150 mg in (b) (4) 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 Capsules), 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[®] (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[®] PLR Section 12.3) be updated to reflect the data obtained from Aqua's pharmacokinetic studies (Studies 11060203 and 11060204), and reflect that an applesauce sprinkling study was not conducted for Aqua's product. 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:

We agree that information pertaining to the sprinkling of the tablet over applesauce should not be included in your proposed labeling. 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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/s/

JOHN J FARLEY
05/21/2013